Synthesis of Carbocycles Using Coinage Metal Catalysis and Formal Synthesis of (±)-Morphine

Julie Brousseau

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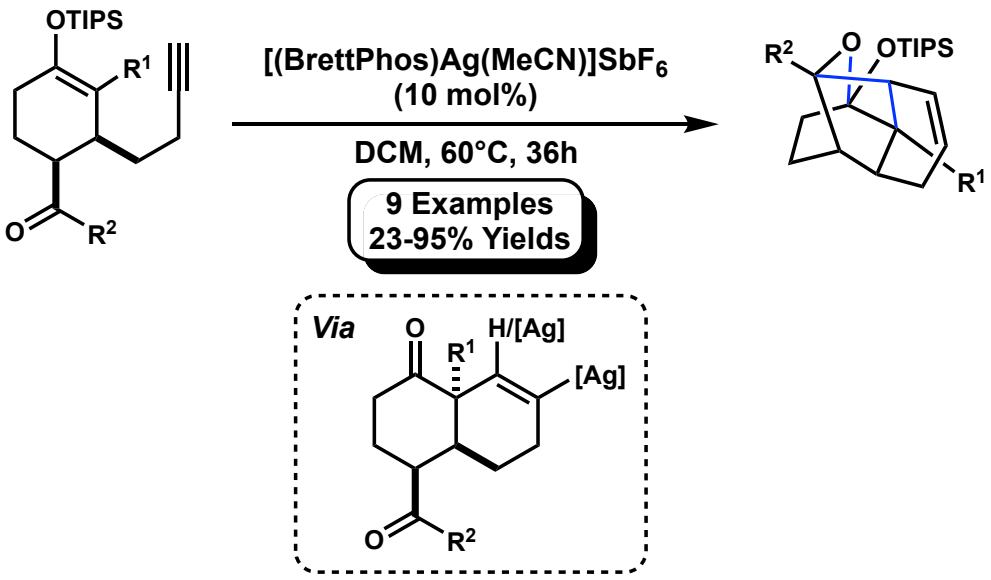
Department of Chemistry and Biomolecular Sciences

Faculty of Science

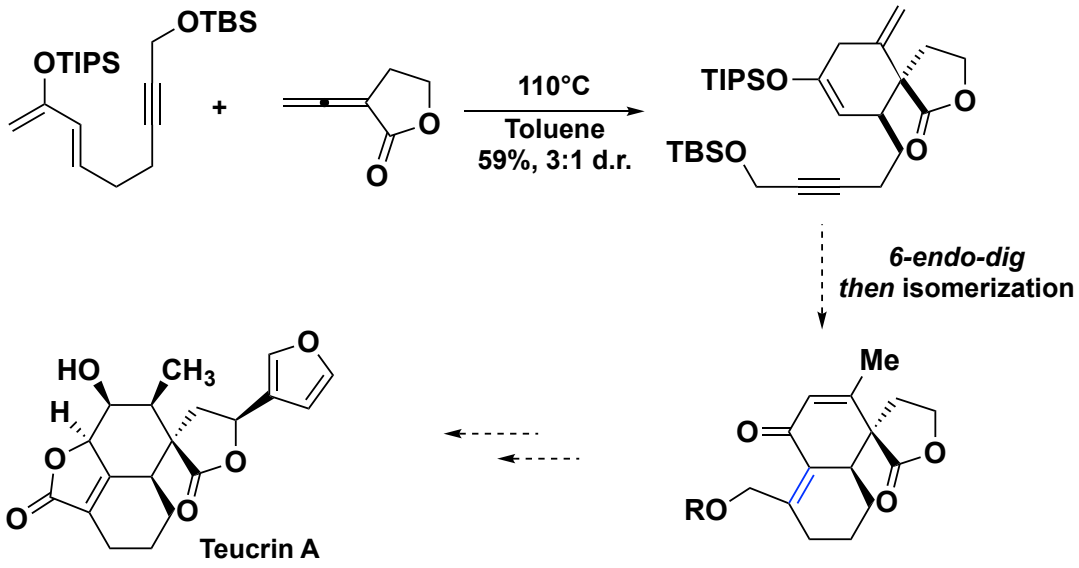
University of Ottawa

ABSTRACT

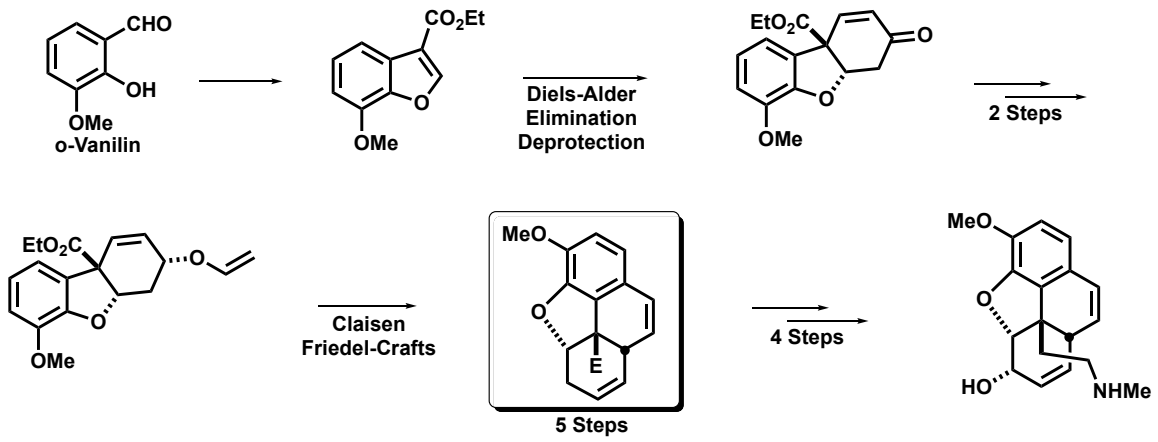
Coinage metals such as copper, silver and gold have captivated mankind with their desirable qualities and social value. Recently, these metals have peaked the interests of scientists, where organic chemists have used them extensively in the homogenous catalysis of organic transformations. In our laboratory, we exploited their π-Lewis acidic properties to activate alkyne to induce intramolecular cyclization of nucleophilic enol ethers. We discovered that modulating the steric and electronic profiles of the ancillary ligand on the cationic metal complexes allowed for the regioselective control of such reactions. During the exploration of the substrate dependency of these transformations, we discovered that unsubstituted alkynes undergo a *6-endo-dig*/acetalization/Prins reaction cascade in the presence of a silver salt such as [(BrettPhos)Ag(MeCN)]SbF_6, resulting in the formation of highly strained polycycles. We have demonstrated that the formation of these products is initiated by a selective *6-endo-dig* cyclization. Further mechanistic studies suggested that the reaction may occur through silver dual catalysis using deuterium-labelling experiments, however, single activation of the starting material would lead to the same product and thus both mechanisms were proposed. The further reactivity of these interesting polycyclic products was also explored.



Total synthesis of natural products is often referred to as an art, as it defines the boundaries of organic chemistry. In our laboratory, we have always been interested in the challenge of ingeniously building architecturally complex molecules. With the development of optimized conditions for the selective formation of decaline cores from silylenol ethers, the application of this methodology to the synthesis of teucrin A was sought. Our synthetic approach is highlighted by a sequential Diels-Alder/*6-endo-dig* cyclization reaction to rapidly assemble the clerodane diterpenoid framework of the natural product. To that end, the synthesis of the target utilized a strategy featuring a Diels-Alder reaction between an exocyclic allene and a silyl enolether, which proceeded in 59% yield at 110°C with a diasteomer ratio of 3:1. Unfortunately, attempts to induce the [4+2] cycloaddition using Lewis acids that were vital to the proposed synthetic route led to either no conversion or hydrolysis of starting material. Since this key step proved challenging, alternative synthetic pathways are currently being investigated in our group.



Since the elucidation of its molecular structure by Robinson in 1925, morphine has received tremendous attention from the synthetic community. Indeed, about 50 formal and total syntheses of morphinans have been reported since the original synthesis by Gate in 1952. Herein, the synthetic efforts achieving a 9-step formal synthesis of (±)-morphine from readily available starting materials such as *o*-vanillin is presented. This synthesis features the quick assembly of the phenanthrofuran framework of the natural product in only five steps. The tetracyclic intermediate was synthetized through the careful orchestration of a Diels-Alder/elimination/deprotection sequence as well as a telescopic Claisen rearrangement/Friedel-Crafts alkylation. Subsequent strategic functional group manipulations allowed us to reach the advanced compound in four more steps and thus intercepting a known intermediate, which required two additional chemical transformations to form morphine.



Overall, the work presented in this thesis represents the development of innovative methods for the creative disconnection of natural products. These advancements promote the rapid assembly of molecular cores found in many bioactive molecules.

ACKNOWLEDGEMENTS

This journey began during my third year of undergraduate studies, when I had the opportunity to attend a course in organic chemistry given by professor Louis Barriault. Not only you have influenced my career choices, but also you've inspired me over the past six years to be bold and opt for the aggressive disconnections. It has been a real privilege to learn from you! Un grand merci également à Julie de toujours nous avoir accueilli chaleureusement et d'avoir pris soin de nous à la façon d'une maman.

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very definition of ‘’sun sparkles”. Your endless energy has brightened my days. Victor, I must admit, you have a cute dog. I have no doubt you’ll finish our natural product. Laurie-Anne, Alexandra, Marina, Charlotte, Rowan, Daniel, Jason, and Weldon, I am glad our paths have crossed. Les ‘’minous”, I will miss you all and do not forget that you are my favourites! ☺

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ABBREVIATIONS

Ac: Acetyl

Aq.: Aqueous

Ar: Aromatic ring

BAIB: bis-acetoxyiodobenzne

BArF: tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

B.C.E: Before Christ Era

Boc: *tert*-butoxycarbonyl

Bmim: 1-butyl-3-methylimidazolium

Bn: Benzyl

Bu: Butyl

Bz: Benzoyl

C.E: Common Era

Cat.: Catalyst

CSA: Camphorsulfonic Acid

Cy: Cyclohexyl

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DCE: 1,2-dichloroethane

DCM: Dichloromethane

DIBAL: Diisobutylaluminum hydride

DIPA: Diisopropylamine

DIPEA: *N,N*-diisopropylethylamine

DMDO: dimethyldioxirane

DMF: Dimethylformamide

DMP: Dess-Martin periodinane

DMSO: Dimethyl sulfoxide

D.P.: Desired product

d.r.: Diastereomeric ratio

E: Ester

EDG: Electron-Donating Group

ent: Enantiomer

Eq.: Equivalents

Et: Ethyl

Et_2O: Diethyl ether

Et_3N: Triethylamine

EWG: Electron-Withdrawing Group

Fur: Furan

HOMO: Highest Occupied Molecular Orbital

HOTf: Triflic acid

HRMS: High resolution mass spectrum

IMDA: Intramolecular Diels-Alder

*i*Pr: isopropyl

IR: Infrared

L: Ligand

L.A.: Lewis Acid

LED: Light-emitting diode

LiHMDS: Lithium bis(trimethylsilyl)amide

LUMO: Lowest Unoccupied Molecular Orbital

M: Metal

m-CBPA: 3-chloroperoxybenzoic acid

Me: Methyl

MeCN: Acetonitrile

MeHQ: Mequinol

MS: Molecular sieves

NBS: *N*-bromosuccinimide

n-BuLi: *n*-butyllithium

NHC: *N*-heterocyclic carbene

NMR: Nuclear magnetic resonance

Nu: Nucleophile

OTf: Trifluoromethanesulfonate

PCC: Pyridinium chlorochromate

Pet. Ether: Petroleum ether

Ph: Phenyl

Phen: Phenanthroline

P.T.: Proton transfer

*p*TSA: *para*-toluenesulfonic acid

rac: racemic

R.E.: Reductive Elimination

Ref.: Reference

SET: Single electron transfer

r.t.: Room temperature

TBAF: tetrabutylammonium fluoride

t-Bu: *Tert*-butyl

t-BuOK: Potassium *tert*-butoxide

TBS: *tert*-butyldimetylsilyl

Temp: Temperature

Tf: Trifluoromethanesulfonyl

TFA: Trifluoroacetic acid

THF: Tetrahydrofuran

TIPS: triisopropylsilyl

TIPSOTf: Triisopropylsilyl trifluoromethanesulfonate

TLC: Thin layer chromatography

TMS: Trimethylsilyl

TON: Turn Over Number

Ts: Tosyl

9-BBN: 9-Borabicyclo(3.3.1)nonane

1 INTRODUCTION

1.1 COINAGE METALS

The coinage metals copper, silver, and gold occur naturally and are among the oldest metals used by ancient humans. More than 5000 years since their discovery, these metals are still highly desired because of their interesting and unique properties. Although gold and silver are so-called precious metals, copper also presents many attractive attributes, demonstrating the value of the coinage metals through their importance in our daily lives. All three metals are excellent electrical and thermal conductors. Copper is currently the cheapest metal of group 11, and undoubtedly the most widely used. Notably, it is extensively used in electrical wiring.[1] Silver is particularly remarkable at reflecting light, making it a critical element in the photography industry.[2] Gold stands out for its resistance to very high temperatures and corrosion.[3] Despite their practical uses, these metals are best known for their decorative value. Although copper, unlike silver and gold, is rarely found in jewellery, it can be observed on the roof of the Parliament of Canada and other iconic monuments.

Table 1.1.1 - Physical Properties of Coinage Metals

Element	Z	Electronic Configuration	Stable Oxidation State	Atomic Radius (pm)
Cu	29	$[Ar]4s^{1}3d^{10}$	0, +1, +2, +3	128
Ag	47	$[Kr]5s^{1}4d^{10}$	0, +1, +2	144
Au	79	$[Xe]6s^{1}5d^{10}4f^{14}$	0, +1, +3	144

Copper (Cu), silver (Ag) and gold (Au) are three elements of the 11th group of the periodical table. Their outer electronic configurations are analogous to alkali metals and can be written as $ns^{1}(n-1)d^{10}$ (Table 1.1). Thus, the oxidation state +1 of the coinage metals is dominant, due to their propensity to lose the single electron in the highest s orbital. This half-filled orbital is also responsible for their compelling electron affinity, and consequently, their Lewis acidity. Copper, silver, and gold have d-electrons and can therefore reach higher oxidation states and can form a variety of coordination complexes. Despite being in the 6th period of the periodic table, gold does not have a greater atomic radius than silver. This characteristic of gold is attributed to the relativistic effect.[4] This phenomenon can be explained by the increased velocity of the electrons to compensate for a large nucleus exerting strong electrostatic attraction. The velocity of gold's electrons becomes comparable to the speed of light. As a result, the mass of the electrons is also greater. Since the mass of electrons is inversely proportional to the Bohr Radius, the electrons are much closer to the nucleus resulting in greater ionization energy for the atom. This causes the contraction of the s and p orbitals, which further shield the 4f and 5d orbitals from the nucleus

(Figure 1.1.1). Consequently, the 4f and 5d orbitals feel less nuclear attraction, leading to their expansion. The decreased size of the 6s orbital and the larger 5d orbital are mostly responsible for the Lewis acid reactivity of gold as well as its attractive colour. More specifically, for a gold(I) complex, the s orbital contributes to a low-lying lowest unoccupied molecular orbital (LUMO), demonstrated by the soft Lewis acidity of this atom. As for the 5d orbital, its expansion raises the energy of the highest occupied molecular orbital (HOMO) energy, thus enhancing the ability for gold to stabilize nearby positive charges through backdonation (Scheme 1.1.1*)*.

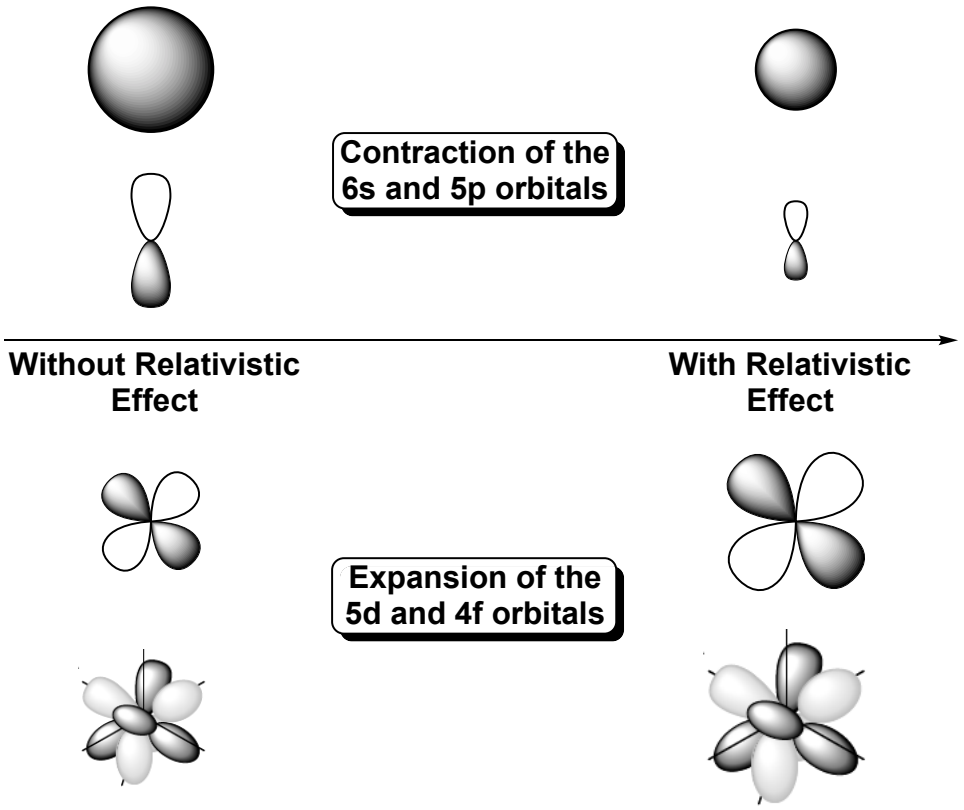
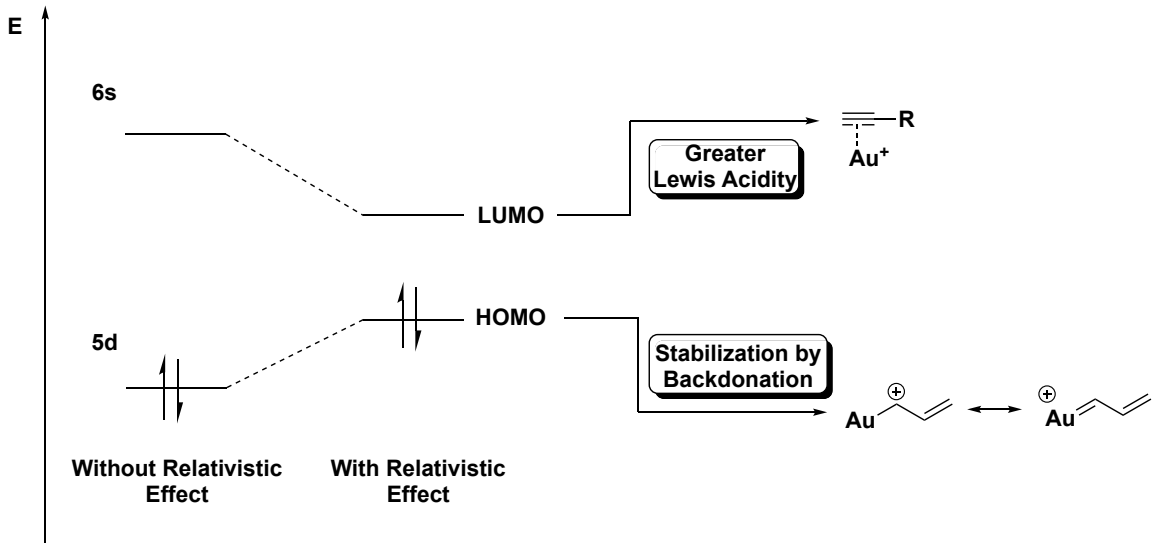


Figure 1.1.1 - Repercussion of the Relativistic Effect on Gold's Orbitals



Scheme 1.1.1 - Consequences of the Relativistic Effect on Gold Reactivity

Moreover, the usefulness of coinage metals in homogenous catalysis has recently been an area of intense research focus. The first of these metals to capture the attention of chemists was copper. As of 2020, the number of copper catalysis-related reports is countless.[5] For a long time, silver was mostly known for its mild oxidation and for halogen scavenging properties. While the use of silver in catalyzed organic transformations has been less notable than that of copper, it can nevertheless be said to have been constant. Silver is best known for its σ- and/or π-Lewis acidity, demonstrated by its ability to activate substrates such as halogens, alkynes and carbonyls. Silver catalysis has also been used to facilitate many different reactions that include cycloadditions, carbonyl and imine allylations, intramolecular heterocyclizations, and aldol reactions.[6] Gold was believed to be inactive towards catalysis of organic transformations for many years and is therefore the youngest member of the triad in organic catalysis. It

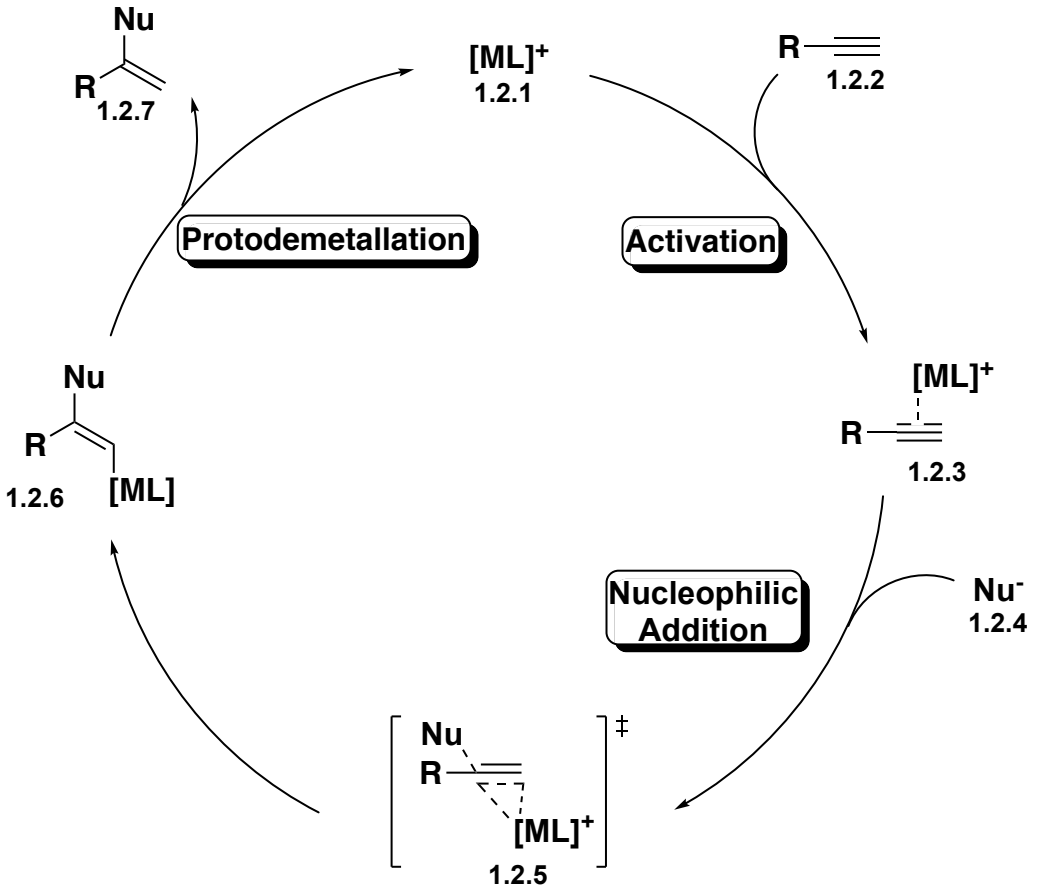
was only in 1986 that Ito and Hayashi reported the first chemical transformation catalyzed by gold(I).[7] The specific chemoselectivity of gold for alkenes, allenes, and alkynes allows transformations to occur under mild conditions in the presence of many functional groups. Since 2000, research activities related to gold catalysis have increased dramatically, leading to the dissemination of many new organic transformations and the publication of several comprehensive reviews[4d,8].

1.2 GENERAL REACTIVITY OF COINAGE METALS WITH ALKYNES

The π-acidity of coinage metals allows them to bind effectively with alkynes. The coordination of the metal centre with the π-bond makes the alkyne electron-deficient and susceptible to nucleophilic addition. It is an effective way to generate new C–C or C–X (X = N, O) bonds in a stereospecific manner.

Generally, the catalytic cycle for the functionalization of alkyne **1.2.2** begins with the coordination of the cationic coinage metal complex **1.2.1** (Scheme 1.2.1). Once the metal-complex **1.2.3** is formed, the substrate is activated towards nucleophilic attack. The nature of the nucleophile can be varied and generally includes alcohols, amines, π-bonds as well as *N*-oxides. The coordination of the metal with the alkyne usually occurs unsymmetrically. Both electronic and steric properties of the substrate influence the regioselectivity of the reaction. The metal centre tends to bind more strongly with the most electron-rich carbon atom of the alkyne and/or the less sterically hindered one. The addition of the

nucleophile **1.2.4** is stereospecific, as shown by the transition state **1.2.5**, as it takes place *trans* to the coordination, resulting in the *trans*-alkynyl metallic complex **1.2.6**. This complex then reacts with an electrophile, typically a proton, to give the demetallated product **1.2.7** and regenerates the catalytic species.



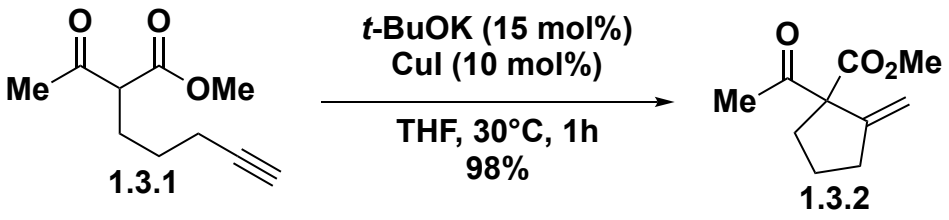
Scheme 1.2.1 - General Mechanism for Alkyne Functionalization Catalyzed by Coinage Metals

1.3 COMPARISON OF COINAGE METALS IN KEY TRANSFORMATIONS WITH ALKYNES

In this section, selected examples of reactions that can be achieved by coinage metals will be presented. Although this list is not exhaustive, it will serve to highlight features of each metal when reacting with alkynes. By comparing the three metals in different reactions, it becomes possible to clearly frame the optimal use of each metal in catalysis.

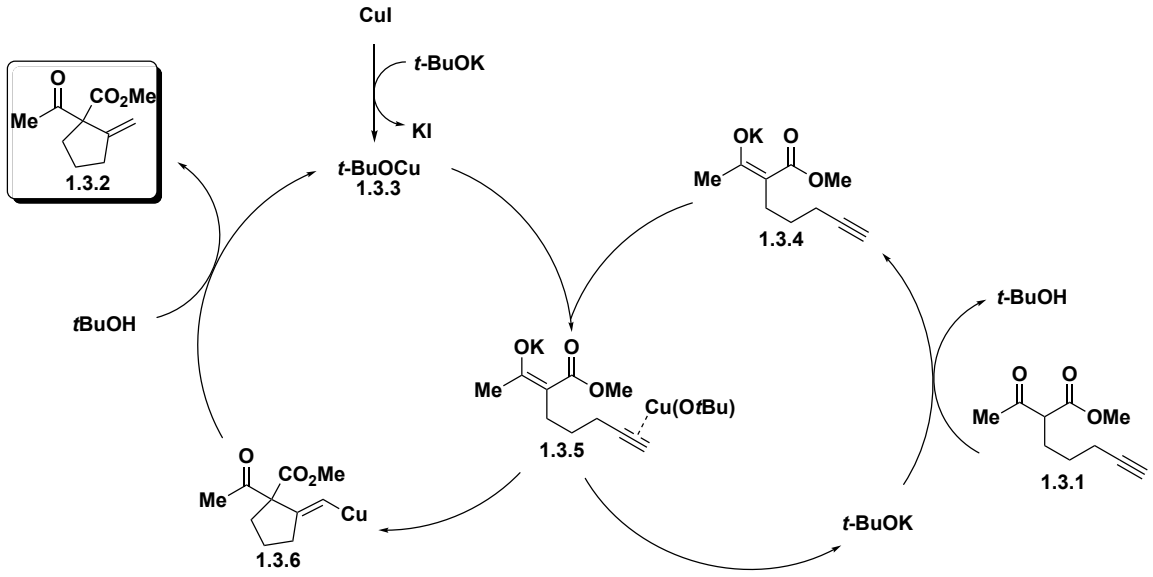
1.3.1 The Conia-ene Reaction

First reported in 1975, the Conia-ene reaction is a thermal cyclization of an alkyl ketone with an alkyne to afford the corresponding α-vinylated ketone.[9] Catalytic Lewis acids have also been used to extend the scope of the reaction to more functionalized substrates under mild conditions.[10] Copper was the first of the coinage metals to be adopted in the catalytic version of this reaction. For instance, Balme *et al.* reported an efficient intramolecular carbocupration of the substrate **1.3.1** using catalytic amounts of copper iodide and *tert*-butoxide to afford the product **1.3.2** in quantitative yield (Scheme 1.3.1.1).[11]



Scheme 1.3.1.1 - Copper-Catalyzed Conia-ene Reaction

The authors suggest that the catalytic cycle begins with X-type ligand exchange between copper iodide and potassium *tert*-butoxide, providing the active catalyst **1.3.3** (Scheme 1.3.1.2). Subsequently, the substrate **1.3.1** is deprotonated by *t*-BuOK to give the enolate **1.3.4**. Cu(I) then activates the enolate to generate the reactive complex **1.3.5** that undergoes carbocupration, leading to the formation of the intermediate **1.3.6**. Protodemetallation regenerated the active catalyst **1.3.3** as well as the desired product **1.3.2**. During the cyclization step, the potassium *t*-butoxide is released and therefore is available to deprotonate another molecule of the substrate **1.3.1** to perpetuate the catalytic cycle.

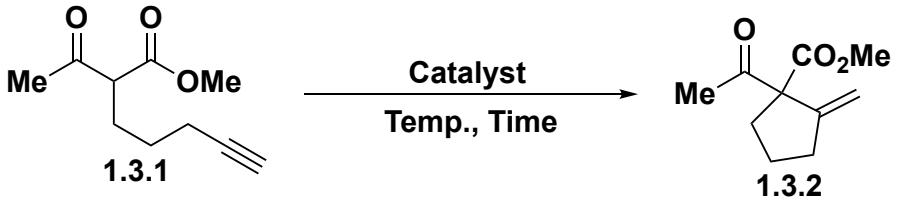


Scheme 1.3.1.2 - Proposed Mechanism for the Intramolecular Carbocupration

Since the original study, many different reaction conditions have been explored in order to perform this reaction under milder conditions and to avoid

the use of strong bases. A stronger Lewis acid is then required for the reaction to occur from the enol tautomer of the substrate, without the need for prior deprotonation. Thus in 2004, Toste *et al.* reported the conversion of the alkyne substrate **1.3.1** into cyclopentene **1.3.2** using gold catalysis (Table 1.3.1).[12]

Table 1.3.1.1 - Optimization of the Conia-ene Reaction Under Mild Conditions

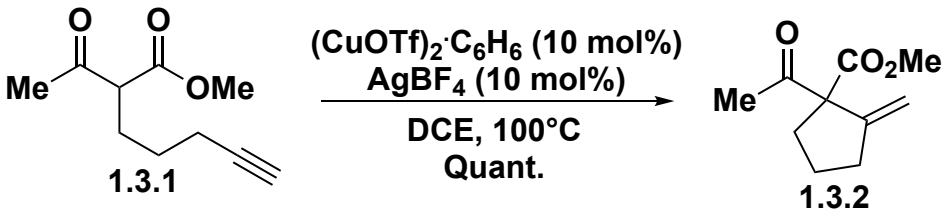


Entry	Catalyst (mol %)	Temperature (°C)	Time	Yield (%)
1	AgOTf (10)	r.t.	18 h	50
2	$AuCl_3$ (10)	r.t.	30 min	30
3	$(PPh_3)AuCl$ (10)	60	6 h	0
4	$(PPh_3)AuOTf$ (10)	r.t.	<15 min	>95
5	$[(Ph_3PAu)_3O]BF_4$ (1) + HOTf (5)	r.t.	<15 min	>95

According to their studies, cationic silver(I) gave the desired product, but even after 18 hours the reaction was not complete (entry 1). Gold(III) chloride allowed rapid consumption of the starting material, but the reaction was not selective, yielding only 30 % of the desired product (entry 2). Use of the Au(I) species

$(PPh_3)AuCl$ did not result in any conversion (entry 3), while the cationic $(PPh_3)AuOTf$ complex generated cyclopentene **1.3.2** in less than 15 minutes and in quantitative yield (entry 4). Generation of the active catalyst could also be achieved *via* protonation of the $[(PPh_3Au)_3O]BF_4$ species, providing an additional catalytic system (entry 5).

More recently, Jin-Heng Li *et al*. reported that the conversion of alkyne **1.3.1** into cyclopropene **1.3.2** could also be achieved by a combination of copper(I) and silver(I) (Scheme 1.3.1.3).[13] Although a temperature of 100°C was required for more than 20 hours, they were able to form the desired product in quantitative yield. In addition, silyl enol ethers react similarly to β-ketoesters in presence of a gold catalyst.[14] In the Barriault group, we have demonstrated that divergent selectivity can be obtained by modifying the ancillary ligand on the cationic gold complex.[15]

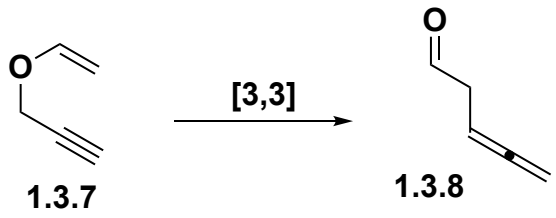


Scheme 1.3.1.3 - Copper/Silver-Cocatalyzed Conia-Ene Reaction

1.3.2 The Claisen Rearrangement

Discovered in 1912 by Ludwig Claisen, this reaction is the [3,3] sigmatropic rearrangement of allyl vinyl ethers into the corresponding γ,δ-unsaturated

carbonyls.[16] The original Claisen rearrangement was thermally induced, but a Lewis acid catalyst can be employed as well to facilitate the reaction.[17] This [3,3] rearrangement can also occur in presence of alkynyl vinyl ethers, generating the corresponding allenes (Scheme 1.3.2.1).



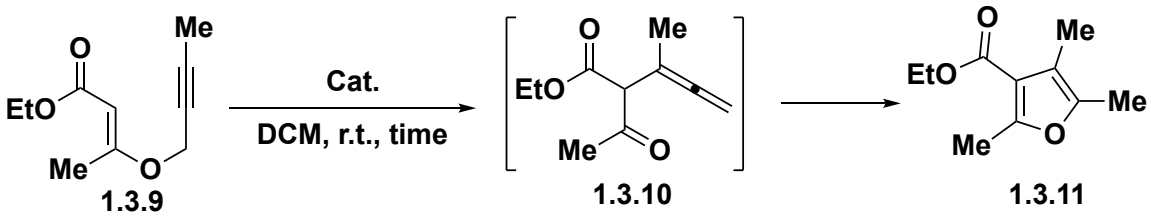
Scheme 1.3.2.1 - Claisen Rearrangement of Alkynyl Vinyl Ether

In 2005, Kirsch *et al.* synthesized highly substituted furans using this approach (Table 1.3.2.1).[18] After the Claisen rearrangement, the generated intermediate **1.3.10** underwent cyclization to form the desired furan **1.3.11**. The latter step was facilitated by the complexation of the allene by the catalyst, favouring the formation of the furan **1.3.11**.

Copper(I) iodide could not catalyze the reaction, yielding no desired product (entry 1). Cationic silver(I) efficiently converted the starting material into the allene **1.3.10** but did not induce further reactivity towards the furan product (entry 2). Gold(III) chloride was shown to be less reactive but was able to convert some of the allene into the desired product **1.3.11** (entry 3). Gold(I) chloride was not reactive enough to activate the starting material **1.3.9** (entry 4). When using cationic gold complexes, the reaction was found to be catalyzed effectively, giving

full conversion within 40 minutes (entries 5-7). The latter results showed that the nature of the counterion plays a role in the efficiency of the reaction. The effects of the counterions in gold catalysis have been studied.[19] These studies demonstrated that a less coordinating ion (X^-) results in greater Lewis acidity of the metal centre. By using this methodology, the authors were able to synthesize 16 different furans, with yields ranging from 72 % to 99 %.

Table 1.3.2.1 - Optimization of the Catalyzed Claisen Rearrangement by Kirsch *et al.*

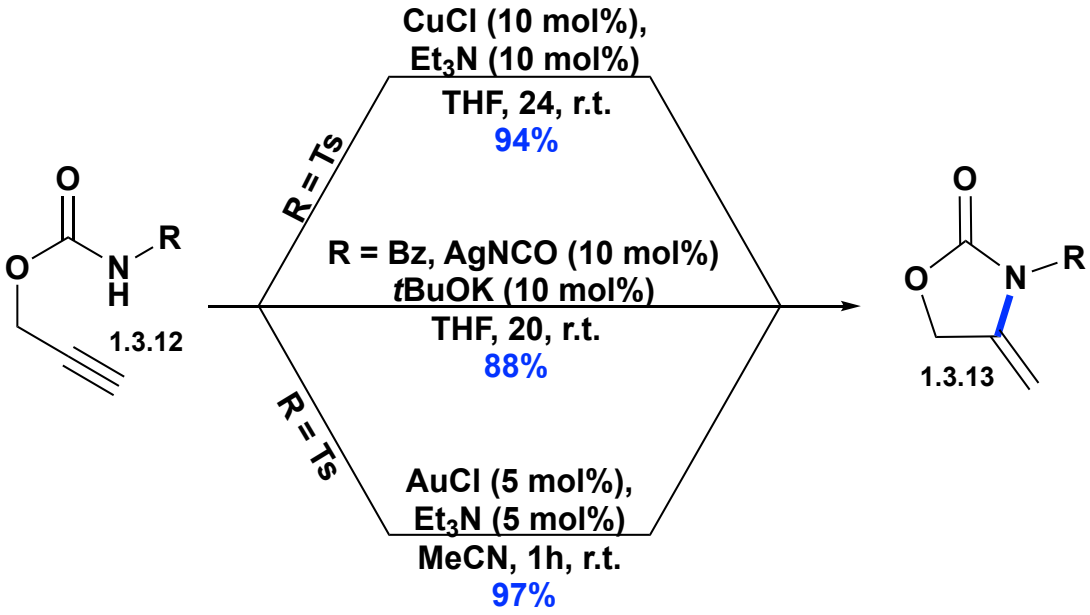


1.3.9 1.3.10 1.3.11

Entry	Catalyst (mol %)	Time	Yield 1.3.10 (%)	Yield 1.3.11 (%)
1	CuI (5)	24 h	0	0
2	$AgBF_4$ (10)	24 h	>95	0
3	$AuCl_3$ (2)	24 h	47	7
4	$(PPh_3)AuCl$ (2)	24 h	0	0
5	$(PPh_3)AuCl$ (2) + $AgBF_4$ (2)	40 min	0	97
6	$(PPh_3)AuCl$ (2) + $AgSbF_6$ (2)	40 min	0	83
7	$(PPh_3)AuCl$ (2) + AgOTf (2)	40 min	0	60

1.3.3 Intramolecular Addition of Nucleophiles onto Alkynes

As shown above, copper, silver, and gold are capable of binding efficiently with allenes, alkenes, and alkynes to activate them towards subsequent organic transformations. Upon coordination with the metal, the LUMO of the π-bonds decrease in energy, which makes them better acceptors for nucleophiles. Indeed, the examples of intramolecular nucleophilic additions onto alkynes catalyzed by coinage metals are countless in the scientific literature. It is undoubtedly a very productive way to make new C-C, C–N or C–O bonds. It is worth mentioning that among these three metals, gold is the best choice for this type of reaction due to its high chemoselectivity. The development of gold catalysis therefore broadens the opportunities in total synthesis for late-stage cyclization on highly functionalized intermediates.[20]



Scheme 1.3.3.1 - Intramolecular Hydroamination Catalyzed by Coinage Metals

The formation of 4-alkylidiene-2-oxazolidinones *via* metal-catalyzed intramolecular hydroamination has been studied since the 1990s (Scheme 1.3.3.1).[21] The 5-*exo*-*dig* cyclization can be performed by any of the coinage metals, as they all converted alkynyl starting material **1.3.12** into the desired cyclic carbamate product **1.3.13** with excellent yields. When the reaction is catalyzed by copper(I) chloride (10 mol%), 24 hours were necessary to obtain the desired product in 94 % yield. In order to decrease the reaction time to four hours, the reaction can be performed at reflux and carbamate **1.3.13** was formed in 91 % yield. As for silver(I), a stronger base is required but the product can be obtained with a similar yield. Gold(I) chloride led to the formation of the product quantitatively after only one hour in acetonitrile. The catalyst loading was also half of that required for the two other metals.

1.4 DUAL CATALYTIC SYSTEMS

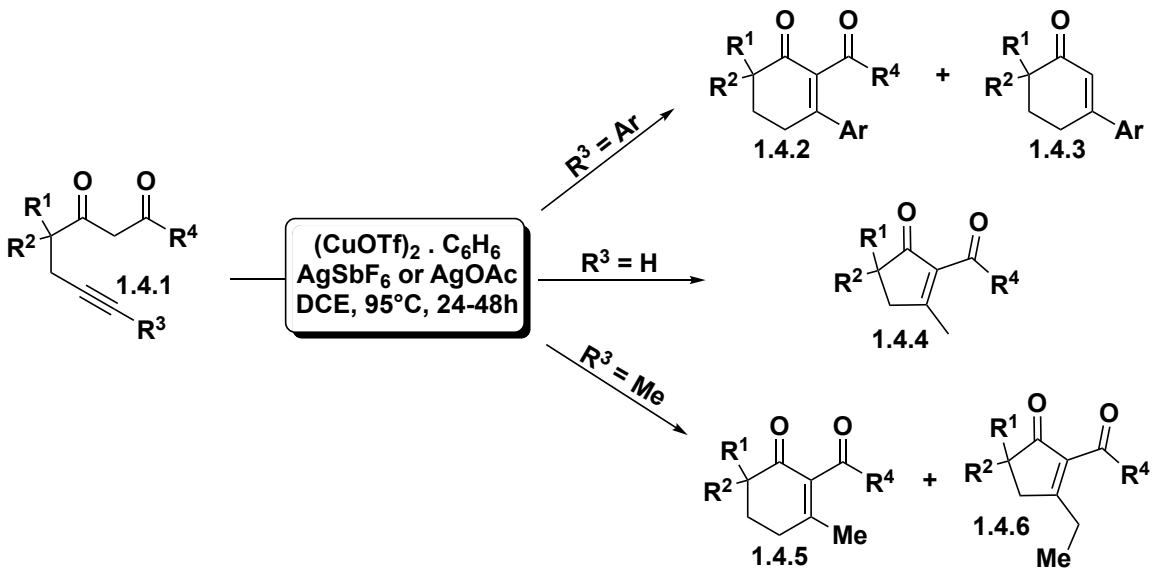
The catalytic potential of coinage metals in organic synthesis can be further improved by combining the reactivity of their complexes. As these processes often promote reaction cascades, they facilitate rapid construction of molecular complexity using simple alkynes as starting materials.

1.4.1 Copper and Silver Dual Activation

The Lewis acidity of copper(I) and silver(I) salts do not limit these catalysts to soft centre activation. Therefore, these metals may achieve differential binding by activating a π-bond as well as a hard donor centre. Indeed, there are a few

examples in the literature where one or both of these metals are used to achieve intramolecular and intermolecular dual activation, enhancing the reactivity of the substrates.

In 2007, Jin-Heng Li *et al.* have developed a copper/silver cocatalyst system for the Conia-ene reaction of linear *ε*-alkynyl β-ketoester **1.4.1** under mild reaction conditions (Scheme 1.4.1.1).[22] These substrates are much less reactive than their isomeric *ε*-alkynyl β-ketoesters, which are generally used for this reaction.



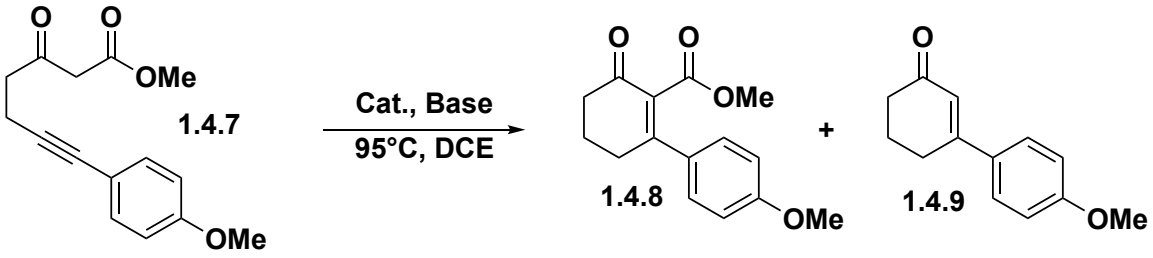
Scheme 1.4.1.1 - Li et al. Copper/Silver Co-Catalyzed Conia-Ene Reaction

Unsurprisingly, the nature of the R^3 group influences the *exo/endo* selectivity of the reaction. More interestingly, when R^3 is an aromatic ring, some decarboxylated 6-*endo-dig* product **1.4.3** was observed along with the desired

product **1.4.2**. As expected, terminal alkynes lead solely to the formation of the 5-*exo-dig* products **1.4.4**. The regioselectivity of the reaction became harder to control when an electronically neutral methyl group was present and a mixture of the 5-*exo-dig* adduct **1.4.6** and the 6-*endo-dig* product **1.4.5** was inevitably obtained.

When copper(I) iodide alone was used, only traces of the products **1.4.2** and **1.4.3** were observed even in the presence of a strong base (entries 1 and 3, Table 1.4.1.1). Although silver(I) acetate was slightly more successful, the conversion of the starting material was limited to 24 % (entry 3).

Table 1.4.1.1 - Optimization of the Dual Catalytic System



Entry	Catalyst (mol %)	Base	Yield 1.4.8 (%)	Yield 1.4.9 (%)
1	CuI (10)	-	Trace	Trace
2	CuI (10)	*t*BuOK	Trace	Trace
3	AgOAc (10)	-	24	Trace
4	$(CuOTf)_2{\cdot}C_6H_6$ (10) + $AgSbF_6$ (10)	-	61	31

When both metals were used synergistically, the total yield of the reaction was 92 % (**1.4.8**/**1.4.9** 2:1, entry 4). In order to explain these results, Li *et al.* claimed that one metal can bind with the two oxygen atoms of the substrate, whereas the second metal can bind with the alkyne and the alkene of the enol (Figure 1.4.1.1).

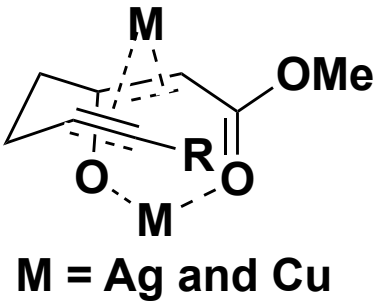
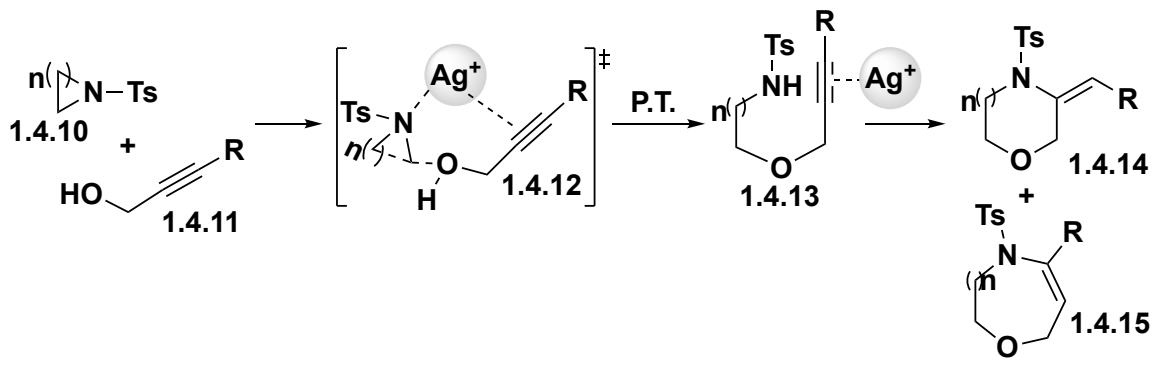


Figure 1.4.1.1 - Proposed Dual Activation

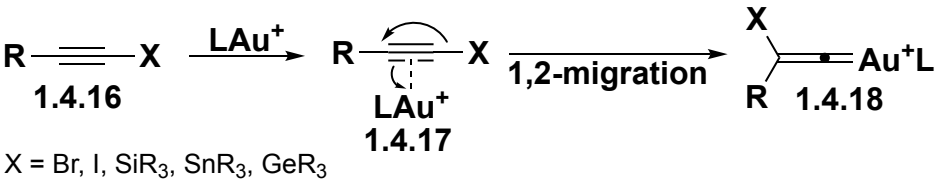
The ability of silver to catalyze challenging transformations *via* differential binding was also demonstrated by the Roy group in 2009.[23] In this work, silver allowed a reaction cascade between aziridine/azetidine with propargyl alcohol to open the small ring **1.4.10** *via* a nucleophilic attack of the alcohol and subsequent cyclization onto the alkyne **1.4.11** (Scheme 1.4.2.1). The authors stated that silver first facilitates intermolecular nucleophilic addition by binding to nitrogen, as shown in **1.4.12**. Using this approach, they were able to prepare 6-, 7-, and 8-membered unsaturated heterocycles **1.4.14** (*exo*) and **1.4.15** (*endo*), depending on the regioselectivity of the cyclization. More than 14 different products were made, all in good yields.



Scheme 1.4.1.2 - Roy Group Reaction Cascade Catalyzed by Silver(I)

1.4.2 Gold Dual Catalysis

Gold's capacity for electron backdonation allows the formation of vinylidene species. Although the first report of gold vinylidene was as belated as 2004, many interesting transformations have emerged from the corresponding reactivity.[24,25] The gold vinylidene species (**1.4.18**) typically generated by activation of an alkyne (**1.4.17**) by gold(I) followed by 1,2-migration of an X group is shown in Scheme 1.4.2.1.

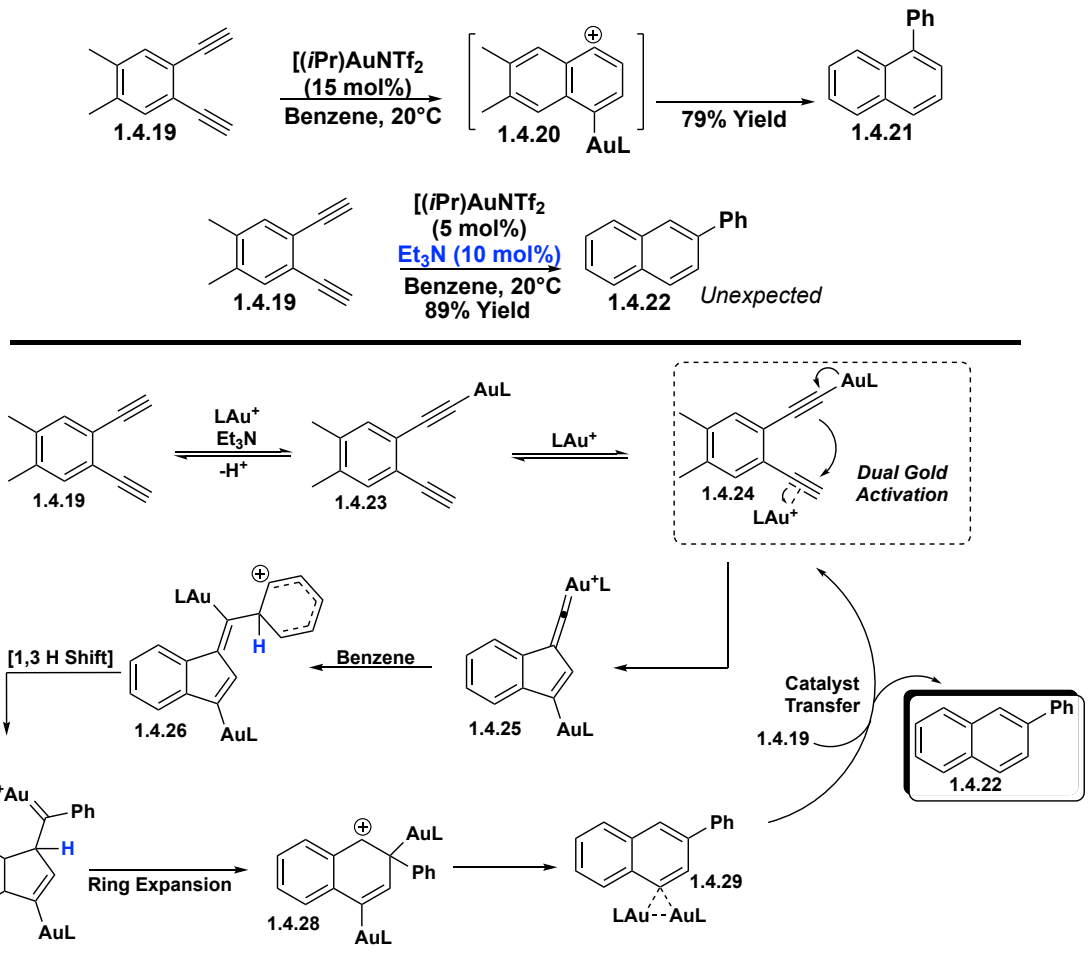


Scheme 1.4.2.1 - Formation of Gold Vinylidene via 1,2-Migration

In 2012, Hashmi's group discovered that it is also possible to generate gold vinylidene species from gold dual catalysis (Scheme 1.4.2.2).[26] While investigating applications of the diyne **1.4.19** in gold catalysis, they generated the

desired naphthalene **1.4.21** in 79 % yield. This compound was formed through activation of one of the alkyne moieties by cationic gold, followed by cyclization to give the carbocation **1.4.20**. This reactive intermediate was then trapped by a molecule of the benzene solvent, leading to the addition of a phenyl group. Surprisingly, when the reaction was performed under basic conditions in the presence of catalytic triethylamine, only traces of **1.4.21** were formed and the unexpected isomer **1.4.22** was predominantly generated in 89 % yield. The authors performed exhaustive kinetic studies and deuteration experiments in order to suggest a mechanism.

Their proposed mechanism starts with the formation of the gold acetalylide **1.4.20**, which is favoured under basic conditions. Upon activation of the second alkyne, the 5-*exo*-*dig* cyclization provides the gold vinylidene **1.4.25**. A molecule of solvent can then trap the electrophilic carbon and form carbocation **1.4.26**. In order to regain aromaticity, a 1,3-hydride shift followed by a ring expansion to generate the secondary carbocation **1.4.28** is suggested. Subsequent gold elimination and catalyst transfer give the observed product **1.4.22** as well as the active species **1.4.24**. Since this pioneering discovery, many other researchers have contributed to the growing field of dual gold catalysis.[25,27]



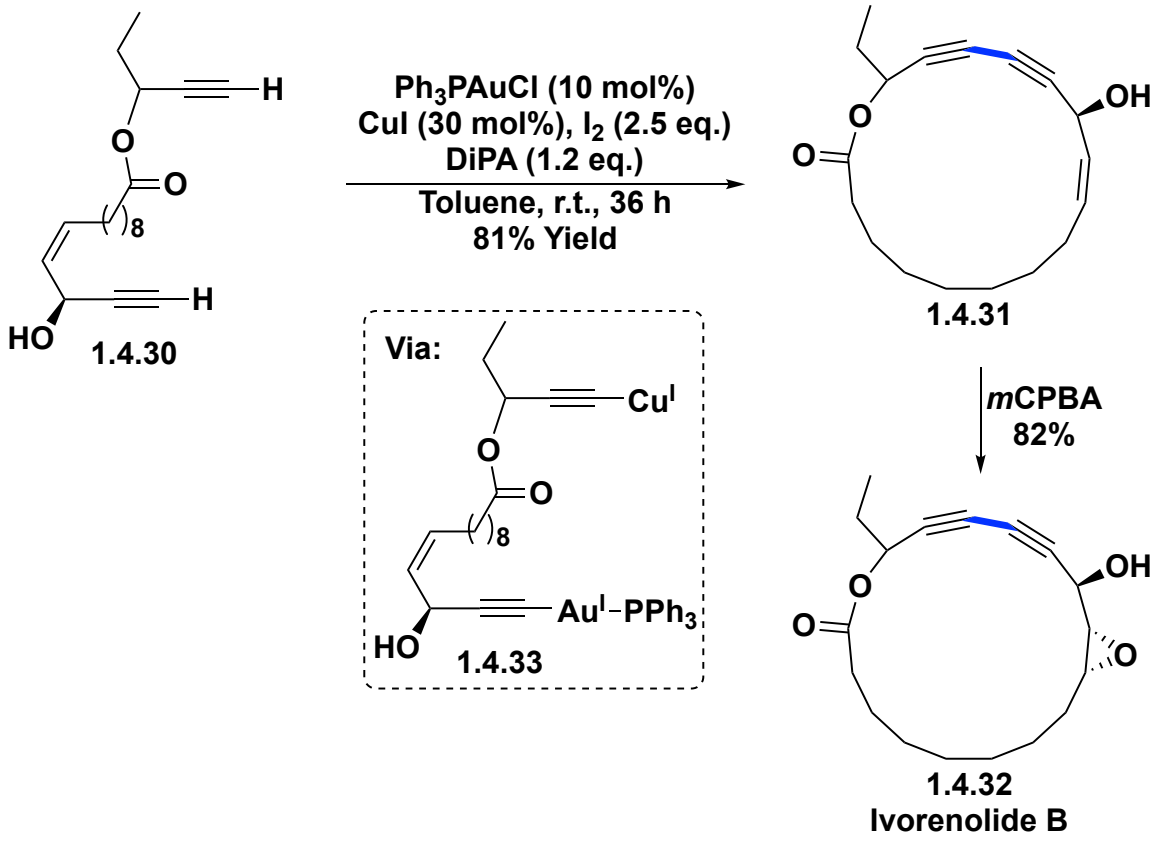
Scheme 1.4.2.2 - Formation of Gold Vinylidene by Dual Gold Catalysis of Diyne

1.4.3 Bimetallic Dual Catalysis

This section would not be complete without mention of bimetallic dual catalysis. The combination of two different coinage metals has proven to be a powerful tool for organic synthesis.

The Mohapatra group demonstrated a good application of this reactivity in the total synthesis of ivorenolide B.[28] They developed a dual gold/copper catalytic

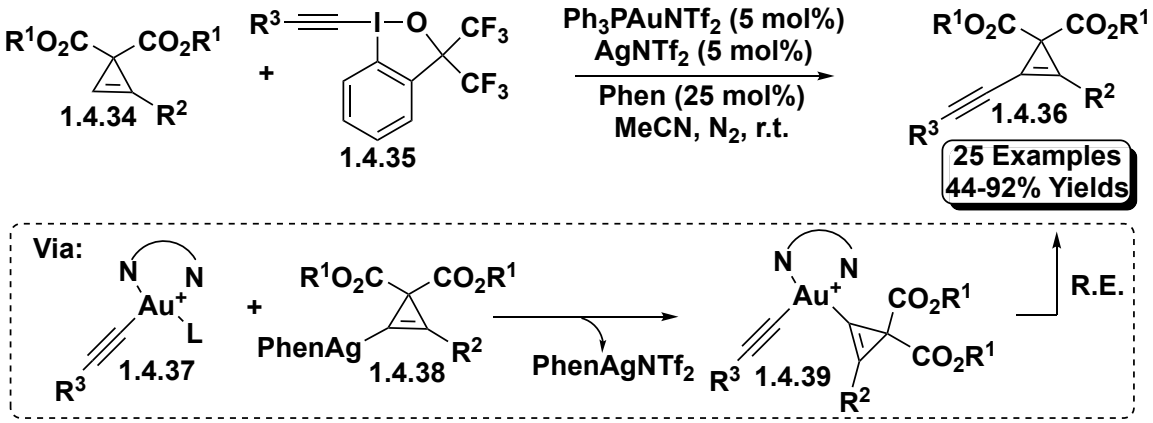
system to perform a difficult Glaser-Hay coupling, allowing the formation of the 17-membered ring **1.4.32** in 81 % yield (Scheme 1.4.3.1).



Scheme 1.4.3.1 - Dual Copper/Gold Catalyzed Key Step for the Total Synthesis of Ivorenolide B

The authors stated that the reaction involved the formation of the reactive intermediate **1.4.33**, which undergoes oxidative transmetallation with iodine to release copper(I) iodide. This step afforded a gold(III) intermediate that, after reductive elimination, gave the desired large ring **1.4.31** and regenerated the catalytic species. The combination of gold(I) and silver(I) was also tested, but only traces of the product were observed.

More recently, Hashmi *et al.* reported a method for direct alkynylation of cyclopropenes using dual gold/silver catalysis (Scheme 1.4.3.2).[29] To do so, they used tri-substituted cyclopropenes **1.4.34** as well as alkynylated hypervalent iodine **1.4.35** in presence of cationic gold and silver complexes and phenanthroline.



Scheme 1.4.3.2 - Dual Silver/Gold Catalyzed Alkylation of Cyclopropenes

They were able to achieve the synthesis of 25 alkynylated cyclopropenes **1.4.36** in good to excellent yields. Extensive mechanistic studies suggest that the reaction occurs via C-H activation of the cyclopropenes by silver(I) to generate the intermediate **1.4.38**. This intermediate undergoes transmetallation with the gold complex **1.4.37**, followed by reductive elimination of **1.4.39** to afford the coupled product and regenerated active gold species.

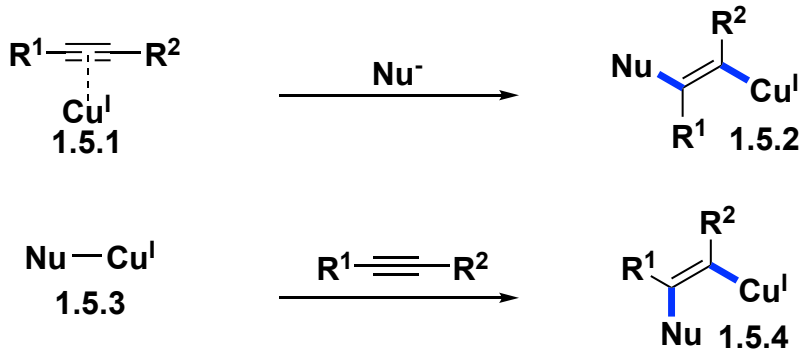
1.5 COMPLEMENTARY REACTIVITY OF COINAGE METALS

Although they all belong to the 11th group of the periodic table, a divergent selectivity can be obtained from the different coinage metals to create a broader library of compounds in the context of specific organic transformations.

1.5.1 Different Selectivity from the Same Metal

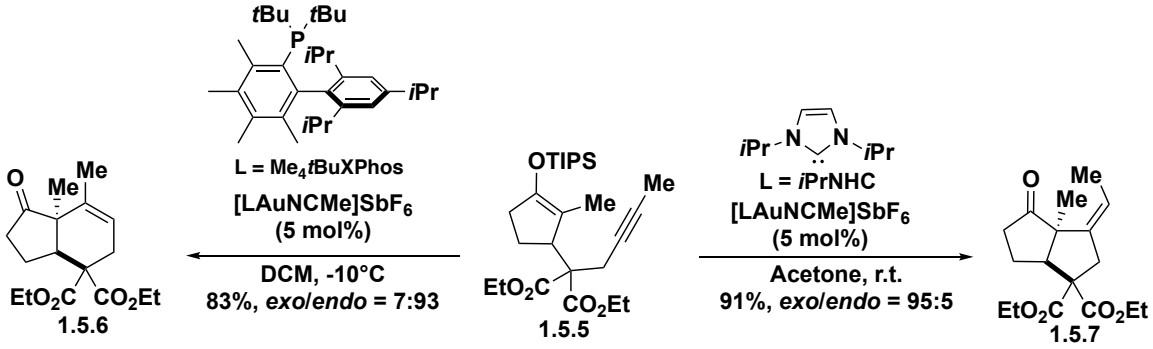
In this chapter, the activation of alkynes to catalyze addition of nucleophiles has been highlighted. Although copper(I) complexes can react as soft Lewis acids, this is not what they are best known for. Indeed, the application of copper(I) for the activation of alkynes is often limited by the need for harsh reaction conditions and high temperatures. In most cases, clean and efficient transformations are obtained through intramolecular processes. The activation of pronucleophiles by copper(I) and their addition to π-bonds is nevertheless a tremendous field of research.

As discussed in *Section 1.2*, the addition of a nucleophile to an activated alkyne is done in a *trans* fashion. However, the addition of a nucleophilic organocopper species to the alkyne would result in the formation of the complementary *cis*-vinylcopper species (Scheme 1.5.1.1).



Scheme 1.5.1.1 - Selective Formation of the (*E*)- and (*Z*)-Vinylcopper Species

In 2011, our group reported that divergent pathways in the carbocyclization of silyl enol ethers onto alkynes could be obtained by modulating the steric and electronic properties of the ancillary ligand on a cationic gold complex.[15a] Starting with silyl enol ether **1.5.5**, the 6-*endo-dig* product **1.5.6** was formed with high selectively using a very bulky and electron-rich Buchwald-type ligand (Scheme 1.5.1.2).



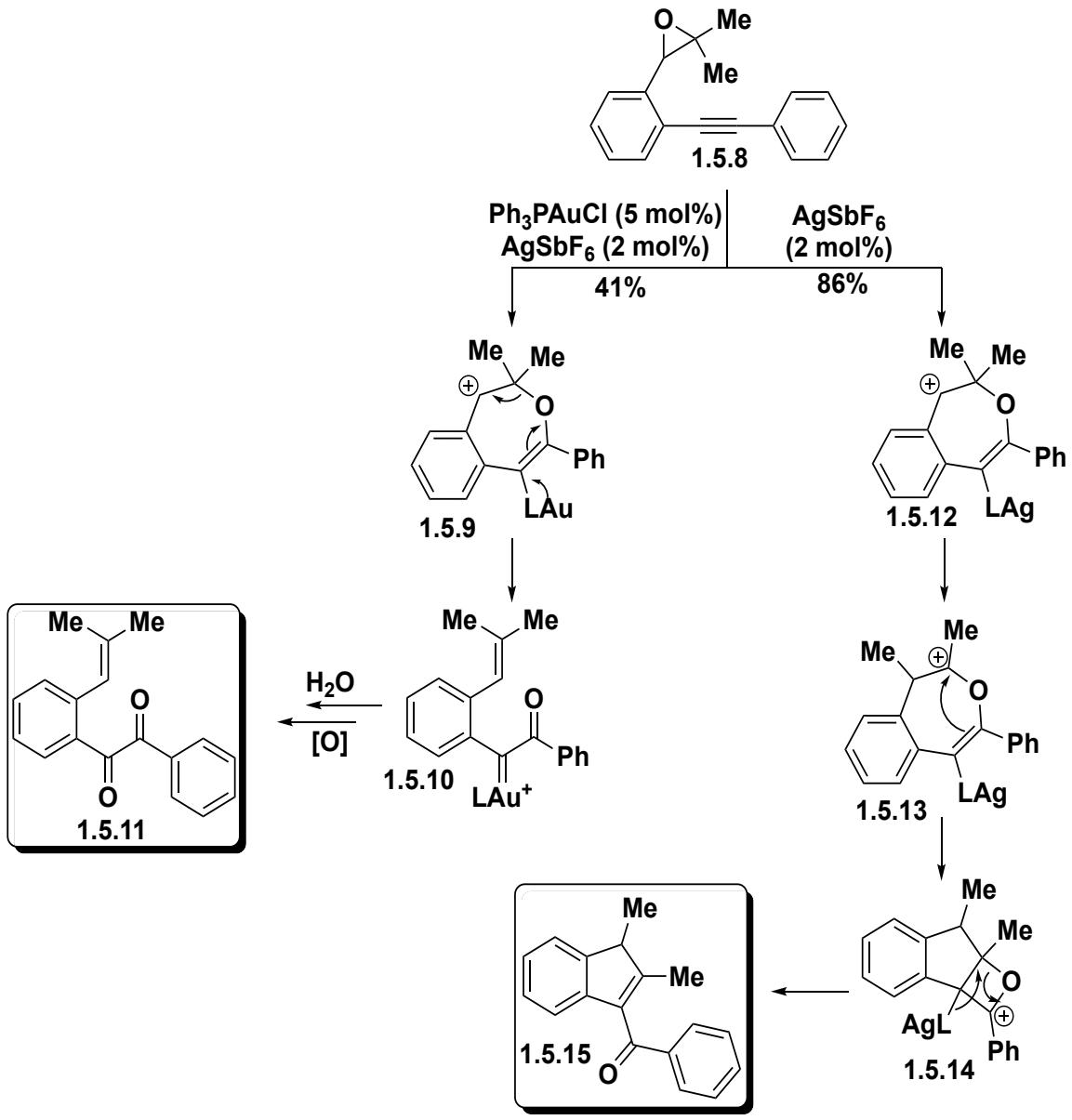
Scheme 1.5.1.2 - Divergent Carbocyclization of Silyl Enol Ethers

On the other hand, the 5-membered ring (**1.5.7**) could be obtained from the 5-*exo-dig* pathway, which was favoured by the use of a strong σ-donating ligand.

The *endo* selectivity was attributed to a distortion of the usual L-Au-X angle, resulting in less stabilization from ligand backdonation and consequently a more cationic process.

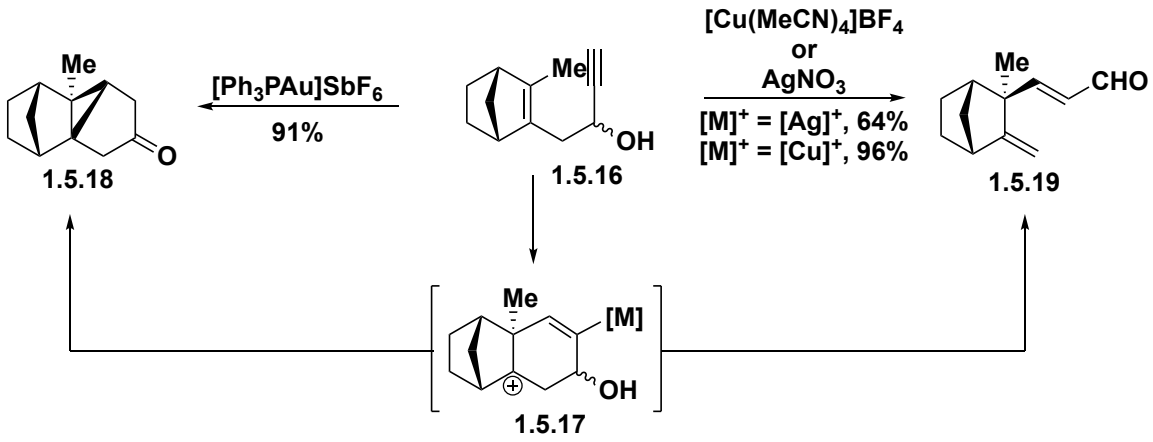
1.5.2 Divergent Reactivity from Different Metals

A given starting material can also react differently with different metal catalysts, leading to divergent product formation.[30] In 2008, Liu *et al.* isolated different products when they used **1.5.8** with silver(I) and gold(I) (Scheme 1.5.2.1).[31] When the reaction was catalyzed by cationic gold, the activated alkyne was trapped by the epoxide, giving the intermediate **1.5.9**. Backdonation from gold allowed the formation of the carbene **1.5.10**, which after oxidation with water gave the 1,2-dicarbonyl compound **1.5.11**. This is the only product they observed where the rest of the material was attributed to being unreacted starting material. When the same substrate **1.5.8** was treated with cationic silver, they isolated the cyclized product **1.5.15** in 86 % yield. The authors suggested that intermediate **1.5.12** undergoes a 1,2 methyl shift followed by a Prins reaction. The oxetane moiety **1.5.14** then opens upon elimination of silver, to give the ketone product **1.5.15**.



Scheme 1.5.2.1 - Divergent Product Formation with Gold and Silver

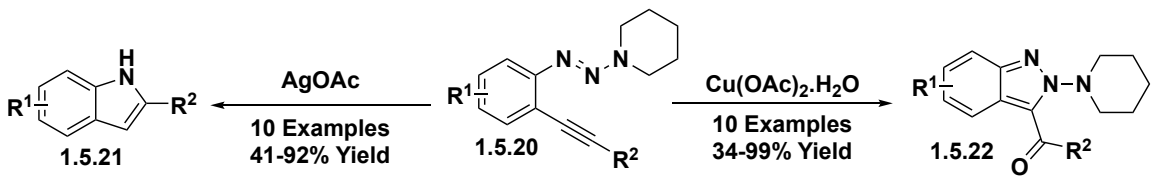
In 2009, the Fehr group reported a novel cyclization-fragmentation reaction of enynol **1.5.16** (Scheme 1.5.2.2).[32]



Scheme 1.5.2.2 - Different Reaction Sequences Catalyzed by Coinage Metals

While copper(I) and silver(I) catalyzed reactions underwent the desired 6-*endo-dig* cyclization/fragmentation reaction sequence to form the α,β-unsaturated aldehyde **1.5.19**, the cyclopropane **1.5.18** was the only product observed when using a gold catalyst. This divergent selectivity can be once again explained by the ability of gold(I) to engage in backdonation.

In addition, coinage metals have been used frequently in heterocyclic synthesis.[33] Divergent syntheses of different heterocyclic frameworks from common starting materials are reported in the literature where product outcomes depend only on the choice of coinage metal catalyst. For instance, Yong Huang *et al.* published a method for the synthesis of indazoles and indoles from triazene-alkyne (Scheme 1.5.2.3).[34] When the alkyne substrate **1.5.20** reacted with silver(I), a 5-*endo-dig* cyclization followed by loss of cyclohexyl hydrazone was observed and the indoles (**1.5.21**) were isolated in moderate to excellent yields. Copper(II) catalysis delivered the indazoles **1.5.22**.



Scheme 1.5.2.3 - Divergent Heterocycle Synthesis with Copper and Silver

In our group, we have also observed that divergent selectivity that can be obtained from coinage metals, and this concept will further be discussed in *Chapter 2*.

1.6 CONCLUSION

The reaction of alkynes catalyzed by coinage metals is an effective strategy toward rapid creation of molecular complexity from simple starting materials. All three metals are able to activate alkynes, making them susceptible to intramolecular and intermolecular nucleophilic addition. Although gold has the advantage of high chemoselectivity, copper and silver allow double activation of substrates that can induce reaction cascades. The coinage metals are mutually compatible and can therefore be combined to accomplish different tasks in a reaction, increasing the level of molecular complexity that can be achieved in a single step. Gold also has the strongest Lewis acidity and the ability to stabilize positive charges through backdonation, which generally leads to unique products.

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2 DIVERSIFICATION OF CARBOCYCLES WITH COINAGE METALS

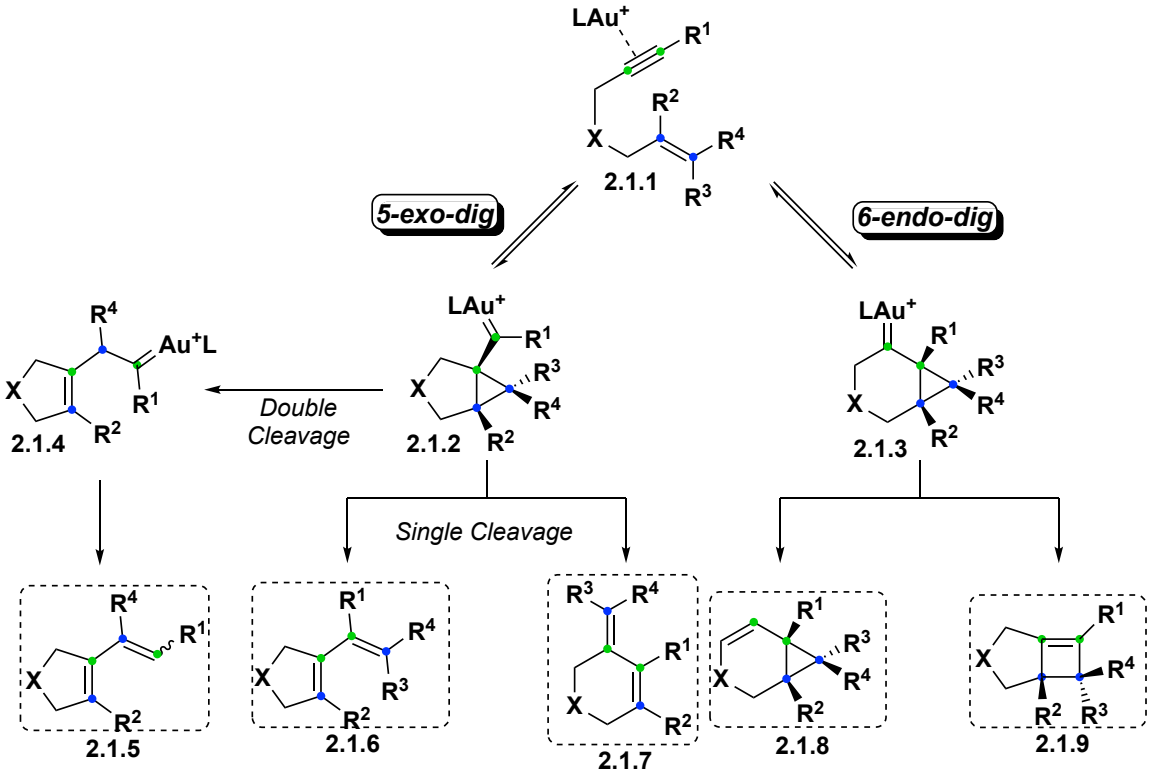
2.1 SELECTIVE INTRAMOLECULAR CYCLIZATIONS

The development of novel synthetic methods to generate new carbon−carbon (C−C) bonds is crucial for the synthesis of bioactive molecules. Molecular complexity may be rapidly generated using the ability of coinage metals to activate π-bonds – this is especially efficient when considering intramolecular cyclization processes. Since the metal can bind unsymmetrically to the two carbon atoms of an alkyne, there is potential for a wide variety of products to be obtained from such transformations.

2.1.1 Cycloisomerizations of Enynes

First described in the 1980s using palladium, the cycloisomerization of 1,n-enynes has been studied extensively.[1] In the presence of a soft Lewis acid catalyst such as gold(I), η^2-alkyne activation makes the alkyne electron-deficient, and in absence of an external nucleophile, intramolecular skeletal rearrangement occurs (Scheme 2.1.1.1).[2] Upon formation of the complex **2.1.1**, a reversible 5-*exo-dig* or 6-*endo-dig* carbocyclization can take place followed by trapping of the carbocationic intermediate, forming **2.1.2** and **2.1.3** respectively. The strained intermediate **2.1.2** can then undergo a single cleavage rearrangement to generate the compounds **2.1.6** and/or **2.1.7**. Double cleavage is also possible and would result in the formation of the intermediate **2.1.4**, which after a 1,2-hydride shift

and elimination would give **2.1.5**. The same product can be formed when the species **2.1.4** undergoes elimination followed by protodeauration. On the other hand, the 6-*endo-dig* adduct **2.1.3** can lead to the formation of the bicyclo[4.1.0]heptane **2.1.8** *via* a similar mechanism as described for **2.1.5**. Alternatively, a ring-expansion of the cyclopropane followed by protodeauration can also occur, giving the product **2.1.9**.

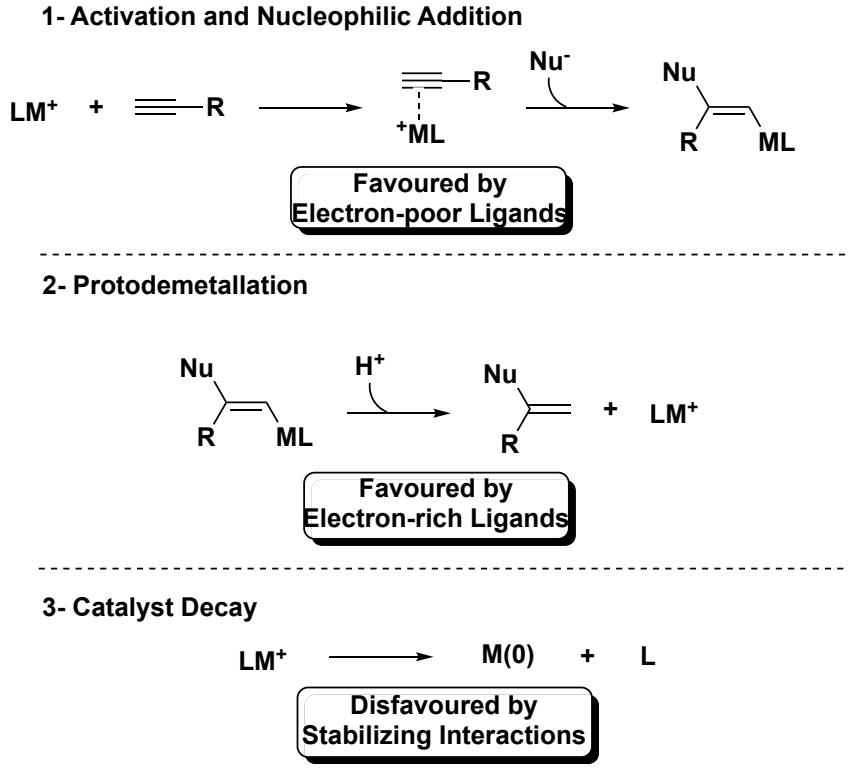


Scheme 2.1.1.1 - Gold-Catalyzed Cycloisomerization of 1,6-Enyes

2.1.2 Ligand Effect on Reactivity

The remarkable structural diversity that can be obtained from very simple starting materials can make it challenging to control the regio- and stereoselectivity of these reactions. While 5-*exo-dig* cyclization is usually the favoured pathway, the electronic and steric profiles of the gold complex can be modulated using ligands in order to favour the alternative 6-*endo-dig* cyclization.[3]

Despite the numerous studies on the effect of ligands in coinage metal catalysis, finding the appropriate match for a desired reaction remains substrate-specific and therefore requires considerable experimentation.

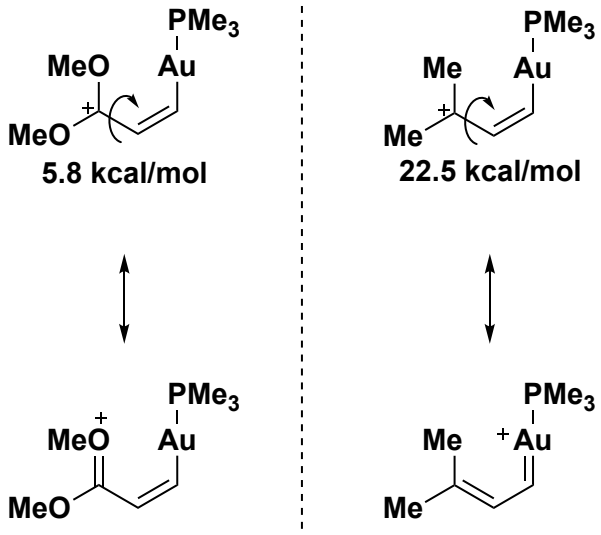


Scheme 2.1.2.1 - Stages of a Gold-Catalyzed Reaction

A Lewis acid metal-catalyzed reaction between an alkyne and a nucleophile can be described in three phases (Scheme 2.1.2.1). The use of ligands to favour each phase can also be rationalized according to the electronic and steric profile of the metal-catalyst. The first stage corresponds to the activation of the alkyne by the metal, followed by addition of a nucleophile to form a vinyl-metal intermediate. This step is favoured by an electron deficient ligand, which increases the cationic property of the metal, resulting in better Lewis acidity towards the relatively nucleophilic alkyne. The second stage is the protodemetallation, which acts to regenerate the active catalyst and releases a molecule of the desired product. In a reaction where this step is rate determining, an electron rich ligand on the cationic metal species serves to make the intermediate more basic towards protons in solution.[3a] The final stage to consider is the decomposition of the active catalyst. In absence of stabilizing interactions, the rapid decomposition of the catalyst results in a low turnover number (TON) of the catalytic system. This step is by far the least understood and seems to be influenced by the nature of the reaction being catalyzed. For instance, the catalyst $[Ph_3PAu]OTf$ is rather stable in solution at room temperature, as long as it is not in the presence of a reducing compound such as an alkyne. Once the alkyne is added to the reaction medium, the rate of catalyst decomposition increases considerably. The Echavarren group has introduced the use of Buchwald-type biphenyl phosphine ligands for cationic coinage metal complexes.[4] These catalysts generally exhibit a better stability than traditional phosphine-based ligands (*i.e.* PPh_3). Although the estimated distance between the metal centre and the arene is greater than the maximum distance for a significant interaction, such

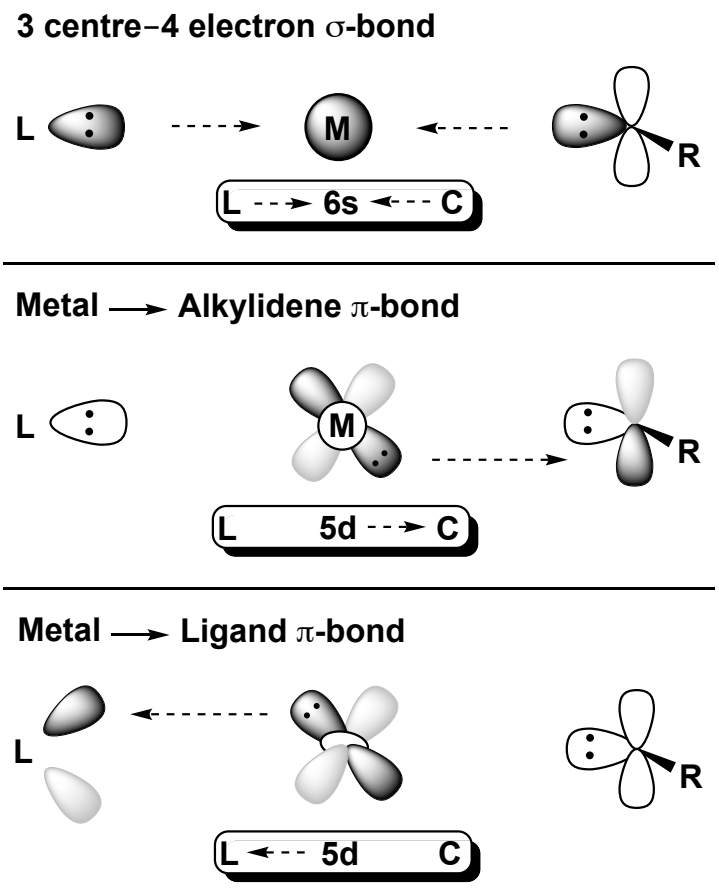
η^2-type interactions have been proposed and may account for the observed stability.

The nature of the ligand on the metallic species influences the reaction kinetics as well as determining which bonds are formed. In order to better understand the distribution of the observed products, a few binding models have been proposed for gold catalysis.[3c,5] To evaluate the bond order of the cationic Au–C species, Toste *et al.* calculated the rotational barrier for the corresponding C–C bond adjacent to the alkene (Scheme 2.1.2.2).[3c] They found that when the carbocation was highly stabilized by heteroatoms, the rotational barrier of the gold-carbon bond was as low as 5.8 kcal/mol with trimethylphosphine as the ligand. When the positive charge was less stabilized by the substrate itself, more stabilization was provided by gold and the rotational barrier increased to 22.5 kcal/mol. These results suggest that the reactivity of a given gold complex greatly depends on the carbene substituents.



Scheme 2.1.2.2 - Rotational Barrier of Vinyl Carbene Gold Species

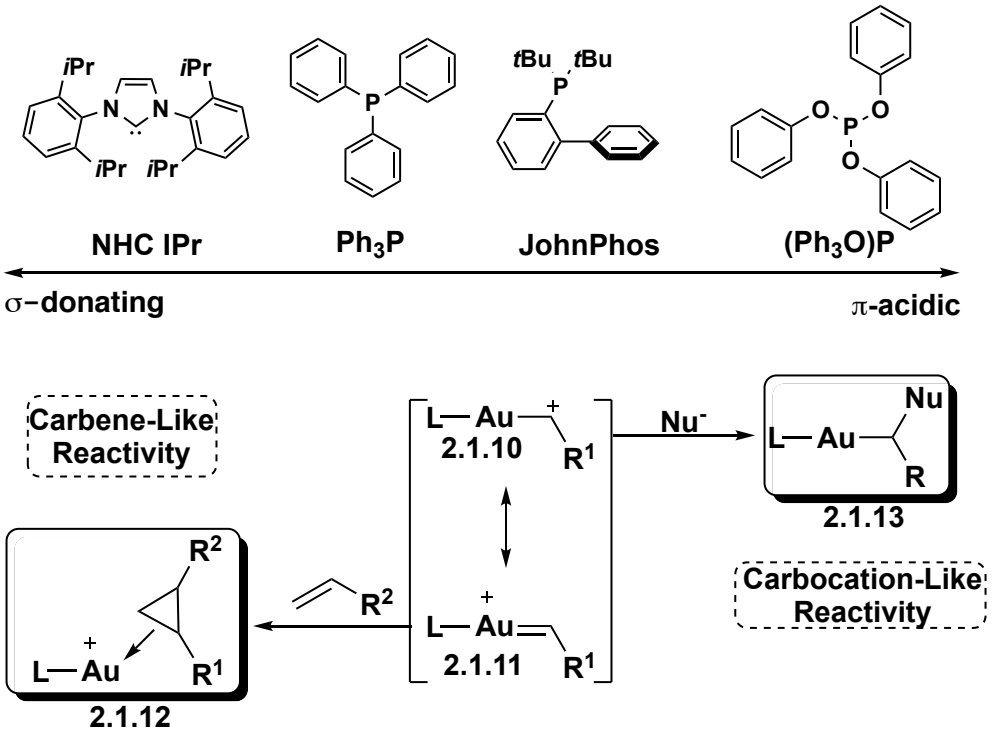
In addition, the authors found that the bond order between carbon and gold as well as gold's ability to backdonate electrons are influenced by the nature of the ancillary ligand.[3c] The representation of interactions between the ligand, the gold, and the carbene is often limited to two resonance structures: a carbocation, or a gold carbene. While the gold carbene representation suggests that there is a double bond between gold and carbon, it rather means that both σ- and π-components to bonding are involved. Indeed, the bond order of the C–Au bond is generally between 0.5 and 1.2 depending on the ancillary ligand. The three main components that must be specified regarding the $L-Au-C$ interactions are outlined in Scheme 2.1.2.3. Since only gold's 6s orbital is vacant, a three-centre-four-electron σ-hyperbond must be formed between the three atoms, as dictated by the Pauli exclusion principle. As a consequence, a highly σ-donating *N*-heterocyclic carbene (NHC) ligand such as NHC-IPr, would decrease the bond order of the Au–C σ-bond ([L:Au–C] *vs* [L–Au:C]). On the other hand, the π-component of the Au–C bond can be divided into two different possible interactions. The filled 5d orbital of gold can donate electron density into π-acceptors of either the ligand or the carbon atom. Following this model, the ligand and the carbon compete for gold's electron density. Thus, π-donating ligands, such as chloride, increase the availability of the 5d electrons that can stabilize the electron deficient carbon by backdonation, resulting in very short Au–C bond. Alternatively, ligands that are strongly π-acidic, such as phosphites, would decrease gold's ability to stabilize the carbocation through backdonation resulting in a π-interaction between the metal centre and its ligand.



Scheme 2.1.2.3 - Binding Interactions in Carbene Gold Species

Considering the electronic properties of a ligand and a substrate, it is possible to estimate the degree of the different bonding components in a C–Au bond. Gold(I) complexes prefer to adopt a linear bis-coordinate geometry. Therefore, strongly σ-donating ligands that reduce the σ-character of the C–Au bond would increase carbene-like activity. Consequently, weakly π-acidic ligands that increase the π-character of the C–Au bond decrease carbocation reactivity. Thus, ligands that possess both of these electronic properties would be ideal for concerted carbene-like reactivity. For instance, NHC ligands are known to promote the formation of cyclopropane products very efficiently. [6] Alternatively,

π-acidic ligands decrease π-character of the C–Au bond, resulting in carbocation-like reactivity. It is also important to note that substrates capable of intercepting the developing positive charge may exhibit carbene-like reactivity, independent of the electronic properties of the ancillary ligand.



Scheme 2.1.2.4 - Ligand Effect on Reactivity

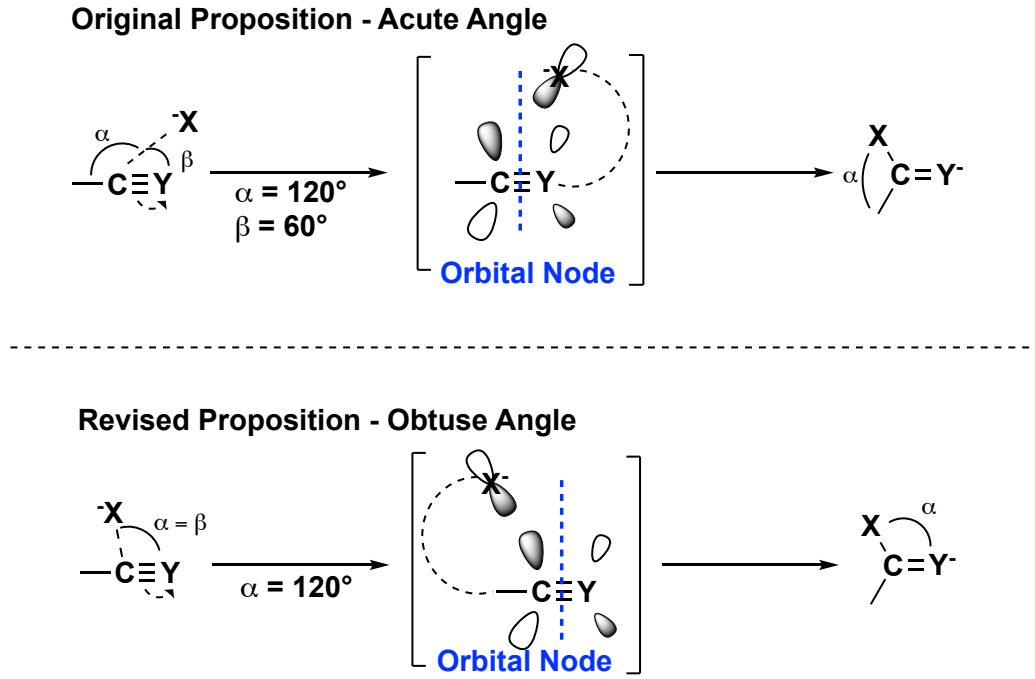
2.1.3 Selective *6-endo-dig* Cyclization

The regioselectivity of an intramolecular cyclization of a nucleophile onto an alkyne can be difficult to control. While many scientists have tried to rationalize reaction outcomes in terms of the effect of the ligand on the catalyst, it appears that this type of transformation remains highly substrate-specific.[3c-d,7] For a given substrate, divergent selectivity can be observed by modulating the steric and

electronic properties of the ancillary ligand on the metal-complex. In many cases, the transformation must be re-optimized for each significant modification to the substrate. Selective 5-*exo*-, 5-*endo*- and 6-*exo-dig* cyclizations onto alkynes using gold catalysis have been intensively studied, however, the 6-*endo-dig* pathway has received considerably less attention.[8] Indeed, favouring the formation of the 6-membered ring over the competitive 5-membered counterpart has proven quite a challenge.[9] The factors that can influence the regioselectivity of such transformations will be discussed in this section.

The Baldwin rules provide useful guidelines on expected and observed selectivity for competitive cyclizations.[10] According to these rules, cyclization is favoured when the length and nature of the linking chain enable the nucleophile to achieve an optimal trajectory. Conversely, a distorted addition angle and/or distance would result in a more challenging cyclization and the corresponding product would be obtained in minor amounts or not observed at all. An important factor to consider when interpreting these rules is the hybridization of the electrophilic carbon. Regarding addition onto a sp-hybridized carbon, the Baldwin rules suggest that an acute addition angle would be favoured, which suggests a predominance of the *endo* product (Scheme 2.1.3.1). However, this trajectory would be stereoelectronically unfavoured due to the proximity of the nucleophile to the node of the targeted π^*-orbital of the alkyne, resulting in a mismatch in orbital symmetry.[11] For this reason, a revised obtuse angle for the addition of a nucleophile onto the alkyne has been proposed.[12] This improved trajectory avoids the destabilizing orbital interaction. The obtuse angle of

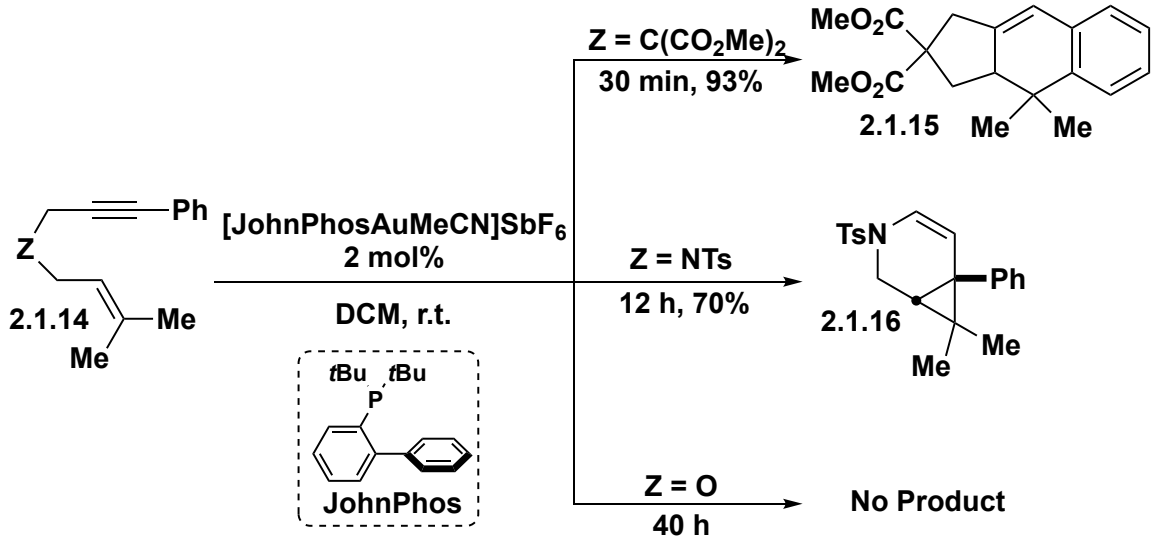
nucleophile approach is comparable to the Bürgi-Dunitz model for addition onto carbonyls.[13] This revised proposal also suggests that the 5-*exo-dig* product would be favoured over the 6-*endo-dig* product, which is generally in accordance with experimental observations.



