Ring-Closing Metathesis Cascade toward a Formal Synthesis of Taxol

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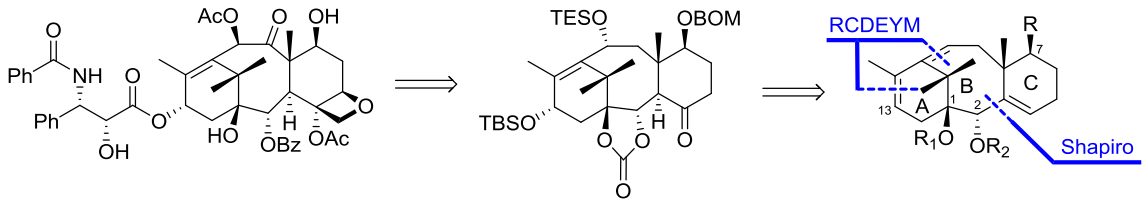
Abstract

Taxol™ and its derivatives are the largest selling anticancer drugs of all time. Numerous synthetic works and total syntheses have been published since its discovery, but to date no high yielding synthesis with less than 37 steps has been achieved. In this thesis is presented our synthetic efforts toward such a robust and efficient synthesis of Taxol.



The optimisation of the Shapiro coupling fragments syntheses were investigated to enhance the robustness of our strategy. Then the C7-deoxy model ABC tricycle ring-system of Taxol, which lacks the oxygenated substituent at C7, has been efficiently synthesised by a dienyne ring-closing metathesis cascade (RCDEYM). This cascade closed the AB 6/8 membered ring system in a single operation. Other dienyne ring-closing metathesis cascades with similar substrates were also performed, assessing the influence of ruthenium catalysts, C1-C2 diol protecting groups (R_1, R_2), and substitution of the alkene at C13.

Synthetic efforts were also devoted to apply such a powerful method toward a formal synthesis of Taxol from an intermediate Holton and co-workers synthesised. During our studies, the C7-oxy group was found to be critical to access the ABC tricyclic core of Taxol by metathesis cascade. Understanding of the importance of this C7-oxy group was undertaken and led to the conception of a metathesis cascade prediction model.

Once the metathesis cascade was optimised, differentiation of the three trisubstituted alkenes present on the ABC tricyclic ring system was studied and elaboration of a formal synthesis was endeavoured.

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 for any other degree at the University of Glasgow or any other institution.

A portion of the work described herein has been published elsewhere as listed below.

"Highly Efficient Synthesis of the Tricyclic Core of Taxol by Cascade Metathesis" Letort, A.; Aouzal, R.; Ma C.; Long D.-L.; Prunet, J. *Org. Lett.* **2014**, *16*, 3300-3303.

Aurelien Letort

Dr. Joëlle Prunet

Acknowledgements

First and foremost, I would like to give my deepest gratitude to my supervisor Dr. Joëlle Prunet for giving me the opportunity to undertake my PhD in her group on such interesting and challenging projects. I also would like to thank her for her support, guidance, accessibility and patience regarding my endless questions over the years (Joëlle !? une dernière question ?).

A special thanks goes to David “Dj. F” France, for his guidance and inspiration during our joint Frunet group meetings and synthetic challenges through the years.

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LepreSean", craziest Irish boy, my second padawan (remove your hands please…) You are my favourite (I told you to remove your hands from my bottom!). -Chao, did you know that you are a weird Chinese girl? -Me? No! You are the weirdo! Weirdo! Weirdo! Weirdo!! Alejandro "tocayo!" the nicest Mexican on the planet. Yehezkiel the friendliest Mexican on the planet. Carlos the strongest Mexican on the planet. Michael "le bordélique" Mathieson, the first Prunet in my heart! Toni, Amaïa, Andres, Jo, Anna, Mhairi, Faustine, Alan (tall guy n°1), Liam (tall guy n°2), Tomicat "Cogsy" (You are a champion), Riccardo "Bambino gelato", Ewen, German Michael, Aliboy and the boyer-boys, Colin "I am sure that this guy is a son of a pear!". Thanks to all my students who made me learnt what patience truly meant. Quentin Llopis (chapeau l'artiste, you are a real Prunet!), David, Alice and of course "The calamity".

Thanks to my friends in France; Alex "Barzi", Vince "Beri" and Jerem "La brute" and my brother "Jo" who fell in love with the Isle of Skye and the Scottish whisky, but more importantly who cheered me up when I needed it the most. Thanks to all of you.

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« Aurélien? Tu sais qu'il y a une panne de micro dans la pièce du fond qui te brouille l'écoute ? » Dr. Joëlle Prunet.

À ma famille, sans qui rien de tout ça n'aurait été possible…

Abbreviations

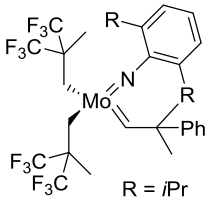
ADmix	Asymmetric dihydroxylation mixture
Ac	Acetyl
AQN	Anthraquinone
Bn	Benzyl
BOM	Benzyloxymethyl
Bu	Butyl
Bz	Benzoyl
CM	Cross metathesis
Cp	Cyclopentadienyl
CSA	Camphor sulfonic acid
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
dba	Dibenzylideneacetone
DHQ	Dihydroquinine
DHQD	Dihydroquinidine
DIBALH	Diisobutylaluminium hydride
DIPA	Diisopropylamine
DIPEA	*N*,*N*-Diisopropylethylamine
DMAO	*N*,*N*-Dimethyl aniline oxide
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DPC	Di-2-pyridyl carbonate
EDCi	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
EE	Ethoxyethyl
ee	Enantiomeric excess
Et	Ethyl
HMPA	Hexamethylphosphoramide

Hz	Hertz
IBX	2-Iodoxybenzoic acid
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
m	*meta*
Me	Methyl
*m*CPBA	*m*-Chloroperoxybenzoic acid
MEM	Methoxyethoxymethyl
Mes	Mesityl
MOM	Methoxymethyl
MOP	Methoxypropyl
MS	Molecular sieves
nbd	Norbornadiene
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
p	*para*
PCC	Pyridinium chlorochromate
Ph	Phenyl
Pin	Pinacolato
Piv	Pivaloyl
PMB	*p*-Methoxybenzyl
PHAL	Phthalazine
PHN	Phenanthrene
ppm	Parts per million
*p*TSA	*p*Toluenesulfonic acid
PYR	Pyrimidinediyl
R	Generalised group
RCDEYM	Ring-closing dialkene alkyne metathesis
RCEYM	Ring-closing alkene alkyne metathesis
RCM	Ring-closing metathesis
RT	Room temperature
t	*tert*
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide

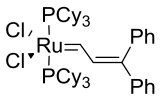
TBDPS	tert-Butyldiphenylsilyl
TBS	tert-Butyldimethylsilyl
TES	Triethylsilyl
THF	Tetrahydrofuran
Tf	Trifluoromethanesulfonyl (triflyl)
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
Tris	2,4,6-Triisopropylbenzenesulfonyl
Troc	Trichloroethylcarbamate
Ts	Tosyl (*p*-toluenesulfonyl)

Table of Catalysts

Here is presented a non-exhaustive list of metathesis catalysts. These catalysts are widely known in metathesis chemistry and will be referred to in this thesis as denominated as follows.



Schrock



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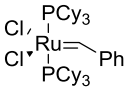

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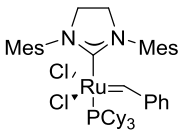
first generation of
Grubbs' catalyst



Grubbs 2
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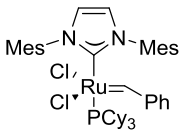
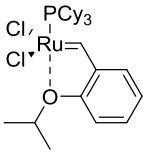
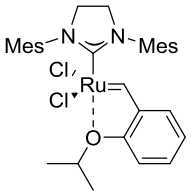
Grubbs' catalyst



Nolan 2
Nolan's catalyst



HG 1
first generation of
Hoveyda-Grubbs' catalyst



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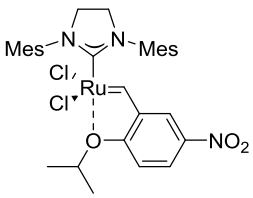
second generation of
Hoveyda-Grubbs' catalyst



Grela
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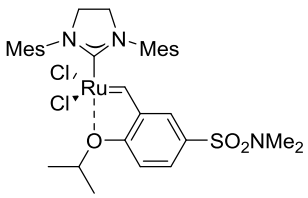


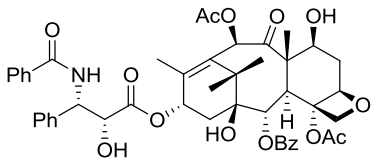
Zhan-1B
modified second generation
of Hoveyda-Grubbs' catalyst

1. Introduction

1.1 Taxol, Generalities

1.1.1 History

Plants have been a major source of new pharmaceuticals, but none of these compounds discovered in the last 30 years have reached the notoriety of paclitaxel or Taxol™ (Figure 1.1). Since the elucidation of its structure in 1971, many applications have been discovered, especially those involving anticancer properties. Now, Taxol **1.1** and its derivatives are the world's bestselling anticancer drugs/medication and generate more than three billion dollars per year.[1]



1.1

Figure 1.1 : Structure of Taxol

The great history of Taxol's development as an anticancer drug started in 1962 during a large campaign led by the *National Cancer Institute (NCI)* and the *United States Department of Agriculture (USDA)* to find new anticancer agents from natural plant extracts. On the 21st of august 1961, the first collection of *Taxus brevifolia* (Figure 1.2) was made by Arthur S. Barclay.[2] *Taxus brevifolia* bark extracts were tested for anticancer activity using KB cell lines and showed relevant cytotoxicity against them. Fresh bark extracts were collected again and tested in 1965 by Monroe Wall and Mansukh Wani at *Research Triangle Institute* in North Carolina. These tests confirmed the bark extracts activity against mouse leukemia in 1969, however this activity was not considered to be better than several other extracts investigated by the *NCI* and *USDA*. Nevertheless, in 1969 pure Taxol was isolated in a 0.01% yield from the bark of the tree, whilst the wood and the needles contained much less Taxol.

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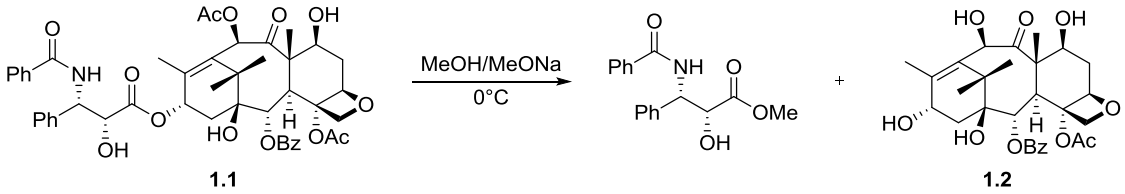
[1] *Mitchell, S. Health Business – Analysis, 27 march 2007.*

[2] Goodman, J.; Walsh, V. (2001). *The Story of Taxol: Nature and Politics in the Pursuit of an Anti-Cancer Drug*. Cambridge University Press. p. 81.

Figure 1.2: Taxus brevifolia

The structure of Taxol was finally elucidated in 1971 using ^{1}H NMR and X-ray analysis of two products obtained after basic treatment of Taxol: 10-deacetylbaccatin III (10-DAB) **1.2** and *N*-benzophenylisoserine methyl ester (Scheme 1.1).



Scheme 1.1: Cleavage of the Taxol side alkyl chain

The first clinical Taxol assays were underwhelming, with modest *in vivo* activity against various leukemias and the Walker 256 carcinosarcoma. Also Taxol was very insoluble in water and could only be isolated in a very modest yield from the bark of the slow-growing tree. In spite of these results, research continued at the *National Cancer Institute* and in the early 1970's Taxol's bioassay results proved to have particularly important activity in a B16 mouse melanoma model. Taxol was selected as a development candidate in 1977 following its shown activity against the new MX-1 and CX-1 mammary and colon xenografts in nude mice.

Interest in this natural product was significantly increased after the discovery of Taxol's mechanism of action as a promoter of tubulin assembly, by Susan Horwitz and co-workers in 1979.[3] The normal function of a cell requires that microtubules be in dynamic

[3] Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665-667.

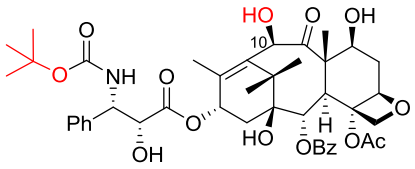
equilibrium with monomeric tubulins; any compound that disrupts this equilibrium is likely to be a cytotoxic agent. Although several compounds, including vinblastine (Velban™) and vincristine (Oncovin™), prevent the assembly of tubulin into microtubules, Taxol was the first compound which was shown to promote microtubule assembly, which will be developed later on.

Taxol completed preclinical formulation and toxicology studies in 1982 and started clinical trials in 1984. The *Food and Drugs Administration* (FDA) approved the use of Taxol to treat ovarian cancer and breast cancer in 1994.[4,5] Taxol was then used against Kaposi carcinosarcoma and non-small cell lung cancers,[6] and is sometimes used in conjunction with other compounds like cisplatin. Despite the fact that Taxol is very efficient, it suffers a serious inconvenience; its availability. To produce only 1 kg of Taxol, 3,000 yew trees or the equivalent of 10,000 kg of bark are needed. A cancer patient needs approximatively 2.5-3 g of Taxol, which means the treatment of each patient consumes about eight 60-year-old yew trees. *Taxus brevifolia* grows for 200 years before it becomes mature so it was clear that an alternative, sustainable source would be needed. Additionally, advanced, expensive technology and complex purification techniques are required for such extractions. That is why other sources of Taxol have been explored.

A solution to this production problem can be found in semisynthesis from intermediates found in the needles of the European yew. The collaboration between *Rhône-Poulenc* and the group of Pierre Potier from *l'Institut de Chimie des Substances Naturelles* of Gif-sur-Yvette led to such an alternative. Pierre Potier's laboratory was on a campus populated by the *Taxus baccata* yew, so needles were available locally in large quantity. By 1981, he had shown that it was feasible to isolate relatively large quantities of the compound 10-deacetylbaccatin III (10-DAB), a plausible first step for a semisynthetic production route to Taxol. By 1988 he co-published a semisynthetic route from needles of *Taxus baccata.*[7] During this synthesis, another compound was identified that was more active than Taxol: Taxotere™ or docetaxel **1.3** (Figure 1.3). One of the major differences between these two taxanes is located on carbon 10. The acetate of Taxol at C10 was

[4] McGuire, G. P.; Hoskins, K. J.; Brady, M. F. *Semin. Oncol*. **1996**, *23*, 40-47. McGuire, G. P.; Rowinsky, E. K.; Rosenshein, N. B. *Ann. Intern. Med*. **1989**, *111*, 273-279. Einzig, A. I.; Wiernik, P. H.; Saaloff, J.; Runowicz, C. D.; Goldberg, G. L. *J. Clin. Oncol*. **1992**, *10*, 1748-1753.
[5] Holmes, F. A.; Walters, R. S.; Theriault, R. L. *J. Natl. Cancer Inst*. **1991**, *83*, 1797-1805.
[6] Ettinger, D. S.; Finkelstein D. M.; Sarma, R. P.; Johnson, D. H. *J. Clin. Oncol*. **1995**, *13*, 1430-1435.
[7] Denis, J.-N.; Greene, A. E.; Guénard, D.; Guéritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917-5919.

replaced by a hydroxyl group, which makes taxotere much more soluble in water. Also, the benzoyl group on the alkyl chain was replaced with a *tert*-butyloxycarbonyl group. In 1990 the first clinical tests started and the FDA approved taxotere in 1996 which was commercialised by *Sanofi-Aventis*.



1.3

Figure 1.3: Structure of the Taxotere

Plant cell cultures represent another alternative, environmentally sustainable source of paclitaxel. Advantages of this method are growth of the material independently of its original location, and not being subjected to seasonality or weather. Selection of cell lines, addition of precursors or optimisation of culture conditions are strategies for the increase of paclitaxel yield in plant cultures. At the moment, *Python Biotech* is the largest producer of paclitaxel by this method, using bioreactors with 75,000 litres capacity. In order to improve the yield of paclitaxel and other taxanes in cell cultures, efforts have been focused on assaying the biosynthetic activities of cultured cells. Other approaches include screening of high-yielding cell lines, optimisation of cultural conditions and production media, induction of secondary metabolite pathways, using mechanical stimulus, ultrasound, and a putative chemical elicitor, methyl jasmonate, combined with *in situ* solvent extraction (two-phase culture), but the complexity of biosynthesis prevented its applicability.[8,9]

[8] Wu, J.; Lin, L. *Appl. Microbiol. Biotechnol*. **2003**, *62*, 151-155.
[9] Zhong, J. J. *J. Biosci. Bioeng*. **2002**, *94*, 591-599.

1.1.2 Structure and Nomenclature

Taxol belongs to the family of taxanes. This family contains more than 300 compounds.[10] Most of the taxanes show a "pentamethyl [9.3.1.0] tricyclopentadecane" diterpenic skeleton (Figure 1.4).

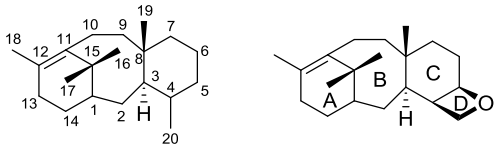


Figure 1.4: Taxanes' numbering and skeleton

The taxane ring A sits in a deformed boat conformation with an alkene in a bridgehead position. The 8-membered ring B is in a chair-boat conformation with two methyl groups in a pseudo axial position, and the C ring, in a half chair conformation, shares a *trans* junction with ring B.

In spite of the large number of compounds in this family, taxanes are classified into 4 groups considering the nature of the oxygenated functions at the C4-C20 positions.

-Group A: This group gathers compounds with an exocyclic alkene at C4 i.e. taxine B.

-Group B: It includes taxanes with an epoxide at C4-C20 position, i.e. baccatin I.

-Group C: This one encompasses taxanes which bear an oxetane ring at C4-C5 carbons, like Taxol or 10-DAB.

-Group D: The last group is the smallest one. Its taxanes do not show the same usual tricyclic skeleton, but two 6-membered rings and one 10-membered ring. For example taxine A, which is a violent poison from the common yew tree, is shown in Figure 1.5.

[10] Baloglu, E.; Kingston, D. G. I. *J. Nat. Prod.*, **1999**, 62, 1448-1472.

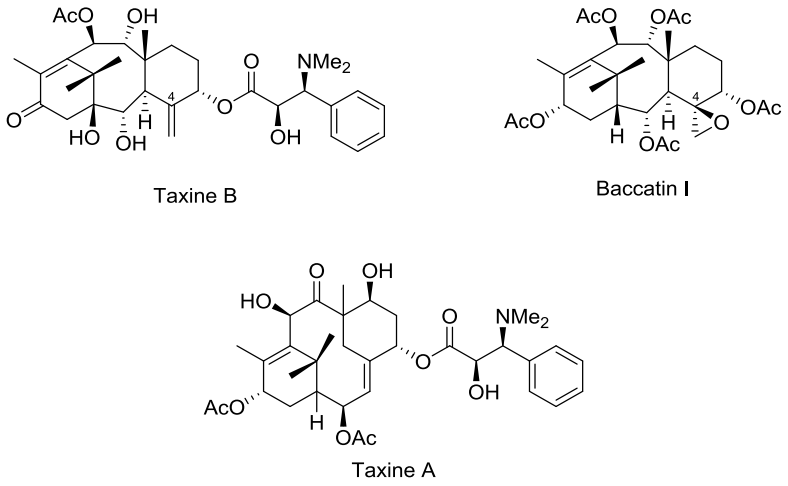
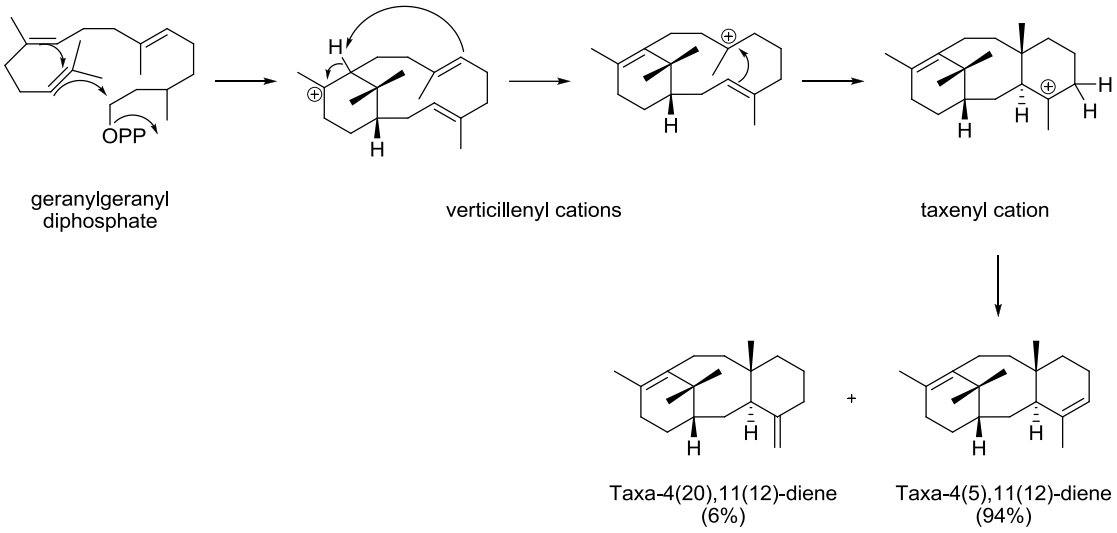


Figure 1.5: Structure of baccatin I, taxine A and B

1.1.3 Biosynthesis

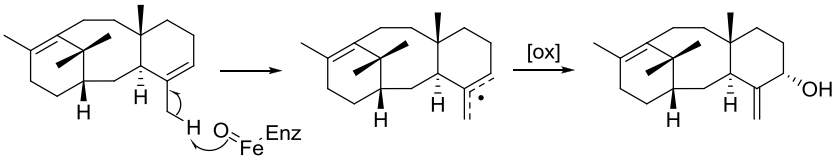
For the last two decades, Taxol biosynthesis studies have led to many major discoveries. The elucidation of biosynthetic mechanisms could aid Taxol production, using cell cultures for example. The first ideas were explored in 1960 and the initial steps were discovered by Croteau and co-workers in 1995.[11] The formation of the taxane skeleton would result from the transformation of geranylgeranyl diphosphate catalysed by an enzyme: taxadiene synthase (TS) (Scheme 1.2).

[11] Koepp, A. E.; Hezari, M.; Zajicek, J.; Vogel, B. S.; LaFever, R. E.; Lewis, N. G.; Croteau R. *J. Biol. Chem.* **1995**, *270*, 8686-8690.



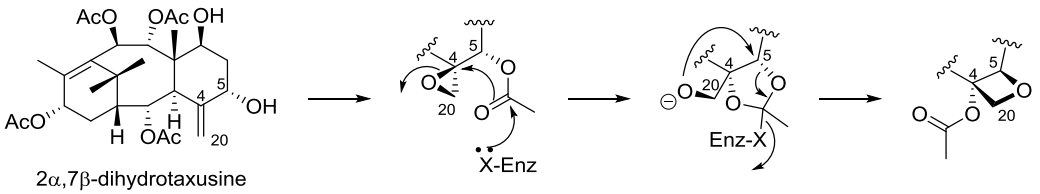
Scheme 1.2: Formation of the taxane skeleton

The transformation of the obtained diene to Taxol comes from the oxygenation of 8 different carbons. Every taxane has an oxygenated function at the C5 carbon; this suggests C5 is the first carbon to be oxygenated. These oxygenated functions are carried out by a taxoid oxygenase enzyme: Cytochrome P450 (Scheme 1.3).



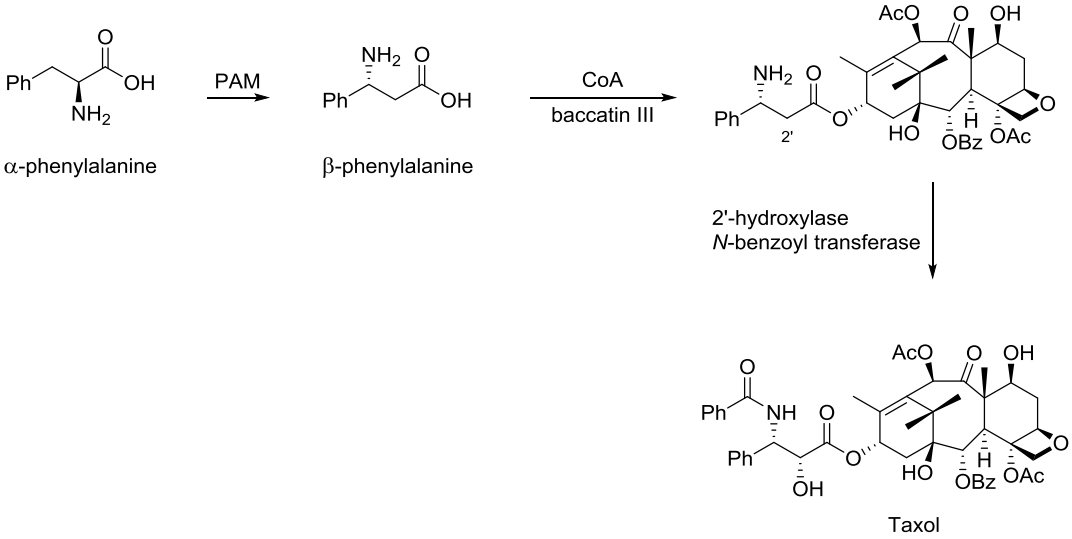
Scheme 1.3: Oxidation at C5 carbon

A succession of oxidations and acetylations would lead to the 2α,7β-dihydrotaxusine. The formation of the oxetane would result from an intramolecular chemical exchange involving the C5-acetoxy group and the C4-epoxide function, which comes from an oxidation of the exocyclic alkene, by a transferase-type mechanism (Scheme 1.4).



Scheme 1.4: Oxetane formation

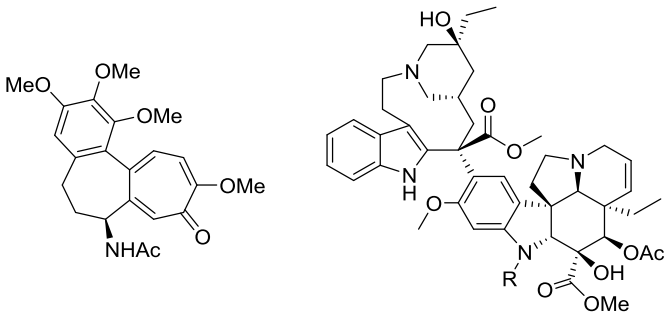
The last part is the coupling of the alkyl side chain, which would come from β-phenylalanine. Taxol is generated after the coupling between β-phenylalanine and baccatin III, which is catalysed by coenzyme A. The β-phenylalanine could come from the natural α-phenylalanine by a reaction with peptidylglycine alpha-amidating monooxygenase (PAM). An oxygenation at C2' carbon followed by a benzoylation of the amine leads to the final compound: Taxol (Scheme 1.5).



Scheme 1.5: Side-chain biosynthesis

1.1.4 Bioactivity

The original mode of operation of Taxol was highlighted by Horwitz and co-workers in 1979.[3] Taxol comes from a family of microtubule bundle poisons, like colchicine, vincristine, and vinblastine (Figure 1.6), but its mode of action is different. Mitotic spindle poisons act on the cell cycle, blocking cell division at mitosis which results in cell apoptosis. However, taxol stabilises microtubule polymers, blocking mitosis, as chromosomes are unable to create the spindle during metaphase which evidently leads to cell apoptosis.



Colchicine

Vincristine, R: CHO
Vinblastine, R: Me

Figure 1.6: Structures of colchicine, vincristine and vinblastine

Microtubules are a component of the cell cytoskeleton and are made of tubulin. These hollow tubular polymers have an outer diameter of 24 nanometres, with an inner diameter of approximately 12 nanometres. Microtubules can grow up to 25 micrometres in length. Tubulin is a heterodimer consisting of an α-subunit and β-subunit.[12] Microtubules are a result of the head to tail self-assembly of these tubulin dimers that form protofilaments, these in turn form the walls of the microtubule. Thirteen of these profilaments are needed to make a microtubule (Figure 1.7).[13]

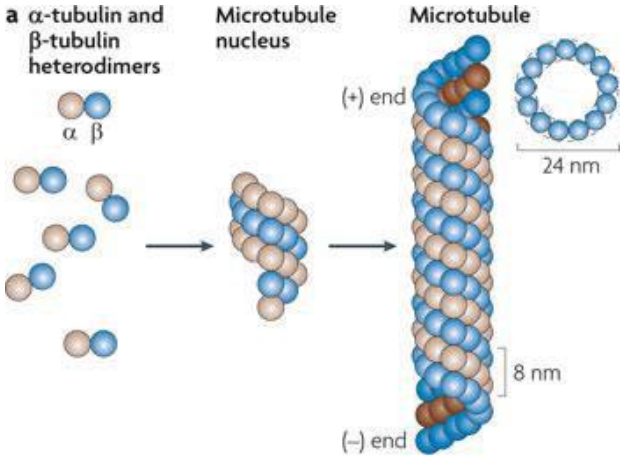


Figure 1.7: Structure of a microtubule

(from Dumontet, C. *Nat. Rev. Drug. Discov.* **2010**, *9*, 790-803.)

[12] Gaskin, F.; Cantor, C. R.; Shelanski, M. L. *J. Molec. Biol.* **1974**, *89*, 737-740.
[13] Nogales, E.; Wolf, S. G.; Downing, K. H. *Nature* **1998**, *391*, 199-203. Dumontet, C. *Nat. Rev. Drug. Discov.* **2010**, *9*, 790-803.

When spindle poisons bind to the β-subunit of tubulin, this affects the equilibrium of the cell and prevents polymerisation of microtubules. The mode of action of Taxol is different to that of normal spindle poisons. Instead of preventing polymerisation, Taxol promotes it and prevents depolymerisation of the microtubules. Taxol can even promote tubulin assembly in the absence of GTP and at low temperatures. The most important discovery was that the microtubules formed in the presence of taxol were stable to depolymerisation in the presence of calcium ions and at 4°C, when both these conditions would normally allow rapid depolymerisation of microtubules (Figure 1.8).

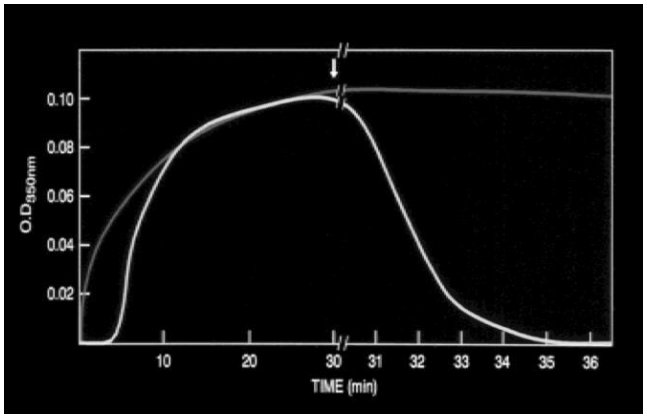


Figure 1.8: Stabilisation of microtubules

Taxol enhancing tubulin polymerisation and mictrotubule stabilisation
White line: no taxol added, Grey line: 10 µm taxol added. $CaCl_2$ (4 nM) is added at 30 min showing no destabilisation of the microtubule.
(Scheme from *J. Nat. Prod*. **2004**, *67*, 136-138)

Microtubules formed in the presence of Taxol are narrower (22 nm outer diameter) than when formed under normal conditions due to only twelve protofilaments forming the microtubule. These abnormal microtubules are located near the poles of the spindle and do not organise themselves into the metaphase position. Instead the abnormal microtubules replicate and form ball-shaped chromosomal masses; this lack of cellular organisation inhibits spindle formation and causes cell death.[14] The Figure 1.9 exemplifies this phenomenon: it shows cells containing diploid (2C) DNA, having two sets of chromosomes, and tetraploid (4C) DNA having four sets of chromosomes and their

[14] Xiao, H.; Verdier-Pinard, P.; Fernandez-Fuentes, N.; Burd, B.; Angeletti, R.; Fiser, A.; Horwitz, S. B.; Orr, G. A. *Proc. Natl. Acad. Sci.* **2006**, *103*, 10166-10173.

evolution after treatment with Taxol. Few hours after injection of Taxol, the tetraploid DNA rapidly increases until no diploid DNA remains. After 27 hours, no diploid DNA remains in the cell, which indicates an absence of cell duplication and therefore the death of the cell.[15]

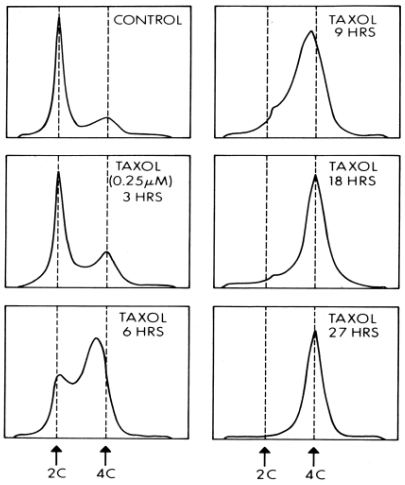


Figure 1.9: Taxol blocking cells during mitosis

DNA from diploids cells (2C) and tetraploid cells (4C) after treatment with taxol. DNA content did not change over the course of the experiment showing that taxol blocks cell division.

(Scheme from *J. Nat. Prod*. **2004**, *67*, 136-138)

1.1.5 Taxol Structure-Activity Relationship

Numerous structure-activity studies have been undertaken on Taxol to understand its biologic activity and try to discover more powerful drugs. The main results are summarised in Figure 1.10. Modifications which occur on the northern side of the molecule slightly change the activity, contrary to the southern side where modifications lead to dramatic loss of activity.

[15] Horwitz, S. B. *J. Nat. Prod.* **2004***, 67,* 136-138.

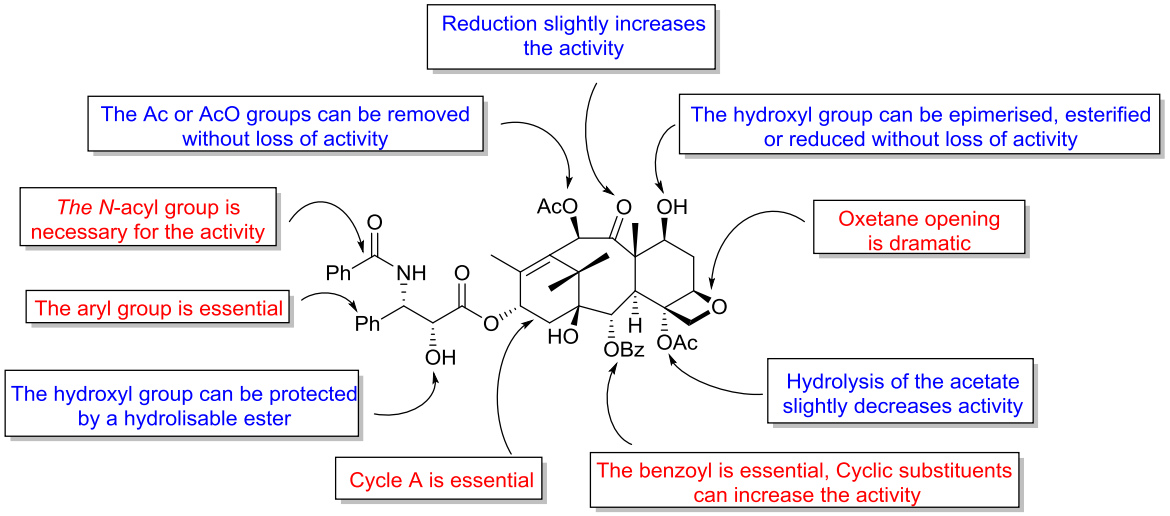


Figure 1.10: Taxol structure-activity relationship

These studies have shown that 7-deoxy Taxol exhibits a similar activity to Taxol.[16] This simpler molecule will be the target of our study toward the Taxol ABC tricycles. SAR studies have already identified many different analogues that could end up being used as treatments in a near future, some of which are already in clinical tests (Figure 1.11).

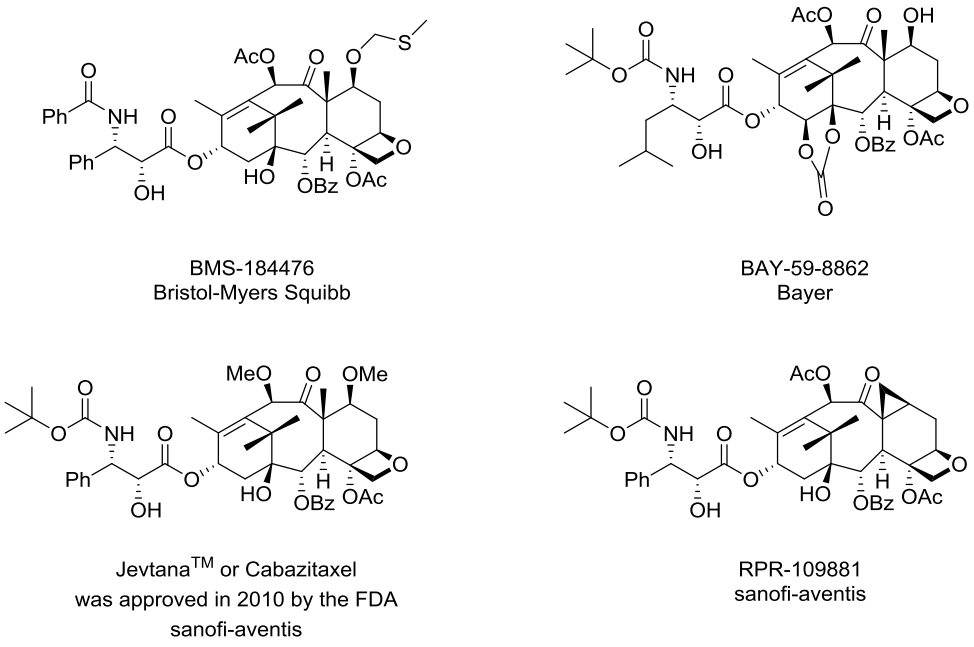


Figure 1.11: Some Taxol analogues in clinical tests

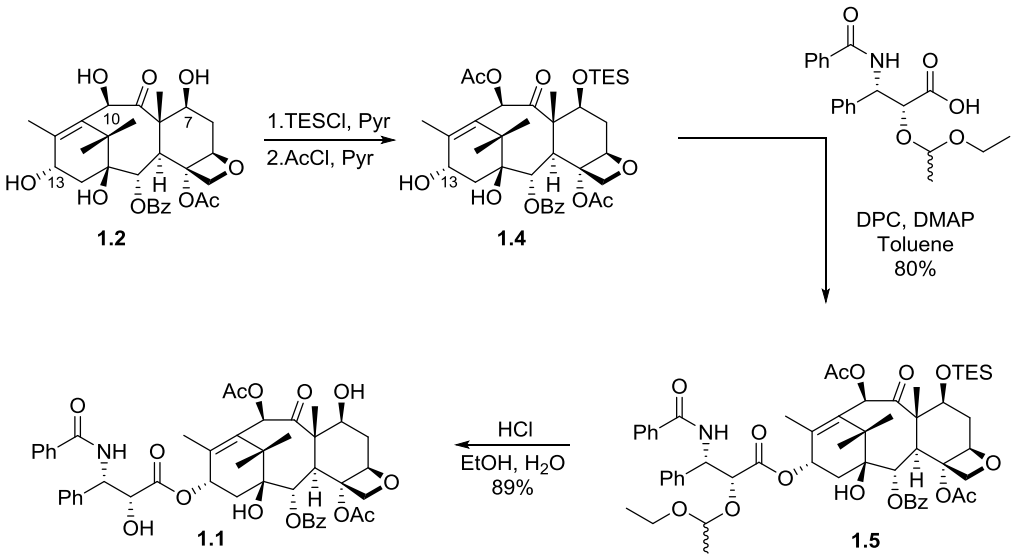
[16] Chaudhary, A. G.; Gharpure, M. M.; Rimoldi, J. M.; Chordia, M. D.; Kingston, D. G. I.; Grover, S.; Lin, C. M.; Hamel, E.; Gunatilaka, L. A. A. *J. Am. Chem. Soc.* **1994**, 116, 4097-4098.

1.2 Taxol Syntheses

Because of its structural complexity, Taxol was, and still remains, an interesting challenging target for organic chemists. More than 200 papers describing synthetic studies toward Taxol have been published and nine total and formal syntheses were achieved, which will be presented. Only the important and relevant points of their syntheses will be discussed.

1.2.1 Hemi-Syntheses

Different research groups have been interested in synthesising Taxol from available and renewable taxane sources, like 10-DAB. 10-DAB was the starting material of the Potier and Greene semi-synthesis in 1988. The hydroxyl group at C7 of 10-DAB was selectively protected as a TES ether and the OH group at C10 was acylated, followed by a coupling with the alkyl side chain at C13. Hydrolysis afforded Taxol in 4 steps (Scheme 1.6).[7]

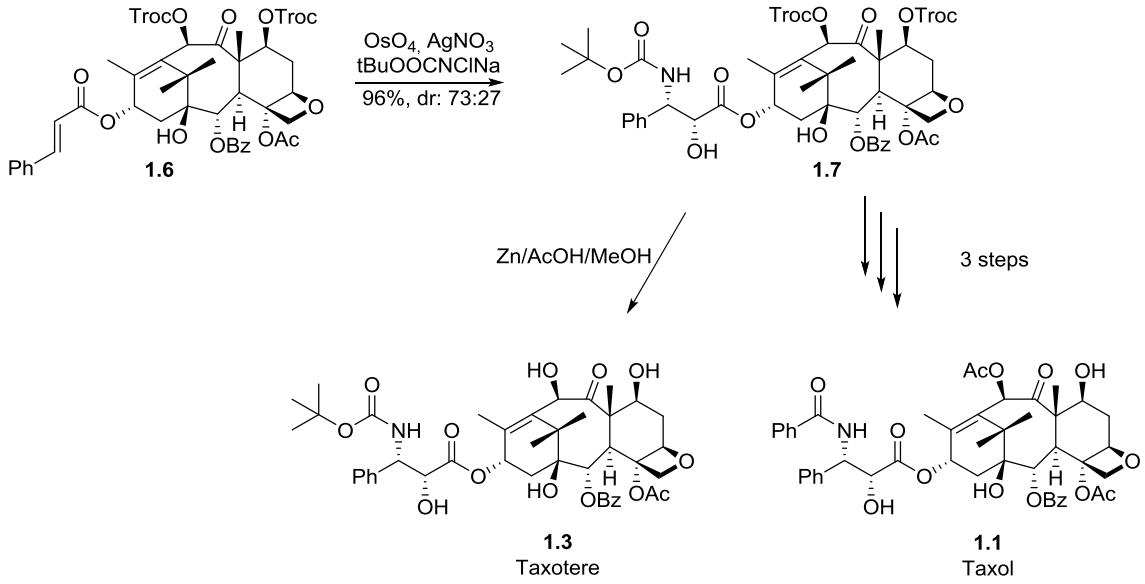


Scheme 1.6: Taxol semi-synthesis by Potier and Greene

Using a similar strategy, Potier and co-workers synthesised taxotere.[17] After the formation of the cinnamic ester **1.6**, Sharpless hydroxyamination afforded intermediate

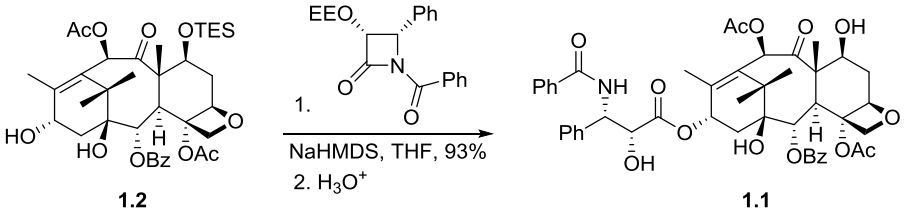
[17] Colin, M.; Guénard, D.; Guéritte-Voegelein, F.; Potier, P. Eur. Pat. Appl. EP 253,738 (Cl.C07D305/14), 20 Jan. **1988**, FR Appl. 86/10,400, 17 Jul. 1986; *Chem. Abstr.* **1988**, *109*, 22762w.

1.7, followed by a simple trichloroethylcarbamate deprotection, promoted by zinc in acetic acid and methanol, which gave taxotere **1.3** (Scheme 1.7).



Scheme 1.7: Taxol and Taxotere semi-syntheses by Potier and co-workers

Another more efficient method was set up by Holton and co-workers and Ojima and co-workers.[18,19] The alkyl side chain was connected by the opening of an optically pure β-lactam (*Scheme 1.8*).



Scheme 1.8: Semi-synthesis of Taxol by Holton, Ojima and co-workers

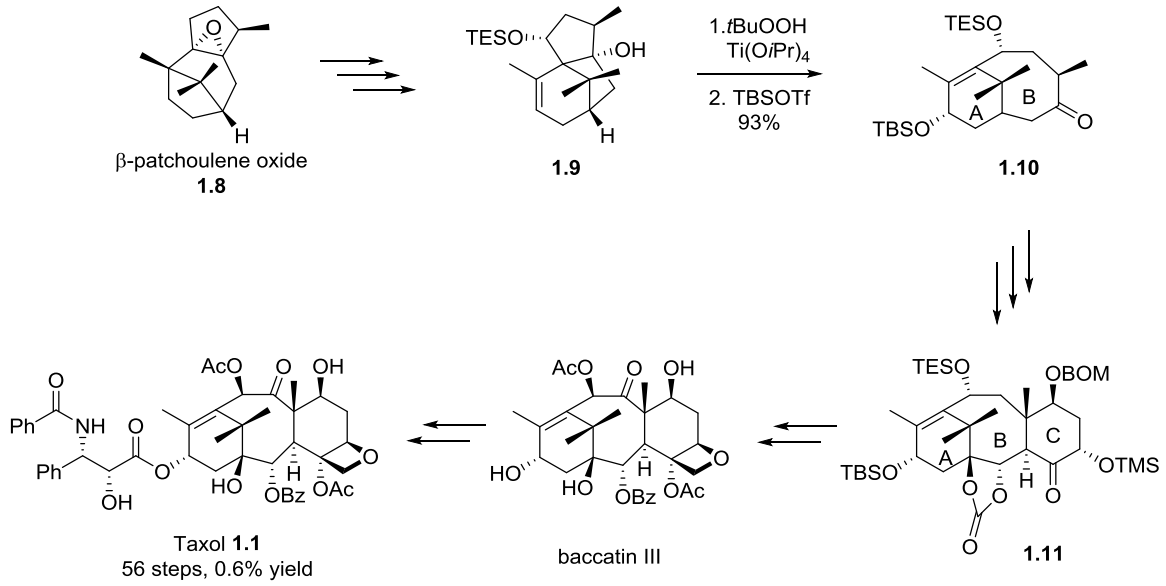
Colin, M.; Guénard, D.; Guéritte-Voegelein, F.; Potier, P. Eur. Pat. Appl. EP 253,739 (Cl.C07D305/14), 20 Jan. **1988**, FR Appl. 86/10,401, 17 Jul. 1986; *Chem. Abstr.* **1988**, *109*, 22763x.

[18] Holton, R. A. Eur. Pat. Appl. EP 400,971, **1990**; *Chem. Abstr*. **1990**, *114*, 164568q.

[19] Ojima, I.; Habus, I.; Zhao, M.; Georg, G. I.; Jayasinhe, L. R. *J. Org. Chem*. **1991**, *56*, 1681-1683. Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y.-H.; Sun, C.-M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985-7012. Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383-389.

1.2.2 Total and Formal Syntheses

In 1994, Holton *et al.* and Nicolaou *et al.* simultaneously published their total synthesis of Taxol.[20,21] Holton's group started from β-patchoulene oxide **1.8**, which they synthesised in 12 steps from (−)-borneol. This epoxide was transformed to tertiary alcohol **1.9**, which underwent epoxidation-Grob fragmentation followed by subsequent TBS protection to form the protected diol AB ring system **1.10** in 93% yield. Further elaboration generated the ABC tricyclic core **1.11**, final elaboration of the D ring and functional group manipulations led to baccatin III. Taxol was finally synthesised by using the β-lactam mentioned above in 56 steps and in 0.6% overall yield (Scheme 1.9).

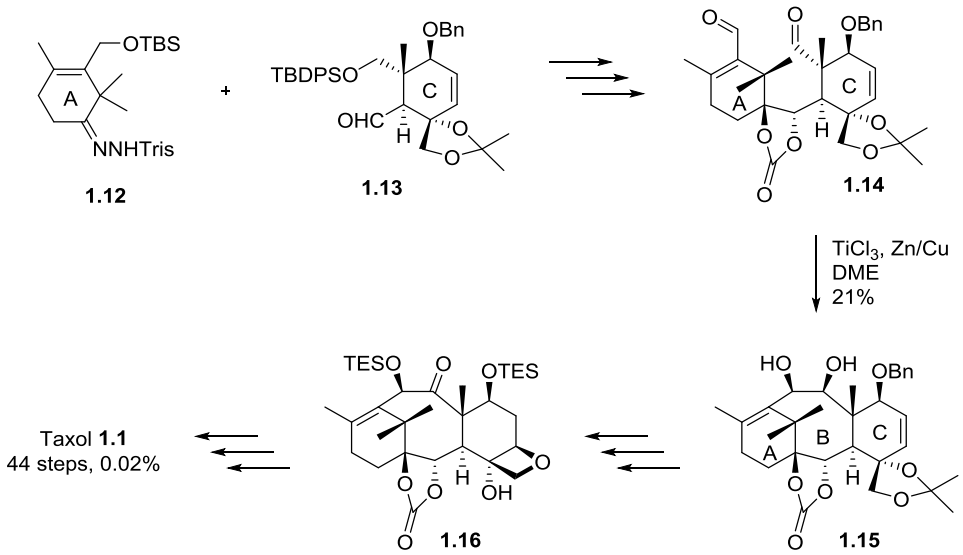


Scheme 1.9: Total synthesis of Taxol by Holton et al.

[20] Holton, R. A.; Somoza, C.; Kim, H.B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597-1598. Holton, R. A.; Somoza, C.; Kim, H.B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599-1600.

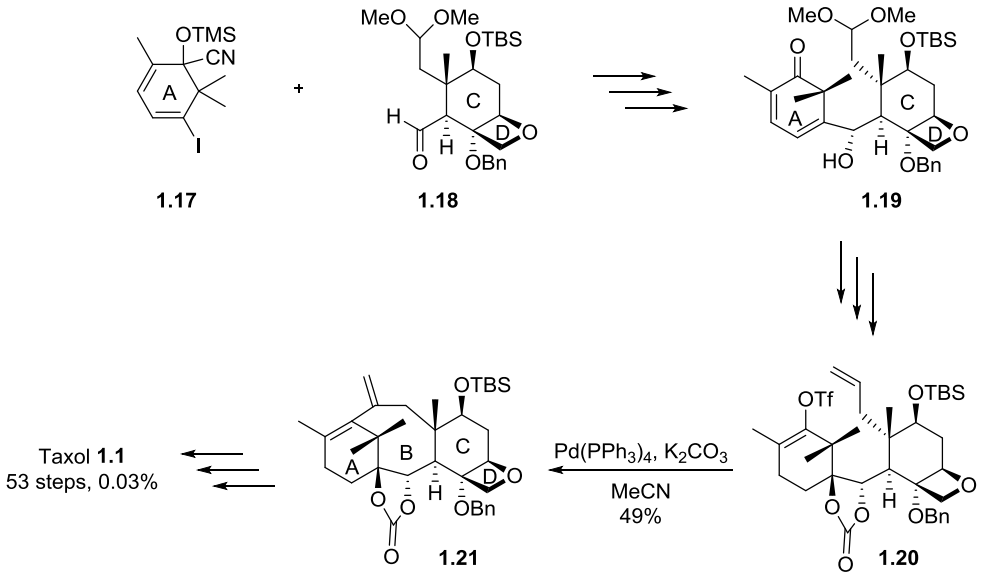
[21] Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J. *Nature* **1994**, 367, 630-634. Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624-633. Nicolaou, K. C.; Liu, J. J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C. K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634-644. Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995**, *117*, 645-652. Nicolaou, K. C.; Ueno, H.; Liu, J. J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653-659.

Nicolaou *et al.* reacted the A and C ring precursors **1.12** and **1.13** by a Shapiro coupling followed by further elaboration to generate the AC bicyclic ring system **1.14**, which underwent an intramolecular McMurry coupling to access the ABC tricyclic core derivative **1.15** in 25% yield. The yield of this reaction was poor due to the formation of side products in great quantity. Formation of the oxetane and allylic oxidation afforded tetracyclic product **1.16** that led to baccatin III thence to Taxol in a 0.02% overall yield in a total of 44 steps (Scheme 1.10).



Scheme 1.10: Nicolaou et al total synthesis of Taxol

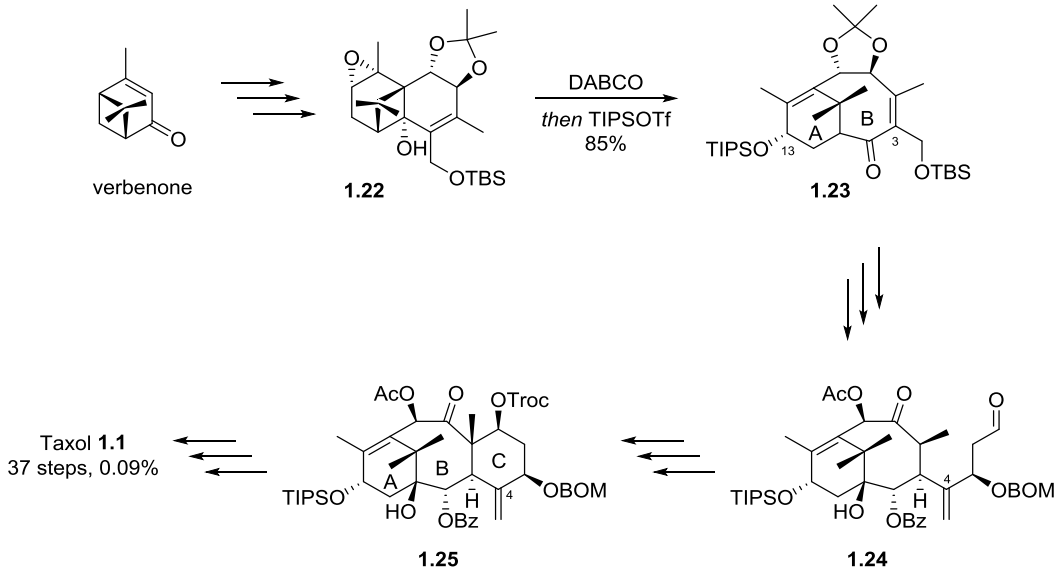
Danishefsky and co-workers decided to build and carry through the entire synthesis the oxetane D ring.[22] The coupling between **1.17** and **1.18**, which came from the (+)-Wieland-Miescher ketone, delivered the tricyclic ACD tricycle **1.19**. After further elaboration, **1.20** was submitted to Heck coupling conditions to close the B ring to afford the ABCD tetracycle compound **1.21** in 49% yield, which led to baccatin III then to Taxol in 53 steps in a total yield of 0.03% (Scheme 1.11).



Scheme 1.11: Danishefsky and co-workers total synthesis of Taxol

[22] Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem. Int. Ed*. **1995**, *34*, 1723-1726. Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D.K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, A. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843-2859.

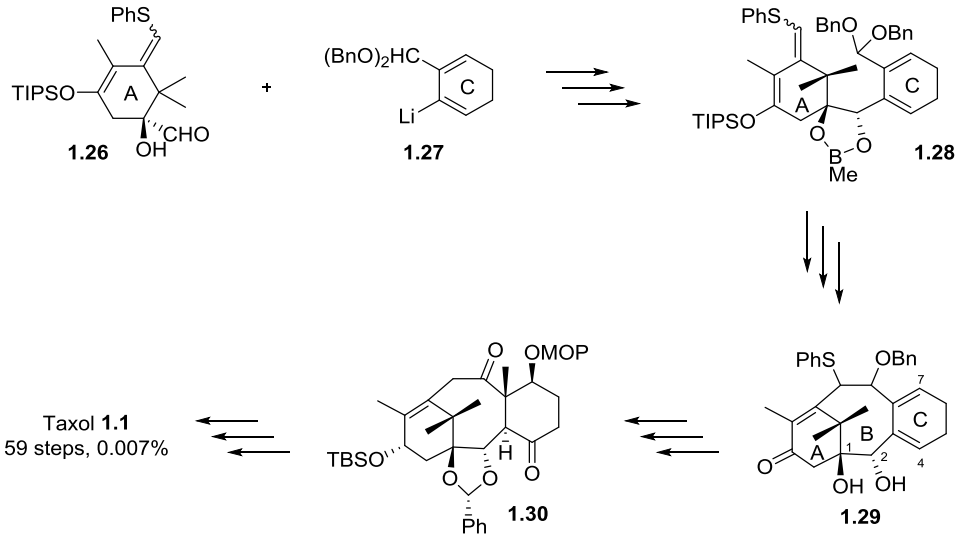
Wender *et al.* started from verbenone, which provided 10 of the 20 carbons of the baccatin III ring system.[23] Subtle chemistry converted verbenone to intermediate **1.22**, which underwent a Grob fragmentation under basic conditions using DABCO, followed by subsequent C13 hydroxyl protection, to afford the AB ring system of Taxol **1.23** in 85% yield. Elaboration of this intermediate at the C3 position afforded **1.24** that underwent an intramolecular aldol condensation to close the C cycle and generate the ABC tricyclic core **1.25**. The synthesis of Taxol was then easily completed after formation of the oxetane ring and installation of the side chain. At the time, the overall synthesis happened to be the shortest recorded synthesis of Taxol counting 37 steps and a total yield of 0.09% yield from commercially available natural verbenone (Scheme 1.12).



Scheme 1.12: Wender et al. total synthesis of Taxol

[23] Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Granicher, C.; Houze, J. B.; Janichen, J.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Mucciaro, T. P.; Muhlebach, M.; Natchus, M. G.; Paulsen, H.; Rawlins, D. B.; Satkofsky, J.; Shuker, A. J.; Sutton, J. C.; Taylor, R.E.; Tomooka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2755-2756. Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R.E. *J. Am. Chem. Soc.* **1997**, *119*, 2757-2758.

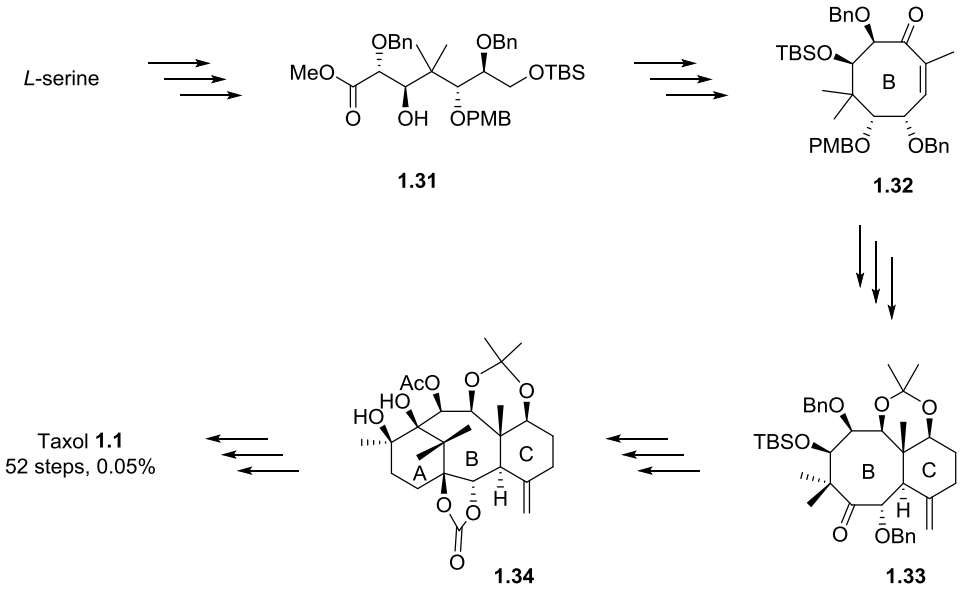
In the late 1990s, Kuwajima and co-workers condensed the vinyllithium ring C precursor **1.27** to a ring A intermediate bearing **1.26** an aldehyde to generate the AC bicycle adduct **1.28**.[24] This bicycle was cyclised in an intramolecular Mukaiyama-aldol like condensation to afford the ABC tricycle core **1.29** after protection of the C1-C2 diol. Oxidation at C4 and C7 generated **1.30**, on which final incorporation of the oxetane gave a baccatin III-like intermediate that easily led to Taxol in 0.007% and 59 steps as illustrated in Scheme 1.13.



Scheme 1.13: Kuwajima and co-workers *total synthesis of Taxol*

[24] Morihira, K.; Hara, R.; Kawahara, S.; Nishimori, T.; Nakamura, N.; Kusama, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1998**, *120*, 12980-12981. Kusama, H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H.; Nakamura, N.; Morihira, K.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 3811-3820.

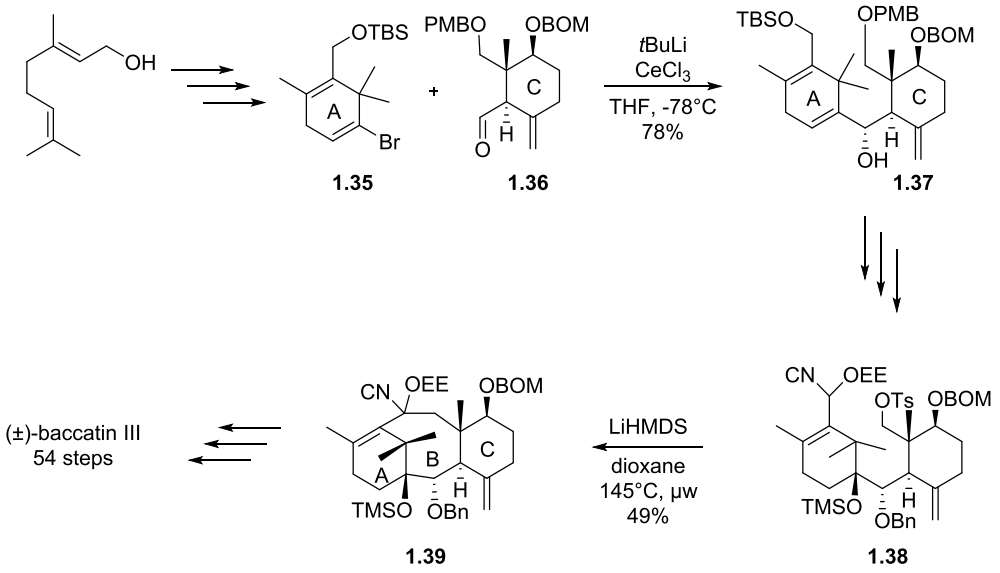
In the total synthesis published by Mukaiyama et al., the strategy they proposed was rather challenging and unique due to the linearity of the synthesis.[25] Ester **1.31** was synthesised from *L*-serine using a series of Mukaiyama-type aldol reactions. The 8-membered ring B **1.32** was formed using a SmI_2-mediated cyclisation. The C and the A rings were then respectively built onto the B ring *via* the BC bicycle **1.33** to generate the ABC tricycle **1.34**. Formation of the oxetane ring and installation of the alkyl side chain afforded Taxol in 52 steps and 0.05% overall yield. (Scheme 1.14).



Scheme 1.14: Mukaiyama et al. total synthesis of Taxol

[25] Mukaiyama, T.; Shiina, I.; Iwadare, H.; Sakoh, H.; Tani, Y.-i.; Hasegawa, M.; Saitoh, K. *Proc. Jpn. Acad.* **1997**, *73B*, 95-100. Mukaiyama, T.; Shiia, I.; Iwadare, H.; Saitoh, H.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem. Eur. J.* **1999**, *5*, 121-161.

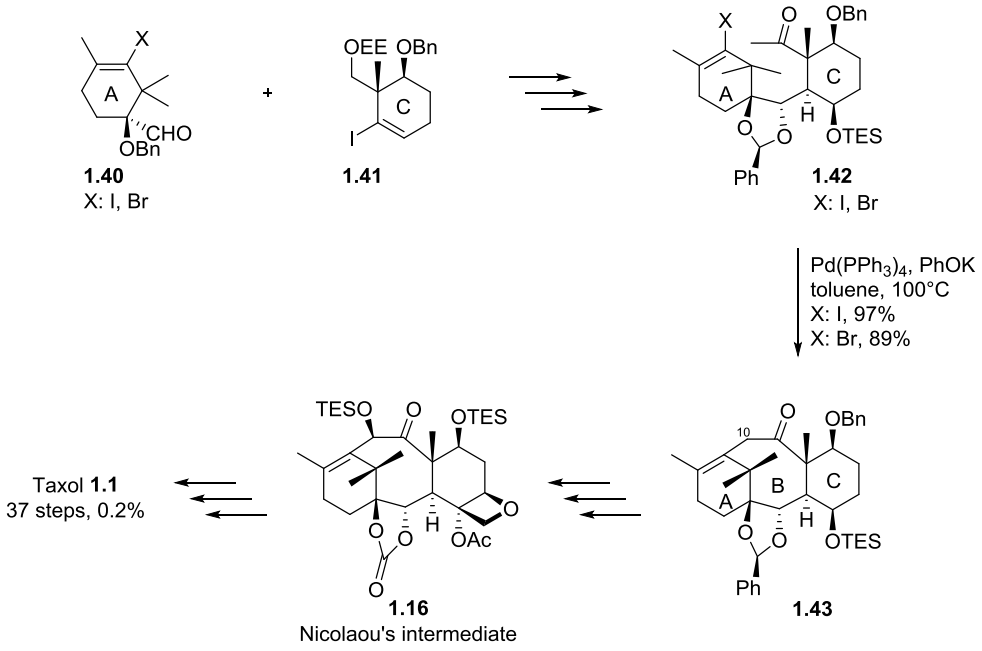
In 2006, Takahashi and co-workers reported a racemic synthesis of (±)-baccatin III.[26] The particularity of this synthesis is that the entire sequence of this formal synthesis of Taxol was produced by a single PhD student using automated synthesizers. Divergent syntheses from the geraniol starting material delivered both vinyl bromide **1.35** and aldehyde **1.36**. Coupling of these two fragments initiated by *t*BuLi generated the AC bicyclic ring system **1.37** in 78% yield and led to the protected cyanohydrin **1.38** after some functionalisation. Under basic conditions, the cyanohydrin **1.38** was treated with LiHMDS under microwave irradiation and cyclised to deliver the ABC tricycle **1.39** in 49% yield, which directly led to (±)-baccatin III in 54 steps, as shown in Scheme 1.15.



Scheme 1.15: Takahashi and co-workers' *formal synthesis of Taxol*

[26] Doi, T.; Fuse, S.; Miyamoto, S.; Nakai, K.; Sasuga, D.; Takahashi, T. *Chem. Asian J.* **2006**, *1*, 370-383.

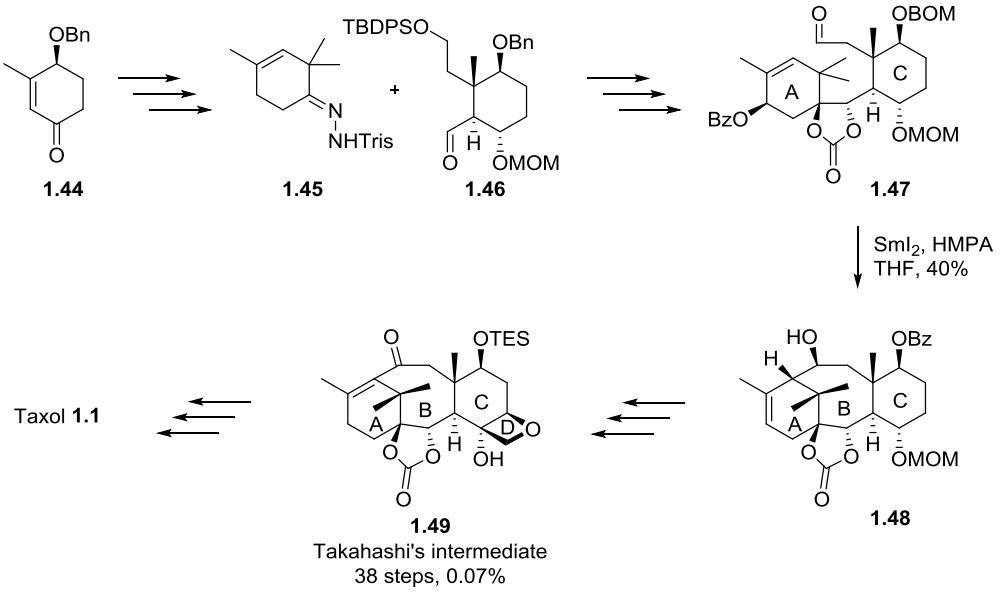
In 2015, Nakada and co-workers reported a formal synthesis based on Nicolaou and co-workers' total synthesis.[21,27] Coupling between ring A **1.40** and ring C fragments **1.41** elaborated an AC bicycle adduct **1.42** after functionalisation. Then an efficient Pd-catalysed intramolecular alkenylation of the methyl ketone **1.42** closed the 8-membered B ring to generate the ABC tricycle **1.43**. Formation of the oxetane and oxidation at C10 delivered Nicolaou's intermediate **1.16**. Compared to the synthesis of Nicolaou and co-workers, this synthesis was shortened to 37 steps and the overall yield of 0.2 % was slightly increased (Scheme 1.16).



Scheme 1.16: Nakada and co-workers' formal synthesis of Taxol

[27] Hirai, S.; Utsugi, M.; Iwamoto, M.: Nakada, M. *Chem. Eur. J.* **2015**, *21*, 355-359.

A few months later, Chida, Sato and co-workers published a formal synthesis based on Takahashi's synthesis.[28] Starting from the known enone **1.44**, aldehyde **1.46** was synthesised in few steps. Shapiro coupling between this aldehyde and the known hydrazone **1.45** conducted to the formation of the AC bicyclic ring system **1.47** after some functionalisation**.** Samarium-mediated cyclisation delivered the ABC tricycle **1.48** in 40%, which underwent oxetane formation followed by the challenging installation of the bridgehead olefin, and finally led to Takahashi's intermediate **1.49** in 38 steps and 0.07% overall yield (Scheme 1.17).



Scheme 1.17 : Chida and co-workers' formal synthesis of Taxol

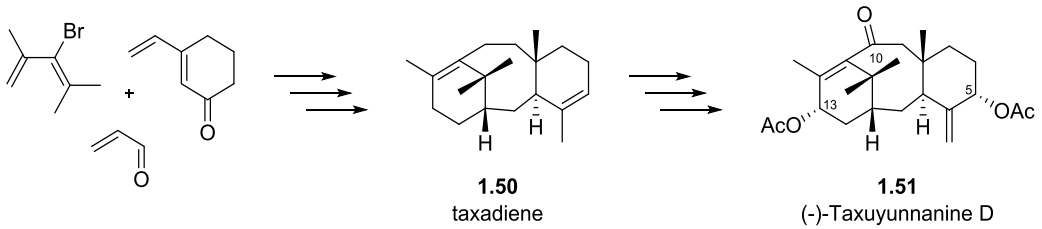
1.2.3 Recent Taxoid Synthesis

In 2014, Baran and co-workers published the synthesis of (−)-taxuyunnanine D, a natural product from the taxane family.[29] After generation of taxadiene **1.40** by a three-component coupling followed by an intramolecular diels-alder (IMDA) strategy to forge the taxane ABC ring system, they performed three successive different allylic oxidations at C5,

[28] Fukaya, K.; Tanaka, Y.; Sato, A.; Kodama, K.; Yamazaki, H.; Ishimoto, T.; Nozaki, Y.; Iwaki, Y.; Yuki, Y.; Umei, K.; Sugai, T.; Yamaguchi, Y.; Watanabe, A.; Oishi, T.; Sato, T.; Chida, N. *Org. Lett.* **2015**, *17*, 2570-2573. Fukaya, K.; Kodama, K.; Tanaka, Y.; Yamazaki, H.; Sugai, T.; Yamaguchi, Y.; Watanabe, A.; Oishi, T.; Sato, T.; Chida, N. *Org. Lett.* **2015**, *17*, 2574-2577.

[29] Wilde, N. C.; Isomura, M.; Mendoza, A.; Baran, P. S. *J. Am. Chem. Soc*. **2014**, *136*, 4909-4912.

C13 and C10 respectively and thus achieved an easy and scalable total synthesis of (−)-taxuyunnanine D **1.51** as summarised in Scheme 1.18.[30]



Scheme 1.18: Baran and co-workers' synthesis of (−)-taxuyunnanine D

As described above, a plethora of different reactions allowed the synthesis of the taxane ABC tricycle. In spite of all the cited examples, one highly developed reaction that efficiently generates the formation of complex cycles was not employed during the above Taxol syntheses, that of ring-closing metathesis.

1.3 Metathesis

Known for more than 40 years, this reaction has only been used for a couple of decades in synthesis and is now one of the most powerful tool for organic chemists. This is due to three chemists who received the Nobel Prize in 2006 for their work: Yves Chauvin for the reaction mechanism, Richard Schrock and Robert Grubbs for the development of reliable and efficient catalysts.[31]

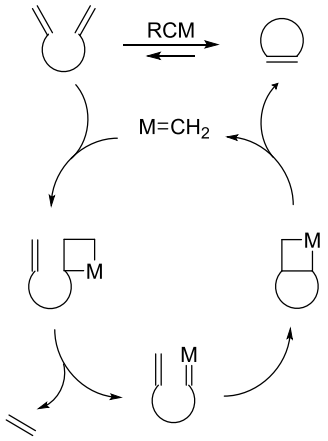
1.3.1 Ring-Closing Metathesis

The olefin metathesis is an exchange between two different double bonds catalysed by transition metals. When the reaction occurs in an intermolecular way, it is called cross metathesis. If the reaction occurs in an intramolecular way, it is called ring-closing

[30] Mendoza, A.; Ishihara, Y.; Baran, P. S. *Nat. Chem*. **2012**, *4*, 21-25.
[31] Chauvin, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 3740-3747. Schrock, R. R. *Angew. Chem. Int. Ed.* **2006**, *45*, 3748-3759. Grubbs, R. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 3760-3765.

metathesis (RCM). RCM can lead to highly functionalised cycles from di-alkenated compounds.

The mechanism of this reaction was proposed by Y. Chauvin in the early 1970s (Scheme 1.19).[32] Chauvin's mechanism involves a succession of [2+2] cycloaddition/cycloreversion of a double bond to a transition metal alkylidene to form a metallacyclobutane intermediate. The produced metallacyclobutane can then cyclorevert to give either the original species or a new alkene and alkylidene reactive part. Another cycloaddition/cycloreversion leads to the cyclic product and regeneration of active catalyst. It is interesting to note that the direct [2+2] cycloaddition of two alkenes is symmetry forbidden and has very high activation energy. However, this reaction can occur in presence of a metal catalyst, in which the *d*-orbital interactions lower the activation energy enough so that the reaction can proceed. In this mechanism every step is equilibrated but the equilibrium is displaced in favour of the product due to the formation of a very volatile molecule: ethylene. This reaction is entropically favoured.



Scheme 1.19: RCM catalytic cycle

Since the discovery of this proposed mechanism, several catalysts were developed. In the 1980's Schrock developed the first catalysts, which were molybdenum (VI) and tungsten (VI)-based. These catalysts presented a major problem for organic chemists. They were extremely sensitive to light and moisture and reacted violently toward some functional groups. That is why Grubbs developed a series of catalysts, ruthenium (II)-based, which were easier to use (Figure 1.12).

[32] Herisson, J.-L.; Chauvin, Y. *Makromol. Chem.* **1971**, *141*, 161-176.

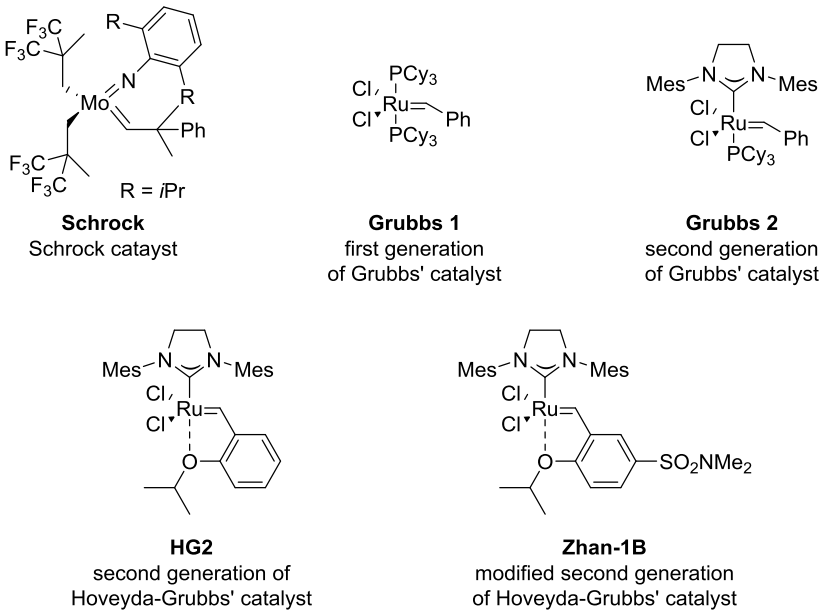
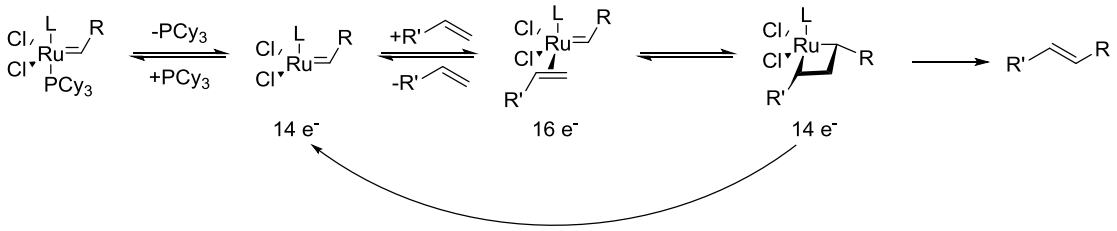


Figure 1.12: Some metathesis catalysts

Every Grubbs' type catalyst contains a ruthenium atom center in an oxidation state (II) with 16 electrons. It is generally coordinated to electron rich phosphines (PCy_3). Even if Chauvin's mechanism is widely accepted, mechanistic studies have shown some relevant details. Thus, the mechanism first step is the dissociation of a phosphine ligand; this allows the generation of an active carbenoid species with 14 electrons. This complex enters the catalytic cycle and forms the 16 electron species coordinated to the alkene. The resulting metallacyclobutane intermediate is also an active 14 electron species and its dissociation releases the metathesis products (Scheme 1.20).

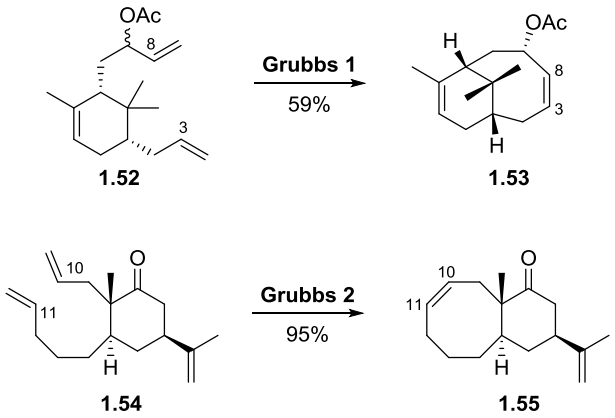


Scheme 1.20: RCM mechanism for the Grubbs' catalysts

1.3.2 Taxoid Syntheses by Ring-Closing Metathesis

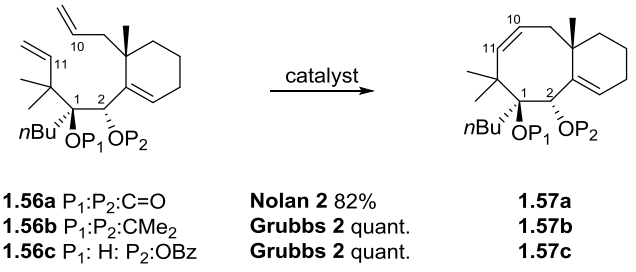
Blechert and co-workers and Srikrishna *et al.* as well as the Prunet group worked on Taxol model syntheses and synthesised Taxol B ring models by ring-closing metathesis. Blechert and co-workers closed the 8-membered ring at the C3-C8 position using Grubbs'

first-generation catalyst and generated the simplified AB ring system **1.53** in 59% yield.[33] Srikrishna and co-workers performed the ring-closing metathesis at the C10-C11 position using Grubbs' second-generation catalyst starting from a pinene derived precursor **1.54** and efficiently synthesised a BC bicycle model **1.55** in 95% yield as shown in Scheme 1.21.[34]



Scheme 1.21: Synthesis of the AB and BC cycles by Blechert and co-workers, *and Srikrishna et al.*

Prunet and co-workers performed a ring-closing metathesis at the C10-C11 position using different protecting group at C1 and C2 using Grubbs' second-generation catalysts. Every substrate **1.56a-c** was able to efficiently lead to the BC Taxol bicycle models **1.57a-c** using this method, as shown in Scheme 1.22.[35]

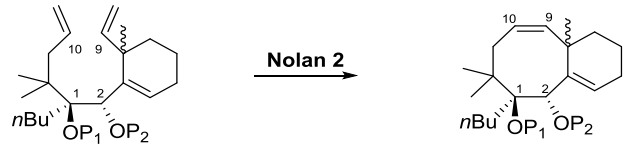


Scheme 1.22: Synthesis of BC bicycle system models

The Prunet group also investigated the possibility to close the 8-membered B ring by ring-closing metathesis at the C9-C10 position with different C1-C2 cyclic protecting

[33] Wenz, M.; Großbach, D.; Beitzel, M.; Blechert, S. *Synthesis* **1999**, *4*, 607-614.
[34] Srikrishna, A.; Dattatraya, H. D.; Kumar, P. R. *Tetrahedron Lett*. **2004**, *45*, 2939-2942.
[35] Ma, C.; Schiltz, S.; Le Goff, X. F.; Prunet, J. *Chem. Eur. J.* **2008**, *14*, 7314-7323.

groups using Nolan's metathesis catalyst.[36] When the carbonate **1.58a** was treated with Nolan's catalyst, the metathesis reaction produced the BC bicycle **1.59a** in 86% yield. Similar results were observed when the acetonide **1.58b** and silane **1.58c** were subjected to the same reaction conditions and yielded the BC bicycles **1.59b** and **1.59c** in 86% yield and 91% yield, respectively (Scheme 1.23).



1.58a P_1:P_2:C=O
1.58b P_1:P_2:CMe_2
1.58c P_1:P_2:Si(*t*Bu)$_2$

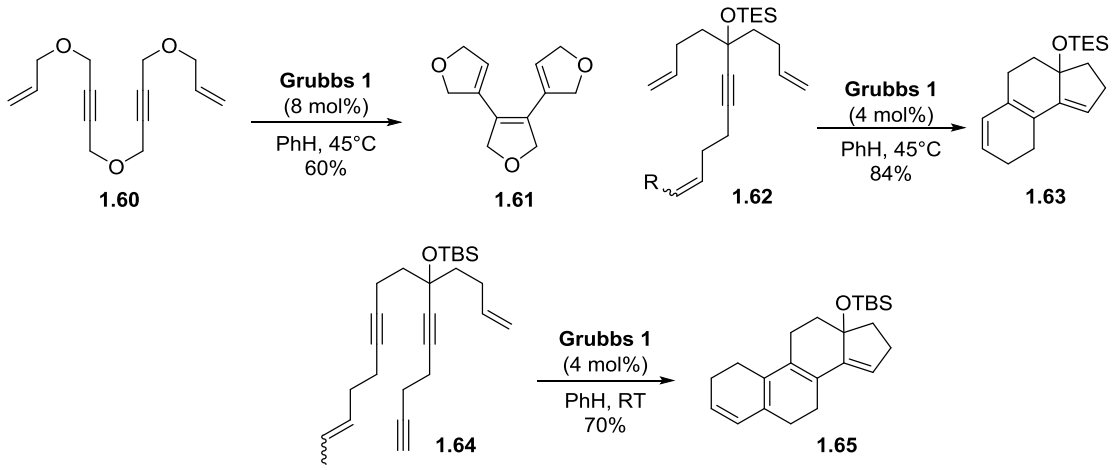
86%, **1.59a**
86%, **1.59b**
91%, **1.59c**

Scheme 1.23: Synthesis of BC bicycle system models

1.3.3 Ring-Closing Dienyne Metathesis

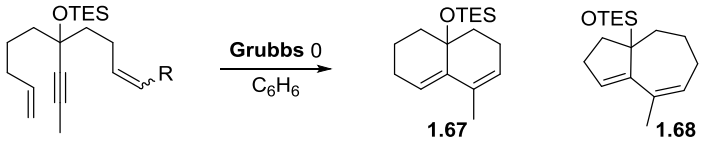
When an initial ring-closing enyne metathesis (RCEYM) sets up a second ring-closing metathesis, the dienyne reaction can be regarded as a tandem or cascade metathesis (RCDEYM). This "domino" sequence is very powerful for the construction of bicyclic ring systems from acyclic starting materials. It was first studied by Grubbs and co-workers.[37] It can be used to synthesise two, three or four different rings during the RCM steps (Scheme 1.24). Using between 4 and 8 mol% of Grubbs 1 (Grubbs' first-generation catalyst) in toluene, they were able to synthesise tri- and tetracyclic products in good yields by using this metathesis cascade. For example **1.60** was easily transformed to the trisdihydrofuran derivative **1.61**. The symmetrical precursor **1.62** underwent a trienyne metathesis cascade and thence generated the tricyclic product **1.63** in 84% yield. Furthermore, an extra alkyne can be added, as seen in the last example. In this case, the cascade formed an additional cycle when precursor **1.64** was submitted to the same conditions and generated the tetracyclic steroid-like product **1.65**.

[36] Bourgeois, D.; Mahuteau, J.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *Synthesis.* **2000**, *2000*, 869-882. Bourgeois, D.; Pancrazi, A.; Ricard, L.; Prunet, J. *Angew. Chem. Int. Ed.* **2000**, *39*, 725-728.
[37] Zuercher, W. J.; Scholl, M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 4291-4298.



Scheme 1.24: RCDEYM by Grubbs and co-workers

For non-symmetrical dienyne precursors, a selectivity problem occurs. Depending on where the first metallacarbene is formed, two products are formed. A way to resolve this issue is to change the type of one olefin to alter its reactivity toward the metathesis catalyst and then favour one of the two possible metathesis products. This matter was well developed by Grubbs and co-workers and is summarised in Scheme 1.25.[38] With two equivalently reactive olefins **1.66a** gave two products **1.67** and **1.68** in a 1:1 ratio, indicating no selectivity for the formation of the first ruthenium carbene. By having an extra methyl group on one of the alkene as in **1.66b**, the formation of **1.68** was prevented and only **1.67** was formed. This experiment clearly indicates that the first ruthenium carbene to be formed was on the most accessible olefin, with none of the other one being produced, and that drove the reaction to the bicycle **1.67** only (Scheme 1.20).



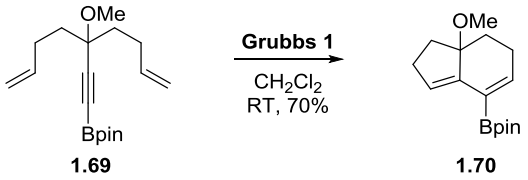
1.66a R: H	86%	1	1
1.66b R: Me	88%	1	0

Scheme 1.25: Grubbs and co-workers example of selectivity issue

Numerous different groups throughout the past decade proved that such a cascade was highly group tolerant and efficient. Renaud and co-workers showed a dienyne cascade

[38] Kim, S.-H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801-10802. Kim, S.-H.; Zuercher, W.J.; Bowden, N.; Grubbs, R. H. *J. Org. Chem*. **1996**, *61*, 1073-1081.

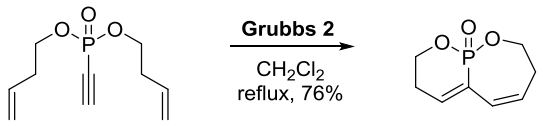
using alkynyl boronate **1.69** to access versatile vinylboronate **1.70** in high yield as shown in Scheme 1.26.[39]



1.69 **1.70**

Scheme 1.26: Reaction of dienyne using an alkynyl boronate

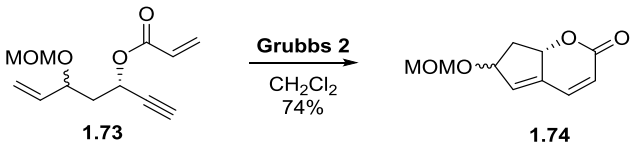
Bicyclic phosphonates such as **1.72** were also efficiently generated by dienyne metathesis cascade using alkynyl phosphonate such as **1.71** (Scheme 1.27).[40]



1.71 **1.72**

Scheme 1.27: Reaction of dienyne phosphonates

In 2007, Krishna *et al.* succeeded in efficiently synthesising unsaturated cyclic lactone **1.74** using the same method, by combining different types of alkenes in a non-symmetrical metathesis precursor **1.73** *en route* to ilexlactone (Scheme 1.28).[41]

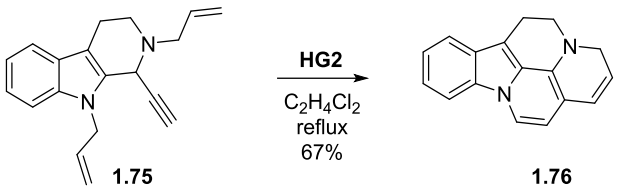


1.73 **1.74**

Scheme 1.28: Dienyne metathesis for lactone formation

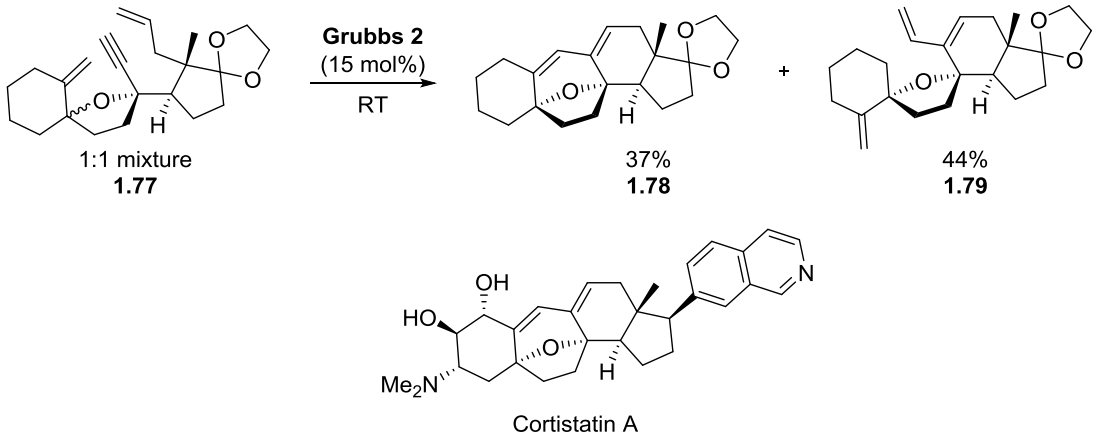
Pérez-Castells and co-workers also demonstrated the versatility of dienyne metathesis to access the highly polycyclic alkaloid **1.76** from indole based dienyne precursor **1.75** (Scheme 1.29).[42]

[39] Renaud, J.; Graf, C.-D.; Oberer, L. *Angew. Chem. Int. Ed*. **2000**, *39*, 3101-3104.
[40] Timmer, M. S. M.; Ovaa, H.; Filippov, D. V.; van der Marel, G. A.; Van Boom, J. H. *Tetrahedron Lett*. **2001**, *42*, 8231-8233.
[41] Krishna, P.R.; Narsingam, M. *Tetrahedron Lett*. **2007**, *48*, 8721-8724.
[42] Gonzalez-Gomez, A.; Dominguez, G.; Perez-Castells, J. *Tetrahedron Lett*. **2005**, *46*, 7267-7270.



Scheme 1.29: Polycyclic alkaloid synthesis

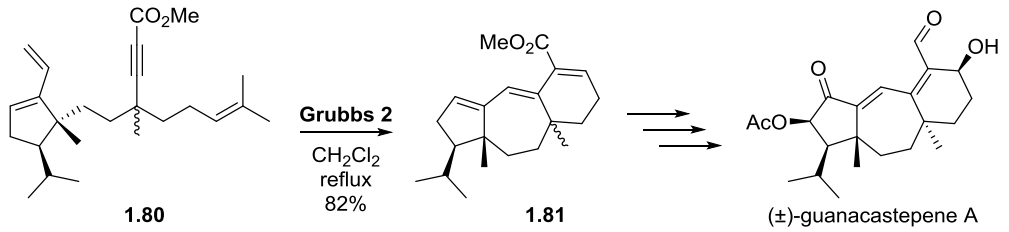
Dienyne metathesis is also found in total synthesis. In 2010, Stoltz and co-workers envisaged the possibility of using RCDEYM to complete the synthesis of cortistatin A (Scheme 1.30).[43] During their model studies, they found that the metathesis precursor **1.77** underwent smooth RCDEYM to afford a tetracyclic model of cortistatin A **1.78** in 37% yield. The low yield is due to the submission of a 1:1 mixture of diastereomers. The other diastereomer only underwent enyne metathesis to give **1.79**. The last and final step of the cascade, used to close the fourth ring, could not occur due to the wrong configuration at the fully substituted carbon centre and was isolated in 44% yield.



Scheme 1.30: Stoltz's model studies toward cortistatin A

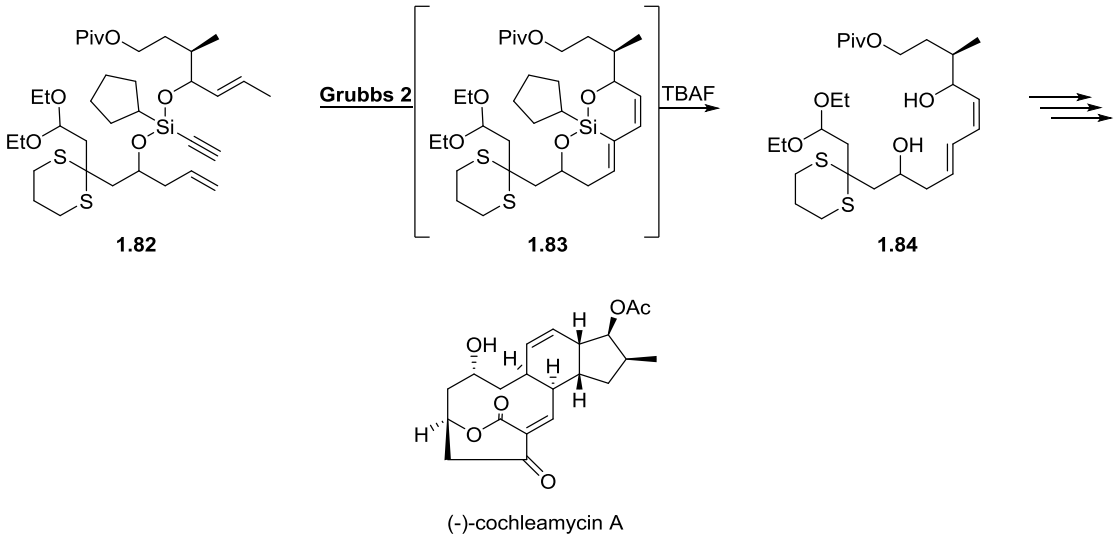
A concise route to a key tricyclic intermediate in the total synthesis of (±)-guanacastepene A using dienyne metathesis was reported.[44] The main feature includes the construction of the fused seven- and six-membered ring system **1.81** in a single operation from the highly unsaturated precursor **1.80**. (Scheme 1.31)

[43] Baumgartner, C.; Ma, S.; Liu, Q.; Stoltz, B. M. *Org. Biomol. Chem.* **2010**, *8*, 2915-2917.
[44] Boyer, F.-D.; Hanna, I.; Ricard, L. *Org. Lett*. **2004**, *6*, 1817-1820.



Scheme 1.31: Synthesis of (±)-guanacastepene A

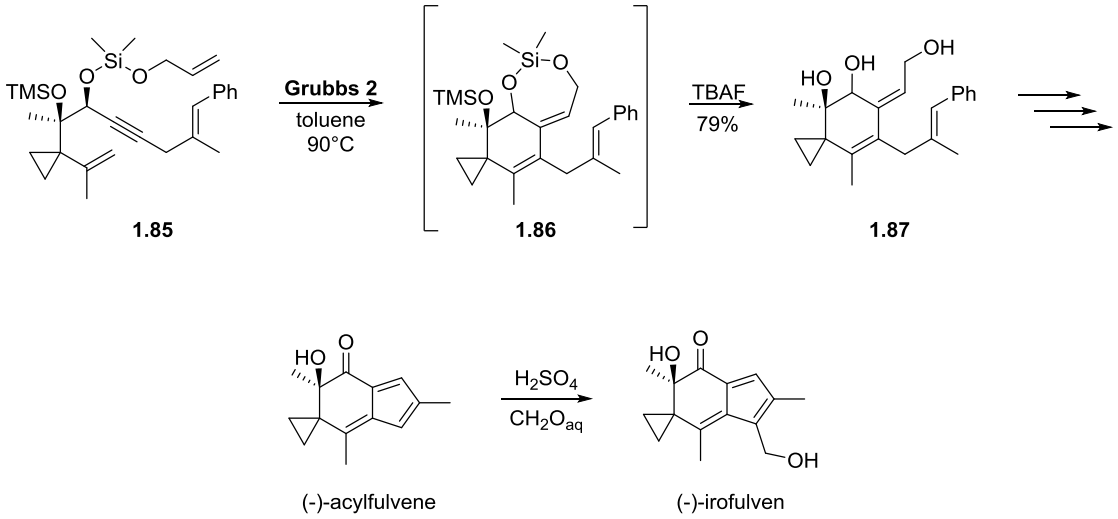
For the synthesis of (−)-cochleamycin A, a conjugated (*E*,*Z*)-diene was synthesized using a dienyne metathesis as a key step. A silicon tether ring-closing metathesis of the dienyne substrate **1.82** proceeded to provide the bicyclic siloxane **1.83**. Removal of the silicon tether afforded the (*E,Z*)-1,3-dienediol **1.84**, which was converted into (−)-cochleamycin A (Scheme 1.32).[45]



Scheme 1.32: Synthesis of (−)-cochleamycin A using dienyne metathesis

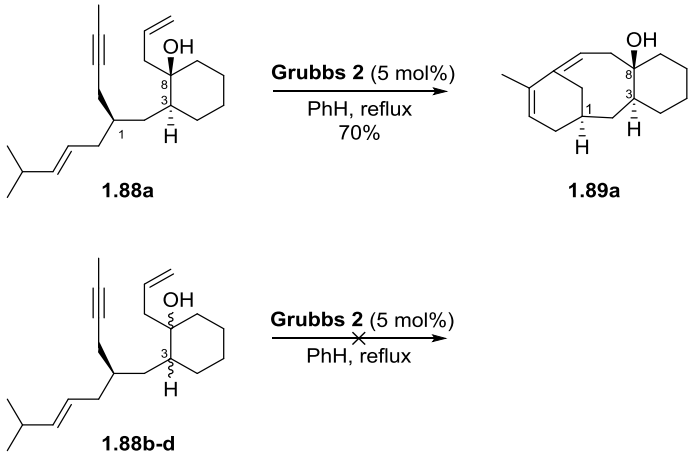
The successful enantioselective syntheses of (−)-acylfulvene and (−)-irofulven were also achieved by use of a silicon tether ring-closing metathesis strategy. Treatment of dienyne precursor **1.85** with Grubbs 2 catalyst afforded the desired 7,6-bicycle **1.86**, which was subsequently converted into the key triol **1.87** after desilylation, as shown in Scheme 1.33.[46]

[45] Mukherjee, S.; Lee, D. *Org. Lett*. **2009**, *11*, 2916-2919.
[46] Movassaghi, M.; Piizzi, G.; Siegel, D. S. *Angew. Chem. Int. Ed.* **2006**, *45*, 5859-5863.



Scheme 1.33: Synthesis of (−)-acylfulvene and (−)-irofulven

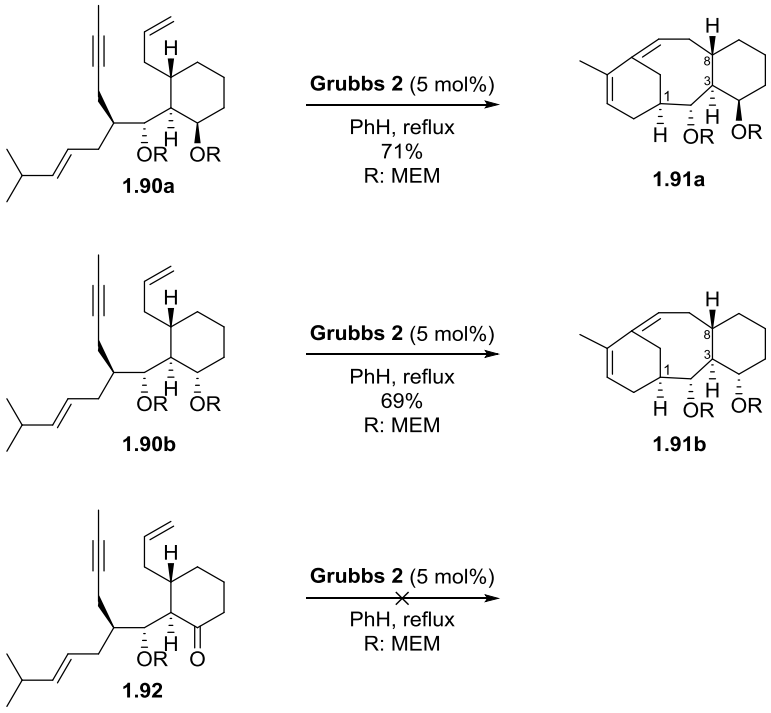
Granja and co-workers synthesised models of taxane analogs using RCDEYM.[47] In this study they investigated the importance of the relative configuration at C1, C3, C4, and C8. First, they found that the *trans* relationship between the substituents at C3 and C8(*S*) was essential for the cyclisation. Indeed when **1.88a** was treated with Grubbs 2 catalyst, tricyclic product **1.89a** was formed in 70% yield. Metathesis precursors **1.88b-d** that did not possess this *trans* relationship and the (*R*)-stereochemistry at C8 could not undergo dienyne metathesis (Scheme 1.34).



