University of East Anglia

STUDIES TOWARDS THE SYNTHESIS OF THE GUAIANOLIDE AND PSEUDOGUAIANOLIDE SKELETON

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PREFACE

The research described within this thesis is, to the best of my knowledge, original and my own work, except where due reference has been made.

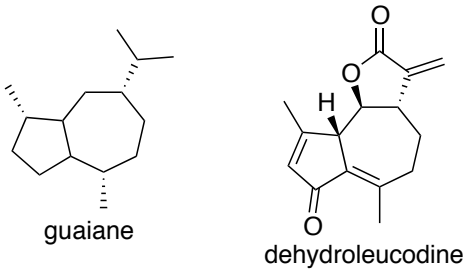
Miklos de Kiss,

Norwich, October 2012.

ABSTRACT

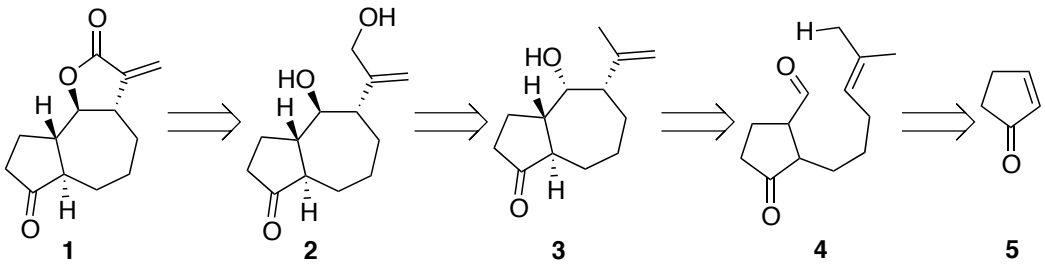
A synthesis of the guaiane skeleton is presented in my thesis.

Guaianolides and pseudoguaianolides are sesquiterpene lactones and share a sommon backbone: the guaiane skeleton. Hundreds of natural products belong to these families of compounds. The guaiane skeleton is characterised by a bicyclo[5.3.0]decane ring system (perhydroazulene). Among the guaianolide family, dehydroleucodine was chosen as a target example.



The first part of the thesis introduces the guaianolide and pseudoguaianolide families. An overview of the biological properties and the biosynthesis are reported. First, structures from componds belonging to these families are described. Then, the biological properties of the dehydroleucodine are reported and, finally, the syntheses of three sesquiterpene lactones are shown.

The second part of the thesis reports my studies towards the synthesis of the guaiane skeleton and dehydroleucodine. The key step of the construction of the perhydroazulene ring system **3** is an intramolecular ene reaction. The lactone is build through an inversion of the alcohol configuration followed by an allylic oxidation **2** and finished by an oxidation of the primary alcohol **1**. A proposal of the synthesis of dehydroleucodine is briefly explained.



The final part is the experimental part.

ACKNOWLEDGEMENTS

My studies were performed in Professor Page's group at the University of East Anglia (Norwich, Norfolk).

I would like to thank my supervisor, Professor Phil Page for his welcome in his laboratory and the confidence Phil granted me for carrying on a subject started years ago.

Of course, I can't forget my fiancée for her daily support through those hard times of research, Doctor Yohan Chan for his help in the lab and outside, and all my lab-mates for the nice atmosphere we work in.

I have a special thought to my so dear friend Franklin, who left us too early. I am sure he would have loved to read this thesis through and give it his mark and corrections.

At last, I need to be grateful for the funding from the University of East Anglia.

List of abbreviations

Ac	acetyl
acac	acetylactonate
aq.	aqueous (solution)
Ar	aromatic (proton)
Bn	benzyl
t-Bu	*tertio*-butyl
n-Bu	Normal butyl
cat.	catalytic
$CDCl_3$	deuterated chloroform
cm^{-1}	wave number
°C	degrees Celsius
CI	chemical ionisation
conc.	concentrated
COSY	correlation spectroscopy (NMR)
Δ	heating
d	doublet
δ	chemical shift
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
de	Diastereoisomeric excess
DIAD	diisopropylazodicarboxylate
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMS	dimethylsulfide

DMSO	dimethylsulfoxide
ee	enantiomeric excess
EI	electron ionisation
equiv.	equivalent
ESI	electrospray ionisation
Et	ethyl
FAB	fast atom bombardment
FT	fourier transform
h	hour(s)
HCl	hydrogen chloride
HOMO	highest occupied molecular orbital
HSAB	hard soft acid base
Hz	Hertz
IBX	2-iodoxybenzoic acid
IR	infrared
J	coupling constant
LDA	lithium diisopropylamine
LUMO	lowest unoccupied molecular orbital
M	molarity
m	multiplet
$MgSO_4$	magnesium sulfate
min	minute(s)
mp	melting point
NMO	*N*-metylmorpholine-*N*-oxide

NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
PDC	Pyridinium dichromate
ppm	parts per million
*p*TSA	*para*-toluenesulfonyl acid
pyr	pyridine
q	quartet
r.t	room temperature
sat.	saturated
s	singlet
SM	starting material(s)
t	triplet
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
UV	ultraviolet

All other abbreviations are used according to the IUPAC nomenclature or SI units

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CHAPTER I:

INTRODUCTION

INTRODUCTION

Syntheses of bioactive natural products have always been interesting in medicinal research for several reasons. First of all, it provides an elucidation and a verification of the structure established directly from the extract of the natural source. Modifications of the actual natural compound can be performed by controlling the synthesis and allow the development of new properties with studies on the structure-activity relationships. Therefore, a synthesis can widen the study of the natural molecule by an easier access to homologues. Indeed, changing the different moieties around a molecule, coupled with biological studies, allows us a closer understanding of the biological mechanism. The starting natural compound can be modified in order to increase its actual properties (absorption, side effects…) and activities.

Towards that aim, the Page group has been involved in the synthesis of the tigliane and diaphnane skeletons characterized by tricyclo[9.3.0.0^{2,7}]tetradecane cores (Figure 1).[1] Among those natural compounds are the esters of phorbol, which are very potent co-carcinogens or tumour promoters (Figure 1).[2]

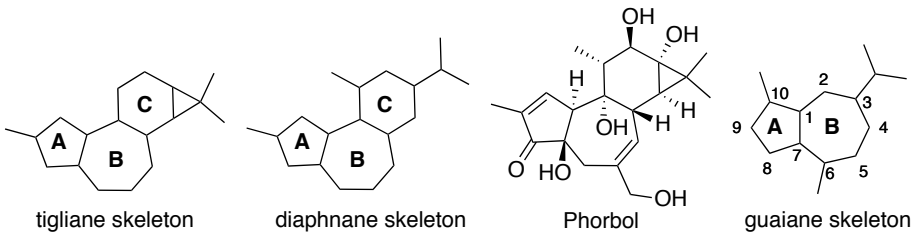


Figure 1

More recently, studies of another family, the guaianolides and pseudoguaianolides, had been started in our laboratory.[3] That family is composed of hundreds of active natural compounds and characterized by a simpler bicyclo[5.3.0]decane core, for example the guaiane skeleton (Figure 1). The approach to that core may allow us to access several natural products.

The following chapters briefly introduce the reader to the guaianolide and pseudoguaianolide families; describe the actual work performed during this Doctoral research; and conclude with the experimental data.

I) Guaianolide and pseudoguaianolide families

1) Generalities

Sesquiterpene lactones constitute a large and diverse group of biologically active chemicals that have been identified in several plant species. For example, in the family *Compositae* (commonly known as the sunflower family), they can cause allergic reactions and can be toxic for animals if overdosed, particularly in grazing livestock. Under specific administration, they can work as drugs for their anti-inflammatory and anticancer effects.[4] Plants containing sesquiterpene lactones have been used in modern and old civilizations (People from developing countries in rural areas like India or Argentina) to treat certain medical problems such as diabete, cancer and peptic ulcer.[5] Sesquiterpene lactones number thousands of natural compounds.[6] Among that family, guaianolides and pseudoguaianolides can be found (Figure 2 and Figure 3). They are characterized by a bicyclo[5.3.0]decane core with a 5-membered ring lactone on the 7-membered ring as shown in Figure 2. A 5-membered ring lactone is generally fused on the carbons 2 and 3 or 3 and 4 on the 7-membered ring with the single bond carbon-oxygen being on the carbon 2 or 4. This α-methylene-γ-lactone moiety in the structure has been shown to be essential for a significant cytotoxicity, and in most of the cases, the presence of a ketone on the 5-membered ring has proved to enhance this bioactivity.[7] The ketone has been observed on all the different carbons of the 5-membered ring (carbons 8, 9 and 10). Repin and thieleanin are representatives of the guaianolide family as is dehydroleucodin. Aromaticin and coronopilin are pseudoguaianolides.

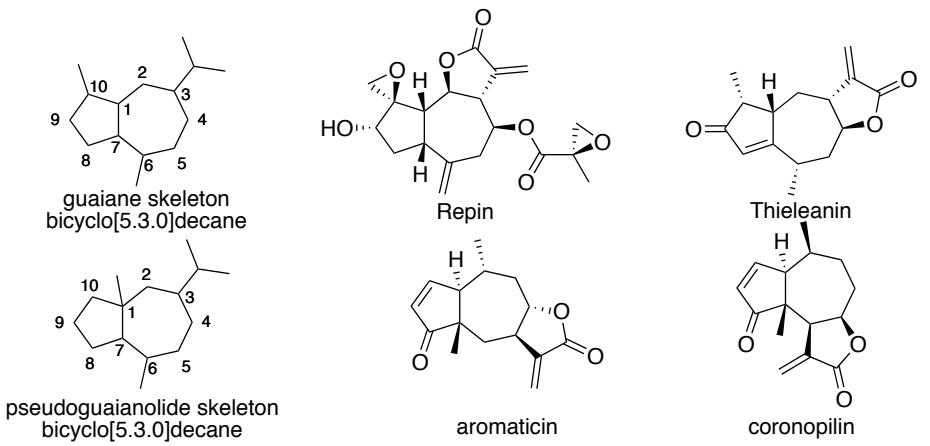
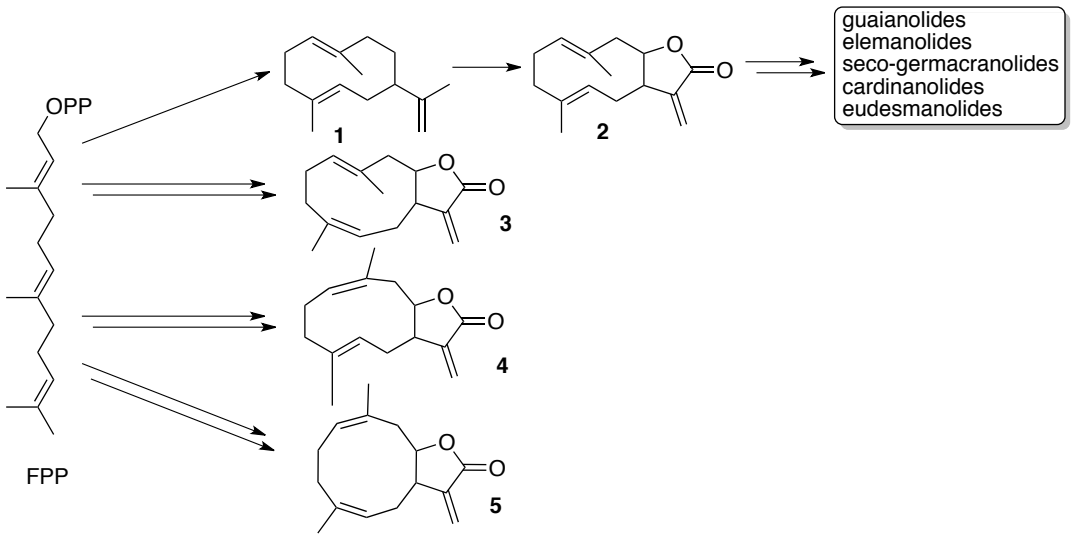


Figure 2

2) Theory for the biosynthesis of guaianolides and pseudoguaianolides

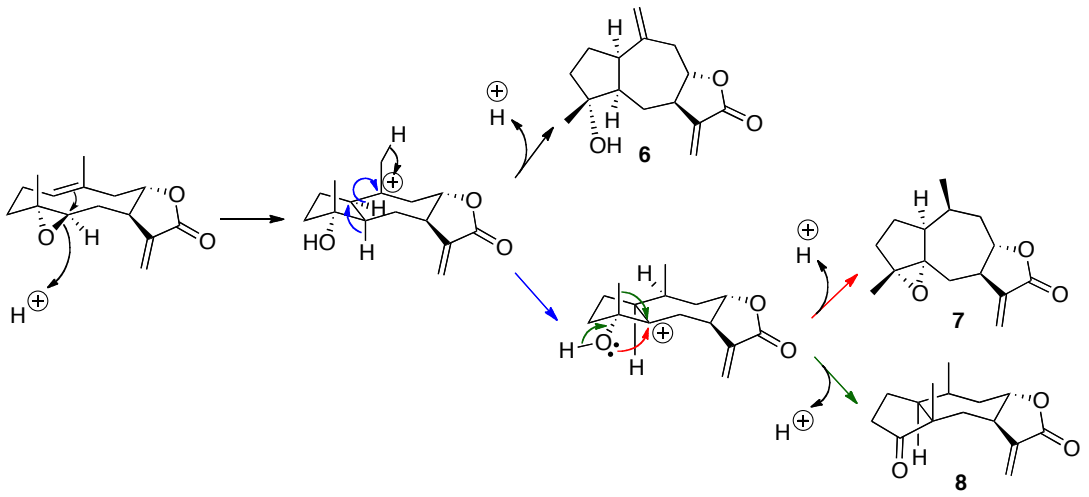
Nature has provided a very wide diversity of natural compounds. Most of these products are thought to have common origins and a very limited number of routes for their biosyntheses.[8a,8b] For example, terpenes and terpenoids in superior organisms find their origin in mevalonic acid, while, in lesser organisms, they derive from 1-deoxy-D-xulose-5-phosphate. For the sesquiterpene family used by superior organisms, the common origin was found to be either in farnesyl pyrophosphate (FPP in Scheme 1) or nerolidyl pyrophosphate.[8a] Because of their interesting biological activities, several fundamental aspects of the biogenesis of sesquiterpenes were studied and are now well known (influence of enzymes and genes that codify for them).[8c] The terminal biogenesis of different natural products responsible for the great structural diversity of compounds has been rarely studied and there are still many unanswered questions on the mechanism responsible for generating such a diversity of molecules. However, one or two steps of the biogenesis process can be performed *in vitro*.



Scheme 1[8b]

trans,trans-Germacradiene (**1** in Scheme 1) is obtained by direct cyclisation of *trans,trans*-FPP which undergoes an enzymatic oxidative modification to afford the corresponding lactone **2** (Scheme 1). From the first biogenetic stage, four different conformations have been isolated: **1**, heliangolides (**3**), melampolides (**4**) and Z,Z-germacranolides (**5**). From the second stage, for the

trans,trans-germacradiene lactone (**2**), five different types of skeletons are produced. Scheme 2 shows the ring closure suffered by an epoxide of *trans,trans*-germacradiene lactone to afford guaianolides on the second stage (**6** and **7** in Scheme 2) and the methyl migration-originated pseudoguaianolides on the third stage (**8** in Scheme 2).



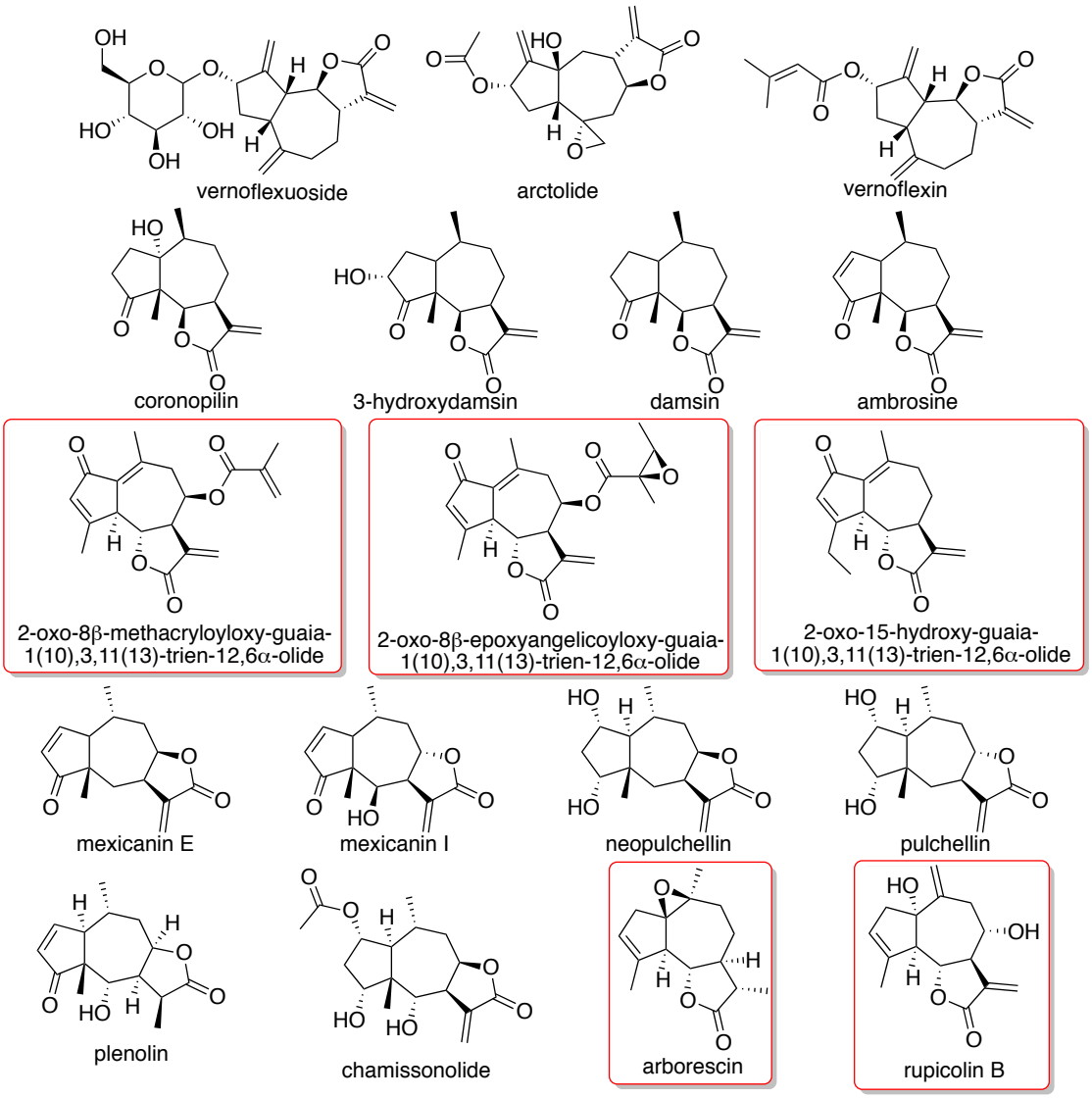
Scheme 2[8b]

3) Biological activities

Guaianolides and pseudoguaianolides are a very wide group of natural products comprising more than 200 varieties known to date. The large variety of that family arises from additional functionalities on the five-membered ring and the seven-membered ring (Figure 3). Those natural compounds have shown a wide range of biological activities such as cytotoxicity,[7b,7c,9a,9b] and high antitumoural,[9c] contraceptive,[9d] allergenic,[9c,9e] antischistosomal,[9f] anthelmintic,[9g] anti-inflammatory,[9h] growth plant regulator activities.[9i-9k] Studies of sesquiterpenes against numerous tumour models have shown that the presence of the α-methylene-γ-lactone was a condition *sine qua non* for biological activity and that the exocyclic double bond was essential for cytotoxicity.[7] However, the presence of cyclopentenone appeared to produce enhanced cytotoxicity but on its own, that moiety in sesquiterpenes displayed no significant activity.[7b,7c]

4) Some guaianolides and pseudoguaianolides

According to the developed pathway in our group,[1] we focused on the *trans*-fused perhydroazulene ring systems. A carbon numbering of the guaiane skeleton was shown on Figure 2 (p3). We looked for a *trans* relative stereochemistry at C1 and C7, and an Alder-ene cyclisation would give the framework for a lactone between C2 and C3 (numbering on Figure 2). The ketone moiety would be originally at C8.



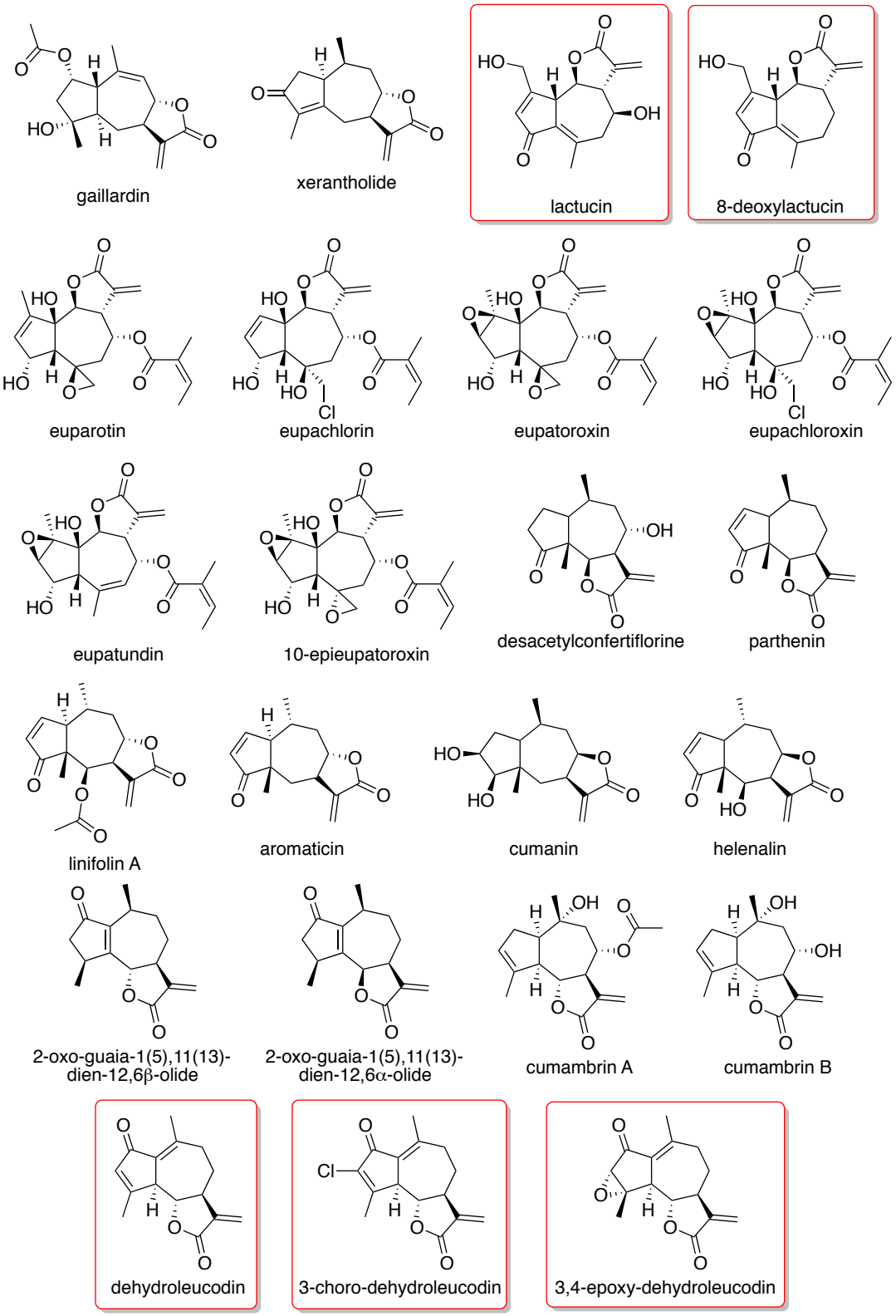

gaillardin
xerantholide
lactucin
8-deoxylactucin
euparotin
eupachlorin
eupatoroxin
eupachloroxin
eupatundin
10-epieupatoroxin
desacetylconfertiflorine
parthenin
linifolin A
aromaticin
cumanin
helenalin
2-oxo-guaia-1(5),11(13)-dien-12,6β-olide
2-oxo-guaia-1(5),11(13)-dien-12,6α-olide
cumambrin A
cumambrin B
dehydroleucodin
3-choro-dehydroleucodin
3,4-epoxy-dehydroleucodin

Figure 3

II) Dehydroleucodine

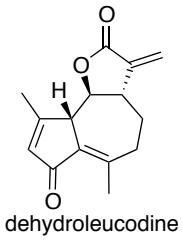


Figure 4

1) Generalities

Dehydroleucodine (Figure 4), a sesquiterpene lactone, was first extracted by Giordano from the aerial part of *Artemisia Douglasiana* Besser (Picture 1[10]).[11] *Artemisia Douglasiana* Besser, from the *Asteraceae* family, can be found in the northern Baja in California and in Argentina.[12] In the USA, it is commonly called Douglas' sagewort or mugwort and in Argentina it is known as "matico".

Picture 1

A hypothesis on its origin was proposed by Keck *et al.* in 1946.[12] Indeed, *Artemisia Douglasiana* Besser, a hexaploid species of inland valleys and moderate altitudes, would found

its origin from amphidiploidy (addition of the chromosomes) of the costal diploid species *Artemisia Suksdorfii* Piper and the interior mountain tetraploid *Artemisia Ludoviciana* Nutt. *Artemisia Douglasiana* Besser combines the essential characters of its presumed parents, and its environment is in an intermediate area between their ranges.

The first report of its occurrence in Argentina was in 1967 by Ariza Espinar. It was probably imported into Argentina through Chile.[11,12]

In Argentina, *Artemisia Douglasiana* Besser is popularly known as "matico", and is used in traditional medicine for stomachache, diarrhoea, intestinal infections and wounds. The "matico" is generally used in an infusion of the boiled leaves. Such popular use prompted pharmaticological studies of that plant and the extraction of the active molecule, dehydroleucodine.[13]

2) Extraction, isolation and characterisation

Aerial parts of *Artemisia Douglasiana* Besser were collected and air-dried. This air-dried material was extracted with chloroform by soaking it in the solvent at room temperature for 48 hours (3 times). The combined organic extracts were concentrated, diluted in 95% ethanol and extracted with 4% aqueous lead(IV) acetate solution. The aqueous extract was filtered through a pad of celite and concentrated to dryness under vacuum. The crude mixture was re-extracted with $CHCl_3$ (3 times) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/hexane gradient) and afforded dehydroleucodine.[14] The purification allowed the isolation of 8 g of dehydroleucodine from 1 kg of cell culture.[5a]

In 2003, Penissi succeeded in elaborating a new efficient method based on HPLC to detect and quantify dehydroleucodine present in plant extracts.[15] The air-dried material was extracted with acetone (6 times) at room temperature, and concentrated under reduced pressure. A stock solution was prepared from the extract by its sonication in DMSO at room temperature for 2 min, before its injection in HPLC. The free form of dehydroleucodine was found to be usually weak chromophore and electrochemically inactive. Therefore, HPLC was combined with postcolumn *o*-phthalaldehyde automatic derivatization to increase the detectability of the natural compound

and fluorescence detection using 360-nm excitation and measuring emission at 450 nm. In optimal experimental conditions, dehydroleucodine showed a well-defined chromatographic peak with a retention time of 7.73 ± 0.04 min (Figure 5). This method allowed 95% recovery of dehydroleucodine.

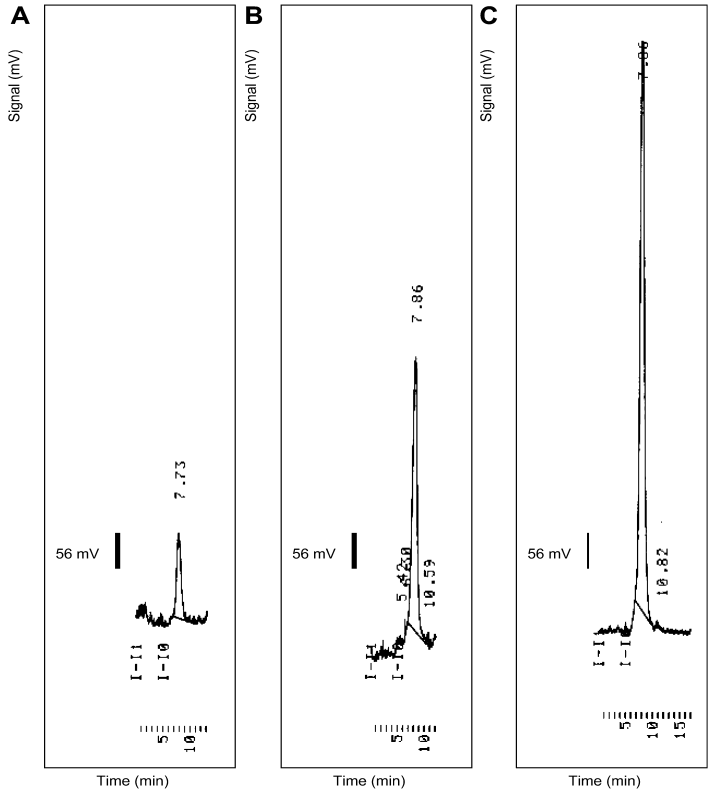


Figure 5: Chromatographic profiles of dehydroleucodine at different concentrations: (A) Low (B) Medium (C) High concentrations.

The extraction and purification of dehydroleucodine permitted its identification: IR ν_{max} /cm^{-1} 1780, 1695, 1635, 1625; Mp = 131 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 8.6 (m), 7.8 (m), 7.7 (d), 7.6 (s), 7.15 (m), 6.4 (m), 4.53 (d), 3.9 (dq), 3.88 (d).[16]

3) Biological activities

Artemisia Douglasiana Besser or "Matico" is well known in Argentinean traditional medicine to exhibit gastric cytoprotective activity and to treat sores in external applications.[13] After further studies, dehydroleucodine was confirmed as gastric cytoprotective agent but it was

reported as well for its antidiarrhoeal activity and its inhibition of the enzyme P450 aromatase, which belongs to the superfamily of cytochrome P450. This terminal enzyme is responsible for the conversion of androgens (e.g. testosterone) into oestrogens by oxidation reactions.

a. Cytoprotective agent against ulcer

In Argentina, folk medicine uses matico in an infusion of the boiled leaves to treat peptic ulcer. Preliminary studies on the aqueous extract of *Artemisia Douglasiana* Besser showed reproducible cytoprotective activity against ulcerogenic agents such as absolute ethanol in rats. Those preliminary results led to the extraction and isolation by Giordano *et al.* of the active molecule, a sesquiterpene lactone of the guaianolide family, dehydroleucodine.[14]

Giordano *et al*. reported dehydroleucodine as having a cytoprotective effect. The comparison of the natural compound with different sesquiterpene lactones revealed that the presence of α-methylene-γ-lactone is essential for the observed antiulcerologenic activity, while the β-unsaturation of the ketone is not necessary. However, this β-substituted cyclopentanone moiety is a requirement for other activities such as the antitumour, antimicrobial and antifeedant properties.[14]

Further studies on the mechanism of the antiulcer action of dehydroleucodine have shown that oral administration of this drug provokes a gastrointestinal cytoprotective activity,[17a] and prevents gastric lesions induced by various necrotizing agents such as absolute ethanol.[17b] This protective effect can be partially explain by the ability of the natural molecule to stimulate the mucus production. It prevents the depletion of endogenous dopamine and the release of serotonin (also called 5-hydroxytryptamine), which are both neurotransmitters involved in pathogenesis of peptic ulcers.[17c]

Mucus plays an important role in the protection of the gastrointestinal mucosa against aggressive environment caused by different factors such as stress or acidic and peptic secretions. Dehydroleucodine induces an increase of the thickness of that mucus layer, and therefore improves the gastrointestinal protection.[17c]

Mast cells can be considered as 'alarm' cells because they are part of an early warning system. These cells detect the presence of foreign substances in the mucosa and trigger the appropriate inflammatory response.[17b] Dehydroleucodine has been observed to provoke changes in mast cell mechanism. It could prevent the release of histamine and serotonin, two valuable markers of mast cell activation, and therefore, reduce the intestinal damages induced by necrosis-inducing agents.[17b]

b. Antidiarrhoeal activity

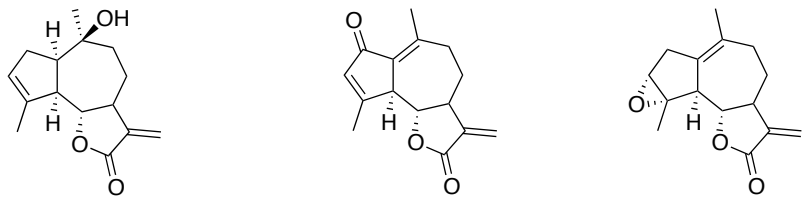
Diarrhoea is a major health problem. It remains the second leading cause of death among children under five years old, just after pneumonia.[18] Most of the drugs, which are useful against diarrhoea, are not accessible to everyone, especially in developing countries where it is the most needed. Indeed, up to 17% of children deaths in the paediatrics ward are due to diarrhoea diseases.[19]

In Argentina, Matico is used against diarrhoea. The dehydroleucodine antidiarrhoeal activity was explored and confirmed with studies on mice and rats.[20] It inhibits the intraluminal fluid accumulation and small intestinal motility in mice. This effect is mediated, at least in part, through the α_2-adrenergic system, which influences adenylate cyclase, enzyme involved in the outside-in signaling cascade. However, the exact mechanism remains unclear due to a large number of parameters to consider such as the behaviour of sensory nerves or hormones. Nevertheless, those results allow the conclusion that dehydroleucodine could represent a useful tool in relieving gastrointestinal colic and diarrhoea as reported in folk medicine.[11]

c. Aromatase inhibitor

Some sesquiterpenes lactones have been investigated for their action as aromatase inhibitors.[21] Aromatase is the enzyme that synthesizes oestrogen. Aromatase inhibitors can be used as drugs to treat breast cancer and ovarian cancer before the menopause. It may also treat or prevent gynaecomastia (widening of male breast tissue) in men. Aromatase inhibitors are used to block oestrogen production or its action on receptors, and are therefore used to treat the diseases that require oestrogen to grow.

The guaianolides 10-*epi*-8-deoxycumambrin B, dehydroleucodine and ludartin (Figure 6) were found to be the most active among the sesquiterpene lactones screened.[21] 10-*epi*-8-Deoxycumambrin B and dehydroleucodine acted as type II ligands to the heme iron (directly bind to the iron atom) present in the active site of aromatase cytochrome P450.[21] They failed to affect the cholesterol side-chain cleavage enzyme activity on human placental mitochondrias, which show a better specificity than aminoglutethimide, an anti-steroid drug currently marketed by Novartis to treat breast cancer by inhibiting the synthesis of steroids from cholesterol.[22] That activity led to further structure-activity relationship studies. α-Methylene-γ-lactone affects the cytotoxicity, and reduction of the β-unsaturation of the lactone does not affect the anti-aromatase activity, but does eliminate the cytotoxic activity of the molecule. Asymmetric reduction of the *exo* double bond of the α-methylene-γ-lactone moiety of 10-*epi*-8-deoxycumambrin B by sodium borohydride gave 11βH,13-dihydro-10-*epi*-8-deoxycumambrin B, which shows an activity similar to aminoglutethimide.[22]



10-*epi*-8-deoxycumambrin B
IC_{50} = 7 μM

Dehydroleucodine
IC_{50} = 15 μM

Ludartin
IC_{50} = 55 μM

Figure 6

Cytochrome P450 aromatase failed to crystallize because of its solubilisation resistance. Consequently, several three-dimensional models were suggested, and one of the most complete and detailed models of cytochrome P450 aromatase was proposed by Graham-Lorence in 1995.[23] Figure 7 represents a three-dimensional model of the binding of sesquiterpene lactone 10-*epi*-deoxycumambrin (white sphere L) or steroid (black sphere S) with cytochrome P450 aromatase.

In that model, Blanco *et al.* proposed the following interactions:[22]

- The lactone at C-12 of L coordinate with the K473 (lysine) of the cytochrome P450 aromatase;

- The hydroxyl group at C-10 is β-oriented and binds the heme iron present in the aromatase active site;

- Reduction of the conjugation of the lactone moiety of L produces a more apolar region, which fills the hydrophobic pocket predicted for the aromatase active site.

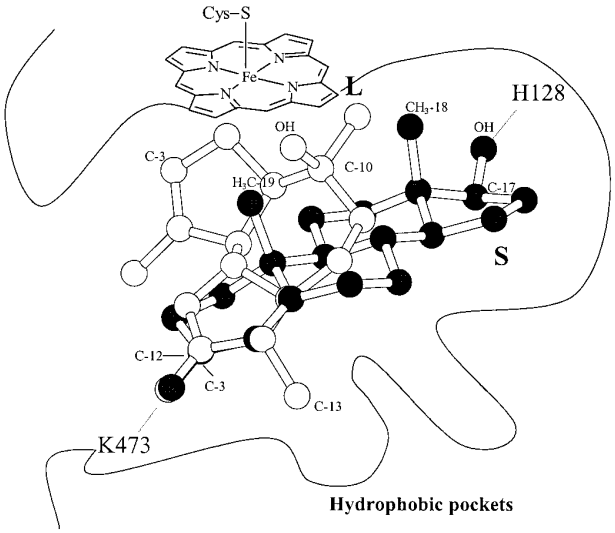


Figure 7[23]

The aromatase P450 inhibitory action of dehydroleucodine prompted a study of whether or not it affects the reproductive tract in males.[24] The results suggested that dehydroleucodine does not affect the plasma concentration of testosterone and oestradiol (sexual hormones) and does not affect testicular activity, whereas it alters several epididymal parameters. The epididymis, a narrow, tightly coiled tube, is a part of the male reproductive system. Spermatozoa are achieved and stored in the epididymis.[24]

d. Anti-obesity potential

Obesity is a worldwide health problem, which has exploded over the last decades. The World Health Organisation (WHO) considered obesity as the fifth leading risk for global death (2008).[25] On a global scale, it has reached epidemic proportions with more than 1.4 billion adults overweight and up to 500 million of them clinically considered as obese. Overall, more than one in ten of the world's adult population is obese.[25]

Numerous studies have tried to assess the impact of obesity on health. Results have shown than it can be associated with multiple pathology especially diabetes, hypertension, osteoarthritis and heart disease.[26]

The main way to treat overweight patients remains a strict diet and physical activities if possible.[25] Until 2010, obesity was treated by two different types of drugs, in addition to diets and physical exercises.[26] The first one inhibits pancreatic lipase, which reduces intestinal fat absorption. The active chemical is tetrahydrolipstatin also known as orlistat and marketed as Xenical® or Alli® (Figure 8). The major side effects are steatorrhea (excess of fat in faeces), incontinence, abnormal flatulence and bowel movements. A reduced calory diet, less than 15 grams of fat per meal, is recommended during the treatment and should minimize those effects. The other one, marketed from 1997, is an anorectic or appetite suppressant. The molecule is called sibutramine and commercialized under the name of Reductil® in Europe (Figure 8). Sibutramine was withdrawn from the market in 2010, in Europe and most other countries, because of important cardiovascular side effects (increased risks of heart attacks and strokes).

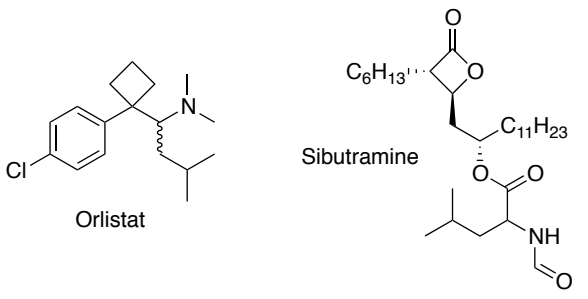


Figure 8

Currently, the only chemical approved by the FDA (US Food and Drug Adminitration) and the European Medicines Agency is orlistat. Because of the adverse side effects, its prescription is recommended for obesity only when the drug benefits outweigh the risks.

The high costs and the hazardous side effects of this drug for obesity treatment prompted research to explore new potential drugs and especially natural products, oriented through new mechanisms of action against obesity.[26]

The adipogenesis is the process through which adipocytes, cells responsible for the accumulation of fat, and thus, the possible development of obesity, are formed. This process is well understood and involves several cell-differentiation steps. Inhibition of this differentiation process may prevent or treat obesity. Studies have demonstrated that dehydroleucodine significantly blocked it by a dramatic downregulation of the expression of adipogenic transcription factors.[27] Adipocytes, also called lipocytes or fat cells, function as energy storage (fat storage).[28] Inhibition of the preadipocyte differentiation process should lead to a decrease of adipocyte quantity, and therefore the body should store less fat.

A significant decrease of lipid droplet accumulation was observed upon addition of dehydroleucodine to the medium.[27] The mechanism of action of this drug is not clearly determined, but an attenuation of the production of transcriptional factors, PPARγ and C-EBPα, during adipogenesis has been observed. The inhibition is dose-dependent, but at too high concentration (>10 μM), dehydroleucodine causes cell toxicity. Studies have shown the importance of the α-methylene-γ-lactone for the preadipocyte differentiation even though dehydro-dehydroleucodine (reduction of the conjugated double bond on the lactone moiety) has also shown blockade of the formation of adipocytes. However, the dehydroleucodine derivative exhibited a 10-fold decrease in this effect. The results suggested that only a specific epimer might be responsible for that activity.

Dehydroleucodine inhibition on adipocyte differentiation suggests that it can be considered as potential therapeutic treatment for obesity or as obesity prevention. With regards to those results, the scope of obesity drugs may be enlarged to other natural products that inhibit adipocyte differentiation.

III) Synthetic approaches towards the bicyclo[5.3.0]decane core

The wide range of biological activities have motivated synthetic research on the building of the bicyclo[5.3.0]decane skeleton (Figure 9) and many routes towards this core were developed.[29] It is a common framework to several natural products. In the sesquiterpene group, eight different subgroups feature this core.

A plethora of approaches have been published to access the bicyclic terpene ring system, often even before completion of the total synthesis. From all those studies, three general approaches can be pointed out. The first one is a synthesis based on strategic disconnection identifying a linear commercial chemical, followed by a cyclisation (in 1 or 2 times).[29b,30] The second method is to build around a pre-existing ring, 5- or 7-membered ring, functionalized and/or chiral if necessary.[29e,31] The last method is rearrangement from another ring system.[31f,32]

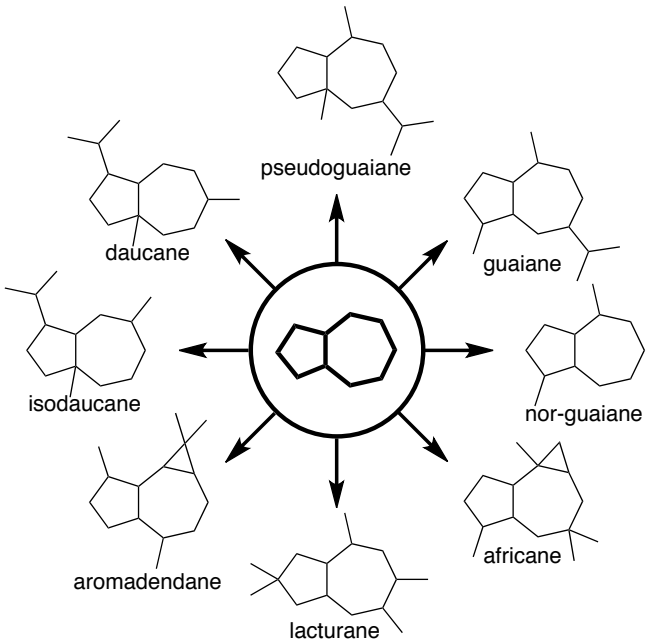


Figure 9

Figure 3 shows examples of molecules from the guaianolide and pseudoguaianolide families. More than 200 natural compounds from those families have been described to date. Because of the wide scope of biological activities, guaianolides and pseudoguaianolides have aroused great interest from biologists, analytical chemists and synthetic chemists.

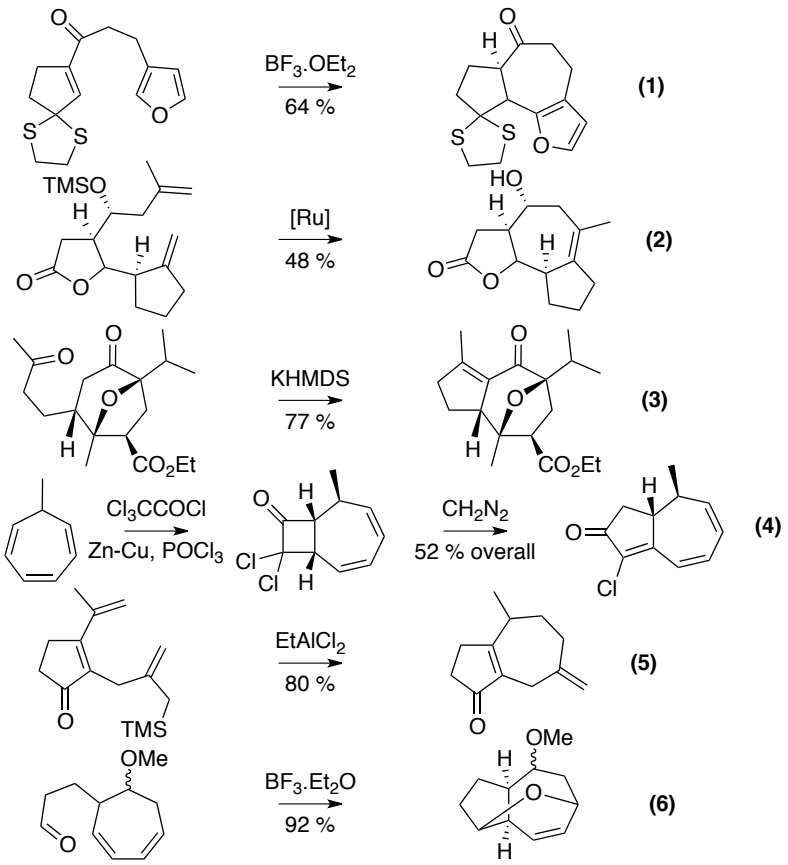
Syntheses of natural compounds allow biologists better understanding of the studies of biomolecular mechanisms of pathologies and of structure-activity relationship (SAR). Moreover, natural molecules provide lead structures for drug research and their synthesis allows modifications of these structures in order to increase biological properties or to avoid any toxicity or undesirable side effects. Besides, configurations of natural compounds are not always clearly established, and thus, their synthesis helps with the confirmation of that stereochemistry.

In the following section some methodologies already used to synthesize guaianolides are briefly explored. Syntheses of a pseudoguaianolide (Scheme 4), a guaianolide (Scheme 6 and Scheme 7) and the first total synthesis of the phorbol (Scheme 8 and Scheme 9) are discussed.

1) Building around a pre-existing ring

a. Overview

Starting from a 5- or 7-membered ring, different cyclisation key steps have been studied. Tanis used an electrophilic substitution to close the 7-membered to obtain the 5,7-fused ring system with control of the fusion stereochemistry (equation 1 Scheme 3).[31] Reiser suggested a ring closing metathesis (RCM) to close the 7-membered ring and obtained a 5,7,5-fused ring system (equation 2 Scheme 3).[40] Many other groups used the RCM approach for the 5,7-fused ring system building.[29g,31d,31g,] Several groups worked on the synthesis of englerin, some of them choosing an enolate addition for the cyclisation method. With a different synthon, Nicolaou[31h] (equation 3 Scheme 3) and Lin[31i] used an enolate addition to cyclise the 5-membered ring, and Maier followed a similar key step to create the ring junction from a 10-membered ring.[31j] Deprès published an example of cycloaddition, followed by a ring expansion as the key steps (equation 4 Scheme 3) in the synthesis of geigerin.[31f] Majetich synthesized (±)-graveolide and (±)-aromaticin:[31c] the perhydroazulene framework was obtained after Michael cyclisation through an allyl silane-based annelation (equation 5 Scheme 3). An elegant hetero-Diels-Alder reaction was a key step in the fusion of the 5- and 7-membered rings (equation 6 Scheme 3) in the synthesis of (±)-dehydrocostus lactone and (±)-estafiatin by Rigby.[31a] The methodology we used (*vide infra)*, an Alder ene cyclisation to obtain the 7-membered ring, was described in 1993 by Kuroda.[29e]



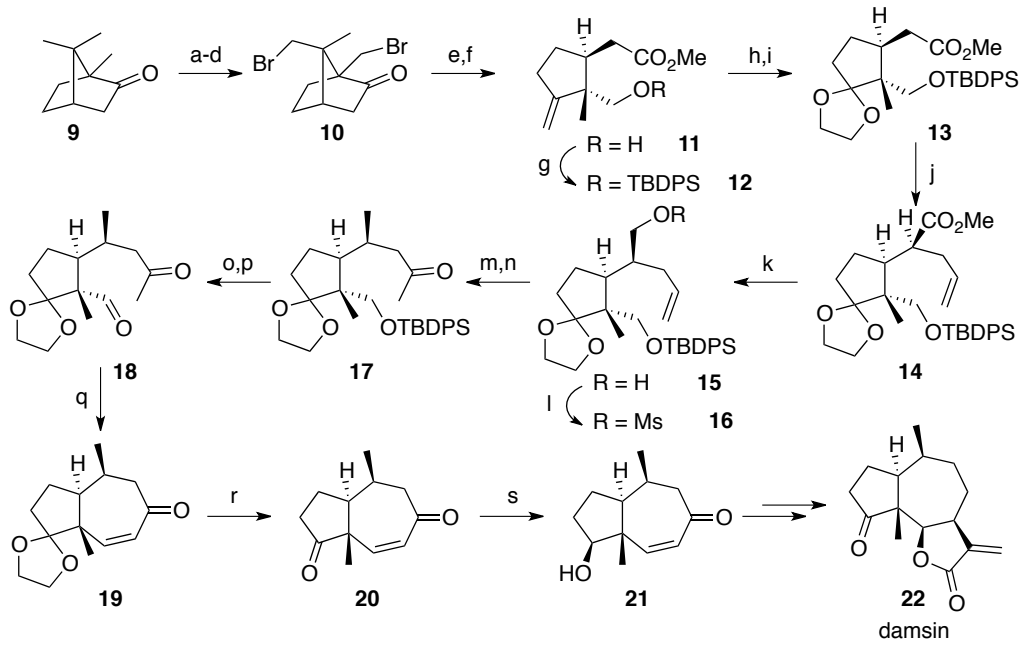
Scheme 3

b. Example: synthesis of damsin by Money

In 1979, Schlessinger reported a synthesis of damsin from a hindrane ring system.[33] Money described another approach to afford damsin in 1996 (Scheme 4).[2,334] He used a different pathway to prepare the synthon **21** from (–)-camphor. Then, he employed Schlessinger's methodology from **21** to damsin **22**.[33]

The synthesis started from the commercially available (–)-camphor **9**. α-Bromination to the ketone was first performed, then two further brominations were carried out, and finally the bromine α to the ketone was removed using a metal reduction to give **10**. An efficient cleavage in basic conditions provided the monocyclic hydroxy-ester **11**. The primary alcohol was protected using a silyl group to give **12**. An oxidative cleavage of the carbon-carbon double bond afforded the ketone, which was protected with ethylene glycol in **13**. The ester **13** underwent a stereoselective alkylation with allyl bromide, providing a new ester **14** as a single

diastereoisomer in 95% yield. The ester **14** was reduced, and the resulting alcohol **15** was converted to the mesylate **16**. The mesylate group was displaced by a hydride to yield the methyl moiety. The carbon-carbon double bond was converted to the ketone **17** using Wacker-Tsuji oxidation. The primary alcohol was deprotected and oxidised using Swern conditions to give the aldehyde **18**. An aldol addition, followed by a dehydration, provided the α,β-unsaturated ketone **19**. Finally, the ketone was unmasked (**20**), and a stereoselective reduction was performed to afford the desired synthon **21** *en route* to damsin **22**.



Scheme 4

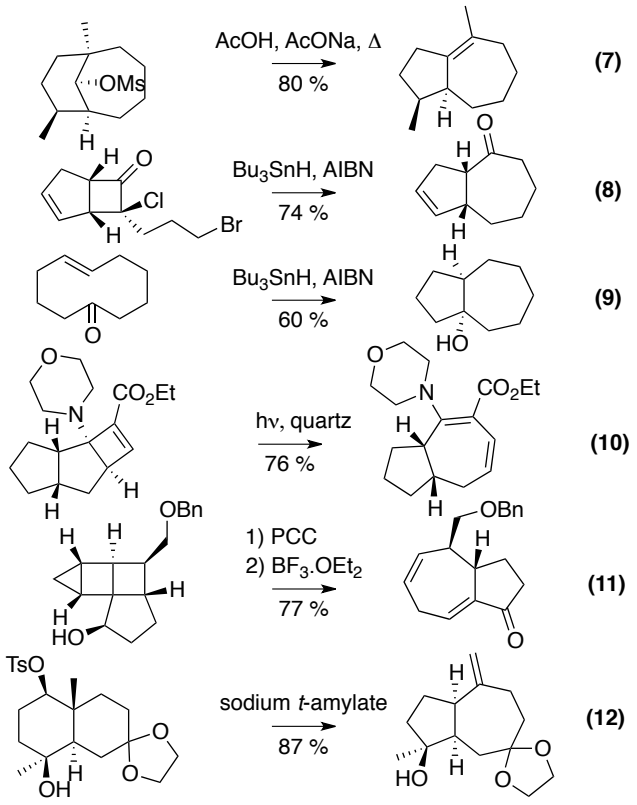
Reagents and conditions: (a) Br_2, HOAc, 80 °C [80%] (b) Br_2, $ClSO_3H$, 5h [75%] (c) Br_2, $ClSO_3H$, 5 days (d) Zn, HOAc:Et_2O (1:1), 0 °C [60% over 2 steps] (e) KOH, DMSO-H_2O (9:1), 90 °C, [85%] (f) K_2CO_3, DMF, CH_3I [94%] (g) TBDPSCl, imidazole, DMF [95%](h) O_3, CH_2Cl_2:MeOH (1:1), −78 °C; Me_2S, −78 °C→RT [92%] (i) $(CH_2OH)_2$, *p*-TsOH, C_6H_6, reflux [92%] (j) LDA, THF, −78 °C; H_2C=$CHCH_2Br$, −78 °C→RT [95%] (k) $LiAlH_4$, THF, 0 °C [96%] (l) MsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C [97%] (m) $LiEt_3BH$, THF; 3M NaOH, 30% H_2O_2 [88%] (n) $PdCl_2$, CuCl, O_2, DMF:H2O (9:1) [91%] (o) TBAF, THF, reflux [90%] (p) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C→RT [95%] (q) 10% KOH, MeOH, 12 days; MsCl, DMAP, Et_3N,CH_2Cl_2, 0 °C; DBU [70%] (r) 1M HCl, Me_2CO [90%] (s) $NaBH_4$, EtOH, −10 °C [87%].

The overall yield to the synthon **21**, following the route described by Money, was 8% over 17 steps.[34] Damsin was synthesized in 1.6% overall yield following this route.

2) Rearrangement of other ring systems

a. Overview

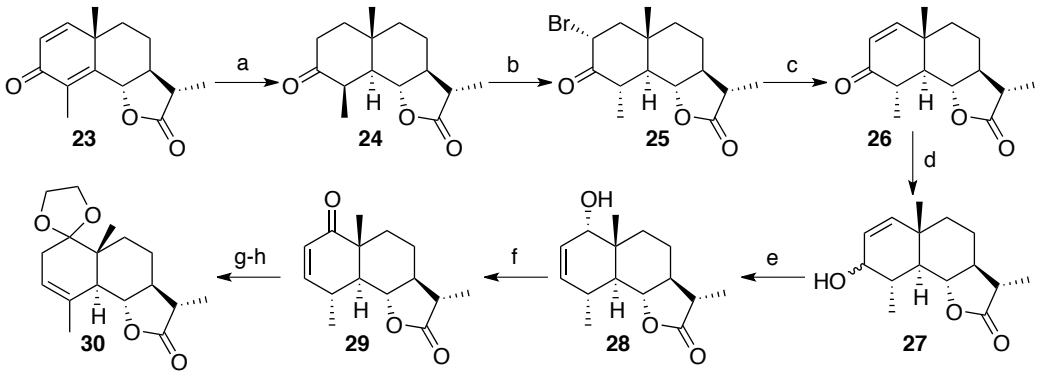
Ring rearrangements is another way to access the bicyclo[5.3.0]decane framework. Several reactions can result in rearrangement of the azulene ring system. One of the first rearrangement methods used was the solvolysis of mesylate (equation **(7)** Scheme 5**)**.[32a,32b] The 5,7-fused ring system can also be accessed through free radical chemistry by ring extension (equation (**8)** Scheme 5)[32c] or transannular cyclisation (equation (**9)** Scheme 5). [32d,32e] Ring extension through addition (equation **(4)** Scheme 3),[31f] thermal,[32h] photochemical (equation (**10)** Scheme 5)[32f] and basic or acidic (equation **(11)** Scheme 5)[32g] conditions were also used to provide access to the azulenic ring system. The bicyclo[5.3.0]decane ring system can also be reached through based-induced rearrangement of perhydronaphthalenes (equation (**12)** Scheme 5).



