Part A: Development of a modular synthetic approach to polycyclic polyprenylated acylphlorogluginols: total synthesis of papuaforin A, B, C, hyperforin and formal synthesis of nemorosone.

Part B: Studies toward the synthesis of ginkgolides

By

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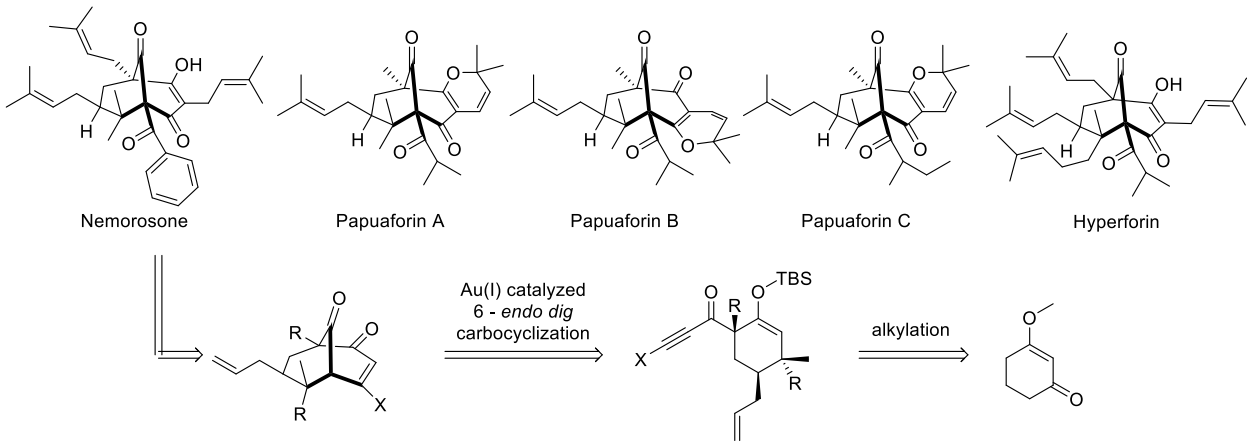
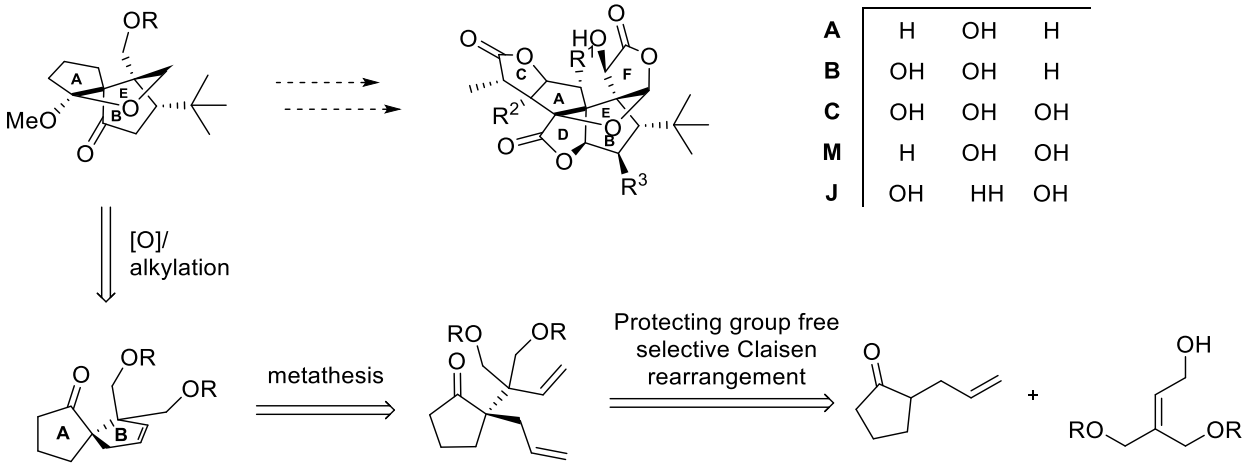
Abstract

Polycyclic Polyprenylated Acylphloroglucinols (PPAPs) are a vast family of natural products, which includes more than 200 members. They contain a stunningly complex molecular architecture which in most cases includes a bicyclo[3.3.1]nonane core. PPAPs have been of interest to the scientific community for their intricate structure, their powerful aid in treating many ailments and large portfolio of biological activities. More particularly, they have been of synthetic interest since 1999 with the first report of an approach to these complicated cores by Nicolaou. Herein, we present the first total synthesis of papuaforin A, papuaforin B, papuaforin C, hyperforin and the formal synthesis of nemorosone following a report by Simpkins and co-workers. We relied on a gold(I)-catalyzed carbocyclization for the construction of the core of this family of natural products.



Ginkgolides are isolated from the ginko tree, *Ginkgo biloba*, a living fossil with records of its existence dating back 280 million years. For centuries, the plant and its extracts have been used extensively for their beneficial properties, especially in China, Japan and India.[1] For example, extract Egb761, one of the most potent fraction, generates over $500 million a year alone. The

ginkgolides possess a truly unique compact diterpene framework of six 5-membered rings with a high content oxygen. Eleven oxygens can be found in ginkgolide C for a core containing only 23 carbons. The ginkgolides also include a very unique feature: a *tert*-butyl group located on the most convoluted ring system: the B ring. Few groups have found success in limning a synthetic route to ginkgolides. Corey's group was the first to achieve the total synthesis of ginkgolide B in 1987. He was also able to complete ginkgolide A a year later. Crimmins and co-workers also achieved the total synthesis of ginkgolide B a decade later in 1999. Herein, we present our new approach toward ginkgolides through a newly developed methodology for the α-allylation of ketones and the creation of highly hindered contiguous quaternary centers. The synthesis is still at an early stage but a synthetic pathway giving access to the ring B with all the key moieties has been extensively investigated.



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It goes without saying that I would like to thank my parents Marie-Renée and Paul. I'm so grateful for all they have given me, pushing me to achieve more and most important of all, believing in myself. Their infinite support for my life's goals have always been close to my heart and I could not have done it without them.

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“My momma always said, “Life was like a box of chocolates. You never know what you’re gonna get”

Forrest Gump

Abbreviations

Ac: acetate

acac: acetoacetonate

Bn: benzyl

dr: diastereomeric ratio

DCE: 1,2-dichloroethene

DCM: dichloromethane

DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DMAP: 4-dimethylaminopyridine

DMF: dimethylformamide

DMP: Dess-Martin periodinane

DMS: dimethyl sulfide

DMSO: dimethylsulfoxide

equiv. or eq.: equivalents

Et: ethyl

Et_2O: diethyl ether

Et_3N: triethylamine

GC/MS: gas chromatography coupled to mass spectrometry

HMPA: hexamethylphosphoramide

HPLC: high-performance liquid chromatography

HRMS: high resolution mass spectrum

IBX: triacetoxyperiodinane

Im: imidazole

L: ligand

L.A.: Lewis acid

LDA: lithium diisopropyl amine

LiHMDS: lithium bis(trimethylsilyl)amide

LiO*t*-Bu: lithium *tert*-butoxide

LiTMP: lithium tetramethylpiperidine

M: metal

m.p.: melting point

m-CPBA: 3-chloroperoxybenzoic acid

Me: methyl

MeCN: acetonitrile

n-BuLi: *n*-butyllithium

NHC: *N*-heterocyclic carbene

NMR: nuclear magnetic resonance

PCC: pyridinium chlorochromate

Pet. ether: petroluem ether

Ph: phenyl

PivCl: pivaloyl chloride

PPAPs: polycyclic polyprenylated acylphloroglucinols

PMB: *para*-methoxybenzyl

Ppm: parts per million

Py: pyridine

r.t.: room temperature

TBAF: tetrabutylammonium fluoride

TBS: *tert*-Butyldimethylsilyl

TBSOTf: *tert*- Butyldimethylsilyl trifluoromethanesulfonate

t-BuLi: *tert*-buthyllithium

TES: triethylsilyl

THF: tetrahydrofuran

THP: tetrahydropyranyl

TIPS: triisopropylsilyl

TIPSOTf: triisopropylsilyl trifluoromethanesulfonate

TLC: thin layer chromatography

TMEDA: *N,N,N',N'*-tetramethylethylenediamine

TMS: trimethylsilyl

TMSOTf: trimethylsilyl trifluoromethanesulfonate

UV: ultraviolet

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References

[1] K. Nakanishi, *Pure Appl. Chem.* **1967**, *14*, 89-113.

CHAPTER 1

Gold catalysis as a proficient tool in total synthesis

1.1 Introduction

Coinage metals have been part of every human culture with evidence of its value dating all the way back to the first Egyptian dynasties in 3100 B.C. The first use of gold as money can be traced back to 700 B.C.; the coin was produced by a Lydian merchant.[2] Today gold, silver and copper are still highly demanded metals for their respective value but also find utilities in our everyday life. For example, gold is now used in electronics for a combination of desired properties like electrical conductivity, capacity to endure high temperature and resistance to corrosion. Silver is also used in electronics as a heat conductor and copper can be easily stretched, molded and shaped. It allowed the construction of many famous icons such as the Statue of Liberty which contains over 80 tons of copper. Copper is also found in electrical wiring, building construction, electronic products and many other everyday items.[3] It is only recently though, that gold was found to be a useful tool in chemistry.

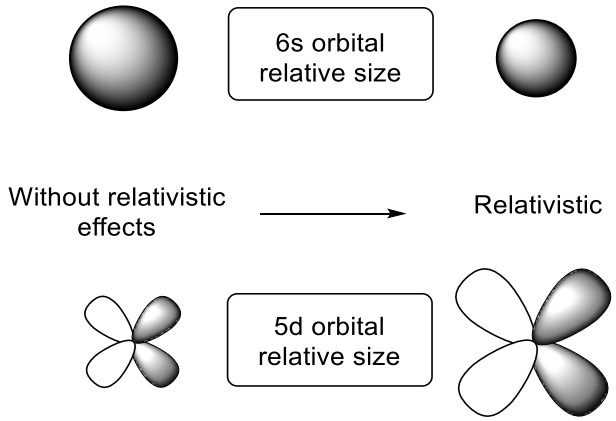
1.2 Gold properties, chemoselectivity and versatility

The utilization of gold in organic reactions and transformations is novel since it was originally assumed that gold was a noble metal with little to no inherent activity. But from the early 1990s, an unprecedented understanding of its potential awoke the enthusiasm of the

chemistry community and led to seminal findings by researchers like Yoshihiko Ito, Tamio Hayashi,[4] Alois Fürstner, Dean Toste, Antonio M. Echavarren, Fabien Gagosz, Suzanne A. Blum, Stephen K. Hashmi and Leming Zhang, just to name a few.

Gold(I) complexes are unique in their selectivity to activate π-bonds while refraining from reacting with other chemical handles in complex molecules. It has been successful in activating allenes, alkenes, dienes, but more particularly alkynes.[5] This characteristic of Au(I) has been attributed to the relativistic effect[6] that manifests itself in many forms. This phenomenon becomes important when the need to consider the velocity of the electrons as significant relative to the speed of light. This effect is especially important in Au and causes the electrons to move faster which in turns makes the electron heavier. Consequently, the mass of electrons is inversely proportional to the Bohr radius of the orbiting electrons. Thus, the electrons are closer to the nucleus and have greater ionization energy, in addition to a smaller radii observed compared to same row elements. The contraction of the s and p electrons indirectly enhance the shielding the 4*f* and 5*d* orbitals from the nucleus and therefore these orbitals feel less nuclear attraction. As a result, the 5*d* orbitals are bigger which increases their π-acidity but also their ability to perform backdonation (***Figure 1.1 and Scheme 1.1)***. Calculation on $AuCH_2^+$ by Irikura and Goddard[7] found that Au featured many different type of bonds and work by Barysz and Pyykko[8] on the proposed triple bond character of AuC^+ gave significant support to backbonding from Au(I) into empty *p* orbitals. The golden color of gold is said to be the result of an excitation of the 5*d* electrons to the Fermi level that occurs at the bandgap of 2.38 eV, which absorbs the blue light.

Figure 1.1 – Relativistic effects on 6s orbitals and 5d of gold

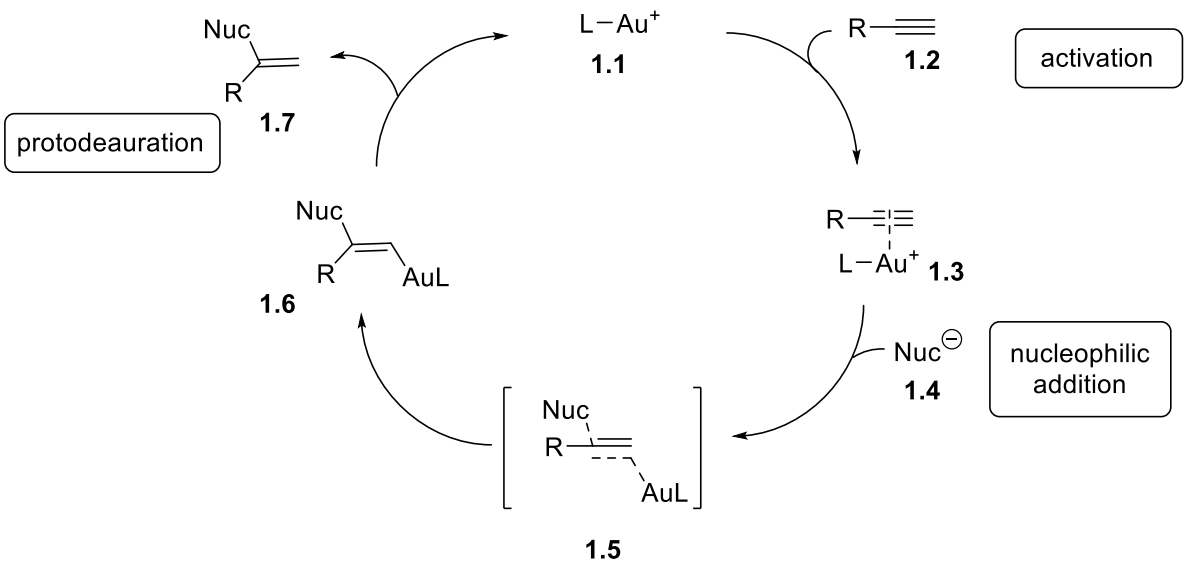


Scheme 1.1 – Implication of relativistic effect on Au properties

1.2.1 General reactivity of gold(I)

The π-acidity of gold catalysts translates to highly selective soft Lewis acid characteristics toward the activation of alkynes facing nucleophilic addition (***Scheme 1.2***). Generally, the gold catalyst **1.1** will activate the alkyne **1.2** to give complex **1.3**. Complex **1.3** is now a potent electrophile capable of reacting with multiple nucleophiles such as alcohols, π-bonds, amines, *N*-oxides, etc. It is important to note that the attack of the nucleophile is done in a *trans* fashion as shown by intermediate **1.5** to give *trans*-alkynyl gold complex **1.6**. The vinyl gold complex **1.6** then reacts with an electrophile, usually a proton to yield protodeaurated product **1.7** and regenerate the reactive gold catalyst **1.1**. The resulting alkene **1.7** from the addition onto an alkyne is normally unreactive toward further addition.

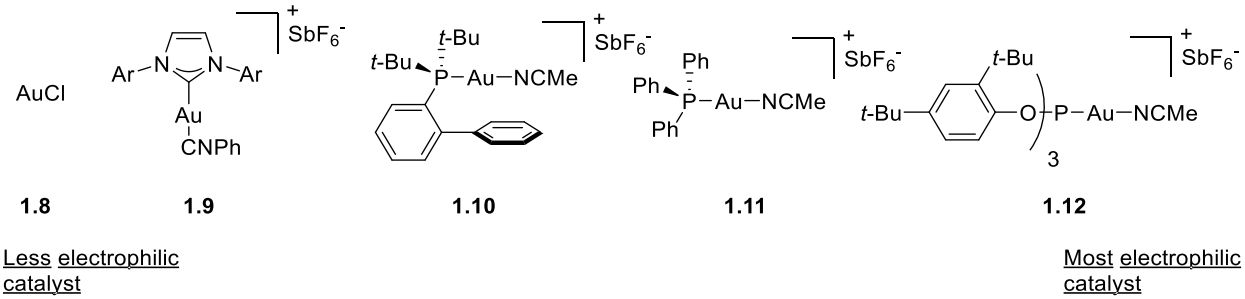
Scheme 1.2 – General outlook on gold(I) reactivity



1.2.2 Ligand/counter anion effect on Au(I) catalysts

The behavior of the gold(I) complexes is shaped by the nature and character of the ligand. Structurally, Au(I) prefers to adopt a linear two-coordinate complex and is amendable to many types of well defined class of ligands like the N-heterocyclic carbenes,[9] Buchwald ligands,[10] Stradiotto ligand[11] and also *tri*-arylphosphine ligands (***Scheme 1.3***). N-Heterocyclic carbenes seem to have found a broader application for gold catalysis but ligand design is still at its dawn since it took advantage almost exclusively of ligands originally designed for palladium chemistry.

Scheme 1.3 – Common Au(I) catalysts in order of electrophilicity



1.8 **1.9** **1.10** **1.11** **1.12**

Less electrophilic catalyst

Most electrophilic catalyst

Overall, the choice of ligand is still in the realm of trial and error but there is subtle advantage to use certain ligands over others.[12] For example, the electrophilic activation of the alkyne by the catalyst seems to be slowed by electron rich ligands while accelerated by electron poor ligands. Paradoxically, electron withdrawing ligands slow the protodeauration process while the electron donating ligands have the inverse effect. Knowing the kinetics of the desired reaction is then desirable, if the limiting step is the activation of the alkyne, then electron deficient ligands might offer better reactivity. If the protodeauration step is slower, then an electron rich ligand might offer a better outcome. Generally through, electron rich ligands seem to perform better.[13]

There is another factor influencing the outcome of the reaction induced by the ligands that is often omitted from discussions: the degradation rate of the Au(I) catalyst to Au(0) (which is catalytically inactive). For instance, PPh_3AuOTf was found to be quite stable in solution with almost no degradation after even a week but this decay accelerated greatly once an alkyne was introduced into the solution. Other types of Ar_3PAu^+ decayed much faster without the presence of alkynes.[12] The degradation of Au(I) catalysts is not adequately studied and it should be kept in mind for future endeavors in studying this metal.

So far, we have highlighted the different neutral ligands but the coordinating anion also serves a purpose that cannot be omitted even though its role remains obscure in most cases. Echavarren[14] and Kirsh[15] studied this variant and found that for certain reactions there was a direct correlation between yield and counter-ion following the trend: $OTf^- < NTf_2^- < BF_4^- < SbF_6^- < [B(3,5\text{-}(CF_3)_2C_6H_3)_4]^-$ (BARF). It was found that BARF could increase yields by up to 10-30% compared to SbF_6^-. Similarly to choosing the appropriate ligand, it's often difficult to anticipate the perfect counter anion for a chosen reaction but ultimately should come down to a good balance between yield increase/cost-effectiveness.

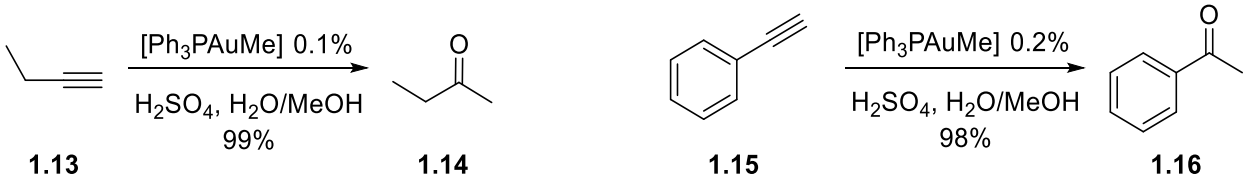
1.3 Key transformations catalyzed by gold catalysis

This section will serve as an introduction to the key disconnection that can be achieved using gold catalysis. This list is not exhaustive but will help highlight examples that are important to offer insight on my contribution to the field.

1.3.1 Addition of heteronucleophiles to alkynes

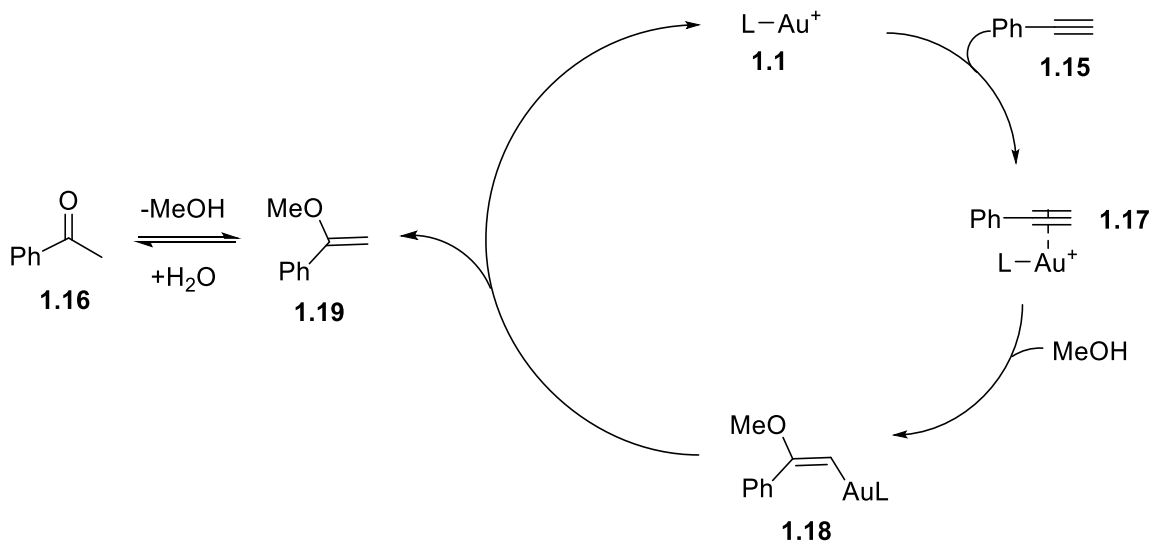
Hydration of alkynes with alcohols appeared as one of the first transformations showcasing the reactivity of Au(I). Teles[16] and Tanaka,[17] reported that Au(I)-Cl in presence of an acid and alcohol/H_2O led to the ketone or ketal resulting from the Markovnikov addition (***Figure 1.2***).

Figure 1.2 – Examples of Au(I) catalyze alkyne hydration



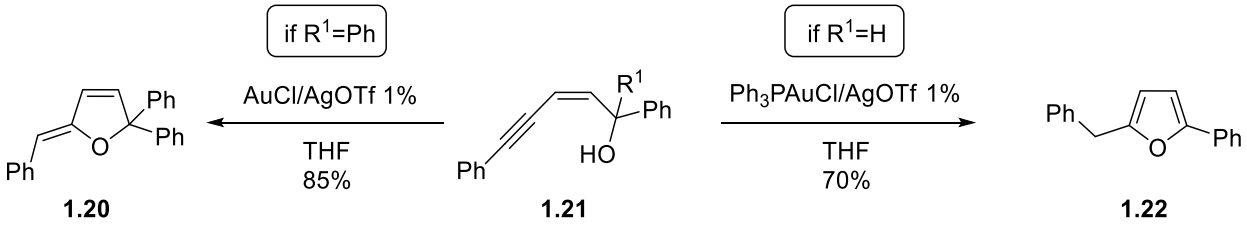
Similarly to the mechanism shown in ***Scheme 1.2***, the mechanism of hydration (***Scheme 1.4***) starts with a complexation of gold catalyst **1.1** to alkyne **1.5** to form **1.17**. MeOH then plays the role of the nucleophile and add to form transalkynyl gold adduct **1.18** resulting from the Markovnikov addition. Protodeauration leads to **1.19** which after exchange with water gives ketone **1.16.**

Scheme 1.4 – Proposed mechanism for the addition of MeOH onto phenylacetylene



The intramolecular addition of alcohols and epoxide is also well documented and allows access to valued heterocycles such as furan derivatives. Lui[18] showed that in presence of $Ph_3AuCl/AgOTf$, a method to form PPh_3AuOTf *in situ*, one could transform (*Z*)-enynols **1.21** into furans **1.22** or dihydrofurans **1.20** (***Scheme 1.5***).

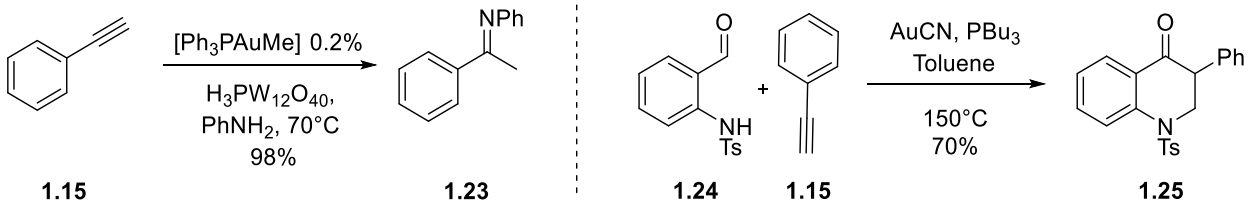
Scheme 1.5 – Intramolecular Au(I) catalyzed addition to form furans and dihydrofurans



The addition of *N*-nucleophiles onto activated alkynes is also possible with one of the first example resulting from Hayashi and Tanaka's research in 2003 (***Scheme 1.6***).[19] Treatment of phenylacetylene **1.15** with Au(I) in presence of aniline led to imine **1.23**. Thereafter, more elaborate tandem reactions were put in place to construct complex structures swiftly like the core

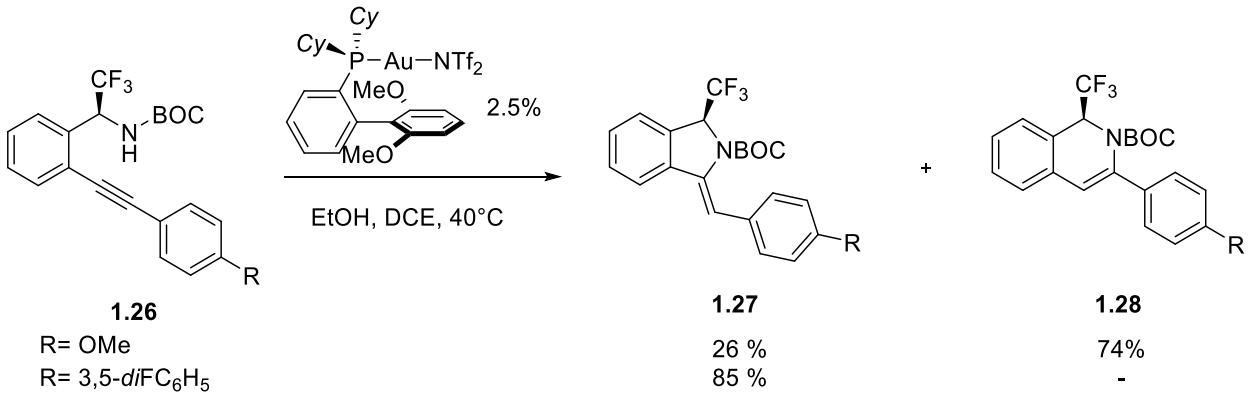
of azaflavones.[20] When *ortho*-formylaniline **1.24** was treated with AuCN in a mixture with phenylacetylene **1.15,** it gave azaflavones derivatives **1.25**. In general though, *N*-nucleophiles required higher temperature probably due to a stronger azaphilicity compared to the oxophilicity of gold.

Scheme 1.6 – N-nucleophile addition



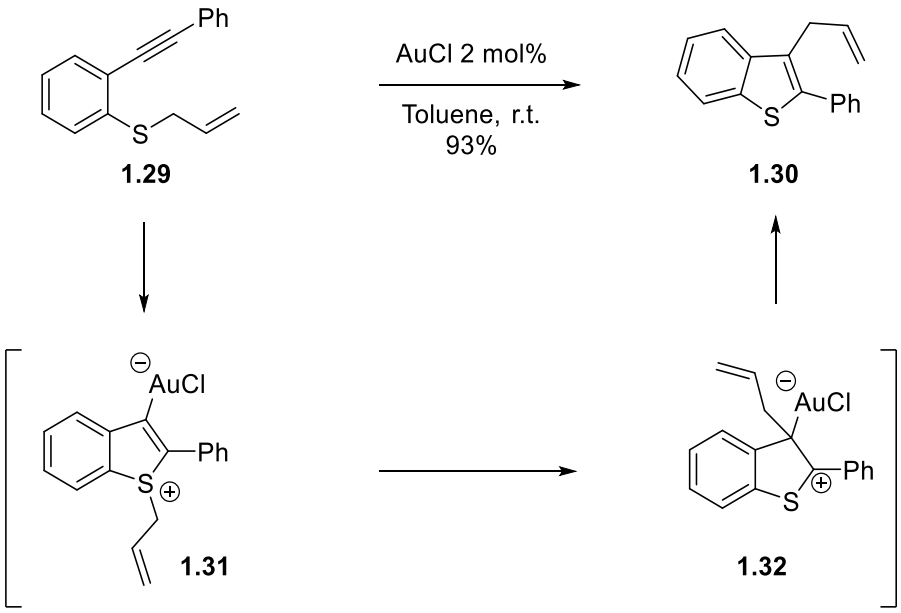
The intramolecular addition of *N*-nucleophiles seems to alleviate the need for high temperature, with addition occurring at more moderate temperature. Catalan and co-workers[21] showed that 40˚C was sufficient to cyclize *o*-alkynylbenzyl carbamates **1.26**. Strikingly, the electronics of the alkynyl phenyl ring influenced the outcome of the cyclization. Electron rich rings, exemplified by the –OMe, were selective for the *6-endo* dig cyclization **1.28** while electron poor arenes led exclusively to *5-exo* dig cyclization **1.27** (***Scheme 1.7***). The same trends were observed by Barriault *et al.* in 2011.[22]

Scheme 1.7 – Cyclization of o-alkynylbenzyl carbamates



Sulfur atoms can also participate in gold catalysis but the examples are scarce as S-nucleophiles are known to poison [Au]. Nakamura and co-workers[23] used *ortho*-alkynylphenyl sulfide **1.29** to produce the 2,3-substituted benzothiophenone **1.30** in great yield. They were unable to employ the benzenethiol directly though (***Scheme 1.8***).

Scheme 1.8 – Cyclization of ortho*-alkynylphenyl sulfide*

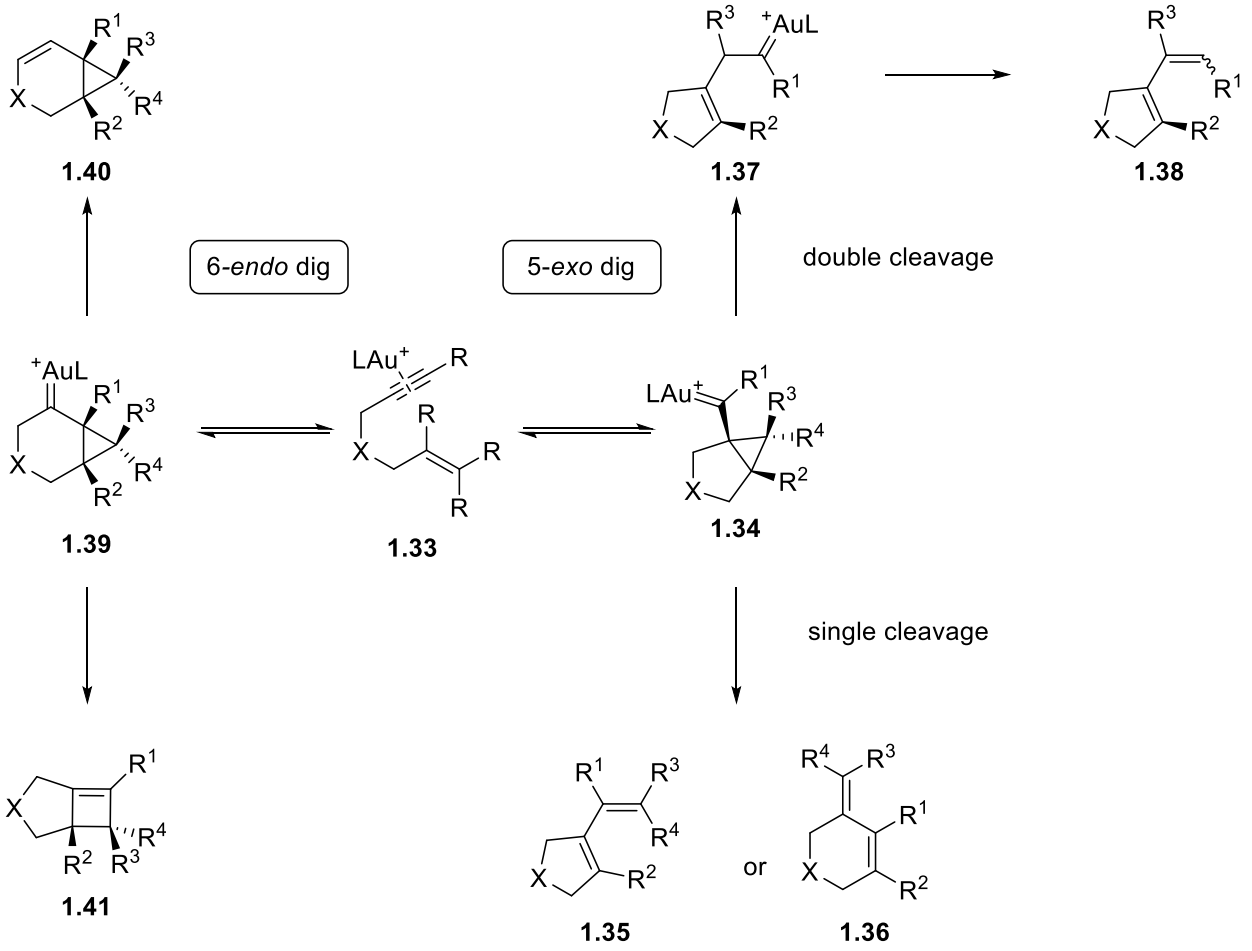


1.3.2 Cycloisomerization of enynes and Conia-type reaction

Cycloisomerization of 1,n-enynes are central reactions in organic chemistry as they allow to build complexity rapidly from readily available starting materials. At its origin, palladium was used to induce an intramolecular Alder-ene reaction. But unlike palladium and platinum, gold can only bind to one alkyne at a time revealing a different mechanism.[24] In fact, an Alder-ene mechanism does not take place but instead a (η^2-alkyne) metal complex **1.33** is formed which plays the role of electrophile in presence of alkene nucleophile. For the case of 1,6-enynes (***Scheme 1.9***), the alkene may react in a 5-*exo* dig fashion to give the corresponding cyclopropyl gold carbene **1.34**. This intermediate can perform and *exo*-type single cleavage to give cyclopentene **1.35** or

endo-type single cleavage to give cyclohexene **1.36**. The double cleavage of **1.34** will lead to product **1.38**. The alkene has also the opportunity to perform a *6-endo* dig attack in which case gold carbene **1.39** would be obtained instead. It can undergo protodeauration to give **1.40** or proceed with a ring expansion and provide cyclobutene **1.41**. However, products resulting from the *6-endo* dig addition are generally less common in the literature as the *5-exo* dig cyclization is more favorable energetically. But through careful choice of substrate and catalyst, one can selectively favor one path over others.

Scheme 1.9 – Possible products generated from the cycloisomerization of 1,6-enynes



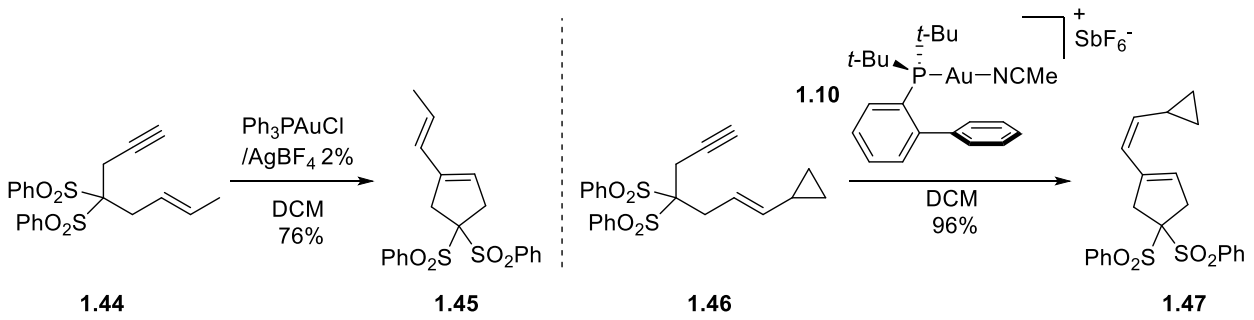
Scheme 1.9 represents gold (I) as a carbene in structure **1.34** but as defined in ***Scheme 1.10***, gold carbene **1.34** is in equilibrium with gold carbocation **1.42** and vinyl gold **1.43**. This has some profound implications, since subtle changes in the electronics of the R substituents can bring about important variations on chemoselectivity and stereoselectivity of the desired transformation. It can embolden a more carbene-like behavior from the metal or push toward a carbocation-like behavior.

*Scheme 1.10 – Other plausible resonance forms of intermediate **1.34***

1.43 **1.34** **1.42**

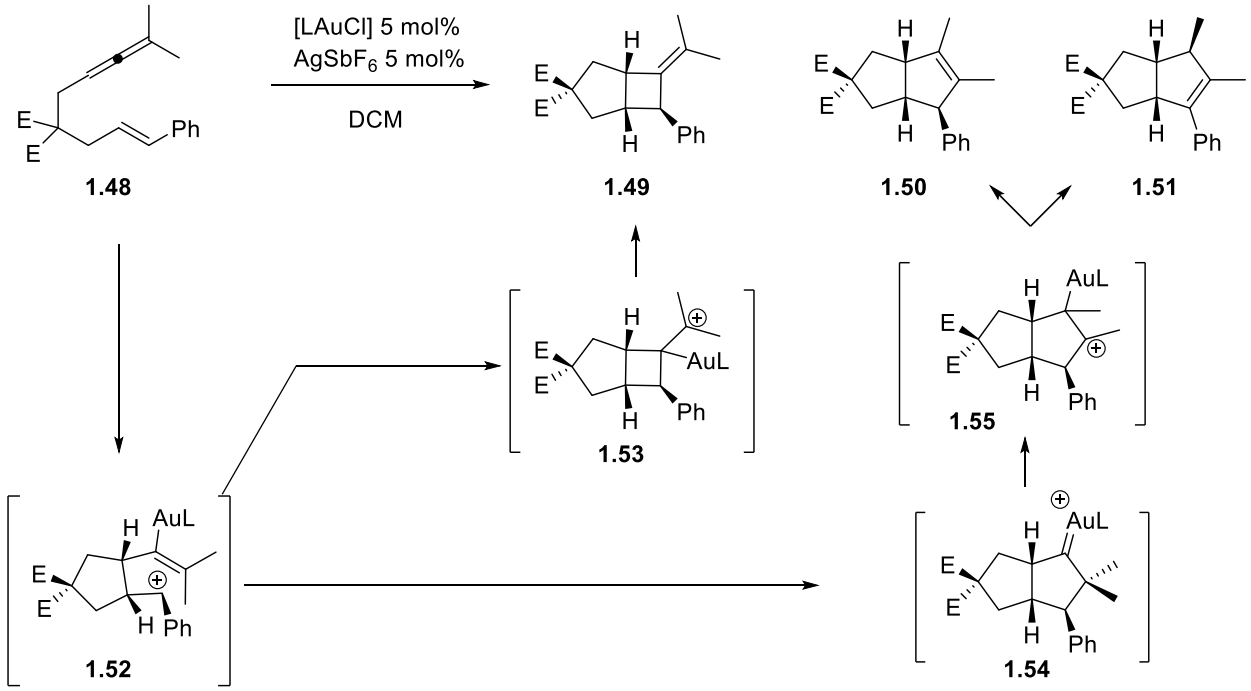
A particularly interesting example of the effects of the R substituents can be found in the discrepancy in olefin selectivity when catalyzing the cycloisomerization of **1.44** and **1.46** (***Scheme 1.11***). **1.44** retained its original (*E*)-configuration while the introduction of an electron donating group in the case of **1.46** afforded the double cleavage adduct **1.47**.[24-25] It is accepted today that cycloisomerization is most likely induced by a carbene-like behavior of gold. This support comes from the collection of products more favorably explained by the intermediate **1.34**,[5c, 5e, 6, 26] but it is of my opinion that as we investigate every aspect of the catalytic cycle of Au(I), we might find that misunderstood effects have great influence on its activity.

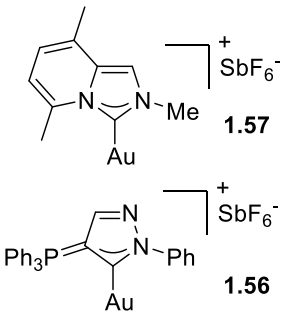
Scheme 1.11 – Substituent effect on olefin geometry



In 2010, Furstner and co-workers[27] showed that π-acidity of the NHC ligands used in three different reactions could modulate the outcome and type of reactivity exhibited by the gold nucleus (***Scheme 1.12***). In the case of ene-allene **1.48**, striking differences in behavior could be observed depending on the nature of the ligand. The stronger net donor nature of catalyst **1.57** was able to better stabilize the net charge of the carbene **1.54** and induced exclusively the formal [3+2] cycloisomerization to **1.50** and **1.51**. In the situation where catalyst **1.56** was used, only cyclobutane **1.49** was observed which was reasoned by the strong π-acceptor properties of the ligand (-0.92 eV compared to -0.63 eV for **1.57**) that reduced the ability of Au(I) to perform backdonation and preferred to follow the cationic pathway. Similar results were reported by Toste with phosphine-type ligands.[28]

*Scheme 1.12 – Control over cycloaddition of eneallene **1.48***



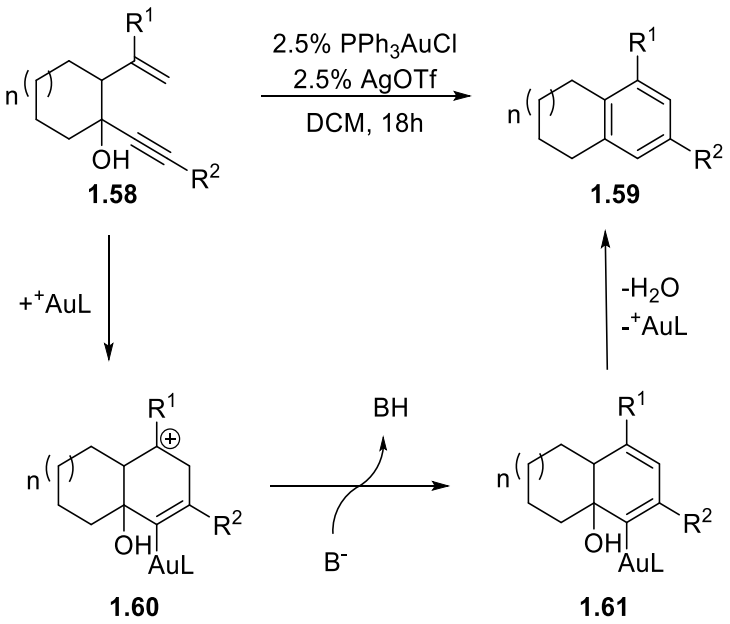


1.49	1.50	1.51
0	62	38
100	0	0

Recently, the concept of selectivity in cycloisomerization and gold catalysis has been the main focus of our research program. The story of our involvement with gold started when Dr. Christiane M. Grisé, who found that she could catalyze benzannulation of 3-hydroxy-1,5-enynes **1.58** to generate tetrahydronaphthalenes **1.59** (***Scheme 1.13***).[29] The yields were found to be greatly influenced by the substituents and also size of the cycloalkyl ring of the starting material **1.58**. It was proposed that in this particular setting, the 6-*endo* dig addition was favored leading to vinyl cationic intermediate **1.60** which after deprotonation gave diene **1.61**. The protodeauration

could in principle occur before or after the dehydration process but overall this resulted in adduct **1.59**.

Scheme 1.13 – Benzulation of 3-hydroxy-1,5-enynes



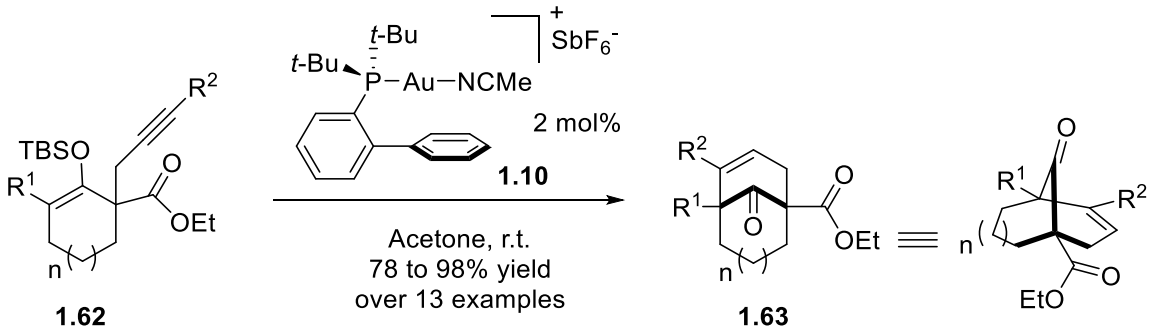
After the introduction of Buchwald type ligands on Au(I) by Echavarren and co-workers[30] in 2005, we were intrigued by their reactivity and potential as catalyst. We were also inspired by the work of Toste[31] and Lee[32] on the cyclization of silyl enol ethers onto alkynes to form bicyclic systems. Before going further in the subject at hand, I would like to mention that even though I have been personally involved in the investigation *6-endo* dig carbocyclization of silyl enol ethers with alkynes, this work was done as part of my undergraduate studies and honours project. Thus, for more details about the following transformations please refer to the publications or honor's project thesis.[33]

Enthused by the utilization of silyl enol ethers as internal nucleophile and the ease of manipulating catalyst **1.10**, we were able to develop a methodology to build bicyclo[m.n.1]alkenone frameworks (***Scheme 1.14***).[33] Bicyclo[3.3.1]alkenone more specifically

is a motif found in the family of natural products known as polycyclic polyprenylated acylphloroglucinols (PPAPs), which includes over 150 natural products. This method gave us a direct entry to the core of those natural products but this subject will be covered in the next chapter dedicated to the synthesis of PPAPs.

Treatment of silyl enol ether **1.62** with 2 mol% of catalyst **1.10** (developed by Echavarren)[30] in acetone at room temperature provided bicycle **1.63** in yields varying from 78% to 98%. This reaction was truly exceptional as it does not require any particular care. i.e. under air and using non-distilled ACS grade solvents. Equally important, the size of the starting material's ring does not impair the operability of this reaction nor does the nature of the substituent at R^1 and R^2.

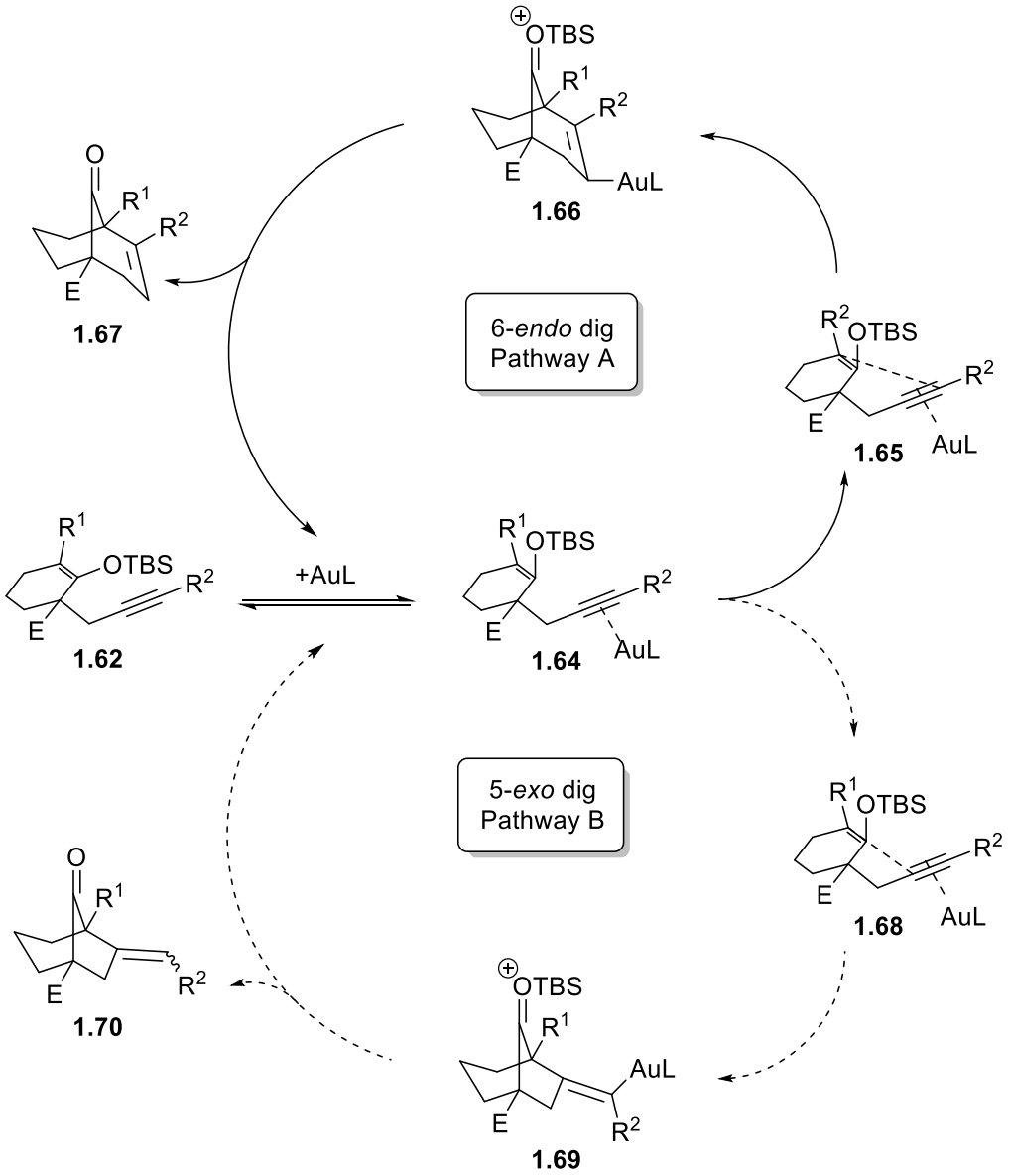
Scheme 1.14 – Au(I) catalyzed construction of bicyclo[m.n.1]alkenone frameworks



We proposed that the mechanism can proceed via 2 distinct pathways (***Scheme 1.15***). In path A, a 6-*endo* dig cyclization of Au-complexed adduct **1.64** gave vinyl gold **1.66** which after protodeauration and subsequent desylilation led to bicyclo[3.3.1]alkenone **1.67.** The competitive path B, gave, through a *5*-exo dig cyclization, bicycle **1.70**. The treatment of silyl enol ether **1.62** though, led exclusively to the *6-endo* dig cyclization **1.67** without ever any trace of *5-exo* dig carbocyclization adduct **1.70**. The exact reasons for this level of selectivity are still elusive,

especially when looking at Nicolaou gold-catalyzed Conia-ene type *5-exo* dig cyclization during total synthesis of platencin, which was achieved with a similar substrate to **1.62** (***Scheme 1.36***).[34]

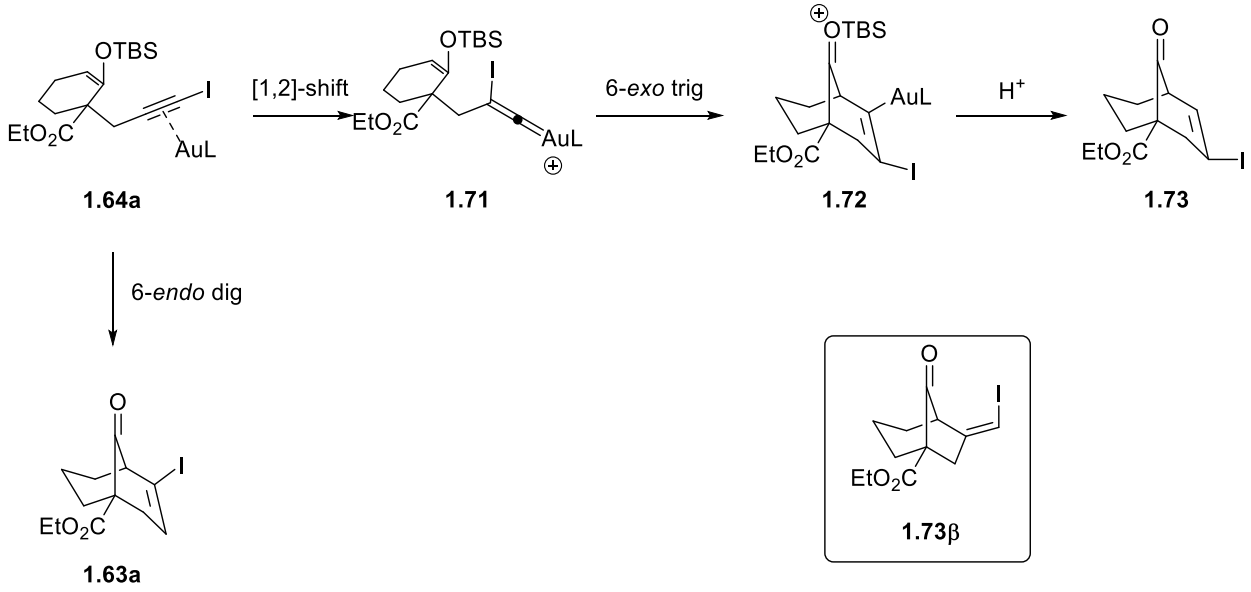
*Scheme 1.15 – Proposed mechanism for cyclization of enyne **1.62***



Interestingly, all substrates behaved as expected, except for iodide **1.64a** where a mixture of *6-endo* dig cyclization product **1.63a** and unanticipated 1,2-migrated adduct **1.73** were observed (***Scheme 1.16***). For molecule **1.64a** a 1.2:1 normal: 1,2-migrated mixture was observed in 88%

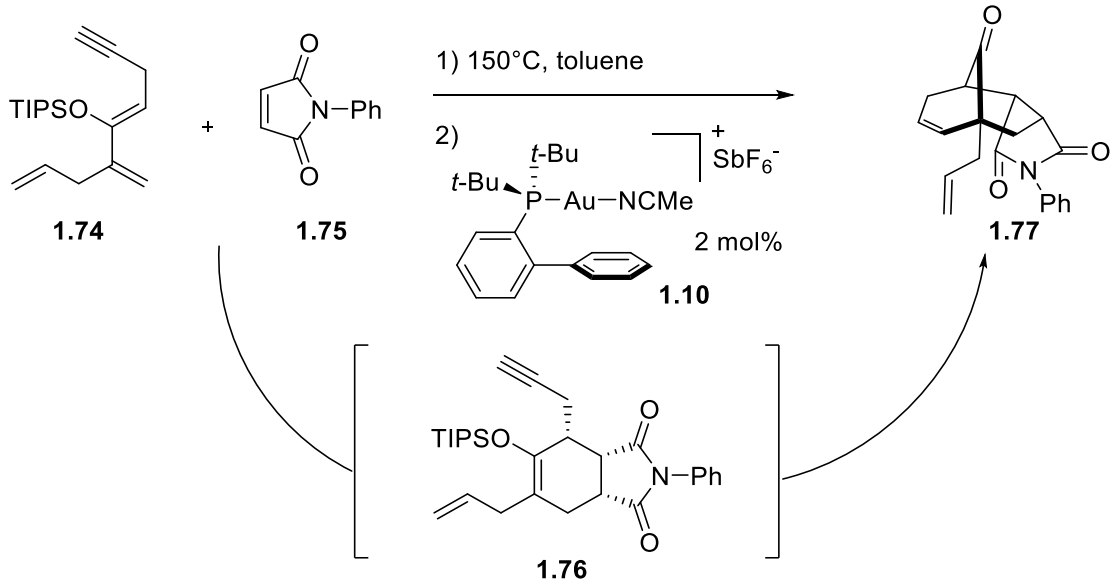
yield. We attributed the 1,2-migration to a [1,2]-shift induced by gold on complex **1.64a** to form vinylidene **1.71**.[35] Following a *6-exo* trig cyclization, we observed bicycle **1.73** (for more information on vinylidenes and reactivity please refer to section 1.3.4). In the original publication, structure **1.73** was wrongfully attributed to the *5-exo* dig cyclized product **1.73β** but was later conclusively attributed to 1,2 migration adduct **1.73**.

Scheme 1.16 – Proposed mechanism for iodide transposition



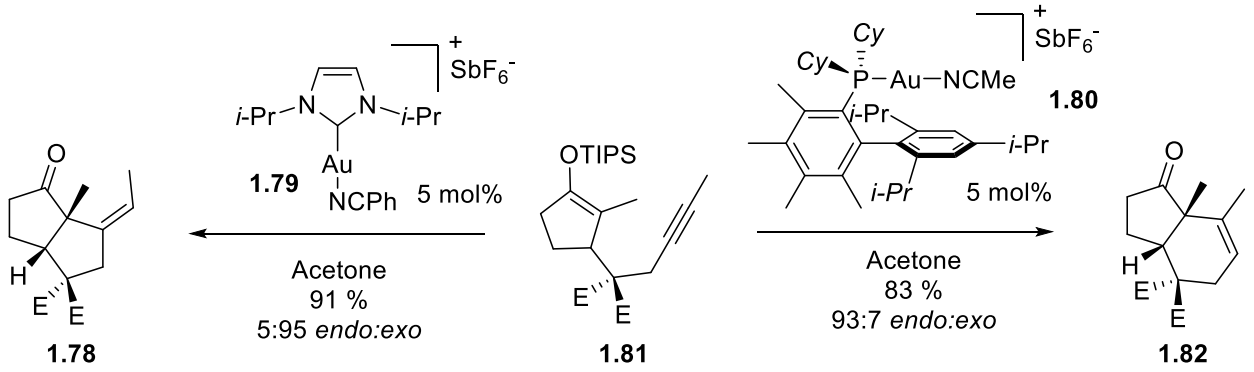
This selective *6-endo* dig cyclization was subsequently used in combination with a Diels-Alder reaction for the construction of more complex scaffolds (***Scheme 1.17***).[36] From heating **1.74** and **1.75** in the microwave, Diels-Alder intermediate **1.76** was obtained. Subsequent treatment with catalyst **1.10** gave *6-endo* dig cyclized product **1.77.**

Scheme 1.17 – One-pot Diels-Alder/ 6-endo dig cyclization



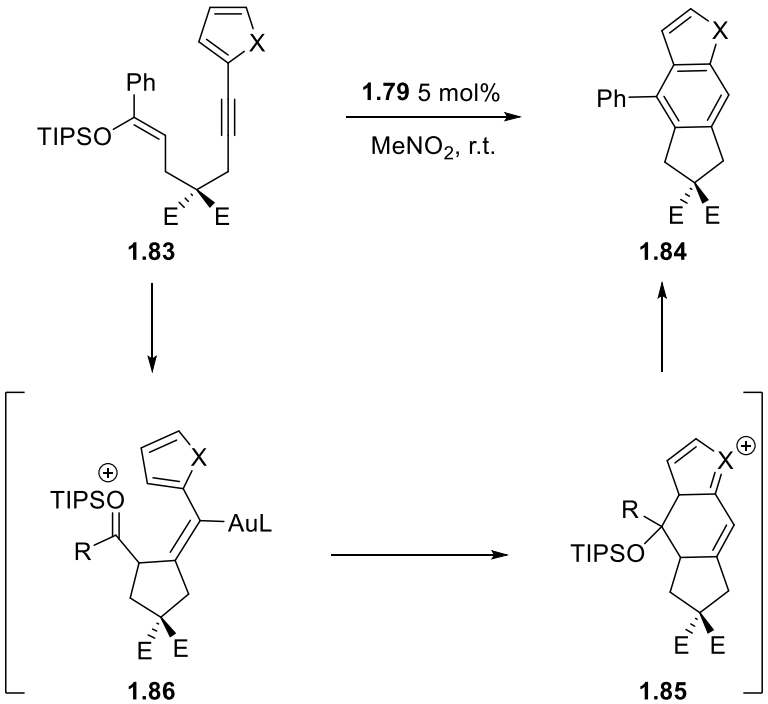
Later, work by Dr. Francis Barabé and Patrick Lévesque[22] showed the selectivity of the *5-exo* vs. *6-endo* cyclization of 1,6-enynes **1.81** could be modulated by the nature of the ligand. Previously, Toste[31] and Lee[32] showed the preference for such cyclization to undergo the 5-*exo* cycloisomerization only. [IPrAuCNPh]SbF_6 (**1.79**) gave exclusive *5-exo* dig cyclization product **1.78** whereas *6-endo* dig cyclization product **1.82** was obtained preferentially with [MeXPhosAuMeCN]SbF_6 (**1.80**)(***Scheme 1.18***). This dissonance in selectivity was attributed to the deformation of the P-Au-C angle, induced by the bulkiness of the Buchwald ligand, which resulted in a diminished Au-*dπ*-→C-*pπ* and proceeded through a more cationic type mechanism. In the most extreme case of angle deformation, X-ray crystallography of the chloride of catalyst **1.80** was found to have an inside angle of 169˚ for the P-Au-Cl bond.

Scheme 1.18 – Catalyst regulated cyclization



Following these results, research by Mathieu Morin and Patrick Lévesque explored the reactivity of 1,6-enynes with heterocycle-substituted alkynes. These substrates could undergo an additional cyclization to get to an array of substituted aromatic compounds (***Scheme 1.19***).[37] When submitted to catalyst **1.79,** 1,6-enyne **1.83** underwent a *5-exo* dig cyclization first to give oxonium **1.86**. The carbocation was then trapped by the heterocycle to give **1.85** and after elimination and tautomerization **1.84** was obtained.

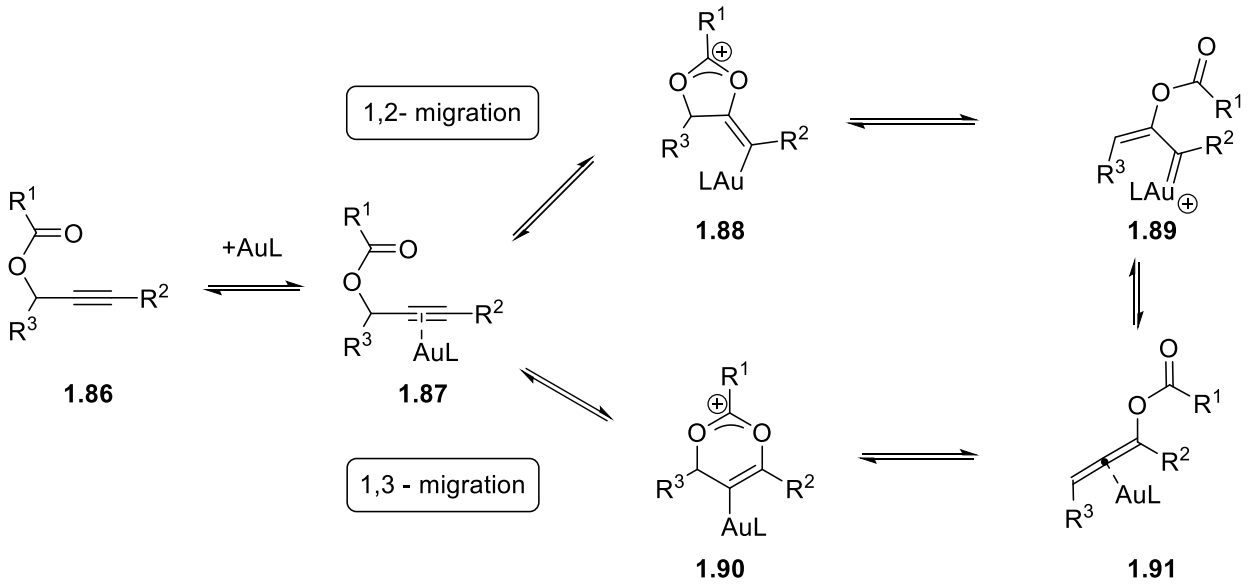
Scheme 1.19 – 5-exo dig polycyclization of 1,6-enynes



1.3.3 Reaction of propargylic carboxylate

The rearrangement of propargylic carboxylates in presence of gold is also very interesting and leads to complex and otherwise hard to access scaffolds (***Scheme 1.20***). Generally, after formation of Au complex **1.87**, the carboxylate can either perform a 1,2-migration to afford gold carbene **1.89** through the formation of a 5-membered carboxonium ring **1.88** resulting from a *5-exo* dig cyclization or a 1,3-migration to provide allene **1.91** resulting from a *6-endo* dig cyclization to give 6-membered ring **1.90**. The resulting carbene **1.89** or allene **1.91** have been known to react with many nucleophile like alkenes, ynamides, imine, sulfides, etc.[5c]

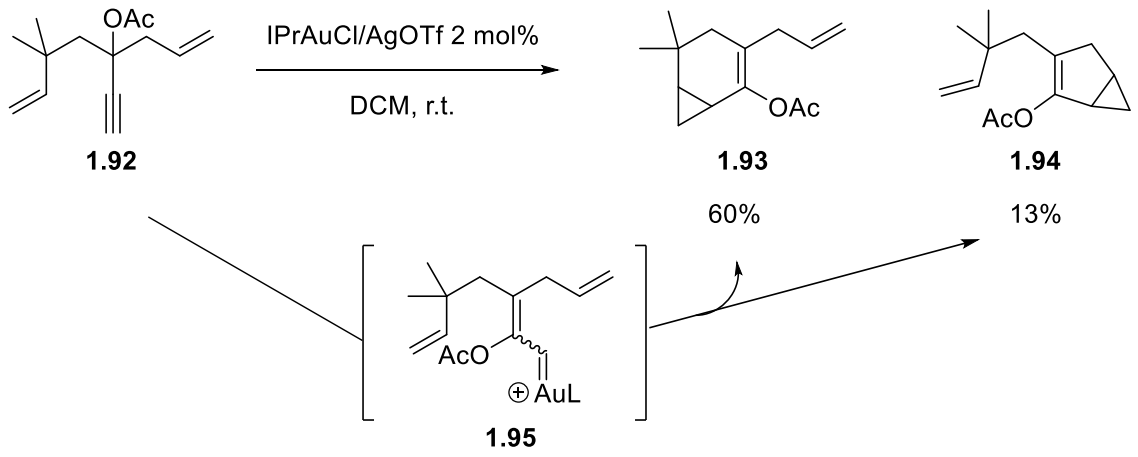
Scheme 1.20 – General reactivity of propargylic carboxylates



Some of the early examples of propargylic carboxylate rearrangement were introduced by Malacria and co-workers. They showed that cycloisomerization of 1,5-enyne with migration of carboxylate can be catalyzed with $PtCl_2$[38] and Au(I)-complexes (***Scheme1.21***).[39] The latter revealed that diene propargylic acetate **1.92** will either form cyclohexene cyclopropane **1.93** or cyclopentene cyclopropane **1.94**. The selectivity was induced by the *gem*-dimethyl that impaired

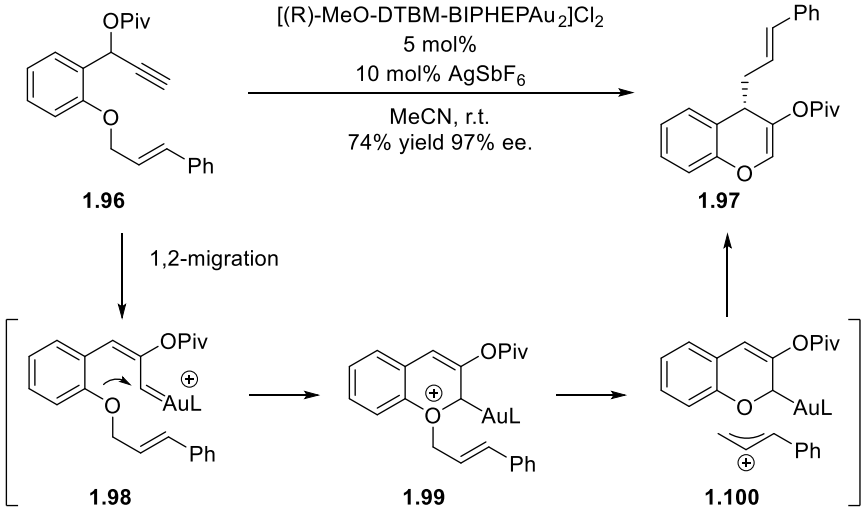
the gold binding and favored the formation of **1.95** where the acetate was *trans* to the *gem*-dimethyl chain. Once the migration was completed and carbene **1.95** was obtained, it reacted with the closest alkene to give a mixture of **1.93** and **1.94** strongly favoring **1.93**.

Scheme 1.21 – Propargylic acetate rearrangement of dienynes



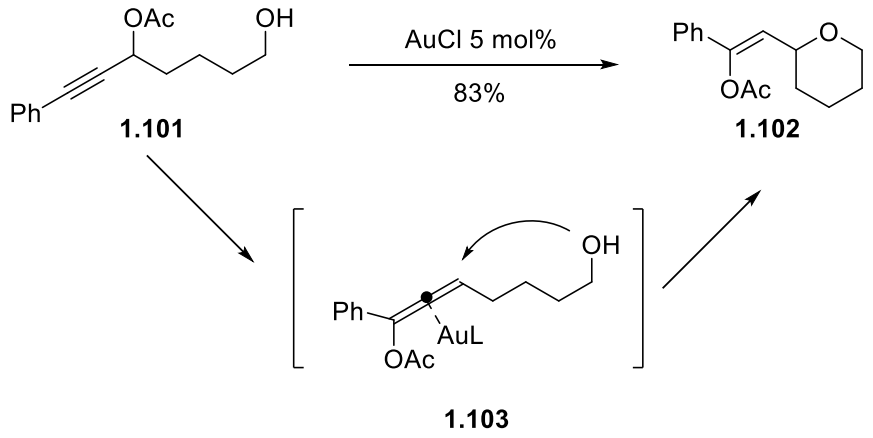
Toste and co-workers reported a nice example of selective 1,2-migration[40] in the synthesis of benzopyran **1.97** from 2-allylether propargyl carboxylate **1.96**. After the 1,2-migration leading to carbene **1.98**, the oxygen of the ether acted as the nucleophile to close the pyran ring of **1.99** which then induced a π-allyl gold complex **1.100** that rearranged to benzopyran **1.97**.

Scheme 1.22 – Benzopyran synthesis from 2-allylether propargyl carboxylate



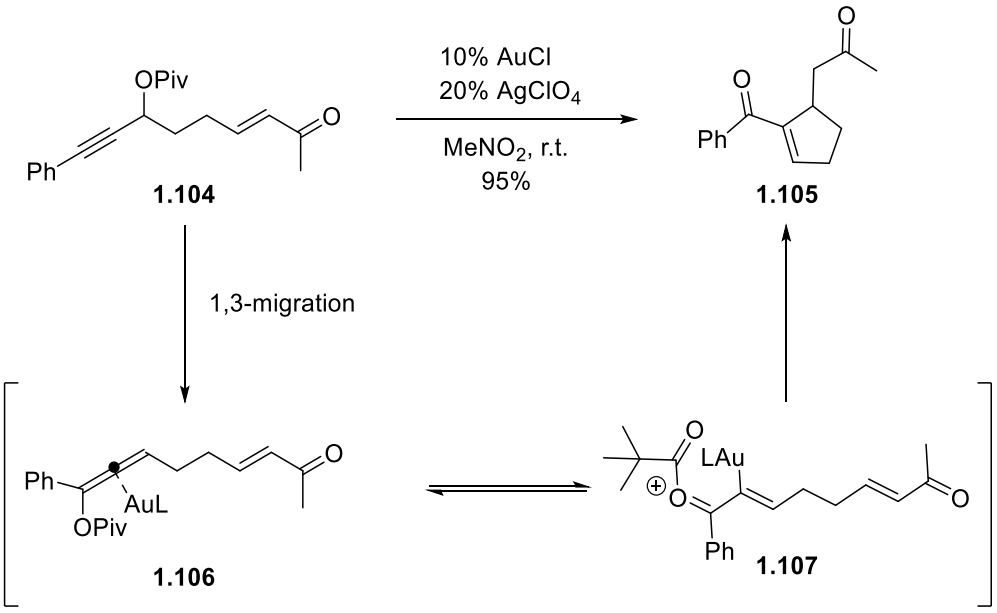
Using propargyl acetate **1.101**, Brabander[41] showed that this substrate underwent a selective 1,3-migration to give allene **1.103**. The latter was trapped intramolecularly with a terminal alcohol to give pyran **1.102** in 83% yield.

Scheme 1.23 – 1,3-Migration of propargyl acetate for the synthesis of pyrans



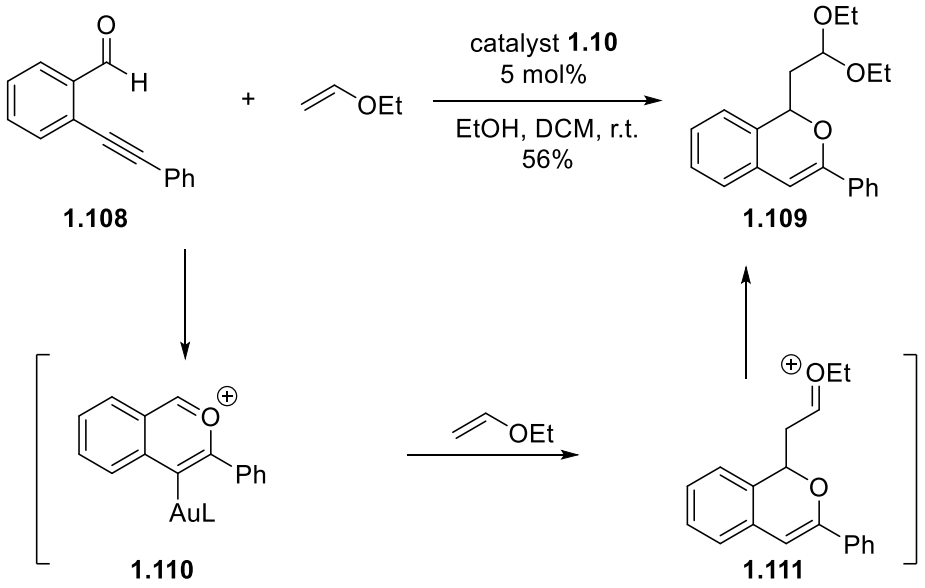
Recently Krafft,[42] showed that a 1,3-migration of 1,6-enonyne **1.104** to allene **1.106** which is in equilibrium with vinyl gold **1.107**. The latter intermediate was converted to cyclopentane **1.105** via conjugate addition (***Scheme 1.24***).

Scheme 1.24 – Cyclization of 1,6-enynes with tandem Michael addition



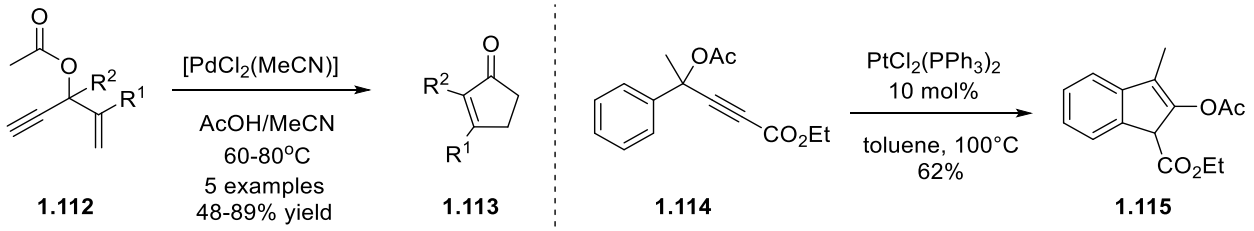
A remarkable application of gold catalysis to 2-alkynyl benzaldehyde **1.108** and subsequent trapping with ethyl vinyl ether was achieved by Hammond[43] to synthesize benzodihydropyran **1.109** (***Scheme 1.25***) in presence of $AuClO_4$. Once activated the alkyne was attacked by the aldehyde to generate intermediate **1.110**, which reacted with ethyl vinyl ether to give **1.111** and finally with EtOH to afford benzodihydropyran **1.109**.

Scheme 1.25 – Annulation of 2-alkynyl benzaldehydes in presence of ethyl vinyl ether



In 1984, Rautenstrauch discovered a particularly interesting transformation in which 1,4–enyne carboxylate **1.112** was converted to cyclopentenone **1.113** in presence of Pd(II) complexes.[44] More recently, Sarpong and co-workers showed that this transformation can be also performed with platinum (II).[45] Indeed, propargyl acetate **1.114** was transformed into cyclopentene **1.115** in 62% yield.

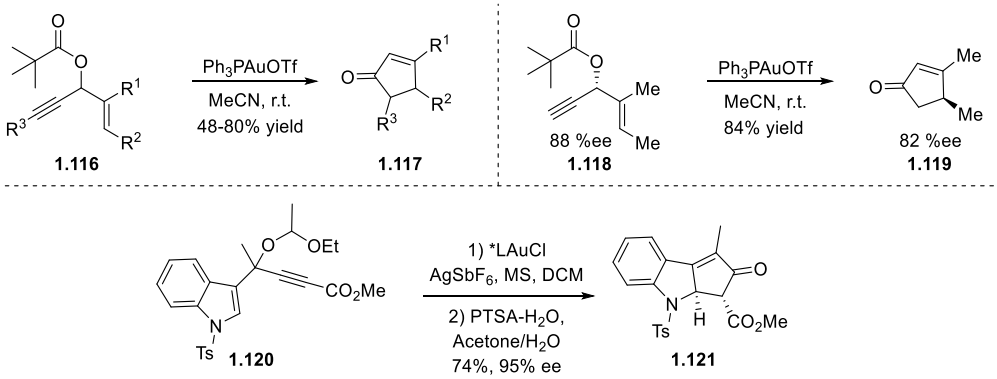
Scheme 1.26 – Rautenstrauch rearrangement catalyzed by palladium and platinum



However, it was the work of Toste and co-workers [46] that captivated our attention. They found that 2-cyclopentenone **1.117** can be obtained from enyne **1.116** in high yield using catalytic amount of $Ph_3PAuOTf$ (***Scheme1.27***). In addition, they demonstrated the high enantiospecificity of the process where the chiral information contained in **1.118** was transferred to **1.119**. In a more recent publication, the same group was able to use a chiral gold ligand to catalyze the enantioselective dearomative Rautenstrauch rearrangement of achiral propargylic carboxylate indole **1.120** to cyclopenta[β]indoles **1.121** in 74% yield and 95% ee.[46b]

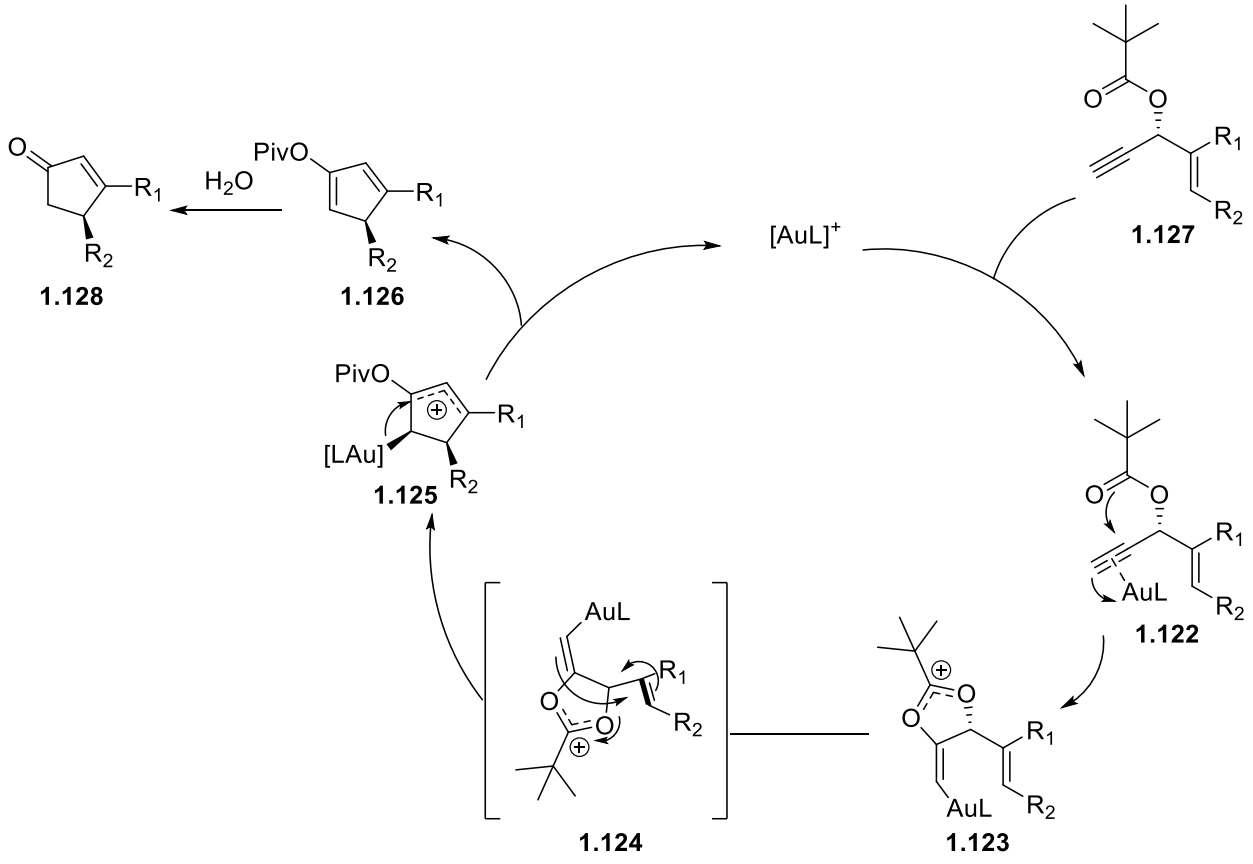
With no application of this rearrangement in total synthesis yet, we regarded this method as a way to approach difficult cyclopentenone rings. The reaction is tolerant of various functionalities as well. We planned for this reaction to be part of a blueprint to the synthesis of ginkgolides. More details about our approach and use of the Rautenstrauch rearrangement is discussed in chapter 3.

Scheme 1.27 – Toste Au(I) catalyzed Rautenstrauch transformation



The proposed mechanism (***Scheme 1.28***) of the Au(I)-catalyzed Rautenstrauch reaction starts by a complexation of the alkyne to form gold complex **1.122** and ensuing a 1,2-migration of the pivaloyl group gives vinyl gold specie **1.123**.[46a, 47] The stereoselectivity can be accounted by the transition state **1.124** where the leaving group is orthogonal to the plan of the olefin. After cyclization, cationic complex **1.125** is obtained which gives diene **1.126** and regenerates the catalyst. This product finally is hydrolyzed to provide 2-cyclopentenone **1.128** with inversion of configuration.

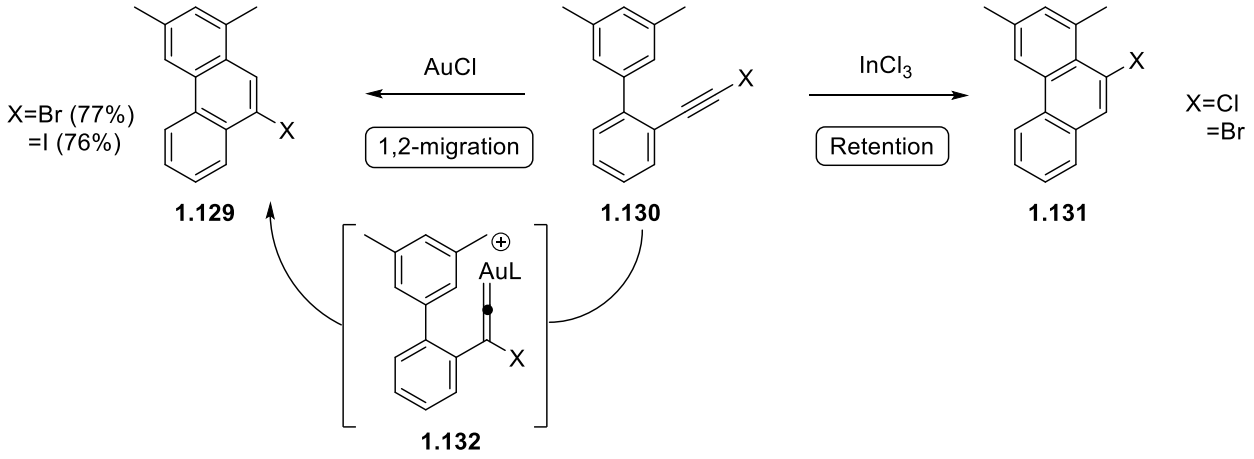
Scheme 1.28 – Proposed mechanism of Au(I)-catalyzed Rautenstrauch rearrangement



1.3.4 Gold vinylidene

At its origin, the simplest of vinylidene: $H_2C=C$, is an unsaturated carbene with ethyne as a tautomer. The formation of vinylidene is a common process known to be initiated by W, Ru, Rh, Mo, Ir, Co, Re and Mn complexes.[48] Few examples exist in the literature on their generation by gold catalysis, but this notion is changing fast.[49] Fürstner[50] was one of the pioneers to attribute the formation of a vinylidene to explain the product resulting from a cycloisomerization (***Scheme1.29***). When treating biaryl **1.130**, substituted with a halogen on the apex of the alkyne, with $InCl_3$ the metal acts as a simple Lewis acid and gives phenanthrene **1.131** with retention. But the same reaction in presence of AuCl gave phenanthrene **1.129** instead where the halide has performed a 1,2-migration. This shift was attributed to the gold activation of the alkyne which induced a 1,2-migration to gold vinylidene intermediate **1.132**. This intermediate is extremely reactive and will react with the aryl group to give final product **1.129** with a transposed halogen.

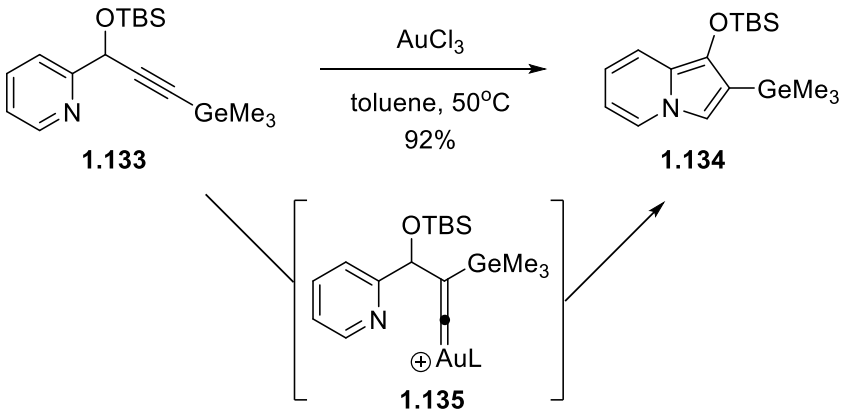
Scheme 1.29 – Phenanthrenes synthesis by Au(I)-catalysis and $InCl_3$



Following Fürstner's findings, Gevorgyan's group[51] has investigated further the formation of such vinylidenes and more specifically the functional groups inducing that 1,2-migration. At first glance, the transformation seemed highly dependent on the substrate and very little on the chosen Au catalyst. In studying the cycloisomerization of propargylic *N*-containing

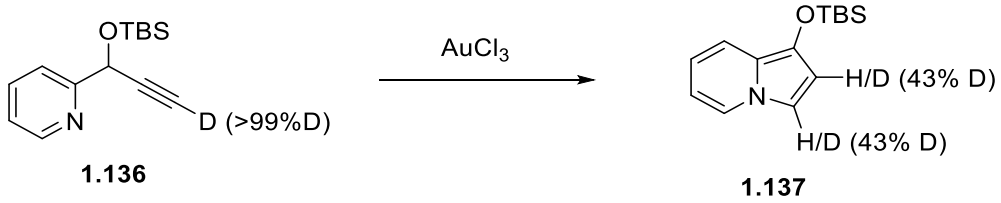
heterocycles, they established that silyl, stannyl and geranyl moieties can undergo the migration and led to the vinylidene. For example (***Scheme1.30***), propargyl pyridine **1.133** will progress by 1,2-migration of the geranyl moiety to gold vinylidene **1.135** and reacted with the pyridine to give heterocycle **1.134**.

Scheme 1.30 – Cycloismerization of propargyl pyridine



In this particular reaction studied by Gevorgyan, they chose to use a pyridine as the nucleophile which will add to alkynes very slowly. This could explain why deuterated alkyne **1.136** under the gold catalysis condition yielded a 1:1 mixture of non-migrated adduct and 1,2-migrated adduct (***Scheme 1.31***). Normally hydrogens do not induce the 1,2-migration.

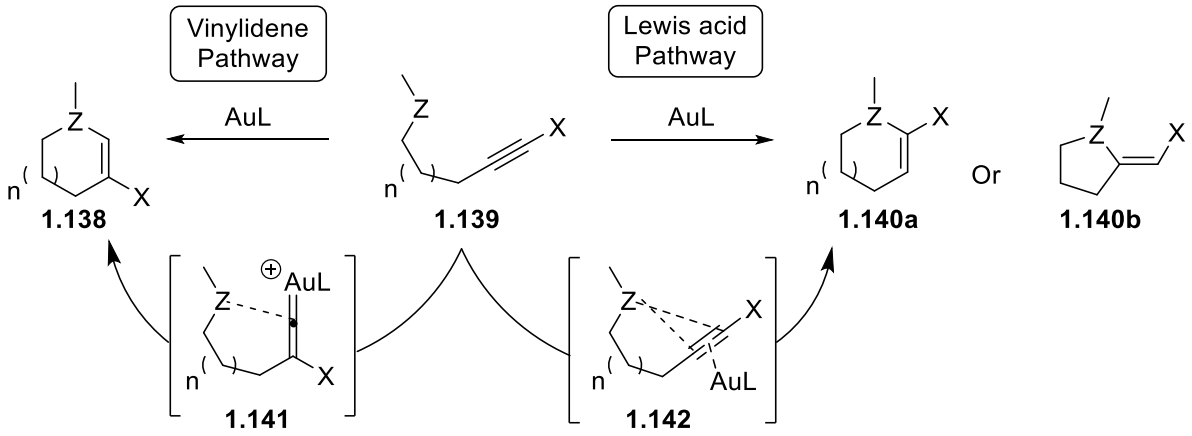
*Scheme 1.31 – Deuterium labelled experiment of **1.136***



These results suggested that the vinylidene pathway and conventional Lewis acid pathway were competing. They are dependent on the electronic nature of the alkyne, the substrate and most probably on the catalyst. This is illustrated by ***Scheme 1.32***; when alkyne **1.139** is subjected to

gold catalysis, it can take the conventional Lewis acid pathway through intermediate **1.142** to *6-endo* dig adduct **1.140a** or *5-exo* dig product **1.140b**. It can also take the vinylidene pathway which leads to a 1,2-migration to intermediate **1.141** and cyclization to product **1.138**.

Scheme 1.32 – Competing pathways



It was important in this chapter to include an introduction on vinylidene chemistry as we observed products resulting from Au(I) vinylidene chemistry during our study of the total synthesis of PPAPs and this will be detailed in chapter 2.

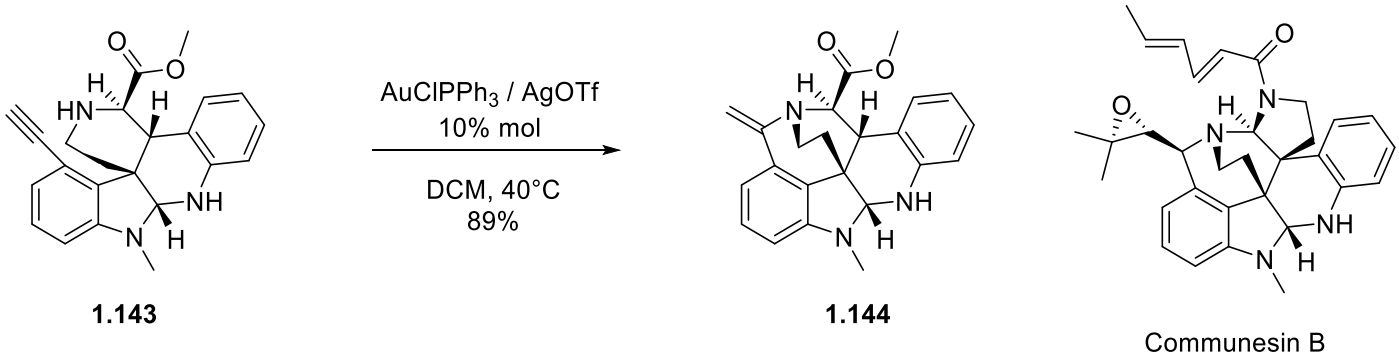
1.4 Application of gold catalysis in total synthesis

The subject of this thesis has for its central focus the synthesis of natural products. Hence, we will take the time to look at the major breakthroughs and ingenious usages of gold catalysis in total synthesis. This is not an exhaustive list of all total syntheses utilizing gold catalysis but a good tribute to the possible disconnections with Au(I)-catalysis and also the chemoselectivity associated with them.

A good landmark example to commence our overview of total syntheses utilizing Au(I) catalysis was in its usage in the synthesis of communesin B (***Scheme1.33***).[52] During the gold

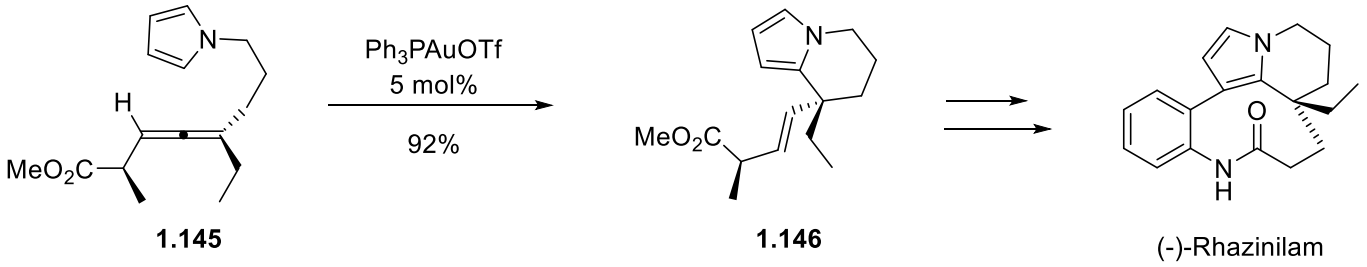
catalyzed step, the starting molecule **1.143** included two secondary and a tertiary amine, an ester and arenes but gold selectively engaged the alkyne with the closest secondary amine to give cyclized adduct **1.144** in 89% yield.

Scheme 1.33 – Synthesis of communesin B



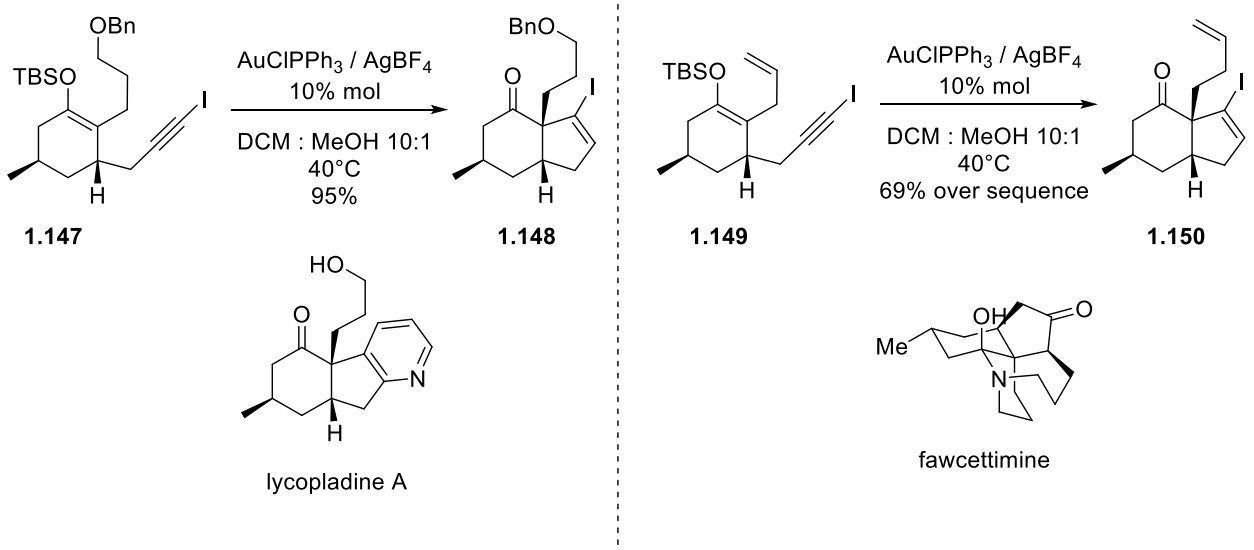
Nelson *et al.*[53] used a Au(I)-catalyzed cyclization of allene **1.145** to achieve the tetrahydroindolizine core **1.146** of (-)-Rhazinilam. They were able to use the pyrrole as a nucleophile and the chirality of the allene to transfer this information to the final product and enabled an enantioselective synthesis.

Scheme 1.34 – Total synthesis of (-)-rhazinilam



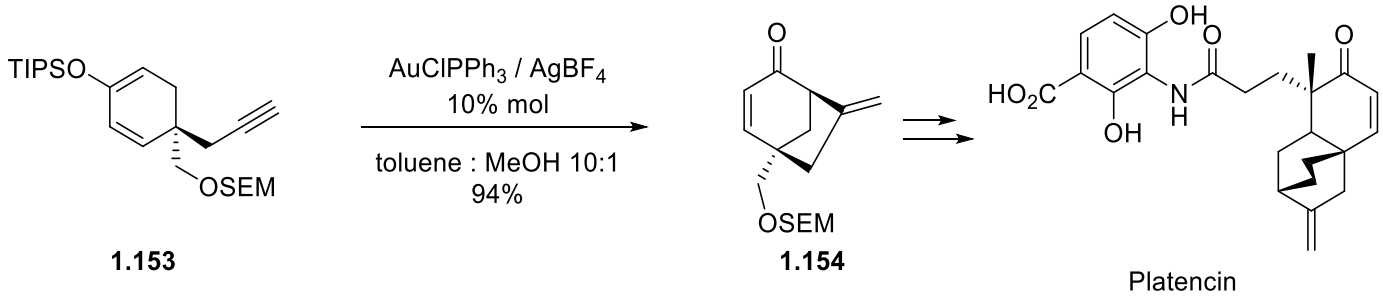
Toste and co-workers developed a Conia-ene type rearrangement using silyl enol ethers as nucleophiles. They were able to apply this methodology to the total synthesis of lycopladine A[31] and fawcettimine[54] using a Au(I)-catalyzed *5-endo* dig cyclization of **1.147** to **1.148** and **1.149** to **1.150** as the key steps (***Scheme 1.35***).

Scheme 1.35 – Total synthesis of (+)-lycopladine A and (+)-fawcettimine



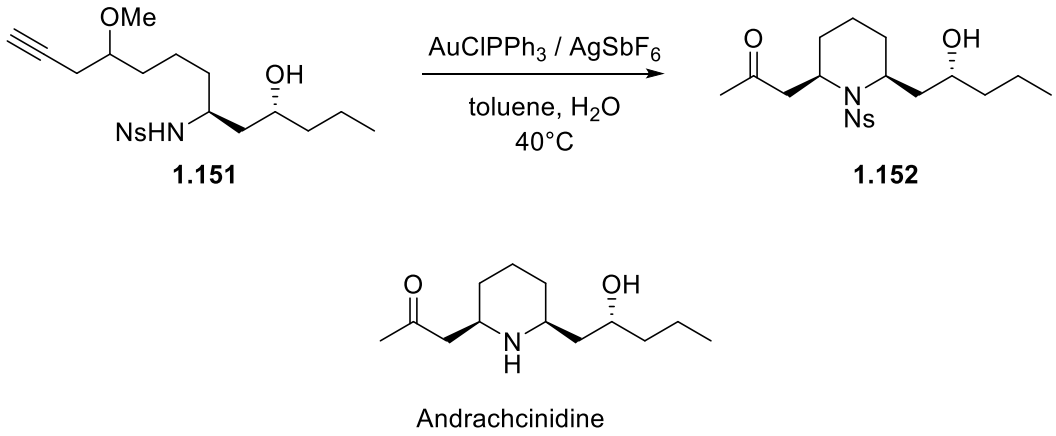
Later Nicolaou[34] used a parent strategy in the total synthesis of (±)-platencin. He performed a *5-exo* dig cyclization of silyl enol ether **1.153** to effectively synthesize bicyclo[3.2.1] enone **1.154** (***Scheme 1.36***).

Scheme 1.36 – Total synthesis of (±)-platencin



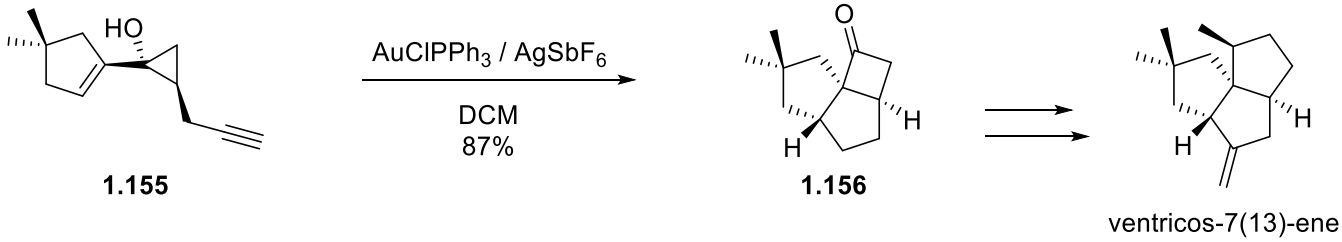
Floreancig[55] showed that alkyne amine **1.151** in presence of [PPh_3AuSbF_6] afforded the product resulting from a tandem hydration/cyclization to Ns-protected andrachcinidine **1.152** (***Scheme 1.37***).

Scheme 1.37 – Total synthesis of (+)-andrachcinidine



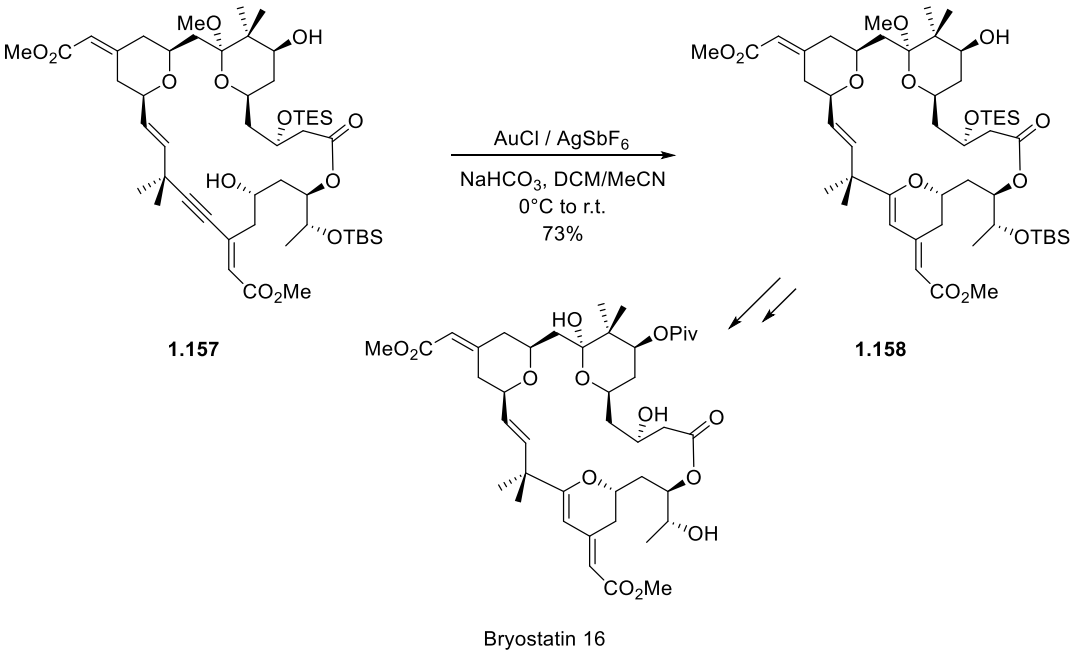
Remarkably, Toste[56] was able to construct an advance intermediate toward ventricosene **1.156** over a tandem Au(I)-catalyzed cycloisomerization/ Wagner-Merwein shift of 1,6-enyne **1.155** in 87% yield (***Scheme 1.38***).

Scheme 1.38 – Total synthesis of (±)-ventricosene



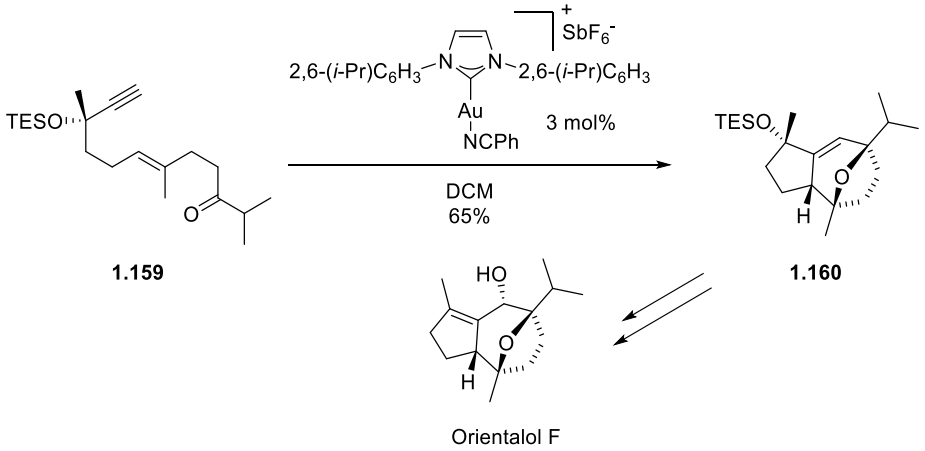
Due to all the functionality present in bryostatin 16, highly chemoselective and mild methods were required to ensure that none of the already installed functional group were deranged. Au(I)-catalysis was found to be highly amendable to the cyclization of dihydropyran **1.158** from alkyne **1.157** and left the rest of molecule intact with a yield of 73% (***Scheme 1.39***).[57a]

Scheme 1.39 – Total synthesis of (±)-bryostatin 16



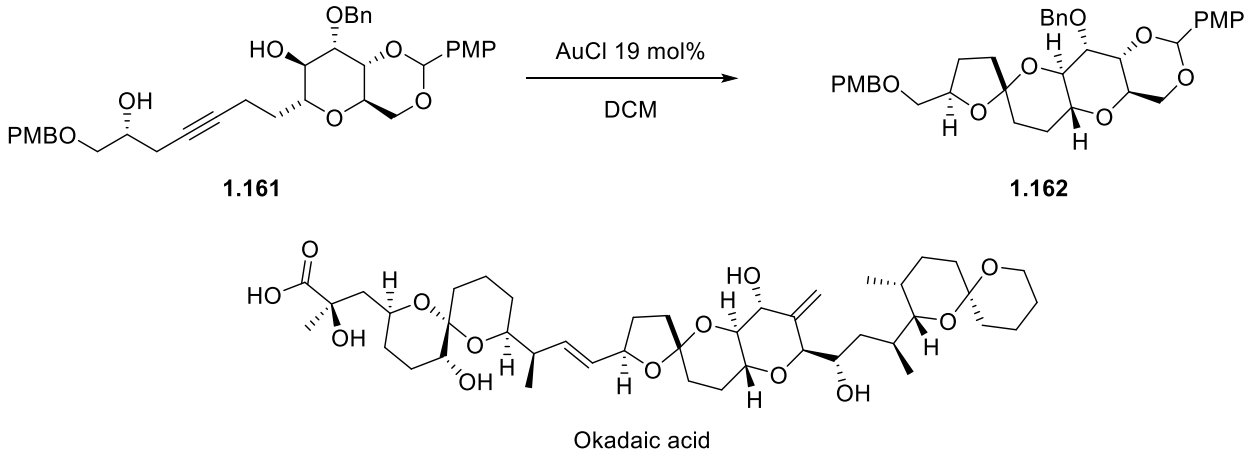
Echavarren et al.[58] performed a formal [2+2+2] alkyne/alkene/carbonyl cycloaddition of ketoenyne **1.159** to sesquiterpene core **1.160**. This intermediate was 3 steps from the natural product (***Scheme 1.40***).

Scheme 1.40 – Total synthesis of (+)-orientalol F



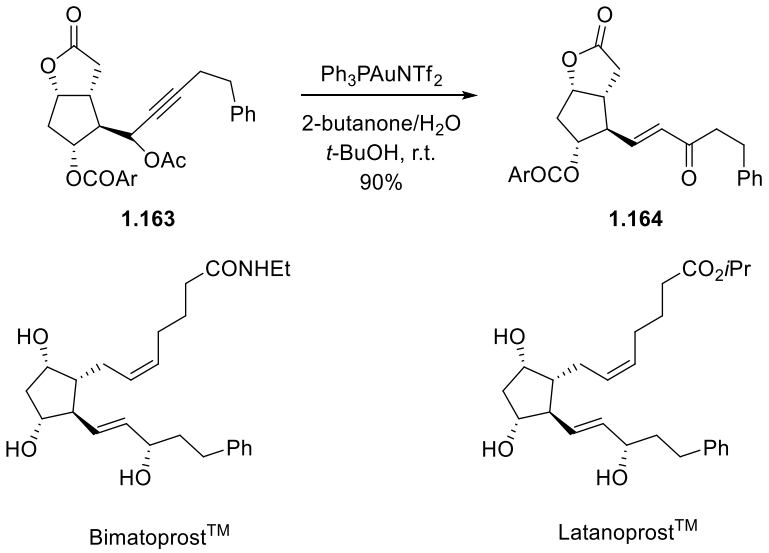
In Forsyth work[59] on okadaic acid, they achieved an acetalization of alkyne diol **1.161** to the desired spiroketal **1.162** which led to a formal synthesis (***Scheme 1.41***).

Scheme 1.41 – Formal synthesis of okadaic acid



Zanoni and Vidari[60] used a gold(I) mediated formal Meyer-Schuster rearrangement to transform propargyl acetal **1.163** into enone **1.164** (***Scheme 1.42***). The mechanism went through a 1,3-migration of the acetyl group to the allene. Subsequent hydrolysis of the resulting acetate led to the enone **1.164**.

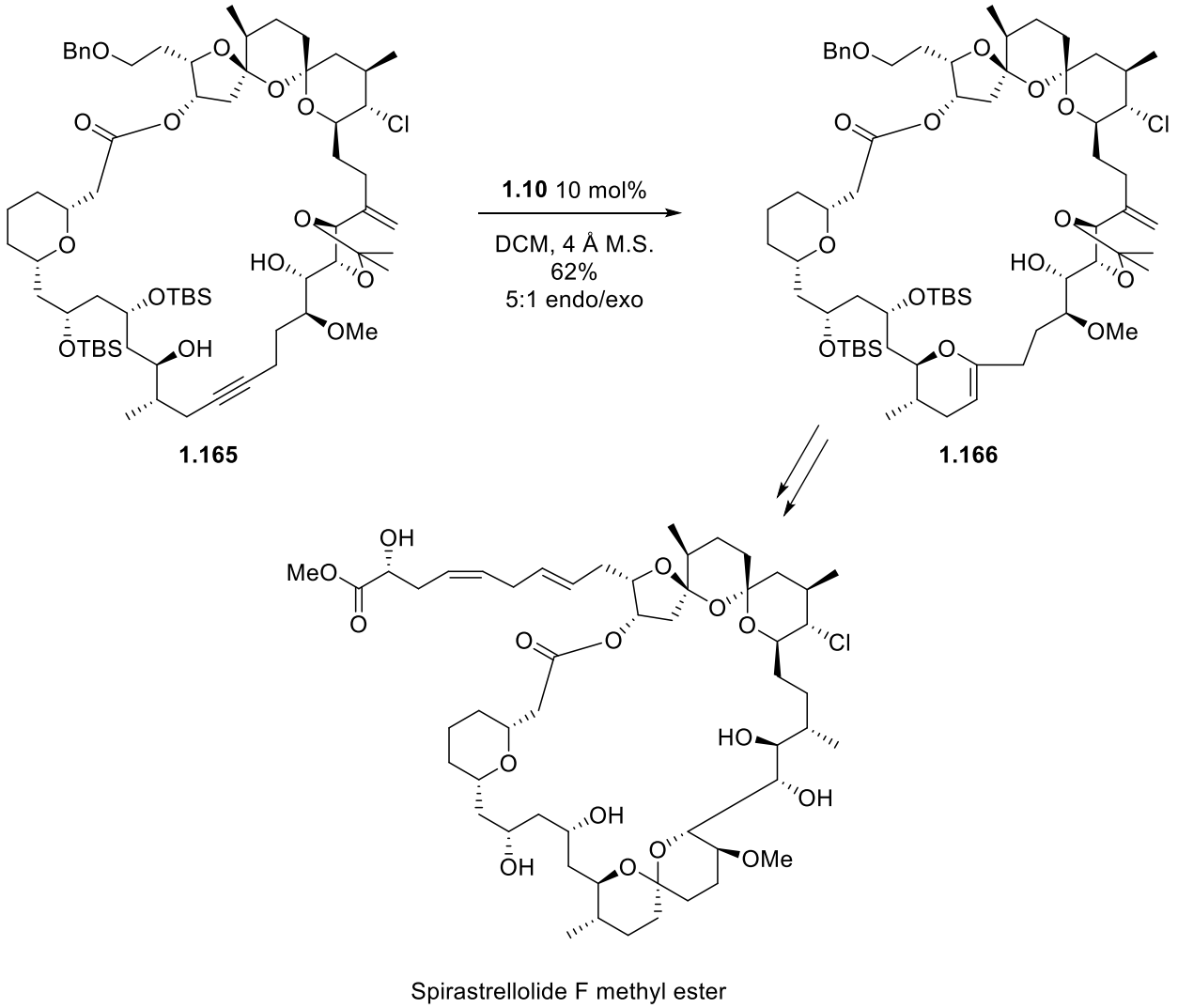
Scheme 1.42 – Total synthesis of prostaglandins: latanoprost and bimatoprost



The same late stage formation of dihydropyran catalyzed by Au(I), originally used by Trost in his total synthesis of Bryostatin 16,[57a] was used by Fürstner[57b] in the synthesis of macrocycle

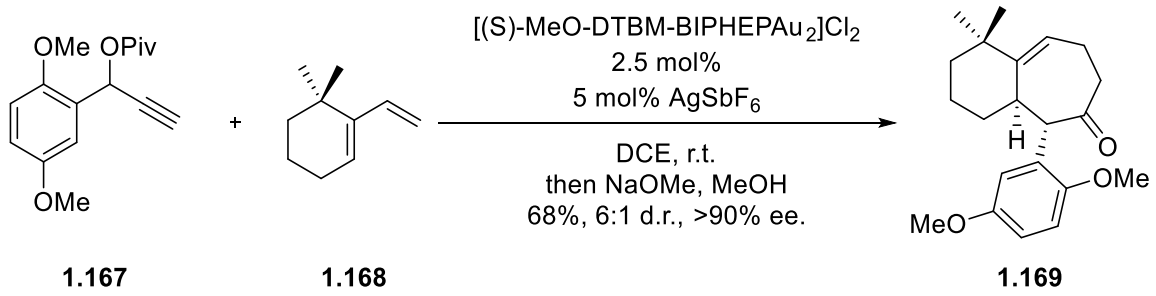
spirastrellolide F methyl ester (***Scheme 1.43***). It enabled the cyclization of 1,4-alkoxy alkyne **1.165** to dihydropyran **1.166**.

Scheme 1.43 – Total synthesis of spirastrellolide F methyl ester

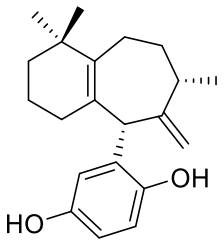


Navado's group[61] developed an enantioselective formal [3+4] cycloaddition (***Scheme 1.44***). The propargyl carboxylate progressed by 1,2-migration to the carbene Au intermediate which reacts with diene **1.168** to give bicycle **1.169**. Intermediate **1.169** was an intermediate in the total synthesis of frondosin A and B by Ovaska.[62]

Scheme 1.44 – Formal enantioselective synthesis of frondosin A and B



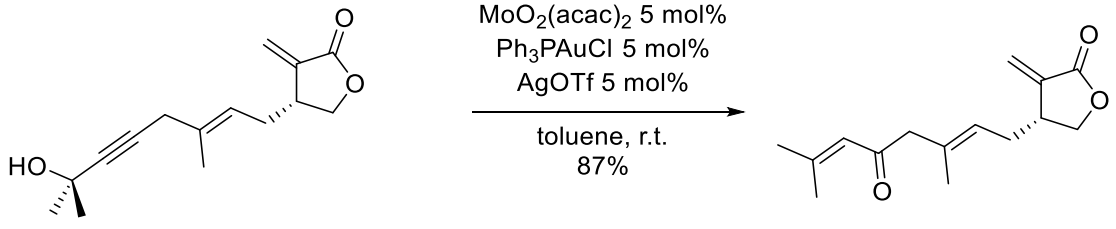
1.167 **1.168** **1.169**



(-)-Frondosin A

During the synthesis of sesquiterpene lactone anthecotulide, the Hodgson's group[63] used a gold catalyzed Meyer-Schuster rearrangement to isomerize propargyl alcohol **1.170** to enone **1.171** with [$Ph_3PAuOTf$] and $MoO_2(acac)$ (***Scheme 1.45***). The molybdenum catalyst facilitated a proposed [3,3]-sigmatropic rearrangement of a molybdate intermediate with a gold coordinated alkyne.

Scheme 1.45 – Total synthesis of (+)-anthecotulide

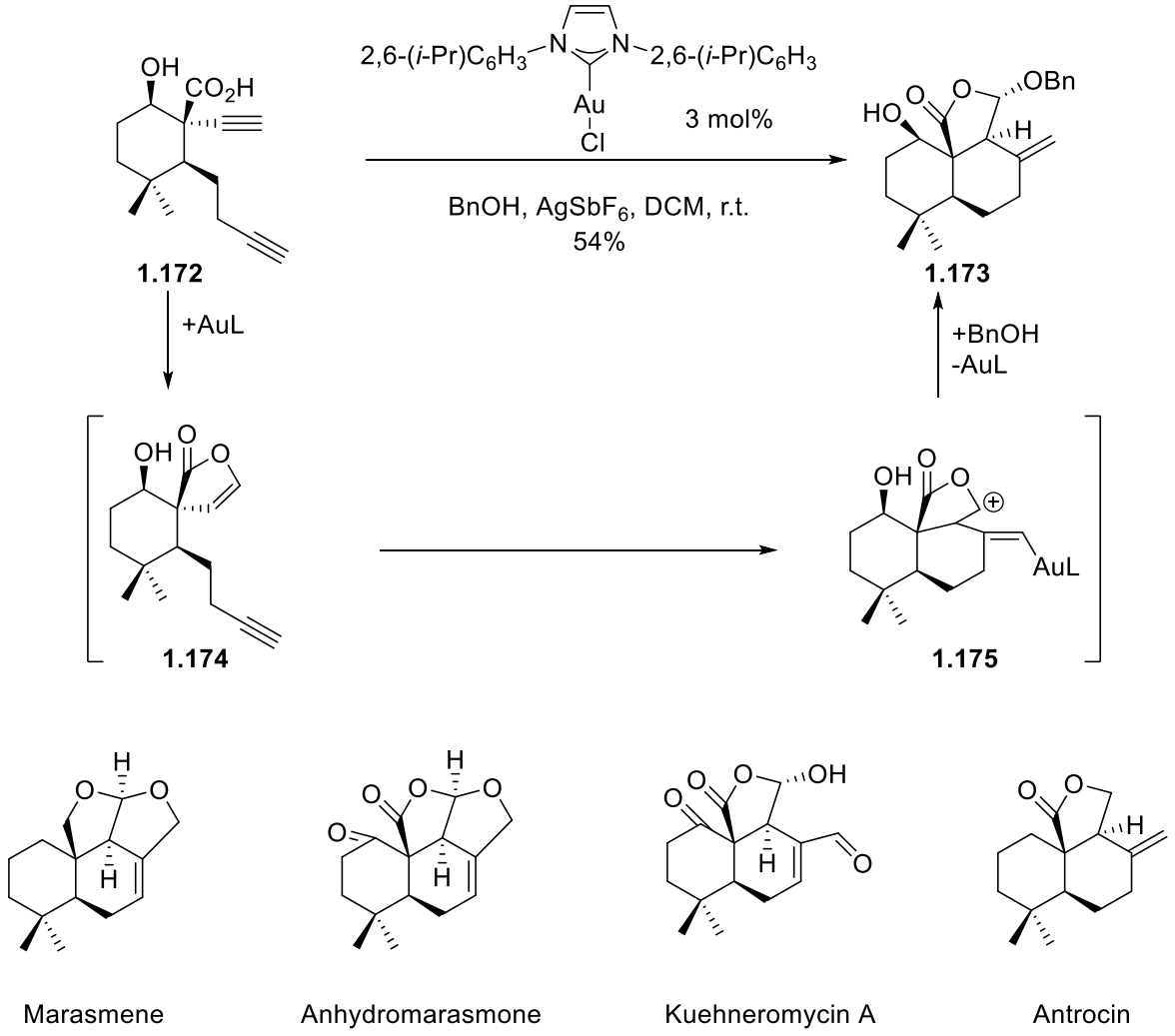


1.170 (+)-Anthecotulide **1.171**

A tandem polycycloisomerization using gold was achieved in the total synthesis of 4 closely related natural products: kuehneromycin A, antrocin, anhydromarasmone and marasmene

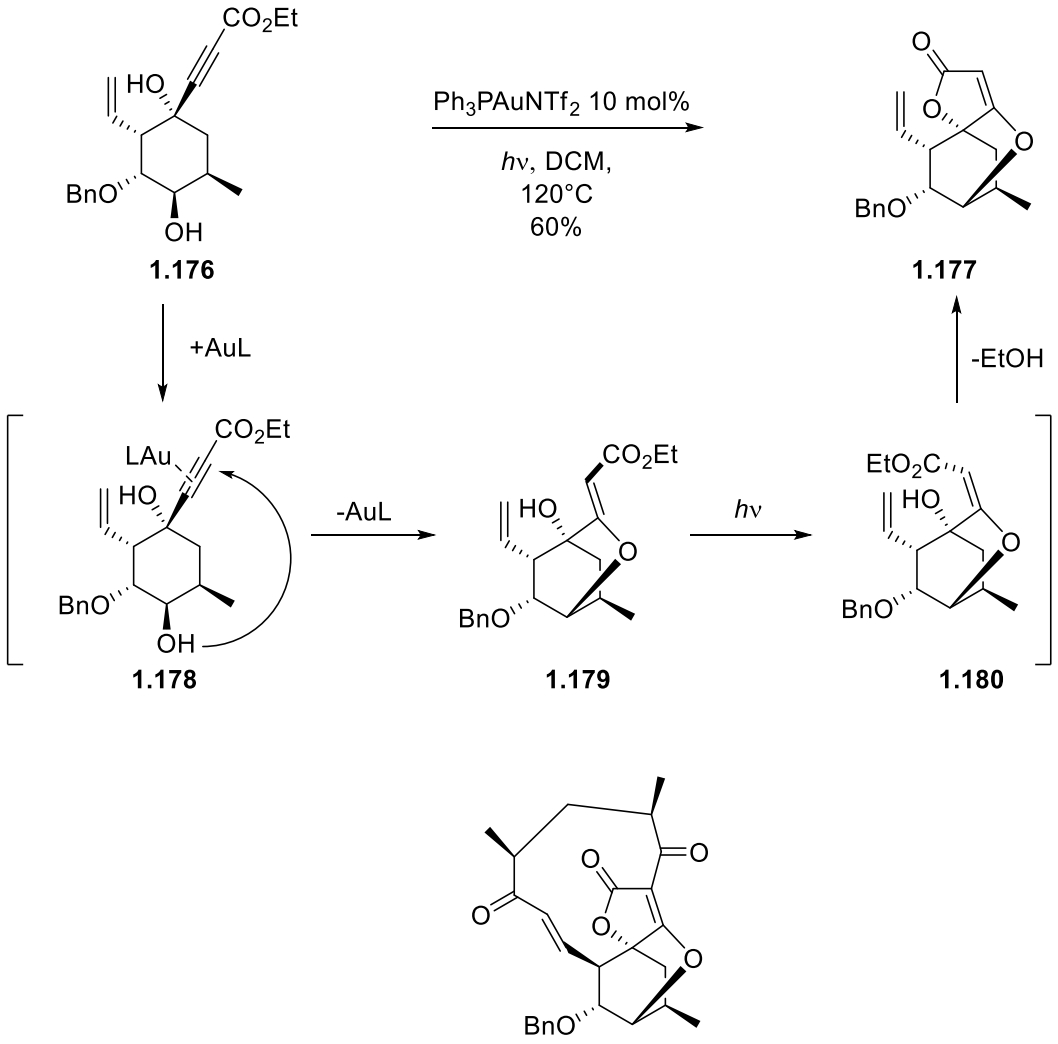
(***Scheme 1.46***).[64] A first cyclization of the carboxylic acid onto vinylic alkyne of **1.172** gave dihydrobutyrolactone **1.174**. Intermediate **1.174** performed a second *6-exo* dig isomerization to give cationic vinyl gold **1.175** that reacted with a molecule of benzyl alcohol to give **1.173**.

Scheme 1.46 – Total synthesis of kuehneromycin A, antrocin, anhydromarasmone, marasmene



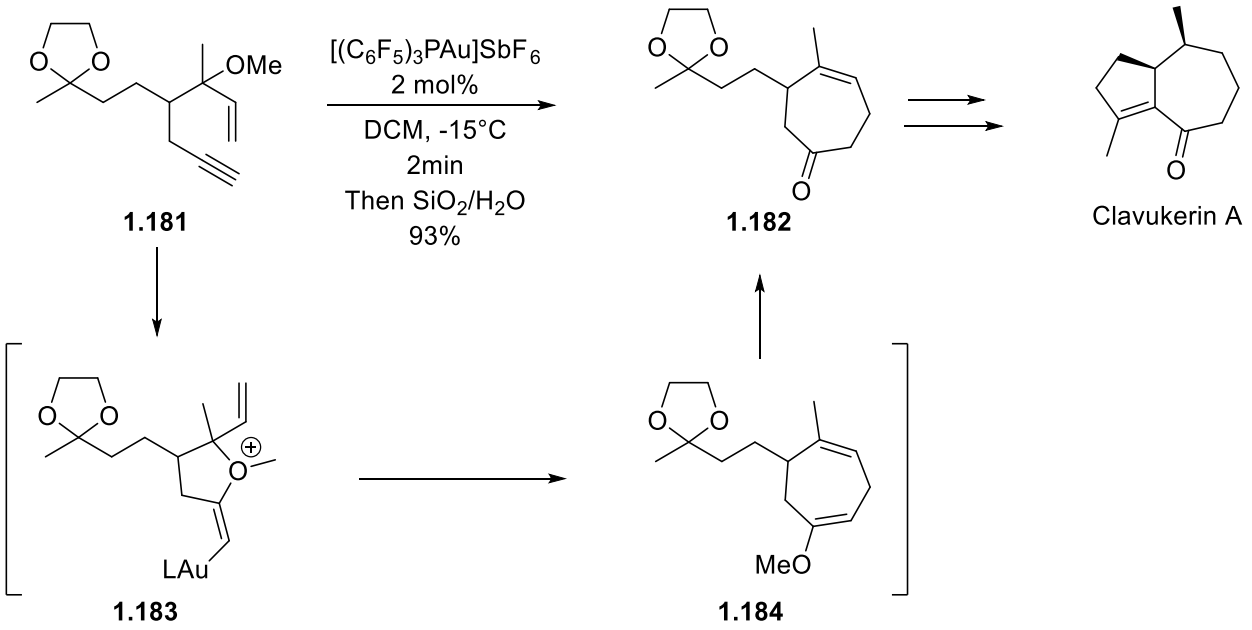
Bihelovic and Saicic[65] performed a *6-exo* dig cyclization of diol **1.176** to *Z* olefin **1.179**. Under irradiation, the olefin isomerized to the *E* form **1.180** which was now able to perform a condensation to arrive to lactone **1.177** for the total synthesis of (-)-atrop-abyssomicin C (***Scheme 1.47***).