Scheme 1.34: Granja and co-workers RCDEYM attempts

[47] Aldegunde, M. J.; Castedo, L.; Granja, J. R. *Org. Lett*. **2008**, *10*, 3789-3792.

In Scheme 1.35, they varied the stereochemistry at C4 in the metathesis precursor. Both diastereomers **1.90a** and **1.90b** easily generated tricyclic systems **1.91a** and **1.91b** in good yield. When the C4-hydroxyl group was oxidised to the ketone **1.92**, no metathesis product was formed. Therefore, the geometry at the C4 position could not be planar but this centre could bear a protected hydroxyl group. Also all the cyclised products possessed the wrong configuration at C1 for Taxol with no inherent *gem*-dimethyl steric hindrance at C15, which facilitated the formation of these tricycles and made this strategy unsuitable for a total synthesis of Taxol.



Scheme 1.35: Influence of stereochemistry at C4 on metathesis

In summary, dienyne ring-closing metathesis is a very powerful and versatile method to construct highly complex, heteroatom-containing polycyclic systems in a single step. Numerous different bond cleavages and bond formations occur during the dienyne metathesis. Therefore, when dienyne metathesis is used for the total synthesis of natural products, retrosynthetic analysis is unique, and the number of chemical steps is generally shortened. In light of all the examples shown above, a good precursor of RCDEYM must have a skeleton that is predisposed to undergo a cascade process, as well as possessing different types of alkenes (terminal *vs* internal), as these are crucial to controlling and driving the reaction toward the desired product.

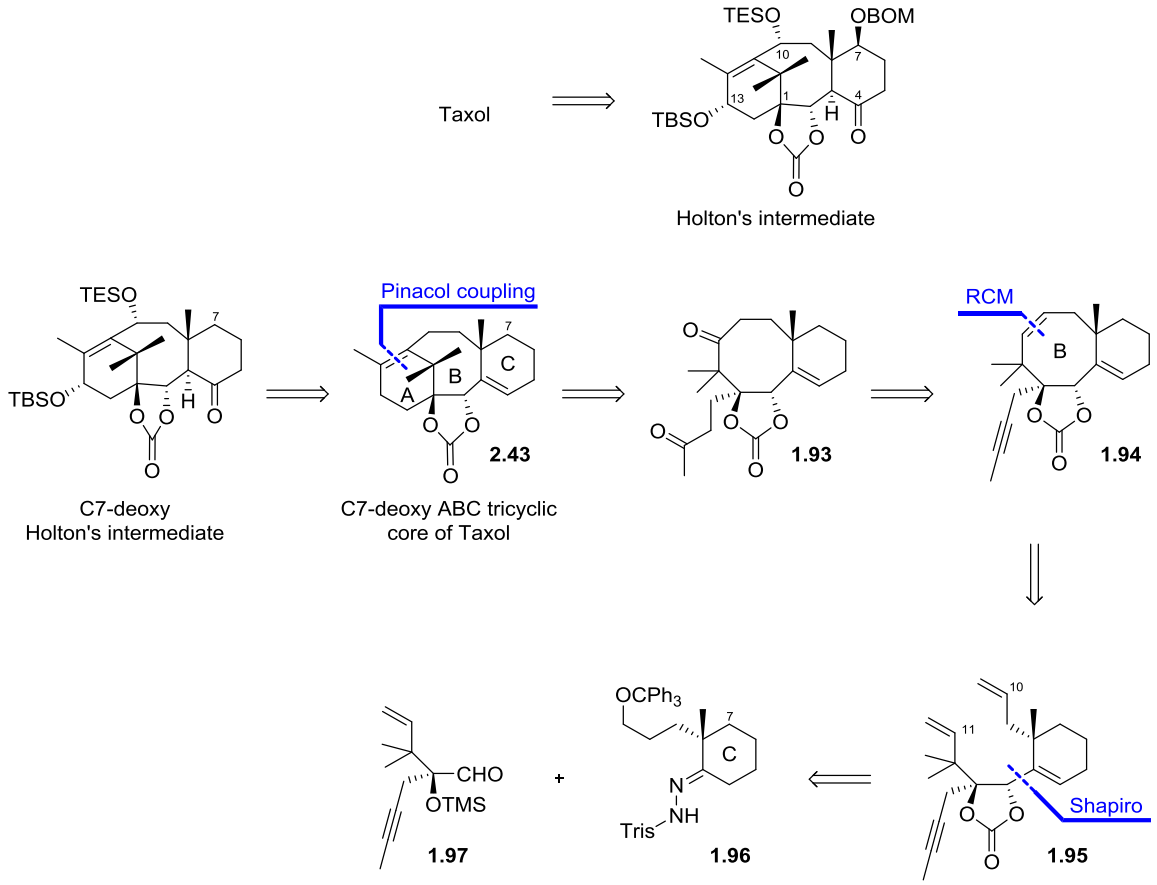
1.4 Project Presentation

In this study, a C7-deoxy Taxol precursor is targeted. This work is the extension of the precedent work performed by Cong Ma and Rémi Aouzal during their PhD thesis in Ecole Polytechnique (France) under the supervision of Dr Joëlle Prunet.

1.4.1 Previous Work

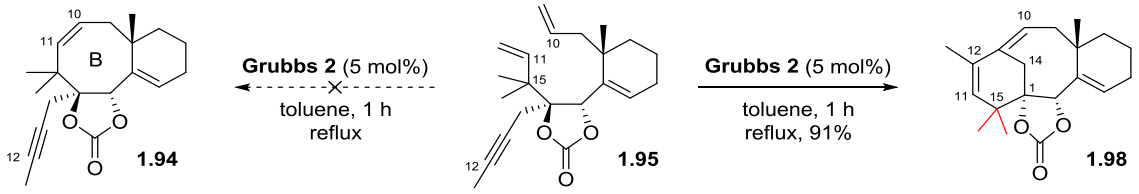
Cong Ma's initial retrosynthesis is outlined in Scheme 1.36.[48] He aimed for a formal synthesis of Taxol, so he chose as his primary target an intermediate Holton and co-workers described in their synthesis.[20] The C7-deoxy Holton intermediate was targeted to test the key metathesis step so it was decided to use a C7-deoxy ring C model as a coupling partner in the Shapiro reaction. It is worth noting that C7-deoxy taxanes do not show significant loss of activity. This C7-deoxy Holton intermediate would be made from the C7-deoxy ABC tricyclic core of Taxol **2.43** by allylic oxidation at C10 and C13, and the ketone at C4 by a hydroboration/oxidation sequence.[22,25] The ring A would be closed by a pinacol coupling between the ketones at C11 and C12, as previously described by Mukaiyama on a similar substrate.[25] The diketone **1.93** would be obtained by functionalisation of the C10-C11 olefin and from hydration of the alkyne moiety. The eight-membered ring B **1.94** would be formed by a ring-closing metathesis (RCM) reaction between the alkenes at C10 and C11. Finally, the metathesis precursor **1.95** would be assembled by a Shapiro reaction between the C7-deoxy hydrazone **1.96** and the aldehyde **1.97** followed by some functionalisation.

[48] C. Ma, PhD Thesis, Ecole Polytechnique (Palaiseau, France), **2008.**



Scheme 1.36 : Initial retrosynthesis for C7-deoxy Taxol

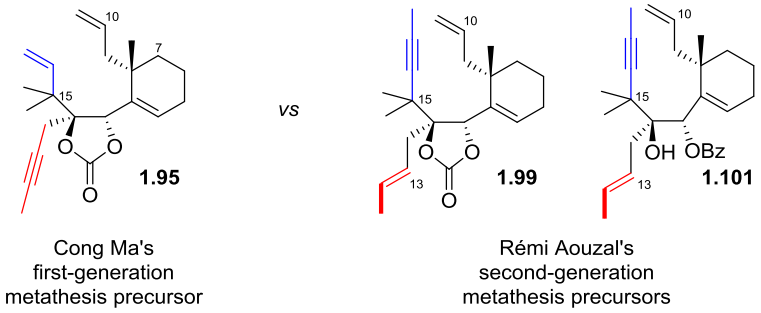
When Cong Ma treated precursor **1.95** with 5 mol% of Grubbs' second-generation catalyst in refluxing toluene, diene metathesis between C10 and C11 did not occur and bicyclic compound **1.94** was not formed. Instead a ring-closing dienyne metathesis cascade formed the 14,15-isotaxane product **1.98** in 91% yield. It is worth noting that this metathesis cascade gave a version of the ABC tricyclic core of Taxol with the bulky *gem*-dimethyl group in the wrong position (Scheme 1.37).



Scheme 1.37: Metathesis cascade reaction

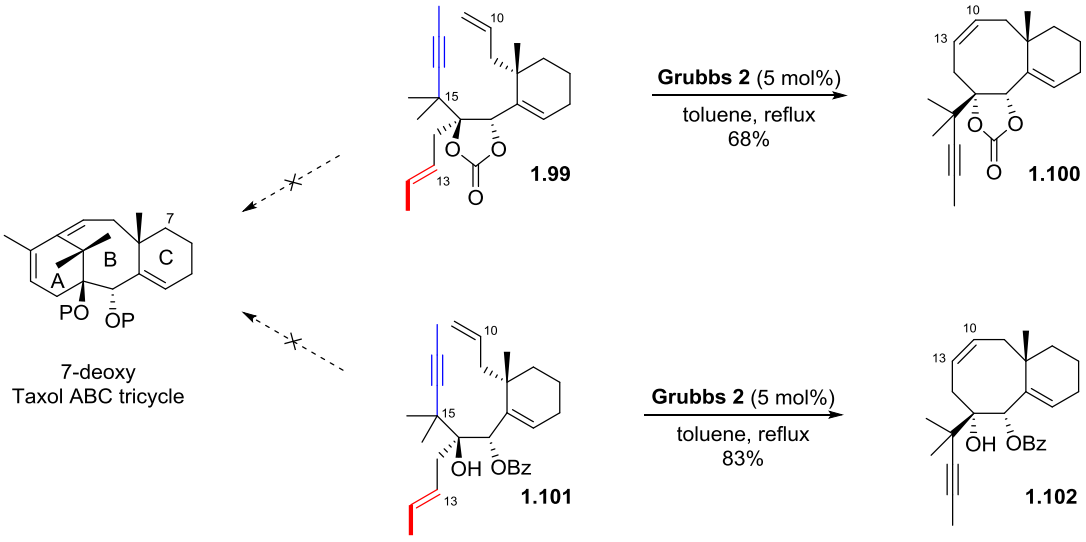
Taking this result into account, the following PhD student, Rémi Aouzal, wanted to take advantage of this very efficient metathesis cascade to synthesise the ABC tricyclic core

of Taxol with the *gem*-dimethyl at the right position.[49] He developed a second-generation metathesis precursor series where the alkyne at C11 and the alkene at C13 have swapped positions compared to Cong Ma's metathesis precursor, as illustrated in Scheme 1.38. It is important to note that this extra methyl group at C13 will not be present in the metathesis products, but will be part of the propene released after the metathesis reactions.



Scheme 1.38 : Structural differences between the metathesis precursors

When Rémi Aouzal treated the carbonate precursor **1.99** with 5 mol% of Grubbs' second generation catalyst in refluxing toluene, the unwanted bicyclic **1.100** was synthesised by diene ring-closing metathesis in 68% yield. When the benzoate derivative **1.101** underwent the same reaction, it afforded the similar unwanted bicyclic derivative **1.102** in 83% yield. Unfortunately, no trace of the ABC tricyclic core of Taxol was formed (Scheme 1.39).



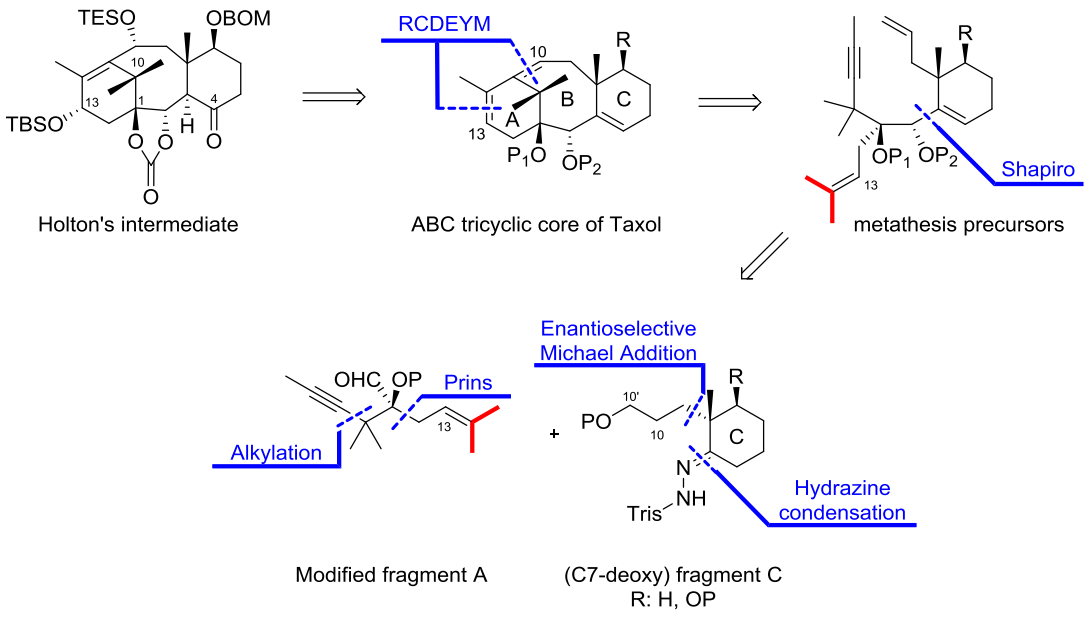
Scheme 1.39 : Metathesis attempts

[49] R. Aouzal, PhD Thesis, Ecole Polytechnique (Palaiseau, France), **2010**.

These failures are probably due to the steric bulk of the *gem*-dimethyl group that hinders the alkyne and disfavours the RCDEYM process. Since this *gem*-dimethyl group is an inherent part of the Taxol skeleton, it is not possible to relieve the steric hindrance at the propargylic position, but another option would be to further increase the steric hindrance of the alkene at C13, so the undesired diene RCM will be disfavoured. Indeed adding an extra methyl group on the C13 alkene could favour the metathesis cascade reaction and therefore deliver the ABC tricyclic core of Taxol.

1.4.2 Thesis Project

The idea of further increasing the steric hindrance around the C13 olefin will be studied in this thesis as well as the synthesis of the Shapiro coupling partners; the modified racemic and enantio-enriched fragment A, C7-deoxy fragment C and fragment C. Synthesis of the metathesis precursors followed by A/B ring system closure in a single operation by ring-closing dienyne metathesis to synthesise the ABC tricyclic core of Taxol, will be developed. Also, with a robust synthesis of the ABC tricyclic core of Taxol in hand, derivatisation of tri-olefinic products will be undertaken to establish a formal synthesis of Taxol based on Holton's synthesis (Scheme 1.40).



Scheme 1.40: Thesis work retrosynthesis

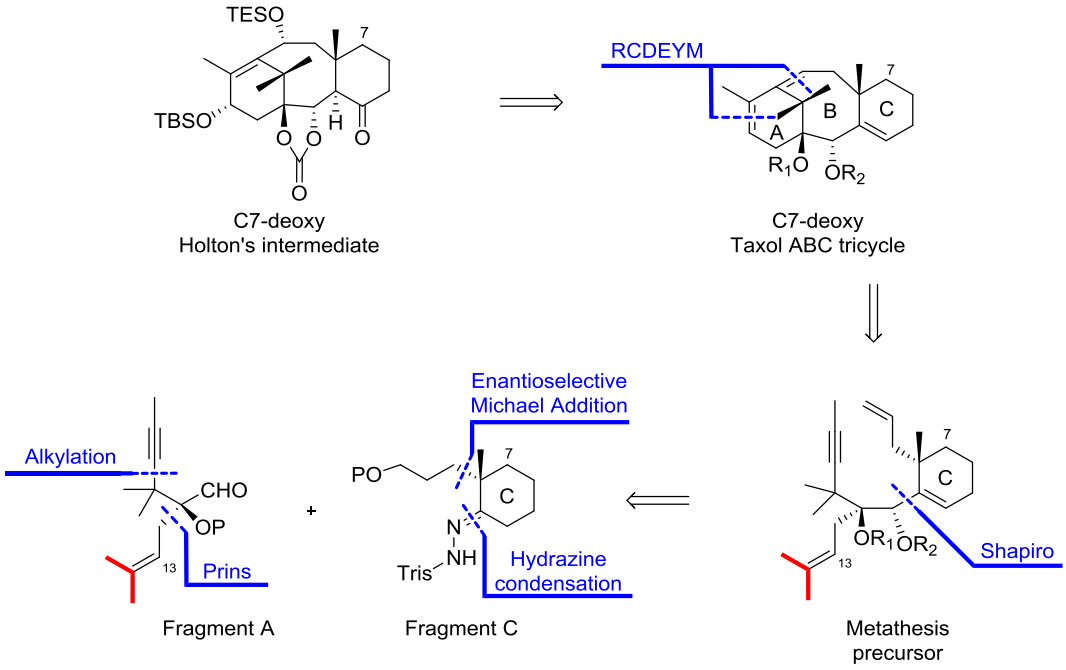
2. Synthesis of C7-deoxy ABC Tricyclic Core of Taxol by Ring-Closing Dienyne Metathesis

2.1 Fragment A Racemic Synthesis

The planned retrosynthesis of the C7-deoxy ABC tricyclic core of Taxol differs from the one of Rémi Aouzal. As explained before, an extra methyl group is going to be added to the C13 olefin in order to access a C7-deoxy ABC tricyclic core of Taxol using a dienyne metathesis to close in a single operation both A and B rings.

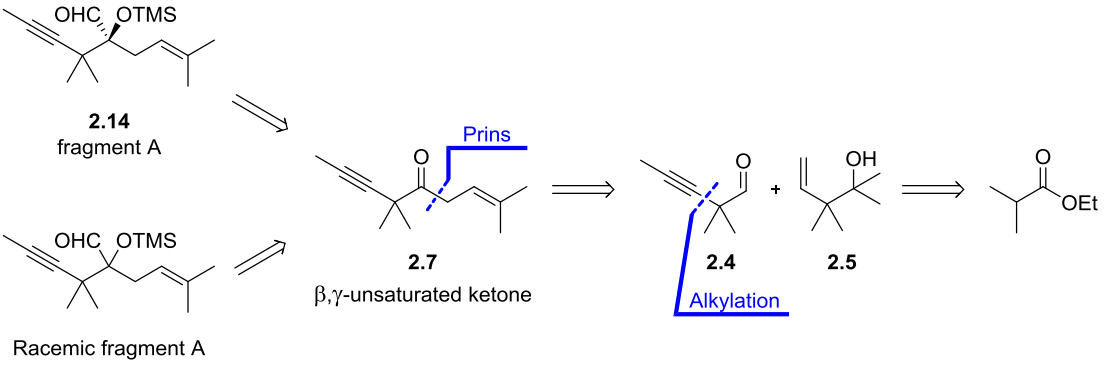
2.1.1 Retrosynthesis

This C7-deoxy Taxol ABC tricycle would be obtained by dienyne metathesis (RCDEYM) from a metathesis precursor bearing a *gem*-dimethyl olefin at C13. This precursor can be made from a Shapiro coupling between 2 different fragments: aldehyde fragment A and known hydrazone fragment C (Scheme 2.1).



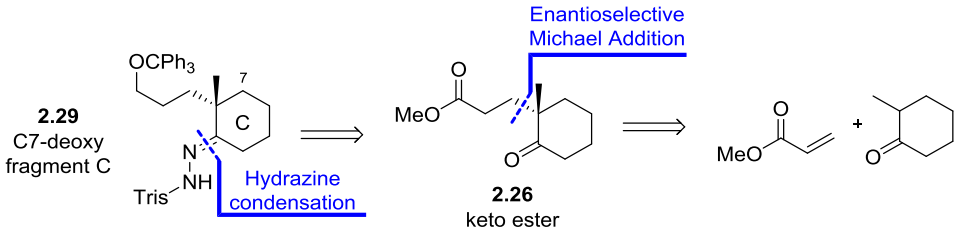
Scheme 2.1: Retrosynthesis of C7-deoxy Taxol ABC tricycle

Racemic and enantio-enriched fragments A would come from a β,γ-unsaturated ketone that can be synthesised in a few steps by simple alkylation and Prins coupling from ethyl isobutyrate, as shown in Scheme 2.2.



Scheme 2.2: Fragments A retrosynthesis

C7-deoxy fragment C can be obtained by hydrazine condensation from a keto ester derivative and an enantioselective Michael addition of 2-methyl cyclohexanone to methyl acrylate, as illustrated in Scheme 2.3.



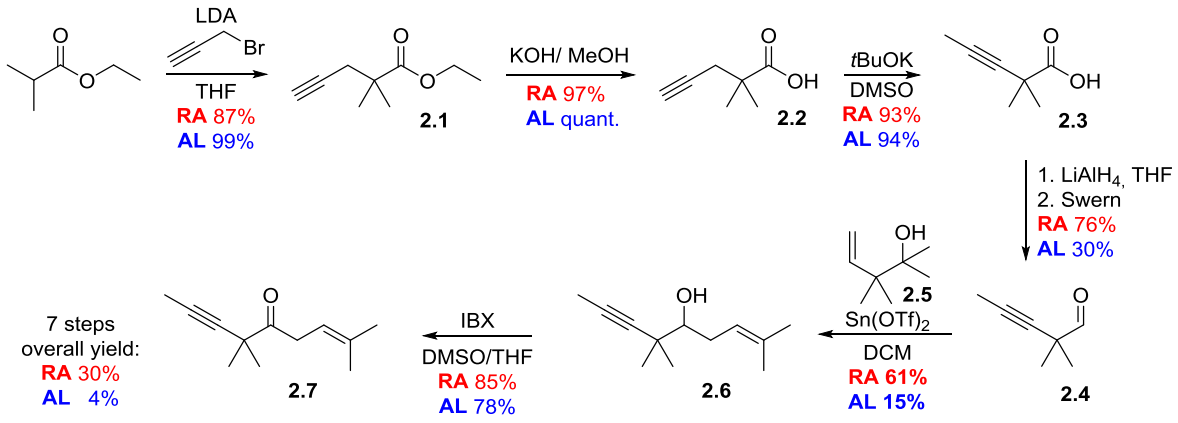
Scheme 2.3: C7-deoxy fragment C retrosynthesis

2.1.2 Synthesis of Ketone 2.7

The β,γ-unsaturated ketone **2.7** had been previously made by Rémi Aouzal as shown in Scheme 2.4. Alkylation of ethyl isobutyrate with propargyl bromide afforded the corresponding alkylated ester **2.1** in 87% yield. This ester was hydrolysed in 97% yield to furnish acid **2.2** followed by an isomerisation of the terminal alkyne, which occurred under basic conditions using potassium *tert*-butoxide in DMSO to generate the internal alkyne **2.3** in 93% yield. The isomerised acid **2.3** was then reduced using $LiAlH_4$ and the resulting alcohol oxidised under Swern conditions to the corresponding aldehyde **2.4** in a yield of 76% over 2 steps. This aldehyde underwent a Prins coupling with the tertiary homoallylic

alcohol **2.5**, to afford the homoallylic alcohol **2.6** in 61% yield.[50,51] IBX oxidation afforded in good yield the corresponding β,γ-unsaturated ketone **2.7** in a 30% overall yield after a total of 7 steps.

When this synthesis was reproduced, similar yields were found for the 3 first steps but the $LiAlH_4$ reduction followed by Swern oxidation produced the volatile aldehyde **2.4** in only 30% yield. Then the Prins coupling was performed with the known tertiary alcohol **2.5** to afford the homoallylic alcohol **2.6** in a disappointing 15% yield. IBX oxidation generated the β,γ-unsaturated ketone **2.7** with an overall yield of 4% from ethyl isobutyrate. Reproduction of this synthesis was not successful and crucial optimisation had to be undertaken, especially for the generation of volatile aldehyde **2.4** and the Prins coupling steps.



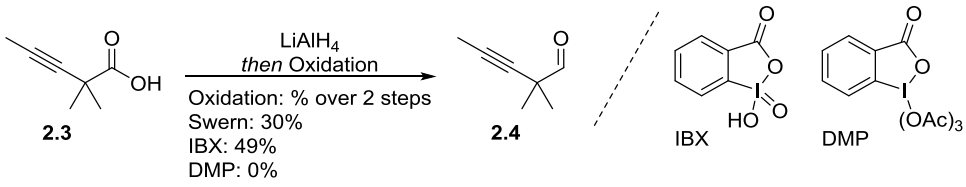
*Scheme 2.4: Remi Aouzal's synthesis of ketone **2.7***

2.1.2.1 Preparation of Aldehyde 2.4

Firstly, optimisation of the aldehyde **2.4** synthesis was engaged, and specifically the reduction-oxidation sequence. Aldehyde **2.4** was found to be highly volatile and was difficult to purify, therefore different oxidation methods with simple purifications were tested to prepare this volatile and rather difficult to isolate product. When Swern oxidation was used, the aldehyde was obtained in a low 30% yield. The reasons behind this low yield was probably due to the work-up and purification that led to a substantial loss of product. When IBX oxidation was employed, the aldehyde was obtained in 49% yield. The IBX work-up was simpler than the one used for the Swern oxidation and could explain the yield

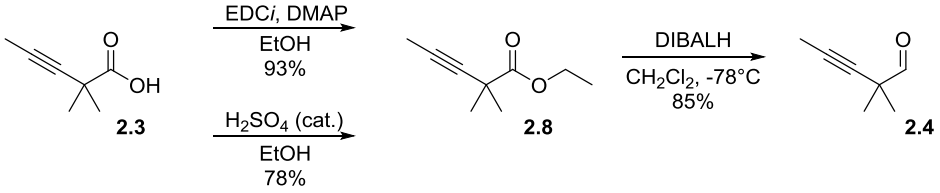
[50] Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S.-I. *J. Am. Chem. Soc*. ***1998***, *120*, *6609-6610.*
[51] Satoh, S.; Suginome, H.; Tokuda, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1791-1794.

increase. Unfortunately DMP oxidation did not lead to any conversion of the aldehyde **2.4** (Scheme 2.5).



*Scheme 2.5: Optimisation of aldehyde **2.4***

Secondly, another way to synthesise this aldehyde **2.4** was to use an esterification-reduction sequence from acid **2.3**. Steglich esterification using EDCi (1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide) and DMAP in ethanol was used and ethyl ester **2.8** was synthesised in 93% yield. Unfortunately EDC*i* is a very expensive reagent so a cheaper method as efficient as this one was sought. Luckily, esterification using concentrated sulfuric acid in ethanol afforded the ester **2.8** in 78% yield. These conditions also efficiently allowed the synthesis of **2.8** on a decagram scale. Finally DIBALH reduction at -78°C in CH_2Cl_2 (low boiling point solvent) afforded the desired aldehyde **2.4** in 85% yield, with simple purification, which resolved the volatility problem of this aldehyde synthesis, as shown in Scheme 2.6.

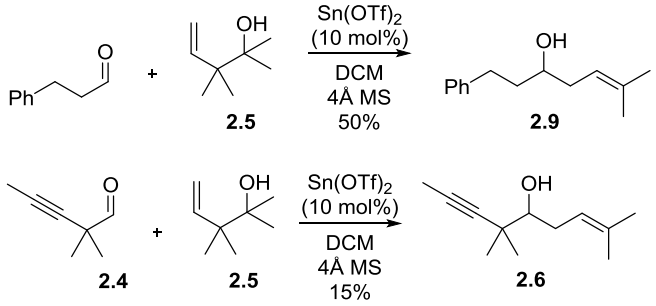


*Scheme 2.6: Alternative synthesis of aldehyde **2.4***

2.1.2.2 Prins Coupling

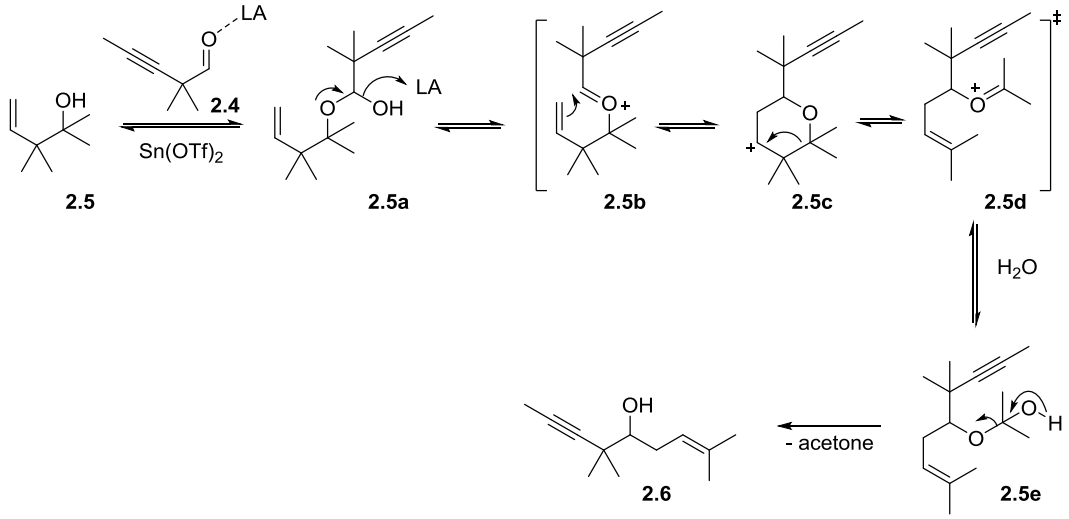
The Prins coupling was first optimised on a cinnamaldehyde substrate model, using 10 mol% of tin triflate and 4Å molecular sieves to ensure dry reaction conditions in CH_2Cl_2. These conditions generated the expected homoallylic alcohol **2.9** in 50% yield. Unfortunately when the same conditions were employed with aldehyde **2.4**, the desired homoallylic alcohol **2.6** was only formed in 15% yield. To explain this lack of reactivity, efforts toward the essential tin triflate Lewis acid were devoted. Thermal activation under vacuum was performed and catalysts from different suppliers were employed but none of

these modifications improved the yield of this coupling. Thoroughly drying and distilling both substrates did not improve the efficiency of the reaction either (Scheme 2.7).



Scheme 2.7: Prins coupling optimisation

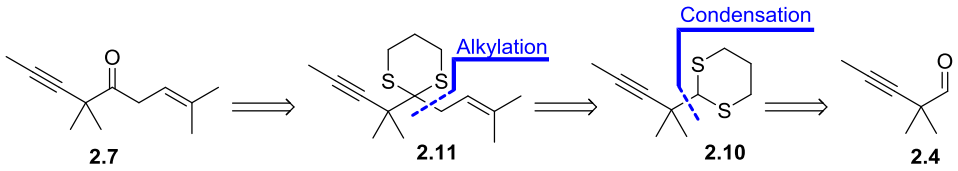
This failure could be explained by the demanding activation energy of this coupling, both substrates, neopentylic aldehyde **2.4** and homoallylic tertiary alcohol **2.5** are highly hindered. In Scheme 2.8, is shown the proposed Prins coupling mechanism between aldehyde **2.4** and homoallylic alcohol **2.5**. This alcohol **2.5** would attack the aldehyde **2.4**, which is activated by the tin triflate Lewis acid to generate hemiacetal **2.5a**. Dehydration of the hemiacetal **2.5a** generates oxonium **2.5b**, which rearranges to the most stable oxonium **2.5d** via carbocation **2.5c**. Water then attacks the most stable oxonium ion and acetone elimination affords homoallylic alcohol **2.6**.



Scheme 2.8: Proposed mechanism for Prins coupling

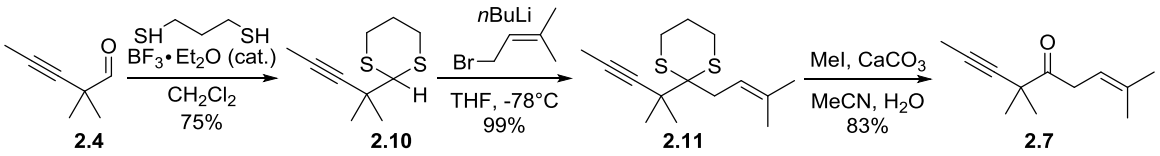
2.1.2.3 Umpolung Strategy from Aldehyde 2.4

At this point, another strategy for the formation of the β,γ-unsaturated ketone **2.7** had to be investigated. Umpolung chemistry was then used to synthesise the desired ketone as shown in Scheme 2.9 where the new retrosynthesis is presented.



*Scheme 2.9: Retrosynthesis of ketone **2.7***

Aldehyde **2.4** was treated with 1,3-propanedithiol and $BF_3.Et_2O$ in CH_2Cl_2 to synthesise in 75% yield the corresponding dithiane **2.10**. This dithiane **2.10** was treated with *n*BuLi in THF at low temperature to generate the dark red coloured dithiane anion that was alkylated by addition of prenyl bromide. The alkylated dithiane **2.11** was formed in 99% yield. Mild deprotection was then tried using methyl iodide and calcium carbonate in a mixture of acetonitrile and water. After 48 h of reaction the desired ketone **2.7** was obtained in 83% yield (Scheme 2.10).

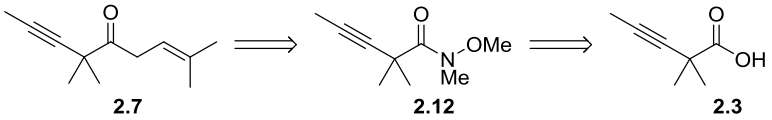


*Scheme 2.10: Synthesis of ketone **2.7***

This umpolung route was successful but not easily reproducible, and the overall yield drastically depended on the quality and freshness of the reagents employed. Also this 3-step sequence was long and time consuming.

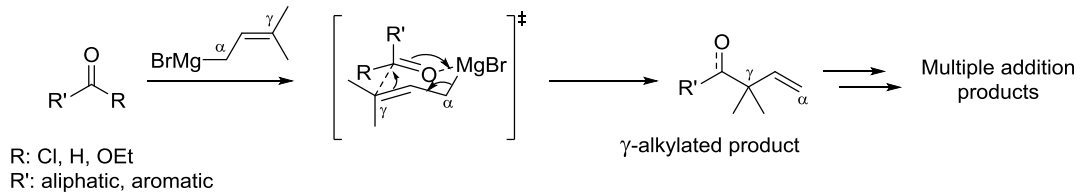
2.1.2.4 Alternative Route to Ketone 2.7 using a Weinreb Amide

Another route, more direct than the previous ones, was explored. This route involves a direct addition of a prenyl moiety to the Weinreb amide **2.12** using a Grignard reagent to obtain ketone **2.7**. This Weinreb amide **2.12** can easily be made from acid **2.3** as shown in Scheme 2.11.



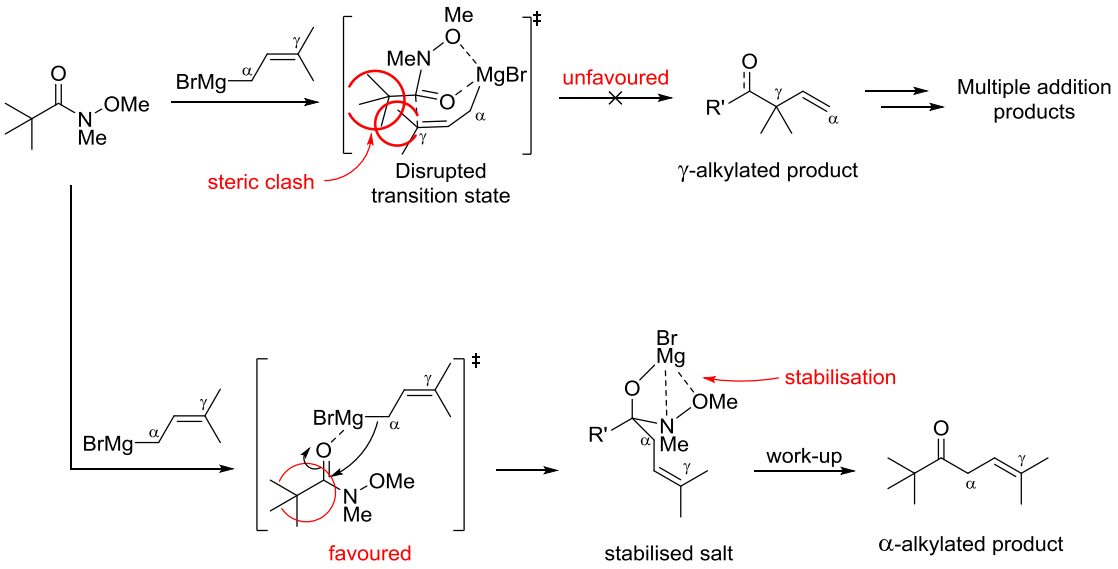
*Scheme 2.11: Retrosynthesis of ketone **2.7** via a Weinreb amide*

Usually, reaction of esters, and acyl chlorides with organomagnesium reagents do not lead to ketones in high yields, because ketone intermediates are more reactive toward the organometallic reagents than their corresponding starting materials. In general, the carbonyl group reacts in a 6-membered transition state to produce the γ-alkylated product as shown in Scheme 2.12. Lone pairs of the carbonyl group stabilise the metallic centre and favour this pathway. Most type of carbonyls are known to react that way and often afford a mixture of α-and γ-alkylated products.



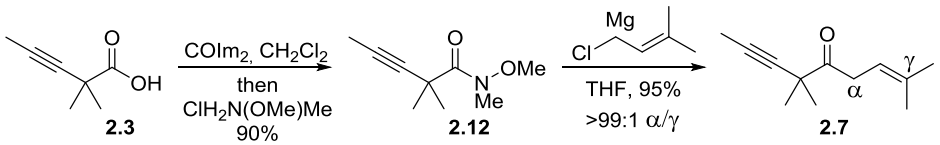
Scheme 2.12: Formation of γ-alkylated non-bulky product by direct alkylation of Grignard reagent

However, bulky Weinreb amides do not follow the same mechanism and lead to the α-alkylated product. Steric clash between bulky substituents of the amide will repulse the γ-position of the prenyl moiety and disfavour this pathway. They also do not undergo further addition of Grignard reagent as the initial adduct, after the first attack of the organometallic reagent, is stabilised by interactions from the Weinreb heteroatoms with the metallic counterpart. So the magnesium derivative would attack from its α-position, less hindered, to afford the desired α-alkylated product **2.7** (Scheme 2.13).



Scheme 2.13: Formation of α-alkylated bulky product by direct alkylation of Grignard reagent

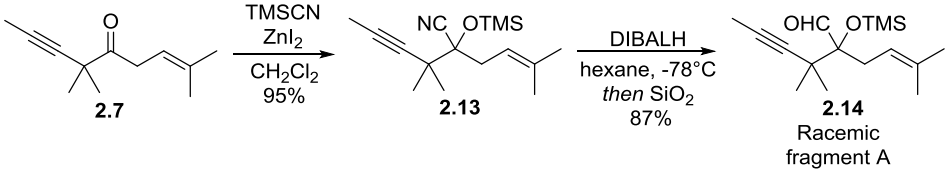
Therefore, acid **2.3** was treated with carbonyldiimidazole in CH_2Cl_2 and after few minutes, the freshly dried Weinreb ammonium salt was added to generate the Weinreb amide **2.12** in 90% yield.[52] Then the β,γ-unsaturated ketone **2.7**, as planned, was synthesised in 95% yield with a perfect selectivity toward the α-alkylated product by treating the amide **2.12** with freshly and cautiously made organomagnesium reagent in THF, as reported in Scheme 2.14.[53,54]



*Scheme 2.14: Synthesis of ketone **2.7** via Weinreb amide **2.12***

2.1.3 Synthesis of Racemic Fragment A: End-Game

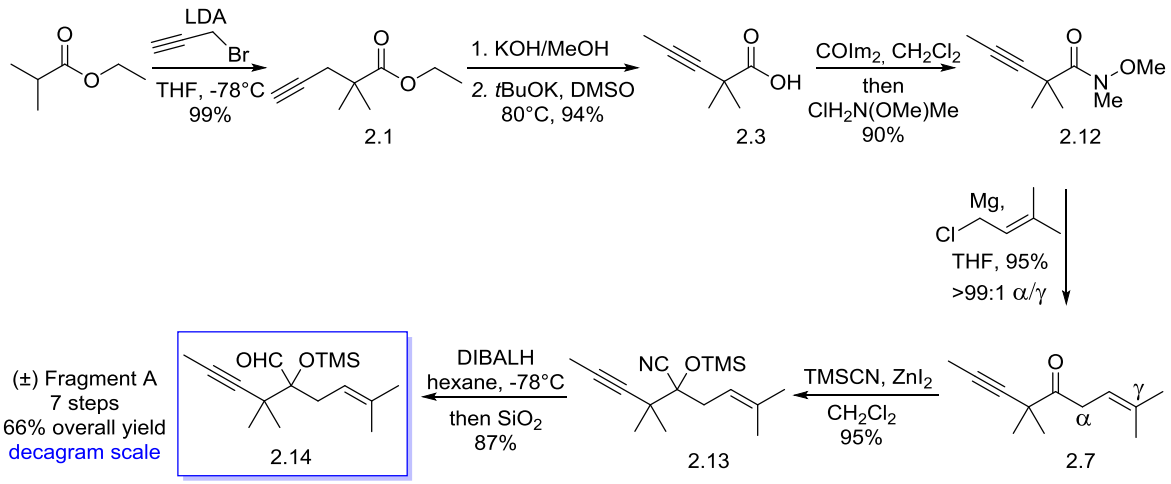
Racemic fragment A **2.14** was then easily synthesised. The β,γ-unsaturated ketone **2.7** was treated with TMSCN and zinc iodide to generate the silylated cyanohydrin **2.13** in 95% yield. This cyanohydrin was then reduced at -78°C using DIBALH in hexane to access the corresponding imine, which was hydrolysed under mild acidic condition, by adding SiO_2 to the reaction mixture, and produced the desired aldehyde **2.14** in 87% yield (Scheme 2.15).



*Scheme 2.15 Synthesis of racemic aldehyde fragment A **2.14***

In summary, the racemic fragment A **2.14** was synthesised in 7 steps with an overall yield of 66% and can be prepared in a single week on a decagram scale, as shown in Scheme 2.16.

[52] Larrive-Aboussafy, C.; Jones, B. P.; Price, K. E.; Hardink, M. A.; McLaughlin, R. W.; Lillie, B. M.; Hawkins, J. M.; Vaidyanathan, R. *Org. Lett.* **2010**, *12*, 324-327.
[53] The stated Grignard reagent easily undergoes Wurtz homo-coupling.
[54] Wurtz, A. *Ann. Chim. Phys.* **1855**, *44*, 275-312.



*Scheme 2.16: Optimised synthesis of racemic aldehyde **2.14***

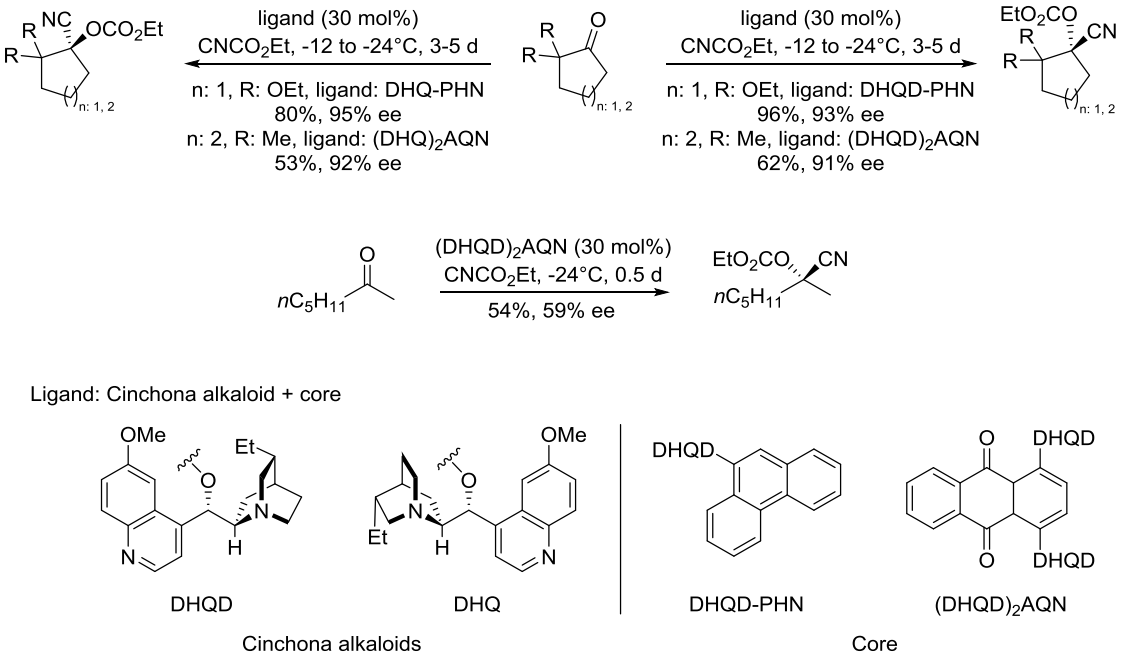
2.2 Toward the Synthesis of an Enantio-Enriched Fragment A via Cyanosilylation

To perform an efficient synthesis of Taxol, an enantiopure fragment A **2.14** is needed. A possible option would be to perform an enantioselective cyanosilylation of ketone **2.7**. Numerous groups have worked on the enantioselective cyanosilylation of aldehydes and ketones. Cyanosilylation of aldehydes are easier to perform due to their more electrophilic properties and are less hindered than ketones. It is also an efficient way of building a fully substituted stereogenic centre.[55]

2.2.1 Cyanosilylation using Cinchona Alkaloids

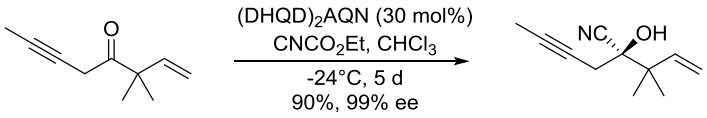
In the early 2000s, Deng and co-workers published their cyanation studies on aldehydes and ketones using tertiary chiral amines, cinchona alkaloids as catalysts.[56] Their results showed promising results with sterically hindered ketones (Scheme 2.17).

[55] North, M.; Usanov, D. L.; Young, C. *Chem. Rev*. **2008**, *108*, 5146-5226. Wang, W.; Liu, X.; Lin, L.; Feng, X. *Eur. J. Org. Chem*. **2010**, 4751-4769.
[56] Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195-6196. Tian, S.-K.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900-9901. Tian, S.-K.; Deng, L. *Tetrahedron* **2006**, *62*, 11320-11330.



Scheme 2.17: Enantioselective cyanohydrin formation

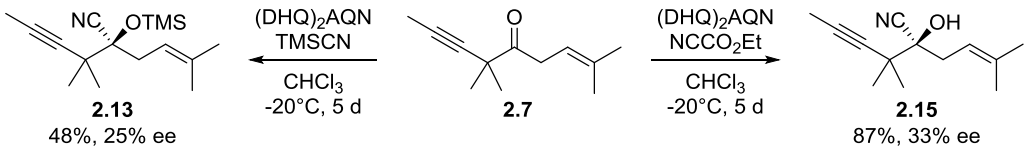
Enantioselective cyanation were also successfully performed in the Prunet group using the strategy Deng and co-workers developed (Scheme 2.18).



Scheme 2.18: Cyanohydrin synthesis in the Prunet group

Enantioselective cyanosilylation reaction under Deng and co-workers conditions led to poor enantioselectivity.[57] Reaction with cyanoformate and $(DHQ)_2AQN$ as the chiral ligand produced **2.15** in 83% yield with 33% ee. Ketone **2.7** was probably too bulky for the chiral catalyst to perfectly match the substrates and therefore give a decent enantioselectivity. When the cyanide source was switched to TMSCN, it directly produced the TMS protected cyanohydrin **2.13** but neither the yield nor the enantioselectivity were increased (Scheme 2.19). Interestingly, no sign of isomerisation of the trisubstituted double bond into conjugation with the ketone was observed during these attempts.

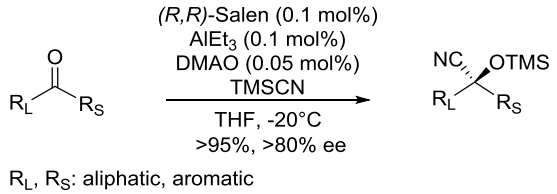
[57] The enantioselectivity of the reaction was determined after Shapiro coupling with hydrazone **2.29**. The d.r. of synthesised diols was determined by the H_4 and H_{13} integrals comparison from the crude ^1H NMR spectrum.



Scheme 2.19: Enantio-enriched cyanosilylation attempts

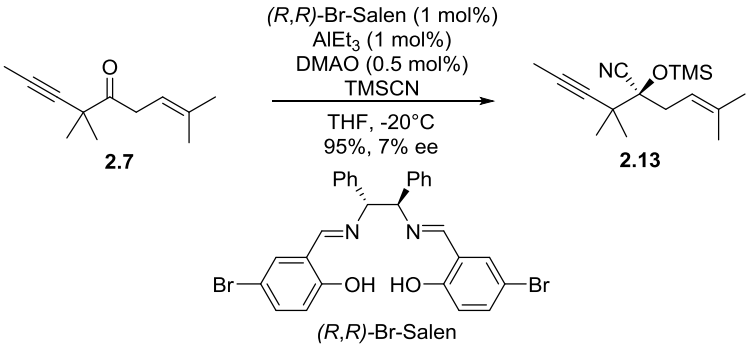
2.2.2 Cyanosilylation using Al-Salen Complexes

A few other promising cyanosilylation methods were tested. For example, Feng and co-workers used an enantioselective cyanosilylation of ketones by a catalytic double-activation method with an aluminium-salen complex and an *N*-oxide (*N*,*N*-dimethyl aniline oxide).[58] Their results appeared to be highly promising as illustrated in this following example (Scheme 2.20).



Scheme 2.20: General salen-mediated cyanosilylation

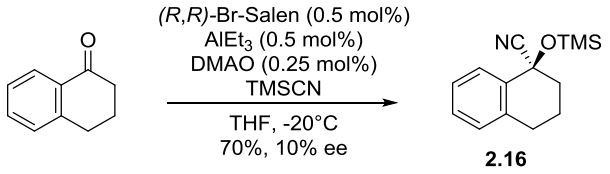
When the reaction was attempted on ketone **2.7**, the reaction gave cyanohydrin **2.13** in 95% yield with only 7% ee (Scheme 2.21).[57] Unfortunately, greater amount of active catalysts and triethyl aluminium did not improve yield nor enantioselectivity.



Scheme 2.21: (R,R)-Br-Salen mediated enantioselective cyanosilylation attempt

[58] Chen, F.-X.; Zhou, H.; Liu, X.; Qin, B.; Feng, X.; Zhang, G.; Jiang Y. *Chem. Eur. J.* **2004**, *10*, 4790-4797.

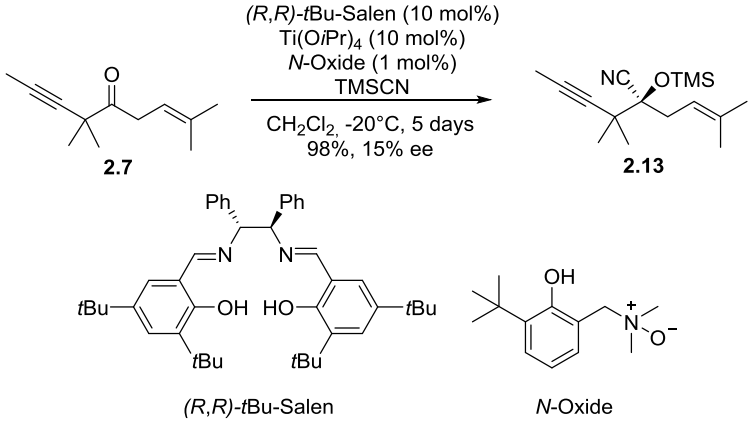
In an attempt to reproduce Feng's results, α-tetralone was submitted to the same conditions. Reagent quantities were increased (fold 5) in order to process the reaction with viable quantities of reagents. Unfortunately, the result was quite disappointing, the cyanohydrin **2.16** was formed in 70% yield and only 10% ee but it remained consistent to the results obtained for cyanohydrin **2.13** (Scheme 2.22).[59] It is important to note that freshly made *N,N*-dimethyl aniline oxide (DMAO) was used but it appeared that this reagent was highly hygroscopic and could have interfered with the reaction and led to a loss of enantioselectivity in these cases.



*Scheme 2.22: Attempt of enantioselective cyanosilylation with α-tetralone **2.16***

2.2.3 Cyanosilylation using Ti-Salen Complexes

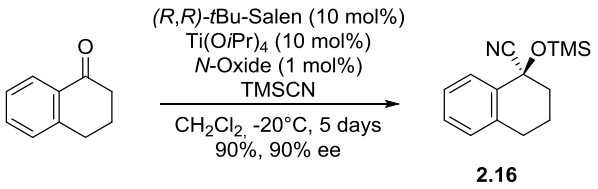
In a similar manner, another set of conditions were tested using a different, more stable, and less hygroscopic *N*-oxide derivative, following another publication from the same authors.[60] The change of *N*-oxide derivative could have made a difference in the cyanosilylation reaction outcome but when the reaction was tested, it afforded the cyanohydrin in 98% yield with a disappointing 15% ee as shown in Scheme 2.23.[57]



Scheme 2.23: tBu-Salen mediated enantioselective cyanosilylation attempt

[59] Enantioselectivity was determined by specific rotation of known compound **2.16**.
[60] He, B.; Chen, F.-X.; Li, Y.; Feng, Y.; Zhang, G. *Eur. J. Org. Chem*. **2004**, 4657-4666.

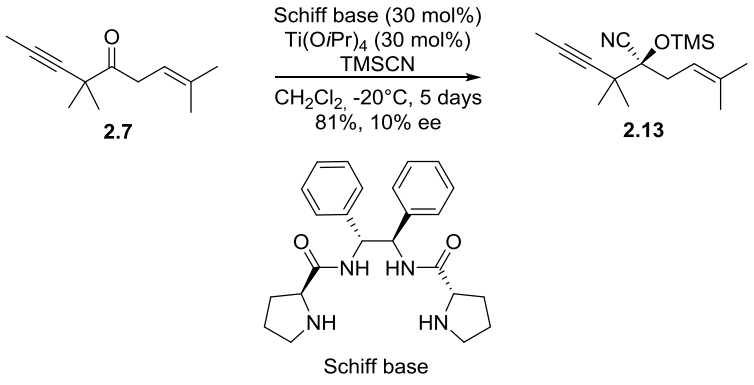
The same reaction was performed on the α-tetralone model substrate. In that case, the reaction gave **2.16** in 90% yield and 90% ee (Scheme 2.24).[59] The structural difference between ketone **2.7** and α-tetralone may explain such a difference in the level of enantioselectivity.



Scheme 2.24: (R,R)-tBu-Salen mediated enantioselective cyanosilylation with known substrate

2.2.4 Cyanosilylation using a Schiff Base

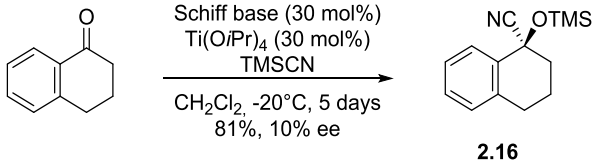
A last enantioselective cyanosilylation experiment was set up as shown in Scheme 2.25. Another work from Feng and co-workers, using an easily feasible (*L)*-proline-derived Schiff base, the soft titanium tetraisopropoxide Lewis acid and TMSCN as a cyanide source, gave the cyanohydrin **2.13** in a good 81% yield, but a low 10% ee.[57,61]



Scheme 2.25: Schiff base promoted enantioselective cyanosilylation attempt

[61] Xiong, Y.; Huang, X.; Gou, S.; Huang, J.; Wen, Y.; Feng, X. *Adv. Synth. Catal.* **2006**, *348*, 538-544.

Once again, to prove the efficiency of the method, the same conditions were tested on α-tetralone. In that case the reaction proceeded in 81% yield but a really poor 10% ee (Scheme 2.26).[59]



2.16

Scheme 2.26: Schiff base promoted enantio-enriched cyanosilylation with known substrate

The conclusion that can be drawn from these experiments is that, even if the cyanosilylation reactions proceeded in very good yield under all the previously mentioned conditions, none of the tested chiral ligands were able to produce **2.13** or **2.15** in more than 33% ee (the best result being with $(DHQ)_2AQN$ and $NCCO_2Et$). Despite the observation of a good 90% ee when the reaction was carried out using *(R,R)-t*Bu-Salen on the α-tetralone model substrate, the low enantioselectivity observed with ketone **2.7** led us to investigate other synthetic routes to prepare the enantiopure fragment A **2.14**.

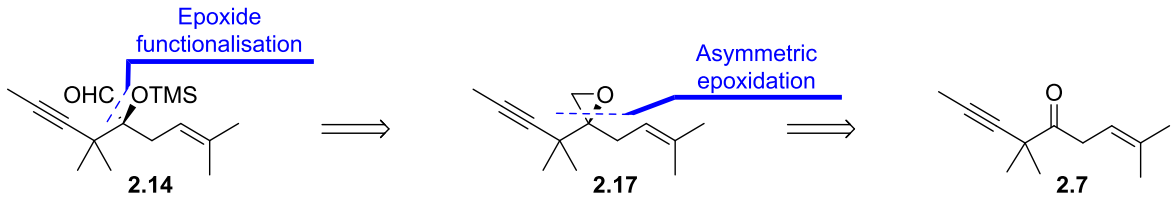
2.3 Toward an Enantiopure Fragment A via an Enantioselective Epoxidation

Another synthetic route was envisaged to prepare the enantiopure fragment A **2.14** using an enantioselective epoxidation.

2.3.1 Retrosynthesis

The retrosynthetic analysis shows that this aldehyde **2.14** can be synthesised from a 1,1-disubstituted epoxide **2.17**, which can be accessed from ketone **2.7** by an asymmetric Corey-Chaykovsky epoxidation to set up the rather challenging fully substituted centre (Scheme 2.27).[62]

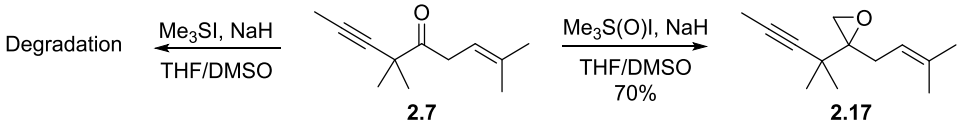
[62] Solladie-Cavallo, A.; Diep-Vohuule, A.; Sunjic, V.; Vinkovic, V. *Tetrahedron Asym.* **1996**, *7*, 1783-1788. Solladie-Cavallo, A.; Roje, M.; Isarno, T.; Sunjic, V.; Vinkovic, V. *Eur. J. Org. Chem*. **2000**, 1077-1880. Breau, L.;



Scheme 2.27: Retrosynthesis

2.3.2 Racemic Attempts

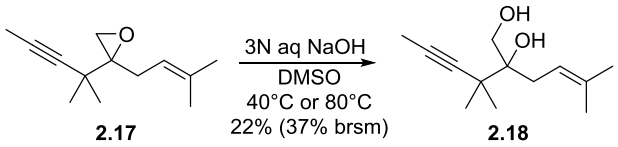
The synthesis of racemic aldehyde **2.14** via a 1,1-disubstituted epoxide was investigated. Ketone **2.7** was thus treated with trimethylsulfonium iodide and sodium hydride but the reaction did not lead to any conversion of starting material. When the trimethylsulfoxonium iodide derivative was used in conjunction with sodium hydride in a mixture of THF and DMSO, the reaction delivered the epoxide **2.17** in 70% yield (Scheme 2.28).



Scheme 2.28*: Formation of epoxide **2.17** using the Corey-Chaykovsky method*

Then this epoxide **2.17** was opened to afford diol **2.18** using 3N aqueous NaOH in DMSO under heating at either 40 or 80°C in a low 22% yield. The reaction was run with different bases, solvent systems, or under heating at different temperatures in order to improve the yield but the best conditions are stated in Scheme 2.29.

Ogilvie, W. W.; Durst, T. *Tetrahedron Lett*. **1990**, *31*, 35-38. Julienne, K.; Metzner, P.; Henryon, V. *J. Chem. Soc. Perkin Trans. 1*, **1999**, 731-736. Zanardi, J.; Leriverend, C.; Aubert, D.; Julienne, K.; Metzner, P. *J. Org. Chem*. **2001**, *66*, 5620-5623. Aggarwal, V. K.; Hynd, G.; Picoul, W.; Vasse, J.-L. *J. Am. Chem. Soc.* **2002**, *124*, 9964-9965. Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R.; Studley, J. R.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc*. **2003**, *125*, 10926-10940. Aggarwal, V. K.; Richardson, J. *Chem. Commun*. **2003**, 2644-2651.



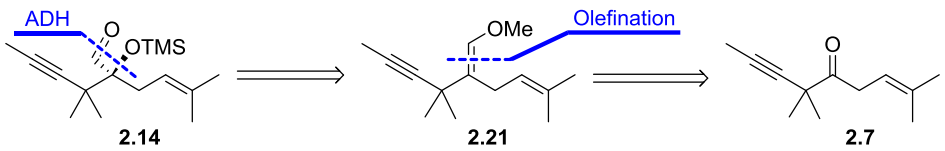
Scheme 2.29: Epoxide opening under basic conditions

A degradation product derived from the diol **2.18** was generated during these tests. The structure of this product could not be fully identified. The degradation product was observed as soon as the reaction converted the epoxide to the diol **2.18**, (when no conversion into diol **2.18** was observed, no degradation product was formed). Unfortunately, it was impossible to avoid the formation of this degradation product. This unwanted product generation was too important and the yield of formation of diol **2.18** too low for a viable route to aldehyde **2.14**. The synthesis via epoxide **2.17** was abandoned and another route was envisaged.

2.4 New Synthetic Approach toward an Enantiopure Fragment A via Catalytic Asymmetric Dihydroxylation

2.4.1 Retrosynthesis

Another synthetic route was envisaged. This time the desired aldehyde fragment A **2.14** would be obtained by a Sharpless catalytic asymmetric dihydroxylation (ADH) reaction of an homologated alkyl enol ether. This enol ether can be obtained from ketone **2.7** by olefination as illustrated in Scheme 2.30.

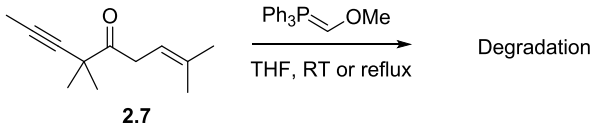


*Scheme 2.30: Retrosynthesis of aldehyde **2.14** using an asymmetric dihydroxylation*

2.4.2 Enol Ether Preparation

2.4.2.1 Wittig Olefination

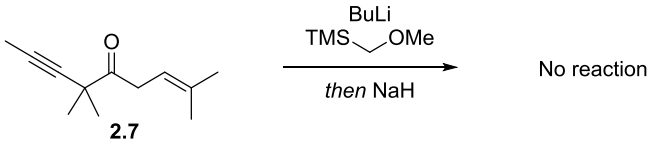
The simplest and easiest way to produce such a homologated enol ether was to use a Wittig reaction. Ylide reagents often lead to olefinic products from carbonyls in good yield. But unfortunately, when ketone **2.7** was treated with the corresponding ylide generated by (methoxymethyl)triphenylphosphonium chloride and LDA in THF, the reaction only afforded degradation of starting material. Increasing the number of equivalents of ylide, the reaction time, and the temperature never led to any conversion in the desired homologated enol ether (Scheme 2.31).



Scheme 2.31: Wittig olefination attempts

2.4.2.2 Peterson Olefination

It was then decided to synthesise this enol ether via a Peterson olefination.[63] So ketone **2.7** was treated with the corresponding α-silane anion but unfortunately no conversion of the ketone **2.7** was observed (Scheme 2.32).

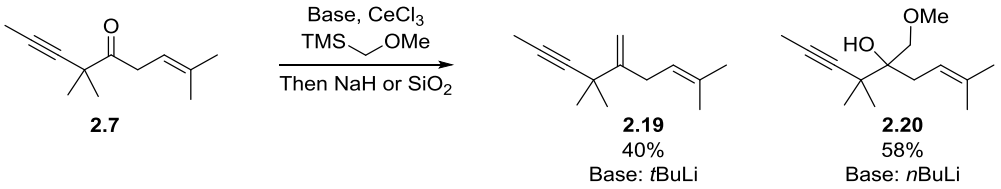


Scheme 2.32: Peterson olefination attempt

Nucleophilic attack onto hindered ketone **2.7** is rather challenging, so the nucleophilicity of the α-silane anion was enhanced by the formation of the corresponding organocerium derivative. Therefore, a few reactions were tested using (methoxymethyl)trimethylsilane and a strong base such as *t* or *n*BuLi with freshly dried cerium trichloride. Elimination of the freshly generated hydroxy-silane moiety was tested

[63] Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780-784.

under either basic condition using NaH or under slightly acidic conditions by means of SiO_2. Unluckily, all these attempts never led to the formation of the desired homologated enol ether, but depending on which base was used to generate α-silane anion, different products were obtained. Indeed, when *t*BuLi was used, the 1,1-disubstituted olefin **2.19** was produced in 40% yield as the major product along with traces of methoxy ether **2.20**. When a less basic but more nucleophilic base was used such as *n*BuLi, the methoxy ether **2.20** was formed in 58% yield without any trace of 1,1-disubstituted olefin **2.19** (Scheme 2.33). Also, in all these attempts the bases were used in a sub-stoichiometric amount compared to the cerium trichloride, which dismisses the possibility of a direct effect of these bases on the reaction mixture.



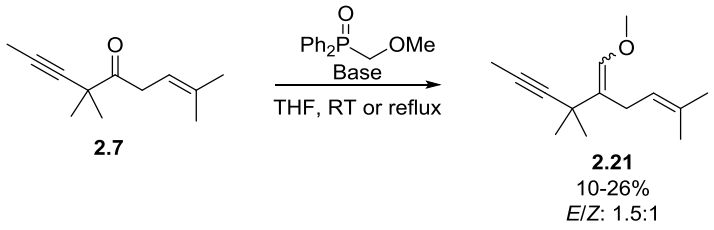
Scheme 2.33: Peterson olefination attempts

Faced to these unsuccessful olefination reactions, a third olefination method was investigated, the Wittig-Horner olefination.

2.4.2.3 Wittig-Horner Olefination

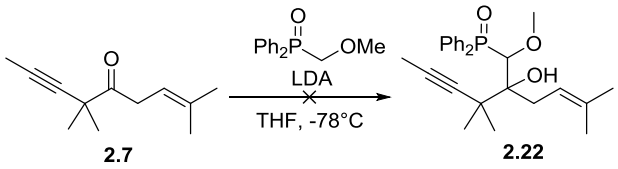
A variant of the well-known Wittig olefination, the Wittig-Horner reaction is often used on either hindered or highly sensitive carbonyl derivatives. Instead of using a triphenylphosphonium reagent, its oxygenated version is used, the diphenylphosphine oxide. With this reagent, the generated anion and is more nucleophilic, compared to the phosphonium ylide.

When the Wittig-Horner olefination was tried using LDA or *n*BuLi as bases and the diphenyl (methoxymethyl)phosphine oxide reagent in THF, the desired methoxy enol ether **2.21** was synthesised from 10 to 26% yield in a 1.5:1 *E*/*Z* ratio (Scheme 2.34).



Scheme 2.34: Wittig-Horner olefination attempts

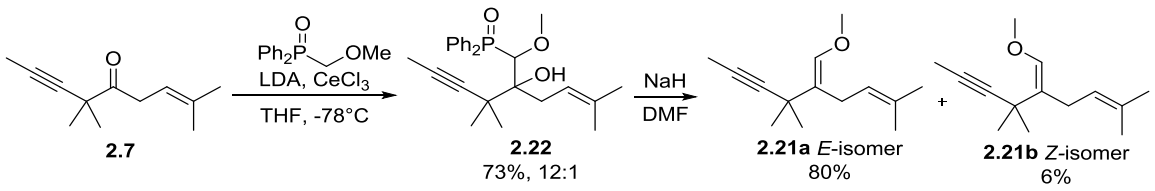
This result finally gave us hope for the conversion of ketone **2.7** to a useful enol ether derivative, after optimisation. In 1979, Warren and co-workers showed that the intermediate such as **2.22** could be isolated after the first condensation if LDA was used as a base at low temperature.[64] Unfortunately, when the same conditions were applied to ketone **2.7**, the reaction did not proceed at all (Scheme 2.35).



Scheme 2.35: Reproduction of Warren's Wittig-Horner olefination

This was probably due to the low reactivity of the generated phosphine oxide anion at -78°C toward the hindered ketone **2.7**. Once again, we tried to enhance the nucleophilicity and reduce the basicity of the anion by the generation of the organocerium species. Therefore, an equivalent of freshly dried cerium trichloride was added to the reaction to generate the corresponding organocerium derivative. Surprisingly, even at -78°C, these conditions afforded the desired, highly hindered phosphine oxide intermediate **2.22** in 73% yield in a 12:1 ratio of diastereomers. This intermediate was then treated with NaH in DMF to access both the *E* and *Z* isomers of the methoxy enol ether **2.21a** and **2.21b** in 80% and 6% yield, respectively (Scheme 2.36). It is interesting to note that, to our knowledge, no other Wittig-Horner olefination was reported in the literature with cerium trichloride.

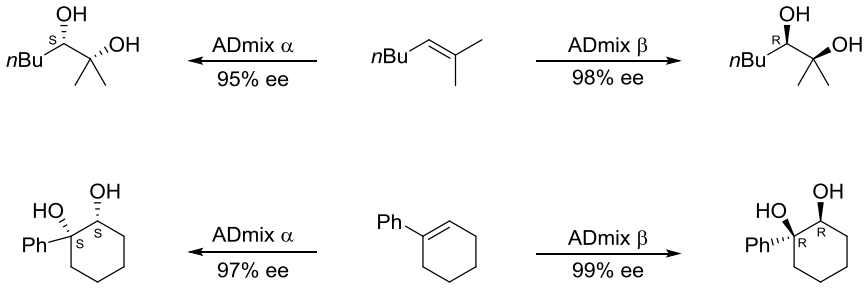
[64] Earnshaw, C.; Wallis, C. J.; Warren, S. *J. Chem. Soc. Perkin Trans. 1* **1979**, 3099-3106.



*Scheme 2.36: Formation of E- and Z-methoxy enol ethers **2.21***

2.4.3 Sharpless Asymmetric Dihydroxylation

The Sharpless dihydroxylation is a powerful and one of the most reliable methods to generate 1,2-diols from broad and different types of olefins, and gives high regio-, diastereo- and enantioselectivities depending on the chosen substrate system, as exemplified in Scheme 2.37.[65,66] When linear tri-substituted olefin was treated with ADmix α or ADmix β, (*S*) and (*R*) 1,2-diols were afforded in 95% ee and 98% ee, respectively. When benzylic cyclic trisubstituted olefin was treated with ADmix α or ADmix β, cyclic (*S*,*S*) and (*R*,*R*) 1,2-diols were afforded in 97% ee and 99% ee respectively.[67,68]

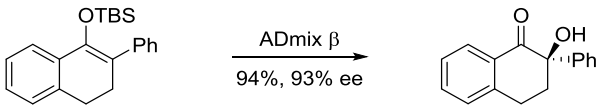


Scheme 2.37: Sharpless asymmetric dihydroxylation reactions of trisubstituted olefins

Moreover, when enol ethers undergo asymmetric dihydroxylation, the reaction generates α-hydroxy ketones, generally in good yields. The following example shown in Scheme 2.38 illustrates well our key synthetic step toward aldehyde fragment A **2.14**. The

[65] For earlier reviews of the asymmetric dihydroxylation reaction, see: Johnson, R. A.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. In *Catalytic Asymmetric Synthesis;* Ojima, I., Ed.; VCH Publishers: New York, **1993**, 227-272. Lohray, B. B. *Tet. Asym.* **1992**, *3*, 1317-1349.
[66] Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94,* 2483-2547.
[67] Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X. L. *J. Org. Chem*. **1992**, *57*, 2768-2771.
[68] No yield was reported for these products in this publication.

hindered tetrasubstituted cyclic silyl enol ether was dihydroxylated using ADmix β to afford the quaternary α-hydroxy ketone in 94% yield in 93% ee.[69]



Scheme 2.38: Sharpless asymmetric dihydroxylation reaction on tetra-substituted olefin

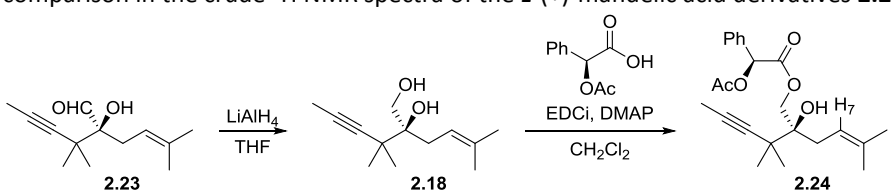
As Sharpless said "*Osmylation of olefins is generally regarded as the most reliable synthetic transformation available to organic chemists. The reasons are simple: OsO_4 reacts with all olefins, and it reacts only with olefins. Admittedly, the "all" and "only" in this latter statement are used with some poetic license; however, no other known organic reaction comes close to achieving such enormous scope coupled with such great selectivity*."[66] This citation reveals the efficiency, versatility and robustness of the catalytic enantioselective dihydroxylation of olefins.

2.4.3.1 *E* Enol Ether Olefin Asymmetric Dihydroxylation

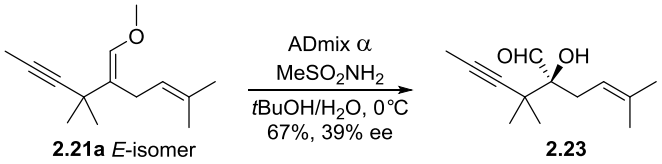
Having a valid route for the formation of *E* and *Z* isomers of **2.21** led us to investigate the Sharpless dihydroxylation. First, the commercially available ADmix α reagent, containing the cinchona-derived ligand alkaloid $(DHQ)_2PHAL$ was used. Under these conditions, the α-hydroxy aldehyde **2.23** was afforded in 67% yield and 39% ee (Scheme 2.39).[70]

[69] Morikawa, K.; Park, J.; Andersson, P. G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993***, 115*, 8463-8464.

[70] Enantioselectivity of products made by asymmetric dihydroxylation were determined by the H_7 integrals comparison in the crude ^1H NMR spectra of the *L*-(+)-mandelic acid derivatives **2.24**.



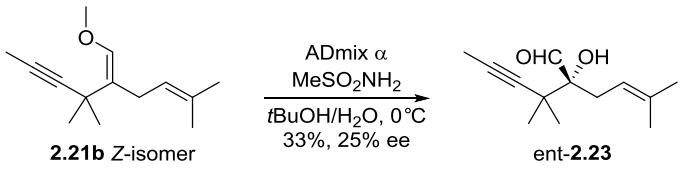
2.23 **2.18** **2.24**



*Scheme 2.39: Asymmetric dihydroxylation attempts on E-**2.21a** using ADmix α*

2.4.3.2 Z Enol Ether Olefin Asymmetric Dihydroxylation

This reaction, using the same conditions, was attempted on the *Z* isomer **2.21b**. In that case aldehyde ent-**2.23** was obtained in 33% yield with a 25% ee (Scheme 2.40).



*Scheme 2.40: Asymmetric dihydroxylation attempt on Z-**2.21b** using ADmix α*

This enantioselectivity was found to be rather low compared to other Sharpless dihydroxylations. It is true that dihydroxylations give better yields and enantioselectivities on mono (terminal) substituted and 1,2 disubstituted *E* olefins. It is worthy to note that few other groups tried to perform a Sharpless dihydroxylation on 1,1,2-trisubstituted olefins, using standard commercially available reagent mixtures, with poor enantioselectivities.[71] They found that more elaborated chiral ligands could lead to better enantioselectivities.

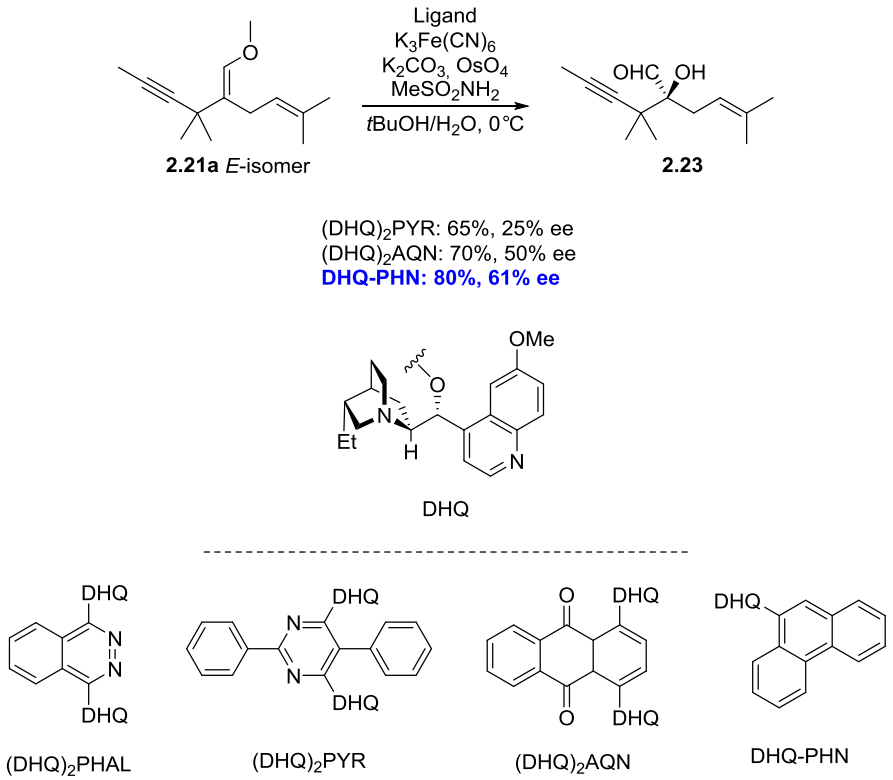
2.4.3.3 Chiral Ligand Screening

Diverse simple and efficient ligands were tested on *E* enol ether **2.21a** to increase the enantiopurity of the α-hydroxy aldehyde **2.23** as shown in Scheme 2.41.[72] When the $(DHQ)_2PHAL$ ligand contained in the ADmix α was switched to $(DHQ)_2PYR$, hydroxy aldehyde **2.23** was obtained in 65% yield in a low 25% ee. When $(DHQ)_2AQN$ was used, the

[71] Blagg, B. S. J.; Boger, D. L. *Tetrahedron* **2002**, *58*, 6343-6349. Zaitsev, A. B.; Adolfsson, H. *Synthesis* **2006**, 1725-1756.

[72] Becker, H.; Sharpless, K. B. *Angew. Chem. Int. Ed*. **1996**, *35*, 448-451. Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem*. **1993**, *58*, 3785-3786. Sharpless, K. B.; Amberg, W.; Seller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem*. **1991**, *56*, 4585-4588. Becker, H.; King, S. B.; Taniguchi, M.; Vanhessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1995**, *60*, 3940-3941.

reaction afforded the desired hydroxy aldehyde **2.23** in 70% yield and a moderate 50% ee. The best result came from the DHQ-PHN ligand, with which the dihydroxylation was performed in 80% yield in an acceptable 61% ee.



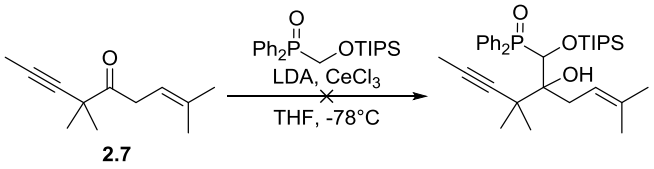
*Scheme 2.41: Asymmetric dihydroxylation attempts on E-**2.21a***

It is worthy to note that bidentate ligands such as $(DHQ)_2PHAL$, $(DHQ)_2PYR$, and $(DHQ)_2AQN$ are bigger than monodentate DHQ-PHN ligand (Scheme 2.41). These large ligands gave poor to moderate enantioselectivities. They are known to give good enantioselectivities on less substituted and less hindered olefin than enol ether **2.21a** and more importantly, benzylic olefins. The only ligand that gave an enantioselectivity superior to 50% is the DHQ-PHN bearing only one chiral alkaloid moiety, which is the smaller ligand. Therefore, the poor enantioselectivity-giving issue of substrate **2.21a** is probably due to a mismatch between the bulky chiral ligand and the hindered 1,1,2-trisubstituted enol ether skeleton. However, smaller ligand such as DHQ-PHN was able to moderately prevent this steric clash and allowed the reaction to proceed in good yield with a better enantioselectivity.

In an effort to further optimise these results, a larger enol ether moiety was synthesised to access better enantioselectivities. The synthesis and the Sharpless catalytic asymmetric dihydroxylation of a TIPS enol ether derivative was investigated.

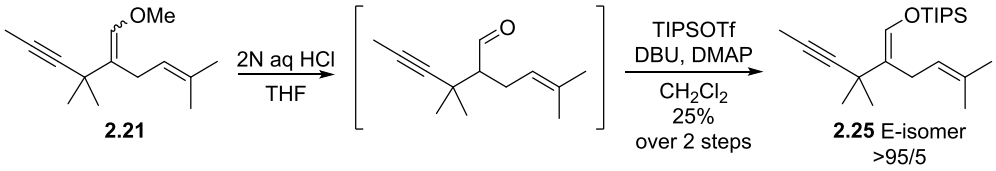
2.4.4 Preparation of TIPS Enol Ether and Asymmetric Dihydroxylation

The Wittig-Horner reaction, which gave the best results for the preparation of the methoxy enol ethers **2.21**, was tried using the TIPS derived phosphine oxide reagent. Under the conditions previously optimised, the reaction did not proceed and the corresponding TIPS protected phosphine oxide derivative could not be synthesised (Scheme 2.42). The starting material **2.7** was fully recovered and a complete degradation of the TIPS phosphine oxide was observed.



Scheme 2.42: TIPS enol ether formation attempt

Following this unwanted result due to the low reactivity of ketone **2.7**, the TIPS enol ether **2.25** generation by homologation was abandoned. Instead, hydrolysis of previously made methoxy enol ethers **2.21** was tried. So methoxy enol ethers **2.21** were treated with an aqueous solution of HCl in THF and the crude aldehyde was treated with TIPSOTf in the presence of DBU and DMAP in dichloromethane to produce the TIPS enol ether *E*-isomer **2.25** in 25% yield over 2 steps in a >95:5 *E/Z* ratio (Scheme 2.43).[73]

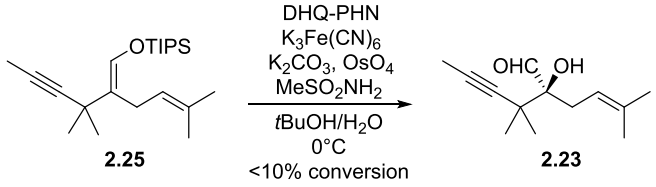


*Scheme 2.43: TIPS enol ether **2.25** formation*

Despite this low yield, enough TIPS enol ether **2.25** was synthesised to try a dihydroxylation reaction. Unfortunately, even after 24 hours of reaction less than 10% of conversion occurred. The substrate **2.25** was too hindered for the reaction to proceed.

[73] Gao, Z. H.; Liu, B.; Li, D.-D. Z. *Tetrahedron* **2005**, *61*, 10734-10737.

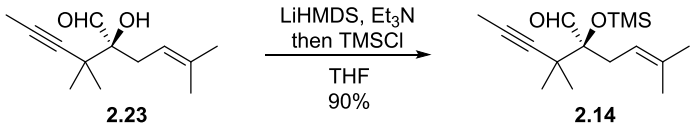
Sadly not enough product was synthesised to determine any enantioselectivity (Scheme 2.44).



*Scheme 2.44: Sharpless reaction on TIPS enol ether **2.25***

2.4.5 Enantio-Enriched Fragment A Synthesis: End-Game

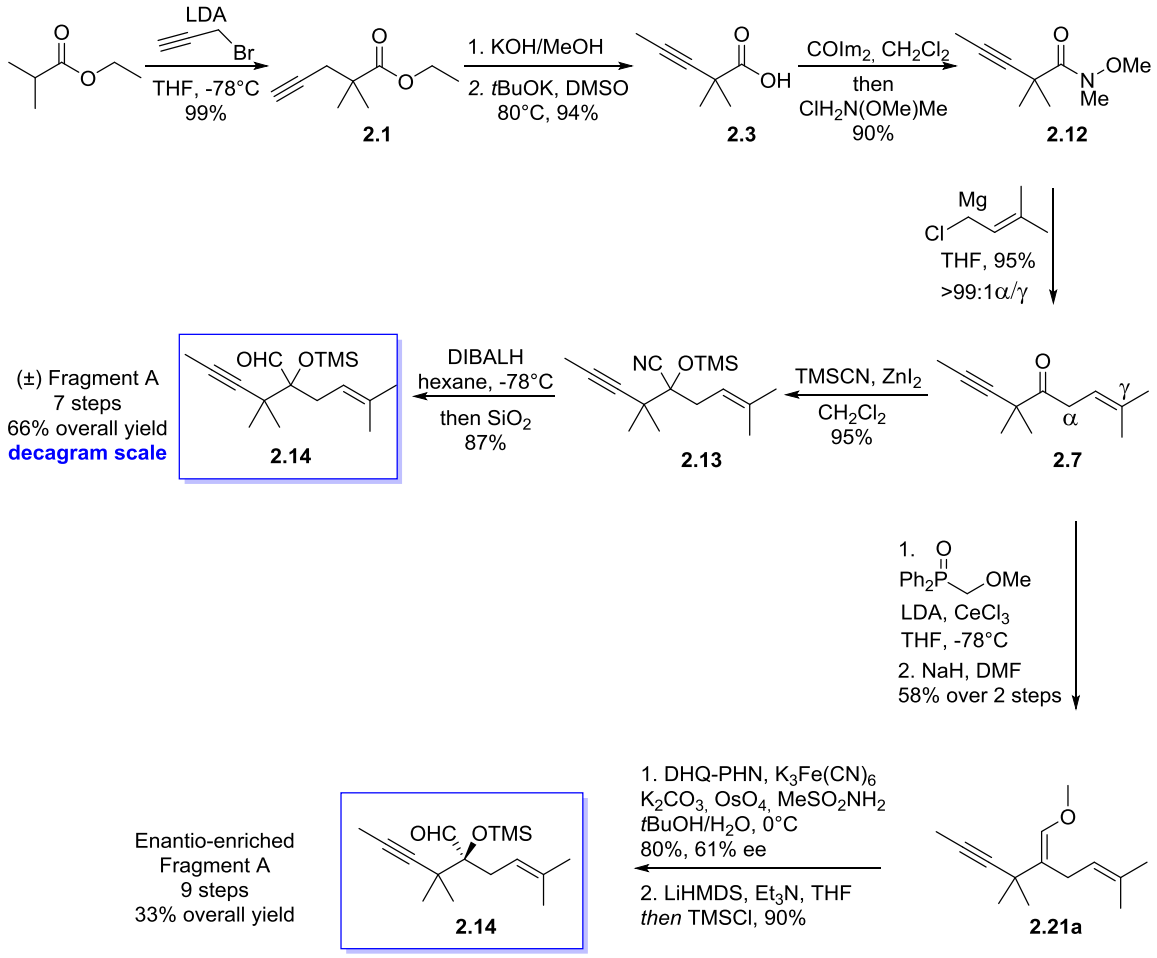
Finally, enantio-enriched fragment A **2.14** was obtained by protection of the tertiary alcohol **2.23** using rather harsh conditions. LiHMDS was used to deprotonate the alcohol and generate a more nucleophilic corresponding alkoxide, which was quenched with TMSCl and Et_3N in 90% yield. Without the strong LiHMDS base, the tertiary alcohol could not be protected (Scheme 2.45).



*Scheme 2.45: Formation of enantio-enriched fragment A **2.14***

2.5 Summary of the Fragment A Synthesis

In summary, racemic (±)-**2.14** and enantio-enriched fragments A **2.14** were divergently synthesised in 7 steps in 66% overall yield and 9 steps in 33% overall yield, respectively. The enantio-enriched fragment A **2.14** was synthesised in 61% ee. This enantiopurity was sufficient for our purposes since the two diastereomers generated by the Shapiro coupling can be separated. Both fragments A were efficiently synthesised even though a more elaborated synthesis had to be prepared to synthesise the enantio-enriched α-hydroxy aldehyde, as illustrated in Scheme 2.46.



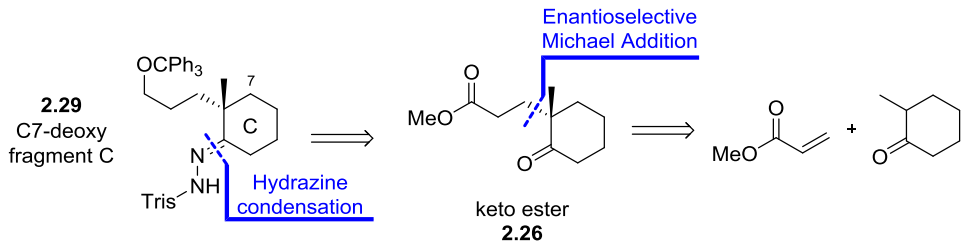
Scheme 2.46: Synthesis of racemic and enantioenriched fragment A

2.6 Synthesis of C7-Deoxy Fragment C

The synthesis of C7-deoxy fragment C is known and has already been published by the Prunet group.[35]

2.6.1 Retrosynthesis

Fragment C **2.29** can be obtained from keto ester **2.26** using a reduction-oxidation sequence, which can be easily made by an enantioselective Michael addition from 2-methylcyclohexane (Scheme 2.47).

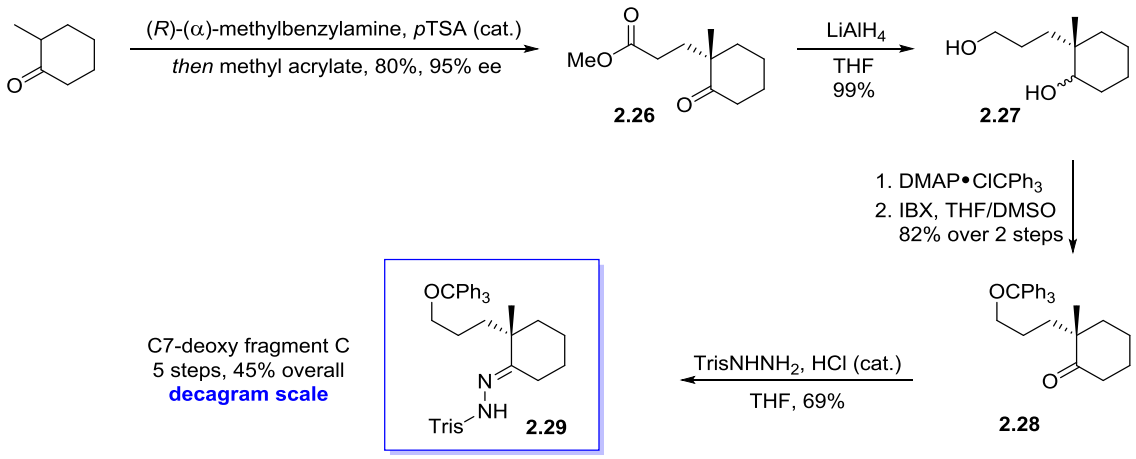


Scheme 2.47: Retrosynthesis of fragment C

2.6.2 Synthesis of C7-deoxy fragment C

The synthesis of optically active hydrazone **2.29** illustrated in Scheme 2.48, began with 2-methylcyclohexanone, which underwent an enantioselective Michael addition using enantiopure (*R*)-α-methylbenzylamine and methyl acrylate according to d'Angelo's method.[74] Then reduction of this newly synthesised keto ester **2.26** using $LiAlH_4$ afforded the known diol **2.27** as 1:1 mixture of diastereomers. The primary alcohol function was then selectively protected as a bulky triphenylmethyl ether. The secondary hydroxyl group was oxidised using IBX in a mixture of DMSO/THF to yield ketone **2.28** in 82% over 2 steps. To the ketone was then condensed triisopropylbenzenesulfonyl hydrazine in the presence of a catalytic amount of concentrated HCl to synthesise the corresponding C7-deoxy fragment C hydrazone **2.29** in 69% yield. The yield of the last step was disappointing compared to the reported 96% yield. During this final step, partial deprotection of the triphenylmethyl group occurred due to the catalytic amount of HCl essential to the hydrazone formation. Indeed, this protecting group is really sensitive to acidic media but also very unreactive toward highly basic conditions. This is the main reason why this protecting group was chosen as it needs to survive a few equivalents of *t*BuLi for the Shapiro coupling.

[74] Cavé, C.; Desmaële, D.; d'Angelo, J.; Riche, C.; Chiaroni, A. *J. Org. Chem.* **1996**, *61*, 4361-4368.



*Scheme 2.48: Enantioselective synthesis of hydrazone **2.29***

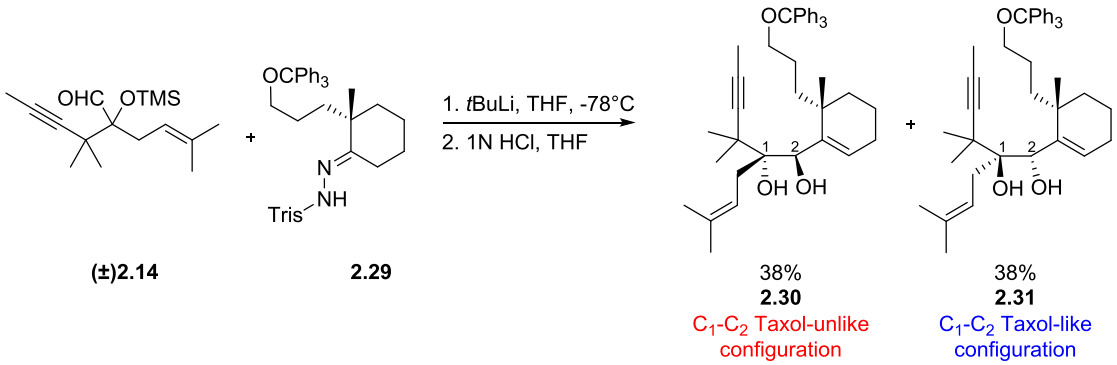
2.7 From Shapiro Products to Metathesis Precursors

As described previously, enantioenriched aldehyde **2.14** was prepared in 9 steps in 33% yield and its racemic version in 66% yield in 7 steps. Also, it had been observed for model aldehydes that the Shapiro coupling was a highly diastereoselective reaction.[75] Therefore, reaction between hydrazone **2.29** and racemic aldehyde **2.14** would only afford 2 diastereoisomers. Racemic aldehyde **2.14** was obtained in larger quantities and in a shorter amount of time, so it was decided to pursue the synthesis of the metathesis precursors with the racemic aldehyde **2.14** to study the influence of the C1-C2 stereochemistry of the precursors on the RCDEYM reaction outcome.

2.7.1 Shapiro Reaction

As shown in Scheme 2.49, hydrazone **2.29** was reacted with *t*BuLi to generate the active vinyl lithium species that was condensed onto racemic aldehyde **2.14** using the conditions the Prunet group previously developed.[48,49] A 1:1 ratio of diastereomeric, C1-C2 diols **2.30** and **2.31** was synthesised in 76% yield as a separable mixture after hydrolysis of the trimethylsilyl ether protecting group under acidic conditions.

[75] Bourgeois, D.; Maiti, G.; Pancrazi, A.; Prunet, J. *Synlett* **2000**, 323-326.



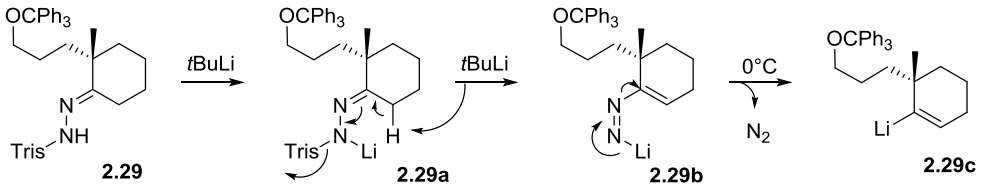
(±)2.14 **2.29**

38% **2.30** C_1-C_2 Taxol-unlike configuration

38% **2.31** C_1-C_2 Taxol-like configuration

*Scheme 2.49: Shapiro coupling using racemic fragment A **2.14** and hydrazone **2.29***

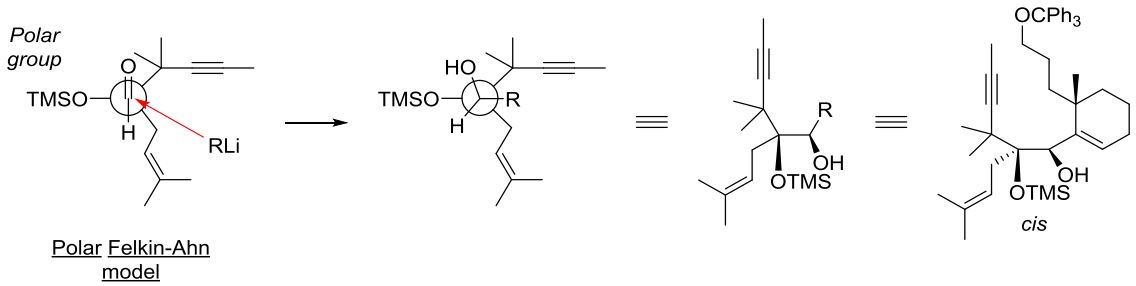
The formation mechanism of the active lithiated species formation is described in Scheme 2.50. The first equivalent of *t*BuLi abstracts the most acidic proton source located onto the hydrazone **2.29** to generate the first lithium salt **2.29a**. A second equivalent of *t*BuLi deprotonates the hydrogen in the α-position of the hydrazone, which leads to the elimination of the sulfinate anion to furnish **2.29b.** This intermediate **2.29b** is stable at low temperature and when the reaction mixture is warmed up to 0°C, an equivalent of nitrogen gas is released and the active vinyl lithium species **2.29c** is generated.



2.29 **2.29a** **2.29b** **2.29c**

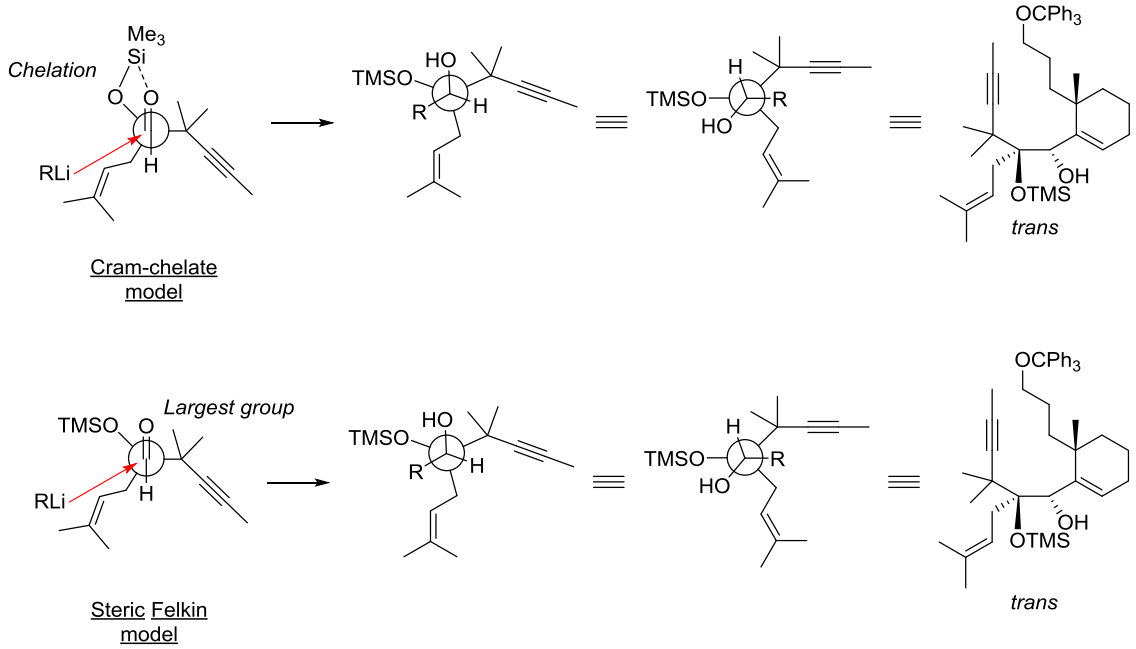
Scheme 2.50: Mechanism of the vinyl lithium intermediate formation

To understand the origin of the diastereoselectivity of the Shapiro coupling under these conditions, a few transition models are examined. In the Felkin-Ahn model, the siloxy moiety (most polar group) is orthogonal to the carbonyl group in the most reactive conformation. This conformation would allow the lithiated nucleophile to attack opposite to the TMS protecting group and form the unobserved *cis* product. Therefore, the Felkin-Ahn model cannot be invoked to explain the experimental results (Scheme 2.51).



Scheme 2.51: Felkin-Ahn model

To obtain the *trans* diol a Cram-chelate model could be involved, as there could be a complexation between the TMS group and the aldehyde group, but such a complexation is unlikely. Another possibility is that the formation of the *trans* product can be explained by a steric Felkin model. The largest group, which contains the *gem*-dimethyl moiety is positioned perpendicularly to the aldehyde and leads to a similar transition state to the one suggested by the Cram-chelate model. These models would give the *trans* product as explained in Scheme 2.52.