Scheme 5

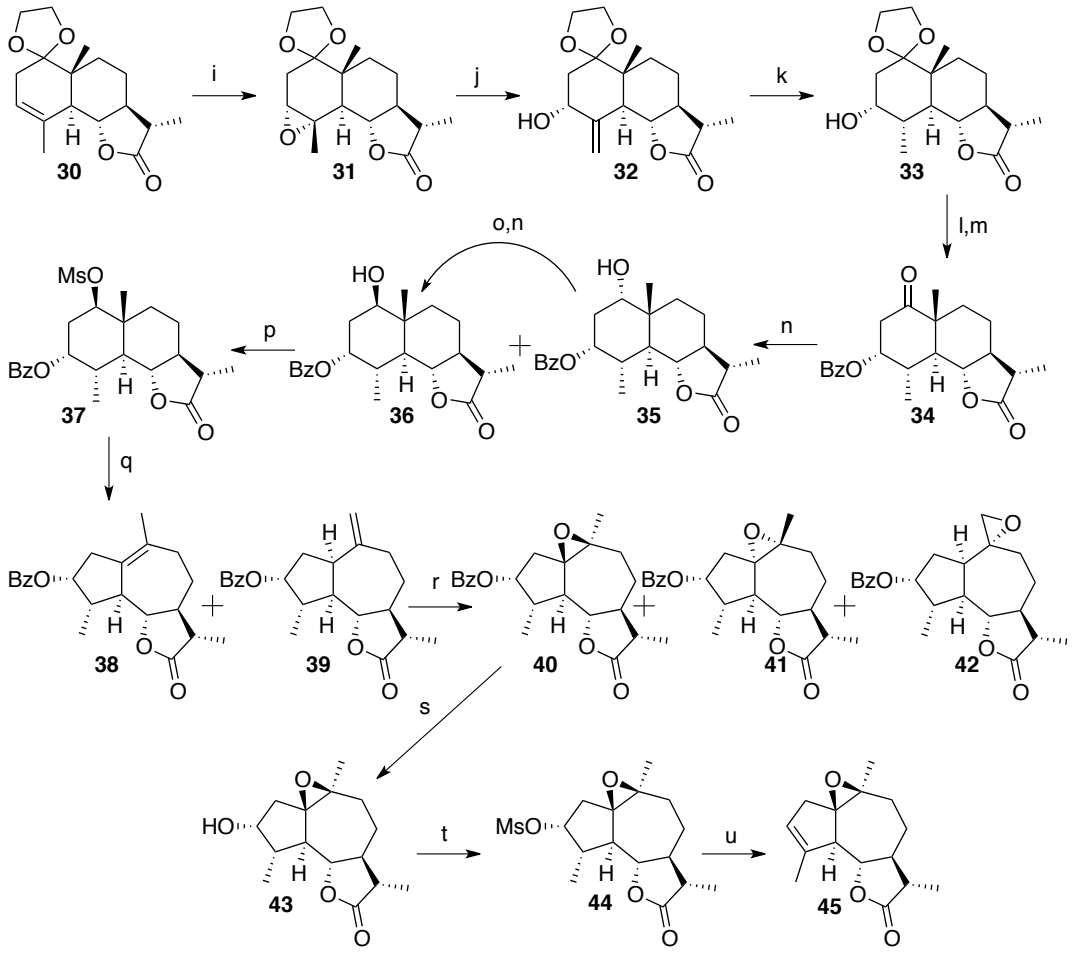
b. Example: synthesis of arborescin by Ando

In 1982, Ando reported the synthesis of arborescin from α-santonin **23**.[35] The synthesis started with the alkene reduction of **23** to afford the saturated ketone **24**. The carbonyl compound **24** was α-brominated, and its dehydrobromination gave the α,β-unsaturated ketone **26**. The Meerwein-Ponndorf-Verley reduction of **26** allowed the formation of a mixture of allylic alcohols **27**, which underwent an allylic rearrangement under acidic conditions to afford the desired allyl alcohol **28**. Oxidation to the unsaturated ketone **29** and subsequent ethylene glycol protection were performed, enabling a rearrangement of the double bond to a more stable trisubstituted one **30**. The carbon-carbon double bond was epoxidised stereoselectively, followed by a regioselective opening to give the allyl alcohol **32** with an exocyclic carbon-carbon double bond. A catalytic hydrogenation of that carbon-carbon double bond provided the methyl group as a single isomer in **33**. The secondary alcohol was protected using benzoyl group, and the ketone was unmasked and subsequently reduced to the alcohol as a 2:1 mixture **36**:**35** in favour of the desired isomer **36**. After mesylation, a solvolytic rearrangement gave a 2:1 mixture of *endo*:*exo*cyclic olefins **38**:**39**. This mixture was epoxidised to afford a new mixture of three epoxides **40**:**41**:**42** and the exocyclic double bond compound **39** from the starting material (a total of 4 separable products). The desired β-epoxide **40** was separated: its secondary alcohol was deprotected to give **42**, converted to **43** and finally dehydrated to afford arborescin **45**. The overall yield for this synthesis, described by Ando, was 0.2% over 21 steps.



Scheme 6

Reagents and conditions: (a) H_2, $Pd/SrCO_3$, EA [34%] (b) Br_2, $CHCl_3$, 0 °C [63%] (c) LiBr, Li_2CO_3, DMF, 120 °C [85%] (d) $Al(Oi\text{-}Pr)_3$, *i*-PrOH, reflux; 2M HCl, 0 °C [99%] (e) 2M HCl : THF = 3:2, reflux [79%] (f) CrO_3.2pyr., CH_2Cl_2, 0 °C [89%] (g-h) *p*-TsOH, ethylene glycol, toluene, reflux, Dean-Stark [67%].



Scheme 7

Reagents and conditions: (i) *m*-CPBA, CH_2Cl_2, RT for 5 days [100%] (j) $Al(Oi\text{-}Pr)_3$, toluene, reflux; 2M HCl [99%] (k) H_2, PtO_2/C, EA [99%] (l) BzCl, pyr. [100%] (m) 50% aqueous AcOH, reflux [75%] (n) $Zn(BH_3)_2$, DME [66% of *cis* reduced product], the *trans* reduced product [33%] was oxidised and reduced again (o) oxidation of *trans* reduced product : CrO_3.pyr., CH_2Cl_2 [94%] (p) only *cis* reduced product used, MsCl, pyr. [91%] (q) KOAc, AcOH, reflux [mixture of *endo:exo* = 2:1, 72%] (r) mixture of *endo-exo* product, *m*-CPBA, CH_2Cl_2, –1 °C [recovery of exoalkene 40%, respectively 22% of β-epoxide (desired compound), 29% of α-epoxide and 3% of *exo*-epoxide] (s) performed on the β-epoxide, 1M aqueous K_2CO_3:MeOH = 1:1, reflux [76%] (t) MsCl, pyr. [84%] (u) Li_2CO_3, LiBr, DMF, 120 °C [49%].

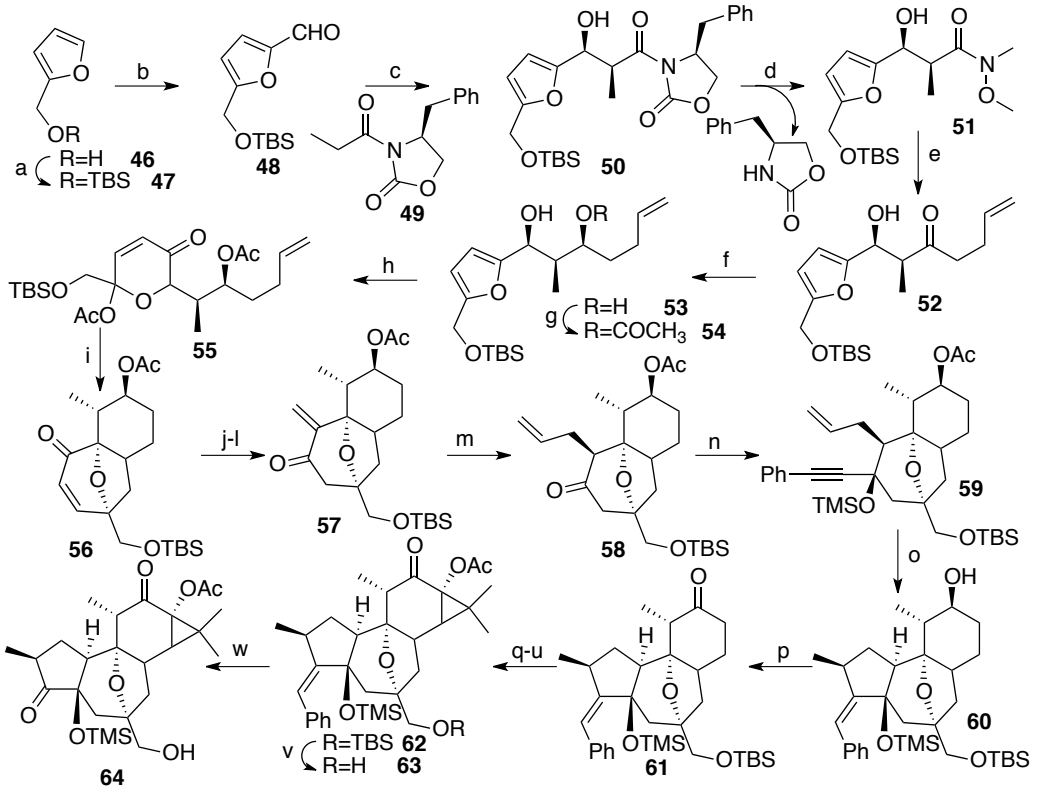
3) Synthesis of phorbol by Wender

In 1989, Wender reported the first synthesis of phorbol in a racemic form.[36a] In 1997, he reported the first formal asymmetric synthesis of phorbol.[36b] Several chemists, such as Dauben,[37] Harwood,[38] Little,[39] McMills,[40] Rigby,[41] studied also the synthesis of phorbol.

The strategy of Wender started from furfuryl alcohol **46**. The free alcohol was protected into **47** and a formylation of the corresponding furyl lithium afforded **48**. An aldol reaction between the aldehyde **48** and the *N*-propionyl oxazolidinone **49** was achieved in high selectivity (98% *de*). The oxazalidinone was transformed into a *N*,*O*-dimethylhydroxylamine to give the Weinreb amide **51** and the 3-butenyl magnesium bromide was added to afford the desired hydroxy-ketone **52**. The ketone was reduced into **53** with high diastereoselectivity (30.6:1). In one pot, the more reactive furfuryl alcohol was protected with a TMS group and the other alcohol was acetylated *in situ*, while the first one was deprotected to afford **54**. The conversion of the furan moiety into a dihydropyran moiety, an Achmatowicz reaction, was performed and followed by the protection of the crude hydroxypiranone with an acetate group to give **55**. A subsequent intramolecular oxidopyrylium-alkene cycloaddition occurred, leading to the desired cycloadduct **56** as a single diastereoisomer. The carbon-carbon double bond of **56** was reduced to afford a saturated ketone, which underwent a Wittig olefination and allylic oxygenation to produce the Michael precursor **57**. Conjugate addition was performed, leading to the desired ketone **58** as a single diastereoisomer. Lithium phenylacetylide was then added to the carbonyl group and the resulting hydroxide was quenched with TMSCl to lead to the β-adduct **59** only. An enyne cyclisation mediated by zircon(II) afforded the 5-membered ring with the acetate deprotection in **60**. The free alcohol was then oxidised to form the ketone **61**, which was deprotonated under kinetic control to allow the addition of phenyl sulfenyl chloride to the least hindered α-carbon. The sulfur was oxidised and thermal elimination of the resulting sulfoxide afforded the acetoxy enone, which underwent a Corey-Chaykovsky reaction of diphenylisopropylsulfonium ylide occurring on the β-face stereoselectively, providing the desired tigliane **62**. Selective deprotection of the primary silyl ether and ozonolysis of the carbon-carbon double bond provided the diketone **64**. Triflic anhydride was added to activate the free alcohol, and cleavage of the ether bridge along with the elimination of the triflate afforded the exocyclic carbon-carbon double bond in **65**. An allylic oxidation was performed by an addition-elimination sequence, leading to the desired allylic acetate **68**. The six-membered ring

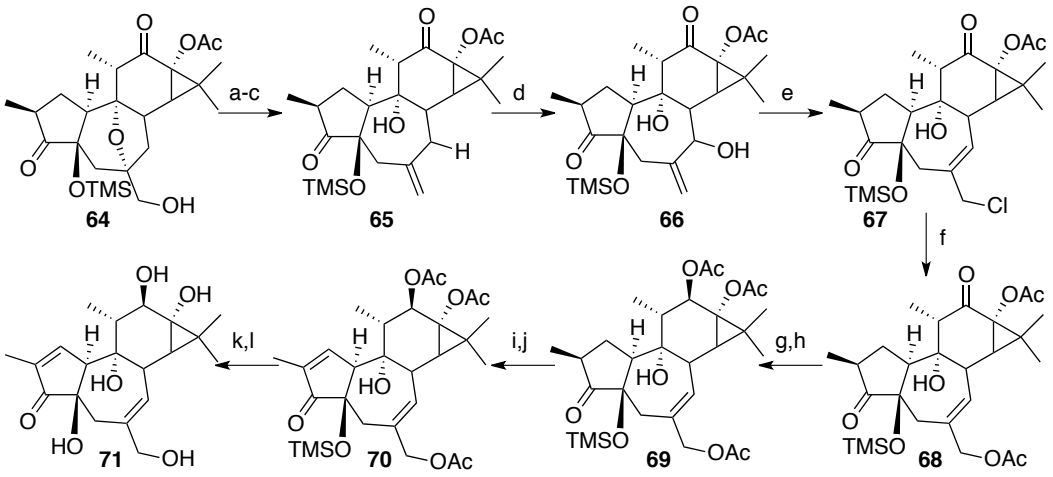
ketone was then selectively and stereoselectively reduced to the β-alcohol, which was protected as the acetate **70**. Final deprotection of the silyl ether and of acetates yielded phorbol **71**.

The overall yield of this route was 0.1% over 32 steps.



Scheme 8

Reagents and conditions: (a) TBDMSCl, imidazole, DMF [99%] (b) *n*-BuLi, THF; DMF; H_3O^+ [75%] (c) Bu_2BOTf, Et_3N, CH_2Cl_2, –78 °C→0 °C [98% d.e., 96% yield] (d) Me_3Al, Me(MeO)NH-HCl, CH_2Cl_2 [86%] (e) 3-butenylMgBr, THF, 60 °C [82%] (f) DIBAL, THF, –78 °C [85%, 30.6/1] (g) TMS-imidazole, THF; AcCl, pyr., DMAP; citric acid, MeOH [82%] (h) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2; Ac_2O, pyr., DMAP [88%, 2/1] (i) DBU, CH_3CN [79%, one diastereoisomer] (j) H_2, Pd/C, EA [95%] (k) KO*t*-Bu, Ph_3PCH_3Br, toluene [79%] (l) SeO_2, *t*-BuOOH, CH_2Cl_2; MnO_2, CH_2Cl_2 [89%] (m) $(CH_2CH)_2Cu(CN)Li_2$, Et_2O [83%, one diastereoisomer] (n) PhCCLi, LiBr, THF; HMPA, TMSCl [75%] (o) Cp_2ZrCl_2, *n*-BuLi, THF; HOAc [93%] (p) PCC, NaOAc, CH_2Cl_2 [94%] (q) LDA, THF, –78 °C; TMSCl; PhSCl, CH_2Cl_2, –78 °C [96%] (r) $Pb(OAc)_4$, benzene [84%] (s) *m*-CPBA, CH_2Cl_2, –20 °C (t) $P(OEt)_3$, benzene [88% on 2 steps] (u) $Ph_2SC(CH_3)_2$, CH_2Cl_2, THF, –78 °C [80%] (v) 49% HF, CH_3CN, 0 °C [96%] (w) O_3, CH_2Cl_2/MeOH, –78 °C; $(NH_2)_2CS$ [89%].



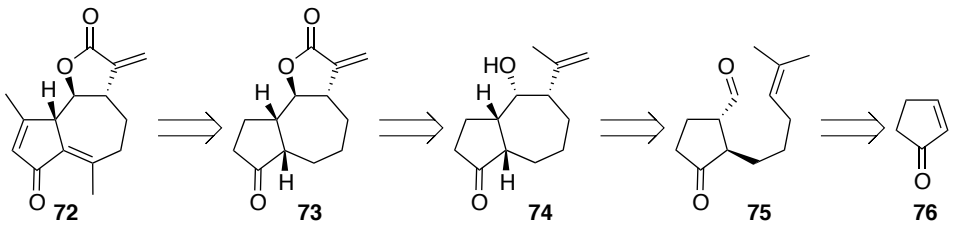
Scheme 9

Reagents and conditions: (a) Tf_2O, pyr., CH_2Cl_2, 0 °C (b) *n*-Bu_4NI, CH_3CN [67% on 2 steps] (c) Zn, EtOH, 80 °C [61%] (d) SeO_2, t-BuOOH, CH_2Cl_2 [54%] (e) $SOCl_2$, pyr. Et_2O, 0 °C (f) KOAc, 18-Crown-6, AgOAc, CH_3CN [71% on 2 steps] (g) $NaBH(OAc)_3$, THF [92%] (h) Ac_2O, DMAP, pyr., CH_2Cl_2 [89%] (i) MSTFA, DMAP DABCO, CH_3CN, 100 °C; NBS, THF [63%] (j) Li_2CO_3, LiBr, DMF, 130 °C [56%] (k) TBAF, THF, –20 °C [88%] (l) $Ba(OH)_2$, MeOH [62%].

IV) Synthetic studies of dehydroleucodine within the Page group

1) Retrosynthesis

To achieve the synthesis of the guainolide skeleton, we were interested in developing further research work previously performed within the group.[1,3] The retrosynthetic proposal for this project is shown below in Scheme 10.



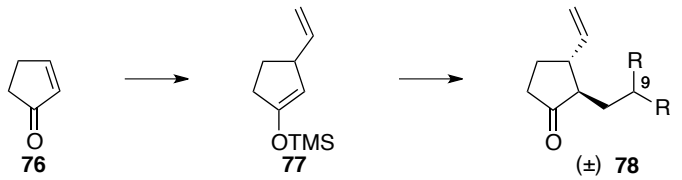
Scheme 10

The carbonyl ene precursor **75** was obtained from cyclopentenone **76** through four key steps. The 1,4-addition onto cyclopentenone was followed by a conjugated aldol addition affording a *trans*-fused ring system. An intramolecular Alder ene reaction on **75** gave the perhydroazulene skeleton **74**, a bicyclo[5.3.0]decane framework with a *cis*-configuration. The α-methylene-γ-lactone was required to be *trans*-fused to the 7-membered ring, so an inversion of configuration should be performed before any oxidation and lactonisation into **73**. The ketone **73** can be oxidised into an α,β-unsaturated compound and oxidative 1,4-addition will afford the desired compound **72**: dehydroleucodine.

2) Key steps

a. Conjugate addition

The sequence of conjugate addition followed by conjugate aldol addition was developed within the group and gave access after two steps to a highly functionalised material that can undergo several transformations. A Michael addition of vinyl Grignard reagent onto cyclopentenone **76**, quenched *in situ* with trimethyl silyl chloride afforded **77**. A Mukaiyama aldol reaction of a Michael acceptor onto **77** afforded **78**. A range of Michael acceptors can be used; the criteria are that C9 needs to be functionalised and the buiding blocks R need to be removable.



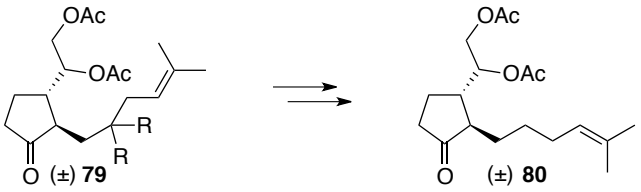
76 **77** (±) **78**

Scheme 11

b. Decarboxylation

The diester moiety incorporated in the second step as a building block could be removed at any point during the synthesis. Initially, we proposed to attempt the decarboxylation immediately

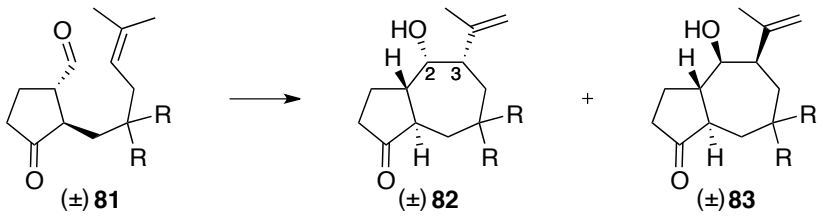
after the addition of prenyl bromide at C9 as the malonyl moiety was only required for the alkylation reaction: from the protected diol **79**, our target was the compound **80**.



Scheme 12

c. Alder-ene reaction

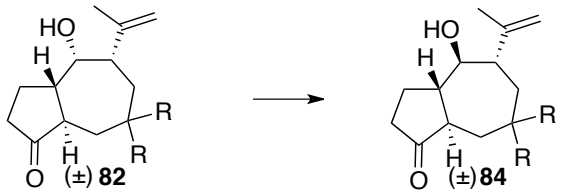
In a previous study, different cyclisation methodologies were attempted. The Diels-Alder reaction approach was unsuccessful, whereas initial investigations regarding the carbonyl-ene reaction yielded promising results, particularly when the Lewis acids $BF_3.OEt_2$ and $Yb(OTf)_3$ were used.[3] The reaction conditions were screened and optimized in order to obtain the racemic carbonyl-ene products **82** and **83** in different diastereoisomeric ratios (Scheme 13). The products obtained have a *trans*-fused ring configuration and, the substituents at the C2 and C3 positions have a *cis* relative configuration.



Scheme 13

d. Configuration inversion

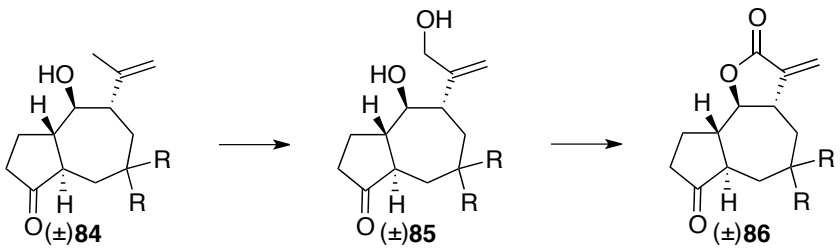
The lactone moiety of dehydroleucodine is *trans*-fused to the seven-membered ring, so the configuration of the carbon centre bearing the alcohol moiety needed to be inverted to obtain the *trans* relative configuration between C2 and C3.



Scheme 14

e. allylic oxidation

The lactone moiety would be obtained through an allylic oxidation followed by oxidation of the resulting primary alcohol to the corresponding carboxylic acid and then lactonisation.



Scheme 15

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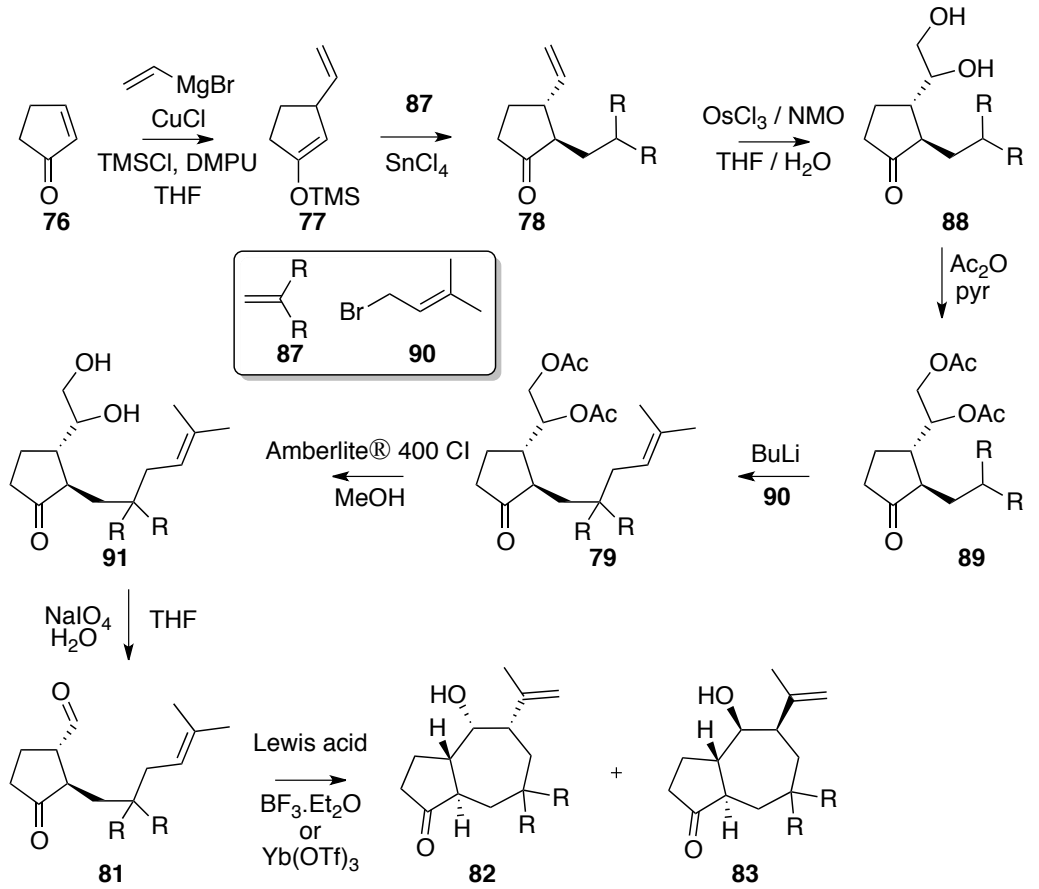
CHAPTER II:

RESULTS AND DISCUSSION

RESULTS AND DISCUSSION

This report covers the author's work towards the synthesis of the guaiane skeleton. The proposed route was inspired by the research previously performed within the group (Scheme 1).[1] The reactions in Scheme 1 show the previous work (R = CO_2Et) and they have been optimised since.



Scheme 1

Our studies were directed towards the synthesis of the tricyclic skeleton of guaianolides such as dehydroleucodine (Figure 1).

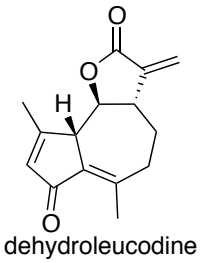
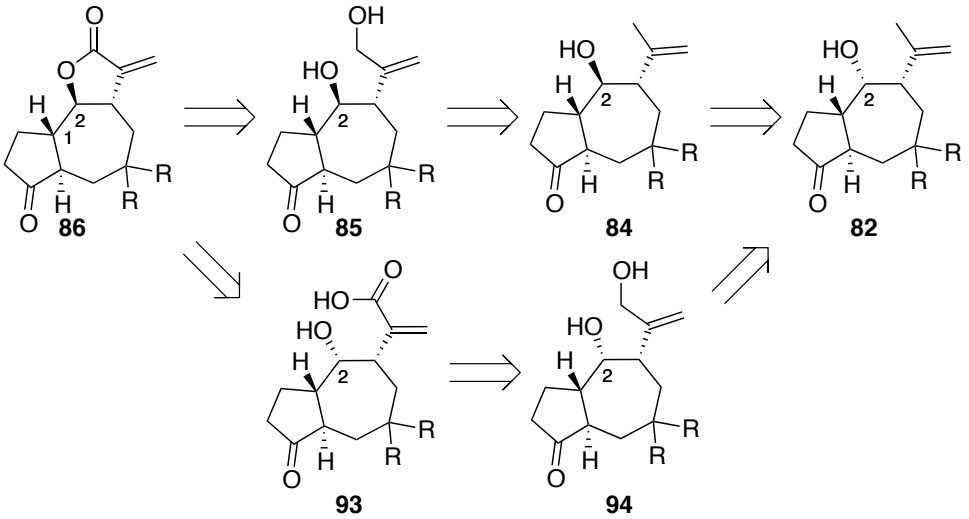


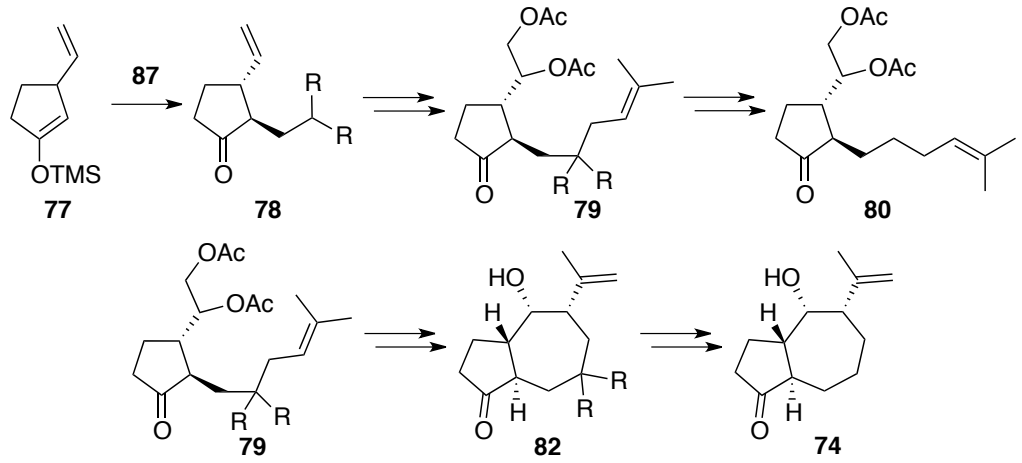
Figure 1

Therefore, our studies were directed towards the buiding of the lactone moiety, which was *trans*-fused to the seven-membered ring. The configuration at C2 needed to be inverted, and the five-membered ring to be closed (Scheme 2).



Scheme 2

The diester moiety **87** was used as a building block for the formation of **79**, but was not present in dehydroleucodine, and therefore needed to be removed (Scheme 3). The decarboxylation of the diester was studied, and syntheses using other methylene malonate moiety were attempted.



Scheme 3

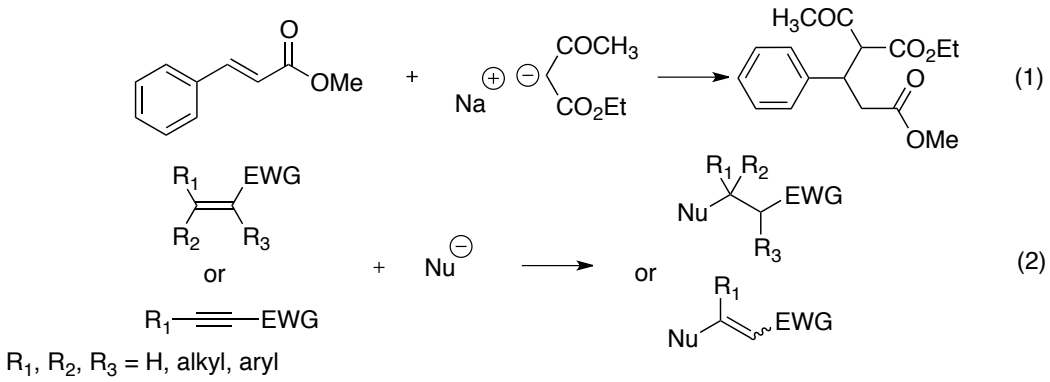
In this second chapter, the key steps of the synthesis are discussed and the author's results presented.

I) Michael addition

1) History

1,4-Addition, also known as conjugate addition,[2] was first observed by T. Komnenos in 1883 as a side product reaction[3] and described by A. Michael in 1887.[4]

Arthur Michael was an American chemist, born in Buffalo (1855), New York, USA.[5] He could not attend Harvard University because of illness and decided later to travel around Europe. During this period, he studied in the laboratory of A. W. von Hofmann then R. Bunsen in Germany, C. A. Wurtz in France and D. Mendeleïev in Russia. Returning to the United States, A. Michael was appointed to the chair of Chemistry at Tufts College (1882) where he met and married one of his students (1888) Helen Abbott Michael (known for her work on chemical properties of plants). He worked in his self-constructed laboratory with his wife in the Isle of Wight in England (1889), came back to Tufts College (1894) and became Professor of Chemistry at Harvard University (1912). He died in 1942. Even though Arthur Michael was working with some of the greatest chemists of his time and got excellent positions, he never obtained any university degrees.



R_1, R_2, R_3 = H, alkyl, aryl

EWG = aldehyde, ketone, ester, amide, nitrile, nitro, sulfoxide, sulfone, phosphine, phosphonate, heteroaryl

Scheme 4

The Michael addition was first reported as the addition of an enolate to an α,β-unsaturated carbonyl compound at the β-carbon (Equation 1 Scheme 4). More generally, it is referred as the addition of a nucleophile to an activated alkene or alkyne (Equation 2 Scheme 4). The Michael donor (nucleophile) can be derived from the deprotonation of an activated C-H bond such as in α position of nitrile and carbonyl (aldehyde, ketone, malonate) compounds, or from organometallic compounds, deprotonated heteroatoms, etc. The Michael acceptor is an α,β-unsaturated electron withdrawing group. The unsaturation can be an alkene or an alkyne and the electron withdrawing group, an ester, an amide, a nitro compound, etc.[6] This reaction is a very convenient process for the creation of C-C bond and is commonly used in total syntheses.

In this section, the conjugate addition of organometallic nucleophiles is discussed, in particular the copper-catalysed conjugate addition of Grignard reagents.

2) Conjugate addition of organometallic compounds

1,4-Addition can be promoted by principally three parameters:

(1) Deactivation towards 1,2-addition;
(2) Steric hindrance and reaction conditions;
(3) Oriented by coordination.

a. Deactivation of 1,2-addition

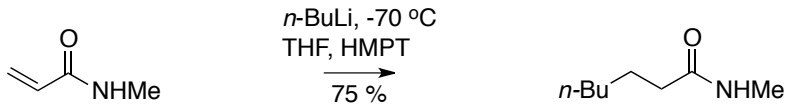
→ *Towards 1,4-addition*

1,2-Addition and 1,4-addition are two different types of nucleophilic addition. 1,2-Addition is the common pathway and generally occurs on carbonyls. Simple alkenes are not reactive but can be activated with a carbonyl group whose nature can favour one pathway over the over. Generally, highly activated carbonyls react in 1,2-additions, whereas less reactive carbonyls mainly afford 1,4-additions. Therefore, the compounds containing carbonyl groups and reacting in 1,4-additions follow the order below:

Amides < esters < nitriles < ketones << aldehydes.[2]

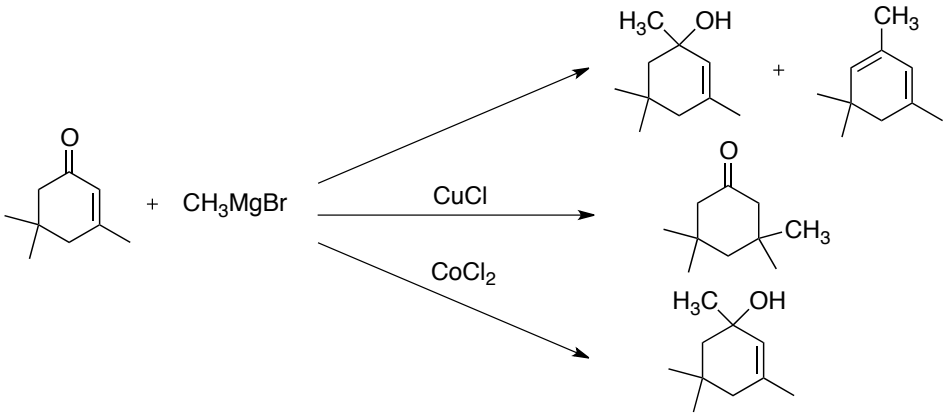
1,4-addition 1,2-addition

For example, addition of organolithiums to α,β-unsaturated aldehydes led only to 1,2-additions, whereas addition of the same organolithiums to α,β-unsaturated ketones or nitriles could give both 1,2- and 1,4-additions.



Scheme 5

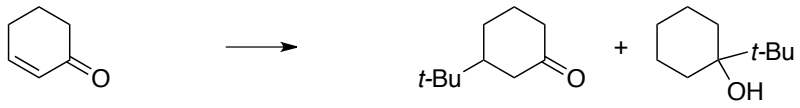
In 1941, early studies from Kharasch and Tawney showed that addition of a catalytic amount of metallic halide could change the result of the reaction (Scheme 6).[7] They reported that the addition of methylmagnesium bromide to isophorone with a catalytic amount of copper(I) chloride (1%) afforded principally the 1,4-addition product (82.5%). Twenty years later, the reactive species was demonstrated to be the organocopper.[8] In 1941, a screening study found that several metals (R_3Al, R_2Cd, R_2Zn) provide exclusively 1,4-addition adducts.[9] Since those studies, conjugate addition of organometallic compounds has been extensively used to create carbon-carbon σ bonds.



Scheme 6

→ *Reaction conditions*

1,4-Addition usually generates kinetic products, while 1,2-addition forms thermodynamic products. Kinetic conditions such as higher temperatures and excess of organometallic reagent increase the rate of formation of the 1,4-adducts over the 1,2-adducts.[10] The use of more polar or more basic solvents and the addition of polar co-solvent can also favour the Michael addition. Minimizing the counterion effect promotes the formation of solvent-separated ion pairs, so an electron transfer effect takes place, thus promoting 1,4-additions.[11]



t-BuMgCl, ether, 25 ºC	70 %	-
t-BuLi, ether, -78 ºC	-	100 %
t-BuLi, THF + 20 % HMPA, -78 ºC	90 %	10 %

Scheme 7

→ *HSAB theory*

The HSAB theory, which means Hard and Soft Acid and Base, is used to explain the stability of compounds, reaction mechanisms and pathways where other theories failed to give explanations. The notion of acid/base refers to the Lewis acid/base properties and not the Brönsted acid/base ones. The soft/hard properties are not to be confused with strong/weak properties of acids and bases. Pearson introduced the theory from 1960 to unify the reactions of organic and inorganic chemistry.[12]

Figure 2

The principle of the theory is that soft acids or sites react faster and form stronger bonds with soft bases or sites, and hard acids or sites react faster and form stronger bonds with hard bases or sites.[13] Hard acids and bases are characterized by a small atomic radius, high electronegativity or positivity and difficulty of oxidation or reduction. Soft acids and bases are characterized by a large radius, low electronegativity or positivity, and ready oxidation or reduction. The HSAB theory is especially employed to explain organometallic reactions such as metathesis reactions.

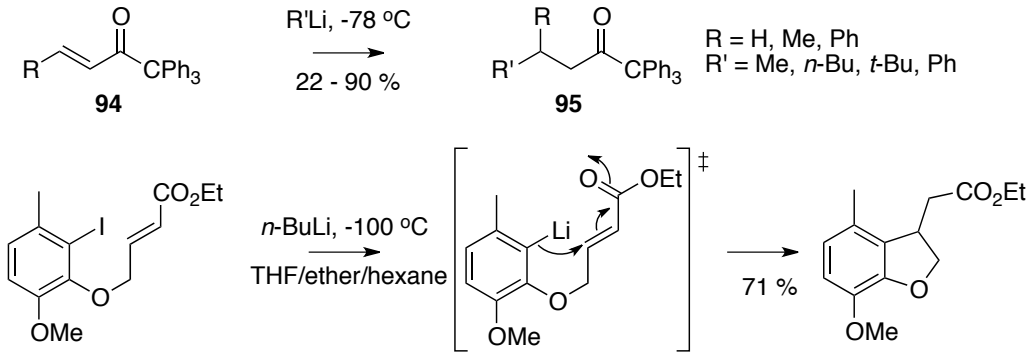
In the case of 1,4-addition, the chemoselectivity can be partially explained by HSAB theory. According to this theory, lithium cation is a stronger acid than magnesium cation, which is stronger than copper one (soft acid); an α,β-unsaturated carbonyl compound is considered as a hard site (base) at C-1 position (carbonyl carbon) and a soft site (base) at C-3. Experiments proved that hard acids (organolithium or magnesium species) mainly attack at the hard base sites (C-1), while the soft acids (organocopper species) attack preferentially the soft base sites (C-3).

Examples of hard acids are H^+, Li^+, Na^+, K^+, Mg^{2+}, Ti^{4+};

Examples of soft acids are Pt^{2+}, Pd^{2+}, Ag^+, Cu^+, Au^+.

b. Steric effect and steric hindrance

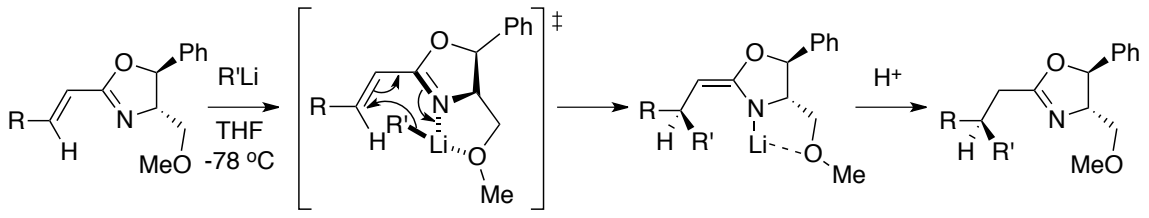
1,4-Adducts can be obtained when Michael acceptors are sterically hindered at C-1, the carbonyl carbon. Trityl enones **95** undergo 1,4-addition even with organolithium compounds.[14] Deactivation of the Michael acceptor coupled with steric hindrance allow the use of more reactive organometallic species. Five-membered ring formation is preferred to seven-membered ring in intramolecular reactions.[15]



Scheme 8

c. Coordination

Conjugate addition may be oriented by coordination of the organometallic compound and can afford a regioselective and enantioselective addition, as shown in the example below (Scheme 9 and Table 1).[16]



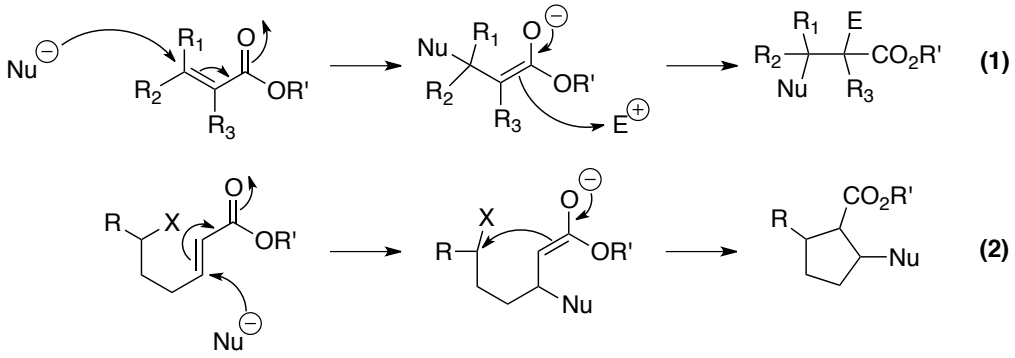
Scheme 9

Entry	R	R'	Yield	% *ee*
1	Cyclohexy*l*	*n*-Bn	79 %	99
2	Me	*n*-Bu	38 %	91
4	Et	Et	73 %	99

Table 1

3) Overview of organometallic conjugate additions

1,4-Addition has seen a renewed interest with the development of tandem 1,4-addition-electrophile trapping protocols (Equation 1 Scheme 10),[16c,17] and Michael initiated ring closure (MIRC) protocols (Equation 2 Scheme 10).[18,19] Additional organometallic reagents have been considered in order to allow a wider range of functionalities on either Michael acceptor or donor.



Scheme 10

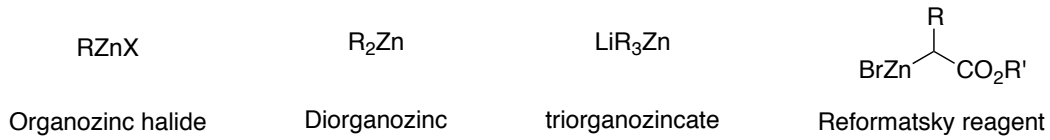
Organometallic reagents generally react in both 1,2- and 1,4-additions; the ratio of 1,2- over 1,4-adducts depends on their reactivity. The more reactive ones are from group IA and IIA (RLi, RNa, RMgBr, R_2Mg) and favour the formation of 1,2-addition products. However, less ionic organometallic species from group IB, IIB, IIIB (RCu, R_2CuLi, R_2Zn) are less reactive and thus more likely to undergo conjugate additions. This is a general observation, and more criteria must be considered (*e.g.* additives, catalysts, reaction conditions).

a. Organocoppers

Organocopper species are the most common reagents among the organometallic compounds to undergo 1,4-addition. The organocopper reagents that are commonly used are generally commercially available, but other organometallic reagents can be also employed such as organomagnesium reagents, which generate *in situ* reactive catalytic quantities of organocopper(I) species when catalysed by copper(I) salts. This discussion is developed below (p.49).

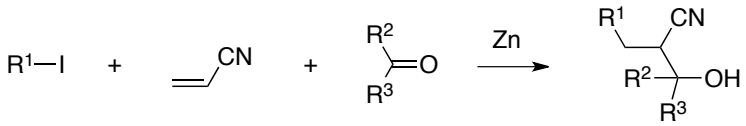
b. Organozincs

Organozincs can be divided into four groups: organozinc halides (RZnX), diorganozincs (R_2Zn), triorganozincates (LiR_3Zn) and α-(alkoxycarbonyl)alkylzinc halides, known as Reformatsky reagents.



Scheme 11

Due to their thermal instability, organozinc halides are usually produced *in situ* from metal insertion with halides, which also provide the less reactive diorganozincs. Organozinc halides are inert towards various functionalities and react exclusively with enones in 1,4-additions.[17]

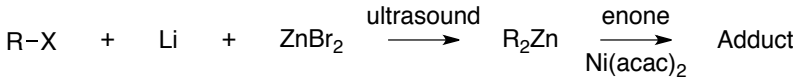


Scheme 12

Entry	R^1	R^2, R^3	Yield
1	$(CH_3)_2CH$	$R^2 = R^3 = Me$	98
2	C_6H_{10}	$R^2 = R^3 = Me$	38 %
4	$(CH_3)_2CH$	$R^2 = C_6H_5$, $R^3 = H$	73 %

Table 2

Dialkyl and diarylzincs have low reactivity towards α,β-unsaturated carbonyls, while diallyl, dibenzyl and dipropargylzinc compounds are highly reactive. Addition of a $[Ni(acac)_2]$ catalyst enhances the reactivity of organozinc species (even dialkyl and diarylzincs), which react easily with α,β-unsaturated aldehydes and enones, even with β,β-disubstituted carbonyls that are inert to organocoppers.[20]



Scheme 13

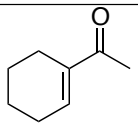
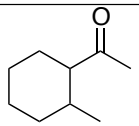
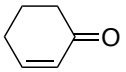
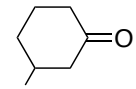
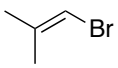
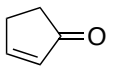
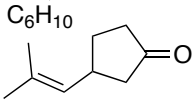
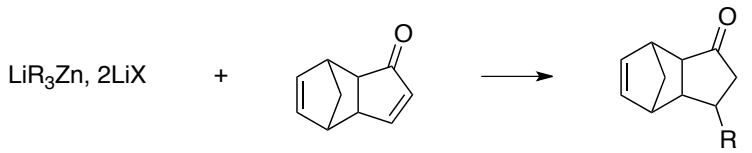
RX	enone	Adduct	% yield
CH_3I			73
$C_6H_{10}Br$			40
			21

Table 3

Knowledge of triorganozincate chemistry and their use are rather limited, although they are more reactive than diorganozincs. Asymmetrical triorganozincate compounds (transmetallation from diorganozinc) enables overcoming ligand wastage by using two methyl substituents that are inert or at least much less reactive than most ligands. Triorganozincate reactivity is decreased

compared to diorganozincs in the presence of β-substituents, but is not influenced by catalysis with transition metals.[21]

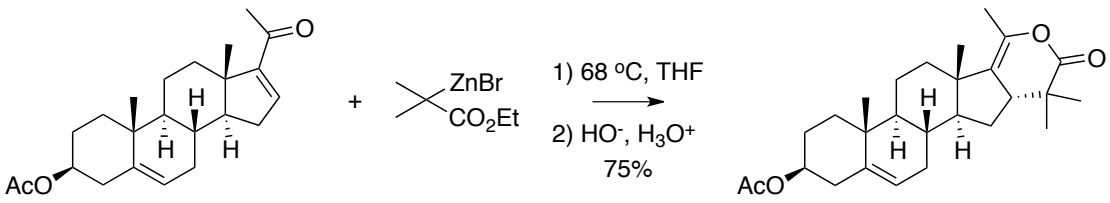


Scheme 14

Entry	R	X	Yield
1	Me	Cl	92%
2	Me	I	68%
3	*n*-Bu	Cl	92%

Table 4

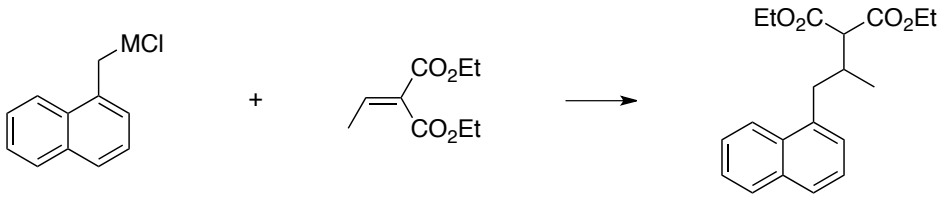
Reformatsky reagents were demonstrated to react with α,β-unsaturated carbonyls in conjugate additions. These reactions were reported as anormalous Reformatsky reactions by Kohler in 1910.[22] In fact, they can afford both 1,2- and 1,4-additions, depending on the steric hindrance, but conjugate addition is preferred under thermodynamic conditions.



Scheme 15

c. Organocadmiums

Diorganocadmium reactivity depends on the nature of the substituents. Diorganocadmium compounds bearing allylic and benzylic ligands react exclusively in 1,2-additions.[23] However, dialkyl and diarylcadmium compounds react by conjugate addition.[24] Diorganocadmium reactivity is increased by the presence of magnesium dihalides (MgX_2), which are byproducts generated by the formation of organocadmiums. That enhanced reactivity decreases the rate of 1,4-addition in favour of 1,2-addition. These metal halides (MgX_2) disfavour conjugate addition, so diorganocadmiums should be purified after synthesis to remove traces of magnesium salt.

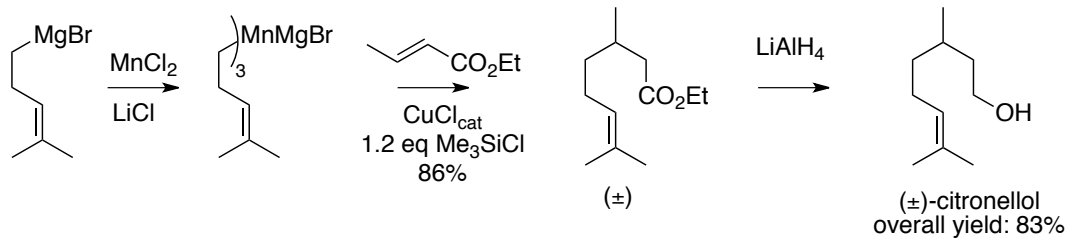


M	yield
Mg	45%
Cd	60%

Scheme 16

d. Organomanganese

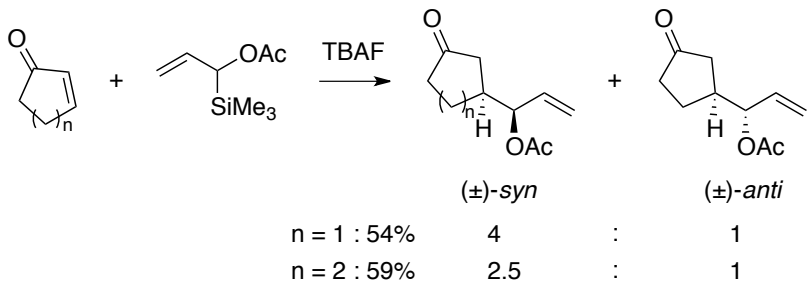
Organomanganese reagents are rarely used in syntheses.[9] However, these latter compounds react more efficiently when they are catalysed by copper(I), and tolerate β,β-substitution when organocopper species and copper-catalysed Grignard reagents are not reactive.[25] The synthesis of (±)-citronellol by Cahiez illustrated the efficiency of organomanganates in conjugate additions. The three substituents attached to manganese were transferred. Me_3SiCl was used to quench *in situ* the enolate formed from the conjugate addition to avoid side reactions such as aldol reaction.[25b]



Scheme 17

e. Organosilanes

Addition of organosilane reagents to α,β-unsaturated carbonyls occurs exclusively under the reaction conditions of silyl cleavage. Organosilane species afford both 1,2- and 1,4-addition products. The use of a Michael acceptor with low electrophilicity and of a Lewis acid such as CsF or TBAF in HMPA increases the conjugate addition product yield.[26]



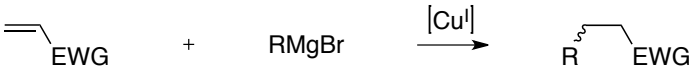
Scheme 18

f. Other organometallic species

Conjugate additions have been observed with other organometallic nucleophiles such as diorganoberrylium, triorganoaluminium in isolated reactions but not in general methodology.[8]

4) Michael addition of Grignard reagents catalysed by copper(I)

In 1941, Kharasch observed that Grignard reagents react in 1,4-additions with α,β-unsaturated ketones when catalysed by copper(I) salt conditions (Scheme 19).[7] In 1952, Gilman reported that the stoichiometric reaction of MeMgBr or MeLi with a copper(I) salt gave a yellow precipitate of a methylcopper species that was highly air unstable and decomposed into copper metal and methane.[27] The yellow solid was shown to be soluble in an ether solution of MeLi. Later, the formula of this organocopper species in solution was determined to be R_2CuLi and was called a Gilman reagent or Gilman cuprate. From 1966, organocopper chemistry started to be developed. That year, House reported evidence of the conjugate addition reactivity of organocopper reagents and other organometallic species when they were catalysed by copper(I) salts.[8] The results from House experiments suggested the formation *in situ* of catalytic organocopper species as the reactive reagents from a small amount of copper(I) and a large amount of organomagnesium and organolithium.

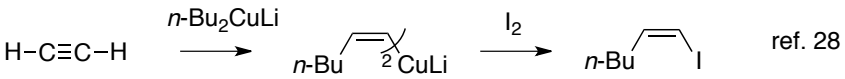


EWG = aldehyde, ketone, ester, amide, nitro

Scheme 19

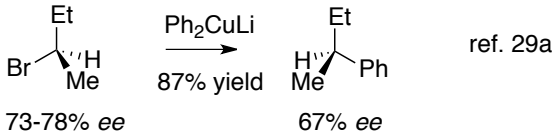
Organocopper(I) reagents are not limited to nucleophilic addition reaction and have been successfully applied to other reactions involving Cu(I)/Cu(III) such as:

- Carbocupration of alkynes:[28]



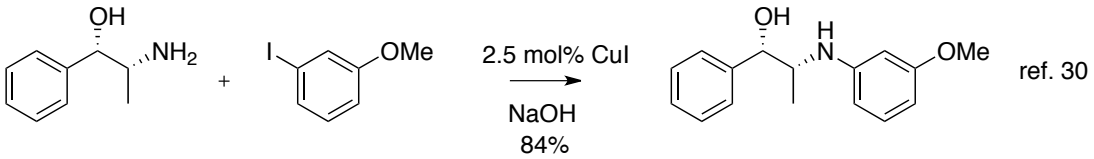
Scheme 20

- Substitution reactions:[29]



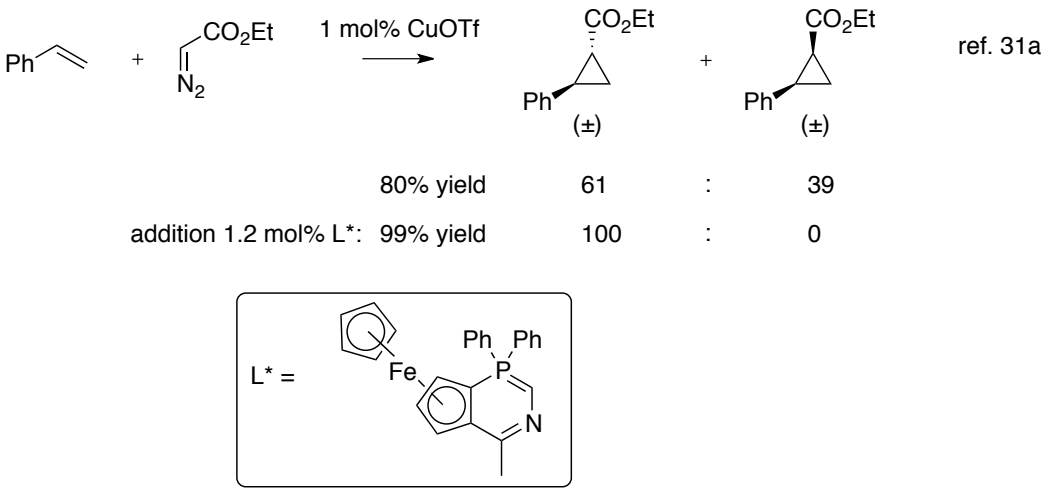
Scheme 21

- C–N bond formation - Ulmann type coupling reaction:[30]



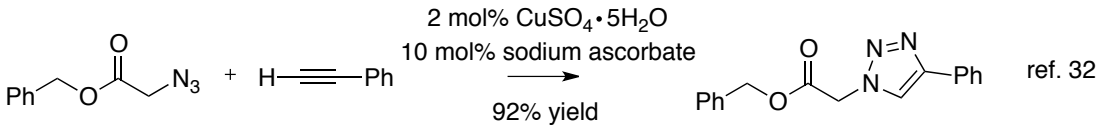
Scheme 22

- Olefin cyclopropanation:[31]



Scheme 23

- Click chemistry:[32]

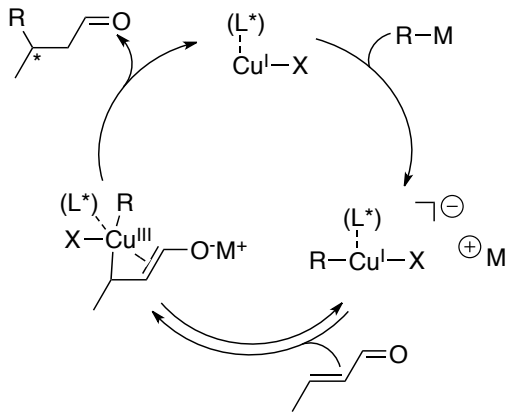


Scheme 24

a. Copper(I) catalysts

Various copper(I) salts have been used to prepare organocopper(I) reagents or to catalyse organometallic compounds for conjugate additions with α,β-unsaturated carbonyls. The most employed copper(I) salts appear to be CuBr.DMS and CuCN, but other source of copper(I) can be found such as CuX (X = Cl, Br, I), CuOAc, CuO*t*-Bu, CuSPh, CuSCN.[33] In some examples of conjugate addition reactions, copper(II) salts can be used with conjugate addition selectivity but it is believed that the reduction of the salts operates *in situ*.[8] But in most cases, copper(II) salts, issued from copper(I) decomposition, are believed to poison conjugate addition reactions. Copper(I) bromide-dimethyl sulfide complex is relatively stable and is easily prepared.[34] It is a pale whitish solid that becomes brownish when it oxidizes to copper(II). The best results are obtained when copper(I) bromide-dimethyl sulfide complex is freshly used.

b. Catalytic cycle



Scheme 25

The mechanism of copper(I)-catalysed conjugate addition is believed to follow the same principles as the stoichiometric organocopper version of the reaction. The catalytic cycle consists of transmetalation, oxidative addition and reductive elimination.[35] The oxidative addition is suggested to be reversible, and so the rate-limiting step is considered to be the reductive elimination. The reaction operates on the Cu(I)/Cu(III) based catalytic cycle, so in the case that the precatalyst used is a copper(II) salt, the mechanism includes a preliminary catalyst reduction step that occurs *in situ*. Poor results from early studies of the copper-catalysed reaction were believed to be due to the presence of copper(II) salt that oxidizes the reaction intermediate, and due to the poor solubility of the copper(I) salt, which leads to heterogenous reactions.

c. Organocopper(I) complex

The simplest organocopper(I) molecule, formulated RCu, is polymeric in ethereal solvents and unreactive if not aggregated with additional copper and metal atoms.[36] The nucleophilic reactivity of organocopper(I) reagents originates from the organocopper(I) ate complexes, empirically described as R_2CuM (homocuprate) or RXCuM (heterocuprate).

