# Formal Synthesis of (+/-) Morphine via an Oxy-Cope/Claisen/Ene Reaction Cascade

*by*

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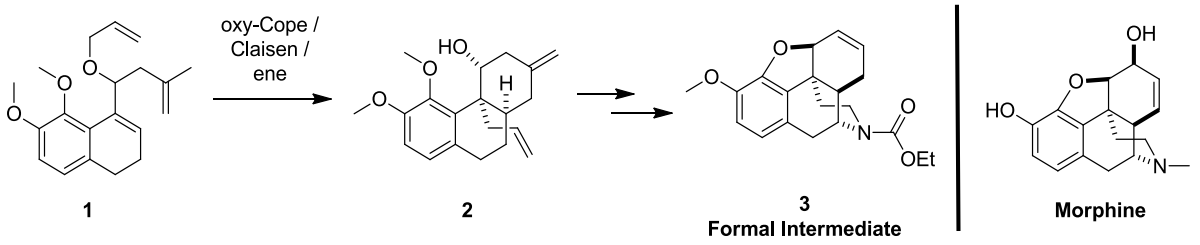
# ABSTRACT




For years now, opium alkaloids and morphinans have been attractive synthetic targets for numerous organic chemists due to their important biological activity and interesting molecular architecture. Morphine is one of the most potent analgesic drugs used to alleviate severe pain. Our research group maintains a longstanding interest in tandem pericyclic reactions such as the oxy-Cope/Claisen/ene reaction cascade and their application to the total synthesis of complex natural products. Herein we report the ventures towards the formal synthesis of (+/-)-morphine based on the novel tandem oxy-Cope/Claisen/ene reaction developed in our laboratory. These three highly stereoselective pericyclic reactions occurring in a domino fashion generate the morphinan core structure **2** via precursor **1** after only 7 steps. The formal synthesis culminated in the production of **3** after a total of 18 linear steps, with an overall yield of 1.0%, successfully intersecting two previous syntheses of the alkaloids, namely the ones of Taber (2002) and Magnus (2009).

*À ma famille, sans qui rien de cela n'aurait été possible*

# ACKNOWLEDGEMENTS

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I also want to thank my parents (Colette and Daniel) who love me and supported me in the many ways that lessened the weight of the different burdens I faced in the last two years. I thank my brother (Raphael) for his endless source of entertainment and considerations. Finally I would like to extend a lot of gratitude and recognize the efforts made by my sweetheart of now 7 years (Cynthia) for tolerating me and my different mood swings, which depended on how chemistry treated me.

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# GLOSSARY OF ABBREVIATIONS

| | |
|---|---|
| 2,4-DNPH | 2,4-Dinitrophenylhydrazine |
| Ac | acetate |
| AIBN | azobisisobutyronitrile |
| Ar | aryl |
| Bn | benzyl |
| Bu | butyl |
| BuLi | *n*-butyllithium |
| Bz | benzoyl |
| cat. | catalyst or catalytic |
| dba | dibenzylideneacetone |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCM | dichloromethane |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DEA | Drug Enforcement Administration |
| DIBAL-H | diisobutylaluminumhydride |
| DME | 1,2-dimethoxyethane |
| DMF | *N,N*-dimethylformamide |
| DMS | dimethylsulfide |
| DMSO | dimethylsulfoxide |
| dod | Dodecyl |
| dppp | 1,3-bis(diphenylphosphino)propane |
| dr | diastereomeric ratio |
| $E^+$ | electrophile |
| equiv | equivalents |
| Et | ethyl |
| GC | gas chromatography |
| GC/MS | gas chromatography coupled to mass spectrometry |
| HMPA | hexamethylphosphoramide |
| HMQC | heteronuclear multiple quantum coherence |
| HRMS | high resolution mass spectrum |
| KHMDS | potassium bis(trimethylsilyl)amide |
| LAH | Lithium aluminum hydride |
| LDA | lithiumdiisopropylamide |
| *m*-CPBA | 3-chloroperoxybenzoic acid |
| Me | methyl |
| MOM | methoxymethyl |
| mp | melting point |
| ms | molecular sieves |
| Ms | mesyl |
| NBS | *N*-bromosuccinimide |
| NMO | *N*-methylmorpholine oxide |
| NMP | *N*-methyl-2-pyrrolidone |
| NOE | nuclear Overhauser effect |
| NOESY | nuclear Overhauser effect spectroscopy |
| *o*-tolyl | *ortho*-toluene group |
| OTf | trifluoromethylsulfonate |
| OTs | toluenesulfonate |

| | |
|---|---|
| ox. | oxidation |
| P | As in -OP : Variable Protecting Group |
| PCC | pyridiniumchlorochromate |
| PG | protecting group |
| Ph | phenyl |
| Piv | pivaoyl $(CH_3)_3C$-CO |
| ppm | parts per million |
| PPTS | pyridinium *p*-toluenesulfonate |
| Pr | propyl |
| PTSA | para toluenesulfonic acid |
| pyr | pyridine |
| quant. | quantitative yield (i.e. >98%) |
| Ra-Ni | Raney nickel |
| Rf | “to-Front” ratio = analyte elution distance / solvent elution distance |
| s-BuLi | *sec* butyllithium |
| TBAB | tetrabutylammonium bromide |
| TBAF | tetrabutylammonium fluoride |
| *t*-Bu | *tert*-butyl |
| *t*-BuLi | *tert* butyllithium |
| TBS | *tert*-butyldimethyl silyl |
| TBDPS | *tert*-Butyldiphenylsilyl |
| TES | triethylsilyl |
| TFA | trifluoroacetic acid |
| TFAA | trifluoro acetic anhydride |
| TfOH | trifluoromethanesulfonic acid |
| tft | trifluorotoluene |
| THF | tetrahydrofuran |
| TMS | Trimethylsilyl |
| TMPDA | *N,N,N′,N′*-Tetramethylpropyldiamine |
| tol | toluene |
| TPAP | tetrapropylammonium perruthenate |
| trisyl | 2,4,6-triisopropylbenzene |
| Troc | 2,2,2-trichloroethoxycarbonyl |
| TsOH | See PTSA |
| xs | Excess |

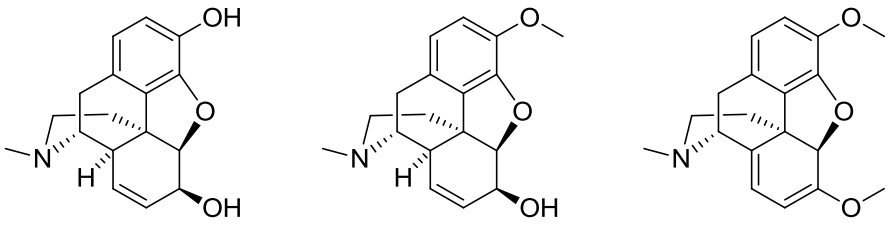
# CHAPTER 1: INTRODUCTION

## 1.1 HISTORICAL ASPECT

### 1.1.1 Ancient History

It is very difficult to decipher ancient written texts for evidence of narcotic uses and more specifically opium uses. It is a general agreement[1] that Sumerians, the people who inhabited what is currently known as Iraq, cultivated poppies and isolated opium from their seed capsules before 3000 B.C. To be more precise, opium is the dried latex obtained from the opium poppy (*Papaver somniferum*). This latex contains many different alkaloids, including ones of the morphinan families, such as morphine, codeine and thebaine, which relieve severe or agonizing pain and suffering.

*Scheme 1.1 – Morphine, Codeine and Thebaine*




morphine codeine thebaine

Around the eight century A.D. Arab traders brought opium to India and China, and it took several centuries for this latex to spread from Asia to all the different parts of Europe. With the use of this mixture of narcotics came addiction and we can read excerpts of manuscripts in the sixteen century where they mention substance abuse and tolerance in parts of Turkey, Egypt, Germany, England and China. The latter country had the biggest substance abuse problem. When they attempted to ban the use of opium, it was quickly suppressed by England who, aided by France, wanted to keep the opium trade alive between China and Europe. In 1804, Friedrich Sertürner was successful in isolating the principal biologically active ingredient of opium, and named it morphine, after the Greek god of dream, Morpheus.[2] He started its distribution in 1815 and the narcotic was first commercially sold by Merck in 1827. The appearance of the hypodermic needle around 1850 expanded the use of morphine. Unfortunately, this alkaloid had as much potential for abuse as did the raw mixture (opium) and this is what started the search for alternative opiates that were safer, less addictive and more potent. In 1898, heroin was synthesized

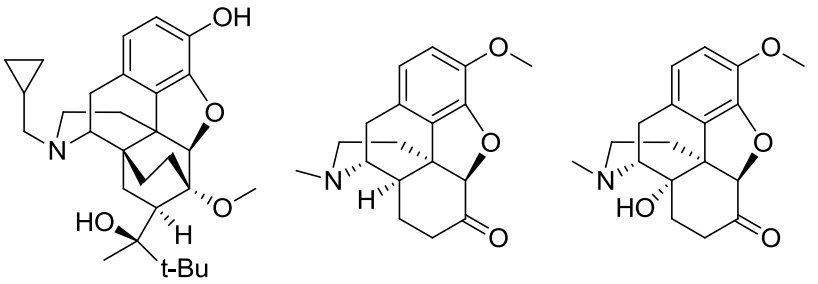
from morphine. It was found to be more potent, and was claimed to be a safer, non-addictive alternative. History has taught us otherwise, but the search for alternative severe-pain management still continues, and although the solution may not be related to morphine, this highly-regulated molecule is still to date, the gold-standard and benchmark of analgesics. It can be found on page 1 and 2 of the World Health Organization Essential Medecines.[3]

Chemically speaking, it took more than a hundred years to elucidate the exact structure of morphine, which was proposed by Robinson in 1925.[4] Following that, it is only in 1952[5] that Marshall D. Gates, Jr., professor of chemistry at the University of Rochester, published the first total synthesis of this alkaloid. From this date, more than thirty different syntheses of morphine were achieved by various researchers around the world, demonstrating the unique appeal that this molecule has for synthetic chemists. More details will be given in a subsequent section about morphine synthesis and its history.

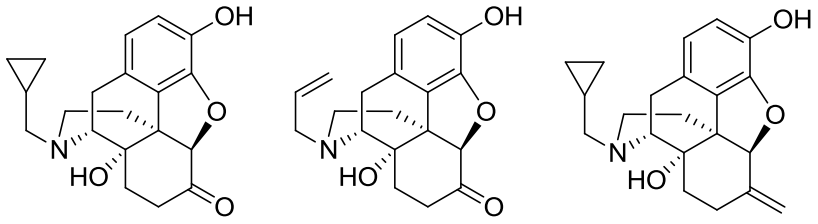
### 1.1.2 Recent History

The worldwide demand for morphine is a hard number to estimate. In the U.S. alone, the DEA Established Aggregate Production Quotas for 2012[6] expressed a quota of 83 tons for morphine (for conversion to derivatives) and 39 tons for direct sale. These numbers are thought to be sufficient to meet the 2012 estimated medical, scientific, research and industrial needs for morphine. As mentioned, a large quantity of morphine is produced for conversion. Many compounds nowadays are derived from morphine such as Oxycodone, Hydrocodone, Naloxone, Naltrexone, Nalmefene and Buprenorphine. These derivatives are used in pain-management (Oxycodone and Hydrocodone), management of alcohol/opiate addiction (Naltrexone and Nalmefene), and for treatment of opioid overdose (Naloxone and Buprenorphine).

*Scheme 1.2 – Synthetic Morphinan Derivatives*




Buprenorphine Hydrocodone Oxycodone




Naltrexone Naloxone Nalmefene

Looking at the worldwide production of the three principal constituents of opium, in 2007, 287.5 tons of morphine were produced, 23.7 tons of codeine and 125.5 tons of thebaine.[7] Production-wise, morphine has always been and still is mainly isolated directly from biological sources, namely the opium poppy. There are no chemical syntheses or fermentation methods that can compete with the low cost of isolation. Of note, the biggest sources of morphinan cultivation and isolation facilities are in Turkey, India, Afghanistan and general South-East Asia, where low wages play a major role in reducing the typical bulk cost of isolated morphine (400$-700$/kg).[8] Should a catastrophe, natural or political, occur in such areas, it is likely that costs of synthetic production could compete with isolation. This fact alone is one of the many reasons morphine still fascinates chemists.

## 1.2 BIOLOGICAL

### 1.2.1 Properties

Setting aside the societal and historical influence that morphine always had on humans, it is relevant to talk about the different biological properties that give this alkaloid its various highly sought-after effects on body and mind.

Morphine is a member of the opioid class. There are many endogenous opioids including endorphins, enkephalins and dynorphins. Interestingly, the term endorphin is a

contraction of “endogenous morphines” meaning “morphine-like molecules made in the body”. These endogenous opioids peptides are released in the body in response to intense period of exercise, excitement, pain and orgasm. Their effects include analgesia, sleepiness and a general feeling of well-being.

Morphine specifically is a phenanthrene opiod receptor agonist.[9] It will bind and activate the μ-opioid receptors of the central nervous system that are sporadically distributed in the brain.[10] This μ-opioid activation mediates analgesia, sedation, euphoria, physical dependence and respiratory depression. It is also, to some degree, a κ-opioid and δ-opioid agonist. These receptors are thought to play a role in the causation of general analgesia, spinal analgesia, pinpoint-pupils (miosis) and general delusions and/or delirium, which can be seen in some sedated patients. In a typical non-opiate user, 120-250 mg of ingested morphine sulfate will prove to be lethal.

If morphine is administered orally, only 40% to 50% of a given dose will reach the central nervous system. Such poor bioavailability is due to poor lipid solubility, ionization at physiologic pH, protein binding and glucoronic acid conjugation. In humans, the half-life of morphine is between 2 and 4 hours. Morphine metabolism consists mainly of rapid CYP450-mediated glucoronidation, producing morphine-6-glucoronide (M6G) and morphine-3-glucoronide (M3G). In smaller amount, less than 5% of morphine is metabolized by demethylation into normorphine via a CYP3A4 and CYP2C8 pathways.

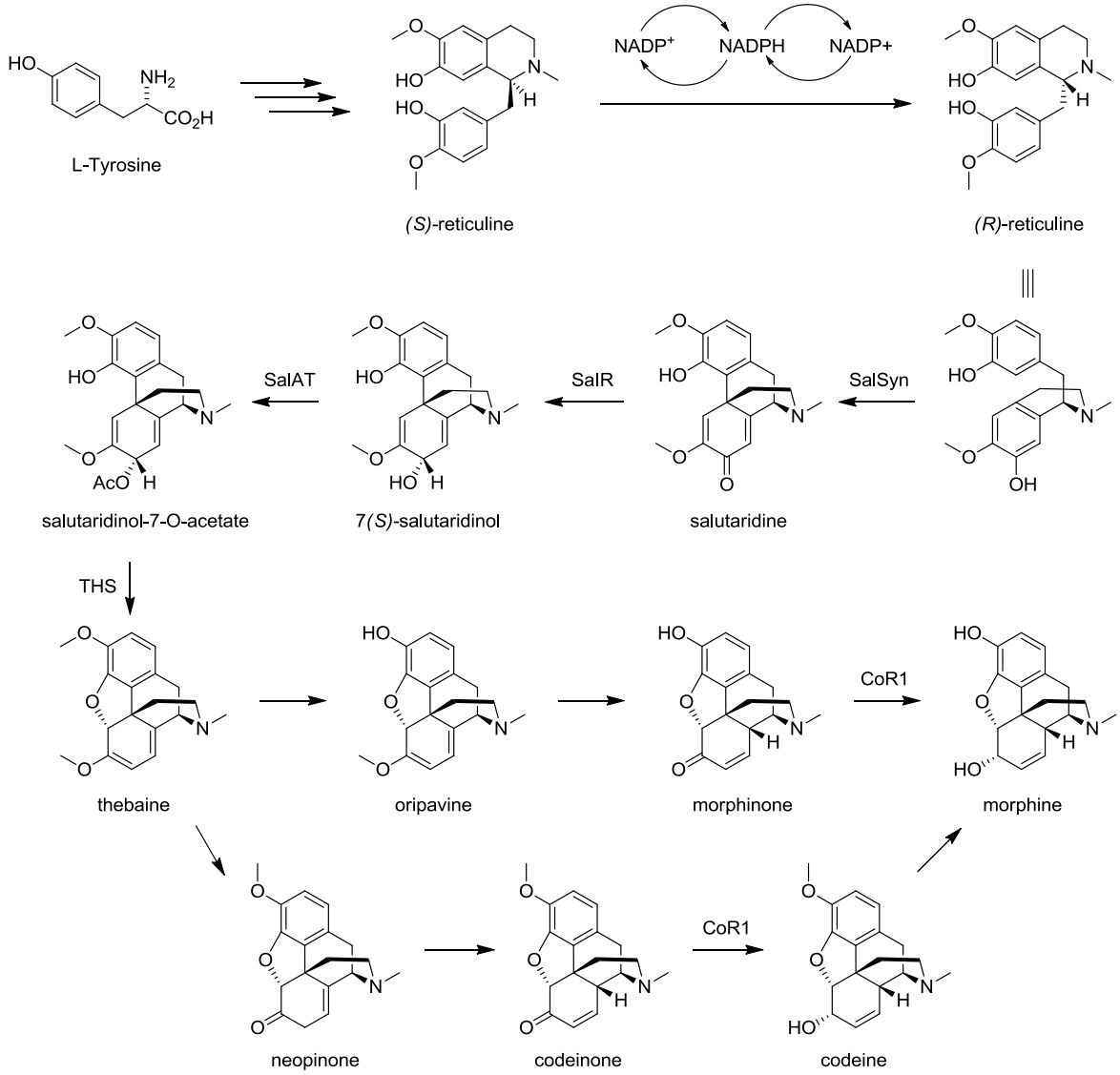
Becoming more and more accepted is the fact that certain animals, vertebrates and invertebrates, as well as humans, produce endogenous morphine in certain organ tissues.[11] For example, it was found that human heart tissue contains morphine and morphine-6-glucoronide, albeit at very low levels (ng/g).[12] It was also found that concentration of endogenous morphine in human serum increases when the patient is affected by a systemic infection. Such increase in concentration is in part due to increased secretion by neutrophils (white blood cells). [13]

### 1.2.2 Biosynthesis

It has been established[14] that two molecules of L-tyrosine are the source of all non-methyl carbons in the skeleton of morphine. One tyrosine is derivatized to dopamine and the other to *p*-hydroxyphenylacetaldehyde. After 4 linear enzyme-catalyzed reactions, including a Pictet-Spengler type reaction, they form the benzylisoquinoline skeleton of (S)-reticuline. Inversion of configuration on *(S)*-reticuline occurs through a NADPH-dependant oxidation-reduction step. The *(R)*-reticuline that is formed is the sole source of material for

the pathway leading to morphinan alkaloids, and as such explains the presence of only (-)-morphine among biological sources (Scheme 1.3).