Scheme 1.47 – Total synthesis of (-)-atrop-abyssomicin C



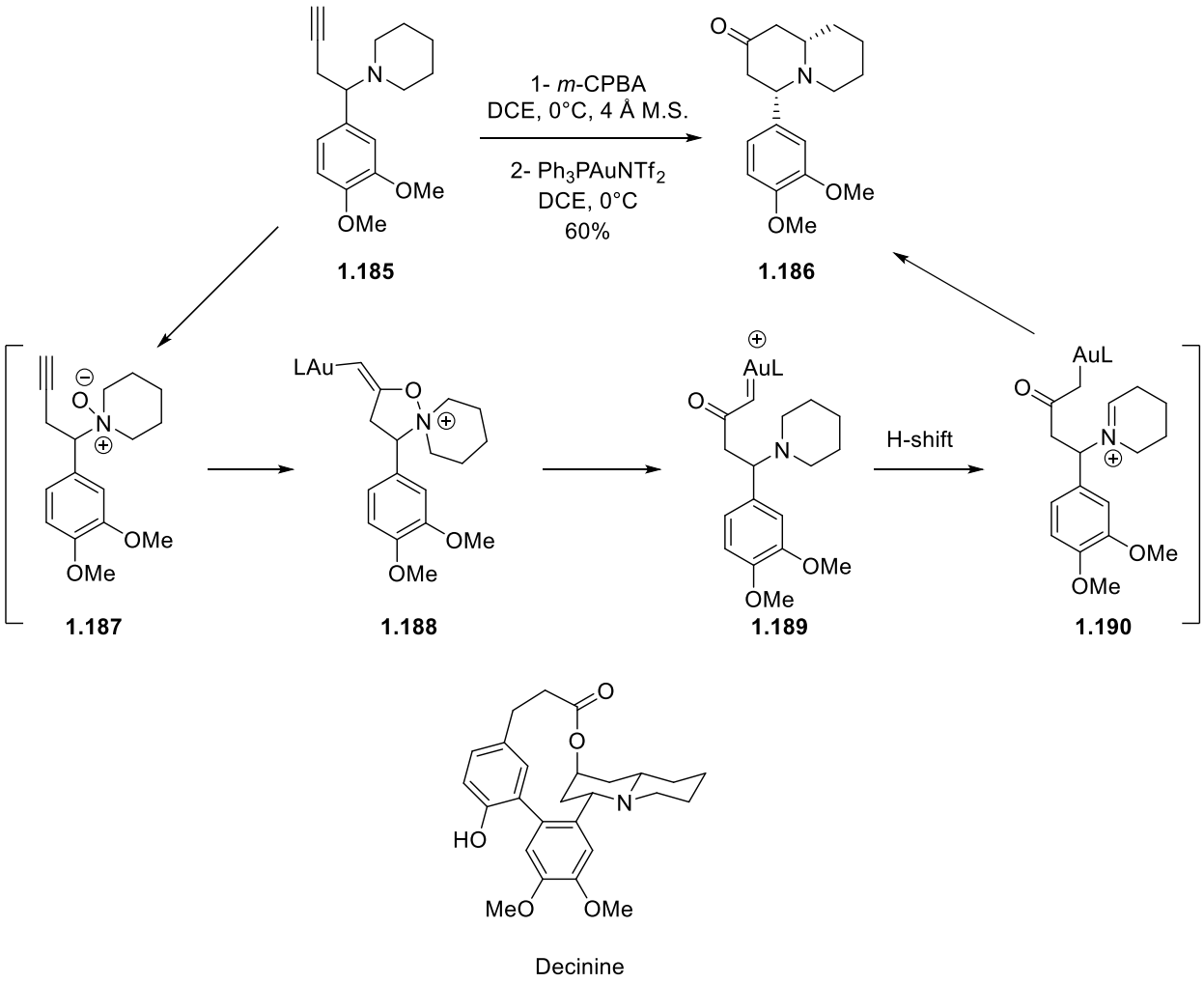
In the synthesis of clavukerin A,[66] the cycloisomerization of methyl ether **1.181** led to unstable cation **1.183** that rearranged to 7-membered methyl vinyl ether **1.184**. After hydrolysis 4-cycloheptenone **1.182** was obtained (***Scheme 1.48***).

Scheme 1.48 – Total synthesis of (±)-clavukerin A



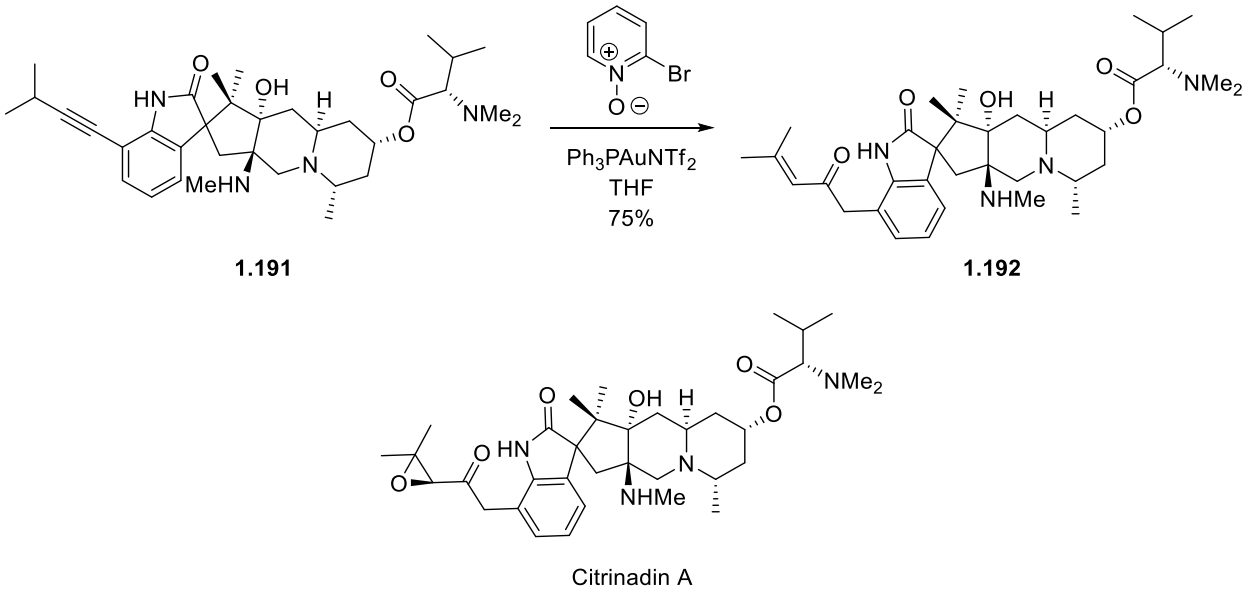
Using a gold annulation process originally developed by Zhang's group, the core of decinine, a 12-membered bicycle was achieved (***Scheme 1.49***).[67] Oxidation of 1-(but-3-yn-1-yl)piperidine **1.185** with m-CPBA gave N-oxide **1.187** and subsequent treatment with [$PPh_3NAuNTf_2$] gave the *5-exo* dig cyclized product **1.188**. Backdonation from gold ensued to give carbene gold **1.189** and induced a hydride shift to iminium **1.190** that gave the final product **1.186**.

Scheme 1.49 – Total synthesis of (±)-decinine



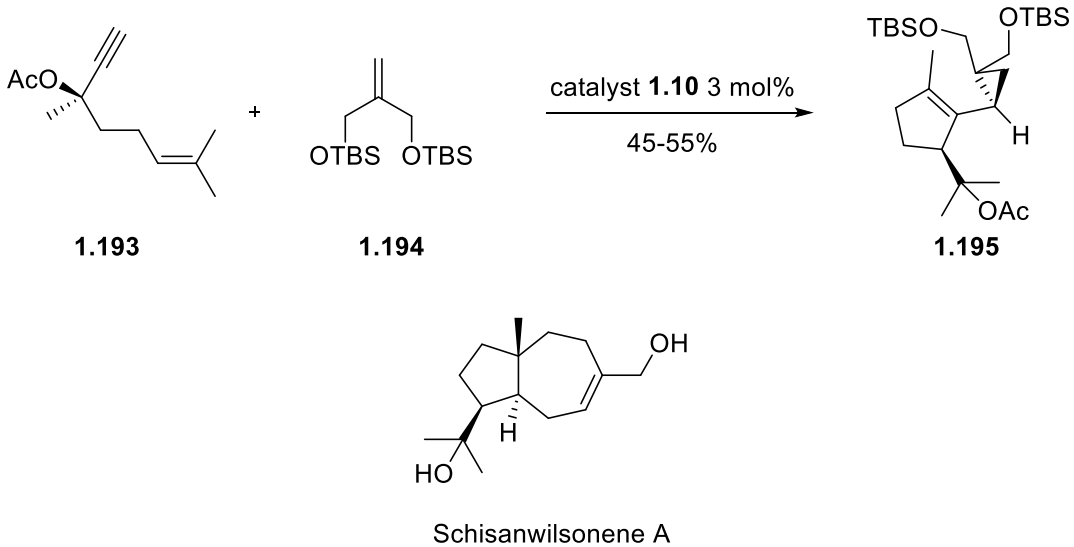
Martin's group showcased another gold-catalyzed reaction developed by Zhang' group in the total synthesis of (-)-citrinadin A (***Scheme 1.50***). They performed the oxidation of alkyne **1.191** to enone **1.192** in presence of an N-oxide.[68] They mentioned that gold catalysis was the only method that worked in their hands. Wood, thereafter, published the total synthesis of (+)-citrinadin B using the same oxidative reaction.[69]

Scheme 1.50 – Total synthesis of (-)-citrinadin A



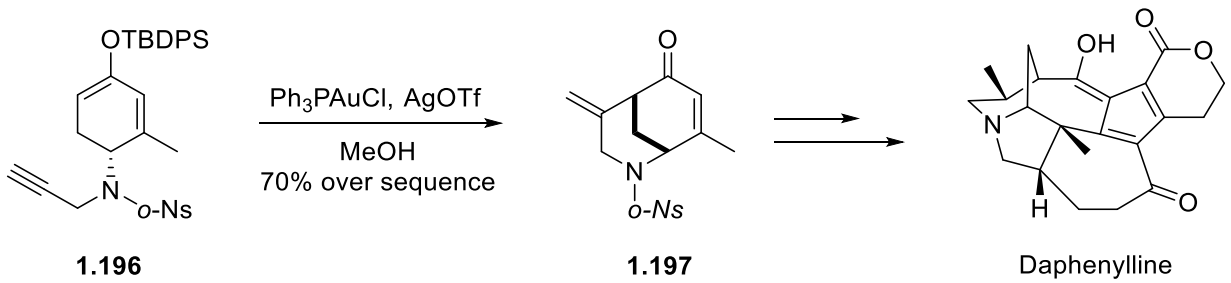
Echavarren and co-workers elaborated a tandem gold catalyzed cyclization/ 1,5-migration/ cyclopropanation and applied it to the synthesis of (+)-schisanwilsonene (***Scheme 1.51***). Starting from acetyl 1,5-enyne **1.193**, in presence of alkene **1.194,** gave cyclopropyl **1.195** on route toward the natural product.

Scheme 1.51 – Total synthesis of (+)-schisanwilsonene



Similar to Nicolaou's approach to platencin, Li *et al.*[70] performed a Conia-ene Au catalyzed *6-exo* dig cyclization of silyl enol ether **1.196** to bicyclo[3.3.1]enone **1.197** in their approach toward daphenylline (***Scheme 1.52***).

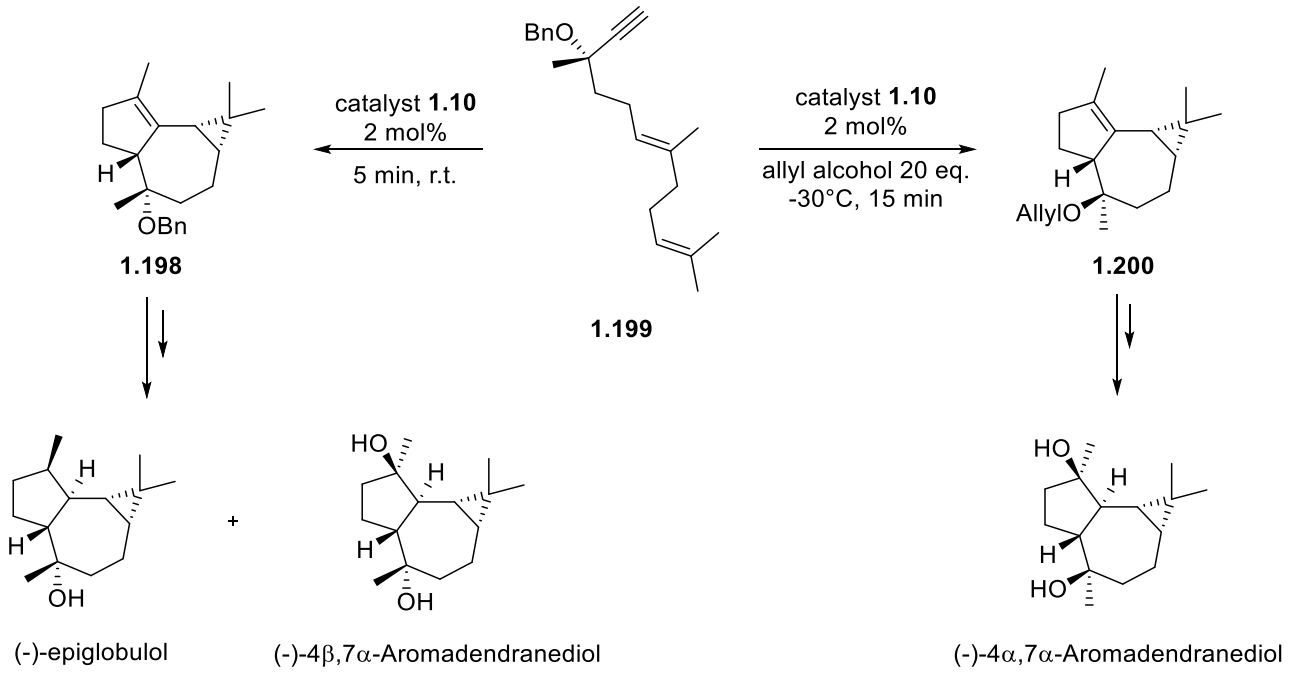
Scheme 1.52 – Total synthesis of daphenylline



1.196 **1.197** Daphenylline

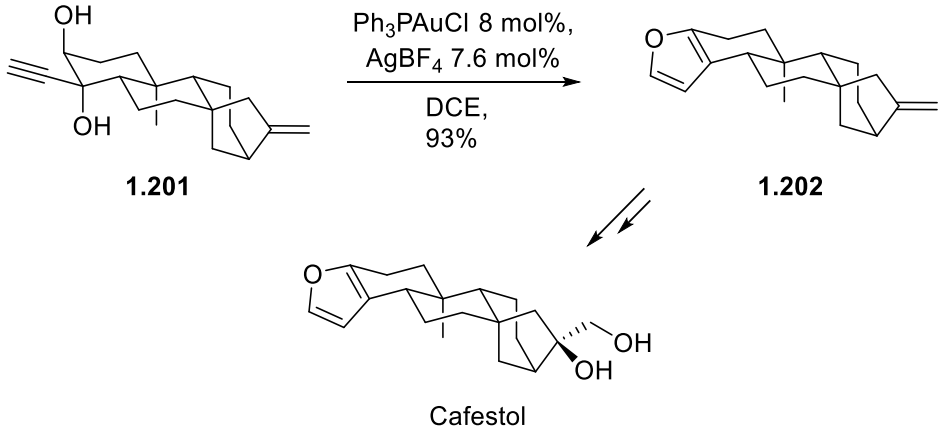
Interestingly, Echavarren's group[71] was able to achieve 3 total synthesis, with stereochemical differences at the ether bond of **1.198** and **1.200**, by subtle change to the gold catalyzed step (***Scheme 1.53***). Adding allyl alcohol to the reaction mixture led to bicycle **1.200** with ether bond upward, but in the case where the substrate is deprived of an extra alcohol, the ether bond finds itself down in structure **1.198**. Through **1.200**, they were able to complete the total synthesis of (-)-4α,7α-Aromadendranediol and with intermediate **1.198** the total synthesis of (-)-epiglobulol and (-)-4β,7α-Aromadendranediol.

Scheme 1.53 – Total syntheses of (-)-epi-sesquiterpenes, (-)-4β,7α- and (-)-4α,7α-Aromadendranediol



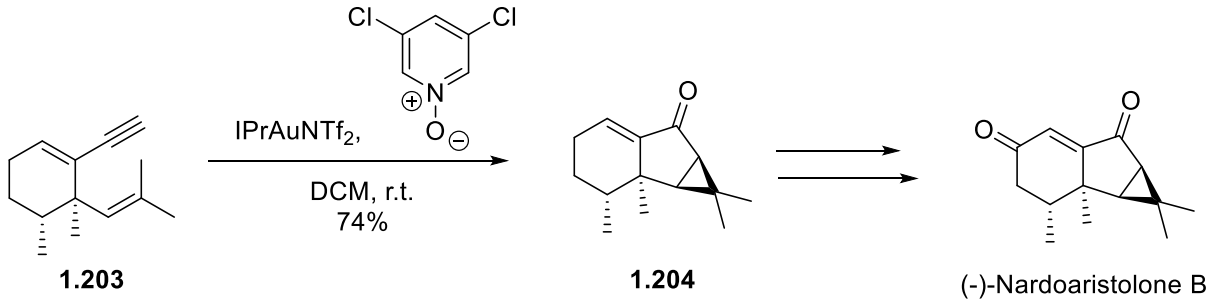
Hong[72] constructed the pyran ring of cafestol through a Au-catalyzed tandem *5-endo* dig cyclization/ elimination of diol **1.201** to pyran **1.202**.

Scheme 1.54 – Total synthesis of (±)-cafestol



Echavarren reported the synthesis of (-)-nardoaristolone B (***Scheme 1.55***).[73] The gold oxidative cyclization of dienyne **1.203** afforded cyclopentanone **1.204** in 74% yield.

Scheme 1.55 – Total synthesis of (-)-nardoaristolone B



1.203 **1.204** (-)-Nardoaristolone B

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CHAPTER 2

Highly modular and concise Total Syntheses of Polycyclic Polyprenylated Acylphloroglucinols

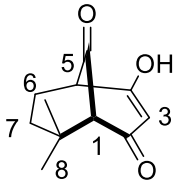
2.1 Introduction to the intricacies of PPAPs

Polycyclic Polyprenylated Acylphloroglucinols (PPAPs) are a vast family of natural products, that includes more than 200 members to its name and is ever increasing with >15 publications in the past 2 years alone on the isolation of new entries from a variety of plants.[74] They contain a stunningly complex molecular architecture that in most cases includes a bicyclo [3.3.1]nonane core. PPAPs have been of interest to the scientific community for their intricate structure, their powerful aid in treating many ailments and large portfolio of biological activities. More particularly, they have been of synthetic interest since 1999 with the first report of an approach to those complicated cores by Nicolaou.[75] The first total synthesis of a PPAPs was reported by Shibasaki's group[76] during the total synthesis of (±)-garsubellin A (**2.2**).

2.1.1 Structures, properties and utilities

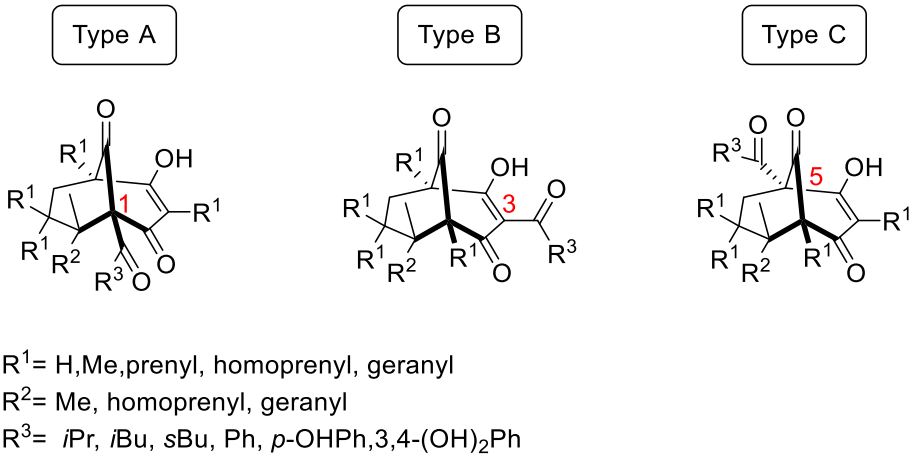
PPAPs are a family of natural products isolated from *Guttiferae* plants, the therapeutic effects of which have been used for centuries.[77] These compounds are characterized by unique, highly oxygenated and densely substituted bicyclo[3.3.1]nonane frameworks (***Figure 2.1***) with few

Figure 2.1 – PPAPs' core



exceptions like enaiemone B (**2.14**) and hyperibone K (**2.8**) that are comprised of a bicyclo[2.3.1]octane and adamantane core respectively (***Scheme 2.1***). These cores are generally ornamented with methyl, prenyl, acyl, geranyl or homo-prenyl groups. These molecules have been divided in 3 main categories: A, B, and C depending on the position of the acyl group (***Figure 2.2***). In group A, the acyl moiety at C-1 is contiguous to a quaternary center at C-8, whereas in group C, the acyl group on C-5 is positioned adjacent to a methylene unit. Group B is characterized by an acyl moiety located at C-3.

Figure 2.2 – Classification of PPAPs

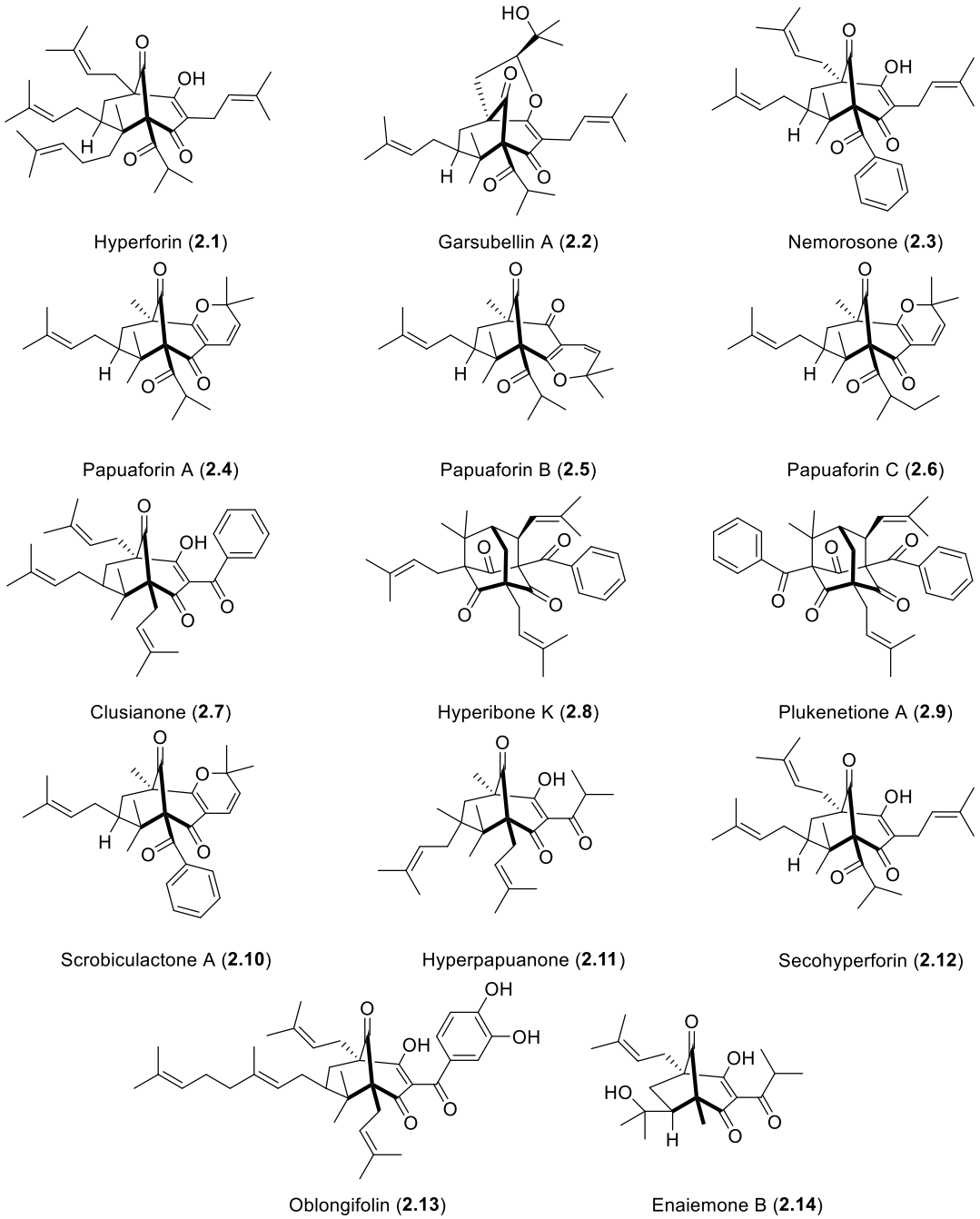


R^1= H,Me,prenyl, homoprenyl, geranyl
R^2= Me, homoprenyl, geranyl
R^3= *i*Pr, *i*Bu, *s*Bu, Ph, *p*-OHPh,3,4-$(OH)_2$Ph

PPAPs display a large array of biological activities. Notably, hyperforin (**2.1**) (***Scheme 2.1***), perhaps the most studied of this family of natural products, is isolated from St. John's wort and displays anti-inflamatory, antibacterial, neuroprotective effects, antidepressamt, inhibitor of the sirtuins, antitumor, antimalarial, antimetastatic[77c] and prevents premature ejaculation.[78] Another well documented member of this family, garsubelllin A (**2.2**) was found to enhance choline acetyltransferase activity by 154% in rat candidates which could help in the treatment of Alzeimer's disease. To enumerate just a few more properties of the able bodies of this family, papuaforin A (**2.4**) has antibacterial properties, nemorosone (**2.3**) is a potent antitumor but the

properties of many PPAPs remain unknown since they have not been fully investigated yet. For example, the original isolation of papuaforin B (**2.5**) and C (**2.6**) yielded such small quantities that testing of their properties was never performed.

Scheme 2.1 – Structures of some polycyclic polyprenylated acylphloroglucinols

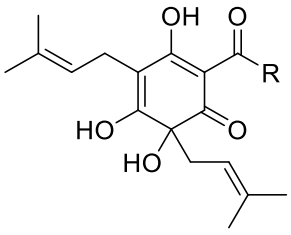


It is to no one's surprise that following their vast potential as treatment for ailments and stellar complexity, PPAPs have charmed the organic synthetic community. They have been surprisingly resilient to synthesis, to even the brightest in this field of research. With two decades of research on these molecules though, we are starting to witness well-constructed approaches and more importantly, feasible syntheses with bolder disconnections.

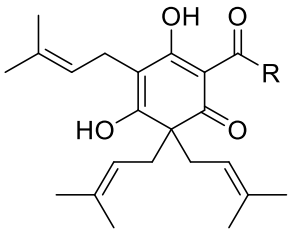
2.1.2 Biosynthesis

The key intermediate in the biosynthesis of PPAPs are monocyclic polyprenylated acylphloroglucinols (MPAPs) (***Figure 2.3***).[79] MPAPs (**BS.3**) are divided in two classes: the α-acids (**2.15**) and β-acids (**2.16**) which differ according to the level of prenylation. α-Acids have 2 prenyl chains whereas β-acids have three. The MPAPs are formed following the cyclization of poly ketone **BS.2** which is the result of the reaction of 3x malonyl-CoA with an acetylSCoA molecule (**BS.1**) (***Scheme 2.2***).

Figure 2.3 – Two classes of MPAPs: α-acids and β-acids



α-acids (**2.15**)

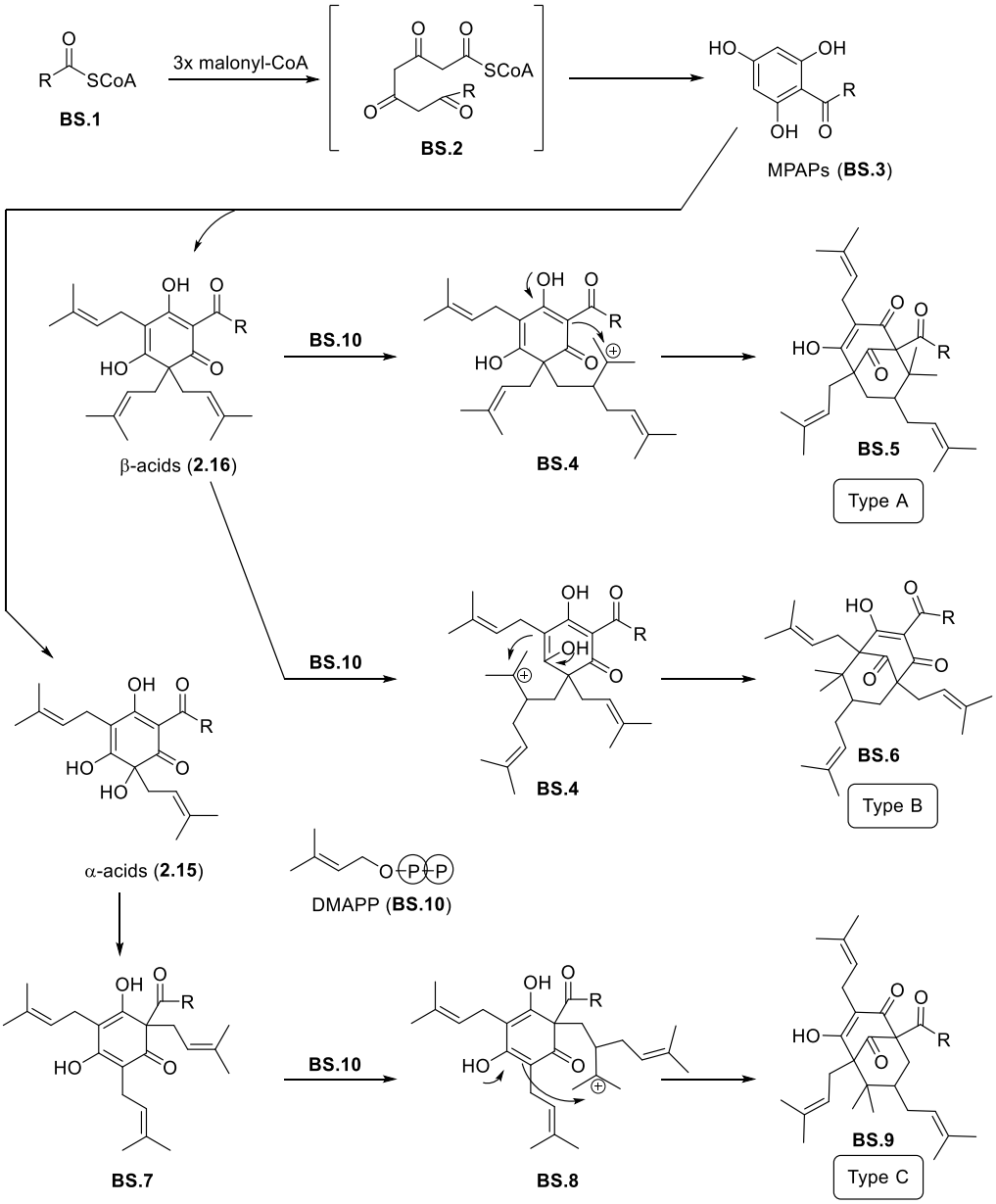


β-acids (**2.16**)

R	α-acids	β-acids
i-Pr	cohumulone	colupulone
i-Bu	humulone	lupulone
sec-Bu	adhumulone	adlupulone

Type A and B are proposed to result from the reaction of β-acids with DMAPP (**BS.10**) to give cation **BS.4**. The cyclization can occur closer to the acyl group to give type A (**BS.5**) or beside the prenyl group to give type B (**BS.6**) PPAPs. Lastly, type C ascend from α-acids (**2.15**) that react with DMAPP (**BS.10**) to give intermediate cation **BS.8**. Upon cyclization with one of the two β-positioned enol, it yields type C (**BS.9**) PPAPs.

Scheme 2.2 – Proposed biosynthesis of the three type of PPAPs



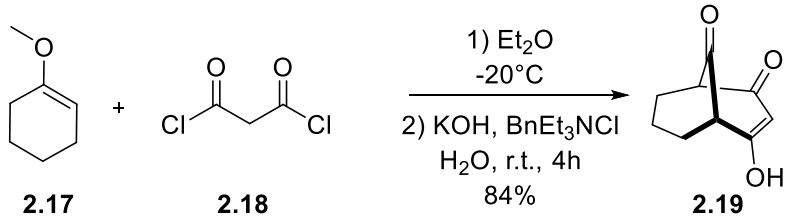
2.1.3 Approaches, strategies and synthetic plans for the synthesis of PPAPs

From a strictly chemical perspective the PPAPs are colossal molecules that have met the demise of many synthetic strategies. At the onset, they seem like approachable targets but one can recognize swiftly that they offer a complex challenge that has been fueling synthetic passions of multiple groups. They have also been a fertile playground for new discoveries. We will now visit some of the most influential synthetic strategies for they have inspired our work or have paved our understanding of the intricacies of this class of natural products. Unfortunately, due to the sheer amount of work done on the subject, we will be covering only a few approaches and total syntheses that have been seminal to the field and determinant in the future it will take.

2.1.3.1 The Effenberger cyclization

Among all strategies to gain entry to the PPAPs scaffolds, the Effenberger cyclization is perhaps the one bicycle-forming reaction that has been the most popularized throughout the efforts. In 1984, Effenberger reported that reaction of methyl enol ether **2.17** with malonyldichloride **2.18** yielded bicyclo[3.3.1]nonane **2.19** (***Scheme 2.3***).[80] This reaction was exceptionally tempting as an approach since it delivered directly the core of PPAPs from readily available starting material.

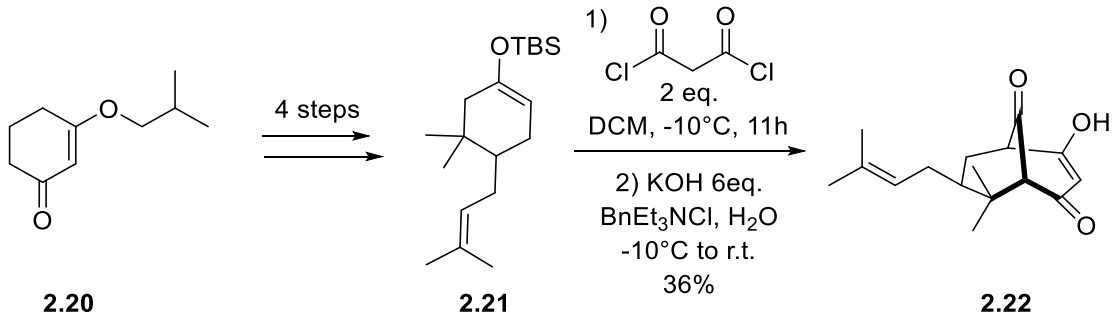
Scheme 2.3 – Effenberger cyclization original finding



2.17 **2.18** **2.19**

The first attempt, at synthesizing PPAPs through this reaction, was led by Stoltz's group (***Scheme 2.4***).[81] Starting from enol ether **2.20**, they were able over 4 steps to install the *gem*-dimethyl functionality and prenyl group contained in most PPAPs before testing the Effenberger cyclization. After modifying the original set of reaction conditions slightly, they achieved 36% of bicycle core **2.22**. Unfortunately, even though the reaction allowed a rapid access to the core of PPAPs, they found that it did not tolerate α-substituents and compared to simpler starting materials the yield was minimal.

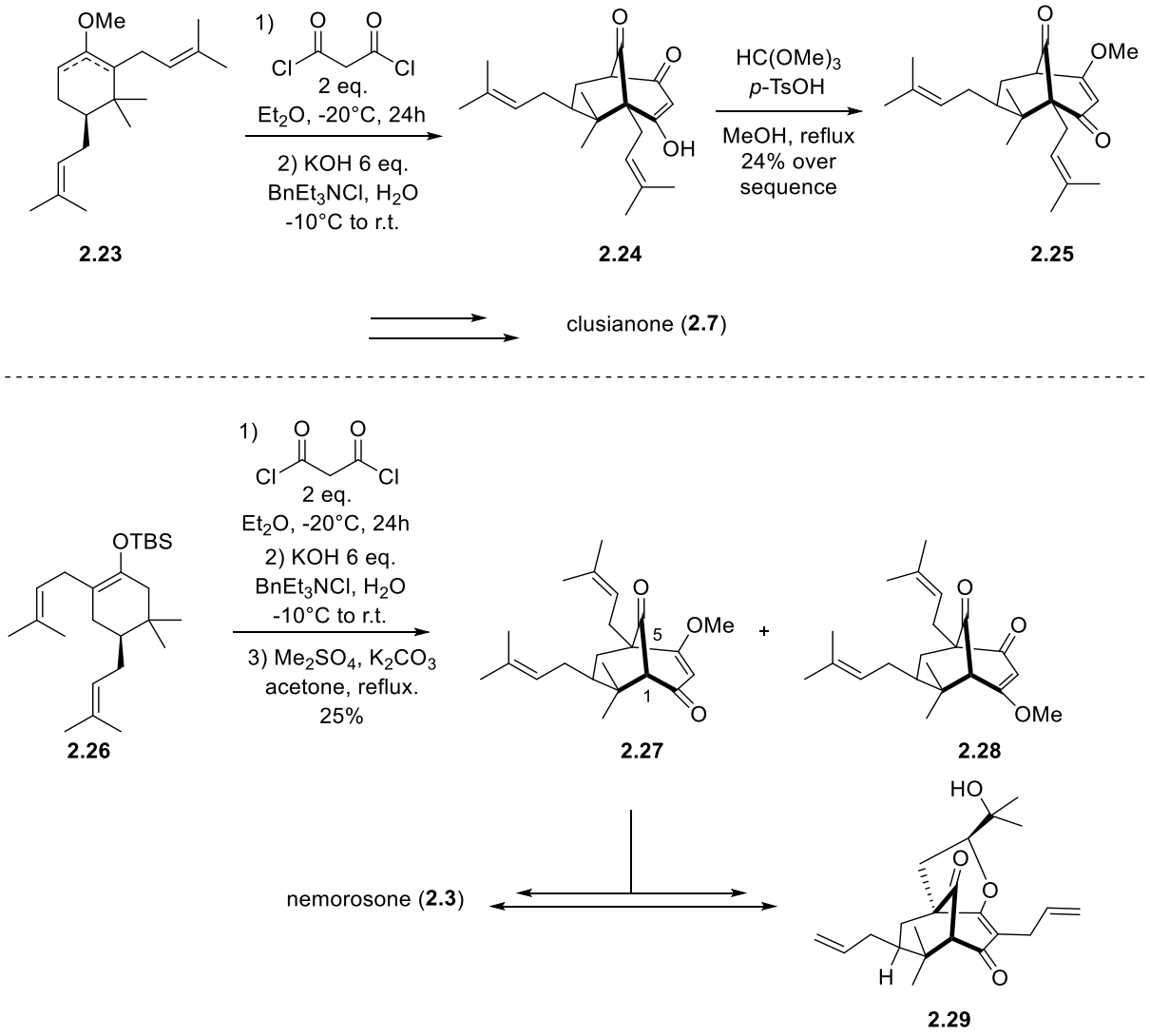
Scheme 2.4 – Stoltz's synthesis of bicyclo[3.3.1]alkenones by Effenberger cyclization



Nevertheless, Simpkins et al. have been successful in utilizing the Effenberger cyclization toward the total synthesis of clusianone (**2.7**), nemorosone (**2.3**) and the formal synthesis of garsubellin A (**2.2**) (***Scheme 2.5***).[82] In their earliest findings, they showed that mono α-substituted methyl vinyl ether **2.23** as a mixture of isomers gave bicycle **2.24**. The β-diketone was thereafter converted to the methyl vinyl ether **2.25** cleanly with trimethylorthoformate and *p*-TsOH to hide the inherent reactivity of the β-diketone moiety. Intermediate **2.25** was then successfully converted into clusianone (**2.7**). In another instance, the mono α-substituted methyl vinyl ether **2.26** also succumbed to the Effenberger cyclization but upon formation of the methyl vinyl ether, they obtained a 1:1 mixture of isomeric methyl vinyl ether **2.27** and **2.28**. For the development of a viable synthetic route, they focused on methyl vinyl ether **2.27** that offered less reluctance to

alkylation at C-1. With bicycle **2.27** in hand, they established a viable synthesis of nemorosone (**2.3**) and intermediate **2.29**, which was used by Danishefsky in the total synthesis of garsubellin A.[83]

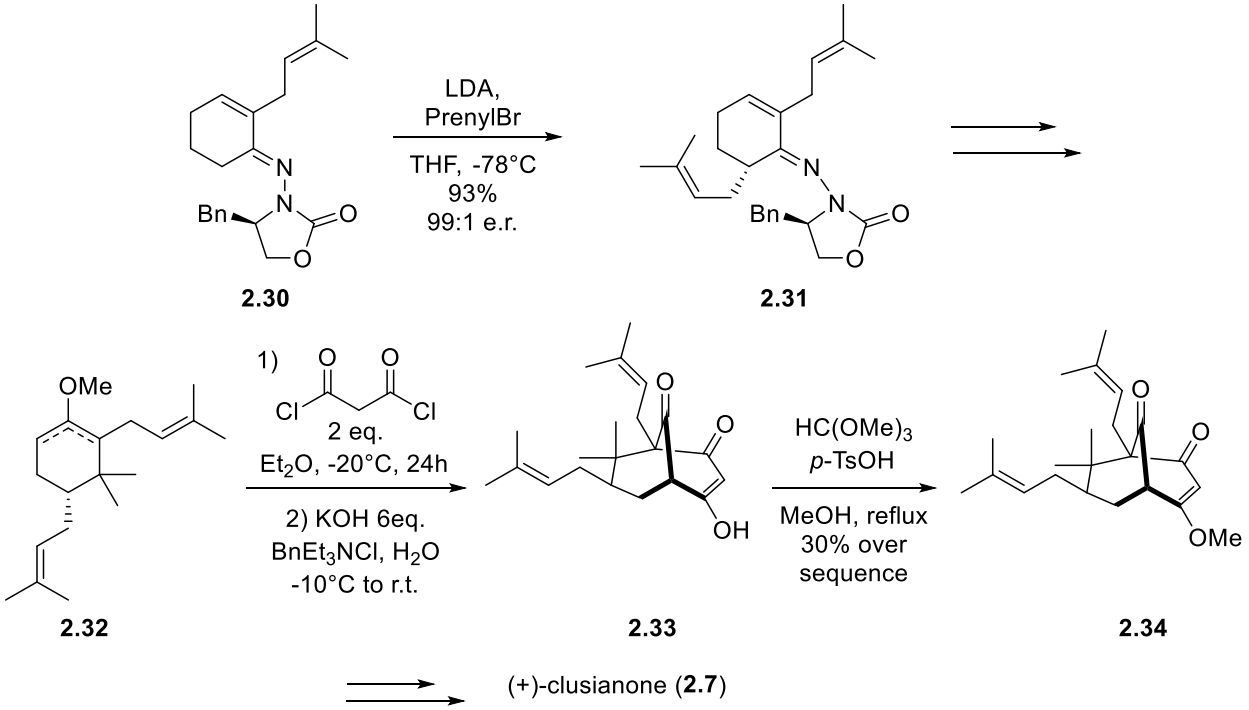
Scheme 2.5 – Simpkins approach: the Effenberger cyclization



Following Simpkins work on PPAPs, Coltart et al. sought to use the same synthetic strategy with some modifications to permit the asymmetric synthesis of clusianone (***Scheme 2.6***).[84] Using a chiral N-amino cyclic carbamate hydrazone, they performed an asymmetric alkylation of hydrazone **2.30** with prenyl bromide in presence of LDA. Prenylated cyclohexene **2.31** was

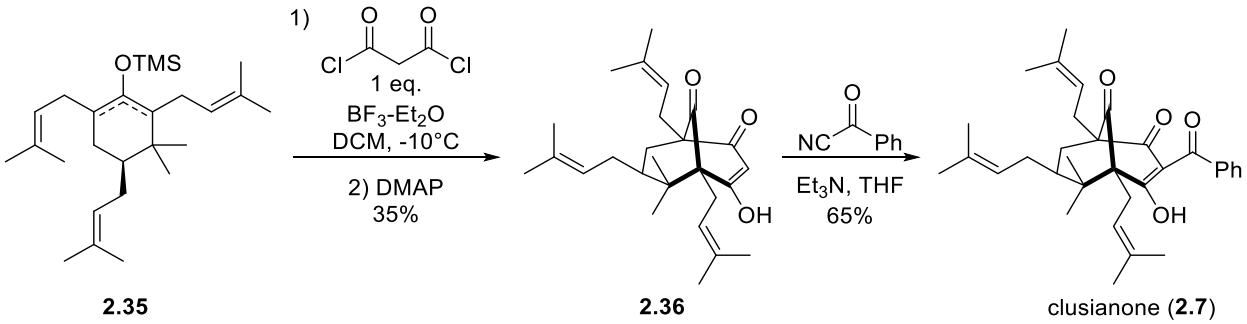
obtained in 93% yield and 99:1 e.r. The latter was converted into asymmetric methyl vinyl ether **2.32** used by Simpkins during the total synthesis of (±)-clusianone (**2.7**). The same group later published the asymmetric total synthesis of the natural enantiomer (-)-clusianone (**2.7**) using the other enantiomer of the hydrazone **2.30**.

Scheme 2.6 – Asymmetric synthesis of (+)-clusianone



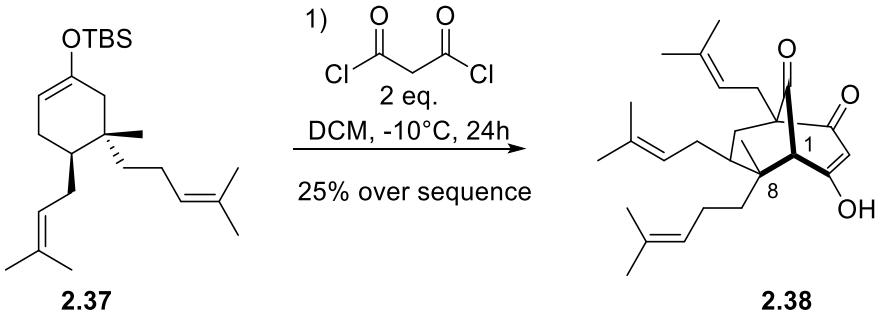
In 2007, Delpech and Marazano[85] showed that di-α-prenylated silyl enol ether can undergo the Effenberger cyclization (***Scheme 2.7***), with the addition of boron trifluoride to the original set of conditions, to give *tri*-prenylated bicycle **2.36** with superior yields to previously reported results by other groups. All that remained was the acylation of C-3 to achieve clusianone (**2.7**).

Scheme 2.7 – Effenberger cyclization of 2,6-prenyl-substituted cyclohexanone for the to total synthesis of clusianone



Mehta applied the Effenberger cyclization to silyl enol ether **2.37** containing a stereogenic center at C-8 (***scheme 2.8***).[86] Satisfyingly, great stereoselectivity was achieved utilizing this method and it allowed the synthesis of advance bicyclo[3.3.1]nonane core **2.38** toward prolifenones A, B and hyperforin (**2.1**).

Scheme 2.8 – Effenberger cyclization with stereogenic center at C-8

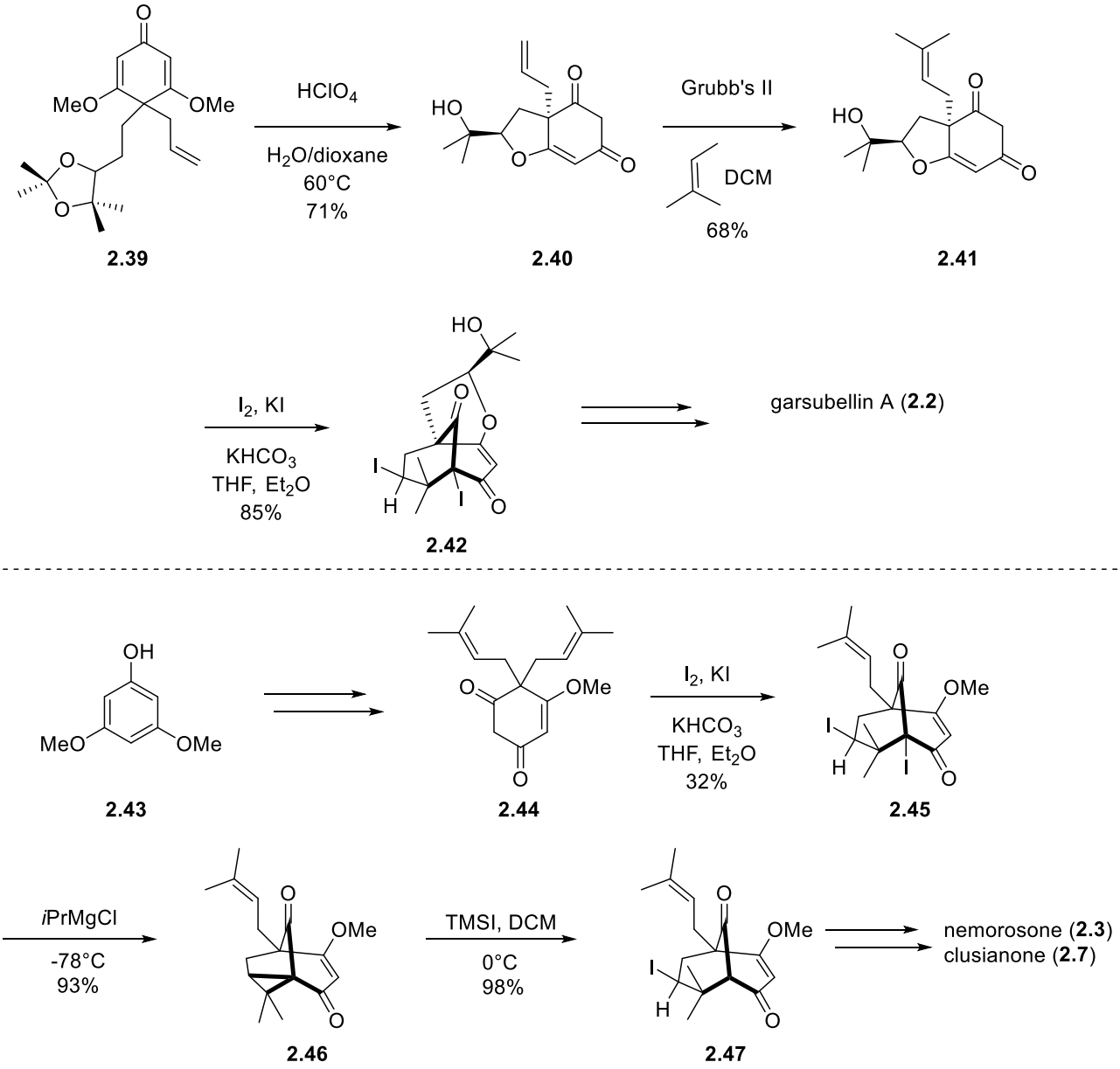


2.1.3.2 Biomimetic synthesis – dearomatization/annulation

Another successful enterprise in the synthesis of PPAPs has been the biomimetic approach, which has for key step a dearomative annulation of α and β-acids (**2.14** and **2.15**) type scaffolds. This strategies has allowed some of the shortest synthesis of PPAPs to date.

Danishefsky and Siegel were the first to successfully utilize this strategy to the total synthesis of garsubellin A (**2.2**) (***Scheme 2.9***).[83] Treatment of **2.39** with perchloric acid in a water/dioxane mixture liberated the masked diols and a Michael addition ensued. Upon prolonged stirring, the reaction mixture equilibrated to diketone **2.40** as the sole diastereomer. The prenyl moiety was installed by means of metathesis in presence of Grubbs 2nd generation and 2-methyl-2-butene to give **2.41** in 68% yield. Iodocarbocyclization of **2.41** provided **2.42** in 85% yield which ultimately led to garsubellin A (**2.2**). The same synthetic plan, with slight modifications, was utilized to access nemorosone (**2.3**) and clusianone (**2.7**) in later reports.[87] 3,5-dimethoxyphenol **2.43** was converted to cyclohexanone **2.44**, followed by an iodocarbocyclization in the presence of iodide, potassium iodide and $KHCO_3$ to give **2.45** in 32% yield. Treatment of diiodo **2.45** with *i*-PrMgCl triggered a Wurtz cyclopropanation to give cyclopropane **2.46** in 93% yield. The bicyclo[3.3.1]alkenone core **2.47** was subsequently obtained by cyclopropane opening in presence of TMSI in DCM. This intermediate was used to synthesize nemorosone (**2.3**) and clusianone (**2.7**) showcasing the versatility of this approach.

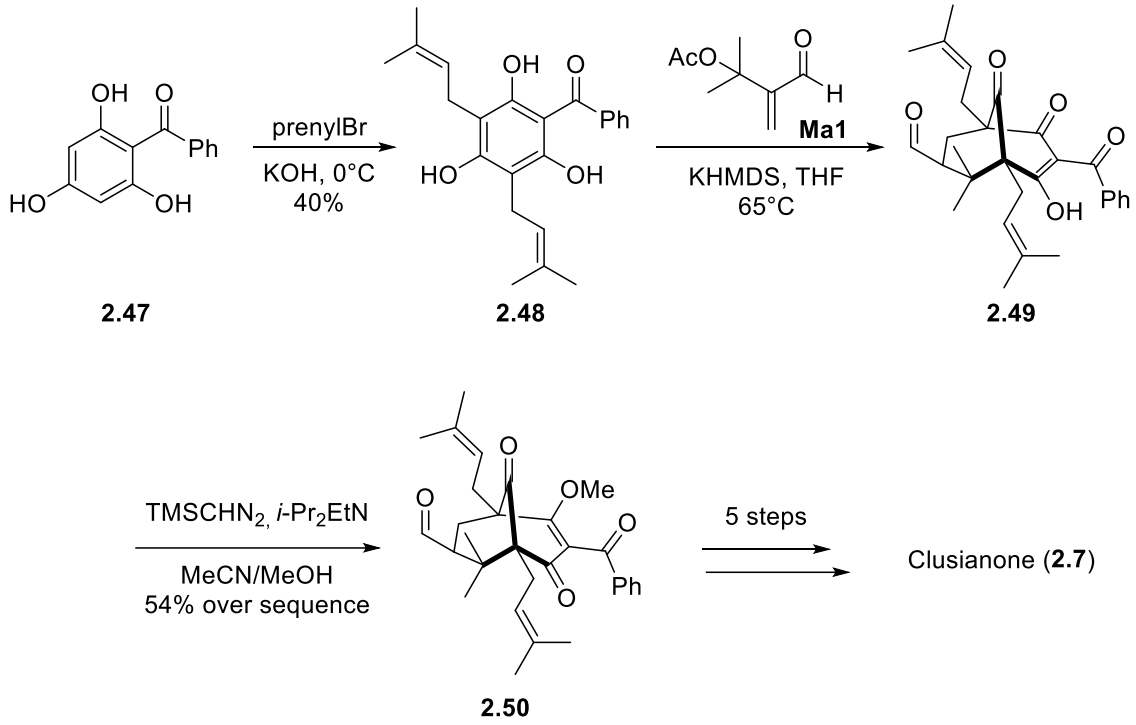
Scheme 2.9 – Iodocarbocyclization/ transannular Wurtz cyclopropanation for the synthesis of garsubellin A, nemorosone and clusianone by Danishefsky



Porco et al. utilized a dearomatization as key reaction to the synthesis of many PPAPs. He established early in the PPAPs research endeavor, the powerful disconnection that dearomatization of MPAPs and derivatives can represent. In 2007, the same group[88] showed that phenyl(2,4,6-trihydroxyphenyl)methanone **2.47** can be bis-prenylated under mild conditions to give

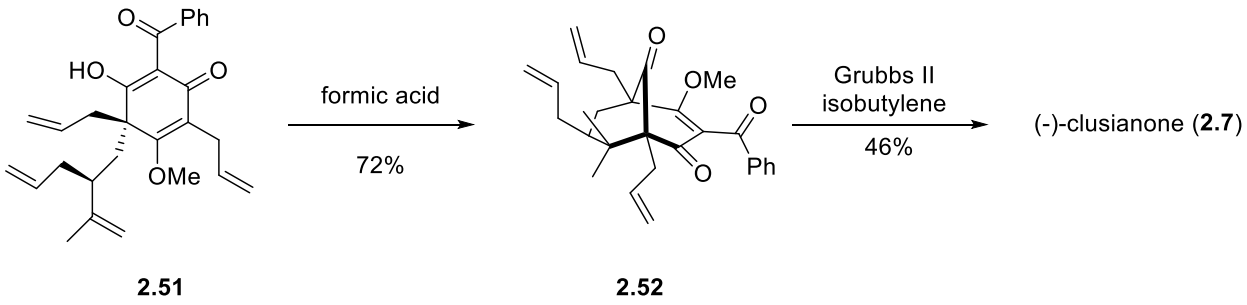
clusiaphenone B **2.48** (***Scheme 2.10***). Subjecting clusiaphenone B **2.48** to the Michael acceptor **Ma1** and KHMDS at 65˚C gave the advanced intermediate **2.49** in only 2 steps from readily available starting material allowing the synthesis of clusianone (**2.7**) in only 8 steps.

Scheme 2.10 – Alkylative dearomative annulation for the 1st generation synthesis of clusianone



In a reengineered asymmetric synthesis of (-)-clusianone (**2.7**),[89] utilizing a biomimetic cationic cyclization, the same group was able to reduce the step count even further. They established the shortest synthesis to date of enantioenriched clusianone (**2.7**) in 6 steps (***Scheme 2.11***). Treatment of (-)-(S,S)-methyl vinyl ether **2.51** with formic acid achieved the desired annulation toward allylclusianone **2.52** which was transformed into the natural product by metathesis using Grubbs 2nd generation and isobutylene. Interestingly, the treatment of (+)-(*R*,*S*) isomer of **2.51** led principally to *O*-cyclization rather than *C*-cyclization which offered the opportunity for a stereodivergent synthesis.

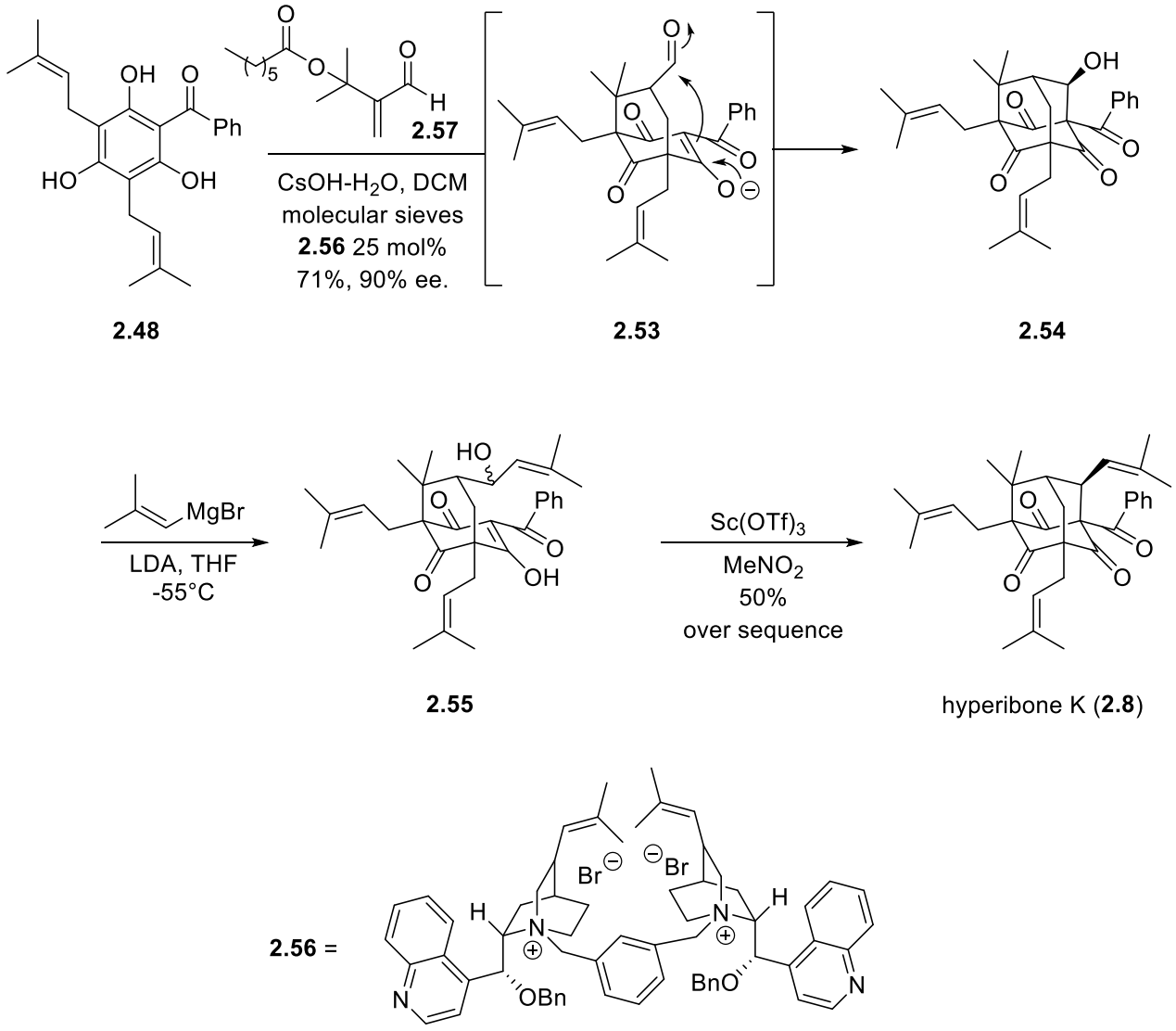
Scheme 2.11 – Cationic annulation for the 2nd generation synthesis of clusianone



2.51 **2.52**

Adamantane bearing PPAPs can seem at first like more intimidating targets then their bicycle peers but a biomimetic driven synthetic plan allowed a facile construction of those cores (***Scheme 2.12***). In the case of hyperibone K (**2.8**),[90] an asymmetric alkylative dearomative annulation of clusiaphenone B **2.48** to bicyclic core **2.53** coupled with an aldol addition gave adamantane core **2.54**. Much credit must be given to this approach for achieving the complex adamantane core in a single transformation from monocyclic starting material. The enantioselectivity arose from the phase-transfer dimeric cinchona alkaloid **2.56** identified as the most effective catalyst for this reaction with 71% yield and 90% ee. Another interesting feature of this synthesis was the realization that aldol product **2.54** and retro aldol product **2.53** were in equilibrium under basic conditions. This allowed chemoselective trapping of the aldehyde with vinyl Grignard reagent to give bicycle **2.55**. Intramolecular cation cyclization of **2.55** catalyzed by $Sc(OTf)_3$ successfully delivered hyperibone K (**2.8**) in 50% over 2 steps.

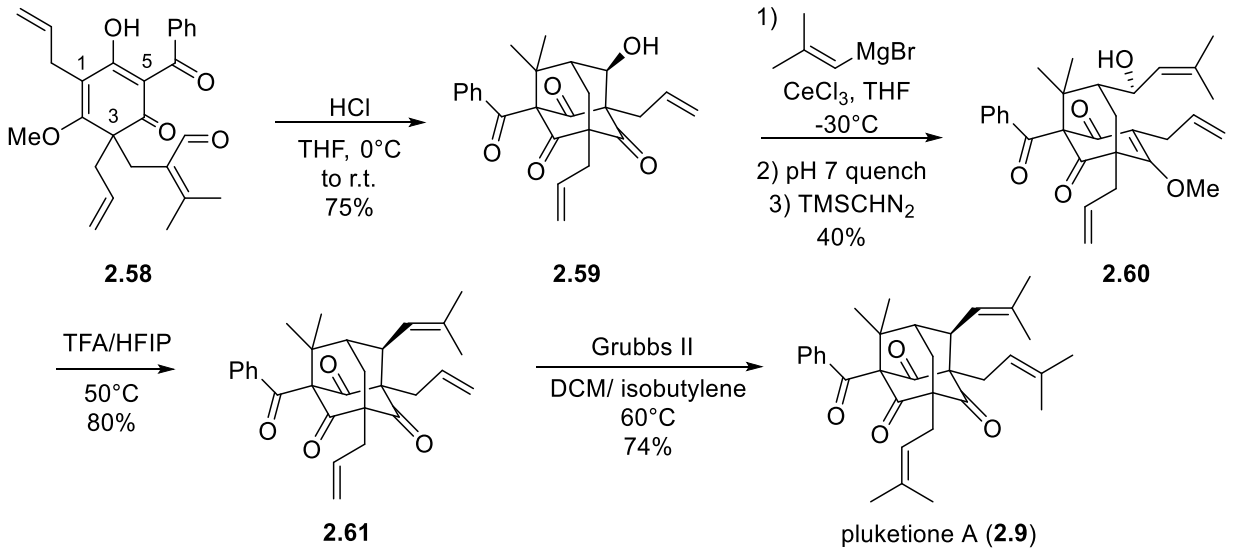
Scheme 2.12 – Alkylative dearomative annulation for the total synthesis of hyperibone K



To access pluketione A (***Scheme 2.13***),[91] Porco developed a site selective dearomative-annulation by masking the prenyl groups of the natural product as their allyl counter-parts. It was found that the methyl ether of intermediate **2.58** protects C-1 from cyclization and proceeds only through the annulation at C-5 and subsequent aldol condensation to give adamantane core **2.59**. The utilization of Grignard reagents to install the vinyl group would fragment **2.59** to type B PPAPs but fortunately the utilization of an organocerium furnished the desired retro-

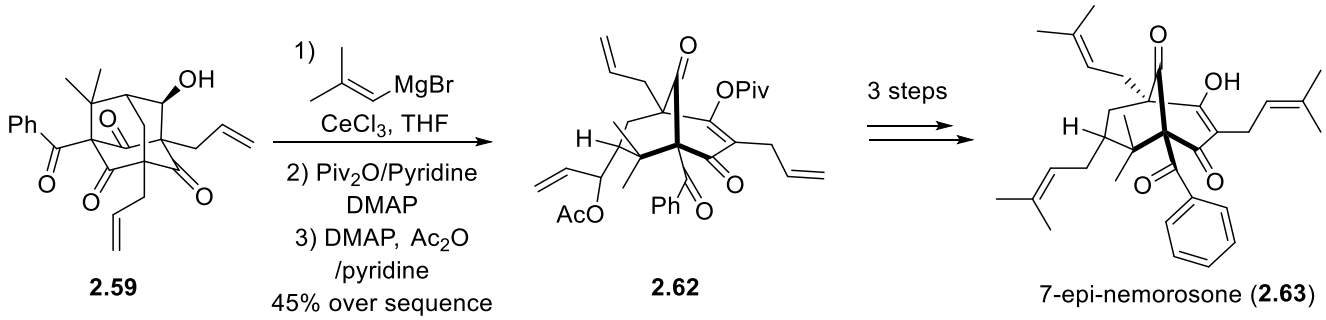
aldol/alkylation product **2.60**. Upon heating with trifluoroacetic acid, a cationic cyclization occured to give adamantane core **2.61**. Metathesis of **2.61** with Grubbs II and isobutylene gave pluketione A.

Scheme 2.13 – Dearomative annulation for the total synthesis of pluketione A



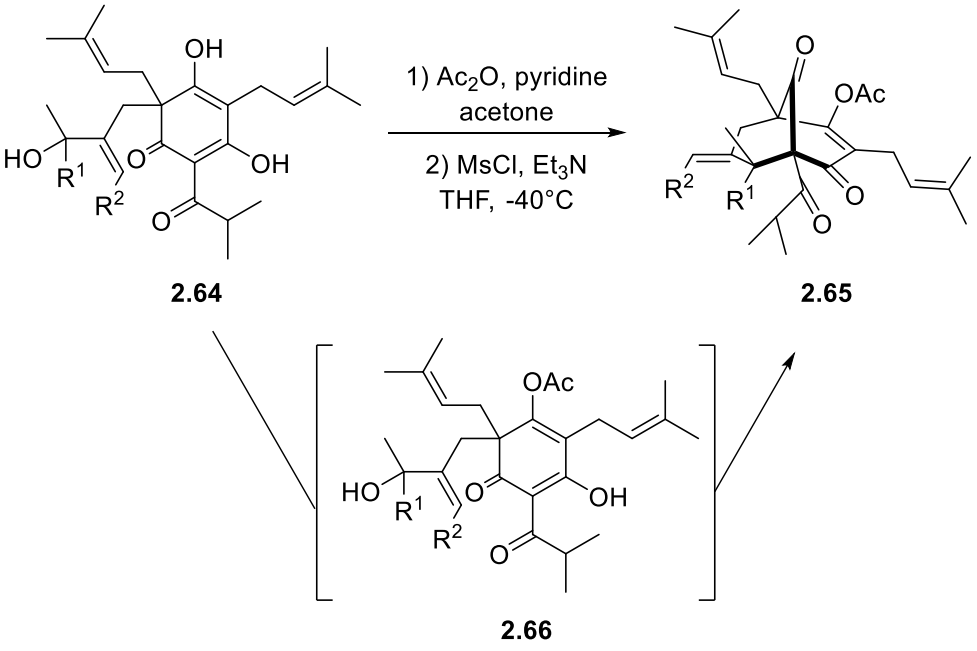
Utilizing adamantyl core **2.59**, a total synthesis to 7-*epi*-nemorosone (**2.63**)[92] was also delineated (***Scheme 2.14***). Protection of the hydroxyl resulting from the organocerium addition with an acetate moiety (**2.62**) has halted the intramolecular cationic cyclization that normally led to adamantane like cores and locked the confirmation into the bicyclic form. Three steps separated **2.62** from 7-*epi*-nemorosone (**2.63**).

*Scheme 2.14 – Synthesis of 7-epi-nemorosone from intermediate **2.59***



Similar to Porco's work, Couladouros' group[93] disclosed an approach to type A PPAPs through a biomimetic cationic annulation induced by the mesylation of the tertiary hydroxyl group of **2.64** (***Scheme 2.15***). The strategy allowed to start from MPAPs-like starting materials **2.64** and converted them to bicyclo[3.3.1]alkenone cores **2.65** through acetylated intermediate **2.66**.

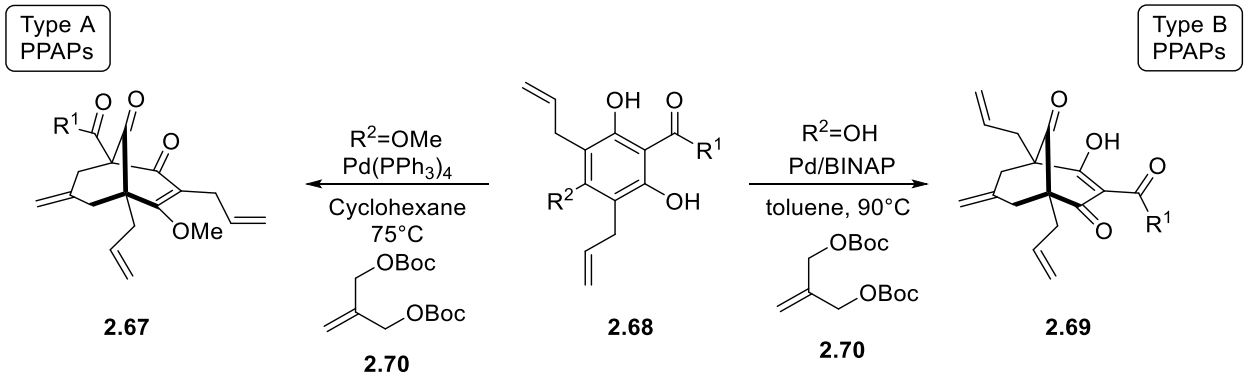
Scheme 2.15 – Couladouros cationic cyclization toward PPAPs' core



Recently, Porco et al. described an expedient synthesis of PPAPs via dearomative conjunctive allylic annulation (***Scheme 2.16***).[94] This methodology allowed the synthesis of type

A and type B PPAPs scaffolds. If the R^2-substituent of MPAP **2.68** was a hydroxyl group, Pd/BINAP in toluene with **2.70** led to type B PPAPs. For R^2= -OME, treatment of **2.68** with $(PPh_3)_4Pd$ in cyclohexane provided type A PPAPs instead.

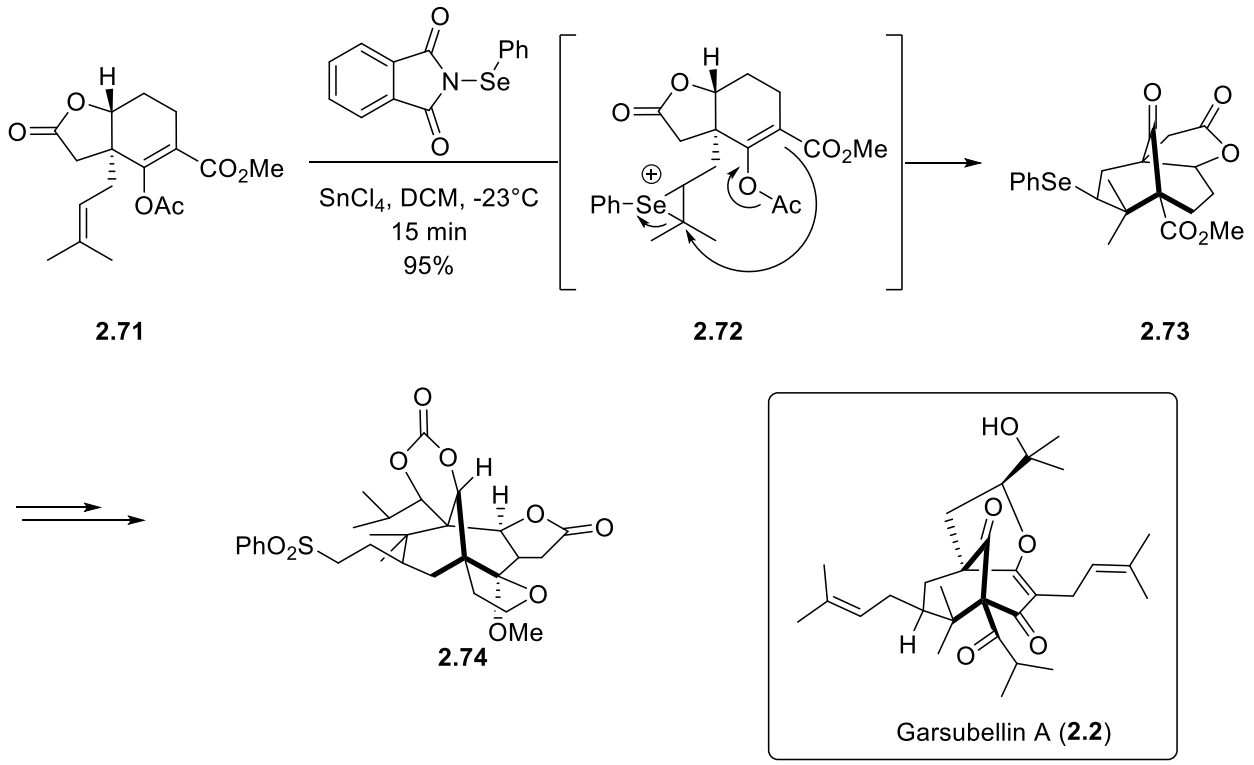
Scheme 2.16 – Rapid synthesis of PPAPs core via dearomative conjunctive allylic annulation



2.1.3.3 Miscellaneous strategies

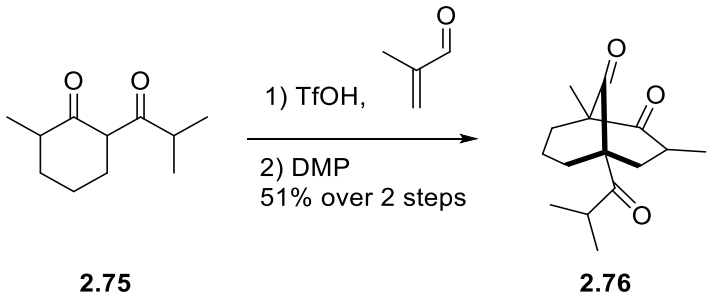
In 1999, Professor K. C. Nicolaou was the first to report a synthetic approach toward PPAPs (***Scheme 2.17***).[75] His approach was aimed at garsubellin A (**2.2**) with a selenocyclization as the key disconnection. The selenocyclyzation of **2.71** afforded bicyclo[3.3.1]nonane core **2.73** in excellent yield (95%). Unfortunately, the furthest intermediate encountered using this synthetic pathway was bicycle **2.74**. **2.74** which included all the necessary chemical handles to finish the synthesis but at first glance seemed more complicated than the target garsubelllin A (**2.2**). No further report using this strategy has been disclosed to date.

Scheme 2.17 – Selenocyclyzation toward garsubellin A



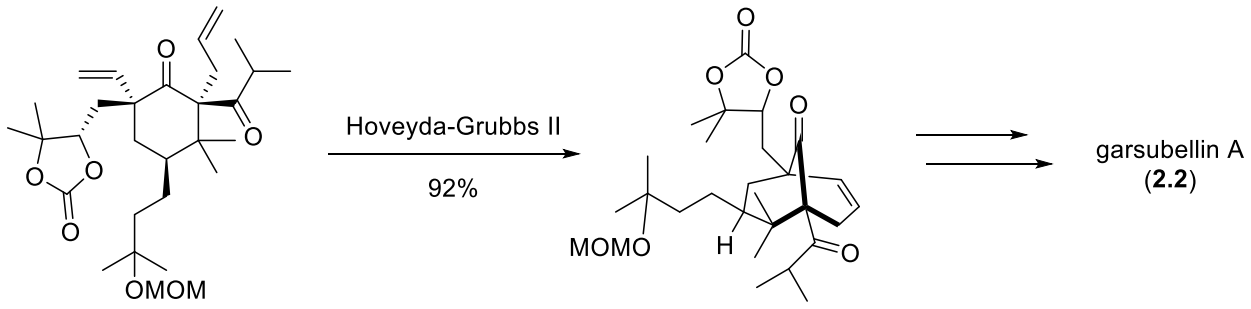
Later in 2005, Nicolaou[95] reported a general approach for the PPAPs bicycle **2.76** core via a Michael addition/aldol sequence of β-ketoester **2.75** with methacrolein in presence of triflic acid (***Scheme 2.18***). Although this sequence did not allow the synthesis of PPAPs, a similar strategy was used by Kraus to gain access to the bicyclic core (***Scheme 2.22***).

Scheme 2.18 – Rapid access to PPAPs' core via Michael/ Aldol sequence



In 2005, Shibasaki[76, 96] completed the first total synthesis of garsubellin A (**2.2**). The synthesis was achieved through the ring closing metathesis of a densely functionalized cyclohexanone **2.77** to give bicycle **2.78**. Oxidation of the resulting alkene and alkylation of a prenyl chain provided the desired natural product.

Scheme 2.19 – Ring closing metathesis for the total synthesis of garsubellin A

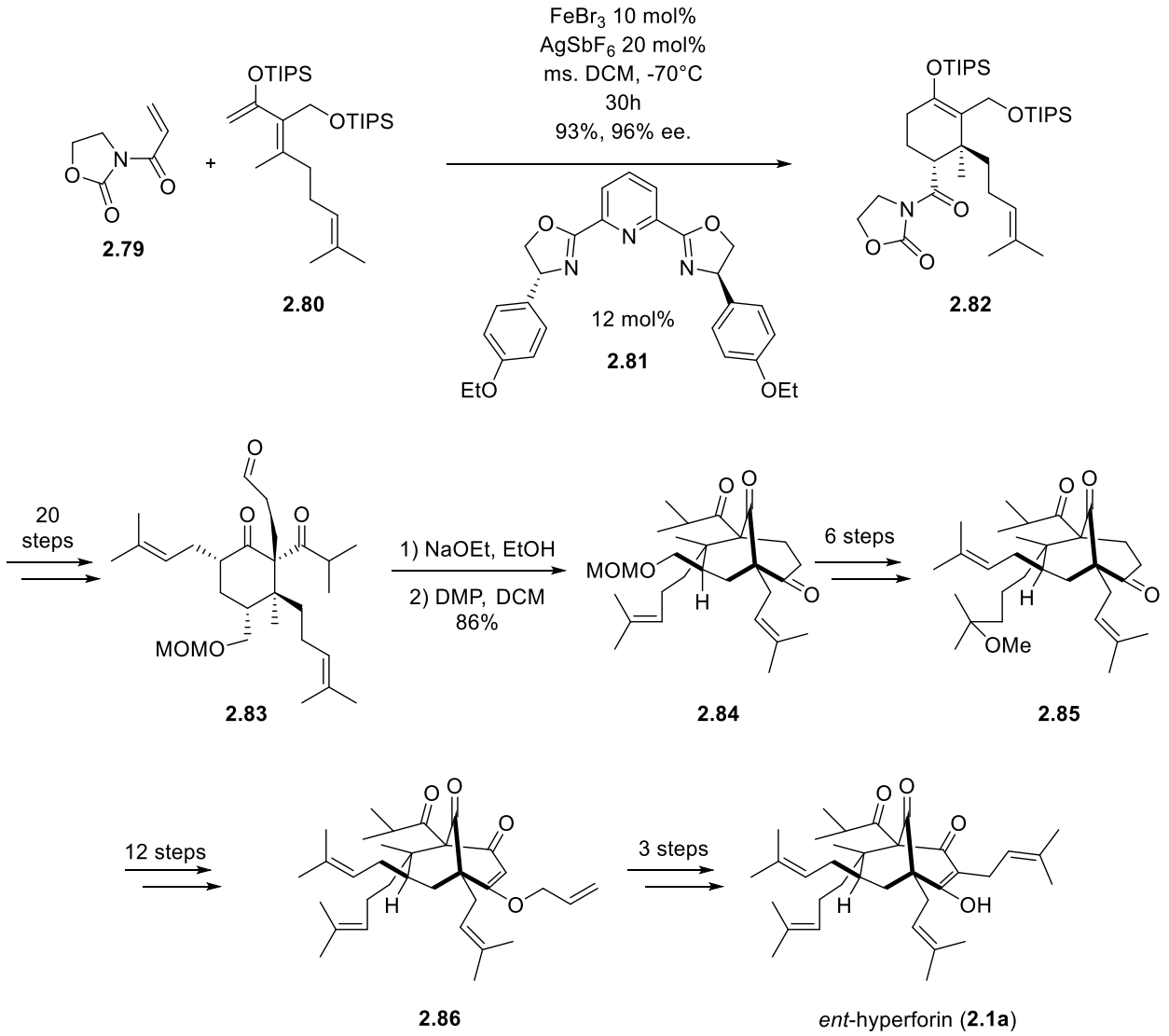


2.77 **2.78**

35 years have gone by since the structure of hyperforin (**2.1**) was revealed by Bestrov[97] and yet no total synthesis had been reported until Shibasaki's group achieved the first total synthesis of *ent*-hyperforin in 51 steps (***Scheme 2.20***).[98] Hyperforin (**2.1**) is considered by many the crown jewel of this family as it transcend in its medical attributes and complexity. Most PPAPs contain a *gem*-dimethyl at C-8 but hyperforin has an extra stereocenter at this position comprised of a methyl group and *homo*-prenyl group. This extra stereogenic center adds another level of complexity to the natural product. Since the synthesis was quite long, we will only be highlighting the key disconnections that enabled this seminal synthesis. One of the most important feature of this synthesis was the asymmetric Diels-Alder reaction between diene **2.80** and oxazolidinone acrylamide **2.79** promoted by cationic Fe-pybox complex **2.81**. This allowed the early introduction of the quaternerary carbon C-8 asymmetrically in 93% yield and 96% ee. **2.82** was transformed into precursor of the bicyclic core **2.83** in 20 steps by alkylations/protections/deprotections

reaction. An aldol/oxidation ensued to give bicycle **2.84** in 86% over 2 steps. 6 steps were required to install the prenyl chain of C-7 resulting in **2.82**. 12 steps were then required for the oxidation to **2.86** showcasing the problems associated with a late oxidative strategy of C-2 and C-4. A Claisen/metathesis/deprotection then followed to yield ent-hyperforin(**2.1a**).

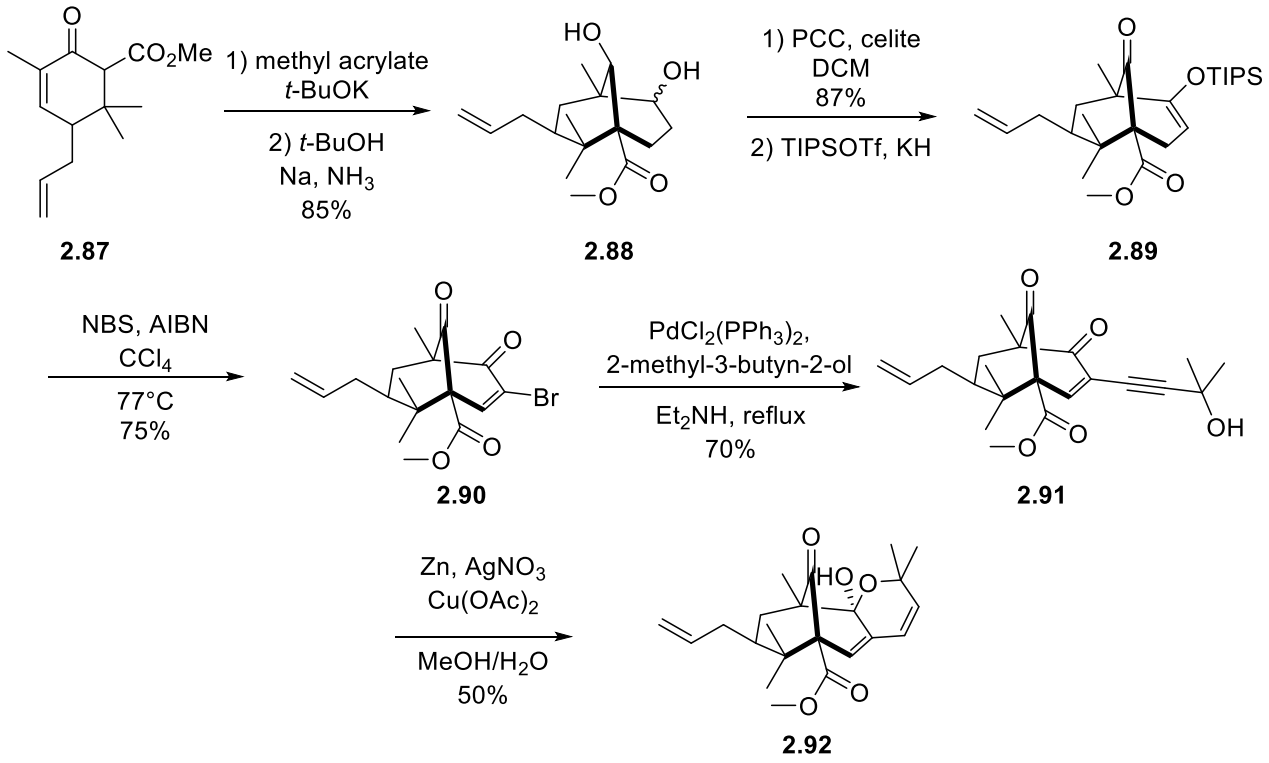
Scheme 2.20 – Shibasaki's synthesis of ent-hyperforin



Kraus' group has been actively involved in finding approaches to PPAPs. Unfortunately, he has been unsuccessful to this day in his endeavors (***Scheme 2.21***).[99] Nevertheless, his group

was among the first to investigate papuaforin A(**4**). Diol **2.88** was prepared from keto ester **2.87** by Michael addition followed by a Birch reduction/cyclization. The diol **2.88** was oxidized in presence of PCC and TIPS enol ether **2.89** was generated with TIPSOTf and KH. Upon treatment with NBS and AIBN, α-bromoenone **2.90** was formed. Vinyl bromide **2.90** was used as a tether for a Sonogashira reaction yielding bicycle **2.91**. The synthetic strategy was then to reduce the alkyne to achieve the pyran ring found in papuaforin A, but instead it resulted in hemiketal **2.92**. No further report using this strategy has been disclosed.

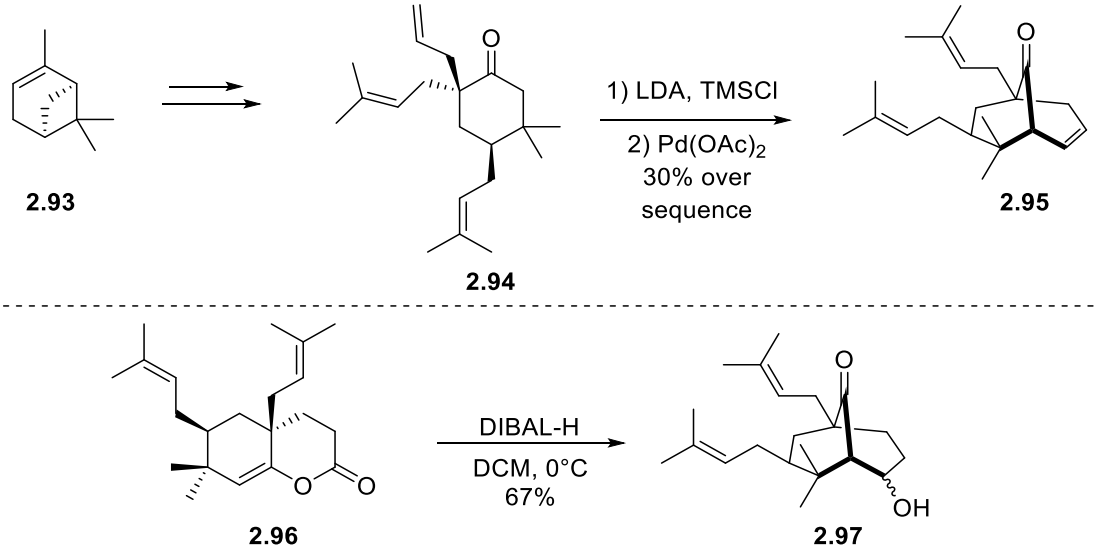
Scheme 2.21 – Michael/ Birch reduction toward papuaforin A



Much like Kraus, Metha's group has also investigated different strategies to gain access to PPAPs.[86, 100] Two of them can be found in ***Scheme 2.22*** whereas the strategy involving the Effenberger cyclization was detailed in ***Scheme 2.8***. In the first approach, they were able to synthesize enantioenriched cyclohexanone **2.94** from α-pinene **2.93**. The silyl enol ether was

formed using LDA and TMSCl and subsequently submitted to a palladium(II)-catalyzed Kende cyclization to obtain prenylated bicycle **2.95** in 30% yield over the two steps. The second approach called for a reduction/aldol sequence initiated by DIBAL-H that gave alcohol **2.97** from **2.96**. Both methodology did not led to the natural products, probably due to a problematic C-2 and C-4 oxidation that needed to occur in both cases.

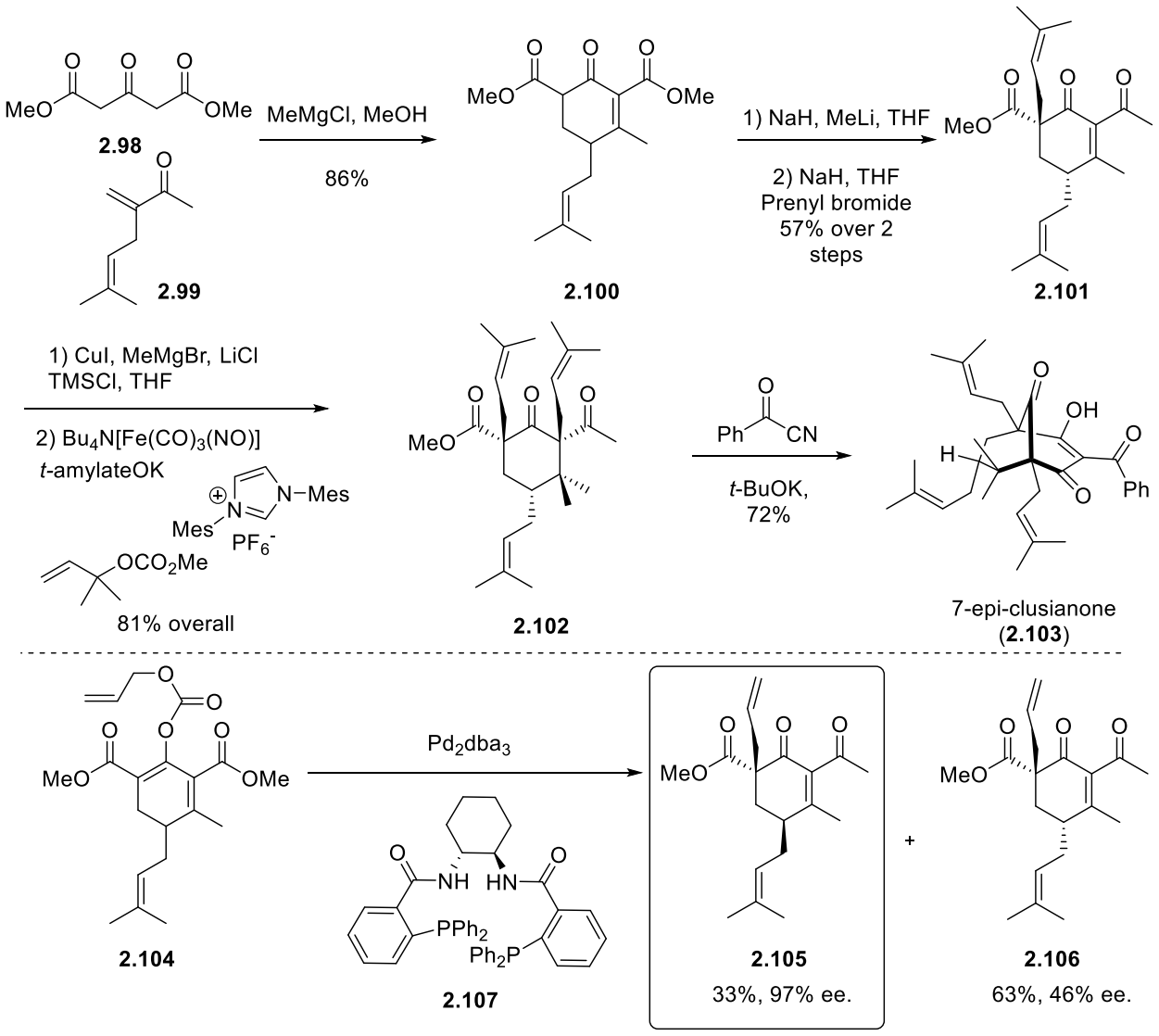
Scheme 2.22 – Different approaches devised by Metha: Kende cyclization and retroaldol/aldol



Plietner and coworkers designed one of the shortest and most modular route to trans-type B PPAPS (***Scheme 2.23***). With this methodology the total synthesis of hyperpapuanone (**2.11**), hyperibone L, 7-*epi*-clusianone (**2.103**) and oblongifolin A were completed in 7 to 8 steps. In the optic of clarity, we will focus exclusively on the synthesis of 7-*epi*-clusianone.[101] Triketone **2.100** was assembled by a Michael addition/Knoevenagel condensation of **2.99** and **2.98**. Alkylation of **2.100** with prenyl bromide gave **2.101** which underwent conjugate addition and iron catalyzed α-allylation to give **2.102**. A tandem Dieckmann condensation/acylation induced by *t*-BuOK afforded 7-*epi*-clusianone (**2.103**) in 72% yield. The same group recently published an

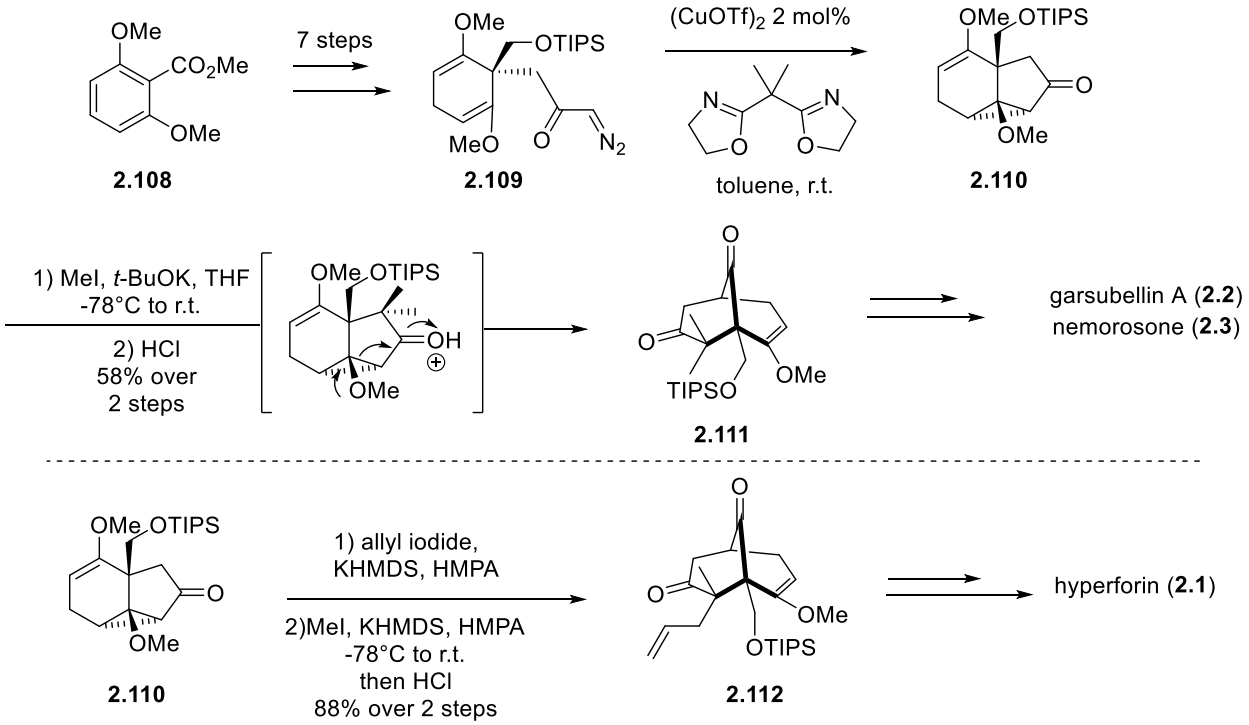
enantioselective route to (+)-clusianone utilizing intermediate **2.100**.[102] The enantioenriched material **2.105** was obtained by asymmetric decarboxylative Tsuji-Trost allylation of allylvinylcarbonate **2.104** using diaminocyclohexane phosphine derived ligands **2.107**. They obtained a separable mixture of **2.105**, the naturally occurring isomer in 33% and 97% ee, and **2.106** with 63% yield and 46% ee. Although **2.105** was not the major product, **2.105** was carried forward to achieve the total synthesis of (+)-clusianone (**2.7**).

Scheme 2.23 – Highly modular total synthesis of trans-type B PPAPs via Dieckmann condensation



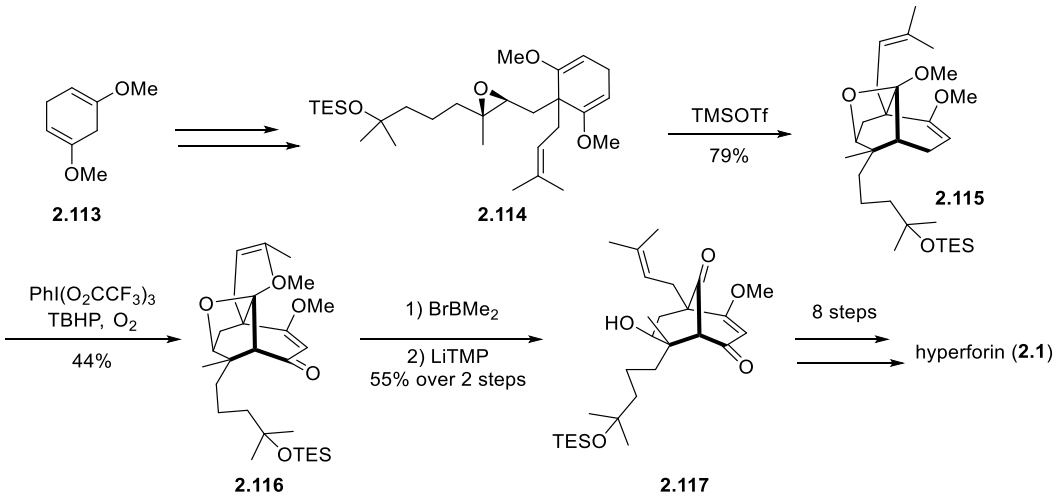
Nakada and co-workers devised an intramolecular cyclopropanation/regioselective ring opening to access the bicyclo[3.3.1]nonane core readily (***Scheme 2.24***).[103] To the demise of this strategy though, the core was containing only few of the vital functional groups and required a high step count to achieve the natural products. Nevertheless, they achieved some of the most desirable PPAPs through this method including garsubellin A (**2.2**), nemorosone (**2.3**) and hyperforin (**2.4**). The method used to access the core was the same for garsubellin A (**2.2**) and nemorsone (**2.3**). Starting from arene **2.108**, a few transforms yielded α-diazo-β-ketone **2.109**. Copper catalyzed intramolecular cyclopropanation gave **2.110**. Stereoselective bis-alkylation, followed by a regioselective ring opening of the cyclopropane gave bicycle **2.111**. The same strategy was used for the synthesis of hyperforin (**2.1**) where cyclopropane **2.110** was alkylated with allyl iodide first, then methyl iodide to create the C-8 stereogenic center of the natural product.

Scheme 2.24 – Intramolecular cyclopropanation, regioselective ring opening for the total synthesis of garsubellin A and nemorosone



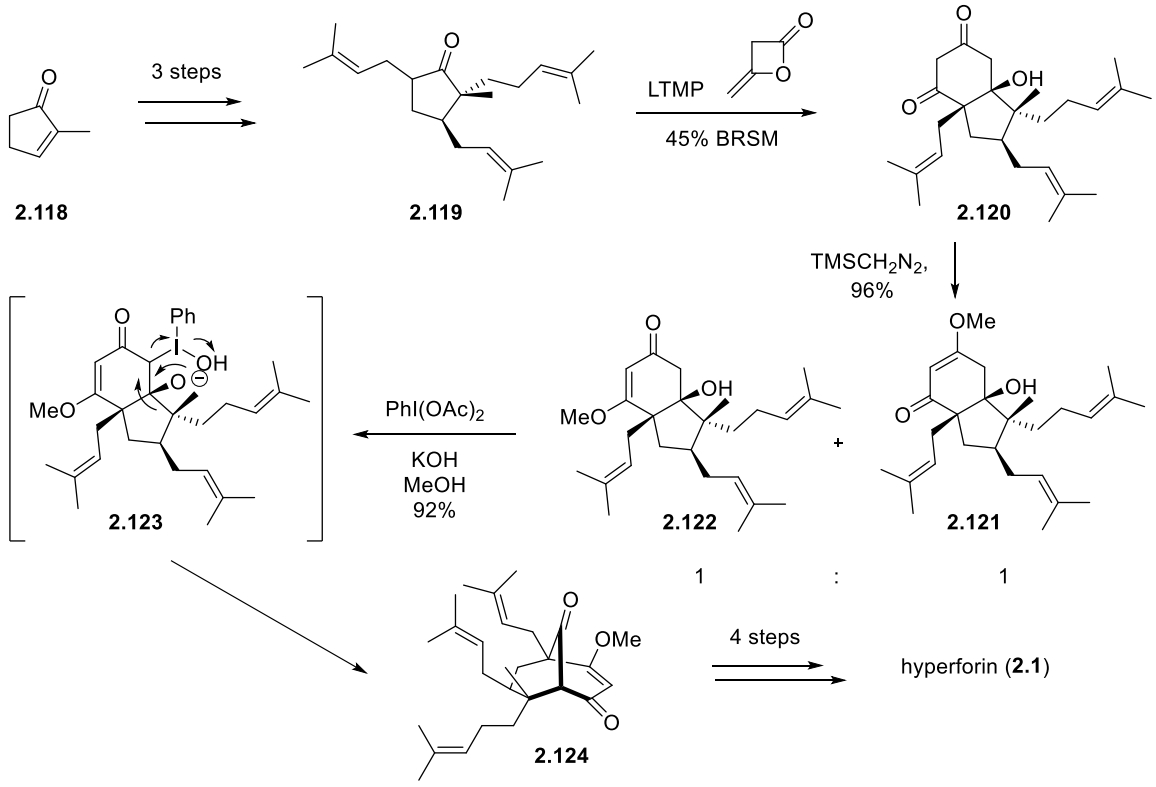
An entirely new synthetic strategy was adopted by professor Shair to access PPAPs scaffolds (***Scheme 2.25***). The group described a modular, 18 steps asymmetric total synthesis of hyperforin (**2.1**) using latent symmetry elements, whereby a Lewis acid-catalyzed epoxide-opening cascade cyclization was used to obtain the bicyclo[3.3.1]nonane core **2.115**.[104] This strategy also enabled the total synthesis of (-)-nemorosone (**2.3**) and (+)-secohyperforin (**2.12**) but we will focus solely on hyperforin (**2.1**) as it was the most synthetically challenging molecule of the three. The synthesis began with dimethoxyvinyl ether **2.113** that was transformed into epoxide **2.114** through a series of C-C bond formations. A TMSOTf catalyzed epoxide opening gave ketal **2.115**. It is also important to mention that the allylic oxidation which has been problematic for many groups prior, was achieved chemoselectively using a combination of hypervalent iodide, TBHP and O_2 to give vinylogous ester **2.116**. Hydrolysis of the ketal was performed in 2 steps by first subjecting **2.166** to $BrBMe_2$ followed by LiTMP-mediated methanol extrusion from the intermediate hemiketal to yield alcohol **2.117**. Bicycle **2.117** was then transformed into hyperforin (**2.1**) over 8 steps.

Scheme 2.25 – Epoxide opening for the total synthesis of hyperforin



The most recent total synthesis of hyperforin (**2.1**) was accomplished by Professor Maimone and is the shortest to date with only 10 steps (***Scheme 2.26***).[105] The key to this sequence is an oxidative fragmentation leading to the bicycle core **2.214**. The initial C-C bond formation reaction allowed the transformation of cyclopentenone **2.118** into prenylated cyclopentanone **2.119**. The enolate of **2.119** was found to engage with simple diketene for a formal C-acylation/ring annulation process leading to complex 5/6-fused bicycle **2.120** as a single diastereomer. β-Diketone **2.120** was reacted with $TMSCH_2N_2$ to give a 1:1 regioisomeric mixture of vinyl methyl ether **2.122** and **2.121**. Unfortunately, only **2.122** was used for the rest of the synthesis. An oxidative ring expansion of **2.122** induced by $PhI(OAc)_2$ in an alkaline media gave bicycle **2.124** in 92% yield which was transformed to hyperforin (**2.1**) in 4 steps.

Scheme 2.26 – Oxidative fragmentation for the shortest synthesis of hyperforin

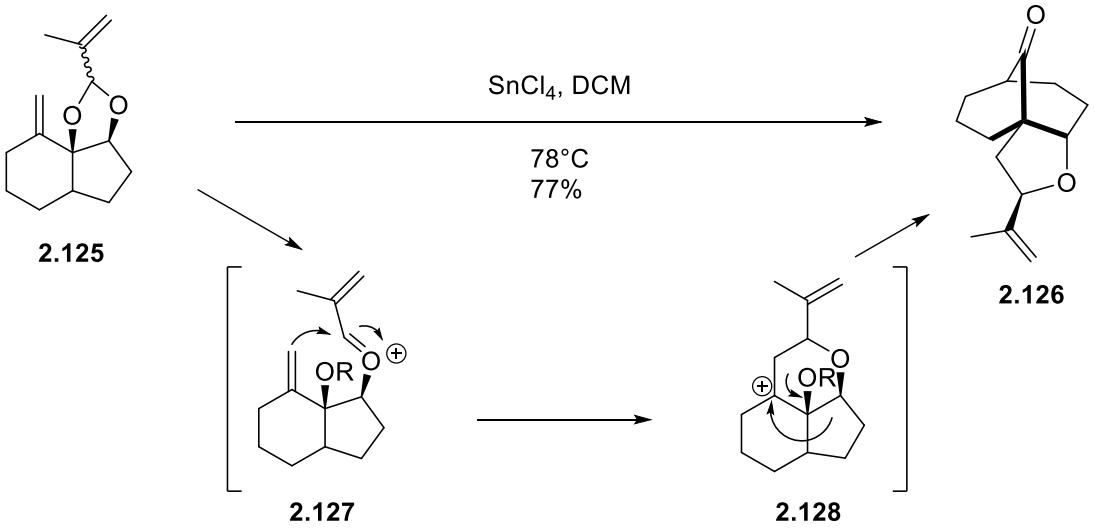


Maimone's approach to hyperforin (**2.1**) is a testament to the knowledge and insight we gained on constructing PPAPs throughout the last decade. In 2010, Shibasaki disclosed the first total synthesis of hyperforin in more than 50 steps, which has been reduced to 10 steps in less than 5 years. It is truly remarkable that we are now able to access such complexity with an elegant and approachable synthetic plans.

2.1.4 Previous approach by our group

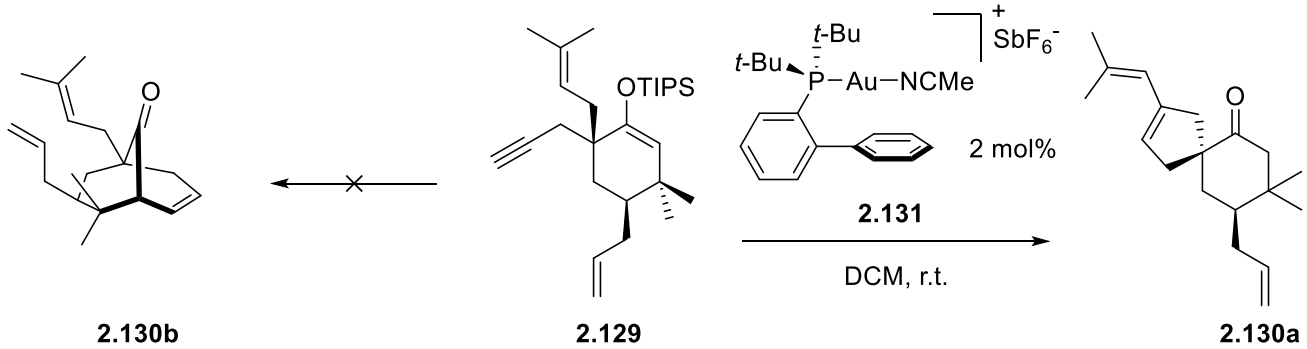
Before formally conducting research on gold catalysis, our group was already interested in the synthesis of PPAPs, more specifically garsubellin A (**2.2**). Originally, we envisioned a Prins-Pinacol reaction to form the bicyclo[3.3.1]alkenone core (***Scheme 2.27***). A former group member, Melina Girardin, synthesized the model tricycle bridged core of garsubellin A **(2.08)** via a Prins-Pinacol reaction cascade.[106] Exposure of acetal **2.125** to tin(IV) chloride afforded the bicyclo[3.3.1]nonane **2.126** in 77% yield. **2.126** was the result of a tin induced acetal opening to intermediate **2.127** and Prins cyclization to tertiary carbocation **2.128**. A semi-pinacolic rearrangement ensued to yield **2.126**. Although this domino reaction gave the core of PPAPs in high diastereoselectivity, this strategy was ultimately dropped since the preparation of the starting material containing all the necessary handles, proved too synthetically challenging and long.

Scheme 2.27 – Prins-Pinacol approach to bicyclo[3.3.1]nonane core



Following the work performed by Fancis Barabé and Genevieve Betournay on *6-endo* dig carbocyclization of enol ethers,[22, 33, 36] former MSc student, Marie-Christine Brochu synthesized advanced silyl enol ether **2.129** (***Scheme 2.28***). The initial intention was to perform a *6-endo* dig cyclization onto the alkyne with the silyl enol ether to form the bicyclo[3.3.1]alkenone **2.130b**. Instead, the cycloisomerization resulting from the reaction of the alkyne with the alkene of the prenyl chain was obtained to give **2.130a**.

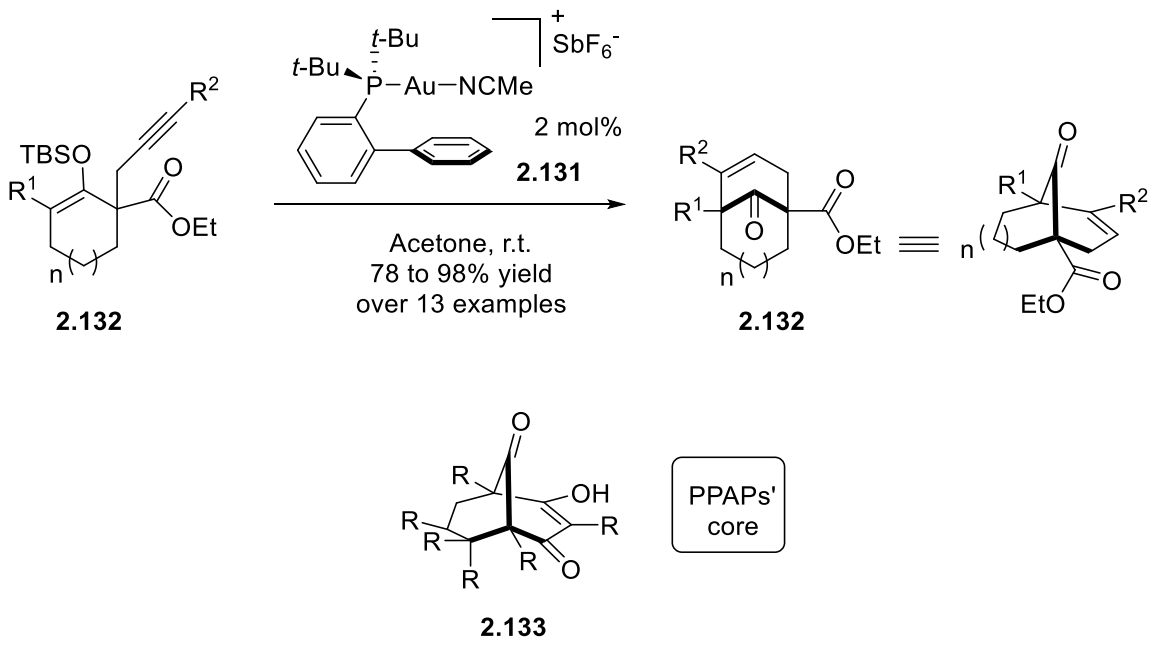
Scheme 2.28 – Gold catalysis to access core of PPAPs



2.2 Gold-catalyzed 6-endo dig cycloisomerization: expedient and modular approach to form bicyclo[3.3.1]alkenone core of PPAPs

This project started following positive results on the *6-endo* dig cycloisomerization of 1,5-enynes **2.132** catalyzed by Au(I)-salts **2.131** (***Scheme 2.29***). While investigating this methodology, we found the substrate scope to be quite general and nondiscriminatory toward substitution at R_1 and R_2 positions. The products resulting from this reaction, bicycle **2.132**, were only a few substituents from the naturally occurring PPAPs **2.133**.

Scheme 2.29 – Au(I)-catalyzed 6-endo dig cycloisomerization products and relationship to PPAPs' core

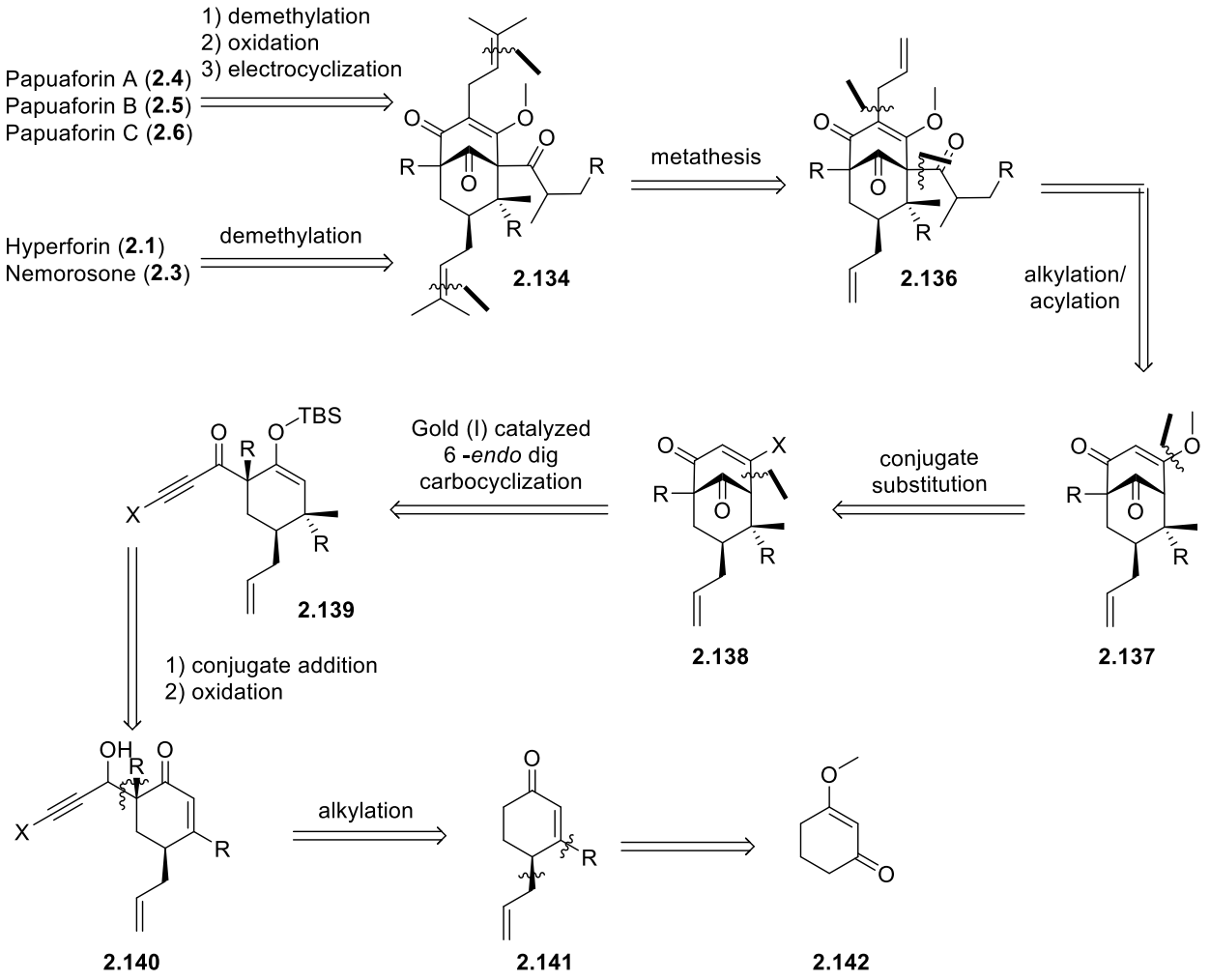


We envisioned that this methodology would unlock, with the adequate synthetic plan, the road to PPAPs as the necessary bicyclo[3.3.1]nonane core was obtained in good yields with a simple starting material.

2.2.1 Retrosynthesis and game plan

With the *6-endo* dig cyclization at the heart of our synthetic project, we delineated a blueprint that would be swift, efficient and easily modulated to provide a general route to PPAPs (***Scheme* 2.30**). In the case of papuaforin A (**2.4**), B (**2.5**) and C (**2.6**), we thought of keeping the pyran ring formation for last. We believed it could be accessed through a selective oxidation of protected β-diketone **2.134** and subsequent 6π electrocyclization. As for hyperforin (**2.1**) and nemorosone (**2.3**), **2.134** would also be the common intermediate following a demethylation. The prenyl chains would originate from a metathesis of their respective allyl chains **2.136**. The C-1 acyl moiety and C-3 allyl chain would be installed by careful acylation and alkylation respectively to methyl vinyl ether **2.137**. Conjugate substitution of bicycle **2.138** would achieve the PPAPs core containing the proper oxidation state **2.137**. The key Au(I)-catalyzed *6-endo* dig cyclization of silyl enol ether **2.139** would give bicyclo[3.3.1]nonane scaffold **2.138**. Finally, silyl enol ether **2.139** would be synthesized by careful stereospecific alkylations starting from commercially available methyl vinyl ether **2.142**.

Scheme 2.30 – Retrosynthetic analysis

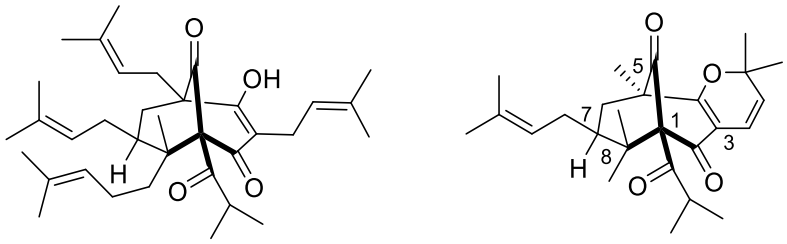


2.2.2 Model substrate to evaluate Au(I)-cyclization

Our original intention, in approaching this project, was to complete the total synthesis of hyperforin (**2.1**) (***Figure 2.4***) first and foremost. It had been recognized as the flagship of this family of natural products for reasons enumerated previously. Following the problematic *6-endo* dig cyclization uncovered by Marie-Christine Brochu though, we decided to study a different molecule papuaforin A (**2.4**) which was first aimed at gaining insight on the different challenges

associated with the synthesis of PAPPs. Papuaforin A (**2.4**) was interesting for many reasons. It had never been synthesized previously. It also contained an extra pyran ring which was never addressed by any other group working in the field of PPAPs. More importantly, the methyl group at C-5 should not interfere with our key disconnection because unlike the prenyl chain, it cannot participate in the Au(I)-catalyzed cyclization. Finally, it also contained a *gem*-dimethyl at C-8 which offered a diminished challenge as an entry point into those complex natural products compared to the stereogenic center of hyperforin (**2.1**) at the same carbon. These elements combined had us believe that papuaforin A (**2.4**) was the perfect candidate to apply our synthetic methodology.

Figure 2.4 – Structure of hyperforin and papuaforin A

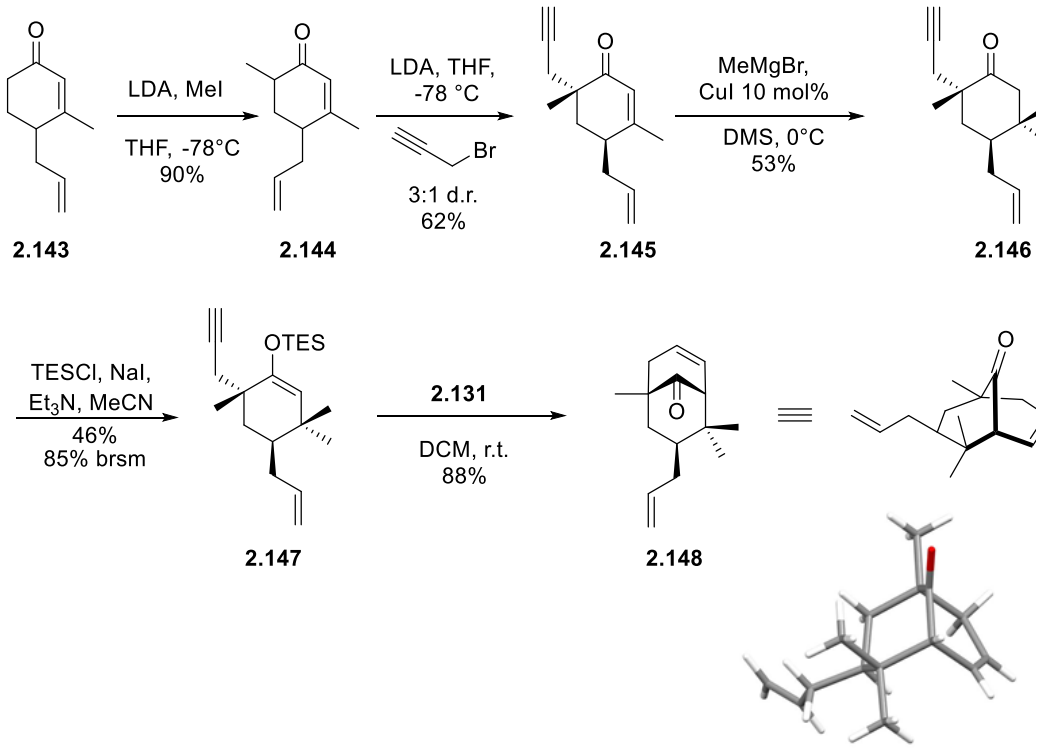


Hyperforin (**2.1**) Papuaforin A (**2.4**)

As proof of concept, we engaged in the synthesis of a model substrate for the gold catalyzed cyclization (***Scheme 2.31***). To build the precursor to the gold rearrangement **2.147**, we chose a similar strategy reported by Stork and Danheiser for the synthesis of 4-substituted cyclohexenones.[107] We took advantage that 4-allylcyclohexenone **2.143** (the synthesis will be described later in this chapter) has only one α-position capable of participating in deprotonation/alkylation processes to install first a methyl group by treating enone **2.143** with LDA and MeI. A second deprotonation/alkylation was executed with propargyl bromide to give a 3:1 mixture of diastereomers, favoring the anti-relationship between the propargyl and allyl chain

of **2.145**. This relationship was important since the majority of PPAPs possess this relative stereochemical information. Treatment of enone **2.145** with catalytical amount of copper iodide with dimethyl sulfide and MeMgBr gave conjugate addition product **2.146** and created at the same time the *gem*-dimethyl quaternary carbon. The last step, before we could contemplate our key reaction, was to form the silyl enol ether **2.147**. This was achieved with TBSCl, Et_3N, NaI in refluxed MeCN overnight and yielded 86% of **2.147** based on the recovery of starting material. To our satisfaction, the exposure of silyl enol ether **2.147** to Au-catalyst **2.131** in DCM gave bicyclo[3.3.1]alkenone **2.148** in 88% yield. The structure of the cyclized product was unambiguously proven by X-ray analysis.

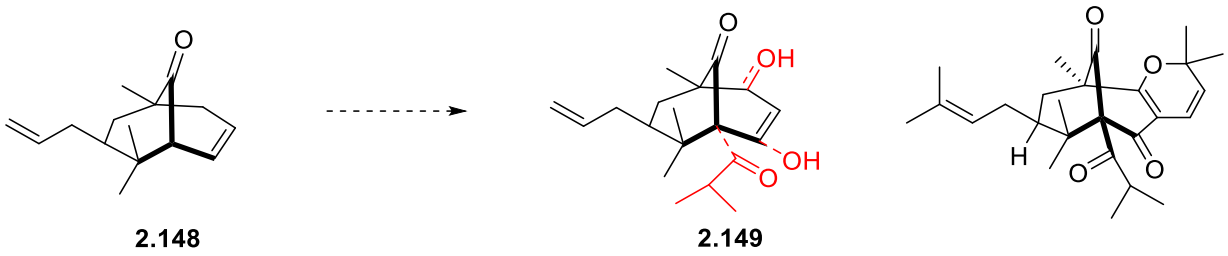
Scheme 2.31 – Au(I)-catalyzed cyclization on model substrate



With a strong route to bicycle **2.148**, we proved the utility of Au(I)-catalysis in accessing PPAPs scaffolds. We were ready to move forward to the natural products but we were facing two

challenging transformations with the current model substrate: 1) the functionalization of C-1 adjacent to the quaternary carbon C-8; 2) the selective oxidation of the cyclic alkene to the corresponding β-diketone (***Scheme 2.32***).

*Scheme 2.32 – Challenging transformation from bicycle **2.148***



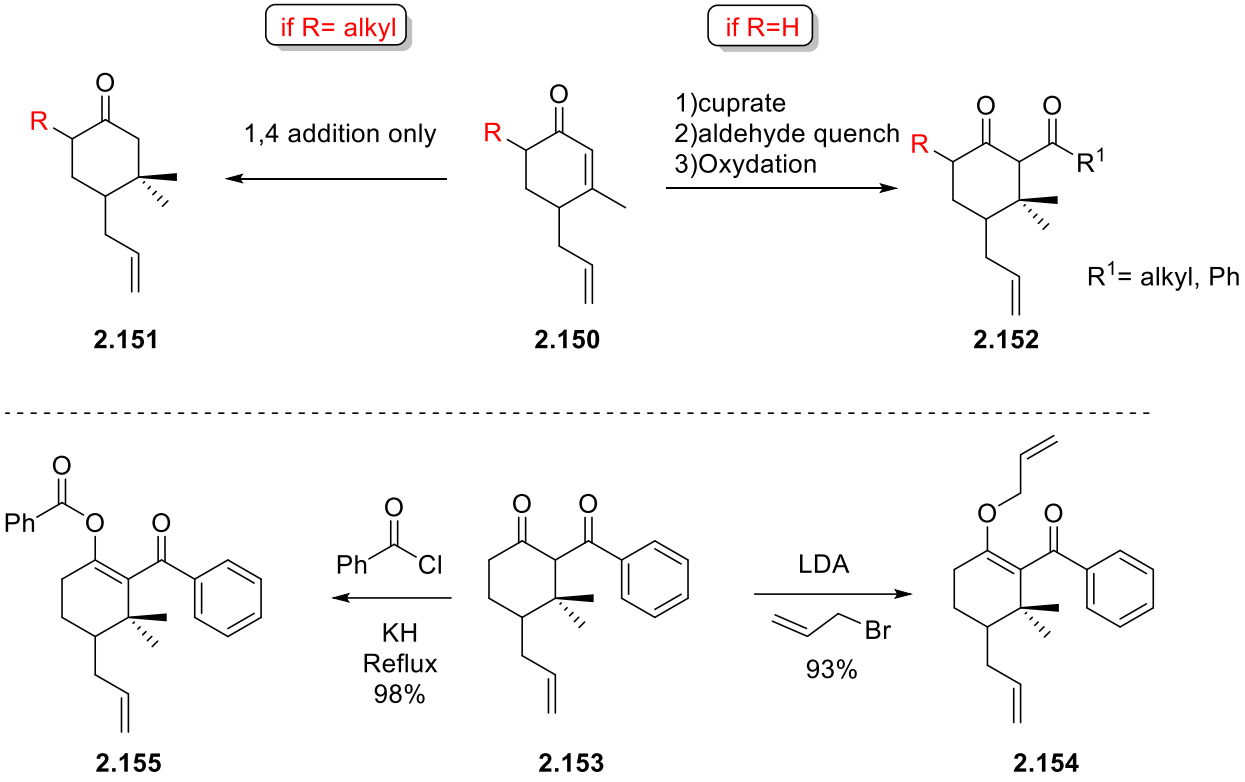
2.148 **2.149** Papuaforin A (**2.4**)

2.3 Paving the way toward the synthesis of papuaforin A

Work by earlier investigators of the PPAPs showed that the functionalization of the bridgehead position adjacent to the *gem*-dimethyl as a late-stage strategy was problematic, poor yielding and lengthy. For this reason, we decided to investigate methods to introduce the acyl functionality earlier in the synthesis. Initially, we intended to install the acyl functionality during the conjugate addition of enone **2.150** by trapping the enolate resulting from the conjugate addition (***Scheme 2.33***). Unfortunately, we discovered this transform to be impossible whenever R was an alkyl group (-Me or allyl), **2.151** was the only product observed. The aldol addition only occured when R=H, resulting in diketone **2.152** after oxidation. Upon investigation of the alkylation of acylated cyclohexanone **2.153**, we observed exclusively *O*-alkylation (**2.155** and **2.154**). Similar results were obtained by Simpkins' group in their elaboration of a route toward nemorosone (**2.3**) and garsubellin A (**2.2**).[82a] This route was studied extensively but never allowed the installation of the propargylic chain necessary to the Au(I)-catalyzed cyclization. We resolved to keep the

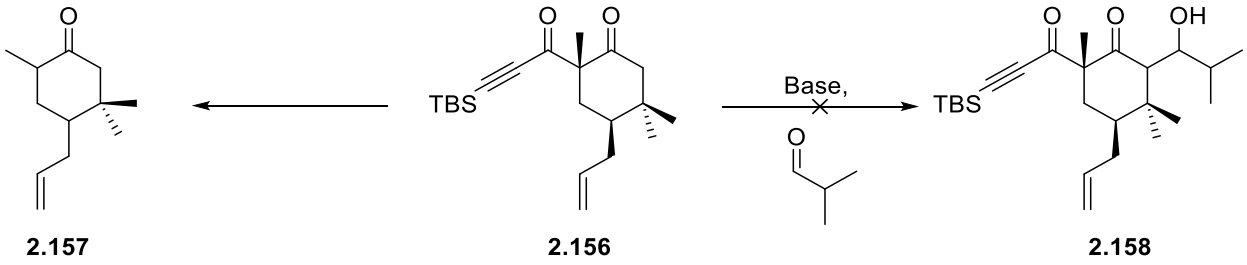
original strategy since the α-position to the *gem*-dimethyl could not be functionalized at this stage and focus on an efficient method for the oxidation of the cyclic alkene.