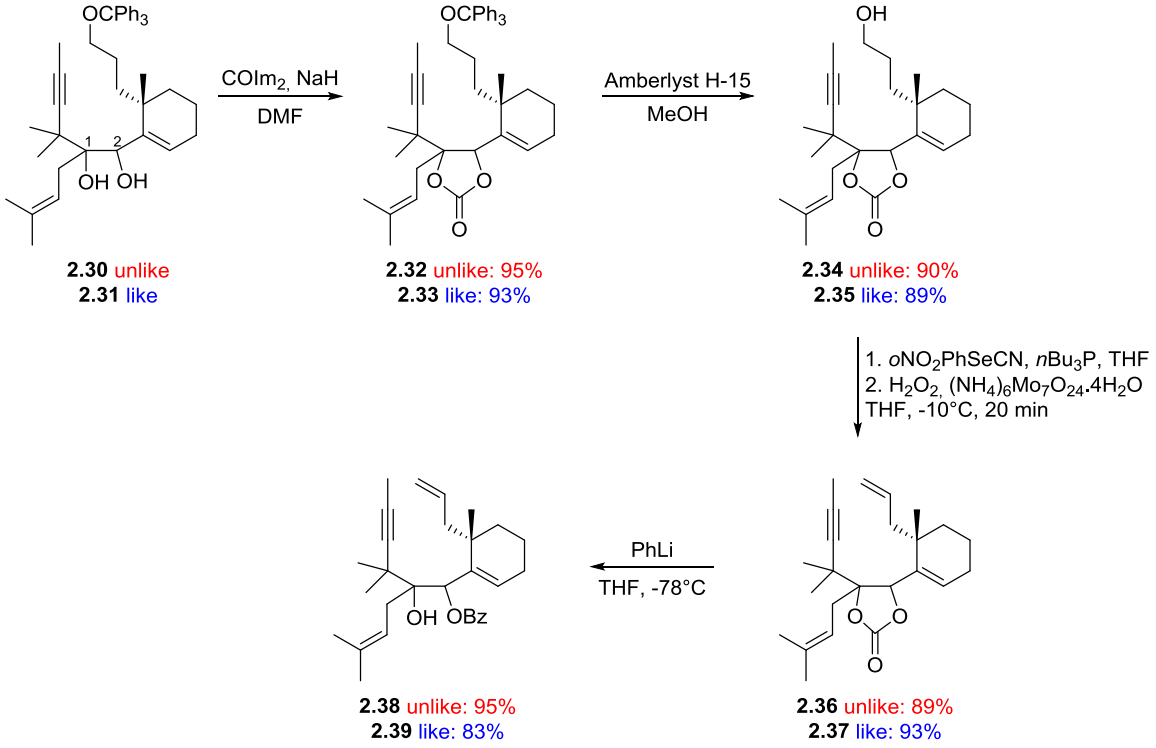


Scheme 2.52: Cram-chelate and steric Felkin models

2.7.2 Metathesis Precursor Synthesis

As shown in Scheme 2.53, these C1-C2 Taxol-unlike/like diols **2.30** and **2.31** were separately submitted to the protection of the C1-C2 diol as cyclic carbonates. Treatment of

diols **2.30** and **2.31** with sodium hydride and carbonyl diimidazole in DMF easily generated the C1-C2 Taxol-unlike carbonate **2.32** in 95% yield and its Taxol-like counterpart **2.33** in 93% yield, respectively. Hydrolysis of the triphenylmethyl ether using Amberlyst H-15, a sulfonic resin, furnished the Taxol-unlike primary alcohol **2.34** in 90% yield and the Taxol-like derivative **2.35** in 89% yield. These primary alcohols then underwent smooth dehydration following the Grieco protocol to furnish the metathesis precursors **2.36** and **2.37** in 89% and 93% yield, respectively.[76] As the Prunet group had previously shown that the nature of the C1-C2 diol protecting group plays a crucial role in the outcome of metathesis reactions, the carbonates **2.36** and **2.37** were converted to their corresponding benzoates **2.38** in 95% yield and **2.39** in 83% yield by treatment with phenyllithium in THF at -78°C.



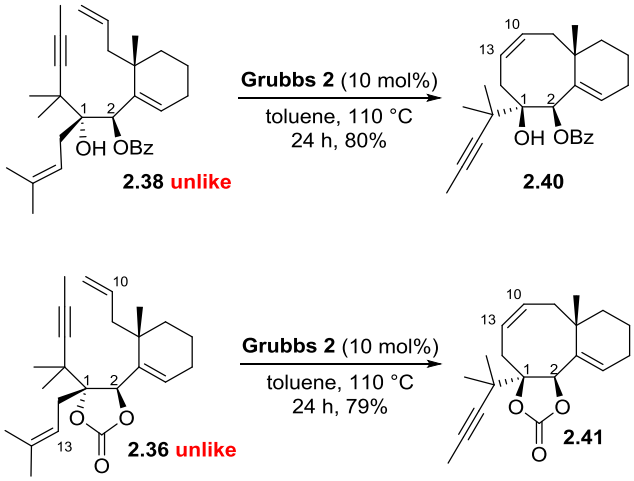
Scheme 2.53: Synthesis of metathesis precursors

[76] Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem*. **1976**, *41*, 1485-1486.

2.8 Ring-Closing Dienyne Metathesis

2.8.1 C1-C2 Taxol-Unlike Configuration

The key metathesis step was then studied. The C1-C2 Taxol-unlike benzoate **2.38** was submitted to the metathesis conditions with 10 mol% of Grubbs' second-generation catalyst in refluxing toluene and led to the formation of bicyclic ring system **2.40** in 80% yield. When carbonate **2.36** was treated with the same conditions, bicycle **3.41** was synthesised in 79% yield (Scheme 2.54). Both products failed to produce the ABC tricyclic ring system of Taxol by dienyne metathesis. Instead they both resulted from a diene metathesis reaction between the olefins at C10 and C13. The steric hindrance around the alkyne might be disfavouring the initial ene-yne metathesis, as the opposite configuration at C1 and C2 for these substrates.



Scheme 2.54: Diene-yne metatheses attempts on C_1-C_2 Taxol-unlike precursors

An X-ray diffraction analysis (Figure 2.1) of the derivative **2.41** established the bicyclic structure of the product and confirmed that it possesses the undesired *cis* relationship between C1 and C2 for Taxol as well as its relative configuration at C1, C2 and C8.

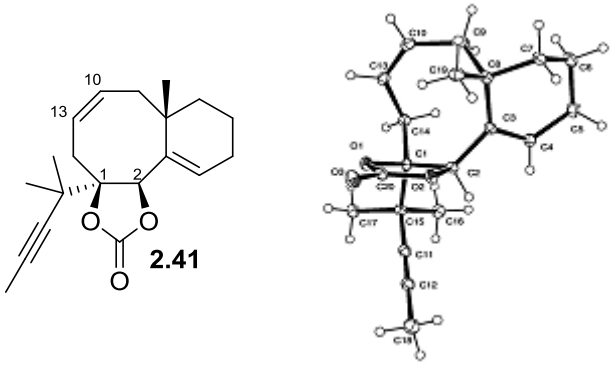
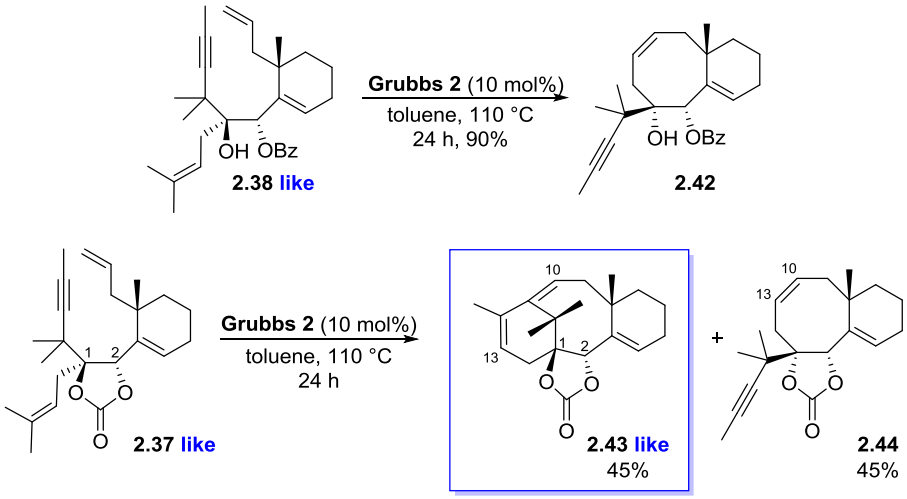


*Figure 2.1: X-ray analysis of **2.41***

2.8.2 C1-C2 Taxol-Like Configuration

When benzoate **2.39** was submitted to the same reaction conditions, it only led to the bicycle **2.42** in 90% yield, as it was observed for the C1-C2 unlike precursors. However, reaction of the C1-C2 Taxol-like carbonate **2.37** with 10 mol% of Grubbs' second-generation catalyst in toluene at reflux led to the desired tricyclic core of Taxol **2.43** in 45% yield, along with 45% of the diene metathesis product **2.44** (Scheme 2.55).

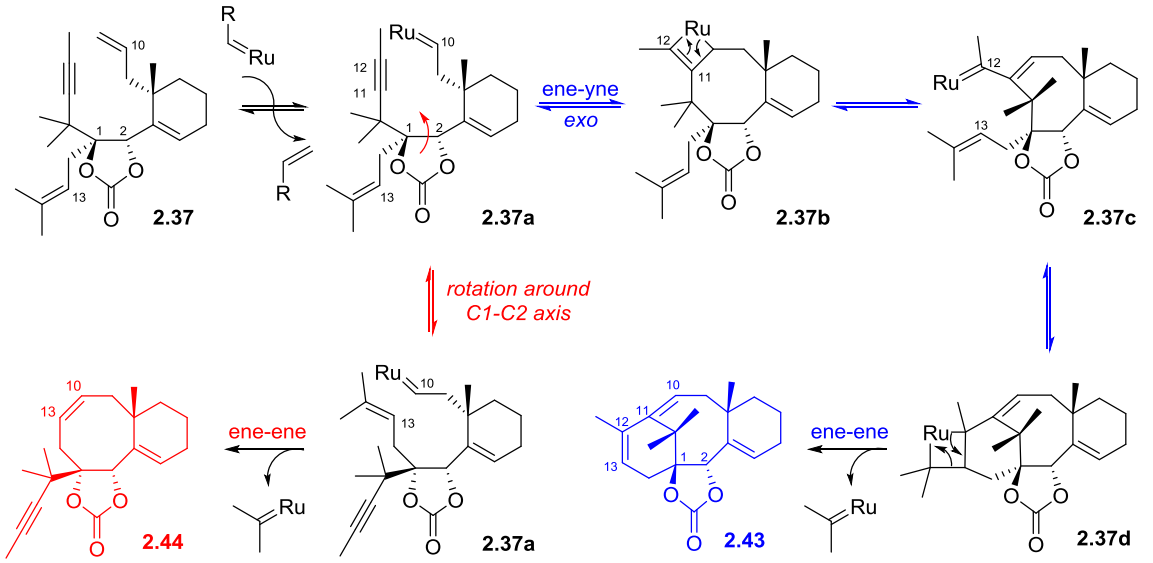


Scheme 2.55: Dienyne metatheses on C_1-C_2 Taxol-like precursors

From these experiments, it can be summarised that the C1-C2 Taxol-like configuration for the diol as well as the carbonate protecting group are essential for a successful metathesis cascade. Other metathesis precursors without these two prerequisites cannot generate the ABC tricyclic core of Taxol by dienyne metathesis.

2.8.3 Proposed Mechanism

In Scheme 2.56 is illustrated a proposed mechanism for the formation of tricycle **2.43** and bicycle **2.44**. First, the most accessible carbene **2.37a** would be generated upon reaction of the active catalyst at the C10 terminal olefin. It is interesting to note that a few studies support the evidence that second-generation catalysts favour alkynes over alkenes. In our case, the hindrance around the alkyne highly disfavours this affinity.[77] From this point, two different intramolecular pathways diverge. The first of the two pathways would be a rotation around the C1-C2 axis to place closer in space the C10 carbene and C13 olefin, which would undergo a ring-closing metathesis and form the undesired bicycle **2.44**. In the second pathway the C10 carbene **2.37a** would undergo an *exo* ene-yne metathesis with hindered alkyne to access the metallacyclobutene **2.37b** that would cycloreverse and generate the vinyl carbene **2.37c.** Another [2+2] cycloaddition and cycloreversion sequence with the C13 olefin would generate the AB ring system in a single operation and produce the tricycle **2.43**.

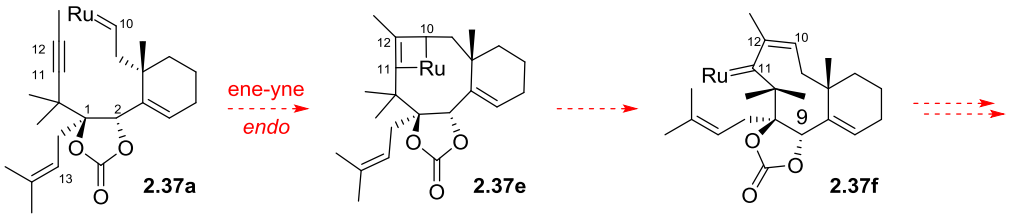


*Scheme 2.56: Proposed mechanism for the formation of both tricycle **2.43** and bicycle **2.44***

It is interesting to highlight that no product issued from another intramolecular ene-yne metathesis pathway was observed.[78] Indeed, an *endo* ene-yne metathesis would

[77] Kim, K. H.; Ok, T.; Lee, K.; Lee, H.-S.; Chang, K. T.; Ihee, H.; Sohn, J.-H. *J. Am. Chem. Soc.* **2010**, *132*, 12027-12033. Wallace, D. J.; Reamer, R. A. *J. Org. Chem*. **2014**, *79*, 5644-5651.
[78] Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2003**, *125*, 9582-9583. Hansen, E. C.; Lee, D. *Acc. Chem. Res.* **2006**, *39*, 509-519.

generate a too strained and high in energy ruthenacyclobutene **2.37e**, so the formation of the C11 ruthenocarbene **2.37f** would be too demanding. Therefore no *endo* ene-yne 9-membered ring metathesis product was observed (Scheme 2.57).



Scheme 2.57: Unobserved endo ene-yne metathesis

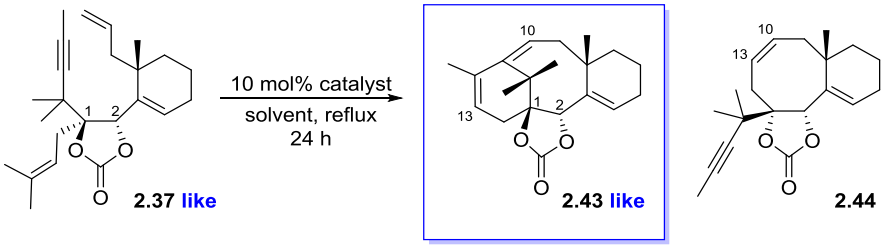
In summary, optimisation of this reaction is not trivial. Indeed, to favour the formation of tricycle **2.43,** the pathway leading to bicycle **2.44** has to be discriminated. Both pathways are intramolecular and the two products were synthesised in a 1:1 ratio during preliminary studies. Thus differentiating these two intramolecular pathways by only changing the reaction conditions without any structural change to the metathesis precursors seems to be challenging.

2.8.4 Metathesis Optimisation

Catalyst and solvent systems were then varied to optimise the yield of the tricyclic product **2.43** (Table 2.1). Unsurprisingly, switching the catalyst to Grubbs' first-generation complex did not lead to any metathesis reaction (entry 1 vs 2). When the Hoveyda-Grubbs 2 complex was used the yield of tricycle **2.43** increased to 59% along with 38% yield of bicycle **2.44** (entry 3). Grela's catalyst, which is a modified Hoveyda-Grubbs 2 catalyst bearing a nitro electron-withdrawing group on the benzylidene ligand, was employed.[79] With this catalyst similar results to those observed with the Hoveyda-Grubbs 2 catalyst were obtained, 55% and 45% yield of tricycle **2.43** and bicycle **2.44**, respectively (entry 4). Another modified Hoveyda-Grubbs 2 catalyst was then tested, the Zhan-1B complex, bearing a *N,N*-dimethyl sulfonamide electron-withdrawing group on the benzylidene ligand.[80] The tricycle **2.43** was obtained in 70% yield in that case along with 20% of the

[79] Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 4038-4040.
[80] Zhang, Z.-Y. J. U.S. Patent UP2007/0043180 A1.

bicycle **2.44** (entry 5). Changing the nature of the solvent and the reaction temperature while using the Zhan-1B catalyst did not bring any improvement (entries 6-9). The reaction did not proceed in refluxing dichloromethane (40°C), and only degradation was observed in refluxing *p*Xylene (140°C). Interestingly, the reaction proceeded faster in refluxing 1,2-dichloroethane (80 °C) than in toluene at the same temperature (entry 7 vs 9).



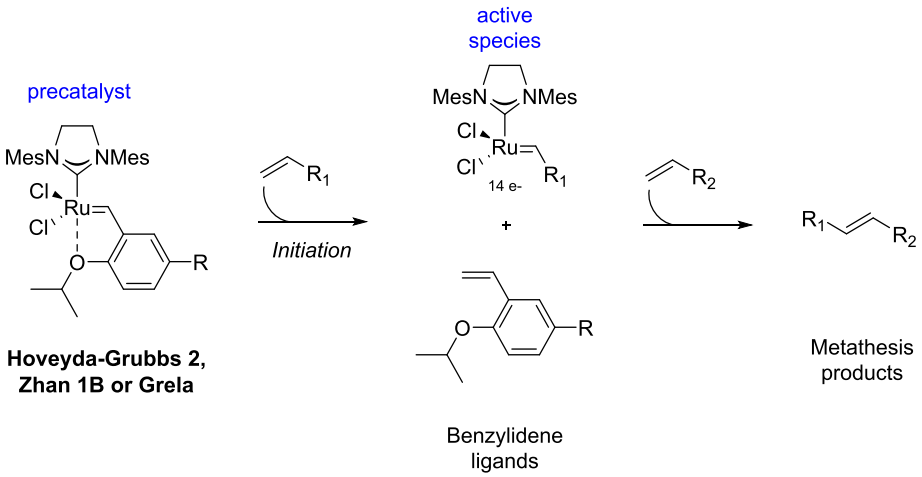
Entry	Catalyst	Solvent	Yield 2.43 (%)	Yield 2.44 (%)
1	Grubbs 1	toluene	0	0
2	Grubbs 2	toluene	45	45
3	Hoveyda- Grubbs 2	toluene	59	38
4	Grela	toluene	55	45
5	***Zhan-1B***	***toluene***	***70***	***20***
6	Zhan-1B	CH_2Cl_2	0	0
7	Zhan-1B	$Cl(C_2H_4)Cl$	65	34
8	Zhan-1B	*p*Xylene	Degradation	
9	Zhan-1B	Toluene, 80°C	40	10*

along with 40% of recovered **2.37*

Table 2.1: Dienyne metathesis optimisation

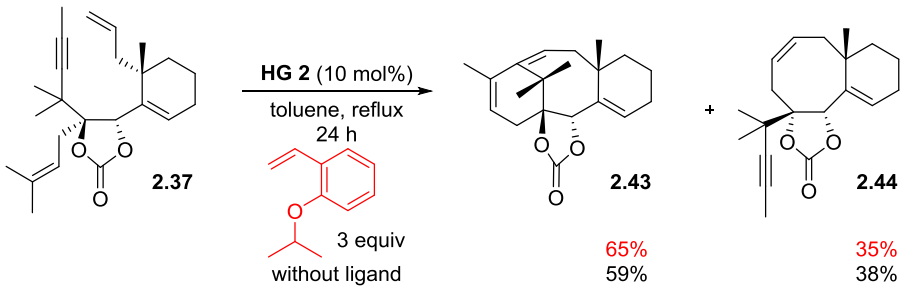
It is known that when electron-withdrawing groups such as $-NO_2$ (Grela) or $-SO_2NMe_2$ (Zhan-1B) are placed on these ligands, the initiation rate of the precatalyst is higher.[81] So these precatalysts are more reactive and efficient and this might explain the different reactivities in the ring-closing dienyne metathesis. The benzylidene ligands play an unclear role in this metathesis reaction since the active species derived from the Hoveyda-Grubbs 2 and modified Hoveyda-Grubbs 2 complexes are identical but give different metathesis outcomes (Scheme 2.58).

[81] Ashworth, I. W.; Hillier, I. H.; Nelson, D. J.; Percy J. M.; Vincent, M. A. *Chem. Commun*. **2011**, *47*, 5428-5430. Nelson, D. J.; Queval, P.; Rouen, M.; Magrez, M.; Toupet, L.; Caijo, F.; Borré, E.; Laurent, I.; Crévisy, C.; Baslé, O.; Mauduit, M.; Percy, J. M. *ACS Catal*. **2013**, *3*, 259-264.



Scheme 2.58: Generation of active metathesis species

To investigate the role of these ligands during the metathesis reaction, we developed reaction conditions in which a stoichiometric quantity of precatalyst benzylidene ligand would be added along with 10 mol% of the metathesis precatalyst. The Hoveyda-Grubbs 2 precatalyst was chosen due to the availability of its benzylidene ligand. Modified Hoveyda-Grubbs 2 catalysts possess more elaborated benzylidene ligands, which are not commercially available. Metathesis precursor **2.37** was treated with 10 mol% of the Hoveyda-Grubbs 2 catalyst, with or without extra benzylidene ligand, in refluxing toluene for 24 hours. It finally appeared that the ligand had very little influence on the metathesis outcome. In the presence of the ligand, the tricycle **2.43** was synthesised in 65% instead of 59% while the bicycle **2.44** was obtained in 35% compared to 38% without ligand. With no clear evidence of the efficiency or role of the benzylidene ligand on the metathesis results, no test with the Zhan-1B sulfonamide benzylidene ligand was performed (Scheme 3.27).



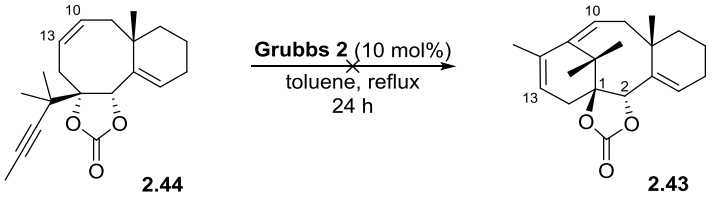
Scheme 2.59: Effect on Hoveyda-Grubbs 2 benzylidene ligand

The reasons why modified Hoveyda-Grubbs 2 precatalysts favoured the formation of the ABC tricyclic core of Taxol **2.43** remains unexplained. The precatalysts behaviour

tended to indicate that when precatalysts possess higher initiation rates, the dienyne metathesis cascade is favoured.

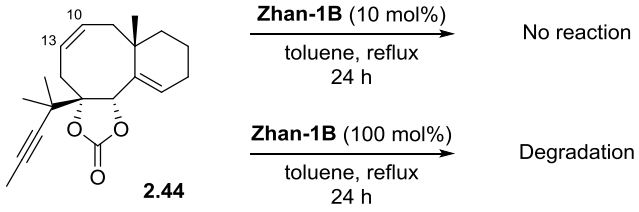
2.8.5 Side Product Recycling

Conversion of bicycle **2.44** to tricycle **2.43** was also attempted. When this side product was re-submitted to the metathesis conditions, no conversion to tricyclic product occurred. This result seems to indicate that the formation of compound **2.44** is not reversible under the reaction conditions (Scheme 2.60).



*Scheme 2.60: Conversion to tricycle **2.43** attempt*

When the Grubbs' second-generation catalyst was switched to the Zhan-1B catalyst, no reaction occurred. When the quantity of catalyst was increased to 100 mol%, no conversion to tricycle **2.43** occurred and only degradation was observed as shown in Scheme 2.61.

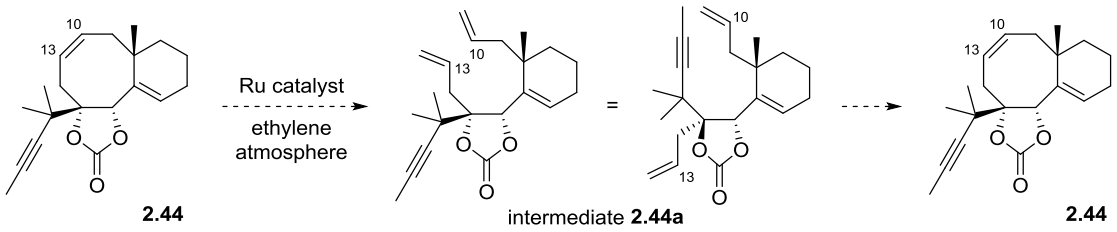


*Scheme 2.61: Attempted conversion to tricycle **2.43** using Zhan-1B catalyst*

It seems that Grubbs' second-generation and Zhan-1B precatalysts cannot perform any ring-opening metathesis on the bicycle **2.44** under the reaction conditions.

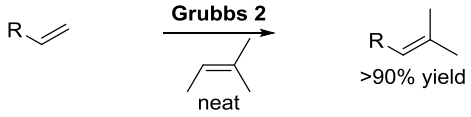
It is important to note that the conversion of bicycle **2.44** into the tricycle **2.43** under an atmosphere of ethylene cannot be successful. Indeed, if **2.44** was treated with a

metathesis catalyst under an ethylene atmosphere, intermediate **2.44a** would be formed by ring-opening metathesis. As exemplified by Rémi Aouzal results,[49] intermediate **2.44a** cannot produce the ABC tricyclic core of Taxol, it would only reform the undesired bicycle **2.44** (Scheme 2.62).



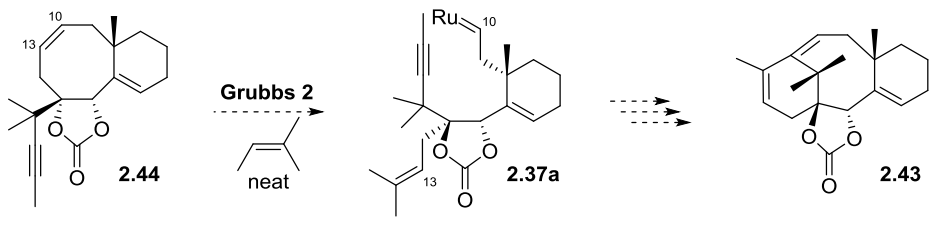
Scheme 2.62: Ring-opening metathesis under an ethylene atmosphere

To override this issue, it was decided to use 2-methyl-2-butene in our reaction.[82] Originally 2-methyl-2-butene was used by Grubbs and co-workers to generate trisubstituted olefins from their terminal homologues in high yield as illustrated in Scheme 2.63.



Scheme 2.63: Generation of trisubstituted olefin by cross metathesis

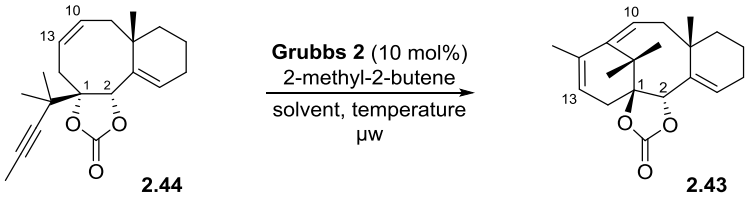
The generation of an essential intermediate carbene, such as **2.37a**, for the ring-closing dienyne metathesis reaction, from the bicycle **2.44** was crucial (Scheme 2.56). 2-methyl-2-butene would be added to the reaction mixture to generate the intermediate **2.37a** by a ring-opening metathesis of the C10-C13 olefin of bicycle **2.44**. This intermediate carbene **2.37a** could then produce the tricycle **2.43** (Scheme 2.64).



*Scheme 2.64: Bicycle **2.44** recycling*

[82] Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett*. **2002**, *4*, 1939-1942.

In Table 2.2 is shown different isomerisation attempts of bicycle **2.44** with 2-methyl-2-butene. When bicycle **2.44** was treated neat with 10 mol% of Grubbs's second-generation catalyst and 2-methyl-2-butene at room temperature, no ring-opening metathesis reaction occurred (entry 1). Increasing the temperature to 40°C did not lead to any improvement (entry 2) nor running the reaction in refluxing toluene (entry 3). Bicycle **2.44** was also treated with 10 mol% of Grubbs's second-generation catalyst in toluene at 110°C under microwave irradiation with 2-methyl-2-butene, but this time again no reaction occurred (entry 4).

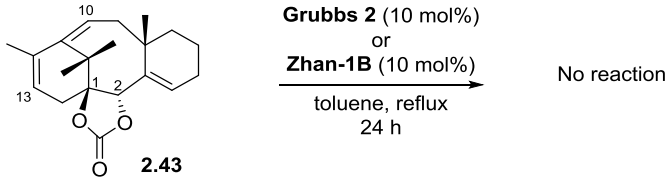


Entry	Solvent	Temperature	μw	Result
1	neat	20°C	No	No reaction
2	neat	40°C	No	No reaction
3	toluene	110°C	No	No reaction
4	toluene	110°C	Yes	No reaction

Table 2.2: Isomerisation attempts

In summary, bicycle **2.44** could not generate the desired intermediate **2.37a** by ring-opening metathesis. Unfortunately, even when 2-methyl-2-butene was added to the reaction mixture, no reaction seemed to occur.

Finally, the stability of the tricycle compound **2.43** under the metathesis condition was also investigated. So the tricycle **2.43** was treated with either 10 mol% of Grubbs's second-generation catalyst or Zhan-1B in refluxing toluene. Gratifyingly, no degradation seemed to occur, nor any conversion to bicycle **2.44** as shown in Scheme 2.65.

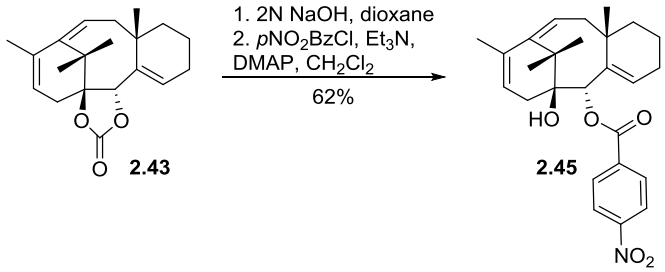


*Scheme 2.65: Tricycle **2.43** isomerisation attempts*

In the light of these results, it seems that bicycle **2.44** and tricycle **2.43** are not part of an equilibrium since no reaction conditions tended to equilibrate one into the other.

2.8.6 X-Ray Analysis

To establish a definite proof of the 6-8-6 taxoid skeleton formation by dienyne ring-closing metathesis, the carbonate **2.43** was hydrolysed under basic conditions. The C2 hydroxyl was treated with *p*-nitrobenzoyl chloride, triethylamine and DMAP in dichloromethane to produce the sensitive crystalline *p*-nitrobenzoylated derivative **2.45** in 62% yield over 2 steps as shown in Scheme 2.66.



*Scheme 2.66: Synthesis of pNO$_2$ benzoate derivative **2.45***

An X-ray diffraction analysis (Figure 2.2) of the derivative **2.45** established the tricyclic structure of the product and confirmed that it possesses the required relative configuration at C1, C2 and C8 for Taxol.

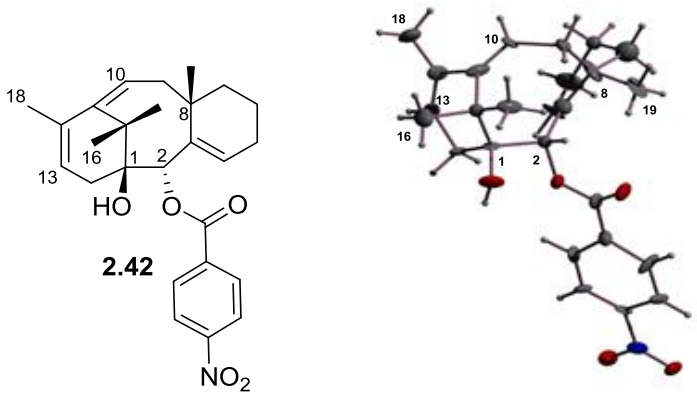
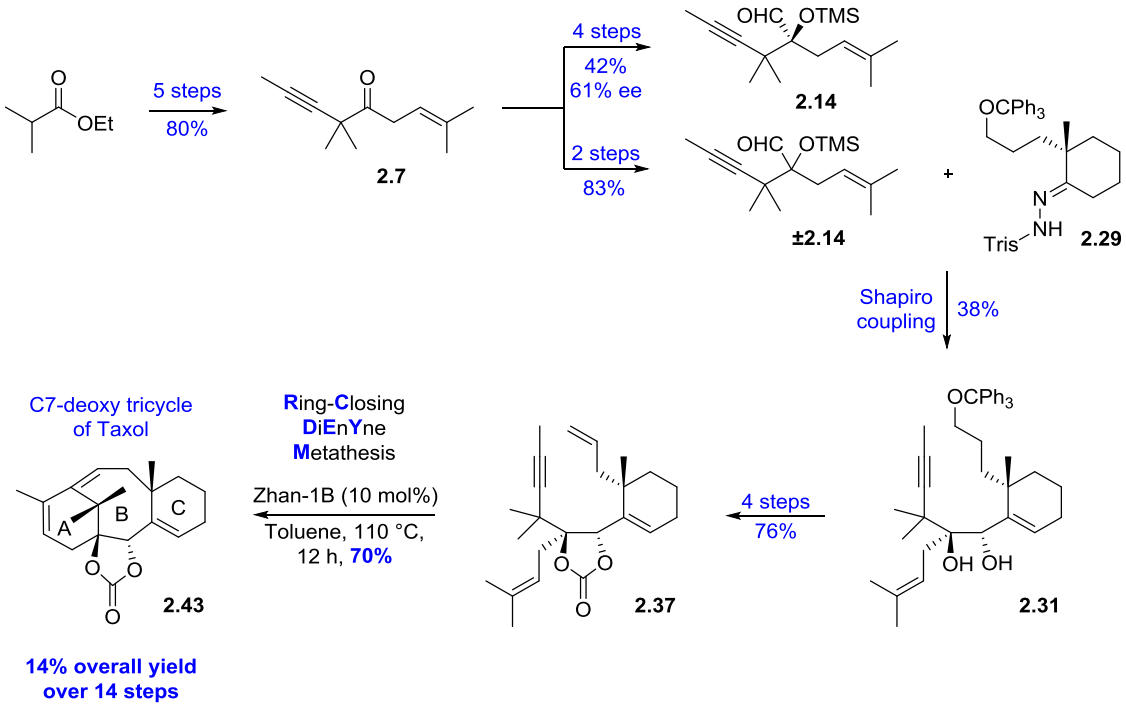


*Figure 2.2: X-ray analysis of **2.45***

2.9 Conclusion

Both racemic and enantio-enriched aldehydes **2.14** were synthesised from ketone **2.7**. Shapiro coupling of (±)-**2.14** with hydrazone **2.29** afforded diols **2.30** and **2.31** that were efficiently transformed to four different metathesis precursors, with different C1-C2 configurations and diol protecting groups. All these precursors underwent metathesis reactions. Only one precursor bearing the essential C1-C2 Taxol-like configuration and the cyclic carbonate diol protecting group **2.37** produced the desired tricycle **2.43**. The ring-closing dienyne metathesis cascade step allowed to close the A and B rings in a single operation to generate the C7-deoxy ABC tricyclic core of Taxol **2.43** in 70% yield. In summary, the C7-deoxy ABC tricyclic core of Taxol has been successfully and efficiently synthesised in 14 steps with an overall yield of 14% as illustrated in Scheme 2.67.



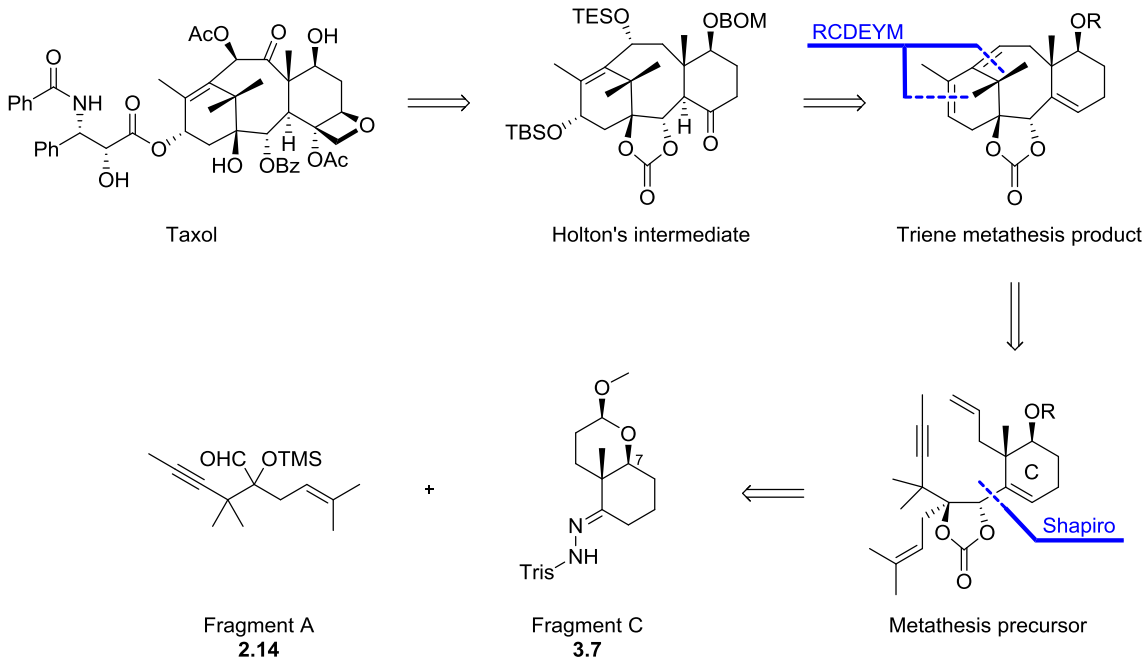
Scheme 2.67: Synthesis summary of the C7-deoxy ABC tricyclic core of Taxol

To apply this efficient strategy to a robust synthesis of Taxol, a C7-oxy fragment C had to be synthesised, followed by Shapiro coupling of both fragment A and C7-oxy fragment C to access the metathesis precursor. We would then need to perform the dienyne closing step and finally install the oxygenated functions from the three alkenes present in the tricyclic core of the metathesis product.

3. Synthesis of the ABC Tricyclic Core of Taxol

3.1 Retrosynthesis

After developing a robust route to the ABC ring system of Taxol in a single operation by ring-closing dienyne metathesis, we aimed to apply this strategy to elaborate a short and concise formal synthesis of Taxol based on Holton's synthesis.[20] Our retrosynthetic analysis involves an intermediate that Holton and co-workers had previously synthesised and could be obtained by selective oxidations of the triolefinic compound. This triene derivative can be synthesised by our previously developed ring-closing dienyne metathesis cascade from a carefully tuned metathesis precursor that can be generated from a Shapiro coupling reaction. The Shapiro coupling can be performed using the previously synthesised aldehyde **2.14** and C7-oxygenated fragment C **3.7** (Scheme 3.1).

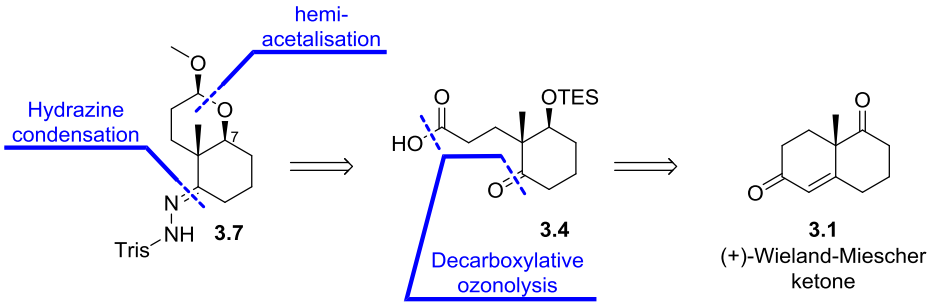


Scheme 3.1: Retrosynthesis using the dienyne metathesis strategy

3.2 Synthesis of Fragment C

3.2.1 Retrosynthesis

The C7-oxy fragment C we planned to use was previously synthesised by Cong Ma, a previous PhD student in the group.[48] The retrosynthesis he developed is shown in Scheme 3.2. The hydrazone required for the Shapiro coupling can be made by hydrazine condensation and acetalisation from a keto acid derivative. This keto acid can be obtained from the known (+)-Wieland-Miescher ketone by diastereoselective reduction and decarboxylative ozonolysis.



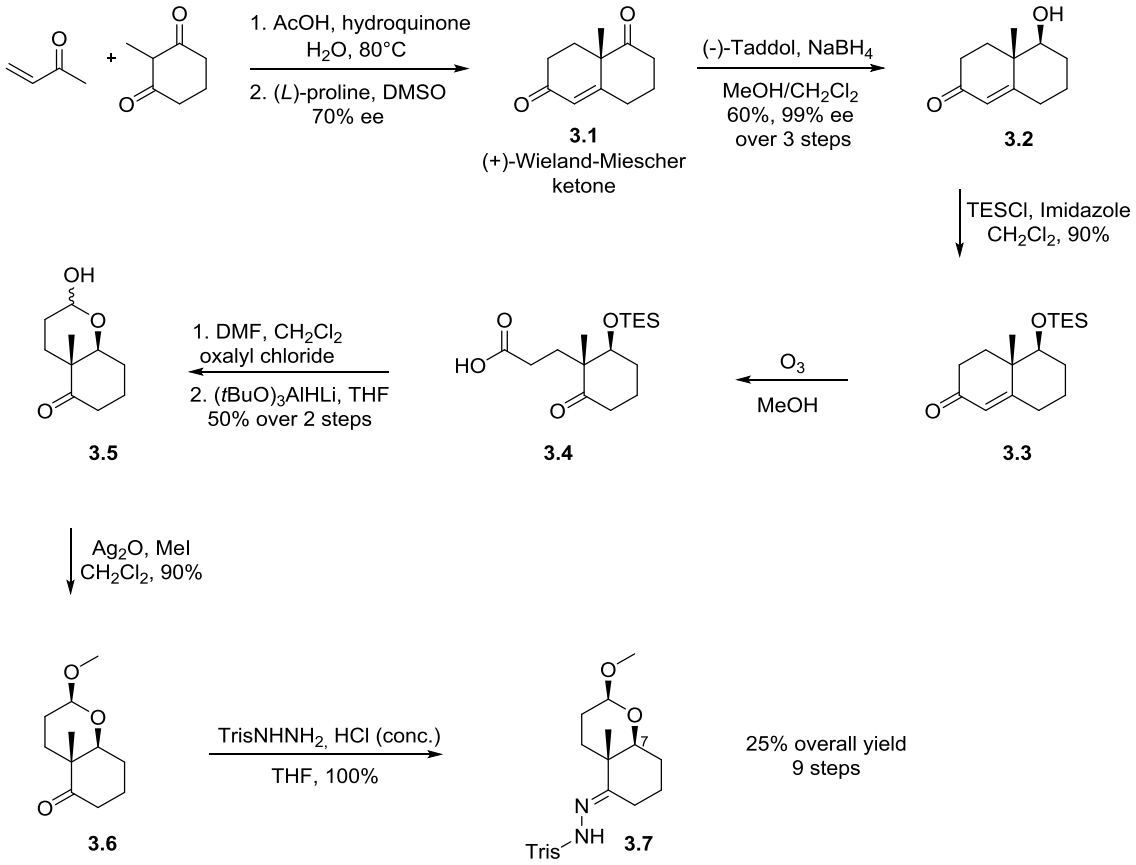
Scheme 3.2: Retrosynthesis of fragment C

3.2.2 Previous Synthesis

The first step of the synthesis of Cong Ma, is a Michael addition between 2-methyl-1,3-cyclohexanedione and methyl vinyl ketone followed by a (*L*)-proline-catalysed Robinson annulation to form the (+)-Wieland-Miescher ketone **3.1** using the Hajos-Parrish reaction conditions.[83] This ketone was then selectively reduced using a stoichiometric equivalent of (−)-Taddol and sodium borohydride, which allowed only the major enantiomer to be reduced. The minor enantiomer underwent decomposition under these conditions.[84] The resulting alcohol **3.2** was synthesised in 60% yield over 3 steps with an enantiomeric excess of 99%. The alcohol **3.2** was then protected using TESCl in 90% yield. This protected enone **3.3** was dissolved in methanol and treated with a stream of ozone at low temperature to furnish the acid derivative **3.4**. Selective carboxylic acid **3.4** reduction

[83] Hajos, Z. G.; Parrish, D. R. *J. Org. Chem*. **1974**, *39*, 1615-1621.
[84] Toda, F.; Kiyoshige, K.; Yagi, M. *Angew. Chem. Int. Ed. Engl*. **1989**, *28*, 320-321.

using Vilsmeier-Haack reagent followed by addition of lithium tri-*t*butoxyaluminium hydride afforded the hemiacetal **3.5** in 50% over 2 steps.[85] Purdie methylation afforded methyl acetal **3.6** in 90% yield as a single diastereomer. Finally the hydrazone **3.7** was synthesised using triisopropylbenzenesulfonyl hydrazide and a catalytic amount of aqueous HCl (conc.) in THF, to quantitatively yield ring C **3.7**. (Scheme 3.3)



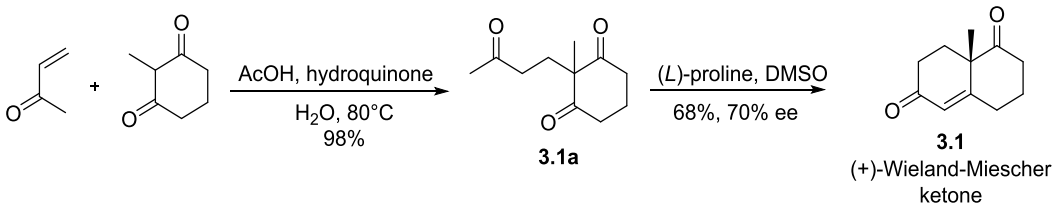
Scheme 3.3: Synthesis of fragment C by Cong Ma

3.2.3 Ring C Synthesis

3.2.3.1 Synthesis of (+)-Wieland-Miescher Ketone

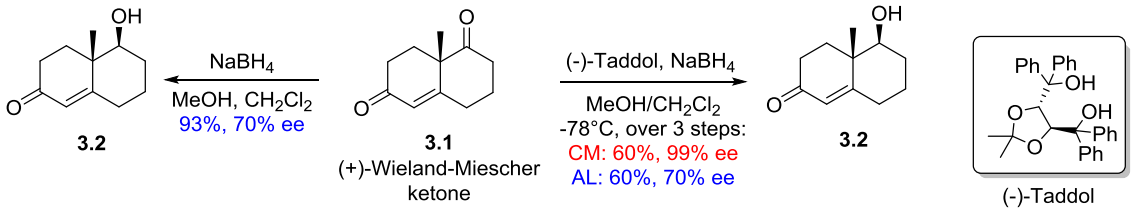
In an attempt to reproduce his results, *meso*-ketone **3.1a** was synthesised as stated above, followed by a (*L*)-proline Robinson annulation in DMSO that gave (+)-Wieland-Miescher ketone **3.1** in 68% yield and 70% ee (Scheme 3.4).[86]

[85] Felpin, F.-X.; Bertrand, M.-J.; Lebreton, J. *Tetrahedron* **2002**, *58*, 7381-7389.
[86] Enantioselectivity was determined by specific rotation of known compound **3.1**.



*Scheme 3.4: Synthesis of (+)-Wieland-Miescher ketone **3.1***

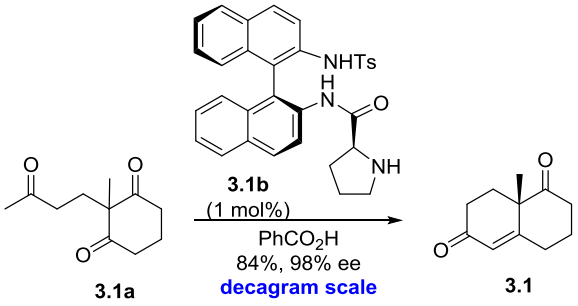
The (+)-Wieland-Miescher ketone **3.1** underwent a ketone reduction using (−)-Taddol and $NaBH_4$ at -78°C in a 1:1 ratio of methanol and CH_2Cl_2.[87] Unfortunately the corresponding alcohol **3.2** was synthesised in 60% yield and 70% ee over 3 steps, while Cong Ma obtained it in 99% ee. A counter experiment was set up without the Taddol chiral derivative, which appeared to show that the use of (−)-Taddol in this reaction was useless since alcohol **3.2** was synthesised in identical enantiomeric excess without (−)-Taddol (Scheme 3.5).[86]



*Scheme 3.5: Reduction of (+)-Wieland-Miescher ketone **3.1***

Enantiopure (+)-Wieland-Miescher ketone **3.1** was thus synthesised using different and more reliable conditions.[88] Bonjoch and co-workers developed a series of (*S*)-binam-(*L*)-prolinamide catalysts to synthesise Wieland-Miescher derivatives in high enantiomeric excess.[89] Using 1 mol% of *N*-tosyl-(*S*)-binam-(*L*)-prolinamide **3.1b** with 2.5 mol% of benzoic acid under neat conditions afforded (+)-Wieland-Miescher ketone **3.1** in 84% yield and 98% ee on a decagram scale (Scheme 3.6).[86]

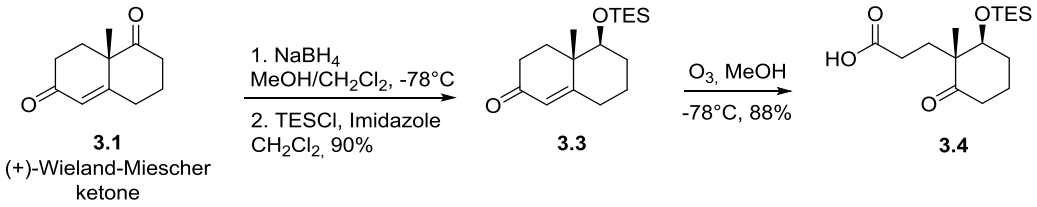
[87] Beck, A. K.; Gysi, P.; La Vecchia, L.; Seebach, D. *Org. Synth.* **1999**, *76*, 12-18.
[88] Viózquez, S. F.; Guillena, G.; Nájera, C.; Bradshaw, B.; Etxebarria-Jardi, G.; Bonjoch, J. *Organic Syntheses* **2011**, *88*, 317-329.
[89] Bradshaw, B.; Etxeberría-Jardí, G.; Bonjoch, J.; Guillena, G.; Nájera, C.; Viózquez, S. F. *Adv. Synth. Catal.* **2009**, *351*, 2482-2490. Guillena, G.; Ramón, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465-1492.



*Scheme 3.6: Synthesis of (+)-Wieland-Miescher ketone **3.1***

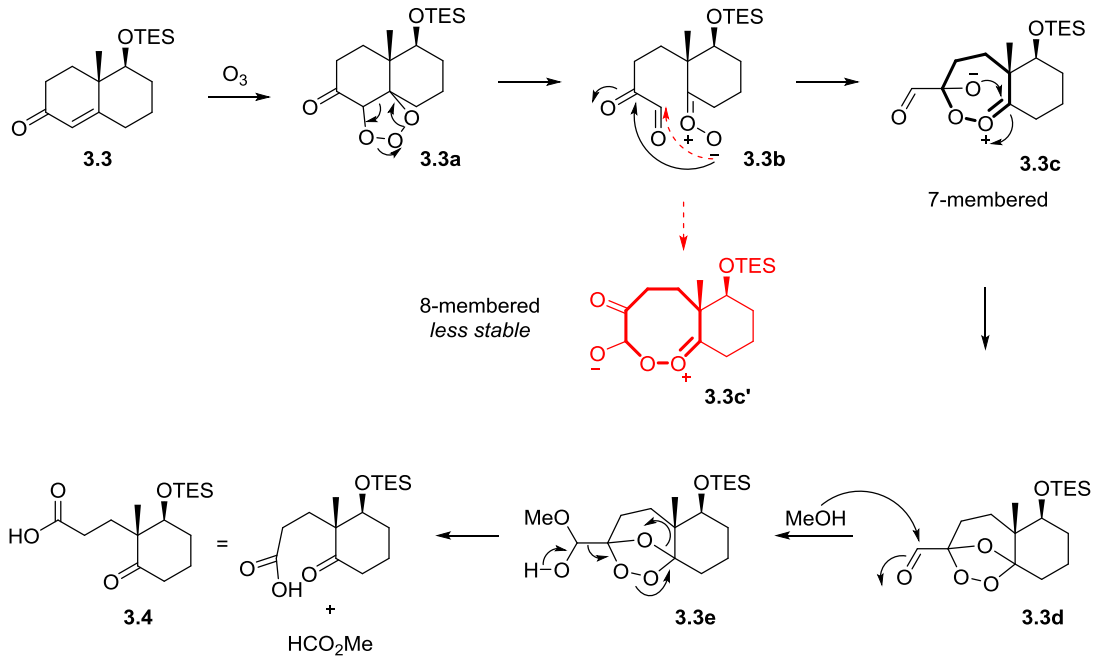
3.2.3.2 Decarboxylative Ozonolysis

Reduction of (+)-Wieland-Miescher ketone **3.1** using $NaBH_4$ in a 1:1 ratio of methanol and CH_2Cl_2 at -78°C, followed by TES protection of the newly formed hydroxyl group afforded **3.3** in 90% yield over 2 steps as a single diastereomer. Decarboxylative ozonolysis of enone **3.3** in dry methanol at -78°C for a few minutes yielded the keto acid derivative **3.4** in 88% yield (Scheme 3.7).



*Scheme 3.7: Synthesis of keto acid **3.4***

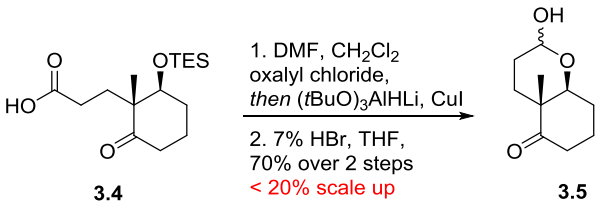
The first step of the proposed mechanism for this decarboxylative ozonolysis is a 1,3-dipolar cycloaddition of ozone onto the enone **3.3** leading to the primary ozonide **3.3a**. Decomposition of the 1,2,3-trioxolane results into the formation of both carbonyl oxide and α-oxo ketone moieties **3.3b**. Intramolecular attack of the carbonyl oxide to the ketone forms the 7-membered peroxide derivative **3.3c** and thus forms the secondary ozonide **3.3d**. It is proposed that the intramolecular formation of 8-membered derivative **3.3c'** is slower than its 7-membered homolog and would form a less stable secondary ozonide. Methanol as solvent then forms hemiacetal **3.3e** that collapses to generate the keto acid **3.4** and an equivalent of methyl formate, as shown in Scheme 3.8.



Scheme 3.8: *Decarboxylative ozonolysis mechanism of enone **3.3***

3.2.3.3 Selective Reductions

Selective reduction of the acid **3.4** using the Vilsmeier-Haack reagent, followed by acid-mediated deprotection yielded hemiacetal **3.5** in 70% on a 0.5 mmol scale. When the same reaction was attempted on a bigger scale, such as 5 mmol, it became impossible to obtain a yield above 20% as illustrated in Scheme 3.9.

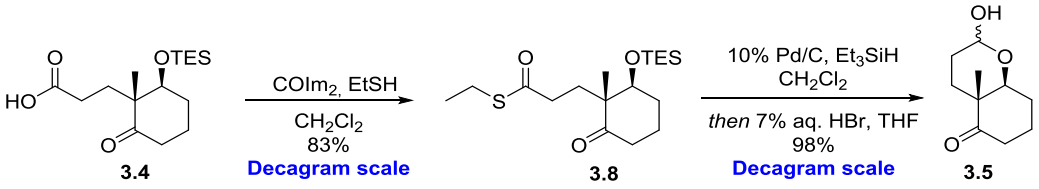


*Scheme 3.9: Reproduction of the synthesis of hemiacetal **3.5***

There are several synthetic routes for the synthesis of aldehydes from the corresponding acid derivatives. Of course, the most useful route involves a direct reduction of carboxylic acids by hydrogenation; however, high pressures and temperatures are required that make control of the chemoselectivity rather challenging.

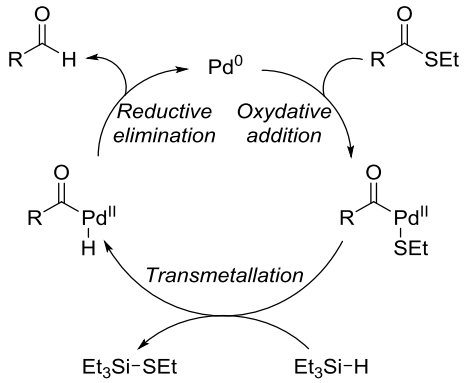
3.2.3.4 Fukuyama Reduction

It was then decided to use a Fukuyama reduction of the thioester derived from our substrate **3.4**.[90] The Fukuyama reduction is a mild alternative that offers good functional group tolerance compared to direct reductions of carboxylic acids or their derivatives using direct reductions. To prepare the substrate for the Fukuyama reduction, the keto acid **3.4** underwent thioesterification using carbonyl diimidazole and ethanethiol in CH_2Cl_2, which efficiently and easily furnished thioester **3.8** in 83% yield on a decagram scale. Then the thioester **3.8** underwent the stated above reduction using 10% Pd/C, triethylsilane in CH_2Cl_2 followed by treatment with an aqueous solution of 7% HBr in THF to deliver in a nearly quantitative yield hemiacetal **3.5** on a decagram scale (Scheme 3.10).



*Scheme 3.10: Synthesis of hemiacetal **3.5***

The mechanism of this reduction is described in Scheme 3.11. An initial oxidative addition of the C(sp^2)-SEt bond of the starting material to Pd(0) occurs to form the acylpalladium species, followed by transmetallation with Et_3SiH affords the acylpalladium hydride. Finally, the desired aldehyde is generated by reductive elimination of this palladium hydride species to produce Pd(0), which re-enters in the catalytic cycle.

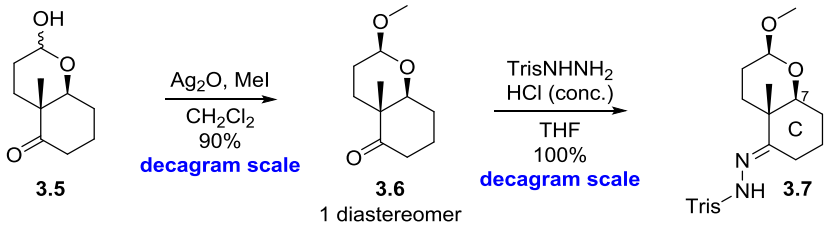


Scheme 3.11: Mechanism of the Fukuyama reduction

[90] Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Lin, S.-C.; Li, L.; Fukuyama, T. *J. Braz. Chem. Soc.*, **1998**, *9*, 381-387.

3.2.3.5 End-Game

Having now developed a robust route to access on a large scale the hemiacetal **3.5** under mild conditions, the ring C **3.7** was synthesised. Hemiacetal **3.5** was submitted to the Purdie methylation conditions using silver(I)oxide and methyl iodide in CH_2Cl_2 to synthesise the most stable diastereomer **3.6** in 90% yield.[91] The last step was the condensation of hydrazine onto the ketone with concentrated hydrochloric acid in THF, which afforded the hydrazone fragment C **3.7** in quantitative yield on a decagram scale (Scheme 3.12).

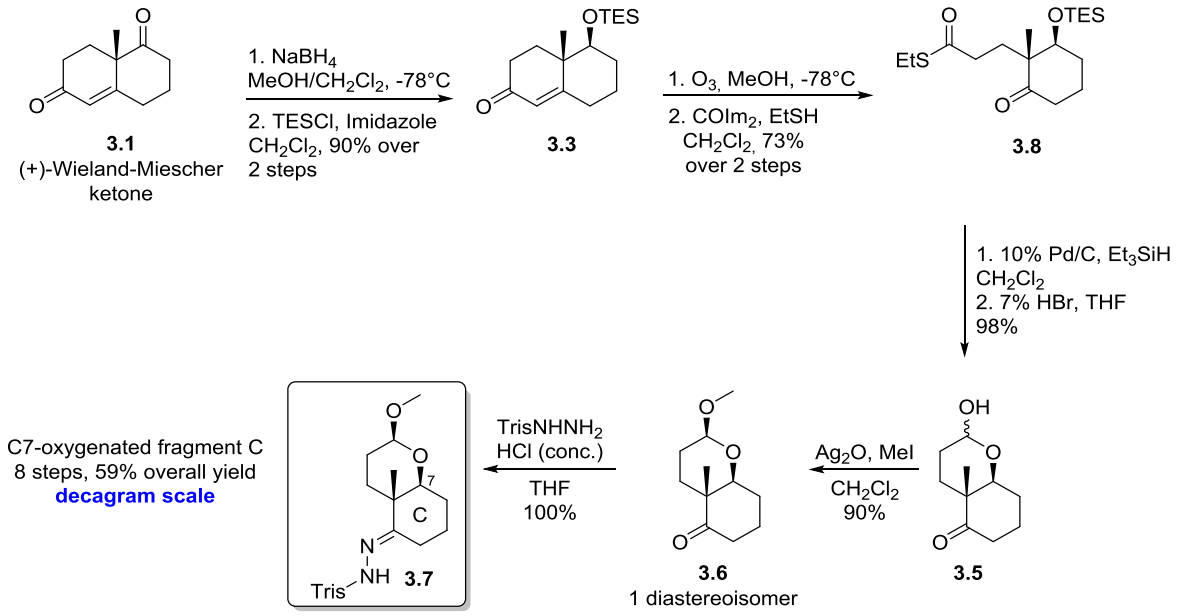


*Scheme 3.12: Synthesis of fragment C **3.7***

3.2.4 New Synthesis of Ring C Summary

The synthesis of hydrazone **3.7** is shown in Scheme 3.13. Starting from (+)-Wieland-Miescher ketone **3.1**, stereoselective reduction and protection of the newly formed hydroxyl group afforded **3.3** in 90% yield over 2 steps. Decarboxylative ozonolysis followed by thioesterification yielded thioester **3.8** in 73% over 2 steps. Mild and efficient Fukuyama reduction followed by acidic deprotection of the TES silyl ether delivered the hemiacetal **3.5** in a nearly quantitative yield. Purdie methylation and hydrazine condensation generated the fragment C **3.7** in 8 steps and 59% overall yield. Each reported yield corresponds to a reaction performed on a decagram scale, which makes this synthesis very robust. Additionally, hydrazone **3.7** encompasses three different stereogenic centres, two of which were set up by substrate control.

[91] Purdie, T.; Irvine, J. C.; *J. Chem. Soc., Trans.* **1903**, *83*, 1021-1037.

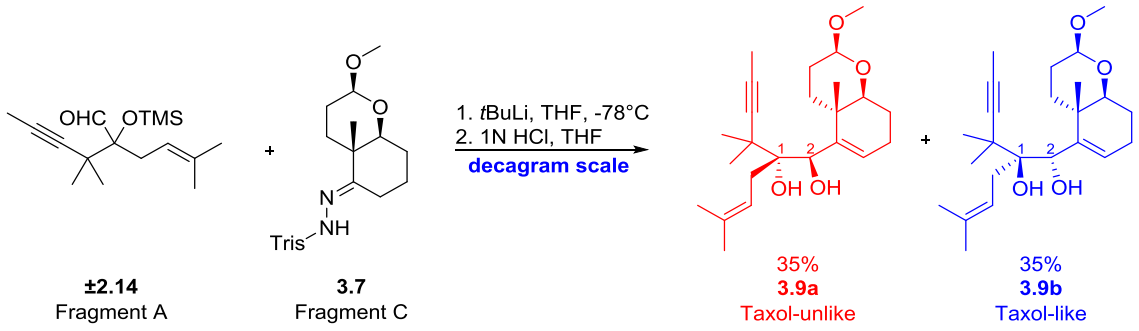


Scheme 3.13: Overall synthesis of the fragment C **3.7**

3.3 From Shapiro Products to Metathesis Precursors

3.3.1 Shapiro Coupling

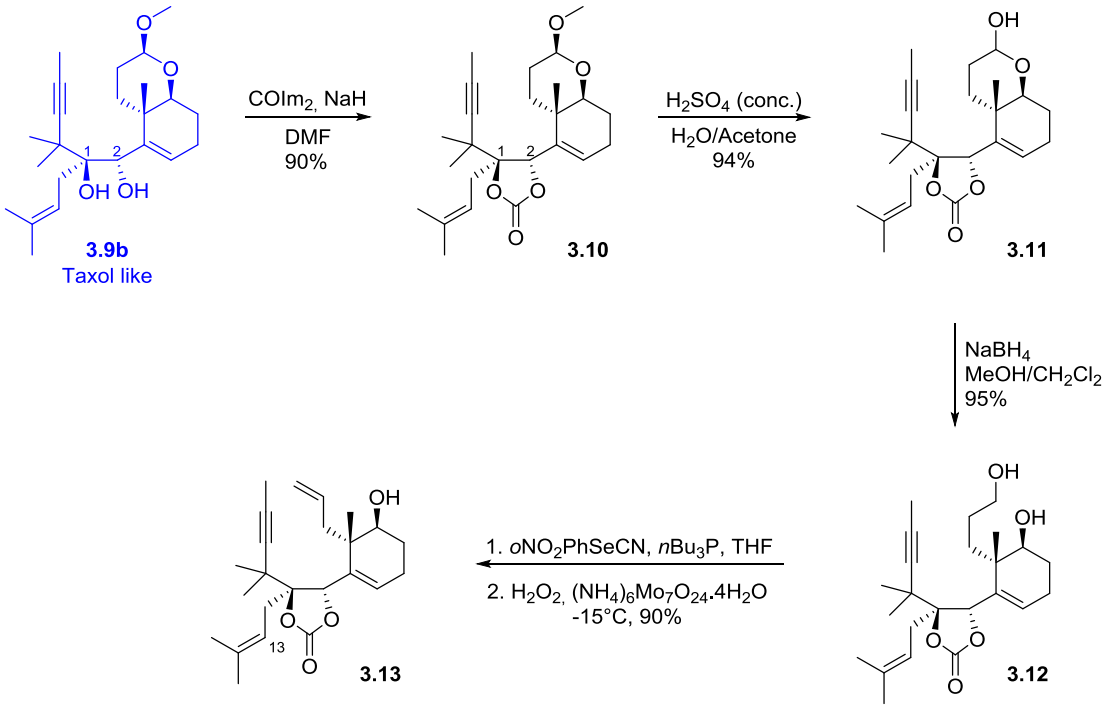
The Shapiro coupling was then investigated between racemic aldehyde (±)-**2.14** and the hydrazone **3.7**. The use of the racemic aldehyde was preferred since its synthesis is shorter and more efficient compared to its enantio-enriched version, even if the Shapiro reaction would generate 2 diastereomers with the racemic aldehyde. The ring C was treated with 2 equivalents of *t*BuLi at -78°C in THF to generate the active vinyl lithium species, which was reacted with aldehyde (±)-**2.14**. Subsequent hydrolysis of the TMS ether in acidic media afforded both C1-C2 Taxol-unlike **3.9a** and Taxol-like **3.9b** diols in a 1:1 ratio, in 70% combined yield over 2 steps (Scheme 3.14).



Scheme 3.14: Shapiro coupling

3.3.2 Synthesis of the Metathesis Precursors

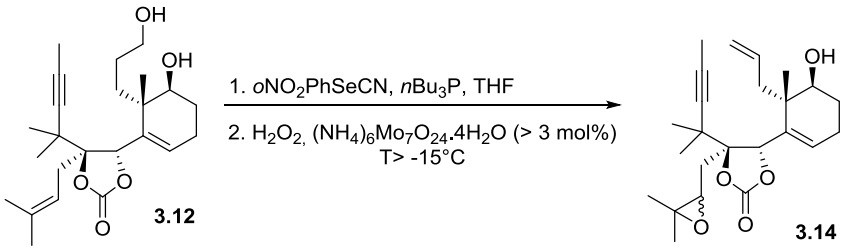
After careful separation of both diastereomers, the C1-C2 Taxol-like diol **3.9b** was protected as the cyclic carbonate **3.10** using sodium hydride and carbonyl diimidazole in DMF in 90% yield. From our metathesis studies on the C7-deoxy derivatives, we know that a C1-C2 cyclic carbonate group is crucial for the ring-closing dienyne metathesis to proceed. Challenging hydrolysis of the methyl acetal under strongly acidic conditions generated by an excess of concentrated sulfuric acid in a 1:1 mixture of acetone and H_2O occurred surprisingly smoothly to deliver the hemiacetal **3.11** in 94% yield. Reduction of this hemiacetal using $NaBH_4$ in a 1:1 ratio of methanol and CH_2Cl_2 delivered the diol **3.12** in 95% yield. The Grieco dehydration was then attempted. The corresponding primary selenoether was generated using a slight excess of *o*-nitrophenyl selenocyanate and *n*-tributyl phosphine under diluted conditions in THF to avoid any side reaction of the secondary hydroxyl group. The crude mixture was then oxidised with hydrogen peroxide and ammonium molybdate tetrahydrate at -15°C in THF for a few minutes, which delivered the metathesis precursor **3.13** in 90% yield (Scheme 3.15).



Scheme 3.15: Synthesis of metathesis precursor **3.13**

It was crucial to perform the oxidation step of the Grieco dehydration very carefully. Indeed, when the reaction conditions are not sufficiently controlled, the internal reaction

temperature raise up above -15°C and overoxidation of the C13 olefin to form the C13 epoxide **3.14** is observed. To minimise the formation of the undesired epoxide **3.14**, the amount of ammonium molybdate tetrahydrate had to stay as low as possible, the maximum quantity required was no more than 3 mol%. Also during the quench of the reaction, large quantity of H_2O and solvent had to be added to efficiently separate the oxidising agent and the product as quickly as possible to avoid overoxidation of metathesis precursor **3.13** (Scheme 3.16).



Scheme 3.16: Overoxidation process during Grieco dehydration

An X-ray diffraction analysis (Figure 3.1) of the derivative **3.10** established that it possessed the required relative configuration at C1, C2, C7 and C8 for Taxol.

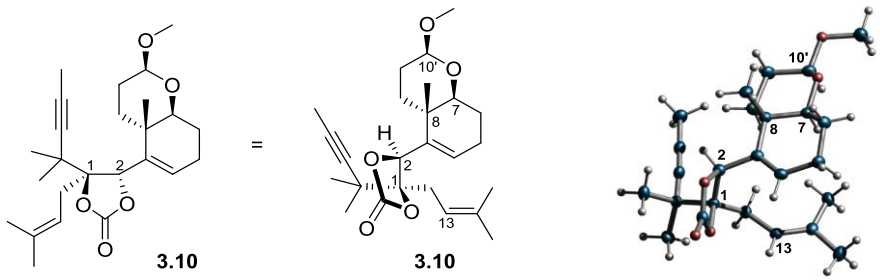
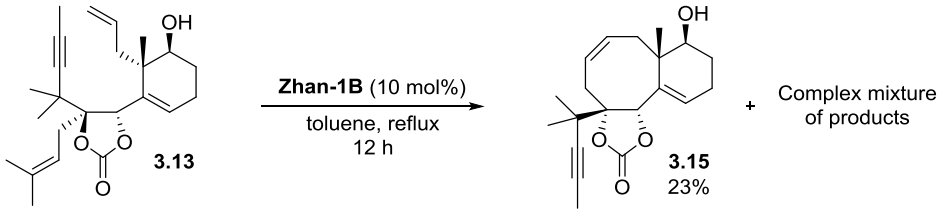


*Figure 3.1: X-ray diffraction analysis of **3.10***

3.4 Metathesis Cascade on the C7 Derivatives

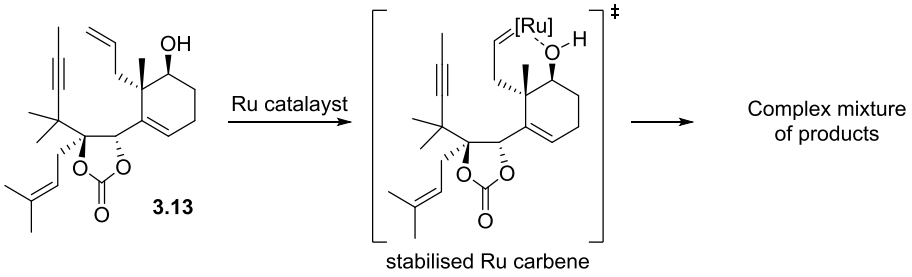
3.4.1 C7-OH

The metathesis precursor **3.13** was then submitted to the previously developed optimum ring-closing dienyne metathesis conditions using 10 mol% of Zhan-1B catalyst in refluxing toluene for 12 h. Unfortunately, these conditions led to 23% yield of bicycle **3.15** along with a complex mixture of side products (Scheme 3.17).



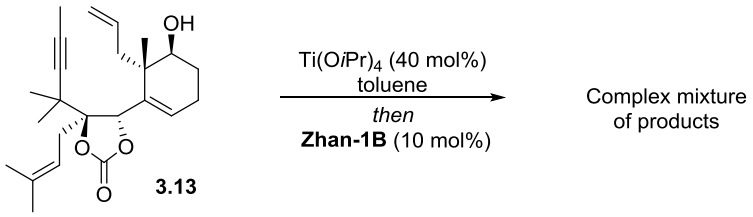
*Scheme 3.17: Metathesis reaction on unprotected hydroxyl precursor **3.13***

We hypothesised that the most readily formed ruthenium carbene would be stabilised by the interaction of the unprotected C7 hydroxyl group, which would explain the complex mixture of products obtained in this reaction (Scheme 3.18).



Scheme 3.18: Stabilised ruthenium carbene

Fürstner and co-workers circumvented similar problems by the addition of Lewis acids in order to suppress the complexation of the ruthenium carbene with unprotected oxo-based groups.[92] When alcohol **3.13** was treated with Ti(O*i*Pr)$_4$ followed by addition of the Zhan-1B complex, no favourable difference was noticed (Scheme 3.19). It was then decided to protect this C7 hydroxyl group prior to any metathesis reaction.

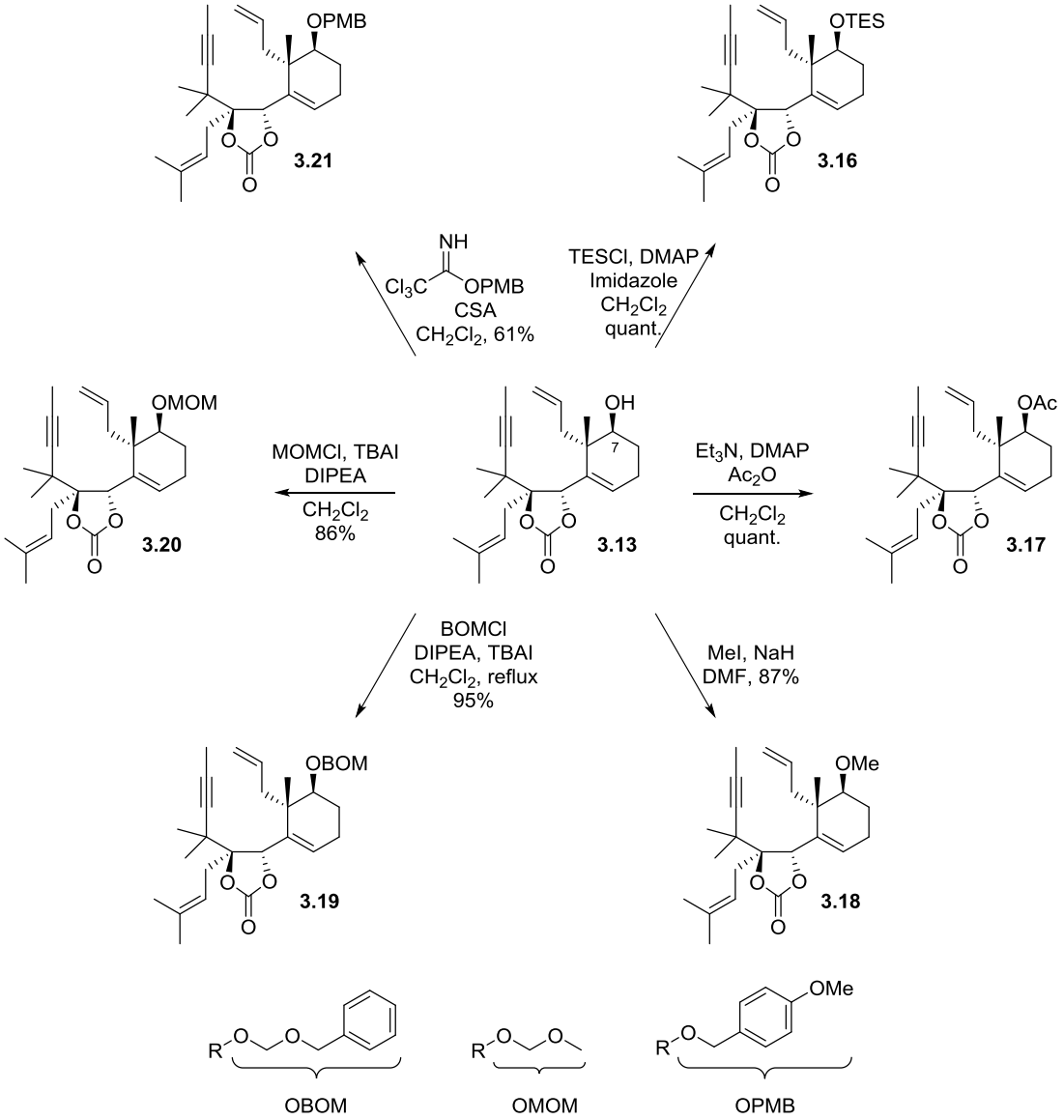


*Scheme 3.19: Metathesis reaction of unprotected precursor **3.13** using a Lewis acid*

[92] Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130-9136. Vedrenne, E.; Dupont, H.; Oualef, S.; El Kaim, L.; Grimaud, L. *Synlett* **2005**, *4*, 670-672. Moïse, J.; Arseniyadis, S.; Cossy, J. *Org. Lett*. **2007**, *9*, 1695-1698. Muthusamy, S.; Azhagan, D. *Eur. J. Org. Chem.* **2014**, 363-370.

3.4.2 Synthesis of Diversely Protected Metathesis Substrates

Since the metathesis reaction of the unprotected C7 hydroxyl did not produce the desired tricycle product, it was decided to probe the effect of a few protecting groups at the C7 position. Easily cleavable protecting groups such as TES silyl ether and acetate were installed at the C7 position. The TES silyl ether **3.16** was synthesised in quantitative yield using TESCl, imidazole and DMAP. The acetate **3.17** was produced in a quantitative yield under classical conditions using triethylamine, acetic anhydride and DMAP. The size of this group was also investigated using small methoxy ether **3.18** that was synthesised in 87% yield using sodium hydride and methyl iodide**.** We extended our investigation to the benzyloxymethyl acetal (BOM) because our target, Holton's intermediate, bears the same protecting group. Alcohol **3.13** was treated with BOMCl, DIPEA and TBAI in refluxing CH_2Cl_2 to generate the BOM precursor **3.19** in 95% yield. The methoxymethyl (MOM) and the electron-rich benzylic protecting group (PMB) were also chosen due to the comparable size of the methoxybenzyl (BOM) group. The MOM derivative **3.20** was obtained in 86% yield upon treatment of alcohol **3.13** with MOMCl, DIPEA and TBAI. Finally the PMB derivative **3.21** was synthesised in 62% yield using PMB trichloroacetimidate and CSA as shown in Scheme 3.20.

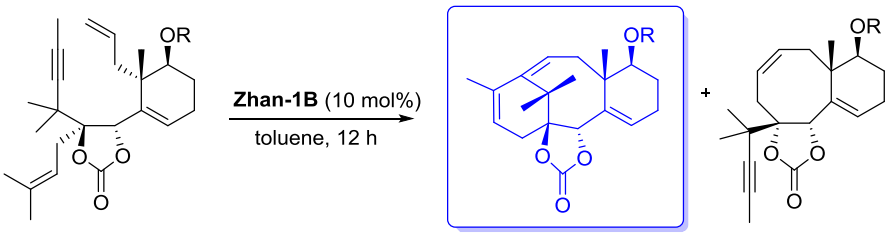


Scheme 3.20: Selection of the C7 protecting groups

3.4.3 Metathesis Results

The ring-closing metathesis cascade was then studied. When the TES precursor **3.16** was submitted to the standard metathesis condition with 10 mol% of Zhan-1B complex in refluxing toluene for 12 h, no tricycle was formed, only the bicyclic side product **3.22** was obtained in 77% yield (entry 1). When the acetate derivative **3.17** underwent the same reaction conditions, only the bicyclic product **3.23** was produced in 80% yield (entry 2). The smaller methoxy ether precursor **3.18** was then submitted to the same metathesis reaction conditions and the desired tricycle **3.24** was synthesised in 45% yield as the major product along with 30% of unwanted bicycle **3.25** (entry 3). This C7 methoxy ether tricycle **3.24** can pave the way to the formation of cabazitaxel (Scheme 3.21). In the entry 4 is shown the

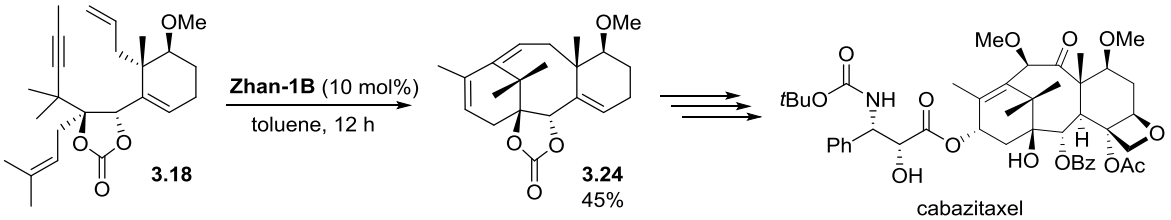
metathesis reaction with the BOM precursor **3.19**, which led to the formation of the desired tricyclic metathesis product **3.26** in 29% yield and the unwanted bicycle **3.27** in 46% yield. The separation of both tri- and bicycle was very challenging by flash chromatography. Large quantities of benzene had to be used, as the major solvent, to cleanly recover both products. When the MOM derivative **3.20** was submitted to the metathesis reaction conditions, the tricycle **3.28** was synthesised in 28% yield and the bicycle side product **3.29** in 54% yield. These results are really similar to the one obtained with the C7-OBOM derivatives (entry 4 *vs* entry 5). Finally the electron rich PMB derivative **3.21** was submitted to the metathesis reaction condition, the tricycle **3.30** was synthesised in 29% yield as the major product, along with 22% yield of the unwanted bicycle **3.31** (Entry 6) as shown in Table 3.1.



Entry	R	**Tricycle** (Yield %)	**Bicycle** (Yield)
1	TES	(0%)	**3.22** (77%)
2	Ac	(0%)	**3.23** (80%)*
3	Me	**3.24** (45%)	**3.25** (30%)
4	BOM	**3.26** (29%)	**3.27** (46%)
5	MOM	**3.28** (28%)	**3.29** (54%)
6	PMB	**3.30** (29%)	**3.31** (22%)

* The reaction was also run with Ti(O*i*Pr)$_4$, but no change to the metathesis outcome was observed

Table 3.1: Effect of the C7 group on the metathesis reaction



Scheme 3.21: Possible synthesis of cabazitaxel

3.4.4 Metathesis Outcome Prediction Model

From the above experiments, we gathered that the C7-hydoxyl group needs to be protected to avoid unfavourable interaction toward the neighbouring ruthenium carbene and that the choice of the C7-protecting group is extremely important for the outcome of the metathesis reaction. This protecting group has to be rather small to possibly direct the formation of the tricycle by mean of ring-closing dienyne metathesis. The Figure 3.2 shows a prediction model based on the metathesis results of the substrates with diverse C7 protecting groups.

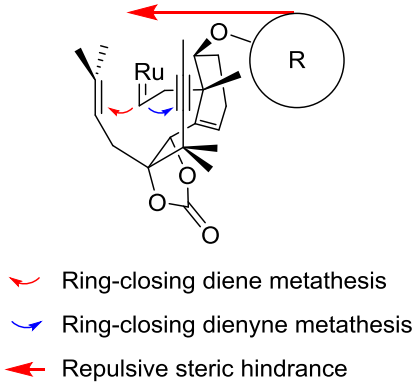


Figure 3.2: Prediction model for the metathesis cascade outcome

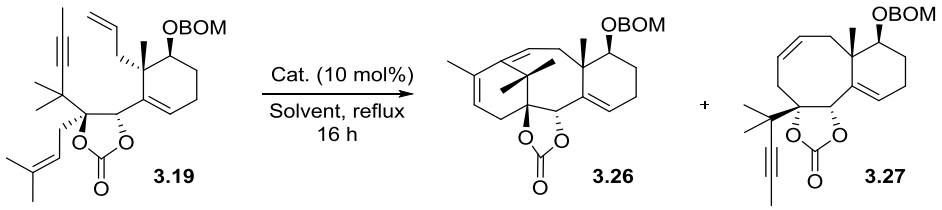
According to the previous experimental results, the BOM protecting group includes this criteria. Also this is the protecting group that needs to be on the C7-hydroxy group due to our target, the Holton's intermediate. Therefore, we chose to persist on the study of the C7-OBOM metathesis outcome to optimise our strategy toward an efficient and robust formal synthesis.

3.5 Metathesis Optimisation of C7-OBOM derivative

3.5.1 Catalyst and Solvent Screening

Our first step for the optimisation of this metathesis reaction was to re-evaluate the influence of the catalyst and the solvent on the metathesis cascade outcome for the C7-OBOM derivative **3.19**. These results are displayed in Table 3.2. It is clear, from entry 1 to

entry 4 that the Zhan-1B complex (entry 3) and Grela catalyst (entry 4) exhibited better results than Grubbs's second-generation and Hoveyda-Grubbs 2 catalysts in terms of product ratio and yield of tricycle **3.26**. Zhan-1B catalyst afforded 29% yield of tricycle **3.26** and 46% yield of bicycle **3.27**, while the Grela catalyst produced 33% yield of tricycle **3.26** along with 57 % yield of bicycle **3.27**. Even if the yield of the combined products with the Zhan-1B (75%) is slightly lower than the Grela catalyst (90%), the ratio of products is similar. Also the poor availability and the higher price of the Grela catalyst made it less attractive than the Zhan-1B catalyst. These are the reasons why we chose to focus our efforts with the latter catalyst. When toluene was changed to a lower boiling point solvent, such as 1,2-DCE, the combined yield was slightly better but the tricycle **3.26** was only obtained in 23% yield (entry 5). In the case of *p*Xylene, a higher boiling point solvent, the starting material **3.16** was not entirely consumed and only the unwanted bicycle **3.27** was formed in 33% yield (entry 6). The reflux temperature of *p*Xylene is 140°C and under these conditions the active catalyst half-life was very limited, as ruthenium black was formed after a few minutes of reaction.



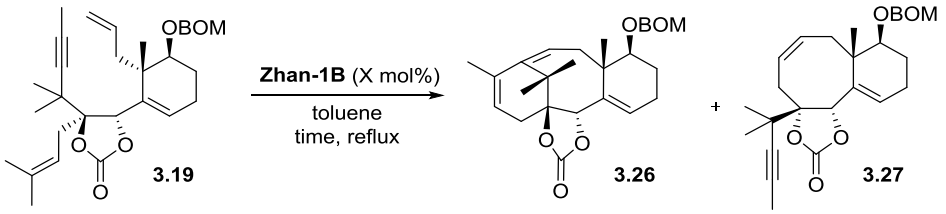
Entry	Catalyst	Solvent	Yield **3.26** (%)	Yield **3.27** (%)
1	G 2	toluene	12	64
2	HG 2	toluene	17	36
3	***Zhan-1B***	***toluene***	***29***	***46***
4	Grela	toluene	33	57
5	Zhan-1B	1,2-DCE	23	63
6	Zhan-1B	*p*Xylene	0	33

Table 3.2: Catalyst-solvent screening

3.5.2 Catalyst Quantity and Reaction Time Optimisation

Changes were also made in the quantity of catalyst and the reaction time and results are displayed in Table 3.3. The previous best conditions to generate the tricycle **3.26** are shown in entry 1. Increasing the catalyst quantity to 50 mol% made the ratio of tricycle

3.26 increased but the yield slightly dropped from 29% to 27%, while the yield of bicycle **3.27** decreased from 46% to 20% (entry 1 *vs* entry 2). Further increasing the amount of the catalyst quantity to 1 equivalent led to the same conclusion; improvement of the ratio of tricycle **3.26** was observed while the yield was increased to 35% along with traces of bicycle **3.27** (entry 3). Then the reaction time was shortened to 0.75 h with 50 mol% and 100 mol% of catalyst (entry 4 and 5). When the reaction was stopped at that time, no starting material remained in both cases, but the ratio of products was unexpected. When 50 mol% of Zhan-1B catalyst was employed the formation of tricycle **3.26** decreased to 12% yield while the bicycle **3.27** was obtained in 58% yield. Similar yields were observed when 100 mol% of catalyst was used (entry 5). Interestingly, it appears that the bicycle **3.27** could slowly convert to the tricycle **3.26** since its yield increases with time (entry 2 *vs* entry 4 and entry 3 *vs* entry 5). What we can conclude from this is the ratio of metathesis products is dramatically time-dependent. It appears, in the first instant of the reaction, that the bicycle **3.27** is by far the first product to be formed while the formation tricycle **3.26** is much slower. Also when a large quantity of catalyst was used, degradation occurred as yields largely decreased.



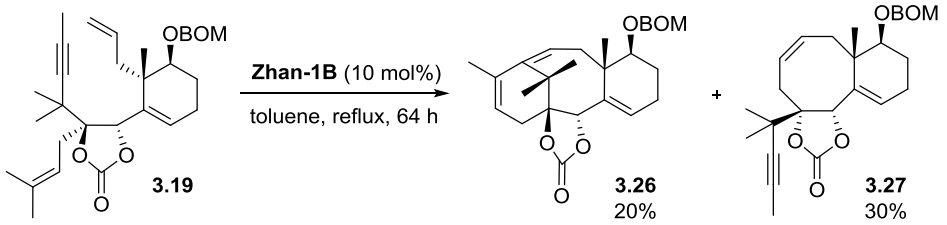
Entry	Zhan-1B (X mol%)	Time	Yield **3.26** (%)	Yield **3.27** (%)
1	10	16 h	29	46
2	50	16 h	27	20
3	***100***	***16 h***	***35***	***traces***
4	50	0.75 h	12	58
5	100	0.75 h	13	57

Table 3.3: Catalyst quantity-reaction time screening

3.5.3 Time-Dependent Metathesis

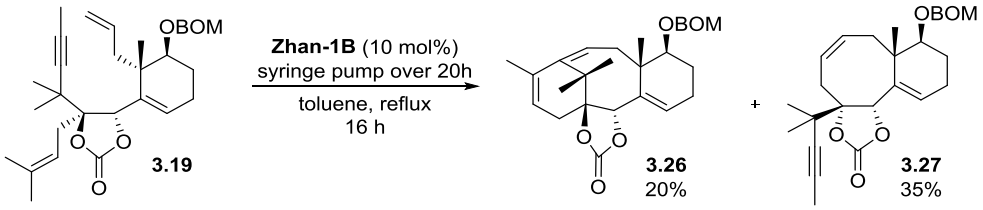
The formation of tricycle **3.26** is slower than the one of the bicyclic derivative **3.27**, but when the reaction time is increased the ratio of products was reversed, which may

indicate a relationship between the late formation of tricycle **3.26** and the consumption/degradation of **3.27**. Therefore, as shown in Scheme 3.22, we tried to evaluate the importance of the reaction time (and maybe to extrapolate some equilibrium constants from this relationship). For the first attempt, 10 mol% of Zhan-1B complex was used to avoid a fast degradation of products, and the reaction time was increased to 64 h in refluxing toluene. In that case, the tricycle **3.26** was obtained in 20% yield along with 30% of bicycle **3.27**. The ratio of tricycle **3.26** to bicycle **3.27** varied from 1:1.6 in 16 h to 1:1.5 in 64 h. We can estimate that the optimum ratio can be reached after 16 h. Also after 64 h both products were obtained in 50% combined yield instead of 75% yield after 16 h.



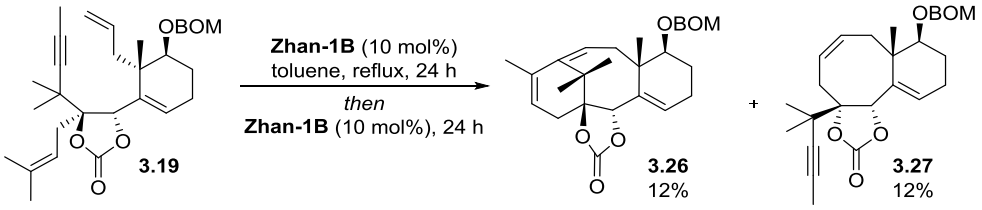
Scheme 3.22: 64 h metathesis reaction

Another time-related experiment was conducted, as shown in Scheme 3.23. This time, 10 mol% of Zhan-1B catalyst was added to the reaction mixture with a syringe pump over 20 h in refluxing toluene, followed by an additional 16 h of reaction time. Unfortunately, the formation yield of the tricycle **3.26** did not improve but the yield of bicycle **3.27** increased to 35%. Slow addition of the catalyst did not bring any improvement.



Scheme 3.23: Slow addition of Zhan-1B catalyst

Zhan-1B catalyst was then added portion-wise over 24 h, but the products were recovered in a 1:1 ratio in 24% combined yield as illustrated in Scheme 3.24

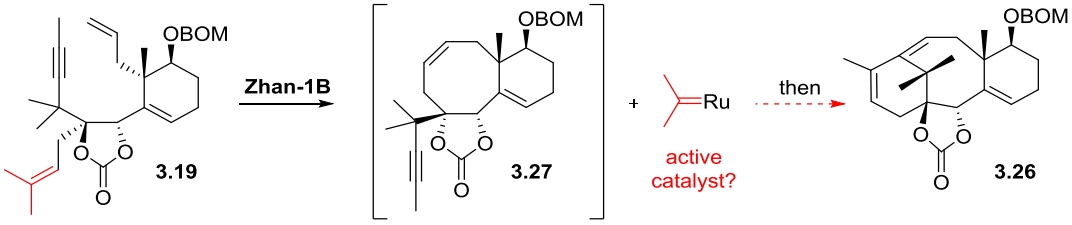


Scheme 3.24: Portion-wise addition of catalyst

It is clear from these experiments that when the reaction time is long even under low catalyst loading, great deterioration of products occurred. The optimum reaction time should be around 16 h, which led to the best results.

3.5.4 Non-Active Catalyst

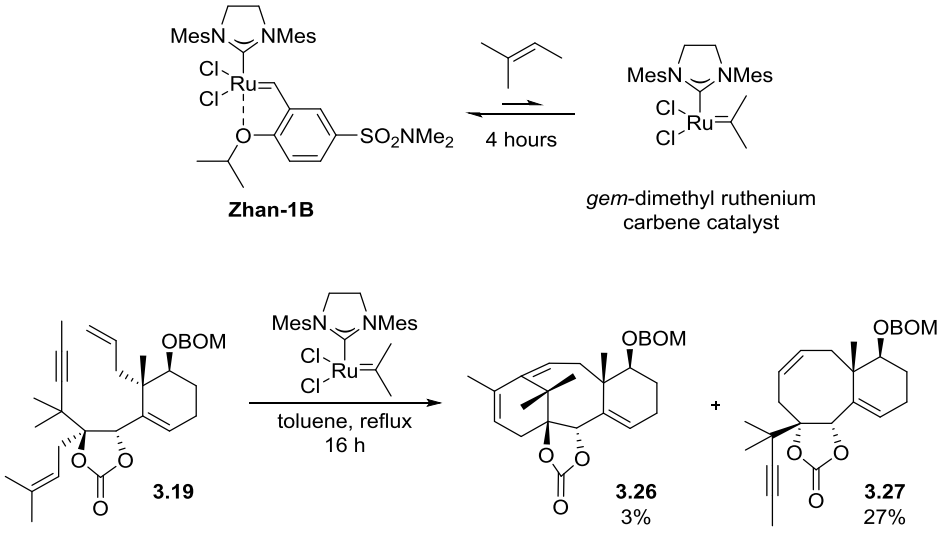
A deeper study of the mechanism was performed to understand the difference between the dienyne *vs* diene metathesis processes, in order to further optimise the generation of tricycle **3.26**. We discovered that the bicycle product **3.27** is formed within the first instants of the reaction, and if the reaction is left to run under the same reaction conditions, we assume that a part of the bicycle **3.27** slowly converts to tricycle **3.26**. So because bicycle **3.27** is generated in the first instants of the reaction, *gem*-dimethyl ruthenium carbene is also produced, as it would be the resulting carbene after the generation of bicycle **3.27** generation (Scheme 3.25). Could this catalyst be active in the metathesis reaction?



Scheme 3.25: Schematic mechanism of the metathesis reaction

To answer this question, we tried to generate this *gem*-dimethyl ruthenium carbene and to use it for the metathesis reaction to see if we could observe a difference on the metathesis outcome. Zhan-1B catalyst was treated with 2-methyl-2-butene and the reaction was left to run for 4 h in an attempt to generate this ruthenium carbene. The

catalyst mixture was added to the reaction mixture and the reaction was run for 16 h in refluxing toluene. Sadly tricycle **3.26** was only generated in 3% yield along with 27% of bicycle **3.27** as shown in Scheme 3.26. This experiment proved the poor reactivity of this *gem*-dimethyl ruthenium carbene and the deleterious effect of 2-methyl-2-butene on the metathesis reaction.



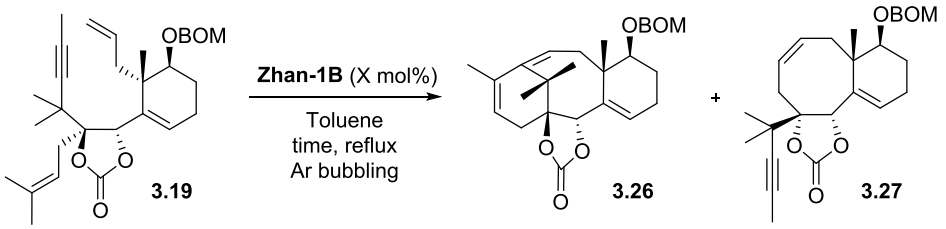
Scheme 3.26: Generation and usage of putative active catalyst

3.5.5 Argon Bubbling Effect on Metathesis

We then tried to remove the 2-methylpropene by bubbling argon through the reaction mixture. For comparison, the result of the standard conditions are given in the entry 1. When 100 mol% of catalyst was added and the reaction ran under a stream of argon for 0.75 h, as expected, the tricycle **3.26** was generated as the minor product in 12% yield and the bicycle **3.27** in 58% yield. Also 50 mol% of the catalyst was recovered (entry 2).[93] When the same reaction was stopped after 4 h, the tricycle **3.26** was synthesised in a 35-40% range of yield, as the only product, while half of the catalyst was recovered after the reaction (entry 3).[94] Similar results were obtained when the reaction time was increased to 16 h (entry 4). In order to compare the efficiency of the degassing method, no argon was bubbled through the mixture when 100 mol% of Zhan-1B catalyst was used for a reaction time of 4 h (entry 5). In this case the reaction was less clean and the product

[93] The Zhan-1B catalyst was recovered in the same purification as the metathesis products by flash chromatography. The recycled catalyst exhibited the same activity as the commercially available catalyst.
[94] This range of yield was obtained from 0.04 mmol and 0.24 mmol scale on dozens of iterations.

more difficult to purify due to the presence of more decomposition products. The tricycle **3.26** was synthesised in 25% yield and less catalyst was recovered. 200 mol% of catalyst was also used on the metathesis reaction for 0.75 h and similar results were obtained even if more degradation was observed (entry 2 *vs* 6) as presented in Table 3.4.



Entry	(X mol%)	Time	Ar bubbling	Recovered catalyst	Yield **3.26** (%)	Yield **3.27** (%)
1	10	16 h	No	-	29	46
2	100	0.75	Yes	50 mol%	12	58
3	***100***	***4 h***	***Yes***	***50 mol%***	***35-40***	***traces***
4	***100***	***16 h***	***Yes***	***50 mol%***	***35-40***	***traces***
5	100	4 h	No	20 mol%	25	Traces
6	200	0.75	Yes	150 mol%	7	30

Table 3.4: Catalyst quantity-reaction time-Ar bubbling effect screening

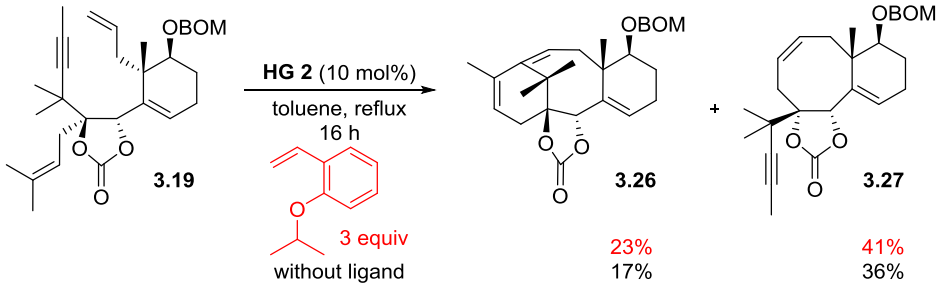
Degassing the reaction mixture seems to have a few beneficial effects. This process happened to slightly increase the formation of the tricycle **3.26**, prevent its degradation with a high catalyst loading and also to prevent the catalyst degradation. Tricycle **3.26** can be obtained in a range of 35 to 40% yield as the only isolable product. Therefore, 2-methylpropene that is generated within the first instant of the metathesis reaction acts as an obstacle toward the conversion of bicycle **3.27** into the desired tricycle **3.26**.