Scheme 2.1.3.1 - Nucleophile Trajectory of Digonal Cyclizations

In order to favour the 6-*endo-dig* product, steric and electronic elements on the substrate can be modulated. For instance, the tether between an alkyne and alkene in 1,6-enynes can be modified. Although the tether is usually functionalized to simplify synthesis of the substrate and/or to facilitate the cyclization *via* the Thorpe-Ingold Effect, it can also influence cyclization regioselectivity. For instance, when Echavarren *et al.* studied the cyclization of 1,6-enyne substrate **2.1.14** in the presence of the cationic complex

[(JohnPhos)Au(MeCN)]SbF_6, they observed different products depending of the nature of the tethering group.[13] When the tether was a malonate, the authors isolated the compound **2.1.15** in 93 % yield after 30 minutes. This formal Diels-Alder adduct was generated though a gold-catalyzed 5-*exo-dig* cyclization, followed by trapping of the carbocation intermediate with the aromatic ring.

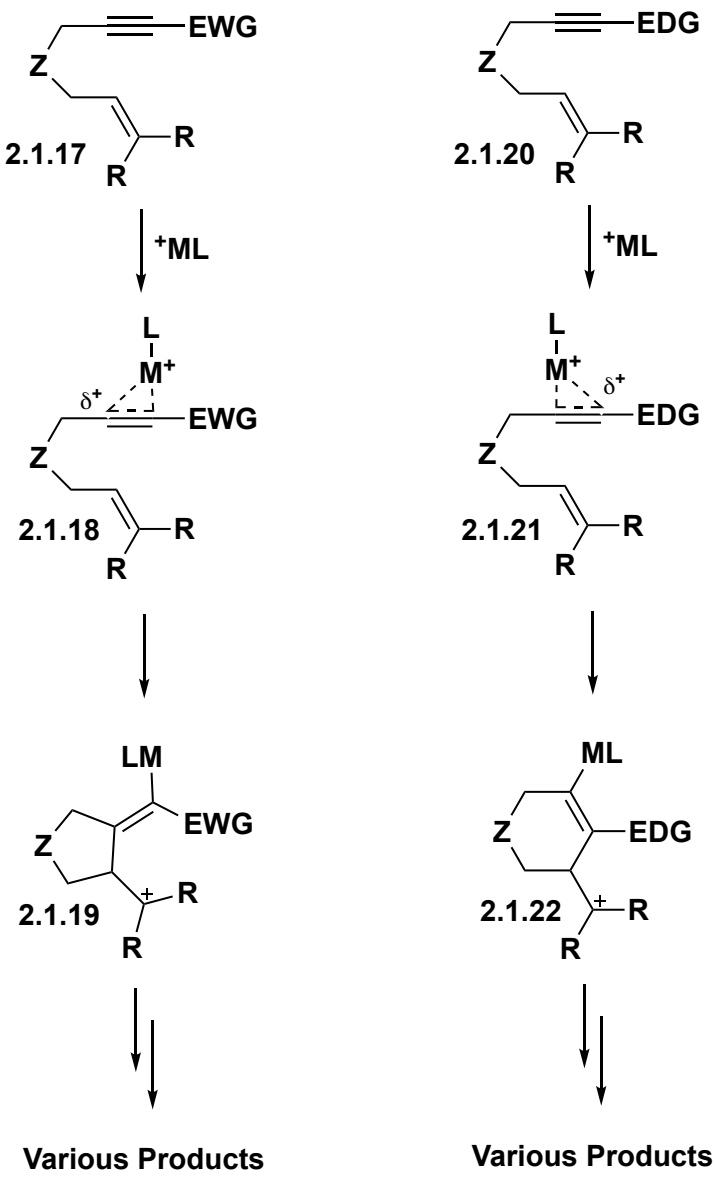


Scheme 2.1.3.2 - Effect of the Tether on Regioselectivity

In contrast, the introduction of nitrogen at this position led to the formation of **2.1.16** in 70 % yield. This product was the result of a selective 6-*endo-dig* cyclization. This result can be explained by stereoelectronic effects, where the lower energy C–N σ^*, compared to the corresponding C–C σ^*, can interact with the adjacent newly formed C–Au σ orbital and provide a stabilizing effect in the transition state. Meanwhile, the use of oxygen as the tether did not lead to any product. The authors attributed the lack of substrate reactivity to the electron withdrawing effect of the oxygen. Due to the inductive effect, this alkyne is

relatively electron-poor and the crucial Lewis-acid complex is less likely to form. It is also worth noting that nitrogen-containing tethers were less reactive than those containing *gem*-diesters for potentially the same reason. The reaction time was much longer and the yield was considerably lower.

Electronic and steric properties of substituents on the alkyne can also play a pivotal role in the regioselectivity of the reaction. The polarization of the alkyne is an important factor to take into account when designing this type of transformation.[14] In general, the soft Lewis acid will bind more strongly to the most electron rich carbon of the alkyne, inducing the development of a partial positive charge on the other carbon atom. The latter is then more susceptible to nucleophilic attack. For instance, if there is an electron-withdrawing group on the alkyne (**2.1.17**), the 5-membered ring **2.1.19** will most likely be formed as an intermediate (Scheme 2.1.3.3). Further reactivity of this intermediate and the resulting product profile depends on reaction conditions. On the other hand, if the alkyne bears an electron-donating group then the metal will prefer to bind to the internal carbon of the alkyne to form the complex **2.1.21**, leading to the formation of the 6-membered ring **2.1.22**. The size of the substituent on the alkyne is also important to consider, as it would be difficult for the nucleophile to add onto the carbon α to a bulky group. The impact of this steric effect on the regioselectivity has proven harder to anticipate.



Scheme 2.1.3.3 - Effect of Alkyne Polarization on Regioselectivity

Finally, certain systems can be reversible in the formation of the first bond and so thermodynamic considerations should be acknowledged. The formation of the 6-membered ring should be thermodynamically favoured. For the formation of polycyclic compounds, internal strain can define the stability of the divergent products.[15] While it can be difficult to determine if an elementary step of an

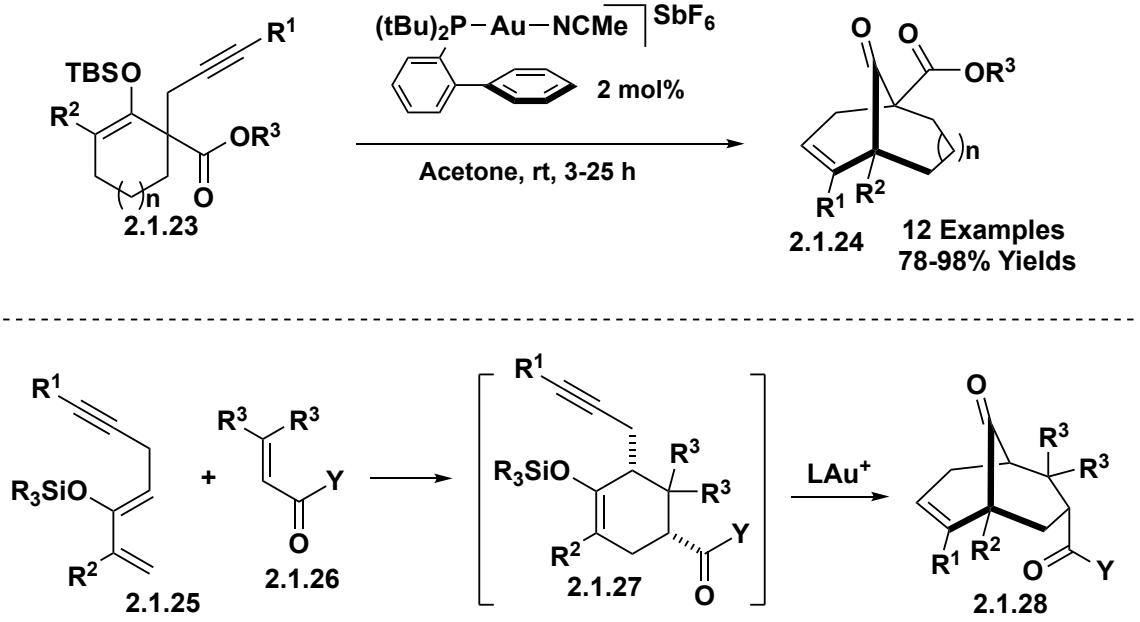
overall transformation is reversible, some experimental data is in favour of such a proposal and will be further discussed in *Section 2.2*.

2.1.4 Selective Carbocyclization of Silyl Enol Ethers

In our group, we have investigated the use of coinage metals to induce selective carbocyclizations of silyl enol ethers and alkynes/alkenes/allenes to form bridged, angular, and fused carbocycles. The development of these efficient methodologies allows for the establishment of novel synthetic routes in the synthesis of complex natural products.[16]

In 2009, we reported the synthesis of carbon-bridged medium-size rings (**2.1.24**) *via* a gold-catalyzed 6-*endo-dig* cyclization (Scheme 2.1.4.1).[17] While some substrates did not have any steric or electronic biases, a ligand optimization allowed us to find reaction conditions that favoured the formation of the desired products. We found that using 2 mol% of the cationic [(JohnPhos)Ag(MeCN)]SbF_6 complex at room temperature in the presence of the substrate **2.1.23** led to the smooth formation of the bridged carbocycles. Two years later, we reported that this gold(I)-catalyzed cyclization can be performed in tandem with the Diels-Alder reaction to generate [3.3.1]bicyclic ketones (**2.1.28**).[18] As shown in Scheme 1.1.4.1, high levels of molecular complexity can be generated in a single operation from simple diene **2.1.25** and dienophile **2.1.26**. Upon the formation of the [4+2] adduct **2.2.27**, the product undergoes a gold(I)-catalyzed 6-*endo-dig* carbocyclization to give [3.3.1]bicyclic ketone

2.1.28. We further demonstrated the usefulness of this transformation in the syntheses of hyperforin, papuaforins A-C, and nemorosone (Figure 2.1.4.1).[19]



Scheme 2.1.4.1 - Synthesis of Bridged Carbocycles via Gold(I)-Catalyzed *6-endo-dig* Cyclization

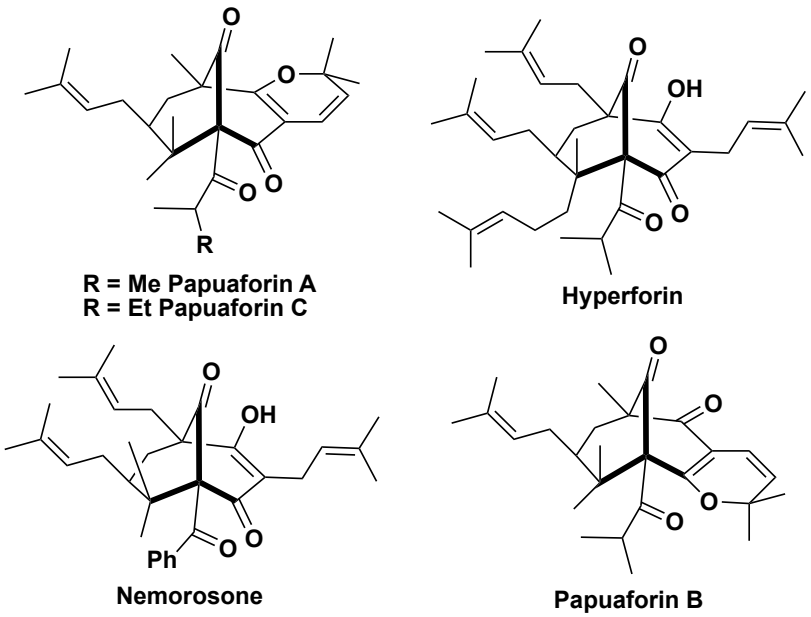
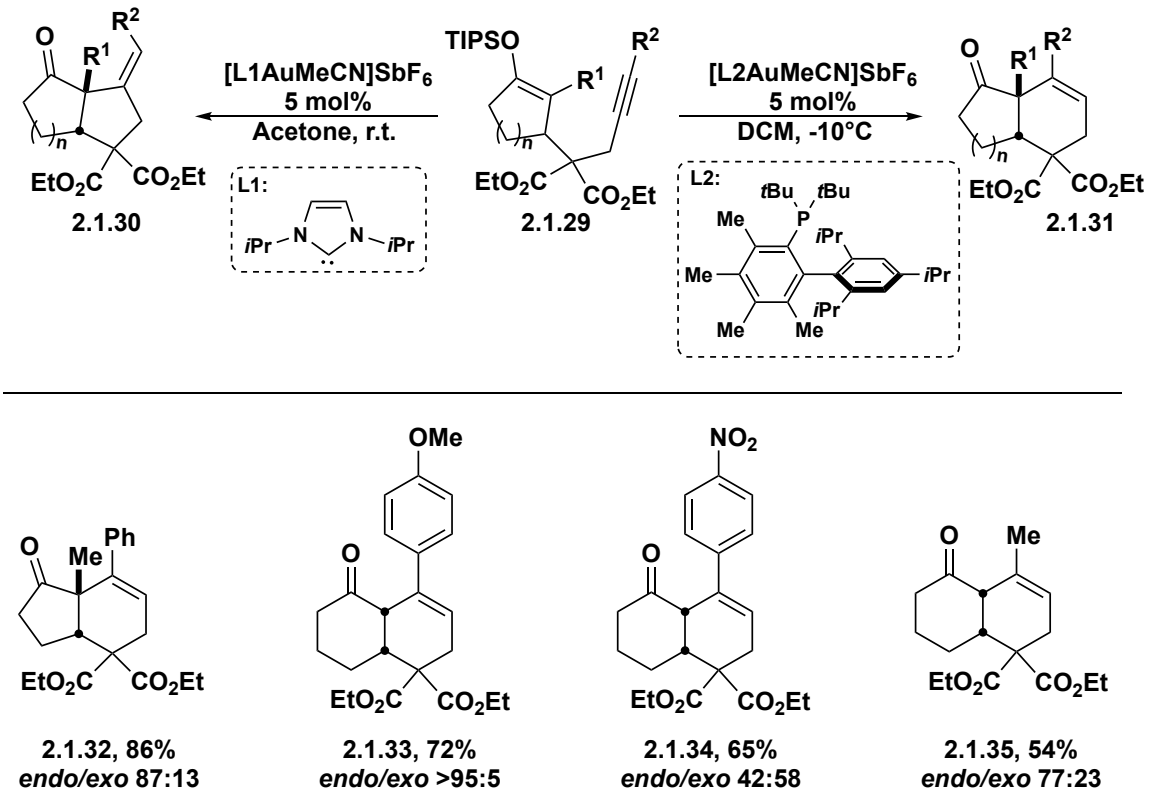


Figure 2.1.4.1 - Molecular Structures of Papuaforins A–C, Hyperforin and Nemorosone

In 2011, our group also reported the divergent synthesis of fused carbocycles using silyl enol ethers.[20] We studied the impact of ancillary ligands on the regioselectivity of the carbocyclization (Scheme 2.1.4.2). The σ-donor ligand **L1** was very efficient in the 5-*exo-dig* cyclization, and the desired products (**2.1.30**, 6 examples) were obtained in less than 10 minutes in excellent yields (86-94 %) and regioselectivities (*exo/endo* 84:16 - >95:5). As for the 6-*endo-dig* cyclization, we found that selectivity was optimal when **L2** was used as a ligand. We suggested that the bulkiness of this Buchwald-type ligand could distort the P−Au−C angle at the transition state, resulting in a reduction of the π-donation from the metal.[21]



Scheme 2.1.4.2 - Gold-Catalyzed Divergent Synthesis of Fused Carbocycles

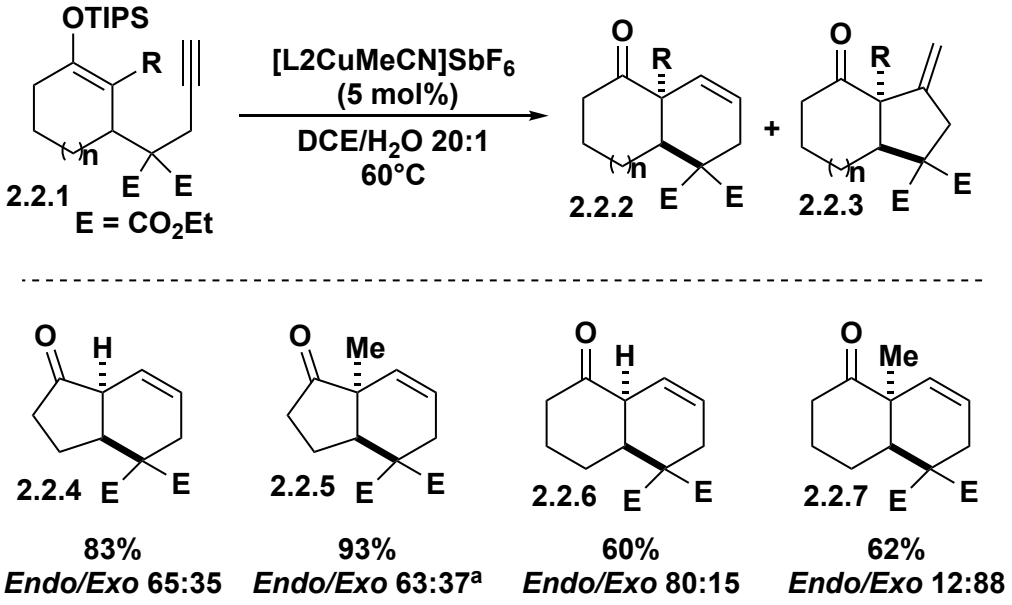
As expected, the selectivity of the reaction varied significantly depending on the electronic properties of substrate **2.1.29**. The substrate leading to **2.1.32** can stabilize the formation of a partial positive charge upon coordination with gold. Thus, the 6-*endo-dig* product can be obtained with a good *endo/exo* selectivity (87:13). The product **2.1.33** can better stabilize this positive charge due to the presence of the *para* methoxy group on the aryl. As a result, the formation of the 6-membered ring was almost exclusive. In contrast, the electron-withdrawing aryl substituent on product **2.1.34** makes formation of *endo* product difficult, and it was not favoured despite the optimized reaction conditions. As for the electronically neutral methyl substituent on **2.1.35**, the 6-*endo-dig* cyclization product was favoured with an *endo/exo* selectivity of 77:23. Based on this last observation, we believe that a thorough condition screening can lead to good regioselectivity for such reactions, even with a substrate that has no electronic bias.

2.2 *6-ENDO-DIG*/ACETALIZATION/PRINS REACTION CASCADE

2.2.1 Project Advent

Encouraged by the results of our previous studies, we decided to extend our selective 6-*endo-dig* cyclization methodology to terminal alkynes.[22] Previous investigations established that terminal alkynes form 5-*exo-dig* cyclization products almost exclusively in presence of Au(I), Hg(II), and Pt(II) catalysts.[23] Drawing inspiration from previous work done in our group and the group of

Echavarren[4], we did thorough ligand and metal screening, including silver and copper catalytic complexes, aimed at favouring the 6-*endo-dig* pathway. We found that for carbocyclization onto terminal alkynes, the cationic complex [(Me_4*t*BuXPhos)Cu(MeCN)]SbF_6 gave the best *endo*:*exo* ratio (Scheme 2.2.1.1). With optimized conditions in hand, we explored the scope of this transformation. To our delight, we found that substrates including both 5- and 6-membered rings led to products (**2.2.4**–**2.2.6**) in good yields favouring the *endo* products. Tetra-substituted silyl enol ethers were overall more challenging to cyclize selectively than their less substituted counterparts. The selectivity of substrates containing 6-membered rings and tetra-substituted silyl enol ethers proved difficult to influence, as exemplified by the generation of compound **2.2.7** in less than 10 % isolated yield (12:88 *endo:exo*)

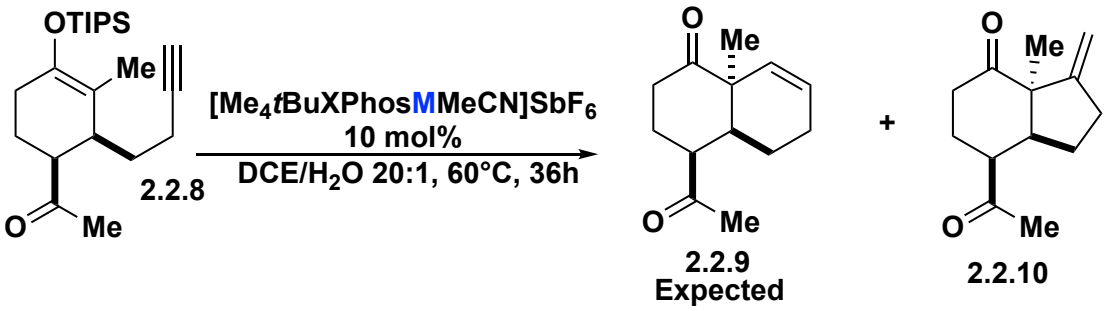


[a]This reaction was performed at r.t.

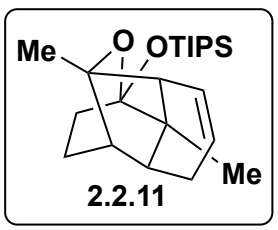
Scheme 2.2.1.1 - 6-*endo-dig* Selective Carbocyclization of Terminal Alkynes

The prevalence of the decalin core in synthesis galvanized our interest in developing conditions that could overcome the selectivity issues present in systems with troublesome functionalities, such as those in product **2.2.7**. We decided to perform the reaction on substrates without malonate moieties to see how the cyclization selectivity could be influenced (Table 2.2.1.1). The absence of the malonate functionality would also allow us to extend the scope of natural products targeted for synthesis. We were particularly interested in exploring the reactivity of the molecular core of **2.2.8** due to its easy accessibility *via endo*-selective [4+2] cycloadditions. A 6-*endo*-selective cyclization on this core would also provide desirable complementarity to a zinc-mediated 5-*exo-dig* cyclization of similar cores published by the Lee group.[24]

Table 2.2.1.1 - Preliminary Results



Entry	Metal	Yield (%)	Ratio 9 : 10 : 11
1	Au	91	0 : 1 : 0
2	Cu	-	-
3	Ag	52	0 : 0 : 1



The investigation began using the ligand Me_4*t*BuXPhos (**L2**), given its propensity to favour the 6-*endo-dig* carbocyclization. We found that the three different metallic complexes gave various outcomes for this reaction. When the reaction was performed using 10 mol% of [**L2**AuNCMe]SbF_6, the 5-*exo-dig* adduct **2.2.10** was exclusively formed in 91 % isolated yield (entry 1). The corresponding copper(I) complex was unreactive and the starting material was fully recovered (entry 2). To our surprise, the cyclization using the silver complex [**L2**AgNCMe]SbF_6 gave the strained polycycle **2.2.11** in 52 % yield. This product is the result of two new C–C bonds as well as one C–O bond. Puzzled by the formation of this unexpected product, we decided to further investigate the mechanism of this reaction as well as its potential applications in organic synthesis.

2.2.2 Optimization

The complexity and rigidity of this polycycle and the purported consecutive formation of three bonds caught our attention. Thus, we decided to optimize the reaction conditions for its formation.

First, the electronic and steric properties of the Buchwald-type ligands on the selectivity of the reaction were investigated (Figure 2.2.2.1). To determine whether the formation of the desired product **2.2.11** relied on ligand effects, we performed the reaction in absence of a ligand by using $AgSbF_6$. As a result, the 5-*exo-dig* product **2.2.10** was isolated in quantitative yield. Of the ligands screened, the relatively less bulky tBuXPhos ligand gave good overall yields

where the desired product **2.2.11** and by-product **2.2.10** were isolated in 64 % yield and in 25 % yield, respectively. We found that JackiePhos favoured formation of **2.2.10**, whereas the more electron-rich BrettPhos ligand preferentially generated the desired product **2.2.11** in 76 % yield. The analogous *t*BuBrettPhos ligand attenuated the yield of the desired product to only 52 %.

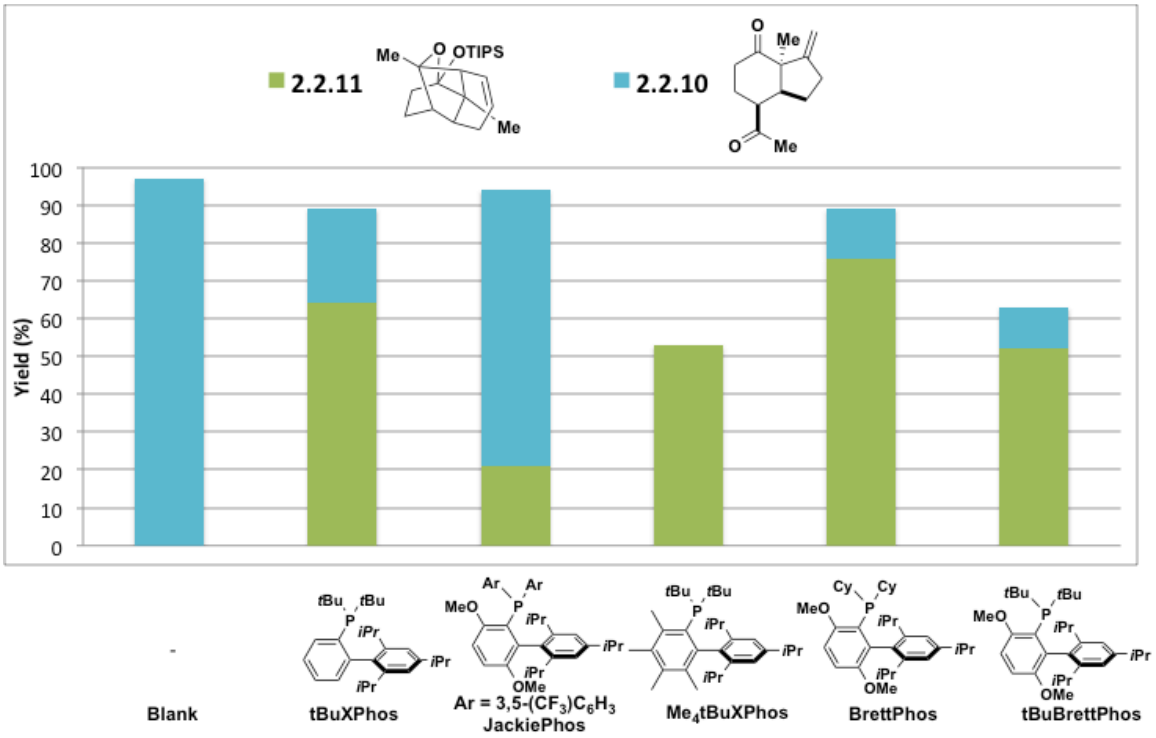
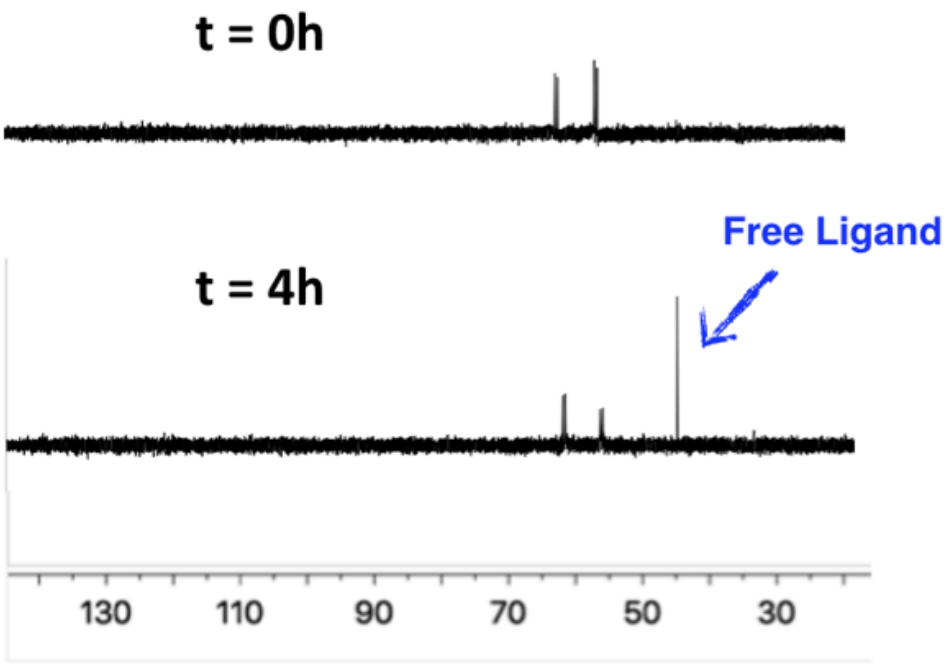


Figure 2.2.2.1 - Ligand Optimization

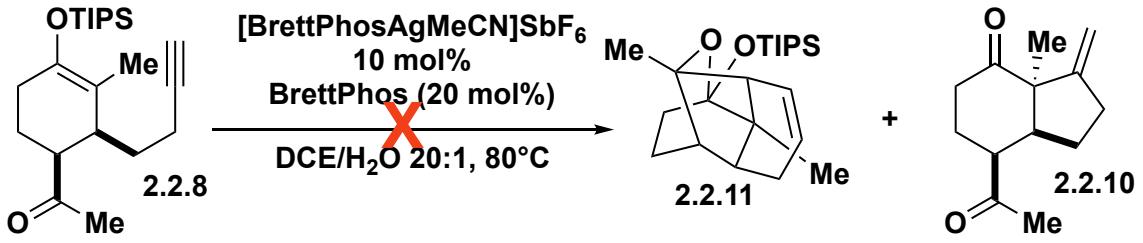
In order to achieve full conversion, a reaction time of 36 hours and 10 mol% of catalyst loading were necessary. Increasing temperature to 80°C resulted in isolation of by-product **2.2.10** in quantitative yield. NMR studies indicated that the phosphine ligand may dissociate from the silver catalyst at high temperature, resulting in loss of selectivity (Figure 2.2.2.2). After 4 hours under

reaction conditions, the phosphine ligand was significantly dissociated from the silver complex, as shown by ^{31}P NMR monitoring. It is important to note that the formation of **2.2.11** is slow, as reflected by the long reaction time required. In contrast, $AgSbF_6$ catalyzes the formation of the 5-*exo* by-product **2.2.10** rapidly, and the reaction is usually complete within an hour. For this reason, incomplete dissociation of the ligand from the catalyst is sufficient to assure the exclusive formation of the by-product. In the hope of preventing formation of by-product **2.2.10**, additional ligand was added to the reaction medium (Scheme 2.2.2.1). Unfortunately, this led to total inhibition of the reaction.



Reaction Conditions: 10 mol% [(Me_4*t*BuXPhos)Ag(MeCN]SbF_6, DCE, 80°C

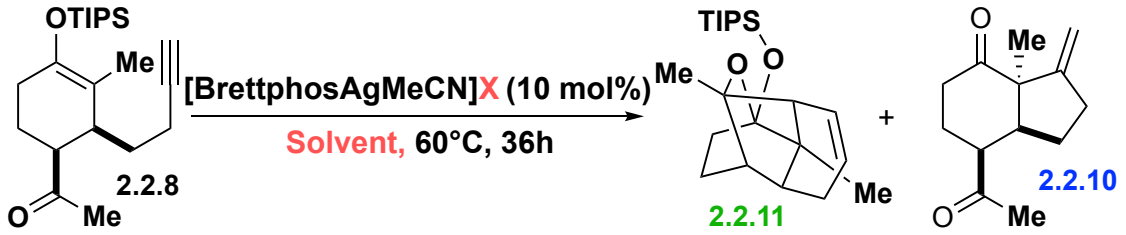
Figure 2.2.2.2 - ^{31}P NMR Monitoring of the Reaction at 80°C



Scheme 2.2.2.1 - Addition of the BrettPhos Ligand

A short solvent screening allowed us to increase both yield and selectivity (Table 2.2.2.1). When the reaction was performed without water as a co-solvent, the yield and selectivity of the reaction remained unchanged (entry 1). When performed in DCM, the reaction yield was improved to 85 % and less than 6 % of **2.2.10** was formed (entry 2).

Table 2.2.2.1 - Solvent and Counter ion Optimization



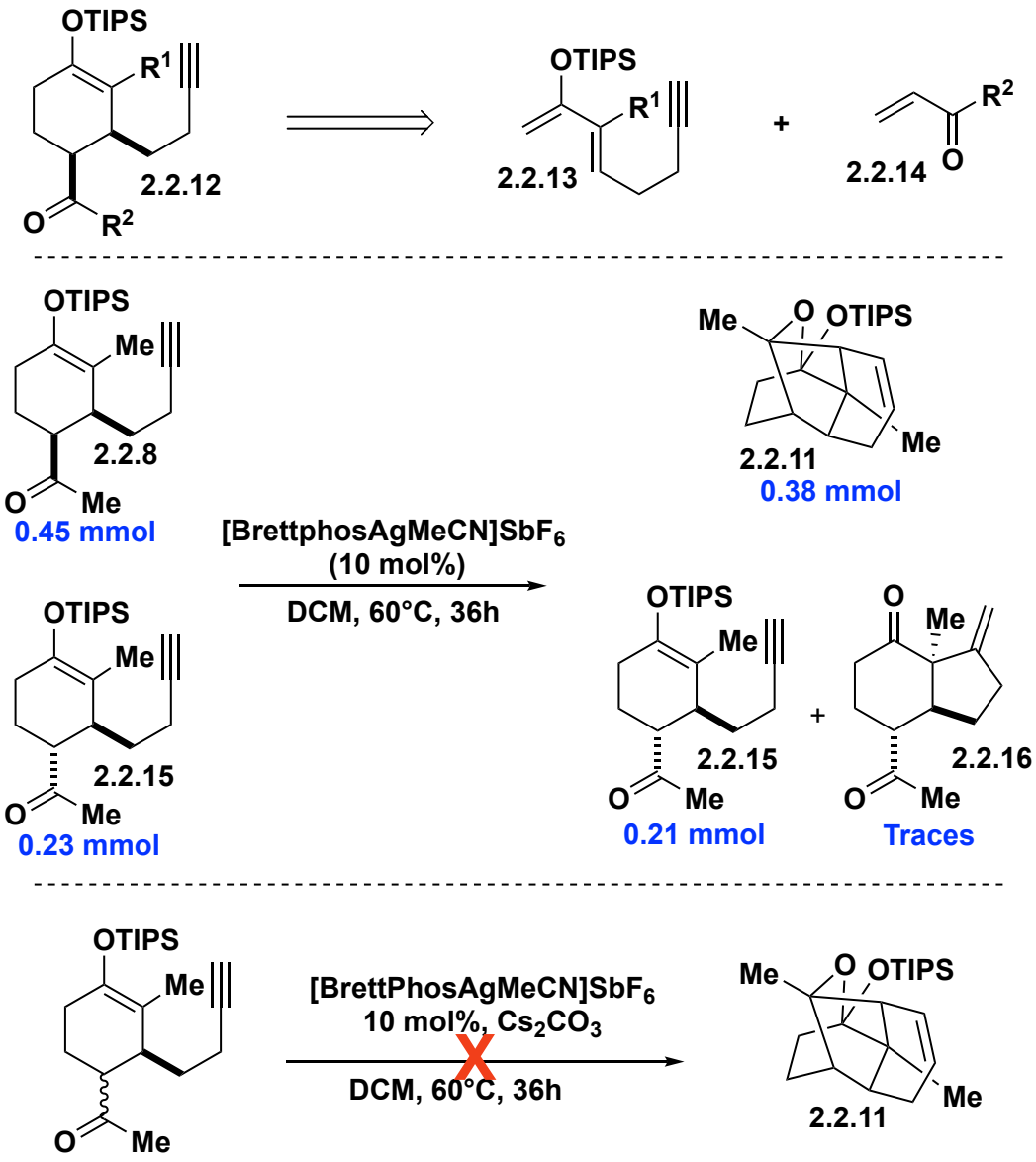
Entry	Solvent	X	Yield (%)	11:10
1	DCE	SbF_6	76	6:1
2	DCM	SbF_6	85	15:1
3	Acetone	SbF_6	3	1:8
4	DCM	BArF	60	2:1

BArF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

Remarkably, the use of acetone as a solvent completely reversed the selectivity of the reaction (entry 3). Finally, we hypothesized that the massive counterion tetrakis[3,5-bis(trifluoromethyl)phenyl]borate should give a more dissociated silver complex that should increase its Lewis acidity. Although the reaction achieved 90 % conversion, we observed a loss of selectivity in the products (entry 4).

2.2.3 Substrate Synthesis and Scope

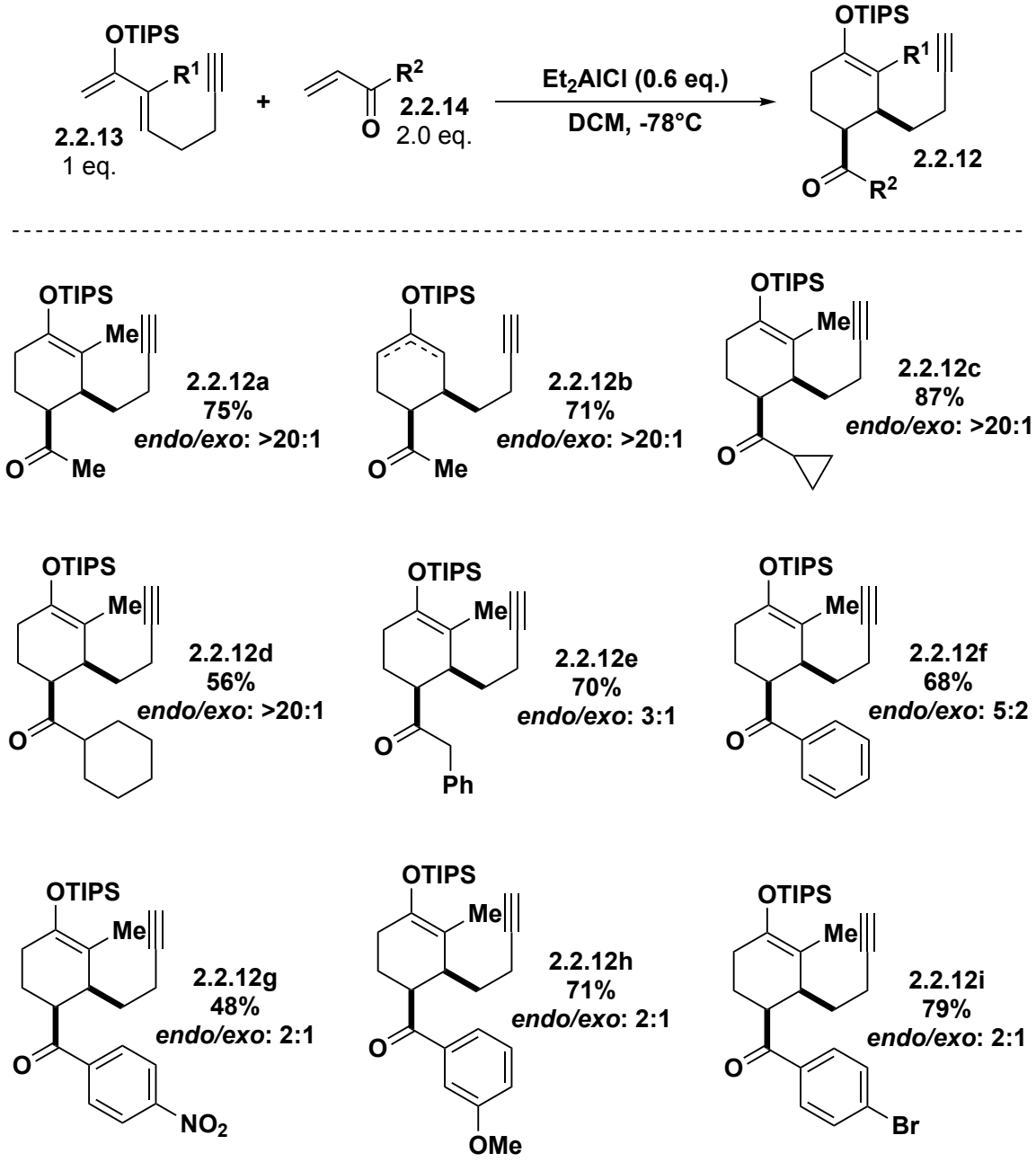
In order to investigate the functional group tolerance and limitations of this silver-catalyzed reaction cascade, we synthesised a variety of substrates. The substrate required is readily accessible *via* an *endo* selective Diels-Alder reaction between diene **2.2.13** and dienophile **2.2.14** (Scheme 2.2.3.1). Since we suspected that bulkier R^2 groups could lead to a mixture of diastereomers for the [4+2] cycloaddition, we also envisaged subjecting diastereomeric mixtures to the silver-catalyzed reaction. Interestingly, when a 2:1 mixture of the *endo* (**2.2.8**) and *exo* **2.2.15** Diels-Alder adducts was used, the *exo* substrate **2.2.15** led to low conversion to the corresponding 5-*exo-dig* product **2.2.16** but mostly remained unaltered. The addition of cesium carbonate to the reaction mixture was attempted for *in situ* isomerization of the stereocentre *α* to the carbonyl group. Unfortunately, the addition of a base into the reaction mixture attenuated the reactivity of the catalyst and only traces of products were observed.



Scheme 2.2.3.1 - Reactivity of the *Endo* and *Exo* Adducts of the Diels-Alder

The substrates required for this methodology were synthesized *via* a Diels-Alder cycloaddition using Et_2AlCl as a Lewis acid (Scheme 2.2.3.2). While the reaction was *endo* selective when R^2 was a relatively small alkyl group (**2.2.12a – 2.2.12d**), mixtures of diastereomers were obtained for bulkier alkyl or aryl groups (**2.2.12e – 2.2.12i**). When R^1 was hydrogen, the double bond of the

product isomerized under these reaction conditions and **2.2.12b** was isolated as a mixture of isomers. In all cases, the yield of the reaction was limited by the competitive hydrolysis of the silyl enol ethers **2.2.13**. Nevertheless, the desired products were obtained in modest to good yields (48-87 %).

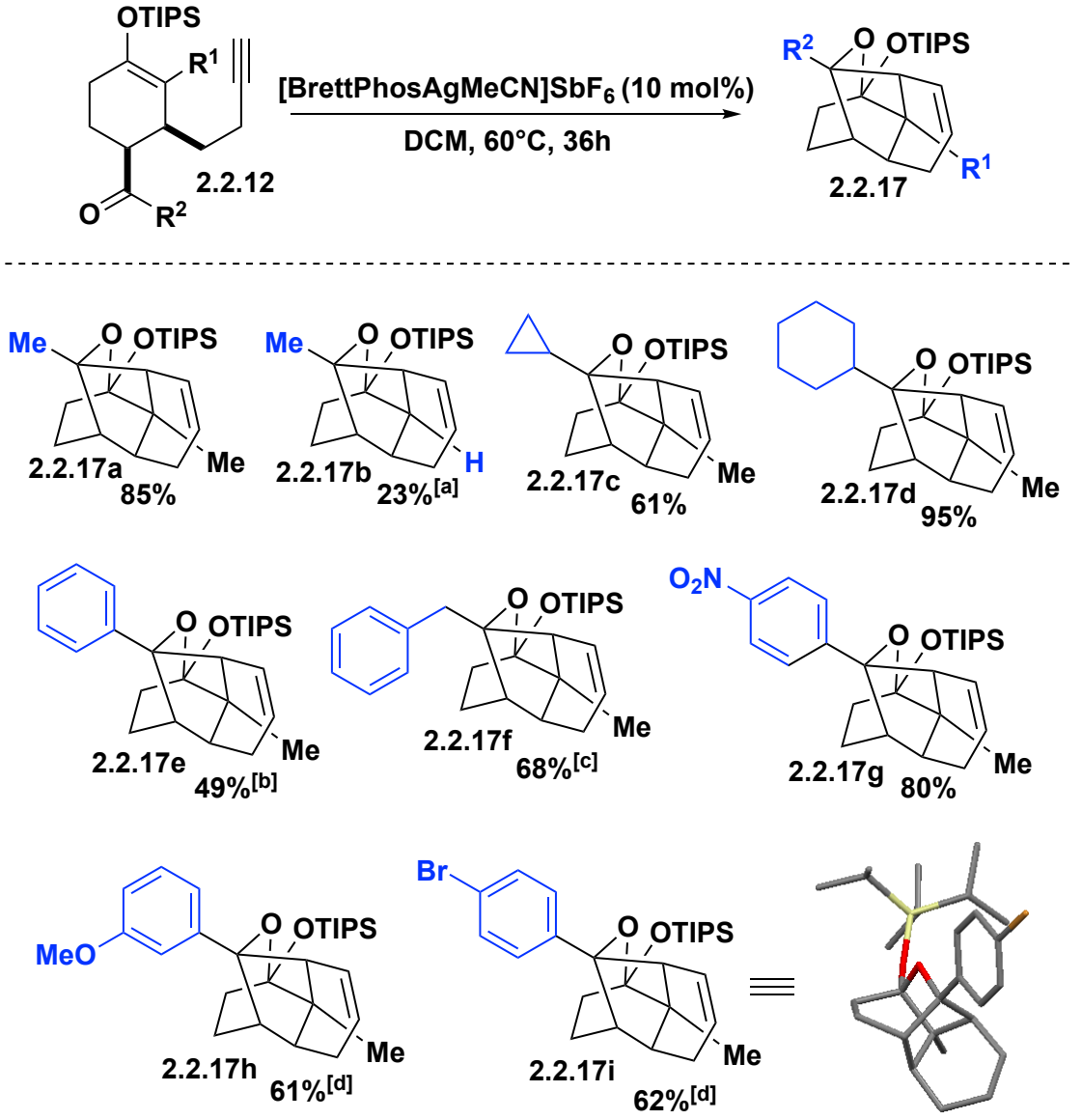


Scheme 2.2.3.2 - Synthesis of the Substrates

When the reaction was performed on larger scale, we had issues reproducing these results. For that reason, many other Lewis acids were tried. In general, strong Lewis acids such as $TiCl_4$, $SnCl_4$, $InCl_3$, and $BF_3{\cdot}Et_2O$ led to hydrolysis of starting material and/or mixture of diastereomers. When 0.2 equivalents of ethylaluminum sesquichloride was used, the desired product was observed as the sole diastereomer in 65 % yield, providing alternative reaction conditions. Iron(III) chloride (50 mol%) also gave **2.2.12a** selectively, but achieving effective conversion of the starting material was challenging. Eventually, we observed that the original conditions gave reproducible results when trace amounts of water were present in the reaction medium. While the active catalyst species remains unknown, the use of water seemed to improve both the yield and the selectivity of this reaction.

With the substrates **2.2.12** in hand, we then explored the scope of this transformation (Scheme 2.2.3.3). First, when R^1 is hydrogen, the reaction proceeds similarly well (**2.2.17b**). The desired reaction cascade also occurred when saturated 3- and 6- membered rings were introduced as the R^2 group and the corresponding compounds were isolated in 61 % (**2.2.17c**) and 95 % (**2.2.17d**) yields, respectively. The reaction also proceeded smoothly in presence of a benzyl group and compound **2.2.17f** was obtained in 68 % yield. Electron-neutral (**2.2.17e**), poor (**2.2.17g**, **2.2.17i**), and rich (**2.2.17h**) aromatic rings were well tolerated and desired products were isolated in good to excellent yields. The structure of compound **2.2.17i** was established by X-ray analysis. Incorporation of aldehydes into the α-carbonyl position led to only traces of

desired product. When amides and esters were incorporated (R^2 = OMe, NMe_2), no conversion was observed and the starting materials were fully recovered. Moreover, in cases where the substrates were only obtainable as mixtures of diastereomers, only the *endo* [4+2] adduct led to the desired product.

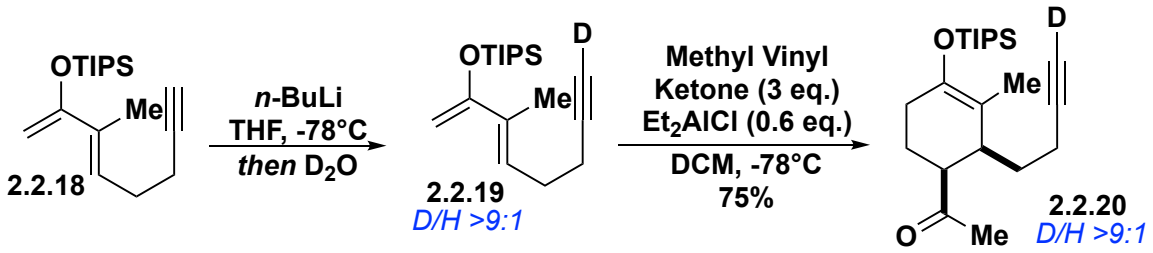


[a] From a complex mixture of isomers. [b] From d.r. = 5:2 (*endo/exo*).
[c] From d.r. = 3:1 (*endo/exo*). [d] From d.r. = 2:1 (*endo/exo*).

Scheme 2.2.3.3 - Scope of the *6-endo-dig*/Acetalization/Prins Reaction Cascade

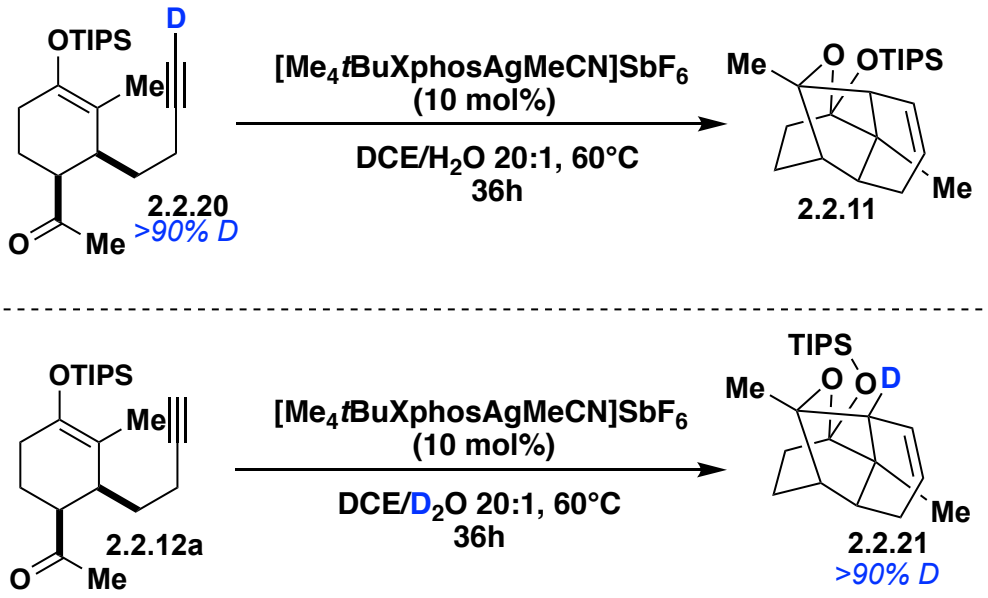
2.2.4 Mechanistic Investigation

To gain valuable insight into the mechanism of this transformation, we performed deuterium-labelling experiments. Deuterated substrate **2.2.20** was first synthesized (Scheme 2.2.4.1). Deprotonation of the diene **2.2.18** with *n*-BuLi at –78 °C followed by quenching with deuterated water allowed the formation of the deuterated diene **2.2.19** with more than 90 % deuterium incorporation. Cycloaddition using methyl vinyl ketone as a dienophile occurred smoothly to complete the synthesis of the desired compound **2.2.20** in 75 % yield.



Scheme 2.2.4.1 - Synthesis of the Deuterated Substrate

Interestingly, the deuterated substrate **2.2.20** under the typical reaction conditions gave exclusively the non-deuterated compound **2.2.11** (Scheme 2.2.4.2). In addition, the reaction of substrate **2.2.12a** with DCE and D_2O as co-solvents gave the deuterated compound **2.2.21** with over 90 % of deuterium incorporation. These two experiments suggest that a fast hydrogen-deuterium exchange occurs prior to the carbocyclization.

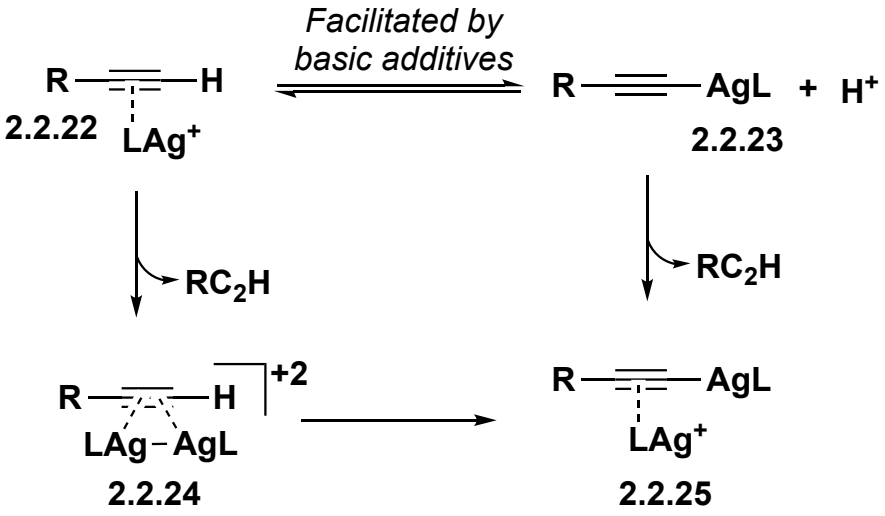


Scheme 2.2.4.2 - Deuterium-Labelling Experiments

The reaction of terminal alkynes with coinage metals to form metal acetylides complexes under basic conditions has been used extensively in organic synthesis.[25] In this case, since there is no base present in the reaction medium, the observations made during the deuterium exchange experiments suggest silver dual-catalysis. The strong aurophilic interactions of binuclear gold(I) lead to interesting reactivity. Similarly to gold, silver can also have binuclear interactions.[26] Since Ag^+ has approximately the same cationic radius as compared to Au^+, the interatomic distance of the argentophilic interaction is within the range of the analogous aurophilic interaction.[27] As for phosphine complexes, advanced calculations have shown that the M−M interaction energy of the dimer $[\{H_3PMCl\}_2]$ was determined to be about –15 kJ/mol for silver and is the largest of the coinage metal triad. While gold has a low coordination number and prefers to adopt a linear geometry,[28] silver can participate in up to four complexations.

For this reason, in absence of bulky phosphine ligands, silver complexes would rather form oligomers or cubane-type tetramers.

From these considerations, it can be hypothesised that the terminal alkyne **2.2.12a** can be dually activated by the silver catalyst (Scheme 2.2.4.3). The formation of a silver acetylide intermediate in the proposed mechanism could explain the rapid hydrogen/deuterium exchange observed in Scheme 2.2.4.2. Upon coordination of silver to the alkyne, the silver acetylide **2.2.23** can be formed. Although metal complexation decreases the pK_a of the terminal alkyne, this step is generally facilitated by a base and can be quite challenging to achieve otherwise.

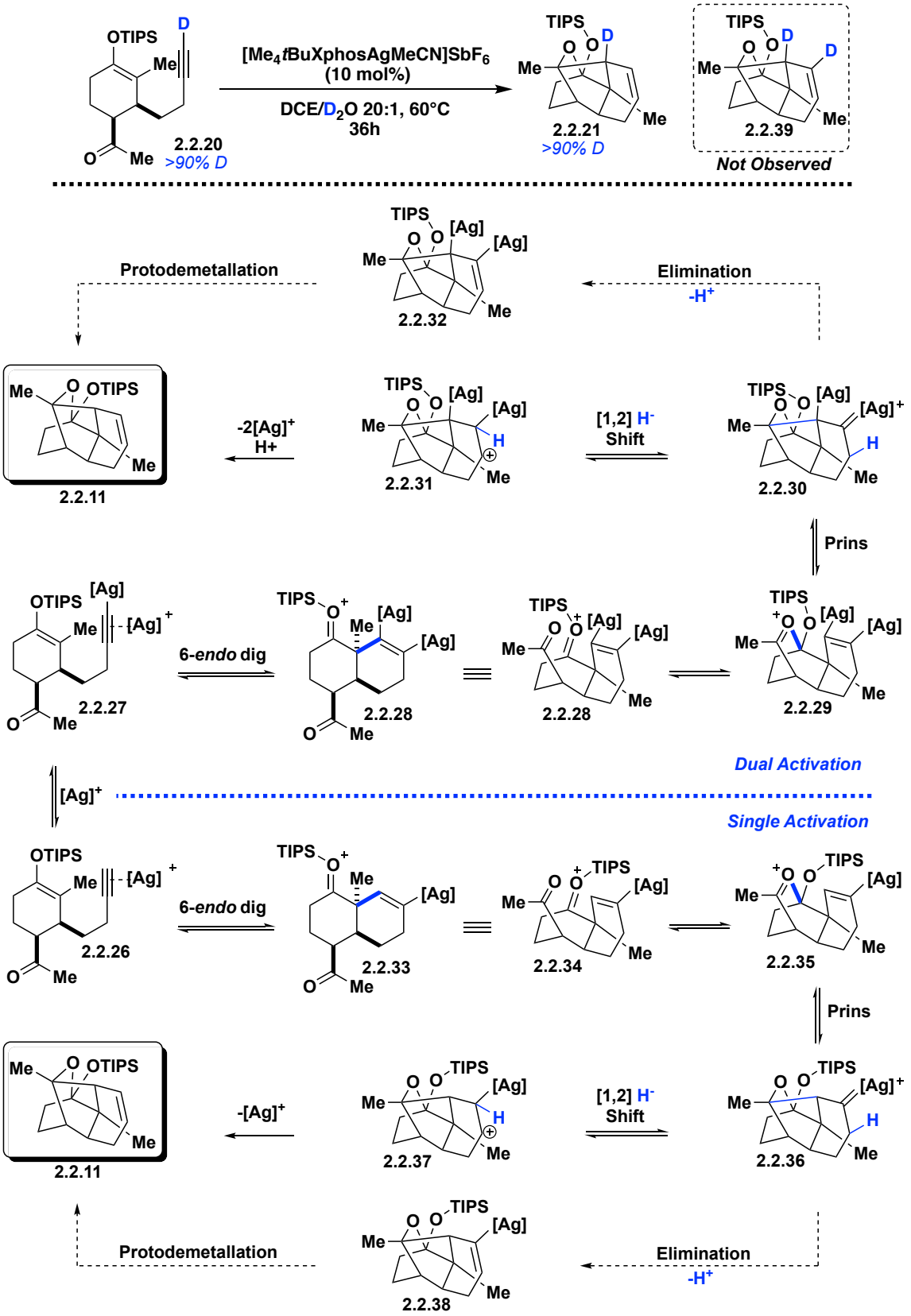


Scheme 2.2.4.3 - Proposed Dual-Silver Activation of the Alkyne

Alternatively, a second silver complex can bind with both the alkyne and the catalyst to generate the binuclear complex **2.2.24**. Since this dicationic

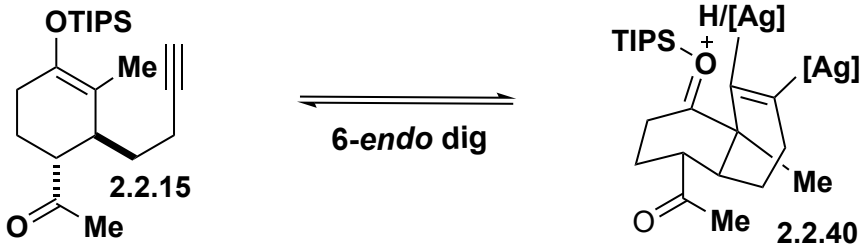
bis(silver) π-alkyne complex involves both faces of the orthogonal π system, it is believed that the formation of this complex leads to significant enhancement of the acidity of the terminal alkyne.[29] Therefore, it becomes easier to deprotonate the alkyne and the activated acetylide species **2.2.25** is formed. In absence of a basic additive, it is expected that a strong conjugated acid will be form during this process. In our system, one might suggest that the carbonyl group of the substrate acts as the base. To support the hypothesis of dual-silver catalysis further, additional kinetic studies would be appropriate.

To explain the formation of the complex product **2.2.11**, we propose the following mechanism (Scheme 2.2.4.4). Upon coordination of silver to the alkyne moiety, the silver acetylide **2.2.27** can be formed. The compound **2.2.27** can undergo a 6-*endo-dig* cyclization to form the bicyclic intermediate **2.2.28**. The nearby carbonyl can rapidly trap the newly formed oxonium ion carrying the TIPS group, leading to oxonium ion **2.2.29**. Since conversion of the *exo* adduct substrates **2.2.15** mostly do not lead to product, we believe that the initial cyclization is reversible. The carbonyl group of **2.2.40** is not close enough to trap the oxonium ion (Scheme 2.2.4.5). Upon back donation from the silver intermediate, the electron-rich olefin can undergo a Prins reaction and attack the oxonium to afford **2.2.30**. From this intermediate, two mechanisms are possible. First, the hydrogen vicinal to the silver atom can undergo a [1,2] hydride shift to form the secondary carbocation **2.2.31**. Elimination of the secondary silver and protodemetallation at the bridge position would lead to the formation of the observed product **2.2.11**.



Scheme 2.2.4.4 - Proposed Mechanisms

Alternatively, the hydrogen vicinal to the silver atom of intermediate **2.2.30** can eliminate to form the double bond of **2.2.32**, followed by protodemetallation of both silver complexes to also afford the product **2.2.11**. Deuterium studies indicated that the protodemetallation step is most likely an intramolecular process. Submitting compound **2.2.20** to the reaction conditions with D_2O as co-solvent resulted in isolation of solely non-deuterated compound **2.2.21**. The absence of deuterium at the most likely site of protodemetallation (**2.2.39**) implies an intramolecular [1,2] hydride shift to form carbocation **2.2.31**. Also, the formation of the product could be possible when the alkyne is activated by only one molecule of the silver catalyst. The mechanism for the 6-*endo*-*dig*/acetalization/Prins reaction cascade would be the same until the formation of intermediate **2.2.36**. This intermediate would then undergo a [1,2] hydride shift to form **2.2.37**, which upon elimination of silver and regeneration of the catalytic species would give the product **2.2.11**. Considerable complexity is built during this reaction, with one C–O bond and two C–C bonds formed stereoselectively.



Scheme 2.2.4.5 - Reactivity of the *exo* Diels-Alder Adduct

2.2.5 Functionalization of the Polycycle 2.2.11

The molecular rigidity of compound **2.2.11** is quite impressive. Within the 12 atoms (11C + 1O) of this molecule's framework can be found two 5-membered rings, four 6-membered rings and two 7-membered rings (Figure 2.2.5.1). This unique feature of this polycycle fuelled our motivation to explore its reactivity.

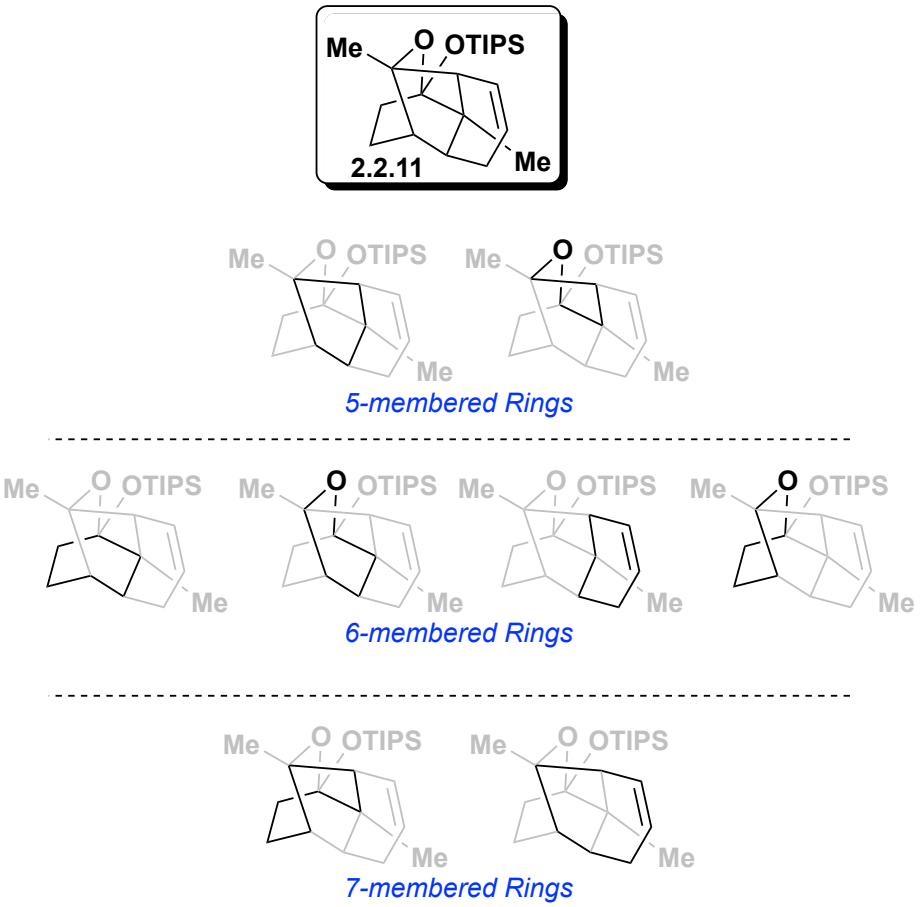
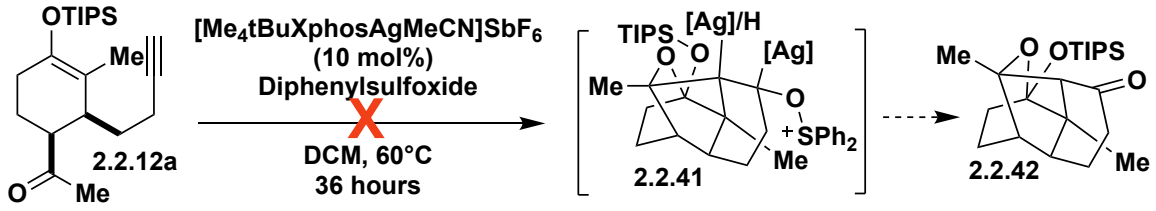


Figure 2.2.5.1 - Molecular Complexity of Polycycle 2.2.11

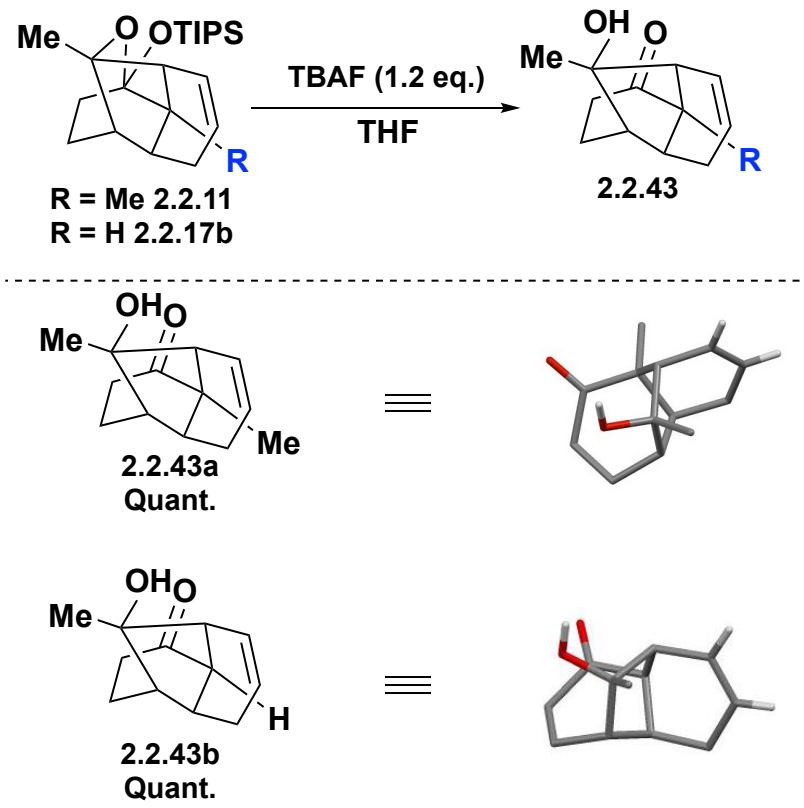
In our proposed mechanism, we suggested a silver-stabilized carbocation as an intermediate (**2.2.30** and **2.2.36**, Scheme 2.2.4.4). To increase the number

of functional groups of the molecule, we tried to intercept this intermediate. Inspired by the work of Toste *et al.*, we added diphenyl sulfoxide to the reaction medium in hopes of isolating the corresponding ketone **2.2.42** (Scheme 2.2.5.1). Due to competition of the sulfoxide addition against the intramolecular [1,2] hydride shift, this product was unfortunately never observed, despite the use of up to five equivalents of sulfoxide and a reaction concentration of 1 M.



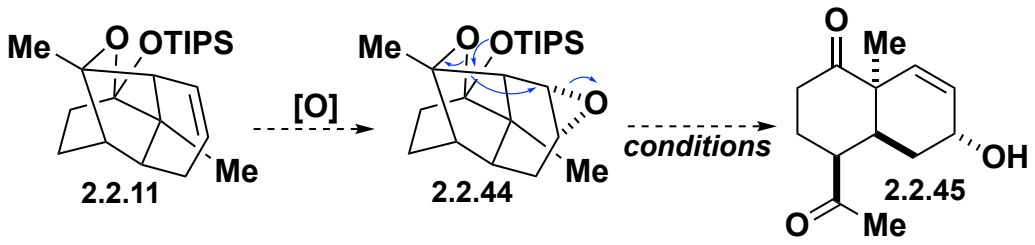
Scheme 2.2.5.1 - Oxidative 6-*endo-dig*/acetalization/Prins

Protecting group removal with TBAF led to the opening of the resulting hemiacetal into the corresponding ketone and tertiary alcohol **2.2.43** (Scheme 2.2.5.2). The reaction proceeded almost instantly and both products **2.2.43a** and **2.2.43b** were obtained quantitatively. The compounds were crystalline and so it was possible to confirm the structures by X-ray crystallography.



Scheme 2.2.5.2 - Deprotection of the Polycycle

Next, we wanted to explore if the rigidity of this framework could be beneficial for the formation of stereospecific bonds. Since the decalin core is ubiquitous in naturals products, we investigated the possibility of an epoxidation of the double bond in **2.2.11**, which, after a Grob fragmentation, would give the highly functionalized decalin **2.2.45** (Scheme 2.2.5.3). We hypothesised that the epoxidation would occur on the bottom face of the molecule due to steric hindrance.



Scheme 2.2.5.3 - Synthesis of Decalin

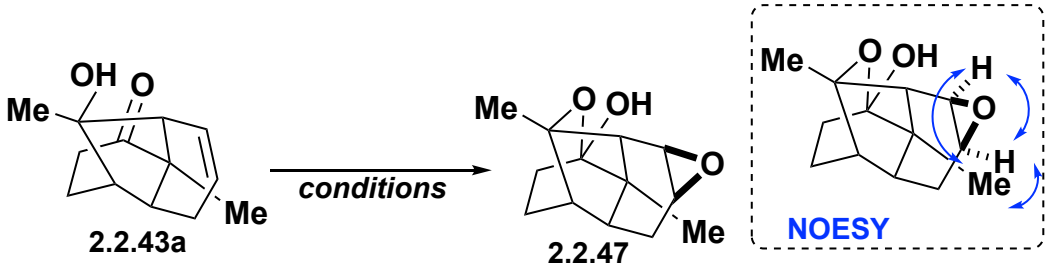
Unfortunately, the epoxidation was not as selective as predicted (Table 2.2.5.1). Between three different oxidants, the best selectivity obtained was 7:3 with *m*CPBA (entry 1). In addition, the diastereomers could not be separated by flash chromatography and we were not able to identify the major relative configuration. The best yield was also obtained with this oxidant, and the desired product **2.2.46** was isolated in 85 % yield. The *in situ* formation of performic acid using formic acid and hydrogen peroxide allowed for the formation of the product in 67 % yield (entry 2). When oxone was mixed with acetone to create dimethyldioxirane (DMDO) *in situ*, poor conversion was observed, and the desired product was formed in only 20 % yield (entry 3). Despite the poor selectivity of the reaction, we attempted to induce the Grob fragmentation of the compound **2.2.46** to form the expected decalin core. Unfortunately, when **2.2.46** was treated with TBAF, the deprotection occurred without further fragmentation and the corresponding hemiacetal was quantitatively isolated. Addition of DBU and the increase in temperature up to 70 °C did not improve the reaction, which still did not result in any conversion to the desired product.

Table 2.2.5.1 - Optimization of the Epoxidation of the Polycycle 2.2.11

Entry	Conditions	Yield (%)	d.r.
1	*m*CPBA (1.5 eq.), r.t.	85	**7:3**
2	Formic acid (3 eq.), H_2O_2 (6 eq.), r.t.	67	**2:1**
3	Oxone (1.25 eq.), $NaHCO_3$ (4.5 eq.) 18Crown6 (0.1 eq.), Acetone, 0°C - r.t.	20	**2:1**

We also performed this reaction sequence on the silyl-deprotected polycyclic compound **2.2.43a**. Interestingly, high selectivity greater than 10:1 was observed when using *m*CPBA in this case (Table 2.2.5.2, entry 1). Notably, the conversion was increased and the product **2.2.47** was isolated quantitatively. The stereochemistry was established by using NOESY experiments and showed that the epoxidation occurred on the top face of the molecule (Figure 2.2.5.2). We believe that this selectivity occurred from the directing ability of the tertiary alcohol. Interestingly, the formation of the epoxide, which induced a conformational change in the molecule, caused the alcohol to cyclize back onto the ketone leading to the corresponding hemiacetal. Performic acid reacted poorly by comparison and only 8 % of product **2.2.47** was generated (entry 2).

Table 2.2.5.2 – Optimization of the Epoxidation of Compound 2.2.44a

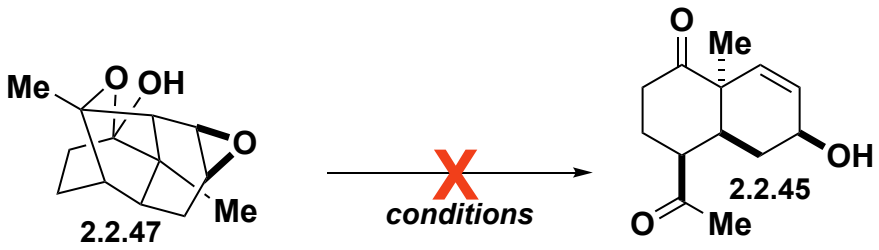


Entry	Conditions	Yield (%)	d.r.
1	*m*CPBA (1.5 eq.), r.t.	>95	**>10:1**
2	Formic acid (3 eq.), H_2O_2 (6 eq.), r.t.	8	**5:1**

With epoxide **2.2.47** in hand, we investigated the formation of the decalin **2.2.45** under basic and acidic conditions (Table 2.2.5.3). As previously mentioned, the epoxide **2.2.47** was unreactive in presence of DBU at 70°C (entry 1). The use of a stronger base, such as sodium hydride, was also unproductive (entry 2). Moreover, the epoxide **2.2.47** completely degraded in acidic medium, in presence of both Lewis and Bronsted acids (entry 3-4).

Although the decalin motif could not be obtained from the unusual polycyclic compound generated using this method, the formation of this product still testifies to the great structural variety that can be obtained using coinage metals.

Table 2.2.5.3 - Optimization of the Grob Fragmentation



Entry	Conditions	Conversion (%)	Yield (%)
1	DBU (2 eq.), 70°C	0	-
2	NaH (1.2 eq.), 0°C - r.t.	0	-
3	$BF_3{\cdot}Et_2O$ (0.3 eq.), -78°C	100	0
4	CSA (1.2 eq.), 0°C - r.t.	100	0

2.3 STUDIES TOWARD THE SYNTHESIS OF TEUCRIN A

With the development of efficient tools for the optimization and selective synthesis of carbocycles using silyl enol ethers, we aspired to apply this knowledge to the synthesis of a natural product.

The structure of teucrin A was elucidated by Popa and Reinbold in 1973.[30] This natural product is a neoclerodane diterpenoid with six stereocentres, of which 5 are contiguous. Teucrin A possesses a decalin motif that we believed could be formed using a selective 6-*endo*-*dig* cyclization (Figure 2.3.1). Since our

transformation has great functional group tolerance, we hypothesised that the cyclization could occur from a highly functionalized Diels-Alder adduct, making the synthesis of the natural product concise, practical, and effective.

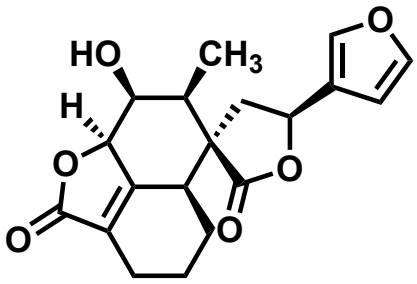
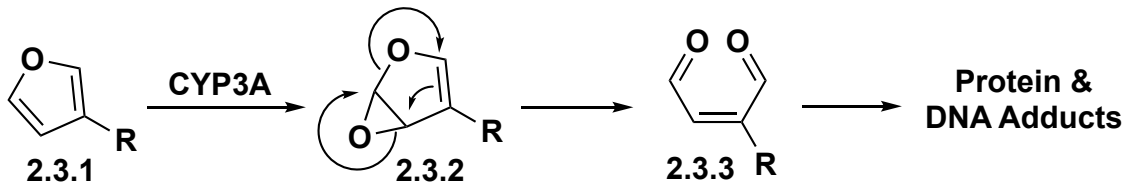


Figure 2.3.1 - Molecular Structure of Teucrin A

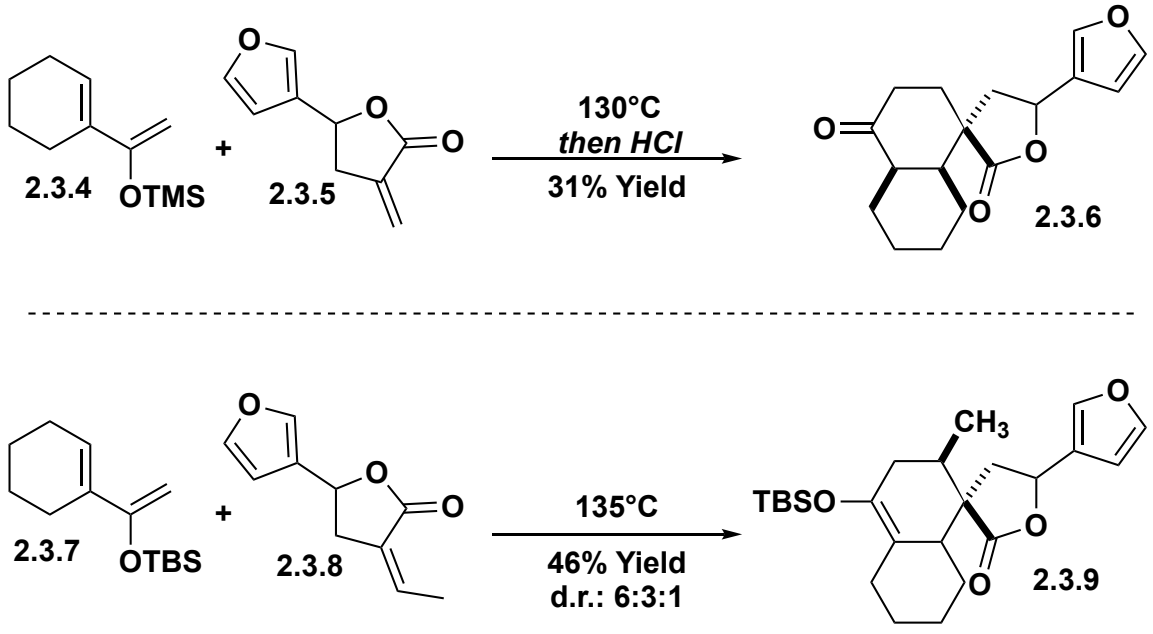
Teucrin A is a natural product found in *Teucrium* species. Its concentration is the highest in the *Teucrium chamaedrys* plant, as it reaches 0.13 %.[31] This plant is used in the liquor industry as a bitter flavouring agent, and, due to its hepatotoxicity, it has been estimated that the tolerable daily intake (TDI) for a human is 0.12 mg/day.[32] Indeed, the compound is metabolized by the enzyme CYP3A, which oxidizes the furan moiety (Scheme 2.3.1). The formation of epoxide **2.3.2** induces a ring opening, resulting in the formation of the conjugated α,β-unsaturated dial **2.3.3**. This highly reactive intermediate then promotes the formation of many protein and DNA adducts.



Scheme 2.3.1 - Metabolism of Teucrin A by CYP3A

2.3.1 Previous Efforts

Although there exists no synthesis of teucrin A to date, Ley *et al.* attempted to synthesise the framework of the natural product in 2011.[33] To do so, the authors imagined a Diels-Alder reaction between the diene **2.3.4** and the dienophile **2.3.5** (Scheme 2.3.1.1). Although dienophile **2.3.5** was stable under acidic conditions, all cycloaddition attempts using Lewis acids were unsuccessful. When the compounds were heated to 130 °C, followed by treatment with hydrochloric acid to induce hydrolysis of the resulting silyl enol ether, the desired compound **2.3.6** was isolated in 31% yield as the sole diastereomer. Any further attempts to increase the yield were unsuccessful.

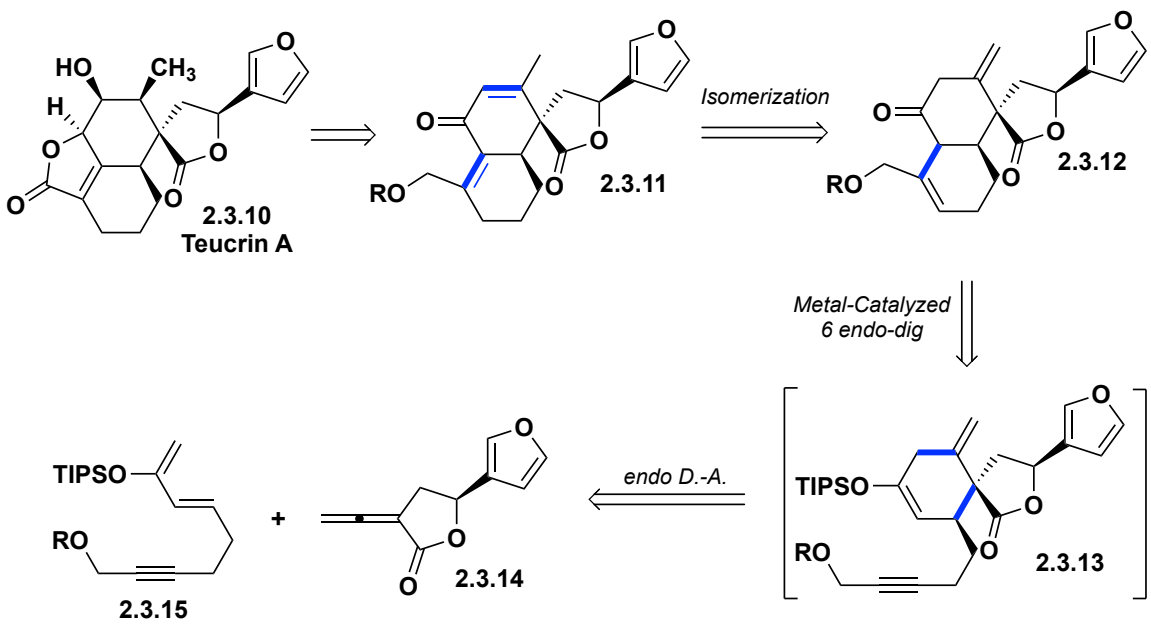


Scheme 2.3.1.1 - Synthetic Efforts Toward the Core of Teucrin A by Ley *et al.*

As for the cycloaddition between analogous diene and dienophile **2.3.7** and **2.3.8**, the product **2.3.9** was generated in 46 % as an inseparable mixture of three diastereomers (d.r. = 6:3:1). The authors claimed that the extra methyl group on the dienophile hindered the *endo* approach, due to steric interactions during the transition state. As a result, the *exo* pathway became more competitive. Ley *et al.* concluded that, due to the poor yield and stereocontrol, the viability of this approach for synthesis is questionable and thus never attempted the total synthesis of teucrin A or any of the related clerodane diterpenoid natural products.

2.3.2 Retro-Analysis and Synthesis Considerations

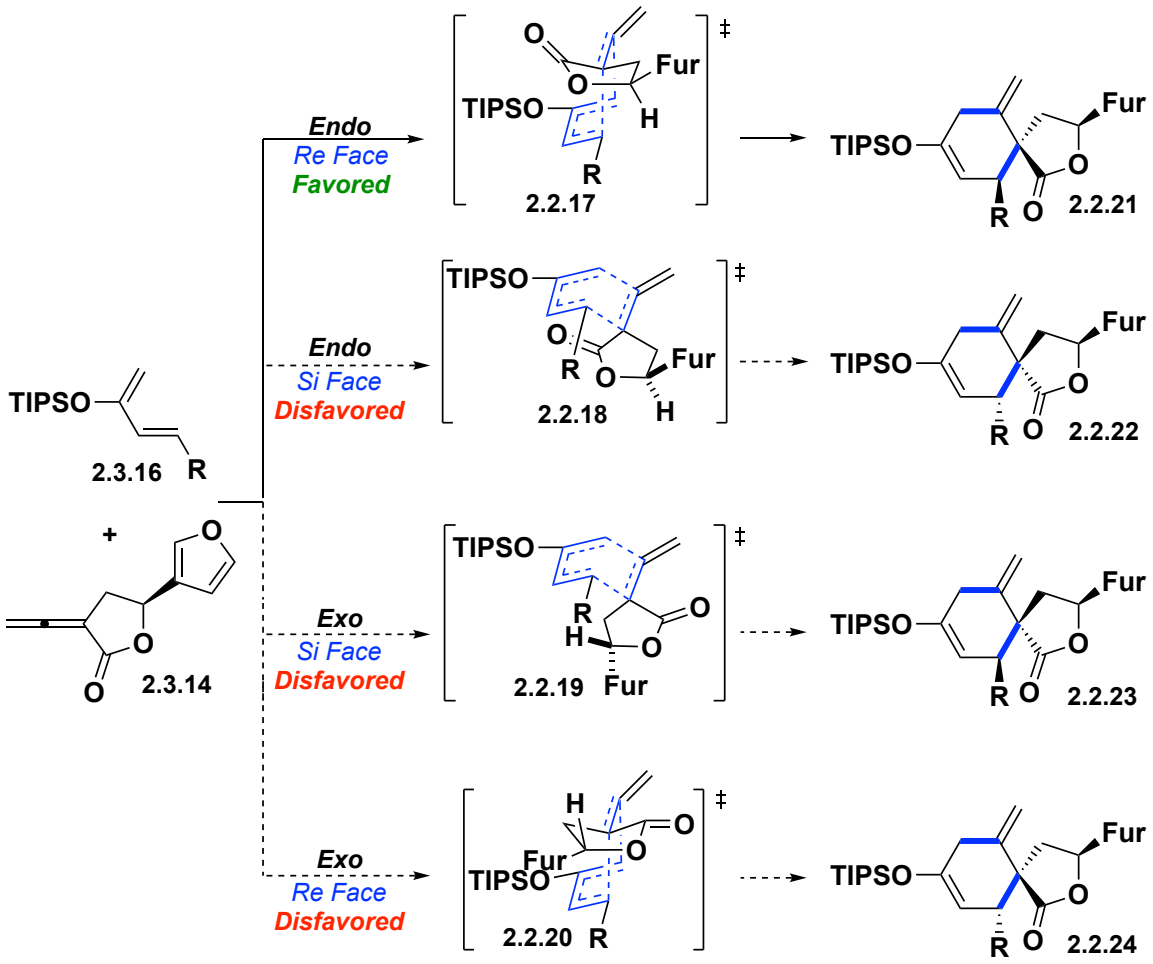
We envisioned that Teucrin A (**2.3.10**, Scheme 2.3.2.1) could easily be derived from the advanced intermediate **2.3.11** after a few functional group manipulations. The divinylketone motif of **2.3.11** could be obtained after the isomerization of both π-bonds of **2.3.12** to form the thermodynamically favoured conjugated system. Decalin **2.3.12** would be the result of a stereospecific Diels-Alder/*6-endo-dig* cyclization sequence. The highly functionalized diene **2.3.15** and dienophile **2.3.14** would be used in an intermolecular [4+2] cycloaddition. Our strategy provides the rapid construction of the advanced intermediate **2.3.11**. The remarkable chemoselectivity of coinage metals allow the cyclization step to occur in presence of many functional groups and greatly contributes the synthetic endeavour.



Scheme 2.3.2.1 - Retrosynthetic Analysis of Teucrin A

To achieve an enantioselective synthesis of teucrin A, the enantiopure formation of dienophile **2.3.14** would be necessary. One might suggest that this stereocenter can then induce stereoselectivity in the Diels-Alder reaction, resulting in the formation of only one diastereomer out of the four possibilities (Scheme 2.3.2.2). Based on Ley's studies, we believe that the *endo* approach of the dienophile would be favoured, due to the extra orbital stabilization at the transition state.[33] Since the furan ring occupies the top face of the molecule, the diene should prefer to approach on the bottom face, resulting in the transition state **2.2.17**. Reaction of the diene on the *re*-face of the dienophile would selectively generate the adduct **2.2.21**. The formation of the *endo* product **2.2.22** from approach to the *si*-face would be disfavoured because of the steric interactions of the furan with the linear chain of the diene (R group), as shown in

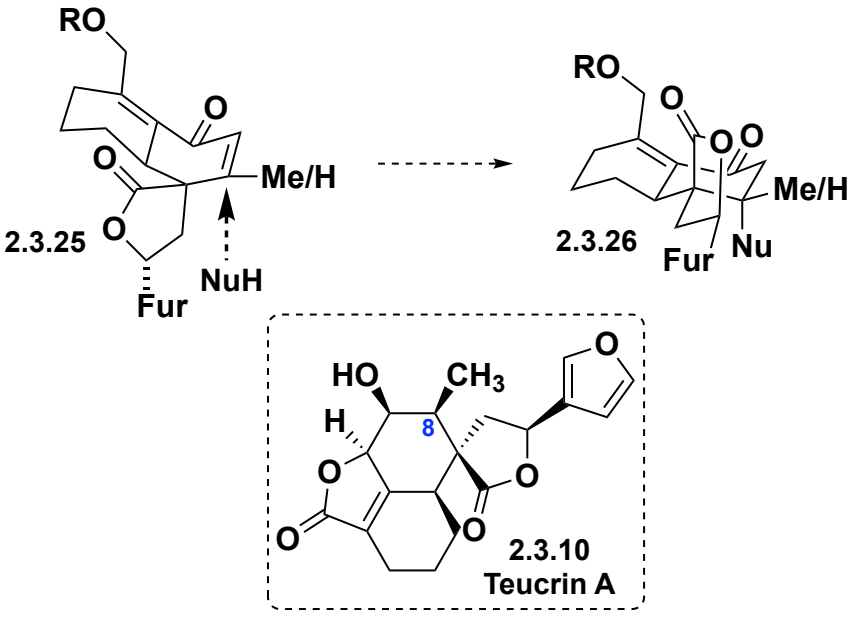
the transition state **2.2.18**. The *exo* Diels-alder reaction, leading to transition state **2.2.19** and **2.2.20** is believed to be less favourable in terms of both electrostatic and steric interactions. For that reason, diastereomers **2.2.23** and **2.2.24** should not be observed experimentally.



Scheme 2.3.2.2 - Expected Selectivity of the Diels-Alder Reaction

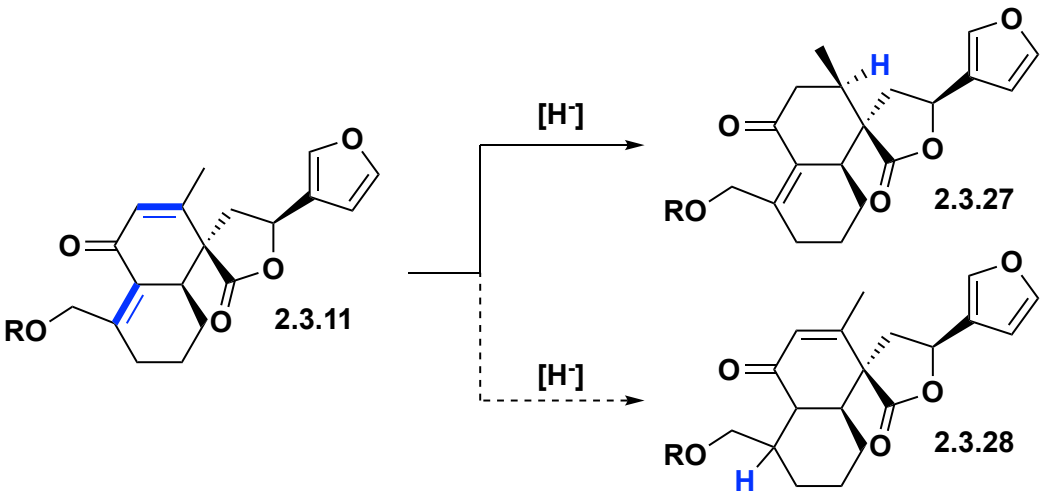
When planning the synthesis, we took early cognizance of the stereochemistry embedded at C^8 (Scheme 2.3.2.3). This stereocenter has an absolute configuration (*S*), with the methyl oriented *syn* to the carbonyl of the

lactone. At the onset, we planned to avoid the use of a trisubstituted dienophile for the intermolecular Diels-Alder as reported by Ley. It is known that Diels-Alder reactions using trisubstituted dienophiles necessitate harsher conditions and tend to proceed in a stepwise manner.[34] The intermediate **2.3.25** would be formed after the Diels-Alder/6-*endo-dig* reaction cascade. Through a 1,4-addition to the α,β-unsaturated carbonyl, one could expect the addition of a nucleophile to proceed through a chair-like transition state to give compound **2.3.26**. One could imagine that the use of an allene as the dienophile (**2.3.14**), would, in principle, limit the steric interactions when forming that pivotal C–C bond to produce the cycloadduct **2.3.12**. To the best of our knowledge, there are only a few examples of such challenging [4+2] cycloadditions reported in the literature.[33,35]



Scheme 2.3.2.3 - C[8] Stereochemistry

Finally, we hypothesised that the 1,4-addition of the hydride would predominately occur on the desired π-bond to form **2.3.27** (Scheme 2.3.2.4). Previous experiments have shown that conjugate addition onto the other alkene to form **2.3.38** is challenging, supposedly due to cyclic torsion and therefore misalignment of the π orbitals with the carbonyl.[36]

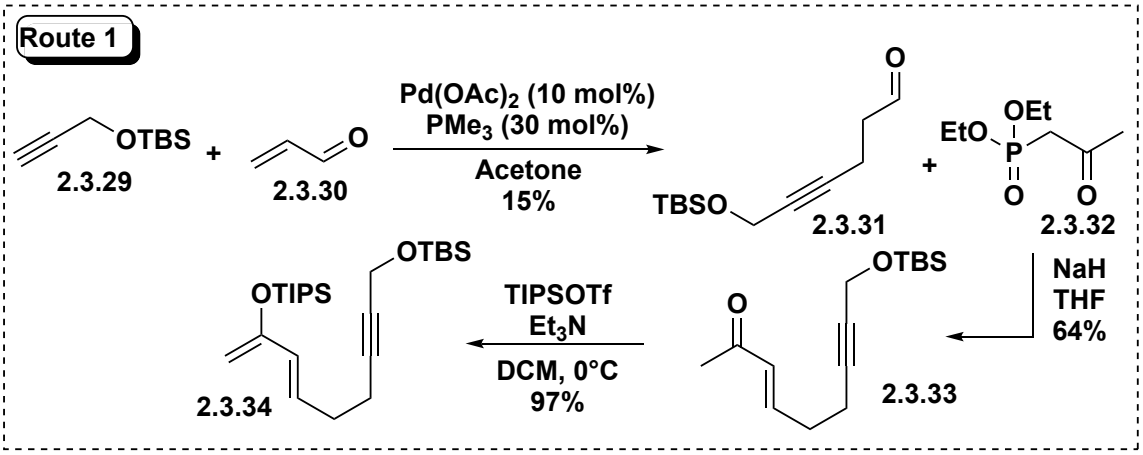


Scheme 2.3.2.4 – Expected Regioselectivity of the 1,4-Reduction of the Enone

2.3.3 Synthesis of the Diene

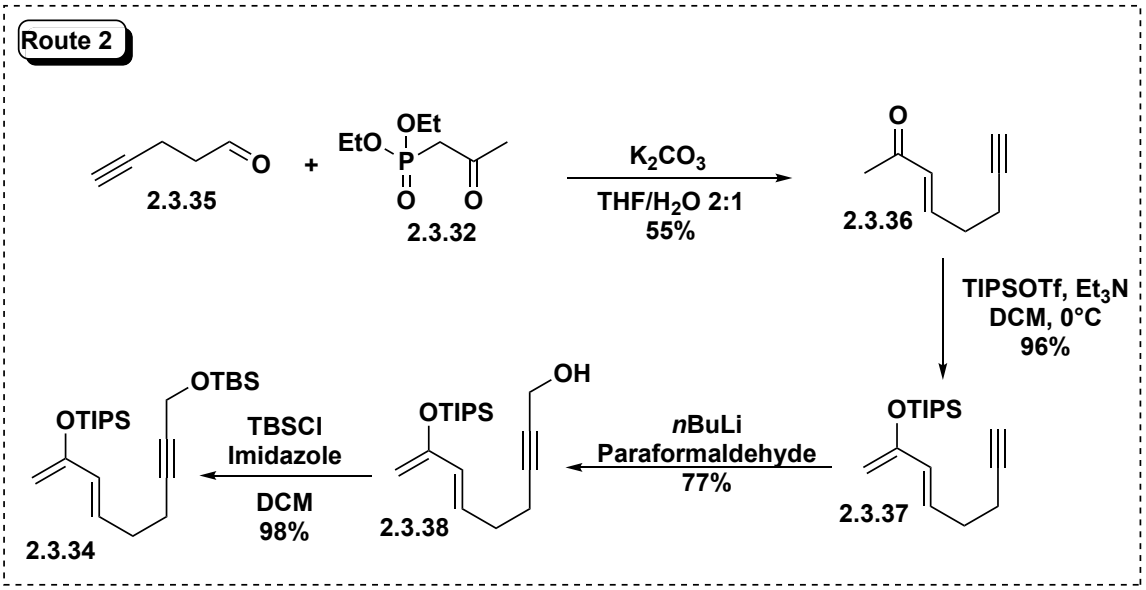
The preparation of diene **2.2.34** began with the 1,4-addition of TBS-protected propargyl alcohol **2.3.29** to acrolein to afford the aldehyde **2.3.31** in 15 % yield.[37] The corresponding cuprate formation using copper iodide has been described in the formal synthesis of Echinopine A and B with a reported 33 % yield.[38] Attempts to reproduce this result were unsuccessful, even when carefully distilled acrolein was used. The following Horner-Wadsworth-Emmons reaction using sodium hydride allowed the formation of ketone **2.3.33** in 64 % yield. The

formation of the silyl enol ether **2.3.34** was quantitative using triethylamine and TIPSOTf in dichloromethane at 0 °C.