*Scheme 1.3 – Morphine Biosynthesis*




The biosynthesis continues with *(R)*-reticuline, the substrate for the salutaridine synthase. The enzyme performs the biphenolic oxidation in a NADPH-dependent process and yields salutaridine, generating the quaternary carbon center and forming the B-ring in the same process. Salutaridinol is then synthesized via a NADPH-dependent salutaridine reductase. The formed hydroxyl will be acetylated via salutaridinol acetyl transferase which allows the syn-$S_N2$' displacement to form the very important precursor thebaine. This precursor can then undergo aromatic demethylation to oripavine, followed by

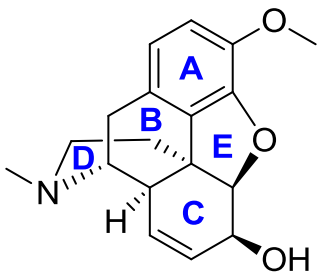
tautomerization of the methyl enol ether of ring C to morphinone and final enone reduction to yield (-)-morphine. If aromatic demethylation does not occur initially, codeine will be the product of a similar sequence. Codeine can also be demethylated *in vivo* to form morphine.

## 1.3 CHEMICAL

### 1.3.1 Properties

Morphine has for long been a fascinating subject among chemists for multiple reasons. The opiate has a pentacyclic ring system (Scheme 1.4) which contains an aromatic ring (ring A), a dihydrofuran ring (ring E), a cis-decalin substructure (rings B/C) and a piperidine ring (ring D). It also bears five contiguous stereocenters with a quaternary carbon center being third (thus in the exact center) in this sequence. It also is a very compact and rigid molecule with relatively few synthetic handles. These properties make morphine a very interesting and challenging target for synthetic chemists.

*Scheme 1.4 – Pentacyclic Ring Structure of (-)-Morphine*




(-)-morphine

As previously mentioned, over thirty different syntheses of morphinan alkaloids have been completed, which demonstrates an unswerving interest for this natural product. The usual challenge in accomplishing the total or formal synthesis of a natural product relies partly on the actual accomplishment, which is accessing the end product or a previously accessed intermediate through a unique route. With (-)-morphine, the paradigm has slightly shifted to one where the utmost accomplishment would be one where the step count is minimized and the yield or scaling capability maximized, when compared to the massive amount of syntheses. Table 1.1 displays a comprehensive but not exhaustive list of total and formal syntheses of morphine, with the corresponding target reached, number of steps and overall yield.

*Table 1.1 – Summary of Syntheses of Morphine and Derivatives*[1]

| Author | Year | Target | Steps | Reported Overall Yield |
|---|---|---|---|---|
| Gates[5] | 1952 | Morphine | 29 | 0.06 |
| Ginsburg[15] | 1954 | rac-Dihydrothebainone | 21 | 8.9 |
| Grewe[16] | 1967 | rac-Dihydrothebainone | 9 | 0.81 |
| Rice[17] | 1980 | Dihydrocodeinone | 14 | 29.7 |
| Evans[18] | 1982 | rac-O-Me-thebainone A | 12 | 16.7 |
| White[19] | 1983 | Codeine | 8[a] | 1.8 |
| Rapoport[20] | 1983 | rac-Codeine | 26 | 1.2 |
| Fuchs[21] | 1987 | rac-Codeine | 23 | 1.3 |
| Tius[22] | 1992 | rac-Thebainone-A | 24 | 1.1 |
| Parker[23] | 1992 | rac-Dihydrocodeinone | 11 | 11.1 |
| Overman[24] | 1993 | Dihydrocodeinone | 14 | 1.9 |
| Mulzer[25] | 1996 | Dihydrocodeinone | 15 | 9.1 |
| Parsons[26] | 1996 | Morphine | 5[b] | 1.8 |
| White[27] | 1997 | ent- Morphine | 28 | 3.0 |
| Mulzer[28] | 1997 | Dihydrocodeinone | 18 | 5.7 |
| Ogasawara[29] | 2001 | Dihydrocodeinone ethylene ketal | 21 | 1.5 |
| Taber[30] | 2002 | Morphine | 27 | 0.51 |
| Trost[31] | 2002 | Codeine | 15 | 6.8 |
| Fukuyama[32] | 2006 | rac-Morphine | 25 | 6.7 |
| Hudlicky[33] | 2007 | ent-Codeine | 15 | 0.23 |
| Iorga/Guillou[34] | 2008 | rac-Codeine | 17 | 0.64 |
| Chida[35] | 2008 | Dihydroisocodeine | 24 | 3.8 |
| Hudlicky[36] | 2009 | Codeine | 18 | 0.19 |
| Magnus[37] | 2009 | rac-Codeine | 13 | 20.1 |
| Stork[38] | 2009 | rac-Codeine | 22 | 2.0 |
| Fukuyama[39] | 2010 | Morphine | 18 | 4.8 |
| Metz[40] | 2011 | rac-Codeine | 24 | 1.3 |

[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

To go over all the mentioned syntheses of Table 1.1 in detail would require too much effort for the added value that it would bring. It is recognized that these publications are the pillars that shaped the field of morphinan alkaloids synthesis. For this discussion, a detailed look of the first synthesis by Marshall Gates will be given, followed by brief discussions on several important approaches and unique routes that were published over the years by some of the researchers listed above. With the exception of Rice's synthesis that will be

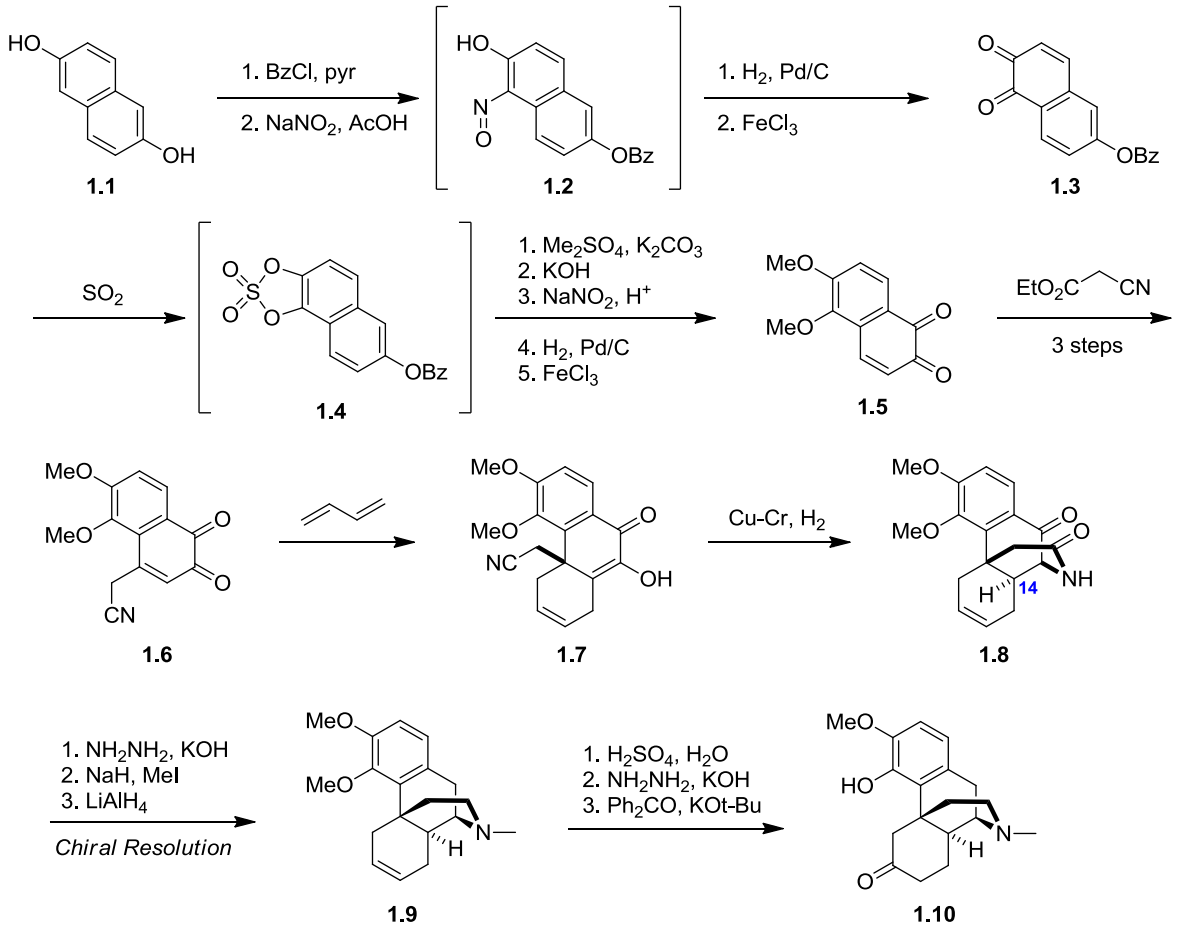
[1] Table model taken directly from the recent review of morphine syntheses by Prof. Hudlicky[7]

discussed for its potential scalability, focus will rotate around the latest advances in morphinan alkaloids synthesis.

### 1.3.1 First Synthesis

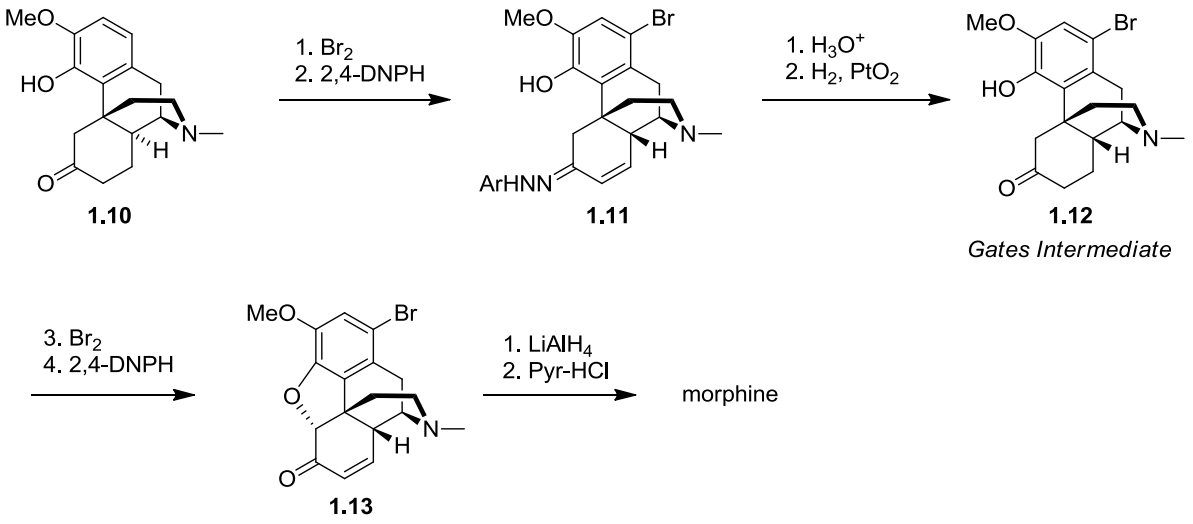
Over half a century ago, in 1952, the first total synthesis of Morphine was accomplished by Marshall Gates.[5] Dihydroxynaphtalene **1.1** was used as the starting material for this synthesis. It included what would become the A,B-ring system of the opiate. A monoprotection / nitrosation / hydrogenation / oxidation sequence led to the formation of ortho quinone **1.3**. Treatment with sulfur dioxide and dimethyl sulfate followed by an identical sequence led to **1.5**, which was set for a Michael-type addition using ethyl cyanoacetate. Reoxidation, hydrolysis and decarboxylation yielded nitrile **1.6**. This served as the substrate for the first key-step consisting of a Diels-Alder reaction with butadiene. The success of that key step yielded **1.7** which effectively formed ring C in the process.

*Scheme 1.5 - First Stages of Gates' Synthesis of Morphine*



Copper-chromite mediated reductive amination gave **1.8** which contained the A,B,C,D ring system of morphine, even though C14 had the wrong configuration. This was followed by a Wolff-Kishner reduction, methylation of the amide, and its reduction to **1.9**. At this point, a chiral resolution using dibenzoyl tartrate was performed to afford the correct enantiomer of the alkaloid, albeit still with the wrong configuration at C14. Access to ketone **1.10** was made possible using sulfuric acid to obtain a regioselective hydration product, followed by hydrazine mediated aromatic monodemethylation and Oppenauer oxidation. Treatment of ketone **1.10** with bromine added two bromine atoms on the molecule, one in α-position of the ketone, as well as on the aromatic ring. Condensation of 2,4-DNPH allowed for elimination of the α-bromine and epimerization at C14 to the thermodynamic product **1.11**. Addition of water and hydrogenation yields the corresponding ketone **1.12** also known as "Gates' Intermediate". This intermediate was for a long time the end-goal in many attempts at synthesizing morphine, for many researchers trying to improve upon Gates' synthesis. Further bromination and treatment with 2,4-DNPH, followed by reduction of the ketone, aromatic debromination and demethylation yielded the sought-after alkaloid.

*Scheme 1.6 – Endgame from Β-Dihydrothebainone to Morphine*

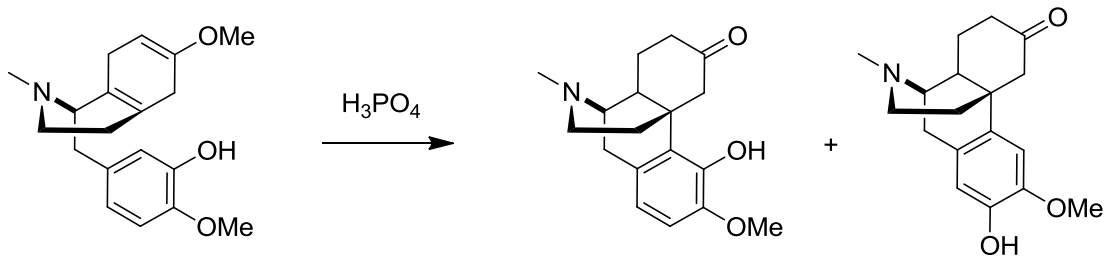



Gates' synthesis of morphine is a 29-step linear sequence with an overall yield of 0.06%. It was nevertheless a groundbreaking achievement at the time, as it set the stage for more than five decades of morphinan alkaloids synthesis and confirmed the hypothesis for the proposed structure of morphine set forward by Sir Robert Robinson in 1925.[41]

### 1.3.2 Potential Scalability

In 1980, Kenner C. Rice[17] published a remarkable synthesis of dihydrothebainone, dihydrocodeinone and nordhydrocodeinone. Rice's approach is concise, elegant, direct and makes use of very robust chemistry, which makes it a prime candidate for a large-scale application. The complete synthesis to dihydrocodeinone is 13 steps, with an overall yield of 29.7% performed on a multigram scale. The key step in this case relies on making the C12-C13 bond using a method set forward by Grewe[16] in 1967. As shown in Scheme 1.7, Grewe was successful in synthesizing dihydrothebainone **1.15** albeit in very low yield (3%), while most of the reaction product consisted of **1.16**, the product of the para-cyclization adduct.

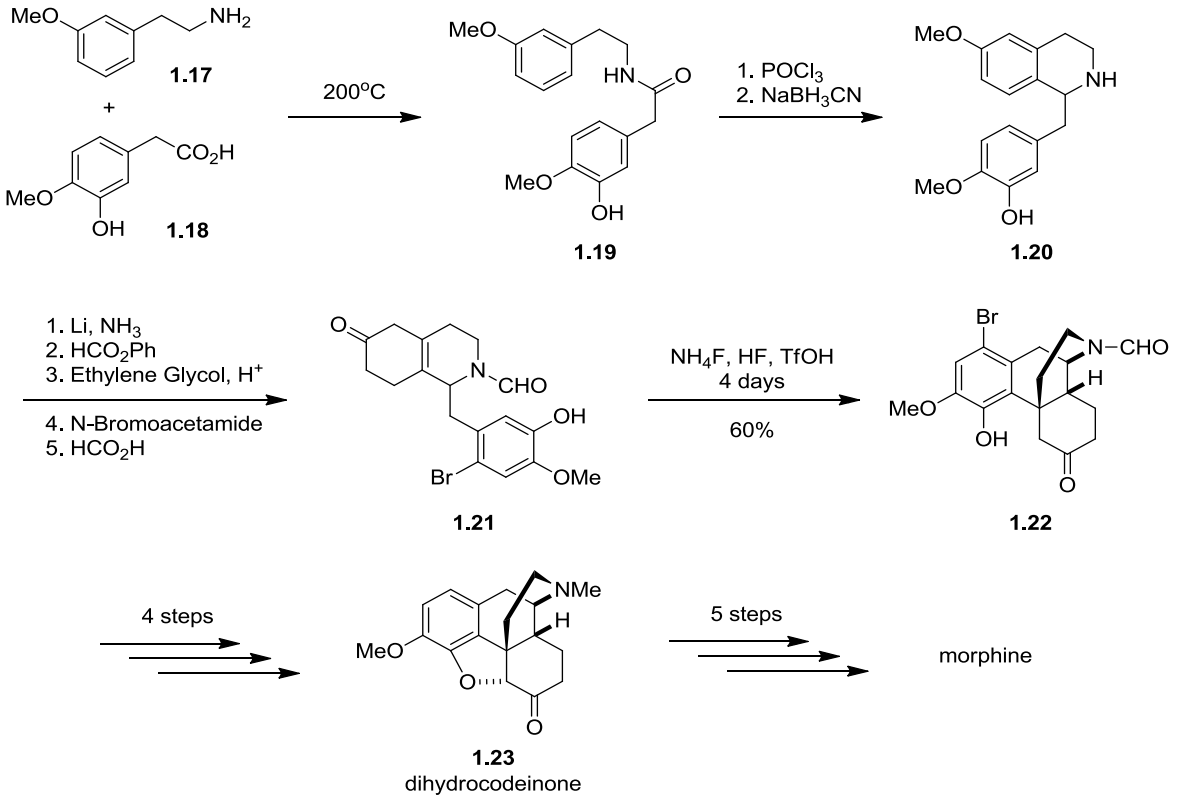
*Scheme 1.7 – Grewe's Cationic Cyclization*




**1.14** **1.15** (3%) **1.16** (37%)

Rice's synthesis starts off with the direct condensation of amine **1.17** and carboxylic acid **1.18**. A Bischler-Napieralski reaction, followed by sodium cyanoborohydride reduction and a short functionalization sequence leads to ketone **1.21** as the substrate required for the Grewe cyclization. This time, as can be observed, the para position of the aromatic ring is protected with a bromine atom, thus limiting the formation of the para-coupling adduct. The key steps proceed relatively slowly, in four days, yielding 60% of ketone **1.22**. Only four steps are required to reach dihydrocodeinone **1.23**, completing the formal synthesis of morphine.

