Ring-Closing Metathesis towards a Formal Synthesis of Taxol

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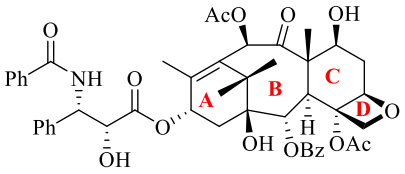
Nothing in life is to be feared, it is only to be understood.

Now is the time to understand more, so that we may fear less.

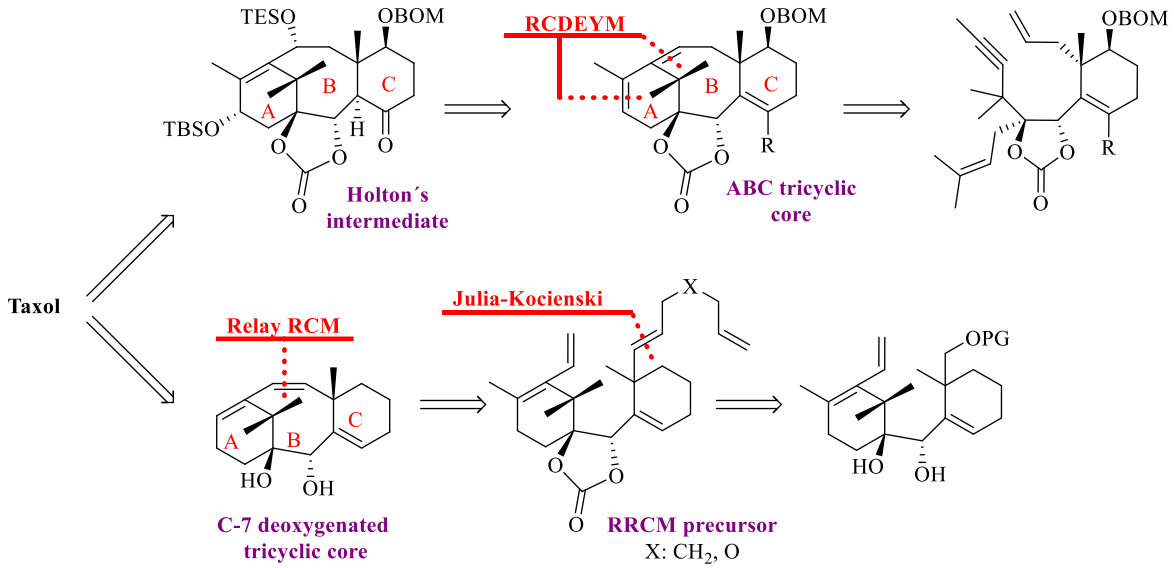
Abstract

Taxol is one of the most notorious examples in the use of naturally occurring compounds as the basis of modern medications and has been recognized as one of the best anticancer drugs in the 21st century. Nowadays, Taxol and its derivatives are the largest selling anticancer drugs generating a revenue of more than three billion dollars annually. Due to its structural complexity, Taxol has been one of the main targets for synthetic chemists around the world and several total and formal synthesis have been published. Two different synthetic efforts toward a formal synthesis of Taxol are presented in this thesis.



Taxol

Initially, a ring-closing dialkene alkyne metathesis (**RCDEYM**) is studied to form the Taxol skeleton. The primary target is the intermediate described by Holton during his synthesis of Taxol. The formation of the ABC tricyclic core by a cascade **RCDEYM** reaction constitutes the key step of this approach. On the other hand, the target molecule in the second route is a C7 deoxygenated tricyclic core and a relay ring-closing methatesis (**RRCM**) was envisioned for the construction of the B ring. Installation of the tether would be possible by a Julia Kocienski olefination



Authors declaration

I declare that, except where explicit reference is made to the contribution of others, the substance of this thesis is the result of my own work and has not been submitted, nor is being concurrently submitted, in candidature for any other degree at the University of Glasgow or any other institution.

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¡Gracias, millones y millones de gracias!

Abbreviations

Ac	Acetyl
acac	Acetylacetonate
Ar	Aryl
BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
Boc	Di-*tert*-butyl dicarbonate
BOM	Benzyloxymethyl
brsm	Based on recovered starting material
Bu	Butyl
Bz	Benzoyl
CM	Cross metathesis
CSA	Camphor sulfonic acid
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DDQ	Dihydroquinine
DIAD	Diisopropyl azodicarboxylate
DIBALH	Diisobutylaluminium hydride
DIPA	Diisopropylamine
DIPEA	*N*,*N*-Diisopropylethylamine
DMAO	*N*,*N*-Dimethylaniline oxide
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
EDCi	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
ee	enantiomeric excess
EE	Ethoxyethyl

EOM	Ethoxy methyl
Et	Ethyl
GTP	Guanosine triphosphate
HMDS	*bis*(Trimethylsilyl)amine
HMPA	Hexamethylphosphoramide
IBX	2-Iodoxybenzoic acid
Im	Imidazole
JKO	Julia-Kocienski olefination
LDA	Lithium diisopropylamide
LHMDS	Lithium *bis*(trimethylsilyl)amide
LTMP	Lithium tetramethylpiperidide
Lut	Lutidine
***m*-CPBA**	*m*-Chloroperoxybenzoic acid
Me	Methyl
MEM	Methoxyethoxymethyl
Mes	Mesityl
MOM	Methoxymethyl acetal
MOP	Methoxypropyl
MPM	Methoxybenzyl
Ms	Methanesulfonyl
NMO	*N*-Methylmorpholine *N*-oxide
PCC	Pyridinium chlorochromate
PG	Protecting group
Ph	Phenyl
Pr	Propyl
PTSA	*p*-Toluenesulfonic acid
Py	Pyridine
RCDEYM	Ring-closing dienyne metathesis
RCEYM	Ring-closing enyne metathesis
RCM	Ring-closing metathesis
RRCM	Relay ring-closing metathesis
rt	Room temperature
TBAF	Tetrabutylammonium fluoride

TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butyl hydroperoxide
TBS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
Tf	Triflyl (trifluoromethanesulfonyl)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
Tol	Toluene
TPAP	Tetrapropylammonium perruthenate
Tris	2,4,6-Triisopropylbenzenesulfonyl
Troc	Trichloroethylcarbamate
Ts	Tosyl (*p*-toluenesulfonyl)

Table of contents

Chapter 1: Introduction

1.1 Taxol

1.1.1 Generalities on Taxol

Taxol (Figure 1.1) is one of the most notorious examples in the use of naturally occurring compounds as the basis of modern medications.[1] Ever since the elucidation of its structure in 1971 and its later approval by the Food and Drugs Administration (FDA) in 1994,[2] Taxol has been widely employed in the treatment of breast[3] and ovarian cancer[2, 4] as well as non-small cell lung cancer.[5] It is recognised as one of the most effective and top selling anticancer drugs generating a revenue of more than three billion dollars annually.[3]

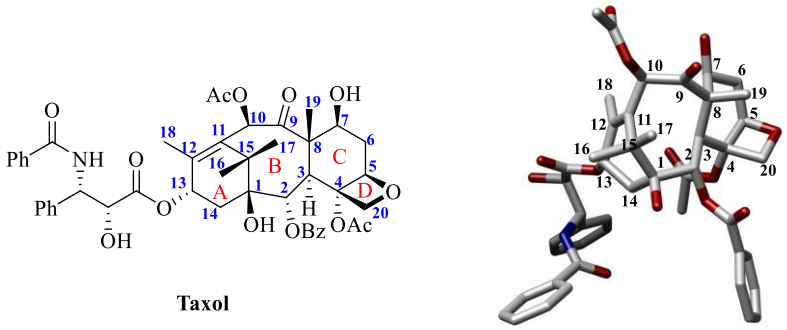


Figure 1.1: Structure of Taxol

As shown in Figure 1.1, Taxol´s skeleton is formed by four fused rings in a 6-8-6-4 configuration and a lateral chain located at the C13 carbon with a total of eleven stereocentres. It shows a diterpenic skeleton where the A rings adopts a deformed boat conformation due to the presence of an alkene in a bridgehead position (C11-C12). The 8-membered ring B sits in a chair-boat conformation and shares a *trans* junction with the six membered C ring (half chair conformation). Moreover, nine of its eleven stereogenic centres are in the 6-8-6 tricyclic bridge skeleton, including the C8 all carbon quaternary centre. Due to its structural complexity, Taxol has been a challenging target for synthetic chemists around the world. Indeed, there have been more than 200 published papers describing studies towards its total and formal synthesis.

All compounds of the taxane family can be classified in four groups taking into account the functional group at the C4 position (Figure 1.2):

- Group A: Exocyclic alkene at C4-C20 (Taxine B)
- Group B: Epoxide at C4-C20 (baccatin I)
- Group C: Oxetane ring C4-C5 (Taxol)
- Group D: 6-10-6 tricyclic core (taxine A)

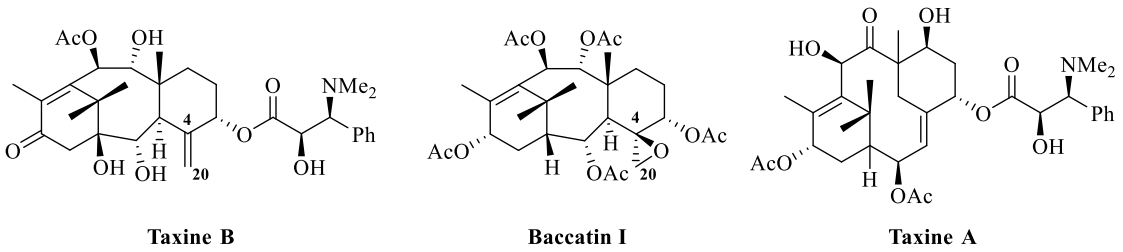
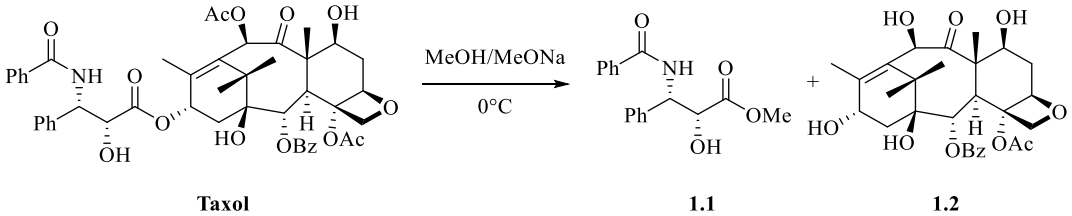


Figure 1.2: Structures of taxine B, baccatin I and taxine A

1.1.2 Discovery of Taxol

Efforts from the National Cancer Institute (NCI) and the United States Department of Agriculture (USDA) towards the discovery of new, naturally occurring, anticancer compounds from plants led to the discovery of Taxol's bioactivity.[6] In 1963 *Taxus brevifolia* bark extracts collected by Arthur Barclay showed cytotoxic activity against KB cells. Later recollection of bark extracts done by Wall and coworkers at the Research Triangle Institute (RTI) in North Carolina in 1965 confirmed in vivo cytotoxic activity against mouse leukaemia.[7]

Pure Taxol was isolated in 1969 in a 0.01% yield from the bark of the tree (the needles and wood contained much less Taxol). Subsequently, the elucidation of its structure took place in 1971 by making significant use of ^{1}H NMR as well as X-ray studies on methyl *N*-benzophenylisoserine **1.1** and 10-deacetylbaccatin III **1.2** (Scheme 1.1). However, low extraction yields and poor water solubility as well as the modest *in vivo* activity against various carcinomas and leukaemia were not very encouraging.[8]



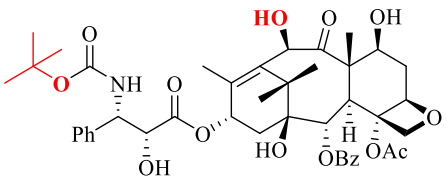
Scheme 1.1: Cleavage of the side chain

Despite this, some additional bioassays were conducted by the NCI in the early 1970s showed a significant activity against a B16 mouse model melanoma and resulted in the selection of Taxol

as a development candidate in 1977. Activity shown against the then new MX-1 and CX-1 mammary and colon xenografts in nude mice were also proved. The interest in this compound increased significantly in 1979 when Schiff and Horwitz discovered its mechanism of action as a promoter of tubulin assembly.[9] By then Taxol was the only known compound capable of disrupting the dynamic equilibrium of microtubules and monomeric tubulin, and its cytotoxic activity was considered towards the development of an anticancer drug. After completion of toxicology studies and preclinical formulation in 1982, Taxol entered phase I clinical studies in 1984 and phase II trials in 1985. As a result, in 1994, the FDA granted the approval of its use for the treatment of breast and ovarian cancer.

Regardless of its remarkable biological activity, Taxol has a major inconvenience: its availability. *Taxus brevifolia* is primarily found in United States of America, but several other yew species can be found around the word, especially in temperate climates.[10] Taxol content is different in each species, with *T. yunnanensis* (Burma, South China) being the one that contains the highest concentration of Taxol in the mature tree's bark. However, the presence of the Taxol analogue cephalomannine does not allow a high yielding industrial separation. *T. media* (Canada) proved to be the most practical yew for Taxol extraction from the leaves and branches of 3 to 5 years old specimens (0.02 - 0.04% yield). These poor yields obtained, in addition to the ecological impact of the extraction, confirm the need of a sustainable source of Taxol.

The first attempt at solving this problem was conducted by Rhône-Poulenc and the group of Pierre Potier from l'Institut de Chimie des Substances Naturelles of Gif-sur-Yvette in 1988 when a semisynthetic route from **1.2**, isolated in relatively large quantities from the needles of *T. baccata*, was published.[11] In the same study, Taxotere™ (Figure 1.3) was also identified as a more active compound in the treatment of breast, lung, prostate and gastric cancer. The free hydroxyl group located at C10 position caused Taxotere to be more water soluble than Taxol.



Taxotere™

Figure 1.3: Structure of the Taxotere™

1.1.3 Bioactivity

As previously mentioned, in 1977 Susan Horwitz carried out the first experiments on Taxol's mechanism of action. Her results showed that nanomolar concentrations of Taxol inhibited the replication of HeLa cells. Further examination proved that Hela cells exposed to Taxol (250 nM) for at least 18h had replicated the DNA and had a tetraploid DNA content but were blocked in the metaphase.[12] As shown in Figure 1.4[13] the modal positions of cells containing diploids (2C) and tetraploids (4C) did not change significantly during the experiment, proving that Taxol blocks cell division, thus causing cellular death. In her research, Horwitz highlighted Taxol's effect on cellular division as a microtubule bundle poison. Even though colchicine, vincristine, and vinblastine, among some other anticancer drugs, also blocked cells in the mitotic cycle, only cells treated with Taxol could reorganize their microtubules.

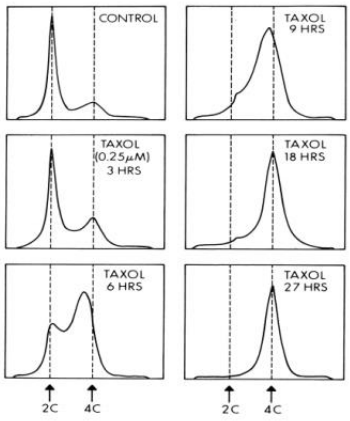


Figure 1.4: Taxol blocking cells during mitosis

Microtubules are considered to be one of the major basic structural elements of the cytoskeleton and are in charge of transporting the genetic material from the mother cell to the daughter cells in the cellular cycle. As shown in Figure 1.5, tubulin is a heterodimer formed by two different subunits (α and β). The longitudinal head to tail self-assembly of tubulin dimers promoted by GTP biding results in the formation of protofilaments that constitute the wall of microtubules (13 dimers of tubulin per turn). These microtubules display an extremely dynamic behaviour that results in the rapid exchange of tubulin dimers at the microtubules ends.[14]

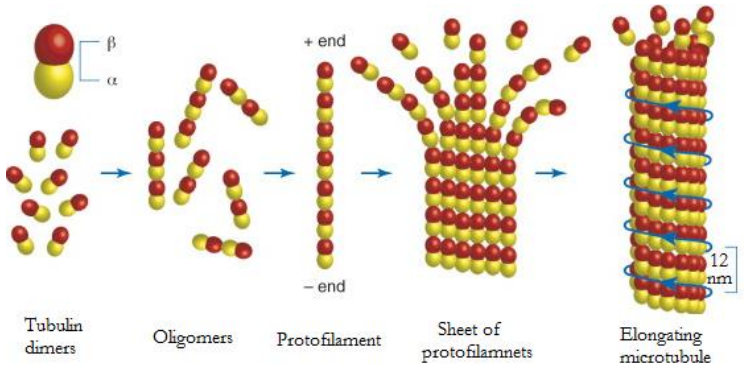


Figure 1.5: Formation of microtubule[15]

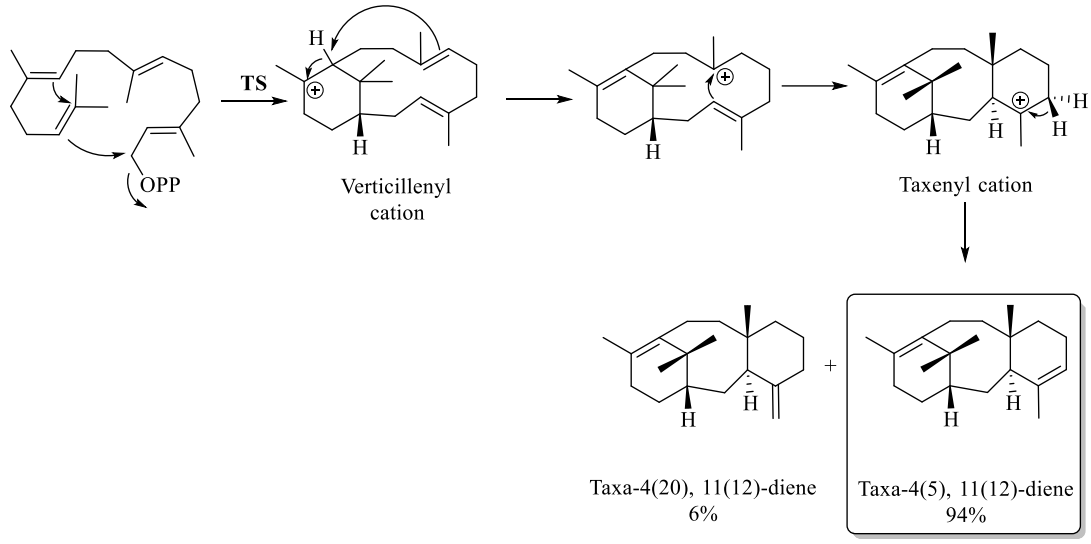
Generally, microtubule bundle poisons were associated with their binding of the β-subunit, thus preventing the polymerisation of microtubules. In contrast, Taxol does not prevent this polymerisation but promotes it. Moreover, Taxol stops the depolymerisation towards the microtubules and is capable of polymerising tubulin, even at low temperatures (4°C) in the absence of GTP, inhibiting the required equilibrium for correct cell replication.[12] In addition, in 1981, it was proved that Taxol has its maximum effect when using a stoichiometric ratio to the tubulin dimer concentration.[16] This novel mechanism of action has a major repercussion on carcinogenic cells (considered to duplicate faster than normal cells), and thus Taxol was considered a promising candidate in anticancer drug development.

1.2 Syntheses of Taxol

1.2.1 Biosynthesis

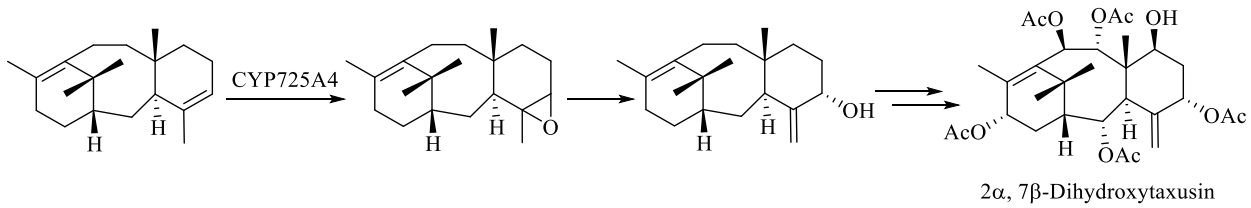
Understanding the biosynthesis of Taxol is the first step for the pharmaceutical industry to offer a viable commercial production pathway free from the current environmental problems. The biogenesis of Taxol can be divided into three conceptually different processes: the construction of the taxane skeleton, the addition of eight oxygenated functional groups and the later assembly of the C13 side chain.

Firstly, enzymatically catalysed cyclisation of the geranylgeranyl diphosphate skeleton by taxadiene synthase (**TS**) results in the formation of the taxane skeleton *via* verticillenyl and taxenyl cations (Scheme 1.2).[17]



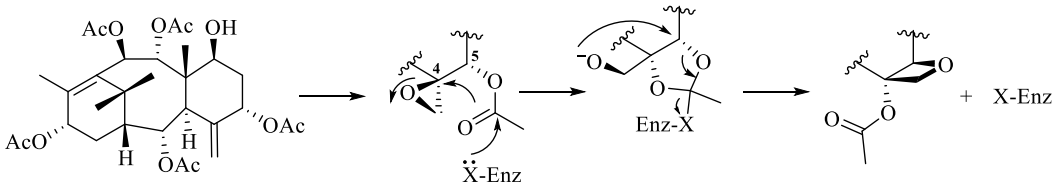
Scheme 1.2: Biosynthesis of ABC tricyclic core of taxol

Since every taxane has an oxygenated function at C5, subsequent oxidation of this position by the taxoid oxygenase enzyme taxadiene-5α-hydroxylase (CYP725A4) is proposed (Scheme 1.3).[18] Chemical and biological studies support an epoxidation-based mechanism followed by a non-selective breakdown of the epoxide intermediate.[19] Further oxidations and acetylations leads to 2α,7β-dihydrotaxusin.



Scheme 1.3: Oxidation of C5 carbon

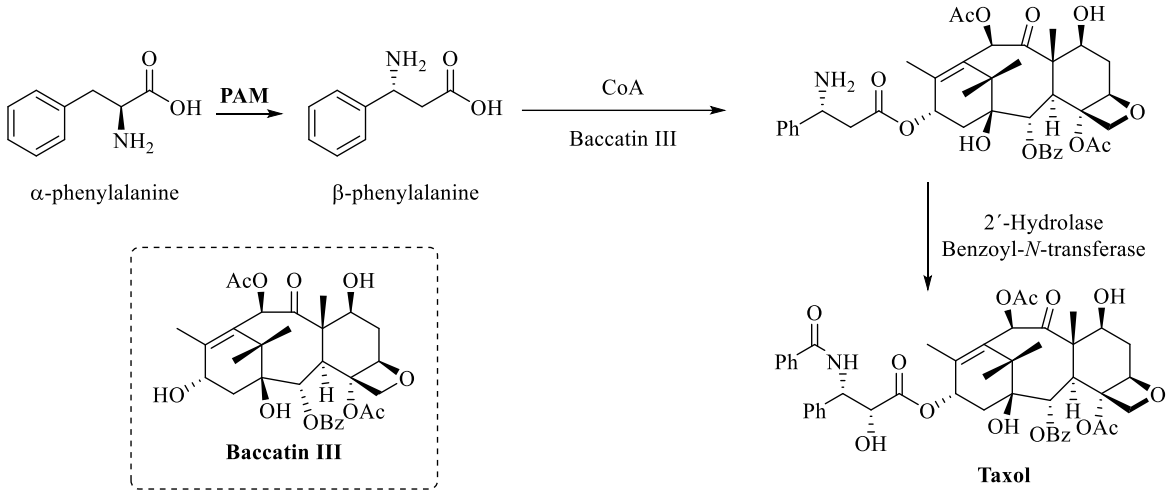
As shown in Scheme 1.4, latter oxetane ring formation is attributed to an oxomutase reaction *via* a transferase type mechanism. The oxidation of the exo cyclic alkene is possibly due to the intramolecular exchange of the C5α-acetoxy group and the C4β -oxide function.



Scheme 1.4: Oxidation of C5 carbon

The final step is the assembly of C13 side chain. Reaction of natural α-phenylalanine with Peptidylglycine Alpha-amidating Monooxygenase (PAM) produces β-phenylalanine (Scheme

1.5). Coupling between β-phenylalanine and baccatin III catalysed by coenzyme A and further hydroxylation of C2´and benzoylation of C2 lead to Taxol.



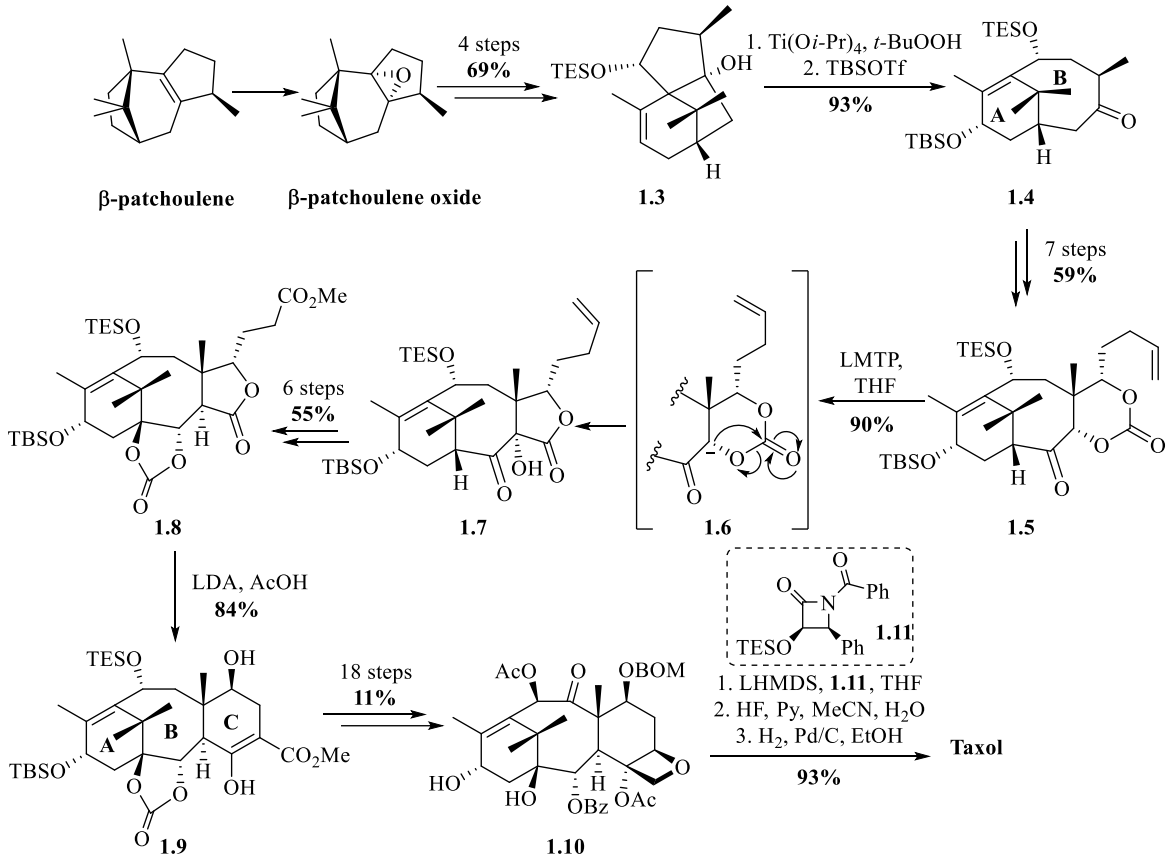
Scheme 1.5: Oxidation of C5 carbon

1.2.2 Total syntheses of Taxol

To date, seven total syntheses of Taxol have been published. In this section only the key points of each synthesis will be discussed.

1.2.2.1 Holton´s synthesis

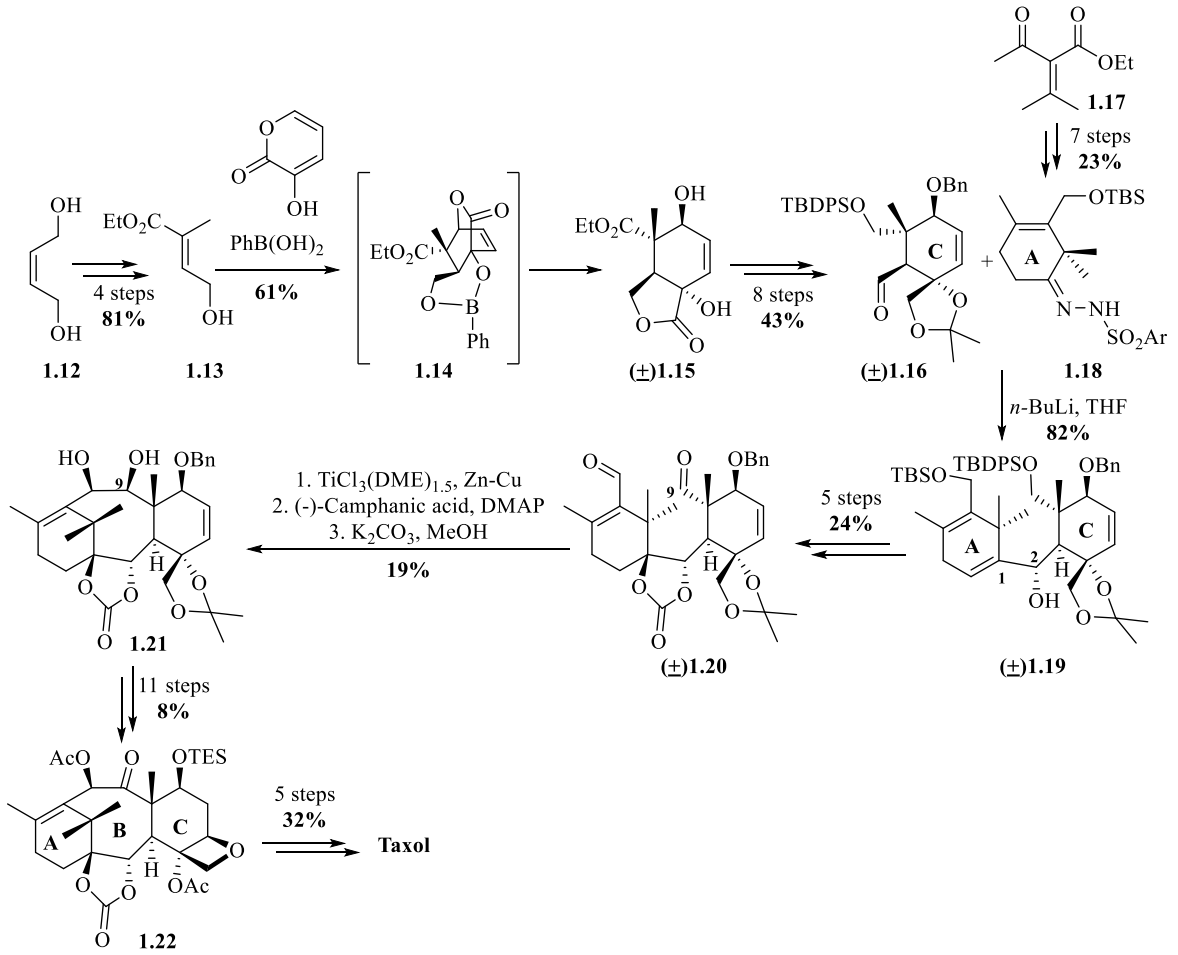
The first total synthesis of Taxol was published in 1994 by Holton and co-workers.[20] This synthesis uses a natural product as starting material and has a linear approach. Starting from β-patchoulene oxide, silylated homoallylic alcohol **1.3** was obtained over four steps in 69% yield (Scheme 1.6). A tandem epoxidation-Grob fragmentation followed by a TBS protection of the secondary alcohol yielded the desired AB bicyclic core **1.4**. For the construction of the C ring, **1.4** was transformed in cyclic carbonate **1.5**, which was then submitted to Chan rearrangement providing lactone **1.7**. Dieckmann condensation of **1.8** afforded ABC tricyclic core **1.9** in 84% yield. After 18 steps involving the decarboxylation and selective oxidation of C5, the introduction of the final missing carbon atom at C4 and its transformation to an exocyclic alkene was followed by the installation of the oxetane ring; advanced intermediate **1.10** was isolated. Addition of the Ojima lactam **1.11** to alcohol **1.10** was followed by global deprotection affording Taxol in 0.6 % overall yield over 56 steps.



Scheme 1.6: Holton´s total synthesis

1.2.2.2 Nicolaou´s synthesis

Simultaneously to Holton's synthesis, the Nicolaou group was working on a convergent approach to Taxol.[21] Starting from dihydroxybutene **1.12** and the β-carbonyl unsaturated ester **1.17**, the C (**(±)1.16**) and A (**1.18**) rings were successfully synthesised. Interestingly, the presence of phenylboronic acid favoured complexation with the two hydroxyl groups *via* intermediate **1.14**, leading to a single diastereomer of the Diels-Alder product (**(±)1.15**). Coupling of fragments **(±)1.16** and **1.18** by a Shapiro reaction gave AC bicycle core **(±)1.19** as a single diastereomer. The C1 hydroxyl group was installed by a regioselective epoxidation followed by a ring-opening epoxide reaction. Further transformations afforded dialdehyde **(±)1.20** that was then submitted to a McMurry cyclisation and a resolution of the racemate product *via* its diastereomeric camphanate esters at C9, constructing the desired ABC tricyclic core **1.21**. After installation of the oxetane ring the tetracyclic core **1.22** was transformed into Taxol in a 0.02% overall yield over 44 steps.



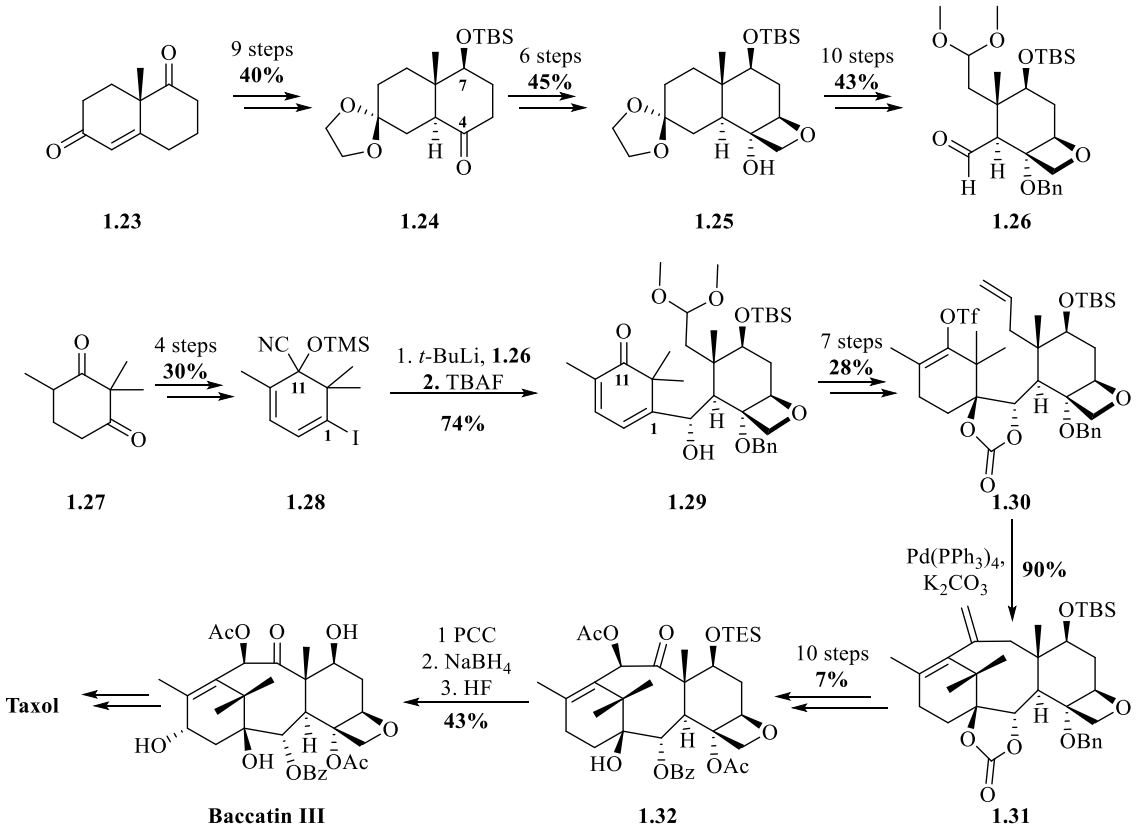
Scheme 1.7: Nicolaou´s total synthesis

1.2.2.3 Danishefsky´s synthesis

In 1996, the Danishefsky group published its convergent synthesis of Taxol.[22] Interestingly, this synthesis is the only approach in which the D ring is installed in an early step. Starting from the Wieland-Miescher ketone **1.23**, the C7 stereocentre was successfully installed and **1.24** was isolated after 9 steps (Scheme 1.8). The ketone motif at C4 was used to install the oxetane ring giving **1.25** and further transformations afforded advanced intermediate **1.26**. Separately, the synthesis of the A ring was successfully accomplished. Starting from diketone **1.27**, vinyl iodide **1.28** was obtained after a hydrazone iodination at C1 followed by a cyanohydrin formation at C11.

Coupling of the two fragments (**1.26** and **1.28**) yielded the ACD tricyclic core **1.29** as a single diastereomer. Construction of the B ring was possible by a very high-yielding intramolecular Heck coupling between the terminal olefin and the triflate in **1.30**. Once the ABCD tetracyclic

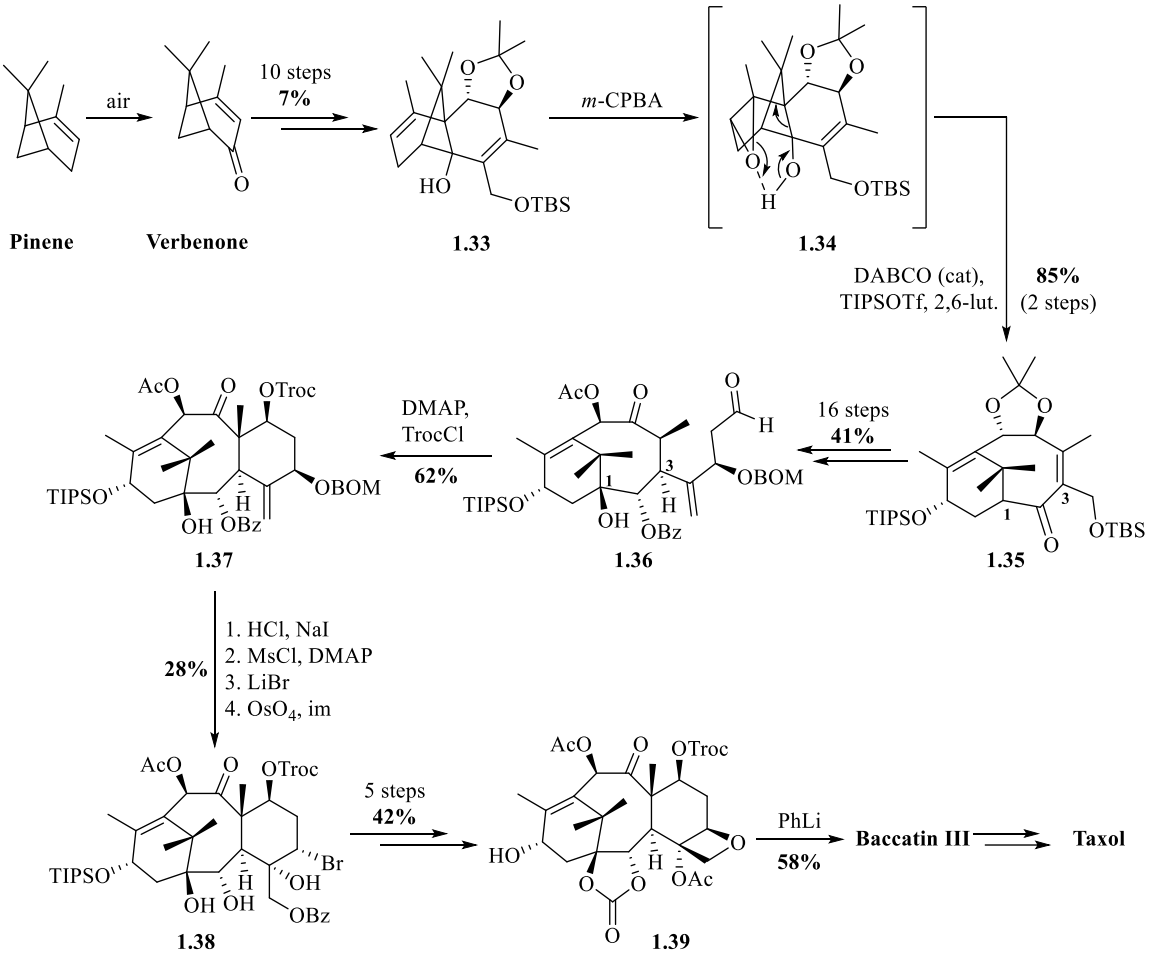
core **1.31** was obtained, Taxol was finally isolated in 0.03% overall yield over 53 steps *via* intermediate **1.32** and baccatin III.



Scheme 1.8: Danishefsky´s total synthesis

1.2.2.4 Wender´s synthesis

In 1997 Wender and co-workers published a linear total synthesis of Taxol.[23] As shown in Scheme 1.9, air oxidation of pinene afforded verbenone. The AB core was obtained after a chemoselective epoxidation of the double bond at **1.33** followed by a DABCO induced Grob fragmentation (*via* transition state **1.34**). Subsequent protection of the free alcohol with TIPS afforded the desired bicyclic system **1.35**. After installation of the C1 hydroxyl group and further functionalisation at the C3 chain, the advanced intermediate **1.36** was obtained. Construction of the C ring **1.37** was achieved through an intramolecular aldol reaction. Once the oxetane ring was formed from **1.38** and the lateral chain was installed Taxol was isolated over 37 steps in total with a 0.09% overall yield.

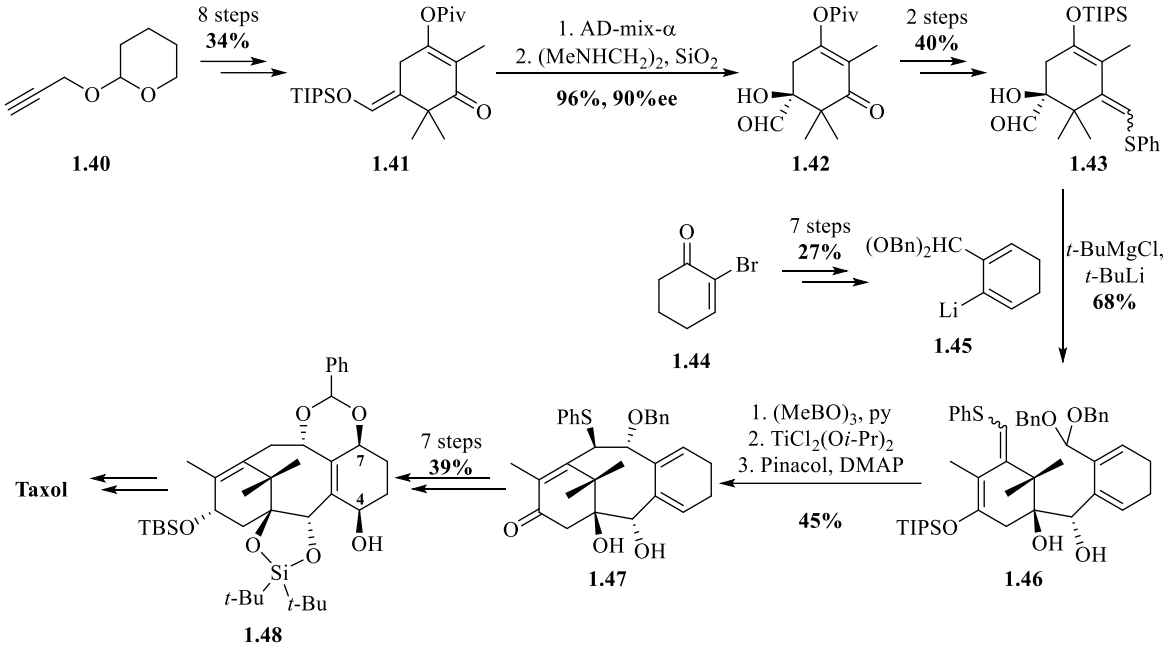


Scheme 1.9: Wender´s total synthesis

1.2.2.5 Kuwajima´s synthesis

In 1998 Kuwajima and co-workers published their convergent synthesis of Taxol.[24] In a similar strategy to the one used by Nicolaou, Kuwajima´s work involves the synthesis of A and C rings. After connecting these two fragments and closing the B ring, the oxetane D ring was installed. The Ojima lactam was once again employed for the tail addition. Starting from the protected propargyl alcohol **1.40**, *E*-silyl enol ether **1.41** was obtained in 34% yield after 8 steps (Scheme 1.10). An asymmetric dihydroxylation was performed affording the α-hydroxy aldehyde **1.42** in 90% ee. Once the pivalate was transformed to its corresponding silyl enol ether and a Peterson olefination was conducted, ring A **1.43** was successfully isolated. Condensation of vinyl lithium ring C **1.45**, obtained from 2-bromocyclohexenone **1.44**, afforded the AC bicyclic diol **1.46** as a single diastereomer. A vinylogous Mukaiyama aldol addition to the acetal motif was then performed for the closure of the B ring (**1.47**). Selective oxidations of the olefins at C4 and C7

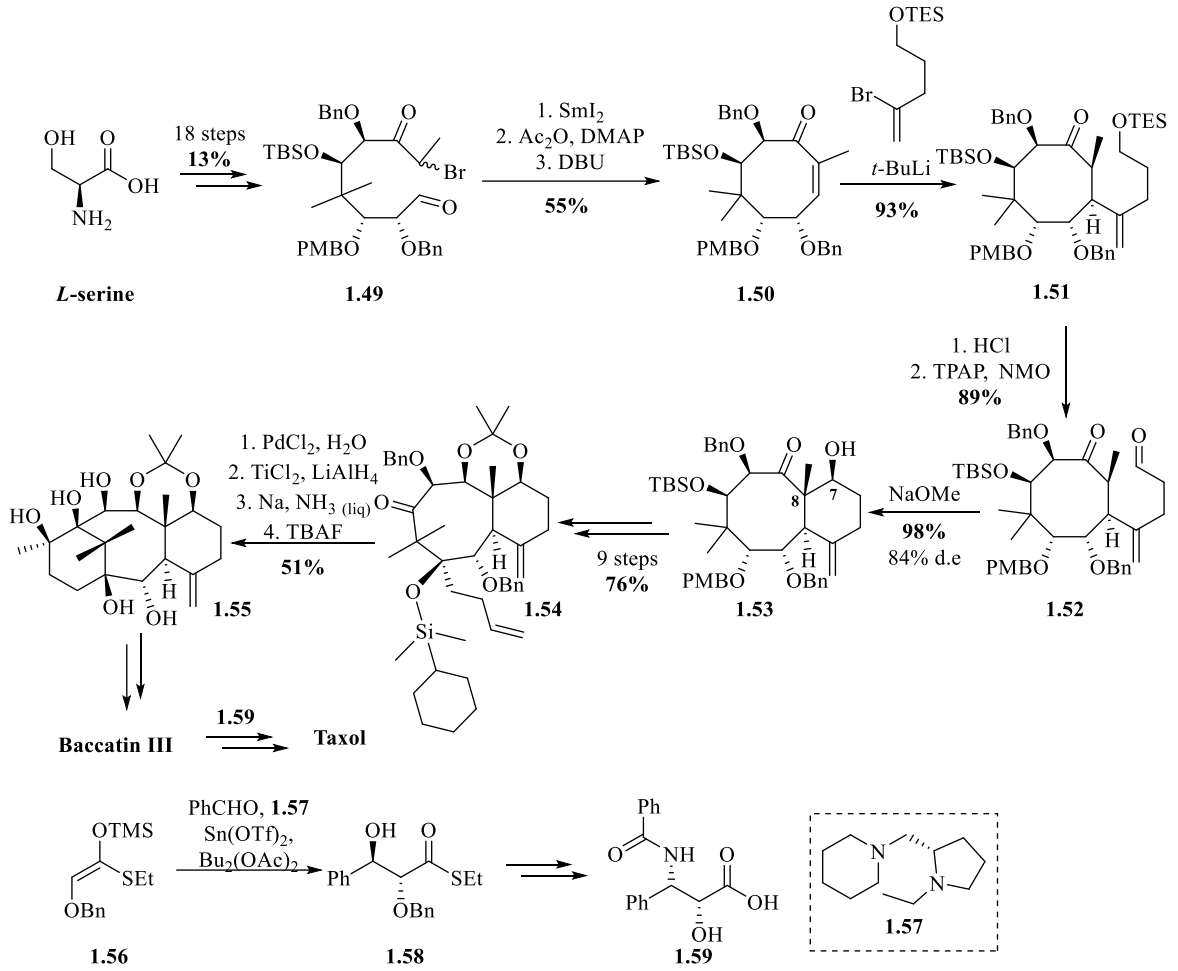
and removal of the thiol yielded advanced intermediate **1.48**. Incorporation of the oxetane ring and addition of the lateral chain gave Taxol in 0.007% overall yield over 59 steps.



Scheme 1.10: Kuwajima´s total synthesis

1.2.2.6 Mukaiyama´s synthesis

One of the most recent total synthesis of Taxol was published in 1999 by Mukaiyama *et al.*[25] In this linear approach, the eight membered B ring was firstly synthesised. Using *L*-Serine as starting material, aldehyde **1.49** was successfully synthesised after several Mukaiyama-type aldol reactions were performed (Scheme 1.12). Ring B **1.50** was formed using a SmI_2-mediated cyclisation followed by the formation of the acetate and its elimination. Installation of the C ring was possible using a Michael addition and an aldol-type reaction as key steps, thus BC bicycle **1.53** was isolated with the correct configuration at C7 and C8 *via* intermediates **1.51** and **1.52**.



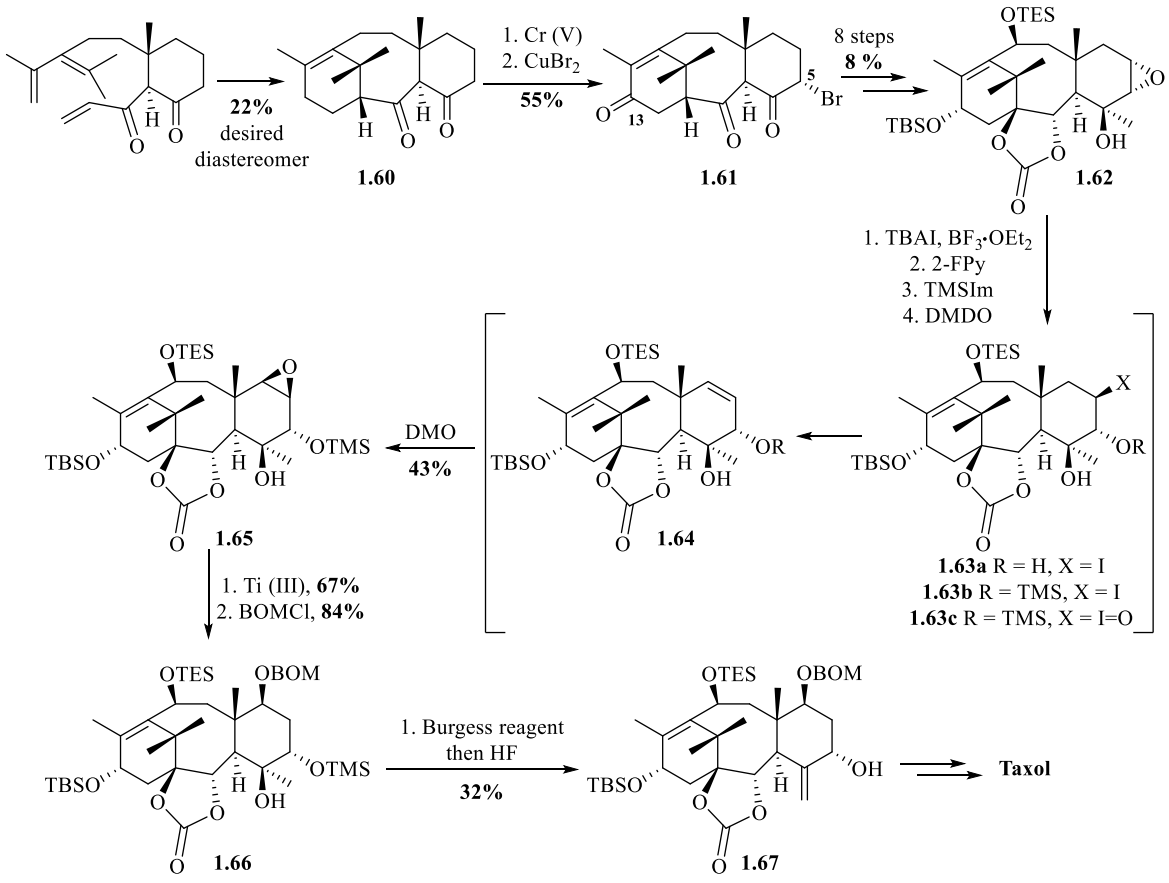
Scheme 1.11: Mukaiyama´s total synthesis

Further transformations yielded diene **1.54** that was then subjected to a Wacker oxidation to transform the terminal double bond into a ketone; this was then followed by an intramolecular pinacol coupling. Deprotection of the benzyl and silyl protecting groups then provided ABC tricyclic core **1.55**. After formation of the oxetane ring, Baccatin III was finally isolated. Interestingly, this synthesis employs a different connection with the side chain. Starting from benzaldehyde and silyl enol ether **1.56**, an asymmetric aldol reaction afforded alcohol **1.58** with 99% *anti* selectivity and 96% ee in the presence of **1.57**. Following the installation off the alkyl side chain (**1.59**), Taxol was obtained in 0.05% overall yield over 52 steps.

1.2.2.7 Baran´s synthesis

In 2012, Baran and co-workers published a scalable enantioselective synthesis of taxanes.[26] This route was further optimised to afford more than 100 g of the tricyclic core **1.60** in a simple batch protocol after performing a Diels Alder reaction that affords the desired diastereomer in 22% yield .[27] A sequence of selective oxidations are the key steps for the transformation of **1.60** into

Taxol. Initially, a Cr(V)-based oxidation at C13 followed by a selective bromination at C5 afforded the advanced intermediate **1.61** in 55% yield over two steps. Further transformations furnished the stable epoxide **1.62** in 8% yield after 8 steps. A stereoselective functionalisation of C7 was achieved in a one pot reaction via intermediates **1.63a-c**. Treatment of **1.62** with TBAI/$BF_3{\cdot}OEt_2$ followed by addition of 2-fluroropyridine, TMS-imidazole and DMDO afforded the desired olefin **1.64**, which was further oxidized to the epoxy-taxane **1.65** in 43% yield. The tertiary alcohol **1.65** was isolated after Ti-mediated epoxide reduction followed by a BOM protection. Subsequent Burgess dehydration-TMS deprotection sequence afforded the allylic alcohol **1.67** in 18% yield over 4 steps. After formation of the oxetane ring and installation of the lateral chain at C13, Taxol was finally isolated in a 0.0014 % overall yield over 39 steps.



Scheme 1.12: Baran´s total synthesis

1.2.2.8 Total syntheses overlook

As mentioned before, the preparation of the highly functionalised ABC system is the key part of Taxol´s total syntheses reported to date. Table 1 summarises the sequence in which the Taxol skeleton was constructed as well as the number of steps and the overall yields.

Table 1.1: Taxol's total syntheses

Group (year)	Approach	Steps	Yield	Sequence
Holton (1994)	Linear	56	0.6%*	A→AB→ABC→ABCD
Nicolaou (1994)	Convergent	44	0.02%	A+C→AC→ABC→ABCD
Danishevsky (1996)	Convergent	53	0.03%	A+CD→ACD→ABCD
Wender (1997)	Linear	37	0.09%	A→AB→ABC→ABCD
Kuwajima (1998)	Convergent	59	0.007%	A+C→AC→ABC→ABCD
Mukaiyama (1998)	Linear	52	0.05%	B→BC→ABC→ABCD
Baran (2020)	Linear	39	0.0014 %	A→ABC→ABCD

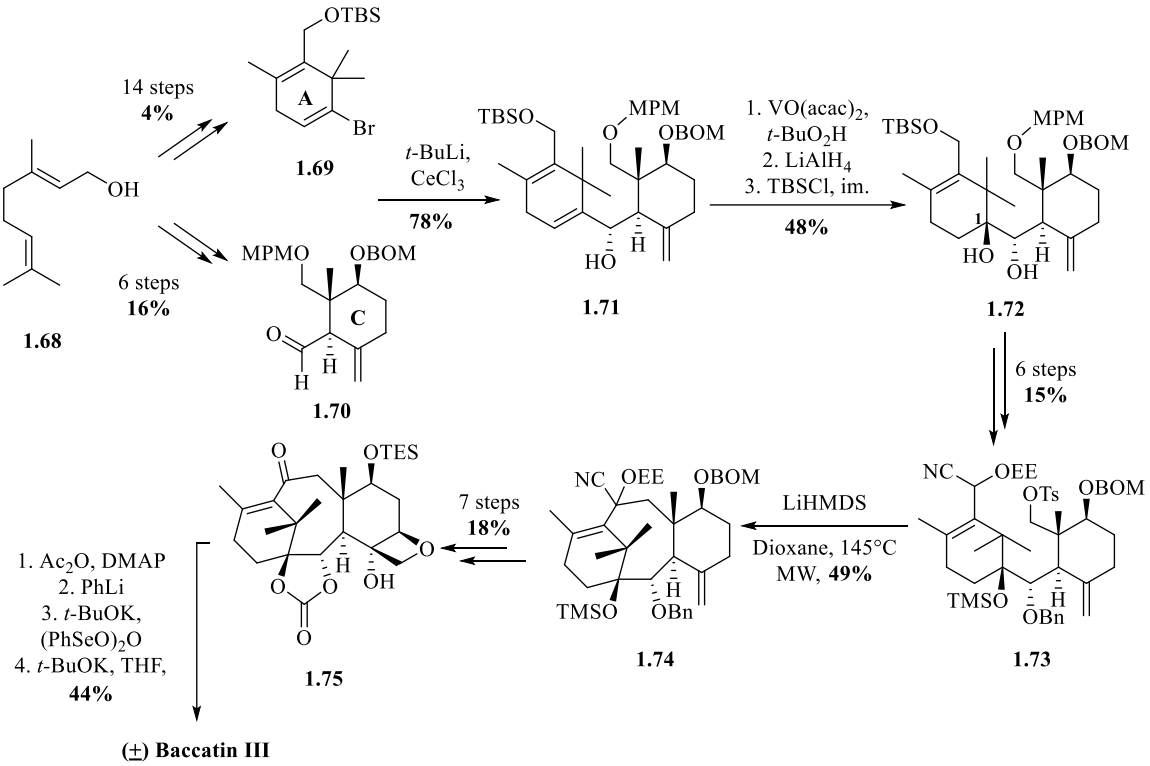
* From a 18 step prepared precursor

1.2.3 Formal syntheses

To date, three formal syntheses of Taxol have been reported. In this section only the key steps of each one will be discussed. Interestingly, the construction of the highly sterically hindered B ring represents the biggest synthetic challenge.

1.2.3.1 Takahashi´s synthesis

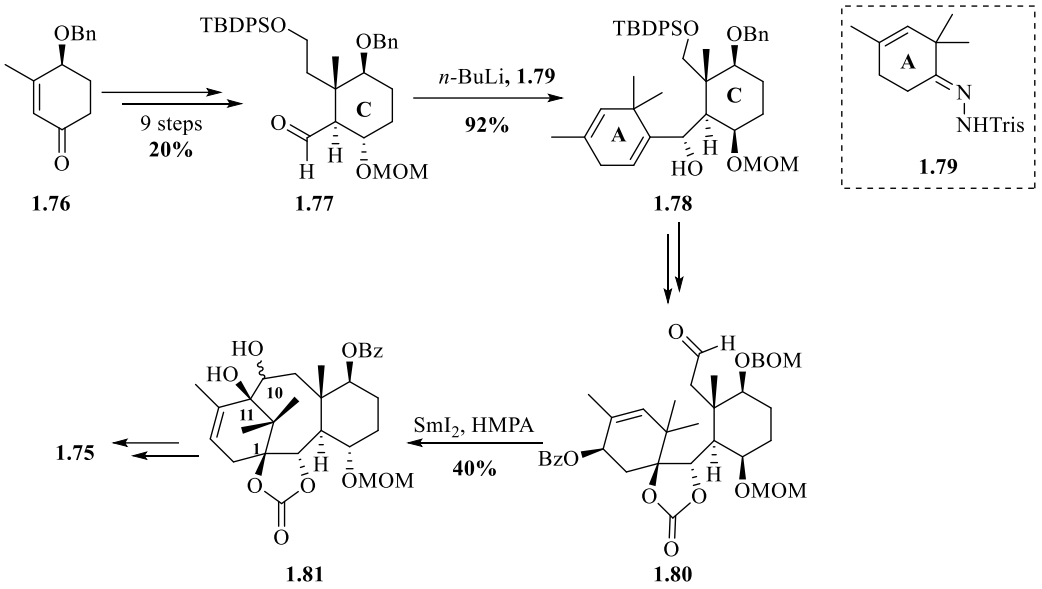
In 2006, Takahashi and co-workers reported a racemic synthesis of baccatin III.[28] Remarkably, all the synthesis was accomplished by a single PhD student and several synthetic steps were performed in automatic synthesisers. Starting from geraniol **1.68**, both A and C ring were successfully synthesised (**1.69** and **1.70** respectively, Scheme 1.13). The coupling of both fragments afforded homoallylic alcohol **1.71** in 78% yield. A selective epoxidation followed by the reductive opening of the epoxide allowed the installation of the hydroxyl group at C1 (**1.72**). A sequence of protections, deprotections, oxidations and cyanohydrin formation yielded **1.73** in 15% yield over 6 steps. Treatment of **1.73** with LiHMDS under microwave irradiation delivered the ABC tricycle core **1.74** in 49% yield. After installation of the D ring, baccatin III was isolated as a racemic mixture *via* intermediate **1.75**.



Scheme 1.13: Takahashi´s formal synthesis

1.2.3.2 Sato-Chida´s synthesis

In 2015 Sato, Chida and co-workers published a formal synthesis of Taxol isolating Takahashi´s intermediate **1.75**.[29] Ring C **1.77** was synthesised from known ketone **1.76** and then coupled with known hydrazone **1.79** by a Shapiro reaction affording **1.78** in 92% yield (Scheme 1.14). After further functionalisation, aldehyde **1.80** was isolated. Formation of the B ring using a samarium mediated cyclisation afforded ABC tricyclic core **1.81**, which was then transformed into the Takahashi intermediate **1.75**. This compound was synthesised in 0.07% overall yield over 38 steps.

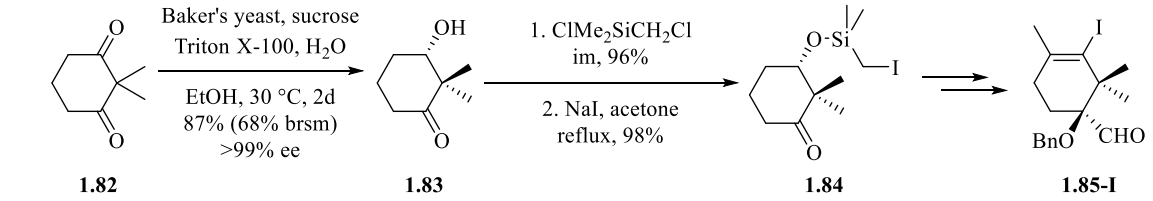


Scheme 1.14: Sato-Chida´s formal synthesis

1.2.3.3 Nakada´s synthesis

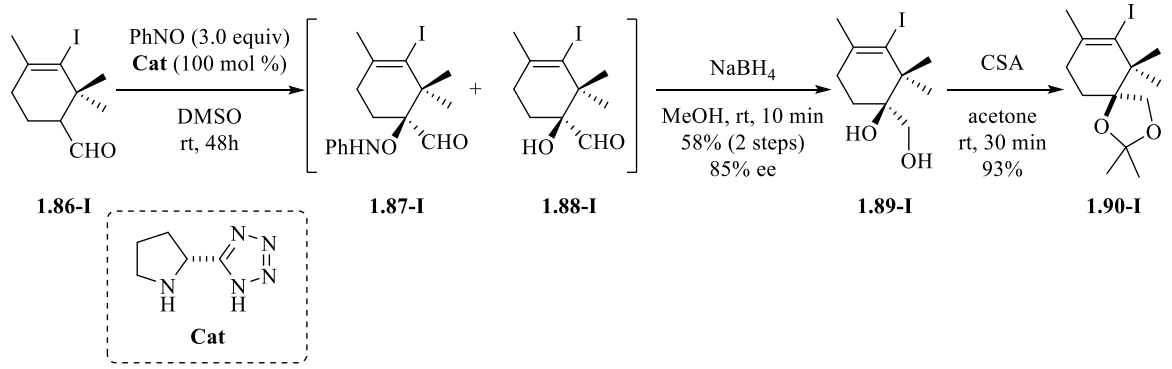
The most recent formal synthesis of Taxol was reported by Nakada and co-workers in 2015.[30] (Scheme 1.15). Three different approaches were explored towards the synthesis of the A-ring **1.85-I** (Scheme 1.15). Initially, using **1.82** as stating material, **1.85-I** was synthesised in 48% yield after 14 steps *via* the silicon-tethered intermediate **1.84** (Scheme 1.15a). Notably, an enantioselective reduction of the ketone in the presence of baker´s yeast is used to set the stereochemistry in **1.83**. The second approach involved the use of an enantioselective organocatalytic reaction starting from aldehyde **1.86-I** and going *via* intermediate **1.89-I** (Scheme 1.15b). The final approach involved the synthesis of brominated fragment A **1.92-Br** using a Sharpless asymmetric dihydroxylation of silyl enol ether **1.91-Br** (Scheme 1.15c).

a) Silicon chemistry



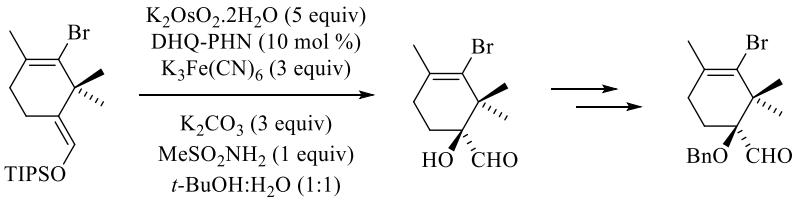
1.82 **1.83** **1.84** **1.85-I**

b) Organocatalysis



1.86-I **1.87-I** **1.88-I** **1.89-I** **1.90-I**

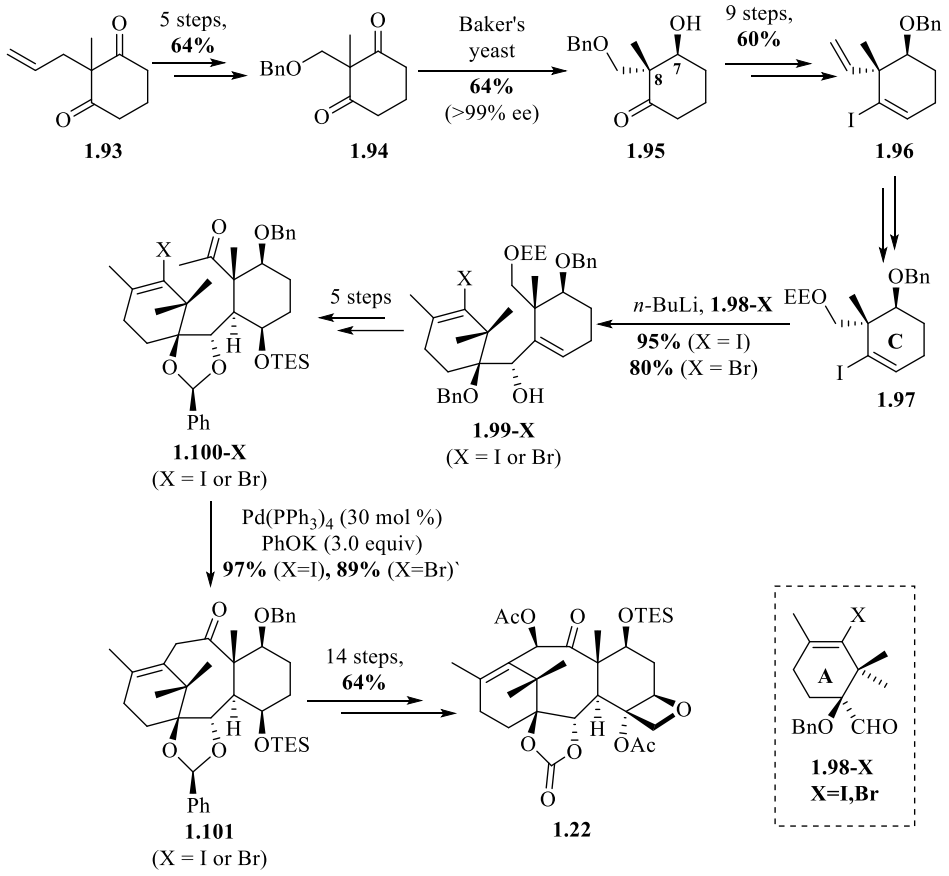
c) Sharpless asymmetric dihydroxylation



1.91-Br **1.88-Br** **1.92-Br**

Scheme 1.15: Nakadas´s synthetic approaches to the A ring of Taxol

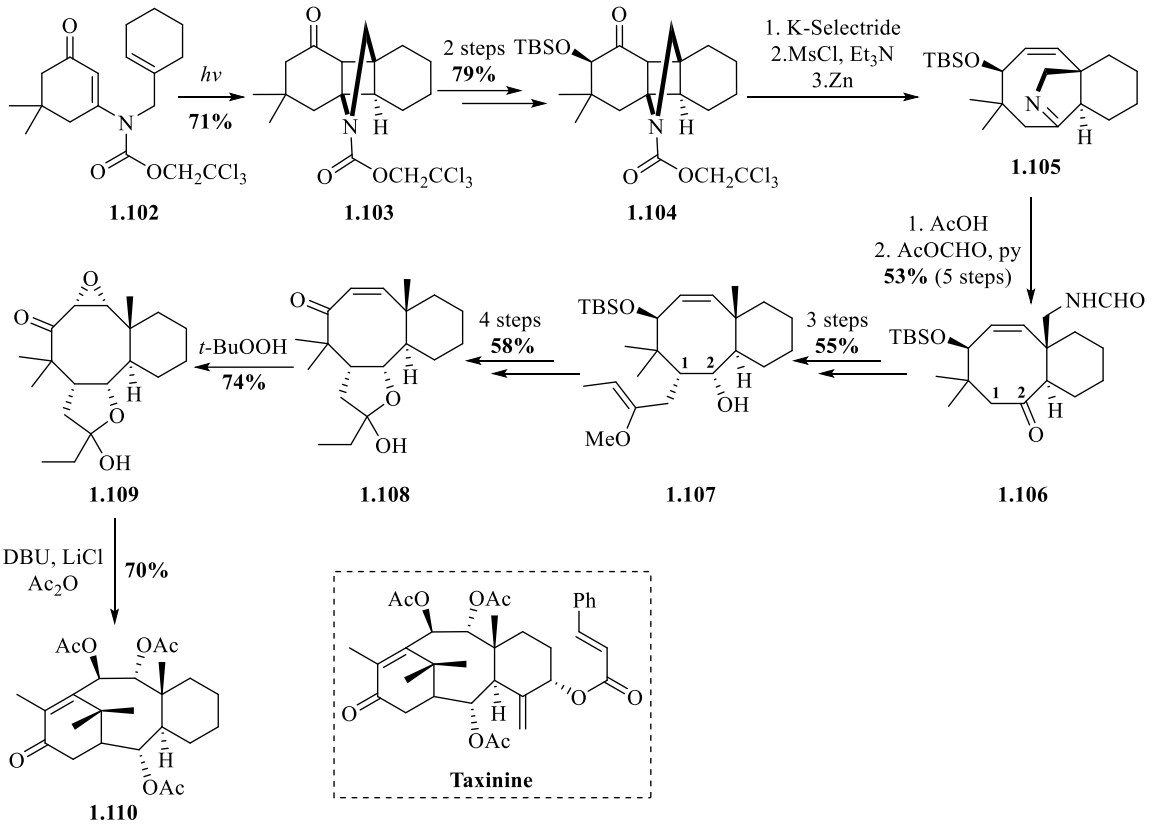
In a parallel fashion, C-ring **1.97** was successfully synthesised (Scheme 1.16). Starting from diketone **1.93**, protected alcohol **1.94** was isolated in 64% yield. [31] An enantioselective reduction catalyzed by baker´s yeast resulted in the correct stereocentres at C7 and C8. Later transformations yielded **1.97** *via* **1.96**. Coupling of the two fragments via a halogen-lithium exchange reaction yielded **1.99-I** and **1.99-Br** in 95% and 80%, respectively. After further functionalisation, the eight-membered ring **1.101** was obtained by a palladium-catalysed alkelynation of methyl ketones **1.100-I** and **1.100-Br**. Subsequent transformations allowed the synthesis of Nicolaou´s intermediate **1.22**.



Scheme 1.16: Nakadas´s formal synthesis of Taxol

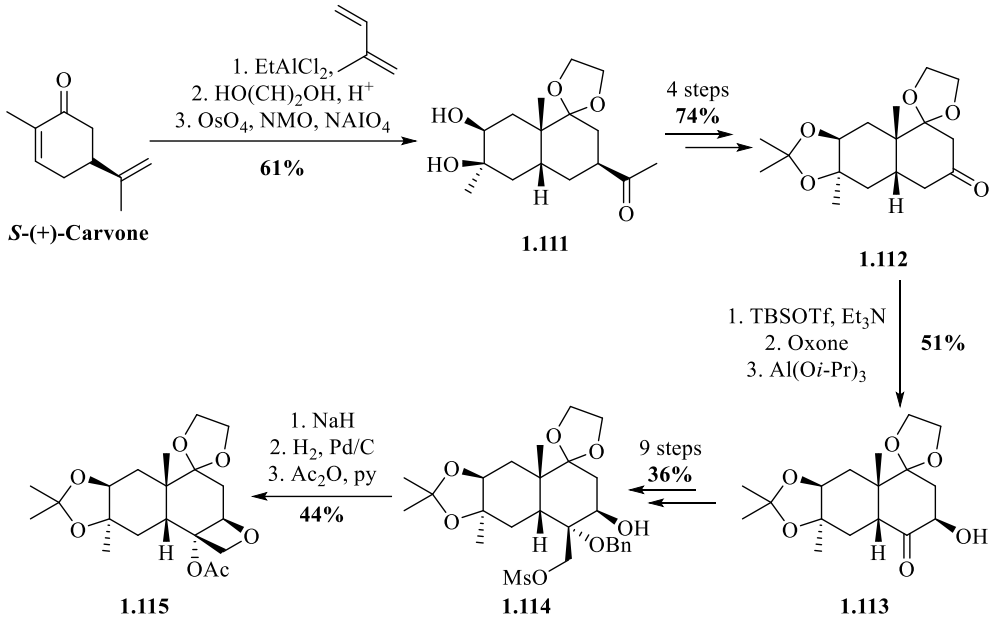
1.2.4 Additional synthetic efforts towards the Taxane skeleton

In 1990 Swindell and coworkers published a stereoselective construction of the taxinine AB system (Scheme 1.17).[32] Starting from enamine **1.102**, an intramolecular [2+2] photoaddition reaction afforded **1.103** in 71% yield. Further transformations resulted in ketone **1.104** that was reduced and then mesylated. A fragmentation-elimination of the mesylate group gave **1.105**, which after hydrolysis and elimination of the imine, reduction of the ketone at C2 and alkylation at C1 afforded alcohol **1.107**. Once the epoxide **1.109** was obtained, a tandem aldol-Payne rearrangement annulation gave the desired AB bicyclic core **1.110** of taxinine in 70% yield.