Scheme 2.3.3.1 - Synthesis of the Diene 2.3.32 - Route 1

Since the yield of the first transformation was quite low, we decided to make the dienophile using the longer route 2 (Scheme 2.3.3.2). The Horner-Wadsworth-Emmons reaction between aldehyde **2.3.35** and the phosphonate **2.3.32** generated the enone **2.3.36** in 55 % yield using potassium carbonate as a base. Silyl enol ether **2.3.37** was formed in 96 % yield within one hour. Deprotonation of the terminal alkyne using *n*-BuLi and a subsequent quench with paraformaldehyde gave propargyl alcohol **2.3.38** in 77 % yield. Finally, protection of the alcohol proceeded smoothly, to furnish the desired diene **2.3.34** in quantitative yield. Although route 2 provides an efficient way to build the diene **2.2.34** on large scale, the synthesis of the diene could be further improved and optimized.

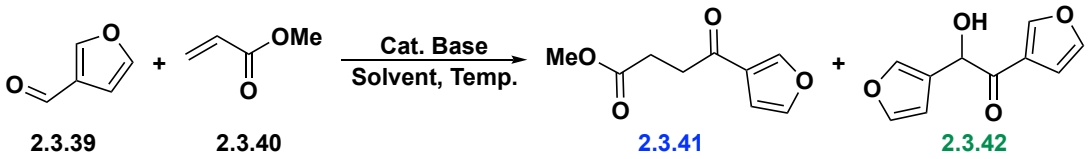


Scheme 2.3.3.2 - Synthesis of the Diene 2.3.32 - Route 2

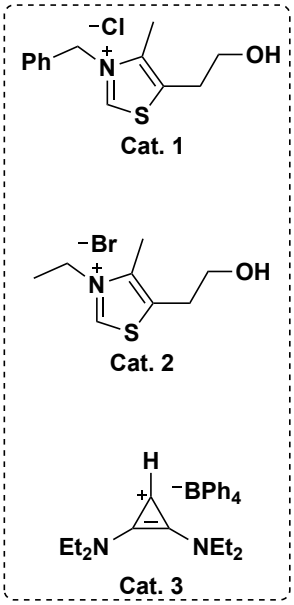
2.3.4 Synthesis of the Dienophile

The synthesis of the dienophile **2.3.14** started with the 1,4-addition of aldehyde **2.3.39** to methyl acrylate **2.3.40** *via* umpolung chemistry (Table 2.3.4.1). Commercially available and widely used catalysts **cat. 1** and **cat. 2** led to a 1:1 mixture of the desired product **2.3.41** and the homocoupling of the aldehyde **2.3.39** to generate the by-product **2.3.42** (entries 1-2). Thus, the desired product was isolated in only 27 % and 24 % yields, respectively. This Stetter reaction is particularly challenging given that the aldehyde **2.3.39** is electron-rich, making the 1,2-addition of the carbene catalyst more difficult. Also, methyl acrylate is a relatively poor Michael acceptor in comparison with the typical α,β-unsaturated ketones used for this type of transformation.

Table 2.3.4.1 - Optimization of the Stetter Reaction



2.3.39 2.3.40 2.3.41 2.3.42

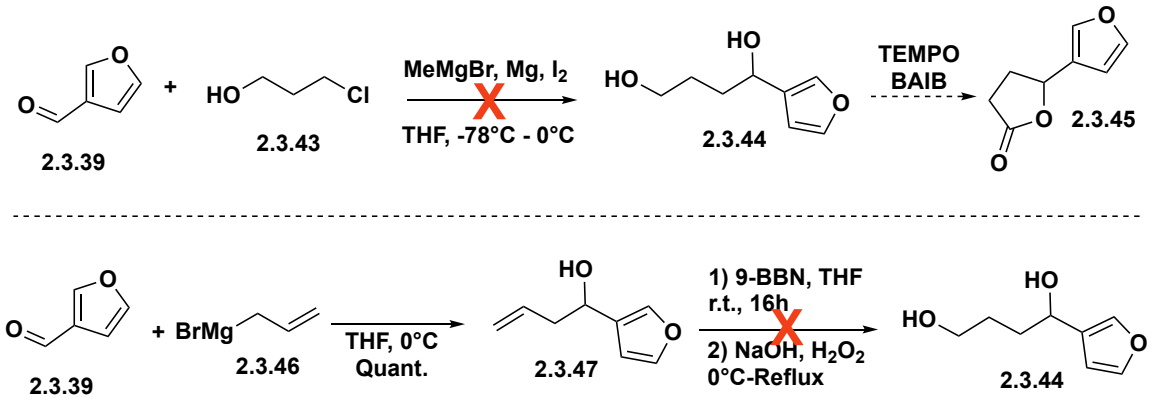


Entry	Cat. (Loading)	Solvent	Temperature (°C)	41 : 42	Yield (%)
1	1 (30 mol%)	1,4-Dioxane	80	1:1	27
2	2 (30 mol%)	1,4-Dioxane	80	1:1	24
3	3 (10 mol%)	DCM	r.t.	-	0
4	3 (50 mol%)	DCM	r.t.	-	0
5	3 (10 mol%)	DCE	50	-	0
6	3 (30 mol%)	1,4-Dioxane	80	-	0
7	1 (20 mol%)	[bmim][PF_6]	80	1:0	19

Gravel's group reported in 2013 that bis(amino)cyclopropenylidene (**Cat. 3**) can be used as an organocatalyst for challenging Stetter reactions.[39] Upon deprotonation, the carbene species generated is highly reactive and can add easily onto electron-rich aldehydes. Our first attempt using the pre-catalyst led to no conversion and the starting material was fully recovered (entry 3). Increasing the catalyst loading and/or the temperature of the reaction did not improve the reactivity and the desired product **2.3.41** was never observed using this catalyst (entries 4-6). A study by Grée *et al.* demonstrated that ionic liquids, such as [bmim][PF_6], can be used for difficult Stetter reaction. Their work presents many examples of substrates that are similar electronically to the one we wanted to use.

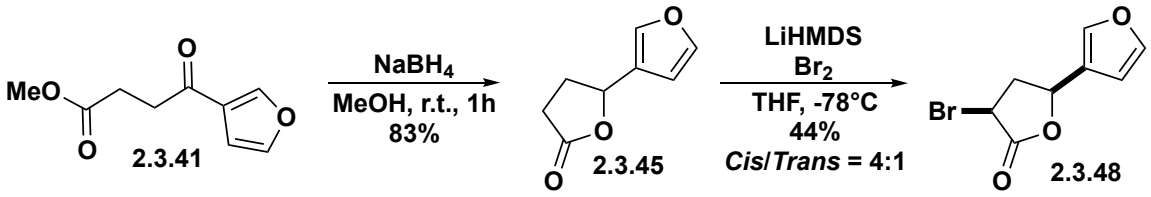
The use of ionic liquids allows reactions to be run at very high concentrations. Using 20 mol% of **Cat. 1** at a concentration of 8 M at 80 °C led to the formation of the desired product **2.3.41** in 19 % (entry 7). While the yield of the transformation was similar to our previous attempts, the reaction was found to be more selective and the by-product **2.3.42** was not observed.

Alternative transformations have also been investigated to make this C–C bond more efficiently (Scheme 2.3.4.1). The 1,2-addition of 3-chloropropanol onto the aldehyde **2.3.39** by the *in situ* formation of the corresponding Grignard reagent was unsuccessful. A new product was detected while following the reaction by TLC, however it degraded upon work-up. Indeed, we believe that diol **2.3.44** is unstable since the C–O bond can be broken easily by electron donation from the electron-rich furan moiety. Oxidative lactonization of the diol **2.3.44** would have led to the desired intermediate **2.3.45**.[40] On the other hand, 1,2-addition of allylmagnesium bromide to form the intermediate **2.3.47** occurred quantitatively, while the subsequent hydroboration led to no product formation.[41]



Scheme 2.3.4.1 - Alternative 1,2-additions

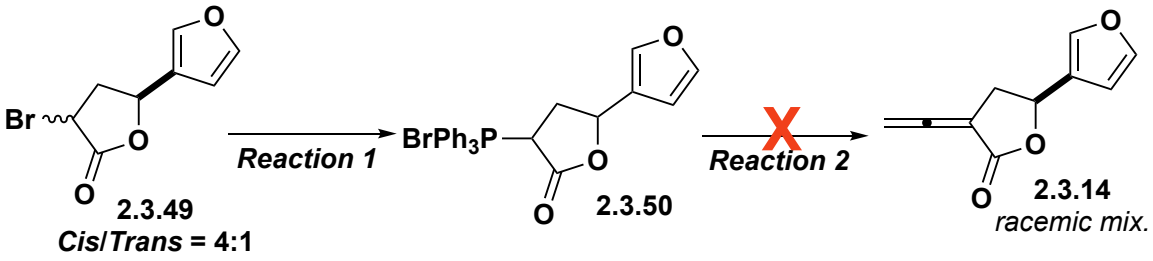
In pursuing the synthesis of the dienophile, we proceeded to the reduction of the compound **2.3.41** (Scheme 2.3.4.2). Upon addition of sodium borohydride and the substrate, the newly formed alkoxide lactonized directly onto the methyl ester and the γ-butyrolactone **2.3.45** was generated in 83 % yield. Bromination of this intermediate occurred in presence of LiHMDS, followed by addition of bromine to form the α-bromo-γ-butyrolactone **2.3.48** in 44 % yield.



Scheme 2.3.4.2 - Synthesis of the *α*-Bromo-*γ*-Butyrolactone

Next, to form the dienophile **2.3.14**, we attempted a Wittig reaction using acetyl chloride. Subsequent elimination of the chloride would provide the allene, as described by Lam *et al.* on similar substrates.[42] Treatment of **2.3.49** with triphenylphosphine at 70–75 °C in toluene and THF led to the formation of a black solid, suggesting degradation (entries 1-2). When diethyl ether was used as a solvent at room temperature, the conversion of the reaction was poor (entry 3). The phosphonium salt **2.3.50** formed in toluene at room temperature overnight as an orange gum (entries 4-5).

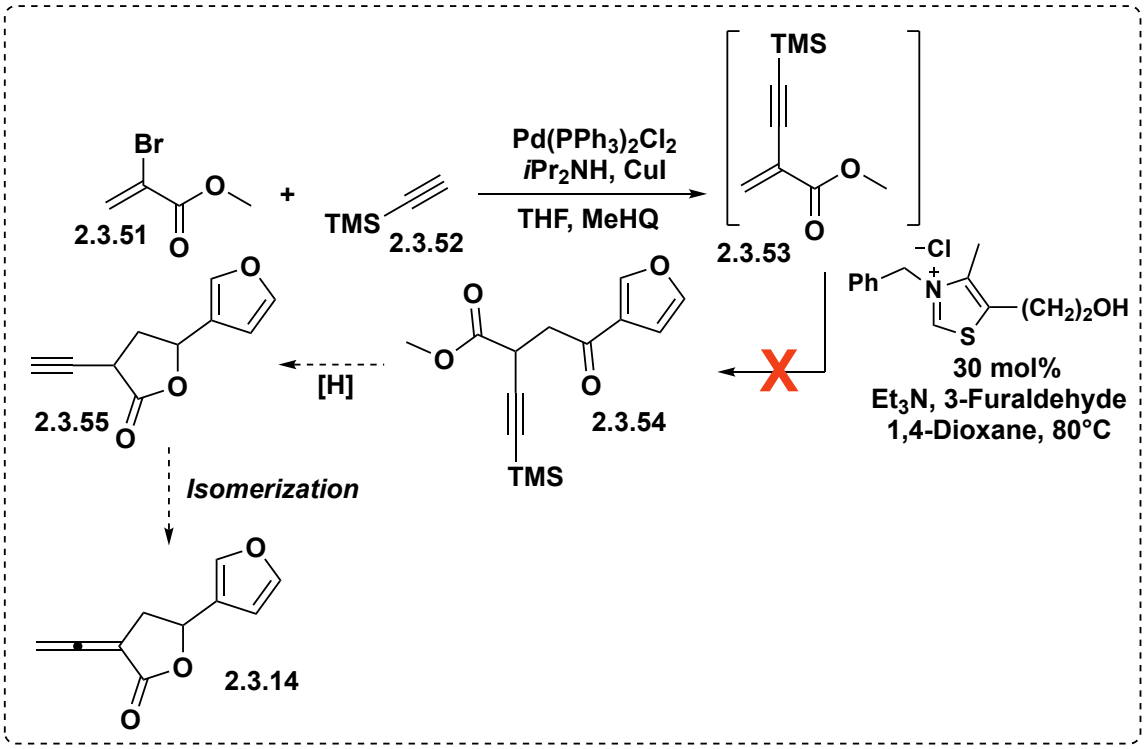
Table 2.3.4.2 - Optimization of the Wittig Reaction



Entry	Reaction 1	Reaction 2
1	PPh_3, Toluene, 75°C, 24h	-
2	PPh_3, THF, 70°C, 24h	-
3	PPh_3, Et_2O, r.t., 24h	-
4	PPh_3, Toluene, r.t., 24h	AcCl (1.1 eq.), Et_3N (2.2 eq.) DCM, 0°C-r.t.
5	CSA (1.2 eq.), 0°C - r.t.	AcCl (2.2 eq.), DiPEA (2.0 eq.) DCM, 0°C-r.t.

Treatment of the resulting salt with acetyl chloride in the presence of a base led to no formation of the desired product. Instead, the reduced lactone **2.3.45** was isolated as the major product, independent of the reaction conditions (entries 4-5).

Since the Wittig reaction to form **2.3.14** was not productive, we envisioned a different route to synthesise the desired dienophile (Scheme 2.3.4.3).

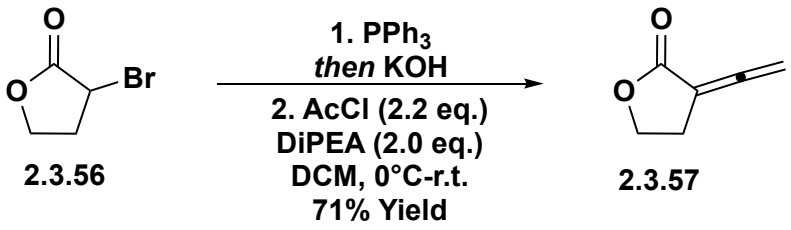


Scheme 2.3.4.3 - Alternative Route for the Synthesis of Dienophile 2.3.14

This route would overcome the poorly yielding bromination as well as the difficult C–C bond formation for the synthesis of the allene moiety. The Sonogashira coupling between the bromide **2.3.51** and TMS-acetylene occurred smoothly, resulting in the unstable product **2.3.53**. After a quick silica plug, the compound was submitted to Stetter reaction conditions, which unfortunately did not lead to the formation of the desired compound **2.3.54**. The formation of this

intermediate followed by reduction (**2.3.55**), deprotection and isomerization would have given access to the allene motif.

The attempted synthesis of dienophile **2.3.14** was not productive and thwarted our efforts to obtain the core of the natural product. For that reason, we decided to investigate the key steps (Diels-Alder and 6-*endo-dig* cyclization) in absence of the furan moiety. Dienophile **2.3.57** was synthesised in two steps from the commercially available α-bromo-γ-butyrolactone **2.3.56** in 71 % yield.[42]

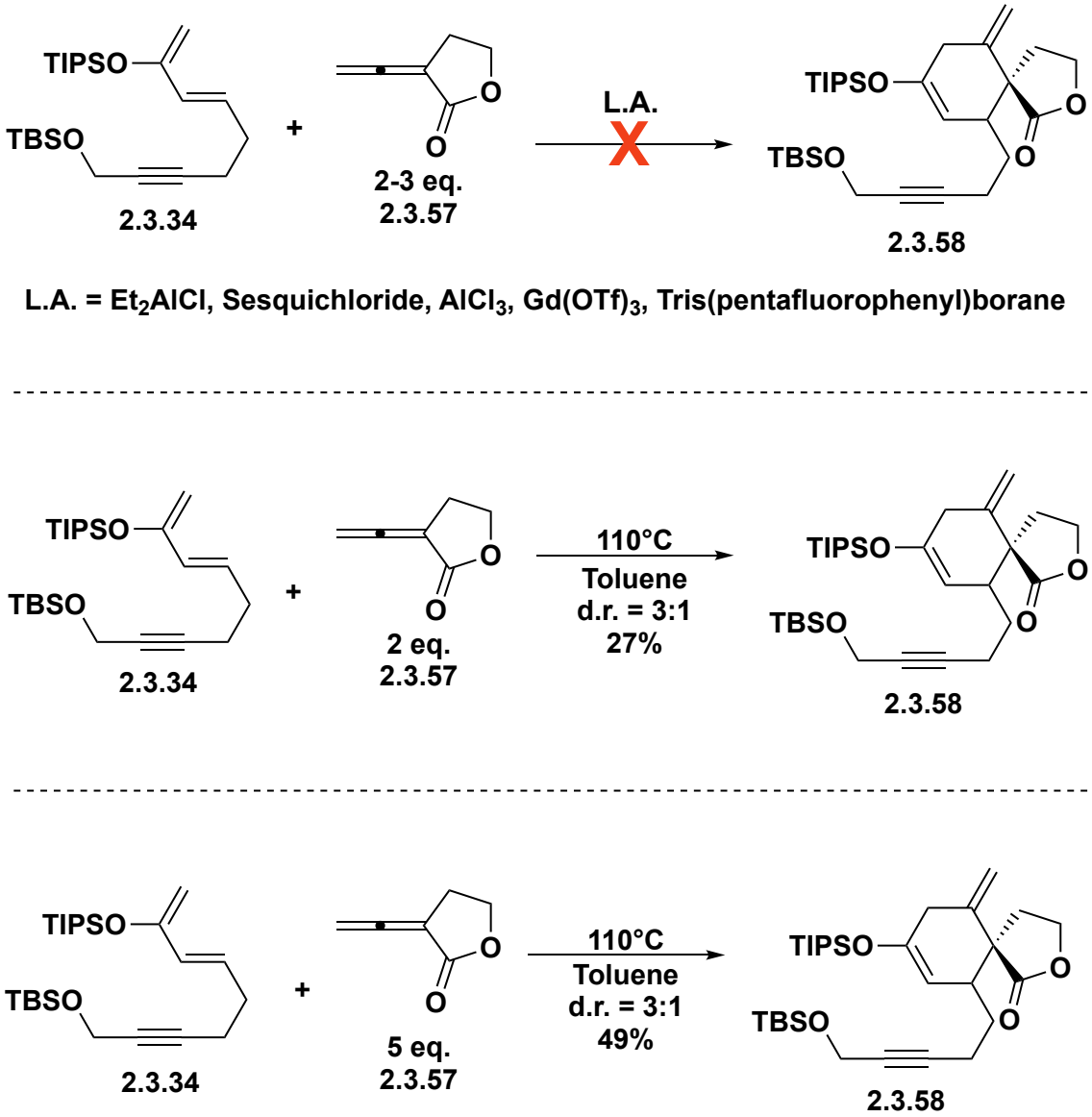


Scheme 2.3.4.4 - Synthesis of the Alternative Dienophile 2.3.53

2.3.5 Investigation of the Diels-Alder Reaction

The [4+2] cycloaddition between the diene **2.3.34** and the dienophile **2.3.57** was examined (Scheme 2.3.4.5). The use of a Lewis acid to catalyze the reaction was unproductive and led mainly to the hydrolysis of the silylenol ether to form the corresponding ketone. Heating the reaction to 110 °C in toluene afforded 27 % of the desired product when 2.0 equivalents of the dienophile were used. Increasing the number of equivalents for **2.3.57** to 5.0 equivalents improved the yield to 49 %.

However, the product was isolated as a mixture of diastereoisomers (3:1) in both cases.



Scheme 2.3.5.1 - Investigation of the Diels-Alder

Since the 6-membered ring adopts a half-chair conformation, it was not possible to determine the stereochemistry of the major product. Both the *endo* and the *exo*

isomers gave similar NOESY signals. The stereochemistry would be easier to establish after the cyclization step and the formation of the second ring.

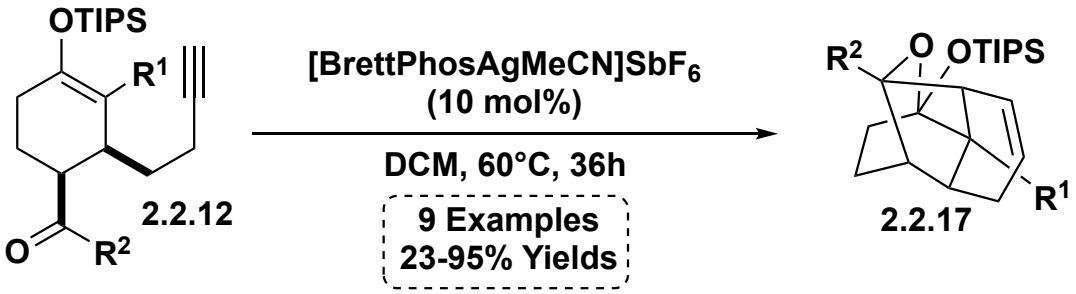
Since both the yield and the selectivity of the Diels-Alder reaction were much lower than expected, further optimization would be required. The allene moiety seems to be unreactive towards the Diels-Alder reaction. Additionally, Ley *et al.* observed that the exocyclic double bond led to poor conversion, even at 135°C.[33] One might suggest that the π orbital of this exocyclic alkene is possibly not be fully conjugated with that of the carbonyl due to cyclic torsion. This would result in a LUMO higher in energy than initially expected, which would make the cycloaddition harder to achieve. For that reason, an analogous open form of the furan functionality could be used to facilitate the [4+2] cycloaddition. The structure of the dienophile used for that key step will require review in the future to allow for efficient and selective assembly of the natural product framework.

2.4 CONCLUSION

Recently it has been demonstrated that coinage metals such as Au-complexes efficiently catalyze intramolecular nucleophilic additions onto alkynes/alkenes/allenes. Of these transformations, 5-*exo*, 5-*endo*, and 6-*exo*-*dig* transformations of alkynes are the most commonly studied, where 6-*endo*-*dig* cyclizations have proven to be the most challenging. We have demonstrated through the optimization and expansion of the Lewis acid coinage metal catalysts

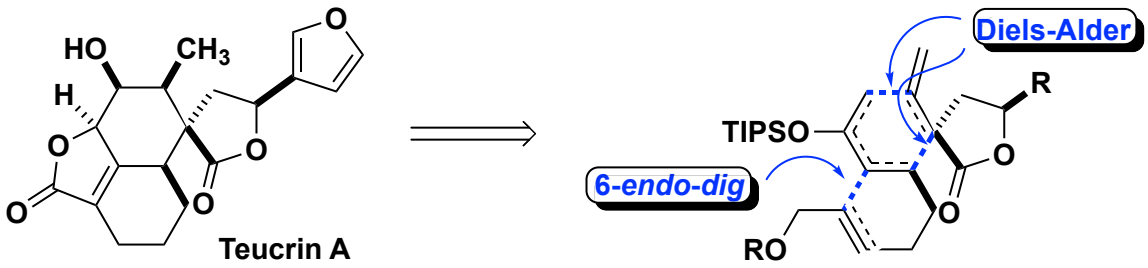
that by modulating the electronic and steric profile of the complex we can selectively catalyze this difficult transformation.

We demonstrated the usefulness of coinage metals in catalysis of selective carbocyclization of silylenol ethers. Herein, we have explored a silver-catalyzed 6-*endo-dig*/acetalization/Prins reaction cascade (Scheme 2.4.1). Deuterium-labelling experiments allowed us to propose a mechanism for its formation. The robustness of the reaction was studied by changing the nature of the R groups and nine different products were synthesised. The highly stained polycycle that was formed also exhibited interesting reactivity, which was further explored.



Scheme 2.4.1 - Silver-Catalyzed Reaction Cascade

We have also investigated the synthesis of Teucrin A via a Diels-alder/6-*endo-dig* cyclization reaction sequence (Scheme 2.4.2). Our approach would have provided a unique and efficient way to access the neoclerodane diterpenoid framework of the natural product. Although the initially designed Diels-Alder reaction showed poor reactivity and selectivity, different synthetic alternatives are currently being investigated in our laboratory.



Scheme 2.4.2 - Synthetic Approach for the Synthesis of Teucrin A

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3 FORMAL SYNTHEIS OF (±)-MORPHINE

3.1 INTRODUCTION

Although it is difficult to establish when the opium poppy (*Papever somniferum*) was first cultivated, it is generally agreed that the Sumerians isolated opium from poppy seed capsules as early as 3000 B.C.E.[1] Opium is the dry latex isolated from the opium poppy and contains many alkaloids, of which morphine, codeine, thebaine, and oripavine are the main constituents (Figure 3.1.1).

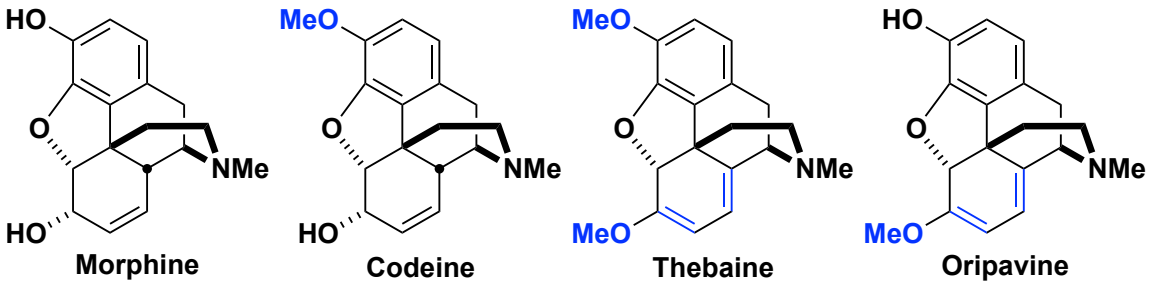


Figure 3.1.1 - Molecular Structures of Morphine, Codeine, Thebaine, and Oripavine

During the 8th century C.E, Arabian traders introduced opium to China and India. Centuries later, these alkaloids were brought to other countries in Europe. The use of these narcotics came with addiction and substance abuse, as described in many manuscripts from the 16th century. As China faced opium addiction most seriously, they attempted to ban the use and distribution of this substance. In a conjoint effort, British and French traders maintained the opium market for trade and consumption.

The active ingredient in opium was isolated in 1805 by Friedrich Sertürner, who named it morphine after the god of dreams, Morpheus.[2] Sertürner began the distribution of morphine in 1815 and the pharmaceutical company, Merck, started its commercialization in 1827.

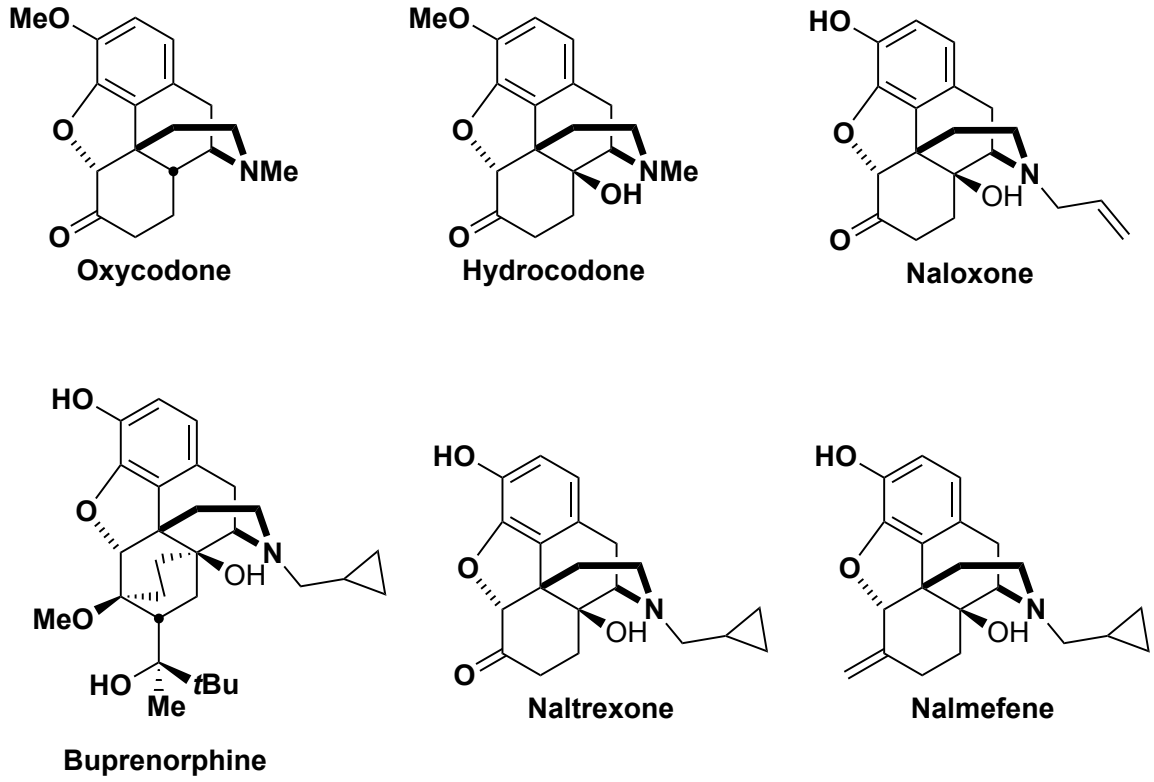


Figure 3.1.2 - Synthetic Analogues of Morphine

As the enhanced consumption of the pure active substance led to a significant increase in abuse, the development of safer and less addictive analogues began. This intensive research led to, among other things, the synthesis of heroin in 1898. Many unnatural derivatives of morphine have been synthesized over the years, generally derived through semisynthetic efforts from

the natural product (Figure 3.1.2). These derivatives can have different functions, such as pain management (oxycodone and hydrocodone), treatment of opioid overdose (naloxone and buprenorphine), and alcohol/opioid addiction (naltrexone, nalmefene).

With worldwide production exceeding 400 tons annually, morphine and its analogues remain to date among the most potent and ubiquitous analgesic agents.[3] Commercially available morphine still originates mostly from natural extraction. The low-cost of isolation is mostly due to the low cost associated with harvesting the plant, which occurs mostly in Afghanistan, Turkey, Australia, and India. While the current cost of morphine is quite low, it remains possible that natural and/or political emergencies in these producing countries could lead to a sharp increase of that cost, making creative synthetic approaches that are waste and cost minimizing more important than ever.

3.1.1 Biological Activity

Morphine is one of the best-known alkaloids in the opioid class. The human body also produces natural opioids, namely endorphins, enkephalins, and dynorphins. In order to induce analgesia, sleepiness, and/or an overall feeling of well-being, the human body releases these endogenous opioids during periods of intense exercise, excitement, pain, and orgasm. It has also been suggested that some living beings, including humans, can produce morphine at very low levels in organ tissues.[4]

Morphine is a phenanthrene opioid receptor agonist and has three target receptors in the human body.[5] First and foremost, it has good affinity with the μ-receptors of the central nervous system, located in the ventral tegmental area of the brain.[6] Upon binding and activation, theses receptors are responsible for the desired analgesia and sedation. On the other hand, these receptors are also associated with the undesired responses, such as modifications in the respiratory system and addiction. To a lesser extent, morphine also binds the κ-opioid and δ-opioid receptors, which are thought to cause analgesia, spinal analgesia, miosis, and delusions/delirium.

With a bioavailability of 80-100 %, depending on the administration route, morphine is best absorbed in the alkaline environments of the upper intestine and the rectal mucosa.[7] Since it undergoes significant first-pass metabolism by the liver, oral administration requires six times the dose of that compared to the parenteral route. While the therapeutic dose of morphine is about 1-7 μg/dL, it becomes toxic at a concentration of 10-100 μg/dL and lethal when it exceeds 400 μg/dL.[8] The therapeutic index of this opiate is 70, which makes it seven times safer than ethanol. Its half-life ranges from 2-4 hours for humans, after which morphine and its metabolites are excreted mostly in the urine.

The enzyme UDP-Glucuronosyltransferase-2B7 (UGT2B7) in the liver is responsible for the formation of morphine-6-glucoronide (M6G) and morphine-3-glucoronide (M3G), which represent 90 % of metabolites.[9] Moreover, around 85 % of the biological effects of morphine are caused by the activity of the M6G

metabolite. Less than 5 % of morphine is converted into *N*-demethylated derivative normorphine *via* the action of the enzymes CYP3A4 and CYP2C8.

3.1.2 Structural Features

Although the commercialization of morphine occurred as early as 1827 by Merck, its molecular structure was not elucidated until 1925.[10] Morphine has a pentacyclic framework, containing an aromatic ring (ring A), a *cis*-decalin substructure (rings B/C), a piperidine moiety (ring D) as well as a dihydrofuran motif (ring E) (Figure 3.1.2.1). The natural product has a total of five contiguous stereocentres. The third stereocentre is a quaternary carbon and is shared by 4 rings (B–E), which contributes greatly to the rigidity of the molecule.

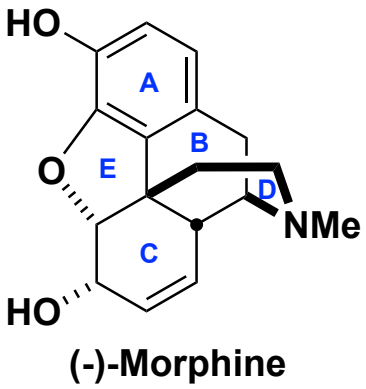


Figure 3.1.2.1 - Pentacyclic Structure of (-)-Morphine

Electronically, morphine has a dissonant connectivity.[11] As shown in Figure 3.1.2.2, it is not possible to assign polarization in order to avoid positive charge on electronegative atoms or a perfect alternation of charges. This feature

has a significant impact on the formation of a synthetic strategy, which would require preeminent tactical synthetic manipulations, thus increasing the number of steps, difficulty in synthesis, and potential for lower and overall yield.

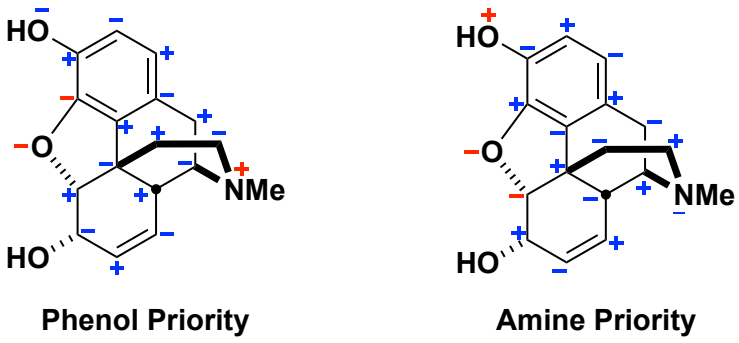
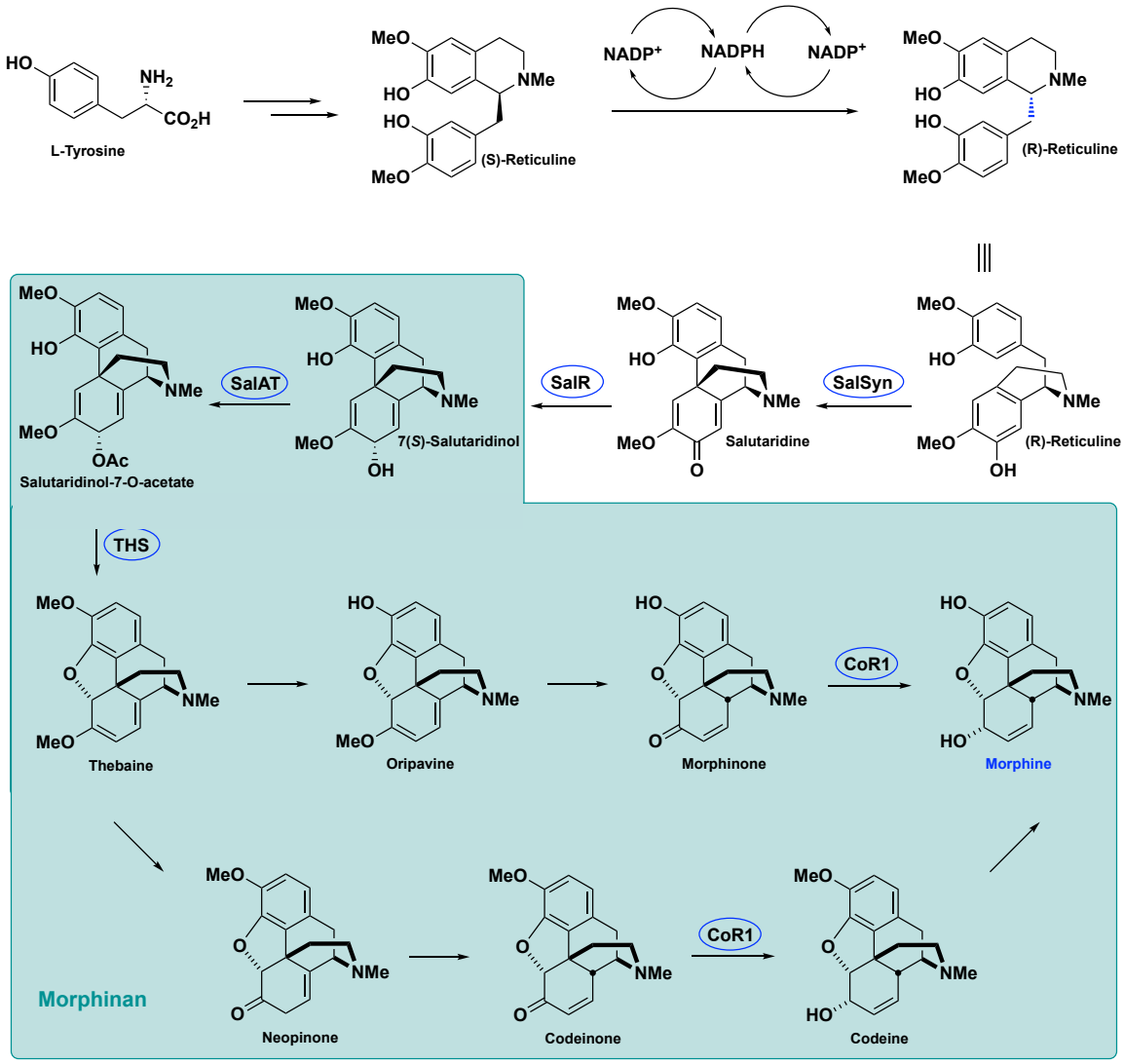


Figure 3.1.2.2 - Dissonant Connectivity

3.1.3 Biosynthesis

It has been determined that all non-methyl carbon atoms of morphinans arise from two molecules of the natural occurring amino acid L-tyrosine (Scheme 3.1.3.1).[12] The tyrosines are then converted into dopamine and *p*-hydroxyphenylacetaldehyde. The next four linear enzyme-catalyzed steps allow the formation of (*S*)-reticuline, a common intermediate in the biosynthesis of many alkaloids. Among these steps, a Pictet-Spengler-like reaction generates the piperidine motif of the natural product. A NADPH-dependant oxidation/reduction sequence then catalyze the inversion of the configuration in order to form (*R*)-reticuline, a specific precursor of all morphinans. This latter step rationalizes why only (-)-morphine is found in nature.



Scheme 3.1.3.1 - Biosynthesis of Morphine and Morphinans

The B-ring of morphine is then formed in a NADPH-dependant biphenolic oxidation catalyzed by the enzyme salutaridine synthase (SalSyn). Stereospecific reduction of salutaridine, once again NADPH-dependant, occurs in the presence of salutaridine reductase to yield 7(*S*)-salutaridinol. The newly formed hydroxyl group is then acetylated by salutaridinol acetyl transferase. The formation of salutaridinol-7-O-acetate initiate the subsequent *syn*-S_N2' *via* thebaine synthase

to generate the E-ring. Aromatic demethylation of thebaine gives the opium constituent oripavine. Subsequent tautomerization of the enol ether and further reduction then yields (-)-morphine. The tautomerization can occur prior to the aromatic demethylation and this sequence generates the morphinans neopinone, codeinone and codeine. Codeine is often given as a painkiller medication, as it can be demethylated *in vivo* by the enzyme CYP2D6, giving the more active (-)-morphine. Moreover, Smolke *et al.* recently engineered yeast to produce the morphinans thebaine and hydrocodone, starting from sugar.[13] Although this method is still limited by its scale, it represents a major advancement in the production of opioids.

3.1.4 Previous Syntheses

Since the original synthesis described by Gates in 1952,[14] about 50 creative total and formal syntheses of morphinan alkaloids have been reported (Table 3.1.4.1).[3,11,15]

Table 3.1.4.1 - Summary of Syntheses of Morphine and Derivatives

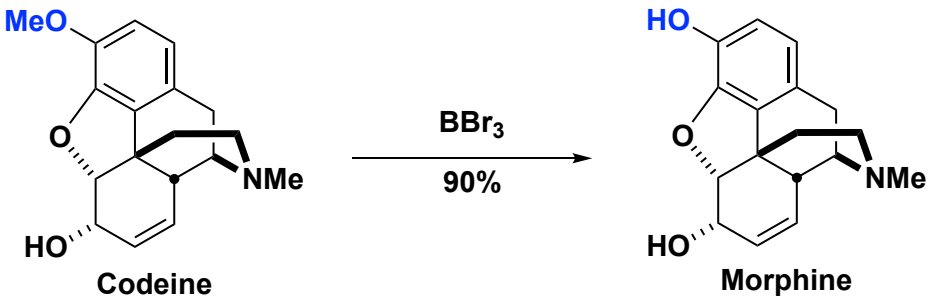
Author	Year	Target	Steps	Reported Overall Yield (%)
Gates[14]	**1952**	**Morphine**	**29**	**0.06**
Ginsburg[16]	1954	*rac*-Dihydrothebainone	21	8.9
Grewe[17]	1967	*rac*-Dihydrothebainone	9	0.81
Rice[18]	**1980**	**Dihydrocodeinone**	**14**	**29.7**

Evans[19]	1982	*rac*-O-Me-thebainone A	12	16.7
White[20]	1983	**Codeine**	8[a]	1.8
Rapoport[21]	1983	***rac*-Codeine**	26	1.2
Fuchs[22]	1987	***rac*-Codeine**	23	1.3
Tius[23]	1992	*rac*-Thebainone-A	24	1.1
Parker[24]	1992	*rac*-dihydrocodeinone	11	11.1
Overman[25]	1993	Dihydrocodeinone	14	1.9
Mulzer[26]	1996	Dihydrocodeinone	15	9.1
Parsons[27]	1996	**Morphine**	5[b]	1.8
White[28]	1997	***ent*-Morphine**	28	3.0
Mulzer[29]	1997	Dihydrocodeinone	18	5.7
Ogasawara[30]	2001	Dihydrocodeinone ethylene ketal	21	1.5
Taber[31]	2002	**Morphine**	27	0.5
Trost[32]	2002	**Codeine**	15	6.8
Fukuyama[33]	2006	***rac*-morphine**	25	6.7
Parker[34]	2006	Dihydrocodeinone	13	4.2
Hudlicky[35]	2007	***ent*-codeine**	15	0.23
Iorga/Guillou[36]	2008	***rac*-codeine**	17	0.64
Chida[37]	2008	Dihydroisocodeine	24	3.8
Hudlicky[38]	2009	**Codeine**	18	0.19
Magnus[39]	2009	***rac*-codeine**	13	20.1
Stork[40]	2009	***rac*-codeine**	22	2.0
Fukuyama[41]	2010	**Morphine**	18	4.8

Metz[42]	2011	***rac*-codeine**	24	1.3
Hudlicky[43]	2011	*ent*-neopinone	14	3.2
Chida[44]	2013	**Morphine**	27	1.9
Fan[45]	2013	***rac*-morphine**	23	0.2
Hudlicky[46]	2013	Dihydrocodeinone	16	0.8
		Hydrocodone	17	0.8
Opatz[47]	2014	Dihydrocodeinone	13	23.4
Hudlicky[48]	2014	***ent*-codeine**	16	0.25
Gaunt[49]	2014	**Morphine**	25	0.9
Hudlicky[50]	2014	*ent*-hydromorphone	12	2.3
Zhang[51]	2015	**Codeine**	17	4.0
Smith[52]	**2016**	***rac*-Morphine**	**9**	**6.6**
Chen[53]	2017	Dihydrocodeine	22	0.9
Fukuyama[54]	2017	**Morphine**	18	0.4
Metz[55]	2018	**Codeine**	25	0.5
Opatz[56]	2018	Thebaine	14	4.8
Hudlicky[57]	2019	*ent*-oxycodone	13	1.5
Barriault[58]	**2019**	***rac*-morphine**	**11**	**0.7**
Opatz[59]	2019	Oxycodone	11	4.2
Hudlicky[60]	2019	*ent*-oxycodone	18	0.3
			16	0.3
			11	3.5
Tu[61]	2019	**Morphine**	16	0.5

[a] *N*-Norreticuline was used as advanced starting material
[b] Only the last five steps of the synthesis have been published in the cited journal

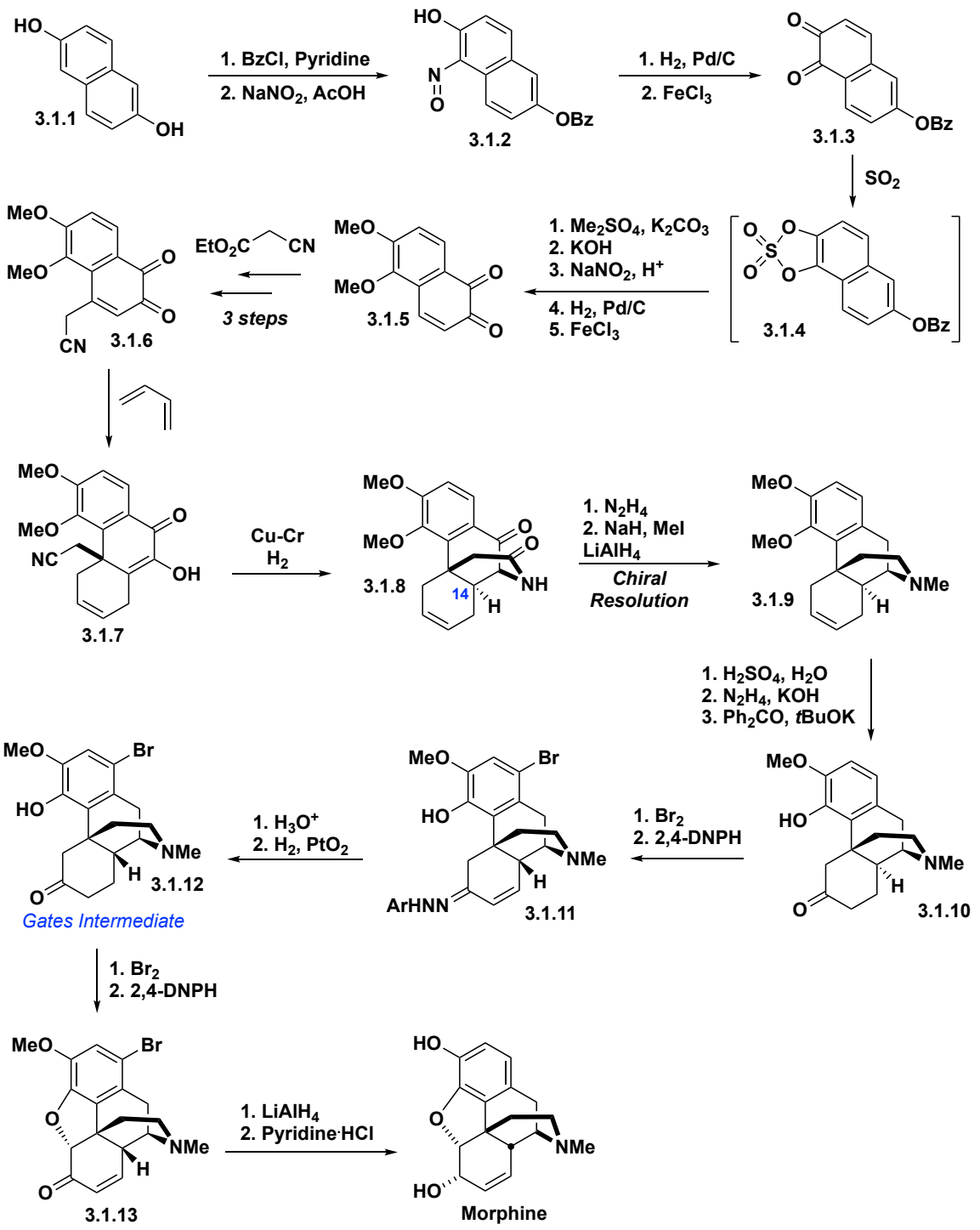
In this extensive list, there are 25 syntheses of morphine and codeine. It is well established that codeine can be converted into morphine in one step (Scheme 3.1.4.1). For this reason, each total synthesis of codeine is also a formal synthesis of morphine. As for the other morphinan alkaloids, a few more steps and functional group manipulations are required in order to form morphine. Reviewing every synthesis of the Table 3.1.4.1 would be a tremendous task. In order to keep this section concise, only a few approaches will be discussed in greater detail.



Scheme 3.1.4.1 - Conversion of Codeine into Morphine

In 1952, Marshall Gates reported the first synthesis of morphine.[14] Although this synthetic route is among the longest, the author has nevertheless described an elegant approach that became the pillar of inspiration for many others to come. Gates employed 2,6-dihydroxynaphthalene **3.1.1** as the primary building block for his synthesis (Scheme 3.1.4.2). The synthesis started with the monoprotection of **3.1.1**, followed by nitrosation, reduction, and oxidation to

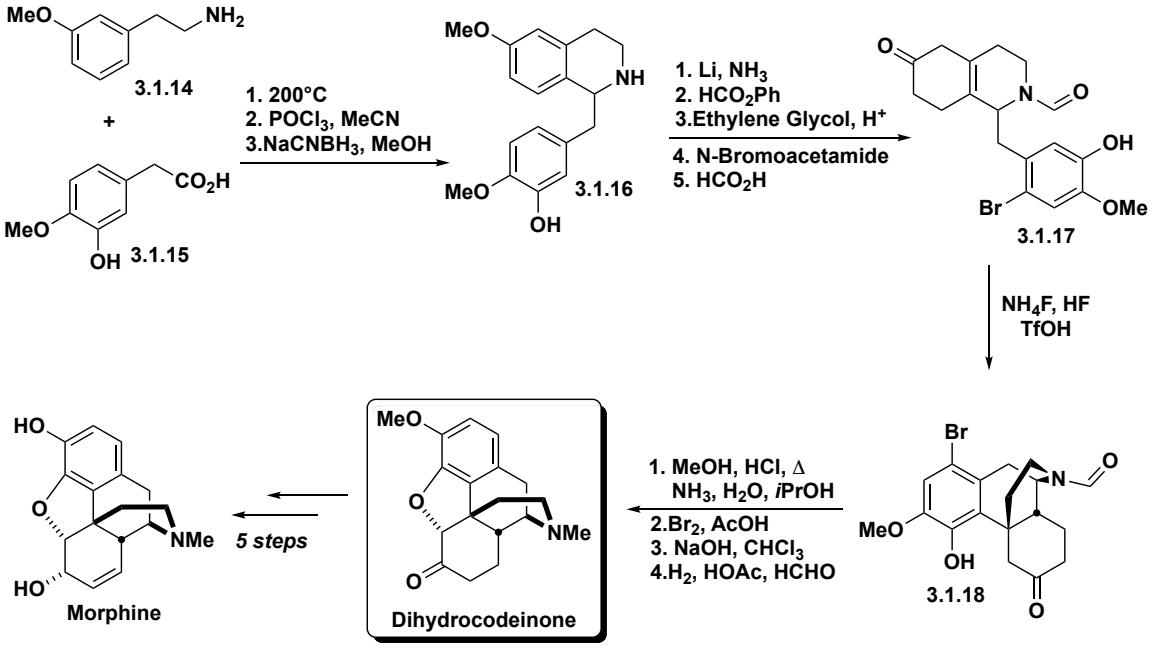
afford the ortho quinone **3.1.3**. Upon treatment with sulphur dioxide, the diketone gave the cyclic sulfate **3.1.4**.



Scheme 3.1.4.2 - Gates' Synthesis of Morphine

Methylation of these oxygen atoms using dimethyl sulfate and subsequent nitrosation, reduction, and oxidation led to the formation of the intermediate **3.1.5**. Michael-addition of ethyl cyanoacetate onto the α,β-unsaturated ketone, followed by oxidation, hydrolysis, and decarboxylation generated **3.1.6**. Formation of the C-ring was then achieved *via* a Diels-Alder reaction using 1,4-butadiene. The D-ring was formed upon exposure of **3.1.7** to copper-chromite, and the subsequent reductive amination provided **3.1.8**. Although the A,B,C,D ring system of morphine was obtained, the configuration was opposite to the desired product at C14 at this stage of the synthesis. Nevertheless, the intermediate **3.1.8** was used for Wolff-Kishner reduction and methylation of the amide followed by its reduction. A chiral resolution using dibenzoyl tartrate of the resulting intermediate gave the epimer of the natural alkaloid. In order to form the ketone **3.1.10**, **3.1.9** underwent an acid-catalyzed regioselective hydration, regioselective demethylation with hydrazine/KOH, and modified Oppenauer oxidation reaction sequence. When **3.1.10** was treated with bromine, α-bromination as well as aromatic bromination occurred. Condensation of 2,4-dinitropheylhydrazine (2,4-DNPH) initiated the elimination of the α-bromine and epimerization of the C14 to form the thermodynamic product **3.1.11,** thus correcting the configuration of the C14. Further addition of water and hydrogenation generated ketone **3.1.12**. This compound often referred to as the "Gates intermediate", was targeted by many researchers who attempted to improve upon this original work. Bromination, condensation with 2,4-DNPH, followed by reduction, aromatic debromination, and demethylation completed Gates' synthesis of morphine.

Rice's synthesis of dihydrocodeinone is worth mentioning.[18] The 14-step synthesis of dihydrocodeinone was achieved with an impressive overall yield of 29.7 %, demonstrating the potential for not only practicality, but also scalability. It is of note that at least five additional steps would be required to convert dihydrocodeinone into the more biologically active morphine molecule.[62,63]



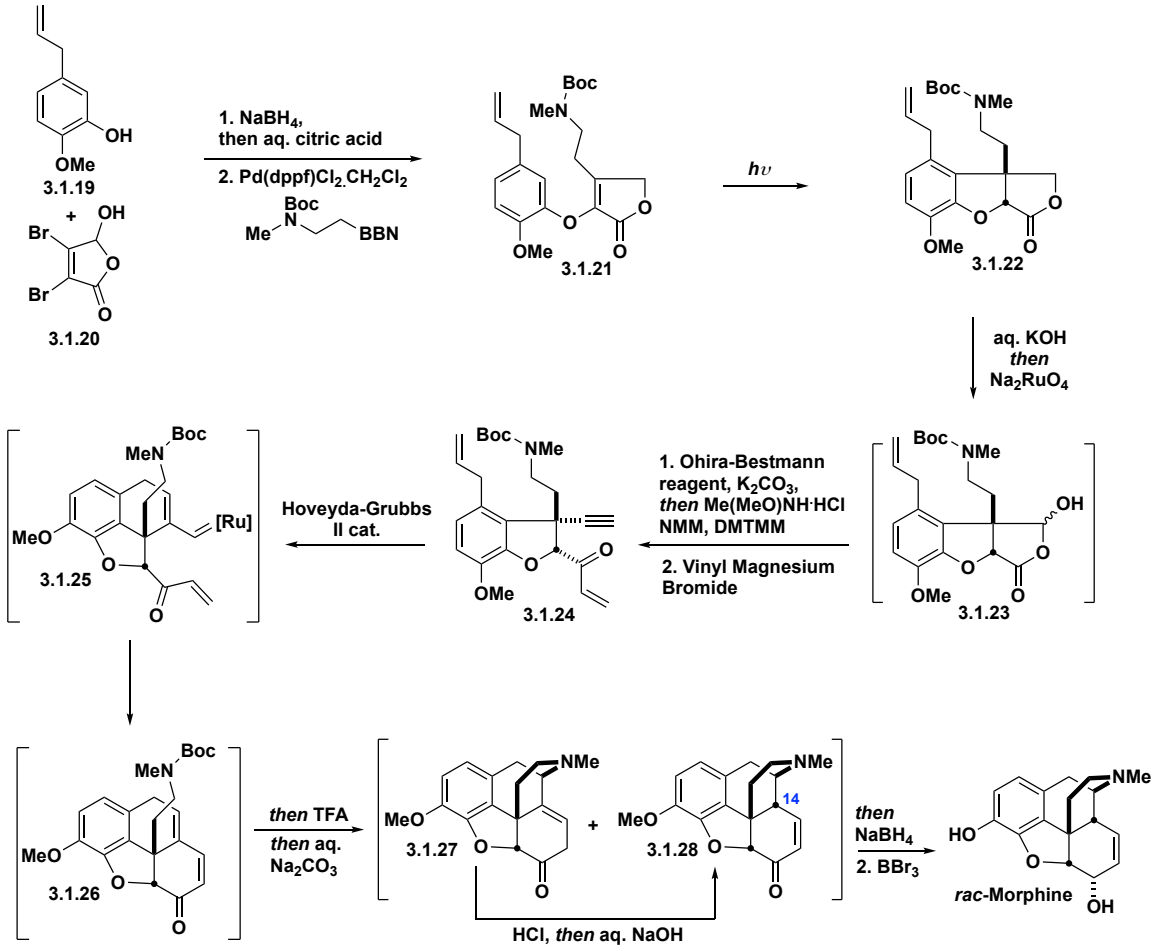
Scheme 3.1.4.3 - Rice's Synthesis of Dihydrocodeinone

Rice's synthesis started with the condensation of amine **3.1.14** and carboxylic acid **3.1.15** (Scheme 3.1.4.3). Bischler-Napieralski reaction and reduction of the formed imine allowed the establishment of the C,D-ring system of the alkaloid. The compound **3.1.16** was then converted into **3.1.17** *via* subsequent Birch reduction, *N*-formylation, ketalization, bromination, and deprotection of the

ketone moiety with formic acid. With compound **3.1.17** in hand, the author performed the key electrocyclization step to form the B-ring, resulting in the formation of **3.1.18**. Further deformylation, reductive amination, α-bromination, base-catalyzed substitution to form the dihydrofuran ring, and aromatic debromination yielded dihydrocodeinone.

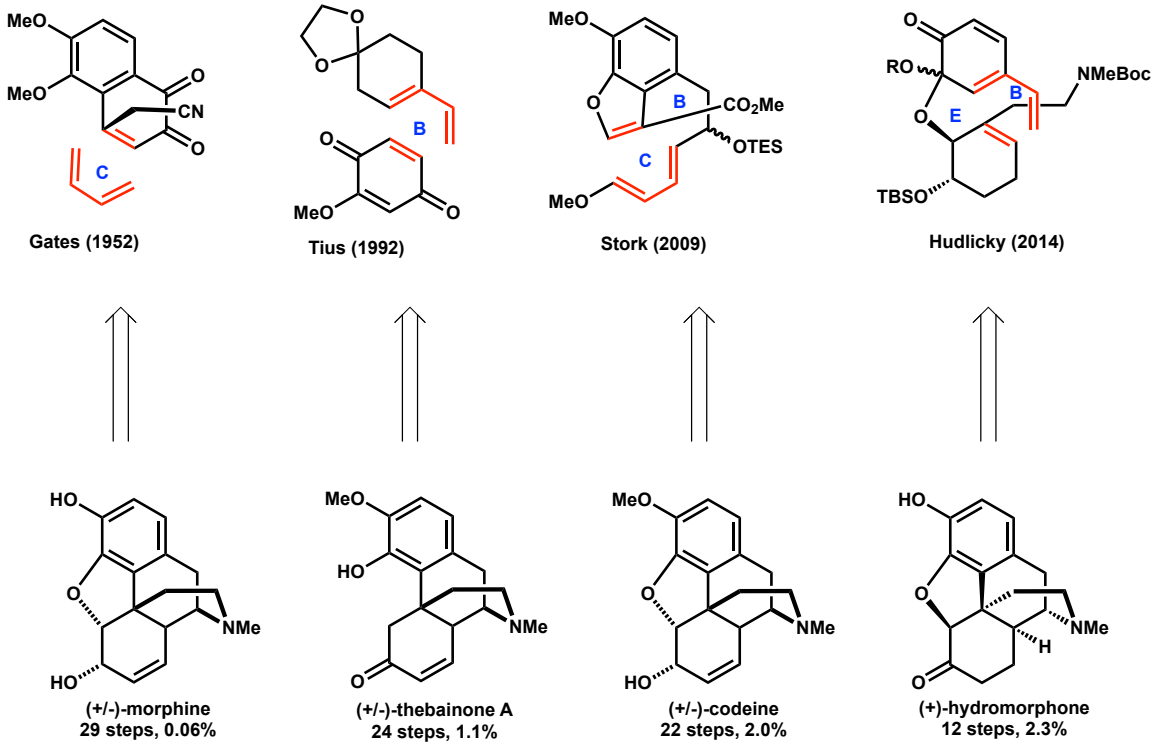
More recently, Smith *et al.* reported an elegant 9-step synthesis of (±)-morphine.[52] Their synthesis is the shortest to date and the natural product was isolated with a 6.6 % overall yield. Smith's synthetic path features an unprecedented ene-yne-ene metathesis cascade, which provides an original way to disconnect the molecule. Their synthesis began with the coupling of phenol **3.1.19** and mucobromic acid **3.1.20** (Scheme 3.1.4.4). A Suzuki-Miyaura coupling was then employed to make the crucial C_{sp3}–C_{sp2} bond in **3.1.21**. A light-promoted 6π electrocyclization followed by a concerted 1,4 hydrogen shift allowed the formation of the required C–C bond to complete assembly of the E-ring (**3.1.22**). Ring-opening of the lactone **3.1.23** under basic conditions followed by treatment with aqueous sodium ruthenate yielded the hemiacetal **3.1.23**. This reactive hemiacetal was trapped *in situ* with dimethyl(diazomethyl)phosphonate in the presence of potassium carbonate to install the alkyne. Formation of the Weinreb amide and 1,2-addition of vinyl magnesium bromide generated the key intermediate **3.1.24**. With intermediate **3.1.24**, the authors were ready to achieve their key ene-yne-ene metathesis cascade, which occurred smoothly in the presence of the Hoveyda-Grubbs II catalyst. The subsequent formation of these two C–C bonds was followed by the

removal of the Boc protecting group *in situ*, and the 1,6-addition of the nitrogen occurred under basic conditions to generate a mixture of the isomers **3.1.27** (neopinone) and **3.1.28** (codeinone). The known conversion of neopinone into codeinone under acidic conditions allowed the exclusive formation of **3.1.28** (codeinone), with the establishment of the correct configuration at C14.[64] Stereospecific reduction of the enone and demethylation yielded the natural product.



Scheme 3.1.4.4 - Smith's Synthesis of (±)- Morphine

Among the previous syntheses of morphinans, some strategic disconnections and transformations are ubiquitous. Due its effectiveness in quickly assembling rings in a stereospecific manner, the Diels-Alder reaction has proven a powerful tool in the synthesis of these alkaloids.



Scheme 3.1.4.5 - Previous Application of the Diels-Alder Reaction in the Synthesis of Morphinans

One of the first applications of the Diels-Alder reaction was described in the original synthesis of morphine for the formation of the C-ring (Scheme 3.1.5.1).[14] In the synthesis of the morphine alkaloid thebainone A reported later by Tius, a Diels-Alder reaction was also used to achieve the formation of the B-ring.[23] In 2009, the synthesis of codeine published by Stork was based on an

intramolecular [4+2] cycloaddition of a benzofuran to establish the B- and C-rings.[40] Finally, Hudlicky used an intramolecular Diels-Alder reaction for the formation hydromorphone in order to generate the B- and E-rings of the morphinans.[50]

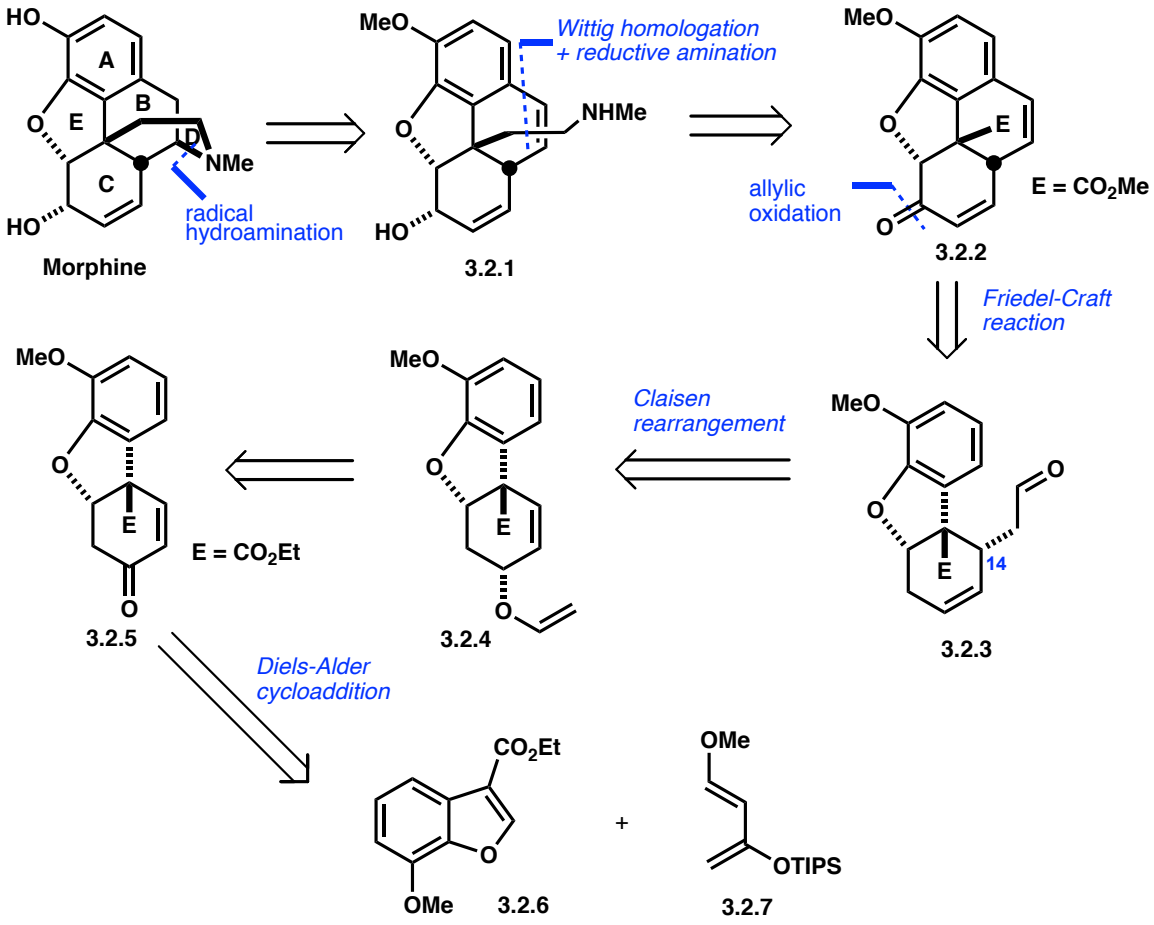
3.2 FORMAL SYNTHESIS OF (±)-MORPHINE

Even after all this devotion from the scientific community, isolation from natural sources remains more competitive in both cost and scale than any synthetic route. The development of a practical and efficient morphine synthesis remains a significant challenge and thus presents the potential for the development of new chemistry. In this context, we describe a nine-step formal synthesis of (±)-morphine enabled by a careful orchestration of transformations that quickly assembles the carbocyclic framework.

3.2.1 Retrosynthetic Analysis

Our retrosynthetic analysis was driven by the goal of minimizing the use of protecting groups and unconventional redox manipulations to quickly assemble the morphine framework.[65] We envisioned that morphine could be obtained by an intramolecular hydroamination of **3.2.1** (formation of the D-ring) followed by a demethylation of the phenol moiety, as demonstrated by Trost *et al.* in 2002.[32a] Intermediate **3.2.1** could be prepared from ester **3.2.2** by simultaneous reduction of the ester into an aldehyde, stereoselective 1,2-reduction of the enone, followed by a Wittig homologation and a reductive amination. The

tetracyclic molecule **3.2.2** could be synthesized from aldehyde **3.2.3** through a Friedel-Crafts reaction (formation of the B-ring) and an allylic oxidation. This aldehyde **3.2.3** could be obtained by Claisen rearrangement of allyl vinyl ether **3.2.4**, controlling the stereochemistry at C14 and directing the unsaturation at the desired position.



Scheme 3.2.1.1 - Retrosynthetic Analysis of (±)-Morphine

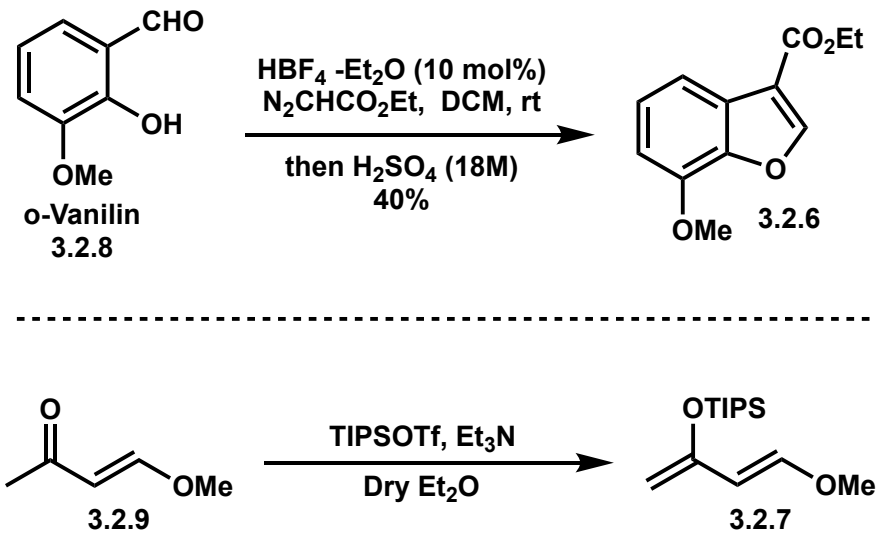
Intermediate **3.2.4** could in turn be prepared by stereoselective 1,2-reduction of the enone compound **3.2.5** and vinylation of the corresponding alcohol. Finally,

key intermediate **3.2.5** could be obtained by an intermolecular Diels-Alder reaction using the benzofuran dienophile **3.2.7** (obtained from *o*-vanillin) and a Danishefsky type diene **3.2.8**, followed by hydrolysis and elimination of the methoxy group. The use of an intermolecular [4+2] cycloaddition combined with telescopic transformations greatly simplifies the synthesis of the phenanthrofuran core of morphine.

3.2.2 Synthesis of the Tetracyclic Framework of Morphine

Our formal synthesis of (±)-morphine is enabled by a careful orchestration of telescopic transformations that quickly assembles the carbocyclic framework. Indeed, our formal synthesis allows the construction of the A, B, C, E-ring system in only five steps. The rapid assembly of this highly functionalized intermediate was key to the effectiveness of our approach.

The dienophile **3.2.6** was formed using the known condensation between ethyl diazoacetate and readily accessible *o*-vanillin **3.2.8** (Scheme 3.2.2.1).[66] Although the literature reports a quantitative yield for this transformation, we have not been able to achieve beyond 40 % despite extensive optimization and careful distillation of the reagents.



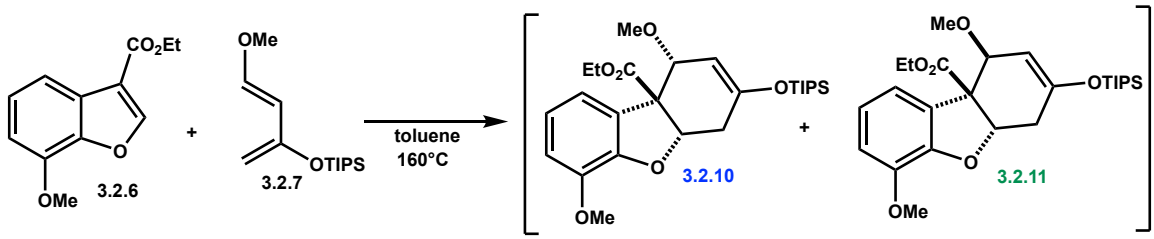
Scheme 3.2.2.1 - Synthesis of the Diene and the Dienophile

The synthesis of the diene **3.2.7** was accomplished using TIPSOTf and triethylamine in diethyl ether from the α,β-unsaturated ketone **3.2.9**. It is important to note that the reaction was sensitive to the nature of the solvent and the product was not formed in dichloromethane or toluene. In addition, the diene **3.2.7** could not be purified by flash chromatography, even if the silica gel was pretreated with a base. In order to prevent the hydrolysis of the silyl enol ether, the diene **3.2.7** was thus used in the Diels-Alder reaction in crude form.

The Diels-Alder reaction between the diene **3.2.7** and the dienophile **3.2.6** followed by deprotection and elimination of the methoxy group proved challenging due to the irreproducible results obtained (Table 3.2.2.1).[67] These reactive partners are a poor electronic match since they are both electron-rich. The electronic push-pulling ability of the benzofuran **3.2.6** has the consequence

of increasing the energy of the LUMO considerably, increasing the HOMO-LUMO gap. For this reason, this formal Diels-Alder reaction is believed to occur mostly stepwise, *via* two subsequent Michael additions. As a result, the cycloaddition preceded with no *endo*/*exo* selectivity as both diastereomers **3.2.10** and **3.2.11** were obtained equally (entries 1-4). The lack of stereocontrol at C14 was irrelevant, as the elimination of the methoxy group should give the enone **3.2.5**..

Table 3.2.2.1 - Optimization of the Diels-Alder Reaction



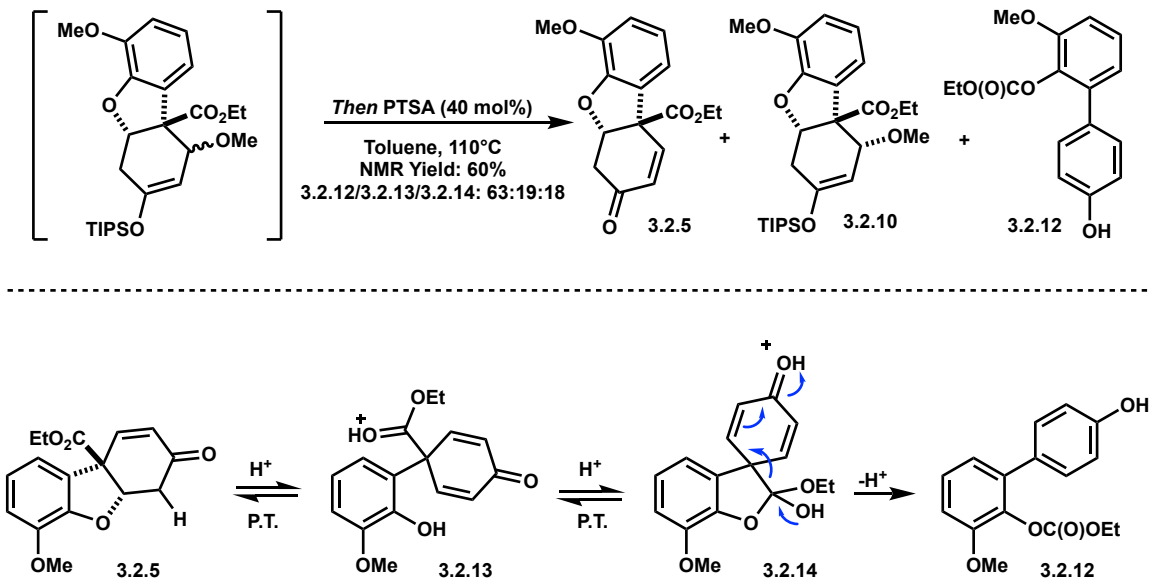
Entry	eq. 3.2.6	Concentration (M)	Time	10 : 11	NMRYield (%)
1	3	0.6	1 Day	55:45	86
2	2	0.6	5 Days	45:55	91
3	2	1.8	16 h	57:43	87
4	2	neat	16 h	57:43	98

At a concentration of 0.6 M in toluene at 160 °C, the challenging Diels-Alder reaction occurred and the products were observed with excellent yields, albeit long reaction time (86-91 %, entries 1-2). We observed that by increasing the concentration of the reaction mixture, the yield increased, and the product could

be obtained in a shorter period of time (entries 3-4). The reaction worked best when performed neat at 160 °C with two equivalents of the dienophile **3.2.6**. After 16 hours, the conversion was complete and the products **3.2.10** and **3.2.11** were obtained quantitatively. Due to the unstable nature of the Diels-Alder adducts, these compounds were not isolated and were carried through the next chemical transformation. The required reactants for the deprotection and elimination steps were simply added to the reaction flask

The combined deprotection of the silylenol ether and elimination of the methoxy group proved to be a challenging step (Scheme 3.2.2.2). The treatment of the Diels-Alder adducts with TBAF or another source of fluoride anion did not lead to the expected outcome; only the rearranged phenol **3.2.12** along with some degradation by-products were observed. After considerable experimentation, we found that the addition of a solution of PTSA (40 mol%) in toluene gave a better selectivity for the formation the desired enone **3.2.5**. Moreover, the adduct **3.2.10** of the Diels-Alder reaction was relatively less reactive under these conditions compared to the adduct **3.2.11**. Therefore, under the optimized reaction conditions, this diastereomer did not fully convert. In addition, the desired enone **3.2.5** is known to be unstable under both acidic and basic conditions.[67] These conditions allow the opening of the furan ring of **3.2.12** to generate **3.2.13** *via* an E1cB elimination. The newly formed phenol moiety can then condense onto the ester to form **3.2.14**, which rearranged readily to afford the stable biphenyl carbonate **3.2.12**. The same rearrangement was also observed

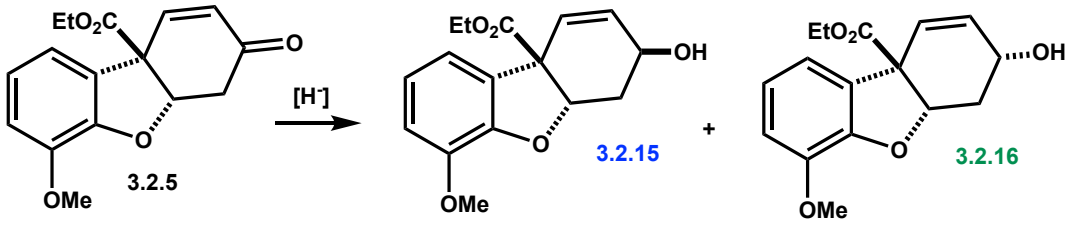
under basic conditions. Owing to its unstable nature, the crude reaction mixture of **3.2.5** was immediately used in the next step without further purification.



Scheme 3.2.2.2 - Deprotection and Elimination

To achieve the stereoselective 1,2-reduction of the enone **3.2.5**, we first tested Luche reduction conditions (Table 3.2.2.2, entry 1). When the reaction was performed in methanol at room temperature, both diastereomers **3.2.15** and **3.2.16** were observed. Using a bulkier reductant such as L-Selectride, only the desired diastereomer **3.2.16** was obtained in 53 % yield over two steps (from the diene **3.2.7** and the dienophile **3.2.6**) (entry 2). This sequence of four chemical transformations was achieved in two reactions and only one purification was required after the 1,2-reduction step. It was noted that an increase in the equivalents of reductant diminished the yield of the reduction (entry 3). Indeed, the formation of by-product **3.2.12** was also observed during this step.

Table 3.2.2.2 - Optimization of the Stereospecifive 1,2-Reduction of Enone 3.2.5

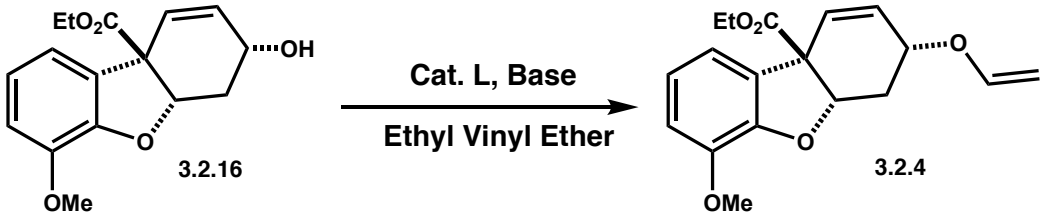


Entry	Conditions	15 : 16	Yield Over 2 Steps (%)
1	$NaBH_4$ (1 eq.) $CeCl_3{\cdot}7H_2O$ (1 eq.) MeOH, r.t.	1:1	45
2	L-Selectride (2 eq.) THF, -50°C	0:1	53
3	L-Selectride (3 eq.) THF, -50°C	0:1	28

In preparation for the formation of the B-ring, the formation of the vinyl ether **3.2.4** from allylic alcohol **3.2.16** was examined, and various catalysts and conditions were screened (Table 3.2.2.3). The use of $Ph_3PAuOAc$ (made *in situ*) led to a poor conversion of 48 %, and the product **3.2.4** was isolated in 30 % yield (entry 1). Using $Pd(OAc)_2$ and 1,10-phenanthroline increased the yield of the transformation to 53 % (entry 2).[68] A similar result was obtained when 1,7-diphenyl-1,10-phenanthroline was used as the ligand (entry 3). The use of a more reactive palladium complex such as $Pd(TFA)_2$ led to an increase in conversion and yield, and the desired product **3.2.4** was isolated in 72 % yield (entries 4–5).[69] Attempts to generate $Pd(OTf)_2$ *in situ* to catalyze this reaction failed and

the allylic alcohol **3.2.16** was almost fully recovered (entry 6). The vinyl ether **3.2.4** is highly acid sensitive and careful purification and storage of the compound was required to avoid hydrolysis.

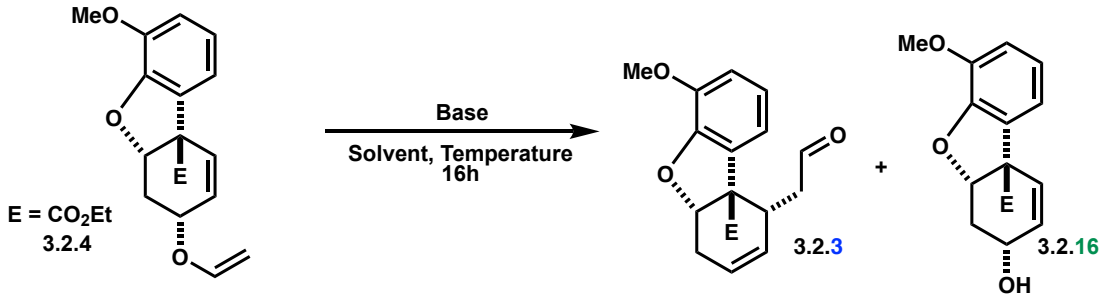
Table 3.2.2.3 - Optimization of the Palladium-Catalyzed Vinylation



Entry	Conditions	Conversion	Yield (%)
1	Ph_3PAuCl (5 mol%), AgOAc (5 mol%), 50°C, 5 Days	48	30
2	$Pd(OAc)_2$ (2 mol%) 1,10-Phenanthroline (2 mol%) Et_3N, 50°C, 2.5 Days	62	53
3	$Pd(OAc)_2$ (2 mol%) 2,7-diphenyl-1,10-phenanthroline (2 mol%) Et_3N, 50°C, 2.5 Days	64	54
4	**$Pd(TFA)_2$ (2 mol%) 1,10-Phenanthroline (2 mol%) Et_3N, 50°C, 2.5 Days**	**83**	**72**
5	$Pd(TFA)_2$ (2 mol%) 2,7-diphenyl-1,10-phenanthroline (2 mol%) Et_3N, 50°C, 2.5 Days	81	68
6	$PdCl_2$ (5 mol%), AgOTf (5 mol%) 1,10-phenanthroline (5 mol%) Et_3N, 50°C, 2.5 Days	<5	-

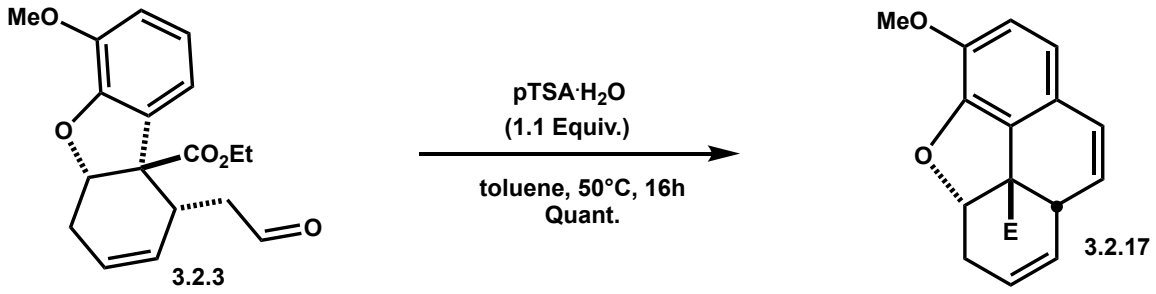
Next, the creation of the carbon–carbon bond between C9 and C14 was performed using a Claisen rearrangement. When vinyl ether **3.2.4** was heated at 110 °C in toluene, only the allylic alcohol **3.2.16** was observed (Table 3.2.2.4, entry 1).

Table 3.2.2.4 - Optimization of the Claisen Rearrangement



Entry	Base	Solvent	Temp. (°C)	Conversion (%)	3 : 16	Yield (%)
1	-	Toluene	110	100	0 : 100	0
2	DBU	Xylene	120	0	-	0
3	DBU	Xylene	160	100	-	0
4	2,6-di*t*butyl-4-methylpyridine	Xylene	160	59	88 : 12	50
5	Proton Sponge	Xylene	160	91	> 95 : 5	65
6	**2,6-Lutidine**	**Xylene**	**160**	**100**	**80 : 20**	**66**

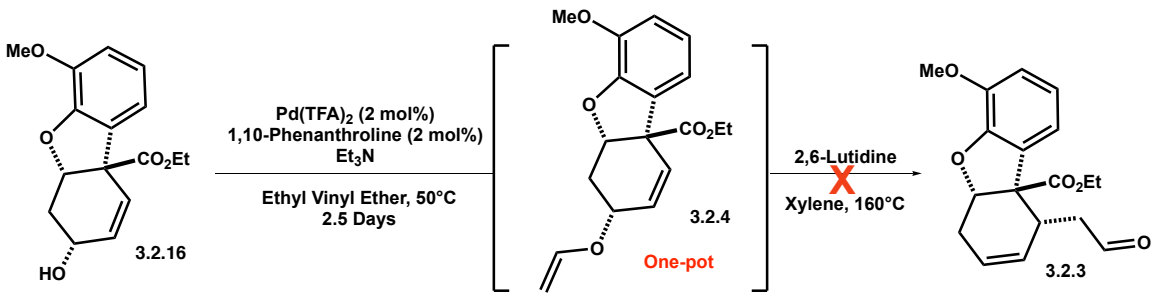
The acid-catalyzed Friedel-Crafts alkylation for the formation of the B-ring occurred smoothly in the presence of *p*-toluenesulfonic acid in toluene at 50 °C.[36] The tetracyclic product **3.2.17** was obtained in quantitative yield within 16 hours.



Scheme 3.2.2.3 - Friedel-Crafts Alkylation for the Formation of the B-Ring

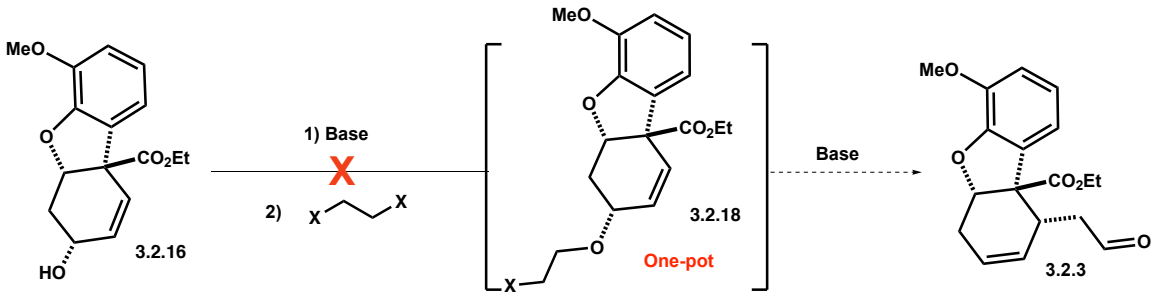
To shorten the 6-step linear sequence from the diene **3.2.7** and the dienophile **3.2.6** to the tetracyclic **3.2.17**, we then explored the possibility of combining some of these reactions. In order to obtain a good conversion, the vinylation step had to be performed in ethyl vinyl ether. This solvent has a relatively low boiling point of 35 °C at a pressure of 1 atmosphere. The following Claisen reaction is performed in xylene and heated to 160 °C. This high temperature is required to promote the [3,3]-sigmatropic rearrangement. Therefore, to achieve to vinylation/Claisen sequence in the desired one-pot manner, the solvent of the first step would have to be removed before performing the second step (Scheme 3.2.2.4). All attempts to do so failed, and the allylic alcohol **3.2.16** was the main product of the overall transformation. The vinyl ether **3.2.4** was formed, as indicated by thin-layer chromatography, however, the remaining palladium traces were acidic enough to induce its hydrolysis rather

than the desired Claisen rearrangement. Adding more equivalents of 2,6-lutidine did not improve the process.



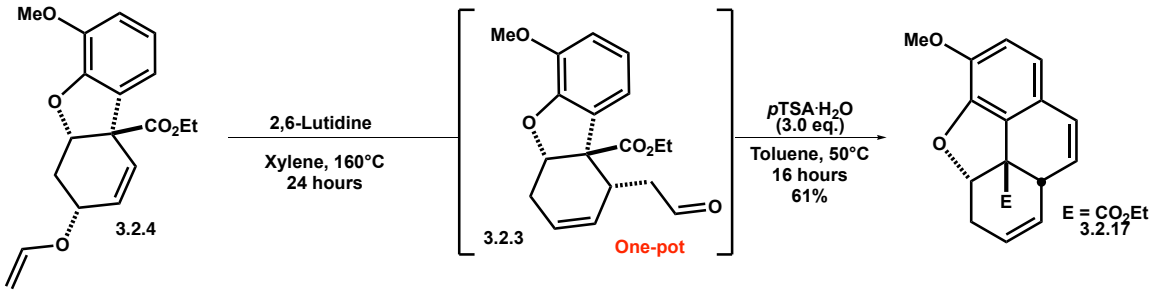
Scheme 3.2.2.4 - Attempts for Telescopic Vinylation/Claisen Rearrangement Sequence

To circumvent this issue, we decided to investigate the possibility to alkylate the allylic alcohol with dibromoethane or diiodoethane (Scheme 3.2.2.5). Upon the formation of the intermediate **3.2.18**, the remaining halogen could be eliminated under the basic reaction condition to form the vinyl ether **3.2.4** *in situ*, which could then undergo the desired Claisen rearrangement. Strong bases like sodium hydride and *n*-butyllithium were used. The product observed under these conditions arose mostly from the saponification of the ester moiety. In order to avoid this side reaction, maleic anhydride was added as an additive to trap any possible hydroxide salts. We then began to observe 1,2-addition of the allylic alcohol **3.2.16** onto maleic anhydride. Silver salts were also added in order to weaken the C–X bond and thus favour the desired substitution. Unfortunately, alkylation of **3.2.16** proved to be problematic under all the reaction conditions attempted.



Scheme 3.2.2.5 - Attempts towards the Telescopic Alkylation/Elimination/Claisen Rearrangement Sequence

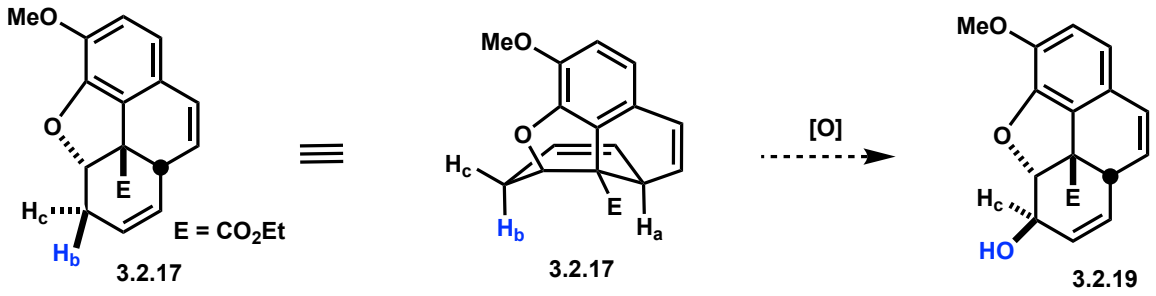
Since the vinylation and the Claisen rearrangement seemed to be incompatible, we investigated instead the possibility of combining the Claisen rearrangement and the Friedel-Crafts alkylation in a one-pot manner. To our delight, addition of 3.0 equivalents of *p*-toluenesulfonic acid after the Claisen rearrangement induced the Friedel-Crafts alkylation and the tetracyclic intermediate **3.2.17** was isolated in 61 % yield (Scheme 3.2.2.6). The yield for the telescopic transformation is comparable to that of the stepwise process.



Scheme 3.2.2.6 - Telescopic Claisen Rearrangement/Friedel-Crafts Alkylation

3.2.3 Functionalization of the Tetracyclic Framework of Morphine

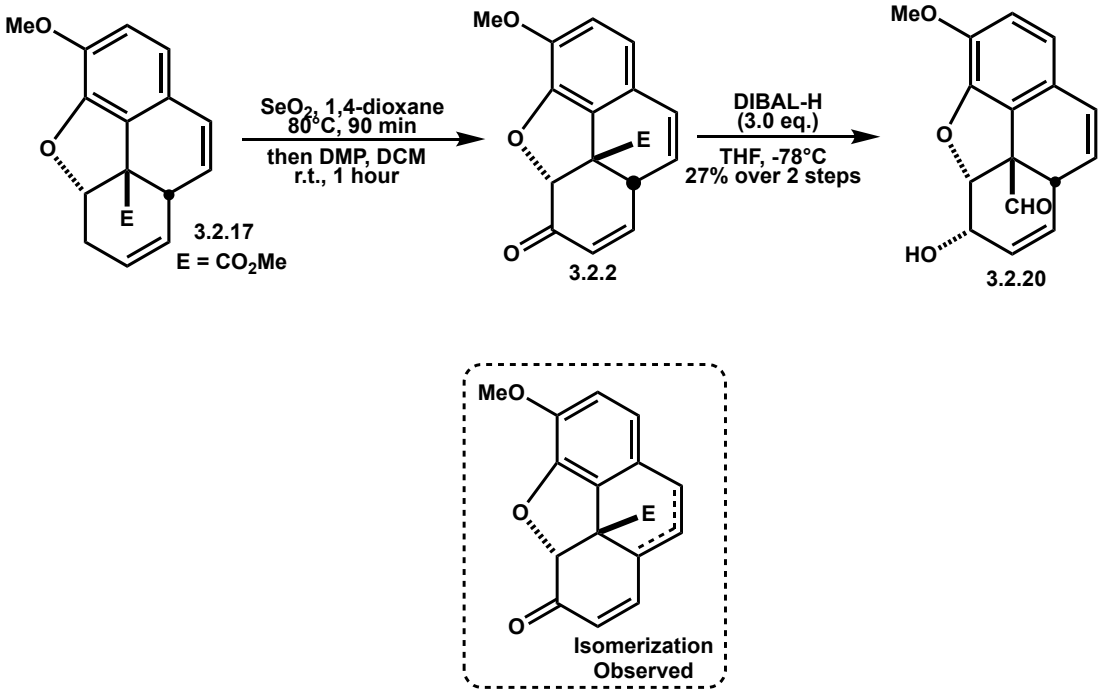
With the morphine phenanthrofuran core **3.2.17** in hand, we envisaged the installation of the allylic alcohol moiety in the C-ring through a sequential C–H oxidation/reduction process at C6. As previously observed by Trost *et al.* on a similar skeleton, direct allylic oxidation of the tetracycle **3.2.17** in presence of selenium dioxide leads to the formation of the undesired stereoisomer **3.2.19** (Scheme 3.2.3.1).[32b] Based upon the favoured conformation of tetracycle **3.2.17**, the proton H_b is stereoelectronically and sterically favoured for allylic oxidation. Based on this consideration, we decided to oxidize the tetracycle **3.2.17** to the enone **3.2.2**. The following 1,2-reduction of the enone **3.2.2** should occur on the less hindered top face and provide the desired diastereoisomer.



Scheme 3.2.3.1 - Expected Stereoselectivity for the Allylic Oxidation of Tetracycle 3.2.17

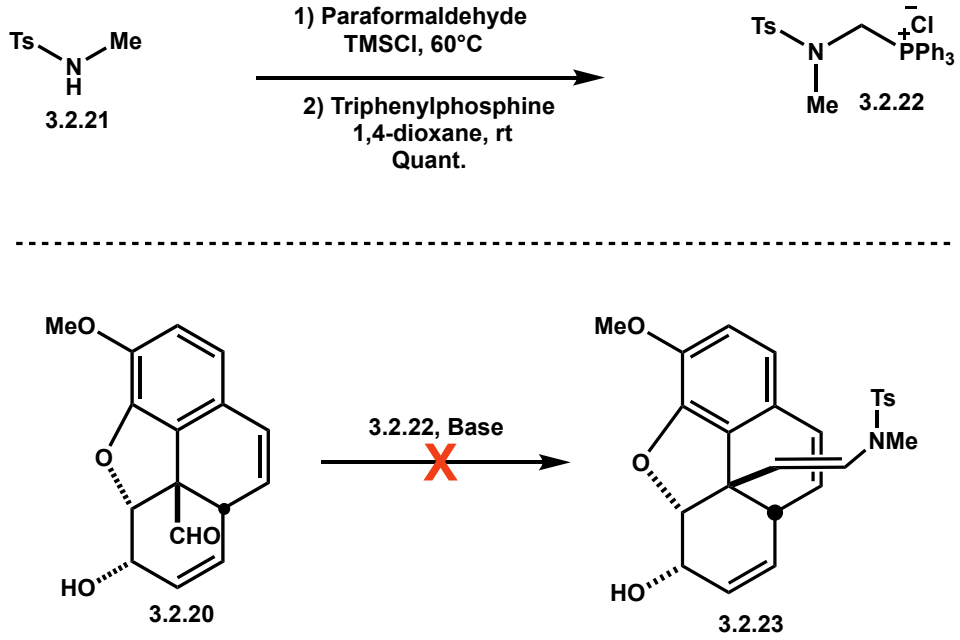
When the tetracycle **3.2.17** was treated with selenium dioxide at 80 °C, full conversion was observed within 90 minutes (Scheme 3.2.3.2). The reaction

mixture was then cooled to room temperature and Dess-Martin periodinane was added to oxidize the allylic alcohol into the enone **3.2.2**. It is difficult to estimate the yield of this transformation since we were not able to isolate the desired product from the selenium-based by-products. Furthermore, we found that double bond in ring B (**3.2.2**) isomerized under acidic conditions and a mixture of isomers was obtained when purified by flash chromatography. Basic treatment of the silica gel with Et_3N proved to be fruitless, as only degradation products were observed. Given the circumstance, the crude product **3.2.2** was treated with the reductant without any further purification. Attempts to improve this transformation using chromium-based oxidants failed and led mostly to degradation of the starting material **3.2.17** or suffered from poor conversion. The enone **3.2.2** was then reduced using 3.0 equivalents of diisobutylaluminum hydride. The challenge of this transformation resides in the stereoselective reduction of the enone moiety while avoiding over-reduction of the ester functional group. To our delight, the corresponding compound **3.2.20** was isolated in a modest yield of 27 % over two steps. About 10 % of the primary alcohol was isolated, resulting from the over-reduction of the ester moiety. We believe that the yield of this transformation is also limited by the base-sensitive nature of **3.2.2**. Moreover, using more equivalents of the reductant led to a decrease in yield, while using less than 3.0 equivalents resulted in only partial conversion of the enone **3.2.2**.