Scheme 2.33 – Substitution investigation of cyclohexanone ***2.150***



We later tried to perform the α-acylation of diketone **2.156** in presence of LDA, K_2CO_3 or NaH but found that these reactions led exclusively to fragmentation product **2.157** without any sign of **2.158** (***Scheme 2.34***). As a result, we decided to keep the acylation as an end-game strategy, following the work of Danishefsky and Simpkins on the subject.

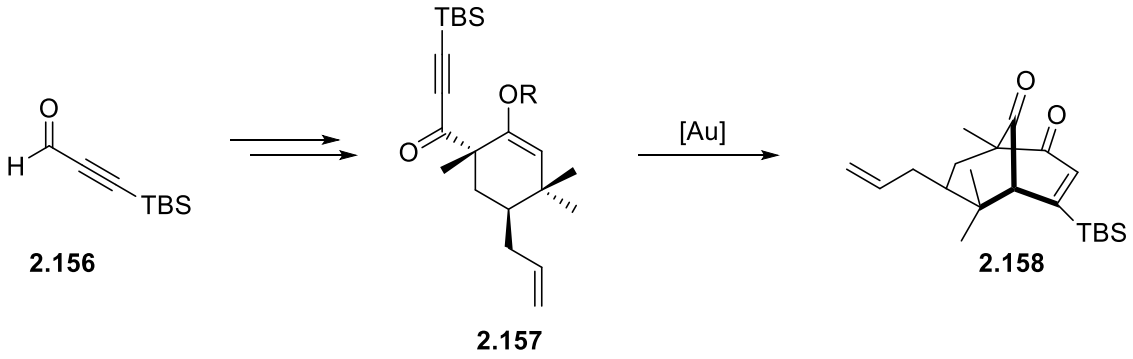
*Scheme 2.34 – Acylation of diketone **2.156***



2.3.1 Original approach: silyl substituted alkyne

We proposed the use of propargyl aldehyde such **2.156** (***Scheme 2.35***). The latter would be incorporated into the enol ether **2.157** which upon exposure to gold(I) catalyst should provide vinyl silane **2.158**. The C-SiR_3 bond would be oxidized to the desired C-OH bond by a Tamao-Fleming-Kumada oxidation reaction.

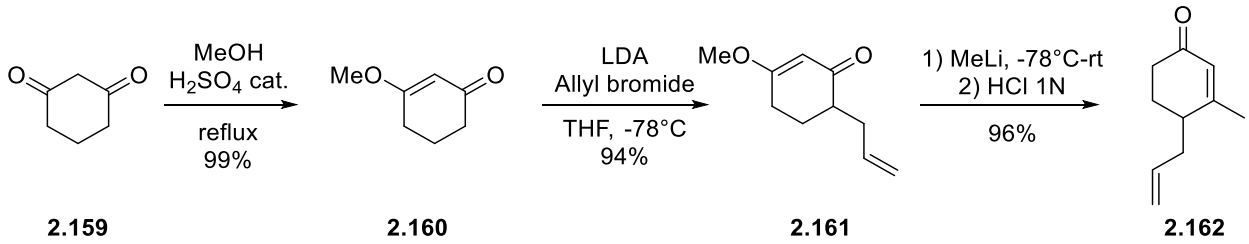
Scheme 2.35 – Synthetic modification to previous model substrate



The preparation of silyl enol ether **2.157** started by the formation of methyl vinyl ether **2.160** from 1,3-cyclohexadione **2.159** in refluxing methanolic H_2SO_4 (***Scheme 2.36***). This reaction was easily scaled past >100g and the resulting product was purified by distillation under reduced pressure to afford quantitative yield of **2.160**. The α-allylation of **2.160** was performed with LDA and allyl bromide and provided 94% yield of **2.161**. The 1,2-addition of MeMgBr onto ketone

2.161 followed by HCl promoted elimination gave 4-allyl-3-methylcyclohex-2-enone **2.162** in 96% yield.

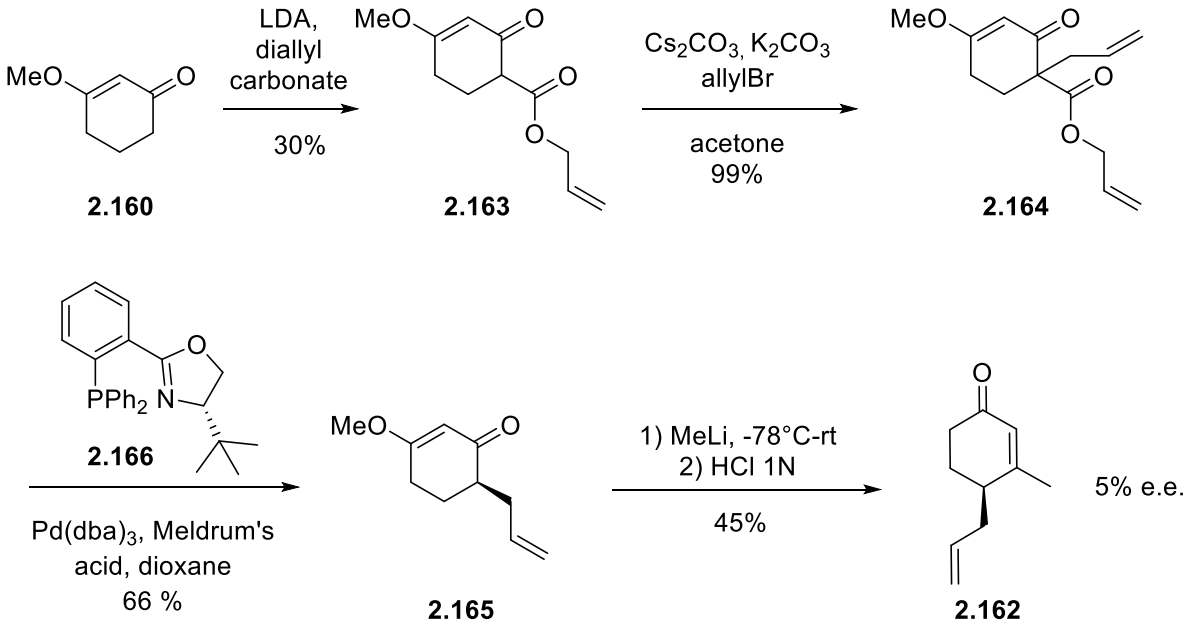
*Scheme 2.36 – Synthesis of enone **2.162***



2.159 **2.160** **2.161** **2.162**

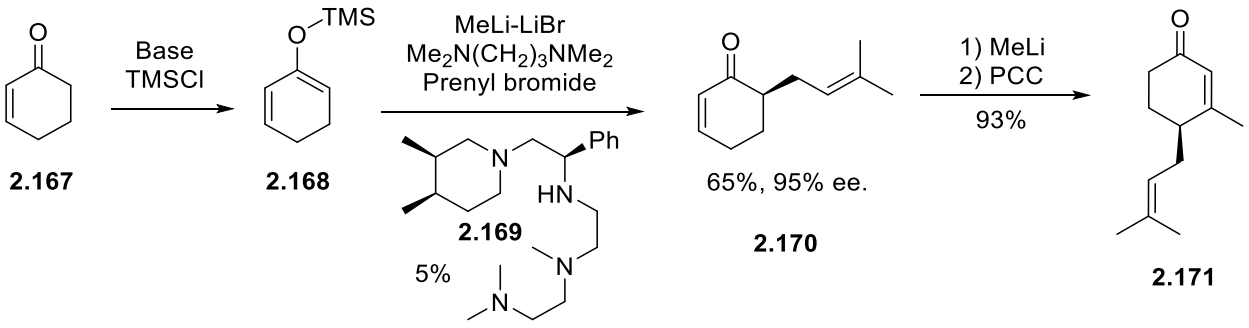
Although we had a strong route to racemic enone **2.162,** we were interested in the enantiopure compound since the allyl chain subsequently controls the configuration of the other stereogenic positions (***Scheme 2.37***). To obtain enantioenriched enone **2.162,** we tried a methodology developed by Stoltz to conduct catalytic enantioselective decarboxylative protonations that only required slight alteration to our original synthetic plan.[84c, 108] Treatment of methyl vinyl ether **2.160** with diallyl carbonate gave ketoester **2.163** in 30% yield. Subsequent alkylation of the allyl chain in presence of a mixture of Cs_2CO_3 and K_2CO_3 gave **2.164** in quantitative yield. **2.164** was treated following Stoltz methodology: $Pd(dba)_3$, chiral phosphinooxazoline **2.166** in presence of Meldrum's acid. Ketone **2.165** resulting from the reaction was immediately pushed forward to enone **2.162** to keep the chiral information intact. To our dismay, only 5% e.e was obtained following this methodology. After a discussion with Professor Stoltz concerning these results, we uncovered that the reaction does not work adequately in presence of α-allylated adducts.

*Scheme 2.37 – Asymmetric synthesis of **2.166** following Stoltz's decarboxylative protonation*



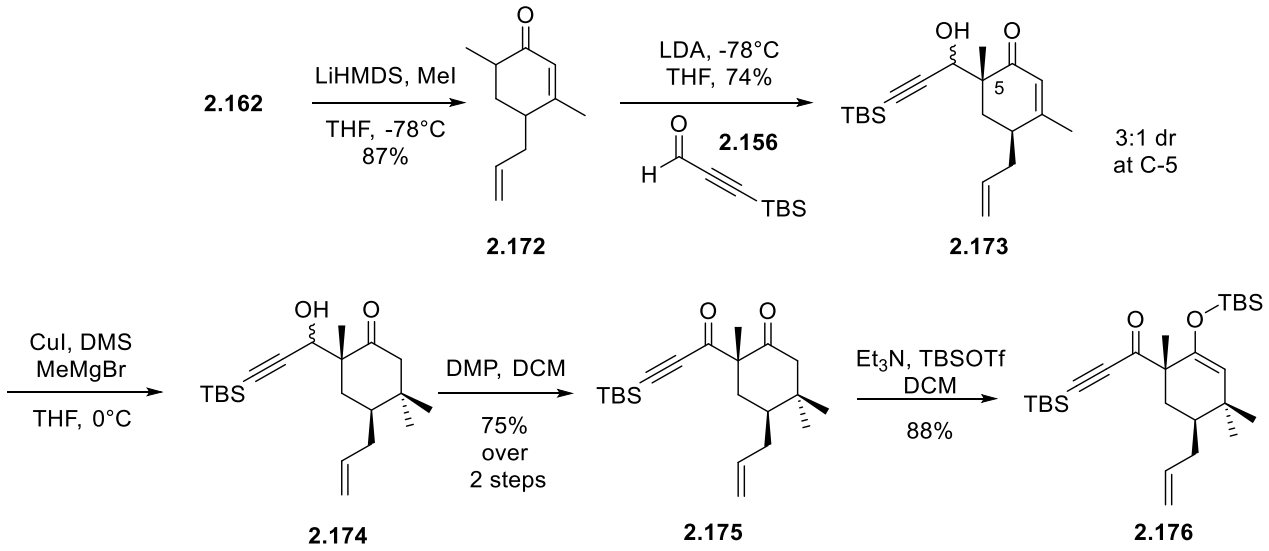
Our interest shifted quickly concerning enantioenriched material since we were aware of work from Shibasaki's laboratory where they showed an enantioselective route to a similar enone **2.171** during the synthesis of garsubellin A (***Scheme 2.38***).[76] The Koga asymmetric alkylation of lithium enolate in presence of chiral polyamine **2.169** afforded enantioenriched α-prenylated enone **2.170** with 95% ee. which was transformed into **2.171** over 2 steps.

*Scheme 2.38 – Shibasaki application of the Koga asymmetric alkylation for the synthesis of enone **2.171***



Returning to the synthesis of our racemic precursor to the cycloisomerization, we first performed an alkylation with methyl iodide, which provided α-methyl enone **2.172** (***Scheme 2.39***). A second alkylation with aldehyde **2.156** gave a 3:1 diastereomeric mixture at C-5 from which alcohol **2.173** was easily separated in 74% yield. Conjugate addition of enone **2.173** led to ketone **2.174** and subsequent oxidation gave diketone **2.175.** The synthesis of silyl enol ether **2.176** was achieved by treatment of ketone **2.175** with Et_3N, TBSOTf in DCM at reflux overnight.

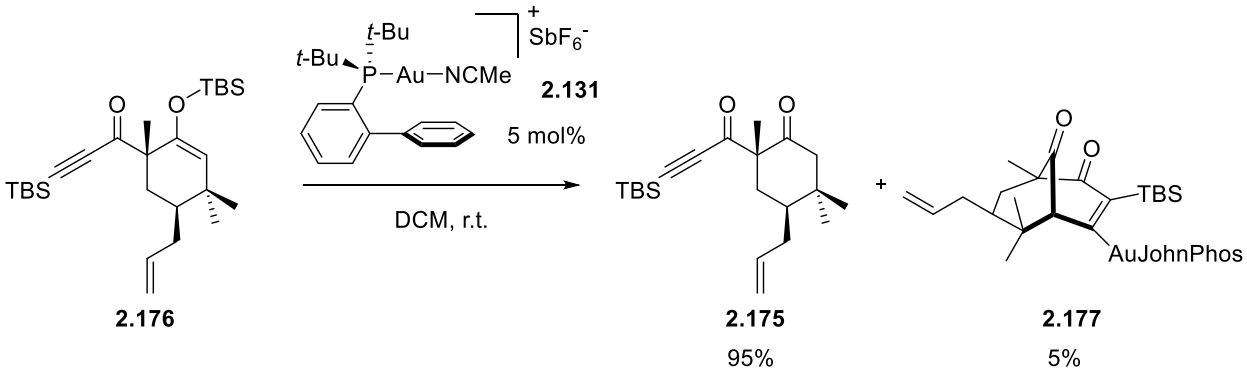
Scheme 2.39 – Synthesis of precursor to Au-catalyzed 6-endo dig cyclization

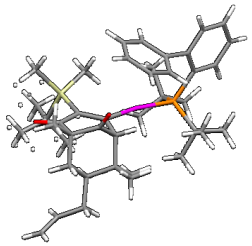


With the precursor to the Au(I)-catalyzed reaction in hand, we were now ready to probe the key disconnection of this synthetic plan. We were confident that the cycloisomerization would not be problematic but upon submission of silyl enol ether **2.176** to the standard reaction conditions, only hydrolysis back to ketone **2.175** was observed with no trace of cyclized adduct. In probing the reaction further, it was noticed that upon mixing the gold catalyst and starting enol a faint new spot appeared on the TLC. After flash chromatography of the newly formed product, we were astonished to find that we isolated stable vinyl gold **2.177** in 5% yield which represented the catalyst loading (***Scheme 2.40***). Gratifyingly, we now could explain the inoperable Au(I) *6-*

endo dig cyclization since the cationic gold intermediate was not regenerated in the cyclization process. We believed that the stability of the vinyl gold **2.177** can be attributed to the electron deficient moiety of the complex which parallels findings by Hammond *et al.*[109] The sterically rich environment probably impairs the protodeauration process as well. Another observation was made once we received the resolved X-ray structure of vinyl gold **2.177**. During the transformation a [1,2]-shift of the TBS group occurred since under normal *6-endo* dig carbocyclization the TBS would find itself at the C-2 position of bicycle **2.177** but instead the TBS was found to occupy the C-3 position exclusively.

*Scheme 2.40 – Product resulting from standard Au(I) cycloisomerization conditions of **2.176***

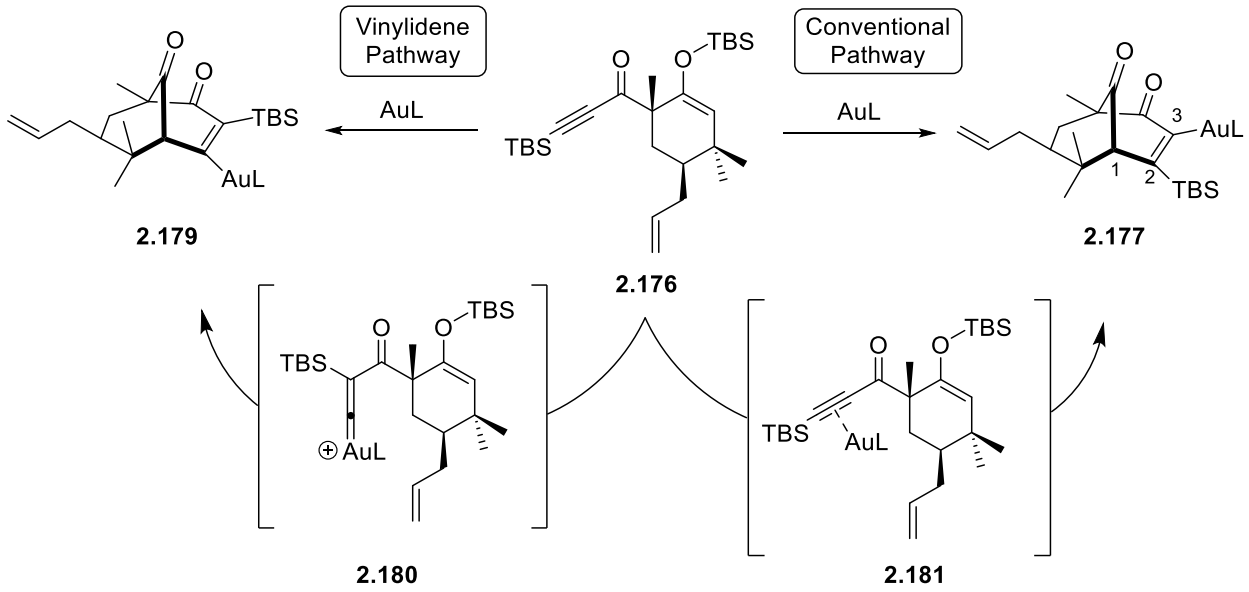




This meant that multiple mechanisms were in operation (***Scheme 2.41***). We proposed that the shift of the silyl group occurred by the formation of vinylidene **2.180** rather than the classical π-Lewis-acid pathway **2.181**. Intermediate **2.180** was extremely reactive and engaged with the silyl

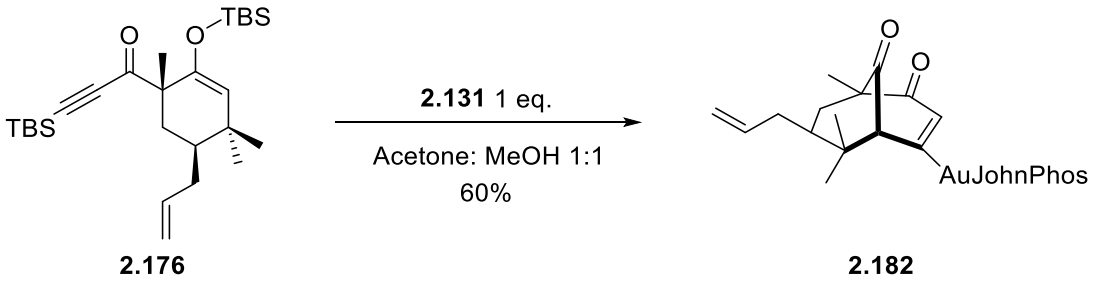
enol ether resulting in bicycle **2.179** rather than **2.177**. For an introduction on gold induced vinylidene chemistry, refer to section 1.3.4.

Scheme 2.41 – Vinylidene/ π-Lewis acid pathways



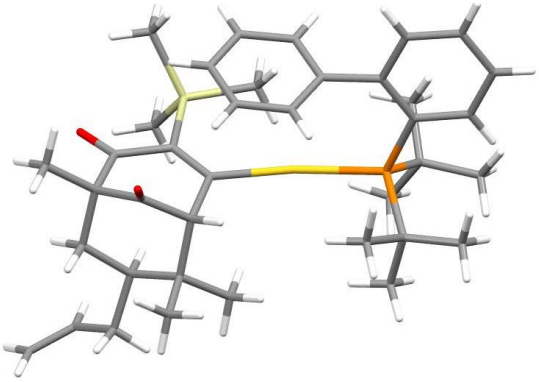
We investigated possible ways to induce the protodeauration and reactivate the catalytic cycle. Unfortunately, all attempts failed to keep the loading of gold catalytic. Under our best set of conditions, desilylated bicycle adduct **2.182** was obtained in 60% yield upon treatment of **2.176** with catalyst **2.131** in a mixture of acetone and methanol (***Scheme 2.42***). Unrealistically though, it required equimolar loading of Au-catalyst.

*Scheme 2.42 – Best conditions for cyclization of **2.176***

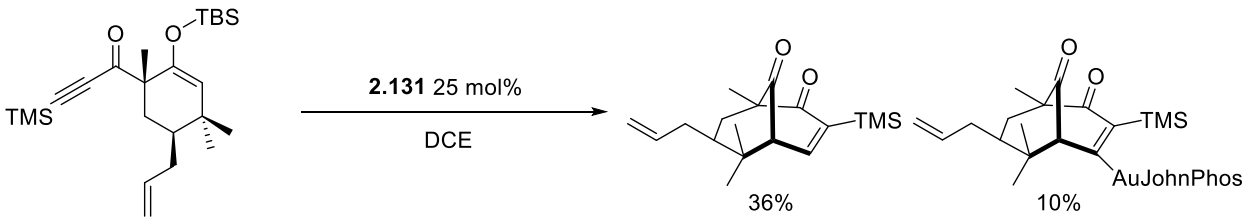


We reasoned that the TBS group might cramp the conventional *6-endo* dig pathway, so we synthesized a silyl enol ether with an alkynyl TMS following the same synthetic pathway. After much investigation, we were able to get turnovers from the catalyst in extremely dry DCE (freshly distilled over CaH_2) yielded 36% of protodeaurated bicycle **2.184** and 10% of vinyl gold **2.185** (***Scheme 2.43***). The structure of vinyl gold **2.185** was confirmed by X-ray (***Figure 2.7***). Regrettably, these set of conditions were highly unreliable and poorly scalable. We decided to change the nature of the functional group at alkynyl position to continue the synthesis. First though, intrigued by the isolation of vinyl gold species, we probed the transformation to explore its generality.

*Figure 2.5 – X-ray structure of **2.185***



*Scheme 2.43 – Best conditions for cyclization of **2.183***



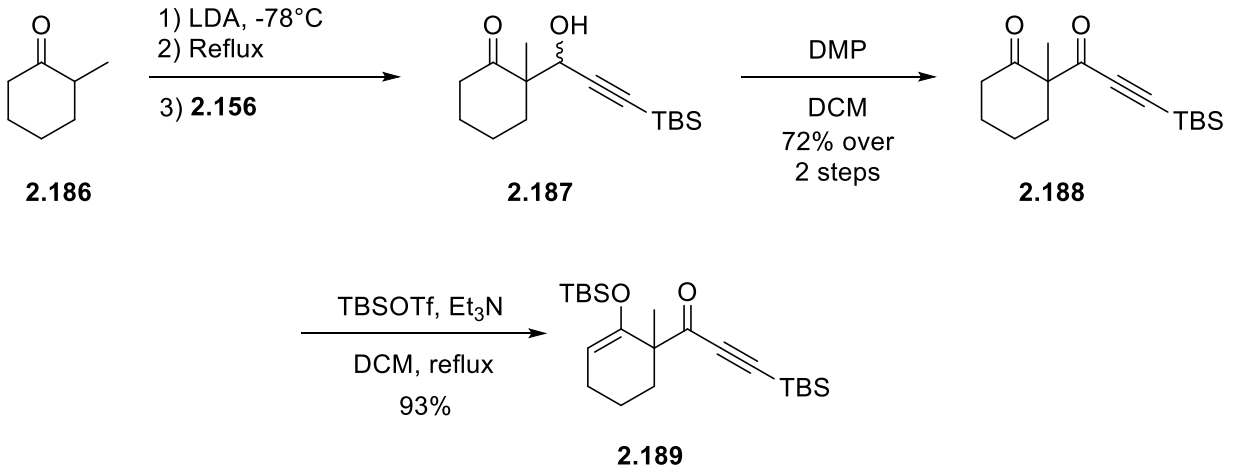
2.183 **2.184** **2.185**

2.3.2 Isolation of stable vinyl gold species

Intrigued by the previously isolated gold complexes, we decided to investigate the generality of this transformation on simpler starting material. The synthesis of this material is delineated in ***Scheme 2.44***. Thermodynamic alkylation of 2-methylcyclohexanone **2.186** with

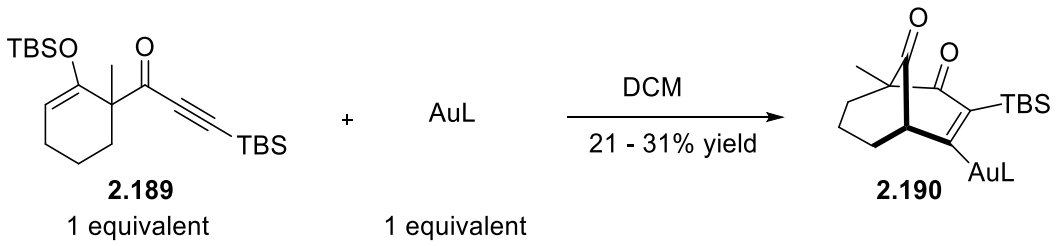
aldehyde **2.156** gave alcohol **2.187**. Oxidation with DMP and silyl enol formation afforded **2.189** in 66% overall yield from **2.186**.

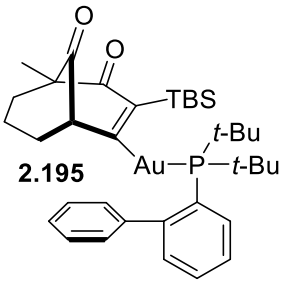
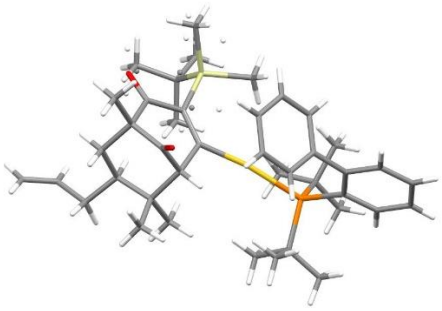
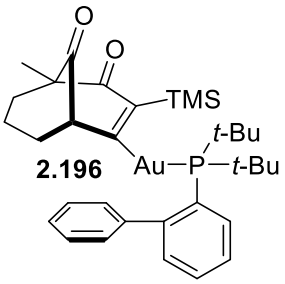
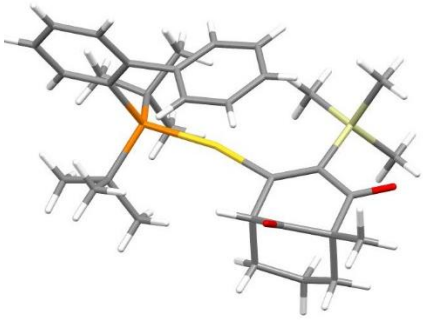
*Scheme 2.44 – Synthesis of silyl enol ether **2.189***

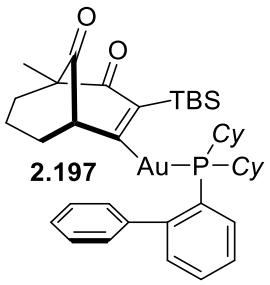
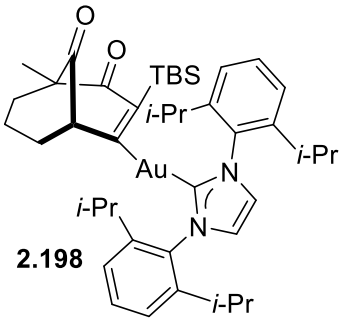
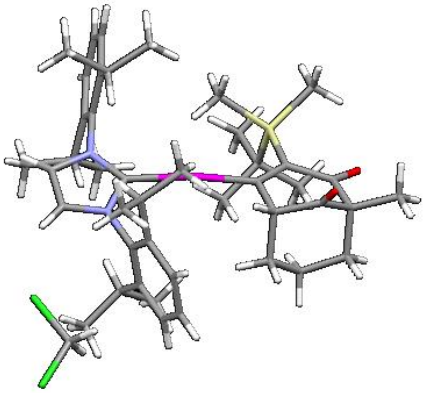
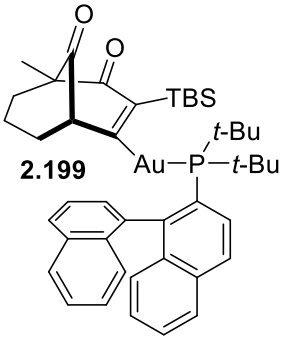
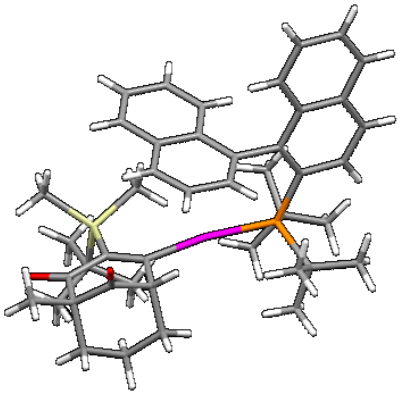


With the ability of synthesizing multiple grams of **2.189** in few steps, we analyzed the vinyl gold formation. We set out to investigate the role of the ligand during this transformation by mixing equimolar quantities of silyl enol ether **2.189** and gold catalyst (***Table 2.1***). Exhausting our library of gold catalysts, we discovered that this process was in fact general and resulted in yields between 21% and 32% of the corresponding vinyl gold adduct (**2.195-2.199**). The rest of the reacted mixture was identified as the hydrolysis of **2.189** back to diketone **2.188**. JohnPhosAu$^+$ (**2.131**) (entries 1 and 2), Cy-JohnPhosAu$^+$ (**2.191**) (entry 3), **2.192** (entry 5) and NHCAu$^+$ (**2.193**) (entry 4) all afforded the corresponding vinylgold which could be isolated by flash chromatography (***Scheme 2.45***). On the other hand, MeXPhos (**2.194**), AuCl, $AuCl_3$, and JohnPhosAg+ did not perform this transformation.

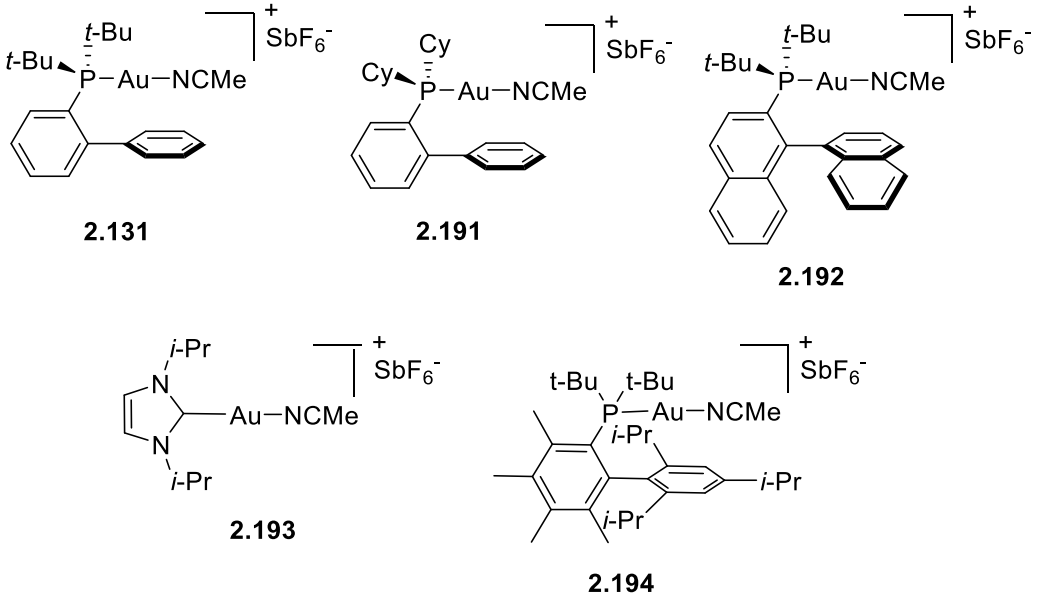
Table 2.1 – Ligand effects of cationic gold specie on cyclization



Entry	Catalyst	Yield (%)	product	X-ray structure
1	**2.131**	27		
2	**2.131**	21		

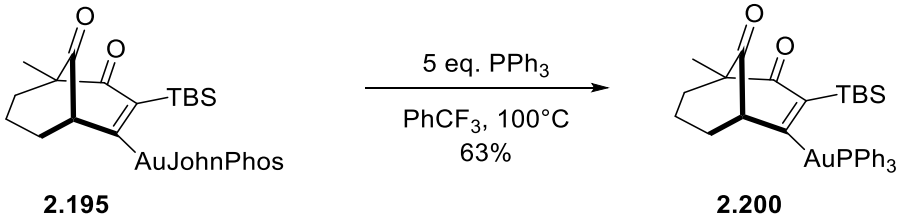
3	**2.191**	32	 **2.197**	No X-ray
4	**2.193**	21	 **2.198**	
5	**2.192**	28	 **2.199**	

Scheme 2.45 – Gold catalyst used to test vinyl gold isolation



We wondered if a ligand exchange could be performed upon heating **2.195** in the presence of a different phosphine. Delightfully, heating a mixture of vinyl goldJohnPhos **2.195** in CF_3Ph with triphenylphosphine gave vinylgoldPPh_3 **2.200** in 63% (***Scheme 2.45***). Unfortunately, although the concept was proven, we have not been able to push this idea further because of time constraints. But this is potentially a great opportunity to tune *in situ* the reactivity of the catalyst and enable new transformations.

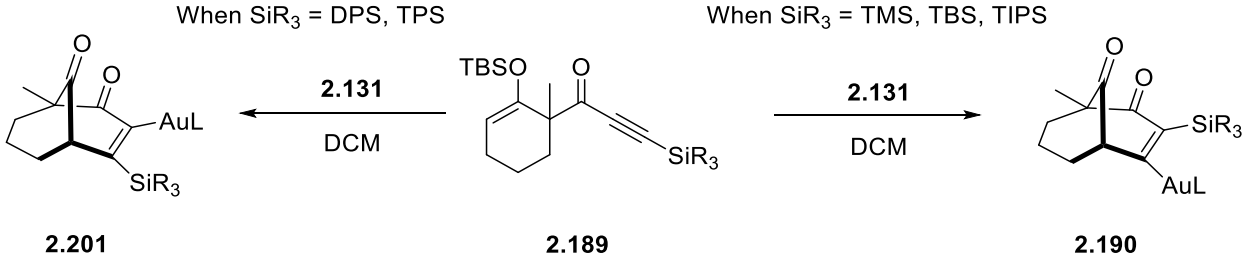
Scheme 2.46 – Ligand exchange in presence of another phosphine



Meanwhile, even though our understanding of vinyl gold isolation and reactivity was flourishing, we remained focused toward the total synthesis of PPAPs. The study and isolation of

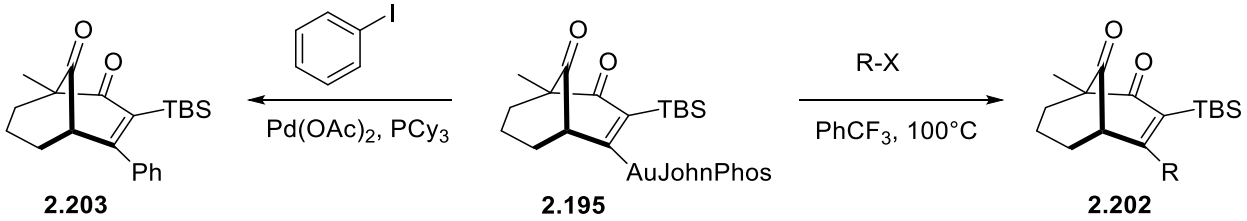
vinyl gold species was performed by Philippe McGee. He established a relationship between the nature of the alkynyl silyl group and its influence on the 1,2-migration.[35] Generally, he found that the catalyst's influence over the outcome of the migration was minimal (***Scheme 2.47***). Instead, it was the silyl group itself that dictated whether the [1,2]-shift would occur. Alkyl silyl (TMS, TBS, TIPS) underwent the shift to bicycle **2.190**, while Ph-silyl adduct (DPS, TPS) proceeded by Lewis-acid catalysis to give vinyl gold **2.201**.

Scheme 2.47 – Chemoselective cyclization depending on the nature of SiR_3



It was also found that, under the right set of conditions, the isolated gold adduct could participate in palladium catalyzed cross-coupling toward products like **2.203** and $C(sp^3)$-$C(sp^2)$ bond formation using electrophilic reagents toward bicyclic system **2.202** (S***heme 2.48***). The latter transform worked with a vast array of electrophiles inclusive of allylBr, NIS, NBS, NFSI, propargyl bromide and other alkyl halides.[35]

Scheme 2.48 – Vinyl gold reactivity in presence of palladium and electrophiles



2.4 Total syntheses of papuaforin A, papuaforin B and papuaforin C

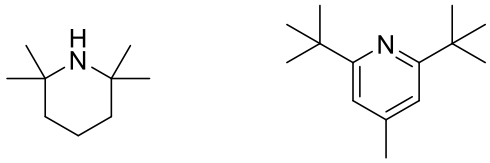
"Simplicity is complexity resolved." *Constantin Brancusi*

We knew from our previous work on *6-endo* dig cyclization that alkynyl bromides were suitable to the cyclization.[33] We devised a short modification to the aforementioned synthetic plan to allow transformation of the silyl group into a bromide.

2.4.1 Accessing the core of PPAPs

To accommodate a more efficient installation of the Br we switched to 3-TMS-propiolaldehyde **2.204** instead of the TBS aldehyde **2.156**. Similar results were obtained following the alkylation to **2.205** in 67% yield (***Scheme 2.49***). A conjugate addition followed by a Dess-Martin oxidation yielded diketone **2.206** in 72% over 2 steps. The replacement of the TMS group in **2.206** by the bromine was achieved using NBS to give bromoethynyl **2.207** in 93% yield. We want to specifically thank Professor André Beauchemin for this suggestion that helped us streamline the synthesis. Relative stereochemistry of diketone **2.207** was confirmed by X-ray crystallography. Surprisingly, submission of **2.207** to our standard conditions to form the silyl enol ethers gave immediate degradation of the starting material. Upon further experimenting, it was found that diketone **2.207** was especially sensitive to bases. Testing of compatible bases showed immediate degradation of **2.207** with the sole presence of solvated Et_3N, K_2CO_3, Hunig's base, diisopropylamine, pyrrole and even proton sponge. Fortunately, two bases were found to be compatible with substrate **2.207**: 2,2,6,6-tetramethylpiperidine (TMP) **2.209** and 2,6-di-*tert*-butyl-

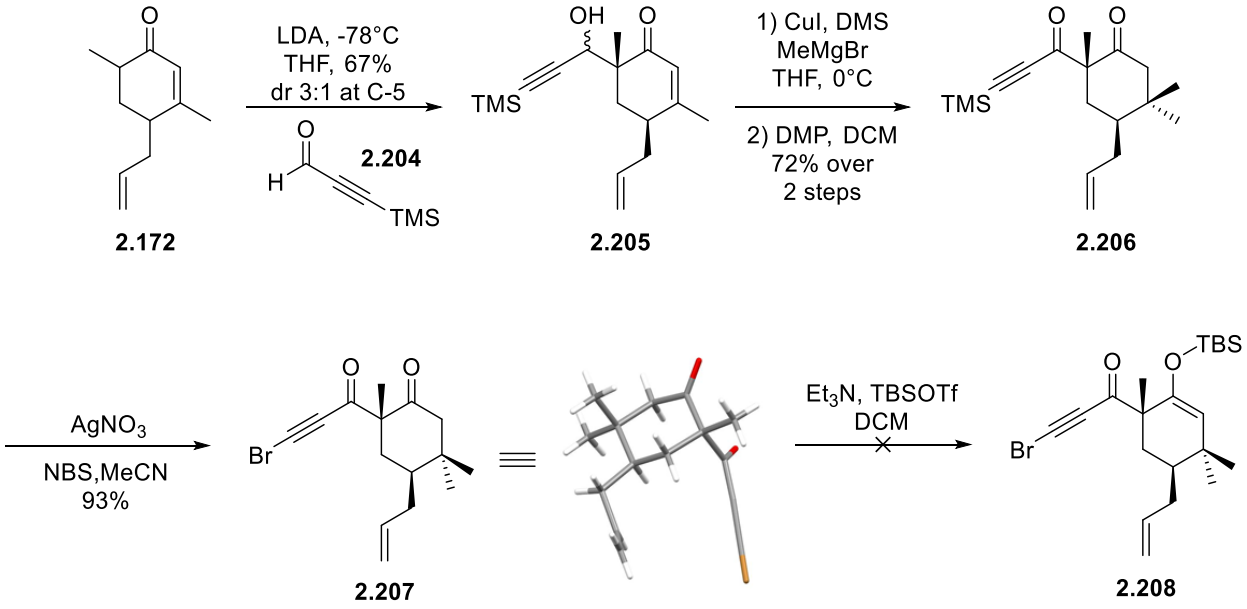
Figure 2.6 – Structure of TMP and DTMP



TMP **2.209** DTMP **2.210**

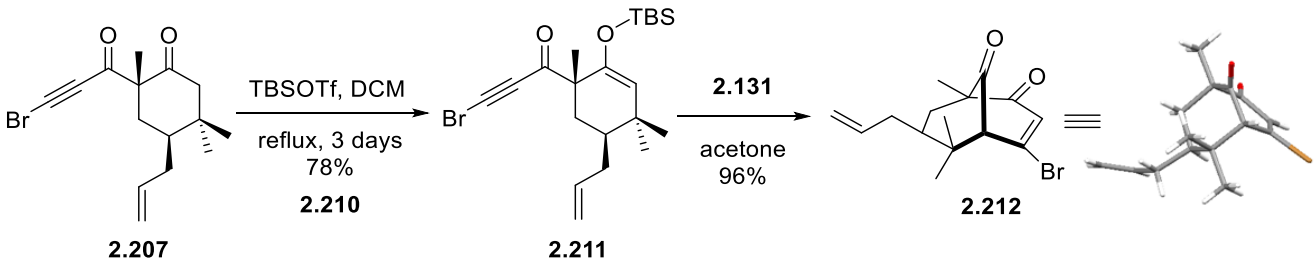
4-methylpyridine (DTMP)[110] which led to **2.210** (***Figure 2.6***). The latter afforded less degradation when submitted to the reaction conditions.

*Scheme 2.49 – Synthesis of bromoethynyl **2.207***



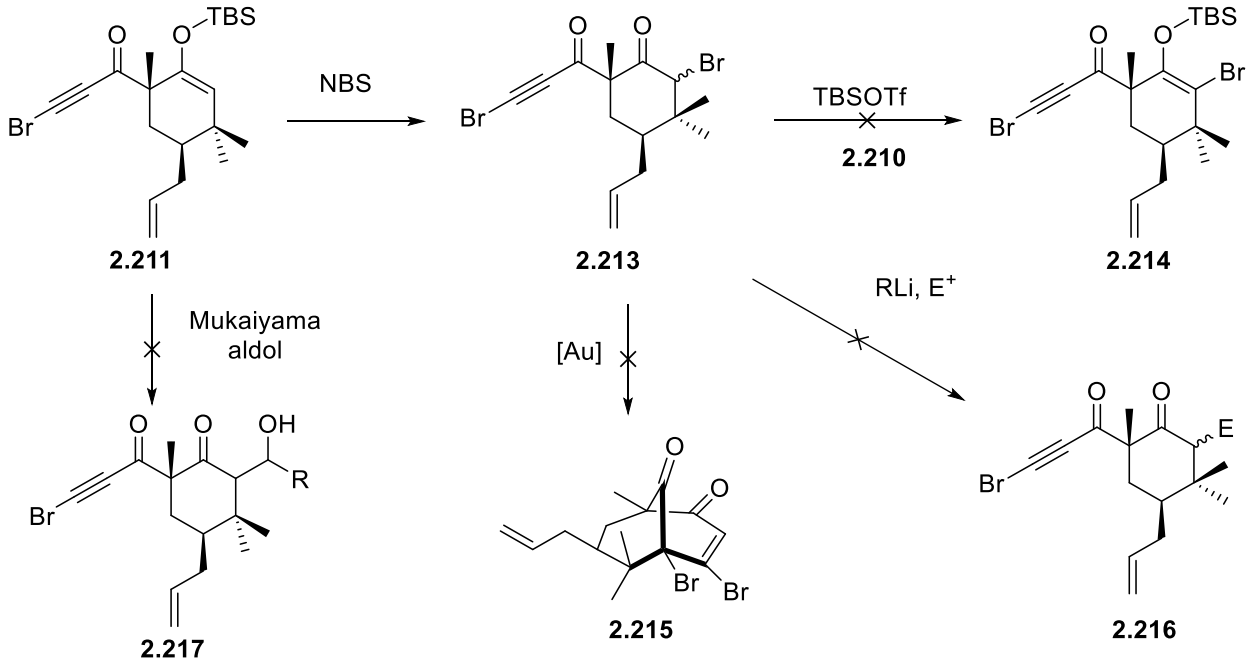
Replacing Et_3N by DTMP allowed the slow conversion of ketone **2.207** to the corresponding silyl enol ether **2.211** over 3 days in 78% yield (***Scheme 2.50***). We were now ready to test the cyclization of **2.211** in presence of Au(I)-salt **2.131**. Gratifyingly, we obtained bicyclo[3.3.1]nonane intermediate **2.212** without a glitch under our standard catalysis conditions. With a yield of 96%, we did not pursue an optimization and decided to move on directly to finding novel ways to substitute the bicyclic core. X-ray crystallography confirmed the structure of **2.212**.

*Scheme 2.50 – Synthesis of pivotal bicyclic core **2.212***



Before moving on though, we wish to highlight some of the failures we encountered trying to utilize **2.211** to further functionalize the starting cyclohexanone ring (***Scheme 2.51***). Unfortunately, Mukaiyama aldol reactions with silyl enol ether **2.211** never produced the desired aldol product **2.217** which could have streamlined our approach. Starting from silyl enol ether **2.211,** we were able to generate α-bromo ketone **2.214**, in presence of NBS, but unfortunately we were never able to form silyl enol ether **2.214**. Lithium-halogen exchange led to degradation instead of **2.216**. Toste[111] showed that gold-catalyzed Conia-ene reaction of β-ketoesters with alkyne can be achieved without the need for a silyl enol ether or an exceptionally strong nucleophile. We reasoned that the proton α to the ketone should be acidic enough and tried to cyclize **2.213** directly but we never observed product **2.215** even at elevated temperatures.

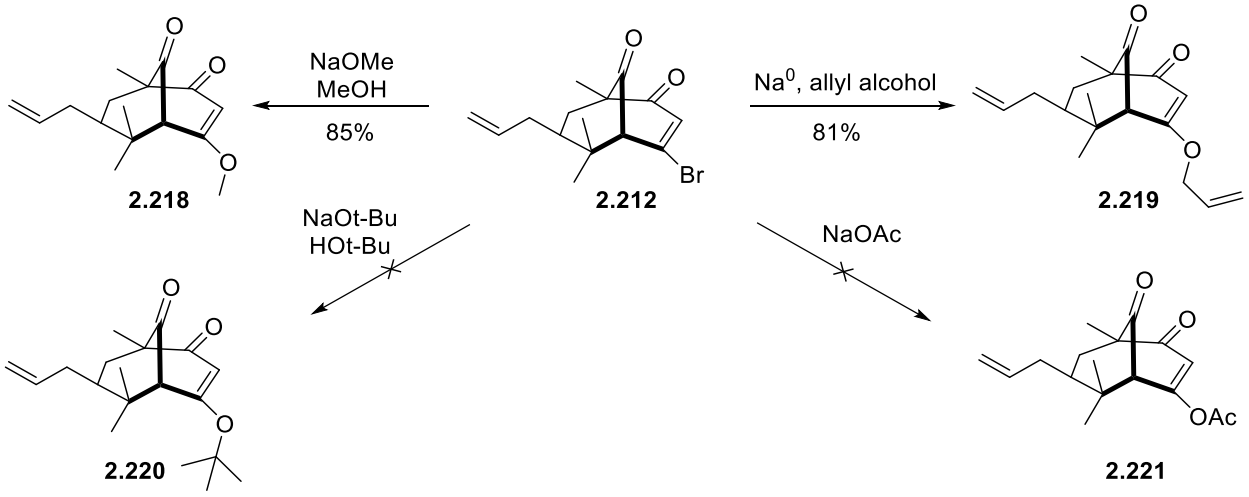
Scheme 2.51 – Attempts at functionalizing cyclohexanone ring system



2.4.2 Knoevenagel condensation approach

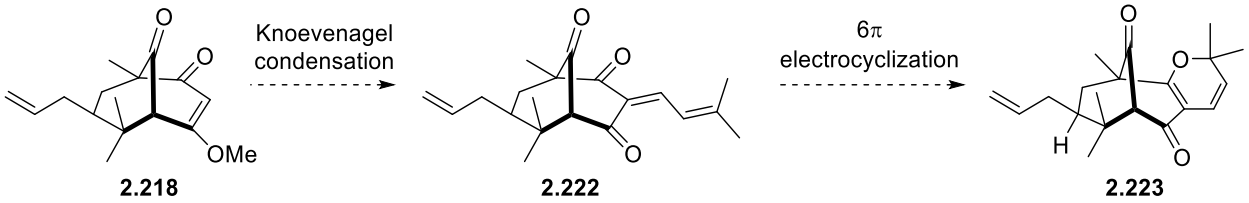
With a solid synthesis of the advanced bicycle intermediate **2.212** in place, we moved forward trying to find new and innovative ways to functionalize the bicyclic core. We started by a quick survey of the compatible nucleophiles for the conjugate substitution of 4-bromoenone **2.212** (***Scheme 2.52***). Methanolic sodium methoxide and allylOH/NaOallyl afforded **2.218** in 85% yield and **2.219** in 81% yield respectively. *tert*-BuONa and NaOAc were found to be unreactive with adduct **2.212**.

*Scheme 2.52 – Conjugate substitution onto **2.212***



We decided to move on with methyl vinyl ether **2.218**. In our analysis of the possible disconnections to achieve the pyran ring system of the papuaforin molecules, we anticipated the Knoevenagel condensation as the best strategy to achieve efficiently conjugate diene **2.222** (***Scheme 2.53***). We reasoned that afterward **2.222** could undergo a 6π-electrocyclization to pyran **2.223**.

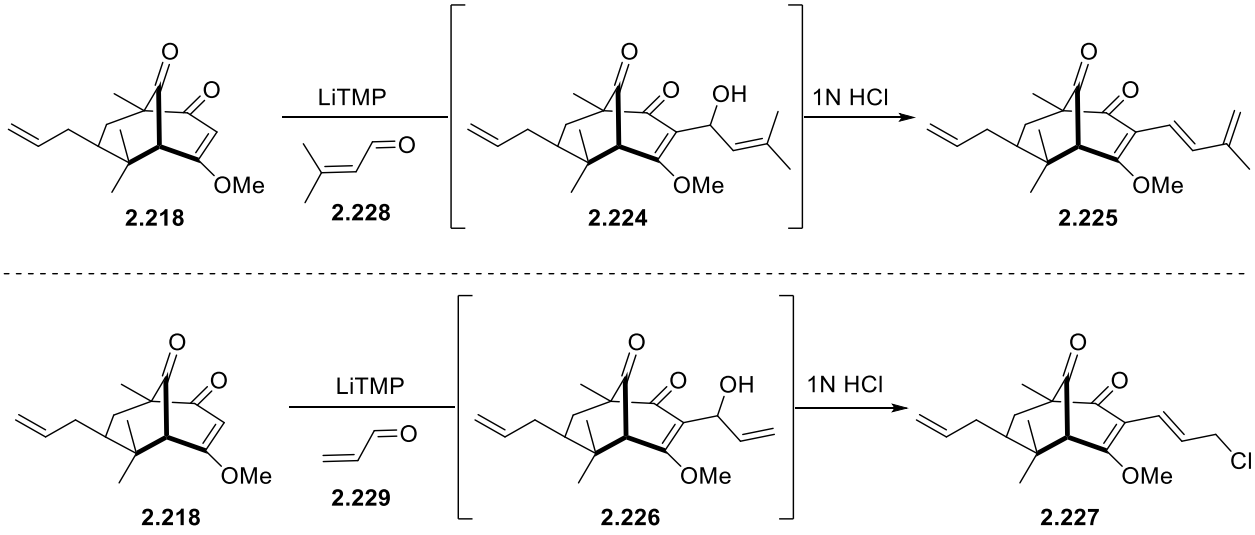
Scheme 2.53 – Synthetic strategy to synthesize pyran ring system of papuaforins



Research by Simpkins' group[82, 112] showed that the proton at C-3 can be selectively deprotonated with LiTMP. Treatment of deprotonated **2.218** with 3-methylbut-2-enal **2.228** did in fact provide intermediate **2.224** but elimination of the alcohol under acidic conditions led to triene **2.225** (***Scheme 2.54***). To resolve this problem, we figured we could use acrolein **2.229** instead, but again we did not observe the desired diene. Instead, the elimination of the alcohol was promoted

by the counterion of the corresponding acid in an Sn2' fashion. Product resulting from the HCl elimination is shown in ***Scheme 2.52*** but similar results were observed in presence of strong acid such as acids like H_2SO_4.

*Scheme 2.54 – Knoevenagel condensation of **2.218***



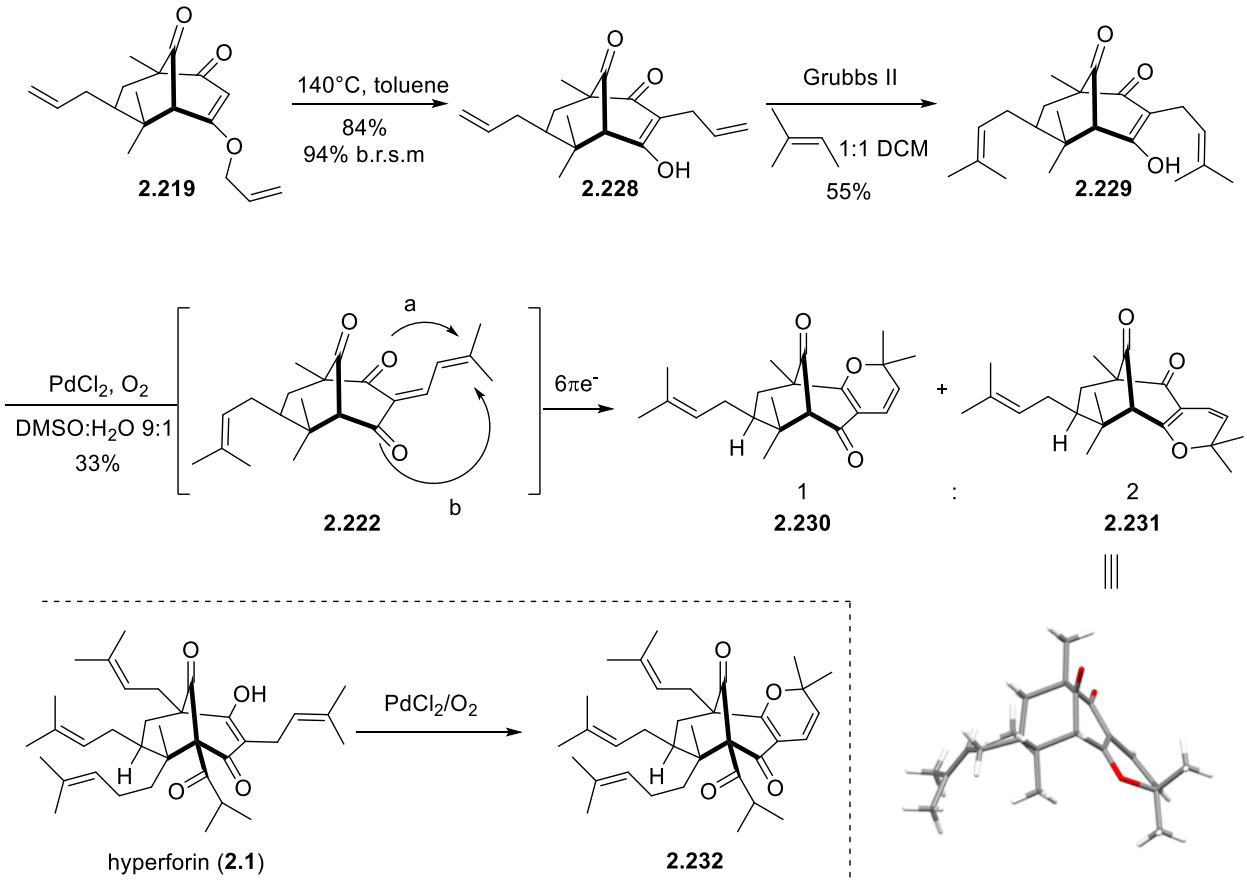
With these deceiving results, we decided to change direction and focus our attention on allylvinyl ether **2.219** with the Claisen rearrangement at the core of the new synthetic strategy.

2.4.3 Claisen approach

In our second approach to the pyran ring system, we wondered if we could perform a Claisen rearrangement of allylvinyl ether **2.219**, which could thereafter be oxidized and following an electrocyclization should in principle offer the desired pyran. We were happy to find that allyl vinyl ether **2.219** converted to Claisen product **2.228** at 140˚C in toluene (***Scheme 2.55***). Metathesis with 2-methylbut-2-ene gave the bis-prenylated bicycle **2.229**. We surveyed the literature for oxidation conditions leading to similar products to the pyran ring of papuaforins and found published work by Verotta[113] using palladium/O_2 system to oxidize and derivate hyperforin

(**2.1)** to dehydrohyperforin **2.232**. Satisfyingly, these conditions allowed also the selective oxidation of the prenyl chain at C-3. Surprisingly, the 6π-electrocyclization ensued without elevated temperature, intermediate **2.222** was never isolated. A 2:1 mixture of **2.231** and **2.230** respectively was obtained which seemed to be the results of steric control over the electrocyclization. Electrocyclization on the bulkiest side a, led to **2.230** and the b side gave the major isomer **2.231**. The structure of **2.231** was confirmed by X-ray crystallography.

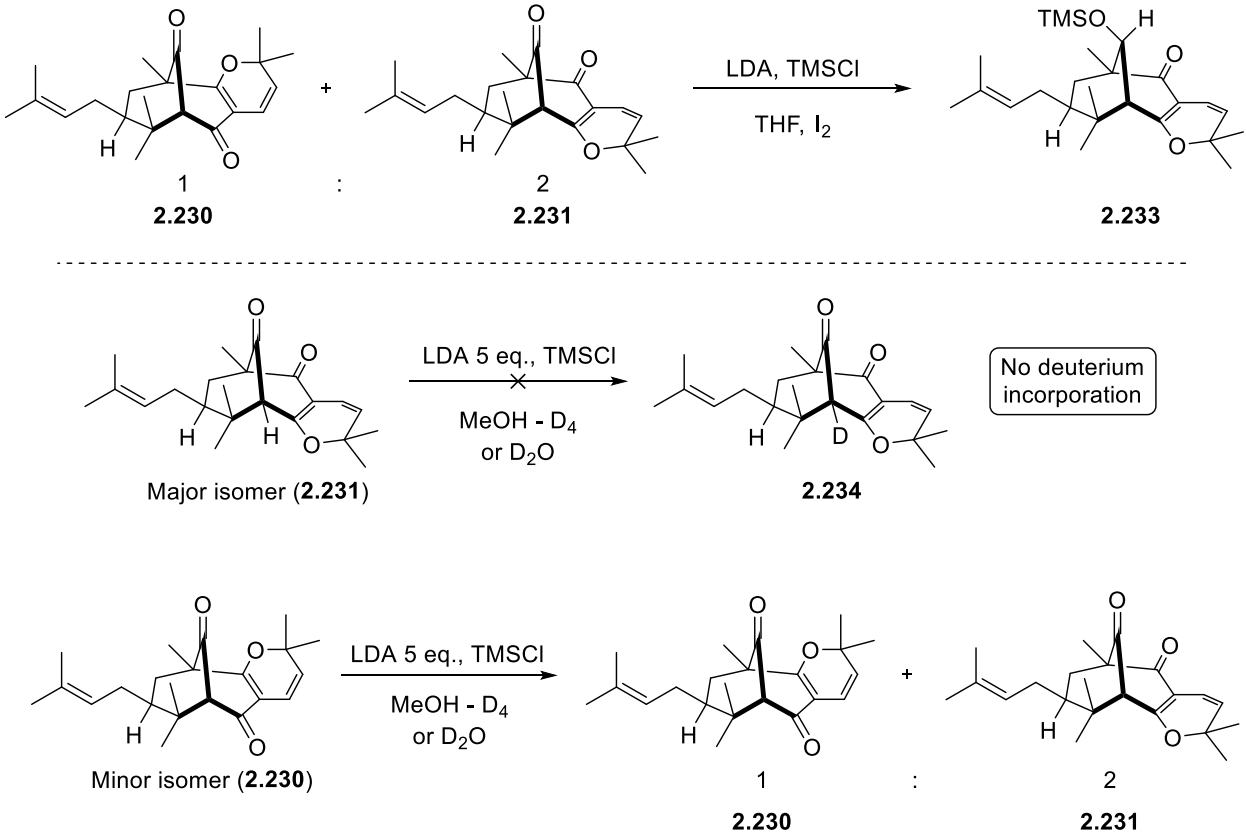
Scheme 2.55 – Synthesis of pyran ring system found in papuaforin molecules



Following literature precedents[83] on the functionalization of the bridgehead position, the original mixture of 1:2 **2.230**:**2.231** was submitted to LDA in presence of TMSCl and iodide to install an iodide at C-1 (***Scheme 2.56***). Unfortunately, the only recoverable product from this

reaction is the reduction of the bridgehead ketone to the reduced protected alcohol **2.233**. Even though unusual, it was not the first time that LDA was utilized as a reducing agent. Biehl used LDA to reduce nitroarenes to their corresponding anilines.[114] Since both isomers were seperable by flash chromatophy and to simplify NMR analysis of the reactive mixture, we underwent deuteration experiments to probe the deprotonation. To our dissatisfaction, the major isomer **2.231** did not incur any deuteration to **2.234**. Surprisingly though, the treatment of the minor isomer **2.230** with LDA in presence of TMSCl and quenched by D_2O allowed the reconversion to a mixture of **2.230** and **2.231** without observable deuteration.

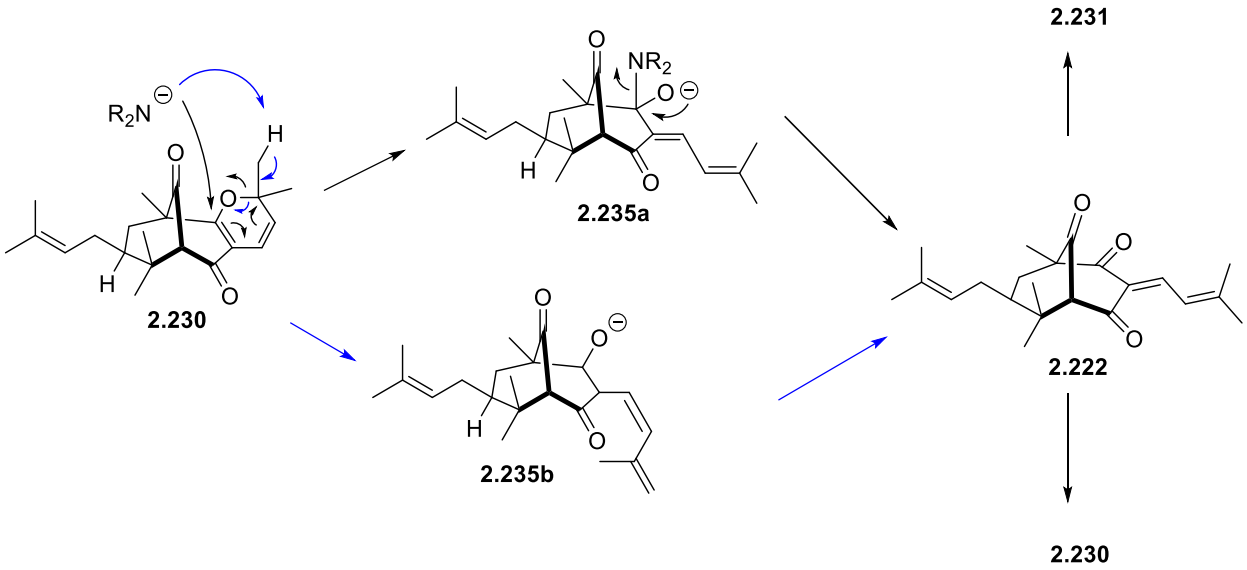
Scheme 2.56 – Attempts at substituting the bridgehead position C-1



In a second attempt at the deuteration of **2.230,** the reaction was quenched by addition of 5 eq. of D_2O, ^1H NMR analysis of the crude mixture didn't show any sign of the starting material

but rather some LDA-starting material complex. Quenching of this mixture with a saturated solution of NH_4Cl led to the 1:2 mixture of **2.230**:**2.231** again. We believed that instead of acting as a base when it comes to reacting with **2.230**, LDA opened the pyran ring to yield **2.235** which after elimination of the amine allowed reconversion of diene **2.222** by a 6π-electrocyclization to the original mixture 1:2 of **2.230**:**2.231** (***Scheme 2.57***). Alternatively, lithium diisopropylamine could led to **2.235b** where a [1,5] hydride shift would subsequently provide **2.222**.

*Scheme 2.57 – Proposed mechanism for the isomerization of **2.231***

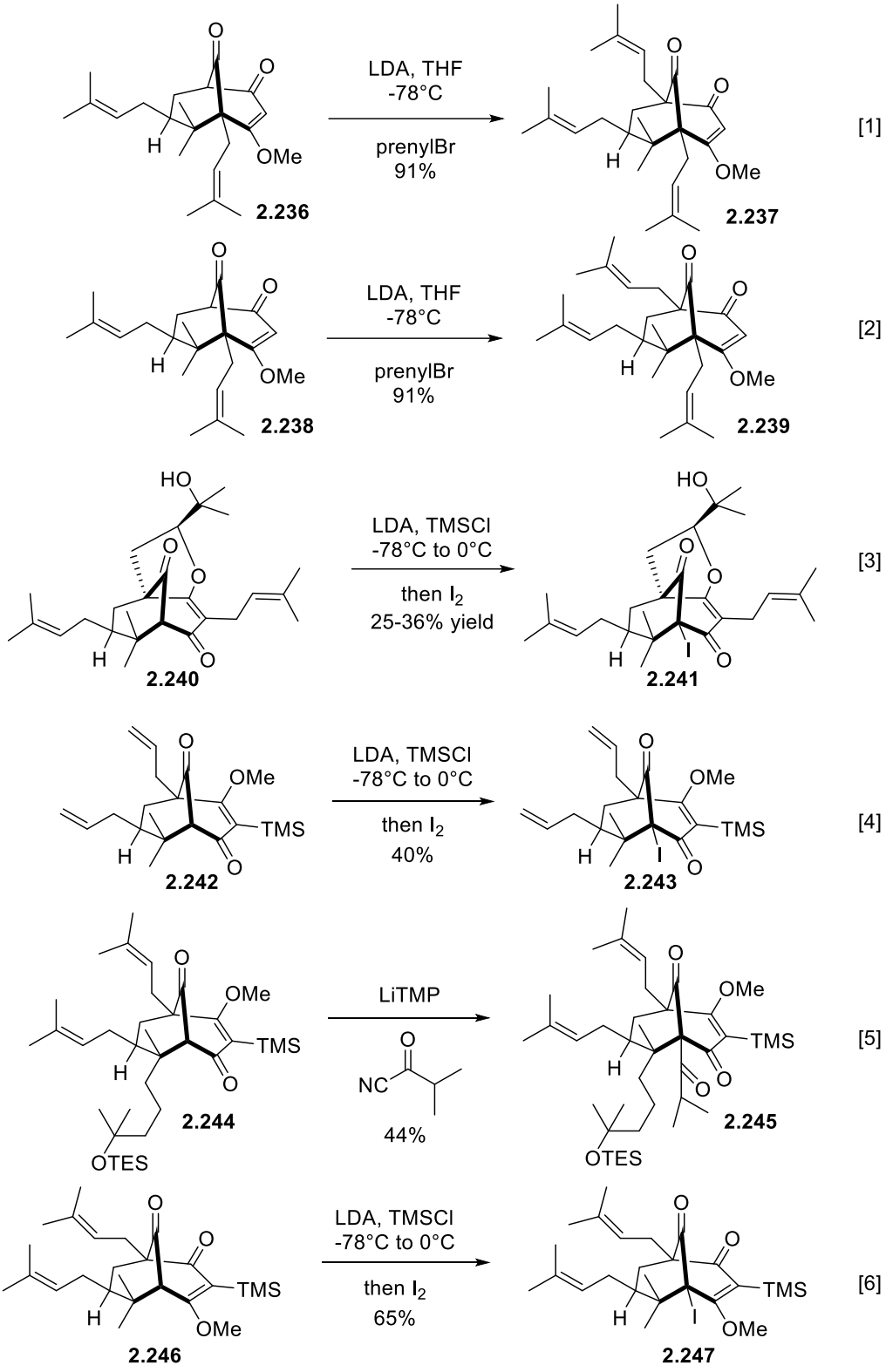


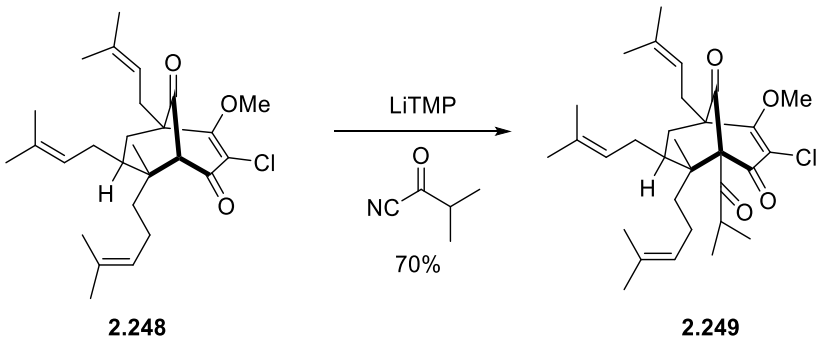
The unsuccessful depotonation of **2.230**/**2.231** was leading nowhere because of obvious issues induced by the substrate itself. In the end, we decided to pursue a similar end-game to Danishefsky's and Simpkins' approaches to PPAPs.

2.4.4 Traditional approaches to papuaforin A & B

Introduction of substituents at C-1 is possibly one of the major pitfalls of any synthesis engaging in late-stage C-1 acylation of type-A PPAPs (***Scheme 2.58***). Simpkins demonstrated that contrary to C-1, C-5 can be easily substituted using conventional methods in good yields whether the methoxy enol is positioned at C-2 (equation 2) or C-4 (equation 1). Substitution at C-1 though, required a step-wise process where one must first install an iodide which is subsequently metalated for its participation in alkylation/acylation reactions. Danishefsky[83] was the first one to resolve the problem and found that the only possible substitution at C-1 was iodide in presence of Lewis acid TMSCl with low yields of 26 to 36% of **2.241** from **2.240** (equation 3). Simpkins used the same strategy to functionalize **2.242** into bridge iodide **2.243** (equation 4).[82a] Shair was able to perform a direct acylation of **2.244** to **2.245** using isobutyryl cyanide as the electrophile (equation 5).[104b] The same reaction was used after by Maimone to achieve the C-1 acylation of **2.248** (equation 7).[105] Unfortunately, these precedents were performed on the isomeric methyl vinyl ether (at C-4) to the one we wished to use in our synthetic pathway. The only example of substitution using a methyl vinyl ether located at C-2 was performed by Simpkins for the iodination of **2.246** to **2.247** (equation 6).[82f] In our hands, the direct acylation of C-2 methyl vinyl ether **2.256** using isobutyryl cyanide did not provide the desired product.

Scheme 2.58 – Methods to substitute C-1

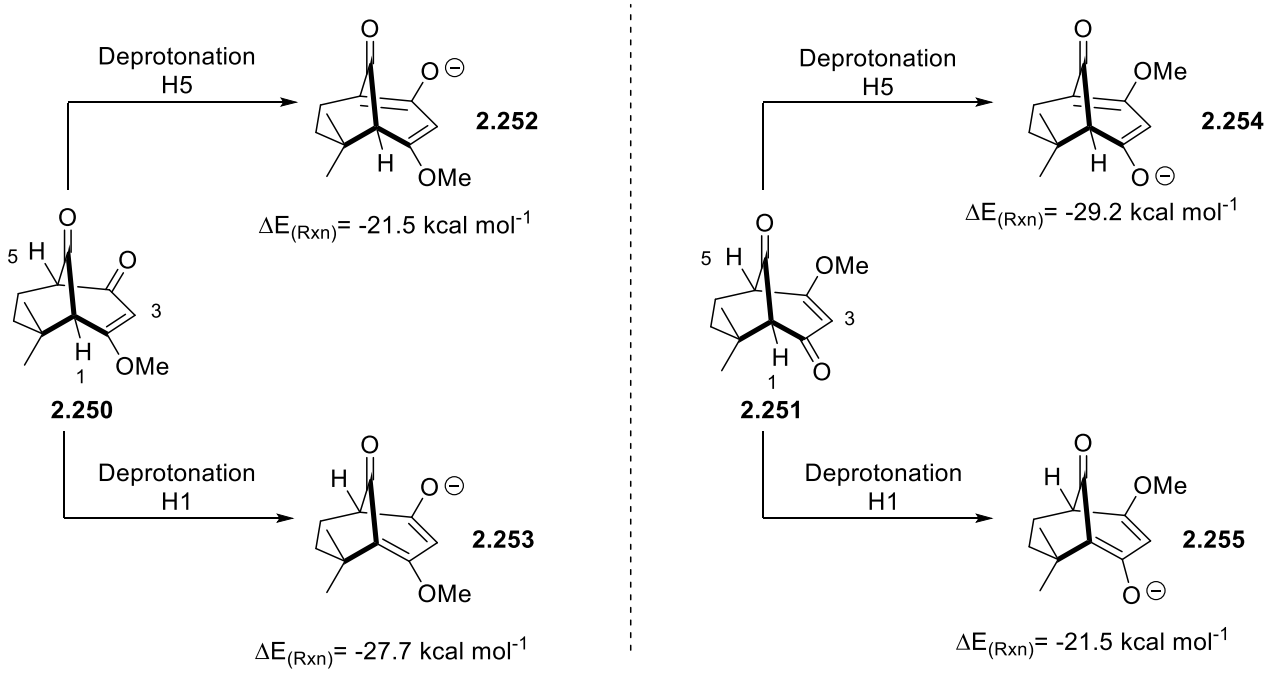




2.248 **2.249** [7]

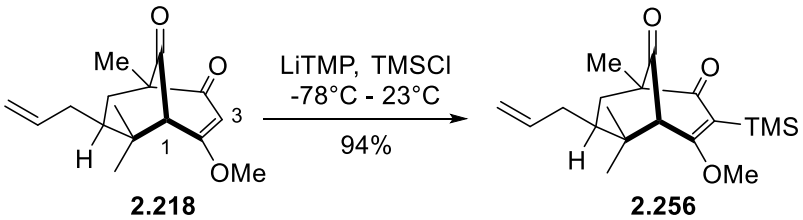
Simpkins and co-workers evaluated the relative energy of deprotanoation of bicycle **2.250**/**2.251** and found that there was a strong energy difference existing between the deprotonation at C-1 depending on the location of the methoxy (***Scheme 2.59***).[82f] Using B3LYP/6-31G*//B3LYP/6-31G* calculations, they found the ΔE_{rxn} values (kcal mol^{-1}) for the deprotonation at C-1 and C-5 of the regioisomeric vinylogous methyl vinyl ethers **2.250** and **2.251**. Surprisingly, they found that deprotonation at C-1 and C-5 were actually favorable with values between -21.5 kcal/mol and -29.2 kcal/mol. For comparison, the deprotonation of cyclohexanone has a calculated value of -27.5 kcal/mol. The deprotonation is favored through the delocalization of the electrons in the ring **2.252-2.255**, which according to the natural bond orbital (NBO) analysis, was a reasonable representation of the resonances structures. Unfortunately, the group also showed that deprotonation with the methoxy at C-2 is 6.2 kcal/mol higher in energy then the C-4 isomer. Overall, they rationalized that the difficult alkylation process is a combination of two factors: 1) exceptional ketone dienolate-like stability of **2.252-2.255**, 2) combined with the obvious steric problems associated with the *gem*-dimethyl and crowded environment.

Scheme 2.59 – Calculated (B3LYP/6-31G//B3LYP/6-31G*) ΔE_{rxn} values for the deprotonation of **2.250** and **2.251** with Me_2N^-*



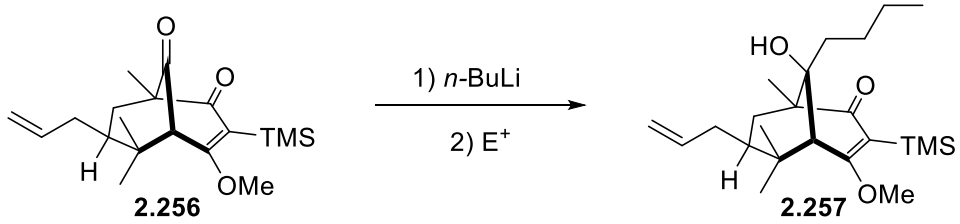
Interestingly, C-3 of **2.218** needed to be protected from deprotonation since it is the most acidic proton in the molecule. Danishefsky coined this sequence of events "differentiation of nonconventional carbanions".[87] The installation of an allyl chain or other groups at the C-3 position prior to the functionalization of C-1 led to side-products and has been well documented by Simpkins.[82a] The best method to protect C-3 is the installation of a TMS by forming the anion of **2.218** with LiTMP and subsequent addition of freshly distilled TMSCl yields **2.256** in 94% yield (***Scheme 2.60***).

Scheme 2.60 – Protection of C-3



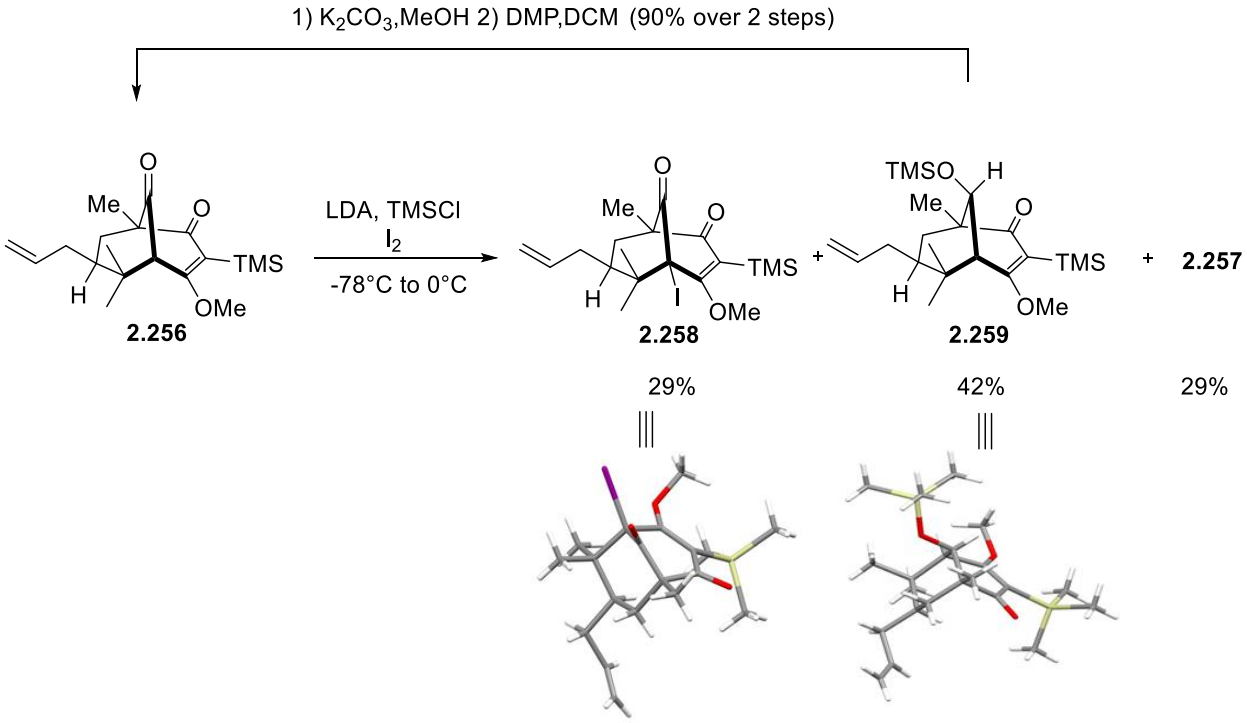
Notably, the deprotonation of **2.256** was delicate, *t*-BuLi and LiTMP did not work due to the bulkiness of the C-1 position. *n*-BuLi on the other hand, led to the exclusive alkylation of bridgehead ketone **2.257** (***Scheme 2.61***). The only base capable to deprotonating the proton at C-1 was LDA since it was non-nucleophilic and relatively small.

Scheme 2.61 – Attempted to use n-BuLi as a base to deprotonate bridgehead proton



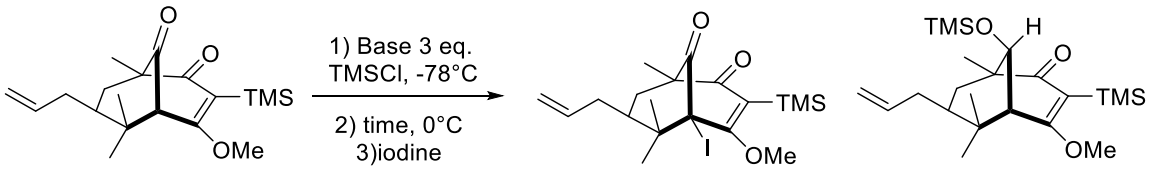
Submission of **2.256** to the exact reaction conditions of Danishefsky led to 29% of bridgehead iodide **2.258** but also 42% of reduced adduct **2.259** and some starting material **2.256** (***Scheme 2.62***). The reduction of the bridgehead ketone was somewhat a surprise since it was never mentioned by the original findings of Danishefsky and briefly addressed once following Simpkins extensive research on PPAPs. Nevertheless, we were able to recycle **2.259** by selective deprotection of alkoxy TMS in methanol/K_2CO_3 and subsequent oxidation with DMP back to **2.257**. The structure of iodide **2.258** and reduced adduct **2.259** were confirmed by X-ray crystallography.

Scheme 2.62 – Iodination of C-1

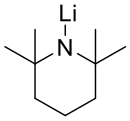
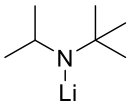
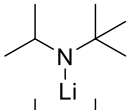
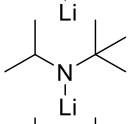
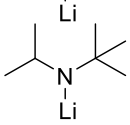
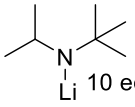


Interested in optimizing the yield of this transformation, we studied the process in more details starting with the base (***Table 2.2***). We knew that LDA provided some deprotonation of the C-1 proton but if we desired to diminish the ratio of reduced/iodinated adduct, we needed to investigate different base that did not possess α-proton that could act as a hydride donor. Unfortunately, LiTMP did not allow deprotonation of the C-1 proton but isopropyl-*tert*-butylamine underwent deprotonation to some extent. The base reacted much slower than LDA and required extended deprotonation time at 0˚C compared to LDA to achieve iodination. This slower deprotonation allowed the observation of an important trend: after 10 min of deprotonation time the reactions reached a plateau to yield ~18% of iodide **2.258** whereas the reduction of the bridgehead ketone kept increasing as the reaction was allowed more reaction time.

*Table 2.2 – Base screening for the iodination of **2.257***

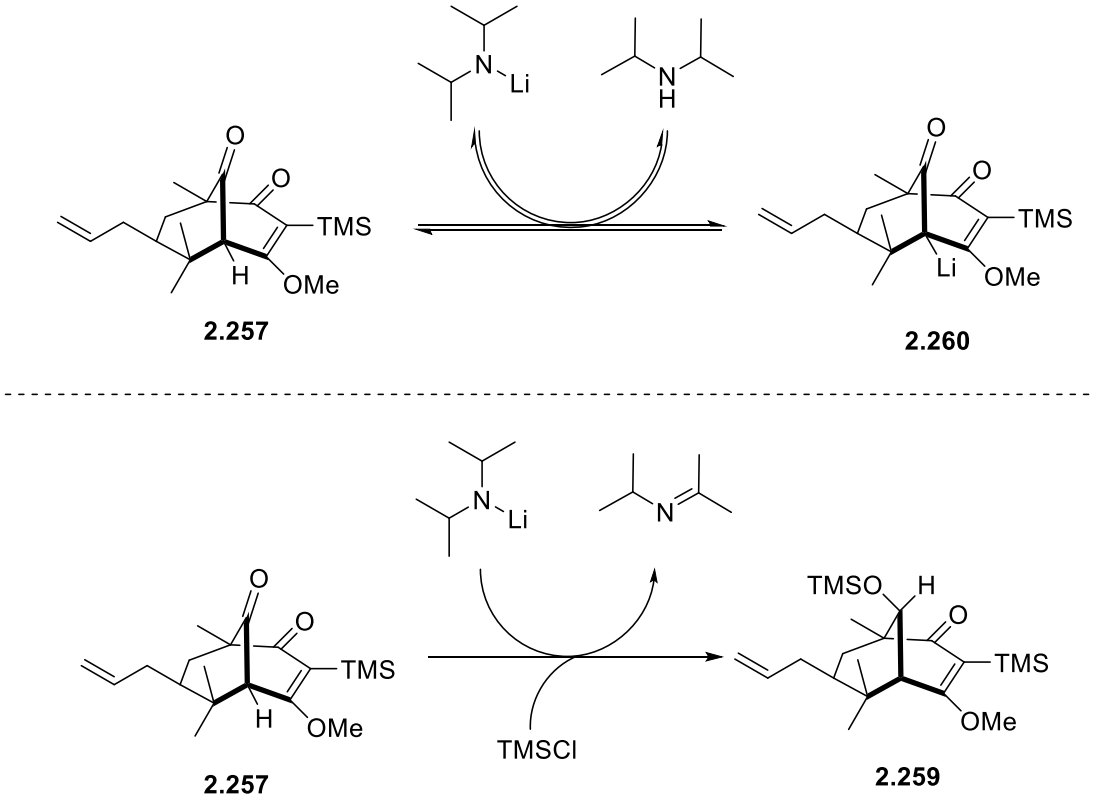


2.257 **2.258** **2.259**

entry	Base	time at 0°C (min)	ratio **2.258**/**2.259**	**2.258**	**2.259**	**2.257**
1	LDA	1	0.69	29	42	29
2		5			no reaction	
3		1	2	3	2	95
4		10	1.75	18	10	72
5		35	1.35	19	14	66
6		60	0.7	15	22	64
7	 10 eq.	15	0.4		degradation	

To explain this trend, we proposed that the deprotonation of **2.257** that gave lithium anion **2.260** was in equilibrium with LDA implying that the pK_a of the C-1 proton must be close to 36 in THF (***Scheme 2.63***). On the other hand, the reduction of the bridgehead ketone was not reversible hence the ever increasing yield of reduced adduct **2.259** and stable yield of iodination **2258**.

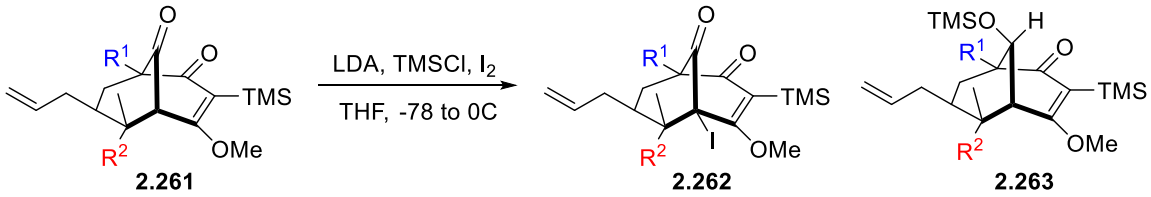
Scheme 2.63 – Proposed mechanism of iodination at C-1



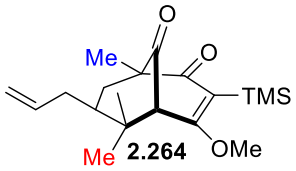
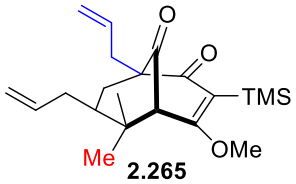
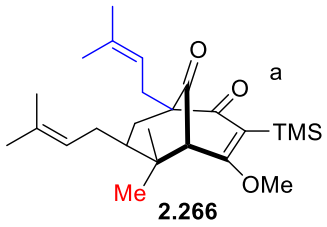
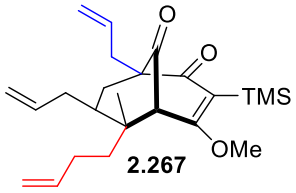
Since we developed a modular synthesis to PPAPs, we have been able to apply the iodination at C-1 on multiple substrate. It was interesting to find that local but also remote elements of the substrate influenced massively the outcome of this reaction (***Table 2.3***). Not surprisingly, bigger R^2 groups led to lower yields of iodide **2.262**. Bicycle **2.267** with the homo-allyl at the R^2 position performed badly when compared with the three other adduct with only 18% of the desired iodide. But to our surprise, a larger substituent at C-5 helped the reaction greatly. The allyl substituent at R^1 led to 60% yield whereas the methyl gave a maximum of 29% yield of iodide **2.262**. It is still unclear how the bulkier substituent at R^2 provided better yields of the iodide **2.262** but we suggest that the equilibrium that exist with the deprotonated **2.261** and LDA are greatly

influenced by the substituents present which must induce a slight confirmation change in the bicyclo[3.3.1]nonane core that allows for a better deprotonation.

Table 2.3 – Substrate screening for the iodination at C-1



2.261 **2.262** **2.263**

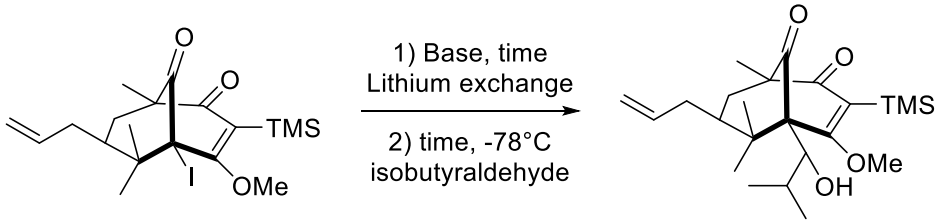
starting material	ratio 2.262/2.263	**2.262**	**2.263**	**2.261**
 **2.264**	0.69	29	42	29
 **2.265**	1.82	60	32	8
 **2.266**	-	65	-	-
 **2.267**	0.44	18	41	35

[a]According to Simpkins results on the same reaction using the same conditons

Having difficulties increasing the yield of this transformation, we decided to move on with the original set of conditions devised by Danishefsky. Although the reaction was poor yielding, we found solace in the fact that we could reconvert the reduced adduct **2.259** back to ketone **2.257**.

Overall very little material was actually wasted during this reaction. The next step in the synthesis implicated a metalation through a lithium-halogen exchange followed by an alkylation onto isobutyraldehyde (***Table 2.4***). We decided to investigate this reaction further as we were unsatisfied with the yield it generated. Danishefsky's group used *i*-PrMgCl to perform the metal-halogen exchange which yielded in our case 55% of alcohol **2.268**. *n*-BuLi also afforded the desired alcohol but was accompanied by some addition onto the bridgehead ketone as a side product whereas *t*-BuLi performed the lithium-halogen exchange with the optimal result of 61% yield of **2.268**. The rest of the reaction mixture was deiodonated product **2.257**.

Table 2.4 – Optimization of the alkylation of C-1



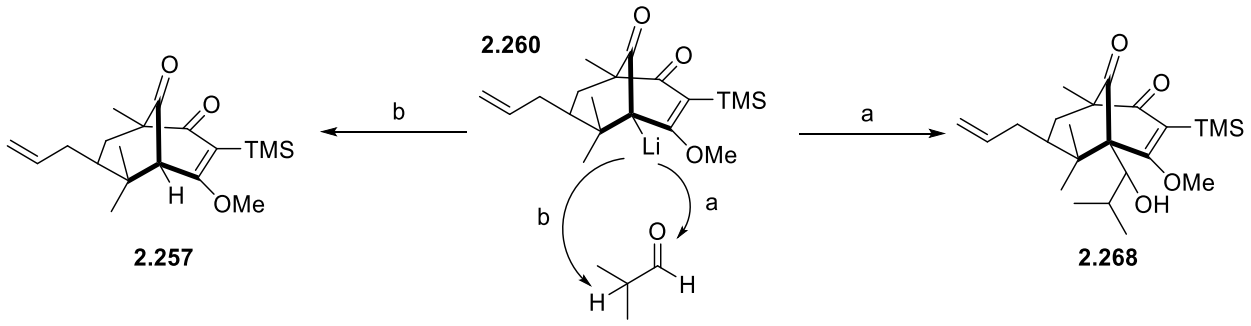
2.258 **2.268**

Base	Equiv. of electrophile	Step 1 time (min)	Step 2 time (min)	yield
t-BuLi	5	20	120	21%
n-BuLi	5	5	30	39%
n-BuLi	5	15	60	49%
n-BuLi	2	5	60	53%
t-BuLi	2	5	60	61%
i-PrMgCl 2 eq.	4.5	5	60	55%

Puzzled by this result, we decided to quench the reaction after the addition of isobutyraldehyde with D_2O, instead of a saturated solution of NH_4Cl only to find no incorporation of deuterium in recovered **2.257**. This inferred from these results that lithium anion **2.260** will

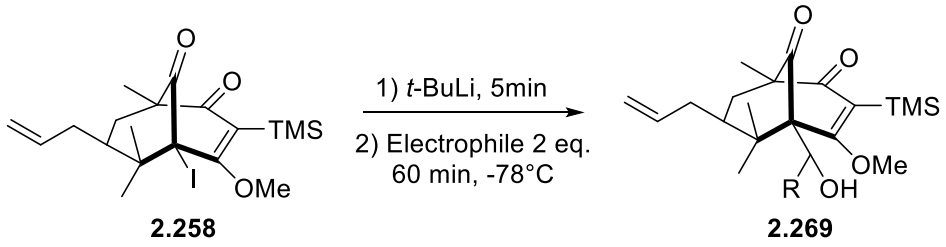
either attack the aldehyde position to give alcohol **2.268** or deprotonate the α-proton to give back **2.257**.

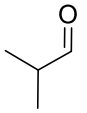
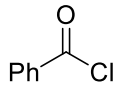
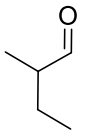
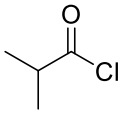
Scheme 2.64 – Competitive alkylation/deprotonation during functionalization of C-1



This suggestion was reinforced when compared with the yields obtained in presence of different aldehydes (***Table 2.5***). With 2-methylbutanal as the electrophile, the yield of the transformation is boosted to 88% yield. Benzoyl chloride allowed for direct acylation of the C-1 position from iodide **2.258** but regrettably isobutyryl chloride does not work in the same fashion.

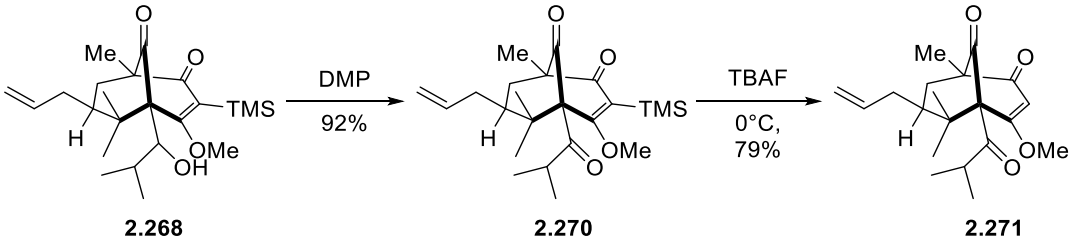
Table 2.5 – Screening of electrophile during functionalization of C-1



	61%		50%
	88%		0%

To continue the synthesis, we engaged first in an oxidation of the alcohol **2.268** toward ketone **2.270** in 92% yield with DMP and subsequent removal of the TMS with TBAF gave **2.271** in 79% yield (***Scheme 2.65***).

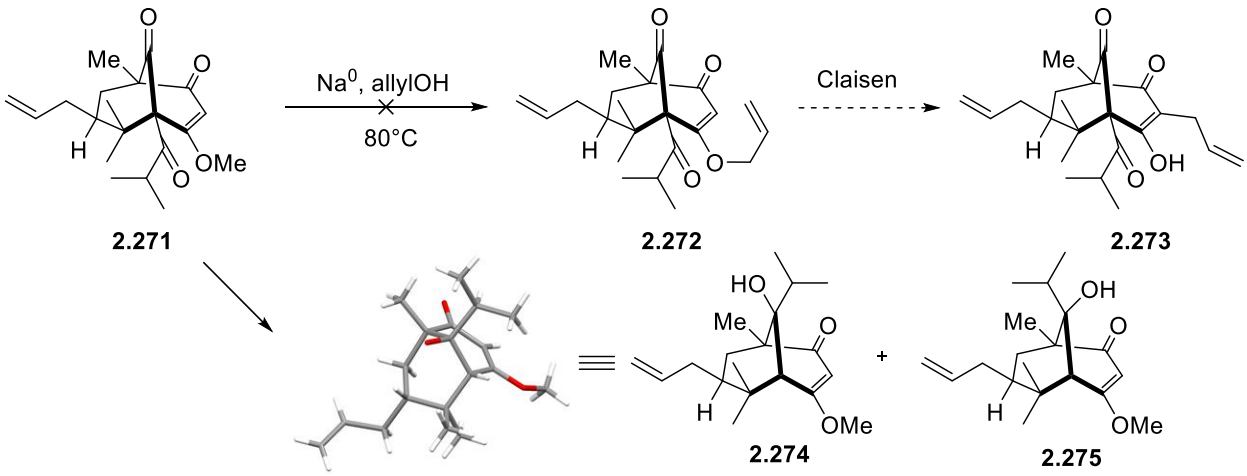
*Scheme 2.65 – Synthesis of methyl enol ether **2.271***



2.268 **2.270** **2.271**

We originally reasoned that we could achieve allylation of the C-3 position **2.273** by a Claisen rearrangement of the corresponding allyl vinyl ether **2.272** which should be obtained by conjugate substitution of **2.271** (***Scheme 2.66***). Interestingly, treatment of **2.271** with allylONa at 80˚ led to the formation of alcohols **2.274** and **2.275**. At first, it was very confusing because **2.271** and **2.274/2.275** have almost identical ^{1}H NMR spectra but we were able to grow crystal of the mixture of **2.274** and **2.275** and their structure were confirmed by X-ray crystallography.

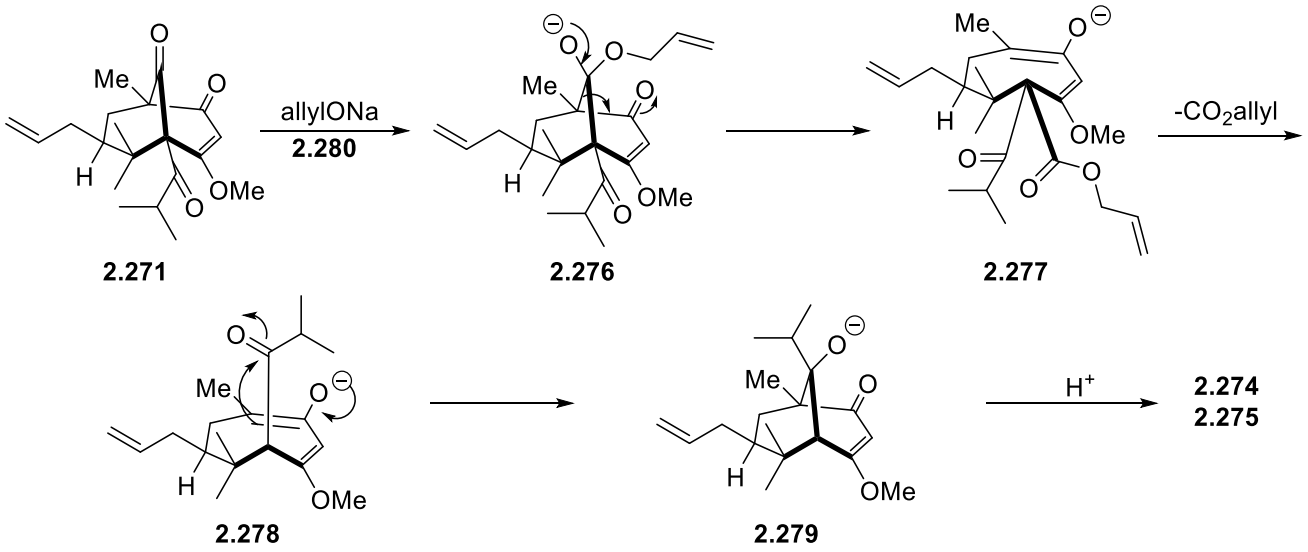
Scheme 2.66 – First attempt at functionalization of C-3



2.271 **2.272** **2.273** **2.274** **2.275**

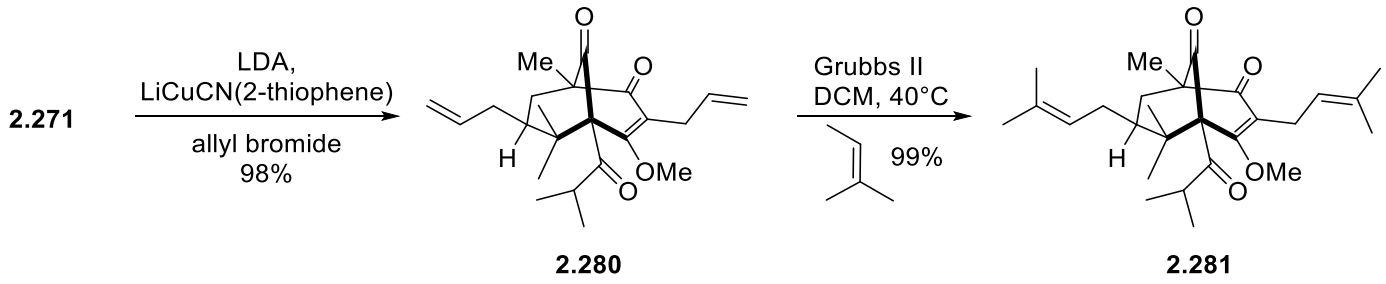
We explained the formation of **2.274** and **2.275** by the attack of allylONa (**2.280**) to the bridgehead ketone to form anion **2.276** which would undergo a retro-Dieckmann condensation reaction to give **2.277**(***Scheme 2.67***). The decarboxylation of **2.277** should follow giving enol **2.278** that would have led to observed products by an intramolecular aldol transform of the latter.

*Scheme 2.67 – Proposed mechanism for the formation of **2.274** and **2.275***



In the midst of this failure, we opted for conditions originally disclosed by Danishefsky using a higher order hetero-organucuprate to install the allyl group at C-3 (***Scheme 2.68***).[87] In our hands, these conditions worked well affording C-3 allylated bicylo **2.280** in almost quantitative yield. Metathesis in presence of Grubbs' 2nd generation catalyst and 2-methylbut-2-ene in DCM gave diprenyl bicycle **2.281** in quantitative yield once again.

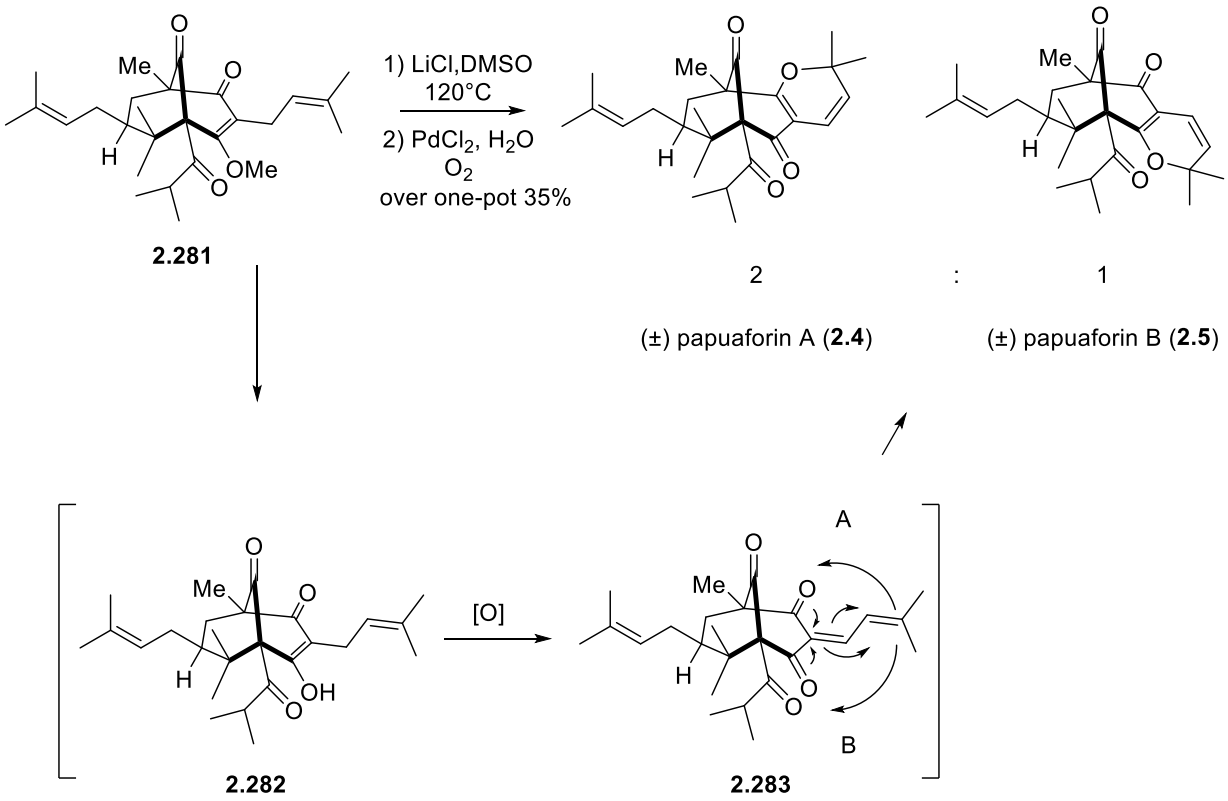
*Scheme 2.68 – Synthesis of **2.281***



2.280 **2.281**

The previously acquired knowledge, on the manufacturing of the pyran ring system utilizing $PdCl_2/O_2$, left us with questions about the removal of the methoxide (***Scheme 2.69***). The method invoked by our predecessors was performed in DMSO and so was the subsequent oxidation. To minimize the step count we pursued a one-pot process. Gratifyingly, a combination of the deprotection of **2.281** with LiCl in DMSO and subsequent oxidation by $PdCl_2/O_2$ to diene **2.833** afforded a 2:1 mixture of papuaforin A (**2.4**) and papuaforin B (**2.5**) respectively in 35% yield. Electrocyclization on the A side of intermediate **2.283** led to papuaforin A and on the B side gave papuaforin B. Overall, the synthetic sequence took 17 steps. To the best of our knowledge it was the only total synthesis of papuaforin A and B to date. Spectral data matched perfectly with the original isolated sample of papuaforin A and B by Sticher.[115] More details about the spectral data can be found in the supporting information.

Scheme 2.69 – Final step in the total syntheses of papuaforin A and papuaforin B

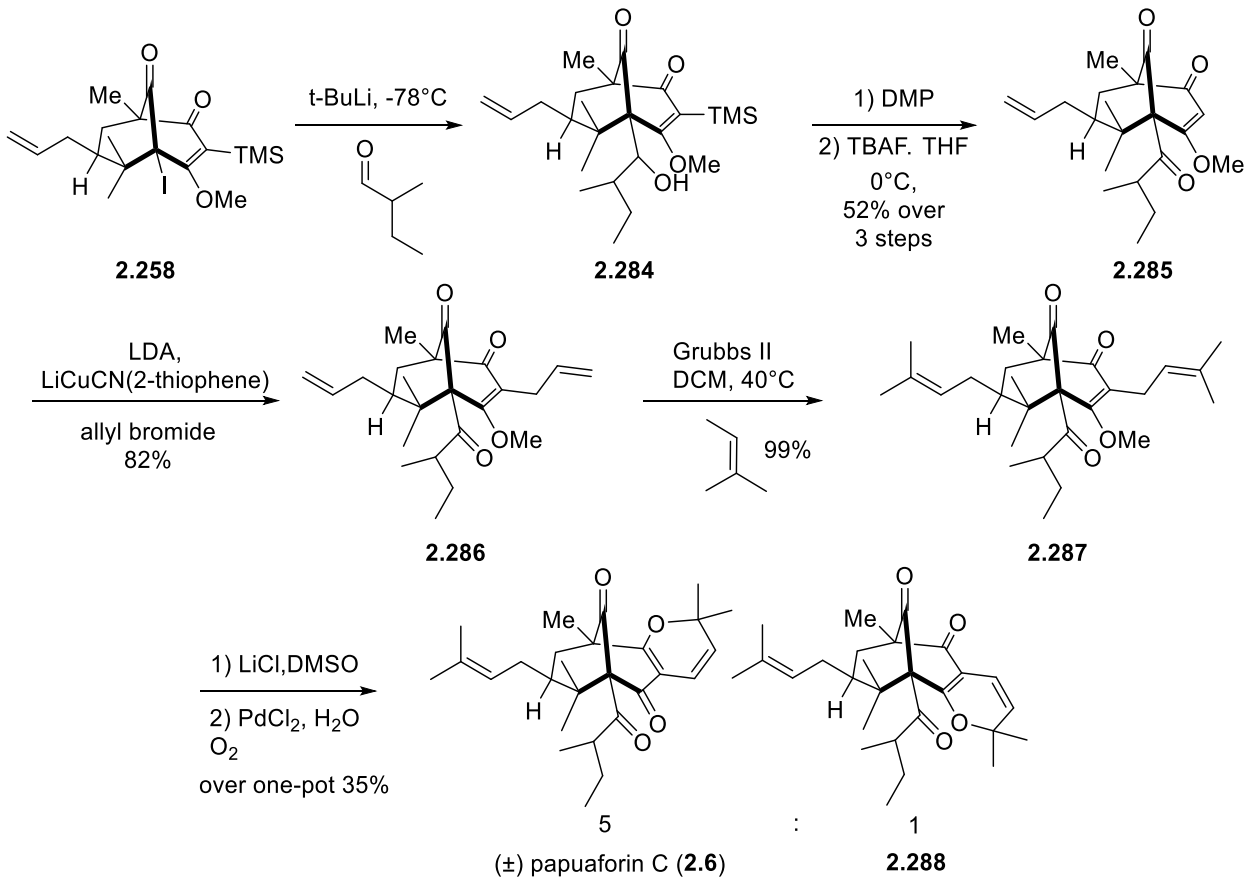


2.4.5 Total synthesis of papuaforin C

Very little needed to be changed to complete papuaforin C (**2.6**) from the original synthetic plan used for papuaforin A (**2.4**) and B (**2.5**). Papuaforin C (**2.6**) differs at the acyl position where it possesses a *sec*-butyl group instead of the *iso*-propyl found in papuaforin A and B (***Scheme 2.70***). Iodide **2.258** underwent a metalation with *t*-BuLi and treated with racemic 2-methylbutanal to give **2.284**. Since we created two new stereogenic centers with this addition, we expected the crude to contain multiple isomers. Thus, we decided to move on directly to the oxidation using DMP and removal of the TMS with TBAF. To our surprise, the sequence resulted in only one diastereomer of **2.285**. We reasoned that since the oxidation conditions with DMP are slightly acidic, it could enolize the acyl functionality to the naturally occurring stereogenic position

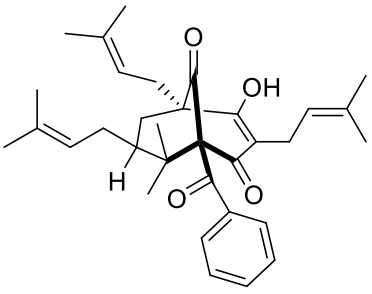
(***Scheme 2.70***). Quantitative cross-metathesis, using the same conditions previously mantioned, afforded **2.287** and finally demethylation/oxidation provided a 5:1 mixture of papuaforin C (**2.6**) and **2.288** respectively in 35% yield. We believe that **2.288** is in fact a natural product that will probably be identified in the future since it is present in such a small quantity compared to papuaforin C (**2.6**), considering that only 1 mg of papuaforin C was originally isolated. Spectral data matched perfectly with the original isolated sample of papuaforin C (**2.6**) by Sticher.[115] Overall, the synthetic sequence took 17 steps. To the best of our knowledge, it is the first and only total synthesis of papuaforin C (**2.6**). More information about the spectral information can be found in the supporting info.

*Scheme 2.70 – Total synthesis of papuaforin C and **2.288***



2.5 Formal synthesis of Nemorosone

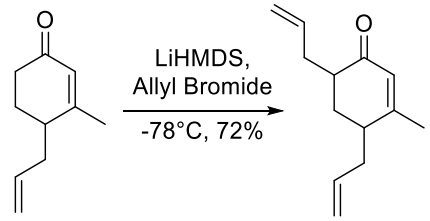
Figure 2.7 – Structure of nemorosone



Nemorosone (**2.3**)

Nemorosone (**2.3**) (***Figure 2.7***) is another type A PPAPs which was synthesized 4 times already by the groups of professors Simpkins, Shair, Danishefsky and Porco.[82f, 87, 92, 104b] Nemorosone (**2.3**) contains a prenyl group at C-3 and a benzoyl group at C-1. To adapt our synthetic plan to this molecule, we simply needed to switch the alkylation of **2.143** to an allyl chain instead of the methyl needed in the papuaforin group (**Scheme 2.71**). In general though, the replacement of the methyl with an allyl chain afforded lower yields during the synthetic sequence especially for the conjugate addition. Therefore, we performed a few optimizations to increase the yields of the reactions. α –Allylation of **2.143** with LiHMDS and allylBr yielded 72% of **2.289**.

*Scheme 2.71 – α-allylation of **2.143***

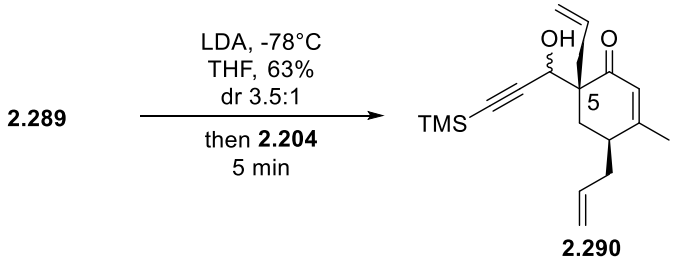


2.143 **2.289**

An optimization of the Adol addition of ketone **2.289** onto aldehyde **2.204** was conducted. The aldehyde was found to be quite sensitive to the choice of base. LiHMDS, KHMDS and additives like HMPA all led to degradation of the aldehyde where the reaction would become instantaneously black upon the addition of aldehyde **2.204** in these settings. Fortunately, LDA was compatible and induced a rapid reaction that was completed after 5 minutes. Longer stirring time afforded reduced yields and quenching of the reaction was performed at -78˚C.

Our best set of conditions was found to be the deprotonation using LDA and only 5 min stirring at -78˚C after the addition of aldehyde **2.204**. We obtained a diastereomeric mixture of 3.5:1 at C-5 which can be easily separated by flash chromatography (***Scheme 2.72***). The optimization of the following conjugate addition was also pursued.

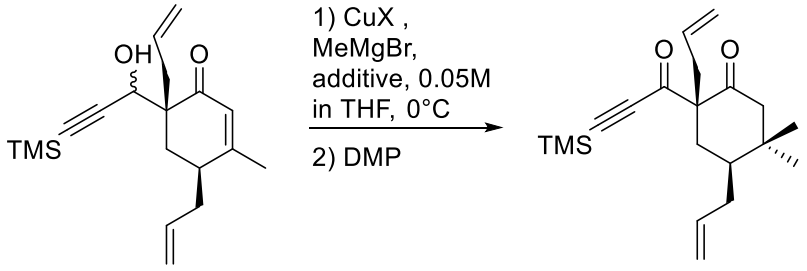
*Scheme 2.72 – Optimal conditions for the aldol addition of **2.289***



The conjugate addition is known to proceed with catalytical amount of CuI but under these conditions the reaction would not yield **2.291.** Therefore, we pursued the equimolar variant trying to troubleshoot the problems (***Table 2.6***). The active complex in this transformation, the Gilman reagent, requires 2 eq. of nucleophile for its formation but during the original probing, more equivalents of the nucleophile MeMgBr were mistakenly added and for the first time, we observed the conjugate addition product. Thereafter, we established that at least 3.2 equiv. of MeMgBr was required for 1.2 eq. of CuI to give 21% yield (entry 1) of **2.291** resulting from the conjugate addition/oxidation sequence (***Table 2.7***). In our hands, a CuI/dimethyl sulfide mixture was the only combination to yield product, conventional additives for cuprate addition like TMSCl, LiCl all prohibited the 1,4-addition (entry 2,4,7,8). Other copper sources did not provide any product (entry 3). Increasing the CuI loading boosted the yields, optimally we found that 2 equiv. of CuI, 5 equiv. of MeMgBr and a concentration of 0.2M in THF under heavy stirring over 5-6 hours provided **2.291** in 73% yield (entry 13). We reasoned that 1 equiv. of MeMgBr was used to deprotonate the

alcohol and the four other equivalents will react with CuI to give overall two equiv. of Gilman's reagents. It is unclear though, why we require two equivalents of the Gilman reagent to achieve optimal yields. The supramolecular arrangement of the alkylative complexe must be different according to the equivalents of reagent present in solution. Further increasing the equivalents of MeMgBr did not significantly modify the outcome of the reaction (entry 15).

Table 2.6 – Optimization of the conjugate addition



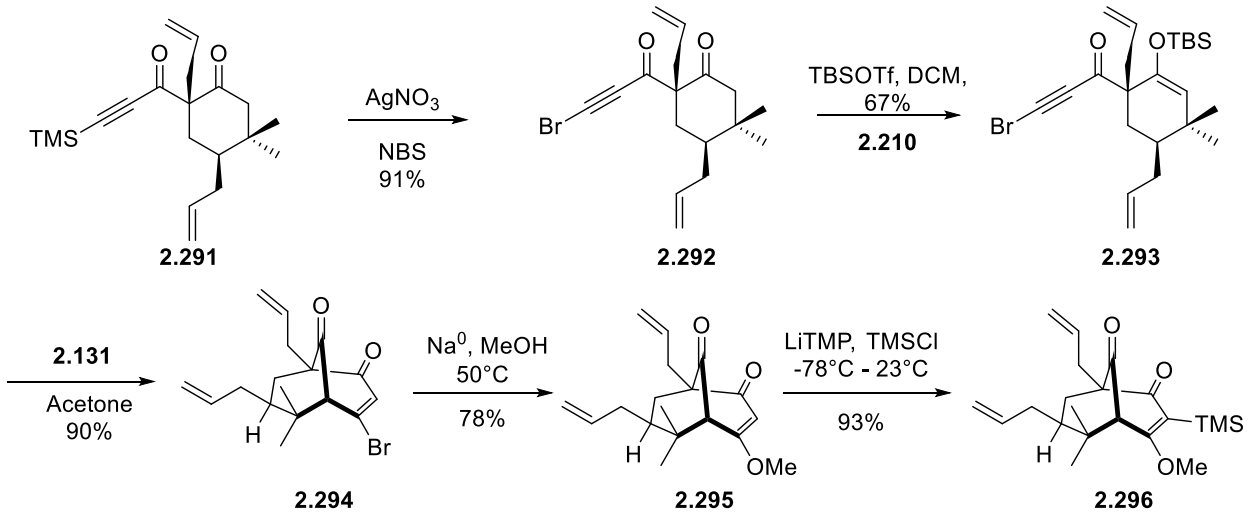
2.290 **2.291**

Entry	eq. of CuX	CuX	Additive	MeMgBr. eq.	Rx time	yield
1	1.2	CuI	10% DMS	3.2	5-6h	21
2	1.2	CuI	DMS, 2.4eq. LiCl	3.2	5-6 h	0
3	1.2	CuBr-DMS	none	3.2	5-6 h	0
4	2	CuI	DMS, 4.4 LiCl	3.2	5-6 h	0
5	2	CuI	10% DMS	4.2	5-6h	29
6	2	CuI	10% DMS	4.2	10h	20
7	2	CuI	10% DMS[e]	4.2	5-6 h	0
8[a]	2	CuI	10% DMS[e]	4.2	5-6 h	0
9	2	CuI	10% DMS	4.2	5-6 h	29
10[b]	2	CuI	10% DMS	4.2	5-6 h	46
11[c]	2	CuI	50% DMS	4.2	5-6 h	53
12[d]	2	CuI	10% DMS	4.2	5-6 h	25
13[d]	2	CuI	10% DMS	5	5-6h	73
14[d]	2	CuI	50% DMS	5	5-6h	72
15[d]	2	CuI	10% DMS	5.5	5-6h	69

[a]performed at -78°C; [b]0.001M; [c]0.1M; [d]0.2M; [e]4.2eq. of TMSCl was also added

With the two major problematic reactions now resolved, we resumed our synthesis of nemorosone (**2.3**) (***Scheme 2.73***). Next, the replacement of the TMS group by a bromide was achieved without incident by the utilization of $AgNO_3$ and NBS to give **2.292** in 91% yield. Bromoethynyl **2.292** was transformed into the corresponding silyl enol ether **2.293** in 67% yield using the methodology developed previously. Contrary to the comparable Au[I]-catalyzed cycloisomerization of **2.219** performed by Marie Christine Brochu, the allyl moiety of **2.293** proceeded via *6-endo* dig cyclization into the desired bicyclo[3.3.1]nonane **2.294** with an appreciable 90% yield. Conjugate substitution with sodium methoxide in MeOH gave 78% yield of methyl vinyl ether **2.295**. Protection of C-3 was performed with LiTMP and TMSCl gave **2.296** in 93% yield, the precursor to an intermediate isolated by Simpkins and co-workers during the synthesis of nemorosone.[82f]

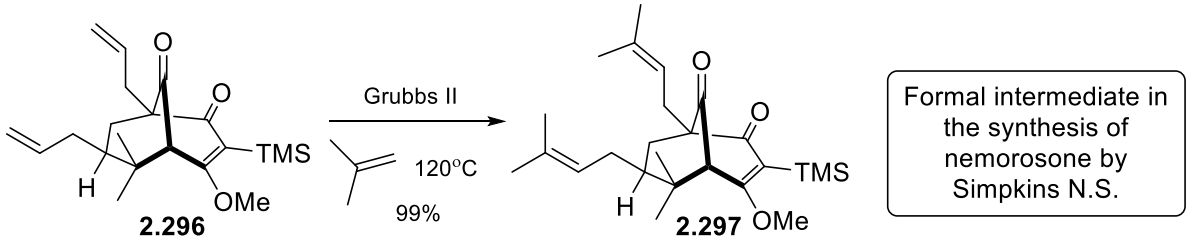
*Scheme 2.73 – Synthesis of bicycle **2.296** toward nemorosone*



To prohibit intramolecular metathesis, we used metathesis conditions developed by Nakada's group during their synthesis of hyperforin.[103d] Diallyl bicycle **2.296** was charged to a sealed tube and isobutene was added followed by Grubbs 2nd generation. The sealed tube was

closed and heated to 120˚C in an oil bath for 1 h to give a quantitative yield of diprenylated bicycle **2.297** (***Scheme 2.74***). With intermediate **2.297** in hand, we completed the formal synthesis of nemorosone based on Simpkins synthesis. Our route allowed the synthesis of **2.296** in 11 steps and 13% overall yield. We were 5 steps away from the natural product with a multigram-scale synthesis of advanced bicycle **2.297**.

Scheme 2.74 – Last step in the formal synthesis of nemorosone



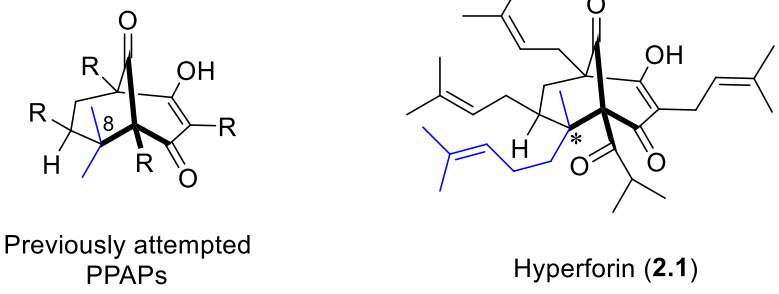
2.6 The Holy Grail: Total synthesis of Hyperforin

With a strong modular synthetic sequence that allowed the synthesis of papuaforin A (**2.4**), B (**2.5**), C (**2.6**) and the formal synthesis of nemorosone (**2.3**), we were now ready to tackle the jewel of this family of natural products: hyperforin (**2.1**)

2.6.1 Version 1

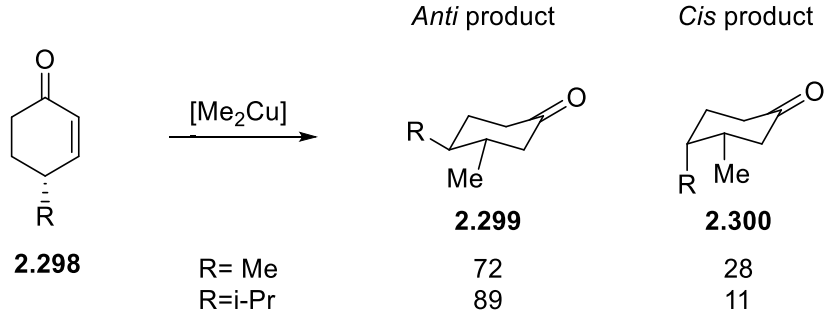
Retrosynthetically, we needed to address the introduction of the homo-prenyl chain at C-8 in a stereoselective fashion (***Scheme 2.75***). We hypothesized that the conjugate addition of the homo-

Scheme 2.75 – Added structural challenge of hyperforin



allyl chain onto enone **2.290** should favor the *anti*-addition adduct directed by the C-7 allyl chain. Work by Riviere and Tostain also supported this idea (***Scheme 2.76***).[116] They identified that 4-substituted cyclohex-2-enone **2.298** underwent conjugate addition selectively through a boat like transition state yielding the *anti*-addition adduct **2.299**.