*Scheme 1.8 – Rice's Synthesis of Morphine*




### 1.3.3 Palladium Catalyzed C12-C13 Formation

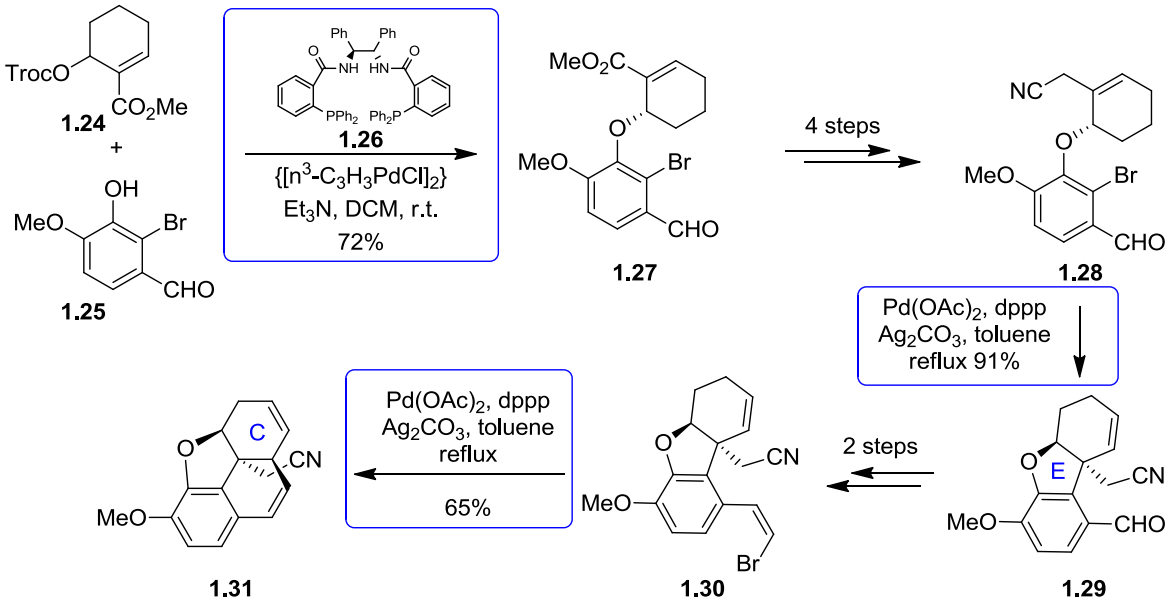
The problematic step in synthesizing morphine is undoubtedly the installation of the quaternary carbon. As we've seen, Gates' synthesis focus on making the phenanthrene skeleton first then finishes off with the closing of ring E and D while Rice's synthesis goes for an early cyclization of ring D and uses cationic chemistry to create the C12-C13 bond and install the quaternary carbon in the process.

Interestingly, many recent syntheses of morphine make extensive use of $Pd^0$ reactivity to perform cross-coupling reactions in order to create this quaternary carbon. This can be easily explained by the simple fact that the C12-C13 bond links a $sp^2$ carbon to an alkyl substituent.

One of the first synthesis that uses such reactivity is Trost's enantioselective synthesis of (-)-codeine.[31] Using Trost's well-known asymmetric allylic alkylation chemistry, he was able to couple the phenolic oxygen of **1.25** to the Pd π-allyl specie created between **1.24** and the chiral catalyst-ligand system generated in situ from **1.26** (Scheme 1.9). Some functional group manipulations were made on product **1.27** to homologate the methyl ester and exchange it for a nitrile group, producing **1.28**. The key step consisted of an

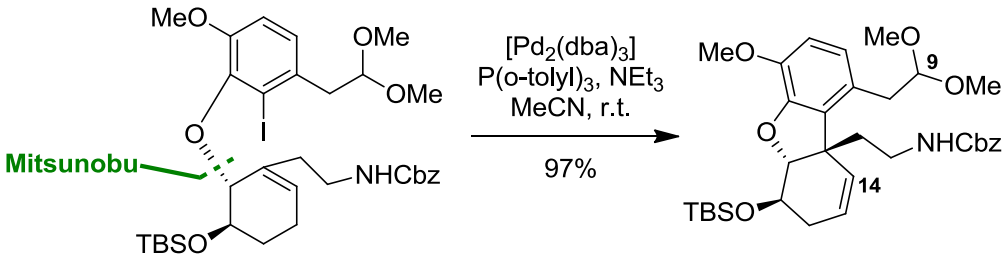
intramolecular Heck reaction yielding **1.29**; essentially forming the E ring in the process. Further functionalization transformed the benzylic aldehyde to vinyl bromide **1.30**, which allowed for a subsequent Heck reaction to form the B ring in **1.31**. The synthesis was completed from **1.31** using a series of allylic oxidation / oxidation / reduction to functionalize ring C, while ring D was formed by reducing the nitrile substituent to a methylamine functional group and performing a questionable irradiation-promoted intramolecular hydroamination with the benzylic alkene.

*Scheme 1.9 – Trost's Synthesis of (-)-Morphine*




This synthesis of codeine is a 15-step synthesis with an overall yield of 6.8%. It is a very concise synthesis that makes heavy use of palladium catalysis as shown in Scheme 1.9. A very similar methodology was applied by Hudlicky in 2007[33] and 2009[36] in his syntheses of ent-codeine and codeine respectively where he used a Mitsunobu reaction on enzymatically synthesized chiral material to form the initial ether bridge of ring E. It was followed by two almost identical intramolecular Heck reactions as the ones shown above.

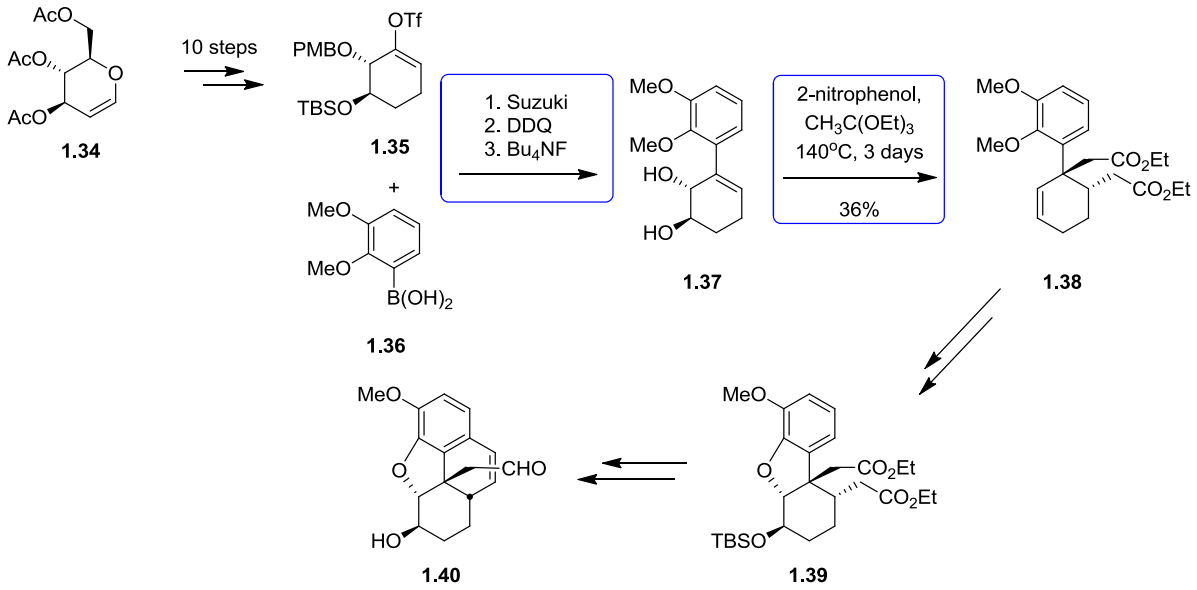
*Scheme 1.10 – Fukuyama's Intramolecular Heck Reaction in 2010*




**1.32** **1.33**

A similar approach to making the C12-C13 bond was demonstrated by Fukuyama[39] in 2010 in his total synthesis of (-)-morphine (Scheme 1.10). Key step material **1.32** was synthesized in 7 steps from cyclohexenone, which included an enzymatic resolution to access enantioenriched material and a Mitsunobu reaction to form the E-ring ether bridge. Intramolecular Heck reaction on **1.32** yielded **1.33** in 97%. TBS deprotection followed by oxidation to the ketone were performed prior to a C14-C9 *β,γ*-aldol reaction which successfully formed the B ring.

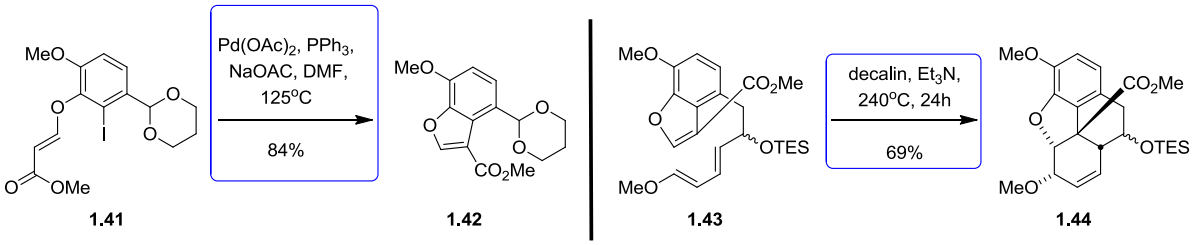
*Scheme 1.11 – Chida's Synthesis of (-)-Dihydroisocodeine from D-Glucal*




As well, in 2008, Chida[35] reported a formal synthesis of (-)-morphine by accessing dihydroisocodeine using a similar C12-C13 palladium catalyzed strategy (Scheme 1.11). D-glucal **1.34** was used as the starting chiral synthon to access vinyl trifalte **1.35** in 10 steps. This time, a Suzuki cross-coupling reaction was performed between **1.35** and boronic acid **1.36** to effect the formation of the C12-C13 bond. Following two deprotection reactions, a

Claisen/Claisen cascade was performed using **1.37** and triethyl orthoacetate, which successfully formed the quaternary carbon at C13 and provided **1.38** in 36% yield. At this point, initial focus was put on closing the E-ring using epoxidation and TBSCl to generate **1.39**. This was followed by DIBAL-H reduction of both esters and montmorillonite K10-promoted B-ring formation. Once **1.40** in hand, chemistry set forward by Parker[23] was applied to close the D-ring using reductive amination and radical cyclization.

*Scheme 1.12 – Stork's Synthesis of (+/-)-Codeine*




**1.41** **1.42** **1.43** **1.44**

Another palladium catalyzed cross-coupling reaction was used by Stork[38] in 2009 in his synthesis of racemic codeine. As shown in Scheme 1.12, an intramolecular Heck reaction was performed on **1.41** (accessed in two steps from commercially available material), this time with the intent of forming a very early E-ring, which is unusual in the history of morphine synthesis. With benzofuran **1.42** on hand, the acetal portion was functionalized to install the diene found in **1.43**. This allowed for an intramolecular endo Diels-Alder reaction which occurred in decalin at 240°C, furnishing **1.44** in 69% yield. This impressive transformation established both ring B and C all the while installing correctly 4 of the 5 consecutive stereocenters and the quarternary carbon.

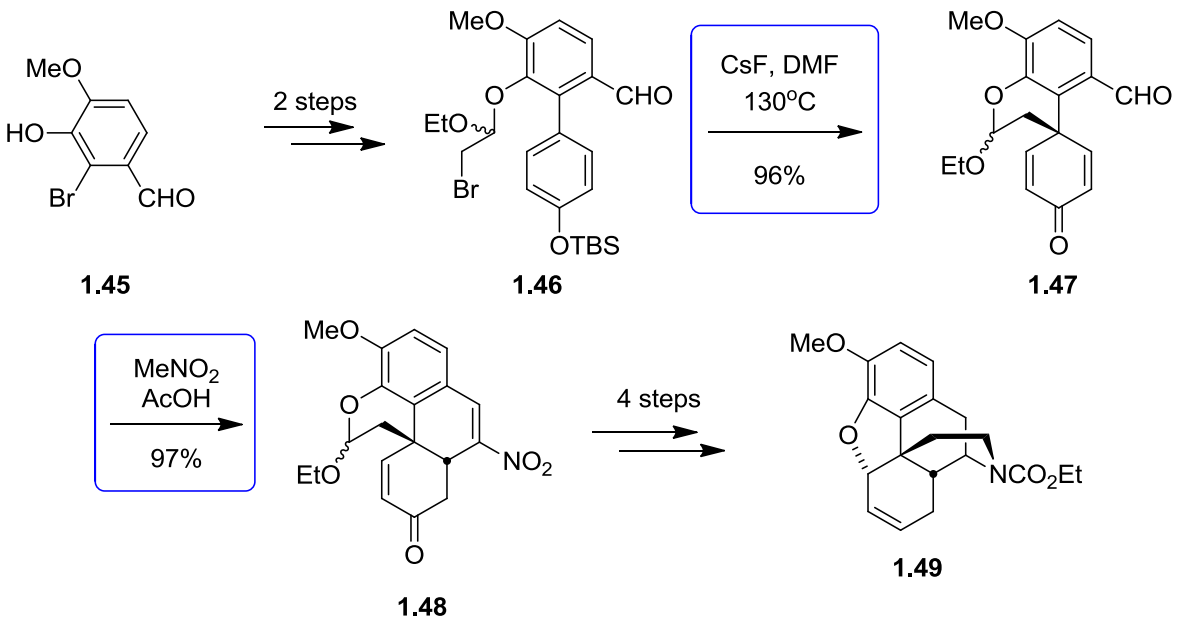
It is clear that the advances in palladium catalysis of the past two decades have considerably influenced morphinan alkaloids synthesis by allowing to straightforwardly create the C12-C13 bond, linking ring A and C together, and even in some cases, creating the quaternary carbon in the process.

### 1.3.4 Unique Approaches

The following example could have been included in the previous subsection, since it also uses a Suzuki cross-coupling reaction as the first step, and this time again to create the C12-C13 linkage. Several characteristics of this synthesis, however, deserve to be pointed out in another light than in the one of palladium catalysis. Such characteristics include a very low step count, extremely high yields, a remarkable synthetic ingenuity, and the fact that the same approach can be used toward synthesizing morphine or galatamine,

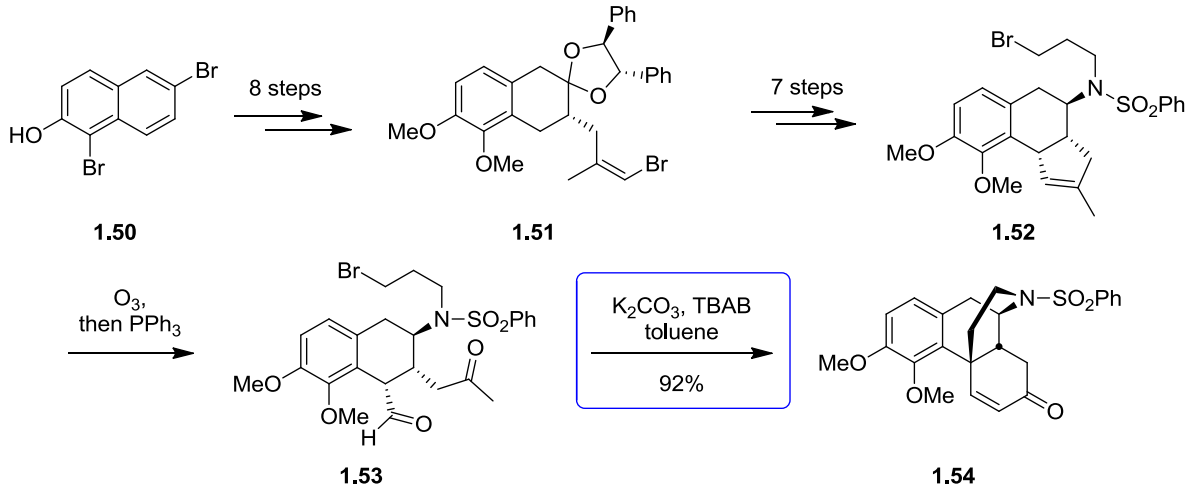
a potent and commercialized cholinesterase inhibitor of the *Amaryllidaceae* alkaloid family. The following work was performed and published by the group of Magnus as a concise synthesis of (+/-)-codeine in 2009[37] (Scheme 1.13).