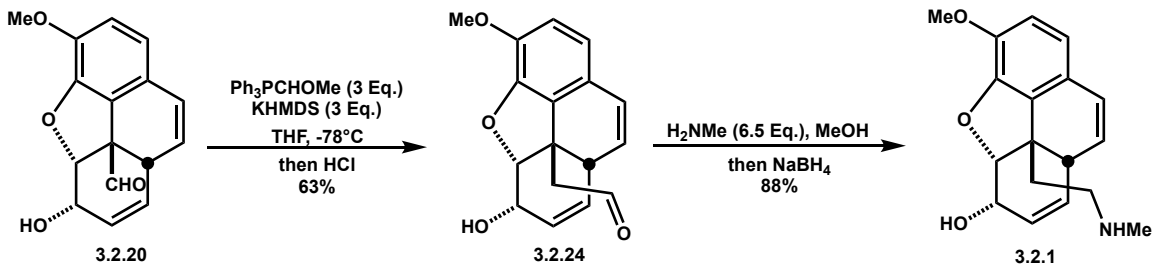
Scheme 3.2.3.2 - Allylic Oxidation and Reduction

For the addition of the last required carbon atom of morphine's scaffold, a Wittig olefination of the aldehyde **3.2.20** was utilized. At first, we attempted to install the nitrogen atom during that step (Scheme 3.2.3.3). To do so, the phosphonium salt **3.2.22** was formed from *N*-methyl-*N*-tosylamine **3.2.21** in two steps.[70] This strategy would generate the enamine **3.2.23** and its reduction would result in the formation of Guillou's precursor for the radical hydroamination.[36] Many reaction conditions were investigated for the formation of this C–C bond, but none of them led to the desired product **3.2.23**. The phosphonium salt **3.2.22** appeared to be deliquescent as it melted instantaneously and thus was stored in the glove box.



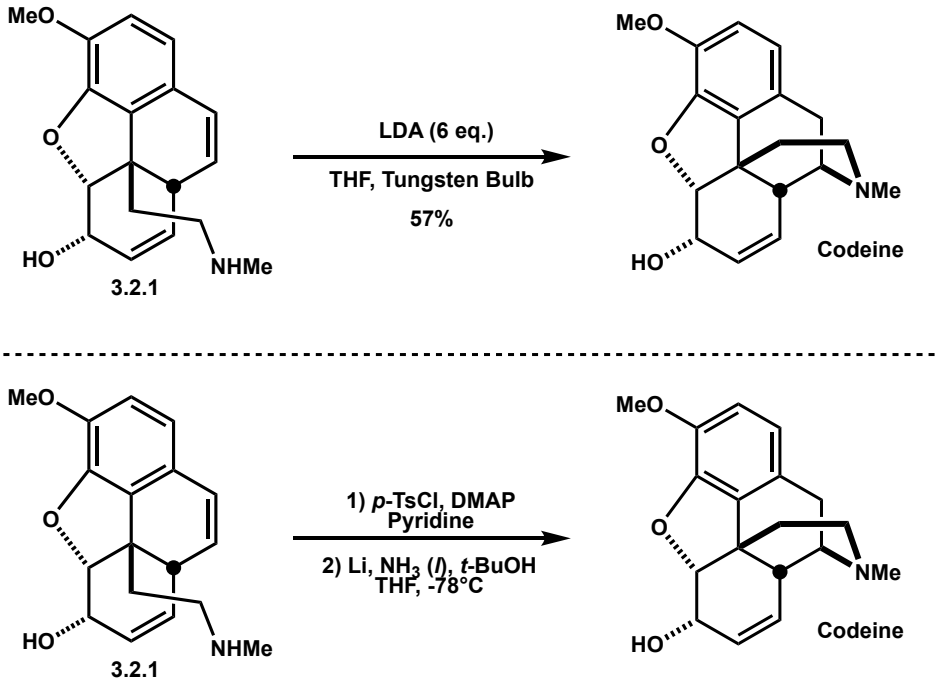
Scheme 3.2.3.3 - Attempted Wittig Olefination

Alternatively, we performed the homologation of the aldehyde **3.2.20** to install C^{16} (Scheme 3.2.3.4). The generated enol ether was hydrolyzed *in situ* using a concentrated solution of HCl (12 M) and the desired compound **3.2.24** was isolated in 63 % yield. Next, typical reductive amination conditions employing methylamine and sodium borohydride led to the formation of the amine **3.2.1** in 88 % yield and concluded our 9-step formal synthesis of (±)-morphine.



Scheme 3.2.3.4 - Completion of the Formal Synthesis of (±)-Morphine

The conversion of the advanced intermediate **3.2.1** into morphine has been described in two and three steps by Trost[32a] and Li,[51] respectively (Scheme 3.2.3.5). Trost *et al.* utilized a tungsten bulb to induce the cyclization of the amine **3.2.1** in the presence of 6.0 equivalents of lithium diisopropylamine. Codeine was isolated in 57 % yield, and then converted into morphine *via* demethylation using boron tribromide.

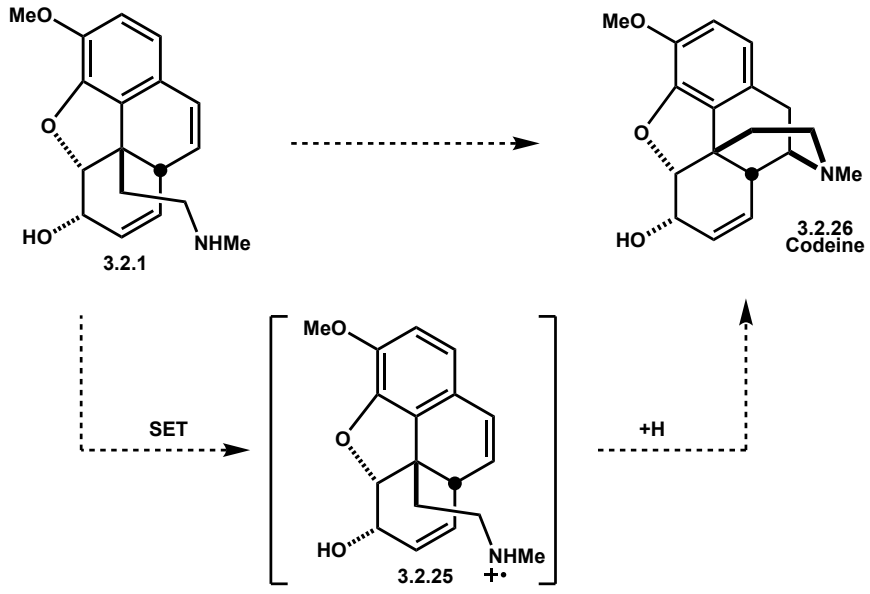


Scheme 3.2.3.5 - Conversion of Amine 3.2.1 into Codeine

As for Li *et al.*, they first installed the tosyl group onto the nitrogen atom and then induced radical cyclization by homolytic cleavage of the S-N bond under Birch-like reaction condition as Guillou *et al.* described in 2008.[36] Therefore, our approach for the synthesis of (±)-morphine allows the formation of the natural product in 11 or 12 steps and is one of the shortest to date.

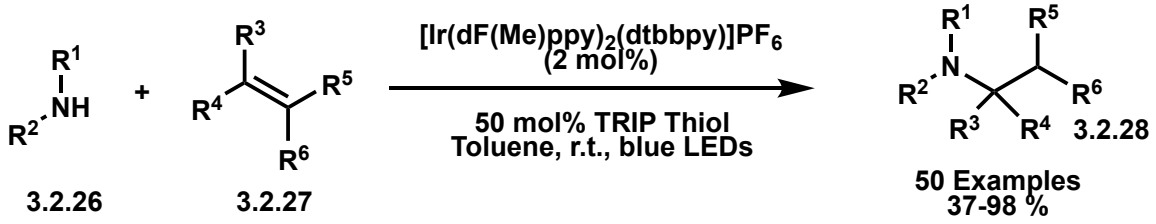
3.2.4 Attempted Photocatalyzed Hydroamination

To convert the advanced intermediate **3.2.1** into codeine **3.2.26**, we have investigated a possible oxidation of the secondary amine to form the corresponding aminium radical cation **3.2.25** using a photoredox catalyst, which could then cyclize onto the styrenyl π-bond. This transformation is more challenging than it appears at first glance. Indeed, the tertiary amine formed is more electron-rich than the starting material and by consequence easier to oxidize which could lead to degradation of the desired product.



Scheme 3.2.4.1 - Radical Intramolecular Hydroamination

Although photocatalyzed oxidations of secondary amines are rare in the literature, Knowles *et* al. have reported such a transformation in 2017 for hydroamination of alkenes (Scheme 3.2.4.2).[71] The single electron transfer is promoted by an excited-state iridium-based photocatalyst and 2,4,6-triisoproprylbenzenethiol is used as a hydrogen donor. This highly hindered thiol was used to prevent the addition of the corresponding thiol radical onto the π-bond rather than the aminium radical cation. In their scope, they present both intra- and intermolecular examples, and the transformation is highly tolerant to a variety of functional groups.

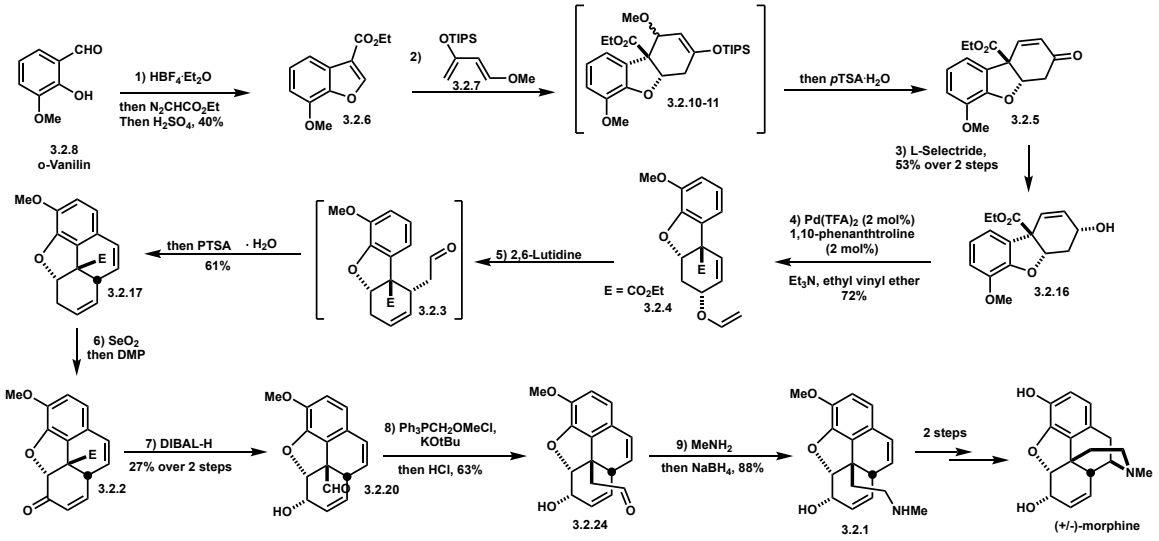


Scheme 3.2.4.2 - Catalytic Hydroamination of Unactivated Olefins Using Secondary Alkyl Amines

Unfortunately, all attempts to apply these conditions for the hydroamination of **3.2.1** to form codeine **3.2.26** failed. Blanks experiments revealed that while compounds were thermally stable, they seemed to degrade when irradiated with blue LEDs.

3.3 CONCLUSION

In conclusion, a 9-step formal synthesis of (±)-morphine is reported. A Diels-Alder/elimination/deprotection sequence as well as a telescopic Claisen rearrangement/Friedel-Crafts alkylation were key in the isolation of the highly functionalized tetracycle intermediate **3.2.17** in only five steps. From this intermediate, efficient functional group manipulations were designed in order to minimize the number of steps required for the formation of the natural product. While there are about 50 syntheses of morphinans in the literature, our approach is distinguished by the absence of protecting groups and innovative use of unconventional redox manipulations. The details of our entire synthesis are provided in Scheme 3.3.1. The overall yield for the formation of (±)-morphine using this route is about 0.7 %. Also, the sensitivity of some intermediates and reactions may prevent the use of this approach on a large scale.



Scheme 3.3.1 - 9-Step Formal Synthesis of (±)-Morphine

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4 CONCLUSION

The multiple applications of coinage metal complexes in organic chemistry provide an unparalleled platform for the discovery of new transformations. The π-Lewis acidity of these catalysts plays a pivotal role in the activation of allenes, alkenes, and alkynes aimed at the construction of C–C, C–O, and C–N bonds. Although these metals all belong to group 11 of the periodic table, they have distinct properties that can be exploited for different uses.

In the context of this thesis, a focus has been placed on utilizing the ability of coinage metal to catalyze regioselective intramolecular carbocyclization reactions of silylenol ethers bearing an alkyne-tether. Although the *5-exo-dig* cyclization is usually favoured, as depicted by the Baldwin rules, we have demonstrated that the selective formation of the 6-membered ring can be achieved through the optimization of the steric and electronic properties of the ancillary ligand on the cationic metal catalyst.

In *chapter 2*, we investigated a novel silver-catalyzed *6-endo-dig*/acetalization/Prins reaction cascade. This transformation generated two C–C bonds as well as one C–O bond, resulting in the formation of a highly strained polycycle. Through the support of deuterium-labelling experiments, we proposed a mechanism for the formation of such interesting polycycles and explored their reactivity towards further functionalization. We have also investigated the synthesis of the natural product Teucrin A through a sequential Diels-Alder/*6-*

endo-dig cyclization. The combination of these key transformations would have provided an efficient and practical way to synthesize the ring system of the natural product. Although the use of an exocyclic allene as the dienophile has showed poor reactivity and selectivity, promising alternatives are currently being studied in our group.

In *chapter 3,* we described a 9-step formal synthesis of (±)-morphine. The morphinans have received a lot of attention from chemists, as reflected by the 50 formal and total syntheses reported in the literature. Our approach provides a unique and rapid way to access the phenanthrofuran core of morphine in only five steps. The synthesis of this framework was achieved through an intermolecular Diels-Alder cycloaddition, followed by a telescopic Claisen rearrangement/Friedel-Crafts. From this advanced intermediate, efficient functional group manipulations were designed in order to minimize the number of steps required for the expedient formation of the natural product.

5 CONTRIBUTION STATEMENT

5.1 CLAIMS TO ORIGINAL RESEARCH

5.1.1 6-*endo-dig*/Acetelylation/Prins Reaction Cascade

Initial reaction conditions for the formation of the polycycle have been found by Francis Barabé, Ph.D. and Patrick Lévesque, M.Sc. They have also characterized the product using NMR spectroscopy. My contributions to this project are listed below:

→ Synthesis and characterization of new polycycles

→ Optimization of the polycycle formation

→ Mechanistic investigations for the formation of the polycycle

→ Exploration and preparation of the scope for the silver-catalyzed reaction cascade

→ Functionalization of the polycycle

→ Isolation, characterization and synthesis of derived products

5.1.2 Efforts Towards the Synthesis of Teucrin A

→ Optimization and synthesis of the diene and dienophile required for the key Diels-Alder in the synthesis of teucrin A.

→ Investigation of the key Diels-Alder reaction for the synthesis of teucrin A

5.1.3 Formal Synthesis of (±)-Morphine

Amandine Xolin, Ph.D., has found the synthetic route for the formation of morphine. She has also optimized most of the reaction conditions up to the formation of the tetracycle. My contributions to this project are listed below:

- → Partial optimization of the synthesis of the phenanthrofuran core of (±)-morphine
- → Development of the telescopic Claisen rearrangement/Friedel-Crafts
- → Functionalization of the phenanthrofuran core of (±)-morphine
- → Exploration of the application of photochemistry for the hydroamination of an advanced intermediate in the synthesis of (±)-morphine

5.2 PUBLICATIONS FROM THIS WORK

- → J. Brousseau, A. Xolin, L. Barriault, ''*A Nine-Step Formal Synthesis of (±)-Morphine", Org. Lett.* **2019**, *21*, 1347-1349.
    - Highlighted: *Synfacts,* **2019**, 15*, 05*, 0464.
- → P. McGee, J. Brousseau, L. Barriault, *"Development of New Gold(I)-Catalyzed Carbocyclization and their Application in the Synthesis of Natural Products", Irs. J. Chem.* **2017**, *57*, 1-11.
- → A manuscript on the silver-catalyzed reaction cascade is in preparation.

5.3 ORAL PRESENTATIONS

→ 102nd Canadian Chemical Conference and Exhibition, ''*Development of Biarylphosphane Coinage Metal Complexes for the Selective Divergent Synthesis of Carbocycles"*, **2019**.

→ 101st Canadian Chemical Conference and Exhibition, ''*The Synthesis of Morphine*, **2018**.

→ Ottawa-Carleton Chemistry Symposium, *"Towards the Total Synthesis of Morphine"*, **2017**.

5.4 POSTER PRESENTATIONS

→ 28th Quebec-Ontario Mini-Symposium on Bioorganic and Organic Chemistry, *"Towards the Total Synthesis of Morphine"*, **2017**.

→ 27th Quebec-Ontario Mini-Symposium on Bioorganic and Organic Chemistry, *"Formation of Polycyclic Compounds Using Silver Catalysis"*, **2016**.

→ Ottawa-Carleton Chemistry Symposium, *"Silver-Catalyzed Reaction Cascade Leading to Highly Stained Molecules"*, **2016**.

→ Synthesis Day at University of Ottawa, *"Silver-Catalyzed Reaction Cascade for the Synthesis of Decaline"*, **2016**.

→ 26th Quebec-Ontario Mini-Symposium on Bioorganic and Organic Chemistry, *"Reaction Cascade Involving Gold Photoredox and Silver Catalysis"*, **2015**.

→ Ottawa-Carleton Chemistry Symposium, *"Intermolecular Cyclization via Photoredox Catalysis"*, **2015**.

6 EXPERIMENTAL PROCEDURES

6.1 GENERAL INFORMATION

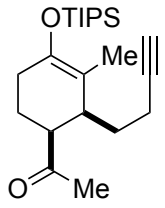
All reactions were performed under nitrogen or argon atmosphere in flame-dried glassware equipped with a magnetic stir bar and a rubber septum, unless otherwise indicated. All commercial reagents were used without purification, unless otherwise noted. When no temperature is mentioned, the reaction was performed at room temperature. Anhydrous solvents were obtained by storing them over 4 A° molecular sieves. *n*-butyllithium and *tert*-butyllithium were titreted using 2,6-di-*tert*-butyl-4-methylphenol and fluorene. Reactions were monitored by thin layer chromatography (TLC) analysis using aluminum plates pre-coated (250 μm thichness) with ultra-pure silica gel (60A, SiliCycle). Thin layer chromatography plates were viewed under UV light and stained with potassium permanganate or *p*-anisaldehyde staining solution. Flash chromatographies were carried out on 230-400 mesh silica gel. Yields refer to products isolated after purification, unless otherwise stated. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AMX 300 MHz or a Bruker AMX 400 MHz instrument. NMR samples were dissolved specified deuterated solvent and chemical shifts are reported in ppm referenced to residual undeuterated solvent. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on the same Bruker instrument (101 MHz). IR spectra were recorded with a Bomem Michaelson 100 FTIR spectrometer. HRMS were

obtained on a Kratos Analytical Concept instrument (University of Ottawa Mass Spectrum Centre).

6.2 6-*ENDO* DIG/ACETALYZATION/PRINS REACTION CASCADE

6.2.1 Diels-Alder Adducts

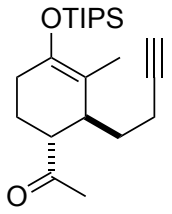
General Procedure 1 (GP1) – Diels-Alder: In a reaction flask was added the enol ether (0.68 mmol) and the dienophile (2.1 mmol, 1.0 eq.) in DCM. The mixture was cooled down to -78°C and a solution of Et_2AlCl in hexanes was added dropwise (1.0 M, 0.40 mmol, 0.60 eq.). Upon completion, the reaction was quenched with a saturated solution of $NaHCO_3$ and then warmed up to room temperature. The aqueous phase was extracted 3 times with DCM and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography (1:3:96 Et_3N/EtOAc/Hexanes) to obtain the *endo* diels-alder adduct.



1-(-2-(But-3-yn-1-yl)-3-methyl-4-((triisopropylsilyl)oxy)cyclohex-3-en-1-yl)ethan-1-one (Compound 2.2.8)

Prepared according to **GP1** in 75% yield (185 mg) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.71-2.63 (m, 2H), 2.23 (s, 3H), 2.19-2.10 (m, 4H), 1.97 (t, *J* = 2.5 Hz, 1H), 1.83-1.77 (m, 2H), 1.76 (s, 3H), 1.50 (q, *J* = 7.5 Hz, 2H), 1.18-1.08 (m, 21H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 211.2 (C), 144.6 (C), 113.8 (C), 84.3 (C), 69.1 (CH), 51.9 (CH), 39.6 (CH), 30.1 (CH_2), 29.5 (CH_2), 29.3 (CH_3), 19.9 (CH_2), 18.2 ($3CH_3$), 18.2 ($3CH_3$), 17.9 (CH_2), 16.7 (CH_3), 13.4 (3CH). **IR** (neat, cm^{-1}): 3309, 2944, 2112, 2866, 1707. **HRMS** (EI): m/z calc'd for $C_{22}H_{38}O_2Si$ [M^+] 362.2641, found 362.2625.

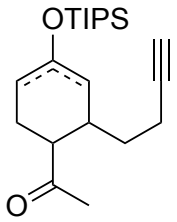


1-(-2-(But-3-yn-1-yl)-3-methyl-4-((triisopropylsilyl)oxy)cyclohex-3-en-1-yl)ethan-1-one (Compound 2.2.15)

In a sealed tube was added the enol ether (0.68 mmol) and the dienophile (2.1 mmol, 1.0 eq.) in DCE. The mixture was heated to 100°C for 18 hours. The reaction was cooled to room temperature and the solvent was evaporated to afford the crude product. The crude product was purified by column chromatography (1:3:96 Et_3N/EtOAc/Hexanes) to obtain the Diels-Alder adduct (*endo/exo* 2:1) in quantitative yield (0.68 mmol).

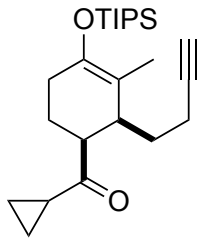
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.67-2.60 (m, 1H), 2.50 (dt, *J* = 6.3, 4.3 Hz, 1H), 2.21-2.10 (m, 3H), 2.17 (s, 3H), 1.98 (t, *J* = 2.6 Hz, 1H), 1.91 (dt, *J* = 12.8, 6.7 Hz, 1H), 1.85-1.74 (m, 2H), 1.67-1.65 (m, 3H), 1.62-1.50 (m, 2H), 1.11-1.04 (m, 21H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 210.5 (C), 144.4 (C), 111.5 (C), 84.3 (C), 68.8

(CH), 49.6 (CH), 39.3 (CH), 31.1 (CH_2), 28.1 (CH_2), 28.1 (CH_3), 22.2 (CH_2), 18.1 ($3CH_3$), 18.1 ($3CH_3$), 15.9 (CH_2), 14.8 (CH_3), 13.2 (3CH). **IR** (neat, cm^{-1}): 3309, 2944, 2112, 2866, 1707. **HRMS** (EI): m/z calc'd for $C_{22}H_{38}O_2Si$ [M^+] 362.2641, found 362.2625.



Compound 2.2.12b

Prepared according to **GP1** in 71% yield. A mixture of isomers and diastereomers was obtained, for a total of 4 different compounds. The mixture was used in the next step, without any further purification.

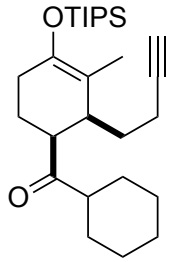


(2-(But-3-yn-1-yl)-3-methyl-4-((triisopropylsilyl)oxy)cyclohex-3-en-1-yl)(cyclopropyl)methanone (Compound 2.2.12c)

Prepared according to **GP1** in 87% yield (230 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.85 (dt, *J* = 11.1, 4.5 Hz, 1H), 2.74 (dd, *J* = 5.0, 5.0 Hz, 1H), 2.19 – 2.07 (m, 5H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.89 – 1.77 (m, 2H), 1.76 (t, *J* = 1.9 Hz, 3H), 1.59 – 1.47 (m, 2H), 1.15 – 1.00 (m, 23H), 0.90 (dt, *J* = 7.5, 3.6

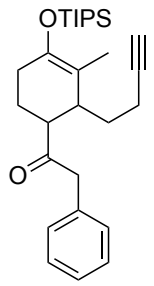
Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 213.0 (C), 144.7 (C), 114.0 (C), 84.6 (C), 68.8 (CH), 52.1 (CH), 39.9 (CH), 30.1 (CH_2), 29.6 (CH_2), 20.1 (CH_2), 20.0 (CH), 18.3 (6CH_3), 18.0 (CH_2), 16.5 (CH_3), 13.4 (3CH), 12.1 (CH_2), 11.6 (CH_2). **IR** (neat, cm^{-1}): 3313, 2943, 2866, 2118, 1693. **HRMS** (EI): m/z calc'd for $C_{24}H_{40}O_2Si$ [M^+] 388.2798, found 388.2802.



(2-(But-3-yn-1-yl)-3-methyl-4-((triisopropylsilyl)oxy)cyclohex-3-en-1-yl)(cyclohexyl)methanone (Compound 2.2.12d)

Prepared according to **GP1** in 56% yield (164 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = (ddd, *J* = 12.7, 4.6, 2.8 Hz, 1H), 2.63 – 2.54 (m, 2H), 2.19 – 2.02 (m, 4H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.92 – 1.76 (m, 4H), 1.74 (t, *J* = 2.0 Hz, 3H), 1.73 – 1.61 (m, 3H), 1.59 – 1.41 (m, 3H), 1.34 – 1.28 (m, 1H), 1.27 – 1.19 (m, 3H), 1.17 – 1.03 (m, 21H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 216.6 (C), 144.6 (C), 113.9 (C), 84.5 (C), 69.0 (CH), 49.4 (CH), 48.6 (CH), 39.9 (CH), 30.4 (CH_2), 30.1 (CH_2), 29.6 (CH_2), 27.7 (CH_2), 26.5 (CH_2), 26.1 (CH_2), 25.5 (CH_2), 20.5 (CH_2), 18.3 (3CH_3), 18.3 (3CH_3), 17.8 (CH_2), 16.7 (CH_3), 13.4 (3CH). **IR** (neat, cm^{-1}): 3312, 2928, 2854, 2119, 1698. **HRMS** (EI): m/z calc'd for $C_{27}H_{46}O_2Si$ [$(M\text{-}Me)^+$] 415.3032, found 415.3051.

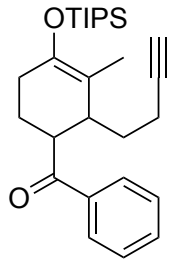


1-(2-(But-3-yn-1-yl)-3-methyl-4-((triisopropylsilyl)oxy)cyclohex-3-en-1-yl)-2-phenylethan-1-one (Compound 2.2.12e)

Prepared according to **GP1** in 70% yield (209 mg) (*endo*/*exo* 3:1).

^{1}H NMR *endo* product (400 MHz, $CDCl_3$): δ = 7.33 – 7.28 (m, 2H), 7.26 – 7.23 (m, 1H), 7.22 – 7.17 (m, 2H), 3.81 (s, 2H), 2.79 (ddd, *J* = 12.6, 4.7, 2.9 Hz, 1H), 2.72 – 2.59 (m, 1H), 2.23 – 2.02 (m, 4H), 2.00 (t, *J* = 2.6 Hz, 1H), 1.88 – 1.79 (m, 1H), 1.75 (t, *J* = 2.0 Hz, 3H), 1.72 – 1.65 (m, 1H), 1.60 – 1.44 (m, 2H), 1.14 – 1.02 (m, 21H). **^{1}H NMR *exo* product** (400 MHz, $CDCl_3$): δ = δ 7.33 – 7.28 (m, 2H), 7.26 – 7.23 (m, 1H), 7.22 – 7.17 (m, 2H), 3.83 – 3.69 (m, 2H), 2.72 – 2.59 (m, 2H), 2.23 – 2.02 (m, 4H), 1.94 (t, *J* = 2.4 Hz, 1H), 1.88 – 1.79 (m, 1H), 1.72 – 1.65 (m, 1H), 1.61 (t, *J* = 2.0 Hz, 3H), 1.60 – 1.44 (m, 2H), 1.14 – 1.02 (m, 21H). **^{13}C NMR *endo* product** (101 MHz, $CDCl_3$): δ = 210.5 (C), 144.7 (C), 134.4 (C), 129.7 (2CH), 128.9 (2CH), 127.2 (CH), 113.9 (C), 84.5 (C), 69.4 (CH), 50.0 (CH), 48.9 (CH_2), 39.7 (CH), 30.0 (CH_2), 29.5 (CH_2), 20.2 (CH_2), 18.3 (6CH_3), 17.9 (CH_2), 16.7 (CH_3), 13.4 (3CH). **^{13}C NMR *exo* product** (101 MHz, $CDCl_3$): δ = 209.8 (C), 144.6 (C), 134.6 (C), 129.6 (2CH), 128.9 (2CH), 127.1 (CH), 111.5 (C), 84.6 (C), 68.9 (CH), 48.5 (CH), 48.1 (CH_2), 39.3 (CH), 31.2 (CH_2), 28.5 (CH_2), 22.9 (CH_2), 18.3 (6CH_3), 15.8 (CH_2), 14.8 (CH_3), 13.4 (3CH). **IR** (neat, cm^{-1}): 3309, 2943,

2866, 2218 1739, 1708. **HRMS** (EI): m/z calc'd for $C_{28}H_{42}O_2Si$ [M^+] 438.2954, found 438.2962.

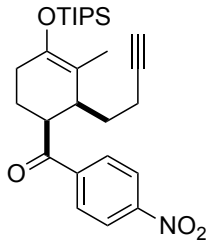


(2-(But-3-yn-1-yl)-3-methyl-4-((triisopropylsilyl)oxy)cyclohex-3-en-1-yl)(phenyl)methanone (Compound 2.2.12f)

Prepared according to **GP1** in 68% yield (196 mg) (*endo*/*exo* 5:2).

^{1}H NMR *endo* product (400 MHz, $CDCl_3$): δ = 7.97 – 7.94 (m, 2H), 7.60 – 7.51 (m, 1H), 7.52 – 7.42 (m, 2H), 3.59 (ddd, *J* = 12.3, 4.8, 2.7 Hz, 1H), 2.58 (dd, *J* = 4.0, 4.0 Hz, 1H), 2.30 – 2.19 (m, 1H), 2.22 – 2.10 (m, 1H), 2.14 – 1.98 (m, 1H), 2.01 – 1.76 (m, 3H), 1.74 (t, *J* = 1.9 Hz, 3H), 1.71 – 1.57 (m, 2H), 1.54 – 1.35 (m, 1H), 1.22 – 1.05 (m, 21H). **^{1}H NMR *exo* product** (400 MHz, $CDCl_3$): δ = 7.93 – 7.90 (m, 2H), 7.95 – 7.88 (m, 1H), 7.60 – 7.51 (m, 1H), 7.52 – 7.42 (m, 2H), 3.47 (ddd, *J* = 8.4, 6.2, 3.7 Hz, 1H), 2.86 – 2.75 (m, 1H), 2.30 – 2.19 (m, 1H), 2.22 – 2.10 (m, 1H), 2.14 – 1.98 (m, 1H), 2.01 – 1.76 (m, 3H), 1.72 (t, *J* = 2.6 Hz, 3H), 1.71 – 1.57 (m, 2H), 1.54 – 1.35 (m, 1H), 1.22 – 1.05 (m, 21H). **^{13}C NMR *endo* product** (101 MHz, $CDCl_3$): δ = 202.9 (C), 144.6 (C), 136.8 (C), 133.2 (CH), 128.9 (2CH), 128.5 (2CH), 113.9 (C), 84.3 (C), 68.5 (CH), 46.1 (CH), 41.6 (CH), 29.8 (CH_2), 29.7 (CH_2), 21.0 (CH_2), 18.3 (6CH_3), 18.0 (CH_2), 16.4 (CH_3), 13.5 (3CH). **^{13}C NMR *exo* product** (101 MHz, $CDCl_3$): δ = 202.7 (C), 144.43 (C), 136.9 (C),

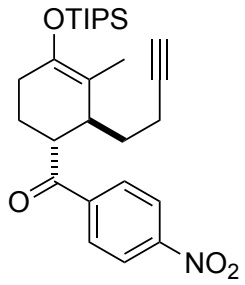
132.9 (CH), 128.8 (2CH), 128.4 (2CH), 111.9 (C), 84.8 (C), 68.8 (CH), 44.9 (CH), 39.9 (CH), 31.4 (CH_2), 29.1 (CH_2), 25.3 (CH_2), 18.3 ($6CH_3$), 15.8 (CH_2), 14.5 (CH_3), 13.4 (3CH). **IR** (neat, cm^{-1}): 3312, 2944, 2867, 2153, 1678. **HRMS** (EI): m/z calc'd for $C_{27}H_{40}O_2Si$ [M^+] 424.2798, found 424.2770.



(2-(But-3-yn-1-yl)-3-methyl-4-((triisopropylsilyl)oxy)cyclohex-3-en-1-yl)(4-nitrophenyl)methanone (Compound 2.2.12g)

Prepared according to **GP1** in 48% yield (153 mg). The *exo* diastereomer was isolated with 24% yield (77 mg). The selectivity of the Diels-Alder reaction was therefore *endo*/*exo* 2:1 with a total yield of 72%.

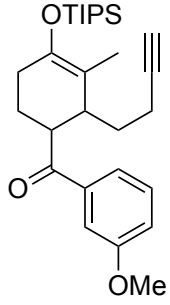
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.8 Hz, 2H), 8.11 (d, *J* = 8.8 Hz, 2H), 3.59 (ddd, *J* = 12.2, 4.8, 2.7 Hz, 1H), 2.60 (q, *J* = 5.3 Hz, 1H), 2.33 – 2.18 (m, 2H), 2.15 – 2.02 (m, 1H), 2.01 – 1.92 (m, 1H), 1.92 – 1.81 (m, 2H), 1.74 (s, 3H), 1.69 (t, *J* = 2.6 Hz, 1H), 1.63 – 1.53 (m, 1H), 1.53 – 1.44 (m, 1H), 1.20 – 1.07 (m, 21H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 201.5 (C), 150.5 (C), 144.8 (C), 141.3 (C), 129.6 (2CH), 124.3 (2CH), 113.6 (C), 83.8 (C), 69.0 (CH), 47.0 (CH), 41.2 (CH), 29.7 (CH_2), 29.6 (CH_2), 20.9 (CH_2), 18.3 ($6CH_3$), 17.9 (CH_2), 16.5 (CH_3), 13.5 (3CH). **IR** (neat, cm^{-1}): 3308, 2943, 2866, 2114, 1686. **HRMS** (EI): m/z calc'd for $C_{27}H_{39}NO_4Si$ [M^+] 469.2648, found 469.2654.



(2-(But-3-yn-1-yl)-3-methyl-4-((triisopropylsilyl)oxy)cyclohex-3-en-1-yl)(4-nitrophenyl)methanone

Prepared according to **GP1** in 24% yield (77 mg). The *endo* diastereomer was isolated with 48% yield (153 mg). The selectivity of the Diels-Alder reaction was therefore *endo*/*exo* 2:1 with a total yield of 72%.

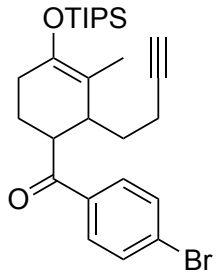
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33-8.29 (m, 2H), 8.06-8.01 (m, 2H), 3.51 (ddd, *J* = 7.0, 5.1, 3.9 Hz, 1H), 2.76-2.71 (m, 1H), 2.24 – 2.16 (m, 4H), 2.02 – 1.95 (m, 1H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.91 – 1.77 (m, 2H), 1.73 – 1.65 (m, 1H), 1.64 – 1.63 (m, 3H), 1.12 – 1.07 (m, 21H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 201.2 (C), 150.1 (C), 144.2 (C), 141.5 (C), 129.2 (2CH), 123.9 (2CH), 111.3 (C), 84.4 (C), 69.1 (CH), 45.0 (CH), 39.7 (CH), 31.2 (CH_2), 28.3 (CH_2), 23.8 (CH_2), 18.1 ($3CH_3$), 18.1 ($3CH_3$), 15.9 (CH_2), 14.6 (CH_3), 13.2 (3CH). **IR** (neat, cm^{-1}): 3308, 2943, 2866, 2114, 1686. **HRMS** (EI): m/z calc'd for $C_{27}H_{39}NO_4Si$ [M^+] 469.2648, found 469.2654.



(2-(But-3-yn-1-yl)-3-methyl-4-((triisopropylsilyl)oxy)cyclohex-3-en-1-yl)(3-methoxyphenyl)methanone (Compound 2.2.12h)

Prepared according to **GP1** in 71% yield (220 mg) (*endo*/*exo* 2:1).

^{1}H NMR *endo* product (400 MHz, $CDCl_3$): δ = 7.55 – 7.43 (m, 2H), 7.37 (td, *J* = 7.9, 2.1 Hz, 1H), 7.13 – 7.07 (m, 1H), 3.86 (s, 3H), 3.56 (ddd, *J* = 12.3, 4.8, 2.7 Hz, 1H), 2.58 (q, *J* = 5.2 Hz, 1H), 2.27 – 2.20 (m, 1H), 2.18 – 2.01 (m, 2H), 2.00 – 1.86 (m, 2H), 1.85 – 1.42 (m, 4H), 1.73 (t, *J* = 4.0 Hz, 3H), 1.22 – 1.06 (m, 21H). **^{1}H NMR *exo* product** (400 MHz, $CDCl_3$): δ = 7.55 – 7.43 (m, 2H), 7.37 (td, *J* = 7.9, 2.1 Hz, 1H), 7.13 – 7.07 (m, 1H), 3.86 (s, 3H), 3.44 (ddd, *J* = 8.4, 6.3, 3.7 Hz, 1H), 2.84 – 2.75 (m, 1H), 2.27 – 2.20 (m, 1H), 2.18 – 2.01 (m, 2H), 2.00 – 1.86 (m, 2H), 1.85 – 1.42 (m, 4H), 1.66 (t, *J* = 4.0 Hz, 3H), 1.22 – 1.06 (m, 21H). **^{13}C NMR *endo* product** (101 MHz, $CDCl_3$): δ = 202.7 (C), 160.2 (C), 144.6 (C), 138.2 (C), 129.9 (CH), 121.1 (CH), 119.7 (CH), 113.0 (CH), 112.7 (C), 84.4 (C), 68.5 (CH), 55.7 (CH_3), 46.3 (CH), 41.8 (CH), 29.8 (CH_2), 29.8 (CH_2), 21.1 (CH_2), 18.3 (6CH_3), 18.0 (CH_2), 16.4 (CH_3), 13.5 (3CH). **^{13}C NMR *exo* product** (101 MHz, $CDCl_3$): δ = 202.6 (C), 160.1 (C), 144.5 (C), 138.3 (C), 129.8 (CH), 120.9 (CH), 119.3 (CH), 113.9 (CH), 111.9 (C), 84.9 (C), 68.8 (CH), 55.6 (CH_3), 45.1 (CH), 39.9 (CH), 31.5 (CH_2), 29.1 (CH_2), 25.4 (CH_2), 18.3 (6CH_3), 15.9 (CH_2), 14.6 (CH_3), 13.4 (3CH). **IR** (neat, cm^{-1}): 3313, 2943, 2866, 2118, 1677. **HRMS** (EI): m/z calc'd for $C_{28}H_{42}O_3Si$ [M^+] 454.2903, found 454.2904.

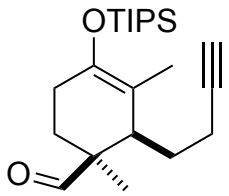


(4-Bromophenyl)(2-(but-3-yn-1-yl)-3-methyl-4-((triisopropylsilyl)oxy)cyclohex-3-en-1-yl)methanone

(Compound 2.2.12i)

Prepared according to **GP1** in 79% yield (270 mg) (*endo*:*exo* 2:1).

^{1}H NMR *endo* product (400 MHz, $CDCl_3$): δ = 7.83 – 7.79 (m, 2H), 7.63 – 7.56 (m, 2H), 3.52 (ddd, *J* = 12.3, 4.8, 2.7 Hz, 1H), 2.82 – 2.68 (m, 1H), 2.26 – 1.86 (m, 5H), 1.85 – 1.41 (m, 4H), 1.73-1.72 (m, 3H), 1.18 – 1.06 (m, 21H). **^{1}H NMR *exo* product** (400 MHz, $CDCl_3$): δ = 7.79 – 7.76 (m, 2H), 7.63 – 7.56 (m, 2H), 3.42 (ddd, *J* = 7.9, 5.9, 3.8 Hz, 1H), 2.82 – 2.68 (m, 1H), 2.26 – 1.86 (m, 5H), 1.64 (t, *J* = 2.2 Hz, 3H), 1.85 – 1.41 (m, 4H), 1.18 – 1.06 (m, 21H). **^{13}C NMR *endo* product** (101 MHz, $CDCl_3$): δ = 201.9 (C), 144.6 (C), 135.5 (C), 132.3 (2CH), 130.0 (2CH), 128.3 (C), 113.7 (C), 84.1 (C), 68.7 (CH), 46.2 (CH), 41.5 (CH), 29.7 ($2CH_2$), 20.9 (CH_2), 18.3 ($6CH_3$), 18.0 (CH_2), 16.4 (CH_3), 13.4 (3CH). **^{13}C NMR *exo* product** (101 MHz, $CDCl_3$): δ = 201.6 (C), 144.4 (C), 135.5 (C), 132.1 (2CH), 130.0 (2CH), 128.0 (C), 111.7 (C), 84.7 (C), 69.0 (CH), 44.8 (CH), 39.9 (CH), 31.4 (CH_2), 28.9 (CH_2), 24.9 (CH_2), 18.3 ($6CH_3$), 15.9 (CH_2), 14.6 (CH_3), 13.4 (3CH). **IR** (neat, cm^{-1}): 3308, 2943, 2866, 2116, 1677. **HRMS** (EI): m/z calc'd for $C_{27}H_{39}BrO_2Si$ [M^+] 504.1882 and 502.1903, found 504.1858 and 502.1884.

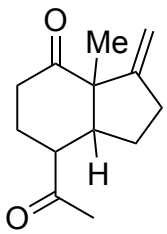


2-(But-3-yn-1-yl)-1,3-dimethyl-4-((triisopropylsilyl)oxy)cyclohex-3-ene-1-carbaldehyde

Prepared according to **GP1** (*endo*:*exo* 5:1). Due to the instability of the compound, it was used as a crude in the next step, without any further purification.

6.2.2 *6-endo-dig*/acetalyzation/Prins Products

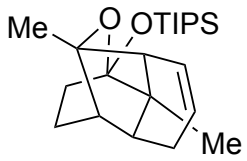
General Procedure 2 (GP2) – *6-endo-dig*/Acetalyzation/Prins: A reaction vessel was charged with a magnetic stirrer and purged with argon. A solution of the silyl enol ether (0.100 mmol), solvent (1.5 ml) and the appropriate Ag(I) catalyst (0.010 mmol) is added via syringe. The reaction mixture is stirred at r.t. or 60°C for 1.5 days. Upon completion, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel eluted with hexane/AcOEt (9:1 to 6:1) to give the cyclization products.



7-Acetyl-3a-methyl-3-methyleneoctahydro-4*H*-inden-4-one

Compound 2.2.16

Prepared according to **GP2** using DCE/H_2O 20:1 as solvent and $AgSbF_6$ as catalyst at 60°C. The product was isolated in 97% yield (20 mg). Spectroscopic data recorded were consistent with that previously reported.[1]

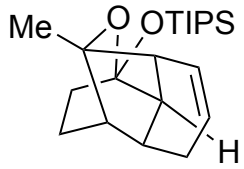


((9a,10-Dimethyl-4,4a,5,6,9,9a-hexahydro-2,5,9-(epimethanetriyl)cyclohepta[*b*]pyran-2(3*H*)-yl)oxy)triisopropylsilane

Compound 2.2.17a

Prepared according to **GP2** using DCM as solvent and [(BrettPhos)Ag(MeCN)]SbF_6 as catalyst at 60°C. The product was isolated in 85% yield (31 mg) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.65-5.55 (m, 2H), 2.32 (dddd, *J* = 18.7, 3.8, 2.1, 2.1 Hz, 1H), 1,99 (dd, *J* = 6.5, 1.3 Hz, 1H), 1.91-1.84 (m, 2H), 1.67-1.64 (m, 2H), 1.62-1.55 (m, 1H), 1.46-1.43 (m, 2H), 1.20 (s, 3H), 1.11-1.05 (m, 21H), 1.01 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 125.6 (CH), 125.5 (CH), 104.6 (C), 93.3 (C), 53.1 (C), 52.4 (CH), 46.7 (CH), 43.3 (CH), 30.7 (CH_2), 29.9 (CH_2), 23.0 (CH_2), 18.4 (6CH_3), 16.6 (CH_3), 13.4 (3CH), 11.0 (CH_3). **IR** (neat, cm^{-1}): 2975, 2862. **HRMS** (EI): m/z calc'd for $C_{22}H_{38}O_2Si$ [M^+] 362.2641, found 362.2659.

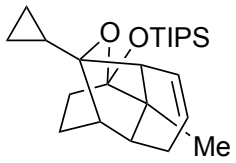


Triisopropyl((9a-methyl-4,4a,5,6,9,9a-hexahydro-2,5,9-(epimethanetriyl)cyclohepta[*b*]pyran-2(3*H*)-yl)oxy)silane

Compound 2.2.17b

Prepared according to **GP2** using DCE as solvent and [(BrettPhos)Ag(MeCN)]SbF_6 as catalyst at 60°C. The product was isolated in 23% yield (8 mg) from a mixture of four isomers) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.67 (ddt, *J* = 8.9, 6.8, 2.0 Hz, 1H), 5.60 – 5.52 (m, 1H), 2.36-2.29 (m, 2H), 2.12-2.09 (m, 2H), 1.97 – 1.88 (m, 2H), 1.73 (dd, *J* = 12.2, 8.8 Hz, 1H), 1.66 – 1.58 (m, 1H), 1.55 – 1.47 (m, 2H), 1.24 (s, 3H), 1.06 (d, *J* = 2.4 Hz, 21H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 126.0 (CH), 125.4 (CH), 103.8 (C), 93.7 (C), 51.8 (CH), 47.8 (CH), 45.7 (CH), 38.7 (CH), 32.0 (CH_2), 31.1 (CH_2), 23.0 (CH_2), 18.2 ($6CH_3$), 16.0 (CH_3), 13.1 (3CH). **IR** (neat, cm^{-1}): 2942, 2866. **HRMS** (EI): m/z calc'd for $C_{21}H_{36}O_2Si$ [M^+] 348.2485, found 348.2513.

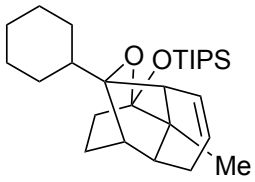


((9a-Cyclopropyl-10-methyl-4,4a,5,6,9,9a-hexahydro-2,5,9-(epimethanetriyl)cyclohepta[*b*]pyran-2(3*H*)-yl)oxy)triisopropylsilane

Compound 2.2.17c

Prepared according to **GP2** using DCM as solvent and [(BrettPhos)Ag(MeCN)]SbF_6 as catalyst at 60°C. The product was isolated in 61% yield (24 mg) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.67 (dddd, *J* = 9.0, 6.8, 2.0, 2.0 Hz, 1H), 5.57 (dddd, *J* = 9.5, 3.7, 2.5, 1.0 Hz, 1H), 2.33 (dddd, *J* = 18.7, 4.6, 2.4 2.4 Hz, 1H), 2.03 (dd, *J* = 6.8, 2.0 Hz, 1H), 1.95 – 1.84 (m, 2H), 1.68 – 1.54 (m, 4H), 1.51 – 1.43 (m, 1H), 1.10 – 1.03 (m, 21H), 1.01 (s, 3H), 0.95 (tt, *J* = 8.5, 5.3 Hz, 1H), 0.52 (dddd, *J* = 8.9, 5.4, 5.4, 3.2 Hz, 1H), 0.44 – 0.31 (m, 2H), 0.26 (dddd, *J* = 8.7, 8.7, 5.7, 3.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 125.8 (CH), 125.4 (CH), 104.5 (C), 94.7 (C), 53.1 (C), 51.9 (CH), 46.3 (CH), 43.5 (CH), 30.9 (CH_2), 30.3 (CH_2), 24.1 (CH_2), 18.4 ($3CH_3$), 18.4 ($3CH_3$), 13.4 (3CH), 11.8 (CH), 10.9 (CH_3), 0.9 (CH_2), 0.6 (CH_2). **IR** (neat, cm^{-1}): 2942, 2866. **HRMS** (EI): m/z calc'd for $C_{24}H_{40}O_2Si$ [M^+] 388.2798, found 388.2779.

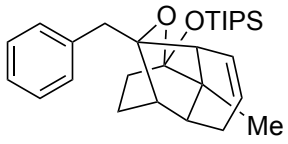


((9a-Cyclohexyl-10-methyl-4,4a,5,6,9,9a-hexahydro-2,5,9-(epimethanetriyl)cyclohepta[*b*]pyran-2(3*H*)-yl)oxy)triisopropylsilane

Compound 2.2.17d

Prepared according to **GP2** using DCM as solvent and [(BrettPhos)Ag(MeCN)]SbF_6 as catalyst at 60°C. The product was isolated in 95% yield (41 mg) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.64 – 5.52 (m, 2H), 2.32 (dddd, *J* = 18.6, 4.4, 2.2, 2.2 Hz, 1H), 2.15 (dd, *J* = 6.4, 1.9 Hz, 1H), 1.92 – 1.83 (m, 2H), 1.77 – 1.58 (m, 9H), 1.47 (dtd, *J* = 13.1, 10.7, 10.1, 3.7 Hz, 2H), 1.32 (qd, *J* = 12.1, 2.9 Hz, 1H), 1.26 – 1.13 (m, 4H), 1.08 (dd, *J* = 7.6, 5.5 Hz, 21H), 1.01 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 125.5 (CH), 125.5 (CH), 104.8 (C), 99.1 (C), 52.3 (C), 49.4 (CH), 45.4 (CH), 43.2 (CH), 40.4 (CH), 31.0 (CH_2), 30.2 (CH_2), 28.2 (CH_2), 28.1 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 26.8 (CH_2), 24.8 (CH_2), 18.5 ($3CH_3$), 18.4 ($3CH_3$), 13.4 (3CH), 10.9 (CH_3). **IR** (neat, cm^{-1}): 2928, 2866. **HRMS** (EI): m/z calc'd for $C_{27}H_{46}O_2Si$ [M^+] 430.3267, found 430.3262.



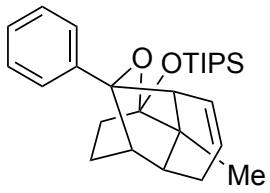
((9a-Benzyl-10-methyl-4,4a,5,6,9,9a-hexahydro-2,5,9-(epimethanetriyl)cyclohepta[*b*]pyran-2(3*H*)-yl)oxy)triisopropylsilane

Compound 2.2.17f

Prepared according to **GP2** using DCM as solvent and [(BrettPhos)Ag(MeCN)]SbF_6 as catalyst at 60°C. The product was isolated in 68% yield (30 mg) (from a mixture of *endo*:*exo* 3:1) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 – 7.15 (m, 5H), 5.73 (dddd, *J* = 10.5, 6.5, 1.9, 1.9 Hz, 1H), 5.69 – 5.62 (m, 1H), 2.84 (d, 13.8 Hz, 1H), 2.84 (d, 13.8 Hz, 1H), 2.34 (dddd, *J* = 18.7, 4.4, 2.3, 2.3 Hz, 1H), 1.97 – 1.89 (m, 2H), 1.84 (ddd, *J* = 12.5, 8.5, 8.5 Hz, 1H), 1.67 – 1.60 (m, 2H), 1.58 (dd, *J* = 4.0, 1.7 Hz, 1H), 1.41 – 1.27 (m, 2H), 1.03 – 0.96 (m, 24H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 138.0 (C),

130.4 (2CH), 127.8 (2CH), 126.1 (CH), 126.1 (CH), 125.5 (CH), 104.9 (C), 96.0 (C), 52.7 (C), 50.2 (CH), 46.1 (CH), 43.3 (CH), 37.7 (CH_2), 30.9 (CH_2), 30.0 (CH_2), 23.5 (CH_2), 18.4 ($3CH_3$), 18.3 ($3CH_3$), 13.2 (3CH), 11.0 (CH_3). **IR** (neat, cm^{-1}): 2925, 2893. **HRMS** (EI): m/z calc'd for $C_{28}H_{42}O_2Si$ [M^+] 438.2954, found 438.2969.



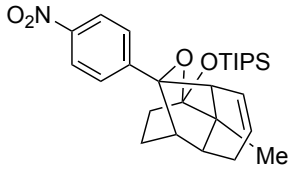
Triisopropyl((10-methyl-9a-phenyl-4,4a,5,6,9,9a-hexahydro-2,5,9-(epimethanetriyl)cyclohepta[*b*]pyran-2(3*H*)-yl)oxy)silane

Compound 2.2.17e

Prepared according to **GP2** using DCM as solvent and [(BrettPhos)Ag(MeCN)]SbF_6 as catalyst at 60°C. The product was isolated in 49% yield (21 mg) (from a mixture of *endo*:*exo* 5:2) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52-7.48 (m, 2H), 7.30-7.20 (m, 3H), 5.69 (dddd, *J* = 9.5, 3.7, 2.7, 0.8 Hz, 1H), 5.55 (dddd, *J* = 9.3, 9.3, 7.1, 2.0 Hz, 1H), 2.43 (dddd, *J* = 18.9, 9.6, 2.4, 2.4 Hz, 1H), 2.29 (dd, *J* = 6.9 Hz, 1.7 Hz, 1H), 2.09 (dddd, *J* = 18.9, 3.9, 1.9, 1.9 Hz, 1H), 2.05-1.98 (m, 2H), 1.83-1.77 (m, 2H), 1.62-1.54 (m, 1H), 1.51-1.42 (m, 1H), 1.24-1.14 (m, 3H). 1.12-1.07 (m, 21H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 140.0 (C), 127.9 (C), 127.0 (2CH), 125. 9 (CH), 125.8 (CH), 125.7 (2CH), 104.4 (C), 95.7 (C), 54.7 (C), 54.4 (CH), 49.2 (CH), 43.3 (CH), 31.0 (CH_2), 30.2 (CH_2), 223.0 (CH_2), 18.3 ($6CH_3$), 13.2 (CH_3), 10.7 (3CH). **IR** (neat,

cm^{-1}): 2945, 2866. **HRMS** (EI): m/z calc'd for $C_{27}H_{40}O_2Si$ [M$^+$] 424.2798, found 424.2764.

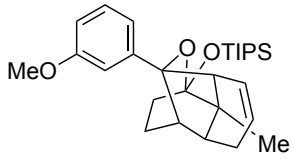


Triisopropyl((10-methyl-9a-(4-nitrophenyl)-4,4a,5,6,9,9a-hexahydro-2,5,9-(epimethanetriyl)cyclohepta[*b*]pyran-2(3*H*)-yl)oxy)silane

Compound 2.2.17g

Prepared according to **GP2** using DCM as solvent and [(BrettPhos)Ag(MeCN)]SbF_6 as catalyst at 60°C. The product was isolated in 80% yield (38 mg) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (dt, *J* = 8.9, 2.4 Hz, 2H), 7.67 (dt, *J* = 8.9. 2.4 Hz, 2H), 5.74 (ddd, *J* = 9.8, 2.9, 2.9 Hz, 1H), 5.54 (dddd, *J* = 19.1, 19.1 4.5, 2.3 Hz, 1H), 2.49 (dddd, *J* = 19.1, 4.5, 4.5 2.3 Hz, 1H), 2.32 (dd, *J* = 6.9, 1.8 Hz, 1H), 2.15 (dddd, *J* = 19.1, 3.9, 3.9 2.0 Hz, 1H), 2.05-1.98 (m, 2H), 1.89-1.81 (m, 2H), 1.57-1.51 (m, 3H), 1.22-1.16 (m, 2H), 1.15-1.11 (m, 21H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 147.6 (C), 147.1 (C), 126.9 (2CH), 126. 4 (CH), 125.1 (2CH), 123.2 (CH), 104.8 (C), 95.2 (C), 55.3 (C), 54.8 (CH), 49.8 (CH), 43.0 (CH), 31.0 (CH_2), 30.1 (CH_2), 23.0 (CH_2), 18.3 (6CH_3), 13.2 (3CH), 10.9 (CH_3). **IR** (neat, cm^{-1}): 2977, 2873. **HRMS** (EI): m/z calc'd for $C_{27}H_{39}O_4NSi$ [M$^+$] 469.2648, found 469.2643.

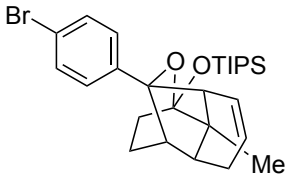


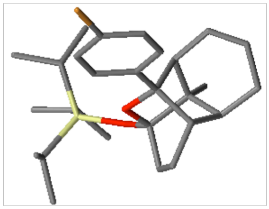
Triisopropyl((9a-(3-methoxyphenyl)-10-methyl-4,4a,5,6,9,9a-hexahydro-2,5,9-(epimethanetriyl)cyclohepta[*b*]pyran-2(3*H*)-yl)oxy)silane

Compound 2.2.17h

Prepared according to **GP2** using DCM as solvent and [(BrettPhos)Ag(MeCN)]SbF_6 as catalyst at 60°C. The product was isolated in 61% yield (28 mg) (from a mixture of *endo*:*exo* 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (t, *J* = 7.9 Hz, 1H), 7.15 (dd, *J* = 2.7, 1.5 Hz, 1H), 7.09 (dt, *J* = 7.7, 1.3 Hz, 1H), 6.80 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H), 5.72 (dddd, *J* = 9.5, 3.7, 2.6, 0.9 Hz, 1H), 5.58 (dddd, *J* = 9.1, 6.9, 2.0, 2.0 Hz, 1H), 3.79 (s, 3H), 2.46 (dddd, *J* = 18.9, 4.8, 2.5, 2.5 Hz, 1H), 2.32 (dd, *J* = 6.9, 2.0 Hz, 1H), 2.15 – 2.07 (m, 1H), 2.05 – 1.97 (m, 2H), 1.86 – 1.79 (m, 2H), 1.66 – 1.57 (m, 1H), 1.48 (ddd, *J* = 12.3, 8.6, 4.2 Hz, 1H), 1.22 – 1.09 (m, 24H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.4 (C), 141.8 (C), 128.8 (CH), 125.9 (CH), 125.9 (CH), 118.1 (CH), 112.9 (CH), 111.1 (CH), 104.6 (C), 95.9 (C), 55.3 (CH_3), 54.9 (C), 54.6 (CH), 49.4 (CH), 43.2 (CH), 31.1 (CH_2), 30.3 (CH_2), 23.3 (CH_2), 18.5 ($3CH_3$), 18.5 ($3CH_3$), 13.5 (3CH), 10.9 (CH_3). **IR** (neat, cm^{-1}): 2943, 2865. **HRMS** (EI): m/z calc'd for $C_{28}H_{42}O_3Si$ [M^+] 454.2903, found 454.2914.





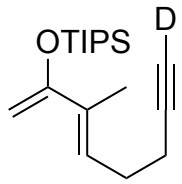
((9a-(4-Bromophenyl)-10-methyl-4,4a,5,6,9,9a-hexahydro-2,5,9-(epimethanetriyl)cyclohepta[*b*]pyran-2(3*H*)-yl)oxy)triisopropylsilane

Compound 2.2.17i

Prepared according to **GP2** using DCM as solvent and [(BrettPhos)Ag(MeCN)]SbF_6 as catalyst at 60°C. The product was isolated in 62% yield (31 mg) (from a mixture of *endo*:*exo* 2:1) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 – 7.36 (m, 4H), 5.73 (dddd, *J* = 9.5, 3.8, 2.6, 1.0 Hz, 1H), 5.55 (dddd, *J* = 9.2, 6.9, 2.0, 2.0 Hz, 1H), 2.46 (dddd, *J* = 18.9, 4.8, 2.5, 2.5 Hz, 1H), 2.28 (dd, *J* = 6.9, 2.0 Hz, 1H), 2.10 (dddd, *J* = 19.0, 4.0, 2.0, 2.0 Hz, 1H), 2.04 – 1.95 (m, 2H), 1.85 – 1.79 (m, 2H), 1.61 – 1.45 (m, 2H), 1.22 – 1.09 (m, 24H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 139.2 (C), 131.0 (2CH), 127.5 (2CH), 126.3 (CH), 125.6 (CH), 121.0 (C), 104.7 (C), 95.4 (C), 54.9 (C), 54.5 (CH), 49.3 (CH), 43.2 (CH), 31.1 (CH_2), 30.2 (CH_2), 23.2 (CH_2), 18.5 ($3CH_3$), 18.4 ($3CH_3$), 13.4 (3CH), 10.8 (CH_3). **IR** (neat, cm^{-1}): 2944, 2866. **HRMS** (EI): m/z calc'd for $C_{27}H_{39}BrO_2Si$ [M^+] 502.1903 and 504.1882, found 502.1884 and 504.1858.

6.2.3 Deuterated Compounds

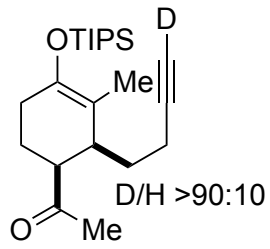


(*E*)-Triisopropyl((3-methylocta-1,3-dien-7-yn-2-yl-8-*d*)oxy)silane

Compound 2.2.19

In a flamed-dried reaction flask was added {[(3*E*)-3-methylocta-1,3-dien-7-yn-2-yl]oxy}(tripropan-2-yl)silane in THF (1.4 M). The solution was cooled down to -78°C and *n*-BuLi (1.2 equiv.) was added dropwise. The reaction mixture was allowed to stir for 1 hour and was then quenched with D_2O. The aqueous phase was extracted with ether 3x, dried over $MgSO_4$, filtered and concentrated under vacuum (>90% Deuterium incorporation).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.15 (t, *J* = 7.0 Hz, 1H), 4.40 (s, 1H), 4.27 (s, 1H), 2.37 (q, *J* = 7.5 Hz, 2H), 2.26 (t, *J* = 7.5 Hz, 2H), 1.77 (s, 3H), 1.24 (sept, *J* = 7.5 Hz), 1.10 (d, *J* = 7.5 Hz, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 157.4 (C), 132.2 (C), 90.5 (CH_2), 83.5 (t, *J*=7.0 Hz, C), 68.3 (t, *J*=38.9 Hz, CH), 27.6 (CH_2), 18.7 (CH_2), 18.2 ($6CH_3$), 13.4 (CH_3), 13.0 (3CH). **IR** (neat, cm^{-1}): 2945, 2867, 2598, 2113. **HRMS** (EI): m/z calc'd for $C_{18}H_{31}DOSi$ [M^+] 293.2285, found 293.2263.

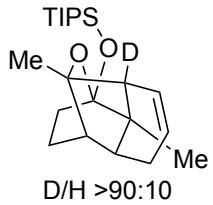


1,2-(But-3-yn-1-yl-4-*d*)-3-methyl-4-((triisopropylsilyl)oxy)cyclohex-3-en-1-yl)ethan-1-one

Compound 2.2.20

Prepared according to **GP1** in 75% yield (185 mg) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.69-2.62 (m, 2H), 2.21 (s, 3H), 2.18-2.08 (m, 4H), 1.82-1.75 (m, 2H), 1.74 (s, 3H), 1.50 (q, *J* = 7.5 Hz, 2H), 1.15-1.06 (m, 21H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 211.2 (C), 144.6 (C), 113.8 (C), 83.8 (t, *J* = 7.5 Hz, C), 68.9 (t, *J* = 38.0 Hz, CH), 51.9 (CH), 39.6 (CH), 30.1 (CH_2), 29.5 (CH_2), 29.2 (CH_3), 19.9 (CH_2), 18.2 ($3CH_3$), 18.2 ($3CH_3$), 17.8 (CH_2), 16.6 (CH_3), 13.4 (3CH). **IR** (neat, cm^{-1}): 2944, 2867, 2112, 1708. **HRMS** (EI): m/z calc'd for $C_{19}H_{30}DO_2Si$ [(M-*i*Pr)$^+$] 320.2156, found 320.2157.



((9a,10-Dimethyl-4,4a,5,6,9,9a-hexahydro-2,5,9-(epimethanetriyl)cyclohepta[*b*]pyran-2(3*H*)-yl-9-*d*)oxy)triisopropylsilane

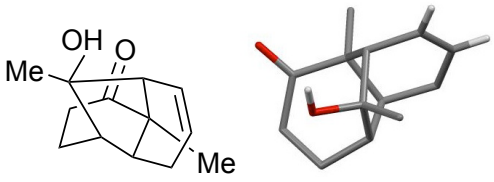
Compound 2.2.21

Prepared according to **GP2** using DCM as solvent and [(BrettPhos)Ag(MeCN)]SbF_6 as catalyst at 60°C. The product was isolated in 48% yield (17 mg) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.62 (dd, *J* = 9.5, 2.0, 2.0 Hz, 1H), 5.57 (ddd, *J* = 9.5, 2.5, 2.5 Hz, 1H), 2.32 (dddd, *J* = 18.5, 4.0, 2.0, 2.0 Hz, 1H), 1.92-1.85 (m, 2H), 1.67-1.64 (m, 2H), 1.62-1.55 (m, 1H), 1.48-1.42 (m, 2H), 1.20 (s, 3H), 1.09-1.06 (m, 21H), 1.01 (3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 125.6 (CH), 125.4 (CH), 104.6 (C), 93.2 (C), 53.0 (C), 51.9 (t, *J* = 21.5 Hz, CH), 46.7 (CH), 43.3 (CH), 30.8 (CH_2), 29.9 (CH_2), 23.1 (CH_2), 18.4 ($3CH_3$), 18.4 ($3CH_3$), 16.6 (CH_3), 13.3 (3CH), 11.0 (CH_3). **IR** (neat, cm^{-1}): 2925, 2865. **HRMS** (EI): m/z calc'd for $C_{22}H_{37D}O_2Si$ [M^+] 363.2683, found 363.2704

6.2.4 Fragmentation and Epoxidation of the Polycycle

General Procedure 3 (GP3) - Deprotection: In a reaction flask containing the polycycle was added a solution of TBAF in THF (1.0 M, 1.2 eq.) dropwise. The reaction was stirred at room temperature for 5 minutes, then diluted with EtOAc and quenched with a saturated solution of aqueous ammonium chloride. The organic phase was separated and the aqueous phase was extracted 2 more times with EtOAc. The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash chromatography (10% EtOAc in hexanes) to afford the desired product.

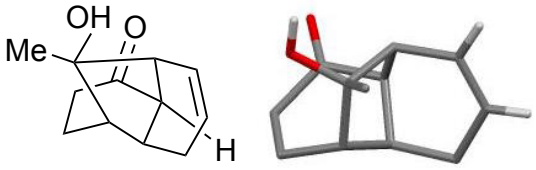


9-Hydroxy-4a,9-dimethyl-2,3,4a,5,8,8a-hexahydro-1,5-methanonaphthalen-4(1*H*)-one

Compound 2.2.43a

Prepared according to **GP3** in quantitative yield as a white powder. The compound was recrystallized with DCM and hexanes, to obtain a clear and sharp crystal.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.79 (ddt, *J* = 9.5, 7.2, 2.3 Hz, 1H), 5.62 – 5.56 (m, 1H), 2.47 – 2.36 (m, 3H), 2.12 – 2.02 (m, 4H), 1.96 (dddd, *J* = 12.7, 8.5, 6.3, 1.8 Hz, 1H), 1.81 (ddt, *J* = 12.7, 9.9, 5.2 Hz, 1H), 1.37 (br., 1H), 1.35 (s, 3H), 1.12 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 218.7 (C), 128.9 (CH), 125.6 (CH), 83.9 (C), 57.1 (CH), 54.3 (C), 53.5 (CH), 44.3 (CH), 36.1 (CH_2), 31.4 (CH_2), 29.0 (CH_3), 20.9 (CH_2), 14.5 (CH_3). **IR** (neat, cm^{-1}): 3443, 2923, 1695. **HRMS** (EI): m/z calc'd for $C_{13}H_{18}O_2$ [M^+] 206.1307, found 206.1312.

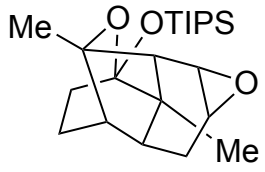


9-Hydroxy-9-methyl-2,3,4a,5,8,8a-hexahydro-1,5-methanonaphthalen-4(1*H*)-one

Compound 2.2.43b

Prepared according to **GP3** in quantitative yield as a white powder. The compound was recrystallized with DCM and hexanes, to obtain a clear and sharp crystal. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.96 (ddt, *J* = 9.5, 7.5, 2.2 Hz, 1H), 5.53 (dt, *J* = 9.3, 3.3 Hz, 1H), 2.60 – 2.44 (m, 3H), 2.42-2.34 (m, 3H), 2.12 – 1.99 (m, 3H), 1.79 (ddt, *J* = 12.8, 11.3, 4.6 Hz, 1H), 1.43 (br., 1H), 1.37 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 215.6 (C), 131.4 (CH), 125.6 (CH), 83.3 (C), 56.2 (CH), 53.5 (CH), 53.4 (CH), 41.1 (CH), 35.9 (CH_2), 32.7 (CH_2), 29.4 (CH_3), 22.1 (CH_2). **IR** (neat, cm^{-1}): 3441, 1696. **HRMS** (EI): m/z calc'd for $C_{12}H_{16}O_2$ [M^+] 192.1150, found 192.1154.

General Procedure 4 (GP4) - Epoxidation: A solution of the starting material (0.049 mmol) in DCM (0.14 mL) was added to a flame-dried reaction flask. *m*CBPA (1.5 eq.) was then added and the reaction mixture was stirred at room temperature for 1 hour. The reaction was then quenched with a saturated solution of $NaHCO_3$ (aq.) and the organic phase was separated. The organic phase was separated and the aqueous phase was extracted 2 more times with DCM. The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash chromatography (10-15% EtOAc in hexanes) to afford the desired product

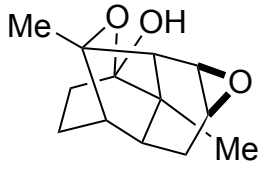


((2a,9-Dimethyloctahydro-2,4,7-(epimethanetriyl)oxireno[2',3':5,6]cyclohepta[1,2-*b*]pyran-4(1a*H*)-yl)oxy)triisopropylsilane

Compound 2.2.46

Prepared according to **GP4** in 85% yield (16 mg) and with a d.r. of 7:3. Based on a NOESY experiment, the major diastereomer is believed to come from epoxidation on the bottom face of the molecule.

^{1}H NMR Major Product (400 MHz, $CDCl_3$): δ = 3.23 (dd, *J* = 6.9, 3.9 Hz, 1H), 3.04-3.01 (m, 1H), 2.18 – 2.12 (m, 1H), 1.94-1.93 (m, 1H), 1.84 – 1.74 (m, 2H), 1.67 – 1.58 (m, 2H), 1.57 – 1.55 (m, 1H), 1.52 – 1.47 (m, 1H), 1.46 – 1.44 (m, 1H), 1.36 (s, 3H), 1.09-1.05 (m, 21H), 1.01 (s, 3H). **^{1}H NMR Minor Product** (400 MHz, $CDCl_3$): δ = 3.16 (t, *J* = 3.5 Hz, 1H), 3.04-3.01 (m, 1H), 2.18 – 2.12 (m, 2H), 1.94-1.93 (m, 2H), 1.84 – 1.74 (m, 1H), 1.67 – 1.58 (m, 2H), 1.57 – 1.55 (m, 1H), 1.52 – 1.47 (m, 1H), 1.30 (s, 3H), 1.13 (s, 3H), 1.09-1.05 (m, 21H). **^{13}C NMR Major Product** (101 MHz, $CDCl_3$): δ = 103.9 (C), 88.3 (C), 54.2 (C), 50.3 (CH), 50.0 (CH), 48.2 (CH), 45.1 (CH), 41.6 (CH), 29.9 (CH_2), 26.9 (CH_2), 23.0 (CH_2), 18.2 ($6CH_3$), 17.8 (CH_3), 13.1 (3CH), 10.8 (CH_3).**^{13}C NMR Minor Product** (101 MHz, $CDCl_3$): δ =104.2 (C), 86.0 (C), 57.6 (C), 53.7 (CH), 50.0 (CH), 48.6 (CH), 45.7 (CH), 41.4 (CH), 30.0 (CH_2), 29.7 (CH_2), 28.1 (CH_2), 18.2 ($6CH_3$), 17.1 (CH_3), 13.1 (3CH), 12.3 (CH_3). **IR** (neat, cm^{-1}): 2925, 2866. **HRMS** (EI): m/z calc'd for $C_{22}H_{38}O_3Si$ [M^+] 378.2590, found 378.2587.



2a,9-Dimethyloctahydro-2,4,7-(epimethanetriyl)oxireno[2',3':5,6]cyclohepta[1,2-*b*]pyran-4(1a*H*)-ol

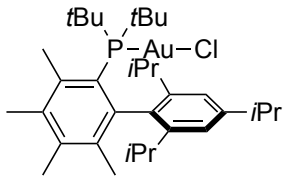
Compound 2.2.47

Prepared according to **GP4** in quantitative yield (10 mg) and with a d.r. greater than 10:1. Based on a NOESY experiment, the major diastereomer is believed to come from epoxidation on the upper face of the molecule.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.24 (dd, *J* = 6.9, 3.9 Hz, 1H), 3.05 (dt, *J* = 3.8, 1.9 Hz, 1H), 2.61 (br., 1H), 2.17 (dd, *J* = 6.9, 2.2 Hz, 1H), 1.97 (dd, *J* = 3.8, 1.9 Hz, 2H), 1.93 – 1.86 (m, 1H), 1.71 – 1.52 (m, 5H), 1.43 (s, 3H), 1.05 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 103.6 (C), 88.7 (C), 52.7 (C), 50.6 (CH), 49.8 (CH), 48.1 (CH), 45.4 (CH), 41.6 (CH), 29.2 (CH_2), 26.5 (CH_2), 22.9 (CH_2), 17.6 (CH_3), 10.4 (CH_3). **HRMS** (EI): m/z calc'd for $C_{13}H_{18}O_3$ [M^+] 222.1256, found 222.1239.

6.2.5 Catalysts

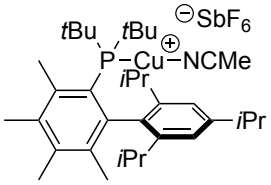
The following catalysts were characterised by Patrick Levesque, M. Sc.



(Me$_4$*t*BuXphos)AuCl

To suspension of a phosphine (0.208 mmol) in DCM (2 mL) was added chloro(dimethylsulfide)gold(I) (61 mg, 0.208 mmol). The mixture was stirred for 4h at room temperature. The solvent was evaporated off under reduced pressure and the residue was triturated with pentane to give (Me_4*t*BuXphos)AuCl (83% yield) as a grey powder.

^{1}H NMR (400 MHz, C_6D_6): δ = 7.37 (s, 2H), 3.21 (sept, *J* = 6.9 Hz, 1H), 2.57 (sept, *J* = 6.7 Hz, 2H), 2.16 (s, 3H), 189 (s, 3H), 1.85 (s, 3H), 1.64 (d , *J* = 6.9 Hz, 6H), 1.60 (s, 3H), 1.52 (d, *J* = 6.7 Hz, 6H), 1.31 (s, 9H), 1,28 (s, 9H), 0.98 (d, *J* = 6.7 Hz, 6H). **^{13}C NMR** (101 MHz, C_6D_6): δ = 151.0 (s, C), 146.9 (s, C), 146.6 (s, C), 146.0 (s, C), 140.2 (d, $J_{C\text{-}P}$ = 2.6 Hz, C), 138.3 (d, $J_{C\text{-}P}$ = 3.3 Hz, C), 138.2 (s, C), 137.8 (d, $J_{C\text{-}P}$ = 9.2 Hz, C), 135.9 (d, $J_{C\text{-}P}$ = 7.0 Hz, C), 129.1 (s, C), 128.8 (s, CH), 123.3 (s, CH), 41.5 (d, $J_{C\text{-}P}$ = 20.2 Hz, 2C), 35.0 (s, CH), 33.3 (d, $J_{C\text{-}P}$ = 8.4 Hz, $3CH_3$), 31.2 (s, 2CH), 27.9 (s, CH_3), 27.9 (s, CH_3), 25.4 (d, $J_{C\text{-}P}$ = 7.7 Hz, $3CH_3$), 25.1 (s, $2CH_3$), 22.6 (s, CH_3), 22.6 (s, CH_3), 17.6 (s, $2CH_3$), 17.1 (s, $2CH_3$). **^{31}P NMR** (162 MHz, $CDCl_3$): δ = 76.51. **HRMS** (EI): m/z calc'd for $C_{33}H_{54}PAuCl$ $[(M\text{-}Cl)^+]$ 677.3550, found 677.3548.



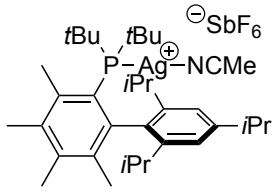
[(Me_4*t*BuXphos)Cu(MeCN)]SbF_6

In a typical reaction, a flame-dried Schlenck flask (50 mL) was charged with $Cu(CH_3CN)_4][SbF_6]$ (0.318 mmol) in DCM (2 mL) and the mixture was stirred

under Ar at r.t. The phosphane ligand Me_4*t*BuXphos (0.318 mmol) was added, the mixture was stirred for 30 min, and then the solvent was evaporated to yield the corresponding copper(I) complex as a white solid in quantitative yield.[3] Crystals were obtained by slow evaporation (hexane/DCM, 10:1 v/v).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (s, 2H), 3.00 (spt, *J* = 6.9 Hz, 1H), 2.60 (s, 3H), 2.40 (spt, *J* = 6.7 Hz, 2H), 2.31 (s, 3H), 2.28 (s, 3H), 2.23 (s, 3H), 1.62 (s, 1H), 1.46 (s, 3H), 1.38 (d, *J* = 15.7 Hz, 18H), 1.33 (d, *J* = 7.0 Hz, 6H), 1.29 (d, *J* = 6.8 Hz, 6H), 0.90 (d, *J* = 6.6 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 151.0 (d, *J* = 2.2 Hz, C), 145.5 (d, *J* = 2.2 Hz, 2C), 144.5 (d, *J* = 32.6 Hz, C), 140.8 (d, *J* = 2.2 Hz, C), 139.1 (s, C), 136.9 (d, *J* = 5.5 Hz, C), 136.1 (d, *J* = 9.5 Hz, C), 130.0 (d, *J* = 21.6 Hz, C), 129.8 (s, C), 125.8 (d, *J* = 1.8 Hz, 2CH), 119.3 (s, C), 37.9 (d, *J* = 9.5 Hz, 2C), 34.1 (s, CH), 32.8 (d, *J* = 9.5 Hz, 6CH_3), 31.1 (s, 2CH), 27.0 (s, CH_3), 25.6 (s, 2CH_3), 25.3 (s, 2CH_3), 24.2 (s, 2CH_3), 22.1 (d, *J* = 3.3 Hz, CH_3), 17.6 (s, CH_3), 17.3 (s, CH_3), 2.6 (s, CH_3). **^{31}P NMR** (121 MHz, $CDCl_3$): δ = 48.7. **HRMS** (EI): m/z calc'd for $C_{35}H_{56}CuNP$ [(M-SbF_6)$^+$] 584.3446, found 584.3434.

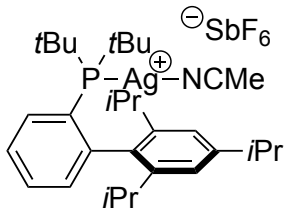
General procedure 5 (GP5) – Silver Catalyst Synthesis: The phosphane ligand (300 mmol) dissolved in acetonitrile (5 mL) was added to a suspension of $AgSbF_6$ (300 mmol) in acetonitrile or THF (5 mL) under Ar. The reaction mixture was stirred for 2 h in the dark at RT, then the solvent was reduced to 3 mL and the solution was filtered through a Celite pad. The solvent was then evaporated to form a white solid which was triturated 2-3 times with pentane and then dried under vacuum. Crystals were obtained by slow evaporation of DCM or $CDCl_3$ at r.t.



[(Me$_4$*t*BuXphos)Ag(MeCN)]SbF$_6$

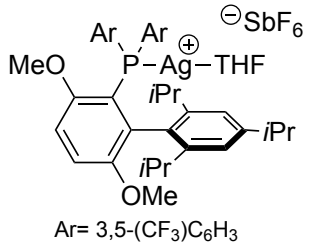
Prepared according to **GP5** in 93% yield as a white powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (s, 2H), 2.98 (spt, *J* = 6.9 Hz, 1H), 2.62 (s, 3H), 2.41 (spt, *J* = 6.7 Hz, 2H), 2.31 (s, 3H), 2.22 (s, 3H), 2.21 (s, 3H), 1.46 (s, 3H), 1.42 (s, 9H), 1.37 (s, 9H), 1.32 (d, *J* = 6.9 Hz, 6H), 1.28 (d, *J* = 6.8 Hz, 6H), 0.89 (d, *J* = 6.6 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 150.1 (s, C), 146.8 (dd, *J* = 1.7, 1.7 Hz, 2C), 144.0 (dd, *J* = 27.9, 1.1 Hz, C), 140.9 (d, J= 2.6 Hz, C), 139.3 (d, *J* = 7.7 Hz, C), 136.7 (d, *J* = 5.1 Hz, C), 136.5 (d, *J* = 8.1 Hz, C), 135.2 (dd, *J* = 12.1, 1.1 Hz, C) , 127.2 (dd, *J* = 19.1, 6.2 Hz, C), 123.8 (s, 2CH), 119.3 (s, C), 38.4 (dd, *J* = 5.9, 4.0 Hz, 2C), 34.0 (s, CH), 33.3 (dd, *J* = 11.9, 1.7 Hz, 6CH_3), 30.8 (s, 2CH), 27.7 (s, CH_3), 26.0 (s, 2CH_3), 25.0 (s, 2CH_3), 24.0 (s, 2CH_3), 22.4 (d, *J* = 3.7 Hz, CH_3), 17.7 (s, CH_3), 17.4 (s, CH_3), 2.1 (s, CH_3). **^{31}P NMR** (121 MHz, $CDCl_3$): δ = 63.1 (d, *J*(^{31}P-^{109}Ag) = 721.2 Hz), *J*(^{31}P-^{107}Ag) = 625.4 Hz). **HRMS** (EI): m/z calc'd for $C_{35}H_{56}AgNP$ [(M-SbF_6)$^+$] 628.3201, found 628.3205.



[(*t*BuXphos)Ag(MeCN)]SbF$_6$

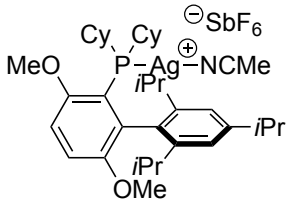
Prepared according to **GP5** as a white powder in 97% yield. Spectroscopic data recorded were consistent with that previously reported.[2]



[(Jackiephos)Ag(THF)]SbF_6

Prepared according to **GP5** in 89% yield as a white powder.

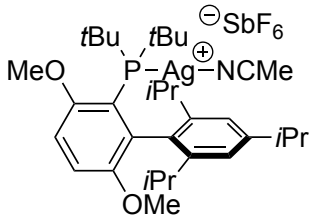
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.94 (s, 2H), 7.76 (d, *J* = 11.7 Hz, 4H), 7.32 (d, *J* = 9.2 Hz, 1H), 7.25 (s, 2H), 7.05 (dd, *J* = 3.0, 9.1 Hz, 1H), 3.71 - 3.68 (m, 3H), 3.78 - 3.58 (m, 4H), 3.38 (s, 3H), 3.00 (spt, *J* = 6.9 Hz, 1H), 2.39 (spt, *J* = 6.8 Hz, 2H), 1.84 (td, *J* = 3.2, 6.7 Hz, 4H), 1.31 (s, 6H), 1.29 (s, 6H), 1.03 (d, *J* = 6.8 Hz, 6H), 0.99 (d, *J* = 6.7 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 155.1 (dd, *J* = 5.2, 2.7 Hz, C), 153.1 (d, *J* = 12.5 Hz, C), 151.0 (s, C), 147.1 (s, 2C), 137.0 (d, *J* = 26.4 Hz, C), 132.6 (dq, *J* = 18.5, 3.4 Hz, 4CH), 132.4 (qd, *J* = 33.9, 10.5 Hz, 4C), 132.1 (d, *J* = 36.9 Hz, 2C), 129.5 (dd, *J* = 14.0, 1.5 Hz, C), 124.7 (br. , 2CH), 122.8 (q, *J* = 272.8 Hz, 4C), 122.5 (s, C), 117.6 (s, CH), 113.2 (dd, *J* = 44.9, 7.0 Hz, C), 112.4 (d, *J* = 4.0 Hz, CH), 68.5 (s, $2CH_2$), 55.5 (s, CH_3), 55.2 (s, CH_3), 34.0 (s, CH), 31.5 (s, 2CH), 25.7 (s, $2CH_2$), 24.6 (s, $2CH_3$), 23.8 (s, $2CH_3$), 23.8 (s, $2CH_3$). **^{31}P NMR** (202 MHz, $CDCl_3$): δ = -4.9 (d, $J(^{31}P\text{-}^{109}Ag)$ = 807.3 Hz), $J(^{31}P\text{-}^{107}Ag)$ = 700.1 Hz). **HRMS** (EI): m/z calc'd for $C_{43}H_{45}AgF_{12}O_3P$ [$(M\text{-}SbF_6)^+$] 975.1965, found 975.1920.



[(Brettphos)Ag(MeCN)]SbF_6

Prepared according to **GP5** in 85% yield as a white powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (s, 2 H), 7.08 (d, *J* = 9.0 Hz, 1 H), 7.01 (dd, *J* = 2.1, 9.1 Hz, 1 H), 3.91 (s, 3 H), 3.55 (s, 3 H), 2.96 (spt, *J* = 6.9 Hz, 1 H), 2.54 - 2.37 (m, 2 H), 2.27 (s, 3 H), 2.31 (spt, *J* = 6.8 Hz, 2 H), 1.97 - 1.84 (m, 2 H), 1.80 (d, *J* = 12.2 Hz, 2 H), 1.69 (t, *J* = 14.5 Hz, 4 H), 1.52 - 1.40 (m, 2 H), 1.33 (d, *J* = 7.0 Hz, 6 H), 1.26 (d, *J* = 6.9 Hz, 6 H), 1.39 - 0.99 (m, 8 H), 0.99 - 0.78 (m, 6 H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 155.3 (dd, J= 6.2, 2.2 Hz, Cquat), 152.6 (d, J= 10.5 Hz, Cquat), 149.6 (s, Cquat), 146.9 (s, 2xCquat), 136.2 (d, J= 20.0 Hz, Cquat), 130.4 (dd, J= 11.4, 1.5 Hz, Cquat), 122.4 (s, 2xCH), 119.3 (s, Cquat), 116.2 (d, J= 35.4, 6.7 Hz, Cquat), 114.7 (d, J= 2.0, CH), 110.8 (d, J= 4.0 Hz, CH), 56.0 (s, CH3), 54.9 (s, CH3), 36.3 (dd, J= 21.4, 4.5 Hz, 2xCH) , 34.7 (d, J= 13.0, 2.0 Hz, 2xCH2), 33.9 (s, CH), 30.8 (2xCH), 30.5 (d, J= 1.5 Hz, 2xCH2), 27.2 (d, J= 12.5 Hz, 2xCH2), 26.8 (d, J= 17.5 Hz, 2xCH2), 25.7 (d, J= 1.1 Hz, 2xCH2), 24.8 (s, 2xCH3), 24.6 (s, 2xCH3), 23.8 (s, 2xCH3), 2.2 (s, CH3); **^{31}P NMR** (202 MHz, $CDCl_3$): δ = 24.8 (d, J(31P-109Ag) = 750.7 Hz), J(31P-107Ag) = 651.0 Hz); **HRMS** (ESI) m/z calc'd for C37H56AgNO2P [(M-SbF6)+] 684.3099, found 684.3106.



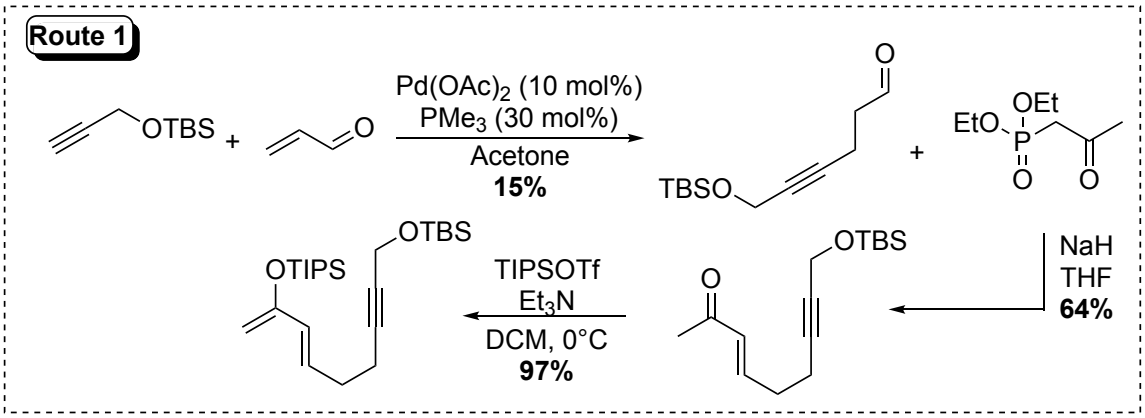
[(*t*BuBrettphos)Ag(MeCN)]SbF$_6$

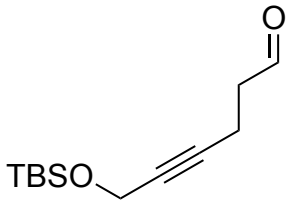
Prepared according to **GP5** in 88% yield as a white powder.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (s, 2H), 7.12 (d, *J* = 9.0 Hz, 1H), 7.07 (d, *J* = 9.0 Hz, 1H), 3.87 (s, 3H), 3.75 (t, *J* = 6.4 Hz, 4H), 3.55 (s, 3H), 2.97 (spt, *J* = 6.8 Hz, 1H), 2.40 (spt, *J* = 6.6 Hz, 2H), 1.90 (quin, *J* = 3.2 Hz, 4H), 1.32 (d, *J* = 7.2 Hz, 6H), 1.29 (d, *J* = 17.0 Hz, 18H), 1.27 (d, *J* = 6.8 Hz, 6H), 0.90 (d, *J* = 6.6 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 155.1 (d, *J* = 5.0 Hz, C), 152.6 (d, *J* = 10.5 Hz, C), 150.0 (s, C), 147.0 (s, 2C), 136.5 (dd, *J* = 21.9, 1.5 Hz, C), 130.3 (dd, *J* = 11.5, 2.0 Hz, C), 122.2 (s, 2CH), 118.4 (dd, *J* = 20.9, 6.5 Hz, C), 114.9 (d, *J* = 2.0 Hz, CH), 110.8 (d, *J* = 4.0 Hz, CH), 70.6 (s, $2CH_2$), 54.7 (s, CH_3), 54.7 (s, CH_3), 37.1 (dd, *J* = 10.5, 5.0 Hz, 2C), 33.8 (s, CH), 32.1 (dd, *J* = 11.0, 2.0 Hz, $6CH_3$), 31.2 (s, 2CH), 25.5 (s, $2CH_2$), 25.2 (s, $2CH_3$, 24.4 (s, $2CH_3$), 23.7 (s, $2CH_3$). **^{31}P NMR** (202 MHz, $CDCl_3$): δ = 57.1 (d, $J(^{31}P\text{-}^{109}Ag)$ = 789.8 Hz), $J(^{31}P\text{-}^{107}Ag)$ = 683.4 Hz). **HRMS** (EI): m/z calc'd for $C_{33}H_{52}AgNO_2P$ [$(M\text{-}SbF_6)^+$] 632.2787, found 632.2784.

6.3 TOWARDS THE SYNTHESIS OF TEUCRIN A

6.3.1 Synthesis of the Diene





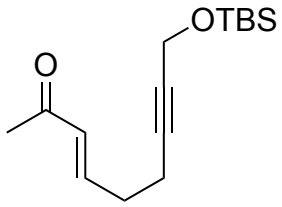
6-((*Tert*-butyldimethylsilyl)oxy)hex-4-ynal

Compound 2.3.31

In a reaction flask was added $Pd(OAc)_2$ (0.05 mmol, 10 mol%) and a solution of trimethylphosphine in toluene (1.0 M, 0.15 mmol, 30 mol%). The mixture was stirred at 110°C under argon for 10 minutes, or until the palladium was completely dissolved. Then, TBS-protected propargyl alcohol (0.5 mmol, 1.0 eq.) in acetone (1 mL) and acrolein (2.5 mmol, 5.0 eq.) was added and the reaction mixture was stirred at 60°C for 16 hours. The reaction was cooled down to room temperature, diluted with diethyl ether and quenched with water. The organic phase was separated and the aqueous phase was extracted 3 more times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified

by flash chromatography (10% diethyl ether in hexanes) to afford the product in 15% yield (17 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.75 (t, *J* = 1.3 Hz, 1H), 4.23 (t, *J* = 2.2 Hz, 2H), 2.62 (tt, *J* = 7.0, 1.1 Hz, 2H), 2.52 – 2.47 (m, 2H), 0.86 (s, 9H), 0.07 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 200.2 (CH), 82.9 (C), 79.7 (C), 51.8 (CH_2), 42.4 (CH_2), 25.8 ($3CH_3$), 18.2 (C), 12.0 (CH_2), -5.2 ($2CH_3$). **IR** (neat, cm^{-1}): 2158, 1729. **HRMS** (EI): m/z calc'd for $C_8H_{13}O_2Si$ [M^+-*t*Bu] 169.0685, found 169.0700.



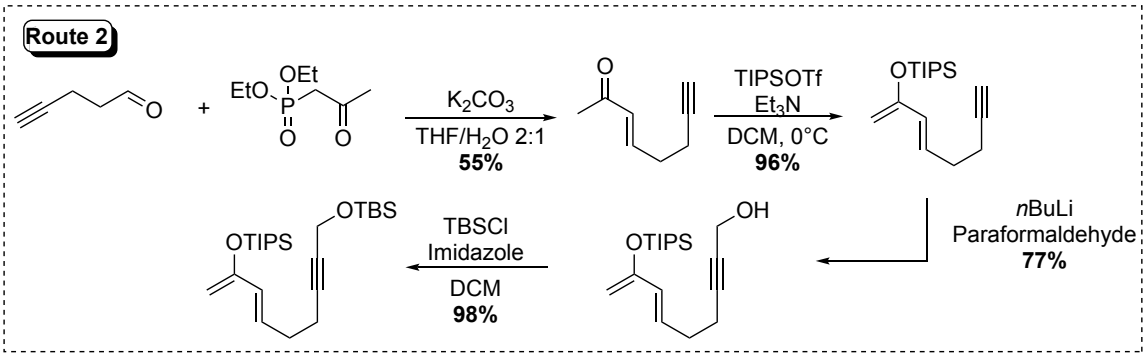
(*E*)-9-((*Tert*-butyldimethylsilyl)oxy)non-3-en-7-yn-2-one

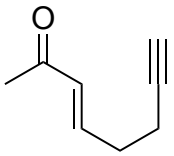
Compound 2.3.33

To a stirred solution of NaH in THF (0.74 mL) at 0°C was added a solution of diethyl (2-oxopropyl)phosphonate (0.25 mmol, 1.0 eq.) in THF (0.14 mL) dropwise. The resulted solution was stirred at 0°C for 30 minutes and then treated with a solution of 6-((*tert*-butyldimethylsilyl)oxy)hex-4-ynal (0.44 mmol, 1.75 eq.) in THF (0.14 mL). The solution was warmed up to room temperature and stirred for 2 additional hours. The reaction mixture was diluted with diethyl ether and quenched with a saturated solution of NH_4Cl (aq). The organic phase was separated and the aqueous phase was extracted 2 more times with EtO_2. The combined organic phase were dried over $MgSO_4$, filtered, and concentrated under

vacuum. The crude product was purified by flash chromatography to afford the desired product as a yellow oil (75 mg, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81 (dt, *J* = 16.1, 6.5 Hz, 1H), 6.12 (dt, *J* = 16.0, 1.4 Hz, 1H), 4.29 (t, *J* = 2.0 Hz, 2H), 2.46 – 2.37 (m, 4H), 2.25 (s, 3H), 0.90 (s, 9H), 0.11 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 198.4 (C), 145.8 (CH), 132.1 (CH), 83.3 (C), 80.0 (C), 51.9 (CH_2), 31.4 (CH_2), 26.9 (CH_3), 25.9 ($3CH_3$), 18.3 (C), 17.9 (CH_2), -5.1 ($2CH_3$). **IR** (neat, cm^{-1}): 2160, 1677. **HRMS** (EI): m/z calc'd for $C_{11}H_{17}O_2Si$ [M^+-*t*Bu] 209.0998, found 209.0980.



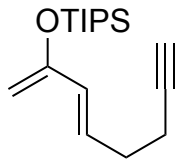


(*E*)-Oct-3-en-7-yn-2-one

Compound 2.3.36

To a solution of 4-pentyn-1-al (12.2 mmol, 1.75 eq.) in THF/H_2O 2:1 (12 ml, 6 ml) was added diethyl (2-oxopropyl)phosphonate (6.96 mmol, 1.0 eq.) and potassium carbonate (9.74 mmol, 1.4 eq.). The reaction mixture was stirred at reflux overnight, then cooled down at room temperature and diluted with ethyl acetate. The organic phase was separated and the aqueous phase was extracted 2 more

times with EtOAc. The combined organic phase were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash chromatography to afford the desired product as a clear oil (469 mg, 55% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.82 (dt, *J* = 16.0, 6.6 Hz, 1H), 6.13 (dt, *J* = 16.0, 1.5 Hz, 1H), 2.49 – 2.43 (m, 2H), 2.39-2.35 (m, 2H), 2.26 (s, 3H), 2.01 (t, *J* = 2.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 198.4 (C), 145.3 (CH), 132.2 (CH), 82.6 (C), 69.5 (CH), 31.2 (CH_2), 27.0 (CH_3), 17.5 (CH_2). **IR** (neat, cm^{-1}): 3290, 2918, 2117, 1671. **HRMS** (EI): m/z calc'd for C_8H_9O [M^+-H] 121.0653, found 121.0646.