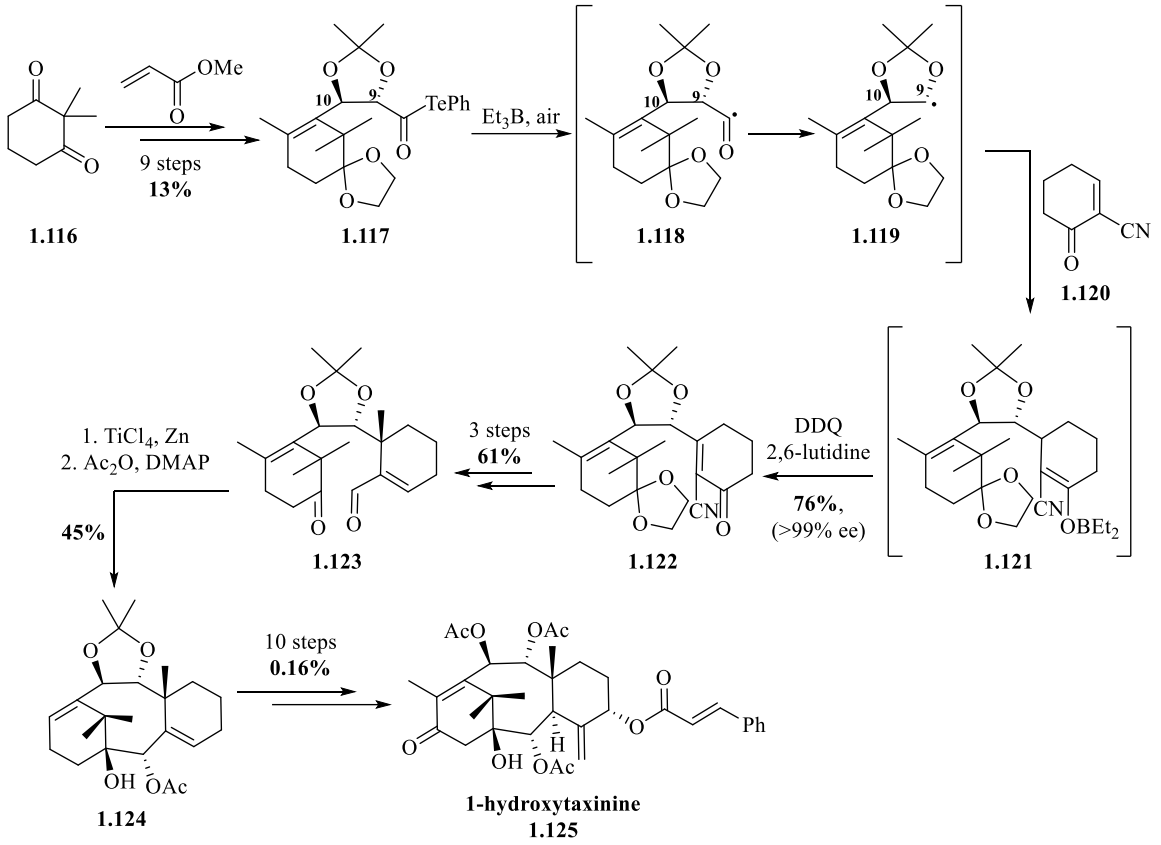
Scheme 1.17: Stereoselective construction of the taxinine AB system

In 2001, Tony Shing´s group accomplished the synthesis of Taxol´s CD ring system using a diasteroselective Diels Alder reaction to set up the correct configuration of the quaternary methyl group at C8 (Scheme 1.18).[33] Starting from *S*-(+)-Carvone, an intermolecular Diels Alder reaction with isoprene followed by ketone protection, dihydroxylation and selective terminal cleavage oxidation furnished **1.111** in 61% yield. Further transformations afforded ketone **1.112** that was then submitted to an Oppenaurer oxidation followed by a Meerwein-Ponndorf-Verley reduction yielding **1.113**. Mesylated alcohol **1.114** was used as starting material for the formation of the D ring. Deprotection of the benzyl group and acetylation of the free alcohol afforded the desired CD bicyclic system **1.115**.



Scheme 1.18: Synthesis of Taxol´s CD system by Shing´s group

More recently, in June 2019, Inoue and co-workers reported a radical-based strategy for the total synthesis of 1-hydroxytaxinine **1.125** (Scheme 1.19).[34] The key step of this approach is the connection of chiral A ring **1.117** and achiral C ring **1.120** using a decarbonylative radical coupling reaction. As shown in Scheme 1.19, A ring **1.117** was prepared in 9 steps form diketone **1.116** and methyl acrylate. Treatment of **1.117** with Et_3B in the presence of oxygen promoted a homolytic cleavage of the C-Te bond generating acyl radical **1.118**. After spontaneous release of carbon monoxide, the α-alkoxy radical **1.119** was obtained. Interestingly, the acetonide protected 1,2-diol redefines the stereochemistry at C9 since **1.120** can only approaches from the opposite side of the bulky C10-substituent in a 1,4-radical addition manner. After oxidation of boron enolate **1.121**, enone **1.122** was obtained as a single enantiomer. Further transformations afforded keto-aldehyde **1.123** that was submitted to a pinnacol coupling thus forming the desired 8- membered ring (**1.124**). Overall, 1-hydroxytaxinine **1.125** was prepared from ketone **1.116** in 26 steps.



Scheme 1.19: Total synthesis of 1-hydroxytaxinine **1.125**

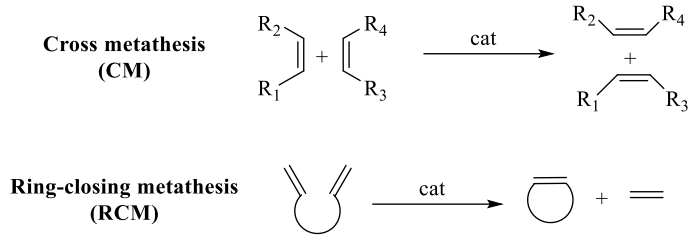
1.3 Olefin metathesis

Olefin metathesis is one of the most used reaction in carbon-carbon bond formation. All its variations have been successfully employed in natural product synthesis and polymer industry due to its tolerance to several functional groups. In this section only a small background on this reaction will be provided, with an emphasis on the construction of the taxane skeleton.

1.3.1 Generalities on the metathesis reaction

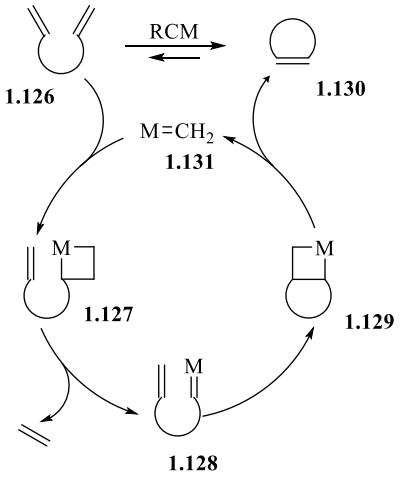
Developed over 40 years ago, olefin metathesis is a transalkylidenation reaction that allows the exchange of substituents of two different olefins by forming a new carbon-carbon bond using transition metals as catalysts. Due to its numerous applications, in 2005 Yves Chauvin, Robert Grubbs and Richard Schrock received the Nobel Prize for their work in this field.[35] Depending on the nature of the olefins employed as starting materials, the reaction can be either intermolecular or intramolecular (Scheme 1.20). The intermolecular process involves the use of two separate substrates and is refereed as cross metathesis (CM) while in an intramolecular

transformation, where the two olefins are on the same molecule, it is denoted as ring-closing metathesis (RCM).



Scheme 1.20: Olefin metathesis

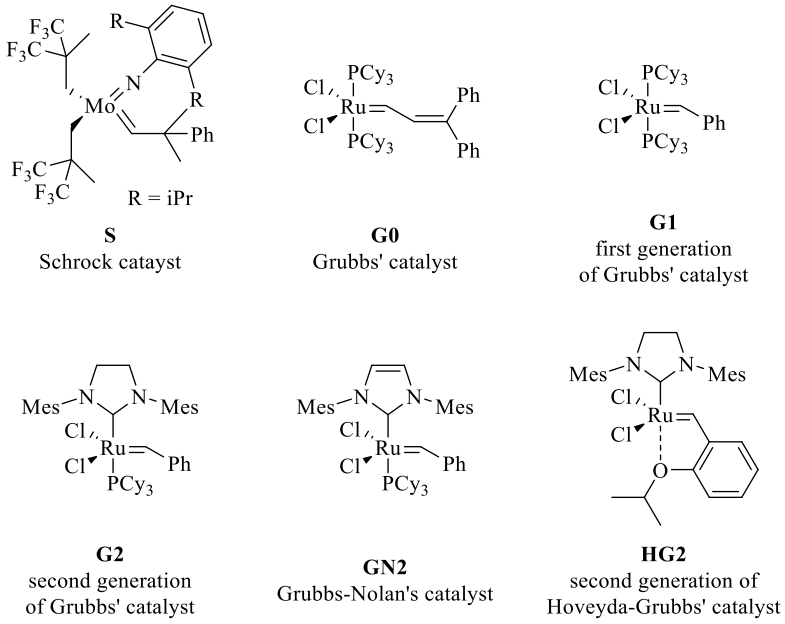
In 1971 Yves Chauvin proposed the currently accepted mechanism of olefin metathesis by studying RCM of 1,7-octadiene.[36] As shown in Scheme 1.21, the first step is the formation of the metallacyclobutane intermediate **1.127** by the [2+2] cycloaddition of a metal methylene complex **1.131**. Even though this [2+2] cycloaddition is forbidden by symmetry and has a high activation energy, interactions with the metal catalyst d-orbital lower the activation energy enough for the reaction to proceed at room temperature. The formation of a new carbene complex **1.128,** with the release of ethylene, drives the reaction towards the desired product **1.130** and allows the recovery of the catalytic species **1.131**.



Scheme 1.21: Olefin metathesis mechanism

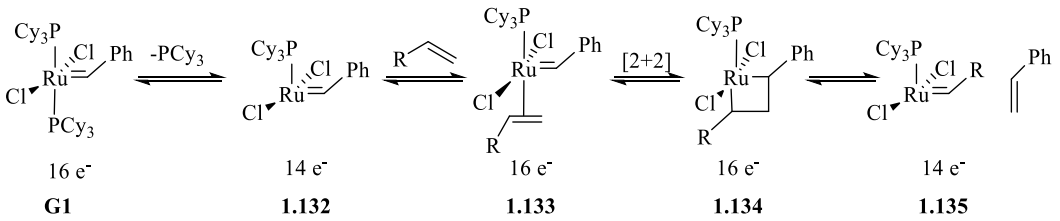
After fortuitous discovery of nickel's capabilities as a catalyst for this reaction, different efforts were made to look for more effective catalysts. In 1984 Richard Schrock synthesised the first catalyst, molybdenum complex **S** (Scheme 1.22), capable of carrying out this transformation.[37] Nevertheless, the lack of versatility towards highly functionalised olefins, especially those containing protonated heteroatoms, limited the use of this complex. In 1992, Grubbs discovered that ruthenium complexes were more tolerant towards several functional groups and

were also easier to handle (air stable). Since then, several generations of catalysts have been developed and successfully used in this transformation; some of them are presented in Scheme 1.22.



Scheme 1.22: Some metathesis catalyst

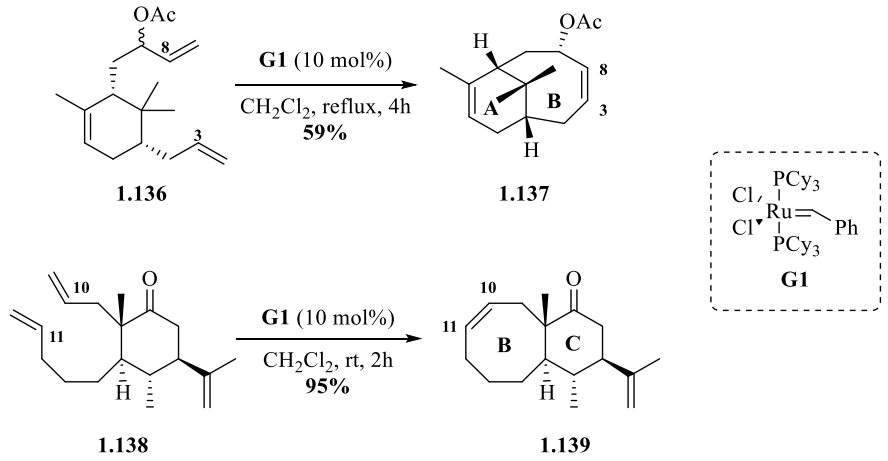
Despite Chauvin's mechanism being widely accepted, later studies on the first- and second-generation catalysts revealed useful information.[38] As shown in Scheme 1.23, the oxidation state of ruthenium in all Grubbs type catalysts is (II). In the case of **G1**, the 16-electron ruthenium is coordinated with two chlorine ligands, two tricyclohexylphosphine ligands and a benzylidene ligand. The loss of one of these electron-rich phosphine ligands leads to the formation of the catalytically active 14-electron ruthenium complex **1.132**. Coordination of this species with the olefin used as the starting material yields a 16-electron carbenoid intermediate **1.133**. Once **1.134** is formed, the reaction proceeds as previously explained in Scheme 1.21.



Scheme 1.23: Activation of **G1**

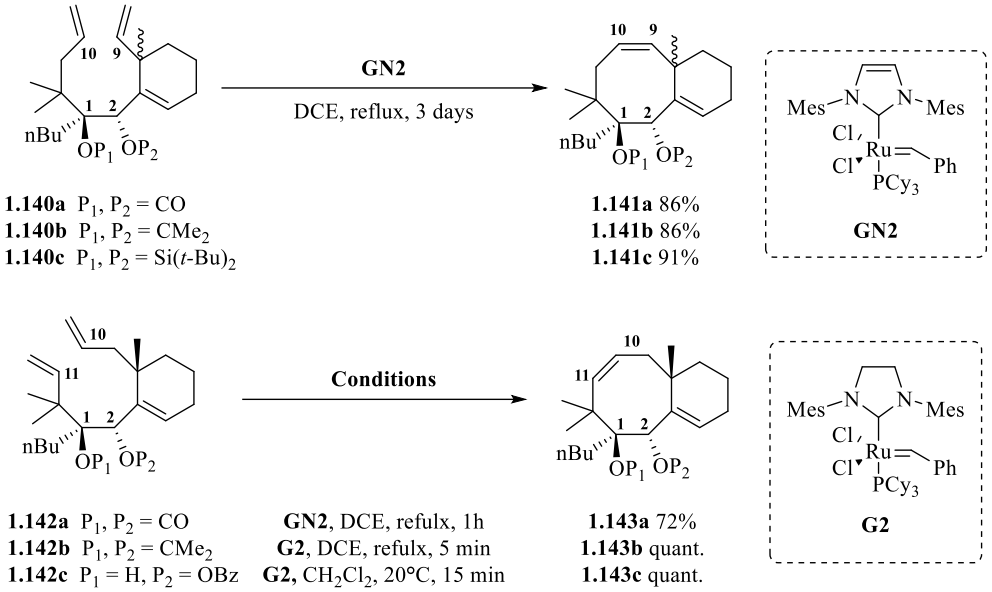
1.3.2 Taxoid synthesis by RCM

Synthesis of eight-membered rings represents a significant challenge for organic chemists due to transannular interactions resulting in unfavourable entropy and enthalpy changes. The presence of an eight-membered ring in the taxoid skeleton exemplifies the need for efficient and high yielding methodologies for its construction. Several attempts have been carried out in this field in order to synthesise Taxol's B ring using RCM. In 1999 Blechert and co-workers reported the synthesis of a simplified Taxol AB ring system starting from **1.136** (Scheme 1.24).[39] A RCM reaction between C3 and C8 was performed, giving **1.137** in 59% yield when using **G1** as catalyst. Interestingly, the outcome of this RCM reaction depended on the stereochemistry of the starting material as only one diastereomer of **1.136** cyclised while the other one underwent dimerisation. Additionally, in 2004 Srikrishna *et al.* successfully synthesised Taxol´s BC skeleton **1.139** in 95% yield after performing a RCM between C10 and C11.[40]



Scheme 1.24: Taxol´s AB and BC bicycles by Blechert and Srikrishna using RCM

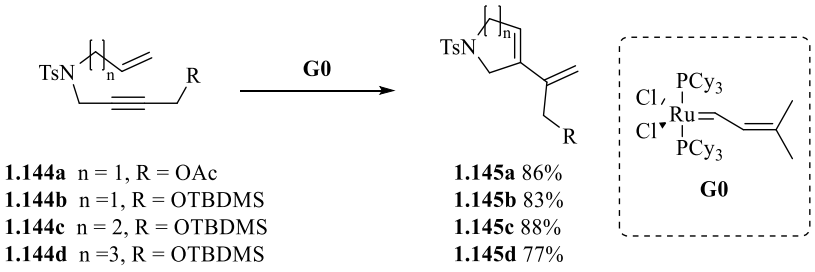
Previous work by the Prunet group also proved RCM as an excellent tool for the synthesis of the BC bicyclic system of Taxol. Initially a RCM at C9-C10 was studied while modifying protecting groups at C1 and C2 (Scheme 1.25).[41] Pleasingly, all substrates employed (**1.140a-c**) lead to the desired products **1.141a-c** in excellent yields. The best result was obtained when the Grubbs-Nolan catalyst G**N2** was used and cyclic silane **1.140c** was employed as starting material. Further experiments were performed to study a RCM between C10 and C11.[42] Once more, different protecting groups at C1 and C2 were tested (**1.142a-c**) as well as the use of **G2** as catalyst. The results were promising as bicyclic cores **1.143a-c** were isolated in excellent yields.



Scheme 1.25: Synthesis of Taxol´s BC bicycle by Prunet *et al.* using RCM

1.3.3 Ring-closing dienyne metathesis (RCDEYM)

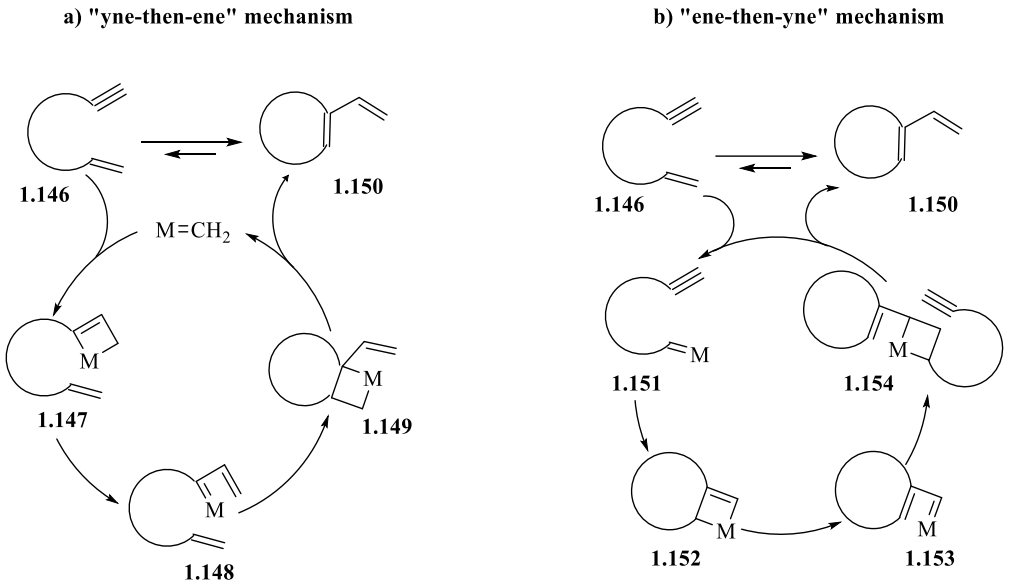
In order to understand the ring-closing dienyne metathesis reaction (RCDEYM), it is necessary to comprehend the ring-closing enyne metathesis (RCEYM). The first example of enyne metathesis with a ruthenium catalyst was reported by Mori and coworkers in the synthesis of five-, six- and seven-membered heterocycles in the presence of 1 mol% of **G0** (Scheme 1.26).[43]



Scheme 1.26: Enyne metathesis reported by Mori *et al.*

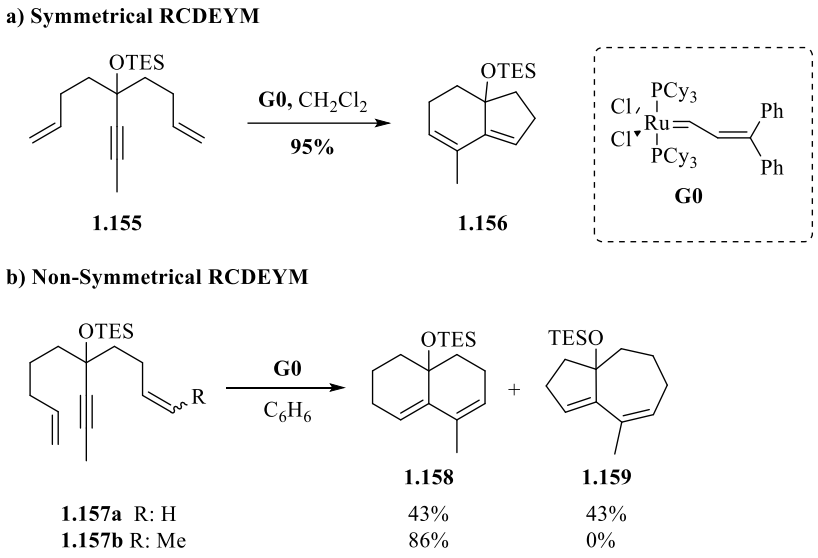
The enyne metathesis mechanistic studies were first achieved using NMR analysis in 1999.[44] Since then, several studies have been performed and two plausible mechanism are currently accepted.[45] As shown in Scheme 1.27, the initial intermolecular reaction of the metal-carbene can occur with either the alkyne or the alkene moiety. Both pathways result in the formation of the same conjugated diene product **1.150** (*exo*-product). The preference between the "yne-then-ene" and the "ene-then-yne" mechanism is determined by the ligands of the catalyst and the electronic and steric properties of the reactive alkene and alkyne in **1.146**. For example, when an enyne containing a terminal alkene and a terminal alkyne under identical steric and electronic

environments; results show the reaction pathway initiates preferably at the alkene and the alkyne when using **G1** and **G2**, respectively. The mechanism leading to the *endo*-product is not presented here since it is not relevant for this project.



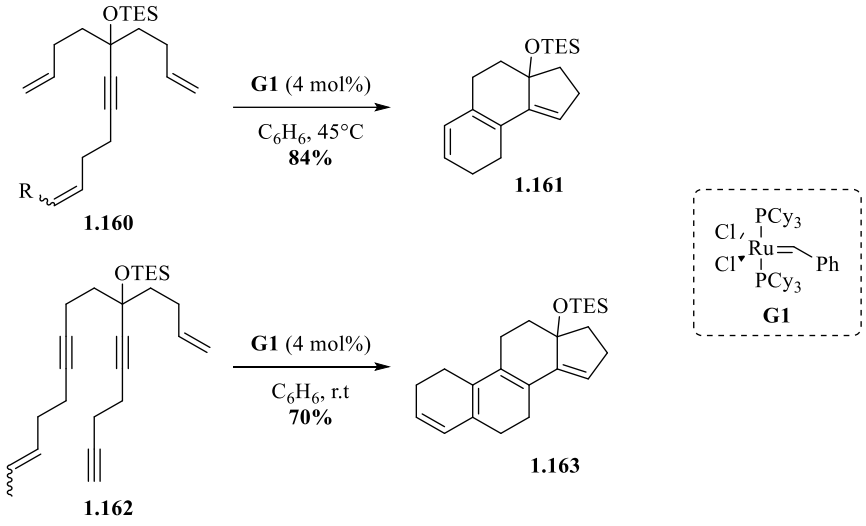
Scheme 1.27: Mechanisms of the enyne metathesis reaction

When a RCEYM reaction results in a second ring-closing metathesis, the dienyne reaction is known as RCDEYM. In 1994, Grubbs and co-workers synthesised fused bicyclic ring **1.156** from symmetrical **1.155** in 95% yield (Scheme 1.28a).[46] Nevertheless, a selectivity problem can be observed when non-symmetrical dienyne precursors are employed. Two different products can be formed depending on where the first metallacarbene is formed. When differentiating the two olefins by adding an extra substituent to one of them, the reactivity can be modified towards the desired compound.[46-47] For example, when **1.157a** was submitted to a RCDEYM, no selectivity between the products **1.158** and **1.159** was observed (Scheme 1.28b). However, the introduction of a methyl group, resulting in compound **1.157b** with two non-equivalently reactive olefins, led to **1.158** as the only product of the metathesis reaction. It is worth mentioning that the extra methyl introduced is not present in the final compound.



Scheme 1.28: RCDEYM by Grubbs

In 1998, Grubbs applied this "domino" sequence to the construction of bicyclic systems from acyclic compounds (Scheme 1.29). For example, the tricycle **1.161** was successfully synthesised by submitting **1.160** to a RCDEYM in the presence of **G1**. Furthermore, extra alkynes can be added, and the tetracyclic steroid-like product **1.163** was produced in 70% yield.[48]

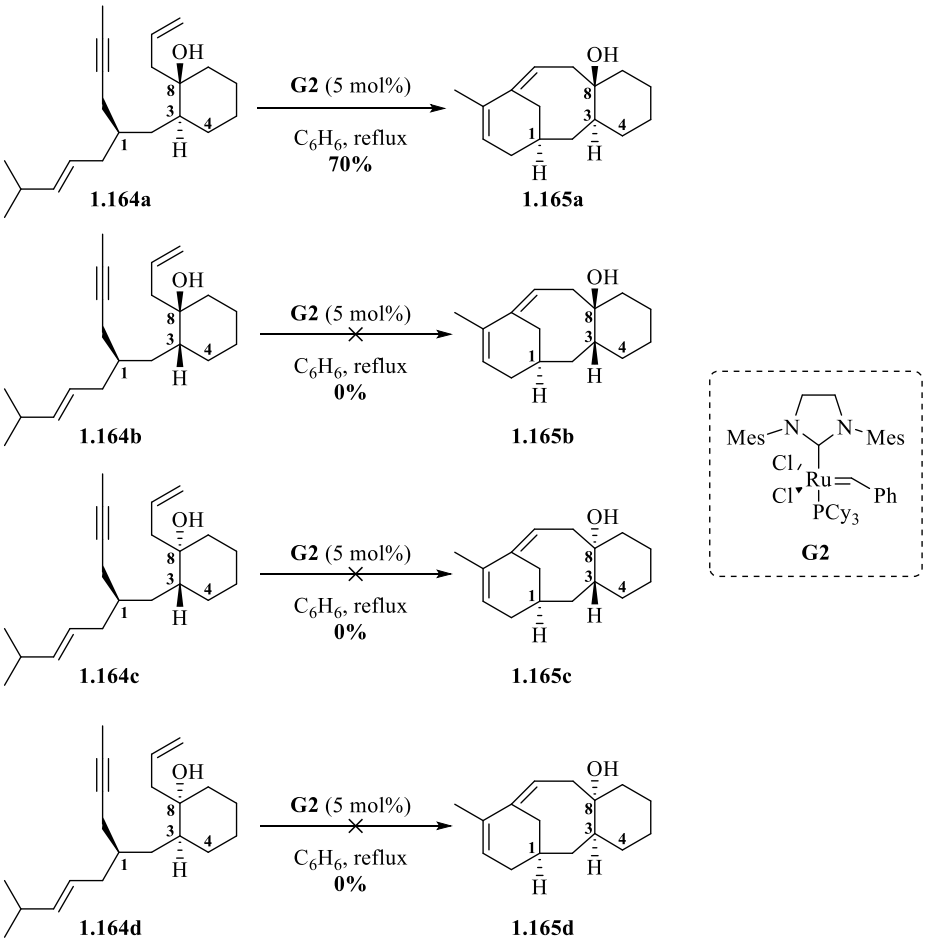


Scheme 1.29: RCDEYM by Grubbs

Different applications have been developed in this field, including the use of alkynyl boronates[49] and bicyclic phosphonates[50] as starting materials, as well as the synthesis of unsatured cyclic lactones,[51] highly polycyclic alkaloids[52] and naturally occurring compounds.[53]

1.3.4 Synthesis of taxane analogues by RCDEYM

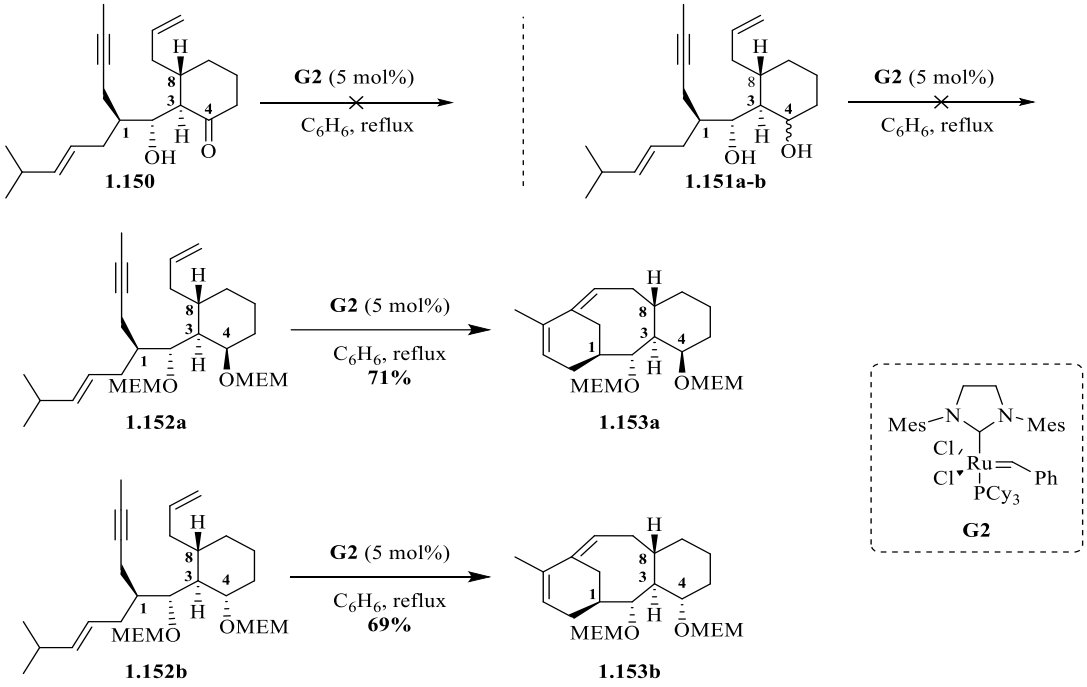
In 2008 Granja and co-workers published the first attempts to synthesise taxane analogues using RCDEYM.[54] The aim of this work was to study the effect of the relative configuration of the C1, C3, C4 and C8 stereocentres in the RCDEYM reaction (Scheme 1.30). It was found that a *trans* relationship between the substituents at C3 and C8(*S*) was essential for the cyclisation as the reaction was not successful when three isomers (**1.164b-d**) were tested and **1.164a** was the only diastereomer that gave the desired metathesis product (**1.165a**). Disappointingly, compound **1.165a** possesses the wrong relative configuration at C1 and C8 for the taxanes.



Scheme 1.30: Granja and co-workers RCDEYM attempts towards taxane synthesis

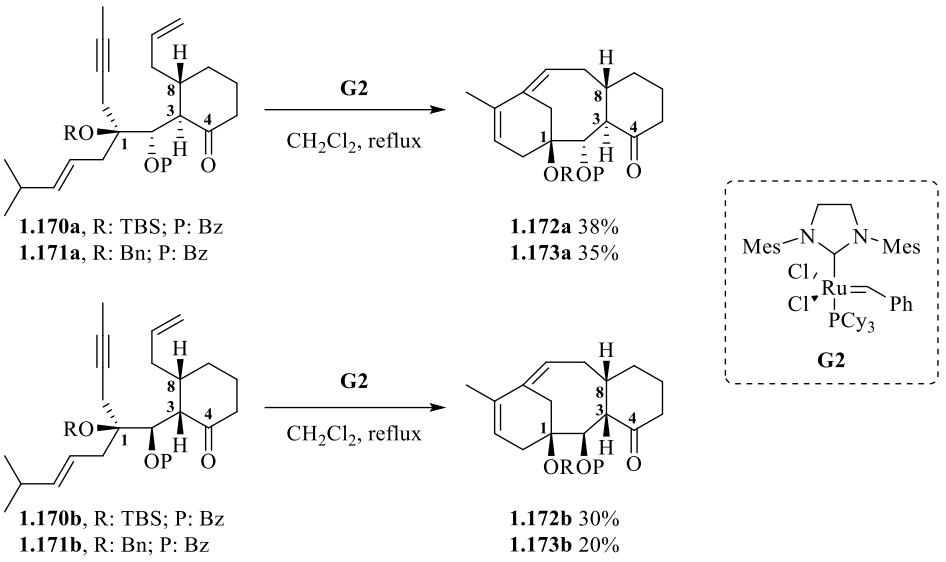
The effect of different substituents at the C4 position was also studied. Initially, only decomposition of ketone **1.166** was observed when **G2** was used as catalyst (Scheme 1.31). Since later attempts to protect the ketone as a ketal failed, reduction to the corresponding alcohol was performed. Decomposition was also observed when submitting the free alcohols **1.167a-b** to RCDEYM. However, after protection of the two hydroxyl groups in **1.168a-b**, the desired

products **1.169a-b** were successfully isolated. Interestingly, the stereochemistry at C4 does not affect the reaction yield. Once again, these compounds have the undesired configuration at C1 for taxane derivatives.



Scheme 1.31: Influence of stereochemistry at C4 on RCDEYM by Granja

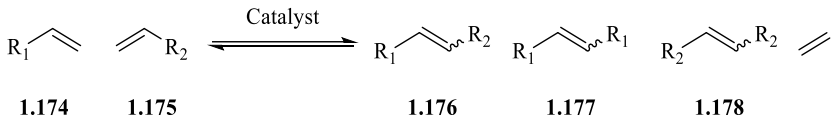
As a continuation of his work, Granja was interested in the introduction of the C1 hydroxyl group present in Taxol.[55] Once the metathesis precursors **1.170a-b** and **1.171a-b** were synthesised, products **1.172a-b** and **1.173a-b** were successfully obtained after submitting the mixture of diastereomers to RCDEYM conditions. Remarkably, the ketone at C4 does not negatively affect the reaction. Additional experiments also showed that all alcohols must be protected for the reaction to occur. In this work, the *gem*-dimethyl of Taxol at C15 is not present, diminishing the steric hindrance around the alkyne.



Scheme 1.32: Granja´s studies towards taxane analogues synthesis by RCDEYM

1.3.5 Relay ring-closing metathesis (RRCM)

The relay ring-closing metathesis reaction (RRCM) involves the initiation of a RCM at a reactive alkene followed by a rapid intramolecular relay of the metal centre to an initially less reactive olefin in the starting material. To fully understand the relay ring-closing metathesis reaction (RRCM) and its importance, it is necessary to comprehend the reactivity difference observed in distinct olefins. Scheme 1.33 shows the possible products obtained in a metathesis reaction starting from two different olefins (**1.174** and **1.175**). In this case, **1.176** is the desired product, compounds **1.177** and **1.178** are homodimers of the CM and the driving force of the reaction is the release of volatile ethylene.



Scheme 1.33: Possible products in CM

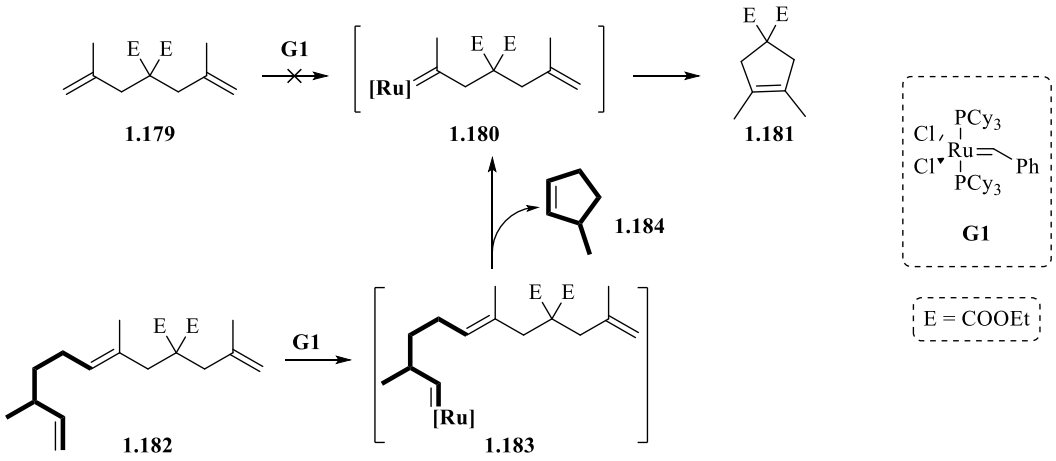
Selectivity towards the formation of **1.176** is desirable and several efforts have been made to avoid dimerisation of the starting materials. In 2003, Grubbs and coworkers proposed a general model where the reactivity and ability to homodimerise of several olefins can be predicted depending on their electronic and steric properties.[56] Four different types of olefins are proposed and their classification depends on the catalyst employed. As shown in Table 1.2, electron-rich unhindered alkenes are more reactive. Olefins will be less reactive if their steric

hindrance and/or electron deficiency is increased, to the point of being completely unreactive (type IV).

Table 1.2 – Classification of olefins

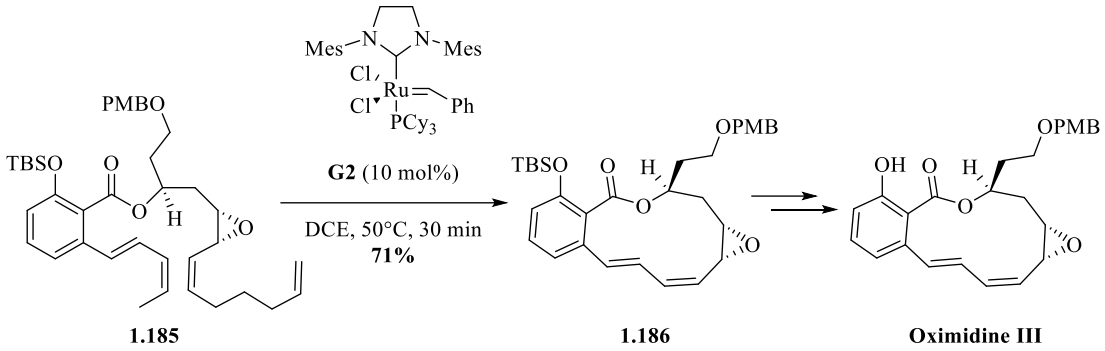
Olefin type	G2	G1
Type I (fast homodimerisation)	Terminal olefins, 1° allylic alcohols, allyl halides	Terminal olefins, 1° allylic alcohols
Type II (slow homodimerisation)	Acrylamide, acrolein, vinyl ketones, vinyl epoxides, 2° allylic alcohols	Styrene, 2° allylic alcohols
Type III (no homodimerisation)	1,1-disbstituted olefins, non-bulky trisubstituted olefins	Vinyl siloxanes
Type IV (inert to CM but no catalyst deactivation)	Protected trisubstituted allyl alcohols	1,1-disubstituted olefins

Even though the first observation of a RRCM was done in 1998 by Parrain and Santelli *et al.*,[57] it was not until 2004 that Hoye and coworkers studied its application in olefin activation.[58] The RRCM strategy consists in the addition of a side chain, encompassing a more active terminal double bond, to an alkene that under conventional metathesis conditions is unreactive. For example, metallic carbene **1.180** was not formed when **1.179**, containing two *gem*-disubstituted terminal olefins, was subjected to RCM in the presence of **G1**. However, when **1.182** was subjected to the same reaction conditions, carbene **1.183** was efficiently formed and volatile cyclic compound **1.184** was released. Once **1.180** was formed, the desired product **1.181** was isolated in 66% yield.



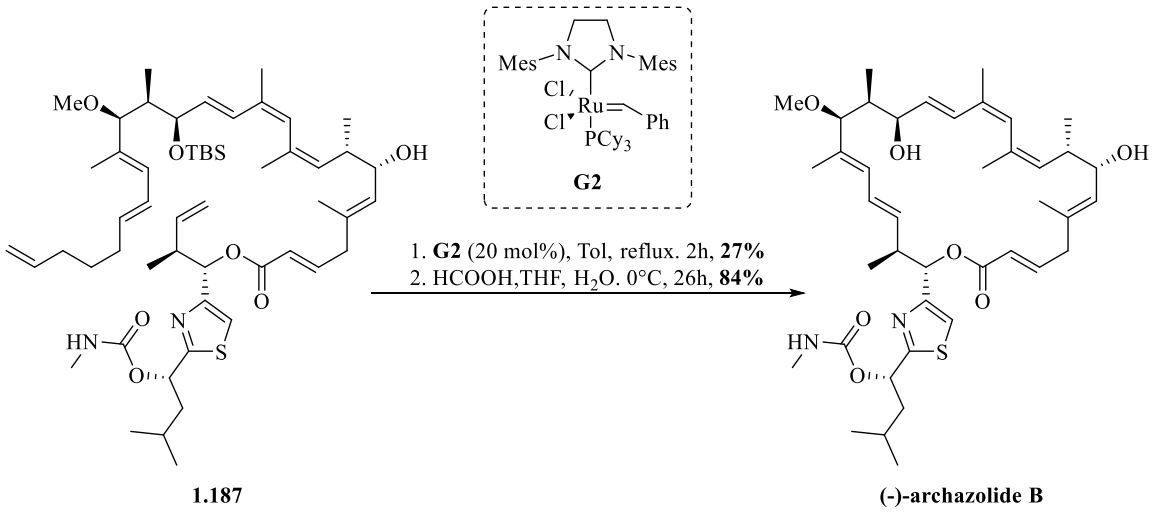
Scheme 1.34: Possible products in CM

Nowadays, several applications of RRCM can be found in the synthesis of natural products. Oximidine III, a macrolactone with promising biological activity, was successfully synthesised by Porco and coworkers in 2004.[59] Cyclisation of **1.185** in the presence of **G2** formed the desired macrocycle **1.186** in 71% yield (Scheme 1.35). Interestingly, a RCM reaction without the addition of the tail let to a poor 15% yield of **1.186**.



Scheme 1.35: RRCM in the total synthesis of oximidine III

Trauner and coworkers employed a RRCM strategy in the total synthesis of (-)-archazolide B in 2007.[60] Starting from **1.187**, the desired macrocycle was formed in 27% yield using **G2** as catalyst. Subsequent deprotection of the TBS group yielded (-)-archazolide B in 84% yield (Scheme 1.36). The conjugated alkene in **1.187** and the size of the new cycle formed must be considered to explain the low yield observed in the RCM step,



Scheme 1.36: RRCM in the total synthesis of (-)-archazolide B

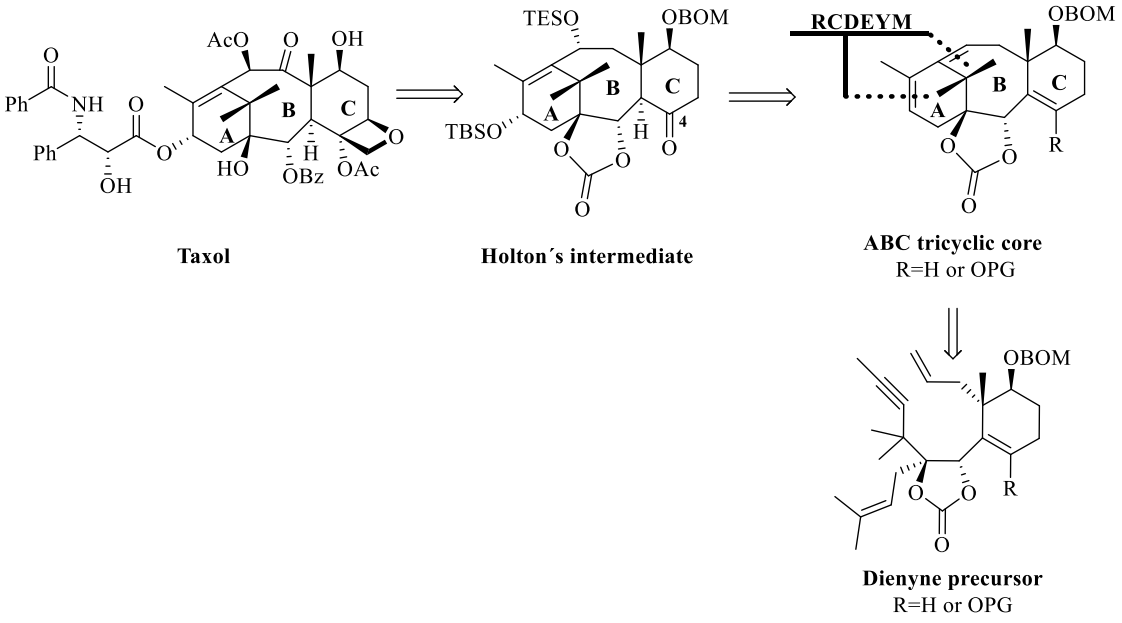
The formation of eight-membered rings has been a challenge for organic chemists due to their unfavourable entropy and enthalpy caused by transannular interactions. The RCM reaction has been widely explored and applied as a versatile tool for the formation of cyclic compounds. In

addition to the examples described above, numerous applications of RCM can be found in the literature.[61] RCDEYM and RRCM are powerful tools for the construction of complex polycyclic systems in a single step and have been widely employed in the synthesis of natural occurring compounds, including several taxanes. Taking this into account, the aim of this project (described in the next section) involves the use of RCDEYM and RRCM in a formal synthesis of Taxol.

1.4 Project aim

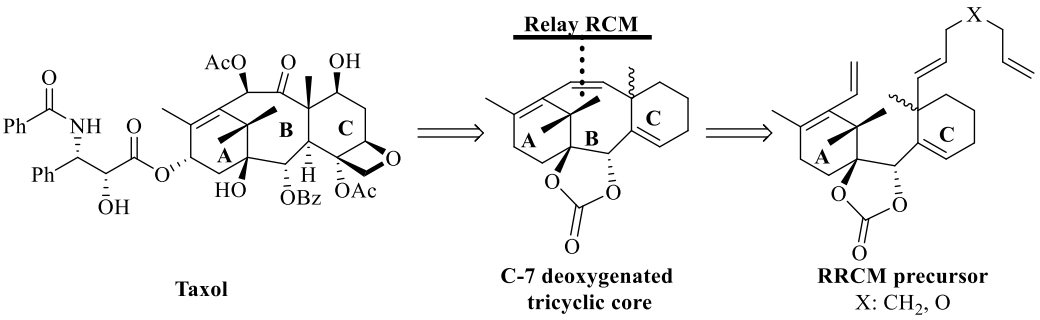
This project is focused on two different synthetic efforts towards a formal synthesis of Taxol, each one described in detail in the next two chapters. Previous work within the Prunet group is also detailed at the beginning of each chapter.

In Chapter 2, a ring-closing dialkene alkyne metathesis (RCDEYM) is envisioned to form the tricyclic core. The primary target is the intermediate described by Holton during his synthesis of Taxol. The formation of the ABC skeleton by a cascade RCDEYM reaction constitutes the key step of this approach (Scheme 1.37)



Scheme 1.37: RCDEYM as key step in the formal synthesis of Taxol

The second strategy, discussed in Chapter 3, involves a relay ring-closing metathesis (RRCM) as the key step for the construction of the B ring once the A and C rings are already coupled (Scheme 1.38). In this case, the target molecule is a racemic C7 deoxygenated tricyclic core. A study on the effect of the lateral chain in the RRCM is also proposed.



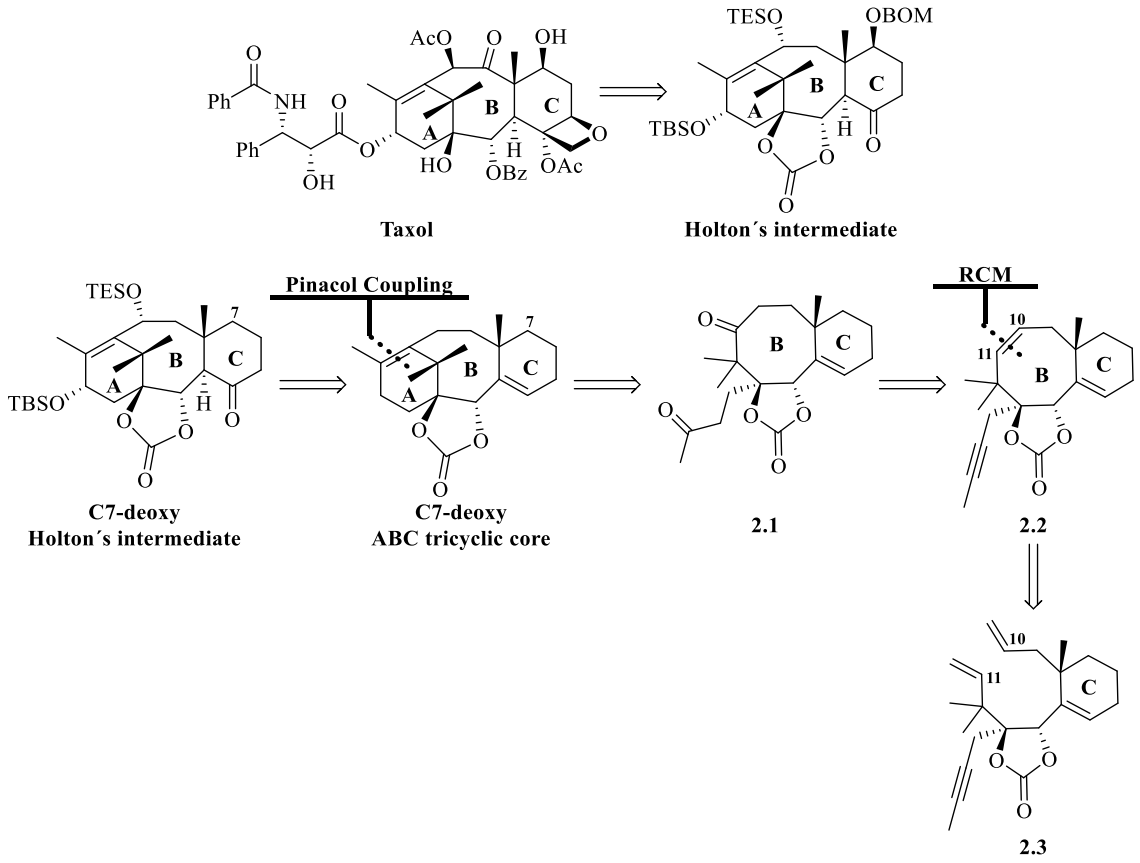
Scheme 1.38: RRCM as key step in the formal synthesis of Taxol

Chapter 2: Towards a formal synthesis of Taxol using a ring-closing dienyne metathesis strategy

In this chapter, a ring-closing dialkene alkyne metathesis (RCDEYM) cascade toward a formal synthesis of Taxol is presented. This work is the extension of the previous work performed by Cong Ma,[62] Rémi Aouzal[63] and Aurélien Letort[64] during their PhD theses under the supervision of Dr Joëlle Prunet.

2.1 Previous work in the group

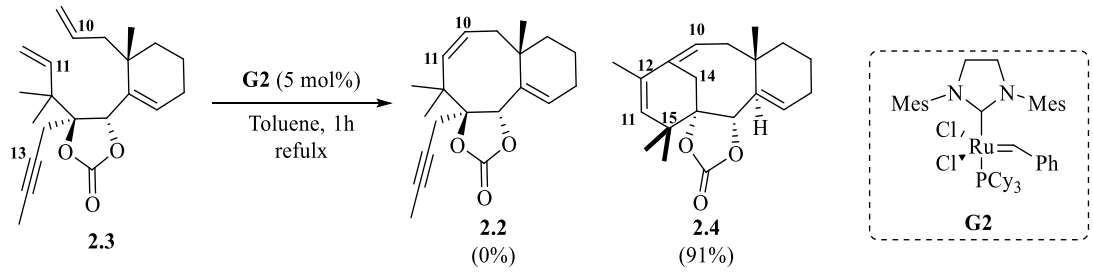
Cong Ma´s retrosynthesis is outlined in Scheme 2.1.[62] In this case, Taxol could be prepared from Holton's intermediate as previously described in his landmark synthesis.[20] In order to investigate the formation of the ABC tricyclic core, Ma chose a model system to work on and aimed for the construction of the C7-deoxy Holton intermediate since C7-deoxy taxanes do not exhibit a significant decrease of biological activity.[65]



Scheme 2.1: Cong Ma´s retrosynthesis for C7-deoxy Holton´s intermediate

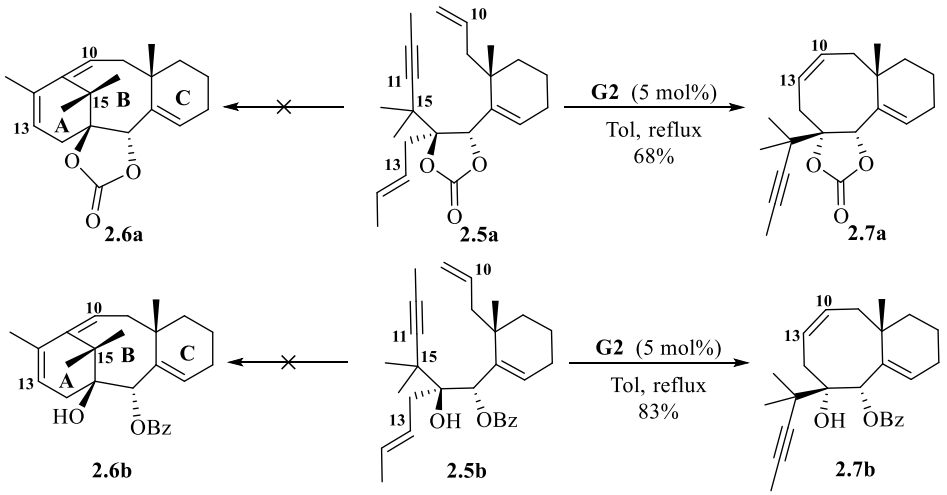
Installation of the A ring in the C7-deoxy ABC tricyclic core from diketone **2.1** could be achieved using a pinacol coupling. Diketone **2.1** would be prepared from alkyne **2.2**, which in turn could be synthesised from diene **2.3** using a RCM reaction.

Once intermediate **2.3** was synthesised, it was submitted to a RCM using 5 mol% of **G2**. Despite full conversion of the stating material achieved after 1 hour, no traces of the desired bicycle **2.2** were observed and instead compound **2.4** was isolated in 91% yield (Scheme 2.2). Unexpectedly, a RCDEYM cascade reaction (involving the alkyne at C13) resulted in the formation of the 6-8-6 tricyclic core of taxol **2.4** where the *gem*-dimethyl group was in the wrong position.



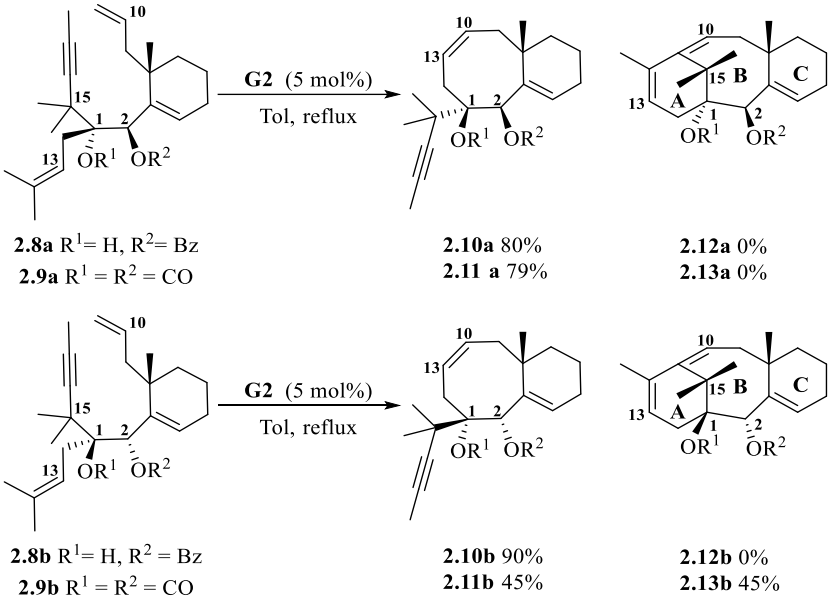
Scheme 2.2: First RCDEYM reaction observed in the Prunet group

The successive PhD student, Rémi Aouzal, proposed to take advantage of this unexpected but efficient metathesis cascade. Thus, he prepared a second generation of metathesis precursors (**2.5a-b**) in which the alkyne group was now positioned at C11 and the alkene group at C13. An extra methyl group was introduced at C13 in order to disfavour the RCM reaction to first take place at this position. Unfortunately, after subjecting **2.5a** and **2.5b** to RCM using 5 mol% of **G2**, the undesired bicyclic cores **2.7a** and **2.7b** were isolated in 68% and 83% yields respectively (Scheme 2.3).[63]



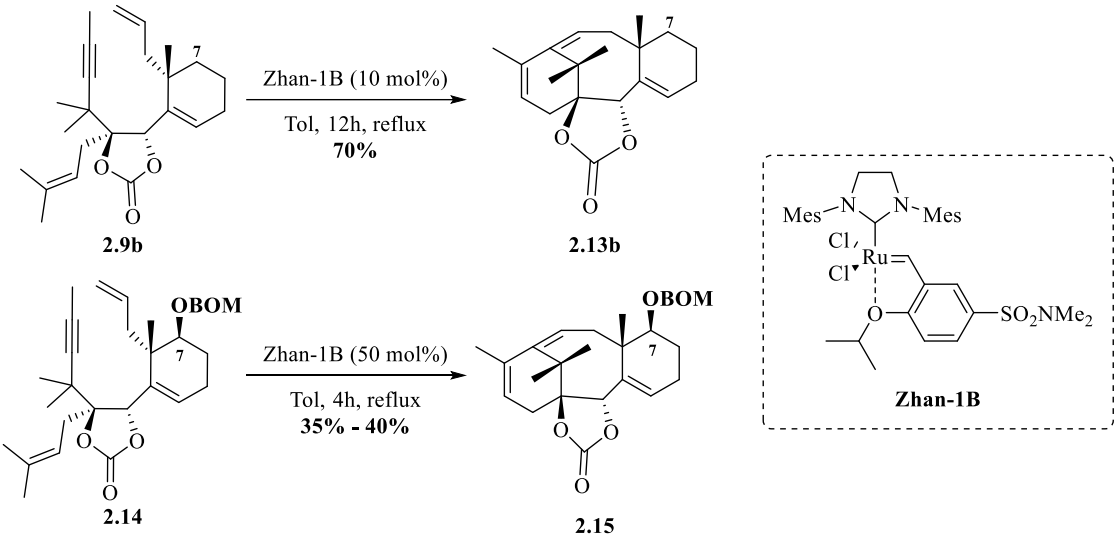
Scheme 2.3: Aouzal's attempts to form the ABC tricycle via RCDEYM

Isolation of **2.7a-b** instead of desired **2.6a-b** was attributed to the high steric hindrance around the alkyne caused by the *gem*-dimethyl group at C15. Since this steric hindrance cannot be decreased because this group is present in the Taxol skeleton, Aurélien Letort proposed to decrease the reactivity of the olefin at C13 by adding an extra methyl group. As shown in Scheme 2.4, a third generation of metathesis precursors were successfully synthesised (**2.8a-b** and **2.9a-b**). Interestingly, the product of the reaction was determined by the protecting group of the diol at C1 and C2 and its relative configuration to C8. Only compound **2.9b** resulted in the formation of desired tricyclic core **2.13b** while bicycles **2.10a-b** and **2.11a** were isolated as the only products when using **2.8a-b** and **2.9a** as starting materials.[64]



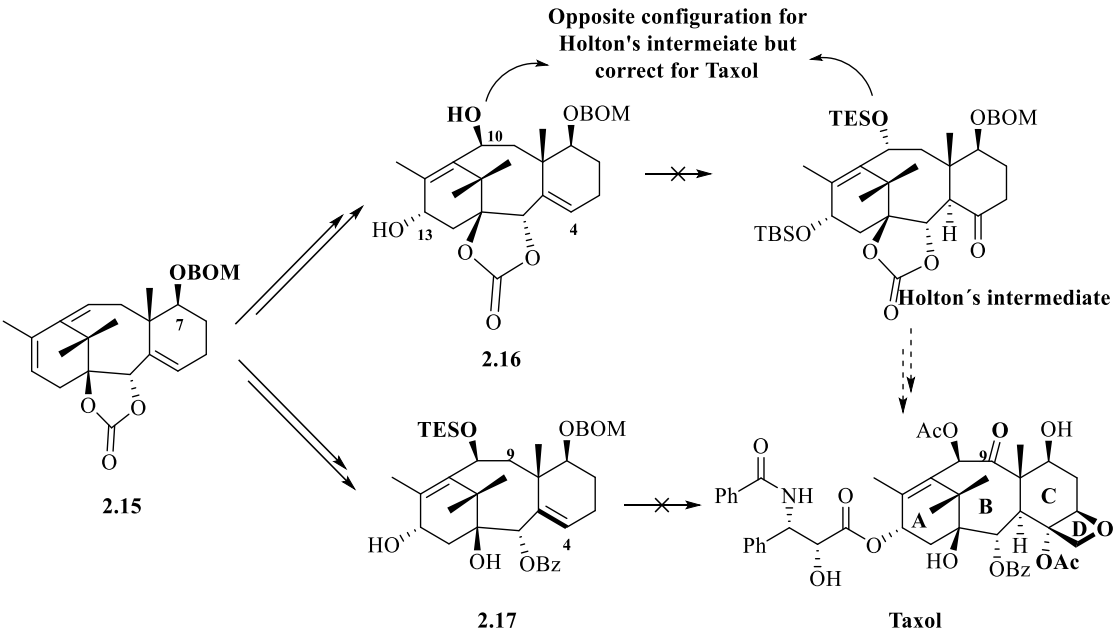
Scheme 2.4: Dienyne metathesis attempts by Letort

After optimisation of the RCDEYM reaction, **2.13b** was isolated in 70% yield after 12 h using **Zhan-1B** as catalyst. Applying the same reaction conditions to the C7-oxygeneted diene **2.14**, led to the formation of the desired tricyclic core **2.15** in a range of 35 to 40% yield as the only isolable product.



Scheme 2.5: Optimised RCDEYM for the synthesis of **2.13b** and **2.15** by Letort

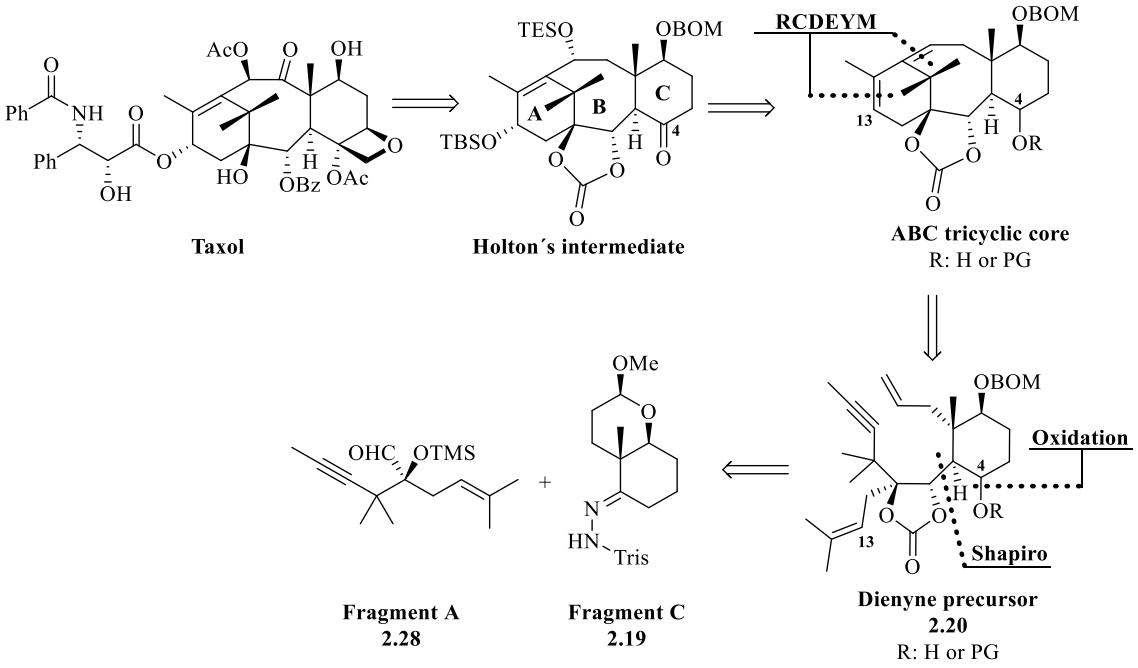
Letort´s final work focused on the synthesis of an advanced Taxol intermediate. Diol **2.16** was successfully prepared from **2.15**. The alcohol at C10 in **2.16** has the opposite configuration to that of Holton´s intermediate but the correct configuration for Taxol. Several attempts made to obtain the opposite diastereomer were unsuccessful. The advanced intermediate **2.17** with five oxygenated functional groups was synthesised using substrate control. At this point, the oxetane D ring and the C9 ketone were the only two oxygenated groups missing. However, numerous efforts towards the functionalisation of the C4 olefin were unsuccessful, thus leading to the conclusion that an early derivatisation must be performed.



Scheme 2.6: Letort´s studies towards Holton´s intermediate

2.2 Project presentation and retrosynthetic analysis

The idea of functionalising the C4 position before the RCDEYM will be discussed in this chapter. Following the revised retrosynthetic route envisioned in the Prunet group, the primary target is the Holton intermediate and the key step is the formation of the ABC tricyclic core by a cascade RCDEYM reaction once C4 has been already oxidised (Scheme 2.7). The A and B rings would be obtained from the dienyne precursor **2.20** bearing a trisubstituted olefin at C13. This compound could be synthesised by a Shapiro coupling between the fragments A and C.

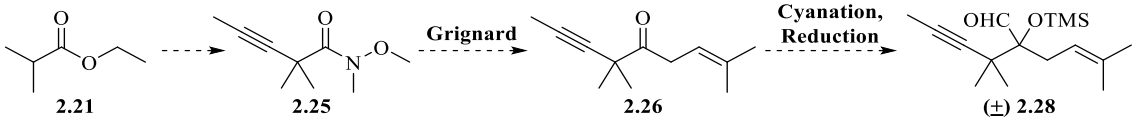


Scheme 2.7: Taxol retrosynthesis using a RCDEYM as the key step

2.3 Synthesis of fragment A

2.3.1 Plan of synthesis of fragment A

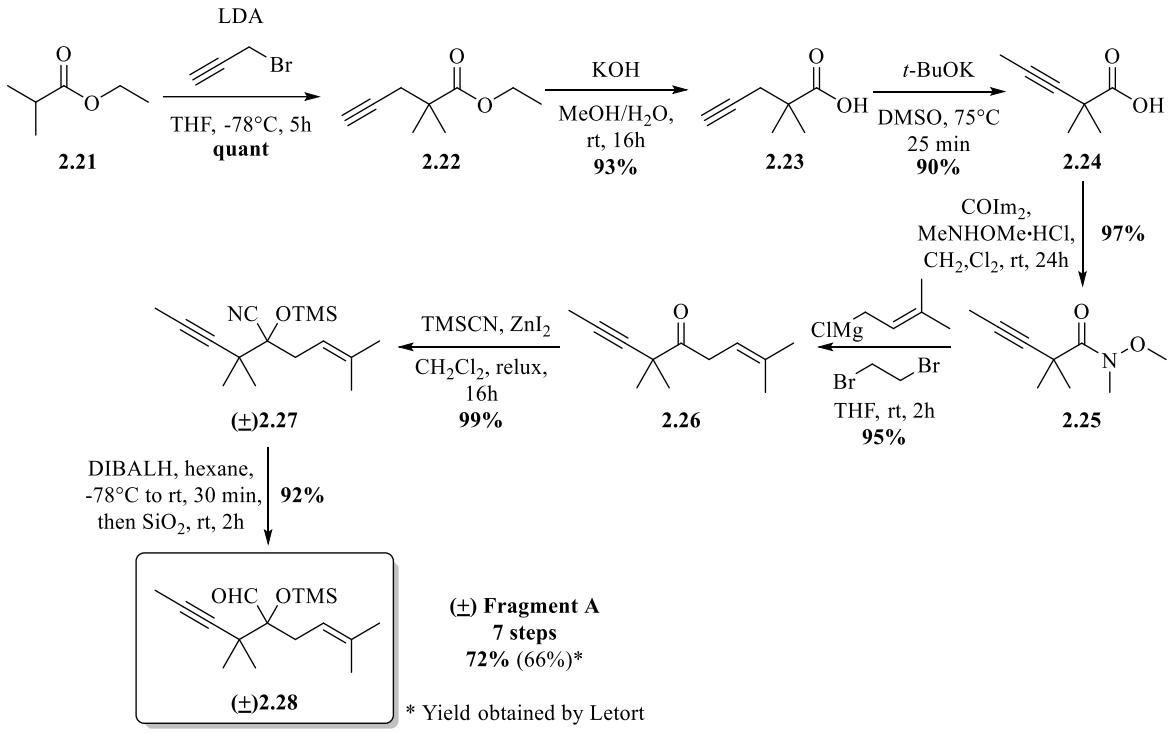
The retrosynthetic analysis for the racemic fragment A **(±)2.28** is presented in Scheme 2.8. Starting from commercially available ester **2.21**, ketone **2.26** could be synthesised by direct addition of a prenyl moiety to Weinreb amide **2.25** using a Grignard reagent. Cyanation of **2.26** followed by reduction to the aldehyde could lead to desired aldehyde **(±)2.28**.



Scheme 2.8: Plan of synthesis of fragment A

2.3.2 Racemic synthesis

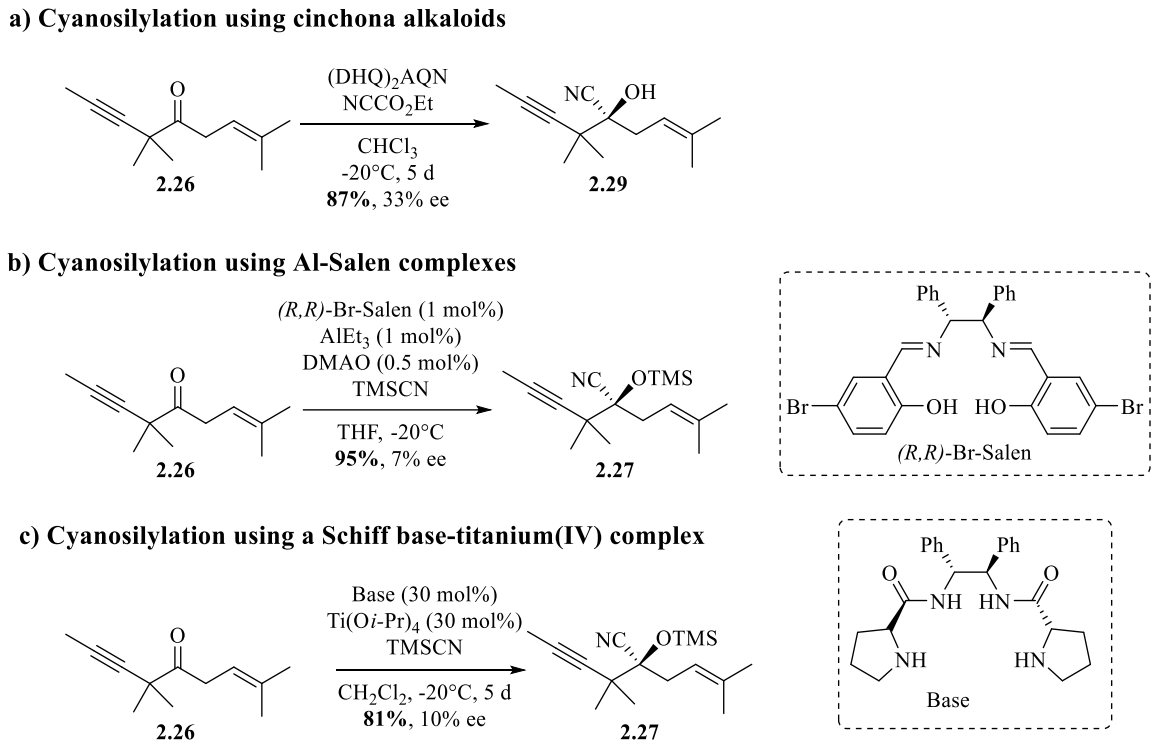
Aldehyde **(±)2.28** has been previously synthesised by Aurélien Letort in 66% overall yield. As shown in Scheme 2.9, this route was optimized. The first step of the synthesis was the alkylation of ethyl isobutyrate **2.21** with propargyl bromide. After *in situ* preparation of LDA using diisopropylamine and *n*-BuLi, ester **2.22** was successfully isolated in quantitative yield. Hydrolysis of the ester followed by isomerisation of the terminal alkyne afforded **2.24** in 84% yield over two steps. Treatment of **2.24** with carbonyldiimidazole and *N,O*-dimethylhydroxylamine resulted in the desired Weinreb amide **2.25**, which was then submitted to a Grignard addition affording stable β,γ-unsaturated ketone **2.26** in 95% yield. Further treatment of **2.26** with TMSCN in the presence of zinc iodide provided the silylated cyanohydrin **(±)2.27** in almost quantitative yield. Reduction of this cyanohydrin **(±)2.27** using DIBALH led to the corresponding imine that was then hydrolysed under mild acidic conditions by adding SiO_2 to the reaction mixture. In summary, the racemic aldehyde **(±)2.28** was obtained in 72% overall yield over 7 steps.



Scheme 2.9: Synthesis of racemic fragment A **(±)-2.28**

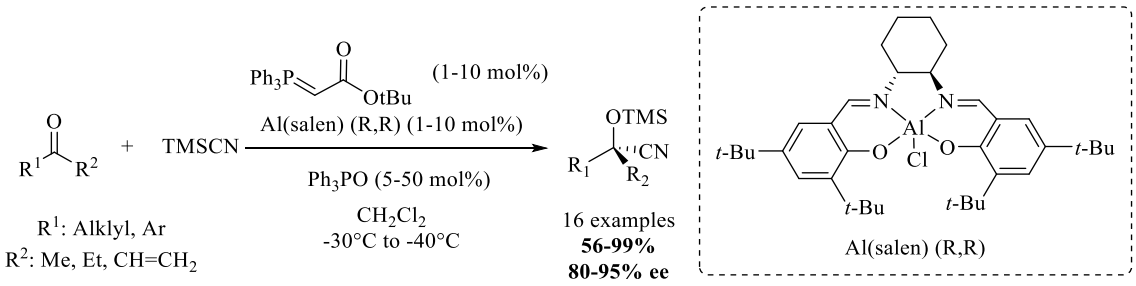
2.3.3 Efforts towards the synthesis of an enantioenriched fragment A

Attempting to further the efficiency of the synthetic route towards Taxol, the synthesis of an enantioenriched fragment A was investigated. Previously in the group, Letort tested the enantioselective cyanosilylation of ketone **2.26** using cinchona alkaloids as catalyst.[66] When performing the reaction with cyanoformate and $(DHQ)_2AQN$ as the chiral ligand, alcohol **2.29** was obtained in 83% yield with 33% ee (Scheme 2.10a). A cyanosilylation using Al-Salen complexes was also attempted, but unfortunately resulted in the formation of cyanohydrin **2.27** in 95% yield but with only 7% ee (Scheme 2.10b). Finally, a cyanosilylation using a Schiff Base was tried,[67] affording the desired cyanohydrin **2.27** in 81% yield, but, once again, with a low (10%) ee (Scheme 2.10c).