In solution, catalytic copper(I) salts can form two different types of complexes from organometallic species, depending on the concentrations and the presence of additives:[36]

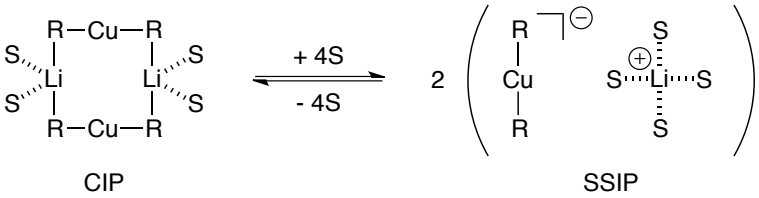
- $[RCuX(L^*)]^-$: Monoorganocuprate if organozinc and organoaluminium species are used or if Grignard reagent is added in low concentration or with external (chiral) ligands (L*) like phosphines and *N*-heterocyclic carbenes;

- $[R_2Cu]^-$: Homocuprate if Grignard reagent is used in excess without external ligands.

In solution, organocopper(I) complexes were observed to form a dynamic equilibrium of two principle structures. These structures are based on the linear array C–Cu–C that needs a countercation charge of +1 per $[R_2Cu]^-$ unit. Studies performed using NMR spectroscopy have shown the fast chemical exchange of the countercation, and the covalent and static character of the C–Cu bond.[37] Organocopper(I) structures are classified into two types[38] (Scheme 26), depending on the solvent, the nature of the cuprate and the presence of Lewis acids:

- CIP: Contact Ion Pair: a cyclic dimeric structure composed of two copper(I) atoms, two countercations and four organic ligands (R). Carbon-copper bonds are covalent, whereas carbon-lithium bonds are principally ionic. This basic cyclic structure can be monomeric or polymeric with the presence of additives such as salts.

- SSIP: Solvent-Separated Ion Pair: a monomeric linear $C–Cu^I–C$ ion unit where the countercation is separated from the ion and coordinated by solvent molecules.



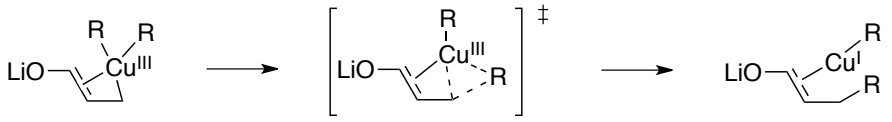
Scheme 26

The two structures are in a constant dynamic equilibrium in solution. In weakly coordinating solvents like Et_2O, organocopper(I) species prefer CIP structures, while in strongly coordinating solvents like THF, in the presence of a Lewis acid or with a crown ether that coordinates the countercation, SSIP structures are dominant. The nature of the salt does not influence the type of structures but can favour the polymerization of the CIP structure.

d. Organocopper(III) complex

NMR spectroscopic evidence suggested that a plausible mechanism for conjugate addition of organocuprate compounds passed through an organocopper(III) species.[39] Organocopper(III) complexes have been recognised to be important intermediates in nucleophilic organocopper(I) reactions.

They result from the oxidative addition of an electrophile to an organocopper(I) complex. Computational studies have revealed that organocopper(III) species were very unstable and characterized by a T-shaped geometry. Generally, T-shaped organocopper(III) complexes undergo reductive elimination without any further activation energy. Addition of a ligand stabilizes them with formation of a tetracoordinated square planar complex. By stabilizing the organocopper(III) complex, detection and in some cases isolation, can be performed, but energy input may be needed for the reductive elimination step to overcome the activation barrier



Scheme 27

e. Influence of parameters

→ *Solvent*

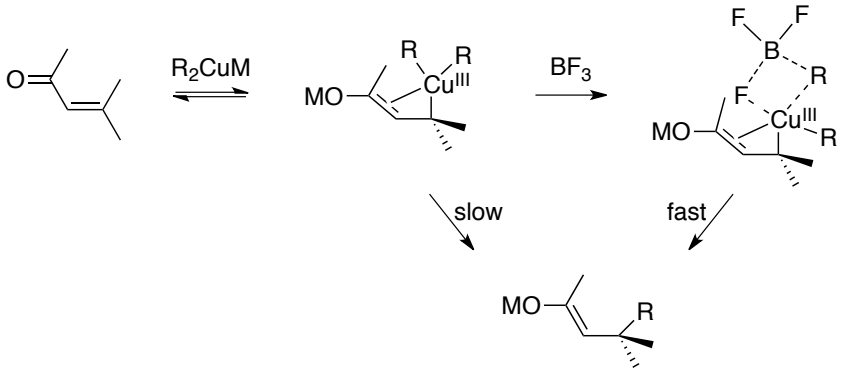
Most of the cuprates are salts and insoluble. Etheral solvents are usually used in organocuprate conjugate additions. The solvent will have an influence on the nature of the organocuprate complex. However, the influence on the reactivity is limited.[38b] Common solvents for the reaction are Et_2O or THF; sometimes, DME and DMS can be also employed. Organocuprate compounds such as Gilman reagents are soluble in etheral solutions, but copper(I) salts have a low solubility that leads to heterogenous reactions.

→ *Lewis acid*

Addition of Lewis acid such as BF_3 can change the selectivity of conjugate addition and increase the reaction activity. Experimental studies suggested that the Lewis acid is increasing the reactivity of the copper reagent rather than activating the α,β-unsaturated carbonyl.[40]

The nature of the complex formed changed from $[(CuMe_3)(BF_3)]$ into $[(CuFMe_2)(MeBF_2)]$.[41] Standard organocopper or copper-catalysed Michael additions operate poorly with β,β-disubstituted α,β-unsaturated carbonyls without any additives, and does not

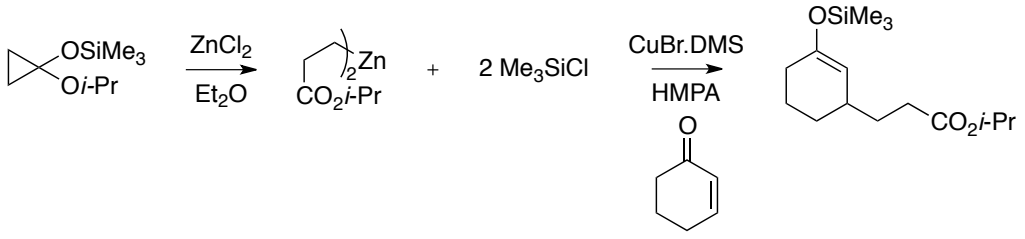
occur with α,β-unsaturated carboxylic acids, whereas addition of a Lewis acid such as BF_3 can lead to satisfying results.[40,42]



Scheme 28

→ *Addition of TMSCl*

In 1980, for a study of the lithium alkylcuprate action on α,β-enals, Normant *et al.* used TMSCl to trap the enolate intermediate.[43] He reported that during his research he obtained better yields than those published before, and the selectivity was changed in favour of the 1,4-addition. In 1984, Nakamura and Kuwajima published a study in which they wanted to show the synthetic utility of homoenolate on 1,4-additions.[44] Trimethylsilyl chloride was generated *in situ* during the formation of the homoenolate. They discovered that, if the TMSCl is removed before the following step, a copper-catalysed 1,4-addition of zinc homoenolate, the reaction is slower, and for some substrates no reaction occurred at all.



Scheme 29

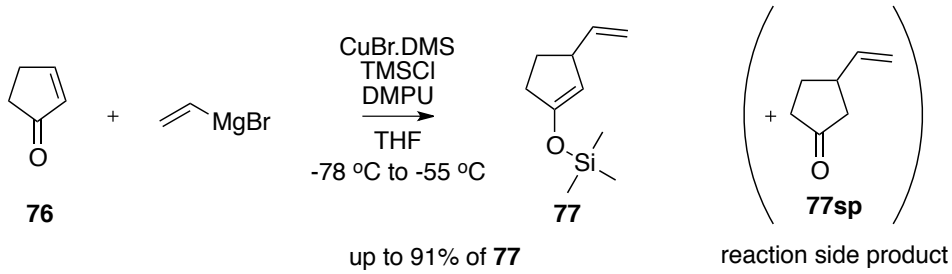
Just after, Corey[45] and Alexakis[46] published their own independent results with Gilman reagent with a TMSCl additive. They both concluded that addition of TMSCl was accelerating the reaction and increasing the yield of organocopper species conjugate addition products.

Corey also showed that no isomerization was occurring with TMSCl. Those results gave clues about a mechanism involving Cu(I)/Cu(III) and suggested that the *O*-silylation was removing a possible reversibility of the organocopper(III) complex formation. This effect could affect the stereoselectivity of the reaction in some cases.[45a] Corey showed that using TMSCl for organocopper compound addition accelerated the reaction and improved the yield of 1,4-adducts by preventing side reactions involving enolates.[45b]

Alexakis reported similar effects concerning the utility of TMSCl to improve conjugate addition of organocopper compounds. He also noted that the *O*-silylation was accelerated by addition of Et_3N or HMPT along with TMSCl.[46] In their absence, almost no silyl enol ether was isolated, but the reaction was still accelerated by the presence of TMSCl.

f. Copper(I)-catalysed addition of vinylmagnesium bromide to 2-cyclopentenone

The Page group has developed and used a methodology in two steps. The first step led to the preparation of silyl 3-vinylcyclopentenol ether **77**, a relatively stable, reactive and convenient starting material.[1,47] It was obtained through a copper(I)-catalysed conjugate addition of vinyl Grignard reagent to 2-cyclopentenone **76** (Scheme 30).



Scheme 30

It was found to be important to handle this reaction meticulously in order to optimize the synthesis as the yield was less than 40 % on occasion. Moreover, the following step required the

synthesis of the diethyl malonate analogue and the preparation of the diethyl methylenemalonate product to be performed in parallel, as the latter compound was not stable and it was necessary to know the precise quantities that we would expect to obtain for the next step.

A solution of vinylmagnesium bromide in THF was slowly added to a solution of copper(I) bromide-dimethyl sulfide complex in THF at −78 °C. The best results were obtained with freshly prepared copper(I) bromide-dimethyl sulfide salt (white powder). Vinylmagnesium bromide was added with caution, slowly and directly into the solution. The mixture was allowed to homogenize and the temperature to stabilize at −78 °C. The yield was lowered by loss of reagent when it crystallized on the flask sides due to the addition or to the too vigorous stirring. Best results were obtained with a slow addition. The starting copper(I) salt was a pale whitish solid, which was insoluble in THF. The result of the vinyl Grignard reagent addition was a clear brown red solution that turned first to a yellow colour and then green. A mixture of DMPU, TMSCl and cyclopentenone **76** was prepared directly in the addition flask. This solution was added very slowly to the reaction mixture with strict controls on the temperature, not to exceeding −70 °C, and on the stirring.

Indeed, two parameters have to be particularly considered: the temperature had to be controlled precisely. The 1,4-addition on cyclopentenone was an exothermic reaction, and thus, had to be slow to avoid the temperature to rise above −70 °C. When the temperature was too high, a significant amount of deprotected product **77sp** was observed. The stirring also needed to be cautiously monitored: when the mixture was stirred too vigorously during the preparation of the copper reagent, crystallization of the Grignard reagent on the side of the flask occured. However, a firm stirring was necessary during the addition of the solution containing the cyclopentenone to avoid the agglomeration of a solid that caused a serious loss in the reaction yield.

With these parameters well controlled, the yield could reach 91% from 5 g of starting material (9.8 g of product). On a bigger scale, parameters were hardly controllable (main problems were due to the stirring), and parallel smaller reactions were preferred. The observed side reactions were principally 1,2-additions and deprotection of the silyl enol ether. The addition of DMPU is known to promote the silylation of the enol in the Michael addition.

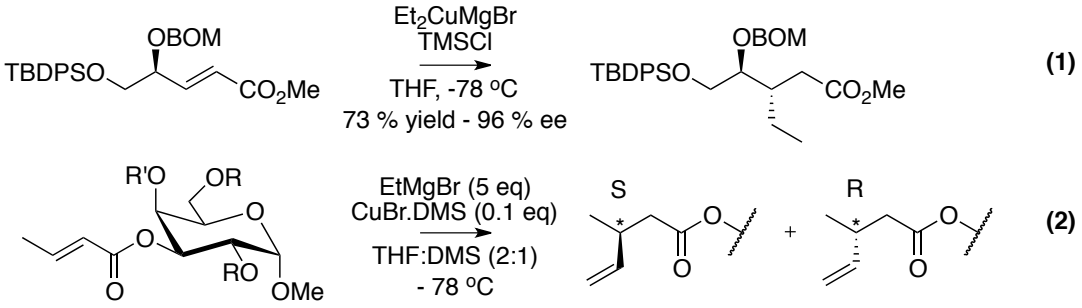
At the end of the addition, the solution was allowed to reach −55 °C for about 3 hours; then Et_3N was added to quench the acidity and to prevent the loss of the silyl group. The work-up and Kügelrohr distillation were immediately performed to prevent any degradation of the product. The next step was attempted on the crude compound without distillation, but this gave poor results.

The crude compound is a dark brown oil, while the pure compound **77** is colourless. The silyl enol ether **77** can be safely stored under argon at low temperature (freezer: −20 °C) in a dry flask for months without significant degradation. However, it decomposed in few hours under other conditions.

g. Asymmetric conjugate addition catalysed by copper(I)

Organocopper(I) reagents generally show no stereospecificity. Chirality in the 1,4-adducts can be created by intramolecular induction or by the use of chiral ligands.[35b]

Chiral centres in 1,4-additions can be introduced by intramolecular induction. Hanessian studied 1,2-induction with γ-alkoxy-α,β-unsaturated esters with good diastereoselectivity (up to 96% *ee*, equation **(1)** Scheme 31).[48] The chirality of the sp^3 carbon depends on the stereochemistry already existing on the molecule, and control over this asymmetry depends on the steric hindrance and is hard to obtain. Another option is the use of a chiral auxiliary that can be attached and removed easily, giving the desired adduct with an efficient diastereocontrol, and thus the final product after removal of the auxiliary in high enantioselectivity. This method is principally applicable with unsaturated esters and amides. Auxiliaries such as camphor-based esters or ephedrine-based amides have shown interesting results. Tadano investigated the use of sugars as chiral auxiliaries and obtained good results (equation **(2)** Scheme 31 and Table 5).[49]



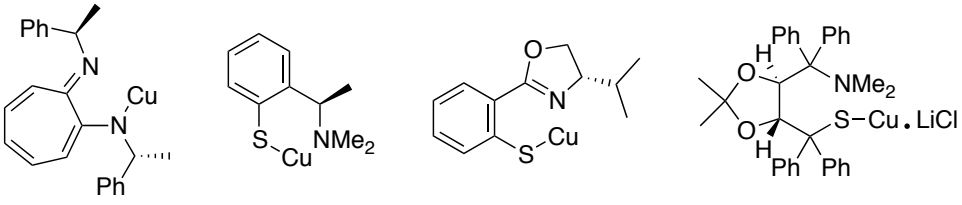
Scheme 31

Entry	R	R'	Yield	*R* : *S*
1	Bn	Bn	82 %	14 : 86
2	Bn	Bz	82 %	97 : 3
3	Me	Piv	80 %	94 : 6
4	Bn	Piv	94 %	98 : 2

Table 5

Optically active ligands have demonstrated the ability to direct copper-catalysed conjugate addition. A full range of chiral ligands, which could be applied to Michael addition and are catalysed by copper(I) salts, was developed. Ligands can be divided into two different classes:

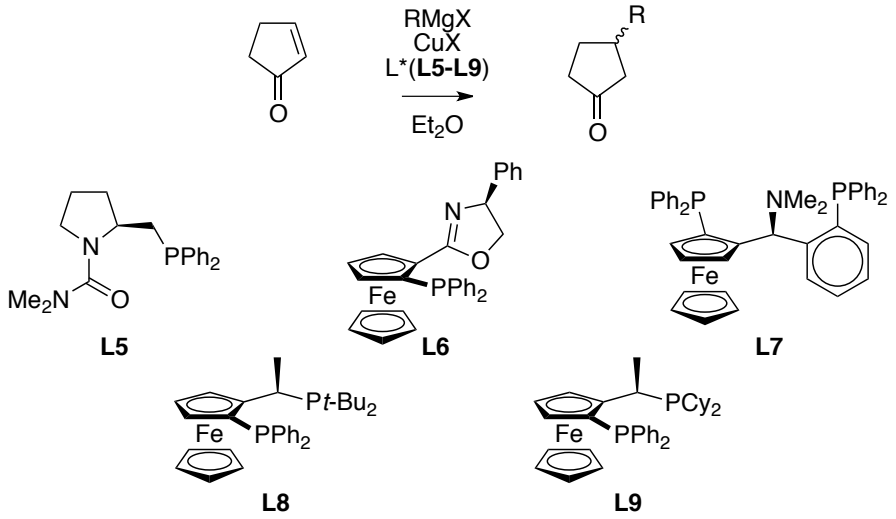
- Non-transferable ligands that share a covalent bond with the copper(I) (**L1**,[50] **L2**,[51] **L3**[52] and **L4**[53]: Scheme 32);
- External (transferable) ligands that are (catalytic) reagents added to the reaction (**L5**,[54] **L6**,[55] **L7**,[35b] **L8**[35b] and **L9**[35b]: Scheme 33).



L1 74 % ee* **L2** 57 % ee* **L3** 87 % ee* **L4** 84 % ee*

* highest ees value obtained

Scheme 32



L5 **L6** **L7** **L8** **L9**

Scheme 33

Entry	RMgX	CuX (equiv)	L* (equiv)	Yield	ee	Major
1	*n*-BuMgCl	CuI (8 %)	L5 (32 %)	70 %	42 %	*S*
2	*n*-BuMgCl	CuI (10 %)	L6 (12 %)	82 %	65 %	*R*
3	EtMgBr	CuCl (5 %)	L7 (6 %)	69 %	6 %	*S*
4	EtMgBr	CuCl (5 %)	L8 (6 %)	99 %	92 %	*R*
5	EtMgBr	CuCl (5 %)	L9 (6 %)	99 %	82 %	*R*

Table 6

In a future work on the subject, asymmetric Michael addition to our starting material, 2-cyclopentenone should be considered. It would allow us the control of the whole stereochemistry throughout almost the entire synthesis. To date, it has not been studied in our laboratory because of the need for more and more material for the study of the later steps of the synthesis. We know the relative configuration and preferred to concentrate on the study of the later steps.

II) Conjugate aldol-type addition

1) Aldol addition

a. Introduction

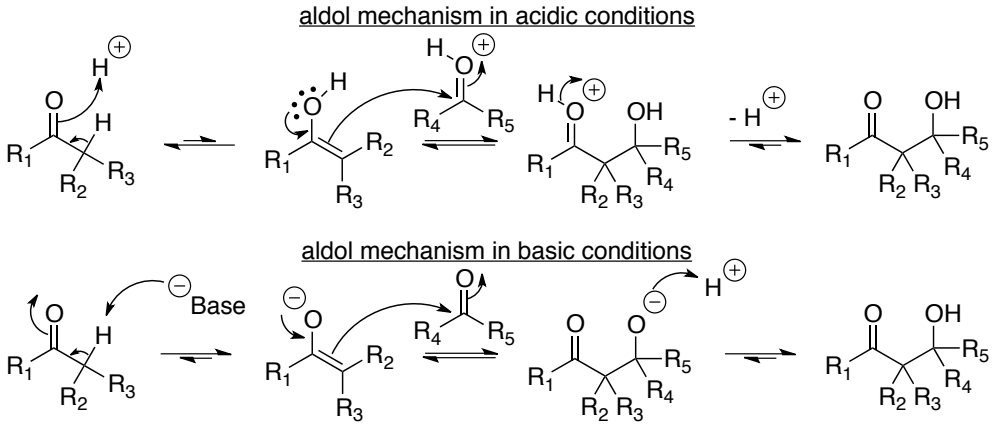
An aldol reaction is the formation of a carbon-carbon bond between two carbonyl compounds, one is acting as a nucleophile under the form of an enol or enolate and the other one is acting as an electrophile. It was first observed and reported independently in 1872 by Alexander Borodin and Charles-Adolphe Wurtz.[56] The new species was named "aldol" by Wurtz as it shared the properties of both **ald**ehyde and alcoh**ol** moieties.[77]

Alexander Borodin (1833-1887) was a Russian scientist and a romantic composer. He was the illegitime son of a Caucasian prince, but officially recognised as the son of one of the prince's serfs. He received a good education and he entered the Medico-Surgical Academy in 1850. He obtained his diploma in medicine and pursued his career in chemistry. In 1869, he reported the bromodecarboxylation of silver salts of carboxylic acids that was wrongly attributed to the Hunsdieckers 70 years later. The Soviet Union promoted the "Hunsdiecker reaction", patented in 1939, as the Borodin reaction. Borodin worked on alkaline condensation of aldehydes and observed the aldol reaction in 1872. He noted some similarities with Wurtz's work published the same year. In fact Borodin is more popular for his musical contribution with his symphonies, his two string quartets and his opera Prince Igor. The French composer, Ravel, wrote a piano piece entitled "A la manière de Borodine" in homage to him. Some of his compositions were adapted for an American musical, Kismet, in 1953.

Charles-Adolphe Wurtz (1817-1884) was one the greatest French organic chemist of the 19th century.[5] Wurtz's name appears among the 72 names of French scientists engraved on the Eiffel tower. Born in Alsace (France), at the border between Germany and France, he studied medicine at the university of Strasbourg and specialized in the chemical section. In 1839, he was appointed "Chef des travaux chimiques" at the medical faculty of Strasbourg and, in 1842, he worked under the supervision of Justus von Liebig in Germany. In 1845, he became the assistant professor of Dumas, his mentor, and received his first chair in 1850 in Versailles. He is well known for the Wurtz reaction, which is the coupling of alkyl halides in the presence of sodium to create a new carbon-carbon bond. In 1872, he published his observations about the autocondensation of acetaldehyde with HCl to afford a compound with the properties of both an aldehyde and an alcohol, and hence called it aldol. He also discovered triethylamine, ethylene glycol and the first epoxide, ethylene oxide. He was a fierce defender of the new concept of valence against the equivalence theory. Indeed, at the time, the accepted theory was the equivalence theory where water was formulated as OH (with O = 8). In contrast, the valence theory suggested a water formula as H_2O (with O = 16). Even though that concept was more developed by Dalton, Avogadro and Cannizzaro, he is well remembered for his advocacy of the theory of atoms.

Originally, the aldol reaction consisted of the reaction of two aldehydes catalysed by a Brönsted acid to produce a β-hydroxyaldehyde, an aldol. The reaction was extended to other types of carbonyls bearing an acidic proton at the α-position with respect to the carbonyl, and the reaction was developed under both acidic and basic conditions. The product, a β-hydroxycarbonyl, can undergo *in situ* dehydration to afford an α,β-unsaturated carbonyl product.

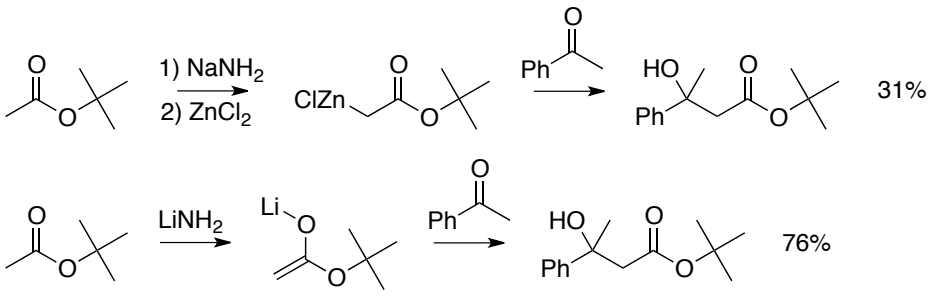
Aldol reactions were performed under acidic conditions but were lacking in efficiency and control. The standard reaction conditions involved the mixing of the two carbonyl reagents along with a Brönsted acid that triggered an equilibrium between the carbonyl species and their reactive enol forms, and the subsequent formation of the adduct. However, side products such as self-condensed or polymerized products were also observed, and problems of reactivity and control of the formation of the desired product were often encountered.



Scheme 34

Crucial progress and renewed interest appeared with the use of a preformed enolate prior to the addition of the electrophile.

Hauser investigated new conditions for a Reformatsky-like reaction in order to mimic the Reformatsky intermediate (Scheme 35).[57] In this study, he tried to form the Reformatsky reactive species under basic conditions. Indeed, instead of employing an α-haloester as starting material and generating the organozinc bromide *in situ* from zinc(0) metal (Reformatsky conditions), he attempted to deprotonate the ester at the α-position and directly exchange the metal with zinc dichloride. He obtained the desired compound, a β-hydroxycarbonyl, but the zinc(II) salt was found not to be necessary, and best results were obtained when using only a base such as lithium amide.



Scheme 35

In 1951, Hauser reported the use of a preformed enolate in an aldol reaction.[57] This report marked the start of a rising interest towards this attractive reaction, showing the possibility for high yields with flexibility in the conditions and control over the stereochemistry.

Since the 1970's, the aldol reaction has emerged as a key tool in providing stereocontrolled chemistry.[58] The great power of this reaction lies in the possibility to control the stereochemistry of the product through several parameters: solvents, the stereocontrolled formation of the enol or enolate, the use of different metals as countercations, the use of chiral ligands and/or the use of chiral auxiliaries.

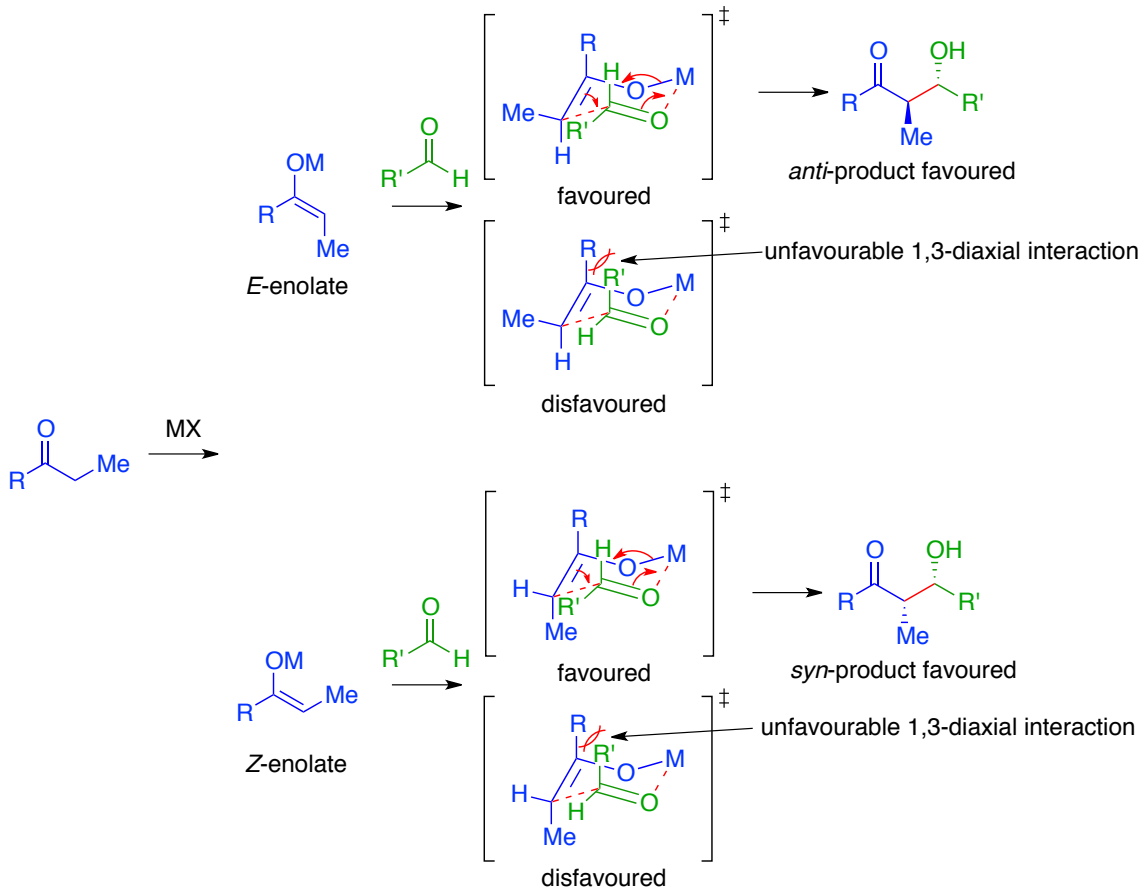
b. Zimmerman-Traxler model

In 1957, Zimmerman and Traxler studied the stereochemistry of an aldol reaction, the Ivanov reaction.[59] The Ivanov reaction is the addition of a preformed dianion enolate of a carboxylic acid to a carbonyl electrophile. Zimmerman and Traxler suggested a transition state involving a six-membered ring in a chair conformation that could rationalize the stereoselectivity observed (Scheme 36).

The priority for the *Z*/*E* enolate assignment follows the Cahn-Ingold-Prelog rule.[60] Although, the alkoxy metal moiety is always considered as highest priority, regardless of the nature of the metal. For more clarity, the enol ether/enolate (the nucleophile) was drawn with only one methyl substituent, and an aldehyde was chosen as the electrophile in order to accentuate the selectivity order between the hydrogen (small group) and the substituent (large group).

The most favoured chair transition state prefers the biggest substituents at the equatorial positions, thus avoiding 1,3-diaxial interactions. The model drawn (Scheme 36) provides only an example of how to correctly place substituents in a Zimmerman-Traxler model and which interactions can influence the product stereochemistry. In this example, an *E*-enolate gives an *anti*-product, and a *Z*-enolate a *syn*-product. This model was used to predict or explain outcomes in many aldol reactions, and is particularly reliable with small coordinating metal counterions such as lithium, boron and magnesium. Boron is particularly good because of the tight regular transition state it forms. However, the selectivity cannot be always explained using Zimmerman-Traxler model, especially for bigger coordinating metals. Irrespective of the enolate geometry,

titanium enolates usually afford the *syn*-product with high stereoselectivity, whereas zinc enolates give preferentially the *anti*-product.[61]

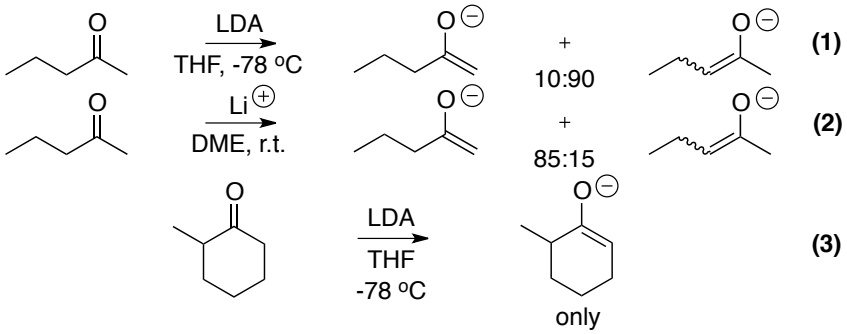


Scheme 36

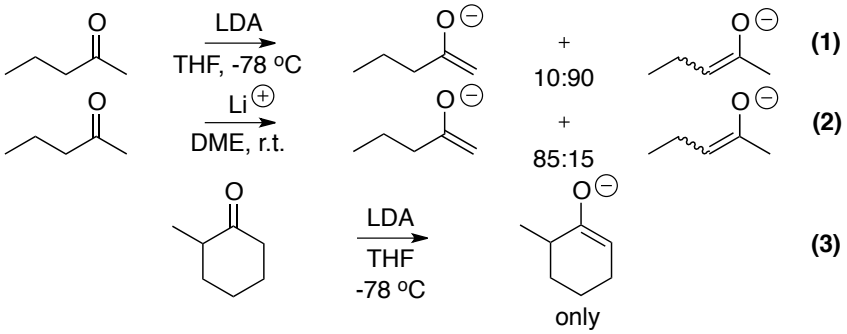
c. Enol/enolate

A range of bases was investigated for the enolate formation; dialkyl- and disilylamine bases have shown to be the most convenient ones.[62] They are relatively strong bases and poor nucleophiles. The most commonly used bases are lithium diisopropylamide (LDA) and lithium hexamethyldisilazide (LiHMDS lithium bis(trimethylsilyl)amide). Other bases, including more hindered bases such as lithium 2,2,6,6-tetramethyl piperidide (LiTMP) or lithium *t*-butyl-*t*-octylamide, were examined but did not demonstrate more selectivity in generating the enolate.

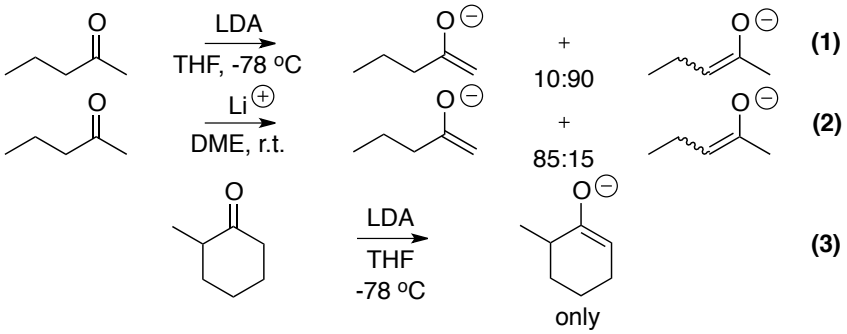
D'Angelo published a study on enolate formation in 1976.[62] The stereochemistry of enolates enolates may be influenced by parameters such as the reaction conditions, thermodynamic



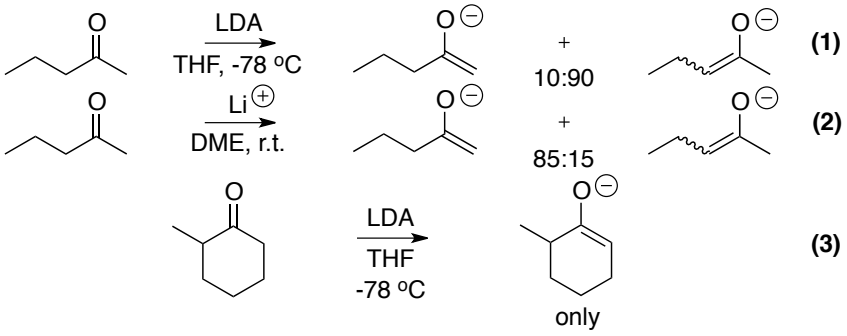
(Equation 1 Scheme 37) or kinetic controls (Equation 2



Scheme 37) and steric hindrance (Equation 3



Scheme 37). In general, smaller R substituents (see Scheme 36 for notation) and/or bigger bases provide *E*-enolates, while bulkier R substituents and smaller bases give preferentially *Z*-enolates.



Scheme 37

Enolates can be trapped as silyl enol ethers[63] or enol esters.[64] Trapped enolates may be separated, and the enolate with the unwanted configuration of the double bond could be then recycled. Methods were developed to engage those silyl enol ethers and enol esters directly in aldol reactions.[61b,65] These processes enabled increased selectivities and yields; they were also a good method to avoid self-aldolization with highly electrophilic compounds such as aldehydes.[66] A silyl enol ether is one of the starting materials in the Mukaiyama aldol addition.

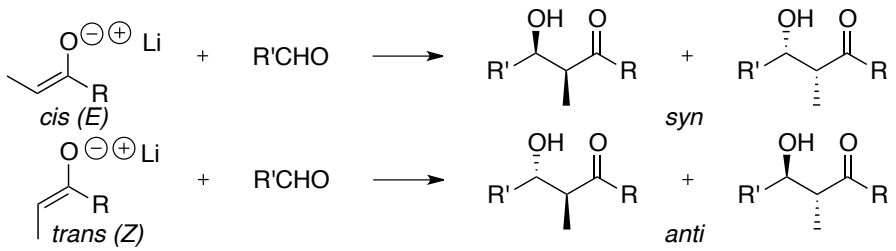
Michael additions of copper-catalysed Grignard reagents or Gilman reagents to α,β-unsaturated carbonyls provide enolate intermediates that can undergo aldol reactions *in situ* upon addition of the electrophile. Another method to generate regio-defined enolates is the reduction of α,β-unsaturated carbonyl species with lithium metal in liquid ammonia.[67] Indeed, the reduction of the carbon-carbon double bond generates an enolate that can react in an aldol addition under specific conditions to avoid any equilibration of the enolate.[68] However, better results are obtained when trapping the enolate with trimethylchlorosilane.

d. Stereoselectivity through chiral auxiliaries

Clayton Heathcock wrote a review in 1981 regarding the possibilities of aldol reaction: "*For the scientist who wishes to synthesize complex organic compounds, the most difficult problem is often establishing the correct configuration at the various chiral centers as the synthesis is being carried out. One of the oldest organic reactions, the aldol condensation, is emerging as a powerful tool for use in achieving such stereocontrol.*"[58]

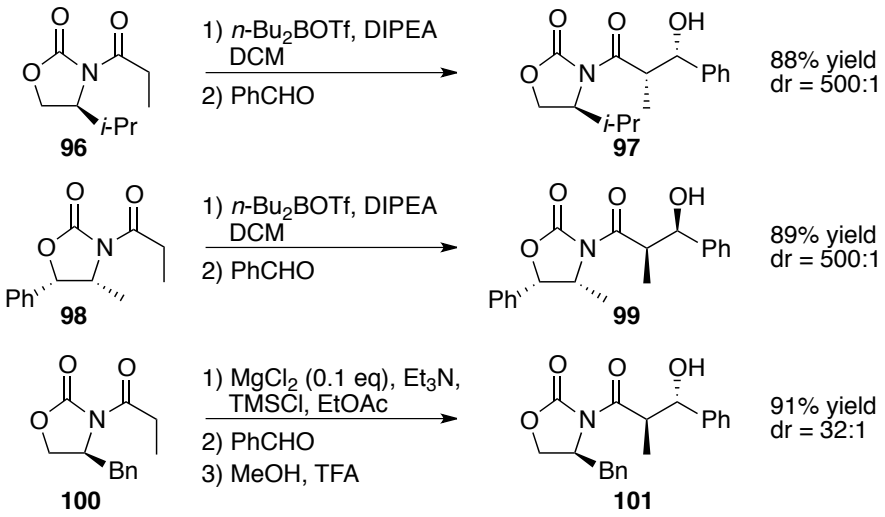
In 1957, Zimmerman and Traxler rationalized the stereochemistry obtained through aldol reactions,[59] but it was only from the 1970's that Dubois showed that relative configuration could be controlled by the enolate configuration and the size of the substituents (Scheme 38).[58,69] A range of substituents was screened to study the stereochemical outcome of the reaction, and an influence on the diastereoselectivity was observed. Also, some metals proved to improve the diastereoselectivity through additional chelation to another function on the enolate or the aldehyde such as a chiral auxiliary.[70]

Those methods permitted the reduction of the number of isomers from four diastereoisomers to only two enantiomers. The number of products could be in turn reduced to one major isomer if the R and/or R' substituents (Scheme 38) possessed chiral centres that could influence the selectivity.



Scheme 38

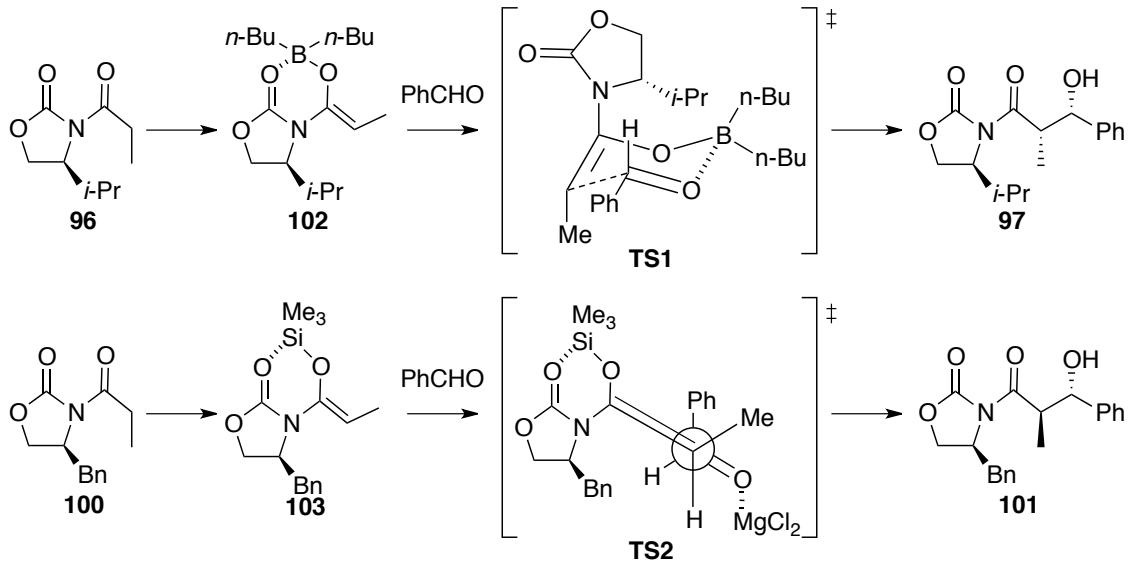
In 1981, Evans introduced the notion of a removable and recyclable chiral auxiliary that could control both diastereoselectivity and enantioselectivity (Scheme 39).[71] Chiral 2-oxazolidinones can be coupled with carboxylic acids or acyl halides to form chiral imides. Those chiral imides can undergo aldol addition with high to almost total enantioselectivity.



Scheme 39

With one equivalent of *n*-BuOTf, the boron is chelated to the two carbonyls from the oxazolidinone and the enolate **102** (Scheme 40). This chelation is broken by the approach of the aldehyde, and a new chelation is formed between the aldehyde and the carbonyl group. In the model **TS1**, the carbonyl function of the oxazolidinone is in *anti* from the other carbonyl groups and the boron. The *i*-propyl group is directed towards the back, so the aldehyde attacks from the front, affording the *syn* product **97**. With an analogue chiral auxiliary presenting an opposite configuration like Y, the other *syn* adduct **99** is obtained.

With an excess of boron base or a Lewis acid, the transition state is different. The Lewis acid chelates the two carbonyls, and the transition state with the aldehyde compound is opened like **TS2**. **TS2** shows that the chiral auxiliary is still directing the approach: the benzyl substituent is directed towards the front, so the aldehyde attacks from behind. The steric hindrance is minimized by placing the substituent of the aldehyde on the less hindered side (Scheme 40). This reaction affords the *anti* product **101**. The other *anti* product can be obtained with a chiral auxiliary presenting an opposite configuration at the asymmetric carbon.



Scheme 40

Evans auxiliaries showed to be highly useful in asymmetric synthesis as great enantioselectivities were obtained.[72] Each of the diastereoisomers can be produced in good yields and selectivity. However, the scope of substrates remained limited, and the chiral oxazolidinone auxiliaries expensive.

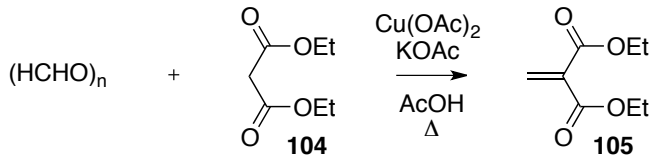
Crimmins reported similar auxiliaries that can overcome some limitations of Evans auxiliaries.[73] Other groups worked on the synthesis and development of new chiral auxiliaries. A carbohydrate-based synthetic method was developed by Pearson. The key step of this strategy was the spiro-fusion of a chiral cyclohexanone with α-hydroxycarboxylic acid.[74] Pearson used Seebach's concept published in 1981, but without any further investigations from him.[75] Page developed an aldol reaction of 1,2-diketones, masked as a non-racemic 2-acyl dithiane oxide, with lithium enolates from esters or lactones: in this methodology, the removable chiral auxiliary was attached to the electrophilic compound of the aldol reaction.[76]

2) Preparation of the Mukaiyama-Michael acceptor

a. Diethyl methylenemalonate

In our synthetic strategy, we were looking for Michael acceptors bearing functionalities that could allow further homologation at a later step. The first one we chose to study was the long-known diethyl methylenemalonate **105**.[77] It was prepared in one step from diethyl malonate **104** in reasonable yield (53%).

Bachman screened different conditions and reported the great importance of an acidic medium, copper(II) salts, sodium salts and an excess of paraformaldehyde. The use of acetic acid as solvent gave the best results. The excess of paraformaldehyde eliminated completely malonate ester from the reaction mixture (the latter substrate could combine with methylene malonic ester to form ethyl propanetetracarboxylate). Potassium acetate served for the hydrolysis. The use of copper(II) acetate was not clearly determined, but yields were significantly lower in the absence of this salt.



Scheme 41

Diethyl methylenemalonate **105** was prepared through a Knoevenagel condensation, which is a modification of the aldol reaction where the nucleophilic addition is followed by dehydration. We supposed that the dehydration was occurring during the distillation step as no polymerization was observed in the concentrated crude mixture prior to the purification process (no solidification of the concentrated crude mixture was observed). On the other hand, the pure compound was highly sensitive and polymerized quickly. Therefore, the distillation apparatus was pre-washed with acid and dried in the oven in order to avoid its polymerization. The distillate was kept at low temperature during the distillation (−78 °C) and stored under argon in a freezer (−20 °C). Even when all those precautions were taken, it could generally not be kept for

more than a week before the polymerization started. At −78 °C, diethyl methylenemalonate **105** was solid. At −20 °C, it was very viscous, and it was liquid at room temperature.

The polymer could be cracked through distillation, and the methylene malonate **105** was recovered, but only in low yields (30%) and polymerization could still re-occur later.

Our primary synthetic route with diethyl methylenemalonate **105** showed limitations, notably upon decarboxylation, so we chose to explore the synthesis of two other malonate moieties:

- Dibenzyl methylenemalonate: it presented the same properties as diethyl methylenemalonate and the benzyl groups could be easily removed through a simple palladium-catalysed hydrogenolysis.

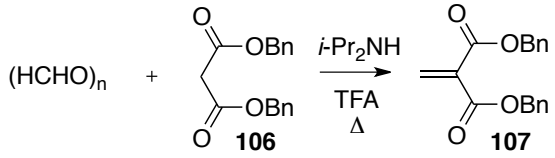
- 2,2-Bis(phenylsulfonyl)ethene: the α-carbon between the two sulfone moieties could be easily functionalized and removal of the sulfone was possible.

b. Dibenzyl methylenemalonate

The synthesis of dibenzyl methylene malonate **107** presented many advantages compared to the other: readily prepared, no purifications needed, possibility of high scale preparation (up to 17.8 g of product).

After heating a mixture of paraformaldehyde and dibenzyl malonate **106** with diisopropylamine and TFA for 48 h and a simple work-up, dibenzyl methylenemalonate was isolated in quantative yield with only few traces of impurities (Scheme 42).[78] Dehydration occurred *in situ,* certainly promoted by the presence of the amine group. The ^{1}H NMR spectroscopic data showed only traces of diisopropylamine, but the viscous oil was pure enough to be used in the following step and was characterized. The synthesis could be performed in relatively high quantities (17.8 g). The product seemed to be less sensitive to polymerization and could be stored in a freezer for weeks. However, purification by chromatography on silica gel led to the decomposition of the product.

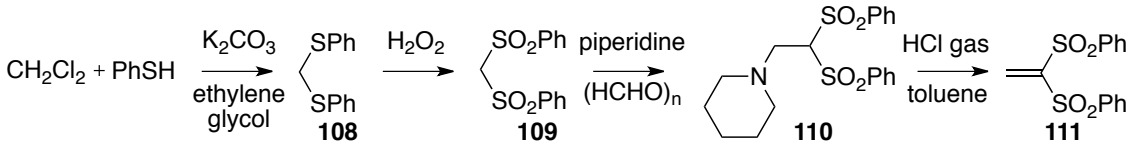
The use of dibenzyl methylene malonate **107** in the synthesis presented the best results and was also more advantageous as the adduct was readily observable under UV-light.



Scheme 42

c. 1,1-Bis(phenylsulfonyl)ethylene

Preparation of 1,1-bis(phenylsulfonyl)ethylene **111** proved to be more laborious than expected:[79] the synthesis required four steps and afforded the product from thiophenol in an average overall yield of 60% (Scheme 43).



Scheme 43

A mixture of K_2CO_3, thiophenol and dichloromethane in ethylene glycol was heated under reflux for three hours to give **108**. The crude compound was purified by distillation under reduced pressure to afford bis(phenylthio)methane **108** in 88% yield. The pure compound was a noxious colourless oil.

Oxidation of the thioether **108** with hydrogen peroxide gave bis(phenylsulfonyl)methane **109** in 78% yield. The product was purified by recrystallization from toluene to afford a white solid.

Bis(phenylsulfonyl)methane **109** was treated with paraformaldehyde and an excess of piperidine to give **110**. This reaction processed through a Knoevenagel-like mechanism that occured in two steps. Presumably, paraformaldehyde and piperidine combined to form an

iminium intermediate that was attacked by the deprotonated carbon α to both sulfones to give **110**. In a second step, elimination of the piperidine afforded the desired compound **111** under strong acidic conditions.

The product **111** was a colourless powder that could be stored for months. At first, the route using this adduct **111** and the sulfone analogues seemed very promising, providing solid products instead of viscous liquids, which were obtained before with the other Michael acceptors **105** and **107**, the possibility of recrystallisation, and the compounds were visible under UV-light.

Unfortunately, this route was shown to have several limitations:

- Lower yields were obtained in most of the reactions;
- The simplicity in the purification of the product **111** (crystallization) was not encountered in the next steps;
- The addition reaction to the α-carbon of the sulfone analogue **89c** failed.

For all these reasons, this route had to be discontinued. These points are further discussed below.

3) Mukaiyama reaction

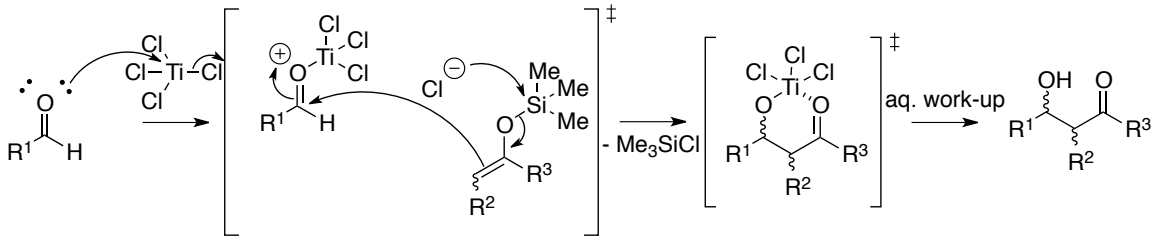
In 1973, Mukaiyama reported that, in the presence of $TiCl_4$, silyl enol ethers of ketones reacted smoothly with ketones or aldehydes to yield the corresponding aldol products in good yields.[80] This new methodology offered new possibilities such as different conditions (Lewis acidic conditions) and the control over the relative stereochemistry. More generally, it has greatly developed the synthetic use of Lewis acids and bases.

Teruaki Mukaiyama (1927-) is a Japanese organic chemist.[81] He received his PhD from the University of Tokyo in 1957. He was appointed full Professor at the Tokyo Institute of Technology in 1963 and Distinguished Professor in 1992. His research covered organic syntheses and synthetic methodologies: sugar chemistry, aldol reaction, coupling reaction (Mukaiyama reagent), oxidation/reduction, Lewis acid/base catalysis, dehydration reaction, asymmetric and total syntheses… His illustrious career has led to more than

900 publications and he has received many rewards and honours. In 1972, he founded the Japanese journal Chemistry Letters. He is a member of the Japan Academy and is also a Foreign Member of the Polish Academy of Sciences, the French Academy of Sciences, as well as a member of the National Academy of Sciences (USA). Oyo Mitsunobu (1934-2003) was one of his notable students. The Society of Synthetic Organic Chemistry of Japan (SSOCJ) established the Mukaiyama award in 2005 to reward each year a young chemist (less than 45 years old) for his contribution to synthetic organic chemistry.

The originality of the Mukaiyama aldol reaction is due to the use of Lewis acidic conditions, leading to good stereocontrol.[65,80,82] Prior to this work, the best way to control the stereochemical outcome of an aldol reaction was to perform the reaction under basic conditions, which could induce several undesired side reactions, and in some cases, low yields. The Mukaiyama approach offered chemo- and regioselectivity in carbon-carbon bond formation.

Under Mukaiyama reaction conditions, the Lewis acid is used in order to activate the electrophilicity of the carbonyl, while the silyl moiety activates the nucleophilicity of the enol. A halide ion is released as the oxocarbenium is formed from the attack of the oxygen atom of the carbonyl group onto the Lewis acid. The released anion attacks the silyl group, and the enolate and activated group react through an aldol reaction mechanism (Scheme 44).



Scheme 44

The original reaction was performed using $TiCl_4$ in stoichiometric quantities, but later other Lewis acids were applied in the reaction ($SnCl_4$, $AlCl_3$, $BCl_3.OEt_2$, $ZnCl_2$, etc…).[82a] The silyl enol ethers can be unsubstituted, mono- and disubstituted, and prepared from aldehydes, ketones, esters or thioesters. Electrophilic carbonyl compounds such as aldehydes, ketones and even acetals have been used successfully in the reaction.[6]

The diastereoselectivity of the Mukaiyama aldol reaction can be directed when the substrates are carefully chosen. However, control of the stereoselectivity is generally relative, unless a chiral Lewis acid is chosen or internal induction is present in the molecule. Contrary to the direct aldol addition, no cyclic intermediate between the enol and the carbonyl can be described, so the stereochemistry cannot be predicted by following the Zimmerman-Traxler chelation model. Mukaiyama reaction intermediates can be represented as open intermediates following the Felkin-Ahn model (Scheme 45).

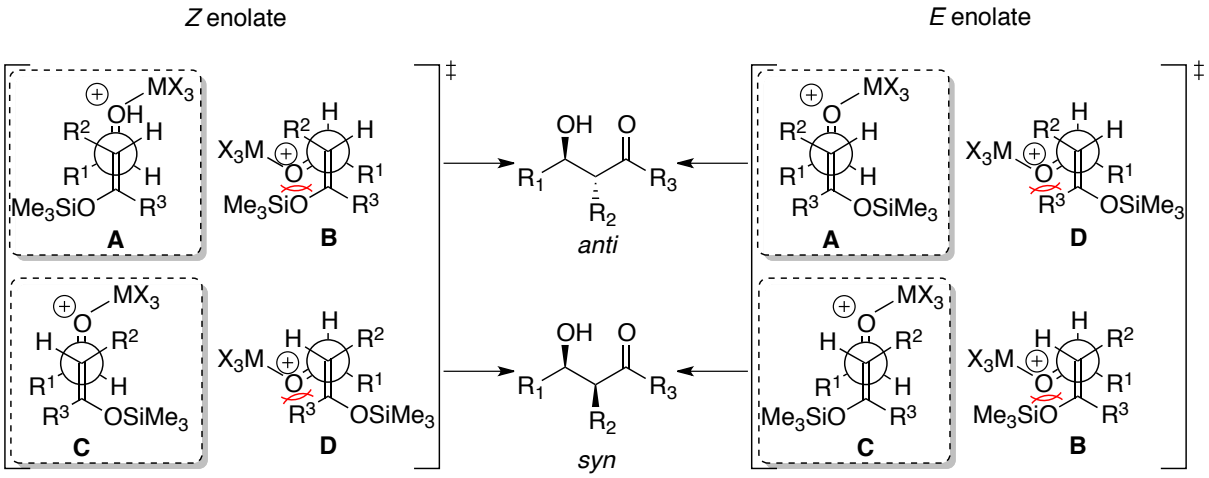
General rules for the determination of diastereoselectivity can be drawn as follow (Scheme 45):[6]

- Stereochemistry of the double bond does not affect the product diastereoselectivity;
- If R^2 is small and R^3 bulky, the *anti*-product is usually the major product;
- If R^2 is large, *syn* diastereoselection is favoured;
- *Syn* product is also predominant when the aldehyde can be chelated.

Transition states are represented in Newman projections in Scheme 45. We assume that the Lewis acid occupies a coordination site that is *cis* to the hydrogen of the aldehyde. In the Newman projections (Scheme 45), models A and C are the most favoured with less dipole-dipole interactions. Models B and D are the results of an anticlockwise rotation: model B bears non-bonded interactions between R_1 and R_3 plus unfavourable dipole-dipole interactions of the two carbon-oxygen bonds. Model D shows non-bonded interactions between oxygen and R^3. A clockwise rotation of models A and B would give similar unfavourable interaction and Lewis acid interactions with R_3 or silyl.[83]

Control of the absolute stereochemistry of the Mukaiyama aldol product can be achieved through the use of chiral enol ethers, chiral aldehydes[84] or even chiral Lewis acid complexes and Lewis bases.[82d]

Catalytic Lewis acid/base conditions have been since developed for the Mukaiyama aldol reaction.[82d,85] Now, it is possible to obtain chiral aldol products from achiral starting materials, using a chiral Lewis acid or base in catalytic quantity.[86]



Scheme 45

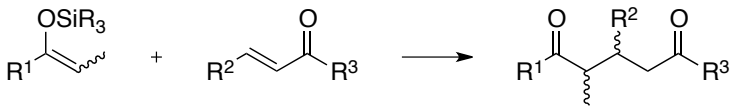
4) Mukaiyama-Michael reaction

a. Introduction

A Mukaiyama-Michael reaction is the Lewis acid-mediated conjugate addition of silyl enol ether to a Michael acceptor. The first example of conjugate addition of silyl enol ether to an α,β-unsaturated carbonyl was published by Mukaiyama in 1974.[65,87] This methodology was considered as a useful tool for the creation of 1,5-dicarbonyl moieties.[82c,88]

Hitchcock performed a screening of reactions of silyl enol ethers and α,β-unsaturated carbonyls that revealed several general tendencies (Scheme 46):[83]

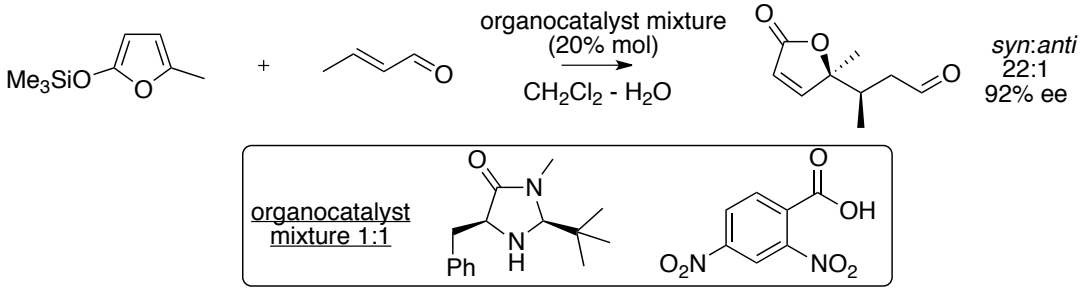
- *Anti* selectivity is favoured when using a silyl enol ether derived from a ketone;
- *Syn* selectivity generally prevails when the silyl enol ether is derived from an ester;
- The configuration of the enol does not affect the product configuration;
- Bulkier substituents give higher selectivities.