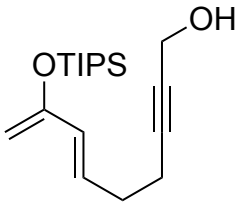
(*E*)-Triisopropyl(octa-1,3-dien-7-yn-2-yloxy)silane

Compound 2.3.37

To a mixture of (*E*)-oct-3-en-7-yn-2-one (11.7 mmol, 1 eq.) and Et_3N (23.3 mmol, 2.0 eq.) in dry dichloromethane (58 mL) was added dropwise triisopropylsilyl trifluoromethanesulfonate (17.5 mmol, 1.5 eq.) at 0 °C under argon. The resulting mixture was stirred at room temperature. After 1 hour, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted twice with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography

(Et_3N/EtO_2/Hexanes 1:2:97) to afford the desired product as a clear oil (3.08g, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.12 (dt, *J* = 15.3, 6.5 Hz, 1H), 5.93 (dt, *J* = 15.2, 1.3 Hz, 1H), 4.25 (s, 1H), 4.20 (s, 1H), 2.37 – 2.26 (m, 4H), 1.95 (t, *J* = 2.5 Hz, 1H), 1.28 – 1.19 (m, 3H), 1.11 (d, *J* = 7.2 Hz, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.1 (C), 129.1 (2CH), 93.8 (CH_2), 83.8 (C), 68.6 (CH), 31.1 (CH_2), 18.6 (CH_2), 18.1 ($6CH_3$), 12.8 (3CH). **IR** (neat, cm^{-1}): 3313, 2944, 2867, 2122. **HRMS** (EI): m/z calc'd for $C_{17}H_{30}OSi$ [M^+] 278.2066, found 278.2058.



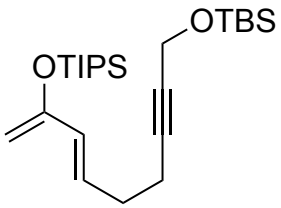
(*E*)-8-((Triisopropylsilyl)oxy)nona-6,8-dien-2-yn-1-ol

Compound 2.3.38

To a solution of (*E*)-triisopropyl(octa-1,3-dien-7-yn-2-yloxy)silane (1.88 mmol, 1.0 eq.) in diethyl ether (3.7 mL) at -78°C was added a solution of *n*BuLi (2.44 mmol, 1.3 eq.) dropwise. After stirring at -78°C for 30 minutes, paraformaldehyde was added (5.63 mmol, 3.0 eq.) and the reaction was slowly warmed up to room temperature and stirred for an additional 12 hours. The reaction mixture was quenched with water and the organic phase was separated. The aqueous phase was extracted 2 more times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash

chromatography (Et_3N/EtOAc/hexanes 1:5:94 – 1:10:89) to afford the desired product in 77% yield (447 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.15 – 6.05 (m, 1H), 5.91 (d, *J* = 15.2 Hz, 1H), 4.25 (s, 1H), 4.22 (s, 2H), 4.19 (s, 1H), 2.32-2.31 (m, 4H), 1.70 (br., 1H), 1.27 – 1.18 (m, 3H), 1.10 (d, *J* = 7.3 Hz, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.0 (C), 129.2 (CH), 129.1 (CH), 93.7 (CH_2), 85.6 (C), 78.9 (C), 51.3 (CH_2), 31.1 (CH_2), 18.9 (CH_2), 18.1 ($6CH_3$), 12.8 (3CH). **IR** (neat, cm^{-1}): 3335, 2943, 2867, 2029. **HRMS** (EI): m/z calc'd for $C_{18}H_{32}O_2Si$ [M^+] 308.2172, found 308.2151.



(*E*)-3,3-Diisopropyl-2,14,14,15,15-pentamethyl-5-methylene-4,13-dioxa-3,14-disilahexadec-6-en-10-yne

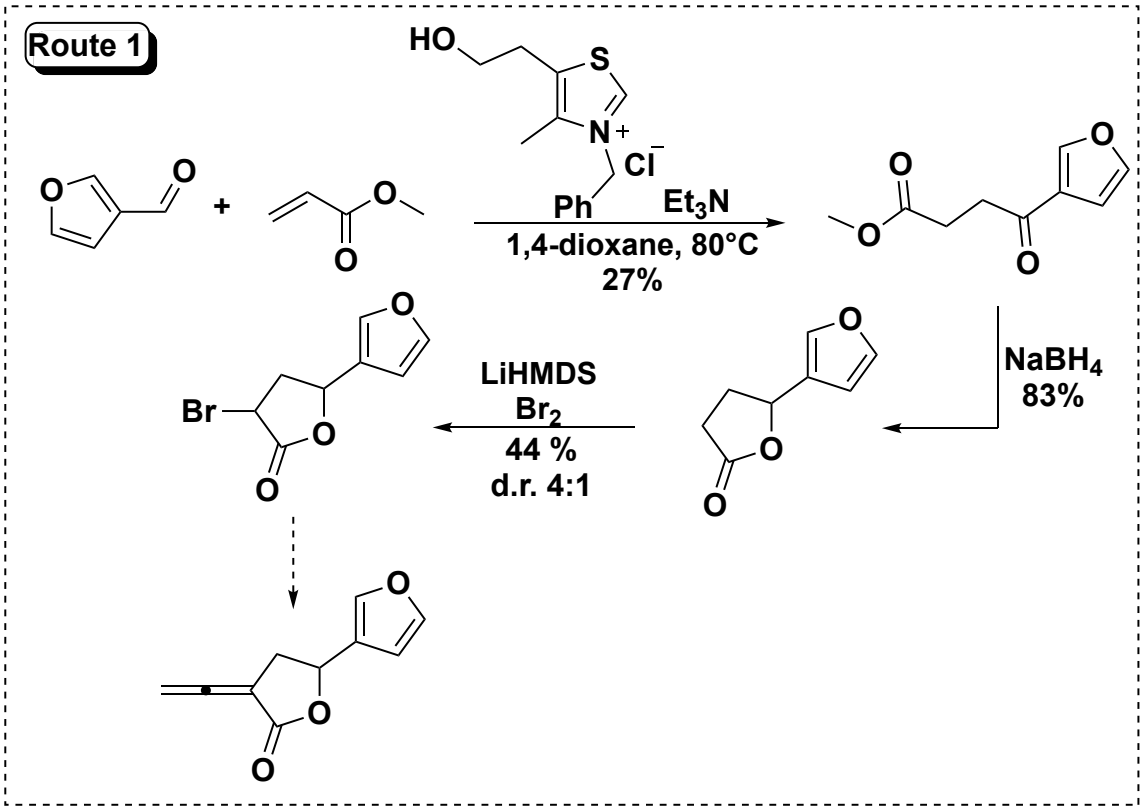
Compound 2.3.34

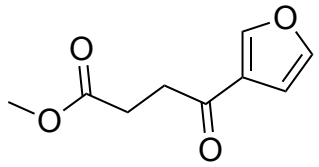
To a solution of (*E*)-8-((triisopropylsilyl)oxy)nona-6,8-dien-2-yn-1-ol (5.51 mmol, 1.0 eq.) and imidazole (13.8 mmol, 2.5 eq.) in dichloromethane (15.8 mL) was added TBSCl (8.27 mmol, 1.5 eq.) at 0°C. The reaction was stirred at 0°C for 90 minutes, and quenched with a saturated solution of NH_4Cl (aq.) and the organic phase was separated. The aqueous phase was extracted 2 more times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was

purified by flash chromatography (Et_3N/EtOAc/hexanes 1:4:95) to afford the desired product in 98% yield (2.28 g).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.13 – 6.05 (m, 1H), 5.91 (d, *J* = 15.2 Hz, 1H), 4.29 (t, *J* = 1.9 Hz, 2H), 4.24 (s, 1H), 4.19 (s, 1H), 2.34 – 2.29 (m, 4H), 1.28 – 1.18 (m, 3H), 1.10 (d, *J* = 7.1 Hz, 18H), 0.91 (s, 9H), 0.11 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.1 (C), 129.4 (CH), 128.9 (CH), 93.6 (CH_2), 84.5 (C), 79.1 (C), 52.0 (CH_2), 31.3 (CH_2), 25.9 ($3CH_3$), 18.9 (CH_2), 18.4 (C), 18.1 ($6CH_3$), 12.8 (3CH), -5.1 ($2CH_3$). **IR** (neat, cm^{-1}): 2946, 2929, 2866, 2168. **HRMS** (EI): m/z calc'd for $C_{24}H_{46}O_2Si_2$ [M^+] 422.3036, found 422.3009.

6.3.2 Synthesis of the Dienophile



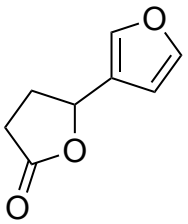


Methyl 4-(furan-3-yl)-4-oxobutanoate

Compound 2.3.41

3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazol-3-ium chloride (10.2 mmol, 30 mol%) and triethylamine (51.0 mmol, 1.0 eq.) were added to 1,4-dioxane at room temperature. The mixture was stirred for 30 minutes, after which time 3-furaldehyde (51 mmol, 1.0 eq.) and methyl acrylate (76.5 mmol, 1.5 eq.) were added. The reaction mixture was warmed up to 80°C and stirred for 16 hours. Upon completion, the reaction was cooled down to room temperature, diluted with ethyl acetate, quenched with a saturated solution of NH_4Cl (aq.), and the organic phase was separated. The aqueous phase was extracted 2 more times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash chromatography (5-15% EtOAc in hexanes) to afford the desired product in 27% yield (2.51 g).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 1.4, 0.8 Hz, 1H), 7.44 (dd, *J* = 1.9, 1.4 Hz, 1H), 6.78 (dd, *J* = 1.9, 0.8 Hz, 1H), 3.70 (s, 3H), 3.10 (t, *J* = 6.7 Hz, 2H), 2.74 (t, *J* = 6.7 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 192.7 (C), 173.2 (C), 147.2 (CH), 144.2 (CH), 127.3 (C), 108.6 (CH), 51.9 (CH_3), 34.9 (CH_2), 27.7 (CH_2). **IR** (neat, cm^{-1}): 3142, 3131, 1721, 1665. **HRMS** (EI): m/z calc'd for $C_9H_{10}O_4$ [M^+] 182.0579, found 182.0555.

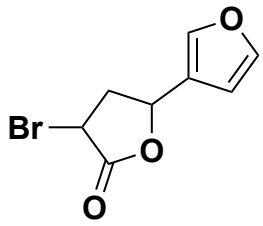


5-(Furan-3-yl)dihydrofuran-2(3*H*)-one

Compound 2.3.45

Methyl 4-(furan-3-yl)-4-oxobutanoate (8.22 mmol, 1.0 eq.) and sodium borohydride (10.3 mmol, 1.25 eq.) were added to methanol (82 mL) at room temperature. The reaction mixture was stirred for 1 hour, and the solvent was then evaporated under vacuum. The crude compound was diluted with ethyl acetate, and the organic phase was separated. The aqueous phase was extracted 2 more time with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was then purified by flash chromatography (5-10% EtOAc in haxanes) to isolate the desired product with 83% yield (1.04 g) and approximately 10% of the opened form (visible on the NMRs).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (dt, *J* = 1.7, 0.9 Hz, 1H), 7.44 (t, *J* = 1.7 Hz, 1H), 6.41 (dd, *J* = 1.9, 0.9 Hz, 1H), 5.50 – 5.46 (m, 1H), 2.66 – 2.53 (m, 3H), 2.28 – 2.18 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 176.6 (C), 144.1 (CH), 139.8 (CH), 124.3 (C), 108.3 (CH), 74.8 (CH), 29.3 (CH_2), 28.7 (CH_2). **IR** (neat, cm^{-1}): 3138, 1771. **HRMS** (EI): m/z calc'd for $C_8H_8O_3$ [M^+] 152.0473, found 152.0465.

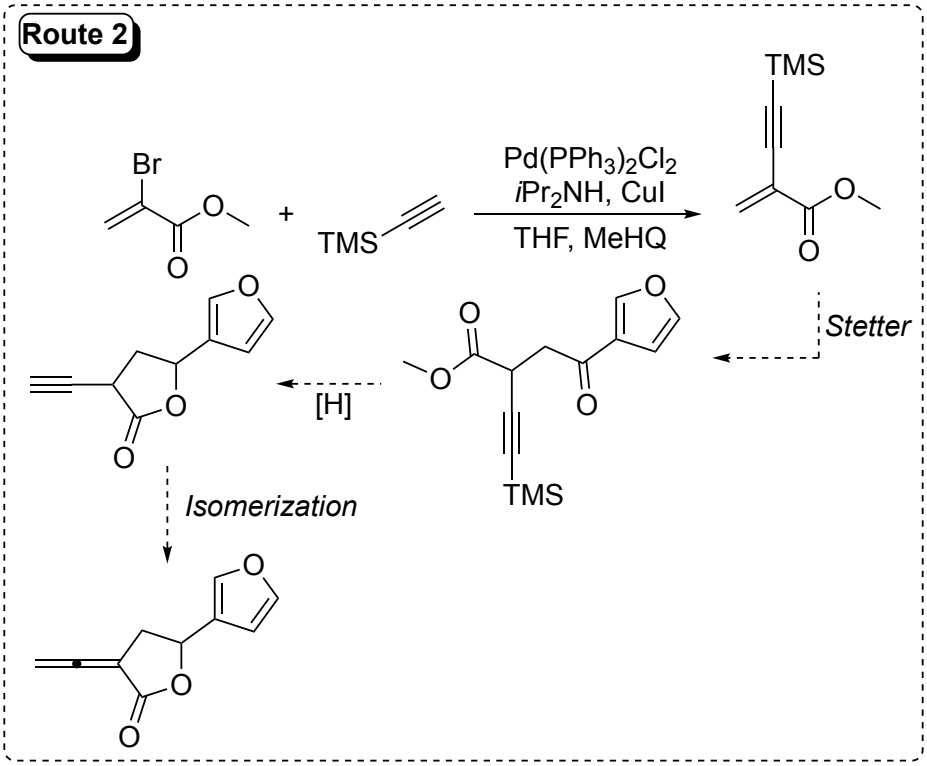


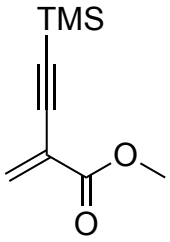
3-Bromo-5-(furan-3-yl)dihydrofuran-2(3*H*)-one

Compound 2.3.49

To a solution of 5-(furan-3-yl)dihydrofuran-2(3*H*)-one (6.8 mmol, 1.0 eq.) in THF (34 mL) at -78°C was added a solution of LiHMDS (7.8 mmol, 1.15 eq.) in THF. The mixture was stirred at -78°C for 30 minutes, and bromide (10.2 mmol, 1.5 eq.) was added dropwise. The reaction was stirred for an additional hour, and then quenched with a saturated solution of NH_4Cl (aq.), and the organic phase was separated. The aqueous phase was extracted 2 more times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash chromatography (10-20% EtOAc in hexanes) to afford the desired product in 44% yield (691 mg) with a d.r. of 2.3:1 (trans/cis). **^{1}H NMR *Trans* Product** (400 MHz, $CDCl_3$): δ = 7.53 (dt, *J* = 1.6, 0.8 Hz, 1H), 7.46 (t, *J* = 1.7 Hz, 1H), 6.42 (dd, *J* = 1.9, 0.9 Hz, 1H), 5.72 (dd, *J* = 9.0, 5.6 Hz, 1H), 4.54 – 4.51 (m, 1H), 2.80 – 2.67 (m, 2H). **^{1}H NMR *Cis* Product** (400 MHz, $CDCl_3$): δ = 7.54 (dt, *J* = 1.6, 0.9 Hz, 1H), 7.47 (t, *J* = 1.8 Hz, 1H), 6.48 (dd, *J* = 1.9, 0.9 Hz, 1H), 5.46 (dd, *J* = 8.9, 6.2 Hz, 1H), 4.66 (dd, *J* = 9.7, 8.6 Hz, 1H), 3.20 (ddd, *J* = 13.6, 8.5, 6.2 Hz, 1H), 2.62 (ddd, *J* = 13.7, 9.7, 8.9 Hz, 1H). **^{13}C NMR *Trans* Product** (101 MHz, $CDCl_3$): δ = 171.9 (C), 144.4 (CH), 140.6 (CH), 122.2 (C), 108.3 (CH), 73.7 (CH), 40.7 (CH_2), 38.5 (CH). **^{13}C NMR *Cis* Product** (101 MHz, $CDCl_3$): 171.9 (C),

144.3 (CH), 140.6 (CH), 122.9 (C), 108.4 (CH), 73.2 (CH), 40.1 (CH_2), 37.5 (CH). **IR** (neat, cm^{-1}): 3137, 1769. **HRMS** (EI): m/z calc'd for $C_8H_7O_3Br$ [M^+] 229.9579 and 231.9558, found 229.9551 and 231.9530.



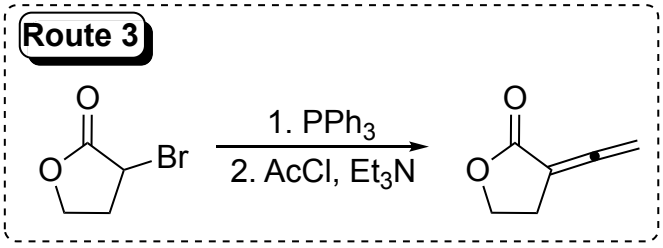


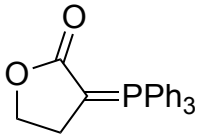
Methyl 2-methylene-4-(trimethylsilyl)but-3-ynoate

Compound 2.3.53

A flame-dried reaction flask equipped with a magnetic stir bar was charged with TMS acetylene (1.4 mmol, 1.0 eq.) in THF/Mequinol (10.5 mL, with 25 mg of MeHQ/100 mL), followed by CuI (0.14 mmol, 10 mol%) and diisopropylamine (2.8 mmol, 2.0 eq.). Then, methyl 2-bromoacrylate (2.8 mmol, 2.0 eq.) and

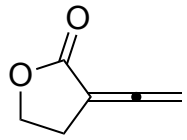
$Pd(PPh_3)_2Cl_2$ (0.035 mmol, 2.5 mol%) were subsequently added and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was filtered through a sintered glass funnel and the mother liquor was collected and concentrated under vacuum. Due to the instability of the compound, it was used as a crude in the next step, without any further purification.





3-(Triphenylphosphoranyliden)dihydro-2(3H)-furanone
Compound 2.3.57

To a solution of triphenylphosphine (2.4 mmol, 1.0 eq.) in THF (1 mL) was added α-Bromo-γ-butyrolactone and the mixture was stirred at 70°C for 24 hours. Upon completion, the reaction mixture was cooled down to room temperature and the phosphonium salt was filtered. The resulting salt was dissolved in dichloromethane and washed with 1.0 M aqueous potassium hydroxide three times, followed by two washes with brine. The organic phase was then dried over $MgSO_4$, filtered and concentrated under vacuum. The ylide was used in the next step, without any further purification.

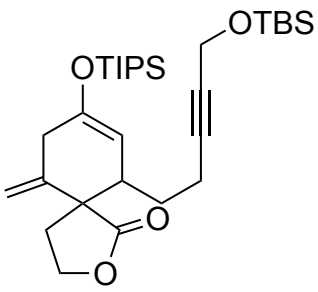


3-Vinylidenedihydrofuran-2(3*H*)-one

Compound 2.3.57

The crude phosphonium ylide (2.0 g, 1.0 eq.) was dissolved in dichloromethane (4.6 mL) and the solution was cooled to 0°C. *N,N*-diisopropylethylamine was added (1.0 mL, 1.0 eq.) and acetyl chloride (6.4 mL, 1.1 eq.) were subsequently added and the resulting mixture was allowed to warm up to room temperature and was stirred for 24 hours. The reaction was cooled to 0°C again and additional DIPEA (1.0 mL, 1.0 eq.) and acetyl chloride (6.4 mL, 1.1 eq.) were added. The reaction was warmed up again at room temperature and stirred for 1 hour. Water was added (4.6 mL) and the biphasic solution was stirred for 20 minutes. The organic phase was separated and the aqueous phase was extracted 2 more times with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The corresponding crude product was purified by flash chromatography (15-20% EtOAc in hexanes) to afford the desired product in 71% yield (455 mg). Spectroscopic data recorded were consistent with that previously reported.[3]

6.3.3 Diels-Alder Product



6-(5-((*Tert*-butyldimethylsilyl)oxy)pent-3-yn-1-yl)-10-methylene-8-((triisopropylsilyl)oxy)-2-oxaspiro[4.5]dec-7-en-1-one

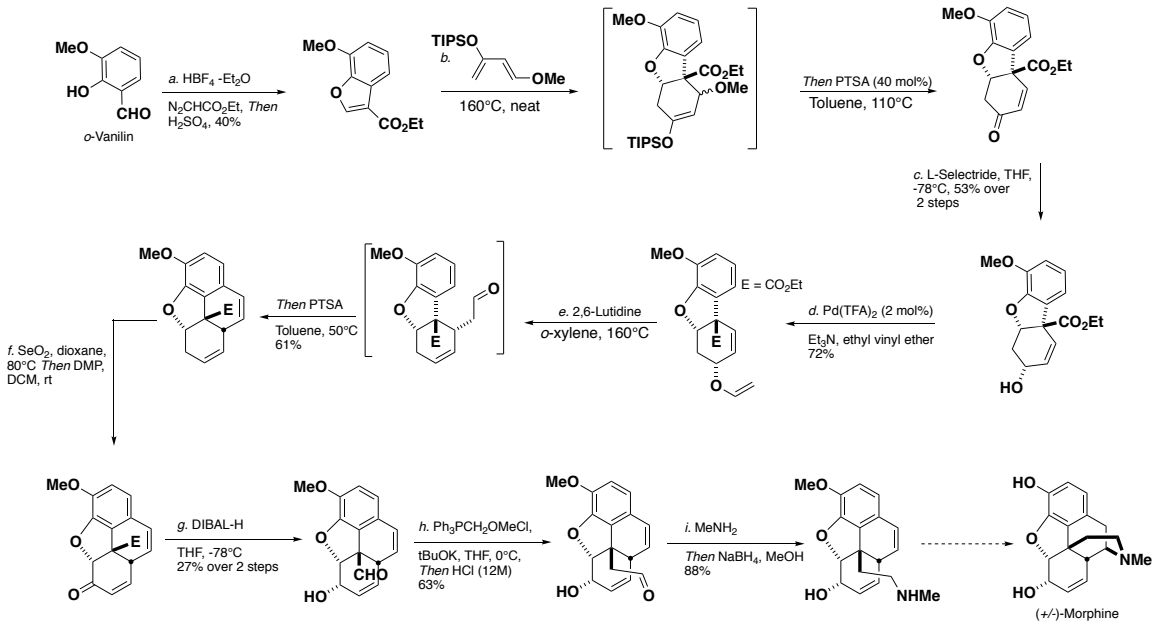
Compound 2.3.58

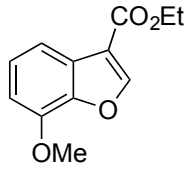
In a flame-dried high pressure flask were added (*E*)-3,3-diisopropyl-2,14,14,15,15-pentamethyl-5-methylene-4,13-dioxa-3,14-disilahexadec-6-en-10-yne (0.12 mmol, 1.0 eq.) and 3-vinylidenedihydrofuran-2(3*H*)-one (0.24 mmol, 2.0 eq.) in toluene (0.6 mL). The reaction mixture was heated at 110°C for 16 hours, then cooled down to room temperature. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography to afford the desired product as a 3:1 diastereomer mixture (31 mg, 49% yield). A NOESY experiment was conducted to determine the stereochemistry of the major diastereoisomer, but it was not conclusive.

^{1}H NMR Major Product (400 MHz, $CDCl_3$): δ = 5.04 – 5.01 (m, 1H), 4.87 (d, *J* = 2.0 Hz, 1H), 4.82 (dd, *J* = 1.7, 1.7 Hz, 1H), 4.31 – 4.25 (m, 3H), 4.20 – 4.10 (m, 1H), 3.05 – 2.98 (m, 1H), 2.94-2.85 (m, 1H), 2.68 – 2.62 (m, 1H), 2.37 – 2.16 (m, 3H), 2.06 (ddd, *J* = 13.0, 6.3, 2.0 Hz, 1H), 1.54 (tdd, *J* = 9.8, 6.9, 3.5 Hz, 1H), 1.42-1.32 (m, 1H), 1.20 – 1.12 (m, 3H), 1.08 (dd, *J* = 6.5, 1.1 Hz, 18H), 0.90 (s, 9H), 0.11 (s, 6H). **^{1}H NMR Minor Product** (400 MHz, $CDCl_3$): δ = 5.17 (d, *J* = 2.2 Hz, 1H), 5.08 (d, *J* = 1.9 Hz, 1H), 5.01 – 4.96 (m, 1H), 4.31 – 4.25 (m, 3H),

4.20 – 4.10 (m, 1H), 2.94-2.85 (m, 2H), 2.49-2.38 (m, 1H), 2.37 – 2.16 (m, 4H), 1.54 (tdd, *J* = 9.8, 6.9, 3.5 Hz, 1H), 1.42-1.32 (m, 1H), 1.20 – 1.12 (m, 3H), 1.08 (dd, *J* = 6.5, 1.1 Hz, 18H), 0.90 (s, 9H), 0.11 (s, 6H). **^{13}C NMR Major Product** (101 MHz, $CDCl_3$): δ = 177.9 (C), 148.6 (C), 140.9 (C), 111.4 (CH_2), 103.8 (CH), 84.3 (C), 79.2 (C), 65.1 (CH_2), 53.5 (C), 52.0 (CH_2), 39.6 (CH), 36.4 (CH_2), 31.6 (CH_2), 28.5 (CH_2), 25.9 ($3CH_3$), 18.4 (C), 18.0 ($3CH_3$), 17.9 ($3CH_3$), 17.2 (CH_2), 12.6 (3CH), -5.1 ($2CH_3$). **^{13}C NMR Minor Product** (101 MHz, $CDCl_3$): δ = 176.4 (C), 149.4 (C), 139.3 (C), 112.1 (CH_2), 103.3 (CH), 84.5 (C), 79.1 (C), 64.2 (CH_2), 52.0 (CH_2), 51.0 (C), 39.9 (CH), 36.6 (CH_2), 35.5 (CH_2), 30.8 (CH_2), 25.9 ($3CH_3$), 18.3 (C), 17.9 ($3CH_3$), 17.7 ($3CH_3$), 16.4 (CH_2), 12.6 (3CH), -5.1 ($2CH_3$). **IR** (neat, cm^{-1}): 2930, 2864, 2165, 1773. **HRMS** (EI): m/z calc'd for $C_{26}H_{43}O_4Si_2$ [M^+-*t*Bu] 475.2700, found 475.2682.

6.4 FORMAL SYNTHESIS OF MORPHINE





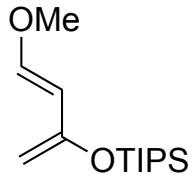
Ethyl 7-methoxy-1-benzofuran-3-carboxylate

Compound 3.2.6

HBF_4•Et_2O (1.32 mL, 9.70 mmol, 10 mol%) was added dropwise to a solution of 2-hydroxy-3-methoxybenzaldehyde **3.2.8** (15.0 g, 98.6 mmol, 1 eq.) in dry CH_2Cl_2 (30 mL) at room temperature. A solution of ethyl diazoacetate (87 wt.% solution in CH_2Cl_2, 19 mL, 157 mmol, 1.6 eq.) in dry CH_2Cl_2 (120 mL) was added dropwise to the reaction mixture with a dropping funnel as the evolution of N_2 gas permitted. Once gas evolution ceased, the reaction mixture concentrated under reduced pressure. Dry CH_2Cl_2 (10 mL) was added to the resulting mixture and H_2SO_4 (6.0 mL, 113 mmol, 1.1 eq.) was added dropwise at room temperature. After 5 to 10 minutes, the mixture was diluted with CH_2Cl_2 and quenched with solid $NaHCO_3$ (9.5 g). The mixture was then filtered through celite and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc 95/5) to afford pure benzofuran **3.2.6** (8.79 g, 40% yield, white amorphous solid).

^{1}H NMR (400 MHz, $CDCl_3$): 8.25 (s, 1H), 7.65 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.28 (t, *J* = 7.9 Hz, 1H), 6.87 (dd, *J* = 7.9, 0.9 Hz, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 4.02 (s, 1H), 1.41 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): 163.5 (C), 151.0 (CH), 145.6 (C), 145.1 (C), 126.5 (C), 125.1 (CH), 115.2 (C), 114.2 (CH), 107.3 (CH), 60.7

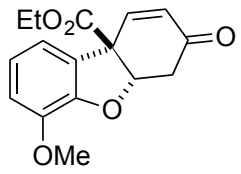
(CH_2), 56.2 (CH_3), 14.5 (CH_3). **IR** (neat, cm^{-1}): 1719, 1498, 1276, 1253, 1233, 1042, 789, 733. **HRMS** (EI): m/z calc'd for $C_{12}H_{12}O_4$ [M^+] 220.0736, found 220.0736.



Methoxy-3-triisopropylsiloxy-1,3-butadiene

Compound 3.2.7

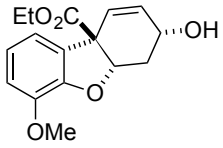
To a mixture of 4-methoxy-3-buten-2-one (8.0 g, 79.9 mmol, 1 eq.) and Et_3N (30 mL, 215 mmol, 2.7 eq.) in dry diethyl ether (130 mL) was added dropwise triisopropylsilyl trifluoromethanesulfonate (24 mL, 89.3 mmol, 1.1 eq.) at 0 °C under argon. The resulting mixture was stirred at room temperature. After 15 hours, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were washed twice with water and twice with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting mixture was diluted with EtOAc and washed again twice with water and twice with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude diene **3.2.7** (orange oil) was directly used in the next step without further purification.



Ethyl-4-methoxy-7-oxo-6,7-dihydrodibenzo[*b*,*d*]furan-9a(5a*H*)-carboxylate

Compound 3.2.5

In a reaction flask, a mixture of dienophile **3.2.6** (3.18 g, 14.5 mmol, 1 eq.) and diene **3.2.7** (7.41 g) was heated at 160 °C under argon. After 16 h, the reaction mixture was cooled down to room temperature and diluted with toluene (270 mL). PTSA•H_2O (1.08 g, 5.78 mmol, 40 mol%) was added and the resulting mixture was stirred under reflux. After 15 hours, the reaction mixture was quenched with 5 wt.% aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude enone **3.2.5** (brown oil) was directly used in the next step without further purification



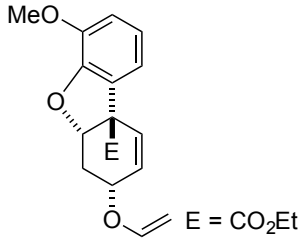
Ethyl-7-hydroxy-4-methoxy-6,7-dihydrodibenzo[*b*,*d*]furan-9a(5a*H*)-carboxylate

Compound 3.2.16

L-selectride (1.0 M in THF, 29 mL, 2 eq.) was added dropwise to a solution of crude enone **3.2.5** (14.5 mmol, 1 eq.) in dry THF (95 mL) at – 78 °C, under argon. The resulting mixture was stirred at – 78 °C. After stirring for 90 min, the mixture was treated with saturated aqueous NH_4Cl. The organic layer was

separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc 7:3) to afford pure enol **3.2.16** (2.22 g, 53% yield from benzofuran **3.2.6**, yellow oil).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07 (dd, J = 7.6, 1.2 Hz, 1H), 6.92 (dd, J = 8.1, 7.6 Hz, 1H), 6.82 (dd, J = 8.1, 1.2 Hz, 1H), 6.05 (ddd, J = 10.1, 5.0, 0.8 Hz, 1H), 5.90 (ddd, J = 10.1, 1.0, 1.0 Hz, 1H), 5.42-5.41 (m, 1H), 4.31-4.22 (m, 2H), 4.21-4.15 (m, 1H), 3.87 (s, 3H), 2.66-2.60 (dddd, J = 15.4, 3.7, 2.5, 0.8 Hz, 1H), 2.25-2.19 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.4 (C), 146.3 (C), 145.2 (C), 130.7 (C), 129.5 (CH), 126.5 (CH), 122.4 (CH), 116.3 (CH), 112.4 (CH), 83.3 (CH), 62.0 (CH_2), 61.8 (CH), 56.1 (CH_3), 55.1 (C), 31.3 (CH_2), 14.3 (CH_3). **IR** (neat, cm^{-1})**:** 3501, 2939, 1726, 1281, 1232, 1217, 1038, 727. **HRMS** (EI): m/z calc'd for $C_{12}H_{12}O_4$ [M^+] 290.1154, found 290.1184.



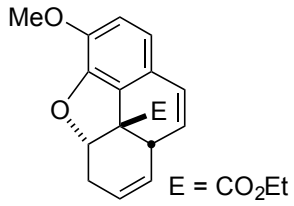
Ethyl-4-methoxy-7-(vinyloxy)-6,7-dihydrodibenzo[*b*,*d*]furan-9a(5a*H*)-carboxylate

Compound 3.2.4

In a dry sealed tube, a mixture of $Pd(TFA)_2$ (36 mg, 0.11 mmol, 0.017 equiv.) and 1,10-phenanthroline (20 mg, 0.11 mmol, 0.017 equiv.) in ethyl vinyl ether (30 mL) was stirred at room temperature for 15 minutes. Et_3N (212 mg, 2.09 mmol,

0.3 eq) and enol **3.2.16** (1.90 g, 6.55 mmol, 1 equiv.) in solution in ethyl vinyl ether (35 mL) were added and the reaction mixture was heated at 50 °C under air atmosphere. After stirring for 40 hours, the reaction mixture was filtered through a pad of celite with EtOAc and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc 9:1) to afford pure ethyl vinyl ether **3.2.4** (1.49 g, 72% yield, colorless oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00 (dd, J = 7.4, 1.4 Hz, 1H), 6.87 (dd, J = 8.1, 7.4 Hz, 1H), 6.80 (dd, J = 8.1, 1.4 Hz, 1H), 6.35 (dd, J = 14.3, 6.7 Hz, 1H), 6.15 (dd, J = 10.1, 1.9 Hz, 1H), 6.02 (dd, J = 10.1, 2.6 Hz, 1H,), 5.57 (dd, J = 8.7, 5.1 Hz, 1H), 4.49-4.43 (m, 1H), 4.27 (dd, J = 14.3, 2.0 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 4.07 (dd, J = 6.7, 2.0 Hz, 1H), 3.86 (s, 3H), 2.50-2.43 (m, 1H), 2.15-2.05 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.2 (C), 150.0 (CH), 146.8 (C), 145.3 (C), 129.1 (CH), 129.0 (C), 127.5 (CH), 121.6 (CH), 116.7 (CH), 112.6 (CH), 88.9 (CH_2), 81.6 (CH), 69.1 (CH), 62.1 (CH_2), 56.5 (C), 56.2 (CH_3), 31.8 (CH_2), 14.2 (CH_3). **IR** (neat, cm^{-1})**:** 2949, 1734, 1618, 1495, 1238, 1196. **HRMS** (EI): m/z calc'd for $C_{12}H_{12}O_4$ [M^+] 316.1311, found 316.1317.



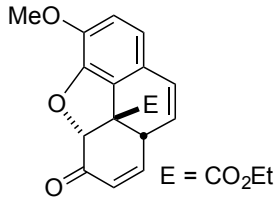
Ethyl-5-methoxy-3,9a-dihydrophenanthro[4,5-*bcd*]furan-3a^1(3a*H*)-carboxylate

Compound 3.2.17

In a dry sealed tube, 2,6-lutidine (16.9 mg, 0.158 mmol, 1 equiv.) was added to a solution of allyl vinyl ether **3.2.4** (50.0 mg, 0.158 mmol, 1 eq.) in dry xylene (2.4 mL). The reaction mixture was stirred at 160 °C under argon. After 24 hours, the reaction mixture was cooled down to room temperature and a solution of PTSA•H_2O (93.0 mg, 0.490 mmol, 3.1 equiv.) in dry toluene (3.9 mL) was added. The reaction mixture was stirred at 50°C for 16 hours, then diluted with EtOAc and quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc 95:05 to 9:1) to afford tetracyclic product **3.2.17** (28.8 mg, 61% yield, white amorphous solid).

Note: 2,6-lutidine was distilled over calcium hydride prior to use.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.71 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.48 (dd, J = 9.5, 1.2 Hz, 1H), 5.91 (dd, J = 9.5, 6.1 Hz, 1H), 5.76-5.70 (m, 1H), 5.44 (ddd, J = 10.2, 4.3, 2.4 Hz, 1H), 5.38 (dd, J = 7.5, 3.9 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 3.54-3.50 (m, 1H), 2.58-2.49 (m, 1H), 2.32-2.25 (m, 1H), 1.18 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 174.3 (C), 146.6 (C), 145.0 (C), 128.0 (CH), 125.8 (CH), 124.7 (CH), 124.5 (CH), 124.4 (C), 124.4 (C), 117.6 (CH), 113.2 (CH), 86.5 (CH), 61.7 (CH_2), 56.4 (CH_3), 52.9 (C), 36.4 (CH), 29.1 (CH_2), 14.2 (CH_3). **IR** (neat, cm^{-1})**:** 2949, 1720, 1504, 1456, 1439, 1281, 1238. **HRMS** (EI): m/z calc'd for $C_{12}H_{12}O_4$ [M^+] 298.1205, found 298.1190.

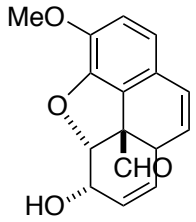


Ethyl-5-methoxy-3-oxo-3,9a-dihydrophenanthro[4,5-*bcd*]furan-3a^1(3a*H*)-carboxylate

Compound 3.2.2

In a reaction flask, SeO_2 (121 mg, 1.09 mmol, 1 equiv) was added to a solution of the tetracycle **3.2.17** (326 mg, 1.09 mmol, 1 equiv) in dry 1,4-dioxane (32.6 mL). The reaction mixture was stirred at 80°C under argon for 90 min. The reaction mixture was then cooled down to room temperature and a solution of Dess-Martin Periodinane (695 mg, 1.64 mmol, 1.5 eq.) in dry dichloromethane (16.3 mL) was added. The mixture was stirred at room temperature for 1 hour, then diluted with EtOAc and quenched with a 5% (w/w) aqueous solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was partially purified with a silica gel plug (hexanes/EtOAc 6:4) to afford a dark red sticky solid **3.2.2** (233 mg) that was used in the subsequent reaction without additional purification.

Note: The product could not be separated from the Se-based by-products due to its tendency to isomerize.



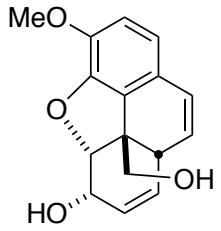
3-Hydroxy-5-methoxy-3,9a-dihydrophenanthro[4,5-*bcd*]furan-3a^1(3a*H*)-carbaldehyde

Compound 3.2.20

The crude compound **3.2.2** (233 mg) was dissolved in dry dichloromethane (2.3 mL) in a flamed-dried reaction flask and the mixture was cooled down to -78°C. A solution of diisobutylaluminum hydride in hexanes (25 wt. %, 2.4 mL) was slowly added over 45 minutes. The resulting mixture was stirred for an additional 30 minutes at -78°C. Upon completion, the reaction mixture was slowly quenched with methanol (0.2 mL over 15 minutes) and then with saturated aqueous NH_4Cl. The biphasic solution was warmed up to room temperature and the organic phase was separated. The aqueous layer was extracted three more times with dichloromethane. The combined organic layers were washed with brine twice, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes/EtOAc, 8:2 to 6:4) to afford the desired product **3.2.20** (80 mg, 27% yield over 2 steps from the tetracycle **3.2.17**, light yellow solid).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.73 (s, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.53 (dd, J = 9.4, 1.0 Hz, 1H), 6.02 (dd, J = 9.4, 6.2 Hz, 1H), 5.84 (dddd, J = 10.2, 3.1, 2.0, 0.9 Hz, 1H), 5.53 (dd, J = 6.5, 0.9 Hz, 1H), 5.34 (ddd, J = 10.2, 2.6, 2.6 Hz, 1H), 4.26-4.20 (m, 1H), 3.85 (s, 3H), 3.24-3.20 (m, 1H), 2.93 (d,

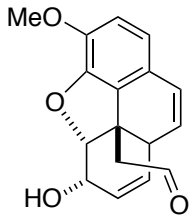
J = 9.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 197.7 (CH), 147.3 (C), 144.5 (C), 131.8 (CH), 128.1 (CH), 126.6 (CH), 125.9 (CH), 124.3 (C), 121.7 (C), 118.4 (CH), 114.0 (CH), 85.1 (CH), 65.2 (CH), 57.5 (C), 56.3 (CH_3), 33.4 (CH). **IR** (neat, cm^{-1}): 3353, 2970, 1379, 1160, 1128, 1108, 951, 817. **HRMS** (EI): m/z calc'd for $C_{12}H_{12}O_4$ [M^+] 270.0892, found 270.0871.



3a^1-(Hydroxymethyl)-5-methoxy-3,3a,3a^1,9a-tetrahydrophenanthro[4,5-*bcd*]furan-3-ol

By-product formed during the reduction of compound **3.2.2** in 10% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.67 (d, J = 8.1 Hz, 1H), 6.60 (d, J = 8.0 Hz, 1H), 6.50 (dd, J = 9.4, 1.0 Hz, 1H), 5.97 (dd, J = 9.4, 6.4 Hz, 1H), 5.85 – 5.80 (m, 1H), 5.38 (dd, J = 6.5, 1.1 Hz, 1H), 5.35 (dt, J = 10.2, 2.6 Hz, 1H), 4.29 – 4.22 (m, 1H), 3.86 (s, 3H), 3.81 – 3.77 (m, 2H), 3.05 (dt, J = 8.5, 2.9 Hz, 1H), 2.83 (d, J = 9.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 146.9 (C), 144.1 (C), 131.7 (CH), 128.7 (CH), 127.2 (CH), 125.9 (C), 125.1 (CH), 124.1 (C), 117.8 (CH), 112.7 (CH), 88.6 (CH), 65.8 (CH), 64.6 (CH_2), 56.1 (CH_3), 48.3 (C), 34.0 (CH). **IR** (neat, cm^{-1}): 3357, 2918, 1505, 1163, 795. **HRMS** (EI): m/z calc'd for $C_{16}H_{16}O_4$ [M^+] 272.1049, found 272.1026.



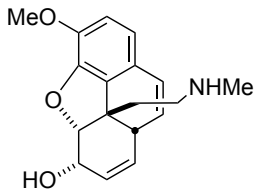
2-(3-Hydroxy-5-methoxy-3,9a-dihydrophenanthro[4,5-*bcd*]furan-3a¹(3a*H*)-yl)acetaldehyde

Compound 3.2.24

A solution of potassium *tert*-butoxide (135 mg, 1.20 mmol, 4.0 equiv) in THF (1 mL) was added via cannula to a solution of Ph_3PCH_2OMeCl (431 mg, 1.26 mmol, 4.2 equiv.) in dry THF (2 mL) at 0°C. The solution turned dark red and was allowed to stir at 0°C for 25 minutes. To this reaction flask in then added a solution of the aldehyde **3.2.20** (81 mg, 0.30 mmol, 1 equiv.) in THF (1.5 mL) and the reaction mixture was stirred at 0°C for 30 minutes. Upon full consumption of the aldehyde **3.2.20**, HCl (12 M, 0.37 mL) was added dropwise and the reaction mixture was stirred at 0°C for another 30 minutes. The reaction was then diluted with EtOAc and quenched with saturated aqueous $NaHCO_3$. The organic phase was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography (hexanes/EtOAc 8:2 to 7:3) to afford the desired product **3.2.24** (54 mg, 63% yield).

¹H NMR (400 MHz, $CDCl_3$): δ = 9.74 (t, *J* = 1.0 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.54 (dd, *J* = 9.3, 0.8 Hz, 1H), 5.97 (dd, *J* = 9.3, 6.5 Hz, 1H), 5.87 (dddd, *J* = 10.3, 3.1, 2.2, 1.0 Hz, 1H), 5.28 (ddd, *J* = 10.3, 3.0, 2.2 Hz,

1H), 5.16 (dd, *J* = 6.5, 1.0 Hz, 1H), 4.56-4.50 (m, 1H), 3.86 (s, 3H), 3.25 (dd, *J* = 18.4, 1.0 Hz, 1H), 3.04-3.00 (m, 1H), 2.85 (d, *J* = 18.4 Hz, 1H), 2.76 (d, *J* = 10.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 201.0 (CH), 146.3 (C), 144.3 (C), 132.8 (CH), 129.2 (CH), 128.0 (C), 127.2 (CH), 125.6 (CH), 123.7 (C), 118.2 (CH), 112.7 (CH), 90.9 (CH), 65.7 (CH), 56.2 (CH_3), 49.5 (CH_2), 43.4 (C), 37.0 (CH). **IR** (neat, cm^{-1}): 3462, 2924, 1717, 1507, 1284, 1272, 1050, 798. **HRMS** (EI): m/z calc'd for $C_{12}H_{12}O_4$ [M^+] 284.1049, found 284.1066.



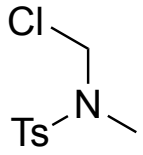
5-Methoxy-3a^1-(2-(methylamino)ethyl)-3,3a,3a^1,9a-tetrahydrophenanthro[4,5-*bcd*]furan-3-ol

Compound 3.2.1

To a solution of the aldehyde **3.2.24** (16 mg, 0.07 mmol, 1 eq.) in dry MeOH (4 mL) was added dropwise methylamine (33 wt.% solution in EtOH, 46 μL, 0.44 mmol, 6.5 equiv.) under argon. The reaction mixture was stirred at room temperature under argon. After 2h15, the reaction mixture was cooled to 0 °C and $NaBH_4$ (3.4 mg, 0.09 mmol, 1.3 equiv.) was added in one portion. The resulting mixture was warmed to room temperature. After 50 minutes, the reaction mixture was diluted with CH_2Cl_2 and quenched with water. The organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude amine was purified by flash

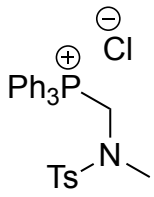
chromatography (MeOH/dichloromethane/ammonium hydroxide 2:8:0 to 2:8:0.1) to afford the secondary amine **3.2.1** (18 mg, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.62 (d, J = 8.0 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 6.49 (d, J = 9.3 Hz, 1H), 5.99 (dd, J = 9.3, 6.5 Hz, 1H), 5.82-5.78 (m, 1H), 5.27 (ddd, J = 10.1, 2.3, 2.3 Hz, 1H), 5.15 (dd, J = 6.5, 0.9 Hz, 1H), 4.23-4.20 (m, 1H), 3.84 (s, 3H), 2.82-2.79 (m, 1H), 2.70 (ddd, J = 11.1, 10.9, 5.1 Hz, 1H), 2.42 (ddd, J = 11.1, 10.9, 5.1 Hz, 1H), 2.45-2.38 (br, 1H), 2.35 (s, 3H), 2.18-2.09 (m, 1H), 1.86 (ddd, J = 13.8, 10.9, 5.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): 146.3 (C), 143.9 (C), 132.2 (CH), 129.3 (CH), 129.2 (C), 127.7 (CH), 125.2 (CH), 123.9 (C), 117.9 (CH), 112.16 (CH), 90.2 (CH), 66.2 (CH), 56.1 (CH_3), 48.0 (CH_2), 45.5 (C), 37.8 (CH), 36.5 (CH_3), 36.0 (CH_2). **IR** (neat, cm^{-1}): 3332, 2970, 2360, 2343, 1380, 1307, 1161, 1128, 1108, 951, 817, 677. **HRMS** (EI): m/z calc'd for $C_{12}H_{12}O_4$ [M^+] 299.1521, found 299.1535.



N-Chloromethyl-N-methyl-4-methylbenzenesulfonamide

In a dry sealed tube was added N-methyl-p-toluenesulfonylamide (5.39 mmol, 1.0 eq.) and paraformaldehyde (6.47 mmol, 1.2 eq.) in trimethylsilyl chloride (17.4 mL). The reaction was heated at 60°C for 12 hours, cooled down to room temperature, and concentrated under vacuum to afford the desired product in quantitative yield. Spectroscopic data recorded were consistent with that previously reported.[4]



(((*N*,4-Dimethylphenyl)sulfonamido)methyl)triphenylphosphonium chloride

Compound 3.2.22

To a solution of triphenylphosphine (4.37 mmol, 1.1 eq.) in anhydrous ether was added N-chloromethyl-N-methyl-4-methylbenzenesulfonamide (3.97 mmol, 1.0 eq.). The reaction mixture was stirred at room temperature for 24 hours. The resulting white slurry was then filtered through a sintered funnel. The collected white solid was washed 3 times with anhydrous ether and dry under high vacuum to afford the phosphonium salt, which was used without any further purification.

6.5 REFERENCES

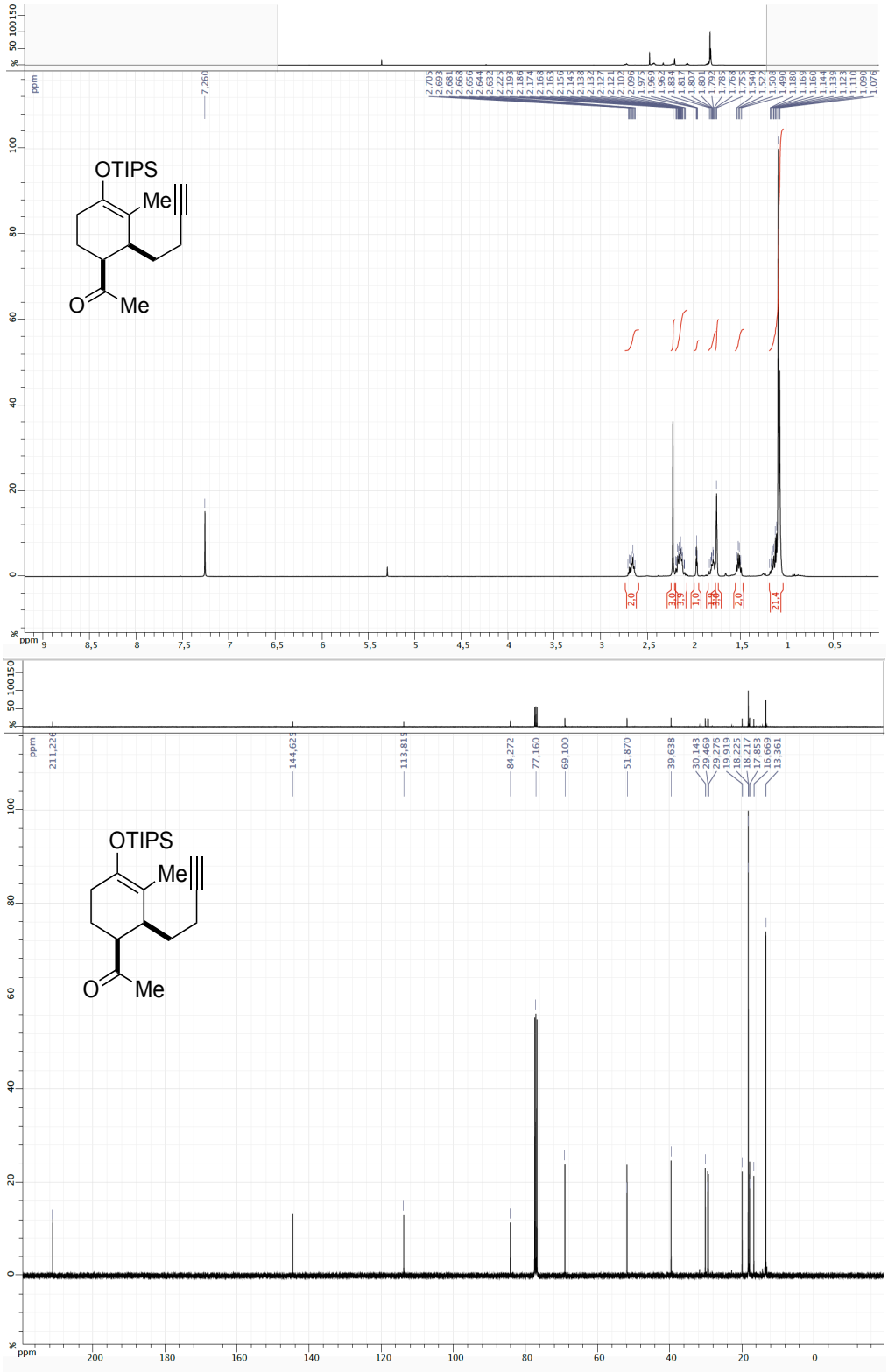
[1] Han, Y.; Zhu, L.; Gao, Y.; Lee, C.-S., *Org. Lett.* **2011**, *13*, 588-591.

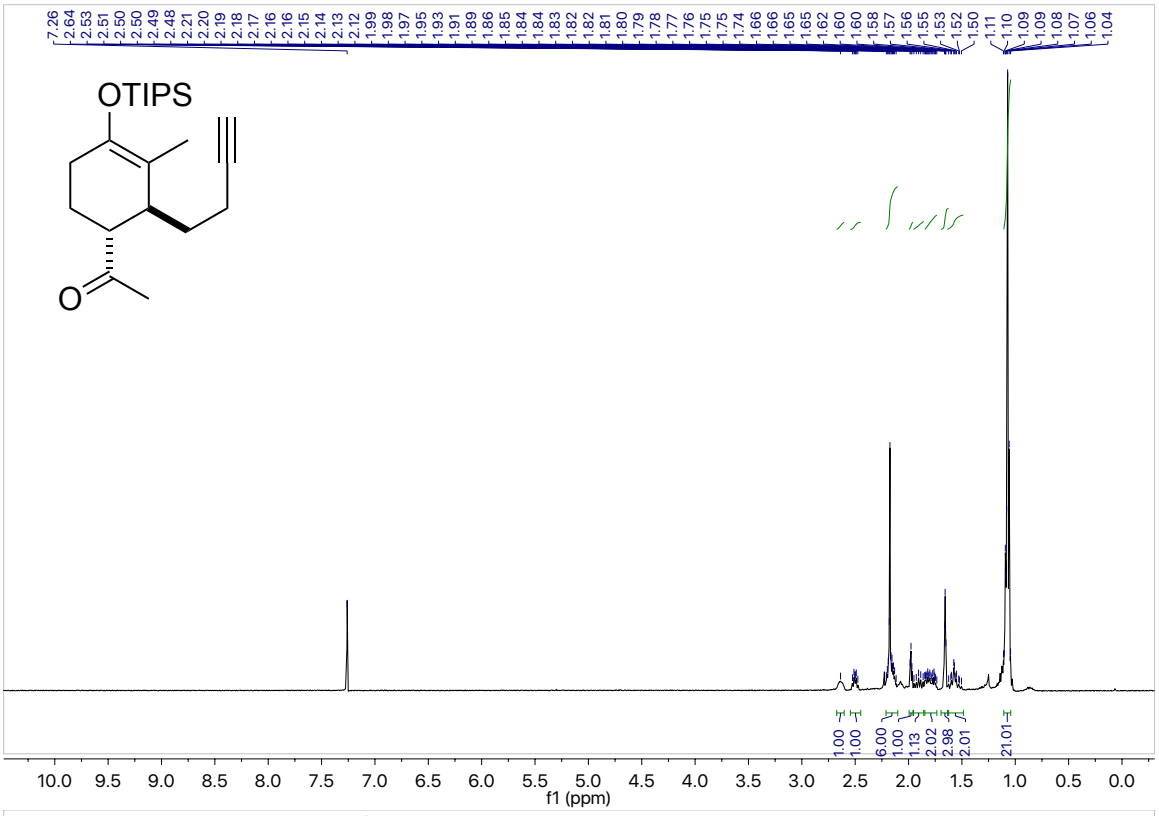
[2] Pérez-Galan, P.; Delpont, N.; Herreo-Gomez, E.; Maseras, F.; Echavarren, A.M., *Chem. Eur. J.* **2010**, *16*, 5324-5332.

[3] Panchal, H.; Clarke, C.; Bell, C.; Karad, S. N.; Lewis, W.; Lam, H. W., *Chem. Commun.* **2018**, *54*, 12389-12392.

[4] Barroso, H.; Moreira, R.; Lopes, F.; Calheiros, T.; Iley, J., *Bioorg. Med. Chem.* **2000**, *8*, 1629-1636.

7 COLLECTIVE SPECTRAL DATA

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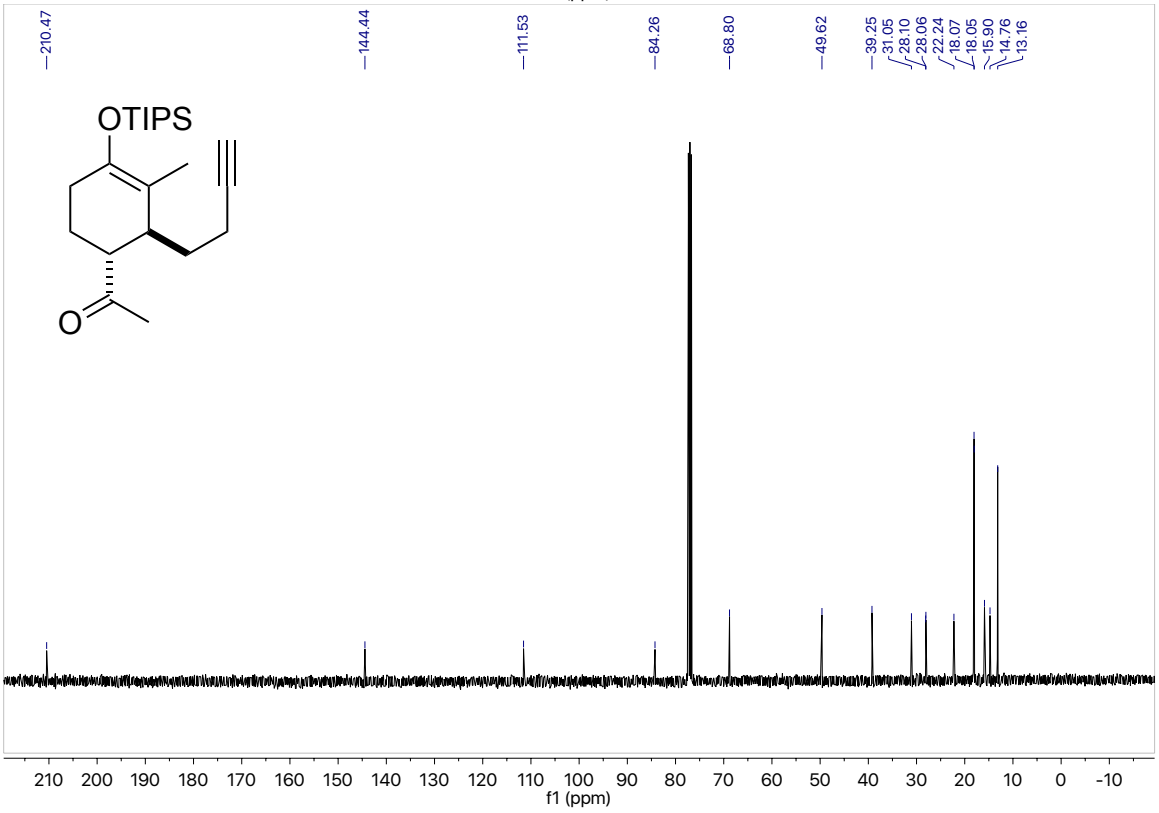
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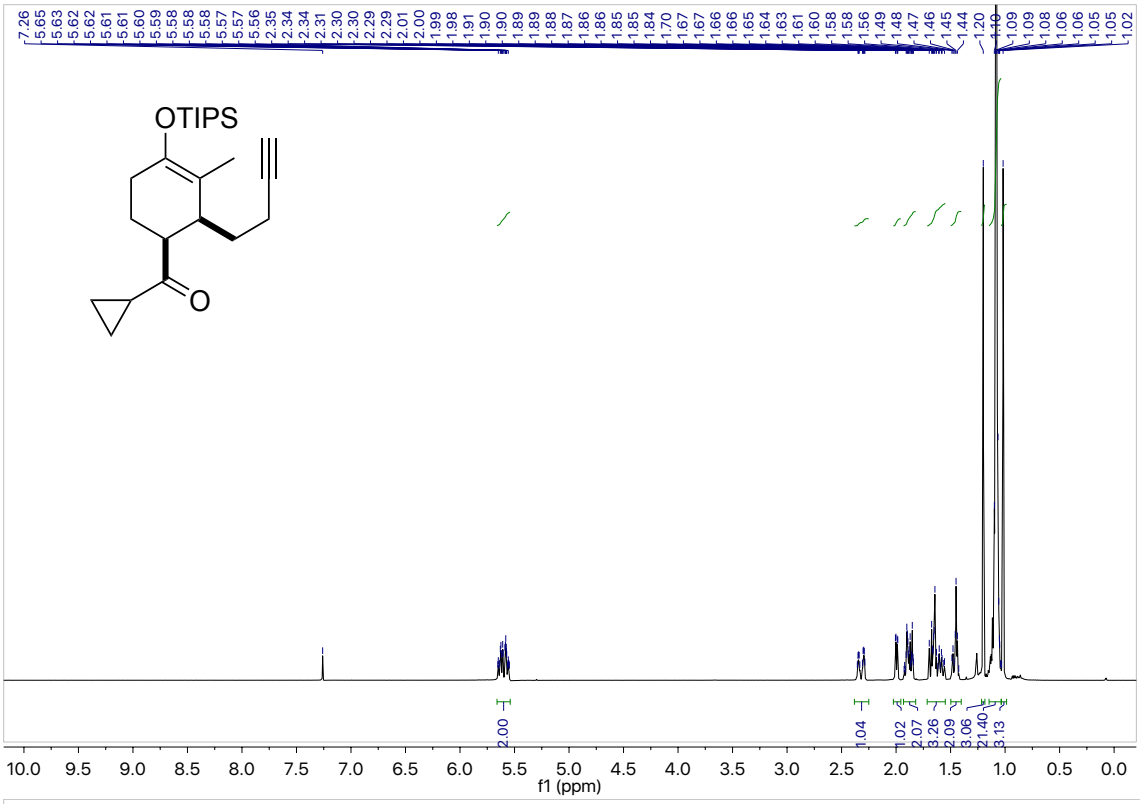
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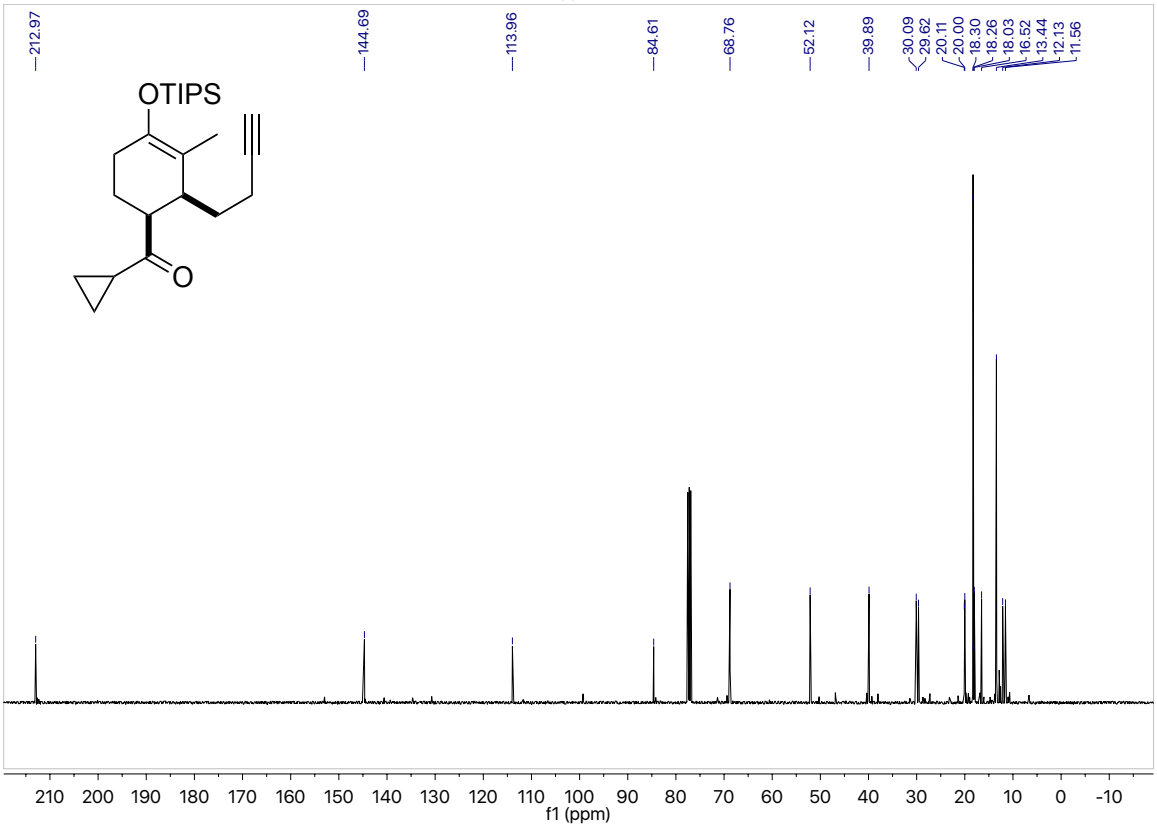
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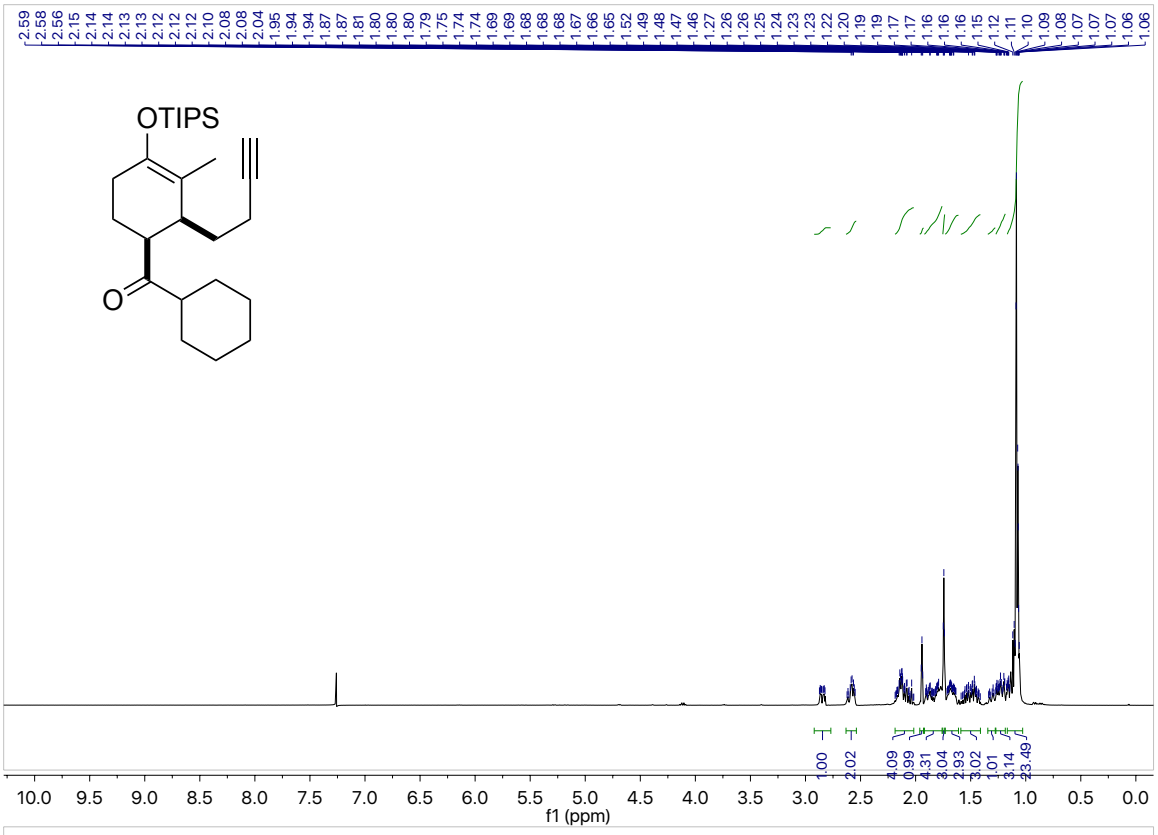
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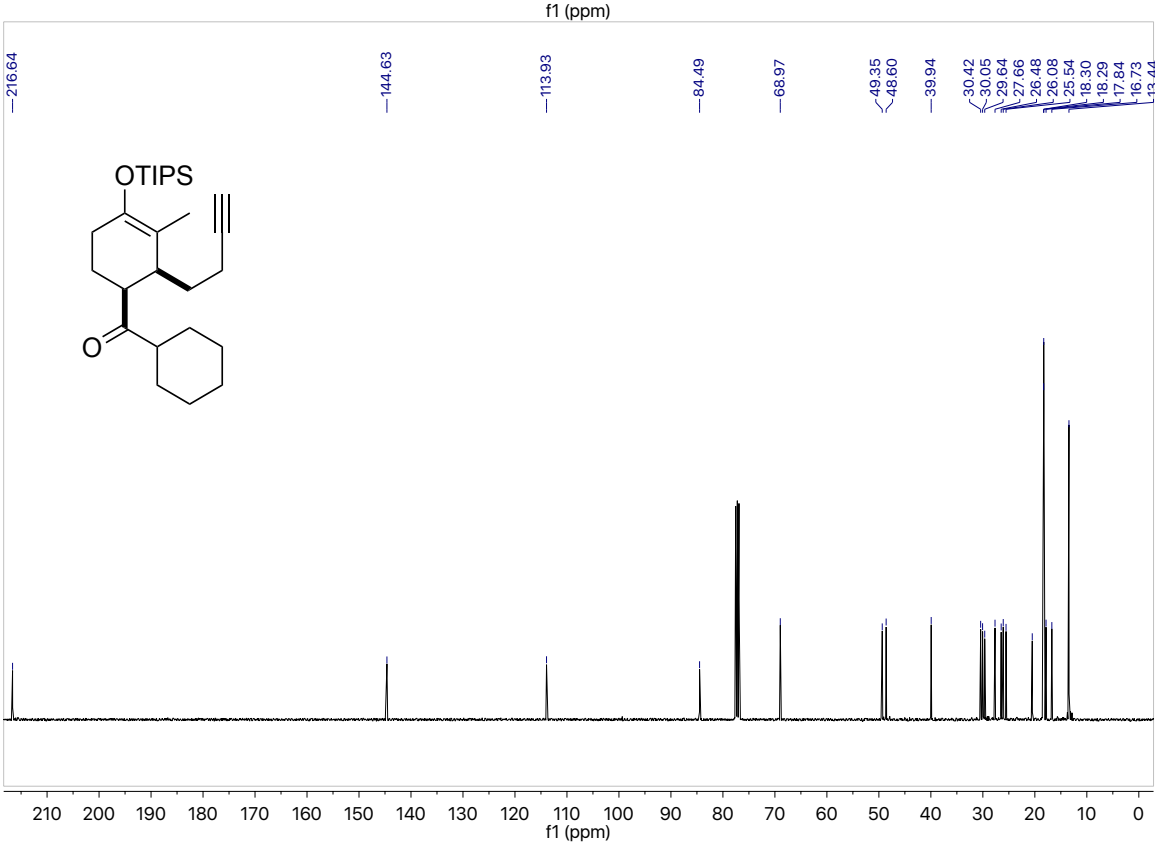
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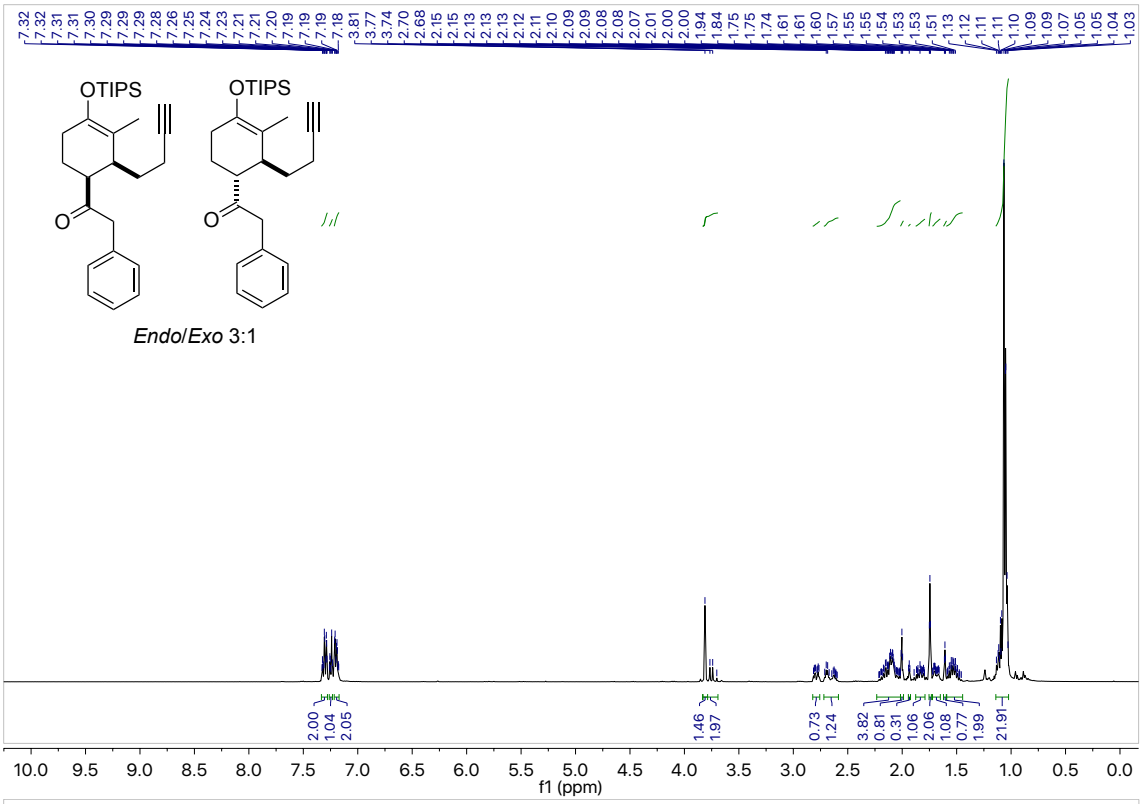
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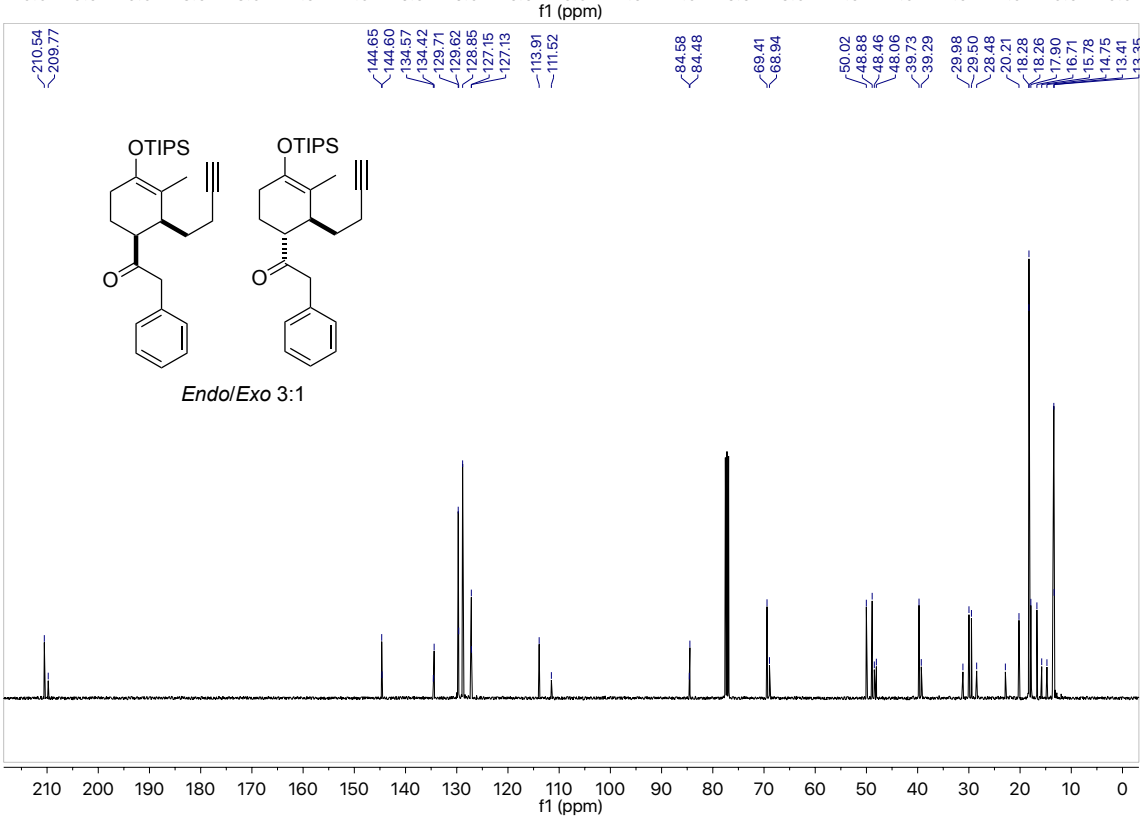
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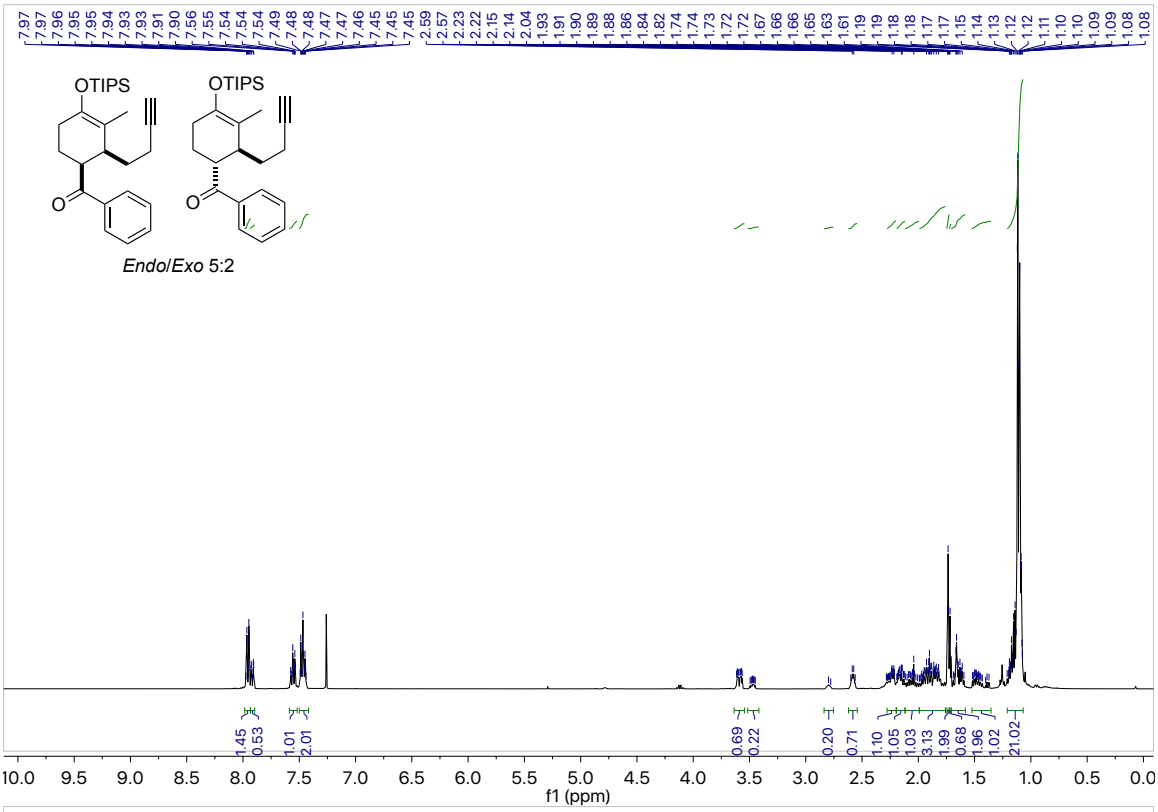
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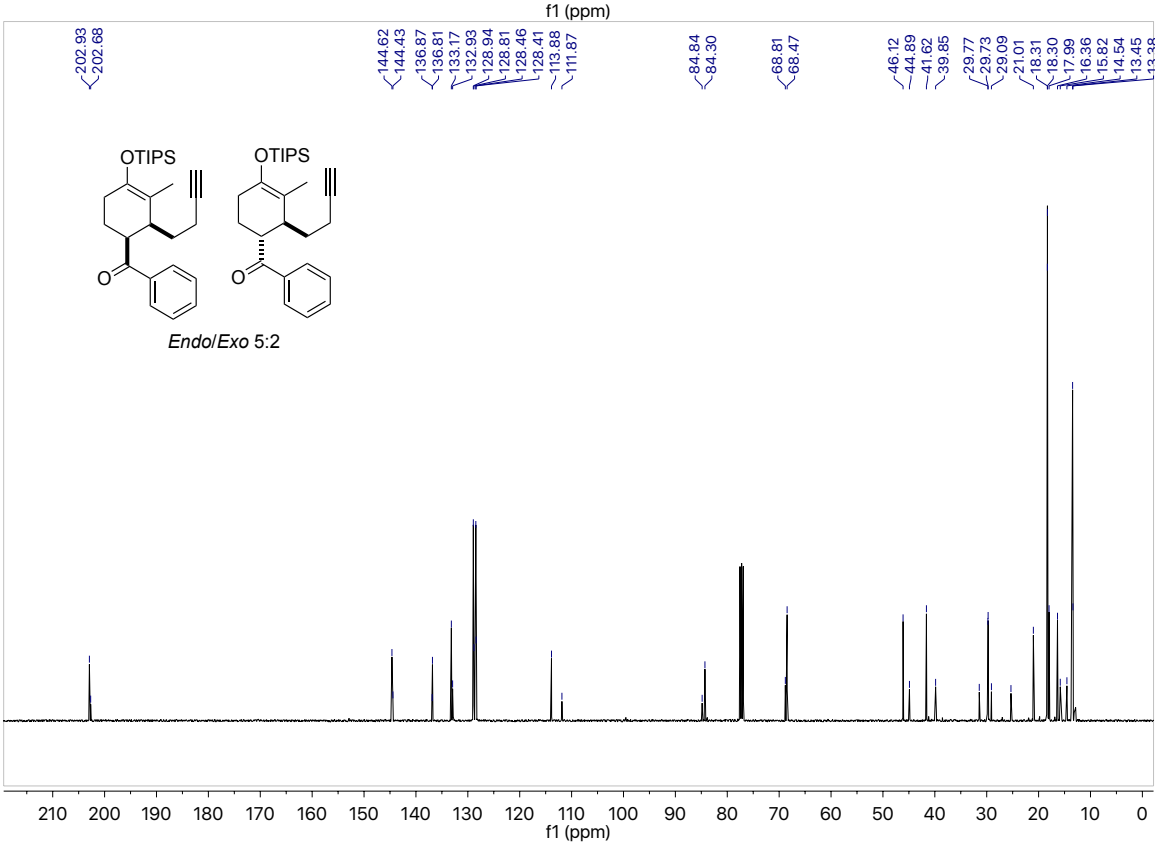
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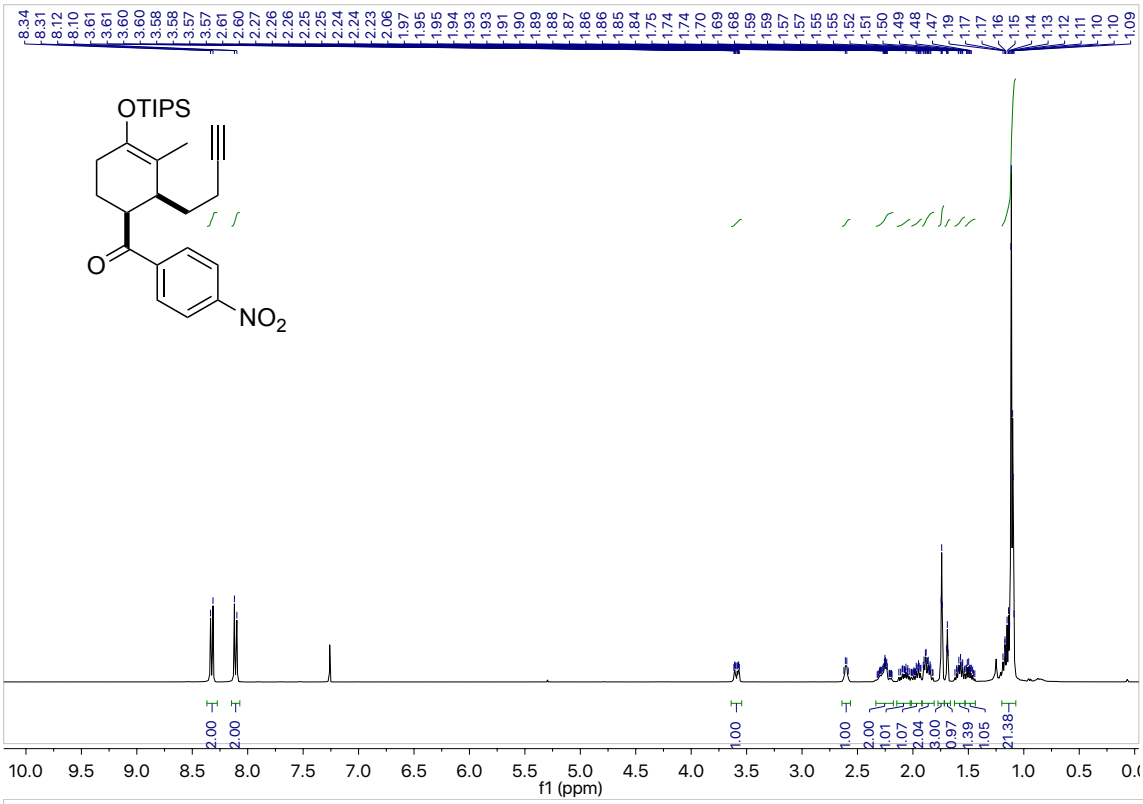
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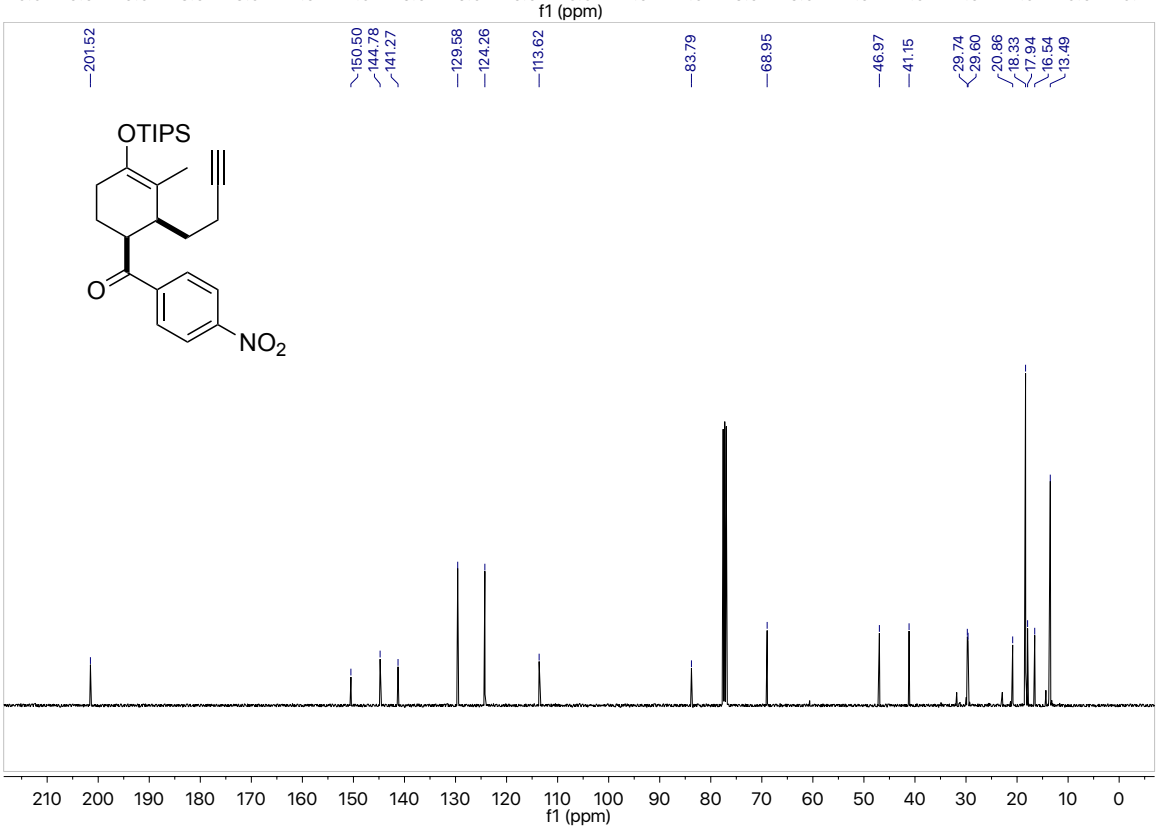
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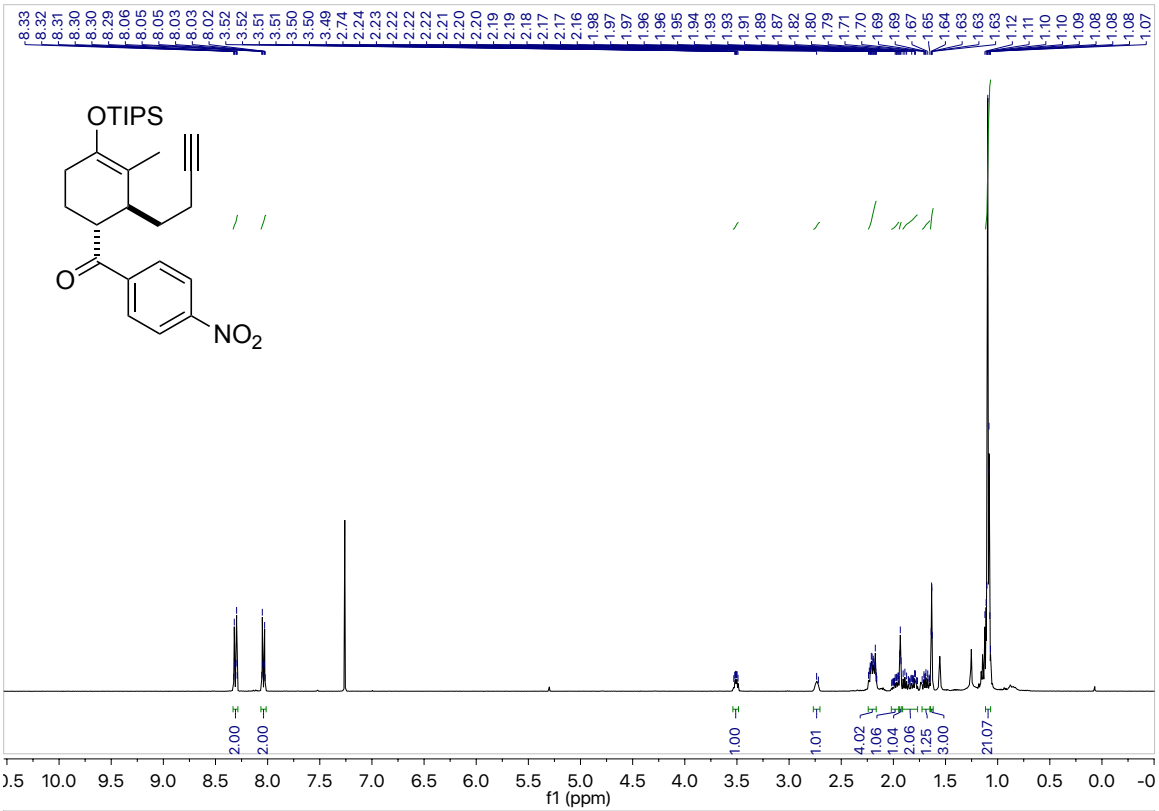
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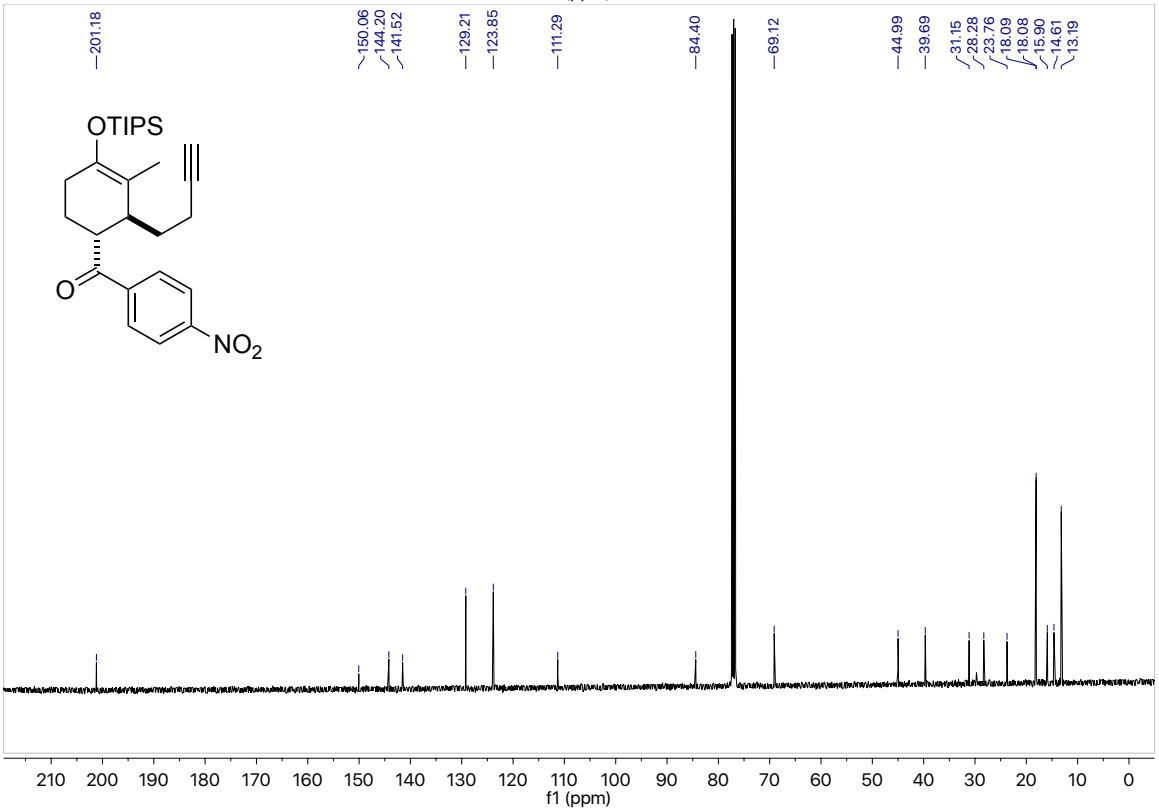
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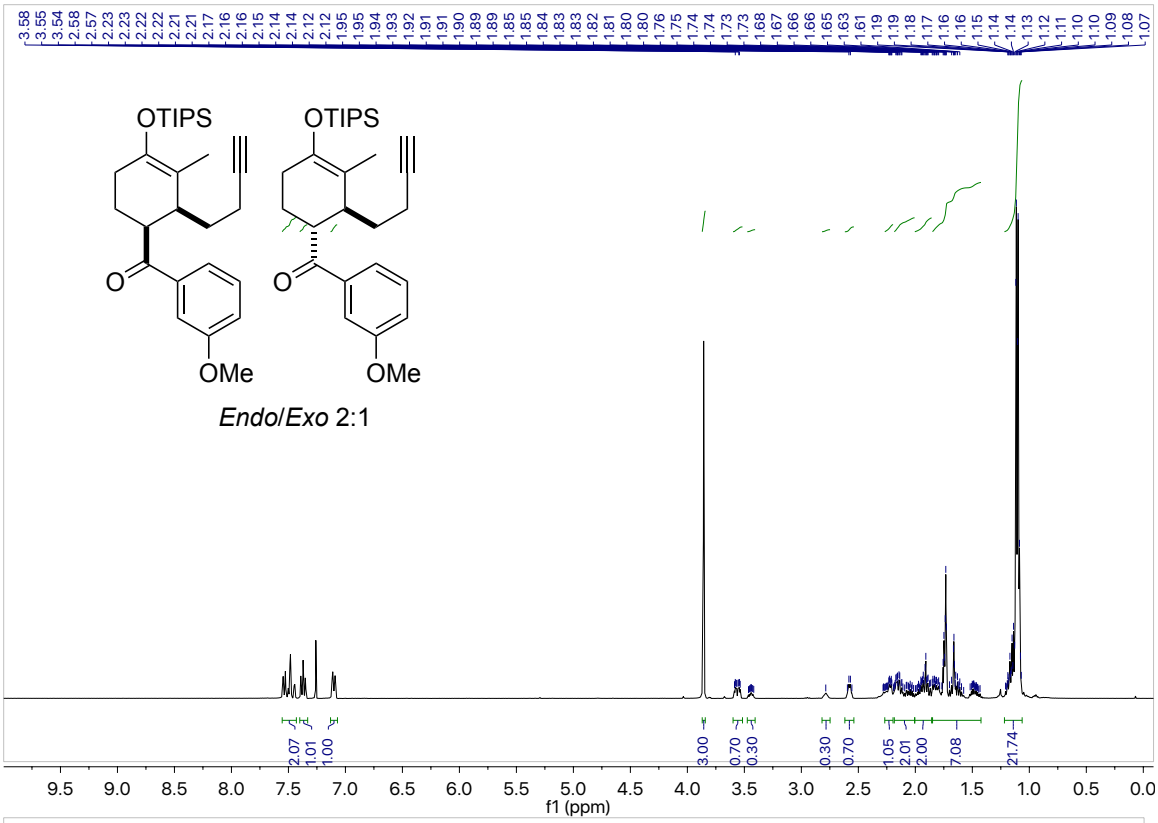
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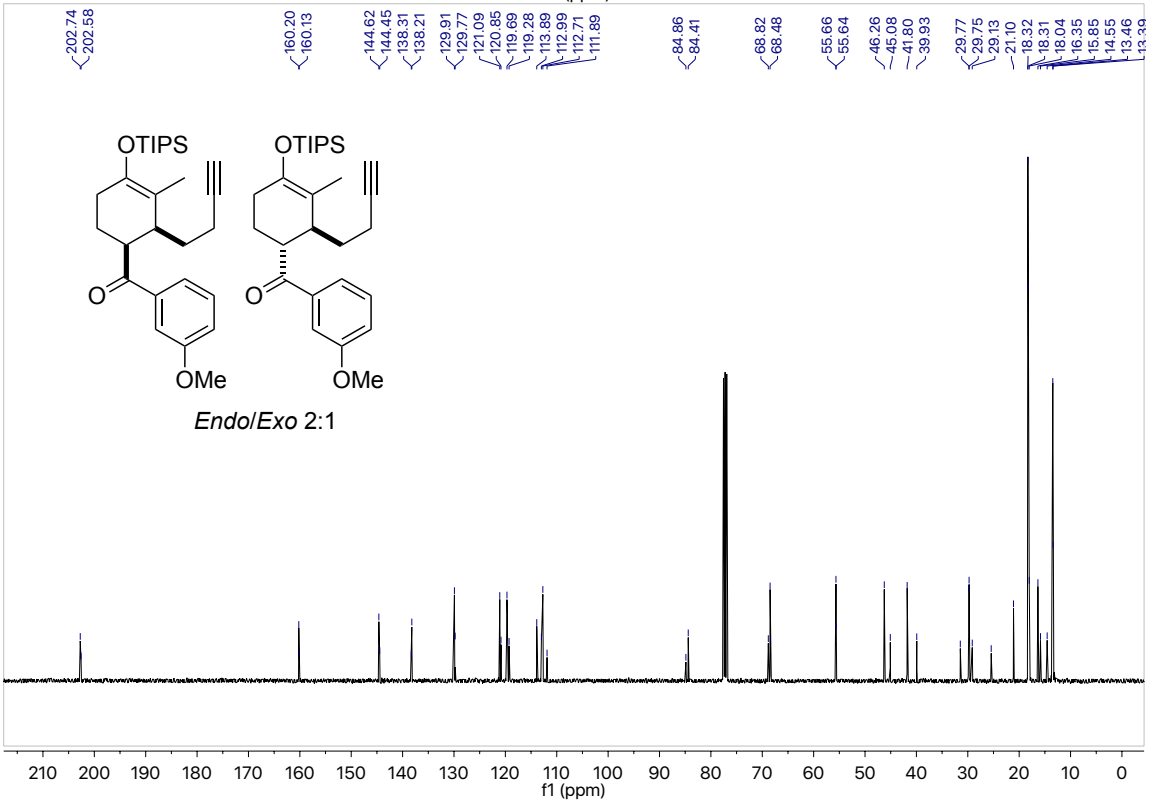
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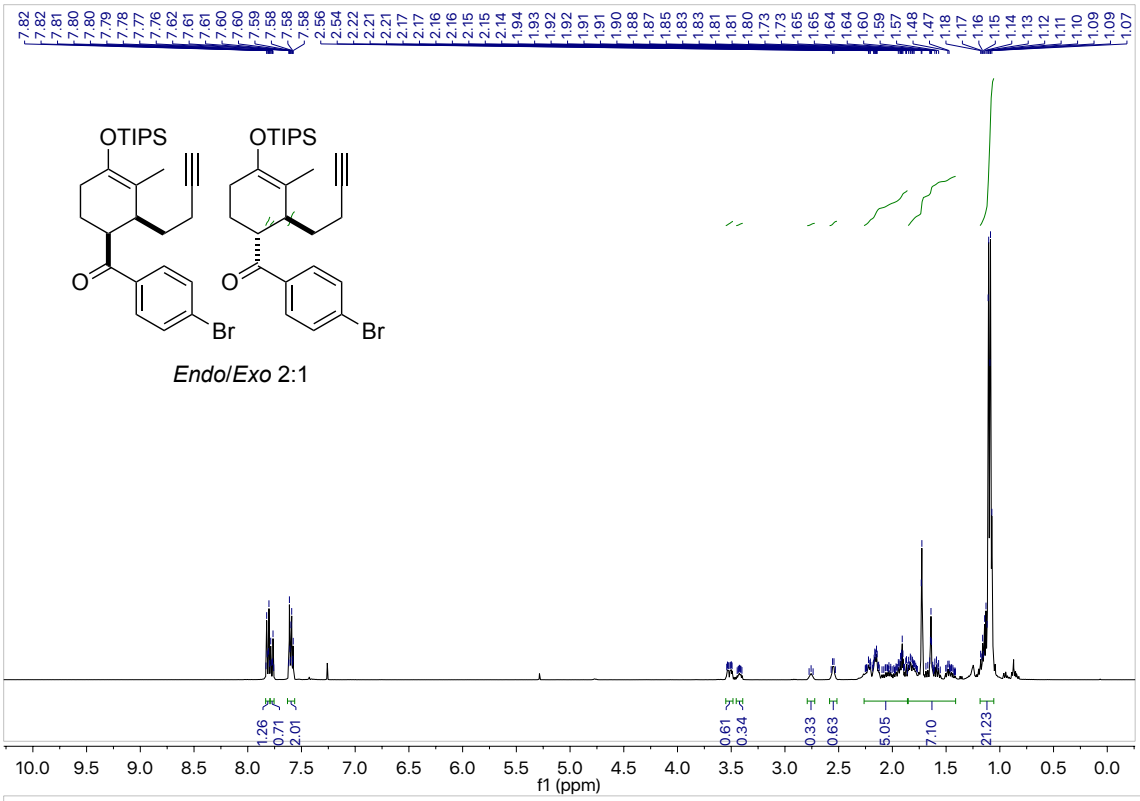
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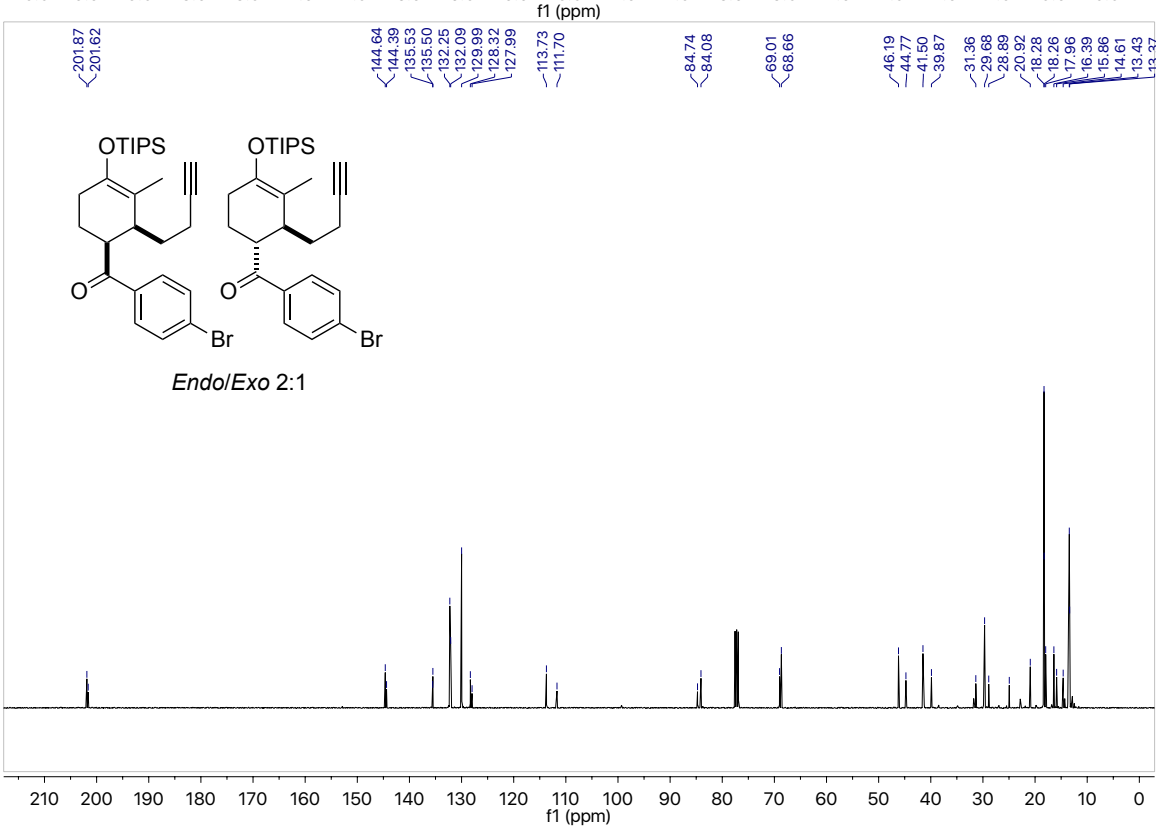
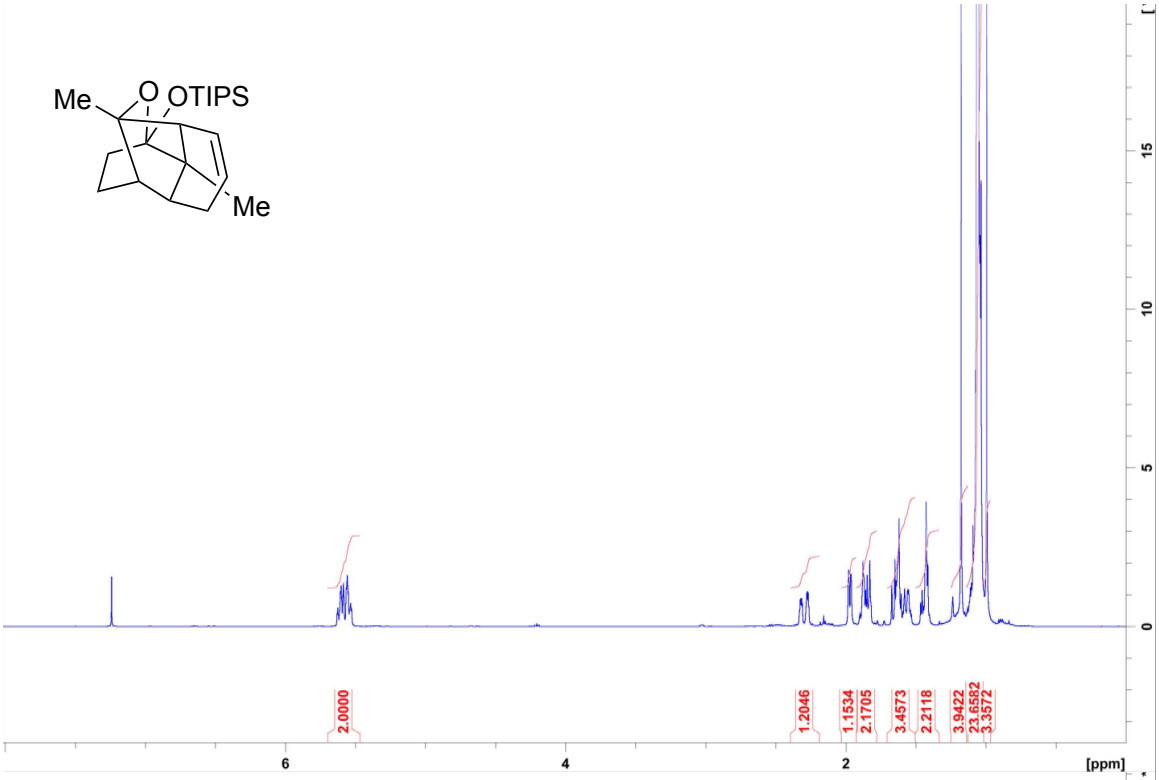
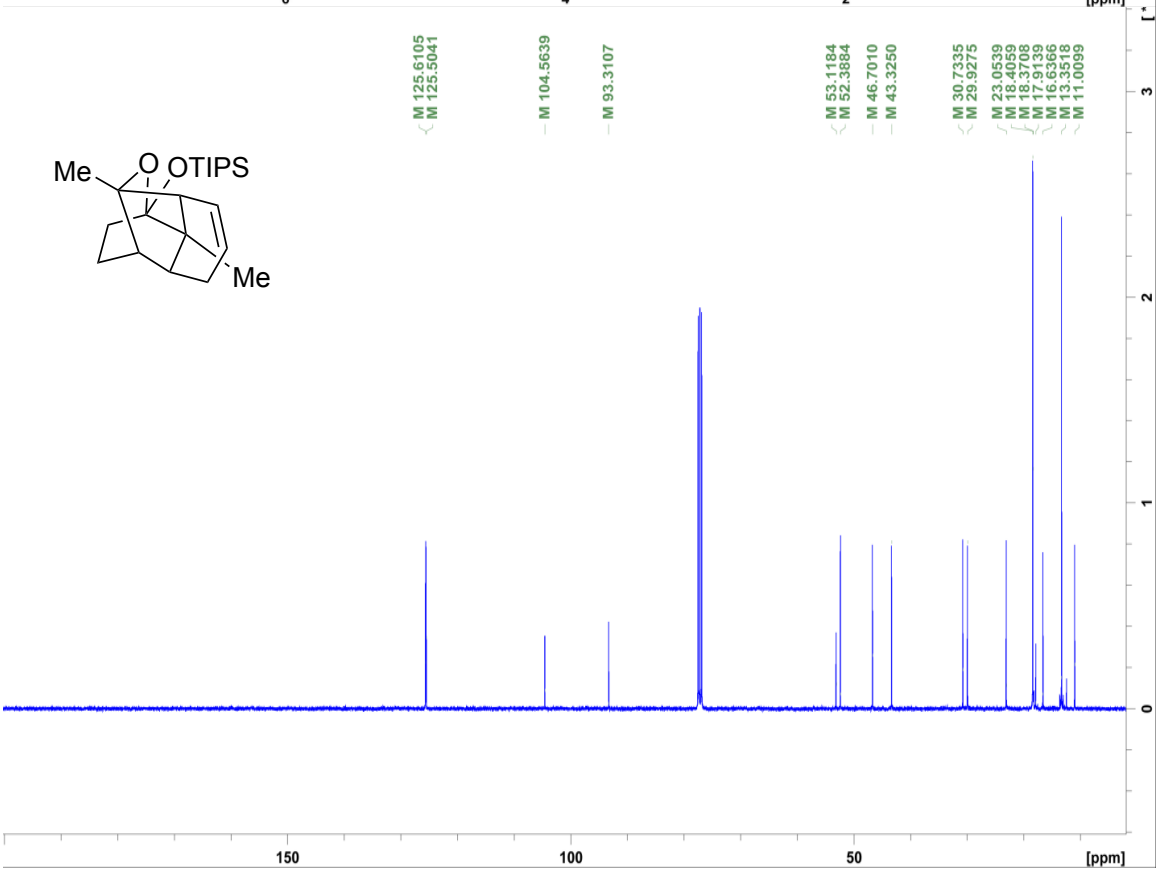
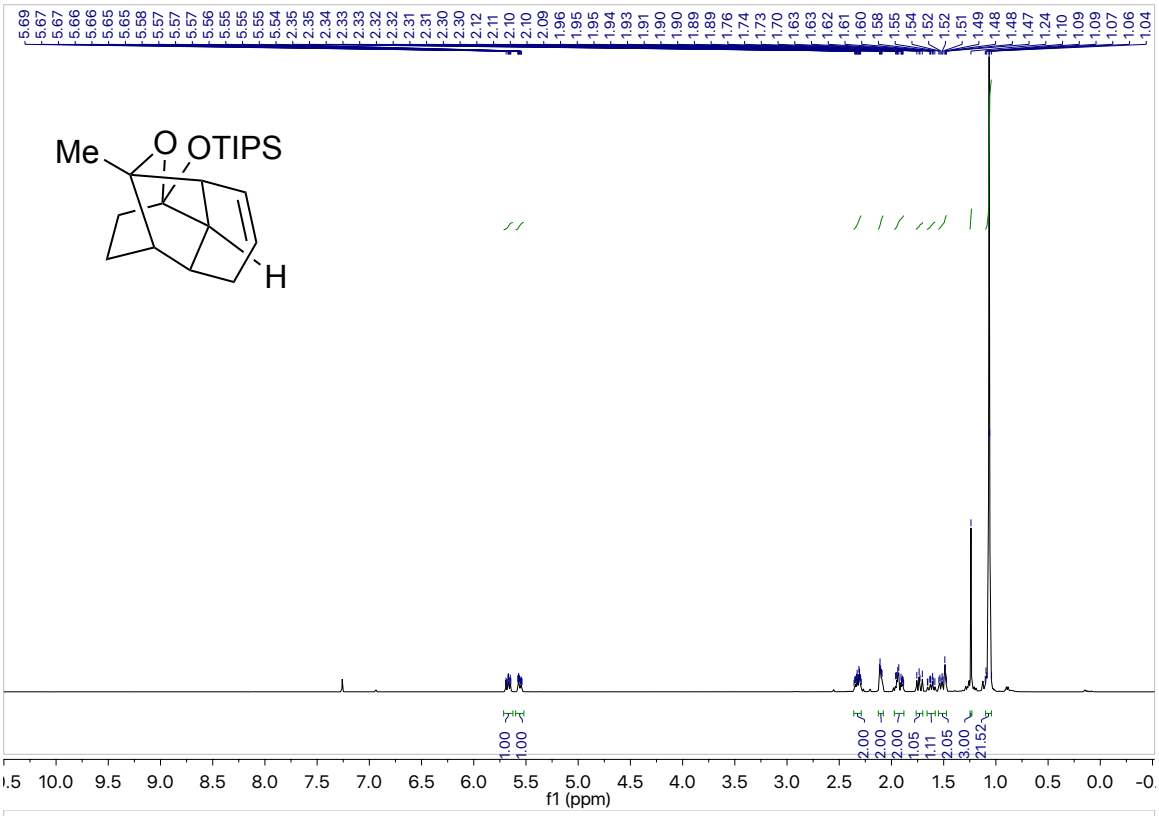
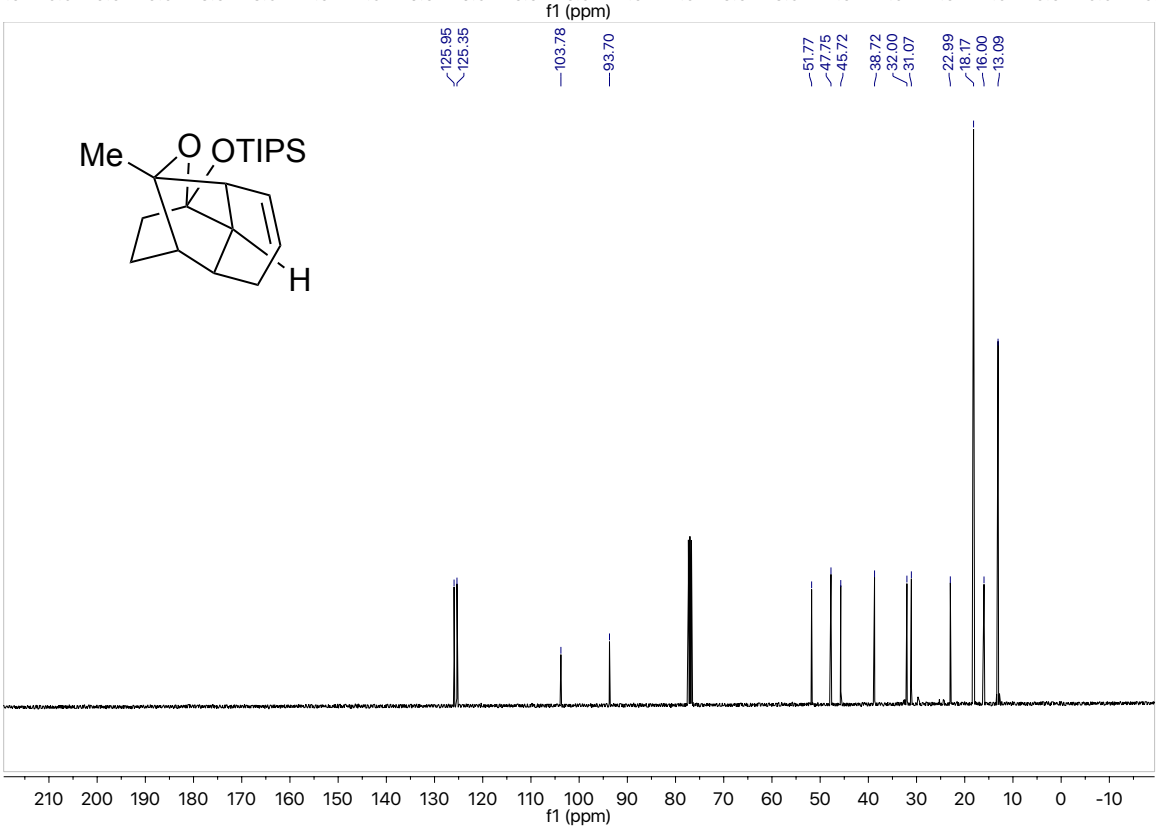
f1 (ppm)