Scheme 2.10: Letort's work towards the synthesis of enantioenriched fragment A

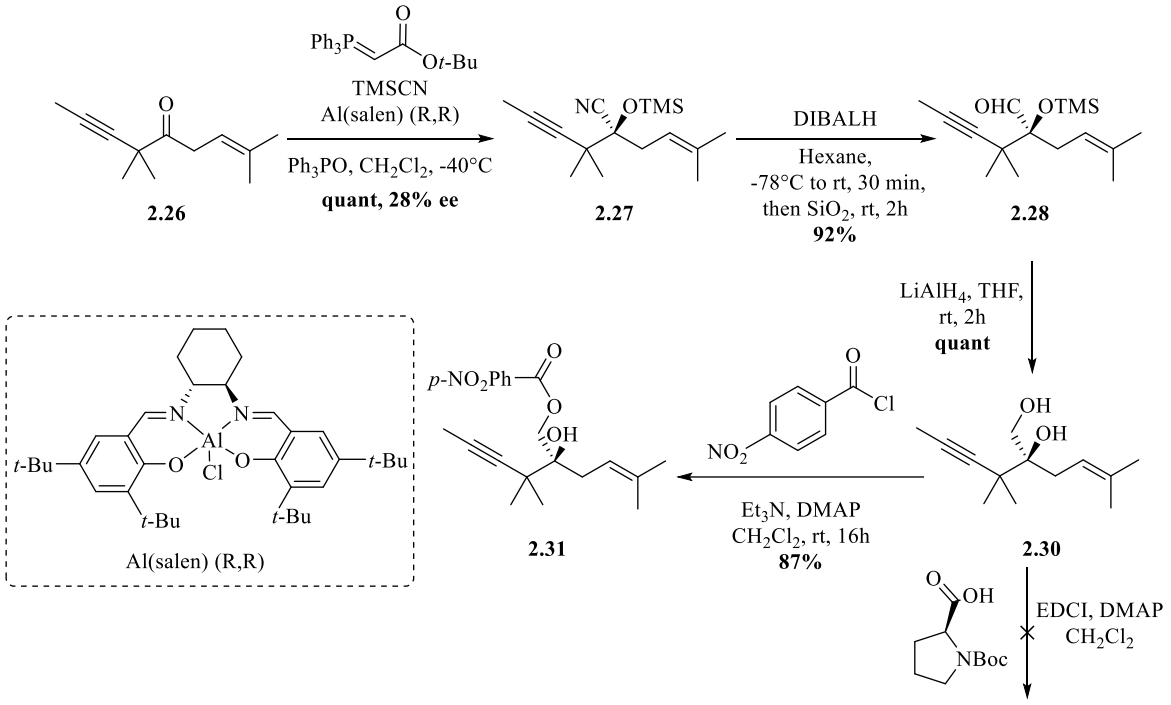
In 2016 Zhou and co-workers reported the activation of a chiral (salen)AlCl complex by a phosphorane for the highly enantioselective cyanosilylation of ketones and enones (Scheme 2.11).[68] Several alkyl and aryl ketones, even in the presence of conjugated enones, afforded the desired cyanohydrins in moderate to good yields with excellent enantioselectivities.



Scheme 2.11: Catalytic asymmetric ketone cyanosilylation by Zhou *et al.*

These conditions were applied to ketone **2.26**, furnishing the desired cyanohydrin **2.27** in quantitative yield. In order to determine the enantiomeric excess, coupling with an enantiopure compound was first envisioned. Reduction of **2.27** using DIBALH afforded **2.28** and its treatment with $LiAlH_4$ yielded deprotected diol **2.30** in quantitative yield. Unfortunately, the esterification attempt with Boc-protected proline was unsuccessful, probably due to the steric hindrance of both substrates, so addition of a chromophore was attempted in order to

determine the enantiomeric excess by chiral HPLC. Nitrobenzoate derivative **2.31** was isolated in 87% yield after coupling of **2.30** with *p*-nitro benzoyl chloride. Inconveniently, separation of the two enantiomers by HPLC with a chiral column was not possible and thus the enantiomeric excess (28% ee) was finally determined after Shapiro coupling of **2.28** with hydrazone **2.71** (Scheme 2.28).

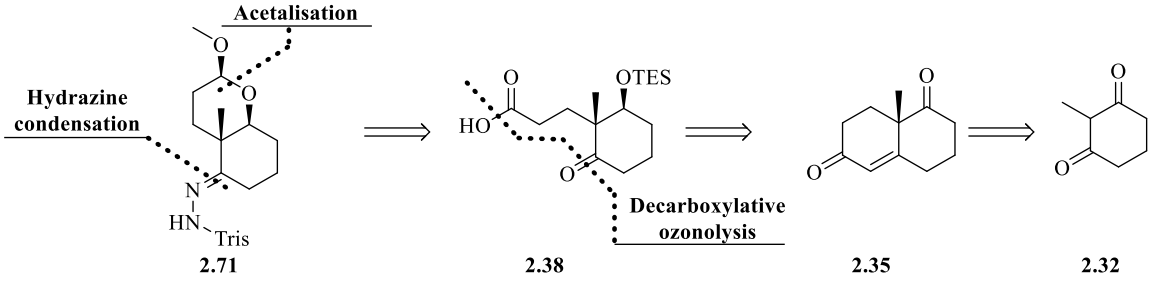


Scheme 2.12: Synthetic efforts towards an enantioenriched fragment A

2.4 Synthesis of fragment C

2.4.1 Retrosynthesis

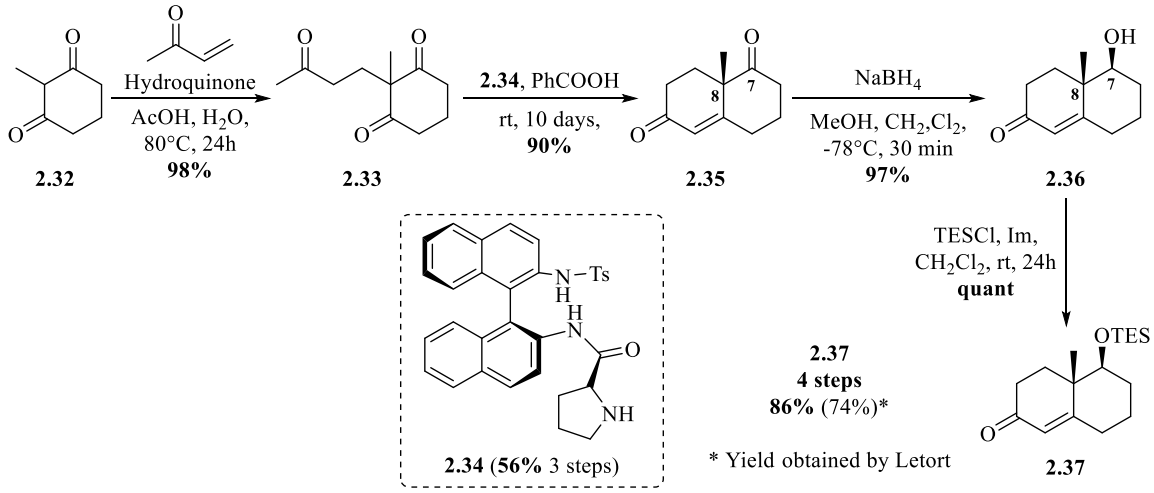
The retrosynthesis of Fragment C is outlined in Scheme 2.13 and uses the same key disconnections proposed by Letort in his thesis.[64] Hydrazone **2.71** could be obtained by hydrazine condensation followed by acetalisation from **2.38,** which in turn could be prepared from the (+)-Wieland-Miescher ketone **2.35** by performing a diastereoselective reduction and consecutively a decarbonylative ozonolysis. Finally, the (+)-Wieland-Miescher ketone **2.35** would be synthesised starting from the commercially available diketone **2.32**.



Scheme 2.13: Retrosynthesis of fragment C

2.4.2 Synthesis of the ozonolysis precursor

The ozonolysis precursor **2.37** has been previously synthesised by Letort in 74% yield over 4 steps, and we used the same pathway, described in Scheme 2.14. Initially, the (+)-Wieland-Miescher ketone **2.35** was synthesised by a Michael addition between **2.32** and methyl vinyl ketone followed by a Robinson annulation catalysed by (*S*)-binam-(*L*)-prolinamide **2.34**.[69] This catalyst is the only source of chirality used in the synthesis of enantiopure fragment C **2.71** and sets the absolute configuration of the quaternary stereocentre at C8. Reduction of **2.35** afforded alcohol **2.36** in 97% yield as a single enantiomer in a substrate-control diastereoselective reaction. Protection of the secondary alcohol using TESCl formed the desired substrate **2.37**, in 86% overall yield over 4 steps from diketone **2.32.**

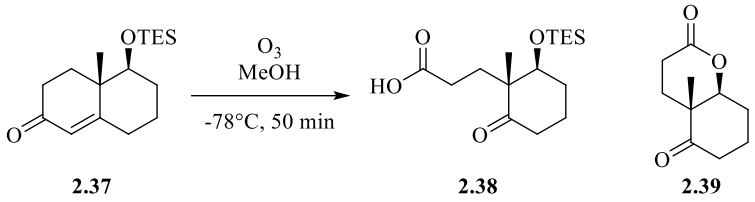


Scheme 2.14: Synthesis of ozonolysis precursor **2.37**

2.4.3 Ozonolysis

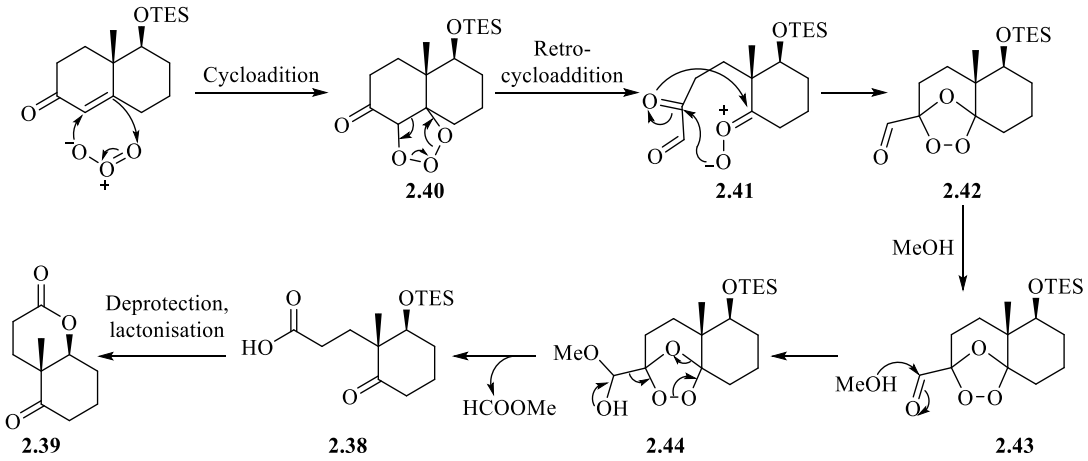
With vinyl ketone **2.37** in hand, the previously reported conditions from Letort´s thesis for the preparation of acid **2.38** were followed, and the ozonolysis reaction was performed using

methanol as solvent. Unfortunately, it was not possible to reproduce the 88% yield obtained by Letort and a complex mixture of products was observed. Depending on the scale and reaction time, the ratio between the starting material **2.37**, carboxylic acid **2.28** and lactone **2.39** varied significatively. Nevertheless, the maximum yield obtained for **2.38** was 53% (63% brsm) when using 3.37 mmol of **2.37**. An increase in the reaction scale resulted in no formation of the desired acid but formation of lactone **2.39** in 66% yield as the only isolable product (Scheme 2.15). The low reproducibility and challenging purification of the product represented one of the major drawbacks in the synthesis.



Scheme 2.15: First ozonolysis attempt

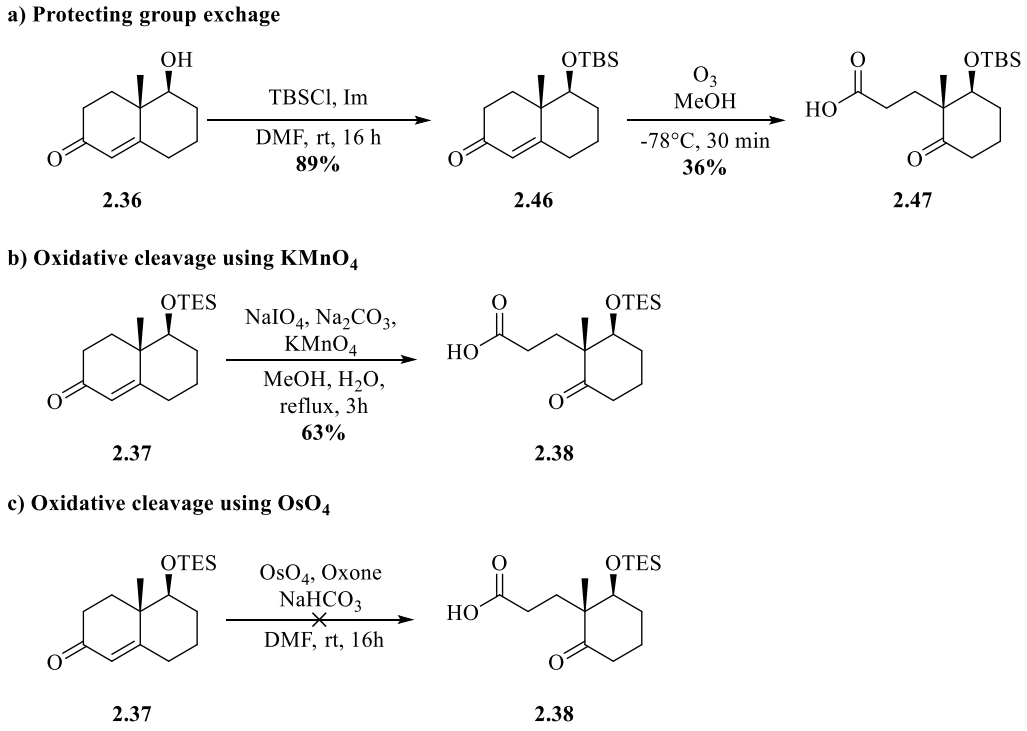
The proposed mechanism for the decarbonylative ozonolysis is shown in Scheme 2.16. Molozonide **2.40** is formed after the [3+2] cycloaddition of **2.37** and ozone. Subsequent retro-cycloaddition leads to carbonyl oxide **2.41**. Once five-membered ring **2.42** is formed, addition of methanol is followed by a rearrangement furnishing the corresponding carboxylic acid **2.38** along with methyl formate. Formation of lactone **2.39** can be explained by *in situ* removal of the TES protecting group and a lactonisation reaction.



Scheme 2.16: Proposed mechanism of decarbonylative ozonolysis

Three alternatives to avoid the formation of lactone **2.39** were explored. Firstly, an exchange of the alcohol protecting group was envisioned (Scheme 2.17a). Treatment of **2.36** with TBSCl

and imidazole afforded TBS protected alcohol **2.46** in excellent yield; however, the ozonolysis reaction produced the carboxylic acid **2.47** in a poor 36% yield.

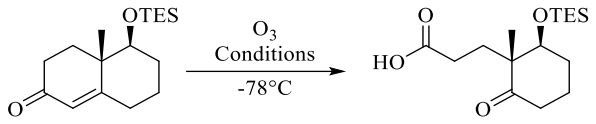


Scheme 2.17: Alternatives to avoid formation of lactone **2.39**

Secondly, an oxidative cleavage with sodium periodate and potassium permanganate was performed, providing **2.38** in 63% yield (Scheme 2.17b).[70] Even though this cleavage emerged as a feasible alternative, when the reaction was scaled up to over 500 mg of **2.46**, the yield dropped dramatically and thus it was no longer a viable option. Finally, an osmium tetroxide-promoted oxidative cleavage was attempted but no reaction was observed and the starting material was fully recovered (Scheme 2.17c).[71]

With these results in hand, an optimisation of the original ozonolysis reaction was attempted. As shown in Table 2.1, entries 1 and 2, the use of dry methanol did not increase the reaction yield. Changing the reaction solvent to dichloromethane led to decomposition products and only traces of **2.38** were observed by the crude ^{1}H NMR (entry 3). When, five equivalents of pyridine were added to the reaction mixture, acid **2.38** was isolated in 42% and 59% yield using wet and dry methanol, respectively (entries 4 and 5). These conditions were easily reproducible, and the reaction could be performed on a six-gram scale (20.3 mmol).

Table 2.1: Ozonolysis optimisation



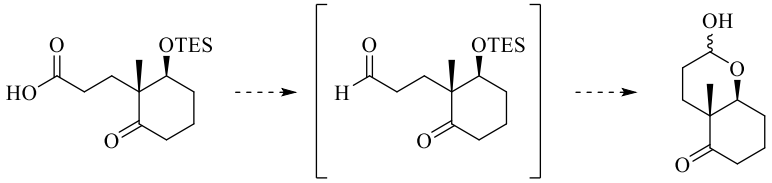
2.37 **2.38**

Entry	Conditions	Yield
1	Wet MeOH	52%*
2	Dry MeOH	53%*
3	Dry CH_2Cl_2, then MeOH	Traces*
4	Wet MeOH, py (5 equiv)	42%*
5	**Dry MeOH, py (5 equiv)**	**59%****

* When using 1.63 mmol of **2.37**
** When using either 1.63 or 20.0 mmol of **2.37**

2.4.4 Towards the synthesis of hemiacetal 2.49

With carboxylic acid **2.38** in hand, the synthesis of hemiacetal **2.49** was explored. Initially, the synthesis of the aldehyde **2.48**, followed by deprotection of the TES group was investigated (Scheme 2.18). Since **2.48** proved to be extremely unstable, the deprotection reaction was carried out on the crude aldehyde without further purification.



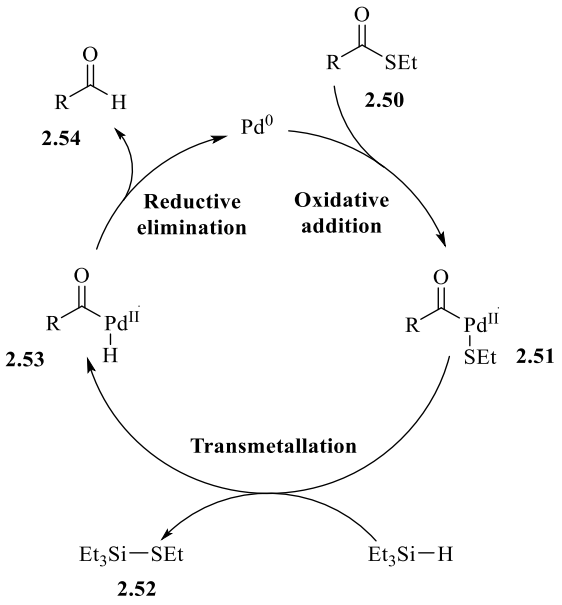
2.38 **2.48** **2.49**

Scheme 2.18: Proposed synthesis of lactol **2.49**

2.4.4.1 Fukuyama reduction

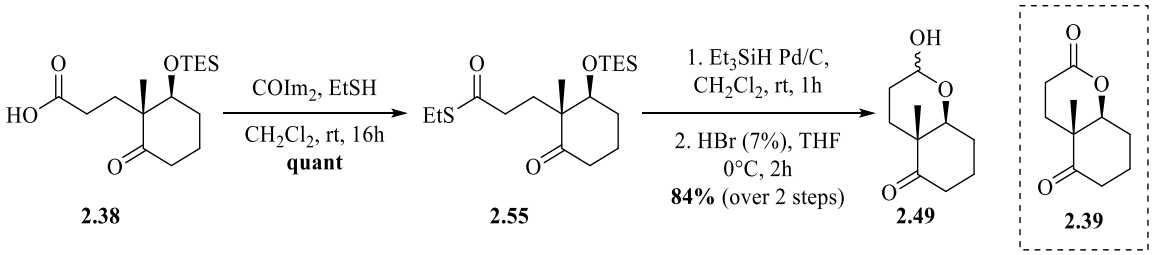
The Fukuyama reaction is the reduction of a thioester to its corresponding aldehyde by a silyl hydride in the presence of a catalytic amount of palladium. Even though it is not a direct reduction of carboxylic acids to aldehydes, it is a mild alternative with a good functional group tolerance. The mechanism of the Fukuyama reduction is shown in scheme 2.19. Starting from thioester **2.50**, the reaction begins with an oxidative addition of the C-SEt bond to the catalytic Pd(0). Transmetallation of **2.51** with triethylsilane affords acylpalladium hydride **2.53**. Finally,

reductive elimination of **2.53** affords the desired aldehyde **2.54** and regenerates the catalytic Pd(0) species.



Scheme 2.19: Mechanism of the Fukuyama reduction

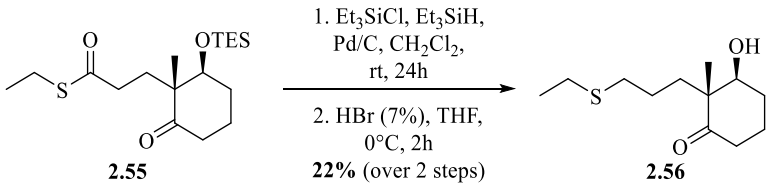
As shown in Scheme 2.20, keto acid **2.38** underwent a thioesterification affording thioester **2.55** in quantitative yield. Although hemiacetal **2.49** was first obtained in 84% yield after the Fukuyama reduction and the acid-catalyzed deprotection, further attempts were not reproducible; furthermore, lactone **2.39** was being isolated instead.



Scheme 2.20: Synthesis of lactol **2.49** *via* a Fukuyama reaction

The lack of reproducibility in synthesizing **2.49** was attributed to the possible poisoning of the Pd(0) catalyst by the presence of small amounts of sulfur-containing compounds remaining in the purified thioester. Unfortunately, reduction of the equivalents of ethanethiol employed in the thio-esterification and degasification of the dichloromethane employed did not improved the results previously obtained. When palladium acetate was used as catalyst for the reduction instead, only starting material was recovered. In a final effort to avoid palladium poising, a catalytic amount of TESCl was added when conducting the Fukuyama reaction. Unfortunately,

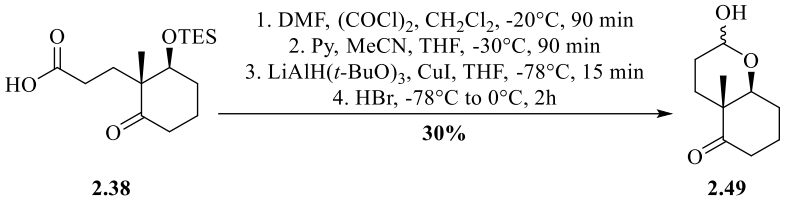
after the deprotection of the TES group, thioether **2.56** instead of hemiacetal **2.49** was obtained as the only product (Scheme 2.21). A precedent in the literature was found that could explain this transformation.[72]



Scheme 2.21: Synthesis of thioether **2.56**

2.4.4.2 Vilsmeier-Haack reduction

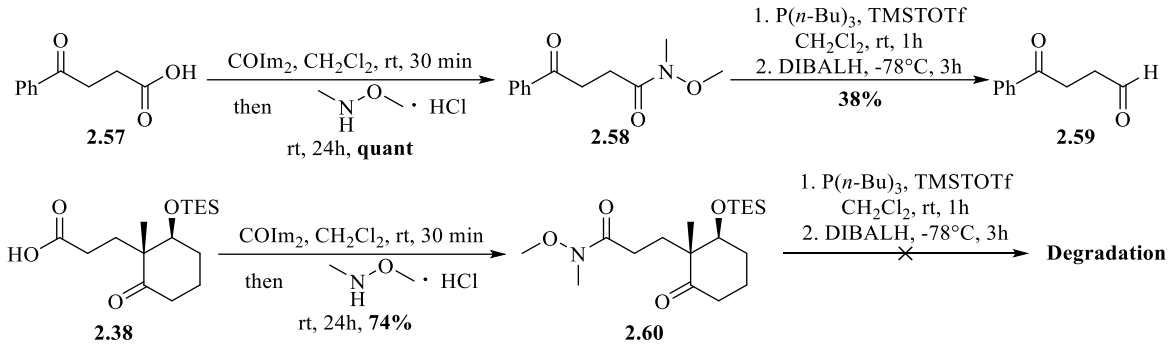
A selective reduction of the acid over the ketone using the Vilsmeier-Haack conditions was attempted (Scheme 2.22).[73] Firstly, the Vilsmeyer-Haack Reagent was formed by dissolving oxalyl chloride in DMF at -20°C and **2.38** was added dropwise, followed by the mild reducing agent LiAlH(*t*-BuO)$_3$. Treatment of the crude product with HBr allowed isolation of the desired lactol **2.49** in 30% yield when 3.82 mmol (1.25 g) of **2.38** were used as starting material. Due to the unsuccessful attempts to improve the yield, these conditions were discarded.



Scheme 2.22: Synthesis of lactol **2.49** *via* a Vilsmeier-Haack reduction

2.4.4.3 Selective reduction *via* Weinreb amide 2.60

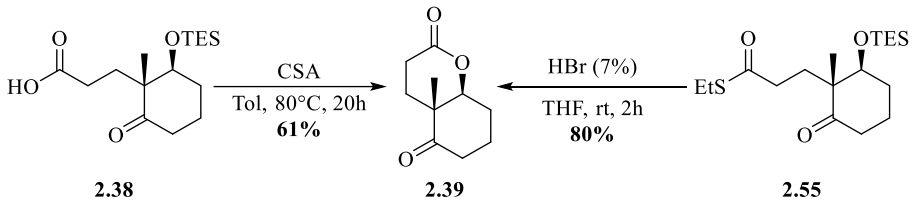
Lastly, a selective reduction of a Weinreb amide in the presence of a ketone was attempted.[74] Using carboxylic acid **2.57** as a model substrate, Weinreb amide **2.58** was obtained in quantitative yield and then treated with tri-butyl phosphine and TMSOTf followed by slow addition of DIBALH, affording desired aldehyde **2.59** in 38% yield (Scheme 2.23). The same conditions were next applied to carboxylic acid **2.38**, giving Weinreb amide **2.60** in 74% yield. Unfortunately, when the reduction was attempted, only decomposition of the starting material was observed.



Scheme 2.23: Selective reduction *via* Weinreb amide **2.60**

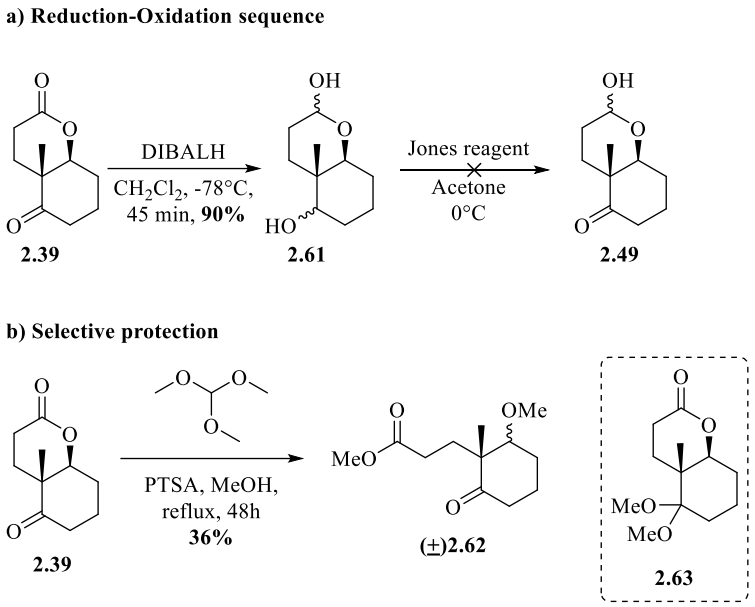
2.4.5 Using lactone 2.39 as starting material

Due to the low reproducibility in the synthesis of hemiacetal **2.49**, the use of lactone **2.39** was considered. Even though **2.39** was isolated as an undesired product in the ozonolysis and the Fukuyama reaction, a new pathway towards its synthesis was implemented. As shown in Scheme 2.24, treatment of **2.38** with CSA afforded lactone **2.39** in 61% yield. Preparation from thioester **2.55** was also achieved in 80% yield.



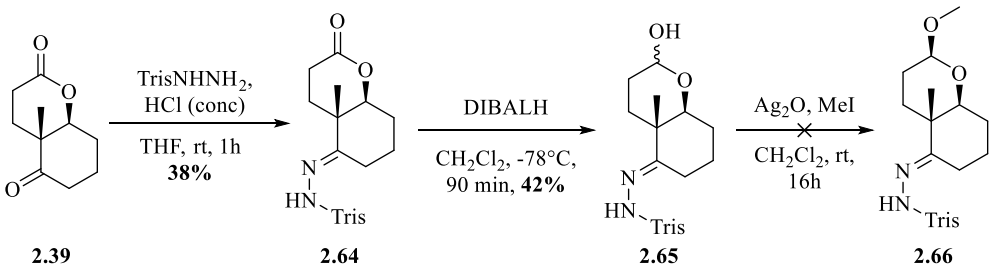
Scheme 2.24: Synthesis of lactone **2.39**

With lactone **2.39** in hand, two different approaches were tested: (a) a reduction-oxidation sequence (Scheme 2.25a) and (b) a selective protection of the ketone (Scheme 2.25b). Initially, complete reduction of the hydroxyl groups was achieved with 2.1 equivalents of DIBALH, affording **2.61** in 90% yield as a mixture of 4 diastereoisomers. Selective oxidation of the alcohol over the hemiacetal was attempted by dissolving the mixture of diastereoisomers in acetone and adding 0.95 equivalents of Jones reagent. A complex mixture of polar compounds was obtained suggesting that protection of the ketone before the reduction was necessary. Selective protection of the ketone over the lactone in **2.39** as a hemiacetal using methyl orthoformate was also studied but afforded methyl ester **(±)2.62** instead of desired **2.63**.



Scheme 2.25: Selective reactions on lactone **2.39**

Disappointed by these results and considering that a hydrazone group is required for the Shapiro coupling, we decided to perform the lactone reduction at a later stage. Condensation of hydrazine with ketone **2.39** was achieved in the presence of catalytic amounts of concentrated hydrochloric acid thus affording the desired hydrazone **2.64** in 38% yield (Scheme 2.26). Reduction of **2.64** using DIBALH led to the isolation of lactol **2.65** in 42% yield. However, methylation of the hydroxyl group with silver(I)oxide and methyl iodide only gave decomposition products.

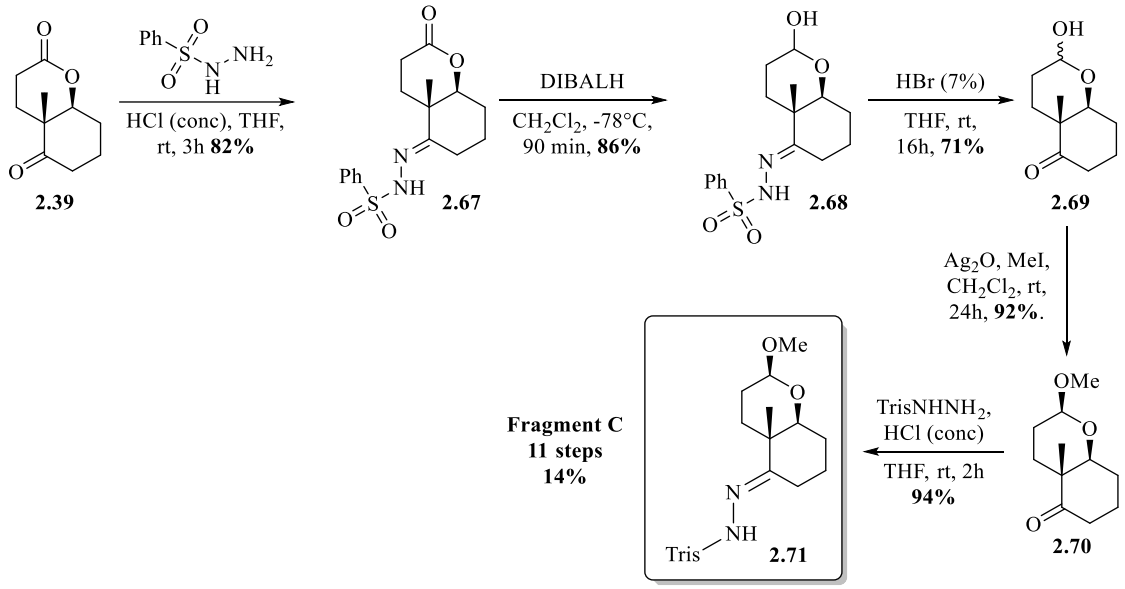


Scheme 2.26: Installation of hydrazone before the lactone reduction

2.4.6 Fragment C: Endgame

As shown in Scheme 2.27, protection of ketone **2.39** as the phenylsulfonyl hydrazone **2.67**, cheaper to prepare than the corresponding trisyl hydrazone **2.64**, allowed the reduction to lactol **2.68** using DIBALH in 86% yield. Copper (II) chloride was tested for the cleavage of the hydrazone, however, after stirring the reaction for three days, full conversion of the starting

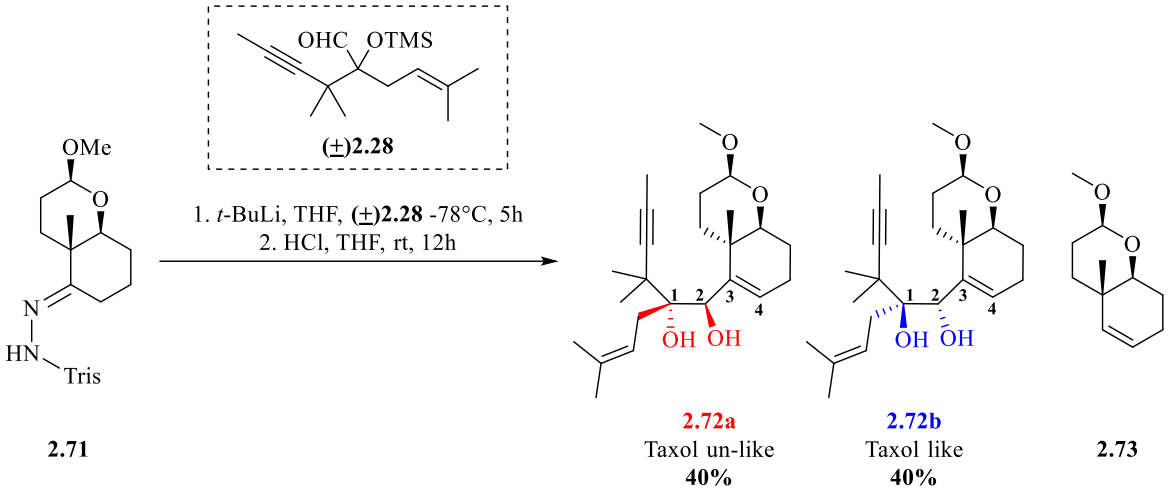
material was not observed. When stirring **2.68** in THF with an aqueous solution of HBr (7%), the desired lactol **2.69** was isolated in 71% yield. Finally, methylation and subsequent hydrazine condensation afforded the desired fragment C **2.71** in 86% for the 2 steps. Overall, the fragment C **2.71** was obtained in 14% yield over 11 steps starting from diketone **2.32**. The ozonolysis reaction and the lactone synthesis are the main drawbacks of this route to prepare this fragment.



Scheme 2.27: Synthesis of fragment C **2.71**

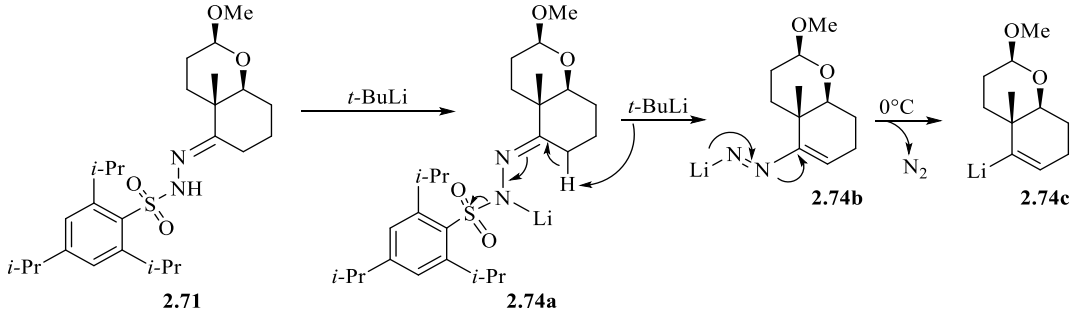
2.5 Shapiro coupling

With racemic fragment A **(±)2.28** and enantiopure fragment C **2.71** in hand, the next step was to couple these two fragments. A Shapiro reaction using *t*-BuLi at -78°C was followed by cleavage of the TMS ether under acidic conditions, affording the two diastereomers **2.72a** and **2.72b** in a 1:1 ratio and in 80% yield over the 2 steps. The diastereomeric ratio of the synthesised diols was then determined by comparison of the integrals of H-4 and H-13 from the crude ^{1}H NMR spectrum. These two diastereomers, which can be separated by flash column chromatography, differ at the C1 and C2 configurations. They will be denominated as **taxol-like** (**2.72b**) and **taxol-unlike** (**2.72a**). Formation of alkene **2.73** was also observed (11% yield).



Scheme 2.28: Shapiro coupling using racemic fragment A **(±)2.28** and fragment C **2.71**.

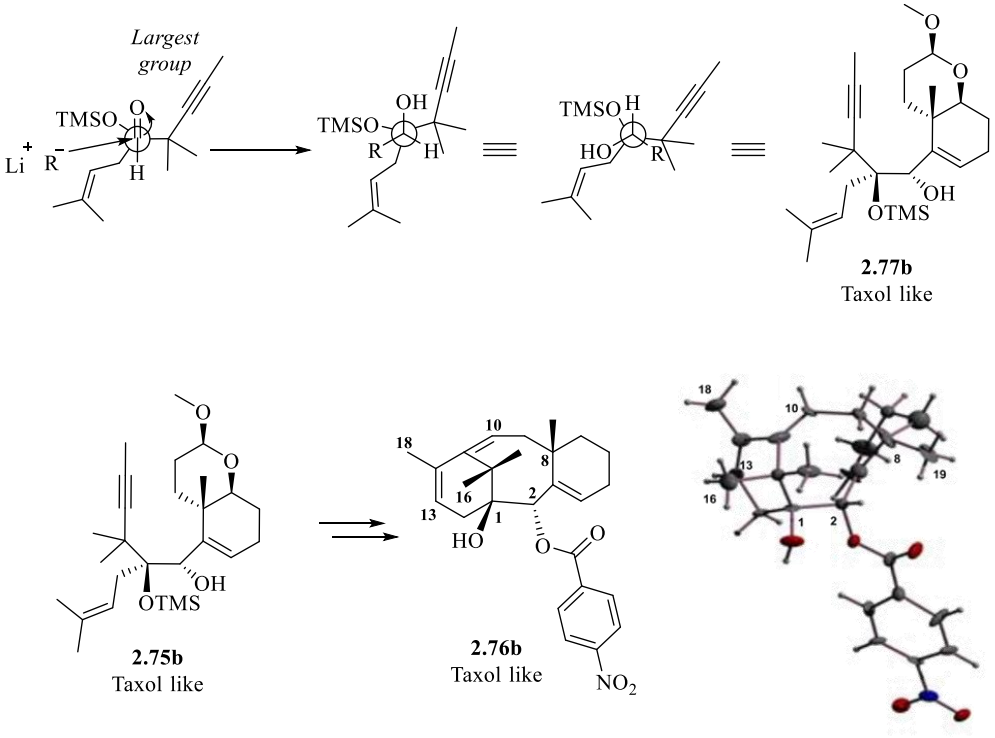
As shown in Scheme 2.29, this reaction proceeds *via* the vinyl lithium intermediate **2.76** and requires two equivalents of *t*-BuLi. The first equivalent deprotonates the nitrogen of **2.71** generating the first lithium salt **2.74a**, while the second one removes a proton in the α-position of the hydrazone promoting the elimination of the sulfinate anion and resulting in the formation of **2.74b**. Increasing the reaction temperature from -78°C to 0°C induces the release of nitrogen and thus generates the active vinyl lithium intermediate **2.76**. Its reaction with aldehyde **(±)2.28** results in the formation of isomers **2.72a-b**, whereas alkene **2.73** is obtained after quenching **2.74c** with water since a 1.2 : 1 ratio of **2.71** to **(±)2.28** was employed. Furthermore, this reaction was performed using the enantio-enriched aldehyde previously synthesised (Scheme 2.12), affording a 28% ee of the desired isomer **2.72b**. As shown in the experimental section and in the appendix section, it is possible to differentiate the protons at the C4 position between diols **2.72a** and **b**.



Scheme 2.29: Formation of the active vinyl lithium intermediate **2.74c**

The steric Felkin-Anh model can explain the diastereoselectivity of the reaction for the Taxol like compound. As shown in Scheme 2.30, in the Newman projection of the aldehyde prior to

the attack of **2.74c**; the largest group (bearing the *gem*-dimethyl moiety) is positioned perpendicular to the carbonyl group. After the addition of reactive vinyl species **2.74c**, a *trans* relationship (i.e. would be *trans* if the B-ring were closed) between the two hydroxyl groups was observed. A similar model can be applied for the Taxol un-unlike alcohol. The absolute configuration for the taxol-like derivate **2.76b** was confirmed by Letort using X-ray diffraction. All the ^{13}C NMR and ^{1}H NMR spectrum of the diols **2.72a-b** and its derivatives were compared to those reported.[64]

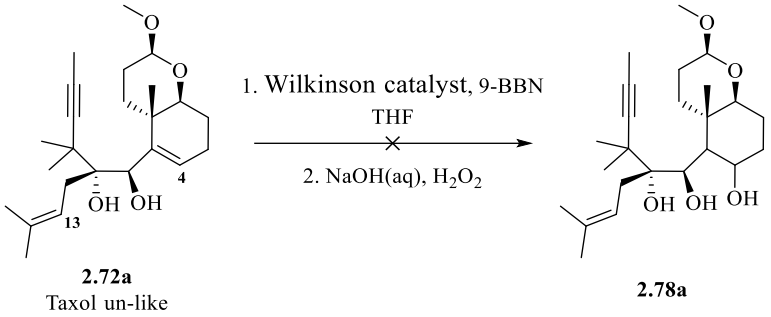


Scheme 2.30: Diastereoselectivity in the Shapiro reaction

2.6 Functionalisation of the C4 position

2.6.1 Initial attempts

Once diols **2.72a-b** were isolated, several attempts to functionalise the C-4 position in both diastereomers were tested. Initially a directed hydroboration using Wilkinson catalyst and 9-BBN in THF was attempted on **2.72a** (Scheme 2.31).[75] After stirring the reaction at room temperature for 24 hours, full conversion of the starting material was not observed but several compounds were distinguishable by TLC. Once the reaction was quenched, ^{1}H NMR revealed several compounds, but no olefinic protons were observed. The lack of selectivity in this hydroboration procedure represented a drawback in the functionalisation of C4 over C13.



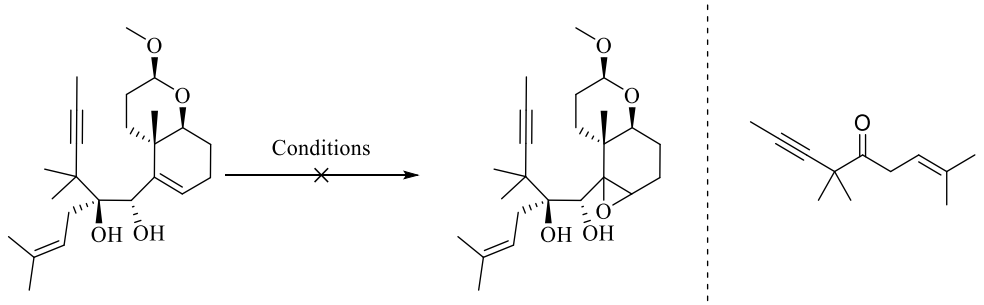
2.72a
Taxol un-like

2.78a

Scheme 2.31: Hydroboration using Wilkinson catalyst

Thus, a selective oxidation of C4 over C13 must be accomplished. Firstly, directed epoxide formation was attempted using two different vanadium complexes (Table 2.2, entries 1 and 2).[76] Unfortunately, in both cases several compounds were observed by TLC and NMR, and ketone **2.26** was isolated after purification, showing the oxidative cleavage of the diol. Sharpless epoxidation was also tried but similar results were obtained (entry 3).

Table 2.2: Attempts to epoxidise the C3-C4 alkene in **2.72b**



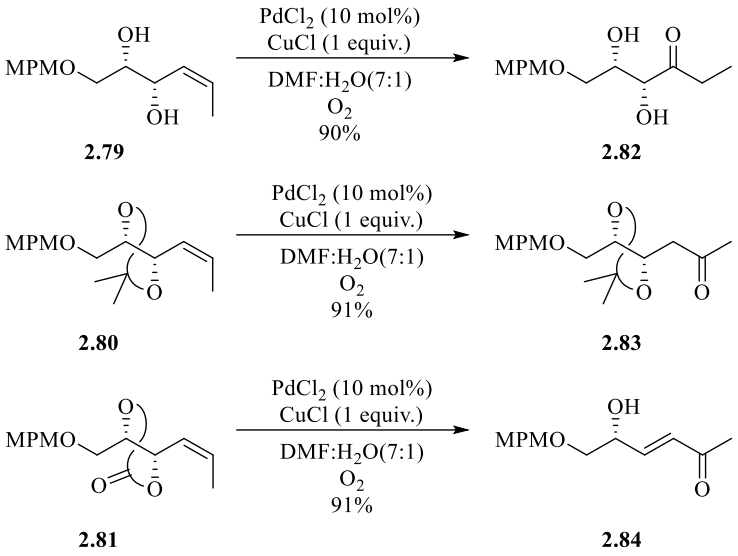
2.72b
Taxol like

2.26

Entry	Conditions	Outcome
1	$VO(acac)_2$, TBHP, CH_2Cl_2	Degradation, oxidative cleavage
2	$V(acac)_3$, TBHP, CH_2Cl_2	Degradation, oxidative cleavage
3	$Ti(O\textit{i}\text{-}Pr)_4$, (+)-Diisopropyl-*L*-tartrate	Degradation, oxidative cleavage

2.6.2 Wacker oxidation

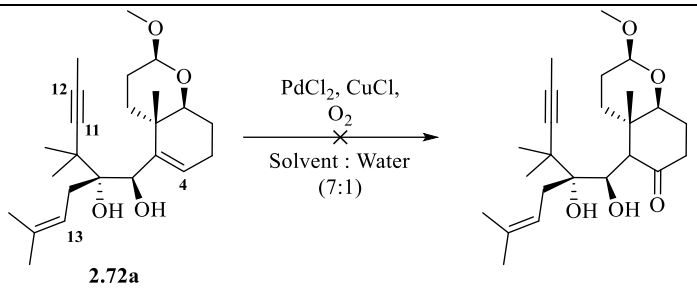
In 1995 Kang and co-workers reported a Pd(II)-catalysed oxidation of internal olefins in the presence of copper chloride.[77] This Wacker oxidation employs milder conditions than the ones used in the epoxidation and thus opens the possibility to avoid the oxidative cleavage previously observed. As shown in Scheme 2.32, this methodology has been successfully applied to free diol **2.79**, as well as acetonide **2.80** and carbonate protected **2.81** diols with a vicinal *Z*-alkene. Ketones **2.82** and **2.83** in addition to α,β-unsaturated ketone **2.84** were isolated in high yields.



Scheme 2.32: Wacker oxidation precedent

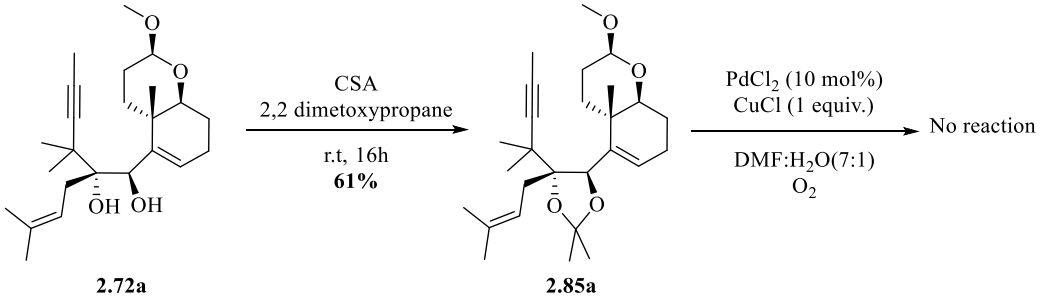
Initially, the reaction was tested on the taxol-unlike diol **2.72a** using DMF as solvent. After stirring the reaction mixture overnight under an oxygen atmosphere, full conversion of the starting material was observed by TLC and a mixture of two isomers in 1:1 ratio was isolated in 60% yield (Table 2.3, entry 1). Despite several analyses being performed on the products (one and two dimensional NMR, MS, HRMS, IR), the identification of the product was not possible. Though, since olefinic protons and carbons (C4 and C13) are observed while no alkyne peaks (C11 and C12) are seen on ^{13}C NMR, it is proposed the reaction proceeds on the triple bond instead of the double bond. When using DCM and THF as solvent, the same product was isolated (entries 2 and 5). Meanwhile in *t*-BuOH and acetonitrile decomposition of the starting material was observed. Although in 2009 Jing and coworkers reported the synthesis of 1,2-diketones by a Wacker-type oxidation of alkynes using molecular oxygen, in our case this transformation was not observed.[78]

Table 2.3: Wacker oxidation in taxol-unlike free diol **2.72a**



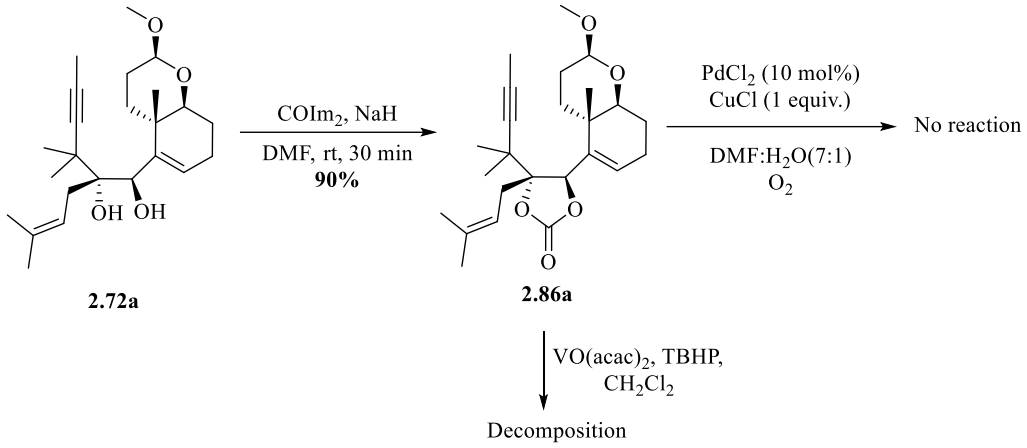
Entry	Solvent	Outcome
1	DMF	Unidentified product (60% yield). No alkyne observed
2	CH_2Cl_2	Unidentified product (30% yield). No alkyne observed
3	*t*-BuOH	Decomposition
4	CH_3CN	Decomposition
5	THF	Unidentified product (43% yield). No alkyne observed

Protection of taxol-unlike diol **2.72a** using 2,2-dimetoxypropane and CSA as catalyst furnished acetonide **2.85a** in 61% yield (Scheme 2.33). Unfortunately, no reaction was observed when employing the Wacker oxidation conditions. Addition of more palladium chloride did not change the result previously obtained.



Scheme 2.33: Wacker oxidation attempt in acetal **2.85a**

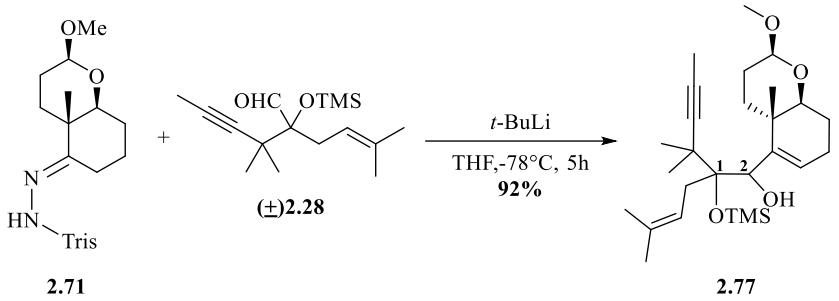
Finally, protection of the taxol-unlike diol **2.75a** using carbonyl diimidazole and sodium hydride in DMF was performed affording the desired carbonate **2.86a** in 90% yield. Once again, after Wacker oxidation conditions were tested, no reaction was observed. Additionally, an epoxidation using $VO(acac)_2$ and TBHP was also tried but decomposition of the starting material was observed.



Scheme 2.34: Wacker oxidation and epoxidation attempts on carbonate **2.86a**

2.6.3 Oxidation attempts on protected alcohol 2.77

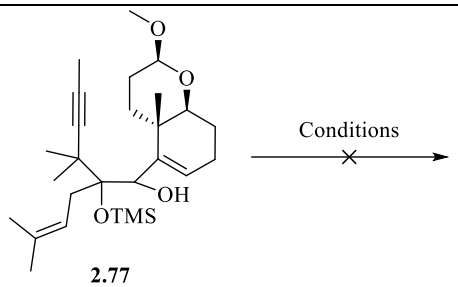
Due to the oxidative cleavage of the diol **2.72b** observed when epoxidation was attempted (Table 2.2), it was proposed to keep the alcohol at C1 protected after the Shapiro coupling. In this case, compound **2.77** was isolated in 92% yield as a mixture of diastereomers, which unfortunately could not be separated.



Scheme 2.35: Shapiro reaction without TMS deprotection

Vanadium-catalysed epoxidation was tested on the mixture of diastereomers (Table 2.4, entries 1 and 2). Although in both cases degradation of the starting material was observed, ketone **2.26** was not isolated and characteristic aldehydes peaks were distinguished in the crude ^{1}H NMR spectrum. Further analysis let us confirm the reaction did not occur at the C3-C4 alkene as planned but cleavage of the acetal moiety was observed among several decomposition products. The same outcome was obtained when Sharpless epoxidation was tried (entry 3). Lastly, Wacker oxidation conditions were tested but once again degradation of the starting material was observed.

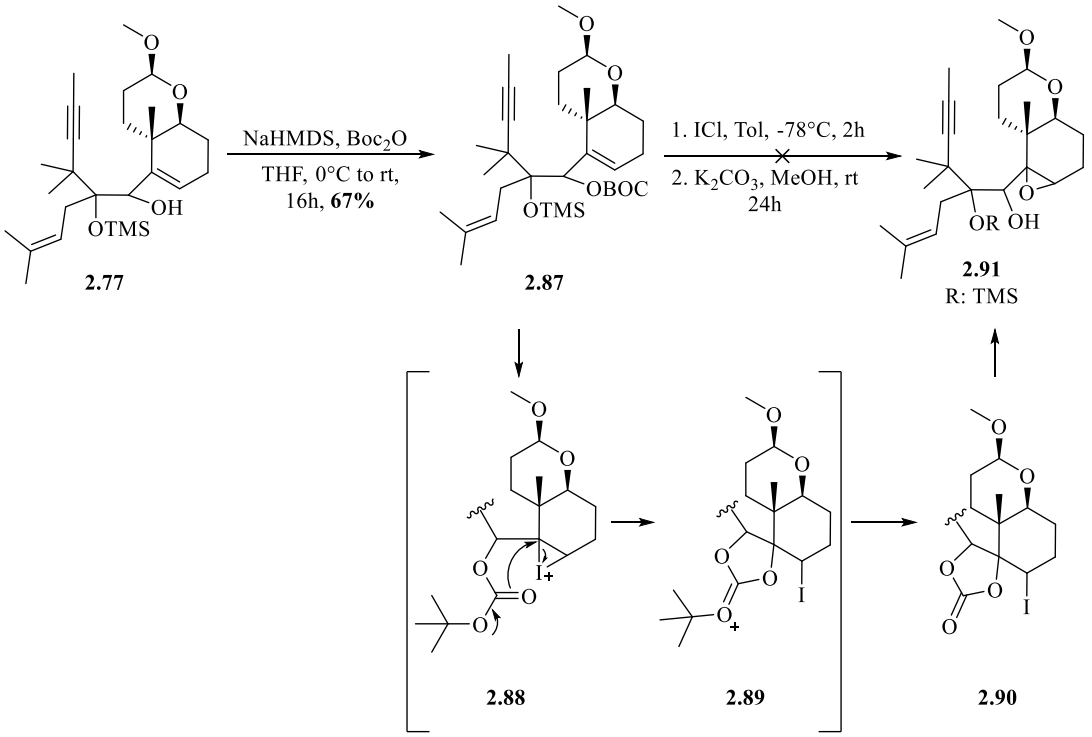
Table 2.4: Attempts to functionalise the C4 position in **2.77**



2.77

Entry	Condition	Outcome
1	$VO(acac)_2$, TBHP, CH_2Cl_2	Degradation
2	$V(acac)_2$, TBHP, CH_2Cl_2	Degradation
3	$Ti(OiPr)_4$, (+)-Diisopropyl *L*-tartrate	Degradation
4	$PdCl_2$, CuCl, O_2, DMF: Water (7:1)	Degradation

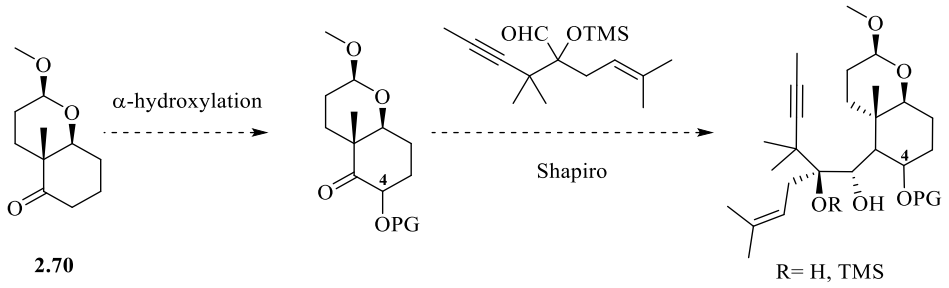
Next, an iodocarbonatation of the Boc protected alcohol **2.77** was envisioned.[79] Treatment of **2.77** with Boc_2O in the presence of NaHDMS afforded **2.87** in 67% yield. After formation of the iodonium ion **2.88** and iodocarbonate intermediate **2.90**, it was expected to obtain epoxide **2.91**. Unfortunately, after quenching the reaction, decomposition of the starting material was observed.



Scheme 2.36: Iodocarbonatation attempt on **2.87**

2.6.4 Functionalisation of C4 *via* an α-hydroxylation

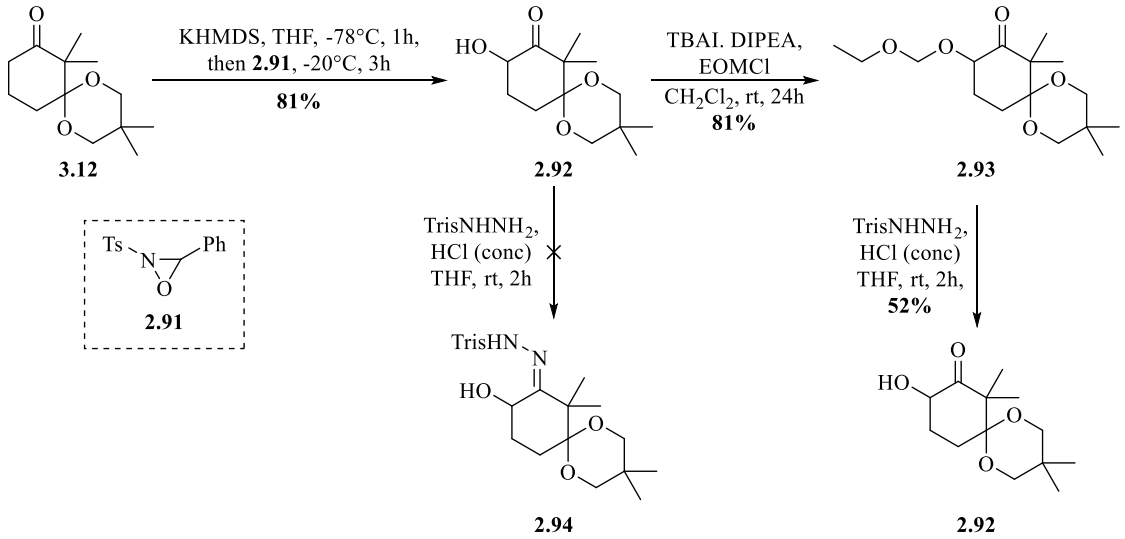
Since previous attempts to oxidise the C4 position after the Shapiro coupling were unsuccessful, a prior functionalisation was investigated (Scheme 2.37). Nevertheless, there are no reports of a Shapiro reaction with an α-alkoxy hydrazone to the best of our knowledge.



2.70

Scheme 2.37: C4 functionalisation prior to the Shapiro coupling

Compound **3.12** was used as a model substrate since it bears a quaternary carbon in the α-position of the ketone and an acetal moiety in the β-position.* Using Davis' oxaziridine **2.91**, alcohol **2.92** was prepared in 81% yield, and its subsequent protection successfully afforded **2.93** (Scheme 2.38). EOMCl (ethoxymethyl chloride) instead of MOMCl (methoxymethyl chloride) was used for the protection of the alcohol due to its availability in the laboratory.



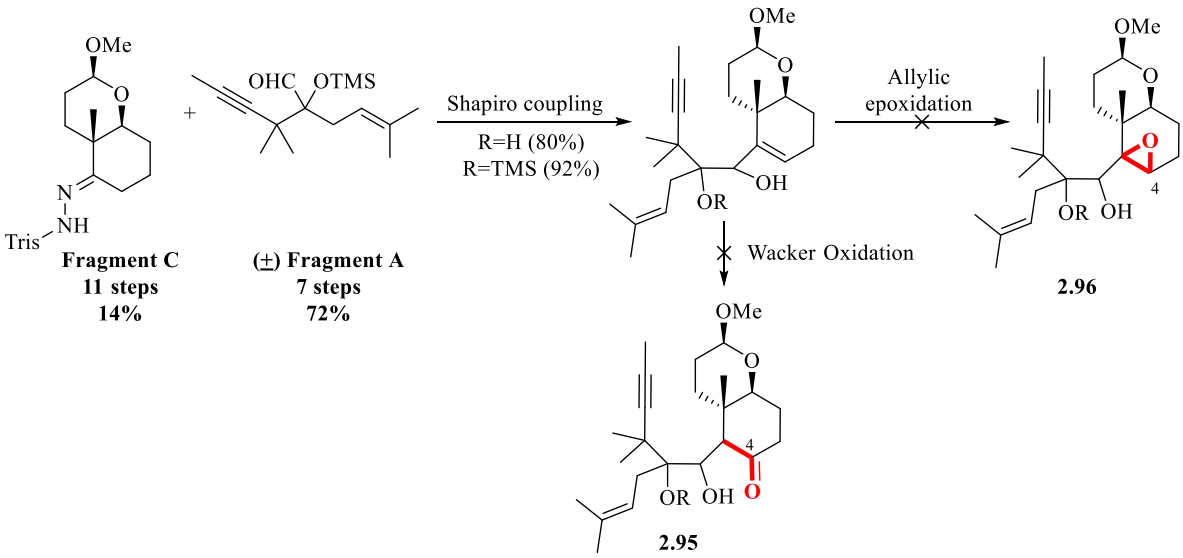
Scheme 2.38: Functionalisation of C4 via an α-hydroxylation

*The synthesis of **3.12** is discussed in detail in Chapter 3, Scheme 3.8

Disappointingly, hydrazone formation was not possible and **2.92** was recovered in 52% yield among several decomposition products. When the hydrazine condensation was attempted prior to the alcohol protection, the reaction was unsuccessful. These results suggested a different protecting group, such as methyl ether, must be employed.

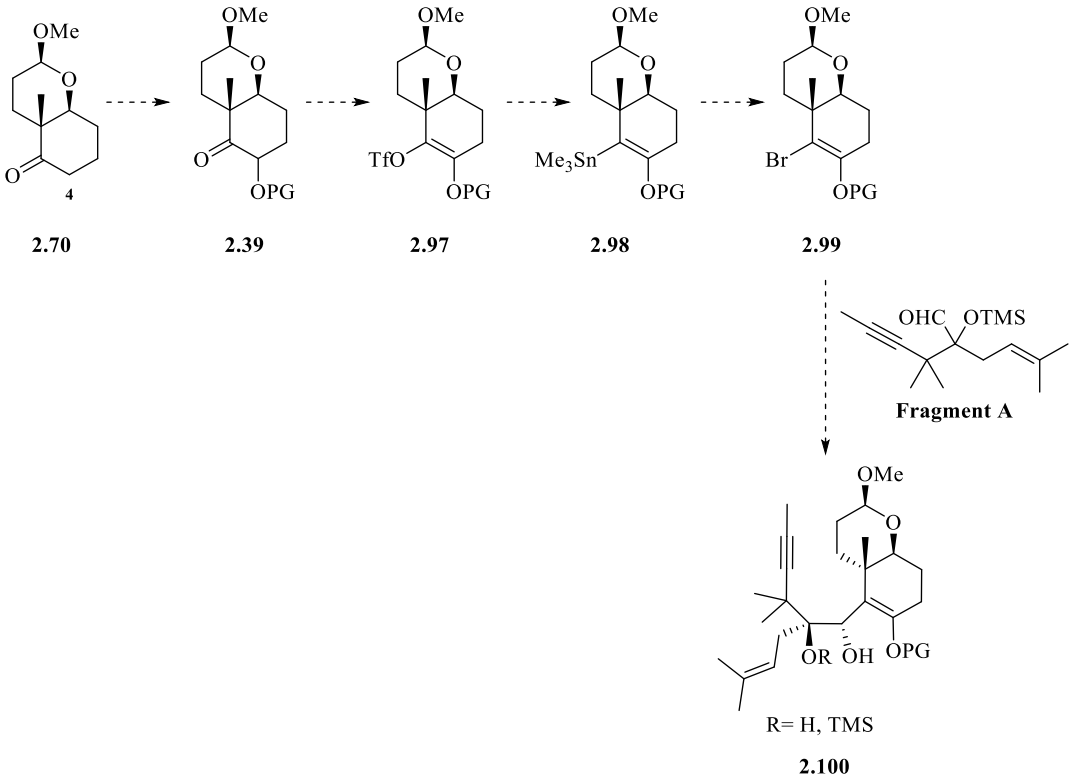
2.7 Conclusion

Racemic fragment A was synthesised in 72% yield over 7 steps while enantiopure fragment C was obtained in 14% yield after 11 steps (Scheme 2.41). The synthesis of an enantioenriched fragment A was attempted using activation of chiral (salen)AlCl complex by a phosphorane but poor enantioselectivity was obtained (28% ee) and further alternatives should be explored. Coupling of both fragments was successfully achieved by a Shapiro reaction but functionalisation of the C4 position has not been possible.



Scheme 2.39: Summary of results

As shown in Scheme 2.42, the early functionalisation of C4 *via* an α-hydroxylation is envisioned. If the Shapiro reaction is not successful with a methyl protecting group, transformation of enol triflate **2.97** into vinyl brominated compound **2.99** by a tin halogen exchange is proposed based on the work conducted by Stéphanie Schiltz during her PhD studies under the supervision of Dr Joëlle Prunet.[80] The advanced intermediate **2.100** is expected to be obtained after metallation of **2.99** and subsequent quenching with the fragment A.[81]



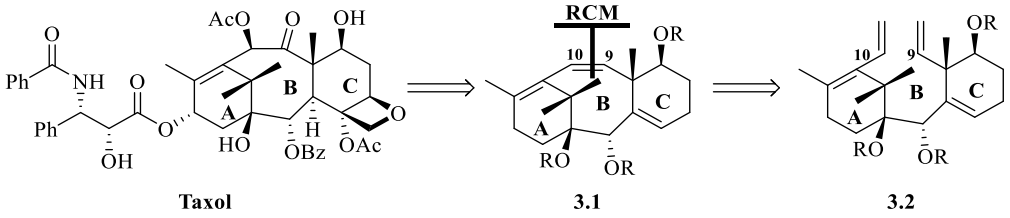
Scheme 2.40: Perspectives

Chapter 3: Relay ring-closing metathesis

In this chapter, a route which involves a relay ring-closing metathesis (RRCM) as the key step towards a formal synthesis of Taxol is presented. This work is an extension of the previous work performed by Damien Bourgeois[41b, 82] and Rémi Aouzal[63] during their PhD theses under the supervision of Dr Joëlle Prunet.

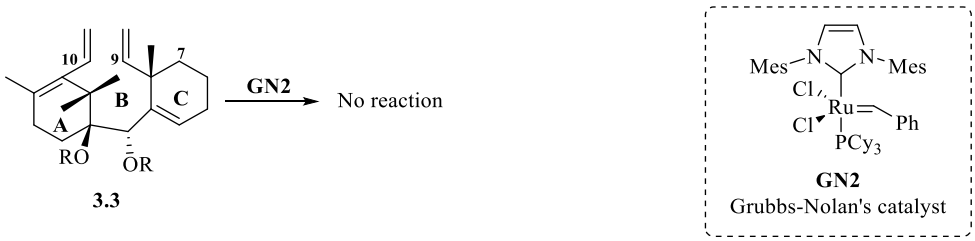
3.1 Previous work in the group

As shown in Scheme 3.1, Damien Bourgeois envisioned the construction of Taxol´s A and C ring prior to the formation of the B ring. A RCM reaction between C9 and C10 of **3.2** was the key step of this approach and would allow the synthesis of the tricyclic core **3.1**.



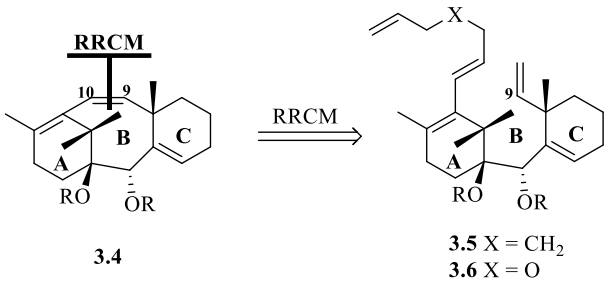
Scheme 3.1: Bourgeois's retrosynthesis

Diene **3.3** was chosen as a model compound for the study of the RCM. It bears two terminal olefins, at C9 and C10, and is not functionalised at the C7 position. Unfortunately, all the RCM reactions performed on **3.3** led to the isolation of the starting material, even when a full equivalent of **GN2** was employed (Scheme 3.2). Based on these results, it was concluded that the olefins at C9 and C10 were unreactive due to electronic or steric reasons and the formation of the carbene at either of them did not take place.



Scheme 3.2: Bourgeois's RCM attempt in **3.3**

A RRCM reaction was envisioned by Rémi Aouzal in an attempt to form the carbene at C10. Two different tethers were proposed and compounds **3.5** and **3.6** (all carbon and oxygenated version, respectively) were to be synthesised (Scheme 3.3).

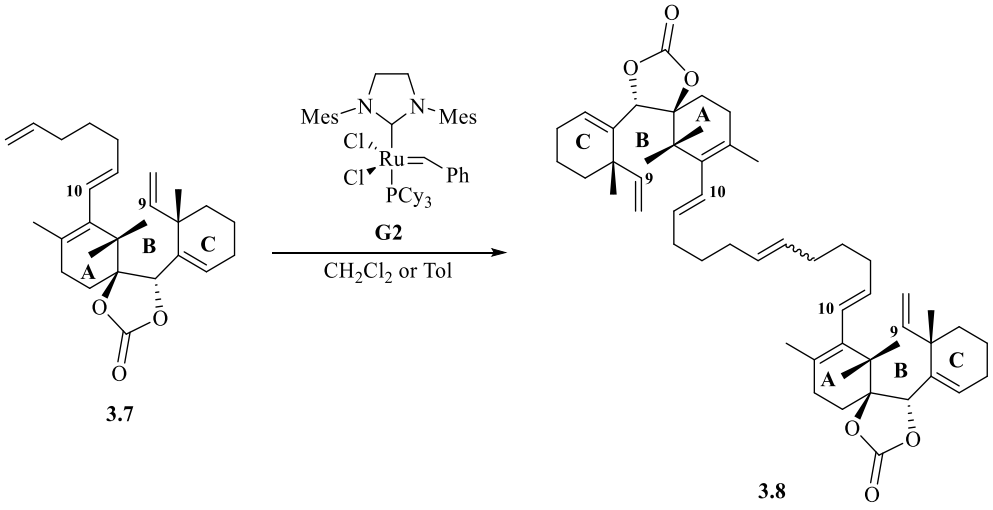


3.4

3.5 X = CH_2
3.6 X = O

Scheme 3.3: Aouzal´s retrosynthesis involving a RRCM

Firstly, a RRCM reaction was performed using **3.7** as the starting material and dichloromethane as solvent but, unfortunately, the dimer **3.8** was isolated as the only product (Scheme 3.4). Dilution of the reaction mixture from 15 mM to 1.5 mM did not favour the intramolecular over the intermolecular reaction. Using toluene as the solvent and increasing the temperature resulted in isolation of **3.8** among other decomposition products.

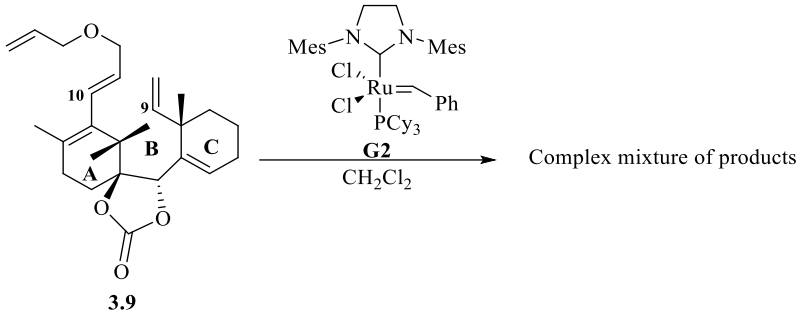


3.7

3.8

Scheme 3.4: Aouzal´s RRCM attempts on **3.7**

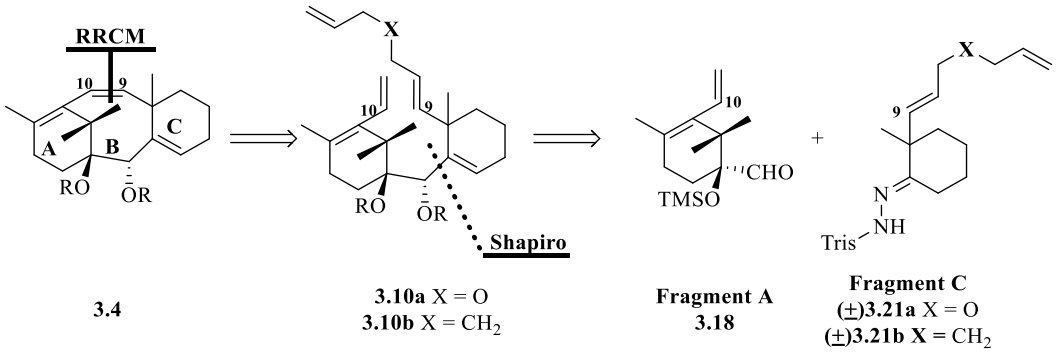
Aouzal also tried a RRCM reaction with **3.9**, displaying an oxygen atom in the tether at C10, but disappointingly a complex mixture of unidentified products was obtained (Scheme 3.5). These results led to the conclusion that the carbene at C10 was not formed and thus the cyclisation could not take place. In this chapter, the installation of the tether at C9 instead of C10 will be investigated.