3.5.6 Benzylidene Ligand Effect

As explained during the study of the C7-deoxy derivatives, the benzylidene ligands of second-generation metathesis catalysts play a crucial role in the outcome of metatheses.[81,95] With this idea in mind, we developed a reaction in which a stoichiometric

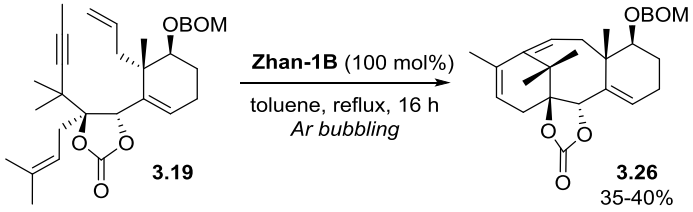
[95] Nelson, D. J.; Manzini, S.; Urbina-Blanco, C. A.; Nolan, S. P. *Chem. Commun.* **2014**, *50*, 10355-10375.

amount of precatalyst benzylidene ligand will be added along with 10 mol% of a metathesis catalyst. The Hoveyda-Grubbs 2 precatalyst was chosen due to the simplicity of its benzylidene ligand. Modified Hoveyda-Grubbs 2 catalysts possess more elaborated ligands, which are not commercially available and more complicated to synthesise. In Scheme 3.27 is shown the reaction with 10 mol% of Hoveyda-Grubbs 2 catalyst with and without extra benzylidene ligand in refluxing toluene for 16 h. It appears that the ligand has a slight beneficial effect for the formation of the tricyclic product but a more pronounced positive effect on the overall yield of the metathesis reaction.



Scheme 3.27: Effect on Hoveyda-Grubbs 2 benzylidene ligand

In summary, the tricycle **3.26** was obtained in a range of 35-40% yield as the sole product from ring-closing dienyne metathesis using 100 mol% of Zhan-1B catalyst, from which half of the injected catalyst can be recovered and more importantly, re-used. The reaction was run in refluxing toluene for 16 h under a stream of argon as reported in Scheme 3.28.

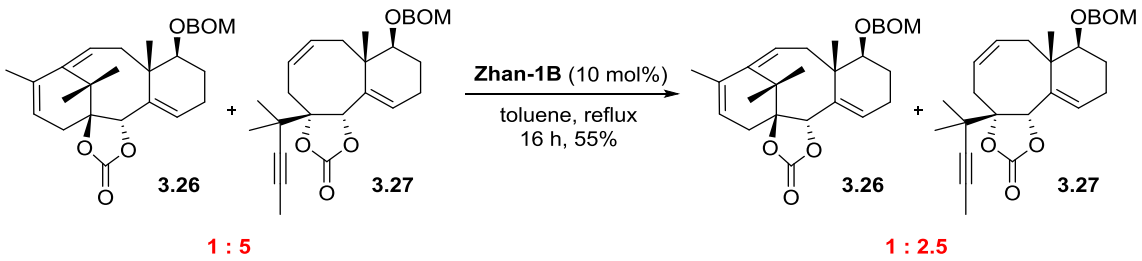


*Scheme 3.28: Synthesis of tricycle **3.26***

3.6 Side-Product Recycling

3.6.1 Isomerisation vs Degradation

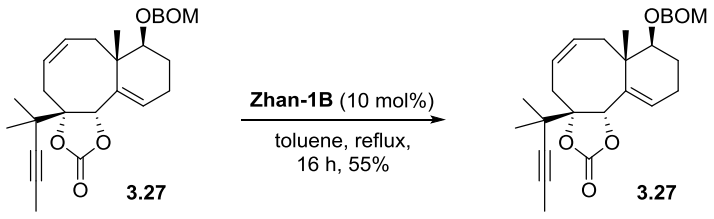
Another question remains. Does the bicycle **3.27** really equilibrate into the desired tricycle **3.26**? To answer this question, we tried to investigate the formation of the tricycle **3.26** during the metathesis reaction. A mixture of the tricycle **3.26** and the bicycle **3.27** in a 1:5 ratio was treated with 10 mol% of Zhan-1B catalyst in refluxing toluene for 16 h. Interestingly, the ratio between both products changed to 1:2.5 and was recovered in 55% yield. This result was encouraging although it might not be due to a direct equilibration of **3.27** to **3.26** but to degradation of **3.27** (Scheme 3.29).



Scheme 3.29: Isomerisation and/or degradation?

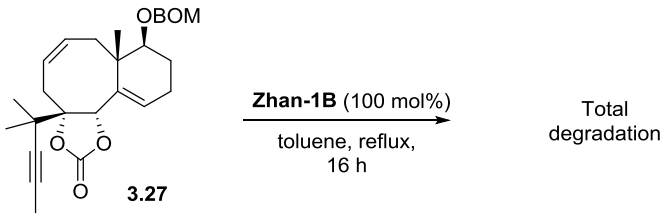
3.6.2 Relative Stability of the Metathesis Products

In order to quantify the phenomenon and confirm our observation from the previous experiment, bicycle **3.27** was resubmitted to the reaction conditions using 10 mol% of catalyst in refluxing toluene for 16 h and bicycle **3.27** was recovered in 55% yield. No other product was found (Scheme 3.30).



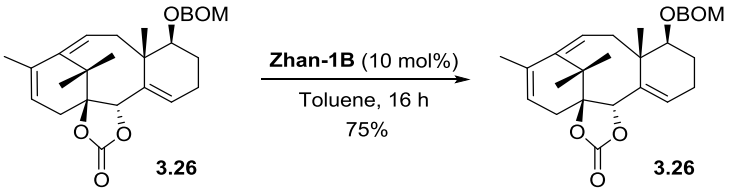
Scheme 3.30: Degradation of bicycle **3.27**

When the same reaction was repeated with 100 mol% of Zhan-1B catalyst in refluxing toluene, the bicycle **3.27** underwent total degradation (Scheme 3.31).



*Scheme 3.31: Degradation of bicycle **3.27***

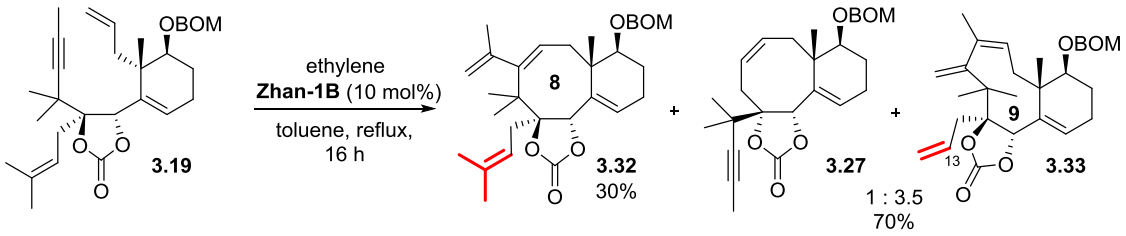
It clearly shows that the bicycle **3.27** cannot easily convert to tricycle **3.26** under these reaction conditions as only degradation occurred. The tricycle **3.26** was resubmitted to the reaction condition to quantify the respective degradation rate of this metathesis product. In that case, tricycle **3.26** was recovered in 75% yield without any trace of other metathesis product. Consequently, tricycle **3.26** showed a slower degradation rate than bicycle **3.27**, as shown in Scheme 3.32.



*Scheme 3.32: Degradation of tricycle **3.26***

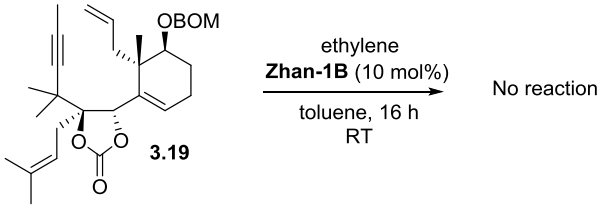
3.6.3 Ethylene Effect

The metathesis reaction was also run under an ethylene atmosphere, in which the metathesis precursor **3.19** was reacted with 10 mol% of the metathesis catalyst in refluxing toluene for 16 h. Surprisingly, no tricycle **3.26** was formed. Product **3.32**, which is an intermediate in the formation of the tricycle **3.26**, was obtained in 30% yield. This product came from an enyne metathesis followed by the quench of the relatively stable vinyl ruthenium carbene by ethylene, generating the conjugated diene **3.32**. Also the unwanted diene metathesis product **3.27** was synthesised along with an inseparable 9-membered ring bicycle **3.33**, in a ratio of 1:3.5 and in 70% combined yield (Scheme 3.33).



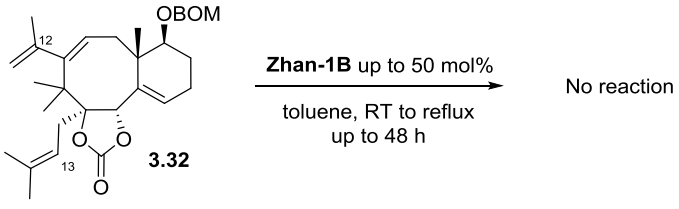
Scheme 3.33: Metathesis reaction under ethylene

This reaction was tested at room temperature. The reactions under an ethylene atmosphere do not generally require high reaction temperatures since the generation of the active catalyst species is faster and its efficiency is greater. Therefore, the effect of high temperature could have explained the formation of the undesired 6/8 membered bicycle **3.27** and 9/6 membered bicycle **3.33**. Unfortunately, no reaction proceeded at room temperature (Scheme 3.34).



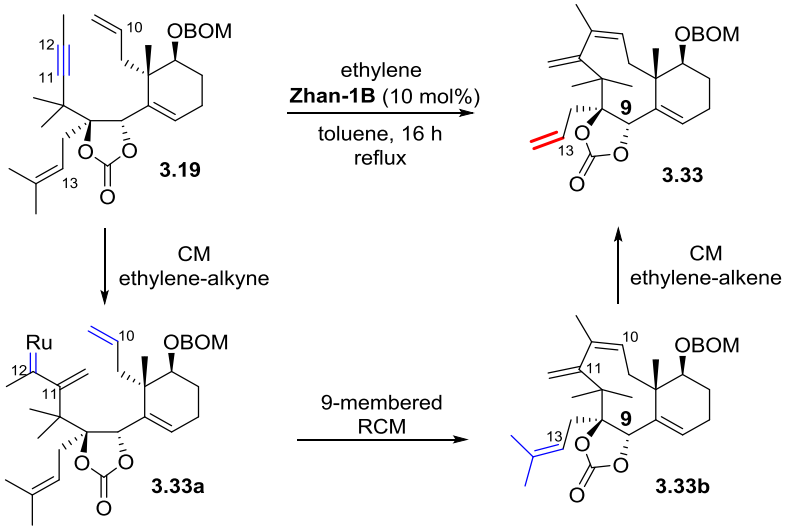
Scheme 3.34: Metathesis reaction under an ethylene atmosphere at room temperature

Conversion of the BC bicycle ring **3.32** into the tricycle **3.26** was also attempted. Different catalysts with loading up to 50 mol% were employed, from room temperature to reflux with a reaction time up to 48 h, but no reaction was observed. On each attempt, the starting material was fully recovered. These failures reinforce the hypothesis that the hindered 1,1-disubtituted C12 olefin is highly non-reactive (Scheme 3.35).



*Scheme 3.35: RCM reaction attempts to synthesise tricycle **3.26***

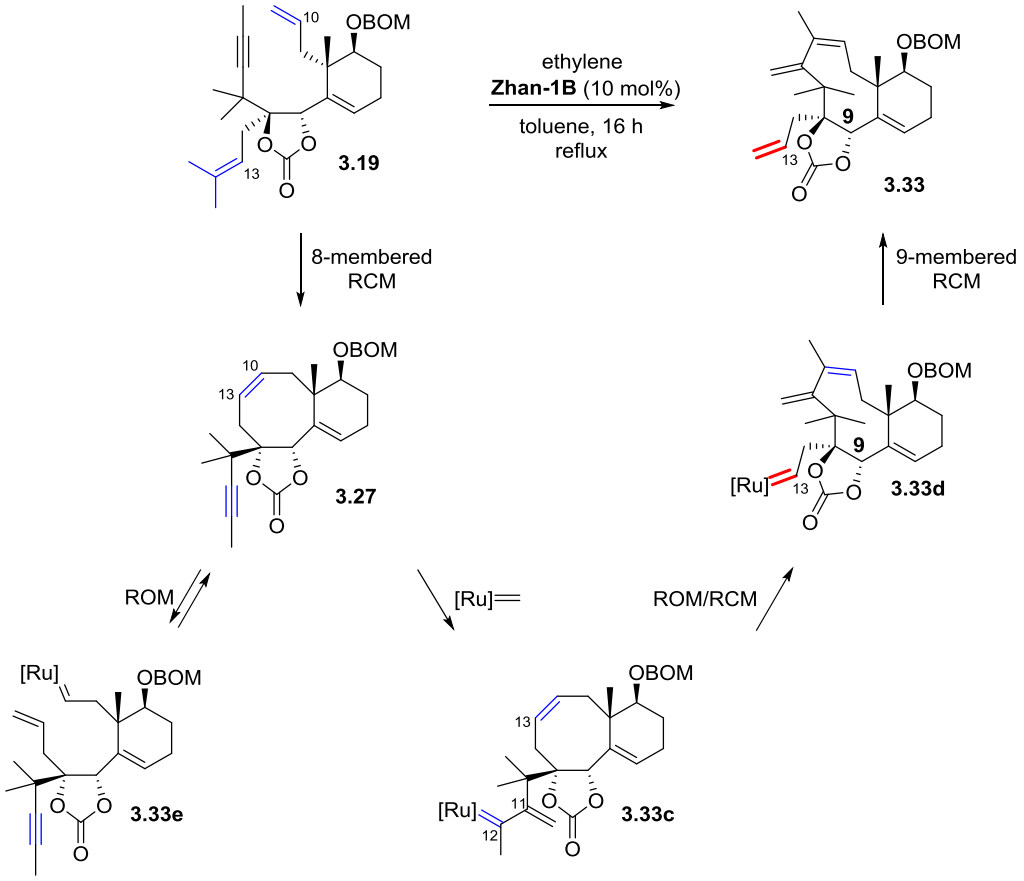
The formation of the 9-membered bicycle **3.33** was surprising and therefore, we envisaged possible mechanisms to explain its formation. A first possible mechanism is illustrated in Scheme 3.36. The first step would be a cross-metathesis between the alkyne and ethylene to generate 1,2-diene **3.33a** by enyne bond reorganisation.[96] Then the less hindered vinyl carbene would form a 9-membered ring **3.33b** with the reactive terminal alkene by ring-closing metathesis. To finish, the C13 olefin would react with ethylene to generate the 9-membered bicycle **3.33**.



Scheme 3.36: First possible mechanism

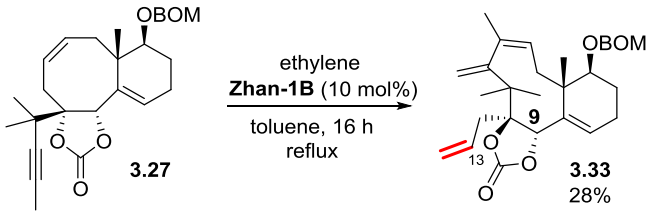
The second mechanism features a ring-closing diene metathesis to form the unwanted 8-membered bicycle **3.27**, which can re-open to produce **3.33e**. As shown previously, intermediate **3.33e** can only close back the C10-C13 olefin to form **3.27**.[49] Bicycle **3.27** can undergo an enyne bond reorganisation with the ruthenium methylidene to generate **3.33c**. Ring-opening metathesis followed by a ring-closing metathesis (ROM/RCM sequence) of the intermediate **3.33c** would generate the 9-membered ring **3.33d** to finally produce **3.33** by regeneration of the terminal olefin (Scheme 3.37).

[96] Tonogakia, K.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 2235-2238. Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317-1382.



Scheme 3.37: Second possible mechanism

To evaluate the two different options, we treated pure bicycle **3.27** with 10 mol% Zhan-1B catalyst in refluxing toluene for 16 h under an atmosphere of ethylene and the 9-membered ring derivative **3.33** was generated in 28% yield (Scheme 3.38). This test clearly indicates that the C10-C13 olefin can be opened and reacts to generate other types of products like the 9-membered-ring **3.33** and tends to validate the second proposed mechanism.

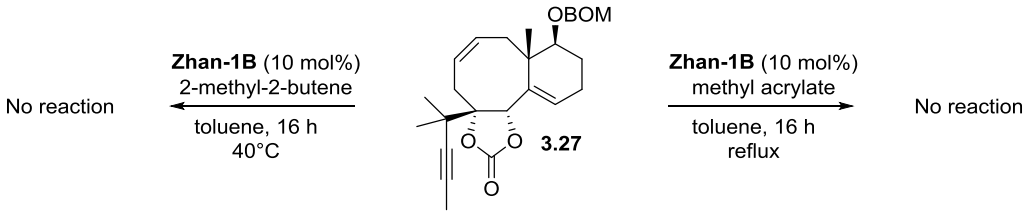


*Scheme 3.38: Conversion of bicycle **3.27** to 9-membered ring **3.33***

Since bicycle **3.27** was converted to the 9-membered bicycle **3.33**, it is worth considering a possible conversion to tricycle **3.26**.

3.6.4 Ring-Opening Metathesis

An atmosphere of ethylene was sufficient to promote the ring-opening metathesis of the C10-C13 olefin and made it react intramolecularly. We tried to reproduce the ring-opening metathesis and perform a cross-metathesis on either C10 or C13 alkenes without ethylene. Unfortunately, when the bicycle **3.27** was submitted to the 2-methyl-2-butene or methyl acrylate with 10 mol% of Zhan-1B catalyst, none of these reactions led to any metathesis product (Scheme 3.39).

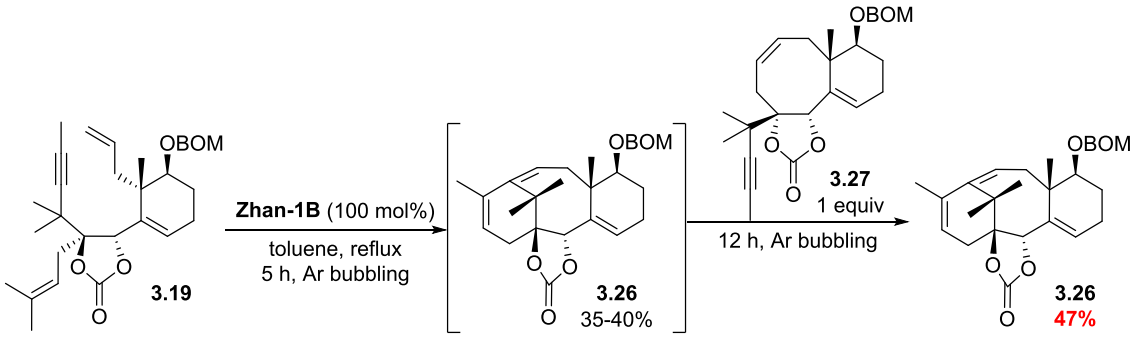


Scheme 3.39: Attempts to open the 8-membered ring

3.6.5 Isomerisation and Degradation Quantification

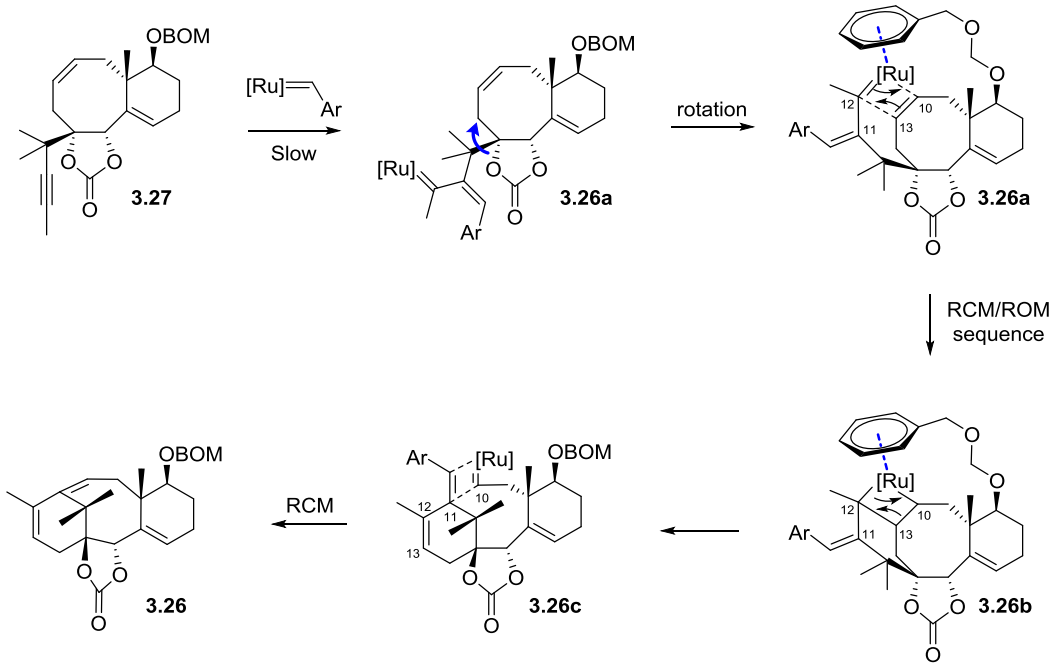
These results show that the C7-OBOM bicycle **3.27** can undergo ring-opening metathesis reaction, but this reaction tends to be rather difficult. In order to prove that this ring-opening metathesis of bicycle **3.27**, followed by further reaction, can be channelled toward the targeted tricycle **3.26**, a last experiment was set up. From our previous results on ring-closing dienyne metathesis, we had shown that the ABC tricyclic core of Taxol **3.26** was synthesised in a range of 35-40% yield. The idea behind this experiment was to submit one equivalent of bicycle **3.27** to the reaction mixture after the bicycle initially formed in the first instants of the reaction is totally consumed. If the final yield of tricycle **3.26** is superior of the usual 35-40% yield, this would indicate that the bicycle can be converted to the tricycle **3.26**. This experiment would quantify both conversion and degradation occurring during the process. Therefore, the precursor **3.19** was reacted with one equivalent of Zhan-1B complex in refluxing toluene for 5 h under a stream of argon to assumedly generate the tricycle **3.26** in 35-40% yield, then one equivalent of bicycle was added and the reaction mixture was run for another 12 h. Under these conditions 47% yield of the desired tricycle **3.26** was obtained as the only identifiable and isolatable product. No bicycle **3.27** remained, as shown in Scheme 3.40. This result definitely indicated that the

extra equivalent of the bicycle **3.27**, added after 5 h of reaction, was converted to the desired tricycle **3.26** in 10% yield, but also suffered from a great amount degradation (about 90%).



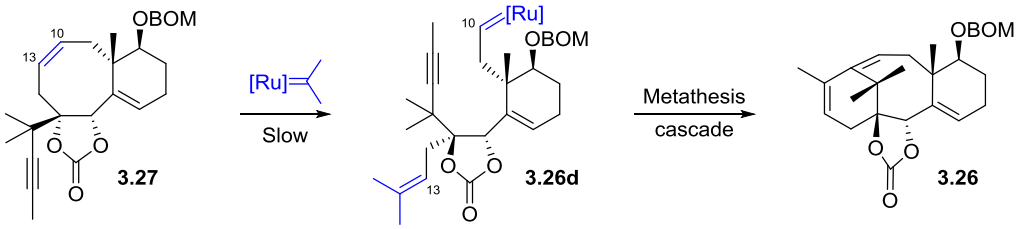
*Scheme 3.40: Conversion of bicycle **3.27** to tricycle **3.26***

In Scheme 3.41, we suggest a proposed mechanism for the conversion of bicycle **3.27** to tricycle **3.26**. First, the ruthenium catalyst would generate the vinyl carbene **3.26a** very slowly, due to the large steric hindrance. This is possibly why a large quantity of catalyst is needed to convert small quantities of bicycle **3.27**. Bond rotations would place the vinyl carbene in the ideal position, close to the C10-C13 olefin, to be able to perform a RCM/ROM sequence. In addition, the position of the phenyl group of the BOM protecting group fits well in the proposed model **3.26a** to stabilise and direct the metathesis to generate **3.26b**. Cycloreversion would produce the C10 carbene **3.26c** that can undergo a last metathesis cycle to form the ABC tricyclic core of Taxol **3.26**.



*Scheme 3.41: Possible mechanism for the conversion of the bicycle **3.27** to the tricycle **3.26***

A simpler mechanism can also be suggested (Scheme 3.42). The bicycle **3.27** can undergo ring-opening metathesis reaction with the *gem*-dimethyl ruthenium carbene to generate **3.26d**, followed by the dienyne metathesis cascade to form the desired tricycle **3.26**.

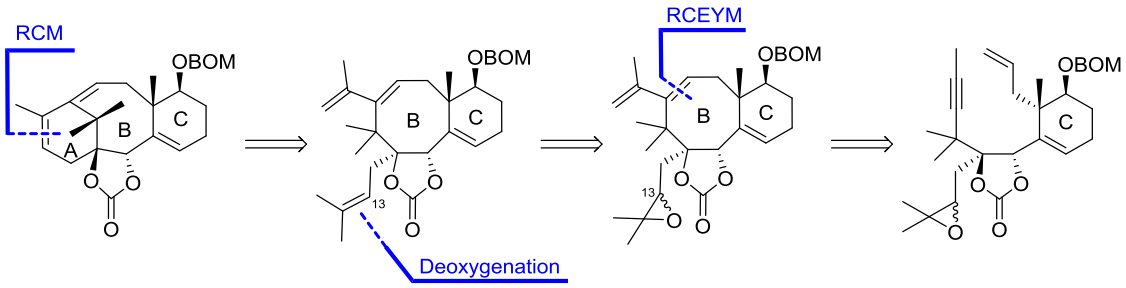


*Scheme 3.42: Possible mechanism for the conversion of the bicycle **3.27** to the tricycle **3.26***

3.6.6 Epoxy C7-OBOM

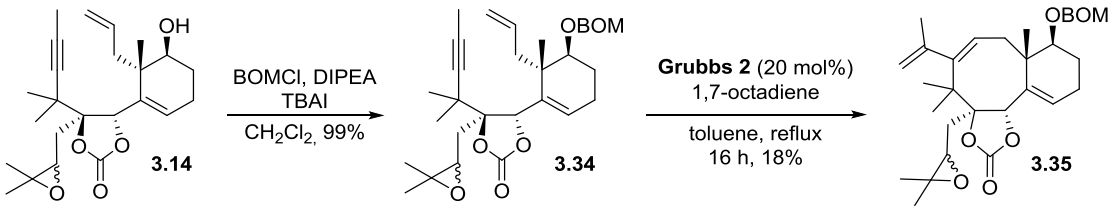
As stated above, a C13 epoxide derivative **3.14** can be easily made as shown in Scheme 3.16. We tried to take advantage of the formation of this side product by performing the metathesis cascade stepwise. Indeed protecting the C13 olefin would avoid the generation of any metathesis side product, such as the bicycle **3.27**. Only one pathway would be possible, a ring-closing enyne metathesis that would generate a BC ring system.

Deoxygenation of the C13 olefin would follow and finally the ring A would be closed by simple ring-closing metathesis to generate the desired ABC tricyclic ring system of Taxol (Scheme 3.43).



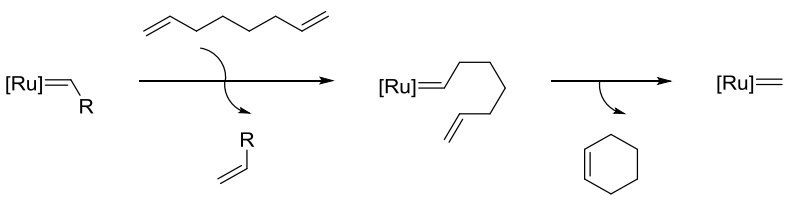
Scheme 3.43: Retrosynthesis of ABC tricycle using a stepwise metathesis strategy

Protection of the secondary C7-hydroxyl group of **3.14** using BOMCl, DIPEA and TBAI in refluxing CH_2Cl_2 generated the BOM protected epoxide **3.34** in 99% yield. Different enyne metathesis conditions were tested with different loadings of Grubbs' second-generation, Hoveyda-Grubbs 2 and Zhan-1B catalysts. Argon or ethylene atmospheres were also used in refluxing toluene. The best conditions were observed when 20 mol% of Grubbs' second-generation catalyst and 1,7-octadiene (as source of ethylene) were used in refluxing toluene for 16 h. Unfortunately the bicycle **3.35** was obtained in only 18% yield as illustrated in Scheme 3.44.



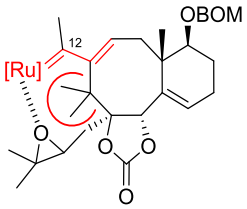
Scheme 3.44: Formation of BC ring system using enyne metathesis

1,7-octadiene was used as a cheap alternative of ethylene to generate the active methylene ruthenium species in higher concentration as shown in Scheme 3.45.



Scheme 3.45: Generation of active ruthenium carbene

The low yield obtained for the metathesis reaction was quite surprising but can be explained by a stabilisation of the final intermediate carbene from the C13 epoxide to the relatively stable vinyl ruthenium carbene. Also, this stable vinyl carbene is quite hindered and regeneration of the C12 olefin might be too challenging (Scheme 3.46).



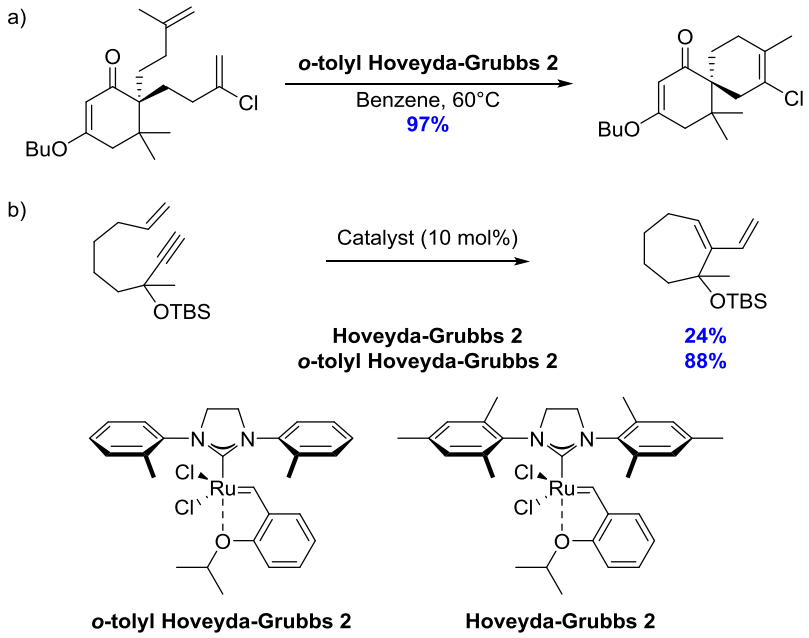
Scheme 3.46: Vinyl ruthenium carbene

3.7 Toward Better Catalysts

Another direction that has not been studied in this global optimisation process is the use of smaller second-generation Hoveyda-Grubbs 2 type catalysts. It has been made clear that having a C7 substituent drastically disfavours the dienyne metathesis process and therefore, drastically reduces the amount of tricycle **3.26** formed. Moreover, the steric hindrance around the alkyne dramatically narrows the access around the alkyne, which limits the rate of the tricycle **3.26** formation. Therefore, smaller catalysts should be used to promote the reactivity of this bulky alkyne. Indeed, reducing the residual bulk of the NHC ligand on the ruthenium centre would allow a better reactivity toward hindered reactive centres. This concept was already explored by Grubbs and co-workers, and efficiently applied toward the synthesis of sterically crowded olefins, like tetra-substituted olefins.[97] A few examples of these studies are shown in Scheme 3.47. In the first example (a), Stoltz and co-workers described a ring-closing metathesis that easily afforded a spirocyclic tetra-substituted olefin product in 97% yield under mild conditions. In the second example (b) reported by Nay and co-workers is a 7-membered ring-closing enyne metathesis on hindered propargylic derivative that was efficiently performed in 88% yield with the smaller

[97] Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589-1592. Laroche, B.; Detraz, M.; Blond, A.; Dubost, L.; Mailliet, P.; Nay, B. *J. Org. Chem.* **2015**, *80*, 5359-5363. White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810-811.

o-tolyl Hoveyda-Grubbs 2 catalyst, while the original and larger version of this catalyst only afforded the desired enyne product in 24% yield.



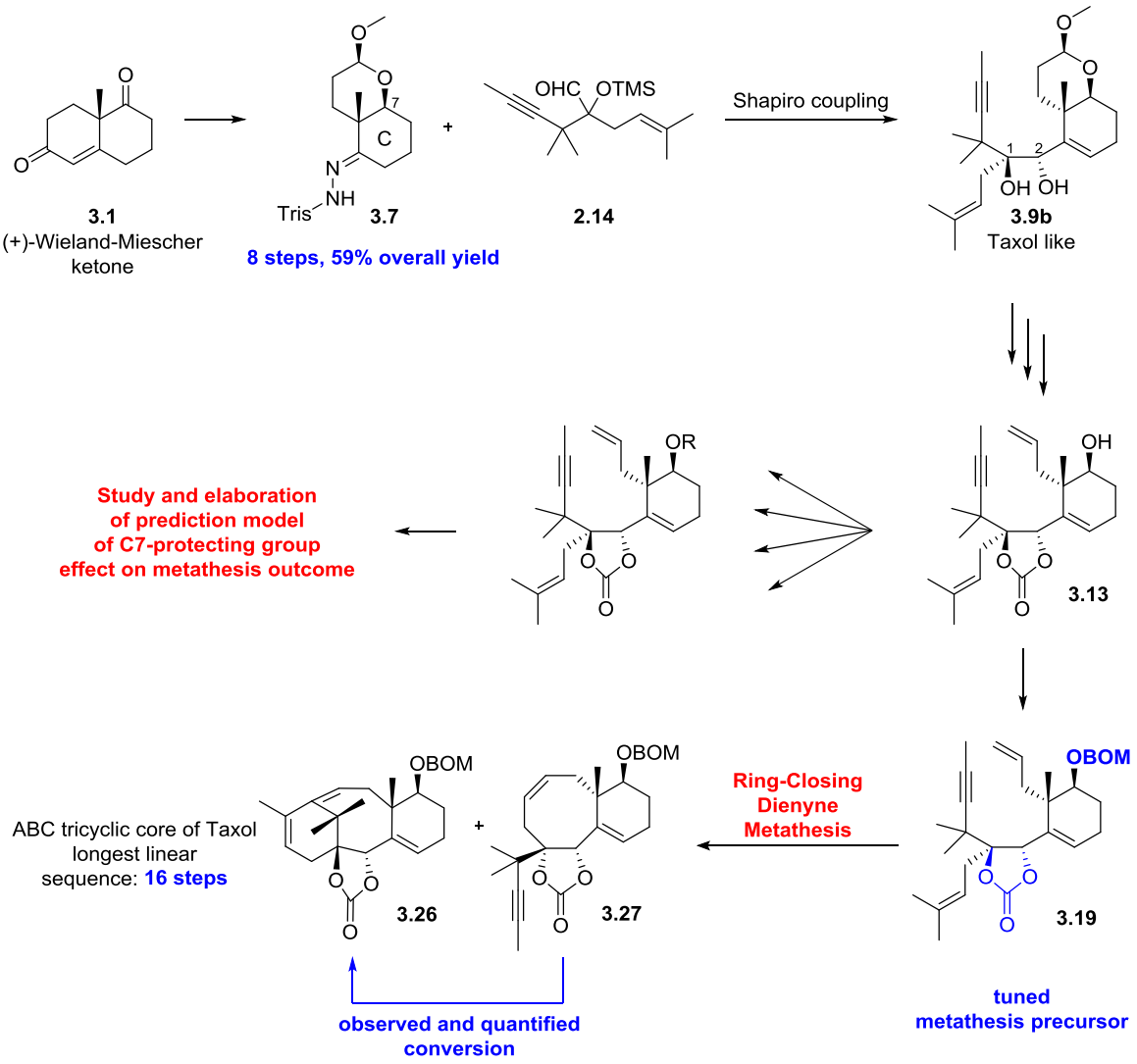
Scheme 3.47: Hindered ring-closing metatheses

The use of this commercially available size-modified Hoveyda-Grubbs second-generation catalyst could be a very good option toward better ring-closing dienyne metathesis efficacy on substrate **3.19**. Indeed, it could promote an easier access to the dienyne metathesis pathway with a catalytic quantity of catalyst, milder conditions, easier purification and finally better yields of the ABC tricyclic core of Taxol.

3.8 Conclusion

In conclusion, starting from the (+)-Wieland-Miescher ketone, a more robust, reliable and scalable synthesis of hydrazone **3.7** was developed. This expeditious synthesis led to perform the Shapiro coupling with aldehyde (±)-**2.14** on a large scale to deliver C1-C2 Taxol-like configuration diol **3.9b**. Efficient generation of different metathesis precursors led to study the critical effect of the C7-protecting group on the metathesis outcome. Experiments showed that these protecting groups had to be rather small to help directing the metathesis cascade. C7-OBOM ABC tricyclic core of Taxol **3.26** was successfully synthesised in a range of 35-40% yield as the only metathesis product. In

addition, the dienyne ring-closing metathesis mechanism was investigated and sufficient evidence was found to demonstrate and quantify the conversion of bicycle **3.27** into the desired tricycle **3.26**, even if this conversion was rather small. Unfortunately, the efficiency of the metathesis was not as successful as for the C7-deoxy derivative **2.43**, but sufficient quantity of product was synthesised to continue the study toward a formal synthesis of Taxol. These synthetic efforts will be disclosed in the next chapter (Scheme 3.48).

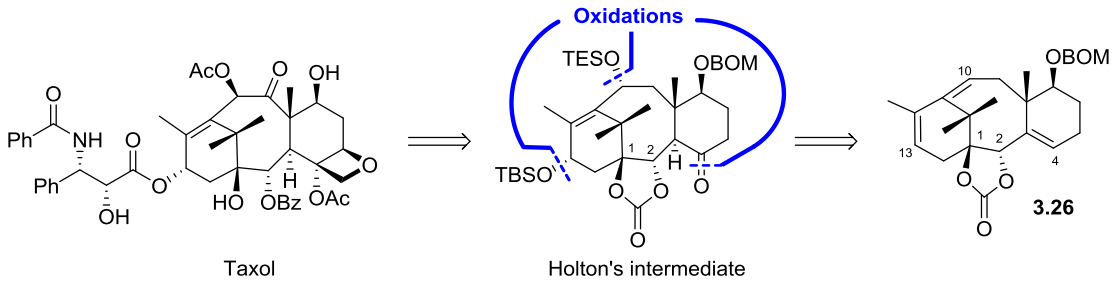


Scheme 3.48: Studies of the ABC tricyclic core of Taxol synthesis

4. Toward a Formal Synthesis of Taxol

4.1 Retrosynthesis

After synthesising the ABC tricyclic core of Taxol by a successful ring-closing dienyne metathesis, we focused our studies toward a formal synthesis of Taxol. As discussed before, the total synthesis that Holton and co-workers developed is one of the more efficient of all, therefore we directed our synthetic efforts toward an intermediate Holton *et al.* synthesised.[20] This intermediate contains a C1-C2 cyclic carbonate and a C7 OBOM protecting group that our previously synthesised tricycle **3.26** also contains. To accomplish the synthesis of this intermediate, selective oxidations at C4, C10 and C13 are needed (Scheme 4.1).



Scheme 4.1: General retrosynthesis

Indeed the first challenge of this synthesis is the discrimination of the three trisubstituted olefins (Figure 4.1). At the C4 position lies a fused trisubstituted olefin close enough for the cyclic carbonate to direct reagents toward this olefin. At the C13 position is found a cyclic trisubstituted olefin and at the C10 position sits a trisubstituted bridgehead olefin. It is noteworthy that these two trisubstituted olefins are not conjugated because the AB bicycle torsion forbids the orbital overlap. That was also observed in the X-ray diffraction analysis of the C7-deoxy tricyclic core of Taxol **2.45** (Figure 2.2).

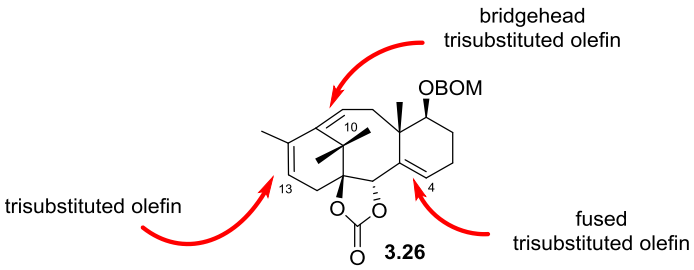


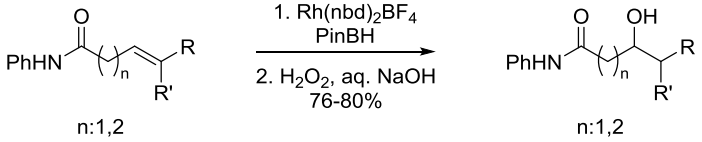
Figure 4.1: Differentiation of the olefins

4.2 Alkenes Differentiation: Reactivity Screening

To classify the reactivity of the triolefinic tricycle **3.26**, different types of reactions were first tested on the C7-deoxy tricycle **2.43**. C7-deoxy **2.43** and C7-OBOM **3.26** derivatives have the same tricyclic skeleton and therefore should have similar reactivities.

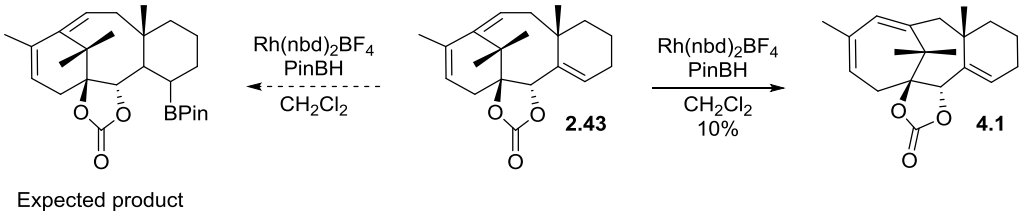
4.2.1 Directed Reactions

Even if hydroboration of trisubstituted alkenes does not proceed very well, Tacaks and co-workers reported interesting results.[98,99] They developed hydroboration reactions using bis(norbornadiene)rhodium(I) tetrafluoroborate and pinacolborane, in which they observed carbonyl-directed hydroboration of trisubstituted olefins (Scheme 4.2).



Scheme 4.2: Carbonyl-directed hydroboration of trisubstituted olefins

Using the reagents stated above, the isomerised tricycle **4.1** was produced in 10% yield and unfortunately, no hydroboration product was observed (Scheme 4.3).

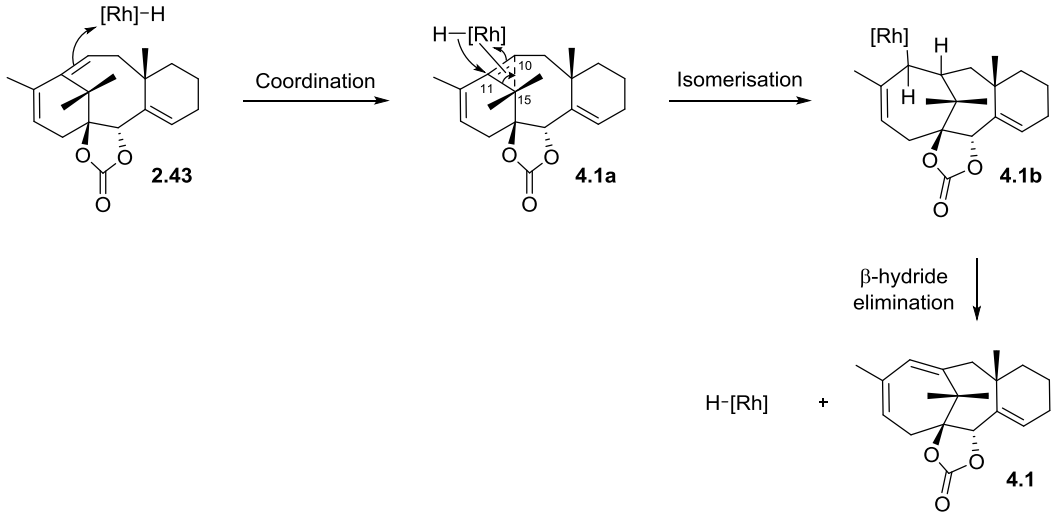


Scheme 4.3: Hydroboration attempt

A possible mechanism of the isomerisation of tricycle **2.43** to **4.1** is shown in Scheme 4.4. First the reactive bridgehead olefin would coordinate the rhodium hydride species to generate derivative **4.1a**. The hydride species would attack at the bridgehead position to

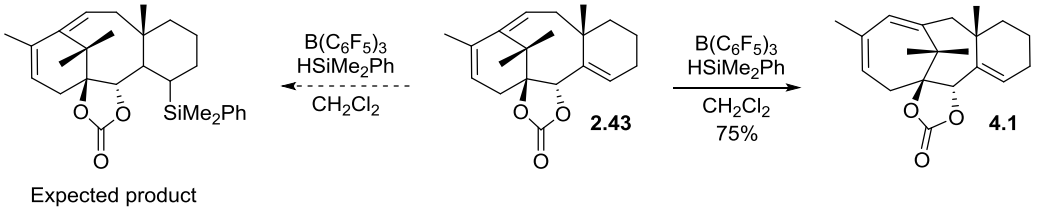
[98] Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1988**, *110*, 6917-6918.
[99] Smith, S. M.; Thacker, N. C.; Takacs, J. M. *J. Am. Chem. Soc*. **2008**, *130*, 3734-3735. Smith, S. M.; Takacs, J. M. *J. Am. Chem. Soc*. **2010**, *132*, 1740-1741.

fragment the C11-C15 bond and isomerise into **4.1b**. β-Hydride elimination of the metalloid adduct **4.1b** would provide the isomerised tricycle **4.1**.



Scheme 4.4: Possible mechanism of isomerisation

Using the same cyclic carbonate directing group strategy, a hydrosilylation was attempted using the tris(pentafluorophenyl)borane Lewis acid and a silane derivative.[100] Cyclic carbonate and borane Lewis acid interactions could have directed the hydrosilylation onto the neighbouring C4 olefin. However when **2.43** was treated with these reagents it rapidly converted to the [4.4.1] tricycle **4.1** in 75% yield (Scheme 4.5).

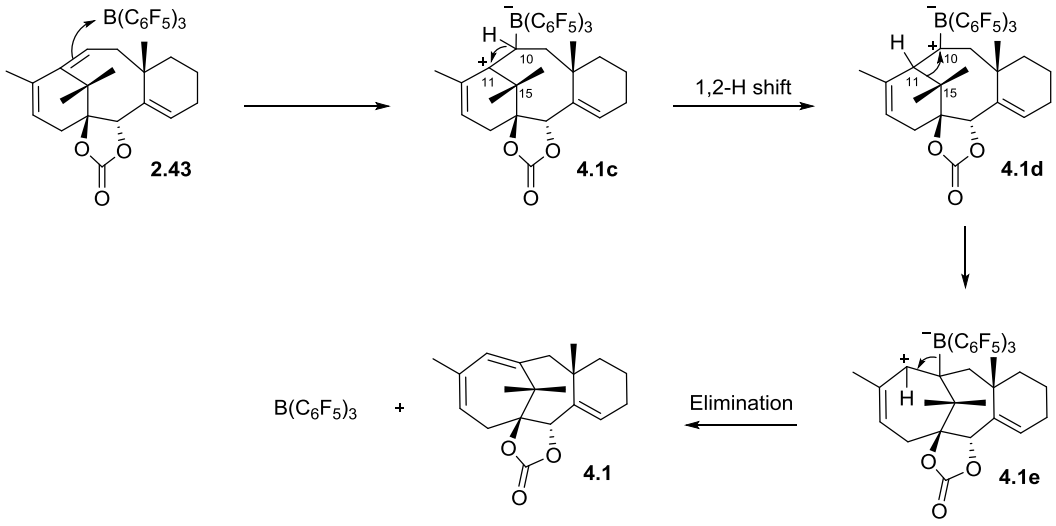


Scheme 4.5: Hydrosilylation attempt

Another possible mechanism can be suggested for these conditions (Scheme 4.6). Reaction between the bridgehead olefin and the borane Lewis acid would generate the C11 carbocation **4.1c** followed by a 1,2-hydride shift to form **4.1d**. The C11-C15 bond would

[100] Rubin, M.; Schwier, T.; Gevorgyan, V. *J. Org. Chem.* **2002**, *67*, 1936-1940.

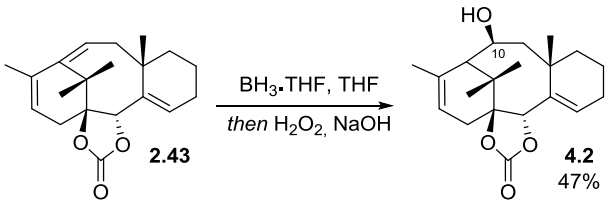
then fragment to neutralise the C10 carbocation and produce the isomerised product **4.1e**, which would undergo elimination of the borane species to provide the tricycle **4.1**.



Scheme 4.6: Possible mechanism of isomerisation

4.2.2 Non-Directed Reactions

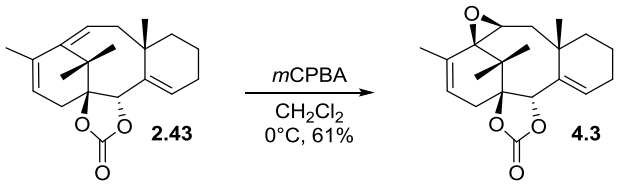
Since the use of metal hydride species led to isomerised tricyclic product **4.1**, more conventional methods were tested to discriminate these three olefins. Therefore, hydroboration of the tricycle **2.43** using borane-THF complex in THF followed by usual oxidation conditions provided the C10 alcohol **4.2** in 47% yield. The stereochemistry of the newly formed alcohol was opposite to the one present in Holton's intermediate as shown in Scheme 4.7.



*Scheme 4.7: Hydroboration of triene **2.43***

Epoxidation of the tricycle **2.43** with 1 equivalent of *m*CPBA was attempted to identify the most reactive olefin under these epoxidation conditions. Once again the

bridgehead olefin was the most reactive position and the epoxide **4.3** was obtained in 61% yield as the sole product (Scheme 4.8).

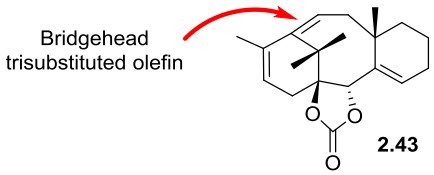


Scheme 4.8: Epoxidation using mCPBA

Unfortunately, this epoxide also has the opposite configuration compared to Holton's intermediate, but the right configuration for Taxol. Apparently, the adjacent *gem*-dimethyl moiety was not bulky enough to avoid the formation of the epoxide on the same face. In that case we believe that the tricycle skeleton conformation would totally block the concave face of the olefin, making the formation of the other diastereoisomer rather difficult.

4.3 C1-C2 Cyclic Carbonate

It was clear that the bridgehead position was the most reactive olefin of the tricyclic skeleton. Therefore, functionalisation of this position needed to be undertaken prior to the other two alkenes (Scheme 4.9).

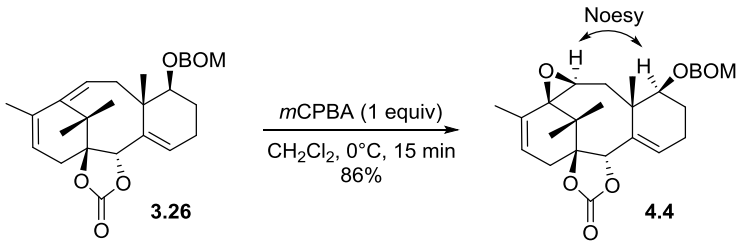


Scheme 4.9: Most reactive olefin

4.3.1 Strain Evaluation

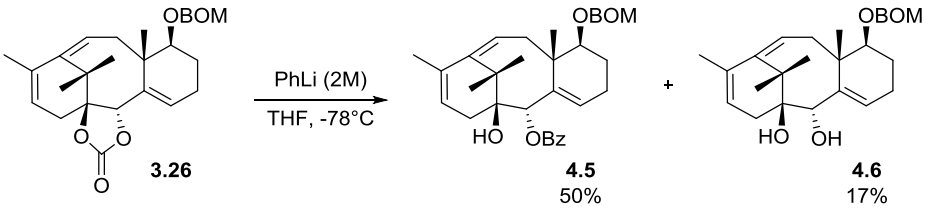
The best result encountered during the preliminary studies was the formation of the epoxide **4.3** in 61% yield. Therefore, it was decided to synthesise the corresponding C7-OBOM epoxide. Also it was interesting to test if the C7-OBOM group could play a role in

the diastereoselectivity of this epoxidation as it could block the convex face of the tricyclic core and lead to the other isomer needed for the formal synthesis. Therefore, the triene **3.26** was treated with 1 equivalent of *m*CPBA at 0°C for only 15 minutes to give a 86% yield of the epoxy derivative **4.4** (Scheme 4.10).



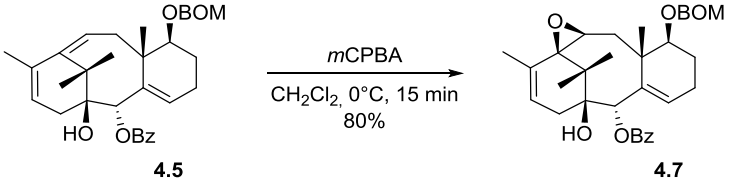
Scheme 4.10: Epoxidation using mCPBA

The configuration of the epoxide is the same as the one observed for the C7-deoxy compound **4.3**. Therefore, it was decided to probe the effect of the C1-C2 protecting group as a C2 benzoate could lead to a more flexible tricycle and therefore limit the formation of the epoxide on the convex face and favour the formation of its concave isomer. To do so, the tricycle **3.26** was treated with phenyl lithium at -78°C in THF to generate both the C2 benzoate **4.5** in 50% yield and the C1-C2 diol **4.6** in 17% yield (Scheme 4.11).



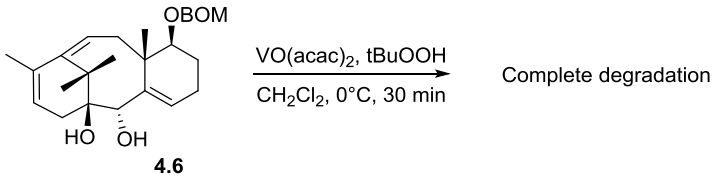
Scheme 4.11: C1-C2 cyclic carbonate opening

When the tricycle **4.5** was treated under the same epoxidation conditions as previously, 80% yield of the C2 benzoate β-epoxide **4.7** was obtained as shown in Scheme 4.12.



*Scheme 4.12: Epoxidation of C2 benzoate tricycle **4.5***

Changing the C1-C2 protecting group did not affect the accessibility of the concave face of the tricycle, so with the C1-C2 diol in hand, a directed allylic epoxidation was used. Therefore, diol **4.6** was treated with $VO(acac)_2$ and *t*-butyl hydroperoxide at 0°C. Unfortunately, total decomposition of the starting diol occurred in less than 30 minutes, as shown in Scheme 4.13.

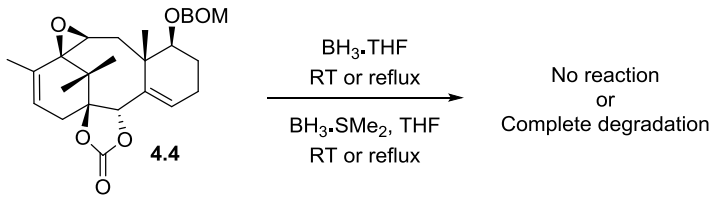


Scheme 4.13: Allylic epoxidation using $VO(acac)_2$

In view of these prior results, it was decided to pursue our studies toward a formal synthesis from the monoepoxide **4.4**, in which the bridgehead position could not react inopportunely.

4.3.2 Hydroboration

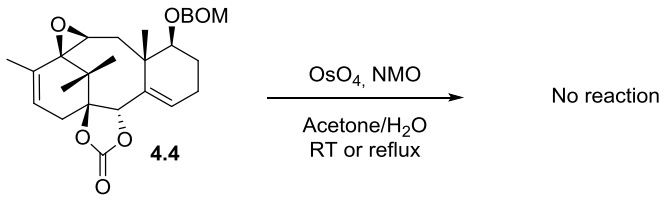
Simple alkene oxidation reactions were then tried to discriminate the remaining C3-C4 and the C12-C13 olefins. Hydroboration reactions were tested using small and reactive borane species such as borane-THF complex or borane-dimethyl sulfide. Both boranes were tested in THF at either room temperature or reflux with amount of reagents from 1 up to 10 equivalents, but the starting material either did not react or only underwent total degradation (Scheme 4.14).



*Scheme 4.14: Hydroboration attempts on **4.4***

4.3.3 Dihydroxylation

Upjohn dihydroxylation was also attempted, but osmium tetroxide and NMO in a 1:1 acetone and water ratio at either room temperature or reflux did not lead to any reaction (Scheme 4.15).

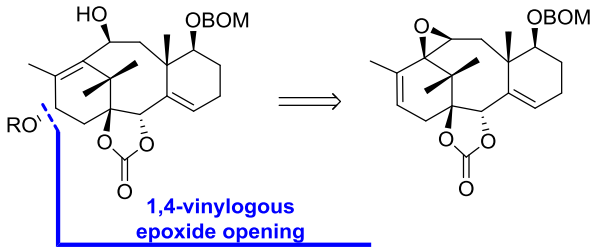


Scheme 4.15: Upjohn dihydroxylation

This was probably due to the large steric hindrance of the adjacent groups around the remaining C3-C4 and C12-C13 olefins as well as the shape of the tricyclic core that could have prohibited any reaction.

4.3.4 Vinylogous Epoxide opening

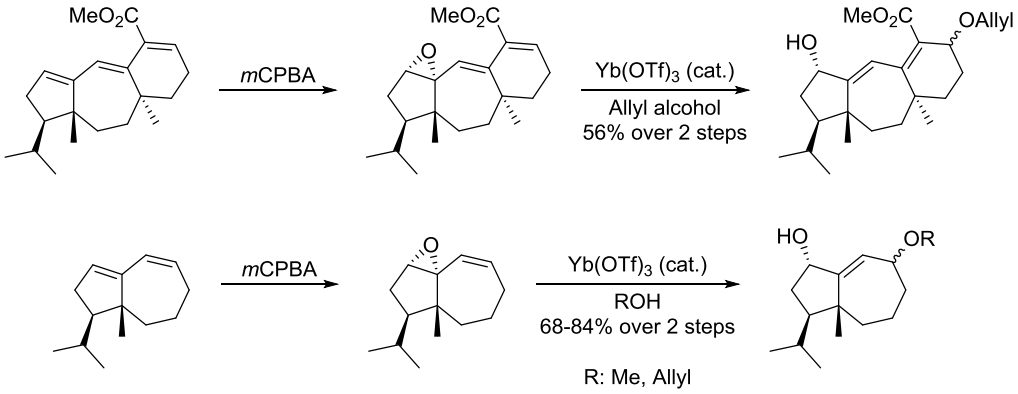
It was decided to take advantage of the vinyl epoxide functionality. Under different activation methods, the vinylic epoxide can be activated, thus increasing the electrophilicity of the alkene toward a 1,4-vinylogous epoxide opening (Scheme 4.16).



Scheme 4.16: Vinylogous epoxide opening *retrosynthesis*

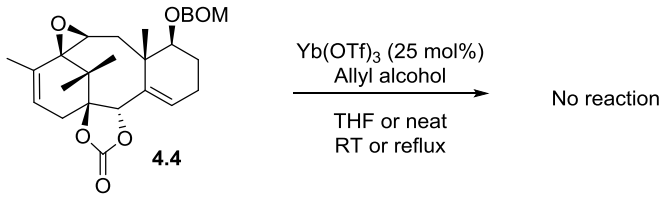
4.3.4.1 Lewis-Acid Catalysed

Hanna and co-workers reported a $Yb(OTf)_3$-catalysed alcoholysis of vinyl epoxides, where S_N2'products were obtained, as mixtures of *anti* and *syn* diastereomers in 56% yield and 68-84% yield over 2 steps on simpler substrates (Scheme 4.17).[101]



Scheme 4.17: Lewis acid catalysed reaction of vinyl epoxides

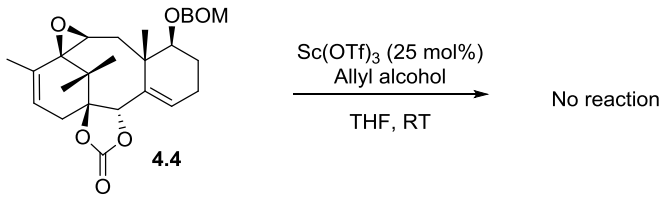
When this reaction was tested on vinyl epoxide **4.4** with 25 mol% of $Yb(OTf)_3$ with allyl alcohol in THF or neat, at room temperature or reflux, the starting material was fully recovered in each case (Scheme 4.18).



*Scheme 4.18: Lewis-acid catalysed reaction of **4.4***

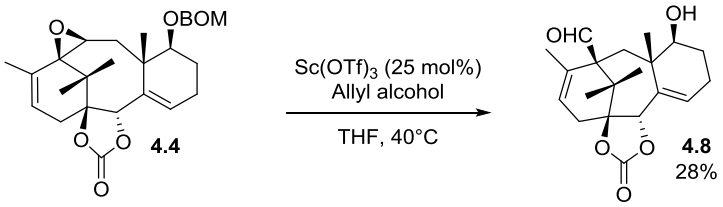
These failures were probably due to the Lewis acid. Indeed this ytterbium triflate catalyst is a mild and soft Lewis acid. Therefore, $Yb(OTf)_3$ was switched to its scandium congener, a much stronger Lewis acid. When vinyl epoxide **4.4** was treated with $Sc(OTf)_3$ and allyl alcohol in THF at room temperature, no conversion was observed (Scheme 4.19).

[101] Boyer, F.-D.; Hanna, I. *J. Org. Chem*. **2005**, *70*, 1077-1080.



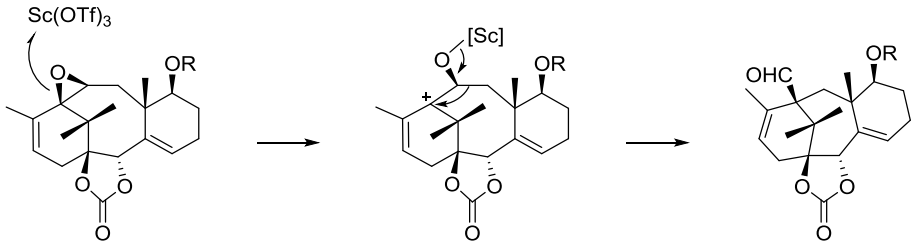
*Scheme 4.19: $Sc(OTf)_3$-catalysed reaction of **4.4***

When the same reaction was heated at 40°C, vinyl epoxide **4.4** underwent a ring-contraction reaction and subsequent C7-BOM deprotection to give **4.8** in 28% yield (Scheme 4.20).



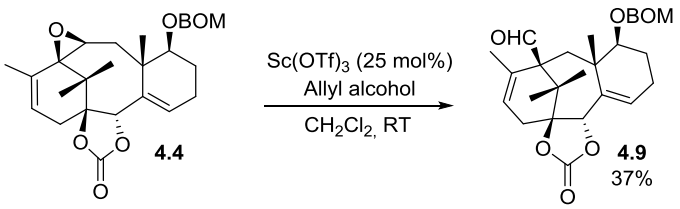
*Scheme 4.20: Ring-contraction reaction of vinyl epoxide **4.4***

A possible mechanism for the ring-contraction reaction is proposed. Opening of the epoxide by the Lewis acid would generate a bridgehead carbocation that would undergo ring contraction to access a 6-7-6 tricyclic aldehyde, as shown in Scheme 4.21.



Scheme 4.21: Possible mechanism for the ring-contraction reaction

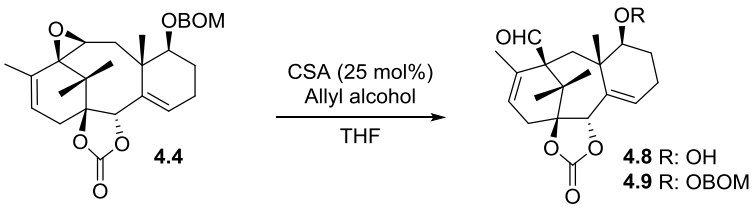
When the same reaction was tried in CH_2Cl_2, a less coordinating solvent than THF, the C7-OBOM ring contraction product **4.9** was formed at room temperature in 37% yield (Scheme 4.22).



*Scheme 4.22: Ring contraction of vinyl epoxide **4.4** in CH_2Cl_2*

4.3.4.2 Brønsted-Acid Catalysed

It is known that $Sc(OTf)_3$ can react with CH_2Cl_2 to generate small quantities of TfOH. We reasoned in this case that maybe the triflic acid generated *in situ* could promote the ring contraction, so we added 25 mol% of CSA in THF and the ring-contraction reaction occurred with partial deprotection of the BOM protecting group. The yield of both products was not determined (Scheme 4.23).



Scheme 4.23: Brønsted-acid catalysed ring contraction

This reaction proves that, even under a catalytic quantity of Brønsted acid, the ring contraction occurred. Therefore, Brønsted-acid mediated opening of vinyl epoxide **4.4** was not attempted.[102]

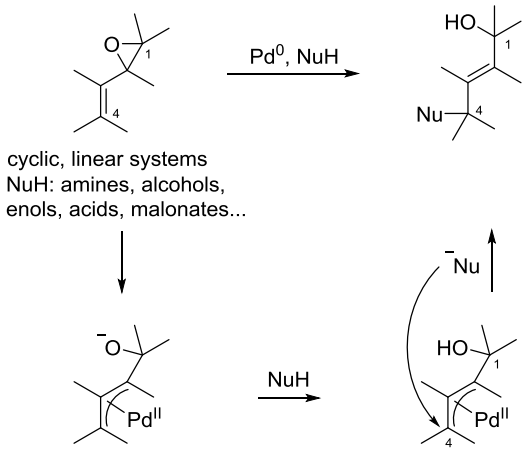
4.3.4.3 Palladium Catalysed

Another class of reaction was tested to open the vinyl epoxide using a palladium catalysed Tsuji-Trost like reaction. This process is well documented in the literature and the general reaction is presented in Scheme 4.24.[103] Pd(0) neutral species would open the

[102] Di Bussolo, V.; Frau, I.; Checchia, L.; Favero, L.; Pineschi, M.; Uccello-Barretta, G.; Balzano, F.; Roselli, G.; Renzi, G.; Crotti, P. *Tetrahedron* **2011**, *67*, 4696-4709. Uchida, K.; Ishigami, K.; Watanabe, H.; Kitahara, T. *Tetrahedron* **2007**, *63*, 1281-1287. Usami, Y.; Suzuki, K.; Mizuki, K.; Ichikawa, H.; Arimoto, M. *Org. Biomol. Chem*. **2009**, *7*, 315-318.; Craven, P. G. E.; Taylor, R. J. K. *Synlett* **2013**, 363-368.

[103] Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tet. Lett*. **1981**, *22*, 2575-2578. Trost B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969-5972. He, J.; Ling, J.; Chiu, P. *Chem. Rev*. **2014**, *114*, 8037-8128.

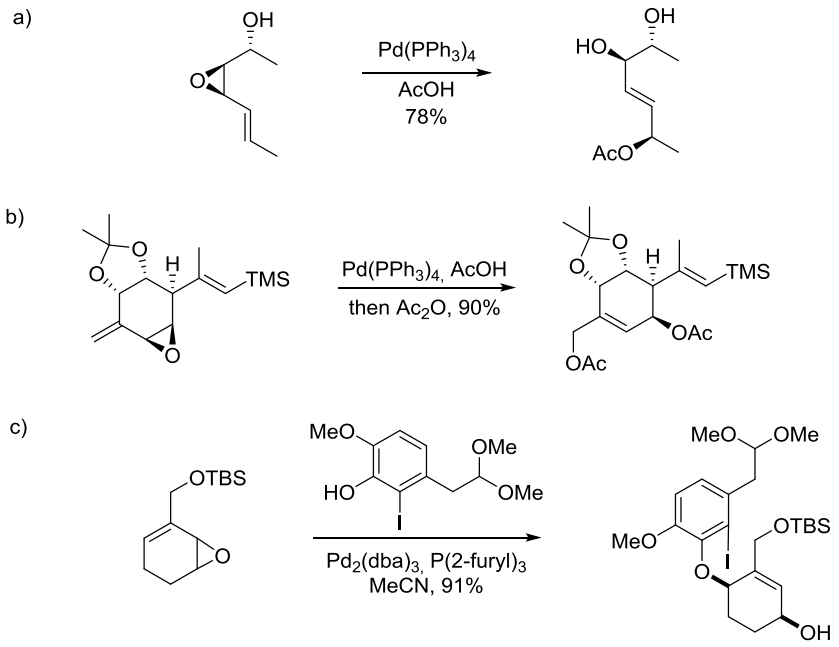
epoxide to generate a π-allyl Pd(II) derivative. Acid-base exchange between the alkoxide and the protic nucleophile followed by nucleophilic attack at the C4 position and by subsequent β-elimination of palladium would produce the expected alcohol.



Scheme 4.24: Tsuji-Trost like reaction of vinyl epoxides

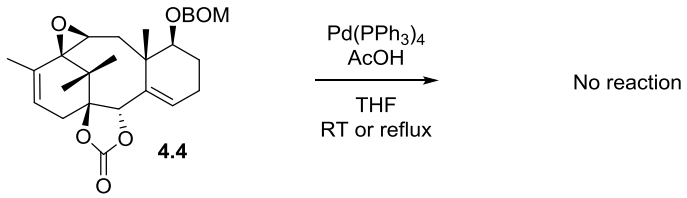
A few examples are shown in Scheme 4.25a, b and c.[104] First a simple vinyl epoxide underwent the ring opening with palladium *tetrakis*(triphenylphosphine) in acetic acid in 78% yield. In equation b), the cyclic system was shown to undergo vinyl epoxide opening under the same set of conditions to give the allylic acetate after subsequent acetylation in 90% yield. In equation c), different conditions were used. A soft phenolic nucleophile and a cyclic trisubstituted olefin were treated with $Pd(dba)_2$ and $P(2\text{-furyl})_3$ in acetonitrile to generate the expected alcohol product in 91% yield. In all these reactions, access to the vinyl epoxide by Pd(0) was rather easy, as no bulky substituents or unfavourable conformations could prevent the formation of the essential π-allyl Pd(II) complex.

[104] Uchida, K.; Yokoshima, S.; Kan, T.; Fukuyama, T. *Org. Lett*. **2006**, *8*, 5311-5313. Macklin, T. K.; Micalizio, G. C. *J. Am. Chem. Soc*. **2009**, *131*, 1392-1393. Yoshida, S.; Asano, M.; Kobayashi, Y. *Tetrahedron Lett*. **2005**, *46*, 7243-7246. Kobayashi, Y.; Yoshida, S.; Asano, M.; Takeuchi, A.; Acharya, H. P. *J. Org. Chem*. **2007**, *72*, 1707-1716.



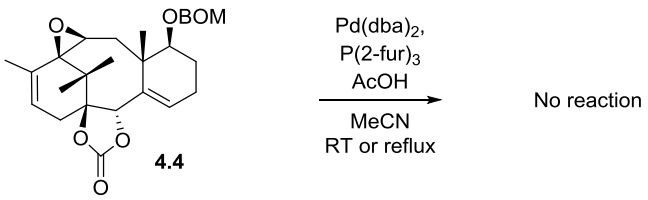
Scheme 4.25: Palladium-catalysed alkoxyation of vinyl epoxides

When the vinyl epoxide **4.4** was treated with palladium *tetrakis*(triphenylphosphine) and acetic acid in THF at either room temperature or reflux, no conversion of vinyl epoxide **4.4** occurred and the starting material was fully recovered each time (Scheme 4.26).



*Scheme 4.26: Palladium-catalysed opening attempt of vinyl epoxide **4.4***

Another set of conditions was tested using $Pd(dba)_2$, $P(2\text{-furyl})_3$ and acetic acid in acetonitrile at either room temperature or reflux, which did not convert any trace of the starting material **4.4** (Scheme 4.27).

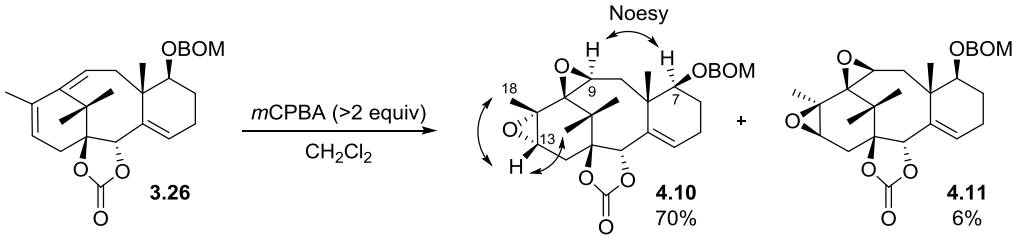


*Scheme 4.27: Other palladium catalysed opening of vinyl epoxide **4.4***

The failure of the above reactions is probably due to the conformation of vinyl epoxide **4.4**, which made the formation of the essential π-allyl Pd(II) complex impossible. It could also explain why all the different reactions tested on this substrate failed. The shape of the molecule blocks the attack of reagents on the concave face and the large bulky *gem*-dimethyl group prevents attack on the convex face, which makes the opening of the vinyl epoxide **4.4** challenging.

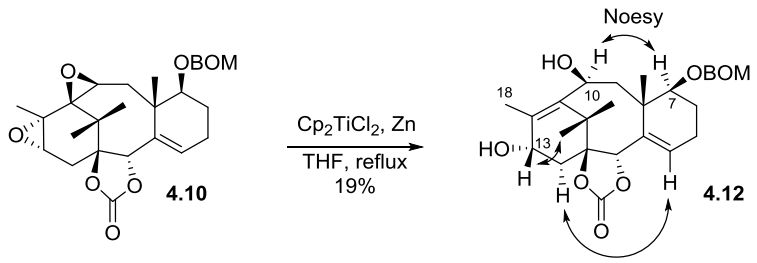
4.3.5 Diepoxidation

More interestingly, when more than 2 equivalents of *m*CPBA were used, 2 diastereomeric diepoxides were formed in 76% yield (70% of *anti* diepoxide **4.10** and 6% of the *syn* diepoxide **4.11**). It is worth mentioning that no epoxidation occurred on the C3-C4 olefin even with a large excess of *m*CPBA (Scheme 4.28).



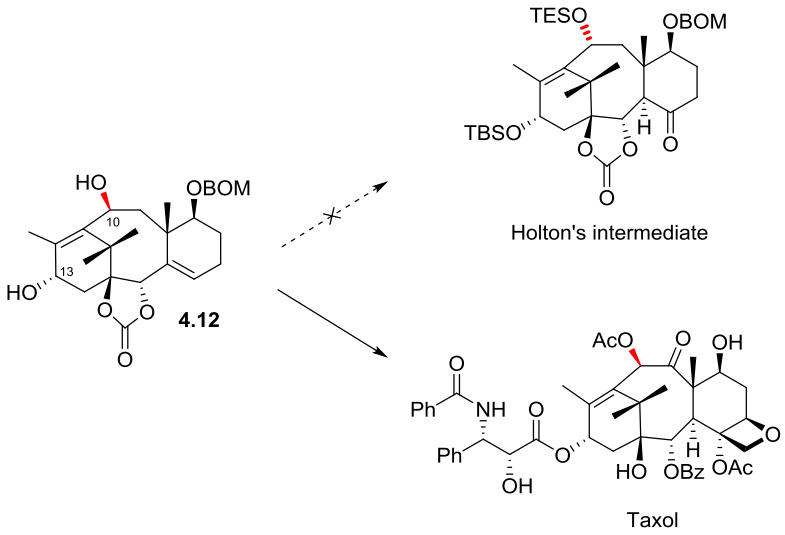
Scheme 4.28: Epoxidation reaction

The *anti* diepoxide **4.10** was then treated with bis(cyclopentadienyl)titanium(IV) dichloride and zinc to form the active Ti(III) species in refluxing THF for a few hours and led to the formation of *anti* 1,4-diol **4.12** in 19% yield (Scheme 4.29). When this reaction was reproduced at room temperature, no conversion into the diol **4.12** occurred. When the reaction was left for a long period of time, complete degradation of products occurred. Also, if the THF was not carefully and cautiously degassed, the reaction did not proceed.



Scheme 4.29: Anti 1,4-diol synthesis

Since the best yield for the synthesis of the *anti* 1,4-diol **4.12** is less than 20% yield, another strategy had to be found. Also, it is interesting to note that when Granja and co-workers tried this 1,3-diepoxide Ti(III) radical opening on similar substrates,[105] no opening of the *anti* 1,3-diepoxide occurred, but only the *cis* 1,3-diepoxide could undergo this reaction. From these results, it is now clear that a formal synthesis is highly compromised since we obtain the opposite configuration at C10 compared to the Holton's intermediate. However, since we obtain the required configuration at C10 for Taxol, we decided to pursue the synthesis of a more advanced Taxol intermediate (Scheme 4.30).

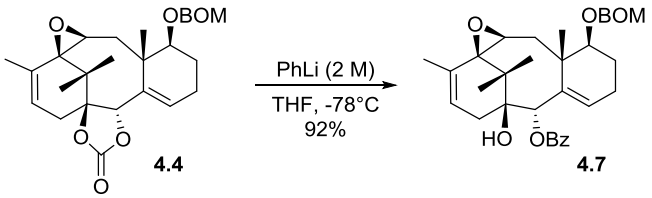


*Scheme 4.30: Stereochemistry comparison of anti 1,4-diol **4.12**, Holton's intermediate and Taxol*

4.4 C2 Benzoate

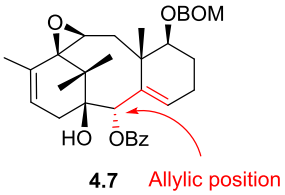
To limit the strain of the tricycle and enhance the reactivity of the vinyl epoxide moiety, the C1-C2 cyclic carbonate protecting group was opened as described previously using a solution of phenyllithium in THF at low temperature. Under these conditions, the C2-benzoate vinylic epoxide **4.7** was efficiently synthesised in 92% yield (Scheme 4.31).

[105] Aldegunde, M. J.; Castedo, L.; Granja, J. R. *Chem. Eur. J.* **2009**, *15*, 4785-4787.



Scheme 4.31: Opening of the C1-C2 cyclic carbonate

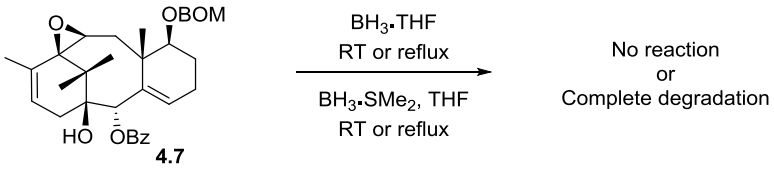
Once again, simple reactions on alkenes were tested. The palladium-catalysed Tsuji-Trost reaction was not attempted on this substrate as the C2 benzoate sits in an allylic position (Scheme 4.32).



Scheme 4.32: C2 benzoate allylic position

4.4.1 Hydroboration

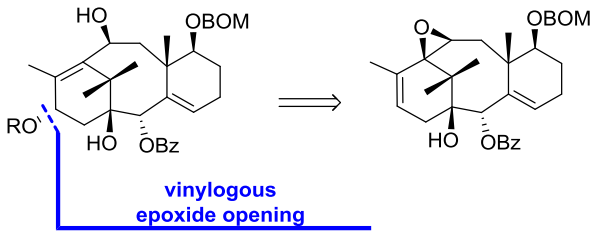
Hydroboration of vinyl epoxide **4.7** was investigated, but once again, using standard borane reagents such as borane-THF complex or borane-dimethyl sulfide complex at room temperature or reflux, did not lead to any of the desired product. Only degradation or no conversion occurred (Scheme 4.33).



Scheme 4.33: Hydroboration attempts

4.4.2 Vinylogous Epoxide Opening

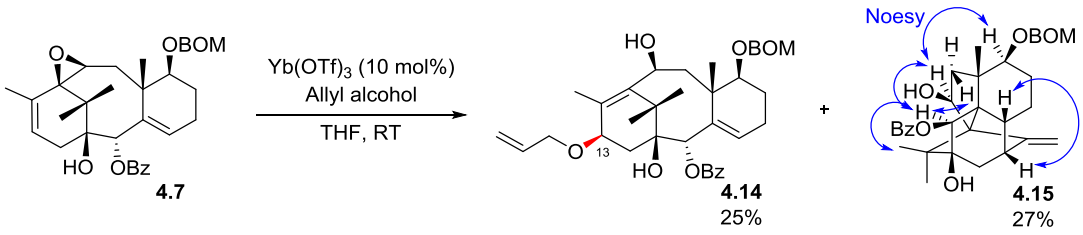
Vinylogous epoxide opening reactions similar to the ones tested with vinyl epoxide **4.7** were investigated (Scheme 4.34).



Scheme 4.34: Vinylogous epoxide opening retrosynthesis

4.4.2.1 Lewis-Acid Catalysed

As for the vinyl epoxide **4.4** with the C1-C2 carbonate protecting group, the benzoate vinyl epoxide **4.7** was treated with $Yb(OTf)_3$ and allyl alcohol at room temperature. In this case, the 1,4-addition product **4.14** was synthesised in 25% yield, with the wrong configuration at C13 for Taxol. Another interesting product was formed during the reaction: the pentacyclic product **4.15** was obtained in 27% yield as shown in Scheme 4.35.

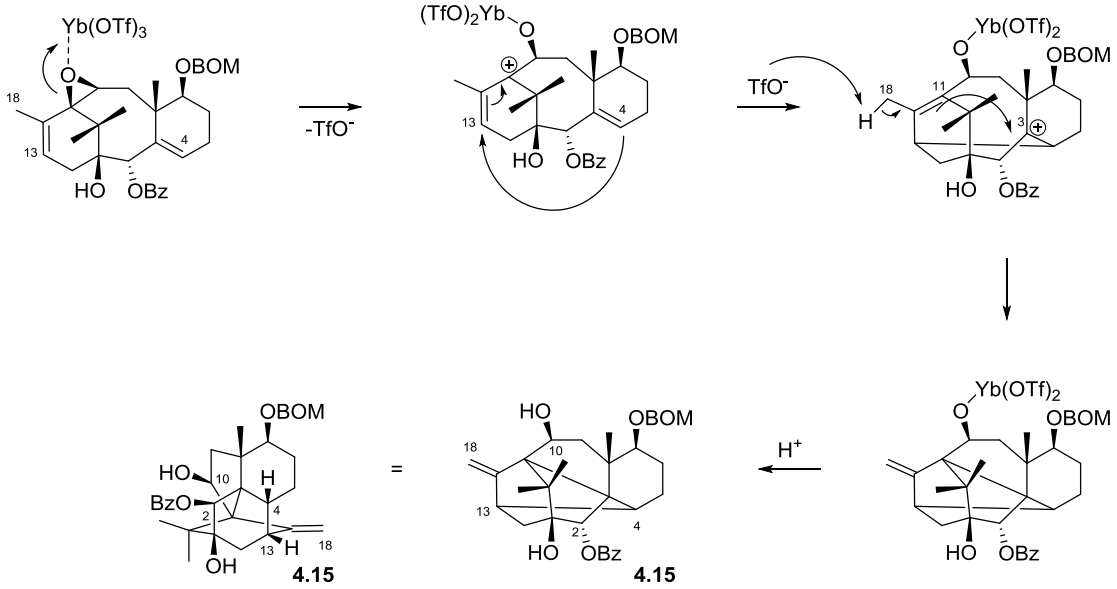


Scheme 4.35: 1,4-addition catalysed by $Yb(OTf)_3$

These results also proved that under the same reaction conditions, the C2 benzoate **4.7** and the carbonate **4.4** did not have the same reactivity. No ring-contraction products such as **4.8** or **4.9** were produced during the reaction with the C2-benzoate series. The internal strain generated by the C1-C2 cyclic carbonate group onto the tricyclic skeleton of **4.4** could explain such a dramatic difference of reactivity at the C13 position.

A possible mechanism for the formation of the pentacyclic product **4.15** is proposed below. Opening of the epoxide, catalysed by the soft ytterbium Lewis acid and generation of the bridgehead carbocation, is followed by the C3-C4 alkene attack at C13 to neutralise the newly formed bridgehead carbocation at C11. Proton abstraction on the C18 methyl group promotes attack of the tetrasubstituted olefin on the C3 carbocation and creates a C11-C3 bond to finally provide the pentacycle **4.15**. This mechanism is highly plausible as

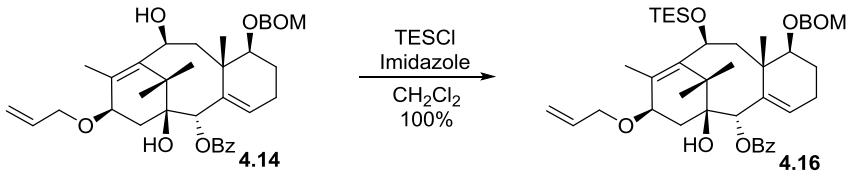
the two reacting C3-C4 and C12-C13 alkenes of the vinyl epoxide **4.7** are close to each other in space (Scheme 4.36).



*Scheme 4.36: Possible mechanism of formation of pentacycle **4.15***

The structure was determined by NMR experiments. The disappearance of characteristic signals corresponding to the C18 methyl group, C3-C4 and C12-C13 olefins were observed. No X-ray diffraction analysis could be obtained, neither the pentacycle derivative **4.15** nor the C2 and C10 *p*NO_2 or *p*Br benzoate derivatives were crystalline.

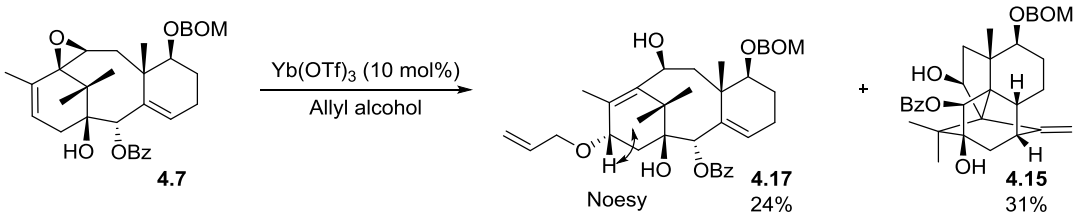
In order to explore the steric hindrance at the C10 position, the C10 alcohol was protected using soft conditions, such as TESCl and imidazole to produce quantitatively the TES protected 1,4-diol adduct **4.16** as shown in Scheme 4.37.



Scheme 4.37: TES protection

To optimise the formation of the 1,4-diol adduct **4.14** and to minimise the formation of the pentacylic core product **4.15**, the reaction was run in allyl alcohol. Surprisingly, without THF, the epimer at C13 of compound **4.14** was obtained. The 1,4-diol **4.17** with the

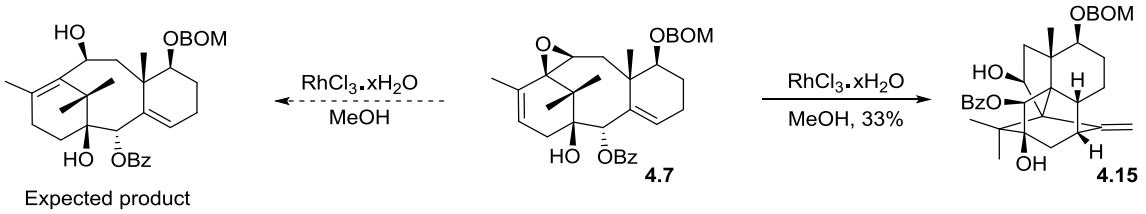
required configurations at C10 and C13 was formed in 24% yield along with 31% of pentacycle **4.15** (Scheme 4.38). It is difficult to give an explanation on the reversed C13 stereochemistry.



*Scheme 4.38: Synthesis of the C13 Taxol-like 1,4-diol **4.17***

4.4.2.2 Transition-Metal Catalysed

Ring opening of the epoxide mediated by transition-metal catalyst was also explored. To do so, rhodium (III) chloride was used, as it is known to easily promote alkene isomerisation.[106] When vinyl epoxide **4.7** was treated with the transition metal chloride, the only product was pentacycle **4.15**, which was formed in 33% yield. No other product could be identified (Scheme 4.39).

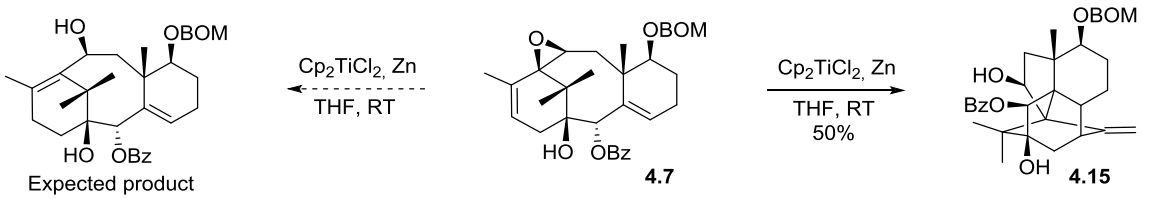


Scheme 4.39: Alkene isomerisation attempt

4.4.2.3 Radical-Mediated

Following the same idea, Ti(III)-radical reaction also afforded the pentacycle **4.15** in 50% yield as the only product (Scheme 4.40).

[106] Corbu, A.; Gauron, G.; Castro, J. M.; Dakir, M.; Arseniyadis, S. *Org. Lett.* **2007**, *9*, 4745-4748. Takemoto, Y.; Ohra, T.; Sugiyama, K.; Imanishi, T.; Iwata, C. *Chem. Pharm. Bull.* **1995**, *43*, 571-577. Bourgeois, D.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *J. Organomet. Chem.* **2002**, *643-644*, 247-252.

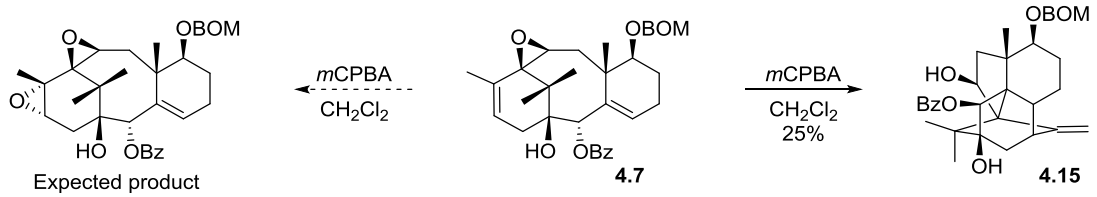


Scheme 4.40: Ti(III)-radical epoxide opening

Since the Ti(III) radical successfully produced pentacycle **4.15** at room temperature, it was clear that the vinyl epoxide **4.7** easily underwent Ti(III)-radical opening. Therefore, it was decided to investigate the Ti(III)-radical opening of a C2 benzoate diepoxide compound.

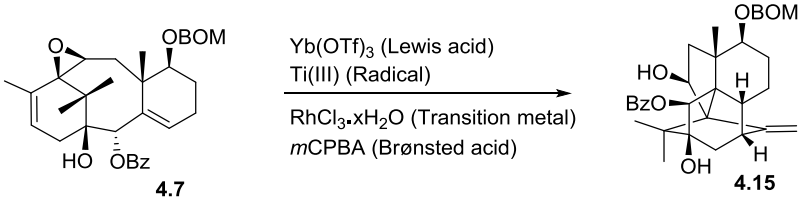
4.4.3 Diepoxidation

Vinyl epoxide **4.7** was treated with *m*CPBA and surprisingly, pentacyclic compound **4.15** was obtained in 25% yield, no diepoxide product was formed (Scheme 4.41).



Scheme 4.41: Epoxidation attempts

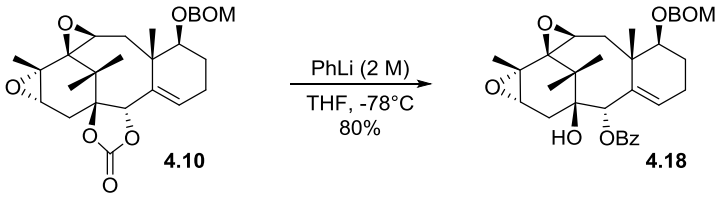
In summary, the formation of this pentacyclic product **4.15** resulted from the reaction of **4.7** with an ytterbium Lewis acid, Ti(III), a transition metal chloride and mild Brønsted acid (Scheme 4.42). In the light of all these results, it was decided to stop investigating functionalisation of vinyl epoxide **4.7.**



*Scheme 4.42: Formation of pentacyclic compound **4.15***

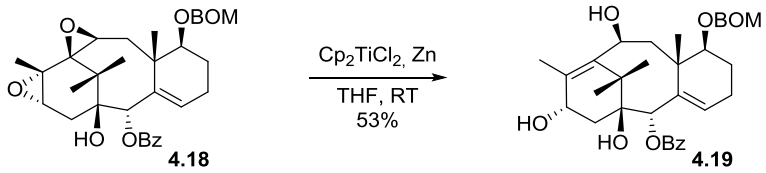
4.4.4 Synthesis of an Advanced Intermediate of Taxol

Since the C2 benzoate monoepoxide **4.7** could not be further epoxidised, it was decided to generate the C2 benzoate diepoxide derivative from the readily available diepoxide **4.10**. Therefore, **4.10** was treated with phenyllithium in THF at -78°C and gave the derivative **4.18** in 80% yield (Scheme 4.43).



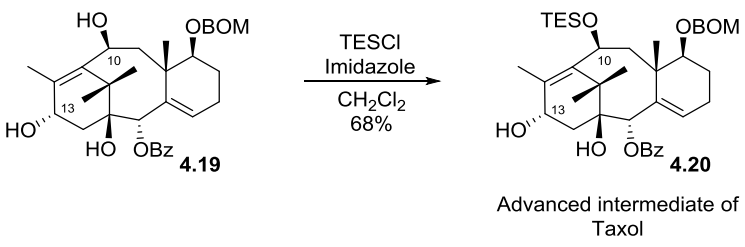
*Scheme 4.43: Synthesis of C2 benzoate **4.18***

The C2 benzoate diepoxide **4.18** was then treated with a freshly made solution of Ti(III) from bis(cyclopentadienyl)titanium(IV) dichloride and zinc. The reaction mixture was stirred at room temperature for a few hours to deliver the 1,4-diol **4.19** in 53% yield (Scheme 4.44).



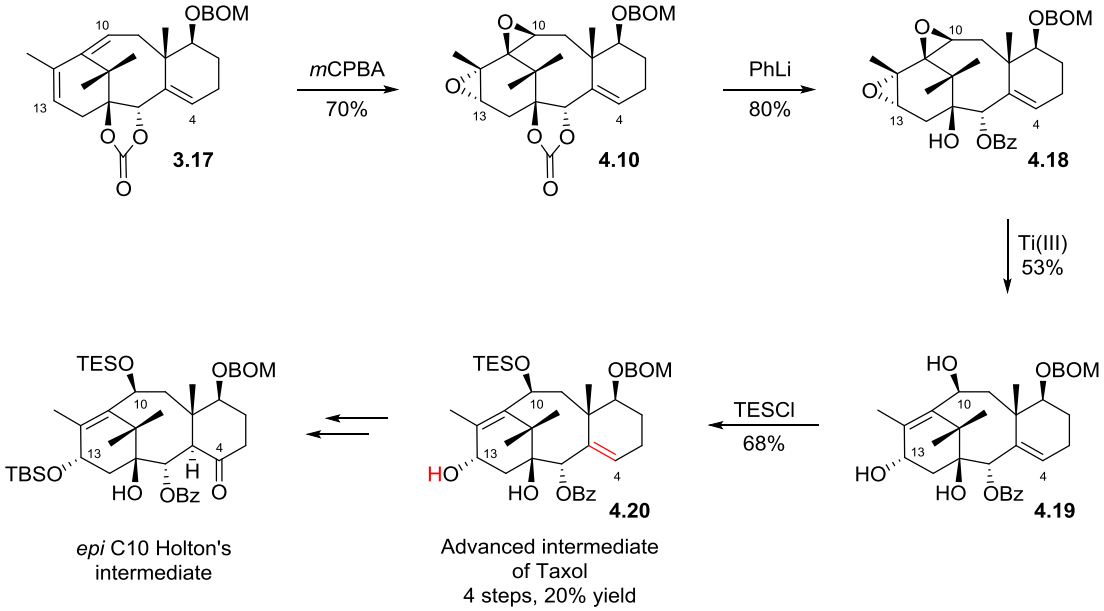
*Scheme 4.44: Formation of the 1,4-diol **4.19***

We then explored the selective protection of the more accessible hydroxyl group (C10 *vs* C13). To do so, diol **4.19** was treated with TESCl and imidazole in CH_2Cl_2 and generated the C10 protected product **4.20** in 68% yield, which showed a better accessibility of the alcohol pointing from the convex face of the ABC tricyclic core of Taxol (Scheme 4.45).



*Scheme 4.45: Selective protection of 1,4-diol **4.19***

In summary, an advanced intermediate for the synthesis of Taxol **4.20** was successfully synthesised from the tricycle **3.26.** An excess of *m*CPBA successfully produced in 70% yield the C10-C11 and C12-C13 diepoxide **4.10**, followed by the synthesis of the C2 benzoate **4.18** in 80% yield, which helped releasing internal strain from the tricyclic skeleton. Installation of the 1,4-diol motif by Ti(III) radical opening delivered **4.19** in 53% yield, followed by the selective protection of the C10 hydroxyl group to give the advanced intermediate of Taxol **4.20** in 68% yield, which was synthesised in 4 steps in an overall yield of 20%. To access the *epi* C10 Holton's intermediate, a few steps are still needed; the protection of the C13 hydroxyl and the oxidation of the C4 olefin (Scheme 4.46).

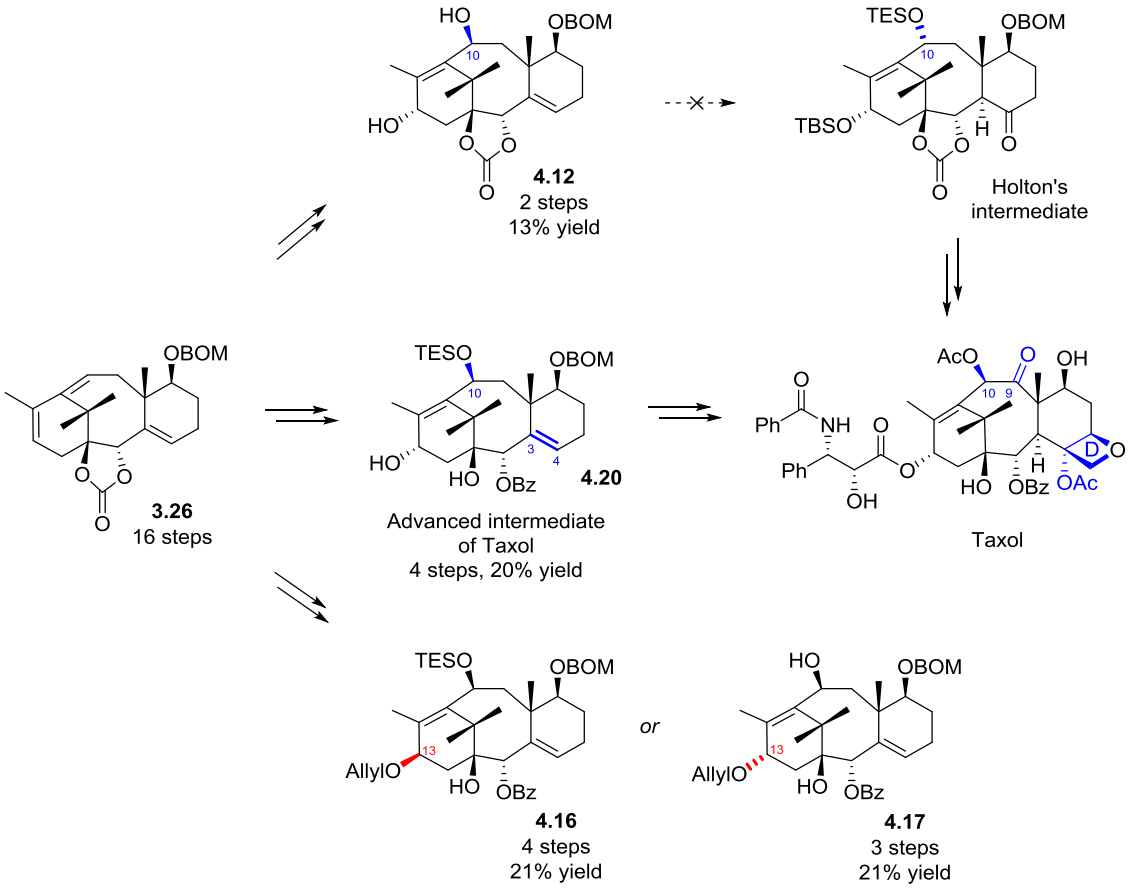


*Scheme 4.46: Summary of the advanced intermediate of Taxol **4.20***

4.5 Conclusion and Perspectives

Investigation on the differentiation of the three trisubstituted olefins of the tricyclic product **3.26** led us to realise that the completion of a formal synthesis of Taxol, based on Holton's synthesis, was challenging. Indeed, the C10 stereocenter of 1,4-diol **4.12** had the opposite configuration to the one of Holton's intermediate but had the right configuration for Taxol. Efforts were devoted to access the opposite C10 isomer, by releasing the strain imposed by the C1-C2 cyclic protecting group. Unfortunately this strategy did not lead to any progress in that matter. Also it appeared that this C1-C2 carbonate prevented the desired reactions, as it was probably generating too much internal strain that was released in producing unwanted compounds. These two reasons made us realise that the target we

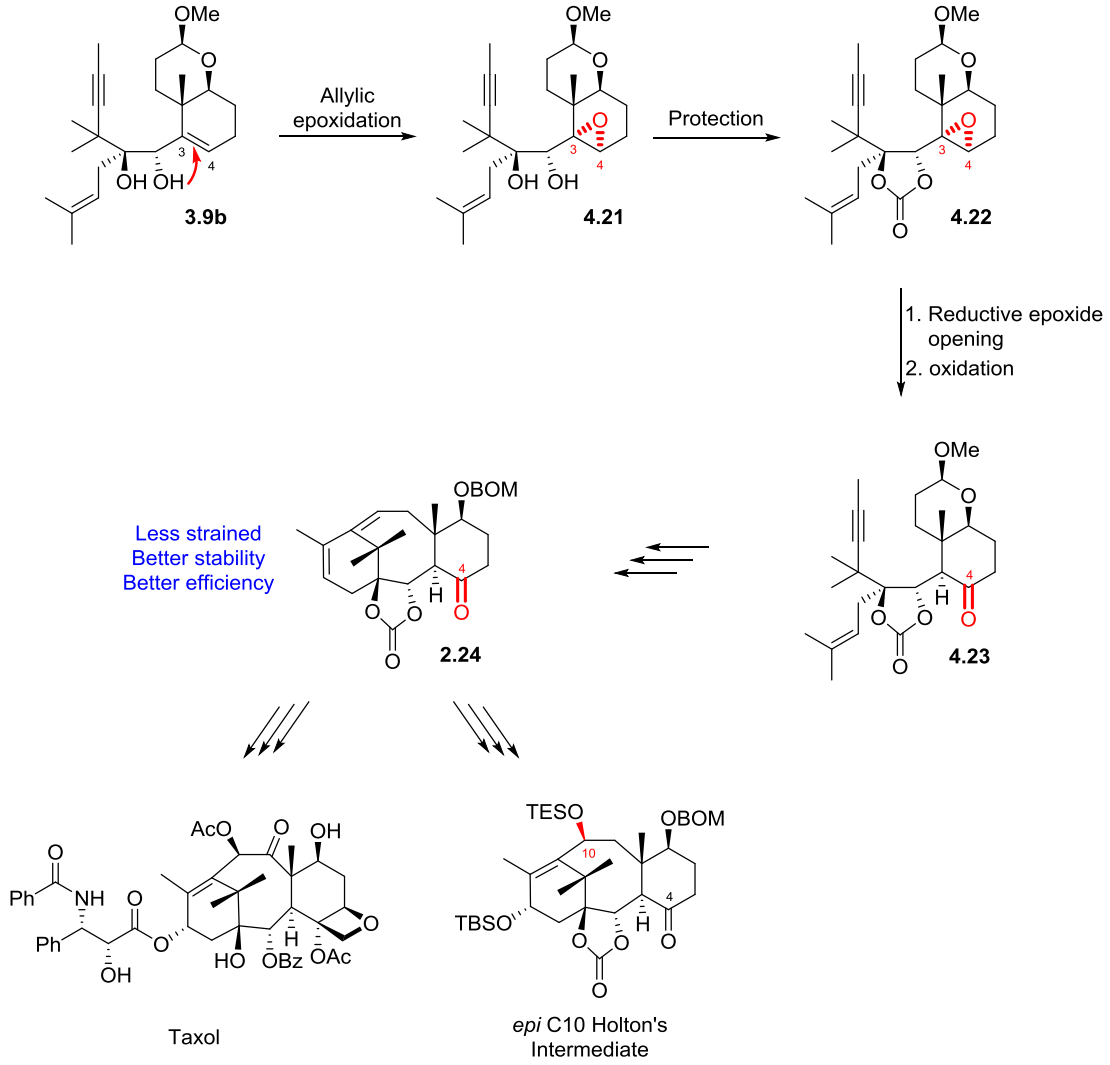
were aiming for was not accessible. Therefore, the easy generation of a benzoate group at C2 position led us to direct ourselves toward a total synthesis of Taxol. Hence an advanced intermediate of Taxol **4.20** bearing five differentiated oxygenated functions, all set up by substrate control, was synthesised. Furthermore, oxygenated products **4.16** and **4.17** were also produced. For these compounds, stereochemistry at C13 was selectively switched upon choice of the solvent. For all these intermediates, only two oxygenated groups were missing: the C9 ketone that can easily be produced from the already present C10 alcohol, and the D ring oxetane, which can be built from the C4 olefin handle (Scheme 4.47).