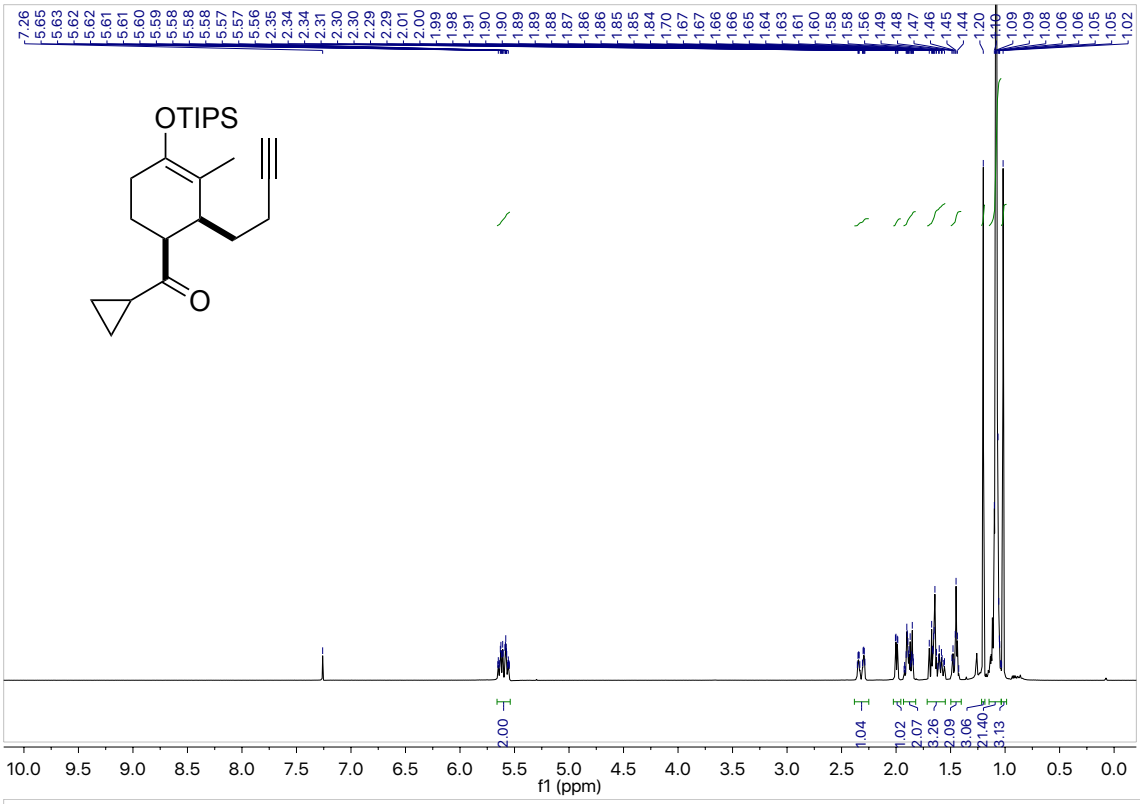

OTIPS
OTIPS
O
O
Br
Br
Endo/Exo 2:1
f1 (ppm)

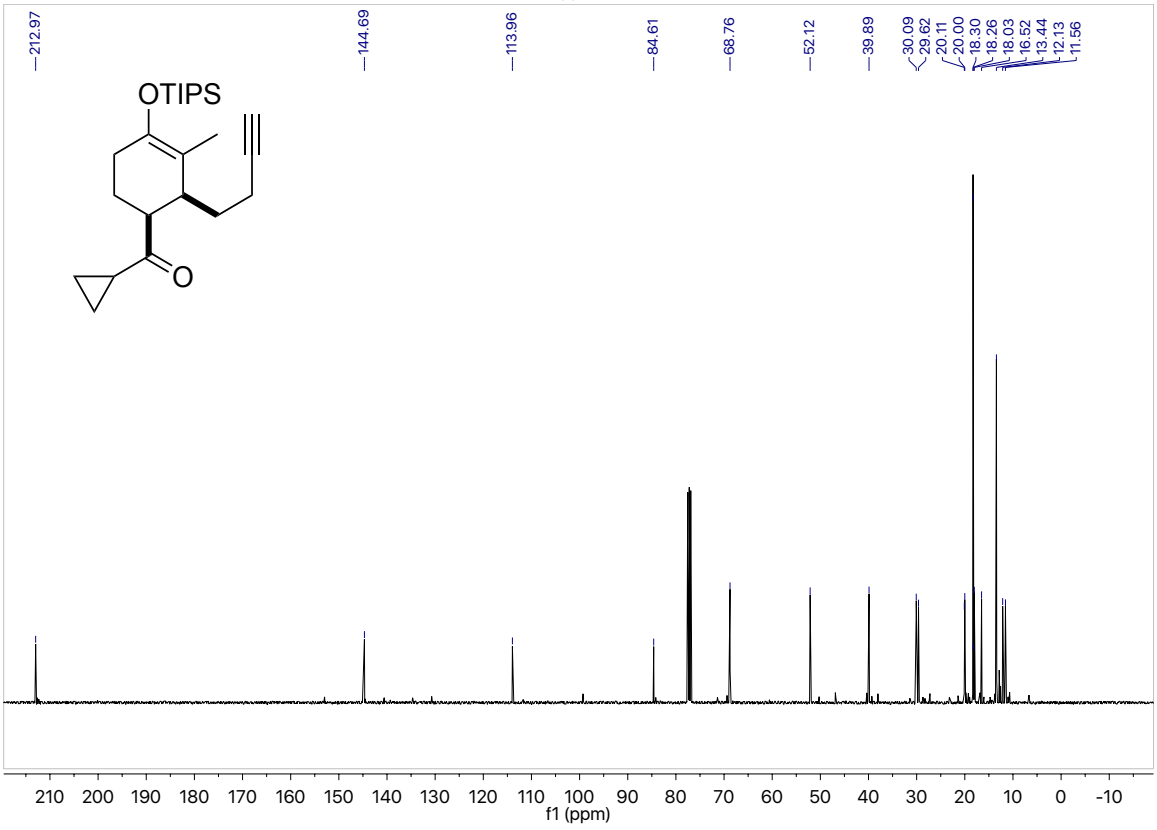

Me
O
OTIPS
Me
2.0000
1.2046
1.1534
2.1705
3.4573
2.2118
3.9422
23.6582
3.3572
6
4
2
[ppm]

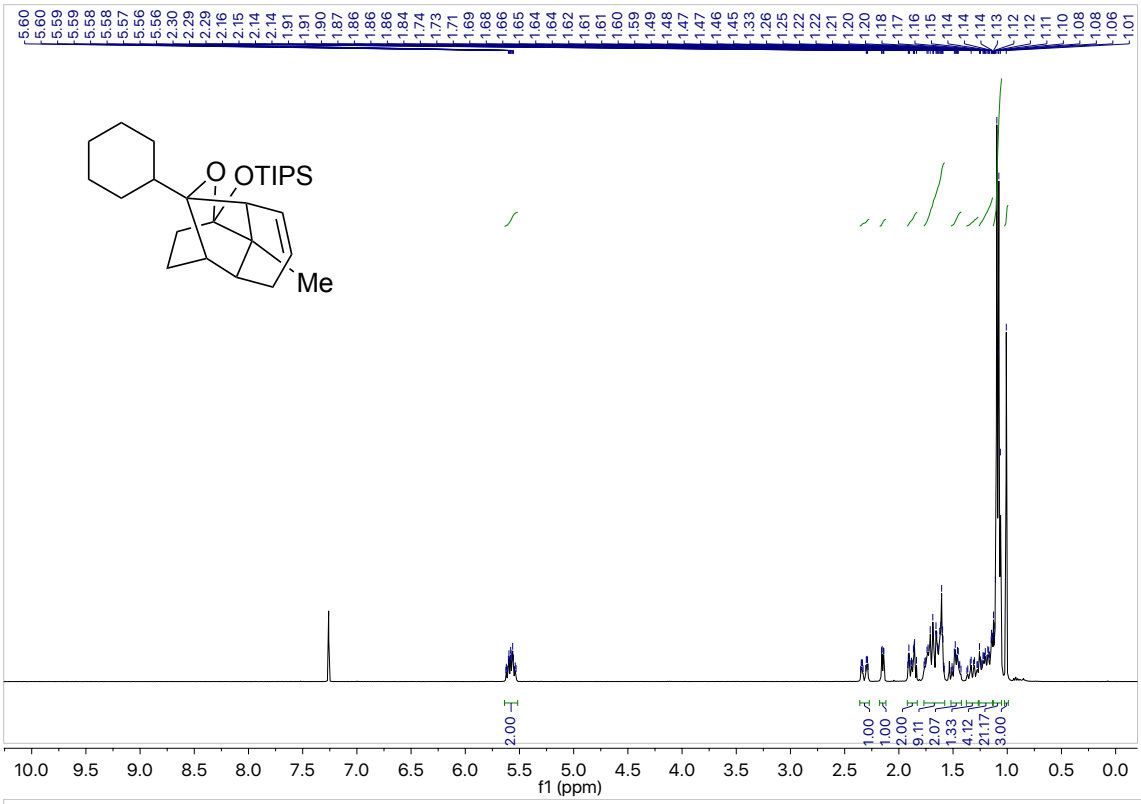

Me
O
OTIPS
Me
M 125.6105
M 125.5041
M 104.5639
M 93.3107
M 53.1184
M 52.3884
M 46.7010
M 43.3250
M 30.7335
M 29.9275
M 23.0539
M 18.4059
M 18.3708
M 17.8139
M 17.6366
M 13.3518
M 11.0099
150
100
50
[ppm]

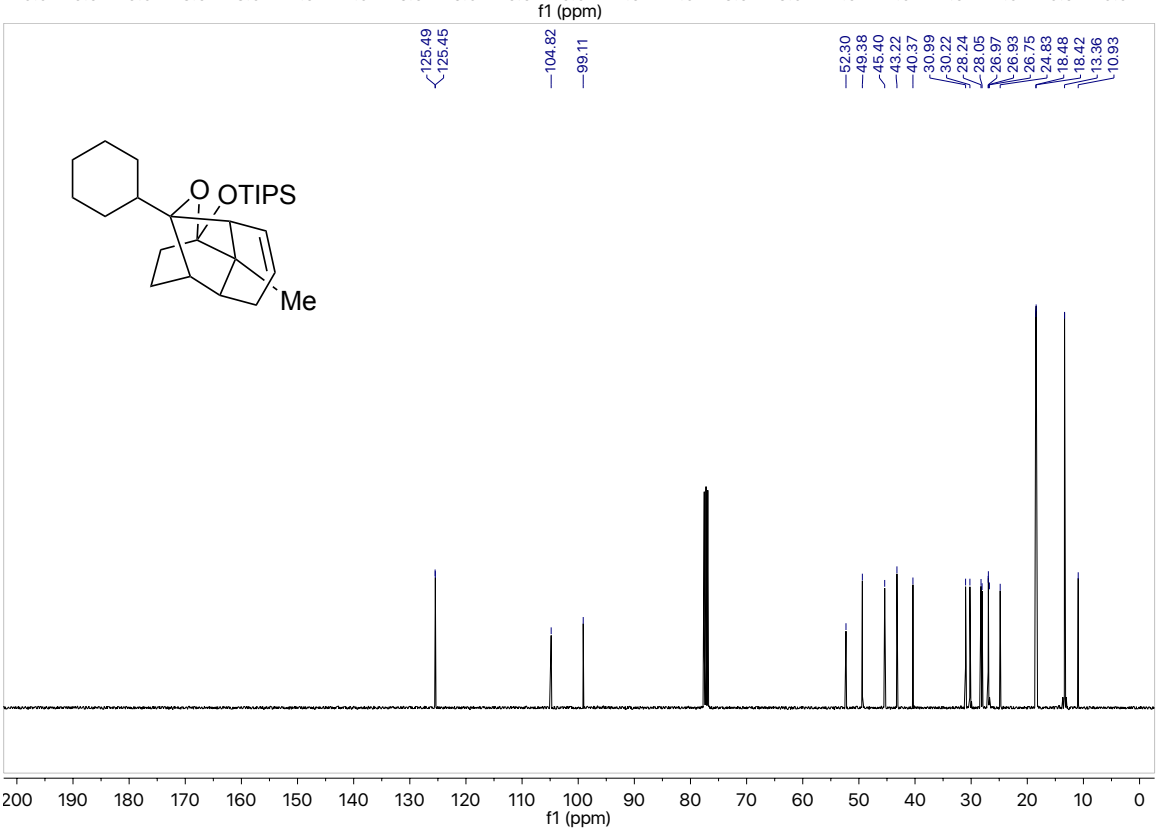

Me
O
OTIPS
H
f1 (ppm)

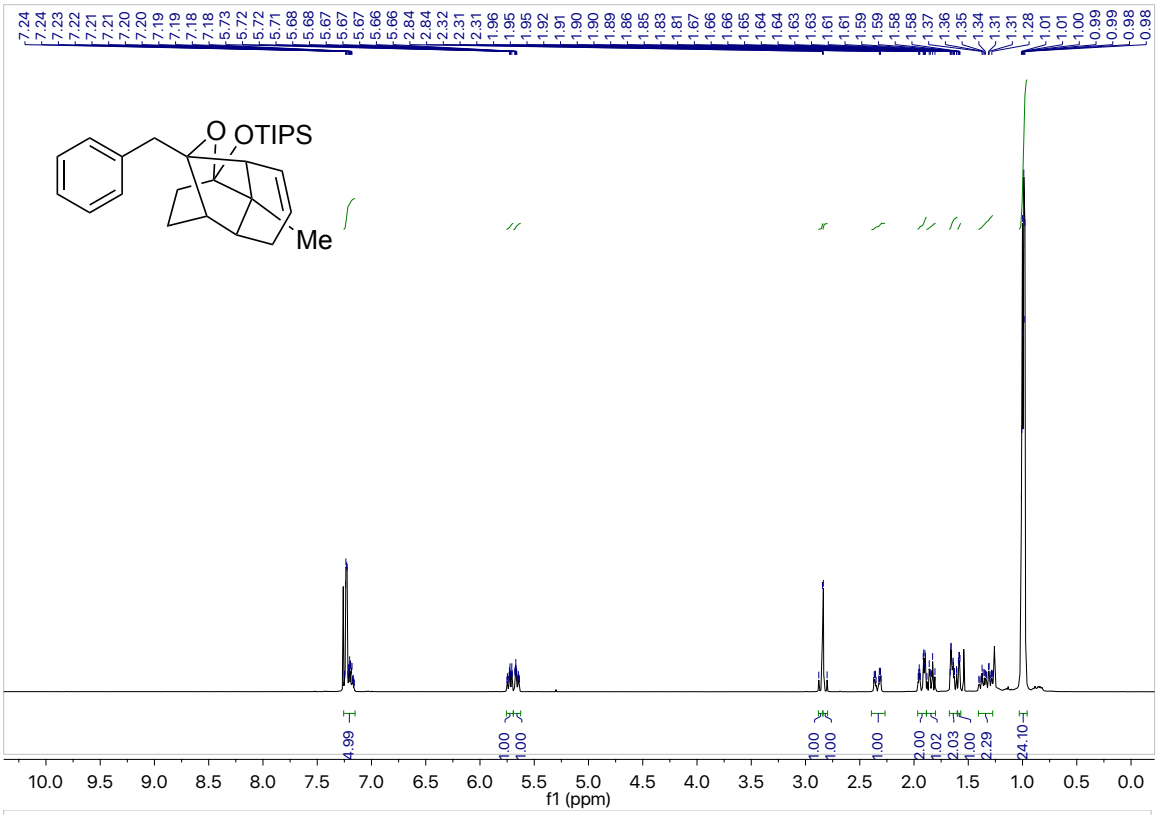

Me
O
OTIPS
H
f1 (ppm)

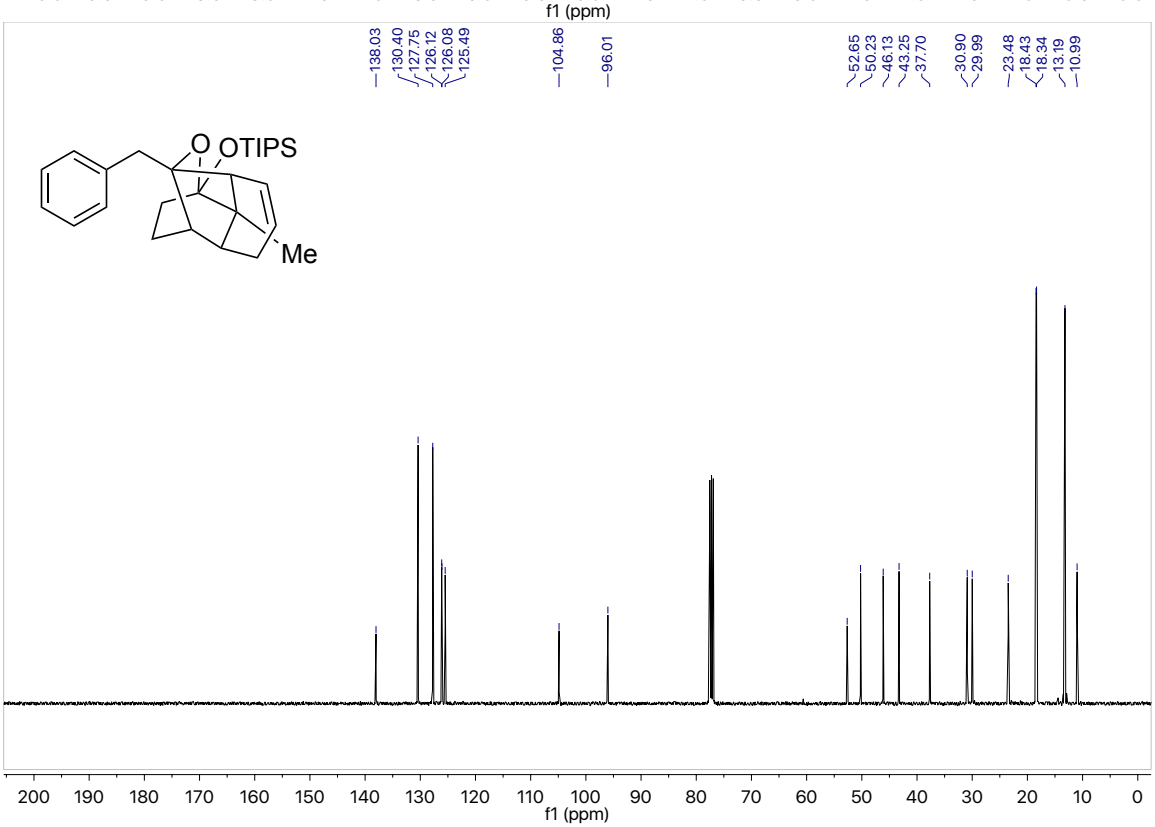

OTIPS
O
f1 (ppm)

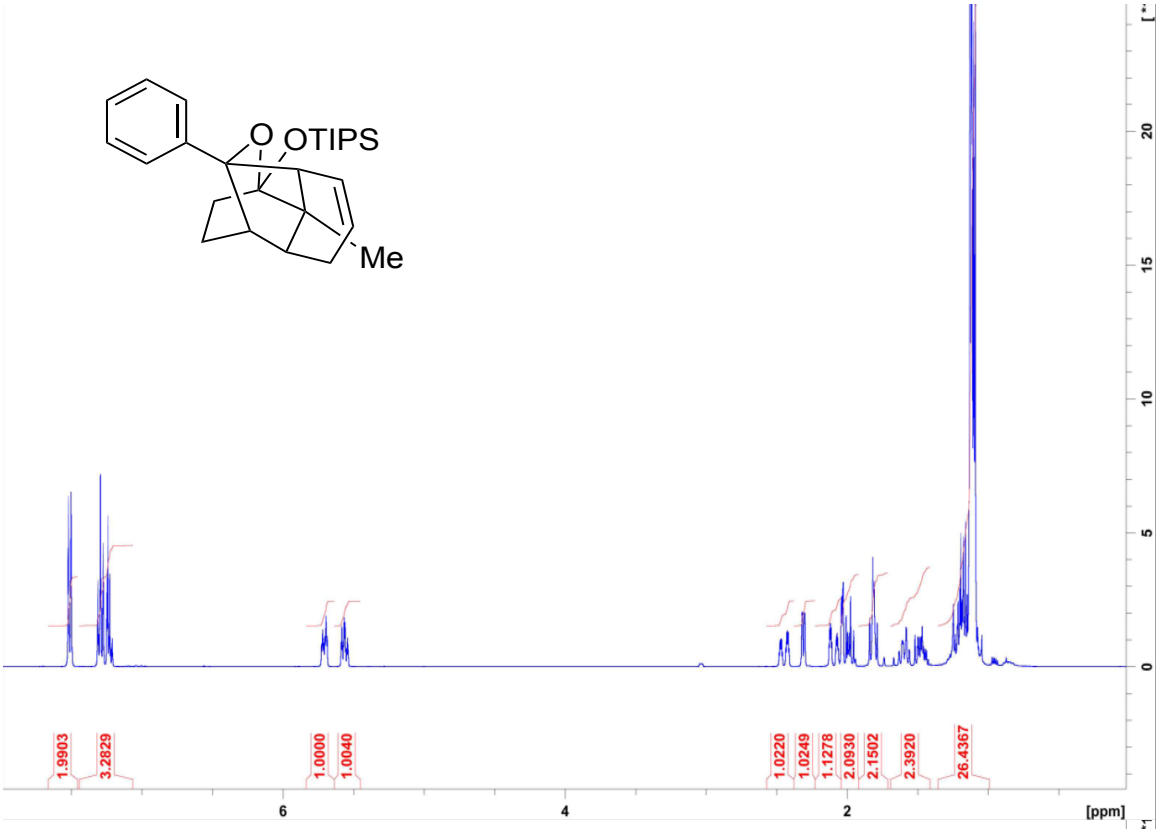

OTIPS
O
f1 (ppm)

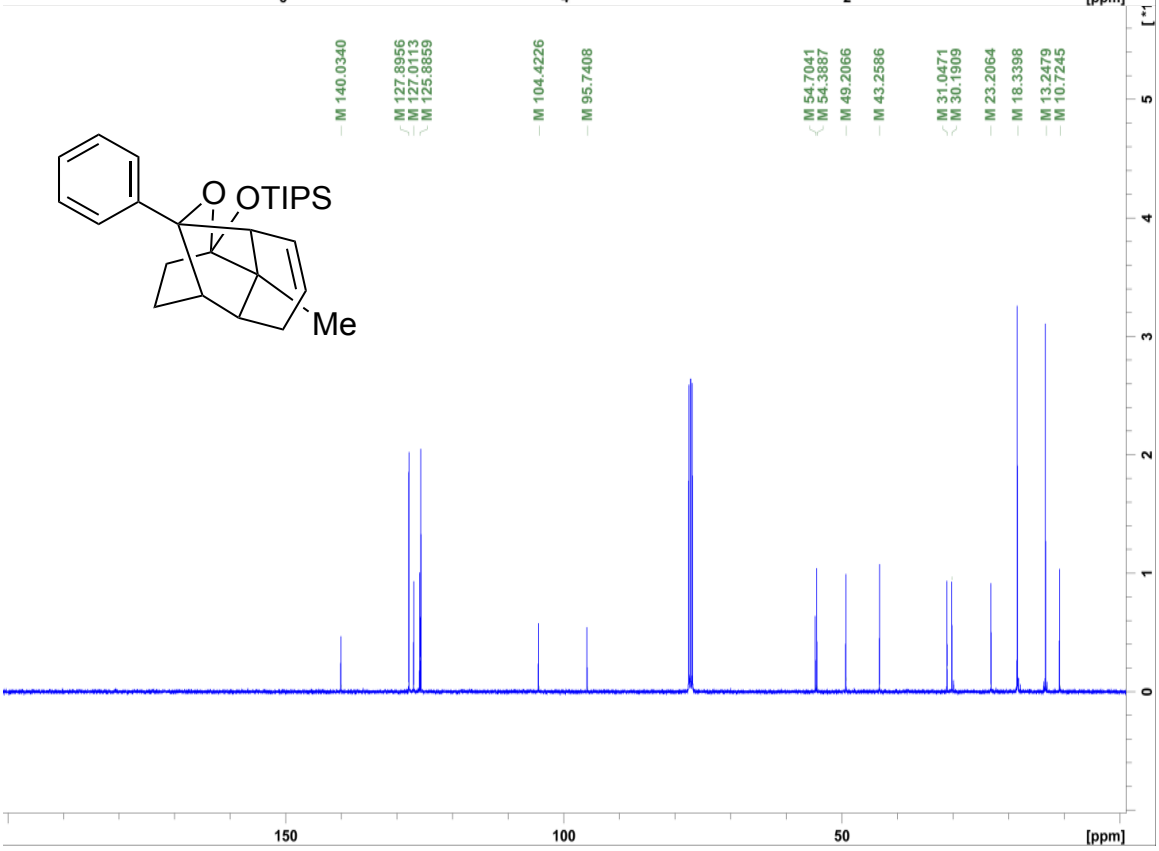

O OTIPS
Me
f1 (ppm)

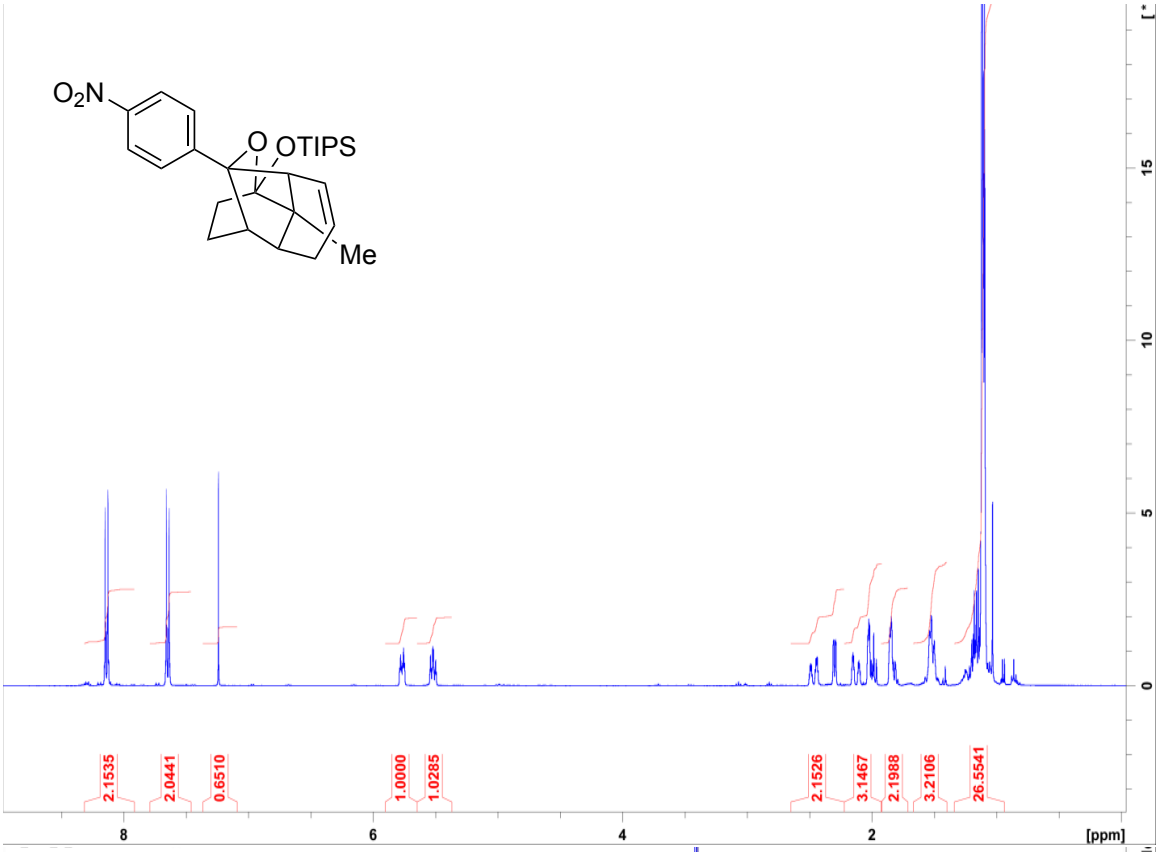

O OTIPS
Me
f1 (ppm)

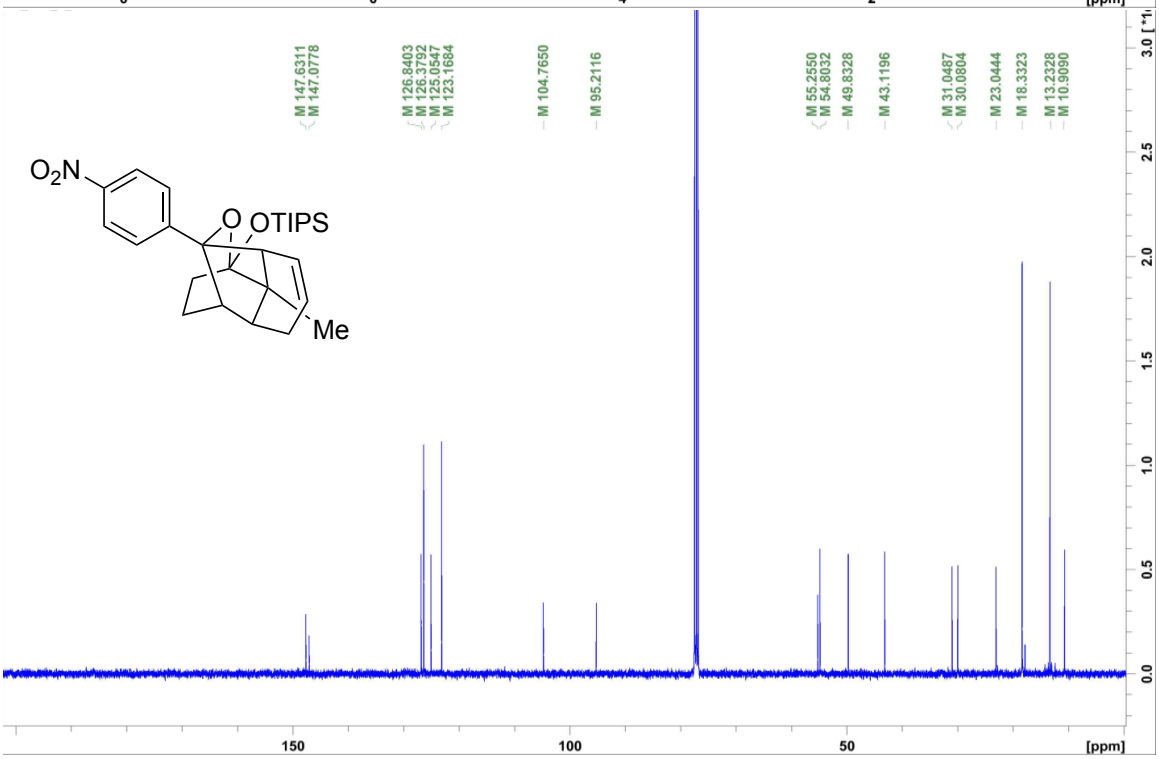

O OTIPS
Me
f1 (ppm)

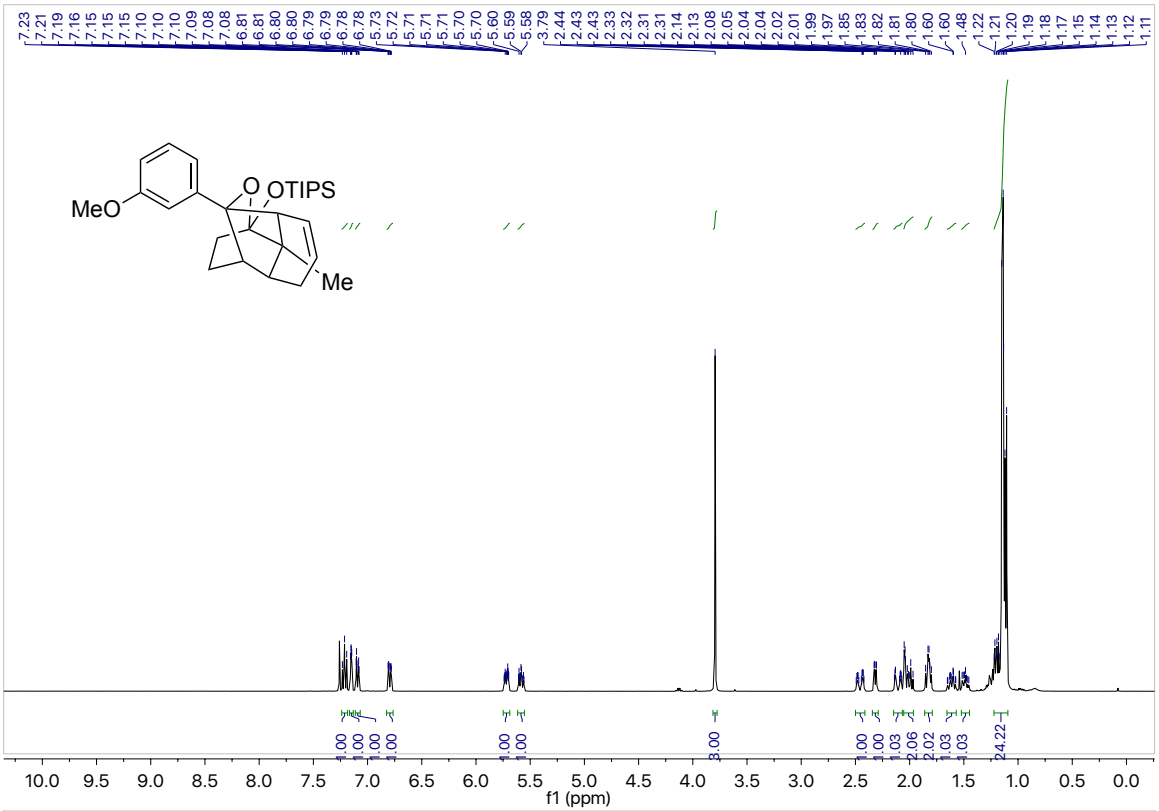

O OTIPS
Me
f1 (ppm)

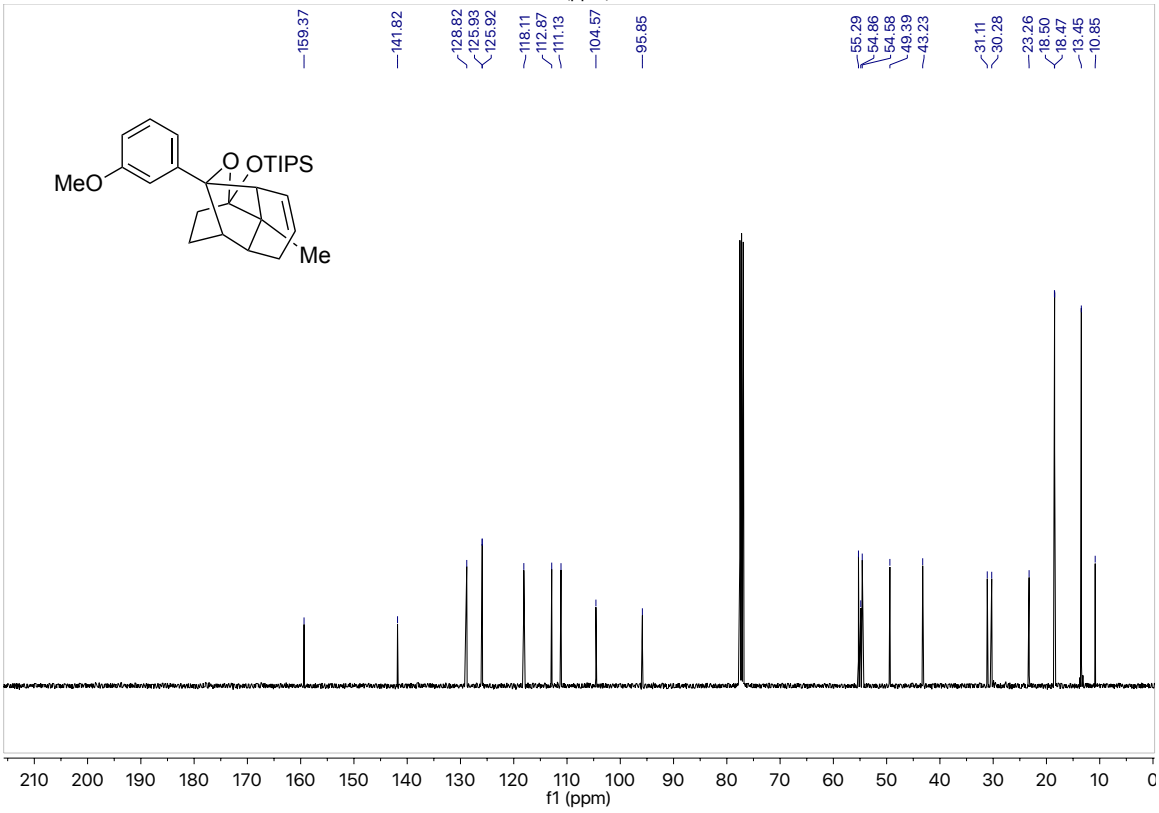

O OTIPS
Me
1.9903
3.2829
1.0000
1.0040
1.0220
1.0249
1.1278
2.0930
2.1502
2.3920
26.4367
6
4
2
[ppm]

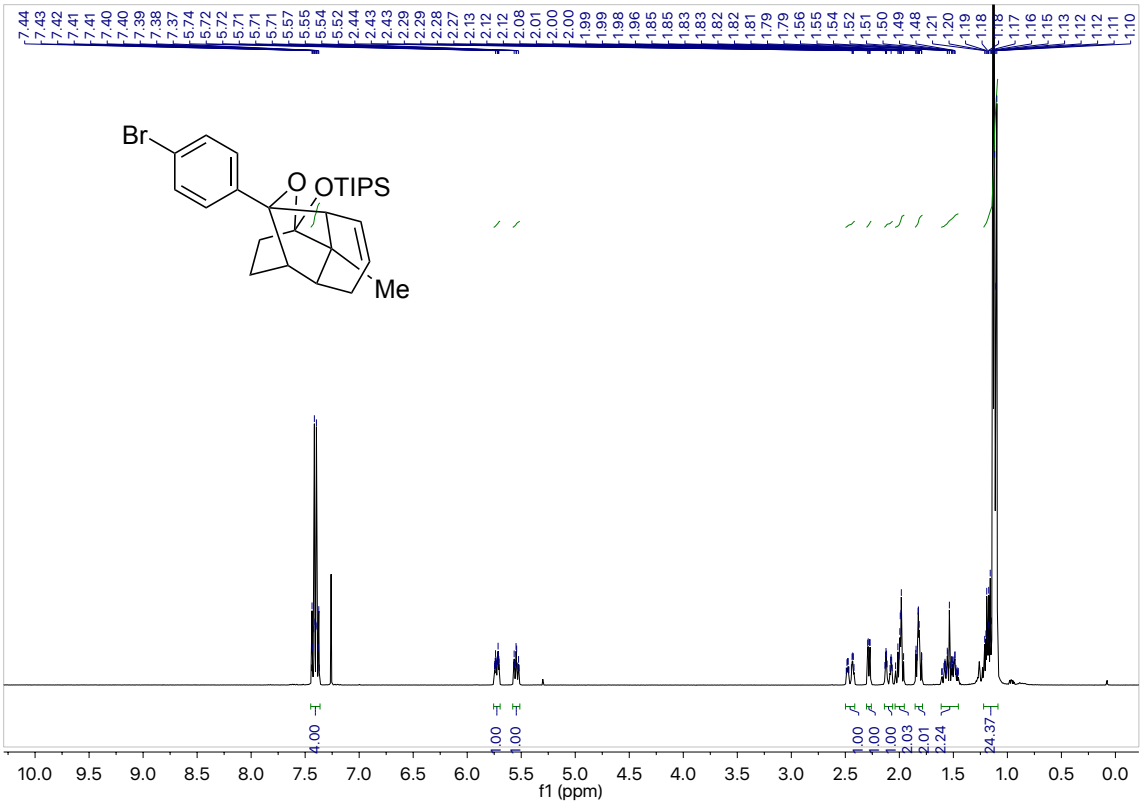

O OTIPS
Me
M 140.0340
M 127.8956
M 127.0113
M 125.8859
M 104.4226
M 95.7408
M 54.7041
M 54.3887
M 49.2066
M 43.2586
M 31.0471
M 30.1909
M 23.2064
M 18.3398
M 13.2479
M 10.7245
150
100
50
[ppm]

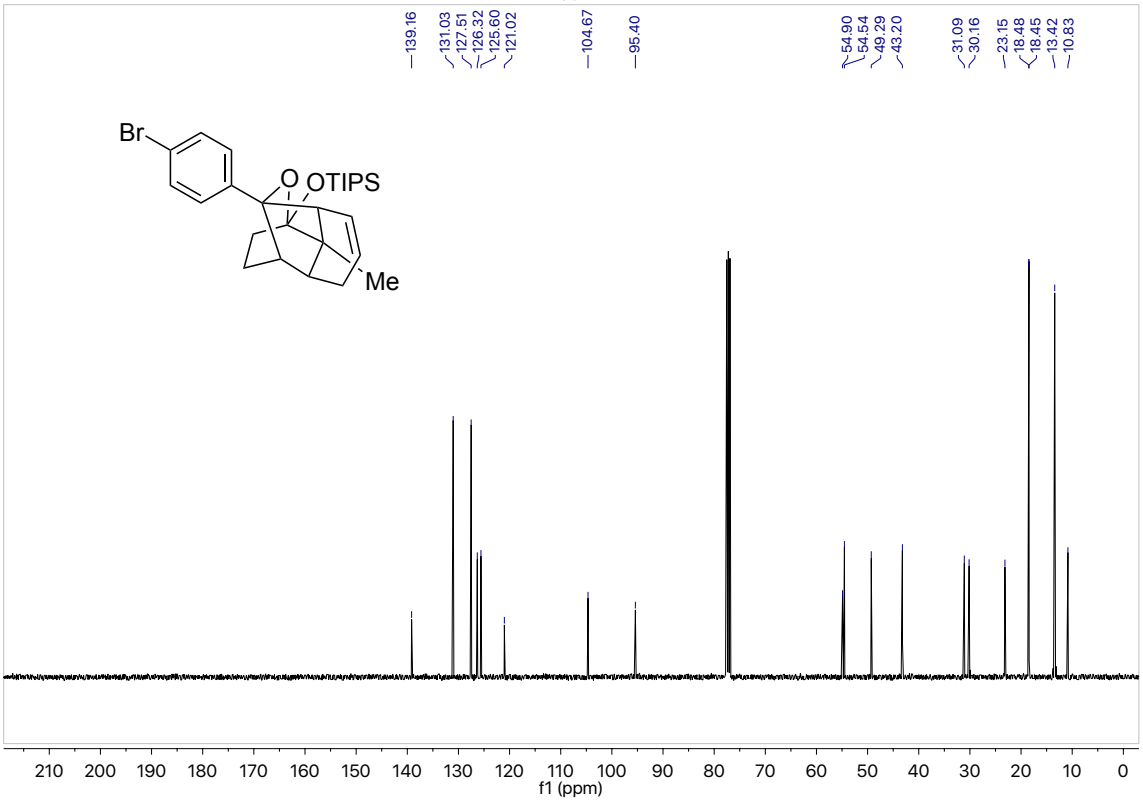

O2N
O OTIPS
Me
2.1535
2.0441
0.6510
1.0000
1.0285
2.1526
3.1467
2.1988
3.2106
26.5541
8
6
4
2
[ppm]

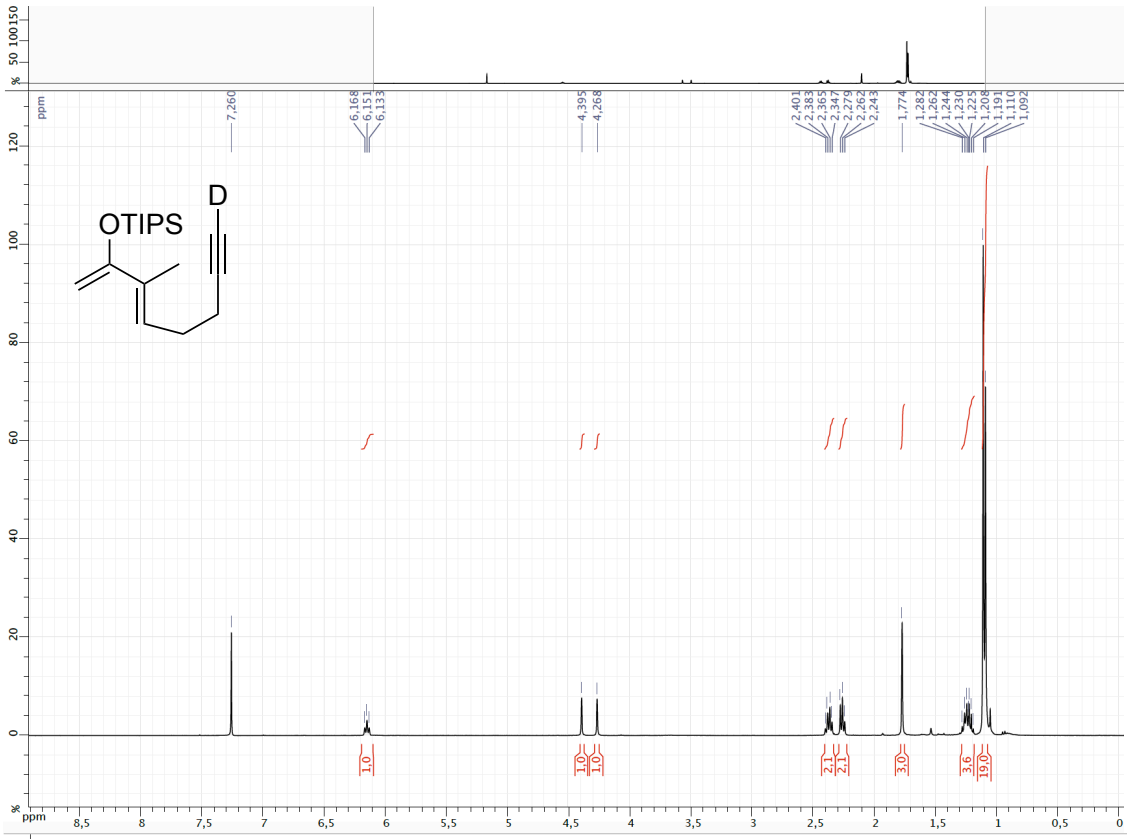

O2N
O OTIPS
Me
M 147.6311
M 147.0778
M 126.8403
M 126.3792
M 125.0547
M 123.1684
M 104.7650
M 95.2116
M 55.2550
M 54.8032
M 49.8328
M 43.1196
M 31.0487
M 30.0804
M 23.0444
M 18.3323
M 13.2328
M 10.9090
150
100
50
[ppm]

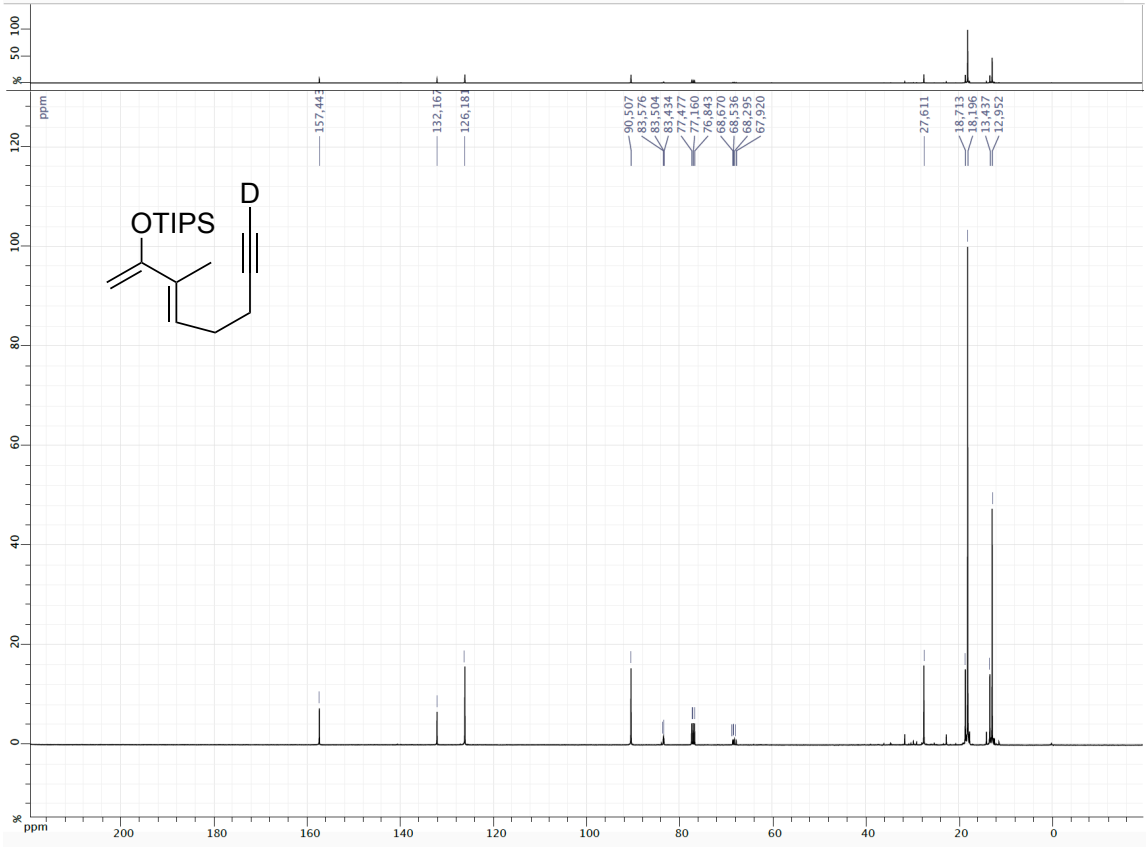

MeO
O OTIPS
Me
f1 (ppm)

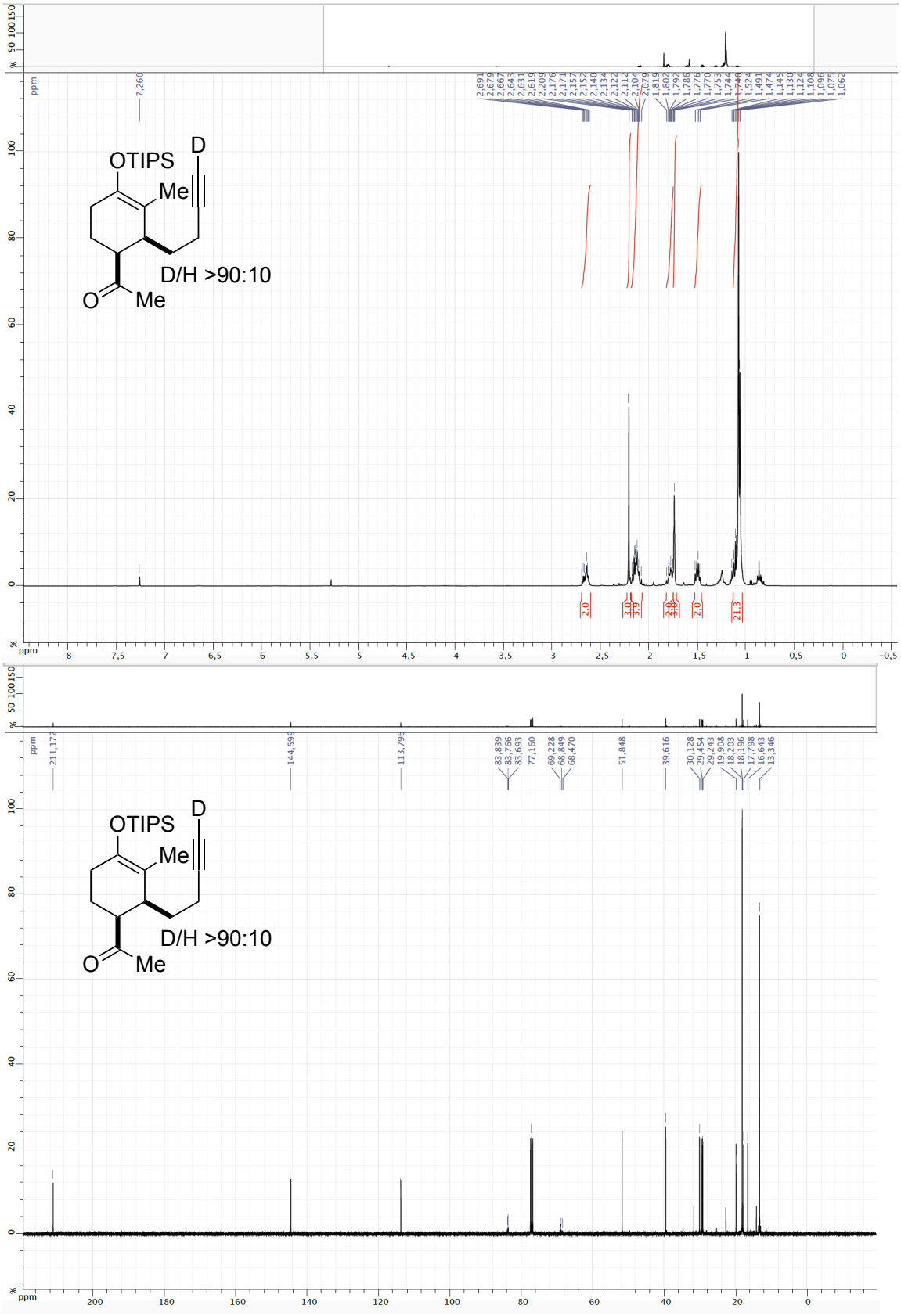

MeO
O OTIPS
Me
f1 (ppm)

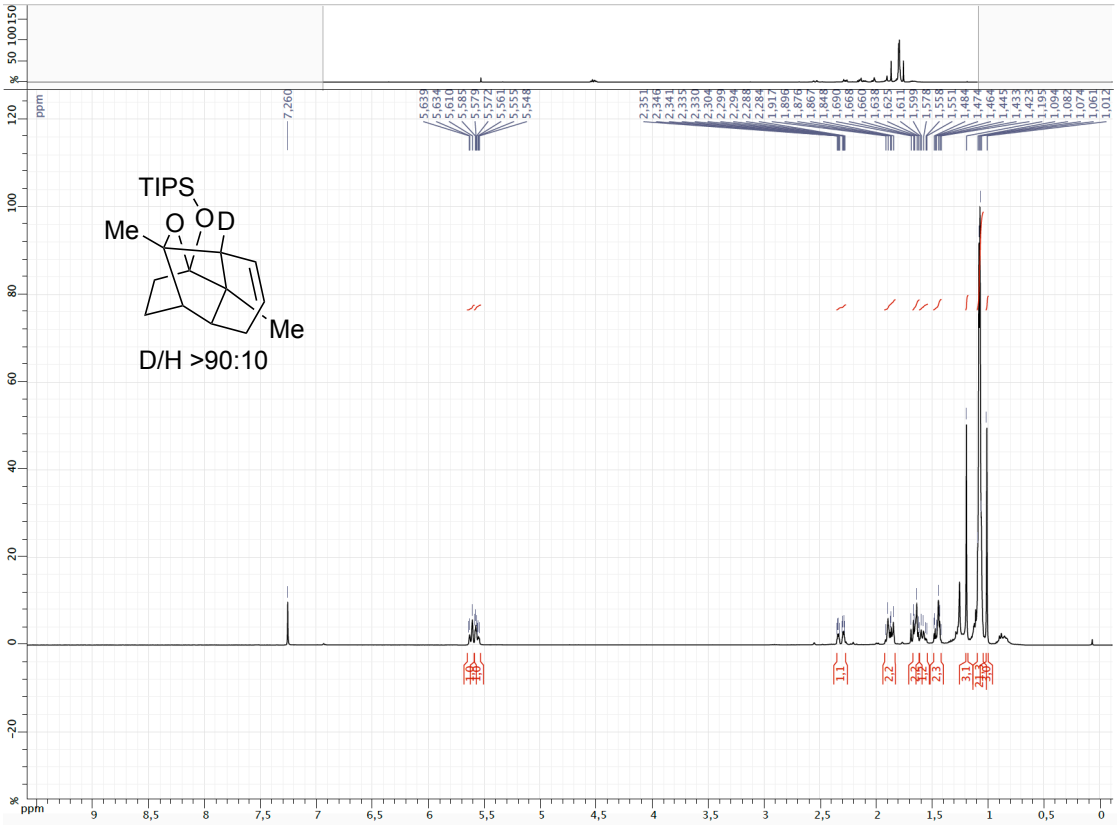

Br
O
OTIPS
Me
f1 (ppm)

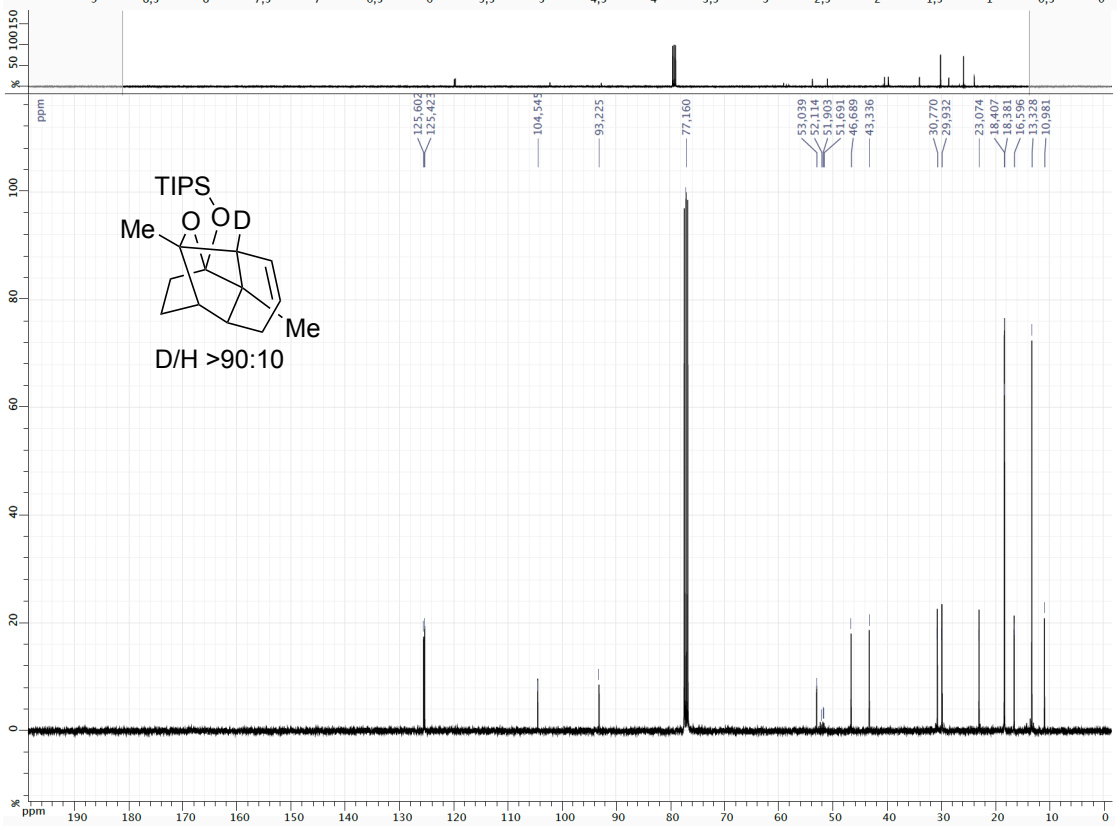

Br
O
OTIPS
Me
f1 (ppm)

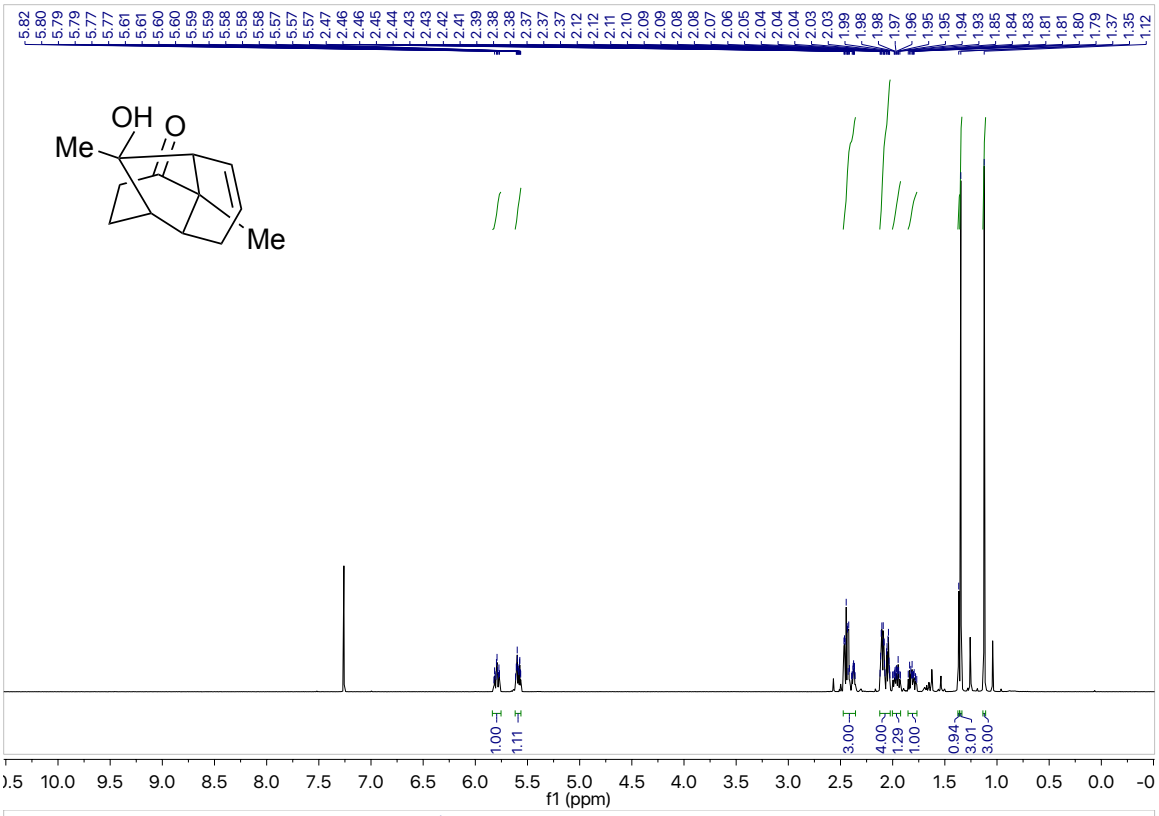

OTIPS
D
7.260
6.168
6.151
6.133
4.395
4.268
2.401
2.383
2.365
2.347
2.279
2.262
2.243
1.774
1.282
1.262
1.244
1.230
1.225
1.208
1.191
1.110
1.092
1.0
1.0
1.0
2.1
2.1
3.0
3.6
19.0
ppm

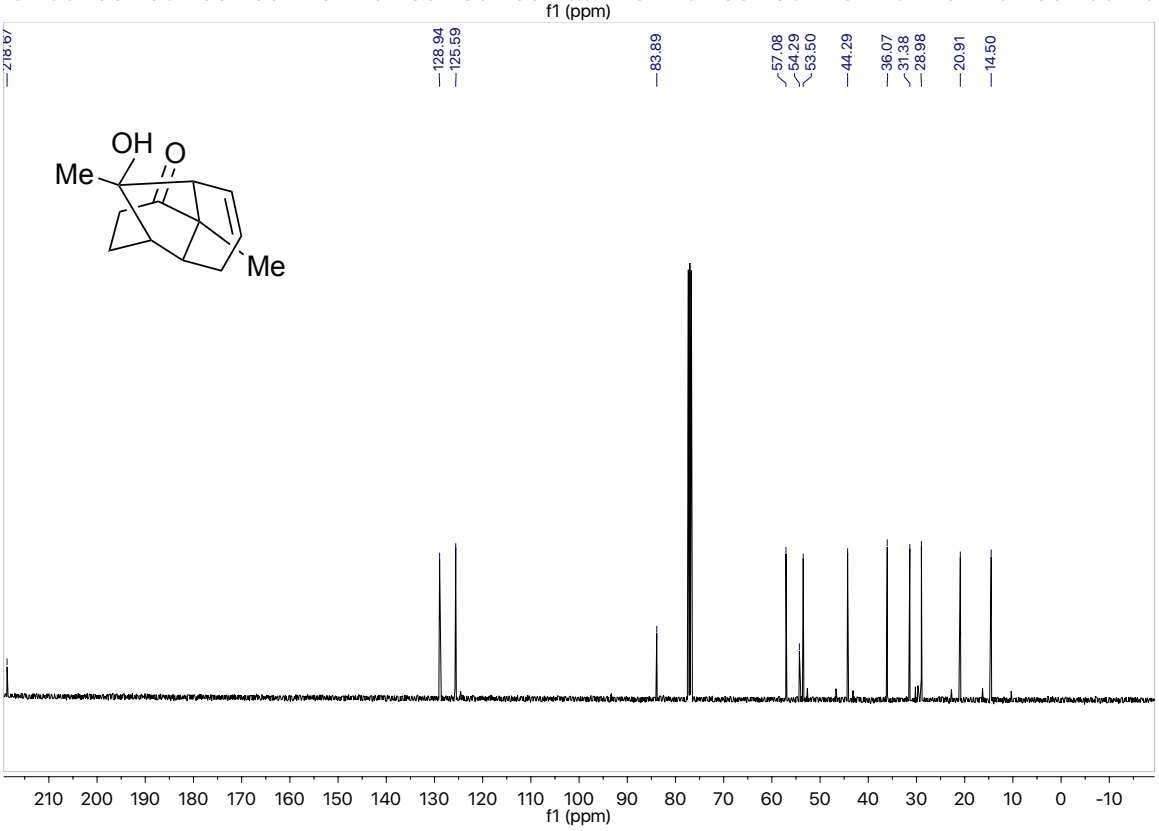

OTIPS
D
157.443
132.167
126.181
90.507
83.576
83.504
83.434
77.477
77.160
76.843
68.670
68.536
68.295
67.920
27.611
18.713
18.196
13.437
12.952
ppm

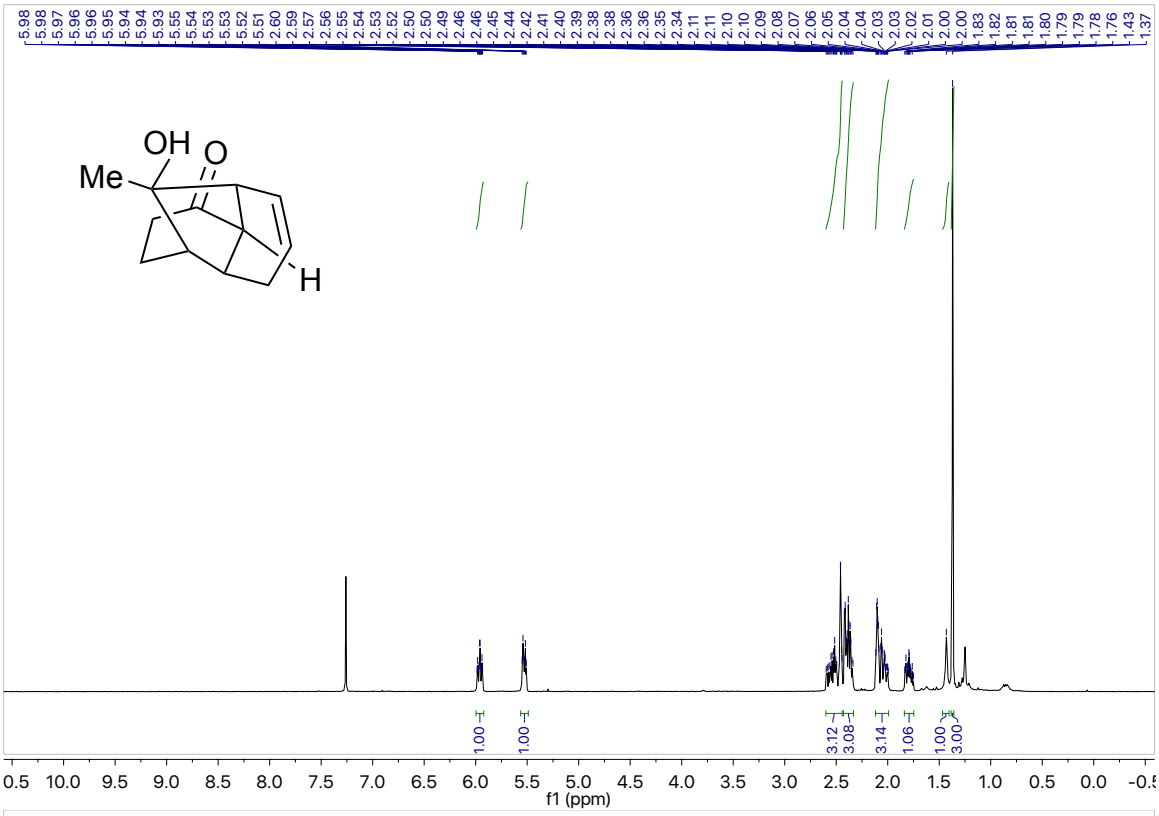

OTIPS
D
Me
D/H >90:10
O
Me

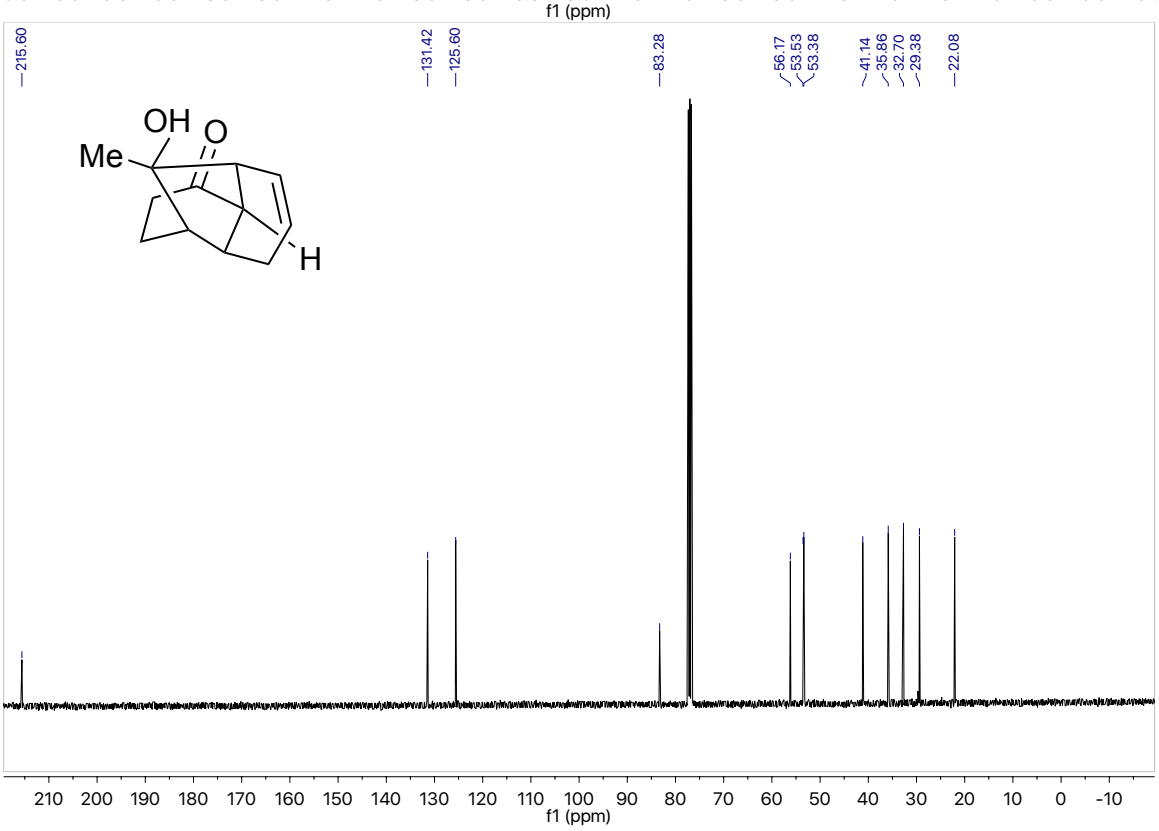

TIPS
Me
O
O
D
Me
D/H >90:10

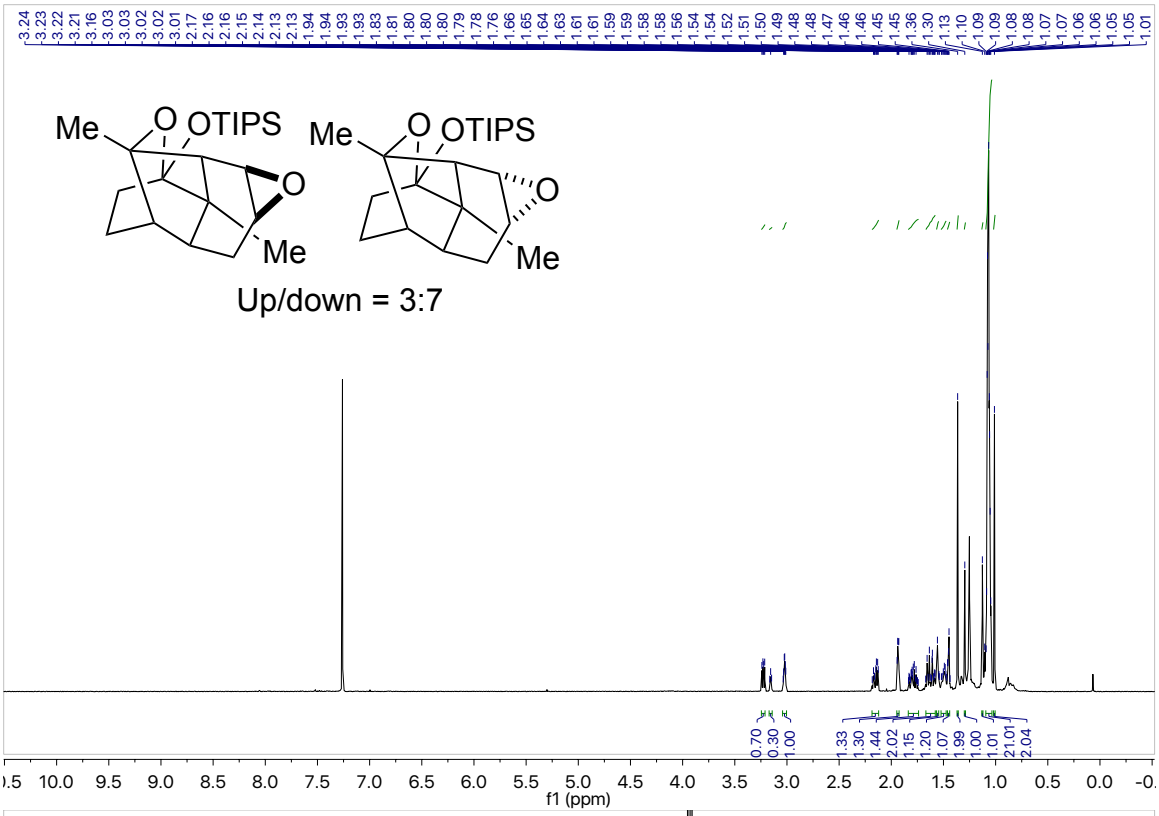

TIPS
Me
O
O
D
Me
D/H >90:10

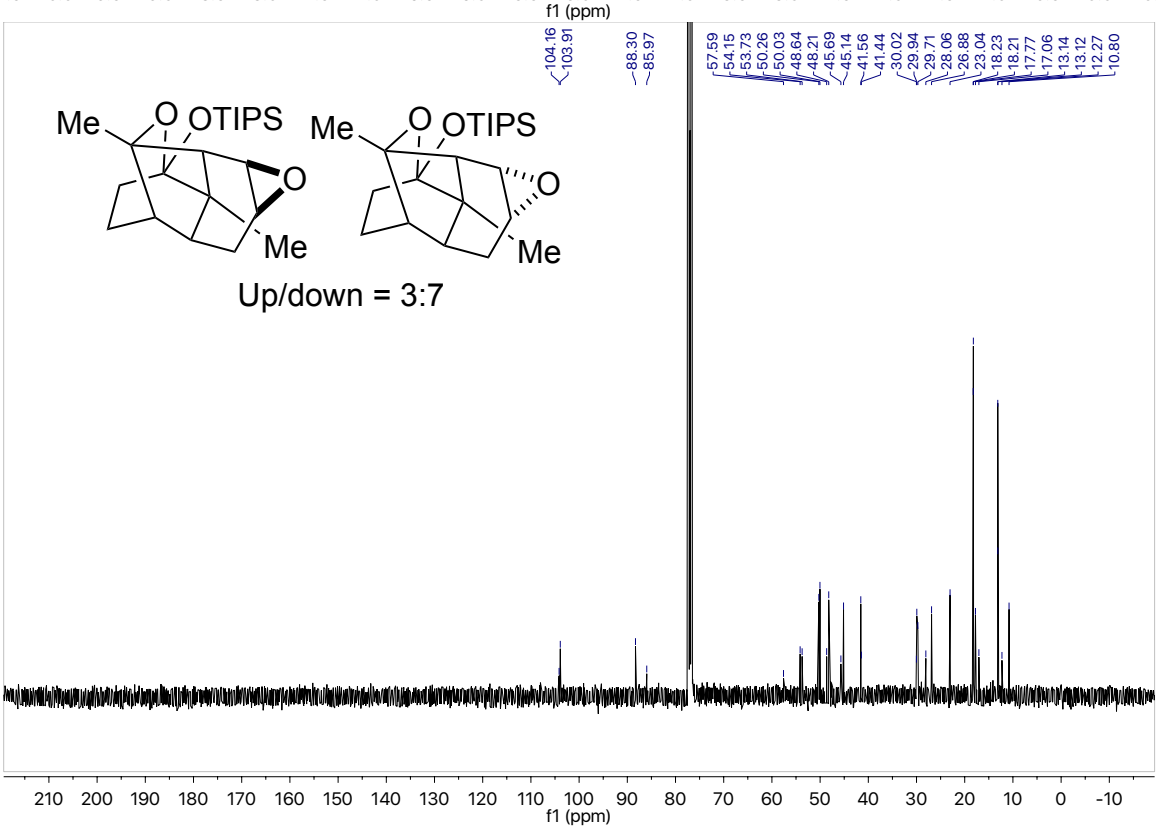

OH
O
Me
Me
f1 (ppm)

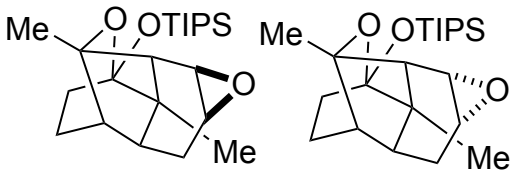

128.94
125.59
83.89
57.08
54.29
53.50
44.29
36.07
31.38
28.98
20.91
14.50
OH
O
Me
Me
f1 (ppm)


OH
O
Me
H
f1 (ppm)


215.60
131.42
125.60
83.28
56.17
53.53
53.38
41.14
35.86
32.70
29.38
22.08
OH
O
Me
H
f1 (ppm)

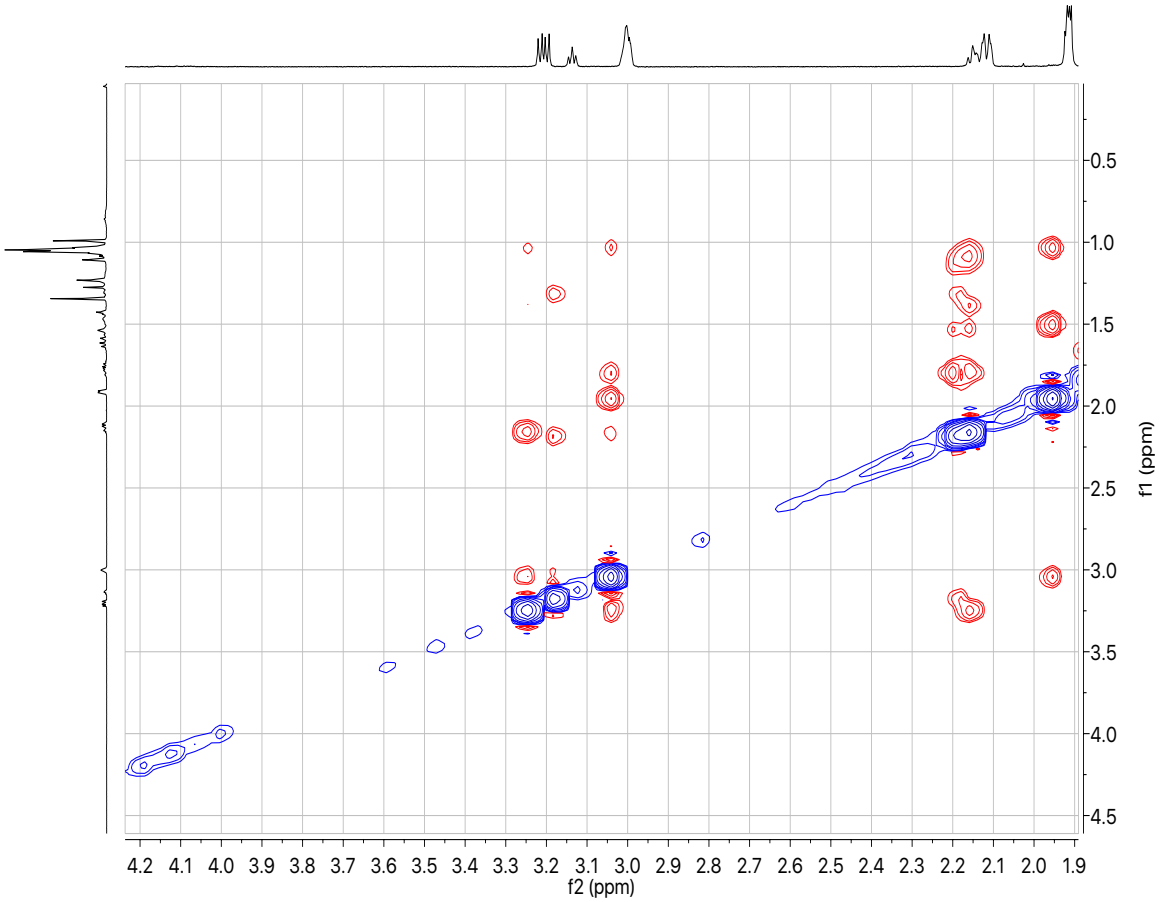

Me
O
OTIPS
O
Me
Me
O
OTIPS
O
Me
Up/down = 3:7
f1 (ppm)

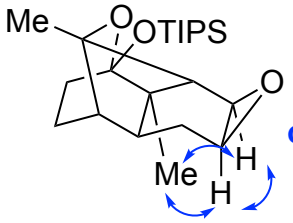

Me
O
OTIPS
O
Me
Me
O
OTIPS
O
Me
Up/down = 3:7
f1 (ppm)



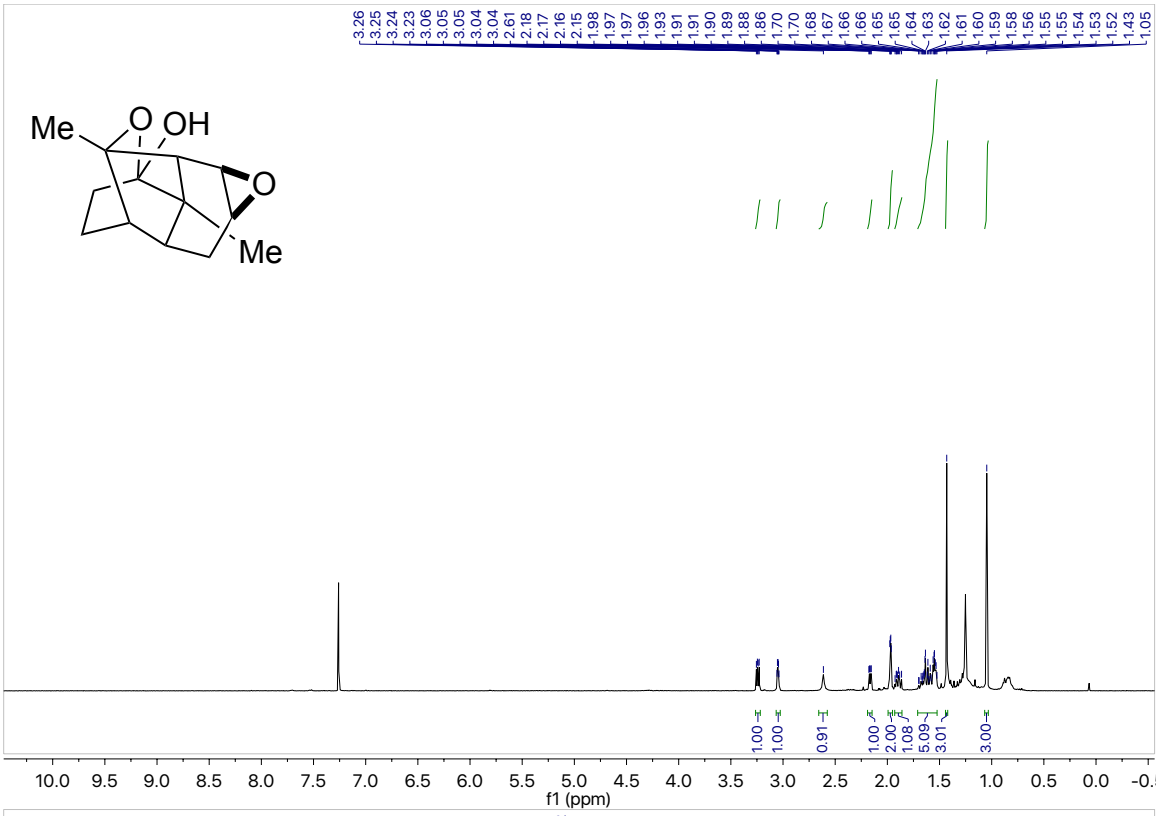
Up/down = 3:7

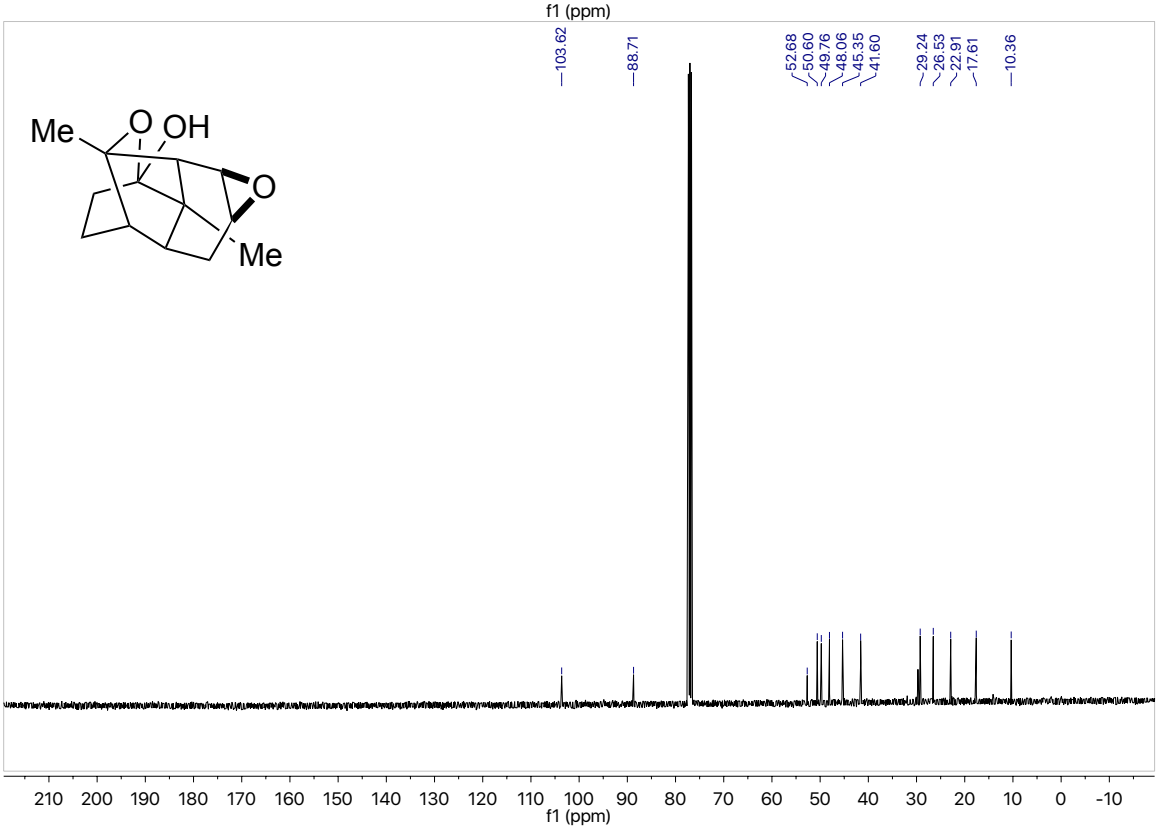
NOESY EXP.