Scheme 46

In some cases, a loss of selectivity was observed. Otera explained this loss of selectivity by a radical mechanism through electron transfer from ketene silyl acetal to Lewis acid.[89] According to the radical mechanism, both the carbon-carbon double bond of the silyl enol ether and the carbon-carbon double bond of the α-enone are free to rotate due to the potential formation of a radical cation. Otera suggested that the use of highly oxophilic Lewis acid such as $TiCl_4$, and bulky silyl and/or bulky alkoxy could avoid the formation of or limit the influence of the radical.[89b]

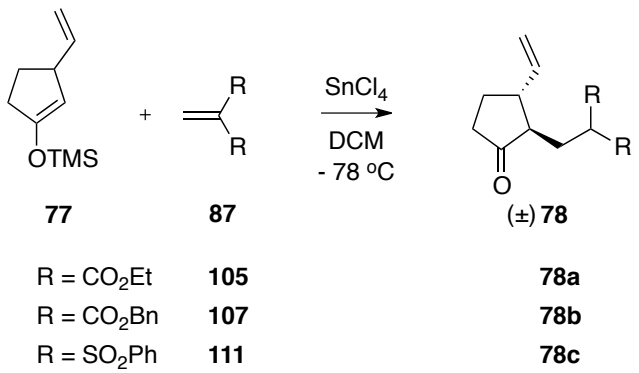
Chiral Lewis acids have also exhibited the ability to induce stereoselectivities in Mukaiyama reactions with a Michael acceptor.[90] MacMillan provided the first enantioselective Mukaiyama-Michael reaction with an unsaturated aldehyde using chiral imidazolidinone as organocatalyst (Scheme 47).[91]



Scheme 47

b. Mukaiyama-Michael reaction of 3-vinyl-1-trimethylsilyloxycyclopent-1-ene with malonate ester

The second step of the methodology developed in our group was a conjugate addition mediated by the Lewis acid $SnCl_4$ between the enol ether **77** and **87** (originally only **105** but later extended to **107** and **111**) to give **78** (Scheme 48).



Scheme 48

The solution of the silyl enol ether **77** and the Michael acceptor **87** (**105**, **107** and **111**) were prepared cautiously to avoid side reactions (due to the remaining traces of acid or base in the starting material). Indeed, diethyl methylenemalonate **105** is moisture and base sensitive, and thus polymerizes quickly. Therefore, the glassware used for the preparation and the storage was previously washed with acid to avoid this polymerization. Silyl enol ether **77** is acid sensitive (removal of the silyl protection in acidic conditions to afford **77sp**, Scheme 30) so during its preparation, the reaction was quenched with an excess of base (Et_3N).

Silyl enol ether **77** was first diluted in dichloromethane at room temperature and was then cooled down to −78 °C. Diethyl methylenemalonate **105** or dibenzyl methylenemalonate **107** was added at low temperature to avoid polymerization, followed by the addition of $SnCl_4$. No polymerization was observed with dibenzyl methylenemalonate **107**, but we preferred to process in this way to prevent this behaviour.

However, 1,1-bis(phenylsulfonyl)ethylene **111** was not soluble in dichloromethane at low temperature, so the addition order was reversed. 1,1-bis(phenylsulfonyl)ethylene **111** was dissolved at room temperature in dichloromethane and the solution temperature was lowered to −78 °C. Fortunately, 1,1-bis(phenylsulfonyl)ethylene **111** did not crystallize at −78 °C in dichloromethane, so the reaction could be performed at this temperature. The silyl enol ether **77** was then added at −78 °C. Tin tetrachloride was diluted in dichloromethane before addition and added to the reaction mixture dropwise, very slowly. The reaction was highly exothermic. Lower yields were obtained when the $SnCl_4$ addition was too quick or when the reaction temperature rose above −72 °C; the main isolated product in such event was exclusively the unprotected 3-

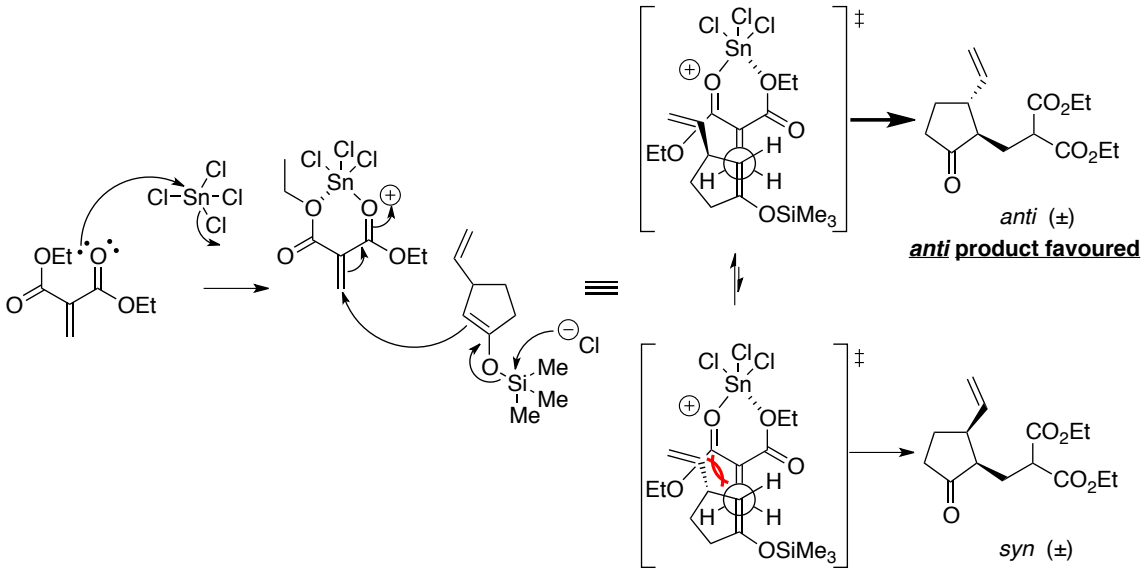
vinylcylopentenone **77sp** (Scheme 30). The addition was performed over a minimum of two hours. The product was purified by column chromatography on silica gel.

Satisfactory results were obtained when starting from dibenzyl methylenemalonate **107** (67% yield) and diethyl methylenemalonate **105** (64% yield).

The yield was slightly lower when using 1,1-bis(phenylsulfonyl)ethylene **111** (54%) and the product was difficult to purify. Indeed, the desired product was found to co-elute with the starting material **111** upon purification by column chromatography, while this did not happen with the two other methylenemalonate esters **105** and **107** because unreacted material decomposed during the reaction.

The reduced yield in the preparation of **78c** (R = SO_2Ph) was believed to result from an activation problem of the α,β-unsaturated sulfone **111**, so stronger Lewis acids were screened. However, the best results were still obtained using $SnCl_4$. We performed the reaction with $SnCl_4$, $TiCl_4$ and $BF_3.OEt_2$ on the three different analogues (R = CO_2Et, CO_2Bn, SO_2Ph). When $BF_3.OEt_2$ was used, lower yields were observed for compounds **78a** (21%) and **78b** (14%) from the diester compounds **105** and **107,** and no reaction occurred with the disulfone **111**. Titanium tetrachloride led to the decomposition of the starting materials when starting from diesters **105** and **107**, and low yields were described with the disulfone **111** (16% yield).

A possible mechanism is shown below for the conjugate addition of our starting materials **77** and **87** (Scheme 49). In the suggested transition state, one can clearly observe the steric influence of the vinyl moiety that would direct the addition in *anti* with respect to the vinyl moiety. The product obtained is a mixture of barely separable isomers (5.4:1, *anti*:*syn*).[1]



Scheme 49

III) Optimization of the initial proposal

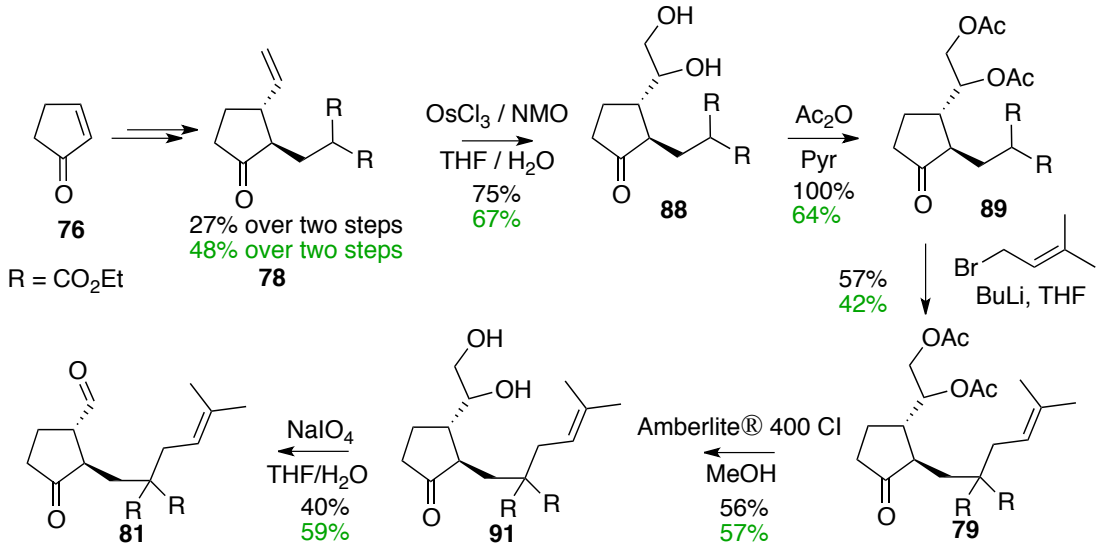
1) Introduction

In this chapter, the optimization of the original synthetic route that was previously elaborated in our laboratories (Scheme 50 with R = CO_2Et)[1] and the extension of this methodology to the synthesis of new analogues is discussed.

This previous work, which seemed simple and promising, led to the synthesis of the perhydroazulene ring system, obtained from the analogues of the diethyl ester only (R = CO_2Et). Syntheses through a similar route, using analogues of dibenzyl ester (R = CO_2Bn) and diphenyl sulfone (R = SO_2Ph), were developed during this project and are described below.

Firstly, the preparation of the pro-Alder-ene compound **81** is discussed.

The first task was to repeat the former student's synthesis and to collect the data for the synthesized compounds. The work from his thesis was repeated carefully, but the results were rather disappointing. The overall yield was similar, but for some reactions, satisfying yields were not retrieved (compounds **88** and **79**) or the yields were not reproducible (compound **89**).



Scheme 50

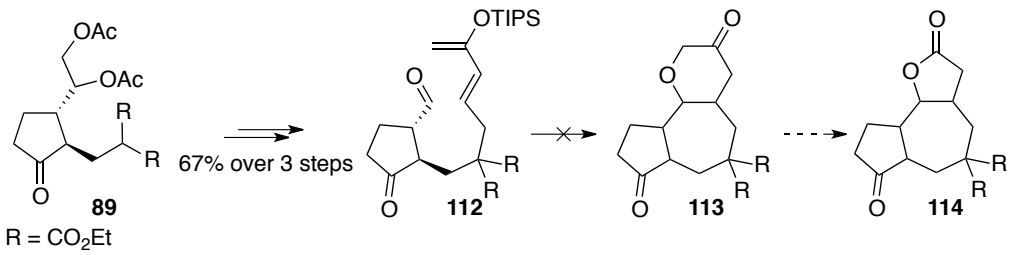
The yields written in black **are the original yields obtained from the published and laboratory work of the former PhD student, while the yields in green are those obtained in our hands when following this original pathway.**

The aldehyde **81** (R = CO_2Et) was previously synthesized in seven steps from the 2-cyclopenten-1-one **76** in a 2.6% overall yield. A similar yield (2.9%) was obtained when this work was repeated rigorously. Therefore, this methodology was highly limited by these low yields, as the planned total synthesis requires at least twice as many steps. Moreover, a decrease of those yields was observed when scaling up the synthesis.

Therefore, an optimization of the reaction conditions or modifications to the synthetic strategy was clearly needed. Yields had to be improved and reactions had to be scaled up as much as possible. The most challenging issues occurred during the first steps, *i.e.* the dihydroxylation, the protection and the addition reactions.

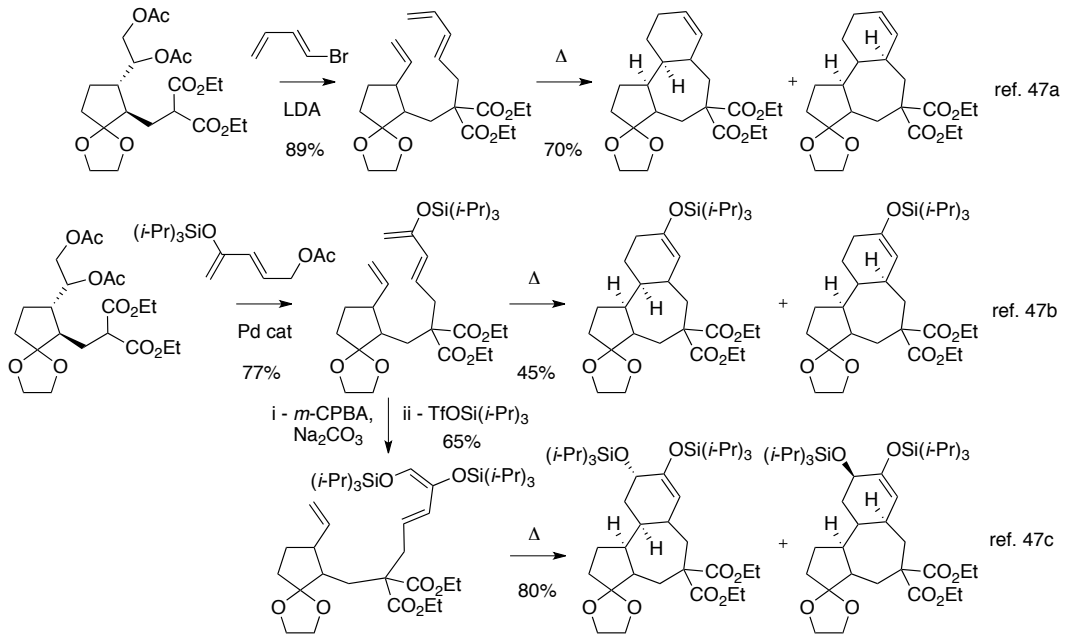
a. Previous work

The absence of optimization of this approach by the previous PhD student can be partly explained by the fact that this strategy was not included in his initial project. Indeed, his original route was based on the 7-membered ring formation occurring through an intramolecular hetero-Diels-Alder reaction in order to reach the guaianolide skeleton (Scheme 51).



Scheme 51

This strategy was the result of investigations previously carried out within the Page group (Scheme 52).[47a,b,d,e] The key step of this methodology was an intramolecular-Diels-Alder reaction forming the fused [6-7]-bicyclic ring system in one step.



Scheme 52

This strategy gave access to the tigliane and diaphnane skeletons. In a similar way, the former student aimed to synthesize the guaianolide skeleton through an hetero-intramolecular-Diels-Alder reaction.

The project was focused on the closure of the 7-membered ring through the formation of a pyrane in a hetero-Diels-Alder reaction. The *pro*-Diels-Alder compound **112** was obtained in

three steps from **89**: a palladium-catalysed nucleophilic addition, followed by the removal of the acetate protecting group and the oxidative cleavage of the *gem*-dihydroxyl moiety.

Entry	Catalyst	Solvent	Temperature	Result
1	-	Toluene	70 °C	Starting material
2	-	Toluene	160 °C	Decomposition
3	Microwaves	Toluene	80/120 °C	Starting material
4	$ZnCl_2$	THF	Room Temperature	Partial desylilation
5	$ZnCl_2$	THF	reflux	Decomposition
6	$BF_3.OEt_2$	Et_2O or THF	−78 °C	Starting material
7	$BF_3.OEt_2$	THF	−78 °C to 20 °C	Desylilation
8	$Yb(OTf)_3$ or $Sc(OTf)_3$	THF	0 °C to 20 °C	Starting material
9	$Yb(OTf)_3$ or $Sc(OTf)_3$	THF	−78 °C to 20 °C	Desylilation
10	Microwaves, 19Kbar	Toluene	120 °C	Decomposition

Table 7

All the attempted intramolecular hetero-Diels-Alder cyclizations were unsuccessful: under Lewis acid-catalysis, microwave irradiation or conventional heating (Table 7). If the Diels-Alder reaction had been successful, rearrangement of the 6-membered ring of compound **113** through a Bayer-Villiger oxidation rearrangement into a 5-membered ring lactone to obtain the guaianolide ring system **114** would have been targeted.

Despite all the work achieved by the former student, this line of investigation had to be aborted and a new strategy had to be considered. So, a [3+2] cycloaddition (Alder-ene reaction) was briefly developed. A range of conditions for this Alder-ene reaction were screened and good results were obtained using $BF_3.OEt_2$ or $Yb(OTf)_3$ in THF at −78 °C.

Time constraints prevented further investigations towards the optimization of the synthesis of the pro-Alder ene compound **81**.

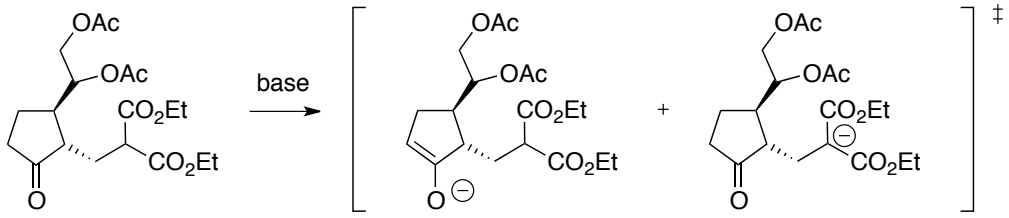
b. Issues of the former methodology

The reproducibility issues encountered with this protection reaction and the different problems with the other steps caused us to reconsider the study from the beginning.

We attempted the dihydroxylation reaction using the former methodology and obtained reasonable results (67%). However, the purity of the product was rather limited, and NMR spectroscopic analyses were not clear. Indeed, the desired compound was coloured, suggesting that some osmium catalyst was remaining even after several columns. Therefore, we decided not only to decrease the amount of catalyst used in the reaction, but also to find a more efficient work-up that would eliminate the remaining traces of osmium as the columns could not perform it.

Concerning the protection reaction, it had to be entirely revised because we could not reach a reproducible yield. The corresponding yield was generally between 10% and 45%, and a good yield of 64% was observed only once on more than a gram scale. After realising that the problem was due to reproducibility issues and not to mis-manipulation, we decided to explore other methodologies, which would allow us to obtain reproducible yields, followed by an optimization.

The nucleophilic substitution reaction using the previous methodology gave limited results in our hands (42%) and the yields dropped when the reaction was scaled up. Side reactions such as addition to the ketone moiety were also observed. This method afforded a complex mixture, which was difficult to purify due to the presence of compounds with similar retention factor values to the actual product. The optimization of this reaction focused on reducing the enolate formation and favouring the formation of the compound deprotonated α to the two esters, the malonate acidic site (Scheme 53).



Scheme 53

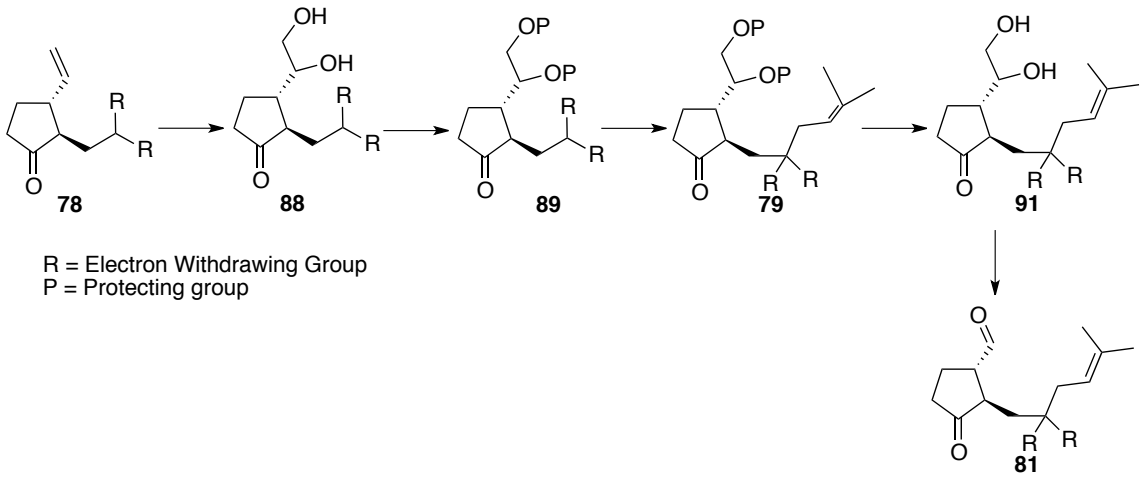
The optimization of the deprotection reaction and the oxidative cleavage step concentrated on adjusting the best quantities and the reaction time to obtain the highest yield and purity.

The problems encountered during the decarboxylation reaction also persuaded us to extend the synthesis to dibenzyl ester (Scheme 50, R = CO_2Bn) and diphenyl sulphone (Scheme 50, R = SO_2Ph) analogues.

2) Dihydroxylation reaction

The vinyl moiety, present in the molecule **77**, masks the aldehyde function that is an important part of the pro-intramolecular-Alder-ene adducts **81**. The aldehyde group is too reactive to be placed at the beginning of the synthesis (and should be introduced last). Another carbon-carbon double bond, which is present in the other part of the pro-intramolecular-Alder-ene adduct **81**, is also introduced later in the structure.

The vinyl carbon-carbon double bond, present in **78**, would be converted selectively into an aldehyde in five steps. The double bond would be converted into a diol that would be protected. At this stage, we would be able to introduce the prenyl, which contains the other carbon-carbon double bond with no risk for this function to interfere in the next steps, followed by the deprotection of the diol and the conversion into an aldehyde to obtain the pro-intramolecular-Alder-ene adduct **81** (Scheme 54).



Scheme 54

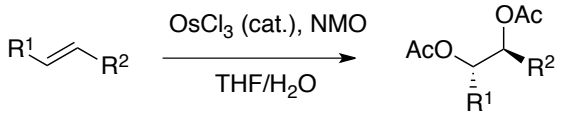
The first step for this transformation is thus a dihydroxylation reaction of the carbon-carbon double of the vinyl moiety of **78**.

Several dihydroxylation reactions are known to date. They can be divided into two types: reactions affording the *syn*-dihydroxylation products, and reactions affording *anti*-dihydroxylation adducts.[92]

a. syn-Dihydroxylation methods

→ *Osmium tetroxide*

OsO_4 is the most used reagent, with $KMnO_4$, for the *syn*-dihydroxylation of alkenes, and generally gives good results. OsO_4 can be used either in stoichiometric quantities or in catalytic quantities.[93] OsO_4 is very expensive, hazardous and toxic, and thus, the method of choice is generally the employment of a catalytic amount of this metal with a secondary oxidant.

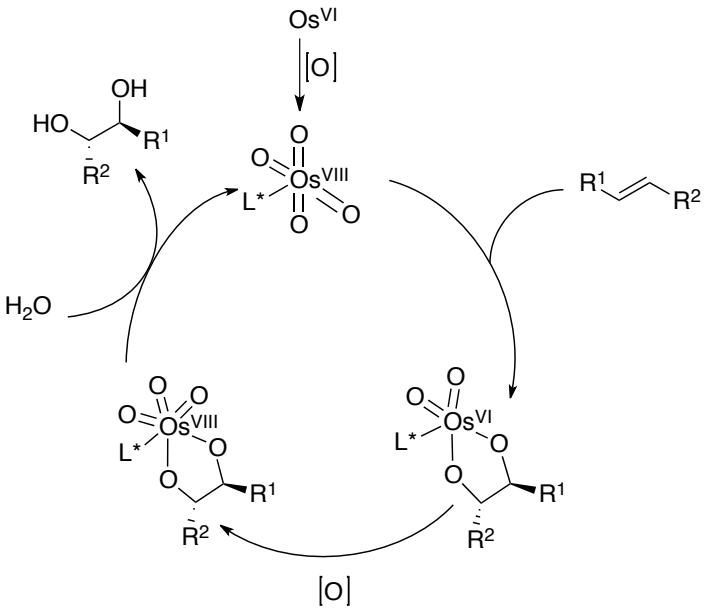


Scheme 55

The catalytic conditions of this reaction, known as the Upjohn dihydroxylation, were developed by VanRheenen *et al.*[94a] Other osmium species can be used as catalyst such as $Os^{III}Cl_3.xH_2O$ or $Os^{VI}K_2O_2(OH)_4$ and are oxidized *in situ* into Os^{VIII}. Re-oxidant sources can be found in NMO, H_2O_2, *t*-BuOOH, $K_2Fe(CN)_6$, and metal chlorates such as $NaClO_3$, $Ba(ClO_3)_2$, $NaClO_4$. Use of $NaIO_4$ affords the formation of aldehydes or ketone from *in situ* oxidative cleavage, whereas O_2 affords principally over-oxidation and decomposition to CO_2.[95] The best results are obtained by using NMO, *t*-BuOOH or $K_2Fe(CN)_6$ as reoxidants, with which the over-oxidation is generally avoided.

The combination of OsO_4 with NMO is probably the most general and effective procedure for alkene *syn*-dihydroxylation. Reactions performed in the presence of trimethylamine *N*-oxide as reoxidant and pyridine lead to better results with hindered alkenes.[94]

The reaction is believed to proceed through a [3+2] cycloaddition mechanism with the formation of a 5-membered ring osmium ester that was isolated.[93] The catalytic cycle is shown in Scheme 56. *Syn*-hydroxylation is generally favoured on the less hindered face of the π-system.[92]



Scheme 56

In general, a racemic product is obtained. Diastereoselective dihydroxylation can be obtained with chiral non-racemic secondary allylic alcohol product by using osmium tetroxide in stoichiometric or catalytic quantities.[96] Chiral auxiliaries can be also introduced into the alkene to direct the addition to form diastereoisomers.[97]

Sharpless *et al.* developed an asymmetric dihydroxylation method using a chiral quinine ligand to direct the addition.[98] His work on stereoselective oxidation reactions (epoxidation, dihydroxylation and oxyamination reactions) brought him the Nobel Prize in Chemistry in 2001, (shared with Knowles and Noyori for their work on asymmetrically catalysed hydrogenation reactions).

→ *Potassium permanganate*

Potassium permanganate used to be the common oxidant for the *syn*-hydroxylation of alkenes.[92] It has the advantage of being relatively cheap, less toxic and hazardous. However, this reaction is barely controllable and encounters many side reactions such as overoxidation and alternative oxidation pathways leading to other undesirable side products. Phase transfer catalysis allows better control. Typical conditions are the dilution of the alkene in dichloromethane and aqueous potassium permanganate, stirred vigorously with a phase transfer agent such as benzyltriethylammonium chloride. Solid-liquid phase transfer is also used. The reaction is believed to proceed through a [3+2] cycloaddition mechanism to form the 5-membered ring manganate ester (Figure 4).

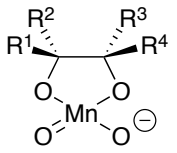
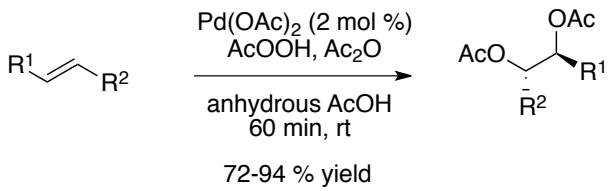


Figure 3

→ *Palladium-catalysed olefin dioxygenation*

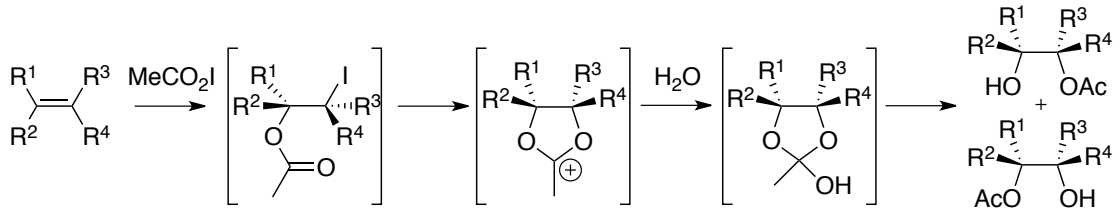
Recently, a palladium-catalysed dihydroxylation was developed by different groups to give direct access to the *cis*-diol monoacetate or diacetate.[99] Different catalytic cycles were suggested but none was confirmed yet. This methodology has shown good results on mono- to trisubstituted alkenes and a tolerance for some functional groups such as cyanide, carboxylic acid. A high stereoselectivity was observed for this procedure (Scheme 57), a *syn*/*anti* ratio from 8/1 to 15/1.



Scheme 57

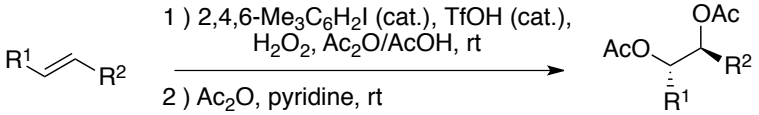
→ *Other syn-hydroxylation methods*

syn-Hydroxylation is also obtained through indirect synthetic approaches such as the formation of halohydrin ester as intermediate. Woodward developed a procedure whereby iodine and silver acetate are added to a solution of an alkene in acetic acid (Scheme 58).[100a] The acetyl hypoiodite, $MeCO_2I$, formed *in situ*, attacks the alkene carbon-carbon double bond to form a *trans*-halohydrin ester on which the halogen is displaced in the presence of silver(I) into a cationic cyclic acetal. The rearrangement induced by the cation allows the formation of two *cis*-diol monoacetates. Tetrasubstituted alkenes generally afford an approximative *cis*/*trans*-diol ratio of about 3:2. Other procedures, avoiding the use of the expensive silver(I) salt, have been reported.[100b] The replacement of the silver(I) acetate by a combination of iodine-potassium with iodide-potassium acetate or by the thallium(I) acetate in Woodward's procedure allows an equivalent result.[100c]



Scheme 58

A novel metal-free methodology has also been developed by Li *et al.*, using an aryl iodide as organocatalyst, and an oxidant such as H_2O_2 or *m*-CPBA with an acid additive (Lewis or Brönsted acid).[101] It has been shown to work on a broad range of olefins with a tolerance of functional groups bearing electron-rich or electron-poor substrates under relatively mild conditions (room temperature). Besides being environmentally friendly, the reaction has shown high diastereoselectivity for *syn*-dihydroxylation (from 4.3:1 and up to >19:1 *dr*).

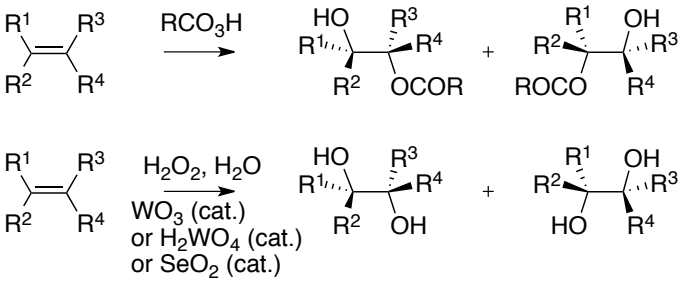


Scheme 59

b. Anti-dihydroxylation reaction

→ *Epoxide opening*

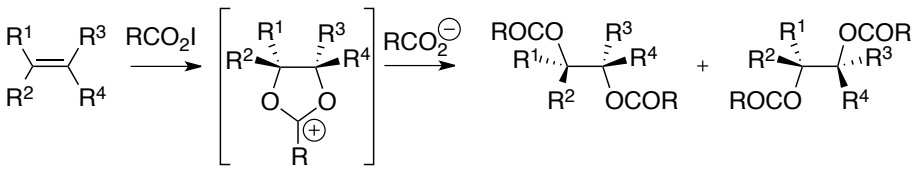
Epoxide openings with a nucleophile lead to the *anti* addition product under acidic conditions. Addition of a suitable peroxycarboxylic acid to the alkene affords a mixture of oxirane stereoisomers that can be opened under catalytic conditions with the remaining carboxylic acid. The monoester can be hydrolysed to yield a mixture of enantiomeric diols. An industrial *anti*-dihydroxylation method is the addition of H_2SO_4 to a mixture of alkene and $NaBO_3$ in acetic anhydride to obtain the corresponding *trans*-1-hydroxy-2-acetoxy derivative.[102] Epoxides formed from the reaction of an alkene with H_2O_2 are opened *in situ* with the addition of an oxide catalyst such WO_3, H_2WO_4 or SeO_2.[103]



Scheme 60

→ *The Prévost reaction*

The mechanism of the Prévost reaction is similar to the Woodward reaction but the opening of the cationic ring is performed through an *anti* nucleophilic attack of the carboxylic acid in excess (Scheme 61).[92]



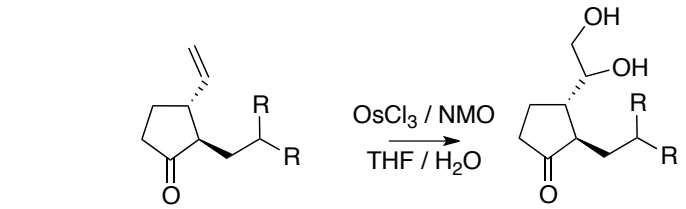
Scheme 61

c. Application of the osmium dihydroxylation

After studying the different methodologies for dihydroxylation, it clearly appeared to us that the method of choice was the osmium-catalysed procedure: no specific configuration is needed in our case, excellent results are reported in the literature, a good tolerance for functional groups is realised.

The results obtained with the former methodology did not satisfy us: the corresponding yield was reasonable even though we expected better results, but the purity of the compound was not satisfactory. NMR spectra were neither resolved nor well defined (broad peaks). The final product kept a dark colour even after several columns. This absence of definition in the NMR spectra and the dark colour were believed to come from the osmium traces remaining in the final

compound ($OsCl_3$ is a black powder). A more appropriate purification processes was therefore needed because the previous work-up or the columns were not efficient.



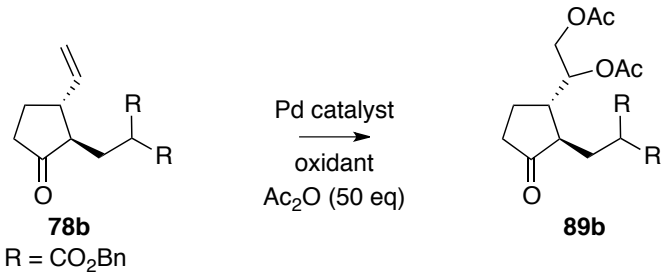
R = CO_2Et	**78a**	**88a**
R = CO_2Bn	**78b**	**88b**
R = SO_2Ph	**78c**	**88c**

Scheme 62

Indeed, quenching the solution with a reducing agent such as Na_2SO_3 and washing the solution reaction with an HCl aqueous solution (2M) several times gave a pale-yellow product (without any dark tint). NMR spectra were clean and resolved. A better yield was also obtained using this process (up to 80% for both diester analogues **88a** and **88b**) and the next step would be carried out with this work-up as the only purification, avoiding the column chromatography step. We obtained a yield slightly lower (69%) but still reasonable when working with the disulfone analogue **88c**.

→ *Palladium diacetoxylation attempts*

In the search for the best dihydroxylation method, we were also interested in a palladium oxidation. Several publications have reported that some olefins could be converted in one step into a diacetoxy product through a palladium-catalysed reaction.[99] This reaction would be interesting for our strategy as it would afford the diacetoxy product in only one step instead of two. Jung *et al.* have developed an interesting process using $Pd(OAc)_2$ as catalyst and AcOOH as oxidant with Ac_2O in AcOH at room temperature. We attempted to apply these conditions to our synthesis and the results are summarized in Table 8.



Scheme 63

Entry	Catalyst (10% mol)	Oxidant (eq)	Temperature	Solvent	Result
1	$Pd(OAc)_2$	AcO_2H (2 eq)	20 °C	AcOH	SM
2	$Pd(OAc)_2$	AcO_2H (4 eq)	20 °C	AcOH	SM
3	$Pd(OAc)_2$	AcO_2H (2 eq)	20 °C	hexane	SM
4	$Pd(OAc)_2$	AcO_2H (4 eq)	60 °C	AcOH	SM
5	$Pd(OAc)_2$	AcO_2H (4 eq)	60 °C	hexane	SM
6	$Pd(OAc)_2$	H_2O_2 (4 eq)	20 °C	hexane	SM
7	$Pd(OAc)_2$	H_2O_2 (4 eq)	20 °C	H_2O:THF	SM
8	$Pd(OAc)_2$	H_2O_2 (4 eq)	60 °C	H_2O:THF	SM
9	$Pd(OAc)_2$	H_2O_2 (4 eq)	60 °C	hexane	SM
10	$Pd(OAc)_2$	$PhI(OAc)_2$ (4 eq)	20 °C	H_2O:AcOH	SM
11	$Pd(OAc)_2$	$PhI(OAc)_2$ (4 eq)	60 °C	H_2O:AcOH	SM
12	$Pd(dppp)(H_2O)_2(OTf)_2$	$PhI(OAc)_2$ (4 eq)	60 °C	H_2O:AcOH	SM

Table 8

Unfortunately, all our attempts were unsuccessful. No traces of diacetoxy compound **89** were observed, and the starting material was generally quantitatively recovered. We also looked for monoacetoxy alcohols but did not find any. The reaction was performed with a range of oxidizing agents (Entries **2**, **6** and **10**, Table 8): AcO_2H, H_2O_2 and $PhI(OAc)_2$, increased reaction

temperature of 60 °C (Entries **4**, **5**, **8**, **11** and **12**, Table 8) and with different palladium catalysts (Entries **1** and **12**, Table 8).

The reaction was also attempted with the compounds **78a** and **78c** in the same conditions as for entry **2**, but no desired product was isolated.

No traces of diacetoxy or even monoacetoxy products were observed, and so this line of investigation was discontinued.

3) Protection of the diol moiety

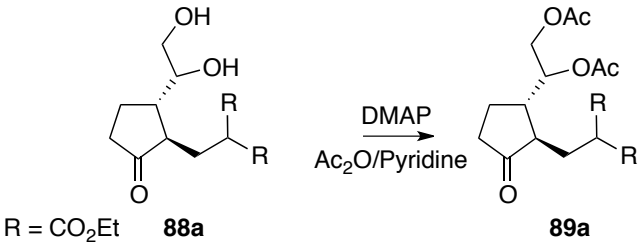
Several methodologies have been developed to convert alcohol moieties into acetoxy groups.[104]

The most common method for the introduction of an acetyl group consists of the addition of the alcohol to a solution of Ac_2O in pyridine. Verley and Bölsing first developed this method of esterification in 1901.[105] Primary and secondary alcohols are generally *O*-acylated through that method without any problems.[106] In 1969, Steglich and Höfle reported the strong catalytic effect of 4-dimethylaminopyridine (DMAP) and 4-pyrrolidinopyridine (PPY) in the increase of the reaction rate of the acylation.[107] This report contributed to the development of DMAP as a catalytic transesterification agent. The use of DMAP allows the *O*-acylation of many alcohols including tertiary alcohols and hindered alcohols that were not acylated in the presence of pyridine only.

Other methodologies can selectively *O*-acylate primary alcohols in the presence of secondary alcohols such as AcCl and collidine in dichloromethane.[108] The acetyl group can be introduced onto highly hindered alcohols using Ac_2O in dichloromethane under high pressure (15 kbar).[109] Lewis acids such as Al_2O_3 or $BF_3.OEt_2$ or $Sc(OTf)_3$ can afford selective results on polyol compounds.[110] Similar selective results can be also obtained through biocatalysis.[111]

→ *Application*

Some problems were encountered when attempting the protection reaction with the previously developed reaction conditions. However, the acetyl protecting group was an interesting protecting function to keep as it is easily removed.



Scheme 64

The previous methodology, which included the addition of a catalytic amount of DMAP to a solution of diol in a 1:1 mixture of Ac_2O:pyridine, was low-yielding and not reproducible: yields below 40% were generally obtained and the remainder was a dark liquid of a complex mixture of degradation products. Despite several attempts to perform the reaction under these conditions or by modifiying the temperature, the time or the quantities of each reagent, we could not reach reproducible results.

Therefore, a methodology giving reproducible and better yields was sought. A large number of bases, from weak (pyridine, Et_3N, $NaHCO_3$), medium (K_2CO_3) to strong bases (NaH, *t*-BuLi, LDA), were screened in different solvents (dichloromethane, toluene, Et_2O, THF, EtOAc, AcOH) (Table 9).

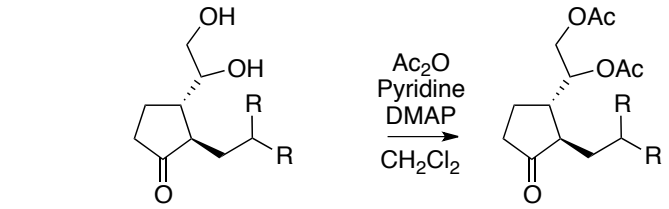
Pyridine and triethylamine gave good results with a slight preference for pyridine (Entries **6** and **7**, Table 9). An excess of 10 equivalents of base was added when using medium ($NaHCO_3$ Entry **5**, K_2CO_3 Entry **4**, Table 9) and weak (pyridine Entry **7**, Et_3N Entry **6**, Table 9) bases, whereas only 2.2 equivalents were employed with strong bases (NaH Entry **1**, *t*-BuLi Entry **2**, LDA Entry **3**, Table 9). The best solvent for this reaction was dichloromethane (Entry **6**, Table 9) at low temperature (0 °C) (Entry **12**, Table 9). However, a degradation of the product was observed in the reaction solution over time. The reaction mixture was stirred for no more than 15 min and directly worked up to avoid degradation.

Entry [a]	Reagent	DMAP	Base	Temperature	Solvent	Result [b]
1	Ac_2O	Yes	NaH	20 °C	CH_2Cl_2	15%
2	Ac_2O	Yes	*t*-BuLi	20 °C	CH_2Cl_2	10%
3	Ac_2O	Yes	LDA	20 °C	CH_2Cl_2	8%
4	Ac_2O	Yes	K_2CO_3	20 °C	CH_2Cl_2	-
5	Ac_2O	Yes	$NaHCO_3$	20 °C	CH_2Cl_2	-
6	Ac_2O	Yes	Et_3N	20 °C	CH_2Cl_2	40%
7	Ac_2O	Yes	Pyridine	20 °C	CH_2Cl_2	42%
8	Tf_2O	Yes	Pyridine	20 °C	CH_2Cl_2	-
9	Ac_2O	Yes	Pyridine	20 °C	AcOH	SM
10	Ac_2O	Yes	Pyridine	20 °C	Et_2O	SM
11	Ac_2O	Yes	Pyridine	60 °C	CH_2Cl_2	-
12	**Ac_2O**	**Yes**	**Pyridine**	**0 °C**	**CH_2Cl_2**	**66%**
13	Ac_2O	No	Pyridine	0 °C	CH_2Cl_2	30%
14 [c]	Ac_2O	Yes	Pyridine	0 °C	CH_2Cl_2	64%
15 [d]	**Ac_2O**	**Yes**	**Pyridine**	**0 °C**	**CH_2Cl_2**	**95%**

Table 9

(a): All the reactions were performed using **88a** (R = CO_2Et), except for Entries 14 and 15 where **88b** was used (R = CO_2Bn); (b): No starting material was recovered and only decomposition was generally observed; (c): The reaction was performed on a 6 g scale of starting material **88b** (R = CO_2Bn); (d): The 6 g of starting material **88b** (R = CO_2Bn) were split into 4 portions of around 1.5 g each.

The reaction was also performed with trifluoroacetic anhydride in order to afford the corresponding diester derivative. The reaction seemed to work (new spot on the TLC plate), but the protecting group was probably too unstable and was lost during the purification process, only degradation products being observed after column chromatography (Entry **8**, Table 9).



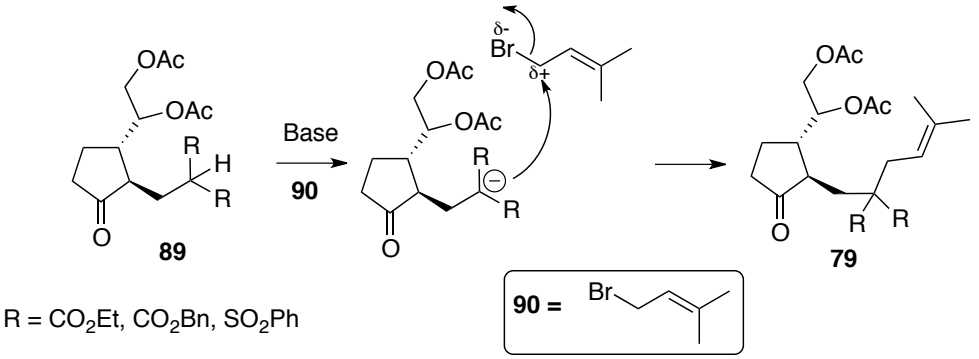
R = CO_2Et **88a** **89a**
R = CO_2Bn **88b** **89b**
R = SO_2Ph **88c** **89c**

Scheme 65

Finally, after many tests, we established the best reaction conditions: the scale of the reaction should be limited to 1.5 g of diol **88**, the temperature has to be carefully monitored and kept between −10 °C and 0 °C, and the reaction should not last more than 15 min. Pyridine, DMAP and acetic anhydride were successively added to a solution of diol in dichloromethane at −10 °C. After 15 min, the reaction was directly quenched with H_2O and worked up. Purification through silica gel chromatography afforded the desired compound **89** as a colourless oil in a yield of up to 99% (66% for **89a** R = CO_2Et, 95% for **89b** R = CO_2Bn and 99% for **89c** R= SO_2Ph). This yield was reproducible and the compounds obtained were pure; chromatography was mainly used to remove the remaining traces of puridine. The lower yield for compound **89a** (R = CO_2Et), compared to **89b**, can be explained by the fact that the optimized reaction scale of 1.5 g of diol was established after the synthesis of **89a** was discontinued.

4) Nucleophilic substitution of prenyl bromide

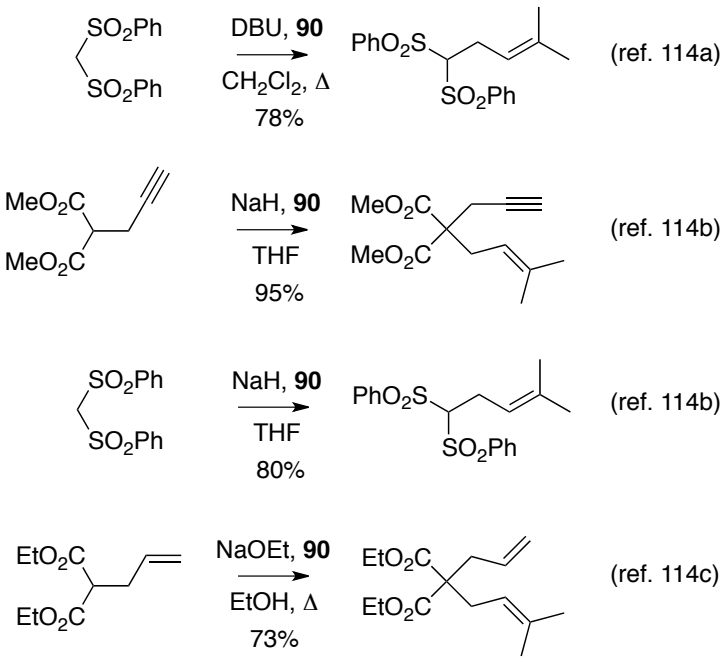
The nucleophile, formed *in situ* from compound **89** through the removal of the proton of malonyl moiety, attacks the prenyl bromide **90** to afford **79** (Scheme 66).



Scheme 66

An allylic rearrangement or allylic shift is sometimes observed in the presence of allylic halides and analogous substrates. This reaction is generally referred as S_N1' or S_N2', depending on the reaction mechanism.[112]

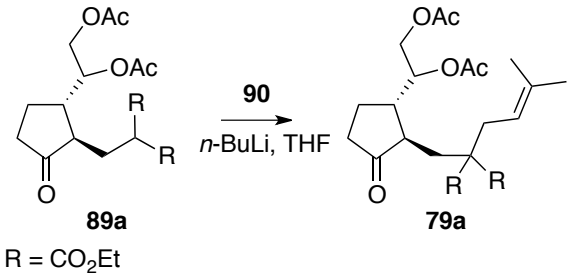
The reaction of prenyl bromide with a malonate moiety has been often described in the literature with a wide range of solvents, bases and conditions.[113]



Scheme 67

→ *Application*

The procedure described in the initial work involved the slow addition of *n*-butyllithium to a solution of the compound **89** and prenyl bromide **90** (3-methylbut-2-enyl bromide) in dry THF at −78 °C (Scheme 66). This methodology gave relatively moderate yields (42-57%) and the purification was difficult. We first thought that some allylic rearrangement may also occur but it was not observed in our hands probably due to the steric hindrance. However, one of the side products isolated resulted from the addition of n-butyllithium to the carbonyl moiety. So, we could deduce that the base used was not adequate as it might be too nucleophilic and tended to react in an addition reaction instead of reacting as a base.



Scheme 68

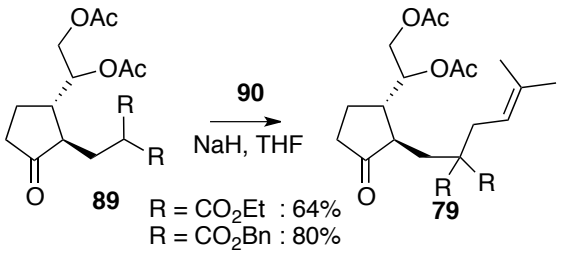
Thus, the main problem seemed to be the nature of the chosen base. The base had to be basic enough to deprotonate the malonate moiety (pK_a = 13.3 in DMSO for dimethyl malonate[114]) but not too nucleophilic, to avoid the addition onto carbonyls. We should only use a slight excess of base (1.1 equivalents) to avoid the formation of the enolate derived from the ketone moiety (pK_a = 25.8 in DMSO for cyclopentanone[114]), and thus avoid the formation of the corresponding alkylated products. Therefore, a range of bases was screened and new conditions were established (Table 10).

In the literature, most of the nucleophilic substitutions of a malonic ester moiety onto alkyl bromide involve NaH as a base.[114b,115] K_2CO_3 should also be strong enough to remove the malonic proton. However, the use of K_2CO_3 as a base did not work in that reaction, and the starting material **89b** (R = CO_2Bn) was fully recovered (Entries **4**-**7**, Table 10).

Entry	Base	Solvent	Temperature	Reaction yield (79b*)
1	*n*-BuLi	THF	−78 °C	42%
2	LDA	THF	−78 °C	35%
3	KHMDS	THF	−78 °C	30%
4	K_2CO_3	THF	0 °C	–
5	K_2CO_3	Acetone	Room temperature	–
6	K_2CO_3	THF	Room temperature	–
7	K_2CO_3	Acetone	Room temperature	–
8	NaH	THF	−78 °C	64%
9	NaH	Et_2O	−78 °C	59%
10	NaH	CH_2Cl_2	−78 °C	30%
11	NaH	THF	0 °C	80%
12	NaH	Et_2O	0 °C	71%
13	NaH	CH_2Cl_2	0 °C	33%

Table 10 (*: for compound 79b R = CO_2Bn)

A range of bases was screened, and the best results were obtained using NaH in THF at 0 °C (Entry **11**, Table 10).



Scheme 69

NaH was added to a solution of the malonate ester **89** in dry THF under nitrogen atmosphere at 0 °C and the reaction was stirred for 24 h at room temperature. The deprotonation reaction was followed using a gas bubbler: the reaction ends when no (hydrogen) gas is formed anymore. At the end of the deprotonation, the grey NaH suspension disappeared and the original colourless mixture became pale yellow. Prenyl bromide **90** was then added to the reaction mixture at 0 °C and the solution was stirred overnight at room temperature. When the diethyl malonate ester compound **89a** (R = CO_2Et) was used, the reaction was performed at −78 °C and left overnight to warm-up (the dry ice/ethyl acetate bath was not refilled with dry ice after the prenyl bromide addition) and the desired product **79a** (R = CO_2Et) was obtained in 64% yield. In the case of the synthesis of the dibenzyl malonate ester analogues (R = CO_2Bn), we observed that the reaction seemed to work better at 0 °C. The desired compound **79b** (R = CO_2Bn) was obtained in 80% yield.

For unknown reasons, the substitution reaction was unsuccessful with the disulphone analogue **89c** (R = SO_2Ph). On paper, the synthesis of the sulfonyl analogues was the most promising one: we should obtain solid products that are generally easier to handle and UV-visible due to the presence of the aromatic substituents on the sulfones. And the most important part is the hypothetically facile removal of the sulfonyl group. Unfortunately, we could not verify this last point.

The first steps of the sulfonyl analogue synthesis were only slightly optimized, as our first aim was to reach the desulfonylation step. This substitution reaction was crucial, being partly the purpose of this sulfonyl function (activation of the α proton): if we could insert the prenyl group, we would be able either to attempt the desulfonylation reaction or to carry out the synthesis on the same pathway.

The starting material **89c** was recovered and the desired product **79c** was never isolated. All the conditions shown in table 9 were also screened without better results. Unfortunately, no product was obtained from the prenyl bromide addition reaction with **89c** as starting material. This absence of reaction is probably due to the steric hindrance of the two sufonyl that are a lot bigger than carbonyl. However, the syntheses with the dibenzyl ester analogues were working with good yields and the decarboxylated analogues were produced with success.

^{1}H NMR spectroscopic analysis (see Appendix) of compound **89c** revealed the presence of the signals of the acidic proton in α to the sulfone moieties at around 5.75 ppm (we can see two signals because we had an inseparable mixture of four stereoisomers: two pairs of enantiomers). The analysis of the ^{1}H NMR spectrum of compound **79b** allowed the observation of the new signals that we were expecting from the prenyl bromide substitution reaction: the most characteristic peaks are the alkene signal at around 4.85 ppm and the two terminal methyl signals at around 1.55 ppm. The acidic proton peak (around 5.75 ppm) disappeared on the ^{1}H NMR spectrum while the new signals corresponding to the two terminal methyl (around 1.55 ppm) appeared. The two latter peaks were the most recognizable as they were the most intense signals (two signals integrating for three protons). However, we never observed these signals on any isolated product when we worked on this reaction with compound **89c** (R = SO_2Ph) as starting material.

Therefore, the investigations conducted with disulphone analogues were discontinued in favour of the dibenzyl ester analogues.

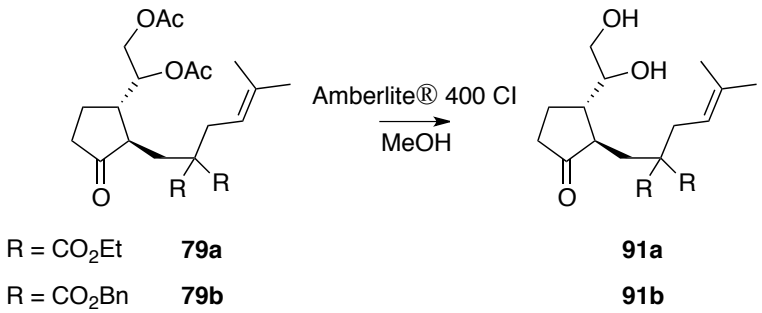
5) Protection removal

The removal of the acyl group is generally performed under basic conditions. Many methodologies have been developed in order to reach that goal:[104]

- K_2CO_3, MeOH, H_2O;[116]
- NaOMe (catalytic), MeOH, H_2O (Zemplen de-*O*-acetylation);
- KCN, EtOH (for acidic or base sensitive substrates);[117]
- Enzymes can afford the resolution of a racemic or meso-substrate with excellent enantioselectivity;[118]
- Different methodologies have been designed to be compatible with other protecting groups such as Mg and MeOH (benzoate and pivaloate are not cleaved).[119]

We decided to use a supported base: Amberlite® 400 Cl. The commercial chloride form of this Amberlite® was activated in an aqueous solution of NaOH (2 M). Amberlite® 400 Cl is a strong basic anion exchange resin with a styrene/divinyl benzene gel matrix and quaternary ammonium functional groups.

→ *Application*



R = CO_2Et **79a** **91a**

R = CO_2Bn **79b** **91b**

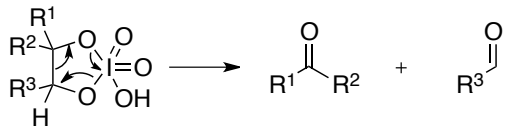
Scheme 70

The diacetyloxy compound **79** was deprotected to give the corresponding diol product **91** by treatment with a supported base, Amberlite® 400 OH (Activated form of Amberlite® 400 Cl) in MeOH under vigorous stirring at room temperature for one day. This pathway afforded the desired product **91** in high yield after filtration through a pad of celite to remove traces of crushed Amberlite® without the need for further purification: **91a** (R = CO_2Et) in 95% and **91b** (R = CO_2Bn) in 86%.

6) Oxidative cleavage

Oxidative carbon-carbon bond cleavage of vicinal diols is a common synthetic procedure that can be achieved using various reagents such as calcium hypochlorite,[120] manganic pyrophosphate,[121] iodine triacetate[122] or sodium bismuthate.[123] However, the most common reagents for this reaction are sodium metaperiodate[124] and lead(IV) acetate. Sodium metaperiodate is more effective with substrates that are soluble in aqueous solutions because of the insolubility of the salt in organic solvents, while lead tetraacetate is used in organic solvents. Generally, sodium metaperiodate is preferred to lead acetate, as this latter compound is difficult to store and to handle. Further, it is a toxic reagent and over-oxidation can occur.

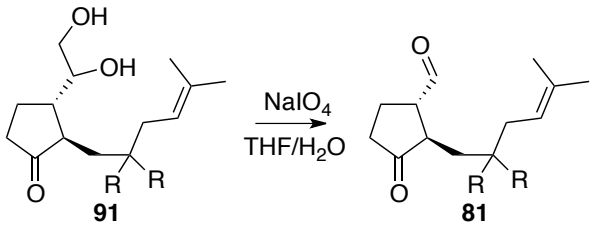
Sodium metaperiodate forms a 5-membered ring iodate ester (Scheme 70), which is opened to give two carbonyl moieties: primary alcohols afford aldehydes, while secondary alcohols produce ketones.[125]



Scheme 71

Sodium metaperiodate cleaves vicinal alcohols, α-hydroxyketones and related functionalities. Carbon-carbon alkene double bonds can be directly cleaved into two carbonyl moieties using sodium metaperiodate with osmium catalyst.