Scheme 3.5: Aouzal´s RRCM attempts on **3.9**

3.2 Project presentation and retrosynthetic analysis

The retrosynthesis for the construction of the B ring of Taxol using a RRCM reaction as the key step is outlined in Scheme 3.6. The tricyclic core **3.4** was selected as the primary target of this project. Unlike the metathesis precursors proposed by Aouzal, in this case the tether would be placed at C9. The synthesis of two different metathesis precursors (with or without oxygen) is envisioned (compounds **3.10a-b**), which could be obtained by a Shapiro coupling between fragments A **(±)3.21a-b** and fragment C **3.18**.

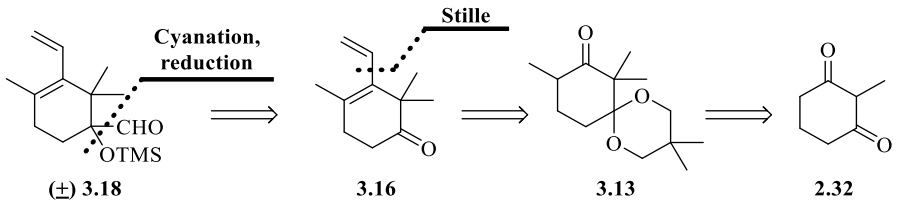


Scheme 3.6: Taxol retrosynthesis using a RRCM as the key step

3.3 Synthesis of fragment A

3.3.1 Retrosynthesis

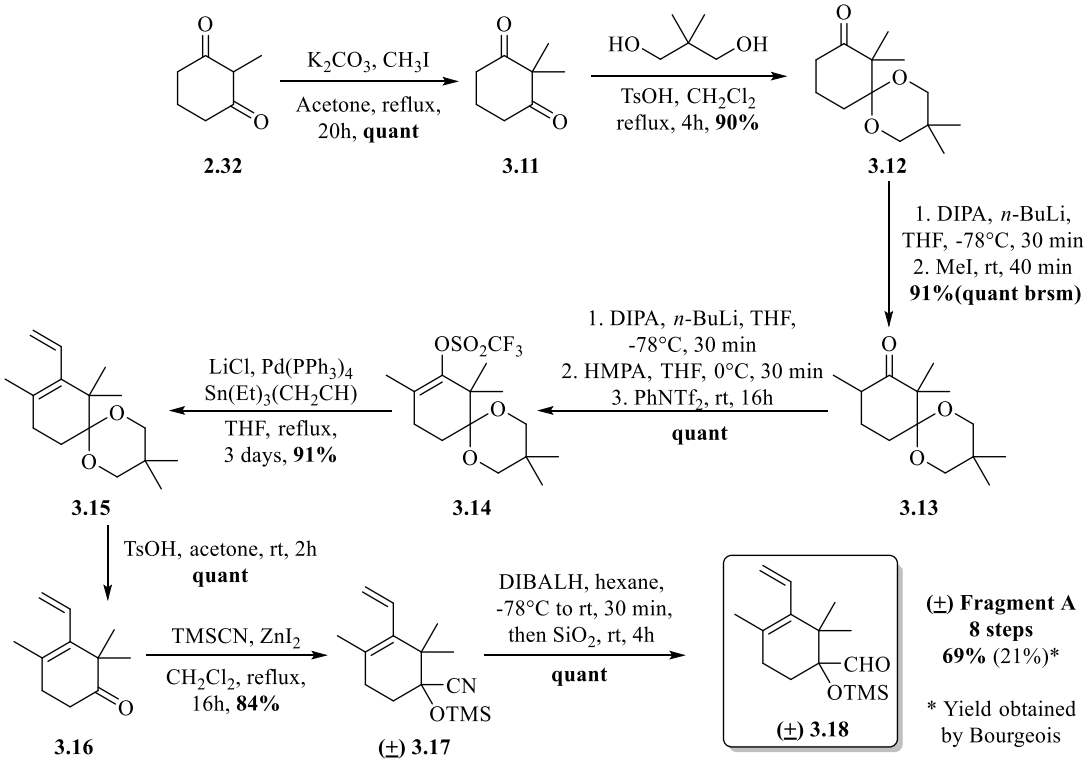
The retrosynthesis of fragment A is outlined in Scheme 3.7 and uses the same key disconnections proposed by Muller *et al.*[83] Aldehyde **(±)3.18** could be obtained by cyanation followed by reduction from the ketone **3.16**, which in turn could be prepared from the ketone **3.13** by performing a Stille reaction on the corresponding vinyl triflate. Finally, ketone **3.13** can be synthesised starting from the commercially available diketone **2.32**.



Scheme 3.7: Retrosynthesis of fragment A **(±)3.18**

3.3.2 Racemic synthesis

Aldehyde **(±)3.18** has been previously synthesised in the Prunet group by Benoît Muller[83] achieving a 21% overall yield. As shown in Scheme 3.8, the first step of the synthesis is the methylation of **2.32** followed by mono-protection of **3.11**, resulting in the isolation of ketone **3.12** in 90% yield for two steps. After methylation of **3.12**, ketone **3.13** was successfully transformed into triflate **3.14**, which was then submitted to a Stille coupling affording stable diene **3.15** in 91% yield for three steps. The use of DMPU instead of HMPA in the synthesis of **3.14** was also investigated, but unfortunately the low yield obtained forced the use of HMPA.



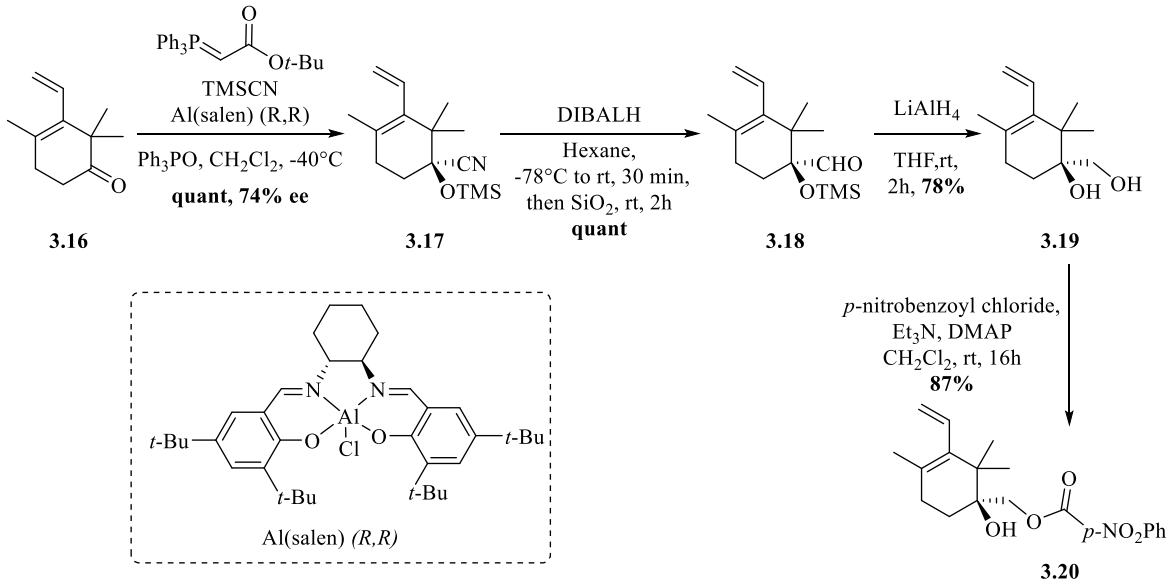
Scheme 3.8: Synthesis of racemic fragment A **(±)3.18**

Later acid-catalysed deprotection of the acetal afforded the desired ketone **3.16** in quantitative yield. Further treatment of **3.16** with TMSCN in the presence of zinc iodide provided the

silylated cyanohydrin **(±)3.17** in 84% yield. Reduction of this cyanohydrin **(±)3.17** using DIBALH led to the corresponding imine that was then hydrolysed under mild acidic conditions by adding SiO_2 to the reaction mixture. In summary, the racemic aldehyde **(±)3.18** was obtained in 69% overall yield over 8 steps.

3.3.3 Efforts towards an enantio-enriched synthesis of fragment A

Following the conditions reported by Zhou and coworkers,[68] ketone **3.16** was submitted to an enantioselective cyanosilylation in the presence of an activated chiral (salen)AlCl complex, furnishing cyanohydrin **3.17** in quantitative yield (Scheme 3.9). In order to determine its enantiomeric excess, aldehyde **3.18** was treated with $LiAlH_4$ and the deprotected diol **3.19** was successfully isolated in 78% yield. After coupling of **3.19** with *p*-nitro benzoyl chloride, a 74% enantiomeric excess of the ester **3.20** was determined by HPLC with a chiral column (see appendix for the chromatograms of the racemic and enantioenriched mixtures).



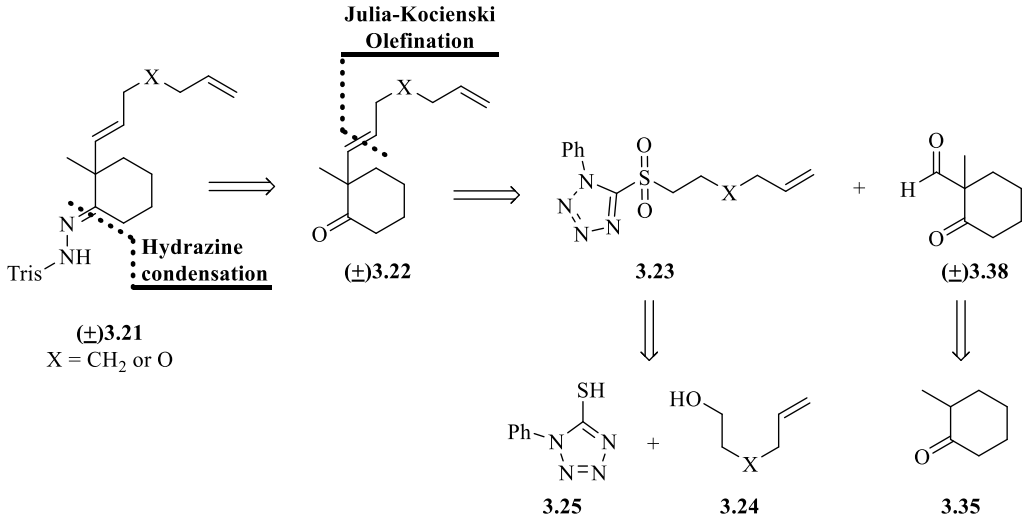
Scheme 3.9: Synthetic efforts towards an enantioenriched fragment A **3.18**

3.4 Synthesis of racemic fragment C

3.4.1 Retrosynthesis

As shown in scheme 3.10, the hydrazone **(±)3.21** could be obtained by a hydrazine condensation to the diene intermediate **(±)3.22**, which in turn would be synthesised by a Julia-Kocienski olefination between the keto-aldehyde **(±)3.38** and the tetrazolylsulfone **3.23**. The

tetrazolylsulfone **3.23** could be obtained from the thiol **3.25** and the alcohol **3.24**. The synthesis of two different hydrazones, with or without an oxygen substituent, was envisaged.

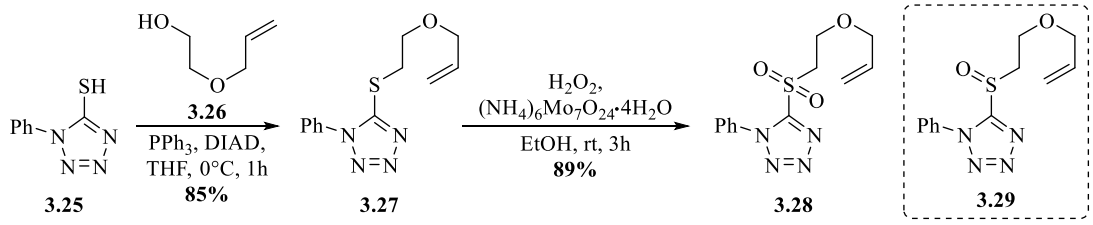


Scheme 3.10: Retrosynthesis of the racemic fragment C **(±)3.21**

3.4.2 Synthesis of the sulfone 3.23

3.4.2.1 Synthesis of the oxygenated sulfone 3.28

Initially, a Mitsunobu-type reaction between the commercially available alcohol **3.26** and thiol **3.25** furnished sulfide **3.27** in 85% yield (Scheme 3.11).[84] Subsequent oxidation of **3.27** with 0.16 equivalents of ammonium hepta-molybdate and 3 equivalents of hydrogen peroxide afforded sulfone **3.28** and sulfoxide **3.29** in 78% and 17% yield, respectively. When 5.7 equivalents of hydrogen peroxide were employed, **3.28** was successfully isolated in 89% yield as the only product.

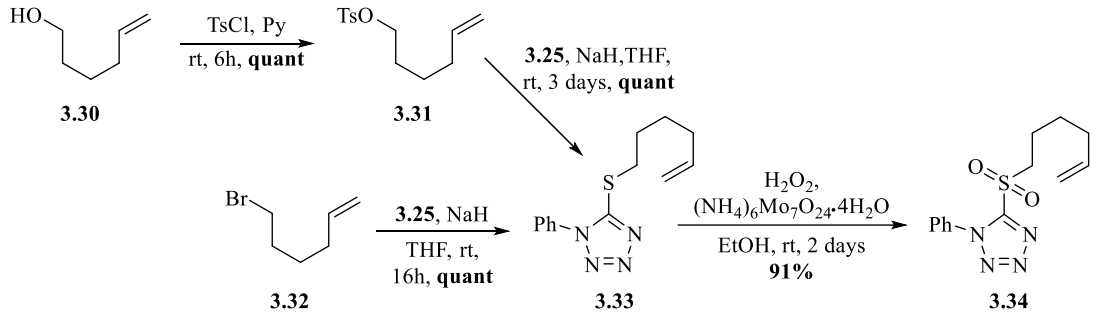


Scheme 3.11: Synthesis of the oxygenated sulfone **3.28**

3.4.2.2 Synthesis of the all carbon sulfone 3.34

Two different pathways for the synthesis of sulfide **3.33** were attempted, using either alcohol **3.30** or alkyl bromide **3.32** as starting material (Scheme 3.12). Firstly, installation of a tosyl group on **3.30** followed by its substitution afforded the desired sulfide **3.33** in quantitative yield. On

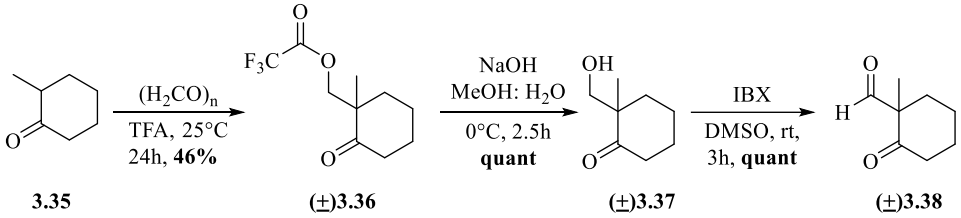
the other hand, direct substitution of bromide in **3.32** furnished **3.33** in a single step. Subsequent oxidation of **3.33** using hydrogen peroxide in the presence of a molybdenum complex yielded the sulfone **3.34** in 91% yield.



Scheme 3.12: Synthesis of the all carbon sulfone **3.34**

3.4.3 Synthesis of the aldehyde (±)3.38

Starting from 2-methylcyclohexanone **3.35** and *p*-formaldehyde, trifluoroacetate **(±)3.36** was obtained in 46% yield in the presence of TFA (Scheme 3.13).[85] Subsequent hydrolysis of **(±)3.36** under basic conditions afforded the desired alcohol **(±)3.37** in quantitative yield. Its oxidation to aldehyde **(±)3.38** was initially attempted by using the Dess-Martin periodinane; but low conversion of the starting material in short reaction times combined with decomposition of the product when increasing the reaction time forced us to change the oxidizing agent. Finally, aldehyde **(±)3.38** was successfully isolated in quantitative yield when an excess of IBX was employed.



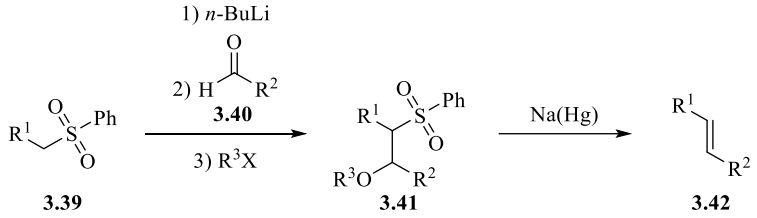
Scheme 3.13: Synthesis of the aldehyde **(±)3.38**

3.4.4 Julia-Kocienski olefination

3.4.4.1 Generalities of the Julia-Kocienski olefination reaction

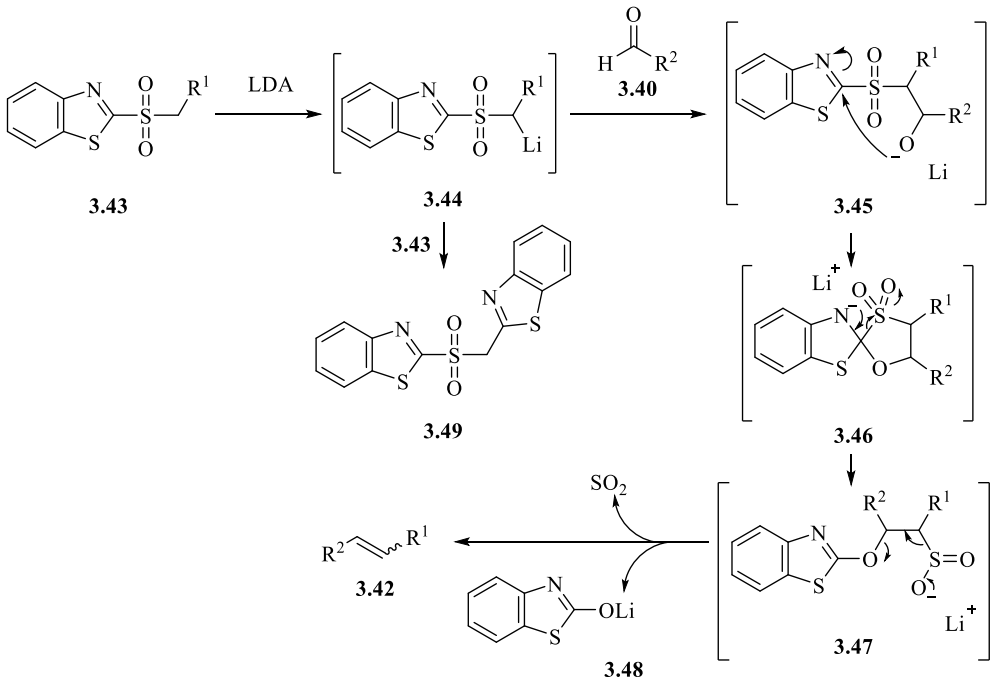
In 1973, Marc Julia and Jean-Marc Paris reported the synthesis of di-, tri- or tetrasubstituted olefins from phenyl sulfones and aldehydes (or ketones).[86] Scheme 3.14 illustrates the synthesis of the disubstituted olefin **3.42** starting from the phenyl sulfone **3.39** and the aldehyde **3.40**.

The stereochemistry of the resulting alkene is independent of the stereochemistry at the sulfone intermediate **3.41** and this reaction exhibits a good *E*-selectivity. Unfortunately, a major disadvantage of this reaction is its low tolerance towards reducible functional groups in the starting materials.



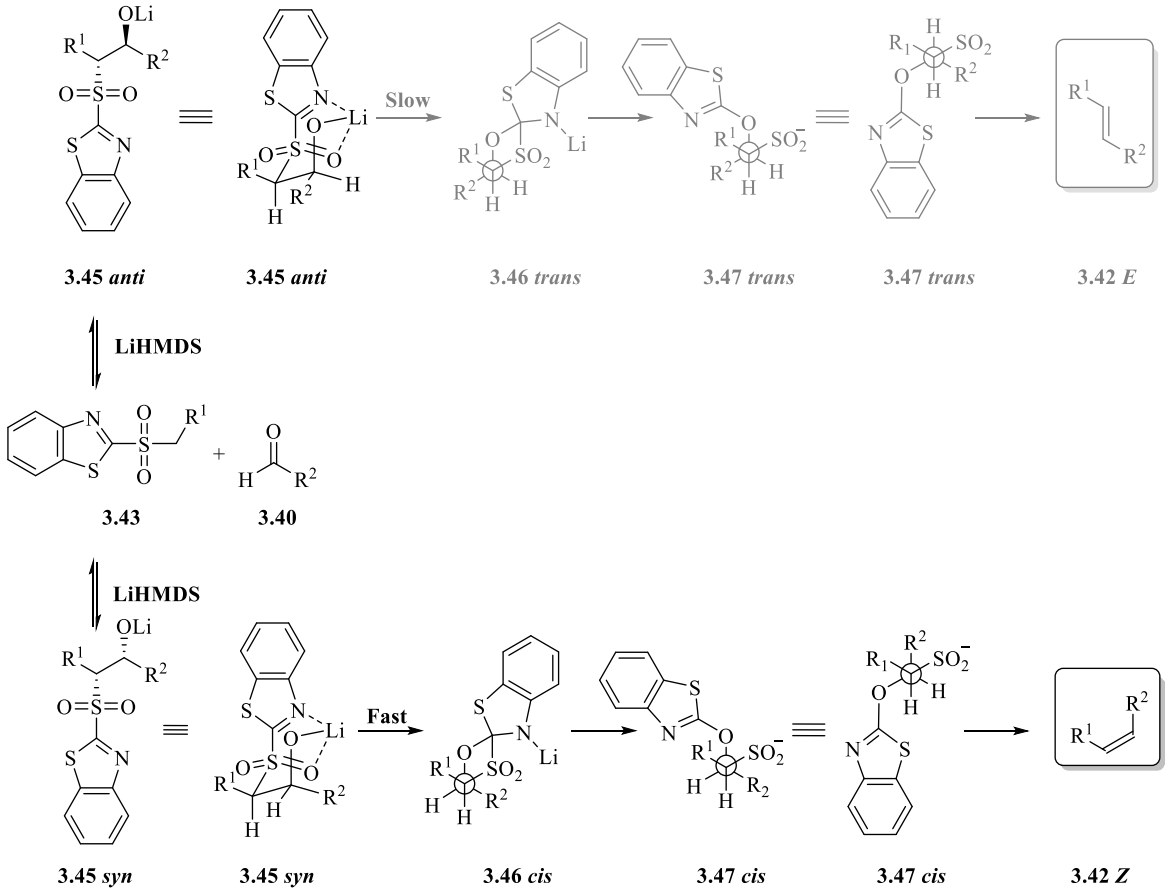
Scheme 3.14: Classical Julia olefination

In 1991, Sylvestre Julia and coworkers explored the replacement of the phenyl sulfones **3.39** used in the classical Julia olefination with the benzothiazol-2-ylsulfones **3.43** (Scheme 3.15).[87] Interestingly, this replacement significantly modifies the reaction pathway. Deprotonation of **3.43** by LDA is followed by reaction of **3.44** with the aldehyde **3.40** to furnish the alkoxide intermediate **3.45**. This alkoxide intermediate is highly reactive and thus results in the formation of the sulfinate **3.47** salt by a Smiles rearrangement. After spontaneous elimination of sulfur dioxide and lithium benzothiazolone **3.48**, the desired alkene **3.42** is finally formed. The intermediate **3.44** can also undergo self-condensation affording the undesired sulfone **3.40**.[88]



Scheme 3.15: Mechanism of the modified Julia olefination

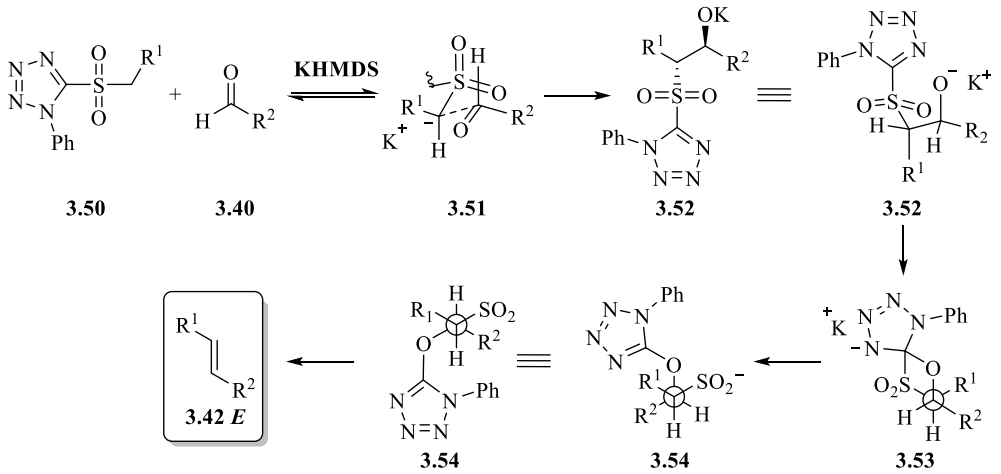
The *E* or *Z* selectivity in the modified Julia olefination is determined by the stereochemistry displayed at the sulfone intermediate **3.44** and it can be influenced to some extent by the reaction conditions. As shown in Scheme 3.16, after treatment of sulfone **3.43** with aldehyde **3.40** in the presence of a base, the *syn* and *anti* configuration of the alkoxide **3.45** are in equilibrium. When a small counterion such as lithium and a polar solvent is employed, a chelate will be formed and thus leading to the closed transition states **3.45** ***anti*** and **3.45** ***syn***. Due to the *gauche* interaction between R^1 and R^2 in **3.45** ***anti***, the Smiles rearrangement takes place faster on the other intermediate exhibiting the *syn* configuration, displacing the equilibrium towards the formation of the *Z* olefin.



Scheme 3.16: Selectivity in the modified Julia olefination with benzothiazol-2-ylsulfones

In 1998, Kocienski and coworkers reported the use of 1-phenyl-1*H*-tetrazol-5-yl sulfones **3.50** as a useful alternative to benzothiazol-2-ylsulfones **3.43** in the modified Julia olefination (Scheme 3.17).[89] This variation, called the Julia-Kocienski olefination (JKO), is distinguished by the ability to provide high levels of *trans* selectivity, and reduce the possibility to obtain the self-condensation product. When using polar solvents and a larger counterion in the base, such as

potassium, the open transition state **3.51** will be favoured. In this case, the *anti* configuration is observed in alkoxide **3.52** which leads to the *E* configuration obtained in the alkene **3.42**.

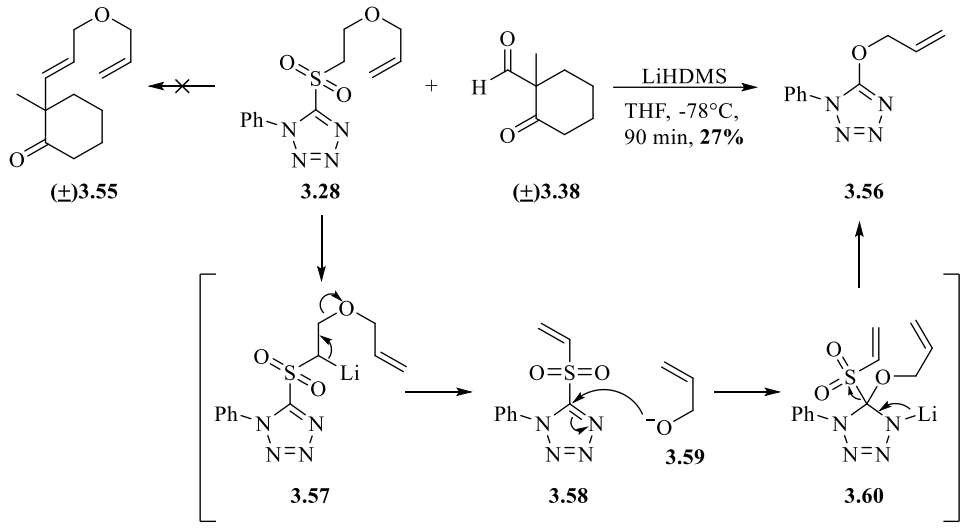


Scheme 3.17: Selectivity in the JKO with 1-phenyl-1*H*-tetrazol-5-yl sulfones **3.50**

Even though the reaction conditions play a key role in the diastereoselectivity of the product obtained, the size of R^1 and R^2 and their steric hindrance cannot be underestimated.

3.4.4.2 Julia-Kocienski olefination using sulfone 3.28 as starting material

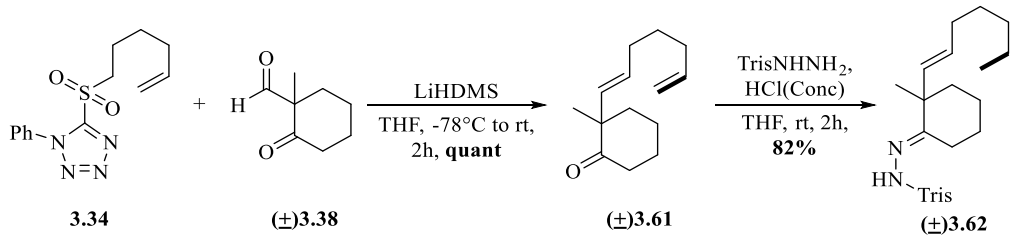
Unfortunately, when sulfone **3.28** was treated with LiHMDS followed by slow addition of aldehyde **(±)3.38**,[84] no traces of the desired diene **(±)3.55** were observed but compound **3.56** was obtained in 27% yield as the only isolable product (Scheme 3.18). A plausible mechanism for this transformation is proposed. After formation of carbanion **3.57** and due to the presence of oxygen in the molecule, the allylic alkoxide **3.59** and the sulfone **3.58** could be formed by β-elimination. Subsequent nucleophilic attack of alkoxide **3.59 on**to **3.58** would furnish the allylic ether **3.56** *via* the intermediate **3.60**.



Scheme 3.18: Julia-Kocienski olefination using sulfone **3.28**

3.4.4.3 Julia-Kocienski olefination using sulfone 3.34 as the starting material

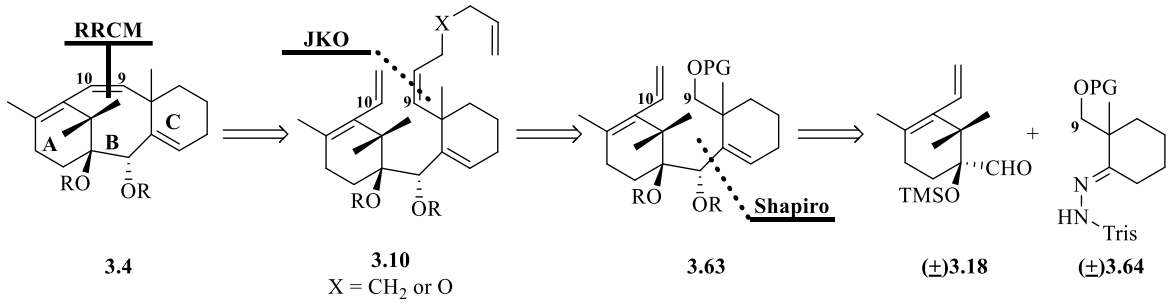
When the sulfone **3.34** was submitted to the previously described JKO reaction conditions, the desired diene **(±)3.61** was successfully isolated in quantitative yield (Scheme 3.19). Unfortunately, after the hydrazine condensation, reduction of the terminal double bond was observed and alkene **(±)3.62** was obtained in 82% yield. A precedent in the literature was found for the reduction of non-hindered olefins by *o*-nitrobenzenesulfonylhydrazide.[90]



Scheme 3.19: Julia Kocienski olefination using sulfone **3.34**

3.4.5 Revised synthesis plan

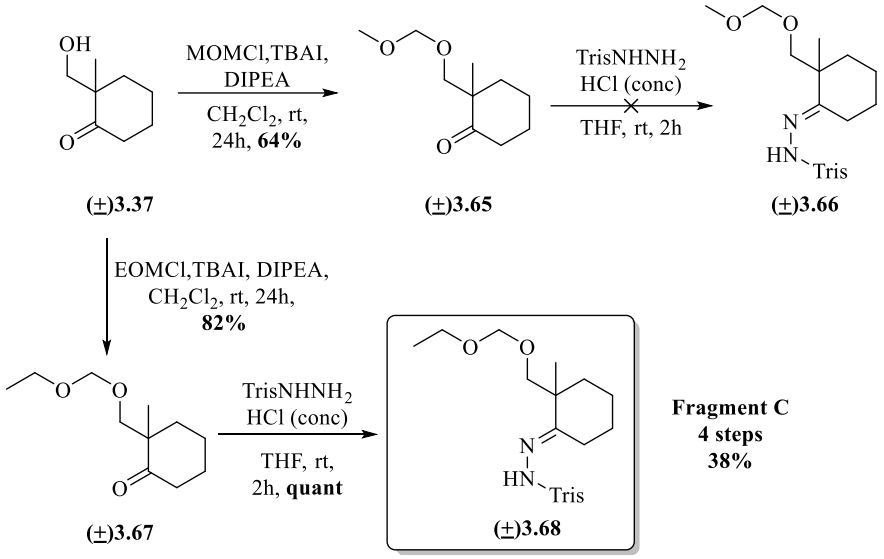
Since none of the hydrazones **3.21a-b** were successfully synthesised, a revised synthesis plan was proposed. As shown in Scheme 3.20, a later installation of the tether in **3.10** was envisioned by a JKO reaction on protected alcohol **3.63**, which in turn can be obtained from the successfully synthesised fragment A **(±)3.18** and the new fragment C **(±)3.64**. This approach is lees convergent but allows for diversification at a later stage in the synthesis.



Scheme 3.20: Revised synthesis plan

3.4.6 Fragment C: Endgame

Treatment of the previously synthesised alcohol **(±)3.37** with MOMCl afforded the desired protected alcohol **(±)3.65** in 64% yield (Scheme 3.21). Later attempts to form the hydrazone **(±)3.66** were unsuccessful and cleavage of the MOM ether was observed in the ^{1}H NMR spectrum of the crude reaction mixture. Finally, the new fragment C **(±)3.68** was obtained in 38% yield over 4 steps when the alcohol was protected as the corresponding ethoxymethyl (EOM) ether.

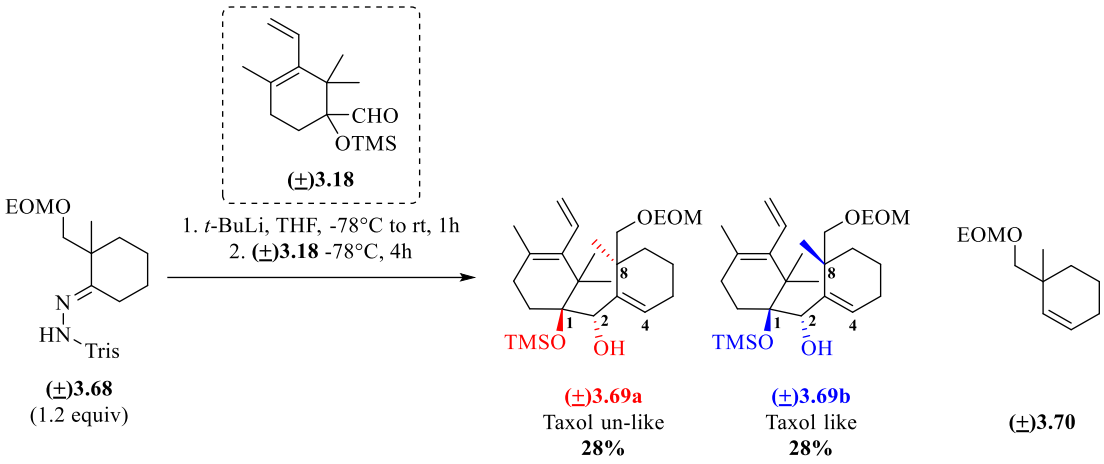


Scheme 3.21: Synthesis of fragment C **(±)3.68**

3.5 Shapiro coupling

With racemic fragments A **(±)3.18** and C **(±)3.68** in hand, the next step was to couple these two fragments. A Shapiro reaction using *t*-BuLi at -78°C afforded a 1:1 mixture of the two diastereomers **(±)3.69a** and **(±)3.69b** in 56% yield (Scheme 3.22). These two diastereomers, which can be separated by flash column chromatography, differ at the relative configuration at

C1 and C2 with respect to C8. They will be denominated as **Taxol-like** (**(±)3.69b**) and **Taxol-unlike** (**(±)3.69a**). Their relative stereochemistry have been determined by X-ray diffraction analysis of a later intermediate. Formation of alkene **(±)3.70** was also observed (42% yield) and is responsible for the low yield obtained for the desired products. Unfortunately, performing the reaction with an excess of *t*-BuLi did not increase the yield of **(±)3.69**.

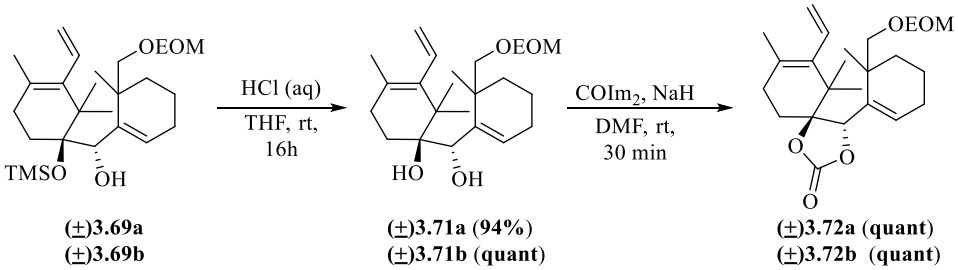


Scheme 3.22: Shapiro coupling using racemic fragments A **(±)3.18** and C **(±)3.68**

3.6 From Shapiro coupling to metathesis precursor

3.6.1 Synthesis of the Julia-Kocienski olefination precursors

After careful separation of both diastereomers **(±)3.69a-b**, the synthesis of the metathesis precursors **3.10** was explored (Scheme 3.20). As shown in scheme 3.23, diols **(±)3.71a-b** were successfully isolated in excellent yield after deprotection of the TMS group in the presence of aqueous HCl. Subsequent treatment with NaH and $COIm_2$ afforded the desired carbonates **(±)3.72a-b** in quantitative yield.

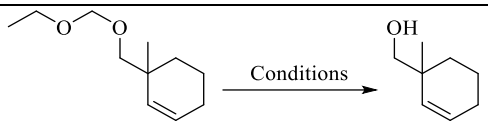


Scheme 3.23: Synthesis of advanced carbonates **(±)3.72a-b**

With **(±)3.72a-b** in hand, the deprotection of the EOM ether was first studied using **(±)3.70** as a model substrate (Table 3.1). Initially, deprotection using $ZnBr_2$ in dichloromethane was

attempted but unfortunately, decomposition of the starting material was observed (entry 1).[91] After treatment of **(±)3.70** with 6N aqueous HCl, 79% of the starting material was recovered but no signals of the deprotected alcohol **(±)3.73** were observed in the crude ^{1}H NMR spectrum (entry 2). Finally, when concentrated sulfuric acid was added dropwise to a solution of **(±)3.70** in a mixture of water and acetone, full conversion was observed and the desired alcohol **(±)3.73** was isolated in 40% yield (entry 3). The low yield obtained was attributed to the high product volatility.

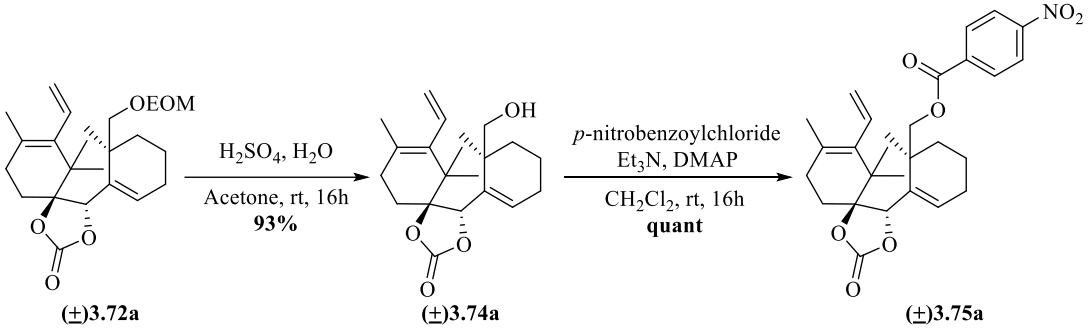
Table 3.1: EOM deprotection on **(±)3.70**



(±)3.70 **(±)3.73**

Entry	Conditions	Yield
1	$ZnBr_2$, CH_2Cl_2	Decomposition
2	6 M HCl (aq), H_2O, THF	79% recovered SM
3	H_2SO_4 (conc), H_2O, Acetone	40%*
*Low yield due to high product volatility		

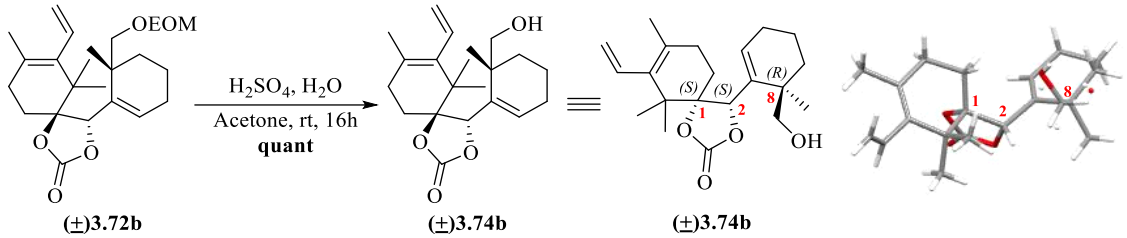
The optimised conditions for the EOM deprotection were applied to both diastereomers **(±)3.72a** and **(±)3.72b**. As shown in Scheme 3.24, the alcohol **(±)3.74a** was isolated in 93% yield and further derivatisation furnished the ester **(±)3.75a** in quantitative yield. Unfortunately, despite several crystallisation methods were tried on **(±)3.74a** and **(±)3.75a**, the formation of crystals of good enough quality to perform an X-ray diffraction analysis was not possible.



(±)3.72a **(±)3.74a** **(±)3.75a**

Scheme 3.24: EOM cleavage in **(±)3.72a** and its further derivatisation

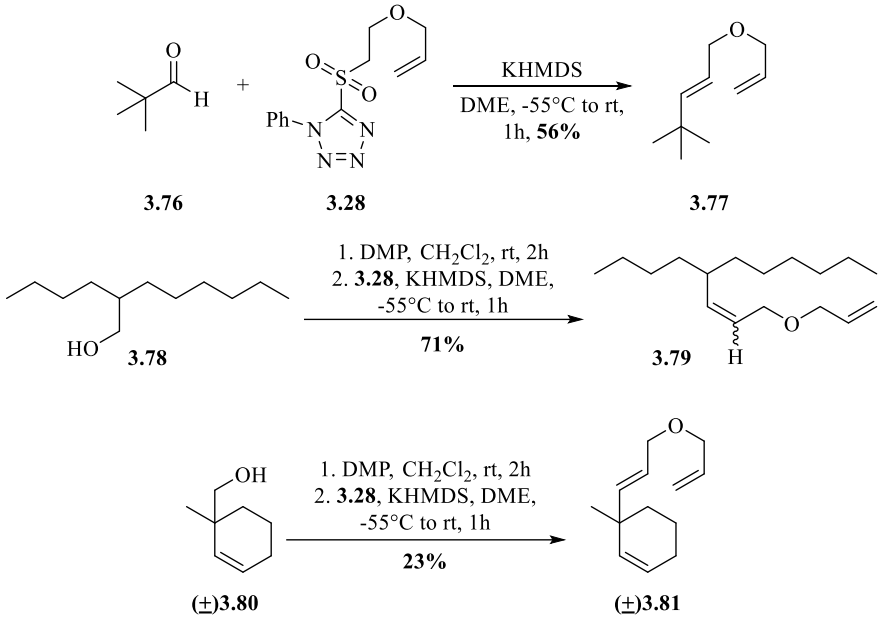
To our delight, when **(±)3.72b** was treated with sulfuric acid, it afforded the free alcohol **(±)3.74b** in quantitative yield as a crystalline solid (Scheme 3.25). Its X-ray diffraction analysis established the bicyclic structure of the product and confirmed that it possessed the required relative configuration at C1, C2 and C8 for Taxol.



Scheme 3.25: EOM cleavage in **(±)3.72b** and X-ray diffraction analysis of **(±)3.74b**

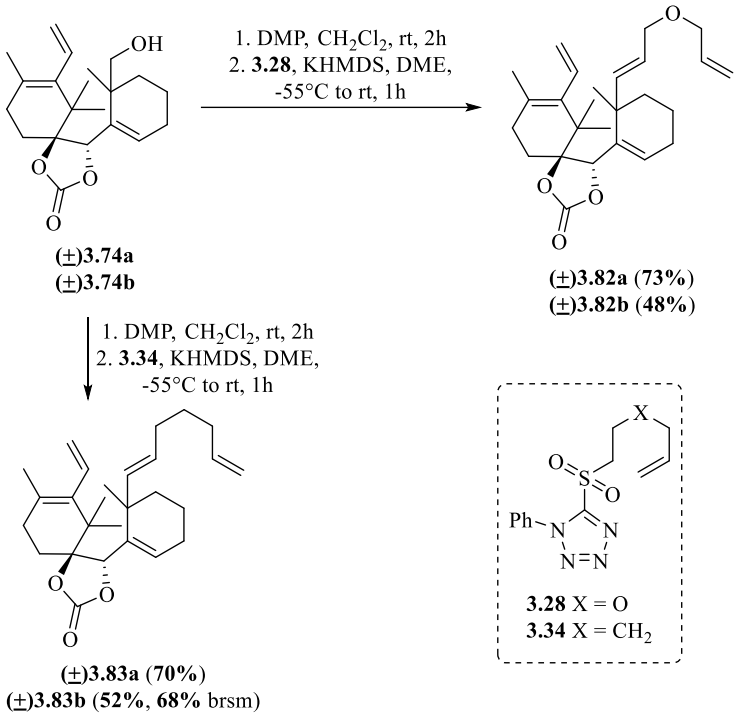
3.6.2 Metathesis precursors synthesis by a Julia-Kocienski olefination

Typically, it is advised to carry out the JKO reaction under "Barbier-like conditions", where the base is added to a mixture of the aldehyde and the sulfone. Due to the presence of an enolisable ketone in **(±)3.38**, this option was not possible when the JKO was first attempted using the sulfone **3.28** (Scheme 3.17). By installing the tether at a later stage, the presence of the enolisable ketone is avoided and thus the "Barbier-like conditions" can be employed. Initially, the aldehyde **3.76** was employed as a model substrate and the diene **3.77** was successfully isolated in 56% yield as single isomer without traces of the undesired ether **3.56** (Scheme 3.26). The oxidation-olefination sequence was then attempted on alcohols **3.78** and **(±)3.80** furnishing diene **3.79** as a 1:1 mixture of *E* and *Z* isomers and triene **(±)3.81** as the *E* isomer exclusively, respectively.



Scheme 3.26: Julia-Kocienski olefination reaction in model substrates

Finally, alcohols **(±)3.74a-b** were oxidised to the corresponding aldehydes and these were treated with KHMDS in the presence of either sulfone **3.28** or **3.34**, resulting in the formation of the RRCM precursors with (**(±)3.82a-b**) or without (**(±)3.83a-b**) oxygen (Scheme 3.27).



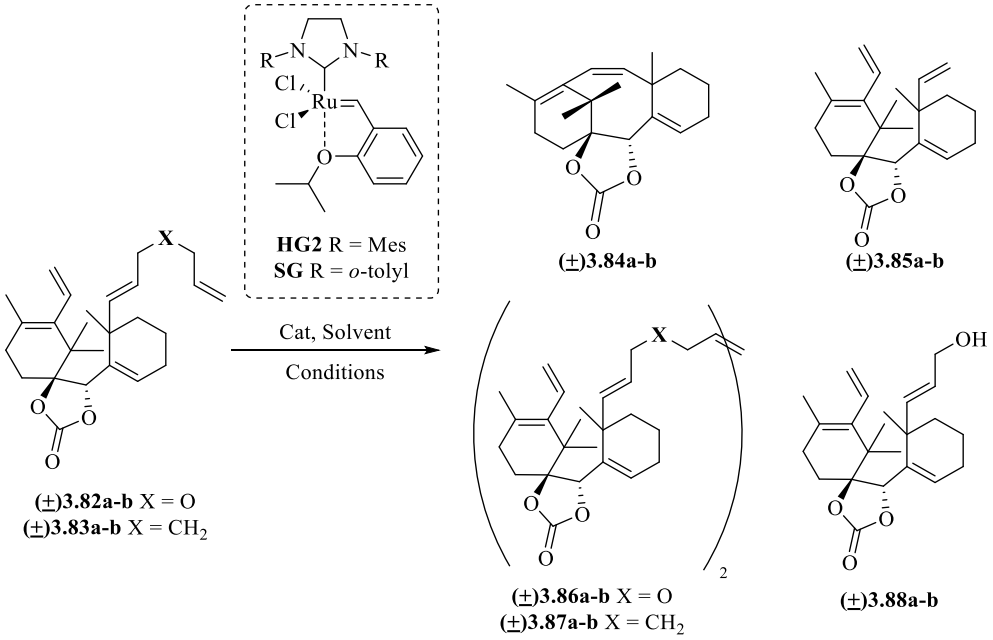
Scheme 3.27: Metathesis precursors synthesis by a Julia-Kocienski olefination

3.7 Relay ring-closing metathesis

The metathesis precursors **(±)3.82a-b** and **(±)3.83a-b** were then submitted to the diverse RRCM conditions outlined in Table 3.2. Initially, the oxygenated versions **(±)3.82a-b** were added dropwise to a refluxed solution of **HG2** in toluene, but traces of the migration-deprotection product **(±)3.88a-b** were observed in the crude ^{1}H NMR spectrum and only a small amount of the starting material was recovered (entries 1 and 2). The "infinite dilution" condition was employed to avoid the dimerization of the starting material by attempting an excess of the catalyst compared to the reagent at any time of the reaction. The use of DCE as solvent avoided the formation of the undesired **(±)3.88b** product but traces of the dimer **(±)3.86b** were observed when **(±)3.82b** was used as the starting material; suggesting that higher temperatures are required for the migration-deprotection process(entry 3).[92] Interestingly, the combination of the Stewart-Grubbs catalyst (**SG**)[93] and DCE afforded the truncated product **(±)3.85a** in 30% yield when 30 mol% of the catalyst were employed with the Taxol un-like metathesis precursor **(±)3.82a** (entry 4). On the basis of this result, we established that RRCM

had taken place but unfortunately the newly formed carbene at C9 was not reactive enough under the reaction conditions to form the desired B ring.

Table 3.2: RRCM attempts



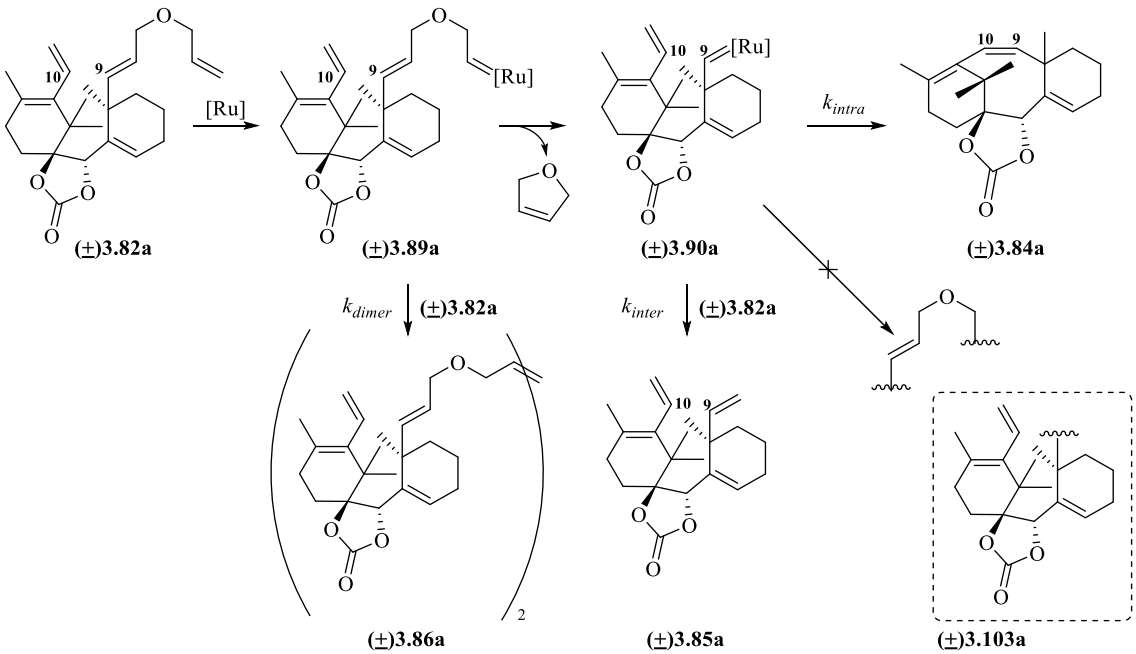
Entry	Starting Material	Cat	Solvent	Conditions	Outcome
1	**(±)3.82a**	**HG2** (30 mol%)	Toluene	110°C, 16 h	**(±)3.88a** (traces) **(±)3.82a** (10%)
2	**(±)3.82b**	**HG2** (30 mol%)	Toluene	110°C, 16 h	**(±)3.88b** (traces) **(±)3.82b** (21%)
3	**(±)3.82b**	**HG2** (30 mol%)	DCE	84°C, 2 days	Mixture of **(±)3.82b** and **(±)3.86b***
4	**(±)3.82a**	**SG** (30 mol%)	DCE	84°C, 2 days	**(±)3.85a** (30%)
5	**(±)3.82b**	**SG** (100 mol%)	DCE	84°C 3 days	**(±)3.82b** (50%) **(±)3.85b** (Traces)
6	**(±)3.83a**	**SG** (30 mol%)	Toluene	110°C, 2 days	**(±)3.85a** (traces) and **(±)3.83a***
7	**(±)3.83b**	**SG** (30 mol%)	Toluene	110°C, 2 days	**(±)3.85b** (traces) and **(±)3.83b***
8	**(±)3.83b**	**SG** (100 mol%)	Toluene	110°C, 3 days	**(±)3.83b** (60%)

* Due to similar R_F, separation of the products was not possible

Since increasing the reaction temperature was not a viable option due to the possible formation of **(±)3.88a-b**, we decided to test the non-oxygenated metathesis precursors **(±)3.83a-b**; unfortunately only traces of the truncated products **(±)3.85a-b** were confirmed by ^{1}H NMR

and HRMS (Table 3.2 entries 6 and 7). Finally, it was decided to explore whether an increase of the catalyst loading could form the desired tricyclic core with the desired Taxol-like configuration. Disappointingly, a 50-60% of the starting material was recovered when a full equivalent of **SG** was employed (entries 5 and 8). A comparison between entries 4 and 5 suggested that the Taxol-like configuration is less reactive towards the relay reaction than the Taxol-unlike one.

As shown in Scheme 3.28, the first carbene is formed in **(±)3.82a** at the most reactive terminal olefin position and thus **(±)3.89a** is obtained. According to the results outlined in Table 3.2, if toluene is used as solvent, the carbene **(±)3.89a** will react with another molecule of **(±)3.82a** and thus the dimerisation product **(±)3.86a** will be obtained. In the case of using DCE, when no dimerisation is observed, the desired relay reaction will occur and the new carbene **(±)3.90a** will be formed. At this stage, either an intra or an inter molecular reaction can occur. The desired tricyclic core **(±)3.84a** is the result of the intramolecular reaction, but unfortunately the reaction rate of the intermolecular reaction is higher and thus the truncation product **(±)3.85a** is obtained. When the reaction was performed using a full equivalent of catalyst (entries 5 and 8), it was expected to convert the starting material in to **(±)3.90** with a faster reaction rate than the reaction to form the truncated product **(±)3.85** or the dimer **(±)3.86**. The possible product (**(±)3.103**) of the intermolecular reaction between **(±)3.95a** and **(±)3.82a** does not occur due to the transition state leading to a highly hindered metallacyclobutane.

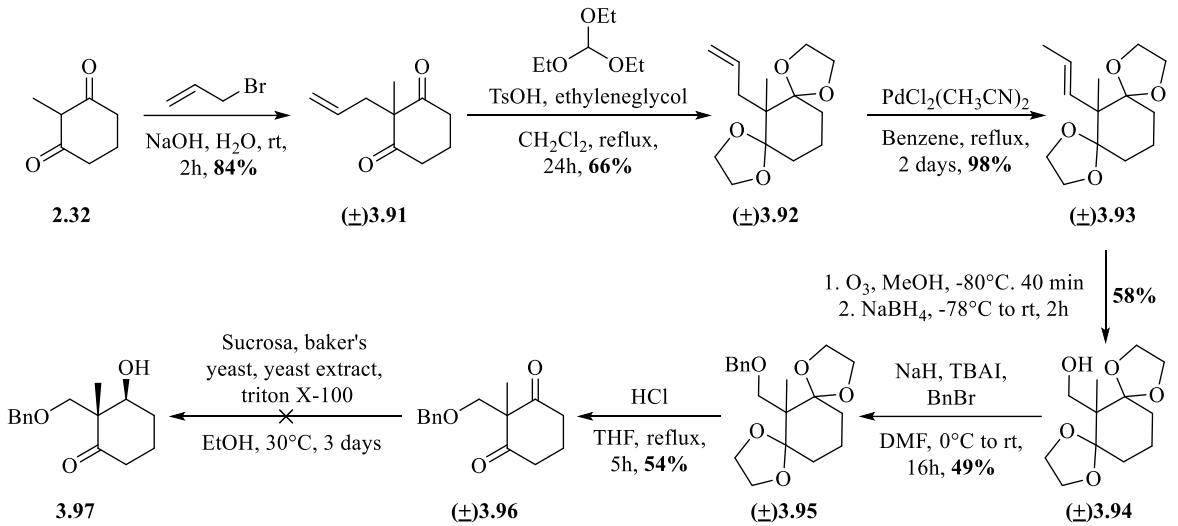


Scheme 3.28: RRCM on **(±)3.82a**

Further optimisation of the RRCM reaction, involving the use of more active catalysts or/and the substitution of the terminal olefin with an alkyl group to decrease its reactivity, is envisioned.

3.8 Towards the synthesis of an enantioenriched fragment C

In 2005, Nakada and coworkers reported an enantioselective reduction of prochiral 1,3-cycloalkanediones bearing a methyl group and a protected hydroxymethyl group at their C2 position using baker's yeast.[94] Following this precedent, addition of 3-bromopropene to diketone **2.32** furnished **(±)3.91**, which was then protected as *bis*-ketal **(±)3.92** (Scheme 3.29). Isomerisation of the double bond in the presence of a palladium catalyst afforded the thermodynamically more stable **(±)3.93** as a single isomer. After alkene **(±)3.93** was submitted to an ozonolysis reaction followed by a reductive workup, alcohol **(±)3.94** was successfully isolated in 58% yield. A subsequent protection-deprotection sequence furnished the desired diketone **(±)3.96** in 26% yield over two steps. Unfortunately, alcohol **3.97** was not obtained when the baker's yeast reduction was applied to **(±)3.96** and 41% of the staring material was recovered instead.

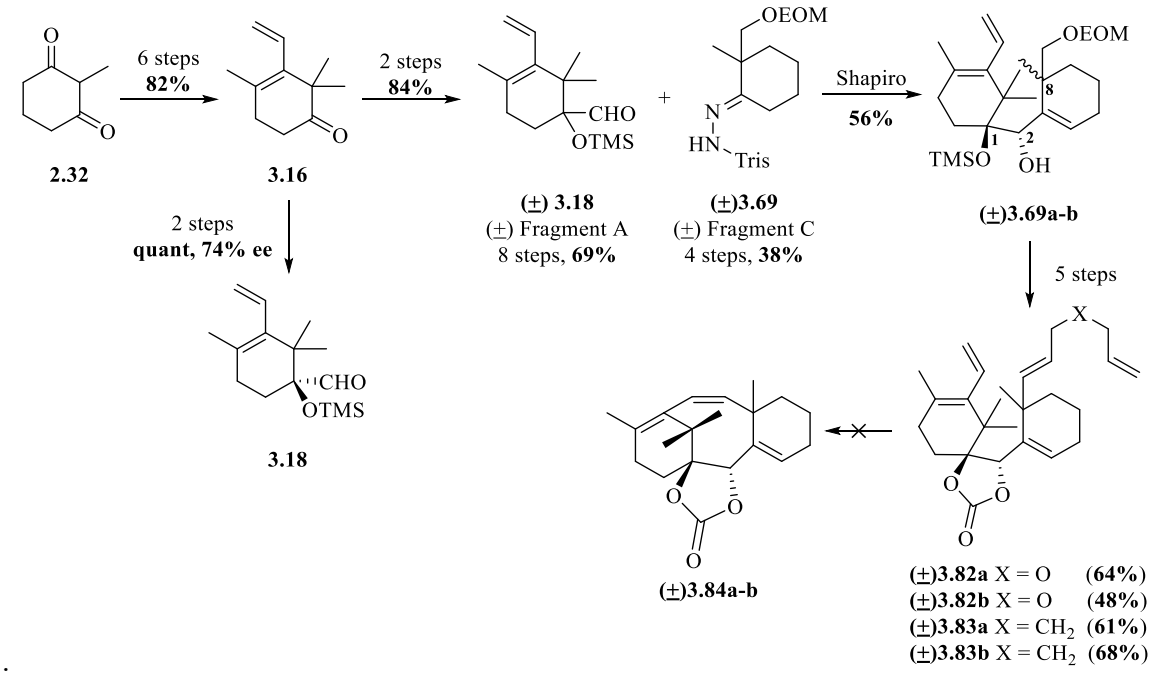


Scheme 3.29: Towards the synthesis of an enantioenriched fragment C

3.9 Conclusion

Racemic fragment A **(±)3.18** was synthesised in 69% yield over 8 steps while fragment C **(±)3.69** was obtained in 38% yield after 4 steps (Scheme 3.30). Additionally, an enantioenriched fragment A was synthesised in quantitative yield and 74% ee from ketone **3.16**. Coupling of both fragments was achieved by a Shapiro reaction and advanced intermediates **(±)3.82a-b** and

(±)3.83a-b were successfully synthesised, but unfortunately the construction of the ABC tricyclic core **(±)3.84a-b** has not yet been possible.



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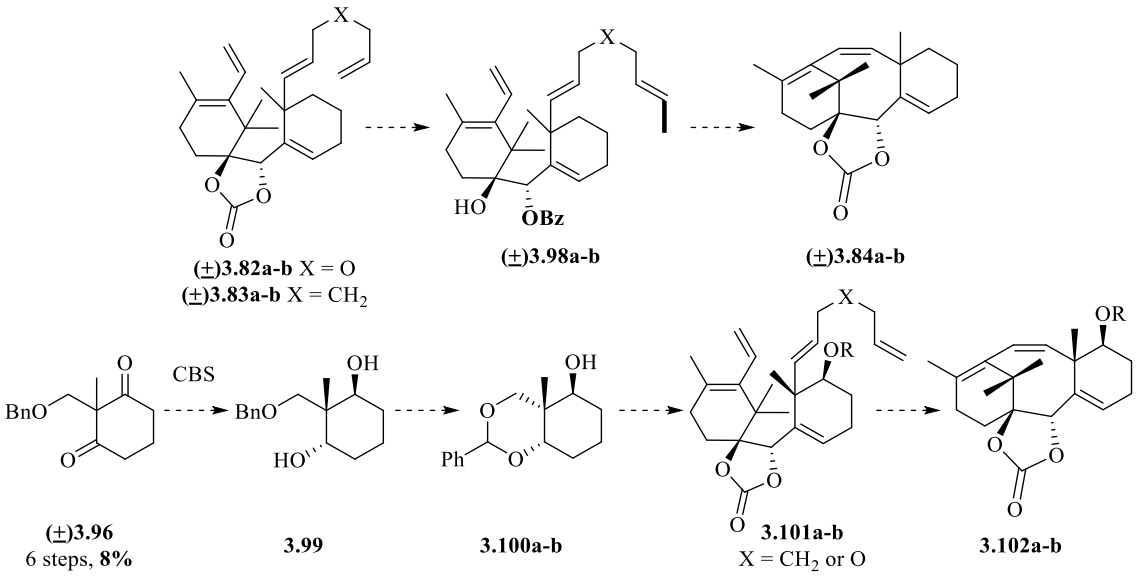
Scheme 3.30: Summary of results

As shown in Scheme 3.31, substitution of the terminal olefin in the metathesis precursors **(±)3.82a-b** and **(±)3.83a-b** is envisioned. In order to decrease the reactivity of the terminal olefin, an extra methyl group would be installed; in addition, the carbonate could be removed to decrease the ring strain in the desired ABC tricycles **(±)3.84a-b** . Furthermore, optimisation of the synthesis of **(±)3.96** must be performed[94] and its reduction towards the enantiopure **(±)3.99** and further cyclisation to **3.102a-b** should be studied.



Scheme 3.31: Perspectives

Chapter 4: Experimental

5.1 General

Apparatus

^{1}H NMR spectra were recorded on either a Bruker AVI DPX-400 or a Bruker DPX-400 (400 MHz) instrument. The chemical shifts are expressed in parts per million (ppm) referenced to TMS. Data are reported as follows: δ, chemical shift; multiplicity (recorded as br, broad; s, singlet; d, doublet; t, triplet; q, quartet and m, multiplet), coupling constants (*J* in Hertz, Hz), integration and assignment (aromatic, Ar). Assignments were obtained using *J*-mod experiments, and when necessary, COSY, NOESY, HMBC and HSQC experiments.

^{13}C NMR spectra were recorded on the same instruments at 100 MHz. The chemical shifts are expressed in parts per million (ppm), referenced to TMS.

Infrared (IR) spectra were obtained on a FTIR-8400 instrument with a Golden Gate™ attachment that uses a type II-a diamond as a single reflection element so that the IR spectrum of the compound (solid or liquid) could be detected directly (thin layer) and are reported in terms of frequency of absorption.

High resolution mass spectrometry (HRMS) was recorded under ESI and EI conditions by the analytical services at the University of Glasgow. Mass spectrum data are reported as m/z

Optical rotations were recorded on an Autopol V polarimeter.

Ozonolysis was carried out using a Degremont Technologies Triogen ozone generator.

HPLC analyses were obtained on a Shimadzu HPLC consisting of a Shimadzu DGU-20A5 degasser, Shimadzu LC-20AT liquid chromatography, Shimadzu CMB-20A communication bus module, Shimadzu SPD-M20A diode array detector and Shimadzu CTO-20A column. Analysis was performed using Shimadzu LabSolutions v5.42 software and separation was achieved using the column described. All HPLC traces of enantio-enriched compounds were compared to the traces of the corresponding racemic compounds prepared in an analogous fashion.

Chromatography

Flash chromatography was performed under forced flow conditions using HPLC graded solvents and EMD Geduran Silica Gel 60 as solid support.

Thin Layer Chromatography (TLC) was performed on Merck silica gel 60 covered aluminum sheets. TLC plates were developed under UV-light and/or with an acidic ethanolic anisaldehyde solution, a $KMnO_4$ solution or a cerium ammonium molybdate solution followed by heating.

Solvents and reagents

Dry solvents such as THF, CH_2Cl_2, Et_2O, CH_3CN, and toluene were collected from an in house solvent purification system (Pure-SolvTM 500 Solvent Purification System). Dry ethanol, methanol, DMF, DMSO, EtOAc, 1,2-dichoromethane were used from commercial bottles. All reagents were used directly from supplier, unless stated otherwise.

General conditions

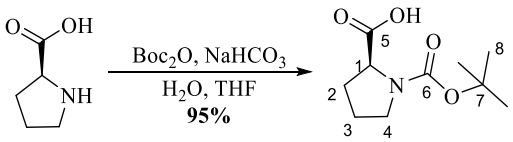
Reactions involving air-sensitive agents and dry solvents were performed in glassware that had been dried in an oven (150°C) or flame-dried prior to use. These reactions were carried out with the exclusion of air using an argon atmosphere. Solvents were degassed using the freeze and thaw method when stated.

Nomenclature

Chem Draw Ultra 14.0 momenclature was used for all compounds. For the description of NMR spectra, the numbering used follows the chain extension as described on the formula, not the IUPAC numbering.

5.2 Preparation of reagents

(*tert*-Butoxycarbonyl)-*L*-proline[95]



Chemical formula: $C_{10}H_{17}NO_4$

MW: 215.25

To a stirred solution of *L*-proline (346 mg, 3.00 mmol) in a saturated aqueous solution of $NaHCO_3$ (4.4 mL) at 0°C was slowly added a solution of Boc_2O (721 mg, 3.30 mmol, 1.10 equiv) in THF (1.6 mL). The reaction mixture was allowed to warm to room temperature and was stirred for 19 h. The THF was then removed under reduced pressure and the resulting solution was acidified to pH 2 by adding an aqueous solution of 1N HCl. The aqueous layer was extracted

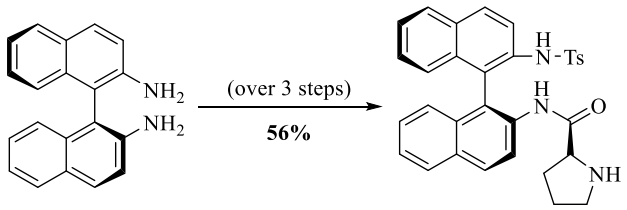
with EtOAc, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the protected carbamate as a pale white solid (615 mg, 2.85 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: The presence of two rotamers was observed in the ^{1}H NMR spectra in a 1:1 ratio. However, it was not possible to differentiate all signals corresponding to each rotamer.4.39–4.18 (m, 1H, ***CH-1***), 3.66–3.25 (m, 2H, ***CH_2-4***), 2.24 (d, *J* = 7.3 Hz, 1H, ***CH_2-2***), 2.15–1.79 (m, 3H, ***CH_2-2,3***), 1.43–1.39 (m, 9H, ***CH_3-8***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 179.0 (***COOH-5***), 175.6 (***COOH-5***), 156.1 (***CO-6***), 153.9 (***CO-6***), 81.2 (***C-7***), 80.30 (***C-7***), 59.0 (***CH-1***), 58.9 (***CH-1***), 46.9 (***CH_2-4***), 46.3 (***CH_2-4***), 30.8 (***CH_2-2***), 28.7 (***CH_2-2***), 28.3 (***CH_3-8***), 28.2 (***CH_3-8***), 24.3 (***CH_2-3***), 23.6 (***CH_2-3***).

HRMS (ESI): Calcd for $C_{10}H_{17}NNaO_4^+$ $[M+Na]^+$, 238.1050; found, 238.1044.

(*R*)-*N*-((*S*)-2'-((4-methylphenyl)sulfonamido)-[1,1'-binaphthalen]-2-yl)pyrrolidine-2-carboxamide (2.34)[69]



Chemical formula: $C_{32}H_{29}N_3O_3S$

MW: 535.66

To a stirred solution of (*S*)-[1,1'-binaphthalene]-2,2'-diamine (1.00 g, 3.52 mmol) in CH_2Cl_2 (42 mL) was added pyridine (3.12 mL, 3.87 mmol, 1.10 equiv) and *p*-toluenesulfonylchloride (650 mg, 3.4 mmol, 0.97 equiv). The reaction mixture was stirred at room temperature for 16 h. EtOAc was added to quench the reaction and the organic layer was washed with an aqueous solution of 1N HCl, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford a pink foam which was used in the next step without further purification.

To a stirred solution of (*tert*-butoxycarbonyl)-*L*-proline (972 mg, 4.51 mmol, 1.60 equiv) in THF (32 mL) at 0°C was slowly added triethylamine (630 μL, 4.51 mmol, 1.60 equiv) and ethyl orthoformate (32 μL, 5.4 mmol, 1.6 equiv). The reaction mixture was stirred at this temperature for 30 min before a solution of the previously obtained pink foam in THF (8 mL) was added dropwise, and the resulting solution was refluxed for 24 h. The reaction mixture was allowed to

cool to room temperature and filtered through a medium porosity sintered glass funnel. The filter cake was washed with THF and the solvent was then removed under reduced pressure to afford a pale-yellow foam which was used in the next step without further purification.

To a stirred solution of the previously obtained yellow foam in CH_2Cl_2 (30 mL) was added trifluoroacetic acid (4.6 mL, 60 mmol, 26 equiv). The reaction mixture was stirred at room temperature for 2 h. The resulting solution was cooled down to 0°C and a saturated aqueous solution of 2.5M NaOH (26 mL) was carefully added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:EtOAc (1:2) to (1:3) to afford the catalyst **2.34** as a white solid (1.05 g, 1.96 mmol, 56% for three steps).

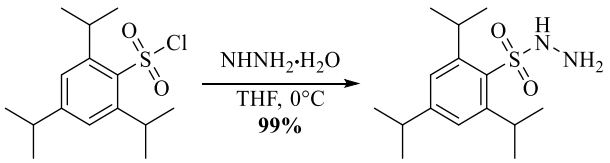
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.30 (bs, 1H, ***NH***), 8.81 (d, *J* = 9.0 Hz, 1H, ***CH-Ar***), 8.18 (d, *J* = 9.1 Hz, 1H, ***CH-Ar***), 8.06 (d, *J* = 9.0 Hz, 1H, ***CH-Ar***), 7.99 (d, *J* = 9.1 Hz, 1H, ***CH-Ar***), 7.94 (d, *J* = 8.2 Hz, 1H, ***CH-Ar***), 7.87 (d, *J* = 8.2 Hz, 1H, ***CH-Ar***), 7.50–7.33 (m, 4H, ***CH-Ar***), 7.18 (dd, *J* = 16.1, 7.9 Hz, 2H, ***CH-Ar***), 7.11 (d, *J* = 8.2 Hz, 2H, ***CH-Ar***), 6.93 (d, *J* = 8.4 Hz, 1H, ***CH-Ar***), 6.86 (d, *J* = 8.4 Hz, 1H, ***CH-Ar***), 6.32 (bs, 1H, ***NH***), 3.30 (dd, *J* = 9.5, 3.9 Hz, 1H, ***CH***), 2.36 (s, 3H, ***CH_3***), 2.22 (dd, *J* = 15.0, 8.3 Hz, 1H, ***CH_2***), 1.85–1.70 (m, 1H, ***CH_2***), 1.62–1.56 (m, 1H, ***CH_2***), 1.28–1.12 (m, 2H, ***CH_2***), 1.02 (bs, 1H, ***NH***), 0.73–0.60 (m, 1H, ***CH_2***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 173.3 (***CO***), 143.9, 136.4, 135.6, 133.7, 132.5, 132.1, 131.2, 130.7, 130.5, 130.1, 129.5, 128.6, 128.1, 127.4, 127.4, 125.6, 125.2, 125.1, 124.1, 120.6, 119.3, 119.2, 116.8, 60.4 (***CH***), 46.1 (***CH_2***), 30.52 (***CH_2***), 25.2 (***CH_2***), 21.5 (***CH_3***).