Scheme 4.47: Summary

This C4 olefin "handle" proved to be very non-reactive during our synthetic investigations. Early stage derivatisation of this C4 olefin needs to be undertaken before the ring-closing metathesis cascade in order to produce a less strained precursor, less prone to side product formation. Therefore, an allylic epoxidation directed by the C1-C2 diol **3.9b** would deliver the corresponding C3-C4 epoxide **4.21**. Protection of the C1-C2 diol would afford carbonate **4.22** followed by a reductive epoxide opening and subsequent

oxidation of the resulting alcohol would deliver the C4 ketone metathesis precursor **4.23**.[107] Ring-closing dienyne metathesis would then construct this new tricyclic core of Taxol **4.24**, followed by the generation of the 1,4-diol unit, the C9 ketone and the ring D oxetane would deliver Taxol via a short, and highly diastereoselective manner (Scheme 4.48).



Scheme 4.48: New route toward the ABC tricyclic core of Taxol

[107] Ranu, B. C.; Das, A. R. *J. Chem. Soc. Perkin Trans. 1*, **1992**, 1881-1882. Ranu, B. C.; Das, A. R. *J. Chem. Soc. Chem. Commun.* **1990**, 1334-1335.

5. EXPERIMENTAL SECTION

General Experimental

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.

All microwave reactions were carried out using a Biotage Initiator system.

Melting points were determined on a Stuart scientific-Melting Point SMP1 apparatus and are uncorrected.

NMR spectra were recorded on a Bruker DPX-400 spectrometer (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz) or a Bruker DPX-500 spectrometer (^{1}H NMR at 500 MHz and ^{13}C NMR at 126 MHz). Chemical shifts are reported in ppm. ^{1}H NMR spectra were recorded with $CDCl_3$ as the solvent using residual $CHCl_3$ (δ= 7.27) as internal standard, and for ^{13}C NMR spectra the chemical shifts are reported relative to the central resonance of $CDCl_3$ (δ = 77.0). Signals in NMR spectra are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), septet (spt), multiplet (m), broad (br) or combination of these, which refers to the spin-spin coupling pattern observed. Spin-spin coupling constants reported are uncorrected. Two dimensional (COSY, HSQC, HMBC, NOESY) NMR spectroscopy was used where appropriate to assist the assignment of signals in the ^{1}H and ^{13}C NMR spectra.

For the description of NMR spectra, the numbering used follows the chain extension or Taxol numbering, not the IUPAC numbering rules.

IR spectra were obtained employing a Shimadzu FTIR-8400 instrument with a Golden Gate™ attachment that uses a type IIa diamond as a single reflection element so that the IR spectrum of the compound (solid or liquid) could be detected directly (thin layer).

High resolution mass spectra were recorded under FAB, ESI and CI conditions by the analytical services at the University of Glasgow.

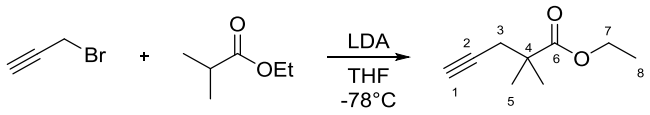
Flash column chromatography was performed using forced flow of the indicated solvent system on EMD Geduran Silica Gel 60 as solid support and HPLC graded solvents as eluant.

Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel 60 covered aluminum sheets. TLC plates were developed under UV-light and/or with an acidic ethanolic anisaldehyde solution or a $KMnO_4$ solution.

All reagents were purchased from commercial suppliers and used without further purification unless otherwise stated.

Liquid reagents were distilled prior to use where stated.

Ethyl 2,2-dimethylpent-4-ynoate (2.1)



***Chemical Formula*:** $C_9H_{14}O_2$

***MW*:** 154.21

Spect. Reference: Witham, C. A.; Mauleón, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5838-5839.

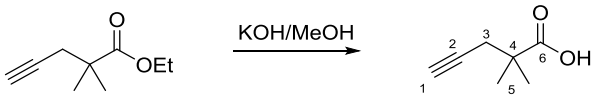
To a solution of diisopropylamine (23.0 mL, 163 mmol, 1.1 equiv) in THF (400 mL) at -78°C was added *n*BuLi (71.0 mL, 2.2M in hexane, 156 mmol, 1.05 equiv). The mixture was stirred at this temperature for 30 min and ethyl isobutyrate (20.0 mL, 149 mmol) in THF (300 mL) was added drop wise over 3 h and 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 (17.6 mL, 80% in toluene, 156 mmol, 1.05 equiv) in THF (100 mL) was added and the mixture was stirred at RT for 3 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (400 mL) and the aqueous phase was extracted with dichloromethane (3x400 mL). The combined organic layers were washed with brine (1.5 L), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography on silica gel (petroleum ether/diethyl ether: 95/5) to afford the title ester **2.1** (22.7 g, 148 mmol, 99%) as a pale yellow oil.

^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm: 4.14 (q, *J* = 7.1 Hz, 2H, ***H7***), 2.43 (d, *J* = 2.6 Hz, 2H, ***H3***), 1.99 (t, *J* = 2.6 Hz, 1H, ***H1***), 1.26 (s, 6H, ***H5***), 1.24 (t, *J* = 7.1 Hz, 3H, ***H8***).

^{13}C NMR (100 MHz, *$CDCl_3$*) δ ppm: 176.6 (***C6***), 81.1 (***C2***), 70.4 (***C1***), 60.7 (***C7***), 41.9 (***C4***), 29.5 (***C3***), 24.5 (2***C5***), 14.2 (***C8***).

IR (ν, cm^{-1}): 3296, 2978, 2934, 2120, 1727, 1471, 1386, 1317, 1302, 1255, 1130, 1028.

2,2-Dimethylpent-4-ynoic acid (2.2)



***Chemical Formula*:** $C_7H_{10}O_2$

***MW*:** 126.16

Spect. Reference: Von Eggers Doering, W.; Yamashita, Y. *J. Am. Chem. Soc.* **1983**, *105*, 5368-5372.

To a solution of propargylated ethyl ester **2.1** (20.0 g, 130 mmol) in MeOH (250 mL) and water (100 mL) was added KOH (11.7 g, 208 mmol, 1.6 equiv). The reaction mixture was stirred for 16 h at RT. A 2N aqueous HCl solution was added to adjust the pH to 1 and the aqueous phase was extracted with CH_2Cl_2 (3x400 mL). The combined organic extracts were washed with a 2N aqueous HCl solution (1 L), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title acid **2.2** (15.3 g, 121 mmol, 93%) as a pale yellow oil was used in the next step without further purification.

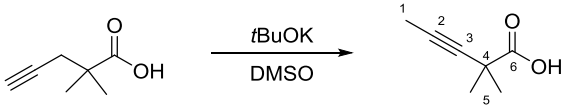
^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm: 2.47 (d, *J* = 2.7 Hz, 2H, ***H3***), 2.03 (t, *J* = 2.7 Hz, 1H, ***H1***), 1.32 (s, 6H, ***H5***).

^{13}C NMR (100 MHz, *$CDCl_3$*) δ ppm: 183.2 (***C6***), 80.7 (***C2***), 70.7 (***C1***), 41.9 (***C4***), 29.3 (***C3***), 24.3 (2***C5***).

IR (ν, cm^{-1}): 3515, 3297, 2977, 2936, 2120, 1699, 1474, 1410, 1367, 1316, 1283, 1227, 1160.

HRMS (EI) Calcd. for $[M]^+$: 126.0681, found: 126.0684.

2,2-Dimethylpent-3-ynoic acid (2.3)



***Chemical Formula*:** $C_7H_{10}O_2$

***MW*:** 126.16

To a solution of acid **2.2** (16.9 g, 134 mmol) in DMSO (200 mL) was added potassium *tert*-butoxide (32.9 g, 269 mmol, 2 equiv), and the mixture was stirred at 75°C for 10 min. A 1N aqueous HCl solution was then added to adjust to pH 1, and the aqueous phase was extracted with Et_2O (3x500 mL). The combined organic extracts were washed with 1N aqueous HCl (1 L), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo.* The crude mixture was then purified by flash chromatography on silica gel (diethyl ether/petroleum ether: 5/5) to afford the title acid **2.3** (15.9 g, 126 mmol, 94%) as a pale yellow oil.

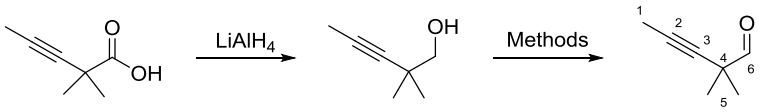
^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 11.23 (br s, CO_2***H***), 1.83 (s, 3H, ***H1***), 1.48 (s, 6H, ***H5***).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 180.6 (***C6***), 80.7 (***C3***), 78.1 (***C2***), 38.2 (***C4***), 27.2 (2***C5***), 3.6 (***C1***).

IR (ν, cm^{-1}): 3532, 2984, 2923, 1707, 1470, 1411, 1267, 1234, 1172, 1057.

HRMS (EI) Calcd. for $[M]^+$: 126.0681, found: 126.0685.

2,2-Dimethylpent-3-ynal (2.4)



***Chemical Formula*:** $C_7H_{10}O$

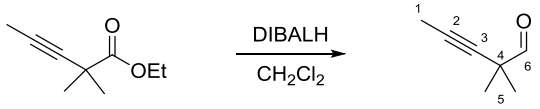
***MW*:** 110.16

To a suspension of lithium aluminum hydride (0.80 g, 20 mmol, 1.0 equiv) in Et_2O (90 mL) at 0°C was added dropwise a solution of **2.3** (2.5 g, 20 mmol) in Et_2O (10 mL). The mixture was stirred at this temperature for 30 min. Excess of lithium aluminum hydride was then quenched with careful addition of ice. A 1N aqueous HCl solution was added to dissolve lithium salts. The aqueous phase was then extracted with Et_2O (3x50 mL). The combined organic extracts were washed with 1N aqueous HCl (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a pale yellow oil that was directly used without further purification.

Method A: To a solution of oxalyl chloride (2.0 mL, 24 mmol, 1.2 equiv) in CH_2Cl_2 (40 mL) at -50°C was added dropwise DMSO (3.3 mL, 46 mmol, 2.3 equiv). The mixture was stirred at this temperature for 10 min, and a solution of the crude alcohol (20 mmol) in CH_2Cl_2 (20 mL) was then added. The mixture was stirred for 30 min, and triethylamine (17 mL, 120 mmol, 6.0 equiv) was added. The temperature was allowed to warm to 0°C, and the mixture was stirred for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (50 mL). The aqueous layer was extracted with Et_2O (3x50 mL), and the combined organic extracts were washed with brine (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel (pentane/dichloromethane: 80/20) to afford the title aldehyde **2.4** (1.7 g, 15 mmol, 76%) as a colourless oil.

Method B: To a solution of the crude alcohol (356 mg, 3.17 mmol) in THF (10 mL) at RT was added a solution of IBX (1.1 g, 3.8 mmol, 1.2 equiv) in DMSO (10 mL). The reaction mixture

was stirred for 12 h. Water (20 mL) was added and the white solids were filtered off. The aqueous was extracted with Et_2O (3x25 mL) and combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (pentane/dichloromethane: 80/20) to afford the title aldehyde **2.4** (171 mg, 1.55 mmol, 49%) as a colourless oil.



To a solution of ester **2.8** (3.0 g, 20 mmol) in dichloromethane (25 mL) at -78°C was added DIBALH (30 mL, 1.0 M in hexane, 30 mmol, 1.5 equiv). The reaction mixture was stirred for 10 min and 3 mL of MeOH and 50 mL of a solution of Rochelle salts were added carefully at -78°C. The reaction mixture was stirred 1 h at RT. The phases were separated and the aqueous one was extracted with dichloromethane (3x50 mL). The organic extracts were washed with brine (150 mL), filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (pentane/dichloromethane: 80/20) to afford the title aldehyde **2.4** (1.9 g, 17 mmol, 85%) as a cololess oil.

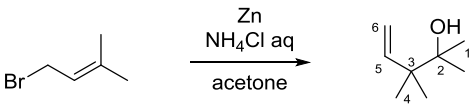
^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm: 9.45 (s, 1H, ***H6***), 1.84 (s, 3H, ***H1***), 1.29 (s, 6H, ***H5***).

^{13}C NMR (100 MHz, *$CDCl_3$*) δ ppm: 199.0 (***C6***), 80.9 (***C3***), 79.6 (***C2***), 42.7 (***C4***), 23.2 (2***C5***), 3.7 (***C1***).

IR (ν, cm^{-1}): 2983, 2924, 2816, 2715, 1737, 1466, 1391, 1264, 1056.

HRMS (EI) Calcd. for $[M]^+$: *m/z* 110.0732, found: 110.0736.

2,3,3-Trimethylpent-4-en-2-ol (2.5)



Formula: $C_8H_{16}O$

MW: 128.2

Spect. Reference: Satoh, S.; Suginome, H.; Tokuda, M. *Bull. Chem. Soc. Jpn*. **1983**, *56*, 1791-1794.

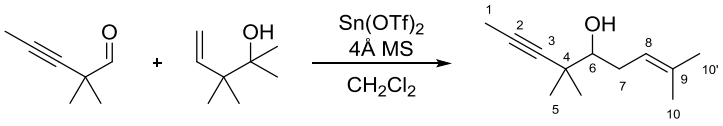
To a solution of prenyl bromide (20.0 g, 134 mmol) in acetone (500 mL) and a saturated aqueous solution of NH_4Cl (60 mL) was added freshly activated Zn dust (17.5 g, 268 mmol, 2.0 equiv). The resulting mixture was stirred at RT for 7 days. A 2N aqueous HCl solution was added to dissolve Zn salts and acetone was removed in vacuo. The aqueous phase was extracted with Et_2O (3x250 mL) and the combined organic phases were washed with brine (500 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (petroleum ether/Et_2O: 8/2 and distilled under reduce pressure to afford the title compound **2.5** (11.68 g, 91.12 mmol, 68%) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.03 (dd, J = 17.5, 10.9 Hz, 1H, ***H5***), 5.19-4.90 (m, 2H, ***H6***), 1.40 (s, 1H, ***OH***), 1.18 (s, 6H, ***CH$_3$***), 1.06 (s, 6H, ***CH$_3$***).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 145.3 (***C5***), 113.5 (***C6***), 74.2 (***C2***), 43.9 (***C3***), 25.4, 22.3 (2***C4***, 2***C1***).

IR (ν, cm^{-1}): 3447, 3082, 2977, 2878, 1636, 1464, 1415, 1372, 1146, 1112, 1008.

2,6,6-Trimethylnon-2-en-7-yn-5-ol (2.6)



Formula: $C_{12}H_{20}O$

MW: 180.29

To a suspension of $Sn(OTf)_2$ (42 mg, 0.1 mmol, 0.1 equiv) with 100 mg of freshly activated powdered 4Å MS in dichloromethane (5 mL) were added aldehyde **2.4** (110 mg, 1.00 mmol) and alcohol **2.5** (0.38 g, 3.0 mmol, 3.0 equiv). The reaction mixture was stirred at RT for 6 h. A 2N aqueous HCl solution (10 mL) was added and the aqueous phase was extracted with dichloromethane (3x10 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (petroleum ether/Et_2O: 98/2) to afford the title alcohol **2.6** (27.0 mg, 0.15 mmol, 15%) as a colourless oil.

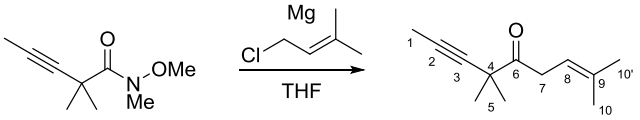
^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm: 5.26 (ddq, *J* = 9.2, 5.8, 1.1 Hz, 1H, ***H8***), 3.29 (dd, *J* = 10.2, 2.6 Hz, 1H, ***H6***), 2.37-2.31 (m, 1H, ***H7***), 2.22-2.07 (m, 1H, ***H7***), 1.90 (br s, 1H, ***OH***), 1.81 (s, 3H, ***H1***), 1.74 (d, *J* = 1.1 Hz, 3H, ***H10***), 1.65 (s, 3H, ***H10'***), 1.21 (s, 3H, ***H5***), 1.17 (s, 3H, ***H5***).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 134.5 (***C9***), 121.3 (***C8***), 84.1 (***C3***), 78.2 (***C2***), 77.5 (***C6***), 36.9 (***C4***), 31.1 (***C7***), 25.9 (***CH$_3$***), 25.6 (***CH$_3$***), 25.5 (***CH$_3$***), 18.0 (***CH$_3$***), 3.5 (***C1***).

IR (ν, cm^{-1}): 3575, 2971, 2921, 2859, 2737, 2052, 1709, 1671, 1450, 1377, 1361, 1288, 1231, 1189, 1139, 1105, 1071, 1044.

HRMS (EI) Calcd for $[M]^+$: *m/z* 180.1514, found 180.1505.

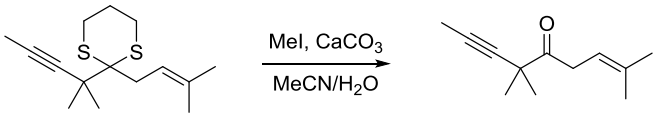
2,6,6-Trimethylnon-2-en-7-yn-5-one (2.7)



***Chemical Formula*:** $C_{12}H_{18}O$

***MW*:** 178.28

<u>*Method A:*</u> To a suspension of magnesium turnings (26 g, 1.1 mol, 10 equiv) in THF (150 mL) was added 1,2-dibromoethane (0.1 mL), followed by a slow addition (30 min) of prenyl chloride (14.1 mL, 119 mmol, 1.1 equiv). The resulting suspension was stirred for an additionnal 15 min. Then the freshly made Grignard reagent was added *via cannula* to a solution of Weinreb amide **2.12** (18.3 g, 108 mmol) in THF (350 mL). The resulting mixture was allowed to stir at RT for 1 h. The reaction was quenched with brine (250 mL). The aqueous layer was extracted with Et_2O (3x250 mL), and the combined organic extracts were washed with brine (500 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel (petroleum ether/diethyl ether: 97/3) to afford the title ketone **2.7** (18.3 g, 103 mmol, 95%) as a colourless oil.



<u>*Method B:*</u> To a solution of dithiane **2.11** (3.38 g, 12.6 mmol) in a 1:1 mixutre of $MeCN/H_2O$ (250 mL) was added $CaCO_3$ (14.0 g, 126 mmol, 10 equiv) followed by MeI (3.1 mL, 50 mmol, 4 equiv). The resulting mixture was allowed to stir at 40°C for 48 h. Then a saturated aqueous solution of $NaHCO_3$ (150 mL) was added and the aqueous layer was extracted with Et_2O (3x150 mL), then the combined organic extracts were washed with brine (250 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was

purified by flash chromatography (petroleum ether/Et_2O: 97/3) to afford the title ketone **2.7** (1.86 g, 10.5 mmol, 83%) as a colourless oil.

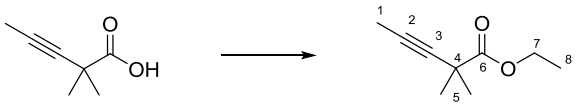
^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm: 5.32 (m, 1H, ***H8***), 3.48 (d, *J* = 5.6 Hz, 2H, ***H7***), 1.83 (s, 3H, ***H1***), 1.74 (s, 3H, ***H10*** or ***H10'***), 1.63 (s, 3H, ***H10*** or ***H10'***), 1.32 (s, 6H, ***H5***).

^{13}C NMR (100 MHz, *$CDCl_3$*) δ ppm: 209.2 (***C6***), 134.9 (***C9***), 116.7 (***C8***), 82.3 (***C3***), 78.9 (***C2***), 43.6 (***C4***), 37.3 (***C7***), 26.4 (2***C5***), 25.7 (***C10*** or ***C10'***), 18.1 (***C10*** or ***C10'***), 3.6 (***C1***).

IR (ν, cm^{-1}): 2981, 2923, 1716, 1450, 1380, 1264, 1113, 1080, 1040.

HRMS (CI, ISO) Calcd. for $[M+H]^+$: *m/*z 179.1436, found: 179.1433.

Ethyl 2,2-dimethylpent-3-ynoate (2.8)



Chemical Formula**:** $C_9H_{14}O_2$

MW: 152.21

Method A: To a solution of acid **2.3** (1.0 g, 7.9 mmol) in ethanol (50 mL) were added EDCi (1.8 g, 9.5 mmol, 1.2 equiv) and DMAP (48 mg, 0.4 mmol, 0.05 equiv). The mixture was stirred at RT for 12 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (50 mL). The aqueous layer was extracted with dichloromethane (3x50 mL) and the organic extracts were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography on silica gel (petroleum ether/Et_2O: 95/5) to afford the title ester **2.8** (1.1 g, 7.3 mmol, 93%) as a yellow oil.

Method B: To a solution of acid **2.3** (14.0 g, 111 mol) in ethanol (300 mL) was added concentrated sulfuric acid (0.30 mL, 5.55 mmol, 0.05 equiv). The mixture was stirred at RT for 12 h. The reaction mixture was concentrated and taken up with Et_2O (300 mL). The organic extracts were washed with an aqueous solution of 5% $NaHCO_3$ (300 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford a yellow oil that was purified by flash chromatography on silica gel (petroleum ether/Et_2O: 95/5) to afford the title ester **2.8** (13.2 g, 86.6 mmol, 78%) as a yellow oil.

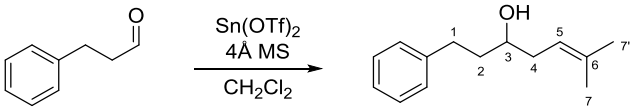
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.18 (q, *J* = 7.1 Hz, 2H, ***H7***), 1.81 (s, 3H, ***H1***), 1.44 (s, 6H, ***H5***), 1.28 (t, *J* = 7.1 Hz, 3H, ***H8***).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 174.3 (***C6***), 81.6 (***C2***), 77.2 (***C3***), 61.4 (***C7***), 38.2 (***C4***), 27.4 (2***C5***), 14.1 (***C8***), 3.6 (***C1***).

IR (ν, cm^{-1}): 2983, 2923, 2230, 1733, 1468, 1383, 1259, 1173, 1143, 1157, 1026.

HRMS (CI, ISO) Calcd. for $[M+H]^+$: *m/*z 155.1072, found: 155.1075.

6-Methyl-1-phenylhept-5-en-3-ol (2.9)



Formula: $C_{14}H_{20}O$

MW: 204.31

Spect. Reference: Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S.-i. *J. Am. Chem. Soc*. **1998**, *120*, 6609-6610.

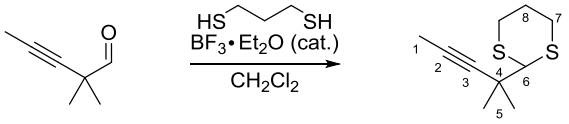
To a suspension of $Sn(OTf)_2$ (42 mg, 0.1 mmol, 0.1 equiv) with 100 mg of freshly activated powdered 4Å MS in dichloromethane (5 mL) were added hydrocinnamaldehyde (130 µL, 1.0 mmol) and alcohol **2.5** (380 mg, 3.00 mmol, 3.0 equiv). The reaction mixture was stirred at RT for 5 h. A 2N aqueous HCl solution (10 mL) was added and the aqueous phase was extracted with dichloromethane (3x10 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (petroleum ether/Et_2O: 9/1) to afford the title compound **2.6** (102 mg, 0.50 mmol, 50%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.51-6.95 (m, 5H, ***H_{Ar}***), 5.31-4.97 (m, 1H, ***H5***), 3.83-3.39 (m, 1H, ***H3***), 2.88-2.58 (m, 2H, ***H1***), 2.19 (t, *J* = 6.8 Hz, 2H, ***H4***), 1.78 (ddd, *J* = 8.9, 7.2, 3.4 Hz, 2H, ***H2***), 1.74 (d, *J* = 0.6 Hz, 3H, ***H7***), 1.64 (s, 3H, ***H7'***), 1.57 (dd, *J* = 5.5, 3.1 Hz, 1H, ***OH***).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 142.2 (***C6***), 135.5 (***C5***), 128.4 (***C_{Ar}***), 128.4 (***C_{Ar}***), 125.8 (***C_{Ar}***), 119.9 (***C_{Ar}***), 71.0 (***C3***), 38.4 (***C1***), 36.3 (***C4***), 32.2 (***C2***), 26.0 (***C7***), 18.0 (***C7'***).

IR (ν, cm^{-1}): 3431, 3040, 2936, 2917, 1498, 1554, 1265, 1051.

2-(2-Methylpent-3-yn-2-yl)-1,3-dithiane (2.10)



***Chemical Formula*:** $C_{10}H_{16}S_2$

***MW*:** 200.36

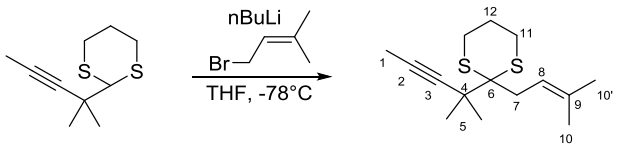
To a solution of aldehyde **2.4** (770 mg, 7.00 mmol) in dichloromethane (40 mL) was added 1,3-propanedithiol (1.0 mL, 10.5 mmol, 1.5 equiv) and boron trifluoride etherate (180 µL, 1.40 mmol, 0.2 equiv) dropwise at 0°C. The reaction mixture was stirred at this temperature for 16 h. A 5% aqueous solution of NaOH (40 mL) was added and the aqueous layer was extracted with dichloromethane (3x40 mL), and the combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (petroleum ether/Et_2O: 95/5) to afford the title dithiane **2.10** (1.05 g, 5.25 mmol, 75%) as a yellow oil.

^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm: 4.08 (s, 1H, ***H6***), 2.93-2.90 (m, 4H, ***H7***), 2.10-2.07 (m, 1H, ***H8***), 1.87-1.82 (m, 1H, ***H8***), 1.84 (s, 3H, ***H1***), 1.40 (s, 6H, ***H5***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 83.7 (***C2*** or ***C3***), 77.9 (***C2*** or ***C3***), 59.6 (***C6***), 36.4 (***C4***), 31.1 (***C7***), 27.9 (2***C5***), 25.8 (***C8***), 3.7 (***C1***).

HRMS (EI) Calcd for $[M]^+$: *m/*z 200.0693, found 200.0692.

2-(3-Methylbut-2-enyl)-2-(2-methylpent-3-yn-2-yl)-1,3-dithiane (2.11)



***Chemical Formula*:** $C_{15}H_{24}S_2$

***MW*:** 268.48

To a solution of dithiane **2.10** (2.60 g, 13.0 mmol) in THF (150 mL) was added at -78°C *n*BuLi (6.8 mL, 2.5 M in hexanes, 17 mmol, 1.3 equiv). The reaction mixture was stirred 30 min at this temperature and 30 min at 0°C and then cooled down to -78°C and prenyl bromide (1.7

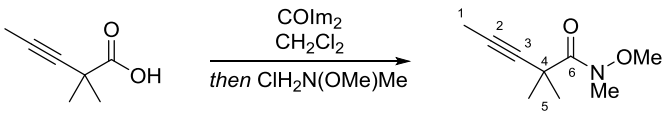
mL, 14 mmol, 1.1 equiv) was added neat. The mixture was stirred and allowed to reach room temperature over a period of 2.5 h. Water (100 mL) and dichloromethane (100mL) were added, the aqueous layer was extracted with dichloromethane (3x100 mL), and the combined organic extracts were washed with a 7% NaOH aqueous solution (250 mL), washed with brine (250 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (petroleum ether/Et_2O: 95/5) to afford the title dithiane **2.11** (3.38 g, 12.6 mmol, 97%) as a yellow oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.57-5.54 (m, 1H, ***H8***), 2.92-2.82 (m, 6H, 2***H7***, 4***H11***), 2.03-1.94 (m, 1H, ***H12***), 1.90-1.79 (m, 1H, ***H12***), 1.84 (s, 3H, ***H1***) 1.75 (d, *J* = 1.2 Hz, 3H, ***H10***), 1.70 (s, 3H, ***H10'***), 1.45 (s, 6H, ***H5***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 132.0 (***C9***), 122.2 (***C8***), 78.6 (***C2*** or ***C3***), 77.2 (***C2*** or ***C3***), 62.2 (***C6***), 42.7 (***C4***), 36.9 (2***C11***), 27.0 (***C7***), 26.6 (***C5***), 26.1 (***C10***), 24.1 (***C12***), 18.3 (***C10'***), 3.7 (***C1***).

HRMS (CI/ISO) Calcd for $[M+H]^+$: *m/*z 269.1398, found 269.1394.

N-Methoxy-N,2,2-trimethylpent-3-ynamide (2.12)



***Chemical Formula*:** $C_9H_{15}NO_2$

***MW*:** 169.22

To a solution of acid **2.3** (15.1 g, 120 mmol) in dichloromethane (250 mL) was added 1,1'-carbonyl diimidazole (23.3 g, 144 mmol, 1.2 equiv). The resulting mixture was stirred for 30 min, then *N*,*O*-dimethylhydroxylamine hydrochloride (14.0 g, 144 mmol, 1.2 equiv) was added. The mixture was allowed to stir at RT for 16 h. The reaction mixture was then quenched with a solution of 1N aqueous HCl (250 mL) and stirred vigorously for 10 min. The mixture was separated and the aqueous layer was extracted with dichloromethane (3x250 mL). The combined organic extracts were washed with a solution of 1N aqueous HCl (500 mL), washed with brine (500 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel (petroleum ether/diethyl ether: 95/5) to afford the title Weinreb amide **2.12** (18.3 g, 108 mmol, 90%) as a colourless oil.

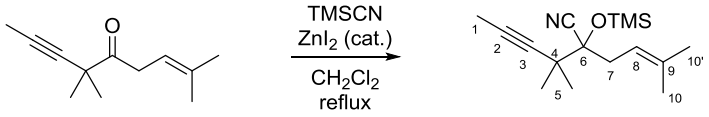
^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 3.76 (s, 3H, ***OMe***), 3.23 (s, 3H, ***NMe***), 1.84 (s, 3H, ***H1***), 1.44 (s, 6H, ***H5***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 174.0 (***C6***), 82.9 (***C3***), 76.5 (***C2***), 60.5 (***OMe***), 37.1 (***C4***), 33.8 (***NMe***), 27.3 (2***C5***), 3.7 (***C1***).

IR (ν, cm^{-1}): 2983, 2935, 2869, 2242, 1659, 1455, 1408, 1382, 1356, 1254, 1169, 1115, 1085, 1021, 999.

HRMS (CI, ISO) Calcd for $[M+H]^+$: *m/*z 170.1181, found 170.1186.

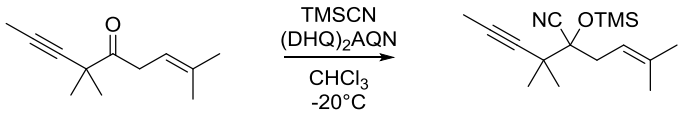
5-Methyl-2-(2-methylpent-3-yn-2-yl)-2-(trimethylsilyloxy)hex-4-enenitrile (2.13)



***Chemical Formula*:** $C_{16}H_{27}NOSi$

***MW*:** 277.48

Method A: To a solution of ketone **2.7** (18.3 g, 103 mmol) in CH_2Cl_2 (300 mL) was added ZnI_2 (6.6 g, 21 mmol, 0.2 equiv) and TMSCN (27.5 mL, 206 mmol, 2.0 equiv). The reaction mixture was refluxed for 16 h and the solvent was removed *in vacuo*. A trap of aqueous NaOCl/NaOH was set up to quench the excess of TMSCN. The crude mixture was purified by flash chromatography (petroleum ether/Et_2O: 99/1) to afford the title cyanohydrin **2.13** (27 g, 98 mmol, 95%) as a colourless oil.



Method B: To a solution of ketone **2.7** (0.36 g, 2.0 mmol) in $CHCl_3$ (7 mL) at -78°C was added $(DHQ)_2AQN$ (0.51 g, 0.6 mmol, 0.3 equiv) and TMSCN (0.54 mL, 4.0 mmol, 2 equiv) dropwise. The reaction mixture was stirred 5 days at -20°C in a freezer. An aqueous 1N HCl solution (10 mL) was added and the aqueous phase was extracted with Et_2O (3x10 mL). The organic extracts were combined and washed with brine (25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (pentane/dichloromethane: 98/2) to afford the title cyanohydrin **2.13** (266 mg, 0.96 mmol, 48%, 25% ee) as a colourless oil.[57]

^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm: 5.34 (ddq, *J* = 8.1, 6.9, 1.2 Hz, 1H, ***H8***), 2.78-2.70 (m, 1H, ***H7***), 2.52 (dd, *J* = 14.5, 8.1 Hz, 1H, ***H7***), 1.82 (s, 3H, ***H1***), 1.79 (d, *J* = 1.2 Hz, 3H, ***H10***), 1.67 (s, 3H, ***H10'***), 1.35 (s, 3H, ***H5***), 1.25 (s, 3H, ***H5***), 0.22 (s, 9H, Si(***CH_3***)$_3$).

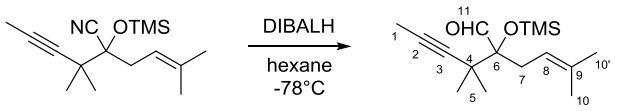
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 136.2 (***C9***), 120.2 (***C8***), 118.7 (***CN***), 82.5 (***C3***), 79.5 (***C2***), 79.2 (***C6***), 40.7 (***C4***), 36.0 (***C7***), 26.0 (2***C5***), 23.5 (***C10***), 18.1 (***C10'***), 3.6 (***C1***), 1.5 (Si(***CH_3***)$_3$).

IR (ν, cm^{-1}): 2978, 2922, 2876, 2240, 1674, 1447, 1382, 1363, 1252, 1126, 1112, 1070.

HRMS (EI) Calcd for $[M]^+$: *m/z* 277.1862, found 277.1863.

$[\alpha]^{24}_D$: + 3.5 (*c* 1.0, $CHCl_3$).

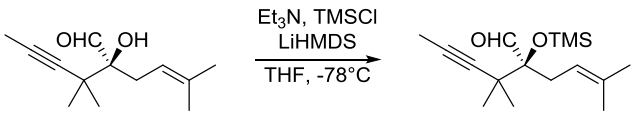
5-Methyl-2-(2-methylpent-3-yn-2-yl)-2-(trimethylsilyloxy)hex-4-enal (2.14)



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

MW: 280.48

Method A: To a solution of cyanohydrin **2.13** (17.8 g, 64.3 mmol) in freshly distilled hexane (600 mL) was added DIBALH (96.5 mL, 1 M in hexane, 96.5 mmol, 1.5 equiv). The reaction mixture was allowed to warm to 0°C and was stirred at this temperature for 20 min. The mixture was then cooled down to -78°C, and EtOAc was added. After stirring for 10 min, SiO_2 (200 g) was added. The mixture was then allowed to warm to room temperature for 12 h. Saturated aqueous NH_4Cl was added (500 mL), the aqueous layer was extracted with dichloromethane (3x500 mL), and the combined organic extracts were washed with brine (1 L), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (pentane/dichloromethane: 9/1) to afford the title aldehyde (±)-**2.14** (15.7 g, 56 mmol, 87%) as a colourless oil.



Method B: To a solution of hydroxyl-aldehyde **2.23** (20 mg, 71 µmol) in THF (2 mL) at -78°C was added Et_3N (97 µL, 0.7 mmol, 10 equiv) and TMSCl (0.12 mL, 0.7 mmol, 10 equiv). The resulting mixture was stirred for 10 min. Then LiHMDS (0.14 mL, 1 M in THF, 0.14 mmol, 2

equiv) was added at that temperature, and the reaction mixture was stirred for 30 min, then quenched by a saturated aqueous solution of $NaHCO_3$ (10 mL), and warmed to room temperature. The aqueous layer was extracted with Et_2O (3x10 mL), and the combined organic extracts were washed with brine (25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (pentane/dichloromethane: 9/1) to afford the title aldehyde **2.14** (16 mg, 57 µmol, 80%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 9.83 (s, 1H, ***CHO***), 5.01 (ddq, *J* = 7.8, 7.4, 1.2 Hz, 1H, ***H8***), 2.93 (ddq, *J* = 14.7, 7.4, 0.8 Hz, 1H, ***H7***), 2.46 (dd, *J* = 14.7, 7.8 Hz, 1H, ***H7***), 1.82 (s, 3H, ***H1***), 1.69 (d, *J* = 1.2 Hz, 3H, ***H10***), 1.63 (s, 3H, ***H10'***), 1.24 (s, 3H, ***H5***), 1.08 (s, 3H, ***H5***), 0.13 (s, 9H, Si(***CH_3***)$_3$).

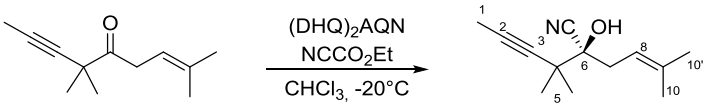
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 204.3 (***CHO***), 134.6 (***C9***), 118.9 (***C8***), 87.3, 84.0 (***C2***, ***C3***), 78.8 (***C6***), 37.4 (***C4***), 32.1 (***C7***), 25.9 (***C10***), 25.7 (***C5***), 24.5 (***C5***), 17.8 (***C10'***), 3.6 (***C1***), 2.7 (Si(***CH_3***)$_3$).

IR (ν, cm^{-1}): 2960, 2921, 2857, 2725, 2253, 1734, 1451, 1380, 1280, 1249, 1211, 1152, 1115, 1049, 1021.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/*z 303.1751, found 303.1741.

$[\alpha]^{24}_D$: + 15.0 (*c* 1.0, $CHCl_3$).

(S)-2-Hydroxy-5-methyl-2-(2-methylpent-3-yn-2-yl)hex-4-enenitrile (2.15)



Chemical Formula: $C_{13}H_{19}NO$

MW: 205,30

To a solution of ketone **2.7** (0.36 g, 2 mmol) in $CHCl_3$ (7 mL) at -78°C was added $(DHQ)_2AQN$ (0.51 g, 0.6 mmol, 0.3 equiv) and $NCCO_2Et$ (400 µL, 4 mmol, 2 equiv) dropwise. The reaction mixture was stirred 5 days at -20°C in a freezer. An aqueous 1N HCl solution (10 mL) was added and the aqueous phase was extracted with Et_2O (3x10 mL). The organic extracts were combined and washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography

(pentane/dichloromethane: 98/2) to afford the title cyanohydrin **2.15** (357 mg, 1.74 mmol, 87%, 35% ee) as a colourless oil.[57]

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.41 (ddspt, *J* = 9.0, 6.6, 1.4 Hz, 1H, ***H8***), 2.74 (s, 1H, ***OH***), 2.66 (dd, *J* = 14.4, 9.0 Hz, 1H, ***H7***), 2.59 (dd, *J* = 14.4, 6.6 Hz, 1H, ***H7***), 1.84 (m, 6H, ***H1***, ***H10***), 1.70 (m, 3H, ***H10'***), 1.40 (s, 3H, ***H5***), 1.38 (s, 3H, ***H5***).

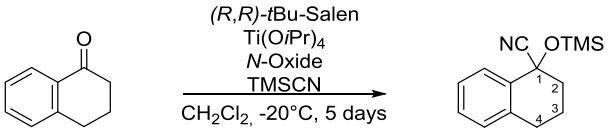
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 140.1 (***C9***), 120.2 (***C8***), 116.5 (***CN***), 81.2 (***C2*** or ***C3***), 79.9 (***C6***), 77.1 (***C2*** or ***C3***), 39.8 (***C4***), 34.3 (***C7***), 26.1 (***C10***), 24.9 (***C5***), 24.4 (***C5***), 18.2 (***C10'***), 3.6 (***C1***).

IR (ν, cm^{-1}): 3210, 3041, 2978, 2945, 2879, 2280, 1686, 1372, 1366, 1232, 1126, 1070.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 228.1359, found 228.1353.

$[\alpha]^{25}_D$: -8.0 (*c* 1.0, $CHCl_3$).

1-((Trimethylsilyl)oxy)-1,2,3,4-tetrahydronaphthalene-1-carbonitrile (2.16)



Chemical Formula: $C_{14}H_{19}NOSi$

MW: 245,40

Spect. Reference: He, B.; Chen, F.-X.; Li, Y.; Feng, X.; Zhang G. *Eur. J. Org. Chem*. **2004**, 4657-4666.

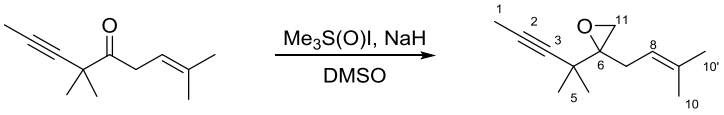
To a solution of (*R*,*R*)-*t*Bu-salen (65 mg, 0.1 mmol, 0.1 equiv) and *N*-oxide (2.2 mg, 10 µmol, 0.1 equiv) in CH_2Cl_2 (2 mL) was added Ti(O*i*Pr)$_4$ (29 µL, 0.1 mmol, 0.1 equiv). The reaction mixture was stirred at 35°C for 1 h. To this solution, at -20°C was added α-tetralone (132 µL, 1 mmol) followed by TMSCN (260 µL, 2.0 mmol, 2.0 equiv) and the reaction mixture was stirred for 6 days at the same temperature and the solvent was removed *in vacuo*. A trap of aqueous NaOCl/NaOH was set up to quench the excess of TMSCN. The crude mixture was purified by flash chromatography (petroleum ether/Et_2O: 99/1) to afford the title cyanohydrin **2.16** (220 mg, 0.90 mmol, 90%) as a colourless oil.[59]

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 7.67 (m, 1H, ***H_{Ar}***), 7.29 (m, 2H, ***H_{Ar}***), 7.13 (m, 1H, ***H_{Ar}***), 2.85 (m, 2H, ***H4***), 2.35 (m, 1H, ***H2***), 2.23 (m, 1H, ***H2***), 2.15-1.95 (m, 2H, ***H3***), 0.24 (s, 9H, (***CH_3***)$_3$Si).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 136.0 (***C_{Ar}***), 135.6 (***C_{Ar}***), 129.2 (***C_{Ar}***), 129.0 (***C_{Ar}***), 127.9 (***C_{Ar}***), 126.6 (***C_{Ar}***), 122.0 (***CN***), 69.8 (***C1***), 37.6 (***C2***), 28.2 (***C4***), 18.6 (***C3***), 1.3 ((***CH_3***)$_3$Si).

$[\alpha]^{24}_D$: -10.0 (*c* 1.4, CH_2Cl_2).

2-(3-Methylbut-2-en-1-yl)-2-(2-methylpent-3-yn-2-yl)oxirane (2.17)



Chemical Formula: $C_{13}H_{20}O$

MW: 192,30

To a solution of $Me_3S(O)I$ (246 mg, 1.12 mmol, 2.0 equiv) in DMSO (2 mL) was added NaH (34 mg, 60% in mineral oil, 0.84 mmol, 1.5 equiv). The reaction mixture was stirred 15 min at room temperature. Then a solution of ketone **2.7** (100 mg, 0.56 mmol) in THF (2 mL) was added dropwise. The reaction mixture was allowed to stir for 20 h at room temperature. A solution of brine (5 mL) was added and the aqueous phase was extracted with Et_2O (3x10 mL). The organic extracts were combined, washed with brine (25 mL) and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 95/5) to afford the title epoxide **2.17** (75 mg, 0.39 mmol, 70%) as a colourless oil.

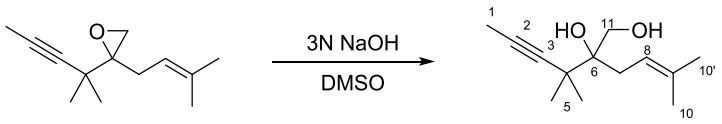
^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.05 (m, 1H, ***H8***), 2.82 (d, *J* = 4.8 Hz, 1H, ***H11***), 2.69 (dd, *J* = 15.4, 8.3 Hz, 1H, ***H7***), 2.56 (d, *J* = 4.8 Hz, 1H, ***H11***), 2.49 (dd, *J* = 15.4, 6.4 Hz, 1H, ***H7***), 1.80 (s, 3H, ***H1***), 1.70 (s, 3H, ***H10***), 1.62 (s, 3H, ***H10'***), 1.23 (s, 3H, ***H5***), 1.21 (s, 3H, ***H5***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 134.2 (***C9***), 118.8 (***C8***), 84.0, 77.6 (***C2***, ***C3***), 62.5 (***C6***), 48.3 (***C11***), 35.2 (***C4***), 28.4 (***C7***), 25.8 (***C10***), 25.6 (2***C5***), 17.8 (***C10'***), 3.6 (***C1***).

IR (ν, cm^{-1}): 3055, 2975, 2920, 2871, 2341, 1471, 1456, 1245, 1123, 1052.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 215.1406, found 215.1408.

5-Methyl-2-(2-methylpent-3-yn-2-yl)hex-4-ene-1,2-diol (2.18)



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

MW: 210,32

To a solution of epoxide **2.17** (50 mg, 0.26 mmol) in DMSO (2.5 mL) was added a 3N aqueous solution of NaOH (1.3 mL, 3.9 mmol, 15 equiv). The reaction mixture was stirred 2 h at 40°C. A solution of brine (5 mL) was added and the aqueous phase was extracted with EtOAc (3x5 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 9/1 to 7/3) to afford the title diol **2.18** (12 mg, 60 µmol, 22%) as a colourless oil.

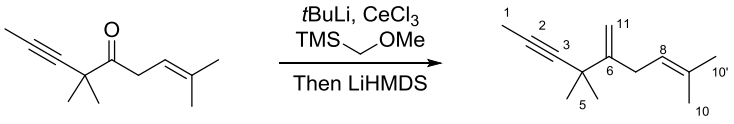
^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm: 5.35 (ddspt, *J* = 8.3, 7.0, 1.4 Hz, 1H, ***H8***), 3.73 (dd, *J* = 11.4, 4.6 Hz, 1H, ***H11***), 3.64 (dd, *J* = 11.4, 5.8 Hz, 1H, ***H11***), 2.47-2.32 (m, 3H, 2***H7***, ***OH6***), 2.21 (dd, *J* = 5.8, 4.6 Hz, 1H, ***OH11***), 1.81 (s, 3H, ***H1***), 1.76 (m, 3H, ***H10***), 1.67 (m, 3H, ***H10'***), 1.27 (s, 3H, ***H5***), 1.25 (s, 3H, ***H5***).

^{13}C NMR (100 MHz, *$CDCl_3$*) δ ppm: 135.5 (***C9***), 119.6 (***C8***), 84.9, 78.3 (***C2***, ***C3***), 76.1 (***C6***), 65.3 (***C11***), 39.3 (***C4***), 32.0 (***C7***), 26.1 (***C10***), 25.0 (***C5***), 25.0 (***C5***), 17.9 (***C10'***), 3.5 (***C1***).

IR (ν, cm^{-1}): 3250, 3030, 2985, 2915, 2395, 1450, 1115, 1045.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 233.1512, found 233.1513.

2,6,6-Trimethyl-5-methylenenon-2-en-7-yne (2.19)



Chemical Formula: $C_{13}H_{20}$

MW: 176,30

To a solution of (methoxymethyl)trimethylsilane (264 µL, 1.70 mmol, 3.0 equiv) in THF (3 mL) was slowly added at -78°C a solution of *t*BuLi (0.75 mL, 1.45 M in pentane, 1.1 mmol, 2.0 equiv). The reaction mixture was stirred 1 h at 0°C and a solution of ketone **2.7** (100

mg, 0.56 mmol) in THF (3 mL) was slowly added. The reaction mixture was allowed to stir at 0°C for 1 h followed by another hour at room temperature. The reaction mixture was cooled down to 0°C and a solution of LiHMDS (1.12 mL, 1.12 mmol, 2 equiv) was added and the reaction mixture was stirred for 16 h at room temperature. A saturated solution of NH_4Cl (5 mL) was added and the aqueous phase was extracted with diethyl ether (3x10 mL). The organic extracts were combined and washed with brine (25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether: 100) to afford the title **2.19** (39 mg, 0.22 mmol, 40%) as a colourless oil.

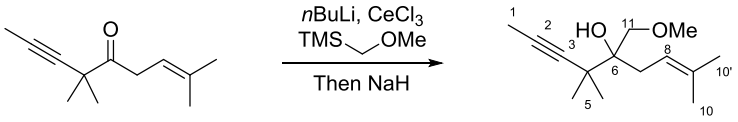
^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm: 5.24 (tspt, *J* = 7.3, 1.4 Hz, 1H, ***H8***), 5.07 (m, 1H, ***H11***), 4.77 (m, 1H, ***H11***), 2.86 (m, 2H, ***H7***), 1.81 (s, 3H, ***H1***), 1.75 (m, 3H, ***H10***), 1.63 (m, 3H, ***H10'***), 1.34 (s, 6H, ***H5***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 153.4 (***C6***), 132.5 (***C9***), 122.8 (***C8***), 107.9 (***C11***), 85.7, 76.1 (***C2***, ***C3***), 36.7 (***C4***), 30.5 (***C7***), 29.2 (2***C5***), 25.7 (***C10***), 17.6 (***C10'***), 3.6 (***C1***).

IR (ν, cm^{-1}): 3094, 2973, 2919, 2858, 2340, 1455, 1376, 1174.

HRMS (CI/ISO) Calcd for $[M+H]^+$: *m/z* 177.1643, found 177.1639.

5-(Methoxymethyl)-2,6,6-trimethylnon-2-en-7-yn-5-ol (2.20)



Chemical Formula: $C_{14}H_{24}O_2$

MW: 224,34

$CeCl_3.7H_2O$ (626 mg, 1.68 mmol, 3.0 equiv) was dried with a gradually increased temperature (120°C to 160°C) under vacuum for 6 h. After the dried cerium trichloride had cooled down, THF (4 mL) was added and the mixture was stirred for 2 h at room temperature. To a solution of (methoxymethyl)trimethylsilane (264 µL, 1.70 mmol, 3.0 equiv) in THF (3 mL) was slowly added at -78°C a solution of *n*BuLi (0.56 mL, 2.05 M in pentane, 1.1 mmol, 2.0 equiv). The reaction mixture was stirred 1 h at 0°C. This solution was transferred at -78°C to the freshly made $CeCl_3$.THF complex solution and the reaction mixture was stirred at the same temperature for 30 min. Then a solution of ketone **2.7** (100

mg, 0.56 mmol) in THF (3 mL) was slowly added. The reaction mixture was allowed to stir at 0°C for 2 h followed by 16 h at room temperature. A saturated aqueous solution of NH_4Cl (10 mL) was added and the aqueous phase was extracted with diethyl ether (3x10 mL). The organic extracts were combined and washed with brine (25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was dissolved in THF (10 mL) and NaH (48 mg, 60% in mineral oil, 1.2 mmol, 2.1 equiv) was added and the reaction mixture was stirred at room temperature for 16 h. A saturated aqueous solution of NH_4Cl (10 mL) was added and the aqueous phase was extracted with diethyl ether (3x10 mL). The organic extracts were combined and washed with brine (25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/diethyl ether: 98/2 to 95/5) to afford the title alcohol **2.20** (72 mg, 0.32 mmol, 58%) as a colourless oil.

^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm: 5.32 (tspt, *J* = 7.6, 1.3 Hz, 1H, ***H8***), 3.46 (d, *J* = 9.4 Hz, 1H, ***H11***), 3.42 (d, *J* = 9.4 Hz, 1H, ***H11***), 3.34 (s, 3H, ***OMe***), 2.42 (d, *J* = 7.6 Hz, 2H, ***H7***), 2.39 (s, 1H, ***OH***), 1.81 (s, 3H, ***H1***), 1.75 (m, 3H, ***H10***), 1.65 (m, 3H, ***H10'***), 1.25 (s, 3H, ***H5***), 1.25 (s, 3H, ***H5***).

^{13}C NMR (100 MHz, *$CDCl_3$*) δ ppm: 133.9 (***C9***), 120.2 (***C8***), 85.2 (***C2***), 77.3 (***C3***), 75.9 (***C6***), 74.9 (***C11***), 59.0 (***OMe***), 39.9 (***C4***), 32.6 (***C7***), 26.1 (***C10***), 25.3 (2***C5***), 24.9 (2***C5***), 17.8 (***C10'***), 3.6 (***C1***).

IR (ν, cm^{-1}): 3564, 3030, 2976, 2919, 2245, 1507, 1450, 1244, 1189, 1121.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 247.1669, found: 247.1662.

5-(Methoxymethylene)-2,6,6-trimethylnon-2-en-7-yne (2.21)

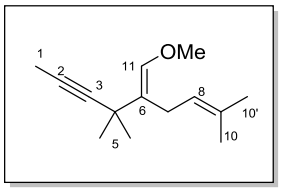
Chemical Formula: $C_{14}H_{22}O$

MW: 206,33

To a solution of the phosphine oxide derivatives **2.22** (170 mg, 0.4 mmol) in DMF (5 mL) at 0°C was added NaH (24 mg, 60% in mineral oil, 0.6 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 16 h. A saturated aqueous solution of NH_4Cl (10 mL)

was added and the aqueous phase was extracted with Et_2O (3x10 mL). The organic extracts were combined and washed with brine (25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (*n*Pentane/CH_2Cl_2: 98/2 to 96/4) to afford the title (*E*) enol ether **2.21a** (66 mg, 0.32 mmol, 80%) and (*Z*) enol ether **2.21b** (5 mg, 25 µmol, 6%) as colourless oils.

(E)-5-(Methoxymethylene)-2,6,6-trimethylnon-2-en-7-yne (2.21a)



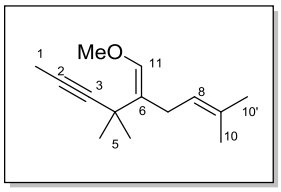
^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.62 (t, *J* = 1.2 Hz, 1H, ***H11***), 5.16 (tspt, *J* = 7.0, 1.4 Hz, 1H, ***H8***), 3.52 (s, 3H, ***OMe***), 2.75 (dd, *J* = 7.0, 1.2 Hz, 2H, ***H7***), 1.81 (s, 3H, ***H1***), 1.72 (m, 3H, ***H10***), 1.63 (m, 3H, ***H10'***), 1.43 (s, 6H, ***H5***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 143.2 (***C11***), 131.5 (***C9***), 123.9 (***C8***), 121.2 (***C6***), 87.0, 75.1 (***C2***, ***C3***), 59.4 (***OMe***), 34.5 (***C4***), 30.8 (***C7***), 29.2 (2***C5***), 25.8 (***C10***), 17.6 (***C10'***), 3.6 (***C1***).

IR (ν, cm^{-1}): 3056, 2979, 2936, 2365, 1715, 1633, 1450, 1365, 1280.

HRMS (CI/ISO) Calcd for $[M+H]^+$: *m/z* 207.1749, found 207.1757.

(Z)-5-(Methoxymethylene)-2,6,6-trimethylnon-2-en-7-yne (2.21b)



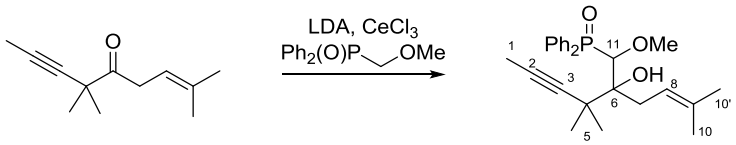
^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 6.18 (s, 1H, ***H11***), 5.12 (tspt, *J* = 6.8, 1.3 Hz, 1H, ***H8***), 3.59 (s, 3H, ***OMe***), 2.82 (d, *J* = 6.8 Hz, 2H, ***H7***), 1.82 (s, 3H, ***H1***), 1.69-1.66 (m, 6H, ***H10***, ***H10'***), 1.29 (s, 3H, ***H5***), 1.26 (s, 3H, ***H5***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 143.1 (***C11***), 130.0 (***C9***), 124.6 (***C8***), 123.0 (***C6***), 85.7, 76.1 (***C2***, ***C3***), 59.4 (***OMe***), 34.1 (***C4***), 29.5 (2***C5***), 25.8 (***C10***), 25.0 (***C7***), 17.7 (***C10'***), 3.6 (***C1***).

IR (ν, cm^{-1}): 3065, 2980, 2935, 2241, 1721, 1638, 1442, 1360, 1280, 1265, 1172.

HRMS (CI/ISO) Calcd for $[M+H]^+$: *m/z* 207.1749, found 207.1757.

(2-Hydroxy-1-methoxy-5-methyl-2-(2-methylpent-3-yn-2-yl)hex-4-en-1-yl)diphenylphosphine oxide (2.22)



Chemical Formula: $C_{26}H_{33}O_3P$

MW: 424,52

$CeCl_3.7H_2O$ (313 mg, 0.84 mmol, 1.5 equiv) was dried with a gradually increased temperature (120°C to 160°C) under vacuum for 6 h. After the dried cerium trichloride had cooled down, THF (2 mL) was added and the mixture was stirred for 2 h at room temperature. To a solution of diisopropylamine (109 µL, 0.78 mmol, 1.4 equiv) in THF (2 mL) was added *n*BuLi (0.41 mL, 1.99 M in pentane, 0.81 mmol, 1.45 equiv) at -78°C and the reaction mixture was stirred for 5 min and allowed to warm up and stirred 10 min at 0°C. Then the phosphine oxide (190 mg, 0.78 mmol, 1.4 equiv) was added and stirred for 30 min at the same temperature. This solution was transferred at -78°C to the freshly made $CeCl_3$.THF complex solution and the reaction mixture was stirred at the same temperature for 30 min. Then a solution of ketone **2.7** (100 mg, 0.56 mmol) in THF (1 mL) was slowly added. The reaction mixture was allowed to warm up and reach room temperature over 16 h. An aqueous saturated solution of NH_4Cl (10 mL) was added and the aqueous phase was extracted with EtOAc (3x10 mL). The organic extracts were combined and washed with brine (25mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/ EtOAc: 7/3) to afford 2 phosphine oxide derivatives in a 12:1 ratio **2.22** (174 mg, 0.41 mmol, 73%) as a white solid.

<u>*Major isomer*</u>

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 8.05-7.97 (m, 2H, ***H_{Ar}***), 7.87-7.80 (m, 2H, ***H_{Ar}***), 7.58-7.42 (m, 6H, ***H_{Ar}***), 5.32-5.25 (m, 1H, ***H8***), 4.49 (d, *J* = 5.0 Hz, 1H, ***H11***), 4.28 (s, 1H, ***OH***), 3.04 (s, 3H, ***OMe***), 2.64-2.40 (m, 2H, ***H7***), 1.78 (s, 3H, ***H1***), 1.65-1.60 (s, 3H, ***H10*** or ***H10'***), 1.44 (s, 3H, ***H10*** or ***H10'***), 1.38 (s, 3H, ***H5***), 1.28 (s, 3H, ***H5***).

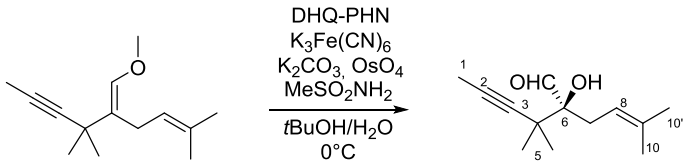
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 133.3 (***C9***), 132.7 (***C_{Ar}***), 132.7 (***C_{Ar}***), 131.4 (***C_{Ar}***), 131.4 (***C_{Ar}***), 128.5 (***C_{Ar}***), 128.4 (***C_{Ar}***), 128.1 (***C_{Ar}***), 128.0 (***C_{Ar}***), 120.1 (***C8***), 86.7 (d, *J* = 15 Hz, ***C11***), 86.6, 81.1

(***C2***, ***C3***), 77.4 (***C6***), 61.7 (***OMe***), 39.9 (***C4***), 35.9 (***C7***), 26.6 (***C5***), 26.5 (***C5***), 26.0 (***C10*** or ***C10'***), 17.9 (***C10*** or ***C10'***), 3.7 (***C1***).

IR (ν, cm^{-1}): 3393, 3055, 2981, 2934, 2922, 2306, 1698, 1621, 1450, 1397, 1265, 1079.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 447.2060, found 447.2047.

(S)-2-Hydroxy-5-methyl-2-(2-methylpent-3-yn-2-yl)hex-4-enal (2.23)



Chemical Formula: $C_{13}H_{20}O_2$

MW: 208,30

To a solution of DHQ-PHN (5 mg, 10 µmol, 0.1 equiv) in *t*BuOH/H_2O (1 mL) were added $K_3Fe(CN)_6$ (100 mg, 0.3 mmol, 3 equiv), K_2CO_3 (40 mg, 0.3 mmol, 3 equiv) and OsO_4 (4 µL, 0.4 µmol, 0.004 equiv). The reaction mixture was stirred 30 min at room temperature. To this mixture was added a solution of sulfonamide (9 mg, 0.1 mmol, 1 equiv) followed by a solution of (*E*) enol ether **2.21a** (20 mg, 0.1 mmol) in *t*BuOH/H_2O (0.5 mL) at 0°C. The reaction mixture was stirred at the same temperature for 6 h. Then Na_2SO_3 (200 mg) added and stirred for 30 min. Water (5 mL) was added and the aqueous phase was extracted with EtOAc (3x10 mL). The organic extracts were combined and washed with brine (25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 95/5) to afford the title hydroxy-aldehyde **2.23** (17 mg, 80 µmol, 80%, 61% ee) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 9.80 (d, *J* = 1.2 Hz, 1H, ***CHO***), 4.98-4.92 (m, 1H, ***H8***), 3.30 (br s, 1H, ***OH***), 3.02 (dd, *J* = 14.8, 8.6 Hz, 1H, ***H7***), 2.46 (dd, *J* = 14.8, 6.4 Hz, 1H, ***H7***), 1.84 (s, 3H, ***H1***), 1.67 (s, 3H, ***H10*** or ***H10'***), 1.65 (s, 3H, ***H10*** or ***H10'***), 1.29 (s, 3H, ***H5***), 1.08 (s, 3H, ***H5***).

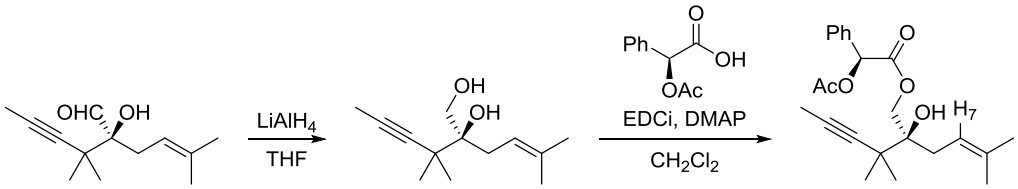
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 205.6 (***CHO***), 135.7 (***C9***), 117.3 (***C8***), 83.3 (***C2*** or ***C3***), 83.0 (***C6***), 79.2 (***C2*** or ***C3***), 36.7 (***C4***), 30.6 (***C7***), 25.8 (***C10*** or ***C10'***), 24.7 (***C5***), 24.1 (***C5***), 17.9 (***C10*** or ***C10'***), 3.5 (***C1***).

IR (ν, cm^{-1}): 3502, 3054, 2978, 2922, 2857, 2306, 1721, 1448, 1383, 1205, 1121, 1039.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 231.1356, found 231.1353.

$[\alpha]^{25}_D$: + 17.0 (*c* 1.5, $CHCl_3$).

(S)-2-hydroxy-5-methyl-2-(2-methylpent-3-yn-2-yl)hex-4-en-1-yl (S)-2-acetoxy-2-phenylacetate (2.24)



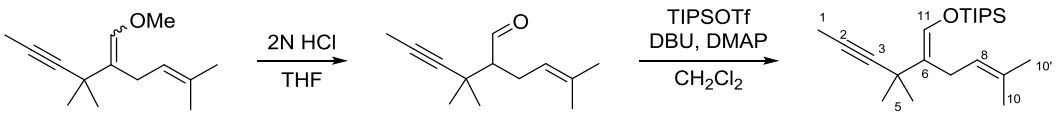
Chemical Formula: $C_{23}H_{30}O_5$

MW: 386.49

To a suspension of lithium aluminium hydride (2.5 mg, 65 µmol, 1.5 equiv) in THF (0.5 mL) was added a solution of aldehyde **2.23** (9 mg, 43 µmol) in THF (0.5 mL). The reaction mixture was stirred for 2 h at RT. Excess of lithium aluminum hydride was then quenched with careful addition of ice and a 1N aqueous HCl solution was added to dissolve lithium salts. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with 1N aqueous HCl, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford diol **2.18**. To a solution of crude alcohol **2.18** in dichloromethane (1 mL) were added (+)-*O*-acetylmandelic acid (41 mg, 0.2 mmol, 5 equiv) and DMAP (0.5 mg, 4 µmol, 0.1 equiv) followed by EDCi (41 mg, 0.2 mmol, 5 equiv). The reaction mixture was stirred for 6 h. A saturated aqueous solution of NH_4Cl (5 mL) was added and the aqueous phase was extracted with dichloromethane (3x5 mL). The organic extracts were combined, washed with a saturated aqueous solution of $NaHCO_3$ (15 mL), washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude ester **2.24**.

Enantioselectivity of products made by asymmetric dihydroxylation were determined by the H_7 integrals comparison in the crude ^1H NMR spectra of the *L*-(+)-*O*-acetylmandelic acid derivatives **2.24**.

(E)-Triisopropyl((5-methyl-2-(2-methylpent-3-yn-2-yl)hexa-1,4-dien-1-yl)oxy)silane (2.25)



Chemical Formula: $C_{22}H_{40}OSi$

MW: 348,65

To a solution of a mixture of enol ethers **2.21** (29 mg, 0.14 mmol) in THF (2 mL) was added a solution of an aqueous 2N HCl (0.7 mL, 1.4 mmol, 10 equiv). The reaction mixture was stirred at room temperature for 40 h. A saturated aqueous solution of $NaHCO_3$ (5 mL) was added and the aqueous phase was extracted with Et_2O (3x5 mL). The organic extracts were combined and washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*.

To a solution of the preceding crude mixture in CH_2Cl_2 (2 mL) were added DMAP (17 mg, 0.14 mmol, 1 equiv) and DBU (41 µL, 0.28 mmol, 2 equiv). The reaction mixture was then allowed to cool down to -78°C and TIPSOTf (75 µL, 0.28 mmol, 2 equiv) was added. The reaction mixture was stirred at this temperature for 4 h. A saturated aqueous solution of $NaHCO_3$ (5 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3x5 mL). The organic extracts were combined and washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (pentane/CH_2Cl_2: 98/2) to afford the title TIPS enol ether **2.25** (20 mg, 57 µmol, 25%) as a (95/5) *E*/*Z* mixture as a colourless oil.

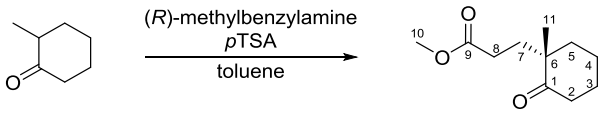
^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 6.63 (s, 1H, ***H11***), 5.16 (tspt, *J* = 6.6, 1.4 Hz, 1H, ***H8***), 2.85 (d, *J* = 6.6 Hz, 2H, ***H7***), 1.80 (s, 3H, ***H1***), 1.67-1.65 (m, 6H, ***H5***), 1.27 (m, 6H, ***H10***, ***H10'***), 1.20-1.11 (m, 3H, Si***CH***), 1.10-1.05 (m, 18H, Si(CH***CH_3)$_3$**).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 136.2 (***C11***), 129.1 (***C9***), 125.1 (***C8***), 124.5 (***C6***), 86.1, 76.0 (***C2***, ***C3***), 34.1 (***C4***), 29.6 (2***C5***), 25.7 (***C10*** or ***C10'***), 24.7 (***C7***), 17.8 (***C10*** or ***C10'***), 17.8 (Si(CH***CH_3)$_3$**), 12.0 (Si***CH***), 3.5 (***C1***).

IR (ν, cm^{-1}): 3050, 2963, 2944, 2944, 2867, 2309, 1636, 1437, 1169.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 371.2741, found 371.2727.

(S)-Methyl 3-(1-methyl-2-oxocyclohexyl)propanoate (2.26)



***Chemical Formula*:** $C_{11}H_{18}O_3$

***MW*:** 198.28

Spect. Reference: Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273-274.

To a solution of 2-methylcyclohexanone (10.0 mL, 82.4 mmol) and (*R*)-(α)-methylbenzylamine (10.5 mL, 82.4 mmol, 1.0 equiv) in 20 mL of toluene was added 30 mg of PTSA. The mixture was stirred at reflux with a Dean Stark apparatus for 4 h. The solvent was then removed *in vacuo*, and methyl acrylate (8.09 mL, 98.9 mmol, 1.2 equiv) was added. The reaction mixture was stirred at RT for 7 days. The reaction mixture was quenched with addition of 30% aqueous acetic acid (15 mL). The aqueous layer was extracted with Et_2O (3x20 mL), and the combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel (petroleum ether/EtOAc: 9/1) to afford the title keto ester **2.26** (13.0 g, 65.5 mmol, 80%, 91% ee) as a colourless oil.

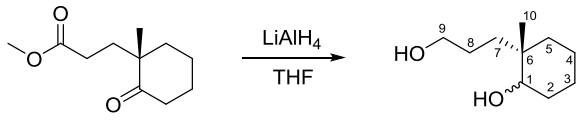
^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm: 3.66 (s, 3H, ***H11***), 2.42-2.26 (m, 2H, ***H8***), 2.15 (ddd, *J* = 15.0, 11.1, 5.2 Hz, 1H, ***H2***), 2.04 (ddd, *J* = 15.0, 11.1, 5.2 Hz, 1H, ***H2***), 1.91-1.54 (m, 8H, ***H3***, ***H4***, ***H5***, ***H7***), 1.07 (s, 3H, ***H11***).

^{13}C NMR (100 MHz, *$CDCl_3$*) δ ppm: 215.3 (***C1***), 174.1 (***C9***), 51.7 (***C10***), 47.9 (***C6***), 39.35 (***C8***), 38.7 (***C2***), 32.5, 29.0, 27.4 (***C3***, ***C4***, ***C5***), 22.4 (***C11***), 21.0 (***C7***).

IR (ν, cm^{-1}): 2935, 2871, 1735, 1702, 1436, 1378, 1302, 1195, 1170, 1122.

$[\alpha]^{20}_D$: -34.0 (*c* 1.35, EtOH), lit: **$[\alpha]^{20}_D$**: -34.3 (*c* 1.36, EtOH), 91% ee.

(2S)-2-(3-Hydroxypropyl)-2-methylcyclohexanol (2.27)



***Chemical Formula*:** $C_{10}H_{20}O_2$

***MW*:** 172.27

Spect. Reference: Tori, M.; Kosaka, K.; Asakawa, Y. *J. Chem. Soc. Perkin Trans I* **1994**, 14, 2039-2042.

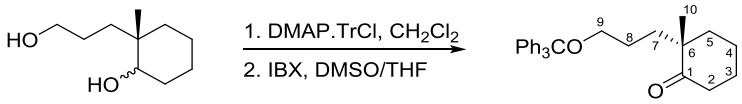
To a suspension of lithium aluminium hydride (5.78 g, 151 mmol, 2.50 equiv) in 130 mL of THF, at 0°C was added dropwise a solution of **2.26** (12.0 g, 60.5 mmol) in 100 mL of THF. The resulting mixture was then allowed to warm to RT and stirred for 3 h. After cooling down to 0°C, ice was slowly added, followed by 1N aqueous HCl to dissolve the aluminium salts. The aqueous layer was extracted with Et_2O (3x100 mL) and the combined organic extracts were washed with brine (250 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title diol as a 1:1 mixture of diastereomers **2.27** (8.85 g, 51.4 mmol, 85%) as a colourless oil.

^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm: 3.68-3.60 (m, 2H, ***H9***), 3.53-3.30 (m, 3H, ***H1***, 2***H2***), 1.76-1.28 (m, 10H, ***H3***, ***H4***, ***H5***, ***H7***, ***H8***), 0.94 (s, 1.5H, ***H10***), 0.88 (s, 1.5H, ***H10***).

^{13}C NMR (100 MHz, *$CDCl_3$*) δ ppm: 77.2 (***C1***), 75.7 (***C1***), 63.9 (***C9***), 63.9 (***C9***), 37.7 (***C6***), 37.1 (***C6***), 36.7 (***CH_2***), 35.1 (***CH_2***), 34.3 (***CH_2***), 30.6 (***CH_2***), 29.7 (***CH_2***), 26.4 (***CH_2***), 26.3 (***CH_2***), 25.0 (***CH_2***), 24.5 (***CH_2***), 23.7 (***C10***), 23.0 (***CH_2***), 21.3 (***CH_2***), 21.2 (***CH_2***), 17.2 (***C10***).

IR (ν, cm^{-1}): 3344, 2929, 2861, 1449, 1377, 1145, 1054, 1008.

(S)-2-Methyl-2-(3-(trityloxy)propyl)cyclohexanone (2.28)



Chemical Formula: $C_{29}H_{32}O_2$

MW: 412.57

Spect. Reference: Ma, C.; Schiltz, S.; Le Goff, X. F.; Prunet J. *Chem. Eur. J*. **2008**, *14*, 7314-7323.

DMAP.TrCl complex (21 g, 52 mmol, 1.2 equiv) was added at room temperature to a solution of diol **2.27** (7.50 g, 43.5 mmol) in dichloromethane (60 mL). The resulting mixture was refluxed for 12 h. After cooling down, diethyl ether (30 mL) was added, and the white salts were filtered off. The solution was dried over $MgSO_4$, filtered and the solvent was concentrated *in vacuo*. To a solution of the crude product in 120 mL of THF was added a solution of IBX (14.6 g, 52.0 mmol, 1.20 equiv) in DMSO (120 mL) and the reaction mixture was stirred at RT for 12 h. Water (200 mL) was added and the organic phase was diluted

with Et_2O (200 mL). The resulting white salts were filtered off and the aqueous layer was extracted with Et_2O (3x250 mL). The combined organic phases were washed with brine (500 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (petroleum ether/Et_2O: 85/15) to afford the title ketone **2.28** (14.9 g, 36.1 mmol, 83%) as a yellow solid.

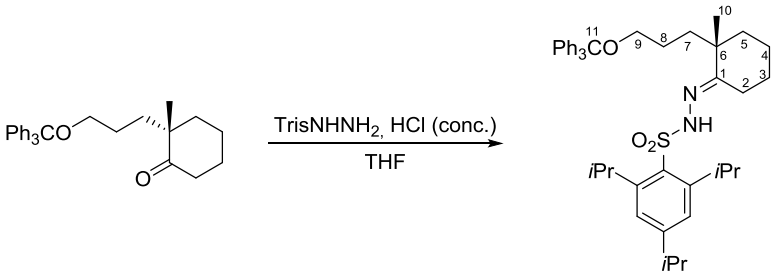
^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm: 7.43 (m, 6H, ***H_{Ar}***), 7.30 (m, 6H, ***H_{Ar}***), 7.25 (m, 3H, ***H_{Ar}***), 3.04 (m, 2H, ***H9***), 2.32 (m, 2H, ***H2***), 1.90 (m, 1H, ***CH_2***), 1.72 (m, 2H, ***CH_2***), 1.72-1.53 (m, 6H, ***CH_2***), 1.47-1.30 (m, 1H, ***CH_2***), 1.05 (s, 3H, ***H10***).

^{13}C NMR (100 MHz, *$CDCl_3$*) δ ppm: 216.1 (***C1***), 144.4 (***C_{Ar}***), 128.7 (***C_{Ar}***), 127.7 (***C_{Ar}***), 126.9 (***C_{Ar}***), 86.5 (***CPh_3***), 64.0 (***C9***), 48.5 (***C6***), 39.4 (***C2***), 38.9 (***CH_2***), 34.0 (***CH_2***), 27.6 (***CH_2***), 24.6 (***CH_2***), 22.6 (***C11***), 21.1 (***CH_2***).

IR: (ν, cm^{-1}): 3087, 3061, 3034, 2938, 2867, 1701, 1490, 1448, 1265, 1074.

$[\alpha]^{26}_D$: -4.8 (*c* 1, $CHCl_3$).

(S)-2,4,6-Triisopropyl-N'-(2-methyl-2-(3-(trityloxy)propyl)cyclohexylidene)benzenesulfonohydrazide (2.29)



Chemical Formula: $C_{44}H_{56}N_2O_3S$

MW: 693.00

To a solution of **2.28** (1.0 g, 2.4 mmol) in 10 mL of THF were added $TrisNHNH_2$ (789 mg, 2.67 mmol, 1.1 equiv) and 2 drops of concentrated HCl and the reaction mixture was stirred for 2 h. A saturated aqueous solution of $NaHCO_3$ (20 mL) was added and the aqueous layer was extracted with Et_2O (3x25 mL). The combined organic extracts were washed with brine (75 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (petroleum ether/Et_2O: 9/1) to afford the title hydrazone **2.29** (1.16 g, 1.67 mmol, 69%) as a white solid.

^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm: 7.41-7.34 (m, 7H, N***H***, ***H_{Ar}***), 7.34-7.11 (m, 9H, ***H_{Ar}***), 7.09 (s, 2H, ***H_{Ar}***), 4.14 (spt, *J* = 6.9 Hz, 2H, Ar***CH***$(CH_3)_2$), 2.86 (td, *J* = 6.2, 1.5 Hz, 2H, ***H9***), 2.79 (spt, *J* = 6.9 Hz, 1H, Ar***CH***$(CH_3)_2$), 2.33 (td, *J* = 14.6, 5.0 Hz, 1H, ***H2***), 1.91 (ddd, *J* = 14.6, 11.3, 5.0 Hz, 1H, ***H2***), 1.80-1.67 (m, 2H, ***CH_2***), 1.66-1.49 (m, 4H, ***CH_2***), 1.50-1.25 (m, 2H, ***CH_2***), 1.22 (2d, *J* = 6.9 Hz, 12H, ArCH(***CH_3***)$_2$), 1.16 (2d, *J* = 6.9 Hz, 6H, ArCH(***CH_3***)$_2$), 1.08-1.02 (m, 1H, ***CH_2***), 0.87 (s, 3H, ***H10***).

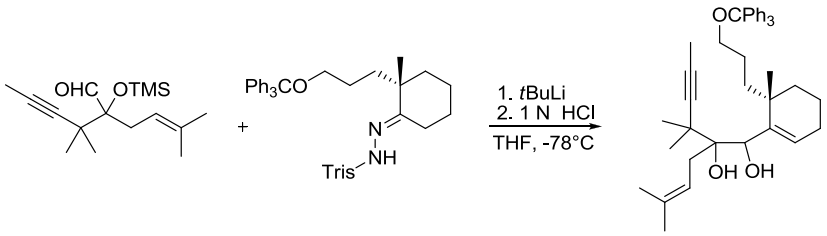
^{13}C NMR (100 MHz, *$CDCl_3$*) δ ppm: 163.1 (***C1***), 153.0 (***C_{Ar}***), 151.1 (***C_{Ar}***), 146.9 (***C_{Ar}***), 144.5 (***C_{Ar}***), 131.4 (***C_{Ar}***), 128.7 (***C_{Ar}***), 128.0 (***C_{Ar}***), 127.7 (***C_{Ar}***), 127.3 (***C_{Ar}***), 126.9 (***C_{Ar}***), 123.5 (***C_{Ar}***), 86.4 (***C11***), 64.1 (***C9***), 41.8 (***C6***), 39.4 (***CH_2***), 34.3 (***CH_2***), 34.2, 29.9 (3***CH***), 25.9 (***CH_2***), 25.0 (4***CH_3***), 24.4 (***CH_3***), 24.1 (***CH_2***), 23.7 (***CH_3***), 23.6 (***CH_2***), 20.1 (***CH_2***).

IR (ν, cm^{-1}): 3262, 2957, 2931, 2867, 1599, 1563, 1495, 1449, 1384, 1325, 1163, 1152, 1070.

HRMS (EI) Calcd for $[M]^+$: *m/*z 692.4012, found 692.3997.

$[\alpha]^{20}_D$: -59.2 (*c* 1.67, CH_2Cl_2).

5-Methyl-1-((S)-6-methyl-6-(3-(trityloxy)propyl)cyclohex-1-enyl)-2-(2-methylpent-3-yn-2-yl)hex-4-ene-1,2-diol (3.30) and (3.31)



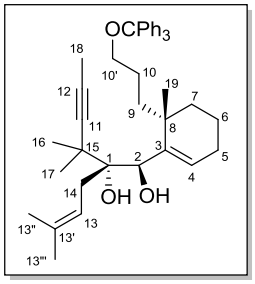
***Chemical Formula*:** $C_{42}H_{52}O_3$

***MW*:** 604.87

To a solution of hydrazone **2.29** (2.02 g, 1.80 mmol, 1.5 equiv) in THF (15 mL) at -78°C was added dropwise *t*BuLi (4.6 mL, 1.4 M in hexane, 6.4 mmol, 3.3 equiv). The solution turned dark red. The solution was stirred at this temperature for 30 min and warmed for a few min to room temperature and intense nitrogen bubbling occured. The mixture was then cooled down to –78°C and a solution of aldehyde (±)-**2.14** (545 mg, 1.94 mmol) in THF (5 mL) was added. The resulting mixture was stirred at -78°C for 5 h and became yellow. The reaction was quenched with saturated aqueous $NaHCO_3$ (25 mL). The aqueous layer was extracted with Et_2O (3x25 mL), and the combined organic extracts were washed with brine (75 mL),

dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was dissolved in THF (10 mL) and a 1 N aqueous solution of HCl (2.9 mL, 2.9 mmol, 1.5 equiv) was then added. The resulting mixture was stirred at room temperature for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (25 mL). The aqueous layer was extracted with Et_2O (3x25 mL), and the combined organic extracts were washed with brine (75 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 95/5) to afford the title diol **2.30** (440 mg, 0.73 mmol, 38%) and the title diol **2.31** (440 mg, 0.73 mmol, 38%) as colourless highly viscous oils.

(1R,2R)-5-Methyl-1-((S)-6-methyl-6-(3-(trityloxy)propyl)cyclohex-1-enyl)-2-(2-methylpent-3-yn-2-yl)hex-4-ene-1,2-diol (2.30)



^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 7.47 (dd, *J* = 8.3, 1.1 Hz, 6H, ***H_{Ar}***), 7.34-7.28 (m, 6H, ***H_{Ar}***), 7.26-7.21 (m, 3H, ***H_{Ar}***), 6.16 (t, *J* = 4.0 Hz, 1H, ***H4***), 5.43 (ddq, *J* = 8.2, 6.8, 1.6 Hz, 1H, ***H13***), 4.48 (d, *J* = 4.5 Hz, 1H, ***H2***), 3.32 (s, 1H, ***OH1***), 3.15-3.02 (m, 2H, ***H10'***), 2.81 (d, *J* = 4.5 Hz, 1H, ***OH2***), 2.42 (m, 2H, ***H14***), 2.08-2.01 (m, 2H, ***H5***), 1.74–1.71 (m, 1H, ***H7***), 1.73 (s, 3H, ***H18***), 1.72 (s, 3H, ***H13"***), 1.69-1.48 (m, 9H, ***H13'''***, ***H6***, ***H9***, ***H10***), 1.32-1.40 (m, 1H, ***H7***), 1.30 (s, 3H, ***H16*** or ***H17***), 1.30 (s, 3H, ***H16*** or ***H17***), 1.03 (s, 3H, ***H19***).

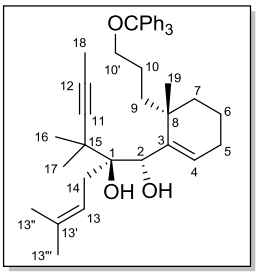
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 146.3 (***C3***), 144.5 (***C_{Ar}***), 131.2 (***C13'***), 128.7 (***C_{Ar}***), 128.2 (***C4***), 127.7 (***C_{Ar}***), 126.8 (***C_{Ar}***), 121.6 (***C13***), 86.9 (***Cquat.***), 86.4 (***Cquat.***), 78.3 (***Cquat.***), 78.3 (***Cquat.***), 70.0 (***C2***), 64.5 (***C10'***), 42.0 (***C8***), 37.1 (***C9*** or ***C10***), 36.5 (***C9*** or ***C10***), 35.2 (***C7***), 33.3 (***C14***), 26.3 (***C16*** or ***C17***), 26.2 (***C16*** or ***C17***), 26.0 (***C13"***), 25.8 (***C5***), 25.7 (***C19***), 24.6 (***C9*** or ***C10***), 18.8 (***C***6***),*** 18.0 (***C13'''***), 3.6 (***C18***).

IR (ν, cm^{-1}): 3500, 3482, 3090, 3063, 3029, 2957, 2936, 2873, 2250, 1682, 1652, 1490, 1448, 1381, 1226, 1092, 1070, 1037, 996.

HRMS (CI, ISO) Calcd for $[M+H]^+$: *m/z* 605.3995, found 605.3996.

$[\alpha]^{25}_D$: +11.4 (*c* 0.9, CH_2Cl_2).

(1S,2S)-5-Methyl-1-((S)-6-methyl-6-(3-(trityloxy)propyl)cyclohex-1-enyl)-2-(2-methylpent-3-yn-2-yl)hex-4-ene-1,2-diol (2.31)



^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 7.44 (dd, *J* = 8.3, 1.1 Hz, 6H, ***H_{Ar}***), 7.31-7.27 (m, 6H, ***H_{Ar}***), 7.25-7.21 (m, 3H, ***H_{Ar}***), 6.17 (t, *J* = 4.0 Hz, 1H, ***H4***), 5.38 (ddq, *J* = 8.3, 7.0, 1.1 Hz, 1H, ***H13***), 4.46 (d, *J* = 4.7 Hz, 1H, ***H2***), 3.22 (s, 1H, ***OH1***), 3.08-3.03 (m, 2H, ***H10'***), 2.72 (d, *J* = 4.7 Hz, 1H, ***OH2***), 2.41 (dd, *J* = 15.8, 8.3 Hz, 1H, ***H14***), 2.35 (dd, *J* = 15.8, 7.0 Hz, 1H, ***H14***), 2.07-2.00 (m, 2H, ***H5***), 1.67 (d, *J* = 1.1 Hz, 3H, ***H13"***), 1.64 (s, 3H, ***H18***), 1.64-1.50 (m, 6H, ***H6***, ***H7***, 2***H9***, 2***H10***), 1.49 (s, 3H, ***H13'''***), 1.44-1.37 (m, 2H, ***H6***, ***H7***), 1.27 (s, 3H, ***H16*** or ***H17***), 1.26 (s, 3H, ***H16*** or ***H17***), 1.13 (s, 3H, ***H19***).

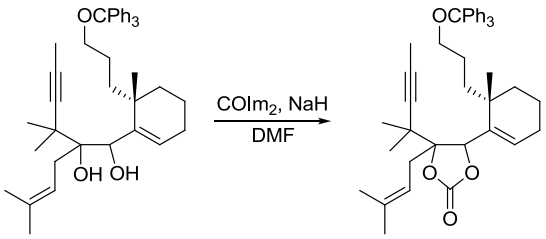
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 147.4 (***C3***), 144.4 (***C_{Ar}***), 131.2 (***C13'***), 128.6 (***C_{Ar}***), 127.7 (***C_{Ar}***), 127.5 (***C4***), 126.8 (***C_{Ar}***), 121.4 (***C***13), 86.7 (***Cquat.***), 86.4 (***Cquat.***), 78.3 (***Cquat.***), 78.3 (***Cquat.***), 70.5 (***C2***), 64.5 (***C10'***), 42.0 (***C8***), 36.7 (***C15***), 35.6 (***C9*** or ***C10***), 35.0 (***C7***), 33.5 (***C14***), 26.4 (***C16*** or ***C17***), 26.3 (***C16*** or ***C17***), 26.0 (***C13"***), 25.9 (***C5***), 24.9 (***C19***), 24.5 (***C9*** or ***C10***), 18.7 (***C6***), 18.0 (***C13'''***), 3.5 (***C18***).

IR (ν, cm^{-1}): 3615, 3501, 3088, 3062, 3026, 2959, 2933, 2870, 2249, 1685, 1648, 1541, 1489, 1448, 1378, 1363, 1341, 1229, 1088, 1074, 1053, 992.

HRMS (EI) Calcd for $[M]^+$: *m/z* 604.3916, found 604.3919.

$[\alpha]^{25}_{D}$: +2.5 (*c* 0.5, CH_2Cl_2).

5-((S)-6-Methyl-6-(3-(trityloxy)propyl)cyclohex-1-enyl)-4-(3-methylbut-2-enyl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (2.32) and (2.33)



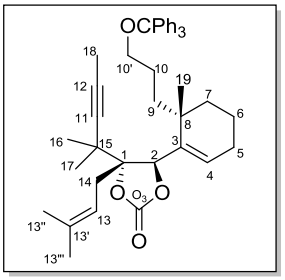
***Chemical Formula*:** $C_{43}H_{50}O_4$

***MW*:** 630.87

To a solution of diol **2.30** (300 mg, 0.48 mmol) in DMF (15 mL) was added sodium hydride (70 mg, 60% in mineral oil, 1.8 mmol, 2.5 equiv) and carbonyl diimidazole (569 mg, 3.51 mmol, 5.0 equiv). The mixture was stirred at room temperature for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (15 mL). The aqueous layer was extracted with Et_2O (3x15 mL), and the combined organic extracts were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 9/1) to afford the title carbonate **2.32** (284 mg, 0.45 mmol, 95%) as a colourless highly viscous oil.

The same procedure was repeated with **2.31** (425 mg, 0.70 mmol) to afford the title carbonate **2.33** (420 mg, 0.66 mmol, 93%) as a colourless highly viscous oil.

(4R,5R)-5-((S)-6-Methyl-6-(3-(trityloxy)propyl)cyclohex-1-enyl)-4-(3-methylbut-2-enyl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (2.32)



^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 7.46 (dd, *J* = 8.3, 1.1 Hz, 6H, ***H_{Ar}***), 7.33-7.29 (m, 6H, ***H_{Ar}***), 7.26-7.21 (m, 3H, ***H_{Ar}***), 5.83 (t, *J* = 4.0 Hz, 1H, ***H4***), 5.34-5.28 (m, 2H, ***H13***, ***H2***), 3.11-3.03 (m, 2H, ***H10'***), 2.74 (dd, *J* = 16.0, 6.3 Hz, 1H, ***H14***), 2.65 (dd, *J* = 16.0, 7.0 Hz, 1H, ***H14***), 2.10 (dt, *J* = 6.7, 4.6 Hz, 2H, ***H5***), 1.88-1.79 (m, 1H, ***H9***), 1.72 (s, 3H, ***H18***), 1.71 (d, *J* = 1.0 Hz, 3H,

H13"), 1.68- 1.58 (m, 8H, ***H6***, ***H7***, ***H9***, 2***H10***, ***H13'''***), 1.41-1.34 (m, 2H, ***H6***, ***H7***), 1.33 (s, 3H, ***H16*** or ***H17***), 1.29 (s, 3H, ***H16*** or ***H17***), 1.11 (s, 3H, ***H19***).

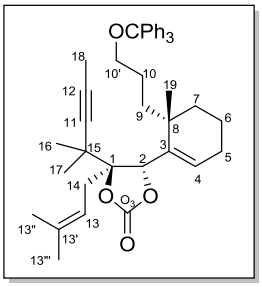
^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm: 155.4 (***CO$_3$***), 144.5 (***C$_{Ar}$***), 139.2 (***C3***), 132.5 (***C4***), 132.1 (***C13'***), 128.7 (***C$_{Ar}$***), 127.7 (***C$_{Ar}$***), 126.8 (***C$_{Ar}$***), 119.3 (***C13***), 89.9 (***Cquat.***), 86.4 (***Cquat.***), 83.3 (***Cquat***.), 80.0 (***C2***), 79.6 (***Cquat.***), 64.1 (***C10'***), 41.8 (***C8***), 36.9 (***C15***), 36.7 (***CH$_2$***), 35.3 (***CH$_2$***), 31.1 (***C14***), 26.4 (***C19***), 25.9 (***C5***), 25.8 (***C13"***), 24.9 (***C16*** or ***C17***), 24.7 (***C16*** or ***C17***), 24.3 (***CH$_2$***), 18.5 (***CH$_2$***), 18.0 (***C13'''***), 3.7 (***C18***).

IR (ν, cm^{-1}): 3088, 3059, 3028, 2936, 2873, 2249, 1797, 1656, 1649, 1541, 1489, 1448, 1389, 1330, 1211, 1181, 1062, 1033.

HRMS (ESI) Calcd for [M+Na]$^+$: *m/z* 653.3601 , found 653.3575.

[α]$^{25}_D$: -3.6 (*c* 0.65, CH_2Cl_2).

(4S,5S)-5-((S)-6-Methyl-6-(3-(trityloxy)propyl)cyclohex-1-enyl)-4-(3-methylbut-2-enyl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (2.33)



^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm: 7.43 (dd, *J* = 8.4, 1.3 Hz, 6H, ***H$_{Ar}$***), 7.32-7.27 (m, 6H, ***H$_{Ar}$***), 7.25-7.21 (m, 3H, ***H$_{Ar}$***), 5.76 (t, *J* = 4.0 Hz, 1H, ***H4***), 5.31-5.26 (m, 2H, ***H2***, ***H13***), 3.11-3.02 (m, 2H, ***H10'***), 2.69 (ddq, *J* = 16.2, 6.3, 0.9 Hz, 1H, ***H14***), 2.58 (dd, *J* = 16.2, 7.0 Hz, 1H, ***H14***), 2.16-2.06 (m, 2H, ***H5***), 1.73-1.68 (m, 1H, ***H9***), 1.66 (d, *J* = 1.4 Hz, 3H, ***H13"***), 1.63-1.58 (m, 4H, ***H6***, ***H7***, ***H9***, ***H10***), 1.57 (s, 3H, ***H18***), 1.51 (s, 3H, ***H13'''***), 1.49-1.45 (m, 2H, ***H6***, H10), 1.43-1.38 (m, 1H, ***H7***), 1.29 (s, 3H, ***H16*** or ***H17***), 1.28 (s, 3H, ***H16*** or ***H17***), 1.13 (s, 3H, ***H19***).

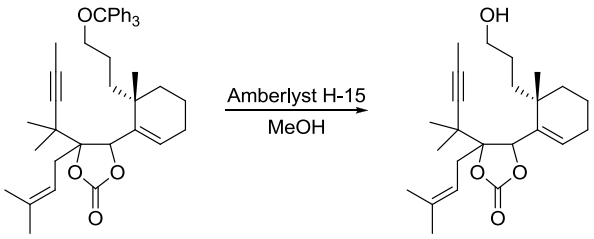
^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm: 155.2 (***CO$_3$***), 144.4 (***C$_{Ar}$***), 141.3 (***C3***), 132.4 (***C13'***), 131.1 (***C4***), 128.7 (***C$_{Ar}$***), 127.7 (***C$_{Ar}$***), 126.9 (***C$_{Ar}$***), 119.1 (***C13***), 89.9 (***Cquat.***), 86.6 (***Cquat.***), 83.0 (***Cquat.***), 80.8 (***C2***), 79.4 (***Cquat.***), 64.4 (***C10'***), 41.9 (***C8***), 36.6 (***C15***), 35.5 (***CH$_2$***), 34.9 (***CH$_2$***), 31.2 (***C14***), 26.0 (***C5***), 25.8 (***C13"***), 25.0 (***C16*** or ***C17***), 25.0 (***C16*** or ***C17***), 24.8 (***C19***), 24.5 (***CH$_2$***), 18.3 (***CH$_2$***), 18.1 (***C13'''***), 3.5 (***C18***).

IR (ν, cm^{-1}): 3089, 3063, 3026, 2940, 2873, 2254, 1790, 1652, 1597, 1541, 1489, 1448, 1382, 1333, 1211, 1185, 1066, 1037.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 653.3601, found 653.3573.

$[\alpha]^{25}_D$: +3.7 (*c* 0.65, CH_2Cl_2).

5-((S)-6-(3-Hydroxypropyl)-6-methylcyclohex-1-enyl)-4-(3-methylbut-2-enyl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (2.34) and (2.35)



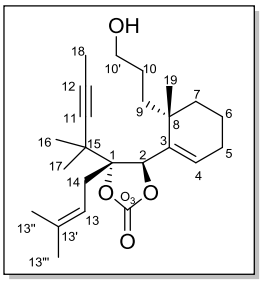
***Chemical Formula*:** $C_{24}H_{36}O_4$

***MW*:** 388.55

To a solution of protected diol **2.32** (391 mg, 0.62 mmol) in MeOH (20 mL) was added Amberlyst H-15 (0.15 g). The mixture was stirred at room temperature for 2 days. The resin was filtered off and the solvents were removed *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 8/2 to 5/5) to afford the title primary alcohol **2.34** (214 mg, 0.55 mmol, 90%) as a colourless highly viscous oil.

The same procedure was repeated with the protected diol **2.33** (300 mg, 0.47 mmol) to afford the primary alcohol **2.35** (167 mg, 0.43 mmol, 89%) as a colourless highly viscous oil.

(4R,5R)-5-((S)-6-(3-Hydroxypropyl)-6-methylcyclohex-1-enyl)-4-(3-methylbut-2-enyl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (2.34)



^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.82 (t, *J* = 4.0 Hz, 1H, ***H4***), 5.29 (ddq, *J* = 7.7, 6.5, 1.5 Hz, 1H, ***H13***), 5.24 (s, 1H, ***H2***), 3.71-3.58 (m, 2H, ***H10'***), 2.72 (ddq, *J* = 16.2, 6.5, 1.0 Hz, 1H, ***H14***),

2.64 (dd, *J* = 16.2, 7.7 Hz, 1H, ***H14***), 2.12-2.05 (m, 2H, ***H5***), 1.78 (s, 3H, ***H18***), 1.75-1.71 (m, 1H, ***CH₂***), 1.69 (d, *J* = 1.5 Hz, 3H, ***H13"***), 1.67-1.63 (m, 2H, ***CH₂***), 1.60-1.53 (m, 5H, ***H13'''***,***CH₂***), 1.53-1.42 (m, 2H, ***CH₂***), 1.39-1.33 (m, 2H, ***OH***, ***H7***), 1.30 (s, 3H, ***H16*** or ***H17***), 1.30 (s, 3H, ***H16*** or ***H17***), 1.10 (s, 3H, ***H19***).