→ *Application:*



Scheme 72

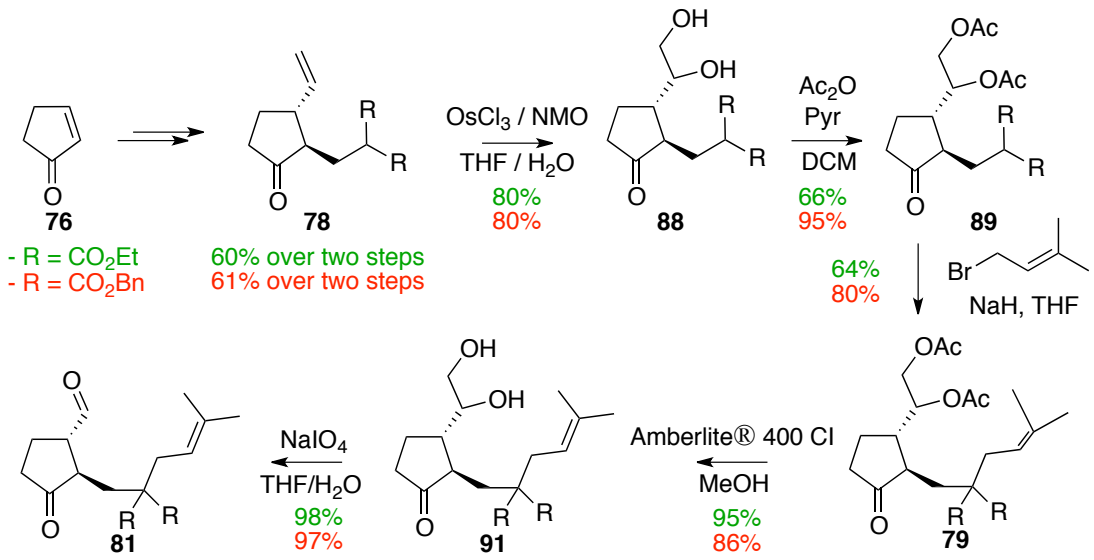
An aqueous solution of sodium metaperiodate was added to a solution of the diol **91** in THF. The reaction was stirred at room temperature for 4 to 5 hours. The reaction was monitored by thin layer chromatography, and quenched as soon as the starting material disappeared. We observed that the product started to decompose after the total consumption of the starting material.

The improvements of the reaction conditions from the previous work were principally on the reaction time (4.5 hours instead of overnight) and on the quantities of oxidizing agent (10 equivalents instead of only 5 equivalents). This optimization allowed us to obtain compound **81** in excellent yields: we reached 98% yield of **81a** (R = CO_2Et) formation and a yield of 97% in the preparation of **81b** (R = CO_2Bn).

7) Conclusion

Other routes have also been explored without success. We attempted addition of prenyl bromide to compound **78** to avoid the protection step, but the substitution reaction worked in poor yields, and the dihydroxylation-oxidative cleavage reactions gave a complex mixture.

Scheme 73 shows the new methodology with the reaction yields obtained for diethyl malonate analogues in green (R = CO_2Et) and dibenzyl malonate analogues in red (R = CO_2Bn).



Scheme 73

Finally, we obtained reactions affording rather clean mixtures and products in good yields. The new methodology presented reactions with reproducible yields and more controlled conditions. We have also prepared an analogue by replacing the original diethyl malonate moiety with the corresponding dibenzyl ester. The original methodology gave the aldehyde **81a** (R = CO_2Et) in less than 3% yield over seven steps. After optimization, the aldehyde **81a** (R = CO_2Et) was obtained in 19% yield and the aldehyde **81b** (R = CO_2Bn) in 31% yield over seven steps.

IV) Decarboxylation

1) Introduction

A decarboxylation reaction results in the elimination of a carboxyl group, releasing carbon dioxide. The carboxylic acid moiety can be replaced by a proton, a halogen atom or otherwise functionalized, depending on the reaction conditions and the mechanisms.[92]

Different processes of decarboxylation have been developed. The most common procedure for decarboxylation is the loss of carbon dioxide from the β-position of another carbonyl moiety, catalysed under acidic or basic conditions. A cyclic mechanism is generally involved in this case.

Other decarboxylation methods usually involve radical mechanisms and are applicable to a large scope of substrates.

However, decarboxylations catalysed by transition metals are emerging. It is a good method for aryl cross-coupling decarboxylation, but limited for reductive decarboxylation.[126]

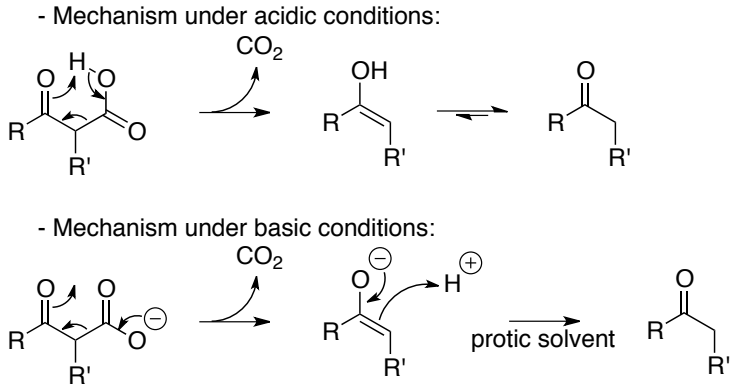
Biologically, aerobic decomposition generally proceeds through oxidation (if needed) and decarboxylation. The enzymes that catalyse the biochemical process of decarboxylation are called decarboxylases or carboxyl-lyases.[127] Those enzymes can add or remove a carboxyl group from an organic compound. An important example is the enzyme ribulose-1,5-bisphosphate carboxylase oxygenase, commonly abbreviated RuBisCO.[128] It is the enzyme responsible for the conversion of atmospheric carbon dioxide into organic material during photosynthesis. It is believed to be the most abundant protein on earth.[128]

2) Ionic mechanism

a. Introduction

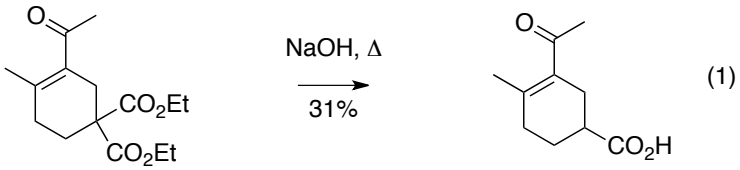
The decarboxylation reaction is an old reaction, resulting in decomposition through pyrolysis and loss of carbon dioxide. Malonic acids and esters were used early in organic syntheses and their decarboxylation has been thoroughly explored.[128] Decarboxylation reactions usually require heating. β-Keto acids, α,β-unsaturated acids, α-phenyl, α-nitro, and α-cyanoacids

can readily release carbon dioxide under acidic or basic conditions in a protic solvent (Scheme 74).[129] Metal salts have also been shown to promote the reaction.[130] In a few cases, decarboxylation can occur spontaneously.[131] The reaction is more likely to proceed if the enol intermediate is stabilized (Scheme 74).



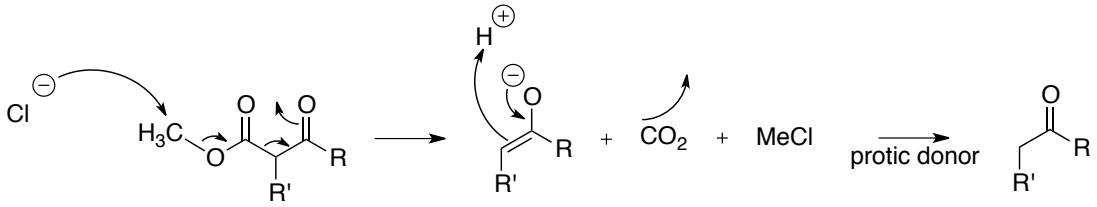
Scheme 74

Decarboxylation of esters is possible under basic conditions (saponification conditions) and heating, but generally it leads to poor yields (Scheme 75).[132]

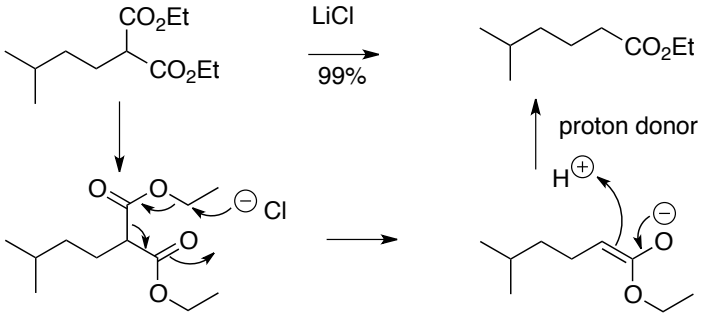


Scheme 75

Krapcho developed a method from methyl (or ethyl)-β-ketoesters, which yielded better results. It can also be applied to decarboxylation reactions that would work under basic or acidic conditions (related to the stability of the enol intermediate, Scheme 76). Krapcho's conditions consist of heating the reaction mixture in the presence of LiCl in DMSO with a proton donor (Scheme 77).[133] NaCl or $MgCl_2$ salts have also been shown to give good results.[134]



Scheme 76



Scheme 77

b. Application

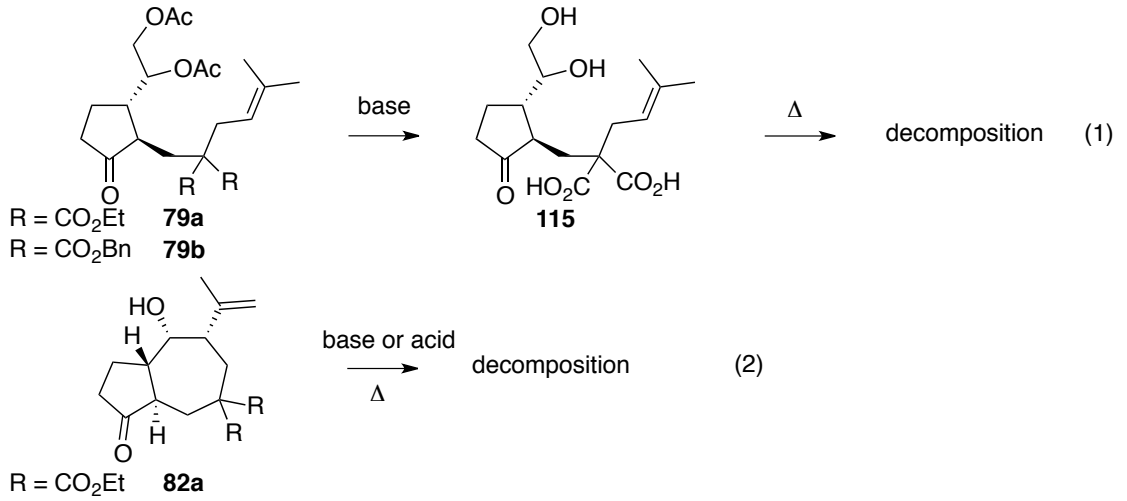
We attempted the reaction on the product from the addition to the malonate moiety **79a** (R = CO_2Et) and **79b** (R = CO_2Bn) (Equation 1 Scheme 78), and on the bicyclo[5.3.0]decane **82a** (R = CO_2Et) (Equation 2 Scheme 78). In both cases, only decomposition products were observed under acidic conditions.

The protected diol compounds **79a** (R = CO_2Et) and **79b** (R = CO_2Bn) afforded the diacid **115** with removal of the alcohol protection after 24 hours. The conditions were stronger (KOH in 1:1 THF:H_2O) than the simple deprotection of the diol (discussed above), and the reaction was carried out for longer reaction times (24 hours). We obtained **115** only as impure traces (5% yield from **79a** and 4% yield from **79b**), and purification of the reaction mixtures was difficult to perform due to the presence decomposed products.

Decomposition of the diacid compounds was observed when heating was applied (Equation 1 Scheme 78). In the case of the bicyclic compound **82a** (R = CO_2Et), the reaction conditions conducted to its degradation only (Equation 2 Scheme 78). No attempts were made

with the compound **82b** (R = CO_2Bn) as we expected similar results as the one obtained with **82a**, and we preferred to concentrate on the study of other methodologies.

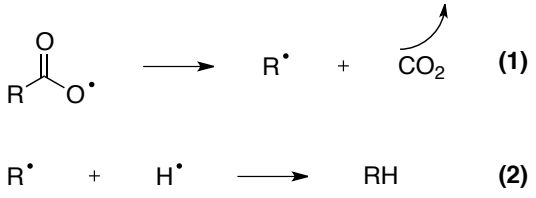
The use of LiCl generated the same results of degradation.



Scheme 78

3) Radical mechanism

Decarboxylation can be achieved through cleavage of a carbon-carbon single bond by fragmentation of a carboxylic radical. Different methods have been developed to form the carboxylic radical, which decomposed into an alkyl radical and carbon dioxide (Equation 1 Scheme 79). The alkyl radical may be trapped with a variety of radical-trapping reagents, depending on the tolerance of the radical precursor. However, we were only interested in a reductive decarboxylation where the carboxyl group was replaced by a proton (Equation 2 Scheme 79).



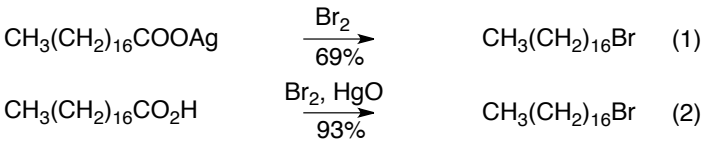
Scheme 79

a. Hunsdiecker reaction

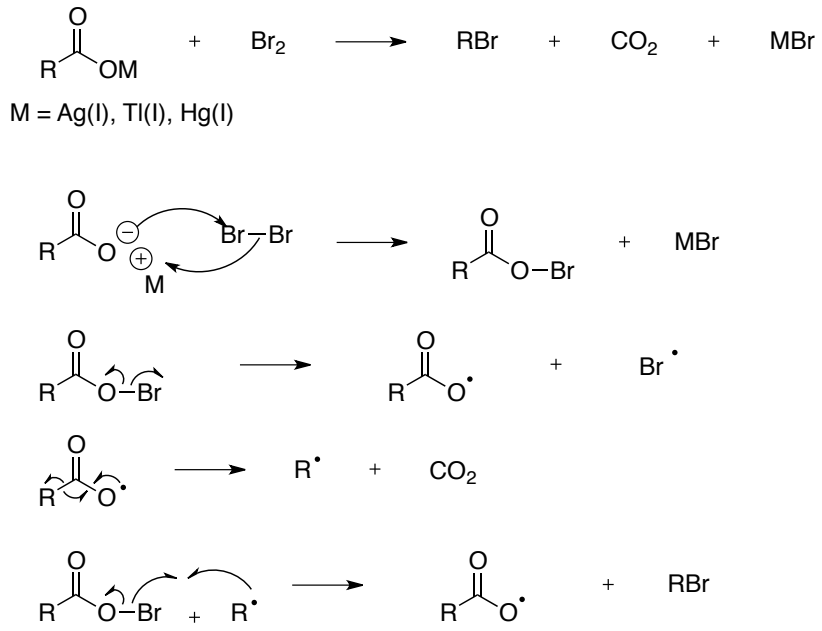
The Hunsdiecker reaction is sometimes also called Borodin reaction because Borodin was the first chemist to report the reaction of carboxylate silver salts with bromine to afford alkyl halide (Equation 1 Scheme 80).[135] It was used for the preparation of aliphatic halides.[136] The Hunsdiecker couple, Heinz and Cläre, patented the forgotten reaction in France and the UK in 1937, then in the USA (1940) and Germany (1941).[137] The first publication of the reaction occurred in 1942.[137] However, the original reaction suffered several limitations.[6] Silver salts, that were heat sensitive, were required to be scrupulously dried in order to obtain good yields. Substrates, which can react with molecular bromine, are incompatible with the reaction.

The reaction was greatly limited by the preparation of the silver carboxylate, but many improvements were introduced. The silver carboxylate salt is preferentially prepared *in situ* through addition of an acyl chloride to a mixture of silver oxide and bromine in CCl_4.[138] Thallium(I) and mercury(I) salts show good results as well (Equation 2 Scheme 80).[139]

Great improvements were made with the development of new methodologies for the formation of radicals from carbonyl compounds. The Kochi reaction and the Barton decarboxylation have shown a relatively wide scope of applications. Other methods such as pyrolysis of peroxy esters or persulfate silver ion decarboxylation are also known, but only a limited number of examples have been studied.[140]



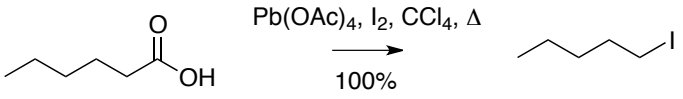
Scheme 80



Scheme 81

b. Kochi modification

Kochi reported the use of lead(IV) acetate.[141] The weak carboxyl-lead(IV) bond can be cleaved to form the carboxyl radical, and decarboxylation of aliphatic carboxylic acids can be achieved (Scheme 82). However, aromatic carboxylic acids fail to undergo decarboxylation under Kochi's conditions.[142]



Scheme 82

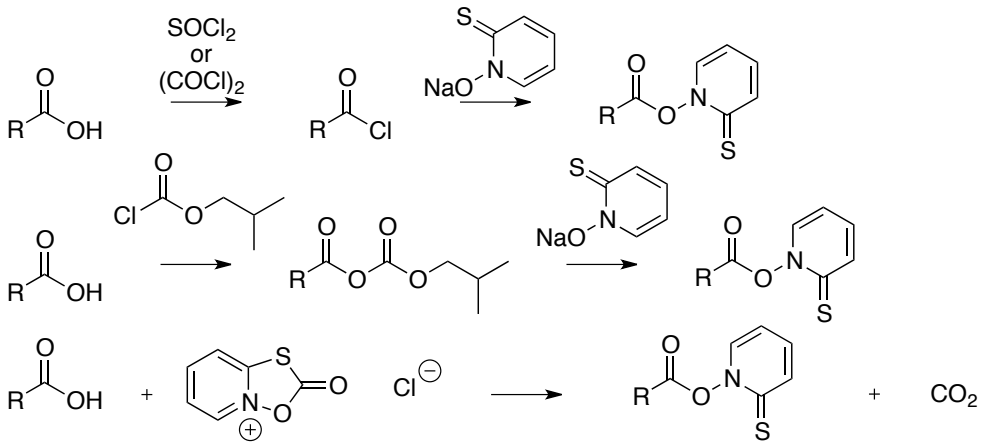
c. ***Barton decarboxylation***

→ *introduction*

Barton developed radical chemistry with the discovery of new reactions working through free radical mechanisms: the Barton reaction, the Barton decarboxylation and the Barton-McCombie deoxygenation.

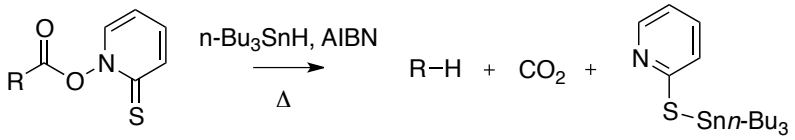
Sir Derek Barton (1918–1998) was an English organic chemist who received the Nobel Prize for chemistry in 1969 with Odd Hassel for their contribution to the development of the concept of conformational analysis in organic chemistry.[5] He received his PhD from Imperial College in 1942 and was appointed Professor in 1953. In 1978, he went to France to become Director of the "Institut de Chimie des Substances Naturelles" (near Paris). He retired from the research institute and traveled to the USA where he taught at the University of Station College (Texas) from 1986. Born the son of a carpenter, Barton was knighted Sir Derek in 1972. Over his career, more than 300 people worked for Barton and he published more than a thousand papers. He described the structure of many natural compounds (alkaloids, terpenoids, steroids). He worked on several natural product syntheses and developed in parallel new reactions (Barton reaction, Barton decarboxylation, Barton-McCombie deoxygenation). He married three times. His first wife was English, his second wife French and the last American. He finished his career as a Distinguished Professor at Texas A&M University where he carried on his work until his last breath. He died at the University at College Station in 1998.

The Barton decarboxylation found its innovative advantage in the scope of applications due to the tolerance of functional groups to the reaction conditions. Barton developed a method using *O*-acyl thiohydroxamate reagents. The carboxyl radical was formed through homolytic cleavage of the weak *N*-carboxyl single bond. This radical generation method has a great potential because neither strong oxidant nor strongly electrophilic species is required. Many methods were devised for the preparation of the radical ester precursor *O*-acyl thiohydroxamate (Scheme 83).[143] This precursor can be prepared even without protecting indoles, phenols, secondary and tertiary alcohols when using isobutyl chloroformate to promote the esterification.



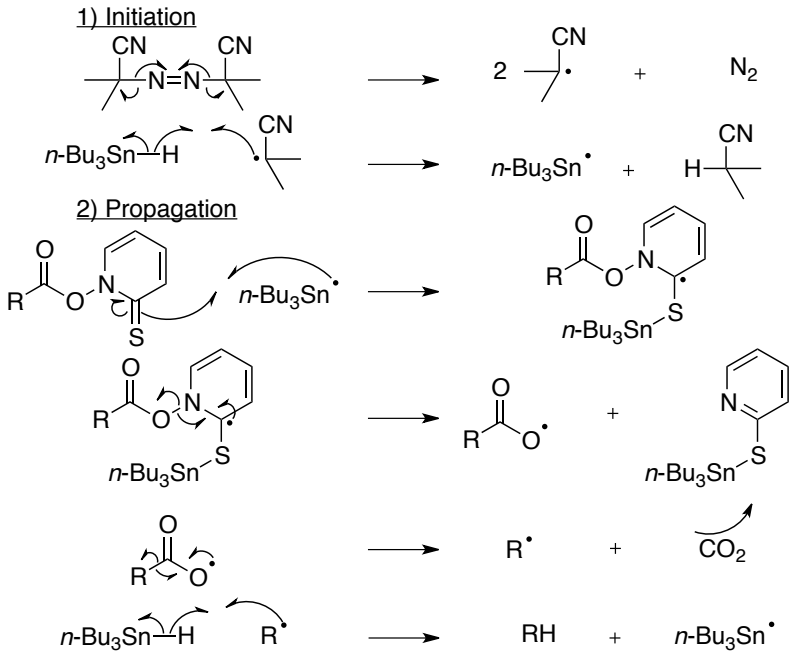
Scheme 83

An appropriate thiophilic radical induces the fragmentation of the *N*-carboxyl bond, thus forming the carboxyl radical (detailed mechanism shown in Scheme 84). The latter loses carbon dioxide and evolves into an alkyl or aryl radical that can be trapped with a hydrogen radical donor or another radical trapping reagent (general equation in Scheme 84).



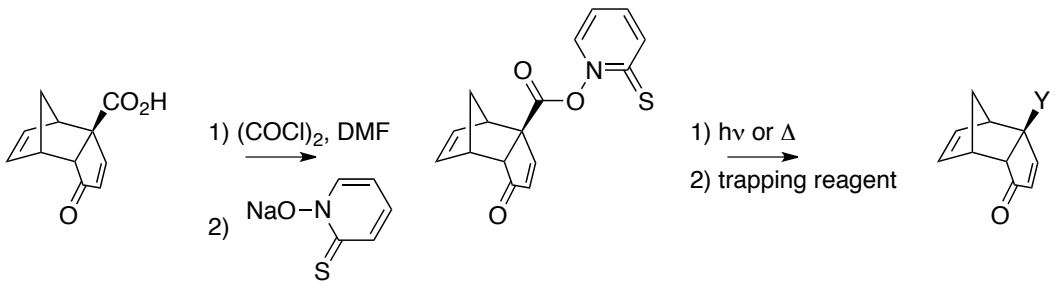
Scheme 84

The radical mechanism of Barton decarboxylation is shown in Scheme 85. The first step of the reaction is the initiation through homolytic cleavage of the radical initiator AIBN upon heating or white light photolysis. The radical generated attacks tri-*n*-butyltin hydride, releasing a tin radical. Tin radicals are thiophilic, and thus attack the sulfur atom of the thiohydroxamate moiety, forming a strong sulfur-tin bond. The *N*-carboxyl bond undergoes a homolytic cleavage that forms the carboxylic radical. The carboxylic radical produces an alkyl or aryl radical with release of carbon dioxide. The alkyl radical is finally trapped with a hydrogen radical from the tri-*n*-butyltin hydride. Tri-*n*-butyltin radical generated propagates the radical chain reaction until total consumption of the ester.



Scheme 85

A variety of radical trapping reagents can be used instead of tri-*n*-butyltin hydride (Scheme 86 and Table 11). The best results take place when the radical trapping reagent releases a thiophilic radical that can carry out the chain reaction.[6] The trap must also be efficient in order to have the desired pathway, prevailing on the side reactions. The other possible side reaction could be the dimerization of the formed radical or the formation of thioether (Entry 2 Table 11).



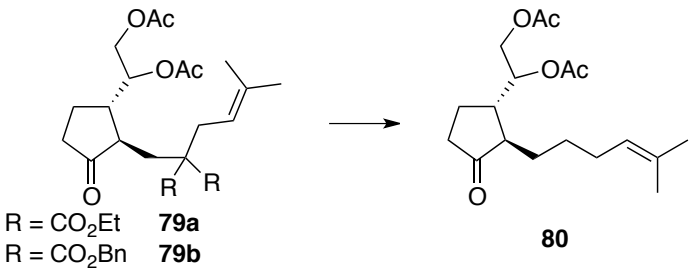
Scheme 86

Entry	Trapping reagent	Y	Yield
1	*t*-BuSH	H	60%
2	none	SPy	90%
3	$BrCCl_3$	Br	93%
4	$(PhSe)_2$	PhSe	94%

Table 11

→ *Decarboxylation attempts*

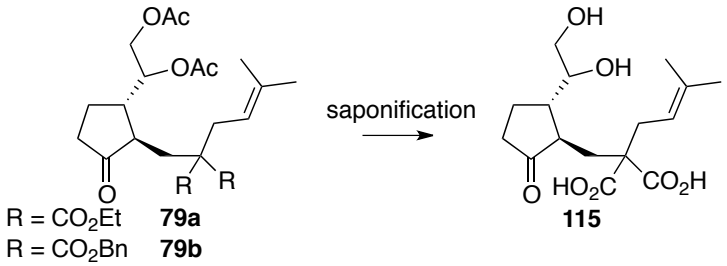
After failure of our route using acidic or basic decarboxylation, we decided to explore the methodology developed by Barton. For practical reasons, we worked on the product **79** of the addition of prenyl bromide to the malonate moiety (Scheme 87) rather than on the bicyclo[5.3.0]decane compound. Indeed, the molecule **79** was more accessible (it was synthesized with a shorter number of steps). The malonate moiety was in place in order to help for the addition of the prenyl group and was then removed. Barton decarboxylation seemed to be the methodology of choice: it was extensively studied and proved its efficiency in synthesis.



Scheme 87

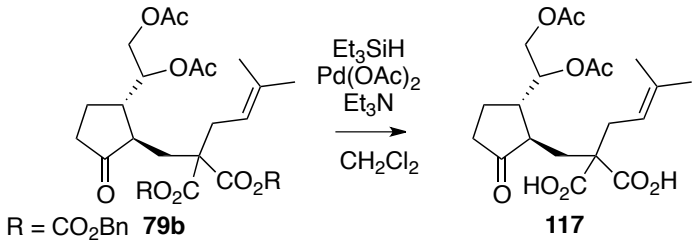
We had to convert the ester into the corresponding diacid to generate the *O*-acyl thiohydroxamate ester and to react the product in a radical reductive decarboxylation (Scheme 90).

Saponification of the diethyl ester **79a** (R = CO_2Et) or dibenzyl ester **79b** (R = CO_2Bn) afforded the diacid **115** with removal of both diol protections (Scheme 88). Purification of this product through silica gel chromatography was complicated and yielded impure material in very low yields (5% yield from **79a** and 4% yield from **79b**).



Scheme 88

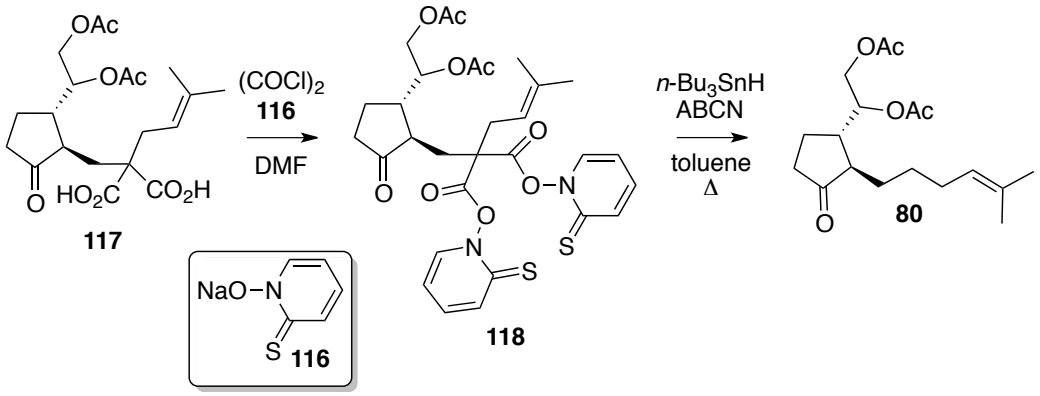
Use of dibenzyl malonate moiety **79b** (R = CO_2Bn) offered the possibility of removing only the benzyl group to give **117** through hydrogenolysis catalysed by palladium(II) acetate.[144] Coleman reported a mild hydrogenolysis methodology that could remove only the two benzyl groups without reducing double bonds.[144a] This method used triethylsilane in the presence of catalytic palladium(II) acetate. In these conditions, the benzyl group was replaced by the triethylsilyl group to form the triethylsilyl ester **79d** (R = $SiEt_3$).[144b] The latter was very unstable and cleaved under usual work-up (addition of saturated aqueous NH_4Cl) to afford the diacid **117**. The reaction needed only filtration through a pad of celite without any further purification and gave the diacid **117** in 73% yield (Scheme 89).



Scheme 89

Esterification of **117** was performed in DMF using $(COCl)_2$ and 2-mercaptopyridine *N*-oxide sodium salt to yield **118**.[145] The corresponding thiohydroxamate diester **118** underwent a

simple work-up (neutral washing and extraction) and was subsequently submitted to the radical reaction conditions as the unpurified mixture.



Scheme 90

We used tri-*n*-butyltin hydride as hydrogen radical donor. 1,1'-Azobis(cyclohexanecarbonitrile) (ABCN) was employed as initiator. A mixture of the crude thiohydroxamate diester, ABCN, and tri-*n*-butyltin hydride was heated under reflux for 4 hours until the total consumption of the starting material. Purification gave the product **80** in 38% yield. The rest of the mixture contained mainly compounds issued from the decomposition of the starting material.

In summary, the Barton decarboxylation afforded the expected compound **80** from the dibenzyl ester **79** over three steps in 28% yield.

We proved through these reactions that decarboxylation could be obtained using Barton methodology. In theory, the same procedure should be applicable to a later stage molecule such as the bicyclic structure. The benzyl malonate compound **79b** (R = CO_2Bn) was demonstrated to be more convenient as promising results were obtained in the sequence of reactions. No optimization of the reaction conditions was attempted because we focused on building the third ring, the lactone.

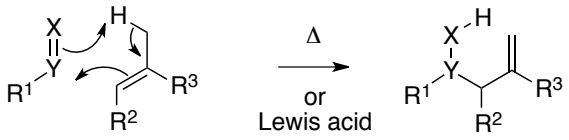
V) Carbonyl-ene cyclization

1) Alder ene reaction

The Alder ene reaction, also known as the ene reaction, is a pericyclic reaction involving an alkene bearing an allylic proton (the ene component) and a multiple bond (the enophile component), resulting in the formation of a carbon-carbon σ-bond and [1,5]-proton shift. Early examples were reported by Treibs (1927),[146] and Grignard (1930),[147] but this reaction was named after Alder who was the first to recognise the reaction and to investigate it.[148]

Kurt Alder (1902–1958) was a German organic chemist. He was the joint recipient of the Nobel Prize of chemistry in 1950 with his teacher Otto Diels "for their discovery and development of the diene synthesis". Alder obtained his PhD in 1926 under the supervision of Otto Diels. He was appointed reader in 1930 then lecturer in 1934 at Kiel University (Germany). In 1936, he became head of the department of the science laboratories of I G Farben-Industrie. His research in the company was concentrated on the development of Buna (discovered in 1935), a synthetic rubber. This rubber was called Buna for the chemical compounds used for its preparation: the copolymer is based on butadiene that polymerized under radical conditions originally initiated by sodium (natrium in German). Nowadays, about 50% of car tyres are made from Buna S (styrene butadiene rubber), which derives from the original Buna. In 1940, he was appointed to the Chair of Experimental Chemistry and Chemical Technology at Cologne University where he taught until his death in 1958.

The general mechanism of the Alder ene reaction is related to the Diels-Alder reaction mechanism (Scheme 91). Instead of the four π-electrons from the diene moiety, four electrons from the ene moiety are involved: the two π-electrons from the double bond and the two σ-electrons from the allylic carbon-hydrogen bond (Scheme 97). This accounts in part for the higher activation energy needed in the Alder ene reaction compared to the Diels-Alder reaction. Indeed, an Alder ene reaction requires energy for the activation of a carbon-hydrogen σ-bond, while a Diels-Alder reaction needs to activate a carbon-carbon π-bond, thus higher temperature and pressure are necessary. Harsh conditions are a limitation to the scope of substrates in the thermal Alder ene reaction.[149]

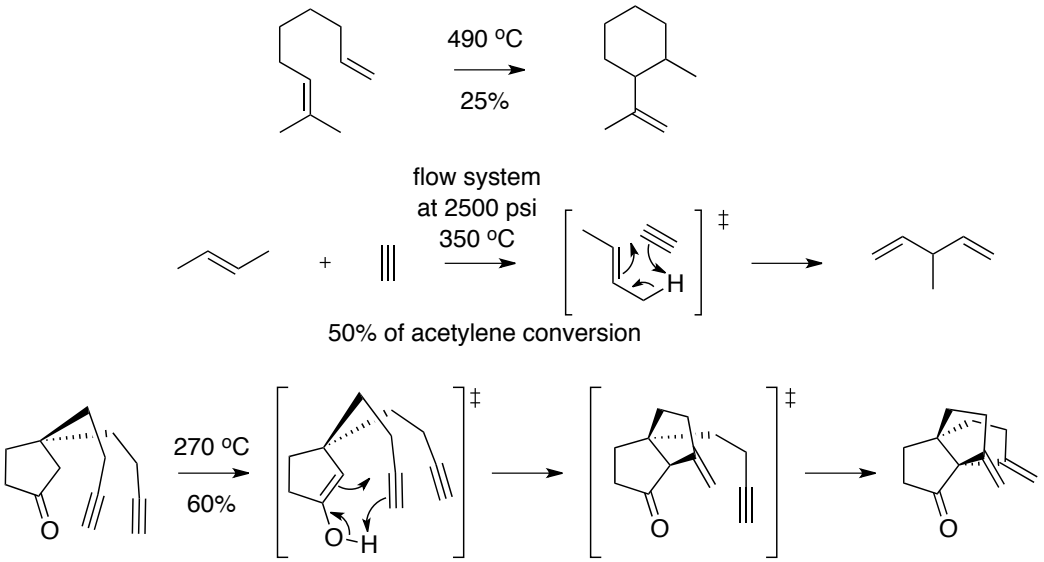


Scheme 91

The "ene" moiety is a molecule with a π-bond bearing an allylic proton. It can be an alkene, alkyne, allene, aromatic, or even cyclopropyl compounds. Some examples were even reported where carbon-heteroatom multiple bond can be used as the "ene" moiety.[150]

The enophile is generally an electron-poor multiple bond. In the case of a carbon-carbon bond, the ene can be activated through an electron-withdrawing group. The enophile moiety can be an alkene, alkyne, carbonyl, or azo compounds, or singlet oxygen.[151] The selenium dioxide-catalysed allylic oxidation is believed to proceed partly through an ene reaction mechanism.

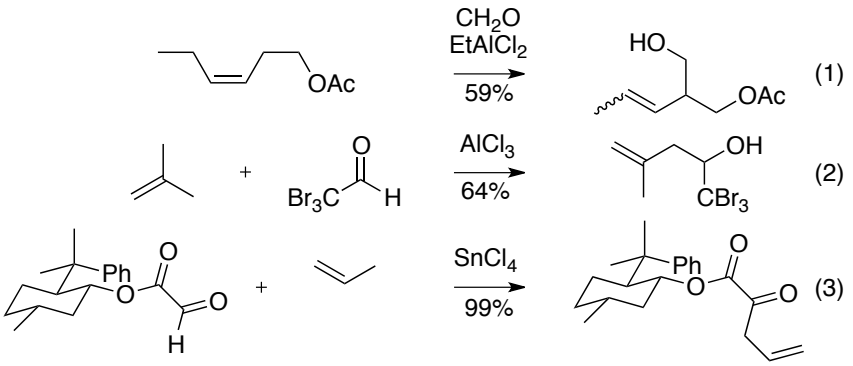
Alder ene reactions were originally thermally promoted, and the reaction required high temperatures, therefore reducing the range of possible substrates for the reaction (Scheme 92).[151] The development of Lewis acid-promoted ene reactions in the late 1970's has opened up new scope for the Alder ene reaction.



Scheme 92

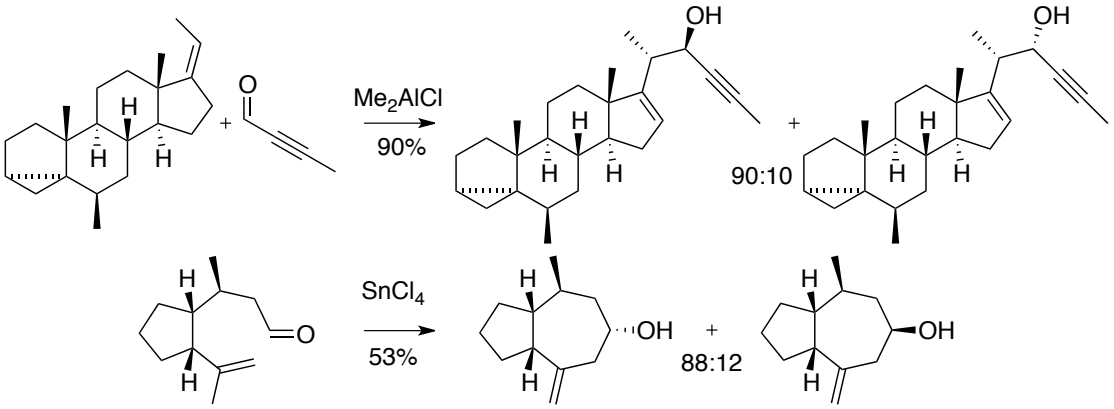
2) Carbonyl-ene reaction

The carbonyl-ene reaction is an Alder-ene reaction where the enophile is a carbonyl moiety. Before the 1970's, development of the carbonyl-ene reaction was hindered by the high activation energy needed. The activation energy could be lowered by Lewis acid catalysis: examples of carbonyl-ene reactions catalysed by Lewis acids such as these were originally restricted to formaldehyde (Equation 1 Scheme 93),[152] chloral or bromal (Equation 2 Scheme 93),[153] and glyoxylates (Equation 3 Scheme 93).[154]



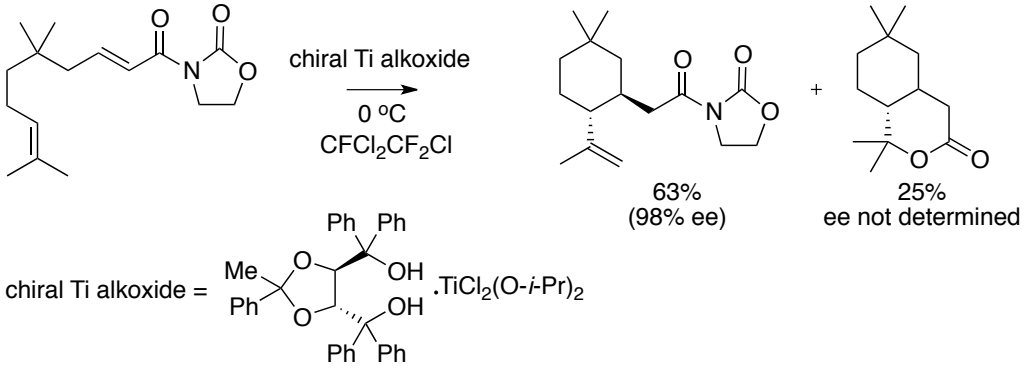
Scheme 93

The use of other Lewis acids enabled further development of the carbonyl-ene reaction. It could be presented as an alternative to the addition of allylic metals to carbonyls.[155] A number of Lewis acids such as $AlCl_3$, $SnCl_4$, $TiCl_4$, $BF_3.OEt_2$ were used to promote the reaction, thus lowering the temperature required to achieve the reaction (Scheme 94).[156] Therefore, under Lewis acid-catalysed conditions, less reactive enophiles and more sensitive functionalities such as substituents on enes and enophiles could be employed.

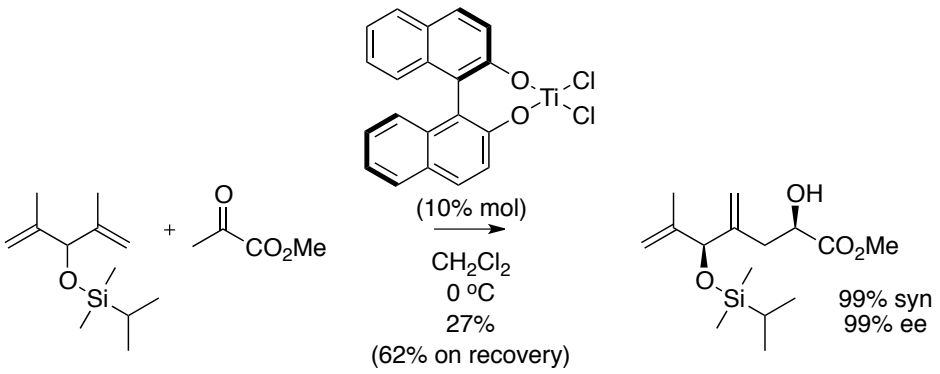


Scheme 94

Chiral Lewis acids have also been developed to induce high levels of enantioselectivity (Scheme 95 and Scheme 96).[157] Some of them have also proven their efficiency in asymmetric desymmetrization. Asymmetric desymmetrization is the ability of a reagent or an enzyme to form a chiral product when starting from a symmetrical molecule such as a *meso* compound (Scheme 96).[158]



Scheme 95



Scheme 96

1) Mechanistic aspects

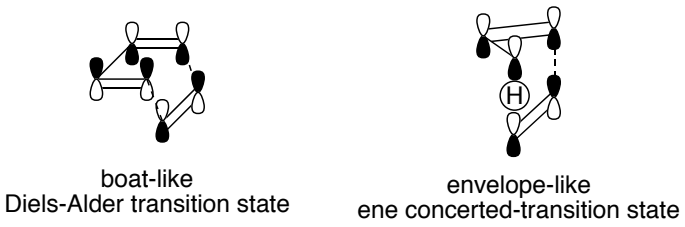
Concerted or stepwise mechanisms can be considered, depending on the starting materials and reaction conditions. In both cases, frontier orbital interactions between the HOMO (highest occupied molecular orbital) of the ene compound and the LUMO (lowest unoccupied molecular orbital) of the enophile component have an impact on the mechanistic and synthetic point of view. Lowering the energy of the LUMO (electron-withdrawing substituent on the enophile) favours the ene reaction and decreases the activation energy needed.[150]

a. Concerted mechanism

The carbonyl-ene reaction (and the ene reaction) is mechanistically related to the Diels-Alder reaction: the prevalent mechanism is a concerted pathway *via* a cyclic six-electron transition state. The Diels-Alder transition state is a six-membered ring where the terminal π-orbitals of the diene overlaps the dienophile π-orbitals (Scheme 97). In the ene mechanism, orientation of the σ-orbital of the allylic carbon-proton bond parallel to the π-orbitals of the neighbouring carbon-carbon double bond maximizes the allylic resonance: one π-orbital of the enophile overlaps the terminal π-orbital of the ene and the other enophile π-orbital overlaps the σ-orbital of the allylic carbon-proton bond of the ene (Scheme 97).

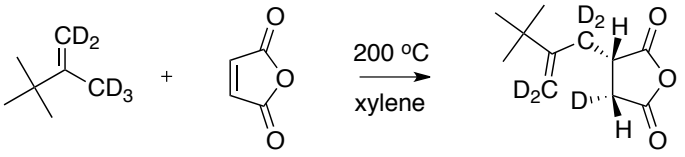
Hoffman suggested a transition state through an envelope conformation with two long carbon-carbon bonds, with one of these carbons bearing the proton that is transferred.[151]

Calculation studies supported this transition state geometry, although the carbon-hydrogen-carbon bond was determined to be at 156° instead of the postulated 180°.[159]



Scheme 97

Studies have shown evidence in favour of a concerted mechanism for most thermal ene reactions: no deuterium transfer to the product from deuteriated solvent, high activation energy needed and lack of isomerization of both products and reagents are consistent with a concerted process.[160] A *cis*-addition of ene and proton to the enophile double bond is another piece of evidence for a concerted mechanism (Scheme 98).[161]



Scheme 98

The *endo* addition is generally more favoured than the *exo* addition, although steric effects have more influence on the outcome of the ene reaction than on the Diels-Alder reaction. The thermal ene reaction of maleic anhydride and *cis*-2-butene yielded the *endo*-product as the major isomer (4:1, *endo*:*exo*), whereas with *trans*-but-2-ene, the ene reaction gave a 57:43 ratio in favour of the *exo*-product.[162]

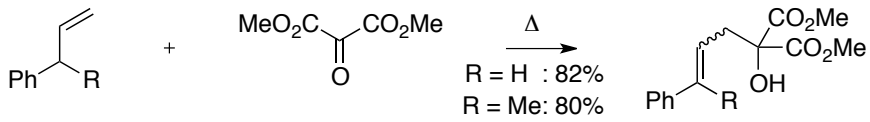
b. Cationic intermediate

The mechanism of the Lewis acid-promoted reaction is not always clear. It can be concerted or stepwise, and, at times, the difference between the two mechanisms is hard to

determine. Concerted mechanisms are single-energy barrier processes, whereas stepwise mechanisms have more energy barriers to cross in order to complete the reaction.[150]

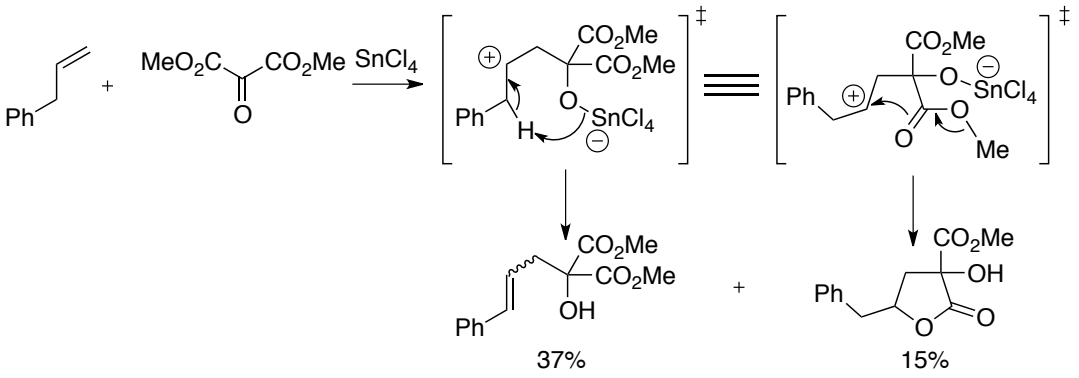
In 1984, Salomon reported modifications to the selectivity and reactivity of the Lewis acid-catalysed ene reaction. The most important difference was the preference for an attack at the less hindered carbon of the enophile for a thermal ene reaction, while the Lewis acid-catalysed ene reaction was directed by another effect. The results suggested an electronic influence of the Lewis acid.[163] Many studies have reported the impact of Lewis acids on the ene reactions, but no conclusive proof of an ionic intermediate has been found.

In 1996, Achmatowicz examined the reactions of allylbenzene and 3-phenylbut-1-ene with oxomalonic ester (Scheme 99).[164] The reactions were previously reported by Stephenson in 1981[165] and Kwart in 1982.[166] The contradictory results were an interesting point to clarify. Stephenson reported a carbonyl-ene reaction product, whereas Kwart obtained cyclized products from the same reactions. Achmatowicz decided to study deeper in order to clarify the mechanism behind these reactions. He showed that both sets of reagents underwent an ene reaction under thermal conditions (Scheme 99).



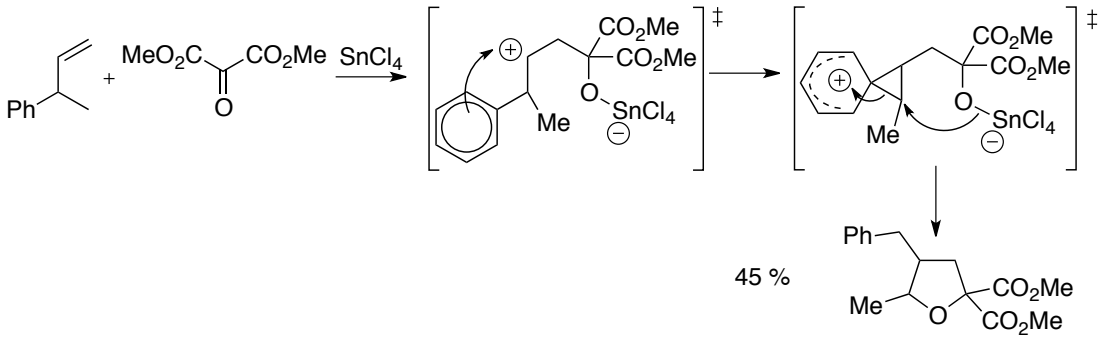
Scheme 99

The reaction was studied under Lewis acid conditions: $SnCl_4$ was used as the Lewis acid in analogy to the work accomplished before.[166,167] Allylbenzene reacted with oxomalonic ester to give two products: the expected ene product (*cf* thermal conditions) and a cyclized product (Scheme 100). The cyclized product was believed to result from an intramolecular reaction of an ionic ene intermediate. However, no evidence could be found to confirm the mechanism. When the ene product was treated with $SnCl_4$, no reaction occurred and the starting material was recovered.



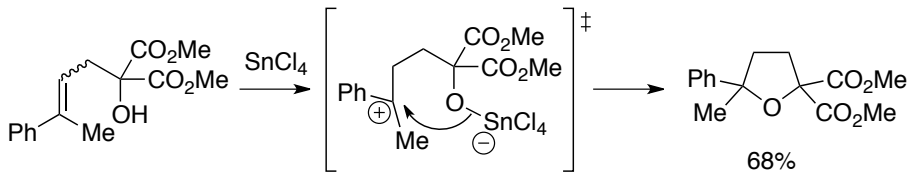
Scheme 100

The same reaction was performed using 3-phenylbut-1-ene with oxomalonate ester. A similar result was expected but only one product, a cyclic compound, arising from the migration of the phenyl group, was obtained (Scheme 101).



Scheme 101

The product could be rationalized by an ionic mechanism. A different cyclic adduct was obtained and no phenyl group migration was observed when the ene product resulting from the thermal conditions was treated with $SnCl_4$ (Scheme 102). These results clearly indicated that a concerted mechanism was occurring under thermal conditions (as expected), whereas the Lewis acid-promoted reaction resulted in an ionic process.

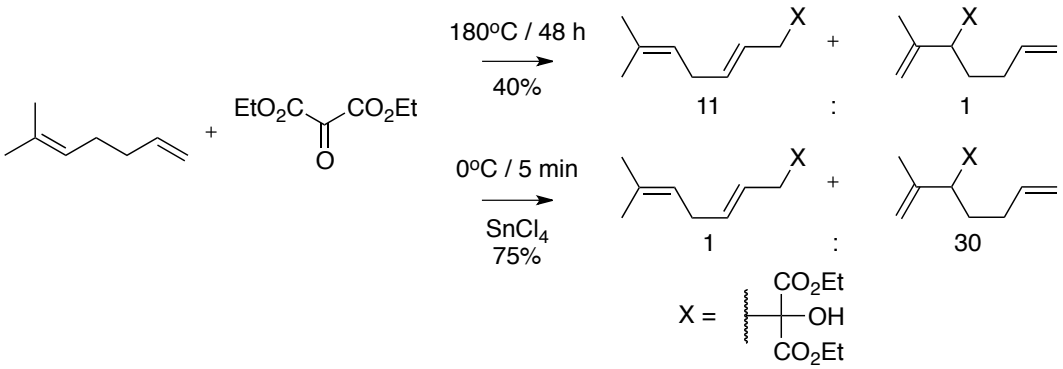


Scheme 102

c. Thermal vs Lewis acid-promoted reaction

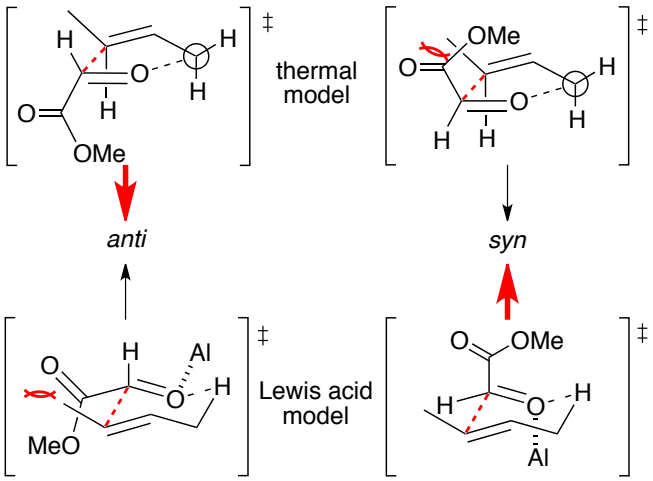
Frequently, the Lewis acid-promoted ene reaction mechanism is seen as a continuum from concerted to stepwise mechanisms.[150] A concerted mechanism is a single-energy barrier process, so only one activation energy should be considered. A stepwise process such as an ionic mechanism requires each step to be pushed forward. The rate-limiting step is the slowest one. In this cationic process, the rate-determining step can be either the formation of the ionic intermediate when the cationic intermediate formation is slow and reversible, and the hydrogen transfer fast, or the hydrogen transfer.

In general, thermal reactions are limited by the steric hindrance of the ene component and/or the steric accessibility of the allylic hydrogen. In the Lewis acid-promoted reaction, stability of the ionic intermediate favours the reaction and directs it. Therefore, 1,1-disubstituted alkenes are more reactive ene components because the positive charge is more stabilized when the carbon is more substituted (Scheme 103).[164] Further, thermal reactions show a small enhancement of reactivity with the addition of an electron-donating substituent on the ene component, whereas the Lewis acid-promoted reaction demonstrates a strong enhancement.[164]



Scheme 103

The envelope model could not explain some results obtained with the Lewis acid-promoted reaction. Therefore, Mikami suggested a six-membered ring chair-like transition state that would occur at a late stage of the reaction mechanism (Scheme 104).[155b]



Scheme 104

d. Radical mechanism

A limited number of examples of ene reactions involving a radical mechanism can be found in the literature. Franzus reported that a free-radical initiator could catalyse reactions of cyclic olefins with ethyl azodicarboxylate.[167]

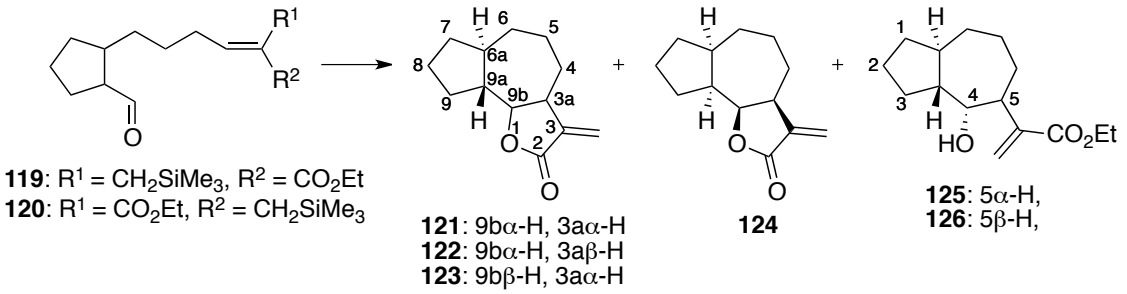
2) Carbonyl-ene cyclization: towards the perhydroazulene ring

a. Perhydroazulene synthesis by Kuroda et al.

In 1993, Kuroda reported the synthesis of α-methylene-γ-lactones fused to a perhydroazulene carbon framework through intramolecular allylsilane cyclization (Scheme 105).[168] The mechanism involved is a Lewis acid-catalysed intramolecular nucleophilic addition of an allyl silane to an aldehyde, followed by a lactonization.

The stereochemistry of the products depends on the configuration of the double bond of the allylsilane moiety (*E* or *Z*) and on the cyclization reagent (Table 12). From our point of view,

despite the low yields, the most interesting results for the synthesis of guaianolide and pseudo-guaianolide skeletons would be obtained using $BF_3.OEt_2$ as the catalyst (Entry **1** and **4** Table 12). Results using $TiCl_4$ indicated an isomerization of one of the bridge carbons (Entry **5** Table 12) or lower yields without lactonization (Entry **2** Table 12). Results using TBAF can also be interesting but not applicable to our methodology, an Alder ene reaction.



Scheme 105

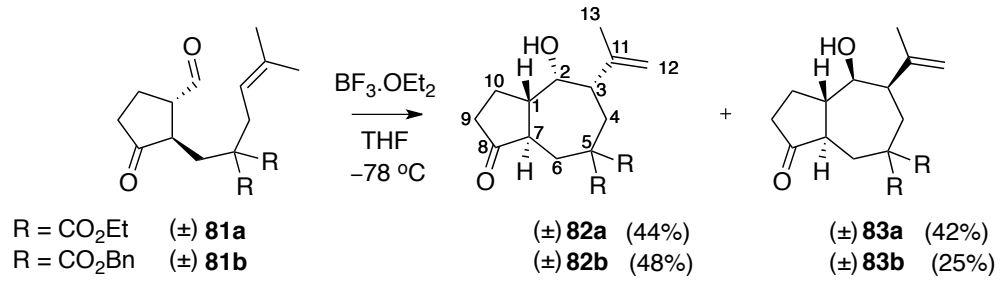
Entry	Substrate	Reagent	Product(s) (ratio)	Yield (%)
1	**119**	$BF_3.OEt_2$	**121**	14
2	**119**	$TiCl_4$	**125** + **126** (53:47)	13
3	**119**	TBAF	—	—
4	**120**	$BF_3.OEt_2$	**121** + **122** (44:56)	19
5	**120**	$TiCl_4$	**124**	45
6	**120**	TBAF	**122** + **123** (41:59)	32

Table 12

b. Reaction

The perhydroazulene skeleton was synthesized through an intramolecular Alder ene reaction. The 1,8-unsaturated aldehyde Alder ene precursor **81** was cyclized using the Lewis acid $BF_3.OEt_2$ at −78 °C in THF for 48 hours. The product was obtained as a mixture of two diastereoisomers with a *trans* relative stereochemistry at the C1-C7 ring junction and a *cis*

relative stereochemistry between the substituents borne by C2 and C3 (Scheme 106). The relative configuration was determined using NMR spectroscopy studies.[1]



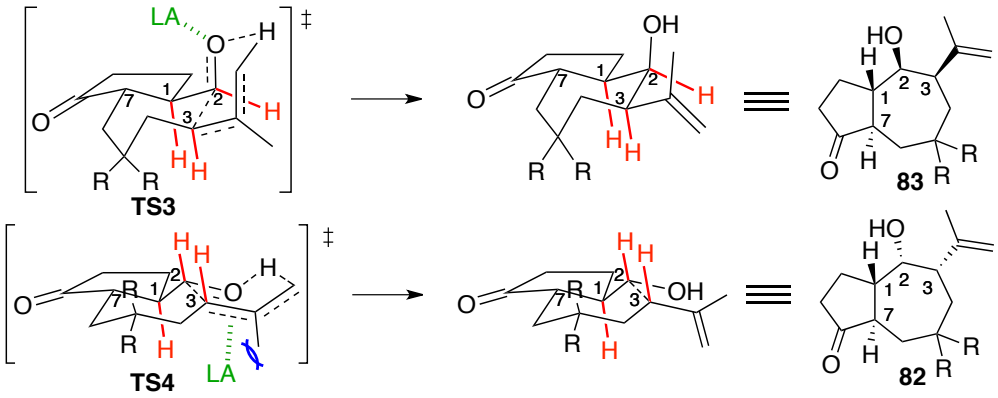
Scheme 106

A previous study investigated a range of Lewis acid catalysts and conditions such as $BF_3.OEt_2$, ZnI_2, $Sc(OTf)_3$, $Yb(OTf)_3$, $InCl_3$, solvent screening and microwave irradiation.[1] Most of these conditions were ineffective and only starting material was recovered. However, the Lewis acids $BF_3.OEt_2$ and $Yb(OTf)_3$ yielded the desired cyclized compounds **82** and **83** that have a guaianolide skeleton.