*Scheme 1.13 - Magnus' Synthesis of (+/-)-Codeine*




As mentioned, one of the two steps required to synthesize **1.46** was a Suzuki cross-coupling reaction using **1.45** and the complementary boronic acid. This was followed with the first key reaction, an *o,p*-phenolic oxidation using cesium fluoride in DMF at 130°C, which generated **1.47** in 96% yield. In his publication, Magnus was able to access both narwedine (used to synthesize enantiopure Galantamine) and codeine through common intermediate **1.47**. Precursor **1.47** was used for the following Henry-aldol/Michael addition cascade furnishing **1.48** in 97% yield, successfully installing the B-ring portion, the cis-decalin structure, and the nitrogen atom of the opiate in a concise way. Only four steps were required from that point to access carbamate **1.49**, formally completing the synthesis of codeine and thus morphine. Noteworthy is the fact that Magnus' synthesis is the only one that comes close to the large-scale feasibility of Rice's synthesis both in terms of step count (18 vs 16) and overall yield (20% vs 29%).

*Scheme 1.14 – Relevant View of Taber's Total Synthesis of (-)-Morphine*

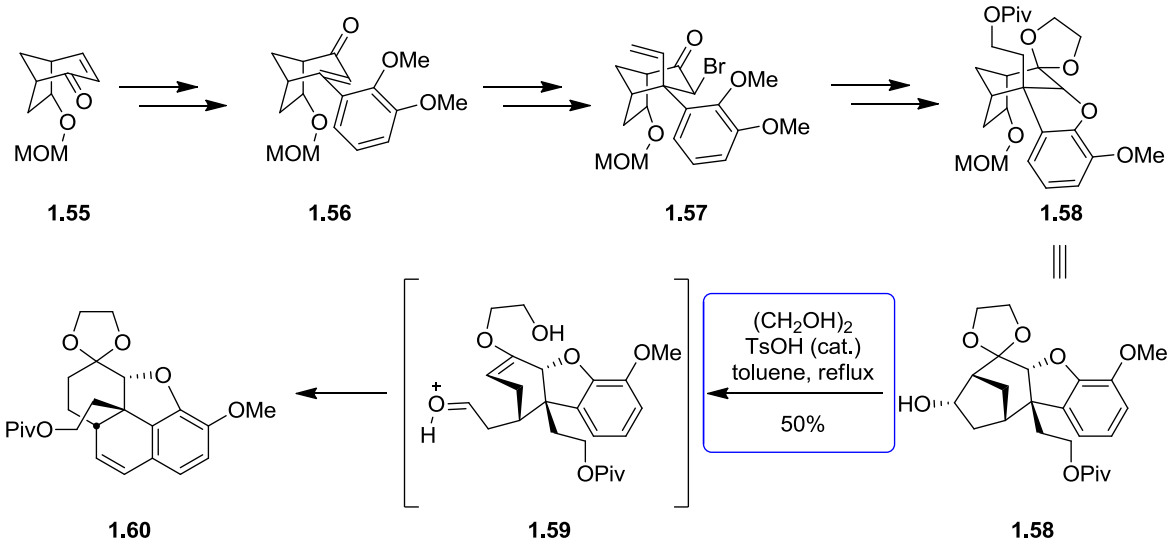



Another unique approach is the one of Taber in 2002.[30] As shown in Scheme 1.14, he started with 1,6-dibromo-2-naphthol **1.50** and functionalized it to hydrobenzoin acetal **1.51**. The use of a chiral hydrobenzoin to form the acetal allowed him to separate the two alkylation diastereomers and obtain enantioenriched material to complete the enantioselective synthesis. Using alkylidene carbene C-H insertion, he was able to obtain the cyclopentene in **1.52**, and several steps were required to transform the acetal portion into the tertiary amine substituent. Subsequent ozonolysis yielded **1.53**, setting the stage for an impressive double cyclization cascade which started with formation of the D-ring by aldehyde enolate alkylation, followed by Robinson annulation to provide ring C. This double alkylation proceeded in 92% yield to form **1.54**. Even though this approach to (-)-morphine is rather long and relatively low yielding, it is unique in how both ring C and D are correctly installed in the same synthetic step.

The following final example is the one of Ogasawara in 2001[29] where he published a distinct route to morphine (Scheme 1.15). Starting from enantioenriched bicyclic enone **1.55**, alkylation with lithiated veratrol provided **1.56,** correctly installing ring A of the alkaloid. Further functionalization to **1.58** included, among other reactions, a diastereoselective vinyl cuprate addition and NBS bromination which were performed according to Mulzer's procedure.[25] Refluxing **1.58** in toluene in the presence of ethylene glycol and tosic acid promoted the retro-aldol required to form the aldehyde of **1.59**, which subsequently underwent *p*-alkylation from the aromatic ring, and elimination, yielding tetracyclic **1.60** in 50% yield. The clever use of the facial bias of starting bicyclic enone **1.55**, the remarkable retro-Aldol/cyclization cascade and the exceptional synthetic design of C-A-E ring formation

with a late B and E ring formation make this approach remarkably unique in the field of morphinan alkaloid synthesis.

*Scheme 1.15 – Ogasawara's Formal Synthesis of Morphine*



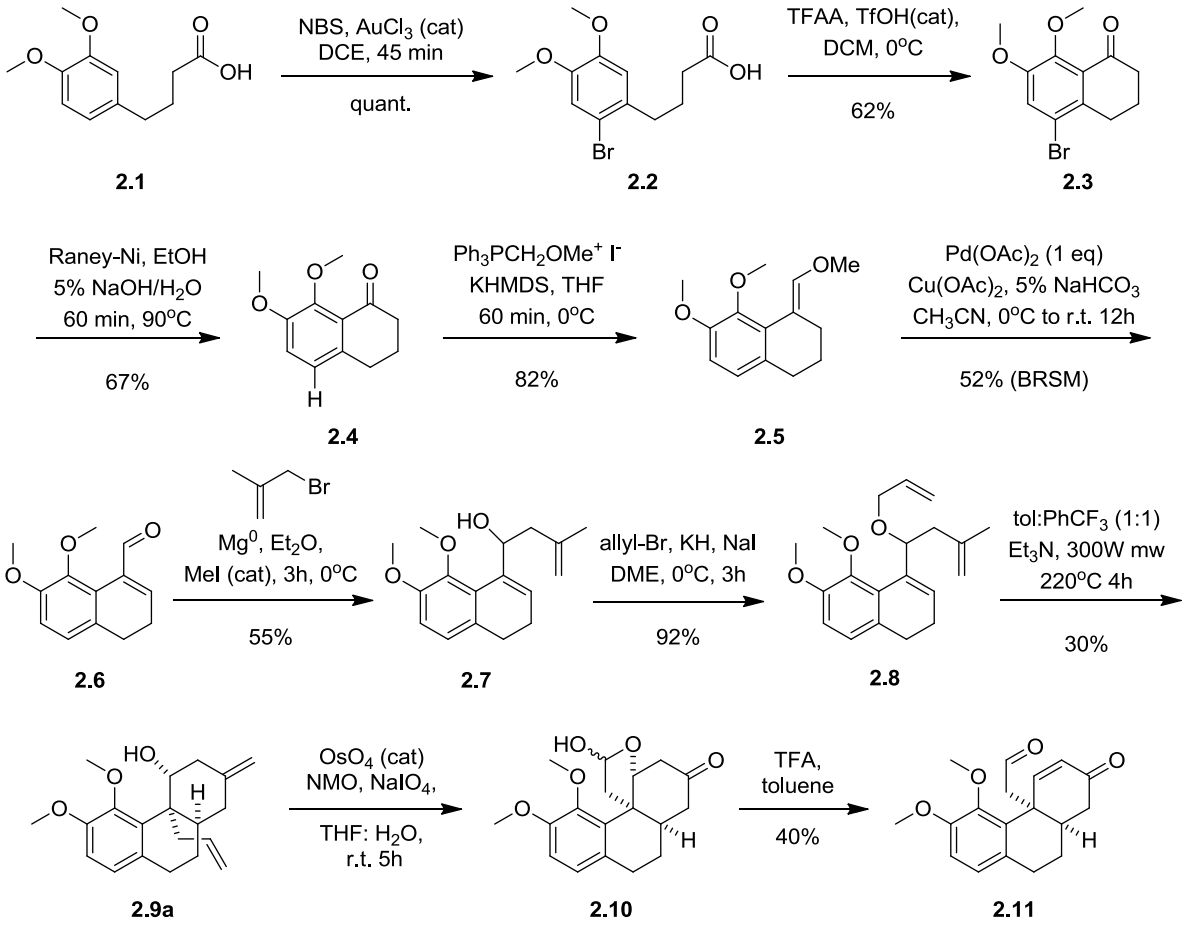
# CHAPTER 2: FORMAL SYNTHESIS OF MORPHINE

## 2.1 IMPROVEMENTS ON PREVIOUS WORK

### 2.1.1 Original Synthesis

As mentioned, this project was started by Kassandra Lepack, former graduate student in the Barriault group. Her work included devising the early steps of the synthesis, which encompassed the key oxy-Cope/Claisen/ene pericyclic reaction cascade. Scheme 2.1 illustrates the reaction sequence Kassandra was able to achieve before her departure from the laboratory. The sequence starts with commercially available carboxylic acid **2.1**, which is brominated quantitatively using a gold-catalyzed aromatic bromination process.[42] The obtained crude mixture is taken directly to a Friedel-Crafts reaction to form brominated tetralone **2.3** in 62% yield over two steps. The bromine is removed using a super-stoichiometric amount of Raney-Nickel[43] in water to generate **2.4** with a yield of 67%. Tetralone **2.4** is the precursor required for a sequence of Wittig reaction and palladium-"catalyzed" oxidation proceeding in 82% and 52% yields respectively, leading to *α,β*-unsaturated aldehyde **2.6**. At this point, a modest yielding Grignard reaction followed by an O-allylation of resulting hydroxyl **2.7** delivers triene **2.8** which has the required framework for the oxy-Cope/Claisen/ene cascade. This cascade of pericyclic reactions leads to the formation of three different products, including the relevant tricyclic **2.9a** in 30% yield. A Lemieux-Johnson procedure followed by TFA-promoted lactol opening leads to enone **2.11**.

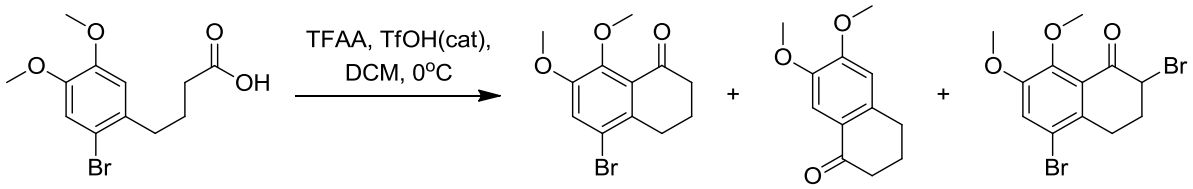
*Scheme 2.1 – Summary of Kassandra Lepack's Sequence Relevant to This Work*




Upon looking at this sequence, it became apparent that key transformations required modifications and/or optimizations for a variety of reasons including but not limited to: cost of goods (reagents), low yields, reaction duration, and inability to use an enantioselective variant. The following sub-sections discuss the studies made on several of these steps as well as the subsequent modifications that were made to improve upon them where possible.

### 2.1.2 Friedel-Crafts

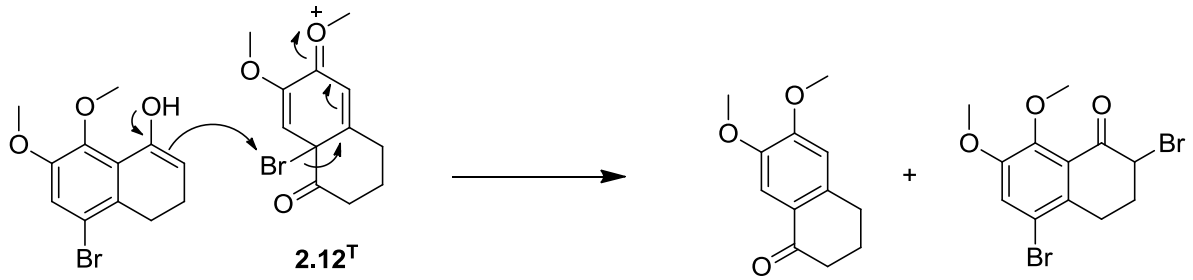
*Scheme 2.2 – Products of the Friedel-Crafts Reaction*




**2.2** **2.3** 62% **2.12** **2.13** 9%

It was already known that alongside desired **2.3**, side-product **2.12** (isolated by Kassandra Lepack) was also formed during the Friedel-Crafts reaction. In order to have *p*-attack from the aromatic group during the reaction, some reagent or transient intermediate has to pick up the bromine in order for the rearomatization to occur. Recent isolation of dibromotetralone **2.13** suggests that an intermolecular mechanism (such as shown in *Scheme* 2.3) could be at play. In this mechanism, enolization of the desired **2.3** occurs, allowing a nucleophilic attack on the corresponding electrophilic bromine of intermediate **2.12**$^{T}$, product of the aforementioned aromatic *p*-substitution. Thinking of this sequence of events as a parallel disproportionation reaction is relevant because whenever it takes place, two potential molecules of desired **2.3** are lost.

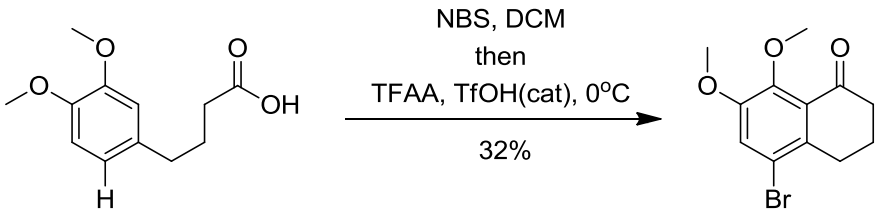
*Scheme 2.3 – Possible Mechanism for Formation of **2.12** and **2.13***




**2.3**$^{T}$ **2.12**$^{T}$ **2.12** **2.13**

Attempts at performing the same transformation under more dilute conditions to lower the possibility of this intermolecular interaction gave similar yields for the sought-after **2.3**. Performing the reaction with polyphosphoric acid also yielded similar results and side-products, which pointed to the fact that the bias might reside in the electronic properties of the substrate.

*Scheme 2.4 – Telescoping of the Aromatic Bromination and Friedel-Crafts Reactions*

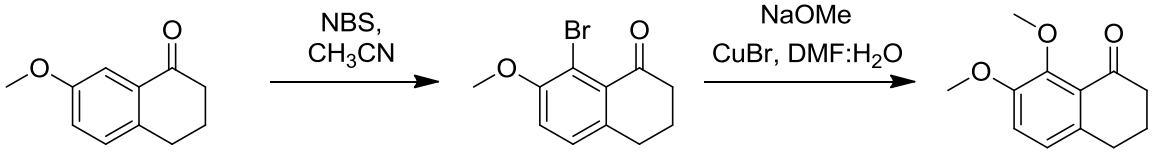



**2.1** **2.3**

Because the crude mixture of the initial aromatic bromination reaction is used for the Friedel-Crafts reaction, there is the potential for telescoping the two reactions together into a single manipulation. In a single attempt (Scheme 2.4), using DCM as the solvent for the bromination, the same procedure with $AuCl_3$ and NBS was followed, but upon noticing reaction completion by NMR, the solution was cooled to 0°C, then TfOH and TFAA were added. Isolation of bromotetralone **2.3** was possible, albeit in a low yield of 32%. In order to push material through the complete sequence, the higher-yielding two steps procedure was preferred.

An alternate route to the non-brominated tetralone **2.4** was published in 2011 by Cabrera and coworkers [44] (Scheme 2.5). Starting with commercially available and inexpensive **2.14**, *N*-bromosuccinimide aromatic bromination followed by aromatic substitution with sodium methoxide will furnish the desired tetralone **2.4** in a reported combined yield of 70%. This approach seems to be a simpler alternative, should this project be further worked on.

*Scheme 2.5 – Alternative Route to Tetralone **2.4***



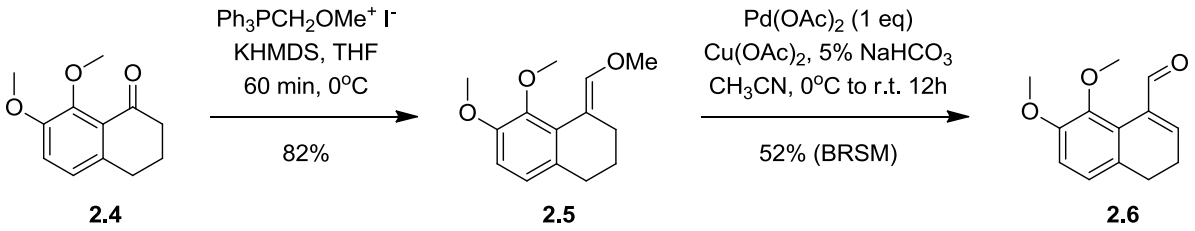

**2.14** **2.15** **2.4**

### 2.1.3 Access to *α,β*-Unsaturated Aldehyde 2.6

One of the transformations that required modification or optimization was the formation of the *α,β*-unsaturated aldehyde **2.6**. The original method, shown in Scheme 2.6 entailed the formation of methyl enol ether **2.5** via a Wittig reaction followed by a palladium-"catalyzed" oxidation. The problems in this transformation resided in the super stoichiometric quantity of palladium acetate required for the reaction, as well as the low

combined yield of 42% over two steps. The sheer quantity of aldehyde **2.6** that would be needed throughout this project made it impractical to keep using such a costly reaction sequence.