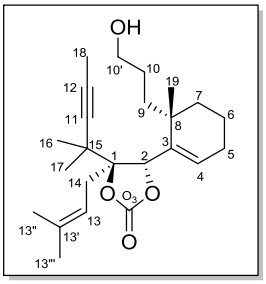
^{13}C NMR (126 MHz, *CDCl₃*) δ ppm: 155.2 (***CO₃***), 139.3 (***C3***), 132.6 (***C4***), 132.1 (***C13'***), 119.2 (***C13***), 90.0 (***C1***), 83.3 (***C11*** or ***C12***), 79.9 (***C2***), 79.5 (***C11*** or ***C12***), 63.3 (***C10'***), 41.8 (***C8***), 36.9 (***C15***), 36.3 (***CH₂***), 35.5 (***C7***), 31.2 (***C14***), 27.2 (***CH₂***), 26.2 (***C19***), 25.9 (***C5***), 25.7 (***C13"***), 24.9 (***C16*** or ***C17***), 24.7 (***C16*** or ***C17***), 18.4 (***C6***), 18.0 (***C13'''***), 3.5 (***C18***).

IR (ν, cm^{-1}): 3486, 3055, 2937, 2873, 2254, 1789, 1652, 1541, 1460, 1389, 1378, 1337, 1255, 1189, 1048.

HRMS (CI, ISO) Calcd for $[M+H]^+$: *m/z* 389.2692 , found 389.2689.

$[\alpha]^{25}_D$: +16.5 (*c* 1.6, CH_2Cl_2).

(4S,5S)-5-((S)-6-(3-Hydroxypropyl)-6-methylcyclohex-1-enyl)-4-(3-methylbut-2-enyl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (2.35)



^{1}H NMR (500 MHz, *CDCl₃*) δ ppm: 5.77 (t, *J* = 4.0 Hz, 1H, ***H4***), 5.32-5.29 (m, 2H, ***H2***, ***H13***), 3.62 (t, *J* = 6.1 Hz, 2H, ***H10'***), 2.70 (ddq, *J* = 16.2, 6.3, 1.0 Hz, 1H, ***H14***), 2.62 (dd, *J* = 16.2, 7.1 Hz, 1H, ***H14***), 2.15-2.06 (m, 2H, ***H5***), 1.81 (s, 3H, ***H18***), 1.69 (d, *J* = 1.5 Hz, 3H, ***H13"***), 1.68-1.64 (m, 1H, ***H7***), 1.60-1.54 (m, 6H, ***H6***, ***H9***, ***H10***), 1.54-1.46 (s, 3H, ***H13'''***), 1.45-1.35 (m, 2H, ***OH***, ***H7***), 1.31 (s, 3H, ***H16*** or ***H17***), 1.30 (s, 3H, ***H16*** or ***H17***), 1.13 (s, 3H, ***H19***).

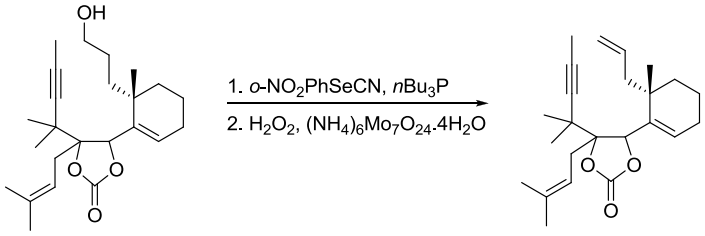
^{13}C NMR (126 MHz, *CDCl₃*) δ ppm: 155.2 (***CO₃***), 140.9 (***C3***), 132.4 (***C13'***), 131.0 (***C4***), 119.1 (***C13***), 90.0 (***C1***), 83.0 (***C11*** or ***C12***), 81.0 (***C2***), 79.4 (***C11*** or ***C12***), 63.5 (***C10'***), 41.8 (***C8***), 36.4 (***C15***), 35.0 (***CH₂***), 34.8 (***C7***), 31.2 (***C14***), 27.1 (***CH₂***), 25.9 (***C5***), 25.8 (***C13"***), 24.9 (***C16*** or ***C17***), 24.9 (***C16*** or ***C17***), 24.8 (***C19***), 18.2 (***C6***), 18.0 (***C13'''***), 3.6 (***C18***).

IR (ν, cm^{-1}): 3508, 3059, 2936, 2877, 2254, 1782, 1649, 1541, 1460, 1389, 1378, 1333, 1207, 1189, 1059, 1037.

HRMS (EI) Calcd for $[M]^+$: *m/z* 388.2614, found 388.2608.

$[\alpha]^{25}_D$: -10.6 (*c* 2.1, CH_2Cl_2).

5-((S)-6-Allyl-6-methylcyclohex-1-enyl)-4-(3-methylbut-2-enyl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (2.36) and (2.37)



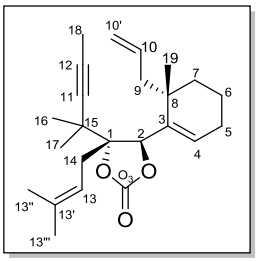
***Chemical Formula*:** $C_{24}H_{34}O_3$

***MW*:** 370.53

To a solution of primary alcohol **2.34** (75 mg, 0.20 mmol) in THF (7 mL) was added *o*-nitrophenylselenocyanate (110 mg, 0.47 mmol 2.4 equiv) and tri-*n*-butylphosphine (120 µL, 0.47 mmol 2.4 equiv). The mixture was stirred at room temperature for 20 min. The reaction was quenched with water (10 mL). The aqueous layer was extracted with Et_2O (4x 15 mL) and the combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil that was used without further purification. A solution of $(NH_4)_6Mo_7O_{24}.4H_2O$ (86 mg) in water (6 mL) and hydrogen peroxide (3 mL, 30% solution) was then prepared. This solution (1.7 mL) was added at -10°C to a solution of the previous compound in THF (3 mL). The mixture was stirred at this temperature for 20 min. The reaction was quenched with water (15 mL). The aqueous layer was extracted with Et_2O (4x25 mL), and the combined organic extracts were washed with brine (75 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 95/5) to afford the title alkene **2.36** (69 mg, 0.19 mmol, 89%) as a pale yellow viscous oil.

The same procedure was repeated with primary alcohol **2.35** (100 mg, 0.26 mmol) to afford the title alkene **2.37** (86 mg, 0.23 mmol, 93%) as a pale yellow viscous oil.

(4R,5R)-5-((S)-6-Allyl-6-methylcyclohex-1-enyl)-4-(3-methylbut-2-enyl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (2.36)



^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm: 5.82-5.71 (m, 2H, ***H4***, ***H10***), 5.31-5.25 (m, 2H, ***H2***, ***H13***), 5.11-5.03 (m, 2H, ***H10'***), 2.70 (ddq, *J* = 16.1, 6.3, 1.0 Hz, 1H, ***H14***), 2.63 (dd, *J* = 16.1, 7.1 Hz, 1H, ***H14***), 2.39 (dd, *J* = 14.1, 6.6 Hz, 1H, ***H9***), 2.16-2.05 (m, 3H, 2***H5***, ***H9***), 1.79 (s, 3H, ***H18***), 1.69 (d, *J* = 1.0 Hz, 3H, ***H13"***), 1.67-1.61 (m, 2H, ***H6***, ***H7***), 1.61-1.55 (m, 1H, ***H6***), 1.59 (s, 3H, ***H13'''***), 1.37-1.33 (m, 1H, ***H7***), 1.31 (s, 3H, ***H16*** or ***H17***), 1.31 (s, 3H, ***H16*** or ***H17***), 1.10 (s, 3H, ***H19***).

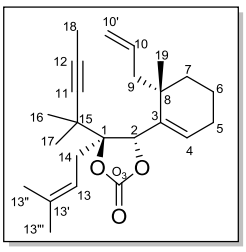
^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm: 155.3 (***CO$_3$***), 139.1 (***C3***), 134.1 (***C4***), 132.5 (***C10***), 132.1 (***C13'***), 119.2 (***C13***), 117.9 (***C10'***), 89.9 (***C1***), 83.2 (***C11*** or ***C12***), 80.1 (***C2***), 79.5 (***C11*** or ***C12***), 44.7 (***C9***), 41.7 (***C8***), 36.8 (***C15***), 35.6 (***C7***), 31.1 (***C14***), 25.8 (***C5***), 25.7 (***C13"***), 25.5 (***C19***), 24.9 (***C16*** or ***C17***), 24.7 (***C16*** or ***C17***), 18.1 (***C6***), 18.0 (***C13'''***), 3.6 (***C18***).

IR (ν, cm^{-1}): 3077, 2977, 2936, 2877, 2254, 1790, 1649, 1638, 1460, 1389, 1378, 1333, 1252, 1188, 1048.

HRMS (ESI) Calcd for [M+Na]$^+$: *m/z* 393.2400, found 393.2385.

$[\alpha]^{26}_{D}$: +17.6 (*c* 1.4, CH_2Cl_2).

(4S,5S)-5-((S)-6-Allyl-6-methylcyclohex-1-enyl)-4-(3-methylbut-2-enyl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (2.37)



^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm: 5.83-5.73 (m, 2H, ***H4***, ***H10***), 5.35-5.29 (m, 2H, ***H2***, ***H13***), 5.11-5.01 (m, 2H, ***H10'***), 2.74 (ddq, *J* = 16.1, 6.2, 1.2 Hz, 1H, ***H14***), 2.67 (dd, *J* = 16.1, 7.1 Hz,

1H, ***H14***), 2.34 (dd, *J* = 13.5, 6.8 Hz, 1H, ***H9***), 2.18-2.08 (m, 3H, 2***H5***, ***H9***), 1.77 (s, 3H, ***H18***), 1.70 (d, *J* = 1.6 Hz, 3H, ***H13"***), 1.68-1.62 (m, 1H, ***H7***), 1.62-1.56 (m, 2H, ***H6***), 1.60 (s, 3H, ***H13'''***), 1.37 (ddd, *J* = 12.5, 8.8, 3.5 Hz, 1H, ***H7***), 1.31 (s, 3H, ***H16*** or ***H17***), 1.31 (s, 3H, ***H16*** or ***H17***), 1.14 (s, 3H, ***H19***).

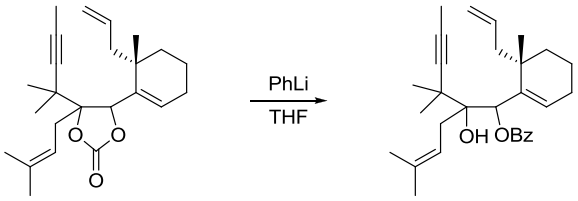
^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 155.2 (***CO_3***), 140.7 (***C3***), 134.3 (***C4***), 132.4 (***C13'***), 131.6 (***C10***), 119.1 (***C13***), 117.9 (***C10'***), 89.8 (***C1***), 83.1 (***C11*** or ***C12***), 80.5 (***C2***), 79.4 (***C11*** or ***C12***), 43.5 (***C9***), 41.7 (***C8***), 36.9 (***C15***), 34.8 (***C7***), 31.2 (***C14***), 25.9 (***C5***), 25.8 (***C13"***), 24.9 (***C16*** or ***C17***), 24.9 (***C16*** or ***C17***), 24.6 (***C19***), 18.1 (***C6***), 18.0 (***C13'''***), 3.5 (***C18***).

IR (ν, cm^{-1}): 3156, 3077, 2980, 2933, 2876, 2254, 1786, 1643, 1463, 1380, 1330, 1201, 1190, 1064, 1046.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 393.2400, found 393.2389.

$[\alpha]^{24}_D$: -6.2 (*c* 1.35, $CHCl_3$).

1-((S)-6-Allyl-6-methylcyclohex-1-enyl)-2-hydroxy-5-methyl-2-(2-methylpent-3-yn-2-yl)hex-4-enyl benzoate (2.38) and (2.39)



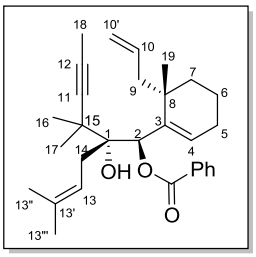
***Chemical Formula*:** $C_{30}H_{40}O_3$

***MW*:** 448.65

To a solution of **2.36** (56 mg, 0.15 mmol) in THF (5 mL) at -78°C was added phenyllithium (1.15 mL, 0.8 M in nBu_2O, 1.43 mmol, 9.0 equiv). The mixture was stirred at this temperature for 1.5 h. A solution of saturated aqueous $NaHCO_3$ (10 mL) was then added and the aqueous phase was extracted with Et_2O (3x15 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 95/5) to afford the title benzoate **2.38** (58 mg, 0.13 mmol, 93%) as a pale yellow viscous oil.

The same procedure was repeated with **2.37** (27 mg, 73 µmol) to afford the title benzoate **2.39** (30 mg, 68 µmol, 83%) as a pale yellow viscous oil.

(1R,2R)-1-((S)-6-Allyl-6-methylcyclohex-1-enyl)-2-hydroxy-5-methyl-2-(2-methylpent-3-yn-2-yl)hex-4-enyl benzoate (2.38)



^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm: 8.07 (dd, *J* = 8.2, 1.2 Hz, 2H, ***H$_{Ar}$***), 7.57-7.51 (m, 1H, ***H$_{Ar}$***), 7.41-7.40 (m, 2H, ***H$_{AR}$***), 6.52 (t, *J* = 4.0 Hz, 1H, ***H4***), 5.99 (s, 1H, ***H2***), 5.68 (ddt, *J* = 17.2, 10.0, 7.3 Hz, 1H, ***H10***), 5.44 (ddq, *J* = 8.1, 6.8, 1.5 Hz, 1H, ***H13***), 5.00-4.92 (m, 2H, ***H10'***), 2.88 (s, 1H, ***OH1***), 2.54-2.38 (m, 3H, ***H9***, 2***H14***), 2.17-2.08 (m, 3H, 2***H5***, ***H9***), 1.74 (d, *J* = 1.5 Hz, 3H, ***H13"***), 1.66-1.58 (m, 2H, ***H6***, ***H7***), 1.61 (s, 3H, ***H13'''***), 1.54-1.48 (m, 1H, ***H6***), 1.37 (s, 3H, ***H16*** or ***H17***), 1.35-1.29 (m, 1H, ***H7***), 1.27 (s, 3H, ***H16*** or ***H17***), 1.25 (s, 3H, ***H18***), 1.12 (s, 3H, ***H19***).

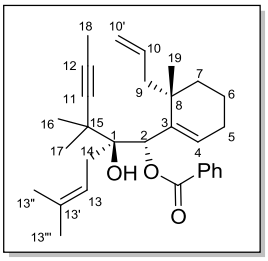
^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm: 164.9 (***COPh***), 142.7 (***C3***), 135.2 (***C10***), 132.6 (***C$_{Ar}$***), 131.5 (***C13'***), 131.3 (***C$_{Ar}$***), 131.2 (***C4***), 129.9 (***C$_{Ar}$***), 128.3 (***C$_{Ar}$***), 120.9 (***C13***), 117.0 (***C10'***), 85.1 (***Cquat.***), 78.9 (***Cquat.***), 78.6 (***Cquat.***), 72.5 (***C2***), 44.0 (***C9***), 42.0 (***C8*** or ***C15***), 36.9 (***C8*** or ***C15***), 35.0 (***C7***), 32.3 (***C***14), 27.6 (***C16*** or ***C17***), 26.1 (***C13"***), 25.8 (***C5***), 25.3 (***C16*** or ***C17***), 25.3 (***C19***), 18.1 (***C13'''***), 18.0 (***C6***), 3.2 (***C18***).

IR (ν, cm^{-1}): 3539, 3155, 3065, 2973, 2933, 2253, 1709, 1602, 1450, 1382, 1317, 1272, 1216, 1177, 1095, 1070.

HRMS (ESI) Calcd for [M+Na]$^+$: *m/z* 471.2870, found 471. 2852.

[α]$^{25}_{D}$: -12.3 (*c* 0.5 $CHCl_3$).

(1S,2S)-1-((S)-6-Allyl-6-methylcyclohex-1-enyl)-2-hydroxy-5-methyl-2-(2-methylpent-3-yn-2-yl)hex-4-enyl benzoate (2.39)



^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 8.07 (dd, *J* = 8.2, 1.2 Hz, 2H, ***H_{Ar}***), 7.57-7.51 (m, 1H, ***H_{Ar}***), 7.47-7.40 (m, 2H, ***H_{Ar}***), 6.49 (t, *J* = 3.9 Hz, 1H, ***H4***), 6.00 (s, 1H, ***H2***), 5.84 (m, 1H, ***H10***), 5.44 (tq, *J* = 6.8, 1.4 Hz, 1H, ***H13***), 5.08-5.01 (m, 2H, ***H10'***), 2.89 (s, 1H, ***OH1***), 2.53 (dd, *J* = 15.8, 6.8 Hz, 1H, ***H14***), 2.49-2.40 (m, 2H, ***H9***, ***H14***), 2.18 (dd, *J* = 13.2, 7.8 Hz, 1H, ***H9***), 2.13-2.07 (m, 2H, ***H5***), 1.74 (d, *J* = 1.4 Hz, 3H, ***H13"***), 1.62-1.53 (m, 3H, 2***H6***, ***H7***), 1.61 (s, 3H, ***H13'''***), 1.39-1.36 (m, 1H, ***H7***), 1.38 (s, 3H, ***H18***) 1.29 (s, 3H, ***H16*** or ***H17***), 1.27 (s, 3H, ***H16*** or ***H17***), 1.09 (s, 3H, ***H19***).

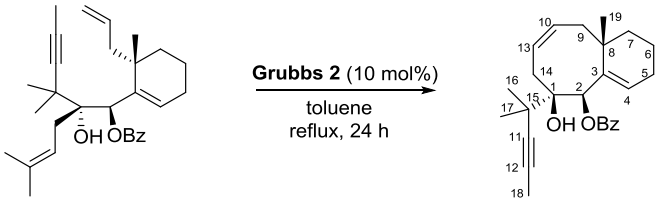
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 165.0 (***COPh***), 142.8 (***C3***), 135.1 (***C10***), 132.6 (***C_{Ar}***), 131.7 (***C13'***), 131.2 (***C_{Ar}***), 131.1 (***C4***), 129.8 (***C_{Ar}***), 128.3 (***C_{Ar}***), 120.7 (***C13***), 117.3 (***C10'***), 85.2 (***Cquat***.), 78.8 (***Cquat***.), 78.6 (***Cquat***.), 73.5 (***C2***), 44.2 (***C9***), 42.0 (***C8*** or ***C15***), 36.9 (***C8*** or ***C15***), 35.7 (***C7***), 32.6 (***C14***), 27.5 (***C16*** or ***C17***), 26.1 (***C13"***), 25.9 (***C5***), 25.6 (***C19***), 25.4 (***C16*** or ***C17***), 18.0 (***C13'''***), 18.0 (***C6***), 3.3 (***C18***).

IR (ν, cm^{-1}): 3542, 3154, 2976, 2932, 2253, 1711, 1452, 1382, 1316, 1271, 1177, 1113, 995.

HRMS (EI) Calcd for $[M]^+$: *m/z* 448. 2977, found 448.2973.

$[\alpha]^{25}_D$: +23.6 (*c* 1.8, $CHCl_3$).

(5R,6R,10S)-6-Hydroxy-10-methyl-6-(2-methylpent-3-yn-2yl)-1,2,3,5,6,7,10,10-octahydrobenzo[8]annulen-5-yl benzoate (2.40)



***Chemical Formula*:** $C_{26}H_{32}O_3$

***MW*:** 392.54

A solution of benzoate **2.36** (53 mg, 0.12 mmol) in toluene (15 mL) was thoroughly degassed (using the freeze-thaw pump technique) and second-generation Grubbs' catalyst (5 mg, 6 µmol, 0.05 equiv) was added and the mixture was stirred at reflux for 6 h. At that time second-generation Grubbs' catalyst (5 mg, 6 µmol, 0.05 equiv) was added and the mixture was stirred at reflux for 16 h. After cooling, the solvent was removed *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 95/5) to afford the title bicycle **2.40** (37 mg, 96 µmol, 80%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 8.15 (dd, *J* = 8.2, 1.1 Hz, 2H, ***H$_{Ar}$***), 7.61-7.56 (m, 1H, ***H$_{Ar}$***), 7.50-7.46 (m, 2H, ***H$_{Ar}$***), 6.19 (s, 1H, ***H2***), 6.06-6.00 (m, 1H, ***H4***), 5.79 (dt, *J* = 11.2, 8.2 Hz, 1H, ***H13***), 5.67-5.59 (m, 1H, ***H10***), 3.25 (dd, *J* = 13.4, 8.2 Hz, 1H, ***H14***), 2.81 (dd, *J* = 15.8, 7.9 Hz, 1H, ***H9***), 2.50 (s, 1H, ***OH1***), 2.32 (dd, *J* = 15.8, 5.6 Hz, 1H, ***H9***), 2.21-2.14 (m, 1H, ***H5***), 2.04-1.96 (m, 1H, ***H5***), 1.83-1.74 (m, 3H, 2***H6***, ***H7***), 1.71 (s, 3H, ***H18***), 1.64-1.60 (m, 1H, ***H14***), 1.34 (s, 3H, ***H16*** or ***H17***), 1.34 (s, 3H, ***H16*** or ***H17***), 1.30-1.28 (m, 1H, ***H7***), 1.03 (s, 3H, ***H19***).

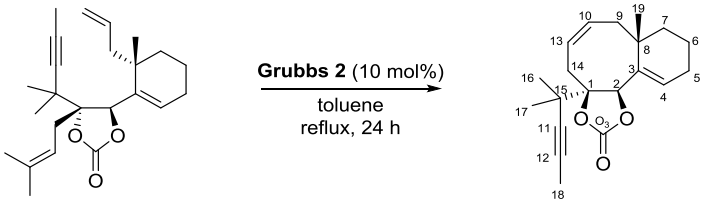
^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 165.8 (***COPh***), 140.5 (***C3***), 133.1 (***C4***), 133.0 (***C$_{Ar}$***), 130.6 (***C$_{Ar}$***), 129.8 (***C$_{Ar}$***), 129.7 (***C13***), 128.5 (***C$_{Ar}$***), 127.0 (***C10***), 84.8 (***Cquat***.), 83.0 (***C2***), 80.1 (***Cquat.***), 79.1 (***Cquat***.), 41.5 (***C8*** or ***C15***), 40.1 (***C8*** or ***C15***), 38.3 (***C14***), 37.3 (***C7***), 30.5 (***C19***), 29.7 (***C9***), 26.6 (***C16*** or ***C17***), 26.3 (***C16*** or ***C17***), 25.5 (***C5***), 18.3 (***C6***), 3.7 (***C18***).

IR (ν, cm^{-1}): 3602, 3070, 3020, 2977, 2924, 2874, 2402, 1714, 1605, 1523, 1453, 1275, 1219, 1116, 1099, 1070, 1027.

HRMS (CI, ISO) Calcd for $[M+H]^+$: *m/z* 393.2430, found 393.2435.

$[\alpha]^{25}_{D}$: +80.8 (*c* 0.58, $CHCl_3$).

(1R,5R,8Z,11S)-11-Methyl-6-(2-methylpent-3-yn-2-yl)-3,5-dioxatricyclo[9.4.0]pentadeca-1(15),8dien-4-one (2.41)



***Chemical Formula*:** $C_{20}H_{26}O_3$

***MW*:** 314.43

A solution of **2.36** (30 mg, 80 µmol) in toluene (25 mL) was thoroughly degassed (using the freeze-thaw pump technique) and second-generation Grubbs' catalyst (3.5 mg, 4.0 µmol, 0.05 equiv) was added and the mixture was stirred at reflux for 6 h. At that time second-generation Grubbs' catalyst (3.5 mg, 4.0 µmol, 0.05 equiv) was added and the mixture was stirred at reflux for 16 h. After cooling, the solvent was removed *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 95/5) to afford the title compound **2.41** (20 mg, 63 µmol, 79%) as a white solid.

M.p.: 144°C.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.95-5.87 (m, 2H, ***H4***, ***H13***), 5.68-5.61 (m, 1H, ***H10***), 5.57 (s, 1H, ***H2***), 2.56-2.45 (m, 3H, ***H9***, 2***H14***), 2.25-2.16 (m, 1H, ***H5***), 2.11 (ddt, *J* = 18.9, 7.1, 3.9 Hz, 1H, ***H5***), 1.90 (dd, *J* = 13.7, 8.1 Hz, 1H, ***H9***), 1.79 (s, 3H, ***H18***), 1.76-1.65 (m, 2H, ***H6***, ***H7***), 1.64-1.58 (m, 1H, ***H6***), 1.57-1.50 (m, 1H, ***H7***), 1.38 (s, 3H, ***H16*** or ***H17***), 1.25 (s, 3H, ***H16*** or ***H17***), 1.19 (s, 3H, ***H19***).

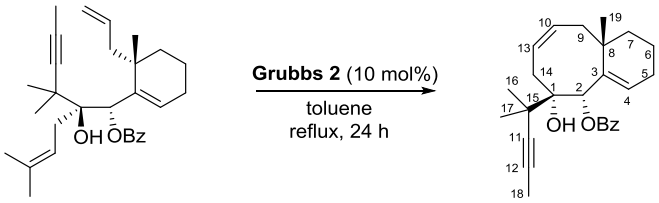
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 154.0 (***CO_3***), 139.4 (***C3***), 135.3 (***C13***), 131.7 (***C4***), 125.6 (***C10***), 91.9 (***Cquat.***), 90.0 (***C***2), 81.9 (***Cquat.***), 79.5 (***Cquat.***), 42.4 (***C7***), 42.0 (***C8*** or ***C15***), 40.8 (***C8*** or ***C15***), 39.3 (***C9***), 28.0 (***C14***), 27.2 (***C19***), 26.4 (***C5***), 24.9 (***C16*** or ***C17***), 24.5 (***C16*** or ***C17***), 17.7 (***C6***), 3.5 (***C18***).

IR (ν, cm^{-1}): 3033, 2986, 2940, 2874, 2254, 1786, 1630, 1461, 1390, 1378, 1353, 1309, 1259, 1280, 1203, 1059.

HRMS (EI) Calcd for $[M]^+$: *m/z* 314.1882, found 314.1881.

$[\alpha]^{25}_D$: +131 (*c* 0.46, $CHCl_3$).

(5S,6S,10S)-6-Hydroxy-10-methyl-6-(2-methylpent-3-yn-2yl)-1,2,3,5,6,7,10,10-octa hydrobenzo[8]annulen-5-yl benzoate (2.42)



***Chemical Formula*:** $C_{26}H_{32}O_3$

***MW*:** 392.54

A solution of benzoate **2.38** (11 mg, 25 µmol) in toluene (10 mL) was thoroughly degassed (using the freeze-thaw pump technique) and second-generation Grubbs' catalyst (1.1 mg, 1.3 µmol, 0.05 equiv) was added and the mixture was stirred at reflux for 6 h. At that time second-generation Grubbs' catalyst (1.1 mg, 1.3 µmol, 0.05 equiv) was added and the mixture was stirred at reflux for 16 h. After cooling, the solvent was removed *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 95/5) to afford the title bicycle **2.42** (8.8 mg, 23 µmol, 90%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 8.10-8.05 (m, 2H, ***H_{Ar}***), 7.57-7.52 (m, 1H, ***H_{Ar}***), 7.47-7.42 (m, 2H, ***H_{Ar}***), 6.21 (dd, *J* = 4.4, 3.3 Hz, 1H, ***H4***), 5.99 (s, 1H, ***H2***), 5.87-5.82 (m, 1H, ***H13***), 5.68 (m, 1H, ***H10***), 2.84 (s, 1H, ***OH1***), 2.65 (dd, *J* = 13.1, 6.5 Hz, 1H, ***H14***), 2.55 (dd, *J* = 13.1, 11.3 Hz, 1H, ***H9***), 2.27 (dd, *J* = 13.1, 6.5 Hz, 1H, ***H9***), 2.22 (m, 1H, ***H5***), 2.08-1.99 (m, 1H, ***H5***), 1.79-1.71 (m, 2H, ***H6***, ***H14***), 1.61-1.55 (m, 2H, ***H6***, ***H7***), 1.53-1.47 (m, 1H, ***H7***), 1.37 (s, 3H, ***H16*** or ***H17***), 1.36 (s, 3H, ***H16*** or ***H17***), 1.32 (s, 3H, ***H18***), 1.25 (s, 3H, ***H19***).

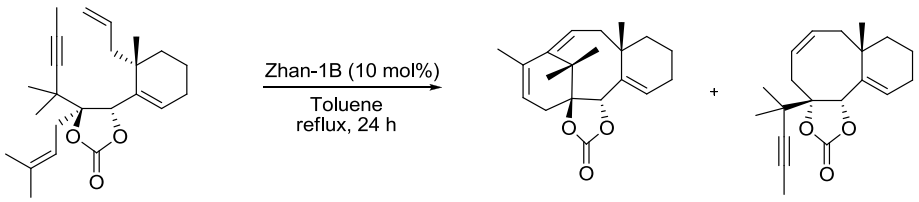
^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 164.3 (***COPh***), 142.6 (***C3***), 132.6 (***C_{Ar}***), 131.2 (***C_{Ar}***), 130.4 (***C13***), 129.9 (***C_{Ar}***), 129.4 (***C4***), 128.2 (***C_{Ar}***), 127.4 (***C10***), 85.2 (***Cquat.***), 79.4 (***Cquat.***), 78.5 (***Cquat.***), 72.4 (***C2***), 41.4 (***C7***), 40.4 (***C8*** or ***C15***), 39.7 (***C14***), 39.1 (***C8*** or ***C15***), 33.6 (***C9***), 28.0 (***C16*** or ***C17***), 26.4 (***C5***), 26.1 (***C19***), 25.9 (***C16*** or ***C17***), 18.4 (***C6***), 3.3 (***C18***).

IR (ν, cm^{-1}): 3530, 3155, 3026, 2978, 2933, 2872, 2253, 1713, 1604, 1469, 1453, 1386, 1319, 1277, 1177, 1119.

HRMS (EI) Calcd for $[M]^+$: *m/z* 392.2351, found 392.2352.

$[\alpha]^{25}_{D}$: +163.4 (*c* 1.48, $CHCl_3$).

(1S,5S,11S)-11,15,18,18-Tetramethyl-2,4-dioxatetracyclo[12.3.1.0]octadeca-6,13,15-trien-3-one (2.43) and (2.44)

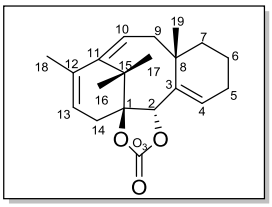


***Chemical Formula*:** $C_{20}H_{26}O_3$

***MW*:** 314.43

A solution of **2.37** (37 mg, 0.10 mmol) in toluene (33 mL) was thoroughly degassed under argon (using the freeze-thaw pump technique) and Zhan-1B catalyst (7 mg, 10 µmol, 0.1 equiv) was added and the mixture was stirred at reflux for 24 h. The resulting mixture was allowed to cool down and the solvent was removed *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 95/5) to afford the title tricycle **2.43** (22 mg, 70 µmol, 70%) as a colourless oil and the title bicycle **2.44** (6.3 mg, 20 µmol, 20%) as a white solid.

(1S,5S,11S)-11,15,18,18-Tetramethyl-2,4-dioxatetracyclo[12.3.1.0]octadeca-6,13,15-trien-3-one (2.43)



^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm: 5.97 (dd, *J* = 5.5, 2.3 Hz, 1H, ***H4***), 5.73 (dd, *J* = 13.2, 6.2 Hz, 1H, ***H10***), 5.13 (s, 1H, ***H2***), 4.98 (m, 1H, ***H13***), 2.83 (dquin, *J* = 18.8, 2.0 Hz, 1H, ***H14***), 2.70 (t, *J* = 13.2 Hz, 1H, ***H9***), 2.19 (dquin, *J* = 18.8, 2.0 Hz, 1H, ***H14***), 2.09 (dtd, *J* = 18.1, 5.5, 1.6 Hz, 1H, ***H5***), 1.98 (dd, *J* = 13.2, 6.2 Hz, 1H, ***H9***), 1.95-1.86 (m, 1H, ***H5***), 1.80 (q, *J* = 2.0 Hz, 3H, ***H18***), 1.75 (dd, *J* = 13.2, 3.6 Hz, 1H, ***H7***), 1.72-1.66 (m, 1H, ***H6***), 1.65-1.60 (m, 1H, ***H6***), 1.58 (s, 3H, ***H17***), 1.48-1.43 (m, 1H, ***H7***), 1.34 (s, 3H, ***H16***), 1.18 (s, 3H, ***H19***).

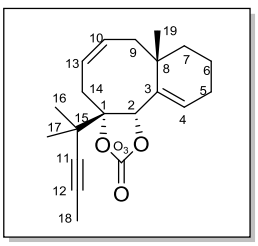
^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm: 154.3 (***CO$_3$***), 146.5 (***C11***), 138.2 (***C12***), 134.9 (***C3***), 129.1 (***C4***), 127.5 (***C10***), 116.0 (***C13***), 93.3 (***C1***), 79.4 (***C2***), 42.2 (***C8*** or ***C15***), 41.2 (***C8*** or ***C15***), 39.4 (***C9***), 35.6 (***C7***), 30.7 (***C14***), 27.2 (***C19***), 25.3 (***C16*** or ***C17***), 25.0 (***C5***), 21.3 (***C16*** or ***C17***), 18.8 (***C18***), 18.6 (***C6***).

IR (ν, cm^{-1}): 3025, 2938, 2872, 1704, 1454, 1433, 1395, 1378, 1275, 1218, 1188, 1025, 1003.

HRMS (EI) Calcd for [M]$^{+}$: *m/z* 314.1882, found 314.1879.

$[\alpha]^{25}_{D}$: +77.0 (*c* 0.56, $CHCl_3$).

(Z)-(2R,6R,11S)-6-(1,1-Dimethyl-but-2-ynyl)-11-methyl-3,5-dioxa-tricyclo[9.4.0.0^{2,6}]pentadeca-1(15),8-dien-4-one (2.44)



M.p.: 80°C.

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm: 5.75 (m, 3H, ***H4***, ***H10***, ***H13***), 5.39 (s, 1H, ***H2***), 2.62-2.48 (m, 3H, ***H9***, 2***H14***), 2.29-2.21 (m, 2H, ***H5***), 1.92-1.81 (m, 2H, ***H6***, ***H9***), 1.74 (s, 3H, ***H18***), 1.72-

1.65 (m, 1H, ***H6***), 1.58-1.54 (m, 2H, ***H7***), 1.40 (s, 3H, ***H16*** or ***H17***), 1.34 (s, 3H, ***H16*** or ***H17***), 1.11 (s, 3H, ***H19***).

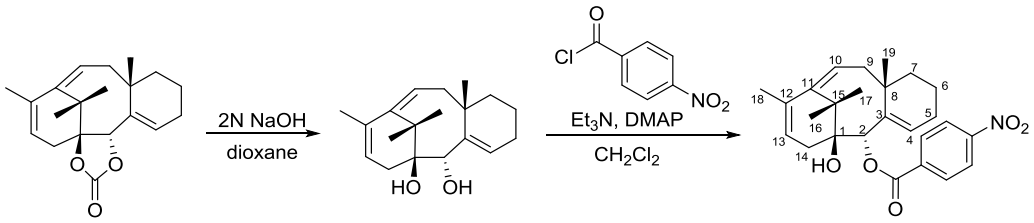
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 155.1 (***CO_3***), 139.4 (***C3***), 129.6 (***C9***), 127.0 (***C4***), 126.5 (***C13***), 91.0 (***Cquat.***), 83.3 (***Cquat.***), 80.9 (***C2***), 80.7 (***Cquat.***), 41.7 (***C7***), 40.0 (***C9***), 39.2 (***C8*** or ***C15***), 39.2 (***C8*** or ***C15***), 31.8 (***C14***), 25.7 (***C16*** or ***C17***), 25.0 (***C5***), 24.9 (***C16*** or ***C17***), 23.8 (***C19***), 17.3 (***C6***), 3.7 (***C18***).

IR (ν, cm^{-1}): 3032, 2981, 2928, 2875, 2855, 2253, 1791, 1643, 1461, 1381, 1332, 1261, 1185, 1127, 1100, 1052, 1037.

HRMS (CI, ISO) Calcd for $[M+H]^+$: *m/z* 315.1960, found 315.1965.

$[\alpha]^{25}_D$: +109 (*c* 0.74, $CHCl_3$).

[(1S,2S,8S,10Z)-1-Hydroxy-8,12,15,15-tetramethyltricyclo[9.3.1.0]pentadeca-3,10,12-trien-2-yl 4-nitrobenzoate (2.45)



***Chemical Formula*:** $C_{26}H_{31}NO_5$

***MW*:** 437.54

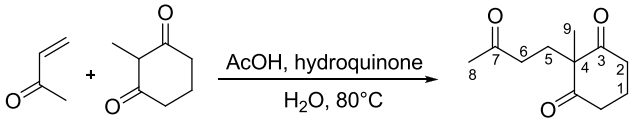
To a solution of tricycle **2.43** (30 mg, 95 µmol) in 1,4-dioxane (4 mL) at 0°C was added a solution of 2N aqueous NaOH (2 mL). The reaction mixture was allowed to stir at RT for 2 days. A solution of saturated aqueous NH_4Cl (5 mL) was then added and the aqueous phase was extracted with Et_2O (3x10 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was dissolved in dichloromethane (2 mL) and triethylamine (26 µL, 0.19 mmol, 2.5 equiv), DMAP (9.6 mg, 76 µmol, 1 equiv) and 4-nitrobenzoyl chloride (28 mg, 0.15 mmol, 2 equiv) were added. The reaction mixture was allowed to stir at RT for 16 h. A solution of saturated aqueous $NaHCO_3$ (5 mL) was then added and the aqueous phase was extracted with Et_2O (3x5 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then

purified by flash chromatography (petroleum ether/Et_2O: 85/15) to afford the title *p*NO_2 benzoate **2.45** (26 mg, 59 µmol, 62%) as a white solid.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 8.32-8.27 (m, 2H, ***H_{Ar}***), 8.23-8.19 (m, 2H, ***H_{Ar}***), 5.97 (dd, *J* = 3.2, 5.0 Hz, 1H, ***H4***), 5.88 (s, 1H, ***H2***), 5.74 (dd, *J* = 12.1, 6.9 Hz, 1H, ***H10***), 5.06 (m, 1H, ***H13***), 3.04 (dd, *J* = 13.5, 12.1 Hz, 1H, ***H9***), 2.95 (m, 1H, ***H14***), 2.13-2.06 (m, 1H, ***H14***), 2.03 (dd, *J* = 13.5, 6.9 Hz, 1H, ***H9***), 1.99-1.90 (m, 1H, ***H5***), 1.85-1.82 (m, 1H, ***H5***), 1.81 (m, 3H, ***H18***), 1.76-1.71 (m, 1H, ***CH_2***), 1.57-1.54 (m, 4H, H17, ***CH_2***), 1.52-1.45 (m, 2H, ***CH_2***), 1.30 (s, 3H, ***H16***), 1.26 (s, 1H, ***OH***), 1.25 (s, 3H, ***H19***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 163.9 (***COPh***), 150.5 (***C_{Ar}***), 148.5 (***C11***), 141.4 (***C12***), 136.9 (***C3***), 136.3 (***CH***), 130.7 (***C_{Ar}***), 128.1 (***CH***), 125.3 (***C10***), 123.6 (***C_{Ar}***), 117.7 (***C13***), 81.0 (***C1***), 76.5 (***C2***), 43.2 (***CH_2***), 42.4 (***CH_2***), 40.6 (***C8*** or ***C15***), 40.3 (***C8*** or ***C15***), 33.6 (***CH_2***), 27.2 (***CH_3***), 26.1 (***CH_3***), 25.8 (***CH_3***), 22.8 (***CH_2***), 19.2 (***CH_2***), 18.6 (***C18***).

2-Methyl-2-(3-oxobutyl)cyclohexane-1,3-dione (3.1a)



***Chemical Formula*:** $C_{11}H_{16}O_3$

***MW*:** 196.24

Spect. Reference: Buchschacher, P.; Fürst, A.; Gutzwiller, J. *Org. Synth*. **1985**, *63*, 37.

To a solution of 2-methylcyclohexadione (10.0 g, 79.0 mmol) in 40 mL of H_2O was added acetic acid (0.30 mL, 4.00 mmol, 0.05 equiv) hydroquinone (17.0 mg, 1.58 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 16 h. After cooling down, the solution was treated with 8 g NaCl and diluted with EtOAc (50 mL), the organic phase was washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (petroleum ether/Et_2O: 85/15 to 7/3) to afford the title compound **3.1a** (15.2 g, 77.4 mmol, 98%) as a pale yellow oil.

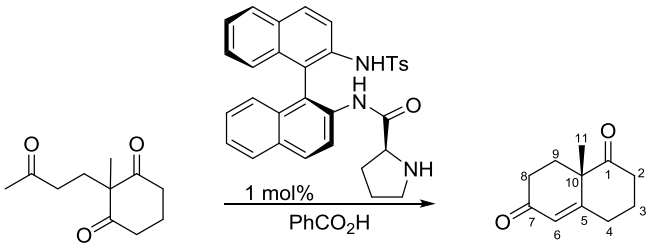
^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 2.79-2.57 (m, 4H, ***CH_2***), 2.36 (t, *J* = 7.4 Hz, 2H, ***CH_2***), 2.12 (s, 3H, ***H10***), 2.05 (t, *J* = 7.4 Hz, 3H, ***CH_2***), 1.98-1.83 (m, 1H, ***CH_2***), 1.26 (s, 3H, ***H11***).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 210.0 (***C3***), 207.5 (***C7***), 64.3 (***C4***), 38.4 (***C8***), 37.8 (***C2***), 30.0 (***CH2***), 29.6 (***CH2***), 20.0 (***C9***), 17.6 (***C1***).

IR (ν, cm^{-1}): 1716, 1694.

MS (EI) $[M+H]^+$: 196.1.

(S)-8-Methyl-3,4,8,8-tetrahydronaphthalene-1,6(2H,7H)-dione (3.1)



***Chemical Formula*:** $C_{11}H_{14}O_2$

***MW*:** 178.23

Spect. Reference: Viózquez, S. F.; Guillena, G.; Nájera, C.; Bradshaw, B.; Etxebarria-Jardi, G.; Bonjoch, J. *Organic Syntheses* **2011**, *88*, 317.

To a flask containing *meso* ketone **3.1a** (56.6 g, 289 mmol) were added *N*-tosyl-(*S*)-binam-(*L*)-prolinamide catalyst (1.55 g, 2.89 mmol, 0.01 equiv) and benzoic acid (880 mg, 7.2 mmol, 0.025 equiv). The mixture was stirred at 22°C for 5 days. After complete reaction, EtOAc (300 mL) was added followed by activated charcoal (10 g), and the mixture was stirred for 15 h at 22°C. The mixture was diluted with hexane (300 mL) and filtered through slurry-packed silica (180 g). The silica cake was eluted with 1:1 EtOAc/hexanes (6 x 300 mL). The filtrate was concentrated *in vacuo* and dried under vacuum for 6 h affording 50 g of a brown oil that crystallized on standing. *t*Butyl methyl ether (15 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 *in vacuo* for 16 h to afford (+)-Wieland-Miescher ketone **3.1** (43.3 g, 243 mmol, 84%, 98% ee).

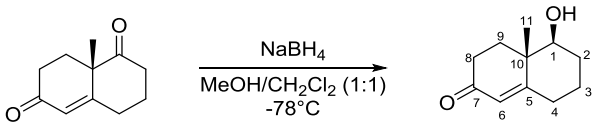
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 5.85 (d, *J* = 1.9 Hz, 1H, ***H6***), 2.78-2.64 (m, 2H, ***H2***, ***H4***), 2.56-2.42 (m, 4H, ***H2***, ***H4***, 2***H8***), 2.20-2.08 (m, 3H, ***H3***, 2***H9***), 1.71 (qt, *J* = 13.3, 4.4 Hz, 1H, ***H3***), 1.45 (s, 3H, ***H11***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 211.0 (***C1***), 198.2 (***C7***), 165.8 (***C5***), 125.8 (***C6***), 50.6 (***C10***), 37.6 (***C2***), 33.6 (***C8***), 31.7 (***C4***), 29.6 (***C9***), 23.2 (***C11***), 22.9 (***C3***).

MS (CI/ISO) $[M+H]^+$: 179.09.

$[\alpha]^{25}_D$: +94 (*c* 1.0, toluene), lit[86]: **$[\alpha]^{25}_D$**: +93 (*c* 1.0, toluene), 97% ee.

(4S,5S)-5-Hydroxy-methyl-4,4,5,6,7,8-hexahydronaphthalen-2(3H)-one (3.2)



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

MW: 180,25

Spect. Reference: Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746-1757.

To a solution of ketone **3.1** (43.3 g, 243 mmol) in (1:1) MeOH/CH_2Cl_2 (700 mL) at -78°C was added $NaBH_4$ (9.2 g, 243 mmol, 1.0 equiv). The reaction mixture was stirred for 15 min. Acetone (200 mL) and H_2O (200 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (200 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/EtOAc: 6/4) to afford the alcoholol **3.2** (43.8 g, 243 mmol, 100%) as a colourless oil.

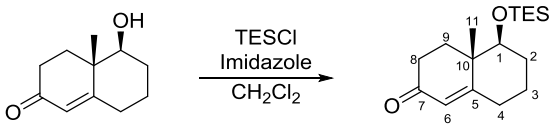
^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.79 (d, *J* = 1.9 Hz, 1H, ***H6***), 3.44 (dd, *J* = 11.6, 3.6 Hz, 1H, ***H1***), 2.49-2.30 (m, 3H, ***H4***, 2***H8***), 2.25-2.15 (m, 2H, ***H4***, ***H9***), 1.93-1.81 (m, 4H, ***H2***, ***H3***, ***H9***, ***OH***), 1.77-1.66 (m, 1H, ***H2***), 1.48-1.36 (m, 1H, ***H3***), 1.21 (s, 3H, ***H11***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 199.5 (***C7***), 168.4 (***C5***), 125.5 (***C6***), 78.3 (***C1***), 41.6 (***C10***), 34.2 (***C9***), 33.7 (***C8***), 32.0 (***C4***), 30.3 (***C2***), 23.1 (***C3***), 15.2 (***C11***).

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 203.1043, found 203.1043.

$[\alpha]^{25}_D$: +185 (*c* 1.5, benzene).

(4S,5S)-4-Methyl-5-((triethylsilyl)oxy)-4,4,5,6,7,8-hexahydronaphthalen-2(3H)-one (3.3)



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

MW: 294,51

To a solution of alcohol **3.2** (43.8 g, 243 mmol) in CH_2Cl_2 (150 mL) were added imidazole (41.3 g, 607 mmol, 2.5 equiv) and TESCl (61 mL, 364 mmol, 1.5 equiv). The reaction mixture was stirred for 16 h. A saturated aqueous solution of $NaHCO_3$ (100 mL) was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (3x150 mL), and the combined organic extracts were washed with brine (300 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 9/1 to 7/3) to afford the title protected alcoholol **3.3** (64.4 g, 219 mmol, 90%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.78 (d, *J* = 1.7 Hz, 1H, ***H6***), 3.40 (dd, *J* = 10.9, 4.9 Hz, 1H, ***H1***), 2.51-2.27 (m, 3H, ***CH_2***), 2.19 (ddt, *J* = 14.7, 4.1, 1.9 Hz, 1H, ***CH_2***), 2.13 (ddd, *J* = 13.6, 5.2, 3.8 Hz, 1H, ***CH_2***), 1.89-1.81 (m, 1H, ***CH_2***), 1.79-1.65 (m, 3H, ***CH_2***), 1.43-1.30 (m, 1H, ***CH_2***), 1.18 (s, 3H, ***H11***), 0.97 (t, *J* = 7.9 Hz, 9H, ***TES***), 0.61 (q, *J* = 7.9 Hz, 6H, ***TES***).

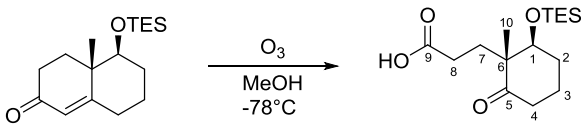
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 199.8 (***C7***), 168.9 (***C5***), 125.3 (***C6***), 78.9 (***C1***), 42.2 (***C10***), 34.6 (***CH_2***), 33.9 (***CH_2***), 32.1 (***CH_2***), 30.8 (***CH_2***), 23.0 (***CH2***), 15.5 (***C11***), 6.9 (***TES***), 5.2 (***TES***).

IR (ν, cm^{-1}): 3019, 2960, 1670, 1625, 1460, 1255, 1100, 1056.

HRMS (CI/ISO) Calcd for $[M+H]^+$: *m/z* 295.2093, found 295.2092.

$[\alpha]^{25}_D$: +105 (*c* 1.0, $CHCl_3$).

3-((1R,6S)-1-Methyl-2-oxo-6-((triethylsilyl)oxy)cyclohexyl)propanoic acid (3.4)



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

MW: 314,50

To a solution of **3.3** (5.0 g, 17 mmol) in MeOH (180 mL) at -78°C was passed a stream of O_3 for 50 min. The reaction mixture was concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O/AcOH: 75/25/0.1) to afford the title acid **3.4** (4.7 g, 15 mmol, 88%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: ^{1}H NMR (500 MHz, *$CDCl_3$*) δ 10.75 (br s, 1H, ***CO_2H***), 3.82 (dd, *J* = 6.5, 2.2 Hz, 1H, ***H1***), 2.41-2.32 (m, 3H, 2***H4***, ***H8***), 2.23 (ddd, *J* = 16.4, 11.3, 5.1 Hz, 1H, ***H8***), 2.09-1.96 (m, 3H, ***CH_2***), 1.88-1.74 (m, 2H, ***CH_2***), 1.71-1.60 (m, 1H, ***CH_2***), 1.09 (s, 3H, ***H10***), 0.95 (t, *J* = 8.0 Hz, 9H, ***TES***), 0.59 (q, *J* = 8.0 Hz, 6H, ***TES***).

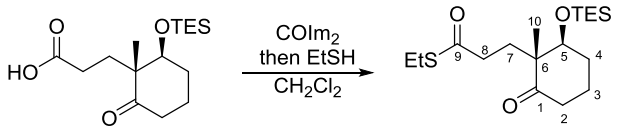
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 214.0 (***C5***), 178.6 (***C9***), 76.5 (***C1***), 54.3 (***C6***), 37.7 (***C4***), 30.1 (***CH_2***), 29.0 (***CH_2***), 29.0 (C8), 20.4 (***CH_2***), 17.6 (***C10***), 6.9 (***TES***), 5.0 (***TES***).

IR (ν, cm^{-1}): 3250, 2980, 1740, 1715, 1250, 1058.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 337.1806, found 337.1794.

$[\alpha]^{25}_D$: -10.5 (*c* 1.0, $CHCl_3$).

(S)-Ethyl 3-((1R,6S)-1-methyl-2-oxo-6-((triethylsilyl)oxy)cyclohexyl)propanethioate (3.8)



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

MW: 358,61

To a solution of acid **3.4** (26.1 g, 83.0 mmol) in CH_2Cl_2 (200 mL) was added carbonyl diimidazole (17.5 g, 107 mmol, 1.3 equiv) and the reaction mixture was stirred for 30 min. Then EtSH (12.0 mL, 166 mmol, 2.0 equiv) was added. The reaction mixture was stirred for 16 h. The volatiles were removed *in vacuo* and H_2O (150 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3x150 mL), and the combined organic extracts were washed with brine (500 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 95/5) to afford the title thioester **3.8** (24.6 g, 68.6 mmol, 83%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 3.83 (dd, *J* = 6.1, 1.8 Hz, 1H, ***H5***), 2.87 (q, *J* = 7.4 Hz, 2H, S***CH_2***), 2.55 (ddd, *J* = 15.4, 11.4, 5.3 Hz, 1H, ***CH_2***), 2.42-2.32 (m, 3H, ***CH_2***), 2.10-1.98 (m, 3H,

CH₂), 1.88-1.80 (m, 1H, ***CH₂***), 1.79-1.72 (m, 1H, ***H4***), 1.72-1.64 (m, 1H, ***CH₂***), 1.25 (t, *J* = 7.4 Hz, 3H, SCH_2***CH₃***), 1.07 (s, 3H, ***H10***), 0.95 (t, *J* = 7.9 Hz, 9H, ***TES***), 0.59 (q, *J* = 7.9 Hz, 6H, ***TES***).

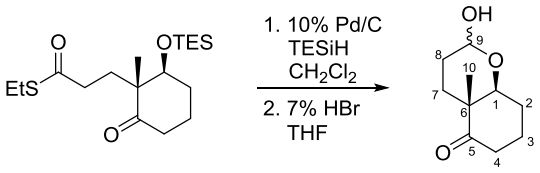
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 213.7 (***C1***), 199.2 (***C9***), 76.8 (***C5***), 54.3 (***C6***), 39.1 (***CH₂***), 37.8 (***CH₂***), 31.1 (***CH₂***), 29.0 (***C4***), 23.3 (S***CH₂***), 20.4 (***CH₂***), 17.6 (***C10***), 14.7 (SCH_2***CH₃***), 6.9 (***TES***), 5.0 (***TES***).

IR (ν, cm^{-1}): 3057, 2964, 2912, 2879, 1704, 1692, 1458, 1419, 1272, 1118, 1079, 1018, 1000.

HRMS (ESI) Calcd for $[M+H]^+$: *m/z* 381.1890, found 381.1878.

$[\alpha]^{25}_D$: -21.1 (*c* 1.0, $CHCl_3$).

(4R,8S)-2-Hydroxy-4-methyloctahydro-5H-chromen-5-one (3.5)



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

MW: 184,24

To a solution of thioester **3.8** (24.6 g, 68.6 mmol) in CH_2Cl_2 (150 mL) were added triethylsilane (21.8 mL, 137 mmol, 2.0 equiv) and 10% Pd/C (7.5 g) 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 *in vacuo*. The crude mixture was dissolved in THF (150 mL) and at 0°C was slowly added an aqueous solution of 7% HBr (150 mL). The resulting mixture was stirred at this temperature for 1h. A saturated aqueous solution of $NaHCO_3$ (500 mL) was slowly added to quench the reaction, the aqueous layer was extracted with EtOAc (3x500 mL), the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/EtOAc: 7/3 to 0/1) to afford the title hemi-acetal **3.5** as a 1:1 mixture of diastereomers (12.6 g, 68.6 mmol, 100%) as a colourless solid.

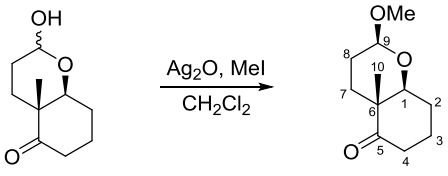
^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.26 (t, *J* = 3.2 Hz, 0.5H, ***H9***), 4.74 (ddd, *J* = 9.5, 6.5, 2.7 Hz, 0.5H, ***H9***), 4.03 (dd, *J* = 11.9, 4.1 Hz, 0.5H, ***H1***), 3.38 (dd, *J* = 11.5, 4.2 Hz, 0.5H, ***H1***), 2.97 (br. s, 0.5H, ***OH***), 2.67 (td, *J* = 14.4, 7.1 Hz, 1H, ***H4***), 2.40 (br s, 0.5H, ***OH***), 2.26-2.16 (m, 1H, ***H4***), 2.06-1.68 (m, 6H, ***CH₂***), 1.66-1.50 (m, 2H, ***CH₂***), 1.27 (s, 1.5H, ***H10***), 1.23 (s, 1.5H, ***H10***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 213.6 (***C5***), 97.0 (***C9***), 91.5 (***C9***), 79.5 (***C1***), 71.7 (***C1***), 48.6 (***C6***), 48.4 (***C6***), 36.5 (***CH_2***), 29.3 (***CH_2***), 29.0 (***CH_2***), 26.0 (***CH_2***), 25.9 (***CH_2***), 24.7 (***CH_2***), 20.8 (***CH_2***), 16.3 (***C10***), 15.3 (***C10***).

IR (ν, cm^{-1}): 3425, 2947, 2877, 1705, 1450, 1373, 1049, 964, 902.

HRMS (EI) Calcd for $[M]^+$: *m/z* 184.1099, found 184.1102.

(2S,4R,8S)-2-Methoxy-4-methyloctahydro-5H-chromen-5-one (3.6)



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

MW: 198,26

To a solution of hemi-acetal **3.5** (12.6 g, 68.6 mmol) in CH_2Cl_2 (100 mL) were added Ag_2O (17.5 g, 75.5 mmol, 1.1 equiv) and MeI (12.8 mL, 206 mmol, 3.0 equiv). The reaction mixture was stirred for 16 h. Then the reaction mixture was filtered and the solvent was concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 8/2) to afford the title acetal **3.6** (12.2 g, 61.7 mmol, 90%) as a white foam.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 4.29 (dd, *J* = 9.7, 2.3 Hz, 1H, ***H9***), 3.50 (s, 3H, ***OMe***), 3.32 (dd, *J* = 11.6, 4.1 Hz, 1H, ***H1***), 2.66 (td, *J* = 14.4, 7.0 Hz, 1H, ***H4***), 2.23-2.13 (m, 1H, ***H4***), 2.04-1.96 (m, 1H, ***H3***), 1.96-1.88 (m, 1H, ***H2***), 1.88-1.82 (m, 1H, ***H2***), 1.81-1.69 (m, 3H, 2***H7***, ***H8***), 1.67-1.58 (m, 1H, ***H8***), 1.58-1.48 (m, 1H, ***H3***), 1.24 (s, 3H, ***H10***).

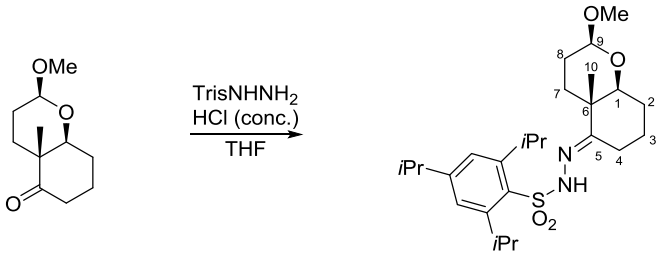
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 213.7 (***C5***), 104.0 (***C9***), 79.3 (***C1***), 56.5 (***OMe***), 48.7 (***C6***), 36.5 (***C4***), 29.3 (***C7***), 27.3 (***C8***), 26.0 (***C2***), 20.9 (***C3***), 16.3 (***C10***).

IR (ν, cm^{-1}): 2854, 2747, 2641, 1736, 1431, 1337, 1264, 1247, 1080, 984, 953.

HRMS (CI/ISO) Calcd for $[M+H]^+$: *m/z* 199.1334, found 199.1331.

$[\alpha]^{25}_D$: +100 (*c* 1.5, $CHCl_3$).

2,4,6-Triisopropyl-N'-((2S,4S,8S)-2-methoxy-4-methyloctahydro-5H-chromen-5-ylidene)benzenesulfonohydrazide (3.7)



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

MW: 478,69

To a solution of acetal **3.6** (14.5 g, 73.2 mmol) in THF (100 mL) were added $TrisNHNH_2$ (23.8 g, 80.5 mmol, 1.1 equiv) and concentrated HCl (4 drops). The reaction mixture was stirred for 3 h. A saturated aqueous solution of $NaHCO_3$ (150 mL) was added to the reaction, the aqueous layer was extracted with Et_2O (3x150 mL), and the combined organic extracts were washed with brine (250 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 8/2) to afford the title hydrazone **3.7** (35.0 g, 73.2 mmol, 100%) as a white foam.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 7.30 (s, 1H, ***NH***), 7.16 (s, 2H, ***H_{Ar}***), 4.22 (dd, *J* = 8.6, 3.2 Hz, 1H, ***H9***), 4.16 (spt, *J* = 6.8 Hz, 2H, Ar***CH***$(CH_3)_2$), 3.47 (s, 3H, ***OMe***), 3.13 (dd, *J* = 9.9, 5.9 Hz, 1H, ***H1***), 2.92 (spt, *J* = 6.9 Hz, 1H, Ar***CH***$(CH_3)_2$), 2.51-2.45 (m, 1H, ***H4***), 2.00 (dd, *J* = 13.7, 6.3 Hz, 1H, ***H4***), 1.96-1.88 (m, 1H, ***H3***), 1.75-1.68 (m, 2H, ***H2***), 1.63-1.53 (m, 4H, ***H7***, ***H8***), 1.40-1.30 (m, 1H, ***H3***), 1.27 (d, *J* = 6.8 Hz, 6H, ArCH(***CH_3***)$_2$), 1.26 (d, *J* = 6.9 Hz, 6H, ArCH(***CH_3***)$_2$), 1.25 (d, *J* = 6.8 Hz, 6H, ***Me***), 1.03 (s, 3H, ***H10***).

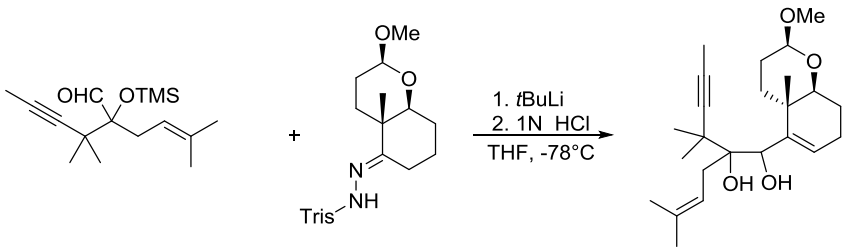
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 161.8 (***C5***), 153.2 (***C_{Ar}***), 151.1 (***C_{Ar}***), 131.2 (***C_{Ar}***), 123.5 (***C_{Ar}***), 104.0 (***C9***), 79.4 (***C1***), 56.4 (***OMe***), 42.1 (***C6***), 34.2 (***CH***), 31.3 (***CH_2***), 29.9 (2***CH***), 27.5 (***CH_2***), 26.1 (***C2***), 24.8, 24.7 (4***CH_3***), 23.6, 23.5 (2***CH_3***), 21.5, 21.5 (***C3***, ***C4***), 17.3 (***C10***).

IR (ν, cm^{-1}): 3240, 2954, 2872, 2836, 2752, 2635, 1712, 1629, 1596, 1550, 1453, 1384, 1326, 1252, 1203, 1160, 1067, 912.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 478.2865, found 478.2867.

$[\alpha]^{29}_D$: +36.0 (*c* 1.0, $CHCl_3$).

((2S,4S,8S)-2-Methoxy-4-methyl-3,4,4,7,8,8-hexahydro-2H-chromen-5-yl)-5-methyl-2-(2-methylpent-3-yn-2-yl)hex-4-ene-1,2-diol (3.9a) and (3.9b)

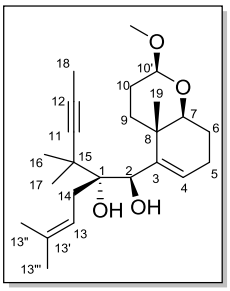


Chemical Formula: $C_{24}H_{38}O_4$

MW: 390,56

To a solution of hydrazone **3.7** (24 g, 50 mmol, 1.2 equiv) in THF (60 mL) at -78°C was added dropwise *t*BuLi (68 mL, 1.47 M in hexane, 100 mmol, 2.4 equiv). The solution turned dark red. The solution was stirred at this temperature for 30 min and warmed for a few min to room temperature and intense nitrogen bubbling occured. The mixture was then cooled down to –78°C and a solution of aldehyde (±)-**2.14** (12 g, 42 mmol) in THF (30 mL) was added. The resulting mixture was stirred at -78°C for 5 h and became yellow. The reaction was quenched with saturated aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with Et_2O (3x150 mL), and the combined organic extracts were washed with brine (500 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was dissolved in THF (150 mL) and a 1N aqueous solution of HCl (63 mL, 63 mmol, 1.5 equiv) was then added. The resulting mixture was stirred at room temperature for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with EtOAc (3x200 mL), and the combined organic extracts were washed with brine (250 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (CH_2Cl_2/EtOAc: 97/3 to 9/1) to afford the title diol **3.9a** (5.7 g, 15 mmol, 35%) and the title compound **3.9b** (5.7 g, 15 mmol, 35%) as colourless highly viscous oils.

(1R,2R)-1-((2S,4S,8S)-2-Methoxy-4-methyl-3,4,4,7,8,8-hexahydro-2H-chromen-5-yl)-5-methyl-2-(2-methylpent-3-yn-2-yl)hex-4-ene-1,2-diol (3.9a)



^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 6.10 (t, *J* = 3.7 Hz, 1H, ***H4***), 5.37-5.29 (m, 1H, ***H13***), 4.41 (d, *J* = 4.8 Hz, 1H, ***H2***), 4.39-4.30 (m, 1H, ***H10'***), 3.53 (s, 3H, ***OMe***), 3.34 (dd, *J* = 10.7, 5.2 Hz, 1H, ***H7***), 3.11-3.04 (m, 2H, 2***OH***), 2.36 (d, *J* = 6.8 Hz, 2H, ***H14***), 2.26-2.16 (m, 2H, ***H5),*** 2.00-1.91 (m, 1H, ***H10***), 1.81 (s, 3H, ***H18***), 1.78-1.69 (m, 5H, 2***H6***, 2***H9***, ***H10***), 1.7 (d, *J* = 1.0 Hz, 3H, ***H13''***), 1.58 (s, 3H, ***H13'''***), 1.30 (s, 3H, ***H16*** or ***H17***), 1.28 (s, 3H, ***H16*** or ***H17***), 1.13 (s, 3H, ***H19***).

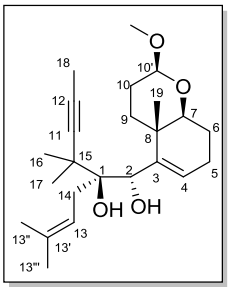
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 143.7 (***C3***), 131.7 (***C13'***), 126.4 (***C4***), 120.7 (***C13***), 104.0 (***C10'***), 86.4 (***C11***), 79.2 (***C12***), 79.0 (***C7***), 78.1 (***C1***), 70.7 (***C2***), 56.3 (***OMe***), 41.7 (***C15***), 37.0 (***C8***), 33.0 (***C14***), 32.7 (***C10***), 27.9 (***C9***), 26.2 (***C16*** or ***C17***), 26.0 (***C16*** or ***C17***), 26.0 (***C13"***), 24.8 (***C5***), 23.4 (***C6***), 18.9 (***C19***), 17.9 (***C13'''***), 3.6 (***C18***).

IR (ν, cm^{-1}): 3053, 2984, 2956, 2305, 1421, 1265, 1165, 1072.

HRMS (EI) Calcd for $[M]^+$: *m/z* 390.2770, found 390.2766.

$[\alpha]^{26}_{D}$: -27.6 (*c* 1.0, $CHCl_3$).

(1S,2S)-1-((2S,4S,8S)-2-Methoxy-4-methyl-3,4,4,7,8,8-hexahydro-2H-chromen-5-yl)-5-methyl-2-(2-methylpent-3-yn-2-yl)hex-4-ene-1,2-diol (3.9b)



^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.99 (t, *J* = 3.8 Hz, 1H, ***H4***), 5.40-5.30 (m, 1H, ***H13***), 4.43 (d, *J* = 4.6 Hz, 1H, ***H2***), 4.35 (dd, *J* = 8.7, 3.8 Hz, 1H, ***H10'***), 3.52 (s, 3H, ***OMe***), 3.34 (dd, *J* =

12.1, 4.0 Hz, 1H, ***H7***), 3.20 (s, 1H, ***OH1***), 2.90 (d, *J* = 4.6 Hz, 1H, ***OH2***), 2.31 (dd, *J* = 15.6, 7.0 Hz, 1 H, ***H14***) 2.42 (dd, *J* = 15.6, 6.8 Hz, 1 H***, H14***), 2.26-2.18 (m, 2H, 2***H5***), 1.89 (dt, *J* = 12.6, 3.6 Hz, 1H, ***H9***), 1.81-1.68 (m, 4H, 2***H6***, 2***H10***), 1.79 (s, 3H, ***H18***), 1.71 (d, *J* = 1.1 Hz, 3H, ***H13"***), 1.59 (s, 3H, ***H13'"***), 1.47 (td, *J* = 12.5, 5.7 Hz, 1H, ***H9***), 1.29 (s, 3H, ***H16*** or ***H17***), 1.27 (s, 3H, ***H16*** or ***H17***), 1.22 (s, 3H, ***H19***).

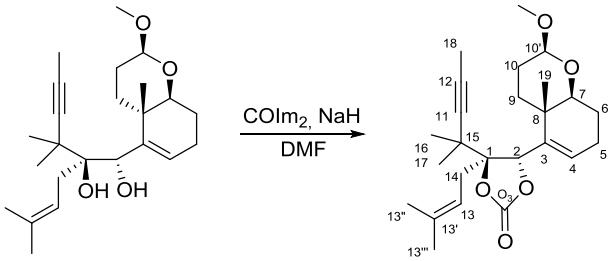
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 146.2 (***C3***), 131.5 (***C13'***), 126.2 (***C4***), 121.2 (***C13***), 103.8 (***C10'***), 86.6 (***C11***), 78.7 (***C12***), 78.3 (***C7***), 78.2 (***C1***), 69.5 (***C2***), 56.3 (***OMe***), 41.8 (***C15***), 37.5 (***C8***), 33.4 (***C14***), 32.5 (***C9***), 28.1 (***C6*** or ***C10***), 26.3 (***C16*** or ***C17***), 26.2 (***C16*** or ***C17***), 26.1 (***C13''***), 24.6 (***C5***), 23.5 (***C6*** or ***C10***), 19.9 (***C19***), 18.1 (***C13'"***), 3.6 (***C18***).

IR (ν, cm^{-1}): 3245, 3054, 2984, 2305, 1868, 1717, 1669, 1557, 1421, 1265, 1065.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 413.2662, found 413.2655.

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

(4S,5S)-5-((2S,4S,8S)-2-Methoxy-4-methyl-3,4,4,7,8,8-hexahydro-2H-chromen-5-yl)-4-(3-methylbut-2-en-1-yl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (3.10)



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

MW: 416,56

To a solution of diol **3.9b** (6.5 g, 17 mmol) in DMF (250 mL) was added sodium hydride (2 g, 60% in mineral oil, 50 mmol, 3 equiv) and carbonyl diimidazole (11 g, 67 mmol, 4 equiv). The mixture was stirred at room temperature for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (150 mL). The aqueous layer was extracted with Et_2O (3x150 mL), and the combined organic extracts were washed with brine (2x350 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 8/2) to afford the title carbonate **3.10** (6.2 g, 15 mmol, 90%) as a colourless crystalline solid.

M.p.: 120°C.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.64 (dd, *J* = 4.8, 2.9 Hz, 1H, ***H4***), 5.36-5.29 (m, 1H, ***H13***), 5.15 (s, 1H, ***H2***), 4.37 (dd, *J* = 9.6, 2.8 Hz, 1H, ***H10'***), 3.53 (s, 3H, ***OMe***), 3.37 (dd, *J* = 10.7, 5.6 Hz, 1H, ***H7***), 2.75-2.62 (m, 2H, 2***H14***), 2.40-2.21 (m, 2H, 2***H5***), 2.02 (ddd, *J* = 12.8, 4.4, 2.8 Hz, 1H, ***H9***), 1.85-1.66 (m, 4H, 2***H6***, 2***H10***), 1.76 (s, 3H, ***H18***), 1.72 (d, *J* = 1.2 Hz, 3H, ***H13"***), 1.62 (s, 3H, ***H13'''***), 1.45 (td, *J* = 13.2, 4.4 Hz, 1H, ***H9***), 1.31 (m, 6H, ***H16***, ***H17***), 1.22 (s, 3H, ***H19***).

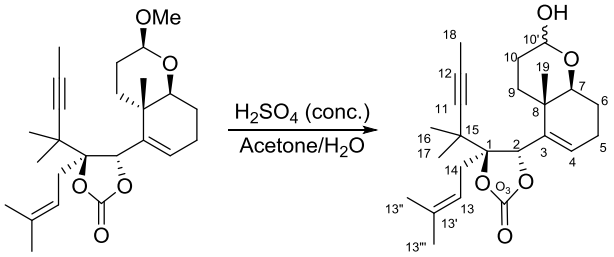
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 155.0 (***CO_3***), 140.2 (***C3***), 132.8 (***C13'***), 129.5 (***C4***), 118.8 (***C13***), 103.7 (***C10'***), 90.0 (***C1***), 83.1 (***C11***), 79.7 (***C12***), 79.1 (***C2***), 77.9 (***C7***), 56.3 (***OMe***), 41.2 (***C15***), 37.3 (***C8***), 32.4 (***C9***), 31.4 (***C14***), 28.0 (***C10***), 26.0 (***C13"***), 25.0 (***C5***), 24.8 (***C16*** or ***C17***), 24.5 (***C16*** or ***C17***), 23.1 (***C6***), 19.5 (***C19***), 18.2 (***C13'''***), 3.5 (***C18***).

IR (ν, cm^{-1}): 3055, 2954, 2857, 2239, 1793, 1450, 1373, 1327, 1265, 1180, 1118, 1056.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 439.2455, found 439.2455.

$[\alpha]^{26}_{D}$: -27.0 (*c* 1.0, $CHCl_3$).

(4S,5S)-5-((4S,8S)-2-Hydroxy-4-methyl-3,4,4,7,8,8-hexahydro-2H-chromen-5-yl)-4-(3-methylbut-2-en-1-yl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (3.11)



Chemical Formula: $C_{24}H_{34}O_5$

MW: 402,53

To a solution of carbonate **3.10** (6.2 g, 15 mmol) in acetone (200 mL) was added H_2O (100 mL) followed by slow addition of H_2SO_4 conc. (26 mL, 0.52 mol, 35 equiv). The reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (250 mL). The aqueous layer was extracted with EtOAc (3x250 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/EtOAc: 7/3) to afford the title hemiacetal **3.11** as a 1:1 mixture of diastereomers (5.7 g, 14 mmol, 94%) as a colourless oil.

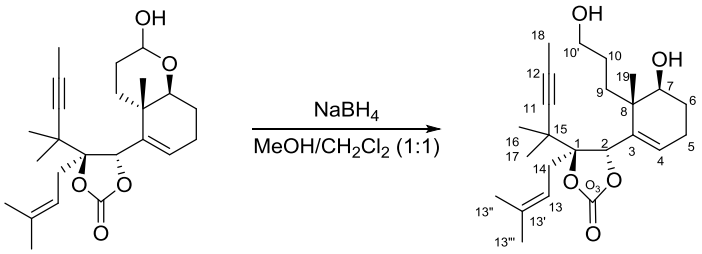
^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.67-5.60 (m, 1H, ***H4***), 5.34-5.26 (m, 1.5H, ***H13***, 0.5***H10'***), 5.14 (s, 1H, ***H2***), 4.80 (ddd, *J* = 9.4, 6.3, 2.8 Hz, 0.5H, 0.5***H10'***), 4.09 (dd, *J* = 12.5, 3.9 Hz, 0.5H, 0.5***H7***), 3.42 (dd, *J* = 11.3, 4.8 Hz, 1H, 0.5***H7***, 0.5***OH***), 2.76-2.60 (m, 2.5H, 2***H14***, 0.5***OH***), 2.37-2.19 (m, 2H, ***H5***), 2.06-1.93 (m, 1H, ***H9***), 1.80-1.63 (m, 4.5H, 2***H6***, 2***H10***, 0.5***H9***), 1.76 (s, 1.5H, ***H18***), 1.75 (s, 1.5H, ***H18***), 1.71-1.69 (m, 3H, ***H13"***) 1.61 (s, 1.5H, ***H13'''***), 1.60 (s, 1.5H, ***H13'''***), 1.46 (td, *J* = 13.3, 4.7 Hz, 0.5H, ***H9***), 1.30 (m, 6H, ***H16***, ***H17***), 1.22 (s, 1.5H, ***H19***), 1.19 (s, 1.5H, ***H19***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 155.1 (***CO_3***), 154.9 (***C20***), 140.4 (***C3***), 140.1 (***C3***), 133.0 (***C13'***), 132.9 (***C13'***), 129.5 (***C4***), 129.3 (***C4***), 118.7 (***C13***), 118.6 (***C13***), 96.8 (***C10'***), 91.4 (***C1***), 90.2 (***C10'***), 90.1 (***C1***), 83.1 (***C11***), 83.0 (***C11***), 79.7 (***C12***), 79.6 (***C12***), 79.1 (***C2***), 78.9 (***C2***), 78.2 (***C7***), 70.2 (***C7***), 41.2 (***C15***), 41.1 (***C15***), 37.3 (***C8***), 37.0 (***C8***), 32.3 (***C9***), 31.4 (***C14***), 31.3 (***C14***), 29.8 (***C10***), 27.8 (***C10***), 26.4 (***C9***), 26.0 (***C13"***), 25.9 (***C13"***), 25.0 (***C16*** or ***C17***), 25.0 (***C16*** or ***C17***), 24.8 (***C16*** or ***C17***), 24.8 (***C16*** or ***C17***), 24.5 (***C5***), 24.4 (***C5***), 23.2 (***C6***), 23.0 (***C6***), 19.4 (***C19***), 18.4 (***C19***), 18.2 (***C13'''***), 18.2 (***C13'''***), 3.5 (***C18***), 3.5 (***C18***).

IR (ν, cm^{-1}): 3393, 3055, 2985, 2848, 2305, 1791, 1650, 1551, 1481, 1335, 1272, 1187, 1033.

HRMS (CI/ISO) Calcd for $[M+H]^+$: *m/z* 403.2484, found 403.2482.

(4S,5S)-5-((5S,6S)-5-Hydroxy-6-(3-hydroxypropyl)-6-methylcyclohex-1-en-1-yl)-4-(3-methylbut-2-en-1-yl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (3.12)



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

MW: 404,55

To a solution of hemiacetal **3.11** (5.7 g, 14 mmol) in (1:1) MeOH/CH_2Cl_2 (200 mL) at 0°C was added $NaBH_4$ (1.6 g, 42 mmol, 3.0 equiv). The reaction mixture was allowed to reach room temperature and stir for 2 h. Acetone (50 mL) and H_2O (50 mL) were added. The aqueous layer was extracted with EtOAc (3x100 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then

purified by flash chromatography (petroleum ether/EtOAc: 5/5 to 0/1) to afford the diol **3.12** (5.3 g, 13 mmol, 95%) as a colourless oil.

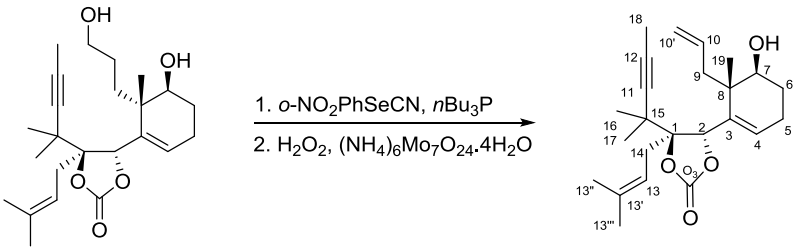
^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.81 (t, *J* = 3.9 Hz, 1H, ***H4***), 5.35-5.26 (m, 2H, ***H2***, ***H13***), 3.84 (br d, *J* = 4.7 Hz, 1H, ***H7***), 3.67-3.56 (m, 2H, ***2H10'***), 2.72 (dd, *J* = 16.1, 6.0 Hz, 1H, ***H14***), 2.62 (dd, *J* = 16.1, 7.3 Hz, 1H, ***H14***), 2.35-2.24 (m, 1H, ***H5***), 2.23-2.13 (m, 1H, ***H5***), 1.90-1.83 (m, 1H, ***H6***), 1.81 (s, 3H, ***H18***), 1.79-1.74 (m, 1H, ***H6***), 1.73-1.68 (m, 1H, ***H10***), 1.70 (d, *J* = 0.9 Hz, 3H, ***H13***"), 1.64 (br s, 1H, ***OH***), 1.60-1.52 (m, 4H, 2H9, ***H10***, ***OH***), 1.58 (s, 3H, ***H13'''***), 1.31 (s, 3H, ***H16*** or ***H17***), 1.30 (s, 3H, ***H16*** or ***H17***), 1.23 (s, 3H, ***H19***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 154.9 (***CO_3***), 138.5 (***C3***), 132.7 (***C13'***), 130.5 (***C4***), 118.9 (***C13***), 90.0 (***C1***), 82.9 (***C11***), 81.8 (***C2***), 79.5 (***C12***), 71.5 (***C7***), 63.3 (***C10'***), 41.9 (***C8***), 41.8 (***C15***), 35.4 (***C10***), 31.0 (***C14***), 26.8 (***C9***), 25.8 (***C13"***), 24.9 (***C6***), 24.8 (***C16*** or ***C17***), 24.7 (***C16*** or ***C17***), 22.0 (***C5***), 20.4 (***C19***), 18.1 (***C13'''***), 3.6 (***C18***).

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 427.2455, found 427.2440.

$[\alpha]^{22}_D$: -12.5 (*c* 1.0, $CHCl_3$).

(4S,5S)-5-((5S,6S)-6-Allyl-5-hydroxy-6-methylcyclohex-1-en-1-yl)-4-(3-methylbut-2-en-1-yl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (3.13)



Chemical Formula: $C_{24}H_{34}O_4$

MW: 386,53

To a solution of diol **3.12** (1.0 g, 2.5 mmol) in THF (70 mL) was added *o*-nitrophenylselenocyanate (680 mg, 3.0 mmol, 1.2 equiv) and tri-*n*-butylphosphine (0.78 mL, 3.0 mmol, 1.2 equiv). The mixture was stirred at room temperature for 20 min. The reaction was quenched with water (10 mL). The aqueous layer was extracted with Et_2O (3x15 mL) and the combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil that was used without further purification. A solution of $(NH_4)_6Mo_7O_{24}.4H_2O$ (90 mg) in water (7 mL) and hydrogen

peroxide (2.9 mL, 30% solution) was then prepared. This solution was added at -15°C to a solution of the previous compound in THF (60 mL). The mixture was stirred at this temperature for 20 min. The reaction was diluted with water (60 mL). The aqueous layer was extracted with EtOAc (3x60 mL), and the combined organic extracts were washed with brine (2x150 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/EtOAc: 8/2) to afford the title alcohol **3.13** (0.87 g, 2.25 mmol, 90%) as a pale yellow viscous oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.94-5.83 (m, 1H, ***H10***), 5.81 (t, *J* = 4.0 Hz, 1H, ***H4***), 5.36-5.29 (m, 2H, ***H2***, ***H13***), 5.18-5.08 (m, 2H, ***H10'***), 3.81 (ddd, *J* = 8.2, 5.7, 2.8 Hz, 1H, ***H7***), 2.77 (dd, *J* = 15.5, 6.2 Hz, 1H, ***H14***), 2.68 (dd, *J* = 15.5, 7.1 Hz, 1H, ***H14***), 2.54 (dd, *J* = 14.2, 6.7 Hz, 1H, ***H9***), 2.35-2.13 (m, 3H, ***H9***, 2***H5***), 1.89-1.80 (m, 1H, ***H6***), 1.77 (s, 3H, ***H18***), 1.75-1.69 (m, 1H, ***H6***), 1.71 (d, *J* = 1.1 Hz, 3H, ***H13"***) 1.62 (br s, 1H, ***OH***), 1.60 (s, 3H, ***H13'''***), 1.33-1.29 (s, 6H, ***H16***, ***H17***), 1.24 (s, 3H, ***H19***).

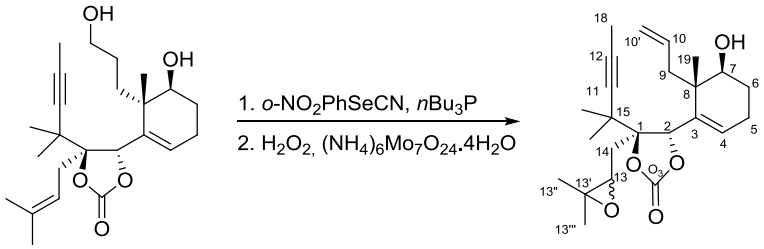
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 155.0 (***CO_3***), 138.8 (***C3***), 134.7 (***C10***), 132.6 (***C4***), 131.1 (***C13'***), 118.9 (***C13***), 118.1 (***C10'***), 89.8 (***C1***), 83.0 (***C11***), 81.0 (***C2***), 79.8 (***C12***), 72.4 (***C7***), 43.7 (***C9***), 42.7 (***C8***), 41.8 (***C15***), 31.2 (***C14***), 25.9 (***C13"***), 24.9 (***C6***), 24.9 (***C16*** or ***C17***), 24.6 (***C16*** or ***C17***), 22.5 (***C5***), 19.7 (***C19***), 18.1 (***C13'''***), 3.5 (***C18***).

IR (ν, cm^{-1}): 3220, 3054, 2985, 2306, 1792, 1550, 1412, 1265, 1040.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 409.2349, found 409.2331.

$[\alpha]^{24}_D$: -29.0 (*c* 1.0, $CHCl_3$).

(4S,5S)-5-((5S,6S)-6-Allyl-5-hydroxy-6-methylcyclohex-1-en-1-yl)-4-((3,3-dimethyloxiran-2-yl)methyl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (3.14)



Chemical Formula: $C_{24}H_{34}O_5$

MW: 402,53

To a solution of diol **3.12** (400 mg, 1.00 mmol) in THF (25 mL) was added *o*-nitrophenylselenocyanate (272 mg, 1.2 mmol, 1.2 equiv) and tri-*n*-butylphosphine (300 µL, 1.2 mmol, 1.2 equiv). The mixture was stirred at room temperature for 20 min. The reaction was quenched with water (10 mL). The aqueous layer was extracted with Et_2O (3x10 mL) and the combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil that was used without further purification. A solution of $(NH_4)_6Mo_7O_{24}.4H_2O$ (116 mg) in water (8 mL) and hydrogen peroxide (4.1 mL, 30% solution) was then prepared. This solution was added at -15°C to a solution of the previous compound in THF (20 mL). The mixture was stirred at this temperature for 60 min. The reaction was diluted with water (30 mL). The aqueous layer was extracted with EtOAc (4x30 mL), and the combined organic extracts were washed with brine (2x100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/EtOAc: 8/2 to 7/3) to afford the title epoxide **3.14** as a 1:1 mixture of diastereomers (360 mg, 0.9 mmol, 90%) as a pale yellow viscous oil.

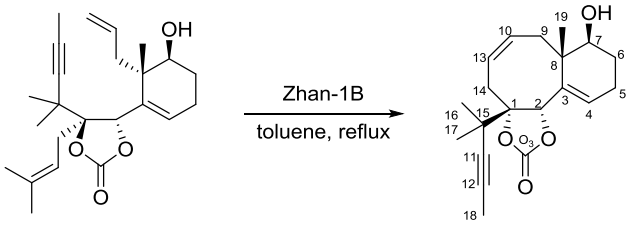
^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.88 (t, *J* = 3.9 Hz, 0.5H, ***H4***), 5.84-5.73 (m, 1.5H, 0.5***H4***, ***H10***), 5.40 (s, 0.5H, ***H2***), 5.33 (s, 0.5H, ***H2***), 5.15-5.04 (m, 2H, ***H10'***), 3.82-3.74 (m, 1H, ***H7***), 3.12 (t, *J* = 4.8 Hz, 0.5H, ***H13***), 3.03 (t, *J* = 5.1 Hz, 0.5H, ***H13***), 2.53-2.43 (m, 1.5H, ***1H9***, 0.5***H14***), 2.38 (dd, *J* = 15.8, 4.8 Hz, 0.5H, ***H14***), 2.34-2.08 (m, 4.5H, ***OH***, 2***H5***, ***H9***, 0.5***H14***), 2.00 (dd, *J* = 15.8, 5.1 Hz, 0.5H, ***H14***), 1.93-1.80 (m, 1H, ***H6***), 1.76 (s, 1.5H, ***H18***), 1.75 (s, 1.5H, ***H18***), 1.74-1.64 (m, 1H, ***H6***), 1.43 (s, 1.5H, ***Me***), 1.36 (s, 1.5H, ***Me***), 1.34 (s, 1.5H, ***Me***), 1.32 (s, 1.5H, ***Me***), 1.32 (s, 1.5H, ***Me***), 1.31 (s, 1.5H, ***Me***), 1.28 (s, 1.5H, ***Me***), 1.25 (s, 1.5H, ***Me***), 1.24 (s, 3H, 2***Me***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 154.5 (***CO_3***), 154.4 (***CO_3***), 138.8 (***C3***), 138.3 (***C3***), 134.3 (***C10***), 134.0 (***C10***), 131.9 (***C4***), 131.0 (***C4***), 118.2 (***C10'***), 118.1 (***C10'***), 89.3 (***C1***), 89.1 (***C1***), 82.6 (***C11*** or ***C12***), 82.4 (***C11*** or ***C12***), 82.2 (***C2***), 81.1 (***C2***), 80.5 (***C11*** or ***C12***), 80.2 (***C11*** or ***C12***), 72.3 (***C7***), 72.2 (***C7***), 60.5 (***C13***), 59.6 (***C13***), 59.5 (***C13'***), 58.9 (***C13'***), 44.3 (***C9***), 43.6 (***C9***), 42.6 (***C8***), 42.4 (***C8***), 41.6 (***C15***), 41.5 (***C15***), 32.8 (***C14***), 31.7 (***C14***), 24.9 (***C6***), 24.7 (***C6***), 24.7 (***Me***), 24.6 (***Me***), 24.5 (***Me***), 24.4 (***Me***), 24.3 (***Me***), 24.2 (***Me***), 22.4 (***C5***), 22.0 (***C5***), 19.9 (***Me***), 19.8 (***Me***), 18.9 (***Me***), 18.9 (***Me***), 3.6 (***C18***), 3.5 (***C18***).

IR (ν, cm^{-1}): 3055, 2984, 2362, 1795, 1541, 1420, 1380, 1265, 1199, 1040.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 425.2298, found 425.2281.

(3S,7S,8S,11S,Z)-8-Hydroxy-7-methyl-3-(2-methylpent-3-yn-2-yl)-3,4,7,7,8,9,10,11-octahydrobenzo[3,4]cycloocta[1,2][1,3]dioxol-2-one (3.15)



Chemical Formula: $C_{20}H_{26}O_4$

MW: 330,42

A solution of **3.13** (35 mg, 90 µmol) in toluene (30 mL) was thoroughly degassed under argon (using the freeze-thaw pump technique) and Zhan-1B catalyst (7.0 mg, 9.0 µmol, 0.1 equiv) was added and the mixture was stirred at reflux for 16 h. The resulting mixture was allowed to cool down and the solvent was removed *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/EtOAc: 85/15) to afford the title bicycle compound **3.15** (9.5 mg, 29 µmol, 23%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.90 (t, *J* = 3.7 Hz, 1H, ***H4***), 5.87-5.79 (m, 1H, ***H13***), 5.69 (td, *J* = 9.0, 7.0 Hz, 1H, ***H10***), 5.28 (s, 1H, ***H2***), 3.57 (br s, 1H, ***H7***), 2.62-2.51 (m, 2H, ***H14***), 2.44-2.31 (m, 2H, ***H5***), 2.28 (dd, *J* = 13.5, 7.0 Hz, 1H, ***H9***), 2.10-2.02 (m, 1H, ***H6***), 1.87 (dd, *J* = 13.5, 9.0 Hz, 1H, ***H9***), 1.84-1.78 (m, 1H, ***H6***), 1.75 (s, 3H, ***H18***), 1.61 (br s, 1H, ***OH***), 1.40 (s, 3H, ***H16*** or ***H17***), 1.34 (s, 3H, ***H16*** or ***H17***), 1.21 (s, 3H, ***H19***).

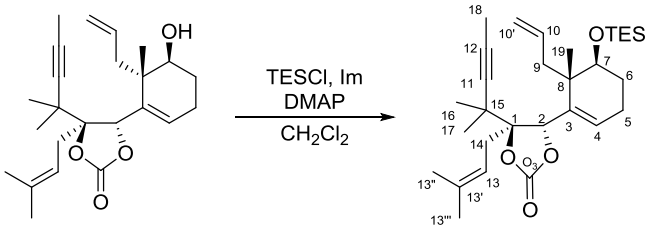
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 154.9 (***CO_3***), 136.9 (***C3***), 128.7 (***C10***), 127.1 (***C13***), 126.8 (***C4***), 91.0 (***C1***), 83.1, 81.0 (***C11***, ***C12***), 80.6 (***C2***), 76.0 (***C7***), 44.5 (***C8***), 39.5 (***C9***), 39.1 (***C15***), 32.0 (***C14***), 25.6, 24.9 (***C16***, ***C17***), 23.7 (***C6***), 20.5 (***C5***), 18.7 (***C19***), 3.7 (***C18***).

IR (ν, cm^{-1}): 3300, 3032, 2923, 2854, 2254, 1798, 1643, 1466, 1272, 1172, 1040.

HRMS (CI/ISO) Calcd for $[M+H]^+$: *m/z* 331.1909, found 331.1912.

$[\alpha]^{25}_D$: +143 (*c* 1.0, $CHCl_3$).

(4S,5S)-5-((5S,6S)-6-Allyl-6-methyl-5-((triethylsilyl)oxy)cyclohex-1-en-1-yl)-4-(3-methylbut-2-en-1-yl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (3.16)



Chemical Formula: $C_{30}H_{48}O_4Si$

MW: 500,79

To a solution of alcohol **3.13** (150 mg, 0.39 mmol) in CH_2Cl_2 (3 mL) were added imidazole (66 mg, 0.97 mmol, 2.5 equiv), DMAP (5 mg, 0.04 mmol, 0.1 equiv) and TESCl (98 µL, 0.58 mmol, 1.5 equiv). The reaction mixture was stirred for 16 h. A saturated aqueous solution of $NaHCO_3$ (10 mL) was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (3x10 mL), and the combined organic extracts were washed with brine (25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 95/5) to afford the title protected alcoholol **3.16** (195 mg, 0.39 mmol, 100%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.82-5.68 (m, 2H, ***H4***, ***H10***), 5.37-5.27 (m, 2H, ***H2***, ***H13***), 5.09-5.00 (m, 2H, ***H10'***), 3.80 (dd, *J* = 6.7, 2.3 Hz, 1H, ***H7***), 2.84-2.74 (m, 1H, ***H14***), 2.62 (dd, *J* = 16.3, 8.2 Hz, 1H, ***H14***), 2.47 (dd, *J* = 14.5, 7.0 Hz, 1H, ***H9***), 2.33-2.21 (m, 1H, ***H5***), 2.17 (dd, *J* = 14.5, 7.6 Hz, 1H, ***H9***), 2.07 (ddt, *J* = 18.5, 6.3, 4.6 Hz, 1H, ***H5***), 1.87-1.80 (m, 1H, ***H6***), 1.78 (s, 3H, ***H18***), 1.69 (s, 3H, ***H13"***), 1.67-1.61 (m, 1H, ***H6***), 1.60 (s, 3H, ***H13'''***), 1.28 (s, 3H, ***H16***), 1.28 (s, 3H, ***H17***), 1.16 (s, 3H, ***H19***), 0.94 (t, *J* = 8.0 Hz, 9H, ***TES***), 0.57 (q, *J* = 8.0 Hz, 6H, ***TES***).

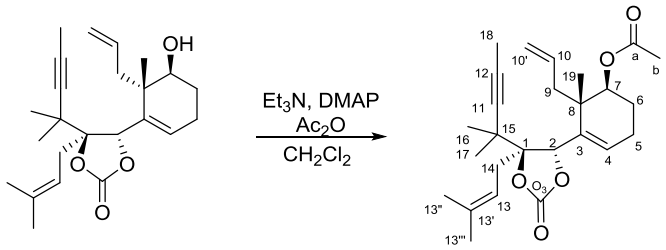
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 155.1 (***CO_3***), 138.4 (***C3***), 134.3 (***C10***), 132.0 (***C13'***), 130.4 (***C4***), 119.5 (***C13***), 117.5 (***C10'***), 90.0 (***C11***), 83.0 (***C12***), 82.8 (***C2***), 79.4 (***C1***), 72.4 (***C7***), 43.8 (***C9***), 42.5 (***C8***), 42.0 (***C15***), 31.1 (***C14***), 25.8 (***C13"***), 25.4 (***C6***), 24.8 (***C16*** or ***C17***), 24.5 (***C16*** or ***C17***), 22.2 (***C5***), 20.7 (***C19***), 18.1 (***C13'''***), 7.0 (***TES***), 5.2 (***TES***), 3.6 (***C18***).

IR (ν, cm^{-1}): 3054, 2955, 2877, 2350, 1792, 1457, 1412, 1280, 1010.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 523.3214, found 523.3192.

$[\alpha]^{25}_D$: -20.0 (*c* 1.0, $CHCl_3$).

(1S,2S)-2-Allyl-2-methyl-3-((4S,5S)-5-(3-methylbut-2-en-1-yl)-5-(2-methylpent-3-yn-2-yl)-2-oxo-1,3-dioxolan-4-yl)cyclohex-3-en-1-yl acetate (3.17)



Chemical Formula: $C_{26}H_{36}O_5$

MW: 428,57

To a solution of alcohol **3.13** (40 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) were added Et_3N (98 µL, 0.7 mmol, 7.0 equiv), DMAP (1.0 mg, 10 µmol, 0.1 equiv) and Ac_2O (47 µL, 0.50 mmol, 5.0 equiv). The resulting mixture was allowed to stir for 4 h at room temperature. A saturated solution of $NaHCO_3$ (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), and the combined organic extracts were washed with a saturated aqueous solution of $CuSO_4$ (5 mL), brine (2x10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 9/1) to afford the protected alcohol **3.17** (43 mg, 0.10 mmol, 100%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.84-5.70 (m, 2H, ***H4***, ***H10***), 5.37-5.28 (m, 2H, ***H2***, ***H13***), 5.12-5.02 (m, 2H, ***H10'***), 4.99 (dd, *J* = 6.6, 2.7 Hz, 1H, ***H7***), 2.76 (dd, *J* = 16.3, 6.0 Hz, 1H, ***H14***), 2.66 (dd, *J* = 16.3, 7.5 Hz, 1H, ***H14***), 2.45 (dd, *J* = 14.3, 6.6 Hz, 1H, ***H9***), 2.26-2.14 (m, 3H, ***H9***, 2***H5***), 2.01 (s, 3H, ***H22***), 1.91-1.78 (m, 2H, ***H6***), 1.77 (s, 3H, ***H18***), 1.70 (d, *J* = 0.9 Hz, 3H, ***H13"***), 1.60 (s, 3H, ***H13'''***), 1.30 (s, 6H, ***H16***, ***H17***), 1.20 (s, 3H, ***H19***).

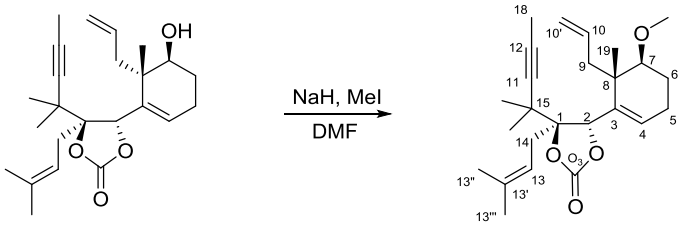
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 170.5 (***Ca***), 154.9 (***CO_3***), 138.1 (***C3***), 133.2 (***C10***), 132.5 (***C13'***), 130.9 (***C4***), 118.9 (***C13***), 118.3 (***C10'***), 89.8 (***C1***), 83.0 (***C11***), 81.4 (***C2***), 79.7 (***C12***), 74.4 (***C7***), 43.8 (***C9***), 41.9 (***C8***), 40.8 (***C15***), 31.2 (***C14***), 25.8 (***C13"***), 24.8 (***C16*** or ***C17***), 24.5 (***C16*** or ***C17***), 22.1 (***C5***), 22.0 (***C6***), 21.1 (***Cb***), 20.2 (***C19***), 18.1 (***C13'''***), 3.5 (***C18***).

IR (ν, cm^{-1}): 3054, 2986, 2439, 1792, 1731, 1427, 1265, 1041.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 451.2455, found 451.2439.

$[\alpha]^{26}_D$: -2.0 (*c* 2.0, $CHCl_3$).

(4S,5S)-5-((5S,6S)-6-Allyl-5-methoxy-6-methylcyclohex-1-en-1-yl)-4-(3-methylbut-2-en-1-yl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (3.18)



Chemical Formula: $C_{25}H_{36}O_4$

MW: 400,56

To a solution of alcohol **3.13** (40 mg, 0.1 mmol) in DMF (1.5 mL) were added at 0°C NaH (6.0 mg, 60% in mineral oil, 0.15 mmol, 1.5 equiv) and MeI (12 µL, 0.20 mmol, 2.0 equiv). The resulting mixture was allowed to stir for 16 h at room temperature. A saturated aqueous solution of $NaHCO_3$ (5 mL) was added and the aqueous layer was extracted with Et_2O (3x5 mL), then the combined organic extracts were washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (petroleum ether/Et_2O: 95/5) to afford the protected alcohol **3.18** (35 mg, 0.09 mmol, 87%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.82-5.68 (m, 2H, ***H4***, ***H10***), 5.35-5.27 (m, 2H, ***H13***, ***H2***), 5.10-4.99 (m, 2H, ***H10'***), 3.30 (s, 3H, ***OMe***), 3.22 (dd, *J* = 8.0, 2.5 Hz, 1H, ***H7***), 2.81 (dd, *J* = 16.3, 6.0 Hz, 1H, ***H14***), 2.64 (dd, *J* = 16.3, 7.0 Hz, 1H, ***H14***), 2.49 (dd, *J* = 14.4, 7.5 Hz, 1H, ***H9***), 2.29-2.16 (m, 2H, ***H9***, ***H5***), 2.13-2.03 (m, 1H, ***H5***), 1.83 (dtd, *J* = 13.4, 6.5, 2.7 Hz, 1H, ***H6***), 1.76 (s, 3H, ***H18***), 1.73-1.67 (m, 1H, ***H6***), 1.70 (d, *J* = 1.2 Hz, 3H, ***H13"***), 1.59 (s, 3H, ***H13'''***), 1.29 (s, 6H, ***H16***, ***H17***), 1.17 (s, 3H, ***H19***).