In this former study, the Alder ene precursor **81a** (R = CO_2Et) was cyclized in the presence of $BF_3.OEt_2$ in dry THF under argon at −78 °C and stirred for 22 h at room temperature to yield the perhydroazulene compounds as a mixture of **82a** (R = CO2Et) in 10% yield and **83a** (R = CO_2Et) in 41% yield.[1] When the intramolecular carbonyl-ene cyclization of **81a** was catalysed by $Yb(OTf)_3$ in dry THF under argon at 0 °C and stirred at room temperature for 5 days, only the isomer **83a** was observed in 46% yield (56% when the starting material recovery was accounted for).[1]

The stereochemistry should result from a concerted carbonyl-ene reaction mechanism. Indeed, if a cationic intermediate was involved, an ion with a carbocation at C11 (see Scheme 106) would be the intermediate, and thus, proton abstraction at C2 would be observed. Therefore, an ionic mechanism would involve a side product with a double bond between C3 and C11, which is more stable than the one obtained (Scheme 106). No such unsaturated product was observed. These observations corroborate our concerted mechanism hypothesis.

The *cis* relative configuration could be rationalized by a mechanism operating through a chair-like transition state (Scheme 107). In the transition state **TS4**, we can see that the Lewis acid (noted LA in Scheme 107) is more hindered than in **TS3**. This could be an explanation for the selectivity of the reaction, especially when using the Lewis acid $Yb(OTf)_3$, which is even bulkier than $BF_3.OEt_2$.



Scheme 107

We chose to focus on the Alder ene reaction catalysed by $BF_3.OEt_2$ in order to obtain the perhydroazulene ring system. This decision was motivated by the fact that the reaction catalysed by $Yb(OTf)_3$ afforded a slightly lower yield than the one catalysed by $BF_3.OEt_2$.

Conditions were screened to optimize the yields: solvent, Lewis acid quantity, temperature and reaction time.

The best solvent for the reaction was THF. In diethyl ether, lower yields were obtained, and in dichloromethane, the starting material decomposed.

The best results were obtained when the aldehyde-ene precursor **81** was treated with 10 equivalents of $BF_3.OEt_2$ in dry THF under argon at −78 °C and the reaction mixture stirred for 48 hours at low temperature (between −78 °C and −50 °C).

R	Eq of $BF_3.OEt_2$	Temperature	Reaction time	Yield of 82 (on recovery)	Yield of 83 (on recovery)	Overall yield
CO_2Et	**5**	−78 °C to r.t.	1 day	15%	25%	40%
CO_2Et	**5**	−78 °C to −50 °C	1 day	13% (24%)	22% (40%)	35% (64%)
CO_2Et	**10**	−78 °C to r.t.	2 days	17%	37%	54%
CO_2Et	**10**	−78 °C to −50 °C	2 days	44%	42%	86%
CO_2Bn	**10**	−78 °C to r.t.	2 days	30%	35%	65%
CO_2Bn	**10**	−78 °C to −50 °C	2 days	48% (58%)	25% (30%)	73% (88%)
CO_2Bn	**10**	−78 °C to −50 °C	5 days	49%	26%	75%

Table 13

The formation of the cyclic compound **82** seemed to be favoured by the presence of the benzyl esters (ratio 2:1 for **82b** (*S*,*S*):**83b** (*R*,*R*)), whereas the cyclization (*cis* configuration: (*S*,*S*) **82a** or (*R*,*R*) **83a**) ratio is 1:1 in the presence of ethyl esters.

The yield of the compound **83** appeared to remain constant (30% yield), while the yield of compound **82** varied (up to 48% yield).

Less decomposition of the product seemed to occur when the reaction mixture was kept at low temperature, but the reaction was slightly slower. After 48 hours, the highest ratio was obtained, and after five days, only marginally better results were obtained (lower yields when the recovery of the starting material was accounted for).

Obtaining both isomers expanded the number of potential target molecules, as guaianolides with both skeletons exist.

VI) Inversion of configuration

In asymmetric synthesis, the inversion of configuration at a carbon bearing an alcohol moiety is often required. Commonly used methodologies include nucleophilic substitution or oxidation of the alcohol function, followed by reduction.

1) Nucleophilic substitution

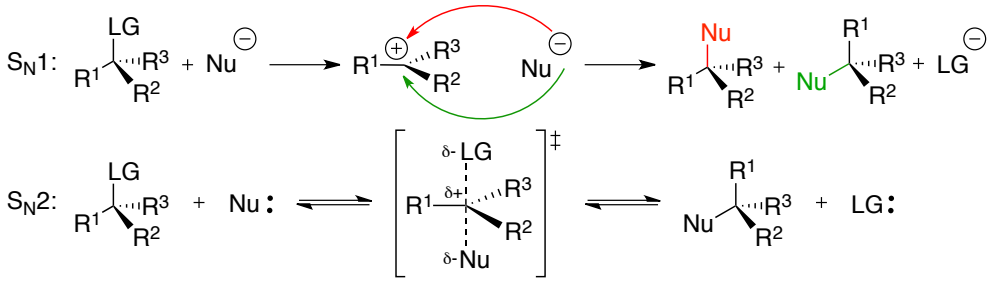
a. Introduction

Nucleophilic substitution is a fundamental reaction in organic chemistry. The reaction results in the displacement of an electron rich moiety (nucleofuge) by another electron rich group (nucleophile). Ingold and Edward D. Hugues studied the substitution mechanism.

Sir Christopher Kelk Ingold (1893–1970) was a British chemist, considered as a pioneer in physical organic chemistry.[5] He has rationalised many general mechanisms such as nucleophilic substitution and elimination, electrophilic addition and substitution, and other mechanisms. In 1934, Ingold published a revolutionary paper on the "Principle of an Electronic Theory of Organic Reaction".[169] He was the first to suggest the presence in solution of organic ions to explain some mechanisms. It was only in 1951 that the manual Ingold wrote became a reference about organic reaction mechanisms. Ingold obtained his PhD in 1918 and a DSc in 1921 from Imperial College. At 31, he was appointed a chair of Organic Chemistry at Leeds University. In 1930, he came back to London where he served as the Head of the Chemistry Department of University College of London until his retirement in 1961. Ingold was knighted in 1958.

Ingold proposed two different mechanisms that can be characterized by their kinetic order (Scheme 108): the nucleophilic substitutions of the first and second orders are termed S_N1 and S_N2, respectively. A S_N1 reaction involves an ionic mechanism, in two steps with the formation of a carbocation intermediate (Scheme 108); the S_N1 rate depends only on the substituted alkyl concentration. In the S_N2 reaction, the elimination of the leaving group (nucleofuge) occurs with a concomitant addition of the nucleophile (Scheme 108). Therefore, S_N2 involves a concerted

mechanism and the reaction rate depends on the concentration of both the product and the nucleophile.



Scheme 108

The two mechanisms compete. The S_N2 reaction is characterized by an *anti*-attack of the nucleophile, which inverts the configuration of the reactive centre; whereas, in the S_N1 reaction, after the formation of a planar carbocation intermediate, a nucleophilic attack can occur from both faces, generally generating a racemic mixture, unless a chiral substituent favours a particular stereochemical outcome.[170]

The S_N1 reaction is favoured when the carbocation intermediate is stabilized, for example in the presence of more substituted alkyl and stabilizing substituents in a polar protic solvent. The S_N2 reaction is favoured in aprotic solvents, when the substituents borne by the reactive centre are unhindered primary and secondary alkyl, and when the group attacking is highly nucleophilic.[171]

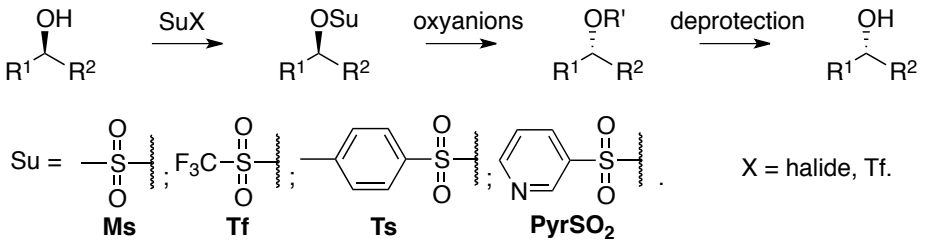
Depending on the reaction conditions, elimination (E1 and E2) can take place instead of the S_N1 and S_N2 reactions.

b. Alcohol inversion

The inversion of configuration of an alcohol requires the activation of the carbon-oxygen bond in order to generate a good leaving group, which is subsequently displaced by a nucleophile such as an oxyanion (Scheme 109). The Mitsunobu reaction is further discussed in a separate section.

The S_N2 reaction mechanism must be favoured in order to obtain complete inversion of configuration at the chiral carbon centre bearing the alcohol moiety. The bulk of R^1 and R^2 (Scheme 109) should be minimized and potential elimination of the sulfonate moiety should be avoided.

The carbon-oxygen bond is generally activated through the formation of a sulfonyl ester (noted **Su** on Scheme 109). Examples of sulfonyl esters, used as leaving groups, are tosylate (**Ts**), mesylate (**Ms**), triflate (**Tf**), and pyridyl sulfonate (**$PyrSO_2$**) esters.[171]



oxyanions	R'
R^3CO_2M	R^3CO-
KNO_3	O_2N-
NO_2 or KNO_2	H-

Scheme 109

The leaving group is generally displaced by a metal carboxylate. Metals such as sodium and potassium carboxylates have shown reasonable results for nucleophilic substitution with inversion of configuration.[172] A tetraalkylammonium carboxylate salt can be also used instead of metal carboxylate to operate the substitution. However, elimination products were observed to some extent with secondary alcohols.[173] Use of salts of cesium carboxylate showed the best results in the inversion reaction and in the suppression of the elimination reaction.[174] The addition of 18-crown-6 to the substitution reaction can also reduce the amount of elimination products.[175] The subsequent hydrolysis of the carboxylate allows the preparation of the free inverted alcohol with an inverted configuration.

Other methodologies, using different nucleophiles for the substitution such as nitrate, superoxide or nitrite ions, have also been reported.[167,174,175a] These methodologies are not general

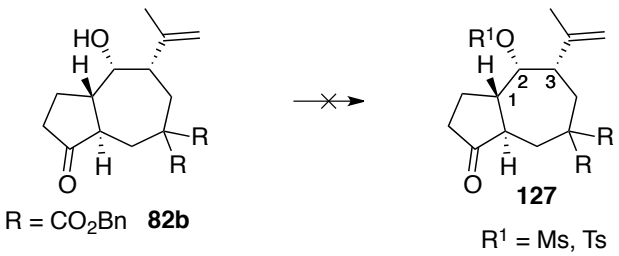
and, in some cases, they afforded the corresponding inverted alcohol. However, side reactions such as racemization, elimination, oxidation or nitration gave undesired products.[172,176]

Another methodology is the esterification of a secondary alcohol *via* the corresponding isourea ether. The alcohol is converted into an isourea using a carbodiimide such as *N,N'*-dicyclohexylcarbodiimide (DCC), which is not isolated. The isourea ether formed is displaced *in situ* with a carboxylic acid to form a carboxylic ester. This ester can be hydrolysed to provide the alcohol with an inverted configuration.[177]

Mitsunobu developed a methodology that is widely used in total synthesis for the inversion of configuration of alcohols, using azocarboxylate compounds and phosphines as reagents in one step (*vide infra*).

c. ***Application***

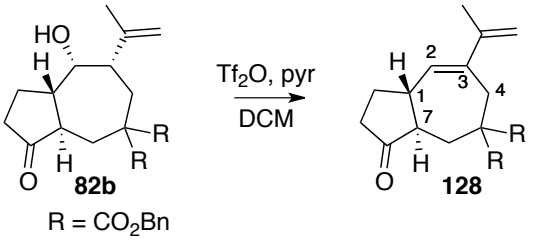
We attempted the substitution of the alcohol function of compound **82b** (R = CO_2Bn). The first step was the conversion of the alcohol moiety into a sulfonyl ester **127**, a good leaving group (Scheme 110). The alcohol sulfonylation attempts were unsuccessful; even when the reaction solution was heated for several days, no new products appeared, only compound **82b** was recovered in 65 to 85% yield (Entries **1**, **4**, **5**, **6** and **7**, Table 14).



Scheme 110

When trifluoromethanesulfonic anhydride was used as the sulfonylation reagent, compound **82** was consumed (Entries **2** and **3**, Table 14). However, no triflate ester was observed in the resulting product mixture (^{19}F NMR spectroscopy). Two new sp^2 carbons were observed using ^{13}C NMR spectrum analysis, and one of the carbons was not correlated to any proton, whereas the second was correlated to an alkene proton (HSQC NMR experiment). This alkene

proton H2 was correlated to proton H1 at the ring junction (COSY NMR experiment). Therefore, we deduced the structure of compound **128**, which matched an expected side reaction. A spontaneous elimination of the triflate could have occurred, yielding the corresponding alkene **128** (Entries **2** and **3**, Table 14; Scheme 111). When the quantity of pyridine and triflic anhydride was reduced, the same elimination reaction was observed (Entry **3,** Table 14). The latter took place at 0 °C, but no reaction occurred at –30 °C; however, when the temperature was allowed to increase slowly from –30 °C to 0 °C, only the elimination product was observed.



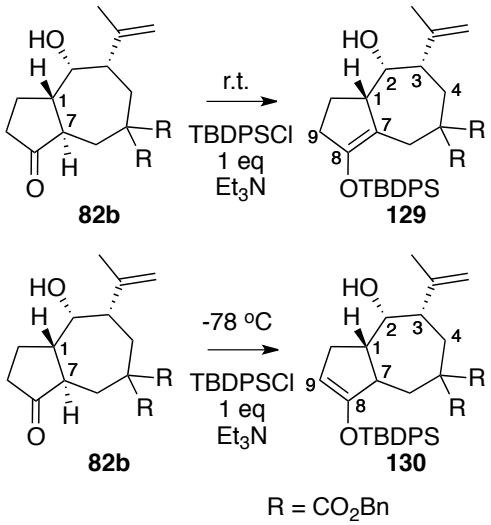
Scheme 111

The use of methanesulfonyl chloride was also unsuccessful as the starting material was recovered (Entries **4** and **5**, Table 14). The same disappointing outcome was observed when sodium hydride and tosyl anhydride were used (Entry **7**, Table 14).

Entry	Sulfonate (equiv)	Base (equiv)	DMAP	Product
1	Ts_2O (1.2)	Pyr (2.4)	—	SM
2	Tf_2O (2.6)	Pyr (5)	—	Elimination
3	Tf_2O (1.2)	Pyr (1)	—	Elimination
4	MsCl (1.2)	Pyr (1.5)	Catalytic	SM
5	MsCl (2)	Pyr (1.5)	Catalytic	SM
6	TsCl (2)	Pyr (2)	Catalytic	SM
7	Ts_2O (1.1)	NaH (2.5)	—	SM

Table 14

We also attempted to protect the alcohol moiety with a silyl protecting group and we observed that the first reaction that occurred was the formation and the trapping of the enolate (Scheme 112). One equivalent of *t*-butyldiphenylsilyl chloride (TBDPSCl) with one equivalent of Et_3N yielded either compound **129** or **130** depending on the reaction temperature (Scheme 112).



Scheme 112

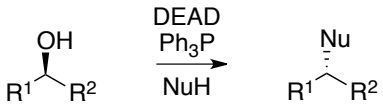
Therefore, two equivalents of reagents were required to protect the alcohol moiety. Depending on the reaction temperature, a different enolate was obtained: at −78 °C, the less substituted kinetic enolate was observed; when the reaction was progressively allowed to warm up from −78 °C to room temperature, the more substituted thermodynamic enolate was afforded. These observations were confirmed by NMR spectra analysis. Consequently, larger excesses of sulfonylating reagent and base were used, but the desired sulfonyl esters were not obtained (Entries **2**, **5** and **6**, Table 14).

2) Mitsunobu reaction

a. Introduction

In 1967, Mitsunobu reported the formation of esters from alcohols and carboxylic acids through the formation of quaternary alkoxyphosphonium salts.[178] Later, he observed that the

reaction proceeded with an inversion of configuration if optically active secondary alcohols were used.[179] The substitution of an alcohol by a nucleophile in the presence of an azodicarboxylate and a phosphine is generally termed as Mitsunobu reaction (Scheme 113).[180]



Scheme 113

Mukaiyama has developed the conditions to perform the reaction successfully even on tertiary alcohols with an inversion of configuration.[181]

A carboxylate ion is generally used as nucleophile for the displacement of the oxyphosphonium function (inversion of the carbon configuration), although phenol or hydroxybenzothiazole can also be employed. However, a large range of nucleophiles can also substitute the oxyphosphonium group, provided the pK_a of the nucleophile is lower than 15.[181,182] Other possible nucleophiles are thiols, thiophenols, imides, hydroxamates, some nitrogen heterocycles and hydrazoic acids. A few cases of carbon-carbon bond formation have been reported with β-diketones or β-ketoesters, but β-diesters are not reactive enough for the reaction.[6] Intramolecular Mitsunobu reactions are also possible.[183]

The preferred phosphine is generally Ph_3P, but *n*-Bu_3P (or Bu_3P) is also commonly used.[183] The principal limitation of the Mitsunobu reaction is the purification, and particularly the removal of the unreacted phosphine and the formed phosphine oxide. A large range of phosphines has been successfully tested such as Me_3P, Ph_2(2-Pyr)P, (*p*-$NMe_3Ph)_3P$ and DPPE (1,2-diphenylphosphinoethane). Phosphines supported on polymer have been developed and chromatography-free separation methodologies have been explored.[184]

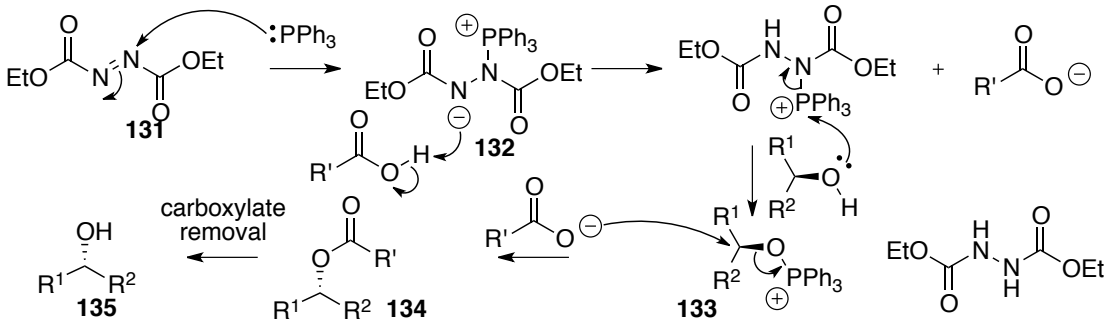
DEAD (diethyl azodicarboxylate) or DIAD (diisopropyl azodicarboxylate) are the common azodicarboxylates used for the Mitsunobu reaction. In general, they can be employed interchangeably. Good yields are obtained if the pK_a of the nucleophile is lower than 11. When the pK_a of the nucleophile is higher than 11, more reactive azodicarboxylates are preferred such as ADDP ((1,1'-azodicarbonyl)dipiperidine), and TMAD (N,N,N',N'-tetramethyl

azodicarboxamide).[183] Me_3P or *n*-Bu_3P, combined with these more reactive azodicarboxylates, afforded better results than Ph_3P. New azodicarboxylates have been also devised, facilitating chromatography separation.[185] DMEAD (di-2-methoxyethyl azodicarboxylate) and the reduced product, the hydrazine, are readily separated from the expected Mitsunobu product and are easier to prepare than DEAD.[183]

A general procedure for the Mitsunobu reaction is the slow addition of DEAD or DIAD to a solution of Ph_3P, followed by the addition of the alcohol, and finally, the acidic nucleophile is added to the mixture. However, homocoupling of the alcohol can be observed, and the addition can be performed in other orders.

b. Mechanism

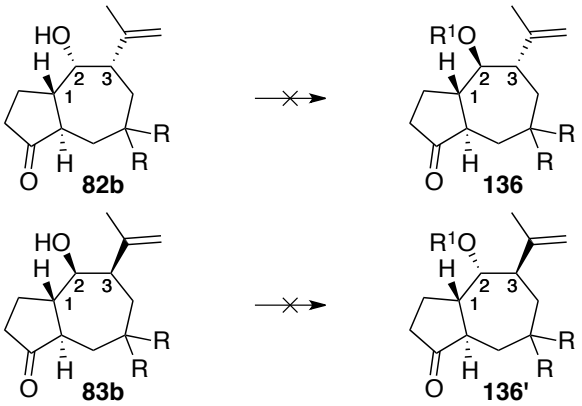
The mechanism of the Mitsunobu reaction is fairly complex and still subject to studies.[183] Mitsunobu proposed the mechanism shown below (Scheme 114).[181] It can be considered overall as an oxidation/reduction reaction where the phosphine is oxidized to the phosphine oxide and the azodicarboxylate **131** reduced to the hydrazine dicarboxylate. Triphenyl phosphine is added to diethyl azodicarboxylate **131** to yield the betaine **132**, which is protonated. After the formation of the alkoxyphosphonium salt **133**, the S_N2 reaction can take place and yields the resulting species **134** with an inversion of the configuration. The carboxylate can be removed to afford the desired inverted alcohol **135**.



Scheme 114

c. ***Application***

All of our different attempts at performing Mitsunobu reaction with **82b** and **83b** were unsuccessful (Table 15). A range of combinations of azodicarboxylates, phosphines and nucleophiles were tried, but they all resulted in the recovery of the starting material (Table 15).



R = CO_2Bn
R^1 = (*p*-NO_2)$C_6H_4CO_2H$, (*p*-MeO)$C_6H_4CO_2H$, Ac

Scheme 115

Entry	Azodicarboxylate	Phosphine	Nucleophile*	Product
1	DIAD	Ph_3P	PNBA	SM
2	DIAD	Bu_3P	PNBA	SM
3	DEAD	Ph_3P	PNBA	SM
4	DEAD	Bu_3P	PNBA	SM
5	DEAD	Bu_3P	AcOH	SM
6	DEAD	Ph_3P	PMBA	SM

(* PNBA: para-nitrobenzoic acid; PMBA: para-methoxybenzoic acid)

Table 15

We attempted to limit the effect of steric hindrance: Bu_3P and acetic acid (a small nucleophile) were used with DEAD (Entry **5**, Table 15). The reaction mixtures were heated to reflux. THF, diethyl ether, dichloromethane and toluene were tested as the reaction solvents. The conditions, shown in the Table 15, are the ones when THF was used as reaction solvent. Dioxane was also employed as solvent to allow higher reflux temperatures. A reaction using a large excess of reactants was also attempted. All the modifications to the reaction conditions, described above, only led to the recovery of the starting material.

3) Oxidation/reduction

a. Introduction

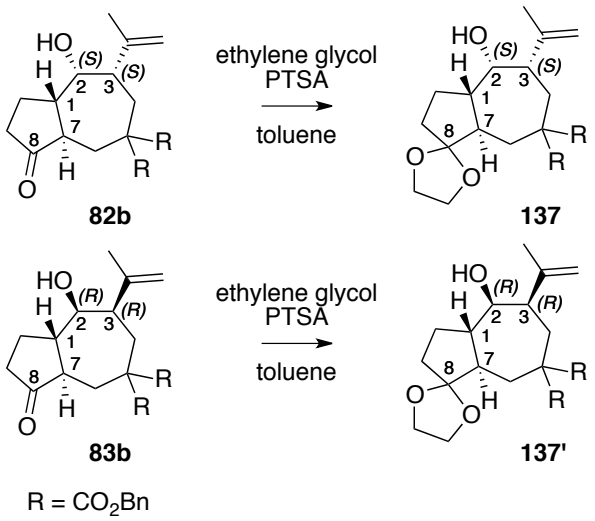
The oxidation-reduction reaction sequence is often used in asymmetric synthesis to provide a racemic mixture of both alcohol epimers. The unwanted epimer can be re-engaged in the same sequence of oxidation and reduction reactions.

A plethora of oxidation reactions, that convert a primary or secondary alcohol into an aldehyde or a ketone, is available such as: chromium oxidations (Jones, PDC, PCC, *etc*), DMSO oxidations (Swern, Pfizner-Moffat, *etc*), hypervalent iodine oxidations (Dess-Martin, IBX, *etc*), ruthenium oxidations, TEMPO oxidations, *etc*. The most commonly used oxidation reagents contain chromium; high yields are normally obtained. One drawback is that these reagents are strong oxidizing reagents, resulting in poor selectivity such as the selectivity between primary and secondary alcohols. However, PDC (pyridinium dichromate) and PCC (pyridinium chlorochromate) are less acidic and moderately less reactive reagents than the Jones reagent, which enlarges the scope of reactions for chromium reagents.

Many reduction reactions, that convert a ketone into an alcohol, are also available. The chemo- and stereoselective reduction of a ketone without reduction or isomerization of a carbon-carbon double bond is required in our case. A hydride donor should be suitable. Metal hydride reagents generally lead to racemic mixtures, but chiral metal hydride reagents have been developed to induce enantioselectivity. If the reaction proceeds in good yield with an achiral metal hydride and the diastereoisomers can be readily separated, a chiral metal hydride might not be required as the undesired compound can be recycled in an oxidation-reduction reaction sequence.

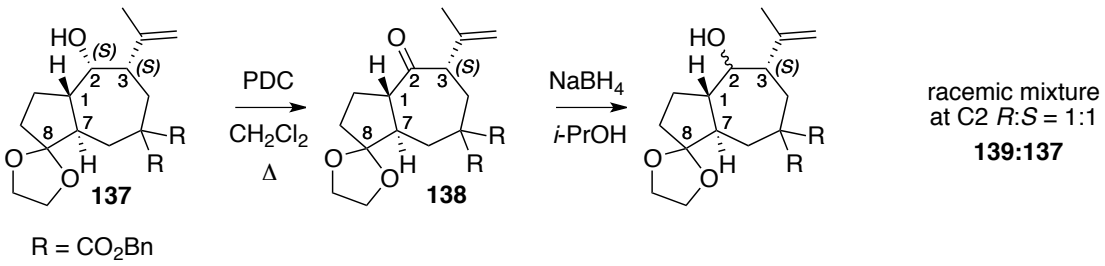
b. Application

Before any oxidation or reduction, the ketone moiety of the starting material **82b** was protected as an acetal **137** (Scheme 116). In the same way, **83b** was converted into **137'**. Unfortunately, this protection proceeded in moderate yields (58% yield for the (*S*,*S*) analogue **137** from **82b** and 37% yield for the (*R*,*R*) analogue **137'** from **83b**).



Scheme 116

The oxidation of the alcohol **137**, followed by the reduction of **138**, provided at last a mixture of the C2 epimers that included the compound **139** with the desired stereochemistry, a *trans*-relative configuration at C2 and C3 (Scheme 117). The alcohol **137** was quantitatively oxidized into **138** using pyridinium dichromate in dichloromethane. The obtained ketone **138** was subsequently reduced into **139** and **137** using sodium borohydride in *iso*-propanol. The oxidation-reduction reaction sequence proceeded in good yields, 81% and 76% yields respectively, using the (*R*,*R*) and the (*S*,*S*) starting materials. The epimers were formed in a ratio close to 1:1 and were readily separated by silica gel flash column chromatography: NMR, IR and mass spectrometry data were consistent with our expected results and allowed us to conclude that formation of the desired epimer **139** had occurred.



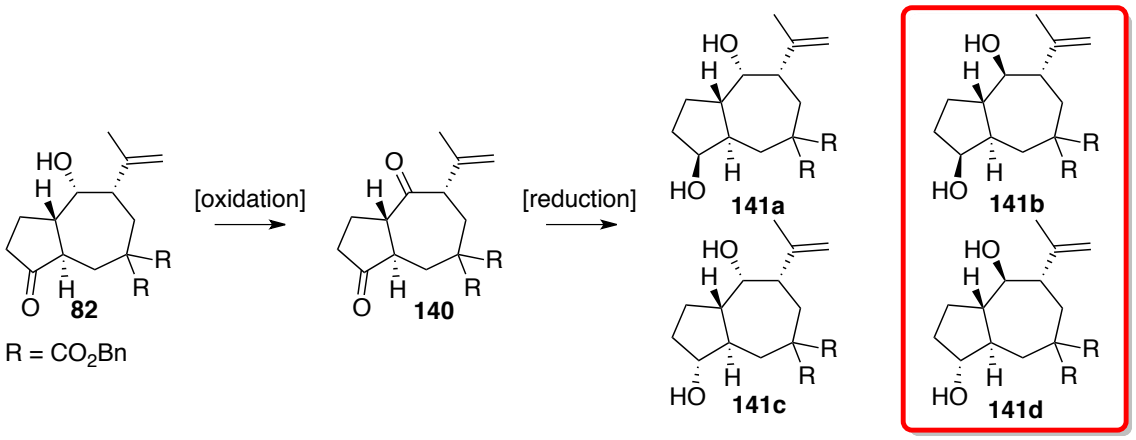
Scheme 117

Finally, the inversion of configuration at the carbon centre bearing the alcohol moiety has been successfully achieved and the desired isomer was isolated. We obtained the desired epimer **139** in only 40% yield. The other epimer **137** was obtained in 36% yield and can be re-engaged in an oxidation-reduction sequence, and therefore increasing the yield of the product **139**.

However, the sequence of reactions suffered a drawback: the protection step. This protection reaction would need to be optimized or avoided. Another optimization of the current work would be to selectively reduce **138** into only one epimer: **139**. This should be included in any future study on the subject.

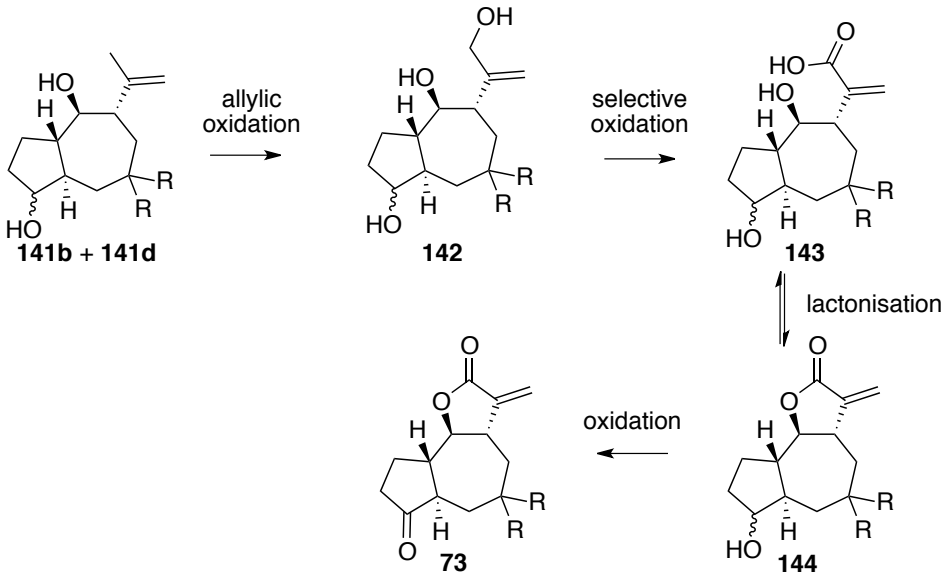
– Other route in perspective

In future work, we could potentially perform this oxidation-reduction sequence directly on **82b** with omission of the protection step (Scheme 118). The ketone at C8 would be also reduced but it should not interfere with the next steps. The omission of the protection step might avoid the loss of a high quantity of material, which is dramatic at such an advanced stage of the synthesis.



Scheme 118

In theory, the isomers **141b** and **141d** could be synthesized selectively. If we could isolate any (or both) of these isomers, we should be able to carry out the synthesis using the diols **141b** and **141d** (Scheme 119). The allylic oxidation should proceed in a similar manner to afford the triol **142**. The primary alcohol function of **142** could be selectively oxidized to form the carboxylid acid **143**, which should readily cyclize (lactonization) into the lactone **144**. Oxidation of the latter would yield the desired compound **73**, which is the skeleton we aimed for. This pathway would avoid the protection and deprotection steps of the ketone, which proceeded (for the protection) in moderate yield. These two limited steps would be replaced with one oxidation step that should proceed in a good yield.



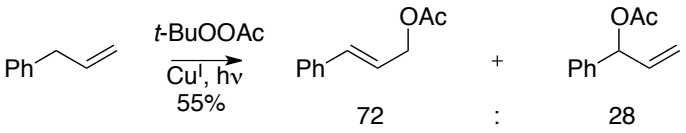
Scheme 119

VII) Allylic oxidation

1) Overview of allylic oxidation methodologies

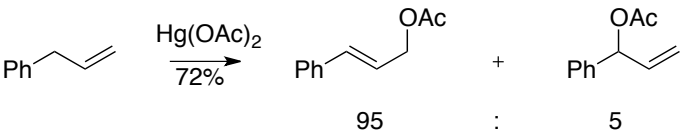
Allylic oxidation is a useful reaction in organic chemistry. It can yield an allylic alcohol or an α,β-unsaturated carbonyl from a carbon-carbon π-bond. In this part, we focused on the formation of allylic alcohols from alkenes.[92] Selenium dioxide is commonly considered as the most efficient reagent for such an oxidation. The selenium dioxide methodology is discussed separately.

A radical reaction was developed by Karasch and Sosnovsky to achieve allylic oxidation from an alkene and a peroxyester in the presence of a catalytic amount of a copper(I) salt (Scheme 120).[186] The main drawback of this methodology is that numerous undesired rearrangements can take place; as a consequence, the reaction is now rarely used.[92]



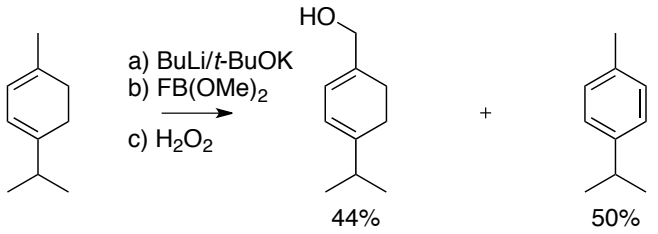
Scheme 120

Some metal acetates such as mercury(II) or palladium(II) acetates react with alkenes to afford the corresponding allylic acetates; a mixture of the expected allylic acetate and a product from a [1,3] rearrangement are generally observed (Scheme 121).[187]



Scheme 121

Allylic metals can undergo a transmetallation with a fluorodimethoxyborane. The corresponding allylic alcohol is usually obtained in low yields with unwanted by-products after oxidation of the boronic acid using hydrogen peroxide (Scheme 122).[188]

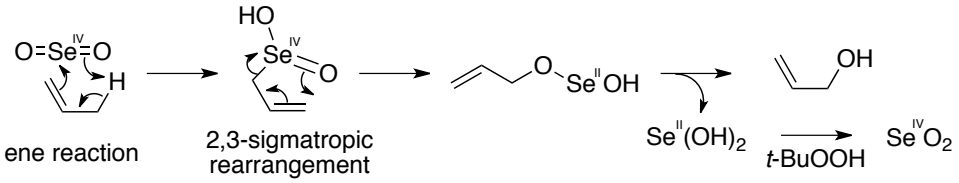


Scheme 122

2) Selenium oxidation mechanism

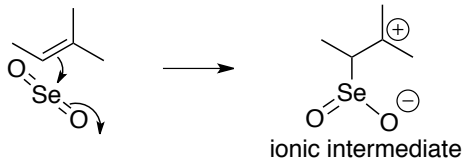
Oxidation using selenium dioxide is the most common procedure for the insertion of an oxygen atom into an allylic carbon-hydrogen bond.[189] It is generally a predictable reaction and provides the corresponding (*E*)-allylic alcohol (Scheme 123).[92]

The reaction mechanism has been shown by Sharpless to proceed through an ene reaction mechanism, followed by a [2,3]-sigmatropic rearrangement (Scheme 123).[190]



Scheme 123

Stephenson showed that an ionic intermediate could also be involved, which allows a rationalization of the stereoselective addition of the selenium dioxide to the π-bond (Scheme 124).[191] He reported that this ionic mechanism was suppressed in basic media.

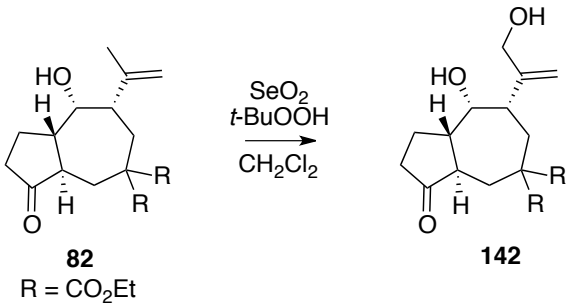


Scheme 124

In 1977, Sharpless reported a novel procedure involving selenium dioxide and *tert*-butyl hydroperoxide.[192] The reoxidation of the reduced selenium(II) regenerated the selenium(IV) dioxide, thus avoiding purification problems due to selenium(II) compounds and organoselenium side-products. He observed that the reaction was cleaner when using *tert*-butyl hydroperoxide with a catalytic amount of selenium dioxide, and reactions were faster in non-coordinating solvents such as dichloromethane. Side products of the selenium dioxide oxidation were principally dienes and over-oxidation of the allylic alcohol into enone, α,β-unsaturated acid or ether. In general, the best results were obtained when the reaction run to about 75% of conversion and stopped.[193,193]

3) Application

In our study towards the synthesis of the lactone moiety, we were interested in the oxidation of the *iso*-propene moiety into the allylic primary alcohol (Scheme 125).



Scheme 125

The allylic oxidation conditions were then screened (Table 16).

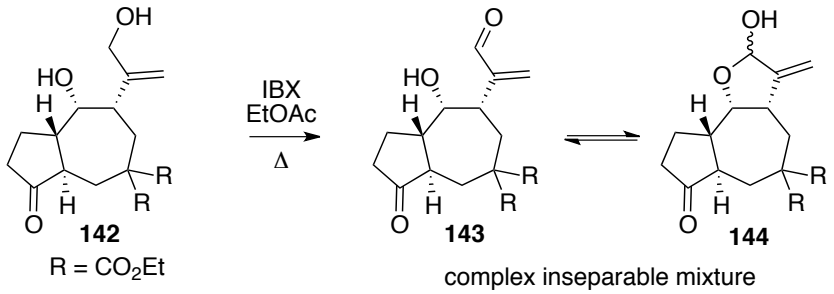
Entry	SeO_2	Oxidant (equiv)	Solvent	Conditions	Time	Yield
1	1 equiv	—	EtOH	r.t. to 80 °C	12 h	—
2	5 equiv	—	EtOH	r.t. to 80 °C	24 h	—
3	0.5 equiv	*t*-BuOOH aq (10 equiv)	CH_2Cl_2	0 °C to r.t.	5 d	—
4	0.5 equiv	*t*-BuOOH org (2 equiv)	CH_2Cl_2	0 °C to r.t.	2 d	21%
5	0.5 equiv	*t*-BuOOH org (2 equiv)	CH_2Cl_2	0 °C to r.t.	24 h	39%

Table 16

The best result is highlighted in the table (Entry **5**, Table 16): *tert*-butyl hydroperoxide was slowly added to a suspension of selenium dioxide in dichloromethane at 0 °C. The suspension was solubilized upon addition of the peroxide. The alkene **82** was added at 0 °C, and the solution was stirred at room temperature for a day (Scheme 125). The reaction was stopped before completion of the reaction and 28% of the starting material **82** was recovered (Entry **5**, Table 16). Accounting for the recovery of the starting material, the desired compound **142** was obtained in 56% yield. Longer reaction times only led to an increase of starting material decomposition.

The allylic alcohol **142** was then oxidized. A complex mixture, which we believed was a mixture of the corresponding aldehyde **143** and lactol **144**, was obtained. Interpretation of the ^1H

NMR spectrum of the crude mixture revealed that an aldehyde was present in low quantity, and the mass spectrum was consistent with the two products suggested (Scheme 126).

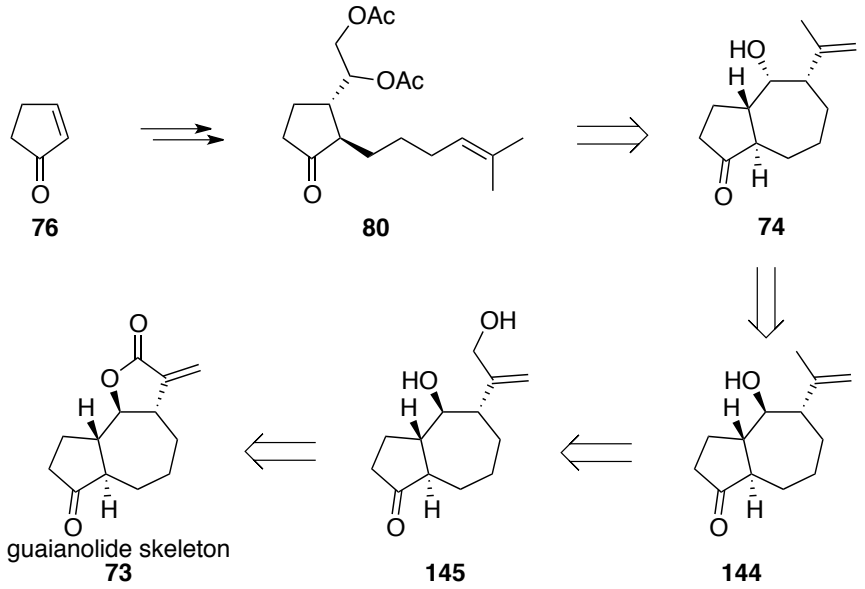


Scheme 126

VIII) Future work

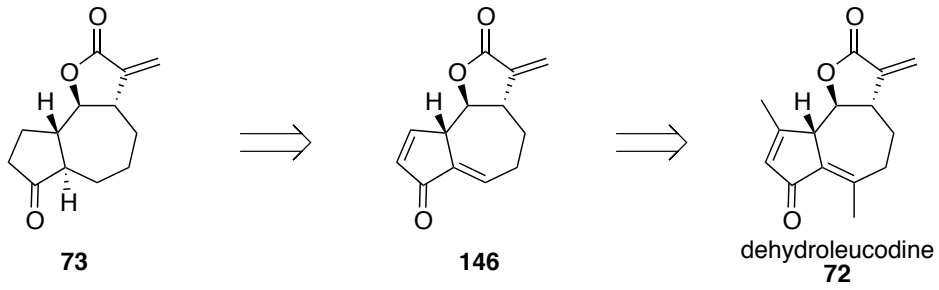
The work I have done and described herein should allow the synthesis of the guaianolide skeleton (Scheme 127).

The keto diacetate molecule **80** was synthesized from the cyclopentenone **76**. The deprotection of the molecule **80**, followed by an oxidative cleavage of the diol and an Alder ene cyclization of the unsaturated keto aldehyde compound would afford **74**. These reactions were optimized for the compounds bearing the dibenzyl and diethyl malonate moieties. The inversion of the alcohol configuration was studied, and the allylic oxidation conditions were optimized, so the compound **144** should be readily accessible. Allylic oxidation of **144** should provide **145**, and further oxidation of the bicyclic compound **145** should yield the tricyclic guaianolide skeleton **73**. All the tools are in place to permit the synthesis of the guaianolide skeleton, and the synthesis can be further explored, towards natural compounds.



Scheme 127

The natural product dehydroleucodine could be a target. The oxidation of the carbon-carbon bonds in the α-position with respect to the ketone would afford the α,β-unsaturated compound **146**, and two consecutive 1,4-oxidative additions would provide the natural product: dehydroleucodine **72** (Scheme 128).



Scheme 128

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CHAPTER III:

EXPERIMENTAL

EXPERIMENTAL

I) General experimental methods and materials

1) Generalities

Air sensitive reactions were carried out in flame-dried glassware under an argon atmosphere. Extractions were performed using the commercial solvent without further purifications except for petroleum ether, fractions 40/60, which was distilled from the commercial solvent. Reaction solvents were freshly distilled under an argon or nitrogen atmosphere before use from calcium hydride for dichloromethane, from sodium metal and benzophenone for THF, and from sodium for toluene. For reaction using DMS, the commercial dry solvent was used.

Compounds were purified by recrystallization when possible, but most of the purifications were run on flash column chromatography. Purified compounds were dried *in vacuo* at room temperature.

2) Chromatography procedures

Silica gel flash column chromatography were carried out using Merck Kieselgel 60, 40-63 µm particule size. Pressure was applied with hand bellows when needed. Crude materials were introduced as liquid when possible or as solid deposit, pre-absorbed onto silica gel. Thin layer chromatography was performed using Merck aluminium-backed plates coated with Kieselgel 60 F254 silica. Plates were visualized by U.V. irradiation at a wavelength of 254 nm, when compounds were U.V. active, or by dipping the plate in an acidic ethanolic solution of vanillin.

3) Analytical tools

Fourier transformation infrared spectroscopy was recorded using a Perkin Elmer System 2000 FT-IR spectrophotometer in the range 4000-400 cm^{-1}. All samples, solid or liquid, were run neat.

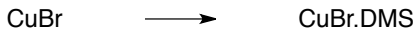
^{1}H and ^{13}C NMR spectra were recorded at 400.13 and 100.62 MHz using a Varian Unity Plus (400 MHz) spectrometer, or at 300.05 and 75.45 MHz using a Varian Gemini 200 (300 MHz) instrument respectively in $CDCl_3$. Chemical shifts are reported in ppm and referenced to the residual solvent $CHCl_3$ present in $CDCl_3$ at δ_H = 7.26 ppm and δ_C = 77.16 ppm. When possible, coupling constants (*J*) are shown denoting the multiplicity as: singlet (s), doublet (d), triplet (t), quarter (q), multiplet (m) or any combination of those such as doublet of doublet (dd), triplet of doublet (dt).

Melting points were recorded using an Electrothermal-IA 9100 melting point instrument.

High Resolution Mass Spectrometry (HRMS) was carried out by the EPSRC national mass spectrometry service at the University of Wales, Swansea, utilizing electrospray ionization (ESI) at times coupled with gas chromatography (GC-ESI), Atmospheric Solids Analysis Probe (ASAP).

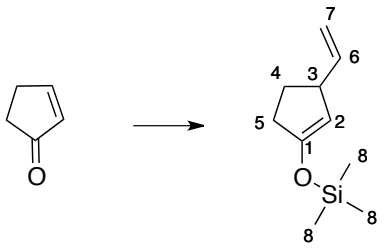
II) Preparation of the silyl enol ether

1) Copper(I) bromide dimethyl sulfide complex



Sodium sulfite (< 1 g) was added to a solution of commercial copper(I) bromide (dark grey powder, 4.0 g, 27.9 mmol) in conc. HBr (10 mL) until the solution changed colour, from purple to brown. The resulting brown solution was poured into water, filtered through a Büchner funnel and the residue was washed with ethanol and diethyl ether. The colourless powder was collected and dried at room temperature under reduced pressure for 1h. The dry solid was dissolved in DMS (15 mL) and heated under reflux for 20 min under a nitrogen atmosphere. The solution was poured into petroleum ether to afford a colourless precipitate that was collected by filtration, dried under reduced pressure and stored at room temperature in a desiccator (82%, 4.70g).

2) (±)-3-Ethenyl-1-trimethylsilyloxycyclopent-1-ene 77[1]

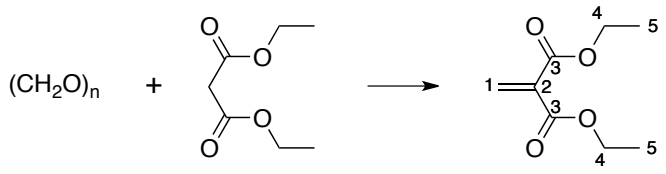


A solution of vinyl magnesium bromide (1 M in THF, 75.0 mL, 75.0 mmol, 1.25 equiv.) was added over 30 min at −78 °C to a solution of CuBr.DMS (1.23 g, 5.97 mmol, 0.1 equiv.) in THF (150 mL) under an argon atmosphere. The solution was stirred at −78 °C for 1 h. A mixture of DMPU (14.4 mL, 119 mmol, 2 equiv.), TMSCl (15.2 mL, 119 mmol, 2 equiv.) and cyclopentenone (5.0 mL, 59.7 mmol, 1 equiv.) was prepared directly in the addition funnel and this mixture was added slowly to the solution of copper(I) reagent previously prepared. The temperature was carefully controlled during the addition (not higher than −70 °C). The solution

was stirred at −78 °C for 1h, and allowed to reach −55 °C over 3 h. At −55 °C, triethylamine (16.6 mL, 119 mmol, 2 equiv.) was added to the solution, which was subsequently diluted with petroleum ether (100 mL), allowed to reach room temperature and petroleum ether (100 mL) added. The mixture was washed with water (3 x 150 mL), and the combined aqueous layers were extracted with petroleum ether (3 x 200 mL). The organic layers were collected, dried over anhydrous magnesium sulfate and concentrated to dryness to give a brown oil. The crude material was purified using a Kügelrohr distillation apparatus under reduced pressure (60-70 °C; 10 mbar) to afford (±)-3-ethenyl-1-trimethylsilyloxycyclopent-1-ene **77** as a colourless oil (9.88 g 91%). The pure compound must be stored under an argon atmosphere in the freezer to slow down any decomposition. b.p. = 62-65 °C (10 mbar); IR ν_{max} (neat) /cm^{-1} 1652 (*C*=*C*-OSi), 1635 (C=C), 1252 (Si-CH_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.55 (1 H, ddd, *J* = 17.1, 9.9, 7.0 Hz, H_6), 4.75 (1 H, dd, *J* = 17.1, 2.0 Hz, H_{7trans}), 4.64 (1 H, dd, *J* = 9.9, 2.0 Hz, H_{7cis}), 4.34 (1 H, d, *J* = 1.9 Hz, H_2), 3.03 (1 H, m, H_3), 2.05 (2 H, m, H_5), 1.88 (1 H, m, H_{4a}), 1.36 (1 H, m, H_{4b}), 0.00 (9 H, s, H_8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2 (C_1), 144.2 (C_6), 112.3 (C_7), 105.5 (C_2), 46.2 (C_3), 33.4 (C_5), 28.9 (C_4), 0.0 (C_8); HRMS (ESI) calcd for $C_{10}H_{18}OSi$ ([M^+]) 182.1127. Found: 182.1128.

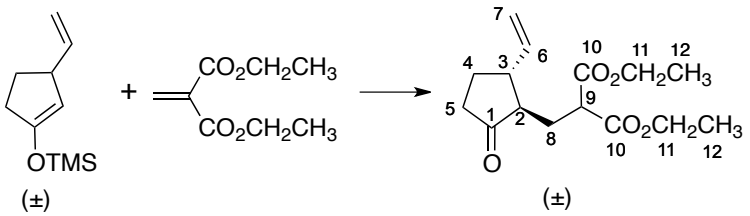
III) Towards the synthesis of the *trans*-bicyclo[5,3,0]decane skeleton using the diethyl malonate moiety

1) Diethyl methylidene malonate 105[2]



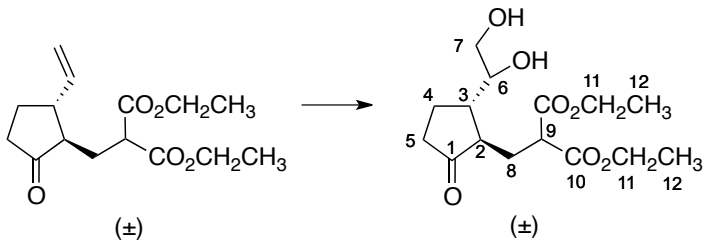
A mixture of paraformaldehyde (12.0 g, 395 mmol, 2 equiv.), diethyl malonate ester (30.0 mL, 198 mmol, 1 equiv.), copper(II) acetate (2.0 g, 10.9 mmol, 0.16 equiv.) and potassium acetate (2.20 g, 21.7 mmol, 0.13 equiv.) in acetic acid (100 mL) was heated at 90 °C with a reflux condenser for 1.5 h, and allowed to reach room temperature and concentrated to dryness under reduced pressure (55 °C, 10 mbar). For the purification, all the distillation apparatus was previously washed with an acidic solution and rinsed with acetone to reduce the polymerization risks. The distillation was performed under reduced pressure (10 mbar) first at 100 °C to remove the last traces of solvent. At 150 °C, the products started distilling and the temperature was increased to 180 °C. Purification *via* vacuum distillation afforded diethyl methylidene malonate **105** as a colourless oil (18.0 g, 53%). To avoid polymerization, the pure product needs to be stored under an argon atmosphere in the freezer. b.p.= 82-87 °C, 10 mbar; IR ν_{max} (neat) /cm^{-1} 1735 (3 C=O), 1250 (2 O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (2 H, s, H_1), 4.27 (4 H, q, J = 7.1 Hz, H_4), 1.31 (6 H, t, J = 7.1 Hz, H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3 (C_3), 135.4 (C_1), 134.3 (C_2), 61.6 (C_4), 14.1 (C_5).

2) (±)-*trans*-2-((Diethyl malonate)methyl)-3-vinyl-cyclopentanone 78a (R = CO_2Et)[1]



A solution of tin tetrachloride (6.35 mL, 54.2 mmol, 1 equiv.) in dry dichloromethane (55 mL) was added at −78 °C over 2 h to a solution of (±)-3-ethenyl-1-trimethylsilyloxycyclopent-1-ene **77** (9.88 g, 54.2 mmol, 1 equiv.) and diethyl methylidene malonate **105** (9.33 g, 54.2 mmol, 1 equiv.) in dry dichloromethane (271 mL) under an argon atmosphere. After addition, the solution was stirred at −78 °C for 3 h. The solution was poured into water (200 mL) and filtered through a pad of Celite®. The Celite® was thoroughly washed with dichloromethane (200 mL). The aqueous layer was extracted with dichloromethane (3 x 200 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated to dryness under reduced pressure. Purification by silica gel flash column chromatography, eluent: petroleum ether/ethyl acetate (9:1), afforded (±)-*trans*-2-((diethyl malonate)methyl)-3-vinyl-cyclopentanone **78a** (R = CO_2Et) as a pale yellow oil (9.94 g, 65%). IR ν_{max} (neat) /cm^{-1} 1732 (3 C=O), 1250 (2 O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (1 H, ddd, J = 7.9, 10.1, 18.0 Hz, H_6), 5.15 (1 H, d, J = 17.0 Hz, H_{7trans}), 5.09 (1 H, d, J = 10.1 Hz, H_{7cis}), 4.17 (4 H, q, J = 7.1 Hz, H_{11}), 3.92 (1 H, t, J = 7.5 Hz, H_9), 2.46-2.27 (2 H, m, H_3, H_{5a}), 2.23-2.02 (4 H, m, H_{4a}, H_{5b}, H_8), 1.99-1.89 (1 H, m, H_2), 1.71-1.53 (1 H, m, H_{4b}), 1.24 (6 H, 2 t, J = 7.1 Hz, H_{12}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.8 (C_1), 169.4 (C_{10}), 169.3 (C_{10}), 139.8 (C_6), 116.1 (C_7), 61.3 (2 C_{11}), 51.1 (C_2), 49.1 (C_9), 47.6 (C_3), 37.1 (C_5), 27.5 (C_4), 27.0 (C_8), 13.9 (2 C_{12}); HRMS (ESI) calcd for $C_{15}H_{26}O_5N$ ($[M+NH_4]^+$) 300.1805. Found: 300.1798.

3) (±)-*trans*-2-((Diethyl malonate)methyl)-3-(1',2'-dihydroxyethyl)-cyclopentanone 88a (R = CO_2Et)[1]



➢ Without optimization

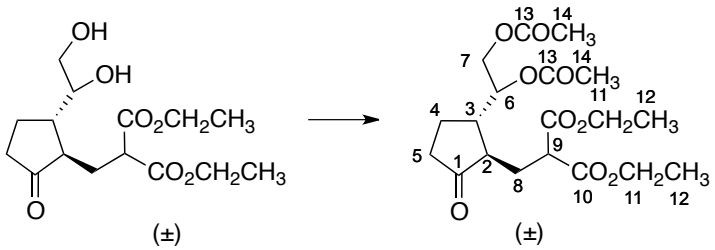
N-Methyl morpholine *N*-oxide monohydrate (1.25 g, 10.6 mmol, 3 equiv.) and osmium trichloride monohydrate 78 (R = CO_2Et) (55 mg, 177 μmol, 0.05 equiv.) were added at 0 °C to a solution of (±)-*trans*-2-((diethyl malonate)methyl)-3-vinyl-cyclopentanone **78a** (R = CO_2Et) (1 g, 3.54 mmol, 1 equiv.) in THF/water (1:1) (70:70 mL). The solution was stirred at room temperature for 24 h. The reaction mixture was diluted with dichloromethane (300 mL) and washed with an aqueous solution of HCl (1 M, 1 x 200 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure. Purification by silica gel flash column chromatography, eluent: petroleum ether/ethyl acetate (6:4), afforded (±)-*trans*-2-((diethyl malonate)methyl)-3-(1',2'-dihydroxyethyl)-cyclopentanone **88a** (R = CO_2Et) as a pale grey oil (0.75 g, 67%).

➢ After optimization

N-Methyl morpholine *N*-oxide monohydrate (3.47 g, 25.6 mmol, 3 equiv.) and osmium trichloride monohydrate 78 (R = CO_2Et) (40 mg, 128 μmol, 0.015 equiv.) were added at 0 °C to a solution of (±)-*trans*-2-((diethyl malonate)methyl)-3-vinyl-cyclopentanone **78a** (R = CO_2Et) (2.41 g, 8.54 mmol, 1 equiv.) in THF/water (1:1) (70:70 mL). The solution was stirred at room temperature for 20 h. The reaction mixture was quenched at 0 °C with sodium sulfite (3.23 g, 25.6 mmol, 3 equiv.), diluted with dichloromethane (300 mL) and washed with an aqueous solution of HCl (2 M, 2 x 200 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure. Purification by silica gel flash column chromatography, eluent: petroleum ether/ethyl acetate (6:4), afforded (±)-*trans*-2-((diethyl

malonate)methyl)-3-(1',2'-dihydroxyethyl)-cyclopentanone **88a** (R = CO_2Et) as a pale yellow oil (1.82 g, 80%). IR ν_{max} (neat) /cm^{-1} 3450 (2 O-H), 1735 (3 C=O) 1243 (2 O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 4.35-4.10 (4 H, m, H_{11}), 4.05-3.87 (2 H, m, H_6, H_9), 3.74-3.55 (2 H, m, H_7), 2.43-1.77 (8 H, m, H_2, H_3, H_4, H_5, H_8), 1.30-1.22 (6 H, m, H_{12}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.5 (C_1), 170.1 (C_{10}), 169.7 (C_{10}), 70.1 (C_6), 64.8 (C_7), 61.8 (C_{11}), 61.6 (C_{11}), 49.6 (C_9), 47.5 (C_2), 44.4 (C_3), 36.7 (C_8), 26.3 (C_5), 19.7 (C_4), 13.9 (C_{12}), 13.8 (C_{12}); HRMS (ESI) calcd for $C_{15}H_{25}O_7$ ($[M+H]^+$) 317.1595. Found: 317.1597.