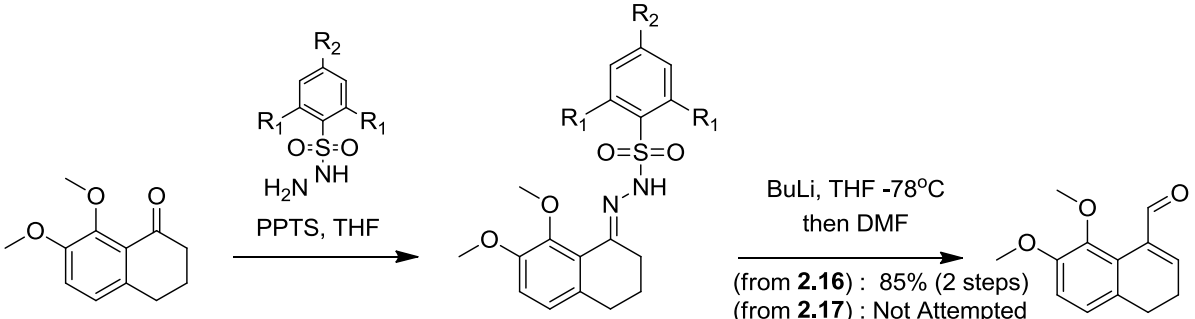
*Scheme 2.6 – Original Synthesis of Enal **2.6***




**2.4** **2.5** **2.6**

A Shapiro reaction combined with dimethylformamide as the electrophile seemed to be a logical alternative to form enal **2.6**. Of note, it was known that former student Kassandra Lepack already attempted to use a Shapiro reaction to form the desired **2.6** using *p*-toluenesulfonyl hydrazide, and obtained a yield of 28% for the combined two steps of hydrazone-formation and Shapiro reaction. It was considered that the use of alternative hydrazides might be the answer in this case.

*Scheme 2.7 – Accessing Enal **2.6** using a Shapiro Reaction*




**2.4** **2.6**

(**2.16**) = $R_1 = R_2 = iPr$
(**2.17** 74%) = $R_1 = H$, $R_2 = Me$

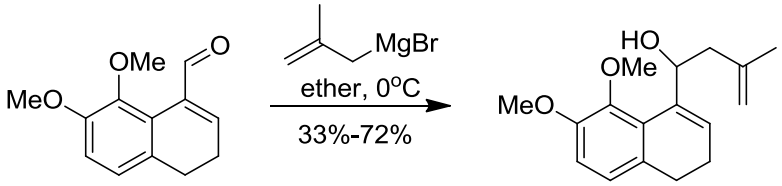
In this regard, trisylhydrazide was synthesized according to a procedure reported in former graduate student Effie Sauer's Ph.D. thesis.[45] Upon attempting hydrazone formation, use of trisylhydrazide furnished a clean crude mixture that showed complete conversion to **2.16** by NMR. For comparison purposes, hydrazone formation was also performed with the simpler *p*-toluenesulfonyl hydrazide and proceeded in 74% yield to give **2.17**. Treatment of **2.16** with n-butyllithium in THF followed by the addition of DMF supplied the desired enal **2.6** in 85% yield from ketone **2.4**. This result effectively surpasses the combined yield of 43% for the Wittig reaction/palladium-catalyzed oxidation sequence, as well as greatly

diminishes the production cost. No efforts were made toward performing the Shapiro reaction using hydrazone **2.17** due to a low isolated yield as well as precedents set by Kassandra Lepack.

### 2.1.4 Allylboration

One of the lowest yielding steps of the sequence that was handed to me is the formation of homoallylic alcohol **2.7** using a Grignard reaction. After attempting the reaction many times, it was easy to appreciate the erratic yields of this transformation (ranging from 33% to 72%, *Scheme* 2.8). It is also important to note that as of now, the products obtained from the key cascade step of the synthesis are obtained as a racemic mixture due to the absence of an enantioselective alkylation step. It was envisioned that imparting a certain enantiomeric excess to this transformation would allow transfer of chirality throughout the pericyclic reaction cascade, ultimately leading to an optically active version of the alkaloid.

*Scheme 2.8 – Original Grignard Reaction to Access Homoallylic Alcohol **2.7***

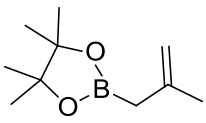



**2.6** **2.7**

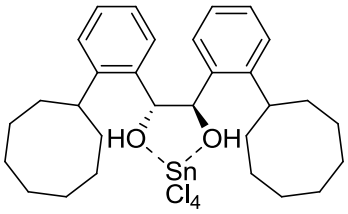
Allylborations appeared to be a viable solution to both the low yielding aspect of the Grignard reaction as well as the possibility of having an enantioselective alkylation step. Even though typical asymmetric allylborations[46] require chiral allylboron reagents, those are usually lengthy to synthesize, relatively unstable and/or hard to manipulate. Recent publications[47,48] demonstrate that they are not necessary to achieve enantiomeric excess and a very simple pinacolborane-derived reagent coupled with enantioselective Brønsted-acid catalysis can achieve similar or better results.

The known methallyl pinacol boronic ester **2.18** was chosen for its stability as well as its high reactivity toward aldehydes (Scheme 2.9). As mentioned, using reagent **2.18** allows to make this alkylation enantioselective merely by adding a chiral Brønsted-acid in catalytic amount, such as binaphthyl-derived chiral phosphoric acid **2.20**[47] or diol-$SnCl_4$ complex **2.19**.[48] With these arguments in hand, it appeared that use of reagent **2.18** should be a good way to improve the poor yielding and somewhat erratic alkylation step.

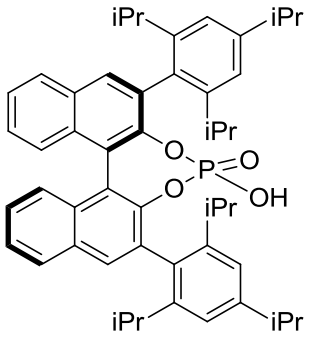
*Scheme 2.9 – Allylboration Reaction and Relevant Chiral Moderators*



**2.18**



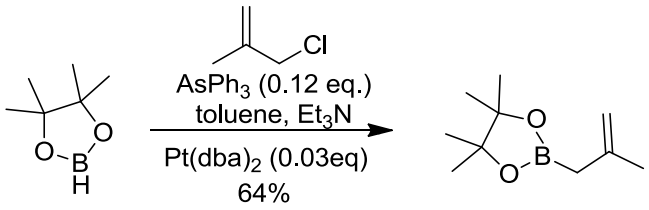
**2.19**



**2.20**

The synthesis of **2.18** was straightforward. Platinum tetrachloroplatinate was used to furnish bis(dibenzylideneacetone)platinum in 45% yield.[49] This catalyst was used in the coupling reaction between the two inexpensive reagents: 1-chloro-2-methylpropene and pinacol borane. The coupling reaction provided methallyl reagent **2.18** in 64% yield[50] (Scheme 2.10).

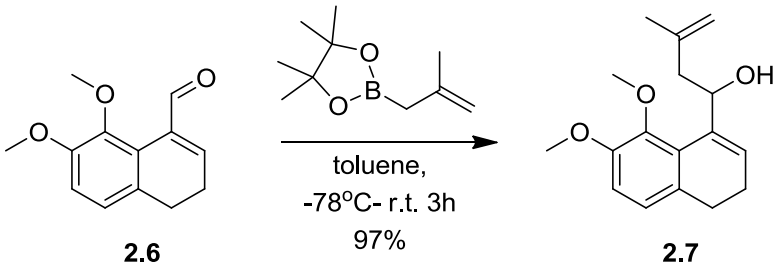
*Scheme 2.10- Synthesis of the Methallyl Boron Reagent **2.18***




**2.18**

The first attempt at using this reagent for the allylboration of aldehyde **2.6** was a success (Scheme 2.11). Homoallylic alcohol **2.7** was obtained in 97% yield while a clean conversion by TLC at -78°C was observed. Repeating the experiment demonstrated the consistency of this high yielding transformation. We were able to improve the yield of the alkylation reaction to form homoallylic alcohol **2.7** from 33%-72% to a consistent 92-97% and at the same time allow us to eventually branch this reactivity to obtain the enantiomerically enriched version of **2.7** only by adding a chiral Brønsted-acid such **2.19** or **2.20** shown in Scheme 2.9.

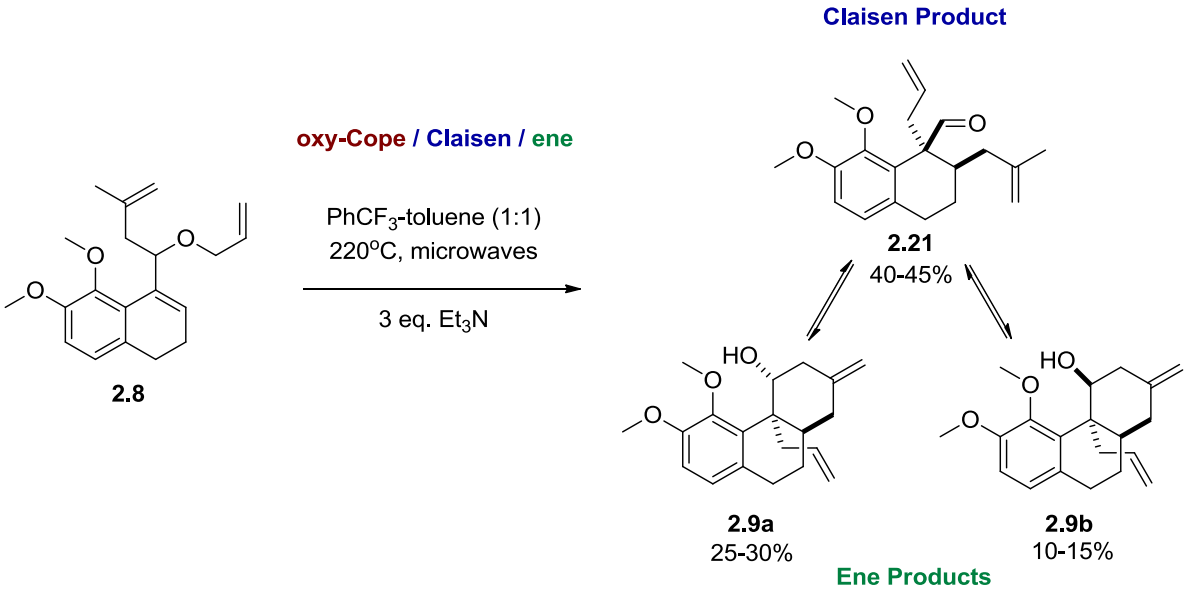
*Scheme 2.11 – Successful Allylboration Reaction*




### 2.1.5 Pericyclic Reaction Cascade

The pericyclic reaction cascade yields three products, as shown in Scheme 2.12. First, aldehyde **2.21**, which is the product of the oxy-Cope / Claisen portion of the cascade, and the two diastereomers **2.9a** and **2.9b**, products of the last pericyclic ene reaction (with **2.21** as the precursor). The typical yields for these three compounds are 40-45% of **2.21**, 25-30% of **2.9a** and 10-15% of **2.9b.**

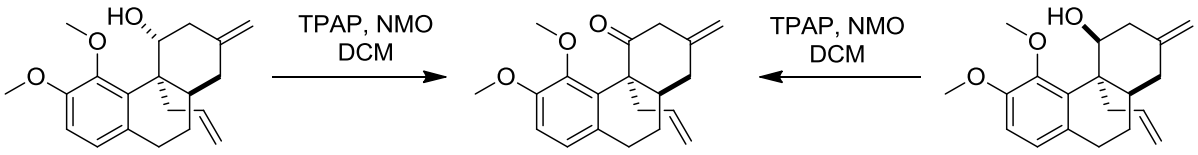
*Scheme 2.12 – Oxy-Cope/Claisen/Ene Products Profile*




Much work has been done on this reaction by former student Kassandra Lepack but the need to go through this sequence many times in order to continue the synthesis has led us to gather data and results over time about this specific transformation as well as its products.

First and foremost, only **2.9a** had been fully characterized (with obtained X-ray crystallography) by Kassandra. At the time, small quantities of **2.9b** were obtained and usually as a mixture of **2.9a**/**2.9b** due to a difficult separation by chromatography. Aldehyde **2.21** was typically isolated as a mixture superior to 10:1 of the aldehyde **2.21** shown in Scheme 2.12 and what is presumed to be its diastereomer. This aldehyde also seems to undergo what appears to be an oxygen-promoted degradation (seeing as the reaction conditions to synthesize it are quite harsh but lack oxygen) in a matter of weeks under standard storage conditions in a freezer. One of my first tasks in this project was to establish the relative configuration of **2.9b**. Scheme 2.13 shows the approach that was taken, where a strongly enriched (>12:1) mixture of **2.9b** and a pure sample of **2.9a** were used and individually oxidized in two separate flasks under the same reaction conditions. Crude NMRs of both mixtures after complete consumption of starting material showed the presence of a single and identical compound, which was purified and characterized as ketone **2.22**. We therefore demonstrated that **2.9b** was the diastereomer of **2.9a** solely at the hydroxyl bearing carbon, and that they are carrying the same cis-decalin structure between ring B and C.

*Scheme 2.13 - Convergent Ley-Griffith Oxidation of **2.9a**/**2.9b** to a Single Compound*




**2.9a** **2.22** **2.9b**

Seeing that microwave-promoted reactions can be perceived as being somewhat unusual, a typical procedure could be of significance for the discussions that follow.

A typical procedure of the oxy-Cope/Claisen/ene reaction starts by adding the substrate in an argon-filled, flame-dried microwave compatible vial with a stir bar and a carboflon (a fluoropolymer doped with carbon black in a vacuum-sealed piece of glass).The carboflon is used to absorb most of the microwaves and transform their energies into heat to allow the non-polar solvent (which is mostly unable to absorb said microwaves) to reach the desired temperature. The solvent and triethylamine were added and the solution was purged with argon.

Following these preparations, this mixture is submitted to microwaves at usually 300W and a temperature in the range of 200°C-240°C for a certain amount of time. Table

2.1 shows the effects of varying solvents, temperatures and reaction times on the product ratios.

*Table 2.1 – Pericyclic Cascade Conditions Screen*

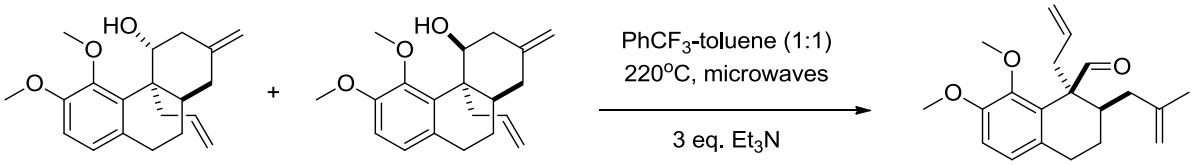
| | Solvent | Carboflon (Y / N) | Temperature °C | Time (h) | Ratio (2.21:2.9a:2.9b) | Yield |
|---|---|---|---|---|---|---|
| **1** | Toluene | Y | 200 | 4 | 1.71 / 1 / 0.38 | 90% |
| **2** | Toluene | Y | 220 | 3.5 | 1.66 / 1 / 0.40 | 89% |
| **3** | Toluene | Y | 220 | 4.5 | 1.33 / 1 / 0.61 | - |
| **4** | $PhCF_3$-Tol (1:1) | N | 220 | 4 | 1.60 / 1 / 0.33 | 88% |
| **5** | $PhCF_3$-Tol (1:1) | N | 220 | 5 | 1.32 / 1 / 0.55 | - |
| **6** | DMF | N | 220 | 3 | 1.10 / 1 / 0.92 | 72% |
| **7** | $C_6H_5Cl$ | N | 240 | 4 | 1.22 / 1 / 0.82 | 78% |

Entries **1** to **3** were completed only in toluene with a carboflon at 200°C - 220°C and it appeared that there was a fine line where optimal quantity of **2.9a** could be produced (assuming aldehyde **2.21** is resubmitted to the same reaction conditions). With higher temperatures and/or reaction times a larger raw quantity of **2.9a** is produced but so is a relatively larger quantity of **2.9b**, both of which are accompanied with a smaller overall yield. Similar observations can be made with the trifluorotoluene:toluene mixture as a solvent (entries **4** and **5**). The slightly more polar mixture of solvent did not require the presence of a carboflon to reach 220°C. This allowed us to obtain a better ratio probably because of the absence of localised heat in the mixture (caused by the carboflon in entries **1-3**). Uses of excessively polar solvents gave poor product ratios (entries **6** and **7**). Factoring in the fact that aldehyde **2.21** can be resubmitted to the reaction conditions, the whole reaction becomes a complex balancing act requiring a minimal quantity of polar solvent to reach 220°C thus avoiding sources of high localised heat, and figuring out the conditions that allow maximizing the yield, the **2.9a**/**2.21** ratio and the **2.9a**/**2.9b** ratio. Entries **2** and **4** were the most used conditions to synthesize more material for use in researching the post-cascade part of the synthesis.

These results also prompted us to study the reversibility of the ene process in this scenario and to probe the possibility of losing **2.9a** to **2.9b** due to it being a thermodynamically favored product. This would explain why larger quantities of **2.9b** are

produced over time during this reaction if **2.9b** is in fact the more stable product. A simple experiment was devised where a mixture of **2.9a** and **2.9b** was submitted to the reaction conditions and formation of a small amount of **2.21** was observed after an hour at 220°C. In this experiment, the **2.9a**:**2.9b** ratio observed at the end was similar to the one in the starting mixture. This result suggests that the ene reaction could be reversible under these conditions for both **2.9a** and **2.9b** (although more experiments would be required to establish this fact with confidence). It also helps support the diastereomeric identity of aldehyde **2.21**.