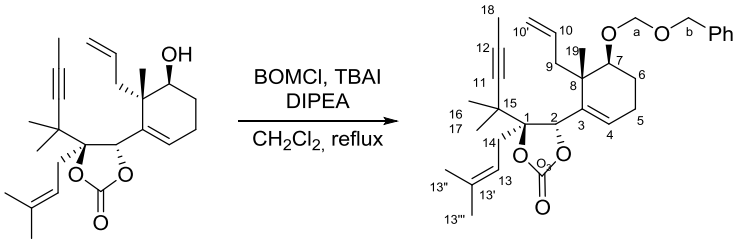
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 155.0 (***CO_3***), 138.9 (***C3***), 134.6 (***C10***), 132.3 (***C13'***), 131.0 (***C4***), 119.1 (***C13***), 117.4 (***C10'***), 89.7 (***C1***), 83.0 (***C11*** or ***C12***), 81.6 (***C2***), 80.7 (***C7***), 79.6 (***C11*** or ***C12***), 56.5 (***OMe***), 43.2 (***C9***), 42.4 (***C8***), 41.9 (***C15***), 31.0 (***C14***), 25.8 (***C13"***), 24.8 (***C16*** or ***C17***), 24.5 (***C16*** or ***C17***), 22.7 (***C5***), 20.5 (***C19***), 20.0 (***C6***), 18.0 (***C13'''***), 3.5 (***C18***).

IR (ν, cm^{-1}): 3074, 2977, 2920, 2208, 1801, 1637, 1458, 1363, 1170, 1090.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 423.2506, found 423.2488.

$[\alpha]^{22}_D$: -28.0 (*c* 2.0, $CHCl_3$).

(4S,5S)-5-((5S,6S)-6-Allyl-5-((benzyloxy)methoxy)-6-methylcyclohex-1-en-1-yl)-4-(3-methylbut-2-en-1-yl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (3.19)



Chemical Formula: $C_{32}H_{42}O_5$

MW: 506,68

To a solution of alcohol **3.13** (1.4 g, 3.7 mmol) in CH_2Cl_2 (50 mL) were added DIPEA (4.8 mL, 28 mmol, 7.5 equiv), TBAI (1.6 g, 4.3 mmol, 1.1 equiv) and BOMCl (3.5 mL, 75% solution, 19 mmol, 5.0 equiv). The resulting mixture was allowed to reflux for 16 h. After the reaction mixture was cooled down to room temperature an aqueous solution of 1N NaOH (25 mL) was added and stirred for 5-10 min. The aqueous layer was extracted with Et_2O (3x50 mL), and the combined organic extracts were washed with a saturated aqueous solution of $CuSO_4$ (2x50 mL) The aqueous copper solution was extracted with Et_2O (3x100 mL) and the combined organic extracts were washed with brine (2x350 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 95/5 to 9/1) to afford the protected alcohol **3.19** (1.7 g, 3.4 mmol, 95%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 7.38-7.29 (m, 5H, ***H_{Ar}***), 5.81 (t, *J* = 3.8 Hz, 1H, ***H4***), 5.79-5.71 (m, 1H, ***H10***), 5.38-5.32 (m, 2H, ***H2***, ***H13***), 5.10-5.02 (m, 2H, ***H10'***), 4.83 (d, *J* = 7.1 Hz, 1H, ***H21***), 4.75 (d, *J* = 7.1 Hz, 1H, ***Ha***), 4.62 (s, 2H, ***Hb***), 3.74 (dd, *J* = 6.5, 2.4 Hz, 1H, ***H7***), 2.87-2.79 (m, 1H, ***H14***), 2.64 (dd, *J* = 16.4, 7.3 Hz, 1H, ***H14***), 2.50 (dd, *J* = 14.5, 6.9 Hz, 1H, ***H9***), 2.33-2.19 (m, 2H, ***H5***, ***H9***), 2.18-2.09 (m, 1H, ***H5***), 1.94-1.81 (m, 2H, 2***H6***), 1.78 (s, 3H, ***H18***), 1.70 (d, *J* = 1.0 Hz, 3H, ***H13***"), 1.60 (s, 3H, ***H13'''***), 1.30 (s, 6H, ***H16***, ***H17***), 1.26 (s, 3H, ***H19***).

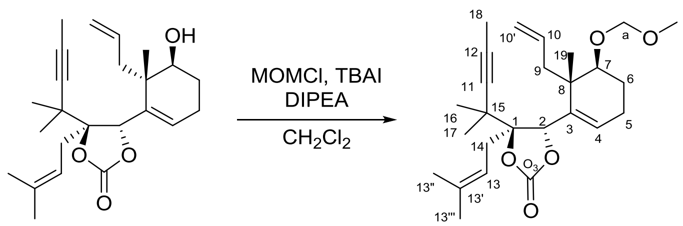
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 155.0 (***CO_3***), 138.3 (***C3***), 137.9 (***C_{Ar}***), 134.0 (***C10***), 132.3 (***C13'***), 130.9 (***C4***), 128.4 (***C_{Ar}***), 127.8 (***C_{Ar}***), 127.7 (***C_{Ar}***), 119.2 (***C13***), 118.0 (***C10'***), 93.9 (***Ca***), 89.8 (***C1***), 83.0 (***C11*** or ***C12***), 82.0 (***C2***), 79.5 (***C11*** or ***C12***), 78.2 (***C7***), 69.7 (***Cb***), 43.8 (***C9***), 42.0 (***C15***), 41.8 (***C8***), 31.0 (***C14***), 25.8 (***C13***"), 24.8 (***C16*** or ***C17***), 24.5 (***C16*** or ***C17***), 22.4 (***C5***), 21.9 (***C6),*** 20.8 (***C19***), 18.1 (***C13'''***), 3.6 (***C18***).

IR (ν, cm^{-1}): 3054, 2986, 2306, 1792, 1558, 1421, 1265, 1041, 1033.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 529.2924, found 529.2916.

$[\alpha]^{25}_D$: -10.0 (*c* 1.0, $CHCl_3$).

(4S,5S)-5-((5S,6S)-6-Allyl-5-(methoxymethoxy)-6-methylcyclohex-1-en-1-yl)-4-(3-methylbut-2-en-1-yl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (3.20)



Chemical Formula: $C_{26}H_{38}O_5$

MW: 430,59

To a solution of alcohol **3.13** (40 mg, 0.10 mmol) in CH_2Cl_2 (3 mL) were added DIPEA (0.12 mL, 0.70 mmol, 7.0 equiv), TBAI (7 mg, 0.02 mmol, 0.2 equiv) and MOMCl (35 µL, 92% solution, 0.40 mmol, 4.0 equiv). The resulting mixture was allowed to stir at room temperature for 16 h. A saturated aqueous solution of $NaHCO_3$ (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), and the combined organic extracts were washed with a saturated aqueous solution of $CuSO_4$ (2x10 mL). The aqueous cuptrate solution was extracted with CH_2Cl_2 (3x20 mL) and the combined organic extracts were washed with brine (2x100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 85/15) to afford the protected alcohol **3.20** (37 mg, 0.09 mmol, 86%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.82-5.70 (m, 2H, ***H4***, ***H10***), 5.36-5.30 (m, 2H, ***H2***, ***H13***), 5.10-5.02 (m, 2H, ***H10'***), 4.69 (d, *J* = 6.9 Hz, 1H, ***Ha***), 4.61 (d, *J* = 6.9 Hz, 1H, ***Ha***), 3.65 (dd, *J* = 6.8, 2.3 Hz, 1H, ***H7***), 3.38 (s, 3H, ***OMe***), 2.81 (dd, *J* = 16.5, 5.9 Hz, 1H, ***H14***), 2.63 (dd, *J* = 16.5, 7.2 Hz, 1H, ***H14***), 2.48 (dd, *J* = 14.4, 7.0 Hz, 1H, ***H9***), 2.32-2.18 (m, 2H, ***H9***, ***H5***), 2.13 (ddt, *J* = 18.7, 6.0, 5.1 Hz, 1H, ***H5***), 1.90-1.74 (m, 2H, ***H6***), 1.78 (s, 3H, ***H18***), 1.70 (d, *J* = 1.1 Hz, 3H, ***H13''***), 1.60 (s, 3H, ***H13'''***), 1.30 (s, 6H, ***H16***, ***H17***), 1.23 (s, 3H, ***H19***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 155.0 (***CO_3***), 138.4 (***C3***), 134.0 (***C10***), 132.3 (***C13'***), 131.0 (***C4***), 119.1 (***C13***), 117.9 (***C10'***), 95.9 (***Ca***), 89.8 (***C1***), 83.0 (***C11***), 81.9 (***C2***), 79.5 (***C12***), 78.0

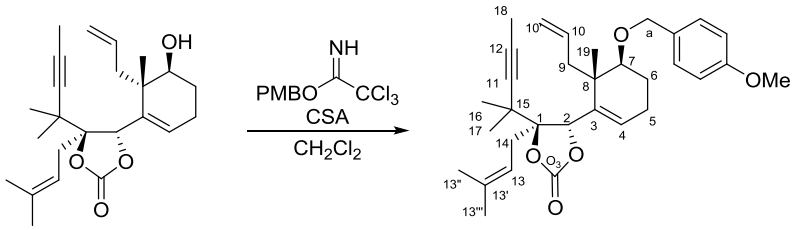
(***C7***), 55.7 (***OMe***), 43.6 (***C9***), 42.0 (***C15***), 41.9 (***C8***), 31.0 (***C14***), 25.8 (***C13"***), 24.8 (***C16*** or ***C17***), 24.5 (***C16*** or ***C17***), 22.5 (***C5***), 22.1 (***C6***), 20.8 (***C19***), 18.1 (***C13'''***), 3.6 (***C18***).

IR (ν, cm^{-1}): 3055, 2986, 2306, 1792, 1541, 1507, 1421, 1260, 1038.

HRMS (CI/ISO) Calcd for $[M+H]^+$: *m/z* 431.2797, found 431.2794.

$[\alpha]^{27}_D$: -12.0 (*c* 1.0, $CHCl_3$).

(4S,5S)-5-((5S,6S)-6-Allyl-5-((4-methoxybenzyl)oxy)-6-methylcyclohex-1-en-1-yl)-4-(3-methylbut-2-en-1-yl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (3.21)



Chemical Formula: $C_{32}H_{42}O_5$

MW: 506,68

To a solution of alcohol **3.13** (0.10 g, 0.26 mmol) in CH_2Cl_2 (5 mL) were added PMB-trichloroacetimidate (0.22 g, 0.78 mmol, 3.0 equiv) and CSA (10 mg, 0.04 mmol, 0.15 equiv). The resulting mixture was refluxed for 24 h. A saturated aqueous solution of $NaHCO_3$ (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), and the combined organic extracts were washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 95/5) to afford the protected alcohol **3.21** (80 mg, 0.16 mmol, 61%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 7.23 (d, *J* = 8.6 Hz, 2H, ***H_{Ar}***), 6.86 (d, *J* = 8.6 Hz, 2H, ***H_{Ar}***), 5.80-5.68 (m, 2H, ***H4***, ***H10***), 5.35-5.30 (m, 2H, ***H2***, ***H13***), 5.06-4.98 (m, 2H, ***H10'***), 4.54 (d, *J* = 11.2 Hz, 1H, ***Ha***), 4.32 (d, *J* = 11.2 Hz, 1H, ***Ha***), 3.81 (s, 3H, ***OMe***), 3.47 (dd, *J* = 7.4, 2.2 Hz, 1H, ***H7***), 2.82 (dd, *J* = 16.3, 5.5 Hz, 1H, ***H14***), 2.63 (dd, *J* = 16.3, 7.6 Hz, 1H, ***H14***), 2.53 (dd, *J* = 14.4, 7.4 Hz, 1H, ***H9***), 2.32-2.19 (m, 2H, ***H5***, ***H9***), 2.10 (dq, *J* = 18.3, 5.9 Hz, 1H, ***H5***), 1.91-1.82 (m, 1H, ***H6***), 1.81-1.73 (m, 1H, ***H6***), 1.77 (s, 3H, ***H18***), 1.70 (s, 3H, ***H13"***), 1.55 (s, 3H, ***H13'''***), 1.29 (s, 6H, ***H16***, ***H17***), 1.22 (s, 3H, ***H19***).

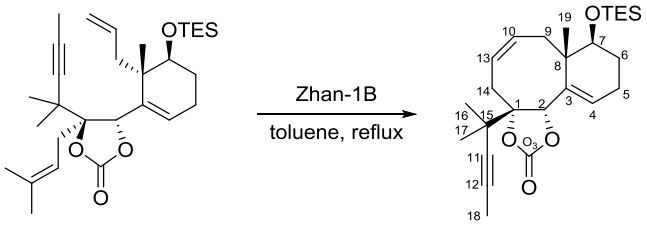
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 158.9 (***C_{Ar}***), 155.0 (***CO_3***), 138.9 (***C3***), 134.5 (***C10***), 132.2 (***C13'***), 131.2 (***C4***), 130.8 (***C_{Ar}***), 128.8 (***C_{Ar}***), 119.3 (***C13***), 117.4 (***C10'***), 113.6 (***C_{Ar}***), 89.9 (***C1***), 83.0 (***C11***), 82.2 (***C2***), 79.5 (***C12***), 79.0 (***C7***), 70.5 (***Ca***), 55.3 (***OMe***), 43.6 (***C8***), 42.5 (***C15***), 42.0 (***C9***), 31.1 (***C14***), 25.8 (***C13"***), 24.8 (***C16*** or ***C17***), 24.5 (***C16*** or ***C17***), 22.7 (***C5***), 20.8 (***C19***), 20.7 (***C6***), 18.0 (***C13'''***), 3.5 (***C18***).

IR (ν, cm^{-1}): 3054, 2978, 2936, 1794, 1666, 1605, 1520, 1438, 1280, 1172, 1025.

HRMS (EI) Calcd for $[M]^+$: *m/z* 506.3032, found 506.3029.

$[\alpha]^{21}_D$: -3.0 (*c* 1.5, $CHCl_3$).

(3S,7S,8S,11S,Z)-7-Methyl-3-(2-methylpent-3-yn-2-yl)-8-((triethylsilyl)oxy)-3,4,7,7,8,9,10,11-octahydrobenzo[3,4]cycloocta[1,2][1,3]dioxol-2-one (3.22)



Chemical Formula: $C_{26}H_{40}O_4Si$

MW: 444,69

A solution of **3.16** (35 mg, 70 µmol) in toluene (23 mL) was thoroughly degassed under argon (using the freeze-thaw pump technique) and Zhan-1B catalyst (5.1 mg, 7.0 µmol, 0.1 equiv) was added and the mixture was stirred at reflux for 3 h. The resulting mixture was allowed to cool down and the solvent was removed *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/EtOAc: 97/3) to afford the title bicycle compound **3.22** (24 mg, 54 µmol, 77%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.83-5.74 (m, 2H, ***H4***, ***H13***), 5.69-5.61 (m, 1H, ***H10***), 5.27 (s, 1H, ***H2***), 3.60 (dd, *J* = 4.6, 2.0 Hz, 1H, ***H7***), 2.61 (ddd, *J* = 14.0, 9.6, 0.9 Hz, 1H, ***H14***), 2.52 (dd, *J* = 14.0, 7.3 Hz, 1H, ***H14***), 2.40-2.30 (m, 1H, ***H5***), 2.27 (dd, *J* = 13.6, 6.5 Hz, 1H, ***H9***), 2.20-2.10 (m, 1H, ***H5***), 1.99-1.91 (m, 1H, ***H6***), 1.84 (dd, *J* = 13.6, 8.5 Hz, 1H, ***H9***), 1.75 (s, 3H, ***H18***), 1.65 (dddd, *J* = 14.0, 7.3, 4.8, 2.0 Hz, 1H, ***H6***), 1.39 (s, 3H, ***H16*** or ***H17***), 1.34 (s, 3H, ***H16*** or ***H17***), 1.10 (s, 3H, ***H19***), 0.96 (t, *J* = 8.0 Hz, 9H, ***TES***), 0.60 (q, *J* = 8.0 Hz, 6H, ***TES***).

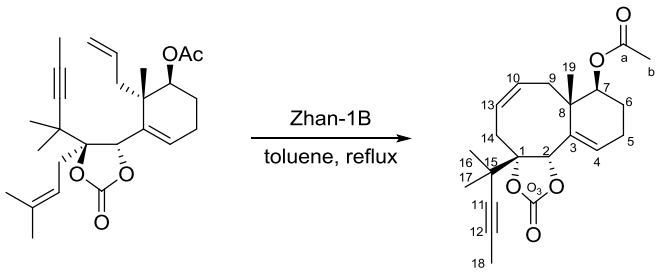
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 155.1 (***CO_3***), 136.4 (***C3***), 128.9 (***C10***), 126.9 (***C13***), 126.2 (***C4***), 91.2 (***C1***), 83.2 (***C11*** or ***C12***), 80.7 (***C2***), 80.6 (***C11*** or ***C12***), 76.3 (***C7***), 44.4 (***C8***), 39.3 (***C9***), 39.2 (***C15***), 32.1 (***C14***), 25.6, 24.9 (***C16***, ***C17***), 24.8 (***C6***), 21.7 (***C5***), 19.3 (***C19***), 7.0 (***TES***), 5.1 (***TES***), 3.7 (***C18***).

IR (ν, cm^{-1}): 3055, 2955, 2877, 1796, 1466, 1427, 1265, 1187, 1056.

HRMS (ESI) Calcd for $[M+H]^+$: *m/z* 467.2588, found 467.2568.

$[\alpha]^{22}_D$: +133 (*c* 2.0, $CHCl_3$).

(3S,7S,8S,11S,Z)-7-Methyl-3-(2-methylpent-3-yn-2-yl)-2-oxo-3,4,7,7,8,9,10,11-octahydrobenzo[3,4]cycloocta[1,2][1,3]dioxol-8-yl acetate (3.23)



Chemical Formula: $C_{22}H_{28}O_5$

MW: 372,46

The same metathesis procedure was repeated with the protected diol **3.17** (36 mg, 84 µmol). The crude mixture was purified by flash chromatography (petroleum ether/Et_2O: 85/15) to afford the title bicycle **3.23** (25 mg, 67 µmol, 80%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.90-5.81 (m, 2H, ***H4***, ***H13***), 5.70-5.63 (m, 1H, ***H10***), 5.31 (s, 1H, ***H2***), 4.88 (dd, *J* = 3.8, 2.4 Hz, 1H, ***H7***), 2.64-2.52 (m, 2H, ***H14***), 2.36-2.25 (m, 3H, 2***H5***, ***H9***), 2.05 (s, 3H, ***H22***), 2.04-1.99 (m, 1H, ***H6***), 1.96 (dd, *J* = 13.5, 8.7 Hz, 1H, ***H9***), 1.91-1.84 (m, 1H, ***H6***), 1.73 (s, 3H, ***H18***), 1.40 (s, 3H, ***H16*** or ***H17***), 1.35 (s, 3H, ***H16*** or ***H17***), 1.10 (s, 3H, ***H19***).

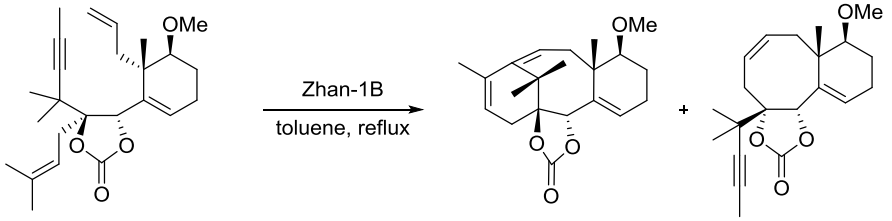
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 170.9 (***Ca***), 154.9 (***CO_3***), 136.3 (***C3***), 128.1 (***C10***), 127.5 (***C13***), 126.7 (***C4***), 91.1 (***C1***), 83.2, 80.9 (***C11***, ***C12***), 80.6 (***C2***), 77.6 (***C7***), 42.7 (***C8***), 39.4 (***C9***), 39.1 (***C15***), 32.0 (***C14***), 25.6, 24.9 (***C16***, ***C17***), 21.4 (***C6***), 21.3 (***C5***), 21.2 (***Cb***), 18.5 (***C19***), 3.6 (***C18***).

IR (ν, cm^{-1}): 3055, 3034, 2984, 2920, 1796, 1726, 1466, 1373, 1249, 1164, 1033.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 395.1829, found 395.1815.

$[\alpha]^{26}_D$: +126 (*c* 2.0, $CHCl_3$).

(3S,9S,10S,13S,Z)-10-Methoxy-6,9,14,14-tetramethyl-9,9,10,11,12,13-hexahydro-4H-3,7-methanobenzo[3,4]cyclodeca[1,2][1,3]dioxol-2-one (3.24) and (3S,7S,8S,11S,Z)-8-methoxy-7-methyl-3-(2-methylpent-3-yn-2-yl)-3,4,7,7,8,9,10,11-octahydrobenzo[3,4]cycloocta[1,2][1,3]dioxol-2-one (3.25)

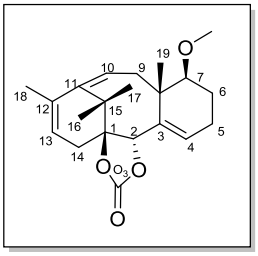


Chemical Formula: $C_{21}H_{28}O_4$

MW: 344,45

The same metathesis procedure was repeated with the protected diol **3.18** (34 mg, 85 µmol). The crude mixture was purified by flash chromatography (petroleum ether/Et_2O: 85/15) to afford the title tricycle **3.24** (13 mg, 38 µmol, 45%) and the bicycle **3.25** (8.8 mg, 25 µmol, 30%) as colourless oils.

(3S,9S,10S,13S,Z)-10-Methoxy-6,9,14,14-tetramethyl-9,9,10,11,12,13-hexahydro-4H-3,7-methanobenzo[3,4]cyclodeca[1,2][1,3]dioxol-2-one (3.24)



^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.90 (dd, *J* = 5.0, 1.5 Hz, 1H, ***H4***), 5.65 (dd, *J* = 13.7, 6.2 Hz, 1H, ***H10***), 5.13 (s, 1H, ***H2***), 4.95 (tq, *J* = 3.5, 1.8 Hz, 1H, ***H13***), 3.43 (s, 3H, ***OMe***), 3.18 (dd, *J* = 12.1, 3.4 Hz, 1H, ***H7***), 2.79 (ddq, *J* = 18.9, 3.5, 1.8 Hz, 1H, ***H14***), 2.68 (dd, *J* = 13.7, 6.2 Hz, 1H, ***H9***), 2.36 (t, *J* = 13.7 Hz, 1H, ***H9***), 2.28-2.15 (m, 2H, ***H5***, ***H14***), 2.06-1.94 (m, 2H, ***H5***, ***H6***),

1.80 (q, *J* = 1.8 Hz, 3H, ***H18***), 1.58 (s, 3H, ***H17***), 1.57-1.52 (m, 1H, ***H6***), 1.33 (s, 3H, ***H16***), 1.10 (s, 3H, ***H19***).

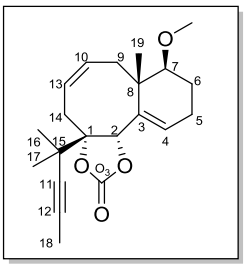
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 154.2 (***CO_3***), 146.5 (***C11***), 138.2 (***C12***), 134.7 (***C3***), 127.9 (***C4***), 127.3 (***C10***), 115.9 (***C13***), 93.3 (***C1***), 79.5 (***C7***), 79.0 (***C2***), 57.2 (***OMe***), 47.8 (***C8***), 41.1 (***C15***), 32.8 (***C9***), 30.6 (***C14***), 25.2 (***C16***), 24.2 (***C5***), 21.6 (***C19***), 21.3 (***C6***), 21.3 (***C17***), 18.8 (***C18***).

IR (ν, cm^{-1}): 3054, 2983, 2931, 1797, 1507, 1434, 1265, 1211, 1172, 1110, 1025.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 367.1880, found 367.1863.

$[\alpha]^{25}_D$: +105 (*c* 1.5, $CHCl_3$).

(3S,7S,8S,11S,Z)-8-methoxy-7-methyl-3-(2-methylpent-3-yn-2-yl)-3,4,7,7,8,9,10,11-octahydrobenzo[3,4]cycloocta[1,2][1,3]dioxol-2-one (3.25)



^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.83-5.77 (m, 2H, ***H13***, ***H4***), 5.70-5.61 (m, 1H, ***H10***), 5.30 (s, 1H, ***H2***), 3.36 (s, 3H, ***OMe***), 3.08 (dd, *J* = 4.4, 2.2 Hz, 1H, ***H7***), 2.59 (ddd, *J* = 13.6, 9.7, 1.0 Hz, 1H, ***H14***), 2.54 (dd, *J* = 13.6, 7.3 Hz, 1H, ***H14***), 2.35-2.25 (m, 2H, ***H5***, ***H9***), 2.23-2.15 (m, 1H, ***H5***), 1.95 (ddt, *J* = 14.2, 6.5, 2.2 Hz, 1H, ***H6***), 1.91-1.84 (m, 2H, ***H6***, ***H9***), 1.74 (s, 3H, ***H18***), 1.39 (s, 3H, ***H16*** or ***H17***), 1.33 (s, 3H, ***H16*** or ***H17***), 1.17 (s, 3H, ***H19***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 155.0 (***CO_3***), 136.9 (***C3***), 128.7 (***C10***), 127.1 (***C13***), 126.6 (***C4***), 91.0 (***C1***), 85.2 (***C7***), 83.2, 80.7 (***C11***, ***C12***), 80.6 (***C2***), 57.0 (***OMe***), 43.8 (***C8***), 39.6 (***C9***), 39.2 (***C15***), 32.1 (***C14***), 25.6, 24.9 (***C16***, ***C17***), 21.5 (***C5***), 19.1 (***C6***), 18.9 (***C19***), 3.7 (***C18***).

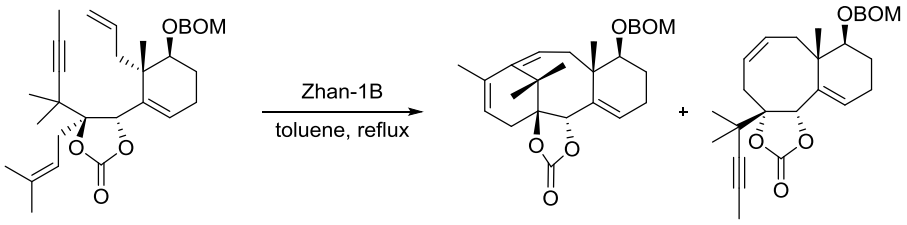
IR (ν, cm^{-1}): 3055, 2944, 2832, 1794, 1647, 1456, 1268, 1117, 1029.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 367.1880, found 367.1862.

$[\alpha]^{25}_D$: +175 (*c* 1.0, $CHCl_3$).

(3S,9S,10S,13S,Z)-10-((Benzyloxy)methoxy)-6,9,14,14-tetramethyl-9,9,10,11,12,13-hexahydro-4H-3,7-methanobenzo[3,4]cyclodeca[1,2][1,3]dioxol-2-one (3.26)

(3S,7S,8S,11S,Z)-8-((Benzyloxy)methoxy)-7-methyl-3-(2-methylpent-3-yn-2-yl)-3,4,7,7,8,9,10,11-octahydrobenzo[3,4]cycloocta[1,2][1,3]dioxol-2-one (3.27)



Chemical Formula: $C_{28}H_{34}O_5$

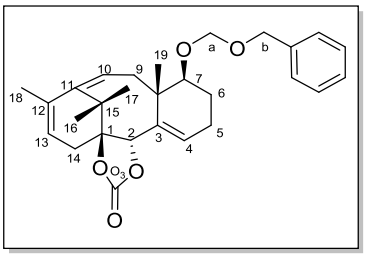
MW: 450,57

<u>*Method A:*</u> The same metathesis procedure was repeated with the protected diol **3.19** (20 mg, 39 µmol). The crude mixture was purified by flash chromatography (benzene/CH_2Cl_2: 75/25) to afford the title tricycle **3.26** (5.3 mg, 12 µmol, 29%) and the bicycle **3.27** (7.9 mg, 18 µmol, 46%) as colourless oils.

<u>*Method B:*</u> A solution of **3.19** (100 mg, 0.20 mmol) in toluene (65 mL) was thoroughly degassed under argon (using the freeze-thaw pump technique) and Zhan-1B catalyst (144 mg, 0.20 mmol, 1.0 equiv) was added and the mixture was stirred at reflux for 16 h while a gentle stream of argon was bubbling through the reaction mixture. The resulting mixture was allowed to cool down and the solvent was removed *in vacuo*. The crude mixture was then purified by flash chromatography (benzene/CH_2Cl_2: 75/25) to only afford the title tricycle compound **3.26** (32-36 mg, 70-80 µmol, 35-40%) as a colourless oil.

<u>*Method C:*</u> A solution of precursor **3.19** (36 mg, 71 µmol) in toluene (24 mL) was thoroughly degassed under argon (using the freeze-thaw pump technique) and Zhan-1B catalyst (52 mg, 71 µmol, 1.0 equiv) was added and the mixture was stirred at reflux for 4 h while a gentle stream of argon was bubbling through the reaction mixture. Then a solution of bicycle **3.27** (32 mg, 71 µmol, 1.0 equiv) in toluene (5 mL) was added to the reaction mixture, which was stirred at reflux for an additional 16 h while a gentle stream of argon was bubbling through. The resulting mixture was allowed to cool down and the solvent was removed *in vacuo*. The crude mixture was then purified by flash chromatography (benzene/CH_2Cl_2: 75/25) to afford the title tricycle compound **3.26** (15 mg, 33 µmol, 47%) as a colourless oil.

(3S,9S,10S,13S,Z)-10-((Benzyloxy)methoxy)-6,9,14,14-tetramethyl-9,9,10,11,12,13-hexahydro-4H-3,7-methanobenzo[3,4]cyclodeca[1,2][1,3]dioxol-2-one (3.26)



^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm: 7.38-7.29 (m, 5H, ***H$_{Ar}$***), 5.91 (dd, *J* = 5.6, 2.1 Hz, 1H, ***H4***), 5.68 (dd, *J* = 13.2, 6.1 Hz, 1H, ***H10***), 5.16 (s, 1H, ***H2***), 4.96 (d, *J* = 7.2 Hz, 1H, ***Ha***), 4.93 (ddq, *J* = 6.2, 3.6, 1.6 Hz, 1H, ***H13***), 4.82 (d, *J* = 7.2 Hz, 1H, ***Ha***), 4.74 (d, *J* = 11.6 Hz, 1H, ***Hb***), 4.65 (d, *J* = 11.6 Hz, 1H, ***Hb***), 3.72 (dd, *J* = 12.1, 3.8 Hz, 1H, ***H7***), 2.78 (ddq, *J* = 19.0, 3.6, 1.6 Hz, 1H, ***H14***), 2.71 (dd, *J* = 13.2, 6.1 Hz, 1H, ***H9***), 2.42 (t, *J* = 13.2 Hz, 1H, ***H9***), 2.26-2.14 (m, 2H, ***H5***, ***H14***), 2.04 (dddd, *J* = 18.4, 11.7, 6.7, 2.1 Hz, 1H, ***H5***), 1.98-1.91 (m, 1H, ***H6***), 1.74-1.65 (m, 1H, ***H6***), 1.71 (dt, *J* = 3.3, 1.6 Hz, 3H, ***H18***), 1.59 (s, 3H, ***H17***), 1.33 (s, 3H, ***H16***), 1.17 (s, 3H, ***H19***).

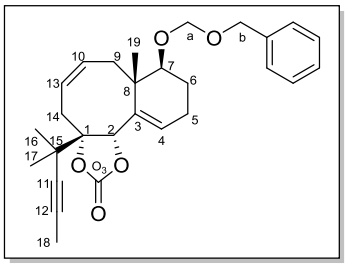
^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm: 154.1 (***CO$_3$***), 146.7 (***C11***), 138.3 (***C12***), 137.6 (***C$_{Ar}$***), 134.6 (***C12***), 128.5 (***C$_{Ar}$***), 128.1 (***C4***), 127.8 (***C$_{Ar}$***), 127.7 (***C$_{Ar}$***), 127.0 (***C10***), 115.8 (***C13***), 93.4 (***C1***), 93.2 (***Ca***), 78.9 (***C2***), 75.5 (***C7***), 70.1 (***Cb***), 47.5 (***C8***), 41.1 (***C15***), 32.8 (***C9***), 30.6 (***C14***), 25.2 (***C16***), 24.1 (***C5***), 22.9 (***C6***), 21.7 (***C19***), 21.3 (***C17***), 18.8 (***C18***).

IR (ν, cm^{-1}): 3056, 3030, 2934, 1801, 1541, 1377, 1338, 1267, 1216, 1159, 1025.

HRMS (ESI) Calcd for [M+Na]$^{+}$: *m/z* 473.2298, found 473.2287.

[α]$^{21}_{D}$: +113 (*c* 1.0, $CHCl_3$).

(3S,7S,8S,11S,Z)-8-((Benzyloxy)methoxy)-7-methyl-3-(2-methylpent-3-yn-2-yl)-3,4,7,7,8,9,10,11-octahydrobenzo[3,4]cycloocta[1,2][1,3]dioxol-2-one (3.27)



^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm: 7.39-7.29 (m, 5H, ***H$_{Ar}$***), 5.89-5.78 (m, 2H, ***H4***, ***H13***), 5.71-5.63 (m, 1H, ***H10***), 5.33 (s, 1H, ***H2***), 4.88 (d, *J* = 7.2 Hz, 1H, ***Ha***), 4.78 (d, *J* = 7.2 Hz, 1H, ***Ha***), 4.67 (d, *J* = 11.5 Hz, 1H, ***Hb***), 4.63 (d, *J* = 11.5 Hz, 1H, ***Hb***), 3.62 (t, *J* = 3.1 Hz, 1H, ***H7***), 2.61 (dd, *J* = 13.5, 10.3 Hz, 1H, ***H14***), 2.55 (dd, *J* = 13.5, 7.3 Hz, 1H, ***H14***), 2.41-2.29 (m, 2H, ***H5***, ***H9***), 2.28-2.20 (m, 1H, ***H5***), 2.00-1.86 (m, 3H, 2***H6***, ***H9***), 1.75 (s, 3H, ***H18***), 1.41 (s, 3H, ***H16*** or ***H17***), 1.35 (s, 3H, ***H16*** or ***H17***), 1.22 (s, 3H, ***H19***).

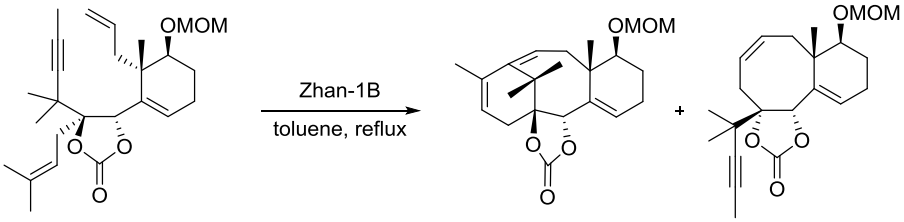
^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm: 155.0 (***CO$_3$***), 137.9 (***C$_{Ar}$***), 136.8 (***C3***), 128.6 (***C10***), 128.5 (***C$_{Ar}$***), 127.8 (***C$_{Ar}$***), 127.7 (***C$_{Ar}$***), 127.2 (***C13***), 126.7 (***C4***), 93.5 (***Ca***), 91.0 (***C1***), 83.2 (***C11*** or ***C12***), 81.5 (***C7***), 80.7 (***C11*** or ***C12***), 80.6 (***C2***), 69.9 (***Cb***), 43.7 (***C8***), 39.7 (***C9***), 39.2 (***C15***), 32.1 (***C14***), 25.6, 24.9 (***C16***, ***C17***), 21.7 (***C5***), 20.9 (***C6***), 19.1 (***C19***), 3.7 (***C18***).

IR (ν, cm^{-1}): 3056, 3014, 2989, 2951, 1791, 1520, 1423, 1400, 1257, 1125, 1041.

HRMS (ESI) Calcd for [M+Na]$^+$: *m/z* 473.2298, found 473.2287.

[α]$^{25}_{D}$: +123 (*c* 1.0, $CHCl_3$).

(3S,9S,10S,13S,Z)-10-(Methoxymethoxy)-6,9,14,14-tetramethyl-9,9,10,11,12,13-hexahydro-4H-3,7-methanobenzo[3,4]cyclodeca[1,2][1,3]dioxol-2-one (3.28) and (3S,7S,8S,11S,Z)-8-(Methoxymethoxy)-7-methyl-3-(2-methylpent-3-yn-2-yl)-3,4,7,7,8,9,10,11-octahydrobenzo[3,4]cycloocta[1,2][1,3]dioxol-2-one (3.29)

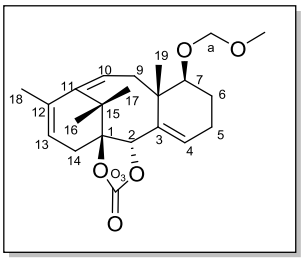


Chemical Formula: $C_{22}H_{30}O_5$

MW: 374,48

The same metathesis procedure was repeated with the protected diol **3.20** (33 mg, 76 µmol). The crude mixture was purified by flash chromatography (petroleum ether/Et_2O: 85/15) to afford the title tricycle compound **3.28** (8.0 mg, 21 µmol, 28%) and the bicycle **3.29** (15 mg, 41 µmol, 54%) as colourless oils.

(3S,9S,10S,13S,Z)-10-(Methoxymethoxy)-6,9,14,14-tetramethyl-9,9,10,11,12,13-hexahydro-4H-3,7-methanobenzo[3,4]cyclodeca[1,2][1,3]dioxol-2-one (3.28)



^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm: 5.91 (dd, *J* = 5.2, 2.0 Hz, 1H, ***H4***), 5.70 (dd, *J* = 12.9, 6.1 Hz, 1H, ***H10***), 5.15 (s, 1H, ***H2***), 4.95 (tq, *J* = 3.3, 1.6 Hz, 1H, ***H13***), 4.82 (d, *J* = 7.0 Hz, 1H, ***Ha***), 4.65 (d, *J* = 7.0 Hz, 1H, ***Ha***), 3.62 (dd, *J* = 12.1, 3.9 Hz, 1H, ***H7***), 3.45 (s, 3H, ***OMe***), 2.79 (ddq, *J* = 18.9, 3.3, 1.6 Hz, 1H, ***H14***), 2.65 (dd, *J* = 13.8, 6.1 Hz, 1H, ***H9***), 2.40 (dd, *J* = 13.8, 12.9 Hz, 1H, ***H9***), 2.26-2.13 (m, 2H, ***H5***, ***H14***), 2.04 (dddd, *J* = 18.5, 11.6, 6.6, 2.0 Hz, 1H, ***H5***), 1.93-1.85 (m, 1H, ***H6***), 1.79 (q, *J* = 1.6 Hz, 3H, ***H18***), 1.75-1.65 (m, 1H, ***H6***), 1.59 (s, 3H, ***H17***), 1.34 (s, 3H, ***H16***), 1.15 (s, 3H, ***H19***).

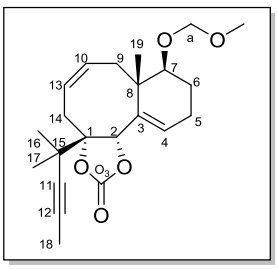
^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm: 154.1 (***CO$_3$***) 146.7 (***C11***), 138.2 (***C12***), 134.6 (***C3***), 128.1 (***C4***), 127.0 (***C10***), 115.8 (***C13***), 95.3 (***C1***), 93.4 (***Ca***), 79.0 (***C2***), 75.7 (***C7***), 55.8 (***OMe***), 47.5 (***C8***), 41.1 (***C15***), 32.8 (***C9***), 30.6 (***C14***), 25.2 (***C16***), 24.2 (***C5***), 23.1 (***C6***), 21.7 (***C19***), 21.3 (***C17***), 18.9 (***C18***).

IR (ν, cm^{-1}): 3049, 2932, 1799, 1558, 1435, 1266, 1020.

HRMS (CI/ISO) Calcd for [M+H]$^+$: *m/z* 375.2171, found 375.2175.

[α]$^{24}_{D}$: +84.0 (*c* 1.0, $CHCl_3$).

(3S,7S,8S,11S,Z)-8-(Methoxymethoxy)-7-methyl-3-(2-methylpent-3-yn-2-yl)-3,4,7,7,8,9,10,11-octahydrobenzo[3,4]cycloocta[1,2][1,3]dioxol-2-one (3.29)



^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm: 5.87-5.79 (m, 2H, ***H4***, ***H13***), 5.71-5.60 (m, 1H, ***H10***), 5.31 (s, 1H, ***H2***), 4.74 (d, *J* = 7.0 Hz, 1H, ***Ha***), 4.62 (d, *J* = 7.0 Hz, 1H, ***Ha***), 3.52 (dd, *J* = 4.0, 2.4 Hz,

1H, ***H7***), 3.40 (s, 3H, ***OMe***), 2.64-2.50 (m, 2H, ***H14***), 2.35-2.28 (m, 2H, ***H5***, ***H9***), 2.27-2.22 (m, 1H, ***H5***), 1.97-1.86 (m, 3H, 2***H6***, ***H9***), 1.75 (s, 3H, ***H18***), 1.40 (s, 3H, ***H16*** or ***H17***), 1.34 (s, 3H, ***H16*** or ***H17***), 1.20 (s, 3H, ***H19***).

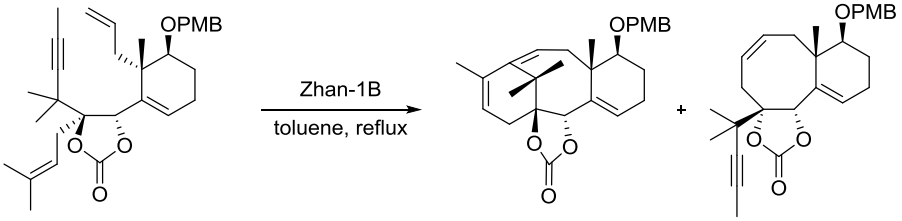
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 155.0 (***CO_3***), 136.8 (***C3***), 128.6 (***C10***), 127.1 (***C13***), 126.7 (***C4***), 95.4 (***Ca***), 91.0 (***C1***), 83.2 (***C11***), 81.3 (***C7***), 80.7 (***C12***), 80.6 (***C2***), 55.8 (***OMe***), 43.6 (***C8***), 39.7 (***C9***), 39.1 (***C15***), 32.1 (***C14***), 25.6, 24.9 (***C16***, ***C17***), 21.7 (***C5***), 21.0 (***C6***), 19.1 (***C19***), 3.7 (***C18***).

IR (ν, cm^{-1}): 3056, 3034, 2987, 2941, 1798, 1527, 1450, 1257, 1041.

HRMS (CI/ISO) Calcd for $[M+H]^+$: *m/z* 375.2171, found 375.2168.

$[\alpha]^{25}_D$: +157 (*c* 1.0, $CHCl_3$).

(3S,9S,10S,13S,Z)-10-((4-Methoxybenzyl)oxy)-6,9,14,14-tetramethyl-9,9,10,11,12,13-hexahydro-4H-3,7-methanobenzo[3,4]cyclodeca[1,2][1,3]dioxol-2-one (3.30) and (3S,7S,8S,11S,Z)-8-((4-methoxybenzyl)oxy)-7-methyl-3-(2-methylpent-3-yn-2-yl)-3,4,7,7,8,9,10,11-octahydrobenzo[3,4]cycloocta[1,2][1,3]dioxol-2-one (3.31)

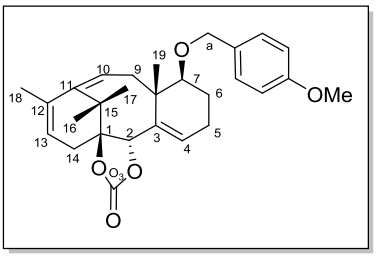


Chemical Formula: $C_{28}H_{34}O_5$

MW: 450,57

The same metathesis procedure was repeated with the protected diol **3.21** (50 mg, 0.10 mmol). The crude mixture was purified by flash chromatography (petroleum ether/Et_2O: 85/15) to afford the title tricycle **3.30** (13 mg, 29 µmol, 29%) and the bicycle **3.31** (9.9 mg, 22 µmol, 22%) as colourless oils.

(3S,9S,10S,13S,Z)-10-((4-Methoxybenzyl)oxy)-6,9,14,14-tetramethyl-9,9,10,11,12,13-hexahydro-4H-3,7-methanobenzo[3,4]cyclodeca[1,2][1,3]dioxol-2-one (3.30)



^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm: 7.33-7.28 (m, 2H, ***H$_{Ar}$***), 6.93-6.89 (m, 2H, ***H$_{Ar}$***), 5.87 (dd, *J* = 5.7, 1.7 Hz, 1H, ***H4***), 5.10 (s, 1H, ***H2***), 5.03 (dd, *J* = 13.0, 6.1 Hz, 1H, ***H10***), 4.88 (tq, *J* = 3.3, 1.6 Hz, 1H, ***H13***), 4.70 (d, *J* = 11.9 Hz, 1H, ***Ha***), 4.38 (d, *J* = 11.9 Hz, 1H, ***Ha***), 3.81 (s, 3H, ***OMe***), 3.30 (dd, *J* = 12.1, 3.3 Hz, 1H, ***H7***), 2.74 (ddq, *J* = 18.8, 3.3, 1.6 Hz, 1H, ***H14***), 2.61 (dd, *J* = 13.8, 6.1 Hz, 1H, ***H9***), 2.26 (dd, *J* = 13.8, 13.0 Hz, 1H, ***H9***), 2.25-2.19 (m, 1H, ***H5***), 2.14 (ddq, *J* = 18.8, 3.3, 1.6 Hz, 1H, ***H14***), 2.05-1.97 (m, 2H, ***H5***, ***H6***), 1.62 (q, *J* = 1.6 Hz, 3H, ***H18***), 1.66-1.60 (m, 1H, ***H6***), 1.53 (s, 3H, ***H17***), 1.28 (s, 3H, ***H16***), 1.14 (s, 3H, ***H19***).

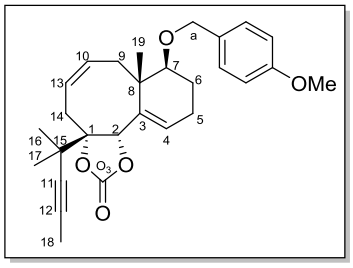
^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm: 159.3 (***C$_{Ar}$***), 154.2 (***CO$_3$***), 146.1 (***C11***), 138.1 (***C12***), 134.9 (***C3***), 130.5 (***C$_{Ar}$***), 129.9 (***C$_{Ar}$***), 127.9 (***C4***), 127.4 (***C10***), 115.6 (***C13***), 113.8 (***C$_{Ar}$***), 93.3 (***C1***), 78.9 (***C2***), 74.9 (***C7***), 69.8 (***Ca***), 55.3 (***OMe***), 47.7 (***C8***), 41.0 (***C15***), 32.6 (***C9***), 30.6 (***C14***), 25.1 (***C16***), 24.2 (***C5***), 21.7 (***C19***), 21.5 (***C6***), 21.2 (***C16***), 18.5 (***C18***).

IR (ν, cm^{-1}): 3054, 2980, 2934, 1797, 1620, 1458, 1420, 1242, 1025.

HRMS (ESI) Calcd for [M+Na]$^+$: *m/z* 473.2298, found 473.2278.

[α]$^{21}_{D}$: +120 (*c* 1.0, $CHCl_3$).

(3S,7S,8S,11S,Z)-8-((4-methoxybenzyl)oxy)-7-methyl-3-(2-methylpent-3-yn-2-yl)-3,4,7,7,8,9,10,11-octahydrobenzo[3,4]cycloocta[1,2][1,3]dioxol-2-one (3.31)



^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm: 7.25 (d, *J* = 8.7 Hz, 2H, ***H$_{Ar}$***), 6.88 (d, *J* = 8.7 Hz, 2H, ***H$_{Ar}$***), 5.84-5.75 (m, 2H, ***H4***, ***H13***), 5.64-5.56 (m, 1H, ***H10***), 5.31 (s, 1H, ***H2***), 4.59 (d, *J* = 11.8 Hz, 1H,

Ha), 4.37 (d, *J* = 11.8 Hz, 1H, ***Ha***), 3.82 (s, 3H, ***OMe***), 3.28 (dd, *J* = 4.2, 2.2 Hz, 1H, ***H7***), 2.60 (dd, *J* = 13.7, 10.9 Hz, 1H, ***H14***), 2.53 (dd, *J* = 13.7, 7.3 Hz, 1H, ***H14***), 2.35-2.27 (m, 2H, ***H9***, ***H5***), 2.20 (ddt, *J* = 19.1, 6.3, 3.1 Hz, 1H, ***H5***), 1.93-1.82 (m, 3H, 2***H6***, ***H9***), 1.73 (s, 3H, ***H18***), 1.39 (s, 3H, ***H16*** or ***H17***), 1.33 (s, 3H, ***H16*** or ***H17***), 1.15 (s, 3H, ***H19***).

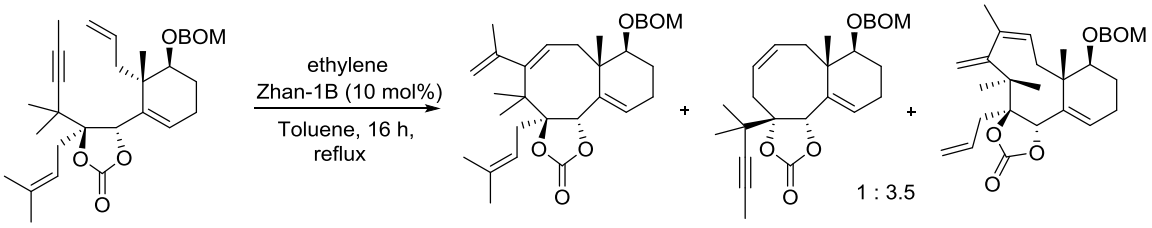
^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 159.0 (***C$_{Ar}$***), 155.0 (***CO$_3$***), 136.9 (***C3***), 131.1 (***C$_{Ar}$***), 129.1 (***C$_{Ar}$***), 128.8 (***C10***), 126.9 (***C13***), 126.6 (***C4***), 113.7 (***C$_{Ar}$***), 91.1 (***C1***), 83.2 (***C11***), 82.0 (***C7***), 80.6 (***C2***), 77.2 (***C12***), 70.3 (***Ca***), 55.3 (***OMe***), 43.8 (***C8***), 39.5 (***C9***), 39.2 (***C15***), 32.1 (***C14***), 25.6, 24.9 (***C16***, ***C17***), 21.7 (***C5***), 19.7 (***C6***), 19.2 (***C19***), 3.7 (***C18***).

IR (ν, cm^{-1}): 3042, 2980, 2943, 2832, 1800, 1612, 1497, 1458, 1257, 1187, 1041.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 473.2298, found 473.2277.

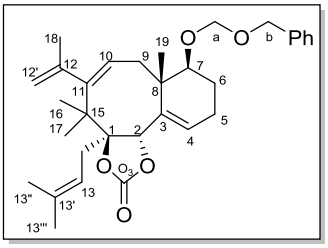
$[\alpha]^{21}_D$: +90.0 (*c* 1.0, $CHCl_3$).

(3S,7S,8S,11S,Z)-8-((Benzyloxy)methoxy)-4,4,7-trimethyl-3-(3-methylbut-2-en-1-yl)-5-(prop-1-en-2-yl)-3,4,7,7,8,9,10,11-octahydrobenzo[3,4]cycloocta[1,2][1,3]dioxol-2-one (3.32) and (3S,8S,9S,12S,Z)-3-Allyl-9-((benzyloxy)methoxy)-4,4,6,8-tetramethyl-5-methylene-3,5,8,8,9,10,11,12-octahydro-4H-benzo[3,4]cyclonona[1,2][1,3]dioxol-2-one (3.33)



Ethylene was bubbled for 2 min through a thoroughly degassed (using the freeze-thaw pump technique) solution of precursor **3.19** (20 mg, 39 µmol) in toluene (13 mL) and Zhan-1B catalyst (3 mg, 4 µmol, 0.1 equiv) was added then ethylene was bubbled through the reaction mixture for another 2 min. The resulting mixture was refluxed under an ethylene atmosphere for 2.5 h. The resulting mixture was allowed to cool down and the solvent was removed *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 85/15) to afford the title bicycle **3.32** (6.0 mg, 12 µmol, 30%) and a 1:3.5 mixture of **3.27** / **3.33** (13 mg, 27 µmol, 70%) as colourless oils.

(3S,7S,8S,11S,Z)-8-((Benzyloxy)methoxy)-4,4,7-trimethyl-3-(3-methylbut-2-en-1-yl)-5-(prop-1-en-2-yl)-3,4,7,7,8,9,10,11-octahydrobenzo[3,4]cycloocta[1,2][1,3]dioxol-2-one (3.32)



Chemical Formula: $C_{32}H_{42}O_5$

MW: 506,68

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 7.36-7.29 (m, 5H, ***H_{Ar}***), 6.07 (t, *J* = 3.6 Hz, 1H, ***H4***), 5.57 (dd, *J* = 10.7, 8.6 Hz, 1H, ***H10***), 5.38 (s, 1H, ***H2***), 5.23 (tq, *J* = 7.2, 0.9 Hz, 1H, ***H13***), 4.95 (d, *J* = 7.1 Hz, 1H, ***Ha***), 4.82 (d, *J* = 7.1 Hz, 1H, ***Ha***), 4.80-4.76 (m, 1H, ***H12'***), 4.69 (d, *J* = 11.7 Hz, 1H, ***Hb***), 4.65 (d, *J* = 11.7 Hz, 1H, ***Hb***), 4.53 (d, *J* = 1.5 Hz, 1H, ***H12'***), 3.71 (dd, *J* = 12.1, 4.4 Hz, 1H, ***H7***), 2.61 (dd, *J* = 15.1, 7.2 Hz, 1H, ***H14***), 2.54-2.45 (m, 2H, ***H9***, ***H14***), 2.40-2.32 (m, 1H, ***H5***), 2.29 (m, *J* = 16.9, 10.7 Hz, 1H, ***H9***), 2.24-2.19 (m, 1H, ***H5***), 2.08 (m, 1H, ***H6***), 1.88-1.79 (m, 1H, ***H6***), 1.77 (s, 3H, ***H18***), 1.72 (d, *J* = 0.9 Hz, 3H, ***H13"***), 1.59 (s, 3H, ***H13'''***), 1.55 (s, 3H, ***H16*** or ***H17***), 1.39 (s, 3H, ***H16*** or ***H17***), 1.13 (s, 3H, ***H19***).

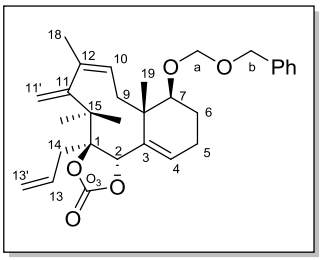
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 154.0 (***CO_3***), 150.3 (***C11***), 150.1 (***C12***), 137.7 (***C_{Ar}***), 136.3 (***C13'***), 134.6 (***C3***), 128.4 (***C_{Ar}***), 127.8 (***C4***), 127.7 (***C_{Ar}***), 127.7 (***C_{Ar}***), 127.6 (***C10***), 117.2 (***C13***), 113.6 (***C12'***), 93.9 (***C1***), 93.8 (***C21***), 80.9 (***C2***), 76.2 (***C7***), 70.1 (***C22***), 43.8 (***C8***), 43.2 (***C15***), 33.6 (***C9***), 30.2 (***C14***), 26.2 (***C18***), 26.1 (***C16*** or ***C17***), 26.0 (***C13"***), 23.9 (***C5***), 23.7 (***C19***), 23.4 (***C16*** or ***C17***), 23.1 (***C6***), 18.4 (***C13'''***).

IR (ν, cm^{-1}): 3056, 3025, 2998, 2921, 2284, 1799, 1686, 1521, 1436, 1265, 1025.

HRMS (CI/ISO) Calcd for $[M+H]^+$: *m/z* 507.3110, found 507.3114.

$[\alpha]^{25}_D$: +94.0 (*c* 1.0, $CHCl_3$).

(3S,8S,9S,12S,Z)-3-Allyl-9-((benzyloxy)methoxy)-4,4,6,8-tetramethyl-5-methylene-3,5,8,8,9,10,11,12-octahydro-4H-benzo[3,4]cyclonona[1,2][1,3]dioxol-2-one (3.33)



Chemical Formula: $C_{30}H_{38}O_5$

MW: 478,63

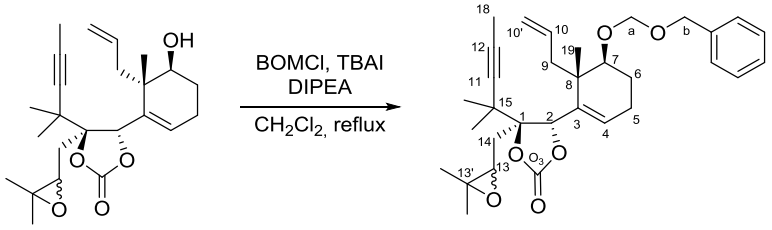
^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm: 7.40-7.33 (m, 4H, ***H_{Ar}***), 7.33-7.29 (m, 1H, ***H_{Ar}***), 5.99 (t, *J* = 4.0 Hz, 1H, ***H4***), 5.73-5.59 (m, 2H, ***H13***, ***H10***), 5.16 (s, 1H, ***H2***), 5.10-5.02 (m, 3H, 2***H13'***, ***H11'***), 4.99 (s, 1H, ***H11'***), 4.86 (d, *J* = 7.1 Hz, 1H, ***H1***), 4.77 (d, *J* = 7.1 Hz, 1H, ***Ha***), 4.68-4.59 (m, 2H, ***Hb***), 3.75 (dd, *J* = 7.8, 2.6 Hz, 1H, ***H7***), 2.73-2.58 (m, 2H, ***H9***), 2.42-2.33 (m, 1H, ***H14***), 2.29-2.22 (m, 1H, ***H5***), 2.21-2.09 (m, 2H, ***H14***, ***H5***), 1.98-1.87 (m, 1H, ***H6***), 1.91 (s, 3H, ***H18***), 1.85-1.76 (m, 1H, ***H6***), 1.32 (s, 3H, ***H17***), 1.24 (s, 3H, ***H19***), 1.23 (s, 3H, ***H16***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 154.8 (***CO_3***), 149.8 (***C11***), 139.6 (***C3***), 138.2 (***C12***), 137.8 (***C_{Ar}***), 133.5 (***C13***), 130.6 (***C4***), 128.4 (***C_{Ar}***), 127.8 (***C_{Ar}***), 127.7 (***C_{Ar}***), 123.0 (***C10***), 118.3 (***C13'***), 113.1 (***C11'***), 98.3 (***C1***), 94.0 (***Ca***), 77.6 (***C7***), 76.4 (***C2***), 69.8 (***Cb***), 52.9 (***C15***), 42.9 (***C14***), 42.2 (***C8***), 38.9 (***C9***), 23.3 (***C18***), 23.1 (***C16***), 22.7 (***C5***), 22.3 (***C6***), 21.1 (***C19***), 18.9 (***C17***).

IR (ν, cm^{-1}): 3045, 2972, 2934, 1794, 1458, 1327, 1272, 1180, 1033.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 501.2611, found 501.2602.

(4S,5S)-5-((5S,6S)-6-Allyl-5-((benzyloxy)methoxy)-6-methylcyclohex-1-en-1-yl)-4-((3,3-dimethyloxiran-2-yl)methyl)-4-(2-methylpent-3-yn-2-yl)-1,3-dioxolan-2-one (3.34)



Chemical Formula: $C_{32}H_{42}O_6$

MW: 522,68

To a solution of alcohol **3.14** (75 mg, 0.19 mmol) in CH_2Cl_2 (5 mL) were added DIPEA (0.98 mL, 5.6 mmol, 30 equiv), TBAI (0.17 g, 0.46 mmol, 2.5 equiv) and BOMCl (0.34 mL, 75% solution, 1.9 mmol, 10 equiv). The reaction mixture was allowed to reflux for 16 h. After the mixture was cooled down to room temperature an aqueous solution of 1N NaOH (5 mL) was added and stirred for 5-10 min. The aqueous layer was extracted with Et_2O (3x5 mL), and the combined organic extracts were washed with a saturated aqueous solution of $CuSO_4$ (2x5 mL) The aqueous copper solution was extracted with Et_2O (3x10 mL) and the combined organic extracts were washed with brine (2x25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 9/1 to 7/3) to afford the protected alcohol **3.34** as a 1:1 mixture of diastereomers (98 mg, 0.19 mmol, 99%) as a colourless oil.

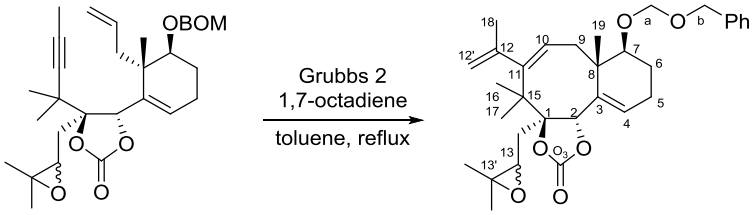
^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 7.39-7.28 (m, 5H, ***H_{Ar}***), 5.89 (t, *J* = 3.9 Hz, 0.5H, ***H4***), 5.77 (t, *J* = 3.8 Hz, 0.5H, ***H4***), 5.76-3.64 (m, 1H, ***H10***), 5.42 (s, 0.5H, ***H2***), 5.38 (s, 0.5H, ***H2***), 5.10-5.00 (m, 2H, ***H10'***), 4.84 (d, *J* = 7.1 Hz, 0.5H, ***Ha***), 4.84 (d, *J* = 7.1 Hz, 0.5H, ***Ha***), 4.75 (d, *J* = 7.1 Hz, 1H, ***Ha***), 4.63 (d, *J* = 7.0 Hz, 1H, ***Hb***), 4.63 (d, *J* = 5.9 Hz, 1H, ***Hb***), 3.77-3.71 (m, 1H, ***H7***), 3.10-3.01 (m, 1H, ***H13***), 2.55 (dd, *J* = 16.0, 4.1 Hz, 0.5H, ***H14***), 2.50-2.41 (m, 1.5H, ***H9***, 0.5***H14***), 2.34-2.24 (m, 1H, ***H5***), 2.23-2.09 (m, 2.5H, ***H5***, ***H9***, 0.5***H14***), 1.95-1.80 (m, 2.5H, 2***H6***, 0.5***H14***), 1.78 (s, 1.5H, ***H18***), 1.77 (s, 1.5H, ***H18***), 1.44 (s, 1.5H, ***Me***), 1.38 (s, 1.5H, ***Me***), 1.35 (s, 1.5H, ***Me***), 1.33 (s, 1.5H, ***Me***), 1.33 (s, 1.5H, ***Me***), 1.31 (s, 1.5H, ***Me***), 1.28 (s, 1.5H, ***Me***), 1.28 (s, 1.5H, ***Me***), 1.27 (s, 1.5H, ***Me***), 1.24 (s, 1.5H, ***Me***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 154.6 (***CO_3***), 154.5 (***CO_3***), 138.6 (***C3***), 138.0 (***C3***), 138.0 (***C_{Ar}***), 137.8 (***C_{Ar}***), 133.7 (***C10***), 133.4 (***C10***), 131.8 (***C4***), 130.8 (***C4***), 128.6 (***C_{Ar}***), 128.5 (***C_{Ar}***), 128.4 (***C_{Ar}***), 127.8 (***C_{Ar}***), 127.7 (***C_{Ar}***), 127.7 (***C_{Ar}***), 127.6 (***C_{Ar}***), 127.0 (***C_{Ar}***), 118.3 (***C10'***), 118.1 (***C10'***), 93.9 (***Ca***), 93.9 (***Ca***), 89.2 (***C1***), 89.1 (***C1***), 82.8 (***C2***), 82.6 (***C11*** or ***C12***), 82.4 (***C11*** or ***C12***), 81.9 (***C2***), 80.0 (***C7***), 78.1 (***C7***), 69.8 (***Cb***), 69.8 (***Cb***), 60.5 (***C13'***), 59.7 (***C13***), 59.5 (***C13***), 58.7 (***C13'***), 44.3 (***C9***), 43.8 (***C9***), 41.9 (***C8***), 41.7 (***C8***), 41.7 (***C15***), 41.6 (***C15***), 32.7 (***C14***), 31.7 (***C14***), 24.7 (***Me***), 24.6 (***Me***), 24.5 (***Me***), 24.5 (***Me***), 24.2 (***Me***), 24.1 (***Me***), 22.4 (***C5***), 22.1 (***C5***), 21.9 (***C6***), 21.6 (***C6***), 20.8 (***Me***), 20.7 (***Me***), 19.1 (***Me***), 19.0 (***Me***), 3.6 (***C18***), 3.5 (***C18***).

IR (ν, cm^{-1}): 3056, 2922, 2365, 1799, 1617, 1558, 1473, 1266, 1040.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 545.2874, found 545.2849.

(3S,7S,8S,11S,Z)-8-((Benzyloxy)methoxy)-3a-((3,3-dimethyloxiran-2-yl)methyl)-4,4,7-trimethyl-5-(prop-1-en-2-yl)-3,4,7,7,8,9,10,11-octahydrobenzo[3,4]cycloocta[1,2][1,3]dioxol-2-one (3.35)



Chemical Formula: $C_{32}H_{42}O_6$

MW: 522,68

A solution of precursor **3.34** (45 mg, 86 µmol), 1,7-octadiene (50 µL, 0.34 mmol, 4 equiv) in toluene (25 mL) was thoroughly degassed under argon (using the freeze-thaw pump technique) and second-generation Grubbs' catalyst (15 mg, 17 µmol, 0.2 equiv) was added and the mixture was stirred at reflux for 24 h. The resulting mixture was allowed to cool down and the solvent was removed *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 8/2) to afford the title bicycle compound **3.35** (8.0 mg, 18 µmol, 18%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 7.39-7.29 (m, 5H, ***H_{Ar}***), 5.88 (dd, *J* = 4.6, 3.3 Hz, 0.5H, ***H4***), 5.78 (dd, *J* = 4.7, 3.1 Hz, 0.5H, ***H4***), 5.67-5.57 (m, 1H, ***H10***), 5.25 (q, *J* = 1.7 Hz, 0.5H, ***H12'***), 5.25 (q, *J* = 1.7 Hz, 0.5H, ***H12'***), 5.17 (q, *J* = 1.7 Hz, 0.5H, ***H12'***), 5.17 (q, *J* = 1.7 Hz, 0.5H, ***H12'***), 5.05 (s, 0.5H, ***H2***), 5.02 (s, 0.5H, ***H2***), 4.82 (m, 1H, ***Ha***), 4.69 (d, *J* = 7.2 Hz, 1H, ***Ha***), 4.65-4.60 (m, 1H, ***Hb***), 4.60-4.55 (m, 1H, ***Hb***), 3.68 (dd, *J* = 10.1, 3.2 Hz, 0.5H, ***H7***), 3.65 (dd, *J* = 10.2, 3.1 Hz, 0.5H, ***H7***), 3.09 (dd, *J* = 5.6, 4.5 Hz, 0.5H, ***H13***), 3.04 (dd, *J* = 6.5, 4.1 Hz, 0.5H, ***H13***), 2.39-2.16 (m, 4H, ***CH_2***), 1.99-1.91 (m, 1.5H, ***CH_2***), 1.78-1.72 (m, 1.5H, ***CH_2***), 1.72-1.66 (m, 1H, ***H9***), 1.65-1.62 (m, 3H, ***H18***), 1.44 (s, 1.5H, ***Me***), 1.42 (s, 1.5H, ***Me***), 1.33 (s, 1.5H, ***Me***), 1.31 (s, 3H, 2***Me***), 1.31 (s, 1.5H, ***Me***), 1.27 (s, 1.5H, ***Me***), 1.26 (s, 1.5H, ***Me***), 1.25 (s, 1.5H, ***Me***), 1.24 (s, 1.5H, ***Me***).

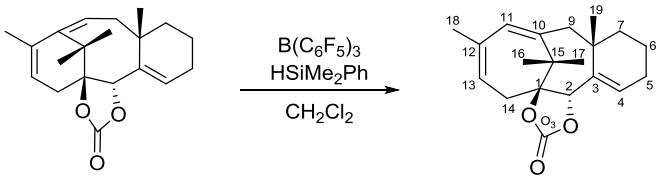
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 154.7 (***CO_3***), 154.7 (***CO_3***), 138.6 (***Cquat***), 138.0 (***C3***), 137.9 (***C3***), 137.7 (***Cquat***), 136.7 (***C12'***), 136.4 (***C12'***), 131.1 (***C4***), 130.2 (***C4***), 128.4 (***C_{Ar}***), 128.4 (***C_{Ar}***), 127.8 (***Cquat***), 127.8 (***Cquat***), 127.7 (***C_{Ar}***), 127.6 (***C_{Ar}***), 127.6 (***C_{Ar}***), 127.6 (***C_{Ar}***), 127.2 (***C10***), 126.9 (***C10***), 93.3 (***Ca***), 93.3 (***Ca***), 89.8 (***C1***), 89.7 (***C1***), 80.8 (***C2***), 80.1 (***C2***), 79.2 (***C7***), 79.1 (***C7***), 69.5 (***Cb***), 69.4 (***Cb***), 60.4 (***C13'***), 59.8 (***C13'***), 59.5 (***C13***), 59.1 (***C13***), 45.2 (***C8*** or ***C15***), 45.2 (***C8*** or ***C15***), 41.4 (***C8*** or ***C15***), 41.1 (***C8*** or ***C15***), 31.3 (***C14***), 30.3 (***C14***), 25.0 (***Me***), 24.9

(***Me***), 24.8 (***Me***), 24.7 (***Me***), 24.6 (***C5***), 24.5 (***C5***), 23.7 (***C9***), 23.7 (***C9***), 22.7 (***C6***), 22.7 (***C6***), 19.1 (***Me***), 19.1 (***Me***), 18.8 (***Me***), 18.7 (***Me***), 18.5 (***Me***), 18.5 (***Me***).

IR (ν, cm^{-1}): 3054, 2976, 2926, 2252, 1795, 1671, 1456, 1379, 1266, 1115, 981.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 545.2874, found 545.2883.

(3S,9S,13S)-6,9,14,14-Tetramethyl-9,9,10,11,12,13-hexahydro-4H-3,8-methanobenzo[3,4]cyclodeca[1,2][1,3]dioxol-2-one (4.1)



Chemical Formula: $C_{20}H_{26}O_3$

MW: 314,43

To a solution of $B(C_6F_5)_3$ (2.5 mg, 4.8 µmol, 0.1 equiv) in CH_2Cl_2 (0.2 mL) were added $HSiMe_2Ph$ (10 µL, 58 µmol, 1.2 equiv) and a solution of triene **2.43** (15 mg, 48 µmol) in CH_2Cl_2 (0.3 mL). The reaction mixture was stirred at room temperature for 16h. The solvent was then concentrated *in vacuo*. The crude mixture was purified by flash chromatography (petroleum ether/Et_2O: 7/3) to afford the title tricycle **4.1** (12 mg, 37 µmol, 75%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.76 (t, *J* = 3.5 Hz, 1H, ***H4***), 5.64-5.57 (m, 2H, ***H11***, ***H13***), 5.45 (s, 1H, ***H2***), 2.62 (d, *J* = 16.1 Hz, 1H, ***H9***), 2.31 (dd, *J* = 14.9, 6.9 Hz, 1H, ***H14***), 2.19 (dd, *J* = 16.1, 1.3 Hz, 1H, ***H9***), 2.16-2.10 (m, 1H, ***H5***), 2.07-1.98 (m, 1H, ***H5***), 1.87 (dd, *J* = 14.9, 8.9 Hz, 1H, ***H14***), 1.79 (m, 1H, ***H6***), 1.72 (s, 3H, ***H18***), 1.67-1.61 (m, 1H, ***H6***), 1.65 (s, 3H, ***H17***), 1.53 (td, *J* = 13.4, 3.5 Hz, 1H, ***H7***), 1.29 (s, 3H, ***H16***), 1.28-1.25 (m, 1H, ***H7***), 1.18 (s, 3H, ***H19***).

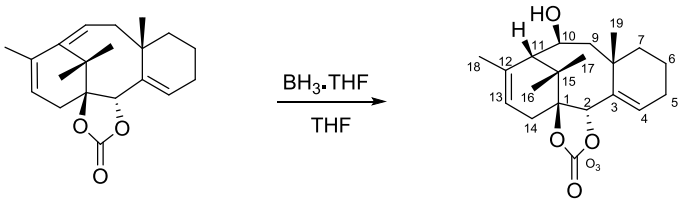
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 151.0 (***CO_3***), 147.5 (***C10***), 141.4 (***C12***), 136.2 (***C3***), 127.5 (***C11***), 125.4 (***C4***), 117.8 (***C13***), 91.5 (***C1***), 74.5 (***C2***), 58.7 (***C15***), 42.1 (***C8***), 37.8 (***C14***), 33.9 (***C7***), 32.8 (***C9***), 27.2 (***C19***), 26.5 (***C16***), 25.0 (***C17***), 23.8 (***C5***), 18.1 (***C6***), 12.9 (***C18***).

IR (ν, cm^{-1}): 3054, 3049, 2978, 2935, 2872, 1736, 1558, 1466, 1427, 1388, 1265, 1149, 1059.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 337.1774, found 337.1758.

$[\alpha]^{25}_D$: +160 (*c* 1.0, $CHCl_3$).

(3S,7S,8S,9S,13S)-8-Hydroxy-6,9,14,14-tetramethyl-7,8,9,9,10,11,12,13-octahydro-4H-3,7-methanobenzo[3,4]cyclodeca[1,2][1,3]dioxol-2-one (4.2)



Chemical Formula: $C_{20}H_{28}O_4$

MW: 332,44

To a solution of triene **2.40** (5.0 mg, 16 µmol) in THF (1 mL) was slowly added a solution of BH_3.THF complex (24 µL, 1 M in THF, 0.024 µmol, 1.5 equiv). The reaction mixture was stirred 20 min at room temperature. The reaction mixture was cooled down to 0°C and MeOH was added to quench excess of reagent, then a H_2O_2 (150 µL, 30% in water) followed by a 1N aqueous solution of NaOH (50 µL) were added. The reaction mixture was allowed to stir for 30 min, then water (3 mL) was added and the aqueous phase was extracted with EtOAc (3x10 mL). The organic extracts were combined and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/EtOAc: 8/2) to afford the title alcohol **4.2** (2.5 mg, 7.5 µmol, 47%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 5.88 (t, *J* = 3.6 Hz, 1H, ***H4***), 5.25 (s, 1H, ***H2***), 5.17 (tq, *J* = 3.0, 1.5 Hz, 1H, ***H13***), 4.24 (dd, *J* = 12.0, 4.7 Hz, 1H, ***H10***), 2.66-2.58 (m, 1H, ***H14***), 2.30-2.15 (m, 4H, ***H5***, ***H9***, ***H11***, ***H14***), 1.99-1.82 (m, 2H, ***H5***, ***H6***), 1.79 (m, 3H, ***H18***), 1.73 (dd, *J* = 15.3, 4.7 Hz, 1H, ***H9***), 1.70-1.65 (m, 2H, ***OH***, ***H6***), 1.55-1.49 (m, 1H, ***H7***), 1.46 (s, 3H, ***H17***), 1.40-1.34 (m, 1H, ***H7***), 1.19 (s, 3H, ***H16***), 1.13 (s, 3H, ***H19***).

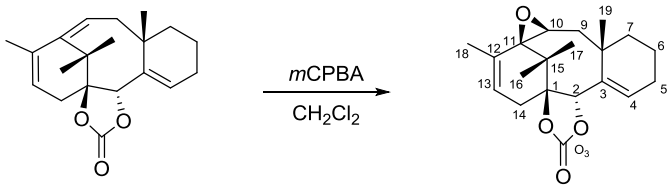
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 154.5 (***CO_3***), 133.8 (***C3***), 132.0 (***C12***), 125.4 (***C4***), 121.1 (***C13***), 90.0 (***C1***), 77.6 (***C2***), 68.5 (***C10***), 59.0 (***C11***), 48.0 (***C9***), 37.5 (***C15***), 35.3 (***C8***), 31.7 (***C8***), 29.7 (***C7***), 29.0 (***C14***), 28.9 (***C16***), 24.3 (***C5***), 23.0 (***C18***), 20.0 (***C17***), 18.0 (***C6***).

IR (ν, cm^{-1}): 3324, 3054, 2926, 2855, 1793, 1507, 1425, 1410, 1265, 1041.

HRMS (CI/ISO) Calcd for $[M+H]^+$: *m/z* 333.2066, found 333.2064.

$[\alpha]^{24}_D$: +116 (*c* 0.75, $CHCl_3$).

(4S,7S,10R,11S,12S)-10,12,13,13-Tetramethyl-1,3,4,11,12,1a-hexahydro-2H,8H-7,10-methanobenzo[3,4]oxireno[2',3':6,7]cyclodeca[1,2][1,3]dioxol-6-one (4.3)



Chemical Formula: $C_{20}H_{26}O_4$

MW: 330,42

To a solution of triene **2.40** (5 mg, 16 µmol) in CH_2Cl_2 (1 mL) was added *m*CPBA (5.5 mg, 0.024 µmol, 1.5 equiv). The reaction mixture was stirred 1 h at room temperature. A 10% aqueous solution of $NaHSO_3$ (2x2 mL) was then added and the aqueous phase was extracted with dichloromethane (3x5 mL). The combined organic extracts were washed a second time with a 10% aqueous solution of $NaHSO_3$ (10 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (15 mL) followed by brine (15 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 9/1) to afford the title vinyl epoxide **4.3** (3.2 mg, 10 µmol, 61%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 6.17 (dd, *J* = 5.6, 2.0 Hz, 1H, ***H4***), 5.26 (tq, *J* = 3.4, 1.8 Hz, 1H, ***H13***), 5.08 (s, 1H, ***H2***), 3.00 (ddq, *J* = 18.8, 3.4, 1.8 Hz, 1H, ***H14***), 2.65 (dd, *J* = 12.5, 4.2 Hz, 1H, ***H10***), 2.34 (ddq, *J* = 18.8, 3.4, 1.8 Hz, 1H, ***H14***), 2.17 (dtd, *J* = 18.5, 5.6, 1.3 Hz, 1H, ***H5***), 2.02 (dd, *J* = 14.2, 4.2 Hz, 1H, ***H9***), 1.97 (dddd, *J* = 18.5, 10.9, 6.6, 2.0 Hz, 1H, ***H5***), 1.90-1.83 (m, 1H, ***H6***), 1.82 (dd, *J* = 14.2, 12.5 Hz, 1H, ***H9***), 1.79-1.65 (m, 2H, ***H7***), 1.55-1.50 (m, 1H, ***H6***), 1.48 (q, *J* = 1.8 Hz, 3H, ***H18***), 1.35 (s, 3H, ***H16***), 1.24 (s, 3H, ***H17***), 1.21 (s, 3H, ***H19***).

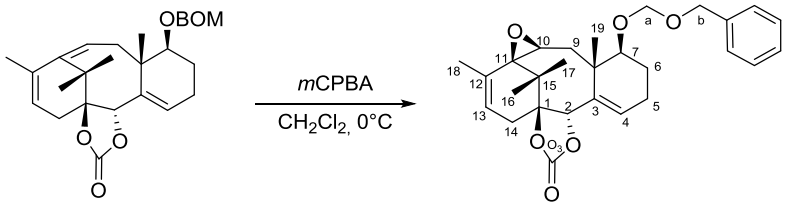
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 154.1 (***CO_3***), 137.6 (***C12***), 133.7 (***C3***), 130.8 (***C4***), 117.9 (***C13***), 91.4 (***C1***), 78.8 (***C2***), 64.9 (***C11***), 59.4 (***C10***), 39.2 (***C15***), 38.3 (***C8***), 37.7 (***C9***), 35.4 (***C6***), 30.3 (***C14***), 28.6 (***C19***), 25.0 (***C5***), 24.1 (***C16***), 18.9 (***C17***), 18.3 (***C7***), 15.7 (***C18***).

IR (ν, cm^{-1}): 3055, 3045, 2941, 1802, 1650, 1558, 1456, 1266, 1026.

HRMS (EI) Calcd for $[M]^+$: *m/z* 330.1831, found 330.1838.

$[\alpha]^{24}_D$: +48.0 (*c* 0.5, $CHCl_3$).

(1S,4S,7S,10R,11S,12S)-1-((Benzyloxy)methoxy)-10,12,13,13-tetramethyl-1,3,4,11,12,12-hexahydro-2H,8H-7,10-methanobenzo[3,4]oxireno[2',3':6,7]cyclodeca[1,2][1,3]dioxol-6-one (4.4)



Chemical Formula: $C_{28}H_{34}O_6$

MW: 466,57

To a solution of triene **3.17** (93 mg, 0.20 mmol) in CH_2Cl_2 (3 mL) was added at 0°C a solution of *m*CPBA (55 mg, 0.24 mmol, 1.2 equiv) in CH_2Cl_2 (1 mL). The resulting mixture was stirred at the same temperature for 30 min. The reaction mixture was washed with a 10% aqueous solution of Na_2SO_3 (2x4 mL), and the aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (25 mL), washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 8/2) to afford the title vinyl epoxide **4.4** (80 mg, 0.17 mmol, 86%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 7.38-7.29 (m, 5H, ***H_{Ar}***), 6.10 (dd, *J* = 5.3, 1.5 Hz, 1H, ***H4***), 5.20 (tq, *J* = 3.4, 1.7 Hz, 1H, ***H13***), 5.10 (s, 1H, ***H2***), 4.97 (d, *J* = 7.3 Hz, 1H, ***Ha***), 4.82 (d, *J* = 7.3 Hz, 1H, ***Ha***), 4.73 (d, *J* = 11.4 Hz, 1H, ***Hb***), 4.64 (d, *J* = 11.4 Hz, 1H, ***Hb***), 3.86 (dd, *J* = 12.1, 3.7 Hz, 1H, ***H7***), 2.96 (ddq, *J* = 18.8, 3.4, 1.7 Hz, 1H, ***H14***), 2.72 (dd, *J* = 14.4, 4.0 Hz, 1H, ***H9***), 2.63 (dd, *J* = 12.5, 4.0 Hz, 1H, ***H10***), 2.34 (ddq, *J* = 18.8, 3.4, 1.7 Hz, 1H, ***H14***), 2.30-2.24 (m, 1H, ***H5***), 2.11 (dddd, *J* = 18.3, 11.7, 6.3, 1.5 Hz, 1H, ***H6***), 2.03-1.97 (m, 1H, ***H6***), 1.75 (dddd, *J* = 18.3, 12.1, 8.5, 6.3 Hz, 1H, ***H6***), 1.56 (dd, *J* = 14.4, 12.5 Hz, 1H, ***H9***), 1.40 (q, *J* = 1.7 Hz, 3H, ***H18***), 1.35 (s, 3H, ***H16***), 1.26 (s, 3H, ***H17***), 1.21 (s, 3H, ***H19***).

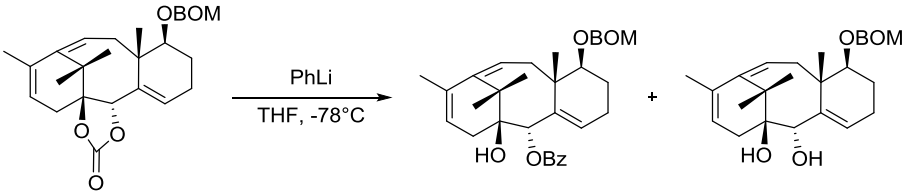
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 153.9 (***CO_3***), 137.8 (***C12***), 137.4 (***C_{Ar}***), 133.7 (***C3***), 129.6 (***C4***), 128.6 (***C_{Ar}***), 127.9 (***C_{Ar}***), 127.9 (***C_{Ar}***) 117.7 (***C13***), 93.2 (***Ca***), 91.4 (***C1***), 78.4 (***C2***), 75.0 (***C7***), 70.4 (***Cb***), 64.8 (***C11***), 58.8 (***C10***), 43.2 (***C8***), 39.2 (***C15***), 31.7 (***C9***), 30.3 (***C14***), 24.2 (***C5***), 24.2 (***C16***), 23.0 (***C19***), 22.6 (***C6***), 18.9 (***C17***), 15.7 (***C18***).

IR (ν, cm^{-1}): 3053, 2980, 2944, 2834, 1798, 1466, 1427, 1265, 1018.

HRMS (CI/ISO) Calcd for $[M+H]^+$: *m/z* 467.2434, found 467.2433.

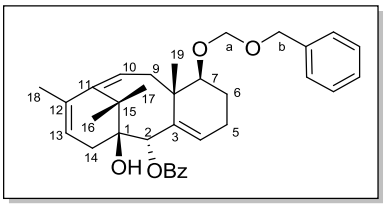
$[\alpha]^{25}_D$: +82.0 (*c* 1.0, $CHCl_3$).

(1S,5S,6S,12S,Z)-1-((Benzyloxy)methoxy)-6-hydroxy-9,12,13,13-tetramethyl-1,2,3,5,6,7,12,12-octahydro-6,10-methanobenzo[10]annulen-5-yl benzoate (4.5) and (1S,5S,6S,12S,Z)-1-((Benzyloxy)methoxy)-9,12,13,13-tetramethyl-1,3,5,7,12,12-hexahydro-6,10-methanobenzo[10]annulene-5,6(2H)-diol (4.6)



To a solution of **3.17** (10 mg, 22 µmol) in THF (2 mL) at -78°C was added phenyllithium (0.1 mL, 2 M in nBu$_2$O, 0.2 mmol, 10 equiv). The mixture was stirred at this temperature for 2 h. A solution of saturated aqueous $NaHCO_3$ (5 mL) was then added and the aqueous phase was extracted with Et_2O (3x10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 8/2 to 4/6) to afford the title benzoate **4.5** (2.0 mg, 3.7 µmol, 17%) and the diol **4.6** (4.7 mg, 11 µmol, 50%) as colourless oils.

(1S,5S,6S,12S,Z)-1-((benzyloxy)methoxy)-6-hydroxy-9,12,13,13-tetramethyl-1,2,3,5,6,7,12,12-octahydro-6,10-methanobenzo[10]annulen-5-yl benzoate (4.5)



Chemical Formula: $C_{34}H_{40}O_5$

MW: 528,69

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 7.98 (dd, *J* = 1.3, 8.3 Hz, 2H, ***H_{Ar}***), 7.54-7.46 (m, 1H, ***H_{Ar}***), 7.41-7.36 (m, 2H, ***H_{Ar}***), 7.29-7.26 (m, 4H, ***H_{Ar}***), 7.22-7.19 (m, 1H, ***H_{Ar}***), 5.88 (dd, *J* = 5.7, 2.5 Hz, 1H, ***H4***), 5.81 (s, 1H, ***H2***), 5.61 (dd, *J* = 12.2, 6.4 Hz, 1H, ***H10***), 4.95 (tq, *J* = 3.4, 1.6 Hz, 1H, ***H13***), 4.85 (d, *J* = 7.1 Hz, 1H, ***Ha***), 4.73 (d, *J* = 7.1 Hz, 1H, ***Ha***), 4.66 (d, *J* = 11.7 Hz, 1H, ***Hb***), 4.57 (d, *J* = 11.7 Hz, 1H, ***Hb***), 3.63 (dd, *J* = 10.7, 3.0 Hz, 1H, ***H7***), 2.86 (ddq, *J* = 18.8, 3.6, 2.0 Hz, 1H, ***H14***), 2.78 (dd, *J* = 13.9, 12.2 Hz, 1H, ***H9***), 2.43 (dd, *J* = 13.9, 6.4 Hz, 1H, ***H9***), 2.05-

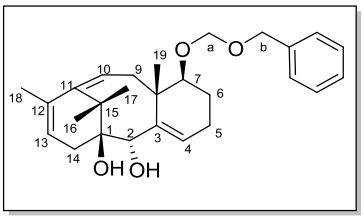
1.98 (m, 1H, ***H14***), 1.98-1.93 (m, 2H, ***OH***, ***H5***), 1.83-1.71 (m, 2H, ***H5***, ***H6***), 1.69 (q, *J* = 1.6 Hz, 3H, ***H18***), 1.54-1.50 (m, 1H, ***H6***), 1.52 (s, 3H, ***H17***), 1.23 (s, 3H, ***H19***), 1.19 (s, 3H, ***H16***).

^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm: 165.7 (***COPh***), 149.8 (***C11***), 141.4 (***C3***), 137.9 (***C$_{Ar}$***), 136.7 (***C12***), 133.0 (***C$_{Ar}$***), 130.6 (***C$_{Ar}$***), 129.7 (***C$_{Ar}$***), 128.5 (***C$_{Ar}$***), 127.9 (***C$_{Ar}$***), 127.6 (***C4***), 126.9 (***C$_{Ar}$***), 126.5 (***C$_{Ar}$***), 124.0 (***C10***), 117.8 (***C13***), 93.5 (***Ca***), 81.3 (***C1***), 79.1 (***C7***), 74.8 (***C2***), 69.9 (***Cb***), 48.1 (***C8***), 43.1 (***C15***), 34.9 (***C9***), 33.6 (***C14***), 25.9 (***C16***), 24.2 (***C5***), 23.2 (***C6***), 23.0 (***C17***), 21.0 (***C19***), 18.4 (***C18***).

HRMS (ESI) Calcd for [M+Na]$^+$: *m/z* 551.2768, found 551.2759.

[α]$^{25}_D$: +160 (*c* 0.5, $CHCl_3$).

(1S,5S,6S,12S,Z)-1-((Benzyloxy)methoxy)-9,12,13,13-tetramethyl-1,3,5,7,12,12-hexahydro-6,10-methanobenzo[10]annulene-5,6(2H)-diol (4.6)



Chemical Formula: $C_{27}H_{36}O_4$

MW: 424,58

^{1}H NMR (500 MHz, *CDCl$_3$*) δ ppm: 7.40-7.34 (m, 4H, ***H$_{Ar}$***), 7.33-7.29 (m, 1H, ***H$_{Ar}$***), 5.86 (dd, *J* = 5.8, 2.1 Hz, 1H, ***H4***), 5.62 (dd, *J* = 12.4, 6.3 Hz, 1H, ***H10***), 4.97 (tq, *J* = 3.6, 1.6 Hz, 1H, ***H13***), 4.95 (d, *J* = 7.1 Hz, 1H, ***Ha***), 4.82 (d, *J* = 7.1 Hz, 1H, ***Ha***), 4.74 (d, *J* = 11.5 Hz, 1H, ***Hb***), 4.66 (d, *J* = 11.5 Hz, 1H, ***Hb***), 4.39 (d, *J* = 1.1 Hz, 1H, ***H2***), 3.71 (dd, *J* = 11.0, 3.0 Hz, 1H, ***H7***), 2.83 (ddq, *J* = 18.8, 3.6, 1.6 Hz, 1H, ***H14***), 2.70 (dd, *J* = 13.4, 12.4 Hz, 1H, ***H9***), 2.56 (s, 1H, ***OH1***), 2.48 (dd, *J* = 13.4, 6.3 Hz, 1H, ***H9***), 2.22 (d, *J* = 1.1 Hz, 1H, ***OH2***), 2.14-2.07 (m, 1H, ***H5***), 1.93 (ddq, *J* = 18.8, 3.6, 1.6 Hz, 1H, ***H14***), 1.89-1.80 (m, 2H, ***H5***, ***H6***), 1.73 (q, *J* = 1.6 Hz, 3H, ***H18***), 1.65-1.59 (m, 1H, ***H6***), 1.49 (s, 3H, ***H17***), 1.24 (s, 3H, ***H19***), 1.22 (s, 3H, ***H16***).

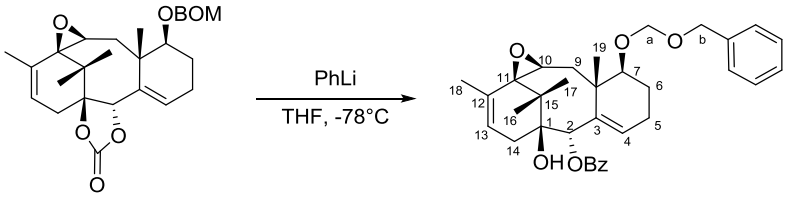
^{13}C NMR (126 MHz, *CDCl$_3$*) δ ppm: 150.3 (***C11***), 144.9 (***C3***), 137.9 (***C$_{Ar}$***), 136.6 (***C12***), 128.5 (***C$_{Ar}$***), 127.8 (***C$_{Ar}$***), 127.7 (***C$_{Ar}$***), 124.8 (***C4***), 123.8 (***C10***), 118.3 (***C13***), 93.6 (***Ca***), 81.6 (***C1***), 78.9 (***C7***), 71.4 (***C2***), 69.9 (***Cb***), 48.3 (***C8***), 43.0 (***C15***), 34.6 (***C9***), 33.3 (***C14***), 25.9 (***C16***), 24.2 (***C5***), 23.5 (***C6***), 22.8 (***C17***), 20.5 (***C19***), 18.4 (***C18***).

IR (ν, cm^{-1}): 3335, 3054, 2986, 1558, 1419, 1265, 1040.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 447.2506, found 447.2500.

$[\alpha]^{25}_D$: +139 (*c* 0.75, $CHCl_3$).

(1R,5S,6S,10S,10S,11S)-10-((Benzyloxy)methoxy)-5-hydroxy-2,10,12,12-tetramethyl-5,6,8,9,10,10,11,11-octahydro-4H-1,5-methanobenzo[4,5]cyclodeca[1,2]oxiren-6-yl benzoate (4.7)



Chemical Formula: $C_{34}H_{40}O_6$

MW: 544,69

To a solution of vinyl epoxide **4.4** (70 mg, 0.15 mmol) in THF (5 mL) at -78°C was added phenyllithium (0.75 mL, 2 M in nBu_2O, 1.5 mmol, 10 equiv). The mixture was stirred at this temperature for 2 h. A solution of saturated aqueous $NaHCO_3$ (5 mL) was then added and the aqueous phase was extracted with Et_2O (3x10 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (petroleum ether/Et_2O: 8/2) to afford the title benzoate **4.7** (72 mg, 0.13 mmol, 88%) as a colourless oil.

^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm: 8.10-8.05 (m, 2H, ***H_{Ar}***), 7.64-7.55 (m, 1H, ***H_{Ar}***), 7.53-7.44 (m, 2H, ***H_{Ar}***), 7.39-7.35 (m, 4H, ***H_{Ar}***), 7.34-7.28 (m, 1H, ***H_{Ar}***), 6.16 (dd, *J* = 5.8, 2.4 Hz, 1H, ***H4***), 5.94 (s, 1H, ***H2***), 5.37 (tq, *J* = 3.3, 1.8 Hz, 1H, ***H13***), 4.93 (d, *J* = 7.2 Hz, 1H, ***Ha***), 4.81 (d, *J* = 7.2 Hz, 1H, ***Ha***), 4.72 (d, *J* = 11.5 Hz, 1H, ***Hb***), 4.64 (d, *J* = 11.5 Hz, 1H, ***Hb***), 3.81 (dd, *J* = 10.5, 3.1 Hz, 1H, ***H7***), 3.08 (ddq, *J* = 18.7, 3.3, 1.8 Hz, 1H, ***H14***), 2.81 (dd, *J* = 12.2, 4.4 Hz, 1H, ***H10***), 2.49 (dd, *J* = 14.2, 4.4 Hz, 1H, ***H9***), 2.23-2.09 (m, 2H, ***H5***, ***H14***), 2.07 (s, 1H, ***OH***), 2.01-1.90 (m, 1H, ***H5***), 1.95 (dd, J = 14.2, 12.2 Hz, 1H, ***H9***), 1.89-1.80 (m, 1H, ***H6***), 1.69-1.56 (m, 1H, ***H6***), 1.46 (q, *J* = 1.8 Hz, 3H, ***H18***), 1.32 (s, 3H, ***H19***), 1.28 (s, 6H, ***H16***, ***H17***).

^{13}C NMR (100 MHz, *$CDCl_3$*) δ ppm: 165.7 (***CO_3***), 140.2 (***C3***), 137.6 (***C_{Ar}***), 136.4 (***C12***), 133.1 (***C_{Ar}***), 130.4 (***C_{Ar}***), 129.7 (***C_{Ar}***), 128.8 (***C4***), 128.5 (***C_{Ar}***), 128.5 (***C_{Ar}***), 127.9 (***C_{Ar}***), 127.8 (***C_{Ar}***), 120.9 (***C13***), 93.6 (***Ca***), 79.8 (***C1***), 78.7 (***C7***), 74.1 (***C2***), 70.1 (***Cb***), 65.6 (***C11***), 60.3 (***C10***), 43.4

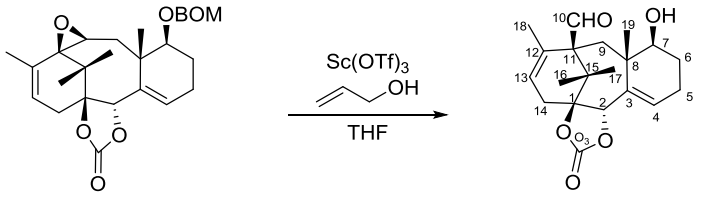
(***C8***), 41.0 (***C15***), 34.2 (***C9***), 33.1 (***C14***), 24.5 (***C16*** or ***C17***), 24.1 (***C5***), 23.1 (***C6***), 22.0 (***C19***), 19.2 (***C16*** or ***C17***), 16.0 (***C18***).

IR (ν, cm^{-1}): 3050, 2967, 2939, 2870, 1721, 1560, 1468, 1267, 1115, 1063.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 567.2717, found 567.2697.

$[\alpha]^{25}_D$: +226 (*c* 1.0, $CHCl_3$).

(3S,7R,8S,9S,12S)-9-Hydroxy-6,8,13,13-tetramethyl-2-oxo-8,8,9,10,11,12-hexahydro-3,7-methanobenzo[3,4]cyclonona[1,2][1,3]dioxole-7(4H)-carbaldehyde (4.8)



Chemical Formula: $C_{20}H_{26}O_5$

MW: 346,42

To a solution of vinyl epoxide **4.4** (7.0 mg, 15 µmol) in THF (0.5 mL) were added allyl alcohol (3.0 µL, 45 µmol, 3.0 equiv) and $Sc(OTf)_3$ (1.8 mg, 3.7 µmol, 0.25 equiv). The mixture was stirred at room temperature for 16 h without any conversion. The resulting mixture then heated at 60°C for 4h. A solution of saturated aqueous $NaHCO_3$ (2 mL) was then added and the aqueous phase was extracted with EtOAc (3x10 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/EtOAc: 9/1 to 6/4) to afford the title aldehyde **4.8** (1.5 mg, 4.2 µmol, 28%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 9.68 (s, 1H, ***H10***), 5.83 (t, *J* = 3.3 Hz, 1H, ***H4***), 5.48 (ddq, *J* = 4.4, 2.8, 1.3 Hz, 1H, ***H13***), 5.06 (s, 1H, ***H2***), 3.56 (dt, *J* = 10.7, 5.2 Hz, 1H, ***H7***), 2.70 (d, *J* = 17.0 Hz, 1H, ***H9***), 2.51-2.44 (m, 1H, ***H14***), 2.36-2.30 (m, 1H, ***H14***), 2.29-2.22 (m, 1H, ***H5***), 2.14-2.05 (m, 1H, ***H5***), 1.84-1.73 (m, 2H, ***H6***), 1.71 (s, 3H, ***H18***), 1.56 (d, *J* = 17.0 Hz, 1H, ***H9***), 1.36 (s, 3H, ***H17***), 1.17 (br s, 1H, ***OH***), 1.17 (s, 3H, ***H16***), 1.13 (s, 3H, ***H19***).

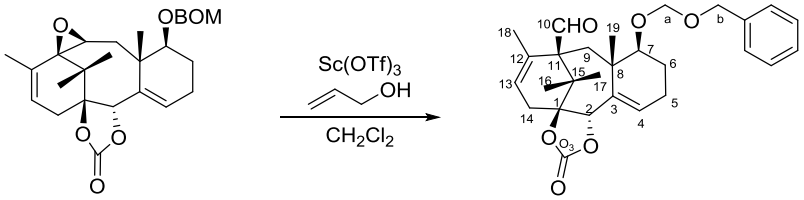
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 203.5 (***C10***), 153.6 (***CO_3***), 133.1 (***C3***), 132.0 (***C12***), 123.7 (***C13***), 121.7 (***C4***), 88.1 (***C1***), 78.2 (***C2***), 70.0 (***C7***), 59.3 (***C11***), 39.9 (***C8***), 39.5 (***C15***), 30.2 (***C14***), 29.8 (***C9***), 27.5 (***C6***), 24.7 (***C19***), 23.9 (***C5***), 21.0 (***C17***), 20.7 (***C18***), 17.8 (***C16***).

IR (ν, cm^{-1}): 3252, 3047, 2984, 2943, 1801, 1720, 1532, 1460, 1265, 1111, 1026.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 369.1672, found 369.1677.

$[\alpha]^{20}_D$: +18.0 (*c* 0.5, $CHCl_3$).

(3S,7R,8S,9S,12S)-9-((Benzyloxy)methoxy)-6,8,13,13-tetramethyl-2-oxo-8,8,9,10,11,12-hexahydro-3,7-methanobenzo[3,4]cyclonona[1,2][1,3]dioxole-7(4H)-carbaldehyde (4.9)



Chemical Formula: $C_{28}H_{34}O_6$

MW: 466,57

To a solution of vinyl epoxide **4.4** (8.0 mg, 17 µmol) in CH_2Cl_2 (0.5 mL) were added allyl alcohol (3.5 µL, 51 µmol, 3.0 equiv) and $Sc(OTf)_3$ (2.0 mg, 4.3 µmol, 0.25 equiv). The mixture was stirred at room temperature for 16 h. A solution of saturated aqueous $NaHCO_3$ (2 mL) was then added and the aqueous phase was extracted with EtOAc (3x5 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/EtOAc: 95/5 to 85/15) to afford the title aldehyde **4.9** (2.9 mg, 6.3 µmol, 37%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 9.65 (s, 1H, ***H10***), 7.38-7.28 (m, 5H, ***H_{Ar}***), 5.85 (dd, *J* = 3.9, 1.5 Hz, 1H, ***H4***), 5.55-5.45 (m, 1H, ***H13***), 5.05 (s, 1H, ***H2***), 4.88 (d, *J* = 7.2 Hz, 1H, ***Ha***), 4.77 (d, *J* = 7.2 Hz, 1H, ***Ha***), 4.66 (d, *J* = 11.8 Hz, 1H, ***Hb***), 4.63 (d, *J* = 11.8 Hz, 1H, ***Hb***), 3.42 (dd, *J* = 11.8, 3.9 Hz, 1H, ***H7***), 2.66 (d, *J* = 17.2 Hz, 1H, ***H9***), 2.49 (dd, *J* = 18.0, 3.1 Hz, 1H, ***H14***), 2.35-2.29 (m, 1H, ***H14***), 2.27-2.19 (m, 1H, ***H5***), 2.07-1.94 (m, 2H, ***H5***, ***H6***), 1.76-1.70 (m, 1H, ***H6***), 1.69 (s, 3H, ***H18***), 1.60 (d, *J* = 17.2 Hz, 1H, ***H9***), 1.35 (s, 3H, ***H17***), 1.21 (s, 3H, ***H19***), 1.16 (s, 3H, ***H16***).