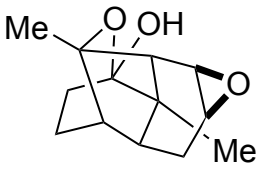




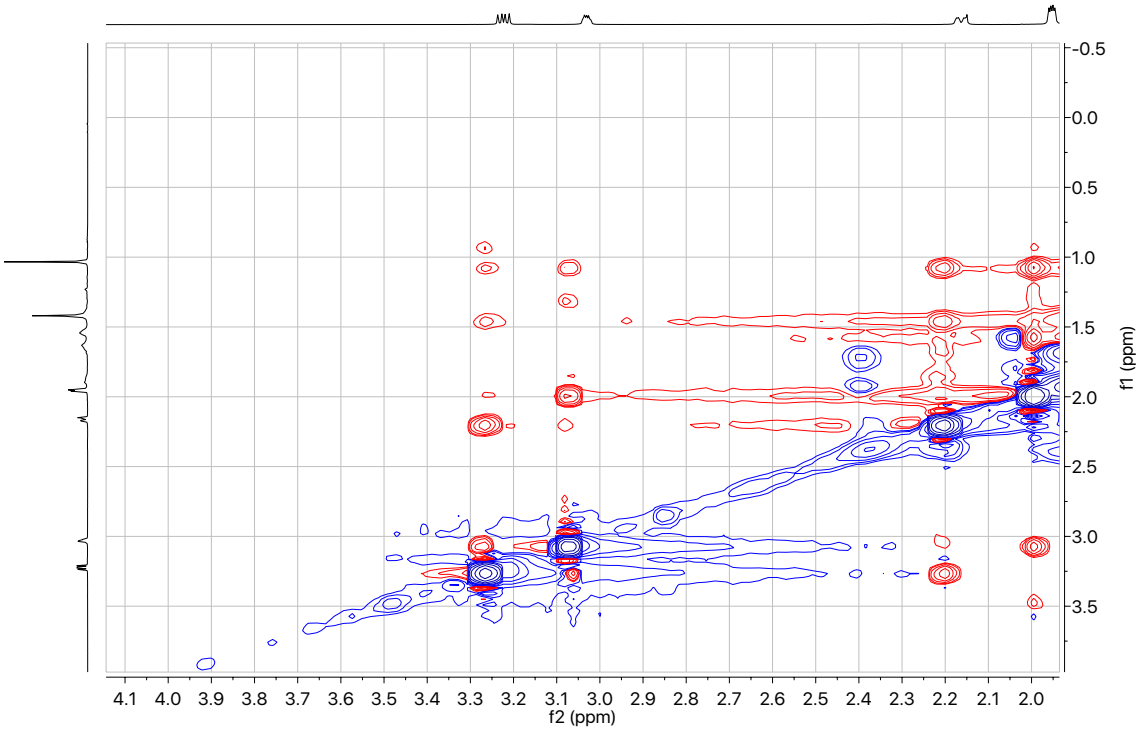
Noesy Signals Observed on the minor diastereomer

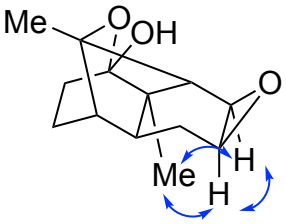

Me
O
OH
O
Me
3.26 3.25 3.24 3.23 3.06 3.05 3.05 3.04 3.04 2.61 2.18 2.17 2.16 2.15 1.98 1.97 1.97 1.96 1.93 1.91 1.91 1.90 1.89 1.88 1.86 1.70 1.70 1.68 1.67 1.66 1.66 1.65 1.65 1.64 1.63 1.62 1.61 1.60 1.59 1.58 1.56 1.55 1.55 1.54 1.53 1.52 1.43 1.05
1.00 1.00 0.91 1.00 2.00 1.08 5.09 3.01 3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


Me
O
OH
O
Me
103.62
88.71
52.68
50.60
49.76
48.06
45.35
41.60
29.24
26.53
22.91
17.61
10.36
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

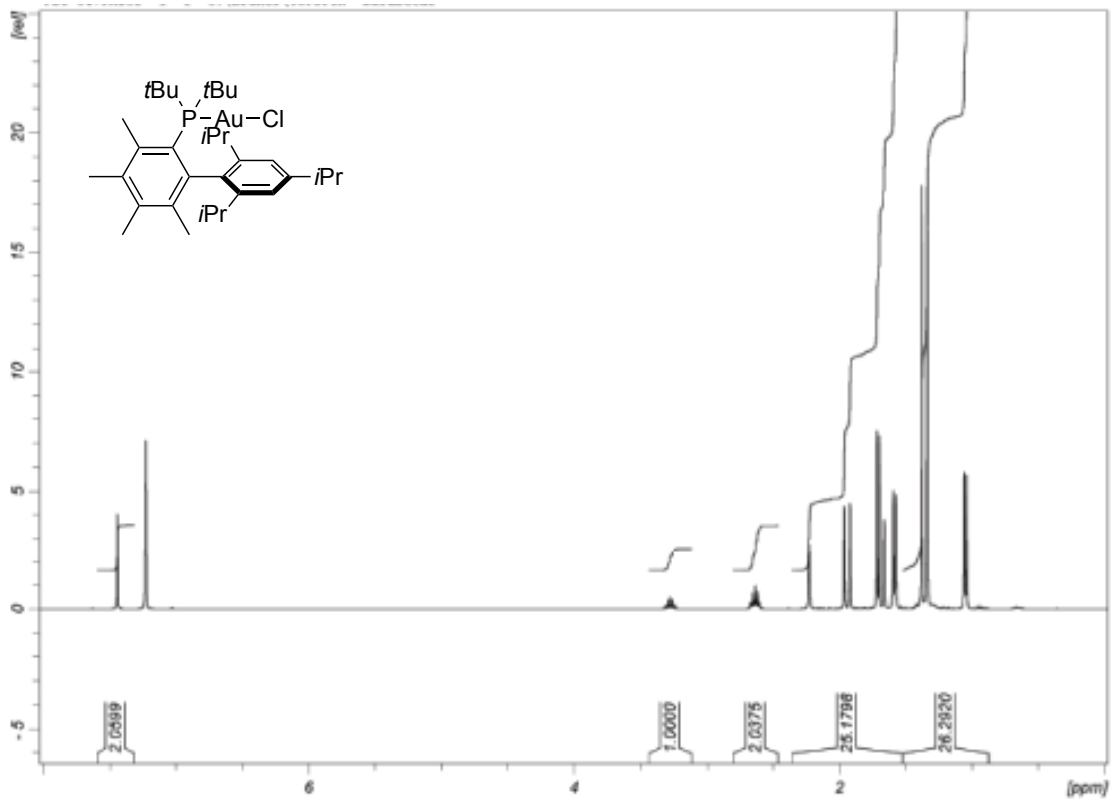


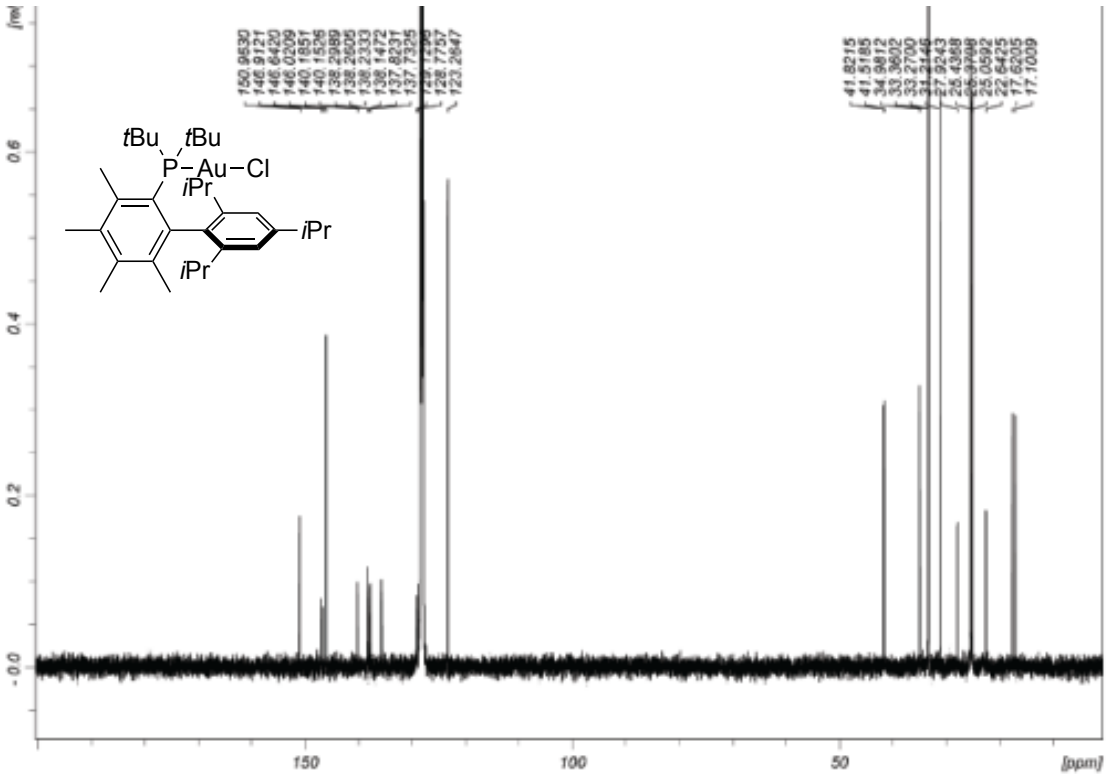
NOESY EXP.

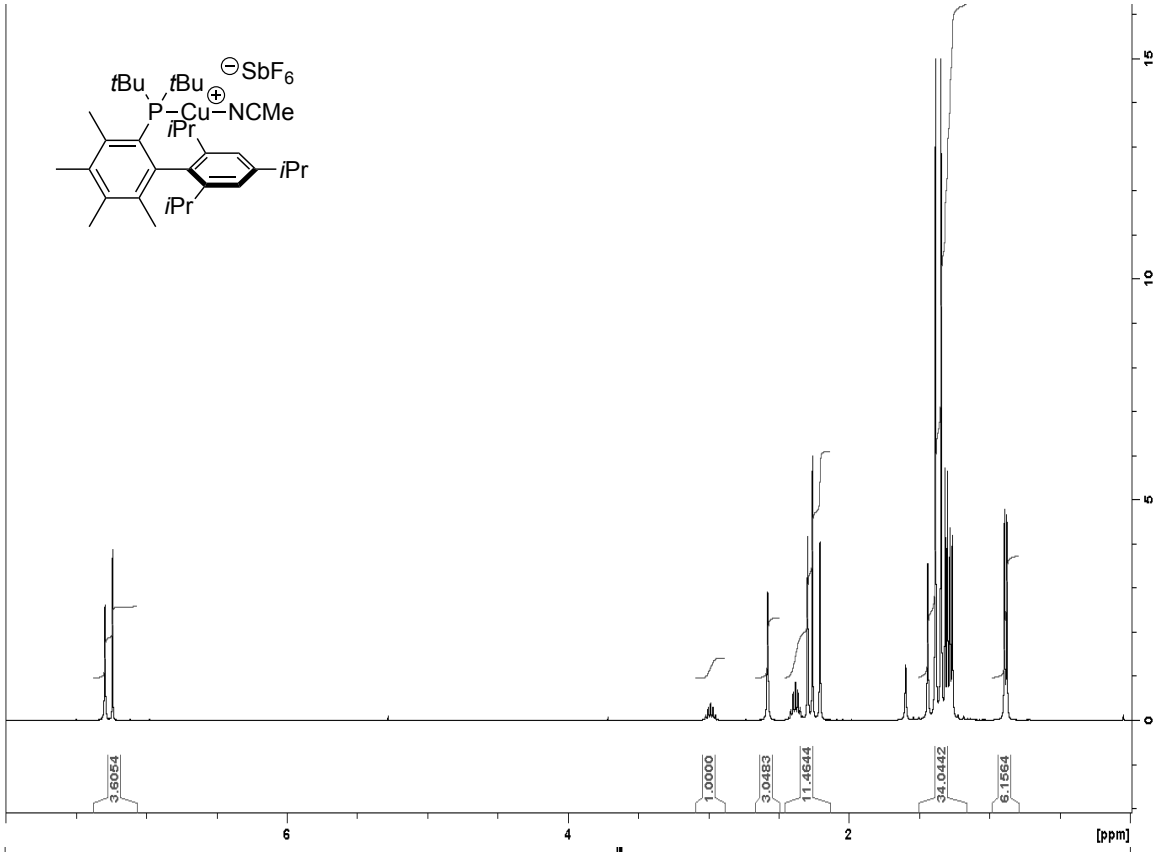


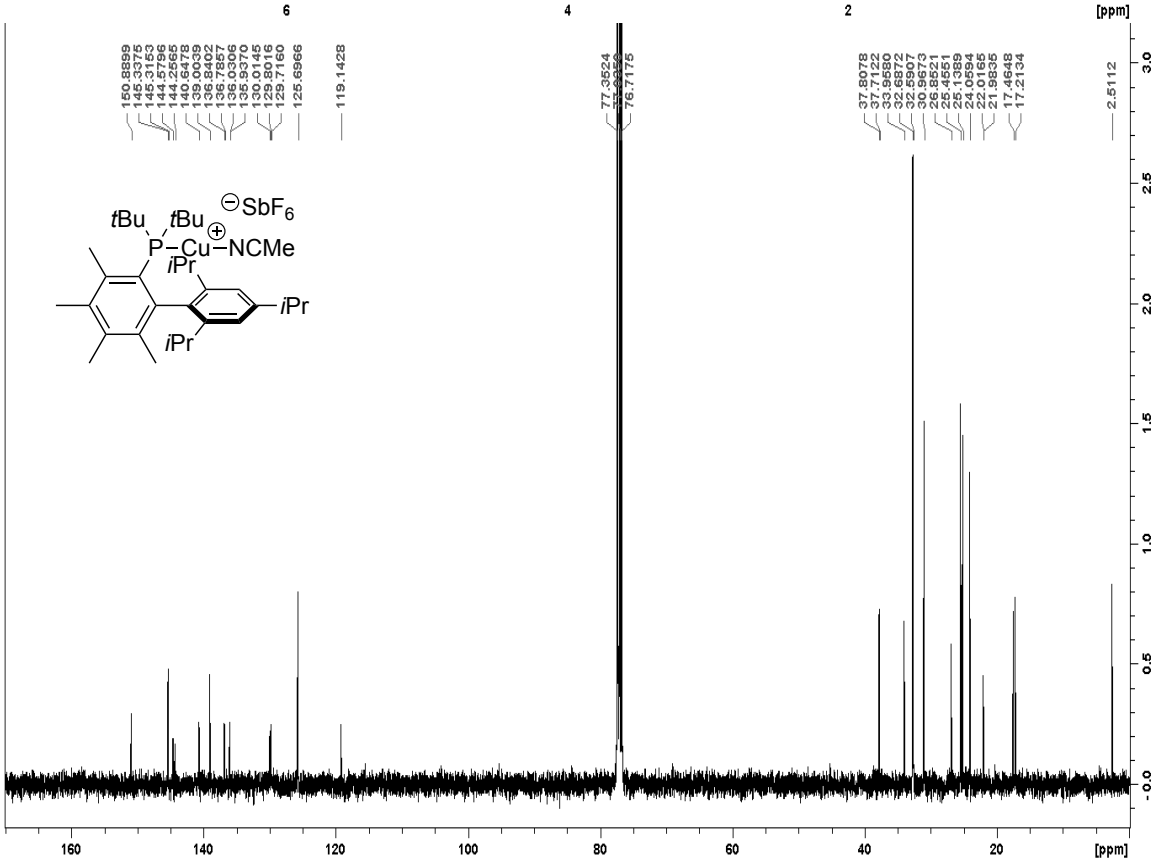


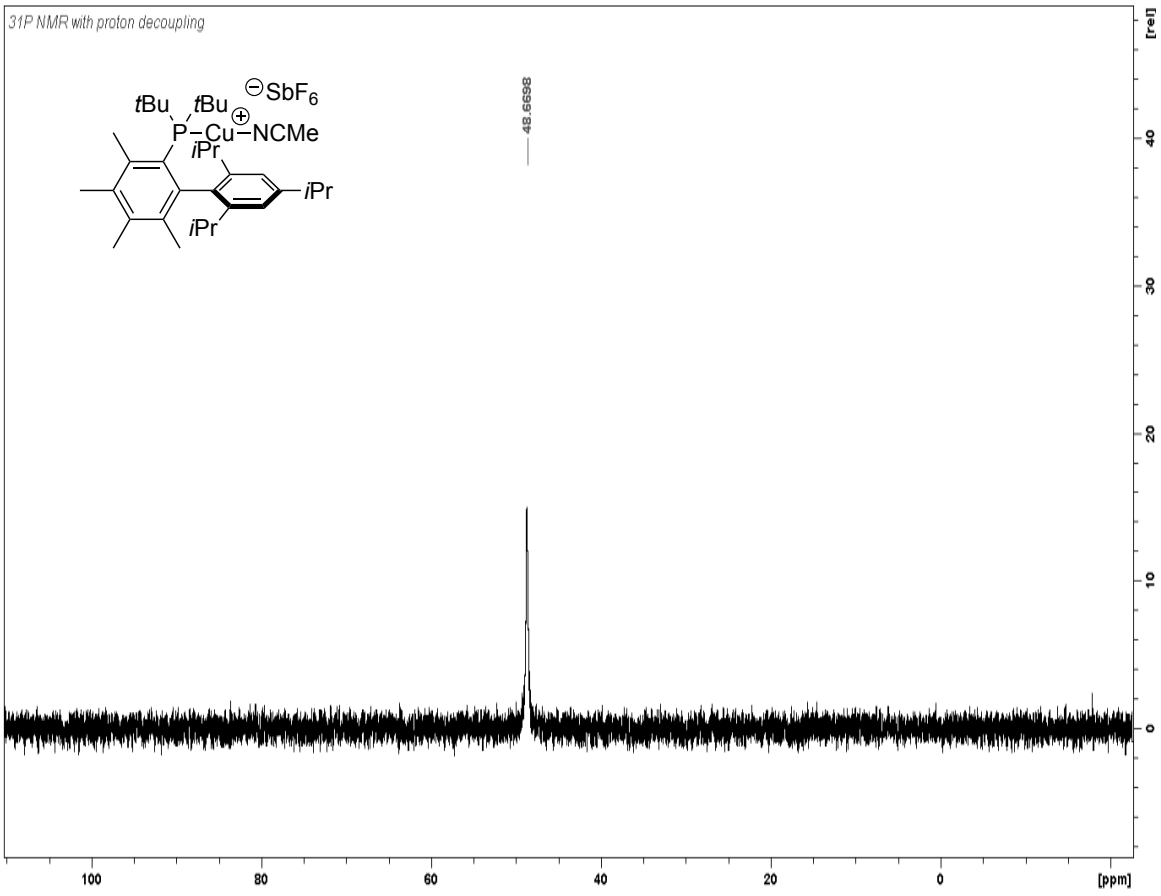
Noesy Signals Observed

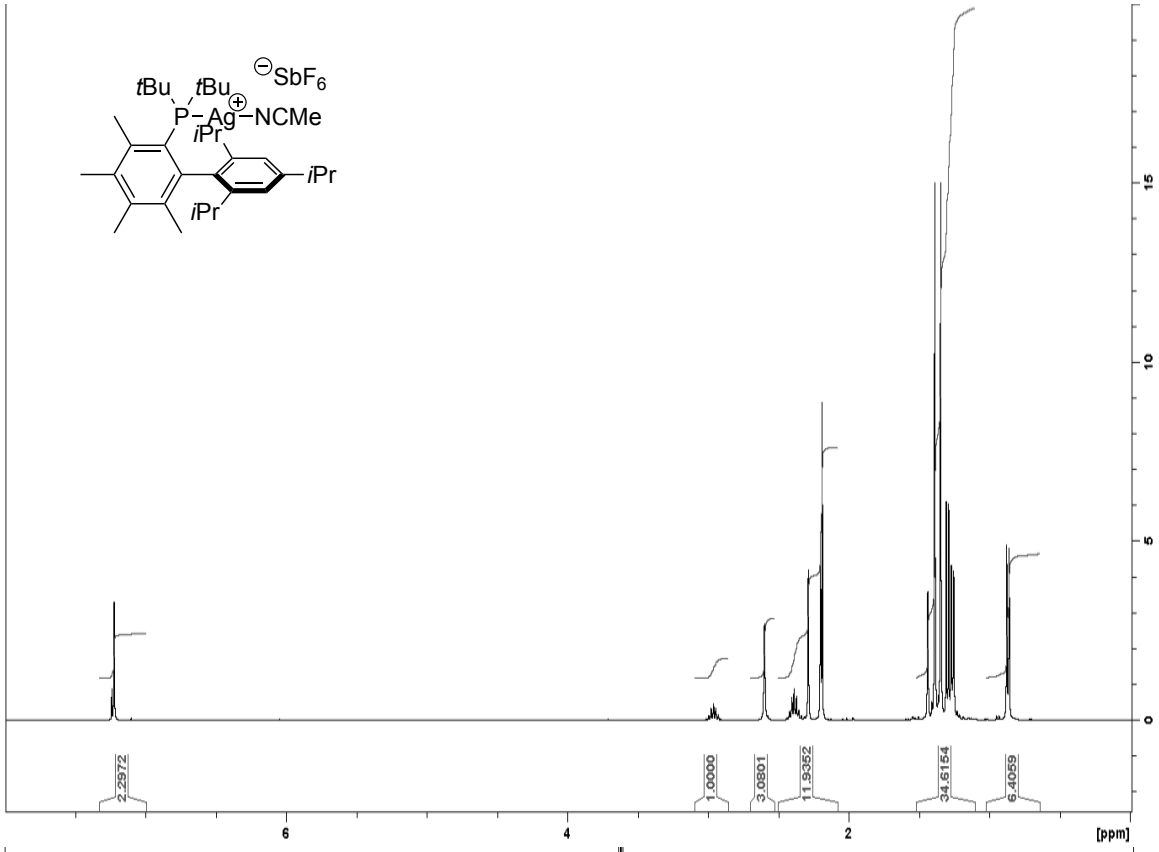

tBu tBu
P–Au–Cl
iPr
iPr
iPr
2.0599
1.0000
2.0375
26.1798
26.2920
6
4
2
[ppm]

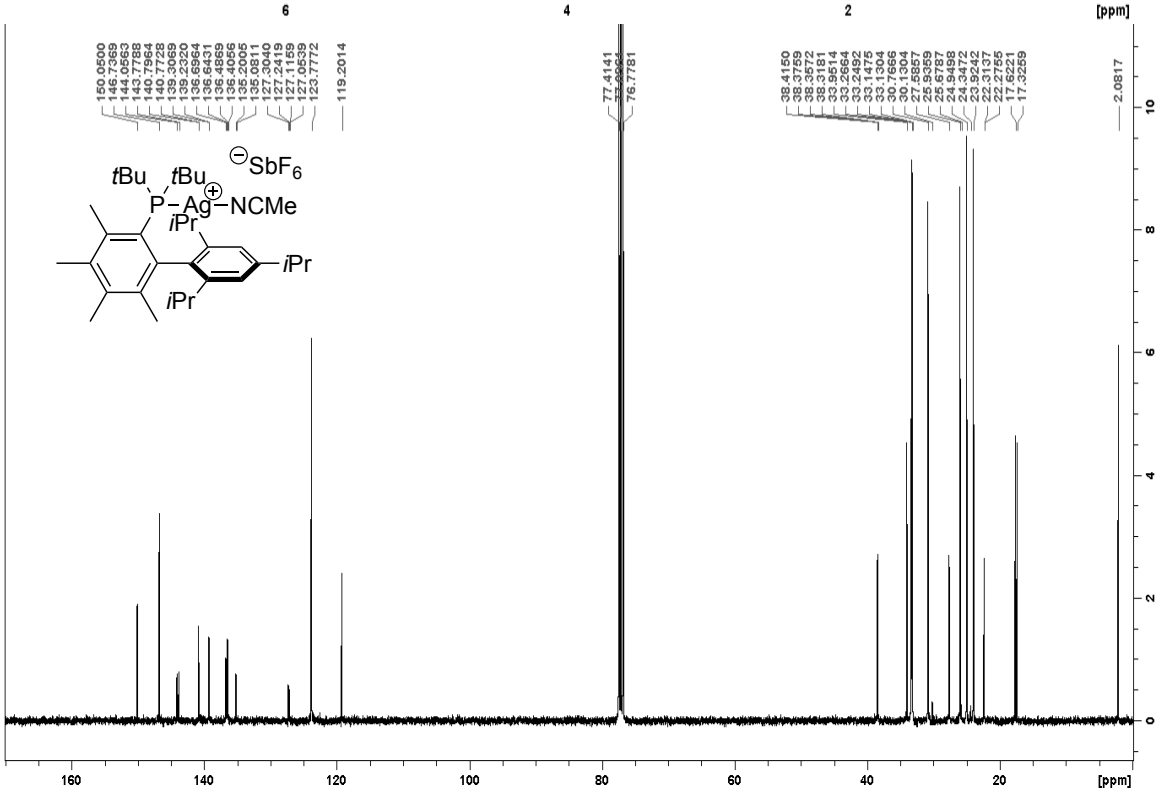

tBu tBu
P–Au–Cl
iPr
iPr
iPr
150
100
50
[ppm]

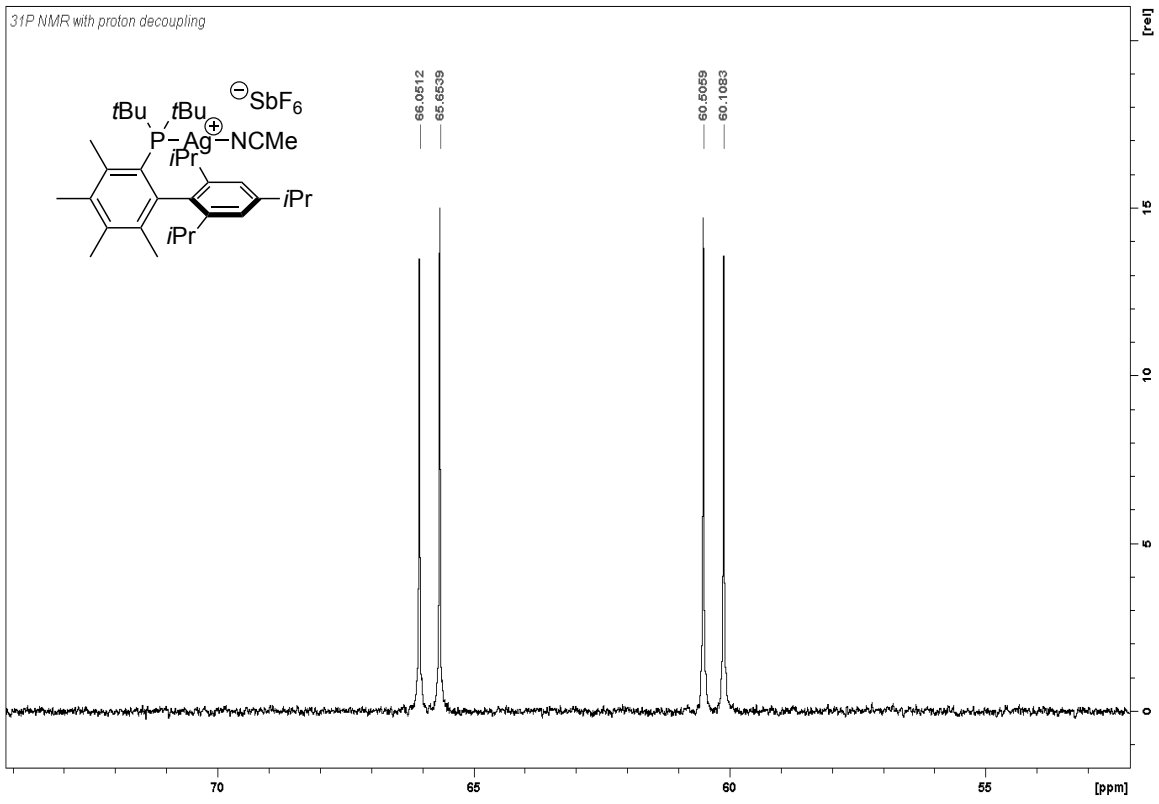

tBu
tBu
⊖SbF6
P–Cu⊕–NCMe
iPr
iPr
iPr
3.6054
1.0000
3.0483
11.4644
34.0442
6.1564
[ppm]

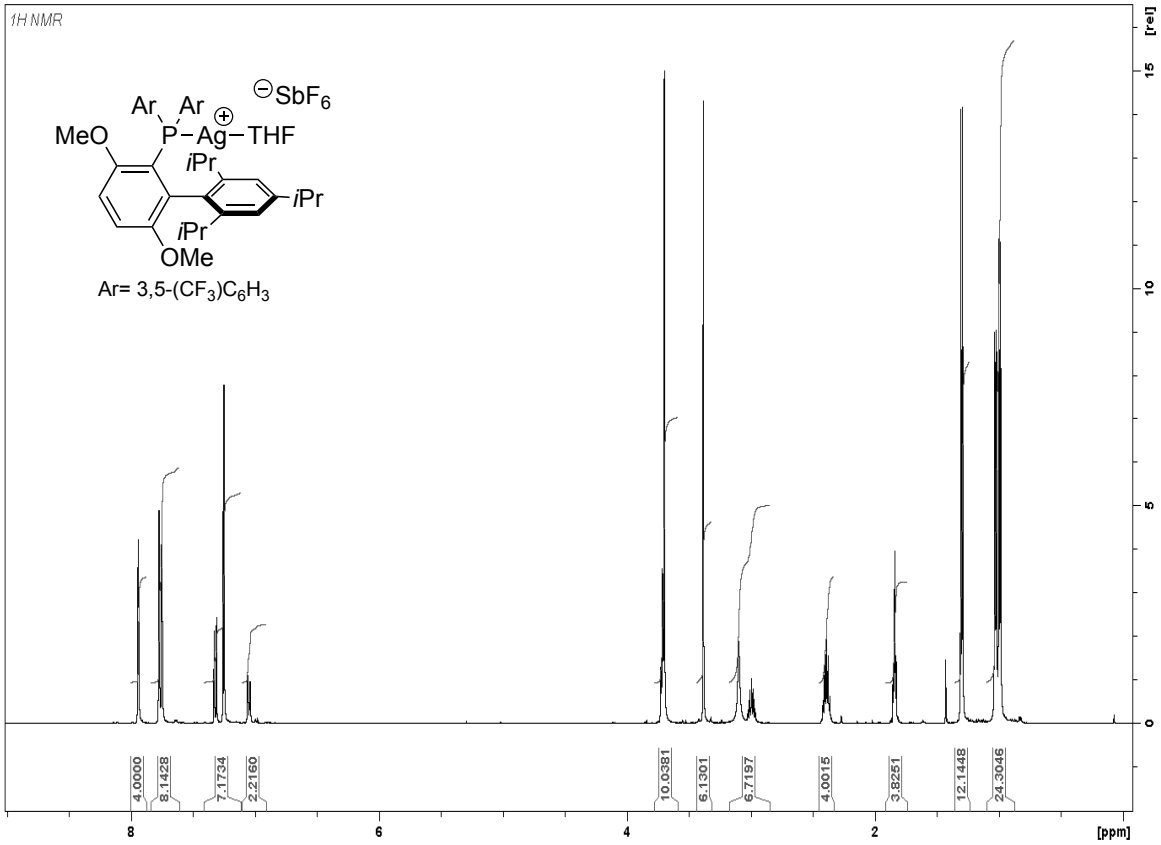

150.8899
145.3375
145.3153
144.5796
144.2565
140.6478
139.0433
136.8402
136.7857
136.0306
135.9370
130.0145
129.8116
129.7160
125.6966
119.1428
77.3524
77.0348
76.7176
37.8078
37.7122
33.9680
32.6872
32.5877
30.9673
26.8521
25.4551
25.1389
24.0694
22.0156
21.9835
17.4648
17.2134
2.5112
tBu
tBu
⊖SbF6
P–Cu⊕–NCMe
iPr
iPr
iPr
[ppm]

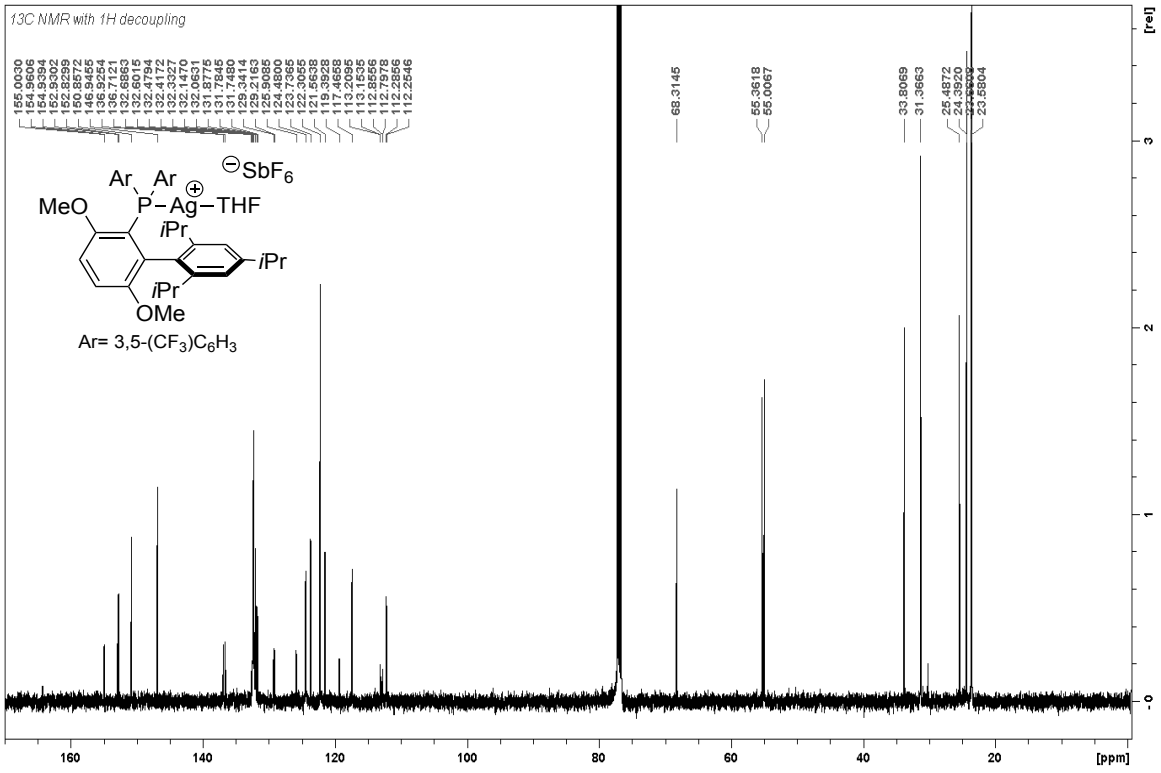

31P NMR with proton decoupling
tBu
tBu
SbF6
P–Cu–NCMe
iPr
iPr
iPr
48.6698
[rel]
40
30
20
10
0
100
80
60
40
20
0
[ppm]

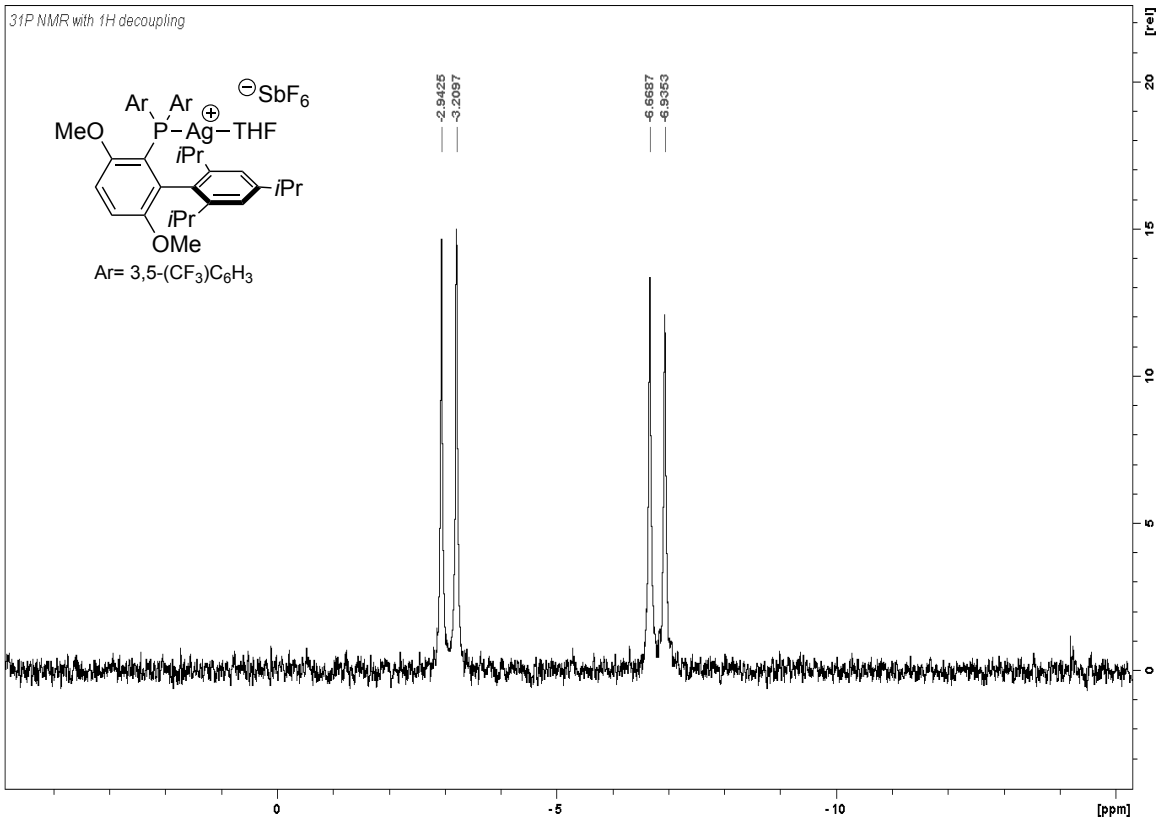

tBu
tBu
P
Ag
NCMe
SbF6
iPr
iPr
iPr
2.2972
1.0000
3.0801
11.9352
34.6154
6.4059
[ppm]

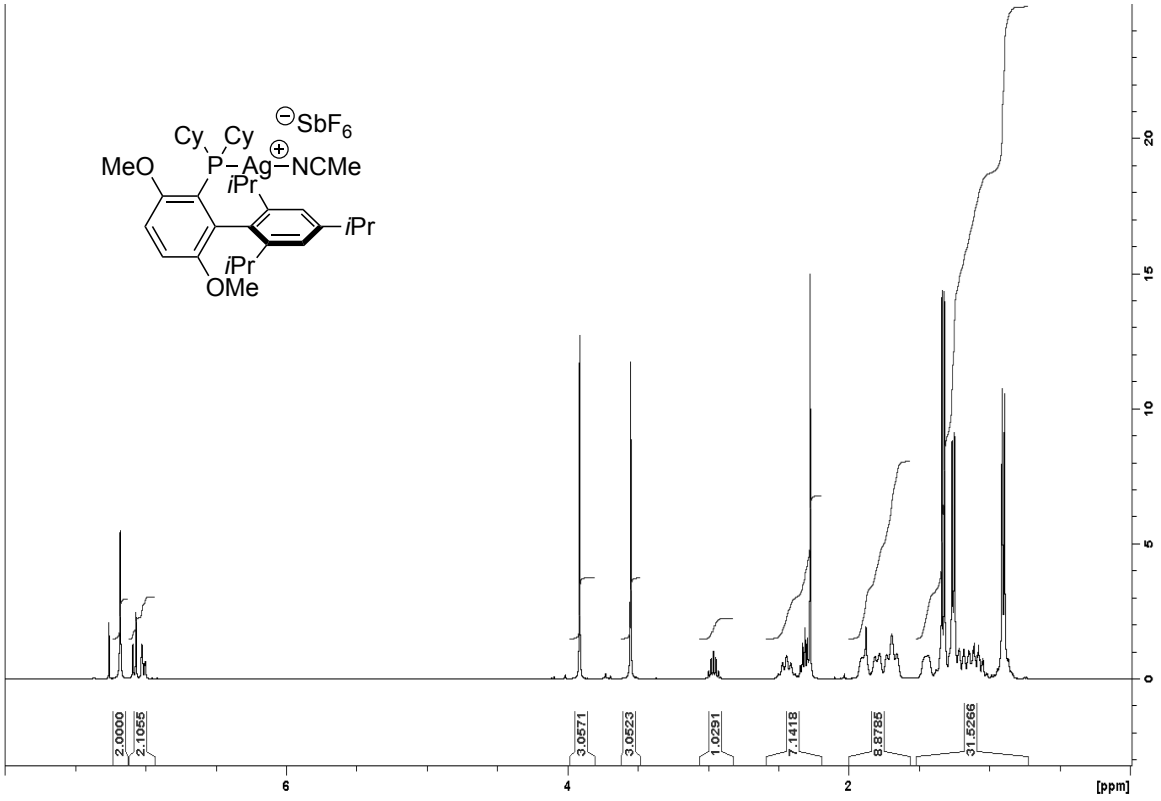

150.0500
146.7369
144.0563
143.7788
140.7964
140.7728
139.3089
138.2330
136.6964
136.6431
136.4889
136.4056
135.2005
135.0811
127.3040
127.2419
127.1159
127.0539
123.7772
119.2014
77.4141
77.0961
76.7781
38.4150
38.3759
38.3572
38.3181
33.9514
33.2964
33.1492
33.1175
33.1304
30.7666
30.1304
27.8857
25.9389
25.5787
24.9498
24.3472
23.9242
22.3137
22.2755
17.6201
17.3259
2.0817
tBu
tBu
P
Ag
NCMe
SbF6
iPr
iPr
iPr
[ppm]

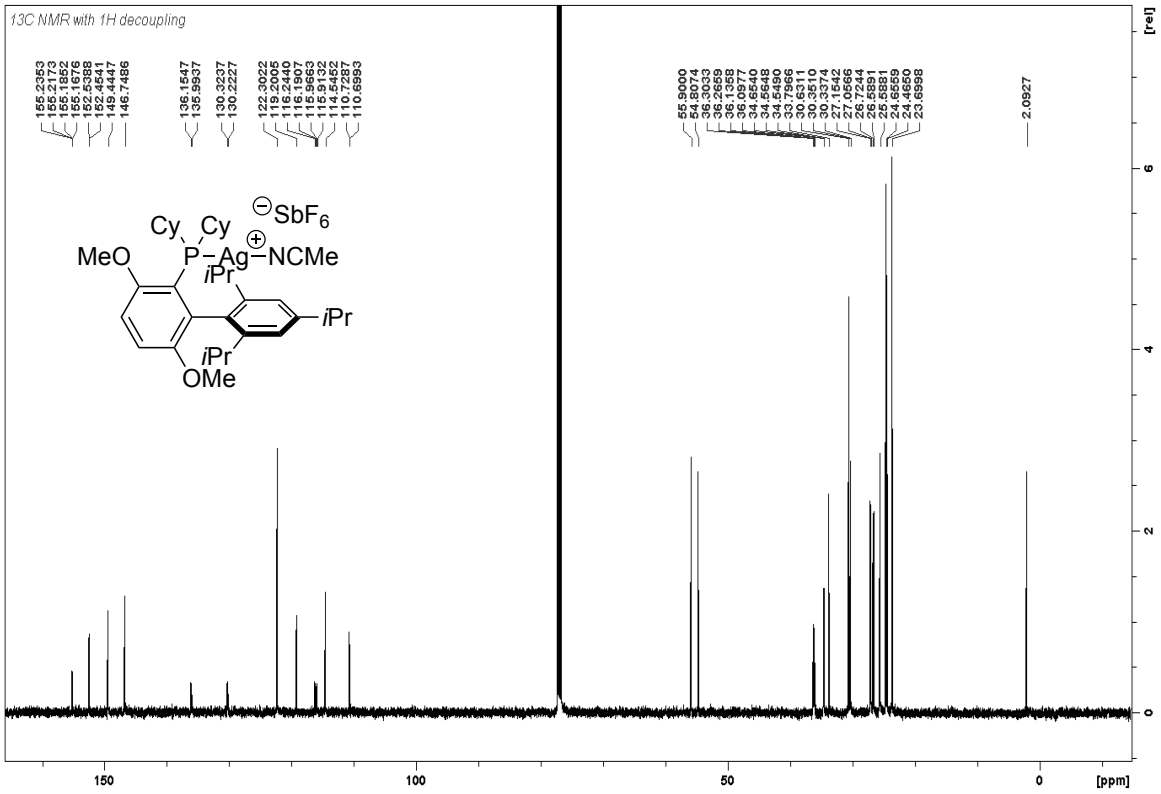

31P NMR with proton decoupling
tBu
tBu
SbF6
P–Ag–NCMe
iPr
iPr
iPr
66.0512
65.6539
60.5059
60.1083
[rel]
15
10
5
0
70
65
60
55
[ppm]

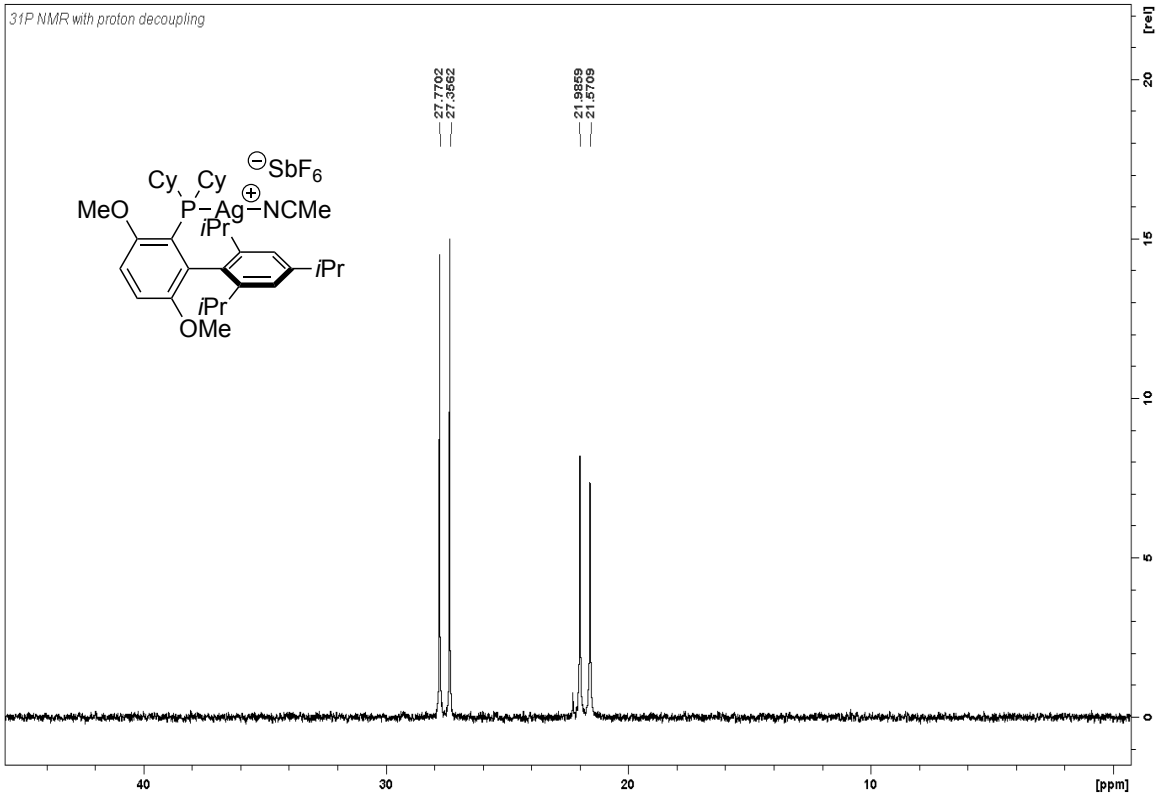

1H NMR
Ar Ar
⊖SbF6
MeO
P–Ag–THF
⊕
iPr
iPr
iPr
OMe
Ar= 3,5-(CF3)C6H3
4.0000
8.1428
7.1734
2.2160
10.0381
6.1301
6.7197
4.0015
3.8251
12.1448
24.3046
[rel]
[ppm]

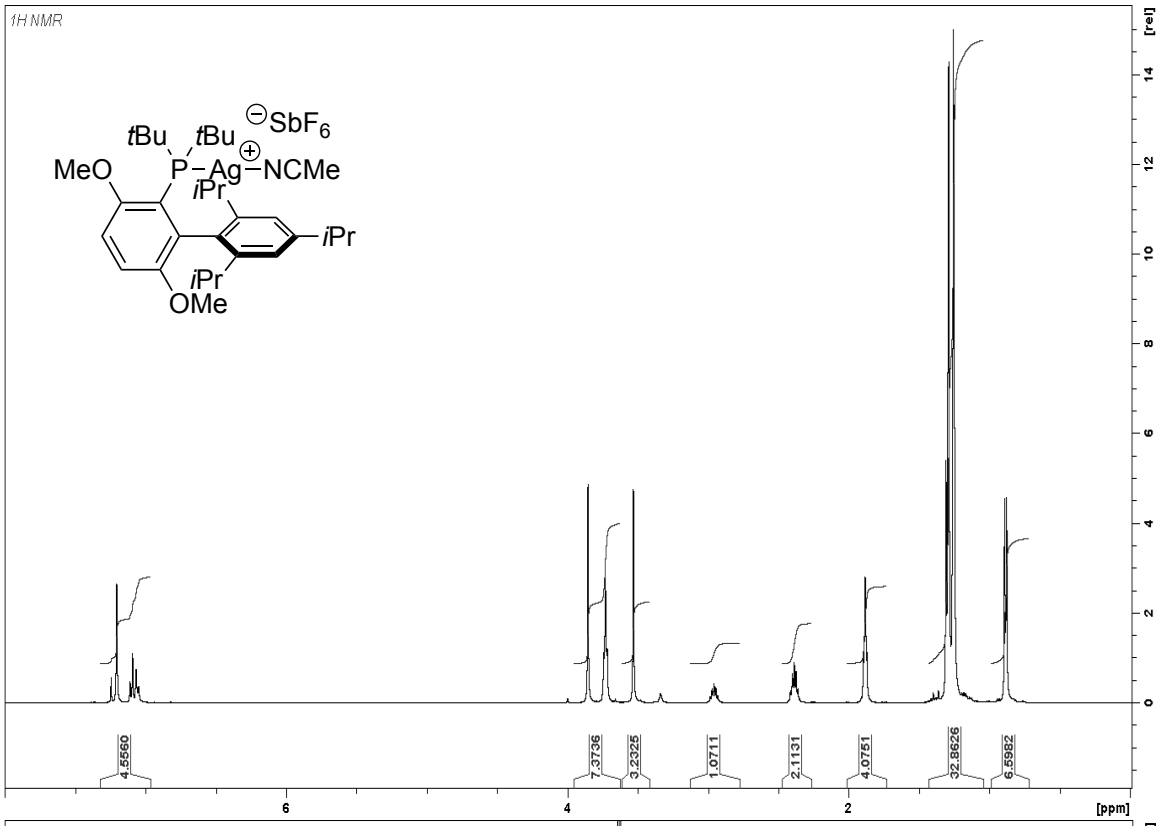

13C NMR with 1H decoupling
155.0030
154.6666
154.3394
152.9302
152.8299
150.8572
146.9455
136.9254
136.7121
132.6863
132.6015
132.4794
132.4172
132.3327
132.1470
132.0531
131.8775
131.7845
131.7480
129.3414
128.5763
128.5085
124.4800
123.7385
122.3055
121.5638
119.3528
119.1468
113.2095
113.1535
112.8556
112.7978
112.2856
112.2546
68.3145
55.3618
55.0067
33.8069
31.3663
25.4872
24.3920
23.5804
Ar Ar
⊖SbF6
MeO
P–Ag–THF
⊕
iPr
iPr
iPr
OMe
Ar= 3,5-(CF3)C6H3
[rel]
[ppm]

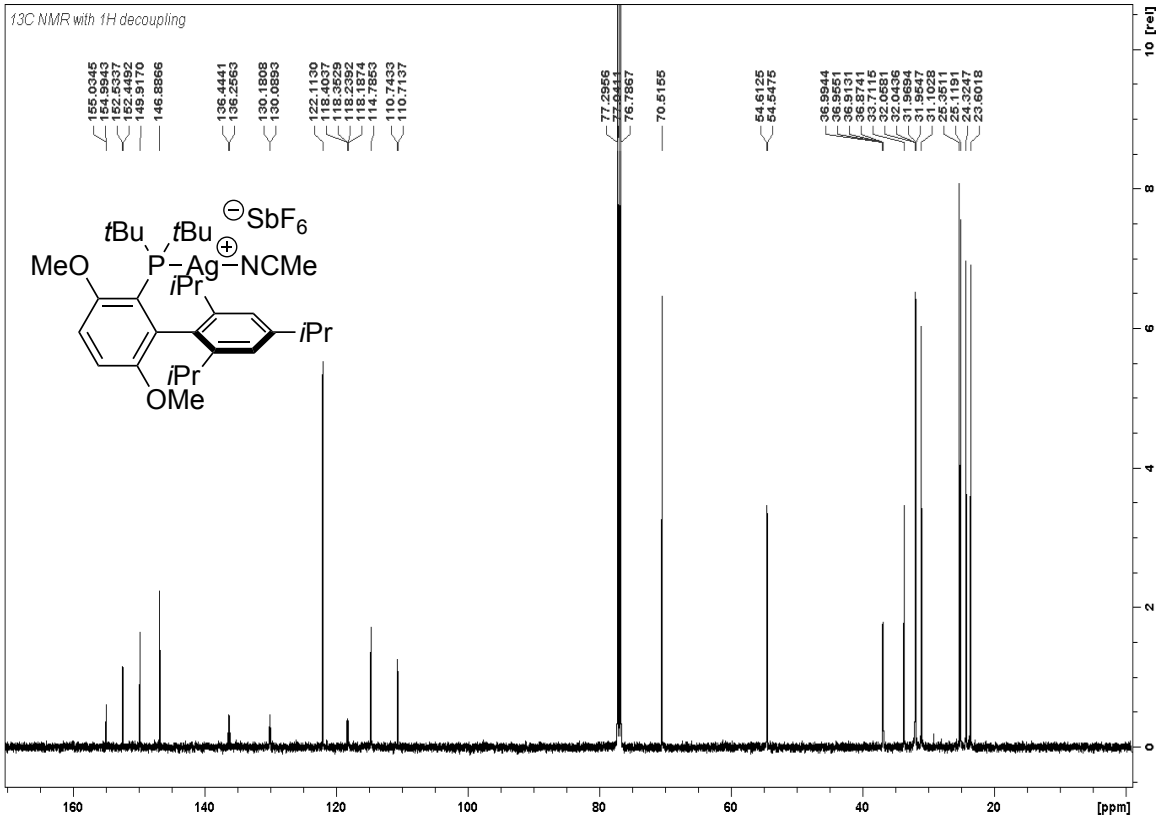

31P NMR with 1H decoupling
Ar Ar
⊕
⊖SbF6
MeO
P−Ag−THF
iPr
iPr
iPr
OMe
Ar= 3,5-(CF3)C6H3
-2.9425
-3.2097
-6.6687
-6.9353
[rel]
20
15
10
5
0
0
-5
-10
[ppm]

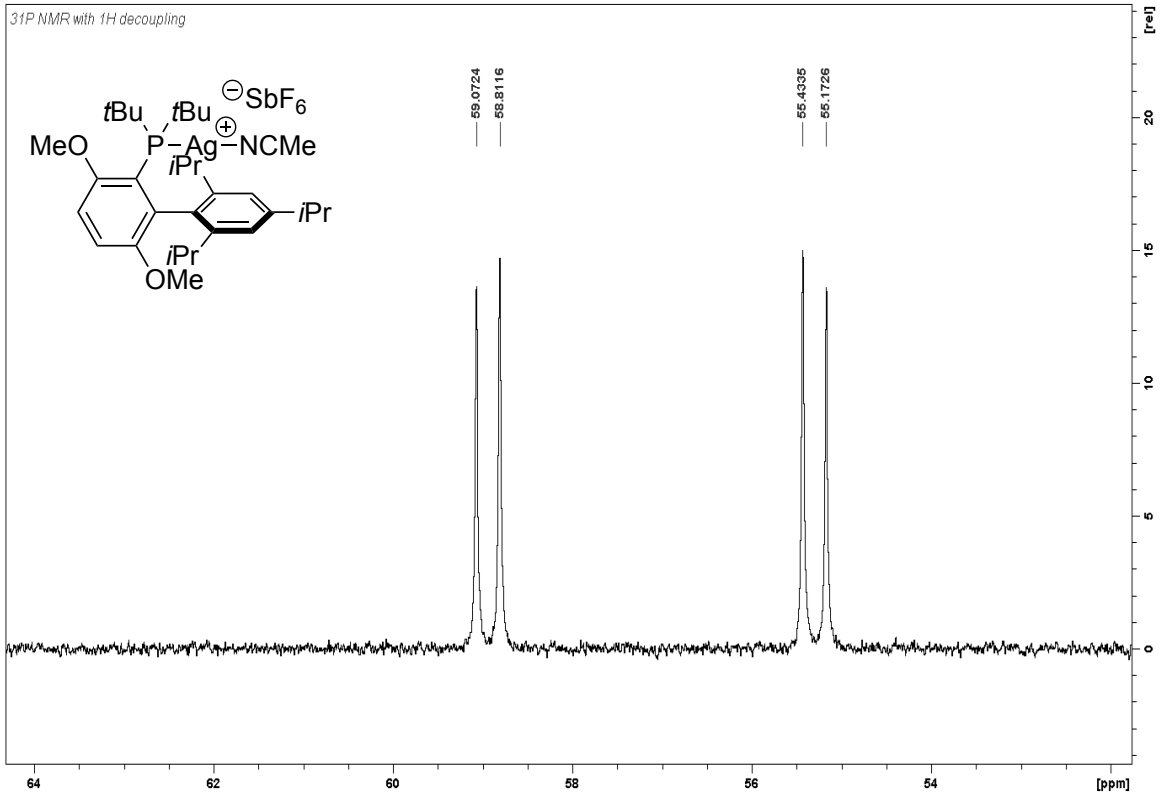

Cy
Cy
⊖SbF6
MeO
P–Ag–NCMe
⊕
iPr
iPr
iPr
iPr
OMe
2.0000
2.1055
3.0571
3.0523
1.0291
7.1418
8.8785
31.5266
6
4
2
[ppm]
0
5
10
15
20

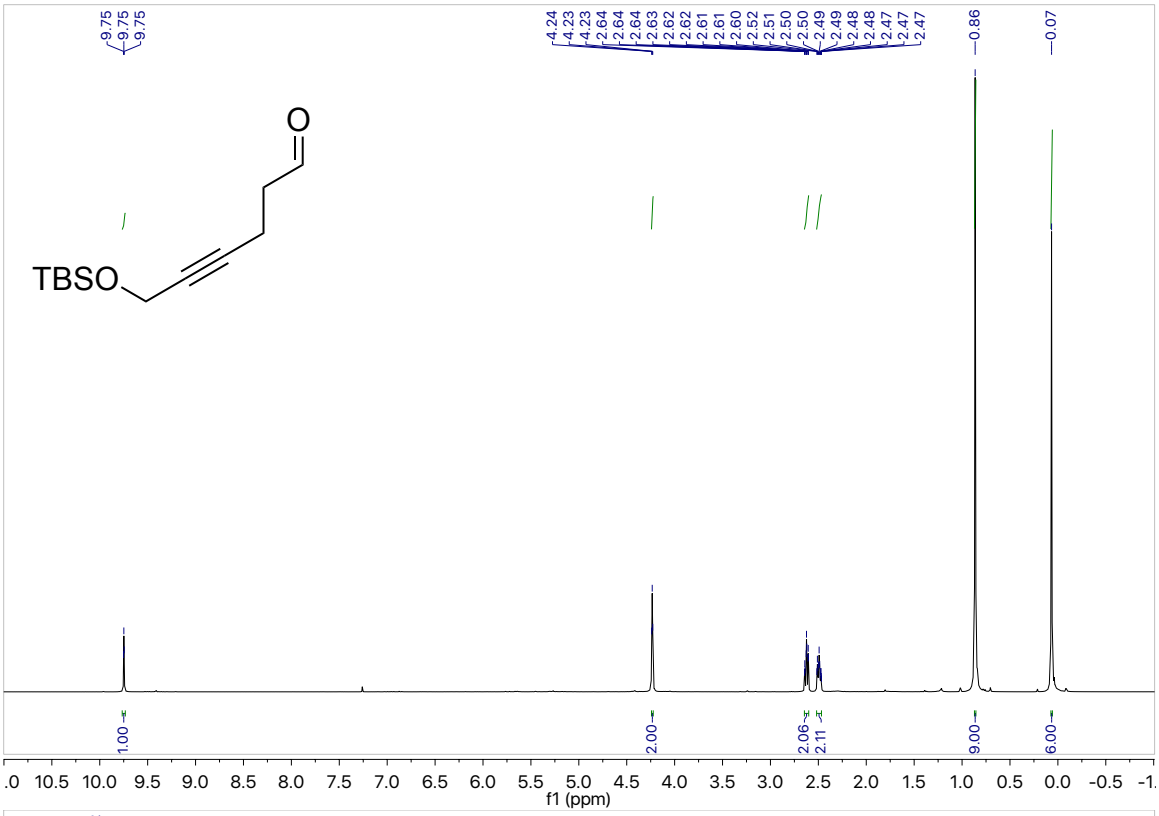

13C NMR with 1H decoupling
155.2353
155.2173
155.1852
155.1676
152.2588
152.0441
149.4447
146.7486
136.1547
135.9937
130.3237
130.2227
122.3022
119.2005
116.2440
116.1907
115.9663
115.9133
114.5452
110.7287
110.6993
55.9000
54.8074
36.3033
36.2669
36.1378
36.0977
34.6540
34.5648
34.5490
33.7966
30.3811
30.3510
30.3374
27.1542
27.0566
26.7244
26.5881
26.5531
24.6559
24.4650
23.6998
2.0927
Cy
Cy
⊖SbF6
MeO
P–Ag–NCMe
⊕
iPr
iPr
iPr
iPr
OMe
150
100
50
0
[ppm]
[rel]
0
2
4
6

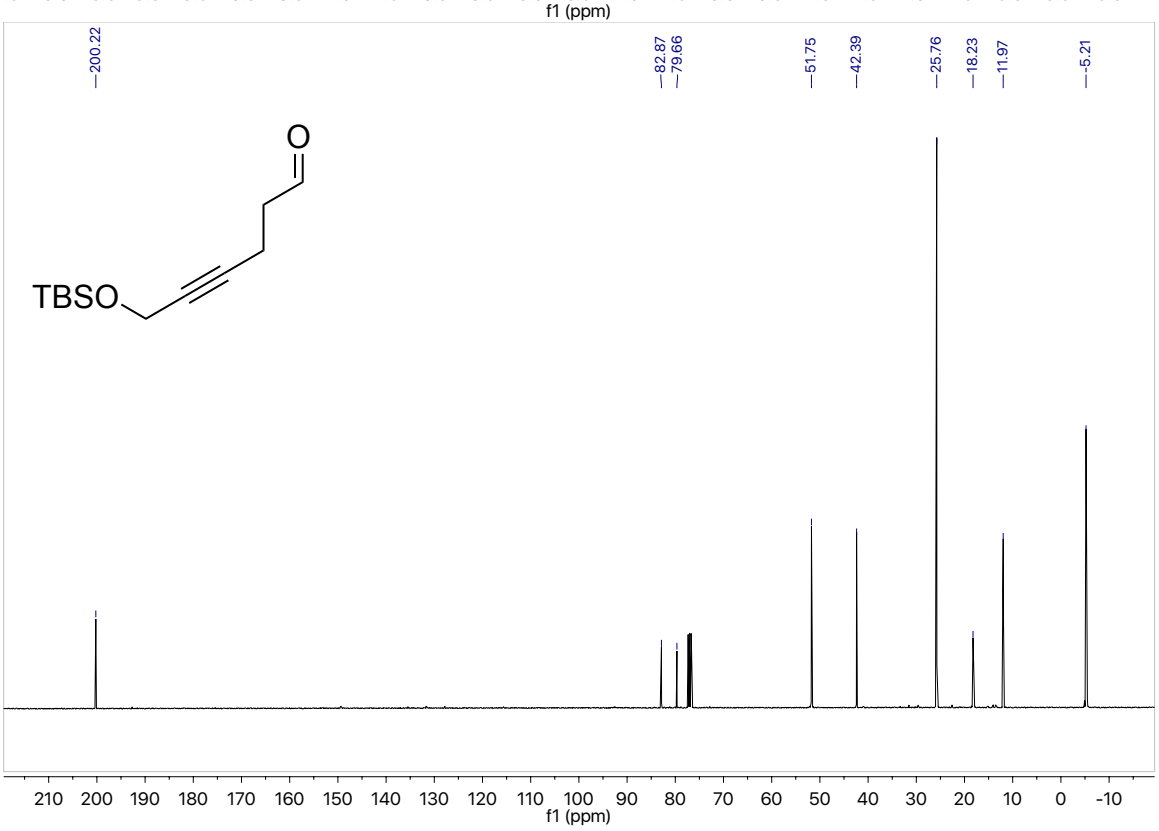

31P NMR with proton decoupling
27.7702
27.3562
21.9859
21.5709
Cy
Cy
⊖SbF6
MeO
P–Ag–NCMe
⊕
iPr
iPr
iPr
iPr
OMe
[rel]
20
15
10
5
0
40
30
20
10
[ppm]

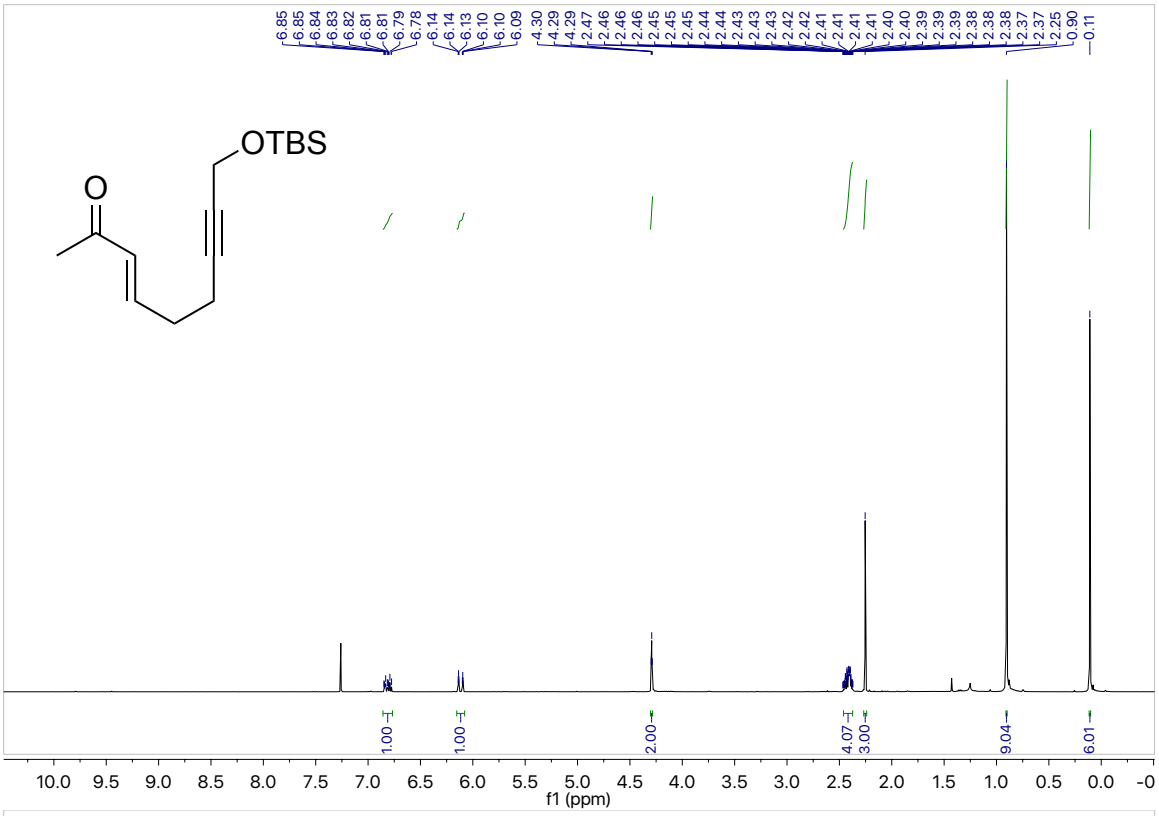

1H NMR
tBu
tBu
⊖SbF6
MeO
P
Ag
⊕
NCMe
iPr
iPr
iPr
OMe
4.5560
7.3736
3.2325
1.0711
2.1131
4.0751
32.8626
6.5982
[rel]
[ppm]

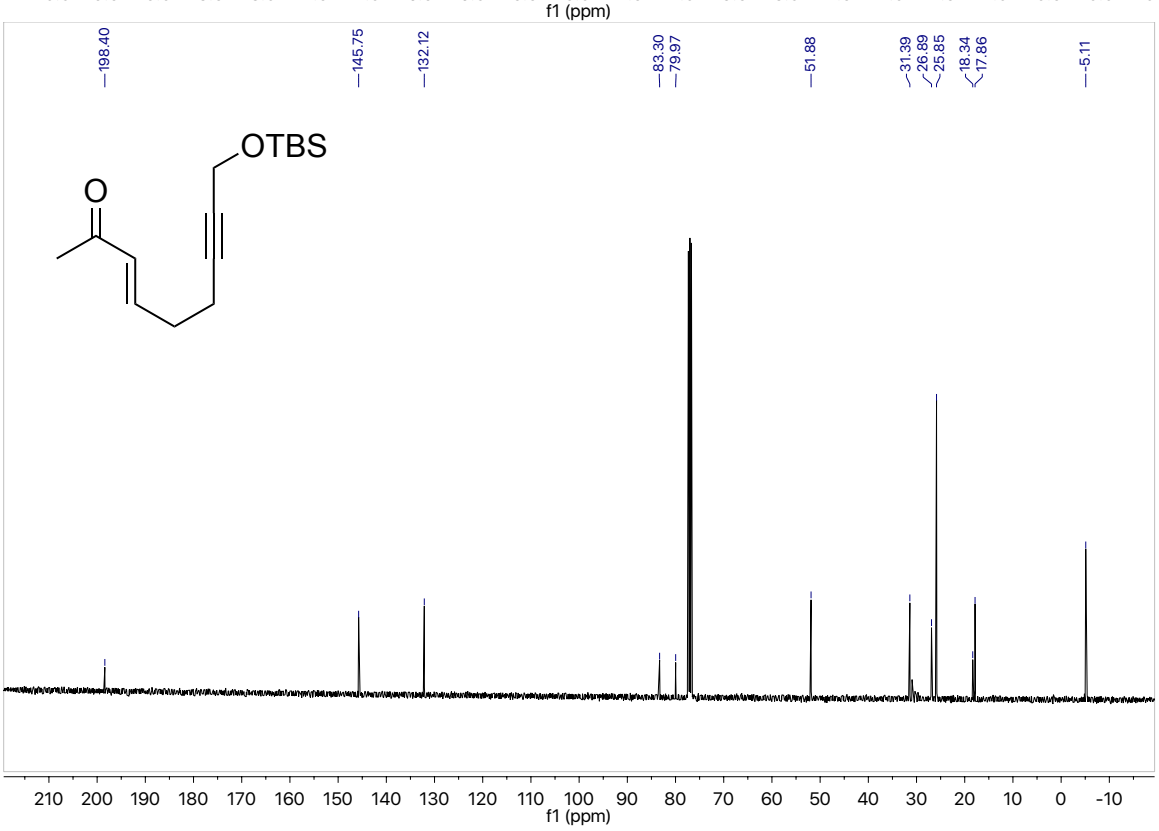

13C NMR with 1H decoupling
155.0345
154.9943
152.5337
152.4492
148.9170
146.8866
136.4441
136.2563
130.1808
130.0893
122.1130
118.4037
118.3229
118.2392
118.1874
114.7853
110.7433
110.7137
77.2956
77.0431
76.7867
70.5155
54.6125
54.5475
36.9944
36.9551
36.9131
36.8741
33.7116
32.0583
32.0436
31.9694
31.9547
31.1028
25.3611
25.1191
24.2417
23.6018
tBu
tBu
⊖SbF6
MeO
P
Ag
⊕
NCMe
iPr
iPr
iPr
OMe
[rel]
[ppm]

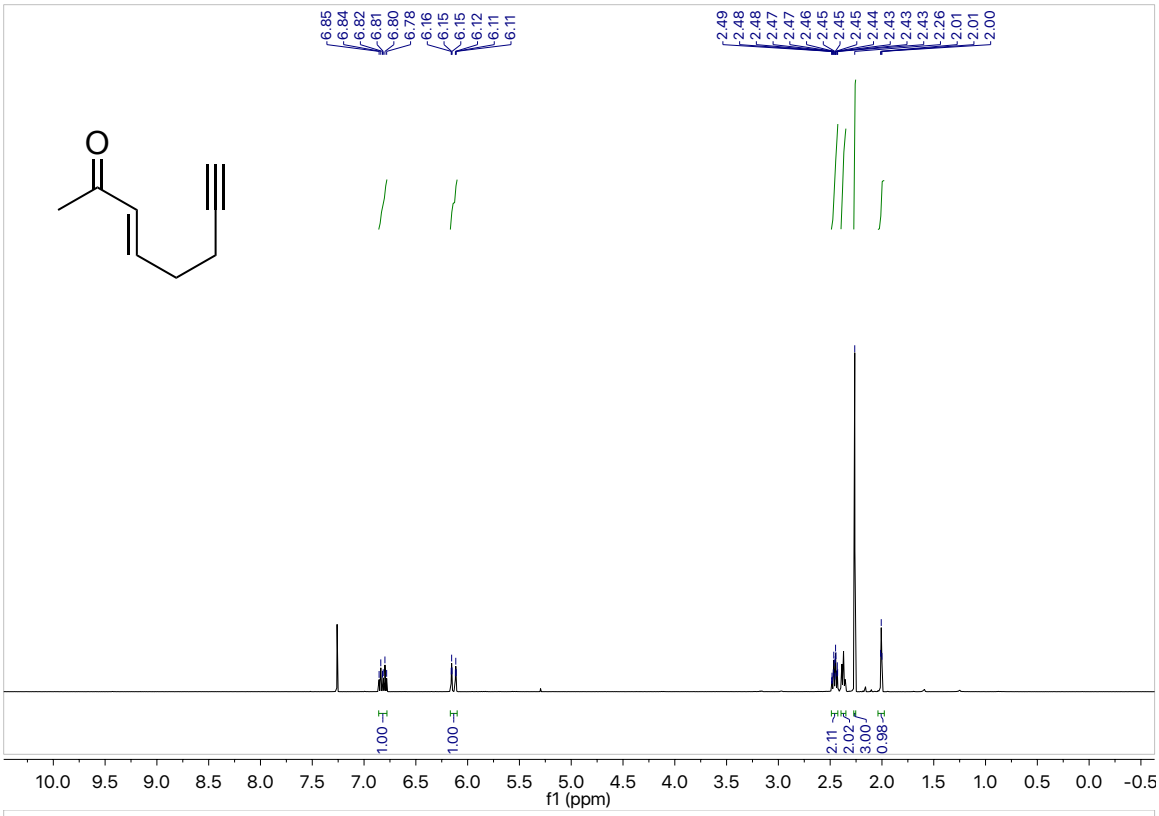

31P NMR with 1H decoupling
59.0724
58.8116
55.4335
55.1726
[rel]
20
15
10
5
0
64
62
60
58
56
54
[ppm]
tBu
tBu
SbF6
MeO
P
Ag
NCMe
iPr
iPr
iPr
OMe

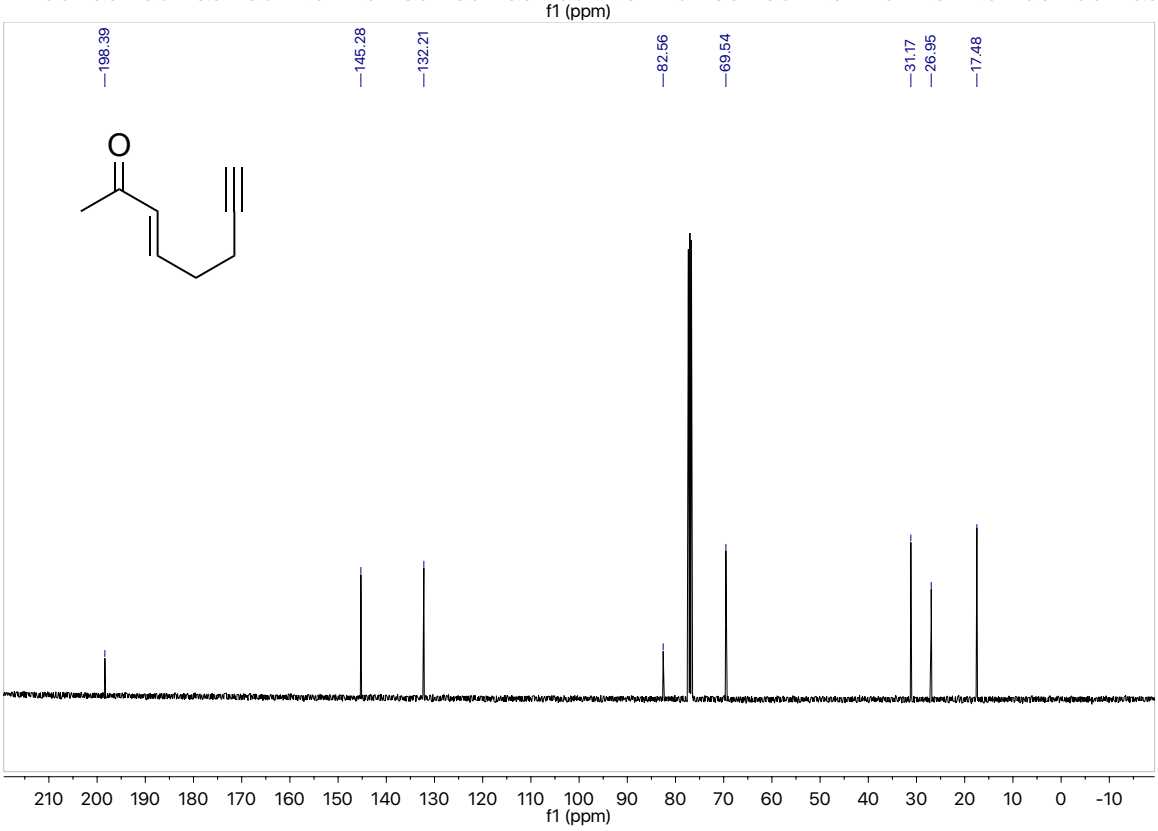

9.75
9.75
9.75
4.24
4.23
4.23
2.64
2.64
2.64
2.63
2.62
2.62
2.61
2.61
2.60
2.52
2.51
2.50
2.50
2.49
2.49
2.48
2.48
2.47
2.47
2.47
0.86
0.07
O
TBSO
1.00
2.00
2.06
2.11
9.00
6.00
f1 (ppm)

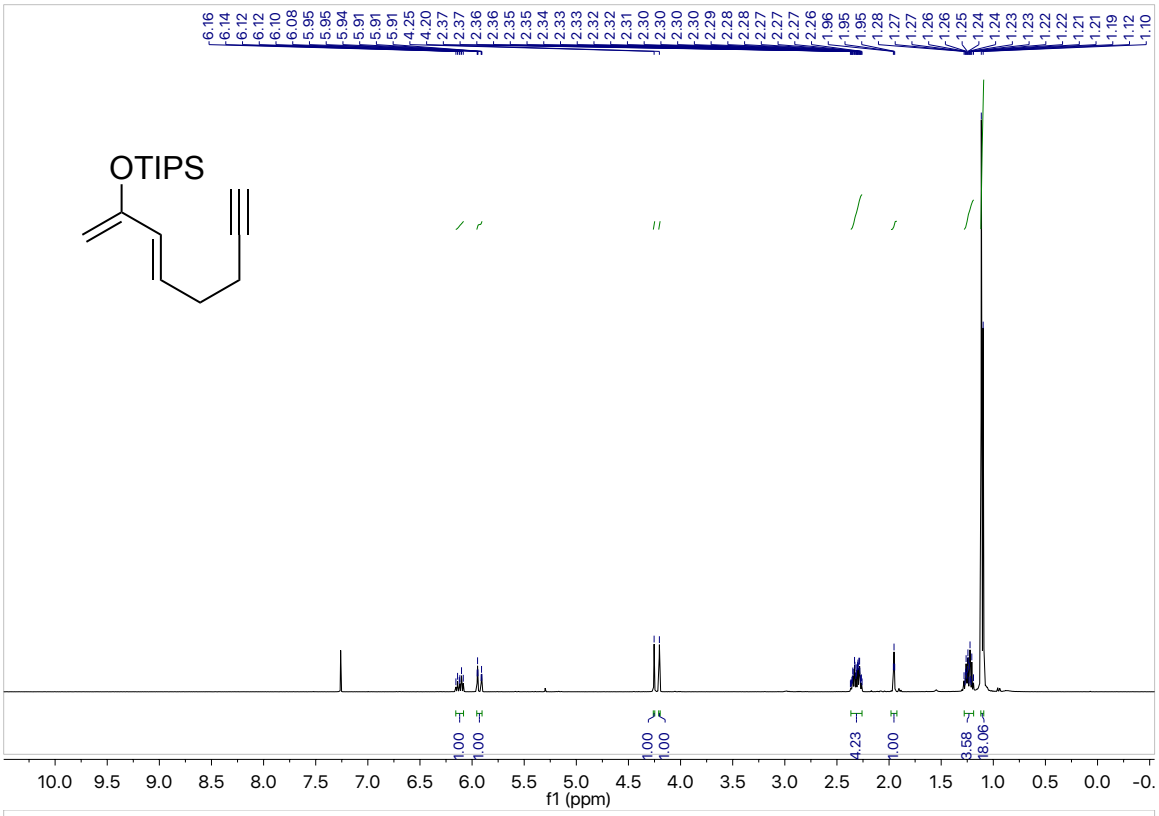

200.22
82.87
79.66
51.75
42.39
25.76
18.23
11.97
5.21
O
TBSO
f1 (ppm)

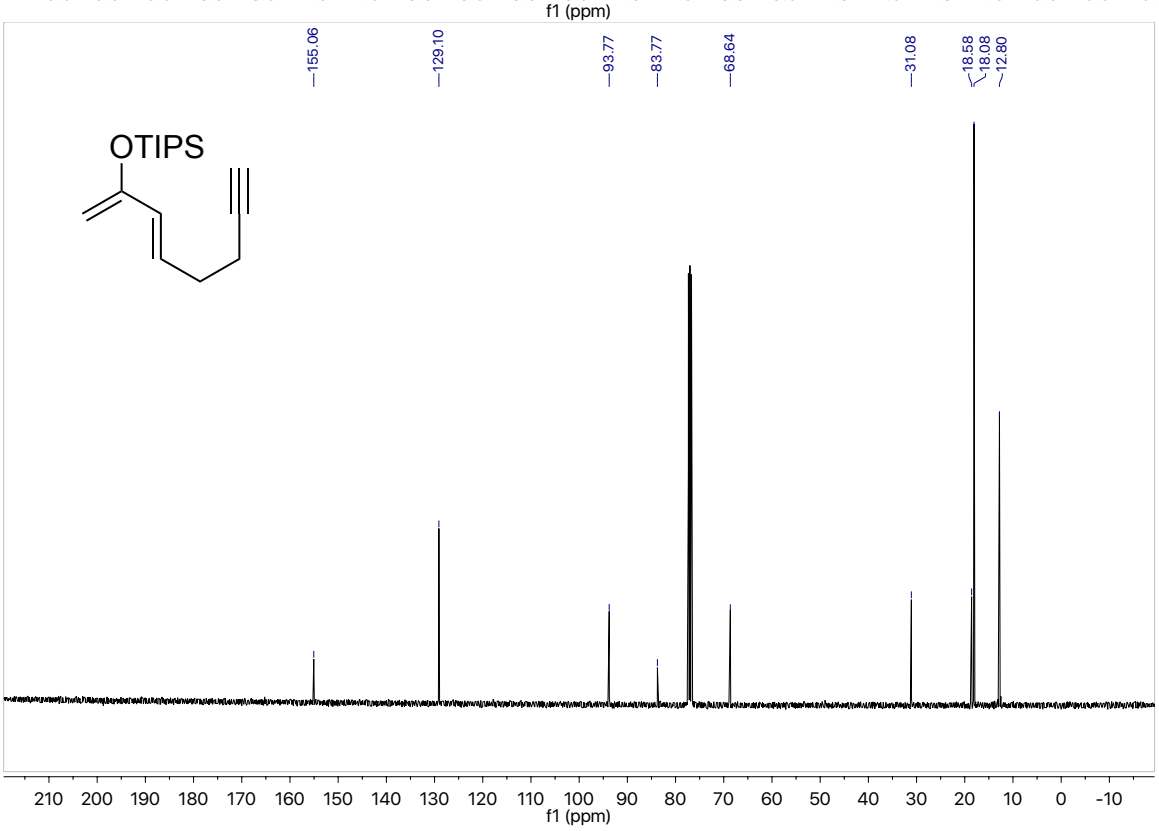

OTBS
O
f1 (ppm)

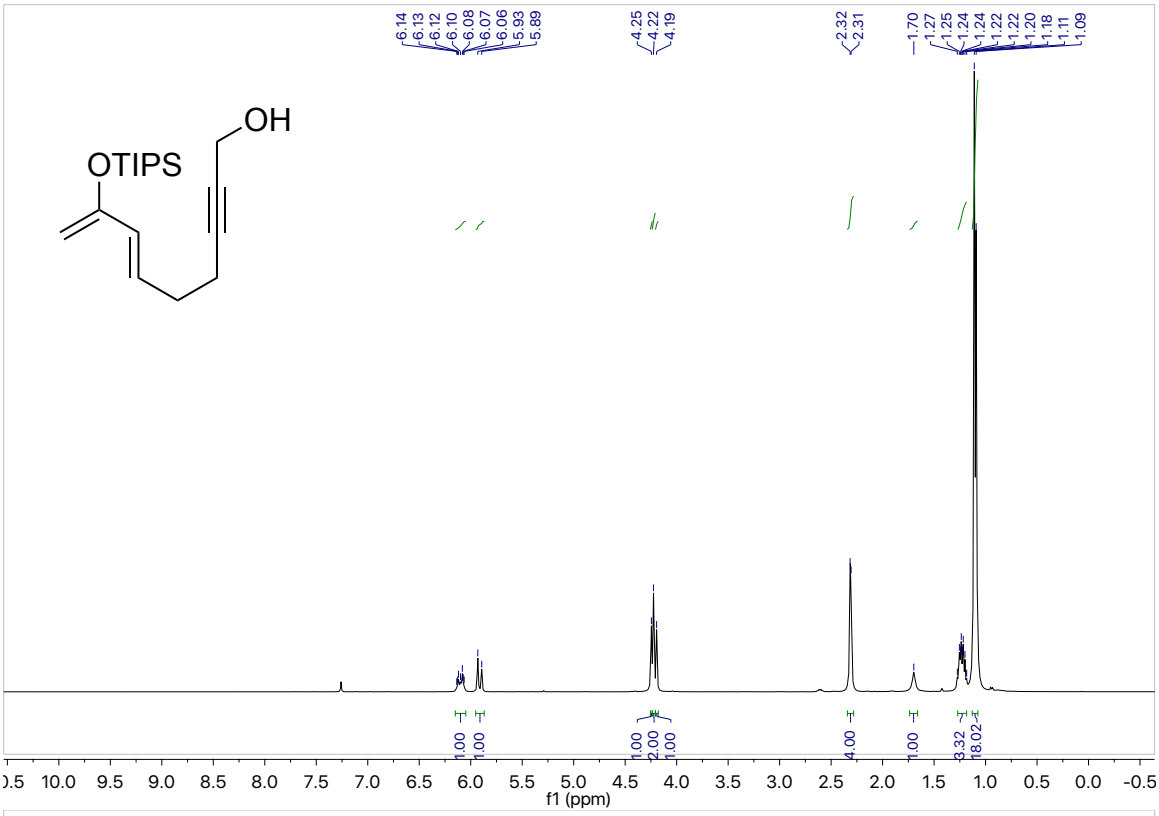

OTBS
O
f1 (ppm)