IR (thin film): 2960, 1598, 1462, 1190, 1157, 908, 738 cm^{-1}.

HRMS (ESI): Calcd for $C_{32}H_{29}N_3NaO_3S^+$ $[M+Na]^+$, 558.1822; found, 558.1798.

2,4,6-Triisopropylbenzenesulfonohydrazide[96]



Chemical formula: $C_{15}H_{26}N_2O_2S$

MW: 298.45

To a stirred solution of 2,4,6-triisopropylbenzenesulfonyl chloride (12.0 g, 39.6 mmol) in THF (60 mL) at -10°C was added hydrazone hydrate (4.36 mL, 87.1 mmol, 2.20 equiv) over 30 min. The reaction mixture was stirred at this temperature for 5 h. Water was added to quench the reaction and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure at 20°C to afford the hydrazide as a white solid (11.6 g, 38.8 mmol, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.20 (s, 2H, ***CH-Ar***), 5.45 (bs, 1H, ***NH***), 4.20–4.11 (m, 2H, ***CH***), 3.65 (bs, 2H, ***NH_2***), 2.97–2.89 (m, 1H, ***CH***), 1.31–1.26 (m, 18H, ***CH_3***).

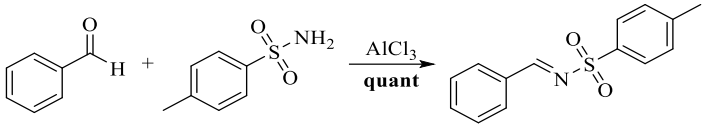
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 153.8 (***C-Ar***), 151.8 (***C-Ar***), 128.6 (***CH-Ar***), 124.0 (***CH-Ar***), 34.2 (***CH***), 29.8 (***CH***), 24.9 (***CH_3***), 23.5 (***CH_3***).

IR (thin film): 3315, 2957, 2866, 1598, 1460, 1425, 1361, 1321, 1161 cm^{-1}.

HRMS (ESI): Calcd for $C_{15}H_{26}N_2NaO_2S^+$ $[M+Na]^+$, 321.1607; found, 321.1595.

MP: 113°C (lit.[97] 113-114°C).

(*E*)-*N*-benzylidene-4-methylbenzenesulfonamide[98]



Chemical formula: $C_{14}H_{13}NO_2S$

MW: 259.32

A mortar was charged with anhydrous $AlCl_3$ (130 mg, 1.0 mmol, 0.50 equiv), *p*-methylbenzenesulfonamide (340 mg, 2.0 mmol, 1.0 equiv) and freshly distilled benzaldehyde (200 μL, 2.0 mmol, 1.0 equiv). The resulting mixture was grounded with a pestle at room temperature for 25 min. The solid mixture was then diluted with EtOAc and filtered through a pad of Celite. The filter cake was washed with EtOAc and the solvent was removed under reduced pressure to afford the benzenesulfonamide as a white solid (520 mg, 2.0 mmol, quant).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.02 (s, 1H, ***CH-CN***), 7.92–7.83 (m, 4H, ***CH-Ar***), 7.60 (d, *J* = 7.4 Hz, 1H, ***CH-Ar***), 7.48 (d, *J* = 7.7 Hz, 2H, ***CH-Ar***), 7.34 (d, *J* = 8.0 Hz, 2H, ***CH-Ar***), 2.43 (s, 3H, ***CH_3***).

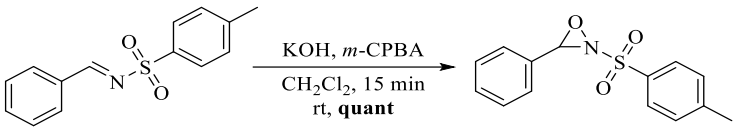
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 170.1 (***CH-CN***), 144.6(***C-Ar***), 135.1 (***C-Ar***), 134.9 (***CH-Ar***), 132.4 (***C-Ar***), 131.3 (***CH-Ar***), 129.8 (***CH-Ar***), 129.1 (***CH-Ar***), 128.1 (***CH-Ar***), 21.6 (***CH_3***).

IR (thin film): 3356, 3259, 1699, 1597, 1155, 1089 cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{13}NNaO_2S^+$ $[M+Na]^+$, 282.0559; found, 282.0551.

MP: 80°C (lit.[99] 79-82°C).

3-Phenyl-2-tosyl-1,2-oxaziridine[100]



Chemical formula: $C_{14}H_{13}NO_3S$

MW: 275.32

To a stirred suspension of powdered KOH (163 mg, 4.07mol, 3.50 equiv) and *m*-CPBA (219 mg, 1.28 mol, 1.10 equiv) in CH_2Cl_2 (0.58 mL) was added a solution of (*E*)-*N*-benzylidene-4-methyl benzenesulfonamide in CH_2Cl_2 (300 mg, 1.16 mmol) in CH_2Cl_2 (1.74 mL). The resulting solution was stirred at room temperature for 15 min and the solvent was the removed under reduced pressure to afford the oxaziridine as a white solid (318 mg, 1.16 mmol, quant).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.93 (d, *J* = 8.3 Hz, 2H, ***CH-Ar***), 7.53–7.29 (m, 7H, ***CH-Ar***), 5.45 (s, 1H, ***CH-CHNO***), 2.46 (s, 3H, ***CH_3***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 146.3 (***C-Ar***), 131.3 (***C-Ar***), 131.3 (***CH-Ar***), 130.4 (***C-Ar***), 130.0 (***CH-Ar***), 129.3 (***CH-Ar***), 128.6 (***CH-Ar***), 128.1 (***CH-Ar***), 76.2 (***CH-CHNO***), 21.7 (***CH_3***).

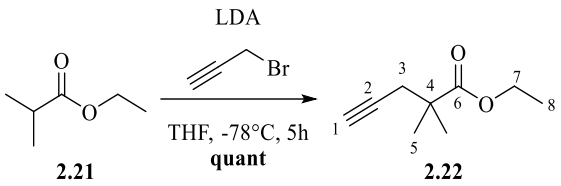
IR (thin film): 2972, 1417, 1379, 1089, 1049 cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{13}NNaO_3S^+$ $[M+Na]^+$, 298.0508; found, 282.0503.

MP: 70°C.

5.3 Experimental procedures and products characterisation

Ethyl 2,2-dimethylpent-4-ynoate (2.22)[64]



Chemical formula: $C_9H_{14}O_2$

MW: 154.21

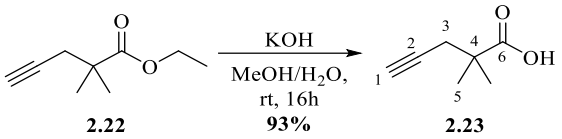
To a stirred solution of diisopropylamine (11.5 mL, 81.9 mmol, 1.10 equiv) in THF (200 mL) at -78°C was added dropwise *n*BuLi (33.0 mL, 2.38M in hexane, 78.5 mmol, 1.05 equiv). The resulting solution was stirred at this temperature for 30 min and ethyl isobutyrate **2.21** (10.0 mL, 74.5 mmol) in THF (150 mL) was added dropwise over 4 h. The reaction mixture was allowed to warm to 0°C for 45 min and then cooled down to -78°C. A solution of propargyl bromide (8.7 mL, 80% in toluene, 78.3 mmol, 1.05 equiv) in THF (50 mL) was added and the mixture was stirred at room temperature for 16 h. A saturated aqueous solution of NH_4Cl. was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (95:5) to afford the ester **2.22** as a pale yellow oil (11.5 g, 74.5 mmol, quant).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.19–4.07 (m, 2H, ***CH_2-7***), 2.43 (d, *J* = 2.6 Hz, 2H, ***CH_2-3***), 1.99 (t, *J* = 2.6 Hz, 1H, ***CH-1***), 1.26 (s, 6H, ***CH_3-5***), 1.28–1.22 (t, *J* = 7.1 Hz, 3H ***CH_3-8***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 176.6 (***CO-6***), 81.1 (***C-2***), 70.4 (***CH-1***), 60.7 (***CH_2-7***), 41.9 (***C-4***), 29.5 (***CH_2-3***), 24.5 (2***CH_3-5***), 14.2 (***CH_3-8***).

IR (thin film): 3293, 2120, 1717, 1217 cm^{-1}.

2,2-Dimethylpent-4-ynoic acid (2.23)[64]



2.22 **2.23**

Chemical formula: $C_7H_{10}O_2$

MW: 126.16

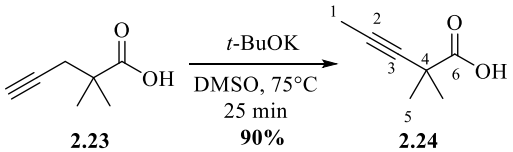
To a stirred solution of propargylated ethyl ester **2.22** (22.7 g, 147 mmol) in MeOH (290 mL) and water (118 mL) was added KOH (13.2 g, 235 mmol, 1.60 equiv). The resulting solution was stirred for 16 h at room temperature. A 2N aqueous HCl solution was added to quench the reaction and adjust the pH to 1. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the acid **2.23** (17.3 g, 137 mmol, 93%) as a pale yellow oil which was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.46 (d, *J* = 2.6 Hz, 2H, ***CH_2-3***), 2.03 (t, *J* = 2.6 Hz, 1H, ***CH-1***), 1.32 (s, 6H, 2***CH_3-5***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 183.2 (***COOH-6***), 80.6 (***C-2***), 70.7 (***CH-1***), 41.9 (***C-4***), 29.2 (***CH_2-3***), 24.3 (2***CH_3-5***).

IR (thin film): 3304, 2976, 1707, 1473 cm^{-1}.

2,2-Dimethylpent-3-ynoic acid (2.24)[64]



2.23 **2.24**

Chemical formula: $C_7H_{10}O_2$

MW: 126.16

To a stirred solution of acid **2.23** (8.18 g, 64.8 mmol) in DMSO (94 mL) was added potassium *tert*-butoxide (18.2 g, 162 mmol, 2.50 equiv) and the resulting solution was stirred at 75°C for 25 min. A 1N aqueous HCl solution was added to quench the reaction and adjust the pH to 1. The

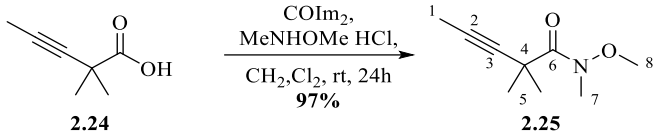
aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with 1N aqueous HCl and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (1:1) to afford the acid **2.24** as a pale yellow oil (7.38 g, 58.5 mmol, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.81 (s, 3H, ***CH_3-1***), 1.47 (s, 6H, 2***CH_3-5***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 180.8 (***COOH-6***), 80.7 (***C-3***), 78.0 (***C-2***), 38.2 (***C-4***), 27.2 (2***CH_3-5***), 3.5 (***CH_3-1***).

IR (thin film): 3298, 1716, 1288, 1174, 1056 cm^{-1}.

N-Methoxy-*N*,2,2-trimethylpent-3-ynamide (2.25)[64]



2.24 **2.25**

Chemical formula: $C_9H_{15}NO_2$

MW: 169.22

To a stirred solution of acid **2.24** (14.7 g, 116 mmol) in dichloromethane (250 mL) was added 1,1'-carbonyl diimidazole (20.9 g, 129 mmol, 1.10 equiv). The resulting mixture was stirred for 30 min, before *N*,*O*-dimethylhydroxylamine hydrochloride (12.5 g, 128 mmol, 1.10 equiv) was added. The reaction mixture was then stirred at room temperature for 24 h. A 1N aqueous HCl solution was added to quench the reaction and the resulting mixture was stirred vigorously for 10 min. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with 1N aqueous HCl and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (95:5) to afford the Weinreb amide **2.25** as a colourless oil (19.1 g, 113 mmol, 97%).

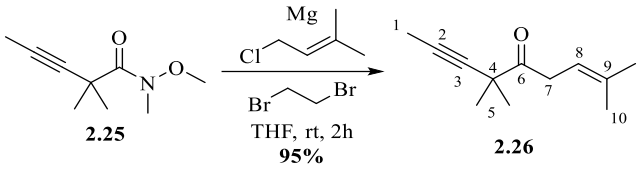
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.74 (s, 3H, ***CH_3-8***), 3.21 (s, 3H, ***CH_3-7***), 1.82 (s, 3H, ***CH_3-1***), 1.43 (s, 6H, 2***CH_3-5***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 174.0 (***C-6***), 82.9 (***C-3***), 76.5 (***C-2***), 60.5 (***CH_3-8***), 37.1 (***C-4***), 33.8 (***CH_3-7***), 27.3 (***2CH_3-5***), 3.7 (***CH_3-1***).

IR (thin film): 2983, 2933, 1658, 1454, 1382, 1355, 1253, 1170, 999 cm^{-1}.

HRMS (ESI): Calcd for $C_9H_{15}NNaO_2^+$ [M+Na]$^+$, 192.0995; found, 192.0996.

2,6,6-Trimethylnon-2-en-7-yn-5-one (2.26)[64]



Chemical formula: $C_{12}H_{18}O$

MW: 178.28

To a stirred suspension of magnesium turnings (27.1 g, 1.10 mol, 10.0 equiv) in THF (150 mL) was added 1,2-dibromoethane (0.1 mL), followed by a dropwise addition of prenyl chloride (14.2 mL, 125 mmol, 1.10 equiv) over 45 min. The resulting suspension was stirred for an additional 15 min. Then the freshly made Grignard reagent was added *via* cannula to a solution of Weinreb amide **2.25** (19.1 g, 113 mmol) in THF (350 mL). The resulting mixture was stirred at room temperature for 2 h. A saturated aqueous solution of NH_4Cl was added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (97:3) to afford the ketone **2.26** as a colourless oil (19.2 g, 107 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.29–5.34 (m, 1H, ***CH-8***), 3.48 (d, *J* = 6.9 Hz, 2H, ***CH$_2$-7***), 1.83 (s, 3H, ***CH$_3$-1***), 1.75 (s, 3H, ***CH$_3$-10***), 1.63 (s, 3H, ***CH$_3$-10***), 1.32 (s, 6H, 2***CH$_3$-5***).

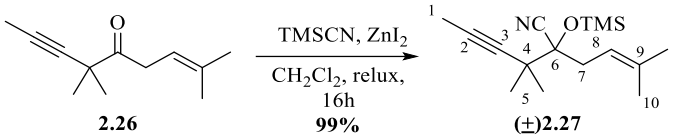
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 209.3 (***CO-6***), 134.9 (***C-9***), 116.7 (***CH-8***), 82.3 (***C-3***), 78.9 (***C-2***), 43.5 (***C-4***), 37.3 (***CH$_2$-7***), 26.3 (2***CH$_3$-5***), 25.7 (***CH$_3$-10***), 18.0 (***CH$_3$-10***), 3.6 (***CH$_3$-1***)

IR (thin film): 2976, 2920, 1720, 1424, 1452 cm^{-1}.

HRMS (ESI): Calcd for $C_{12}H_{18}NaO$, 201.1250; found, 201.1243.

5-Methyl-2-(2-methylpent-3-yn-2-yl)-2-((trimethylsilyl)oxy)hex-4-enenitrile ((±)2.27)[64]

Method A



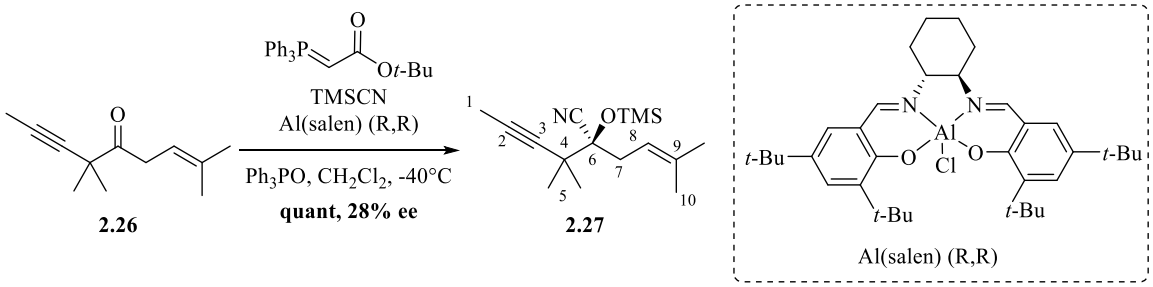
2.26 **(±)2.27**

Chemical formula: $C_{16}H_{27}NOSi$

MW: 277.48

To a stirred solution of ketone **2.26** (300 mg, 1.68 mmol) in CH_2Cl_2 (5 mL) was added ZnI_2 (108 mg, 0.338 mmol, 0.20 equiv) and TMSCN (444 μL, 3.38 mmol, 2.0 equiv). The reaction mixture was refluxed for 16 h and then allowed to cool down to room temperature. The volatiles were removed under reduced pressure with a trap of aqueous NaOCl/NaOH set up to quench the excess of TMSCN. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (99:1) to afford the cyanohydrin **(±)2.27** as a colourless oil (461 mg, 1.63 mmol, 99%).

Method B



2.26 **2.27**

To a stirred solution of ketone **2.26** (270 mg, 1.51 mmol) in CH_2Cl_2 (1.50 mL) at -40°C was added (salen)AlCl (*R,R*) (91 mg, 0.15 mmol, 0.10 equiv), (*tert*-butoxycarbonylmethylene) triphenylphosphorane (58 mg, 0.15 mmol, 0.10 equiv) and Ph_3PO (210 mg, 0.75 mmol, 0.50 equiv). The resulting solution was stirred at -40°C for 30 min before TMSCN (400 μL, 3.0 mmol, 2.0 equiv) was added dropwise. The reaction mixture was stirred for 4 days at -40°C and then allowed to warm to room temperature. The volatiles were removed under reduced pressure with a trap of aqueous NaOCl/NaOH set up to quench the excess of TMSCN. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (99:1) to afford the cyanohydrin **2.27** as a colourless oil (421 mg, 1.51 mmol, quant). The separation of the two isomers was not possible by chiral HPLC when using either an AD-H or an OD-H column with

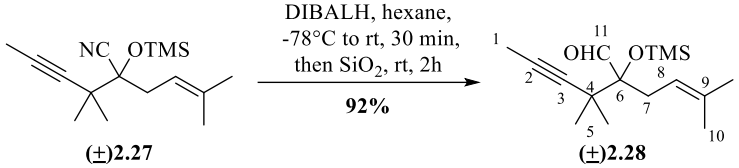
an injection volume of 20 μL and using 5-10% *i*PrOH in hexanes. After transformation to the aldehyde **(±)2.28**, it was coupled with the hydrazone **2.71** and the enatiomeric excess was calculated based on the diastereomer ratio of **2.72a** and **2.72b** (^{1}H NMR and ^{13}C NMR in the appendix section).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.41–5.29 (m, 1H, ***CH-8***), 2.72 (dd, *J* = 14.5, 7.0 Hz, 1H, ***CH_2-7***), 2.51 (dd, *J* = 14.5, 8.0 Hz, 1H, ***CH_2-7***), 1.81 (s, 3H, ***CH_3-1***), 1.78 (s, 3H, ***CH_3-10***), 1.66 (s, 3H, ***CH_3-10***), 1.34 (s, 3H, ***CH_3-5***), 1.24 (s, 3H, ***CH_3-5***), 0.21 (s, 9H, ***$Si(CH_3)_3$***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 136.2 (***C-9***), 120.2 (***CH-8***), 118.7(***CN***), 82.5 (***C-3***), 79.5 (***C-2***), 79.2 (***C-6***), 40.7 (***C-4***), 36.0 (***CH_2-7***), 26.0 (***CH_3-5***), 25.9 (***CH_3-5***), 23.5 (***CH_3-10***), 18.1 (***CH_3-10***), 3.6 (***CH_3-1***), 1.5 (***$Si(CH_3)_3$***).

HRMS (ESI): Calcd for $C_{16}H_{27}NNaO_2Si^+$ $[M+Na]^+$, 300.1754; found, 300.1750.

5-Methyl-2-(2-methylpent-3-yn-2-yl)-2-((trimethylsilyl)oxy)hex-4-enal ((±)2.28)[64]



(±)2.27 **(±)2.28**

Chemical formula: $C_{16}H_{28}O_2Si$

MW: 280.48

To a stirred solution of cyanohydrin **(±)2.27** (417 mg, 1.50 mmol) in freshly distilled hexane (24.5 mL) at -78°C was added DIBALH (2.25 mL, 1 M in hexane, 2.25 mmol, 1.50 equiv). The reaction mixture was allowed to warm to 0°C and was stirred at this temperature for 30 min. The mixture was then cooled down to -78°C, and EtOAc was added dropwise. The resulting mixture was stirred at this temperature for 20 min and then SiO_2 (5.3 g) was added. The reaction mixture was then allowed to warm to room temperature and stirred for 2 h. The resulting suspension was filtered, and the silica was washed thoroughly with EtOAc. The solvent was removed under reduced pressure and the crude mixture was then purified by flash chromatography using pentane: CH_2Cl_2 (95:5) to (9:1) to afford the aldehyde **(±)2.28** as a colourless oil (171 mg, 0.61 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.82 (s, 1H, ***CHO***), 5.05–4.92 (m, 1H, ***CH-8***), 2.92 (dd, *J* = 14.8, 7.4 Hz, 1H, ***CH_2-7***), 2.45 (dd, *J* = 14.8, 7.8 Hz, 1H, ***CH_2-7***), 1.81 (s, 3H, ***CH_3-1***), 1.67

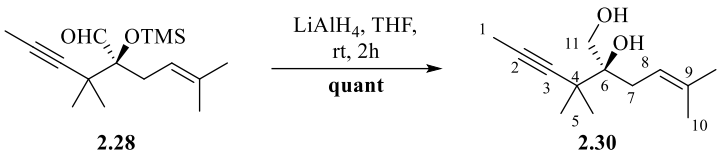
(s, 3H, ***CH₃-10***), 1.61 (s, 3H, ***CH₃-10***), 1.22 (s, 3H, ***CH₃-5***), 1.07 (s, 3H, ***CH₃-5***), 0.12 (s, 9H, ***Si(CH₃)₃***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 204.4 (***CHO***), 134.7 (***C-9***), 118.8 (***CH-8***), 87.3 (***C-6***), 84.0 (***C-3***), 78.8 (***C-2***), 37.4 (***C-4***), 32.1 (***CH₂-7***), 25.9 (***CH₃-10***), 25.6 (***CH₃-5***), 24.4 (***CH₃-5***), 17.8 (***CH₃-10***), 3.6 (***CH₃-1***), 2.7 (***Si(CH₃)₃***).

IR (thin film): 2976, 1738, 1377, 1249, 1153 cm^{-1}.

HRMS (ESI): Calcd for $C_{16}H_{28}NaO_2Si^+$ $[M+Na]^+$, 303.1751; found, 303.1738.

5-Methyl-2-(2-methylpent-3-yn-2-yl)hex-4-ene-1,2-diol (2.30)



2.28 **2.30**

Chemical formula: $C_{13}H_{22}O_2$

MW: 210.32

To a stirred suspension of $LiAlH_4$ (23 mg, 0.60 mmol, 1.5 equiv) in THF (1.0 mL) was added a solution of the aldehyde **2.28** (177 mg, 0.40 mmol) in THF (1.0 mL). The reaction mixture was stirred at room temperature for 2 h. An aqueous solution of Rochelle salt was added to quench the reaction and the resulting mixture was stirred at room temperature for 16h. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the diol **(±)2.30** as a colourless oil (127 mg, 0.60 mmol, quant).

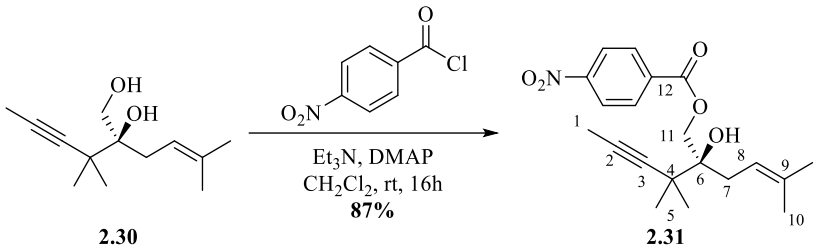
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.25–5.17 (m, 1H, ***CH-8***), 3.59 (dd, *J* = 11.4, 4.7 Hz, 1H, ***CH₂-11***), 3.50 (dd, *J* = 11.3, 6.0 Hz, 1H, ***CH₂-11***), 2.34–2.19 (m, 3H, ***CH₂-7, OH***), 2.13–2.02 (m, 1H, ***OH***), 1.67 (s, 3H, ***CH₃-1***), 1.62 (s, 3H, ***CH₃-10***), 1.53 (s, 3H, ***CH₃-10***), 1.12 (s, 6H, 2***CH₃-5***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 135.5 (***C-9***), 119.6 (***CH-8***), 84.9 (***C-3***), 78.3 (***C-6***), 76.1 (***C-2***), 65.3 (***CH₂-11***), 39.3 (***C-4***), 31.9 (***CH₂-7***), 26.1 (***CH₃-5***), 25.0 (***CH₃-10***), 24.9 (***CH₃-10***), 17.9 (***CH₃-5***), 3.5 (***CH₃-1***).

IR (thin film): 2970, 2918, 1452, 1382, 1265, 1030 cm^{-1}.

HRMS (ESI): Calcd for $C_{13}H_{22}NaO_2^+$ $[M+Na]^+$, 233.1512; found, 233.1506.

2-Hydroxy-5-methyl-2-(2-methylpent-3-yn-2-yl)hex-4-en-1-yl 4-nitrobenzoate (2.31)



2.30 **2.31**

Chemical formula: $C_{20}H_{25}NO_5$

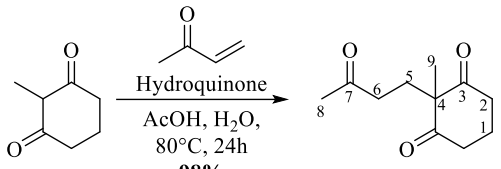
MW: 359.42

To a stirred solution of diol **2.30** (115 mg, 0.550 mmol) in CH_2Cl_2 (12 mL) was added triethylamine (200 μL, 1.43 mmol, 2.60 equiv), DMAP (68 mg, 0.55 mmol, 1.0 equiv) and 4-nitrobenzoyl chloride (204 mg, 1.10 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature for 16 h. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (9:1) to (6:4) to afford the alcohol **2.31** as a pale yellow oil (172 mg, 0.48 mmol, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.20–8.30 (m, 4H, ***CH-Ar***), 5.33 (t, *J* = 7.6 Hz, 1H, ***CH-8***), 4.52–4.46 (m, 2H, ***CH_2-11***), 2.45–2.57 (m, 2H, ***CH_2-7***), 2.24 (s, 1H, ***OH***), 1.77 (s, 3H, ***CH_3-1***), 1.71 (s, 3H, ***CH_3-10***), 1.61 (s, 3H, ***CH_3-10***), 1.33 (bs, 6H, ***CH_3-5***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 164.6 (***CO-12***), 150.6 (***C-NO_2***), 135.7 (***C-Ar***), 135.5 (***C-9***), 130.8 (***CH-Ar***), 123.6 (***CH-Ar***), 118.8 (***CH-8***), 84.1 (***C-3***), 78.5 (***C-6***), 75.5 (***C-2***), 68.0 (***CH_2-11***), 39.9 (***C-4***), 32.0 (***CH_2-7***), 26.1 (***CH_3-5***), 25.2 (***CH_3-10***), 25.0 (***CH_3-10***), 17.9 (***CH_3-5***), 3.6 (***CH_3-1***).

2-Methyl-2-(3-oxobutyl)cyclohexane-1,3-dione (2.33)[64]



2.32 **2.33**

Chemical formula: $C_{11}H_{16}O_3$

MW: 196.25

To a stirred solution of 2-methylcyclohexadione **2.32** (10.0 g, 79.0 mmol) in H_2O (40 mL) was added acetic acid (0.23 mL, 3.96 mmol, 0.05 equiv), hydroquinone (44.0 mg, 0.40 mmol, 0.005 equiv) and freshly distilled methyl vinyl ketone (12.9 mL, 158 mmol, 2.0 equiv). The reaction mixture was stirred at 80°C for 24 h. After cooling down, a saturated aqueous solution of NaCl was added to quench the reaction. The aqueous layer was extracted with EtOAc, and the organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrate under reduced pressure. The crude mixture was purified by flash chromatography using petroleum ether:Et_2O: (8:2) to (7:3) to afford the diketone **2.33** as a pale yellow oil (15.2 g, 77.4 mmol, 98%).

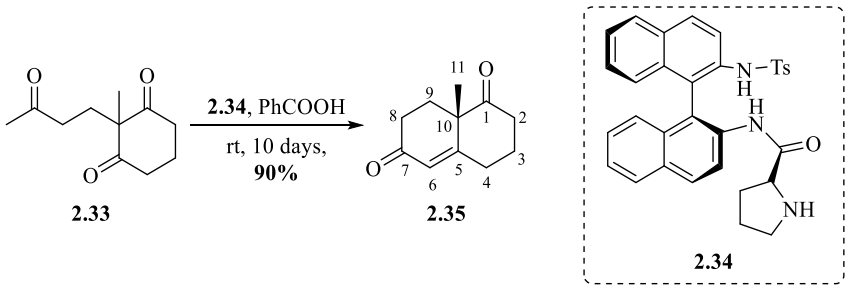
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.78–2.53 (m, 4H, ***CH_2***), 2.32 (t, *J* = 7.5 Hz, 2H, ***CH_2***), 2.08 (s, 3H, ***CH_3-8***), 2.05–2.00 (m, 3H, ***CH_2***), 1.95–1.82 (m, 1H, ***CH_2***), 1.22 (s, 3H, ***CH_3-9***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 201.0 (***CO-3***), 207.5 (***CO-7***), 64.3 (***C-4***), 38.3 (***CH_3-8***), 37.7 (***CH_2-2***), 29.9 (***CH_2***), 29.5 (***CH_2***), 20.0 (***CH_3-9***), 17.5 (***CH_2-1***).

IR (thin film): 1713, 1690 cm^{-1}.

HRMS (ESI): Calcd for $C_{11}H_{16}NaO_3^+$ $[M+Na]^+$, 219.0992; found 219.0993.

(*S*)-8a-Methyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione (2.35)[64]



Chemical formula: $C_{11}H_{14}O_2$

MW: 178.23

To a flask containing *meso* ketone **2.33** (17.7 g, 90.2 mmol) were added *N*-tosyl-(*S*)-binam-(*L*)-prolinamide catalyst **2.34** (485 mg, 0.900 mmol, 0.01 equiv) and benzoic acid (276 mg, 2.26 mmol, 0.025 equiv). The reaction mixture was stirred at 22°C for 5 days. After complete reaction, EtOAc (95 mL) was added followed by activated charcoal (3.15 g), and the resulting mixture was stirred for 15 h at 22°C. The mixture was diluted with hexane (95 mL) and filtered through slurry-packed silica (180 g). The silica cake was eluted with EtOAc:hexanes (1:1). The filtrate was concentrated under reduced pressure and dried under vacuum for 6 h affording a brown oil that crystallized on standing. *t*-Butyl methyl ether (5.0 mL) was added, and the mixture was warmed to 45 °C with a water bath to dissolve the solids. The solution was cooled to room temperature over 1 h, then placed in a freezer at -15 °C for 12 h, resulting in the formation of large reddish-brown crystals. The supernatant was removed, and the final traces of solvent were removed under vacuum for 16 h to afford (+)-Wieland-Miescher ketone **2.35** (14.5 g, 81.3 mmol, 90%, 98% ee).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.85 (s, 1H, ***CH-6***), 2.60–2.76 (m, 2H, ***CH_2-2,4***), 2.51–2.34 (m, 4H, ***CH_2-2,4,8***), 2.16–2.02 (m, 3H, ***CH_2-3,9***), 1.67 (ddt, *J* = 17.6, 13.3, 6.6 Hz, 1H, ***CH_2-3***), 1.41 (s, 3H, ***CH_3-11***).

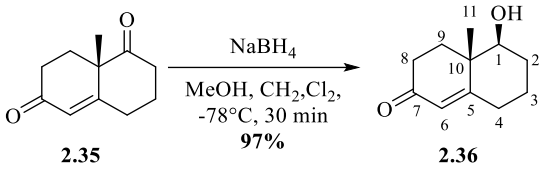
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 211.1 (***CO-1***), 198.3 (***CO-7***), 165.9 (***C-5***), 125.8 (***CH-6***), 50.6 (***C-10***), 37.7 (***CH_2-2***), 33.6 (***CH_2-8***), 31.8 (***CH_2-4***), 29.6 (***CH_2-9***), 23.3 (***CH_3-11***), 22.9 (***CH_2-3***).

IR (thin film): 1713, 16970 cm^{-1}.

HRMS (ESI): Calcd for $C_{11}H_{14}O_2^+$ $[M]^+$, 178.0994; found, 178.0991.

$[\alpha]_D$: +94 (*c* 1.0, toluene), 97% ee. (lit.[64] **$[\alpha]_D$**: +94 (*c* 1.0, toluene), 97% ee).

(4a*S*,5*S*)-5-Hydroxy-4a-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (2.36)[64]



2.35 **2.36**

Chemical formula: $C_{11}H_{16}O_2$

MW: 180.25

To a stirred solution of ketone **2.35** (17.7 g, 99.3 mmol) in MeOH:CH_2Cl_2 (1:1) (286 mL) at -78°C was added $NaBH_4$ (3.77 g, 99.3 mmol, 1.0 equiv). The reaction mixture was stirred at this temperature for 30 min. Acetone was carefully added to quench the reaction followed by slow addition of H_2O. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:EtOAc (6:4) to (3:7) to afford the alcohol **2.36** as a colourless oil (17.6 g, 96.6 mmol, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.77 (d, *J* = 0.8 Hz, 1H, ***CH-6***), 3.41 (d, *J* = 11.4 Hz, 1H, ***CH-1***), 2.46–2.26 (m, 3H, ***CH_2-4,8***), 2.23–2.10 (m, 2H, ***CH_2-4,9***), 1.96–1.76 (m, 4H, ***CH_2-2,3,9,OH***), 1.72–1.61 (m, 1H, ***CH_2-2***), 1.41 (tdd, *J* = 12.5, 8.3, 4.2 Hz, 1H, ***CH_2-3***), 1.18 (s, 3H, ***CH_3-11***).

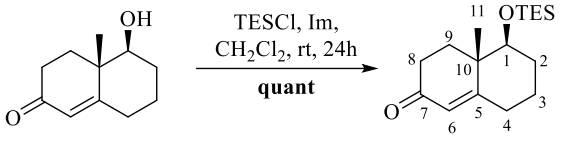
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 199.7 (***CO-7***), 168.6 (***C-5***), 125.4 (***CH-6***), 78.2 (***CH-1***), 41.6 (***C-10***), 34.2 (***CH_2-9***), 33.7 (***CH_2-8***), 32.0 (***CH_2-4***), 30.2 (***CH_2-2***), 23.1 (***CH_2-3***), 15.2 (***CH_3-11***).

IR (thin film): 3420, 1659 cm^{-1}.

HRMS (ESI): Calcd for $C_{11}H_{16}O_2^+$ $[M]^+$, 180.1150; found, 180.1144.

$[\alpha]_D$: +182 (*c* 1.5, benzene).(lit.[64] **$[\alpha]_D$**: +185 (*c* 1.0, benzene))

(4a*S*,5*S*)-4a-Methyl-5-((triethylsilyl)oxy)-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (2.37)[64]



2.36 **2.37**

Chemical formula: $C_{17}H_{30}O_2Si$

MW: 294.51

To a stirred solution of alcohol **2.36** (17.1 g, 95.0 mmol) in CH_2Cl_2 (60 mL) were added imidazole (16.2 g, 238 mmol, 2.50 equiv) and TESCl (24.0 mL, 142 mmol, 1.50 equiv). The reaction mixture was stirred at room temperature for 24 h. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (9:1) to (7:3) to afford the protected alcohol **2.37** as a colourless oil (27.9 g, 219 mmol, quant).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.75 (s, 1H, ***CH-6***), 3.45–3.32 (m, 1H, ***CH-1***), 2.44–2.24 (m, 3H, ***CH$_2$***), 2.13 (dddd, *J* = 10.5, 10.0, 7.0, 2.1 Hz, 2H, ***CH$_2$***), 1.83 (ddd, *J* = 7.6, 5.5, 2.8 Hz, 1H, ***CH$_2$***), 1.78–1.64 (m, 3H, ***CH$_2$***), 1.35 (d, *J* = 13.1 Hz, 1H, ***CH$_2$***), 1.15 (s, 3H, ***CH$_3$-11***), 0.95 (td, *J* = 7.9, 2.1 Hz, 9H, ***CH$_3$-TES***), 0.63–0.54 (m, 6H, ***CH$_2$-TES***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 199.8 (***CO-7***), 168.9 (***C-5***), 125.3 (***CH-6***), 78.9 (***CH-1***), 42.2 (***C-10***), 34.6 (***CH$_2$***), 33.9 (***CH$_2$***), 32.1 (***CH$_2$***), 30.8 (***CH$_2$***), 23.0 (***CH$_2$***), 15.5 (***CH$_3$-11***), 6.9 (***CH$_3$-TES***), 5.2 (***CH$_2$-TES***).

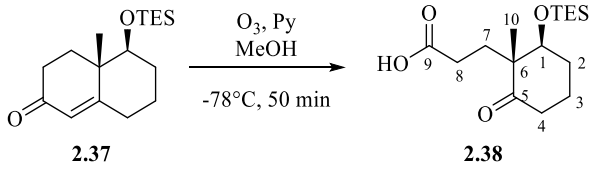
IR (thin film): 2912, 2873, 1681, 1672, 1107, 1078 cm^{-1}.

HRMS (ESI): Calcd for $C_{17}H_{30}NaO_2Si^+$ $[M+Na]^+$, 317.1907; found, 317.1893.

[α]$_D$: +108 (*c* 1.0, $CHCl_3$).(lit.[64] **[α]$_D$**: +105 (*c* 1.0, toluene))

3-((1*R*,6*S*)-1-Methyl-2-oxo-6-((triethylsilyl)oxy)cyclohexyl)propanoic acid (2.38)[64]

Method A

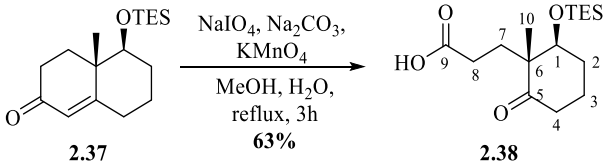


Chemical formula: $C_{16}H_{30}O_4Si$

MW: 314.50

To a stirred solution of **2.37** (6.0 g, 20 mmol) in MeOH (213 mL) at -78°C was added pyridine (8.14 mL, 100 mmol, 5.0 equiv). A stream of O_3 was passed for 50 min and the reaction mixture was then allowed to stir at room temperature for 2 h. The solvent was removed under reduced pressure and the crude mixture was purified by flash chromatography using petroleum ether:Et_2O:AcOH (80:20:0.1) to afford the acid **2.38** as a colourless oil (3.8 g, 12 mmol, 60%).

Method B



To a stirred solution of enone **3.37** (550 mg, 1.83 mmol) in MeOH (16 mL) was added a solution of Na_2CO_3 (208 mg, 1.96 mmol, 1.05 equiv) in H_2O (0.73 mL). The reaction mixture was refluxed for 5 min before a solution of $NaIO_4$ (2.09 g, 9.40 mmol, 5.13 equiv) and $KMnO_4$ (15 mg, 0.1 mmol, 0.05 equiv) in H_2O (11 mL) was added dropwise. The resulting solution was refluxed for 3 h and the reaction mixture was filtered through a sintered funnel to remove the inorganic material. The filter cake as washed with water and CH_2Cl_2. The filtrate was acidified to pH 1 by addition of a 1M HCl. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O:AcOH (80:20:0.1) to afford the acid **2.38** as a colourless oil (361 mg, 1.15 mmol, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.81 (dd, *J* = 6.5, 1.9 Hz, 1H, ***CH-1***), 2.46-2.26 (m, 3H, ***CH_2-4,8***), 2.22 (ddd, *J* = 16.4, 11.6, 4.9 Hz, 1H, ***CH_2-8***), 2.08–1.95 (m, 3H, ***CH_2***), 1.81 (m, 2H,

CH₂), 1.65 (dd, *J* = 9.1, 6.6 Hz, 1H, ***CH₂***), 1.07 (s, 3H, ***CH₃-10***), 0.94 (t, *J* = 7.9 Hz, 9H, ***CH₃-TES***), 0.58 (q, *J* = 8.0 Hz, 6H, ***CH₂-TES***).

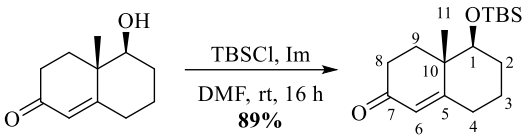
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 214.0 (***CO-5***), 178.9 (***COOH-9***), 76.5 (***CH-1***), 54.3 (***C-6***), 37.7 (***CH₂-4***), 30.1 (***CH₂***), 29.0 (***CH₂***), 29.0 (***CH₂***), 20.4 (***CH₂***), 17.5 (***CH₃-10***), 6.9 (***CH₂-TES***), 5.0 (***CH₃-TES***).

IR (thin film): 3259, 2975, 1742, 1718, 1249, 1050 cm^{-1}.

HRMS (ESI): Calcd for $C_{16}H_{30}NaO_4Si^+$ $[M+Na]^+$, 337.1806; found, 337.1797.

[α]$_D$: -10.8 (*c* 1.0, $CHCl_3$).

(4a*S*,5*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-4a-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (2.46)[80]



2.36 **2.46**

Chemical formula: $C_{17}H_{30}O_2Si$

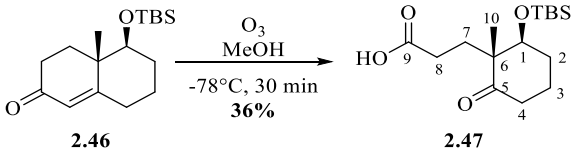
MW: 294.51

To a stirred solution of alcohol **2.36** (300 mg, 1.66 mmol) in DMF (0.40 mL) were added imidazole (226 mg, 3.32 mmol, 2.0 equiv) and TBSCl (500 mg, 3.32 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature for 16 h. Water was added to quench the reaction and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (30:1) to (25:5) to afford the protected alcohol **2.46** as a white solid (433 mg, 1.47 mmol, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.71 (d, *J* = 1.6 Hz, 1H, ***CH-6***), 3.31 (dd, *J* = 10.8, 5.0 Hz, 1H, ***CH-1***), 2.44–2.22 (m, 3H, ***CH₂***), 2.17–1.99 (m, 2H, ***CH₂***), 1.85–1.73 (m, 1H, ***CH₂***), 1.64 (tdd, *J* = 13.1, 12.3, 7.4 Hz, 3H, ***CH₂***), 1.32 (ddd, *J* = 13.2, 11.1, 4.5 Hz, 1H, ***CH₂***), 1.11 (s, 3H, ***CH₃-11***), 0.84 (s, 9H, ***CH₃-SiC(CH₃)₃***), -0.01 (d, *J* = 6.9 Hz, 6H, ***CH₃-Si(CH₃)₂***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 199.7 (***C-1***), 168.8 (***C-3***), 125.4 (***C-2***), 78.9 (***C-7***), 42.2 (***C-8***), 34.8 (***CH_2***), 33.9 (***CH_2***), 32.1 (***CH_2***), 30.8 (***CH_2***), 25.8 (***$SiC(CH_3)_3$***), 23.0 (***CH_2***), 18.0 (***$SiC(CH_3)_3$***), 15.6 (***CH_3-8***), -5.0 (***$Si(CH_3)_2$***).

3-((1*R*,2*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-methyl-6-oxocyclohexyl)propanoic acid (2.47)[80]



2.46 **2.47**

Chemical formula: $C_{16}H_{30}O_4Si$

MW: 314.50

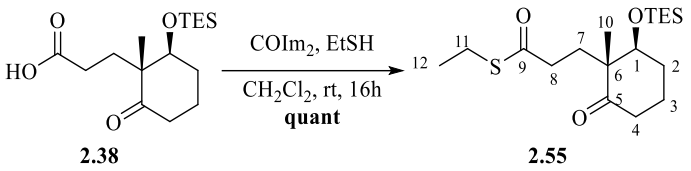
To a stirred solution of protected alcohol **2.46** (412 mg, 1.40 mmol) in MeOH (15 mL) at -78°C was passed a stream of O_3 for 50 min. The reaction mixture was then allowed to stir at room temperature for 2 h. The solvent was removed under reduced pressure and the crude mixture was purified by flash chromatography using petroleum ether:Et_2O:AcOH (80:20:0.1) to afford the acid **2.47** as a colourless oil (158 mg, 0.500 mmol, 36%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 10.78 (bs, 1H, ***COOH***), 3.85–3.69 (m, 1H, ***CH-1***), 2.30 (dt, *J* = 13.2, 6.4 Hz, 3H, ***CH_2***), 2.16 (d, *J* = 4.9 Hz, 1H, ***CH_2***), 2.06–1.90 (m, 3H, ***CH_2***), 1.83–1.58 (m, 3H, ***CH_2***), 1.02 (s, 3H, ***CH_3-10***), 0.83 (s, 9H, ***CH_3-$SiC(CH_3)_3$***), 0.00 (d, *J* = 4.0 Hz, 6H, ***CH_3-$Si(CH_3)_2$***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 214.1 (***CO-5***), 179.3 (***COOH***), 76.4 (***CH-1***), 54.1 (***C-6***), 37.6 (***CH_2-4***), 30.1 (***CH_2***), 29.0 (***CH_2***), 28.7 (***CH_2***), 25.7 (***C-$SiC(CH_3)_3$***), 20.3 (***CH_2***), 17.9 (***CH_3-$SiC(CH_3)_3$***), 17.7 (***CH_3-10***), -4.3 (***CH_3-$Si(CH_3)_2$***), -5.1 (***CH_3-$Si(CH_3)_2$***).

HRMS (ESI): Calcd for $C_{16}H_{30}NaO_4Si^+$ $[M+Na]^+$, 337.1806; found, 337.1795.

_S_-Ethyl 3-((1_R_,6_S_)-1-methyl-2-oxo-6-((triethylsilyl)oxy)cyclohexyl)propanethioate (2.55)[64]



2.38 **2.55**

Chemical formula: $C_{18}H_{34}O_3SSi$

MW: 358.61

To a stirred solution of acid **2.38** (811 mg, 2.58 mmol) in CH_2Cl_2 (6.30 mL) was added carbonyl diimidazole (543 mg, 3.35 mmol, 1.30 equiv). The reaction mixture was stirred for 30 min before EtSH (318 μL, 5.16 mmol, 2.0 equiv) was added. The reaction mixture was stirred for 16 h at room temperature and the volatiles were removed under reduced pressure. Water was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (95:5) to afford the thioester **2.55** as a colourless oil (924 mg, 68.6 mmol, quant)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.81 (d, *J* = 6.1 Hz, 1H, ***CH-1***), 2.86 (q, *J* = 7.4 Hz, 2H, ***CH$_2$-11***), 2.54 (ddd, *J* = 15.6, 11.4, 5.4 Hz, 1H, ***CH$_2$***), 2.43–2.28 (m, 3H, ***CH$_2$***), 2.13–1.92 (m, 3H, ***CH$_2$***), 1.88–1.63 (m, 3H, ***CH$_2$***), 1.23 (t, *J* = 7.4 Hz, 3H, ***CH$_3$-12***), 1.06 (s, 3H, ***CH$_3$-10***), 0.94 (t, *J* = 7.9 Hz, 9H, ***CH$_3$-TES***), 0.58 (q, *J* = 8.0 Hz, 6H, ***CH$_2$-TES***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 213.8 (***CO-5***), 199.2 (***CO-9***), 76.8 (***CH-1***), 54.3 (***C-6***), 39.1 (***CH$_2$***), 37.7 (***CH$_2$***), 31.0 (***CH$_2$***), 28.9 (***CH$_2$***), 23.3 (***CH$_2$-11***), 20.4 (***CH$_2$***), 17.6 (***CH$_3$-10***), 14.7 (***CH$_3$-12***), 6.9 (***CH$_3$-TES***), 5.0 (***CH$_2$-TES***).

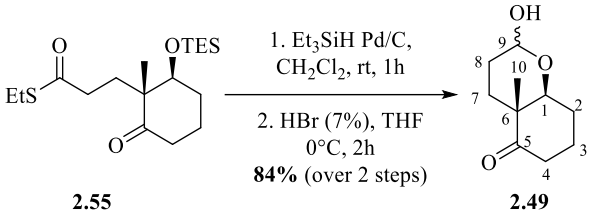
IR (thin film): 2949, 2873, 1708, 1460, 1114, 1078, 1018 cm^{-1}.

HRMS (ESI): Calcd for $C_{18}H_{34}NaO_3SSi^+$ $[M+Na]^+$, 381.1890; found, 381.1876.

[α]$_D$: -20.4 (*c* 1.0, $CHCl_3$)

(4a*R*,8a*S*)-2-Hydroxy-4a-methyloctahydro-5*H*-chromen-5-one (2.49)[64]

Method A



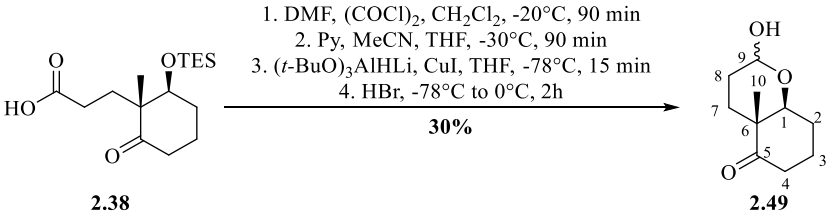
2.55 **2.49**

Chemical formula: $C_{10}H_{16}O_3$

MW: 184.24

To a stirred solution of thioester **2.55** (117 mg, 0.32 mmol) in CH_2Cl_2 (4.60 mL) were added triethylsilane (102 μL, 0.64 mmol, 2.0 equiv) and 10% Pd/C (34 mg) portionwise. The reaction mixture was stirred for 30 min. Then the reaction mixture was filtered through a short pad of Celite and the solvent was concentrated under reduced pressure. The crude mixture was dissolved in THF (150 mL), cooled down to 0°C and an aqueous solution of 7% HBr (3.5 mL) was slowly added. The resulting mixture was stirred at this temperature for 2h. A saturated aqueous solution of $NaHCO_3$ was slowly added to quench the reaction. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:EtOAc (7:3) to afford the hemiacetal **2.49** as a 1:1 mixture of diastereomers (49 mg, 0.27 mmol, 84%).

Method B

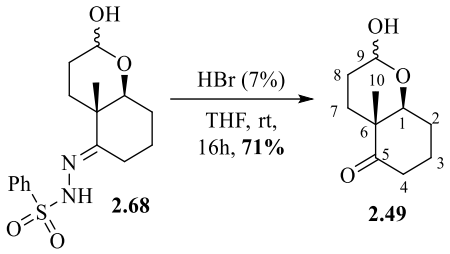


2.38 **2.49**

To a stirred solution of DMF (2.94 mL, 38.2 mmol, 10.0 equiv) in CH_2Cl_2 (10.0 mL) at -20°C was added oxalyl chloride (1.0 mL, 11.5 mmol, 3.0 equiv). The resulting mixture was stirred at this temperature for 90 min and then was concentrated under reduced pressure. The resulting mixture was then cooled down to -30°C and diluted with acetonitrile (5.0 mL) and THF (12.5 mL). A solution of the acid **2.38** (1.25 g, 3.82 mmol) in THF (5.0 mL) and pyridine (1.0 mL) was added dropwise and the resulting solution was allowed to stir at -30°C for 90 min. The

solution was then cooled down to -78°C and a solution of CuI (72 mg, 0.38 mmol, 0.1 equiv) and $LiAlH(t\text{-}BuO)_3$ (1.96 g, 7.64 mmol, 2.0 equiv) in THF (15 mL) was slowly added. The resulting mixture was stirred at -78°C for 15 min and an aqueous solution of 7% HBr was added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine and an aqueous saturated solution of $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (8:2) to (6:4) to afford the hemiacetal **2.49** as a 1:1 mixture of diastereomers (216 mg, 1.17 mmol, 30%).

Method C



To a stirred solution of hydrazine **2.68** (320 mg, 0.94 mmol) in THF (17 mL) was added dropwise an aqueous solution of 7% HBr (10 mL). The reaction mixture was stirred at room temperature for 16 h. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:EtOAc (7:3) to afford the **2.49** as a with solid (126mg, 0.67 mmol, 71%).

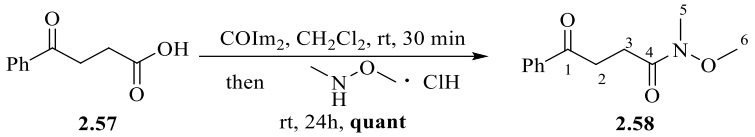
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.23 (d, *J* = 3.6 Hz, 0.5H, ***CH-9***), 4.71 (dd, *J* = 9.6, 2.2 Hz, 0.5H, ***CH-9***), 4.00 (dd, *J* = 12.0, 4.1 Hz, 0.5H, ***CH-1***), 3.91 (bs, 0.5H, ***OH***), 3.36 (dd, *J* = 11.6, 4.2 Hz, 0.5H, ***CH-1***), 3.16 (bs, 0.5H, ***OH***), 2.75–2.54 (m, 1H, ***CH_2-4***), 2.26–2.12 (m, 1H, ***CH_2-4***), 2.04–1.46 (m, 8H, ***CH_2***), 1.23 (s, 1.5H, ***CH_3-10***), 1.19 (s, 1.5H, ***CH_3-10***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 213.6 (***CO-5***), 96.9 (***CH-9***), 91.4 (***CH-9***), 79.4 (***CH-1***), 71.6 (***CH-1***), 48.6 (***C-6***), 48.4 (***C-6***), 36.4 (***CH_2***), 29.3 (***CH_2***), 28.9 (***CH_2***), 26.0 (***CH_2***), 25.8 (***CH_2***), 24.7 (***CH_2***), 20.8 (***CH_2***), 16.2 (***CH_3-10***), 15.2 (***CH_3-10***).

IR (thin film): 3471, 2931, 2872, 1705, 1452, 1053 cm^{-1}.

HRMS (ESI): Calcd for $C_{10}H_{16}NaO_3^+$ $[M+Na]^+$, 207.0992; found, 207.0987.

N-Methoxy-*N*-methyl-4-oxo-4-phenylbutanamide (2.58)



2.57 2.58

Chemical formula: $C_{12}H_{15}NO_3$

MW: 221.26

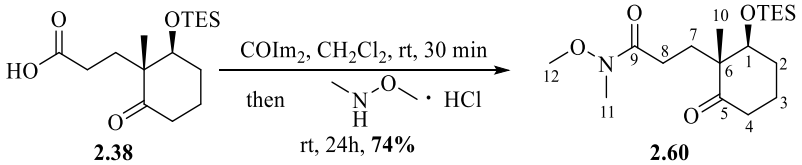
To a stirred solution of acid **2.57** (392 mg, 2.20 mmol) in CH_2Cl_2 (4.8 mL) was added carbonyl diimidazole (393 mg, 2.42 mmol, 1.10 equiv). The reaction mixture was stirred 30 min at room temperature before *N*,*O*-dimethylhydroxylamine hydrochloride (236 mg, 2.42 mmol, 1.10 equiv) was added. The resulting mixture was stirred at room temperature for 24 h. An aqueous solution of 1N HCl was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the Weinreb amide **2.58** as a colourless oil (492 mg, 2.2 mmol, quant).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.04–7.95 (m, 2H, ***CH-Ar***), 7.54 (ddd, *J* = 6.7, 4.0, 1.3 Hz, 1H, ***CH-Ar***), 7.49–7.40 (m, 2H, ***CH-Ar***), 3.77 (s, 3H, ***CH$_3$-6***), 3.33 (td, *J* = 6.7, 2.1 Hz, 2H, ***CH$_2$-2***), 3.20 (s, 3H, ***CH$_3$-5***), 2.89 (t, *J* = 6.2 Hz, 2H, ***CH$_2$-3***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 199.0 (***CO-1***), 173.3 (***CO-4***), 136.8 (***C-Ar***), 133.1 (***CH-Ar***), 128.6 (***CH-Ar***), 128.1 (***CH-Ar***), 61.3 (***CH$_3$-6***), 33.0 (***CH$_2$-2***), 32.3 (***CH$_3$-5***), 26.1 (***CH$_2$-3***).

IR (thin film): 2920, 1685, 1660, 1448, 1361 cm^{-1}.

N-Methoxy-*N*-methyl-3-((1*R*,6*S*)-1-methyl-2-oxo-6-((triethylsilyl)oxy)cyclohexyl) propanamide (2.60)



2.38 2.60

Chemical formula: $C_{18}H_{35}NO_4Si$

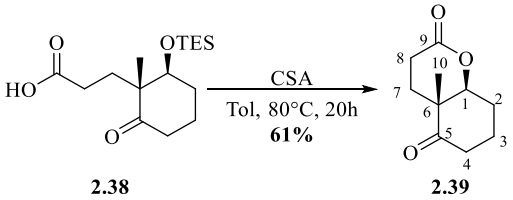
MW: 357.57

To a stirred solution of acid **2.38** (208 mg, 0.660 mmol) in CH_2Cl_2 (1.5 mL) was added carbonyl diimidazole (118 mg, 0.730 mmol, 1.10 equiv). The reaction mixture was stirred 30 min at room temperature before *N*,*O*-dimethylhydroxylamine hydrochloride (71 mg, 0.73 mmol, 1.1 equiv) was added. The resulting mixture was stirred at room temperature for 24 h. An aqueous solution of 1N HCl was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (1:1) to afford the Weinreb amide **2.58** as a pale yellow oil (174 mg, 0.470 mmol, 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.93–3.83 (m, 1H, ***CH-1)***, 3.65 (s, 3H, ***CH_3-12***), 3.15 (s, 3H, ***CH_3-11***), 2.23 (m, 7H, ***CH_2***), 1.79–1.65 (m, 3H, ***CH_2***), 1.06 (s, 3H, ***CH_3-10***), 0.98–0.87 (m, 9H, ***CH_3-TES***), 0.57 (q, *J* = 7.9 Hz, 6H, ***CH_2-TES***).

(4a*R*,8a*S*)-4a-Methylhexahydro-2*H*-chromene-2,5(3*H*)-dione (2.39)

Method A



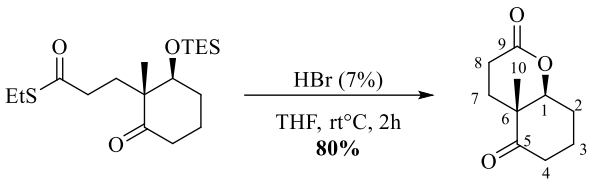
2.38 **2.39**

Chemical formula: $C_{10}H_{14}O_3$

MW: 182.22

To a stirred solution of acid **2.38** (5.15 g, 16.3 mmol) in toluene (123 mL) was added CSA (4.96 g, 21.3 mmol, 1.30 equiv). The reaction mixture was refluxed for 20 h and then the solvent was removed under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether: Et_2O (1:1) to afford the lactol **2.39** as a pale yellow oil (1.81 g, 9.93 mmol).

Method B



2.55 **2.39**

To a stirred solution of thioester **2.55** (717 mg, 1.99 mmol) in THF (4.3 mL) at 0°C was added an aqueous solution of 7% HBr (4.3 mL). The reaction mixture stirred at this temperature for 2 h. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether (7:3) to afford the lactone **2.39** as a pale yellow oil (290 mg, 1.59 mmol, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.19 (dd, *J* = 11.6, 4.4 Hz, 1H, ***CH-1***), 2.75–2.57 (m, 3H, ***CH_2-4,8***), 2.35–2.19 (m, 2H, ***CH_2-2,8***), 2.15–1.98 (m, 3H, ***CH_2-2,3***), 1.84–1.75 (m, 1H, ***CH_2-7***), 1.63–1.54 (m, 1H, ***CH_2-7***), 1.23 (s, 3H, ***CH_3-10***).

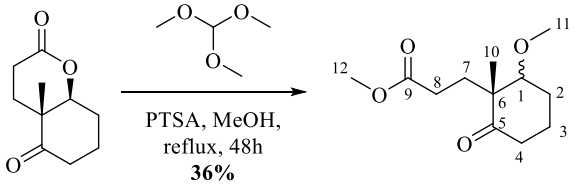
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 210.4 (***CO-5***), 170.7 (***CO-9***), 81.5 (***CH-1***), 48.3 (***C-6***), 36.4 (***CH_2-7***), 27.0 (***CH_2-3***), 26.6 (***CH_2-2***), 25.9 (***CH_2-8***), 20.1 (***CH_2-4***), 16.6 (***CH_3-10***).

IR (thin film): 2953, 1745, 1712, 1462, 1217, 1055 cm^{-1}.

HRMS (ESI): Calcd for $C_{10}H_{14}NaO_3^+$ $[M+Na]^+$, 205.0835; found, 205.0839.

[α]$_{25}$: -41.6 (*c* 1.50, CH_2Cl_2)

Methyl 3-((1*R*)-2-methoxy-1-methyl-6-oxocyclohexyl)propanoate ((±)2.62)



2.39 **(±)2.62**

Chemical formula: $C_{12}H_{20}O_4$

MW: 228.29

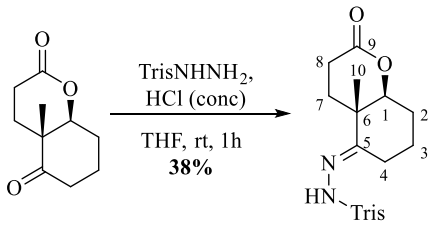
To a stirred solution of hemiacetal **2.39** (138 mg, 0.74 mmol) in MeOH (7.4 mL) was added trimethylorthoformate (99 μL, 0.90 mmol, 1.2 equiv) and PTSA (258 mg, 1.36 mmol, 1.80 equiv) The reaction mixture was refluxed for 2 days. The reaction mixture was allowed to cool to room temperature and an aqueous solution of 1M of MeONa was added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether$_2$:EtOAc (6:4) to afford ester **(±)2.62** as a pale yellow oil (62 mg, 0.27 mmol, 36%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.69–3.53 (m, 3H, ***CH$_3$-12***), 3.38–3.19 (m, 3H, ***CH$_3$-11***), 3.21–3.17 (m, 1H, ***CH-1***), 2.41–1.79 (m, 9H, ***CH$_2$***), 1.65–1.56 (m, 1H, ***CH$_2$-9***), 1.12–1.07 (m, 3H, ***CH$_3$-10***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 213.2 (***CO-5***), 174.2 (***CO-9***), 173.9 (***CO-9***), 85.9 (***CH-1***), 84.7 (***CH-1***), 57.2 (***CH$_3$-11***), 57.1 (***CH$_3$-11***), 53.6 (***C-6***), 53.4 (***C-6***), 51.6 (***CH$_3$-12***), 51.6 (***CH$_3$-12***), 37.7 (***CH$_2$***), 37.6 (***CH$_2$***), 30.5 (***CH$_2$***), 29.1(***CH$_2$***), 28.9 (***CH$_2$***), 27.6 (***CH$_2$***), 23.4 (***CH$_2$***), 23.3 (***CH$_2$***), 20.2 (***CH$_2$***), 19.5 (***CH$_3$-10***), 17.4 (***CH$_3$-10***)

HRMS (ESI): Calcd for $C_{12}H_{20}NaO_4^+$ $[M+Na]^+$, 251.1254; found, 251.1255.

2,4,6-Triisopropyl-*N'*-((4a*S*,8a*S*,*E*)-4a-methyl-2-oxooctahydro-5*H*-chromen-5-ylidene)benzenesulfonohydrazide (2.64)



2.39 **2.64**

Chemical formula: $C_{25}H_{38}N_2O_4S$

MW: 462.65

To a stirred solution of ketone **2.39** (120 mg, 0.660 mmol) in THF (10 mL) at 0°C was added $TrisNHNH_2$ (200 mg, 0.67 mmol, 1.0 equiv) and 2 drops of concentrated HCl. The reaction mixture was stirred at room temperature for 1 h. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined

organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether: Et_2O (8:2) to afford the hydrazone **2.64** as a white solid (252 mg, 0.250 mmol, 38%).

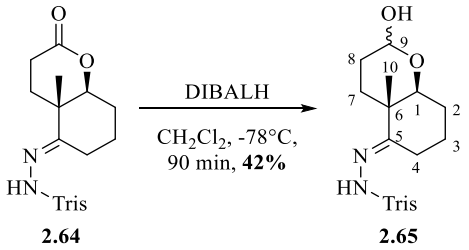
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.85 (bs, 1H, ***NH***), 7.10 (s, 2H, ***CH-Ar***), 4.16–4.04 (m, 2H, ***CH-iPr***), 3.94 (dd, *J* = 12.0, 4.2 Hz, 1H, ***CH-1***), 2.89–2.81 (m, 1H, ***CH-iPr***), 2.65–2.29 (m, 3H, ***CH$_2$***), 2.01–1.82 (m, 4H, ***CH$_2$***), 1.63 (m, 3H, ***CH$_2$***), 1.22–1.13 (m, 18H, ***CH$_3$-iPr***), 0.96 (s, 3H, ***CH$_3$-10***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 170.9 (***CO-9***), 158.8 (***CN-5***), 153.5 (***C-Ar***), 151.2 (***C-Ar***), 130.9 (***C-Ar***), 123.6 (***C-Ar***), 82.3 (***CO-1***), 41.6 (***C-6***), 34.1 (***CH-iPr***), 29.8 (***CH-iPr***), 28.7 (***CH$_2$-2***), 27.0 (***CH$_2$-8***), 26.1 (***CH$_2$-3***), 24.8 (***CH$_3$-iPr***), 24.7 (***CH$_3$-iPr***), 23.5 (***CH$_3$-iPr***), 23.5 (***CH$_3$-iPr***), 21.6 (***CH$_2$-4***), 20.9 (***CH$_2$-7***), 17.0 (***CH$_3$-10***)

IR (thin film): 2960, 1460, 1363, 1330, 1190, 1124 cm^{-1}.

HRMS (ESI): Calcd for $C_{25}H_{38}N_2NaO_4S^+$ $[M+Na]^+$, 485.2444; found, 485.2422.

***N'*-((4a*S*,8a*S*,*E*)-2-Hydroxy-4a-methyloctahydro-5*H*-chromen-5-ylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (2.65)**



2.64 **2.65**

Chemical formula: $C_{25}H_{40}N_2O_4S$

MW: 464.67

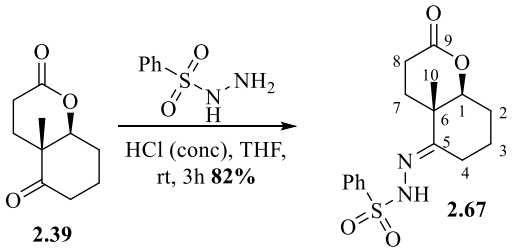
To a stirred solution of hydrazone **2.64** (102 mg, 0.220 mmol) in CH_2Cl_2 (3.3 mL) at -78°C was added DIBALH (0.22 mL, 1 M in hexane, 0.22 mmol, 1.0 equiv) dropwise. The reaction mixture was stirred at this temperature for 30 min. MeOH was added to quench the reaction and the resulting solution was allowed to warm up to room temperature. An aqueous solution of Rochelle salt was added and the reaction mixture was stirred for 24 h. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over

anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (8:2) to afford the hemiacetal **2.65** as a white solid (43 mg, 0.092 mmol, 42%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.14 (s, 2H, ***CH-Ar***), 4.19 (dq, *J* = 13.5, 6.7 Hz, 2H, ***CH-iPr***), 4.08 (d, *J* = 10.2 Hz, 1H, ***CH-1***), 3.21 (dd, *J* = 10.6, 5.3 Hz, 1H, ***CH-9***), 2.89 (dt, *J* = 13.8, 6.9 Hz, 1H, ***CH-iPr***), 2.60 (td, *J* = 14.4, 7.1 Hz, 1H, ***CH_2-4***), 2.17 (dd, *J* = 14.9, 3.8 Hz, 1H, ***CH_2-4***), 2.00–1.93 (m, 1H, ***CH_2-8***), 1.80–1.44 (m, 7H, ***CH_2***), 1.26–1.22 (m, 18H, ***CH_3- iPr***), 1.14–1.10 (m, 3H, ***CH_3-10***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 163.8 (***CN-5***), 153.1 (***C-Ar***), 151.5 (***C-Ar***), 131.0 (***C-Ar***), 123.7 (***CH-Ar***), 89.1 (***CO-9***), 80.0 (***CO-1***), 48.5 (***C-6***), 36.4 (***CH_2-4***), 34.1 (***CH-iPr***), 29.7 (***CH-iPr***), 29.6 (***CH_2***), 25.9 (***CH_2***), 25.1 (***CH_2***), 24.9 (***CH_3-iPr***), 24.8 (***CH_3-iPr***), 20.7 (***CH_2***), 16.1 (***CH_3-1***).

***N'*-((4a*S*,8a*S*,*E*)-4a-Methyl-2-oxooctahydro-5*H*-chromen-5-ylidene)benzenesulfonohydrazide (2.67)**



Chemical formula: $C_{16}H_{20}N_2O_4S$

MW: 336.41

To a stirred solution of ketone **2.39** (400 mg, 2.19 mmol) in THF (13 mL) at 0°C was added phenyl hydrazine (417 mg, 2.42 mmol, 1.10 equiv) and 2 drops of concentrated HCl. The reaction mixture was stirred at room temperature for 2 h and 30 min. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using pretroleum ether:EtOAc (1:1) to afford the hydrazone **2.67** as a white solid (605 mg, 1.79 mmol, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.96–7.90 (m, 2H, ***CH-Ar***), 7.56 (m, 3H, ***CH-Ar***), 7.40 (bs, 1H, ***NH***), 4.01 (dd, *J* = 12.0, 4.2 Hz, 1H, ***CH-1***), 2.72–2.48 (m, 3H, ***CH_2***), 2.15 (d, *J* = 4.5 Hz, 1H, ***CH_2***), 1.99–1.74 (m, 5H, ***CH_2***), 1.38–1.31 (m, 1H, ***CH_2***), 1.02 (s, 3H, ***CH_3-10***).

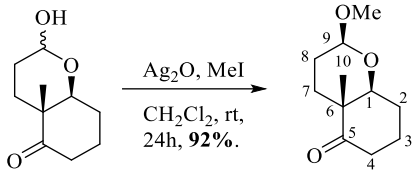
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 170.9 (***CO-9***), 161.5 (***CN-5***), 137.9 (***C-Ar***), 133.4 (***CH-Ar***), 128.9 (***CH-Ar***), 128.1 (***CH-Ar***), 82.2 (***CH-1***), 41.7 (***C-6***), 28.8 (***CH_2***), 27.1 (***CH_2***), 26.1 (***CH_2***), 21.9 (***CH_2***), 20.8 (***CH_2***), 17.0 (***CH_3-10***).

IR (thin film): 2158, 2019, 1977, 1264, 1172, 1126, 910, 747 cm^{-1}.

HRMS (ESI): Calcd for $C_{16}H_{20}N_2O_4S^+$ $[M]^+$, 336.1146; found, 336.1144

MP: 164°C.

(2*S*,4a*R*,8a*S*)-2-Methoxy-4a-methyloctahydro-5*H*-chromen-5-one (2.70)[64]



2.69 **2.70**

Chemical formula: $C_{11}H_{18}O_3$

MW: 198.26

To a stirred solution of hemiacetal **2.69** (1.74 g, 9.44 mmol) in CH_2Cl_2 (14 mL) was added Ag_2O (2.40 g, 10.4 mmol, 1.10 equiv) and MeI (1.80 mL, 28.8 mmol, 3.0 equiv). The resulting solution was stirred at room temperature for 2 days. The reaction mixture was filtered through a pad of Celite, the filter cake was washed with CH_2Cl_2 and the filtrate was then concentrated under reduced pressure to afford to afford the acetal **2.70** as a white foam (1.72 g, 8.67 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.28 (dd, *J* = 9.5, 2.3 Hz, 1H, ***CH-9***), 3.49 (s, 3H, ***OCH_3***), 3.30 (dd, *J* = 11.4, 4.3 Hz, 1H, ***CH-1***), 2.72–2.57 (m, 1H, ***CH_2-4***), 2.18 (dd, *J* = 15.0, 4.9 Hz, 1H, ***CH_2-4***), 2.01–1.50 (m, 8H, ***CH_2***), 1.23 (s, 3H, ***CH_3-10***).

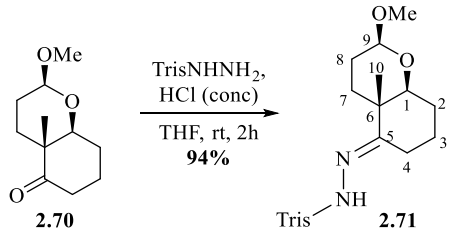
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 213.7 (***CO-5***), 104.0 (***CH-9***), 79.3 (***CH-1***), 56.5 (***OCH_3***), 48.7 (***C-6***), 36.5 (***CH_2-4***), 29.3 (***CH_2-7***), 27.3 (***CH_2-8***), 26.0 (***CH_2-2***), 20.9 (***CH_2-3***), 16.3 (***CH_3-10***).

IR (thin film): 2947, 1710, 1066 cm^{-1}.

HRMS (EI): Calcd for $C_{11}H_{18}O_3^+$ $[M]^+$, 198.1256; found, 198.1270.

$[\alpha]_D$: +102 (*c* 1.5, $CHCl_3$).

2,4,6-Triisopropyl-*N'*-((2*S*,4a*S*,8a*S*,*E*)-2-methoxy-4a-methyloctahydro-5*H*-chromen-5-ylidene)benzenesulfonohydrazide (2.71)[64]



Chemical formula: $C_{26}H_{42}N_2O_4S$

MW: 478.69

To a stirred solution of ketone **2.70** (1.72 g, 8.67 mmol) in THF (12 mL) at 0°C was added $TrisNHNH_2$ (2.82 g, 9.52 mmol, 1.1 equiv) and 3 drops of concentrated HCl. The reaction mixture was stirred at room temperature for 2 h. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether: Et_2O (8:2) to (6:4) to afford the hydrazone **2.71** as a white solid (3.92 mg, 8.20 mmol, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.30 (bs, 1H, ***NH***), 7.16 (s, 2H, ***CH-Ar***), 4.21 (dd, *J* = 8.1, 3.3 Hz, 1H, ***CH-9***), 4.16 (dt, *J* = 13.5, 6.8 Hz, 2H, ***CH- iPr***), 3.46 (s, 3H, ***CH_3-OMe***), 3.16–3.09 (m, 1H, ***CH-1***), 2.97–2.85 (m, 1H, ***CH- iPr***), 2.51–2.43 (m, 1H, ***CH_2-4***), 2.00 (dd, *J* = 13.7, 6.2 Hz, 1H, ***CH_2-4***), 1.95–1.89 (m, 1H, ***CH_2***), 1.75–1.68 (m, 2H, ***CH_2***), 1.64–1.54 (m, 4H, ***CH_2***), 1.44–1.33 (m, 1H, ***CH_2***), 1.28–1.22 (m, 18H, ***CH_3- iPr***), 1.02 (s, 3H, ***CH_3-10***).