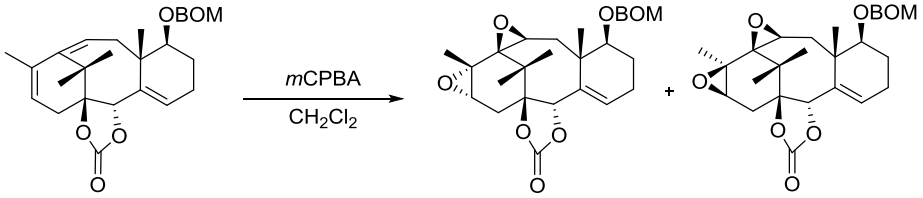
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 203.7 (***C10***), 153.7 (***CO_3***), 137.6 (***C_{Ar}***), 132.9 (***C12***), 131.3 (***C3***), 128.4 (***C_{Ar}***), 127.9 (***C_{Ar}***), 127.7 (***C_{Ar}***), 124.0 (***C13***), 121.6 (***C4***), 93.6 (***Ca***), 88.0 (***C1***), 78.3 (***C7***), 78.2 (***C2***), 70.0 (***Cb***), 59.5 (***C11***), 39.6 (***C8***), 39.4 (***C15***), 30.6 (***C9***), 30.1 (***C14***), 25.9 (***C16***), 24.3 (***C5***), 23.7 (***C6***), 21.0 (***C17***), 20.7 (***C18***), 17.9 (***C19***).

IR (ν, cm^{-1}): 3049, 2989, 2953, 1801, 1717, 1632, 1446, 1425, 1345, 1267, 1190, 1026.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 489.2248, found 489.2235.

$[\alpha]^{20}_D$: +32.0 (*c* 0.75, $CHCl_3$).

(1R,3S,6S,10S,10S,11S)-10-((Benzyloxy)methoxy)-1,10,12,12-tetramethyl-1,2,6,8,10,10,11,11-octahydro-3H,9H-1,3-methanobenzo[3,4]bis(oxireno)[2',3':6,7;2'',3'':8,9]cyclodeca[1,2][1,3]dioxol-5-one (4.10) and (4.11)

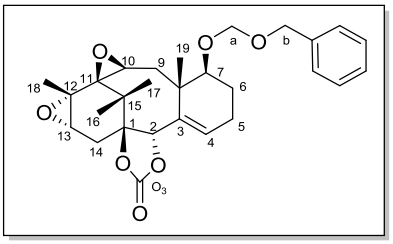


Chemical Formula: $C_{28}H_{34}O_7$

MW: 482,57

To a solution of triene **3.17** (50 mg, 0.11 mmol) in CH_2Cl_2 (3 mL) was added at 0°C a solution of *m*CPBA (76 mg, 0.33 mmol, 3.0 equiv) in CH_2Cl_2 (1 mL). The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was washed with a 10% aqueous solution of Na_2SO_3 (2x2 mL) and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) washed with brine (10 mL) and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 6/4) to afford the title epoxide **4.10** (37 mg, 77 µmol, 70%) and the epoxide **4.11** (3 mg, 6 µmol, 6%) as colourless oils.

(1R,1S,2S,3S,6S,10S,10S,11S)-10-((Benzyloxy)methoxy)-1b,10,12,12-tetramethyl-1b,2,6,8,10,10,11,11-octahydro-3H,9H-1,3-methanobenzo[3,4]bis(oxireno)[2',3':6,7;2'',3'':8,9]cyclodeca[1,2][1,3]dioxol-5-one (4.10)



^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 7.40-7.34 (m, 4H, ***H_{Ar}***), 7.33-7.28 (m, 1H, ***H_{Ar}***), 6.04 (dd, *J* = 4.9, 2.5 Hz, 1H, ***H4***), 4.97 (s, 1H, ***H2***), 4.96 (d, *J* = 7.1 Hz, 1H, ***Ha***), 4.83 (d, *J* = 7.1 Hz, 1H, ***Ha***), 4.74 (d, *J* = 11.6 Hz, 1H, ***Hb***), 4.65 (d, *J* = 11.6 Hz, 1H, ***Hb***), 4.03 (dd, *J* = 12.1, 3.9 Hz, 1H, ***H7***), 3.26 (d, *J* = 4.8 Hz, 1H, ***H13***), 3.05 (dd, *J* = 12.5, 4.1 Hz, 1H, ***H10***), 3.04 (d, *J* = 16.6 Hz, 1H, ***H14***), 2.66 (dd, *J* = 14.7, 4.1 Hz, 1H, ***H9***), 2.36-2.21 (m, 2H, ***H5***), 2.12 (dd, *J* = 16.6, 4.8 Hz, 1H, ***H14***), 2.06-1.99 (m, 1H, ***H6***), 1.77 (qd, *J* = 12.1, 6.9 Hz, 1H, ***H6***), 1.38 (s, 3H, ***H17***), 1.37 (m, *J* = 14.7, 12.5 Hz, 1H, ***H9***), 1.19 (s, 6H, ***H16***, ***H18***), 1.16 (s, 3H, ***H19***).

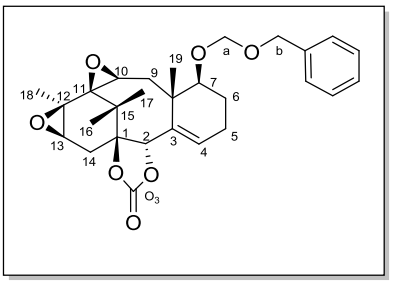
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 153.4 (***CO_3***), 137.6 (***C_{Ar}***), 132.4 (***C3***), 130.8 (***C4***), 128.5 (***C_{Ar}***), 127.8 (***C_{Ar}***), 127.8 (***C_{Ar}***), 93.4 (***Ca***), 91.4 (***C1***), 78.6 (***C2***), 75.1 (***C7***), 70.2 (***Cb***), 65.1 (***C11***), 60.4 (***C10***), 60.1 (***C12***), 59.3 (***C13***), 42.8 (***C8***), 39.7 (***C15***), 30.8 (***C9***), 28.4 (***C14***), 24.0 (***C5***), 23.5 (***C19***), 23.4 (***C17***), 22.8 (***C6***), 19.0, 16.7 (***C18***, ***C16***).

IR (ν, cm^{-1}): 3049, 2987, 2958, 1801, 1684, 1543, 1400, 1214, 1093.

HRMS (CI/ISO) Calcd for $[M+H]^+$: *m/z* 483.2383, found 483.2379.

$[\alpha]^{21}_{D}$: +70.0 (*c* 1.0, $CHCl_3$).

(1R,1R,2R,3S,6S,10S,10S,11S)-10-((Benzyloxy)methoxy)-1,10,12,12-tetramethyl-1,2,6,8,10,10,11,11-octahydro-3H,9H-1,3-methanobenzo [3,4]bis(oxireno)[2',3':6,7;2'',3'':8,9]cyclodeca[1,2][1,3]dioxol-5-one (4.11)



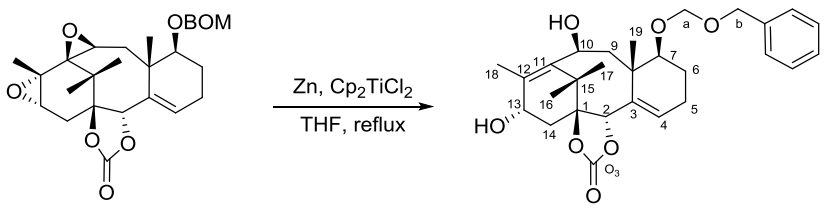
^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 7.37-7.34 (m, 4H, ***H_{Ar}***), 7.32-7.28 (m, 1H, ***H_{Ar}***), 5.76 (t, *J* = 3.5 Hz, 1H, ***H4***), 5.09 (s, 1H, ***H2***), 4.93 (d, *J* = 7.0 Hz, 1H, ***Ha***), 4.83 (d, *J* = 7.0 Hz, 1H, ***Ha***), 4.74 (d, *J* = 11.8 Hz, 1H, ***Hb***), 4.67 (d, *J* = 11.8 Hz, 1H, ***Hb***), 3.80 (dd, *J* = 11.9, 4.5 Hz, 1H, ***H7***), 3.48 (d, *J* = 3.4 Hz, 1H, ***H13***), 2.96 (dd, *J* = 7.8, 6.5 Hz, 1H, ***H10***), 2.76 (dd, *J* = 15.2, 6.5 Hz, 1H, ***H9***), 2.38 (d, *J* = 15.4 Hz, 1H, ***H14***), 2.36-2.31 (m, 2H, ***H5***), 2.07 (dd, *J* = 15.4, 3.4 Hz, 1H, ***H14***), 2.07-2.01 (m, 1H, ***H6***), 1.85-1.74 (m, 1H, ***H6***), 1.71 (s, 3H, ***H16*** or ***H17***), 1.53 (s, 3H, ***H16*** or ***H17***), 1.11 (dd, *J* = 15.2, 7.8, 1H, ***H9***), 1.08 (s, 3H, ***H19***), 1.02 (s, 3H, ***H18***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 149.3 (***CO_3***), 137.6 (***C_{Ar}***), 134.4 (***C2***), 128.5 (***C_{Ar}***), 127.8 (***C_{Ar}***), 127.6 (***C_{Ar}***), 126.8 (***C4***), 93.5 (***Ca***), 87.5 (***C1***), 75.7 (***C7***), 73.4 (***C2***), 70.0 (***Cb***), 68.2 (***C11***), 64.3 (***C12***), 62.4 (***C13***), 55.5 (***C15***), 55.2 (***C10***), 42.6 (***C8***), 33.7 (***C9***), 28.4 (***C14***), 26.4 (***C17***), 24.8 (***C16***), 23.3 (***C5***), 23.1 (***C19***), 22.9 (***C6***), 12.5 (***C18***).

HRMS (EI) Calcd for $[M]^+$: *m/z* 482.2305, found 482.2307.

$[\alpha]^{25}_{D}$: +59.0 (*c* 0.75, $CHCl_3$).

(3S,5S,8S,9S,10S,13S)-10-((Benzyloxy)methoxy)-5,8-dihydroxy-6,9,14,14-tetramethyl-5,8,9,9,10,11,12,13b-octahydro-4H-3,7-methanobenzo[3,4]cyclodeca[1,2][1,3]dioxol-2-one (4.12)



Chemical Formula: $C_{28}H_{36}O_7$

MW: 484,59

Zinc dust (0.20 g, 3.0 mmol) was added to a solution of Cp_2TiCl_2 (0.25 g, 1.0 mmol) in anhydrous and degassed THF (2.5 mL). The suspension was vigorously stirred for 2 h. The freshly made green solution of $[Cp_2TiCl]_2$ (0.83 mL, 0.2 M in THF, 0.16 mmol, 5 equiv) was added to a solution of diepoxide **4.10** (16 mg, 33 µmol) in THF (1.5 mL). The resulting mixture was stirred at reflux for 16 h. A 1N aqueous solution of HCl (5 mL) was added and the resulting mixture was stirred for 5 min. The aqueous layer was extracted with EtOAc (3x10 mL), drier over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/EtOAc: 3/7) to afford the title 1,4-diol **4.12** (3 mg, 6.3 µmol, 19%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 7.42-7.35 (m, 4H, ***H_{Ar}***), 7.34-7.29 (m, 1H, ***H_{Ar}***), 5.65 (t, *J* = 3.3 Hz, 1H, ***H4***), 5.47 (s, 1H, ***H2***), 4.91 (d, *J* = 7.3 Hz, 1H, ***Hα***), 4.79 (d, *J* = 7.3 Hz, 1H, ***Hα***), 4.78 (d, *J* = 11.9 Hz, 1H, ***Hb***), 4.66 (d, *J* = 11.9 Hz, 1H, ***Hb***), 4.67-4.63 (m, 1H, ***H13***), 4.59 (dd, *J* = 11.6, 6.1 Hz, 1H, ***H10***), 3.41 (dd, *J* = 11.8, 4.6 Hz, 1H, ***H7***), 2.32 (dd, *J* = 14.6, 6.1 Hz, 1H, ***H9***), 2.35-2.27 (m, 1H, ***H5***), 2.24 (dd, *J* = 13.3, 6.5 Hz, 1H, ***H14***), 2.25-2.15 (m, 1H, ***H5***), 1.98-1.94 (m, 1H, ***H6***), 1.83-1.78 (m, 1H, ***H6***), 1.79 (s, 3H, ***H17***), 1.78 (dd, *J* = 13.3, 7.8 Hz, 1H, ***H14***), 1.68 (dd, *J* = 14.6, 11.6 Hz, 1H, ***H9***), 1.61 (s, 3H, ***H18***), 1.43 (s, 1H, ***OH***), 1.32 (s, 3H, ***H16***), 1.15 (s, 3H, ***H19***), 1.11 (br s, 1H, ***OH***).

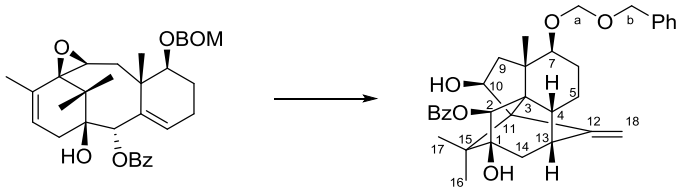
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 150.5 (***CO_3***), 150.4 (***C11***), 137.9 (***C_{Ar}***), 135.2 (***C12***), 135.2 (***C4***), 128.5 (***C_{Ar}***), 127.9 (***C_{Ar}***), 127.2 (***C_{Ar}***), 123.2 (***C4***), 93.3 (***C1***), 92.1 (***Cα***), 76.1 (***C13***), 75.3 (***C7***), 73.8 (***C2***), 70.0 (***Cb***), 63.5 (***C10***), 59.9 (***C15***), 39.9 (***C8***), 39.3 (***C9***), 37.2 (***C14***), 26.9 (***C17***), 25.4 (***C16***), 24.2 (***C19***), 23.1 (***C5***), 22.8 (***C6***), 11.5 (***C18***).

IR (ν, cm^{-1}): 3366, 3054, 2986, 2927, 1744, 1543, 1427, 1280.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 507.2353, found 507.2332.

$[\alpha]^{21}_D$: +43.0 (*c* 0.75, $CHCl_3$).

(1S,2S,3S,5R,6R,8S,11S)-3-((Benzyloxy)methoxy)-1,8-dihydroxy-2,9,9-trimethyl-10-methylenedecahydro-1H-2,8:6,9-dimethanobenzoazulen-11-yl benzoate (4.15)



Chemical Formula: $C_{34}H_{40}O_6$

MW: 544,69

Method A: To a solution of vinyl epoxide **4.7** (10 mg, 20 µmol) in THF (0.3 mL) were added allyl alcohol (13 µL, 0.2 mmol, 10 equiv) and $Yb(OTf)_3$ (4 mg, 6 µmol, 0.3 equiv). The mixture was stirred at room temperature for 16 h. A solution of saturated aqueous $NaHCO_3$ (2 mL) was then added and the aqueous phase was extracted with EtOAc (3x5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (CH_2Cl_2/EtOAc: 95/5) to afford the unpure alcohol **4.14** (3.0 mg, 5.0 µmol, 25%) and the title pentacycle **4.15** (3.0 mg, 5.5 µmol, 27%) as colourless oils.

Method B: Zinc dust (0.20 g, 3.0 mmol) was added to a solution of Cp_2TiCl_2 (0.25 g, 1.0 mmol) in anhydrous and degassed THF (2.5 mL). The suspension was vigorously stirred for 2 h. The freshly made green solution of $[Cp_2TiCl]_2$ (0.55 mL, 0.2 M in THF, 0.11 mmol, 5 equiv) was added to a solution of vinyl epoxide **4.7** (12 mg, 22 µmol) in THF (1.5 mL). The resulting mixture was stirred at room temperature for 2 h. A 1N aqueous solution of HCl (5 mL) was added and the reaction mixture was stirred for 5 min. The aqueous layer was extracted with EtOAc (3x10 mL), drier over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/EtOAc: 8/2) to afford the title pentacycle **4.15** (6.0 mg, 11 µmol, 50%) as a colourless oil.

Method C: To a solution of vinyl epoxide **4.7** (6.0 mg, 11 µmol) in MeOH (0.3 mL) was added $RhCl_3.xH_2O$ (0.2 mg, 1.1 µmol, 0.1 equiv). The resulting mixture was stirred for 16 h. The reaction mixture was filtered through a small plug of SiO_2, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/EtOAc: 8/2) to afford the title pentacycle **4.15** (2.0 mg, 3.6 mmol, 33%) as a colourless oil.

Method D: To a solution of vinyl epoxide **4.7** (37 mg, 68 µmol) in CH_2Cl_2 (3 mL) was added at 0°C a solution of *m*CPBA (18 mg, 78 µmol, 1.1 equiv) in CH_2Cl_2 (1 mL). The resulting mixture was stirred at the same temperature for 16 h. The reaction mixture was washed with a 10% aqueous solution of Na_2SO_3 (2x2 mL), and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), washed with brine (10 mL) and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 6/4) to afford the title pentacycle **4.15** (9.0 mg, 0.17 mmol, 25%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 8.09 (dd, *J* = 8.3, 1.2 Hz, 2H, ***H_{Ar}***), 7.65-7.59 (m, 1H, ***H_{Ar}***), 7.53-7.46 (m, 2H, ***H_{Ar}***), 7.39-7.34 (m, 4H, ***H_{Ar}***), 7.33-7.29 (m, 1H, ***H_{Ar}***), 6.00 (d, *J* = 1.7 Hz, 1H, ***H2***), 4.87 (s, 1H, ***H18***), 4.85 (d, *J* = 7.1 Hz, 1H, ***Ha***), 4.81 (s, 1H, ***H18***), 4.74 (d, *J* = 7.1 Hz, 1H, ***Ha***), 4.70 (d, *J* = 12.1 Hz, 1H, ***Hb***), 4.61 (d, *J* = 12.1 Hz, 1H, ***Hb***), 4.48 (dd, *J* = 12.0, 6.0 Hz, 1H, ***H10***), 3.29 (dd, *J* = 11.8, 3.0 Hz, 1H, ***H7***), 2.73 (s, 1H, ***OH***), 2.58 (dd, *J* = 12.1, 6.9 Hz, 1H, ***H4***), 2.42 (t, *J* = 2.8 Hz, 1H, ***H13***), 2.27 (dd, *J* = 12.0, 6.0 Hz, 1H, ***H9***), 1.99 (t, *J* = 12.0 Hz, 1H, ***H9***), 1.91 (ddd, *J* = 12.7, 2.8, 1.7 Hz, 1H, ***H14***), 1.81 (dd, *J* = 12.7, 2.8 Hz, 1H, ***H14***), 1.76-1.66 (m, 2H, ***H5***, ***H6***), 1.55 (s, 3H, ***H17***), 1.37-1.28 (m, 1H, ***H6***), 1.25 (br s, 1H, ***OH***), 1.21-1.14 (m, 1H, ***H5***), 0.99 (s, 3H, ***H16***), 0.99 (s, 3H, ***H19***).

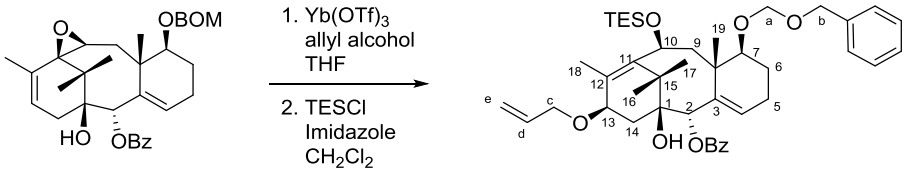
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 167.7 (***COPh***), 157.5 (***C12***), 137.9 (***C_{Ar}***), 133.4 (***C_{Ar}***), 129.9 (***C_{Ar}***), 129.7 (***C_{Ar}***), 128.6 (***C_{Ar}***), 128.5 (***C_{Ar}***), 127.7 (***C_{Ar}***), 127.6 (***C_{Ar}***), 103.5 (***C18***), 93.5 (***Ca***), 81.7 (***C7***), 80.5 (***C2***), 80.0 (***C1***), 75.8 (***C10***), 69.6 (***Cb***), 63.6 (***C11***), 62.4 (***C3***), 50.9 (***C15***), 49.6 (***C8***), 45.1 (***C13***), 42.4 (***C9***), 39.0 (***C4***), 35.1 (***C14***), 26.0 (***C5***), 24.9 (***C6***), 21.8 (***C16***), 21.0 (C***17***), 14.8 (***C19***).

IR (ν, cm^{-1}): 3321, 3034, 2965, 2929, 1733, 1698, 1565, 1463, 1267, 1113.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 567.2717, found 567.2706.

$[\alpha]^{23}_D$: -38.0 (*c* 0.5, $CHCl_3$).

(1S,5S,6S,8R,11S,12S)-8-(Allyloxy)-1-((benzyloxy)methoxy)-6-hydroxy-9,12,13,13-tetramethyl-11-((triethylsilyl)oxy)-1,2,3,5,6,7,8,11,12,12-decahydro-6,10-methanobenzo[10]annulen-5-yl benzoate (4.16)



Chemical Formula: $C_{43}H_{60}O_7Si$

MW: 717,03

To a solution of vinyl epoxide **4.7** (10 mg, 20 µmol) in THF (0.3 mL) were added allyl alcohol (13 µL, 0.2 mmol, 10 equiv) and $Yb(OTf)_3$ (4 mg, 6 µmol, 0.3 equiv). The mixture was stirred at room temperature for 16 h. A solution of saturated aqueous $NaHCO_3$ (2 mL) was then added and the aqueous phase was extracted with EtOAc (3x5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The next reaction was carried out without any further purification. To the crude alcohol **4.14** in CH_2Cl_2 (0.5 mL) were added imidazole (3.4 mg, 50 µmol, 2.5 equiv) and TESCl (4.2 µL, 25 µmol, 1.25 equiv). The reaction mixture was stirred for 1 h. A saturated aqueous solution of $NaHCO_3$ (2 mL) was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (3x5 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 8/2) to afford the title protected alcohol **4.16** (3.9 mg, 5.5 µmol, 100%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 8.09-8.03 (m, 2H, ***H_{Ar}***), 7.61-7.56 (m, 1H, ***H_{Ar}***), 7.51-7.44 (m, 2H, ***H_{Ar}***), 7.38-7.34 (m, 4H, ***H_{Ar}***), 7.33-7.29 (m, 1H, ***H_{Ar}***), 5.98 (dddd, *J* = 17.2, 10.3, 6.2, 5.3 Hz, 1H, ***Hd***), 5.82 (dd, *J* = 5.3, 1.6 Hz, 1H, ***H4***), 5.72 (s, 1H, ***H2***), 5.33 (dq, *J* = 17.2, 1.5 Hz, 1H, ***He***), 5.22 (dq, *J* = 10.3, 1.5 Hz, 1H, ***He***), 4.98 (d, *J* = 6.7 Hz, 1H, ***Ha***), 4.95 (dd, *J* = 11.0, 6.1 Hz, 1H, ***H13***), 4.89 (d, *J* = 6.7 Hz, 1H, ***Ha***), 4.78 (d, *J* = 11.8 Hz, 1H, ***Hb***), 4.52 (d, *J* = 11.8 Hz, 1H, ***Hb***), 4.22 (ddt, *J* = 12.6, 5.3, 1.5 Hz, 1H, ***Hc***), 3.97 (ddt, *J* = 12.6, 6.2, 1.5 Hz, 1H, ***Hc***), 3.73 (dd, *J* = 11.8, 3.8 Hz, 1H, ***H7***), 3.44 (dd, *J* = 9.3, 4.4 Hz, 1H, ***H10***), 2.72 (dd, *J* = 14.0, 9.3 Hz, 1H, ***H9***), 2.31-2.22 (m, 2H, ***H14***), 2.18-2.13 (m, 1H, ***H6***), 2.11-2.05 (m, 2H, ***H5***), 1.99 (dd, *J* = 14.0, 4.4 Hz, 1H, ***H9***), 1.80 (s, 3H, ***H18***), 1.78-1.68 (m, 1H, ***H6***), 1.66 (s, 3H, ***H17***), 1.30 (s, 3H, ***H16***), 1.12 (s, 3H, ***H19***), 0.97 (t, *J* = 7.9 Hz, 9H, ***TES***), 0.61 (q, *J* = 7.9 Hz, 6H, ***TES***).

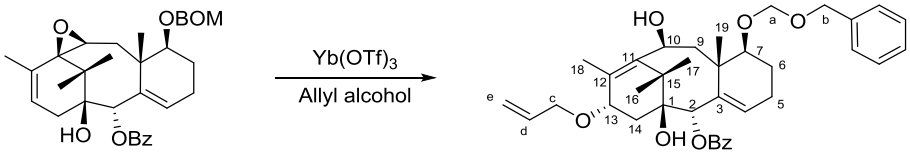
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 165.7 (***COPh***), 144.2 (***C3***), 142.1 (***C11***), 137.8 (***C_{Ar}***), 135.3 (***Cd***), 133.0 (***C_{Ar}***), 132.5 (***C12***), 130.5 (***C_{Ar}***), 129.7 (***C_{Ar}***), 128.5 (***C_{Ar}***), 128.4 (***C_{Ar}***), 127.8 (***C_{Ar}***), 127.7 (***C_{Ar}***), 120.8 (***C4***), 117.1 (***Ce***), 95.9 (***Ca***), 84.2 (***C1***), 79.0 (***C7***), 77.6 (***C10***), 73.5 (***C2***), 70.8 (***Cc***), 69.6 (***Cb***), 68.5 (***C13***), 42.6 (***C8***), 41.7 (***C14***), 41.1 (***C15***), 34.6 (***C9***), 31.8 (***C16***), 24.6 (***C6***), 24.2 (***C5***), 24.0 (***C19***), 19.6 (***C17***), 19.2 (***C18***), 7.0 (***TES***), 5.0 (***TES***).

IR (ν, cm^{-1}): 3053, 2986, 1716, 1698, 1535, 1491, 1427, 1265, 1046.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 739.4001, found 739.3966.

$[\alpha]^{22}_D$: +40.0 (*c* 0.5, $CHCl_3$).

(1S,5S,6S,8S,11S,12S)-8-(Allyloxy)-1-((benzyloxy)methoxy)-6,11-dihydroxy-9,12,13,13-tetramethyl-1,2,3,5,6,7,8,11,12,12-decahydro-6,10-methanobenzo[10]annulen-5-yl benzoate (4.17)



Chemical Formula: $C_{37}H_{46}O_7$

MW: 602,77

To a solution of vinyl epoxide **4.7** (13 mg, 24 µmol) in allyl alcohol (0.5 mL) was added $Yb(OTf)_3$ (1.5 mg, 2.4 µmol, 0.1 equiv) The mixture was stirred at room temperature for 16 h. A solution of saturated aqueous $NaHCO_3$ (2 mL) was then added and the aqueous phase was extracted with EtOAc (3x5 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (CH_2Cl_2/EtOAc: 95/5) to afford the title alcohol **4.17** (3.5 mg, 5.8 µmol, 24%) and pentacycle **4.15** (4.1 mg, 7.4 µmol, 31%) as colourless oils.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 8.13-8.08 (m, 2H, ***H_{Ar}***), 7.63-7.57 (m, 1H, ***H_{Ar}***), 7.52-7.46 (m, 2H, ***H_{Ar}***), 7.37-7.32 (m, 4H, ***H_{Ar}***), 7.32-7.28 (m, 1H, ***H_{Ar}***), 6.11 (s, 1H, ***H2***), 5.98 (ddt, *J* = 17.3, 10.5, 5.4 Hz, 1H, ***Hd***), 5.68 (t, *J* = 3.5 Hz, 1H, ***H4***), 5.34 (dq, *J* = 17.3, 1.5 Hz, 1H, ***He***), 5.22 (dq, *J* = 10.5, 1.5 Hz, 1H, ***He***), 4.85 (d, *J* = 7.2 Hz, 1H, ***Ha***), 4.76 (d, *J* = 7.2 Hz, 1H, ***Ha***), 4.69 (d, *J* = 11.6 Hz, 1H, ***Hb***), 4.62 (d, *J* = 11.6 Hz, 1H, ***Hb***), 4.60-4.56 (m, 2H, ***H10***, ***H13***), 4.14-4.02 (m, 2H, ***Hc***), 3.44 (dd, *J* = 6.8, 3.0 Hz, 1H, ***H7***), 2.81 (dd, *J* = 13.6, 6.7 Hz, 1H, ***H9***), 2.18-

2.06 (m, 1H, ***H5***), 2.00-1.71 (m, 5H, ***H5***, 2***H6***, 2***H14***), 1.66 (s, 3H, ***H18***), 1.58 (br. s, 1H, ***OH***), 1.55 (dd, *J* = 13.6, 7.2 Hz, 1H, ***H9),*** 1.48 (s, 3H, ***H19***), 1.44 (br. s, 1H, ***OH***), 1.39 (s, 3H, ***H17***), 1.12 (s, 3H, ***H16***).

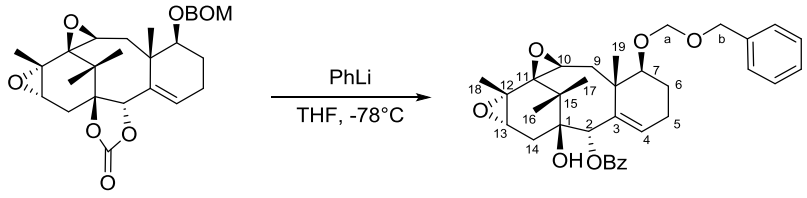
^{1}H NMR (500 MHz, C_6D_6) δ ppm: 8.25 (dd, *J* = 1.4, 8.3 Hz, 2H, ***H$_{Ar}$***), 7.33-7.25 (m, 3H, ***H$_{Ar}$***), 7.10-7.04 (m, 5H, ***H$_{Ar}$***), 6.51 (s, 1H, ***H2***), 5.93 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H, ***Hd***), 5.71 (t, *J* = 3.3 Hz, 1H, ***H4***), 5.34 (dq, *J* = 17.2, 1.8 Hz, 1H, ***He***), 5.10 (dq, *J* = 10.4, 1.8 Hz, 1H, ***He***), 4.65 (d, *J* = 7.1 Hz, 1H, ***Ha***), 4.62 (dd, *J* = 6.9, 6.5 Hz, 1H, ***H10***), 4.54 (d, *J* = 7.1 Hz, 1H, ***Ha***), 4.53 (d, *J* = 12.1 Hz, 1H, ***Hb***), 4.54-4.50 (m, 1H, ***H13***), 4.47 (d, *J* = 12.1 Hz, 1H, ***Hb***), 4.00 (ddt, *J* = 13.1, 5.2, 1.8 Hz, 1H, ***Hc***), 3.91 (ddt, *J* = 13.1, 5.2, 1.8 Hz, 1H, ***Hc***), 3.40 (dd, *J* = 7.9, 3.1 Hz, 1H, ***H7***), 2.92 (dd, *J* = 13.7, 6.9 Hz, 1H, ***H9***), 2.04-1.92 (m, 3H, ***H5***, 2***H14***), 1.78 (s, 3H, ***H18***), 1.73-1.66 (m, 2H, ***H5***, ***H6),*** 1.65 (s, 3H, ***H19***), 1.61 (dd, *J* = 13.7, 6.5 Hz, 1H, ***H9***), 1.61-1.57 (m, 1H, ***H6***), 1.46 (s, 3H, ***H17***), 1.35-1.29 (m, 2H, 2***OH***), 1.14 (s, 3H, ***H16***).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 164.6 (***COPh***), 145.6 (***C12***), 141.7 (***C3***), 137.9 (***C$_{Ar}$***), 135.4 (***Cd***), 133.0 (***C$_{Ar}$***), 130.6 (***C$_{Ar}$***), 129.5 (***C$_{Ar}$***), 128.5 (***C$_{Ar}$***), 128.4 (***C$_{Ar}$***), 128.1 (***C11***), 127.8 (***C$_{Ar}$***), 127.7 (***C$_{Ar}$***), 117.3 (***C4***), 116.6 (***Ce***), 94.0 (***Ca***), 91.2 (***C10*** or ***C13***), 84.0 (***C1***), 79.7 (***C7***), 72.3 (***C2***), 70.8 (***C10*** or ***C13***), 70.1 (***Cc***), 69.9 (***Cb***), 65.3 (***C15***), 43.0 (***C14***), 41.5 (***C8***), 32.9 (***C9***), 25.6 (***C16***), 24.8 (***C19***), 22.6 (***C6***), 22.2 (***C17***), 21.9 (***C5***), 10.9 (***C18***).

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 607.3030, found 607.3020.

$[\alpha]^{22}_{D}$: -36.0 (*c* 0.5, $CHCl_3$).

(1R,1S,2S,4S,5S,9S,9S,10S)-9-((Benzyloxy)methoxy)-4-hydroxy-1,9,11,11-tetramethyl-1,2,4,5,7,8,9,9,10,10-decahydro-3H-1,4-methanobenzo[6,7]cyclodeca[1,2:3,4]bis(oxirene)-5-yl benzoate (4.18)



Chemical Formula: $C_{34}H_{40}O_7$

MW: 560,69

To a solution of diepoxide **4.10** (25 mg, 51 µmol) in THF (2.5 mL) at -78°C was added phenyllithium (0.22 mL, 2 M in nBu_2O, 0.45 mmol, 9.0 equiv). The mixture was stirred at

this temperature for 2 h. A solution of saturated aqueous $NaHCO_3$ (2 mL) was then added and the aqueous phase was extracted with Et_2O (3x5 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 7/3) to afford the title benzoate **4.18** (23 mg, 41 µmol, 80%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 8.08-8.02 (m, 2H, ***H_{Ar}***), 7.64-7.57 (m, 1H, ***H_{Ar}***), 7.52-7.44 (m, 2H, ***H_{Ar}***), 7.40-7.35 (m, 4H, ***H_{Ar}***), 7.33-7.28 (m, 1H, ***H_{Ar}***), 6.13 (dd, *J* = 5.5, 2.5 Hz, 1H, ***H4***), 5.75 (s, 1H, ***H2***), 4.95 (d, *J* = 7.1 Hz, 1H, ***Ha***), 4.83 (d, *J* = 7.1 Hz, 1H, ***Ha***), 4.75 (d, *J* = 11.7 Hz, 1H, ***Hb***), 4.66 (d, *J* = 11.7 Hz, 1H, ***Hb***), 3.96 (dd, *J* = 11.4, 3.4 Hz, 1H, ***H7***), 3.22 (d, *J* = 4.6 Hz, 1H, ***H13***), 3.14 (dd, *J* = 12.0, 4.1 Hz, 1H, ***H10***), 3.12 (d, *J* = 16.6 Hz, 1H, ***H14***), 2.48 (dd, *J* = 14.4, 4.1 Hz, 1H, ***H9***), 2.34 (s, 1H, ***OH***), 2.26-2.13 (m, 2H, ***H5***), 2.01 (dd, *J* = 16.6, 4.6 Hz, 1H, ***H14***), 1.89 (ddt, *J* = 11.4, 5.6, 2.8 Hz, 1H, ***H6***), 1.70-1.60 (m, 1H, ***H6***), 1.64 (dd, *J* = 14.4, 12.0 Hz, 1H, ***H9***), 1.31 (s, 3H, ***H17***), 1.26 (s, 3H, ***H19***), 1.21 (s, 6H, ***H16***, ***H19***).

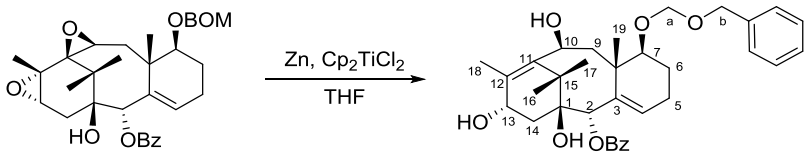
^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 165.4 (***OPh***), 138.0 (***C3***), 137.7 (***C_{Ar}***), 133.2 (***C_{Ar}***), 131.1 (***C4***), 130.2 (***C_{Ar}***), 129.7 (***C_{Ar}***), 128.5 (***C_{Ar}***), 128.5 (***C_{Ar}***), 127.9 (***C_{Ar}***), 127.7 (***C_{Ar}***), 93.6 (***Ca***), 79.8 (***C1***), 77.6 (***C7***), 74.4 (***C2***), 70.1 (***Cb***), 64.3 (***C11***), 61.1 (***C10***), 60.2 (***C13***), 59.9 (***C12***), 42.9 (***C8***), 41.4 (***C15***), 31.5 (***C9***), 31.3 (***C14***), 24.2 (***C5***), 23.6 (***C17***), 23.0 (***C6***), 22.6 (***C19***), 19.2, 17.7 (***C16***, ***C19***).

IR (ν, cm^{-1}): 3054, 2986, 1717, 1520, 1421, 1265, 1020.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 583.2666, found 583.2652.

$[\alpha]^{25}_D$: +28.0 (*c* 1.0, $CHCl_3$).

(1S,5S,6S,8S,11S,12S)-1-((Benzyloxy)methoxy)-6,8,11-trihydroxy-9,12,13,13-tetramethyl-1,2,3,5,6,7,8,11,12,12-decahydro-6,10-methanobenzo[10]annulen-5-yl benzoate (4.19)



Chemical Formula: $C_{34}H_{42}O_7$

MW: 562,70

Zinc dust (0.20 g, 3.0 mmol) was added to a solution of Cp_2TiCl_2 (0.25 g, 1.0 mmol) in anhydrous and degassed THF (2.5 mL). The suspension was vigorously stirred for 2 h. The freshly made green solution of $[Cp_2TiCl]_2$ (0.93 mL, 0.2 M in THF, 0.19 mmol, 5.0 equiv) was added to a solution of diepoxide **4.18** (21 mg, 37 µmol) in THF (1.5 mL). The resulting mixture was stirred at room temperature for 4 h. A 1N aqueous solution of HCl (5 mL) was added and the resulting mixture was stirred for 5 min. The aqueous layer was extracted with EtOAc (3x10 mL), drier over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/EtOAc: 3/7) to afford the title 1,4-diol **4.19** (11 mg, 20 µmol, 53%) as a colourless oil.

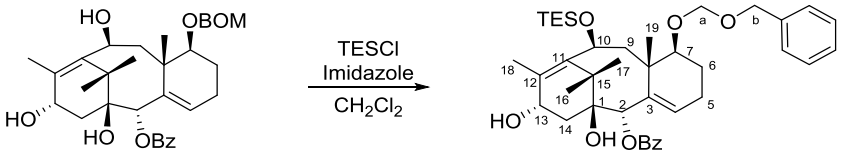
^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 8.09-8.03 (m, 2H, ***H_{Ar}***), 7.62-7.56 (m, 1H, ***H_{Ar}***), 7.50-7.44 (m, 2H, ***H_{Ar}***), 7.44-7.36 (m, 4H, ***H_{Ar}***), 7.34-7.28 (m, 1H, ***H_{Ar}***), 5.90 (dd, *J* = 4.9, 2.5 Hz, 1H, ***H4***), 5.70 (s, 1H, ***H2***), 5.08 (dd, *J* = 11.8, 5.2 Hz, 1H, ***H10***), 4.98 (d, *J* = 7.3 Hz, 1H, ***Ha***), 4.87 (d, *J* = 12.2 Hz, 1H, ***Hb***), 4.82 (d, *J* = 7.3 Hz, 1H, ***Ha***), 4.68 (d, *J* = 12.2 Hz, 1H, ***Hb***), 4.61-4.53 (m, 1H, ***H13***), 3.86 (dd, *J* = 12.2, 3.9 Hz, 1H, ***H7***), 2.50-2.46 (m, 2H, ***H14***), 2.36 (dd, *J* = 14.5, 5.2 Hz, 1H, ***H9***), 2.28 (s, 1H, ***OH***), 2.23-2.15 (m, 2H, ***H5***), 2.14-2.09 (m, 2H, ***OH***, ***H9***), 1.96-1.89 (m, 1H, ***H6***), 1.84 (d, *J* = 1.1 Hz, 3H, ***H18***), 1.70-1.63 (m, 1H, ***H6***), 1.65 (s, 3H, ***H17***), 1.57 (br s, 1H, ***OH***), 1.17 (s, 3H, ***H19***), 1.07 (s, 3H, ***H16***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 165.5 (***COPh***), 144.8 (***C3***), 138.0 (***C_{Ar}***), 137.1 (***C12***), 136.3 (***C11***), 133.1 (***C_{Ar}***), 130.3 (***C_{Ar}***), 129.7 (***C_{Ar}***), 128.5 (***C_{Ar}***), 128.5 (***C_{Ar}***), 127.7 (***C_{Ar}***), 127.2 (***C_{Ar}***), 123.4 (***C4***), 93.1 (***Ca***), 79.3 (***C1***), 75.5 (***C7***), 74.1 (***C2***), 70.0 (***Cb***), 69.2 (***C13***), 67.7 (***C10***), 42.6 (***C8***), 41.4 (***C15***), 38.5 (***C14***), 38.2 (***C9***), 28.2 (***C16***), 24.2 (***C19***), 23.9 (***C5***), 22.8 (***C6***), 19.9 (***C17***), 16.8 (***C18***).

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 585.2823, found 585.2808.

$[\alpha]^{21}_D$: +60.0 (*c* 1.0, $CHCl_3$).

(1S,5S,6S,8S,11S,12S)-1-((Benzyloxy)methoxy)-6,8-dihydroxy-9,12,13,13-tetramethyl-11-((triethylsilyl)oxy)-1,2,3,5,6,7,8,11,12,12-decahydro-6,10-methanobenzo[10]annulen-5-yl benzoate (4.20)



Chemical Formula: $C_{40}H_{56}O_7Si$

MW: 676,97

To a solution of diol **4.19** (6.7 mg, 12 µmol) in CH_2Cl_2 (1 mL) were added imidazole (8.2 mg, 0.12 mmol, 10 equiv) and TESCl (10 µL, 60 µmol, 5 equiv). The reaction mixture was stirred for 16 h. A saturated aqueous solution of $NaHCO_3$ (1 mL) was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (3x5 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography (petroleum ether/Et_2O: 65/35) to afford the title protected alcohol **4.20** (5.5 mg, 8.2 µmol, 68%) as a colourless oil.

^{1}H NMR (500 MHz, *$CDCl_3$*) δ ppm: 8.08-8.04 (m, 2H, ***H_{Ar}***), 7.61-7.54 (m, 1H, ***H_{Ar}***), 7.50-7.44 (m, 2H, ***H_{Ar}***), 7.39-7.34 (m, 4H, ***H_{Ar}***), 7.33-7.28 (m, 1H, ***H_{Ar}***), 5.88 (dd, *J* = 5.8, 2.3 Hz, 1H, ***H4***), 5.72 (s, 1H, ***H2***), 4.99 (d, *J* = 6.7 Hz, 1H, ***Ha***), 4.96 (dd, *J* = 11.4, 5.7 Hz, 1H, ***H10***), 4.90 (d, *J* = 6.7 Hz, 1H, ***Ha***), 4.79 (d, *J* = 11.8 Hz, 1H, ***Hb***), 4.59-4.54 (m, 1H, ***H13***), 4.53 (d, *J* = 11.8 Hz, 1H, ***Hb***), 3.75 (dd, *J* = 12.2, 4.0 Hz, 1H, ***H7***), 2.48 (d, *J* = 6.7 Hz, 2H, ***H14***), 2.27-2.18 (m, 1H, ***H5***), 2.23 (dd, *J* = 15.0, 5.7 Hz, 1H, ***H9***), 2.17-2.09 (m, 3H, ***H5***, ***H6***, ***H9***), 2.08 (s, 1H, ***OH1***), 1.86 (d, *J* = 1.0 Hz, 3H, ***H18***), 1.81-1.71 (m, 1H, ***H6***), 1.69 (s, 3H, ***H17***), 1.54 (br s, 1H, ***OH13***), 1.14 (s, 3H, ***H19***), 1.07 (s, 3H, ***H16***), 0.97 (t, *J* = 8.0 Hz, 9H, ***TES***), 0.60 (d, *J* = 8.0 Hz, 6H, ***TES***).

^{13}C NMR (126 MHz, *$CDCl_3$*) δ ppm: 165.6 (***COPh***), 145.2 (***C3***), 137.8 (***C_{Ar}***), 136.9 (***C11***), 134.9 (***C12***), 133.1 (***C_{Ar}***), 130.4 (***C_{Ar}***), 129.7 (***C_{Ar}***), 128.5 (***C_{Ar}***), 128.5 (***C_{Ar}***), 127.8 (***C_{Ar}***), 127.7 (***C_{Ar}***), 122.9 (***C4***), 95.8 (***Ca***), 79.4 (***C1***), 78.9 (***C7***), 74.1 (***C2***), 69.6 (***Cb***), 69.2 (***C13***), 68.0 (***C10***), 42.8 (***C15***), 41.5 (***C8***), 39.4 (***C9***), 38.5 (***C14***), 27.9 (***C16***), 24.5 (***C6***), 24.4 (***C19***), 23.9 (***C5***), 19.7 (***C17***), 16.8 (***C18***), 6.9 (***TES***), 4.9 (***TES***).

IR (ν, cm^{-1}): 3421, 3049, 2984, 2961, 2882, 1717, 1675, 1430, 1409, 1206, 1095, 1005.

HRMS (ESI) Calcd for $[M+Na]^+$: *m/z* 699.3688, found 699.3653.

$[\alpha]^{26}_D$: +10.0 (*c* 0.75, $CHCl_3$).

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[93] The Zhan-1B catalyst was recovered in the same purification as the metathesis products by flash chromatography. The recycled catalyst exhibited the same activity as the commercially available catalyst.
[94] This range of yield was obtained from 0.04 mmol and 0.24 mmol scale on dozens of iterations.
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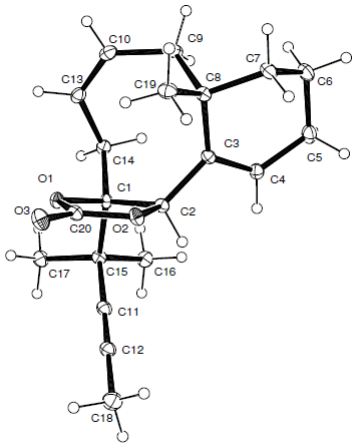
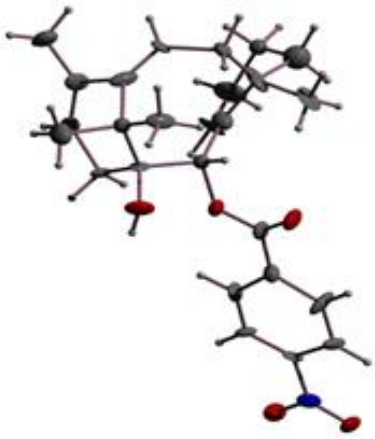
7. APPENDICES

Crystal data and structure refinement for **2.41**.



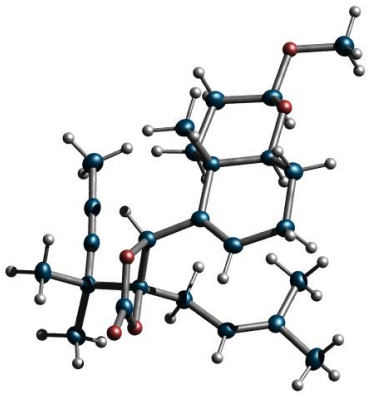
Identification code	CCDC 1405009
Empirical formula	C20 H26 O3
Formula weight	314.41
Temperature	100 K
Wavelength	0.71073
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimension	a = 7.5528(2) Å
	b = 11.6745(3) Å
	c = 19.2152(6) Å
	α = 90 °
	β = 90 °
	γ = 90 °
Volume	1694.30(8) $Å^3$
Z	4
Density (calculated)	1.233 g/cm^3
Radiation type	MoK\a
Absorption coefficient	0.081 µ/mm
F(000)	680.0
Theta range for data collection	2.336 - 27.506 °
Index ranges	−9<=h<=+9; −15<=k<=+15; −24<=l<=+24
R*int*	0.043
Absorption correction type	Gaussian
Refinement method	Full-matrix least-squares on F^2
Final R indices [I>2sigma(I)]	R1 = 0.0316, wR2 = 0.0765
R indices (all data)	R1 = 0.0398, wR2 = 0.0975
Largest diff. peak and hole	0.23 and -0.15 e.$Å^{-3}$

Crystal data and structure refinement for **2.45**.

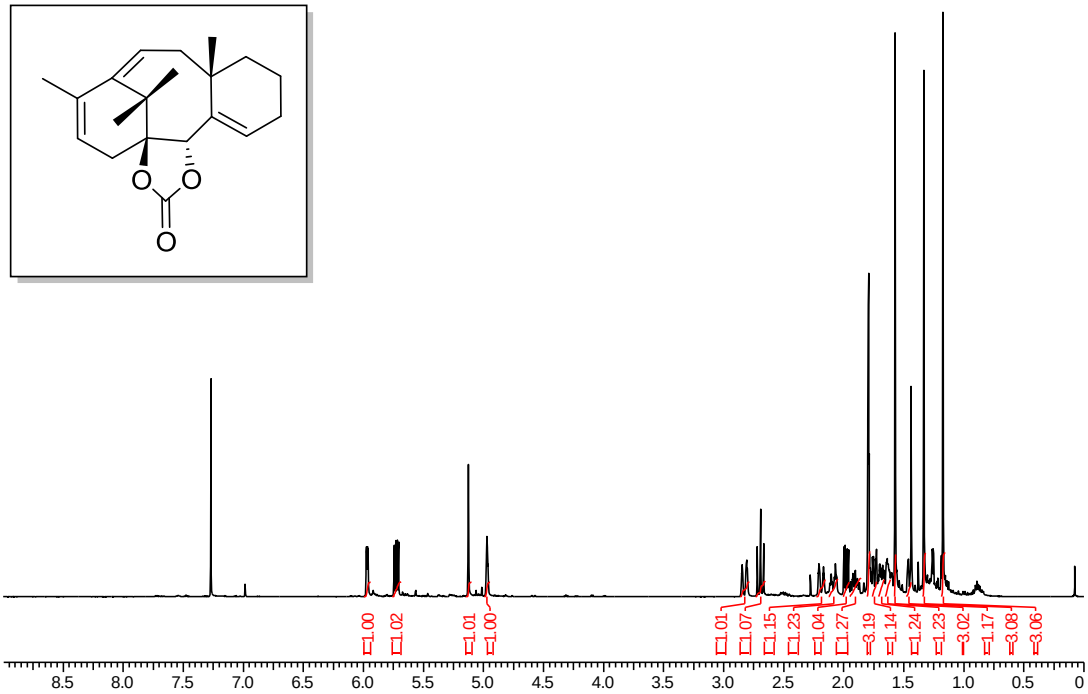


Identification code	CCDC 976581
Empirical formula	C26 H31 N O5
Formula weight	437.52
Temperature	150(2) K
Wavelength	0.71073
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 7.4950(6) Å
	b = 10.4454(9) Å
	c = 35.197(3) Å
	α = 90 °
	β = 90 °
	γ = 90 °
Volume	2755.5(4) A^3
Z	4
Calculated density	1.055 Mg/m^3
Absorption coefficient	0.073 mm^{-1}
F(000)	936
Crystal size	0.370 x 0.102 x 0.060 mm
Theta range for data collection	2.034 to 23.296 deg
Limiting indices	-7<=h<=8, -11<=k<=11, -33<=l<=39
Reflections collected / unique	12353 / 3802 [R(int) = 0.0806]
Completeness to theta = 25.242	0.78
Absorption correction	Empirical
Max. and min. transmission	1.000 and 0.786
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3802 / 22 / 276
Goodness-of-fit on F^2	1.054
Final R indices [I>2sigma(I)]	R1 = 0.1164, wR2 = 0.2886
R indices (all data)	R1 = 0.1565, wR2 = 0.3085
Absolute structure parameter	-1.9(10)
Extinction coefficient	0.103(15)
Largest diff. peak and hole	0.34 and -0.31 $e.A^{-3}$

Crystal data and structure refinement for **3.10**.



Identification code	**3.10**
Empirical formula	C25 H36 O5
Formula weight	416.54
Temperature	150(2) K
Wavelength	1.54178
Crystal system	Monoclinic
Space group	P 21
Unit cell dimensions	a = 8.9770(3) Å
	b = 10.9223(4) Å
	c = 11.4891(4) Å
	α = 90 °
	β = 90.838(3) °
	γ = 90 °
Volume	1126.38(7) A^3
Z	2
Calculated density	1.228 Mg/m^3
Absorption coefficient	0.673 mm^{-1}
F(000)	452
Crystal size	0.447 x 0.280 x 0.181 mm
Theta range for data collection	3.848 to 67.273 deg
Limiting indices	-10<=h<=10, -13<=k<=13, -13<=l<=13
Reflections collected / unique	16134 / 4041 [R(int) = 0.0196]
Completeness to theta = 67.679	0.993
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4041 / 1 / 279
Goodness-of-fit on F^2	1.042
Final R indices [I>2sigma(I)]	R1 = 0.0246, wR2 = 0.0648
R indices (all data)	R1 = 0.0247, wR2 = 0.0649
Absolute structure parameter	0.01(4)
Extinction coefficient	0.0098(7)
Largest diff. peak and hole	0.188 and -0.118 $e.A^{-3}$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1.14
1.24
1.23
3.02
1.17
3.08
3.06
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7.5
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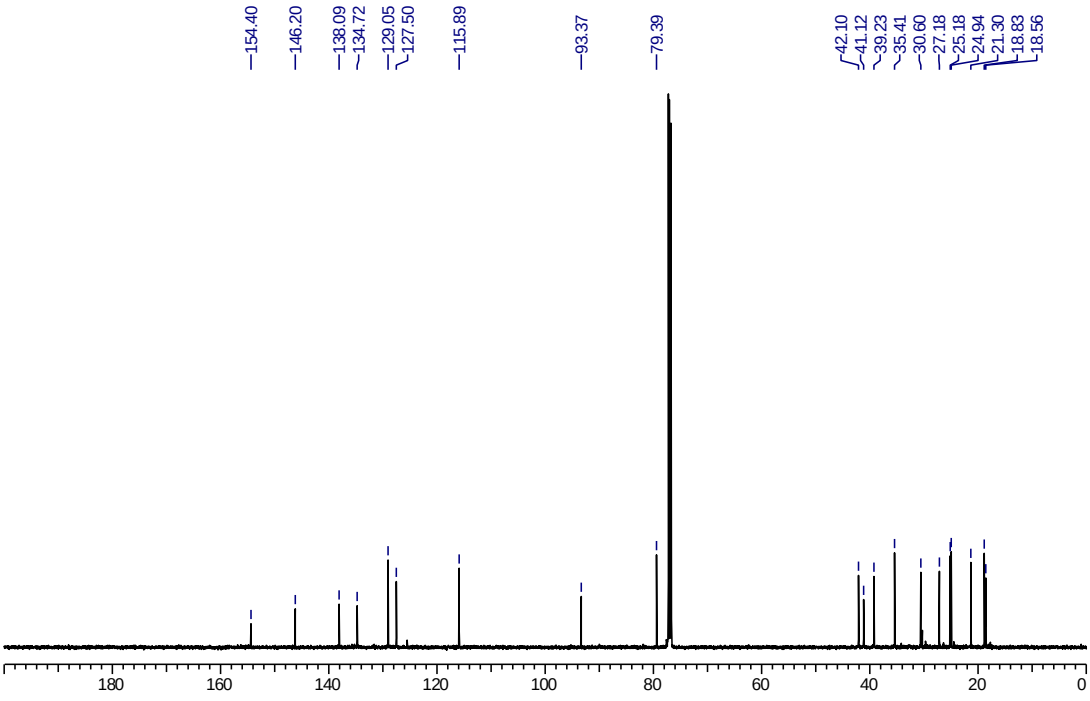
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35.41
30.60
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80
60
40
20
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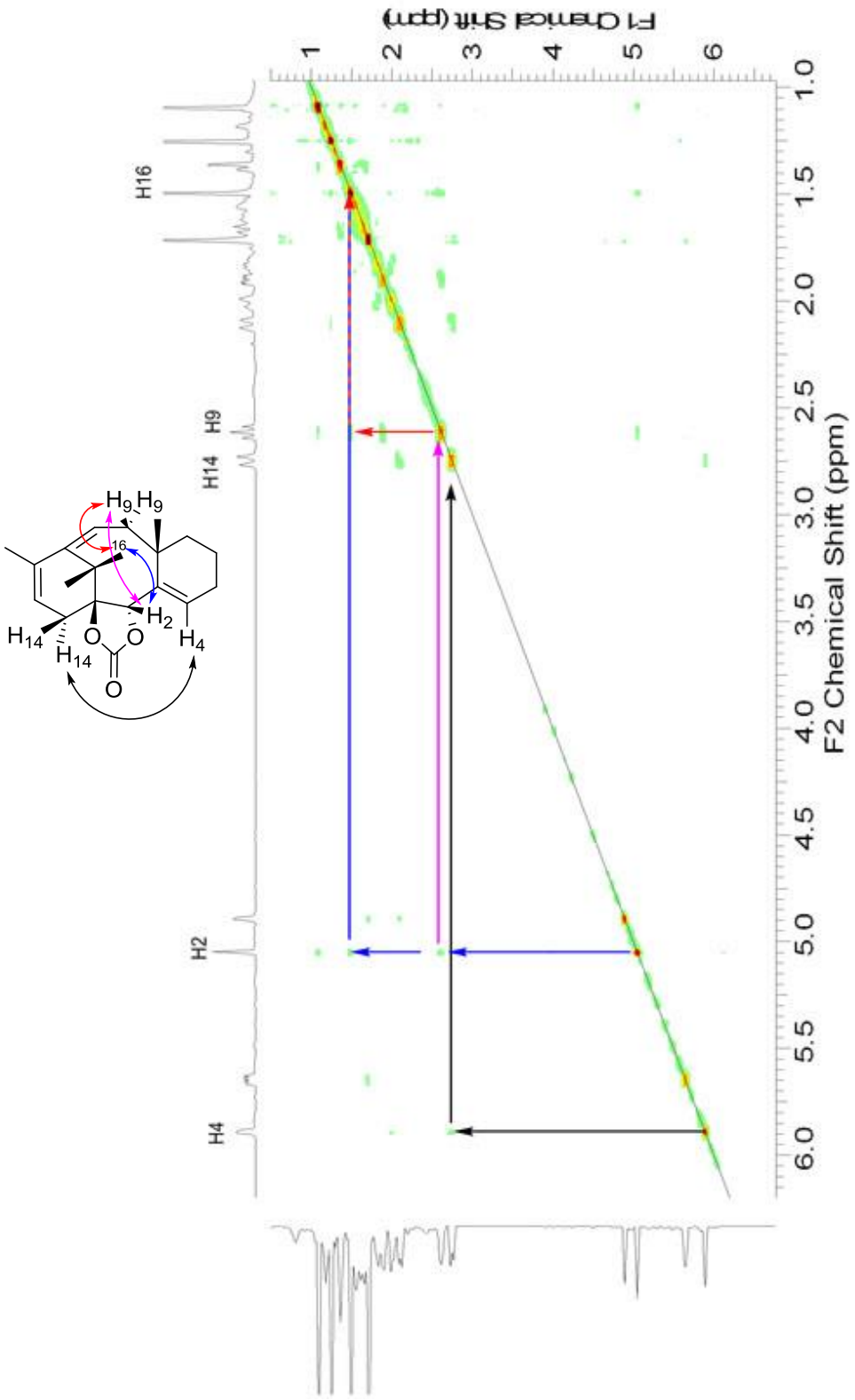
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H2
H14
H14
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O
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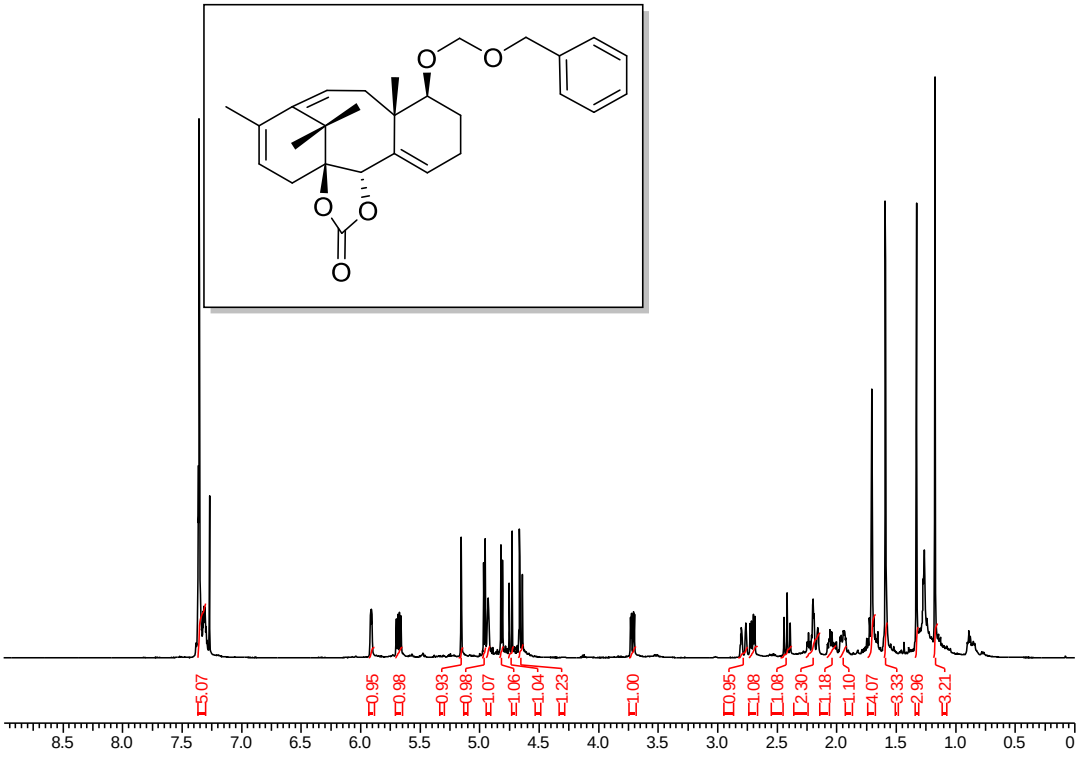
H4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1.08
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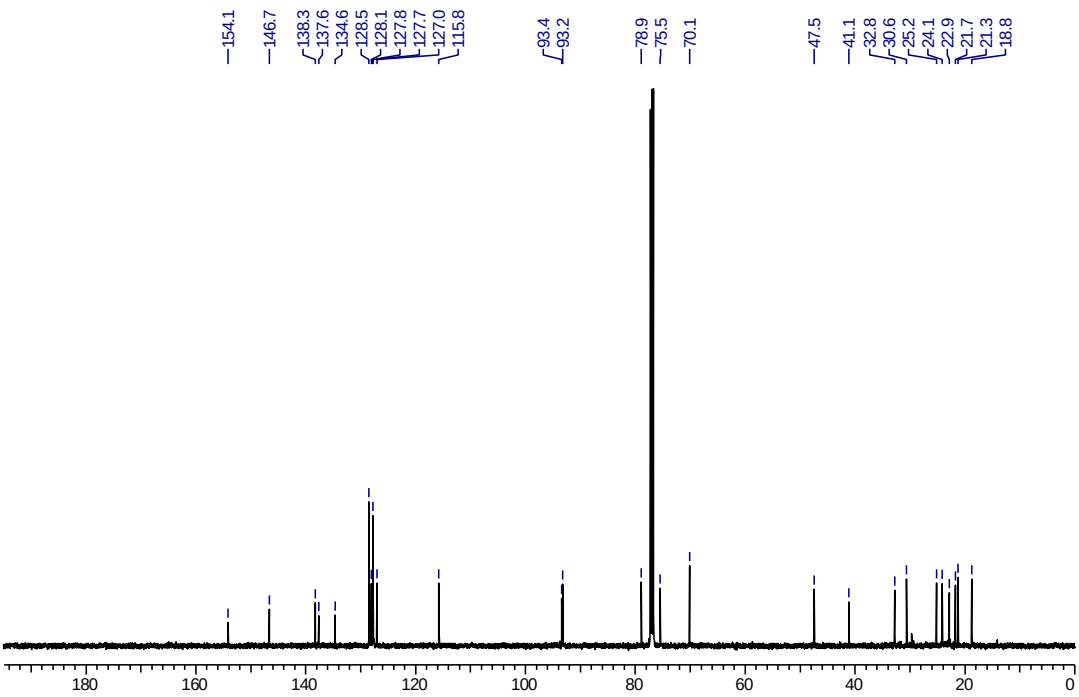
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75.5
70.1
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32.8
30.6
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60
40
20
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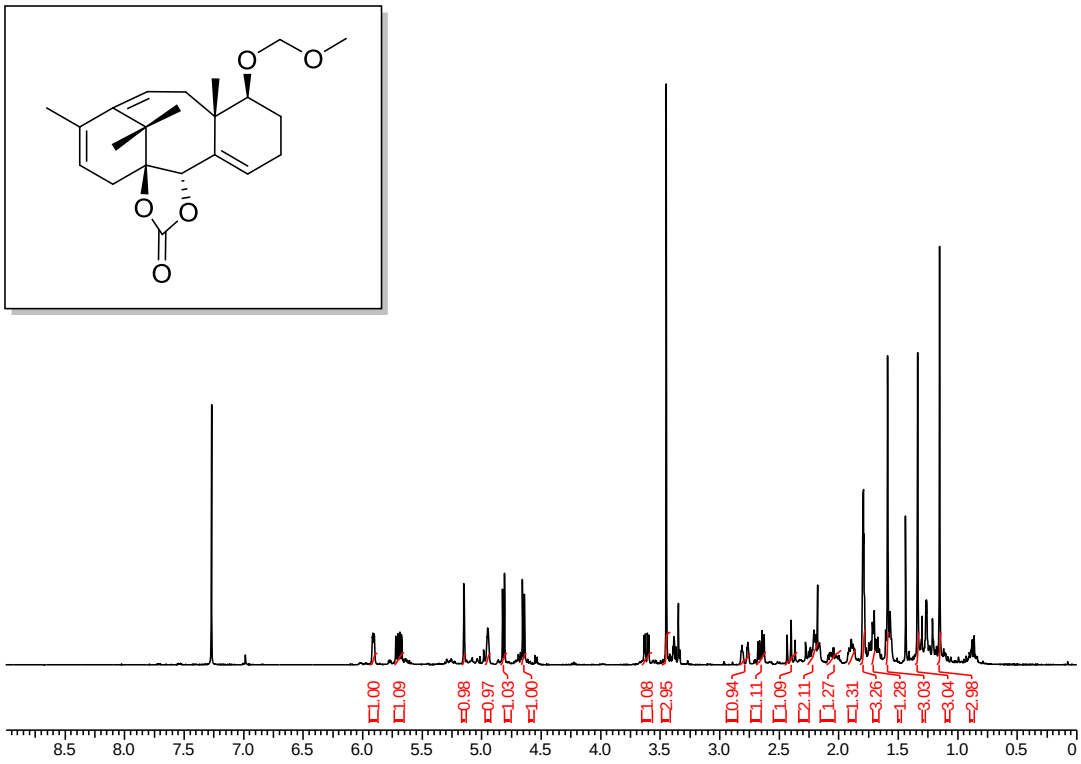
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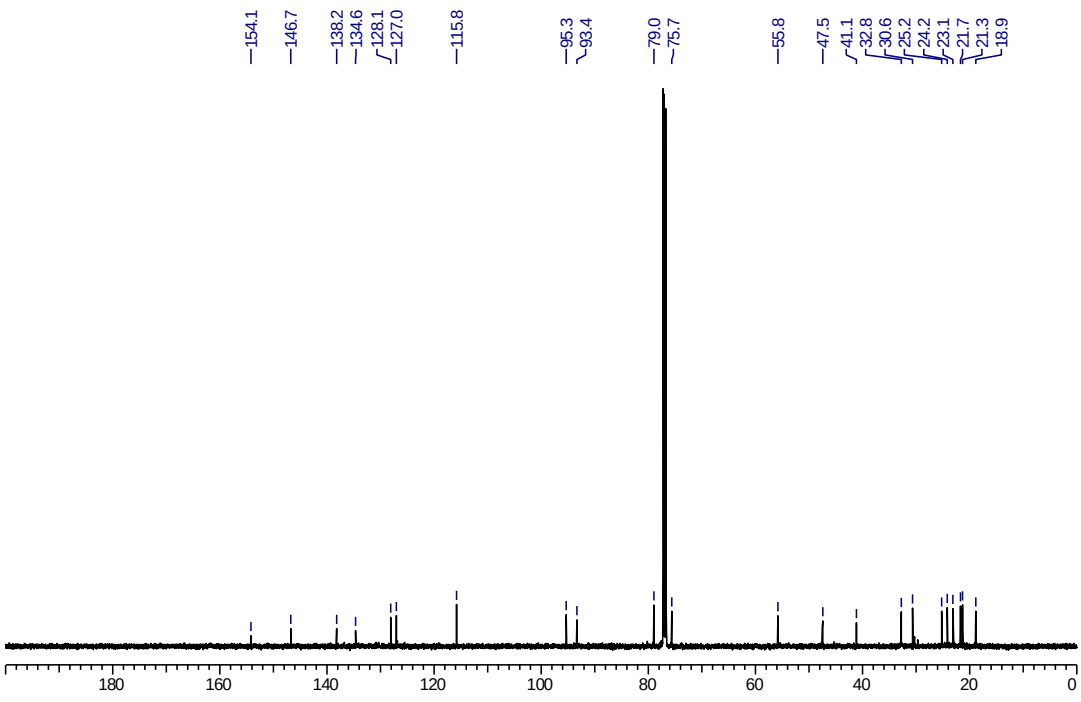
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41.1
32.8
30.6
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21.3
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80
60
40
20
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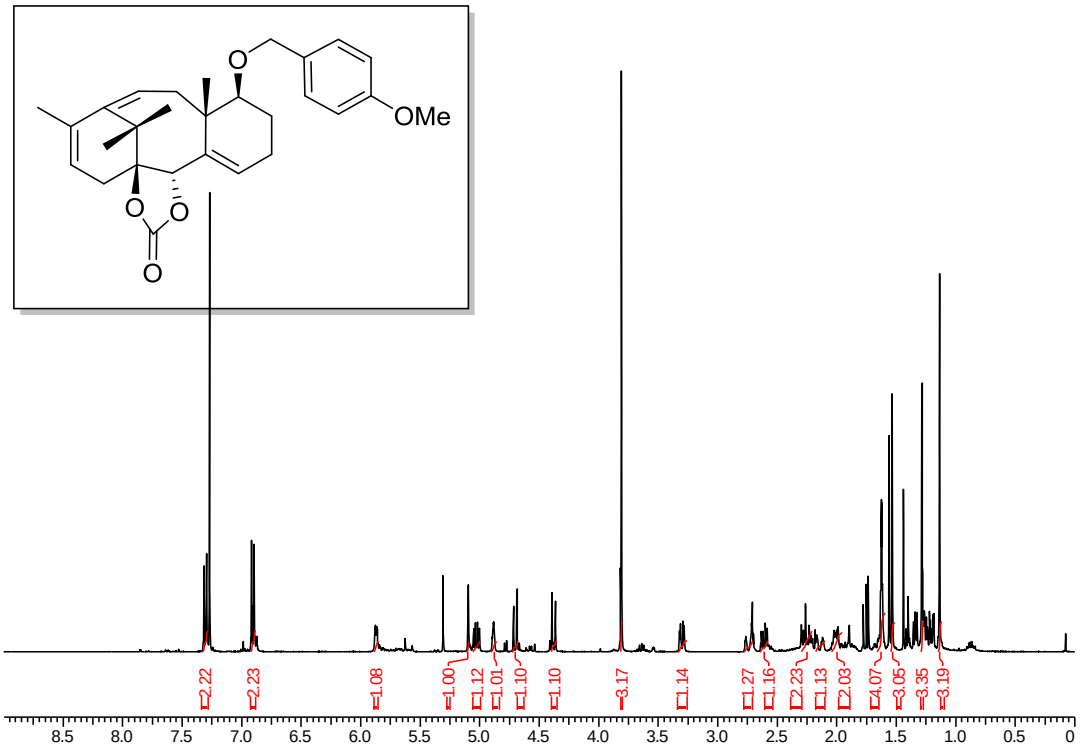
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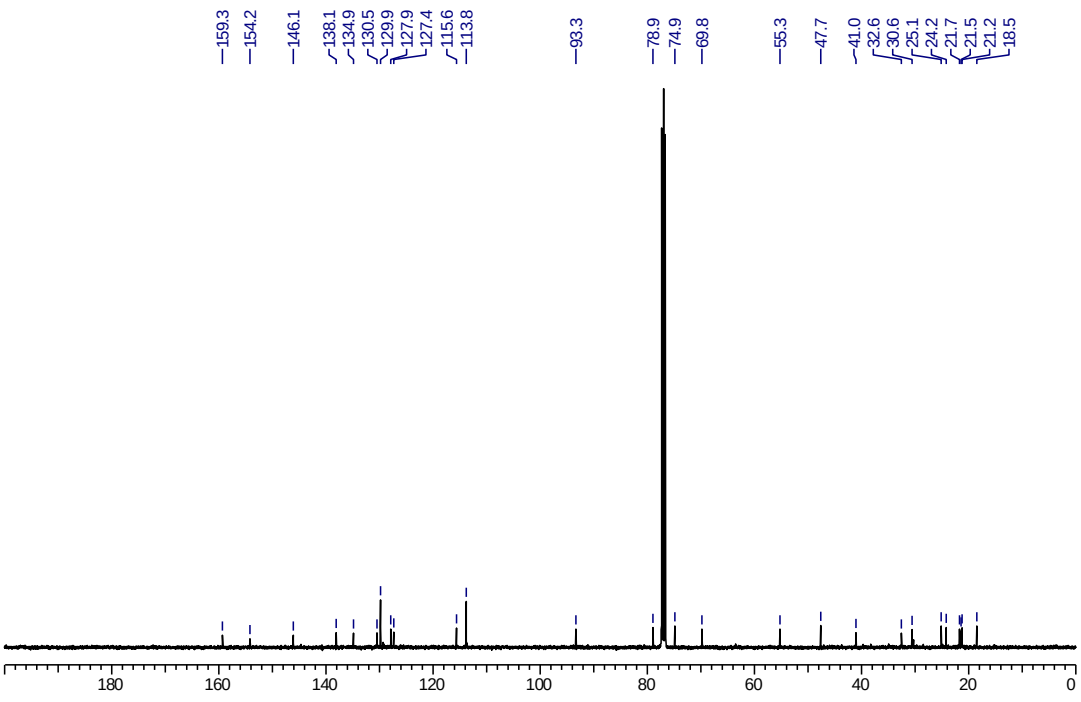
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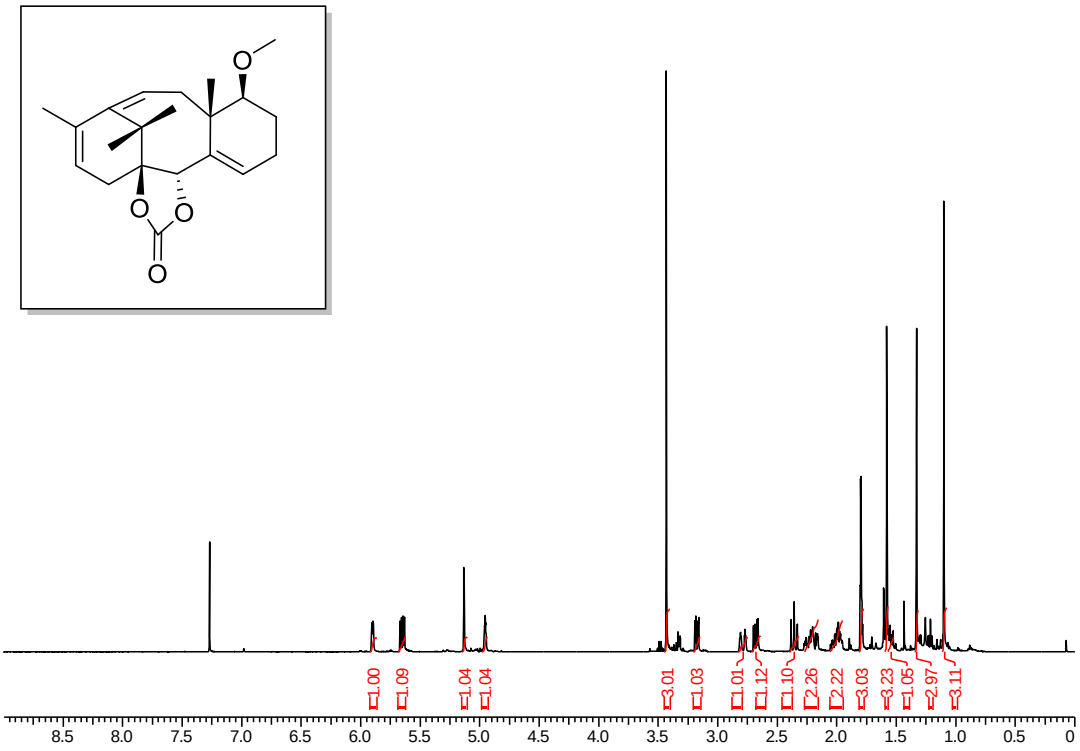
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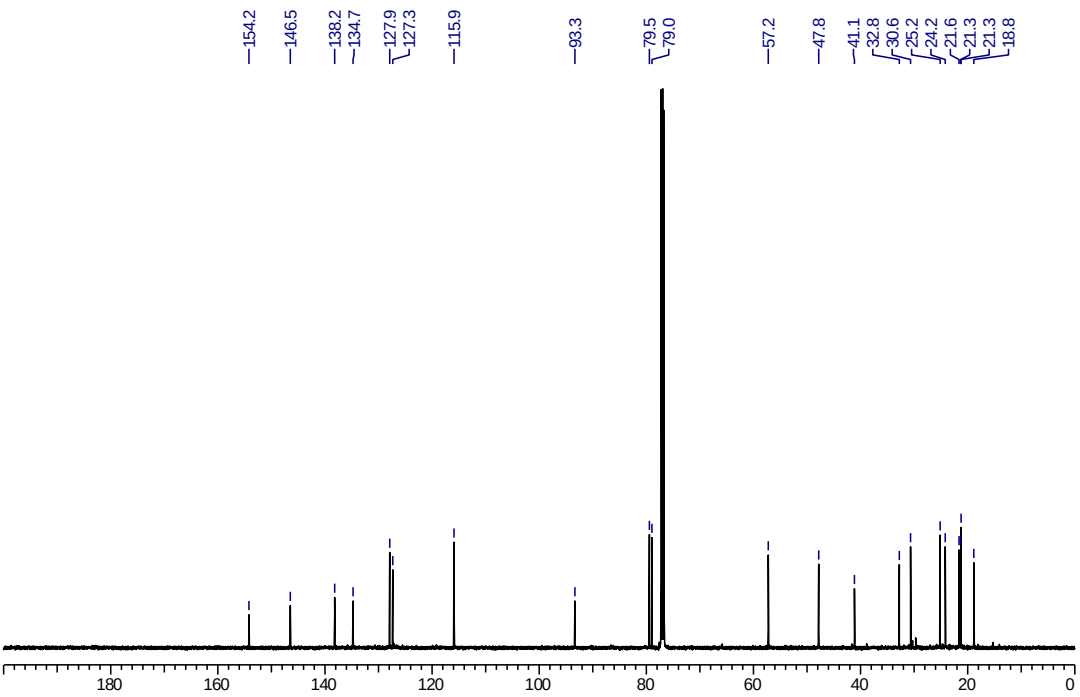
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32.8
30.6
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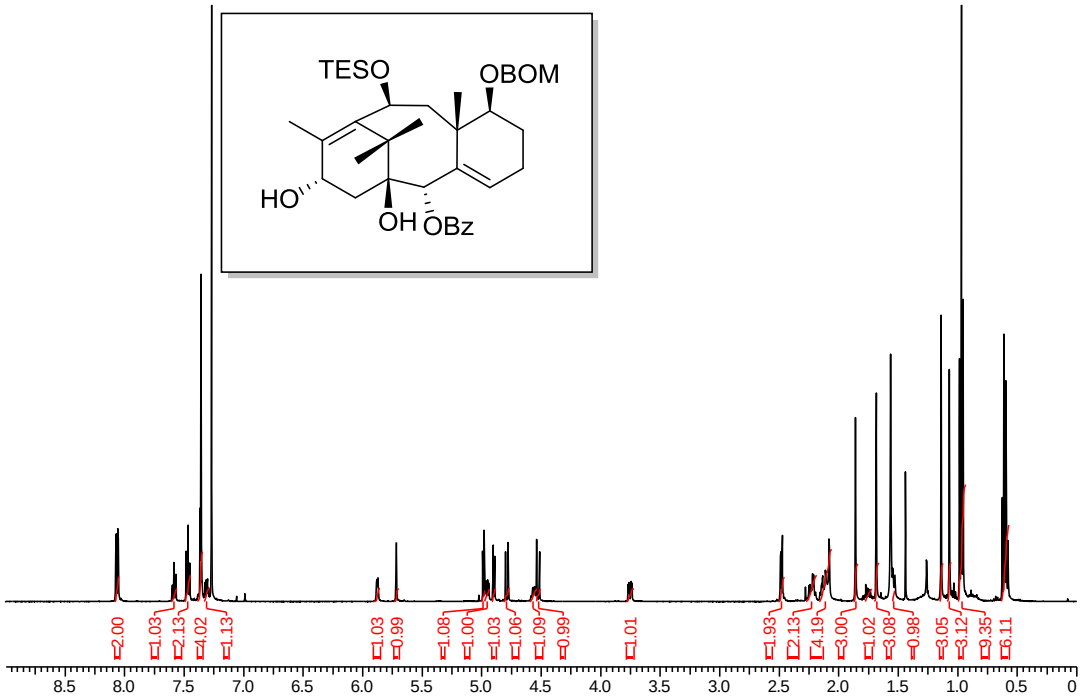
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OBz
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1.00
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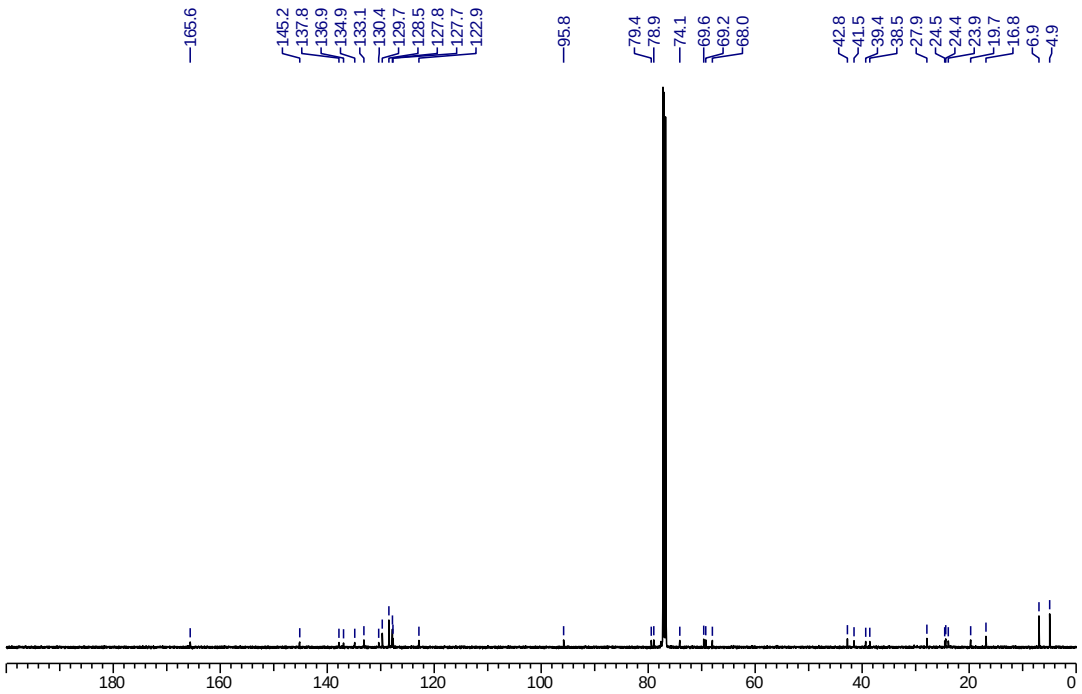
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78.9
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38.5
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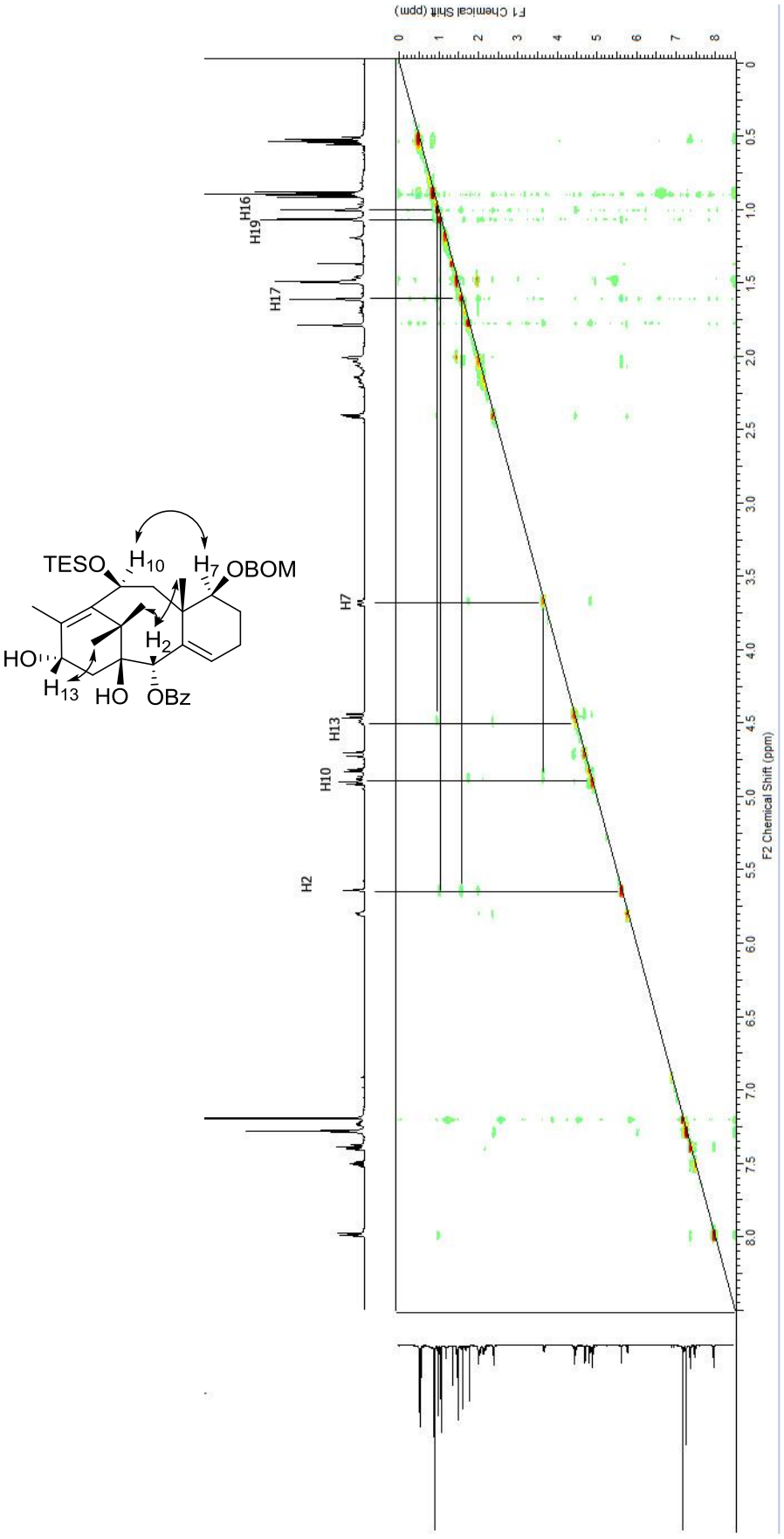
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F2 Chemical Shift (ppm)
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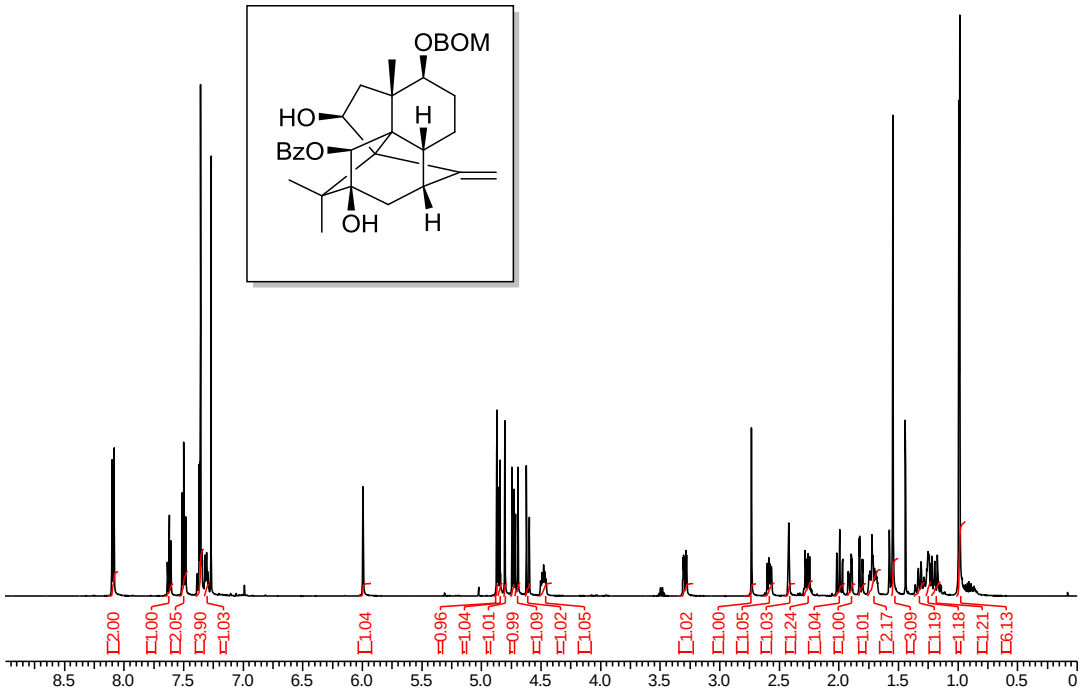
HO
H13
HO
OBz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H
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3.90
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1.04
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1.04
1.01
0.99
1.09
1.02
1.05
1.02
1.00
1.05
1.03
1.24
1.04
1.00
1.01
2.17
3.09
1.19
1.18
1.21
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6.0
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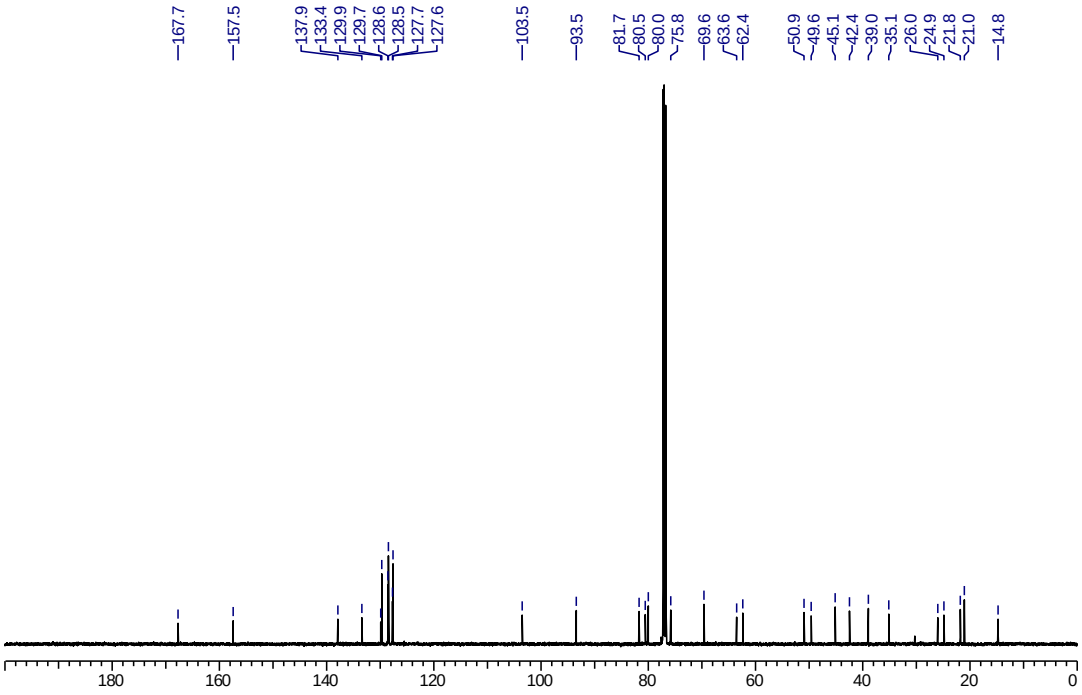
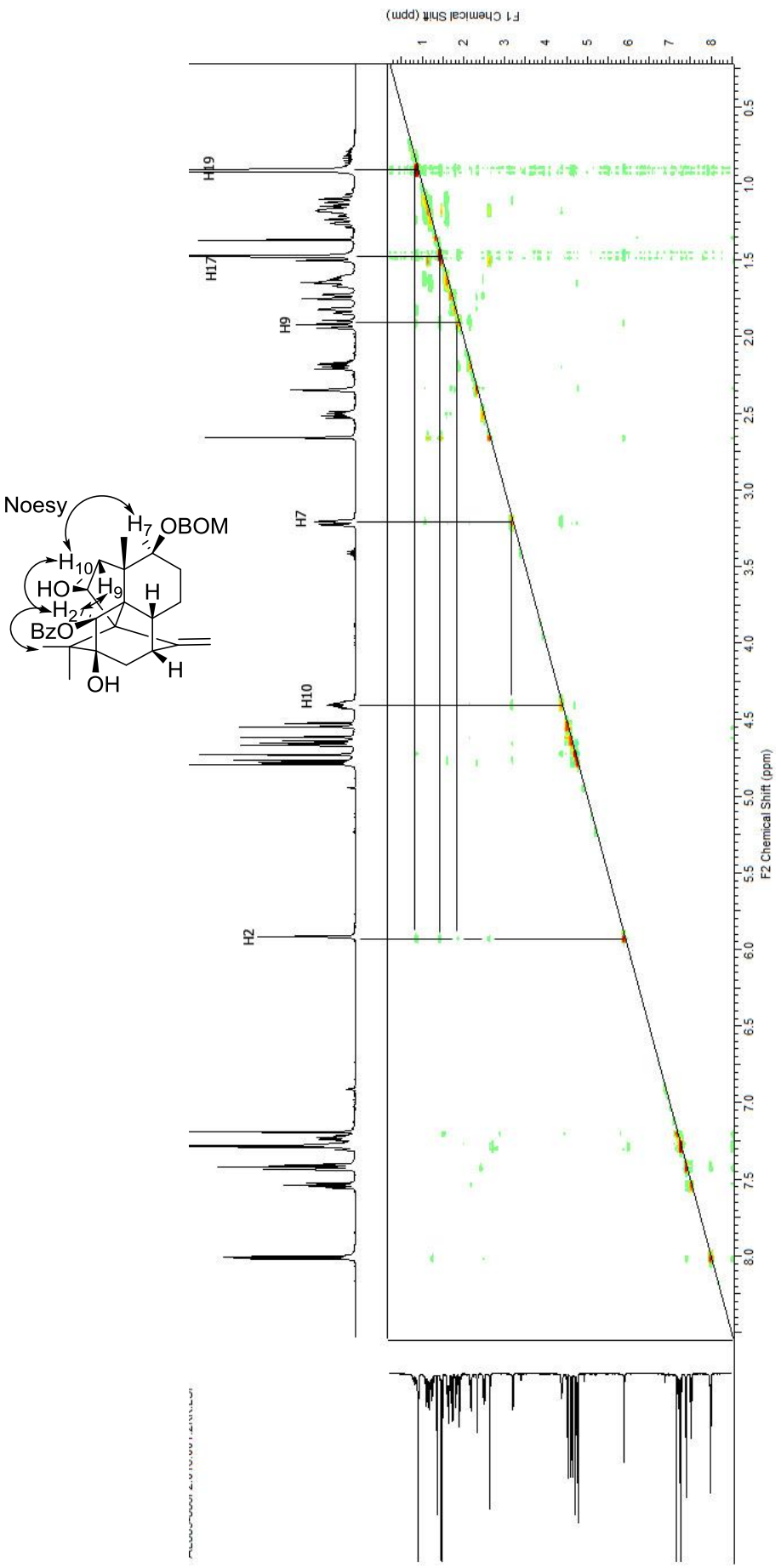
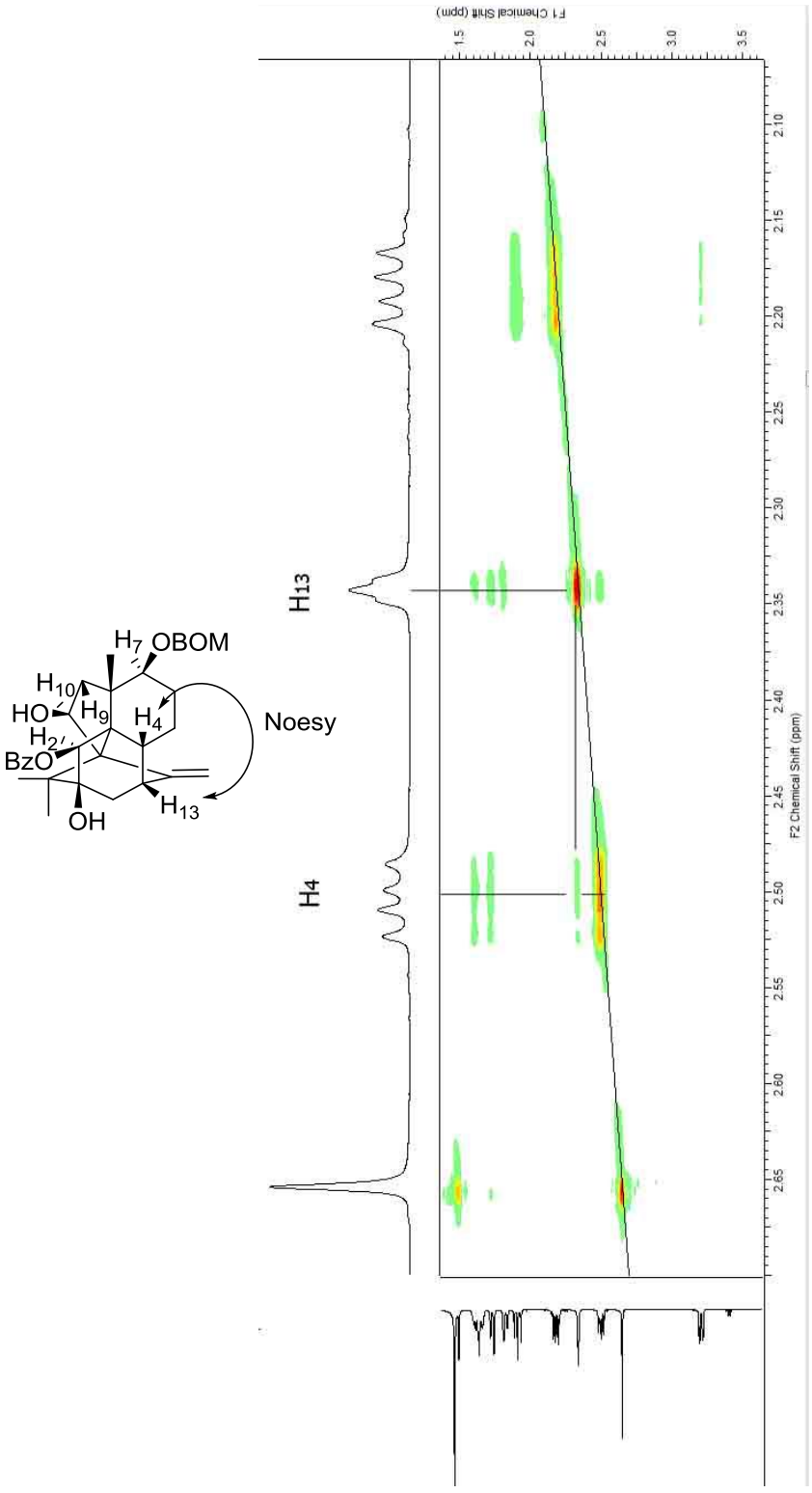
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0


167.7
157.5
137.9
133.4
129.9
129.7
128.6
128.5
127.7
127.6
103.5
93.5
81.7
80.5
80.0
75.8
69.6
63.6
62.4
50.9
49.6
45.1
42.4
39.0
35.1
26.0
24.9
21.8
21.0
14.8
180
160
140
120
100
80
60
40
20
0


Noesy
H7
OBOM
H10
HO
H9
H
H2
BzO
OH
H
H19
H17
H9
H7
H10
H2
F1 Chemical Shift (ppm)
F2 Chemical Shift (ppm)


H7 OBOM
H10
HO
H9
H4
H2'
BzO
OH
H13
Noesy
H13
H4
F1 Chemical Shift (ppm)
F2 Chemical Shift (ppm)