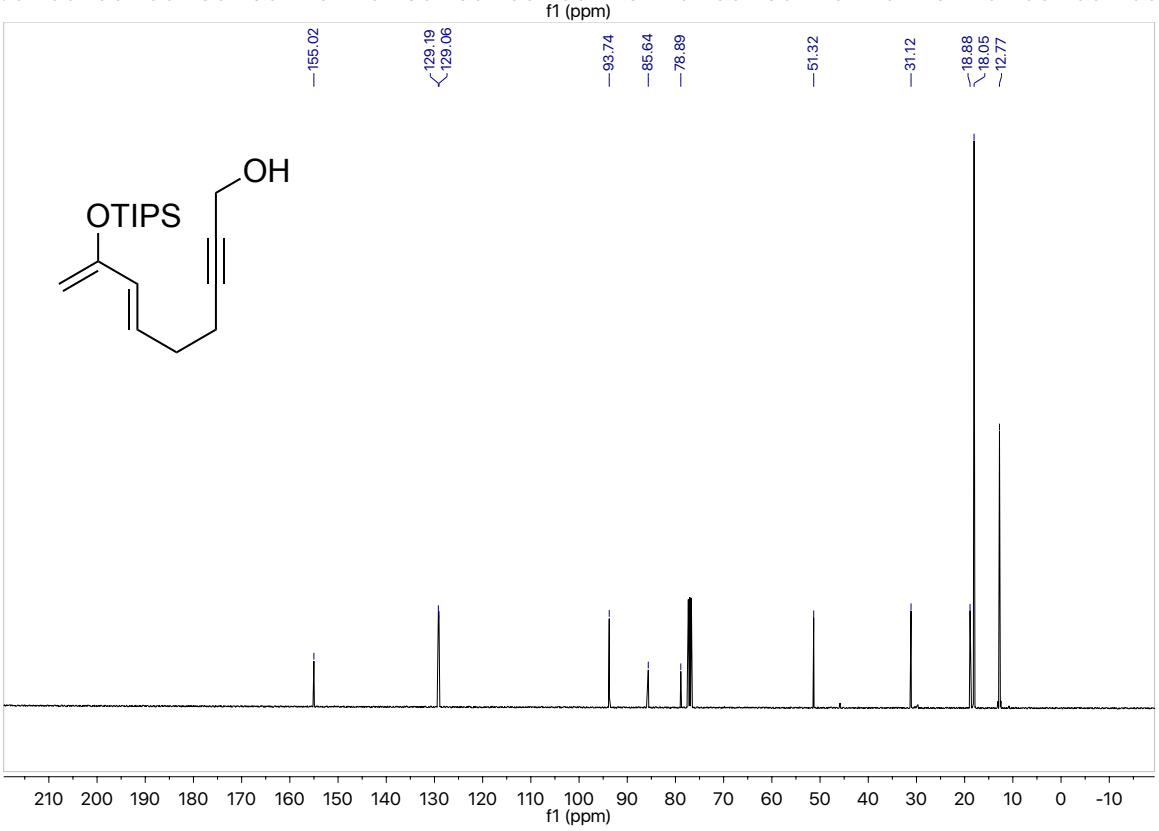

6.85
6.84
6.82
6.81
6.80
6.78
6.16
6.15
6.15
6.12
6.11
6.11
2.49
2.48
2.48
2.47
2.47
2.46
2.45
2.45
2.45
2.44
2.43
2.43
2.26
2.01
2.01
2.00
O
1.00
1.00
2.11
2.02
3.00
0.98
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

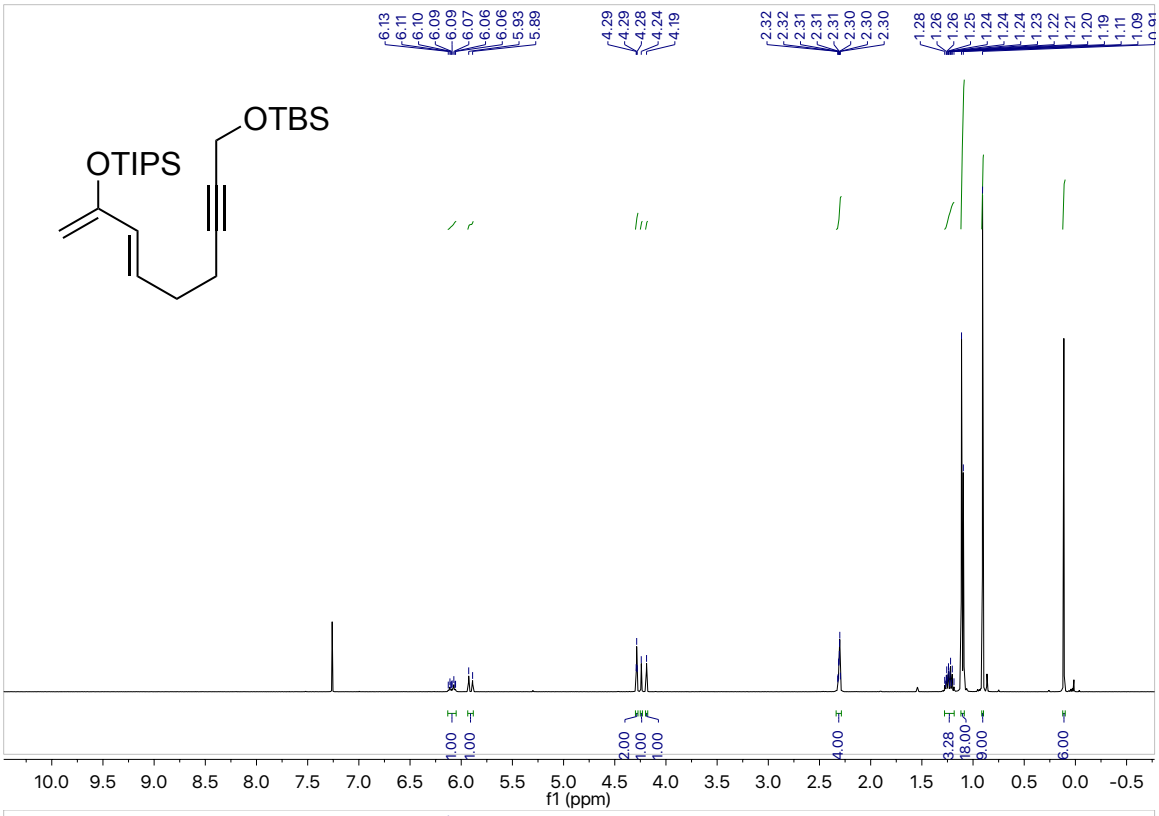

198.39
145.28
132.21
82.56
69.54
31.17
26.95
17.48
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

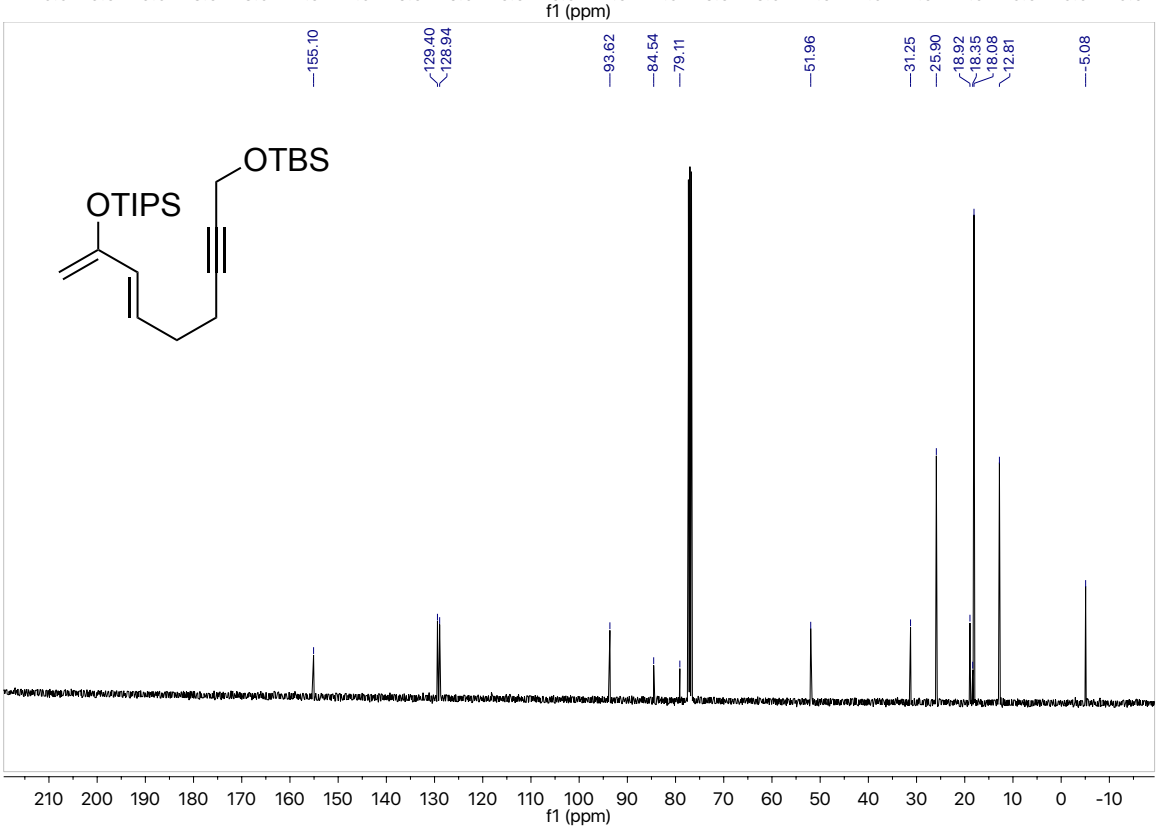

OTIPS
6.16 6.14 6.12 6.12 6.10 6.08 5.95 5.95 5.94 5.91 5.91 5.91 4.25 4.20 2.37 2.37 2.36 2.36 2.35 2.35 2.34 2.33 2.33 2.32 2.32 2.31 2.30 2.30 2.30 2.30 2.29 2.28 2.28 2.27 2.27 2.27 2.26 1.96 1.95 1.95 1.28 1.27 1.27 1.26 1.26 1.25 1.24 1.24 1.23 1.23 1.22 1.22 1.21 1.21 1.19 1.12 1.10
1.00 1.00 1.00 1.00 4.23 1.00 3.58 18.06
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)

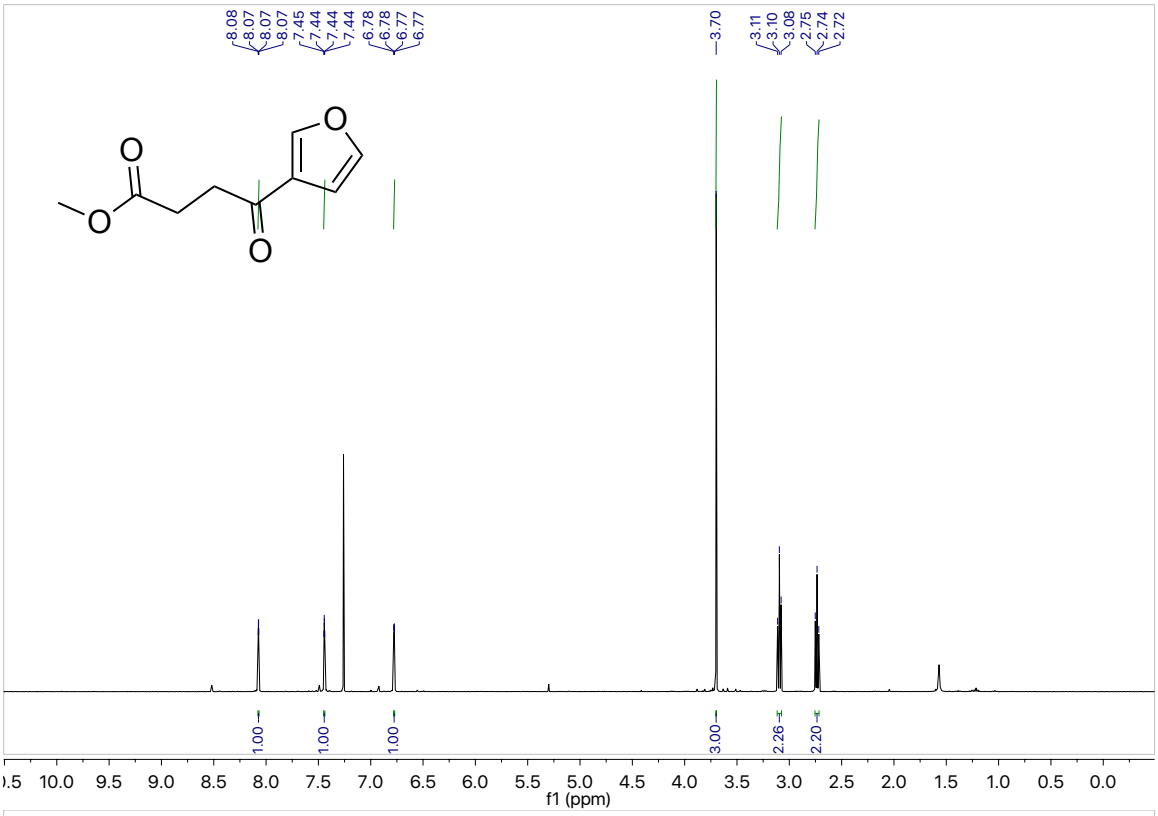

OTIPS
155.06 129.10 93.77 83.77 68.64 31.08 18.58 18.08 12.80
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH
OTIPS
6.14
6.13
6.12
6.10
6.08
6.07
6.06
5.93
5.89
4.25
4.22
4.19
2.32
2.31
1.70
1.27
1.25
1.24
1.24
1.22
1.22
1.20
1.18
1.11
1.09
1.00
1.00
1.00
2.00
1.00
4.00
1.00
3.32
18.02
f1 (ppm)


OH
OTIPS
155.02
129.19
129.06
93.74
85.64
78.89
51.32
31.12
18.88
18.05
12.77
f1 (ppm)


OTBS
OTIPS
f1 (ppm)


OTBS
OTIPS
f1 (ppm)


8.08
8.07
8.07
8.07
7.45
7.44
7.44
7.44
6.78
6.78
6.77
6.77
3.70
3.11
3.10
3.08
2.75
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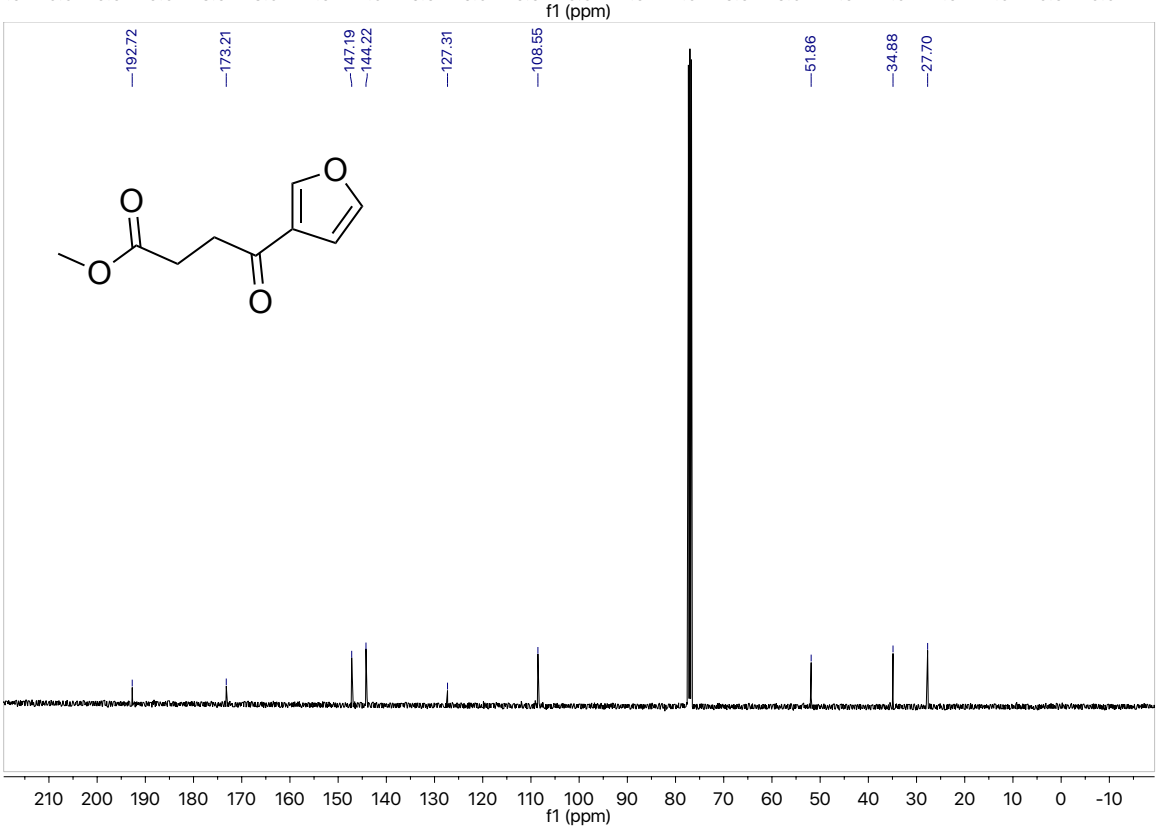
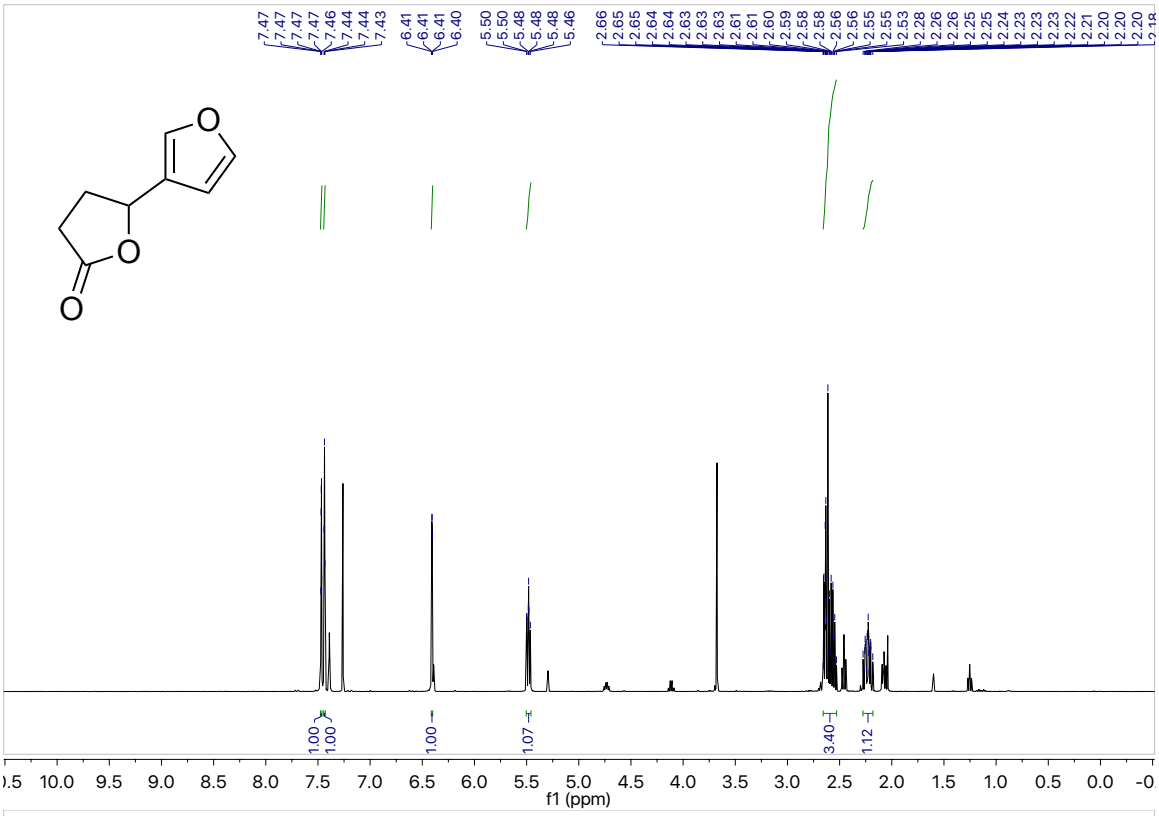
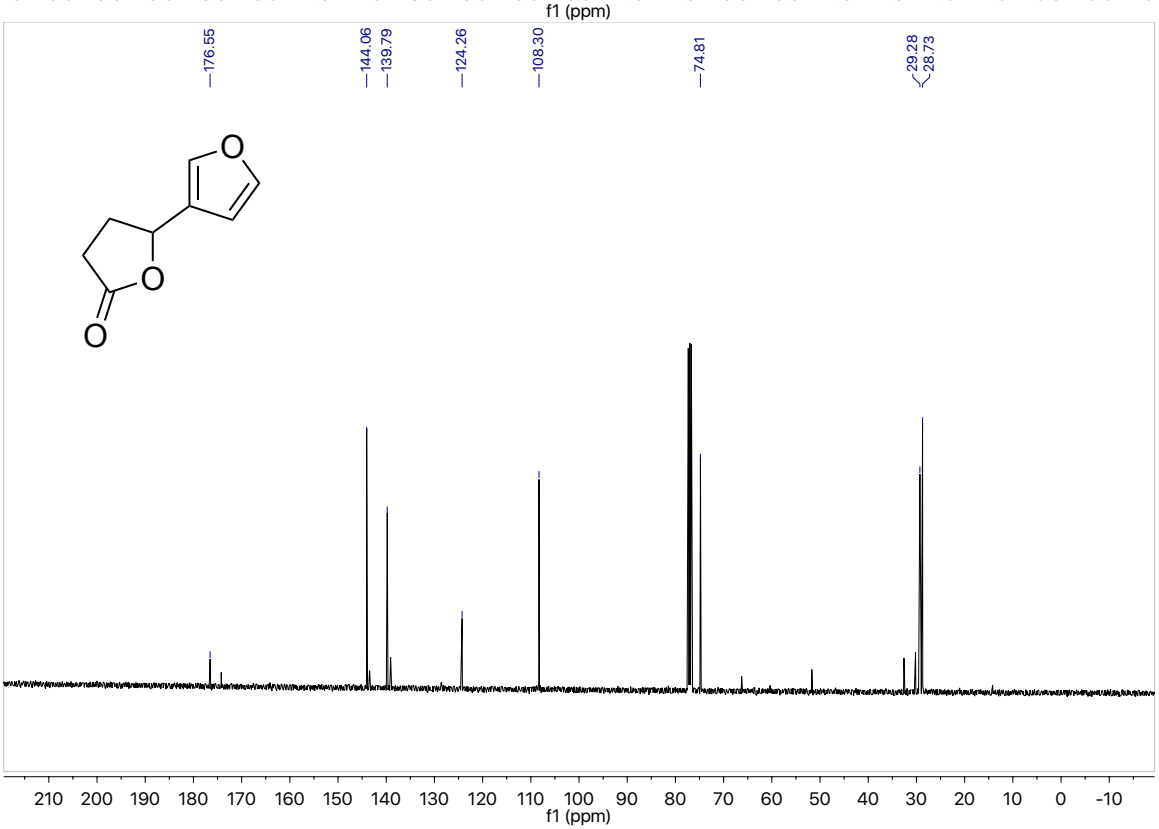
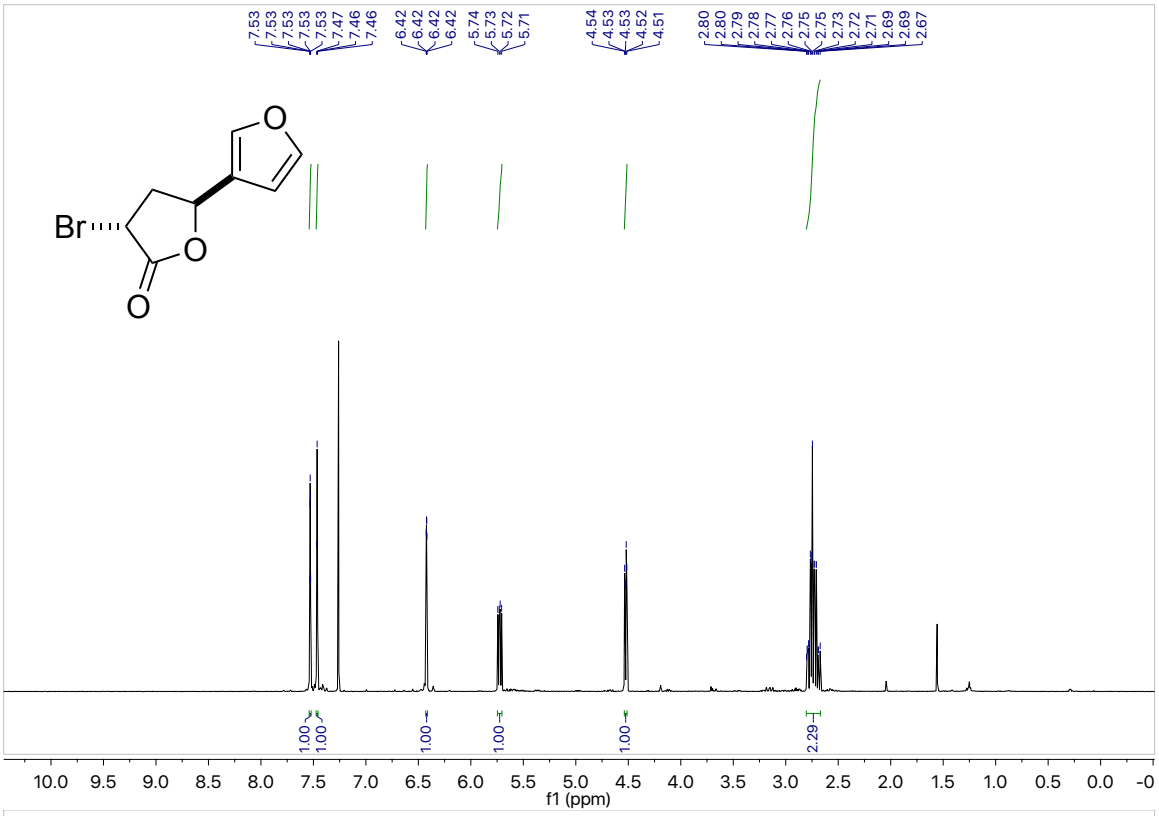
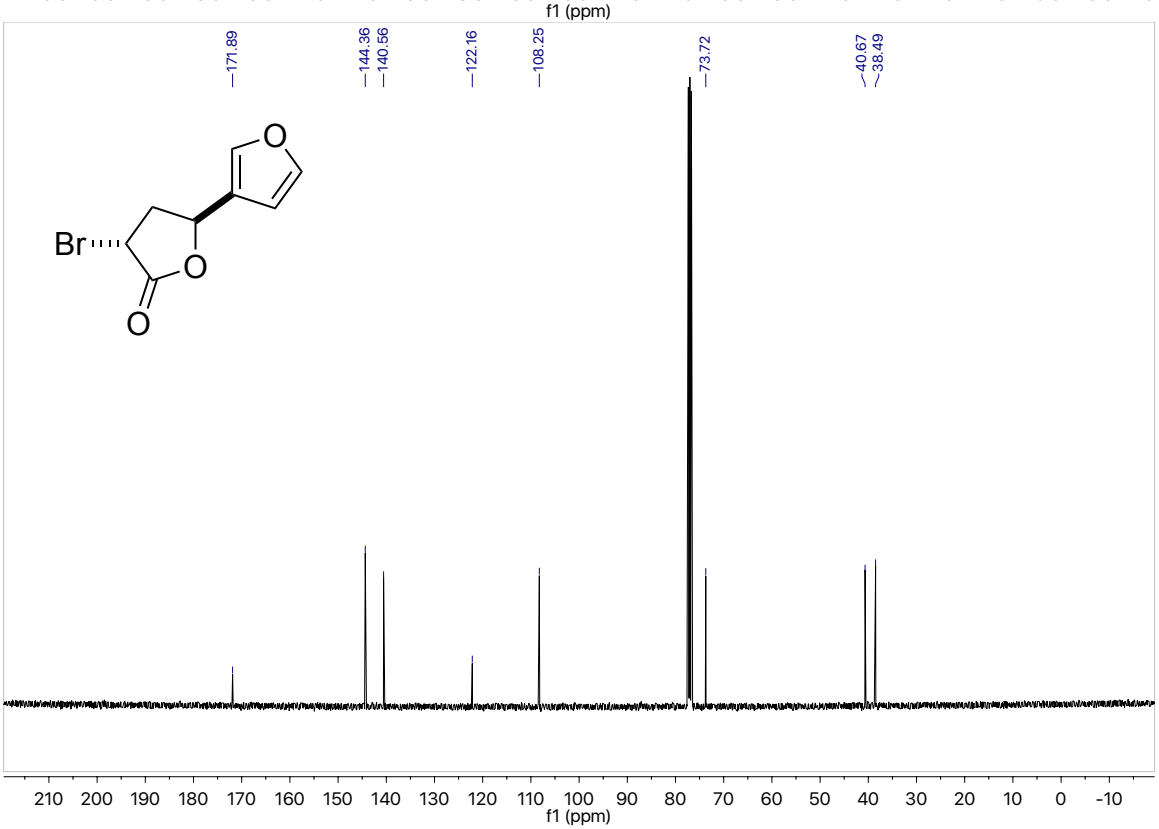
1.00
1.00
3.00
2.26
2.20
f1 (ppm)

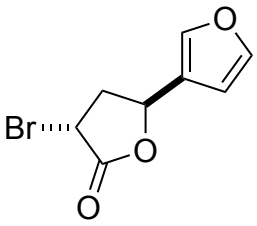

192.72
173.21
147.19
144.22
127.31
108.55
51.86
34.88
27.70
O
O
O
O
f1 (ppm)


7.47
7.47
7.47
7.47
7.46
7.44
7.44
7.43
6.41
6.41
6.41
6.40
5.50
5.50
5.48
5.48
5.48
5.46
2.66
2.65
2.65
2.64
2.64
2.63
2.63
2.61
2.61
2.60
2.59
2.58
2.58
2.56
2.56
2.55
2.55
2.53
2.28
2.26
2.26
2.25
2.25
2.24
2.23
2.23
2.22
2.21
2.20
2.20
1.00
1.00
1.00
1.07
3.40
1.12
f1 (ppm)

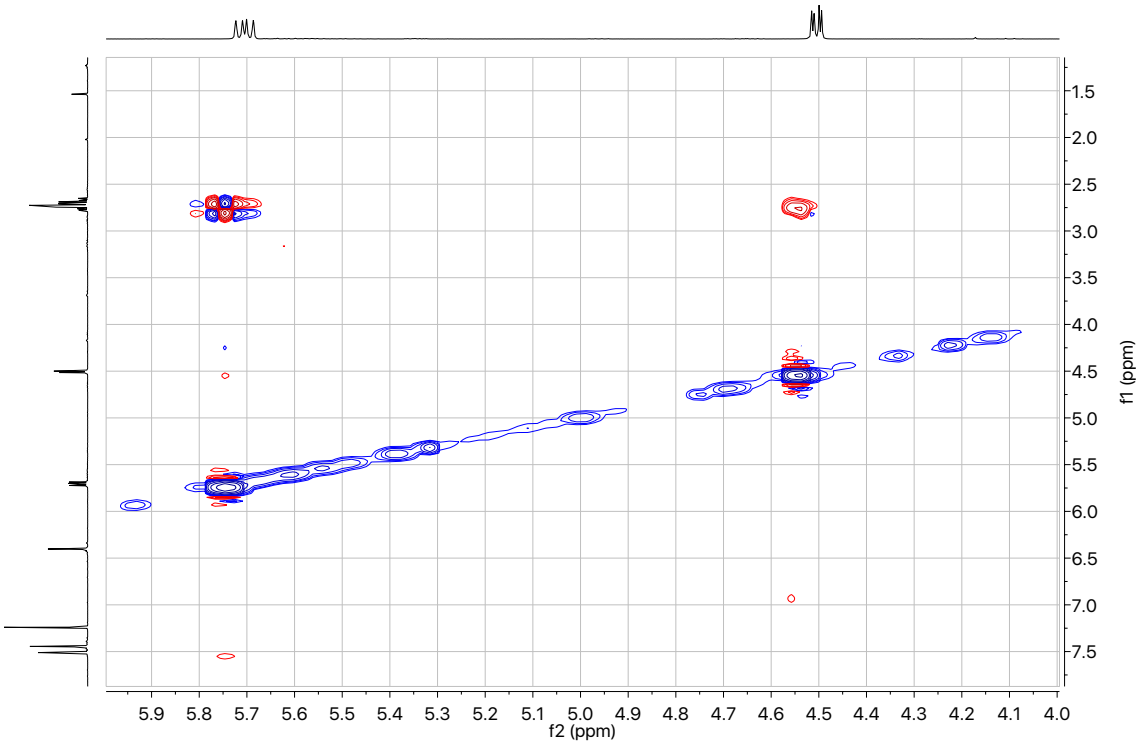

176.55
144.06
139.79
124.26
108.30
74.81
29.28
28.73
f1 (ppm)

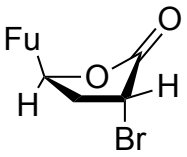

7.53
7.53
7.53
7.53
7.53
7.47
7.46
7.46
6.42
6.42
6.42
6.42
5.74
5.73
5.72
5.71
4.54
4.53
4.53
4.52
4.51
2.80
2.80
2.79
2.78
2.77
2.76
2.75
2.75
2.73
2.72
2.71
2.69
2.69
2.67
Br
O
O
O
1.00
1.00
1.00
1.00
1.00
2.29
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)


171.89
144.36
140.56
122.16
108.25
73.72
40.67
38.49
Br
O
O
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

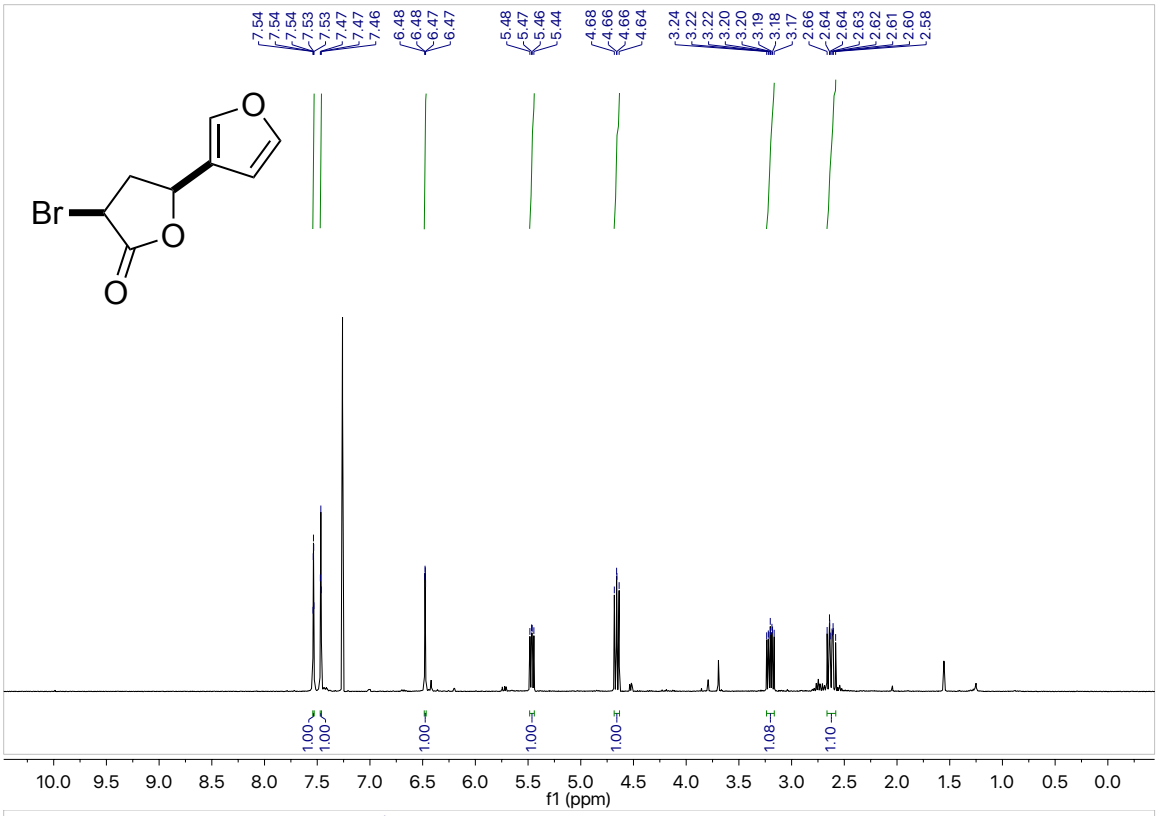


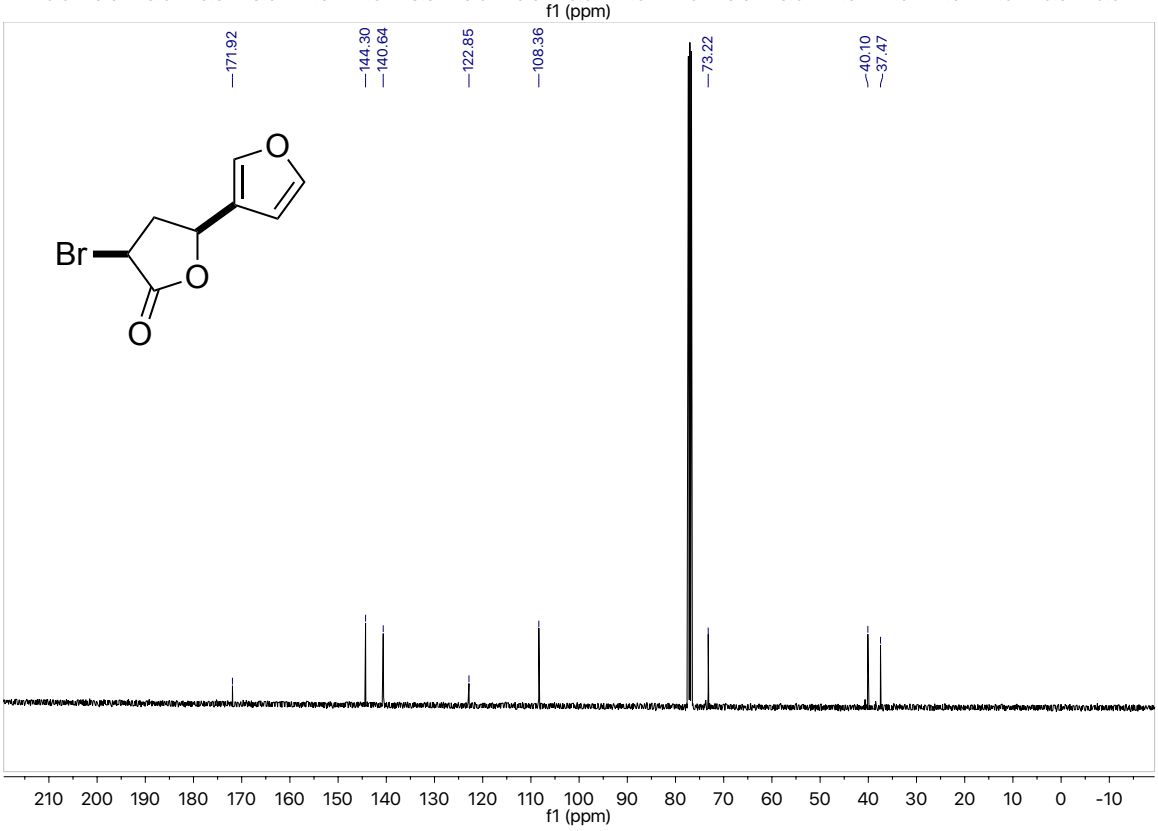
NOESY EXP.

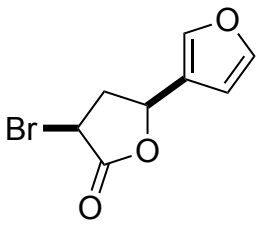




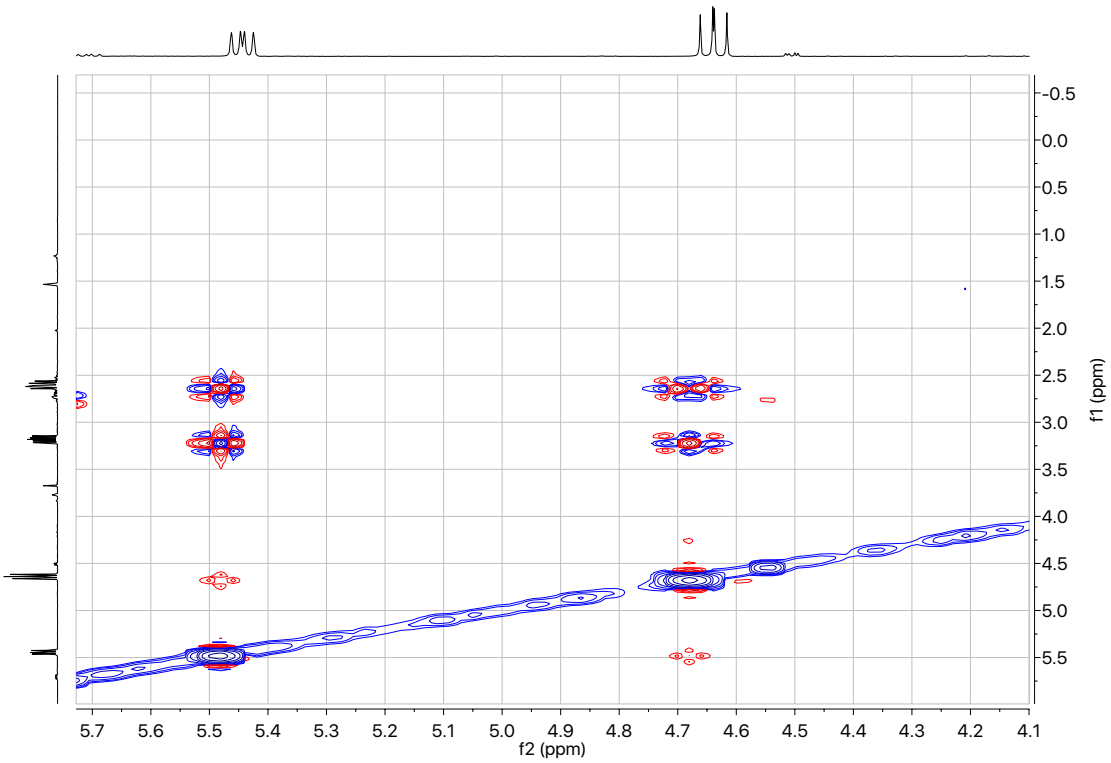
No Noesy Signal Observed

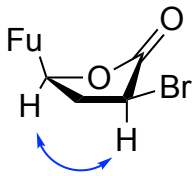

7.54
7.54
7.54
7.53
7.53
7.47
7.47
7.46
6.48
6.48
6.47
6.47
5.48
5.47
5.46
5.44
4.68
4.66
4.66
4.64
3.24
3.22
3.22
3.20
3.20
3.19
3.18
3.17
2.66
2.64
2.64
2.63
2.62
2.61
2.60
2.58
Br
O
O
O
1.00
1.00
1.00
1.00
1.00
1.00
1.08
1.10
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


171.92
144.30
140.64
122.85
108.36
73.22
40.10
37.47
Br
O
O
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

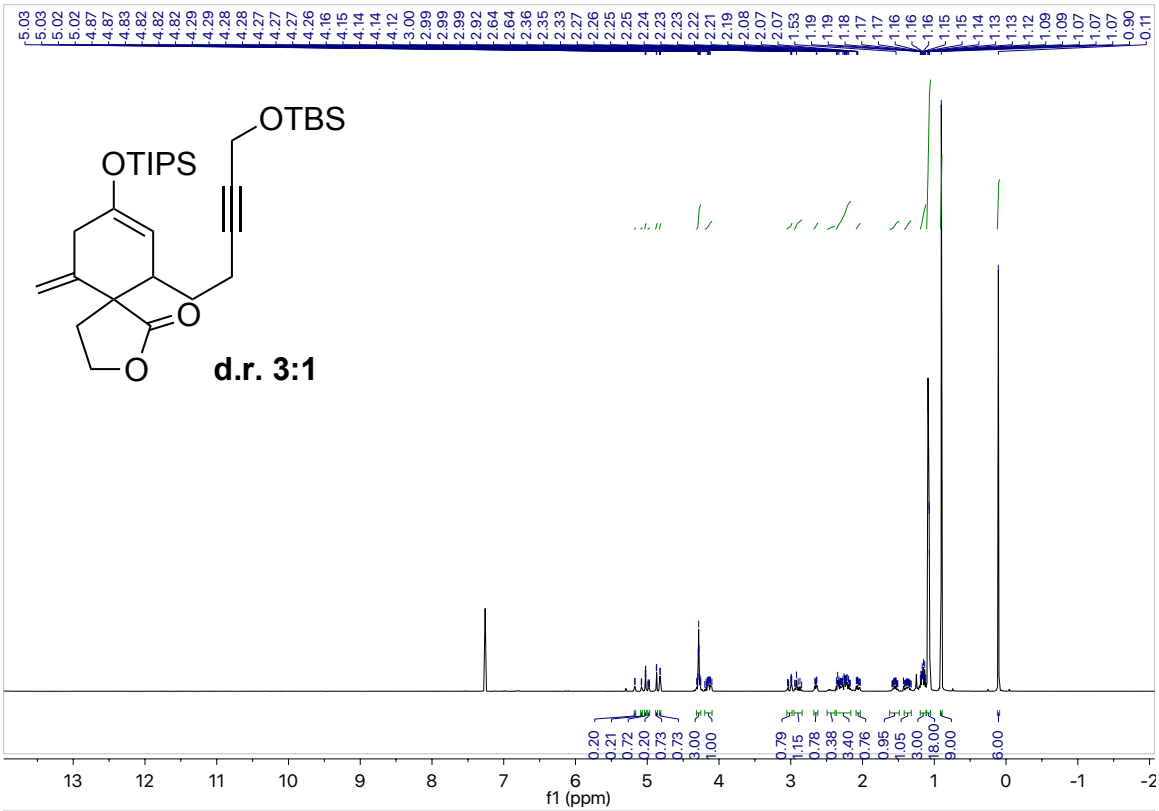


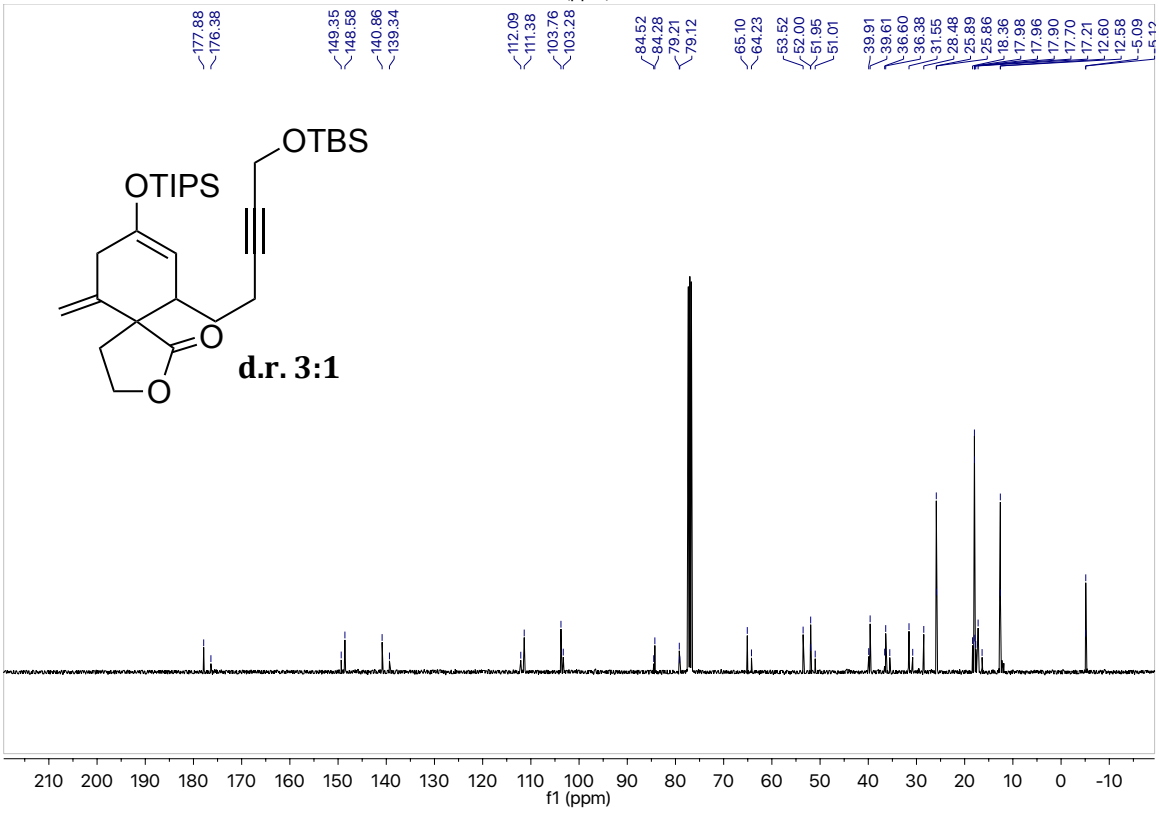
NOESY EXP.

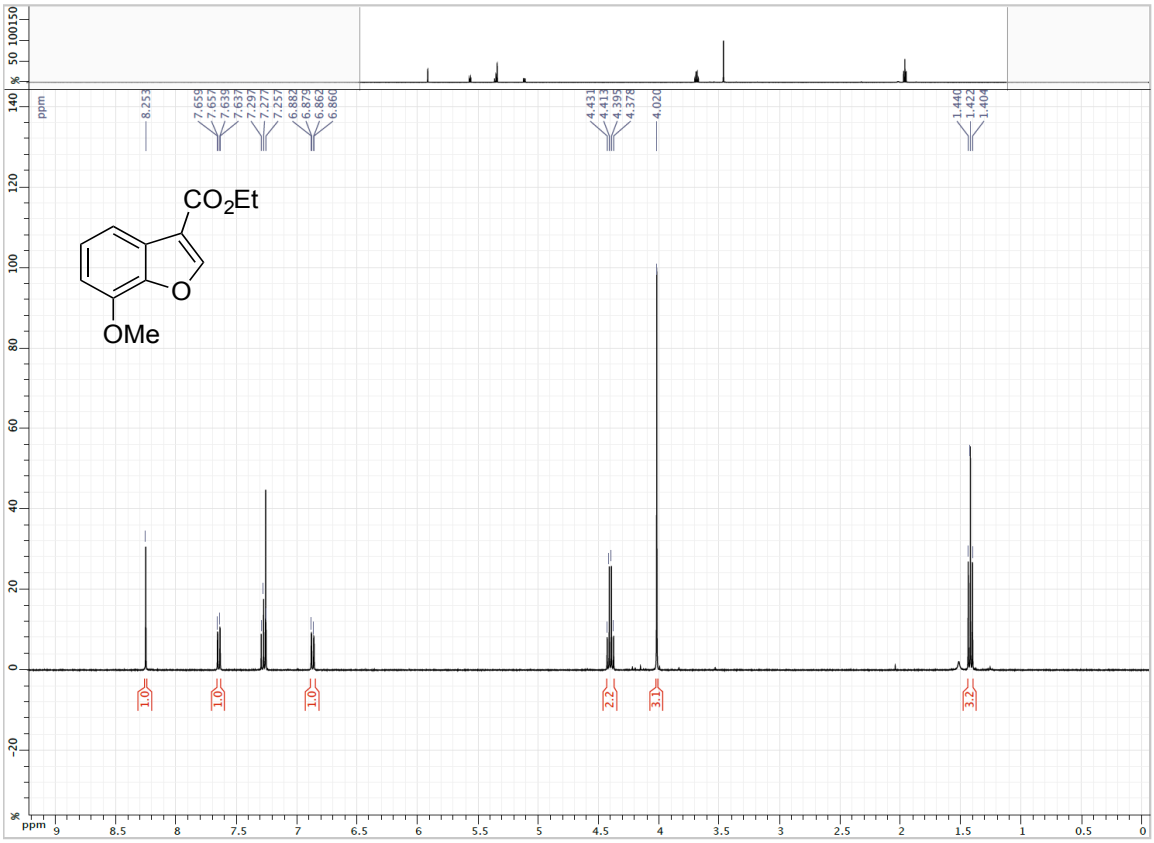


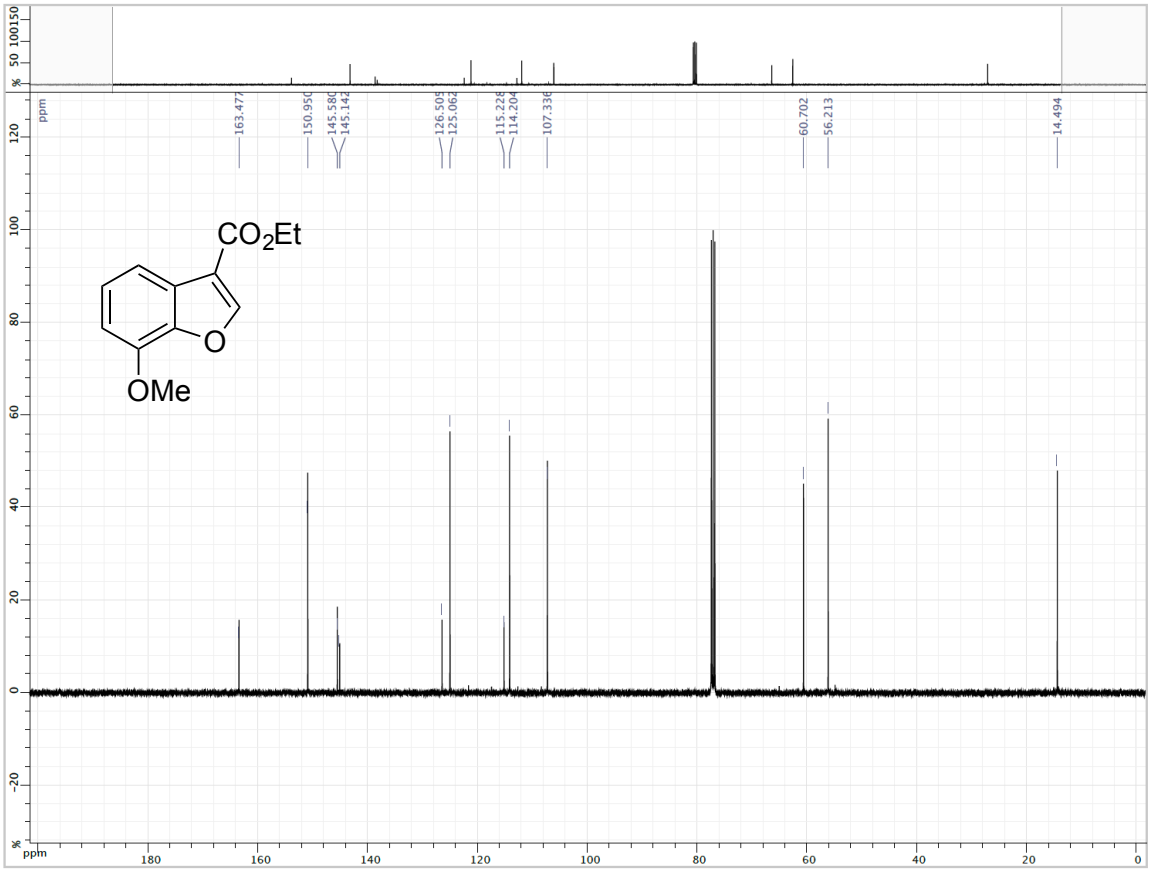


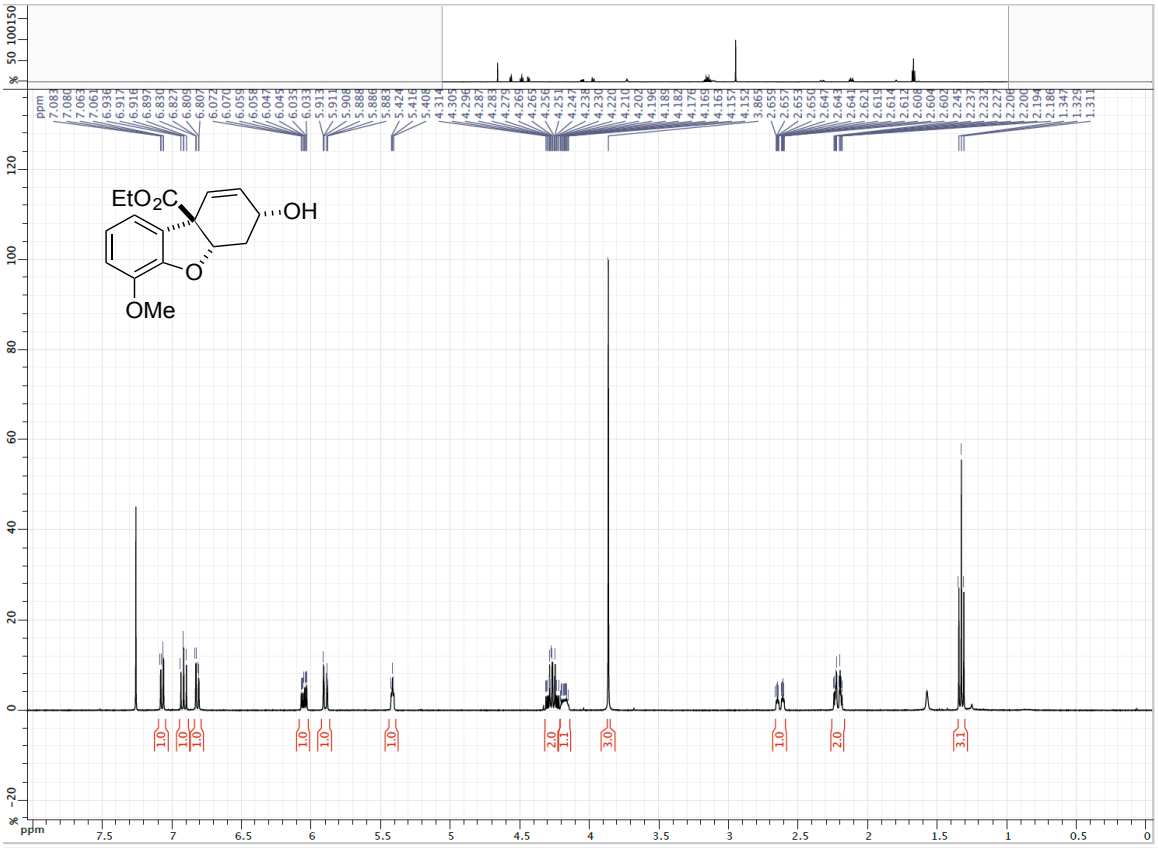
Noesy Signal Observed

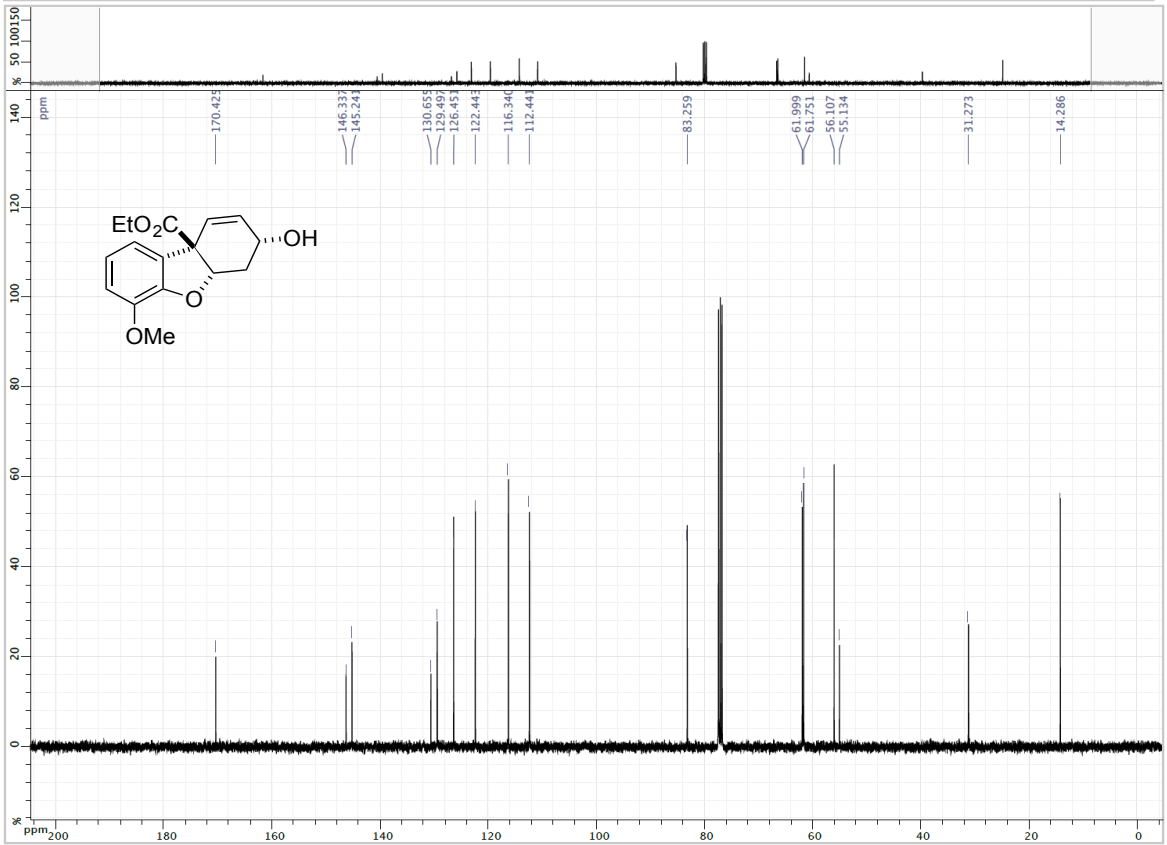

OTBS
OTIPS
O
O
d.r. 3:1
f1 (ppm)

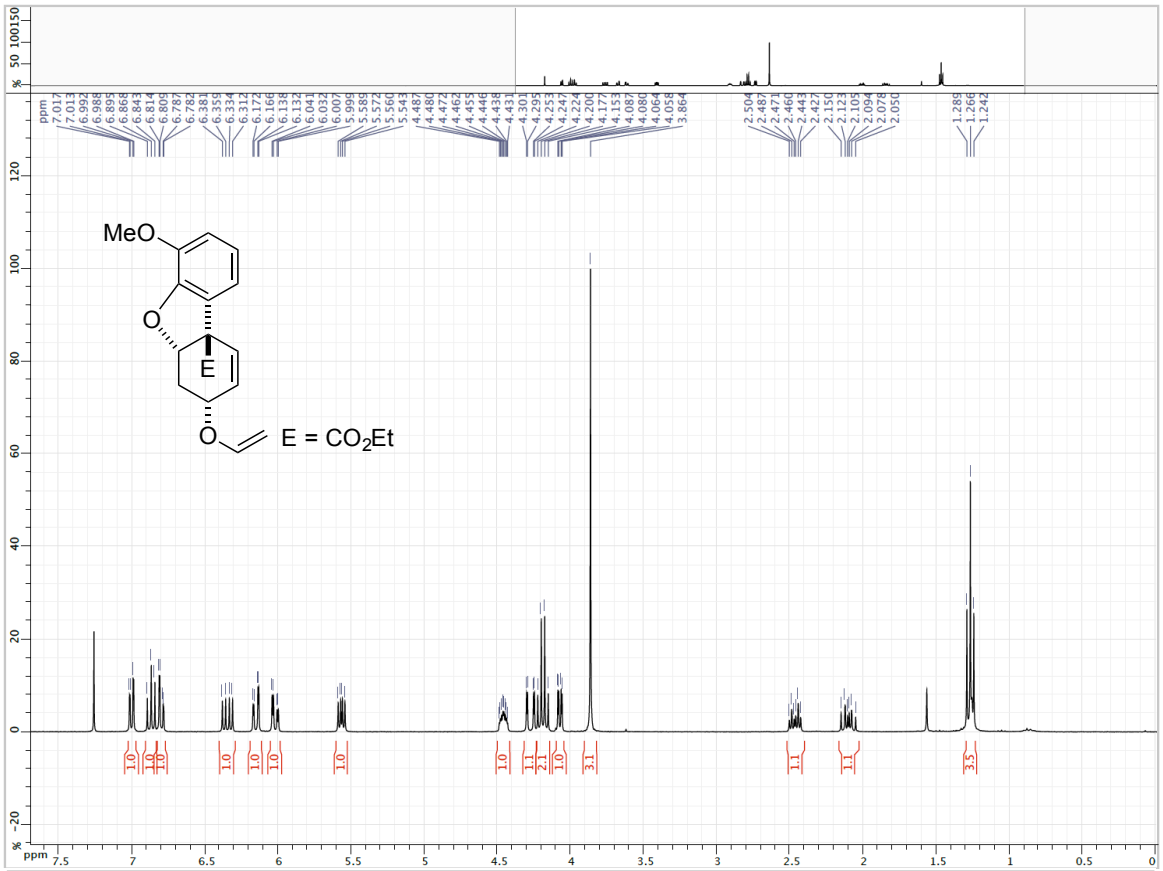

OTBS
OTIPS
O
O
d.r. 3:1
f1 (ppm)

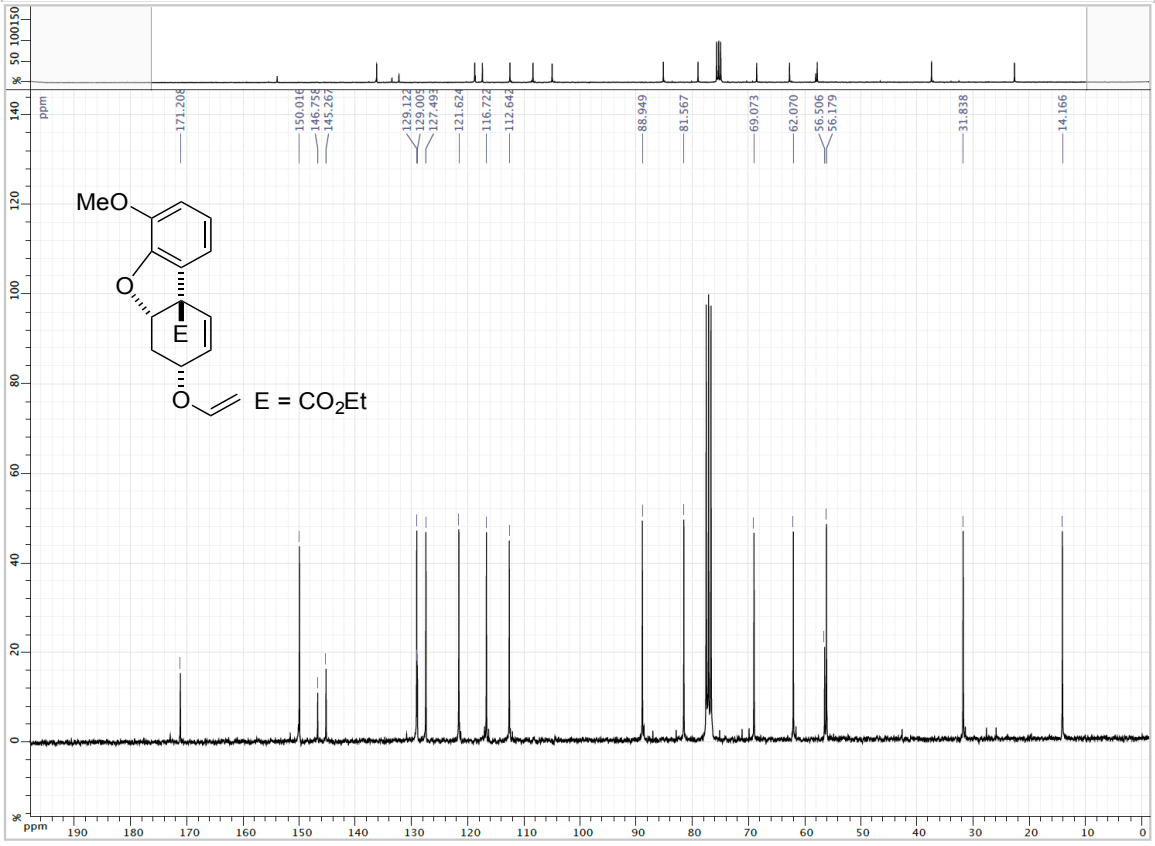

CO2Et
O
OMe
8.253
7.659
7.657
7.639
7.637
7.297
7.277
7.257
6.882
6.879
6.862
6.860
4.431
4.413
4.395
4.378
4.020
1.440
1.422
1.404
1.0
1.0
1.0
2.2
3.1
3.2
ppm

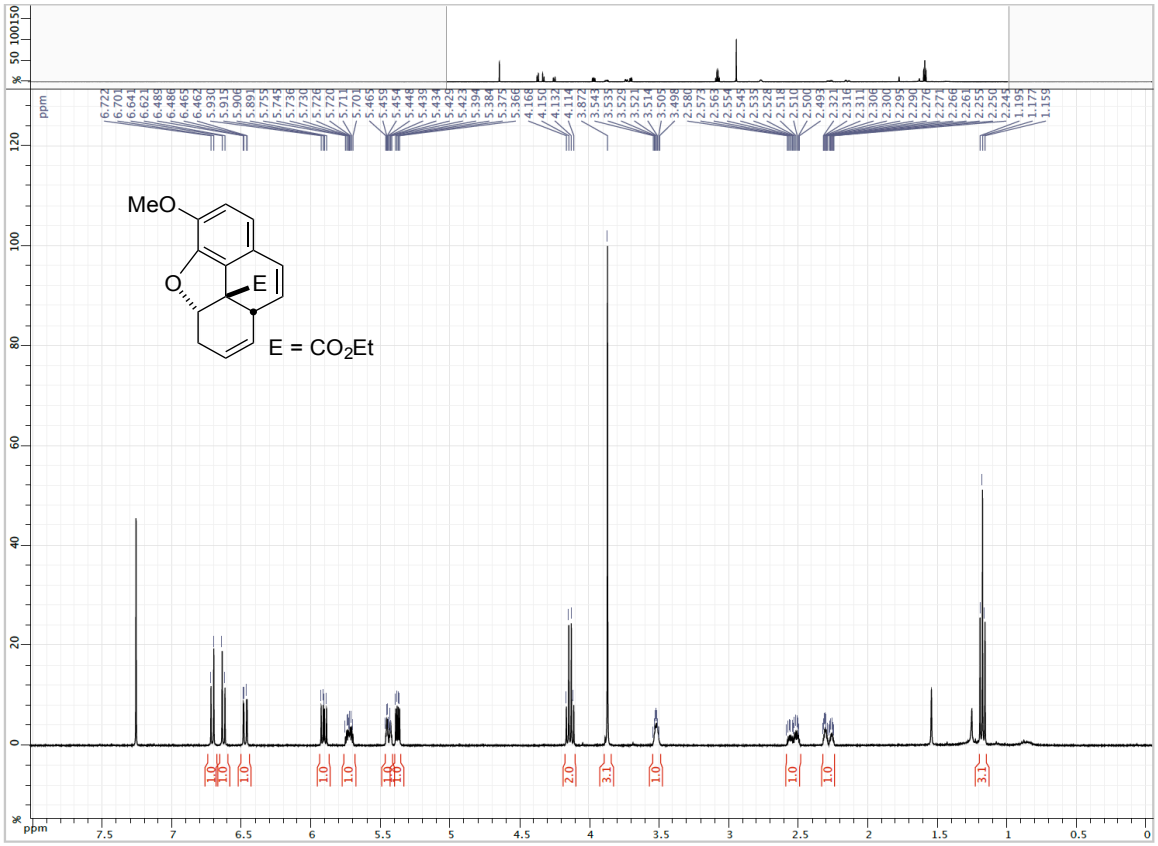

CO2Et
O
OMe
163.477
150.950
145.580
145.142
126.505
125.062
115.228
114.204
107.338
60.702
56.213
14.494
ppm

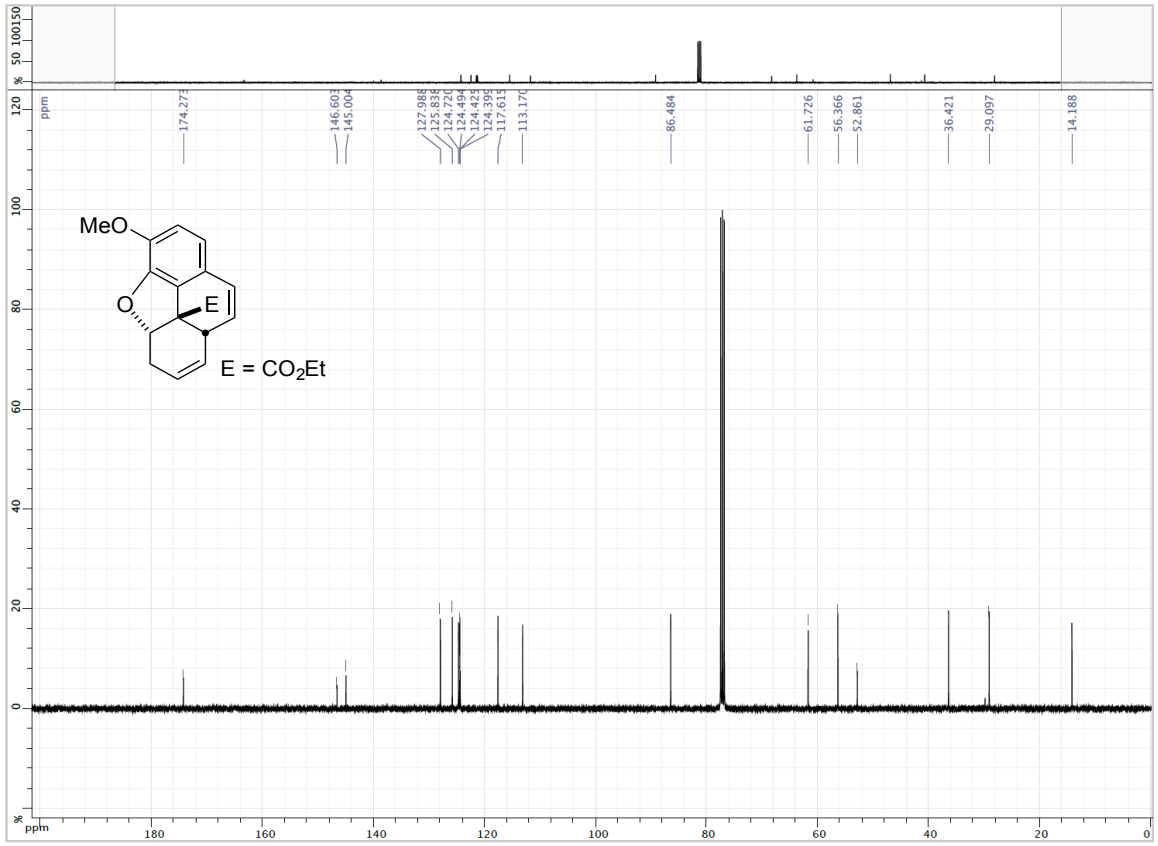

EtO2C
OH
O
OMe

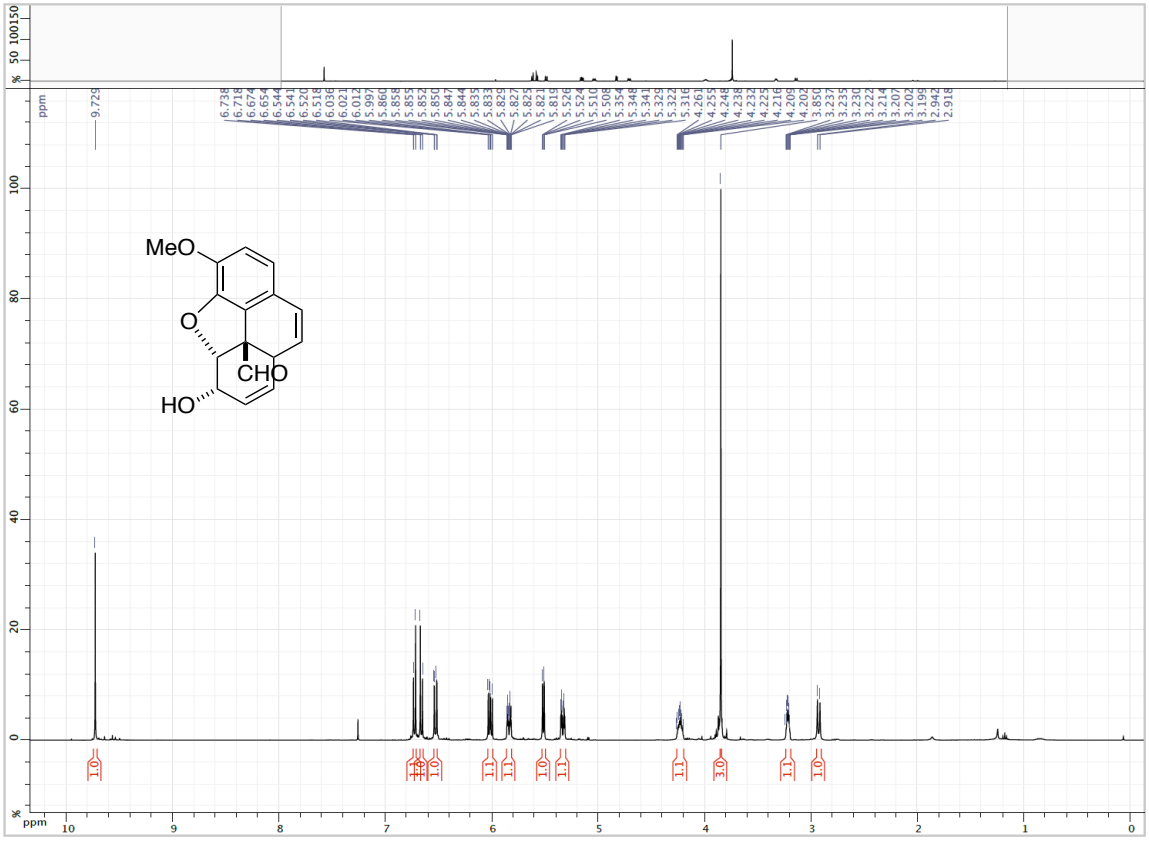

EtO2C
OH
O
OMe

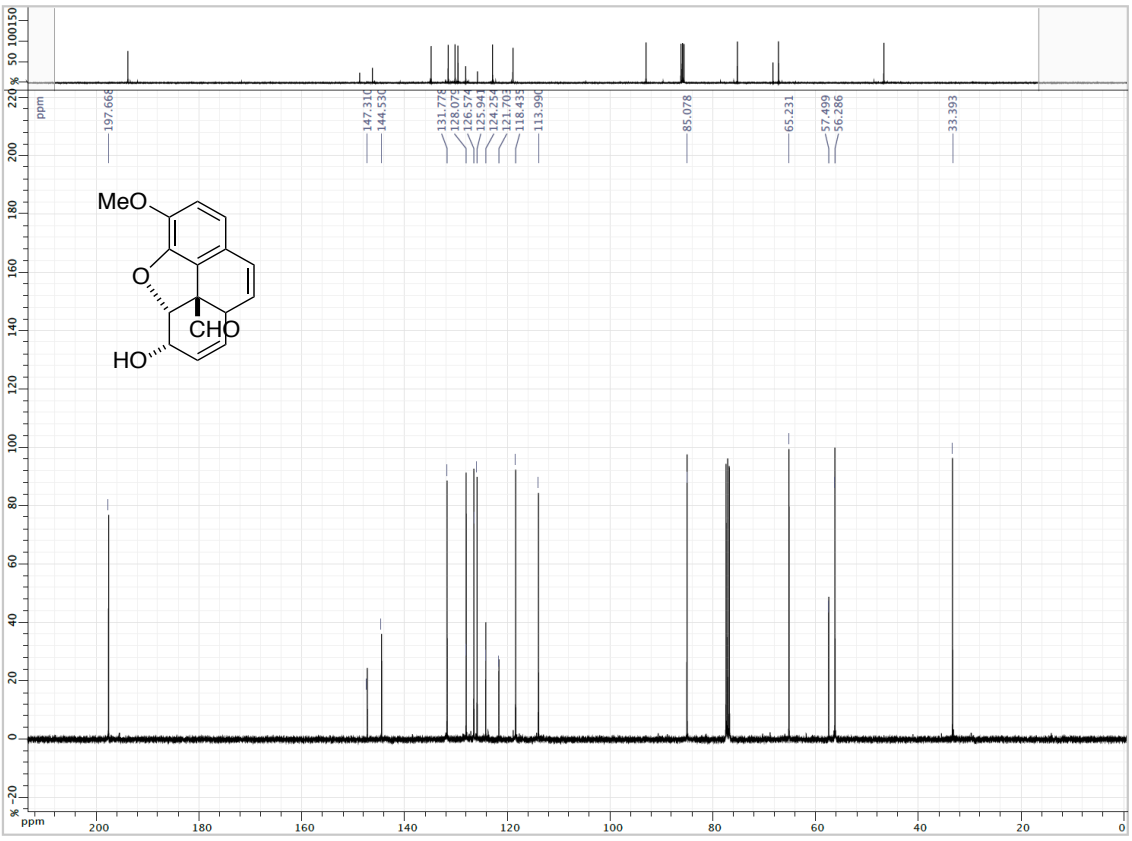

MeO
O
E
O
E = CO2Et

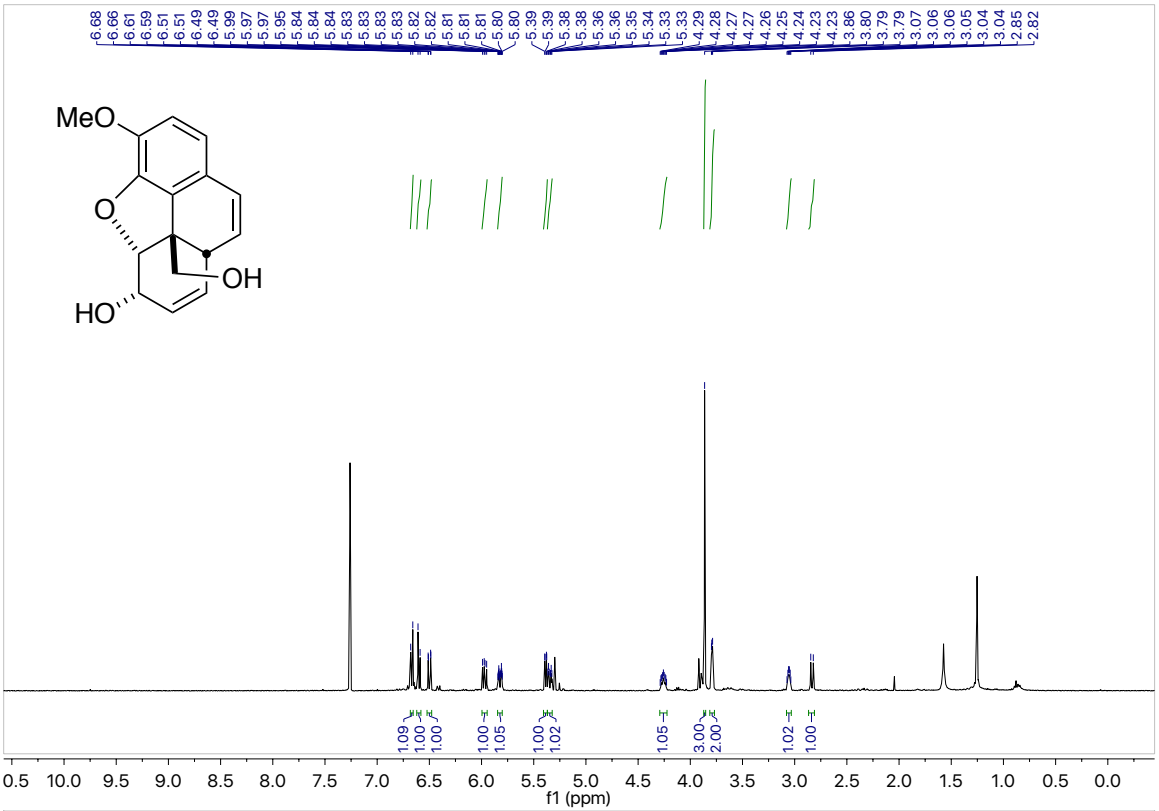

MeO
O
E
O
E = CO2Et

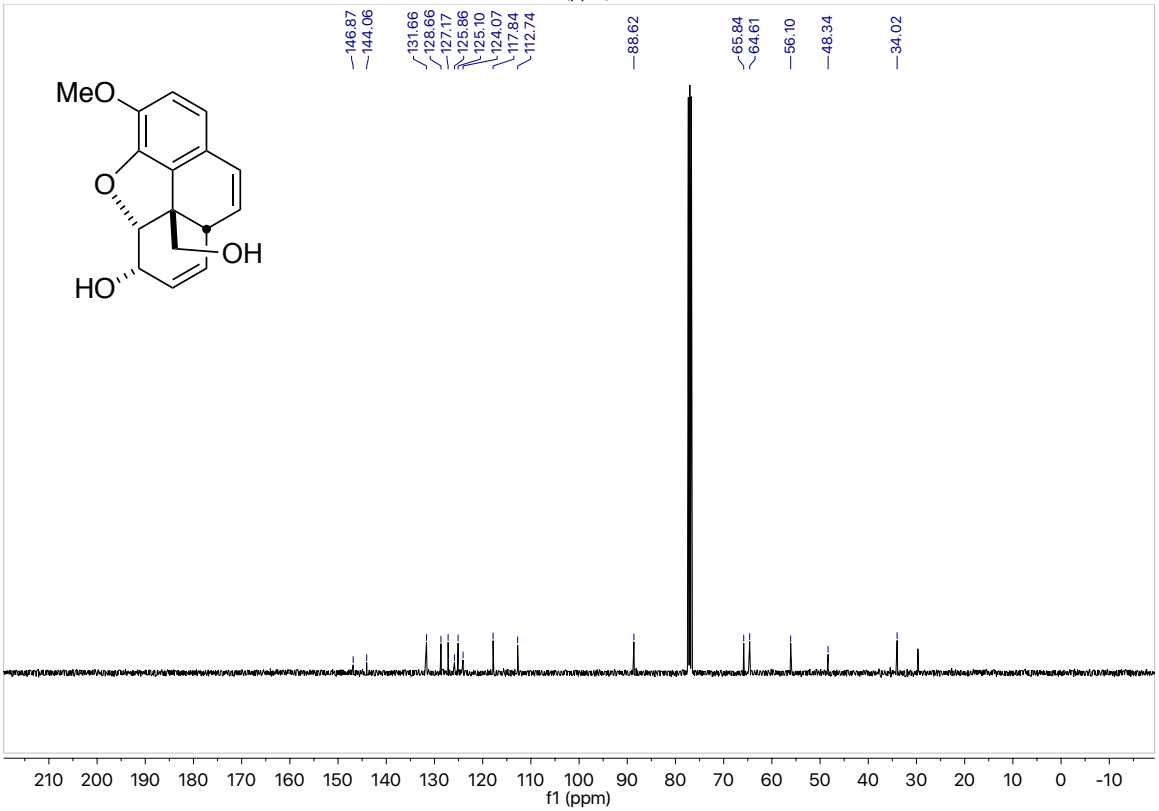

MeO
O
E
E = CO2Et

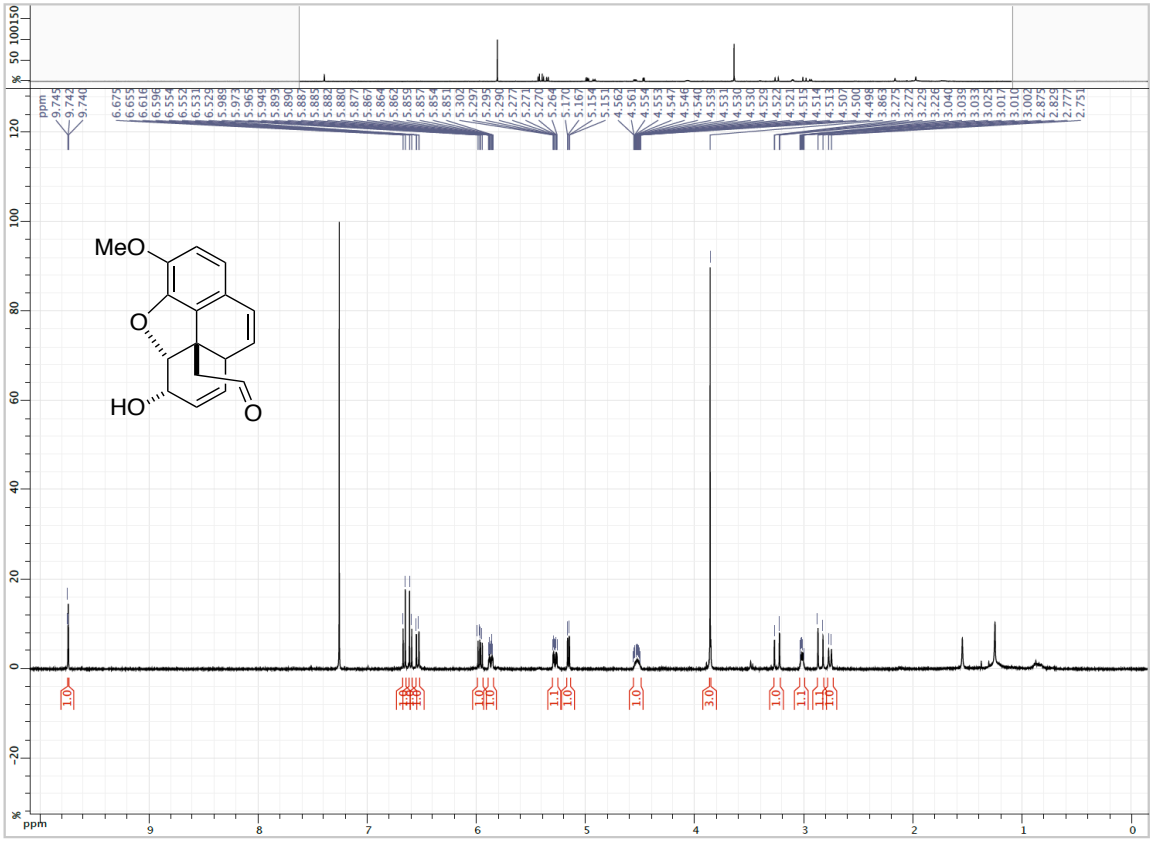

MeO
O
E
E = CO2Et

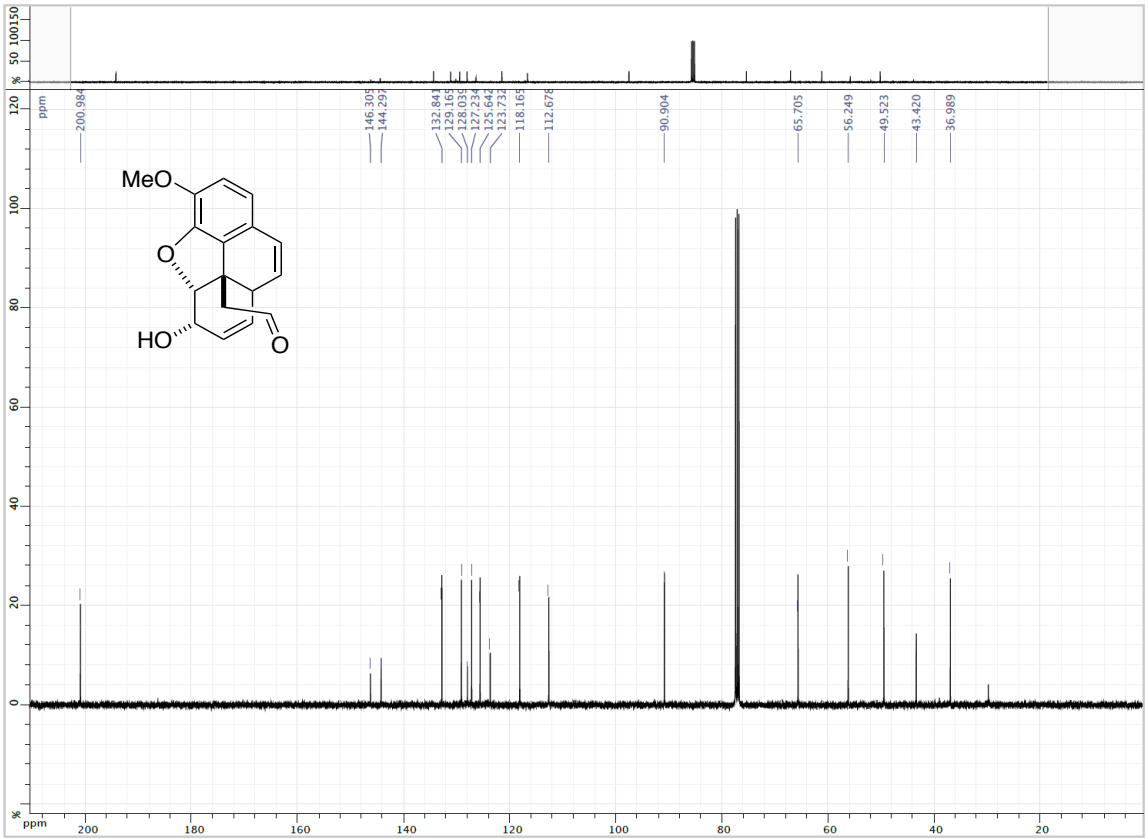

MeO
O
CHO
HO

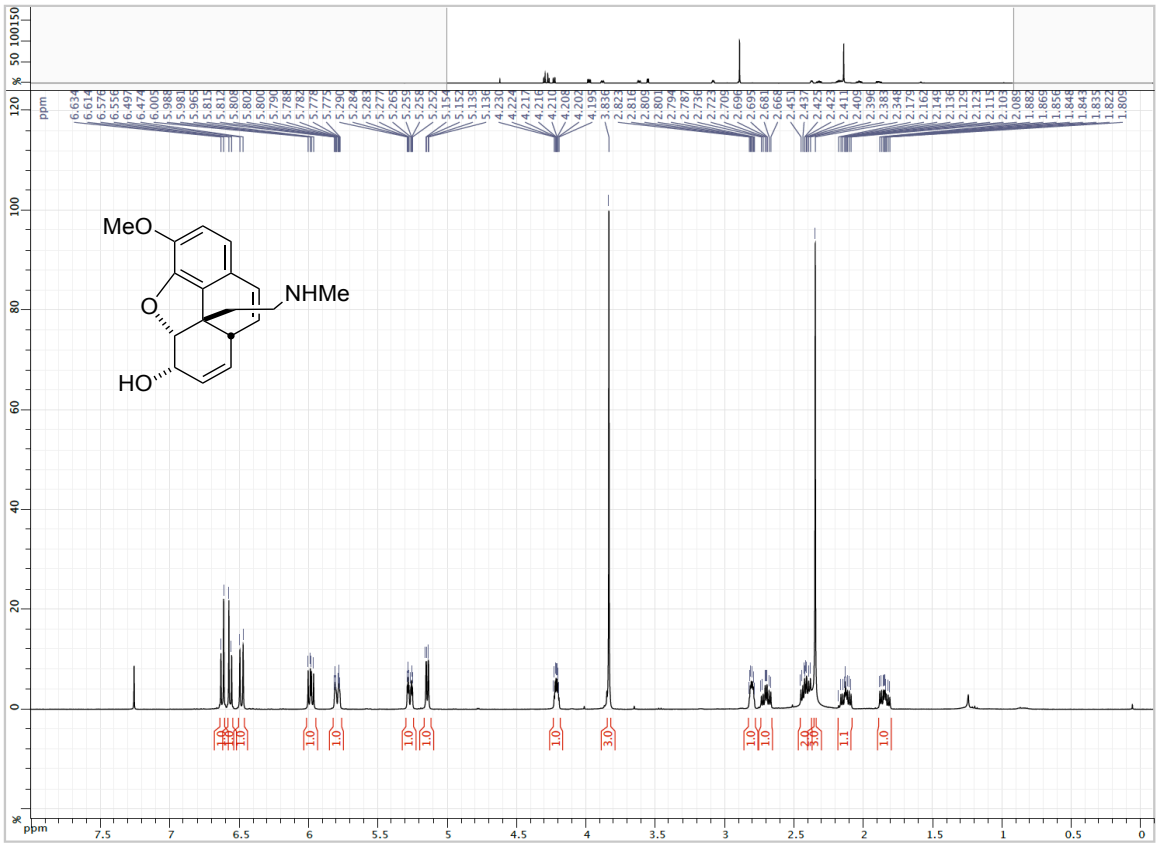

MeO
O
CHO
HO

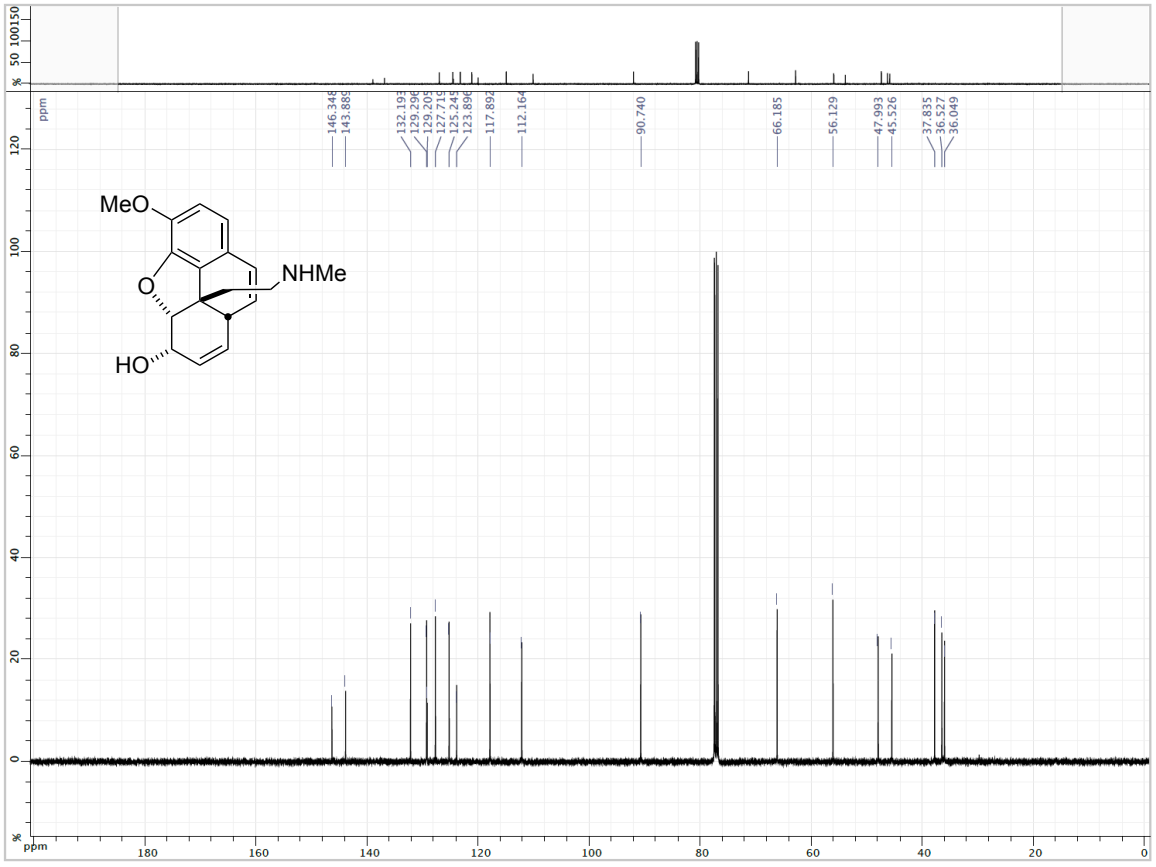

MeO
O
OH
HO
f1 (ppm)


MeO
O
OH
HO
f1 (ppm)


MeO
O
HO
O


MeO
O
HO
O


MeO
NHMe
O
HO
ppm


MeO
NHMe
O
HO
ppm