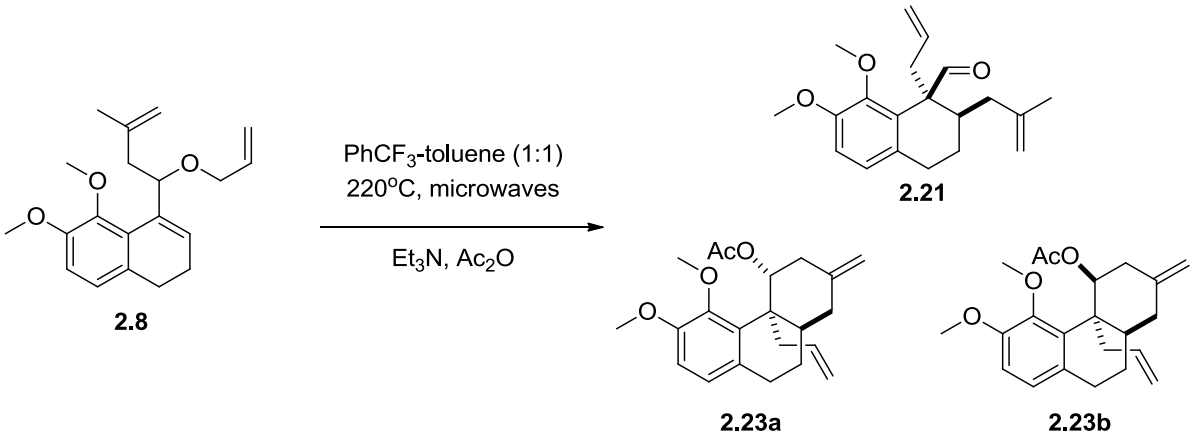
*Scheme 2.14 – Reversibility of the Ene Reaction*




**2.9a** **2.9b** **2.21**

After establishing the reversibility of the last pericyclic reaction in the cascade we sought to investigate the possibility that mostly **2.9a** is formed at first and as the reaction proceeds, more and more **2.9b** is formed through a route such as **2.9a** →**2.21** → **2.9b**. In such event, the possibility of trapping the formed hydroxyl at that temperature by using acetic anhydride to form the acetate was hypothesized to potentially stop the loss of **2.9a** to **2.9b** by blocking the retro-ene process. The reaction was carried out with the usual conditions, with the addition of acetic anhydride, and the products observed were acetate **2.23a** and what looked like acetate **2.23b** in a 3:1 ratio after 4h at 220°C with little to no traces of **2.9a** or **2.9b**.

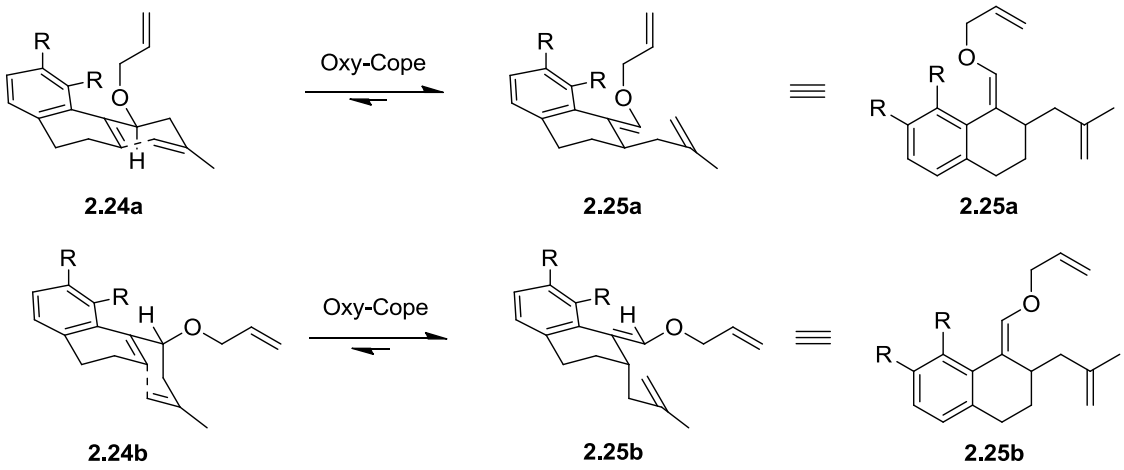
*Scheme 2.15 – Attempt at Driving the Reaction toward the Kinetic Product*




With these results in hand, it seems that the difference in energy for the transition states leading to the two diastereomers is fairly small and that under these conditions 3:1 of **2.9a:2.9b** is the best obtainable ratio.

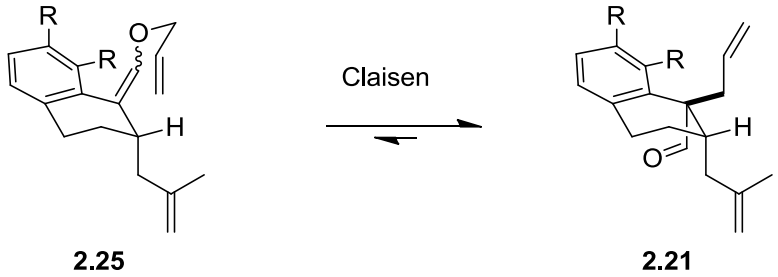
Basic conformational analysis on every step of this pericyclic reaction cascade can be performed in an attempt to explain the product formation profile of this reaction. The oxy-Cope reaction can proceed through two distinct transition states in which the forming C-ring will possess a chair-like transition state, which is assumed to be the lowest energy transition state for this transformation. Scheme 2.16 shows the two possibilities in which the methallyl component can adopt a pseudo-equatorial (**2.24a**) or pseudo-axial (**2.24b**) conformation, while the adjacent ring sits in a boat-like conformation. The product of going through conformation **2.24a** should yield enol-ether **2.25a** with a cis-relation to the aromatic ring while the product of **2.24b** should yield the trans isomer **2.25b**.

*Scheme 2.16 – Possible Conformations for the Oxy-Cope Reaction*




The ratio of the intermediates resulting from the oxy-Cope reaction is unknown due to a rapid Claisen rearrangement that consumes the enol-ether as it is formed. In some way, it is possible to disregard the **2.25a**/**2.25b** proportions, since both intermediates will most-likely undergo the Claisen rearrangement on the face opposing the methallyl substituent for steric reasons (Scheme 2.17). The Claisen product should therefore possess an aldehyde syn to the methallyl group, and thus set the stage for an intramolecular ene transformation leading to a cis-decalin framework. This would effectively form the correct B-C ring junction of morphine.

*Scheme 2.17 – Possible Conformations for the Claisen Reaction*




When looking at the intramolecular ene reaction, four plausible distinct conformations leading to transition states can be identified (Scheme 2.18). These four structures converge into the two different empirically observed diastereomers. The following scheme demonstrates that two conformational parameters can be toggled to create a total of four conformations for this transformation. The first parameter is the conformation of the B-ring, which can adopt two different chairs. This change will affect which substituent is in axial position during the pericyclic reaction on the forming C-ring. i.e.: In **2.26a** and **2.26b**,

the aryl ring is the only axial substituent whereas in **2.26c** and **2.26d** the allyl chain and alkyl chain are in 1,2 diaxial position. The second parameter that can be toggled is the orientation of the $\pi^*_{C\text{-}O}$ orbital. Since rotation around the C-CO bond is allowed, there are ultimately two energy minima conformations that allow a viable $\pi_{C\text{-}C} \rightarrow \pi^*_{C\text{-}O}$ overlap. This C-CO bond orientation will consequently also dictate the conformation of the forming C-ring (either chair-like, **2.26a** and **2.26d** or boat-like, **2.26b** and **2.26c**). These conformations were hypothesized based on the assumption that the high-energy pericyclic ene process would occur in an energy-minimized chair-like transition state.[51] Table 2.2 shows the different characteristics of these four different conformatons and supports the product formation profile observed under standard conditions (when stopping the reaction after a minimal amount of time to observe **2.9a** and **2.9b** in a near 3:1 ratio).

*Scheme 2.18 – Possible Conformations for the Intramolecular Ene Reaction*

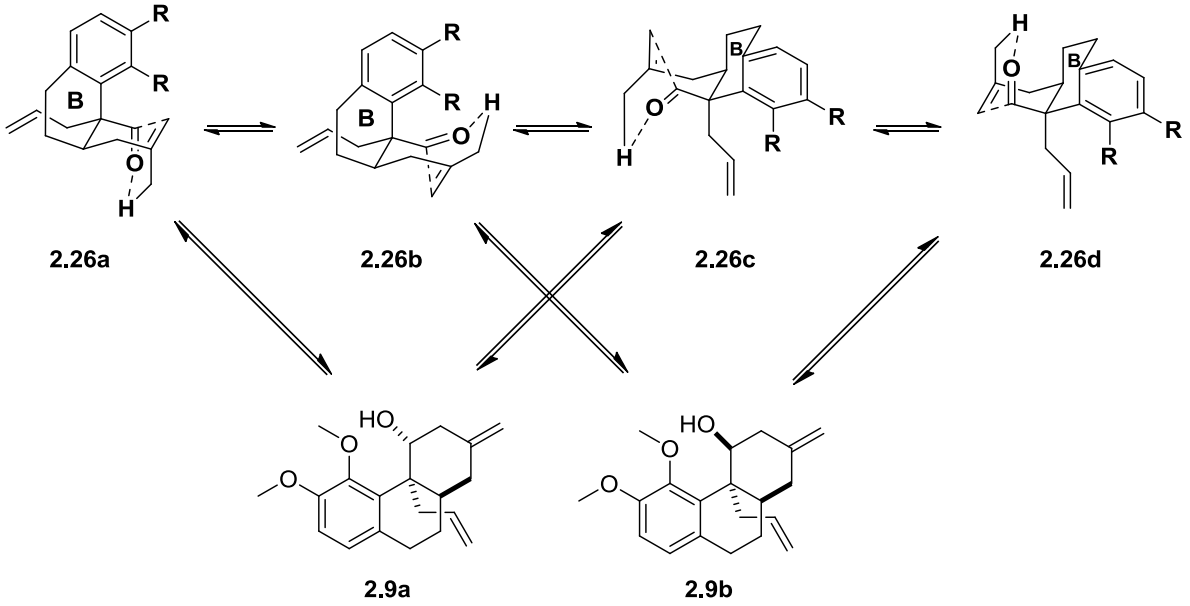


*Table 2.2 – Description of the Possible Conformations for the Ene Reaction*

| Conformation | Forming Ring | Axial Substituents of the Forming Ring | Outcome |
|---|---|---|---|
| **2.26a** | Chair | Aromatic Ring | **2.9a** |
| **2.26b** | Boat | Aromatic Ring | **2.9b** |
| **2.26c** | Boat | Allyl Subst. and Alkyl Subst. | **2.9a** |
| **2.26d** | Chair | Allyl Subst. and Alkyl Subst. | **2.9b** |

Assuming a very slow retro-ene reaction, and rapid exchange between conformations, it is possible to envision that this process approaches a Curtin-Hammett control where the transition state energy dictates the initial product ratios. Seeing as the retro-ene process does occur (which is why it is **not** under real Curtin-Hammett control), the 3:1 initial ratio slowly degrades to almost 1:1 for **2.9a:2.9b** over time, due to thermodynamic equilibration.

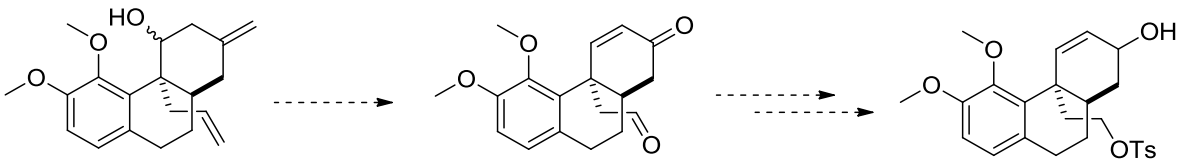
## 2.2 LACTOL OPENING

It can be noted that Kassandra worked on some parts of the following section, but for the exception of section 2.2.1, work performed by her will be explicitly specified where relevant and appropriate. It could have been included in subchapter 2.1 since the following can be considered an improvement of her work, but a significant amount of effort and time were spent on my part for this subject to have its own subchapter.

### 2.2.1 Initial Post-Cascade Work By Kassandra

As shown in Scheme 2.19, the initial vision was to use both **2.9a** and **2.9b** to perform an oxidative cleavage of both alkenes. An *in-situ β*-elimination of the hydroxyl group leading to enone **2.11** was assumed, expediently allowing both **2.9a** and **2.9b** to converge into valuable **2.30**.

*Scheme 2.19 – Initial Post-Pericyclic Cascade Plan*




**2.9a/2.9b** **2.11** **2.30**

Unfortunately, the number of methods to oxidatively (or even reductively) cleave alkenes while leaving the rest of the molecule untouched is limited. Most methods rely on the special reactivity of ozone toward alkenes[52] or go through a dihydroxylation/oxidative

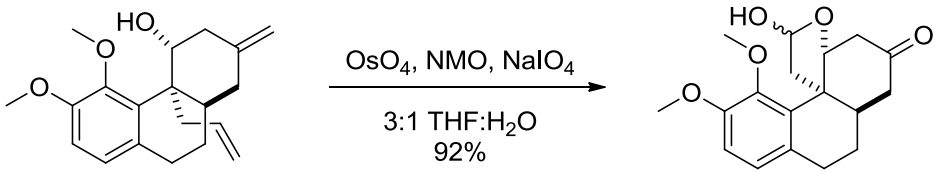
cleavage process.[53] At first, both methods were attempted using a mixture of **2.9a** and **2.9b** but the resulting mixture was very complex. It was thus decided to use pure samples to study this reactivity, envisioning it would be possible to go back at a later time to use the **2.9a**/**2.9b** mixture.

*Table 2.3 – Attempted Oxidative Cleavage for **2.9a** and **2.9b***

| Compound | Conditions | Result |
|---|---|---|
| **2.9a** | Ozone, DCM -78°C then $PPH_3$ or DMS | Degradation |
| **2.9b** | Ozone, DCM -78°C then $PPH_3$ or DMS | Degradation |
| **2.9a** | $OsO_4$, NMO, $NaIO_4$, THF:$H_2O$ | Single Compound |
| **2.9b** | $OsO_4$, NMO, $NaIO_4$, THF:$H_2O$ | Complex Mixture |

While ozonolysis only led to degradation, a Lemieux-Johnson protocol using osmium tetroxide, NMO and sodium periodate led to the sole production of **2.10** in typically high yield using **2.9a** as the starting material. The same protocol using **2.9b** leads to a relatively complex mixture of products.

*Scheme 2.20 – Lemieux-Johnson Protocol on **2.9a***




**2.9a** **2.10**

Although **2.10** (Scheme 2.20) could not be fully characterized[2] due to is very labile nature and the presence of two diastereomers, enough information was present in its H, C, and DEPT spectra to make us confident that **2.10** was the right structure.

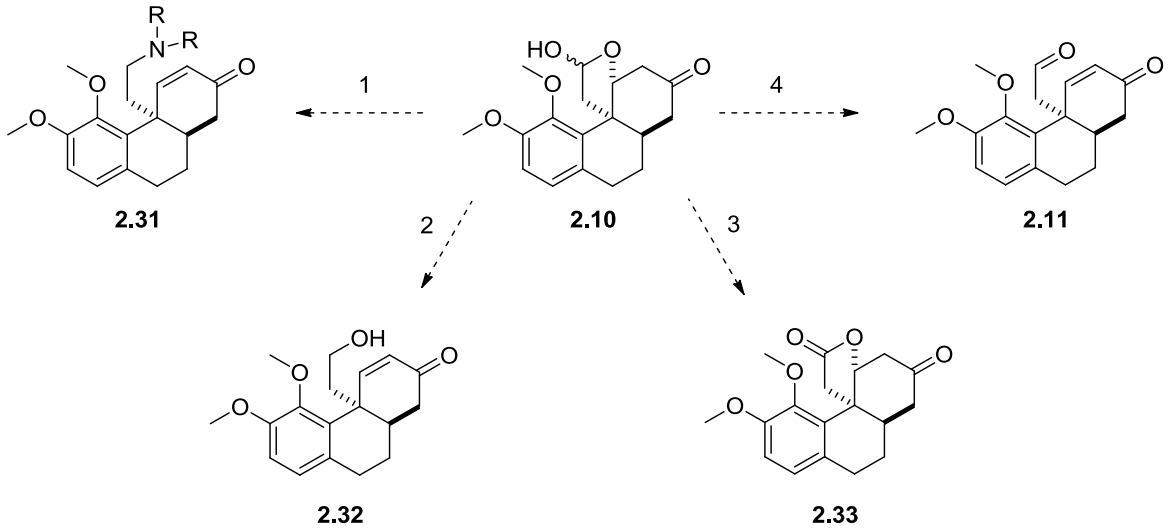
### 2.2.2 Devising Approaches to Opening of Lactol 2.10

It is interesting to note that small amounts of the desired enone **2.11** could be seen in the NMR of crude or "purified" sample of lactol **2.10** demonstrating the instability of the

[2] The 92% yield was obtained through the use of an internal standard (naphthalene) both during the reaction and after the reaction (added to the crude mixture).

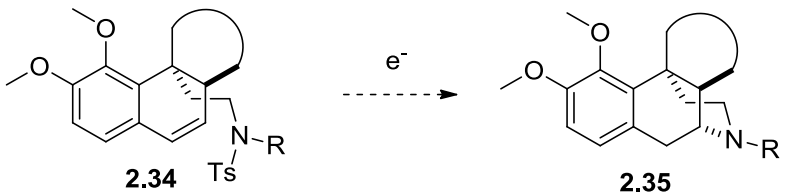
hemi-acetal functionality in this particular compound. With this in mind, several approaches were concocted in order to productively use lactol **2.10**. Four of these possibilities are shown in Scheme 2.21.

*Scheme 2.21 – Possibilities in Working with Lactol **2.10***




The first two possibilities (1 and 2) were to selectively reduce or perform a reductive amination on the masked aldehyde of **2.10**, but these approaches were believed to be too problematic for several reasons. First, a secondary amine would be necessary for a reductive amination in order to avoid 1,4 nucleophilic addition on the enone functionality, but it was known[23] that a tosylated amine was required in a future step to efficiently promote the D-ring radical heterocyclization (Scheme 2.22). The fact that tosylamines are poor substrates for reductive aminations due to their electron-deficient nitrogen indicated that a more electron rich amine would be required but so would additional deprotection and protection steps. This idea was abandoned for these uninteresting prospects.