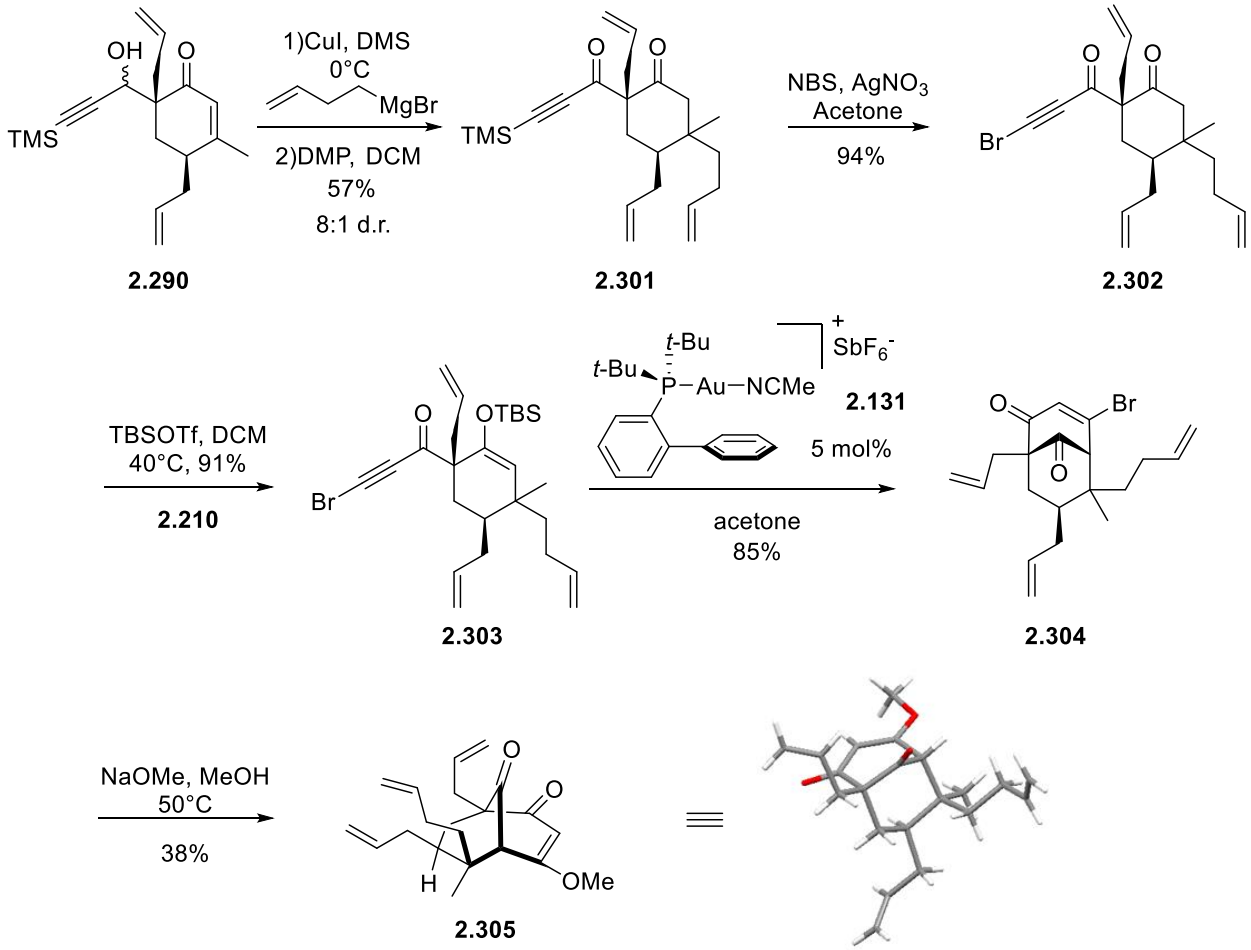
Scheme 2.76 – Riviere and Tostain study of 4-substituted cyclohex-2-enone



Correlating Tostain and Riviere's findings, the conjugate addition of enone **2.290** with homoallylMgBr provided **2.301** with good selectivity, yielding an 8:1 inseparable diastereomer mixture (***Scheme 2.77***). Since the ^{1}H NMR of the mixture was too messy to single out any signal that could have established the relative stereochemistry of the newly formed stereogenic center by spectroscopy techniques, we continued the synthesis with the well-established sequence until we reached a separable intermediate. This intermediate was found to be bicycle methyl vinyl ether **2.305**. **2.305** was synthesized by transposition of the TMS by a bromide from **2.301** to alkynyl bromide **2.302** with $AgNO_3$ and NBS. Silyl enol ether **2.210** resulted from the treatment of **2.302** with **2.210** and TBSOTf at reflux over 3 days. The Au[I]-catalyzed *6-endo* dig cyclization worked without any problem to yield 85% of bicycle **2.304** and subsequent conjugate addition with sodium methoxide gave **2.305** as a separable mixture of diastereomers where the major diastereomer was isolated in 38% yield. Its sturdy structure allowed for crystallization but the X-ray data revealed that the homo-allyl chain at C-8 was *syn* to the allyl chain at C-7. Unfortunately, hyperforin (**2.1**)

has the opposite relationship where the homo-prenyl chain at C-8 must be *trans* to the prenyl at C-7. To our advantage though, many PPAPs are found to contain this cis-relationship between C-7 and C-8 stereocenters which increased the modularity of our synthetic strategy.

Scheme 2.77 – Synthesis of advance bicycle ***2.305***

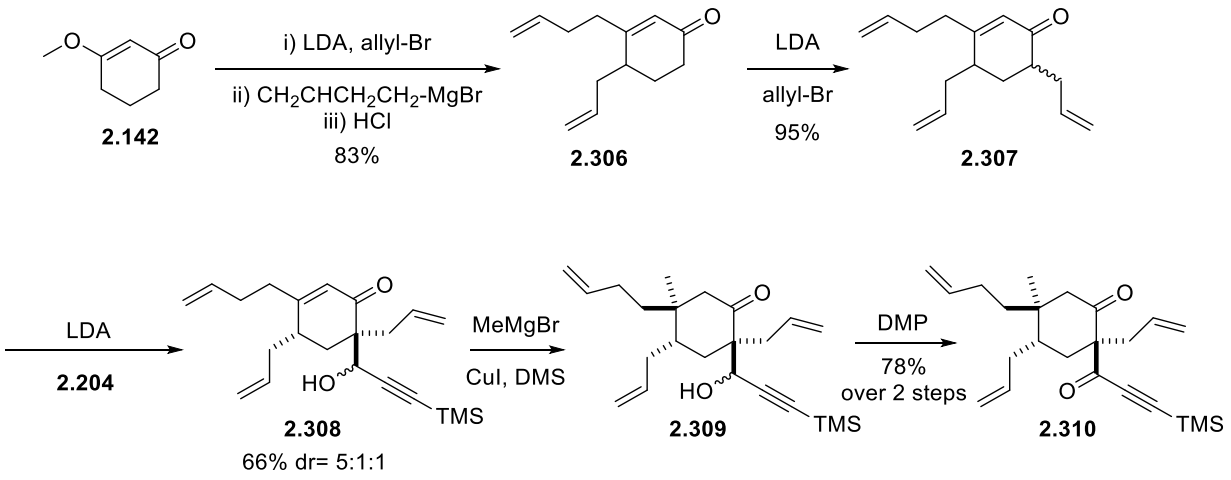


2.6.2 Version 2

We reasoned that a logical way to fix this issue was to inverse the introduction of the alkyl groups at C-8. In order to introduce this variation, we needed to go all the way back to the start of the synthetic sequence and we installed the homo-allyl chain earlier (***Scheme 2.78***). One pot α-

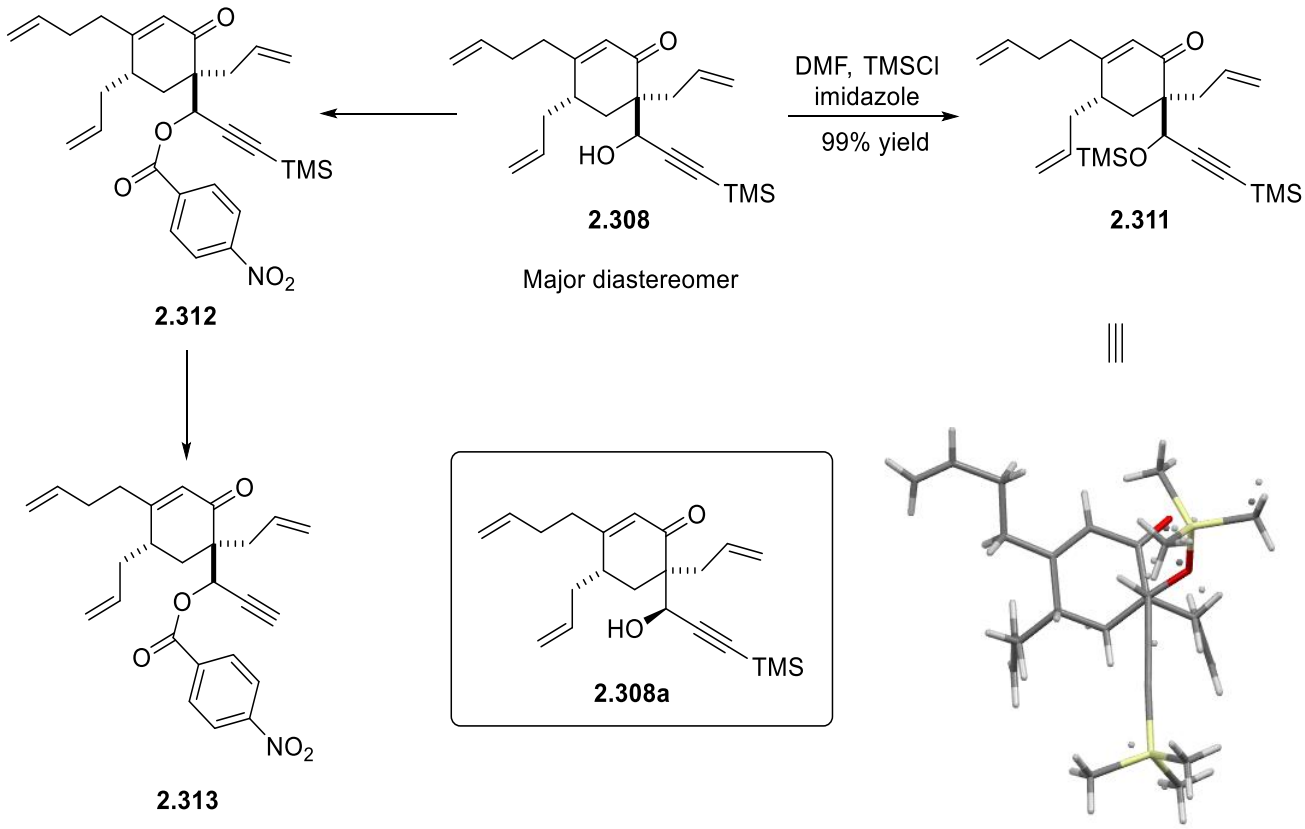
allylation/1,2-addition of the homo-allyl chain/elimination gave enone **2.306** in 83% yield. A second α-allylation using LDA for the deprotonation gave enone **2.307**. Aldol addition to aldehyde **2.204** provided alcohol **2.308** as a 5:1:1 mixture of diastereomers. The major diastereomer can be separated from the others in 66% yield. Upon testing the cuprate addition of the methyl group, we were astonished to find that the reaction resulted in a single diastereomer of diketone **2.310** after oxidation. These were encouraging results, the ^{1}H NMR data also suggested that we were in presence of another diastereomer than the one obtained during our first attempt at hyperforin (**2.1**). But before continuing, we wanted to investigate the source of this exemplar selectivity. Thus, we needed to find out the relative stereochemistry of the major diastereomer of **2.308**.

*Scheme 2.78 – Synthesis of cyclohexanone **2.310***



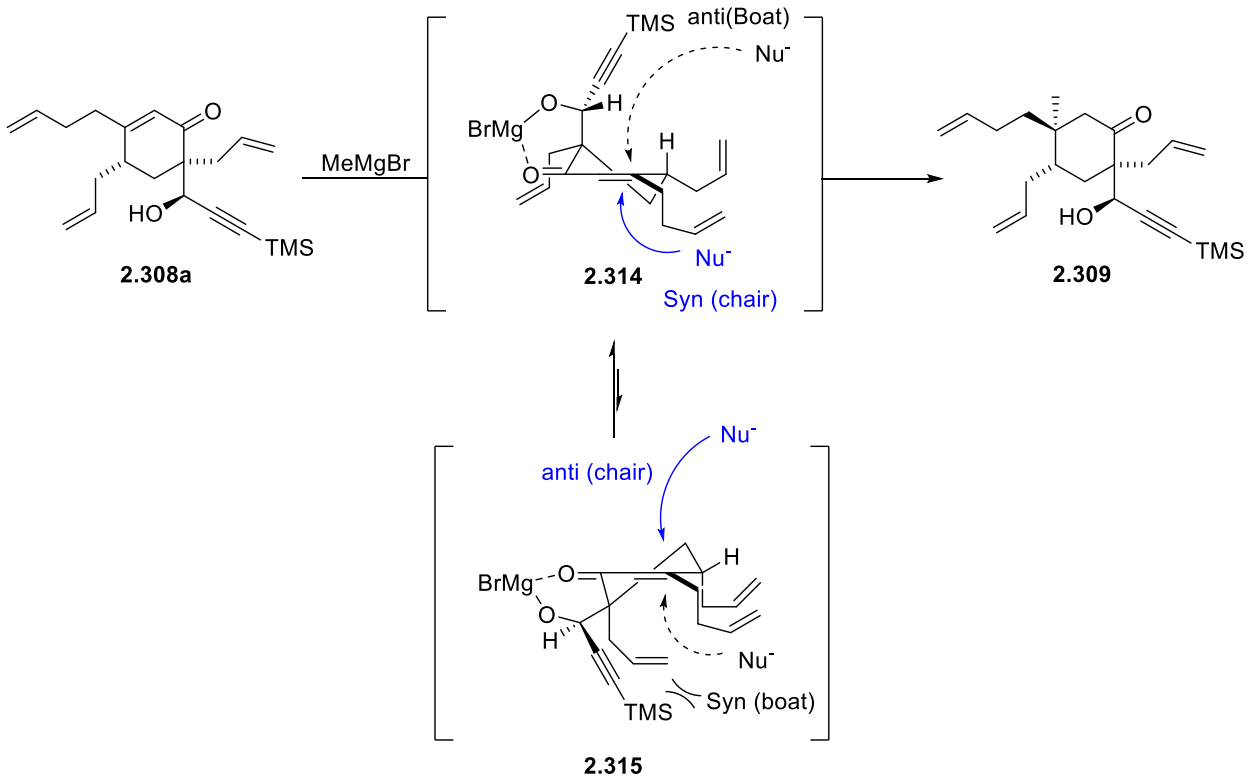
Unfortunately, the free alcohol **2.309** was not a solid. We tried installing a benzoyl *p*-nitro group to the pendant alcohol but both TMS protected alkynyl **2.312** and TMS-free alkynyl **2.313** were found to be viscous oils (***Scheme 2.79***). To our surprise, bis-silylated adduct **2.311** provided the necessary crystal for X-ray analysis. The analysis revealed that the major isomer has the relative configuration of **2.308a**.

*Scheme 2.79 – Modification to **2.308** to get a crystal*



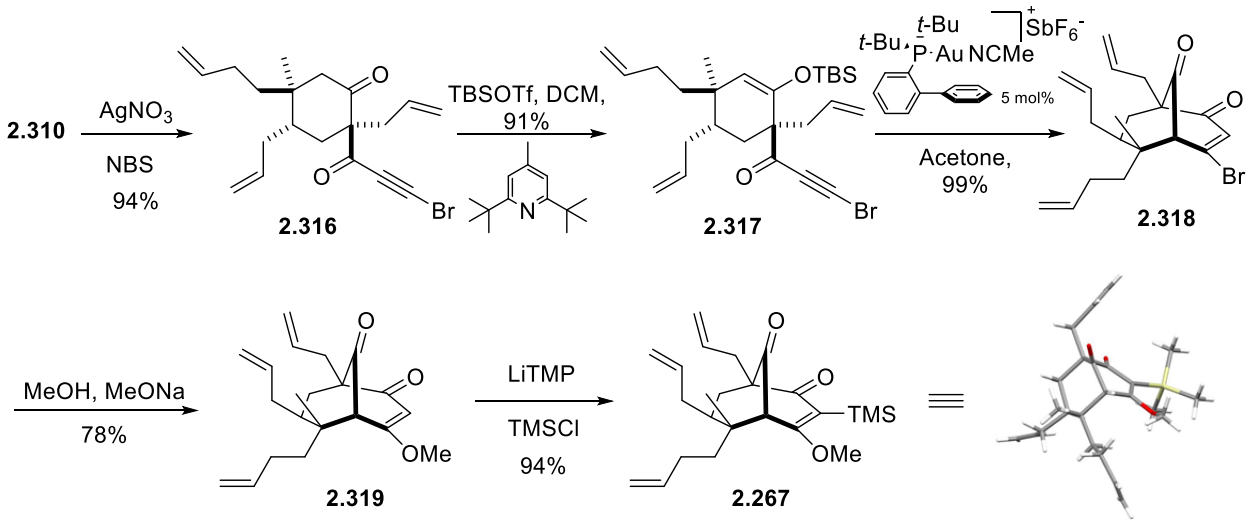
We reasoned the unusual diastereoselectivity through the formation of the Mg-chelated intermediate **2.314** (***Scheme 2.80***). The latter can adopt a conformation in which the axial substituent shielded the top face, thus favoring the *syn* approach of the organocopper reagent to provide **2.309**. In practice, **2.314** should be in equilibrium with half-chair **2.315**, but this conformation induces serious steric clash between the ethynyl chain and the cyclohexane ring favoring conformation **2.314**.

Scheme 2.80 – Proposed mode of action of the conjugate addition.



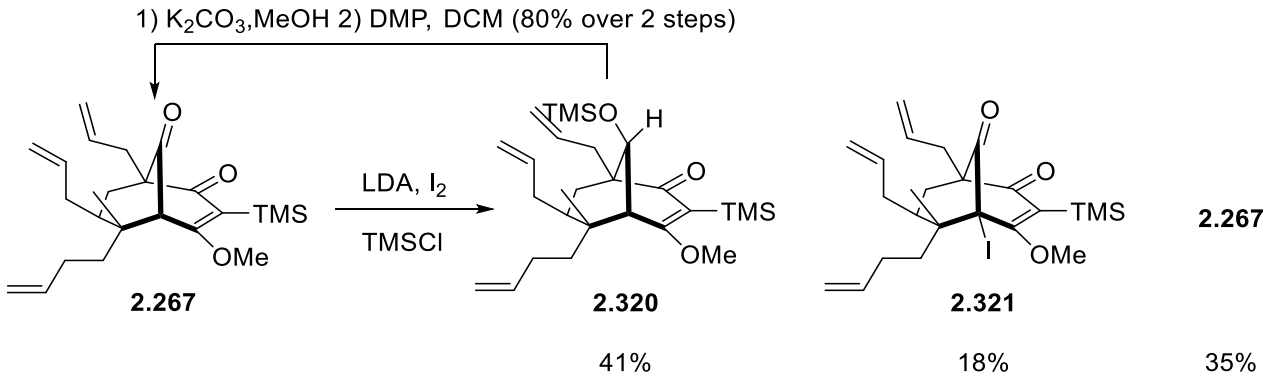
Transposition of the TMS in presence of $AgNO_3$ and NBS for a bromide gave **2.316** (S***cheme 2.81***). The silyl enol ether formation went smoothly following our original set of conditions to give **2.131** in 91% yield ready to undergo the Au(I)-catalyzed carbocyclization to **2.318** in quantitative yield. This reaction was highly reliable and could be scaled up to 10g. Conjugate substitution with sodium methoxide provided methyl vinyl ether **2.319**, followed by a protection of the C-3 position with LiTMP and TMSCl that gave **2.267** in 94% yield. We were able to verify the relative stereochemistry **2.267** by X-ray crystallography and gratifyingly it matched the one found in the natural product.

*Scheme 2.81 – Synthesis of advanced intermediate **2.267***



For the vital C-1 acylation, we used Danishefsky' sequence to synthesize head bridge iodide **2.321** in 18% yield (***Scheme 2.82***). Again, the intermediate **2.321** was accompanied by reduced adduct **2.320** in 41% yield and recoverable starting material in 35% yield. **2.320** could be recycled back to ketone **2.267** by selective deprotection and oxidation in 80% over the 2 reactions.

*Scheme 2.82 – Iodination of **2.267** at C-1*



The alkylation of the bridgehead position was low yielding but nevertheless 24 % of acylated adduct **2.322** could be isolated over the course of the metalation/alkylation/oxidation/deprotection sequence (***Scheme 2.83***). Deprotonation of the C-3

position with LDA, formation of the hetero-organocuprate reagent in presence of lithium 2-thienylcyanocuprate and subsequent exposure to allylBr provided 91% yield of methyl allylhyperforin **3.323**. Utilization Nakada metathesis reaction conditions provided 85% of tetraprenylated methyl hyperforin **3.324** in 85% yield. Finally, the C-2 methyl ether was cleaved under Krapcho's conditions to give hyperforin (**2.1**). The sequence leading to hyperforin has 17 steps. The final product matched other samples of hyperforin isolated or synthesized. More information about the spectral information can be found in the supporting information. Before professor Maimone's[105] recent disclosure of the total synthesis of hyperforin in only 10 steps, we had the shortest synthesis of hyperforin closely followed by Shair's[104a] approach that counted 18 steps (***Table 2.7***).

Scheme 2.83 – Total synthesis of hyperforin

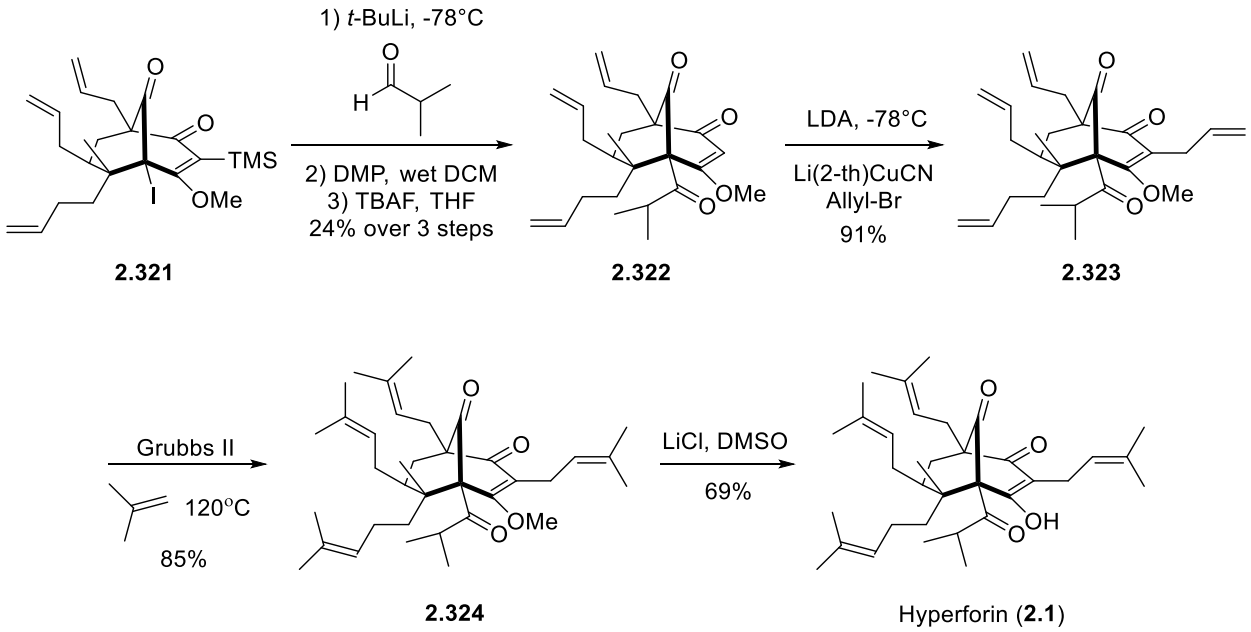
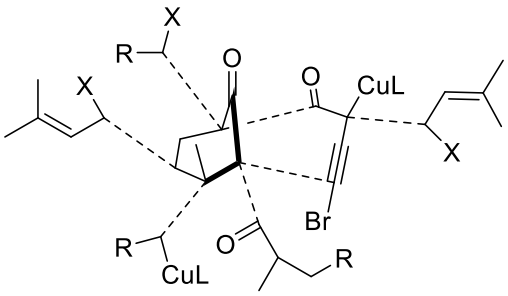


Table 2.7 – Evolution of the step count in the total syntheses of hyperforin

	Steps	Year
Maimone	10	2015
Barriault	17	2014
Shair	18	2013
Nakada	35	2013
Shibasaki	51	2010

2.7 Conclusion

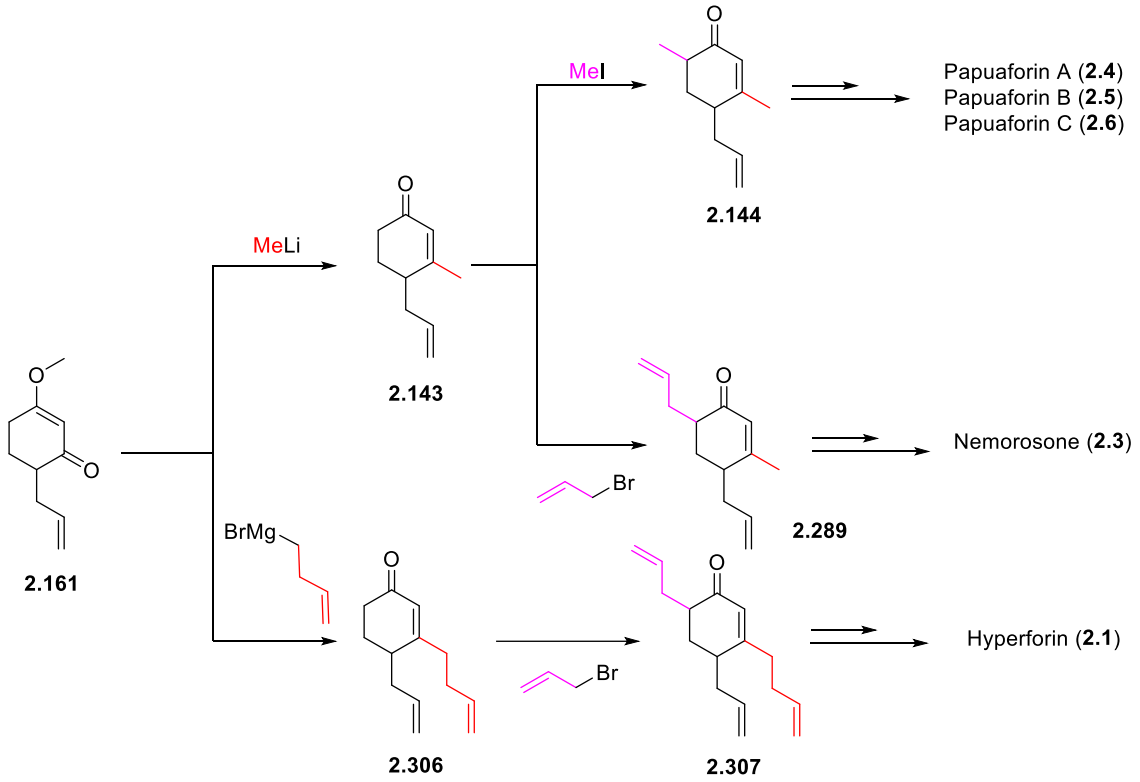
Figure 2.8 – Key disconnections



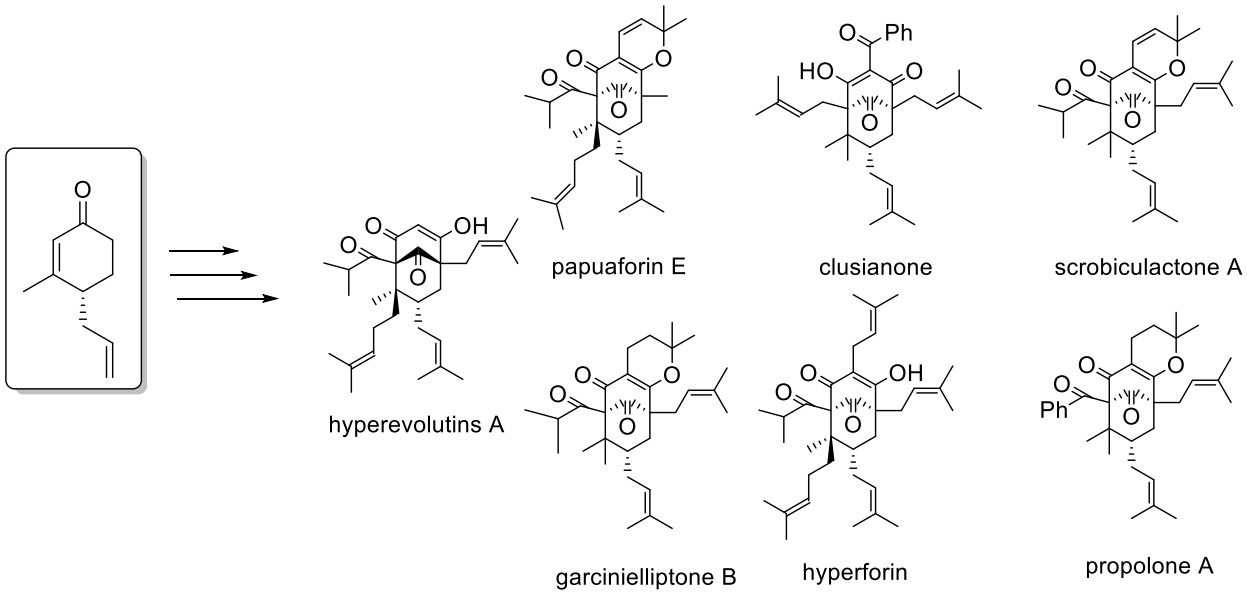
We have designed a truly modular synthetic sequence that permitted the first total synthesis of papuaforin A (***2.4***), B (**2.5**) and C (**2.6**), the formal synthesis of nemorosone (**2.3**) and finally one of the shortest synthesis of hyperforin (**2.1**) to date (***Figure 2.8***). At the core of this methodology lies a Au(I)-catalyzed *6-endo* dig cyclization coupled with stereoselective and chemoselective alkylations. Only 8 steps are necessary to gain entry to the decagram scalable bicyclo[3.3.1]nonane core which can thereafter be selectively tailored to the desired naturally occurring PPAPs. This would be an exemplar methodology to study further the medicinal potential of this family of natural products through swift and efficacious structure and relationship studies.

We showed that careful introduction of the desired functionality through the pivotal intermediates (**2.161** and **2.143**) allowed for late-stage functionalization and unified access to a wide variety of PPAPs (***Scheme 2.83*** and ***Scheme 2.84***). It would be easy to apply this methodology to the wide range of structures found in the family of PPAPs.

Scheme 2.84 – Pivotal intermediates toward PPAPs



Scheme 2.85 – Other achievable PPAPs utilizing our methodology



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CHAPTER 3

Toward the total synthesis of ginkgolide C

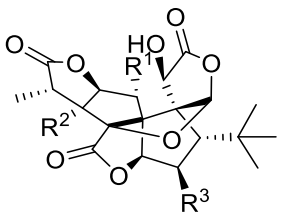
3.1 Introduction

Ginkgolides are isolated from the ginko tree, *Ginkgo biloba*, a living fossil with records of its existence dating back 280 million years ago.[117] Of an average height of 20 to 35m, the trees where only known to the orient until they started exportation throughout the world after the 18th century. For centuries, the tree and its extracts have been used extensively for their beneficial properties, especially in China, Japan and India.[1] For example, extract Egb761, one of the most potent fraction, generates over $500 million a year alone.[118] The natural extract of the ginko tree is marketed as a dietary supplement but is believed to enhance cognitive functions and potential treatment for dementia and Alzheimer's disease. There ia also evidence of the ginko extract showing promise to treat high blood pressure, macular degeneration, peripheral arterial disease and alleviate the menopause side-effects.[119] But above all else, ginkgolides are potent platelet-activating factor (PAF) antagonist.[118a, 120]

In 1932, Furukuwa intrigued by the therapeutic potential of the natural extract isolated four terpene from the bark of the *Ginkgo biloba* that he believed to be responsible for its activity.[121] Due to the complexity of the natural products isolated, it took over 35 years before the structure could be elucidated. In 1967, Nakanishi's group was able to attribute the appropriate structure of ginkgolide A (**3.1**), B (**3.2**), C (**3.3**) and M (**3.4**) shown in ***Figure 3.1***.[1] Ginkgolide J (**3.5**) was

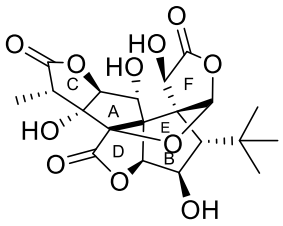
isolated in a later finding in 1987, by Weinges *et al.*[122] The 5 ginkgolides differ from one another by the presence of a hydroxyl group or hydrogen at the R^1, R^2 and R^3 positions.

Figure 3.1 – Ginkgolide's family



	R^1	R^2	R^3
A (3.1)	H	OH	H
B (3.2)	OH	OH	H
C (3.3)	OH	OH	OH
M (3.4)	H	OH	OH
J (3.5)	OH	H	OH

Figure 3.2 – Ginkgolide C with identified cycles



Ginkgolide C (**3.3**)

The ginkgolides possess a truly unique compact diterpene framework of six 5-membered rings with a high content of oxygen. Up to 11 oxygens can be found in ginkgolide C (**3.3**) for a core containing only 23 carbons. The ginkgolides also include a very unique feature: a *tert*-Butyl group located on the most convoluted ring system: the B ring. The most complex of the ginkgolides, ginkgolide C (**3.3**), contains a total of 12 stereocenters all of which are contiguous. The B cyclopentane ring (***Figure 3.2***) alone, has stereocenters at its 5 carbons including 2 contiguous spirocycles and a *tert*-Butyl group.

These unique features, bioactivity and high complexity of the ginkgolides have made them an interesting target for the organic chemists and scientific community with well over 100 publications on the properties and effects of the ginkgolides. However, the study of this family of natural products is still in its early stages because of the remarkable structural complexity that obscures derivatization efforts and further research.

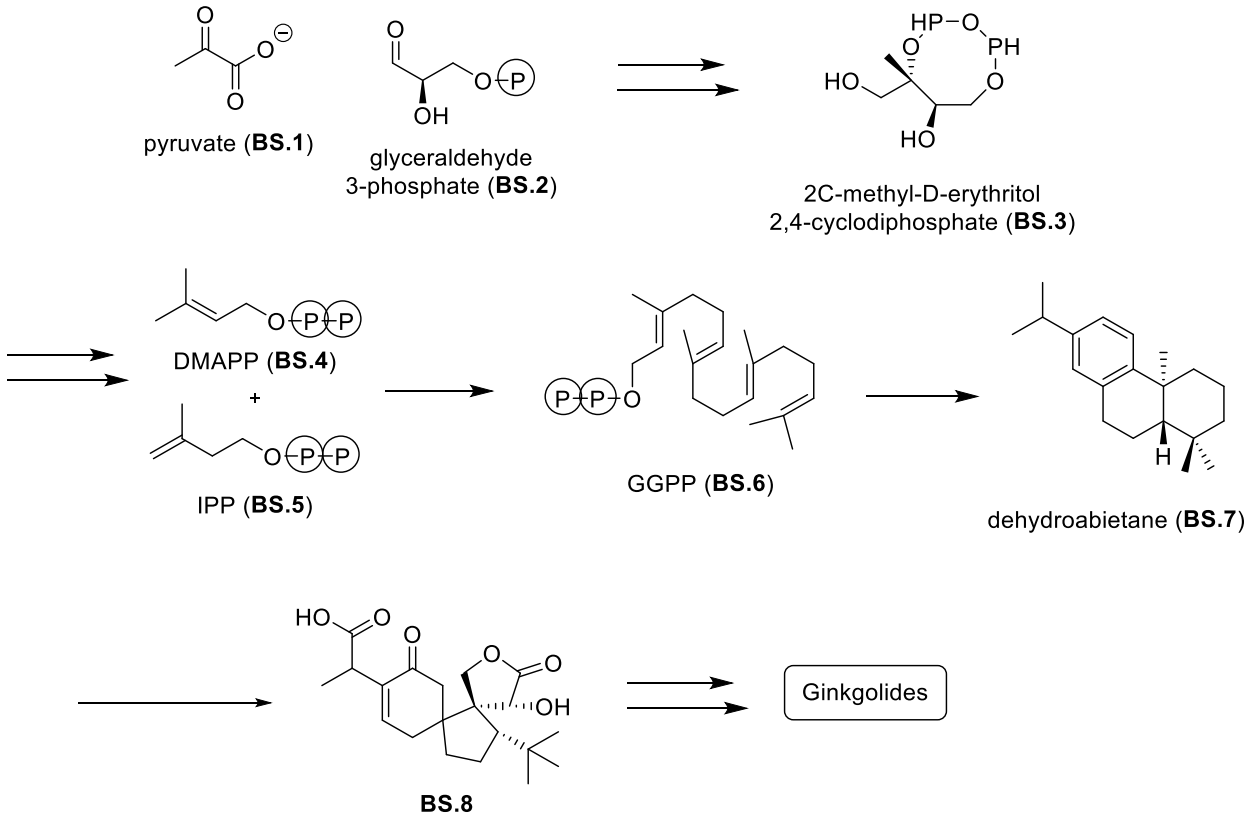
Few groups have found success in limning a synthetic route to ginkgolides. Corey's group was the first to achieve the total synthesis of ginkgolide B (**3.2**) in 1987[118b] and a year later, the

same group completed ginkgolide A (**3.1**).[123] Crimmins and co-workers also achieved the total synthesis of ginkgolide B (**3.2**) a decade later in 1999.[124] It is also worth mentioning that Anderson's group has been interested in synthesizing ginkgolides but has only been able to achieve the simpler D-E-F-ring system without publishing further on the subject.[125] Ginkgolide J (**3.5**) and M (**3.4**) are present in smaller proportion in the natural extract but can be access by semi-synthesis from naturally extracted ginkgolide A-C.[126] However, to the best of our knowledge, there is no existing report of a total synthesis of ginkgolide C.

3.1.1 Biosynthesis of ginkgolides

When the ginkgolides were identified by Nakanishi, he described the biosynthesis to originate from dimethylallyl pyrophosphate (**BS.4**) and isopentenyl pyrophosphate (**BS.5**) resulting from the mevalonate pathway(***Scheme 3.1***).[127] In this pathway, three molecules of acetyl co-enzyme A react and are reduce to give mevalonic acid, which is then phosphorylated. It was later found that the ginkgolides are indeed formed from DMAPP (**BS.4**) and IPP (**BS.5**) but these molecules result from an orthogonal pathway starting from pyruvate (**BS.1**) and glyceraldehyde 3-phosphate (**BS.2**). **BS.1** and **BS.2** come together to give 2C-methyl-D-erythritol-2,4-cyclodiphosphate (**BS.3**). Thereafter, **BS.3** is transformed into DMAPP (**BS.4**) and IPP (**BS.5**) rather than through the conventional mevalonate pathway. DMAPP (**BS.4**) and IPP (**BS.5**) react together to give the universal diterpene geranylgeranyl pyrophosphate (**BS.6**) which is converted to dehydroabietane (**BS.7**) and subsequently to ginkgolides through intermediate **B.S.8.**

Scheme 3.1 – Biosynthetic pathway to ginkgolides

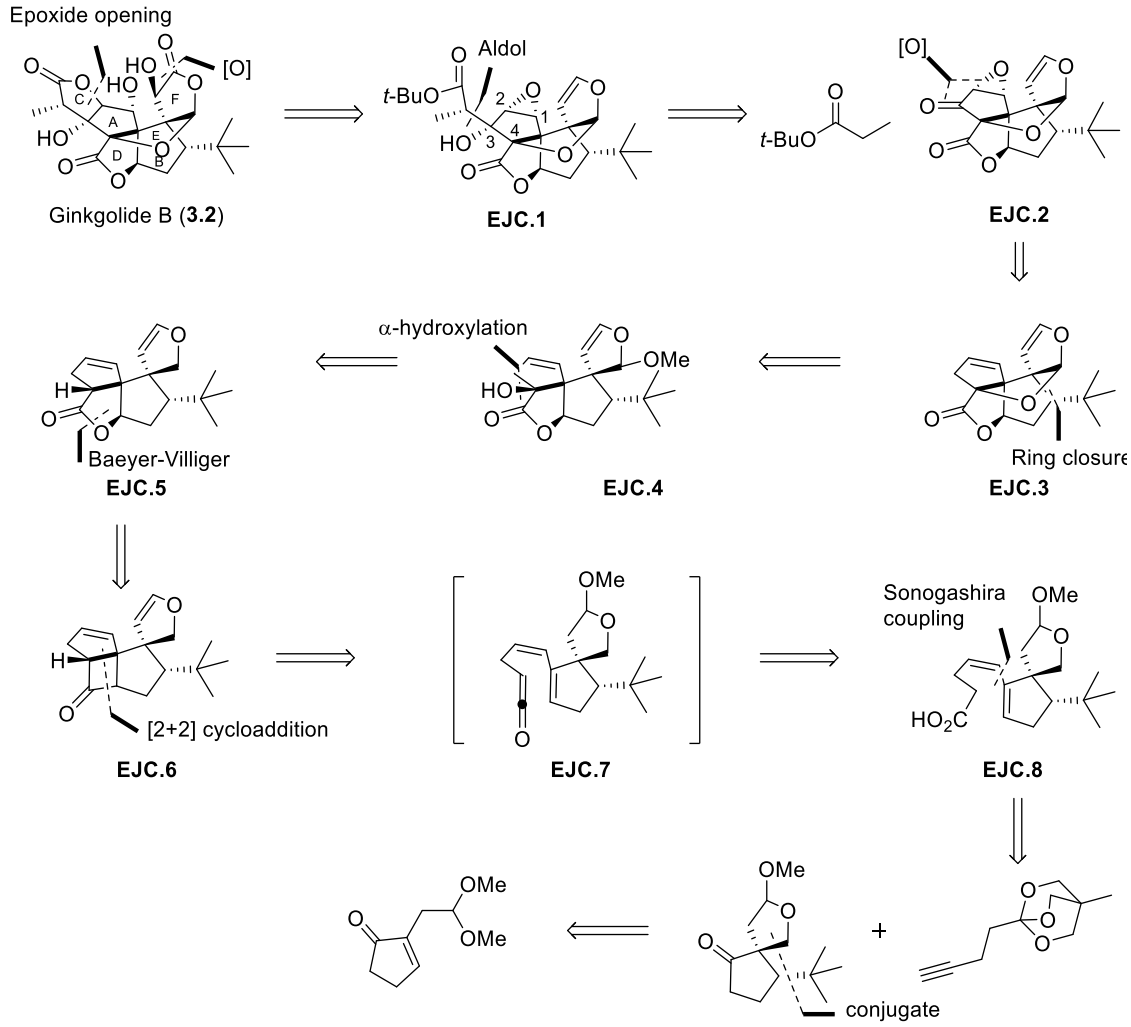


3.1.2 Corey's strategy toward the synthesis of ginkgolides

As a pioneer in his endeavor toward the total synthesis of ginkgolides, we will start by a retrosynthetic analysis of Corey's approach to ginkgolide B (***Scheme 3.2***).[118b] Starting from **EJC.1**, the F ring needed to be masked as the vinyl ether to hide its inherent activity. The C ring has risen from an oxylactonization transform to give ginkgolide B (**3.2**). **EJC.1** was accessed through a highly selective aldol reaction of **EJC.2** with *tert*-butyl propionate. **EJC.2** was the result of an allylic oxidation followed by selective epoxidation which was the key in setting the *trans* relationship between the C ring and alcohol at C-1 in subsequent steps. The E ring of **EJC.3** was formed through a ring closure of tertiary hydroxyl group at C-4 in **EJC.4** which was installed through an α-hydroxylation of **EJC.5**. The D ring was shaped though a remarkably selective

Baeyer-Villiger oxidation of cyclobutanone **EJC.6**. This bring us to the key step in Corey approach to ginkgolide B which resided in an intramolecular [2+2] cycloaddition of ketene **EJC.7** formed *in situ* from carboxylic acid **EJC.8**. This approach is important as it allowed the construction of important features of the natural product expeditiously, inclusive of the contiguous A-F ring system on the B ring, as well as the cyclobutanone allowing rapid access to ring D. **EJC.8** was constructed through C-C bond transform of synthon **EJC.9** and **EJC.10**. The installation of the peculiar *t*-Bu group was performed early in the synthesis by means of a conjugate addition to enone **EJC.11**.

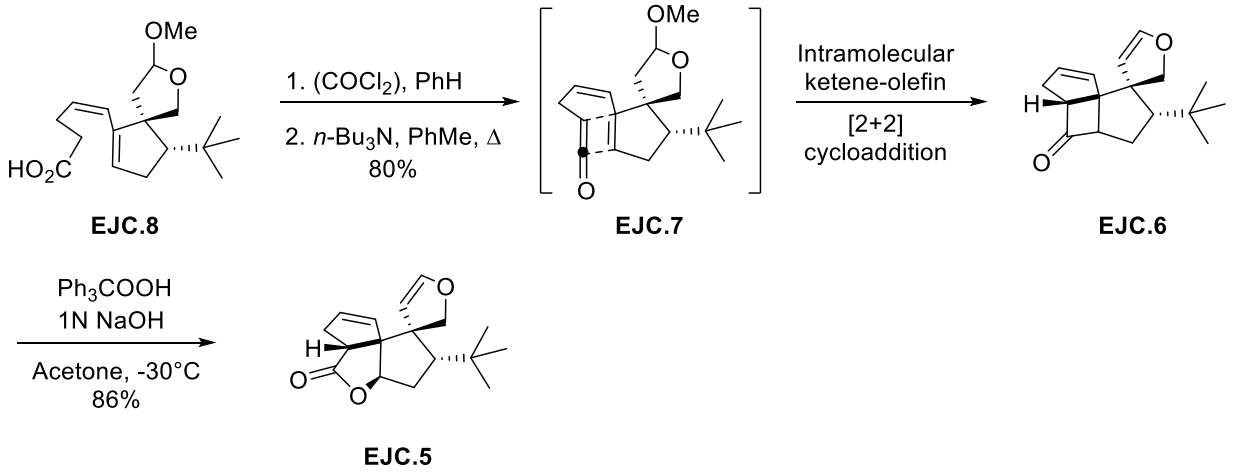
Scheme 3.2 – Corey's retrosynthetic analysis of (±)-ginkgolide B



We will now revisit some of the key features that allowed the success of Corey and co-workers' total synthesis of ginkgolide A (**3.1**)[123] and B (**3.2**)[118b, 128] with a focus on ginkgolide B as it was the main aim of its research efforts and thereafter delineated an approach to ginkgolide A from a late-stage intermediate of ginkgolide B. As mentioned earlier, the key reaction of this synthesis was the formation of cyclobutanone **EJC.6** through an intramolecular [2+2] cycloaddition of intermediate **EJC.7** (***Scheme 3.3***). Ketene **EJC.7** was accessed by treating **EJC.8** with oxalyl chloride, in benzene, to provide the acid chloride which was subsequently treated with

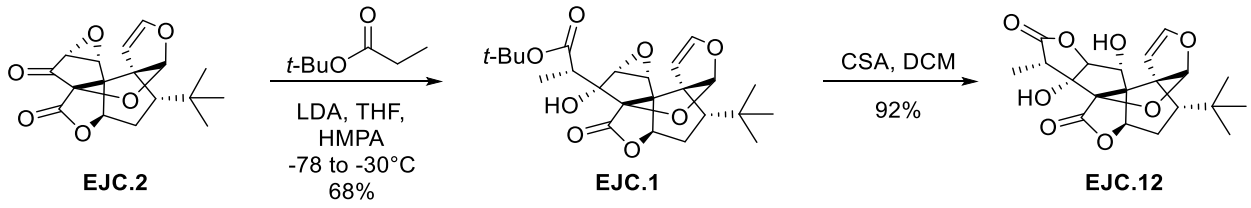
tri-butyl amine at reflux to get **EJC.6** with a yield of 80%. It is also important to note that during the reaction, *tri*-butyl amine hydrochloride was generated and catalyzed the elimination of the methoxy group at the anomeric position. This exemplar reaction allowed a streamline installation of the A and D ring system in a stereospecific fashion directed by the interaction with the bulky *t*-Bu group.

Scheme 3.3 – Key step in Corey's approach of (±)-ginkgolide B



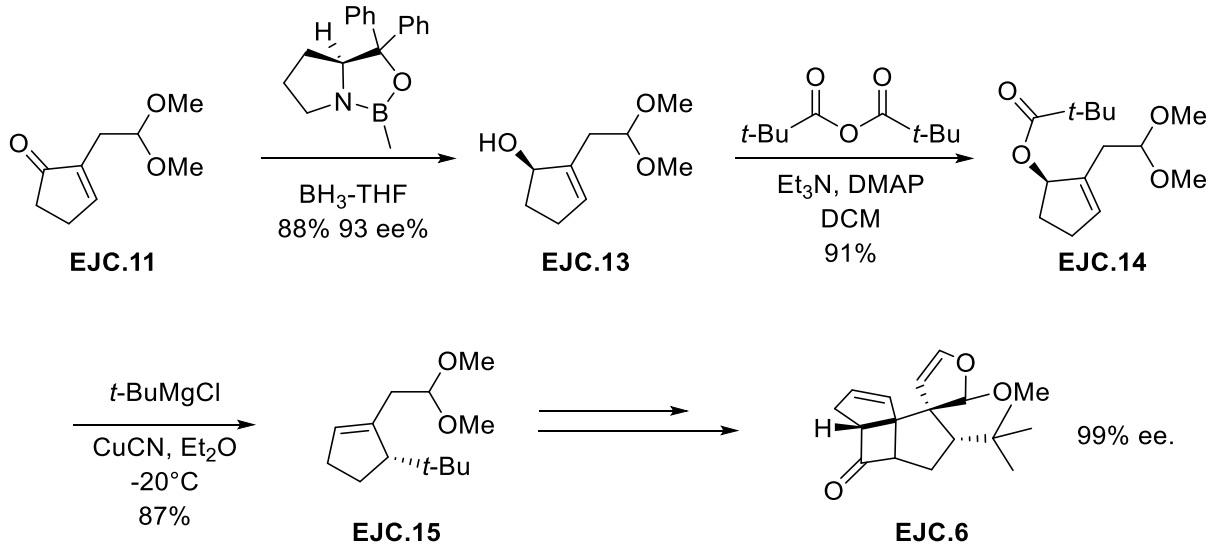
An issue of chemoselectivity arose, to finalize the formation of the D ring, a Baeyer-Villiger oxidation was needed without involving the two alkenes of intermediate **EJC.6** (***Scheme 3.3***). Unfortunately, *m*-CPBA was found to be unselective but the oxidation of the cyclobutanone was successfully achieved with triphenylmethyl hydroperoxide in presence of sodium hydroxide at -30˚C to give γ-lactone **EJC.5** in 86% yield.

Scheme 3.4 – Construction of the C ring system



Another captivating feature of the synthesis was the late stage installation of the C ring system through a highly selective aldol transform (***Scheme 3.4***). Treatment of *tert*-butyl propionate with LDA in a mixture of THF/HMPA and later exposure to **EJC.2** led to the highly stereospecific and chemoselective addition to give **EJC.1** as 8:1 mixture of diastereomers where the major diastereomer has identical relative stereochemistry to the one found in ginkgolides. Following the aldol condensation, the C ring was closed by treating **EJC.1** with CSA in DCM which induced the lactonization and epoxide opening to give **EJC.12.** The latter was converted to ginkgolide B (**3.2**).

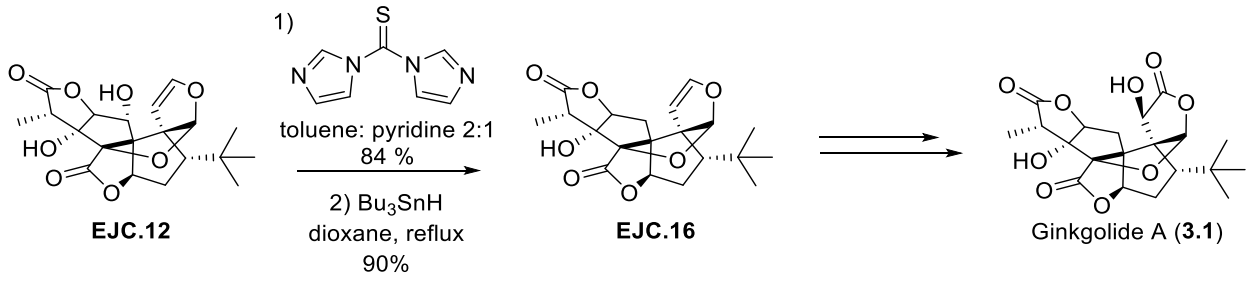
*Scheme 3.5 – Enantioselective route to **EJC.6***



In a later contribution, Corey et al. showed that **EJC.6** could be accessed enantioselectively with some simple modifications to the original route utilized to obtain ginkgolide B (***Scheme 3.5***).[128b] From enone **EJC.11**, they employed the Corey-Bakshi-Shibata reduction to obtain

alcohol **EJC.13** in 88% yield and 93% ee. The pivalate ester **EJC.14** was generated in presence of pivalic anhydride, Et_3N and DMAP. The chirality was set by means of an anti-S_N2' displacement following the treatment of **EJC.14** with *t*-BuMgCl in presence of catalytic CuCN which gave **EJC.15** in 87% yield. The following was then converted to **EJC.6** an intercepted intermediate of the original published route to ginkgolide B. After recrystallization, **EJC.6** was obtained in 99% ee. Thus, following this methodology, ginkgolide B could be synthesized in its naturally occurring enantiomeric form.

Scheme 3.6 – Corey's total synthetic approach to (±)-ginkgolide A



After publishing on ginkgolide B, Corey also developed a route to ginkgolide A[123] from late intermediate **EJC.12** (***Scheme 3.6***). He performed a selective deoxygenation of adduct **EJC.12** at C-1 through the formation of a thiocarbonylimadazole and its subjection to *tri*-n-butyltin hydride at reflux which afforded **EJC.16** in good yields.

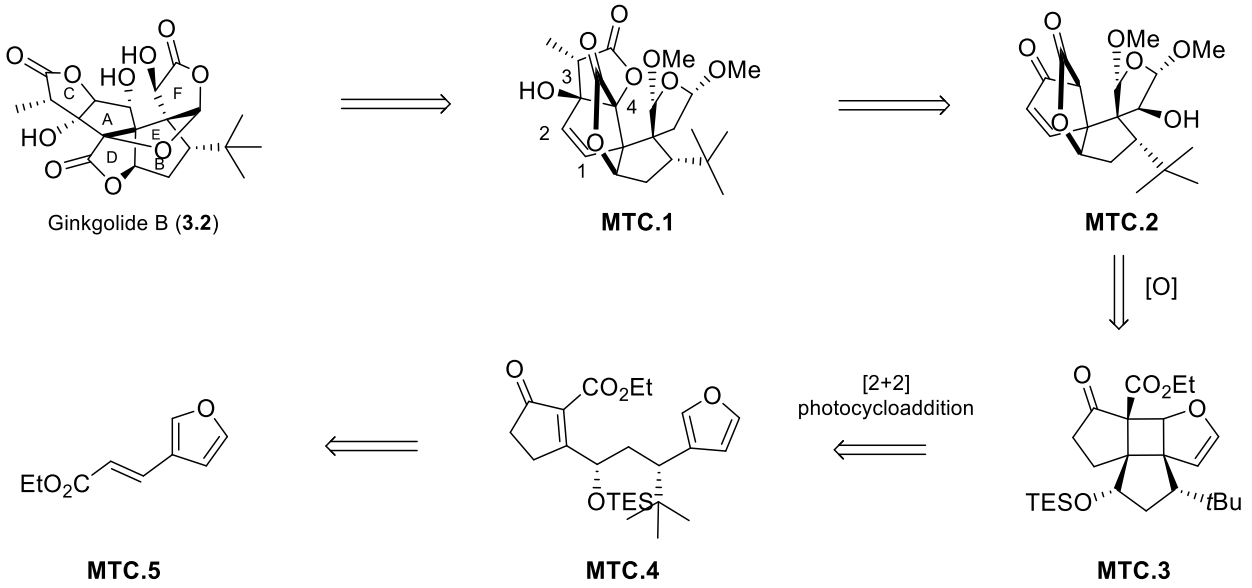
Overall, Corey's contribution provided insight to the challenges associated with this family of natural products and problematics linked to the many complex stereocenters and congested environment. The information furnished by his findings are vital to anyone ever wishing to engage in such targets. The comprehensive work of Corey's synthetic approach attest to why probably no other laboratory, other than Crimmins, tried to resolve the challenge that ginkgolides are.

3.1.3 Crimmins Strategy toward the synthesis of ginkgolides

Eleven years later, in 1999, Crimmins and co-workers were also successful in synthesizing Ginkgolide B (**2.2**).[124, 129] At its core, Crimmins' approach relies on a [2+2] photocycloaddition, a field of research in which he has been heavily involved.[130] The idea might resemble Corey's approach but Crimming opens the resulting cyclobutane ring to liberate the A-B-D-F ring system rather than a pre-synthon to one of the five-membered ring.

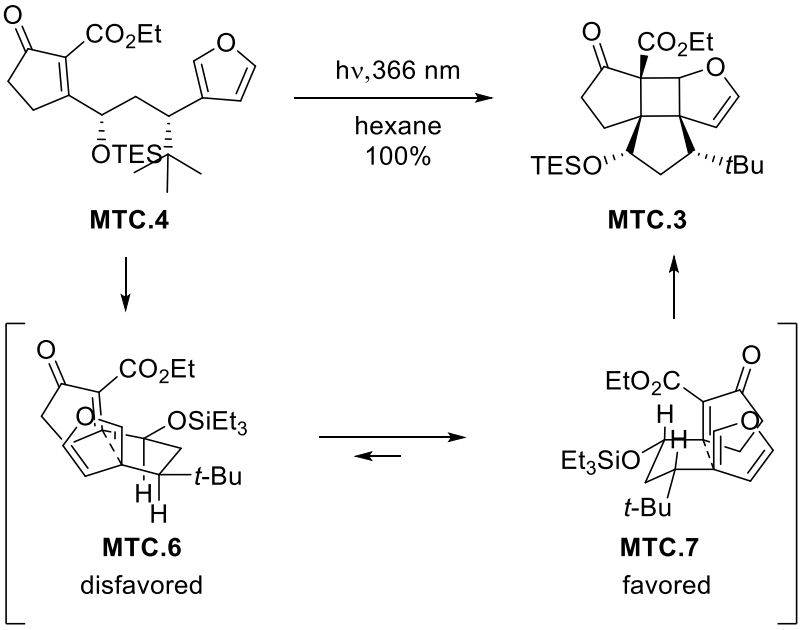
As a late synthetic plan, Crimmins and co-workers decided to adopt a similar strategy to Corey seminal work, a late installation of the C ring system (***Scheme 3.7***). Retrosynthetically, Ginkgolide B (**2.2**) resulted from the opening of γ-lactone **MTC.1** at C-4 under acidic conditions and the C ring system was synthesized using the epoxide/ oxylactonization trick of Corey. The γ-lactone of **MTC.1** was accessed through an α-hydroxylation of **MTC.2** at the ketoester positon C-4, followed by an esterification and intramolecular aldol condensation. **MTC.2** was the result of a fragmentation of the cyclobutane ring of **MTC.3** between C-4 and F ring. **MTC.3** was obtained after subjecting enone alkene **MTC.4** to a photo-induced [2+2] cycloaddition. This reaction allowed the crucial introduction of all the necessary functional group and moieties to pivotal intermediate **MTC.3** to carry forward the total synthesis of ginkgolide B. Finally, **MTC.4** was derived from furan ester **MTC.5** following a conjugate addition to install the *t*-Bu group and C-C bond formation sequence.

Scheme 3.7 – Crimmins' retrosynthetic approach of (±)-ginkgolide B



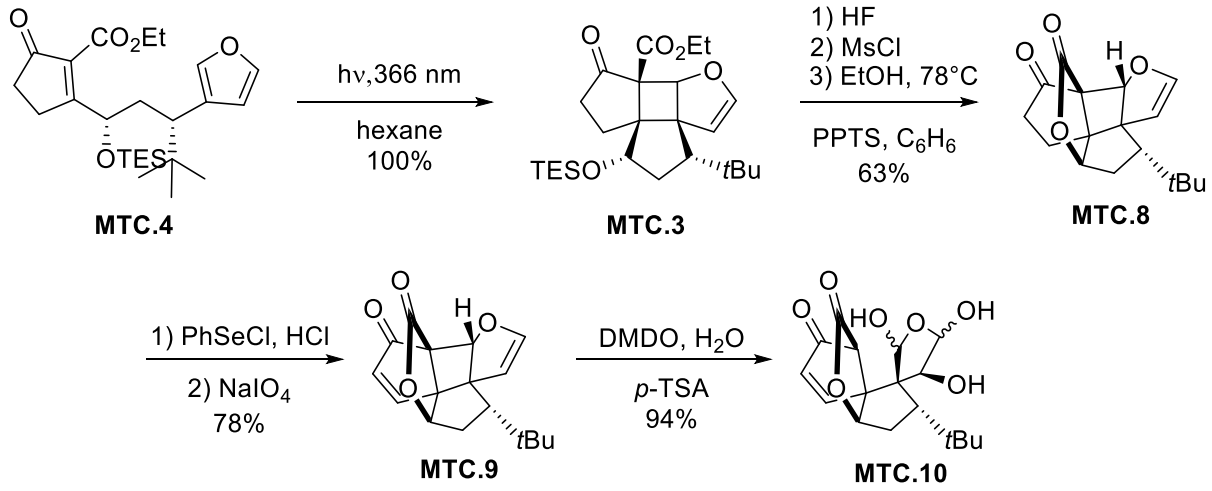
We will now briefly look at the key reactions that enabled the synthetic endeavor of Crimmins' group toward ginkgolide B (**2.2**). The intramolecular [2+2] photocycloaddition of **MTC.4** yielded, quantitatively, cyclobutane **MTC.3** with >98:2 diastereoselectivity, upon irradiation with 366 nm light (***Scheme 3.7***). It is proposed that **MTC.4** can adopt two conformations during the [2+2] (***Scheme 3.8***). In conformation **MTC.6**, the envelope of the future B ring is pointing up into the reactive site and the steric clash between the ester/TES group disfavor this conformation over **MTC.7**. In **MTC.7,** the envelope of the future B ring is pointing downward, away from the reaction site, and the steric clash between ester/TES group is minimized. Noteworthy, after much investigation it was found that the OTES group and *t*-Bu needed to be *syn*, otherwise poor diastereoselectivity incurred, favoring the unnatural diastereomer.[124b]

Scheme 3.8 – Origin of selectivity during the [2+2] photocycloaddition



Surprisingly, the cyclobutane ring of **MTC.3** was substantially more resilient to its opening then they originally anticipated. They predicted the bonds to be weakened by the electron withdrawing groups of the ketoester. However, the π overlap of the enol ether oxygen lone pair with the alkene was believed to diminish its donor ability, thus preventing the cyclobutane's rupture. Nevertheless, they proceeded with the construction of the D ring system by removing the TES group with hydrofluoric acid from **MTC.3**. Mesylation of the corresponding alcohol with MsCl and lactonization in EtOH afforded γ-lactone **MTC.8** with 63% yield over 3 steps (***Scheme 3.9***). Oxidation of **MTC.8** with PhSeCl and $NaIO_4$ gave enone **MTC.9**. They could now proceed with cleaving the cyclobutane ring. They found that selective oxidation of the vinyl ether alkene with DMDO allowed the fracture of the cyclobutane ring between C-4 and the F ring system in 94% yield to give **MTC.10** as a mixture of diastereomers at the anomeric positions. The latter was carried to ginkgolide B using a similar approach to Corey.

Scheme 3.9 – Key sequence in Crimmins' approach of (±)-ginkgolide B



3.2 Route A toward ginkgolide C: gold(I)-catalyzed Rautenstrauch approach

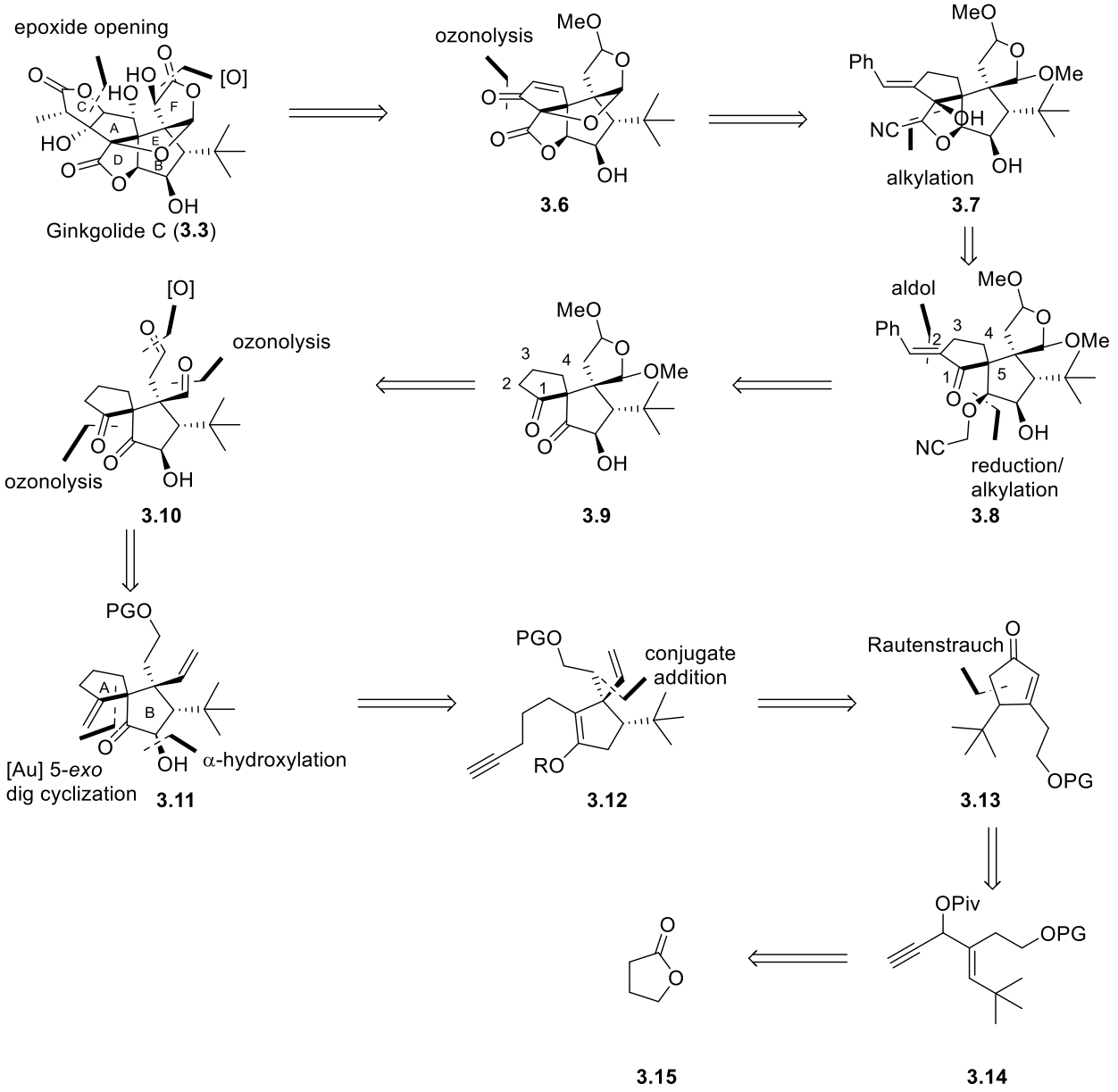
In approaching ginkgolide C (**3.3**), we reasoned that we should focus primarily on a robust strategy for the synthesis of the more complex B ring and the rest of the molecule should be more accessible. We also deliberately wanted to showcase the power of gold-catalysis in total synthesis by including two Au(I)-catalyzed key steps: a Rautenstrauch rearrangement to form the B ring and a 5-*exo* dig cyclization to construct the A-B spirobicycle ring system.

3.2.1 Retrosynthetic analysis

We envisioned that ginkgolide C (**3.3**) would come from enone **3.6**, closely related to **EJC.2** used by Corey (***Scheme 3.10***). Thus, we were planning on fashioning the C-ring as an end-game strategy similarly to Corey and Crimmins. Enone **3.6** would be the result of a sequence of ozonolysis/oxidation of alkene **3.7.** The D ring of **3.7** would be constructed by an intramolecular aldol addition of cyano methyl ether **3.8.** This method should provide the proper approach for the

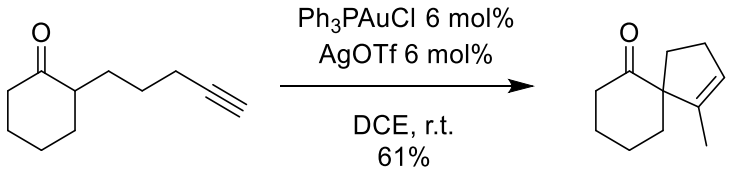
desired stereogenic center at C-1. Aldol condensation at C-2 of **3.9** with benzaldehyde and reduction/O-alkylation of the B ring ketone should give **3.8**. Under acidic conditions dialdehyde **3.10** should provide the F ring system. Deprotection/oxidation/oxonolysis of **3.11** should give **3.10**. The spirobicycle system A-B **3.11** would be the result of a 5-*exo* dig cyclization of vinyl enol ether **3.12** with the alkyne chain.

Scheme 3.10 – Retrosynthetic approach to ginkgolide C using the Rautenstrauch reaction



Davies and co-workers showed that the formation of spirobicycles is possible by gold catalysis.[131] Unsubstituted cyclohexanone **3.16** can undergo cyclization with PPh_3AuOTf to afford spiro[5.4]decane **3.17** (***Scheme 3.11***). We believed that this methodology would be amenable to the synthesis of **3.11**.

Scheme 3.11 – Formation of spirobicycle by 5-exo dig cyclization



3.16 **3.17**

Continuing with the retrosynthetic analysis, vinyl ether **3.12** would be the result of a conjugate addition of a vinyl group. The selectivity would arise from the steric clash prompted by the *t*-Bu during the organocuprate addition. We are now at another critical step in the synthesis with a second gold catalyzed cycloisomerization. The Rautenstrauch rearrangement should provide entry to the B ring of ginkgolides (for more information about the Rautenstrauch rearrangement look at section 1.3.3). This method would give us the opportunity to install the *t*-Bu group quite early in the synthetic endeavor. More importantly, it would provide all the necessary handles to build the rest of the molecule. Pivaloyl 1,4-enyne **3.14** would serve as the precursor to this rearrangement. Finally, γ-butyrolactone **3.15** would be the ultimate starting material only a few steps from 1,4-enyne **3.14**.

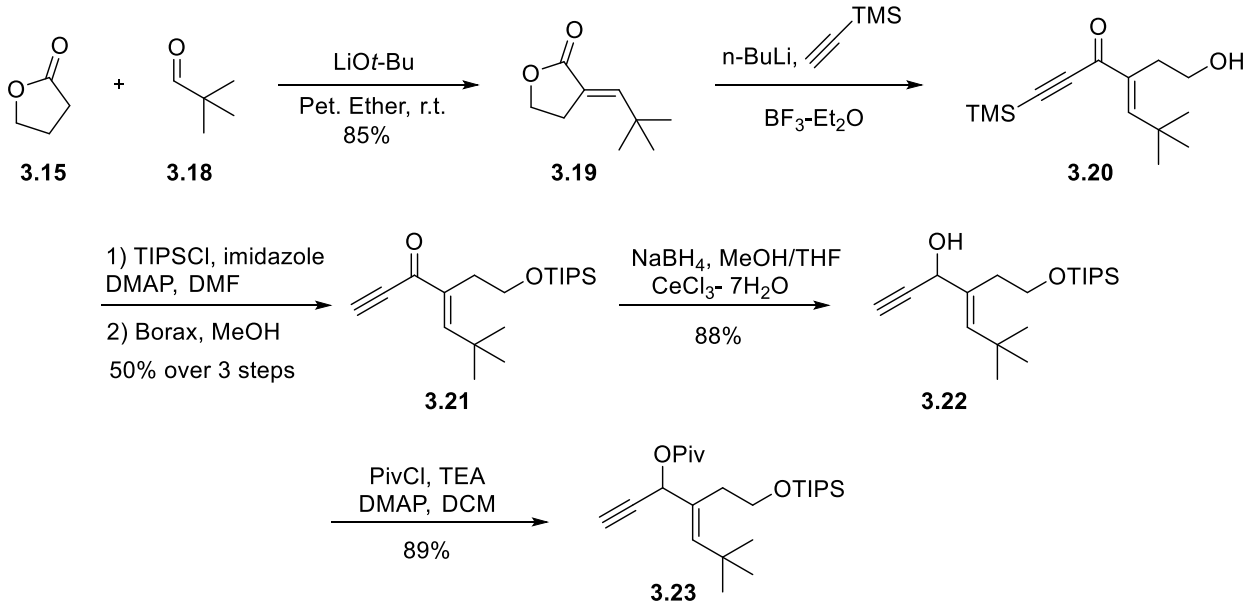
3.2.2 Optimization of the Rautenstrauch rearrangement

It is important to mention before going deeper in the subject at hand, that most of the work performed on the Rautenstrauch approach to ginkgolides was completed in collaboration with Dr. David Lapointe. He was able to establish a viable synthetic route to the enyne precursor **3.23**/**3.24** to the Rautenstrauch rearrangement. He also showed the rearrangement to work but was unable to optimize the process and go further in the synthesis.

This chapter will not be going into details on the problems associated with the development of the Rautenstrauch precursor **3.23/3.24** as it was well detailed in Dr. Davis Lapointe's thesis. We will focus instead on the optimization of the rearrangement and problems incurred in functionalizing the B ring toward the total synthesis of ginkgolide C.

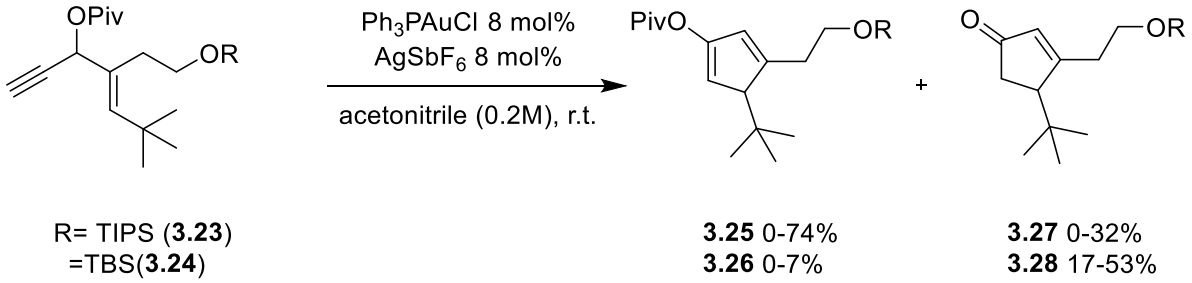
The synthesis of the Rautenstrauch precursor **3.23,** started with the treatment of γ-butyrolactone **3.15** with pivalaldehyde **3.18** to give aldol condensation product **3.19** (***Scheme 3.12***). This reaction was found to work best using lithium *tert*-butoxide in petroleum ether and exclusively yielded the *E* olefin in 85% yield. Lactone **3.19** was then added to a freshly prepared solution of deprotonated trimethylsilylacetylene in presence of BF_3 etherate to give enyne **3.20**. Alcohol **3.20** was then protected with TIPSCl in presence of DMAP/imidazole in a solution of DMF. The alkynyl TMS was subsequently removed using borax in MeOH to give ketoenyne **3.21** in 50% yield over 3 steps. Ketone **3.21** was reduced selectively using the Luche reduction. Sodium borohydride accompanied of cerium chloride heptahydrate afforded alcohol **3.22** in 88% yield. Treatment of alcohol **3.22** with PivCl, Et_3N and DMAP in DCM gave the Rautenstrauch precursor pivaloyl carboxylate **3.23** in 89% yield.

Scheme 3.12 – Synthesis of Rautenstrauch precursor



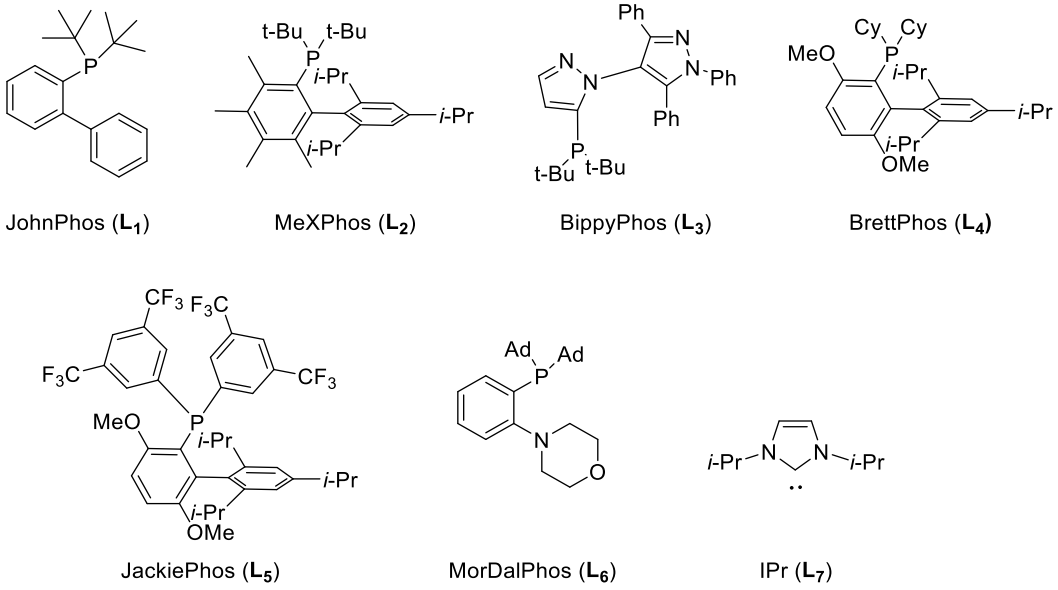
Originally, Dr. David Lapointe demonstrated that the Rautenstrauch rearrangement worked with $Ph_3PAuCl/AgSbF_6$ as the catalyst system in acetonitrile following the Toste report[46a] on the same reaction (***Scheme 3.13***). It was noted though, that the reaction was highly unreproducible. In the case of the TBS protected alcohol **3.24** for example, the desired enone **3.27** could be formed with up to 53% yield, yet the next time it only provided 17%. There was also another issue that arose with this reaction, the hydrolysis of intermediate **3.25** or **3.26** was never completed with up to 74% of unhydrolyzed product in the case of the cyclization of TIPS protected diene **3.25**.

Scheme 3.13 – Initial result of Au-catalyzed Rautenstrauch rearrangement by Dr. David Lapointe



This called for significant improvements, if we envisaged to apply this methodology to the synthesis of ginkgolides. We required a reproducible reaction, amenable on large scale. This was where I started contributing to this project with the optimization of the Rautenstrauch rearrangement. Since our laboratory has been involved in gold chemistry for a while now, this reaction was the perfect opportunity to test our library of gold catalysts. For this reaction we limited ourselves to gold salts catalysts with Buchwald-type ligands: JohnPhos (**L**$_1$), MeXPhos (**L**$_2$), BrettPhos(**L**$_4$); N-heterocyclic carbene IPr (**L**$_7$); Stradiotto's ligand MorDalPhos (**L**$_6$) and BippyPhos (**L**$_3$) originally developed by Pfizer (***Figure 3.3***).[132]

Figure 3.3 – Ligands used to catalyze the Rautenstrauch reaction

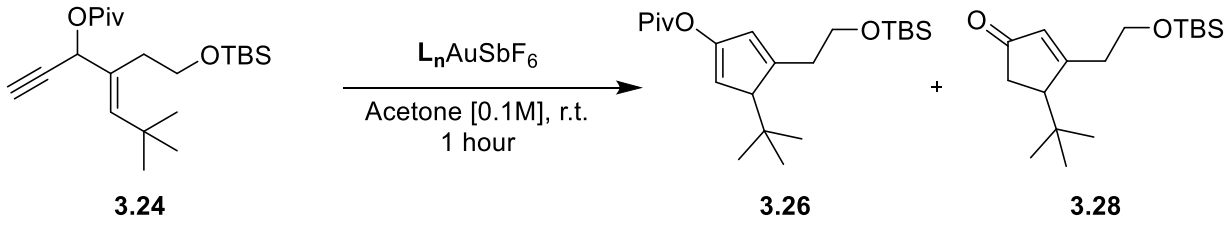


Looking at Dr. David Lapointe results, I suggested that TBS protected enyne **3.24** was probably the more appropriate adduct to perform the preliminary testing as it offered better yields in his original findings. In a first time, a catalyst screening was performed in acetone at a concentration of 0.1 M (***Table 3.1***). The gold catalysts used were all pre-formed gold salts which served two purposes. The first was the ease of manipulation and second to minimize the silver

present in solution. Through my experience with gold catalysis, I found that sometimes silver can have a negative effect on the reaction results especially when the reactive catalyst is formed *in situ* like in the case of the $Ph_3PAuCl/AgSbF_6$ system where the $[Ph_3PAuSbF_6]$ is filtered from insoluble AgCl but often leaves unreacted $AgSbF_6$ solubilized. A recent paper by Shi and co-workers coined the term "silver effect" to explain large discrepancies that exist between reaction that are said to be catalyzed by gold but actually require silver to undergo the described transformation.[133] Whereas with gold salts catalyst, one can recrystallize them to increase their purity. Usually the silver impurities leave a silver/gray hue to the gold white salts which disappear completely after 2-3 recrystallizations.

During the initial ligand optimization, we found that $\mathbf{L_{5\text{-}8}}$ (entries 5-8) where ill-performing ligands for this transformation as they led to poor conversion. MeXphos ($\mathbf{L_2}$) (entry 2) appeared to be the strongest catalyst with an NMR yield of 57 % (***Table 3.1***). $\mathbf{L_1}$ (entry 1) afforded only 29% yield but was found to be an extremely fast, the reaction was done in less than 5 minutes. $\mathbf{L_{3\text{-}5}}$ all afforded comfortable yield varying from 38 to 46 % (entries 3-5). Further attempts at optimizing $\mathbf{L_{3\text{-}5}}$ did not provide better yields.

Table 3.1 – Ligand effect on Rautenstrauch reaction catalyzed in acetone



3.24 **3.26** **3.28**

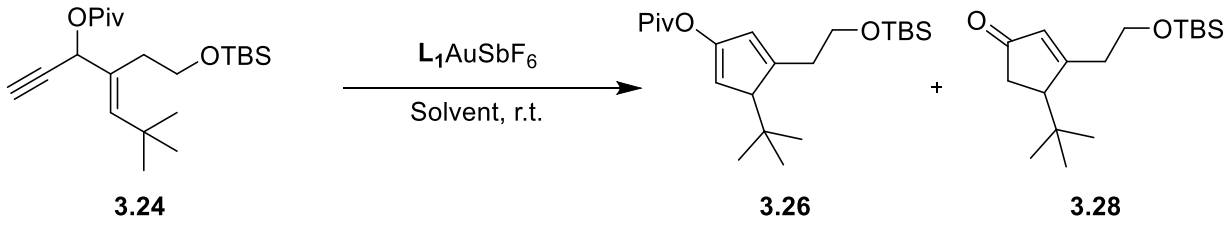
Entry	Ligand	3.28	3.26	Combined yield
1	$\mathbf{L_1}$	29	0	29
2	$\mathbf{L_2}$	57	0	57

3	**L_3**	42	0	42
4	**L_4**	46	0	46
5	**L_5**	38	0	38
6	**$L_6 - BF_4$**	8	0	8
7	**L_7**	11	2	13
8	**L_8**	20	0	20

*NMR yields with mesitylene as standard

A solvent screen was carried out with JohnPhosAuSbF$_6$, the results of which can be found in ***Table 3.2***. Chlorinated solvents (entries 1, 2, 5-7) where found to be all suitable to the reaction but with low yields of enone **3.28**. When the reaction was performed in DCM (entry 6) for an extended period of time, 22% yield was obtained and when the same reaction was diluted to a concentration of 0.01 M (entry 7) yields increased to 36%. Further dilution did not improve the yields but increased dramatically the reaction time. Interestingly, chloroform (entry 5) was found to give the highest combined yields so far but allowing only very slow hydrolysis of diene **3.26** probably due to its low solubility with water. This particular entry gave important insight on the problems associated with this reaction which subsequently resonated with the rest of the experiments. The cyclization to pivaloyl diene **3.26** was a fast reaction that normally occured in a clean fashion but the hydrolysis of **3.26** toward enone **3.28** appeared problematic. Probably through an intermolecular process since lower concentration helped to increase the yields. Finally, it was found that exposure of enyne **3.24** to **L_1**AuSbF$_6$ for three days in acetonitrile (entry 8) yielded 66% of enone **3.28** at low concentration.

Table 3.2 – Solvent effect on Rautenstrauch reaction catalyzed by JohnPhosAuSbF$_6$



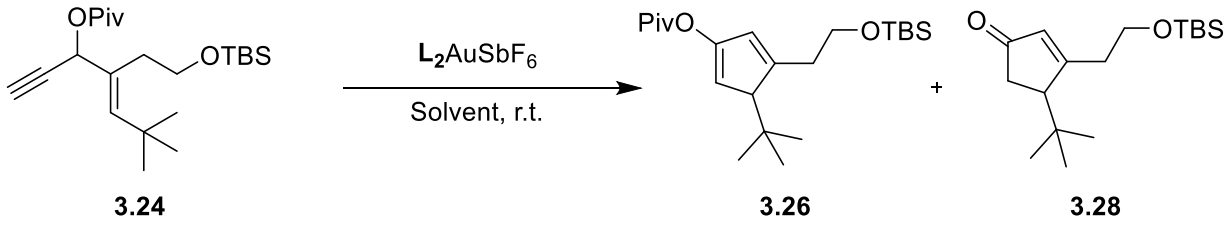
3.24 **3.26** **3.28**

Entry	solvent	Time (hours)	[C]	3.28	3.26	Combined yield
1	DCM	1	0.1	18	0	18
2	DCE	1	0.1	28	0	28
3	Acetone	1	0.1	29	0	29
4	Toluene	1	0.1	22	0	22
5	$CHCl_3$	2	0.1	19	57	76
6	DCM	2	0.1	22	0	22
7	DCM	2	0.01	36	0	36
8	MeCN	72	0.01	66	0	66

*NMR yields with mesitylene as standard

A solvent screen with MeXPhos (**L$_2$**) (***Table 3.3***) was also performed and revealed a much slower reaction than with JohnPhos (**L$_1$**). Satisfyingly though, the slower kinetics of the reaction induced better yields of enone **3.28** overall. Unhydrolyzed adduct **3.26** was also present in considerable amount in most entries. Entries 2, 3 and 4 demonstrated the effect of the concentration on the reaction. A concentration of 0.2M in acetone allowed the reaction to go faster but delivered only 39% of **3.28** whereas in the more dilute setting of entry 3, 74% of **3.28** was obtained over 12 hours. Over-dilution to 0.01M delivered a combine **3.28**+**3.26** yield of 89% over 3 days but only 23% of enone **3.28**. When the reaction was catalyzed in THF, polymerization of the solvent occurred. Chlorinated solvents (entries 1,7,8) gave fast cyclization to **3.26** but would undergo hydrolysis extremely slowly.

Table 3.3 – Solvent effect on Rautenstrauch reaction catalyzed by MeXPhosAuSbF$_6$



3.24 **3.26** **3.28**

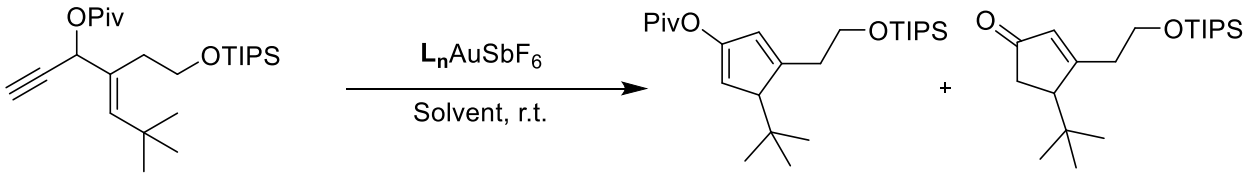
Entry	solvent	Time (hours)	[C]	3.28	3.26	Combined yield
1	DCM	2	0.1	36	4	40
2	acetone	72	0.01	23	66	89
3	acetone	12	0.1	74	0	74
4	acetone	1	0.2	39	11	50
5	THF	12	0.1	0	0	0
6	$MeNO_2$	12	0.1	17	21	38
7	$CHCl_3$	1	0.1	12	59	71
8	DCE	1	0.1	11	58	69

*NMR yields with mesitylene as standard

In summary, two solvents stood out for the catalysis of Rautenstrauch rearrangement: acetone and acetonitrile are respectively fast and slow solvents for this transformation. For the catalyst, **L$_1$** proved to be the fastest while **L$_2$** was the slowest. A combination of a fast solvent and slow catalyst seemed to offer the best yield of enone **3.28**. With **L$_1$**, the best reaction conditions afforded the desired product **3.28** (66%) in acetonitrile over 72 hours. With **L$_2$**, the best yield was obtained in acetone at a concentration of 0.1 M over 12 hours for 74%. It was discovered later that purification by flash chromatography of the crude incurred a loss in isolated yield that could amount up to 20% of the expected NMR yield. It was also distinguished that the reaction using **L$_2$** as the ligand offered decreased yields as the reaction was scaled up.

For these reasons, we decided to investigate a modified starting material **3.23**. It was found that the TIPS protected enyne **3.23** reacted in a similar fashion with $\mathbf{L_2}$ as the ligand in acetone and gave **3.27** in 73% yield over 3 days (entry 1) (***Table 3.4***). As discussed previously, the utilization of MeXPhos ($\mathbf{L_2}$) seemed to be problematic when scaling up. Some stable conditions were engineered using Johnphos ($\mathbf{L_1}$) as the ligand. In the case of enyne **3.23**, gold catalysis ran in chloroform would cycloisomerize **3.23** to **3.25** exclusively. **3.25** was isolated as the sole product with up to 90% yield in chloroform. We thought we could combine the fast hydrolysis of **3.25** in acetone with the benefit of a clean cycloisomerization in chloroform. By running the reaction first in chloroform with $\mathbf{L_1}AuSbF_6$ at 0.1M for one hour (entry 3) and then adding acetone, we could now increase the yield of enone **3.27** to 68% yield. It was later found that only 20 minutes was sufficient (entries 4 and5) to have full conversion of the starting material. This methodology also seemed to be amendable to large scale as 3.5g and 7g batches gave reproducible results.

Table 3.4 – Optimized results for the Rautenstrauch rearrangement



3.23 **3.25** **3.27**

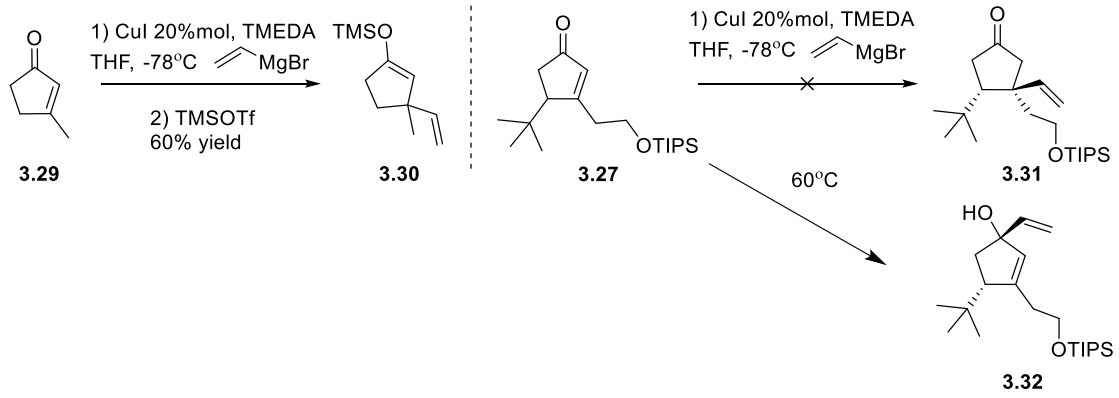
entry	solvent	catalyst	Rx time (min)	[C]	3.27	3.25	Combined yields	Comments
1	Acetone	$\mathbf{L_2}$	72h	0.1	73	0	73	50mg scale
2	Acetone	$\mathbf{L_2}$	72h	0.01	23	66	89	50mg scale
3	Chloroform then acetone	$\mathbf{L_1}$	60 and 60	0.1	68	0	68	50mg scale
4	Chloroform then acetone	$\mathbf{L_1}$	20 and 20	0.05	66	0	66	3.5g scale
5	Chloroform then acetone	$\mathbf{L_1}$	20 and 20	0.05	65	0	65	7g scale

*Isolated yields

In conclusion, two distinct techniques were used to perform the cycloisomerization converting enyne **3.23** to cyclopentenone **3.27**. The first method used $\mathbf{L_2}AuSBF_6$ as catalyst and required 72h at a concentration of 0.1M to give 73% of **3.27** on 50mg scale. The second set of conditions took advantage of the fast-acting $\mathbf{L_1}AuSbF_6$ with a mixture of chloroform/acetone as the solvent system to give 68% yield of **3.27** as a highly scalable process.

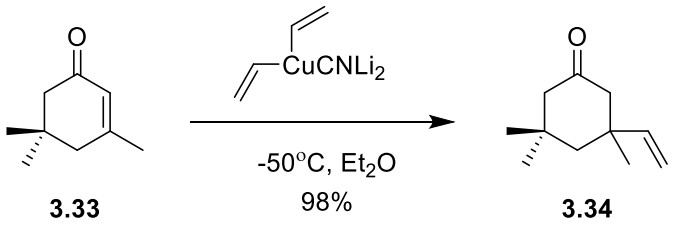
With the problem of the Rautenstrauch reaction now resolved, we could continue our efforts toward ginkgolide C. We reasoned that with enone **3.27** in hand, we would easily be able to perform a conjugate addition controlled by the *t*-Bu group to form the quaternary carbon of the future F ring. Preliminary work on the conjugate addition was done by Dr. David Lapointe where he showed the ability of model substrate **3.29** to undergo smooth conjugate addition with catalytic CuI, TMEDA and vinyl magnesium bromide at -78˚C (***Scheme 3.14***). Unfortunately, when the same methodology was applied to enone **3.27** nothing but starting material was isolated. Upon heating to room temperature, again only starting material was observed. Elevated temperatures (60˚C), exclusively led to 1,2 addition product **3.32** as a single diastereomer. This was an early sign that we would need to resort to extraordinary methods to install the quaternary center.

Scheme 3.14 – Conjugate addition essays



We were quickly stopped, as we found that enone **3.27** was unreactive toward conjugate addition of normal organocuprate reagents. We then decided to investigate Lipstutz[134] and Alexaskis[135] extensive work on difficult conjugate addition. Early on, Lipstutz recognized that the conjugate addition of congested enone was problematic and developped a new series of organocuprate reagents capable of facilitating those transformations. For example, he was able to install a vinyl group and create a new quaternary carbon onto enone **3.33** with a higher order organocuprate reagent (***Scheme 3.15***). He later disclosed similar addition reaction with lithium vinyl 2-thienylcyanocuprate.

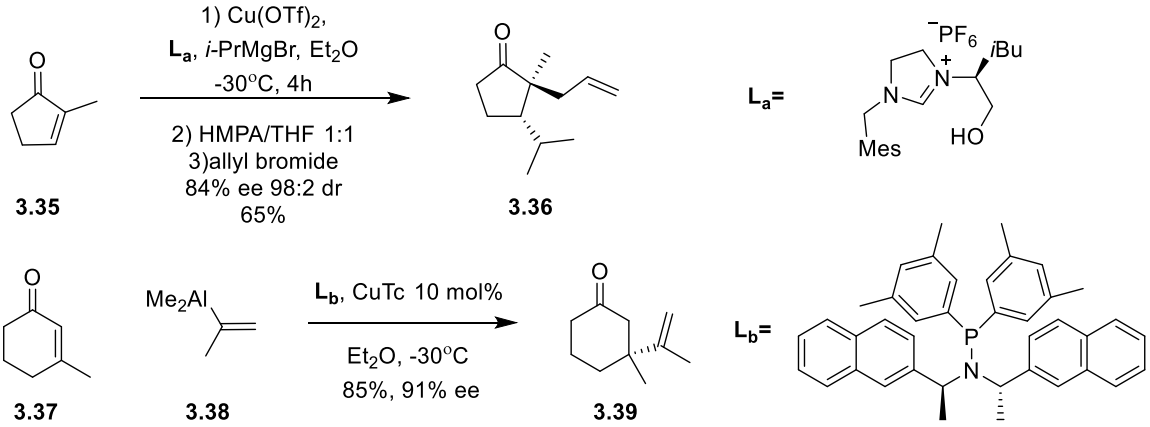
Scheme 3.15 – Lipstutz's conjugate addition of a vinyl group onto hindered enone



3.33 **3.34**

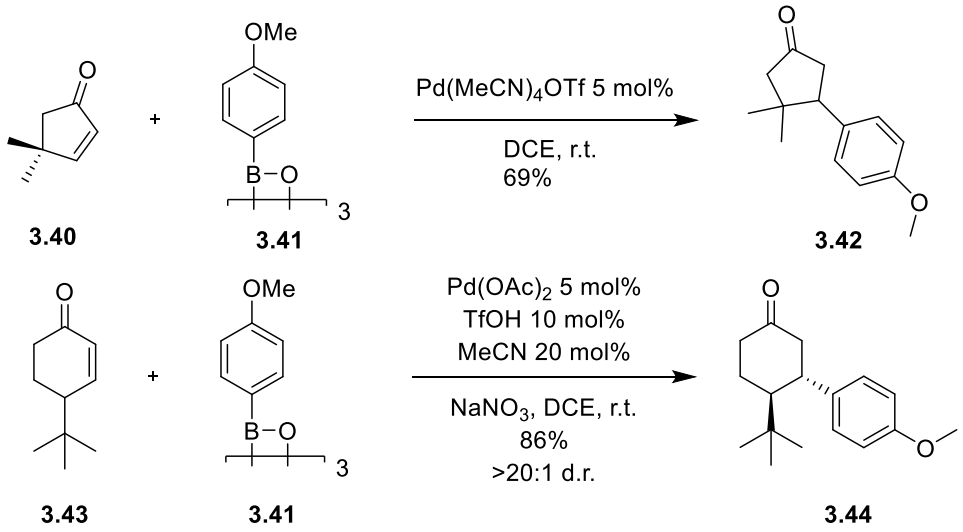
Alexakis has been involved actively in asymmetric conjugate addition (ACA). Although we were not interested in an ACA because the *t*-Bu would be controlling the addition, the work of his laboratory and contributors on congested system gave us the inspiration to try these reaction conditions. He showed that the formation of contiguous quaternary and tertiary stereocenters could be achieved by sequential asymmetric conjugate addition and Mg-enolate trapping of **3.35** to **3.36** (***Scheme 3.16***). Even though the conjugate additions were traditionally done with magnesium and lithium nucleophiles, Alexakis demonstrated that aluminum alkyls accelerated and, even enabled additions that would not work with other nucleophiles. The rationale was attributed to the high Lewis acidity of the alane activating the enone toward conjugate addition. For example, quaternary carbon of ketone **3.39** was easily made from enone **3.37** and alane **3.38** in presence of CuTc.

Scheme 3.16 – Alexakis' asymmetric conjugate addition in crowded environment



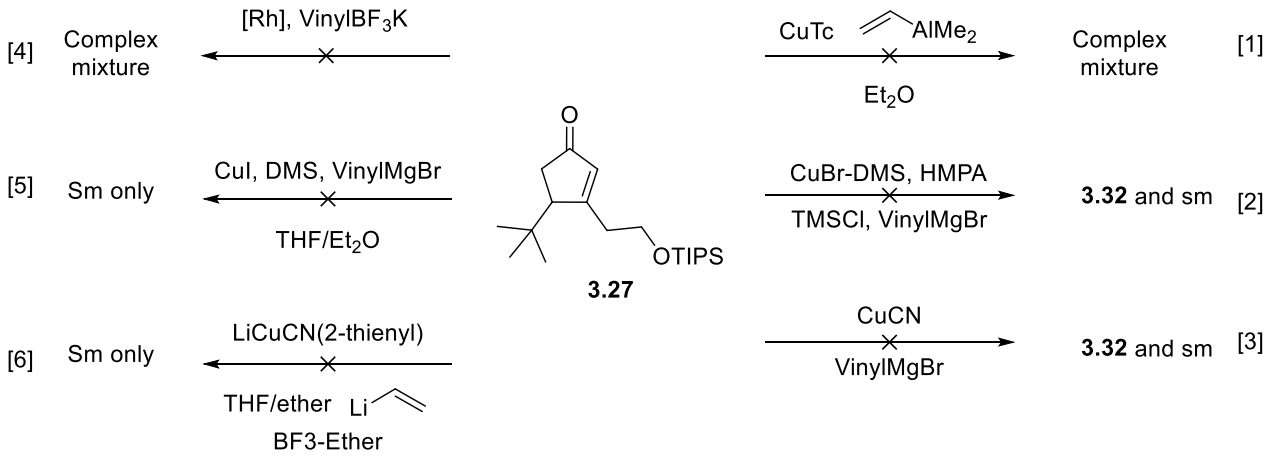
The construction of congested carbon-carbon bonds through conjugate addition was still an unresolved problem but Lee *et al.*[136] have been able to install aromatic rings next to highly hindered γ-substituted enones (***Scheme 3.17***). Even though this method was not compatible with the synthesis of ginkgolides, since it only worked with arenes, the scope undertaken by the authors highly resembled the steric engendered by our starting enone **3.27**. In the first example, they were able to perform a conjugate addition to γ-*gem*-dimethyl cyclopent-2-enone (**3.40**) and in the second example highlighted they were able to perform the addition next to a γ-*t*-Bu group (**3.43**).

Scheme 3.17 – Palladium catalyzed conjugate addition in highly hindered adducts



Following the high amount of conditions for conjugate additions, we chose to focus our attention on the ones that were successful in crowded environments (***Scheme 3.18***). Submission to the set of condition 1, where vinyl alane is the nucleophile, we obtained a complex mixture of products and no identifiable 1,4-addition. Conditions 2 and 5 with copper bromide and copper iodide respectively in presence of various additives like HMPA and TMSCl known to help conjugate addition, still provided only starting material or 1,2-addition product **3.32**. Rhodium (condition 4) also known to catalyze conjugate additions, normally on less congested system, provided degradation. Vinyl 2-thinyl heteroorganocuprate (condition 6) and vinyl higher order organo cuprate (condition 3) were also fruitless.

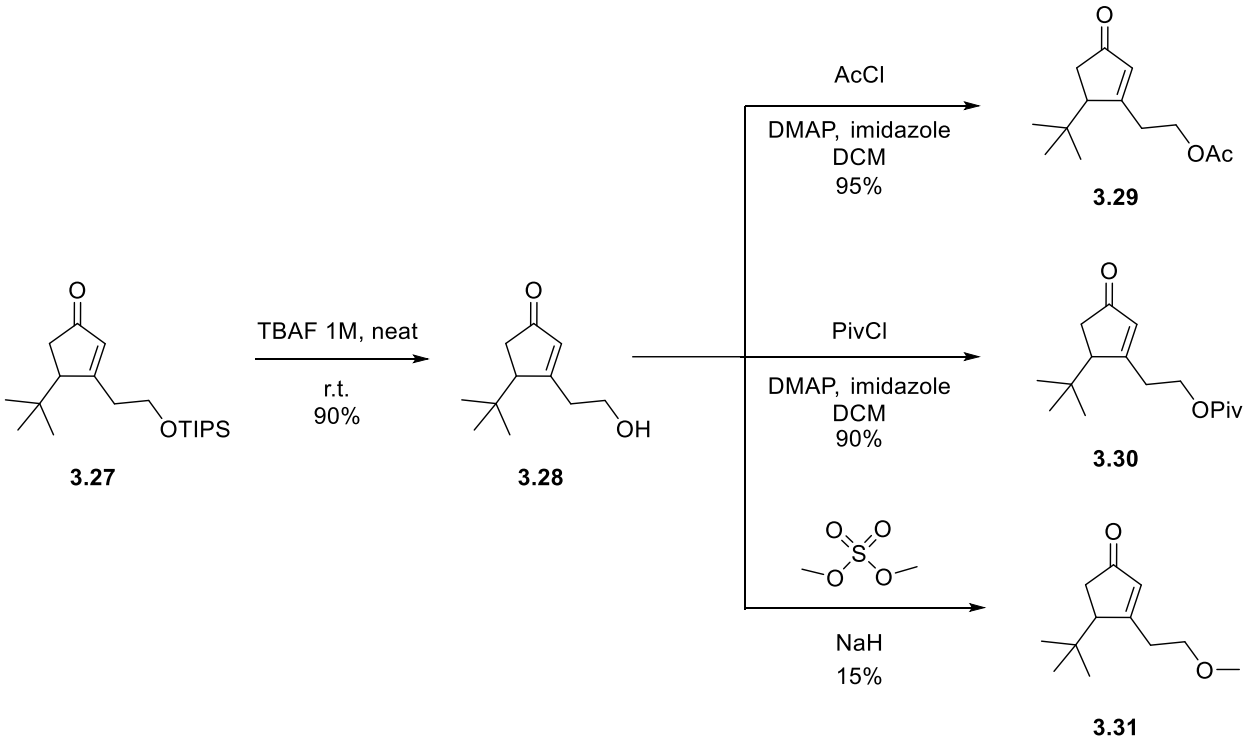
Scheme 3.18 – Conjugate addition trials



Conjugate addition to enone **3.27** proved to be more difficult than anticipated. We wondered if this could be attributed to the bulky TIPS protecting group that would disrupt the supramolecular complex necessary during the conjugate addition. To test this hypothesis, we deprotected enone **3.27** with TBAF to give primary alcohol **3.28** (***Scheme 3.19***). We were then able to protect the alcohol under standard conditions with an acyl to give **3.28**, pivaloyl to give **3.30** and a methyl to give **3.31**. The latter was introduced as the smallest protecting group possible

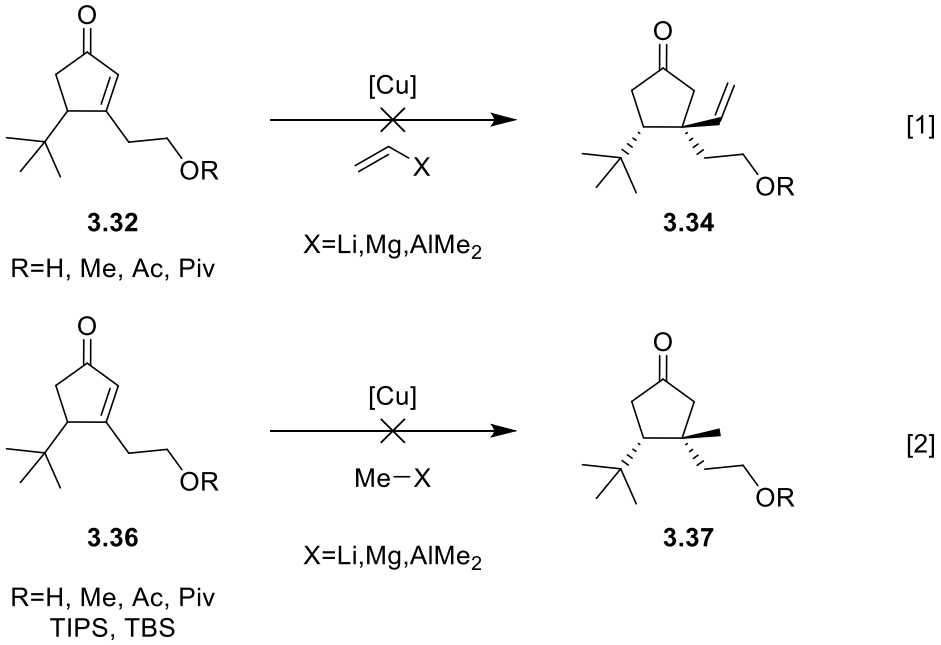
to test this hypothesis. We also contemplated the idea that ester **3.29** and **3.30** would help the conjugate addition by directing the approach of the organocuprate reagent.

*Scheme 3.19 – Changing protective group of β-chain of enone **3.27***



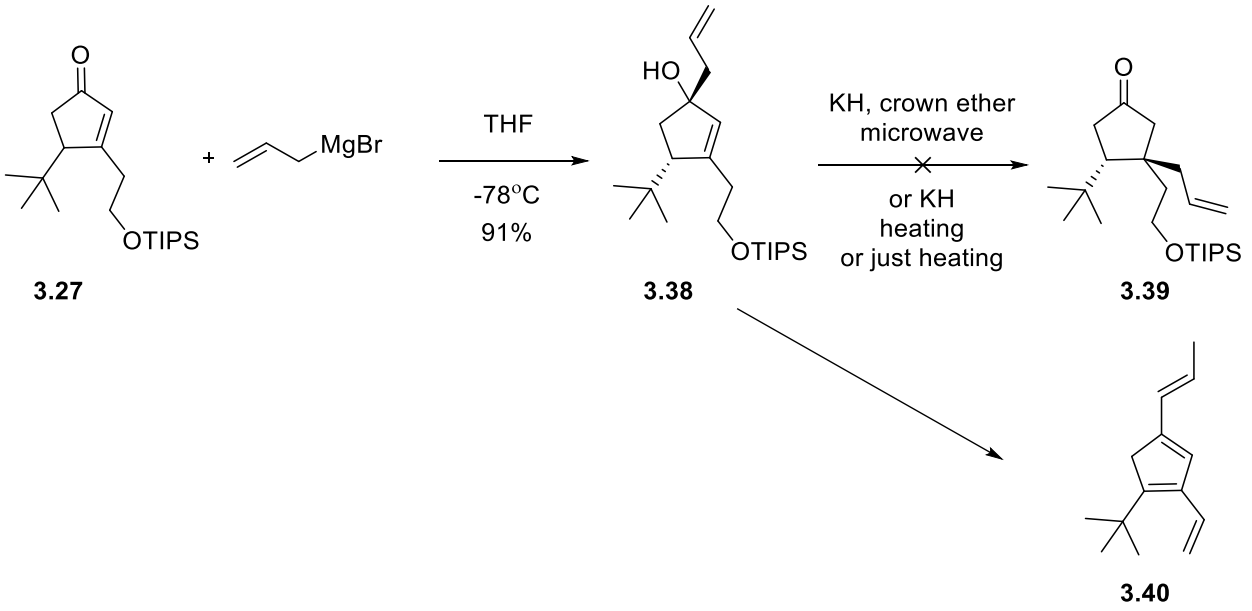
Unfortunately, our original hypothesis proved to be wrong as showed by equation [1] (***Scheme 3.20***). We were unable, under any set of conditions and type of nucleophile, to perform a conjugate addition on scaffold **3.32**. The reaction always resulted in recovery of starting material or 1,2-addition. We wondered if the problem was linked to the utilization of a vinyl nucleophile as it has been noted that vinyl cuprate species are more difficult reagent during conjugate addition then their methyl counter-part better known as the Gilman's reagent. Unfortunately, we were never able to install a methyl group either under any circumstances. Overall, the conjugate addition onto enone **3.27,** in our hands, proved to be inoperable. In light of these experiments, it was clear that we needed to find an alternative route to functionalizing the quaternary carbon alpha to the *t*-Bu.

Scheme 3.20 – Failure during the conjugate addition



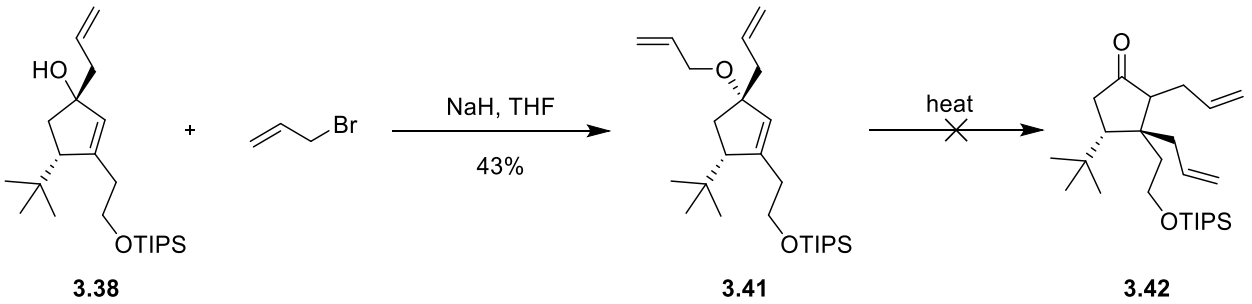
Since the more direct approach of conjugate additions was leading nowhere, we decided to investigate intramolecular processes as a way to generate the desired quaternary carbon. Since previous experiments showed that addition to the ketone to be facile, we examined the Oxy-Cope rearrangement (***Scheme 3.21***). Using allylMgBr, 1,5-diene **3.38** was obtained in 91% yield. The latter is submitted to typical thermal oxy-cope condition but no reaction occured or degradation incurred upon over-heating (>150˚C). Using KH and 18-crown-6 ether led exclusively to double elimination adduct **3.40**. Interestingly, even though we did not envision the elimination of the –OTIPS group as a possible outcome from this reaction, it proved to be a fairly general degradation pathway of substrate **3.38** and alike as it was reported at numerous occasion during the extent of our research.

Scheme 3.21 – Oxy-Cope rearrangement tryouts



In a similar vein, we examined a tandem oxy-Cope/Claisen rearrangement of triene **3.41** (***Scheme 3.22***). Triene **3.41** was synthesized in 43% yield by treatment of tertiary alcohol **3.38** with allyl bromide and sodium hydride. Upon heating of **3.41** no distinguishable product was observed, a black tar resulted.

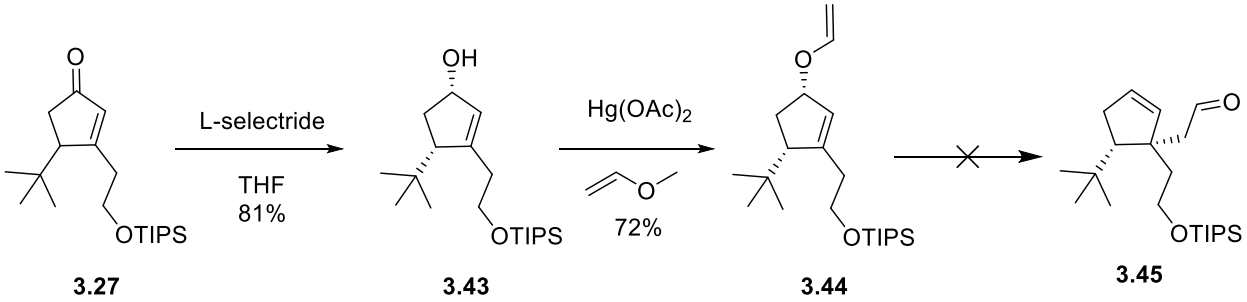
Scheme 3.22 – Tandem Cope/Claisen rearrangement.



Staying in the realm of sigmatropic rearrangement, we sought to perform the Claisen rearrangement of vinyl ether **3.44** (***Scheme 3.23***). To construct **3.44**, we selectively reduced enone **3.27** with L-selectride to get alcohol **3.43** diastereoselectivly and the vinyl ether **3.44** was formed in presence of methyl vinyl ether and mercury diacetate. Noteworthy, the utilization of sodium

borohydride led to the unselective reduction of ketone **3.27** (3:1 dr) and left the alkene untouched. Regrettably, the Claisen rearrangement did not produce the desired aldehyde **3.45**, no determinable product could be isolated.

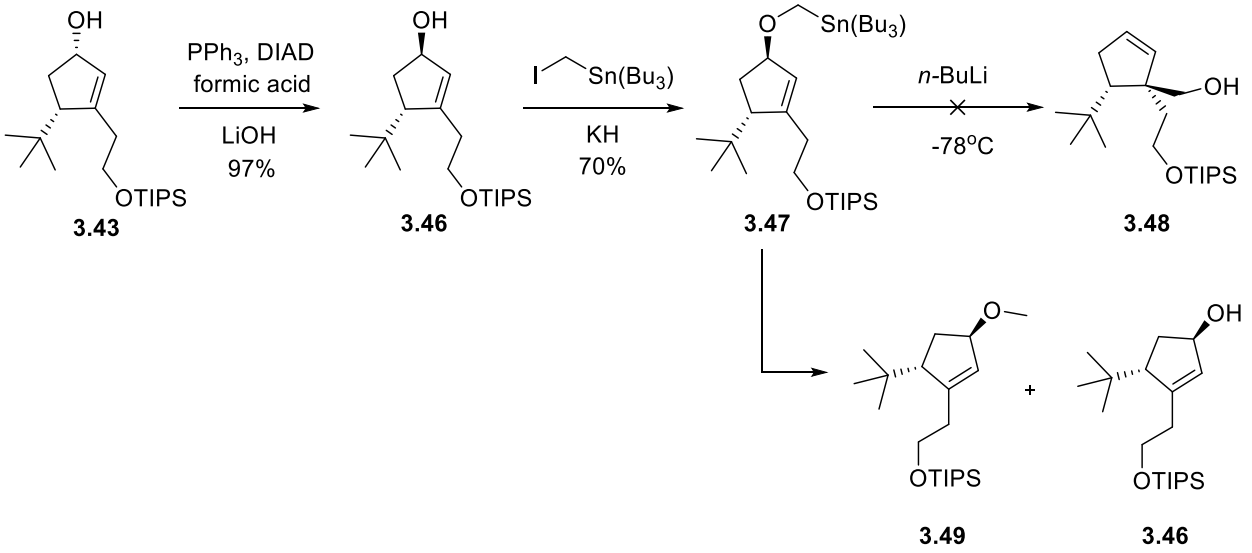
Scheme 3.23 – Claisen rearrangement



3.27 **3.43** **3.44** **3.45**

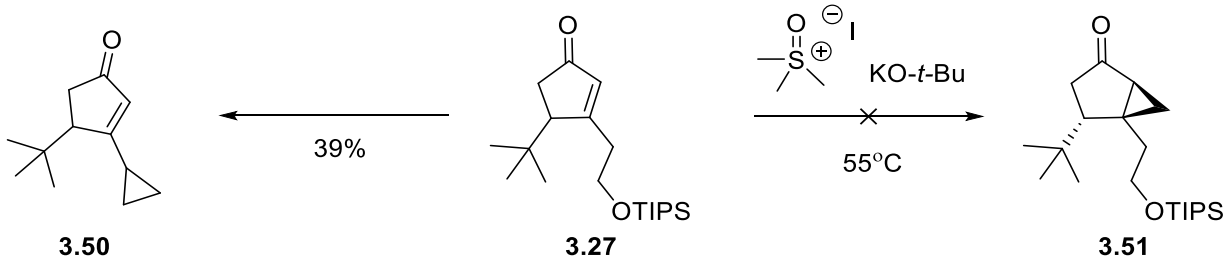
We attempted a last sigmatropic rearrangement by employing the [2,3]-Wittig rearrangement (***Scheme 3.24***). Since the smaller chain of the quaternary center needed to be anti to the *t*-Bu in the ginkgolides we inversed the stereochemistry of alcohol **3.43** by means of a Mitsunobu reaction to **3.46**. Stannyl methyl ether **3.47** was formed by treating alcohol **3.46** with KH and (iodomethyl)*tri*-butyltin. To our surprise, Wittig rearrangement precursor **3.47** did not led to alcohol **3.48**. Instead, methyl ether **3.49** resulting from the unrearranged methyl anion following the addition of n-BuLi and the free alcohol **3.46** were obtained. This rearrangement usually occurs at low temperature but even upon heating to r.t., the substrate was not converted to the desired product.

Scheme 3.24 – [2,3]-Wittig rearrangement



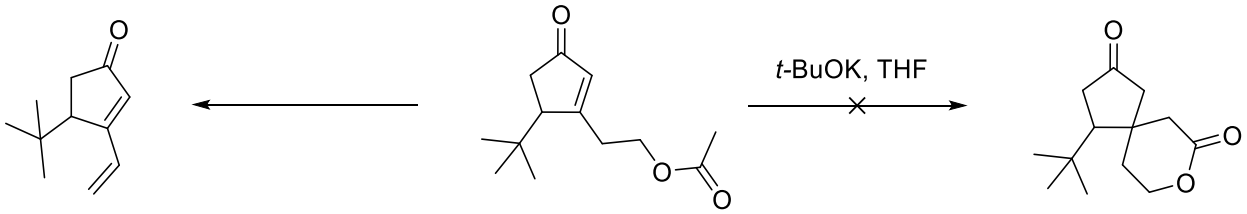
In an effort to substitute the alkene, we performed a Corey-Chaykovsky cyclopropanation. This reaction can be performed using dimethylsulfonium methylide or dimethyloxosulfonium methylide but enone **3.27** was unmoved by the first. Dimethyloxosulfonium methylide (S***cheme 3.25***) on the other hand, led to the exclusive formation of cyclopropane **3.50** resulting from an elimination of the silyoxy ether group and subsequent 1,6-addition to give adduct **3.50**. Frustratingly, once again the β-position remained intact.

Scheme 3.25 – Corey-Chaykovsky cyclopropanation



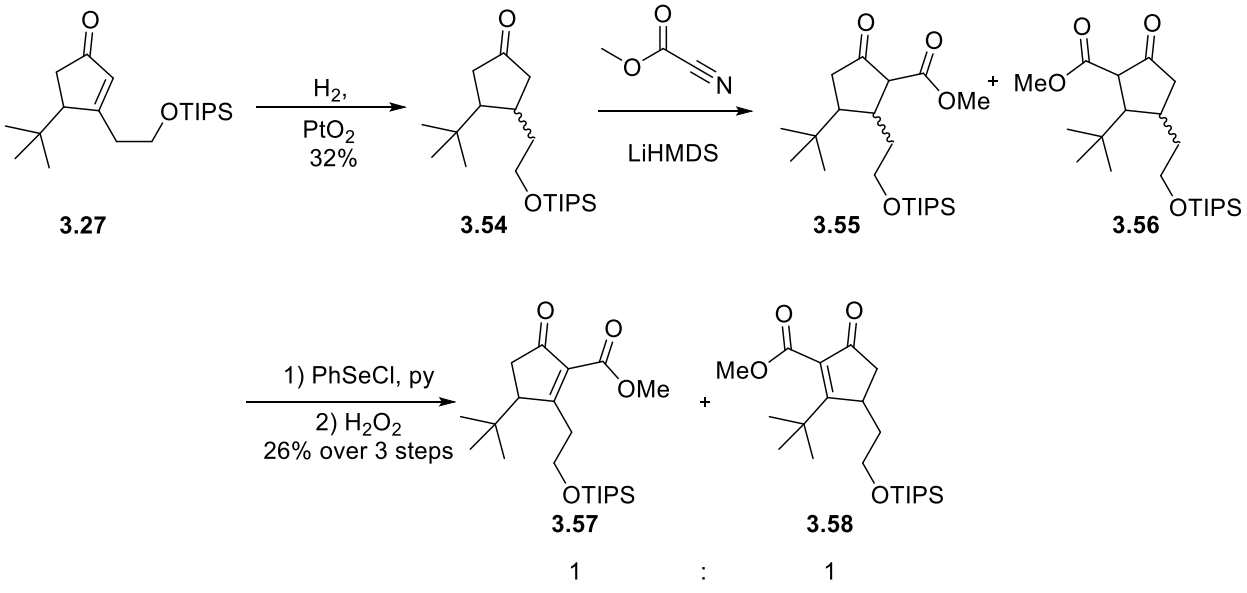
We also suggested that acetate protected enone **3.29** could undergo an intramolecular Michael addition to give spirobicycle **3.52** (***Scheme 3.26***). Deceptively, this yielded solely the elimination product **3.53** in almost quantitative yield.

Scheme 3.26 – Intramolecular Michael addition



In our last attempt at functionalizing the enone, we decided to investigate the installation of an α-ester to increase the enone electophilicity toward conjugate addition (***Scheme 3.27***). We found that the alkene **3.27** was reduced using Adam's catalyst to give ketone **3.54**. Subsequently, ketone **3.54** was treated with LiHMDS and methyl carbonocyanidate to give a mixture of **3.55** and **3.56**. Selenium oxidation provided a 1:1 mixture of **3.57** and **3.58** with 26% yield over three steps. Surprisingly, no chemoselectivity was observed during the installation of the ester, we thought originally that the *t*-Bu would block the α-position to its side. In the end, we abandoned this route since the sequence was low yielding, unselective and extended the synthesis sequence by too many steps.

Scheme 3.27 – More reactive enone through the installation of methyl ester



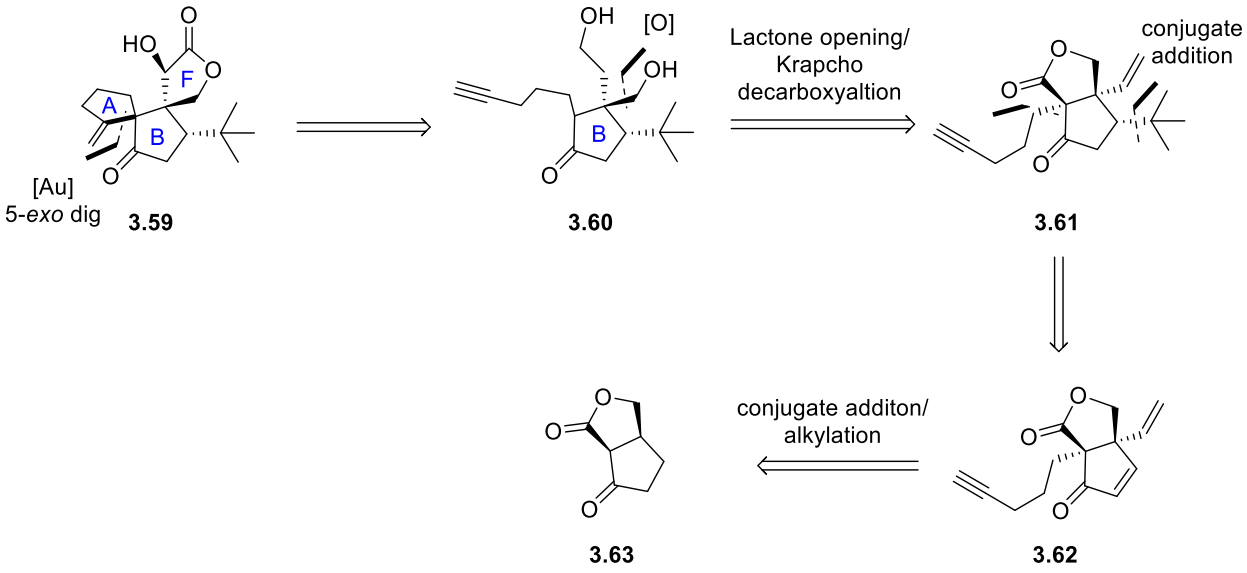
We invested time and energy into the Rautenstrauch rearrangement route, believing that enone **3.27** would had enabled the synthesis of ginkgolides but unfortunately the creation of a quaternary carbon next to the *t*-Bu proved to be an impenetrable problem with the present methodologies. In the end, we attributed this problem to the steric clash induced by the *t*-Bu and decided to modify our original synthetic route to push back the installation of the *t*-Bu group after the quaternary center of the F ring has been formed.

3.3 Route B toward ginkgolide C: overcoming the quaternary center formation through a classical approach

Even though the Rautenstrauch route did not achieve the desired result, it certainly helped to identify the problems associated with the synthesis of the B ring system. From this information, we delineated a new synthetic route that would embrace a similar synthetic mentality in approaching the B ring. Classical chemistry would install the necessary quaternary carbon of the future F ring and we would subsequently install the *t*-Bu moiety.

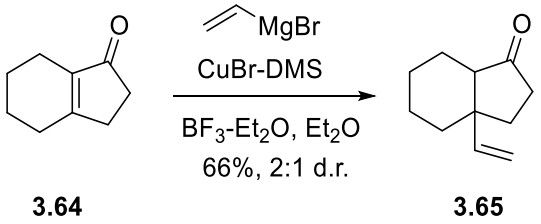
Still motivated with the idea of showcasing [Au]-catalysis as a powerful tool in synthesis, we decided to keep the 5-*exo* dig cyclization part of our original plan to achieve **3.59** from **3.60** (***Scheme 3.28***). The congested B ring system would be revealed from the opening of lactone/Krapcho decarboxylation of bicycle **3.61**. We expected the utilization of bicyclic ketoester **3.63** would be the key to a successful synthetic sequence as it would dictate the stereochemistry of the vinyl chain and pentyne chain during the alkylation processes. The *t*-Bu would be introduced through a conjugate addition onto enone **3.62**.

Scheme 3.28 – 2nd generation retrosynthetic approach



The inspiration to use a fused bicyclic system came from the work of Sorensen on the synthesis of pleuromutilin (***Scheme 3.29***).[137] He was able to catalyze the conjugate addition of an ethene to bicyclic enone **3.64** in presence of copper bromide and boron trifluoride to give ketone **3.65** as a mixture of diastereomer 2:1 dr. Although poor selectivity was achieved, we were convinced that in the 5-5 fused bicyclic system such as **3.63**, only one isomer should be observed.

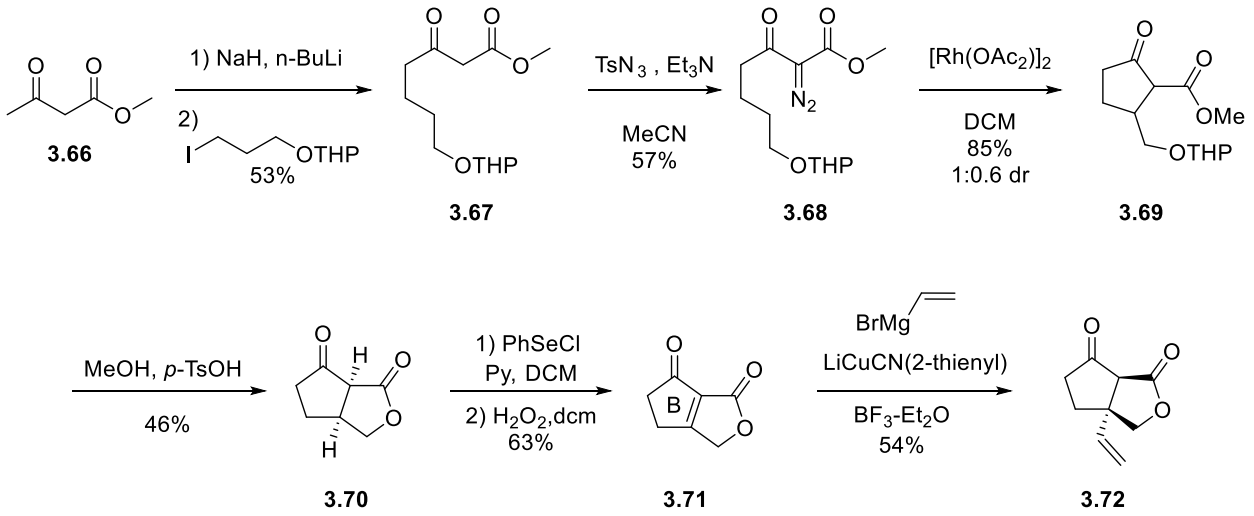
Scheme 3.29 – Sorensen conjugate addition in the synthesis of pleuromutilin



Bicyclic ketoester **3.70** was known in the literature but the methods delineated afforded inconsistent yields and reproducibility issues (***Scheme 3.30***).[138] Therefore, we engineered a new route utilizing cabenoid rhodium catalyzed C-H cyclization based on Moody and Padwa's work.[139] Starting from methyl acetoacetate **3.66**, selective mono alkylation resulted from the

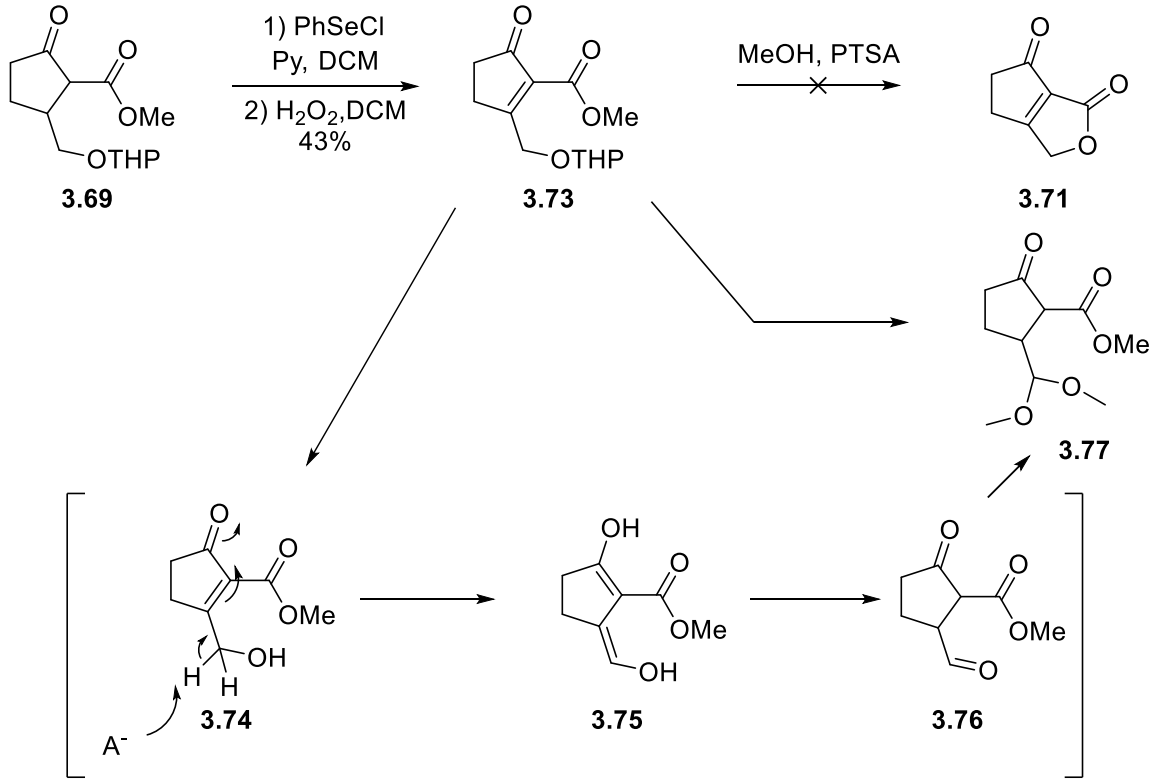
double deprotonation with NaH/*n*-BuLi to give adduct **3.67**. Following Rodriguez[140] methodology for diazo-transfer, we were able to form **3.68** in 57% with tosyl azide. Treatment diazo adduct **3.68** with $[Rh(OAc_2)]_2$ yielded cyclic ketoester **3.69** in 85% with a 1:0.6 mixture of diastereomers. It was unimportant though, as the ketone will be oxidized to the enone in subsequent steps. The THP was cleaved under acidic conditions and the free alcohol readily cyclized to give **3.70** in 46% yield. Interestingly, enone **3.71** was never synthesized in the literature previously but was easily obtain upon selenium oxidation of ketoester **3.70**. We were facing now the construction of the quaternary carbon of the future F ring system and stumbled into a complicated conjugate addition process again. Ultimately, we found that using lithium (2-thienyl)cyoanocuprate with boron trifluoride yielded **3.72** in 54%.