4) <u>(±)-*trans*-2-((Diethyl malonate)methyl)-3-((1'RS),2'-diacetoxyethyl)-cyclopentanone 89a (R = CO_2Et)</u>[1]



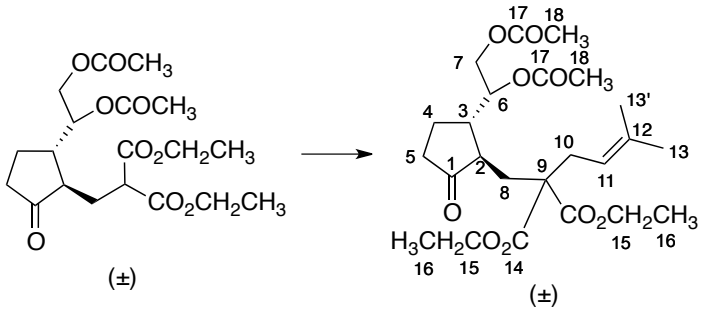
- <u>Without optimization</u>

(±)-*trans*-2-((Diethyl malonate)methyl)-3-(1',2'-dihydroxyethyl)-cyclopentanone **88a** (R = CO_2Et) (2 g, 6.33 mmol, 1 equiv.) was added to a 1:1 solution of acetic anhydride : pyridine (150:150 mL). The reaction mixture was stirred at room temperature overnight, quenched with 50 mL of water, extracted with dichloromethane (3 x 100 mL) and washed with a saturated aqueous solution of $CuSO_4$ (2 x 150 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure. Purification by silica gel flash column chromatography, eluent: petroleum ether/ethyl acetate (8:2 to 7:3), afforded (±)-*trans*-2-((diethyl malonate)methyl)-3-((1'*RS*),2'-diacetoxyethyl)-cyclopentanone **89a** (R = CO_2Et) as a colourless oil (1.62 g, 64%).

➢ After optimization

Pyridine (12.4 mL, 153 mmol, 10 equiv.) was added at 0 °C to a solution of (±)-*trans*-2-((diethyl malonate)methyl)-3-(1',2'-dihydroxyethyl)-cyclopentanone **88a** (R = CO_2Et) (4.84 g, 15.3 mmol, 1 equiv.) in dichloromethane (500 mL), and dimethylaminopyridine (1.12 g, 9.18 mmol, 0.6 equiv.) and acetic anhydride (6.4 mL, 67.3 mmol, 4.4 equiv.) were added. The reaction mixture was stirred at 0 °C for 30 min, quenched with 50 mL of water, extracted with dichloromethane (3 x 100 mL) and washed with a saturated aqueous solution of $CuSO_4$ (2 x 150 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure. Purification by silica gel flash column chromatography, eluent: petroleum ether/ethyl acetate (8:2 to 7:3), afforded (±)-*trans*-2-((diethyl malonate)methyl)-3-((1'*RS*),2'-diacetoxyethyl)-cyclopentanone **89a** (R = CO_2Et) as a colourless oil (4.03 g, 66%). IR ν_{max} (neat) /cm^{-1} 1735 (5 C=O), 1241 (4 C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30-5.05 (1 H, m, H_6), 4.45-3.85 (7 H, m, H_7, H_9, H_{11}), 2.45-1.70 (14 H, m, H_2, H_3, H_4, H_5, H_8, H_{14}), 1.30-1.20 (6H, t, *J* = 7.0, 11.0 Hz, H_{12}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.5 (C_1), 170.8 (C_{13}), 170.6 (C_{13}), 169.4 (C_{10}), 169.2 (C_{10}), 69.7 (C_6), 63.4 (C_7), 61.4 (C_{11}), 48.7 (C_9), 47.0 (C_2), 42.0 (C_3), 37.1 (C_8), 27.1 (C_5), 20.9 (C_4), 20.8 (C_{14}), 20.6 (C_{14}), 13.9 (C_{12}), 13.8 (C_{12}); HRMS (ESI) calcd for $C_{19}H_{32}O_9N$ ($[M+NH_4]^+$) 418.2072. Found: 418.2059.

5) (±)-*trans*-2-(6'-(5',5'-Bis(ethylcarboxylate)-hex-2'-ene))-3-((1"RS),2"-diacetoxyethyl)-cyclopentanone 79a (R = CO_2Et)[1]



- Without optimization

n-BuLi (140 μL, 1.5 mmol, 1.2 equiv.) was slowly added at −78 °C a solution of (±)-*trans*-2-((diethyl malonate)methyl)-3-((1'*RS*),2'-diacetoxyethyl)-cyclopentanone **89a** (R = CO_2Et) (0.5 g, 1.25 mmol, 1 equiv.) in dry THF (150 mL) under an argon atmosphere and the solution was stirred for 4 h at −78 °C. Prenyl bromide (120 μL, 1.5 mmol, 1.2 equiv.) was subsequently added at −78 °C and the reaction mixture was allowed to reach room temperature overnight. The reaction mixture was quenched at 0°C with water (30 mL), extracted with dichloromethane (3 x 200 mL) and washed with saturated aqueous NH_4Cl (200 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated to dryness under reduced pressure. Purification by silica gel flash column chromatography, eluent: petroleum ether/ethyl acetate (8:2), afforded (±)-*trans*-2-(6'-(5',5'-bis(ethylcarboxylate)-hex-2'-ene))-3-((1"*RS*),2"-diacetoxyethyl)-cyclopentanone **79a** (R = CO_2Et) as colourless oils (0.25 g, 42%).

- After optimization

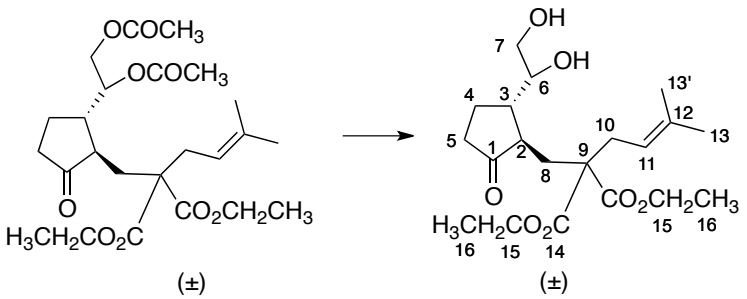
Solid NaH (95%, 230 mg, 9.10 mmol, 1.2 equiv.) was added at −78 °C in two portions to a solution of (±)-*trans*-2-((diethyl malonate)methyl)-3-((1'*RS*),2'-diacetoxyethyl)-cyclopentanone **89a** (R = CO_2Et) (3.04 g, 7.59 mmol, 1 equiv.) in dry THF (150 mL) under an argon atmosphere and the solution was stirred for 4 h at −78 °C. Prenyl bromide (750 μL, 9.10 mmol, 1.2 equiv.) was subsequently added at −78 °C and the reaction mixture was allowed to reach room temperature overnight. The reaction mixture was quenched at 0°C with water (30 mL), extracted with dichloromethane (3 x 200 mL) and washed with saturated aqueous NH_4Cl (200 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated to dryness under reduced pressure. Purification by silica gel flash column chromatography, eluent: petroleum ether/ethyl acetate (8:2), afforded (±)-*trans*-2-(6'-(5',5'-bis(ethylcarboxylate)-hex-2'-ene))-3-((1"*RS*),2"-diacetoxyethyl)-cyclopentanone **79a** (R = CO_2Et) as a separable mixture of diastereoisomers (55:45), as colourless oils (2.27 g, 64%).

First isomer eluting from the column: IR ν_{max} (neat) /cm^{-1} 1740 (5 C=O), 1244 (4 C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 5.18 (1 H, m, H_6), 4.91 (1 H, m, H_{11}), 4.20 (1 H, dd, *J* = 11.6, 5.1 Hz, H_{7a}), 4.15-4.02 (5 H, m, H_{7b}, H_{15}), 2.65-2.46 (2 H, m, H_{10}), 2.30-1.95 (14 H, m, H_2, H_3, H_4, H_5, H_8, H_{18}), 1.61 (3 H, s, H_{13} or $H_{13'}$), 1.53 (3 H, s, H_{13} or $H_{13'}$), 1.22-1.11 (6 H, m, H_{16}); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 218.4 (C_1), 171.4 (C_{17}), 171.2 (C_{17}), 170.6 (C_{14}), 170.4 (C_{14}), 135.5 (C_{12}), 117.6 (C_{11}), 70.5 (C_6), 63.3 (C_7), 61.3 (C_{15}) 61.1 (C_{15}), 56.4 (C_9), 46.7 (C_2), 42.9 (C_3), 36.1 (C_5), 32.5 (C_{10}), 31.8 (C_8), 25.8 (C_4), 20.7 (C_{17}), 20.6 (C_{17}), 17.8 (C_{13} and $C_{13'}$), 13.7 (2 x C_{16}); HRMS (ESI) calcd for $C_{24}H_{40}O_9N$ ($[M+NH_4]^+$) 486.2698. Found: 486.2689.

Second isomer eluting from the column: IR ν_{max} (neat) /cm^{-1} 1740 (5 C=O), 1244 (4 C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 5.18-5.10 (1 H, m, H_6) 5.02-4.92 (1 H, m, H_{11}), 4.39 (1 H, dd, *J* = 12.1, 3.1 Hz, H_{7a}), 4.25-4.05 (5 H, m, H_{15}, H_{7b}), 2.67 (2 H, d, *J* = 7.51 Hz, H_{10}), 2.33-1.86 (13 H, m, H_2, H_3, H_{4a}, H_5, H_8, H_{18}), 1.70-1.55 (7 H, m, H_{13}, $H_{13'}$, H_{4b}), 1.29-1.55 (6 H, m, H_{16}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.5 (C_1), 171.6 (C_{17}), 171.4 (C_{17}), 171.0 (C_{14}), 170.7 (C_{14}), 135.8 (C_{12}), 118.0 (C_{11}), 74.1 (C_6), 63.4 (C_7), 61.5 (C_{15}), 61.3 (C_{15}), 57.0 (C_9), 47.8 (C_2), 43.2 (C_3), 36.0 (C_5), 32.8 (C_{10}), 32.4 (C_8), 23.3 (C_4), 21.1 (C_{17}), 20.8 (C_{17}), 18.0 (C_{13} and $C_{13'}$), 14.0 (C_{16}), 13.97 (C_{16}); HRMS (ESI) calcd for $C_{24}H_{40}O_9N$ ($[M+NH_4]^+$) 486.2698. Found: 486.2689.

6) (±)-*trans*-2-(6'-(5',5'-Bis(ethylcarboxylate)-hex-2'-ene))-3-((1"RS),2"-dihydroxyethyl)-cyclopentanone 91a (R = CO_2Et)[1]



Amberlite® 400 Cl (10 g) was activated by stirring for 3 h in an aqueous solution of NaOH (2 M, 200 mL). The resin was filtered, and washed with ethanol and diethyl ether.

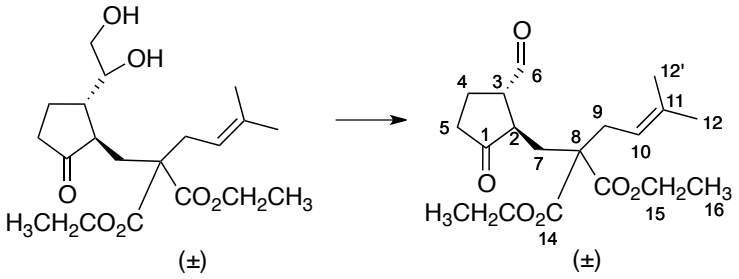
The activated Amberlite® 400 Cl was added to a solution of the mixture of both isomers (±)-*trans*-2-(6'-(5',5'-bis(ethylcarboxylate)-hex-2'-ene))-3-((1"*RS*),2"-diacetoxyethyl)-cyclopentanone **79a** (R = CO_2Et) (2.27 g, 4.85 mmol) in methanol (100 mL). The solution was stirred for 2 days. The solution was filtered through a pad of Celite® to remove all the Amberlite®, and the residue was washed with methanol. The filtrate was dried over anhydrous

sodium sulfate and concentrated to dryness to afford (±)-*trans*-2-(6'-(5',5'-bis(ethylcarboxylate)-hex-2'-ene))-3-((1"*RS*),2"-dihydroxyethyl)-cyclopentanone as a colourless **91a** (R = CO_2Et) oil in 95% yield (1.76 g) as a mixture of isomers. The ratio was not precisely determined because most of the mixture was hardly separable. However, a small sample of each isomer was isolated for the characterisation.

First isomer eluting from the column: IR ν_{max} (neat) /cm^{-1} 3459 (2 O-H), 1732 (3 C=O), 1297 (2 C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.92 (1 H, m, H_{11}), 4.28-4.00 (5 H, m, H_6, H_{15}), 3.75 (1 H, dd, *J* = 11.1, 9.0 Hz, H_{7a}), 3.59 (1 H, dd, *J* = 11.1, 3.4 Hz, H_{7b}), 2.74 (1 H, dd, *J* = 14.7, 7.3 Hz, H_{10a}), 2.61 (1 H, dd, *J* = 14.7, 8.6 Hz, H_{10b}), 2.53-2.46 (1 H, m, H_2), 2.36-2.29 (1 H, m, H_{5a}), 2.08-1.86 (4 H, m, H_4, H_{5b}, H_{8a}), 1.80-1.71 (2 H, m, H_3, H_{8b}), 1.70 (3 H, s, H_{13} or $H_{13'}$), 1.61 (3 H, s, H_{13} or $H_{13'}$), 1.27-1.17 (6 H, m, H_{16}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.0 (C_1), 174.4 (C_{14}), 171.7 (C_{14}), 136.8 (C_{12}), 117.6 (C_{11}), 65.0 (C_6), 62.2 (C_{15}), 62.1 (C_{15}), 60.7 (C_7), 58.5 (C_9), 51.0 (C_2), 45.6 (C_3), 36.4 (C_5), 34.4 (C_{10}), 33.2 (C_4), 29.9 (C_8), 23.7 (C_{13} or $C_{13'}$), 18.3 (C_{13} or $C_{13'}$), 14.3 (C_{16}), 14.2 (C_{16});

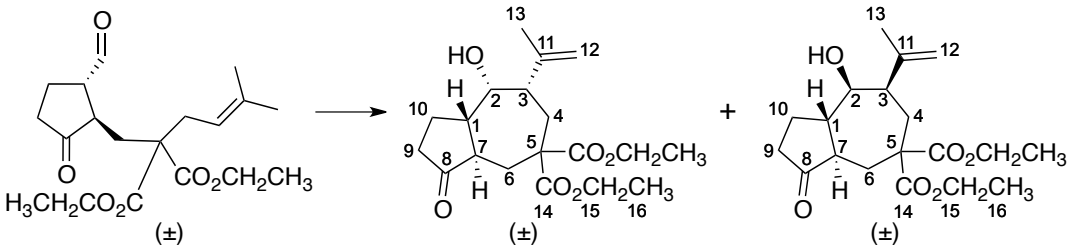
Second isomer eluting from the column: IR ν_{max} (neat) /cm^{-1} 3459 (2 O-H), 1732 (3 C=O), 1297 (2 C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.93 (1 H, m, H_{11}), 4.28-4.05 (5 H, m, H_6, H_{15}), 3.77 (1 H, m, H_{7a}), 3.55 (1 H, m, H_{7b}), 2.72 (1 H, dd, *J* = 7.6 Hz, H_{10a}), 2.58 (1 H, dd, *J* = 7.6 Hz, H_{10b}), 2.50-2.29 (3 H, m, H_2, H_5), 2.15-1.89 (5 H, m, H_3, H_4, H_8), 1.69 (3 H, s, H_{13} or $H_{13'}$), 1.60 (3 H, s, H_{13} or $H_{13'}$), 1.37-1.22 (6 H, m, H_{16}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.5 (C_1), 174.0 (C_{14}), 171.3 (C_{14}), 136.4 (C_{12}), 117.3 (C_{11}), 64.6 (C_6), 61.8 (C_{15}), 61.7 (C_{15}), 60.3 (C_7), 58.1 (C_9), 50.6 (C_2), 45.2 (C_3), 36.0 (C_5), 34.6 (C_{10}), 32.8 (C_4), 29.6 (C_8), 25.9 (C_{13} or $C_{13'}$), 17.9 (C_{13} or $C_{13'}$), 13.9 (C_{16}), 13.8 (C_{16}); HRMS (ESI) calcd for $C_{20}H_{33}O_7$ ($[M+H]^+$) 385.2224. Found: 385.2221.

7) (±)-*trans*-2-(6'-(5',5'-Bis(ethylcarboxylate)-hex-2'-ene))-3-formyl-cyclopentanone 81a (R = CO_2Et)[1]



Sodium metaperiodate (18.6 g, 86.5 mmol, 10 equiv.) was added at 0 °C to a solution of (±)-*trans*-2-(6'-(5',5'-bis(ethylcarboxylate)-hex-2'-ene))-3-((1"*RS*),2"-dihydroxyethyl)-cyclopentanone **91a** (R = CO_2Et) (3.33 g, 8.65 mmol, 1 equiv.) in THF/water (1:1) (440 mL). The reaction mixture was stirred at room temperature for 4.5 h at room temperature, and diluted with dichloromethane (500 mL) and washed with brine (2 x 300 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure. Purification by silica gel flash column chromatography, eluent petroleum ether/ethyl acetate (8:2), afforded (±)-*trans*-2-(6'-(5',5'-bis(ethylcarboxylate)-hex-2'-ene))-3-formyl-cyclopentanone **81a** (R = CO_2Et) as a colourless oil (2.97 g, 98%). IR ν_{max} (neat) /cm^{-1} 1727 (4 C=O), 1221 (2 C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (1 H, d, *J* = 3.9 Hz, H_6), 4.97 (1 H, m, H_{10}), 4.25-4.05 (4 H, m, H_{14}), 2.91-2.80 (1 H, m, H_3), 2.71-2.53 (3 H, m, H_2, H_9), 2.44-2.30 (1 H, m, H_{5a}), 2.29-2.08 (3 H, m, H_{4a}, H_{5b}, H_{7a}), 2.04-1.89 (2 H, m, H_{4b}, H_{7b}), 1.67 (3 H, s, H_{12} or $H_{12'}$), 1.60 (3 H, s, H_{12} or $H_{12'}$), 1.24 (6 H, t, *J* = 9.5 Hz, H_{15}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.3 (C_1), 201.3 (C_6), 171.4 (C_{13}), 171.3 (C_{13}), 135.9 (C_{11}), 117.4 (C_{10}), 61.5 (C_{14}), 61.3 (C_{14}), 56.9 (C_8), 54.9 (C_3), 46.0 (C_2), 35.7 (C_5), 32.0 (C_9), 31.5 (C_7), 25.9 (C_{12} or $C_{12'}$) 21.1 (C_4) 17.8 (C_{12} or $C_{12'}$) 13.80 (2 x C_{15}); HRMS (ESI) calcd for $C_{19}H_{27}O_6$ ([M+H^+]) 352.1886. Found: 352.1891.

8) (±)-(2R)-Hydroxy-(3R)-isopropenyl-5,5-bis(ethylcarboxylate)-8-oxo-*trans*-bicyclo[5,3,0]decane 83a (R = CO_2Et) and (±)-(2S)-hydroxy-(3S)-isopropenyl-5,5-bis(ethylcarboxylate)-8-oxo-*trans*-bicyclo[5,3,0]decane 82a (R = CO_2Et)[1]



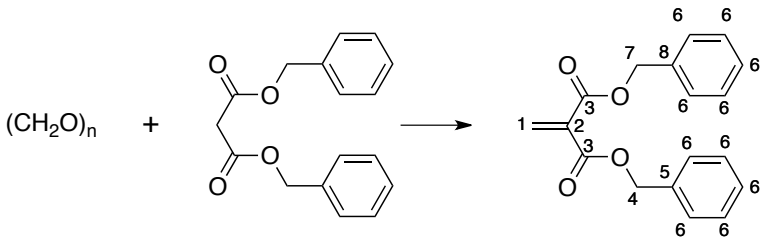
Boron trifluoride diethyl etherate (10.7 mL, 84.2 mmol, 10 equiv.) was added at −78 °C to a solution of (±)-*trans*-2-(6'-(5',5'-bis(ethylcarboxylate)-hex-2'-ene))-3-formyl-cyclopentanone **81a** (R = CO_2Et) (2.97 g, 8.42 mmol, 1 equiv.) in dry THF (170 mL) under an argon atmosphere. The solution was allowed to reach room temperature and stirred for 2 days. The solution was diluted with dichloromethane (300 mL) and washed with a saturated solution of $NaHCO_3$ (3 x 200 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give a crude yellow oil. Purification by silica gel flash column chromatography, eluent: petroleum ether/ethyl acetate (8:2 to 6:4), afforded (±)-(2*R*)-hydroxy-(3*R*)-isopropenyl-5,5-bis(ethylcarboxylate)-8-oxo-*trans*-bicyclo [5,3,0]decane **83a** (R = CO_2Et) (1.25 g, 42%) and (±)-(2*S*)-hydroxy-(3*S*)-isopropenyl-5,5-bis(ethylcarboxylate)-8-oxo-*trans*-bicyclo[5,3,0]decane **82a** (R = CO_2Et) (1.29 g, 44%).

(±)-(2*R*)-Hydroxy-(3*R*)-isopropenyl-5,5-bis(ethylcarboxylate)-8-oxo-*trans*-bicyclo[5,3,0] decane **83** (R = CO_2Et): IR ν_{max} (neat) /cm^{-1} 3542 (O-H), 1730 (3 C=O), 1245 (2 C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 4.95 (1 H, m, H_{12a}), 4.82 (1 H, s, H_{12b}), 4.22-4.05 (4 H, m, H_{15}), 3.86 (1 H, s, H_2), 2.66 (1 H, dd, *J* = 15.2, 2.9 Hz, H_{6a}), 2.51-2.35 (3 H, m, H_{4a}, H_7, H_{9a}), 2.21-2.10 (3 H, m, H_3, H_{4b}, H_{9b}), 2.06-1.90 (4 H, m, H_1, H_{6b}, H_{10}), 1.82 (3 H, s, H_{13}), 1.22 (6 H, m, H_{16}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.0 (C_8), 172.8 (C_{14}), 172.8 (C_{14}), 149.2 (C_{11}), 111.6 (C_{12}), 68.1 (C_2), 61.7 (C_{15}), 61.5 (C_{15}), 55.5 (C_5), 50.2 (C_1), 47.3 (C_3), 45.2 (C_7) 37.5 (C_9), 32.9 (C_6), 29.4 (C_4), 23.6 (C_{13}), 22.7 (C_{10}), 14.1 (C_{16}), 14.1 (C_{16}); HRMS (ASAP) calcd for $C_{19}H_{29}O_6$ ($[M+H]^+$) 353.1959. Found: 353.1959.

(±)-(2*S*)-Hydroxy-(3*S*)-isopropenyl-5,5-bis(ethylcarboxylate)-8-oxo-*trans*-bicyclo[5,3,0] decane **82** (R = CO_2Et): IR ν_{max} (neat) /cm^{-1} 3533 (O-H), 1731 (3 C=O), 1255 (2 C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 4.96 (1 H, m, H_{12a}), 4.85 (1 H, s, H_{12b}), 4.20-4.11 (4 H, m, H_{15}), 3.36 (1 H, t, *J* = 9.5 Hz, H_2), 2.73 (1 H, d, *J* = 13.1 Hz, H_{6a}), 2.51-2.39 (2 H, m, H_{9a}, H_{10a}), 2.29 (1 H, m, H_{4a}) 2.24-2.19 (2 H, m, H_3, H_{9b}), 2.16-2.09 (3 H, m, H_{4b}, H_{6b}, H_7), 1.77 (3 H, s, H_{13}), 1.74 (1 H, m, H_1), 1.57 (1 H, m, H_{10b}), 1.23 (6 H, m, H_{16}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.5 (C_8), 172.4 (C_{14}), 171.9 (C_{14}), 146.6 (C_{11}), 113.7 (C_{12}), 77.3 (C_2), 61.6 (C_{15}), 61.5 (C_{15}), 54.9 (C_5), 51.7 (C_1), 49.4 (C_3), 47.7 (C_7), 36.6 (C_9), 34.2 (C_4), 31.5 (C_6), 26.2 (C_{13}), 19.1 (C_{10}), 13.9 (C_{16}), 13.8 (C_{16}); HRMS (ASAP) calcd for $C_{19}H_{29}O_6$ ($[M+H]^+$) 353.1959. Found: 353.1959.

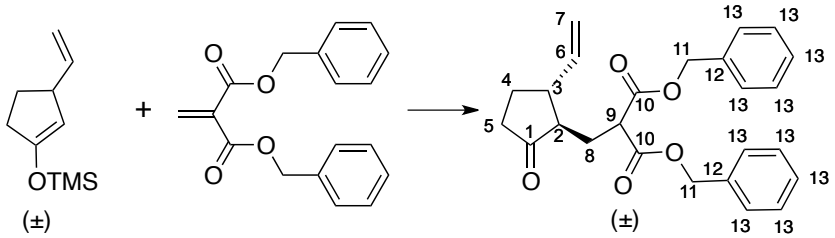
IV) Towards the synthesis of the *trans*-bicyclo[5,3,0]decane skeleton using the dibenzyl malonate moiety

1) Dibenzyl methylidene malonate 107[3]



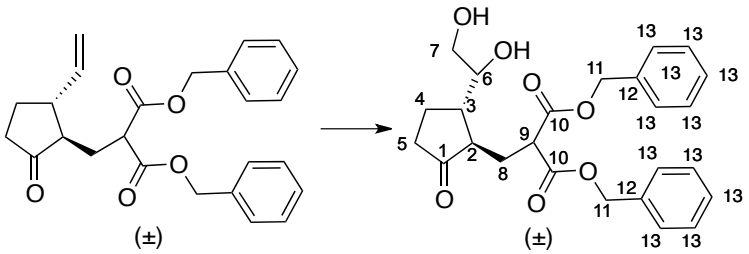
Diisopropyl amine (12.7 mL, 90.0 mmol, 1.5 equiv.), half of the paraformaldehyde (in total 7.20 g, 240 mmol, 4 equiv.) and TFA (7.4 mL, 96.0 mmol, 1.6 equiv.) were added to a solution of dibenzyl malonate ester **106** (15 mL, 60.0 mmol, 1 equiv.) in THF (500 mL) under an argon atmosphere. The mixture was heated to reflux. When the solution was at reflux, the other half of the paraformaldehyde was added to the mixture and the solution was stirred under reflux for 2 days. The solution was cooled down to room temperature, concentrated under reduced pressure, diluted with dichloromethane (600 mL), washed with saturated aqueous $CuSO_4$ (2 x 350 mL), dried over $MgSO_4$ and concentrated to dryness under reduced pressure to afford quantitatively dibenzyl methylidene malonate **107** (17.8 g) as a colourless oil. The product was enough pure to be used in the next reaction without any further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (10 H, m, H_6), 6.60 (2 H, s, H_1), 5.26 (4 H, s, H_4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (C_5), 135.7 (C_1), 135.4 (C_3), 134.5 (C_2), 128.7 (C_6), 128.6 (C_6), 128.5 (C_6), 128.4 (C_6), 128.3 (C_6), 128.2 (C_6), 67.3 (C_4); HRMS (ESI) calcd for $C_{18}H_{16}O_4Na$ ($[M+Na]^+$) 319.0941. Found: 319.0940.

2) (±)-*trans*-2-(Dibenzyl malonate)methyl-3-vinyl-cyclopentanone 78b (R = CO_2Bn)



Dibenzyl methylidene malonate **107** (17.8 g, 60.0 mmol, 1 equiv.) was added at −20 °C to a solution of (±)-3-ethenyl-1-trimethylsilyloxycyclopent-1-ene **77** (12.0 g, 66.0 mmol, 1.1 equiv.) in dichloromethane (150 mL) under an argon atmosphere. At −78°C, a solution of $SnCl_4$ (7.1 mL, 60.0 mmol, 1 equiv.) in dichloromethane (10 mL) was added over 2 h to the reaction mixture. After the addition, the reaction mixture was stirred at −78 °C for 2.5 h and poured onto water (200 mL). The resulting mixture was filtered through a pad of Celite® and the Celite® was thoroughly washed with dichloromethane (200 mL). The aqueous layer was extracted with dichloromethane (3 x 200 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated to dryness under reduced pressure. Purification by silica gel flash column chromatography, eluent: petroleum ether/ethyl acetate (9:1), afforded (±)-*trans*-2-((dibenzyl malonate)methyl)-3-vinyl-cyclopentanone **78b** (R = CO_2Bn) as a colourless oil (16.1 g, 67%); IR ν_{max} (neat) /cm^{-1} 1732 (3 C=O), 1247 (2 O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.26 (10 H, m, H_{13}), 5.63 (1 H, ddd, *J* = 8, 10.2, 17.1 Hz, H_6), 5.15-5.10 (4 H, m, H_{11}), 5.09-5.01 (2 H, m, H_7), 4.07 (1 H, dd, *J* = 7.4, 7.9 Hz, H_9), 2.43-2.26 (2 H, m, H_3, H_{5a}), 2.20-2.02 (4 H, m, H_{4a}, H_{5b}, H_8), 1.94-1.83 (1 H, m, H_2), 1.61-1.51 (1 H, m, H_{4b}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.7 (C_1), 169.2 (C_{10}), 169.1 (C_{10}), 139.7 (C_6), 135.4 (C_{12}), 128.5 (C_{13}), 128.4 (C_{13}), 128.3 (C_{13}), 128.3 (C_{13}), 128.2 (C_{13}), 116.2 (C_7), 67.3 (C_{11}), 67.0 (C_{11}), 51.1 (C_2), 49.1 (C_9), 47.6 (C_3), 37.1 (C_5), 27.5 (C_4), 27.1 (C_8); HRMS (ASAP) calcd for $C_{25}H_{27}O_5$ ($[M+H]^+$) 407.1853. Found: 407.1849.

3) (±)-*trans*-2-((Dibenzyl malonate)methyl)-3-(1',2'-dihydroxyethyl)-cyclopentanone 88b (R = CO_2Bn)

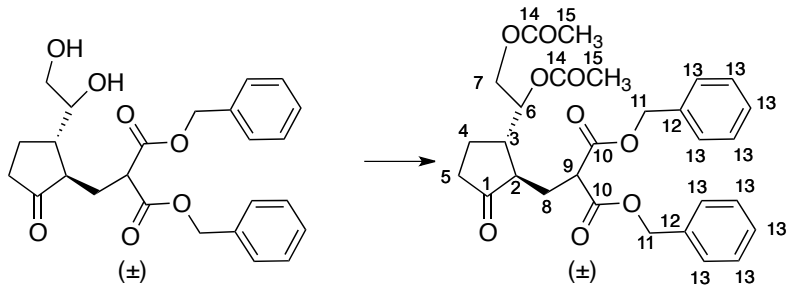


(±)-*trans*-2-((Dibenzyl malonate)methyl)-3-vinyl-cyclopentanone (14.4 g, 35.4 mmol, 1 equiv.) was divided in two similar portions in two different flasks.

N-Methyl morpholine oxide (14.4 g, 106 mmol, 3 equiv.) and osmium trichloride monohydrate (249 mg, 0.71 mmol, 0.02 equiv.) were added at 0 °C to the solutions of (±)-*trans*-2-((dibenzyl malonate)methyl)-3-vinyl-cyclopentanone **78b** (R = CO_2Bn) (14.4 g, 35.4 mmol, 1 equiv.) in THF/water (1:1) (600 mL). The solutions were stirred overnight at room temperature. The reaction mixtures were quenched at 0 °C with Na_2SO_3 (13.4 g, 106 mmol, 3 equiv.) and diluted with dichloromethane (250 mL each one) and collected together for the work up and the purification. The mixture was extracted with dichloromethane (3 x 400 mL), washed with an aqueous solution of HCl 2 M (3 x 400 mL) and brine (400 mL), dried over Na_2SO_4 and concentrated to dryness under reduced pressure to afford a pale yellow oil. Purification by silica gel flash column chromatography, eluent: petroleum ether/ethyl acetate (3:7), afforded an inseparable mixture of isomers (±)-*trans*-2-((dibenzyl malonate)methyl)-3-(1',2'-dihydroxyethyl)-cyclopentanone **88b** (R = CO_2Bn)as colourless oil (12.4 g, 80%); IR ν_{max} (neat) /cm^{-1} 3425 (2 O-H), 1725 (3 C=O), 1152 (2 O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (10 H, m, H_{13}), 5.12 (4 H, m, H_{11}), 4.06 (1 H, m, H_9), 3.89-3.51 (3 H, m, H_6, H_7), 3.27 (1 H, b, C_6-O-H), 2.76 (1 H, b, C_7-O-H), 2.39-1.78 (8 H, m, H_2, H_3, H_4, H_5, H_8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.2 (C_1), 219.9 (C_1), 170.3 (C_{10}), 169.9 (C_{10}), 169.6 (C_{10}), 169.5 (C_{10}), 134.4 (C_{12}), 128.8 (C_{13}), 128.6 (C_{13}), 128.5 (C_{13}), 128.5 (C_{13}), 128.4 (C_{13}), 76.8 (C_6), 70.4 (C_6), 67.6 (C_{11}), 67.5 (C_{11}), 65.1 (C_7), 64.8 (C_7), 50.0 (C_9), 49.6 (C_9), 49.9 (C_2), 47.5 (C_2), 44.9 (C_3), 44.5 (C_3), 37.4

(C_8), 37.0 (C_8), 29.1 (C_5), 26.8 (C_5), 23.8 (C_4), 19.9 (C_4); HRMS (ESI) calcd for $C_{25}H_{29}O_7$ ($[M+H]^+$) 441.1908. Found: 441.1908.

4) (±)-*trans*-2-((Dibenzyl malonate)methyl)-3-(1',2'-diacetoxyethyl)-cyclopentanone 89b (R = CO_2Bn)

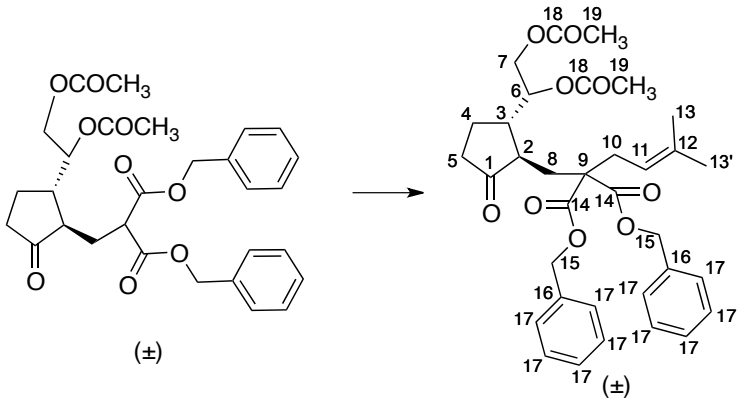


(±)-*trans*-2-((Dibenzyl malonate)methyl)-3-(1',2'-diacetoxyethyl)-cyclopentanone **88b** (R = CO_2Bn) (9.79 g, 22.2 mmol, 1 equiv.) was divided in six similar portions (around 1.5 g) in six different flasks. When the reaction was attempted on larger scale, the yield would drop to 30%.

Pyridine (17.9 mL, 222 mmol, 10 equiv.), DMAP (1.60 g, 13.1 mmol, 0.6 equiv.) and acetic anhydride (9.2 mL, 97.5 mmol, 4.4 equiv.) were added at 0 °C to the solutions of (±)-*trans*-2-((dibenzyl malonate)methyl)-3-(1',2'-dihydroxyethyl)-cyclopentanone **88b** (R = CO_2Bn) (9.79 g, 22.2 mmol, 1 equiv.) in dichloromethane (200 mL). The reaction mixtures were stirred at 0 °C for 15 min and quenched with water. All the reaction mixtures were collected together for the work-up and the purification. The mixture was extracted with dichloromethane (3 x 250 mL), washed with a saturated solution of $CuSO_4$ (2 x 150 mL), dried over Na_2SO_4 and concentrated to dryness to afford a colourless oil. Purification by silica gel flash column chromatography, eluent: petroleum ether/ethyl acetate (7:3), afforded an inseparable mixture (ratio 6:4) of isomers (±)-*trans*-2-((dibenzyl malonate)methyl)-3-(1',2'-diacetoxyethyl)-cyclopentanone **89b** (R = CO_2Bn) as a colourless oil (11.0 g, 95%) ; IR ν_{max} (neat) /cm^{-1} 1732 (5 C=O), 1220 (4 O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.23 (10 H, m, H_{13}), 5.24-5.20 (0.6 H, m, H_6), 5.13-5.08 (4 H, m, H_{11}), 5.04-5.01 (0.4 H, m, $H_{6'}$), 4.33 (0.4 H, dd, *J* = 2.8, 12.1 Hz, $H_{7a'}$), 4.24 (0.6 H, dd, J = 4.5, 11.7 Hz, H_{7a}), 4.12-3.99 (2 H, m, H_{7b}, H_9), 2.40-1.94 (13 H, m, H_2, H_3, H_{4a}, H_5, H_8, H_{15}), 1.80-1.70 (0.6 H, m, H_{4b}), 1.54-1.49 (0.4 H, m, $H_{4b'}$); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 218.6 (C_1), 218.4 (C_1), 171.0 (C_{14}), 170.9 (C_{14}), 170.8 (C_{14}), 170.5 (C_{14}), 169.3 (C_{10}), 169.3 (C_{10}), 169.2 (C_{10}), 169.1 (C_{10}), 135.6 (C_{12}), 135.5 (C_{12}), 128.7 (C_{13}), 128.5 (C_{13}), 128.4 (C_{13}), 74.9 (C_6), 69.8 (C_6), 67.4 (C_{11}), 67.3 (C_{11}), 63.7 (C_7), 63.5 (C_7), 49.1 (C_9), 49.0 (C_9), 49.0 (C_2), 47.1 (C_2), 43.2 (C_3), 42.0 (C_3), 37.2 (C_8), 37.0 (C_8), 29.3 (C_5), 27.3 (C_5), 23.9 (C_4), 21.2 (C_4), 21.0 (C_{15}), 20.8 (C_{15}); HRMS (ESI) calcd for $C_{29}H_{36}O_9N$ ($[M+NH_4]^+$) 542.2385. Found: 542.2377.

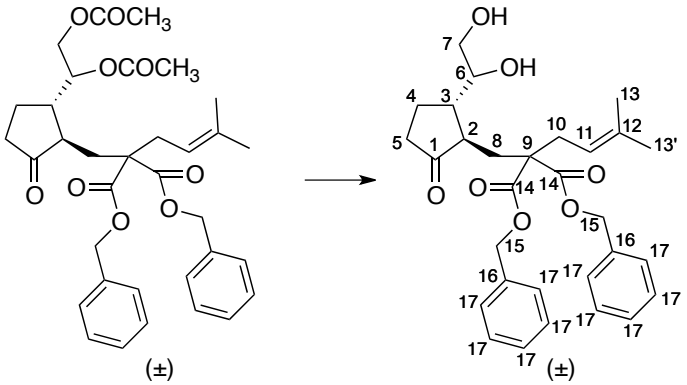
5) <u>(±)-*trans*-2-(6'-(5',5'-Bis(benzylcarboxylate)-hex-2'-ene))-3-(1",2"-diacetoxyethyl)-cyclopentanone 79b (R = CO_2Bn)</u>



NaH (784 mg, 31.0 mmol, 1.2 equiv.) was added at 0 °C to a solution of (±)-*trans*-2-((dibenzyl malonate)methyl)-3-(1',2'-diacetoxyethyl)-cyclopentanone **89b** (R = CO_2Bn) (13.6 g, 25.8 mmol, 1 equiv.) in THF (520 mL) under an argon atmosphere. The resulting colourless suspension was stirred for 24 h at room temperature to afford a clear yellow solution. Prenyl bromide (3.3 mL, 28.4 mmol, 1.1 equiv.) was added at 0 °C to the reaction mixture and the crude solution was stirred at room temperature overnight. The reaction mixture was quenched at 0°C with water (200 mL), extracted with dichloromethane (3 x 250 mL), washed with a saturated aqueous solution of saturated aqueous NH_4Cl (200 mL), dried over Na_2SO_4 and concentrated to dryness under reduced pressure to afford a yellow oil. Purification by silica gel flash column chromatography, eluent: petroleum ether/ethyl acetate (75:25), afforded an inseparable mixture (ratio 6:4) of isomers (±)-*trans*-2-(6'-(5',5'-bis(benzylcarboxylate)-hex-2'-ene))-3-(1",2"-diacetoxyethyl)-cyclopentanone **79b** (R = CO_2Bn) as a colourless oil (12.3 g, 80%); IR ν_{max}

(neat) /cm^{-1} 1741 (5 C=O), 1221 (4 O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.20 (10 H, m, H_{17}), 5.22-5.18 (0.6 H, m, H_6), 5.10-4.98 (4.4 H, m, H_{15}, $H_{6'}$), 4.90-4.83 (1 H, m, H_{11}), 4.36 (0.4 H, dd, *J* = 2.9, 12.1 Hz, $H_{7a'}$), 4.20 (0.6 H, dd, *J* = 5.2, 11.6 Hz, H_{7a}), 4.20 (0.6 H, dd, *J* = 6.1, 11.4 Hz, H_{7b}), 4.04 (0.4 H, dd, *J* = 5.6, 12.2 Hz, $H_{7b'}$), 2.71-2.57 (2 H, m, H_{10}), 2.34-1.92 (13 H, m, H_2, H_3, H_{4a}, H_5, H_8, H_{19}), 1.86-1.75 (1 H, m, H_{4b}), 1.59-1.57 (3 H, m, H_{13} or $H_{13'}$), 1.50-1.48 (3 H, m, H_{13} or $H_{13'}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.7 (C_1), 218.6 (C_1), 171.3 (C_{14} or C_{18}), 171.3 (C_{14} or C_{18}), 171.2 (C_{14} or C_{18}), 171.1 (C_{14} or C_{18}), 171.0 (C_{14} or C_{18}), 170.8 (C_{14} or C_{18}), 170.7 (C_{14} or C_{18}), 170.6 (C_{14} or C_{18}), 136.2 (C_{12}), 135.8 (C_{16}), 135.8 (C_{16}), 135.7 (C_{16}), 135.7 (C_{16}), 128.7 (C_{17}), 128.7 (C_{17}), 128.7 (C_{17}), 128.6 (C_{17}), 128.5 (C_{17}), 128.4 (C_{17}), 128.4 (C_{17}), 128.3 (C_{17}), 128.1 (C_{17}), 117.8 (C_{11}), 117.5 (C_{11}), 74.4 (C_6), 70.6 (C_6), 67.4 (C_{15}), 67.2 (C_{15}), 63.5 (C_7), 63.4 (C_7), 57.2 (C_9), 56.9 (C_8), 48.3 (C_2), 46.8 (C_2), 43.2 (C_3), 43.0 (C_3), 36.2 (C_5), 36.0 (C_5), 33.0 (C_{10}), 32.8 (C_{10}), 32.1 (C_8), 26.0 (C_{13} or $C_{13'}$), 21.1 (C_{19}), 20.9 (C_{19}), 20.8 (C_4), 18.0 (C_{13} or $C_{13'}$); HRMS (ESI) calcd for $C_{34}H_{44}O_9N$ ($[M+NH_4]^+$) 610.3011. Found: 610.3003.

6) (±)-*trans*-2-(6'-(5',5'-Bis(benzylcarboxylate)-hex-2'-ene))-3-(1",2"-dihydroxyethyl)-cyclopentanone 91b (R = CO_2Bn)

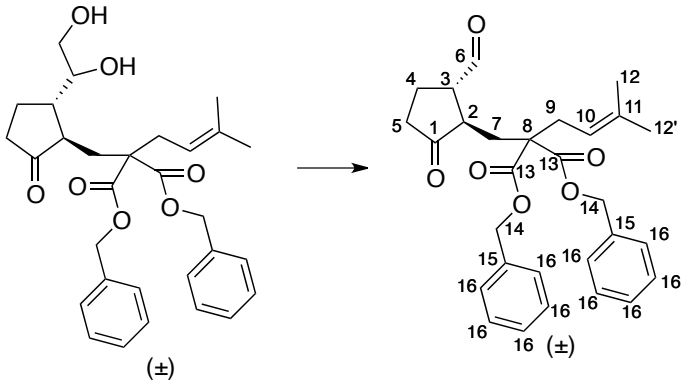


Amberlite® 400 Cl (10 g) was activated by stirring for 3 h in an aqueous solution of NaOH (2 M, 200 mL). The resin was filtered, and washed with ethanol and diethyl ether.

The activated Amberlite® 400 Cl was added to a solution of (±)-*trans*-2-(6'-(5',5'-bis(benzylcarboxylate)-hex-2'-ene))-3-(1",2"-diacetoxyethyl)-cyclopentanone **79b** (R = CO_2Bn) (12.1 g, 20.3 mmol) in methanol (400 mL). The solution was stirred for 1 day. The solution was

filtered through a pad of Celite® to remove all the Amberlite® and the residue was washed with methanol. The organic layer was dried over anhydrous sodium sulfate and concentrated to dryness to afford an inseparable mixture (ratio 6:4) of (±)-*trans*-2-(6'-(5',5'-bis(benzylcarboxylate)-hex-2'-ene))-3-(1",2"-dihydroxyethyl)-cyclopentanone **91b** (R = CO_2Bn) as a colourless oil in 86% yield (8.91 g). IR ν_{max} (neat) /cm^{-1} 3456 (2 O-H), 1732 (3 C=O), 1217 (2 C-O); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.18 (10 H, m, H_{17}), 5.16-4.95 (4 H, m, H_{15}), 4.92-4.84 (1 H, m, H_{11}), 4.13-4.09 (0.6 H, m, H_6), 3.74-3.66 (1 H, m, $H_{6'}$, $H_{7a'}$), 3.59-3.53 (1.6 H, m, H_{7a}, H_{7b}), 2.80-2.73 (1 H, m, H_{10a}), 2.68-2.59 (1 H, m, H_{10b}), 2.51-2.46 (1 H, m, H_2), 2.40-2.13 (2 H, m, H_5), 2.08-1.69 (5 H, m, H_3, H_4, H_8), 1.62-1.60 (3 H, m, H_{13} or $H_{13'}$), 1.50-1.49 (3 H, m, H_{13} or $H_{13'}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.9 (C_1), 172.8 (C_{14}), 170.9 (C_{14}), 136.7 (C_{12}), 135.5 (C_{16}), 135.0 (C_{16}), 128.6 (C_{17}), 128.5 (C_{17}), 128.4 (C_{17}), 128.2 (C_{17}), 117.1 (C_{11}), 69.3 (C_6), 67.6 (C_{15}), 58.3 (C_7), 57.5 (C_9), 47.4 (C_2), 45.4 (C_3), 35.9 (C_5), 35.5 (C_{10}), 30.2 (C_8), 25.9 (C_4), 18.9 (C_{13} or $C_{13'}$), 17.9 (C_{13} or $C_{13'}$); HRMS (ESI) calcd for $C_{30}H_{37}O_7$ ($[M+H]^+$) 509.2534. Found: 509.2529.

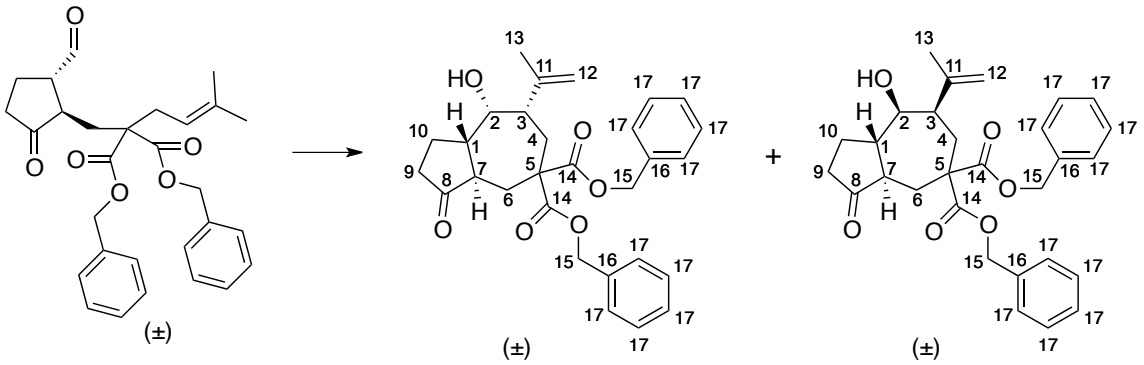
7) (±)-*trans*-2-(6'-(5',5'-Bis(benzylcarboxylate)-hex-2'-ene))-3-formyl-cyclopentanone 81b (R = CO_2Bn)



Sodium metaperiodate (4.0 g, 18.4 mmol, 10 equiv.) was added at 0 °C to a solution of (±)-*trans*-2-(6'-(5',5'-bis(benzylcarboxylate)-hex-2'-ene))-3-(1",2"-dihydroxyethyl)-cyclopentanone **91b** (R = CO_2Bn) (0.94 g, 1.84 mmol, 1 equiv.) in THF/water (1:1) (95 mL). The reaction mixture was stirred at room temperature for 4.5 h at room temperature, and diluted with dichloromethane (200 mL) and washed with brine (2 x 100 mL). The organic layer was dried

over anhydrous sodium sulfate and concentrated to dryness under reduced pressure. Purification by silica gel flash column chromatography, eluent petroleum ether/ethyl acetate (8:2), afforded (±)-*trans*-2-(6'-(5',5'-bis(benzylcarboxylate)-hex-2'-ene))-3-formyl-cyclopentanone **81b** (R = CO_2Bn) as a colourless oil (846 mg, 97%). IR ν_{max} (neat) /cm^{-1} 1725 (4 C=O), 1216 (2 C-O); ^1H NMR (400 MHz, $CDCl_3$) δ 9.56 (1 H, d, *J* = 4.1 Hz, H_6), 7.30-7.26 (10 H, m, H_{16}), 5.12-5.07 (4 H, m, H_{14}), 4.90 (1 H, tt, *J* = 1.5, 9.9 Hz), 2.78-2.56 (4 H, m, H_2, H_3, H_9), 2.33-1.98 (5 H, m, H_{4a}, H_5, H_7), 1.94-1.82 (1 H, m, H_{4b}), 1.61 (3 H, s, H_{12} or $H_{12'}$), 1.51 (3 H, s, H_{12} or $H_{12'}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.3 (C_1), 201.3 (C_6), 171.1 (C_{13}), 171.0 (C_{13}), 136.2 (C_{11}), 135.4 (C_{15}), 135.4 (C_{15}), 128.5 (C_{16}), 128.5 (C_{16}), 128.4 (C_{16}), 128.4 (C_{16}), 128.3 (C_{16}), 117.1 (C_{10}), 67.3 (C_{14}), 67.1 (C_{14}), 57.0 (C_8), 54.6 (C_3), 45.8 (C_2), 35.6 (C_5), 32.8 (C_9), 32.1 (C_7), 25.8 (C_{12} or $C_{12'}$) 21.0 (C_4) 17.8 (C_{12} or $C_{12'}$); HRMS (ESI) calcd for $C_{29}H_{33}O_6$ ([M+H^+]) 477.2272. Found: 477.2269.

8) <u>(±)-(2R)-Hydroxy-(3R)-isopropenyl-5,5-bis(benzylcarboxylate)-8-oxo-*trans*-bicyclo[5,3,0]decane 83b (R = CO_2Bn) and (±)-(2S)-hydroxy-(3S)-isopropenyl-5,5-bis(benzylcarboxylate)-8-oxo-*trans*-bicyclo[5,3,0]decane 82b (R = CO_2Bn)</u>



Boron trifluoride diethyl etherate (5.5 mL, 43.5 mmol, 10 equiv.) was added at −78 °C to a solution of (±)-*trans*-2-(6'-(5',5'-bis(benzylylcarboxylate)-hex-2'-ene))-3-formyl-cyclopentanone **81b** (R = CO_2Bn) (2.07 g, 4.35 mmol, 1 equiv.) in dry THF (90 mL) under an argon atmosphere. The solution was allowed to reach room temperature and stirred for 2 days. The solution was diluted with dichloromethane (200 mL) and washed with a saturated solution of $NaHCO_3$ (3 x 100 mL). The organic layer was dried over anhydrous magnesium sulfate and

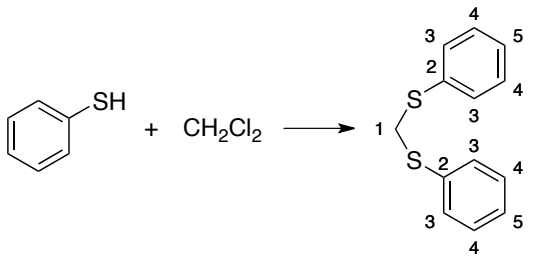
concentrated under reduced pressure to give a crude yellow oil. Purification by silica gel flash column chromatography, eluent: petroleum ether/ethyl acetate (8:2 to 6:4), afforded (±)-(2*R*)-hydroxy-(3*R*)-isopropenyl-5,5-bis(benzylcarboxylate)-8-oxo-*trans*-bicyclo [5,3,0]decane **83b** (R = CO_2Bn) (418 mg, 25% or 30% based on starting material recovery) and (±)-(2*S*)-hydroxy-(3*S*)-isopropenyl-5,5-bis(benzyl carboxylate)-8-oxo-*trans*-bicyclo[5,3,0]decane **82b** (R = CO_2Bn) (827 mg, 48% or 58% based on starting material recovery). After purification, 16% of starting material (±)-*trans*-2-(6'-(5',5'-bis(benzylylcarboxylate)-hex-2'-ene))-3-formyl-cyclopentanone was recovered.

(±)-(2*R*)-Hydroxy-(3*R*)-isopropenyl-5,5-bis(benzylcarboxylate)-8-oxo-*trans*-bicyclo[5,3,0] decane **83b** (R = CO_2Bn): IR ν_{max} (neat) /cm^{-1} 3424 (O-H), 1722 (3 C=O), 1254 (2 C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.16 (10 H, m, H_{17}), 5.13-4.92 (4 H, m, H_{15}), 4.88 (1 H, t, *J* = 1.4 Hz, H_{12a}), 4.74 (1 H, s, H_{12b}), 3.78 (1 H, s, H_2), 2.69 (1 H, dd, *J* = 3, 15.2 Hz, H_{6a}), 2.48 (1 H, dd, J = 10.6, 14.9 Hz, H_{4a}), 2.43-2.34 (2 H, m, H_7, H_{9a}) 2.17-2.15 (1 H, m, H_{4b}), 2.13-2.11 (1 H, m, H_{9b}), 2.04 (1 H, d, *J* = 10.6 Hz, H_3), 2.01-1.95 (2 H, m, H_{6b}, H_{10a}), 1.91-1.83 (2 H, m, H_{10b}, H_1), 1.66 (3 H, s, H_{13}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.8 (C_8), 172.2 (C_{14}), 172.1 (C_{14}), 148.8 (C_{11}), 135.5 (C_{16}), 135.4 (C_{16}), 128.6 (C_{17}), 128.6 (C_{17}), 128.4 (C_{17}), 128.3 (C_{17}), 128.2 (C_{17}), 128.0 (C_{17}), 111.5 (C_{12}), 67.8 (C_2), 67.3 (C_{15}), 67.2 (C_{15}), 55.6 (C_5), 50.0 (C_1), 47.1 (C_3), 45.0 (C_7), 37.5 (C_9), 32.9 (C_6), 29.8 (C_4), 23.5 (C_{13}), 22.9 (C_{10}); HRMS (ESI) calcd for $C_{29}H_{36}O_6N$ ($[M+NH_4]^+$) 494.2537. Found: 494.2531.

(±)-(2*S*)-Hydroxy-(3*S*)-isopropenyl-5,5-bis(benzylcarboxylate)-8-oxo-*trans*-bicyclo[5,3,0] decane **82b** (R = CO_2Bn): IR ν_{max} (neat) /cm^{-1} 3543 (O-H), 1725 (3 C=O), 1217 (2 C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.15 (10 H, m, H_{17}), 5.10-4.95 (4 H, m, H_{15}), 4.86 (1 H, d, *J* = 1.2 Hz, H_{12a}), 4.70 (1 H, s, H_{12b}), 3.30 (1 H, t, *J* = 9.6 Hz, H_2), 2.77 (1 H, m, H_{6a}), 2.43-2.36 (2 H, m, H_{4a}, H_{10a}), 2.26 (1 H, d, *J* = 15.2 Hz, H_{9a}) 2.08-2.14 (2 H, m, H_3, H_{10b}), 1.93-1.96 (2 H, m, H_{6b}, H_7), 1.86 (1 H, dd, *J* = 10, 15.2 Hz, H_{9b}), 1.76-1.68 (1 H, m, H_1), 1.66 (3 H, m, H_{13}), 1.53-1.48 (1 H, m, H_{7b}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.3 (C_8), 172.1 (C_{14}), 171.6 (C_{14}), 146.4 (C_{11}), 135.4 (C_{16}), 135.3 (C_{16}), 128.7 (C_{17}), 128.7 (C_{17}), 128.6 (C_{17}), 128.5 (C_{17}), 128.1 (C_{17}), 113.9 (C_{12}), 77.2 (C_2), 67.6 (C_{15}), 67.5 (C_{15}), 55.3 (C_5), 51.9 (C_1), 49.5 (C_3), 47.9 (C_7), 36.9 (C_{10}), 34.5 (C_9), 31.9 (C_6), 26.5 (C_4), 19.3 (C_{13}); HRMS (ESI) calcd for $C_{29}H_{36}O_6N$ ($[M+NH_4]^+$) 494.2537. Found: 494.2533.