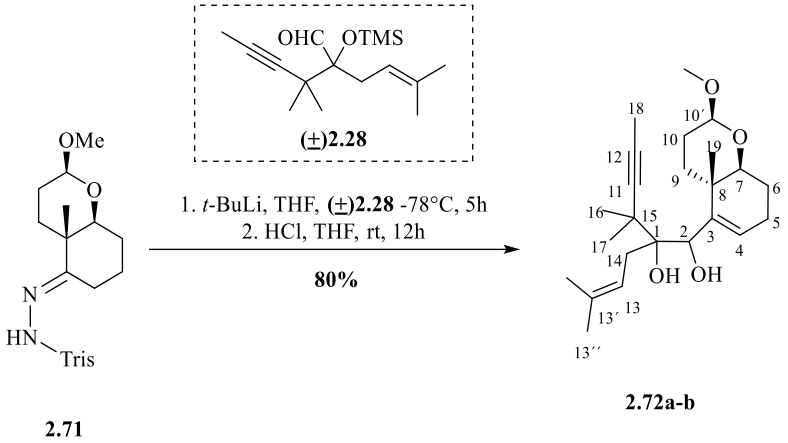
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 161.8 (***CN-5***), 153.2 (***C-Ar***), 151.1 (***2C-Ar***), 131.2 (***C-Ar***), 123.5 (***2CH-Ar***), 104.0 (***CH-9***), 79.4 (***CH-1***), 56.4 (***CH_3-OMe***), 42.1 (***C-6***), 34.2 (***CH- iPr***), 31.3 (***CH_2***), 29.9 (2***CH-iPr***), 27.5 (***CH_2***), 26.1 (***CH_2***), 24.8 (2***CH_3-iPr***), 24.7 (2***CH_3-iPr***), 23.6 (***CH_3-iPr***), 23.5 (***CH_3-iPr***), 21.5 (2***CH_2***), 17.3 (***CH_3-10***).

IR (thin film): 2955, 2858, 1707, 1598, 1460, 1332, 1067 cm^{-1}.

HRMS (ESI): Calcd for $C_{26}H_{42}N_2NaO_4S^+$ $[M+Na]^+$, 501.2757; found, 501.2743.

$[\alpha]_D$: +35.8 (*c* 1.0, $CHCl_3$)

1-((2*S*,4a*S*,8a*S*)-2-Methoxy-4a-methyl-3,4,4a,7,8,8a-hexahydro-2*H*-chromen-5-yl)-5-methyl-2-(2-methylpent-3-yn-2-yl)hex-4-ene-1,2-diol (2.72a-b)[64]



2.71 **2.72a-b**

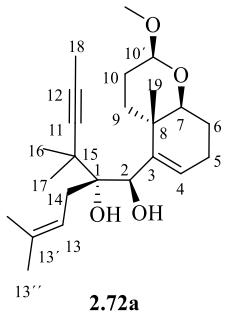
Chemical formula: $C_{24}H_{38}O_4$

MW: 390.56

To a stirred solution of hydrazone **2.71** (644 mg, 1.34 mmol, 1.20 equiv) in THF (1.6 mL) at -78°C was added dropwise *t*-BuLi (234 µL, 1.14 M in hexane, 2.67 mmol, 2.40 equiv). The solution turned dark red. The resulting solution was stirred at this temperature for 30 min and warmed for a few min to room temperature and intense nitrogen bubbling occurred. The reaction mixture was then cooled down to -78°C and a solution of aldehyde **(±)2.28** (314 mg, 1.12 mmol) in THF (0.8 mL) was added. The resulting mixture was stirred at -78°C for 5 h and became yellow. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was dissolved in THF (2.2 mL) and a 1N aqueous solution of HCl (1.1 mL) was then added. The resulting mixture was stirred at room temperature overnight. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography CH_2Cl_2:EtOAc (97:3) to (9:1) to afford the title diols **2.72a** (217 mg, 5.50 mmol, 40%) and **2.72b** (215 mg, 5.50 mmol, 40%) as highly viscous

colourless oils, as well as **2.73** (27.3 mg, 0.15 mmol, 11%) as a colourless oil (resulting from the excess of hydrazone **2.71** employed).

(1*R*,2*R*)-1-((2*S*,4a*S*,8a*S*)-2-Methoxy-4a-methyl-3,4,4a,7,8,8a-hexahydro-2*H*-chromen-5-yl)-5-methyl-2-(2-methylpent-3-yn-2-yl)hex-4-ene-1,2-diol (2.72a)



2.72a

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.07 (t, *J* = 3.7 Hz, 1H, ***CH-4***), 5.32 (ddd, *J* = 7.0, 5.7, 1.3 Hz, 1H, ***CH-13***), 4.44–4.30 (m, 2H, ***CH-2,10´***), 3.51 (s, 3H, ***CH_3-OMe***), 3.32 (dd, *J* = 10.8, 5.2 Hz, 1H, ***CH-7***), 3.11-3.04 (m, 2H, ***2OH***), 2.39–2.21 (m, 2H, ***CH_2-14***), 2.25–2.17 (m, 2H, ***CH_2-5***), 2.01–1.90 (m, 1H, ***CH_2-10***), 1.79 (s, 3H, ***CH_3-18***), 1.78–1.69 (m, 5H, ***CH_2***), 1.70 (m, 3H, ***CH_3-H13´***)1.56 (s, 3H, ***CH_3-H13´***), 1.27 (s, 3H, ***CH_3-16***), 1.22 (s, 3H, ***CH_3-17***), 1.11 (s, 3H, ***CH_3-19***).

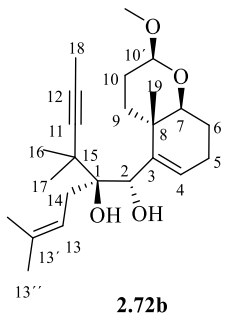
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 143.6 (***C-3***), 131.7 (***C-13´***), 126.4 (***CH-4***), 120.7 (***CH-13***), 104.0 (***CH-10´***), 86.4 (***C-11***), 79.3 (***C-12***), 79.0 (***CH-7***), 78.1 (***C-1***), 70.7 (***C-2***), 56.3 (***CH_3-OMe***), 41.7 (***C-15***), 37.0 (***C-8***), 33.0 (***CH_2-14***), 32.7 (***CH_2-10***), 27.9 (***CH_2-9***), 26.2 (***CH_3-16***), 26.2 (***CH_3-17***), 26.0 (***CH_3-13´***), 24.8 (***CH_2-5***), 23.4 (***CH_2-6***), 18.9 (***CH_3-19***), 17.9 (***CH_3-13´***), 3.6 (***CH_3-18***).

IR (thin film): 2493, 2918, 2362, 1454, 1228, 1112, 1095 cm^{-1}.

HRMS (ESI): Calcd for $C_{24}H_{38}NaO_4^+$ $[M+Na]^+$, 413.2662; found, 413.2651.

[α]$_D$: -27.6 (*c* 1.0, $CHCl_3$).

(1*S*,2*S*)-1-((2*S*,4a*S*,8a*S*)-2-Methoxy-4a-methyl-3,4,4a,7,8,8a-hexahydro-2*H*-chromen-5-yl)-5-methyl-2-(2-methylpent-3-yn-2-yl)hex-4-ene-1,2-diol (2.72b)



2.72b

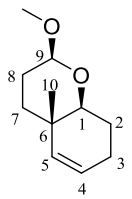
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.98 (t, *J* = 3.8 Hz, 1H, ***CH-4***), 5.35 (t, *J* = 6.9 Hz, 1H, ***CH-13***), 4.41 (d, *J* = 4.6 Hz, 1H, ***CH-2***), 4.34 (dd, *J* = 8.5, 4.0 Hz, 1H, ***CH-10'***), 3.51 (s, 3H, ***CH$_3$-OMe***), 3.36–3.30 (m, 1H, ***CH-7***), 3.17 (s, 1H, ***OH-1***), 2.85 (d, *J* = 4.6 Hz, 1H, ***OH-2***), 2.49–2.39 (m, 1H, ***CH$_2$-14***), 2.32 (m, 1H, ***CH$_2$-14***), 2.25–2.17 (m, 2H, ***CH$_2$-5***), 1.91–1.85 (m, 1H, ***CH$_2$-9***), 1.81–1.75 (m, 4H, ***CH$_2$-4,10***), 1.74–1.67 (m, 6H,***CH$_3$-18,13''***), 1.58 (s, 3H, ***CH$_3$-13''***), 1.46 (td, *J* = 12.5, 5.9 Hz, 1H, ***CH$_2$-9***), 1.28 (s, 3H, ***CH$_3$-16***), 1.26 (s, 3H, ***CH$_3$-17***), 1.20 (s, 3H, ***CH$_3$-19***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 146.2 (***C-3***), 131.5 (***C-13'***), 126.2 (***CH-4***), 121.3 (***CH-13***), 103.8 (***CH-10'***), 86.6 (***C-11***), 78.7 (***C-12***), 78.3 (***CH-7***), 78.2 (***CH-1***), 69.5 (***CH-2***), 56.3 (***CH$_3$-OMe***), 41.8 (***C-15***), 37.5 (***C-8***), 33.4 (***CH$_2$-14***), 32.5 (***CH$_2$-9***), 28.1 (***CH$_2$***), 26.3 (***CH$_3$-16***), 26.2 (***CH$_3$-17***), 26.1 (***CH$_3$-13''***), 24.6 (***CH$_2$-5***), 23.5 (***CH$_2$***), 19.9 (***CH$_3$-19***), 18.1 (***CH$_3$-13''***), 3.6 (***CH$_3$-18***).

IR (thin film): 3495, 2947, 2914, 2835, 1868, 1454, 1382, 1265, 1065 cm^{-1}.

HRMS (ESI): Calcd for $C_{24}H_{38}NaO_4^+$ $[M+Na]^+$, 413.2662; found, 413.2648.

(2*S*,4a*S*,8a*S*)-2-Methoxy-4a-methyl-3,4,4a,7,8,8a-hexahydro-2*H*-chromene (2.73)[101]



2.73

Chemical formula: $C_{11}H_{18}O_2$

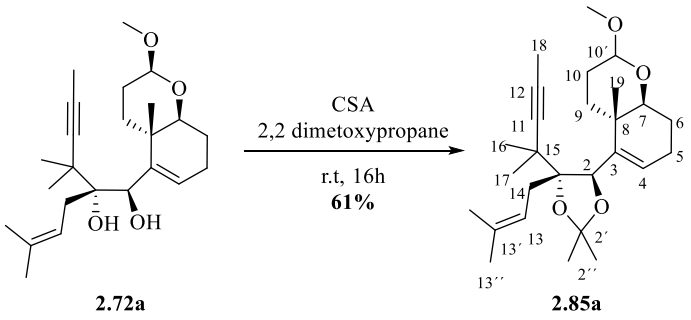
MW: 182.26

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.47–5.36 (m, 2H, ***CH-4, 5***), 4.37 (dd, *J* = 8.4, 4.2 Hz, 1H, ***CH-9***), 3.51 (s, 3H, ***CH_3-OMe***), 3.27 (dd, *J* = 11.6, 4.5 Hz, 1H, ***CH-1***), 2.21–2.12 (m, 2H, ***CH_2-3***), 1.79–1.65 (m, 4H, ***CH_2-2, 8***), 1.57 (dd, *J* = 12.7, 3.3 Hz, 1H, ***CH_2-7***), 1.41 (td, *J* = 12.8, 6.2 Hz, 1H, ***CH_2-7***), 1.04 (s, 3H, ***CH_3-10***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 135.5 (***CH-5***), 124.4 (***CH-4***), 104.4 (***CH-9***), 78.5 (***CH-1***), 56.4 (***CH_3-OMe***), 35.0 (***CH_2-7***), 34.2 (***C-6***), 27.9 (***CH_2-8***), 25.4 (***CH_2-3***), 23.7 (***CH_2-2***), 19.6 (***CH_3-10***).

HRMS (ESI): Calcd for $C_{11}H_{18}NaO_2^+$ $[M+Na]^+$, 205.1204; found, 205.1202

(4a*S*,*8a*S)-5-((4*R*,5*R*)-2,2-Dimethyl-5-(3-methylbut-2-en-1-yl)-5-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-4-yl)-2-methoxy-4a-methyl-3,4,4a,7,8,8a-hexahydro-2*H*-chromene (2.85a)



Chemical formula: $C_{27}H_{42}O_4$

MW: 430.63

To a stirred solution of **2.72a** (211 mg, 0.540 mmol) in 2,2-dimetoxypropane (5.0 mL) was added CSA (15 mg, 0.64 μmol, 0.01 equiv). The reaction mixture was stirred at room temperature for 16 h. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether: Et_2O (9:1) to afford the acetal **2.85a** as a pale yellow oil (141 mg, 0.330 mmol, 61%) and as a 7:3 mixture of diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: The presence of two diastereomers was observed in the NMR spectra in a 0.7 (M):0.3 (m) ratio. 6.01 (d, *J* = 3.6 Hz, 1H, ***CH-13***), 5.51 (dd, *J* = 3.5, 2.1

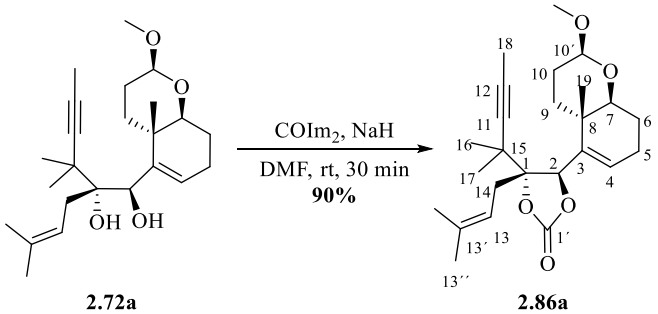
Hz, 1H, ***CH-4***), 4.84 (s, 1H, ***CH-2***), 4.68 (m) (d, *J* = 2.8 Hz, 0.3H, ***CH-10´***), 4.34 (M) (dd, *J* = 8.6, 3.4 Hz, 0.7H, ***CH-10´***), 3.85 (m) (dd, *J* = 12.4, 4.1 Hz, 0.3H, ***CH-7***), 3.50 (M) (d, *J* = 6.6 Hz, 2.1H, ***CH_3-OMe***), 3.41 (M) (dd, *J* = 11.8, 4.3 Hz, 0.7 H, ***CH-7***), 3.30 (m) (s, 0.9H, ***CH_3-OMe***), 2.69–2.46 (m, 2H, ***CH_2-14***), 2.36–2.16 (m, 2H, ***CH_2-9***), 1.91 (M) (t, *J* = 8.4 Hz, 1.3H, ***CH_2-10***), 1.78 (s, 3H, ***CH_3-18***), 1.75–1.64 (m, 3H, ***CH_2-5,6,10***), 1.68 (s, 3H, ***CH_3-2´´***), 1.60 (s, 3H, ***CH_3-2´´***), 1.58–1.52 (m, 0.7H, ***CH_2-10***), 1.45–1.36 (m, 6H, ***CH_3-13´´***), 1.29 (s, 3H, ***CH_3-16 or 17***), 1.23 (s, 3H, ***CH_3-16 or 17***), 1.21 (s, 1H, ***CH_3-16 or 17***), 1.17 (s, 3H, ***CH_3-19***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: The presence of two diastereomers was observed in the NMR spectra. 139.4 (m) (***C-3***), 139.0 (M) (***C-3***), 130.0 (M) (***C-13´***), 129.9 (m) (***C-13´***), 127.8 (M) (***CH-13***), 127.6 (m) (***CH-13***), 122.4 (m) (***CH-4***), 122.3 (M) (***CH-4***), 104.9 (M) (***C-1***), 104.8 (m) (***C-1***), 103.8 (M) (***CH_3-10'***), 97.8 (m) (***CH_3-10'***), 87.1 (M) (***C-11***) , 86.0 (m) (***C-11***), 78.4 (***C-2'***), 77.6 (M) (***CH-2***), 77.5 (m) (***CH-2***), 76.7 (M) (***CH-7***), 76.3 (m) (***CH-7***), 70.6 (***C-12***), 56.2 (M) (***CH_3-OMe***), 54.0 (m) (***CH_3-OMe***), 38.7 (M) (***C-8***), 38.6 (m) (***C-8***), 38.0 (M) (***C-15***), 37.8 (m) (***C-15***), 32.5 (***CH_2-14***), 31.3 (***CH_2-9***), 28.6 (m) (***CH_2-10***), 27.9 (M) (***CH_2-10***), 27.7 (m) (***CH_3-2''***), 27.2 (M) (***CH_3-2''***) , 26.9 (***CH_3-13''***), 26.4 (***CH_3-16 or 17***), 26.3 (***CH_3-16 or 17***), 25.0 (M) (***CH_2-5***), 24.8 (m) (***CH_2-5***), 23.1 (M) (***CH_2-6***), 22.84 (m) (***CH_2-6***), 19.23 (***CH_3-13''***), 18.35 (m) (***CH_3-19***), 18.16 (M) (***CH_3-19***), 3.48 (***CH_3-18***).

IR (thin film): 3495, 2947, 2914, 2835, 1868, 1454, 1382, 1265, 1065 cm^{-1}.

HRMS (ESI): Calcd for $C_{27}H_{42}NaO_4^+$ $[M+Na]^+$, 453.2975; found, 453.2955.

(4*R*,5*R*)-5-((2*S*,4a*S*,8a*S*)-2-Methoxy-4a-methyl-3,4,4a,7,8,8a-hexahydro-2*H*-chromen-5-yl)-4-(3-methylbut-2-en-1-yl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (2.86a)



2.72a **2.86a**

Chemical formula: $C_{25}H_{36}O_5$

MW: 416.56

To a stirred solution of diol **2.72a** (540 mg, 1.44 mmol) in DMF (20 mL) was added NaH (60 %) (166 mg, 4.17 mmol, 3.0 equiv) and *N,N*-carbonyl diimidazole (1.16 g, 7.15 mmol, 5.0 equiv). The reaction mixture was stirred at room temperature for 30 min. A saturated aqueous solution of NH_4Cl was added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (8:2) to afford the carbonate **2.86a** as a pale yellow oil (541 mg, 1.30 mmol, 90%).

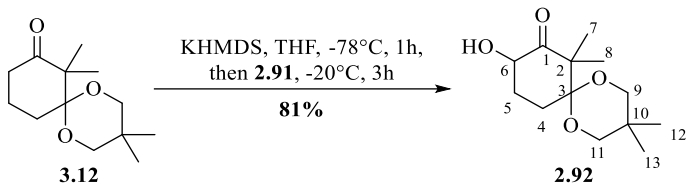
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.65 (t, *J* = 3.7 Hz, 1H, ***CH-4***), 5.33 (s, 1H, ***CH-2***), 5.27 (t, *J* = 6.6 Hz, 1H, ***CH-13***), 4.36 (dd, *J* = 9.4, 2.8 Hz, 1H, ***CH-10'***), 3.51 (s, 3H, ***CH$_3$-OMe***), 3.30 (dd, *J* = 11.0, 5.0 Hz, 1H, ***CH-7***), 2.68–2.55 (m, 2H, ***CH$_2$-14***), 2.36–2.25 (m, 2H, ***CH$_2$-5***), 2.09–2.02 (m, 1H, ***CH$_2$-9***), 1.77 (s, 3H, ***CH$_3$-18***), 1.85–1.71 (m, 4H, ***CH$_2$-6,10***), 1.68 (s, 3H, ***CH$_3$-13''***), 1.57 (s, 3H, ***CH$_3$-13''***), 1.54 (d, *J* = 3.9 Hz, 1H, ***CH$_2$-9***), 1.28 (s, 6H, ***CH$_3$-16,17***), 1.17 (s, 3H, ***CH$_3$-19***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 154.9 (***CO-1'***), 138.9 (***C-3***), 132.6 (***C-13'***), 130.3 (***CH-4***), 119.0 (***CH-13***), 103.8 (***CH-10'***), 89.7 (***C-1***), 83.1 (***C-11***), 80.2 (***C-12***), 79.6 (***CH-2***), 78.5 (***CH-7***), 56.4 (***CH$_3$-OMe***), 41.9 (***C-15***), 36.2 (***C-8***), 32.2 (***CH$_2$-9***), 31.2 (***CH$_2$-14***), 27.7 (***CH$_2$-10***), 25.8 (***CH$_3$-13''***), 24.9 (***CH$_2$-5***), 24.8 (***CH$_3$-16*** or ***17***), 24.3 (***CH$_3$-16*** or ***17***), 23.1 (***CH$_2$-6***), 18.6 (***CH$_3$-19***), 18.1 (***CH$_3$-13''***), 3.6 (***CH$_3$-18***).

IR (thin film): 2918, 2361, 1799, 1444, 1323, 1165, 1024 cm^{-1}.

HRMS (ESI): Calcd for $C_{25}H_{36}NaO_5^+$ $[M+Na]^+$, 439.2455; found, 439.2440.

9-Hydroxy-3,3,7,7-tetramethyl-1,5-dioxaspiro[5.5]undecan-8-one (2.92)



3.12 **2.92**

Chemical formula: $C_{13}H_{22}O_4$

MW: 242.32

To a stirred solution of ketone **3.12** (904 mg, 3.99 mmol) in THF (47 mL) at -78°C was added KHMDS (880 mg, 4.41 mmol, 1.10 equiv). The reaction mixture was stirred at this temperature

for 1h before **2.91** (2.20 g, 7.99 mmol, 2.0 equiv) was added portionwise. The resulting solution was stirred at room temperature for 24 h. A saturated aqueous solution of $NaHCl_4$ was added to quench the reaction. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (6:4) to afford the alcohol **2.92** as a white solid (782 mg, 3.23 mmol, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.40 (dd, *J* = 11.9, 7.7 Hz, 1H, ***CH-6***), 3.70 (d, *J* = 11.4 Hz, 1H, ***CH_2-9 or 11***), 3.51 (d, *J* = 11.4 Hz, 1H, ***CH_2-9 or 11***), 3.38 (dd, *J* = 11.4, 2.7 Hz, 1H, ***CH_2-9 or 11***), 3.28 (dd, *J* = 11.4, 2.6 Hz, 1H, ***CH_2-9 or 11***), 2.81–2.71 (m, 1H, ***CH_2-4 or 5***), 2.27–2.16 (m, 1H, ***CH_2-4 or 5***), 1.75 (td, *J* = 14.5, 4.0 Hz, 1H, ***CH_2-4 o 5***), 1.43–1.30 (m, 1H, ***CH_2-4 or 5***), 1.27 (s, 3H, ***CH_3-7***), 1.21 (s, 3H, ***CH_3-8***), 1.15 (s, 3H, ***CH_3-12***), 0.72 (s, 3H, ***CH_3-13***).

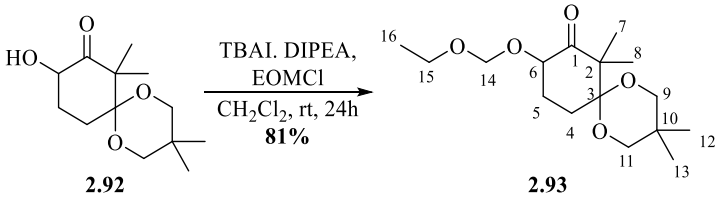
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 213.0 (***C-1***), 101.9 (***C-3***), 71.0 (***CH-6***), 70.7 (***CH_2-9 or 11***), 69.7 (***CH_2-9 or 11***), 54.4 (***C-2***), 29.8 (***C-10***), 28.2 (***CH_2-4 or 5***), 23.2 (***CH_3-12***), 22.8 (***CH_3-7***), 22.2 (***CH_3-13***), 19.4 (***CH_2-4 or 5***), 16.1 (***CH_3-8***).

IR (thin film): 3307, 1712, 173, 1166, 1120, 1078, 918 cm^{-1}.

HRMS (ESI): Calcd for $C_{13}H_{22}NaO_4^+$ $[M+Na]^+$, 265.1410; found, 265.1406.

MP: 79°C.

9-(Ethoxymethoxy)-3,3,7,7-tetramethyl-1,5-dioxaspiro[5.5]undecan-8-one (2.93)



Chemical formula: $C_{16}H_{28}O_5$

MW: 300.40

To a stirred solution of **2.92** (769 mg, 3.17 mmol) in CH_2Cl_2 (95 mL) was added TBAI (234 mg, 0.63 mmol, 0.20 equiv), DIPEA (3.86 mL, 22.2 mmol, 7.0 equiv) and EOMCl (1.17 mL, 12.6 mmol, 4.0 equiv). The reaction mixture was stirred at room temperature for 24 h. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was

extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (7:3) to afford the protected alcohol **2.93** as a pale yellow oil (775 mg, 2.58 mmol, 81%).

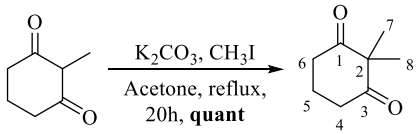
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.72 (dd, *J* = 24.8, 7.1 Hz, 2H, ***CH_2-14***), 4.44 (dd, *J* = 11.8, 7.1 Hz, 1H, ***CH-6***), 3.68–3.63 (m, 2H, ***CH_2-15, 9 or 11***), 3.55–3.52 (m, 2H, ***CH_2-15, 9 or 11***), 3.36–3.22 (m, 2H, ***CH_2-9, 11***), 2.73-2.69 (m, 1H, ***CH_2-4 or 5***), 2.02–1.99 (m, 1H, ***CH_2-4 or 5***), 1.84–1.72 (m, 1H, ***CH_2-4 or 5***), 1.52–1.50 (m, 1H, ***CH_2-4 or 5***), 1.19-1.15 (m, 9H, ***CH_3-7, 8, 16***), 1.10 (s, 3H, ***CH_3-12 or 13***), 0.68 (s, 3H, ***CH_3-12 or 13***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 209.2 (***C-1***), 101.4 (***C-3***), 94.2 (***CH_2-14***), 75.0 (***CH-6***), 70.6 (***CH_2-9 or 11***), 69.5 (***CH_2- 9 or 11***), 63.6 (***CH_2-15***), 55.2 (***C-2***), 29.7 (***C-10***), 26.1 (***CH_2-4 or 5***), 23.1 (***CH_3-7 or 8***), 22.4 (***CH_3-12 or 13***), 22.1 (***CH_3-12 or 13***), 19.7 (***CH_2-4 or 5***), 16.4 (***CH_3-7 or 8***), 15.1 (***CH_3-16***).

IR (thin film): 2951, 1726, 1473, 1446, 1382, 1116, 1055 cm^{-1}.

HRMS (ESI): Calcd for $C_{16}H_{28}NaO_5^+$ $[M+Na]^+$, 323.1829; found, 323.1819.

2,2-Dimethylcyclohexane-1,3-dione (3.11)[83]



2.32 **3.11**

Chemical formula: $C_8H_{12}O_2$

MW: 140.18

To a stirred solution of diketone **2.32** (25.0 g, 198 mmol) in acetone (30 mL) was added K_2CO_3 (54.8 g, 396 mmol, 2.0 equiv) and MeI (31 mL, 490 mmol, 2.5 equiv). The reaction mixture was refluxed for 20h. The resulting mixture was filtered and the filter cake was washed with Et_2O. Brine was added to the filtrate and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:EtOAc (8:2) to afford the diketone **(±)3.22** as a white solid (27.8 g, 198 mmol, quant).

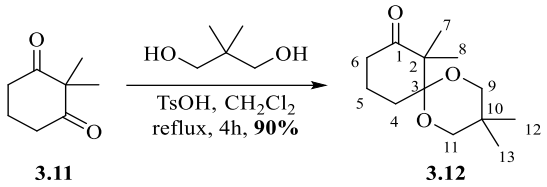
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.72–2.62 (m, 4H, ***CH_2-4,6***), 1.99–1.87 (m, 2H, ***CH_2-5***), 1.29 (s, 6H, ***CH_3-7,8***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 210.3 (***CO-1,3***), 61.6 (***C-2***), 37.2 (***CH_2-4,6***), 22.1 (***CH_3-7,8***), 17.9 (***CH_2-5***).

IR (thin film): 1695, 910, 373 cm^{-1}.

HRMS (EI): Calcd for $C_8H_{12}O_2^+$ $[M]^+$, 140.0837; found, 140.0843.

3,3,7,7-Tetramethyl-1,5-dioxaspiro[5.5]undecan-8-one (3.12)[83]



3.11 **3.12**

Chemical formula: $C_{13}H_{22}O_3$

MW: 226.32

To a stirred solution of diketone **3.11** (8.80 g, 62.8 mmol) in CH_2Cl_2 (130 mL) was added 2,2-dimethylpropane-1,3-diol (19.9 g, 191 mmol, 3.04 equiv) and *p*-toluenesulfonic acid (200 mg, 1.05 mmol, 0.016 equiv). The reaction mixture refluxed for 4h. The solvent was removed under reduced pressure and the resulting mixture was diluted with hexane and washed with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the acetal **3.12** as a white crystalline solid (12.7 g, 56.4 mmol, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.62 (d, *J* = 11.1 Hz, 2H, ***CH_2-9, 11***), 3.32 (dd, *J* = 10.3, 1.3 Hz, 2H, ***CH_2-9, 11***), 2.40 (t, *J* = 7.0 Hz, 2H, ***CH_2-6***), 2.24–2.15 (m, 2H, ***CH_2-4***), 1.72–1.61 (m, 2H, ***CH_2-5***), 1.19 (s, 6H, ***CH_3-7,8***), 1.15 (s, 3H, ***CH_3-12 or 13***), 0.71 (s, 3H, ***CH_3-12 or 13***).

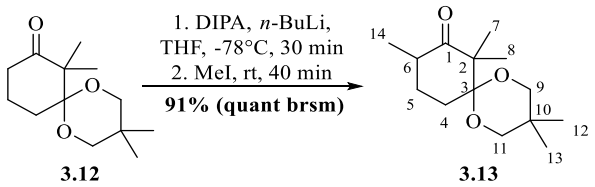
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 213.3 (***CO-1***), 101.9 (***C-3***), 70.2 (***CH_2-9,11***), 55.4 (***C-2***), 36.4 (***CH_2-6***), 29.8 (**C-10**), 23.2 (***CH_3-12 or 13***), 22.3 (***CH_3-12 or 13***), 20.7 (***CH_2-5***), 19.4 (***CH_3-7,8***), 18.7 (***CH_2-4***).

IR (thin film): 1674, 1112, 910, 739 cm^{-1}.

HRMS (ESI): Calcd for $C_{13}H_{22}NaO_3^+$ $[M+Na]^+$, 249.1461; found, 249.1464.

MP: 67°C (lit.[29b] 68°C).

3,3,7,7,9-Pentamethyl-1,5-dioxaspiro[5.5]undecan-8-one (3.13)[83]



3.12 **3.13**

Chemical formula: $C_{14}H_{24}O_3$

MW: 240.34

To a stirred solution of freshly distilled DIPA (2.45 mL, 17.5 mmol, 1.23 equiv) in THF (33 mL) at -78°C was slowly added *n*-BuLi (12.5 mL, 1.41 M in hexane, 17.6 mmol, 1.23 equiv). The resulting solution was stirred at -78°C for 30 min and then treated with a solution of ketone **3.12** (3.23 g, 14.2 mmol) in THF (10 mL). The reaction mixture was allowed to warm up to room temperature and stirred for 40 min. The resulting yellow solution was cooled down to -78°C and MeI (1.40 mL, 22.5 mmol, 1.60 equiv) was added to the reaction mixture. The reaction mixture was allowed to warm to room temperature and was then stirred for 1h. A saturated aqueous solution of $NaHCl_4$ was added and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (9:1) to afford the ketone **3.13** as a white crystalline solid (3.83 g, 16.0 mmol, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.71 (d, *J* = 11.3 Hz, 1H, ***CH_2-9 or 11***), 3.50 (d, *J* = 11.3 Hz, 1H, ***CH_2-9 or 11***), 3.37–3.25 (m, 2H, ***CH_2-9 or 11***), 2.74–2.66 (m, 1H, ***CH_2-4***), 2.64–2.53 (m, 1H, ***CH-6***), 1.87 –1.80 (m, 1H, ***CH_2-5***), 1.77 –1.73 (m, 1H, ***CH_2-4***), 1.29–1.22 (m, 1H, ***CH_2-5***), 1.20 (s, 3H, ***CH_3-7 or 8***), 1.18 (s, 3H, ***CH_3-12 or 13***), 1.14 (s, 3H, ***CH_3-12 or 13***), 1.01 (d, *J* = 6.5 Hz, 3H, ***CH_3-14***), 0.70 (s, 3H, ***CH_3-7 or 8***).

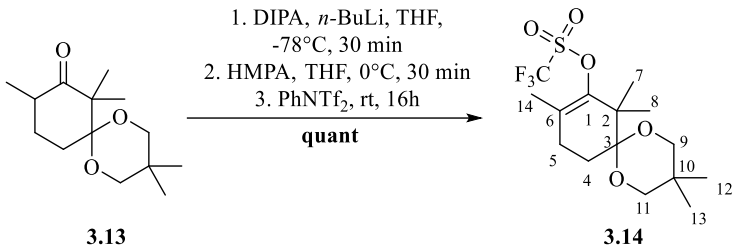
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 214.0 (***CO-1***), 102.2 (***C-3***), 70.5 (***CH_2-9 or 11***), 69.7 (***CH_2-9 or 11***), 55.0 (***C-2***), 39.2 (***CH-6***), 29.8 (***C-10***), 27.8 (***CH_2-5***), 23.2 (***CH_3-12, 13 or 14***), 22.3 (***CH_3-7 or 8***), 21.1 (***CH_2-4***), 16.3 (***CH_3-7 or 8***), 14.9 (***CH_3-12, 13 or 14***).

IR (thin film): 2954, 1708, 1128, 1112, 1087, 1029 cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{24}NaO_3^+$ $[M+Na]^+$, 263.1618; found, 263.1616.

MP: 78°C-80°C° (lit.[102] 79.5°C-81.5°C).

3,3,7,7,9-Pentamethyl-1,5-dioxaspiro[5.5]undec-8-en-8-yl trifluoromethanesulfonate (3.14)[83]



3.13 **3.14**

Chemical formula: $C_{15}H_{23}F_3O_5S$

MW: 372.40

To a stirred solution of freshly distilled DIPA (6.4 mL, 45 mmol, 2.2 equiv) in THF (116 mL) at -78°C was slowly added *n*-BuLi (18.7 mL, 2.40 M in hexane, 44.8 mmol, 2.2 equiv). The resulting solution was stirred at -78°C for 30 min and then treated with a solution of ketone **3.13** (4.91 g, 20.4 mmol) in THF (45 mL) and HMPA (9.3 mL, 53 mmol, 2.6 equiv). The yellow reaction mixture was stirred at 0°C for 30 min. A solution of $PhNTf_2$ (11.6 g, 32.6 mmol, 1.6 equiv) in THF (23 mL) was added and the resulting solution was stirred at room temperature for 16h. Water was added, and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (100:2.5) to afford the triflate **3.14** as a white crystalline solid (7.60 g, 20.4 mmol, quant).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.64 (d, *J* = 11.3 Hz, 2H, ***CH_2-9,11***), 3.38 (dd, *J* = 10.3, 1.3 Hz, 2H, ***CH_2-9,11***), 2.07 (bs, 4H, ***CH_2-4,5***), 1.75 (s, 3H, ***CH_3-14***), 1.21 (s, 6H, ***CH_3-7,8***), 1.18 (s, 3H, ***CH_3-12***), 0.73 (s, 3H, ***CH_3-13***).

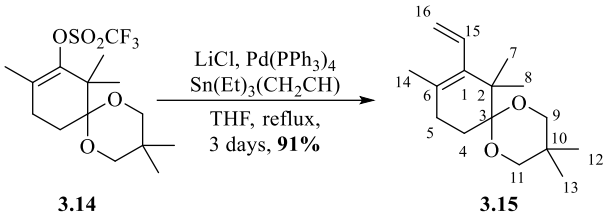
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 147.0 (***C-1***), 124.4 (***C-6***), 118.7 (q, *J* = 250 Hz, ***CF_3***), 99.9 (***C-3***), 70.5 (***CH_2-9,11***), 45.3 (***C-2***), 29.8 (***C-10***), 27.7 (***CH_2-5***), 23.0 (***CH_3***), 22.1 (***CH_3***), 20.5 (***CH_3***), 18.1 (***CH_2-4***), 17.3 (***CH_3-14***).

IR (thin film): 2967, 2880, 1689, 1400, 1242, 1209, 1141, 1020 cm^{-1}.

HRMS (ESI): Calcd for $C_{15}H_{23}F_3NaO_5S^+$ $[M+Na]^+$, 35.1111; found, 395.1105.

MP: 78°C.

3,3,7,7,9-Pentamethyl-8-vinyl-1,5-dioxaspiro[5.5]undec-8-ene (3.15)[83]



Chemical formula: $C_{16}H_{26}O_2$

MW: 250.38

To a stirred slurry of LiCl (5.99 g, 141 mmol, 3.0 equiv) and $Pd(PPh_3)_4$ (5.44 g, 4.71 mmol, 0.10 equiv) in THF (300 mL) was added vinyl triflate **3.14** (17.5 g, 47.0 mmol) and triethyl(vinyl)stannane (21 mL, 72 mmol, 1.5 equiv). The reaction mixture was refluxed for 3 days and the resulting solution was allowed to cool down to room temperature. Et_2O was added to dilute the reaction mixture and the organic layer was washed with water, a 5% aqueous solution of NH_4OH and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (97:3) to afford the diene **3.15** as a pale yellow oil (10.7 g, 42.7 mmol, 91%).

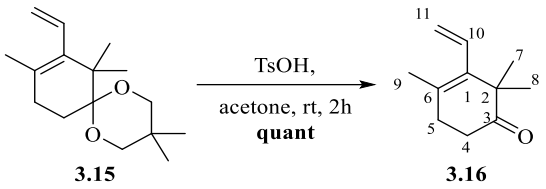
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.16 (ddd, *J* = 17.6, 11.2, 1.0 Hz, 1H, ***CH-15***), 5.25 (dd, *J* = 11.2, 2.7 Hz, 1H, ***CH_2-16***), 4.97 (dd, *J* = 17.6, 2.7 Hz, 1H, ***CH_2-16***), 3.70 (d, *J* = 11.1 Hz, 2H, ***CH_2-9, 11***), 3.37 (dd, *J* = 10.3, 1.3 Hz, 2H, ***CH_2-9, 11***), 2.12–1.93 (m, 4H, ***CH_2-4,5***), 1.68 (s, 3H, ***CH_3-14***), 1.18 (s, 3H, ***CH_3-12 or 13***), 1.09 (s, 6H, ***CH_3-7,8***), 0.72 (s, 3H, ***CH_3-12 or 13***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 137.1 (***C-1***), 135.3 (***CH-15***), 126.5 (***C-6***), 118.9 (***CH_2-16***), 100.2 (***C-3***), 70.2 (***CH_2-9,11***), 43.2 (***C-2***), 29.9 (***CH_2-5***), 29.8 (***C-10***), 23.2 (***CH_3***), 22.5 (***CH_3***), 22.3 (***CH_3***), 21.0 (***CH_3-14***), 18.4 (***CH_2-4***).

IR (thin film): 2102, 2050, 1500, 1066, 1103, 1066 cm^{-1}.

HRMS (ESI): Calcd for $C_{16}H_{26}NaO_2^+$ $[M+Na]^+$, 273.1825; found, 273.1819.

2,2,4-Trimethyl-3-vinylcyclohex-3-en-1-one (3.16)[83]



Chemical formula: $C_{11}H_{16}O$

MW: 164.25

To a stirred solution of acetal **3.15** (10.7 g, 42.8 mmol) in acetone (360 mL) was added a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was stirred at room temperature for 2h and the solvent was then removed under reduced pressure. A saturated aqueous solution of $NaHCO_3$ was added to the resulting mixture and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (95:5) to afford the ketone **3.16** as a pale yellow oil (7.03 g, 42.8 mmol, quant).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.21–6.05 (m, 1H, ***CH-10***), 5.34 (dd, *J* = 11.2, 2.4 Hz, 1H, ***CH_2-11***), 5.07 (dd, *J* = 17.6, 2.3 Hz, 1H, ***CH_2-11***), 2.54 (t, *J* = 7.0 Hz, 2H, ***CH_2-4***), 2.39 (t, *J* = 6.9 Hz, 2H, ***CH_2-5***), 1.78 (s, 3H, ***CH_3-9***), 1.16 (s, 6H, ***CH_3-7,8***).

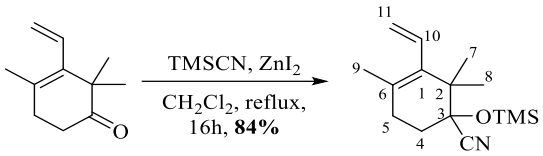
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 215.1 (***C-3***), 137.4 (***C-1***), 133.9 (***CH-10***), 128.7 (***C-6***), 119.8 (***CH_2-11***), 46.7 (***C-2***), 35.9 (***CH_2-4***), 31.8 (***CH_2-5***), 24.8 (***CH_3-7,8***), 21.1 (***CH_3-9***).

IR (thin film): 2943, 1708, 910, 739 cm^{-1}.

HRMS (ESI): Calcd for $C_{11}H_{16}NaO$, 187.1093$^+$ $[M+Na]^+$; found, 187.1089.

2,2,4-Trimethyl-1-((trimethylsilyl)oxy)-3-vinylcyclohex-3-ene-1-carbonitrile (((±))3.17)[83]

Method A



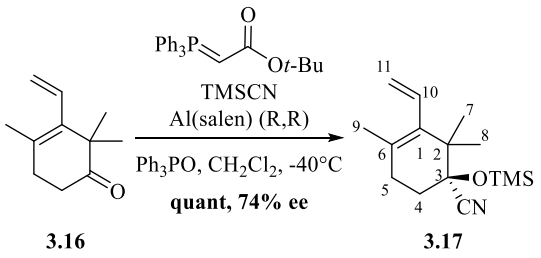
3.16 **(±) 3.17**

Chemical formula: $C_{15}H_{25}NOSi$

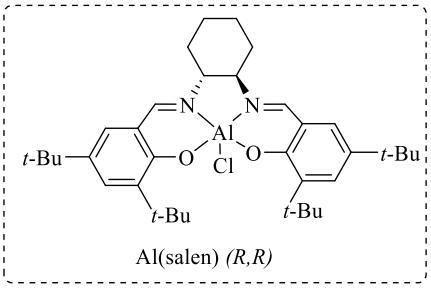
MW: 263.46

To a stirred solution of ketone **3.16** (1.82 g, 11.1 mmol) in CH_2Cl_2 (55 mL) was added ZnI_2 (709 mg, 2.22 mmol, 0.20 equiv) and TMSCN (2.90 mL, 22.2 mmol, 2.0 equiv). The reaction mixture was refluxed for 16 h and then allowed to cool down to room temperature. The volatiles were removed under reduced pressure with a trap of aqueous NaOCl/NaOH set up to quench the excess of TMSCN. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (100:5) to afford the cyanohydrin **(±)3.17** as a colourless oil (2.47 g, 9.37 mmol, 84%).

***Method B*[68]**



3.16 **3.17**



Al(salen) *(R,R)*

To a stirred solution of ketone **3.16** (246 mg, 1.50 mmol) in CH_2Cl_2 (1.50 mL) at -40°C was added (salen)AlCl (*R,R*) (91 mg, 0.15 mmol, 0.10 equiv), (*tert*-butoxycarbonylmethylene) triphenylphosphorane (58 mg, 0.15 mmol, 0.10 equiv) and Ph_3PO (210 mg, 0.75 mmol, 0.50 equiv). The resulting solution was stirred at -40°C for 30 min before TMSCN (400 µL, 3.0 mmol, 2.0 equiv) was added dropwise. The reaction mixture was stirred for 4 days at -40°C and then allowed to warm to room temperature. The volatiles were removed under reduced pressure with a trap of aqueous NaOCl/NaOH set up to quench the excess of TMSCN. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (100:5) to afford the cyanohydrin **3.17** as a colourless oil (396 mg, 1.51 mmol, quant).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.19–6.02 (m, 1H, ***CH-10***), 5.29 (dd, *J* = 11.2, 2.5 Hz, 1H, ***CH_2-11***), 4.98 (dd, *J* = 17.6, 2.5 Hz, 1H, ***CH_2-11***), 2.44–2.26 (m, 1H, ***CH_2-4 or 5***), 2.38–

2.29 (m, 1H, ***CH_2-4 or 5***), 2.06–1.97 (m, 2H, ***CH_2-4 or 5***), 1.68 (s, 3H, ***CH_3-9***), 1.19 (s, 3H, ***CH_3-7 or 8***), 1.01 (s, 3H, ***CH_3-7 or 8***), 0.24 (s, 9H, ***CH_3-OTMS***).

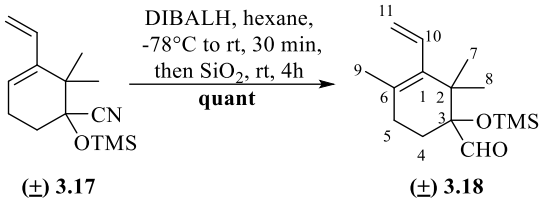
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 135.6 (***C-1***), 134.6 (***CH-10***), 126.9 (***C-6***), 121.3 (***CN***), 119.6 (***CH_2-11***), 76.2 (***C-3***), 42.3 (***C-2***), 30.9 (***CH_2-4 or 5***), 29.5 (***CH_2-4 or 5***), 23.5 (***CH_3-7 or 8***), 22.3 (***CH_3-7 or 8***), 20.9 (***CH_3-9***), 1.3 (***CH_3-OTMS***).

IR (thin film): 1253, 1147, 1126, 910, 846, 737 cm^{-1}.

HRMS (ESI): Calcd for $C_{15}H_{25}NNaOSi^+$ $[M+Na]^+$, 286.1598; found, 286.1588.

[α]$_D$: -72.8 (*c* 1.0, $CHCl_3$).

2,2,4-Trimethyl-1-((trimethylsilyl)oxy)-3-vinylcyclohex-3-ene-1-carbaldehyde ((±)3.18)[83]



Chemical formula: $C_{15}H_{26}O_2Si$

MW: 266.46

To a stirred solution of cyanohydrin **(±)3.17** (2.47 g, 9.38 mmol) in freshly distilled hexane (90 mL) at -78°C was added DIBALH (14 mL, 1 M in hexane, 14 mmol, 1.5 equiv). The reaction mixture was allowed to warm to 0°C and was stirred at this temperature for 30 min. The mixture was then cooled down to -78°C, and EtOAc was added dropwise. The resulting mixture was stirred at this temperature for 20 min and then SiO_2 (30 g) was added. The reaction mixture was then allowed to warm to room temperature and stirred for 2 h. The resulting suspension was filtered and the silica was washed thoroughly with EtOAc. The solvent was removed under reduced pressure to afford the aldehyde **(±)3.18** as a pale yellow oil (2.50 g, 9.38 mmol, quant).

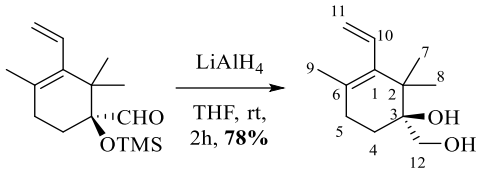
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.78 (s, 1H, ***CHO***), 6.13 (dd, *J* = 17.6, 11.1 Hz, 1H, ***CH-10***), 5.29 (dd, *J* = 11.2, 2.5 Hz, 1H, ***CH_2-11***), 4.98 (dd, *J* = 17.6, 2.5 Hz, 1H, ***CH_2-11***), 2.17 (t, *J* = 6.8 Hz, 2H, ***CH_2-4***), 1.90 (t, *J* = 6.8 Hz, 2H, ***CH_2-5***), 1.69 (s, 3H, ***CH_3-9***), 1.04 (s, 3H, ***CH_3-7 or 8***), 0.96 (s, 3H, ***CH_3-7 or 8***), 0.13 (s, 9H, ***CH_3-OTMS***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 205.0 (***C-CHO***), 136.9 (***C-1***), 134.8 (***CH-10***), 127.1 (***C-6***), 119.3 (***CH_2-11***), 83.0 (***C-3***), 40.7 (***C-2***), 29.7 (***CH_2-4***), 27.8 (***CH_2-5***), 24.0 (***CH_3-7 or 8***), 22.4 (***CH_3-7 or 8***), 20.9 (***CH_3-9***), 2.4 (***CH_3-OTMS***).

IR (thin film): 1728, 1251, 910, 842 cm^{-1}.

HRMS (ESI): Calcd for $C_{15}H_{26}NaO_2Si^+$ $[M+Na]^+$, 289.1594; found, 289.1580.

(*S*)-1-(Hydroxymethyl)-2,2,4-trimethyl-3-vinylcyclohex-3-en-1-ol (3.19)



3.18 **3.19**

Chemical formula: $C_{12}H_{20}O_2$

MW: 196.29

To a stirred suspension of $LiAlH_4$ (57 mg, 1.5 mmol, 1.5 equiv) in THF (3.5 mL) was added a solution of the aldehyde **3.18** (270 mg, 1.00 mmol) in THF (3.5 mL). The reaction mixture was stirred at room temperature for 2 h. An aqueous solution of Rochelle salt (10% wt)was added to quench the reaction and the resulting mixture was stirred at room temperature for 16h. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the diol **3.19** as a white solid (153 mg, 0.78 mmol, 78%).

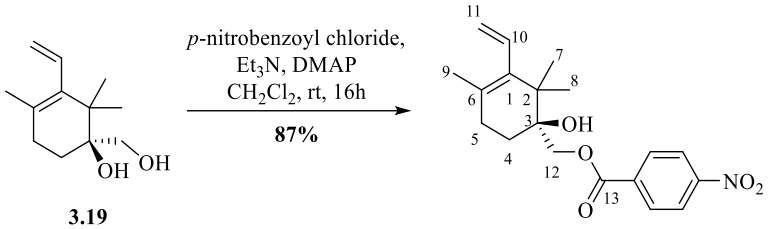
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.11 (dd, *J* = 17.1, 11.6 Hz, 1H, ***CH-10***), 5.28 (d, *J* = 11.1 Hz, 1H, ***CH_2-11***), 4.94 (d, *J* = 17.6 Hz, 1H, ***CH_2-11***), 3.72 (d, *J* = 11.0 Hz, 1H, ***CH_2-12***), 3.47 (d, *J* = 10.9 Hz, 1H, ***CH_2-12***), 2.11–2.02 (m, 4H, ***CH_2-5, 2OH***), 1.87–1.68 (m, 2H, ***CH_2-4***), 1.68 (s, 3H, ***CH_3-9***), 1.06 (s, 3H, ***CH_3-7 or 8***), 0.93 (s, 3H, ***CH_3-7 or 8***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 137.0 (***C-1***), 135.0 (***CH-10***), 127.5 (***C-6***), 119.3 (***CH_2-11***), 74.9 (***C-3***), 65.0 (***CH_2-12***), 40.4 (***C-2***), 29.1 (***CH_2-5***), 26.3 (***CH_2-4***), 22.8 (***CH_3-9***), 22.7 (***CH_3-7 or 8***), 21.2 (***CH_3-7 or 8***).

IR (thin film): 3379, 2974, 1618, 1458, 915 cm^{-1}.

HRMS (ESI): Calcd for $C_{12}H_{20}NaO_2^+$ $[M+Na]^+$, 219.1356; found, 219.1358.

(*S*)-(1-Hydroxy-2,2,4-trimethyl-3-vinylcyclohex-3-en-1-yl)methyl 4-nitrobenzoate (3.20)



3.19 **3.20**

Chemical formula: $C_{19}H_{23}NO_5$

MW: 345.40

To a stirred solution of diol **3.19** (37 mg, 0.19 mmol) in CH_2Cl_2 (4.1 mL) was added triethylamine (66 μL, 0.47 mmol, 2.5 equiv), DMAP (23 mg, 0.19 mmol, 1.0 equiv) and *p*-nitrobenzoyl chloride (71 mg, 0.38 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature for 16 h. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (1:1) to afford the alcohol **3.20** as a white solid (57 mg, 0.16 mmol, 87%) and with 74% *ee* determined by chiral HPLC when using an AD-H column with an injection volume of 20 μL and using 5% *i*PrOH in hexanes as eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.29–8.17 (m, 4H, ***CH-Ar***), 6.13 (dd, *J* = 17.6, 11.0 Hz, 1H, ***CH-10***), 5.32 (dd, *J* = 11.1, 2.4 Hz, 1H, ***CH$_2$-11***), 4.99 (dd, *J* = 17.6, 2.4 Hz, 1H, ***CH$_2$-11***), 4.54 (d, *J* = 11.6 Hz, 1H, ***CH$_2$-12***), 4.44–4.39 (m, 1H, ***CH$_2$-12***), 2.23–2.02 (m, 2H, ***CH$_2$-4 or 5***), 1.94–1.87 (m, 2H, ***CH$_2$-4 or 5***), 1.70 (s, 3H, ***CH$_3$-9***), 1.14 (s, 3H, ***CH$_3$-7 or 8***), 1.07 (s, 3H, ***CH$_3$-7 or 8***).

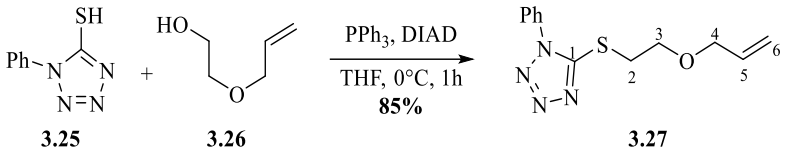
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 165.1 (***C-13***), 136.9 (***C-1***), 135.5 (***C-Ar***), 134.7 (***CH-10***), 130.7 (***CH-Ar***), 130.6 (***C-Ar***), 127.4 (***C-6***), 123.5 (***CH-Ar***), 119.6 (***CH_2-11***), 74.3 (***C-3***), 68.9 (***CH_2-12***), 40.9 (***C-2***), 29.4 (***CH_2-4 or 5***), 27.2 (***CH_2-4 or 5***), 23.1 (***CH_3-7 or 8***), 22.3 (***CH_3-7 or 8***), 21.0 (***CH_3-9***).

HRMS (ESI): Calcd for $C_{19}H_{23}NaO_5^+$ $[M+Na]^+$, 368.1468; found, 368.1456.

MP: 121°C.

[α]$_D$: -29.8 (*c* 1.0, $CHCl_3$), 74% ee.

5-((2-(Allyloxy)ethyl)thio)-1-phenyl-1*H*-tetrazole (3.27)



3.25 **3.26** **3.27**

Chemical formula: $C_{12}H_{14}N_4OS$

MW: 262.33

To a stirred solution of alcohol **3.26** (210 μL, 2.00 mmol) and thiol **3.25** (463 mg, 2.59 mmol, 1.30 equiv) in THF (7.32 mL) at 0°C was added DIAD (512 μL, 2.60 mmol, 1.30 equiv) and PPh_3 (577 mg, 2.20 mmol, 1.10 equiv). The reaction mixture was stirred at this temperature for 1h and then a saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (8:2) to (6:4) to afford the sulfide **3.27** as colourless oil (447 mg, 1.70 mmol, 85%).

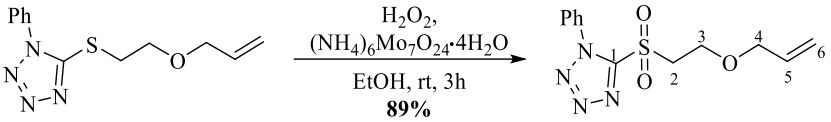
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.72–7.38 (m, 5H, ***CH-Ar***), 5.87 (m, 1H, ***CH-5***), 5.22 (m, 2H, ***CH_2-6***), 4.02 (m, 2H, ***CH_2-4***), 3.83 (t, *J* = 5.9 Hz, 2H, ***CH_2-3***), 3.61 (t, *J* = 5.9 Hz, 2H, ***CH_2-2***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 154.2 (***C-1***), 134.1 (***CH-5***), 133.6 (***C-Ar***), 130.1 (***CH-Ar***), 129.8 (***CH-Ar***), 123.8 (***CH-Ar***), 117.6 (***CH_2-6***), 72.0 (***CH_2-4***), 67.8 (***CH_2-3***), 33.3 (***CH_2-2***).

IR (thin film): 2175, 2162, 1596, 1499, 1384, 1089, 1012, 762 cm^{-1}.

HRMS (ESI): Calcd for $C_{12}H_{14}N_4NaOS^+$ $[M+Na]^+$, 285.0781; found, 285.0771.

5-((2-(Allyloxy)ethyl)sulfonyl)-1-phenyl-1*H*-tetrazole (3.28)



3.27 **3.28**

Chemical formula: $C_{12}H_{14}N_4O_3S$

MW: 294.33

To a stirred solution of sulfide **3.27** (3.90 g, 14.9 mmol) in ethanol (200 mL) at 0°C was added $(NH_4)_6Mo_7O_{24}\cdot H_2O$ (2.94 g, 2.38 mmol, 0.160 equiv) and 30% H_2O_2 (9.60 mL, 84.9 mmol, 5.70 equiv). The resulting mixture was stirred at room temperature for 3 days. Brine was added to quench the reaction and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (7:3) to (1:1) to afford the sulfone **3.28** as a white solid (3.89 g, 13.2 mmol, 89%). When 3 equivalents of H_2O_2 were used instead, sulfoxide **3.29** was obtained as a white solid in 17% yield along with sulfone **3.28** in 78% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.81–7.45 (m, 5H, ***CH-Ar***), 5.69 (m, 1H, ***CH-5***), 5.27–5.02 (m, 2H, ***CH_2-6***), 3.89–3.77 (m, 6H, ***CH_2-2,3,4***).

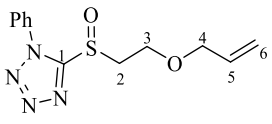
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 154.0 (***C-1***), 133.2 (***CH-5***), 133.1 (***C-Ar***), 131.5 (***CH-Ar***), 129.6 (***CH-Ar***), 125.7 (***CH-Ar***), 118.3 (***CH_2-6***), 72.2 (***CH_2***), 62.8 (***CH_2***), 56.3 (***CH_2***).

IR (thin film): 2160, 2011, 2004, 1350, 1151, 906, 731 cm^{-1}.

HRMS (ESI): Calcd for $C_{12}H_{14}N_4NaO_3S^+$ $[M+Na]^+$, 317.0679; found, 301.0677

MP: 51°C.

5-((2-(Allyloxy)ethyl)sulfinyl)-1-phenyl-1*H*-tetrazole (3.29)



3.29

Chemical formula: $C_{12}H_{14}N_4O_2S$

MW: 278.33

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.76–7.55 (m, 5H, ***CH-Ar***), 5.78 (m, 1H, ***CH-5***), 5.28–5.11 (m, 2H, ***CH_2-6***), 4.03–3.84 (m, 5H, ***CH_2***), 3.72 (dq, *J* = 7.4, 4.8 Hz, 1H, ***CH_2-2***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 156.4 (***C-1***), 133.4 (***CH-5***), 132.9 (***C-Ar***), 131.6 (***CH-Ar***), 129.9 (***CH-Ar***), 124.9 (***CH-Ar***), 118.1 (***CH_2-6***), 72.3 (***CH_2-4***), 61.6 (***CH_2-3***), 53.6 (***CH_2-2***).

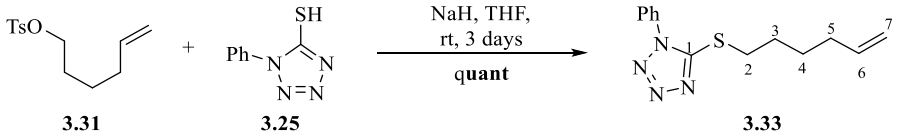
IR (thin film): 1496, 1350, 1151, 1014, 910, 762 cm^{-1}.

HRMS (ESI): Calcd for $C_{12}H_{14}N_4NaO_2S^+$ $[M+Na]^+$, 301.0730; found, 301.0723.

MP: 88°C.

5-(Hex-5-en-1-ylthio)-1-phenyl-1*H*-tetrazole (3.33)

Method A



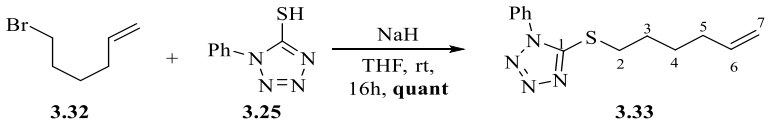
3.31 **3.25** **3.33**

Chemical formula: $C_{13}H_{16}N_4S$

MW: 260.36

To a stirred suspension of NaH (438 mg, 10.9 mmol, 1.31 equiv) in THF (15 mL) at 0°C was slowly added the thiol **3.25** (1.63 g, 9.15 mmol, 1.10 equiv). The reaction mixture was stirred at this temperature for 30 min followed by slow addition of the tosylated alcohol **3.31** (2.11 g, 8.30 mmol). The resulting mixture was stirred at room temperature for 3 days and water was then added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the sulfide **3.33** as a colourless oil (2.16 g, 8.30 mmol, quant).

Method B



3.32 **3.25** **3.33**

To a stirred suspension of NaH (360 mg, 9.00 mmol, 1.20 equiv) in THF (14 mL) at 0°C was slowly added the thiol **3.25** (1.47 g, 8.25 mmol, 1.10 equiv). The reaction mixture was stirred at this temperature for 30 min followed by slow addition of alkene **3.32** (1.0 mL, 7.5 mmol). The

resulting mixture was stirred at room temperature for 3 days and water was then added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the sulfide **3.33** as a colourless oil (1.98 g, 7.59 mmol, quant).

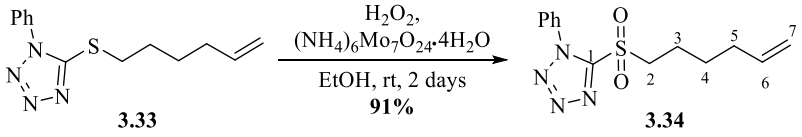
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.71–7.42 (m, 5H, ***CH-Ar***), 5.77 (m, 1H, ***CH-6***), 5.09–4.87 (m, 2H, ***CH_2-7***), 3.40 (m, 2H, ***CH_2-2***), 2.09 (m, 2H, ***CH_2-5***), 1.83 (m, 2H, ***CH_2-3***), 1.54 (m, 2H, ***CH_2-4***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 154.4 (***C-1***), 138.0 (***CH-6***), 133.7 (***C-Ar***), 130.1 (***CH-Ar***), 129.8 (***CH-Ar***), 123.8 (***CH-Ar***), 115.1 (***CH_2-7***), 33.2 (***CH_2-2 or 5***), 33.1 (***CH_2-2 or 5***), 28.5 (***CH_2-3***), 27.8 (***CH_2-4***)

IR (thin film): 2924, 2856, 1597, 1500, 1413, 910 cm^{-1}.

HRMS (ESI): Calcd for $C_{13}H_{16}N_4NaS^+$ $[M+Na]^+$, 283.0988; found, 283.0978.

5-(Hex-5-en-1-ylsulfonyl)-1-phenyl-1*H*-tetrazole (3.34)



Chemical formula: $C_{13}H_{16}N_4O_2S$

MW: 276.36

To a stirred solution of sulfide **3.33** (2.16 g, 8.30 mmol) in ethanol (110 mL) at 0°C was added $(NH_4)_6Mo_7O_{24}·H_2O$ (1.64 mg, 1.33 mmol, 0.160 equiv) and 30% H_2O_2 (5.40 mL, 47.3 mmol, 5.7 equiv). The resulting mixture was stirred at room temperature for 3 days. Brine was added to quench the reaction and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:EtOAc (8:2) to afford the sulfone **3.34** as a colourless oil (2.09 g, 7.55 mmol, 91%).

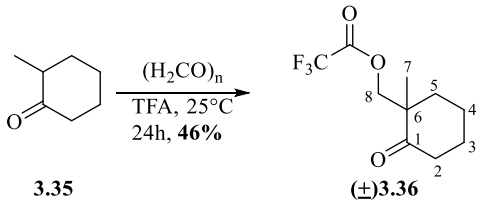
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.77–7.51 (m, 5H, ***CH-Ar***), 5.76 (m, 1H, ***CH-6***), 5.10–4.95 (m, 2H, ***CH_2-7***), 3.74 (m, 2H, ***CH_2-2***), 2.12 (m, 2H, ***CH_2-5***), 2.03–1.89 (m, 2H, ***CH_2-3***), 1.69–1.52 (m, 2H, ***CH_2-4***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 153.4 (***C-1***), 137.2 (***CH-6***), 133.0 (***C-Ar***), 131.4 (***CH-Ar***), 129.7 (***CH-Ar***), 125.0 (***CH-Ar***), 115.7 (***CH_2-7***), 55.8 (***CH_2-2***), 32.9 (***CH_2-5***), 27.3 (***CH_2-4***), 21.4 (***CH_2-3***).

IR (thin film): 3306, 2941, 2831, 1448, 1028, 734 cm^{-1}.

HRMS (ESI): Calcd for $C_{13}H_{16}N_4NaO_2S^+$ $[M+Na]^+$, 315.0886; found, 315.0879

(1-Methyl-2-oxocyclohexyl)methyl 2,2,2-trifluoroacetate ((±)3.36)



3.35 **(±)3.36**

Chemical formula: $C_{10}H_{13}F_3O_3$

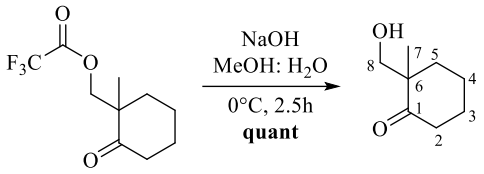
MW: 238.21

To a stirred solution of **3.35** (10.0 mL, 82.5 mmol) in TFA (mL) was added *p*-formaldehyde (8.0 mL, 37% in H_2O, 99 mmol, 1.2 equiv) and the reaction mixture was stirred at 25°C for 24h. Et_2O was added to dilute the resulting mixture and the organic layer was washed several times with an aqueous saturated solution of $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (95:5) to (8:2) to afford the trifluoroacetate **(±)3.36** as a colourless oil (8.96 g, 37.6 mmol, 46%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.45 (d, *J* = 11.0 Hz, 1H, ***CH_2-8***), 4.29 (d, *J* = 11.0 Hz, 1H, ***CH_2-8***), 2.51 (m, 1H, ***CH_2-2***), 2.34 (m, 1H, ***CH_2-2***), 2.07–1.96 (m, 1H, ***CH_2***), 1.84–1.65 (m, 5H, ***CH_2***), 1.22 (s, 3H, ***CH_3-7***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 212.0 (***CO-1***), 157.3 (q, *J* = 40 Hz, ***$COCF_3$***), 114.5 (q, *J* = 290 Hz, ***CF_3***), 71.9 (***CH_2-8***), 48.3 (***C-6***), 38.4 (***CH_2-5***), 35.5 (***CH_2***), 26.9 (***CH_2***), 20.7 (***CH_2***), 20.1 (***CH_3-7***).**IR (thin film):** 1782, 1697, 1209, 1161 cm^{-1}.

2-(Hydroxymethyl)-2-methylcyclohexan-1-one ((±)3.37)



(±)3.36 **(±)3.37**

Chemical formula: $C_8H_{14}O_2$

MW: 142.20

To a stirred solution of trifluoroacetate **(±)3.36** (24.5 g, 103 mmol) in a 1:1 mixture of MeOH:H_2O (114 mL) at 0°C was added NaOH (5.80 g, 145 mmol, 1.41 equiv). The reaction mixture was stirred at this temperature for 2.5h and a saturated aqueous solution of NH_4Cl was then added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the alcohol **(±)3.37** as a pale yellow oil (14.6 g, mmol, quant).

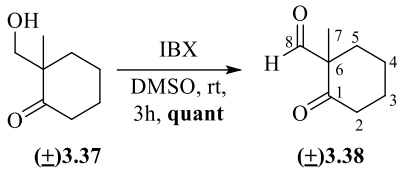
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.48 (d, *J* = 1.3 Hz, 2H, ***CH_2-8***), 2.71 (bs, 1H, ***OH***), 2.55–2.42 (m, 1H, ***CH_2-2***), 2.26 (m, 1H, ***CH_2-2***), 2.01 (m, 1H, ***CH_2***), 1.89–1.46 (m, 5H, ***CH_2***), 1.17 (s, 3H, ***CH_3-7***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 218.4 (***CO-1***), 69.0 (***CH_2-8***), 50.1 (***C-6***), 38.9 (***CH_2-2***), 35.5 (***CH_2***), 27.3 (***CH_2***), 20.7 (***CH_2***), 20.2 (***CH_3-7***).

IR (thin film): 3454, 2938, 1691, 1450, 1265, 1037, 735 cm^{-1}.

HRMS (ESI): Calcd for $C_8H_{14}NaO_2^+$ $[M+Na]^+$, 165.0886; found, 165.0881.

1-Methyl-2-oxocyclohexane-1-carbaldehyde ((±)3.38)



Chemical formula: $C_8H_{12}O_2$

MW: 140.18

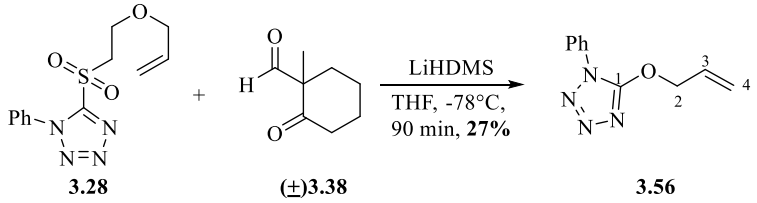
To a stirred solution of alcohol **(±)3.37** (1.42 g, 10.0 mmol) in DMSO (30 mL) was added IBX (7.92 g, 30.0 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 3h. The resulting mixture was then filtered and the filter cake was washed with Et_2O. Water was added to the filtrate and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the aldehyde **(±)3.38** as a pale yellow oil (1.40 g, 10 mmol, quant).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.50 (s, 1H, ***CHO-5***), 2.54–2.24 (m, 3H, ***CH₂***), 2.01–1.91 (m, 1H, ***CH₂***), 1.82–1.55 (m, 4H, ***CH₂***), 1.24 (s, 3H, ***CH₃-7***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 209.7 (***CO-1***), 201.0 (***CHO-5***), 61.3 (***C-6***), 40.6 (***CH₂***), 34.7 (***CH₂***), 26.7 (***CH₂***), 21.7 (***CH₂***), 17.9 (***CH₃-7***).

HRMS (CI/Isobutane): Calcd for $C_8H_{13}O_2^+$ $[M+H]^+$, 141.0916; found, 141.0910.

5-(Allyloxy)-1-phenyl-1*H*-tetrazole (3.56)



Chemical formula: $C_{10}H_{10}N_4O$

MW: 202.22

To a stirred solution of sulfone **3.28** (135 mg, 0.460 mmol) in THF (2.1 mL) at -78°C was added LiHMDS (0.92 mL, 1M in THF, 0.92 mmol, 2.0 equiv). The reaction mixture was stirred at this temperature for 15 min before a solution of aldehyde **(±)3.38** (76 mg, 0.54 mmol, 1.2 equiv) in THF (1.2 mL) was added. The resulting solution was stirred at -78°C for 90 min and a saturated aqueous solution of NH_4Cl was then added to quench the reaction. The aqueous layer was

extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (7:3) to (1:1) to afford **(±)3.56** as a colourless oil (25 mg, 0.12 mmol, 27%).

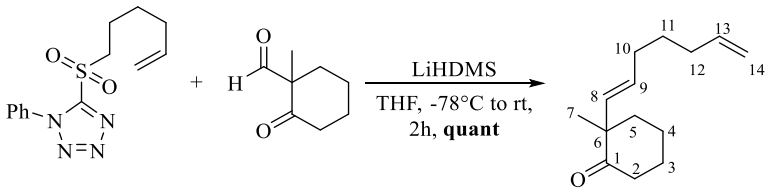
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.70 (m, 2H, ***CH-Ar***), 7.47 (m, 3H, ***CH-Ar***), 6.20–6.00 (m, 1H, ***CH-3***), 5.50–5.39 (m, 2H, ***CH_2-4***), 5.10 (d, *J* = 5.9 Hz, 2H, ***CH_2-2***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 159.9 (***C-1***), 133.3 (***C-Ar***), 130.4 (***CH-3***), 129.5 (***CH-Ar***), 128.9 (***CH-Ar***), 121.6 (***CH-Ar***), 120.9 (***CH_2-4***), 74.1 (***CH_2-2***).

IR (thin film): 1799, 1595, 1558, 1506, 1451 cm^{-1}.

HRMS (ESI): Calcd for $C_{10}H_{10}N_4NaO^+$ $[M+Na]^+$, 225.0747; found, 225.0740.

(*E*)-2-(Hepta-1,6-dien-1-yl)-2-methylcyclohexan-1-one ((±)3.61)



3.34 **(±)3.38** **(±)3.61**

Chemical formula: $C_{14}H_{22}O$

MW: 206.33

To a stirred solution of sulfone **3.34** (135 mg, 0.460 mmol) in THF (2.1 mL) at -78°C was added LiHMDS (0.92 mL, 1M in THF, 0.92 mmol, 2.0 equiv). The reaction mixture was stirred at this temperature for 15 min before a solution of aldehyde **(±)3.38** (132 mg, 0.94 mmol, 2.0 equiv) in THF (1.2 mL) was added. The resulting solution was stirred at -78°C for 2h and a saturated aqueous solution of NH_4Cl was then added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:CH_2Cl_2 (8:2) to afford the diene **(±)3.61** as a colourless oil (95 mg, 0.46 mmol, quant).

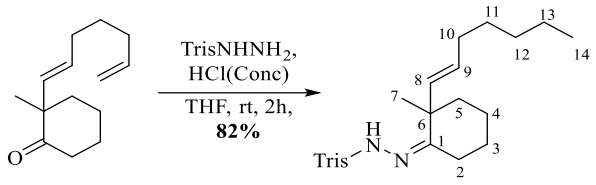
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.88–5.70 (m, 1H, ***CH-13***), 5.56 (d, *J* = 15.9 Hz, 1H, ***CH-8***), 5.33 (dt, *J* = 15.8, 6.8 Hz, 1H, ***CH-9***), 5.07–4.86 (m, 2H, ***CH_2-14***), 2.53 (m, 1H, ***CH_2-2***), 2.27 (m, 1H, ***CH_2-2***), 1.98 (m, 6H, ***CH_2***), 1.80–1.38 (m, 6H, ***CH_2***), 1.12 (s, 3H, ***CH_3-7***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 213.8 (***CO-1***), 138.6 (***CH-13***), 134.8 (***CH-8***), 130.7 (***CH-9***), 114.6 (***CH_2-14***), 51.3 (***C-6***), 40.4 (***CH_2***), 39.2 (***CH_2***), 33.1 (***CH_2***), 32.2 (***CH_2***), 28.4 (***CH_2***), 27.7 (***CH_2***), 24.6 (***CH_3-7***), 21.8 (***CH_2***).

IR (thin film): 2916, 2858, 1708, 1448, 972 cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{22}NaO^+$ $[M+Na]^+$, 229.1563; found, 229.1555.