Scheme 3.30 – Synthesis of the bicyclic keto ester



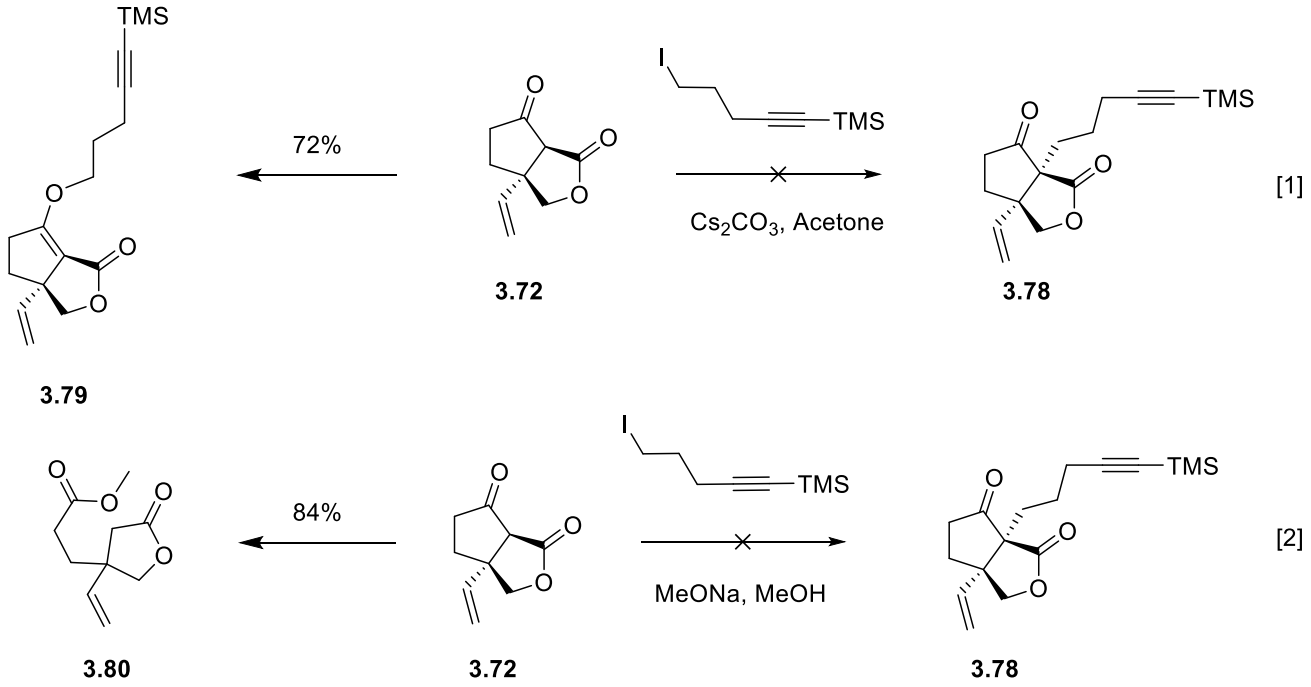
When going from mono-cyclic ketoester **3.69** to bicyclic ketoester **3.70**, if the sequence of deprotection/cyclization/selenium oxidation was inversed, acetal **3.77** was obtained instead (***Scheme 3.31***). We believed that this side-product originated from a conjugate deprotonation of deprotected alcohol **3.74** to give diol **3.75**. After tautomerization, keto aldehyde **3.76** was converted to acetal **3.77**.

Scheme 3.31 – Side-product formation upon inversion of deprotection/cyclization/oxidation steps



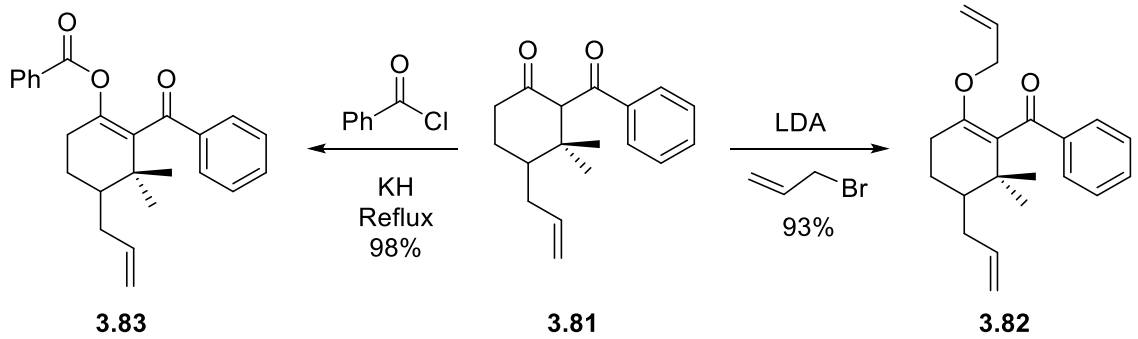
A study of the *C*-Alkylation of the ketoester **3.72** was undertaken without any success (***Scheme 3.32***). Upon treatment with Cs_2CO_3, a methodology used during our earlier work on 6-*endo* dig carbocyclization of 1,5-enyne,[33] a clean conversion toward *O*-alkylation product **3.79** was obtained instead of the desired *C*-alkylation adduct **3.78**. Conventional strong bases were also scouted; sodium hydride, potassium hydride and LDA resulted in *O*-alkylation as well. We also had a look at methanolic sodium methoxide but unfortunately, it led exclusively to the retro-Dieckmann condensation adduct **3.80**.

*Scheme 3.32 – Attempts at C-alkyaltion of keto-ester **3.72***



In view of these results, it reminded us of similar occurrence during our study of the PPAPs natural products (***Scheme 3.33***). We encountered a roadblock in the *C*-functionalization of diketone **3.81** which only led to *O*-alkylation adduct **3.82** and **3.83**. Since we were never able to resolve this problem, we decided to drop this route as we believed simultaneously that our next pathway would allow a more expeditious route towards the ginkgolides.

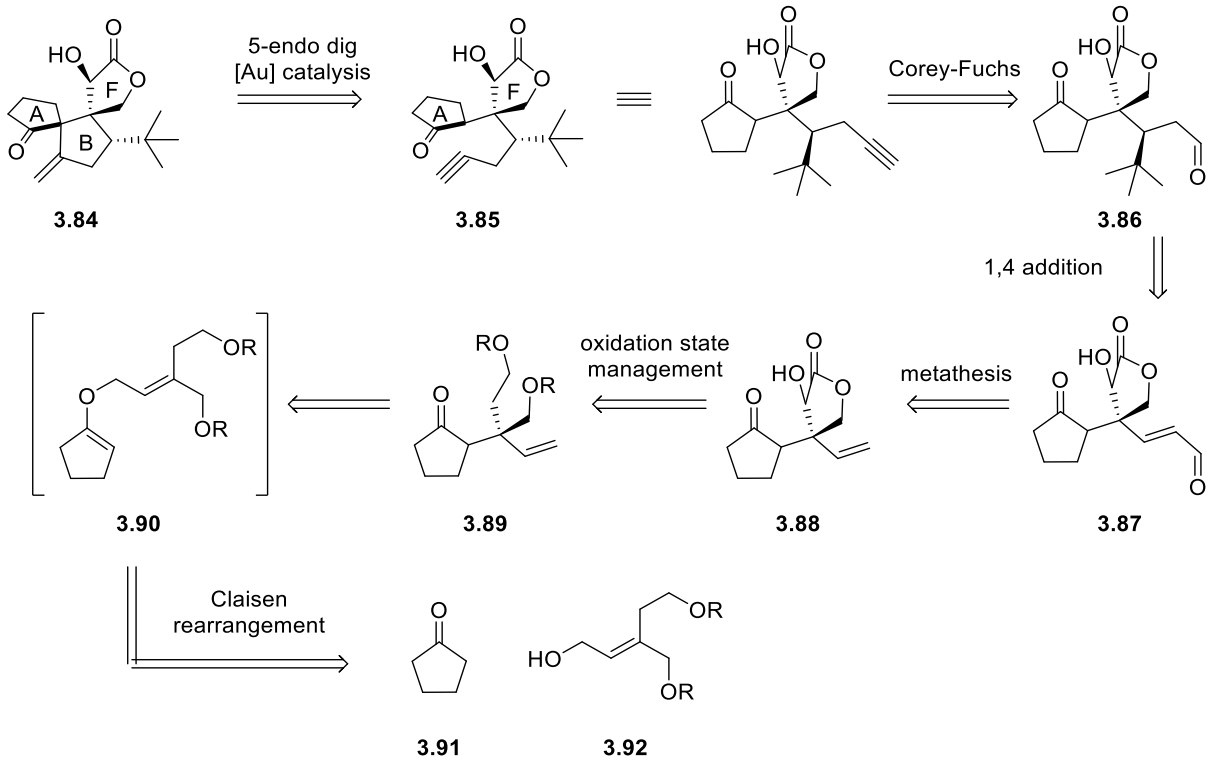
*Scheme 3.33 – Attempt at C-functionalization of hindered ketone **3.81***



3.4 Route C toward ginkgolide C: Late formation of ring B

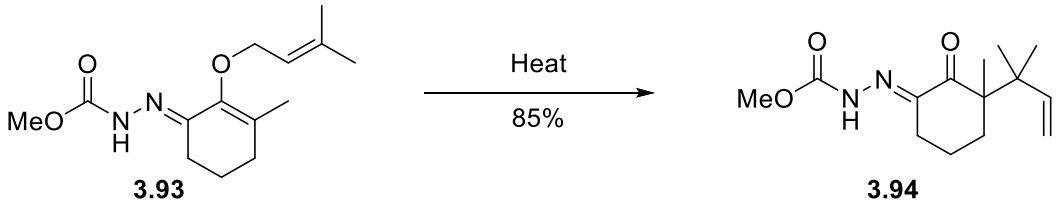
In this 3rd generation synthetic plan, we envisioned an approach where all substituents of the B ring would be installed in an acyclic fashion. Cyclization would then provide the A-B-F ring system (***Scheme 3.34***). The key to this approach resided in the utilization of a Claisen rearrangement to build the quaternary center necessary to the future F ring in a hindered setting. Not letting go of our idea of using gold catalysis, we again entertained the gold-catalyzed 5-*exo* dig cyclization as our best entry into A-B-F ring system **3.84** from ketone **3.85**. The major difference from the two previous approaches resided in the fact that we started with the A ring already in place and aimed at closing the B ring subsequently. The previous methods would engage in the formation of the B ring first. The alkyne would come from a Corey-Fuchs reaction of aldehyde **3.86**. The *t*-Bu group should be installed by means of a conjugate addition onto enone **3.87**. Metathesis should enable the formation of enone **3.87** from **3.88** which would come from oxidation reactions of intermediate **3.89**. Finally, the key to the success resides in building the quaternary carbon center using a Claisen rearrangement of cyclopentanone **3.91** and allylic alcohol **3.92**.

Scheme 3.34 – 3rd generation retrosynthetic approach



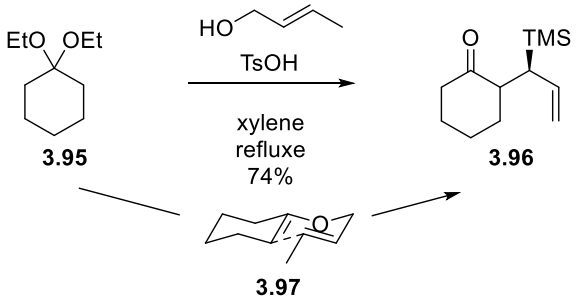
The vinyl ethers precursor for the Claisen rearrangement (**3.90**) [141] are not synthesized easily especially when one of the substrate is expensive or difficult to prepare. They are also at risk to hydrolyze to the corresponding ketone. However, they offered an unparalleled method of forming highly congested environment in substrats. Ponaras[142] showed that two contiguous quaternary carbons could be built through a Claisen rearrangement of vinyl ether **3.93** to ketone **3.94** (***Scheme 3.35***). This encouraged us to try and access the A-B-F ring system in a similar fashion.

Scheme 3.35 – Claisen rearrangement to build congested quaternary carbons



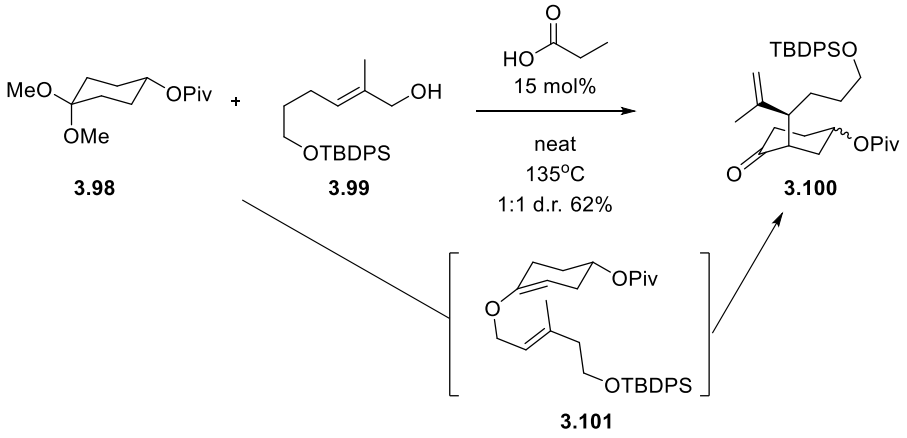
Hirokuza[143] showed that the Claisen precursor **3.97** can be formed *in situ* from an allyl alcohol and ketal **3.95** in presence of an acid (***Scheme 3.36***). Generally, the ketal **3.95** were generated from the corresponding ketones.

Scheme 3.36 – α-allylation from acetal and allylic alcohol



Similar conditions were applied to the synthesis of vinigrol by Barriault *et al*. (***Scheme 3.37***)[144] to convert methyl acetal **3.98** to α-allylated ketone **3.100**. In this example, it was important to use a method in which good yields could be obtained with equimolar amount of the allylic alcohol. The equilibrium toward vinyl ether **3.101** was maintained by distilling out MeOH. It is also important to mention that propionic acid is the perfect acid for this transformation since it was mild enough not to induce undesirable chemistry on the starting material but capable of catalyzing the formation of vinyl allyl ether intermediate **3.101**.

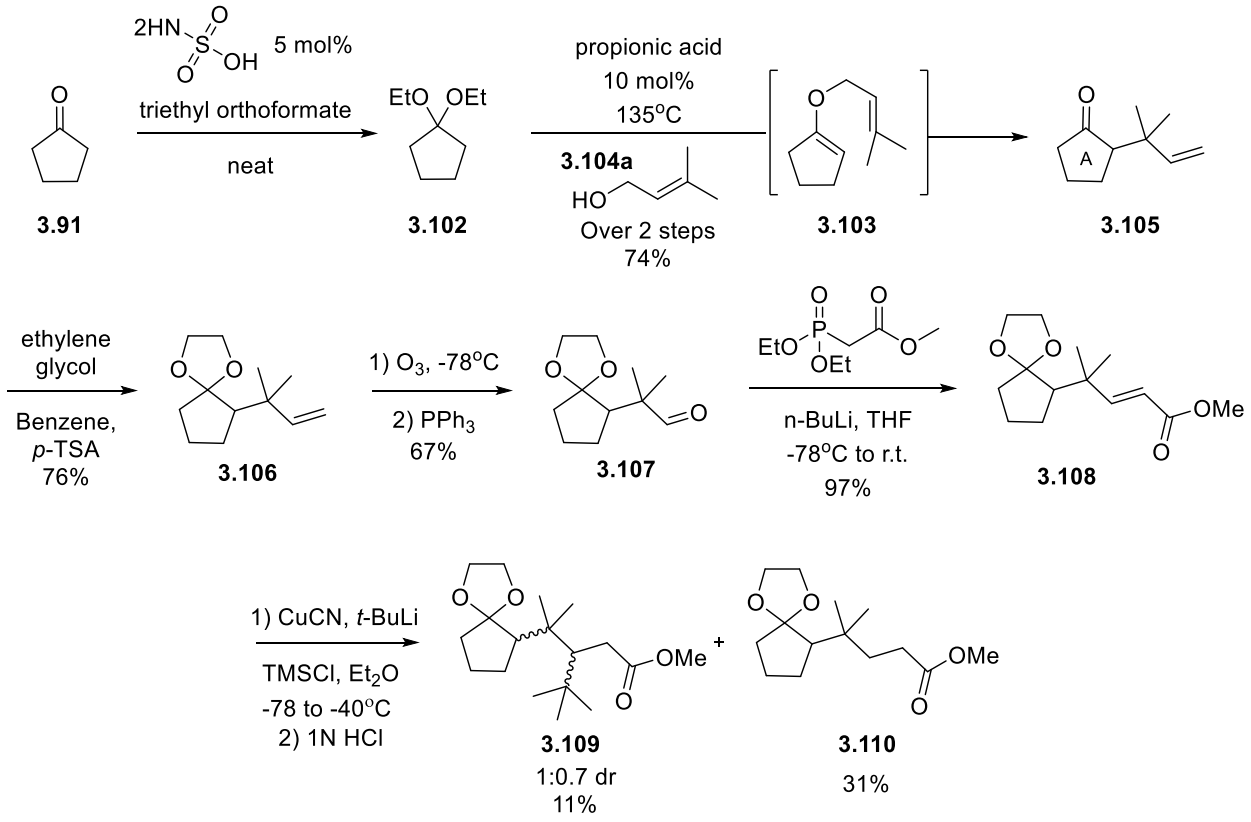
Scheme 3.37 – Claisen rearrangement in the synthesis of vinigrol by Barriault



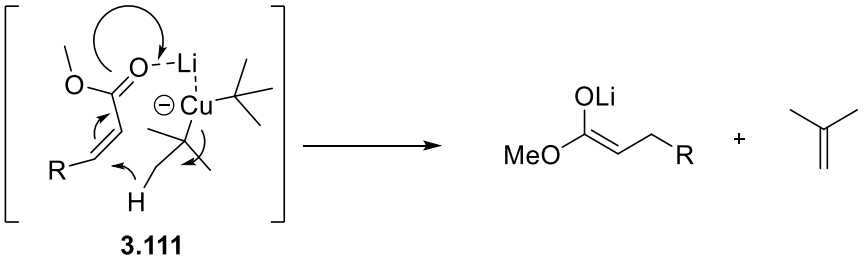
We began our investigation using a model substrate in which the F ring will be replaced by *gem*-dimethyl for the ease of synthesis (***Scheme 3.38***). To this end, the ethyl ketal **3.102** was prepared from cyclopentanone **3.91** following a methodology developed by Suo.[145] After isolation, ketal **3.102** was treated with 3-methylbut-2-en-1-ol **3.104** (1 equivalent) and in presence of propionic acid provided α-allylated ketone **3.105** in 74% over 2 steps. These exciting results indicated that we could build the desired quaternary carbon center from simple starting materials. With grams of ketone **3.105** now accessible, we continued our foray in this synthetic strategy. The goal was to prove that we could achieve the A-B ring system before moving on to more complicated allyl alcohol then **3.104**. Ketone **3.105** was masked into ketal **3.106** with ethylene glycol and *p*-TSA in benzene. The reaction vessel was equipped with a Dean-stark apparatus. Initially, our intention was to perform a metathesis to achieve **3.108** in one step as intermolecular hetero-metathesis with an electron poor and mono-substituted alkene gave good selectivity. Unfortunately, we were unable to obtain the desired metathesis adduct. This was probably due to the *gem*-dimethyl at the vinylogous position of alkene **3.105** blocking the approach of the [Ru]-catalyst. We then turned our attention toward ozonolosis to produce aldehyde **3.107** which was submitted to the Horner-Wadsworth-Emmons reagent to afford the enone **3.108** in almost quantitative yield. At this point, we were ready to install the *t*-Bu. Although, the introduction of a *t*-Bu group by conjugate addition has been repeatedly proven to work adequately, it wasn't clear at first glance if the installation of such a bulky group next to a quaternary carbon would be possible. Upon the formation of the higher order di-*tert*-Butyl cyanocuprate reagent, we obtained a mixture of 2 products. The minor product in low 11% yield was a 1:0.7 dr mixture of the desired conjugate addition adduct **3.109**. However, it was accompanied by a significant amount of enone **3.110** resulting from a competitive hydride reduction. This results indicated that enone **3.108** is so

hindered that the organo cuprate prefers to release a hydride through probably an elimination-type mechanism shown in ***Scheme 3.39*** of intermediate **3.111**.

Scheme 3.38 – Model substrate to test construction of A-B-F ring system



*Scheme 3.39 – Proposed mechanism for reduce enone **3.108***



3.111

Even though the conjugate addition of the *t*-Bu gave the desired product, the latter was the minor compound from this reaction. We extrapolated that the bulkier group, required in the natural product instead of the *gem*-dimethyl, would only promote further the reduction over the 1,4-

addition. The accumulation of failures left us on the edge of dropping the synthesis of ginkgolides altogether. We realized though that we still had a dormant opportunity with the Claisen rearrangement.

3.5 Development of a general one-pot Claisen reaction for expedient α-allylation of ketones

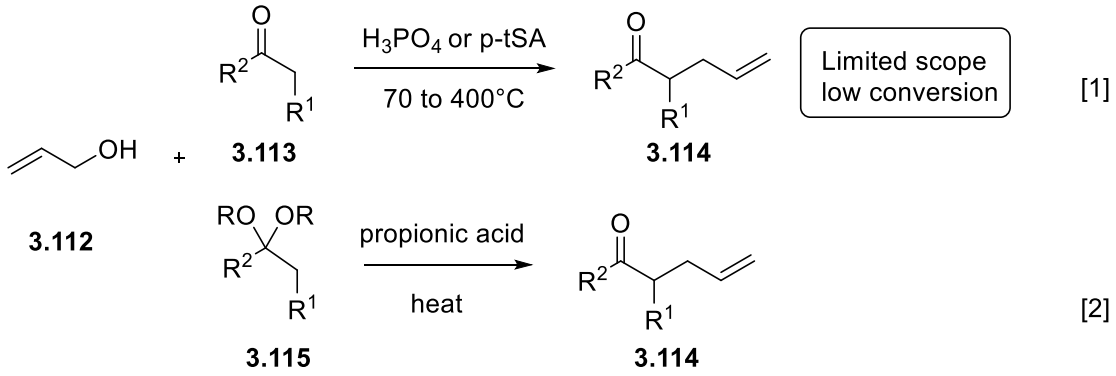
Among all the questions that the last synthetic approach raised; Why a one-pot approach to Claisen products from ketones had not been developed yet was mind boggling. Both processes should in principle be compatible since they are the result of acid catalysis and heat. In an attempt to give ourselves time to think about another possible route toward ginkgolides, we investigated a methodology that allowed the one-pot α-allylation of ketones through the Claisen rearrangement.

The Claisen rearrangement is a remarkable reaction that has been present in countless syntheses due to its robustness and utility in creating challenging C-C bonds.[141] To its demise though, finding the synthetic handle to install the vinyl allyl ether necessary for the [3,3]-sigmatropic rearrangement is not always easy. It has been shown that these rearrangement reactions traditionally go under thermal conditions with or without the help of Lewis acids. Transitions metal catalysis has also been successful in providing Claisen adducts with Hg(II), Pd(II) or Ir under milder reaction temperatures.

As mentioned previously, Kuwajima *et al.*[143] (***Scheme 3.36***) showed that in presence of an allyl alcohol, p-toluenesulfonic acid and heat, the corresponding ketal was converted to the Claisen rearrangement product through the formation *in situ* of the allylvinyl ether. This concept was then further investigated by Griffith *et al.*[146] where they showed that propionic acid suffices to catalyze the alcohol exchange. Depending on the substituents present, this reaction was found

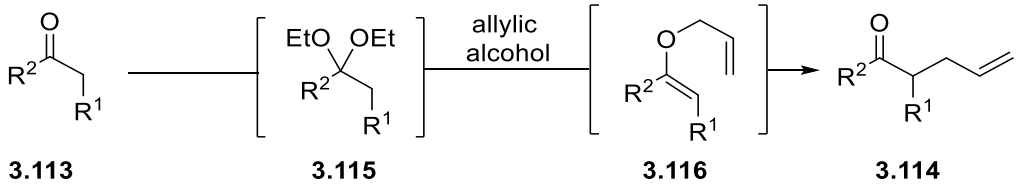
to be quite stereoselective (equation 2 of ***Scheme 3.40***). Although this methodology works well, isolation of ketals can be difficult as they tend to hydrolyze back to the ketone if not attended carefully. A more streamlined approach has been engineered by Dow chemical company[147] where they submitted the ketone directly to the allylic alcohol with phosphoric acid or p-toluenesulfonic acid, but it required high temperatures (70 to 400°C). This method has a limited scope due to isomerization, poly-allylation and poor conversion (equation 1).

Scheme 3.40 – Previous example of α-allylation from ketones and ketals



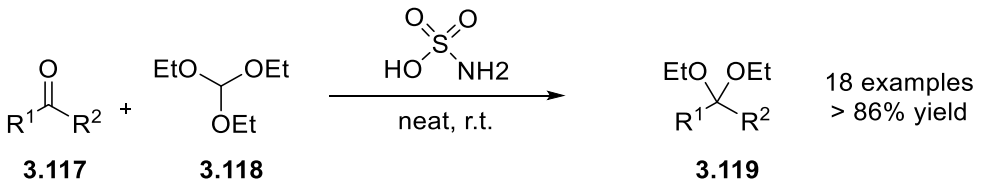
In order to bring the better of both previously described methods of ***Scheme 3.40***, we combined both processes to have an expedient one-pot synthesis of α-allylated products from ketones. The idea was to form ketal **3.115** *in situ* and submit it to the desired allyl alcohol to undergo a Claisen rearrangement through intermediate **3.116** and obtain α-allylated ketone **3.114** (***Scheme 3.41***). Upon initial experimenting with the Claisen part of the desired transformation, we noticed that any acid stronger then propionic acid would lead to degradation of even the simplest starting material. This meant that we could not use any stronger acid then propionic acid for the second part of the transformation. Unfortunately, the formation of the ketal **3.115** required a strong acid, propionic acid was found to be useless at carrying the ketal formation even at 100˚C.

Scheme 3.41 – Proposed mechanism of action of one-pot α-allylation of ketones



Searching the literature, we found that sulfamic acid[145] was capable of catalyzing the ketal formation in presence of triethyl othoformate. More interestingly, sulfamic acid is insoluble in reaction mixture and can be filtered off at the end of reaction. The reaction was also studied neat (***Scheme 3.42***) which alleviated the need for solvent removal once the ketal was formed. Deceivably, treating the crude filtered ketal **3.119** with the Claisen rearrangement conditions gave irreproducible results and poor yields. We later found that a small amount of sulfamic acid is actually soluble in the reaction mixture which leads to degradation during the Claisen rearrangement part.

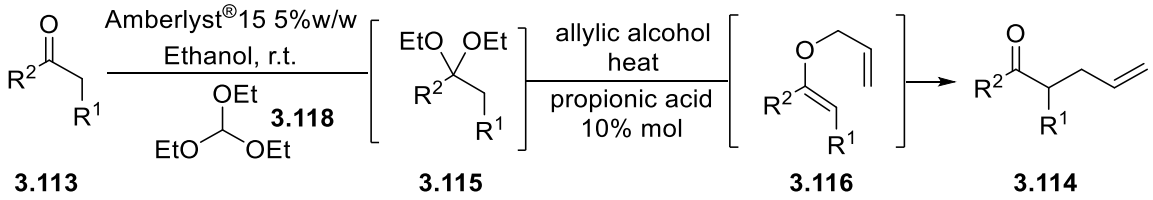
Scheme 3.42 – Sulfamic acid catalyzed acetalization



By replacing the sulfamic acid with Amberlyst®15 resin, we were able to achieve the desired transform in a one-pot fashion without any degradation (***Scheme 3.43***). The treatment of ketone **3.113** with triethyl othoformate **3.118** and 5% per weight of amberlyst®15, catalyzed the formation of ketal **3.115** in less than 1 hour for most substrates. It was noted that 2 mL of ethanol per gram/mL of ketone was necessary to push equilibrium in favor of ketal **3.115,** otherwise it resulted in an incomplete conversion. The resin was easily filtered out and the crude is treated with the desired allylic alcohol in presence of 10% mol propionic acid and heated between 130 to 170°C

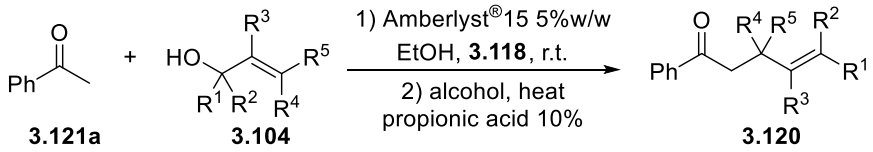
to afford **3.114** in 31 to 99% yields via the formation *in situ* of vinyl allyl ether **3.116** and the [3,3]-sigmatropic shift.

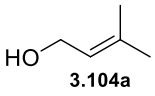
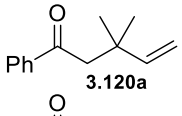
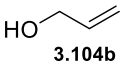
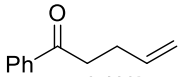
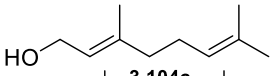
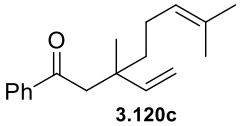
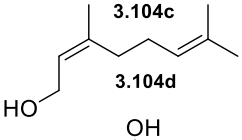
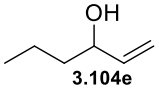
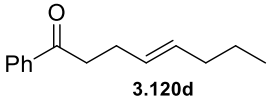
Scheme 3.43 – One-pot α-allylation reaction conditions



Having established the reaction conditions, we evaluated the scope and limitations of the reaction. First, we examined the α-allylation of primary carbons using acetophenone (***Table 3.5***). This methodology was amendable to most allylic alcohols with primary (**3.104a-d**) and secondary alcohols (**3.104e**) affording yields of 75% and higher. Tertiary alcohols though, proved to be more difficult as it generated too many side products. We attributed this low conversion to the challenging formation of the intermediary vinylallyl ether **3.116**.

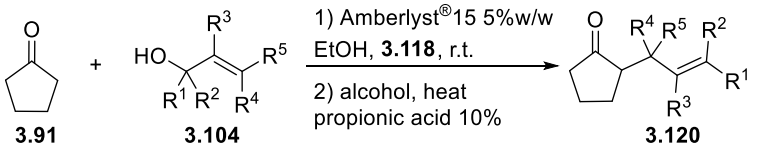
Table 3.5 – Scope of the one-pot Claisen rearrangement of acetophenone



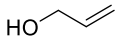
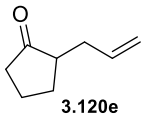
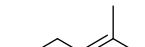
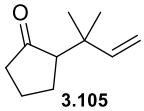
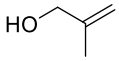
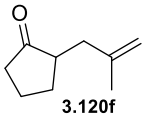
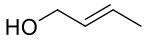
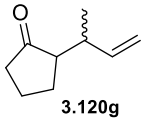
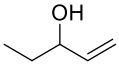
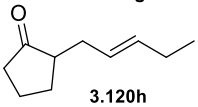
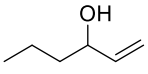
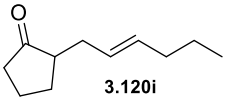
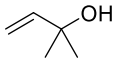
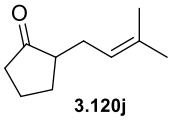
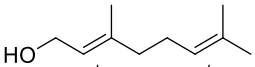
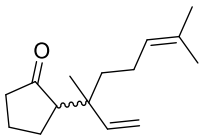
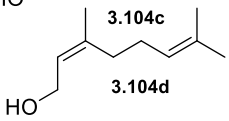
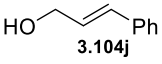
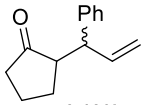
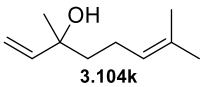
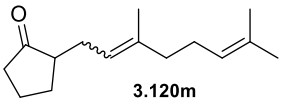
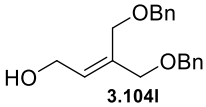
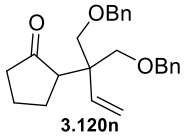
Entry	alcohol	product	T(°C)	yield(%)
1	 3.104a	 3.120a	130	75
2	 3.104b	 3.120b	170	92
3	 3.104c	 3.120c	140	99
4	 3.104d		160	75
5	 3.104e	 3.120d	170	99

We pursued the investigation with the α-allylation of secondary carbons using cyclopentanone **3.91** as starting ketone (***Table 3.6***). This choice was made in order to test the limits of cyclopentanone as it is a good starting material for the synthesis of ginkgolides. Primary (entries 1-4,10 and 12) and secondary (entries 5 and 6) alcohols again gave similar yields ranging from 51% to 83% yields. We were pleased to see that encumbered alcohols like geraniol **3.104c**, nerol **3.104d** and **3.104l** behaved under the reaction condition to afford highly crowded quaternary carbons at the β-position (entries 8, 9 and 12). Product **3.120n** (entry 12) was especially interesting since upon deprotection of the benzyl groups, we would have the necessary handles to form the F ring of ginkgolides. Noteworthy, most of the products formed had strong olfactive properties and many were used in fragrances and accounted for the lower yields compared to the acetophenone array. Some of these substrates were volatile or possessed high vapor pressure. For example, **3.120m** better known as apritone is the natural product found in apricots and is responsible for its distinctive odor. Ketone **3.120h** is known as jasminone B and has the odor of coconut and jasmine and is commonly use in the fragrances industry. Tertiary alcohols proved more difficult as they required higher temperature to permit the rearrangement to occur but also led to decomposition if heated over an extended period or at higher temperatures (entries 7 and 11). Linalool **3.104k** gave 47% of ketone **3.120m** (entry 11) as a mixture of *trans*/*cis* 1/0.63 and **3.104l** gave a 36% yield of ketone **3.120j** (entry 7).

Table 3.6 – Scope of the one-pot Claisen rearrangement on cyclopentanone



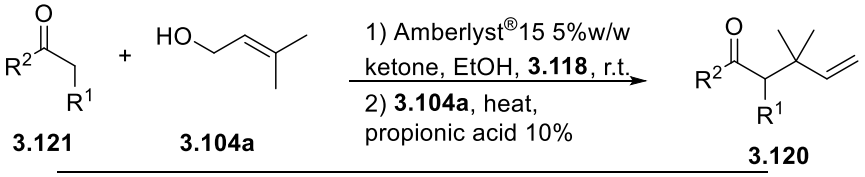
3.91 + 3.104 → 3.120

Entry	Alcohol	Product	T(°C)	Yield(%)
1	 3.104b	 3.120e	130	61
2	 3.104a	 3.105	130	66
3	 3.104f	 3.120f	130	53
4	 3.104g	 3.120g	130	65[a]
5	 3.104h	 3.120h	130	63
6	 3.104e	 3.120i	130	73
7	 3.104i	 3.120j	150	36
8	 3.104c	 3.120k	140	81[b]
9	 3.104d		150	61[c]
10	 3.104j	 3.120l	140	83[d]
11	 3.104k	 3.120m	150	47[e]
12	 3.104l	 3.120n	140	51

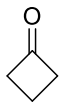
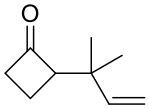
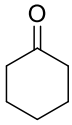
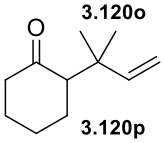
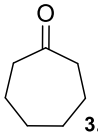
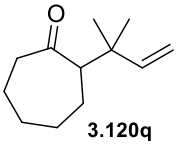
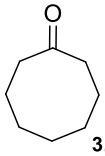
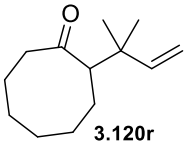
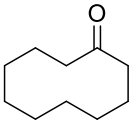
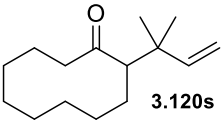
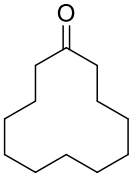
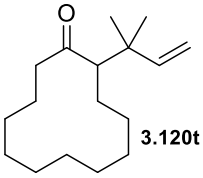
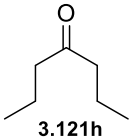
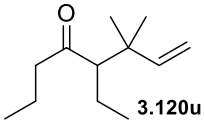
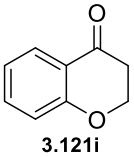
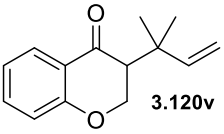
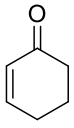
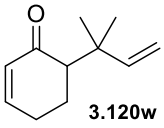
[a] d.r. ratio of 1:0.9 was obtained; [b] d.r. ratio of 1:0.9; [c] d.r. ratio of 1:0.33; [d] d.r. ratio of 1:1 was obtained; [e] a mixture of 1/0.63 trans/cis was obtained

We thought it was also important to perform a ketone scope with 3-methylbut-2-en-1-ol **3.104a** as it allows the formation of highly congested β-positions. We were also motivated by the fact that the *gem*-dimethyl are a common trait among natural products (***Table 3.7***). Cyclic ketones (**3.121b-g,i**) (entries 1 to 6 and 8) worked adequately with yields between 54 and 99%. We were surprised to see that the rearrangement worked also on cyclobutanone **3.121b** (entry 1) under prolonged exposure at 160°C (3 days). Under these conditions, the formation of the precursor to the Claisen rearrangement is fast but the rearrangement is very lengthy. At a lower reaction temperature than 160˚C, only the allyl vinyl ether was observed. Cyclohexanone **3.121c** (entry 3) worked the best of the smaller rings yielding 92% of **3.120p**. 7-,8- and 10-member ring (entries 3, 4 and 5) behaved similarly with yields between 75-77%. But cyclododecanone **3.121g** (entry 6) afforded the best yield (99%) of all ketones and was truly a "spot to spot" reaction. Acyclic ketone **3.121h** (entry 7) and enone **3.121i** also succumbed to the reaction conditions. Enone **3.121i** (entry 9) afforded product **3.120w** in 24% yield and was included to show the limitation of this methodology has conjugate addition was observed along with many other reactions. However, the reaction was found to be general and allowed in good yield to build highly hindered β-quaternary carbons from cyclic and acyclic ketones.

Table 3.7 – Scope of the one-pot Claisen rearrangement on array of ketones



3.121 **3.104a** **3.120**

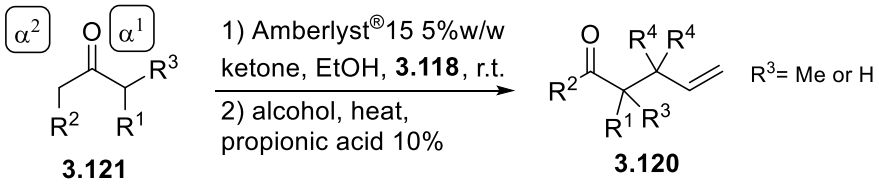
Entry	Ketone	product	T(°C)	yield(%)
1	 **3.121b**	 **3.120o**	160[a]	54
2	 **3.121c**	 **3.120p**	150	92
3	 **3.121d**	 **3.120q**	150	77
4	 **3.121e**	 **3.120r**	150	76
5	 **3.121f**	 **3.120s**	150	75
6	 **3.121g**	 **3.120t**	150	99
7	 **3.121h**	 **3.120u**	145	69
8	 **3.121i**	 **3.120v**	145	74
9	 **3.121j**	 **3.120w**	145	24

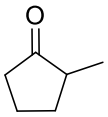
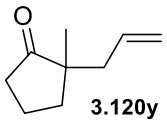
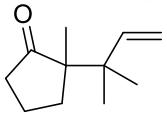
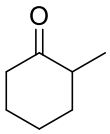
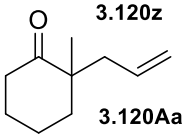
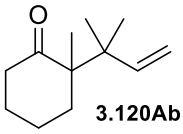
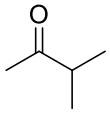
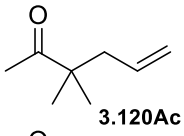
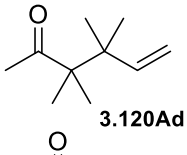
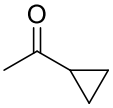
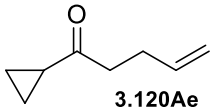
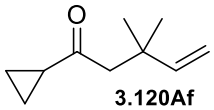
[a] the reaction was heated for 3 days

Lastly, we were intrigued with the sort of selectivity incurred when these conditions were applied to unsymmetrical ketones (***Table 3.8***). We were pleased to find that excellent to full chemoselectivity was observed. The simplest of allylic alcohol **3.104b** with ketone **3.121k-m** (entries 1, 3, 5) appeared to afford the product resulting from the thermodynamic vinylallyl ether as the major adduct. Strong chemoselectivity could be achieved, on the other hand, using the more congested allyl alcohol 3-methylbut-2-en-1-ol **3.121** which was selective for **3.120z**, **3.120Ab** and **3.120Ad** respectively using ketone **3.121k**, **3.121l** and **3.121m** (entries 2, 4, 6).

When treated with allyl alcohol **3.104b**, 2-methylcyclopentanone **3.121k** (entry 1) and methyl isopropyl ketone **3.121m** (entry 5) are the most selective with an observed ratio of 1/0.23 and 1/0.18 for α^1/α^2 substitution (***Table 3.8***). On the other hand, exclusive α^1-allyltion was experienced when allylic alcohol **3.104a** (entries 2 and 6) were used instead with yields of 78% and 65% respectively for ketone **3.121k** and **3.121m**. If present, the α^2-allylated adduct was not observed by ^{1}H and ^{13}C NMR. Selectivity erosion was observed for 2-methylcyclohexanone **3.121l** as the ratio of product obtained reflected a mixture of 1/0.58 and 1/0.36 of α^1/α^2 substitution with alcohol **3.140b** (entry 3) and **3.140a** (entry 4) respectively. Similar to other ketones though, allylic alcohol **3.104a** was once again more selective for the α^1 position. Ketone **3.121n**, on the other hand, afforded the inverse trend as the α^2-allylation was observed exclusively for allyl alcohol **3.104b** (entry 7) and a ratio of 0.36/1 α^1/α^2 with **3.104a** (entry 8). These results were not surprising considering the strain imposed by the cyclopropyl during the formation of the Claisen precursor. Interestingly, the sigmatropic rearrangement of more encumbered ketones like **3.121K** and **3.121l** were found to give better yields and required reduced temperature then their de-methylated affiliate cyclopentanone **3.91** and cyclohexanone **3.121c**.

Table 3.8 – Scope of one-pot Claisen rearrangement of unsymmetrical ketones



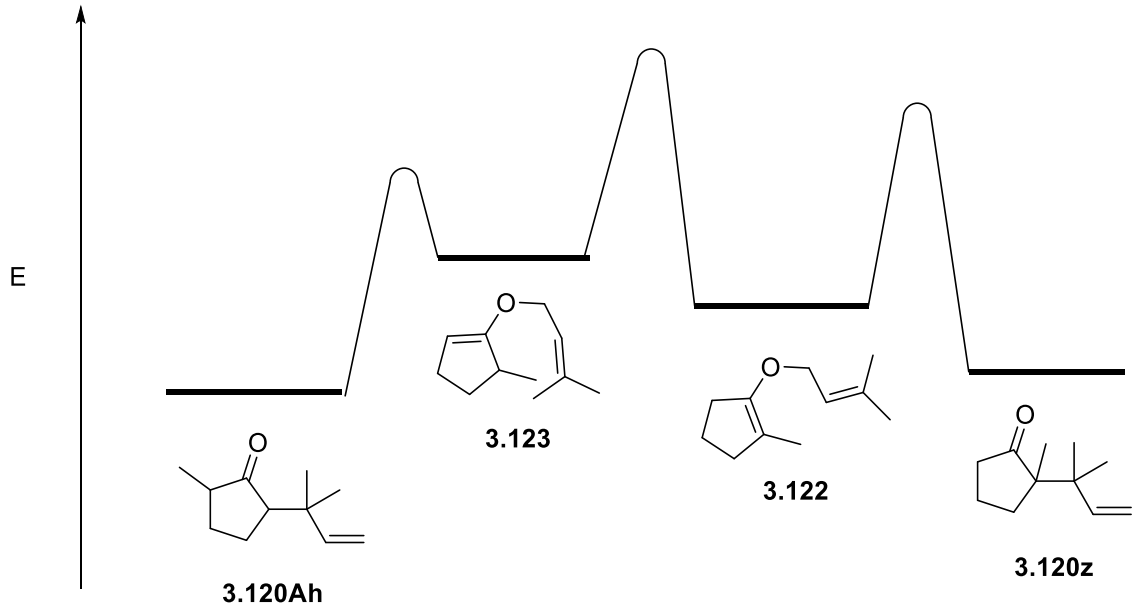
Entry	Ketone	Alcohol	Major product	T(°C)	Yield(%)	selectivity[a]
1	 **3.121k**	**3.104b**	 **3.120y**	130	93	1/0.2
2		**3.104a**	 **3.120z**	130	78	>25:1
3	 **3.121l**	**3.104b**	 **3.120Aa**	130	64	1/0.6
4		**3.104a**	 **3.120Ab**	130	75	1/0.4
5	 **3.121m**	**3.104b**	 **3.120Ac**	140	93	1/0.2
6		**3.104a**	 **3.120Ad**	140	65	>25:1
7	 **3.121n**	**3.104b**	 **3.120Ae**	130	78	>25:1
8		**3.104a**	 **3.120Af**	130	60	0.4/1

[a] $\alpha\alpha^1/\alpha^2$

In order to explain this selectivity a few options are available (***Figure 3.4***). Assuming the activation energy of the Claisen rearrangement of vinyl allyl ether **3.123** is lower in energy than **3.122** because of the diminished steric clash and with the additional assumption that vinyl allyl ether **3.122** is thermodynamically more stable than **3.123** because of the formation of the more

substituted alkene. The latter assumption has been investigated by a quick calculation of the base energy of the intermediates by Chem3D (MM2) where **3.123** was found to have a base energy of 15.9 kcal/mol and **3.122** 12.6 kcal/mol resulting in a $\Delta E = 3.29$ kcal/mol. Ketone **3.120z** would be favored if the interconversion between **3.123** and **3.122** is the slow step.

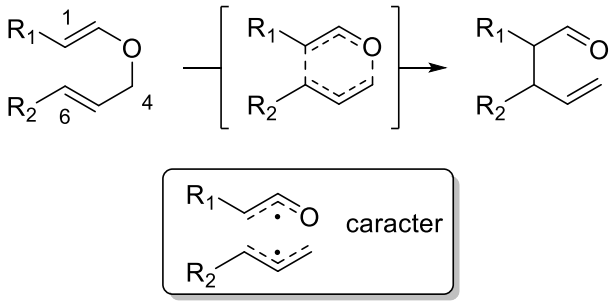
Figure 3.4 – Energy diagram if interconversion between Claisen precursor is slow



The Curtin-Hammet principle can't be omitted as a viable option either, but would imply that the conversion of vinyl allyl ether **3.122** toward **3.120z** would have a lower activation energy than **3.123** toward **3.120Ah**.

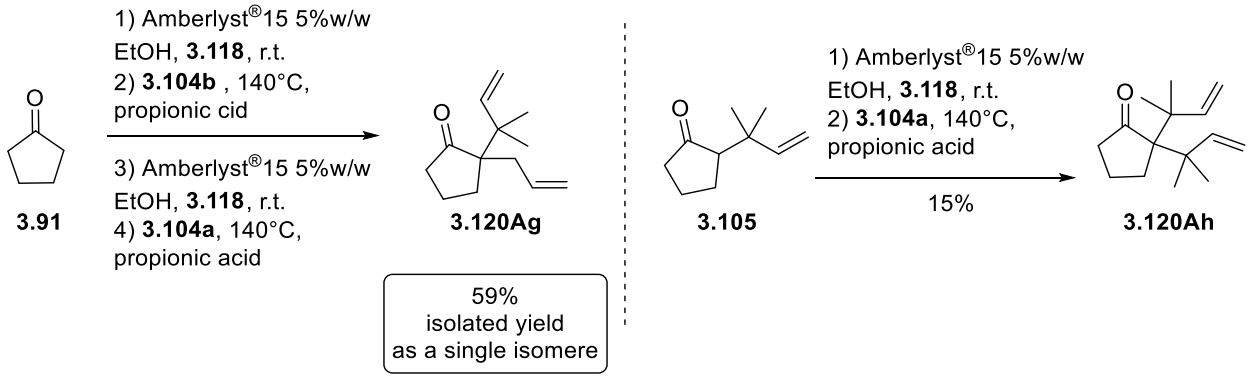
In the event that the reaction would follow a non-concerted mechanism, Gajewski and Gilbert[148] showed the influence of substituents at C-1, C-4 and C-6 on a possible diradical character early dissociative transition state (***Scheme 3.44***) and could explain the selectivity observed. Further investigation on the origin of this selectivity will need be done through further probing of the system and computational studies.

Scheme 3.44 – Gajewski and Gilbert early dissociative transition state proposal



To push the limits of this methodology, we pursued a one-pot double allylation of cyclopentanone **3.91** with 2 different allylic alcohols. Gratifyingly, we were able to achieve di-allylated adduct **3.120Ag** in 59% yield and as a single isomer. It is important to note that the order in which the alcohols are added is crucial for this reaction to work. The first Claisen must be performed with allyl alcohol **3.104b**, followed by 3-methylbut-2-en-1-ol **3.104a**. Otherwise, the inverse addition sequence led to mono-substituted ketone **3.105** only. Noteworthy, we were able to build three contiguous quaternary carbons using this methodology starting from ketone **3.105** and allylic alcohol **3.104a** with a modest yield of 15% of **3.120Ah**. While the yield was not exceptional, it is worth mentioning[149] that few methods exist for the construction of contiguous quaternary centers, which remains an unsolved problem for obvious issues.

Scheme 3.45 – Tandem double α-allylation of cyclopentanone and formation of complex adducts



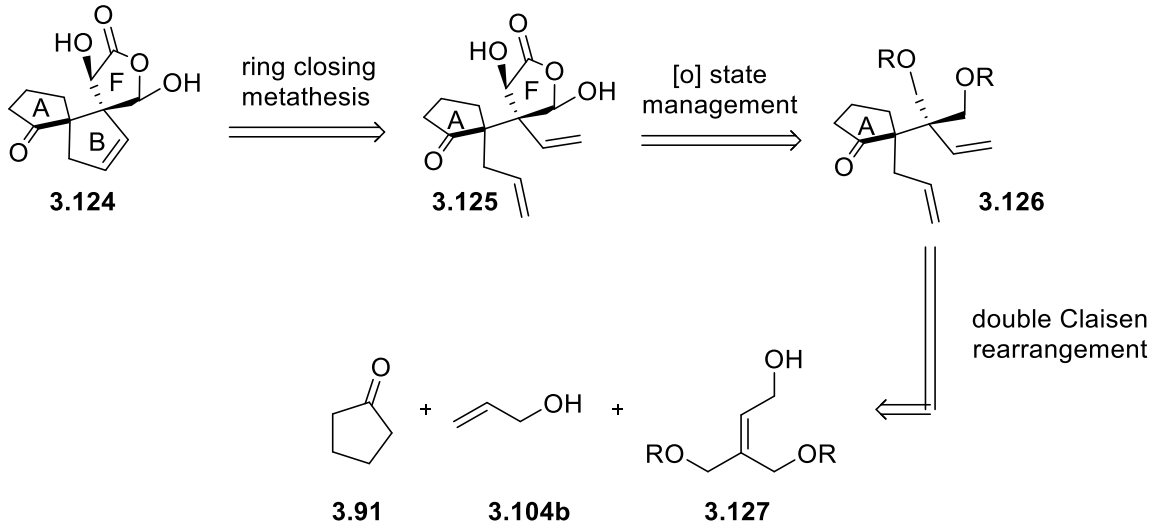
In conclusion, we developed a one-pot methodology to perform the expedient α-allylation of ketones. This method was shown to be compatible with an array of ketones and allyl alcohols inclusive of primary, secondary and tertiary alcohols. Overall, we prepared 34 individual examples and showed that the methodology could be extended to unsymmetrical ketones with great selectivity without the need for protecting groups. All reactions were performed on a minimum of 1 g of starting ketone which shows that this reaction is amendable on large scale. We were able to safely get ketone **3.120Ag** with the same yield on 10 g and 25 g scale. Contemplating how easily we could form two contiguous quaternary carbon centers utilizing this robust methodology. We developed a new synthetic approach toward ginkgolide C which will be described in the next section.

3.6 Route D toward ginkgolide C: Late installation of *tert*-butyl group

"If you really believe in what you're doing, work hard, take nothing personally and if something blocks one route, find another. Never give up." Laurie Nataro

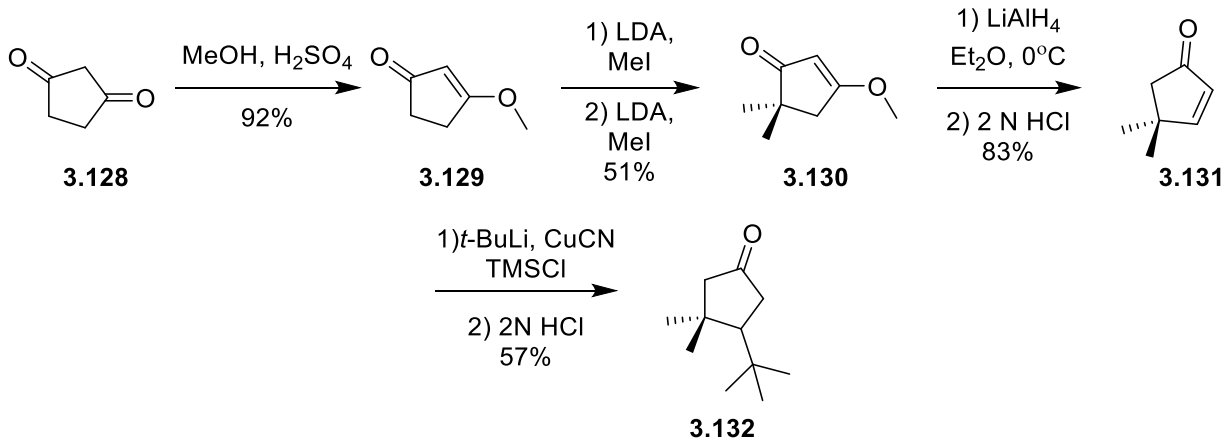
The motivation behind this route was the ease under which we could generate two contiguous quaternary carbon utilizing the Claisen rearrangement described in the previous section (***Scheme 3.46***). We envisioned that the A-B-F ring system **3.124** could be directly formed from diene **3.125** by mean of ring closing metathesis. The F-ring would come from oxidation and carbon addition reactions to protected diol **3.126**. Similarly to example shown in ***Scheme 3.45***, we thought of utilizing a double Claisen rearrangement of ketone **3.91** in presence of allyl alcohol **3.104b** and **3.127**.

Scheme 3.46 – 4th generation retrosynthetic approach



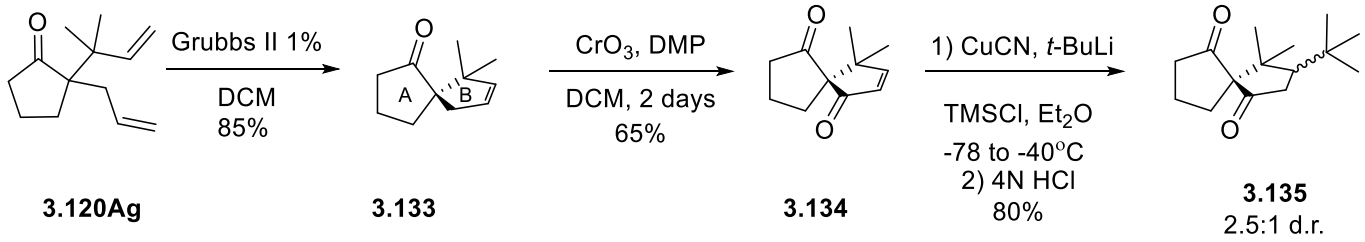
To stay on the cautious side of things, we studied a model substrate where the F-ring system was replaced by a *gem*-dimethyl to ensure the installation of the *t*-Bu group was feasible in a cyclic system as it proved problematic in route C on the acyclic adduct **3.108**. We devised a short synthesis of γ-gem-dimethyl enone **3.131** based on the synthetic sequence used in the early stages of PPAPs (***Scheme 3.47***). Starting with cyclopenta-1,3-dione **3.128**, we formed methyl vinyl ether **3.129** in MeOH with a catalytic amount of sulfuric acid in 92% yield. A one-pot double methylation with LDA and MeI gave α-*gem*-dimethyl ketone **3.130** in 51% yield. The ketone was reduced with lithium aluminium hydride and the resulting alcohol was eliminated to enone **3.131** in 83% yield under biphasic acidic conditions. The conjugate addition of the *t*-Bu was then tested and we were pleased to see that the reaction worked well with the cyclic system. The reduction of the enone was not observed and the reaction yielded 56% of **3.132**. The actual yield was probably higher as **3.132** was extremely volatile and possessed a really powerful smell of fresh pine.

Scheme 3.47 – Investigation of the conjugate addition of t-Bu group to cyclic systems



Since ketone **3.120Ag** could easily be access through our methodology, we decided to scout ahead and investigate the possible problem we might encounter in a system closer to the one we would like to employ for ginkgolide C (***Scheme 3.48***). We started by testing the ring closing metathesis, which would give the spirobicycle A-B ring system of ginkgolides. The metathesis reaction worked well yielding **3.133** in 85% yield and required very little catalyst loading. This methodology called for the elaboration of an allylic oxidation of alkene **3.133**. Techniques utilizing selenium proved useless, they only led to unreacted starting material even at elevated temperature. Utilizing copper and peroxides gave the desired allylic alcohol as a mixture of diastereomers. We found that we could directly access keto enone **3.134** in 65% yield upon treatment of alkene **3.133** with CrO_3 and 3,5-dimethylpyrazole. Thereafter, we tested the installation of the *t*-Bu group, and similarly to **3.131** the reaction afforded diketone **3.135** without incident in 80% yield as a 2.5:1 mixture of diastereomers.

Scheme 3.48 – Model substrate to probe reactivity of A-B ring system



We originally envisioned that the approached of the *t*-Bu group would be preferably occurring on the *si* face opposite to the A ring's carbonyl to give the desired natural product stereochemistry (***Scheme 3.49***). After separation of both diastereomers and crystallization, we were able to get an X-ray of the major diastereomer. We were surprised to find that the *t*-Bu was added preferentially to the *re* face. We reasoned afterward, that this selectivity is probably due to the ketone of ring A directing the addition of the *t*-Bu group. We will need to inverse this trend if we ever plan on using this approach since we would need diastereomer **3.135b** to get to ginkgolide C.

*Scheme 3.49 – Result from the conjugate addition of the t-Bu group on **3.134***

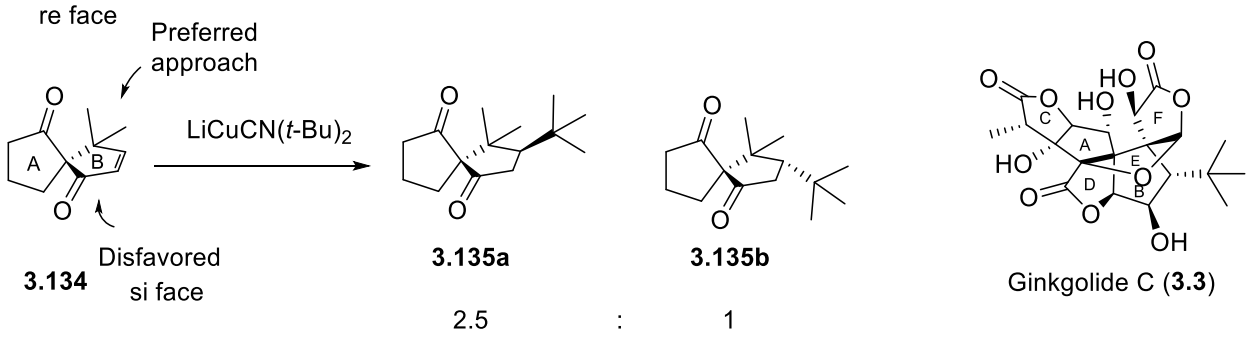
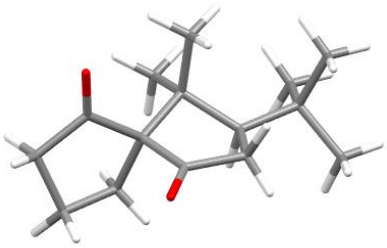
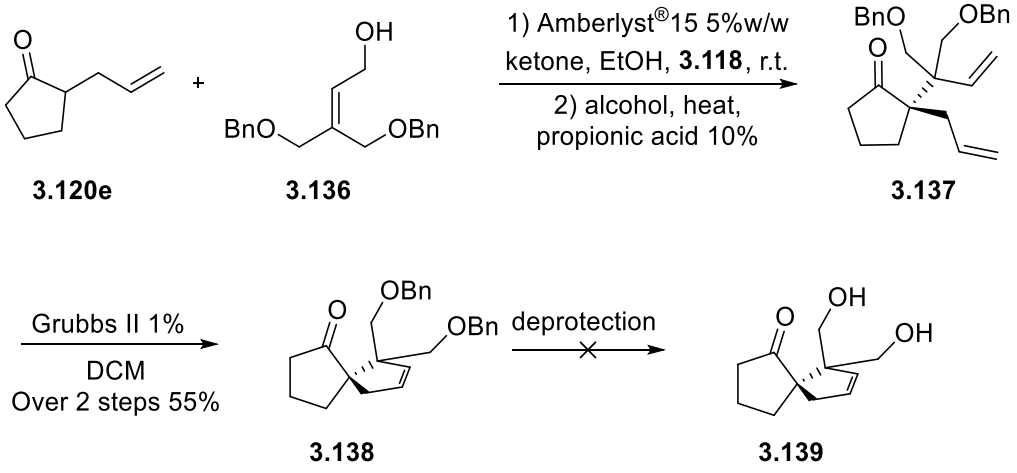


*Figure 3.5 – X-ray of major diastereomer of diketone **3.135a***



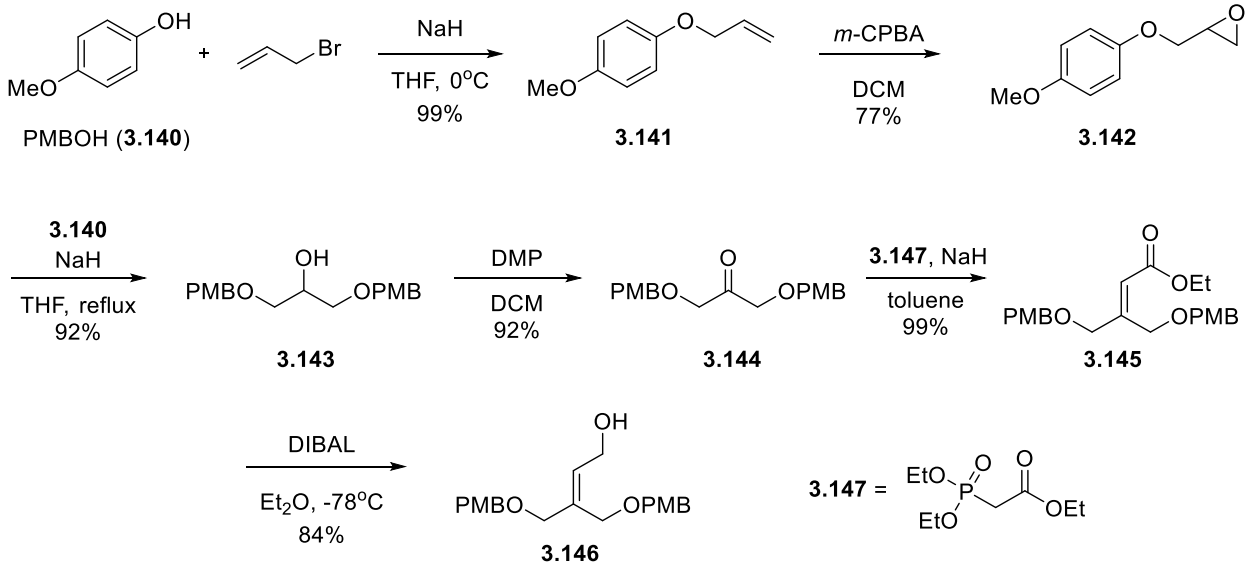
It was now time to investigate the synthesis of ginkgolides head on, for this we needed to find a good starting allyl alcohol that would provide the necessary reactive handle to generate the F ring system later in the synthesis (***Scheme 3.50***). We decided to start with known dibenzylated allyl alcohol **3.136**[150] which provided di-allylated **3.137** without a hiccup following our one-pot Claisen methodology. In accordance with our test substrate, the RCM also worked well to give spirobicycle **3.138**. We then hoped to pursue the chromium allylic oxidation of **3.138**. Unfortunately, this led to an unresolved complex mixtures of products. Other oxidative methods were not amendable to this substrate either. We also tried to remove the benzyl groups but under hydrogenation methods, we observed the reduction of the alkene first and utilization of oxidative methods like DDQ led to degradation.

*Scheme 3.50 – Roadblock in using benzylated allylic alcohol **3.136***



Resolved in the potential of this synthetic pathway, we synthesized the PMB variant of the previously benzyl allylic alcohol **3.136** to ease the deprotection process. Unfortunately, the alcohol wasn't known in the literature thus we needed to find a new and cheap way to make it (***Scheme 3.51***). The sequence is initiated by a standard allylation of PMBOH **3.140** with sodium hydride and allyl bromide to give **3.141** in 99% yield. The epoxide **3.142** was formed using m-CPBA in DCM and subsequently opened with PMBOH under basic condition to afford symmetrical alcohol **3.143**. Upon oxidation to ketone **3.144** with DMP and subsequent olefination Horner-Wadsworth-Emmons, we obtained enone **3.145** which was reduced with DIBAL to give the desired allylic alcohol **3.146**. The overall sequence was 6 steps with an overall 56% yield and included only affordable starting material and reproducible yields.

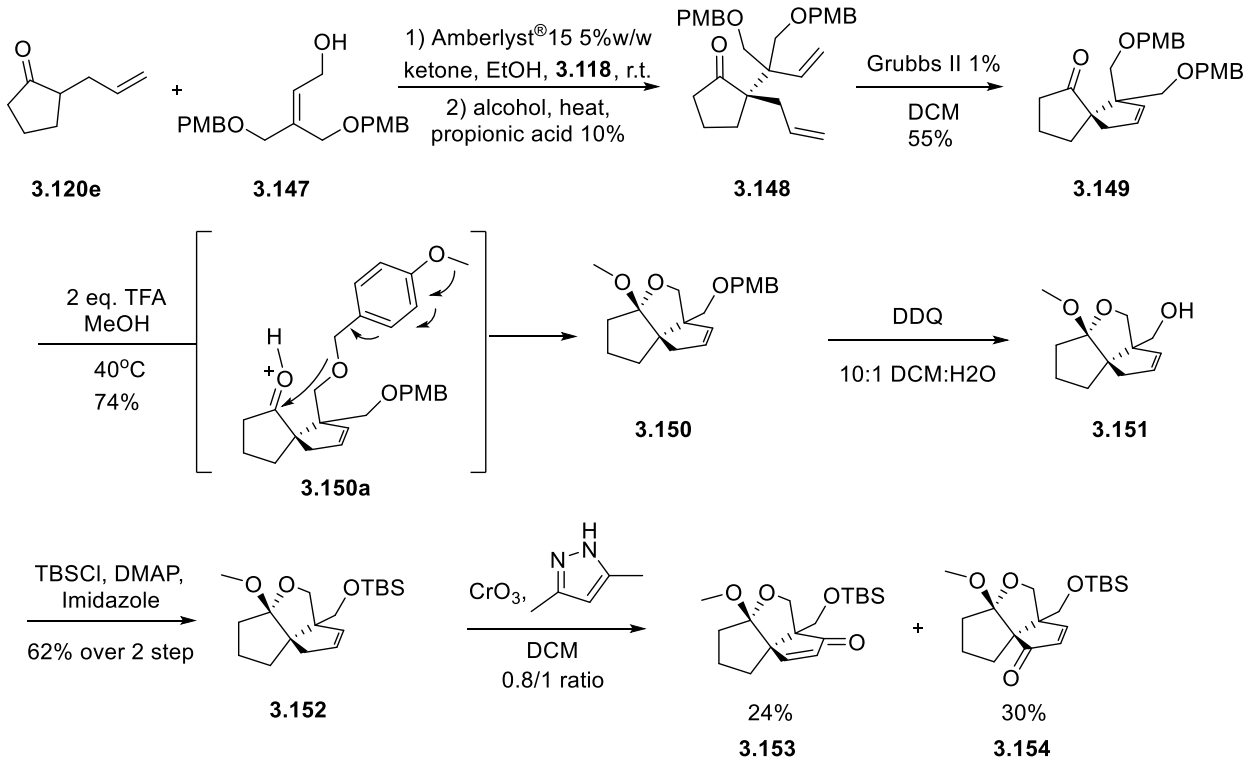
Scheme 3.51 – Development of an affordable and scalable route to PMB protected allylic alcohol



Once again the one-pot Claisen rearrangement of ketone **3.120e** with the PMB protected alcohol **3.147** led to di-allyl ketone **3.148** without any issue and was cyclized immediately to give spirobicycle **3.149** (***Scheme 3.52***). We decided to tackle the deprotection of the PMB group early

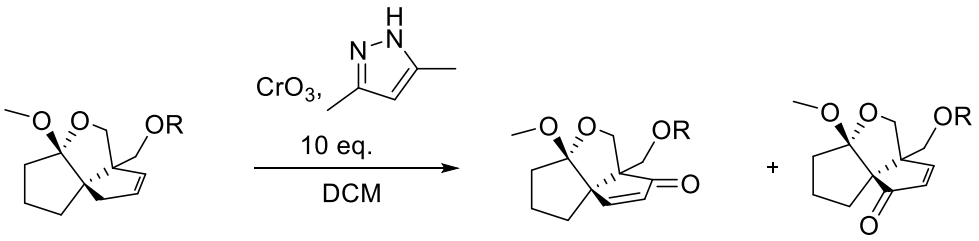
on and to our surprise we found in our first attempts at the deprotection, that 2 equivalents of TFA were able to remove exclusively the PMB group closest to the ketone without cleaving the other. This level of selectivity wasn't expected but we gladly took advantage of it and is believed to proceed through intermediate **3.150a**. The selective deprotection was performed in MeOH to form the acetal **3.150** *in situ* simultaneously in 74% yield. DDQ was then used to cleave the other PMB and afforded free alcohol **3.151**. The free alcohol was protected once again with a TBS group under standard conditions since the free alcohol **3.151** or PMB protected **3.150** wouldn't support the following allylic oxidation. Upon oxidation with chromium oxide, contrary to our previous findings using substrate **3.133**, we observed two isomers **3.153** and **3.154** in a 0.8/1 separable mixture respectively.

Scheme 3.52 – New promising route utilizing PMB protected allylic alcohol



Unsatisfied with the mixture of isomers, we investigated this reaction further trying to maximize the output of enone **3.154**. Conventional allylic oxidation utilizing SeO_2 only afforded starting material. Oxidative methods using copper afforded a small amount of the allylic alcohol but was accompanied with numerous side products. Attempts at using the $Mn(OAc)_3/H_2O_2$ system reported by Shing's group[151] led to a better ratio favoring enone **3.157** over **3.156** in a 1/0.7 (entry 2)(***Table 3.9***) but was also accompanied by many undesirables that could not be separated from the desired isomer. We also examined a methodology developed by Doyle and co-workers [152] (entry 3) which gave a better ratio of isomer **3.154/3.153** (1/0.5) but was also accompanied by other oxidation products and a minimal yield of 15%. Trusting that the chromium method offered the best opportunity for optimization, we looked into modifying the protecting group of the pendant alcohol to observe its influence on the oxidation. Unfortunately, the protecting group has very minimal effect on the outcome of the ratio. Generally, the bigger protecting groups TBS, TIPS and Pivaloyl (entry 1, 4, 7) favored the desired isomer **3.157** but the differences were minimal. Heating (entry 8) of the mixture provided a full conversion to the oxidation product but was accompanied by many decomposition products. Finally, increasing the number of equivalent of CrO_3/DMP to 40 eq. (entry 9) at r.t. led to a full conversion of all the starting material but obliterated the selectivity observed with the smaller loading of chromium with an observed mixture of 1:1 of **3.156/3.157**. Although the oxidation conditions are not optimized, we moved forward with isomer **3.154** and investigated the installation of the *t*-Bu group.

Table 3.9 – Optimization of the allylic oxidation



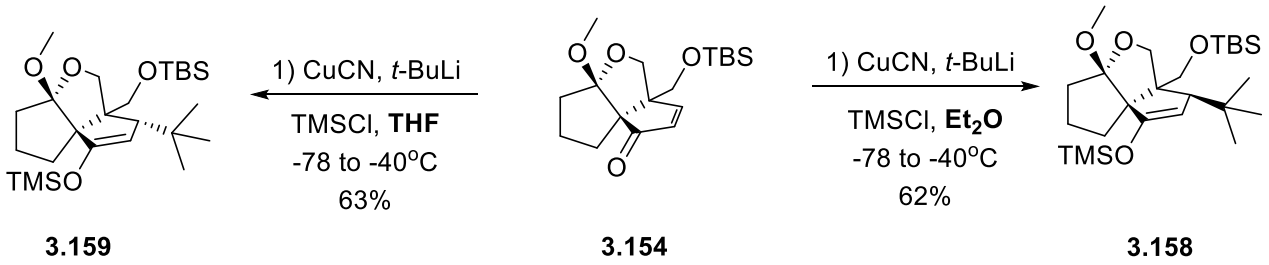
3.155 **3.156** **3.157**

Entry	R=	Conversion	Ratio[c]	
1	TBS	60	0.85	1
2	TBS[a]	40	0.70	1
3	TBS[b]	-	0.50	1
4	TIPS	55	0.80	1
5	Acetate	62	1	1
6	Benzoyl	60	1.05	1
7	Pivaloyl	56	0.90	1
8	TBS[d]	90	0.95	1
9	TBS[e]	100	1	1

[a]Oxidized using $Mn(OAc)_3$, TBHP, O_2, EtOAc.
[b]Oxidized using $Rh_2(cap)_4$, TBHP, DCE, 40°C.
[c]^{1}H NMR ratios
[d]Heating the reaction at 40°C
[e]with 40eq. of CrO_3/DMP

Compound **3.154** was treated with $(t\text{-Bu})_2CuCN$ in Et_2O to produce **3.155** in 62% yield as a sole diastereomer as product (***Scheme 3.53***). Although the reaction was highly stereoselective, NOESY experiments indicated that isomer **3.155** bears the wrong stereochemistry. Fortunately, the diastereoselectivity of the reaction could be completely reversed by changing the solvent to THF. Almost exclusive formation of the desired isomer **3.159** possessing the correct stereochemistry was obtained in 63% yield (10:1 dr).

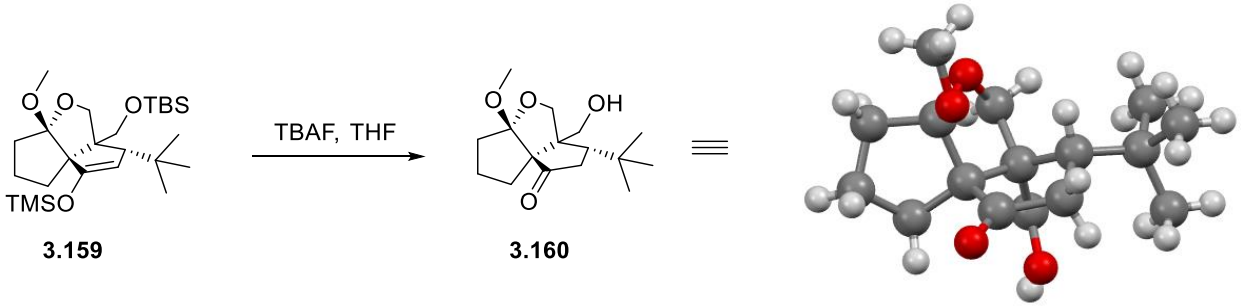
Scheme 3.53 – Effect of solvent on conjugate addition of t-Bu group



3.159 **3.154** **3.158**

Furthermore, the relative stereochemistry of **3.159** was confirmed unequivocally by X-ray crystallography using the unprotected alcohol **3.160** (***Scheme 3.54***). This represented an important milestone in the ginkgolide synthesis. We were now able to build an A-B ring system that included the quaternary carbon of the future F-ring next to the *t*-Bu moiety with the desired stereochemistry swiftly.

*Scheme 3.54 – X-ray confirmation of ketone **3.160***

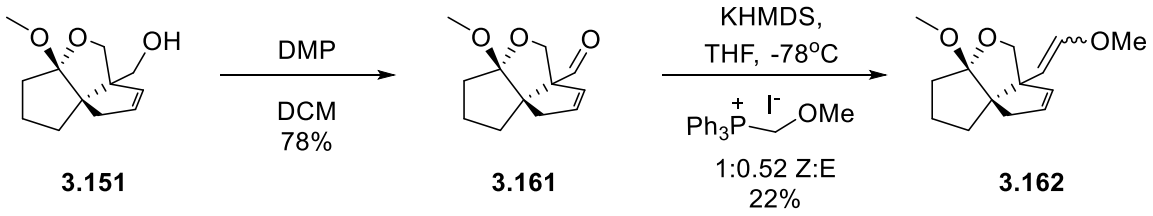


3.159 **3.160**

The sequences shown in ***Scheme 3.52*** was not optimized since the results were obtained a week before I was set to start writing my thesis. But I'm confident that better selectivity during the allylic oxidation can be induced by changing the starting material or modifying the methodology. We did have the time though, to investigate the formation of the F-ring system from alcohol **3.151** (***Scheme 3.55***). The free alcohol chain needed to be extended by one carbon to provide the necessary backbone for the F-ring system. We found that oxidizing the alcohol **3.151** to the aldehyde **3.156** with DMP and subsequent Wittig reaction with

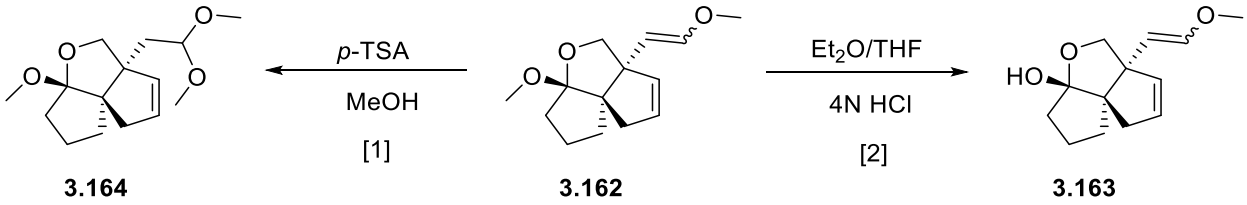
(methoxymethyl)triphenylphosphonium iodide gave methyl vinyl ether as a mixture 1:0.52 Z:E. The ylide was found to be highly unstable and required the reaction to be kept at -78˚C. Upon quenching with a NH_4Cl solution or 1N HCl only the methyl vinyl ether **3.162** was recuperated.

*Scheme 3.55 – Extending alcohol **3.151** by one carbon*



Further hydrolysis probing (***Scheme 3.56***) was performed and we found that acetal **3.164** can be formed upon treatment of vinyl ether **3.159** with catalytic amount of *p*-TSA in MeOH. Biphasic hydrolysis conditions left the vinyl ether intact while forming hemiketal **3.163**.

*Scheme 3.56 – Methyl vinyl ether's **3.157** hydrolysis investigation*

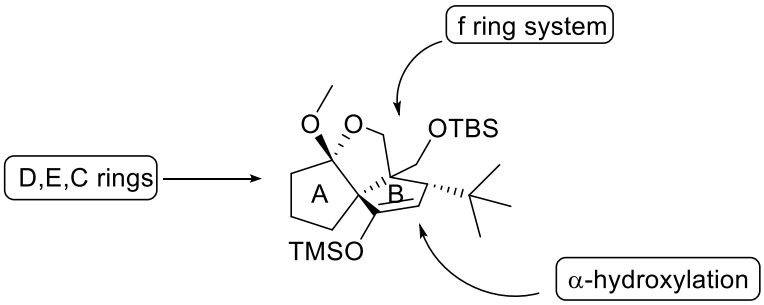


The research on the total synthesis on ginkgolide C is well positioned to continue pursuing this target. A big portion of the most complicated functionality have been installed on the B ring system while providing the chemical handles to keep going with the rest of the synthesis.

3.6 Future work needed

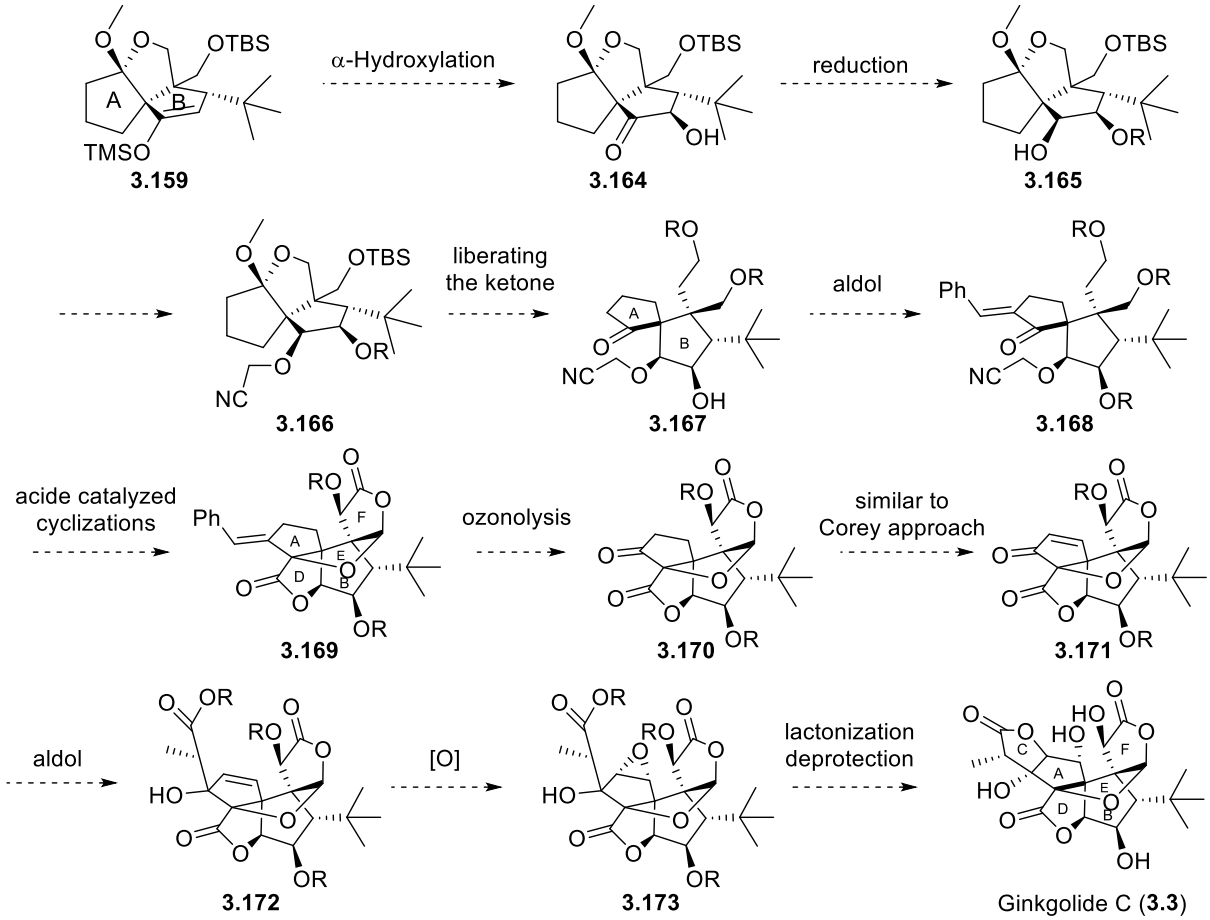
With the A-B ring system well established, we now need to finish the F ring and construct the D, E, C ring in a similar fashion to the synthetic approaches of the Corey and Crimmins (***Figure 3.6***).

*Figure 3.6 – Missing connection to spiro core **3.159***



We expect silyl enol ether **3.159** to be the perfect way to introduce the hydroxyl group stereoselectivly of **3.164** following the treatment of **3.159** with Davis oxaziridine or under Rubottom oxidation conditions (***Scheme 3.57***). While the A ring ketone is masked as the ketal, we should reduce the ketone to alcohol **3.165**. Depending on the selectivity obtained for the reduction, we might need to perform an inversion of the resulting alcohol using a Mitsunobu inversion. We can then install the methylcyano group of **3.166** that will as surrogate for the D ring system for a later intramolecular aldol. It is then necessary to liberate the ketone of ring A **3.167** to perform an aldol condensation with benzaldehyde and give enone **3.168**. At this point, we will need to perform multiple cyclization to close the D, E and F rings to give A-B-D-E-F ring system **3.169**. An ozonolysis of **3.169** should give ketone **3.170** which will be oxidized to the enone **3.171.** Intermediate **3.171** is a comparable intermediate to the one use by Corey in the synthesis of ginkgolide B and should allow us to quickly finish the synthesis following their method for the installation of the C ring through an aldol to give **3.172**, epoxidation to **3.173** and lactonization should afford ginkgolide C (**3.3**).

Scheme 3.57 – Proposed synthetic route of intermediate 3.155 toward ginkgolide C



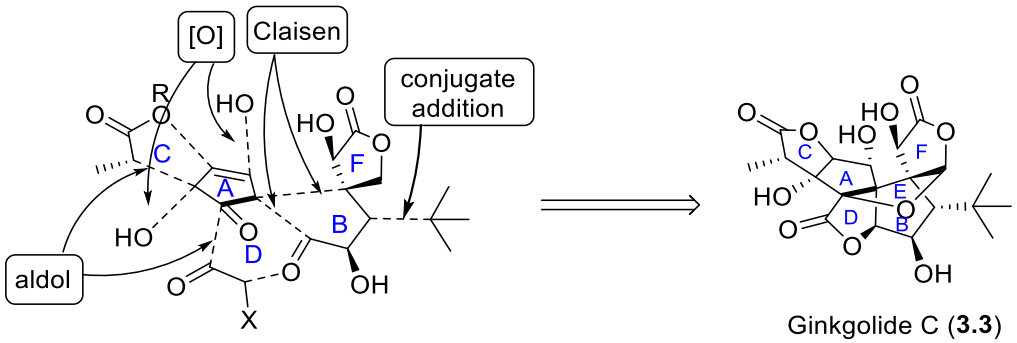
3.7 Conclusion

We looked into 4 possible routes toward ginkgolide C (**3.3**). The first route investigated involved the Rautenstrauch rearrangement which we were able to optimize. Unfortunately, we were never able to create the desired quaternary carbon necessary for the F-ring because of the steric engendered by the *t*-Bu group. Secondly, we looked into forming the quaternary carbon first but we were stopped in our path by problematic *O*-alkylation. For the third approach, we investigated the Claisen rearrangement and found that the conjugate addition of the *t*-Bu group on an acyclic

system did not work with the expected proficiency. In our last approach, we proved successful in utilizing a methodology permitting a one-pot Claissen rearrangement of ketones but we did not have the necessary time to bring the project to its ending.

So far, the synthesis of our most advance intermediate silyl enol ether **3.159** takes 13 steps for the shortest sequence. This intermediate has all the necessary handles to proceed forward with the synthesis of ginkgolide C (**3.3**), following the synthetic plan delineated in ***Scheme 3.57***. Time will tell if this approach will be successful, nonetheless we are confident that further investigation of this route will achieve the desired goal as the more complex elements of the natural product are already installed. ***Figure 3.7*** highlights the main disconnection toward ginkgolide C.

Figure 3.7 – Main disconnection of the latest synthetic strategy toward ginkgolide C



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CHAPTER 4

Summary

4.1 Claims to original research

1. The first total synthesis of papuaforin A, B and C utilizing a gold(I)-catalyzed cycloisomerization.
2. The total synthesis of the flagship of PPAPs, hyperforin, utilizing a gold(I)-catalyzed cycloisomerization.
3. The formal synthesis of nemorosone.
4. The discovery and early investigation of chromatographically stable vinyl gold species
5. The investigation of an expedient novel method for the α-allylation of ketones and unsymmetrical ketones.
6. Exploration of 4 synthetic routes towards the synthesis of ginkgolides.
7. The efficient synthesis of the ABE core of ginkgolides with all the necessary chemical handle to pursue the synthesis of ginkgolides.

4.2 Publications from this work

1. Barabé, F.; Bétournay, G.; Bellavance, G.; Barriault, L. **Gold-Catalyzed Synthesis of Carbon-Bridged Medium-Sized Rings.** *Org. Lett.*, **2009**, 11 (18), 4236–4238.

   Highlited in : -ChemInform, 41 DOI: 10.1002/chin.201004053

2. Sow B.; Bellavance, G.; Barab**é**, F.; Barriault, L. **One-pot Diels–Alder cycloaddition/gold(I)-catalyzed 6-endo-dig cyclization for the synthesis of the complex bicyclo[3.3.1]alkenone framework.** *Beilstein J. Org. Chem.* **2011**, 7, 1007-1013.
3. **Barabé, F.; Levesque P.;Sow, B.; Bellavance, G.; Bétournay G.; Barriault L. Gold(I)-catalyzed formation of bridged and fused carbocycles.** *Pure Appl. Chem.* **2013**, 85 (6), 1161-1173.

   Highlited in: -ChemInform, 44 DOI: 10.1002/chin.201344211

4. Bellavance, G.; Barriault L. **Total Syntheses of Hyperforin and Papuaforins A–C, and Formal Synthesis of Nemorosone Through a Gold(I)-Catalyzed Carbocyclization.** *Angew. Chem. Int. Ed.* **2014**, 53, 6701-6704.

   Highlighted in: *-ChemInform*, 46 doi: 10.1002/chin.201501214

   -Synfacts **2014**, 10(8), 780

5. McGee, P., Bellavance, G., Korobkov, I., Tarasewicz, A. and Barriault, L. **Synthesis and Isolation of Organogold Complexes through a Controlled 1,2-Silyl Migration**. *Chem. Eur. J.* **2015**, *21, 9662-9665.*
6. A complete article on the construction of PPAPs is in preparation
7. An article on expedient one-pot α-allylation of ketone from allylic alcohols is in preparation

4.3 Presentations of this work

Location	Conference type
Honolulu - 2015	Pacifichem 2015 – (Poster)

Bates College - 2015	Gordon Research Conferences: Organic Reactions and Processes – (Poster)
Ottawa convention center - 2015	*98th canadien chemistry conference and exhibition (CSC) – (presentation)*
Same as above	*16th symposium on the latest trends in organic synthesis (LTOS)* – (Poster)
Brock University - 2014	
Ottawa convention center - 2014	*19th International Symposium on Homogeneous Catalysis* – (Poster)
Quebec convention center - 2013	*96th Canadian chemistry conference and exhibition* – (presentation)
Sherbrook - 2013	*24nd edition of QOMSBOC* conference – (Poster)
University of Ottawa - 2013	*OCCI conference* – (Poster)
University of Ottawa - 2012	1st place winner during *synthesis day symposium* (Poster)
Concordia University - 2011	*22nd edition of QOMSBOC* conference – (Poster)

CHAPTER 5

Experimental Section

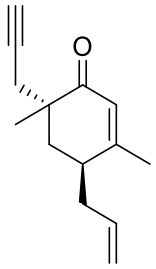
5.1 Polycyclic polyprenylated acylphloroglucinols

Unless otherwise indicated, all reactions were performed under either an argon or nitrogen atmosphere in flame-dried glassware equipped with a Teflon coated magnetic stir bar and a rubber septum. Where no temperature was specified, the reactions were ran at ambient temperature (23 °C). Reagent quantities (mmol) were calculated based on their reported purities. Anhydrous THF and Et_2O were obtained by storing the solvent over a bed of 4 A˚ molecular sieves. Et_3N, TMSCl, DIPA and CH_2Cl_2 were distilled from CaH_2. Commercially available reagents were used as received unless otherwise stated. *n*-Butyllithium and *tert*-butyllithium were titrated using 2,6-di-*tert*-butyl-4-methylphenol and fluorene. Grignard reagents were titrated according to Love's protocol. Microwave reactions were performed using a CEM Model ESP-1500 Plus microwave oven equipped with a pressure monitoring device and an EST-300 Plus fiber optic temperature probe. The reaction vessel was a quartz tube to which was added the reaction mixture as well as a carboflonTM to aid in the absorption of microwave radiation. Reactions were monitored by TLC analysis using aluminum plates pre-coated (250 μm thickness) with ultra-pure silica gel (60A, SiliCycle). TLC plates were viewed using UV light and stained with either *p*-anisaldehyde, potassium permanganate, or phosphomolybdic acid staining solutions. Flash chromatography was carried out on 230–400 mesh silica gel (60A, SiliCycle).

^{1}H and ^{13}C NMR, spectra were recorded on either Bruker Avance 300 MHz, Bruker Avance 400MHz, Bruker Avance 500 MHz, Bruker AMX 500 or Varian INOVA 500 MHz

spectrometers in the specified deuterated solvents. IR spectra were recorded on a Bomen Michaelson 100 FTIR spectrometer. HRMS spectra were obtained using a Kratos Analytical Concept spectrometer. Melting points were recorded using a Gallenkamp P1106G Melting Point Apparatus.

5.1.1 Model substrate



(2.145) 4-allyl-3,6-dimethyl-6-(prop-2-ynyl)cyclohex-2-enone

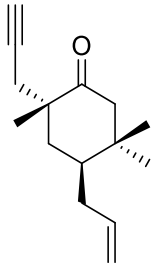
A solution of *n*-BuLi (1.60 M in hexanes, 21.8 mL, 35.0 mmol) was added slowly to diisopropylamine (5.17 mL, 36.6 mmol) in THF (150 mL) at −78 °C for 45 min. 4-allyl-3,6-dimethylcyclohex-2-enone (**2.172**) (5.00 g, 33.3 mmol) was added at −78 °C for 60 min and then propargyl bromide (2.49 mL, 39.9 mmol) was added. The mixture was stirred at r.t. for 3 h. An aqueous saturated solution of NH_4Cl was added and the aqueous layers were extracted with ethyl acetate (3x). The combined organic phases were dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated. The crude residue was purified by flash chromatography (10% EtOAc:hexanes) to give enone **2.145** (4.92 g, 90%) as a yellow-orange oil.

IR (neat, cm^{-1}) νmax: 3305(br.) 3305, 3077, 2976, 2930, 1674.

^1H NMR (400 MHz, $CDCl_3$) δ 5.78(s,1H), 5.69(m,1H), 5.10(m,2H), 2.49(m,2H), 2.35 (m, 1H), 2.15(m,3H), 2.01(t, J= 2.65, 1H), 1.93 (s,3H), 1.57(dd, J= 13.82, 10.29, 1H), 1.16(s, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 202.6(C), 163.0 (C), 135.3(CH), 126.5 (CH), 118.1 (CH_2), 80.5 (C), 71.4 (CH), 44.0 (C), 38.5 (CH_2), 36.9 (CH), 36.7 (CH_2), 26.8 (CH_2), 22.3 (2xCH_3).

HRMS (EI) m/z calcd for $C_{14}H_{18}O$ 202.1358 found 202.1379.



(2.146) 4-allyl-2,5,5-trimethyl-2-(prop-2-ynyl)cyclohexanone

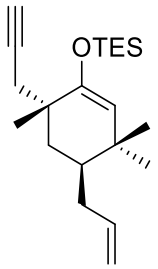
To a solution of CuI (63.0 mg, 0.33 mmol) and enone **2.145** (306 mg, 1.52 mmol) in THF (15.0 mL) and Me_2S (1.50 mL) at 0 °C was slowly added MeMgBr (1.11 mL, 3.0 M in Et_2O, 3.33 mmol) over 1 hour. The mixture was then stirred 1 h at 0 °C, then the reaction was stopped by adding NH_4Cl aqueous solution, and extracted with Et_2O. The organic phase was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography to provide **2.146** (176 mg, 53%) a dark orange oil.

IR (neat, cm^{-1}) νmax: 3310, 3076, 2965, 2931, 2871, 2124, 1716, 1640, 1436.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76(m,1H), 5.02(m,2H), 2.49(0.5H), 2.45(m,1H), 2.37(m,2H), 2.33(m,0.5H), 2.00(m, 2.5), 1.70(m,2.5H), 1.26(t, 1H), 1.09(s,3H), 1.04(s, 3H), 0.96(m, 1H), 0.73(m, 3H).

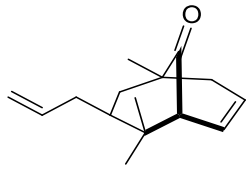
^{13}C NMR (400 MHz, $CDCl_3$) δ 213.2 (C), 137.6 (CH), 116.3 (CH_2), 79.5 (C), 71.5 (CH), 52.9 (CH_2), 48.0 (C), 41.5 (CH), 40.0 (CH_2), 39.3 (C), 34.2 (CH_2), 29.8 (CH_3), 27.8 (CH_2), 22.2 (CH_3), 20.1 (CH_3).

HRMS (EI) m/z calcd for $C_{15}H_{22}O$ 218.1671 found 218.1659.



(2.147) 4-Allyl-2,5,5-trimethyl-2-(prop-2-ynyl)cyclohexanone

Ketone **2.146** (300 mg, 1.37 mmol) was dissolved in acetonitrile (30.0 mL), and Et_3N (0.383 mL, 2.74 mmol) was added. Then flame-dried NaI (0.309 g, 2.04 mmol) and TBSCl (310 mg, 2.04 mmol) were added. The reaction mixture was allowed to reflux overnight and was then quenched with $NaHCO_3$ saturated solution, and the aqueous phase was extracted with DCM (3x). The organic phases were then combined and concentrated. The resulting mixture was filtered through a small silica pad and washed with solution of 7% EtOAc in hexanes and concentrated again. The crude enol ether **2.145** (209 mg, 46%) was then directly used for the next reaction without further purification.



(2.131) 7-allyl-5,8,8-trimethylbicyclo[3.3.1]non-2-en-9-one

A solution of silyl enol ether **2.147** (20.0 mg, 0.060 mmol) and (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) (0.92 mg, 0.0012 mmol) in DCM (1 mL) was stirred for 6 h at r.t. The solvent was evaporated and the residue was purified by flash column chromatography on silica (10% EtOAc:hexanes) to give 88% of bicycle **2.131** as a white solid.

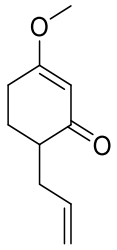
IR (neat, cm^{-1}) νmax 3081(l) 3039(l) 2967(br.) 2921(br.) 1709(l) 1449(l) 918(l) 842(l) 638(l).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82(m, 1H), 5.76(m, 1H), 5.63(dddd, J = 9.5 Hz, 6.03 Hz, 1.94 Hz, 1.94 Hz, 1H), 5.03(m, 1H), 2.41(m,3H), 2.25(m, 1H), 2.03(m, 1H), 1.82(dd, J=13.91 Hz, 4.51 Hz, 1H), 1.59(ddd, J=13.72 Hz, 10.78 Hz, 8.62 Hz, 2H), 1.28(m, 4H), 1.02(s, 3H), 0.99(s, 3H), 0.79(s, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 216.5 (C), 138.0 (CH), 129.8 (CH), 126.6 (CH), 116.0 (CH_2), 60.3 (CH), 46.0 (CH_2), 45.6 (CH_2), 42.4 (C), 38.1 (CH), 34.1 (C), 29.7 (CH_2), 26.1 (CH_3), 23.5 (CH_3), 20.8 (CH_3).

HRMS (EI) m/z calcd for $C_{15}H_{22}O$ 218.1671 found 218.1652.

5.1.2 Synthesis intermediates and natural products



(2.161) 6-allyl-3-methoxycyclohex-2-enone

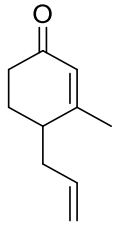
A solution of *n*-BuLi (9.7 M in hexanes, 13.1 mL, 127 mmol) was added slowly to freshly distilled diisopropylamine (19.0 mL, 133 mmol) in THF (300 mL) at −78°C and the solution was stirred for 30 min at -78°C and 15 min at 0°C before cooling to -78°C. A solution of 3-methoxycyclohex-2-enone (**2.160**) (15.3 g, 121 mmol) in THF (20 mL) was cannulated at −78°C and the solution was stirred for 60 min to obtain a slurry. Allyl bromide (12.6 mL, 146 mmol) was added in one portion, the mixture was stirred 1h at -78°C and 3h at r.t. A saturated solution of NH_4Cl was added and the aqueous layer was extracted with ethyl acetate (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (25-30% EtOAc:hexanes) to give 6-allyl-3-methoxycyclohex-2-enone (**2.161**) (18.9 g, 102 mmol, 94%) as a lightly yellow oil.

IR (neat, cm^{-1}) ν_{max}: 2948, 2378, 1658, 1610, 1380, 1191.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.63-1.73 (m, 1 H) 2.00-2.07 (m, 1 H) 2.07-2.14 (m, 1 H) 2.21-2.27 (m, 1 H) 2.38-2.42 (m, 2 H) 2.59-2.65 (m, 1 H) 3.66 (s, 3 H) 5.00-5.06 (m, 2 H) 5.32 (s, 1 H) 5.70-5.81 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 25.8 (CH_2) 27.9 (CH_2) 34.0 (CH_2) 44.7 (CH) 55.6 (CH_3) 101.9 (CH) 116.6 (CH_2) 136.3 (CH) 177.7 (C) 200.4 (C).

HRMS (EI) *m/z* calcd for $C_{10}H_{14}O_2$ [M^+] 166.0994, found: 166.0991.



(2.162) 4-allyl-3-methylcyclohex-2-enone

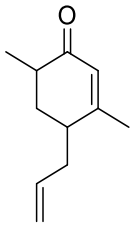
A solution of methyllithium (1.6 M in Et_2O, 225 mL, 360 mmol) was added in one portion to a solution of 6-allyl-3-methoxycyclohex-2-enone (**2.161**) (49.83 g, 300 mmol) in dry ether (500 mL) at −78 °C and stirred for 30 min. The mixture was allowed to heat up to r.t. for 90min. An aqueous solution of 1 N HCl (210ml) was added and heavily stirred. After stirring for 1 h at r.t., water was added. The aqueous layer was extracted with ethyl acetate (3x), and the combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude oil was purified by chromatography (7-15 % EtOAc:hexanes) to give 4-allyl-3-methylcyclohex-2-enone (**2.162**) (44.26 g, 295 mmol, 98%) as a clear yellow oil. Spectral data was in accordance with reported data and full characterization is available through the literature[1].

*Alternatively **4-allyl-3-methylcyclohex-2-enone** can be prepared in a one pot fashion starting with 3-methoxycyclohex-2-enone:

A solution of *n*-BuLi (2.4 M in hexanes, 0.233 mL, 8.72 mmol) was added slowly to freshly distilled diisopropylamine (1.30 mL, 9.12 mmol) in THF (30 mL) at −78°C and the solution was stirred for 30 min at -78°C and 15 min at 0°C before being recooled to -78°C. A solution of 3-methoxycyclohex-2-enone (**2.160**) (1 g, 7.93 mmol) in THF (3 mL) was cannulated at −78°C and the solution was stirred for 60 min to obtain a slurry. Allyl bromide (0.857 mL, 9.91 mmol) was added in one portion, the mixture was stirred 1h at -78°C and 3h at r.t. The solution was then recooled to -78°C and MeLi (1.5 M in Et_2O, 13.2 mL, 19.8 mmol) was added in one portion. The resulting mixture was stirred for 30 min at -78°C. It was then warmed to r.t. and stirred for one more hour. A solution of 1 M of HCl (30.0 mL) was then added and stirred vigorously for 1h. Water (30.0 ml) was then added with brine (30.0 mL) and Et_2O (30.0 mL), the phases were

[1] Johnson, S. W.; McCarry E. B.; Markezich, L. R.; Boots, G.S.; JACS, 1980, 352

sperated and the aqueous layer was extracted with ethyl acetate (3x), and the combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude oil was purified by chromatography (7-15% EtOAc:hexanes) to give 4-allyl-3-methylcyclohex-2-enone (**2.162**) (0.785 g, 5.23 mmol, 66%) as a clear yellow oil.



(2.172) 4-allyl-3,6-dimethylcyclohex-2-enone

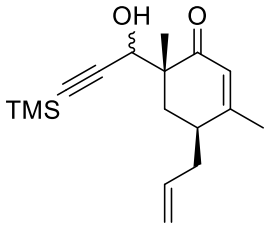
LiHMDS (19.5 g, 113 mmol) was charged to 1L flame dried flask. THF (500 mL) was added at r.t. and stirred, once all LiHMDS was dissolved the solution was cooled to −78°C and 4-Allyl-3-methylcyclohex-2-enone (**2.162**) (15.5 g, 103 mmol) in THF (30.0 mL) was cannulated to the solution. The solution was stirred 1h at -78°C, 1h at -43°C and iodomethane (7.68 mL, 123 mmol) was added. The mixture was allowed to warm to r.t. and stirred for 3-4 h. A saturated solution of NH_4Cl was added and the aqueous layer was extracted with ether (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (3-7% EtOAc:hexanes) to give 4-allyl-3,6-dimethylcyclohex-2-enone (**2.172**) (14.8 g, 90.0 mmol, 87%) as a lightly yellow oil.

IR (neat, cm^{-1}) ν_{max}: 3077, 2964, 2930, 2872, 1673, 1639, 1443, 1378.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.09 (d, *J* = 6.9 Hz, 3H) 1.71-1.80 (m, 1H) 1.95 (s, 3H) 1.99 (ddd, *J* = 13.5, 4.8, 2.8 Hz, 1H) 2.18-2.33 (m, 2H) 2.37-2.48 (m, 2H) 5.07-5.12 (m, 2H) 5.79 (s, 1H) 5.74-5.85 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.4 (CH_3) 22.9 (CH_3) 34.5 (CH_2) 35.6 (CH_2) 35.9 (CH) 39.2 (CH) 117.1 (CH_2) 126.4 (CH) 136.5 (CH) 164.0 (C) 201.9 (C).

HRMS (EI) *m/z* calcd for $C_{11}H_{16}O$ [M^+] 164.1201, found: 164.1205.



(2.173) 4-allyl-6-(1-hydroxy-3-(trimethylsilyl)prop-2-ynyl)-3,6-dimethylcyclohex-2-enone

A solution of *n*-BuLi (9.8 M in hexanes, 5.18 mL, 50.0 mmol) was added slowly to freshly distilled diisopropylamine (7.57 mL, 53.1 mmol) in THF (250 mL) at −78°C and the solution was stirred for 30 min at -78°C and 15 min at 0°C. 4-Allyl-3,6-dimethylcyclohex-2-enone (**2.172**) (7.93 g, 48.3 mmol) was cannulated to the solution at -78°C. After stirring for 60 min, 3-(trimethylsilyl)propiolaldehyde (**2.204**) (7.32 g, 58.0 mmol) was added and the mixture was stirred at -78°C for 10 min. The resulting mixture was quenched with a saturated solution of NH_4Cl at -78°C. Distilled water was added and the aqueous layer was extracted with EtOAc:Et_2O 1:3 (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by chromatography (5-15% EtOAc:hexanes) to give alcohol enone (**2.173**) (9.39 g, 32.3 mmol, 67%) as a mixture of two diastereomers.

Major diastereoisomer (last on TLC)

IR (neat, cm^{-1}) ν_{max}: 3421, 2928, 2856, 1657, 1471, 1249, 1060, 838, 811, 776.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.16 (s, 9 H) 1.20 (s, 3 H) 1.71 (dd, *J*=14.3, 8.6 Hz, 1 H) 1.96 (s, 3 H) 2.13 (m, 2 H) 2.51-2.56 (m, 2 H) 2.69 (s, 1 H) 4.54 (s, 1 H) 5.10-5.14 (m, 2 H) 5.66-5.76 (m, 1 H) 5.83 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -0.2 (3x CH_3) 17.2 (CH_3) 22.1 (CH_3) 36.7 (CH) 36.9 (CH_2) 37.4 (CH_2) 48.2 (C) 66.8 (CH) 91.2 (C) 102.5 (C) 117.8 (CH_2) 126.0 (CH) 135.2 (CH) 163.5 (C) 202.8 (C).

m.p. 53-54; HRMS (EI) *m/z* calcd for $C_{16}H_{23}O_2Si$ [M^+] 275.1467 (-Me), found: 275.1461.

Minor diastereoisomer (second last on TLC)

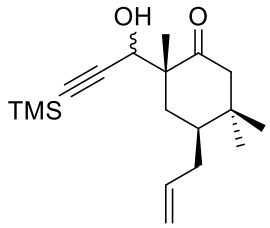
IR (neat, cm^{-1}) ν_{max}: 3427, 2962, 1647, 1247, 1053, 1000, 837, 759.

^{1}H NMR, (400 MHz, CDCl3) δ ppm 0.14 (s, 9 H) 1.17 (s, 3 H) 1.73 (dd, *J*=14.3, 6.5 Hz, 1 H) 1.97 (s, 3 H) 2.16 (dt, *J*=14.2, 9.0 Hz, 1 H) 2.35 (dd, *J*=14.3, 5.9 Hz, 1 H) 2.48-2.55 (m, 1 H) 2.64 (d, *J*=6.3 Hz, 1 H) 2.65-2.72 (m, 1 H) 4.47 (d, *J*=6.3 Hz, 1 H) 5.08-5.13 (m, 2 H) 5.77 (dddd, *J*=15.7, 11.4, 7.8, 6.2 Hz, 1 H) 5.86 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -0.2 (3x CH_3) 22.2 (CH_3) 22.6 (CH_3) 33.5 (CH_2) 37.3 (CH_2) 37.8 (CH) 48.4 (C) 68.6 (CH) 91.5 (C) 103.8 (C) 117.5 (CH_2) 127.0 (CH) 135.9 (CH) 164.4 (C) 202.2 (C).

HRMS (EI) *m/z* calcd for $C_{17}H_{26}O_2Si$ [M^+] 290.1702, found: 290.1656.

mp. 68-70.



(2.174) 4-allyl-2-(1-hydroxy-3-(trimethylsilyl)prop-2-ynyl)-2,5,5-trimethylcyclohexanone

To a solution of purified CuI[2](9.47 g, 49.7 mmol) and enone (**2.173**) (7.84 g, 41.2 mmol, 2 eq.) in THF (250 mL), Me_2S (25 mL) was added at 0°C and the solution was stirred until the solution became homogenous. MeMgBr (41.4 mL, 3.0 M in Et_2O, 124 mmol, 5eq.) was added over 90 min with a syringe pump under heavy stirring. After the addition was completed, the reaction became a very dense dark green solution and the solution was allowed to warm back to r.t. and stirred for 5 h. A saturated solution of NH_4Cl was added with equal amount of distilled water. The mixture was extracted with Et_2O (3x). The combined organic phases were dried over $MgSO_4$ and filtered over a short pad of celite. The crude was concentrated and filtered over celite one more time using ether to wash the celite pad and concentrated again. The residue was not purified any further and was use for the next step.

Major diastereomer:

IR (neat, cm^{-1}) ν_{max}: 3421, 2956, 2358, 1703, 1247, 1066, 842.

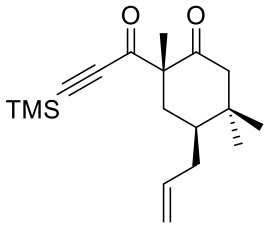
^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.17 (s, 9 H) 0.76 (s, 3 H) 1.05 (s, 3 H) 1.09 (s, 3 H) 1.23 (dd, *J*=14.7, 12.9 Hz, 1 H) 1.60 (m, 1 H) 1.72-1.80 (m, 1 H) 2.03 (br.s., 1 H) 2.08 (d, *J*=13.7 Hz, 1 H) 2.20 (dd, *J*=14.9, 3.9 Hz, 1 H) 2.33-2.40 (m, 1 H) 2.55 (d, *J*=13.5 Hz, 1 H) 4.91 (s, 1 H) 5.00-5.06 (m, 2 H) 5.69-5.79 (m, 1 H).

[2] Purified according to 5th edition of "Purification of laboratory chemicals", Armarego, L., F., W.; Chai, L., L., C.

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -0.3 (3x CH_3) 16.6 (CH_3) 20.2 (CH_3) 29.6 (CH_3) 34.1 (CH_2) 39.1 (CH_2) 39.5 (C) 41.0 (CH) 52.9 (CH_2) 53.4 (C) 66.9 (CH) 92.3 (C) 102.4 (C) 116.1 (CH_2) 137.4 (CH) 212.7 (C).

HRMS (EI) *m/z* calcd for $C_{18}H_{30}O_2Si$ [M^+] 306.2015, found: 306.1995.

m.p. 86-87.



(2.175) 4-allyl-2,5,5-trimethyl-2-(3-(trimethylsilyl)propioloyl)cyclohexanone

To a solution of crude alcohol (**2.173**) in wet DCM (150 mL) was added Dess-Martin periodinane (13.7 g, 32.3 mmol). The reaction was stirred for 1 h and quenched with a 1:1 mixture of 5% $NaHCO_3$ solution and saturated solution of $Na_2S_2O_3$ under heavy stirring for 30 min. The resulting mixture was then separated and the aqueous phase was extracted 3x with DCM. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (5% EtOAc:hexanes) to provide diketone **2.175** (5.48 g, 18.0 mmol, 72 %) as a white solid over 2 steps.

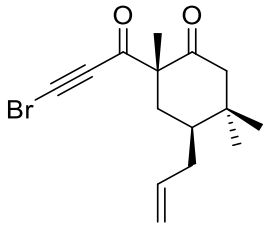
IR (neat, cm^{-1}) ν_{max}: 3074, 2961, 2931, 2855, 1722, 1668, 1454, 1252, 1252, 1047, 848, 762.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.24 (s, 9 H) 0.74 (s, 3 H) 1.01 (s, 3 H) 1.25 (s, 3 H) 1.29 (dd, *J*=14.70, 12.55 Hz, 1 H) 1.59-1.71 (m, 2 H) 2.13 (d, *J*=13.5 Hz, 1 H) 2.36-2.41 (m, 1 H) 2.44 (d, *J*=13.5 Hz, 1 H) 2.67 (dd, *J*=14.6, 3.2 Hz, 1 H) 5.03-5.10 (m, 2 H) 5.79 (dddd, *J*=17.1, 10.0, 8.2, 5.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -0.9 (3x CH_3) 19.9 (CH_3) 20.4 (CH_3) 29.6 (CH_3) 34.1 (CH_2) 38.7 (CH_2) 39.3 (C) 42.7 (CH) 55.5 (CH_2) 63.4 (C) 98.8 (C) 101.6 (C) 116.4 (CH_2) 137.3 (CH) 188.6 (C) 207.7 (C).

HRMS (EI) *m/z* calcd for $C_{18}H_{28}O_2Si$ [M^+] 304.1859, found: 304.1848.

m.p. 51-55.



(2.207) 4-allyl-2-(3-bromopropioloyl)-2,5,5-trimethylcyclohexanone

To a solution of diketone **2.175** (1.49 g, 6.41 mmol) in dry acetone (30 mL), was added $AgNO_3$ (0.545 g, 3.21 mmol). The mixture was stirred for 5 min before the addition of recrystallized NBS (1.25 g, 7.05 mmol). The reaction was stirred 2h at r.t. before it was filtered over celite and washed with acetone. The filtrate was concentrated and purified by flash chromatography (5% EtOAc:hexanes) to afford diketone **2.207** (1.87 g, 5.99 mmol, 93 %) as a white solid stable to air and moisture for weeks.

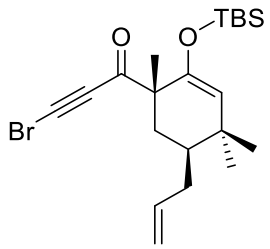
IR (neat, cm^{-1}) ν_{max}: 2967, 2937, 2864, 1772, 1669, 1447, 1369, 1660.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.75 (s, 3 H) 1.02 (s, 3 H) 1.26 (s, 3 H) 1.31 (dd, 1 H) 1.59-1.73 (m, 2 H) 2.15 (d, *J*=13.5 Hz, 1 H) 2.36-2.41 (m, 2 H) 2.63 (dd, *J*=14.6, 3.2 Hz, 1 H) 5.06-5.10 (m, 2 H) 5.75-5.85 (m, *J*=16.4, 10.8, 8.3, 5.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 19.9 (CH_3) 20.2 (CH_3) 29.6 (CH_3) 34.0 (CH_2) 38.3 (CH_2) 39.3 (C) 42.8 (CH) 55.6 (CH_2) 60.3 (C) 63.7 (C) 77.2 (C) 116.5 (CH_2) 137.2 (CH) 186.9 (C) 207.0 (C).

HRMS (EI) *m/z* calcd for $C_{15}H_{19}BrO_2$ [M^+] 310.0568, found: 310.0540.

m.p. 88-89.



(2.211) 1-(5-allyl-2-((tert-butyldimethylsilyl)oxy)-1,4,4-trimethylcyclohex-2-en-1-yl)-3-bromoprop-2-yn-1-one

2,6-Di-tert-butyl-4-methylpyridine[3] (12.6 g, 61.5 mmol) was charged to a flame dried flask under argon atmosphere. DCM (30 mL) was then added. To the stirred solution, diketone (**2.207**) (3.83 g, 12.3 mmol) was added in one portion, followed by dropwise addition of TBSOTf (11.3 mL, 49.2 mmol) and the solution was stirred 3 days at 40°C in an oil bath[4]. The aged brown solution was quenched slowly with a solution of 5% $NaHCO_3$ and the aqueous phase was extracted 3x with DCM. The organic phases were combined, dried over $MgSO_4$ and concentrated. The mixture was purified immediately by flash chromatography (pure hexanes to recuperate 2,6-di-tert-butyl-4-methylpyridine, 30% benzene:hexanes to recuperate the desired silane enol ether **2.211** (4.09 g, 9.61 mmol, 78 %) (a pale yellow oil which became a white solid if left in the fridge o/n) and 5% EtOAC:hexanes to recuperate residual starting material **2.207**.

IR (neat, cm^{-1}) ν_{max}: 2962, 2929, 2856, 2358, 2175, 1670, 1463, 1251, 1155, 1054, 871, 827, 777.

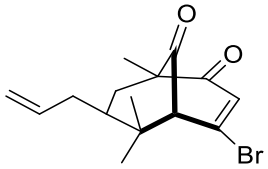
[3] Commercially available or can be made on large scale following this methodology: Stang, J. P.; Anderson, G. A.; J. Org. Chem., Vol. 41, No. 18, **1976**.
[4] Lower temperature provide lower yields and higher temperature degrades starting material

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.17 (d, *J*=1.8 Hz, 6 H) 0.82 (s, 3 H) 0.87 (s, 9 H) 1.02 (s, 3 H) 1.29 (s, 3 H) 1.31-1.34 (m, 1 H) 1.45-1.68 (m, 2 H) 2.03 (dd, *J*=14.0, 2.6 Hz, 1 H) 2.24-2.30 (m, 1 H) 4.65 (s, 1 H) 4.97-5.02 (m, 2 H) 5.64-5.75 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -5.0 (CH_3) -4.3 (CH_3) 18.2 (C) 22.3 (CH_3) 23.1 (CH_3) 25.7 (3xCH_3) 29.3 (CH_3) 34.2 (CH_2) 35.1 (C) 36.5 (CH_2) 40.1 (CH) 54.0 (C) 57.9 (C) 79.2 (C) 116.0 (CH_2) 117.6 (CH) 137.8 (CH) 148.4 (C) 190.0 (C).

HRMS (EI) *m/z* calcd for $C_{21}H_{33}BrO_2Si$ [M^+] 367.0729 (-*t*-Bu), found: 367.0727.

m.p. 68-69.



(2.212) 7-allyl-4-bromo-1,6,6-trimethylbicyclo[3.3.1]non-3-ene-2,9-dione

To a solution of silane enol ether **2.211** (1.41 g, 3.31 mmol) in dry acetone (10 mL) was added JohnPhosAuCN-SbF_6 (0.128 g, 0.166 mmol, 5% loading). The resulting mixture was left open to air at r.t. and followed by TLC. After 30 min all the starting material had disappeared. The mixture was concentrated and purified by flash chromatography (3-5% EtOAc:hexanes) to afford bicycle **2.212** (0.980 g, 3.17 mmol, 96%) as a white solid.

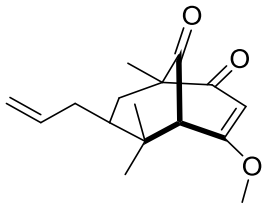
IR (neat, cm^{-1}) ν_{max}: 3078, 2973, 2937, 1738, 1675, 1594, 1374, 1275, 1143, 993.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.91 (s, 3 H) 1.18 (s, 3 H) 1.27 (s, 3 H) 1.32 (t, *J*=13.4 Hz, 1 H) 1.56-1.66 (m, 1 H) 1.72-1.79 (m, 1 H) 1.99 (dd, *J*=13.7, 4.3 Hz, 1 H) 2.25-2.30 (m, 1 H) 3.28 (s, 1 H) 4.96-5.01 (m, 2 H) 5.56-5.67 (m, 1 H) 6.83 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.3 (CH_3) 20.6 (CH_3) 27.5 (CH_3) 33.9 (CH_2) 37.8 (CH) 41.9 (C) 42.2 (CH_2) 60.6 (C) 70.6 (CH) 117.1 (CH_2) 135.6 (CH) 136.1 (CH) 145.8 (C) 197.4 (C) 205.5 (C).

HRMS (EI) *m/z* calcd for $C_{15}H_{19}BrO_2$ [M^+] 296.0412 (-Me), found: 296.0351.

m.p. 94-96.



(2.218) 7-allyl-4-methoxy-1,6,6-trimethylbicyclo[3.3.1]non-3-ene-2,9-dione

Sodium methoxide (1.17 g, 21.69 mmol) was charged to flame-dried flask. Methanol (20.0 mL) was then added slowly. Once the solution was homogenous, bicycle **2.212** (2.25 g, 7.23 mmol) was added in one portion to the stirred solution at r.t. which was then heated to 45˚C in an oil bath. After 3h, the solvent was evaporated and the crude was purified directly by flash chromatography (15-20% EtOAc:hexanes) to afford *O*-methylatedtrione **2.218** (1.68 g, 6.40 mmol, 89%) as a white solid.

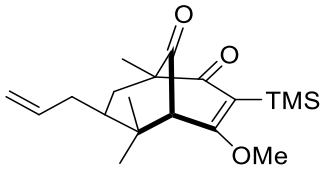
IR (neat, cm^{-1}) ν_{max}: 3085, 2965, 2936, 1730, 1656, 1603, 1443, 1374, 1194, 998, 926, 735.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.88 (s, 3 H) 1.03 (s, 3 H) 1.18 (s, 3 H) 1.24-1.31 (m, 1 H) 1.58-1.66 (m, 1 H) 1.72-1.79 (m, 1 H) 2.00 (dd, *J*=13.7, 4.5 Hz, 1 H) 2.21-2.27 (m, 1 H) 2.85 (s, 1 H) 3.74 (s, 3 H) 4.95-4.99 (m, 2 H) 5.57-5.67 (m, 1 H) 5.68 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.5 (CH_3) 20.4 (CH_3) 27.0 (CH_3) 34.0 (CH_2) 38.7 (CH) 41.3 (C) 42.0 (CH_2) 56.5 (CH_3) 60.1 (C) 65.5 (CH) 105.4 (CH) 116.8 (CH_2) 136.5 (CH) 174.6 (C) 197.6 (C) 207.8 (C).

m.p. 160-162

HRMS (EI) *m/z* calcd for $C_{16}H_{22}O_3$ [M^+] 262.1569, found: 262.1579.



(2.256) 7-allyl-4-methoxy-1,6,6-trimethyl-3-(trimethylsilyl)bicyclo[3.3.1]non-3-ene-2,9-dione

To a solution of *O*-methylatedtrione **2.218** (1.25 g, 4.76 mmol) in THF (24 mL) at -78 °C was added a freshly prepared solution of LiTMP (10.5 mL, 1 M in THF, 10.5 mmol). The reaction mixture was stirred for 5 min before addition of freshly distilled TMSCl[5] (2.56 mL, 20.0 mmol). The reaction mixture was stirred and allowed to warm to -40 °C over 2 h. The reaction was quenched with a saturated solution of NH_4Cl, and the product was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude was purified by flash chromatography (5-10 % EtOAc: hexanes) to afford vinylsilane **2.256** (1.49 g, 4.46 mmol, 94%) as a white solid.

IR (neat, cm^{-1}) ν_{max}: 3077, 2973, 2897, 1732, 1644, 1558, 1333, 1214, 1158, 1037, 844, 760, 639.

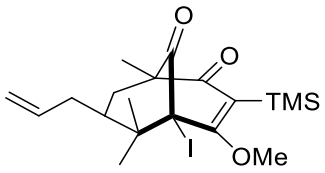
[5] Distilled over CaH_2

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.18 (s, 9 H) 0.92 (s, 3 H) 1.09 (s, 3 H) 1.14 (s, 3 H) 1.24 (t, *J*=13.0 Hz, 1 H) 1.56-1.71 (m, 2 H) 1.98 (dd, *J*=13.5, 4.3 Hz, 1 H) 2.21-2.26 (m, 1 H) 3.27 (s, 1 H) 3.74 (s, 3 H) 4.95-5.00 (m, 2 H) 5.56-5.66 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 0.5 (3x CH_3) 15.8 (CH_3) 20.8 (CH_3) 25.8 (CH_3) 33.7 (CH_2) 38.2 (CH) 42.1 (C) 42.2 (CH_2) 56.1 (CH_3) 60.2 (C) 60.8 (CH) 116.7 (CH_2) 123.1 (C) 136.5 (CH) 178.9 (C) 201.5 (C) 208.8 (C).

HRMS (EI) *m/z* calcd for $C_{19}H_{30}O_3Si$ [M^+] 320.1808 (-Me), found: 320.1749.

m.p. 93-96.



(2.258) 7-allyl-5-iodo-4-methoxy-1,6,6-trimethyl-3-(trimethylsilyl)bicyclo[3.3.1]non-3-ene-2,9-dione

To a solution of vinylsilane **2.256** (1.67 g, 5 mmol) in THF (5.00 mL) was added freshly distilled TMSCl (3.19 mL, 24.99 mmol) (distilled over CaH_2) (mmol) at room temperature and then cannulated to a freshly prepared LDA solution (0.58 M in THF, 30 mL, 17.5 mmol) at -78˚C. After stirring for 10 min at -78 °C, the reaction mixture was allowed to warm to 0°C in an ice bath. After stirring for 30 sec at 0 °C, iodide (3.81 g, 15.0 mmol) in THF (5 mL) was added to the resulting solution via cannula. The resulting solution was stirred for 15 min at 0 °C, quenched with saturated aqueous $Na_2S_2O_3$, diluted with Et_2O, and extracted 3x with Et_2O.The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (40-60% benzene:hexanes then 5% EtOAc:hexanes) to afford iodide **2.258** (0.666 g, 1.45 mmol, 29%) as a

crystalline pale yellow solid, the reduced sylilated bridgehead ketone **2.259** (0.857 g, 2.10 mmol, 42%) as a white solid and vinylsilane **2.256** (0.480 g, 1.44 mmol, 29%) as a white solid.