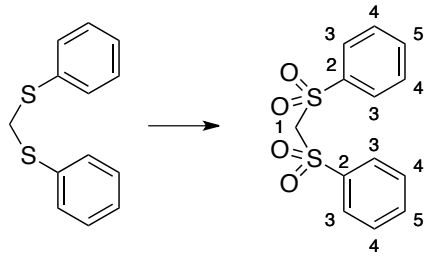
V) Attempt of the synthesis of the *trans*-bicyclo[5,3,0]decane skeleton using the bis(phenylsulfonyl) malonate moiety

1) Bis(phenylthio)methane 108[4]



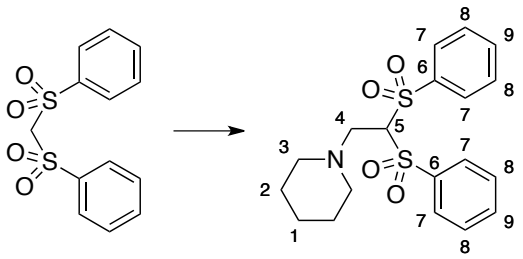
A mixture of K_2CO_3 (30.0 g, 218 mmol, 1 equiv.), dichloromethane (25 mL, 391 mmol, 2 equiv.) and thiophenol (22 mL, 215 mmol, 1 equiv.) in ethylene glycol (110 mL) was refluxed at 80 °C for 3 h. The solution was allowed to reach room temperature and poured onto water (500 mL), extracted with toluene (2 x 200 mL), washed with water (3 x 150 mL), dried over anhydrous magnesium sulfate and concentrated to dryness under reduced pressure. The crude material was purified by reduced pressure distillation (196-203 °C, 10 mbar) to afford bis(phenylthio)methane **108** as a pale yellow solid in 88% yield (21.8 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.42 (4 H, m, H_3), 7.34-7.30 (4 H, m, H_4), 7.28-7.23 (2 H, m, H_5), 4.35 (2 H, s, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0 (C_2), 130.7 (C_5), 129.1 (C_4), 127.2 (C_3), 40.6 (C_1); HRMS (GC-ESI) calcd for $C_{13}H_{12}S_2$ (M^+) 232.0376. Found: 232.0390.

2) Bis(phenylsulfonyl)methane 109[4]



Hydrogen peroxide (28.1 mL, 916 mmol, 5 equiv.) was added at 0 °C to a solution of bis(phenylthio)methane **108** (42.5 g, 183 mmol, 1 equiv.) in AcOH/Ac_2O (4:1) (500 mL) and stirred at 0 °C for 2 h, allowed to reach room temperature and stirred at room temperature for 24 h. The reaction mixture was poured onto cold water. The resulting precipitate was collected and washed with cold water. The crude product was recrystallised in toluene to afford bis(phenylsulfonyl)methane **109** as a colourless solid in 78% yield (42.2 g); m.p.: 120.5-121.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.95 (4 H, m, H_3), 7.74-7.70 (2 H, m, H_5), 7.62-7.58 (4 H, m, H_4), 4.74 (2 H, s, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5 (C_2), 135.0 (C_5), 129.5 (C_4), 129.0 (C_3), 74.6 (C_1); HRMS (ESI) calcd for $C_{13}H_{16}O_4S_2N$ ($[M+NH_4]^+$) 314.0515. Found: 314.0516.

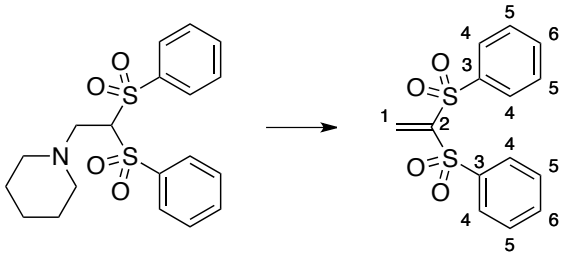
3) 1-(2,2-Bis(phenylsulfonyl)ethyl)piperidine 110[4]



Piperidine (80 mL, 844 mmol, 10 equiv.) was added dropwise at −5 °C to paraformaldehyde (10.2 g, 337 mmol, 4 equiv.) in dry methanol (260 mL). The reaction temperature should not be higher than 5 °C. A solution of bis(phenylsulfonyl)methane **109** (25.0

g, 84 mmol, 1 equiv.) in dioxane (120 mL) was slowly added to the reaction mixture at −5 °C. After 45 min at 0 °C, a mixture of cold water/ice (200 mL) was added and the mixture was stirred for 15 min. The resulting solid was filtered to afford 1-(2,2-bis(phenylsulfonyl)ethyl)piperidine **110** as a pale yellow solid that was dried overnight in a vacuum oven at 50 °C. the solid, which was not fully dried, was used in the next step; m.p.: 140.0-142.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.97 (4 H, m, H_7), 7.70-7.66 (2 H, m, H_9), 7.58-7.54 (4 H, m, H_8), 4.60 (1 H, t, J = 5.9 Hz, H_5), 3.06 (2 H, d, J = 6.2 Hz, H_4), 2.44 (4 H, s, H_3), 1.56 (4 H, q, J = 5.6 Hz, H_2), 1.42 (2 H, q, J = 5.6 Hz, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0 (C_6), 134.5 (C_9), 129.7 (C_7), 129.0 (C_8), 54.4 (C_5), 53.9 (C_4), 53.1 (C_3), 25.6 (C_2), 23.9 (C_1); HRMS (ESI) calcd for $C_{19}H_{23}O_4S_2N$ ($[M+H]^+$) 394.1141. Found: 394.1142.

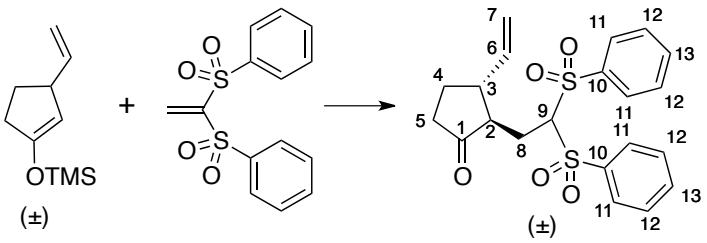
4) 2,2-Bis(phenylsulfonyl)ethane 111[4]



A vigorously stirred suspension of crude 1-(2,2-bis(phenylsulfonyl)ethyl)piperidine **110** (around 35 g) in toluene (400 mL) was treated with a stream of HCl gas (resulting in a dropping of concentrated H_2SO_4 onto NaCl solid). After 6 h of a fast stream of HCl gas into the solution, the suspension was heated to reflux to afford a clear colourless solution (no suspension). The solution was refluxed for 4 h. The solution was allowed to cool down to room temperature overnight. The reaction mixture was filtered to remove the colourless precipitate, piperidine hydrochloride and the precipitate was washed with toluene (400 mL). The solution was dried over anhydrous magnesium sulfate and concentrated to dryness under reduced pressure. The crude material was recrystallised in toluene to afford 2,2-bis(phenylsulfonyl)ethane as a pale yellow solid in 87% yield **111** over 2 steps (22.5 g). The desired 2,2-bis(phenylsulfonyl)ethane was obtained in 60% yield over 4 steps from the commercial thiophenol; m.p.: 123.4-125.1 °C [lit.[5] 120-125 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.95 (4 H, m, H_4), 7.69-7.66 (2 H, m, H_6),

7.57-7.54 (4 H, m, H_5), 7.23 (1 H, m, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6 (C_2), 139.2 (C_1), 139.0 (C_3), 134.6 (C_4), 129.3 (C_5), 129.1 (C_6); HRMS (ASAP) calcd for $C_{14}H_{16}O_4S_2N$ ($[M+NH_4]^+$) 326.0515. Found: 326.0509.

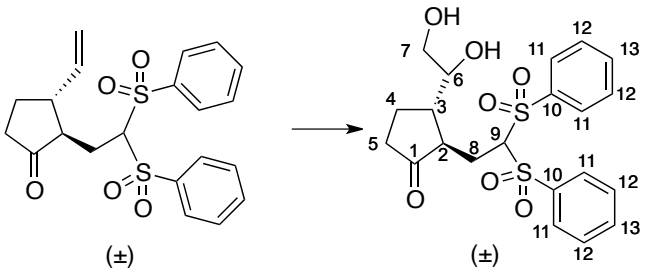
5) (±)-*trans*-2-(2'(1',1'-Bis(phenylsulfonyl)ethyl))-3-vinyl-cyclopentanone 78b (R = SO_2Ph)



(±)-3-Ethenyl-1-trimethylsilyloxycyclopent-1-ene (8.64 g, 47.4 mmol, 1 equiv.) was added at −40 °C to a solution 2,2-bis(phenylsulfonyl)ethene **77** (14.6 g, 47.4 mmol, 1 equiv.) in dichloromethane (120 mL) under an argon atmosphere. At −78°C, a solution of $SnCl_4$ (5.6 mL, 47.4 mmol, 1 equiv.) in dichloromethane (8 mL) was added drop by drop over 2 h to the reaction mixture. After the addition, the reaction mixture was stirred at −78 °C for 2.5 h and poured onto water (200 mL). The resulting mixture was filtered through a pad of Celite® and the Celite® was thoroughly washed with dichloromethane (200 mL). The aqueous layer was extracted with dichloromethane (3 x 200 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated to dryness under reduced pressure. Purification by silica gel flash column chromatography, eluent: petroleum ether/ethyl acetate (9:1), afforded (±)-*trans*-2-(2'(1',1'-bis(phenylsulfonyl)ethyl))-3-vinyl-cyclopentanone **78b** (R = SO_2Ph) as a pale yellow solid (10.6 g, 54%); m.p.: 166.5-168.8 °C; IR ν_{max} (neat) /cm^{-1} 1728 (C=O), 1371 (S=O), 1152 (S=O),; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97-7.92 (4 H, m, H_{13}), 7.73-7.66 (2 H, m, H_{13}), 7.54-7.53 (4 H, m, H_{13}), 5.82 (1 H, ddd, J = 8.4, 10.2, 17.1 Hz, H_6), 5.65 (1 H, dd, J = 4.1, 7.9 Hz, H_9), 5.17 (2 H, dd, J = 8.5, 9.9 Hz, H_7), 2.66-2.56 (1 H, m, H_9), 2.46-2.31 (3 H, m, H_3, H_{5a}), 2.29-2.08 (3 H, m, H_{4a}, H_{5b}, H_8), 1.76-1.64 (1 H, m, H_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.5 (C_1), 139.7 (C_6), 137.8 (C_{10}), 137.8 (C_{10}), 134.7 (C_{13}), 134.6 (C_{13}), 129.9 (C_{11}), 129.5 (C_{11}),

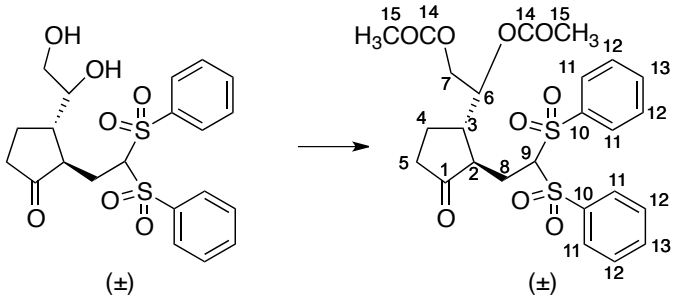
129.1 (C_{12}), 129.1 (C_{12}), 12.0 (C_{12}), 117.1 (C_7), 79.1 (C_9), 50.0 (C_8), 48.8 (C_2), 37.3 (C_3), 27.5 (C_5), 24.8 (C_4); HRMS (ESI) calcd for $C_{21}H_{26}O_5S_2N$ ($[M+NH_4]^+$) 436.1247. Found: 436.1241.

6) (±)-*trans*-2-(2'(1',1'-Bis(phenylsulfonyl)ethyl))-3-(1',2'-dihydroxyethyl)-cyclopentanone 88b (R = SO_2Ph)



N-Methyl morpholine oxide in water (2.0 g, 14.3 mmol, 3 equiv.) and a solution of osmium trichloride monohydrate (7 mL, 5 mg/mL, 0.02 equiv.) were added at 0 °C to a solution of (±)-*trans*-2-(2'(1',1'-bis(phenylsulfonyl)ethyl))-3-vinyl-cyclopentanone **78b** (R = SO_2Ph) (2.0 g, 4,78 mmol, 1 equiv.) in THF/water (1:1) (80 mL). The solutions were stirred for 4 days at room temperature. The reaction mixture was quenched at 0 °C with Na_2SO_3 (1.90 g, 14.3 mmol, 3 equiv.) then diluted with dichloromethane (75 mL). The mixture was extracted with dichloromethane (2 x 75 mL), washed with a solution of HCl 2 M (2 x 100 mL) dried over Na_2SO_4 and concentrated to dryness under reduced pressure to afford a yellow solid. Purification by silica gel flash column chromatography, eluent: petroleum ether/ethyl acetate (3:7), afforded an inseparable mixture of isomers (±)-*trans*-2-(2'(1',1'-bis(phenylsulfonyl)ethyl))-3-(1',2'-dihydroxyethyl)-cyclopentanone **88b** (R = SO_2Ph) as a colourless solid in 69% yield (1.48 g); IR ν_{max} (neat) /cm^{-1} 3437 (O-H), 1727 (C=O), 1371 (S=O), 1171 (S=O), ^1H NMR (300 MHz, $CDCl_3$) δ 7.97-7.92 (4 H, m, H_{13}), 7.73-7.66 (2 H, m, H_{13}), 7.54-7.53 (4 H, m, H_{13}), 5.82 (1 H, ddd, *J* = 8.4, 10.2, 17.1 Hz, H_6), 5.65 (1 H, dd, *J* = 4.1, 7.9 Hz, H_9), 5.17 (2 H, dd, *J* = 8.5, 9.9 Hz, H_7), 2.66-2.56 (1 H, m, H_9), 2.46-2.31 (3 H, m, H_3, H_{5a}), 2.29-2.08 (3 H, m, H_{4a}, H_{5b}, H_8), 1.76-1.64 (1 H, m, H_2); ^{13}C NMR (75 MHz, $CDCl_3$) HRMS (ESI) calcd for $C_{21}H_{28}O_7S_2N$ ($[M+H]^+$) 470.1302. Found: 470.1299.

7) (±)-*trans*-2-(2'(1',1'-Bis(phenylsulfonyl)ethyl))-3-(1',2'-diacetoxyethyl)-cyclopentanone 89c (R = SO_2Ph)



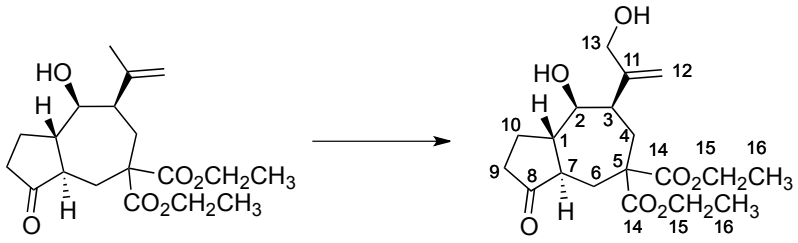
The protection reaction was done on small amount (no more than 1.5 g) or the yield reaction decreased a lot. We performed the reaction in parallele batches of 1.5 g of starting material **88b**.

In order, pyridine (1.1 mL, 13.6 mmol, 10 equiv.), DMAP (100 mg, 0.818 mmol, 0.6 equiv.) and acetic anhydride (570 μL, 7.80 mmol, 5.7 equiv.) were added at 0 °C to the solutions of (±)-*trans*-2-(2'(1',1'-bis(phenylsulfonyl)ethyl))-3-(1',2'-dihydroxyethyl)-cyclopentanone **88b** (R = SO_2Ph) (617 mg, 1.36 mmol, 1 equiv.) in dichloromethane (45 mL). The reaction mixtures were stirred at 0 °C for 5-10 min and quenched at 0 °C with water. The mixture was extracted with dichloromethane (3 x 50 mL), washed with a saturated solution of $CuSO_4$ (3 x 50 mL), dried over Na_2SO_4 and concentrated to dryness to afford a colourless oil. Purification by silica gel flash column chromatography, eluent: petroleum ether/ethyl acetate (1:1), afforded an inseparable mixture (65(*):35(')) of isomers (±)-*trans*-2-(2'(1',1'-bis(phenylsulfonyl)ethyl))-3-(1',2'-diacetoxyethyl)-cyclopentanone **89b** (R = SO_2Ph) as a colourless powder (720 mg, 99%) ; IR ν_{max} (neat) /cm^{-1} 1735 (3 C=O), 1378 (S=O), 1280 (2 O-C), 1174 (S=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97-7.79 (4 H, m, H_{11}), 7.71-7.61 (2 H, m, H_{13}), 7.59-7.47 (4 H, m, H_{12}), 5.80 (0.35 H, dd, *J* = 1.9, 9.4 Hz, $H_{9'}$), 5.73 (0.65 H, t, *J* = 5.7 Hz, H_{9*}), 5.31-5.28 (0.65 H, m, H_{6*}), 5.11-5.07 (0.35 H, m, $H_{6'}$), 4.41 (0.35 H, dd, *J* = 2.9, 12.3 Hz, $H_{7a'}$), 4.30 (0.65 H, dd, *J* = 4.7, 11.7 Hz, H_{7a*}), 4.17-4.07 (1 H, m, H_{7b}), 2.81-2.72 (0.35 H, m, $H_{5a'}$), 2.70-2.59 (1 H, m, H_2), 2.44-2.01 (12.3 H, m, H_3, H_{4a*}, H_{4b*}, $H_{4a'}$, H_{5a*}, H_{5b*}, $H_{5b'}$, H_8, H_{15}), 1.61 (0.35 H, m, $H_{4b'}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.1 (C_1), 170.7 (C_{14}), 170.7 (C_{14}), 134.7 (C_{10}), 134.6 (C_{10}), 134.5

(C_{13}), 134.5 (C_{13}), 130.0 (C_{11}), 129.6 (C_{11}), 129.5 (C_{11}), 129.2 (C_{12}), 129.2 (C_{12}), 129.2 (C_{12}), 78.9 ($C_{9'}$), 78.3 (C_{9*}), 74.9 ($C_{6'}$), 69.0 (C_{6*}), 63.5 (C_{7*}), 63.4 ($C_{7'}$), 47.7 ($C_{2'}$), 46.4 (C_{2*}), 44.6 (C_{3*}), 43.1 ($C_{3'}$), 37.7 ($C_{8'}$), 37.1 (C_{8*}), 26.7 ($C_{5'}$), 26.7 (C_{5*}), 25.0 (C_{4*}), 23.9 ($C_{4'}$), 21.0 (C_{15}), 20.8 (C_{15}); HRMS (ESI) calcd for $C_{25}H_{32}O_9S_2N$ ($[M+NH_4]^+$) 554.1513. Found: 554.1508.

VI) Allylic oxidation

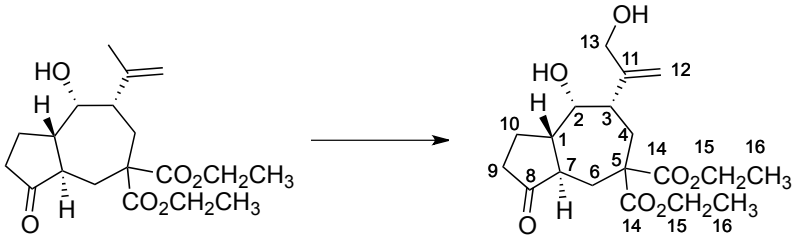
1) (±)-(2R)-Hydroxy-(3R)-(2'-(prop-2'-en-1'-ol))-5,5-bis(ethylcarboxylate)-8-oxo-*trans*-bicyclo[5,3,0]decane



tert-Butyl hydroperoxide (70% aqueous solution, 540 μL, 4.17 mmol, 10 equiv.) was added dropwise at 0 °C to selenium dioxide (24 mg, 0.204 mmol, 0.5 equiv.) in dichloromethane (0.1 M) and stirred for 1 h. A solution of (±)-(2*R*)-hydroxy-(3*R*)-isopropenyl-5,5-bis(ethylcarboxylate)-8-oxo-*trans*-bicyclo [5,3,0]decane (727 mg, 2.06 mmol, 1 equiv.) in dichloromethane (20 mL) was added to the previously prepared mixture at room temperature and stirred for 21 h at room temperature. The reaction mixture was quenched with MeOH (6 mL) and an aqueous solution of NaOH (0.2 M, 4 mL) and stirred for 2 h. The solution was treated with water (20 mL), extracted with petroleum ether (3 x 30 mL) washed with brine (30 mL), dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure. The residue was purified by flash column chromatography, eluent petroleum ether/ethyl acetate (6:4 to 4:6), to afford the desired compound (±)-(2*R*)-hydroxy-(3*R*)-(2'-(prop-2'-en-1'-ol))-5,5-bis(ethylcarboxylate)-8-oxo-*trans*-bicyclo [5,3,0]decane as a colourless oil (20 mg; 13%); IR ν_{max} (neat) /cm^{-1} 3040 (O-H) 1735 (3 C=O) 1238 (2 C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (1 H, d, *J* = 1 Hz, H_{12a}), 5.02 (1 H, s, H_{12b}), 4.21-4.10 (6 H, m, H_{13}, H_{15}), 3.92 (1 H, s, H_2), 2.80 (1 H, dd, *J* = 2, 15.2 Hz, H_{6a}), 2.56 (1 H, dd, *J* = 10.1, 14.4 Hz, H_{4a}), 2.48-2.37 (3 H, m, H_3, H_7,

H_{9a}), 2.23-2.10 (1 H, m, H_{9b}), 2.30 (3 H, d, *J* = 14.5 Hz, H_{4b}), 2.20 (1 H, d, *J* = 13.5 Hz, H_{10a}), 1.95-1.84 (2 H, m, H_1, H_{10b}), 1.78 (1 H, dd, J = 10.7, 15.2 Hz, H_{6b}), 1.25-1.18 (6 H, m, H_{16}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.9 (C_8), 172.9 (C_{14}), 172.7 (C_{14}), 151.8 (C_{11}), 114.5 (C_{12}), 70.3 (C_2), 65.2 (C_{13}), 61.7 (C_{15}), 61.6 (C_{15}), 55.5 (C_5), 51.2 (C_1), 45.6 (C_3), 45.3 (C_7) 37.5 (C_9), 33.0 (C_6), 29.3 (C_4), 22.5 (C_{10}), 14.1 (C_{16}), 14.0 (C_{16}); HRMS (ESI) calcd for $C_{19}H_{32}O_7N$ ($[M+NH_4]^+$) 386.2173. Found: 386.2176.

2) (±)-(2*S*)-Hydroxy-(3*S*)-(2'-(prop-2'-en-1'-ol))-5,5-bis(ethylcarboxylate)-8-oxo-*trans*-bicyclo[5,3,0]decane 142 (R = CO_2Et)[6]

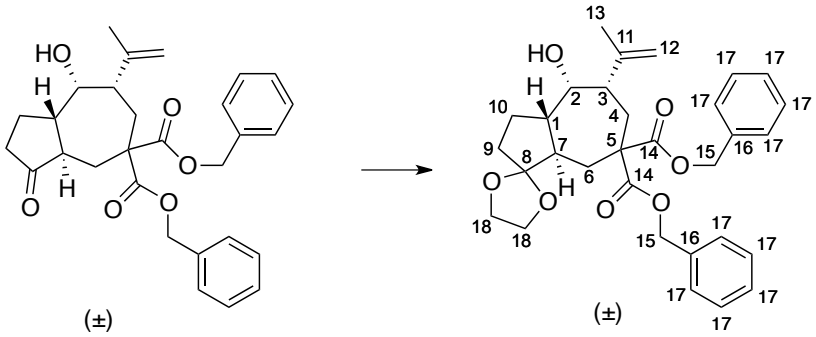


tert-Butyl hydroperoxide (5 M in decane, 825 μL, 4.13 mmol, 2 equiv.) was added dropwise at room temperature to selenium dioxide (79 mg, 0.709 mmol, 0.5 equiv.) in dichloromethane (0.7 M) and stirred for 30 min. A solution of (±)-(2*S*)-hydroxy-(3*S*)-isopropenyl-5,5-bis(ethylcarboxylate)-8-oxo-*trans*-bicyclo [5,3,0]decane **82** (R = CO_2Et) (147 mg, 0.417 mmol, 1 equiv.) in dichloromethane (8 mL) was added to the previously prepared mixture at room temperature and stirred for 5 days at room temperature. The reaction mixture was quenched with water (5 mL), extracted with dichloromethane (3 x 20 mL) and concentrated to dryness under reduced pressure. Purification by silica gel flash column chromatography, eluent: petroleum ether/ethyl acetate (3:7), afforded some starting material (±)-(2*S*)-hydroxy-(3*S*)-isopropenyl-5,5-bis(ethylcarboxylate)-8-oxo-*trans*-bicyclo[5,3,0]decane **82** (R = CO_2Et) (201 mg, 28%) and the desired compound (±)-(2*S*)-hydroxy-(3*S*)-(2'-(prop-2'-en-1'-ol))-5,5-bis(ethylcarboxylate)-8-oxo-*trans*-bicyclo[5,3,0]decane **142** (R = CO_2Et) as a colourless oil (295 mg, 39% or 54% on material recovery); IR ν_{max} (neat) /cm^{-1} 3034 (O-H) 1725 (3 C=O) 1217 (2 C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20 (1 H, s, H_{12a}), 4.99 (1 H, s, H_{12b}), 4.19-4.05 (6 H, m, H_{13}, H_{15}), 3.46 (1 H, t, *J* = 9.5 Hz, H_2), 2.77 (1 H, d, *J* = 15.1 Hz, H_{6a}), 2.46-2.36 (2 H, m, H_{9a},

H_{10a}), 2.29-2.04 (3 H, m, H_3, H_{4a}, H_{9b}), 1.98 (1 H, d, J = 11.3 Hz, H_7), 1.86 (1 H, dd, J = 9.8, 15.3 Hz, H_{4b}), 1.76 (1 H, dd, J = 10.5, 15.2 Hz, H_{6b}), 1.74-1.65 (1 H, m, H_1), 1.58-1.43 (1 H, m, H_{10b}), 1.24-1.16 (6 H, m, H_{16}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.6 (C_8), 172.4 (C_{14}), 172.3 (C_{14}), 151.2 (C_{11}), 113.2 (C_{12}), 79.3 (C_2), 65.2 (C_{13}), 61.8 (C_{15}), 55.0 (C_5), 51.9 (C_1), 48.1 (C_7), 45.7 (C_3) 36.7 (C_9), 35.8 (C_4), 31.5 (C_6), 26.2 (C_{10}), 14.0 (C_{16}), 13.9 (C_{16}); HRMS (ESI) calcd for $C_{19}H_{32}O_7N$ ($[M+NH_4]^+$) 386.2173. Found: 386.2175.

VII) Inversion of the alcohol configuration

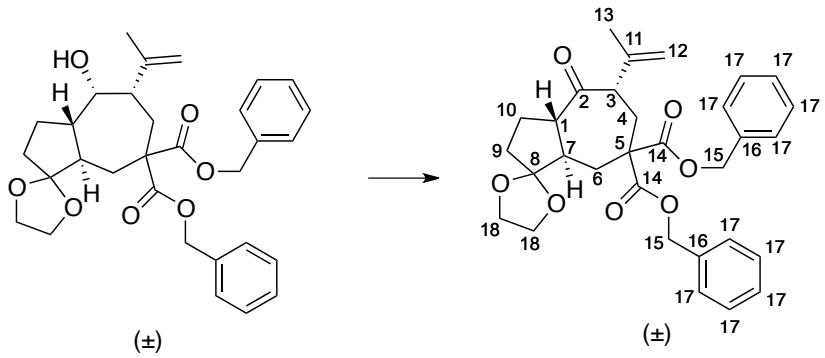
1) (±)-(2*S*)-Hydroxy-(3*S*)-isopropenyl-5,5-bis(benzylcarboxylate)-8-(1',4'-dioxaspiro)-*trans*-bicyclo[5,3,0]decane 137 (R = CO_2Bn)



In a Dean-Stark apparatus, ethylene glycol (2.2 mL, 38.2 mmol, 25 equiv.) and *p*-toluenesulfonic acid (29 mg, 0.152 mmol, 0.1 equiv.) was added to a solution of (±)-(2*S*)-hydroxy-(3*S*)-isopropenyl-5,5-bis(benzylcarboxylate)-8-oxo-*trans*-bicyclo[5,3,0]decane **82b** (R = CO_2Bn) (728 mg, 1.53 mmol, 1 equiv.) in toluene (31 mL) and the solution was heated to reflux for 5 h. The solution was cooled down to room temperature, diluted with dichloromethane (20 ml), washed with $NaHCO_3$ (10 mL), extracted with dichloromethane (3 x 30 mL), dried over anhydrous magnesium sulphate and concentrated to dryness under reduced pressure. Purification by silica gel flash column chromatography, eluent: petroleum ether/ethyl acetate (8:2-75:25), afforded (±)-(2*S*)-hydroxy-(3*S*)-isopropenyl-5,5-bis(benzyl carboxylate)-8-(1',4'-dioxaspiro)-*trans*-bicyclo[5,3,0]decane **137** (R = CO_2Bn) as a pale yellow oil (454 mg, 58%); IR ν_{max} (neat) /cm^{-1} 3540 (O-H) 1725 (2 C=O) 1218 (2 C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.19 (10 H,

m, H_{17}), 5.14-4.99 (4 H, m, H_{15}), 4.82 (1 H, d, *J* = 1.5 Hz, H_{12a}), 4.69 (1 H, s, H_{12b}), 3.86-3.79 (4 H, m, H_{18}), 3.19 (1 H, t, *J* = 9.6 Hz, H_2), 2.29 (1 H, d, *J* = 15.0 Hz, H_{6a}), 2.21-2.14 (2 H, m, H_{4a}, H_3), 2.11-2.05 (1 H, m, H_{10a}), 2.00 (1 H, dd, *J* = 10.7, 15.0 Hz, H_{6b}), 1.95-1.87 (1 H, m, H_{4b}), 1.82 (1 H, d, *J* = 10.7 Hz, H_7), 1.79-1.74 (1 H, m, H_9), 1.72-1.66 (1 H, m, H_1), 1.65 (3 H, s, H_{13}), 1.48-1.38 (1 H, m, H_{10b}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2 (C_{14}), 172.1 (C_{14}), 147.0 (C_{11}), 135.7 (C_{16}), 135.6 (C_{16}), 128.7 (C_{17}), 128.5 (C_{17}), 128.4 (C_{17}), 128.3 (C_{17}), 118.0 (C_8), 113.5 (C_{12}), 78.0 (C_2), 67.3 (C_{15}), 67.2 (C_{15}), 65.1 (C_{18}), 64.9 (C_{18}), 55.4 (C_5), 51.8 (C_1), 48.9 (C_3), 43.9 (C_7) 34.7 (C_9), 34.2 (C_4), 30.9 (C_6), 27.4 (C_{10}), 19.2 (C_{13}); HRMS (ESI) calcd for $C_{31}H_{40}O_7N$ ($[M+NH_4]^+$) 538.2799. Found: 538.2791.

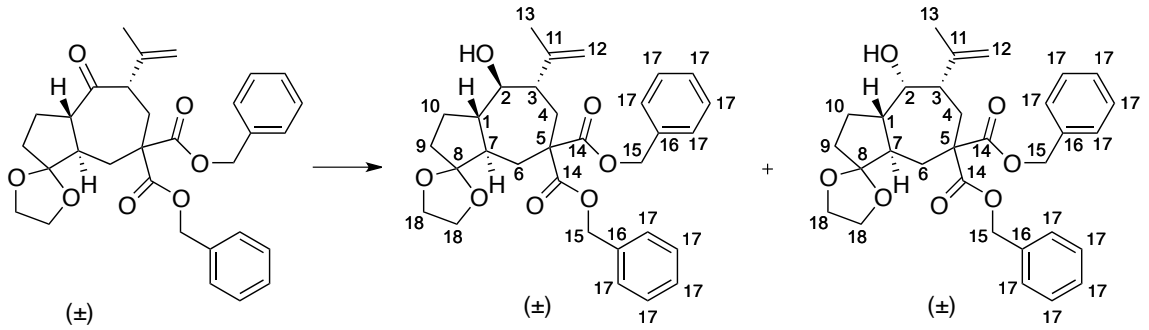
2) (±)-2-Oxo-(3*S*)-isopropenyl-5,5-bis(benzylcarboxylate)-8-(1',4'-dioxaspiro)-*trans*-bicyclo[5,3,0]decane 138 (R = CO_2Bn)



Pyridinium dichromate (951 mg, 2.53 mmol, 4 equiv.) was added to a solution of (±)-(2*S*)-hydroxy-(3*S*)-isopropenyl-5,5-bis(benzylcarboxylate)-8-(1',4'-dioxaspiro)-*trans*-bicyclo[5,3,0] decane **137** (R = CO_2Bn) (329 mg, 0.632 mmol, 1 equiv.) in dichloromethane (1.3 mL) under an argon atmosphere and the solution was refluxed for 3 h. The mixture was diluted with diethyl ether (30 mL), filtered through a pad of Celite® and the Celite® was washed thoroughly with diethyl ether, dried over anhydrous magnesium sulphate and concentrated to dryness under reduced pressure. The desired compound (±)-2-oxo-(3*S*)-isopropenyl-5,5-bis (benzylcarboxylate)-8-(1',4'-dioxaspiro)-*trans*-bicyclo[5,3,0]decane **138** (R = CO_2Bn) (328 mg) was obtained quantitatively without any further purification; IR ν_{max} (neat) /cm^{-1} 1729 (2 C=O) 1224 (2 C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.20 (10 H, m, H_{17}), 5.14-5.03 (4 H, m, H_{15}),

4.87 (1 H, d, J = 1.3 Hz, H_{12a}), 4.64 (1 H, s, H_{12b}), 3.87-3.81 (4 H, m, H_{18}), 3.15 (1 H, d, J = 10.5 Hz, H_3), 2.73-2.65 (1 H, m, H_1), 2.48 (2 H, d, H_{4a}, H_{6a}), 2.33 (1 H, dd, J = 10.9, 15.1 Hz, H_{6b}), 2.13 (1 H, dd, J = 10.8, 15.4 Hz, H_{4b}), 2.05-1.95 (2 H, m, H_{10a}, H_7), 1.76-1.72 (2 H, m, H_9), 1.70 (4 H, m, H_{10b}, H_{13}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6 (C_2), 171.6 (C_{14}), 171.3 (C_{14}), 143.4 (C_{11}), 135.2 (C_{16}), 135.2 (C_{16}), 128.5 (C_{17}), 128.5 (C_{17}), 128.2 (C_{17}), 128.2 (C_{17}), 128.1 (C_{17}), 117.2 (C_8), 113.1 (C_{12}), 67.4 (C_{15}), 67.3 (C_{15}), 65.5 (C_{18}), 64.4 (C_{18}), 56.6 (C_1), 55.2 (C_5), 53.4 (C_3), 44.3 (C_7) 33.8 (C_9), 32.2 (C_4), 30.5 (C_6), 21.6 (C_{13}), 20.2 (C_{10}); HRMS (ESI) calcd for $C_{31}H_{38}O_7N$ ($[M+NH_4]^+$) 536.2643. Found: 536.2638.

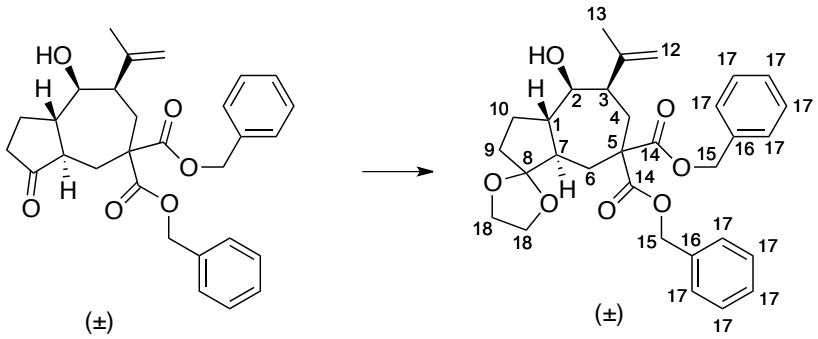
3) (±)-(2*R*)-Hydroxy-(3*S*)-isopropenyl-5,5-bis(benzylcarboxylate)-8-(1',4'-dioxaspiro)-*trans*-bicyclo[5,3,0]decane 139 (R = CO_2Bn)



Sodium borohydride (17 mg, 0.441 mmol, 2.2 equiv.) was added at 0 °C to a solution of (±)-2-oxo-(3*S*)-isopropenyl-5,5-bis(benzylcarboxylate)-8-(1',4'-dioxaspiro)-*trans*-bicyclo[5,3,0] **138** (R = CO_2Bn) decane (104 mg, 0.201 mmol, 1 equiv.) in *i*-PrOH (2 mL). The reation was stirred at room temperature overnight and heated at 50 °C for 2 h. No starting material appeared on the TLC so the reaction was stopped, quenched at 0 °C with water (3 mL), extracted with dichloromethane (3 x 15 mL), dried over anhydrous sodium sulphate and concentrated to dryness under reduced pressure. Purification by silica gel flash column chromatography, eluent: petroleum ether/ethyl acetate (8:2 to 6:4), afforded the unwanted isomer (±)-(2*S*)-hydroxy-(3*S*)-isopropenyl-5,5-bis(benzylcarboxylate)-8-(1',4'-dioxaspiro)-*trans*-bicyclo[5,3,0]decane **137** (R = CO_2Bn) (38 mg, 36%) and the desired compound (±)-(2*R*)-hydroxy-(3*S*)-isopropenyl-5,5-bis(benzylcarboxylate)-8-(1',4'-dioxaspiro)-*trans*-bicyclo [5,3,0]decane **139** (R = CO_2Bn) (42 mg, 40%); IR ν_{max} (neat) /cm^{-1} 3547 (O-H) 1728 (2 C=O) 1231 (2 C-O); ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.38-7.21 (10 H, m, H_{17}), 5.17-5.00 (4 H, m, H_{15}), 4.86 (1 H, d,*J* = 1.3 Hz, H_{12a}), 4.75 (1 H, s, H_{12b}), 3.92-3.84 (4 H, m, H_{18}), 3.71 (1 H, s, H_2), 2.59 (1 H, dd,*J* = 10.3, 14.9 Hz, H_{6a}), 2.30 (1 H, d, *J* = 14.8 Hz, H_{10a}), 2.23 (1 H, t, *J* = 10.9 Hz, H_3), 2.16 (1 H, d, *J* = 10.4 Hz, H_7), 2.10 (1 H, d, *J* = 15.0 Hz, H_{6b}), 2.05-1.98 (1 H, m, H_{10b}), 1.89-1.72 (4 H, m, H_4, H_9), 1.59 (3 H, m, H_{13}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7 (C_{14}), 172.6 (C_{14}), 149.5 (C_{11}), 135.7 (C_{16}), 135.7 (C_{16}), 128.6 (C_{17}), 128.6 (C_{17}), 128.3 (C_{17}), 128.3 (C_{17}), 128.2 (C_{17}), 128.1 (C_{17}), 118.3 (C_8), 111.0 (C_{12}), 68.7 (C_2), 67.1 (C_{15}), 67.1 (C_{15}), 65.2 (C_{18}), 64.5 (C_{18}), 55.8 (C_5), 50.0 (C_1), 46.8 (C_7), 41.0 (C_3) 35.0 (C_9), 31.8 (C_{10}), 29.5 (C_6), 23.6 (C_{13}), 23.4 (C_4); HRMS (ASAP) calcd for $C_{31}H_{37}O_7$ ($[M+H]^+$) 521.2534. Found: 536.2526.

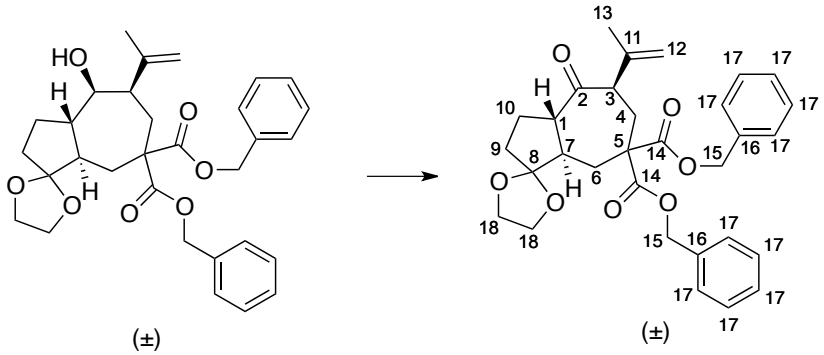
4) <u>(±)-(2*R*)-Hydroxy-(3*R*)-isopropenyl-5,5-bis(benzylcarboxylate)-8-(1',4'-dioxaspiro)-*trans*-bicyclo[5,3,0]decane</u>



In a Dean-Stark apparatus, ethylene glycol (2.4 mL, 42.5 mmol, 25 equiv.) and *p*-toluenesulfonic acid (32 mg, 0.170 mmol, 0.1 equiv.) was added to a solution of (±)-(2*R*)-hydroxy-(3*R*)-isopropenyl-5,5-bis(benzylcarboxylate)-8-oxo-*trans*-bicyclo[5,3,0]decane **83** (R = CO_2Bn) (810 mg, 1.70 mmol, 1 equiv.) in toluene (34 mL) and the solution was heated to reflux for 6 h. The solution was cooled down to room temperature, diluted with dichloromethane (20 ml), washed with $NaHCO_3$ (10 mL), extracted with dichloromethane (3 x 20 mL), dried over anhydrous magnesium sulphate and concentrated to dryness under reduced pressure. Purification by silica gel flash column chromatography, eluent petroleum ether/ethyl acetate (85:15), afforded (±)-(2*R*)-hydroxy-(3*R*)-isopropenyl-5,5-bis(benzylcarboxylate)-8-(1',4'-dioxaspiro)-*trans*-bicyclo[5,3,0]decane as a colourless oil (325 mg, 37%). IR ν_{max} (neat) /cm^{-1} 3464 (O-H), 1725 (2 C=O), 1216 (2 C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.24 (10 H, m, H_{17}), 5.20-5.02

(4 H, m, H_{15}), 4.88 (1 H, d, J = 1.3 Hz, H_{12a}), 4.77 (1 H, s, H_{12b}), 3.93-3.80 (4 H, m, H_{18}), 3.74 (1 H, s, H_2), 2.62 (1 H, dd, J = 10.4, 14.8 Hz, H_{6a}), 2.35-2.30 (1 H, m, H_{4a}), 2.28-2.22 (1 H, m, H_7), 2.18 (1 H, d, J = 10.3 Hz, H_3), 2.13 (1 H, d, J = 15.0 Hz, H_{6b}), 2.06 (1 H, t, J = 5.4 Hz, H_{4b}), 1.90-1.82 (2 H, m, H_1, H_{10a}), 1.82-1.76 (3 H, m, H_9, H_{10b}), 1.72 (3 H, s, H_{13}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5 (C_{14}), 172.5 (C_{14}), 149.4 (C_{11}), 135.6 (C_{16}), 135.6 (C_{16}), 128.5 (C_{17}), 128.5 (C_{17}), 128.2 (C_{17}), 128.1 (C_{17}), 128.1 (C_{17}), 128.0 (C_{17}), 118.2 (C_8), 110.9 (C_{12}), 68.7 (C_2), 67.0 (C_{15}), 66.9 (C_{15}), 65.1 (C_{18}), 64.4 (C_{18}), 55.7 (C_5), 46.7 (C_1), 40.9 (C_7) 34.9 (C_9), 31.7 (C_4), 29.3 (C_6), 23.4 (C_{13}), 23.3 (C_{10}); HRMS (ESI) calcd for $C_{31}H_{40}O_7N$ ($[M+NH_4]^+$) 538.2799. Found: 538.2793.

5) (±)-2-Oxo-(3*R*)-isopropenyl-5,5-bis(benzylcarboxylate)-8-(1',4'-dioxaspiro)-*trans*-bicyclo[5,3,0]decane

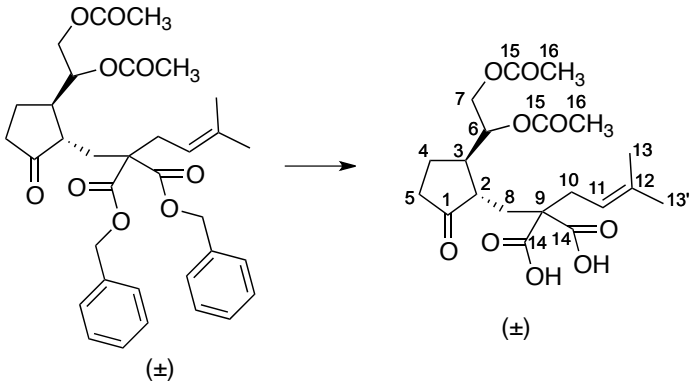


Pyridinium dichromate (103 mg, 0.276 mmol, 2 equiv.) was added to a solution of (±)-(2*R*)-hydroxy-(3*R*)-isopropenyl-5,5-bis(benzylcarboxylate)-8-(1',4'-dioxaspiro)-*trans*-bicyclo[5,3,0] decane (72 mg, 0.138 mmol, 1 equiv.) in dichloromethane (1.4 mL) and the solution was heated to reflux for 4 h. The reaction mixture was diluted with diethyl ether (50 mL) and filtered through a pad of Celite® and the Celite® was washed thoroughly with diethyl ether. The filtrate was concentrated to dryness under reduced pressure to afford quantitatively (±)-2-oxo-(3*R*)-isopropenyl-5,5-bis(benzylcarboxylate)-8-(1',4'-dioxaspiro)-*trans*-bicyclo[5,3,0] decane as yellow oil (72 mg). IR ν_{max} (neat) /cm^{-1} 1725 (2 C=O) 1220 (2 C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.24 (10 H, m, H_{17}), 5.25-5.00 (4 H, m, H_{15}), 4.90 (1 H, s, H_{12a}), 4.67 (1 H, s, H_{12b}), 3.91-3.76 (4 H, m, H_{18}), 3.18 (1 H, d, J = 10.6 Hz, H_3), 2.73-2.68 (1 H, m, H_1), 2.53-

1.49 (2 H, m, H_{4a}, H_{6a}), 2.38-2.25 (1 H, m, H_{6b}), 2.20-1.95 (3 H, m, H_{4b}, H_7, H_{9a}), 1.83-1.66 (6 H, m, H_{9b}, H_{10}, H_{13}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.0 (C_2), 171.9 (C_{14}), 171.6 (C_{14}), 143.6 (C_{11}), 135.5 (C_{16}), 128.7 (C_{17}), 128.7 (C_{17}), 128.5 (C_{17}), 128.4 (C_{17}), 128.3 (C_{17}), 117.4 (C_8), 113.3 (C_{12}), 67.5 (C_{15}), 65.6 (C_{18}), 64.3 (C_{18}), 56.7 (C_1), 55.3 (C_3), 44.5 (C_7) 33.8 (C_{10}), 32.9 (C_4), 30.6 (C_6), 21.6 (C_{13}), 20.3 (C_9); HRMS (ESI) calcd for $C_{31}H_{38}O_7N$ ($[M+NH_4]^+$) 536.2643. Found: 536.2638.

VIII) Decarboxylation

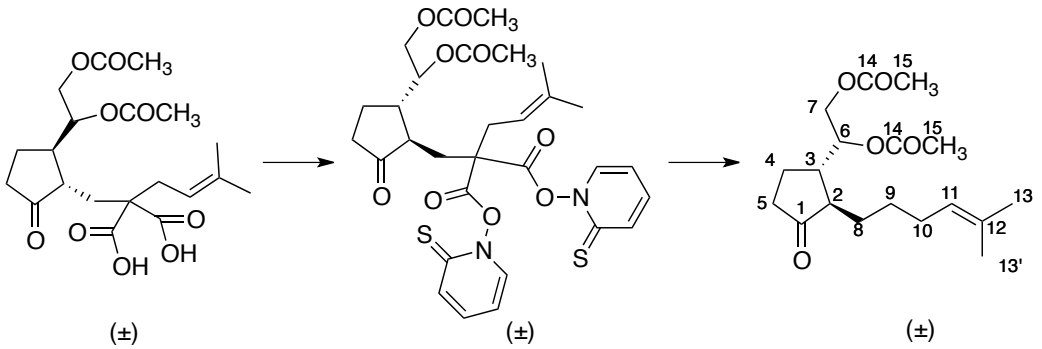
1) (±)-*trans*-2-(6'-(5',5'-Bis(carboxylic acid)-hex-2'-ene))-3-(1",2"-diacetoxyethyl)-cyclopentanone 117 (R = CO_2Bn)[7]



Et_3N (22 μL, 0.16 mmol, 0.28 equiv.) and $Pd(OAc)_2$ (13 mg, 0.056 mmol, 0.1 equiv.) were added to a solution of Et_3SiH (250 μL, 1.56 mmol, 2.7 equiv.) in dichloromethane (4 mL). The solution was stirred for 15 min. A solution of (±)-*trans*-2-(6'-(5',5'-bis(benzylcarboxylate)-hex-2'-ene))-3-(1",2"-diacetoxyethyl)-cyclopentanone **79** (R = CO_2Bn) (335 mg, 0.565 mmol, 1 equiv.) in dichloromethane (0.5 mL) was slowly added to the reaction mixture. The solution was stirred for 18 h at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl (15 mL), extracted with diethyl ether (3 x 20 mL) and washed with brine. The organic layer was dried over anhydrous sodium sulphate, filtered through a pad of Celite®, and concentrated to dryness to afford (±)-*trans*-2-(6'-(5',5'-bis(carboxylic acid)-hex-2'-ene))-3-(1",2"-diacetoxyethyl)-cyclopentanone **117** (R = CO_2Bn) as a colourless oil (171 mg, 73%). IR

ν_{max} (neat) /cm^{-1} 3540 (O-H) 1725 (5 C=O) 1450 (O-H) 1240 (2 C-O) 1215 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26-5.22 (0.6 H, m, H_6), 5.12 (0.4 H, td, *J* = 3.1, 6.2 Hz, H_6), 5.00-4.94 (1 H, m, H_{11}), 4.36 (0.4 H, dd, *J* = 3.1, 12 Hz, H_{7a}), 4.25 (0.6 H, dd, *J* = 4.8,11.7 Hz, H_{7a}), 4.16 (0.6 H, dd, *J* = 6.2, 11.7 Hz, H_{7b}), 4.07 (0.4 H, dd, *J* = 6.2, 12.0 Hz, H_{7b}), 2.72-2.57 (2 H, m, H_2, H_3), 2.25-1.87 (14 H, m, H_4, H_5, H_8, H_{10}, H_{16}), 1,68 (3 H, s, H_{13} or $H_{13'}$), 1.62 (3 H, m, H_{13} or $H_{13'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.4 (C_1), 171.8, 171.4 (C_{14}), 170.8, 166.1 (C_{15}), 135.1, 135.0 (C_{12}), 118.1, 114.6 (C_{11}), 73.3, 71.0 (C_6), 63.5 (C_7), 58.9 (C_9), 58.5 (C_8), 47.2, 47.0 (C_2), 43.0 (C_3), 35.9 (C_5), 33.0, 32.9 (C_{10}), 25.8 (C_{13} or $C_{13'}$) 23.2 (C_4), 20.7, 20.6 (C_{16}), 18.0 (C_{13} or $C_{13'}$); HRMS (ASAP) calcd for $C_{20}H_{28}O_9N$ ($[M+H]^+$) 430.2072. Found: 430.2067.

2) <u>(±)-*trans*-2-(6'-(Hex-2'-ene))-3-(1",2"-diacetoxyethyl)-cyclopentanone 80 (R = CO_2Bn)</u>



Oxalyl chloride (110 μL, 1.24 mmol, 3 equiv.) was added to a solution of (±)-*trans*-2-(6'-(5',5'-bis(carboxylic acid)-hex-2'-ene))-3-(1",2"-diacetoxyethyl)-cyclopentanone **117** (R = CO_2Bn) (171 mg, 0.415 mmol, 1 equiv.) in dichloromethane (4 mL) followed by the addition of a drop of dimethylformamide. 2-Mercaptopyridine-*N*-oxide sodium salt (186 mg, 1.24 mmol, 3 equiv.) was added when no more gas was formed. The reaction was stirred for 1h and concentrated to dryness under reduced pressure to afford (±)-*trans*-2-(6'-(5',5'-bis(thiohydroxamylcarboxylate)-hex-2'-ene))-3-(1",2"-diacetoxyethyl)-cyclopentanone **118** (R = CO_2Bn) as a crude mixture. The crude mixture was directly used in the next step: the Barton decarboxylation reaction.

A solution of Bu_3SnH (920 μL, 3.39 mmol, 8.2 equiv.) and 1,1'-Azobis(cyclohexanecarbonitrile) (9 mg, 0.035 mmol, 0.08 equiv.) in dry toluene (10 mL) was added to a solution of the crude mixture of (±)-*trans*-2-(6'-(5',5'-bis(thiohydroxamylcarboxylate)-hex-2'-ene))-3-(1",2"-diacetoxyethyl)-cyclopentanone **118** (R = CO_2Bn) (all the crude mixture from the previous step was engaged) in dry toluene (12 mL) under an argon atmosphere at room temperature. The reaction was heated under reflux for 4 h, cooled down to room temperature, quenched with water (10 mL), extracted with dichloromethane (3 x 30 mL) and washed with brine (20 mL). Organic layers were dried over anhydrous sodium sulphate and concentrated to dryness under reduced pressure. Purification by silica gel flash column chromatography, eluent petroleum ether/ethyl acetate (9:1), afforded (±)-*trans*-2-(6'-(hex-2'-ene))-3-(1",2"-diacetoxyethyl)-cyclopentanone **80** (R = CO_2Bn) (51 mg, 38% over two steps); IR ν_{max} (neat) /cm^{-1} 1741 (3 C=O) 1222 (2 C-O); ^1H NMR (400 MHz, $CDCl_3$) δ 5.27-5.16 (0.6 H, m, H_6), 5.11-4.98 (1.4 H, m, H_6, H_{11}), 4.26 (0.4 H, td, *J* = 2.8, 12.5 Hz, H_{7a}), 4.75 (0.6 H, dd, *J* = 3.7, 11.9 Hz, H_{7a}), 4.08-3.95 (1 H, m, H_{7b}), 2.98-2.80 (1 H, m, H_3), 2.59-2.16 (6 H, m, H_2, H_5, H_{10}, H_{4a}), 2.08-1.87 (7 H, m, H_{4b}, H_{15}), 1.79-1.70 (0.4 H, m, H_{8a}), 1.68 (3 H, s, H_{13} or $H_{13'}$), 1.57 (3 H, s, H_{13} or $H_{13'}$), 1.55-1.48 (0.6 H, m, H_{8a}), 1.38-1.1.07 (3 H, m, H_{8b}, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.6 (C_1); 171.5, 171.2, 170.8, 170.3 (C_{14}); 134.8, 134.9 (C_{12}); 121.1, 120.1 (C_{11}); 74.3, 74.1, 71.3, 71.1 (C_6), 64.1, 64.0, 63.4, 63.4 (C_7); 44.9, 44.7, 44.2, 43.9 (C_3); 38.9, 38.8, 38.7, 38.7 (C_2); 29.5, 29.4, 29.1, 28.9, 28.8, 28.7, 28.6 (C_5, C_{10}, C_8, C_9); 25.7 (C_{13}); 23.6 (C_4); 21.2, 20.9, 20.8 (C_{13}); HRMS (ASAP) calcd for $C_{18}H_{32}O_5N$ ($[M+NH_4]^+$) 342.2275. Found: 342.2282.

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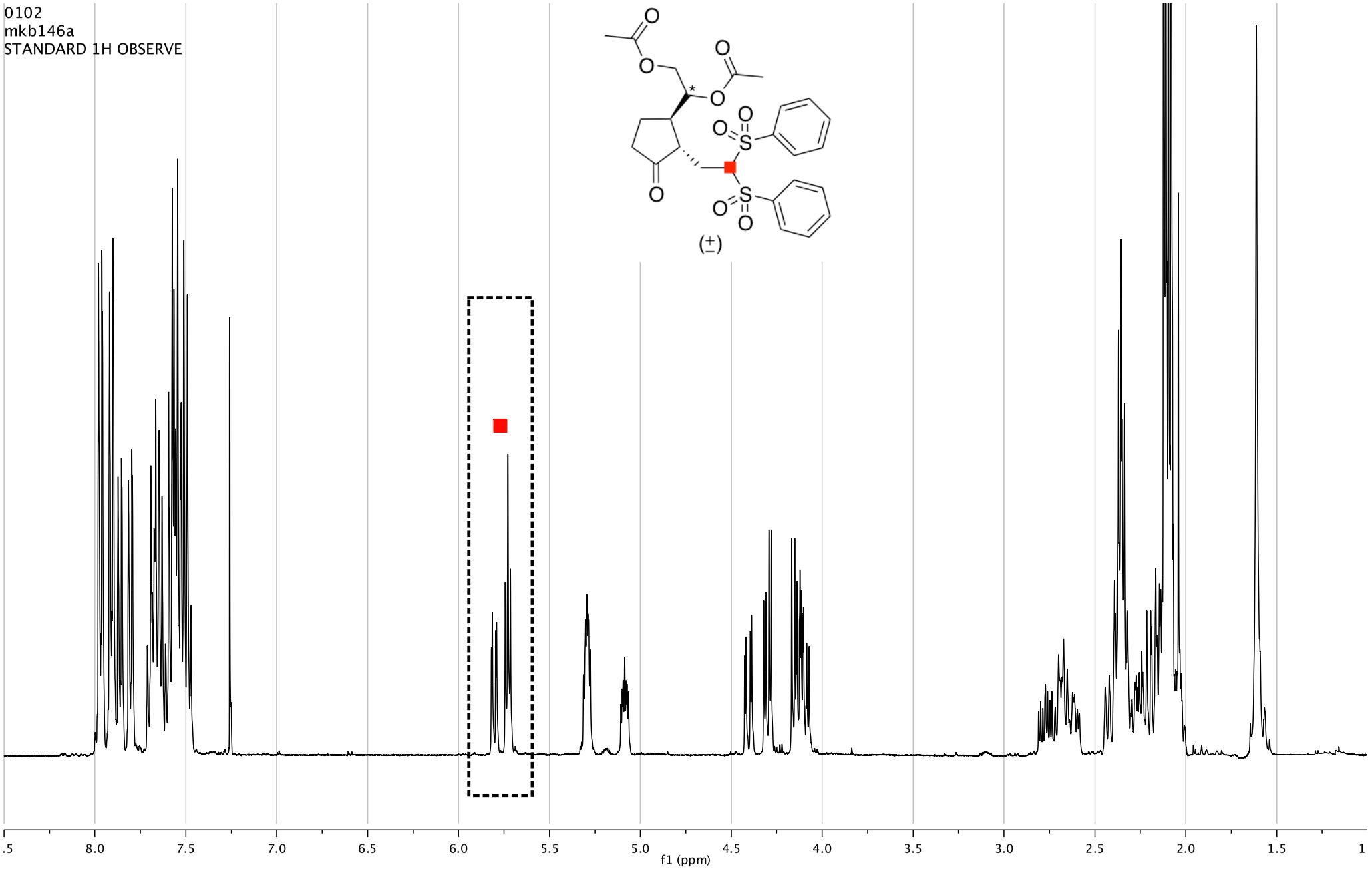
APPENDIX

(±)-*trans*-2-(2'(1',1'-Bis(phenylsulfonyl)ethyl))-3-(1',2'-diacetoxyethyl)-cyclopentanone 89c



(±)-*trans*-2-(6'-(5',5'-Bis(benzylcarboxylate)-hex-2'-ene))-3-(1",2"-diacetoxyethyl)-cyclopentanone 79b