(*Z*)-1-(2-((*E*)-Hept-1-en-1-yl)-2-methylcyclohexylidene)-2-(2,4,6-triisopropylphenyl)hydrazine ((±)3.62)



(±)3.61 **(±)3.62**

Chemical formula: $C_{29}H_{48}N_2O_2S$

MW: 488.78

To a stirred solution of ketone **(±)3.61** (888 mg, 4.30 mmol) in THF (25 mL) at 0°C was added $TrisNHNH_2$ (1.44 g, 4.84 mmol, 1.10 equiv) and 2 drops of concentrated HCl. The reaction mixture was stirred at room temperature for 2 h. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether: CH_2Cl_2 (7:3) to (3:7) to afford the hydrazone **(±)3.62** as a white solid (1.73 g, 3.54 mmol, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.98 (bs, 1H, ***NH***), 7.08 (s, 2H, ***CH-Ar***), 5.18 (d, *J* = 15.8 Hz, 1H, ***CH-8***), 4.93–4.74 (m, 1H, ***CH-9***), 4.18 (m, 2H, ***CH-iPr***), 2.88–2.76 (m, 1H, ***CH-iPr***), 2.49 (d, *J* = 14.6 Hz, 1H, ***CH_2-2***), 1.88–1.79 (m, 1H, ***CH_2-2***), 1.77–1.61 (m, 4H, ***CH_2***), 1.45 (d, *J* = 12.7 Hz, 3H, ***CH_2***), 1.33–1.03 (m, 25H, ***7CH_2***, ***18CH_3-iPr***), 0.90 (s, 3H, ***CH_3-7***), 0.80–0.73 (m, 3H, ***CH_3-14***)

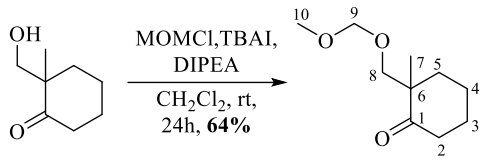
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 161 (***CN-1***), 152.8 (***C-Ar***), 151.2 (***2C-Ar***), 136.8 (***CH-8***), 131.7 (***C-Ar***), 130.1 (***CH-9***), 123.4 (***2CH-Ar***), 44.7 (***C-6***), 40.1 (***CH_2***), 34.1 (***CH-iPr***), 32.6 (***CH_2-2***), 31.3 (***CH_2***), 29.7 (***2CH-iPr***), 28.9 (***CH_2***), 25.9 (***CH_2***), 24.9 (***CH_3***), 24.9 (***CH_3***), 23.7 (***CH_2***), 23.6 (***CH_3***), 23.5 (***CH_3***), 22.4 (***CH_2***), 22.0 (***CH_2***), 14.0 (***CH_3-14***).

IR (thin film): 1448, 2928, 1705, 1600, 1448, 1334, 1192, 1126 cm^{-1}.

HRMS (ESI): Calcd for $C_{29}H_{48}N_2NaO_2S^+$ $[M+Na]^+$, 511.3329; found, 511.3344.

MP: 59°C.

2-((Methoxymethoxy)methyl)-2-methylcyclohexan-1-one ((±)3.65)



(±)3.37 **(±)3.65**

Chemical formula: $C_{10}H_{18}O_3$

MW: 186.25

To a stirred solution of alcohol **(±)3.37** (469 mg, 3.30 mmol) in CH_2Cl_2 (5.0 mL) was added TBAI (243 mg, 0.658 mmol, 0.20 equiv), DIPEA (4.00 mL, 23.1 mmol, 7.0 equiv) and MOMCl (1.00 mL, 13.2 mmol, 4.0 equiv). The reaction mixture was stirred at room temperature for 24h and a saturated aqueous solution of $NaHCO_3$ was then added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (8:2) to afford the protected alcohol **(±)3.65** as a colourless oil (393 mg, 2.11 mmol, 64%).

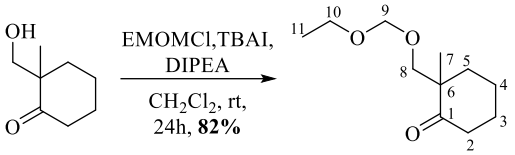
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.59 (qd, *J* = 6.5, 0.8 Hz, 2H, ***CH_2-9***), 3.57 (s, 2H, ***CH_2-8***), 3.32 (s, 3H, ***CH_3-10***), 2.48–2.34 (m, 2H, ***CH_2-2***), 1.91–1.61 (m, 6H, ***CH_2-3,4,5***), 1.12 (s, 3H, ***CH_3-7***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 214.0 (***CO-1***), 96.7 (***CH_2-9***), 72.9 (***CH_2-8***), 55.2 (***CH_3-10***), 49.4 (***C-6***), 39.0 (***CH_2-2***), 36.3 (***CH_2-5***), 27.1 (***CH_2-3***), 21.1 (***CH_2-4***), 21.0 (***CH_3-7***).

IR (thin film): 2926, 2868, 1705, 1450, 1150, 1111, 1049, 918 cm^{-1}.

HRMS (ESI): Calcd for $C_{10}H_{18}NaO_3^+$ $[M+Na]^+$, 209.1148; found, 209.1147.

2-((Ethoxymethoxy)methyl)-2-methylcyclohexan-1-one ((±)3.67)



(±)3.37 **(±)3.67**

Chemical formula: $C_{11}H_{20}O_3$

MW: 200.28

To a stirred solution of alcohol **(±)3.37** (2.13 g, 14.9 mmol) in CH_2Cl_2 (30 mL) was added TBAI (1.05 g, 2.84 mmol, 0.20 equiv), DIPEA (5.2 mL, 29.9 mmol, 2.0 equiv) and EOMCl (2.3 mL, 29.8 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature for 24h and a saturated aqueous solution of $NaHCO_3$ was then added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (8:2) to afford the protected alcohol **(±)3.67** as a colourless oil (2.45 g, 12.2 mmol, 82%).

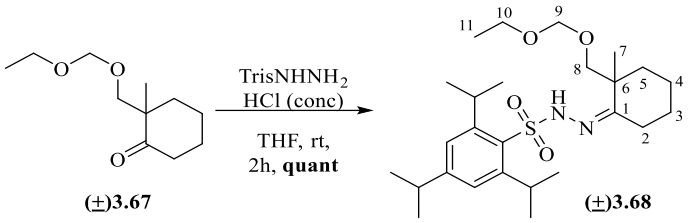
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.68–4.62 (m, 2H, ***CH_2-9***), 3.57 (m, 4H, ***CH_2-8,10***), 2.44–2.36 (m, 2H, ***CH_2-2***), 1.94–1.59 (m, 6H, ***CH_2-3,4,5***), 1.21 (t, *J* = 7.1 Hz, 3H, ***CH_3-11***), 1.12 (s, 3H, ***CH_3-7***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 214.1 (***CO-1***), 95.4 (***CH_2-9***), 73.0 (***CH_2-8***), 63.3 (***CH_2-10***), 49.5 (***C-6***), 39.0 (***CH_2-2***), 36.3 (***CH_2-6***), 27.1 (***CH_2-3 or 4***), 21.1, (***CH_2-3 or 4***) 21.0 (***CH_3-7***), 15.1 (***CH_3-11***).

IR (thin film): 2932, 2870, 1705, 1450,1115, 1099 cm^{-1}.

HRMS (ESI): Calcd for $C_{11}H_{20}NaO_3^+$ $[M+Na]^+$, 223.1305; found, 223.1297

(*Z*)-*N'*-(2-((Ethoxymethoxy)methyl)-2-methylcyclohexylidene)-2,4,6-triisopropylbenzenesulfonohydrazide ((±)3.68)



Chemical formula: $C_{26}H_{44}N_2O_4S$

MW: 480.71

To a stirred solution of ketone **(±)3.67** (4.31 g, 21.5 mmol) in THF (125 mL) at 0°C was added $TrisNHNH_2$ (7.00 g, 23.6 mmol, 1.10 equiv) and 3 drops of concentrated HCl. The reaction mixture was stirred at room temperature for 2 h. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O(8:2) to (1:1) to afford the hydrazone **(±)3.68** as a white solid (10.3 g, 21.5 mmol, quant).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.14 (s, 2H, ***CH-Ar***), 4.42 (dd, *J* = 15.9, 6.6 Hz, 2H, ***CH_2-9***), 4.16 (dt, *J* = 13.5, 6.7 Hz, 2H, ***CH-iPr***), 3.48–3.31 (m, 4H, ***CH_2-8,10***), 2.89 (dd, *J* = 13.8, 6.9 Hz, 1H, ***CH-iPr***), 2.20 (t, *J* = 5.9 Hz, 2H, ***CH_2-2***), 1.65–1.49 (m, 6H, ***CH_2-3,4,5***), 1.24 (m, 18H, ***CH_3-iPr***), 1.13 (t, *J* = 7.1 Hz, 3H, ***CH_3-11***), 0.98 (s, 3H, ***CH_3-7***).

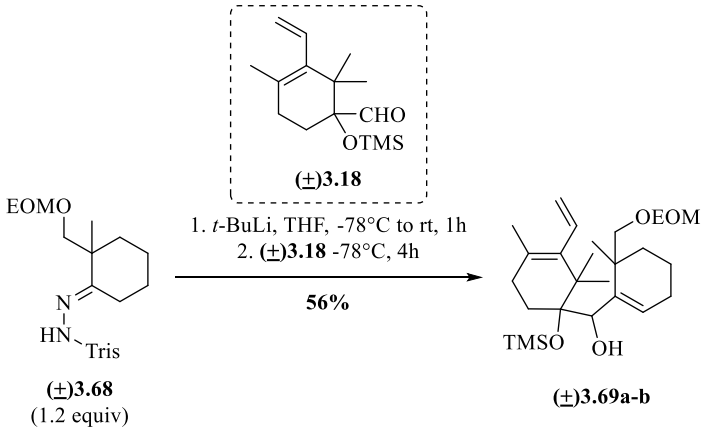
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 161.1 (***C-1***), 152.8 (***C-Ar***),151.0 (***2C-Ar***), 131.3 (***C-Ar***), 123.3 (***CH-Ar***), 95.1 (***CH_2-9***), 73.9 (***CH_2-8***), 62.8 (***CH_2-10***), 42.6 (***C-6***), 35.5 (***CH_2-3 or 5***), 34.0 (***CH-iPr***), 29.6 (***CH-iPr***), 25.2 (***CH_2-3 or 5***), 24.7 (***CH_3-iPr***), 24.6 (***CH_3-iPr***), 23.4 (***CH_3-7***), 23.2 (***CH_2-2***), 22.5 (***CH_3-iPr***), 20.8 (***CH_2-4***), 14.9 (***CH_3-11***).

IR (thin film): 1598, 1163, 1114, 1035, 1014, 921 cm^{-1}.

HRMS (ESI): Calcd for $C_{26}H_{44}NaN_2O_4S^+$ $[M+Na]^+$, 503.2914; found, 503.2917.

MP: 87°C.

(6-((Ethoxymethoxy)methyl)-6-methylcyclohex-1-en-1-yl)(2,2,4-trimethyl-1-((trimethylsilyl)oxy)-3-vinylcyclohex-3-en-1-yl)methanol ((±)3.69a-b)

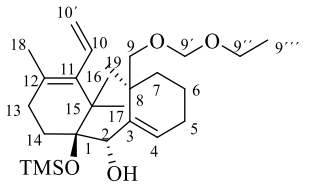


Chemical formula: $C_{26}H_{46}O_4Si$

MW: 450.74

To a stirred solution of hydrazone **(±)3.68** (4.80 g, 10.0 mmol, 1.20 equiv) in THF (12 mL) at -78°C was added dropwise *t*-BuLi (12.4 mL, 1.60 M in hexane, 19.8 mmol, 2.40 equiv). The solution turned dark red. The resulting solution was stirred at this temperature for 30 min and warmed for a few min to room temperature and intense nitrogen bubbling occurred. The red reaction mixture was then cooled down to -78°C and a solution of aldehyde **(±)3.18** (2.21 g, 8.30 mmol) in THF (6.0 mL) was added. The resulting mixture was stirred at -78°C for 4 h and became yellow. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography petroleum ether:Et_2O (10:0.25) to afford the title alcohols **(±)3.69a** (1.05 g, 2.33 mmol, 28%) and **(±)3.69b** (1.05 g, 2.33 mmol, 28%) as highly viscous yellow oils, as well as **(±)3.70** (775 mg, 4.21 mmol, 42%) as a colourless oil (resulting in part from the excess of hydrazone **(±)3.68** employed).

(*R)-((*R**)-6-((Ethoxymethoxy)methyl)-6-methylcyclohex-1-en-1-yl)((*R**)-2,2,4-trimethyl-1-((trimethylsilyl)oxy)-3-vinylcyclohex-3-en-1-yl)methanol ((±)3.69a)**



(±)3.69a

Chemical formula: $C_{26}H_{46}O_4Si$

MW: 450.74

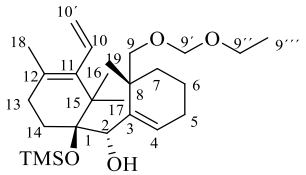
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.16 (dd, *J* = 17.2, 11.6 Hz, 1H, ***CH-10***), 5.99 (bs, 1H, ***CH-4***), 5.24 (dd, *J* = 11.1, 2.6 Hz, 1H, ***CH$_2$-10´***), 4.91 (dd, *J* = 17.6, 2.6 Hz, 1H, ***CH$_2$-10´***), 4.65 (s, 2H, ***CH$_2$-9´***), 4.61 (s, 1H, ***CH-2***), 3.78 (bs, 1H, ***OH***), 3.63–3.45 (m, 4H, ***CH$_2$-9,9´´***), 2.30 (dd, *J* = 17.3, 8.2 Hz, 1H, ***CH$_2$-5***), 2.17–2.01 (m, 2H, ***CH$_2$-13 or 14***), 1.87 (dd, *J* = 17.6, 5.1 Hz, 1H, ***CH$_2$-5***), 1.76–1.71 (m, 1H, ***CH$_2$-7***), 1.68 (s, 3H, ***CH$_3$-18***), 1.63–1.53 (m, 4H, CH2-6, ***CH$_2$-13 or 14***), 1.34 (dd, *J* = 13.4, 6.9 Hz, 1H, ***CH$_2$-7***), 1.20 (t, *J* = 7.1 Hz, 3H, ***CH$_3$-9´´´***), 1.13–1.01 (m, 9H, ***CH$_3$-16,17,19***), 0.12 (s, 9H, ***CH$_3$-OTMS***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 141.3 (***C-3***), 137.3 (***C-11***), 136.4 (***CH-10***), 130.6 (***CH-4***), 127.8 (***C-12***), 118.7 (***CH$_2$-10´***), 95.2 (***CH$_2$-9´***), 76.2 (***C-1***), 74.0 (***CH$_2$-9***), 70.9 (***CH-2***), 63.1 (***CH$_2$-9´´***), 43.7 (***C-15***), 38.1 (***C-8***), 33.9 (***CH$_2$-7***), 29.4 (***CH$_2$-5***), 28.1 (***CH$_2$-13 or 14***), 26.0 (***CH$_3$-16 or 17***), 25.4 (***CH$_2$-13 or 14***), 23.6 (***CH$_3$-19***), 21.8 (***CH$_3$-16 or 17***), 21.4 (***CH$_3$-18***), 18.1 (***CH$_2$-6***), 15.1 (***CH$_3$-9´´´***), 1.1 (***CH$_3$-OTMS***).

IR (thin film): 2931, 1375, 1251, 1097, 1047 cm^{-1}.

HRMS (ESI): Calcd for $C_{26}H_{46}NaO_4Si^+$ $[M+Na]^+$, 473.3058; found, 473.3040.

(*R)-((*S**)-6-((Ethoxymethoxy)methyl)-6-methylcyclohex-1-en-1-yl)((*R**)-2,2,4-trimethyl-1-((trimethylsilyl)oxy)-3-vinylcyclohex-3-en-1-yl)methanol ((±)3.69b)**



(±)3.69b

Chemical formula: $C_{26}H_{46}O_4Si$

MW: 450.74

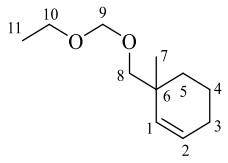
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.17 (dd, *J* = 17.4, 11.0 Hz, 1H, ***CH-10***), 6.02 (bs, 1H, ***CH-4***), 5.25 (dd, *J* = 11.0, 2.8 Hz, 1H, ***CH_2-10´***), 4.91 (dd, *J* = 17.6, 2.8 Hz, 1H, ***CH_2-10´***), 4.66 (s, 1H, ***CH-2***), 4.63 (s, 2H, ***CH_2-9´***), 3.84 (bs, 1H, ***OH***), 3.59–3.31 (m, 4H, ***CH_2-9,9´´***), 2.37–2.24 (m, 1H, ***CH_2-5***), 2.17–1.99 (m, 2H, ***CH_2-13 or 14***), 1.87 (dd, *J* = 17.7, 5.8 Hz, 1H, ***CH_2-7***), 1.78–1.72 (m, 1H, ***CH_2-7***), 1.68 (s, 3H, ***CH_3-18***), 1.62–1.53 (m, 4H, ***CH_2-6***, ***CH_2-13 or 14***), 1.47–1.39 (m, 1H, ***CH_2-7***), 1.26–1.14 (m, 6H, ***CH_3-9´´´, 19***), 1.10–1.02 (m, 6H, ***CH_3-16, 17***), 0.13 (s, 9H, ***CH_3-OTMS***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 141.3 (***C-3***), 137.3 (***C-11***), 136.5 (***CH-10***), 131.2 (***CH-4***), 127.7 (***C-12***), 118.7 (***CH_2-10´***), 95.2 (***CH_2-9´***), 76.1 (***C-1***), 74.2 (***CH_2-9***), 70.4 (***CH-2***), 63.1 (***CH_2-9´***), 43.7 (***C-15***), 38.1 (***C-8***), 34.1 (***CH_2-7***), 29.3 (***CH_2-5***), 27.8 (***CH_2-13 or 14***), 25.9 (***CH_2-13 or 14***), 24.0 (***CH_3-19***), 23.7 (***CH_3-16 or 17***), 21.3 (***CH_3-18***), 18.3 (***CH_2-6***), 15.1 (***CH_3-9´´´***), 1.3 (***CH_3-OTMS***).

IR (thin film): 2931, 2357, 1465, 1251, 1097, 910 cm^{-1}.

HRMS (ESI): Calcd for $C_{26}H_{46}NaO_4Si^+$ $[M+Na]^+$, 473.3058; found, 473.3052.

3-((Ethoxymethoxy)methyl)-3-methylcyclohex-1-ene ((±)3.70)



(±)3.70

Chemical formula: $C_{11}H_{20}O_2$

MW: 184.28

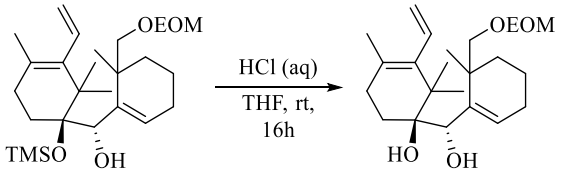
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.68 (dt, *J* = 10.1, 3.7 Hz, 1H, ***CH-2***), 5.43 (d, *J* = 10.1, 1H, ***CH-1***), 4.66 (s, 2H, ***CH_2-9***), 3.58 (q, *J* = 7.1 Hz, 2H, ***CH_2-10***), 3.27 (m, 2H, ***CH_2-8***), 1.95 (m, 2H, ***CH_2-3***), 1.67–1.52 (m, 3H, ***CH_2-4, 5***), 1.38–1.34 (m, 1H, ***CH_2-5***) 1.21 (t, *J* = 7.1 Hz, 3H, ***CH_3-11***), 0.99 (s, 3H, ***CH_3-7***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 133.6 (***CH-1***), 127.2 (***CH-2***), 95.4 (***CH_2-9***), 76.3 (***CH_2-8***), 63.0 (***CH_2-10***), 35.7 (***C-6***), 32.2 (***CH_2-5***), 25.2 (***CH_2-3***), 24.9 (***CH_3-7***), 18.9 (***CH_2-4***), 15.2 (***CH_3-11***).

IR (thin film): 1112, 1047, 910, 742 cm^{-1}.

HRMS (ESI): Calcd for $C_{11}H_{20}NaO_2^+$ $[M+Na]^+$, 207.1356; found, 207.1358.

(1*R**)-1-((1*R**)-(6-((Ethoxymethoxy)methyl)-6-methylcyclohex-1-en-1-yl)(hydroxy)methyl)-2,2,4-trimethyl-3-vinylcyclohex-3-en-1-ol ((±)3.71a-b)



(±)3.69a
(±)3.69b

(±)3.71a (94%)
(±)3.71b (quant)

Chemical formula: $C_{23}H_{38}O_4$

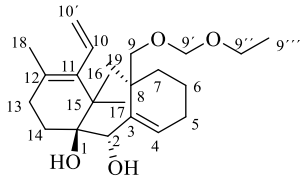
MW: 378.55

To a stirred solution of alcohol **(±)3.69a** (342 mg, 0.758 mmol) in THF (2.7 mL) was added a 1N aqueous solution of HCl (2.7 mL) and the resulting mixture was stirred at room temperature overnight. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The

crude mixture was then purified by flash chromatography petroleum ether:Et_2O (8:2) to (1:1) to afford the alcohol **(±)3.71a** as a colourless oil (268 mg, 0.708 mmol, 94%).

The same experimental procedure was applied to alcohol **(±)3.69b** (417mg, 0.92 mmol) to afford the alcohol **(±)3.71b** as a colourless oil (348 mg, 0.92 mmol, quant).

(*R)-1-((*R**)-((*R**)-6-((Ethoxymethoxy)methyl)-6-methylcyclohex-1-en-1-yl)(hydroxy)methyl)-2,2,4-trimethyl-3-vinylcyclohex-3-en-1-ol ((±)3.71a)**



(±)3.71a

Chemical formula: $C_{23}H_{38}O_4$

MW: 378.55

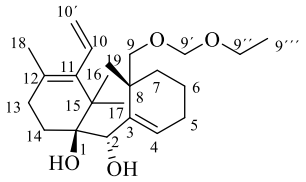
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.56–6.45 (m, 1H, ***CH-4***), 6.17 (dd, *J* = 17.3, 11.3 Hz, 1H, ***CH-10***), 5.25 (dd, *J* = 11.0, 2.7 Hz, 1H, ***CH_2-10´***), 4.91 (dd, *J* = 17.6, 2.6 Hz, 1H, ***CH_2-10´***), 4.69–4.64 (m, 2H, ***CH_2-9´***), 4.23 (s, 1H, ***CH-2***), 3.65–3.57 (m, 3H, ***CH_2-9 , 2CH_2-9´´***), 3.39 (s, 1H, ***OH***), 3.26 (d, *J* = 9.6 Hz, 1H, ***CH_2-9***), 3.08 (d, *J* = 1.4 Hz, 1H, ***OH***), 2.07 (dd, *J* = 9.0, 5.6 Hz, 4H, ***CH_2***), 1.96–1.80 (m, 3H, ***CH_2***), 1.66 (s, 3H, ***CH_3-18***), 1.63–1.57 (m, 2H, ***CH_2***), 1.41–1.32 (m, 1H, ***CH_2-7***), 1.25–1.15 (m, 6H, ***CH_3-9´´´, CH_3-16 or 17***), 1.06 (s, 3H, ***CH_3-19***), 0.91 (s, 3H, ***CH_3-16 or 17***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 142.1 (***C-3***), 138.1 (***C-11***), 136.2 (***CH-10***), 130.7 (***CH-4***), 127.3 (***C-12***), 118.6 (***CH_2-10´***), 95.5 (***CH_2-9´***), 75.7 (***C-1***), 75.4 (***CH_2-9***), 69.0 (***CH-2***), 63.7 (***CH_2-9´´***), 43.9 (***C-15***), 38.5 (***C-8***), 34.7 (***CH_2***), 28.7 (***CH_2***), 27.4 (***CH_2-13 or 14***), 25.9 (***CH_2-13 or 14***), 24.7 (***CH_3-19***), 23.6 (***CH_3-16***), 23.5 (***CH_3-17***), 21.1 (***CH_3-18***), 18.7 (***CH_2***), 15.1 (***CH_3-9´´´***).

IR (thin film): 3426, 2910, 1463, 1384, 1112 cm^{-1}.

HRMS (ESI): Calcd for $C_{23}H_{38}NaO_4^+$ $[M+Na]^+$, 401.2662; found, 401.2653.

(*R)-1-((*R**)-((*S**)-6-((Ethoxymethoxy)methyl)-6-methylcyclohex-1-en-1-yl)(hydroxy)methyl)-2,2,4-trimethyl-3-vinylcyclohex-3-en-1-ol ((±)3.71b)**



(±)3.71b

Chemical formula: $C_{23}H_{38}O_4$

MW: 378.55

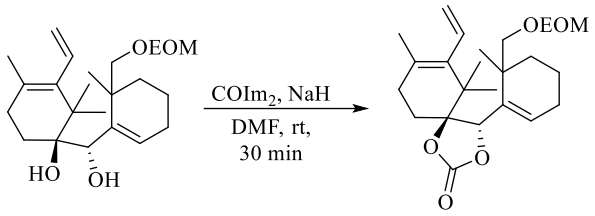
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.25–6.08 (m, 2H, ***CH-4, CH-10***), 5.26 (dd, *J* = 11.1, 2.7 Hz, 1H, ***CH_2-10′***), 4.92 (dd, *J* = 17.6, 2.7 Hz, 1H, ***CH_2-10′***), 4.64 (s, 2H, ***CH_2-9′***), 4.35 (d, *J* = 4.2 Hz, 1H, ***CH-2***), 3.57 (q, *J* = 7.1 Hz, 2H, ***CH_2-9′′***), 3.39–3.30 (m, 2H, ***CH_2-9***), 3.00 (s, 1H, ***OH***), 2.62 (bs, 1H, ***OH***), 2.23–2.02 (m, 3H, ***CH_2***), 1.98–1.85 (m, 1H, ***CH_2-13 or 14***), 1.80–1.72 (m, 2H, ***CH_2***), 1.68 (s, 3H, ***CH_3-18***), 1.62–1.56 (m, 2H, ***CH_2-6***), 1.54–1.47 (m, 1H, ***CH_2-5***), 1.42–1.35 (m, 1H, ***CH_2-7***), 1.22–1.16 (m, 9H, ***CH_3-9′′′, CH_3-16 or 17, CH_3-19***), 1.07 (s, 3H, ***CH_3-16 or 17***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 144.8 (***C-3***), 137.6 (***C-11***), 136.1 (***CH-10***), 129.7 (***CH-4***), 127.6 (***C-12***), 118.7 (***CH_2-10′***), 95.2 (***CH_2-9′***), 76.0 (***C-1***), 75.2 (***CH_2-9***), 72.4 (***CH-2***), 63.3 (***CH_2-9′′***), 43.7 (***C-15***), 38.2 (***C-8***), 34.8 (***CH_2-7***), 28.7 (***CH_2-5***), 27.7 (***CH_2-13 or 14***), 25.6 (***CH_2-13 or 14***), 25.1 (***CH_3-16 or 17***), 23.9 (***CH_3-16 or 17***), 22.9 (***CH_3-19***), 21.2 (***CH_3-18***), 18.3 (***CH_2-6***), 15.1 (***CH_3-9′′′***).

IR (thin film): 3423, 2927, 1446, 1383, 1109, 1041 cm^{-1}.

HRMS (ESI): Calcd for $C_{23}H_{38}NaO_4^+$ $[M+Na]^+$ 401.2662; found, 401.2645

(4*R,5*S**)-4-(6-((Ethoxymethoxy)methyl)-6-methylcyclohex-1-en-1-yl)-6,6,8-trimethyl-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-2-one ((±)3.72a-b)**



(±)3.71a (94%)
(±)3.71b (quant)

(±)3.72a (quant)
(±)3.72b (quant)

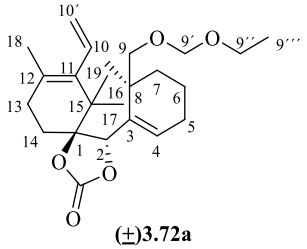
Chemical formula: $C_{24}H_{36}O_5$

MW: 404.55

To a stirred solution of diol **(±)3.71a** (253 mg, 0.670 mmol) in DMF (9.3 mL) was added NaH (60 %) (79 mg, 2.0 mmol, 3.0 equiv) and *N,N*-carbonyl diimidazole (541 mg, 3.34 mmol, 5.0 equiv). The reaction mixture was stirred at room temperature for 30 min. A saturated aqueous solution of NH_4Cl was added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (8:2) to afford the carbonate **(±)3.71a** as a pale yellow oil (271 mg, 0.670 mmol, quant).

The same experimental procedure was applied to alcohol **(±)3.71b** (262 mg, 0.690 mmol) to afford the carbonate **(±)3.72b** as a colourless oil (279 mg, 0.670 mmol, quant).

(4*R,5*R**)-4-((*R**)-6-((Ethoxymethoxy)methyl)-6-methylcyclohex-1-en-1-yl)-6,6,8-trimethyl-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-2-one ((±)3.72a)**



(±)3.72a

Chemical formula: $C_{24}H_{36}O_5$

MW: 404.55

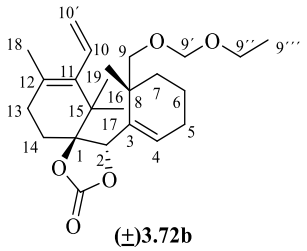
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.05 (dd, *J* = 17.4, 11.2 Hz, 1H, ***CH-10***), 5.84 (t, *J* = 3.9 Hz, 1H, ***CH-4***), 5.26 (dd, *J* = 11.1, 2.4 Hz, 1H, ***CH_2-10´***), 5.03 (s, 1H, ***CH-2***), 4.93 (dd, *J* = 17.6, 2.4 Hz, 1H, ***CH_2-10´***), 4.53 (s, 2H, ***CH_2-9´***), 3.55–3.43 (m, 2H, ***CH_2-9´´***), 3.29–3.18 (m, 2H, ***CH_2-9***), 2.28–1.95 (m, 5H, ***CH_2***), 1.85–1.78 (m, 1H, ***CH_2***), 1.72–1.65 (m, 1H, ***CH_2***), 1.61 (s, 3H, ***CH_3-18***), 1.60–1.52 (m, 2H, ***CH_2***), 1.32 (dd, *J* = 9.3, 5.0 Hz, 1H, ***CH_2***), 1.13 (t, *J* = 7.1 Hz, 3H, ***CH_3-9´´´***), 1.09 (s, 3H, ***CH_3-19***), 1.06 (s, 6H, ***CH_3-16, 17***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 155.2 (***CO_3***), 137.5 (***C-11***), 134.7 (***C-3***), 134.6 (***CH-10***), 133.2 (***CH-4***), 127.9 (***C-12***), 119.8 (***CH_2-10´***), 94.9 (***CH_2-9´***), 89.8 (***C-1***), 77.6 (***CH-2***), 72.9 (***CH_2-9***), 63.1 (***CH_2-9´´***), 42.8 (***C-15***), 38.0 (***C-8***), 33.6 (***CH_2***), 28.9 (***CH_2***), 25.6 (***CH_2***), 25.1 (***CH_2***), 24.4 (***CH_3-16 or 17***), 23.2 (***CH_3-19***), 20.8 (***CH_3-18***), 20.7 (***CH_3-16 or 17***), 17.9 (***CH_2***), 14.9 (***CH_3-9´´´***).

IR (thin film): 2974, 1797, 1458, 1386, 1178, 1043 cm^{-1}.

HRMS (ESI): Calcd for $C_{24}H_{36}NaO_5^+$ $[M+Na]^+$, 427.2455; found, 427.2448

(4*R**,5*R**)-4-((*S**)-6-((Ethoxymethoxy)methyl)-6-methylcyclohex-1-en-1-yl)-6,6,8-trimethyl-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-2-one ((±)3.72b)



(±)3.72b

Chemical formula: $C_{24}H_{36}O_5$

MW: 404.55

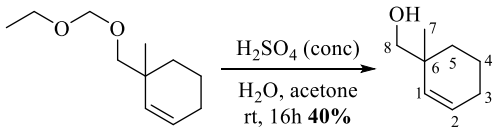
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.10 (dd, *J* = 17.4, 11.1 Hz, 1H, ***CH-10***), 5.87 (t, *J* = 3.9 Hz, 1H, ***CH-4***), 5.35 (s, 1H, ***CH-2***), 5.31 (dd, *J* = 11.1, 2.5 Hz, 1H, ***CH_2-10´***), 4.97 (dd, *J* = 17.6, 2.5 Hz, 1H, ***CH_2-10´***), 4.66 (s, 2H, ***CH_2-9´***), 3.61–3.49 (qd, 2H, ***CH_2-9´´***), 3.49–3.41 (m, 2H, ***CH_2-9***), 2.32–2.29 (m, 1H, ***CH_2-5***), 2.19–2.13 (m, 2H, ***CH_2***), 2.10–1.95 (m, 2H, ***CH_2***), 1.76–1.58 (m, 4H, ***CH_2***), 1.65 (s, 3H, ***CH_3-18***), 1.40–1.35 (m, 1H, ***CH_2***), 1.20 (t, *J* = 7.1 Hz, 3H, ***CH_3-9´´***), 1.13 (s, 3H, ***CH_3-16 or 17***), 1.10 (s, 3H, ***CH_3-16 or 17***), 0.98 (s, 3H, ***CH_3-19***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 155.5 (***CO_3***), 138.1 (***C-11***), 135.0 (***C-3***), 134.8 (***CH-10***), 132.4 (***CH-4***), 128.0 (***C-12***), 119.9 (***CH_2-10´***), 95.5 (***CH_2-9´***), 89.9 (***C-1***), 77.8 (***CH-2***), 75.6 (***CH_2-9***), 63.4 (***CH_2-9´´***), 43.0 (***C-15***), 37.7 (***C-8***), 34.9 (***CH_2***), 29.1 (***CH_2***), 25.6 (***CH_2***), 25.2 (***CH_2***), 24.8 (***CH_3-16 or 17***), 23.4 (***CH_3-19***), 20.9 (***CH_3-18***), 20.7 (***CH_3-16 or 17***), 18.1 (***CH_2***), 15.1 (***CH_3-9´´***).

IR (thin film): 1789, 1463, 1386, 1346, 1178, 1047 cm^{-1}.

HRMS (ESI): Calcd for $C_{24}H_{36}NaO_5^+$ $[M+Na]^+$, 427.2455; found, 427.2440.

(1-Methylcyclohex-2-en-1-yl)methanol ((±)3.73)



(±)3.70 **(±)3.73**

Chemical formula: $C_8H_{14}O$

MW: 126.20

To a stirred solution of protected alcohol **(±)3.70** (1.43 g, 7.92 mmol) in acetone (60 mL) and water (30 mL) was slowly added concentrated H_2SO_4 (7.4 mL). The reaction mixture was stirred at room temperature for 14 h. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction and the aqueous layer was then extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (9:1) to afford the alcohol **(±)3.73** as a colourless oil (395mg, 3.13 mmol, 40%).

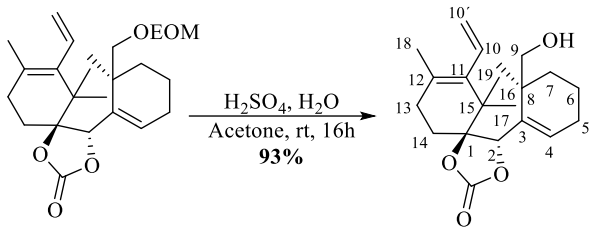
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.79 (dt, *J* = 10.0, 3.7 Hz, 1H, ***CH-2***), 5.37 (d, *J* = 10.1 Hz, 1H, ***CH-1***), 3.34 (m, 2H, ***CH_2-8***), 1.95 (m, 2H, ***CH_2-5***), 1.72–1.58 (m, 3H, ***CH_2-3, 2CH_2-4***), 1.39–1.27 (m, 1H, ***CH_2-3***), 0.95 (s, 3H, ***CH_3-7***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 132.8 (***CH-1***), 129.2 (***CH-2***), 71.4 (***CH_2-8***), 37.0 (***C-6***), 31.6 (***CH_2-5***), 25.1 (***CH_2-3***), 24.3 (***CH_3-7***), 19.0 (***CH_2-4***).

IR (thin film): 3358, 2927, 2866, 1452, 1033, 910 cm^{-1}.

HRMS (ESI): Calcd for $C_8H_{14}NaO^+$ $[M+Na]^+$, 149.0937; found, 149.0933.

(4*R,5*R**)-4-((*R**)-6-(Hydroxymethyl)-6-methylcyclohex-1-en-1-yl)-6,6,8-trimethyl-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-2-one ((±)3.74a)**



(±)3.72a **(±)3.74a**

Chemical formula: $C_{21}H_{30}O_4$

MW: 346.47

To a stirred solution of protected alcohol **(±)3.72a** (278 mg, 0.680 mmol) in acetone (11 mL) and water (6 mL) was slowly added concentrated H_2SO_4 (1.5 mL). The reaction mixture was stirred at room temperature for 16 h. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction and the aqueous layer was then extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (6:4) to afford the alcohol **(±)3.73a** as a white solid (220 mg, 0.630 mmol, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.09 (dd, *J* = 17.5, 11.2 Hz, 1H, ***CH-10***), 6.01 (t, *J* = 4.0 Hz, 1H, ***CH-4***), 5.30 (dd, *J* = 11.1, 2.5 Hz, 1H, ***CH_2-10'***), 5.19 (s, 1H, ***CH-2***), 4.96 (dd, *J* = 17.6, 2.5 Hz, 1H, ***CH_2-10'***), 3.60 (d, *J* = 11.2 Hz, 1H, ***CH_2-9***), 3.45 (d, *J* = 11.2 Hz, 1H, ***CH_2-9***), 2.30–2.20 (m, 1H, ***CH_2-5***), 2.18–2.12 (m, 3H, ***CH_2-13 or 14, OH***), 2.02–1.94 (m, 1H, ***CH_2-5***), 1.81–1.68 (m, 4H, ***CH_2***), 1.64 (s, 3H, ***CH_3-18***), 1.69–1-49 (m, 1H, ***CH_2-6***), 1.41–1.35 (m, 1H, ***CH_2-7***), 1.10 (s, 6H, ***CH_3-16, 17***), 0.92 (s, 3H, ***CH_3-19***).

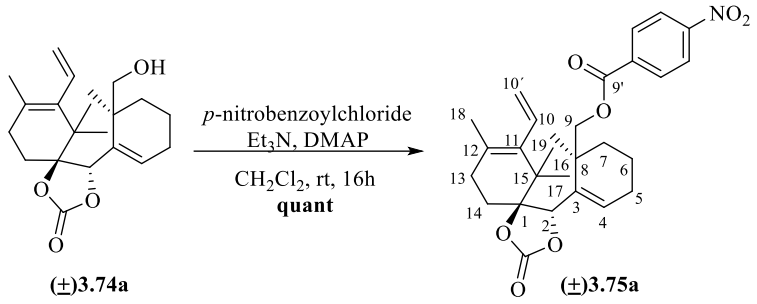
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 155.3 (***CO_3***), 137.3 (***C-11***), 135.2 (***C-3***), 134.6 (***CH-10***), 134.2 (***CH-4***), 128.2 (***C-12***), 119.9 (***CH_2-10'***), 89.8 (***C-1***), 77.3 (***CH-2***), 69.9 (***CH_2-9***), 43.1 (***C-15***), 39.1 (***C-8***), 34.1 (***CH_2-7***), 29.0 (***CH_2-5***), 25.7 (***CH_2-13 or 14***), 25.0 (***CH_2-13 or 14***), 24.1 (***CH_3-16 or 17***), 22.7 (***CH_3-19***), 21.4 (***CH_3-16 or 17***), 20.9 (***CH_3-18***), 18.2 (***CH_2-6***).

IR (thin film): 3493, 2914, 1786, 1346, 1039 cm^{-1}.

HRMS (ESI): Calcd for $C_{21}H_{30}NaO_4^+$ $[M+Na]^+$, 369.2036; found, 369.2024.

MP: 159°C.

((*R)-1-Methyl-2-((4*R**,5*R**)-6,6,8-trimethyl-2-oxo-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-4-yl)cyclohexan-1-yl)methyl 4-nitrobenzoate((±)3.75a)**



Chemical formula: $C_{28}H_{33}NO_7$

MW: 495.57

To a stirred solution of alcohol **(±)3.74a** (212 mg, 0.610 mmol) in CH_2Cl_2 (13 mL) was added triethylamine (222 μL, 1.59 mmol, 2.60 equiv), DMAP (75 mg, 0.61 mmol, 1.0 equiv) and *p*-nitrobenzoyl chloride (226 mg, 1.22 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature for 16 h. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (6:4) to afford the ester **(±)3.75a** as a pale yellow solid (210 mg, 0.62 mmol, quant).

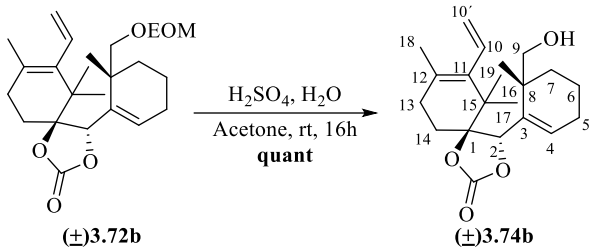
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.30 (d, *J* = 8.6 Hz, 2H, ***CH-Ar***), 8.17 (d, *J* = 8.6 Hz, 2H, ***CH-Ar***), 6.10 (dd, *J* = 17.3, 10.8 Hz, 1H, ***CH-10***), 6.02 (s, 1H, ***CH-4***), 5.32 (d, *J* = 11.0 Hz, 1H, ***CH_2-10'***), 5.11 (s, 1H, ***CH-2***), 4.99 (d, *J* = 17.7 Hz, 1H, ***CH_2-10'***), 4.17 (s, 2H, ***CH_2-9***), 2.35–2.19 (m, 3H, ***CH_2***), 2.12–2.05 (m, 1H, ***CH_2-13 or 14***), 1.97–1.89 (m, 2H, ***CH_2-5, 7***), 1.79–1.64 (m, 6H, ***3CH_2, CH_3-18***), 1.57–1.50 (m, 1H, ***CH_2-7***), 1.29 (s, 3H, ***CH_3-19***), 1.14 (s, *J* = 3.0 Hz, 3H, ***CH_3-16 or 17***), 1.13 (s, *J* = 3.0 Hz, 3H, ***CH_3-16 or 17***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 164.4 (***C-9***), 155.0 (***CO_3***), 150.7 (***C-NO_2***), 136.0 (***C-11***), 135.2 (***C-3***), 134.9 (***C-Ar***), 134.5 (***CH-4 or 10***), 134.5 (***CH-4 or 10***), 130.6 (***CH-Ar***), 128.2 (***C-12***), 123.7 (***CH-Ar***), 120.2 (***CH_2-10'***), 89.7 (***C-1***), 78.2 (***CH-2***), 69.7 (***CH_2-9***), 42.9 (***C-15***), 37.8 (***C-8***), 33.8 (***CH_2-7***), 29.0 (***CH_2-5***), 25.7 (***CH_2-13 or 14***), 25.6 (***CH_2-13 or 14***), 24.3 (***CH_3-16 or 17***), 23.3 (***CH_3-19***), 21.0 (***CH_3-16 or 17***), 20.9 (***CH_3-18***), 17.9 (***CH_2-6***).

IR (thin film): 2912, 2360, 1793, 1726, 1529, 1346, 1267, 719 cm^{-1}.

HRMS (ESI): Calcd for $C_{28}H_{33}NNaO_7^+$ $[M+Na]^+$, 518.2149; found, 518.2150.

(4*R,5*R**)-4-((*S**)-6-(Hydroxymethyl)-6-methylcyclohex-1-en-1-yl)-6,6,8-trimethyl-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-2-one ((±)3.74b)**



Chemical formula: $C_{21}H_{30}O_4$

MW: 346.47

To a stirred solution of protected alcohol **(±)3.72b** (340 mg, 0.840 mmol) in acetone (14 mL) and water (7 mL) was slowly added concentrated H_2SO_4 (1.8 mL). The reaction mixture was stirred at room temperature for 16 h. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction and the aqueous layer was then extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (6:4) to afford the alcohol **(±)3.73b** as a white solid (292 mg, 0.840 mmol, quant).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.11 (dd, *J* = 17.6, 11.1 Hz, 1H, ***CH-10***), 5.91 (t, *J* = 4.0 Hz, 1H, ***CH-4***), 5.32 (dd, *J* = 11.1, 2.5 Hz, 1H, ***CH_2-10'***), 5.09 (s, 1H, ***CH-2***), 4.98 (dd, *J* = 17.6, 2.5 Hz, 1H, ***CH_2-10'***), 3.51 (dd, *J* = 10.8, 5.0 Hz, 1H, ***CH_2-9***), 3.33 (dd, *J* = 10.7, 4.9 Hz, 1H, ***CH_2-9***), 2.30–1.98 (m, 5H, ***4CH_2***, ***OH***), 1.85 (dd, *J* = 8.5, 3.8 Hz, 2H, ***CH_2***), 1.73–1.59 (m, 5H, ***CH_2-6***, ***CH_3-18***), 1.43–1.30 (m, 2H, ***CH_2***), 1.15–1.07 (m, 9H, ***CH_3-16, 17, 19***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 155.4 (***C-CO_3***), 137.5 (***C-11***), 134.9 (***C-3***), 134.8 (***CH-10***), 133.6 (***CH-4***), 128.1 (***C-12***), 119.9 (***CH_2-10'***), 90.1 (***C-1***), 78.2 (***CH-2***), 68.8 (***CH_2-9***), 42.9

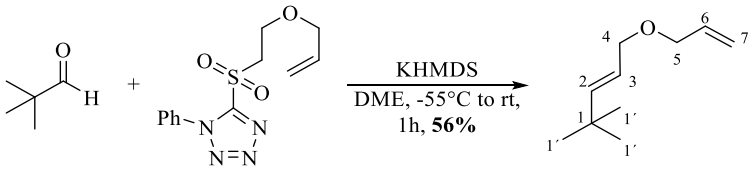
(***C-15***), 39.3 (***C-8***), 33.5 (***CH₂-7***), 29.0 (***CH₂-5***), 25.7 (***CH₂-13 or 14***), 25.2 (***CH₂-13 or 14***), 24.3 (***CH₃-16 or 17***), 22.8 (***CH₃-19***), 20.9 (***CH₃-16 or 17***), 20.8 (***CH₃-18***), 18.1 (***CH₂-6***).

IR (thin film): 3477, 1795,73, 1390, 1176 cm^{-1}.

HRMS (ESI): Calcd for $C_{21}H_{30}NaO_4^+$ $[M+Na]^+$, 369.2036; found, 369.2023.

MP: 155°C.

(*E*)-1-(Allyloxy)-4,4-dimethylpent-2-ene (3.77)



3.76 **3.28** **3.77**

Chemical formula: $C_{10}H_{18}O$

MW: 154.25

To a stirred solution of aldehyde **3.76** (112 mg, 1.30 mmol) and sulfone **3.28** (1.14 g, 3.88 mmol, 3.0 equiv) in DME (44 mL) at -55°C was slowly added KHMDS (5.2 mL, 1M in THF, 5.2 mmol, 4.0 equiv). The reaction mixture stirred at this temperature for 1h and the resulting solution was then warmed up to room temperature and stirred for 1h. Brine was added to quench the reaction and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (95:5) to afford the diene **3.77** as a colourless oil (112 mg, 0.72 mmol, 56%).

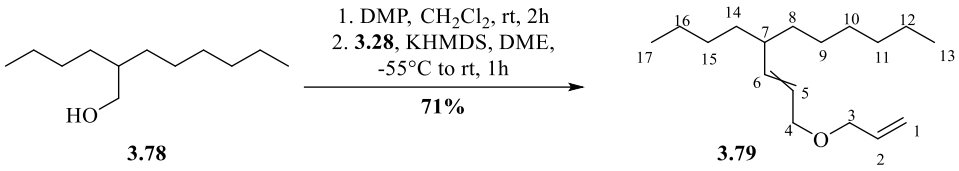
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.84 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H, ***CH-6***), 5.63 (dt, *J* = 15.7, 1.2 Hz, 1H, ***CH-2***), 5.38 (dt, *J* = 15.7, 6.2 Hz, 1H, ***CH-3***), 5.18 (ddd, *J* = 17.2, 3.3, 1.6 Hz, 1H, ***CH₂-7***), 5.09 (ddd, *J* = 10.4, 3.0, 1.2 Hz, 1H, ***CH₂-7***), 3.92–3.80 (m, 4H, ***CH₂-4, 5***), 0.93 (s, 9H, ***CH₃-1'***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 145.5 (***CH-2***), 134.9 (***CH-6***), 121.0 (***CH-3***), 117.0 (***CH₂-7***), 71.2 (***CH₂-4 or 5***), 70.9 (***CH₂-4 or 5***), 32.9 (***C-1***), 29.4 (***CH₃-1'***).

IR (thin film): 2956, 1462, 1361, 1259, 1070, 974 cm^{-1}.

HRMS (ESI): Calcd for $C_{10}H_{18}NaO^+$ $[M+Na]^+$, 177.1250; found, 177.1246.

5-(3-(Allyloxy)prop-1-en-1-yl)undecane (3.79)



Chemical formula: $C_{17}H_{32}O$

MW: 252.44

To a stirred solution of alcohol **3.78** (105 μL, 0.469 mmol) in H_2O-saturated CH_2Cl_2 (12 mL) was added DMP (400 mg, 0.943 mmol, 2.0 equiv). The resulting cloudy solution stirred at room temperature for 2h. The reaction mixture was diluted with Et_2O and then concentrated under reduced pressure. Et_2O was then added and the organic phase was washed with a saturated aqueous solution of $Na_2S_2O_3$ and a saturated aqueous solution of $NaHCO_3$. The aqueous layers were back-extracted with Et_2O and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

To a stirred solution of this crude mixture and sulfone **3.28** (416 mg, 1.41 mmol, 3.0 equiv) in DME (16 mL) at -55°C was slowly added KHMDS (1.9 mL, 1M in THF, 1.9 mmol, 4.0 equiv). The reaction mixture was stirred at this temperature for 1h and the resulting solution was then warmed up to room temperature and stirred for 1h. Brine was added to quench the reaction and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (94:4) to afford the diene **3.79** as a colourless oil (85 mg, 0.33 mmol, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: The presence of two diastereomers was observed in the NMR spectra. However, it was not possible to differentiate all signals corresponding to each

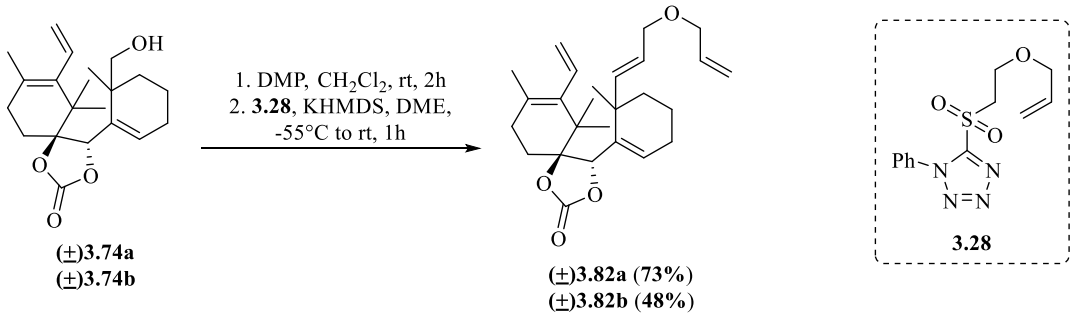
diastereoisomer. 5.92 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H, ***CH-2***), 5.60–5.34 (m, 2H, ***CH-5,6***), 5.26 (dd, *J* = 17.2, 1.7 Hz, 1H, ***CH_2 trans-1***), 5.16 (dd, *J* = 10.4, 1.7 Hz, 1H, ***CH_2 cis-1***), 3.96 –3.94 (m, 4H, ***CH_2-3,4***), 1.94 (bs, 1H, ***CH-7***), 1.32–1.14 (m, 16H, ***CH_2***), 0.88–0.84 (m, 6H, ***CH_3-13,17***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 139.4 (***CH-6***), 135.0 (***CH-2***), 125.8 (***CH-5***), 116.8 (***CH_2-1***), 70.9 (***CH_2-3 or 4***), 70.6 (***CH_2-3 or 4***), 42.5 (***CH-7***), 35.1 (***CH_2***), 34.8 (***CH_2***), 31.9 (***CH_2***), 29.5 (***CH_2***), 29.4 (***CH_2***), 27.2 (***CH_2***), 22.8 (***CH_2***), 22.7 (***CH_2***), 14.1 (***CH_3-13,17***).

IR (thin film): 2924, 2854, 1724, 1458, 1377, 1095, 972 cm^{-1}.

HRMS (ESI): Calcd for $C_{17}H_{32}NaO^+$ $[M+Na]^+$, 275.2345; found, 275.2336.

(4*R,5*R**)-4-(6-((*E*)-3-(Allyloxy)prop-1-en-1-yl)-6-methylcyclohex-1-en-1-yl)-6,6,8-trimethyl-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-2-one ((±)3.82a-b)**



(±)3.74a
(±)3.74b

(±)3.82a (73%)
(±)3.82b (48%)

Chemical formula: $C_{26}H_{36}O_4$

MW: 412.57

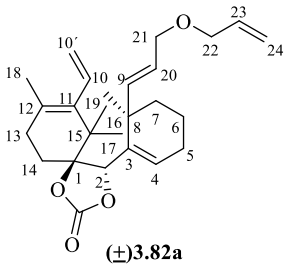
To a stirred solution of alcohol **(±)3.74a** (76 mg, 0.22 mmol) in H_2O-saturated CH_2Cl_2 (5.6 mL) was added DMP (187 mg, 0.44 mmol, 2.0 equiv). The resulting cloudy solution stirred at room temperature for 2h. The reaction mixture was diluted with Et_2O and then concentrated under reduced pressure. Et_2O was then added and the organic phase was washed with a saturated aqueous solution of $Na_2S_2O_3$ and a saturated aqueous solution of $NaHCO_3$. The aqueous layers were back-extracted with Et_2O and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

To a stirred solution of this crude mixture and sulfone **3.28** (194 mg, 0.66 mmol, 3.0 equiv) in DME (7.5 mL) at -55°C was slowly added KHMDS (0.97 mL, 0.9 M in THF, 0.88 mmol, 4.0 equiv). The reaction mixture stirred at this temperature for 1h and the resulting solution was then warmed up to room temperature and stirred for 1h. Brine was added to quench the reaction

and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (8:2) to afford the *E*-alkene **(±)3.82a** as a highly viscous colourless oil (66 mg, 0.16 mmol, 73% for two steps).

The same experimental procedure was applied to alcohol **(±)3.74b** (100 mg, 0.29 mmol) to afford the *E*-alkene **(±)3.82b** as a highly viscous colourless oil (46 mg, 0.11 mmol, 48% for two steps).

(4*R,5*R**)-4-((*S**)-6-((*E*)-3-(Allyloxy)prop-1-en-1-yl)-6-methylcyclohex-1-en-1-yl)-6,6,8-trimethyl-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-2-one ((±)3.82a)**



(±)3.82a

Chemical formula: $C_{26}H_{36}O_4$

MW: 412.57

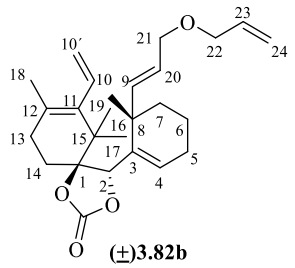
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.08 (dd, *J* = 17.5, 11.2 Hz, 1H, ***CH-10***), 5.96–5.83 (m, 2H, ***CH-4***, ***CH-23***), 5.65–5.55 (m, 2H, ***CH-9***, ***CH-20***), 5.34–5.22 (m, 2H, ***CH_2-10' and 24***), 5.17 (dd, *J* = 10.4, 1.5 Hz, 1H, ***CH_2-24***), 4.95 (dd, *J* = 17.6, 2.4 Hz, 1H, ***CH_2-10'***), 4.90 (s, 1H, ***CH-2***), 4.04–3.93 (m, 4H, ***CH_2-21,22***), 2.27 (dd, *J* = 17.5, 9.0 Hz, 1H, ***CH_2-5***), 2.21–2.12 (m, 2H, ***CH_2***), 2.06 (d, *J* = 6.2 Hz, 2H, ***CH_2***), 1.75–1.67 (m, 1H, ***CH_2***), 1.65 (s, 3H, ***CH_3-18***), 1.60–1.47 (m, 4H, ***CH_2***), 1.13–1.00 (m, 9H, ***CH_3-16, 17 and 19***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 155.4 (***CO_3***), 140.3 (***CH-9***), 137.5 (***C-11***), 134.9 (***C-3***), 134.7 (***CH-4 or 10***), 134.6 (***CH-4 or 10***), 132.2 (***CH-23***), 127.9 (***C-12***), 126.6 (***CH-20***), 119.9 (***CH_2-10'***), 117.0 (***CH_2-24***), 89.9 (***C-1***), 78.9 (***CH-2***), 70.9 (***CH_2-21 or 22***), 70.5 (***CH_2-21 or 22***), 43.0 (***C-15***), 40.1 (***C-8***), 38.0 (***CH_2-7***), 29.1 (***CH_2-5***), 25.6 (***CH_2-13 or 14***), 25.4 (***CH_2-13 or 14***), 25.0 (***CH_3-16, 17 or 19***), 20.9 (***CH_3-18***), 20.6 (***CH_3-16, 17 or 19***), 18.0 (***CH_2-6***).

IR (thin film): 2927, 2850, 1797, 1446, 1344, 1176 1041 cm^{-1}.

HRMS (ESI): Calcd for $C_{26}H_{36}NaO_4^+$ $[M+Na]^+$, 435.2506; found, 435.2500

(4*R,5*R**)-4-((*R**)-6-((*E*)-3-(Allyloxy)prop-1-en-1-yl)-6-methylcyclohex-1-en-1-yl)-6,6,8-trimethyl-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-2-one ((±)3.82b)**



Chemical formula: $C_{26}H_{36}O_4$

MW: 412.57

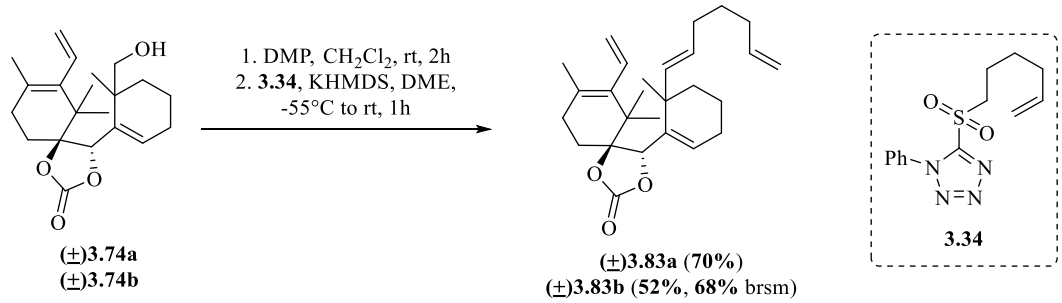
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.08 (dd, *J* = 17.6, 11.1 Hz, 1H, ***CH-10***), 5.95–5.79 (m, 2H, ***CH-4, CH-23***), 5.60–5.49 (m, 2H, ***CH-9, CH-20***), 5.34–5.11 (m, 3H, ***CH_2-24, CH_2-10′***), 4.95 (dd, *J* = 17.6, 2.5 Hz, 1H, ***CH_2-10′***), 4.87 (s, 1H, ***CH-2***), 4.08–3.78 (m, 4H, ***CH_2-21, CH_2-22***), 2.27 (d, *J* = 8.5 Hz, 1H, ***CH_2-5***), 2.21–2.13 (m, 2H, ***CH_2***), 2.13–1.95 (m, 2H, ***CH_2***), 1.72–1.55 (m, 7H, ***4CH_2, CH_3-18***), 1.53–1.47 (m, 1H, ***CH_2-7***), 1.25 (d, *J* = 12.3 Hz, 3H, ***CH_3-16,17 or 19***), 1.07 (d, *J* = 9.3 Hz, 3H, ***CH_3-16,17 or 19***), 0.99 (s, 3H, ***CH_3-16,17 or 19***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 155.4 (***CO_3***), 139.6 (***CH-9***), 138.3 (***C-11***), 135.0 (***C-3***), 134.9 (***CH-4 or 10***), 134.6 (***CH-4 or 10***), 131.2 (***CH-23***), 127.6 (***C-12***), 125.5 (***CH-20***), 119.8 (***CH_2-10′***), 117.0 (***CH_2-24***), 90.0 (***C-1***), 78.0 (***CH-2***), 71.4 (***CH_2-21 or 23***), 70.6 (***CH_2-21 or 23***), 42.9 (***C-15***), 39.6 (***C-8***), 37.7 (***CH_2-7***), 29.2 (***CH_2-5***), 25.5 (***CH_2-13 or 14***), 25.4 (***CH_2- 13 or 14***), 25.2 (***CH_3-16, 17 or 19***), 23.9 (***CH_3-16, 17 or 19***), 20.9 (***CH_3-18***), 20.5 (***CH_3-16, 17 or 19***), 18.0 (***CH_2-6***).

IR (thin film): 3340, 2947, 1795, 1068, 1033, 862 cm^{-1}.

HRMS (ESI): Calcd for $C_{26}H_{36}NaO_4^+$ $[M+Na]^+$, 435.2506; found, 435.2500.

(4*R,5*R**)-4-(6-((*E*)-Hepta-1,6-dien-1-yl)-6-methylcyclohex-1-en-1-yl)-6,6,8-trimethyl-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-2-one ((±)3.83a-b)**



(±)3.74a
(±)3.74b

(±)3.83a (70%)
(±)3.83b (52%, 68% brsm)

Chemical formula: $C_{27}H_{38}O_3$

MW: 410.60

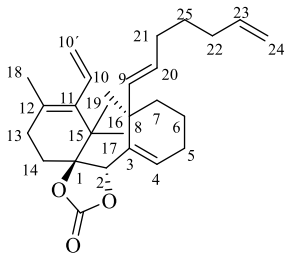
To a stirred solution of alcohol **(±)3.74a** (23 mg, 0.066 mmol) in H_2O-saturated CH_2Cl_2 (1.7 mL) was added DMP (57 mg, 0.13 mmol, 2.0 equiv). The resulting cloudy solution stirred at room temperature for 2h. The reaction mixture was diluted with Et_2O and then concentrated under reduced pressure. Et_2O was then added and the organic phase was washed with a saturated aqueous solution of $Na_2S_2O_3$ and a saturated aqueous solution of $NaHCO_3$. The aqueous layers were back-extracted with Et_2O and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

To a stirred solution of this crude mixture and sulfone **3.34** (58 mg, 0.20 mmol, 3.0 equiv) in DME (2.3 mL) at -55°C was slowly added KHMDS (0.30 mL, 0.9 M in THF, 0.27 mmol, 4.0 equiv). The reaction mixture stirred at this temperature for 1h and the resulting solution was then warmed up to room temperature and stirred for 1h. Brine was added to quench the reaction and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:CH_2Cl_2 (6:4)

to afford the *E*-alkene **(±)3.83a** as a highly viscous colourless oil (19 mg, 0.046 mmol, 70% for two steps).

The same experimental procedure was applied to alcohol **(±)3.74b** (120 mg, 0.36 mmol) to afford the *E*-alkene **(±)3.83b** as a highly viscous colourless oil (75 mg, 0.18 mmol, 52% for two steps).

(4*R,5*R**)-4-((*S**)-6-((*E*)-Hepta-1,6-dien-1-yl)-6-methylcyclohex-1-en-1-yl)-6,6,8-trimethyl-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-2-one ((±)3.83a)**



(±)3.83a

Chemical formula: $C_{27}H_{38}O_3$

MW: 410.60

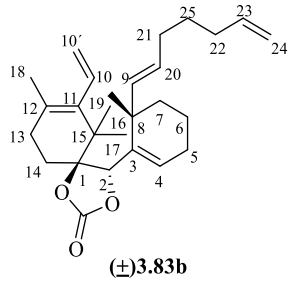
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.09 (dd, *J* = 17.3, 11.6 Hz, 1H, ***CH-10***), 5.88 (s, 1H, ***CH-4***), 5.78 (dt, *J* = 16.7, 8.4 Hz, 1H, ***CH-9***), 5.46–5.40 (m, 1H, ***CH-20***), 5.35–5.27 (m, 2H, ***CH_2-10', CH-23***), 5.06–4.90 (m, 4H, ***CH-2, CH_2-10', CH_2-24***), 2.28 (d, *J* = 13.4 Hz, 1H, ***CH_2***), 2.17–2.10 (m, 2H, ***CH_2***), 2.10–2.02 (m, 5H, ***CH_2***), 1.79–1.68 (m, 2H, ***CH_2***), 1.66 (s, 3H, ***CH_3***), 1.58–1.53 (m, 3H, ***CH_2***), 1.51–1.44 (m, 4H, ***CH_2***), 1.17–1.11 (m, 2H, ***CH_2***), 1.07 (s, 6H, ***CH_3***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 155.5 (***CO_3***), 138.6 (***CH-9***), 138.0 (***C-11***), 137.8 (***CH-23***), 134.9 (***C-3***), 134.8 (***CH-10***), 131.9 (***CH-4***), 130.3 (***CH-20***), 128.0 (***C-12***), 119.9 (***CH_2-10'***), 114.6 (***CH_2-24***), 89.9 (***C-1***), 79.0 (***CH-2***), 43.0 (***C-15***), 40.0 (***C-8***), 38.4 (***CH_2-7***), 33.2 (***CH_2-21 or 22***), 32.1 (***CH_2-21 or 22***), 29.1 (***CH_2-5***), 28.8 (***CH_2-25***), 25.7 (***CH_2-13 or 14***), 25.4 (***CH_2-13 or 14***), 25.2 (***CH_3-16, 17 or 19***), 25.1 (***CH_3- 16, 17 or 19***), 21.0 (***CH_3-18***), 20.5 (***CH_3-16, 17 or 19***), 18.1 (***CH_2-6***).

IR (thin film): 2954, 2922, 2852, 1805, 1456, 1174 cm^{-1}.

HRMS (ESI): Calcd for $C_{27}H_{38}NaO_3^+$ $[M+Na]^+$, 433.2713; found, 433.2710.

(4*R,5*R**)-4-((*R**)-6-((*E*)-Hepta-1,6-dien-1-yl)-6-methylcyclohex-1-en-1-yl)-6,6,8-trimethyl-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-2-one ((±)3.83b)**



(±)3.83b

Chemical formula: $C_{27}H_{38}O_3$

MW: 410.60

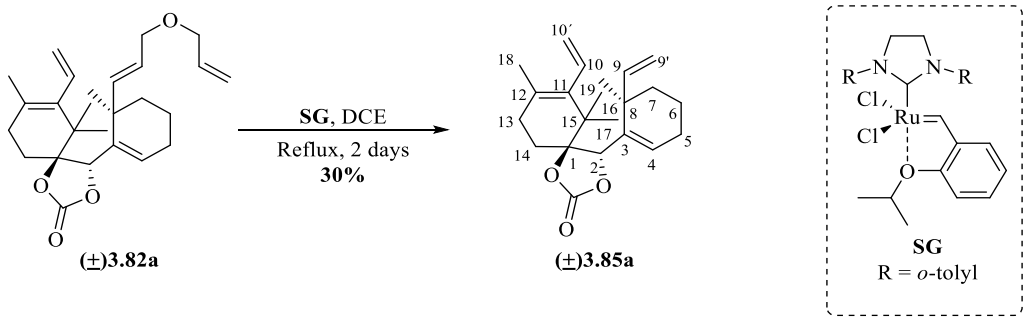
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.09 (dd, *J* = 17.9, 11.0 Hz, 1H, ***CH-10***), 5.83 (bs, 1H, ***CH-4***), 5.81–5.71 (m, 1H, ***CH-9***), 5.48–5.37 (m, 1H, ***CH-20***), 5.28–5.21 (m, 2H, ***CH_2-10', CH-23***), 5.06–4.92 (m, 3H, ***CH_2-24, CH_2-10'***), 4.88 (s, 1H, ***CH-2***), 2.35–2.23 (m, 1H, ***CH_2***), 2.21–2.07 (m, 3H, ***CH_2***), 2.07–1.84 (m, 5H, ***CH_2***), 1.71–1.65 (m, 4H, ***CH_2, CH_3-18***), 1.63–1.36 (m, 6H, ***CH_2***), 1.24 (s, 3H, ***CH_3-19***), 1.07 (s, 3H, ***CH_3-16 or 17***), 1.00 (s, 3H, ***CH_3-16 or 17***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 155.5 (***CO_3***), 138.9 (***C-11***), 138.5 (***CH-9***), 137.5 (***CH-23***), 135.0 (***C-3***), 134.8 (***CH-10***), 130.8 (***CH-4***), 129.0 (***CH-20***), 127.6 (***C-12***), 119.8 (***CH_2-10'***), 114.6 (***CH_2-24***), 89.9 (***C-1***), 78.0 (***CH-2***), 42.9 (***C-15***), 39.6 (***C-8***), 38.1 (***CH_2-7***), 33.2 (***CH_2-21 or 22***), 32.3 (***CH_2-21 or 22***), 29.2 (***C-5***), 28.4 (***C-25***), 25.5 (***CH_2-13 or 14***), 25.4 (***CH_2-13 or 14***), 25.3 (***CH_3-16 or 17***), 24.0 (***CH_3-19***), 21.0 (***CH_3-18***), 20.5 (***CH_3-16 or 17***), 18.1 (***CH_2-6***).

IR (thin film): 2927, 1789, 1452, 1344, 1265, 1176, 1039 cm^{-1}.

HRMS (ESI): Calcd for $C_{27}H_{38}NaO_3^+$ $[M+Na]^+$, 433.2713; found, 433.2706.

(4*R,5*R**)-6,6,8-Trimethyl-4-((*S**)-6-methyl-6-vinylcyclohex-1-en-1-yl)-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-2-one ((±)3.85a)**



Chemical formula: $C_{22}H_{30}O_3$

MW: 342.48

To a stirred solution of the Stewart-Grubbs catalyst **SG** (9.0 mg, 0.015 mmol, 0.30 equiv) in dry and degassed DCE (23 mL) at 50°C was slowly added a solution of carbonate **(±)3.82a** (20 mg, 0.048 mmol) in DCE (1.0 mL). The reaction mixture was warmed to reflux and stirred for 2 days. The resulting mixture was cooled down to room temperature and diluted with a small amount of CH_2Cl_2. The crude mixture was dry loaded and purified by flash chromatography using petroleum ether:Et_2O (9:1) to afford the truncated product **(±)3.85a** as a pale yellow oil (5.0 mg, 0.014 mmol, 30%).

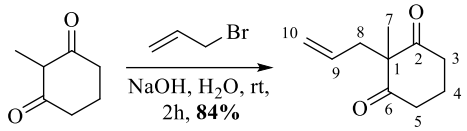
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.09 (dd, *J* = 17.6, 11.0 Hz, 1H, ***CH-10***), 5.92 (t, *J* = 4.0 Hz, 1H, ***CH-4***), 5.73 (dd, *J* = 17.5, 10.6 Hz, 1H, ***CH-9***), 5.31 (dd, *J* = 11.1, 2.5 Hz, 1H, ***CH$_2$-10'***), 5.16 (dd, *J* = 10.6, 1.0 Hz, 1H, ***CH$_2$-9'***), 5.06 (dd, *J* = 17.5, 1.0 Hz, 1H, ***CH$_2$-9'***), 4.96 (dd, *J* = 17.6, 2.5 Hz, 1H, ***CH$_2$-10'***), 4.92 (s, 1H, ***CH-2***), 2.32–2.26 (m, 1H, ***CH$_2$-5***), 2.18–2.12 (m, 2H, ***CH$_2$***), 2.10–2.04 (m, 2H, ***CH$_2$***), 1.75–1.70 (m, 1H, ***CH$_2$***), 1.66 (s, 3H, ***CH$_3$-18***), 1.52–1.56 (m, 3H, ***CH$_2$***), 1.27–1.22 (m, 1H, ***CH$_2$***), 1.07 (s, 6H, ***CH$_3$-16, 17***), 1.07 (s, 3H, ***CH$_3$-19***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 155.5 (***CO_3***), 145.5 (***CH-9***), 137.4 (***C-11***), 134.9 (***C-3***), 134.8 (***CH-10***), 132.4 (***CH-4***), 128.0 (***C-12***), 120.0 (***CH_2-10'***), 114.6 (***CH_2-9'***), 89.9 (***C-1***), 78.9 (***CH-2***), 43.0 (***C-15***), 40.9 (***C-8***), 38.0 (***CH_2-7***), 29.1 (***CH_2-5***), 25.7 (***CH_2-13 or 14***), 25.4 (***CH_2-13 or 14***), 25.1 (***CH_3-16, 17 or 19***), 24.5 (***CH_3-16, 17 or 19***), 21.0 (***CH_3-18***), 20.5 (***CH_3-16, 17 or 19***), 18.0 (***CH_2-6***).

IR (thin film): 2941, 2904, 1788, 1178, 1043, 912 cm^{-1}.

HRMS (ESI): Calcd for $C_{22}H_{30}NaO_3^+$ $[M+Na]^+$, 365.2087; found, 365.2071.

2-Allyl-2-methylcyclohexane-1,3-dione ((±)3.91)[94]



2.32 **(±)3.91**

Chemical formula: $C_{10}H_{14}O_2$

MW: 166.22

To a stirred solution of diketone **2.32** (30.0 g, 237 mmol) in a 1M aqueous solution of NaOH (240 mL) was added 3-bromopropene (41 mL, 470 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature for 2 days. Brine was added to quench the reaction and the aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the diketone **(±)3.91** as a pale yellow oil (33.0 g, 198 mmol, 84%).

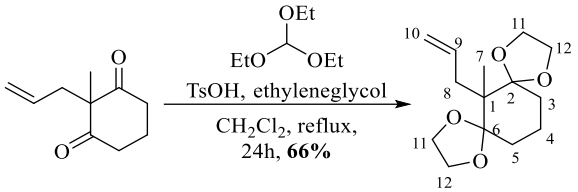
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.63–5.49 (m, 1H, ***CH-9***), 5.05 (m, 2H, ***CH_2-10***), 2.67–2.59 (m, 4H, ***CH_2-3, 5***), 2.52 (d, *J* = 7.3 Hz, 2H, ***CH_2-8***), 2.02–1.84 (m, 2H, ***CH_2-4***), 1.23 (s, 3H, ***CH_3-7***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 209.8 (***CO-2,6***), 132.2 (***CH-9***), 119.2 (***CH_2-10***), 65.2 (***C-1***), 41.3 (***CH_2-8***), 38.2 (***CH_2-3,5***), 19.6 (***CH_3-7***), 17.5 (***CH_2-4***).

IR (thin film): 3288, 2916, 2830, 1695, 1020 cm^{-1}.

HRMS (ESI): Calcd for $C_{10}H_{14}NaO_2^+$ $[M+Na]^+$, 189.0886; found, 189.0882.