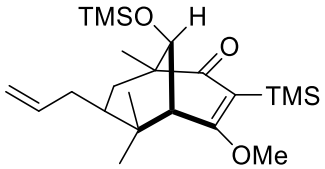
IR (neat, cm^{-1}) ν_{max}: 2985, 2939, 2358, 1733, 1651, 1650, 1544, 1255, 842, 756.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.27 (s, 9 H) 0.92 (s, 3 H) 1.24 (s, 3 H) 1.27 (s, 3 H) 1.30-1.38 (m, 1 H) 1.65-1.74 (m, 1 H) 1.90-1.99 (m, 2 H) 2.36-2.41 (m, 1 H) 3.93 (s, 3 H) 4.98-5.03 (m, 2 H) 5.60 (dddd, *J*=16.7, 10.3, 8.6, 5.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 0.5 (3xCH_3) 17.5 (CH_3) 20.7 (CH_3) 29.0 (CH_3) 36.3 (CH_2) 39.6 (CH) 41.3 (CH_2) 48.0 (C) 62.7 (C) 66.3 (CH_3) 85.9 (C) 117.1 (CH_2) 125.6 (C) 136.4 (CH) 178.9 (C) 200.2 (C) 200.4 (C).

HRMS (EI) *m/z* calcd for $C_{19}H_{29}IO_3Si$ [M^+-Me] 445.0696, found: 445.0695.

m.p. 75-80.



(2.259) 7-allyl-4-methoxy-1,6,6-trimethyl-3-(trimethylsilyl)-9-(trimethylsilyloxy)bicyclo [3.3.1]non-3-en-2-one

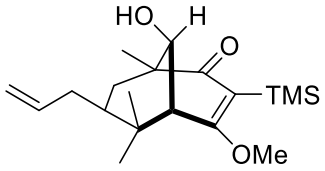
IR (neat, cm^{-1}) ν_{max}: 2985, 2939, 2358, 1733, 1650, 1544, 1255, 1222, 842.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.14 (m, 9 H) 0.16 (s, 9 H) 0.91 (s, 3 H) 0.97 (s, 3 H) 1.11 (s, 3 H) 1.29 (m, 3 H) 1.61 (m, 1 H) 2.19 (m, 1 H) 2.61 (d, *J*=3.1 Hz, 1 H) 3.69 (s, 3 H) 3.73 (d, *J*=3.1 Hz, 1 H) 4.94 (m, 2 H) 5.60 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -0.0 (3x CH_3) 0.7 (3x CH_3) 20.4 (CH_3) 24.0 (CH_3) 27.4 (CH_3) 32.5 (CH_2) 34.4 (C) 34.8 (CH_2) 38.6 (CH) 48.7 (C) 49.8 (CH) 55.3 (CH_3) 74.4 (CH) 115.8 (CH_2) 120.4 (C) 138.0 (CH) 183.0 (C) 206.9 (C).

HRMS (EI) *m/z* calcd for $C_{22}H_{40}O_3Si_2$ [M^+] 408.2516, found: 408.2522.

m.p. 90-94.



7-allyl-9-hydroxy-4-methoxy-1,6,6-trimethyl-3-(trimethylsilyl)bicyclo[3.3.1]non-3-en-2-one

Compound **2.259** (0.360 g, 0.881 mmol) was dissolved in methanol (10 mL). K_2CO_3 (0.608 g, 4.41 mmol) was added to the mixture and the solution was heated at 40˚C for 12h. The solution was then concentrated and purified by flash chromatography (15% EtOAc:hexanes) to afford the free alcohol (0.295 g, 0.877 mmol, 99%) as a white solid.

IR (neat, cm^{-1}) ν_{max}: 3448, 2970, 1620, 1558, 1332, 1226, 844, 729.

^{1}H NMR (400 MHz, $CDCl_3$ δ ppm 0.14 (s, 9 H) 0.93 (s, 3 H) 1.06 (s, 3 H) 1.15 (s, 3 H) 1.34 (m, 3 H) 1.60 (m, 1 H) 2.02 (s, 1 H) 2.21 (m, 1 H) 2.80 (d, *J*=2.9 Hz, 1 H) 3.72 (s, 3 H) 3.87 (d, *J*=2.9 Hz, 1 H) 4.93 (m, 2 H) 5.59 (m, 1 H).

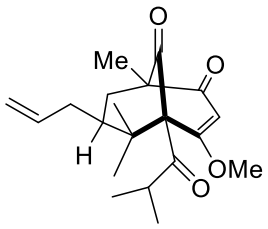
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 0.6 (3x CH_3) 19.9 (CH_3) 23.7 (CH_3) 27.3 (CH_3) 32.3 (CH_2) 34.2 (C) 34.7 (CH_2) 38.6 (CH) 48.4 (C) 49.1 (CH) 55.5 (CH_3) 74.3 (CH) 115.9 (CH_2) 120.1 (C) 137.7 (CH) 183.1 (C) 206.6 (C).

HRMS (EI) *m/z* calcd for $C_{19}H_{32}O_3Si$ [M^+] 336.2121, found: 336.2106.

m.p. 115-118.

The bridgehead alcohol can be oxidized to vinylsilane **2.256** using DMP:

The alcohol (0.303g, 0.900 mmol) was dissolved in wet DCM (15 mL). Dess-Martin periodinane (0.573 g, 1.35 mmol) was added and the reaction was stirred for 1 h before being quenched with a 1:1 mixture of 5% $NaHCO_3$ solution and saturated solution of $Na_2S_2O_3$ under heavy stirring for 30min. The resulting mixture was then separated and the aqueous phase was extracted 3x with DCM. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (5-7 % EtOAc:hexanes) to provide vinylsilane **2.256** (0.276 g, 0.824 mmol, 92 %) as a white solid.



(2.271) 7-allyl-5-isobutyryl-4-methoxy-1,6,6-trimethylbicyclo[3.3.1]non-3-ene-2,9-dione

Iodide **2.256** (0.405g, 0.880 mmol) was charged to a flame dried flask and THF (7.00 mL) was added. The resulting mixture was cooled to -78˚C and *t*-BuLi (1.6 M solution in pentane, 1.26 mL, 2.02 mmol) was added dropwise to obtain a bright yellow solution. After stirring the solution for 5 min at -78˚C, freshly distilled isobutyraldehyde (0.161 mL. 1.75 mmol) (distilled over $CaSO_4$) was added dropwise and the reaction was allowed to stir for 1h at -78 ˚C before quenching with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The organic layers were combined, dried over $MgSO_4$ and concentrated.

The crude was not purified further and dissolved in wet DCM (7.00 mL) and DMP (1.87 g, 4.40 mmol) was added in one portion. The solution was allowed to age for 3 days at r.t. The resulting solution was then quenched with a 1:1 mixture of 5% $NaHCO_3$ solution and saturated solution of $Na_2S_2O_3$ under heavy stirring for 30 min. The resulting mixture was then separated and the aqueous phase was extracted 3x with DCM. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was rapidly purified over a pad of silica (5% EtOAc:hexanes) to remove excess impurities.

The resulting residue was put under an atmosphere of argon. THF (7.00 mL) was added and the solution was cooled to 0˚C before adding TBAF (1M solution in THF, 1.05 mL, 1.06 mmol) dropwise. The mixture was stirred at 0˚C for 1h before quenching the solution with NH_4Cl. The aqueous phase was extracted 3x with Et_2O. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (10-15-30% EtOAc:hexanes) to afford O-methylatedtetraone **2.271** (0.133 g, 0.400 mmol, 45%) as a white solid.

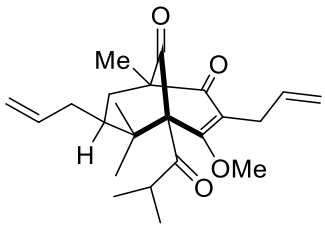
IR (neat, cm^{-1}) ν_{max}: 2975, 2933, 2360, 1720, 1654, 1601, 1242.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.00 (d, *J*=6.5 Hz, 3 H) 1.03 (s, 3 H) 1.17 (d, *J*=6.5 Hz, 3 H) 1.22 (br.s, 6 H) 1.32 (dd, *J*=13.6, 12.8 Hz, 1 H) 1.59-1.64 (m, 1 H) 1.68-1.76 (m, 1 H) 1.96 (dd, *J*=13.7, 4.5 Hz, 1 H) 2.24-2.35 (m, 2 H) 3.81 (s, 3 H) 4.95-4.99 (m, 2 H) 5.54-5.64 (m, 1 H) 5.95 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.6 (CH_3) 15.9 (CH_3) 21.18 (CH_3) 21.19 (CH_3) 24.0 (CH_3) 33.6 (CH_2) 40.7 (CH) 41.9 (CH) 42.6 (CH_2) 45.2 (C) 56.3 (CH_3) 61.0 (C) 75.8 (C) 107.1 (CH) 116.9 (CH_2) 136.6 (CH) 173.1 (C) 195.7 (C) 207.4 (C) 208.5 (C).

HRMS (EI) *m/z* calcd for $C_{20}H_{28}O_4$ [M^+] 332.1988, found: 332.2006.

m.p. 82-84.



(2.280) 3,7-diallyl-5-isobutyryl-4-methoxy-1,6,6-trimethylbicyclo[3.3.1]non-3-ene-2,9-dione

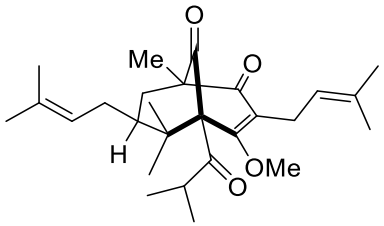
A solution of *n*-BuLi (2.4 M in hexanes, 0.474 mL, 1.14 mmol) was added slowly to freshly distilled diisopropylamine (0.165 mL, 1.16 mmol) in THF (2 mL) at −78°C and the solution was stirred for 30 min at -78°C and 15 min at 0°C. A solution of O-methylatedtetraone **2.271** (124 mg, 0.373 mmol) in THF (0.500 mL) was canulated in the mixture at -78˚C. The solution was stirred for 10 min before the addition of a solution of lithium 2-thienylcyanocuprate (0.25M in THF, 2.98 mL, 0.746 mmol) at -78˚C. After stirring for 20 min, allyl bromide (0.484 mL, 5.60 mmol) was added dropwise to the solution and it was stirred another 20 min before quenching with NH_4Cl. The aqueous phase was extracted 3x with Et_2O. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (3-5-10% EtOAc:hexanes) to afford compound **2.280** (138mg, 0.365 mmol, 98%) as a colorless oil.

IR (neat, cm^{-1}) ν_{max}: 2933, 2362, 1724, 1658, 1598, 1240, 918.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.01 (s, 3 H) 1.02(d, *J*= 6.6 Hz, 3H) 1.16 (d, *J*=6.7 Hz, 3 H) 1.21 (s, 3H) 1.26 (s, 3 H) 1.28-1.31 (m, 1 H) 1.57-1.65 (m, 1 H) 1.75 (dddd, *J*=12.8, 10.5, 4.6, 2.6 Hz, 1 H) 1.94 (dd, *J*= 13.72, 4.51 Hz, 1H) 2.26-2.32 (m, 1 H) 2.37 (sept., *J*=6.5 Hz, 1 H) 3.40 (m, 2 H) 4.10 (s, 3 H) 4.95-5.03 (m, 3 H) 5.12 (dq, *J*= 10.29, 1.60 Hz, 1 H) 5.54-5.64 (m, 1 H) 5.87-5.97 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.4 (2xCH_3) 21.3 (CH_3) 21.5 (CH_3) 24.3 (CH_3) 28.5 (CH_2) 33.5 (CH_2) 40.5 (CH) 42.6 (CH_2) 42.7 (CH) 45.2 (C) 60.5 (CH_3) 60.6 (C) 77.2 (C) 115.7 (CH_2) 116.9 (CH_2) 120.4 (C) 136.5 (CH) 136.6 (CH) 170.3 (C) 196.3 (C) 208.0 (C) 208.9 (C).

HRMS (EI) *m/z* calcd for $C_{23}H_{32}O_4$ [M^+] 372.2301, found: 372.2290.



(2.281) 5-isobutyryl-4-methoxy-1,6,6-trimethyl-3,7-bis(3-methylbut-2-en-1-yl)bicyclo[3.3.1] non-3-ene-2,9-dione

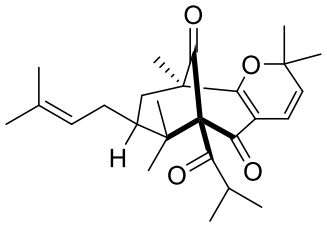
Compound **2.280** (81.0 mg, 0.217 mmol) was dissolved in DCM (0.75 mL), to which 2-methyl-2-butene (4.95 mL, 46.8 mmol) was then added. The resulting mixture was added to a pre-dried seal tube under argon atmosphere containing Grubbs 2nd generation catalyst (18 mg, 0.022 mmol). The resulting red mixture was heated at 40˚C for 2 hours and the solution was allowed to go back to r.t. To the resulting mixture ethyl vinyl ether (0.2 mL) was added and stirred for 2 min before it was concentrated. The residue was purified by flash chromatography (3-5% EtOAc:hexanes) to afford compound **2.281** (92.0 mg, 0.215 mmol, 99%) as a colorless oil.

IR (neat, cm^{-1}) ν_{max}: 2979, 2933, 1722, 1658, 1596, 1242.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.02 (s, 3 H) 1.03 (d, *J*=6.5 Hz, 3 H) 1.15 (d, *J*=6.5 Hz, 3 H) 1.20 (s, 3 H) 1.26 (s, 3 H) 1.28 (dd, J=13.5, 12.5 Hz, 1H) 1.54 (s, 3 H) 1.57-1.62 (m, 2 H) 1.65 (s, 3 H) 1.67-1.68 (m, 6 H) 1.91 (dd, *J*=13.7, 4.1 Hz, 1 H) 2.08-2.12 (m, 1 H) 2.36 (sept., *J*=6.5 Hz, 1 H) 3.19-3.24 (m, 1 H) 3.36-3.42 (m, 1 H) 4.05 (s, 3 H) 4.91-4.94 (m, 1 H) 4.97-5.00 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.49 (CH_3) 16.53 (CH_3) 17.8 (CH_3) 18.1 (CH_3) 21.3 (CH_3) 21.4 (CH_3) 23.5 (CH_2) 24.3 (CH_3) 25.6 (CH_3) 25.8 (CH_3) 27.3 (CH_2) 40.4 (CH) 42.8 (CH_2) 43.7 (CH) 45.2 (C) 60.4 (CH_3) 60.6 (C) 77.3 (C) 122.4 (2xCH) 123.0 (C) 132.9 (C) 133.3 (C) 169.9 (C) 196.6 (C) 208.2 (C) 209.2 (C).

HRMS (EI) *m/z* calcd for $C_{27}H_{40}O_4$ [M^+] 428.2927, found: 428.2924.



(2.4) Papuaforin A

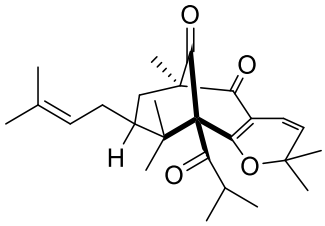
Compound **2.281** (38 mg, 0.089 mmol) was dissolved in dry DMSO (1.10 mL) and LiCl (30 mg, 0.71 mmol) was added in one portion. The resulting mixture was degassed for 10 min before heating at 120˚C for 120 min. The resulting dark solution was then allowed to cool down to r.t. To this mixture was added $PdCl_2$ (21mg, 0.120 mmol) and distilled water (0.11 mL). Oxygen was then bubbled through the stirred solution for 90 seconds. Water was added and extracted with EtOAc (3x). The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified in a first time by flash chromatography (15% EtOAc:hexanes) to eliminate most impurities. The resulting mixture of papuaforin A **(2.4)** and papuaforin B (**2.5**) was then purified again by prep Flash (5% EtOAc:hexanes) to afford papuaforin A (**2.4**) (8.6 mg, 0.021 mmol, 24%) and Papuaforin B (**2.5**) (4.3 mg, 0.010 mmol, 12%).

IR (neat, cm^{-1}) ν_{max}: 2954, 2362, 1731, 1641, 1579, 1456, 1411, 1328, 1116.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.02 (s, 3 H) 1.03 (d, *J*=6.5 Hz, 3 H) 1.12 (d, *J*=6.5 Hz, 3 H) 1.24 (s, 3 H) 1.28 (s, 3 H) 1.38-1.41 (m, 1 H) 1.39 (s, 3 H) 1.51-1.54 (m, 1 H) 1.49 (s, 3 H) 1.55 (s, 3 H) 1.65 (s, 3 H) 1.62-1.72 (m, 1 H) 1.95 (dd, *J*=13.4, 4.0 Hz, 1 H) 2.04-2.14 (m, 2 H) 4.94-4.98 (m, 1 H) 5.37 (d, *J*=10.0 Hz, 1 H) 6.48 (d, *J*=10.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 15.3 (CH_3) 15.8 (CH_3) 17.8 (CH_3) 20.5 (CH_3) 21.6 (CH_3) 22.8 (CH_3) 25.7 (CH_3) 26.4 (CH_2) 28.1 (CH_3) 28.3 (CH_3) 40.3 (CH_2) 42.3 (CH) 43.2 (CH) 46.3 (C) 52.6 (C) 81.9 (C) 83.4 (C) 113.9 (C) 115.7 (CH) 122.6 (CH) 123.9 (CH) 133.3 (C) 170.8 (C) 188.6 (C) 207.0 (C) 209.2 (C).

HRMS (EI) *m/z* calcd for $C_{26}H_{36}O_4$ [M^+] 412.2614, found: 412.2605.



(2.5) Papuaforin B

IR (neat, cm^{-1}) ν_{max}: 2954, 2352, 1731, 1654, 748.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.05 (s, 3 H) 1.08 (d, *J*=6.6 Hz, 3 H) 1.15 (d, *J*=6.4 Hz, 3 H) 1.24 (s, 3 H) 1.32-1.35 (m, 1 H) 1.35 (s, 3 H) 1.50 (s, 3 H) 1.54 (s, 6 H)1.63-1.66(m, 1 H) 1.66 (s, 3 H)1.67-1.68 (m, 1 H) 1.97 (dd, *J*=13.8, 4.3 Hz, 1 H) 2.10-2.15 (m, 1 H) 2.40 (sept., *J*=6.6 Hz, 1 H) 4.93-4.96 (m,1H) 5.39 (d, *J*=10.1 Hz, 1 H) 6.51 (d, *J*=10.1 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 16.2 (CH_3) 16.8 (CH_3) 17.8 (CH_3) 21.3 (CH_3) 21.5 (CH_3) 24.0 (CH_3) 25.8 (CH_3) 27.4 (CH_2) 29.0 (CH_3) 29.4 (CH_3) 40.7 (CH) 42.5 (CH_2) 43.7 (CH) 46.2 (C)

61.0 (C) 75.6 (C) 83.8 (C) 115.1 (C) 115.9 (CH) 122.3 (CH) 124.1 (CH) 133.4 (C) 167.3 (C) 191.9 (C) 206.7 (C) 208.9 (C).

HRMS (EI) *m/z* calcd for $C_{26}H_{36}O_4$ [M^+] 412.2614, found: 412.2539.

NMR comparison of synthetic and natural papuaforin A (**2.4**)

The references pertaining to the comparison study can be found at the end of the supporting information. The following pages will compare the natural papuaforin A (**2.4**) from ref. 9 with the synthetic equivalent resulting from the work presented in this publication. All NMR data have been acquired using $CDCl_3$ solvent.

The positional numbering Scheme used for these tables is shown below.

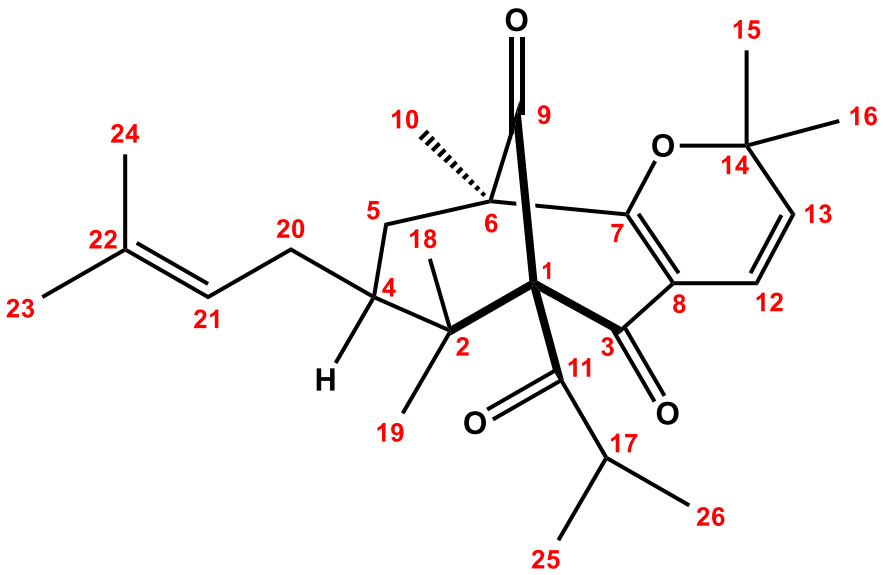


*Table 5.1 – ^{1}H NMR comparison of synthetic and natural papuaforin A (**2.4**)*

	ref. 9	*This work*
Position	*500 MHz*	*400 MHz*
12	*6.49 (d, J=10.0, 1H)*	*6.48 (d, J=10.0, 1H)*
13	*5.37 (d, J=10.0, 1H)*	*5.37 (d, J=10.0, 1H)*
21	*4.97 (br.t, J=6.4, 1H)*	*4.94-4.98 (m, 1H)*
20b	*2.14 (m, 1H)*	*2.04-2.14 (m, 2H)*
17	*2.11 (m, 1H)*	
5 eq.	*1.96 (dd, J=12.9,3.7,1H)*	*1.95 (dd, J= 13.4,4.0, 1H)*
20a	*1.68 (m, 1H)*	*1.62-1.72 (m, 1H)*
23	*1.66 (br.s, 3H)*	*1.65 (s, 1H)*
24	*1.56 (br.s, 3H)*	*1.55 (s, 3H)*
4	*1.50 (m, 1H)*	*1.51-1.54 (m, 1H)*
15	*1.50 (br.s, 3H)*	*1.49 (s, 3H)*
16	*1.40 (s, 3H)*	*1.39 (s, 3H)*
5 ax.	*1.39 (t, J=12.9, 1H)*	*1.38-1.41 (m, 1H)*
10	*1.29 (s,3H)*	*1.28 (s, 3H)*
18	*1.25 (s,3H)*	*1.24 (s, 3H)*
25	*1.13 (d,J=6.5,3H)*	*1.12 (d, J=6.5, 3H)*
26	*1.04 (d, 1H)*	*1.03 (d, J=6.5, 3H)*
19	*1.03 (s,3H)*	*1.02 (s,3H)*

*Table 5.2 – ^{13}C NMR comparison of synthetic and natural papuaforin A (**2.4**)*

	Ref. 9	*This work*
Position	*75 MHz*	*125 MHz*
11	*209.1*	*209.2*
9	*207.0*	*207.0*
3	*188.6*	*188.6*
2	*170.8*	*170.8*
22	*133.3*	*133.3*
13	*123.9*	*123.9*
21	*122.6*	*122.6*
12	*115.8*	*115.7*
8	*114.0*	*133.9*
9	*83.4*	*83.4*
14	*81.9*	*81.9*
6	*52.6*	*52.6*

2	*46.4*	*46.3*
4	*43.3*	*43.2*
17	*42.3*	*42.3*
5	*40.3*	*40.3*
16	*28.3*	*28.3*
15	*28.2*	*28.1*
20	*26.5*	*26.4*
23	*25.7*	*25.7*
19	*22.8*	*22.8*
26	*21.6*	*21.6*
25	*20.5*	*20.5*
24	*17.8*	*17.8*
18	*15.8*	*15.8*
10	*15.3*	*15.3*

NMR comparison of synthetic and natural papuaforin B (**2.5**)

The references pertaining to the comparison study can be found at the end of the supporting information. The following pages will compare the natural papuaforin B (**2.5**) from ref. 9 with the synthetic equivalent resulting from the work presented in this publication. All NMR data have been acquired using $CDCl_3$ solvent.

The positional numbering Scheme used for these tables is shown below.

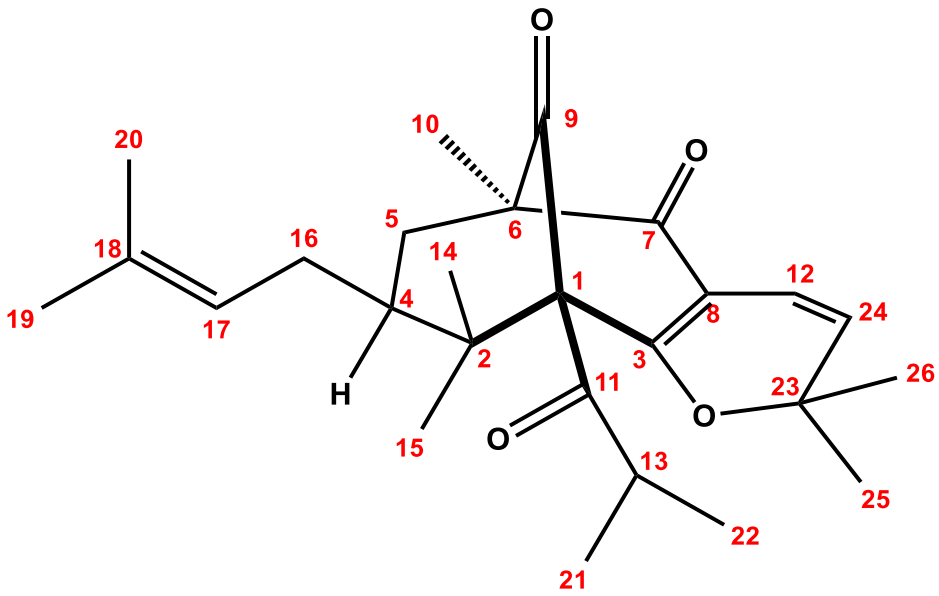
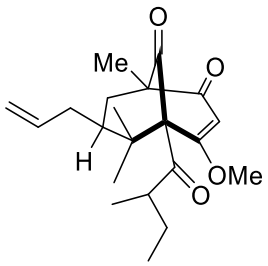


*Table 5.3 – ^{1}H NMR comparison of synthetic and natural papuaforin B (**2.5**)*

	ref. 9	*This work*
Position	*500 MHz*	*500 MHz*
12	*6.51 (d, J=10.0, 1H)*	*6.51 (d, J=10.1, 1H)*
24	*5.40 (d, J=10.0, 1H)*	*5.39 (d,J=10.1, 1H)*
17	*4.96 (m, 1H)*	*4.93-4.96 (m,1H)*
13	*2.40 (sept., J=6.6, 1H)*	*2.40 (sept., J=6.6, 1H)*
16b	*2.14 (m,1H)*	*2.10-2.15 (m, 1H)*
5 eq.	*1.99 (dd, J=4.0, 13.7, 1H)*	*1.97 (dd, J=13.8, 4.3, 1H)*
19	*1.67 (s, 3H)*	*1.67-1.68 (m, 1H)*
4	*1.66 (m, 1H)*	*1.66 (s, 3H)*
16a	*1.65 (m, 1H)*	*1.63-1.66 (m, 1H)*
26	*1.55 (s, 3H)*	*1.54 (s, 6H)*
20	*1.55 (s, 3H)*	
25	*1.50 (s, 3H)*	*1.50 (s, 3H)*
14	*1.36 (s,3H)*	*1.35 (s, 3H)*
5 ax.	*1.33 (m,1H)*	*1.32-1.35 (m, 1H)*
10	*1.25 (s,3H)*	*1.24 (s,3H)*
21	*1.16 (d, J= 6.6, 3H)*	*1.15 (d, J=6.4, 3H)*
22	*1.09 (d, J=6.6, 3H)*	*1.08 (d, J=6.6, 3H)*
15	*1.06 (s, 3H)*	*1.05 (s, 3H)*

*Table 5.4 – ^{13}C NMR comparison of synthetic and natural papuaforin B (**2.5**)*

	Ref. 9	This work
Position	75 MHz	125 MHz
11	209.1	208.9
9	206.6	206.7
7	191.9	191.9
3	167.3	167.3
18	133.4	133.4
12	124.1	124.1
17	122.3	122.3
24	115.9	115.9
8	115.2	115.1
23	83.7	83.8
1	75.8	75.6
6	61.1	61.0
2	46.3	46.2
4	43.7	43.7
5	42.5	42.5
13	40.8	40.7
26	29.4	29.4
25	29.0	29.0
16	27.4	27.4
19	25.8	25.8
14	24.0	24.0
21	21.5	21.5
22	21.3	21.3
20	17.8	17.8
15	16.8	16.8
10	16.2	16.2



(2.285) 7-allyl-4-methoxy-1,6,6-trimethyl-5-(2-methylbutanoyl)bicyclo[3.3.1]non-3-ene-2,9-dione

Iodide **2.258** (0.250 g, 0.543 mmol) was charged to a flame dried flask and THF (4.00 mL) was added. The resulting mixture was cooled to -78˚C and *t*-BuLi (1.6 M solution in pentane, 0.781 mL, 1.25 mmol) was added dropwise to obtain a bright yellow solution. After stirring the solution for 5 min at -78˚C, 2-methylbutanal (0.116 mL. 1.09 mmol) (distilled over $CaSO_4$) was added dropwise and the reaction was allowed to stir for 1h at -78 ˚C before quenching with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The organic layers were combined, dried over $MgSO_4$ and concentrated.

The crude was not purified further and was dissolved in wet DCM (6 mL) and DMP (0.950 g, 2.24 mmol) was added in one portion. The solution was allowed to age for 3 days at r.t. The resulting solution was then quenched with a 1:1 mixture of 5% $NaHCO_3$ solution and saturated solution of $Na_2S_2O_3$ under heavy stirring for 30 min. The resulting mixture was then separated and the aqueous phase was extracted 3x with DCM. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was rapidly purified over a pad of silica (5% EtOAc:hexanes) to remove excess impurities.

The resulting residue was put under an atmosphere of argon. THF (6.00 mL) was added and the solution was cooled to 0˚C before adding a TBAF (1 M solution in THF, 0.537 mL, 0.537 mmol)

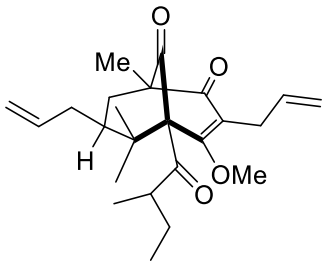
dropwise. The mixture was stirred at 0˚C for 1h before quenching the solution with NH_4Cl. The aqueous phase was extracted 3x with Et_2O. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (10-15-30% EtOAc:hexanes) to afford *O*-methylatedtetraone **2.285** (0.115 g, 0.309 mmol, 61%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2958, 1722, 1658, 1598, 1232.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.83 (t, *J*=7.4 Hz, 3 H) 1.03 (s, 3 H) 1.15 (d, *J*=6.5 Hz, 3 H) 1.21 (b.s, 6 H) 1.27-1.36 (m, 2 H) 1.46-1.53 (m, 1 H) 1.55-1.63 (m, 1 H) 1.68-1.75 (m, 1 H) 1.95 (dd, *J*=13.6, 4.6 Hz, 1 H) 1.99-2.07 (m, 1 H) 2.24-2.29 (m, 1 H) 3.79 (s, 3 H) 4.94-4.98 (m, 2 H) 5.53-5.64 (m, 1 H) 5.94 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 11.6 (CH_3) 15.6 (CH_3) 16.0 (CH_3) 17.4 (CH_3) 24.0 (CH_3) 27.5 (CH_2) 33.5 (CH_2) 42.0 (CH) 42.6 (CH_2) 45.2 (C) 47.5 (CH) 56.3 (CH_3) 61.0 (C) 75.9 (C) 107.1 (CH) 116.9 (CH_2) 136.5 (CH) 173.2 (C) 195.7 (C) 207.2 (C) 208.1 (C).

HRMS (EI) *m/z* calcd for $C_{21}H_{30}O_4$ [M^+] 346.2144, found: 346.2148.



(2.286) 3,7-diallyl-4-methoxy-1,6,6-trimethyl-5-(2-methylbutanoyl)bicyclo[3.3.1]non-3-ene-2,9-dione

A solution of *n*-BuLi (2.4 M in hexanes, 0.499 mL, 1.20 mmol) was added slowly to freshly distilled diisopropylamine (0.173 mL, 1.22 mmol) in THF (2 mL) at −78°C and the solution was

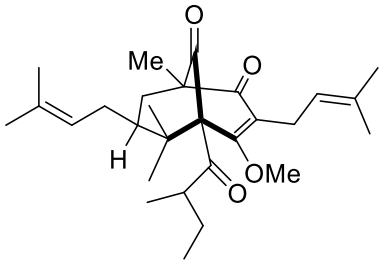
stirred for 30 min at -78°C and 15 min at 0°C. A solution of O-methylatedtetraone **2.285** (0.136 mg, 0.393 mmol) in THF (1 mL) was canulated in the mixture at -78˚C. The solution was stirred for 10 min before the addition of a solution of lithium 2-thienylcyanocuprate (0.25 M in THF, 3.14 mL, 0.785 mmol) at -78˚C. After stirring for 20 min, allyl bromide (0.510 mL, 5.89 mmol) was added dropwise to the solution and it was stirred another 20 min before quenching with NH_4Cl. The aqueous phase was extracted 3x with Et_2O. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (3-5-10% EtOAc:hexanes) to afford compound **2.286** (124 mg, 0.320 mmol, 82%) as a colorless oil.

IR (neat, cm^{-1}) ν_{max}: 2958, 2356, 1722, 1658, 1596, 1242, 1072, 987, 916.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.83 (t, *J*=7.5 Hz, 3 H) 1.01 (s, 3 H) 1.15 (d, *J*=6.5 Hz, 3 H) 1.21 (s, 3 H) 1.25 (s, 3 H) 1.27-1.36 (m, 2 H) 1.54-1.65 (m, 2 H) 1.70-1.78 (m, 1 H) 1.93 (dd, *J*=13.7, 4.7 Hz, 1 H) 2.06-2.14 (m, 1 H) 2.26-2.31 (m, 1 H) 3.32-3.48 (m, 2H) 4.09 (s, 3 H) 4.95-5.03 (m, 3 H) 5.09 (qd, *J*=10.2, 1.7 Hz, 1 H) 5.53-5.64 (m, 1 H) 5.85-5.95 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 11.6 (CH_3) 16.4 (CH_3) 16.5 (CH_3) 17.5 (CH_3) 24.4 (CH_3) 27.7 (CH_2) 28.4 (CH_2) 33.5 (CH_2) 42.6 (CH_2) 42.7 (C) 45.2 (CH) 47.4 (CH) 60.5 (CH_3) 60.6 (C) 77.4 (C) 115.7 (CH_2) 116.8 (CH_2) 120.4 (C) 136.4 (CH) 136.6 (CH) 170.5 (C) 196.2 (C) 207.9 (C) 208.5 (C).

HRMS (EI) *m/z* calcd for $C_{24}H_{34}O_4$ [M^+] 386.2457, found: 386.2472.



(2.287) 4-methoxy-1,6,6-trimethyl-3,7-bis(3-methylbut-2-en-1-yl)-5-(2-methylbutanoyl) bicyclo[3.3.1] non-3-ene-2,9-dione

Compound **2.286** (0.113 mg, 0.292 mmol) was dissolved in DCM (0.5 mL), to which 2-methyl-2-butene (6.66 mL, 62.9 mmol) was then added. The resulting mixture was added to a pre-dried seal tube under argon atmosphere containing Grubbs 2nd generation catalyst (25 mg, 0.029 mmol, 10% loading). The resulting red mixture was heated at 40˚C for 2 hours and the solution was allowed to go back to r.t. To the resulting mixture, ethyl vinyl ether (2.00 mL) was added and stirred for 2 min before it was concentrated under reduced pressure. The residue was purified by flash chromatography (3-5% EtOAc:hexanes) to afford compound **2.287** (129 mg, 0.292 mmol, 99%) as a colorless oil.

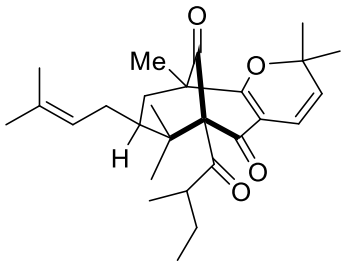
IR (neat, cm^{-1}) ν_{max}: 2933, 2347, 1726, 1660, 1593, 1452, 1245.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.85 (t, *J*=7.5 Hz, 3 H) 1.02 (m, 3 H) 1.14 (d, *J*=6.5 Hz, 3 H) 1.20 (s, 3 H) 1.25 (s, 3 H) 1.28-1.36 (m, 2 H) 1.53 (s, 3 H) 1.57-1.62 (m, 3 H) 1.65 (s, 3 H) 1.68 (m,6 H) 1.90 (dd, *J*=13.5, 4.1 Hz, 1 H) 2.07-2.15 (m, 2 H) 3.17-3.23 (m, 1 H) 3.41-3.48 (m, 1 H) 4.04 (s, 3 H) 4.90-4.99 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 11.7 (CH_3) 16.5 (CH_3) 16.6 (CH_3) 17.5 (CH_3) 17.8 (CH_3) 18.1 (CH_3) 23.3 (CH_2) 24.4 (CH_3) 25.6 (CH_3) 25.8 (CH_3) 27.3 (CH_2) 27.6 (CH_2) 42.8 (CH_2) 43.8 (CH)

45.3 (C) 47.3 (CH) 60.3 (CH_3) 60.6 (C) 77.4 (C) 122.3 (CH) 122.4 (CH) 123.0 (C) 132.9 (C) 133.3 (C) 170.1 (C) 196.5 (C) 208.2 (C) 208.8 (C).

HRMS (EI) *m/z* calcd for $C_{28}H_{42}O_4$ [M^+] 442.3083, found: 442.3083.



(2.6) Papuaforin C

Compound **2.287** (120 mg, 0.271 mmol) was dissolved in dry DMSO (3.61 mL) and LiCl (92mg, 2.169 mmol) was added in one portion. The resulting mixture was degassed for 10 min before heating at 120˚C for 120 min. The resulting dark solution was then allowed to cool down to r.t. To this mixture was added $PdCl_2$ (65 mg, 0.366 mmol) and distilled water (0.5 mL). Oxygen was then bubbled through the stirred solution for 90 seconds. Water was added and extracted with EtOAc (3x). The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified in a first time by flash chromatography (15% EtOAc:hexanes) to eliminate most impurities. The resulting residue was then purified again by prep Flash (1-5% EtOAc:Hexanes) to afford papuaforin C (**2.6)** (48 mg, 0.113 mmol, 41%) and the other isomer (10 mg, 0.023 mmol, 8%) which hasn't been identified as a natural product yet.

IR (neat, cm^{-1}) ν_{max}: 2954, 2356, 1730, 1637, 1587, 1328, 1114.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.78 (t, *J*=7.5 Hz, 3 H) 1.02 (s, 3 H) 1.12 (d, *J*=6.5 Hz, 3 H) 1.24 (s, 3 H) 1.28 (s, 3 H) 1.30-1.34 (m, 1 H) 1.38-1.43 (m, 1 H) 1.39 (s, 3 H) 1.46-1.53 (m, 1 H) 1.50 (s, 3 H) 1.55 (s, 3 H) 1.65 (s, 3 H) 1.65-1.74 (m, 2 H) 1.80-1.88 (m, 1 H) 1.94 (dd, *J*=13.5,

3.9 Hz, 1 H) 2.10-2.15 (m, 1 H) 4.94-4.98 (m, 1 H) 5.37 (d, *J*=10.0 Hz, 1 H) 6.48 (d, *J*=10.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 11.6 (CH_3) 15.3 (CH_3) 15.8 (CH_3) 16.7 (CH_3) 17.8 (CH_3) 22.8 (CH_3) 25.7 (CH_3) 26.4 (CH_2) 27.5 (CH_2) 28.2 (CH_3) 28.2 (CH_3) 40.3 (CH_2) 43.3 (CH) 46.4 (C) 49.0 (CH) 52.6 (C) 81.8 (C) 83.4 (C) 114.0 (C) 115.8 (CH) 122.6 (CH) 124.0 (CH) 133.3 (C) 170.7 (C) 188.7 (C) 207.0 (C) 208.7 (C).

HRMS (EI) *m/z* calcd for $C_{27}H_{38}O_4$ [M^+] 426.2770, found: 426.2750.

NMR comparison of synthetic and natural papuaforin C (**2.6**)

The references pertaining to the comparison study can be found at the end of the supporting information. The following pages will compare the natural papuaforin C (**2.6**) from ref. 9 with the synthetic equivalent resulting from the work presented here. All NMR data have been acquired using $CDCl_3$ solvent.

The positional numbering Scheme used for these tables is shown below.

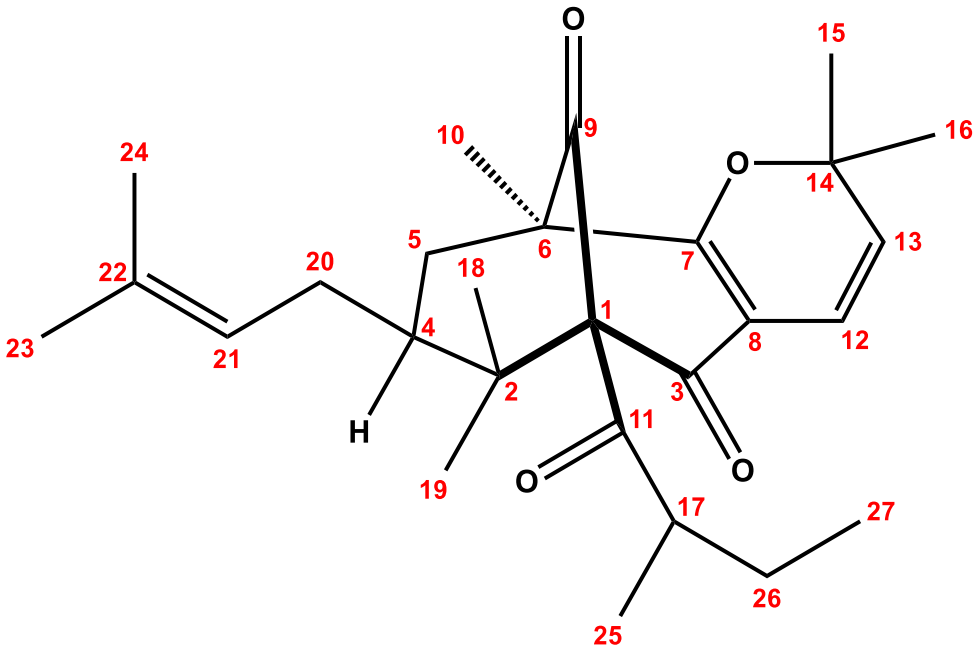


*Table 5.5 – ^{1}H NMR comparison of synthetic and natural papuaforin C (**2.6**)*

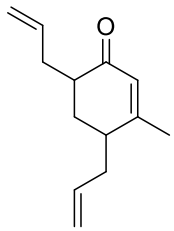
	ref. 9	*This work*
Position	*500 MHz*	*400 MHz*
12	*6.48 (d, J=10.0, 1H)*	*6.48 (d, J=10.0, 1H)*
13	*5.38 (d, J=10.0, 1H)*	*5.37 (d, J=10.0, 1H)*
21	*4.97 (t, J= 7.3, 1H)*	*4.94-4.98 (m, 1H)*
20a	*2.13 (m, 1H)*	*2.10-2.15 (m, 1H)*
5 eq.	*1.95 (dd, J= 13.7, 4.1, 1H)*	*1.94 (dd, J=13.5, 3.9, 1H)*
17	*1.85 (m, 1H)*	*1.80-1.88 (m, 1H)*

26a	*1.70 (m, 1H)*	*1.65-1.74 (m, 2H)*
20b	*1.67 (m, 1H)*	
23	*1.65 (br.s, 3H)*	*1.65 (s, 3H)*
24	*1.56 (br.s, 3H)*	*1.55 (s, 3H)*
15	*1.51 (s, 3H)*	*1.50 (s, 3H)*
4	*1.51 (m, 1H)*	*1.46-1.53 (m, 1H)*
16	*1.40 (s, 3H)*	*1.39 (s, 3H)*
5 ax.	*1.39 (m, 1H)*	*1.38-1.43 (m, 1H)*
26b	*1.31 (m, 1H)*	*1.30-1.34 (m, 1H)*
10	*1.29 (s, 3H)*	*1.28 (s, 3H)*
18	*1.25 (s, 3H)*	*1.24 (s, 3H)*
25	*1.13 (d,* J*=6.5, 3H)*	*1.12 (d,* J*=6.5, 3H)*
19	*1.03 (s, 3H)*	*1.02 (s, 3H)*
27	*0.79 (t,* J*= 7.5, 3H)*	*0.78 (t,* J*=7.5, 3H)*

*Table 5.6 – ^{13}C NMR comparison of synthetic and natural papuaforin C (**2.6**)*

	Ref. 9	*This work*
Position	*75 MHz*	*125 MHz*
11	*208.7*	*208.7*
9	*207.0*	*207.0*
3	*188.7*	*188.7*
7	*170.7*	*170.7*
22	*133.3*	*133.3*
13	*124.0*	*124.0*
21	*122.6*	*122.6*
12	*115.8*	*115.8*
8	*114.0*	*114.0*
1	*83.4*	*83.4*
14	*81.8*	*81.8*
6	*52.6*	*52.6*
17	*49.0*	*49.0*
2	*46.4*	*46.4*
4	*43.3*	*43.3*
5	*40.3*	*40.3*
16	*28.3*	*28.2*
15	*28.2*	*28.2*
26	*27.5*	*27.5*
20	*26.5*	*26.4*

23	*25.7*	*25.7*
18	*22.8*	*22.8*
24	*17.8*	*17.8*
25	*16.7*	*16.7*
19	*15.8*	*15.8*
10	*15.3*	*15.3*
27	*11.6*	*11.6*



(2.289) 4,6-diallyl-3-methylcyclohex-2-enone

LiHMDS (13.4 g, 80.0 mmol) was charged to 1L flame dried flask. THF (500 mL) was added at r.t. and stirred, once all LiHMDS was dissolved the solution was cooled to −78 °C and 4-Allyl-3-methylcyclohex-2-enone (**2.162**) (10 g, 66.6 mmol) dissolved in THF (30 mL) was cannulated at −78 °C. The solution was stirred 1h at -78°C, 1h at -41°C and allyl bromide (7.49 mL, 87 mmol) was added. The mixture was allowed to warm to r.t. and stirred for 5 h. A saturated solution of NH_4Cl was added and the aqueous layer was extracted with ethyl acetate (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (3-7% EtOAc:hexanes) to give 4,6-diallyl-3-methylcyclohex-2-enone **2.289** (9 g, 47.3 mmol, 72%, 82% brsm) as a lightly yellow oil.

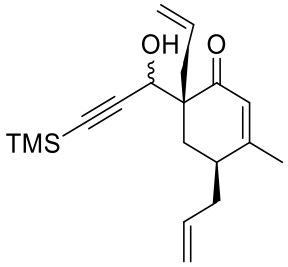
Major diastereomer:

IR (neat, cm^{-1}) ν_{max}: 2925, 2358, 1666, 991, 910.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.69-1.76 (td, *J*=12.9, 4.9 Hz, 1 H) 1.94 (ap.s, 3 H) 1.97-2.09 (m, 2 H) 2.14-2.22 (m, 1H) 2.28-2.32 (m, 1 H) 2.35-2.41(m, 2 H) 2.57-2.63 (m, 1 H) 4.97-5.10 (m, 4 H) 5.65-5.81 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 22.8 (CH_3) 31.0 (CH_2) 33.9 (CH_2) 35.6 (CH_2) 38.9 (CH) 40.5 (CH) 116.6 (CH_2) 117.2 (CH_2) 126.5 (CH) 136.1 (CH) 136.2 (CH) 164.1 (C) 200.2 (C).

HRMS (EI) *m/z* calcd for $C_{13}H_{18}O$ [M^+] 190.1358, found: 190.1322.



(2.290) 4,6-diallyl-6-(1-hydroxy-3-(trimethylsilyl)prop-2-yn-1-yl)-3-methylcyclohex-2-enone

A solution of *n*-BuLi (9.8 M in hexanes, 5.48 mL, 53.7 mmol) was added slowly to freshly distilled diisopropylamine (8.02 mL, 56.3 mmol) in THF (250 mL) at −78°C and the solution was stirred for 30 min at -78°C and 15 min at 0°C. 4,6-diallyl-3-methylcyclohex-2-enone (**2.289**) (9.74 g, 51.2 mmol) was dissolved in THF (30.0 mL) and canulated to the solution at −78 °C. After stirring for 60 min, 3-(trimethylsilyl)propiolaldehyde (**2.204**) (7.75 g, 61.4 mmol) was added and the mixture was stirred at -78°C for 10 min. The resulting mixture was quenched with a saturated solution of NH_4Cl at -78°C. Distilled water was added and the aqueous layer was extracted with EtOAc: Et_2O 1:3 (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by chromatography (5-15% EtOAc:hexanes) to give alcohol enone **2.290** (10.3 g, 32.4 mmol, 63%) as a mixture of diastereoisomere

Major diastereomer:

IR (neat, cm^{-1}) ν_{max}: 3439, 3076, 2958, 2858, 2172, 1652, 1250, 843.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.17 (s, 9 H) 1.77 (dd, *J*=14.4, 11.1 Hz, 1 H) 1.95 (s, 3 H) 2.07-2.19 (m, 3 H) 2.39-2.40 (m, 1 H) 2.50-2.61 (m, 2 H) 2.84 (dd, *J*=13.9, 6.3 Hz, 1 H) 4.59 (s, 1 H) 5.03-5.13 (m, 4 H) 5.64-5.80 (m, 2 H) 5.85 (s, 1 H).

^{13}C NMR (100 MHz, CDCl3) δ ppm -0.3 (3x CH_3) 22.0 (CH_3) 34.7 (CH_2) 35.4 (CH_2) 35.9 (CH) 36.7 (CH_2) 51.9 (C) 66.0 (CH) 92.1 (C) 102.4 (C) 117.8 (CH_2) 118.6 (CH_2) 127.0 (CH) 134.5 (CH) 134.9 (CH) 163.6 (C) 200.9 (C).

HRMS (EI) *m/z* calcd for $C_{19}H_{28}O_2Si$ [M^+] 316.1859, found: 316.1851.

m.p. 55-58.

Minor diastereomer:

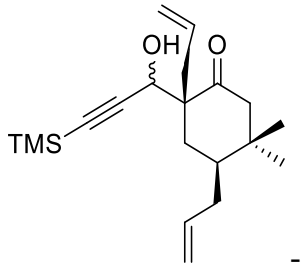
IR (neat, cm^{-1}) ν_{max}: 2956, 2360, 1647, 1249, 987, 842, 759.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.15 (s, 9 H) 1.82 (dd, *J*=14.5, 8.6 Hz, 1 H) 1.97 (s, 3 H) 2.17-2.22 (m, 2 H) 2.37 (dd, *J*=13.9, 8.0 Hz, 1 H) 2.46-2.57 (m, 3 H) 2.78-2.85 (m, 1 H) 4.44 (d, *J*=7.1 Hz, 1 H) 5.07-5.15 (m, 4 H) 5.63-5.82 (m, 2 H) 5.90 (s, 1 H).

^{13}C NMR (100 MHz, CDCl3) δ ppm -0.2 (3x CH_3) 22.5 (CH_3) 32.1 (CH_2) 37.1 (CH_2) 37.15 (CH) 39.2 (CH_2) 51.5 (C) 67.7 (CH) 92.0 (s, 1 C) 103.9 (s, 1 C) 117.5 (CH_2) 119.1 (CH_2) 127.9 (CH) 133.4 (CH) 135.7 (CH) 164.5 (C) 201.1 (C).

HRMS (EI) *m/z* calcd for $C_{19}H_{28}O_2Si$ [M^+] 316.1859, found: 316.1842.

m.p. 63-65.



(2,4-diallyl-2-(1-hydroxy-3-(trimethylsilyl)prop-2-yn-1-yl)-5,5-dimethylcyclohexanone

To a solution of purified CuI (6.02 g, 31.6 mmol) and enone **2.290** (5.00 g, 15.8 mmol, 2 eq.) in THF (158 mL), Me_2S (15.8 mL) was added at 0°C and the solution was stirred until the solution became homogenous. MeMgBr (26.3 mL, 3.0 M in Et_2O, 79.0 mmol, 5eq.) was added over 90 min with a syringe pump under heavy stirring. After the addition was completed the reaction became a very dense dark green solution and the solution was allowed to warm back to r.t. and stirred for 5 h. A saturated solution of NH4Cl was added with equal amount of distilled water. The mixture was extracted with EtOAc:Et_2O 1:1 (3x). The combined organic phases were dried over $MgSO_4$ and filtered over a short pad of celite. The crude was concentrated and filtered over celite one more time using ether to wash the celite pad and concentrated again. The residue was not purified any further and was use for the next step.

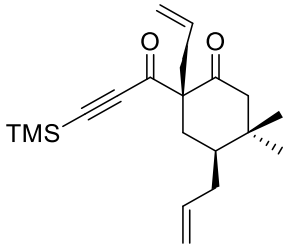
Major diastereomer:

IR (neat, cm^{-1}) ν_{max}: 2960, 2362, 1704, 1249, 910, 840, 759.

^{1}H NMR (400 MHz, CDCl3) δ ppm 0.18 (s, 9 H) 0.73 (s, 3 H) 1.04 (s, 3 H) 1.38 (dd, *J*=14.80,12.94 Hz, 1 H) 1.62 (ddd, *J*=13.9, 10.6, 8.3 Hz, 1 H) 1.73-1.81 (m, 1 H) 2.04 (dd, *J*=14.89,4.02 Hz, 1 H) 2.07 (d, *J*=14.01 Hz 1 H) 2.17 (dd, *J*=13.5, 7.6 Hz, 1 H) 2.25 (d, *J*=7.74, 1 H) 2.37 (ddd, *J*=13.8, 5.3, 2.4 Hz, 1 H) 2.53 (d, *J*=14.1 Hz, 1 H), 2.62 (dd, *J*=13.6, 7.2 Hz, 1 H) 5.00-5.16 (m, 4 H) 5.75 (dddd, *J*=17.0, 10.2, 8.3, 5.4 Hz, 1 H) 6.03 (dddd, *J*=17.3, 9.9, 7.3, 7.3 Hz, 1 H).

^{13}C NMR (100 MHz, CDCl3) δ ppm -0.3 (3x CH_3) 20.1 (CH_3) 29.6 (CH_3) 34.1 (CH_2) 35.8 (CH_2) 36.2 (CH_2) 39.1 (C) 41.0 (CH) 53.6 (CH_2) 56.6 (C) 67.2 (CH) 93.1 (C) 102.4 (C) 116.1 (CH_2) 119.0 (CH_2) 135.8 (CH) 137.3 (CH) 211.8 (C).

HRMS (EI) *m/z* calcd for $C_{20}H_{32}O_2Si$ [M^+] 317.1937 (-Me), found: 317.1958.



(2.291) 2,4-diallyl-5,5-dimethyl-2-(3-(trimethylsilyl)propioloyl)cyclohexanone

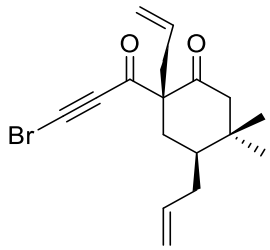
To a solution of crude alcohol in wet DCM (130 mL) was added Dess-Martin periodinane (8.71 g, 20.5 mmol). The reaction was stirred for 1 h and quenched with a 1:1 mixture of 5% $NaHCO_3$ solution and saturated solution of $Na_2S_2O_3$ under heavy stirring for 30min. The resulting mixture was then separated and the aqueous phase was extracted 3x with DCM. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (5% EtOAc:hexanes) to provide diketone **2.291** (3.83 g, 11.6 mmol, 73 %) as a white solid over 2 step.

IR (neat, cm^{-1}) ν_{max}: 2970, 2356, 1720, 1666, 1253, 844.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.25 (s, 9 H) 0.73 (s, 3 H) 1.00 (s, 3 H) 1.31-1.37 (m, 1 H) 1.61-1.73 (m, 2 H) 2.12 (d, *J*=13.5 Hz, 1 H) 2.36-2.46 (m, 3 H) 2.51-2.61 (m, 2 H) 5.04-5.10 (m, 4 H) 5.66-5.85 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -0.9 (3xCH_3) 19.9 (CH_3) 29.5 (CH_3) 34.2 (CH_2) 35.8 (CH_2) 38.7 (CH_2) 39.2 (C) 42.4 (CH) 55.9 (CH_2) 67.0 (C) 99.3 (C) 102.0 (C) 116.3 (CH_2) 118.9 (CH_2) 132.6 (CH) 137.3 (CH) 187.4 (C) 206.9 (C).

HRMS (EI) *m/z* calcd for $C_{20}H_{30}O_2Si$ [M^+] 330.2015, found: 330.1988.



(2.292) 2,4-diallyl-2-(3-bromopropioloyl)-5,5-dimethylcyclohexanone

To a solution of diketone **2.291** (4.72 g, 14.3 mmol) in dry acetone (150 mL), was added $AgNO_3$ (1.21 g, 7.14 mmol). The mixture was stirred for 5 min before the addition of NBS (2.80 g, 15.7 mmol). The reaction was stirred 2 h at r.t. before it was filtered over celite and washed with acetone. The filtrate was concentrated and purified by flash chromatography (5% EtOAc:hexanes) to afford diketone **2.292** (4.40 g, 13.5 mmol, 91 %) as a white solid stable to air and moisture for weeks.

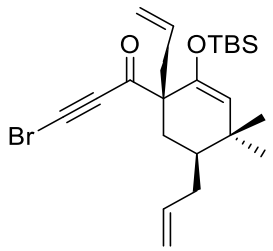
IR (neat, cm^{-1}) ν_{max}: 2358, 2173, 1683, 1652, 1558, 1259, 748.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.73 (s, 3 H) 1.00 (d, *J*=5.1 Hz, 3 H) 1.33 (dd, *J*=14.5, 12.5 Hz, 1 H) 1.58-1.74 (m, 2 H) 2.14 (d, *J*=13.5 Hz, 1 H) 2.34 (d, *J*=13.5 Hz, 1 H) 2.35-2.40 (m, 1 H) 2.42-2.47 (m, 1 H) 2.53-2.59 (m, 2 H) 5.05-5.09 (m, 4 H) 5.62-5.72 (m, 1 H) 5.75-5.85 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 19.9 (CH_3) 29.5 (CH_3) 34.1 (CH_2) 35.3 (CH_2) 38.5 (CH_2) 39.2 (C) 42.5 (CH) 55.9 (CH_2) 60.7 (C) 67.2 (C) 77.8 (C) 116.4 (CH_2) 119.3 (CH_2) 132.2 (CH) 137.1 (CH) 185.8 (C) 206.2 (C).

HRMS (EI) *m/z* calcd for $C_{17}H_{21}O_2Br$ [M^+] 321.0490 (-Me), found: 321.0468.

m.p. 65-68.



(2.293) 3-bromo-1-(1,5-diallyl-2-((tert-butyldimethylsilyl)oxy)-4,4-dimethylcyclohex-2-en-1-yl)prop-2-yn-1-one

2,6-Di-tert-butyl-4-methylpyridine (10.9 g, 53.2 mmol) was charged to a flame dried flask under argon atmosphere. DCM (105 mL) was then added. To the stirred solution, diketone **2.292** (3.59 g, 10.6 mmol) was added in one portion, followed by dropwise addition of TBSOTf (9.78 mL, 42.6 mmol) and the solution was stirred 2 days at 40°C in an oil bath[6]. The aged brown solution was quenched slowly with a solution of 5% $NaHCO_3$ and the aqueous phase was extracted 3x with DCM. The organic phases were combined, dried over $MgSO_4$ and concentrated. The mixture was purified immediately by flash chromatography (pure hexanes to recuperate 2,6-di-tert-butyl-4-methylpyridine, 30% benzene:hexanes to recuperate desired silane enol ether **2.293** (3.21 g, 7.11 mmol, 67 %) a pale yellow oil and 5% EtOAC:hexanes to recuperate residual starting material.

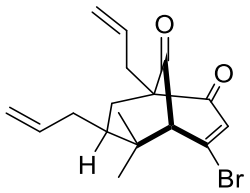
IR (neat, cm^{-1}) ν_{max}: 2954, 2929, 2358, 2175, 1670, 1261, 1149, 829, 738.

[6] Lower temperature provide no enol and higher temperature degrades starting material

^{1}H NMR (400 MHz, CDCl3) δ ppm 0.17 (s, 3 H) 0.18(s, 3 H) 0.78 (s, 3 H) 0.88 (s, 9 H) 1.01 (s, 3 H) 1.44-1.63 (m, 3 H) 1.78 (d, *J*=11.96, 1 H) 2.24-2.29 (m, 2 H) 2.64 (ddt, *J*=13.3, 4.9, 1.4 Hz, 1 H) 4.70 (s, 1 H) 4.98-5.12 (m, 4 H) 5.56-5.74 (m, 2 H).

^{13}C NMR (100 MHz, CDCl3) δ ppm -5.2 (CH_3) -4.4 (CH_3) 18.1 (C) 23.1 (CH_3) 25.6 (3x CH_3) 29.3 (CH_3) 32.0 (CH_2) 34.2 (CH_2) 34.9 (C) 37.9 (CH_2) 39.7 (CH) 57.2 (C) 58.2 (C) 79.5 (C) 116.0 (CH_2) 118.6 (CH_2) 119.1 (CH) 133.9 (CH) 137.8 (CH) 146.2 (C) 189.8 (C).

HRMS (EI) *m/z* calcd for $C_{19}H_{26}O_2SiBr$ [M^+] 393.0885 (-t-Bu), found: 393.0878.



(2.294) 1,7-diallyl-4-bromo-6,6-dimethylbicyclo[3.3.1]non-3-ene-2,9-dione

To a solution of silane enol ether **2.293** (3.21 g, 7.11 mmol) in dry acetone (75.0 mL) was added JohnPhosAuCN-SbF_6 (0.274 g, 0.355 mmol, 5% loading). The resulting mixture was left open to air at r.t. and followed by TLC. After 30 min all the starting material had disappeared. The mixture was concentrated and purified by flash chromatography (3-5% EtOAc:hexanes) to afford bicycle **2.294** (2.168 g, 6.43 mmol, 90%) as a white solid.

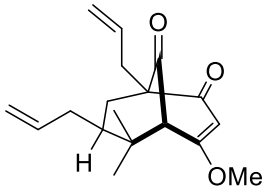
IR (neat, cm^{-1}) ν_{max}: 3078, 2971, 2937, 1735, 1675, 1594, 1394, 1373, 1274, 1234, 1141, 916.

^{1}H NMR (400 MHz, CDCl3) δ ppm 0.91 (s, 3 H) 1.26 (s, 3 H) 1.39 (ap.t., *J*=13.3 Hz, 1 H) 1.58-1.66 (m, 1 H) 1.68-1.76 (m, 1 H) 1.92 (dd, *J*=13.5, 4.3 Hz, 1 H) 2.24-2.29 (m, 1 H) 2.41-2.52 (m, 2 H) 3.26 (s, 1 H) 4.95-5.09 (m, 4 H) 5.60 (ddt, *J*= 17.12, 10.12, 7.05, 1 H) 5.70 (dddd, , *J*=16.76, 10.34, 8.28, 5.59, 1 H) 6.83 (s, 1 H).

^{13}C NMR (100 MHz, CDCl3) δ ppm 20.6 (CH_3) 27.4 (CH_3) 33.9 (CH_2) 34.4 (CH_2) 37.7 (CH) 40.7 (CH_2) 42.2 (C) 63.8 (C) 70.9 (CH) 117.2 (CH_2) 118.7 (CH_2) 133.3 (CH) 135.8 (CH) 136.1 (CH) 145.6 (C) 196.9 (C) 204.8 (C).

HRMS (EI) *m/z* calcd for $C_{17}H_{21}O_2Br$ [M^+] 336.0725, found: 336.0733.

m.p. 69-71.



(2.295) 1,7-diallyl-4-methoxy-6,6-dimethylbicyclo[3.3.1]non-3-ene-2,9-dione

Sodium chunks (0.251 g, 10.9 mmol) were charged to flame-dried flask and the flask was cooled in an ice bath. Methanol (23.0 mL) was then added slowly. Once the solution was homogenous, bicycle **2.294** (2.17 g, 6.43 mmol) was added in one portion to the stirred solution at r.t. which was then heated to 45˚C in an oil bath. After 3h, the solvent was evaporated and the crude was purified directly by flash chromatography (15-20% EtOAc:hexanes) to afford *O*-methylatedtrione **2.295** (1.45 g, 5.03 mmol, 78%) as a white solid.

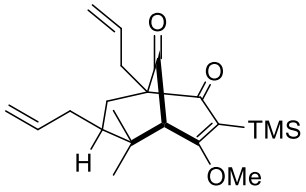
IR (neat, cm^{-1}) ν_{max}: 3070, 2971, 1724, 1657, 1558, 1333, 1087.

^{1}H NMR (400 MHz, CDCl3) δ ppm 0.89 (s, 3 H) 1.02 (s, 3 H) 1.34 (t, 1 H) 1.59-1.67 (m, 1 H) 1.70-1.77 (m, 1 H) 1.94 (dd, *J*=13.6, 4.4 Hz, 1 H) 2.21-2.26 (m, 1 H) 2.42-2.54 (m, 2 H) 2.83 (s, 1 H) 3.74 (s, 3 H) 4.95-5.01 (m, 3 H) 5.05-5.11 (m, 1 H) 5.57-5.67 (m, 1 H) 5.69-5.79 (m, 2 H).

^{13}C NMR (100 MHz, CDCl3) δ ppm 20.4 (CH_3) 27.0 (CH_3) 34.0 (CH_2) 34.6 (CH_2) 38.7 (CH) 40.4 (CH_2) 41.7 (C) 56.5 (CH_3) 63.3 (C) 65.8 (CH) 105.8 (CH) 116.8 (CH_2) 118.1 (CH_2) 134.0 (CH) 136.5 (CH) 174.4 (C) 197.1 (C) 207.0 (C).

HRMS (EI) *m/z* calcd for $C_{18}H_{24}O_3$ [M^+] 288.1725, found: 288.1734.

m.p. 69-70.



(2.296) 1,7-diallyl-4-methoxy-6,6-dimethyl-3-(trimethylsilyl)bicyclo[3.3.1]non-3-ene-2,9-dione

To a solution of *O*-methylatedtrione **2.295** (0.154g, 0.534 mmol) in THF (3 mL) at -78 °C was added a freshly prepared solution of LiTMP (1.18 mL, 1 M in THF, 1.18 mmol). The reaction mixture was stirred for 5 min before addition of freshly distilled TMSCl (0.287 mL, 2.24 mmol). The reaction mixture was stirred and allowed to warm to -40 °C over 2 h. The reaction was quenched with a saturated solution of NH_4Cl, and the product was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude was purified by flash chromatography (5-10 % EtOAc: hexanes) to afford vinylsilane **2.296** (0.18g, 0.499 mmol, 93%) as a white solid.

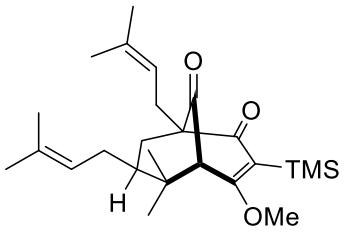
IR (neat, cm^{-1}) ν_{max}: 3077, 2973, 1730, 1646, 1565, 1335, 1215, 843, 763, 627.

^{1}H NMR (400 MHz, CDCl3) δ ppm 0.17 (s, 9 H) 0.92 (s, 3 H) 1.08 (s, 3 H) 1.28 (t, 1 H) 1.59-1.63 (m, 2 H) 1.93 (dd, *J*=13.3, 3.9 Hz, 1 H) 2.20-2.25 (m, 1 H) 2.44 (ddd, *J*=27.7, 13.7, 7.0 Hz, 2 H) 3.24 (s, 1 H) 3.73 (s, 3 H) 4.94-5.05 (m, 4 H) 5.56-5.73 (m, 2 H).

^{13}C NMR (100 MHz, CDCl3) δ ppm 0.4 (3x CH_3) 20.9 (CH_3) 25.7 (CH_3) 33.7 (CH_2) 34.9 (CH_2) 38.2 (CH) 40.8 (CH_2) 42.6 (C) 56.0 (CH_3) 61.0 (CH) 63.2 (C) 116.6 (CH_2) 117.9 (CH_2) 123.6 (C) 133.8 (CH) 136.5 (CH) 178.1 (C) 201.2 (C) 208.0 (C).

HRMS (EI) *m/z* calcd for $C_{21}H_{32}O_3Si$ [M^+] 360.2121, found: 360.2120.

m.p. 54-56.



(2.297) 4-methoxy-6,6-dimethyl-1,7-bis(3-methylbut-2-en-1-yl)-3-(trimethylsilyl) bicyclo[3.3.1] non-3-ene-2,9-dione

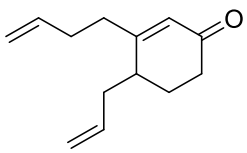
Compound **2.295** (30 mg, 0.083 mmol) and Grubbs II catalyst (7.06 mg, 8.32 µmol, 10 mol %) was added to a sealed tube. Liquid isobutene (5 mL) was condensed in a separate round bottom flasked cooled to -78°C and added to the sealed tube cooled to -78 °C via cannula. The closed sealed tube was slowly warm up to 120 °C. After stirring for 4 h, the sealed tube was cooled to -78 ºC and opened and the tube was warmed up to room temperature to vent off the excess isobutene. The residue was purified by flash chromatography (3-5% EtOAc:hexanes) to afford **2.297** (35 mg, 0.084 mmol, 100%) as a transparent oil.

IR (neat, cm^{-1}) ν_{max}: 2954, 2347, 1731, 1647, 1562, 1274, 844, 750.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.16 (s, 9 H) 0.93 (s, 3 H) 1.08 (s, 3 H) 1.27 (t, *J*=13.1 Hz, 1 H) 1.52 (s, 3 H) 1.54-1.58 (m, 2 H) 1.58 (s, 3 H) 1.62 (s, 3 H) 1.65 (s, 3 H) 1.91 (dd, *J*=13.1, 4.1 Hz, 1 H) 2.01-2.06 (m, 1 H) 2.28-2.34 (m, 1 H) 2.37-2.42 (m, 1 H) 3.21 (s, 1 H) 3.73 (s, 3 H) 4.91-4.96 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 0.4 (3xCH_3) 17.9 (CH_3) 18.0 (CH_3) 21.0 (CH_3) 25.8 (CH_3) 25.8 (CH_3) 25.8 (CH_3) 27.9 (CH_2) 29.6 (CH_2) 39.4 (CH) 41.0 (CH_2) 42.9 (C) 55.8 (CH_3) 61.1 (CH) 63.7 (C) 119.6 (CH) 122.3 (CH) 123.5 (C) 133.3 (C) 133.7 (C) 177.9 (C) 202.0 (C) 208.5 (C).

HRMS (EI) *m/z* calcd for $C_{25}H_{40}O_3Si$ [M^+] 416.2747, found: 416.2720.



(2.306) 4-allyl-3-(but-3-en-1-yl)cyclohex-2-enone

A freshly prepared solution of but-3-en-1-ylmagnesium bromide (1 M in Et_2O, 36.1 mL, 36.1 mmol) was added in one portion to a solution of 6-allyl-3-methoxycyclohex-2-enone (**2.261**) enone (5.00 g, 30.1 mmol) in dry ether (150 mL) at −78 °C for 30 min. The mixture was then stirred at r.t. for 90 min. An aqueous solution of 1 N HCl (25.0 ml) was added and heavily stirred. After stirring for 1 h at r.t., water was added. The aqueous layer was extracted with ethyl acetate (3x), and the combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude oil was purified by chromatography (5-10% EtOAc:hexanes) to give 4-allyl-3-(but-3-en-1-yl)cyclohex-2-enone **2.306** (4.12 g, 21.6 mmol, 72%) as a clear transparent oil.

*Alternatively **4-allyl-3-(but-3-en-1-yl)cyclohex-2-enone (2.306)** can be prepared in a one pot fashion starting with 3-methoxycyclohex-2-enone:

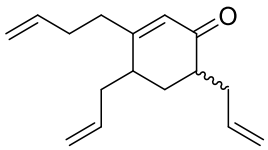
A solution of *n*-BuLi (9.5 M in hexanes, 8.54 mL, 81.0 mmol) was added slowly to freshly distilled diisopropylamine (12.08 mL, 85 mmol) in THF (250 mL) at −78°C and the solution was stirred for 30 min at -78°C and 15 min at 0°C before being recooled to -78°C. A solution of 3-methoxycyclohex-2-enone (**2.160**) (9.3 g, 73.7 mmol) in THF (35 mL) was cannulated at −78°C and the solution was stirred for 60 min to obtain a slurry. Allyl bromide (7.97 mL, 92 mmol) was added in one portion, the mixture was stirred 1h at -78°C and 3h at r.t. The solution was then recooled to -78°C and a freashly prepared solution of but-3-en-1-ylmagnesium bromide (0.15 M in Et_2O, 1.01 L, 158 mmol) was added in one portion. The resulting mixture was stirred for 30 min at -78°C. It was then warmed to r.t. and stirred for one more hour. A solution of 2 M of HCl (250 mL) was then added and stirred vigorously for 1h. Water (100 mL) was then added with brine (100 mL) and Et_2O (250 mL), the phases were separated and the aqueous layer was extracted with ethyl acetate (3x), and the combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude oil was purified by chromatography (5-10% EtOAc:hexanes) to give 4-allyl-3-(but-3-en-1-yl)cyclohex-2-enone (**2.306**) (11.6 g, 60.9 mmol, 83%) as a clear yellow oil.

IR (neat, cm^{-1}) ν_{max}: 2933, 2356, 1674, 1263, 916, 756.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.89-2.03 (m, 2 H) 2.13-2.47 (m, 9 H) 4.96-5.11 (m, 4 H) 5.70-5.81 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 25.9 (CH_2) 31.2 (CH_2) 33.4 (CH_2) 34.9 (CH_2) 35.6 (CH_2) 37.8 (CH) 115.6 (CH_2) 117.2 (CH_2) 125.8 (CH) 136.0 (CH) 136.9 (CH) 167.9 (C) 199.3 (C).

HRMS (EI) *m/z* calcd for $C_{13}H_{18}O$ [M^+] 190.1350, found: 190.1392.



(2.307) 4,6-diallyl-3-(but-3-en-1-yl)cyclohex-2-enone

LiHMDS (11.5 g, 68.6 mmol) was charged to 1L flame dried flask. THF (150 mL) was added at r.t. and stirred, once all LiHMDS was dissolved the solution was cooled to −78 °C and 4-allyl-3-(but-3-en-1-yl)cyclohex-2-enone (**2.306**) (10.9 g, 57.2 mmol) in THF(30 mL) was cannulated at −78 °C. The solution was stirred 1h at -78°C and then 1h at -40°C before cooling it again at -78°C and allyl bromide (6.43 mL, 74.3 mmol) was added. The mixture was allowed to warm to r.t. and stirred for 3 h. A saturated solution of NH_4Cl was added and the aqueous layer was extracted with ethyl acetate (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (2-5% EtOAc:hexanes) to give 4,6-diallyl-3-(but-3-en-1-yl)cyclohex-2-enone (**2.307)** (12.5 g, 90 mmol, 95%) as a lightly yellow oil.

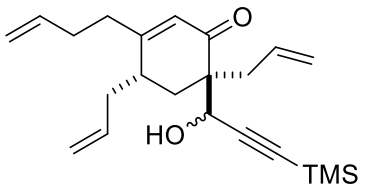
Major diastereomer:

IR (neat, cm^{-1}) ν_{max}: 2974, 2362, 1668, 1271, 908, 752.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.70 (td, *J*=13.0, 5.4 Hz, 1 H) 2.00-2.10 (m, 2 H) 2.17-2.46 (m, 8 H) 2.60-2.67 (m, 1 H) 4.97-5.10 (m, 6 H) 5.66-5.82 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 31.0 (CH_2) 31.2 (CH_2) 34.0 (CH_2) 34.8 (CH_2) 35.7 (CH_2) 37.8 (CH) 40.6 (CH) 115.6 (CH_2) 116.6 (CH_2) 117.2 (CH_2) 125.5 (CH) 136.1 (CH) 136.2 (CH) 136.9 (CH) 167.0 (C) 200.3 (C).

HRMS (EI) *m/z* calcd for $C_{16}H_{22}O$ [M^+] 230.1671, found: 230.1641.



(2.308) 4,6-diallyl-3-(but-3-en-1-yl)-6-(1-hydroxy-3-(trimethylsilyl)prop-2-yn-1-yl) cyclohex-2-en-1-one

A solution of *n*-BuLi (2.4 M in hexanes, 1.90 mL, 4.56 mmol) was added slowly to freshly distilled diisopropylamine (0.681 mL, 4.78 mmol) in THF (22 mL) at −78°C and the solution was stirred for 30 min at -78°C and 15 min at 0°C. 4,6-diallyl-3-(but-3-en-1-yl)cyclohex-2-enone (**2.307**) (1 g, 4.34 mmol) was cannulated to the solution at −78°C. After stirring for 60 min, 3-(trimethylsilyl)propiolaldehyde (**7**) (0.770 mL, 5.21 mmol) was added and the mixture was stirred at -78°C for 15 min. The resulting mixture was quenched with a saturated solution of NH_4Cl at -78°C. Distilled water was added and the aqueous layer was extracted with Et_2O (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by chromatography (3-5-7-10-15% EtOAc:hexanes) to give alcohol enone **2.308** (1.03 g, 2.87 mmol, 66%) as a sole diastereoisomere[7].

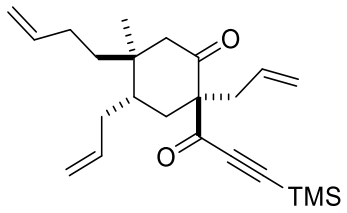
IR (neat, cm^{-1}) ν_{max}: 2964, 2356, 1660, 1253, 989, 844, 756.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.18 (s, 9 H) 1.79 (dd, *J*=14.3, 10.8 Hz, 1 H) 2.07-2.43 (m, 8 H) 2.51-2.62 (m, 2 H) 2.83-2.88 (m, 1 H) 4.57 (d, *J*=4.5 Hz, 1 H) 4.99-5.14 (m, 6 H) 5.64-5.82 (m, 3 H) 5.85 (s, 1 H).

[7] Only two diastereoisomeres could be observed but the one that came out first by TLC was found to give the unnatural stereochemistry. The one that was isolated for the synthesis was the last spot to come out by TLC and was the natural diastereoisomeres proven by the x-ray of a later product.

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -0.2 (3x CH_3) 31.4 (CH_2) 33.9 (CH_2) 34.7 (CH) 34.8 (CH_2) 35.1 (CH_2) 36.7 (CH_2) 51.7 (C) 66.1 (CH) 92.2 (C) 102.4 (C) 115.8 (CH_2) 117.8 (CH_2) 118.6 (CH_2) 125.9 (CH) 134.5 (CH) 134.9 (CH) 136.8 (CH) 165.9 (C) 201.1 (C).

HRMS (EI) *m/z* calcd for $C_{22}H_{32}O_2Si$ [M^+] 356.2172, found: 356.2102.



(2.310) 2,4-diallyl-5-(but-3-en-1-yl)-5-methyl-2-(3-(trimethylsilyl)propioloyl)cyclohexanone

To a solution of purified CuI (9.29 g, 48.8 mmol, 2 eq.) and enone **2.308** (8.70 g, 24.40 mmol,) in THF (244 mL), Me2S (25 mL) was added at 0 °C and the solution was stirred until the solution became homogenous. MeMgBr (40.7 mL, 3.0 M in Et_2O, 122 mmol, 5eq.) was added over 90 min with a syringe pump under heavy stirring. After the addition was completed the reaction became a very dense dark green solution and the solution was allowed to warm back to r.t. and stirred for 12 h. A large quantity of saturated solution of NH_4Cl was added with equal amount of distilled water. The mixture was extracted with Et2O (3x). The combined organic phases were dried over $MgSO_4$ and filtered over a short pad of celite. The crude was concentrated and filtered over celite one more time using ether to wash the celite pad and concentrated again. The residue was not purified any further and was use for the next step

To a solution of the crude alcohol in wet DCM (200 mL) was added Dess-Martin periodinane (13.5 g, 31.7 mmol). The reaction was stirred for 1 h and quenched with a 1:1 mixture of 5% $NaHCO_3$ solution and saturated solution of $Na_2S_2O_3$ under heavy stirring for 30min. The resulting mixture was then separated and the aqueous phase was extracted 3x with DCM. The organic phases were

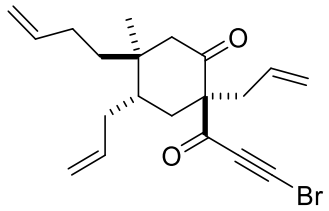
combined, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (1.5-3% EtOAc: hexanes) to provide diketone **2.310** (8.70 g, 19.0 mmol, 78 %) as a pale yellow oil over 2 steps.

IR (neat, cm^{-1}) ν_{max}: 2964, 2352, 1720, 1668, 844, 763.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.25 (s, 9 H) 0.73 (s, 3 H) 1.30-1.50 (m, 3 H) 1.59-1.67 (m, 1 H) 1.76-1.83 (m, 1 H) 1.92-2.00 (m, 2 H) 2.09 (d, *J*=13.3 Hz, 1 H) 2.31-2.36 (m, 1 H) 2.40-2.49 (m, 2 H) 2.52-2.61 (m, 2 H) 4.95 (t, *J*= 11.4, 1 H) 5.02-5.10 (m, 5 H) 5.66-5.84 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -0.9 (3x CH_3) 19.3 (CH_3) 27.6 (CH_2) 33.7 (CH_2) 35.5 (CH_2) 38.7 (CH_2) 39.5 (CH) 40.4 (C) 41.4 (C) 52.2 (CH_2) 66.8 (C) 99.3 (C) 102.1 (C) 114.7 (CH_2) 116.5 (CH_2) 119.0 (CH_2) 132.6 (CH) 137.0 (CH) 138.4 (CH) 187.4 (C) 207.3 (C).

HRMS (EI) *m/z* calcd for $C_{22}H_{31}O_2$ [M^+] 355.2093 (-Me), found: 355.2089.



(2.316) 2,4-diallyl-2-(3-bromopropioloyl)-5-(but-3-en-1-yl)-5-methylcyclohexan-1-one

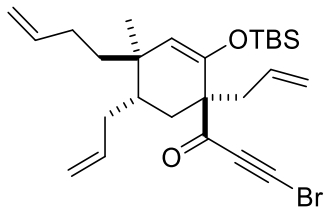
To a solution of diketone **2.310** (1.94 g, 5.25 mmol) in dry acetone (45.0 mL), was added $AgNO_3$ (0.446 g, 2.63 mmol). The mixture was stirred for 5 min before the addition of NBS (1.03 g, 5.78 mmol). The reaction was stirred 2h at r.t. before it was filtered over celite and washed with acetone. The filtrate was concentrated and purified by flash chromatography (2-4% EtOAc:Hexanes) to afford diketone **2.316** (1.86 g, 4.93 mmol, 94 %) as a white solid.

IR (neat, cm^{-1}) ν_{max}: 2939, 2179, 1716, 1666, 910.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.73 (s, 3 H) 1.30-1.50 (m, 3 H) 1.57-1.66 (m, 1 H) 1.75-1.83 (m, 1 H) 1.89-1.99 (m, 2 H) 2.11 (d, *J*=13.3 Hz, 1 H) 2.31-2.35 (m, 1 H) 2.39-2.47 (m, 2 H) 2.54-2.58 (m, 2 H) 4.92-5.10 (m, 6 H) 5.62-5.84 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 19.3 (CH_3) 27.6 (CH_2) 33.5 (CH_2) 35.0 (CH_2) 38.5 (CH_2) 39.6 (CH) 40.3 (CH_2) 41.4 (C) 52.2 (CH_2) 60.8 (C) 67.1 (C) 77.7 (C) 114.7 (CH_2) 116.6 (CH_2) 119.3 (CH_2) 132.1 (CH) 136.9 (CH) 138.3 (CH) 185.7 (C) 206.7 (C).

HRMS (EI) *m/z* calcd for $C_{20}H_{25}O_2Br$ [M^+] 335.0647 [-allyl], found: 335.0792.



(2.317) 3-bromo-1-(1,5-diallyl-4-(but-3-en-1-yl)-2-((tert-butyldimethylsilyl)oxy)-4-methyl cyclohex-2-en-1-yl)prop-2-yn-1-one

2,6-di-*tert*-butyl-4-methylpyridine (6.53 g, 31.8 mmol) was charged to a flame dried flask under argon atmosphere. DCM (50 mL) was then added. To the stirred solution, diketone **2.316** (2.40 g, 6.36 mmol) was added in one portion, followed by dropwise addition of TBSOTf (5.84 mL, 25.4 mmol) and the solution was stirred 3 days at 40°C in an oil bath[8]. The aged brown solution was quenched slowly with a solution of 5% $NaHCO_3$ and the aqueous phase was extracted 3x with DCM. The organic phases were combined, dried over $MgSO_4$ and concentrated. The mixture was purified immediately by flash chromatography (pure hexanes to recuperate 2,6-di-*tert*-butyl-4-

[8] Lower temperature provide no enol and higher temperature degrades starting material

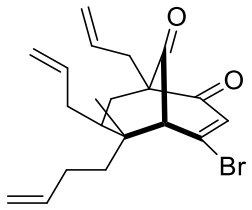
methylpyridine, 30% benzene:hexanes to recuperate desired silane enol ether **2.317** (2.83 g, 5.76 mmol, 91 %) as a pale yellow oil and 5% EtOAC:hexanes to recuperate residual starting material.

IR (neat, cm^{-1}) ν_{max}: 2939, 2362, 2179, 1668, 1249, 1222, 1040, 910, 835, 781.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.19 (m, 6 H) 0.79 (s, 3 H) 0.88 (s, 9 H) 1.20-1.28 (m, 1 H) 1.51-1.62 (m, 3 H) 1.71-1.79 (m, 2 H) 1.98-2.04 (m, 2 H) 2.19-2.28 (m, 2 H) 2.62-2.67 (m, 1 H) 4.68 (s, 1 H) 4.90-5.12 (m, 6 H) 5.57-5.85 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -4.9 (CH_3) -4.4 (CH_3) 18.1 (C) 23.3 (CH_3) 25.6 (3xCH_3) 29.1 (CH_2) 31.8 (CH_2) 33.7 (CH_2) 35.0 (CH) 37.9 (CH_2) 38.2 (C) 39.9 (CH_2) 57.0 (C) 58.3 (C) 79.6 (C) 114.0 (CH_2) 116.1 (CH_2) 117.2 (CH) 118.6 (CH_2) 133.9 (CH) 137.5 (CH) 139.4 (CH) 147.6 (C) 189.9 (C).

HRMS (EI) *m/z* calcd for $C_{22}H_{30}O_2BrSi$ [M^+] 433.1198 (-*t*-Bu), found: 433.1196.



(2.318) 1,7-diallyl-4-bromo-6-(but-3-en-1-yl)-6-methylbicyclo[3.3.1]non-3-ene-2,9-dione

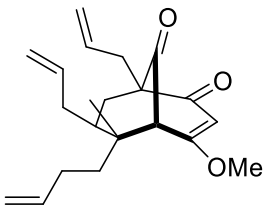
To a solution of silane enol ether **2.317** (2.21 g, 3.31 mmol) in dry acetone (40.0 mL) was added JohnPhosAuCN-SbF_6 (0.174 g, 0.225mmol, 5% loading). The resulting mixture was left open to air at r.t and followed by TLC. After 30 min all the starting material had disappeared. The mixture was concentrated and purified by flash chromatography (3-5% EtOAc:hexanes) to afford bicycle **2.318** (1.68 g, 4.45 mmol, 99%) as a colorless oil.

IR (neat, cm^{-1}) ν_{max}: 2943, 1731, 1668, 1595, 910.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.86 (s, 3 H) 1.46 (t, *J*=13.2 Hz, 1 H) 1.51-1.59 (m, 2 H) 1.62-1.74 (m, 2 H) 1.92 (dd, *J*=13.7, 4.5 Hz, 1 H) 2.00-2.09 (m, 1 H) 2.31-2.35 (m, 2 H) 2.41-2.52 (m, 2 H) 3.46 (s, 1 H) 4.95-5.04 (m, 5 H) 5.08 (d, *J*=1.4 Hz, 1 H) 5.54-5.84 (m, 3 H) 6.83 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 17.5 (CH_3) 27.7 (CH_2) 34.1 (CH_2) 34.4 (CH_2) 36.1 (CH_2) 37.4 (CH) 40.4 (CH_2) 44.9 (C) 63.6 (C) 66.4 (CH) 115.1 (CH_2) 117.2 (CH_2) 118.8 (CH_2) 133.2 (CH) 136.0 (CH) 136.4 (CH) 137.5 (CH) 145.3 (C) 196.5 (C) 204.6 (C).

HRMS (EI) *m/z* calcd for $C_{20}H_{25}O_2Br$ [M^+] 376.1038, found: 376.1015.



(2.319) 1,7-diallyl-6-(but-3-en-1-yl)-4-methoxy-6-methylbicyclo[3.3.1]non-3-ene-2,9-dione

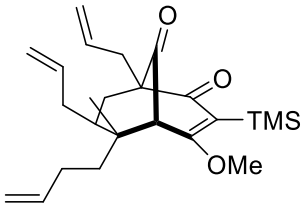
Sodium chunks (0.145 g, 6.31 mmol) were charged to flame-dried flask and the flask was cooled in an ice bath. Methanol (23.0 mL) was then added slowly. Once the solution was homogenous, bicycle **2.318** (1.70 g, 4.51 mmol) was added in one portion to the stirred solution at r.t. which was then heated to 45˚C in an oil bath. After 1 h, the solvent was evaporated and the crude was purified directly by flash chromatography (7-15% EtOAc:hexanes) to afford O-methylatedtrione **2.319** (1.17 g, 3.57 mmol, 78%) as a colorless oil.

IR (neat, cm^{-1}) ν_{max}: 2948, 1730, 1652, 1602, 1218, 910.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.83 (s, 3 H) 1.13 (td, *J*=13.1, 3.8 Hz, 1 H) 1.37 (dd,*J*=13.0,13.4 Hz, 1 H) 1.53-1.74 (m, 3 H) 1.88-1.97 (m, 2 H) 2.17-2.29 (m, 2 H) 2.39-2.51 (m, 2 H) 3.08 (s, 1 H) 3.71 (s, 3 H) 4.91-5.01 (m, 5 H) 5.02-2.08 (m, 1 H) 5.53-5.63 (m, 1 H) 5.66-5.78 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 17.3 (CH_3) 27.4 (CH_2) 34.1 (CH_2) 34.6 (CH_2) 37.7 (CH_2) 38.4 (CH) 40.2 (C) 44.3 (CH_2) 56.4 (CH_3) 61.6 (CH) 63.0 (C) 106.0 (CH) 114.5 (CH_2) 116.8 (CH_2) 118.1 (CH_2) 133.9 (CH) 136.3 (CH) 138.3 (CH) 174.2 (C) 196.8 (C) 207.0 (C).

HRMS (EI) *m/z* calcd for $C_{21}H_{28}O_3$ [M^+] 328.2038, found: 328.2048.



(2.267) 1,7-diallyl-6-(but-3-en-1-yl)-4-methoxy-6-methyl-3-(trimethylsilyl)bicyclo[3.3.1]non-3-ene-2,9-dione

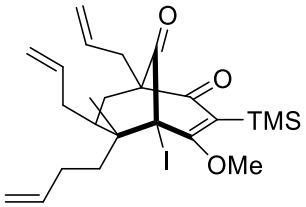
To a solution of *O*-methylatedtrione **2.319** (1.00 g, 3.04 mmol) in THF (10 mL) at -78 °C was added a freshly prepared solution of LiTMP (6.70 mL, 1M in THF, 6.70 mmol). The reaction mixture was stirred for 5 min before addition of freshly distilled TMSCl (1.63 mL, 12.79 mmol). The reaction mixture was stirred and allowed to warm to -40 °C over 2 h. The reaction was quenched with a saturated solution of NH_4Cl, and the product was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude was purified by flash chromatography (1.5-5% EtOAc: hexanes) to afford vinylsilane **2.267** (1.15 g, 2.86 mmol, 94%) as a white solid.

IR (neat, cm^{-1}) ν_{max}: 2943, 2341, 1730, 1645, 1558, 1242, 1211, 916, 842.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.17 (s, 9 H) 0.88 (s, 3 H) 1.32 (t, *J*=13.0 Hz, 1 H) 1.49 (dd, *J*=9.3, 7.7 Hz, 2 H) 1.53-1.64 (m, 1 H) 1.68-1.75 (m, 1 H) 1.94-2.09 (m, 3 H) 2.17-2.21(m, 1 H) 2.37-2.48 (m, 2 H) 3.24 (s, 1 H) 3.72 (s, 3 H) 4.92-5.03 (m, 6 H) 5.56-5.78 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 0.3 (3xCH_3) 19.9 (CH_3) 27.7 (CH_2) 33.8 (CH_2) 34.9 (CH_2) 35.9 (CH) 38.0 (CH_2) 40.3 (CH_2) 45.2 (C) 57.0 (CH_3) 59.9 (CH) 62.9 (C) 114.8 (CH_2) 116.7 (CH_2) 118.0 (CH_2) 125.7 (C) 133.7 (CH) 136.1 (CH) 138.0 (CH) 178.6 (C) 201.7 (C) 207.8 (C).

HRMS (EI) *m/z* calcd for $C_{24}H_{36}O_3Si$ [M^+] 400.2434, found: 400.2413.



(2.321) 1,7-diallyl-6-(but-3-en-1-yl)-5-iodo-4-methoxy-6-methyl-3-(trimethylsilyl)bicyclo [3.3.1]non-3-ene-2,9-dione

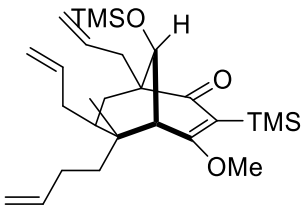
To a solution of vinylsilane **2.267** (2.05g, 5.12 mmol) in THF (5 mL) was added freshly distilled TMSCl (3.27 mL, 25.6 mmol) (distilled over CaH_2) at room temperature and then cannulated to a freshly prepared LDA solution (1.43 M in THF, 12.5 mL, 17.91 mmol) at -78˚C. After stirring for 10 min at -78 °C, the reaction mixture was allowed to warm to 0°C. After stirring for 30 sec at 0 °C, iodide (3.90 g, 15.35 mmol) in THF (5.00 mL) was added to the resulting solution via cannula. The resulting solution was stirred for 15 min at 0 °C, quenched with saturated aqueous $Na_2S_2O_3$, diluted with Et_2O, and extracted 3x with Et_2O.The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (30-60% benzene:hexanes then 5% EtOAc:hexanes) to afford iodide **2.231** (0.4799g, 0.911 mmol, 18%) as a pale yellow oil, the reduced sylilated bridgehead ketone **2.320** (0.99g, 2.085 mmol, 40.7%) as a white solid and vinylsilane **2.231** (0.7151 g, 1.785 mmol, 34.9%) as a white solid.

IR (neat, cm^{-1}) ν_{max}: 2954, 2352, 1733, 1654, 1546, 1249, 844, 748.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.27 (s, 9 H) 0.91 (s, 3 H) 1.45 (t, *J*=13.5 Hz, 1 H) 1.67-2.00 (m, 5 H) 2.05-2.22 (m, 2 H) 2.28-2.33 (m, 1 H) 2.46-2.51 (m, 1 H) 2.56-2.62 (m, 1 H) 3.91 (s, 3 H) 4.94-5.12 (m, 6 H) 5.57-5.67 (m, 1 H) 5.70-5.84 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 0.5 (3xCH_3) 21.4 (CH_3) 28.2 (CH_2) 35.9 (CH_2) 36.1 (CH_2) 36.5 (CH) 38.0 (CH_2) 40.6 (CH_2) 50.0 (C) 64.5 (C) 66.8 (CH_3) 88.4 (C) 114.7 (CH) 117.2 (CH) 118.7 (CH) 126.9 (C) 133.9 (CH) 136.0 (CH) 138.2 (CH) 178.8 (C) 199.4 (C) 199.9 (C).

HRMS (EI) *m/z* calcd for $C_{23}H_{32}IO_3Si$ [M^+-Me] 511.1165, found: 511.1174.



(2.320) 1,7-diallyl-6-(but-3-en-1-yl)-4-methoxy-6-methyl-3-(trimethylsilyl)-9 -((trimethylsilyl) oxy) bicyclo[3.3.1]non-3-en-2-one

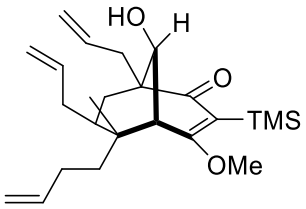
IR (neat, cm^{-1}) ν_{max}: 2948, 2362, 1650, 1573, 1245, 1091, 837.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.15 (s, 18 H) 1.07 (s, 3 H) 1.11-1.19 (m, 1 H) 1.26-1.35 (m, 2 H) 1.39-1.48 (m, 2 H) 1.54-1.62 (m, 1 H) 1.87-2.02 (m, 2 H) 2.10 (dd, *J*=14.1, 7.8 Hz, 1 H) 2.15-2.20 (m, 1 H) 2.46-2.51 (m, 1 H) 2.67 (d, *J*=3.1 Hz, 1 H) 3.67 (s, 3 H) 3.94 (d, *J*=2.9 Hz, 1 H) 4.89-4.99 (m, 6 H) 5.44-5.62 (m, 2 H) 5.68-5.78 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 0.5 (3xCH_3) 0.6 (3xCH_3) 22.4 (CH_3) 28.2 (CH_2) 32.1 (CH_2) 34.9 (CH_2) 37.14 (CH_2) 37.16 (CH) 37.9 (C) 39.4 (CH_2) 47.8 (CH) 52.3 (C) 56.5 (CH_3) 71.3 (CH) 114.1 (CH_2) 115.8 (CH_2) 117.8 (CH_2) 124.5 (C) 134.0 (CH) 137.5 (CH) 139.0 (CH) 183.3 (C) 206.9 (C).

HRMS (EI) *m/z* calcd for $C_{27}H_{46}O_3Si_2$ [M^+] 474.2985, found: 474.2966.

m.p. 75-78.



1,7-diallyl-6-(but-3-en-1-yl)-9-hydroxy-4-methoxy-6-methyl-3-(trimethylsilyl)bicycle [3.3.1]non-3-en-2-one

Silyl **2.320** (0.709 g, 1.49 mmol) was dissolved in methanol (10.0 mL). K_2CO_3 (1.03g, 7.46 mmol) was added to the mixture and the solution was heated at 40˚C for 12h. The solution was then concentrated and purified by flash chromatography (5-15% EtOAc:hexanes) to afford the alcohol (0.589g, 1.46 mmol, 98%) as a white solid.

IR (neat, cm^{-1}) ν_{max}: 3463, 2943, 2352, 1637, 1564, 908, 837, 729.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.16 (s, 9 H) 1.12 (s, 3 H) 1.15-1.23 (m, 1 H) 1.34-1.38 (m, 1 H) 1.41-1.51 (m, 3 H) 1.56-1.65 (m, 1 H) 1.77 (d, *J*=4.1 Hz, 1 H) 1.90-1.99 (m, 2 H) 2.08 (dd, *J*=13.9, 9.4 Hz, 1 H) 2.19-2.24 (m, 1 H) 2.71 (dd, *J*=13.7, 5.1 Hz, 1 H) 2.81 (d, *J*=3.1 Hz, 1 H) 3.70 (s, 3 H) 4.01 (t, *J*=3.2 Hz, 1 H) 4.91-5.07 (m, 6 H) 5.50-5.61 (m, 2 H) 5.69-5.79 (m, 1 H).

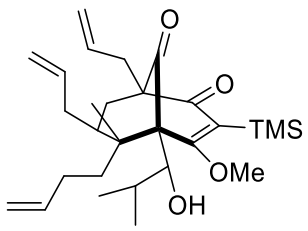
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 0.5 (3xCH_3) 21.8 (CH_3) 28.1 (CH_2) 31.8 (CH_2) 34.9 (CH_2) 37.1 (CH) 37.5 (C) 37.9 (CH_2) 39.3 (CH_2) 47.4 (CH) 51.8 (C) 56.9 (CH_3) 70.7 (CH) 114.2 (CH_2) 116.0 (CH_2) 117.4 (CH_2) 124.3 (C) 134.8 (CH) 137.4 (CH) 139.0 (CH) 183.8 (C) 206.3 (C).

HRMS (EI) *m/z* calcd for $C_{24}H_{38}O_3Si$ [M^+] 402.2590, found: 402.2537.

m.p. 85-90.

The alcohol can be oxidized to vinylsilane (**2.267**) using DMP:

Alcohol (1.21 g, 3.00 mmol) was dissolved in wet DCM (35.0 mL). Dess-Martin periodinane (1.53 g, 3.60 mmol) was added and the reaction was stirred for 1 h before being quenched with a 1:1 mixture of 5% $NaHCO_3$ solution and saturated solution of $Na_2S_2O_3$ under heavy stirring for 30min. The resulting mixture was then separated and the aqueous phase was extracted 3x with DCM. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (3-5 % EtOAc:hexanes) to provide vinylsilane (**2.267**) (1.14 g, 2.84 mmol, 95 %) as a white solid.



1,7-diallyl-6-(but-3-en-1-yl)-5-(1-hydroxy-2-methylpropyl)-4-methoxy-6-methyl-3-(trimethylsilyl)bicyclo[3.3.1]non-3-ene-2,9-dione

Iodide **2.321** (1.40 g, 2.66 mmol) was charged to a flame dried flask and THF (13 mL) was added. The resulting mixture was cooled to -78˚C and *t*-BuLi (1.6 M solution in pentane, 3.66 mL, 5.85 mmol) was added dropwise to obtain a bright yellow solution. After stirring the solution for 7 min at -78˚C, freshly distilled isobutyraldehyde (0.485 mL. 5.32 mmol) (distilled over $CaSO_4$) was added dropwise and the reaction was allowed to stir for 1h at -78 ˚C before quenching with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The organic layers were combined, dried over $MgSO_4$ and concentrated. The crude was purified quickly over silica to remove excess of vinylsilane **2.267** that forms in the reaction and keeping all fraction with

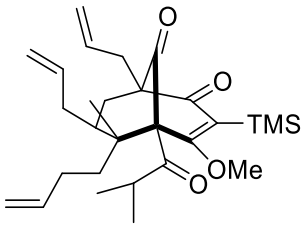
material above venylsilane **2.267** Rf were recuperated and the crude alcohol (0.6937 g) and was used for the next step without any further purification.

IR (neat, cm^{-1}) ν_{max}: 2964, 2356, 1708, 1650, 1550, 1253, 846.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.22 (s, 9 H) 0.64 (d, *J*=7.1 Hz, 3 H) 1.01 (d, *J*=6.9 Hz, 3 H) 1.13 (s, 3 H) 1.34-1.42 (m, 2 H) 1.51-1.59 (m, 1 H) 1.67-1.75 (m, 1 H) 1.83-1.92 (m, 2 H) 2.11-2.32 (m, 4 H) 2.39-2.51 (m, 2 H) 3.95 (s, 3 H) 4.27 (dd, *J*=12.0, 2.0 Hz, 1 H) 4.44 (d, *J*=12.0 Hz, 1 H) 4.94-5.09 (m, 6 H) 5.54-5.69 (m, 2 H) 5.75-5.84 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 0.8 (3xCH_3) 14.5 (CH_3) 17.6 (CH_3) 22.4 (CH_3) 30.9 (CH_2) 32.0 (C) 34.3 (CH_2) 35.3 (CH_2) 35.5 (CH_2) 41.9 (CH_2) 44.7 (CH) 50.1 (C) 63.5 (CH_3) 64.8 (C) 66.7 (C) 77.7 (CH) 114.6 (CH_2) 116.7 (CH_2) 118.6 (CH_2) 124.7 (C) 133.5 (CH) 136.6 (CH) 138.7 (CH) 185.2 (C) 199.3 (C) 215.2 (C).

HRMS (EI) *m/z* calcd for $C_{25}H_{37}O_4Si$ [M^+] 429.2461 (-*i*-pr), found: 429.2491.



1,7-diallyl-6-(but-3-en-1-yl)-5-isobutyryl-4-methoxy-6-methyl-3-(trimethylsilyl)bicycle [3.3.1]non-3-ene-2,9-dione

The crude alcohol (0.694 g, 1.48 mmol) was dissolved in wet DCM (30.0 mL) and DMP (3.11 g, 7.34 mmol) was added in one portion. The solution was allowed to age for 3 days at r.t. in a sealed tube. The resulting solution was then quenched with a 1:1 mixture of 5% $NaHCO_3$ solution and saturated solution of $Na_2S_2O_3$ under heavy stirring for 30 min. The resulting mixture was then

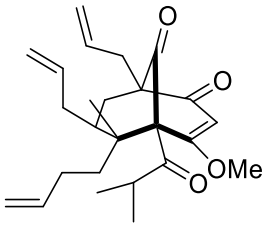
separated and the aqueous phase was extracted 3x with DCM. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified over silica rapidly (2-5% EtOAc:hexanes) to afford *O*-methylatedvinylsilanetetraone (0.389 g, 0.826 mmol, 31% over 2 step).

IR (neat, cm^{-1}) ν_{max}: 2933, 2362, 1726, 1652, 1558, 1253, 850.

^1H NMR, (400 MHz, $CDCl_3$) δ ppm 0.28 (s, 9 H) 1.00 (s, 3 H) 1.06 (d, *J*=6.5 Hz, 3 H) 1.17 (d, *J*=6.5 Hz, 3 H) 1.23-1.29 (m, 1 H) 1.32 (t, *J*= 13.1 Hz, 1 H) 1.46-1.53 (m, 1 H) 1.67-1.75 (m, 1 H) 1.84 (dd, *J*=13.3, 4.1 Hz, 1 H) 2.01-2.17 (m, 2 H) 2.26-2.39 (m, 3 H) 2.42-2.52 (m, 2 H) 3.96 (s, 3 H) 4.90-5.08 (m, 6 H) 5.55-5.82 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 1.1 (3x CH_3) 12.6 (CH_3) 21.2 (CH_3) 21.6 (CH_3) 31.2 (CH_2) 33.6 (CH_2) 35.2 (CH_2) 37.2 (CH_2) 40.6 (CH) 40.7 (CH_2) 44.5 (CH) 47.9 (C) 63.2 (CH_3) 63.4 (C) 79.6 (C) 114.3 (CH) 116.9 (CH) 118.8 (CH) 125.6 (C) 133.3 (CH_2) 136.4 (CH_2) 139.0 (CH_2) 180.4 (C) 200.8 (C) 208.2 (C) 209.2 (C).

HRMS (EI) *m/z* calcd for $C_{28}H_{42}O_4Si$ [M^+] 470.2852, found: 470.2874.



(2.322) 1,7-diallyl-6-(but-3-en-1-yl)-5-isobutyryl-4-methoxy-6-methylbicyclo[3.3.1]non-3-ene-2,9-dione

O-methylatedvinylsilanetetraone (0.389 g, 0.826 mmol) was put under an atmosphere of argon in a 25mL round bottom flask. THF (4.00 mL) was added and the solution was cooled to 0˚C before

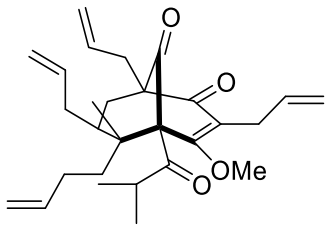
adding a TBAF (1 M solution in THF, 0.991 mL, 0.991 mmol) dropwise. The mixture was stirred at 0˚C for 1h before quenching the solution with NH_4Cl. The aqueous phase was extracted 3x with Et_2O. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (10-15% EtOAc:hexanes) to afford *O*-methylatedtetraone **2.322** (0.252 g, 0.631 mmol, 76%) as transparent oil.

IR (neat, cm^{-1}) ν_{max}: 2943, 2362, 1733, 1652, 1604, 1224, 916.

^1H NMR (500 MHz, $CDCl_3$) δ ppm 1.02 (d, *J*=6.7 Hz, 3 H) 1.05 (s, 3 H) 1.17 (d, *J*=6.5 Hz, 3 H) 1.38 (t, *J*=13.0 Hz, 1 H) 1.61-1.74 (m, 2 H) 1.79-1.87 (m, 3 H) 1.92 (dd, *J*=13.52, 4.51 Hz, 1 H) 2.01-2.12 (m, 1 H) 2.18-2.24 (m, 1 H) 2.24-2.31 (m, 1 H) 2.46-5.58 (m, 2 H) 3.77 (s, 3 H) 4.90-5.11 (m, 6 H) 5.56-5.77 (m, 3 H) 5.94 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 15.1 (CH_3) 21.2 (CH_3) 21.3 (CH_3) 29.8 (CH_2) 34.1 (CH_2) 34.4 (CH_2) 36.2 (CH_2) 39.6 (CH) 40.6 (CH_2) 41.1 (CH) 47.7 (C) 56.2 (CH_3) 63.9 (C) 76.1 (C) 107.5 (CH) 114.4 (CH_2) 117.1 (CH_2) 118.5 (CH_2) 133.5 (CH) 136.1 (CH) 138.6 (CH) 172.4 (C) 195.3 (C) 206.6 (C) 208.6 (C).

HRMS (EI) *m/z* calcd for $C_{25}H_{34}O_4$ [M^+] 398.2457, found: 398.2446.



(2.323) 1,3,7-triallyl-6-(but-3-en-1-yl)-5-isobutyryl-4-methoxy-6-methylbicycle[3.3.1]non-3-ene-2,9-dione

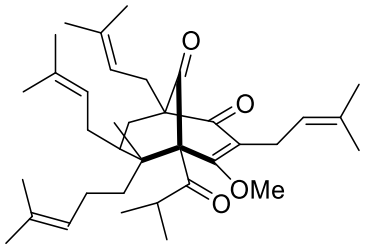
A solution of *n*-BuLi (2.4 M in hexanes, 0.031 mL, 0.075 mmol) was added slowly to freshly distilled diisopropylamine (0.011 mL, 0.077 mmol) in THF (0.1 mL) at −78°C and the solution was stirred for 30 min at -78°C and 15 min at 0°C. A solution of *O*-methylatedtetraone (10 mg, 0.025 mmol) **2.322** in THF (0.05 mL) was canulated in the mixture at -78˚C. The solution was stirred for 10 min before the addition of a solution of lithium 2-thienylcyanocuprate (0.25 M in THF, 0.301 mL, 0.075 mmol) at -78˚C. The resulting solution was stirred at -78˚C for 5 min and 30min at -40˚C. The solution was then cooled to -78˚C again and allyl bromide (0.033 mL, 0.376 mmol) was added dropwise to the solution and it was stirred another 90 min at -40˚C before quenching with NH_4Cl. The aqueous phase was extracted 3x with Et_2O. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (2-5% EtOAc:hexanes) to afford bicyclotetraallyl **2.323** (10 mg, 0.023 mmol, 91%) as a colorless oil.

IR (neat, cm^{-1}) ν_{max}: 2927, 2362, 1724, 1658, 1595, 1245, 914.

^1H NMR, (500 MHz, $CDCl_3$) δ ppm 1.02 (s, 3 H) 1.04 (d, *J*=6.7 Hz, 3 H) 1.17 (d, *J*=6.4 Hz, 3 H) 1.39 (t, *J*=13.1 Hz, 1 H) 1.60-1.70 (m, 2 H) 1.74-1.80 (m, 1 H) 1.84-1.91 (m, 2 H) 1.95-2.01 (m, 1 H) 2.13-2.20 (m, 1 H) 2.23-2.28 (m, 1 H) 2.4 (sept, *J*= 6.44 Hz, 1 H) 2.45-2.50 (m, 1 H) 2.52-2.56 (m, 1 H) 3.34-3.39 (m, 1 H) 3.44-3.50 (m, 1 H) 4.08 (s, 3 H) 4.90-4.93 (m, 1 H) 4.96-5.00 (m, 5 H) 5.03-5.07 (m, 1 H) 5.08-5.11 (m, 1 H) 5.55-5.63 (m, 1 H) 5.66-5.78 (m, 2 H) 5.88-5.95 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 14.2 (CH_3) 21.4 (CH_3) 21.4 (CH_3) 28.4 (CH_2) 30.5 (CH_2) 34.0 (CH_2) 34.9 (CH_2) 36.6 (CH_2) 40.6 (CH_2) 40.8 (CH) 41.6 (CH) 47.8 (C) 60.4 (CH_3) 63.3 (C) 77.9 (C) 114.3 (CH_2) 115.8 (CH_2) 117.0 (CH_2) 118.5 (CH_2) 120.4 (C) 133.7 (CH) 136.3 (CH) 136.6 (CH) 138.8 (CH) 169.2 (C) 195.9 (C) 207.0 (C) 209.1 (C).

HRMS (EI) *m/z* calcd for $C_{28}H_{38}O_4$ [M^+] 438.2770, found: 438.2744.



(2.324) O-methylated hyperforin

Compound (**2.323**) (7.5 mg, 0.017 mmol) and Grubbs II catalyst (1.45 mg, 1.71 μmol, 10 mol %) was added to a sealed tube. Liquid isobutene (2 mL) was condensed in a separate round bottom flasked cooled to -78°C and added to the sealed tube via cannula in the sealed tube cooled at -78 °C. The closed sealed tube was slowly warm up to 120 °C. After stirring for 4 h, the sealed tube was cooled to -78 ºC and opened and the tube was warmed up to room temperature to vent off the excess isobutene. The residue was purified by flash chromatography (2-4% EtOAc:hexanes) to afford *O*-methylated hyperforin (**2.324**) (8 mg, 0.015 mmol, 85%) as a transparent oil.

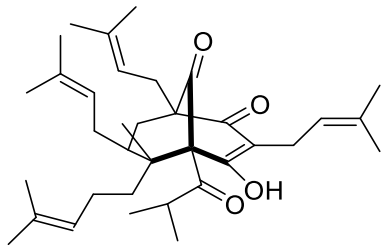
IR (neat, cm^{-1}) ν_{max}: 2927, 2362, 1722, 1660, 1592, 1446, 1375, 1240.

^{1}H NMR, (500 MHz, $CDCl_3$) δ ppm 1.03 (s, 3 H) 1.05 (d, *J*=6.4 Hz, 3 H) 1.15 (d, *J*=6.4 Hz, 3 H) 1.37 (t, *J*= 12.9 Hz, 1 H) 1.41-1.47 (m, 1 H) 1.53 (s, 3 H) 1.59 (s, 3 H) 1.60-1.72 (m, 2H) 1.62 (s, 3 H) 1.64 (s, 3 H) 1.66 (m, 9 H) 1.68 (s, 3 H) 1.79 (dd, *J*=13.4, 4.4 Hz, 1 H) 1.85 (td, *J*=13.5, 4.9 Hz, 1 H) 1.89-196 (m, 1 H) 2.08-2.16 (m, 2 H) 2.36 (sept., *J*=6.5 Hz, 1 H) 2.42 (dd, *J*=6.4 Hz, 2 H) 3.23 (dd, *J*=15.7, 5.9 Hz, 1 H) 3.36 (dd, *J*= 16.2, 6.2 Hz, 1 H) 4.01 (s, 3 H) 4.90-4.96 (m, 2 H) 4.99-5.02 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 13.8 (CH_3) 17.8 (CH_3) 17.9 (CH_3) 18.1 (CH_3) 21.3 (CH_3) 21.3 (CH_3) 23.7 (CH_3) 25.1 (CH_3) 25.6 (CH_2) 25.7 (CH_3) 25.9 (CH_3) 25.9 (CH_3) 28.0 (CH_2) 29.6 (CH_2)

29.7 (C) 37.6 (CH_2) 40.3 (CH_2) 40.6 (CH) 43.4 (CH_2) 47.7 (C) 60.6 (CH) 63.9 (CH_3) 78.1 (C) 119.7 (C) 122.4 (C) 122.5 (C) 123.5 (C) 124.7 (C) 131.3 (CH) 132.8 (CH) 133.3 (CH) 134.1 (CH) 169.2 (C) 196.7 (C) 207.6 (C) 209.5 (C).

HRMS (EI) *m/z* calcd for $C_{31}H_{45}O_4$ [M^+-*i*-Pr] 481.3318, found: 481.3328.



(2.1) Hyperforin

O-methylated hyperforin (**2.324**) (15 mg, 0.027 mmol) was dissolved in dry DMSO (1 mL) and LiCl (0.017 mg, 0.408 mmol) was added in one portion. The resulting mixture was degassed for 10 min before heating at 120˚C for 1h. The resulting dark solution was then allowed to cool down to r.t. Water (10 mL) and brine (2 mL) was added and extracted with unstabilized Et_2O (3x) and once with EtOAc. The organic phases were combined, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (5-10% EtOAc:hexanes) to afford hyperforin (**2.1**) (10 mg, 0.019 mmol, 69%).

IR (neat, cm^{-1}) ν_{max}: 2927, 1718, 1601, 1571, 1211, 644.

^{1}H NMR, (500 MHz, MeOD) δ ppm 0.97 (s, 3 H) 1.03 (d, *J*=6.6 Hz, 3 H) 1.09 (d, *J*=6.4 Hz, 3 H) 1.39 (dd, *J*=13.3, 12.2 Hz, 1 H) 1.58 (s, 3 H) 1.59 (s, 3 H) 1.62 (d, *J*=0.8 Hz, 3 H) 1.64 (d, *J*=0.8 Hz, 3 H) 1.65 (s, 3 H) 1.63-1.68 (m, 1 H) 1.68 (s, 6 H) 1.70 (m, 3 H) 1.70-1.77(m, 3 H) 1.86-2.01 (m, 3 H) 2.02-2.11 (m, 2 H) 2.41 (dd, *J*=14.6, 7.1 Hz, 1 H) 2.50 (dd, *J*=14.6, 6.9 Hz, 1 H) 3.07 (dd,

J=14.9, 6.9 Hz, 1 H) 3.13 (dd, *J*=14.9, 6.9 Hz, 1 H) 4.94-5.03 (m, 3 H) 5.09 (tt, *J*=7.1, 1.3 Hz, 1 H).

^{13}C NMR (125 MHz, MeOD) δ ppm 15.3 (CH_3) 17.9 (CH_3) 18.1 (CH_3) 18.2 (CH_3) 18.3 (CH_3) 21.2 (CH_3) 22.0 (CH_3) 22.6 (CH_2) 25.5 (CH_2) 25.9 (CH_3) 26.0 (C) 26.1 (CH_3) 26.2 (CH_3) 28.7 (CH_2) 30.7 (CH_2) 37.9 (CH_2) 40.8 (CH_2) 43.0 (CH) 43.1 (CH) 49.5 (C) 120.9 (CH) 122.1 (C) 122.6 (CH) 123.9 (CH) 126.1 (CH) 131.9 (C) 133.6 (C) 134.3 (C) 134.7 (C) 208.9 (C) 211.8 (C).

HRMS (ESI-MS) *m/z* calcd for $C_{35}H_{51}O_4$ [M-H] 535.3787, found: 535.3788.

NMR comparison of synthetic and natural Hyperforin (**2.1**)

The references pertaining to the comparison study can be found at the end of the supporting information. The following pages will compare the natural hyperforin (**2.1**) from many references with the synthetic equivalent resulting from the work presented in this publication. All NMR data have been acquired using CD_3OD solvent except for ref. 8 that is pesented in $CDCl_3$.

The positional numbering Scheme used for these tables is shown below.

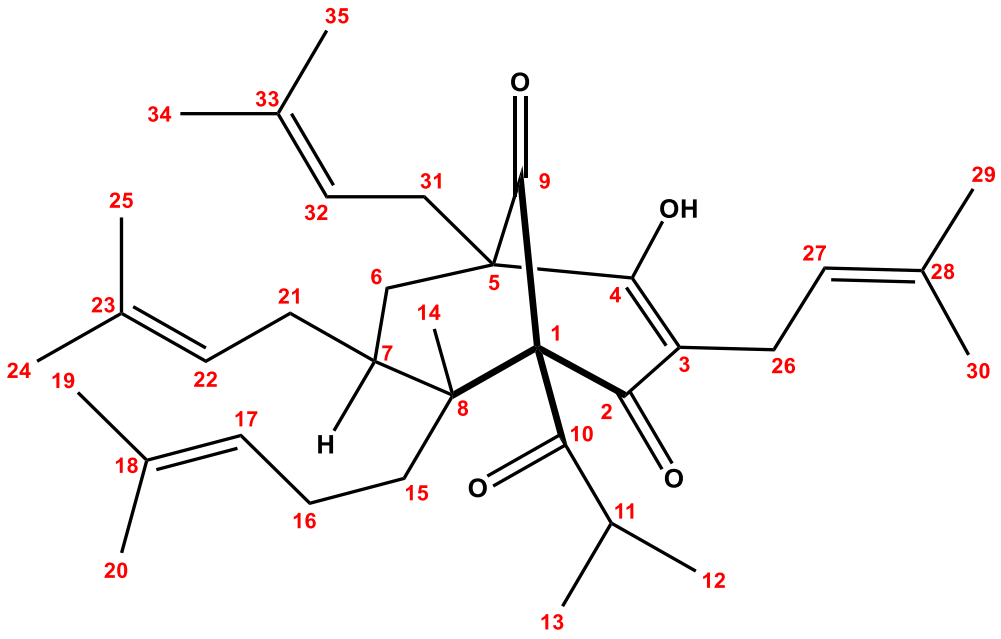


*Table 5.7 – ^{1}H NMR comparison of synthetic and natural hyperforin (**2.1**)*

	Ref. 1	*Ref. 2*	*Ref. 3*	*Ref. 4*	*Ref. 5*
Position	*200 MHz*	*500 MHz*	*600 MHz*	*600 MHz*	*600 MHz*
27	*5.14-4.92 (m, 4H)*	*5.00 (m, 1H)*	*5.04 (t, J = 5.8, 1H)*	*5.10 (t-quint, J = 7.2, 1.5, 1H)*	*5.18 (tt, J = 7.2, 1.2, 1H)*
22		*4.92 (m, 1H)*	*4.93 (m, 1H)*	*5.01 (t-quint, J = 7.3, 1.5, 1H)*	*5.11 (tt, J = 7.2, 1.2, 1H)*
32		*4.90 (m, 1H)*	*4.91 (m, 1H)*	*4.99 (br t, J = 7.8, 1H)*	*4.76 (tq, J = 7.2, 1.2, 1H)*
17		*4.87 (m, 1H)*	*4.89 (m, 1H)*	*4.96 (t, J = 6.5, 1H)*	*4.76 (tq, J = 7.2, 1.2, 1H)*
26a	*3.20-3.00 (m, 2H)*	*3.05 (dd, 1H)*	*3.03 (dd, J = 14.8, 7.3, 1H)*	*3.14 (dd, J = 14.6, 7.2, 1H)*	*3.20 (septet, J = 7.2, 2H)*
26b		*2.99 (dd, 1H)*	*2.99 (dd, J = 14.8, 7.1, 1H)*	*3.09 (br, 1H)*	
31a	*2.57-2.34 (m, 2H)*	*2.41 (dd, 1H)*	*2.38 (dd, J = 14.5, 7.0, 1H)*	*2.51 (dd, J = 14.7, 6.7, 1H)*	*2.49 (dd, J = 7.2, 4.8, 2H)*
31b		*2.32 (dd, 1H)*	*2.29 (dd, J = 14.5, 6.5, 1H)*	*2.41 (dd, J = 14.6, 7.0, 1H)*	
11	*2.10 (sept, J = 6.5, 1H)*	*2.02 (m, 1H)*	*2.07 (m, J = 6.5, 1H)*	*2.10 (br, 1H)*	*2.11 (m, 1H)*
16a	*2.15-1.20 (m, 9H)*	*1.95 (m, 1H)*	*1.97 (m, 1H)*	*2.06 (m, 1H)*	*2.02 (m, 2H)*
6a		*1.85 (m, 2H)*	*1.88 (dd, J = 13.4, 4.1, 1H)*	*1.97 (m, 1H)*	
21a			*1.87 (m, 2H)*	*1.91 (m, 2H)*	*2.02 (m, 1H)*
21b		*1.82 (m, 1H)*			*1.92 (m, 1H)*
7		*1.65 (m, 1H)*	*1.70 (m, 1H)*	*1.91 (m, 1H)*	*1.80 (m, 2H)*
15a		*1.64 (m, 1H)*	*1.66 (m, 1H)*	*1.74 (m, 1H)*	
16b		*1.59 (m, 2H)*	*1.64 (m, 1H)*	*1.73 (m, 1H)*	*1.80 (m, 1H)*
15b			*1.60 (m, 1H)*	*1.68 (m, 2H)*	*1.75 (m, 1H)*
6b		*1.30 (m, 1H)*	*1.27 (dd, J = 13.4, 13.0, 1H)*		*1.27 (m, 1H)*
30	*1.71-1.69 (m, 3H)*	*1.61 (s, 3H)*	*1.60 (s, 3H)*	*1.71 (s, 3H)*	*1.70 (s, 3H)*
19	*1.68 (m, 6H)*	*1.59 (s, 3H)*	*1.58 (s, 3H)*	*1.69 (s, 3H)*	*1.64 (s, 3H)*
34		*1.59 (3H)*	*1.58 (s, 3H)*	*1.69 (s, 3H)*	*1.60 (s, 6H)*
35	*1.66-1.62 (m, 9H)*	*1.56 (3H)*	*1.55 (s, 3H)*	*1.66 (s, 3H)*	
24		*1.55 (3H)*	*1.53 (s, 3H)*	*1.646 (s, 3H)*	*1.50 (s, 3H)*
29		*1.53 (3H)*	*1.53 (s, 3H)*	*1.63 (s, 3H)*	*1.50 (s, 3H)*
25	*1.58 (s, 6H)*	*1.49 (s, 3H)*	*1.49 (s, 3H)*	*1.59 (s, 3H)*	*1.50 (s, 3H)*
20		*1.48 (s, 3H)*	*1.46 (s, 3H)*	*1.585 (s, 3H)*	*1.47 (s, 3H)*
12	*1.09 (d, J = 6.5, 3H)*	*0.99 (d, 3H)*	*0.99 (d, J = 6.5, 3H)*	*1.09 (d, J = 6.5, 3H)*	*1.15 (dd, 6H)*
13	*1.03 (d, J = 6.5, 3H)*	*0.94 (d, 3H)*	*0.95 (d, J = 6.5, 3H)*	*1.03 (br, 3H)*	

14	0.97 (s, 3H)	0.88 (s, 3H)	0.87 (s, 3H)	0.98 (s, 3H)	0.98 (s, 3H)

	Ref. 6	Ref. 7	Ref. 8	this work
Position	500 MHz	500 MHz	600 MHz	500 MHz
27	5.15-5.11 (m, 1H)	5.12 (t, J = 7.0, 1H)	5.10-5.00 (1H, m)	5.09 (tt, J=7.1, 1.3, 1H)
22	5.07-4.97 (m, 3H)	5.04-4.95 (m, 3H)	5.00-4.88 (3H, m)	4.94-5.03 (m, 3H)
32				
17				
26a	3.17 (dd, J = 14.7, 7.0, 1H)	3.12 (dd, J = 14.6, 7.2, 1H)	3.10 (1H, d, J = 14.4, 7.2 Hz)	3.13 (dd, J= 14.9, 6.9, 1H)
26b	3.11 (dd, J = 14.7, 6.7, 1H)	3.07 (dd, J = 14.7, 7.1, 1H)	3.05 (1H, d, J = 14.4, 7.2 Hz)	3.07 (dd, J=14.9, 6.9, 1H)
31a	2.54 (dd, J = 14.1, 6.7, 1H)	2.49 (dd, J = 14.4, 6.9, 1H)	2.47 (1H, d, J = 14.4, 6.6 Hz)	2.5 (dd, J=14.6, 6.9, 1H)
31b	2.44 (dd, J = 14.1, 7.0, 1H)	2.40 (dd, J = 14.6, 6.8, 1H)	2.37 (1H, J = 14.4, 6.6 Hz)	2.41 (dd, J=14.6, 7.1, 1H)
11	2.19-1.90 (m, 5H)	2.14 (septet, J = 6.5, 1H)	2.20-2.11 (2H, m)	2.02-2.11 (m, 2H)
16a		2.10-2.02 (m, 1H)		
6a		2.02-1.87 (m, 3H)	2.01-1.91 (1H, m)	1.86-2.01 (m, 3H)
21a			1.97 (1H, dd, J = 13.2, 4.8 Hz)	
21b			1.88 (1H, dd, J = 13.2, 4.2 Hz)	
7	1.79-1.66 (m, 4H)	1.78-1.72 (m, 3H)	1.75-1.62 (4H, m)	1.70-1.77 (m, 3H)
15a				
16b				
15b		1.66-1.63 (m, 1H)		1.63-1.68 (m, 1H)
6b	1.47-1.38 (m, 1H)	1.37 (dd, J = 13.3, 12.2, 1H)	1.43-1.34 (1H, m)	1.39 (dd, J= 13.3, 12.2, 1H)
30	1.74 (s, 3H)	1.71 (s, 3H)	1.69 (3H, s)	1.70 (m, 3H)
19	1.72 (s, 6H)	1.68 (s, 6H)	1.67 (6H, s)	1.68 (s, 6H)
34				
35	1.69 (s, 3H)	1.66 (s, 3H)	1.64 (3H, s)	1.65 (s, 3H)
24	1.68 (s, 3H)	1.64 (s, 3H)	1.62 (3H, s)	1.64 (d, J=0.8, 3H)
29	1.66 (s, 3H)	1.63 (s, 3H)	1.62 (3H, s)	1.62 (d, J=0.8, 3H)
25	1.62 (s, 3H)	1.59 (s, 3H)	1.58 (3H, s)	1.59 (s, 3H)

20	*1.61 (s, 3H)*	*1.58 (s, 3H)*	*1.57 (3H, s)*	*1.58 (s, 3H)*
12	*1.12 (d, J = 6.4, 3H)*	*1.09 (d, J = 6.5, 3H)*	*1.08 (1H, d, J = 6.6 Hz)*	*1.09 (d, J= 6.4, 3H)*
13	*1.06 (d, J = 6.4, 3H)*	*1.04 (d, J = 6.5, 3H)*	*1.03 (1H, d, J = 6.6 Hz)*	*1.03 (d, J= 6.6, 3H)*
14	*1.01 (s, 3H)*	*0.97 (s, 3H)*	*0.96 (3H, s)*	*0.97 (s, 3H)*

*Table 5.8 – ^{13}C NMR comparison of synthetic and natural hyperforin (**2.1**)*

	Ref. 1	*Ref. 2*	*Ref. 3*	*Ref. 4*	*Ref. 5*	*Ref. 6*	*Ref. 7*	*Ref. 8*	*this work*
Position	*50 MHz*	*125 MHz*	*150 MHz*	*150 MHz*	*150 MHz*	*125 MHz*	*125 MHz*	*150 MHz*	*125 MHz*
10	*211.7*	*211.78*	*212.9*	*211.70*	*209.64*	*na*	*211.7*	*na*	*211.8*
9	*208.8*	*208.85*	*212.3*	*208.82*	*209.64*	*na*	*208.8*	*na*	*208.9*
2	*185.3*	*na*	*210.0*	*na*	*208.35*	*na*	*na*	*na*	*na*
4	*181.2*	*na*	*182.2*	*na*	*181.59*	*na*	*na*	*na*	*na*
33	*134.7*	*134.71*	*134.1*	*134.69*	*133.36*	*135.44*	*134.6*	*134.1*	*134.7*
23	*134.2*	*134.25*	*133.9*	*134.25*	*133.19*	*135.04*	*134.2*	*134.0*	*134.3*
28	*133.5*	*133.60*	*132.5*	*133.58*	*132.93*	*132.63*	*133.5*	*132.4*	*133.6*
18	*131.8*	*131.84*	*131.6*	*131.81*	*131.61*	*na*	*131.8*	*131.6*	*131.9*
17	*126.1*	*126.04*	*126.3*	*126.05*	*126.61*	*126.98*	*126.0*	*126.4*	*126.1*
22	*123.8*	*123.77*	*124.1*	*123.74*	*122.71*	*124.73*	*123.8*	*124.1*	*123.9*
27	*122.6*	*122.53*	*123.7*	*122.54*	*122.31*	*123.66*	*122.6*	*123.6*	*122.6*
3	*122.1*	*122.12*	*121.5*	*122.10*	*121.21*	*122.82*	*122.1*	*121.7*	*122.1*
32	*120.9*	*120.86*	*121.3*	*120.85*	*120.25*	*121.90*	*120.9*	*121.6*	*120.9*
1	*82.6*	*82.00*	*82.7*	*82.74*	*82.42*	*na*	*82.6*	*na*	*na*
5	*60.8*	*60.00*	*61.2*	*na*	*58.27*	*na*	*60.7*	*na*	*na*
8	*49.5*	*49.10*	*49.5*	*49.54*	*47.81*	*na*	*49.5*	*na*	*49.5*
11	*43.0*	*43.00*	*43.3*	*43.10*	*42.57*	*43.94*	*43.1*	*43.3*	*43.1*
7	*43.0*	*42.95*	*42.8*	*43.00*	*41.57*	*43.68*	*43.0*	*42.8*	*43.0*
6	*40.8*	*40.82*	*40.7*	*40.80*	*40.27*	*41.68*	*40.8*	*40.7*	*40.8*
15	*37.9*	*37.92*	*38.0*	*37.88*	*37.68*	*38.81*	*37.9*	*38.0*	*37.9*
31	*30.7*	*30.69*	*30.8*	*36.05*	*30.03*	*31.59*	*30.7*	*30.9*	*30.7*
21	*28.6*	*28.62*	*28.8*	*30.70*	*27.66*	*29.52*	*28.6*	*28.7*	*28.7*
34	*26.2*	*26.15*	*26.1*	*28.62*	*25.01*	*27.02*	*26.2*	*26.2*	*26.2*
29	*26.1*	*26.05*	*26.0*	*26.16*	*24.99*	*26.90*	*26.1*	*26.1*	*26.1*
24	*26.0*	*25.97*	*26.0*	*25.98*	*24.90*	*26.83*	*26.0*	*26.0*	*26.0*
19	*25.9*	*25.87*	*25.9*	*25.90*	*24.88*	*26.74*	*25.9*	*25.9*	*25.9*
16	*25.4*	*25.42*	*25.6*	*25.43*	*24.00*	*26.33*	*25.4*	*25.6*	*25.5*
26	*22.5*	*22.50*	*22.8*	*22.50*	*22.40*	*23.43*	*22.5*	*22.9*	*22.6*
12	*22.0*	*21.98*	*21.0*	*21.99*	*20.44*	*22.86*	*22.0*	*22.2*	*22.0*
13	*21.2*	*21.16*	*19.8*	*20.85*	*19.36*	*22.01*	*21.2*	*21.2*	*21.2*
35	*18.3*	*18.25*	*18.2*	*18.25*	*18.14*	*19.10*	*18.3*	*18.3*	*18.3*
25	*18.2*	*18.15*	*18.2*	*18.15*	*18.10*	*19.01*	*18.2*	*18.2*	*18.2*
20	*18.1*	*18.09*	*18.1*	*18.10*	*18.01*	*18.94*	*18.1*	*18.1*	*18.1*
30	*17.9*	*17.84*	*17.9*	*17.84*	*17.92*	*18.70*	*17.9*	*17.9*	*17.9*

14	*15.3*	*15.31*	*15.2*	*15.30*	*15.80*	*16.13*	*15.3*	*15.3*	*15.3*

*References for papuaforin A (**2.4**), papuaforin B (**2.5**), papuaforin C (**2.6**), hyperforin (**2.1**) NMR comparison:*

1- Erdelmeier, C. A. J. Pharmacopsychiatry ***1998***, 31 *(Supplement 1), 2-6.*
2- Adam, P. A.; Arigoni, D.; Bacher, A.; Eisenreich, W. J. Med. Chem. ***2002***, 45, *4786-4793.*

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6- (NMR for ent-hyperforin) Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. Tetrahedron ***2010***,66, *6569-6584.*

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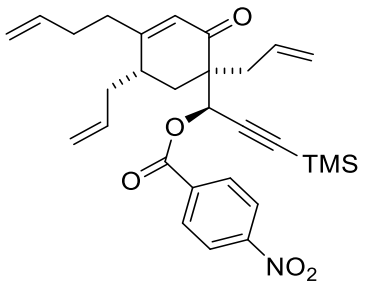
5.1.3 Miscellaneous and side products encountered during PPAPs synthesis



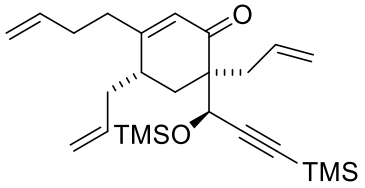
(2.312) 1-(1,5-diallyl-4-(but-3-en-1-yl)-2-oxocyclohex-3-en-1-yl)-3-(trimethylsilyl)prop-2-yn-1-yl 4-nitrobenzoate

IR (neat, cm^{-1}) ν_{max}: 2962, 1731, 1670, 1525, 1263, 1095, 715.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.19 (s, 9 H) 1.84 (dd, *J*=14.4, 11.3 Hz, 1 H) 2.10-2.44 (m, 7 H) 2.55-2.60 (m, 1 H) 2.67-2.74 (m, 1 H) 3.09 (dd, *J*=13.7, 5.7 Hz, 1 H) 5.03-5.16 (m, 6 H) 5.65-5.84 (m, 4 H) 5.87 (s, 1 H) 8.17 (dt, *J*=9.0, 2.0 Hz, 2 H) 8.26 (dt, *J*=8.9, 2.1 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -0.4 (3x CH_3) 31.5 (CH_2) 33.8 (CH_2) 34.7 (CH) 34.9 (2x CH_2) 36.7 (CH_2) 50.8 (C) 67.8 (CH) 94.1 (C) 98.4 (C) 116.0 (CH_2) 118.0 (CH_2) 118.6 (CH_2) 123.5 (2xCH) 125.6 (CH) 131.0 (2xCH) 133.7 (CH) 134.6 (CH) 135.0 (C) 136.7 (CH) 150.6 (C) 163.2 (C) 165.0 (C) 198.2 (C).