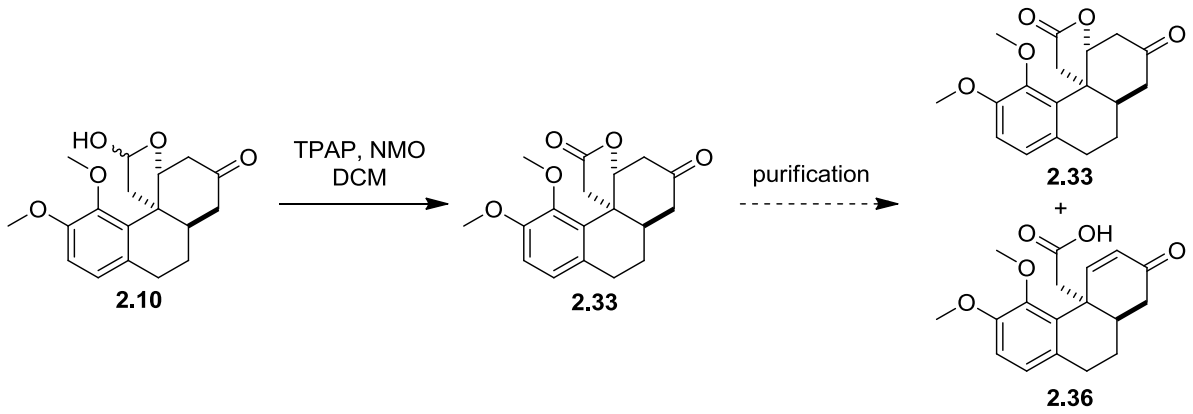
*Scheme 2.22 – Required Tosylamine in D-Ring Radical Reductive Detosylation*




Selective aldehyde reduction to the hydroxyl was avoided again to circumvent the possible 1,4 nucleophilic attack on enone **2.32**. Possibility #3 was to oxidize the hemi-acetal functionality to the corresponding lactone. The chosen Griffith-Ley oxidation proceeded

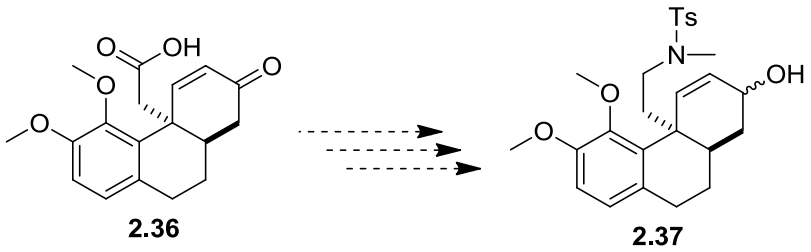
correctly as indicated by several key NMR signals on isolated lactone **2.33**. Unfortunately, the crude mixture was not clean enough for characterization and any sort of purification (acid-base wash / treated or untreated silica / recrystallization) would yield an inseparable mixture of carboxylic acid **2.36** and lactone **2.33**.

*Scheme 2.23 – Attempt at Oxidizing Hemi-Acetal **2.10***



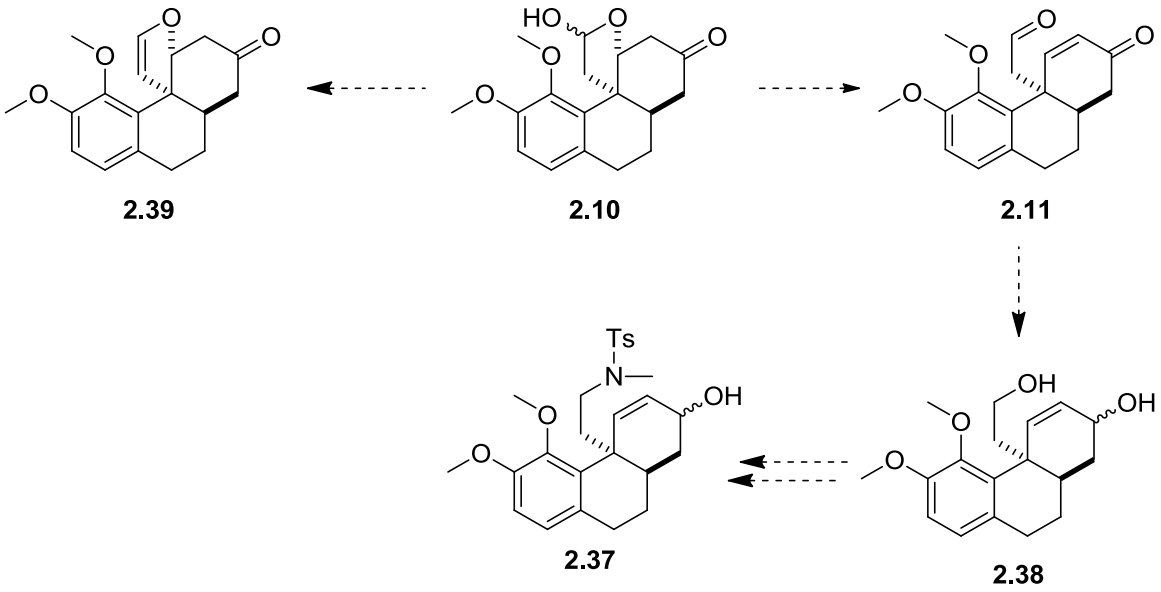

Our inability to access a pure sample of carboxylic acid **2.36** was somewhat disconcerting. Had this worked, our approach would have included a selective 1,2 enone reduction, followed by amide coupling with a primary amine to install the required nitrogen component. Further reduction and tosylation to obtain **2.37** would have placed us in a viable position to complete the synthesis of the opiate (Scheme 2.24).

*Scheme 2.24 - Goal for a Lactone-Opening Route*



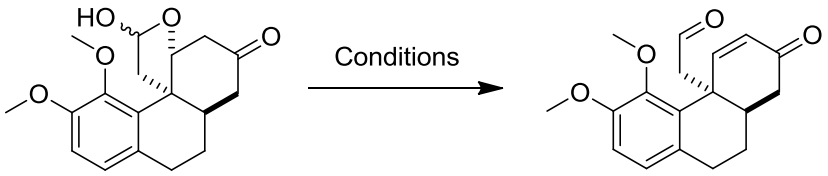

Finally, possibility #4 included formal dehydration of the molecule, effectively removing one equivalent of water. It was envisioned that this would force the molecule to unmask the aldehyde and adopt structure **2.11** (Scheme 2.25). As shown, the possibility of cyclic enol ether **2.39** formation was a concern, it also being a viable product of formal dehydration.

*Scheme 2.25 – Dehydration of **2.10** and End Goal of This Strategy*




To specify, the contribution of Kassandra on this matter was to attempt several conditions for the aforementioned transformation, and in this regard, she was able to identify conditions that produced a 40% yield of enone **2.11**; (*Scheme* 2.1), namely trifluoroacetic acid in toluene. This step was erratic and the yields were far from consistent from one reaction to the other. One has to remember that hemi-acetal **2.10** is used as a mixture of diastereomers (diastereomeric at the anomeric carbon). We hypothesized that the low yield might be explained by one diastereomer being more reactive under these conditions than the other one, possibly for stereoelectronic reasons. Disregarding the actual cause, it was clear that this erratic and low-yielding reaction would be a significant bottleneck in the synthesis and set ourselves on identifying new methods to effect the same transformation.

*Table 2.4 – Attempted Conditions for Lactol **2.10** Opening to Enone **2.11***

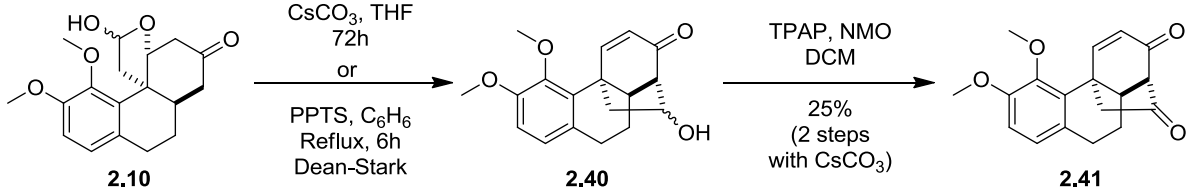



**2.10** **2.11**

| Entry | Conditions | Yield / Result |
|---|---|---|
| A | Acetic Acid Glacial, DCM, r.t. | 27% |
| B | PPTS, THF, 4Å MS, reflux | 33% |
| C | $K_2CO_3$, Acetone, 1d | 50% |
| D | TFAA, DCM, $Et_3N$ | 28% |
| E | $Me_2SO_4$, $K_2CO_3$, Acetone | 25% |

As depicted in Table 2.4, none of the attempted conditions had significantly higher yields or consistency than the conditions found by Kassandra. Acidic and basic conditions were attempted, as well as conditions prone to transform the hemi-acetal hydroxyl into a leaving group. Harsher conditions such as PPTS in benzene at reflux or cesium carbonate in THF for three days even yielded small amounts of the aldol product **2.40** as a diastereomeric mixture, which was characterized as the oxidized diketone **2.41** (Scheme 2.26). Of note, any attempt to purify enone **2.11** on silica would yield back a small amount of lactol **2.10**, probably due to the silica's Lewis acidity and its water content. This made following any of the aforementioned reactions very difficult by conventional TLC (which would always show a mixture of enone **2.11** and lactol **2.10**) and they thus had to be followed by NMR.

*Scheme 2.26 – Aldol Reaction while Attempting to Open Lactol **2.10***

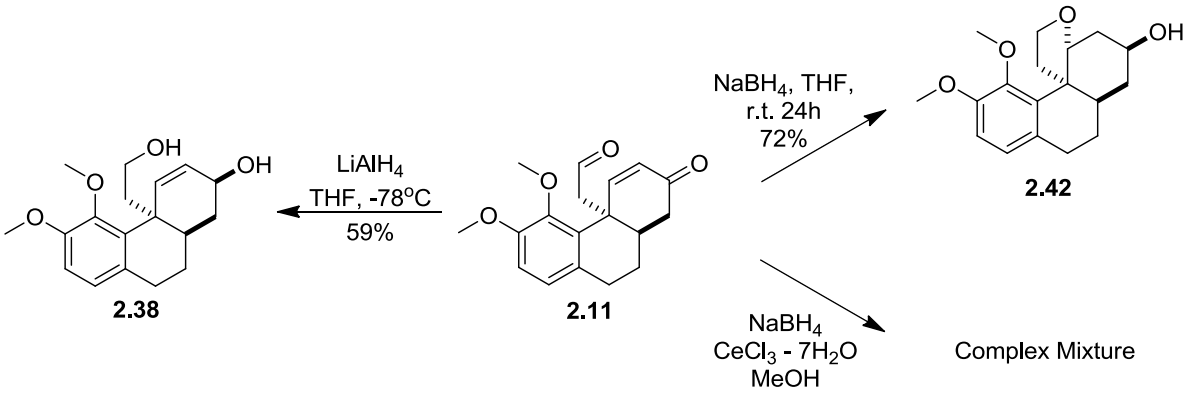



**2.10** **2.40** **2.41**

Nevertheless, it was possible to use the small amounts of enone **2.11** (which was unfortunately never characterized itself for aforementioned reasons) and perform the subsequently intended reaction; a 1,2 reduction of both the aldehyde and the *α,β*-unsaturated ketone. One of the last reactions Kassandra performed during her time in the lab was an attempt at this transformation using DIBAL-H and if memory serves, she

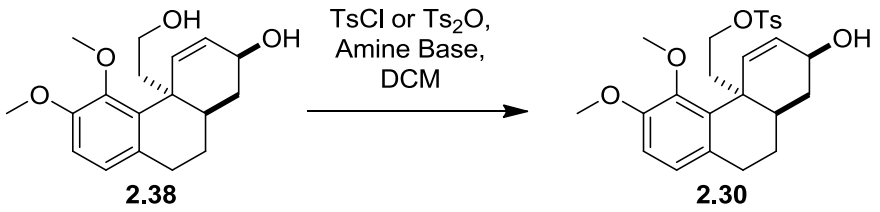
obtained a complex mixture of products. Weaker reducing conditions were therefore attempted such as sodium borohydride and separately Luche reduction conditions, known to favor 1,2 reduction.[54] Unfortunately, sodium borohydride only yielded **2.42** which is probably the product of initial aldehyde reduction, followed by very rapid 1,4 nucleophilic addition and final ketone reduction. Luche reduction conditions yielded a complex mixture of products, but this was somewhat expected because it is known that these conditions, when used in a molecule bearing both an aldehyde and a *α,β*-unsaturated ketone, can effect selective ketone reduction.[55,56] This is due to the cerium Lewis acidity which, in the presence of methanol, can mask the aldehyde as the dimethoxy-acetal, but keep the ketone untouched, leaving it available for reduction.

*Scheme 2.27 – Attempts at Reducing Enone **2.11***




Finally, the third attempt at reduction used lithium aluminum hydride as a solution in THF. A rapid and clean, although low-yielding, conversion to the desired diol **2.38** was observed. At this point, selective tosylation of the primary hydroxyl group followed by displacement by TsNHMe was the most expedient way to get to compound **2.37** (Scheme 2.25). Unfortunately, after attempting many different conditions, tosylated **2.30** could never be isolated in viable quantity (Table 2.5).[57] Although small amounts of **2.30** were obtained in some attempts, not enough was obtained for proper characterization at the time.

*Table 2.5 – Attempted Conditions for Selective Tosylation of Diol **2.38***




**2.38** **2.30**

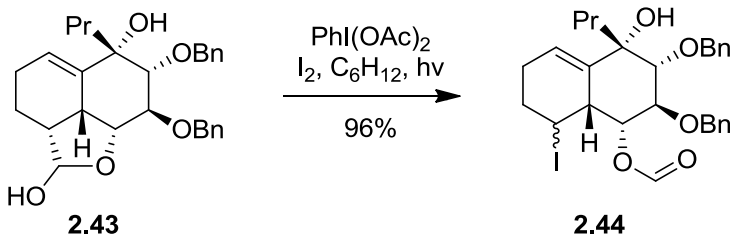
| Entry | Amine Base | Agent | Additive | Solvent | Result |
|---|---|---|---|---|---|
| **1** | Pyridine | TsCl | DMAP | DCM | Complex Mixture |
| **2** | $Et_3N$ | TsCl | - | DCM | <20% **2.30** |
| **3** | $Et_3N$ | TsCl | - | THF | Mostly Rec. SM |
| **4** | $Et_3N$ | $Ts_2O$ | - | DCM | Rec. SM |
| **5** | - | TsCl | TMPDA | Toluene | <30% **2.30** |

At that point, more **2.9a** had to be synthesized in order to be able to continue through that route. This seemed like a good point to take a step back and look at the sequence as a whole and consider our options. Several problems still persisted in that sequence such as an increasing step counts, a number of low yielding transformations, some intermediates were problematic to work with, and there would be an increasing number of functional group interconversion down the road. These problems pushed us toward finding a new route past the pericyclic reaction cascade. This particular approach was therefore abandoned.

### 2.2.3 Suarez Radical Opening

An atypical approach to working with hemi-acetals came to light when former graduate student Jason Poulin stumbled onto the Suarez lactol fragmentation reaction[58] while working on a hemi-acetal of his own during his work on vinigrol.[59] Such transformation used in the synthesis of an Angelmicin B precursor (Mootoo and al.)[60] is depicted in Scheme 2.28. The initial process forms a hydroxyl-based radical, which, being highly unstable, fragments the lactol by homolitically breaking the C-C bond of the anomeric center. The formed carbon based radical can thus react with an iodine molecule to form the final product. (Mechanism available in Scheme 2.29)

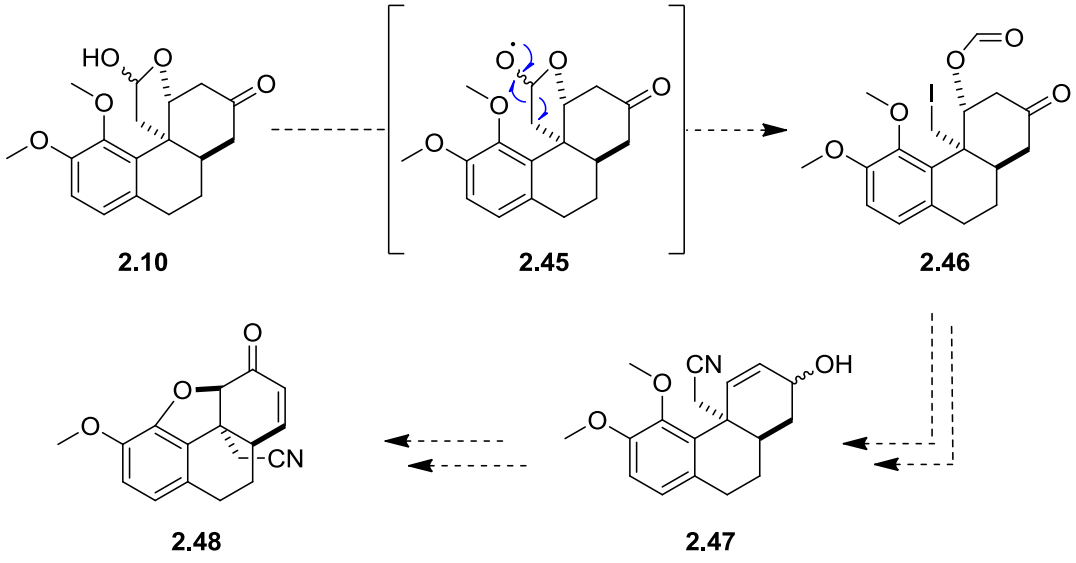
*Scheme 2.28 – Example of the Suarez Lactol Fragmentation*




**2.43** **2.44**

This reactivity would allow us to gain access to a carbon framework with a significantly different functional group map. In this case, access to formate **2.46** was envisioned (Scheme 2.29). At this point, formate elimination would readily occur, for it being in the *β* position of a carbonyl. Then, further 1,2 reduction of the formed enone could be performed to obtain the allylic alcohol portion of **2.47**. This would be followed by a substitution of the iodide by a nitrile group, adding both the required extra carbon and nitrogen atom that would ultimately become part of the alkaloid. With an intermediate such as **2.47** came the possibility of intersecting a previous synthesis of morphine such as the one by Trost[31] through intermediate **2.48**. According to his publication, only three additional synthetic steps would be required in order to access the final structure of morphine.