6-Allyl-6-methyl-1,4,8,11-tetraoxadispiro[4.1.4^7.3^5]tetradecane ((±)3.92)[94]



(±)3.91 **(±)3.92**

Chemical formula: $C_{14}H_{22}O_4$

MW: 254.33

To a stirred solution of diketone **(±)3.91** (395 mg, 2.38 mmol) in CH_2Cl_2 (8.0 mL) was added *p*-toluenesulfonic acid (46 mg, 0.24 mmol, 0.10 equiv), ethylene glycol (1.2 mL, 21 mmol, 9.0 equiv) and triethyl orthoformate (2.9 mL, 18 mmol, 7.5 equiv). The reaction mixture was refluxed for 24h. The resulting solution was allowed to cool down to room temperature and a saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (1:1) to afford the acetal **(±)3.92** as a pale yellow solid (400 mg, 1.57 mmol, 66%).

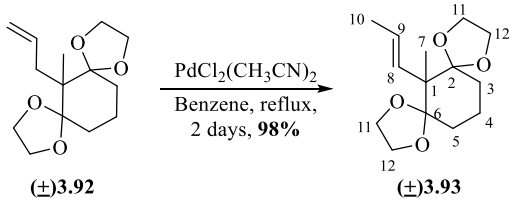
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.04–5.91 (m, 1H, ***CH-9***), 4.96–4.83 (m, 2H, ***CH_2-10***), 4.02–3.84 (m, 8H, ***CH_2-11,12***), 2.35–2.32 (m, 2H, ***CH_2-8***), 1.64–1.52 (m, 6H, ***CH_2-3, 4, 5***), 1.14 (s, 3H, ***CH_3-7***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 137.8 (***CH-9***), 114.1 (***CH_2-10***), 113.0 (***C-6,2***), 65.3 (***CH_2-11 or 12***), 63.8 (***CH_2-11 or 12***), 49.7 (***C-1***), 34.9 (***CH_2-8***), 30.2 (***CH_2-3,5***), 18.6 (***CH_2-4***), 17.2 (***CH_3-7***).

IR (thin film): 3396, 2937, 2883, 1722, 1444, 1066 cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{22}NaO_4^+$ $[M+Na]^+$, 277.1410; found, 277.1403.

(*E*)-6-Methyl-6-(prop-1-en-1-yl)-1,4,8,11-tetraoxadispiro[4.1.4^7.3^5]tetradecane ((±)3.93)[94]



(±)3.92 **(±)3.93**

Chemical formula: $C_{14}H_{22}O_4$

MW: 254.33

To a stirred solution of **(±)3.92** (8.10 g, 31.8 mmol) in benzene (81 mL) was added $PdCl_2(CH_3CN)_2$ (81 mg, 0.31 mmol, 0.010 equiv). The reaction mixture was refluxed for 2 days and the solvent was then removed under reduced pressure. The resulting mixture was diluted with EtOAc and CH_2Cl_2 and filtered through a pad of Celite. The filter cake was washed with EtOAc and the filtrate was concentrated under reduced pressure to afford the alkene **(±)3.93** as a white solid (7.96 g, 31.3 mmol, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.78 (dd, *J* = 15.8, 1.5 Hz, 1H, ***CH-8***), 5.59 (dq, *J* = 15.7, 6.3 Hz, 1H, ***CH-9***), 3.95–3.83 (m, 8H, ***CH_2-11, 12***), 1.70 (dd, *J* = 6.3, 1.6 Hz, 3H, ***CH_3-10***), 1.67–1.56 (m, 6H, ***CH_2-3, 4, 5***), 1.15 (s, 3H, ***CH_3-7***).

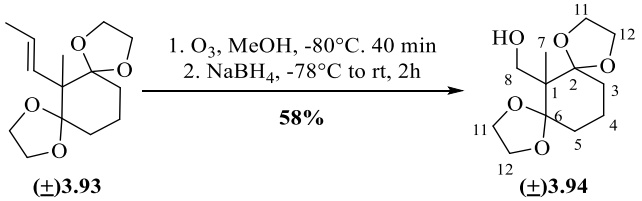
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 131.3 (***C-8***), 126.3 (***CH-9***), 112.6 (***C-2,6***), 65.2 (***CH_2-11 or 12***), 65.1 (***CH_2-11 or 12***), 52.5 (***C-1***), 30.8 (***CH_2-3,5***), 18.9 (***CH_3-10***), 18.8 (***CH_2-4***), 15.1 (***CH_3-7***).

IR (thin film): 2953, 2883, 2245, 1155, 1066 cm^{-1}.

HRMS (ESI): Calcd for $C_{14}H_{22}NaO_4^+$ $[M+Na]^+$, 277.1410; found, 277.1404.

MP: 66°C.

(6-Methyl-1,4,8,11-tetraoxadispiro[4.1.4^7.3^5]tetradecan-6-yl)methanol ((±)3.94)[94]



Chemical formula: $C_{12}H_{20}O_5$

MW: 244.29

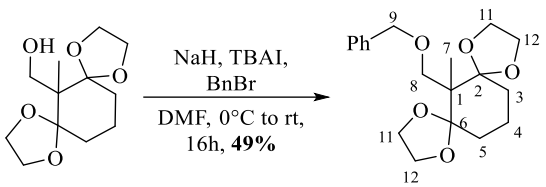
To a stirred solution of alkene **(±)3.93** (1.33 g, 5.23 mmol) in MeOH (43 mL) at -78°C was passed a stream of O_3 for 50 min. $NaBH_4$ (417 mg, 11.0 mmol, 2.0 equiv) was added the solution and the resulting mixture was allowed to warm up to room temperature. The solvent was removed under reduced pressure and the residue was diluted with EtOAc and a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and

concentrated under reduced pressure to afford the alcohol **(±)3.94** as a white solid (735 mg, 3.00 mmol, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.02–3.92 (m, 8H, ***CH_2-11,12***), 3.82 (t, *J* = 6.0 Hz, 2H, ***CH_2-8***), 3.14 (t, *J* = 6.0 Hz, 1H, ***OH***), 1.68–1.56 (m, 6H, ***CH_2-3,4,5***), 1.10 (d, *J* = 6.9 Hz, 3H, ***CH_3-7***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 112.9 (***C-2,6***), 65.0 (***CH_2-8***), 64.9 (***CH_2-11 or 12***), 64.6 (***CH_2-11 or 12***), 50.5 (***C-1***), 30.3 (***CH_2-3,5***), 18.7 (***CH_2-4***), 12.5 (***CH_3-7***).

6-((Benzyloxy)methyl)-6-methyl-1,4,8,11-tetraoxadispiro[4.1.4^7.3^5]tetradecane ((±)3.95)[94]



(±)3.94 **(±)3.95**

Chemical formula: $C_{19}H_{26}O_5$

MW: 334.41

To a stirred suspension of NaH (135 mg, 3.30 mmol, 1.10 equiv) and TBAI (110 mg, 0.30 mmol, 0.10 equiv) at 0°C in THF (6.6 mL) was added a solution of alcohol **(±)3.94** (735 mg, 3.00 mmol) in THF (2.7 mL). To the resulting mixture was added a solution of benzyl bromide in DMF (660 μL). The reaction mixture was allowed to warm to room temperature and stirred for 16h. A saturated aqueous solution of NaH_4Cl was added to quench the reaction. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:EtOAc (3:1) to afford the ether **(±)3.95** as a white solid (490 mg, 1.47 mmol, 49%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.36–7.23 (m, 5H, ***CH-Ar***), 4.50 (s, 2H, ***CH_2-9***), 3.98–3.85 (m, 8H, ***CH_2-11, 12***), 3.62 (s, 2H, ***CH_2-8***), 1.83 (dt, *J* = 12.5, 6.2 Hz, 2H, ***CH_2***), 1.66–1.54 (m, 4H, ***CH_2***), 1.05 (s, 3H, ***CH_3-7***).

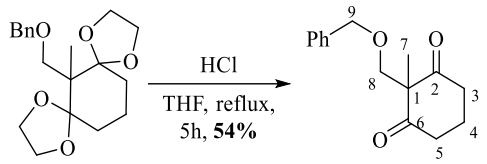
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 138.9 (***C-Ar***), 128.0 (***CH-Ar***), 127.1 (***CH-Ar***), 127.0 (***CH-Ar***), 112.3 (***C-2,6***), 73.4 (***CH_2-9***), 72.0 (***CH_2-8***), 65.1 (***CH_2-11 or 12***), 64.6 (***CH_2-11 or 12***), 50.9 (***C-1***), 31.4 (***CH_2***), 18.7 (***CH_2***), 14.1 (***CH_3-7***).

IR (thin film): 2879, 1774, 1141, 1093, 1068, 1029 cm^{-1}.

HRMS (ESI): Calcd for $C_{19}H_{26}NaO_5^+$ $[M+Na]^+$, 357.1672; found, 357.1670.

MP: 53°C

2-((Benzyloxy)methyl)-2-methylcyclohexane-1,3-dione ((±)3.96)[94]



(±)3.95 **(±)3.96**

Chemical formula: $C_{15}H_{18}O_3$

MW: 246.31

To a stirred solution of acetal **(±)3.95** (488 mg, 1.45 mmol) in THF (3.2 mL) was added a 2M aqueous solution of HCl and the reaction mixture was refluxed for 5h. The resulting solution was cooled down to room temperature and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:Et_2O (3:1) to afford the ketone **(±)3.96** as a white solid (192 mg, 0.782 mmol, 54%).[64]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.38–7.16 (m, 5H, ***CH-Ar***), 4.40 (s, 2H, ***CH_2-9***), 3.67 (s, 2H, ***CH_2-8***), 2.79–2.53 (m, 4H, ***CH_2-3,5***), 2.10–1.82 (m, 2H, ***CH_2-4***), 1.13 (s, 3H, ***CH_3-7***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 210.9 (***C-2,6***), 137.6 (***C-Ar***), 128.3 (***CH-Ar***), 127.7 (***CH-Ar***), 127.4 (***2CH-Ar***), 76.3 (***CH_2-8***), 73.5 (***CH_2-9***), 63.6 (***C-1***), 39.6 (***CH_2-3,5***), 17.7 (***CH_3-7***), 16.9 (***CH_2-4***).

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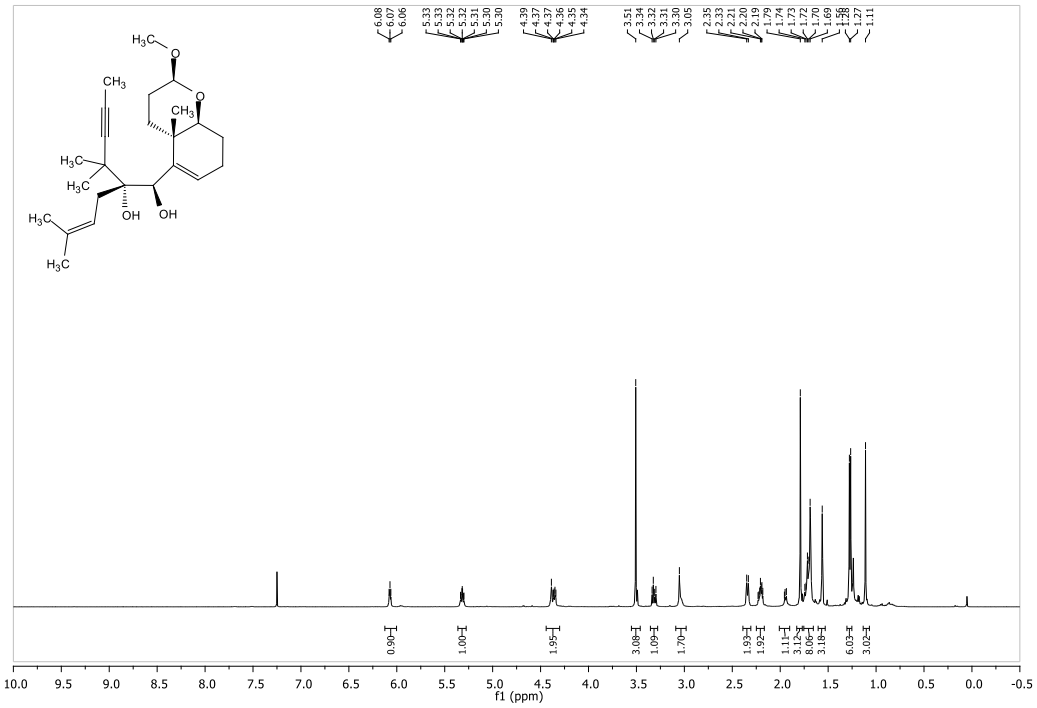
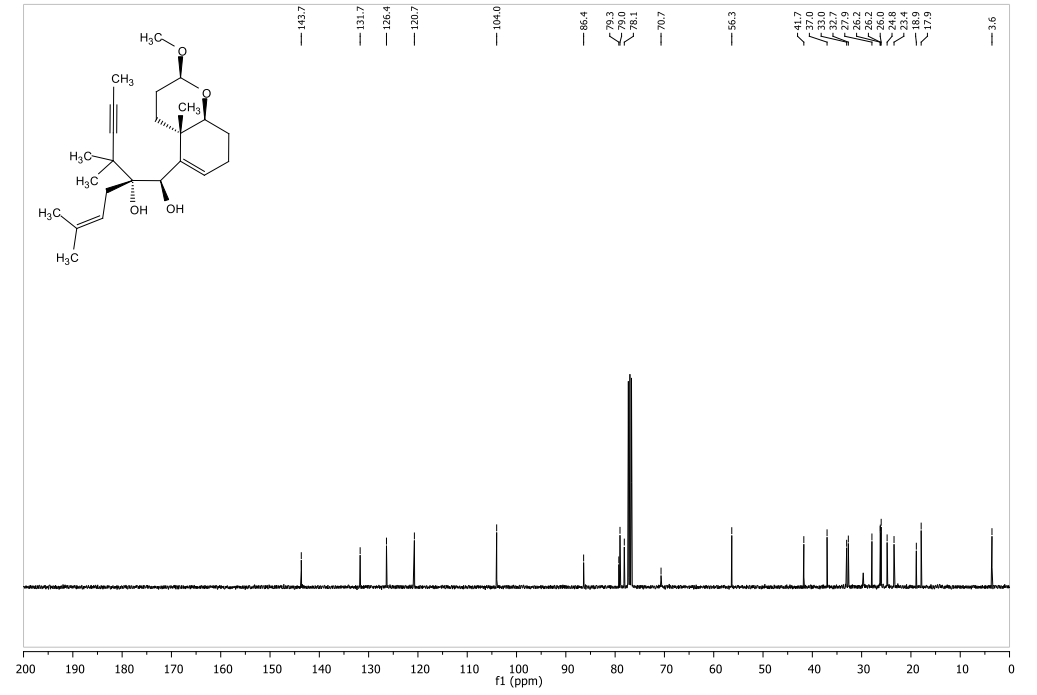
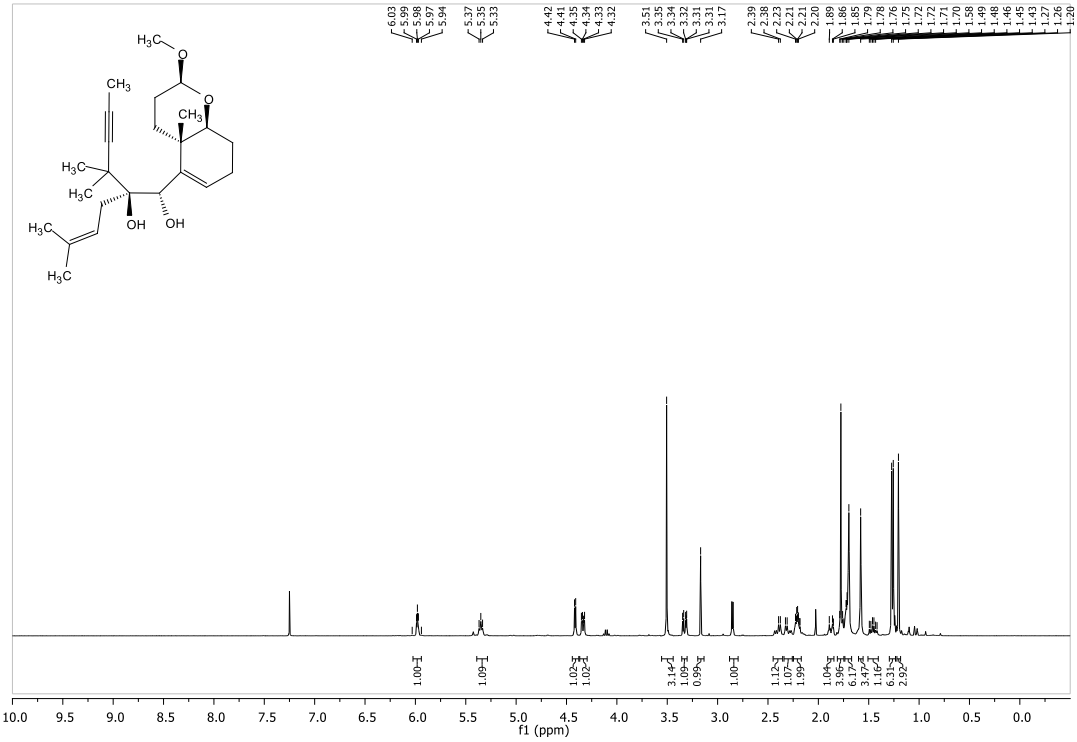
Appendices

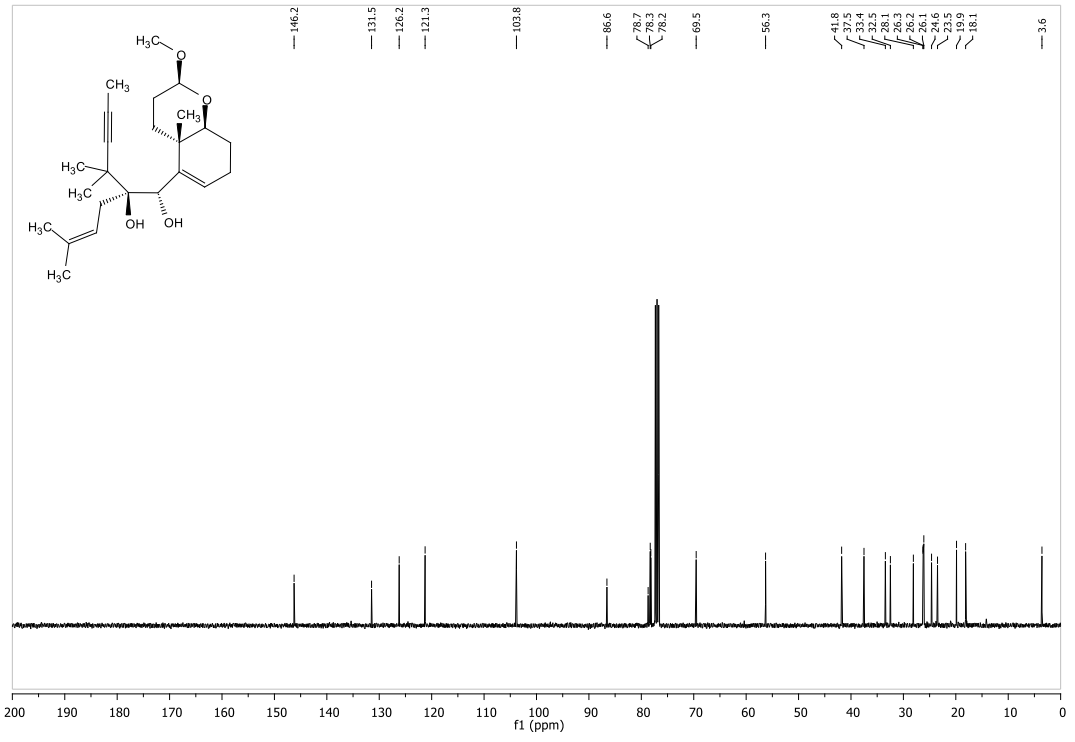
^{1}H NMR and ^{13}C NMR of 2.72a





^{1}H NMR and ^{13}C NMR of 2.72b





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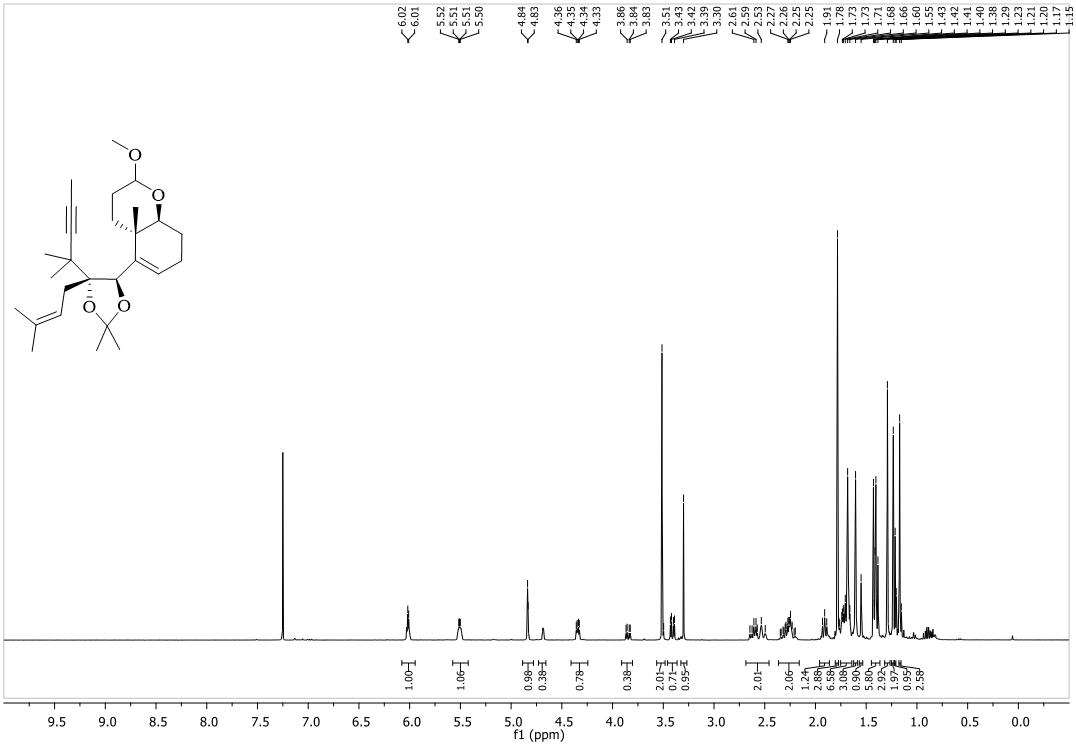

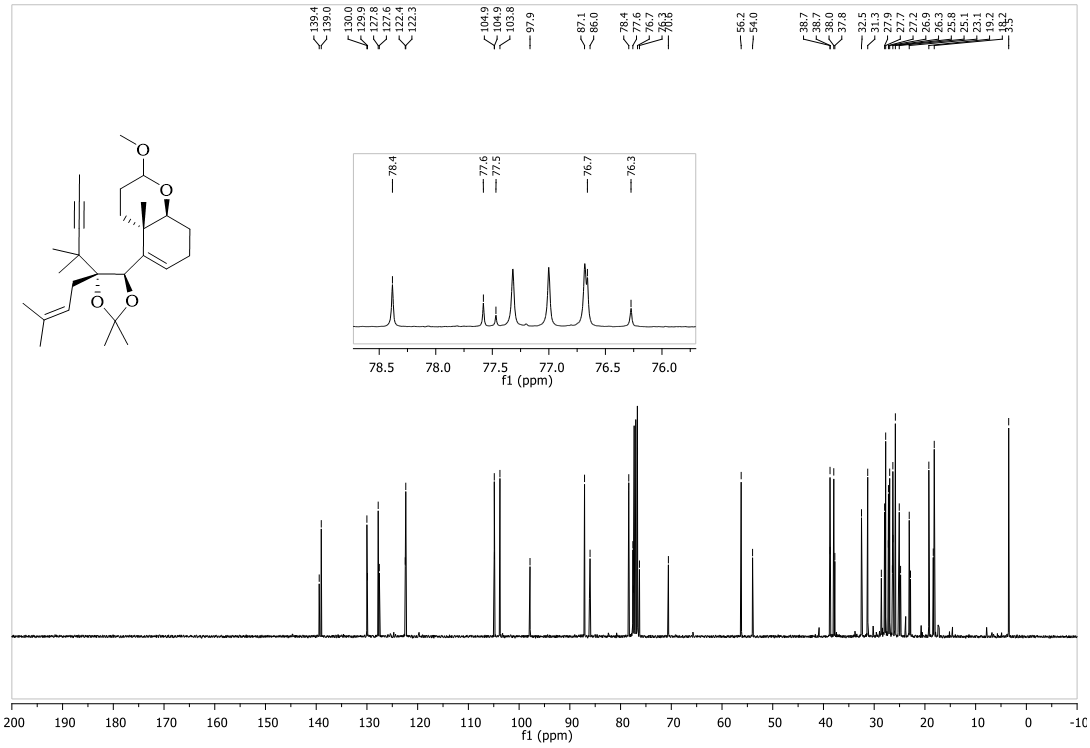

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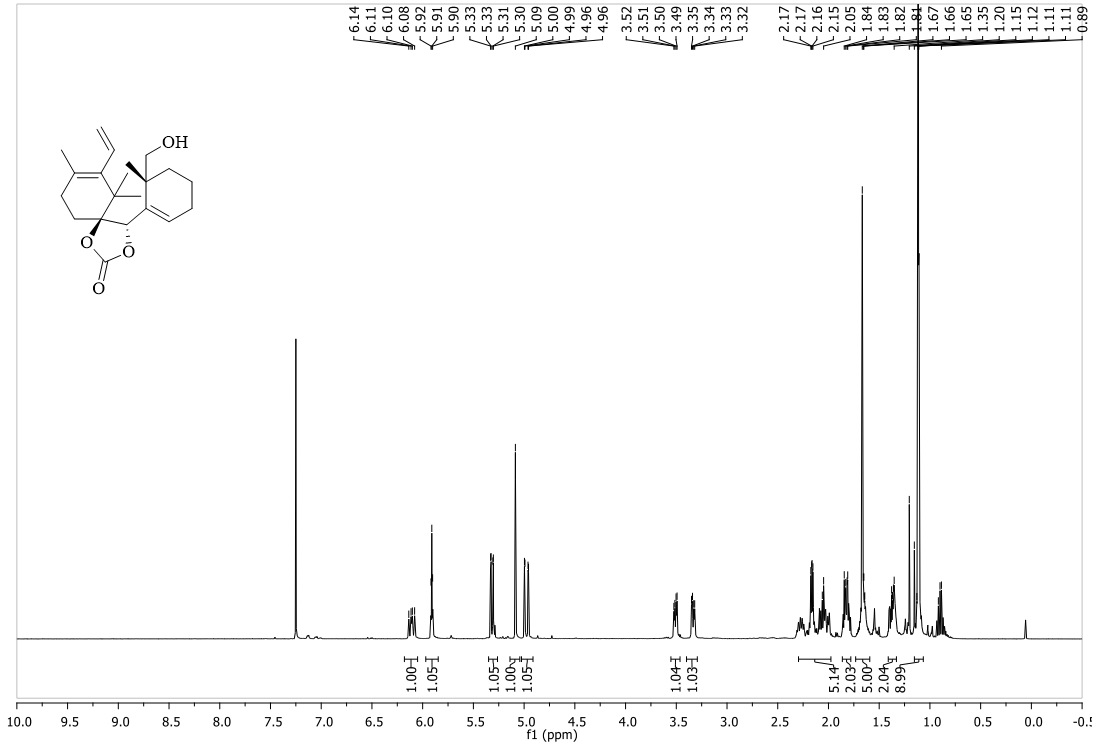

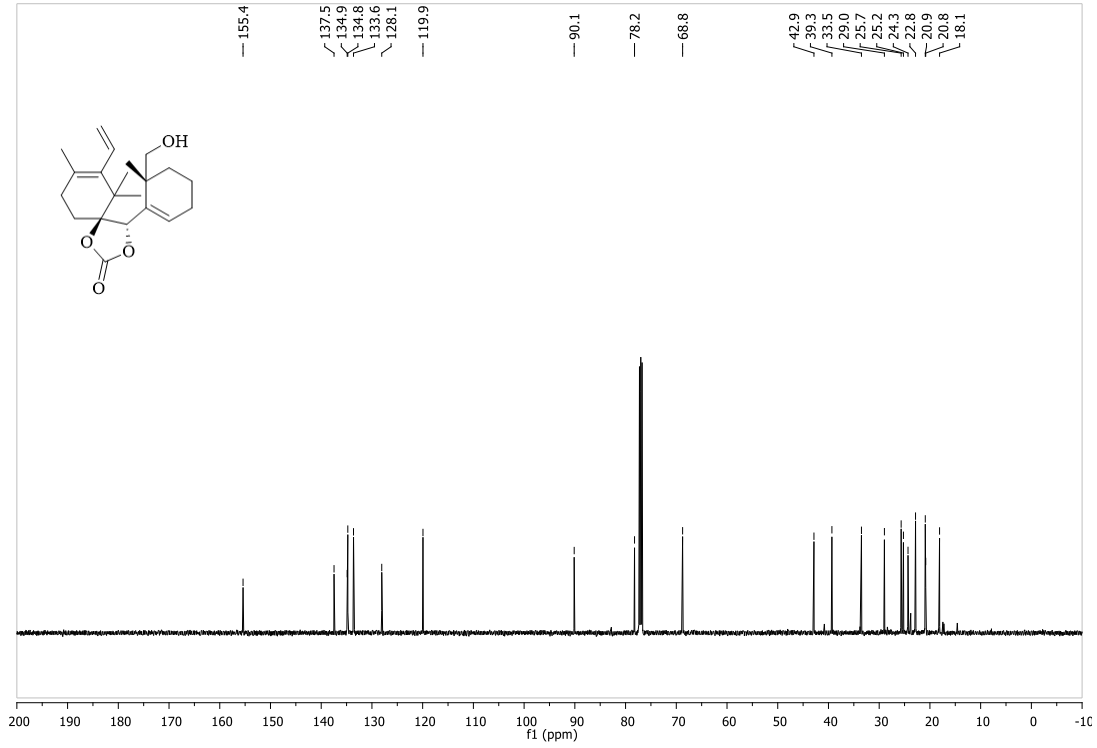

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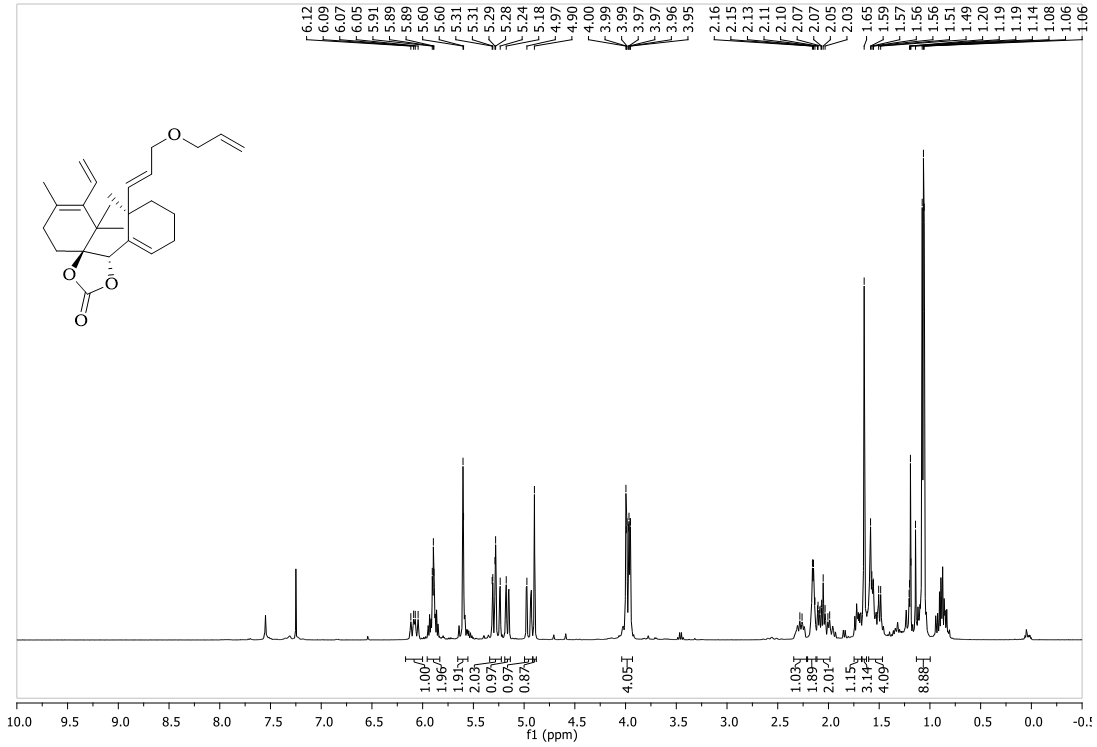

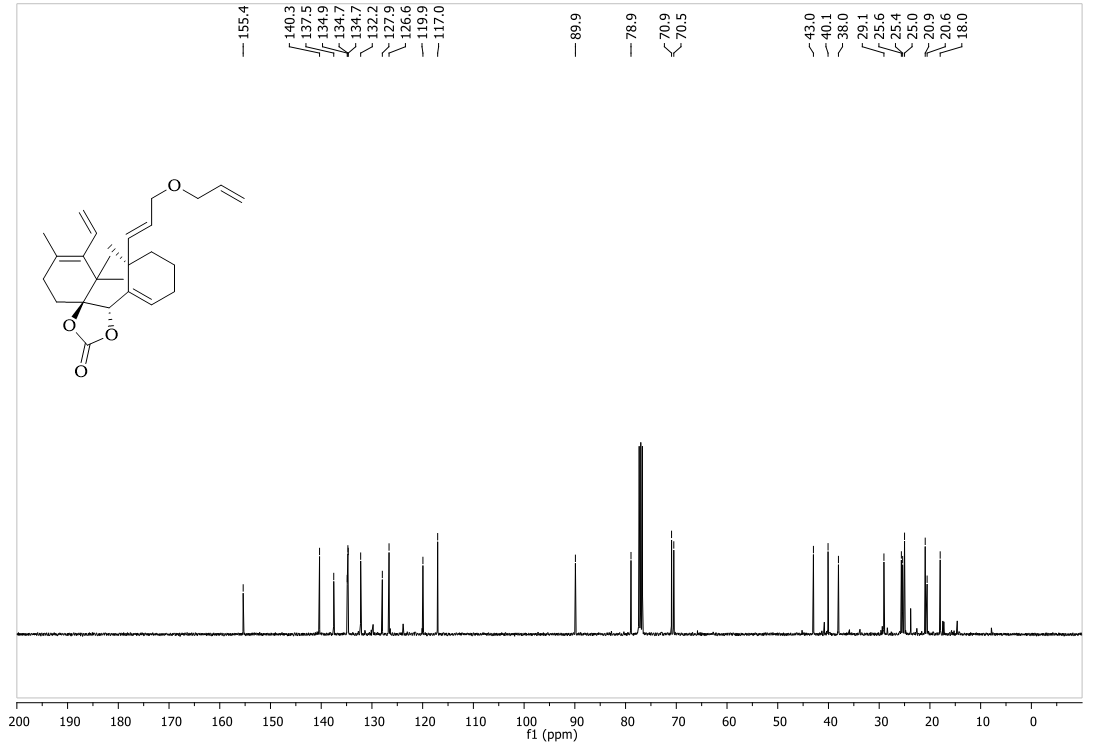

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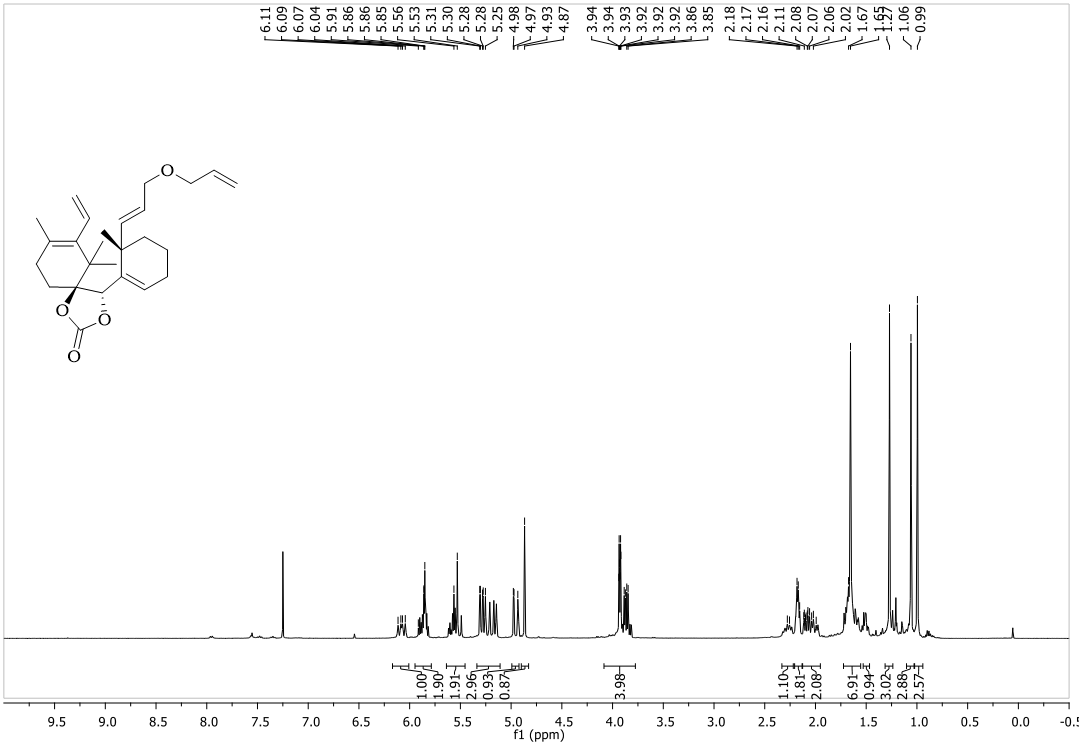

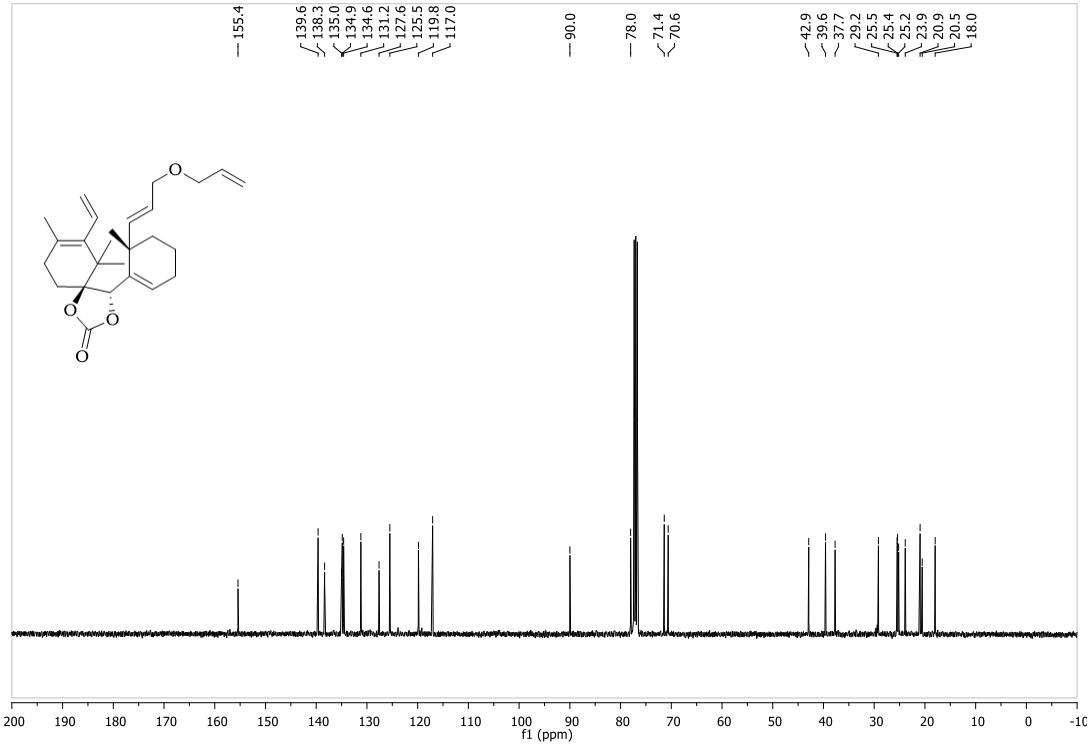

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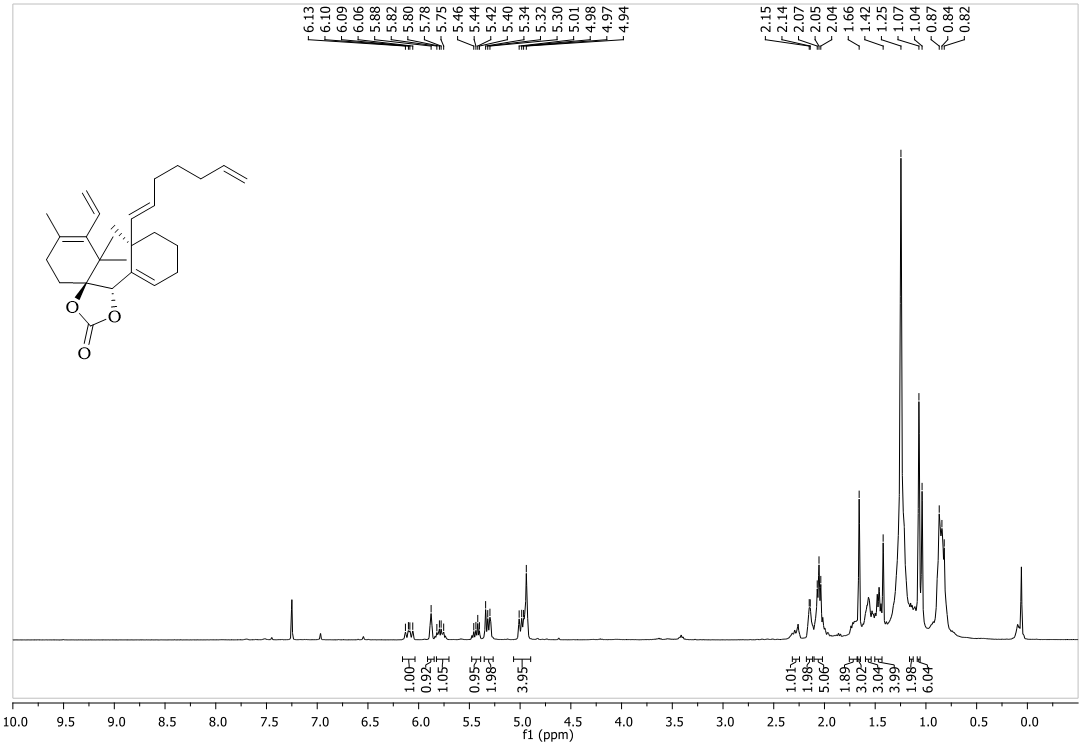

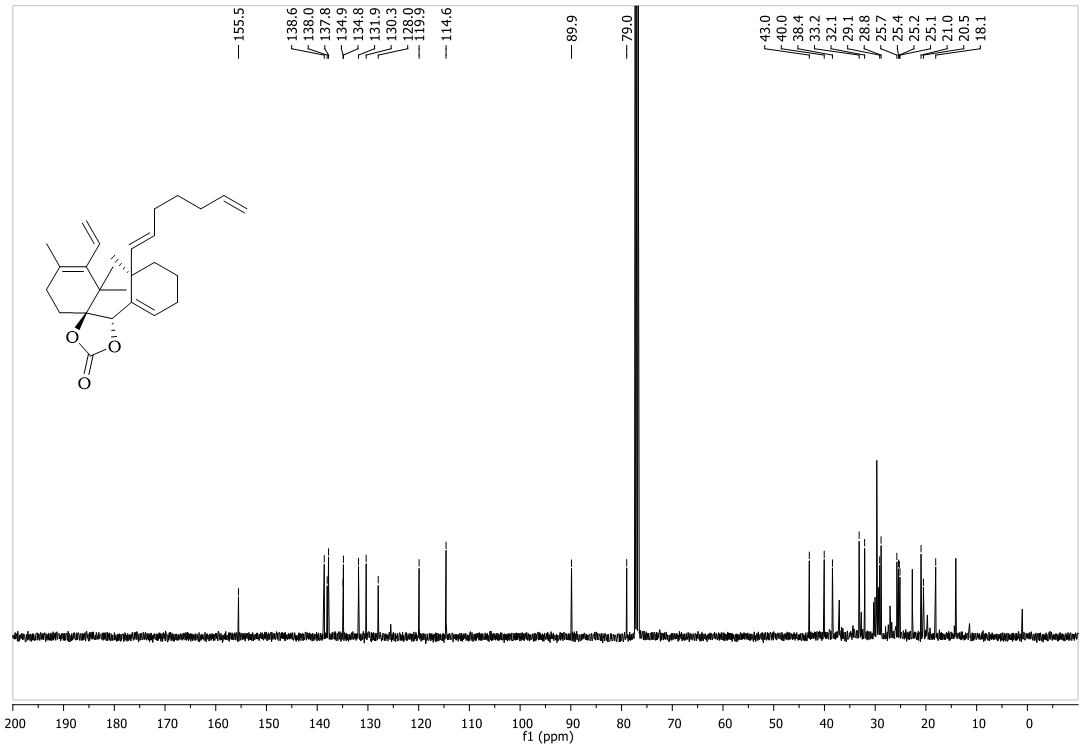

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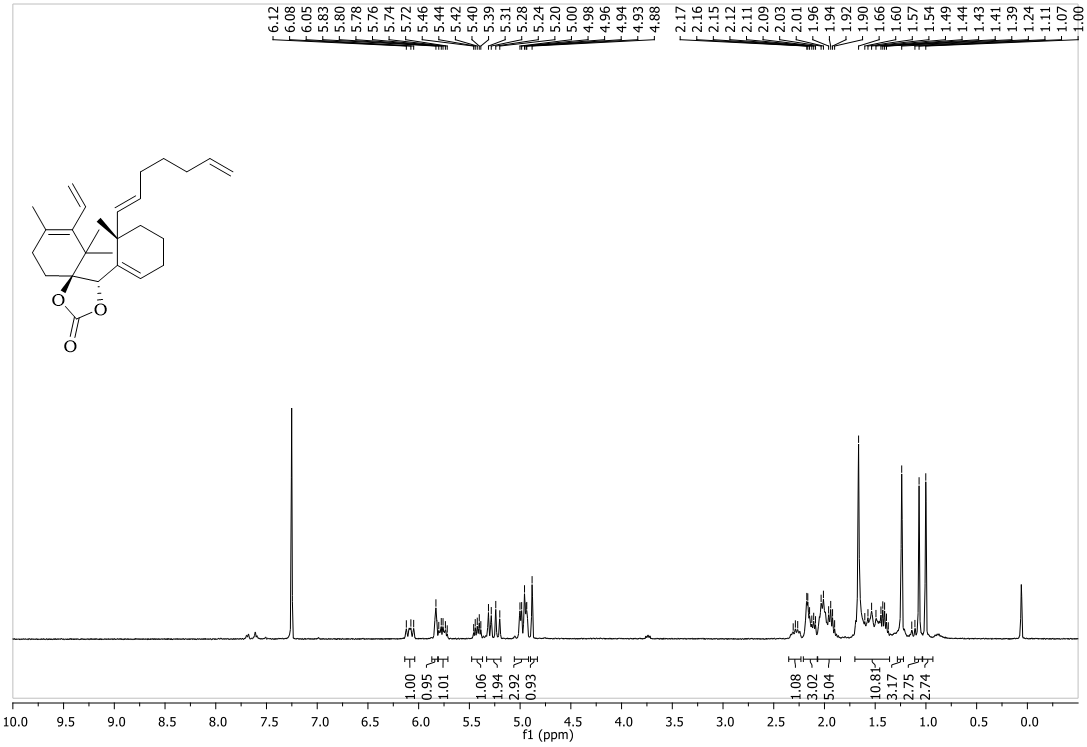
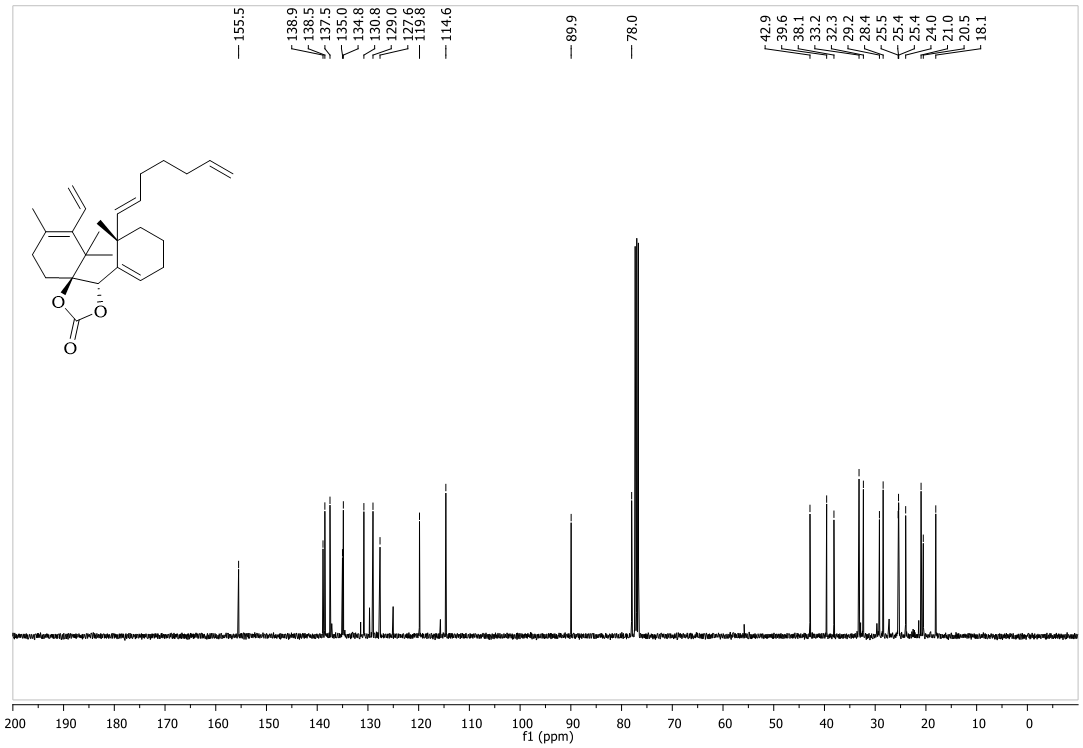
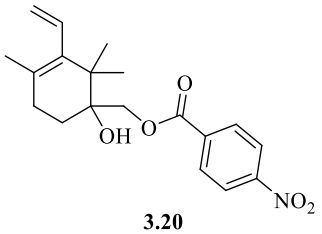




Chiral HPLC for the nitro derivate 3.20 (racemic mixture)



3.20

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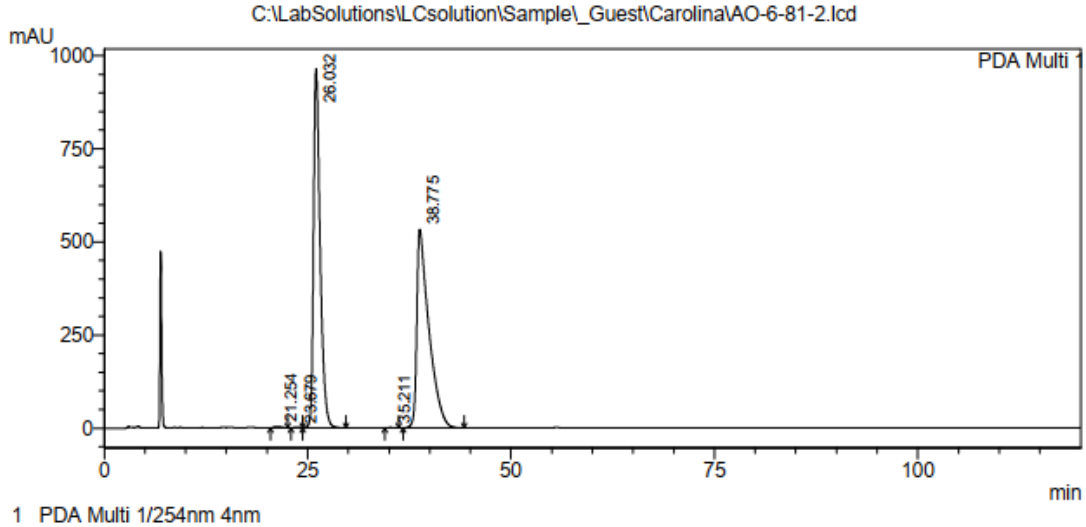
Sample Name	: AO-6-81-1
Sample ID	: AO-6-81-1
Injection Volume	: 20 uL
Data File Name	: AO-6-81-2.lcd
Method File Name	: 5%iPrOH-1mLmin.lcm
Data Acquired	: 07/02/2020 12:12:22
Data Processed	: 07/02/2020 14:12:25
5% 1.0mL/min	
AD-H	

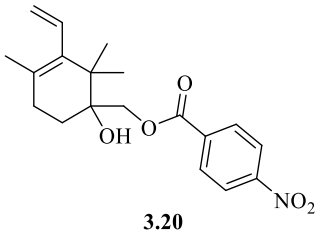


1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.254	179176	3196	0.163	0.213
2	23.679	73048	1640	0.066	0.109
3	26.032	54515817	962795	49.602	64.130
4	35.211	39631	762	0.036	0.051
5	38.775	55098642	532933	50.132	35.497
Total		109906313	1501325	100.000	100.000

Chiral HPLC for the nitro derivate 3.20 (enantio-enriched mixture)



3.20

C:\LabSolutions\LCsolution\Sample_Guest\Carolina\AO-7-09-1 EP1.lcd

Acquired by	: Admin
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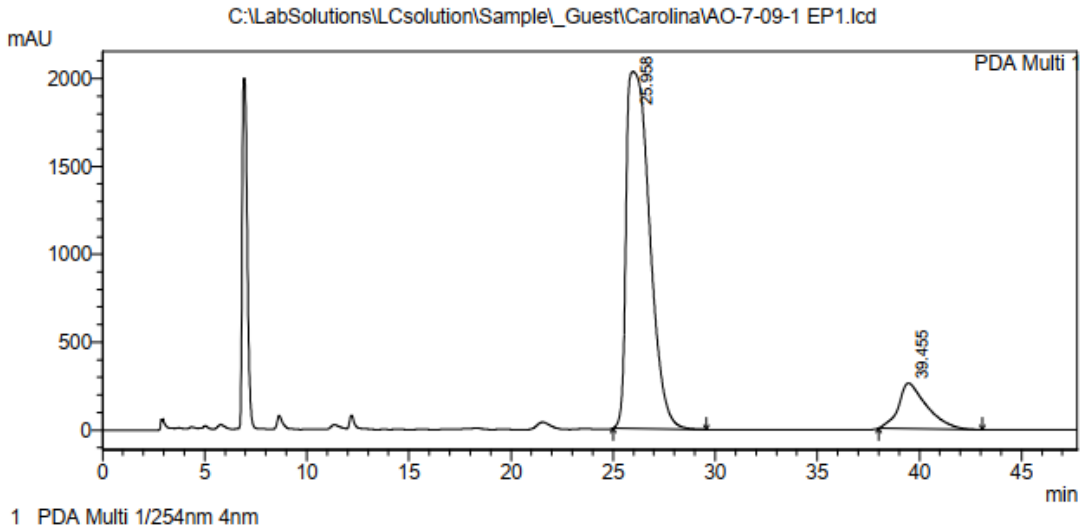
Sample ID	: AO-7-09-1 EP
Injection Volume	: 20 uL
Data File Name	: AO-7-09-1 EP1.lcd
Method File Name	: 20%B-1mlmin.lcm
Data Acquired	: 02/03/2020 16:23:07
Data Processed	: 02/03/2020 17:10:51

5% IPA 1.0mL/min
AD-H

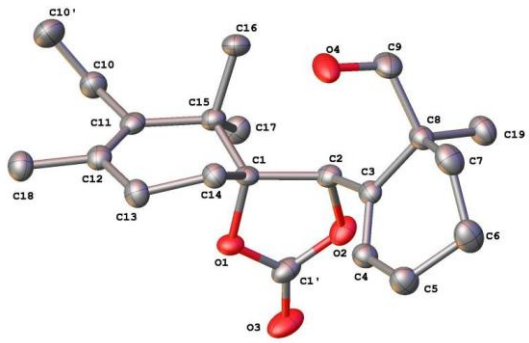


1 PDA Multi 1/254nm 4nm

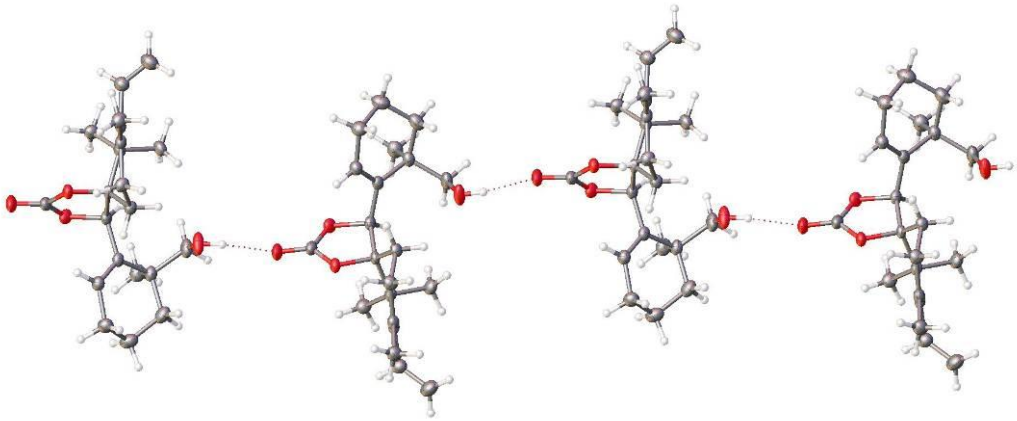
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	25.958	161330391	2029344	86.678	88.708
2	39.455	24795981	258322	13.322	11.292
Total		186126372	2287666	100.000	100.000

Crystal data and structure refinement for (±)3.57b



View showing the structure and atom labelling scheme for **(±)3.57b**, displacement ellipsoids drawn at 50% probability level. Below view showing H-bonded chain.



Refinement

Crystal data, data collection and structure refinement details are summarized in Table 1.

Computing details

Data collection: *CrysAlis PRO* 1.171.40.45a (Rigaku OD, 2019); cell refinement: *CrysAlis PRO* 1.171.40.45a (Rigaku OD, 2019); data reduction: *CrysAlis PRO* 1.171.40.45a (Rigaku OD, 2019); program(s) used to solve structure: ShelXT (Sheldrick, 2015); program(s) used to refine structure: *SHELXL* (Sheldrick, 2015); molecular graphics: Olex2 (Dolomanov *et al.*, 2009); software used to prepare material for publication: Olex2 (Dolomanov *et al.*, 2009).

References

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Sheldrick, G. M. (2015). *Acta Cryst.* A**71**, 3–8.

Sheldrick, G. M. (2015). *Acta Cryst.* C**71**, 3–8.

(2019ncsx0326_1a)

Crystal data

$C_{21}H_{30}O_4$	$F(000)$ = 752
M_r = 346.45	D_x = 1.241 Mg m^{-3}
Monoclinic, $P2_1/c$	Cu $K\alpha$ radiation, λ = 1.54178 Å
a = 6.99076 (5) Å	Cell parameters from 29302 reflections
b = 21.0167 (2) Å	θ = 4.1–70.2°
c = 12.63672 (9) Å	μ = 0.67 mm^{-1}
β = 92.5471 (6)°	T = 100 K
V = 1854.79 (3) Å^3	(cut) irregular plate, colourless
Z = 4	0.24 × 0.13 × 0.03 mm

Data collection

XtaLAB AFC11 (RCD3): quarter-chi single diffractometer	3388 independent reflections
Radiation source: Rotating-anode X-ray tube, Rigaku (Cu) X-ray Source	3179 reflections with $I > 2\sigma(I)$
Mirror monochromator	R_{int} = 0.045
Detector resolution: 10.0000 pixels mm^{-1}	θ_{max} = 68.2°, θ_{min} = 4.1°
□ scans	h = -8→8
Absorption correction: gaussian *CrysAlis PRO* 1.171.40.45a (Rigaku Oxford Diffraction, 2019) Numerical absorption correction based on gaussian integration over a multifaceted crystal model Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.	k = -25→25
T_{min} = 0.699, T_{max} = 1.000	l = -15→15
56106 measured reflections	

Refinement

Refinement on F^2	Primary atom site location: dual
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.036$	H-atom parameters constrained
$wR(F^2) = 0.095$	$w = 1/[\sigma^2(F_o^2) + (0.0446P)^2 + 0.7019P]$ where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.06$	$(\Delta/\sigma)_{max} = 0.001$
3388 reflections	$\Delta\rangle_{max} = 0.24$ e Å^{-3}
237 parameters	$\Delta\rangle_{min} = -0.19$ e Å^{-3}
1 restraint	

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}	Occ. (<1)
O1	0.47259 (11)	0.67711 (4)	0.49509 (6)	0.0246 (2)	
O2	0.63604 (13)	0.73135 (4)	0.37938 (6)	0.0290 (2)	
O3	0.33866 (15)	0.69854 (5)	0.33514 (8)	0.0436 (3)	
O4	1.02726 (14)	0.78001 (6)	0.69421 (8)	0.0412 (4)	0.930 (3)
H4	1.113415	0.783002	0.742445	0.062*	0.930 (3)
C12	0.53844 (17)	0.58807 (6)	0.68921 (9)	0.0251 (3)	
C1	0.66399 (15)	0.68370 (5)	0.54826 (9)	0.0206 (2)	
C14	0.62850 (17)	0.70364 (6)	0.66096 (9)	0.0234 (3)	
H14A	0.570658	0.746639	0.660910	0.028*	
H14B	0.751671	0.705427	0.702655	0.028*	
C11	0.66043 (17)	0.57019 (6)	0.61564 (9)	0.0240 (3)	
C3	0.76672 (16)	0.80355 (6)	0.51285 (9)	0.0218 (2)	
C2	0.75763 (17)	0.73476 (6)	0.47642 (9)	0.0228 (3)	
H2	0.889597	0.720375	0.460428	0.027*	
C15	0.76292 (16)	0.61766 (6)	0.54451 (9)	0.0232 (3)	

C8	0.96272 (17)	0.83531 (6)	0.52706 (9)	0.0252 (3)	
C1'	0.47260 (19)	0.70190 (6)	0.39842 (10)	0.0291 (3)	
C4	0.60455 (17)	0.83580 (6)	0.52291 (9)	0.0258 (3)	
H4A	0.488100	0.813388	0.509069	0.031*	
C13	0.49515 (18)	0.65663 (6)	0.71166 (9)	0.0268 (3)	
H13A	0.502518	0.663263	0.789291	0.032*	
H13B	0.362117	0.665839	0.686093	0.032*	
C10	0.70847 (18)	0.50201 (6)	0.60021 (11)	0.0304 (3)	
H10	0.681734	0.483958	0.532235	0.036*	
C18	0.42730 (19)	0.54284 (6)	0.75552 (10)	0.0311 (3)	
H18A	0.433936	0.499885	0.725731	0.047*	
H18B	0.293320	0.556532	0.755781	0.047*	
H18C	0.482319	0.542663	0.828218	0.047*	
C17	0.76085 (19)	0.59264 (6)	0.42975 (10)	0.0288 (3)	
H17A	0.628639	0.583824	0.405046	0.043*	
H17B	0.836425	0.553432	0.427354	0.043*	
H17C	0.816179	0.624752	0.383927	0.043*	
C16	0.97402 (17)	0.62258 (6)	0.58533 (10)	0.0293 (3)	
H16A	1.047634	0.645914	0.533728	0.044*	
H16B	1.027487	0.579753	0.594928	0.044*	
H16C	0.980851	0.645180	0.653224	0.044*	
C5	0.58968 (19)	0.90447 (6)	0.55421 (11)	0.0318 (3)	
H5A	0.559964	0.907318	0.629938	0.038*	
H5B	0.483711	0.924829	0.512085	0.038*	
C19	1.04864 (19)	0.84290 (7)	0.41781 (10)	0.0334 (3)	
H19A	1.062540	0.800932	0.385251	0.050*	
H19B	1.174490	0.863288	0.426149	0.050*	
H19C	0.963632	0.869334	0.372417	0.050*	
C7	0.9432 (2)	0.90095 (7)	0.58012 (11)	0.0348 (3)	
H7A	0.928982	0.894668	0.657020	0.042*	
H7B	1.062477	0.925355	0.571121	0.042*	
C6	0.7754 (2)	0.93969 (6)	0.53618 (12)	0.0368 (3)	
H6A	0.788531	0.946868	0.459415	0.044*	

H6B	0.773703	0.981647	0.571740	0.044*	
C9	1.10329 (19)	0.79567 (7)	0.59644 (11)	0.0353 (3)	
H9A	1.134652	0.756076	0.558477	0.042*	0.930 (3)
H9B	1.223417	0.819984	0.609133	0.042*	0.930 (3)
H9BC	1.032664	0.773302	0.651539	0.042*	0.070 (3)
H9BD	1.164255	0.763200	0.552271	0.042*	0.070 (3)
C10'	0.7859 (2)	0.46490 (7)	0.67478 (13)	0.0411 (3)	
H10A	0.814438	0.481448	0.743632	0.049*	
H10B	0.813012	0.421644	0.659562	0.049*	
O4A	1.235 (2)	0.8318 (8)	0.6416 (14)	0.058 (6)*	0.070 (3)
H4AA	1.289376	0.812067	0.692493	0.087*	0.070 (3)

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0207 (4)	0.0286 (4)	0.0237 (4)	0.0003 (3)	-0.0071 (3)	0.0000 (3)
O2	0.0395 (5)	0.0293 (5)	0.0174 (4)	-0.0030 (4)	-0.0071 (3)	0.0011 (3)
O3	0.0494 (6)	0.0366 (5)	0.0421 (6)	-0.0025 (4)	-0.0297 (5)	0.0036 (4)
O4	0.0290 (6)	0.0649 (8)	0.0287 (6)	-0.0159 (5)	-0.0104 (4)	0.0148 (5)
C12	0.0264 (6)	0.0282 (6)	0.0201 (6)	-0.0024 (5)	-0.0043 (5)	0.0010 (5)
C1	0.0168 (5)	0.0256 (6)	0.0190 (5)	-0.0001 (4)	-0.0045 (4)	-0.0004 (4)
C14	0.0244 (6)	0.0270 (6)	0.0188 (6)	-0.0015 (5)	0.0002 (4)	-0.0014 (4)
C11	0.0238 (6)	0.0260 (6)	0.0216 (6)	0.0006 (5)	-0.0058 (4)	0.0015 (4)
C3	0.0231 (6)	0.0266 (6)	0.0157 (5)	-0.0017 (4)	-0.0009 (4)	0.0012 (4)
C2	0.0231 (6)	0.0282 (6)	0.0169 (5)	0.0008 (5)	-0.0026 (4)	0.0001 (4)
C15	0.0219 (6)	0.0260 (6)	0.0216 (6)	0.0024 (4)	-0.0016 (4)	0.0006 (5)
C8	0.0217 (6)	0.0315 (6)	0.0221 (6)	-0.0030 (5)	-0.0005 (4)	0.0003 (5)
C1'	0.0353 (7)	0.0254 (6)	0.0257 (6)	0.0019 (5)	-0.0108 (5)	0.0004 (5)
C4	0.0233 (6)	0.0283 (6)	0.0256 (6)	-0.0016 (5)	-0.0005 (5)	-0.0002 (5)
C13	0.0295 (6)	0.0289 (6)	0.0224 (6)	-0.0029 (5)	0.0037 (5)	-0.0021 (5)
C10	0.0288 (6)	0.0281 (6)	0.0344 (7)	0.0014 (5)	0.0023 (5)	0.0009 (5)
C18	0.0350 (7)	0.0315 (7)	0.0267 (6)	-0.0046 (5)	0.0016 (5)	0.0015 (5)
C17	0.0333 (7)	0.0286 (6)	0.0247 (6)	0.0029 (5)	0.0031 (5)	-0.0023 (5)

C16	0.0220 (6)	0.0319 (7)	0.0337 (7)	0.0036 (5)	-0.0025 (5)	0.0032 (5)
C5	0.0306 (7)	0.0294 (7)	0.0355 (7)	0.0018 (5)	0.0035 (5)	-0.0030 (5)
C19	0.0298 (7)	0.0412 (7)	0.0295 (7)	-0.0045 (5)	0.0045 (5)	0.0005 (5)
C7	0.0321 (7)	0.0371 (7)	0.0349 (7)	-0.0098 (6)	0.0009 (5)	-0.0060 (6)
C6	0.0390 (8)	0.0287 (7)	0.0432 (8)	-0.0036 (6)	0.0069 (6)	-0.0064 (6)
C9	0.0256 (6)	0.0461 (8)	0.0334 (7)	-0.0074 (6)	-0.0084 (5)	0.0056 (6)
C10'	0.0384 (8)	0.0337 (7)	0.0510 (9)	0.0064 (6)	0.0000 (6)	0.0083 (6)

Geometric parameters (Å, º) for (2019ncsx0326_1a)

O1—C1	1.4769 (13)	C11—C10	1.4864 (17)
O1—C1'	1.3280 (15)	C3—C2	1.5176 (16)
O2—C2	1.4624 (13)	C3—C8	1.5276 (16)
O2—C1'	1.3307 (16)	C3—C4	1.3317 (17)
O3—C1'	1.2061 (15)	C15—C17	1.5421 (16)
O4—C9	1.4056 (17)	C15—C16	1.5450 (16)
C12—C11	1.3429 (17)	C8—C19	1.5382 (17)
C12—C13	1.5019 (17)	C8—C7	1.5425 (18)
C12—C18	1.5057 (17)	C8—C9	1.5335 (18)
C1—C14	1.5156 (15)	C4—C5	1.5014 (17)
C1—C2	1.5675 (16)	C10—C10'	1.321 (2)
C1—C15	1.5523 (16)	C5—C6	1.5206 (19)
C14—C13	1.5195 (16)	C7—C6	1.513 (2)
C11—C15	1.5408 (16)	C9—O4A	1.306 (14)
C1'—O1—C1	110.16 (9)	C11—C15—C17	110.03 (10)
C1'—O2—C2	110.06 (9)	C11—C15—C16	108.09 (9)
C11—C12—C13	122.59 (11)	C17—C15—C1	110.37 (9)
C11—C12—C18	124.60 (11)	C17—C15—C16	107.80 (10)
C13—C12—C18	112.78 (10)	C16—C15—C1	110.50 (10)
O1—C1—C14	105.70 (9)	C3—C8—C19	108.89 (10)
O1—C1—C2	101.18 (8)	C3—C8—C7	110.22 (10)
O1—C1—C15	107.35 (9)	C3—C8—C9	112.24 (10)

C14—C1—C2	116.42 (9)	C19—C8—C7	110.06 (11)
C14—C1—C15	111.58 (9)	C9—C8—C19	107.68 (11)
C15—C1—C2	113.35 (9)	C9—C8—C7	107.71 (11)
C1—C14—C13	110.21 (10)	O1—C1'—O2	112.57 (10)
C12—C11—C15	123.28 (11)	O3—C1'—O1	123.72 (13)
C12—C11—C10	120.98 (11)	O3—C1'—O2	123.71 (12)
C10—C11—C15	115.72 (10)	C3—C4—C5	125.71 (11)
C2—C3—C8	118.50 (10)	C12—C13—C14	114.31 (10)
C4—C3—C2	119.30 (11)	C10'—C10—C11	124.30 (13)
C4—C3—C8	121.96 (11)	C4—C5—C6	111.03 (11)
O2—C2—C1	102.12 (9)	C6—C7—C8	113.83 (11)
O2—C2—C3	108.43 (9)	C7—C6—C5	109.65 (11)
C3—C2—C1	119.30 (9)	O4—C9—C8	111.84 (11)
C11—C15—C1	109.99 (9)	O4A—C9—C8	110.9 (8)
O1—C1—C14—C13	54.62 (12)	C15—C1—C14—C13	-61.75 (12)
O1—C1—C2—O2	-18.82 (10)	C15—C1—C2—O2	95.78 (10)
O1—C1—C2—C3	100.59 (11)	C15—C1—C2—C3	-144.80 (10)
O1—C1—C15—C11	-68.24 (11)	C15—C11—C10—C10'	119.62 (14)
O1—C1—C15—C17	53.36 (12)	C8—C3—C2—O2	-123.00 (10)
O1—C1—C15—C16	172.50 (9)	C8—C3—C2—C1	120.85 (11)
C12—C11—C15—C1	-15.67 (15)	C8—C3—C4—C5	-3.41 (19)
C12—C11—C15—C17	-137.47 (12)	C8—C7—C6—C5	61.33 (15)
C12—C11—C15—C16	105.05 (13)	C1'—O1—C1—C14	137.79 (10)
C12—C11—C10—C10'	-58.88 (18)	C1'—O1—C1—C2	16.01 (11)
C1—O1—C1'—O2	-6.36 (13)	C1'—O1—C1—C15	-103.00 (10)

C1—O1—C1'—O3	174.20 (12)	C1'—O2—C2—C1	16.83 (12)
C1—C14—C13—C12	42.77 (14)	C1'—O2—C2—C3	-109.98 (11)
C14—C1—C2—O2	-132.79 (10)	C4—C3—C2—O2	51.49 (14)
C14—C1—C2—C3	-13.37 (15)	C4—C3—C2—C1	-64.66 (14)
C14—C1—C15—C11	47.12 (12)	C4—C3—C8—C19	-106.61 (13)
C14—C1—C15—C17	168.72 (10)	C4—C3—C8—C7	14.21 (16)
C14—C1—C15—C16	-72.14 (12)	C4—C3—C8—C9	134.27 (12)
C11—C12—C13—C14	-11.61 (16)	C4—C5—C6—C7	-46.69 (15)
C3—C8—C7—C6	-43.35 (15)	C13—C12—C11—C15	-2.08 (18)
C3—C8—C9—O4	-53.42 (15)	C13—C12—C11—C10	176.29 (11)
C3—C8—C9—O4A	-154.9 (9)	C10—C11—C15—C1	165.87 (10)
C3—C4—C5—C6	19.99 (18)	C10—C11—C15—C17	44.07 (14)
C2—O2—C1'—O1	-7.52 (14)	C10—C11—C15—C16	-73.41 (13)
C2—O2—C1'—O3	171.91 (12)	C18—C12—C11—C15	176.26 (11)
C2—C1—C14—C13	166.00 (10)	C18—C12—C11—C10	-5.36 (18)
C2—C1—C15—C11	-179.10 (9)	C18—C12—C13—C14	169.87 (10)
C2—C1—C15—C17	-57.50 (12)	C19—C8—C7—C6	76.77 (14)
C2—C1—C15—C16	61.64 (12)	C19—C8—C9—O4	-173.25 (11)
C2—C3—C8—C19	67.73 (13)	C19—C8—C9—O4A	85.3 (9)
C2—C3—C8—C7	-171.45 (10)	C7—C8—C9—O4	68.08 (14)
C2—C3—C8—C9	-51.40 (14)	C7—C8—C9—O4A	-33.4 (9)

C2—C3—C4—C5	-177.70 (11)	C9—C8—C7—C6	-166.10 (11)

Hydrogen-bond geometry (Å, º) for (2019ncsx0326_1a)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O4—H4···O3^{i}	0.84	1.96	2.7873 (13)	169
O4*A*—H4*AA*···O3^{i}	0.84	1.83	2.598 (18)	151

Symmetry code: (i) *x*+1, -*y*+3/2, *z*+1/2.

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