HRMS (EI) *m/z* calcd for $C_{29}H_{35}NO_5Si$ [M^+] 505.2284, found 505.2268.



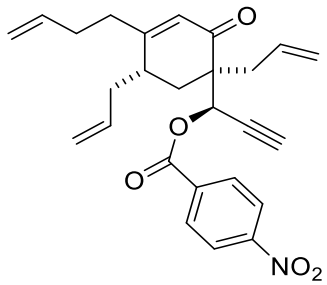
(2.311) 4,6-diallyl-3-(but-3-en-1-yl)-6-(3-(trimethylsilyl)-1-((trimethylsilyl)oxy)prop-2-yn-1-yl)cyclohex-2-en-1-one

IR (neat, cm^{-1}) ν_{max}: 2952, 1676, 1249, 1087, 871, 835, 759.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.08 (s, 9 H) 0.15 (s, 9 H) 1.69 (dd, *J*=14.4, 10.9 Hz, 1 H) 2.07-2.14 (m, 3 H) 2.20-2.40 (m, 4 H) 2.46-2.52 (m, 1 H) 2.63-2.71 (m, 1 H) 2.87 (dd, *J*=13.9, 5.7 Hz, 1 H) 4.56 (s, 1 H) 4.98-5.12 (m, 6 H) 5.64-5.84 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -0.3 (3x CH_3) -0.0 (3x CH_3) 31.5 (CH_2) 33.9 (CH_2) 34.2 (CH_2) 34.9 (CH) 35.3 (CH_2) 36.9 (CH_2) 52.4 (C) 66.4 (CH) 91.2 (C) 104.2 (C) 115.7 (CH_2) 117.6 (CH_2) 117.6 (CH_2) 126.0 (CH) 134.9 (CH) 135.0 (CH) 137.1 (CH) 164.0 (C) 199.5 (C).

Mp. 38.0-40.5; HRMS (EI) *m/z* calcd for $C_{25}H_{40}O_2Si_2$ [M^+] 428.2567, found 428.2540.



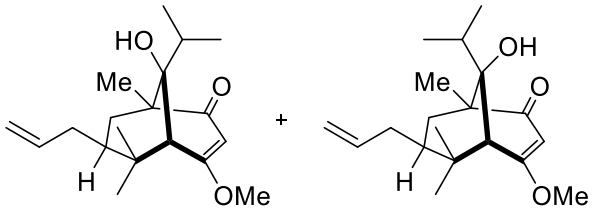
(2.313) 1-(1,5-diallyl-4-(but-3-en-1-yl)-2-oxocyclohex-3-en-1-yl)prop-2-yn-1-yl 4-nitrobenzoate

IR (neat, cm^{-1}) ν_{max}: 2360, 1731, 1670, 1525, 1263, 1095, 914, 717.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.93 (dd, *J*=14.5, 11.0 Hz, 1 H) 2.16 (dd, *J*=14.6, 4.8 Hz, 1 H) 2.20-2.36 (m, 4 H) 2.39-2.46 (m, 1 H) 2.50-2.56 (m, 1 H) 2.62 (d, *J*=2.2 Hz, 1 H) 2.67-2.75 (m, 1 H) 3.13 (dd, *J*=13.7, 5.7 Hz, 1 H) 5.03-2.16 (m, 6 H) 5.64-5.81 (m, 3 H) 5.82 (s, 1 H) 5.84 (d, *J*=2.4 Hz, 1 H) 8.17 (dt, *J*=9.1, 2.1 Hz, 2 H) 8.27 (dt, *J*=9.0, 2.1 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 31.5 (CH_2) 33.9 (CH_2) 34.2 (CH_2) 34.6 (CH) 35.0 (CH_2) 36.7 (CH_2) 50.6 (C) 67.6 (CH) 76.7 (CH) 77.3(C) 116.1 (CH_2) 118.2 (CH_2) 118.9 (CH_2) 123.6 (2xCH) 125.8 (CH) 131.0 (2xCH) 133.4 (CH) 134.3 (CH) 134.8 (C) 136.7 (CH) 150.7 (C) 163.2 (C) 165.1 (C) 197.8 (C).

HRMS (EI) *m/z* calcd for C26H27NO5 [M^+] 433.1889, found 433.1898.



(2.274 and 2.275) 7-allyl-9-hydroxy-9-isopropyl-4-methoxy-1,6,6-trimethylbicyclo[3.3.1] non-3-en-2-one

Sodium (4.15 mg, 0.180 mmol) was added to allyl alcohol (1.00 mL) in a r.b.f. and stirred until all sodium has been consumed. **2.271** (1.2 mg, 0.036mmol) was diluted in a minimum of allyl alcohol and added to the solution of sodium allyl alkoxide. The r.b.f. was fitted with a refrigerant and heated at 80°C o/n. The resulting mixture was purified by flash chromatography (10 % EtOAc:hexanes) to provide a mixture of alcohols **2.274** and **2.275**.

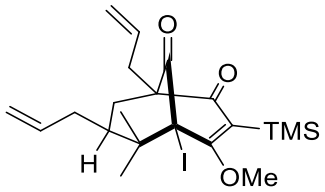
IR (neat, cm^{-1}) ν_{max}: 3475, 2948, 2347, 1645, 1610, 1365, 1203, 752.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.80 (d, *J*=6.9 Hz, 3 H) 0.87 (s, 3 H) 0.97 (d, *J*=6.7 Hz, 3 H) 1.15 (s, 3 H) 1.27 (s, 3 H) 1.47 (dd, *J*=14.7, 8.0 Hz, 1 H) 1.73 (m, 1H) 1.78 (dd, *J*=14.70, 6.07, 1 H) 1.91 (dt, *J*=13.6, 6.7 Hz, 1 H) 2.10 (s, 1 H) 2.19 (s, 1 H) 2.32 (s, 1 H) 3.64 (s, 3 H) 4.91 (m, 2 H) 5.24 (s, 1 H) 5.61 (dddd, *J*=16.9, 10.2, 8.4, 5.7 Hz, 1 H).

^{13}C NMR (missing carbons) (100 MHz, $CDCl_3$) δ ppm 18.7 (CH_3) 19.2 (CH_3) 20.0 (CH_3) 24.1 (CH_3) 33.9 (CH_3) 35.7 (CH) 35.8 (CH) 36.2 (CH_2) 36.8 (CH_2) 40.5 (CH) 54.4 (CH_3) 55.3 (CH) 79.3 (C) 102.7 (CH) 115.9 (CH_2) 138.8 (CH) 178.1 (C) 203.5 (C).

HRMS (EI) *m/z* calcd for $C_{19}H_{30}O_3$ [M^+] 306.2195, found: 306.2217.

m.p. 120-125.



(2.265) 1,7-diallyl-5-iodo-4-methoxy-6,6-dimethyl-3-(trimethylsilyl)bicyclo[3.3.1]non-3-ene-2,9-dione

To a solution of vinylsilane (1.00 g, 2.77 mmol) in THF (5 mL) was added freshly distilled TMSCl (1.77 mL, 13.9 mmol) (distilled over CaH_2) (mmol) at room temperature and then cannulated to a freshly prepared LDA solution (0.75 M in THF, 13.0 mL, 9.71 mmol) at -78˚C. After stirring for 10 min at -78 °C, the reaction mixture was allowed to warm to 0°C. After stirring for 30 sec at 0 °C, iodide (2.11 g, 8.32 mmol) in THF (5.00 mL) was added to the resulting solution via cannula. The resulting solution was stirred for 15 min at 0 °C, quenched with saturated aqueous $Na_2S_2O_3$, diluted with Et_2O, and extracted 3x with Et_2O.The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (40-60% benzene:hexanes then 5% EtOAc:hexanes) to afford iodide **2.265** (0.64 g, 1.316 mmol, 47%) as a crystalline pale yellow solid, the bridgehead alcohol (0.598 g, 0.598 mmol, 22%) as a white solid and starting vinylsilane (0.254 g, 0.704 mmol, 25%) as a white solid.

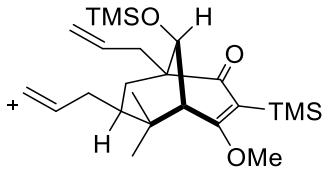
IR (neat, cm^{-1}) ν_{max}: 2977, 2358, 2341, 1652, 1251, 846, 750.

^{1}H NMR (400 MHz, CDCl3) δ ppm 0.26 (s, 9 H) 0.90 (s, 3 H) 1.24 (s, 3 H) 1.43 (t, 1 H) 1.67-1.75 (m, 1 H) 1.80 (dd, 1 H) 1.85-1.92 (m, 1 H) 2.37 (ddd, *J*=13.7, 5.0, 2.3 Hz, 1 H) 2.48 (dd, *J*=14.1, 7.6 Hz, 1 H) 2.58 (dd, 1 H) 3.94 (s, 3 H) 4.97-5.12 (m, 4 H) 5.60 (dddd, *J*=16.8, 10.3, 8.4, 5.5 Hz, 1 H) 5.80 (dddd, *J*=17.2, 10.1, 7.6, 6.7 Hz, 1 H).

^{13}C NMR (100 MHz, CDCl3) δ ppm 0.5 (3xCH_3) 20.7 (CH_3) 29.0 (CH_3) 36.0 (CH_2) 36.3 (CH_2) 38.8 (CH_2) 39.6 (CH) 47.8 (C) 65.0 (C) 66.0 (CH_3) 85.8 (C) 117.1 (CH_2) 118.7 (CH_2) 125.6 (C) 133.9 (CH) 136.4 (CH) 179.0 (C) 199.7 (C) 199.8 (C).

HRMS (EI) *m/z* calcd for $C_{21}H_{31}IO_3Si$ [M^+] 486.1087, found: 486.1058.

m.p. 89-91



1,7-diallyl-4-methoxy-6,6-dimethyl-3-(trimethylsilyl)-9-(trimethylsilyloxy)bicyclo[3.3.1]non-3-en-2-one

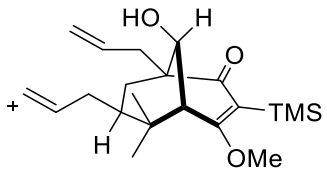
IR (neat, cm^{-1}) ν_{max}: 2948, 2366, 1645, 1571, 1091, 837.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.14 (s, 9 H) 0.15 (s, 9 H) 0.89 (s, 3 H) 1.11 (s, 3 H) 1.23-1.43 (m, 4 H) 1.56-1.64 (m, 1 H) 2.07-2.12 (m,1 H) 2.15-2.21 (m, 1 H) 2.47-2.52 (m, 1 H) 2.64 (d, *J*=3.1 Hz, 1 H) 3.68 (s, 3 H) 3.95 (d, *J*=2.8 Hz, 1 H) 4.91-4.99 (m, 4 H) 5.45-5.64 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 0.6 (3x CH_3) 0.6 (3x CH_3) 24.3 (CH_3) 27.4 (CH_3) 32.3 (CH_2) 34.8 (CH_2) 35.1 (C) 37.1 (CH_2) 38.6 (CH) 49.4 (CH) 52.3 (C) 55.2 (CH_3) 71.2 (CH) 115.7 (CH_2) 117.6 (CH_2) 120.9 (C) 134.2 (CH) 137.8 (CH) 182.5 (C) 206.3 (C).

HRMS (EI) *m/z* calcd for $C_{24}H_{42}O_3Si_2$ [M^+] 434.2672, found: 434.2661.

m.p. 80-84.

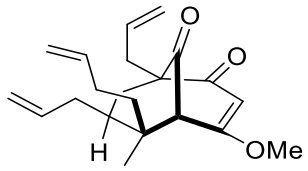


1,7-diallyl-9-hydroxy-4-methoxy-6,6-dimethyl-3-(trimethylsilyl)bicyclo[3.3.1]non-3-en-2-one

^{1}H NMR (400 MHz, CDCl3) δ 1H NMR (400 MHz, $CDCl_3$) δ ppm 0.15 (s, 9 H) 0.94 (s, 3 H) 1.16 (s, 3 H) 1.36 (m, 2 H) 1.65 (m, 3 H) 2.06 (dd, *J*=13.6, 9.5 Hz, 1 H) 2.22 (m, 1 H) 2.73 (dd, *J*=13.82, 5.29 Hz, 1 H) 2.87 (d, *J*=3.14 Hz, 1H) 3.72 (s, 3 H) 4.03 (d, *J*=3.14 Hz, 1H) 4.96 (m, 4 H) 5.58 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 0.6 (3x CH_3) 23.7 (CH_3) 27.3 (CH_3) 31.9 (CH_2) 34.7 (CH_2) 37.9 (CH_2) 38.5 (CH) 48.9 (CH) 51.9 (C) 55.5 (CH_3) 70.7 (CH) 104.3 (CH) 115.9 (CH_2) 117.2 (CH_2) 120.8 (C) 135.0 (CH) 137.7 (CH) 182.9 (C) 205.6 (C).

HRMS (EI) *m/z* calcd for $C_{21}H_{31}O_3Si$ [M^+] 362.2277, found: 362.2270.



(2.305) 1,7-diallyl-6-(but-3-en-1-yl)-4-methoxy-6-methylbicyclo[3.3.1]non-3-ene-2,9-dione

Wrong diastereomer proved by X-ray:

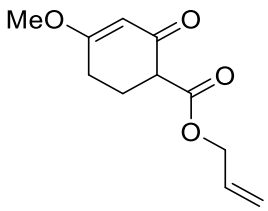
IR (neat, cm^{-1}) ν_{max}: 2939, 2362, 1731, 1658, 1604, 1217, 1178, 997, 916.

^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.01 (s, 3 H) 1.21 (ddd, *J*=13.8, 12.1, 4.4 Hz, 1 H) 1.33 (td, *J*=12.9, 4.9 Hz, 1 H) 1.44 (t, *J*=13.2 Hz, 1 H) 1.66 (ddd, *J*=13.6, 10.7, 8.4 Hz, 1 H)

1.76-1.83 (m, 1 H) 1.92 (dd, *J*=13.5, 4.5 Hz, 1 H) 1.95-2.03 (m, 1 H) 2.19-2.29 (m, 2 H) 2.41-2.53 (m , 2 H) 3.2 (s, 1 H) 3.7 (s, 3 H) 4.94-5.00 (m, 4 H) 5.04 (ddd, *J*=10.5, 3.4, 1.4 Hz, 1 H) 5.08 (ddd, *J*=10.4, 1.7, 1.5 Hz, 1 H) 5.60 (dddd, *J*=16.3, 10.7, 8.3, 5.5 Hz, 1 H) 5.68-5.83 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 23.9 (CH_3) 27.2 (CH_2) 31.4 (CH_2) 33.6 (CH_2) 34.6 (CH_2) 40.0 (CH_2) 40.3 (CH) 43.8 (C) 56.5 (CH_3) 60.6 (CH) 63.2 (C) 106.2 (CH) 115.0 (CH_2) 116.9 (CH_2) 118.1 (CH_2) 134.0 (CH) 136.6 (CH) 138.2 (CH) 174.6 (C) 197.0 (C) 207.2 (C).

HRMS (EI) *m/z* calcd for $C_{21}H_{28}O_3$ [M^+] 328.2038, found: 328.2088.



(2.163) allyl 4-methoxy-2-oxocyclohex-3-ene-1-carboxylate

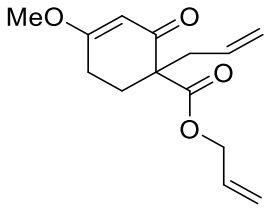
A solution of n-BuLi (2.4 M in hexanes, 10.4 mL, 25.0 mmol) was added slowly to freshly distilled diisopropylamine (3.73 mL, 26.2 mmol) in THF (79 mL) at −78°C and the solution was stirred for 30 min at -78°C and 15 min at 0°C before being recooled to -78°C. A solution of 3-methoxycyclohex-2-enone (**2.160**) (3.00 g, 23.8 mmol) in THF (5 mL) was cannulated at −78°C and the solution was stirred for 60 min to obtain a slurry. Diallyl carbonate (4.46 mL, 28.5 mmol) was added in one portion, the mixture was stirred 1h at -78°C and 3h at r.t. A saturated solution of NH_4Cl was added and the aqueous layer was extracted with ethyl acetate (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (25-30% EtOAc:hexanes) to give allyl 4-methoxy-2-oxocyclohex-3-ene-1-carboxylate **(2.163)** (1.52 g, 7.23 mmol, 30%) as a lightly yellow oil.

IR (neat, cm^{-1}) ν_{max}: 1733, 1652, 1602, 1380, 1147.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.13-2.20 (m, 1 H) 2.30-2.46 (m, 2 H) 2.5 (m, 1 H) 3.34 (dd, *J*=9.0, 4.9 Hz, 1 H) 3.69 (s, 3 H) 4.64 (d, *J*=5.7 Hz, 2 H) 5.20-5.23 (m, 1 H) 5.29-5.34 (m, 1 H) 5.39 (s, 1 H) 5.85-5.95 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 24.1 (CH_2) 27.0 (CH_2) 52.2 (CH) 55.8 (CH_3) 65.7 (CH_2) 101.7 (CH) 118.4 (CH_2) 131.8 (CH) 169.9 (C) 178.3 (C) 193.4 (C).

HRMS (EI) *m/z* calcd for $C_{11}H_{14}O_4$ [M^+] 210.0892, found: 210.0898.



(2.164) allyl 1-allyl-4-methoxy-2-oxocyclohex-3-ene-1-carboxylate

Cesium carbonate (2.46 g, 7.57 mmol) and potassium carbonate (1.05 g, 7.46 mmol) were added to a solution of **2.163** (1.50 g, 7.57 mmol) in acetone (40.0 mL) at r.t. Allyl bromide was added (0.789 mL, 9.08 mmol) and the solution was refluxed o/n. Thereafter, the mixture was filtered over celite and concentrated. The crude residue was purified by flash chromatography (10-20% EtOAc:hexanes) to give allyl 1-allyl-4-methoxy-2-oxocyclohex-3-ene-1-carboxylate (**2.164**) (1.87 g, 7.47 mmol, 30%) as a lightly yellow oil.

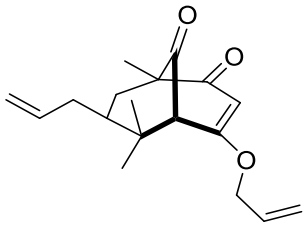
IR (neat, cm^{-1}) ν_{max}: 1730, 1654, 1606, 1382, 1186.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.81-1.88 (m, 1 H) 2.23-2.32 (m, 2 H) 2.42-2.55 (m, 2 H) 2.61 (dd, *J*=13.9, 7.3 Hz, 1 H) 3.59 (s, 3 H) 4.49 (dt, *J*=5.5, 1.4 Hz, 2 H) 4.96-5.03 (m, 2 H) 5.10 (dq,

J=10.5, 1.3 Hz, 1 H) 5.18 (dq, *J*=17.2, 1.5 Hz, 1 H) 5.28 (d, *J*=0.8 Hz, 1 H) 5.64 (dddd, *J*=17.1, 10.0, 7.3, 7.3 Hz, 1 H) 5.77 (dddd, *J*=17.2, 10.7, 5.6, 5.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 25.8 (CH_2) 27.9 (CH_2) 38.3 (CH_2) 55.4 (C) 55.6 (CH_3) 65.4 (CH_2) 101.3 (CH) 118.0 (CH_2) 118.5 (CH_2) 131.5 (CH) 133.2 (C) 170.7 (C) 177.4 (C) 194.7 (C).

HRMS (EI) *m/z* calcd for $C_{14}H_{18}O_4$ [M^+] 250.1205, found: 250.1201.



(2.219) 7-allyl-4-(allyloxy)-1,6,6-trimethylbicyclo[3.3.1]non-3-ene-2,9-dione

Sodium (0.022 g, 0.961 mmol) was added to allyl alcohol (3.00 mL) in a r.b.f. and stirred until all sodium has been consumed. **2.212** (0.230 g, 0.739 mmol) was diluted in a minimum of allyl alcohol and added to the solution of sodium allyl alkoxide. The r.b.f. was fitted with a refrigerant and heated at 50°C for 1 h. The resulting mixture was purified by flash chromatography (2 % EtOAc:hexanes) to provide **2.219** (0.602 g, 0.1735 mmol, 81%).

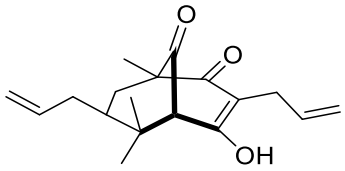
IR (neat, cm^{-1}) ν_{max}: 3081, 2971, 2934, 1733, 1652, 1601, 1340, 1210, 1095, 990.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.88 (s, 3 H) 1.05 (s, 3 H) 1.17 (s, 3 H) 1.27 (m, 1 H) 1.61 (m, 1 H) 1.76 (m, 1 H) 2.00 (m, 1 H) 2.24 (m, 1 H) 2.87 (s, 1 H) 4.42 (m, 2 H) 4.96 (m, 2 H) 5.32 (dd, *J*=10.5, 1.1 Hz, 1 H) 5.38 (dd, *J*=17.3, 1.3 Hz, 1 H) 5.67 (m, 1 H) 5.67 (s, 1 H) 5.94 (m, *J*=16.9, 11.0, 5.7, 5.4 Hz, 1 H).

^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 15.5 (CH_3) 20.5 (CH_3) 27.1 (CH_3) 34.0 (CH_2) 38.7 (CH) 41.3 (C) 42.0 (CH_2) 60.1 (C) 65.5 (CH) 70.2 (CH_2) 106.2 (CH) 116.8 (CH_2) 119.5 (CH_2) 130.7 (CH) 136.6 (CH) 173.3 (C) 197.7 (C) 207.8 (C).

HRMS (EI) *m/z* calcd for $C_{18}H_{24}O_3$ [M^+] 288.1725, found: 288.1734.

m.p. 72-74.



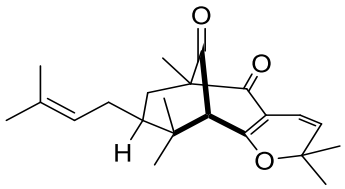
(2.228) 3,7-diallyl-4-hydroxy-1,6,6-trimethylbicyclo[3.3.1]non-3-ene-2,9-dione

A solution of allyl enol ether (0.100 g, 0.347 mmol) in toluene was placed in a sealed tube and heated at 140°C for 7 hours before the solution was allowed to cool back down to r.t. The mixture was concentrated and the crude residue was purified by flash chromatography (50 % EtOAc:hexanes) to give **2.228** (0.084 g, 0.291 mmol, 84%) as a lightly yellow oil.

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.77 (s, 3 H) 0.99 (s, 3 H) 1.04 (s, 3 H) 1.14 (t, *J*=7.3 Hz, 1 H) 1.21 (t, *J*=12.9 Hz, 2 H) 1.61 (m, 2 H) 1.77 (dd, *J*=13.5, 4.3 Hz, 1 H) 2.20 (m, 1 H) 2.93 (m, 3 H) 4.82 (dd, *J*=10.1, 2.3 Hz, 1 H) 4.88 (dd, *J*=17.2, 2.2 Hz, 1 H) 4.94 (s, 1 H) 4.98 (d, *J*=4.7 Hz, 1 H) 5.68 (m, 1 H).

^{13}C NMR (400 MHz, DMSO-d6) δ 16.4 (CH_3) 20.4 (CH_3) 26.2 (CH_3) 26.9 (CH_2) 33.3 (CH_2) 38.3 (CH) 40.6 (C) 40.7 (C) 41.23 (CH_2) 41.84 (CH_2) 58.0 (C) 113.8 (C) 115.2 (CH_2) 116.3 (CH_2) 136.6 (CH) 137.4 (CH) 208.1 (C). (Missing carbonyl)

HRMS (EI) *m/z* calcd for $C_{18}H_{24}O_3$ [M^+] 288.1725, found: 288.1707.



Major isomer: (2.231) 2,2,6,9,9-pentamethyl-8-(3-methylbut-2-en-1-yl)-2,6,7,8,9,10-hexahydro-5H-6,10-methanocycloocta[b]pyran-5,11-dione

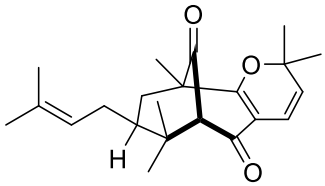
Grubb's 2nd generation (0.106 g, 0.125 mmol, 15% loading) was added to a solution of **2.228** (0.24 g, 0.832mmol) in DCM (3.00 mL) and the solution was heated at 40°C for 24h. The solution was thereafter concentrated and diluted in DMSO: H_2O 9:1 (2 mL). $PdCl_2$ (0.166 g, 0.941 mmol) was added and O_2 was bubbled through the solution by means of a balloon for 1h. The crude residue was purified by flash chromatography (20 % EtOAc:hexanes) to give a separable mixture of **2.231** and **2.230** as crystalline solids.

IR (neat, cm^{-1}) ν_{max}: 2979, 2366, 1731, 1654, 1587.

^1H NMR, (400 MHz, $CDCl_3$) δ ppm 0.89 (s, 3 H) 1.12 (s, 3 H) 1.20 (s, 3 H) 1.22-1.29 (m, 1 H) 1.40 (s, 3 H) 1.47 (s, 3 H) 1.54 (s, 3 H) 1.63-1.65 (m, 2 H) 1.65 (s, 3 H) 2.01 (dd, *J*=13.7, 4.1 Hz, 1 H) 2.05-2.09 (m, 1 H) 2.83 (s, 1H) 4.95-4.98 (m, 1 H) 5.29 (d, *J*=10.2 Hz, 1 H) 6.39 (d, *J*=10.0 Hz, 1 H).

^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 16.0 (CH_3) 17.9 (CH_3) 20.6 (CH_3) 25.8 (CH_3) 27.3 (CH_3) 28.0 (CH_2) 28.8 (CH_3) 29.4 (CH_3) 40.2 (CH) 42.1 (CH_2) 42.2 (C) 60.1 (C) 65.3 (CH) 82.4 (C) 112.7 (C) 115.3 (CH) 122.3 (CH) 123.7 (CH) 133.2 (C) 168.2 (C) 193.7 (C) 207.3 (C).

HRMS (EI) *m/z* calcd for $C_{22}H_{30}O_3$ [M^+] 342.2195, found: 342.2182.



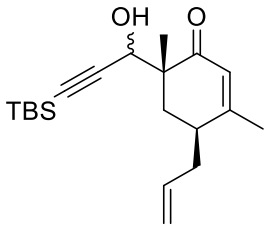
Minor isomer: (2.230) 2,2,7,7,10-pentamethyl-8-(3-methylbut-2-en-1-yl)-2,6,7,8,9,10-hexahydro-5H-6,10-methanocycloocta[b]pyran-5,11-dione

IR (neat, cm^{-1}) ν_{max}: 2974, 2356, 1733, 1647, 1575, 1326, 1108.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.84 (s, 3 H) 1.09 (s, 3 H) 1.23 (s, 3 H) 1.29-1.35(m, 1H) 1.36 (s, 3 H) 1.44 (s, 3 H) 1.55 (s, 3 H) 1.65 (s, 5 H) 1.99 (dd, *J*=13.8, 3.8 Hz, 1 H) 2.07-2.14 (m, 1 H) 2.90 (s, 1 H) 4.98-5.01 (m, 1 H) 5.3 (d, *J*=10.0 Hz, 1 H) 6.4 (d, *J*=10.0 Hz, 1 H).

^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 15.1 (CH_3) 17.8 (CH_3) 20.5 (CH_3) 25.7 (CH_3) 26.5 (CH_3) 27.2 (CH_2) 27.9 (CH_3) 28.2 (CH_3) 39.8 (CH_2) 41.3 (CH) 42.3 (C) 52.5 (C) 74.3 (CH) 81.4 (C) 113.5 (C) 115.9 (CH) 122.6 (CH) 123.5 (CH) 133.2 (C) 171.4 (C) 189.7 (C) 206.6 (C).

HRMS (EI) *m/z* calcd for $C_{22}H_{30}O_3$ [M^+] 342.2195, found: 342.2182.



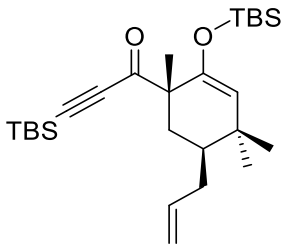
(2.173) 4-allyl-6-(3-(tert-butyldimethylsilyl)-1-hydroxyprop-2-ynyl)-3,6-dimethylcyclohex-2-enone

A solution of *n*-BuLi (2.5 M in hexanes, 1.66 mL, 3.04 mmol) was added slowly to freshly distilled diisopropylamine (0.453 mL, 3.18 mmol) in THF (15 mL) at −78°C and the solution was stirred for 30 min at -78°C and 15 min at 0°C. 4-Allyl-3,6-dimethylcyclohex-2-enone (**2.172**) (0.475 g, 2.89 mmol) was cannulated to the solution at -78°C. After stirring for 60 min, 3-(*tert*-butyldimethylsilyl)propiolaldehyde (0.584 g, 3.47 mmol) was added and the mixture was stirred at -78°C for 10 min. The resulting mixture was quenched with a saturated solution of NH_4Cl at -78°C. Distilled water was added and the aqueous layer was extracted with Et_2O (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by chromatography (5-15% EtOAc:hexanes) to give alcohol enone (**2.173**) (0.588 g, 1.78 mmol, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.10 (d, *J*=1.4 Hz, 6 H) 0.93 (s, 9 H) 1.22 (s, 3 H) 1.72 (dd, *J*=14.1, 8.8 Hz, 1 H) 1.97 (s, 3 H) 2.11-2.19 (m, 2 H) 2.50-2.54 (m, 2 H) 2.63 (d, *J*=4.1 Hz, 1 H) 4.56 (d, *J*=3.9 Hz, 1 H) 5.08-2.13 (m, 2 H) 5.64-5.74 (m, 1 H) 5.83 (s, 1 H).

^{13}C NMR (400 MHz, $CDCl_3$) δ ppm; -4.7 (CH_3) -4.7 (CH_3) 16.5 (C) 17.2 (CH_3) 22.2 (CH_3) 26.1 (3xCH_3) 36.8 (CH) 37.0 (CH_2) 37.5 (CH_2) 48.3 (C) 66.8 (CH) 89.5 (C) 103.1 (C) 117.9 (CH_2) 126.1 (CH) 135.1 (CH) 163.4 (C) 202.7 (C).

HRMS (EI) *m/z* calcd for $C_{16}H_{23}O_2Si$ [M^+-*t*-Bu] 275.1467, found: 275.1467.



(2.176) 1-(-5-allyl-2-((tert-butyldimethylsilyl)oxy)-1,4,4-trimethylcyclohex-2-en-1-yl)-3-(tert-butyldimethylsilyl)prop-2-yn-1-one

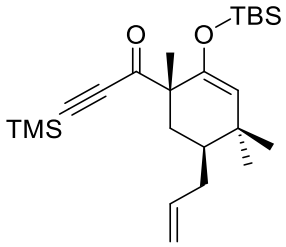
Synthesized according to the methodology described for **2.317.** It was isolated as clear oil (0.31g, 88 % yield).

IR (neat, cm^{-1}) ν_{max}: 2929, 2358, 1672, 823.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 5.75-5.66 (m, 1 H), 5.03-4.96 (m, 2H), 4.65 (s, 1 H), 2.30-2.25 (m, 1 H), 2.07 (dd, *J* = 14.2, 2.6 Hz, 1 H), 1.64-1.50 (m, 2 H),1.37-1.29 (m, 1 H), 1.32 (s, 3 H), 1.02 (s, 3 H), 0.96 (s, 9 H), 0.87 (s, 9 H), 0.82 (s, 3 H),0.18 (s, 3 H), 0.17 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 190.72 (C), 148.66 (C), 137.86 (CH), 117.55 (CH), 115.99 (CH_2), 101.72 (C), 97.59 (C), 53.83 (C), 39.99 (CH), 36.56 (CH_2), 35.04 (C), 34.13 (CH_2), 29.27 (CH_3), 26.07 (3xCH_3), 25.76 (3xCH_3), 23.21 (CH_3), 22.48 (CH_3), 18.18 (C), 16.64 (C), -4.27 (CH_3), -4.84 (CH_3), -5.12 (2xCH_3).

HRMS (EI) *m/z* calcd for $C_{27}H_{48}O_2Si_2$ 460.3193, found 460.3235.



(2.183) 1-(-5-allyl-2-((tert-butyldimethylsilyl)oxy)-1,4,4-trimethylcyclohex-2-en-1-yl)-3-(trimethylsilyl)prop-2-yn-1-one

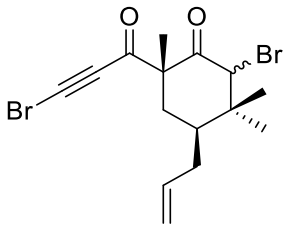
Synthesized according to the methodology described for **2.317.** It was isolated as clear oil (0.45g, 90 % yield).

IR (neat, cm^{-1}) ν_{max}: 2957, 2354, 1650, 827.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.76-5.66 (m, 1 H), 5.04-4.97 (m, 2 H), 4.65 (s, 1 H), 2.32-2.25 (m, 1 H), 2.05 (dd, *J* =14.0, 2.2 Hz, 1 H), 1.64-1.55 (m, 3 H), 1.30 (s, 3 H), 1.04 (s, 3 H), 0.87 (s, 9 H), 0.83 (s, 3 H), 0.23 (s, 9 H), 0.18 (s, 3 H), 0.17 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 191.13 (C), 148.78 (C), 137.92 (CH), 117.39 (CH), 115.88 (CH_2), 101.15 (C), 98.98 (C), 53.77 (C), 39.91 (CH), 36.65 (CH_2), 35.06 (C), 34.19 (CH_2), 29.29 (CH_3), 25.72 (3xCH_3), 23.18 (CH_3), 22.34 (CH_3), 18.18 (C), -0.75 (3xCH_3), -4.21 (CH_3), -4.95 (CH_3).

HRMS (EI) *m/z* calcd for $C_{24}H_{42}O_2Si_2$ [$(M-C_4H_9)^+$] 361.2014, found 361.2039.

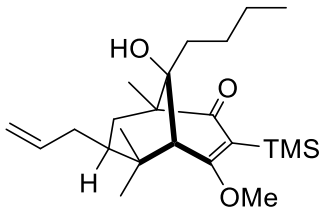


(2.213) 4-allyl-6-bromo-2-(3-bromopropioloyl)-2,5,5-trimethylcyclohexanone

NBS (22 mg, 0.123 mmol) was added to a solution of vinyl enol ether (**2.208**) (50 mg, 0.118 mmol) in DCM (5 mL). The r.b.f. was shielded with foil and stirred for two hours before the mixture was concentrated and purified by chromatography (5% EtOAc:hexanes) to give dibromo (**2.213**) (0.03 g, 0.075 mmol, 63%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.95 (s, 3 H) 1.12 (s, 3 H) 1.12 (t, *J*=13.72 Hz, 1 H) 1.35 (s, 3 H) 1.68 (m, 1 H) 2.22 (m, 1 H) 2.35 (m, 1 H) 2.63 (dd, *J*=14.5, 3.9 Hz, 1 H) 4.07 (s, 1 H) 5.08 (m, 1 H) 5.12 (m, 1 H) 5.87 (m, 1 H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 19.7 (CH_3) 23.3 (CH_3) 27.5 (CH_3) 33.8 (s, 1 C) 35.1 (s, 1 C) 35.4 (CH) 40.1 (C) 60.3 (C) 61.9 (C) 65.3 (CH) 77.20(C) 116.6 (CH_2) 136.8 (CH) 181.3 (C) 198.9 (C).



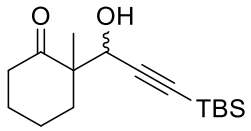
(2.257) 7-allyl-9-butyl-9-hydroxy-4-methoxy-1,6,6-trimethyl-3-(trimethylsilyl)bicycle [3.3.1]non-3-en-2-one

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.15 (s, 9 H) 0.88 (t, *J*=7.2 Hz, 3 H) 0.93 (s, 3 H) 0.99 (s, 3 H) 1.17 (s, 3 H) 1.22-1.69 (m, 11 H) 2.19-2.25 (m, 1 H) 2.62 (s, 1 H) 3.78 (s, 3 H) 4.91-4.96 (m, 2 H) 5.57-5.64 (m, 1 H).

^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 0.7 (3xCH_3) 14.0 (CH_3) 16.4 (CH_3) 23.2 (CH_2) 24.8 (CH_3) 25.1 (CH_2) 27.7 (CH_3) 34.6 (CH_2) 35.8 (CH_2) 36.0 (CH) 37.8 (CH_2) 38.3 (CH) 50.3 (CH) 52.3 (C) 55.2 (CH_3) 77.5 (C) 115.8 (CH_2) 119.5 (C) 138.0 (CH) 182.6 (C) 206.4 (C).

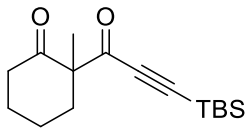
HRMS (EI) *m/z* calcd for $C_{23}H_{40}O_3Si$ [M^+] 392.2747, found: 392.2737.

5.1.4 Vinyl gold



(2.187) 2-(3-(tert-butyldimethylsilyl)-1-hydroxyprop-2-yn-1-yl)-2-methylcyclohexan-1-one

2-methylcyclohexanone (33.8 mmol) was added to LDA (30.4 mmol) in THF (165 ml) at -78 °C and the reaction was warmed to room temperature and then refluxed for 5 hours. Cooled down at -78 °C and then the corresponding 3-(*tert*-butyldimethylsilyl)propiolaldehyde (38.9 mmol, dilued in 10 ml of THF) was added via a cannula. The mixture was stirred for 15 minutes and then quenched with dilued NH_4Cl. The aqueous layer was extracted with EtOAc (2 x 25ml) and then the combined organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated under reduce pressure. The crude was use as was for the Dess-Martin oxidation. This was following the methodology described by barriault *et al.*[35]



(2.188) 2-(3-(tert-butyldimethylsilyl)propioloyl)-2-methylcyclohexan-1-one

Dess-Martin periodinane (16.8 mmol) was added to the alcohol **2.187** (9.31 mmol) dilued in DCM (50 ml). The reaction was let stir at room temperature for 30 minutes and then 100 ml of 50 % $Na_2S_2O_3$ (sat.) and 50 % $NaHCO_3$ (5 %) was added. Stir vigorously for 60 minutes and the aqueous phase was extracted with DCM (50 ml). The combined organic phase was dried over magnesium sulfate and filtrated over cotton. The solvent was then remove under reduce pressure and the crude was purified by flash column chromatography on silica gel (eluted with hexanes: ethyl acetate

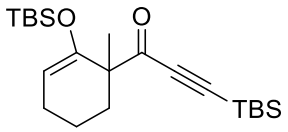
(96:4) to give the corresponding ketone **2.188** (3.8 g, 72 % yield). This was following the methodology described by barriault *et al.*[35]

IR (neat, cm^{-1}) ν_{max}: 2931, 2364, 1720, 1666.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.68-2.59 (m, 1 H), 2.50-2.44 (m, 2 H), 2.07-1.95 (m, 1 H), 1.78-1.58 (m, 3 H), 1.58-1.47 (m, 1 H), 1.30 (s, 3 H), 0.96 (s, 9 H), 0.18 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 208.4 (C), 188.2 (C), 100.4 (C), 99.9 (C), 63.8 (C), 41.3 (CH_2), 37.6 (CH_2), 27.52 (CH_2), 25.9 (3xCH_3), 22.5 (CH_2), 20.8 (CH_3), 16.6 (C), -5.3 (2xCH_3).

HRMS (EI) *m/z* calcd for C16H26O2Si [$(M-C4H9)^{+}$] 221.0992, found 221.0998.



(2.189) 3-(tert-butyldimethylsilyl)-1-(2-((*tert*-butyldimethylsilyl)oxy)-1-methylcyclohex-2-en-1-yl)prop-2-yn-1-one

t-butyldimethylsilyl triflate (10.24 mmol) was added to the corresponding diketone **2.188** (5.12 mmol) and Et_3N (15.36 mmol) in DCM (30 ml) at room temperature. The mixture was refluxed overnight and then a solution of saturated NaHCO3 (25 ml) was added. The aqueous layer was extracted with DCM (2 x 25ml). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated under reduce pressure. The crude was purified by flash column chromatography on silica gel (eluted with benzene:hexanes (30:70)) to give the desired silyl enol ether **2.189** (4.5g, 93 % yield) . This was following the methodology described by barriault *et al.*[35]

IR (neat, cm^{-1}) ν_{max}: 2927, 2357, 1660, 1244.

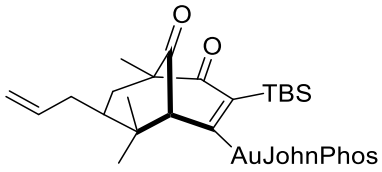
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.87 (dd, *J* = 4.9, 3.3 Hz, 1 H), 2.17- 2.03 (m, 3 H), 1.74-1.67 (m, 1 H), 1.58-1.48 (m, 2 H), 1.29 (s, 3 H), 0.96 (s, 9 H), 0.86 (s, 9 H), 0.17 (s, 3 H), 0.16 (s, 3 H), 0.15 (s, 3 H), 0.12 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 191.2 (C), 151.1 (C), 103.2 (CH), 101.7 (C), 96.4 (C), 54.1 (C), 33.9 (CH2), 26.0 (3xCH3), 25.6 (3xCH3), 24.1 (CH2), 20.1 (CH3), 18.8 (C), 18.2 (CH2), 16.7 (C), -4.4 (CH3), -5.0 (CH3), -5.2 (CH3), -5.2 (CH3).

HRMS (EI) *m/z* calcd for $C_{22}H_{40}O_2Si_2$ [M^+] 392.2567, found 392.2531.

General procedure for vinylgold formation

Add LAu(I) (0.2 mmol) to the silyl enol ether **2.188** (0.61 mmol) diluted in freshly distilled DCM (4 ml) at room temperature and stirred for 30 minutes. Evaporate the solvent under reduce pressure and the crude was purified by flash column chromatography on silica gel (eluted with hexanes:ethyl acetate (90:10)) to give the desired vinyl gold species as a white solid.



(2.179) [3-(tert-butyldimethylsilyl)-5,8,8-trimethyl-4,9-dioxo-7-(prop-2-en-1-yl)bicyclo[3.3.1]non-2-en-2-yl]gold[di-tert-butyl(2-phenylphenyl)phosphine]

(59 mg, 50 % yield)

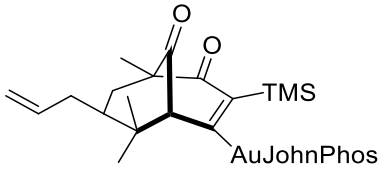
IR (neat, cm^{-1}) ν_{max}: 2960, 1704, 1631, 904, 731.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.89 (t, *J* = 6.9 Hz, 1H), 7.48-7.38 (m, 3 H), 7.22-7.12 (m, 3H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.92 (7, *J* = 7.4 Hz, 1H), 5.61-5.50 (m, 1 H), 4.93-4.88 (m, 2 H), 3.37 (d, *J* = 7.5 Hz, 1H), 2.17-2.12 (m, 1 H), 1.89 (dd, *J* = 13.4, 4.2 Hz, 1 H), 1.66-1.35 (m, 2 H), 1.47 (d, *J* = 14.2 Hz, 9 H), 1.39 (d, *J* = 14.5 Hz, 9 H), 1.20 (s, 3 H), 1.19 (s, 3 H), 0.84 (s, 12 H), 0.36 (s, 3 H), 0.22 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 220.7 (d, *J* = 111.9 Hz, C), 210.6 (d, *J* = 3.3 Hz, C), 204.8 (d, *J* = 13.2 Hz, C), 150.2 (d, *J* = 15.5 Hz, C), 147.1 (d, *J* = 4.7 Hz, C), 142.3 (d, *J* = 5.2 Hz, C), 137.4 (CH), 134.7 (CH), 133.2 (d, *J* = 7.5 Hz, CH), 130.0 (d, *J* = 2.3 Hz, CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.4 (CH), 127.9 (d, J = 33.4 Hz, C), 127.6 (CH), 126.3 (d, *J* = 5.2 Hz, CH), 116.0 (CH2), 75.6 (CH), 61.3 (C), 42.9 (CH2), 41.7 (C), 37.7 (CH), 36.8 (d, *J* = 11.8 Hz, C), 36.7 (d, *J* = 9.9 Hz, C), 33.8 (CH2), 30.8 (d, *J* = 7.0 Hz, 3xCH3), 30.5 (d, *J* = 7.1 Hz, 3xCH3), 28.8 (CH3), 28.0 (3xCH3), 21.7 (CH3), 18.0 (C), 15.8 (CH3), 1.4 (CH3), -2.3 (CH3).

HRMS (ESI) m/z calcd for $C_{41}H_{60}O_2PSiAu$ [M+Na+] 863.3652, found 863.3663.

m.p. (Dec. 231 ºC)



(2.185) [5,8,8-trimethyl-4,9-dioxo-7-(prop-2-en-1-yl)-3-(trimethylsilyl)bicyclo[3.3.1]non-2-en-2-yl]gold[di-tert-butyl(2-phenylphenyl)phosphine]

(20 mg, 69 % yield)

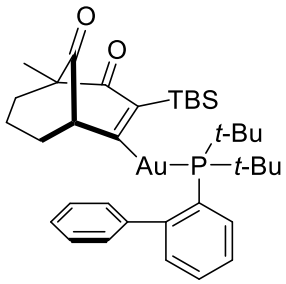
IR (neat, cm^{-1}) ν_{max}: 2923, 1701, 1627, 1461.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.91-7.87 (m, 1H), 7.48-7.42 (m, 2 H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.23-7.15 (m, 3H), 7.02 (d, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 5.62-5.53 (m, 1 H), 4.95-4.89 (m, 2 H), 3.29 (d, *J* = 2.7 Hz, 1H), 2.15-2.11 (m,1 H), 1.86 (dd, *J* = 13.0, 2.5 Hz, 1 H), 1.58-1.51 (m, 2 H), 1.46 (d, *J*=14.3 Hz, 9 H), 1.39 (d, *J*=14.5 Hz, 9 H), 1.20 (s, 3 H), 1.16 (s, 3 H), 0.91-0.85 (m, 1 H), 0.83 (s, 3 H), 0.24 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 218.4 (d, *J* = 112.7 Hz, C), 210.7 (d, *J* = 3.4 Hz, C), 204.4 (d, *J* = 13.2 Hz, C), 150.3 (d, *J* = 16.6 Hz, C), 149.9 (d, *J* = 4.8 Hz, C), 142.5 (d, *J* = 5.3 Hz, C), 137.6 (CH), 134.8 (CH), 133.3 (d, *J* = 7.4 Hz, CH), 130.1 (d, *J* = 2.2 Hz, CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 127.9 (d, J = 33.6 Hz, C), 127.8 (CH), 126.4 (d, *J* = 5.1 Hz, CH), 115.8 (CH2), 75.1 (CH), 61.9 (C), 42.5 (CH2), 41.6 (C), 37.5 (CH), 37.0 (d, *J* = 13.2 Hz, C), 36.8 (d, *J* = 11.3 Hz, C), 33.8 (CH2), 30.9 (d, *J* = 7.2 Hz, 3xCH3), 30.7 (d, *J* = 7.0 Hz, 3xCH3), 28.9 (CH3), 21.8 (CH3), 16.0 (CH3), 2.4 (3xCH3).

HRMS (ESI) *m/z* calcd for $C_{38}H_{54}O_2PSiAu$ [M^+] 798.3296, found 798.3286.

m.p. (Dec. 222 ºC)



(2.131) [3-(tert-butyldimethylsilyl)-5-methyl-4,9-dioxobicyclo[3.3.1]non-2-en-2-yl]gold[ditert-butyl(2-phenylphenyl)phosphine]

(215 mg, 84 % yield)

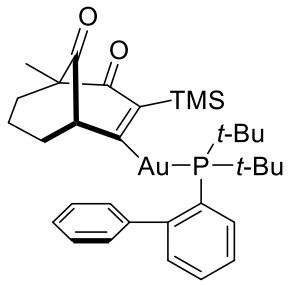
IR (neat, cm^{-1}) ν_{max}: 2927, 1703, 1086.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.92-7.87 (m, 1 H), 7.52-7.42 (m, 3 H), 7.24-7.20 (m, 3 H), 7.13-7.07 (m, 2 H), 3.55-3.52 (m, 1 H), 2.02-1.96 (m, 1 H), 1.87- 1.78 (m, 2 H), 1.54-1.46 (m, 2 H), 1.44 (d, *J* = 1.5 Hz, 9 H), 1.40 (d, *J* = 1.5 Hz, 9 H), 1.38-1.28 (m, 1 H), 1.17 (s, 3 H), 0.86 (s, 9 H), 0.34 (s, 3 H), 0.21 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 219.6 (d, *J* = 109.8 Hz, C), 213.5 (d, *J*=3.3 Hz, C), 205.3 (d, *J* = 12.7 Hz, C), 150.0 (d, *J* = 15.9 Hz, C), 145.1 (d, *J*=5.1 Hz, C), 142.5 (d, *J* = 5.2 Hz, C), 134.6 (CH), 133.4 (d, *J* = 7.6 Hz, CH), 130.1 (d, *J* = 2.0Hz, CH), 129.2 (CH), 129.2 (CH), 129.0 (CH), 128.6 (CH), 127.8 (d, *J* = 33.9 Hz, C), 127.5 (CH), 126.4 (d, *J* = 5.1 Hz, CH), 62.1 (CH), 62.0 (C), 42.0 (CH2), 37.6 (d, *J* = 20.3 Hz, C), 36.7 (d, *J* = 17.9 Hz, C), 30 .8 (d, *J* = 6.2 Hz, 3xCH3), 30.7 (d, J = 6.4 Hz, 3xCH3), 30.4 (CH2), 28.1 (3xCH3), 18.0 (CH2), 17.7 (C), 16.0 (CH3), 0.4 (CH3), -2.2 (CH3).

HRMS (EI) *m/z* calcd for $C_{36}H_{52}O_2PSiAu$ [M-C4H9^{+}] 715.2424, found 715.2472.

m.p. (Dec. 215 ºC).



(2.131) [5-methyl-4,9-dioxo-3-(trimethylsilyl)bicyclo[3.3.1]non-2-en-2-yl]gold[di-tertbutyl(2-phenylphenyl)phosphine]

(21 mg, 77 % yield)

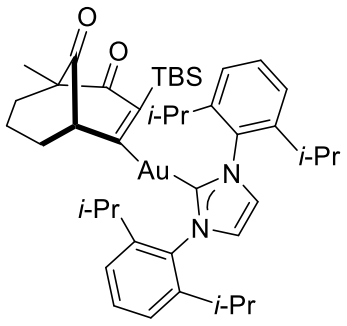
IR (neat, cm^{-1}) ν_{max}: 2943, 1699, 1633, 1085.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.89 (t, *J* = 7.2 Hz, 1 H), 7.50-7.40 (m, 3 H), 7.25-7.17 (m, 3 H), 7.13-7.07 (m, 2 H), 3.50-3.48 (m, 1 H), 1.99-1.93 (m, 1 H), 1.86-1.76 (m, 2 H), 1.50-1.45 (m, 2 H), 1.43 (d, *J* = 4.0 Hz, 9 H), 1.39 (d, *J* = 4.2 Hz, 9 H), 1.34-1.28 (m, 1 H), 1.17 (s, 3 H), 0.25 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 217.3 (d, *J* = 109.6 Hz, C), 213.7 (d, *J* = 3.7 Hz, C), 205.3 (d, *J* = 12.9 Hz, C), 150.2 (d, *J* = 16.6 Hz, C), 147.4 (d, *J* = 5.1 Hz, C), 142.7 (d, *J* = 5.5 Hz, C), 134.7 (CH), 133.1 (d, *J* = 7.7 Hz, CH), 130.2 (d, *J* = 1.9 Hz, CH), 129.3 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 127.9 (d, J = 33.7 Hz, C), 127.6 (CH), 126.6 (d, *J* = 5.2 Hz, CH), 62.2 (C), 61.9 (CH), 41.9 (CH2), 37.6 (d, *J* = 19.7 Hz, C), 37.0 (d, *J* = 18.3 Hz, C), 30.9 (d, *J* = 4.4 Hz, 3xCH3), 30.8 (d, *J* = 4.4 Hz, 3xCH3), 30.3 (CH2), 18.0 (CH2), 16.0 (CH3), 1.9 (3x CH3).

HRMS (ESI) *m/z* calcd for $C_{33}H_{46}O_2PSiAu$ [M^+] 730.2670, found 730.2657.

m.p. (Dec. 219 ºC).



(2.193) [3-(tert-butyldimethylsilyl)-5,8,8-trimethyl-4,9-dioxobicyclo[3.3.1]non-2-en-2-yl]gold[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]

(22 mg, 63 % yield)

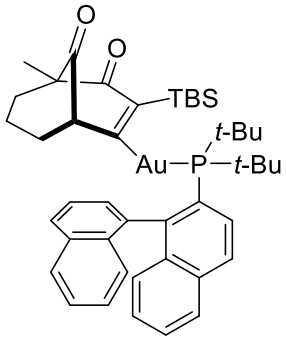
IR (neat, cm^{-1}) ν_{max}: 2962, 2927, 1708, 1635, 1458.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.49 (t, *J* = 7.8 Hz, 2 H), 7.32-7.27 (m, 4 H), 7.19 (s, 2 H), 3.17-3.14 (m, 1 H), 2.66-2.57 (m, 4 H), 1.74-1.68 (m, 1 H), 1.62- 1.58 (m, 1 H), 1.34 (d, *J* = 6.8 Hz, 6 H), 1.30 (d, *J* = 6.8 Hz, 6 H), 1.21 (d, *J* = 6.8 Hz, 6 H), 1.18 (d, *J* = 6.8 Hz, 6 H), 1.15-1.08 (m, 2 H), 1.00 (s, 3 H), 0.91-0.80 (m, 2 H), 0.65 (s, 9 H), -0.09 (s, 3 H), -0.24 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 216.5 (C), 214.4 (C), 204.5 (C), 194.3 (C), 146.5 (C), 145.6 (2xC), 145.5 (2xC), 134.7 (2xC), 130.4 (2xCH), 124.2 (2xCH), 124.1 (2xCH), 123.3 (2xCH), 62.3 (CH), 62.2 (C), 41.9 (CH2), 30.4 (CH2), 28.8 (2xCH), 28.7 (2xCH), 28.0 (3xCH3), 24.5 (2xCH3), 24.5 (2xCH3), 23.9 (2xCH3), 23.8 (2xCH3), 17.9 (CH2), 17.2 (C), 16.1 (CH3), -1.0 (CH3), -2.4 (CH3).

HRMS (ESI) m/z calcd for $C_{43}H_{61}O_2N_2SiAu$ $[M^+]$ 862.4168, found 862.4193.

M.p. (Dec. 254 ºC).



(2.192) [5,8,8-trimethyl-4,9-dioxo-2-(triphenylsilyl)bicyclo[3.3.1]non-2-en-3-yl]gold[di-tert-butyl[1-(naphthalen-1-yl)naphthalen-2-yl]phosphine]

Diastereomer 1:

(69 mg, 70 % yield), mixture of diastereomers (1:1)

IR (neat, cm^{-1}) ν_{max}: 2927, 1708, 1635, 1458.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.10-7.09 (m, 11 H), 6.87 (d, *J* =9.4 Hz, 1 H), 6.73 (d, *J* =9.2 Hz, 1 H), 3.65 (s, 1 H), 1.96-1.26 (m, 6 H), 1.48 (d, *J* =14.9 Hz, 9 H), 1.42 (d, *J* =14.4 Hz, 9 H), 1.21 (s, 3 H), 0.71 (s, 9 H), 0.04 (s, 3 H), -0.79 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 219.6 (d, *J* = 110.1 Hz, C), 213.6 (d, *J* = 3.4 Hz, C), 205.3 (d, *J* = 13.1 Hz, C), 147.4 (d, *J* = 15.9 Hz, C), 145.0 (d, *J* = 5.6 Hz, C), 137.0 (d, *J* = 7.1 Hz, C), 134.4 (d, *J* = 8.4 Hz, C), 133.9 (C), 133.7 (d, *J* = 1.7 Hz, C), 133.3 (C), 129.9 (CH), 129.3 (CH), 128.9 (CH), 128.7 (CH), 128.3 (d, *J* = 1.2 Hz, CH), 127.8 (CH), 127.4 (CH), 127.2 (d, *J* = 34.0 Hz, C), 127.1 (d, *J* = 5.1 Hz, CH), 126.8 (CH), 126.4 (CH), 126.2 (CH), 125.9 (CH), 125.9 (CH), 62.3 (CH), 62.2 (C), 42.2 (CH2), 37.9 (d, *J* = 20.2 Hz, C), 36.6 (d, *J* = 17.5 Hz, C), 31.3 (d, *J* = 7.5 Hz,

3xCH3), 30.9 (d, *J* = 6.7 Hz, 3xCH3), 30.4 (CH2), 27.9 (3xCH3), 18.0 (CH2), 17.7 (C), 16.0 (CH3), -1.3 (CH3), -2.7 (CH3).

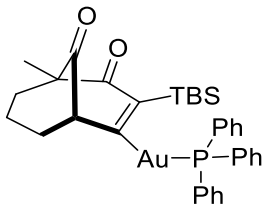
Diastereomer 2:

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.10-7.09 (m, 11 H), 6.89 (d, *J* =8.9 Hz, 1 H), 6.70 (d, *J* =8.7 Hz, 1 H), 2.18 (s, 1 H), 1.96-1.26 (m, 6 H), 1.49 (d, *J* =14.4 Hz, 9 H), 1.39 (d, *J* =14.4 Hz, 9 H), 1.12 (s, 3 H), 0.82 (s, 9 H), 0.40 (s, 3 H), 0.08 (s, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 218.9 (d, *J* = 110.6 Hz, C), 213.5 (d, *J* = 3.8 Hz, C), 205.2 (d, *J* = 13.2 Hz, C), 147.4 (d, *J* = 15.5 Hz, C), 145.3 (d, *J* = 5.1 Hz, C), 136.4 (d, *J* = 6.6 Hz, C), 134.4 (d, *J* = 9.0 Hz, C), 133.7 (2xC), 133.4 (C),130.1 (CH), 130.0 (CH), 128.7 (CH), 128.6 (CH), 128.2 (d, *J* = 1.2 Hz, CH), 127.8 (CH), 127.4 (CH), 127.1 (d, *J* = 5.9 Hz, CH), 126.9 (d, *J* = 33.0 Hz, C), 126.7 (CH), 126.1 (CH), 126.0 (CH), 126.0 (CH), 125.9 (CH), 61.9 (C), 60.23 (CH), 41.9 (CH2), 37.5 (d, *J* = 17.9 Hz, C), 37.3 (d, *J* = 17.0 Hz, C), 31.4 (d, *J* = 7.1 Hz, 3xCH3), 30.9 (d, *J* = 7.10 Hz, 3xCH3), 30.3 (CH2), 28.3 (3xCH3), 17.9 (CH2), 17.6 (C), 16.1 (CH3), 0.1 (CH3), -1.9 (CH3)

HRMS (EI) *m/z* calcd for $C_{44}H_{56}O_2PSiAu$ [M^+] 872.3453, found 872.3431.

m.p. (Dec. 256 ºC)



(2.200) [5,8,8-trimethyl-4,9-dioxo-2-(triphenylsilyl)bicyclo[3.3.1]non-2-en-3-yl]gold[*tri*-phenylphosphine]

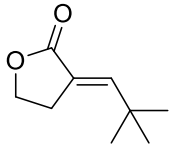
Triphenylphosphine (0.034 g, 0.129 mmol) was added to a solution of vinyl gold **2.131** (0.02 g, 0.026 mmol) in $PhCF_3$ (0.30 mL) and the mixture was heated at 100°C for 1h. The reaction was cooled down to r.t. and the crude residue was purified by flash column chromatography on silica gel (5-10-15% EtOAc:hexanes) to give triphenyl phosphine vinyl gold **2.200** (0.012 g, 0.016 mmol, 62.9%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.23 (s, 3 H) 0.37 (s, 3 H) 0.84-0.95 (m, 1 H) 0.87 (s, 9 H) 1.15 (s, 3 H) 1.38-1.47 (m, 1 H) 1.50-1.65 (m, 1 H) 1.88-1.92 (m, 1 H) 1.98-2.07 (m, 1 H) 2.26-2.31 (m, 1 H) 3.97-4.00 (m, 1 H) 7.45-7.51 (m, 15 H).

^{31}P NMR (400 MHz, $CDCl_3$) δ ppm 41.73.

5.2 Ginkgolides

5.2.1 Route A: Rautenstrauch synthesis intermediates



(3.19) (*E*)-3-(2,2-dimethylpropylidene)dihydrofuran-2(3H)-one

In a 500 mL round bottom flask equipped with a stir bar was added lithium *tert*-butoxide (9.64 g, 120.4 mmol, 2 equiv.) and 200 mL of petroleum ether (0.3 M). To this suspension, was added via syringe trimethylacetaldehyde 75 mol% in *tert*-butanol (8.56 mL, 60.2 mmol, 1 equiv.). The flask was then placed in an ice bath and to the mixture was added in one portion γ-butyrolactone (**3.15**) (9.20 mL, 120 mmol, 2 equiv.). An exothermic reaction follows the additions of γ-butyrolactone, therefore the ice bath was kept under the flask to avoid any reaction runaways. After 10-15 minutes, the ice bath was removed and the reaction was allowed to stir at ambient temperature

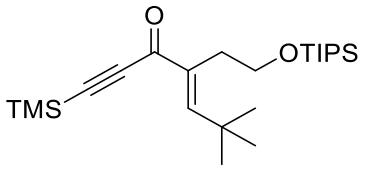
overnight. The reaction mixture appearance changed from a heterogeneous suspension to a pale yellow milky solution. After being stirred overnight, the reaction solution was filtered over celite and the remaining solid was washed with diethylether. The filtrate was evaporated under reduced pressure and dried under high vacuum. The crude oil was then purified by flash chromatography to afford (E)-3-(2,2-dimethylpropylidene)dihydrofuran-2(3H)-one (**3.19**) (7.05 g, 45.7 mmol, 76%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2960, 2870, 1757, 1667, 1223, 1177, 1038, 726.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 6.74 (t, *J* = 2.8 Hz, 1H) 4.33 (t, *J* = 7.4 Hz, 2H) 3.02 (td, *J* = 7.4, 2.8 Hz, 2H) 1.16 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 150.5, 121.4, 65.3, 34.0, 29.4, 25.5.

HRMS (EI) *m/z* calcd for $C_9H_{14}O_2$ [M^+] 154.0994, found 154.0983.



(3.21) (*E*)-6,6-dimethyl-4-(2-((triisopropylsilyl)oxy)ethyl)-1-(trimethylsilyl)hept-4-en-1-yn-3-one

In a flame dried 250 mL round bottom flask equipped with a stir bar and under an argon atmosphere was added ethynyltrimethylsilane (2.94 mL, 20.8 mmol, 1.2 equiv.) and 40 mL of dry THF. The solution was cooled to -78 °C, then a solution *n*-butyllithium 2.5 M in hexanes (8.30 mL, 20.8 mmol, 1.2 equiv.) was slowly added. The solution was allowed to slowly warm to approximately -40°C for 30 minutes. The reaction mixture was then cooled to -78 °C again, and BF_3·THF (2.20

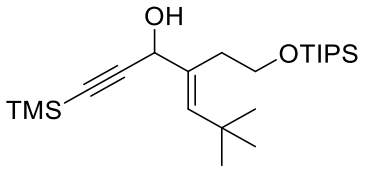
mL, 19.9 mmol, 1.15 equiv.) was added in one portion. The mixture was then stirred for an additional 10 minutes at -78 ºC, then the lactone **3.19** (2.67 g, 17.3 mmol, 1.0 eq.) was added to the mixture as a THF solution (20 mL). The resulting mixture was allowed to warm to ambient temperature and stirred for 1-2 hours. When judged complet by TLC, the reaction mixture was quenched by the addition of a saturated solution of ammonium chloride. Then more water was poured into the mixture and the aqueous layer was extracted with ether (4X). The combined organic layer were dried over sodium sulfate, filtered and concentrated under vacuum. 4.52 g of crude alcohol **3.20** was recovered as a colorless oil, the product was used without further purification in the next step. The crude alcohol dissolved in DMF (85 mL, 0.2 M) in a 250 mL flask equipped with a stir bar, to this solution were added imidazole (2.36 g, 34.7 mmol, 2.4 equiv.) and *N*,*N*-4-dimethylaminopyridine (DMAP, 200 mg, 1.7 mmol, 10 mol%).To this solution was added slowly TBSCl (3.13g, 20.8 mmol, 1.2 equiv.) at ambient temperature. When the reaction was judged completed by TLC, 35 min approximately 50 mL of ether was poured into the reaction and it was transfer into an extraction funnel, in which approx. 400 mL of water were added. The aqueous layer was extracted with ether (~ 4X, 50-100 mL), the combined organic layer where then wash 3X with water, then brine, concentrated under reduce pressure. The crude product was purified by flash chromatography (5% ether/ petroleum ether). The product **3.21** was isolated as colorless oil in 53% yield starting from γ–butyrolactone **3.19**.

IR (neat, cm^{-1}) ν_{max}: 2960, 2867, 1636, 1465, 1365, 1252, 1106, 1086, 846.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.27 (s, 1H), 3.64 (t, *J* = 7.4 Hz, 2H), 2.72 (t, *J* = 7.3 Hz, 2H), 1.23 (s, 9H), 1.03 (m, 21H), 0.24-0.22 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 181.5, 162.0, 137.8, 100.6, 98.6, 62.3, 34.5, 30.6, 29.3, 18.2, 12.1, -0.6.

HRMS (EI) *m/z* calcd for $C_{23}H_{44}O_2Si_2$ [M^+- C_3H_7] 365.2332, found 365.2346.



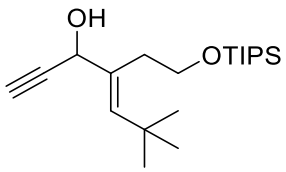
(*E*)-6,6-dimethyl-4-(2-((triisopropylsilyl)oxy)ethyl)-1-(trimethylsilyl)hept-4-en-1-yn-3-ol

In a 25 mL round bottom flask equipped with a stir bar, was added lithium borohydride (430 mg, 8.81 mmol, 3.6 equiv.) and 5 mL of THF then cooled to 0 ºC. To the stirring suspension was added portion wise cerium chloride heptahydrate (1.37 g, 3.67 mmol, 1.5 equiv.), hydrogen gas bubbled-off the solution. After the reaction stopped bubbling, ketone (1.0 g, 2.45 mmol, 1.0 equiv.) was dissolved in 3 mL of THF (0.3 M in total) and the solution was added to the LiBH4/CeCl3 mixture. The reaction was allowed to warm to ambient temperature and it was stirred until it was judged complete by TLC. Once completed, a saturated solution of ammonium chloride was added to reaction mixture. The heterogeneous mixture was poured into an extraction funnel and extracted with ether. The combined organic layers where dried over magnesium sulfate, filtered and concentrated under reduce pressure. The crude product was use without purification in the next step.

IR (neat, cm^{-1}) ν_{max}: 3390, 2945, 1698, 1012.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 5.70 (s, 1H), 4.87 (d, *J* = 8.4 Hz, 1H), 4.63 (d, *J* = 8.1 Hz, 1H), 3.98 (ddd, *J* = 9.7, 5.4, 4.3 Hz, 1H), 3.76 (td, *J* = 9.4, 3.4 Hz, 1H), 2.76 (ddd, *J* =14.8, 5.2, 3.4 Hz, 1H), 2.66 (ddd, *J* = 14.7, 9.0, 4.1 Hz, 1H), 1.12 (s, 9H), 1.12-1.08 (m, 21H), 0.16 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 142.3, 135.8, 106.6, 90.4, 70.4, 64.5, 33.0, 31.3, 30.8, 18.1, 12.0, -0.02.



(3.21) (*E*)-6,6-dimethyl-4-(2-((triisopropylsilyl)oxy)ethyl)hept-4-en-1-yn-3-ol

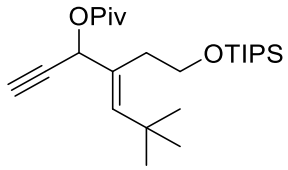
The crude alcohol **3.22** was diluted in approximately 10 mL of methanol and to the solution was added a stir bar and a ~50 mg of potassium carbonate. The mixture was stirred at ambient temperature for ~15 minutes. When the reaction was completed, the base was filtered off the solution and the product concentrated under reduced pressure. The crude product was purified by flash chromatography and yield the terminal alkyne **3.22** as a colorless oil in 74% yield.

IR (neat, cm^{-1}) ν_{max}: 3390, 3312, 2945, 2868, 2723, 2108, 1715, 1668, 1464, 1092.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.69 (s, 1H), 4.92 (d, *J* = 8.0 Hz, 1H), 4.66 (ddd, *J* = 8.0, 2.2, 0.4 Hz, 1H), 3.99 (ddd, *J* = 9.7, 5.3, 4.2 Hz, 1H), 3.78 (td, *J* = 9.4, 3.3 Hz, 1H), 2.78 (ddd, *J* = 14.9, 5.2, 3.3 Hz, 1H), 2.65 (ddd, *J* = 14.8, 9.1, 4.1 Hz, 1H), 2.50 (d, *J* = 2.2 Hz, 1H), 1.14 (s, 9H), 1.16-1.07 (m, 21H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 142.3, 135.4, 84.9, 73.7, 69.8, 64.4, 33.1, 31.3, 30.6, 18.1, 12.0.

HRMS (EI) *m/z* calcd for $C_{20}H_{38}O_2Si$ [M^+- C_3H_7] 295.2093, found 295.2102.



(3.23) (*E*)-6,6-dimethyl-4-(2-((triisopropylsilyl)oxy)ethyl)hept-4-en-1-yn-3-yl pivalate

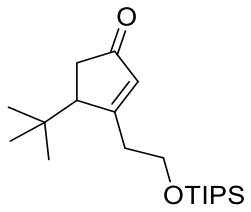
To a solution of secondary alcohol **3.22** (6.53 g, 19.3 mmol) in DCM (96 mL), Et_3N (8.06 mL, 5.85 mmol), DMAP (0.236 mg, 1.928 mmol), and PivCl (2.97 mL, 24.1 mmol) were added in order. The reaction was followed by TLC and all starting material disappeared after 3 hours. The reaction was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (20-30% EtOAc:hexanes) to give pivalate alcohol **3.23** (6.63 g, 15.7 mmol, 81%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2900, 2868, 1738, 1464, 1141, 1098, 882.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 5.80 (d, *J* = 0.6 Hz, 1H), 5.75 (dd, *J* = 2.2, 0.9 Hz, 1H), 3.83 (dtt, *J* = 29.0, 10.4, 5.5 Hz, 2H), 2.68 (ddd, *J* = 13.6, 10.0, 5.6 Hz, 1H), 2.57 (ddd, *J* = 13.5, 9.9, 6.0 Hz, 1H), 2.50 (d, *J* = 2.2 Hz, 1H), 1.21 (s, 9H), 1.15 (s, 9H), 1.09-1.04 (m, *J* = 2.7 Hz, 21H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 177.1, 143.6, 130.2, 80.6, 74.7, 69.3, 63.0, 38.8, 33.1, 32.1, 31.1, 27.1, 18.2, 12.1.

HRMS (EI) *m/z* calcd for $C_{25}H_{46}O_3Si$ [M^+- C_3H_7] 379.2668, found 379.9746.



(3.27) 4-(tert-butyl)-3-(2-((triisopropylsilyl)oxy)ethyl)cyclopent-2-en-1-one

Pivalate **3.23** (5.6g, 13.3 mmol) was dissolved in chloroform (132 mL) at r.t. and goldJohnPhos (0.511 g, 0.662 mmol, 5% loading) was added in one portion. The reaction was allowed to stir for 15 min after witch acetone (132 mL) was added in one portion. After 15 min the reaction was followed by TLC and all starting material and intermediate have been consumed. The crude was concentrated and flashed over silica (5-10% EtOAC:hexanes) to give enone **3.27** (2.9 g, 8.56 mmol, 65 %). The unhydrolysed adduct can be found as an impurity in most reaction.

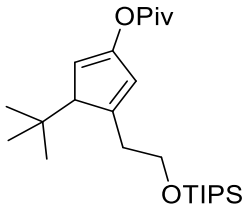
Alternatively, the reaction can also be performed in acetone with similar yield. To a solution of pivalate **3.23** (1eq.) in acetone (0.1M) was added [MeXPhosAuMeCN]SbF_6 (5% loading) at r.t. and the solution stirred for 72h at the same temperature. The mixture was then concentrated and the crude was flashed over silica (5-10% EtOAC:hexanes) to give enone **3.27** (73 %). The previous method was prefered even though the yield was better in the ladderbecause [MeXPhosAuMeCN]SbF_6 was much more expensif and doesn't allow a dramatic increase in yield.

IR (neat, cm^{-1}) ν_{max}: 2960, 2867, 1705, 1605, 1464, 1103, 680.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.08 (d, *J* = 1.3 Hz, 1H), 3.92 (qt, *J* = 9.3, 6.6 Hz, 2H), 2.86-2.78 (m, 1H), 2.77-2.75 (m, 1H), 2.62 (dt, *J* = 16.3, 6.3 Hz, 1H), 2.42 (dd, *J* = 18.6, 6.5 Hz, 1H), 2.28 (dd, *J* = 18.6, 2.0 Hz, 1H), 1.08-1.04 (m, 21H), 0.98 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 209.0, 181.7, 132.4, 61.8, 54.7, 40.3, 38.0, 34.3, 28.5, 18.1, 12.0.

HRMS (EI) *m/z* calcd for $C_{20}H_{38}O_2Si$ [M^+- C_3H_7] 295.2093, found 295.2095.



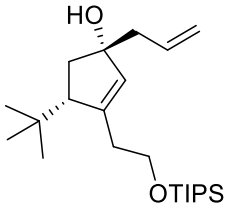
(3.25) 3-(tert-butyl)-4-(2-((triisopropylsilyl)oxy)ethyl)cyclopenta-1,4-dien-1-yl pivalate

IR (neat, cm^{-1}) ν_{max}: 2960, 2867, 1735, 1464, 1105, 883.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.00 (dq, *J* = 2.8, 1.4 Hz, 1H), 5.86 (t, *J* = 1.8 Hz, 1H), 3.84 (t, *J* = 7.6 Hz, 2H), 2.85-2.79 (m, 1H), 2.78-2.54 (m, 2H), 1.28 (s, 9H), 1.08-1.05 (m, 22H), 1.02 (s, 8H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 12.0 (3xCH) 18.0 (6x CH_3) 27.1 (3xCH_3) 28.9 (3xCH_3) 33.7 (C) 35.8 (CH_2) 39.0 (C) 61.9 (CH) 63.2 (CH_2) 115.0 (CH) 125.7 (CH) 148.6 (C) 150.6 (C) 176.2 (C).

HRMS (EI) *m/z* calcd for $C_{25}H_{46}O_3Si$ [M^+- C_3H_7] 379.2668, found 379.2662.



(3.38) 1-allyl-4-(tert-butyl)-3-(2-((triisopropylsilyl)oxy)ethyl)cyclopent-2-en-1-ol

To a solution of enone **3.27** (0.25 g, 0.738 mmol) in THF (8mL) at -78˚C, was added a solution of allylmagnesium bromide (0.812 mL, 0.812 mmol, 1M in Et_2O) slowly. The reaction mixture was then allowed to warm to the r.t. and after 1 hour, no more sign of the starting material was visible by TLC. The reaction was quenched with a saturated solution of NH_4Cl. The aqueous phase was

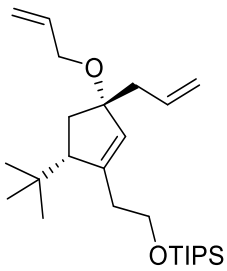
extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residues residue was purified by flash chromatography (10-15% EtOAc:hexanes) to give alcohol **3.38** (0.256 g, 0.672 mmol, 91%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2941, 2866, 1463, 1365, 1099, 881, 678.

^1H NMR (400 MHz, C_6D_6) δ ppm 0.91 (s, 9 H) 1.11-1.13 (m, 21 H) 1.35 (s, 1 H) 1.67 (dd, *J*=13.7, 6.3 Hz, 1 H) 2.07 (dd, *J*=13.7, 8.4 Hz, 1 H) 2.27-2.33 (m, 3 H) 2.36-2.41 (m, 1 H) 2.50-2.58 (m, 1 H) 3.84 (t, *J*=7.1 Hz, 2 H) 5.05-5.06 (m, 1 H) 5.08-5.10 (m, 1 H) 5.48 (q, *J*=1.4 Hz, 1 H) 5.59-6.00 (m, 1 H).

^{13}C NMR (100 MHz, C_6D_6) δ ppm 12.3 ($3xCH_3$) 18.3 ($6xCH_3$) 28.5 (3xCH) 33.2 (C) 36.2 (CH_2) 41.8 (CH_2) 46.5 (C) 56.7 (CH) 62.7 (CH_2) 81.3 (C) 117.8 (CH_2) 134.5 (CH) 135.0 (CH) 145.7 (C).

HRMS (EI) *m/z* calcd for $C_{20}H_{39}O_2Si$ [M^+-C3H5] 339.2719, found 339.2723.



(3.41) (2-(3-allyl-3-(allyloxy)-5-(tert-butyl)cyclopent-1-en-1-yl)ethoxy)triisopropylsilane

To a cooled suspension of NaH (25 mg, 0.630 mmol, 60% w/w) in THF (2 mL) at 0˚C, was added dropwise a solution of tertiary alcohol **3.38** (0.2g, 0.525 mmol) in THF (1mL). The solution was allowed to stir for 10 min before allyl bromide (0.055mL, 0.630 mmol) was added in one portion and the reaction was allowed to warm at r.t. and stirred o/n. The reaction was quenched with a

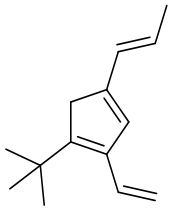
saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residues residue was purified by flash chromatography (5% EtOAc:hexanes) to give allyl ether **3.41** (95 mg, 0.226 mmol, 43%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2930, 1204, 887.

^1H NMR (400 MHz, C_6D_6) δ ppm 0.92 (s, 9 H) 1.10-1.14 (m, 21 H) 1.86-1.97 (m, 2 H) 2.25-2.29 (m, 1 H) 2.34-2.53 (m, 3 H) 2.53-2.61 (m, 1 H) 3.84-3.87 (m, 2 H) 3.95-3.98 (m, 2 H) 5.07-5.13 (m, 3 H) 5.37-5.43 (m, 1 H) 5.58 (d, *J*=0.8 Hz, 1 H) 5.92-6.10 (m, 2 H).

^{13}C NMR (100 MHz, C_6D_6) δ ppm 12.3 ($3xCH_3$) 18.3 ($6xCH_3$) 28.5 (3xCH) 33.7 (C) 36.4 (CH_2) 36.8 (CH_2) 44.8 (CH_2) 56.0 (CH) 62.7 (CH_2) 63.9 (CH_2) 87.0 (C) 114.6 (CH_2) 117.1 (CH_2) 132.5 (CH) 135.2 (CH) 137.0 (CH) 147.2 (C).

HRMS (EI) *m/z* calcd for $C_{23}H_{43}O_2Si$ [M^+-allyl] 379.3032, found 379.3033.



(3.40) (E)-1-(tert-butyl)-4-(prop-1-en-1-yl)-2-vinylcyclopenta-1,3-diene

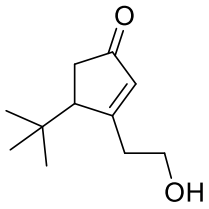
Tertiary alcohol **3.38** (100 mg, 0.263 mL) was charged to a microwave flask and a carboflon was added. Toluene (4mL) was added and KH (35 mg, 0.263mmol, 30% w/w) slurry was added dropwise to the side of the reaction vessel. The reaction was then heated at 120˚C for 1h after which all starting material was consumed and afforded dandralene **3.40** (23 mg, 0.122 mmol, 47%) instead of the desired oxy-cope product.

IR (neat, cm^{-1}) ν_{max}: 2927, 2364, 1118, 833.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.26 (s, 9 H) 1.78 (dd, *J*=6.9, 1.6 Hz, 3 H) 3.22 (s, 2 H) 5.09 (dd, *J*=11.0, 1.6 Hz, 1 H) 5.29 (dd, *J*=17.4, 1.0 Hz, 1 H) 5.74 (dq, *J*=15.5, 6.7 Hz, 1 H) 6.25-6.30 (m, 1 H) 6.39 (s, 1 H) 6.95 (dd, *J*=17.2, 11.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 18.3 (CH_3) 31.4 (3xCH_3) 34.1 (C) 42.0 (CH_2) 113.2 (CH_2) 123.8 (CH) 127.3 (CH) 128.4 (CH) 131.4 (CH) 136.2 (C) 142.2 (C) 150.2 (C).

HRMS (EI) *m/z* calcd for $C_{14}H_{20}$ [M^+] 188.1565, no accurate mass found.



(3.28) 4-(tert-butyl)-3-(2-hydroxyethyl)cyclopent-2-en-1-one

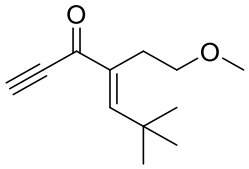
To neat TIPS protected alcohol **3.27** (1.03 g, 3.04 mmol) was added a solution of TBAF (6.08 mL 6.08 mmol, 1 M in THF) in a 25mL flamed dried r.b.f. and stirred 1 hour before the TLC showed that all the starting material was consumed. At that point ether was added and the solution was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (20-50% EtOAc:hexanes) to give alcohol **3.28** (0.499 g, 2.74 mmol, 90%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 3346, 2956, 2339, 1683, 1600, 1558, 1043.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.96 (s, 9 H) 1.89 (s, 1 H) 2.27 (dd, *J*=18.7, 2.1 Hz, 1 H) 2.42 (dd, *J*=18.6, 6.47 Hz, 1 H) 2.64 (dt, *J*=16.8, 6.5 Hz, 1 H) 2.74 (d, *J*=6.5 Hz, 1 H) 2.83 (dt, *J*=16.7, 6.9 Hz, 1 H) 3.89 (t, *J*=6.6 Hz, 2 H) 6.07 (d, *J*=1.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 28.3 (3xCH_3) 34.2 (C) 37.4 (CH_2) 40.1 (CH_2) 54.5 (CH) 60.5 (CH_2) 132.2 (CH) 181.0 (C) 208.8 (C).

HRMS (EI) *m/z* calcd for $C_{11}H_{18}O_2$ [M^+] 182.1307, found 182.1309.



(E)-4-(2-methoxyethyl)-6,6-dimethylhept-4-en-1-yn-3-one

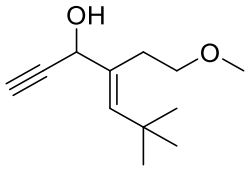
To a solution of TMS protected free alcohol ketone (1.43 g, 5.66 mmol) in THF (20.0 mL) was added NaH (0.294 g, 7.36 mmol, 60% w/w). Once the bubbling stopped dimethyl sulfate (0.812 mL, 8.50 mmol) was added and heated at 60˚C o/n. The reaction was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residues residue was purified by flash chromatography (5-15% EtOAc:hexanes) to give methyl ether (0.165 g, 0.849 mmol, 15 %) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2358, 1747, 1683, 1652, 746.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.24 (s, 9 H) 2.75 (t, *J*=7.4 Hz, 2 H) 3.22 (s, 1 H) 3.31 (s, 3 H) 3.33-3.36 (m, 2 H) 7.28 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 25.7 (CH_2) 30.3 (3xCH_3) 34.6 (C) 58.6 (CH_3) 71.1 (CH_2) 79.7 (C) 79.7 (CH) 137.1 (C) 162.8 (CH) 180.7 (C).

HRMS (EI) *m/z* calcd for $C_{11}H_{15}O$ [M^+-OMe] 163.1123, found: 163.1134.



(E)-4-(2-methoxyethyl)-6,6-dimethylhept-4-en-1-yn-3-ol

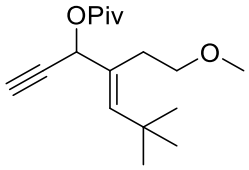
To a suspension of $CeCl_3$ heptahydrate (0.475 g, 1.27 mmol) in MeOH (10.0 mL) cooled to 0˚C, was added in small portion $NaBH_4$ (0.193 g, 5.10 mmol). The solution bubbles violently, once normalized the mixture was allowed to warm to r.t. and the enone was immediately added and the reduction was done in less than 20 min by TLC. Once completed, a saturated solution of ammonium chloride was added to reaction mixture. The heterogeneous mixture was poured into an extraction funnel and extracted with ether. The combined organic layers where dried over magnesium sulfate, filtered and concentrated under reduce pressure. The crude residue was purified by flash chromatography (30-40% EtOAc:hexanes) to give alcohol (0.120 g, 0.610 mmol, 72 %) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2956, 2358, 1683, 1652, 1558, 1099.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.11 (s, 9 H) 2.51 (d, *J*=2.2 Hz, 1 H) 2.63-2.76 (m, 2 H) 3.38 (s, 3 H) 3.47 (td, *J*=8.9, 4.2 Hz, 1 H) 3.61 (ddd, *J*=9.2, 4.9, 4.7 Hz, 1 H) 4.53 (d, *J*=8.0 Hz, 1 H) 4.62 (dd, *J*=8.0, 2.0 Hz, 1 H) 5.66 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 27.5 (CH_2) 31.0 (3xCH_3) 32.9 (C) 58.6 (CH_3) 69.6 (CH) 73.0 (CH_2) 73.7 (CH) 84.5 (C) 134.7 (CH) 142.5 (C).

HRMS (EI) *m/z* calcd for $C_{12}H_{19}O_2$ [M^+-H] 195.1385, found: 195.1380.



(E)-4-(2-methoxyethyl)-6,6-dimethylhept-4-en-1-yn-3-yl pivalate

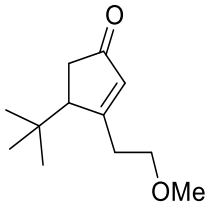
To a solution of the alcohol (0.120 g, 0.609 mmol) in DCM (10 mL), Et_3N (0.255 mL, 1.826 mmol), DMAP (7.44 mg, 0.061 mmol), and PivCl (0.094 mL, 0.761 mmol) were added in order. The reaction was followed by TLC and all starting material disappeared after 3 hours. The reaction was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (20-30% EtOAc:hexanes) to give pivalate alcohol (0.161 g, 0.574 mmol, 94 %) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2958, 2358, 1733, 1558, 1139, 1112.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.13 (s, 9 H) 1.21 (s, 9 H) 2.50 (d, *J*=2.2 Hz, 1 H) 2.58 (ddd, *J*=13.4, 9.7, 5.9 Hz, 1 H) 2.67 (ddd, *J*=13.7, 9.8, 5.9 Hz, 1 H) 3.34 (s, 3 H) 3.45-3.56 (m, 2 H) 5.73 (dd, *J*=2.3, 0.9 Hz, 1 H) 5.79 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 27.0 (3xCH_3) 28.5 (CH_2) 30.9 (3xCH_3) 32.9 (C) 38.7 (C) 58.6 (CH_3) 69.0 (CH) 71.9 (CH_2) 74.7 (CH) 80.3 (C) 129.7 (C) 143.4 (CH) 176.9 (C).

HRMS (EI) *m/z* calcd for $C_{17}H_{28}O_3$ [M^+] 280.2038, found: 280.2060.



(3.31) 4-(tert-butyl)-3-(2-methoxyethyl)cyclopent-2-en-1-one

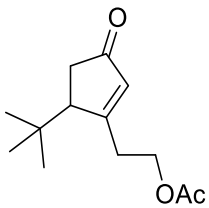
Pivalate (0.161 g, 0.574 mmol) was dissolved in acetone (6 mL) at r.t. and goldMeXPhos (0.027 g, 0.029 mmol, 5% loading) was added in one portion. The reaction was allowed to stir o/n. The crude was concentrated and flashed over silica (5-10% EtOAC:hexanes) to give enone **3.31** (0.067 g, 0.343 mmol, 60 %).

IR (neat, cm^{-1}) ν_{max}: 2900, 2362, 1701, 1604.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.97 (s, 9 H) 2.27 (dd, *J*=18.6, 2.2 Hz, 1 H) 2.42 (dd, *J*=18.6, 6.5 Hz, 1 H) 2.61 (dt, *J*=17.1, 6.3 Hz, 1 H) 2.72-2.73 (m, 1 H) 2.83 (ddd, *J*=17.2, 6.9, 6.5 Hz, 1 H) 3.35 (s, 3 H) 3.55-3.64 (m, 2 H) 6.05 (q, *J*=1.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 28.4 ($3xCH_3$) 30.9 (C) 34.7 (CH_2) 40.1 (CH_2) 54.6 (CH) 58.8 (CH_3) 70.4 (CH_2) 132.0 (CH) 180.9 (C) 208.8 (C).

HRMS (EI) *m/z* calcd for $C_{12}H_{20}O_2$ [M^+] 196.1463, found 196.1468.



(3.29) 2-(5-(tert-butyl)-3-oxocyclopent-1-en-1-yl)ethyl acetate

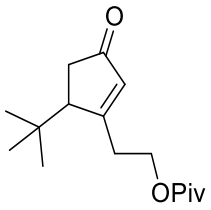
To a solution of alcohol **3.28** (0.100 g, 0.549 mmol) in DCM (4.00 mL), Et_3N (0.229 mL, 1.646 mmol), DMAP (6.70 mg, 0.055 mmol), and acetyl chloride (0.049 mL, 0.686 mmol) were added in order. The reaction was followed by TLC and all starting material disappeared after 3 hours. The reaction was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (20-30% EtOAc:hexanes) to give acetylated alcohol **3.29** (0.118 g, 0.527 mmol, 96%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2954, 2354, 1733, 1690, 1604, 1558, 1226, 1041.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.96 (s, 9 H) 2.03 (s, 3 H) 2.27 (dd, *J*=18.6, 1.6 Hz, 1 H) 2.42 (dd, *J*=18.6, 6.7 Hz,1 H) 2.63-2.70 (m, 1 H) 2.72-2.74 (m, 1 H) 2.89 (dt, *J*=16.6, 7.0 Hz, 1 H) 4.23-4.33 (m, 2 H) 6.03 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 20.8 (CH_3) 28.3 (3xCH_3) 33.4 (CH_2) 34.1 (C) 40.1 (CH_2) 54.3 (CH) 61.7 (CH_2) 132.4 (CH) 170.8 (C) 179.3 (C) 208.3 (C).

HRMS (EI) *m/z* calcd for $C_{13}H_{20}O_3$ [M^+] 224.1412, found 224.1442.



(3.30) 2-(5-(tert-butyl)-3-oxocyclopent-1-en-1-yl)ethyl pivalate

To a solution of alcohol **3.28** (0.200 g, 0.549 mmol) in DCM (8.00 mL), Et_3N (0.459 mL, 3.29 mmol), DMAP (13 mg, 0.11 mmol), and PivCl (0.169 mL, 1.372 mmol) were added in order. The reaction was followed by TLC and all starting material disappeared after 3 hours. The reaction was

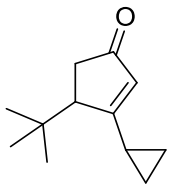
quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residues residue was purified by flash chromatography (20-30% EtOAc:hexanes) to give pivalate alcohol **3.30** (0.285 g, 1.07 mmol, 97%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2956, 2360, 1726, 1695, 1604, 1149.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.97 (s, 9 H) 1.16 (s, 9 H) 2.28 (dd, *J*=18.6, 2.2 Hz, 1 H) 2.42 (dd, *J*=18.1, 6.7 Hz, 1 H) 2.67 (dt, *J*=17.1, 5.9 Hz, 1 H) 2.74-2.75 (m, 1 H) 2.91 (dt, *J*=17.0, 7.1 Hz, 1 H) 4.29 (dd, *J*=6.9, 6.1 Hz, 2 H) 6.05 (q, *J*=1.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 27.1 ($3xCH_3$) 28.3 ($3xCH_3$) 33.5 (CH_2) 34.2 (C) 38.7 (C) 40.2 (CH_2) 54.2 (CH) 61.6 (CH_2) 132.6 (CH) 178.3 (C) 179.6 (C) 208.4 (C).

HRMS (EI) *m/z* calcd for $C_{16}H_{26}O_3$ [M^+] 266.1882, found 266.1885.



(3.50) 4-(tert-butyl)-3-cyclopropylcyclopent-2-en-1-one

To a solution of enone **3.27** (0.100 g, 0.295 mmol) in DMSO (1.00 mL) was added all at once dimethylmethanesulfinic iodide (0.066 g, 0.298 mmol) and potassium *t*-butoxide (0.033 g, 0.295 mmol) in a small r.b.f. at r.t. The solution was stirred at r.t. for 30 min before heating it to 55˚C for 3h. The mixture was cooled to r.t. and water was added and extracted with Et_2O 3x. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was

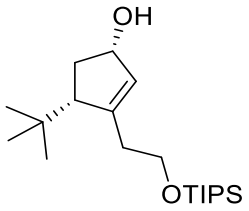
purified by flash chromatography (15% EtOAc:hexanes) to give cyclopropyl **3.51** (0.036 g, 0.102 mmol, 35%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2931, 1683, 1271.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.72-0.77 (m, 1 H) 0.82-0.89 (m, 1 H) 1.01 (s, 9 H) 1.09-1.21 (m, 1 H) 1.54-1.60 (m, 2 H) 2.27 (dd, *J*=1.6, 18.4 Hz, 1 H) 2.43 (dd, *J*=6.7, 18.4 Hz, 1 H) 2.86 (d, *J*=6.7 Hz, 1 H) 5.57 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 13.3 (CH_2) 14.4 (CH_2) 15.2 (CH) 28.3 (3xCH_3) 34.6 (C) 40.5 (CH_2) 55.4 (CH) 124.5 (CH) 188.8 (C) 208.5 (C).

HRMS (EI) *m/z* calcd for $C_{12}H_{18}O$ [M^+-*t*-Bu] 121.0653, found: 121.0685.



(3.43) 4-(tert-butyl)-3-(2-((triisopropylsilyl)oxy)ethyl)cyclopent-2-en-1-ol

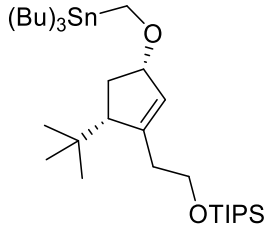
To a cooled solution of enone **3.27** (0.200 g, 0.591 mmol) in THF (3.00 mL) at -10˚C, L-selectride (0.709 mL, 0.709mmol, 1 M in THF) was added dropwise. After 1 hour no more starting material was visible by TLC so the reaction was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (30-50% EtOAc:hexanes) to give alcohol **3.43** (0.163 g, 0.479 mmol, 81%) as a clear oil and sole diastereomere.

IR (neat, cm^{-1}) ν_{max}: 3313, 2941, 2866, 2354, 1099, 881.

^{1}H NMR (400 MHz, C_6D_6) δ ppm 0.90 (s, 9 H) 1.10-1.13 (m, 21 H) 1.23-1.25 (m, 1 H) 1.40-1.45 (m, 1 H) 2.13-2.21 (m, 2 H) 2.34-2.42 (m, 1 H) 2.53-2.61 (m, 1 H) 3.82 (t, *J*=7.3 Hz, 2 H) 4.49-4.51 (m, 1 H) 5.53 (s, 1 H).

^{13}C NMR (100 MHz, C_6D_6) δ ppm 12.3 (3x CH) 18.2 (6xCH_3) 28.6 (3xCH_3) 33.1 (C) 36.2 (CH_2) 37.7 (CH_2) 56.6 (CH) 62.8 (CH_2) 74.5 (CH) 131.8 (CH) 146.8 (C).

HRMS (EI) *m/z* calcd for $C_{17}H_{33}O_2Si$ [M^+- *i*-Pr] 297.2250, found 297.2262.



(3.47) (2-(5-(tert-butyl)-3-((tributylstannyl)methoxy)cyclopent-1-en-1-yl)ethoxy)triisopropylsilane

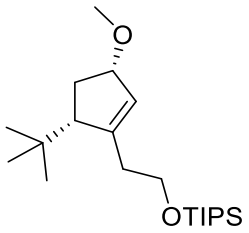
To a slurry of unwashed KH (40 mg, 0.299 mmol, 30% w/w) in THF (2 mL), was added alcohol **3.43** (60 mg, 0.176 mmol) in THF (1mL). The resulting mixture was stirred at r.t. for 1 hour before adding tributyl(iodomethyl)stannane (0.114 g, 0.264 mmol). The resulting solution was stirred at r.t. o/n and quenched with a saturated solution of $NaHCO_3$. The aqueous phase was extracted 3x with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (5-10% EtOAc:hexanes) to give stannyl ether **3.47** (0.163 g, 0.479 mmol, 81%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2954, 2867, 2362, 1652, 1456.

^{1}H NMR (400 MHz, C_6D_6) δ ppm 0.95-0.99 (m, 18 H) 1.01-1.05 (m, 6 H) 1.09-1.14 (m, 21 H) 1.35-1.45 (m, 6 H) 1.61-1.69 (m, 6 H) 1.73-1.79 (m, 1 H) 2.20-2.31 (m, 2 H) 2.40-2.47 (m, 1 H) 2.59-2.67 (m, 1 H) 3.80-3.89 (m, 4 H) 4.20-4.22 (m, 1 H) 5.89 (s, 1 H).

^{13}C NMR (100 MHz, C_6D_6) δ ppm 9.3 (3xCH_2) 12.3 (3xCH) 14.0 (3xCH_3) 18.3 (6xCH_3) 27.7 (3xCH_2) 28.7 (3xCH_3) 29.6 (3xCH_2) 33.4 (C) 34.0 (CH_2) 36.5 (CH_2) 56.6 (CH) 59.0 (CH_2) 62.8 (CH_2) 86.7 (CH) 129.0 (CH) 147.5 (C).

HRMS (EI) *m/z* calcd for $C_{33}H_{68}O_2SiSn$ [M^+] 644.4011, found 644.4017.



(3.49) (2-(5-(tert-butyl)-3-methoxycyclopent-1-en-1-yl)ethoxy)triisopropylsilane

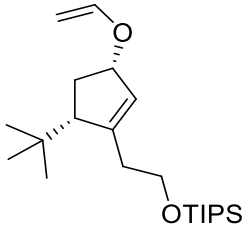
To a cooled solution of stannyl ether **3.47** (47 mg, 0.073 mmol) in THF (1.00 mL) at -78˚C was added n-BuLi solution (0.032 mL, 0.08 mmol, 2.5 M in hexanes). The solution was stirred at -78˚C for 30 min and after 1h at r.t. No more sign of the starting material was observable so the reaction was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (10% EtOAc:hexanes) to give methyl allyl ether **3.49** (0.022 g, 0.056 mmol, 77%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2954, 2864, 1463, 1093, 881.

^{1}H NMR (400 MHz, C_6D_6) δ ppm 0.95 (s, 9 H) 1.09-1.13 (m, 21 H) 1.68 (ddd, *J*=13.5, 5.7, 4.5 Hz, 1 H) 2.14 (dt, *J*=13.5, 8.0 Hz, 1 H) 2.24-2.27 (m, 1 H) 2.39-2.46 (m, 1 H) 2.58-2.66 (m, 1 H) 3.19 (s, 3 H) 3.85 (t, *J*=7.2 Hz, 2 H) 4.12-4.15 (m, 1 H) 5.79 (s, 1 H).

^{13}C NMR (100 MHz, C_6D_6) δ ppm 12.3 (3xCH) 18.2 (6xCH_3) 28.6 (3xCH_3) 33.4 (C) 34.0 (CH_2) 36.4 (CH_2) 55.9 (CH_3) 56.3 (CH) 62.8 (CH_2) 83.6 (CH) 128.9 (CH) 147.5 (C).

HRMS (EI) *m/z* calcd for $C_{18}H_{35}O_2Si$ [M^+ - *i*-Pr] 311.2406, found: 311.2401.



(3.44) (2-(5-(tert-butyl)-3-(vinyloxy)cyclopent-1-en-1-yl)ethoxy)triisopropylsilane

$Hg(OAc)_2$ (0.100 g, 0.294 mmol) was added to a solution of allylic alcohol **3.43** (0.094 g, 0.294 mmol) in ethyl vinyl ether (4.00 mL) in a sealed tube at r.t. The reaction was allowed to stir o/n after which it was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (5% EtOAc:hexanes) to give vinyl allyl ether **3.44** (77 mg, 0.211 mmol, 72%) as a clear oil.

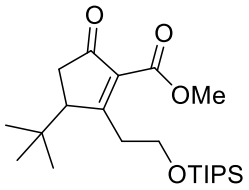
IR (neat, cm^{-1}) ν_{max}: 2954, 2866, 2358, 1099.

^{1}H NMR (400 MHz, C_6D_6) δ ppm 0.91 (s, 9 H) 1.08-1.12 (m, 21 H) 1.71-1.76 (m, 1 H) 2.12 (dt, *J*=14.0, 8.2 Hz, 1 H) 2.20-2.23 (m, 1 H) 2.33-2.41 (m, 1 H) 2.52-2.60 (m, 1 H) 3.80 (t, *J*=7.1 Hz,

2 H) 4.03 (dd, *J*=6.9, 1.6 Hz, 1 H) 4.33 (dd, *J*=14.4, 1.5 Hz, 1 H) 4.65-4.67 (m, 1 H) 5.70-5.72 (m, 1 H) 6.42 (dd, *J*=14.3, 6.9 Hz, 1 H).

^{13}C NMR (100 MHz, C_6D_6) δ ppm 12.3 (3xCH) 18.2 (6xCH_3) 28.5 (3xCH_3) 33.4 (C) 34.1 (CH_2) 36.3 (CH_2) 56.6 (CH) 62.6 (CH_2) 80.9 (CH) 87.4 (CH_2) 127.6 (CH) 149.1 (C) 151.2 (CH).

HRMS (EI) *m/z* calcd for $C_{20}H_{39}OSi$ [M^+ - venyl alcoxide] 323.2770, found: 323.2754.



(3.57) Methyl 3-(tert-butyl)-5-oxo-2-(2-((triisopropylsilyl)oxy)ethyl)cyclopent-1-ene-1-carboxylate

LiHMDS (0.027 g, 0.161 mmol) was charged to r.b.f. and dissolved in THF (1.00 mL) and cooled to -78˚C. To the resulting solution, cyclic ketone **3.54** (50 mg, 0.147 mmol) was added and stirred at -40˚C for 1h. The solution was then cooled again to -78˚C and methyl cyanoformate (0.014 mL, 0.176 mmol) was added and kept at the same temperature. After 10 min the solution was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was submitted to the next reaction without further purification.

To a solution of DCM (2.00 mL) with PhSeCl (31 mg, 0.160 mmol) and pyridine (0.018 mL, 0.218 mmol) was added the crude from last reaction at 0˚C. After stirring for 1.5h, 1N HCL was added to quench the reaction and the resulting organic phase was washed with $NaHCO_3$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated.

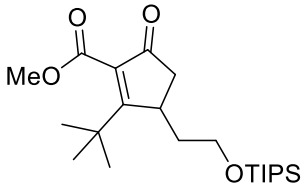
The crude product was then dissolved in DCM (5mL) once more and 30% H_2O_2 (0.045 mL, 0.436 mmol, 30% in water) was added over 30 min at 0˚C. After stirring the reaction for 2h, water was added and a saturated solution of $NaHCO_3$. The organic extracts were combined and washed with a saturated solution of $Na_2S_2O_3$. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (10-25% EtOAc:hexanes) to give ketoester as a mixture of 2 separable isomers in a 1:1 ratio. Isomer 1 **3.57** (15 mg, 0.038 mmol, 26%) (ester installed on opposite side of *t*-Bu) and isomer 2 **3.58** (14 mg, 0.035mmol) (ester installed on same side of *t*-Bu) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2942, 1715, 1103, 819.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.98 (s, 9 H) 1.01-1.04 (m, 21 H) 2.42-2.45 (m, 2 H) 2.78-2.84 (m, 1 H) 2.93 (dd, *J*=6.1, 2.2 Hz, 1 H) 3.37-3.43 (m, 1 H) 3.81 (s, 3 H) 3.83-3.89 (m, 1 H) 3.94-3.99 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 11.8 (3xCH) 17.9 (6xCH_3) 28.6 (3xCH_3) 35.6 (C) 36.3 (CH_2) 41.3 (CH_2) 51.9 (CH) 53.3 (CH_3) 63.0 (CH_2) 134.6 (C) 163.9 (C) 188.8 (C) 203.0 (C).

HRMS (EI) *m/z* calcd for $C_{19}H_{33}O_4Si$ [M^+-*i*-Pr] 353.2148, found: 353.2104.



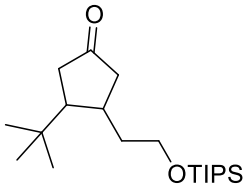
(3.58) Methyl 2-(tert-butyl)-5-oxo-3-(2-((triisopropylsilyl)oxy)ethyl)cyclopent-1-ene-1-carboxylate

IR (neat, cm^{-1}) ν_{max}: 2937, 1749, 1702, 1236, 1103.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.01-1.07 (m, 21 H) 1.28 (s, 9 H) 2.25 (dd, *J*=18.4, 1.0 Hz, 1 H) 2.28-2.35 (m, 1 H) 2.58 (ddd, *J*=18.5, 6.6, 0.8 Hz, 1 H) 3.26-3.31 (m, 1 H) 3.67 (dd, *J*=10.1, 4.2 Hz, 1 H) 3.72 (dd, *J*=10.8, 4.9 Hz, 1 H) 3.81 (s, 3 H) 3.81-3.87 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 11.9 (3xCH) 18.0 (6xCH_3) 29.3 (3xCH_3) 36.2 (C) 38.6 (CH_2) 38.7 (CH) 41.8 (CH_2) 52.3 (CH_3) 61.7 (CH_2) 135.1 (C) 166.9 (C) 188.7 (C) 204.2 (C).

HRMS (EI) *m/z* calcd for $C_{19}H_{33}O_4Si$ [M^+-*i*-Pr] 353.2148, found: 353.21665.



(3.54) 3-(tert-butyl)-4-(2-((triisopropylsilyl)oxy)ethyl)cyclopentan-1-one

To a solution of enone **3.27** (0.100 mg, 0.295 mmol) in EtOH, adam's catalyst (8 mg, 0.03 mmol) was added in one portion and H_2 was bubbled slowly though the stirred solution. After the balloon (party balloon size) was emptied of H_2 the reaction didn't show any starting material left. The reaction was filtered over a celite pad and concentrated. Thereafter the crude was purified by flash chromatography (5-10% EtOAc:hexanes) to give ketone **3.54** (32 mg, 0.094 mmol, 32%) as a clear oil.

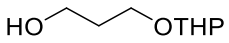
IR (neat, cm^{-1}) ν_{max}: 2916, 1733, 1099, 659.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.89 (s, 9 H) 0.99-1.09 (m, 21 H) 1.41-1.49 (m, 1 H) 1.78-1.89 (m, 2 H) 1.94-2.00 (m, 1 H) 2.09-2.17 (m, 1 H) 2.22-2.49 (m, 3 H) 3.62-3.68 (m, 1 H) 3.70-3.75 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 11.9 (3xCH) 18.0 (6xCH_3) 27.7 (3xCH_3) 33.3 (CH) 33.3 (C) 40.2 (CH_2) 40.8 (CH_2) 44.7 (CH_2) 51.6 (CH) 61.5 (CH_2) C_{quad} of carbonyl out of spectra (estimated to be at ~220ppm).

HRMS (EI) *m/z* calcd for $C_{17}H_{33}O_2Si$ [M^+-*i*-Pr] 297.2250, found: 297.2240.

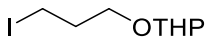
5.2.2 Route B: synthesis intermediates



3-((tetrahydro-2H-pyran-2-yl)oxy)propan-1-ol

To a solution of 1,3-propanediol (2.00 mL, 27.9 mmol) and TsOH (0.053 g, 0.279 mmol) in DCM (38.0 mL), was added dropwise with a syringe pump, a solution of DHP (2.67 mL, 29.3 mmol) in DCM (13.0 mL). After the addition was completed the reaction was stirred for 2 hours at r.t. and then poured in an extraction funnel with water. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residues residue was purified by flash chromatography (15-25% EtOAc:hexanes) to give mono-protected alcohol (2.24 g, 14.0 mmol, 50 %) as a clear oil.

Spectral data was identical to the one found in the literature[153].

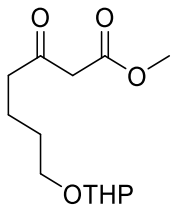


2-(3-iodopropoxy)tetrahydro-2H-pyran

To a solution of mono protected alcohol (1.00 g, 6.24 mmol) in a 1:2 mixture of benzene:ether (18mL : 35mL), was added PPh3 (1.97 g, 7.49 mmol), followed by imidazole (0.510 g, 7.49

mmol). The solution was stirred until complete dissolution of all reagents and then iodide (1.90 g, 7.49 mmol) was added at r.t. The resulting slurry was stirred in the dark for 1 hour before being diluted in ether (150 mL) and washed with a saturated solution of $Na_2S_2O_3$. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (5% EtOAc:hexanes) to give iodo chain (1.32 g, 4.89 mmol, 78 %) as a clear oil.

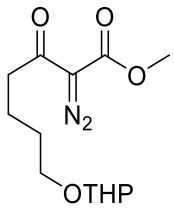
Spectral data was identical to the one found in the literature[153].



(3.67) methyl 3-oxo-7-((tetrahydro-2H-pyran-2-yl)oxy)heptanoate

To a slurry of NaH (0.428 g, 10.70 mmol, 60% w/w) at 0˚C in THF (50.0 mL), was added dropwise methyl acetoacetate **3.66** (1.05 mL, 9.73 mmol). After the addition was completed the reaction was allowed to warm back to r.t. for 30 min and then cooled again to 0˚C. n-BuLi (4.09 mL, 10.2 mmol, 2.5 M in hexanes) was added and the solution was stirred 1 h at 0˚C before 2-(3-iodopropoxy)tetrahydro-2H-pyran (2.83 g, 10.5 mmol) was added. The solution was stirred 3 hours and quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (20% EtOAc:hexanes) to give diketone **3.67** (1.33 g, 5.15 mmol, 53%) as a clear oil.

Spectral data was identical to the one found in the literature[139].



(3.68) Methyl 2-diazo-3-oxo-7-((tetrahydro-2H-pyran-2-yl)oxy)heptanoate

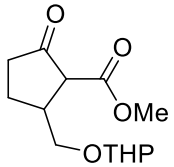
To a solution of ketone ester **3.67** (1.33 g, 5.15 mmol) and TsN_3 (0.833 g, 5.41 mmol) in acetonitrile (13.0 mL), was added Et_3N (1.435 mL, 10.30 mmol) and stirred o/n at r.t. The reaction mixture was then diluted in 1N NaOH and extracted with EtOAc 3x. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (20% EtOAc:hexanes) to give diazo adduct **3.68** (0.8370 g, 2.94 mmol, 57%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2929, 2129, 1726, 1655, 1306, 750.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.45-1.55 (m, 4 H) 1.56-1.70 (m, 5 H) 1.72-1.80 (m, 1 H) 2.83 (t, *J*=7.3 Hz, 2 H) 3.35 (dt, *J*=9.7, 6.2 Hz, 1 H) 3.41-3.47 (m, 1 H) 3.70 (dt, *J*=9.7, 6.3 Hz, 1 H) 3.78 (s, 3 H) 3.78-3.83 (m, 1H) 4.52 (t, *J*=3.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 19.5 (CH_2) 21.0 (CH_2) 25.4 (CH_2) 29.1 (CH_2) 30.6 (CH_2) 39.8 (CH_2) 52.0 (CH_3) 62.1 (CH_2) 67.0 (CH_2) 75.6 (C) 98.7 (CH) 161.7 (C) 192.5 (C).

HRMS (EI) *m/z* calcd for $C_8H_{11}N_2O_4$ [M^+- THP] 199.0719, found: 199.0728.



(3.69) Methyl 2-oxo-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)cyclopentane-1-carboxylate

$Rh_2(OAc)_4$ (0.20 g, 0.448 mmol, 5% loading) was suspended in dry DCM (45 mL). A solution of diazo adduct **3.68** (2.55g, 8.97 mmol) in DCM (45 mL) was added dropwise to the rhodium suspension over 3 h to ensure slow formation of N_2. The reaction was then filtered over celite and the filtrate was concentrated and was purified by flash chromatography (20% EtOAc:hexanes) to give cyclopentanone **3.69** (1.96 g, 7.65 mmol, 85%) as a clear oil with 2 main diastereomere in a 1:0.62 ratio.

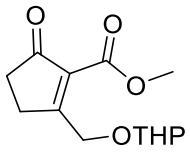
Major Diastereomer

IR (neat, cm^{-1}) ν_{max}: 2927, 1724, 1245, 1030.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.46-1.51 (m, 5 H) 1.63-1.76 (m, 2 H) 2.09-2.19 (m, 1 H) 2.27-2.49 (m, 2 H) 2.83-2.91 (m, 1 H) 3.10 (d, *J*=10.4 Hz, 1 H) 3.43-3.50 (m, 2 H) 3.69-3.71 (m, 2 Hz, 4 H) 3.73-3.76 (m, 1 H) 4.56 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 18.9 (CH_2) 23.8 (CH_2) 25.3 (CH_2) 30.2 (CH_2) 38.1 (CH_2) 41.1 (CH) 52.3 (CH_3) 58.6 (CH) 61.8 (CH_2) 68.7 (CH_2) 98.3 (CH) 169.5 (C) 211.4 (C).

HRMS (EI) *m/z* calcd for $C_{13}H_{20}O_5$ [M^+-THP] 171.0657, found: 171.0652.



(3.73) Methyl 5-oxo-2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)cyclopent-1-ene-1-carboxylate

To a solution of DCM (45 mL) with PhSeCl (1.94 g, 10.2 mmol) and pyridine (1.12 mL, 13.9 mmol) was added ketoester **3.69** (2.37 g, 9.25 mmol) at 0˚C. After stirring for 1.5h, 1 N HCL was added to quench the reaction and the resulting organic phase was washed with $NaHCO_3$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated.

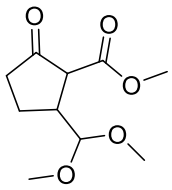
The crude product was then dissolved in DCM (45.0 mL) once more and 30% H_2O_2 (2.83 mL, 27.7 mmol, 30% in water) was added over 30 min at 0˚C. After stirring the reaction for 2h, water was added and a saturated solution of $NaHCO_3$. The aqueous phase was extracted 3x with EtOAc. The organic extracts were combined and washed with a saturated solution of $Na_2S_2O_3$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (10-25% EtOAc:hexanes) to give ketoester **3.73** (1.00 g, 3.93 mmol, 43%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2975, 1728, 1233, 1024.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.53-1.63 (m, 5 H) 1.70-1.83 (m, 3 H) 2.49 (t, *J*=4.9 Hz, 1 H) 2.87 (d, *J*=5.1 Hz, 1 H) 3.50-3.56 (m, 1 H) 3.80-3.85 (m, 1 H) 3.82 (m, 3 H) 4.64-4.66 (m, 1 H) 4.75 (d, *J*=18.2 Hz, 1 H) 4.97 (d, *J*=18.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 19.3 (CH_2) 25.2 (CH_2) 27.9 (CH_2) 30.3 (CH_2) 34.8 (CH_2) 51.9 (CH_3) 62.5 (CH_2) 66.3 (CH_2) 99.0 (CH) 130.5 (C) 163.2 (C) 186.8 (C) 203.1 (C).

HRMS (EI) *m/z* calcd for $C_{13}H_{18}O_5$ [M^+-THP] 153.0552, found: 153.0564.



(3.77) Methyl 2-(dimethoxymethyl)-5-oxocyclopentane-1-carboxylate

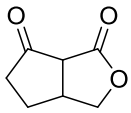
To a solution of ketoester **3.73** (0.237 g, 0.930 mmol) in MeOH (5.00 mL) was added p-TsOH monohydrate (8.85 mg, 0.047 mmol) and the solution was heated to 65˚C for 4h before it was cooled to r.t. The reaction was then concentrated and directly purified by flash chromatography (20 % EtOAc:hexanes) to give dimethoxy acetal **3.77** (0.156 g, 0.721 mmol, 78%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 1751, 1450, 1273, 1116, 1053.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.68-1.78 (m, 1 H) 2.09-2.17 (m, 1 H) 2.30 (ddd, *J*=19.1, 10.5, 9.0 Hz, 1 H) 2.42 (ddd, *J*=19.0, 9.0, 2.8 Hz, 1 H) 2.99 (tt, *J*=10.1, 6.3 Hz, 1 H) 3.12 (d, *J*=10.0 Hz, 1 H) 3.35 (s, 3 H) 3.36 (s, 3 H) 3.73 (s, 3 H) 4.26 (d, *J*=5.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 22.1 (CH_2) 37.9 (CH_2) 43.5 (CH) 52.5 (CH_3) 54.3 (CH_3) 55.0 (CH_3) 57.1 (CH) 106.6 (CH) 169.5 (C) 211.1 (C).

HRMS (EI) *m/z* calcd for $C_{10}H_{16}O_5$ [M^+] 216.0998, found: 216.1004.

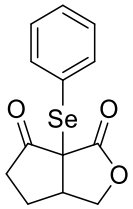


(3.71) Tetrahydro-1H-cyclopenta[c]furan-1,6(3H)-dione

To a solution of THP protected alcohol **3.69** (0.25 g, 0.975 mmol) in MeOH (6 mL) was added *p*-TsOH monohydrate (9.28 mg, 0.049 mmol, 5% loading). The solution was then heated to reflux for 1 hour after which the solution was concentrated and purified by flash chromatography (20% EtOAc:hexanes) to give bicyclic system **3.71** (0.063 g, 0.450 mmol, 46%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.76-1.86 (m, 1 H) 2.26-2.37 (m, 3 H) 3.28 (d, *J*=8.8 Hz, 1 H) 3.31-3.38 (m, 1 H) 4.11 (dd, *J*=9.5, 3.4 Hz, 1 H) 4.47 (dd, *J*=9.5, 7.2 Hz, 1 H).

Spectral data was identical to the one found in the literature[138b].



6a-(phenylselanyl)tetrahydro-1H-cyclopenta[c]furan-1,6(3H)-dione

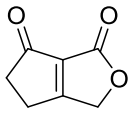
To a solution of DCM (6 mL) with PhSeCl (0.215 g, 1.12 mmol) and pyridine (0.124 mL, 1.53 mmol) was added cyclic ketoester **3.70** (0.143 g, 1.02 mmol) at 0˚C and then its allowed to warm to r.t. After stirring the reaction o/n, 1 N HCL was added to quench the reaction and the resulting organic phase was washed with $NaHCO_3$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (10-25% EtOAc:hexanes) to give selanyl (0.190 g, 0.644 mmol, 63%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2927, 1770, 1728, 1136, 740.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.68-1.78 (m, 1 H) 2.15-2.28 (m, 2 H) 2.36-2.45 (m, 1 H) 3.01-3.07 (m, 1 H) 3.97 (d, *J*=5.1 Hz, 2 H) 7.32 (t, *J*=7.4 Hz, 2 H) 7.42 (tt, *J*=6.5, 1.0 Hz 1 H) 7.65 (dd, *J*=8.0, 1.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 24.8 (CH_2) 36.9 (CH_2) 45.6 (CH) 57.2 (C) 70.5 (CH_2) 124.6 (C) 129.5 (2xCH) 130.3 (CH) 137.5 (2xCH) 170.8 (C) 206.0 (C).

HRMS (EI) *m/z* calcd for $C_{13}H_{12}O_3Se$ [M^+] 295.9952, found: 295.9931.



(3.71) 4,5-dihydro-1H-cyclopenta[c]furan-1,6(3H)-dione

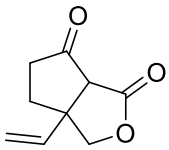
The selenide adduct (1.80 g, 6.10 mmol) was then dissolved in DCM (30.0 mL) and 30% H_2O_2 (2.83 mL, 27.7 mmol, 30% in water) was added over 30 min at 0˚C. After stirring the reaction for 2h[9], water was added and a saturated solution of $NaHCO_3$. The aqueous phase was extracted 3x with EtOAc. The organic extracts were combined and washed with a saturated solution of $Na_2S_2O_3$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (50-90% EtOAc:hexanes) to give ketoester **3.71** (0.85 g, 6.15 mmol, 100 %) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 1765, 1707, 962, 753.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.96-2.98 (m, 2 H) 2.99-3.02 (m, 2 H) 5.08 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 24.6 (CH_2) 41.6 (CH_2) 70.0 (CH_2) 135.5 (C) 164.0 (C) 195.5 (C) 202.3 (C).

HRMS (EI) *m/z* calcd for $C_7H_6O_3$ [M^+] 138.0317, found: 138.0336.



(3.72) 3a-vinyltetrahydro-1H-cyclopenta[c]furan-1,6(3H)-dione

[9] After 1h of stirring a white precipitate forms and then disappear after 1h and 30 min.

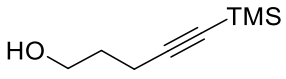
A solution of vinylmagnesium bromide (1.09 mL, 1.09 mmol, 1M in THF) was added to a mixture of 2-thienylcyano cuprate (4.34 mL, 1.09 mmol, 0.25 M in THF) in Et_2O (3 mL) at -78˚C. The mixture was stirred 1h at -78˚C before adding enone **3.71** (0.100 g, 0.724 mmol) and BF_3-Et_2O (0.183 mL, 1.45 mmol). The reaction was stirred 4 h at -40˚C and followed by TLC. Once all the starting material was consumed the reaction was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (40-60% EtOAc:hexanes) to give diketone **3.72** (0.065 g, 0.391 mmol, 54%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2356, 1773, 1726, 1147, 1014.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.08 (dt, *J*=13.5, 9.2 Hz, 1 H) 2.29-2.36 (m, 1 H) 2.46 (dd, *J*=9.1, 6.4 Hz, 2 H) 3.26 (d, *J*=1.6 Hz, 1 H) 4.25 (s, 2 H) 5.22 (d, *J*=17.4 Hz, 1 H) 5.30 (d, *J*=10.8 Hz, 1 H) 5.97 (dd, *J*=17.4, 10.8 Hz, 1 H).

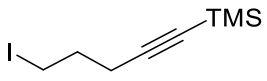
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 30.3 (CH_2) 37.4 (CH_2) 51.6 (C) 59.1 (CH) 74.9 (CH_2) 116.1 (CH_2) 136.9 (CH) 169.1 (C) 205.7 (C).

HRMS (EI) *m/z* calcd for $C_9H_{10}O_3$ [M^+] 166.0630, found: 166.0624.



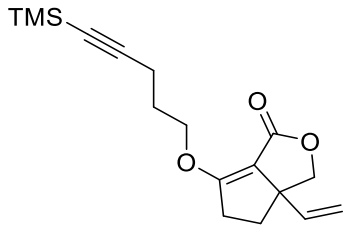
5-(trimethylsilyl)pent-4-yn-1-ol

Spectral data and procedure used to make the material was identical to the one found in the literature[154].



(5-iodopent-1-yn-1-yl)trimethylsilane

Spectral data and procedure used to make the material was identical to the one found in the literature[154].



(3.79) 6-((5-(trimethylsilyl)pent-4-yn-1-yl)oxy)-3a-vinyl-3,3a,4,5-tetrahydro-1H-cyclopenta[c]furan-1-one

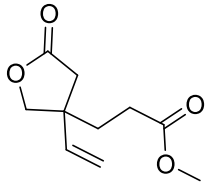
To a solution of ketoester **3.72** (0.02g, 0.120 mmol) in acetone (5mL) was added Cs_2CO_3 (0.118 g, 0.361 mmol) and (5-iodopent-1-yn-1-yl)trimethylsilane (0.042 g, 0.156 mmol) in a r.b.f. at r.t. The heterogeneous mixture was then heated to 50˚C o/n. The mixture was then filtered over a pad celite. The filtrate was then concentrated and purified by flash chromatography (10% EtOAc:hexanes) to give vinyl ether **3.79** (0.025 g, 0.086 mmol, 72%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2956, 1735, 1110, 845.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.12 (s, 9 H) 1.89-1.94 (m, 3 H) 2.01 (td, *J*=11.8, 8.4 Hz, 1 H) 2.34 (t, *J*=7.2 Hz, 2 H) 2.52 (dd, *J*=17.0, 8.3 Hz, 1 H) 2.95 (ddd, *J*=17.3, 11.0, 6.8 Hz, 1 H) 4.02 (d, *J*=8.4 Hz, 1 H) 4.21 (d, *J*=8.4 Hz, 1 H) 4.61 (t, *J*=6.1 Hz, 2 H) 5.15 (d, *J*=10.4 Hz, 1 H) 5.21 (d, *J*=17.2 Hz, 1 H) 5.96 (dd, *J*=17.1, 10.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 0.1 (3x CH_3) 16.3 (CH_2) 28.5 (CH_2) 33.8 (CH_2) 37.9 (CH_2) 58.1 (C) 73.7 (CH_2) 77.3 (CH_2) 85.2 (C) 101.6 (C) 105.9 (C) 113.6 (CH_2) 139.7 (CH) 164.4 (C) 165.4 (C).

HRMS (EI) *m/z* calcd for $C_{16}H_{21}O_3Si$ [M^+-Me] 289.1260, found: 289.1244.



(3.80) Methyl 3-(5-oxo-3-vinyltetrahydrofuran-3-yl)propanoate

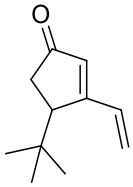
Sodium chunks (3.87 mg, 0.168 mmol) were added to MeOH (2.0 mL) and stirred until the metal was fully dissolved. Ketoester **3.72** (20 mg, 0.120 mmol) was then added and the reaction was allowed to stir o/n at r.t. before it was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (40% EtOAc:hexanes) to give retro-Dieckmann adduct **3.80** (20 mg, 0.101 mmol, 84%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 1778, 1728, 1436, 1170, 1012.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.90-1.95 (m, 2 H) 2.24-2.28 (m, 2 H) 2.40 (d, *J*=17.0 Hz, 1 H) 2.57 (d, *J*=17.1 Hz, 1 H) 3.65 (s, 3 H) 4.06 (d, *J*=9.0 Hz, 1 H) 4.18 (d, *J*=9.2 Hz, 1 H) 5.13 (d, *J*=17.6 Hz, 1 H) 5.25 (d, *J*=10.8 Hz, 1 H) 5.74 (dd, *J*=17.6, 10.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 29.5 (CH_2) 32.1 (CH_2) 38.5 (CH_2) 45.8 (C) 51.8 (CH_3) 75.9 (CH_2) 116.1 (CH_2) 138.8 (CH) 173.0 (C) 175.5 (C).

HRMS (EI) *m/z* calcd for $C_{10}H_{14}O_4$ [M^+] 198.0892, found: 198.0896.



(3.53) 4-(*tert*-butyl)-3-vinylcyclopent-2-en-1-one

To a solution of 2-(5-(*tert*-butyl)-3-oxocyclopent-1-en-1-yl)ethyl acetate (50 mg, 0.223 mmol) in THF (5mL) was added KO*t*-Bu (0.025 g, 0.223 mmol) and stirred o/n. The reaction was then quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (10% EtOAc:hexanes) to give elimination adduct **3.53** (21 mg, 0.021 mmol, 57%) as a clear oil.

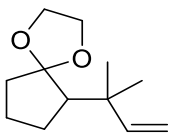
IR (neat, cm^{-1}) ν_{max}: 2954, 1689, 1228.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.92 (s, 9 H) 2.32-2.37 (m, 1 H) 2.46 (ddd, *J*=18.4, 6.8, 2.3 Hz, 1 H) 2.88 (d, *J*=7.4 Hz, 1 H) 5.43-5.46 (m, 1 H) 5.70-5.75 (m, 1 H) 6.20 (s, 1 H) 6.51-5.59 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 28.2 ($3xCH_3$) 34.6 (C) 40.6 (CH_2) 52.2 (CH) 120.8 (CH_2) 130.3 (CH) 134.4 (CH) 176.4 (C) 208.7 (C).

HRMS (EI) *m/z* calcd for $C_{11}H_{16}O$ [M^+] 164.1201, found: 164.1221.

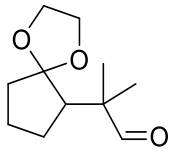
5.2.3 Route C: synthesis intermediates



(3.106) 6-(2-methylbut-3-en-2-yl)-1,4-dioxaspiro[4.4]nonane

To a solution of 2-(2-methylbut-3-en-2-yl)cyclopentan-1-one **3.105** (2.00 g, 13.1 mmol) and ethylene glycol (1.47 mL, 26.3 mmol) in benzene (65 mL) was added p-TSA (0.125 g, 0.657 mmol). The r.b.f. was equipped with a dean-stark apparatus and the mixture was brought to reflux. The heat was kept o/n and the cooled to r.t. The reaction mixture was dropped in an extraction funnel containing a saturated solution of $NaHCO_3$. The aqueous phase separated and extracted 3x with ether. The organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (10% EtOAc:hexanes) to give ketal **3.106** (1.97 g, 10.0 mmol, 76 %) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.04 (s, 3 H) 1.06 (s, 3 H) 1.44-1.59 (m, 4 H) 1.70-1.75 (m, 2 H) 1.92 (dd, *J*=10.4, 8.6 Hz, 1 H) 3.75-3.79 (m, 1 H) 3.82-3.92 (m, 3 H) 4.86 (q, *J*=1.6 Hz, 1 H) 4.90 (q, *J*=1.6 Hz, 1 H) 6.04 (dd, *J*=18.0, 10.4 Hz, 1 H).



(3.107) 2-methyl-2-(1,4-dioxaspiro[4.4]nonan-6-yl)propanal

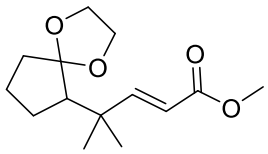
To a cooled solution of ketal **3.106** (1.83 g, 9.32 mmol) in a 1:1 mixture of DCM:MeOH (50.0 mL) at -78˚C was bubbled ozone until the solution turned blue. At that moment, the solution was allowed to warm to r.t. and triphenylphosphine (4.89 g, 18.7 mmol) was added. The resulting mixture was stirred for 10 min and then it was concentrated under reduce pressure. The crude residue was purified by flash chromatography (3-10% EtOAc:hexanes) to give aldehyde **3.107** (1.23 g, 6.24 mmol, 67 %) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2921, 1733, 1108, 977.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.01 (s, 3 H) 1.09 (s, 3 H) 1.56-1.62 (m, 2 H) 1.63-1.73 (m, 3 H) 1.83-1.89 (m, 1 H) 2.34 (t, *J*=9.0 Hz, 1 H) 3.76-3.86 (m, 4 H) 9.58 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 19.4 (CH_3) 21.5 (CH_2) 22.8 (CH_3) 25.0 (CH_2) 37.0 (CH_2) 46.5 (C) 52.8 (CH) 63.5 (CH_2) 64.2 (CH_2) 117.8 (C) 206.0 (CH).

HRMS (EI) *m/z* calcd for $C_{11}H_{18}O_3$ [M^+] 198.1256, found: 198.1240.



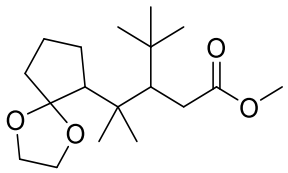
(3.108) methyl (E)-4-methyl-4-(1,4-dioxaspiro[4.4]nonan-6-yl)pent-2-enoate

To a solution of methyl diethylphosphonoacetate (0.481 mL, 2.65 mmol) in THF (12.0 mL) at -78˚C, *n*-BuLi (1.06 mL, 2.65 mmol, 2.5 M in hexanes) was added in one portion. After 30 min, the aldehyde **3.107** (0.500 g, 2.52 mmol) was added and the reaction was allowed to stir 20 min -78˚C and warmed to r.t. for o/n stirring. Thereafter, the reaction was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (5% EtOAc:hexanes) to give ester **3.108** (0.621 g, 2.44 mmol, 97%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2945, 1703, 1301.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.08 (s, 3 H) 1.09 (s, 3 H) 1.46-1.62 (m, 4 H) 1.66-1.79 (m, 2 H) 2.01 (t, *J*=9.2 Hz, 1 H) 3.70 (s, 3 H) 3.74-3.86 (m, 4 H) 5.69 (d, *J*=15.9 Hz, 1 H) 7.20 (d, *J*=16.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 21.1 (CH_2) 24.3 (CH_3) 26.2 (CH_2) 26.6 (CH_3) 37.8 (CH_2) 38.3 (C) 51.3 (CH) 54.6 (CH_3) 63.1 (CH_2) 64.2 (CH_2) 116.4 (CH) 118.2 (C) 158.9 (CH) 167.9 (C).



(3.109) Methyl 3-(2-(1,4-dioxaspiro[4.4]nonan-6-yl)propan-2-yl)-4,4-dimethylpentanoate

t-BuLi (4.31 mL, 7.33 mmol, 1.7 M in pentane) was added to a suspension of CuCN (0.328 g, 3.66 mmol) in dry ether (12.0 mL) cooled to -78°C. The resulting mixture was kept at -78°C for 15 min followed by 30 min at -45°C (dry ice: acetonitrile). The reaction was then cooled again to -78°C and a solution of enone **3.108** (0.621 g, 2.44 mmol) in ether (5.0 mL) was added dropwise. Next, freshly distilled TMSCl (0.624 mL, 4.88 mmol) was added. The mixture was allowed to warm to -45°C and was stirred for 45 min before quenching with NH_4Cl. The aqueous phase was extracted 3x with ether. The organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (3-5-10% EtOAc:hexanes) to give ester **3.109** (0.083 g, 0.266 mmol, 11 %) with a d.r. of 1:0.66 and also the reduced enone adduct **3.110** (0.195 g, 0.761 mmol, 31%) as clear oils.

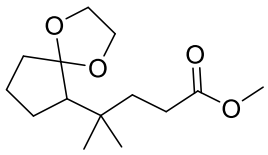
<u>Major diastereomer</u>

IR (neat, cm^{-1}) ν_{max}: 2952, 1733, 1149.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.83 (s, 3 H) 0.99 (m, 9 H) 1.14 (m, *J*=5.3 Hz, 3 H) 1.33-1.63 (m, 4 H) 1.68-1.78 (m, 2 H) 2.16-2.29 (m, 2 H) 2.32-2.39 (m, 2 H) 3.61 (s, 3 H) 3.69-3.77 (m, 1 H) 3.81-4.04 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 21.4 (CH_2) 22.1 (CH_3) 24.0 (CH_3) 26.7 (CH_2) 30.6 (3xCH_3) 34.0 (CH_2) 36.4 (C) 38.7 (CH_2) 40.5 (C) 47.9 (CH) 51.5 (CH) 52.1 (CH_3) 62.5 (CH_2) 64.2 (CH_2) 118.9 (C) 175.8 (C).

HRMS (EI) *m/z* calcd for $C_{17}H_{29}O_4$ [M^+-Me] 297.2066, found: 297.2044.



(3.110) Methyl 4-methyl-4-(1,4-dioxaspiro[4.4]nonan-6-yl)pentanoate

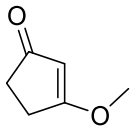
IR (neat, cm^{-1}) ν_{max}: 2952, 1731, 1149, 945.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.86 (s, 3 H) 0.92 (s, 3 H) 1.37-1.43 (m, 1 H) 1.48-1.58 (m, 4 H) 1.65-1.77 (m, 3 H) 1.82-1.87 (m, 1 H) 2.18 (ddd, *J*=15.1, 11.9, 5.1 Hz, 1 H) 2.33 (ddd, *J*=15.1, 12.0, 5.1 Hz, 1 H) 3.59 (s, 3 H) 3.71-3.74 (m, 1 H) 3.79-3.90 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 21.2 (CH_3) 24.5 (CH_3) 25.6 (CH_2) 26.1 (CH_2) 29.2 (CH_2) 34.3 (C) 36.1 (CH_2) 38.1 (CH_2) 51.3 (CH) 52.1 (CH_3) 62.7 (CH_2) 63.9 (CH_2) 118.7 (C) 175.1 (C).

HRMS (EI) *m/z* calcd for $C_{14}H_{24}O_4$ [M^+] 256.1675, found: 256.1694.

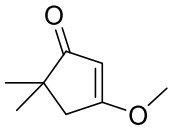
5.2.1 Route D: synthesis intermediates



(3.129) 3-methoxycyclopent-2-en-1-one

To a solution of cyclopentane-1,3-dione **3.128** (3.00 g, 30.6mmol) in MeOH (150 mL) was added H_2SO_4 (0.163 mL, 3.06 mmol) and the mixture was refluxed o/n. The reaction was cooled to r.t. and the pH was neutralized to 7 by adding KOH. The solvent was then evaporated and the crude was dissolved in DCM and brine was added. The aqueous phase was extracted 3x with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (40% EtOAc:hexanes) to give methyl vinyl ether **3.129** (3.17 g, 28.3 mmol, 92%) as a white solid.

Spectral data was identical to the one found in the literature[155]



(3.130) 3-methoxy-5,5-dimethylcyclopent-2-en-1-one

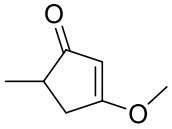
To a solution of methyl vinyl ether **3.129** (3.17 g, 28.3 mmol) in THF (100 mL) at -78˚C was added a freshly prepared solution of LDA (31.1 mL, 31.1 mmol, 1M in THF) and the mixture was stirred for 1h at the same temperature and MeI (2.12 mL, 33.9 mmol) was added. The reaction was warmed to r.t. and allowed to stir for 3 h. The solution was then cooled to -78˚C and a solution of LDA (31.1 mL, 31.1 mmol, 1 M in THF) was added and the mixture was stirred for 1h at the same temperature and MeI (2.12 mL, 33.9 mmol) was added. The reaction was warmed to r.t. and allowed to stir for 3 h. The reaction was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated (never above 30˚C on the rotavap, highly volatile material). The crude residue

was purified by flash chromatography (20-30% EtOAc:hexanes) to give mono-alkylated adduct (0.544 g, 4.32 mmol, 15.26 %) and di-alkylated adduct **3.130** (2.00 g, 14.27 mmol, 51%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 3421, 1677, 1588, 1350, 1132, 991.

Spectral data was identical to the one found in the literature[156].

HRMS (EI) *m/z* calcd for $C_8H_{12}O_2$ [M^+] 140.0837, found: 140.0861.



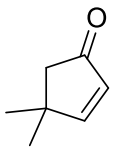
3-methoxy-5-methylcyclopent-2-en-1-one

IR (neat, cm^{-1}) ν_{max}: 3550, 1684, 1588, 1353.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.17 (d, *J*=7.4 Hz, 3 H) 2.18 (ddd, *J*=17.6, 2.7, 1.0 Hz, 1 H) 2.48 (quintuplet of doublet, *J*=7.4, 2.9 Hz, 1 H) 2.80 (ddd, *J*=17.6, 7.3, 1.1 Hz, 1 H) 3.80 (s, 3 H) 5.23 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.6 (CH_3) 36.8 (CH_2) 39.9 (CH) 58.5 (CH_3) 103.0 (CH) 189.5 (C) 208.6 (C).

HRMS (EI) *m/z* calcd for $C_7H_{10}O_2$ [M^+] 126.0681, found: 126.0663.

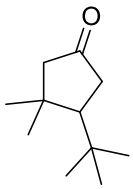


(3.131) 4,4-dimethylcyclopent-2-en-1-one

To a solution of methyl vinyl ether **3.130** (1.00 g, 7.13mmol) in Et_2O (35.7 mL) was added $LiAlH_4$ (0.325 g, 8.56 mmol) at 0˚C. After 30 min all starting material was consumed and a solution of 2N HCl (5mL) was added slowly and dropwise to the solution at 0˚C. Once the quenching contained, the ice bath was removed and the reaction was stirred heavily at r.t. The reaction was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated (never above 30˚C on the rotavap, highly volatile material). The crude residue was purified by flash chromatography (5% EtOAc:hexanes) enone **3.131** (0.65 g, 5.90 mmol, 83%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2968, 2343, 1734, 1462.

Spectral data was identical to the one found in the literature[157].



(3.132) 4-(tert-butyl)-3,3-dimethylcyclopentan-1-one

t-BuLi (12.6 mL, 21.4 mmol, 1.7M in pentane) was added to a suspension of CuCN (0.957 g, 10.7 mmol) in dry ether (35 mL) cooled to -78°C. The resulting mixture was kept at -78°C for 15 min followed by 30 min at -45°C (dry ice: acetonitrile). The reaction was then cooled again to -78°C and a solution of enone **3.131** (0.785 g, 7.13 mmol) in ether (5 mL) was added dropwise. Next, freshly distilled TMSCl (1.82 mL, 14.25 mmol) was added. The mixture was allowed to warm to -45°C and was stirred for 45 min before quenching with NH_4Cl. The aqueous phase was extracted 3x with ether. The organic layers were dried over $MgSO_4$, filtered and concentrated (never above

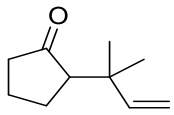
30˚C on the rotavap, highly volatile material). The crude residue was purified by flash chromatography (3-5% EtOAc:hexanes) to give ketone **3.132** (0.679 g, 4.03 mmol, 57 %) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2941, 1741, 1201.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.01 (s, 9 H) 1.05 (s, 3 H) 1.29 (s, 3 H) 1.89 (dd, *J*=11.2, 9.8 Hz, 1 H) 1.99 (dd, *J*=17.7, 0.9 Hz, 1 H) 2.17-2.21 (m, 1 H) 2.29 (dd, *J*=2.7, 1.0 Hz, 1 H) 2.32-2.32 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 23.6 (CH_3) 29.7 (3x CH_3) 30.9 (CH_3) 33.9 (C) 40.3 (CH_2) 40.7 (C) 55.7 (CH) 58.4 (CH_2) 218.2 (s, 1 C).

HRMS (EI) *m/z* calcd for $C_{11}H_{20}O$ [M^+] 168.1514, too volatile.



(3.105) 2-(2-methylbut-3-en-2-yl)cyclopentan-1-one

cyclopentanone (1.00 ml, 11.3 mmol) was added to a round bottom flask equipped with a stir bar. Triethoxyformate (2.06 mL, 12.38 mmol, 1.1 eq. mol) was then added followed by Ethanol 99% (2mL). Amberlyst® 15 (50 mg, 5% per w/mL) was added in one portion and the mixture was stirred slowly for 12h[10]. The solution was filtered over a small celite pad (1-2 cm) and the reaction vessel and celite pad were washed with dichloromethane (5-10 mL). The filtrate was equipped with a stir bar and a small distillation apparatus was installed and heated at 110°C to remove any residual

[10] Most acetals were formed completely after 1h but in order to make the metodology as general as possible all acetals were allowed 12h of stirring.

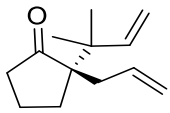
ethanol, DCM as well as ethyl formate. Thereafter, the solution was cooled to r.t. and the desired alcohol (1.1 eq.) as well as propionic acid (10% mol) was added. The resulting mixture was heated at 130°C for 2h with the distillation apparatus before transferring the crude into a sealed tube for overnight heating at 130°C. The crude was then directly flashed over silica to afford the desired α-allylated adduct **3.105** (1.14 g, 7.46 mmol, 66%).

IR (neat, cm^{-1}) ν_{max}: 2960, 1731, 1147, 910, 748.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.09 (s, 3 H) 1.13 (s, 3 H) 1.55-1.72 (m, 2 H) 1.88-2.09 (m, 4 H) 2.20-2.28 (m, 1 H) 4.93 (dd, *J*=7.9, 1.3 Hz, 1 H) 4.96 (s, 1 H) 5.84 (dd, *J*=17.0, 11.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 20.2 (CH_2) 24.5 (CH_3) 25.5 (CH_3) 26.4 (CH_2) 38.5 (C) 40.2 (CH_2) 57.1 (CH) 111.6 (CH_2) 145.7 (CH) 219.7 (C).

HRMS (EI) *m/z* calcd for $C_{10}H_{16}O$ [M^+] 152.1201, found: 152.1189.



(3.120Ag) 2-allyl-2-(2-methylbut-3-en-2-yl)cyclopentan-1-one (#)

Cyclopentanone **3.105** (5.00 ml, 56.5 mmol) was added to a round bottom flask equipped with a stir bar. Triethoxyformate (10.3 mL, 62.1 mmol, 1.1 eq. mol) was then added followed by Ethanol 99% (10.0 mL). Amberlyst® 15 (250 mg, 5% per w/mL) was added in one portion and the mixture was stirred slowly for 12h[11]. The solution was filtered over a small celite pad (2-5 cm) and the reaction vessel and celite pad were washed with dichloromethane (20 mL). The filtrate was

[11] Most acetals were formed completely after 1h but in order to make the metodology as general as possible all acetals were allowed 12h of stirring.

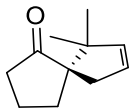
equipped with a stir bar and a small distillation apparatus was installed and heated at 110°C to remove any residual ethanol, DCM as well as ethyl formate. Thereafter, the solution was cooled to r.t. and allyl alcohol (4.08 mL, 59.3 mmol, 1.1 eq.) as well as propionic acid (0.421 mL, 5.65 mmol, 10% mol) was added. The resulting mixture was heated at 130°C for 2h with the distillation apparatus before transferring the crude into a sealed tube for overnight heating at 130°C. The crude was then cooled back to r.t. and triethoxyformate (10.33 mL, 62.1 mmol, 1.1 eq. mol) was added, followed by Ethanol 99% (10.0 mL). Amberlyst® 15 (250 mg, 5% per w/mL) was added in one portion and the mixture was stirred slowly for 12h. The solution was filtered over a small celite pad (2-5 cm) and the reaction vessel and celite pad were washed with dichloromethane (20.0 mL). The filtrate was equipped with a stir bar and a small distillation apparatus was installed and heated at 110°C to remove any residual ethanol, DCM as well as ethyl formate. Thereafter, the solution was cooled to r.t. and 3-methylbut-2-en-1-ol (6.31 mL, 62.1 mmol, 1.1 eq.) as well as propionic acid (0.421 mL, 5.65 mmol, 10% mol) was added. The resulting mixture was heated at 130°C for 2h with the distillation apparatus before transferring the crude into a sealed tube for overnight heating at 130°C. The crude was cooled and directly flashed over silica to afford the desired bis-α-allylated adduct **3.120Ag** (4.42 g, 22.98 mmol, 41%).

IR (neat, cm^{-1}) ν_{max}: 2964, 1728, 1637, 1151, 912.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.04 (s, 3 H) 1.05 (s, 3 H) 1.59-1.68 (m, 1 H) 1.77-1.88 (m, 2 H) 2.05-2.10 (m, 2 H) 2.13-2.17 (m, 2 H) 2.49 (dd, *J*=13.1, 6.7 Hz, 1 H) 4.94-5.05 (m, 4 H) 5.58-5.69 (m, 1 H) 5.93 (dd, *J*=17.4, 11.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 19.0 (CH_2) 22.5 (CH_3) 22.7 (CH_3) 30.3 (CH_2) 38.9 (CH_2) 40.8 (CH_2) 42.1 (C) 55.9 (C) 112.7 (CH_2) 117.9 (CH_2) 135.0 (CH) 144.9 (CH) 223.4 (C).

HRMS (EI) *m/z* calcd for $C_{13}H_{20}O$ [M^+] 192.1514, found: 192.1512.



(3.133) 6,6-dimethylspiro[4.4]non-7-en-1-one

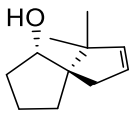
To a solution of bis-alkene **3.120Ag** (2.00 g, 10.4 mmol) in dry DCM (100 mL) was added Grubbs' catalyst 2nd generation (87 mg, 0.104mmol, 1% loading) at r.t. The reaction was then refluxed in an oil bath and followed by TLC. After 1h, no more starting material was present and methyl vinyl ether (2mL) was added and stirred at refluxed for 5 min. The reaction was then cooled and concentrated under reduced pressure. The crude residue was purified by flash chromatography (3-5-10% EtOAc:hexanes) to give spiro ketone **3.133** (1.32 g, 8.04 mmol, 77 %) as clear red oil.

IR (neat, cm^{-1}) ν_{max}: 2916, 1455, 1037, 869.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.98 (s, 3 H) 1.02 (s, 3 H) 1.73-1.90 (m, 3 H) 2.07-2.17 (m, 2 H) 2.21-2.33 (m, 2 H) 2.48-2.53 (m, 1 H) 5.50-5.51 (m, 1 H) 5.54-5.56 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 19.3 (CH_2) 22.7 (CH_3) 25.5 (CH_3) 32.8 (CH_2) 38.6 (CH_2) 41.9 (CH_2) 48.0 (C) 60.1 (C) 125.3 (CH) 141.4 (CH) 220.8 (C)

HRMS (EI) *m/z* calcd for $C_{11}H_{16}O$ [M^+] 164.1201, found: 164.1222



6,6-dimethylspiro[4.4]non-7-en-1-ol

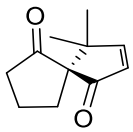
To a solution of Ketone **3.133** (0.493 g, 3 mmol) in DCM (20.0 mL) was added DIBAL-H (2.68 mL, 3.30mmol, 25% w/w in pentane) at -78°C. The reaction was followed by TLC and was found to be done in less then 30 min. the reaction was then quenched following the Fieser method. Slowly add 0.04x (x = # mmol of DIBAL-H used in reaction) mL of water at 0°C, then 0.04x mL of 15% aqueous sodium hydroxide and finally add 0.1x mL of water. Warm to r.t. and stir for 30 min and filter over celite. The celite was washed with DCM and the filtrate was concentrated and the crude residue was purified by flash chromatography (15-25% EtOAc:hexanes) to give alcohol (0.41 g, 2.47 mmol, 82%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2916, 1455, 1037, 861.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.11 (s, 3 H) 1.13 (s, 3 H) 1.16 (s, 1 H) 1.36 (dd, *J*=11.3, 8.7 Hz, 1 H) 1.53-1.70 (m, 2 H) 1.73-1.93 (m, 4 H) 2.02-2.08 (m, 1 H) 4.08 (d, *J*=2.0 Hz, 1 H) 5.39-5.45 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 19.6 (CH_2) 24.7 (CH_3) 24.9 (CH_3) 29.3 (CH_2) 33.7 (CH_2) 42.3 (CH_2) 46.7 (C) 59.7 (C) 79.7 (CH) 124.4 (CH) 143.5 (CH).

HRMS (EI) *m/z* calcd for $C_{11}H_{18}O$ [M^+] 166.1358, found: 166.1379.



(3.134) 4,4-dimethylspiro[4.4]non-2-ene-1,6-dione

To a suspension CrO_3 (1.10 g, 11.0 mmol) in DCM (6 mL) was added 3,5-dimethylpyrazole (1.05 g, 11.0 mmol) and the solution was stirred for 15 min. The solutions became deep red at that point and homogenous. A solution of alkene **3.133** (0.18 g, 1.10 mmol) in DCM (1.00 mL) was added

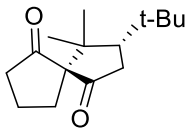
in one portion and the reaction was allowed to stir for 3 days. Ether was then added and the mixture was filtered over a thick celite pad. The celite pad was washed with ether and the filtrate was concentrated and the crude residue was purified by flash chromatography (10-15% EtOAc:hexanes) to give enone **3.134** (0.072 g, 0.404 mmol, 37%) as an orange oil.

IR (neat, cm^{-1}) ν_{max}: 2950, 1754, 1735, 1240, 880.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.07 (s, 3 H) 1.11 (s, 3 H) 1.86-1.95 (m, 1 H) 1.97-2.04 (m, 1 H) 2.15-2.25 (m, 2 H) 2.34-2.45 (m, 2 H) 6.07 (d, *J*=5.7 Hz, 1 H) 7.54 (d, *J*=5.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 19.7 (CH_2) 21.5 (CH_3) 28.4 (CH_3) 28.7 (CH_2) 39.2 (CH_2) 47.2 (C) 72.1 (C) 130.0 (CH) 172.7 (CH) 205.9 (C) 213.5 (C).

HRMS (EI) *m/z* calcd for $C_{11}H_{14}O_2$ [M^+] 178.0994, found: 178.0951.



(3.135b) 3-(tert-butyl)-4,4-dimethylspiro[4.4]nonane-1,6-dione

t-BuLi (2.68 mL, 4.56 mmol, 1.7 M in pentane) was added to a suspension of CuCN (0.204 g, 2.278 mmol) in dry ether (8 mL) cooled to -78°C. The resulting mixture was kept at -78°C for 15 min followed by 30 min at -45°C (dry ice: acetonitrile). The reaction was then cooled again to -78°C and a solution of enone **3.134** (0.271 g, 1.52 mmol) in ether (3.00 mL) was added dropwise. Next, freshly distilled TMSCl (0.388 mL, 3.04 mmol) was added. The mixture was allowed to warm to -45°C and was stirred for 45 min before quenching with HCL 10%. The reaction was then allowed to stir for 20 min to ensure complete hydrolysis of silyl vinyl ether. A saturated solution of NH_4Cl was added and the aqueous phase was extracted 3x with ether. The organic layers were

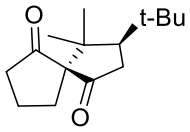
dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (3-5-10% EtOAc:hexanes) to give diketone **3.135** as a mixture of 2 separable diastereomers. The first diastereomer was the natural isomer where the t-Bu group was down (0.07 g, 0.296 mmol, 20 %) and the second was the one where the t-Bu was up (0.170 g, 0.720 mmol, 47%) as it was demonstrated by the x-ray analysis. A dr of 3:1 was obtained in favor of the unnatural diastereomer.

IR (neat, cm^{-1}) ν_{max}: 2954, 2364, 1743, 1712, 1122.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.84 (s, 3 H) 1.00 (s, 9 H) 1.12 (s, 3 H) 1.73 (ddd, *J*=12.5, 10.9, 7.2 Hz, 1 H) 1.89-1.94 (m, 1 H) 1.97-2.06 (m, 1 H) 2.08-2.17 (m, 2 H) 2.20-2.25 (m, 1 H) 2.27-2.34 (m, 1 H) 2.54 (dd, *J*=19.6, 9.8 Hz, 1 H) 2.89 (dd, *J*=11.6, 9.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 19.2 (CH_2) 21.1 (CH_3) 23.9 (CH_3) 27.8 (CH_2) 30.0 (3xCH_3) 33.9 (C) 38.8 (CH_2) 40.7 (CH_2) 47.6 (C) 50.1 (CH) 76.2 (C) 214.0 (2xC).

HRMS (EI) *m/z* calcd for $C_{15}H_{24}O_2$ [M^+] 236.1776, found: 236.1758.



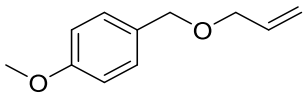
(3.135a) 3-(tert-butyl)-4,4-dimethylspiro[4.4]nonane-1,6-dione

IR (neat, cm^{-1}) ν_{max}: 2954, 1733, 1708, 1222.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.98 (s, 9 H) 1.16 (s, 3 H) 1.18 (s, 3 H) 1.85-1.90 (m, 3 H) 2.02-2.08 (m, 1 H) 2.09-2.16 (m, 1 H) 2.23-2.32 (m, 2 H) 2.34-2.43 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 18.7 (CH_2) 20.5 (CH_3) 26.4 (CH_3) 30.1 (3x CH_3) 31.2 (CH_2) 33.9 (C) 38.5 (CH_2) 40.8 (CH_2) 47.5 (C) 53.3 (CH) 73.2 (C) 215.1 (s, 1 C) 215.6 (s, 1 C).

HRMS (EI) *m/z* calcd for $C_{15}H_{24}O_2$ [M^+] 236.1776, found: 236.1773.



(3.141) 1-((allyloxy)methyl)-4-methoxybenzene

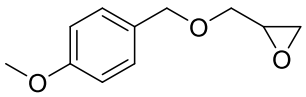
A solution of 4-methoxybenzyl alcohol (**3.140**) (20.0 g, 145 mmol) in THF (45.0 mL) was added slowly to a suspension of NaH (7.24 g, 181 mmol, 60% w/w) in THF (100 mL) cooled to 0°C. Once the addition was complete the ice bath was removed and the mixture was allowed to warm to r.t. for 30 min. Allyl bromide (31.3 mL, 362 mmol) was added, followed by tetrabutylammonium iodide (0.535 g, 1.48 mmol) and allowed to stir for 18 hours. The reaction was quenched with NH_4Cl saturated solution and extracted 3x with ether. The organic layers were dried over MgSO4, filtered and concentrated. The crude residue was purified by flash chromatography (5-10% EtOAc:hexanes) to give 1-((allyloxy)methyl)-4-methoxybenzene (**3.141**) (25.5 g, 143 mmol , 99%) as a transparent oil.

IR (neat, cm^{-1}) ν_{max}: 2839, 1515, 1238, 811.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.80 (s, 3 H) 4.00 (dt, *J*=5.7, 1.4 Hz, 2 H) 4.45 (s, 2 H) 5.19 (dq, *J*=10.5, 1.3 Hz, 1 H) 5.29 (dq, *J*=17.2, 1.6 Hz, 1 H) 5.94 (ddd, *J*=17.0, 10.6, 5.6 Hz, 1 H) 6.86-6.89 (m, 2 H) 7.26-7.28 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 55.2 (CH_3) 70.8 (CH_2) 71.8 (CH_2) 113.8 (2xCH) 117.0 (CH_2) 129.3 (2xCH) 130.4 (CH) 134.8 (C) 159.2 (C).

HRMS (EI) *m/z* calcd for $C_{11}H_{14}O_2$ [M^+] 178.0994, found: 178.0970.



(3.142) 2-(((4-methoxybenzyl)oxy)methyl)oxirane

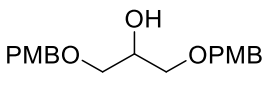
To a solution of 1-((allyloxy)methyl)-4-methoxybenzene **3.141** (24.0 g, 134 mmol) in DCM (500 mL) was added *m*-CPBA (48.3 g, 202 mmol) and stirred for 2 days at r.t. The solution was then quenched with a saturated solution of $NaHCO_3$ and $Na_2S_2O_3$. The organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (5-10% EtOAc:hexanes) to give 2-(((4-methoxybenzyl)oxy)methyl)oxirane **3.142** (20.0 g, 103 mmol , 77%) as a transparent oil.

IR (neat, cm^{-1}) ν_{max}: 2840, 1612, 1440, 829.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.59 (dd, *J*=5.1, 2.7 Hz, 1 H) 2.77 (dd, *J*=5.0, 4.2 Hz, 1 H) 3.13-3.17 (m, 1 H) 3.39 (dd, *J*=11.4, 5.9 Hz, 1 H) 3.71 (dd, *J*=11.5, 3.0 Hz, 1 H) 3.78 (s, 3 H) 4.50 (q, *J*=11.4 Hz, 2 H) 6.86 (ddd, *J*=9.1, 2.7, 2.4 Hz, 2 H) 7.26 (ddd, *J*=8.8, 2.3, 2.1 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 44.3 (CH_2) 50.8 (CH) 55.2 (CH_3) 70.5 (CH_2) 72.9 (C) 113.8 (2xCH) 129.4 (2xCH) 129.9 (C) 159.3 (C).

HRMS (EI) *m/z* calcd for $C_{11}H_{14}O_3$ [M^+] 194.0943, found: 194.0941.



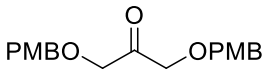
(3.143) 1,3-bis((4-methoxybenzyl)oxy)propan-2-ol

To a slurry of NaH (6.44 g, 161 mmol, 60% w/w) in THF (100 mL) cooled to 0°C was added slowly a solution of *p*-methoxybenxyl alcohol (**3.140**) (22.3 g, 161 mmol) in THF (46.0 mL). The solution was then allowed to stir 10 min at r.t. before 2-(((4-methoxybenzyl)oxy)methyl)oxirane (28.6 g, 146 mmol) was added in one portion. The mixture was then refluxed o/n and then cooled to r.t. The solution was quenched with a saturated solution of NH_4Cl and the aqueous phase was extracted 3x with EtOAc. The organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (20-30-40% EtOAc:hexanes) to give 1,3-bis((4-methoxybenzyl)oxy)propan-2-ol **3.143** (45.0 g, 135 mmol, 92%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2880, 1612, 1512, 1246, 813.

Spectral data was identical to the one found in the literature[158].

HRMS (EI) *m/z* calcd for $C_{11}H_{15}O_4$ [M^+-PMB] 211.0970, found: 211.0975.



(3.144) 1,3-bis((4-methoxybenzyl)oxy)propan-2-one

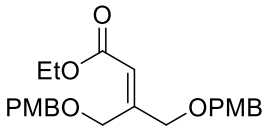
The alcohol **3.143** (5.43 g, 16.34 mmol) was dissolved in wet DCM (125 mL). Dess-Martin periodinane (8.31 g, 19.60 mmol) was added and the reaction was stirred for 3 h before being quenched with a 1:1 mixture of saturated $NaHCO_3$ solution and saturated solution of $Na_2S_2O_3$ under heavy stirring for 30min. The resulting mixture was then separated and the aqueous phase was extracted 3x with DCM. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (5-10 % EtOAc:hexanes) to provide ketone **3.144** (4.98 g, 15.07 mmol, 92 %) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2994, 1733, 1510, 1246, 1095, 1031, 815.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.80 (s, 6 H) 4.18 (s, 4 H) 4.49 (s, 4 H) 6.85-6.89 (m, 4 H) 7.22-7.26 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 55.3 (2xCH_3) 73.1 (2xCH_2) 73.3 (2xCH_2) 113.9 (4xCH) 129.1 (2xC) 129.6 (4xCH) 159.5 (2xC) 205.9 (C).

Spectral data was identical to the one found in the literature[158].



(3.145) ethyl 4-((4-methoxybenzyl)oxy)-3-(((4-methoxybenzyl)oxy)methyl)but-2-enoate

To a slurry of NaH (3.38 g, 85.0 mmol, 60% w/w) in dry toluene (250 mL) cooled to 0°C was added slowly ethyl 2-(diethoxyphosphoryl)acetate (16.84 mL, 85.0 mmol). After completion of the addition, the reaction was allowed to return to r.t. and stirred for 15min until full consumption of the NaH. The solution was cooled to 0°C again and 1,3-bis((4-methoxybenzyl)oxy)propan-2-one **3.144** (26.7 g, 81.0 mmol) was added in one portion. The formation of a thick paste occurs immediately that often obstruct proper stirring but doesn't affect the outcome. The solution was allowed to stand for 45min after which a minimum of EtOH 99% was added dropwise until the paste was dissolved (±0.5mL of EtOH per gram of starting material). The reaction was then stirred for another 45 min before quenching it with a saturated solution of NH_4Cl and the aqueous phase was extracted 3x with EtOAc. The organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (10-20% EtOAc:hexanes)

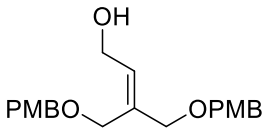
to give ethyl 4-((4-methoxybenzyl)oxy)-3-(((4-methoxybenzyl)oxy)methyl)but-2-enoate (**3.145**) (32.0 g, 80.0 mmol, 99%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 1704, 1612, 1512, 817.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.25 (t, *J*=7.2 Hz, 3 H) 3.78 (s, 3 H) 3.79 (s, 3 H) 4.14 (q, *J*=7.1 Hz, 2 H) 4.21 (d, *J*=1.6 Hz, 2 H) 4.41 (s, 2 H) 4.48 (s, 2 H) 4.64 (s, 2 H) 6.10 (quin., *J*=1.6 Hz, 1 H) 6.83-6.89 (m, 4 H) 7.18-7.22 (m, 2 H) 7.23-7.27 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 14.2 (CH_3) 55.2 (CH_3) 55.2 (CH_3) 60.0 (CH_2) 67.0 (CH_2) 69.8 (CH_2) 72.5 (CH_2) 72.6 (CH_2) 113.7 (2xCH) 113.8 (2xCH) 115.8 (CH) 129.3 (2xCH) 129.3 (2x CH) 130.0 (C) 130.1 (C) 155.1 (C) 159.2 (C) 159.3 (C) 166.2 (C).

HRMS (EI) *m/z* calcd for $C_{23}H_{27}O_6$ [M^+-H] 399.1808, found: 399.1811.



(3.146) 4-((4-methoxybenzyl)oxy)-3-(((4-methoxybenzyl)oxy)methyl)but-2-en-1-ol

Ethyl 4-((4-methoxybenzyl)oxy)-3-(((4-methoxybenzyl)oxy)methyl)but-2-enoate (**3.145**) (4.54 g, 11.3 mmol) was disolved in DCM (50.0 mL) and cooled to -78°C. A DIBAL (27.6 mL, 34.0 mmol, 25% w/w in hexanes) solution was then added and allowed to stir 30 min at -78°C followed by 30 min at 0°C. The Fieser method was employed to quench the reaction, first 1.34mL of water was added really slowly (high risk of intense exotherm and explosion) at 0°C, followed by 1.34mL of a 15% NaOH solution and finally 3.4mL of water. The following was stirred for 30 min and then the resulting solid was filtered off with a celite pad. The filtrate was concentrated and the crude residue was purified by flash chromatography (20-30-40% EtOAc:hexanes) to give 4-((4-

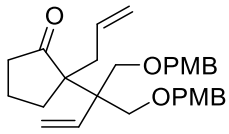
methoxybenzyl)oxy)-3-(((4-methoxybenzyl)oxy)methyl)but-2-en-1-ol (**3.146**) (3.43g, 9.57mmol, 84%)

IR (neat, cm^{-1}) ν_{max}: 1029, 1247, 1515, 2340.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.98 (t, *J*=5.9 Hz, 1 H) 3.79 (s, 6 H) 3.98 (s, 2 H) 4.05 (s, 2H) 4.18 (t, *J*=6.2 Hz, 2 H) 4.41 (s, 2 H) 4.42 (s, 2 H) 5.92 (t, *J*=6.7 Hz, 1 H) 6.83-6.87 (m, 4 H) 7.20-7.23 (s, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 55.3 (2xCH_3) 58.7 (CH_2) 65.7 (CH_2) 71.9 (CH_2) 72.4 (CH_2) 72.4 (CH_2) 113.8 (2xCH) 113.8 (2xCH) 129.4 (2xCH) 129.5 (2xCH) 129.9 (C) 130.3 (C) 131.0 (CH) 136.5 (C) 159.2 (C) 159.3 (C).

HRMS (EI) *m/z* calcd for $C_{21}H_{26}O_5$ [M^+] 358.1780, found: 358.1762.

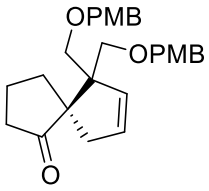


(3.148) 2-allyl-2-(1-((4-methoxybenzyl)oxy)-2-(((4-methoxybenzyl)oxy)methyl)but-3-en-2-yl)cyclopentan-1-one

2-allylcyclopentan-1-one **3.120e** (1.00 g, 8.05 mmol) was added to a round bottom flask equipped with a stir bar. Triethoxyformate (1.47 mL, 8.86 mmol, 1.1 eq. mol) was then added followed by Ethanol 99% (2.00 mL). Amberlyst® 15 (50 mg, 5% per w/mL) was added in one portion and the mixture was stirred slowly for 12h[12]. The solution was filtered over a small celite pad (1-2 cm) and the reaction vessel and celite pad were washed with dichloromethane (5 mL). The filtrate was

[12] Most acetals were formed completely after 1h but in order to make the metodology as general as possible all acetals were allowed 12h of stirring.

equipped with a stir bar and a small distillation apparatus was installed and heated at 110°C to remove any residual ethanol, DCM as well as ethyl formate. Thereafter, the solution was cooled to r.t. and 4-((4-methoxybenzyl)oxy)-3-(((4-methoxybenzyl)oxy)methyl)but-2-en-1-ol (**3.147**) (3.03g, 8.46 mmol, 1.1 eq.) as well as propionic acid (60 mL, 0.805 mmol, 10% mol) was added. The resulting mixture was heated at 130°C for 2h with the distillation apparatus before transferring the crude into a sealed tube for overnight heating at 150°C. The crude was cooled and quickly flashed over silica to afford the desired bis-α-allylated adduct (**3.148**) (2.11 g) in an inseparable mixture with side-products and isomers. The mixture was used directly in the next step.



(3.149) 6,6-bis(((4-methoxybenzyl)oxy)methyl)spiro[4.4]non-7-en-1-one

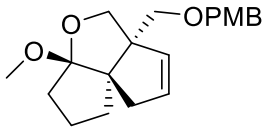
To a solution of bis-alkene **3.148** (2.11 g) in dry DCM (45 mL) was added Grubbs' catalyst 2nd generation (76 mg, 0.091 mmol, 2% loading) at r.t.. The reaction was then refluxed in an oil bath and followed by TLC. After 1h, no more starting material was present and methyl vinyl ether (2.00 mL) was added and stirred at refluxed for 5 min. The reaction was then cooled and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5-10-15% EtOAc:hexanes) to give spiro ketone **3.149** (0.835 g, 1.91 mmol, 24 % over 2 steps) as clear red oil.

IR (neat, cm^{-1}) ν_{max}: 2908, 1728, 1512, 1249, 1087.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.55-1.66 (m, 1 H) 1.81-1.92 (m, 2 H) 2.10-2.31 (m, 4 H) 2.54 (dt, *J*=16.4, 1.9 Hz, 1 H) 3.52 (s, 2 H) 3.62 (d, *J*=8.8 Hz, 1 H) 3.66 (d, *J*=8.6 Hz, 1 H), 3.78 (s, 6 H) 4.19 (d, *J*=11.4 Hz, 1 H) 4.27 (d, *J*=11.4 Hz, 1 H) 4.36 (d, *J*=11.8 Hz, 1 H) 4.43 (d, *J*=11.6 Hz, 1 H) 5.57 (dt, *J*=5.5, 1.4 Hz, 1 H) 5.75 (dt, *J*=5.3, 2.16 Hz, 1 H) 6.84 (dd, *J*=8.5, 6.4 Hz, 4 H) 7.16 (dd, *J*=17.0, 8.5 Hz, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 20.1 (CH_2) 34.1 (CH_2) 38.3 (CH_2) 44.3 (CH_2) 55.2 (CH_3) 55.2 (CH_3) 57.4 (C) 57.6 (C) 69.9 (CH_2) 72.2 (CH_2) 72.6 (CH_2) 72.9 (CH_2) 113.6 (2xCH) 113.6 (2xCH) 128.7 (CH) 128.8 (2x CH) 129.0 (2xCH) 130.7 (C) 130.8 (C) 134.0 (CH) 158.9 (C) 159.0 (C) 220.4 (C).

HRMS (EI) *m/z* calcd for $C_{19}H_{23}O_3$ [M^+-OPMB], found: 299.1613.



(3.150) 3a-methoxy-5a-(((4-methoxybenzyl)oxy)methyl)-1,2,3,3a,5a,8-hexahydro-5H-dicyclopenta[b,c]furan

Spiro adduct **3.149** (1.86 g, 4.26 mmol) was dissolved in MeOH to which TFA (0.652 mL, 8.52 mmol) was added and stirred at 40°C o/n. The resulting mixture was concentrated and purified by flash chromatography (5-10-15 % EtOAc:hexanes) to provide angular fused carbocycle **3.150** (1.61 g) as a clear oil in an inseparable mixture with 1-methoxy-4-(methoxymethyl)benzene. The mixture was submitted directly to the cleavage of the PMB ether.

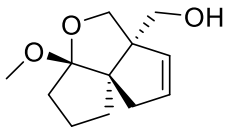
(In mixture with 1-methoxy-4-(methoxymethyl)benzene)

IR (neat, cm^{-1}) ν_{max}: 2911, 1517, 1246, 1118.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.44-1.63 (m, 5 H) 1.97-2.02 (m, 2 H) 2.92 (dt, *J*=17.2, 2.3 Hz, 1 H) 3.26 (s, 3 H) 3.33 (d, *J*=8.8 Hz, 1 H) 3.41 (d, *J*=8.6 Hz, 1 H) 3.63 (d, *J*=8.6 Hz, 1 H) 3.79 (s, 3 H) 3.92 (d, *J*=8.6 Hz, 1 H) 4.43 (s, 2 H) 5.60 (dt, *J*=5.8, 2.2 Hz, 1 H) 5.71 (dt, *J*=5.8, 2.3 Hz, 1 H) 6.83-6.87 (m, 2 H) 7.20-7.23 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 23.9 (CH_2) 33.9 (CH_2) 34.5 (CH_2) 42.3 (CH_2) 50.8 (CH_3) 55.2 (CH_3) 62.9 (C) 63.8 (C) 73.1 (CH_2) 73.2 (CH_2) 75.7 (CH_2) 113.7 (2xCH) 119.7 (C) 129.0 (2xCH) 130.5 (C) 130.7 (CH) 133.6 (CH) 159.1 (C).

HRMS (EI) *m/z* calcd for $C_{20}H_{26}O_4$ [M^+] 330.1831, found: 330.1800.



(3.151) 3a-methoxy-1,2,3,3a-tetrahydro-5H-dicyclopenta[b,c]furan-5a(8H)-yl)methanol

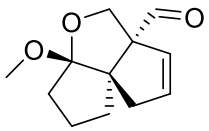
PMB ether **3.150** with 1-methoxy-4-(methoxymethyl)benzene (1.41 g, 4.26 mmol) was dissolved in a mixture of 10:1 DCM:H_2O (20.0 mL). DDQ (1.21 g, 5.33 mmol) was added in one portion and the originally transparent bi-phase solution turns immediately black. The mixture was allowed to stir for 1 hour at r.t. before it was filtered over a small pad of celite and the residue was concentrated and purified by flash chromatography (20-30-40 % EtOAc:hexanes) to provide alcohol **3.151** (0.600 g, 2.85 mmol, 67 % over 2-steps) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 3453, 2916, 2354, 1455, 1110, 732.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.38 (s, 1 H) 1.57-1.69 (m, 4 H) 2.00-2.05 (m, 2 H) 2.14-2.18 (m, 1 H) 2.92 (dt, *J*=17.3, 2.2 Hz, 1 H) 3.27 (s, 3 H) 3.62 (s, 2 H) 3.71 (d, *J*=8.8 Hz 1 H) 3.75 (d, *J*=8.8 Hz 1 H) 5.49 (dt, *J*=5.7, 2.3 Hz, 1 H) 5.90 (dt, *J*=5.7, 2.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 23.8 (CH_2) 33.6 (CH_2) 34.3 (CH_2) 42.6 (CH_2) 50.9 (CH_3) 62.6 (C) 65.0 (CH_2) 65.2 (C) 74.9 (CH_2) 120.1 (C) 132.0 (CH) 133.9 (CH).

HRMS (EI) *m/z* calcd for $C_{12}H_{18}O_3$ [M^+] 210.1256, found: 210.1240.



(3.161) 3a-methoxy-1,2,3,3a-tetrahydro-5H-dicyclopenta[b,c]furan-5a(8H)-carbaldehyde

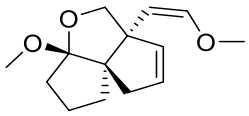
The alcohol **3.151** (0.300 g, 1.43 mmol) was dissolved in wet DCM (15.0 mL). Dess-Martin periodinane (0.726 g, 1.71 mmol) was added and the reaction was stirred for 3 h before being quenched with a 1:1 mixture of saturated $NaHCO_3$ solution and saturated solution of $Na_2S_2O_3$ under heavy stirring for 30min. The resulting mixture was then separated and the aqueous phase was extracted 3x with DCM. The organic phases were combined, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (5-10 % EtOAc:hexanes) to provide aldehyde **3.161** (0.232 g, 1.11 mmol, 78 %) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2936, 1716, 1118, 1047.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.54-1.70 (m, 4 H) 1.91-2.01 (m, 1 H) 2.02-2.07 (m, 1 H) 2.13 (dt, *J*=17.6, 2.3 Hz, 1 H) 3.09 (dt, *J*=17.6, 2.4 Hz, 1 H) 3.28 (s, 3 H) 3.61 (d, *J*=9.0 Hz, 1 H) 4.52 (d, *J*=9.0 Hz, 1 H) 5.38 (dt, *J*=5.7, 2.4 Hz, 1 H) 6.02 (dt, *J*=5.8, 2.4 Hz, 1 H) 9.55 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 23.5 (CH_2) 33.0 (CH_2) 35.1 (CH_2) 41.9 (CH_2) 50.9 (CH_3) 66.7 (C) 71.0 (CH_2) 75.0 (C) 119.3 (C) 127.4 (CH) 136.7 (CH) 200.8 (CH).

HRMS (EI) *m/z* calcd for $C_{12}H_{16}O_3$ [M^+] 208.1099, found: 208.1101.



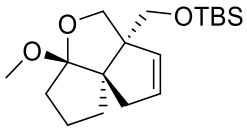
(3.162) 3a-methoxy-5a-((Z)-2-methoxyvinyl)-1,2,3,3a,5a,8-hexahydro-5H-dicyclopenta[b,c]furan

To a solution of KHMDS (0.326 g, 1.64 mmol) in THF (5.0 mL) at -78°C was added (methoxymethyl)triphenylphosphonium chloride (0.534 g, 1.56 mmol). The solution became a deep red and stirring was kept at -78°C before adding aldehyde **3.161** (0.162 g, 0.779 mmol). The red color of the mixture was immedialtly lost and became pale yellow. The solution was stirred 15 min at -78°C and then allowed to warm to r.t. The reaction is quenched with a saturated solution of NH_4Cl and the aqueous phase was extracted 3x with EtOAc. The organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (10-20% EtOAc:hexanes) to give methyl enol ether **3.162** (40 mg, 0.169 mmol, 22%) as a clear oil as a ratio of 1:0.52 - *Z: E* but also some reduced aldehyde (0.055 g, 0.262 mmol, 34%).

Major isomer (cis or *Z*) – attributed with coupling contstant (12.9 Hz for trans and 6.7 Hz for cis)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.39-1.72 (m, 4 H) 1.99-2.07 (d, 3 H) 2.90 (d, *J*=17.0 Hz, 1 H) 3.30 (s, 3 H) 3.53 (s, 3 H) 3.83 (d, *J*=8.8 Hz, 1 H) 3.96 (d, *J*=8.6 Hz, 1 H) 4.32 (d, *J*=6.7 Hz, 1 H) 5.59 (s, 2 H) 5.86 (d, *J*=6.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 23.5 (CH_2) 35.3 (CH_2) 36.1 (CH_2) 40.7 (CH_2) 51.0 (CH_3) 59.8 (CH_3) 63.4 (C) 64.4 (C) 78.0 (CH_2) 107.8 (CH) 118.5 (C) 128.7 (CH) 134.8 (CH) 146.6 (CH).



(3.152) tert-butyl((3a-methoxy-1,2,3,3a-tetrahydro-5H-dicyclopenta[b,c]furan-5a(8H)-yl)methoxy) dimethylsilane

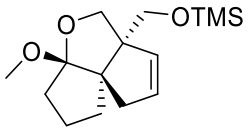
The alcohol **3.151** (0.232 g, 1.10 mmol) was dissolved in DCM (4.00 mL), Imidazole (0.180 g, 2.64 mmol), DMAP (13 mg, 0.110 mmol) and TBSCl (0.199 g, 1.322 mmol) were sequentially added to the mixture at ambient temperature. The reaction was allowed to stir o/n and quenched with a saturated solution of NaHCO3 and extracted 3x with DCM. The organic layers were dried over MgSO4, filtered and concentrated. The crude residue was purified by flash chromatography (3-5% EtOAc:hexanes) to give the protected alcohol **3.152** (0.320 g, 0.986 mmol, 90%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2950, 2331, 1253, 1105.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.01 (s, 1 H) 0.02 (s, 1 H) 0.9 (s, 9 H) 1.44-1.65 (m, 4 H) 1.97-2.12 (m, 3 H) 2.90 (dt, *J*=17.0, 2.3 Hz, 1 H) 3.27 (s, 3 H) 3.57 (d, *J*=9.6 Hz, 1 H) 3.58 (d, *J*=9.6 Hz, 1 H) 3.63 (d, *J*=8.4 Hz, 1 H) 3.91 (d, *J*=8.6 Hz, 1 H) 5.52 (dt, *J*=5.8, 2.2 Hz, 1 H) 5.70 (dt, *J*=5.8, 2.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -5.6 (CH_3) -5.5 (CH_3) 18.1 (C) 23.8 (CH_2) 25.8 (3xCH_3) 34.0 (CH_2) 34.2 (CH_2) 42.5 (CH_2) 50.8 (CH_3) 62.6 (C) 64.9 (C) 65.6 (CH_2) 75.0 (CH_2) 119.9 (C) 130.7 (CH) 133.7 (CH).

HRMS (EI) *m/z* calcd for $C_{14}H_{23}O_3Si$ [M^+-*t*-Bu] 267.1416, found: 267.1430.



((3a-methoxy-1,2,3,3a-tetrahydro-5H-dicyclopenta[b,c]furan-5a(8H)-yl)methoxy) trimethylsilane

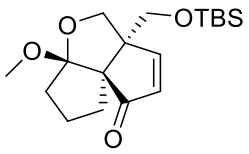
The alcohol **3.151** (0.077 g, 0.366 mmol) was dissolved in DCM (3 mL), Imidazole (60 mg, 0.879 mmol), DMAP (4.5 mg, 0.037 mmol) and TMSCl (0.056 mL, 0.439 mmol) were sequentially added to the mixture at ambient temperature. The reaction was allowed to stir o/n and quenched with a saturated solution of NaHCO3 and extracted 3x with DCM. The organic layers were dried over MgSO4, filtered and concentrated. The crude residue was purified by flash chromatography (5-10% EtOAc:hexanes) to give the protected alcohol (0.077 g, 0.273 mmol, 74%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2956, 1249, 1097, 837.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.06 (s, 9 H) 1.41-1.48 (m, 1 H) 1.52-1.63 (m, 3 H) 1.95-2.08 (m, 3 H) 2.91 (dt, *J*=17.1, 2.3 Hz, 1 H) 3.26 (s, 3 H) 3.46 (d, *J*=9.6 Hz, 1 H) 3.55 (d, *J*=9.6 Hz, 1 H) 3.61 (d, *J*=8.5 Hz, 1 H) 3.92 (d, *J*=8.5 Hz, 1 H) 5.54 (dt, *J*=5.8, 2.2 Hz, 1 H) 5.69 (dt, *J*=5.8, 2.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -0.6 (3xCH_3) 23.9 (CH_2) 34.0 (CH_2) 34.2 (CH_2) 42.4 (CH_2) 50.8 (CH_3) 62.6 (C) 64.7 (C) 65.4 (CH_2) 75.2 (CH_2) 119.8 (C) 130.7 (CH) 133.7 (CH).

HRMS (EI) *m/z* calcd for $C_{15}H_{26}O_3Si$ [M^+] 282.1651, found: 282.1698.



(3.154) 5a-(((tert-butyldimethylsilyl)oxy)methyl)-3a-methoxy-1,2,3,3a,5,5a-hexahydro-8H-dicyclopenta[b,c]furan-8-one

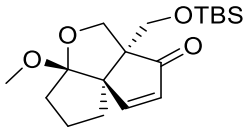
To a suspension CrO_3 (0.136 g, 1.356 mmol) in DCM (1.00 mL) was added 3,5-dimethylpyrazole (0.130 g, 1.356 mmol) and the solution was stirred for 15 min. The solutions became deep red at that point and homogenous. A solution of alkene **3.152** (0.044 g, 0.136 mmol) in DCM (1.00 mL) was added in one portion and the reaction was allowed to stir for 3 days. Ether was then added and the mixture was filtered over a thick celite pad. The celite pad was washed with ether and the filtrate was concentrated and The crude residue was purified by flash chromatography (10-15% EtOAc:hexanes) to give a mixture of 2 isomers. The allylic oxidation occurs preferentially at the spiro junction **3.154** (0.100 g, 0.295 mmol, 30%) then the quaternary center **3.153** (80.5 mg, 0.238 mmol, 24%) with a ratio of 1:0.8 respectively.

IR (neat, cm^{-1}) ν_{max}: 2883, 1713, 1097, 831.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.02 (s, 6 H) 0.84 (s, 9 H) 1.59-1.69 (m, 2 H) 1.72-1.77 (m, 1 H) 1.79-1.86 (m, 1 H) 2.01-2.14 (m, 2 H) 3.18 (s, 3 H) 3.59 (d, *J*=9.6 Hz, 1 H) 3.70 (d, *J*=9.6 Hz, 1 H) 3.78 (d, *J*=9.0 Hz, 1 H) 3.95 (d, *J*=9.0 Hz, 1 H) 6.10 (d, *J*=5.7 Hz, 1 H) 7.47 (d, *J*=5.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -5.6 (2xCH_3) 18.1 (C) 24.1 (CH_2) 25.7 (3x CH_3) 28.2 (CH_2) 33.6 (CH_2) 51.1 (CH_3) 63.4 (C) 64.5 (CH_2) 68.1 (C) 71.7 (CH_2) 120.5 (C) 132.3 (CH) 163.8 (CH) 207.3 (C).

HRMS (EI) *m/z* calcd for $C_{14}H_{21}O_4Si$ [M^+-*t*-Bu] 281.1209, found: 281.1188.



(3.153) 5a-(((tert-butyldimethylsilyl)oxy)methyl)-3a-methoxy-1,2,3,3a,5,5a-hexahydro-6H-dicyclopenta[b,c]furan-6-one

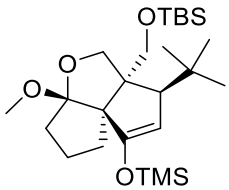
Top isomer (assigned because of the different ^1H and ^{13}C signal of the TBS and later proved by X-ray)

IR (neat, cm^{-1}) ν_{max}: 2916, 1712, 1253, 837.

^1H NMR (400 MHz, $CDCl_3$) δ ppm -0.02 (s, 3 H) 0.01 (s, 3 H) 0.79 (s, 9 H) 1.62-1.82 (m, 4 H) 2.04-2.09 (m, 1 H) 2.47-2.51 (m, 1 H) 3.22 (s, 3 H) 3.52 (d, *J*=9.4 Hz, 1 H) 3.69 (d, *J*=9.4 Hz, 1 H) 3.79 (d, *J*=10.0 Hz, 1 H) 3.95 (d, *J*=10.0 Hz, 1 H) 5.96 (d, *J*=5.9 Hz, 1 H) 7.30 (d, *J*=5.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -5.85 (CH_3) -5.76 (CH_3) 18.0 (C) 24.4 (CH_2) 25.7 (3x CH_3) 31.4 (CH_2) 34.1 (CH_2) 51.0 (CH_3) 63.4 (CH_2) 64.3 (C) 68.5 (C) 68.8 (CH_2) 118.7 (C) 130.3 (CH) 167.3 (CH) 210.3 (C).

HRMS (EI) *m/z* calcd for $C_{18}H_{30}O_4Si$ [M^+] 338.1913, found: 338.1908.



(3.158) tert-butyl((6-(tert-butyl)-3a-methoxy-8-((trimethylsilyl)oxy)-1,2,3,3a-tetrahydro-5H-dicyclopenta[b,c]furan-5a(6H)-yl)methoxy)dimethylsilane

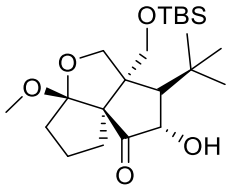
t-BuLi (0.460 mL, 0.780 mmol, 1.7M in pentane) was added to a suspension of CuCN (35mg, 0.390 mmol) in dry ether (2.00 mL) cooled to -78°C. The resulting mixture was kept at -78°C for 15 min followed by 30 min at -45°C (dry ice: acetonitrile). The reaction was then cooled again to -78°C and a solution of enone **3.154** (88 mg, 0.260 mmol) in ether (1.00 mL) was added dropwise. Next, freshly distilled TMSCl (0.066 mL, 0.520 mmol) was added. The mixture was allowed to warm to -45°C and was stirred for 45 min before quenching with NH_4Cl. The aqueous phase was extracted 3x with ether. The organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (3-5% EtOAc:hexanes) to give vinyl ether **3.158** (0.076 g, 0.162 mmol, 62%) as a clear oil with the unnatural stereochemistry.

IR (neat, cm^{-1}) ν_{max}: 2950, 1683, 1662, 1247, 1110, 837.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.03 (s, 6 H) 0.18 (s, 9 H) 0.88 (s, 9 H) 0.91 (s, 9 H) 1.36-1.44 (m, 1 H) 1.46-1.55 (m, 1 H) 1.60-1.66 (m, 1 H) 1.77-1.85 (m, 1 H) 1.94-2.02 (m, 2 H) 2.40 (d, *J*=2.2 Hz, 1 H) 3.18 (s, 3 H) 3.50 (d, *J*=10.0 Hz, 1 H) 3.55 (d, *J*=8.8 Hz, 1 H) 3.60 (d, *J*=10.0 Hz, 1 H) 4.14 (d, *J*=8.8 Hz, 1 H) 4.49 (d, *J*=2.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -5.6 (CH_3) -5.5 (CH_3) 0.4 (3x CH_3) 18.3 (C) 23.7 (CH_2) 25.9 (3x CH_3) 27.9 (CH_2) 30.0 (3x CH_3) 33.4 (CH_2) 33.8 (C) 49.7 (CH) 52.2 (CH_3) 59.2 (C) 67.9 (CH_2) 70.3 (CH_2) 71.2 (C) 105.1 (CH) 118.4 (C) 152.6 (C).

HRMS (EI) *m/z* calcd for $C_{24}H_{45}O_4Si_2$ [M^+-Me] 453.2856, found: 453.2881.



6-(tert-butyl)-5a-(((tert-butyldimethylsilyl)oxy)methyl)-7-hydroxy-3a-methoxyoctahydro-8H-dicyclopenta[b,c]furan-8-one

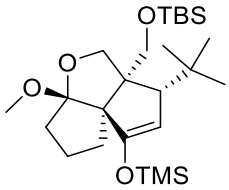
Pure *m*-CPBA (0.012 g, 0.068 mmol) was added to a solution of silyl enol ether **3.158** (0.32 g, 0.068 mmol) in DCM (1.00 mL) and the mixture was stirred at r.t. for 1 hour before the TLC showed no more sign of the starting material. The crude residue was directly purified by flash chromatography (5-10-15% EtOAc:hexanes) to give α-ketohydroxy (0.023 g, 0.056 mmol, 82%) as a clear oil and sole diastereomer.

IR (neat, cm^{-1}) ν_{max}: 2947, 1743, 1253, 858.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.04 (d, *J*=3.9 Hz, 6 H) 0.85 (s, 9 H) 1.09 (s, 9 H) 1.54-1.60 (m, 2 H) 1.78-1.87 (m, 1 H) 1.96-2.00 (m, 2 H) 2.12 (d, *J*=12.7 Hz, 1 H) 2.18-2.27 (m, 1 H) 2.69 (wide s, 1 H) 3.17 (s, 3 H) 3.62 (d, *J*=9.4 Hz, 1 H) 3.68 (d, *J*=10.8 Hz, 1 H) 3.73 (d, *J*=10.8 Hz, 1 H) 4.27 (d, *J*=9.4 Hz, 1 H) 4.46 (d, *J*=12.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -5.8 (CH_3) -5.6 (CH_3) 17.9 (C) 24.8 (CH_2) 25.7 (3x CH_3) 27.5 (CH_2) 30.6 (3x CH_3) 33.2 (CH_2) 33.3 (C) 46.6 (CH) 50.7 (CH_3) 59.2 (C) 65.1 (CH_2) 68.8 (C) 72.0 (CH_2) 76.8 (CH) 121.3 (C) 214.0 (C).

HRMS (EI) *m/z* calcd for $C_{18}H_{31}O_5Si$ [M^+-*t*Bu] 355.1941, found: 355.1903.



(3.159) tert-butyl((6-(tert-butyl)-3a-methoxy-8-((trimethylsilyl)oxy)-1,2,3,3a-tetrahydro-5H-dicyclopenta[b,c]furan-5a(6H)-yl)methoxy)dimethylsilane

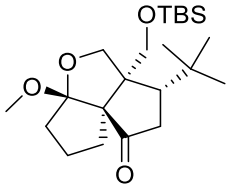
t-BuLi (8.98 mL, 13.9 mmol, 1.7M in pentane) was added to a suspension of CuCN (623mg, 6.96 mmol) in dry THF (23.0 mL) cooled to -78°C. The resulting mixture was kept at -78°C for 15 min followed by 30 min at -45°C (dry ice: acetonitrile). The reaction was then cooled again to -78°C and a solution of enone **3.154** (1.57 g, 4.64 mmol) in THF (5mL) was added dropwise. Next, freshly distilled TMSCl (1.19 mL, 9.28 mmol) was added. The mixture was allowed to warm to -45°C and was stirred for 45 min before quenching with NH_4Cl. The aqueous phase was extracted 3x with ether. The organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (5-10-15% EtOAc:hexanes then another flash at 30-40-50-60 benzene: hexanes to obtain ultra-pure sample) to give vinyl ether **3.159** (1.35 g, 2.88 mmol, 62%) as a clear oil with the stereochemistry found in the natural product.

IR (neat, cm^{-1}) ν_{max}: 2921, 1650, 1463, 1247.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.04 (d, *J*=3.5 Hz, 6 H) 0.19 (s, 9 H) 0.89 (s, 9 H) 0.93 (s, 9 H) 1.53-1.55 (m, 2 H) 1.63-1.76 (m, 2 H) 1.82-1.89 (m, 1 H) 1.96-2.00 (m, 1 H) 2.24 (d, *J*=2.2 Hz, 1 H) 3.24 (s, 3 H) 3.55 (d, *J*=8.0 Hz, 1 H) 3.65 (d, *J*=10.4 Hz, 1 H) 3.85 (d, *J*=10.4 Hz, 1 H) 4.16 (d, *J*=8.0 Hz, 1 H) 4.55 (d, *J*=2.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -5.6 (CH_3) -5.5 (CH_3) 0.3 (3xCH_3) 18.3 (C) 24.3 (CH_2) 25.9 (3x CH_3) 27.4 (CH_2) 29.6 (3x CH_3) 33.8 (C) 34.5 (CH_2) 50.3 (CH) 56.7 (CH_3) 61.1 (CH_2) 61.3 (C) 70.5 (C) 74.9 (CH_2) 103.9 (CH) 118.5 (C) 153.5 (C).

HRMS (EI) *m/z* calcd for $C_{\#\#}H_{\#\#}O_{\#}$ [M^+-Me] 453.2856, found: 453.2881.



6-(tert-butyl)-5a-(((tert-butyldimethylsilyl)oxy)methyl)-3a-methoxyoctahydro-8H-dicyclopenta[b,c]furan-8-one

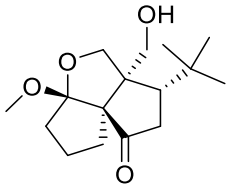
TBAF (0.669 mL, 0.669 mmol, 1 M in THF) was added to a solution of silyl vinyl enol ether **3.159** (0.285 g, 0.608 mmol) in THF (7 mL) at r.t. and fallow-up by TLC showed full conversion of the sm after 15 min. The reaction was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with ether. The organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (10% EtOAc:hexanes) to ketone (0.184 g, 0.463 mmol, 76%) as a clear oil.

IR (neat, cm^{-1}) ν_{max}: 2937, 1735, 1467, 1087, 771.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.00 (s, 3 H) 0.01 (s, 3 H) 0.81 (s, 9 H) 1.03 (s, 9 H) 1.52-1.60 (m, 1H) 1.65-1.78 (m, 2 H) 1.80-1.86 (m, 1 H) 2.00-2.06 (m, 1 H) 2.22 (ddd, *J*=13.9, 9.8, 7.6 Hz, 1 H) 2.36 (dd, *J*=17.8, 8.8 Hz 1 H) 2.43 (dd, *J*=17.8, 12.7 Hz, 1 H) 2.59 (dd, *J*=12.7, 8.8 Hz, 1 H) 3.25 (s, 3 H) 3.50 (d, *J*=10.7 Hz, 1 H) 3.59 (d, *J*=8.7 Hz, 1 H) 4.00 (d, *J*=10.6 Hz, 1 H) 4.17 (d, *J*=8.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm -6.10 (CH_3)-5.7 (CH_3) 17.7 (C) 23.2 (CH_2) 25.7 (3x CH_3) 28.3 (CH_2) 29.6 (3x CH_3) 33.2 (C) 34.3 (CH_2) 41.9 (CH_2) 50.4 (CH) 51.2 (CH_3) 60.8 (C) 63.1 (CH_2) 72.9 (C) 77.6 (CH_2) 121.9 (C) 216.4 (C).

HRMS (EI) *m/z* calcd for $C_{22}H_{40}O_4Si$ [M^+] 396.2696, found: 396.2724.



(3.160) 6-(tert-butyl)-5a-(hydroxymethyl)-3a-methoxyoctahydro-8H-dicyclopenta[b,c]furan-8-one

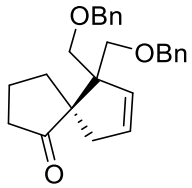
TBAF (0.208 mL, 1 M in THF, 0.208 mmol) was added to a solution of protected alcohol (0.055 g, 0.139 mmol) in THF (1.37 mL) at r.t. and the mixture was allowed to stir o/n. The reaction was quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted 3x with ether. The organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography (10-20-30% EtOAc:hexanes) to free alcohol **3.160** (0.03 g, 0.106 mmol, 77%) as a white crystalline solid.

IR (neat, cm^{-1}) ν_{max}: 2945, 1740, 800.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.05 (s, 9 H) 1.4 (wide s, 1 H) 1.52-1.62 (m, 1 H) 1.70-1.89 (m, 3 H) 2.01-2.07 (m, 1 H) 2.23-2.29 (m, 1 H) 2.35 (dd, *J*=17.9, 9.3 Hz, 1 H) 2.43 (dd, , *J*=18.0, 12.2 Hz, 1 H) 2.56 (dd, *J*=12.2, 9.4 Hz, 1 H) 3.24 (s, 3 H) 3.61 (d, *J*=8.8 Hz, 1 H) 3.66 (d, *J*=11.0 Hz, 1 H) 4.10 (d, *J*=11.2 Hz, 1 H) 4.14 (d, *J*=8.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 23.3 (CH_2) 28.3 (CH_2) 29.4 (3x CH_3) 33.2 (C) 34.3 (CH_2) 41.9 (CH_2) 50.5 (CH) 51.2 (CH_3) 60.5 (C) 63.2 (CH_2) 72.8 (C) 77.7 (CH_2) 122.1 (C) 216.9 (C).

HRMS (EI) *m/z* calcd for $C_{16}H_{26}O_4$ [M^+] 282.1831, found: 282.1841.



(3.138) 6,6-bis((benzyloxy)methyl)spiro[4.4]non-7-en-1-one

Procedure[13]

IR (neat, cm^{-1}) ν_{max}: 2927, 2364, 1726, 1509, 1087.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.59-1.69 (m, 1 H) 1.83-1.93 (m, 2 H) 2.10-2.34 (m, 4 H) 2.55 (dt, *J*=16.5, 2.1 Hz, 1 H) 3.58 (s, 2 H) 3.69 (d, *J*=8.6 Hz, 1 H) 3.72 (d, *J*=8.6 Hz, 1 H) 4.28 (d, *J*=12.0 Hz, 1 H) 4.36 (d, *J*=12.0 Hz, 1 H) 4.45 (d, *J*=12.2 Hz, 1 H) 4.51 (d, *J*=12.2 Hz, 1 H) 5.60 (td, *J*=3.9, 1.9 Hz, 1 H) 5.76 (dt, *J*= 5.3, 2.8 Hz, 1 H) 7.21-7.33 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 20.1 (CH_2) 34.1 (CH_2) 38.3 (CH_2) 44.4 (CH_2) 57.4 (C) 57.6 (C) 70.1 (CH_2) 72.6 (CH_2) 72.9 (CH_2) 73.3 (CH_2) 127.2 (2xCH) 127.35 (CH) 127.36 (CH) 127.4 (2xCH) 128.2 (2xCH) 128.2 (2xCH) 128.8 (CH) 133.9 (CH) 138.5 (C) 138.7 (C) 220.3 (C).

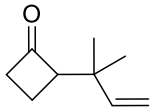
HRMS (EI) *m/z* calcd for $C_{25}H_{28}O_3$ [M^+] 376.2038, found: 376.2092.

5.2.2 One pot α-allylation of ketones by Claisen rearrangement

[13] Same procedure as for **3.148**

General procedure:

Ketone (1.00 ml or 1.00 g) was added to a round bottom flask equipped with a stir bar. Triethoxyformate (1.1 eq. mol) was then added followed by Ethanol 99% (2.00 ml per ml/g of starting material). Amberlyst® 15 (50 mg, 5% per w/w or mL) was added in one portion and the mixture was stirred slowly for 12h[14]. The solution was filtered over a small celite pad (1-2 cm) and the reaction vessel and celite pad are washed with dichloromethane (5-10 mL). The filtrate was equipped with a stir bar and a small distillation apparatus was installed and heated at 110°C to remove any residual ethanol, DCM as well as ethyl formate. Thereafter, the solution was cooled to r.t. and the desired alcohol (1.1 eq.) as well as propionic acid (10% mol) was added. The resulting mixture was heated at 130°C for 2h with the distillation apparatus before transferring the crude into a sealed tube for overnight heating at the appropriate temperature (130°C to 170°C depending on the substrate). The crude was then directly flashed over silica to afford the desired α-allylated adduct.



(3.120o) 2-(2-methylbut-3-en-2-yl)cyclobutan-1-one

Isolated (1.00 g, 7.23 mmol, 54%)

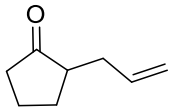
IR (neat, cm^{-1}) ν_{max}: 2966, 1763, 1080, 914, 736.

[14] Most ketals were formed completely after 1h but in order to make the metodology as general as possible all acetals were allowed 12h of stirring.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.05 (s, 3 H) 1.08 (s, 3 H) 1.74-1.83 (m, 1 H) 1.93-2.03 (m, 1 H) 2.69-2.78 (m,1 H) 2.84-2.94 (m, 1 H) 3.18-3.24 (m, 1 H) 4.96 (dd, *J*=8.8, 1.2 Hz, 1 H) 5.00 (d, *J*=1.4 Hz, 1 H) 5.78 (dd, *J*=17.2, 11.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 13.0 (CH_2) 24.1 (CH_3) 24.9 (CH_3) 38.1 (C) 44.3 (CH_2) 69.7 (CH) 112.2 (CH) 144.7 (CH_2) 211.2 (C).

HRMS (EI) *m/z* calcd for $C_9H_{14}O$ [M^+] 138.1045, found: 138.1057.



(3.120e) 2-allylcyclopentan-1-one

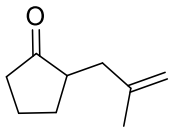
Isolated (0.85 g, 6.88 mmol, 61%)

IR (neat, cm^{-1}) ν_{max}: 2964, 2330, 1735, 1155, 912.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.46-1.57 (m, 1 H) 1.67-1.79 (m, 1 H) 1.91-2.18 (m,5 H) 2.23-2.30 (m, 1 H) 2.42-2.48 (m, 1 H) 4.95-5.03 (m, 2 H) 5.71 (m, *J*=17.0, 10.1, 6.9, 6.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 20.5 (CH_2) 28.9 (CH_2) 33.8 (CH_2) 38.0 (CH_2) 48.5 (CH) 116.3 (CH_2) 135.8 (CH) 220.3 (C).

HRMS (EI) *m/z* calcd for $C_8H_{12}O$ [M^+] 124.0888, found: 124.0876.



(3.120f) 2-(2-methylallyl)cyclopentan-1-one

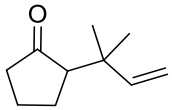
Isolated (0.79 g, 5.73 mmol, 53%)

IR (neat, cm^{-1}) ν_{max}: 2964, 1735, 1155, 887, 730.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.42-1.49 (m, 1 H) 1.63 (s, 3 H) 1.69-1.75 (m, 1 H) 1.82 (dd, *J*=14.3, 9.6 Hz, 1 H) 1.91-1.97 (m, 1 H) 2.02-2.16 (m, 3 H) 2.21-2.27 (m, 1 H) 2.44 (dd, *J*=14.2, 3.2 Hz, 1 H) 4.62 (s, 1 H) 4.68 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 20.4 (CH_2) 21.9 (CH_3) 29.2 (CH_2) 37.9 (CH_2) 37.9 (CH_2) 47.2 (CH) 111.5 (CH_2) 143.3 (C) 220.6 (C).

HRMS (EI) *m/z* calcd for $C_9H_{14}O$ [M^+] 138.1045, found: 138.1041.



(3.105) 2-(2-methylbut-3-en-2-yl)cyclopentan-1-one

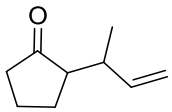
Isolated (1.14 g, 7.45 mmol, 66%)

IR (neat, cm^{-1}) ν_{max}: 2960, 1731, 1147, 910, 748.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.09 (s, 3 H) 1.13 (s, 3 H) 1.55-1.72 (m, 2 H) 1.88-2.09 (m, 4 H) 2.20-2.28 (m, 1 H) 4.93 (dd, *J*=7.9, 1.3 Hz, 1 H) 4.96 (s, 1 H) 5.84 (dd, *J*=17.0, 11.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 20.2 (CH_2) 24.5 (CH_3) 25.5 (CH_3) 26.4 (CH_2) 38.5 (C) 40.2 (CH_2) 57.1 (CH) 111.6 (CH_2) 145.7 (CH) 219.7 (C).

HRMS (EI) *m/z* calcd for $C_{10}H_{16}O$ [M^+] 152.1201, found: 152.1189.



(3.120g) 2-(but-3-en-2-yl)cyclopentan-1-one

Isolated (1.01 g, 7.31 mmol, 65%)

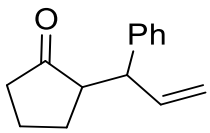
dr 1:0.9

IR (neat, cm^{-1}) ν_{max}: 2962, 1731, 1149, 910.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.89 (d, *J*=6.9 Hz, 3 H, minor dia) 1.05 (d, *J*=6.9 Hz, 3 H, major dia) 1.60-1.73 (m, 4 H) 1.89-2.13 (m, 6 H) 2.12-2.18 (m, 1 H) 2.20-2.29 (m, 2 H) 2.63-2.71 (m, 2 H) 4.93-4.99 (m, 4 H) 5.60 (ddd, *J*=17.1, 10.4, 7.2 Hz, 1 H, major dia) 5.77 (ddd, *J*=17.2, 10.3, 7.0 Hz, 1 H, minor dia).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.0 (CH_3, minor) 17.8 (CH_3, major) 20.5 (2xCH_2) 24.6 (CH_2, minor) 25.0 (CH_2,major) 36.3 (CH, major) 36.7 (CH, minor) 38.9 (CH_2, major) 39.0 (CH_2, minor) 53.4 (CH, minor) 54.0 (CH, major) 113.4 (CH_2,minor) 114.8 (CH_2, major) 140.1 (CH, major) 142.1 (CH, minor) 220.1 (C) 220.2 (C).

HRMS (EI) *m/z* calcd for $C_9H_{14}O$ [M^+] 138.1045, found: 138.10520.



(3.120l) 2-(1-phenylallyl)cyclopentan-1-one

Isolated (1.87 g, 9.34 mmol, 83%)

dr 1:1

Highest Rf diastereomer

IR (neat, cm^{-1}) ν_{max}: 2952, 1735, 916, 750, 700.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.47-1.57 (m, 1 H) 1.64-1.78 (m, 2 H) 1.87 (ddd, *J*=18.6, 10.0, 8.6 Hz, 1 H) 1.97-2.05 (m, 1 H) 2.19-2.26 (m, 1 H) 2.53-2.60 (m, 1 H) 3.86 (t, *J*=6.1 Hz, 1 H) 5.07 (dt, *J*=17.2, 1.4 Hz, 1 H) 5.13 (dt, *J*=10.4, 1.4 Hz, 1 H) 6.18 (ddd, *J*=17.2, 10.3, 7.0 Hz, 1 H) 7.13-7.15 (m, 2 H) 7.16-7.20 (m, 1 H) 7.24-7.28 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 20.5 (CH_2) 26.4 (CH_2) 38.7 (CH_2) 48.3 (CH) 53.1 (CH) 115.1 (CH_2) 126.5 (CH) 128.3 (2xCH) 128.8 (2xCH) 139.7 (CH) 141.2 (C) 219.6 (C).

HRMS (EI) *m/z* calcd for $C_{14}H_{16}O$ [M^+] 200.1201, found: 200.1207.

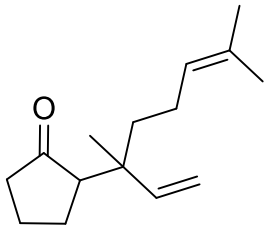
Lowest Rf diastereomer

IR (neat, cm^{-1}) ν_{max}: 2964, 1735, 912, 682.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.64-1.76 (m, 1 H) 1.83-2.15 (m, 4 H) 2.27-2.34 (m, 1 H) 2.45-2.51 (m, 1 H) 3.92 (dd, *J*=8.2, 4.1 Hz, 1 H) 5.04 (dd, *J*=17.0, 0.9 Hz, 1 H) 5.09 (dd, *J*=9.5, 0.7 Hz, 1 H) 5.95-6.04 (m, 1 H) 7.18-7.24 (m, 3 H) 7.27-7.31 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 20.6 (CH_2) 25.7 (CH_2) 38.9 (CH_2) 48.6 (CH) 54.6 (CH) 117.4 (CH_2) 126.4 (CH) 127.9 (2xCH) 128.5 (2xCH) 137.3 (CH) 142.6 (C) 219.1 (C)

HRMS (EI) *m/z* calcd for $C_{14}H_{16}O$ [M^+] 200.1201, found: 200.1189.



(3.120k) 2-(3,7-dimethylocta-1,6-dien-3-yl)cyclopentan-1-one

Isolated with nerol as alcohol (1.50 g, 6.81 mmol, 61%) and with geraniol as alcohol (2.00 g, 9.08 mmol, 81%)

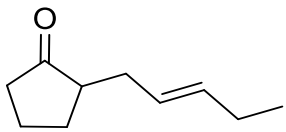
Major diastereomer (was characterize in a mixture of 1/0.25 d.r. ratio)

IR (neat, cm^{-1}) ν_{max}: 2964, 1731, 1147, 910, 750.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.11 (s, 3 H) 1.39 (ddd, *J*=13.4, 10.4, 6.4 Hz, 1 H) 1.57 (s, 3 H) 1.61-1.71 (m, 3 H) 1.66 (s, 3H) 1.85-2.06 (m, 6 H) 2.20-2.27 (m, 1 H) 4.92 (dd, *J*=17.4, 1.4 Hz, 1 H) 5.02 (dd, *J*=10.8, 1.4 Hz, 1 H) 5.08 (m, 1 H) 5.77 (dd, *J*=17.5, 10.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 17.6 (CH_3) 19.7 (CH_3) 20.3 (CH_2) 22.6 (CH_2) 25.7 (CH_3) 26.2 (CH_2) 38.5 (CH_2) 40.5 (CH_2) 41.6 (C) 55.8 (CH) 112.9 (CH_2) 124.7 (CH) 131.2 (C) 144.1 (CH) 219.9 (C).

HRMS (EI) *m/z* calcd for $C_{15}H_{24}O$ [M^+-Me] 206.1671, found: 206.1611



(3.120h) (E)-2-(pent-2-en-1-yl)cyclopentan-1-one [jaminone B]

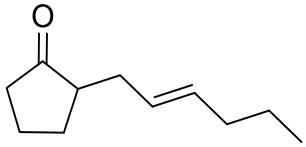
Isolated (1.08 g, 7.07 mmol, 63%)

IR (neat, cm^{-1}) ν_{max}: 2960, 1735, 1153, 956, 750.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.91 (t, *J*=7.5 Hz, 3 H) 1.48-1.57 (m, 1 H) 1.66-1.78 (m, 1 H) 1.9-2.15 (m, 7 H) 2.20-2.28 (m, 1 H) 2.34-2.40 (m, 1 H) 5.25-5.32 (m, 1 H) 5.42-5.48 (m, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 13.7 (CH_3) 20.6 (CH_2) 25.4 (CH_2) 28.8 (CH_2) 32.5 (CH_2) 38.2 (CH_2) 49.0 (CH) 125.9 (CH) 134.1 (CH) 220.7 (C)

HRMS (EI) *m/z* calcd for $C_{10}H_{16}O$ [M^+] 152.1201, found: 152.1190



(3.120i) (E)-2-(hex-2-en-1-yl)cyclopentan-1-one

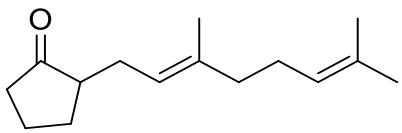
Isolated (1.36 g, 8.18 mmol, 73%)

IR (neat, cm^{-1}) ν_{max}: 2956, 1737, 968, 738.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.84 (t, *J*=7.3 Hz, 3 H) 1.32 (sext., *J*=7.3 Hz, 2 H) 1.52-1.59 (m, 1 H) 1.67-1.79 (m, 1 H) 1.89-2.00 (m, 4 H) 2.03-2.16 (m, 3 H) 2.22-2.29 (m, 1 H) 2.36-5.42 (m, 1 H) 5.26-5.33 (m, 1 H) 5.38-5.45 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 13.5 (CH_3) 20.6 (CH_2) 22.5 (CH_2) 28.8 (CH_2) 32.6 (CH_2) 34.5 (CH_2) 38.2 (CH_2) 49.0 (C) 127.1 (C) 132.4 (C) 220.8 (C)

HRMS (EI) *m/z* calcd for $C_{11}H_{18}O$ [M^+] 166.1358, found: 166.1377



(3.120m) (*E*)-2-(3,7-dimethylocta-2,6-dien-1-yl)cyclopentan-1-one [Apritone]

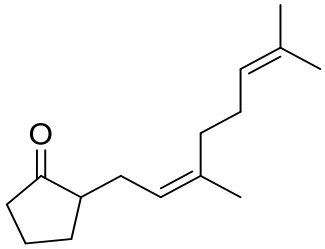
Isolated (0.98 g, 4.03 mmol, 47%) as a mixture of isomers

IR (neat, cm^{-1}) ν_{max}: 2962, 1737, 1151, 750.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.49-1.57 (m, 1 H) 1.59 (d, *J*=4.1 Hz, 3 H) 1.66 (s, 3 H) 1.68 (d, *J*=1.2 Hz, 3 H) 1.71-1.81 (m, 1 H) 1.93-2.19 (m, 9 H) 2.25-2.32 (m, 1 H) 2.39-2.44 (m, 1 H) 5.05-5.09 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 17.6 (CH_3) 20.7 (CH_2) 23.4 (CH_3) 25.7 (CH_3) 26.5 (CH_2) 27.7 (CH_2) 29.1 (CH_2) 31.9 (CH_2) 38.2 (CH_2) 49.5 (CH) 122.2 (CH) 124.2 (CH) 131.6 (C) 137.0 (C) 221.1 (C).

HRMS (EI) *m/z* calcd for $C_{15}H_{24}O$ [M^+] 220.1827, found: 220.1826.



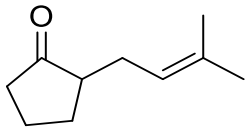
(3.120m) (*Z*)-2-(3,7-dimethylocta-2,6-dien-1-yl)cyclopentan-1-one

IR (neat, cm^{-1}) ν_{max}: 2911, 1737, 1151, 750.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.50-1.57 (m, 1 H) 1.59 (s, 6 H) 1.66 (d, *J*=0.8 Hz, 3 H) 1.71-1.80 (m, 1 H) 1.93-2.16 (m, 9 H) 2.25-2.32 (m, 1 H) 2.37-2.43 (m, 1 H) 5.04-5.09 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 16.1 (CH_3) 17.7 (CH_3) 20.7 (CH_2) 25.7 (CH_3) 26.6 (CH_2) 27.8 (CH_2) 28.9 (CH_2) 38.3 (CH_2) 39.7 (CH_2) 49.4 (CH) 121.4 (CH) 124.2 (CH) 131.4 (C) 136.9 (C) 221.1 (C).

HRMS (EI) *m/z* calcd for $C_{15}H_{24}O$ [M^+] 220.1827, found: 220.1837



(3.120j) 2-(3-methylbut-2-en-1-yl)cyclopentan-1-one

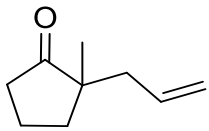
Isolated (0.614 g, 4.03 mmol, 36%)

IR (neat, cm^{-1}) ν_{max}: 2964, 1735, 1153.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.50-1.56 (m, 1 H) 1.59 (s, 3 H) 1.67 (s, 3 H) 1.70-1.80 (m, 1 H) 1.92-2.18 (m, 4 H) 2.28(ddt, *J*=18.5, 8.5, 1.5 Hz, 1 H) 2.36-2.41 (m, 1 H) 5.06 (tt, *J*=7.3, 1.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 17.7 (CH_3) 20.7 (CH_2) 25.7 (CH_3) 27.9 (CH_2) 29.0 (CH_2) 38.2 (CH_2) 49.4 (CH) 121.4 (CH) 133.3 (C) 221.1 (C).

HRMS (EI) *m/z* calcd for $C_{10}H_{16}O$ [M^+] 152.1201, found: 152.1203.



(3.120y) 2-allyl-2-methylcyclopentan-1-one

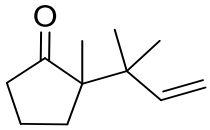
Isolated (1.20 g, 8.69 mmol, 93%) as 1/0.23 mixture of isomers in favor of the most substituted isomers

IR (neat, cm^{-1}) ν_{max}: 2960, 1735, 914, 748.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.97 (s, 3 H) 1.61-1.68 (m, 1 H) 1.78-1.94 (m, 3 H) 2.04-2.30 (m, 4 H) 4.99-5.04 (m, 2 H) 5.61-5.71 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 18.6 (CH_3) 21.8 (CH_2) 35.0 (CH_2) 37.6 (CH_2) 40.9 (CH_2) 48.1 (C) 118.1 (CH_2) 133.8 (CH) 223.0 (C).

HRMS (EI) *m/z* calcd for $C_9H_{14}O$ [M^+] 166.1358, found: 166.1377



(3.120z) 2-methyl-2-(2-methylbut-3-en-2-yl)cyclopentan-1-one

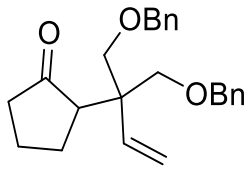
Isolated (1.21 g, 7.28 mmol, 78%)

IR (neat, cm^{-1}) ν_{max}: 2966, 1731, 1055, 912, 750.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.94 (s, 3 H) 0.99 (s, 3 H) 1.02 (s, 3 H) 1.51-1.56 (m, 1 H) 1.60-1.71 (m, 1 H) 1.80-1.88 (m, 1 H) 1.99-2.10 (m, 2 H) 2.19-2.26 (m, 1 H) 4.89-4.97 (m, 2 H) 5.90 (dd, *J*=17.4, 11.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 18.6 (CH_3) 18.7 (CH_2) 22.1 (CH_3) 22.2 (CH_3) 33.7 (CH_2) 40.3 (CH_2) 40.9 (C) 52.4 (C) 112.3 (CH_2) 145.0 (CH) 223.1 (C).

HRMS (EI) *m/z* calcd for $C_{11}H_{18}O$ [M^+] 166.1358, found: 166.1377



(3.120n) 2-(1-(benzyloxy)-2-((benzyloxy)methyl)but-3-en-2-yl)cyclopentan-1-one

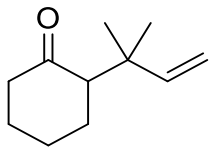
Isolated (0.65 g, 1.79 mmol, 51%)

IR (neat, cm^{-1}) ν_{max}: 2968, 1735, 740.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.58-1.69 (m, 1 H) 1.76-1.88 (m, 1 H) 1.90-1.95 (m, 1 H) 1.97-2.07 (m, 2 H) 2.20 (ddd, *J*=17.8, 7.8, 1.5 Hz, 1 H) 2.39 (ddd, *J*=11.3, 8.3, 1.0 Hz, 1 H) 3.55 (d, *J*=8.8 Hz, 1 H) 3.70 (d, *J*=9.0 Hz, 1 H) 3.81 (d, *J*=8.8 Hz, 1 H) 3.92 (d, *J*=8.8 Hz, 1 H) 4.48-4.55 (m, 4 H) 5.05 (dd, *J*=17.8, 1.2 Hz, 1 H) 5.16 (dd, *J*=11.3, 1.1 Hz, 1 H) 5.77 (dd, *J*=17.9, 11.3 Hz, 1 H) 7.24-7.33 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 13C NMR (101 MHz, CHLOROFORM-D) δ ppm 20.7 (CH_2) 25.5 (CH_2) 40.0 (CH_2) 47.3 (C) 50.5 (CH) 70.8 (CH_2) 71.1 (CH_2) 73.2 (CH_2) 73.3 (CH_2) 115.6 (CH_2) 127.27 (CH) 127.33 (2xCH) 127.36 (CH) 127.39 (2xCH) 128.2 (2xCH) 128.2 (2xCH) 138.59 (C) 138.60 (CH) 138.7 (C) 219.5 (C).

HRMS (EI) *m/z* calcd for $C_{24}H_{28}O_3$ [M^+-Bn] 273.1491, found: 273.1510.



(3.120p) 2-(2-methylbut-3-en-2-yl)cyclohexan-1-one

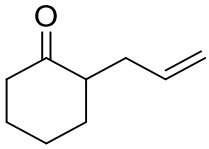
Isolated (1.48 g, 8.90 mmol, 92%)

IR (neat, cm^{-1}) ν_{max}: 2933, 1708, 1124, 910, 748.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.10 (d, *J*=8.2 Hz, 6 H) 1.42 (qd, *J*=12.6, 3.3 Hz, 1 H) 1.53-1.69 (m, 2 H) 1.82-1.88 (m, 1 H) 1.99-2.05 (m, 1 H) 2.07-2.13 (m, 1 H) 2.20-2.29 (m, 3 H) 4.90 (dd, *J*=9.3, 1.3 Hz, 1 H) 4.93 (d, *J*=1.4 Hz, 1 H) 5.95 (dd, *J*=17.4, 11.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 23.6 (CH_3) 25.4 (CH_3) 25.9 (CH_2) 28.6 (CH_2) 30.1 (CH_2) 38.0 (C) 44.1 (CH_2) 59.5 (CH) 110.9 (CH_2) 147.3 (CH) 212.2 (C).

HRMS (EI) *m/z* calcd for $C_{11}H_{18}O$ [M^+] 166.1358, found: 166.1364



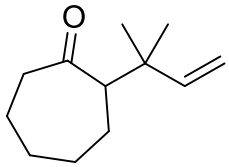
2-allylcyclohexan-1-one

IR (neat, cm^{-1}) ν_{max}: 2927, 1708, 910.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.26 (m, 1 H) 1.55-1.66 (m, 2 H) 1.79-1.84 (d, 1 H) 1.90-2.11 (m, 3 H) 2.22-2.38 (m, 3 H) 2.46-2.52 (m, 1 H) 4.94-4.99 (m, 2 H) 5.73 (dddd, *J*=17.1, 10.0, 7.7, 6.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 24.9 (CH_2) 27.8 (CH_2) 33.3 (CH_2) 33.7 (CH_2) 41.9 (CH_2) 50.2 (CH) 116.1 (CH_2) 136.4 (CH) 212.3 (C)

HRMS (EI) *m/z* calcd for $C_9H_{14}O$ [M^+] 138.1045, found: 138.04884.



(3.120q) 2-(2-methylbut-3-en-2-yl)cycloheptan-1-one

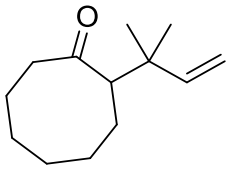
Isolated (1.17 g, 6.49 mmol, 77%)

IR (neat, cm^{-1}) ν_{max}: 2933, 1697, 910, 750.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.94 (s, 3 H) 0.96 (s, 3 H) 0.99-1.06 (m, 1 H) 1.11-1.39 (m, 3 H) 1.73-1.85 (m, 4 H) 2.16-2.24 (m, 2 H) 2.28 (td, *J*=12.3, 3.5 Hz, 1 H) 4.82 (dd, *J*=17.4, 1.2 Hz, 1 H) 4.87 (dd, *J*=10.8, 1.2 Hz, 1 H) 5.73 (dd, *J*=17.4, 10.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 24.0 (CH_3) 25.5 (CH_3) 25.7 (CH_2) 26.2 (CH_2) 27.9 (CH_2) 29.5 (CH_2) 39.1 (C) 43.7 (CH_2) 61.5 (CH) 111.5 (CH_2) 145.7 (CH) 215.8 (C)

HRMS (EI) *m/z* calcd for $C_{12}H_{20}O$ [M^+] 180.1514, found: 180.1504.



(3.120r) 2-(2-methylbut-3-en-2-yl)cyclooctan-1-one

Isolated (1.18 g, 6.05 mmol, 76%)

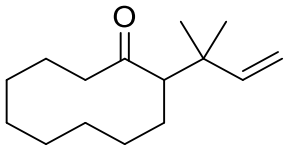
IR (neat, cm^{-1}) ν_{max}: 2923, 1703, 910, 750.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.01 (d, *J*=9.6 Hz, 6 H) 1.27-1.43 (m, 4 H) 1.57-1.71 (m, 4 H) 1.74-1.81 (m, 1 H) 1.87-1.98 (m, 1 H) 2.21 (ddd, *J*=13.3, 5.9, 3.5 Hz, 1 H) 2.39 (td, *J*=12.8, 3.6

Hz, 1 H) 2.46 (dd, *J*=11.4, 2.9 Hz, 1 H) 4.90 (dd, *J*=17.4, 1.0 Hz, 1 H) 4.95 (dd, *J*=10.8, 1.2 Hz, 1 H) 5.82 (dd, *J*=17.4, 10.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 23.8 (CH_3) 25.0 (CH_2) 25.7 (CH_3) 25.8 (CH_2) 26.7 (CH_2) 27.6 (CH_2) 28.2 (CH_2) 39.3 (C) 44.6 (CH_2) 58.9 (CH) 111.7 (CH_2) 146.4 (CH) 220.0 (C).

HRMS (EI) *m/z* calcd for $C_{13}H_{22}O$ [M^+] 194.1671, found: 194.1666.



(3.120s) 2-(2-methylbut-3-en-2-yl)cyclodecan-1-one

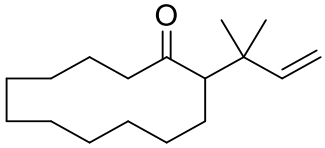
Isolated (1.03 g, 4.63 mmol, 75%)

IR (neat, cm^{-1}) ν_{max}: 3914, 1699, 748.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.98 (s, 3 H) 0.99 (s,3H) 1.19-1.41 (m, 8 H) 1.52-1.60 (m, 3 H) 1.63-1.69 (m, 1 H) 1.71-1.86 (m, 2 H) 2.39 (ddd, *J*=15.5, 8.4, 3.1 Hz, 1 H) 2.53-2.62 (m, 2 H) 4.91 (dd, *J*=17.4, 1.2 Hz, 1 H) 4.96 (dd, *J*=10.7, 1.3 Hz, 1 H) 5.80 (dd, *J*=17.4, 10.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 23.9 (CH_2) 24.0 (CH_3) 24.7 (CH_2) 24.8 (CH_3) 25.1 (CH_2) 25.2 (CH_2) 25.6 (CH_2) 25.8 (CH_2) 26.9 (CH_2) 39.9 (C) 46.2 (CH_2) 62.7 (CH) 111.7 (CH_2) 146.4 (CH) 217.2 (C).

HRMS (EI) *m/z* calcd for $C_{15}H_{26}O$ [M^+] 222.1984, found: 222.1980



(3.120t) 2-(2-methylbut-3-en-2-yl)cyclododecan-1-one

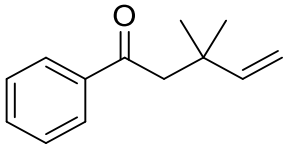
Isolated (1.36 g, 5.43 mmol, 99%)

IR (neat, cm^{-1}) ν_{max}: 2931, 1699, 910, 748.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.95 (s, 3 H) 0.96 (s, 3 H) 1.00-1.06 (m, 1 H) 1.11-1.41 (m, 14 H) 1.52-1.60 (m, 1 H) 1.64-1.73 (m, 2 H) 2.32 (ddd, *J*=16.7, 7.9, 3.4 Hz, 1 H) 2.39-2.49 (m, 2 H) 4.84-4.91 (m, 2 H) 5.77 (dd, *J*=17.3, 10.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 22.3 (CH_2) 22.4 (CH_2) 24.54 (CH_3) 24.56 (CH_2) 24.7 (CH_2) 25.3 (CH_3) 25.4 (2x CH_2) 26.0 (CH_2) 26.5 (CH_2) 26.8 (CH_2) 38.7 (C) 41.6 (CH_2) 61.8 (CH) 111.5 (CH_2) 146.3 (CH) 214.8 (C).

HRMS (EI) *m/z* calcd for $C_{17}H_{30}O$ [M^+] 250.2297, found: 250.2332.



(3.120a) 3,3-dimethyl-1-phenylpent-4-en-1-one

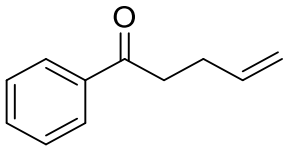
Isolated (1.21 g, 6.41 mmol, 75%)

IR (neat, cm^{-1}) ν_{max}: 2956, 1674, 910, 688.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.17 (s, 6 H) 2.95 (s, 2 H) 4.90 (d, *J*=10.6 Hz, 1 H) 4.95 (d, *J*=17.4 Hz, 1 H) 5.96 (dd, *J*=17.4, 10.8 Hz, 1 H) 7.42 (t, *J*=7.6 Hz, 2 H) 7.52 (t, *J*=7.3 Hz, 1 H) 7.91 (dd, *J*=8.0, 1.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 27.2 (2x CH_3) 36.6 (C) 49.1 (CH_2) 110.5 (CH_2) 128.2 (2xCH) 128.4 (2xCH) 132.7 (CH) 138.3 (C) 147.3 (CH) 199.3 (C).

HRMS (EI) *m/z* calcd for $C_{13}H_{16}O$ [M^+] 188.1201, found: 188.1238.



(3.120b) 1-phenylpent-4-en-1-one

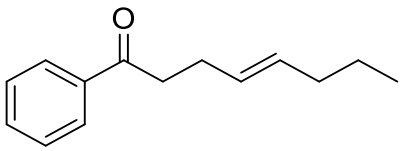
Isolated (1.27 g, 7.92 mmol, 92%)

IR (neat, cm^{-1}) ν_{max}: 3057, 2337, 1683, 1207, 910, 744.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 2.28 (q, *J*=7.0 Hz, 2 H) 2.80 (t, *J*=7.3 Hz, 2 H) 4.82 (dt, *J*=10.2, 0.6 Hz, 1 H) 4.90 (dd, *J*=17.0, 1.6 Hz, 1 H) 5.71 (dddd, *J*=17.0, 10.3, 6.6, 6.6 Hz, 1 H) 7.20 (t, *J*=7.5 Hz, 2 H) 7.30 (t, *J*=7.3 Hz, 1 H) 7.74 (d, *J*=7.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 27.4 (CH_2) 36.9 (CH_2) 114.5 (CH_2) 127.3 (2xCH) 127.9 (2xCH) 132.2 (CH) 136.3 (C) 136.8 (CH) 198.1 (C).

HRMS (EI) *m/z* calcd for $C_{11}H_{12}O$ [M^+] 160.0888, found: 160.0873.



(3.120d) (E)-1-phenyloct-4-en-1-one

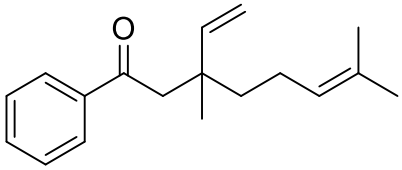
Isolated (1.73 g, 8.55 mmol, 99%)

IR (neat, cm^{-1}) ν_{max}: 2956, 2339, 1685, 968, 742.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.86 (t, *J*=7.3 Hz, 3 H) 1.34 (sext., *J*=7.3 Hz, 2 H) 1.92-1.96 (m, 2 H) 2.39-2.43 (m, 2 H) 3.00 (t, *J*=7.4 Hz, 2 H) 5.46 (t, *J*=3.6 Hz, 2 H) 7.42 (t, *J*=7.6 Hz, 2 H) 7.51 (t, *J*=7.3 Hz, 1 H) 7.93 (d, *J*=7.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 13.5 (CH_3) 22.4 (CH_2) 27.1 (CH_2) 34.5 (CH_2) 38.5 (CH_2) 127.9 (2xCH) 128.4 (2xCH) 128.6 (CH) 131.2 (CH) 132.8 (CH) 136.9 (C) 199.5 (C).

HRMS (EI) *m/z* calcd for $C_{14}H_{18}O$ [M^+] 202.1358, found: 202.1334.



(3.120c) 3,7-dimethyl-1-phenyl-3-vinyloct-6-en-1-one

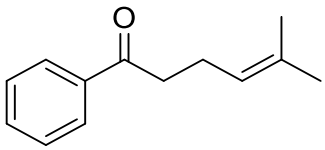
Isolated with nerol as alcohol (1.65 g, 6.45 mmol, 75%) and with geraniol as alcohol (2.18 g, 8.49 mmol, 99%)

IR (neat, cm^{-1}) ν_{max}: 2958, 2356, 1687, 756.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.16 (s, 3 H) 1.50-1.56 (m, 2 H) 1.56 (s, 3H) 1.64 (d, *J*=1.0 Hz, 3 H) 1.91 (q, *J*=8.2 Hz, 2 H) 2.94-3.02 (m, 2 H) 4.94 (dd, *J*=17.5, 1.1 Hz, 1 H) 4.58 (dd, *J*=10.9, 1.1 Hz, 1 H) 5.04-5.09 (m, *J*=7.1, 7.1, 2.7, 1.3, 1.3 Hz, 1 H) 5.88 (dd, *J*=17.4, 10.8 Hz, 1 H) 7.41-7.45 (m, 2 H) 7.50-7.55 (m, 1 H) 7.89-7.91 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 17.6 (CH_3) 23.0 (CH_2) 23.4 (CH_3) 25.6 (CH_3) 39.8 (C) 40.7 (CH_2) 47.5 (CH_2) 111.9 (CH_2) 124.6 (CH) 128.2 (2xCH) 128.4 (2xCH) 131.3 (C) 132.7 (CH) 138.5 (C) 146.1 (CH) 199.4 (C).

HRMS (EI) *m/z* calcd for $C_{18}H_{24}O$ [M^+] 256.1827, found: 256.1838.



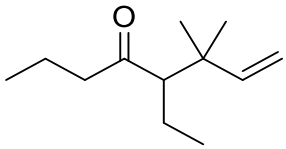
5-methyl-1-phenylhex-4-en-1-one

IR (neat, cm^{-1}) ν_{max}: 2972, 1657, 1445, 1049, 688.

^1H NMR, (400 MHz, $CDCl_3$) δ ppm 1.62 (s, 3 H) 1.68 (s, 3 H) 2.41 (q, *J*=7.3 Hz, 2 H) 2.98 (t, *J*=7.3 Hz, 2 H) 5.16 (tt, *J*=7.2, 1.4 Hz, 1 H) 7.42-7.46 (m, 2 H) 7.51-7.55 (m, 1 H) 7.93-7.95 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 17.6 (CH_3) 22.9 (CH_2) 25.6 (CH_3) 38.7 (CH_2) 122.9 (CH) 128.0 (2xCH) 128.5 (2xCH) 132.7 (C) 132.8 (CH) 137.0 (C) 200.0 (C).

HRMS (EI) *m/z* calcd for $C_{13}H_{16}O$ [M^+] 188.1201, found: 188.1191.



(3.120u) 5-ethyl-6,6-dimethyloct-7-en-4-one

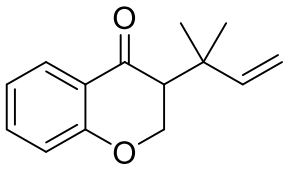
Isolated (0.90 g, 4.92 mmol, 69%)

IR (neat, cm^{-1}) ν_{max}: 2964, 2360, 1708, 912, 750.

^1H NMR, (400 MHz, $CDCl_3$) δ ppm 0.73 (t, *J*=7.4 Hz, 3 H) 0.85 (t, *J*=7.3 Hz, 3 H) 0.96 (s, 3 H) 0.97 (s, 3 H) 1.33-1.42 (m, 1 H) 1.45-1.63 (m, 3 H) 2.21-2.30 (m, 2 H) 2.41-2.49 (m, 1 H) 4.84-4.92 (m, 2 H) 5.78 (dd, *J*=17.4, 10.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 12.9 (CH_3) 13.7 (CH_3) 16.3 (CH_2) 21.2 (CH_2) 24.0 (CH_3) 24.9 (CH_3) 39.3 (C) 49.4 (CH_2) 62.4 (CH) 111.4 (CH_2) 146.5 (CH) 214.6 (C).

HRMS (EI) *m/z* calcd for $C_{12}H_{22}O$ [M^+] 182.1671, found: 182.1665.



(3.120v) 3-(2-methylbut-3-en-2-yl)chroman-4-one

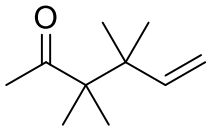
Isolated (1.07 g, 4.95 mmol, 74%)

IR (neat, cm^{-1}) ν_{max}: 2964, 2362, 1683, 1604, 1479, 918, 759.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.12 (s, 3 H) 1.17 (s, 3 H) 2.36 (t, *J*=4.8 Hz, 1 H) 4.42 (dd, *J*=12.1, 4.4 Hz, 1 H) 4.52 (dd, *J*=12.0, 5.1 Hz, 1 H) 4.96 (td, *J*=9.2, 1.0 Hz, 2 H) 5.84 (dd, *J*=17.4, 10.8 Hz, 1 H) 6.84 (dd, *J*=8.2, 0.6 Hz, 1 H) 6.90-6.94 (m, 1 H) 7.37 (ddd, *J*=8.5, 7.0, 1.8 Hz, 1 H) 7.82 (dd, *J*=7.9, 1.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 23.3 (CH_3) 26.8 (CH_3) 38.7 (C) 53.8 (CH) 68.9 (CH_2) 112.2 (CH_2) 117.3 (CH) 121.0 (CH) 122.0 (C) 126.9 (CH) 135.4 (CH) 145.5 (CH) 161.1 (C) 192.9 (C).

HRMS (EI) *m/z* calcd for $C_{14}H_{16}O_2$ [M^+] 216.1150, found: 216.1160.



(3.120Ad) 3,3,4,4-tetramethylhex-5-en-2-one

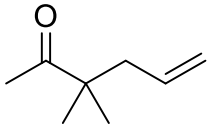
Isolated (0.94 g, 6.07 mmol, 65%)

IR (neat, cm^{-1}) ν_{max}: 2955, 1697, 1108, 914, 750.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.95 (s, 6 H) 1.05 (s, 6 H) 2.06 (s, 3 H) 4.90 (dd, *J*=17.4, 1.4 Hz, 1 H) 4.96 (dd, *J*=10.9, 1.3 Hz, 1 H) 5.86 (dd, *J*=17.4, 10.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 21.3 (2x CH_3) 22.6 (2x CH_3) 29.2 (CH_3) 41.0 (C) 52.2 (C) 112.4 (CH_2) 144.8 (CH) 214.0 (C).

HRMS (EI) *m/z* calcd for $C_9H_{15}O$ [M^+-Me] 139.1123, found: 139.1138.



(3.120Ac) 3,3-dimethylhex-5-en-2-one

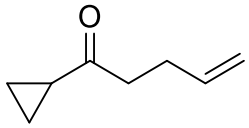
Isolated (1.10 g, 8.72 mmol, 93%) as 1/0.18 mixture of isomers in favor of the most substituted isomer

IR (neat, cm^{-1}) ν_{max}: 2968, 1704, 916, 748.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.11 (s, 6 H) 2.12 (s, 3 H) 2.25 (d, *J*= 7.5 Hz, 1H) 5.01-5.03 (m, 1 H) 5.06 (s, 1 H) 5.62-5.73 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 24.1 (2x CH_3) 25.3 (CH_3) 43.9 (CH_2) 47.7 (C) 117.9 (CH_2) 134.0 (CH) 213.4 (C).

HRMS (EI) *m/z* calcd for $C_8H_{14}O$ [M^+] 126.1045, found: 126.1021.



(3.120Ae) 1-cyclopropylpent-4-en-1-one

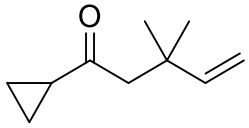
Isolated (1.05 g, 8.46 mmol, 78%)

IR (neat, cm^{-1}) ν_{max}: 3005, 1739, 1699, 1388, 1240, 914, 732.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.82-0.87 (m, 2 H) 0.98-1.02 (m, 2 H) 1.88-1.95 (m, 1 H) 2.32-2.37 (m, 2 H) 2.64 (t, *J*=7.3 Hz, 2 H) 4.96 (dq, *J*=10.2, 1.4 Hz, 1 H) 5.03 (dq, *J*=17.1, 1.7 Hz, 1 H) 5.81 (dddd, *J*=17.0, 10.3, 6.5, 6.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 10.6 (2x CH_2) 20.4 (CH) 27.9 (CH_2) 42.5 (CH_2) 115.1 (CH_2) 137.2 (CH) 210.1 (C).

HRMS (EI) *m/z* calcd for $C_8H_{12}O$ [M^+] 124.0888, too volatile to find mass.



(3.120Af) 1-cyclopropyl-3,3-dimethylpent-4-en-1-one

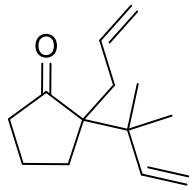
Isolated (0.98 g, 6.46 mmol, 60%) as 1/0.36 mixture of isomers in favor of the less substituted isomer

IR (neat, cm^{-1}) ν_{max}: 2953, 1691, 1380, 1076, 914.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 0.79-0.84 (m, 2 H) 0.96-1.00 (m, 2 H) 1.12 (s, 6 H) 1.85-1.92 (m, 1 H) 2.54 (s, 2 H) 4.92 (dd, *J*=6.8, 1.1 Hz, 1 H) 4.96 (dd, *J*=13.4, 1.1 Hz, 1 H) 5.93 (dd, *J*=17.4, 10.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 11.2 (2x CH_2) 22.1 (CH) 27.1 (2x CH_3) 36.5 (C) 55.7 (CH_2) 110.6 (CH_2) 147.4 (CH) 210.0 (C).

HRMS (EI) *m/z* calcd for $C_{10}H_{16}O$ [M^+] 152.1201, found: 152.1206.



(3.120Ag) 2-allyl-2-(2-methylbut-3-en-2-yl)cyclopentan-1-one

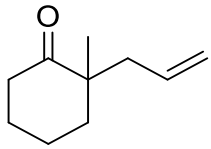
Isolated (2.55 g, 13.3 mmol, 59%). Started the reaction with cyclopentanone (2.00 mL, 22.6 mmol)

IR (neat, cm^{-1}) ν_{max}: 2964, 1728, 1637, 1151, 912.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.04 (s, 3 H) 1.05 (s, 3 H) 1.59-1.68 (m, 1 H) 1.77-1.88 (m, 2 H) 2.05-2.10 (m, 2 H) 2.13-2.17 (m, 2 H) 2.49 (dd, *J*=13.1, 6.7 Hz, 1 H) 4.94-5.05 (m, 4 H) 5.58-5.69 (m, 1 H) 5.93 (dd, *J*=17.4, 11.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 19.0 (CH_2) 22.5 (CH_3) 22.7 (CH_3) 30.3 (CH_2) 38.9 (CH_2) 40.8 (CH_2) 42.1 (C) 55.9 (C) 112.7 (CH_2) 117.9 (CH_2) 135.0 (CH) 144.9 (CH) 223.4 (C).

HRMS (EI) *m/z* calcd for $C_{13}H_{20}O$ [M^+] 192.1514, found: 192.1512.



(3.120Aa) 2-allyl-2-methylcyclohexan-1-one

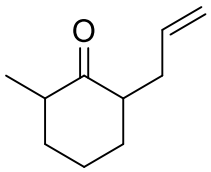
Isolated (0.798 g, 5.24 mmol, 64%) as 1/0.58 mixture of isomers in favor of the most substituted isomer

IR (neat, cm^{-1}) ν_{max}: 2933, 1704, 914.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.05 (s, 3 H) 1.53-1.60 (m, 1 H) 1.64-1.86 (m, 5 H) 2.21 (dd, *J*=13.9, 7.3 Hz, 1 H) 2.31-2.38 (m, 3 H) 4.99-5.02 (m, 1 H) 5.04 (t, *J*=1.1 Hz, 1 H) 5.62-5.73 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 21.0 (CH_2) 22.6 (CH_3) 27.3 (CH_2) 38.6 (CH_2) 38.8 (CH_2) 41.9 (CH_2) 48.4 (C) 117.8 (CH_2) 133.8 (CH) 215.4 (C).

HRMS (EI) *m/z* calcd for $C_{10}H_{16}O$ [M^+] 152.1201, found: 152.1201.



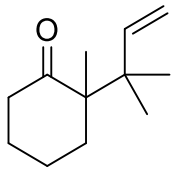
(3.120Ab) 2-allyl-6-methylcyclohexan-1-one

IR (neat, cm^{-1}) ν_{max}: 2933, 1704, 1236, 914.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.07 (d, *J*=6.9 Hz, 3 H) 1.45-1.55 (m, 1 H) 1.62-1.81 (m, 3 H) 1.86-2.00 (m, 2 H) 2.11-2.18 (m, 1 H) 2.41-2.57 (m, 3 H) 4.98-5.05 (m, 2 H) 5.65-5.76 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.7 (CH_3) 20.3 (CH_2) 31.8 (CH_2) 34.8 (CH_2) 35.0 (CH_2) 43.0 (CH) 48.3 (CH) 116.5 (CH_2) 135.9 (CH) 216.0 (C).

HRMS (EI) *m/z* calcd for $C_{10}H_{16}O$ [M^+] 152.1201, found: 152.1202.



(3.120Ab) 2-methyl-2-(2-methylbut-3-en-2-yl)cyclohexan-1-one

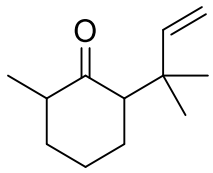
Isolated (1.11 g, 6.16 mmol, 75%) as 1/0.36 mixture of isomers in favor of the most substituted isomer

IR (neat, cm^{-1}) ν_{max}: 2941, 1701, 910, 748.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.05 (s, 3 H) 1.07 (s, 3 H) 1.09 (s, 3 H) 1.49-1.63 (m, 2 H) 1.66-1.75 (m, 2 H) 1.79-1.85 (m, 1 H) 1.86-1.94 (m, 1 H) 2.32-2.36 (m, 2 H) 4.93 (dd, *J*=17.5, 1.5 Hz, 1 H) 4.98 (dd, *J*=10.8, 1.6 Hz, 1 H) 6.04 (dd, *J*=17.4, 10.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 19.2 (CH_3) 20.4 (CH_2) 22.7 (CH_3) 22.7 (CH_3) 24.2 (CH_2) 33.2 (CH_2) 40.3 (CH_2) 42.0 (C) 52.5 (C) 112.1 (CH_2) 145.7 (CH) 216.4 (C).

HRMS (EI) *m/z* calcd for $C_{12}H_{20}O$ [M^+] 180.1514, found: 180.1511.



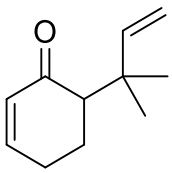
2-methyl-6-(2-methylbut-3-en-2-yl)cyclohexan-1-one

IR (neat, cm^{-1}) ν_{max}: 2933, 1704, 1451, 910, 750.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.05 (d, *J*=6.9 Hz, 3 H) 1.08 (s, 6 H) 1.48-1.54 (m, 1 H) 1.58-1.65 (m, 1 H) 1.67-1.77 (m, 2 H) 1.85-1.98 (m, 2 H) 2.30 (dd, *J*=9.2, 6.1 Hz, 1 H) 2.49 (sext., *J*= 6.9 Hz, 1 H) 4.90-4.97 (m, 2 H) 5.90 (dd, *J*=17.4, 10.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 15.6 (CH_3) 21.3 (CH_2) 24.5 (CH_3) 26.1 (CH_3) 28.0 (CH_2) 33.6 (CH_2) 38.5 (C) 44.9 (CH) 56.9 (CH) 111.3 (CH_2) 146.7 (CH) 216.0 (C).

HRMS (EI) *m/z* calcd for $C_{12}H_{20}O$ [M^+] 180.1514, found: 180.1500.



(3.120w) 6-(2-methylbut-3-en-2-yl)cyclohex-2-en-1-one

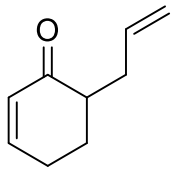
Isolated (0.40 g, 2.46 mmol, 24%)

IR (neat, cm^{-1}) ν_{max}: 2359, 1676, 1275, 748.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.14 (s, 3 H) 1.17 (s, 3 H) 1.77-1.87 (m, 1 H) 2.04-2.12 (m, 1 H) 2.20 (dd, *J*=11.2, 4.5 Hz, 1 H) 2.23-2.32 (m, 1 H) 2.34-2.43 (m, 1 H) 4.92 (dd, *J*=2.7, 1.4 Hz, 1 H) 4.96 (dd, *J*=9.5, 1.3 Hz, 1 H) 5.89-5.96 (m, 2 H) 6.78-6.83 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 24.1 (CH_3) 25.1 (CH_2) 26.2 (CH_2 and CH_3) 38.8 (C) 55.1 (CH) 110.9 (CH_2) 131.3 (CH) 147.1 (CH) 148.1 (CH) 200.8 (C).

HRMS (EI) *m/z* calcd for $C_{11}H_{16}O$ [M^+] 164.1201, found: 164.1218.



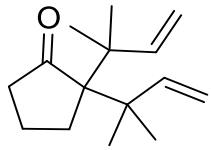
6-allylcyclohex-2-en-1-one

IR (neat, cm^{-1}) ν_{max}: 2916, 1674, 912.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.67-1.76 (m, 1 H) 2.05-2.15 (m, 2 H) 2.30-2.39 (m, 3 H) 2.58-2.65 (m, 1 H) 5.01-5.08 (m, 2 H) 5.71-5.82 (dddd, *J*=17.1, 9.9, 7.8, 6.5 Hz, 1 H) 5.98 (dt, *J*=10.1, 2.0 Hz, 1 H) 6.92 (dddd, *J*=10.0, 4.6, 3.5, 1.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 25.2 (CH_2) 27.3 (CH_2) 33.6 (CH_2) 46.1 (CH) 116.7 (CH_2) 129.5 (CH) 136.1 (CH) 149.7 (CH) 200.9 (C).

HRMS (EI) *m/z* calcd for $C_8H_{12}O$ [M^+] 136.0888, found: 136.0873.



(3.120Ah) 2,2-bis(2-methylbut-3-en-2-yl)cyclopentan-1-one

Isolated (0.22 g, 0.10 mmol, 15%)

IR (neat, cm^{-1}) ν_{max}: 2972, 1639, 1257, 1047, 908, 752.

^{1}H NMR, (400 MHz, $CDCl_3$) δ ppm 1.06 (s, 6 H) 1.11 (s, 6 H) 1.38-1.48 (m, 2 H) 1.86-1.93 (m, 4 H) 4.91 (dd, *J*=9.6, 1.4 Hz, 2 H) 4.94-4.95 (m, 2 H) 5.84 (dd, *J*=17.2, 11.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 23.3 (4xCH_3) 24.6 (CH_2) 25.1 (CH_2) 38.3 (2xC) 59.1 (CH_2) 111.4 (2x CH_2) 145.9 (2x CH) 218.4 (C). (Missing C_{quad})

HRMS (EI) *m/z* calcd for $C_{15}H_{24}O$ [M^+] 220.1827, no mass could be adequately found

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