*Scheme 2.29 – Goals for the Suarez Fragmentation Route*



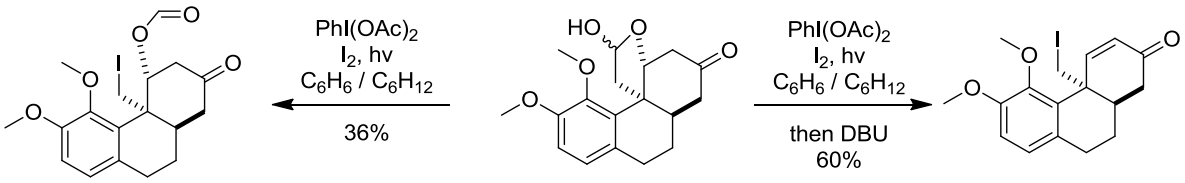

**2.10** **2.45** **2.46**

**2.48** **2.47**

Initial results were promising. Submitting lactol **2.10** to phenyliodo(diacetate), iodine, and light from two tungsten light bulbs in a mixture of benzene and cyclohexane yielded an approximate 36% yield of formate **2.46** (easily identified by crude NMR). Difficulty in characterizing this compound led us to believe that there was substantial lability of the

formate functionality due to the observation of NMR olefinic peaks usually present in *α,β* position of a carbonyl. Addition of DBU at the end of the reaction in a second attempt confirmed our hypothesis showing a single less polar product by TLC. Purification allowed us to conclude enone **2.49** was formed from the *in situ* elimination of the formate in a moderate 60% yield that was very consistently reproducible.

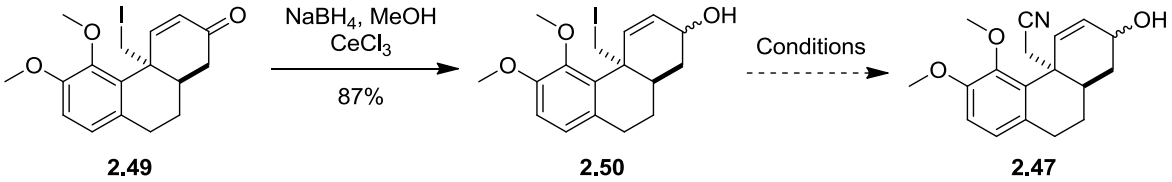
*Scheme 2.30 – Suarez Lactol Fragmentation on Lactol **2.10***




**2.46** **2.10** **2.49**

Subsequent Luche reduction of *α,β*-unsaturated ketone **2.49** to allylic alcohol **2.50** proceeded smoothly in 87% yield as shown in Scheme 2.31. The only transformation required from **2.50** to generate nitrile **2.47** was a $S_N2$ type displacement of the iodide with a cyanide anion, which seemed a relatively trivial transformation. Regrettably, none of the attempted conditions for this transformation yielded the wanted compound **2.47**. Typical conditions were attempted at first, such as shown in Table 2.6, entries **1-3,** where potassium cyanide was used as the salt in high polarity solvents (DMF, DMSO) at medium temperature. A complex mixture or recovered starting material was obtained in all cases with no trace of **2.47** in the crude NMR spectra. Entry **4**, **6** and **8** show the addition of additives such as crown ethers to render the cyanide anion more nucleophilic (in DMF and toluene) as well as silver nitrate to maybe increase the leaving group character of the iodide. Microwaves were used as well as the energy source for some variants of this transformation such as shown by entry **5** since it is commonly used for anionic displacement reactions[61], unfortunately only degradation was observed. Finally, at entry **7**, replacement of the iodide using a radical process was also attempted where the primary carbon radical would be formed, which could react in an intermolecular fashion with a TsCN molecule and eject a tosyl radical by cleavage of the weak S-C bond.[62] Again this only yielded a complex mixture of product.

*Scheme 2.31 – Luche Reduction and Attempts at Installing the Nitrile Group*




**2.49** **2.50** **2.47**

*Table 2.6 – Attempted Conditions for Displacement of Iodide by Cyanide*

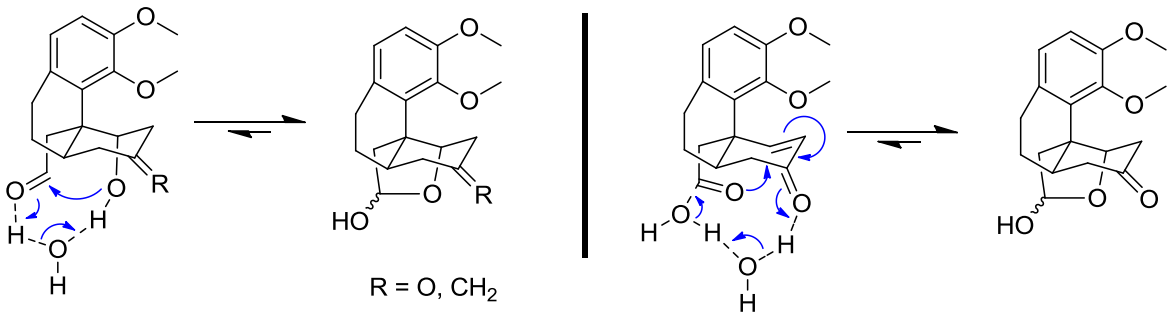
| Entry | Condition | Salt | Solvent | Result |
|---|---|---|---|---|
| **1** | 80°C – 4h | KCN | DMF | Complex Mixture |
| **2** | 80°C – 4h | KCN | DMSO | Complex Mixture |
| **3** | 50°C – 24h | KCN | DMF | Rec. SM |
| **4** | 18-Crown-6, 50°C – 5h | KCN | DMF | Rec. SM |
| **5** | µw - 80°C | KCN | DMF | Degradation |
| **6** | 18-Crown-6, reflux – 4h | KCN | Toluene | Degradation |
| **7** | AIBN, $Bu_3SnCl$, $NaBH_3CN$ | TsCN | tBuOH | Complex Mixture |
| **8** | $AgNO_3$, 80°C – 4h | NaCN | DMSO | Degradation |

This problematic displacement can be explained by the proximity of the quaternary carbon center. Although a cyanide anion is one of the (if not *the*) least hindered nucleophile used in such displacement reactions, the steric bulk from the molecule probably forces the iodide to stay in a specific part around the rotation axis of the C-$CH_2$I bond. Therefore, since the cyanide nucleophile has to come in from a 180° angle, logic states that in a bulky environment (which is the case here) most of the bulk should be at that exact same location on the molecule, blocking the approach path thus preventing the displacement. After a certain amount of resources used on this approach, it seemed preferable to cut our losses short and abandon this route altogether.

### 2.2.4 Sidestepping Lactol 2.10

As mentioned in the section's title, an approach where oxidative cleavage of both olefins was still at play but lactol **2.10** was avoided altogether was pursued. We hypothesized that hemi-acetal formation was a fairly rapid process originating from an intermediate such as **2.51** (Scheme 2.32) where the gem-disubstituted double bond may or may not have been oxidized yet. This is in comparison with a mechanism where oxidation of aforementioned double bond would allow rapid *in situ* elimination of the *β* hydroxyl yielding intermediate **2.53**, which could be followed by rapid addition of the aldehyde on the ketone π-system and tautomerization.

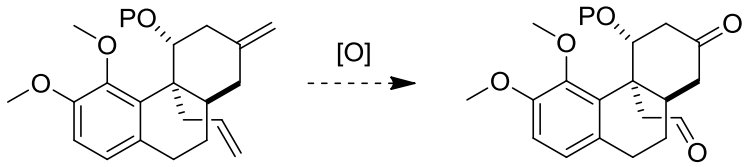
*Scheme 2.32 – Possible Mechanisms for Formation of Hemi-Acetal **2.10***




**2.51** **2.52** **2.53** **2.10**

If the first mechanism is truly what is happening in the reaction media, then it seems logical to think that protection of the hydroxyl group would most-likely suppress such mechanism and allow the isolation of an intermediate such as **2.55** (Scheme 2.33). At this point, rapid work-up and addition of an aprotic solvent followed by addition of base and quick reduction should yield the required diol.

*Scheme 2.33 – Possible Oxidative Cleavage of a Protected **2.54***

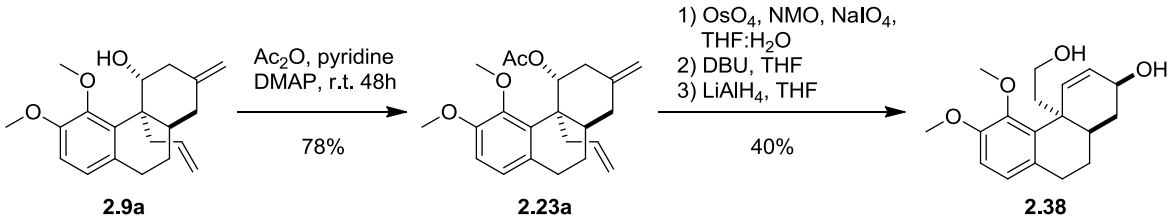



**2.54** **2.55**

After attempting to install a tosyl, trimethylsilyl and mesyl group unsuccessfully, an acetate group[3] was successfully installed in 78% yield, gaining access to **2.23a** (Scheme 2.34). Interestingly, the steric bulk of the nearby quaternary carbon probably only allowed for a less sterically demanding $sp^2$-hybridized substituent on the oxygen. As shown in Scheme 2.34, four consecutive steps of protection, oxidative-cleavage, DBU promoted elimination and lithium aluminum hydride reduction to diol **2.38** were successfully completed. Even though the yields were fairly consistent, the combination of an added step, a similarly low overall yield of 30% compared to the previous sequence and a diminished "elegance" factor, all pointed to the fact that it was not realistically superior to the available alternative.

[3] This was done before we noticed we could add acetic anhydride during the pericyclic reaction cascade to obtain compound **2.23a** directly.

*Scheme 2.34 – Protection / Oxidative-Cleavage / Elimination / Reduction Sequence*




**2.9a** **2.23a** **2.38**

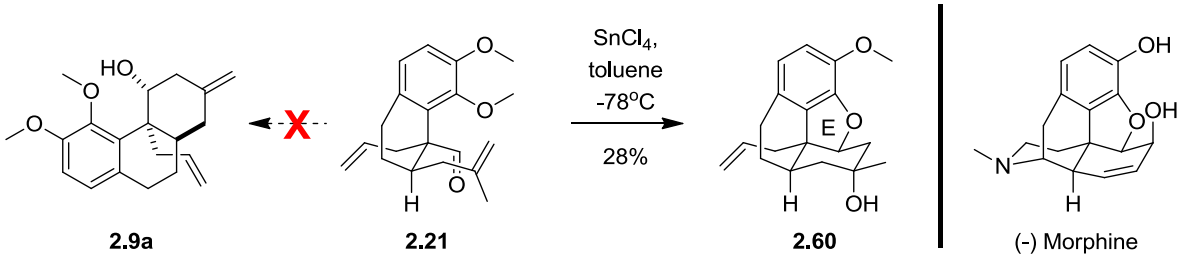
This concluded our work on the direct oxidative cleavage of both double bonds on compound **2.9a**. This work made it possible to access diol **2.38** through two different routes and at that time, we were willing to use that sequence if no suitable alternative approach could be found.

## 2.3 OXY-COPE/CLAISEN + PRINS

### 2.3.1 Original Result

The following subchapter is the result of considerate amount of efforts that spawned from an unexpected result during a specific experiment. The experiment was about investigating ways to enhance the yields for the intramolecular ene reaction in the pericyclic cascade. One of the reactions attempted included using aldehyde **2.21**, which is the intermediate product of the oxy-Cope/Claisen part of the cascade, and submitting it to a strong Lewis acid. This was done at low temperature hoping to perform the ene reaction in a selective fashion and generate **2.9a** exclusively (Scheme 2.35). What was envisioned was a synthetic step where key-step starting material **2.8** would be submitted to microwaves at lower temperature and shorter reaction times, obtaining mostly aldehyde **2.21**. It would then be taken out of the reactor, cooled to -78°C and a Lewis acid would be added to catalyze the last transformation.

*Scheme 2.35 – Attempt at the Intramolecular Ene Reaction Using a Lewis Acid*

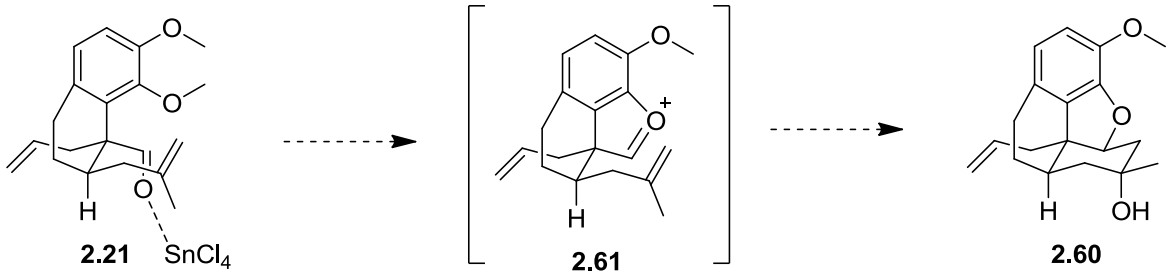



**2.9a** **2.21** **2.60** (-) Morphine

Unfortunately, the expected outcome did not take place seeing as the NMR signals for **2.9a** were nowhere to be found in the crude NMR of this reaction. After much

purification, product **2.60** was isolated out of this complex mixture. As seen in the previous scheme, the best yield was an irreproducible 28% (usual yields rotated around 10-15%). The fact that the E-ring of morphine is already present in **2.60** was of great surprise due to the fact that many planned synthetic steps that were envisioned to install this ring were formally being avoided. Major products for this transformation were not characterized due to our inability to isolate specific components cleanly enough, but many features found in the NMR spectra suggested a plethora of rearrangements or Prins reactions from either the methallyl or allyl substituents on **2.21.** Contrary to **2.60**, they all shared the comparatively uninteresting feature of still having both of their aromatic methoxy groups present, indicative of the lack of ring E.

*Scheme 2.36 - Proposed Mechanism to Access **2.60***

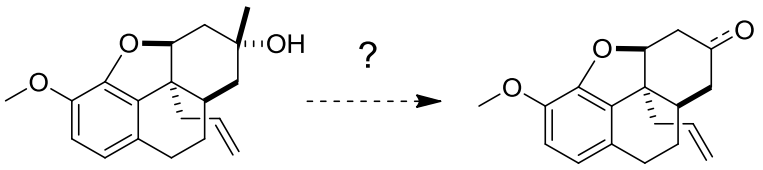



A mechanism was hypothesized to explain this fortunate transformation. As shown in Scheme 2.36, activation of the aldehyde on **2.21** could be followed by initial condensation from the proximal oxygen on the aromatic ring. At this point, the extra methyl could be picked up by a floating chloride anion. The formed oxonium **2.61** would then stimulate a nucleophilic attack from the gem-disubstituted double bond to form a tertiary carbocation, which would be quenched from the least-hindered bottom face by a water molecule or tin-oxide.

We can't disprove or support the mentioned mechanism at this point. Further efforts toward isolating other products of this transformation might enlighten us on this reactivity.

Regarding the feasibility of using **2.60** to progress toward synthesizing morphine, there is a clear problem that arises when looking at the tertiary hydroxyl group on the molecule. In prior approaches, a practical synthetic handle (a gem-disubstituted double bond) was available, on which could be performed among other reactions, an oxidative cleavage, whereas now, the amount of options to selectively cleave the methyl group are close to none.

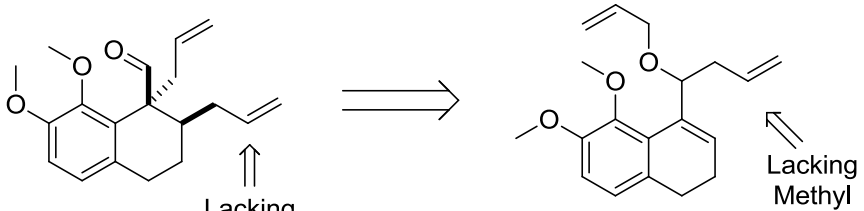
*Scheme 2.37 – Difficulty in Selectively Cleaving a Specific C-C Bond on **2.60***




**2.60** **2.63**

The above transformation is much more difficult to perform in organic chemistry and instead of trying to optimize the transformation from **2.21** to **2.60** (Scheme 2.35), it was decided that efforts would be better spent attempting to use this reactivity to generate a sought tetracyclic compound that was easier to work with. In other words, modifying the initial substrate in a specific way might allow us to avoid the aforementioned problem.

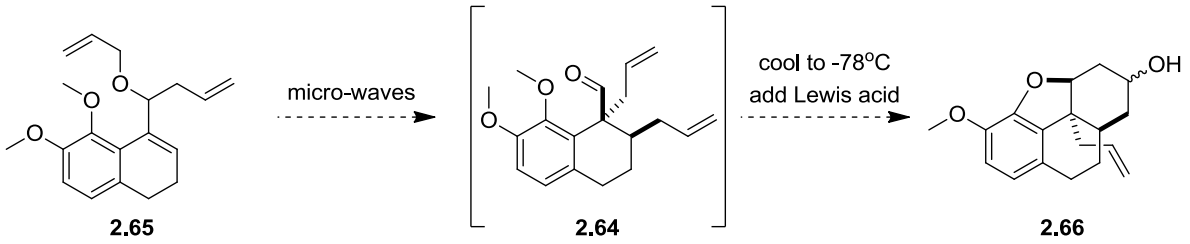
*Scheme 2.38 – Vision on Pericyclic Cascade Substrate Variation*




**2.64** **2.65**

As shown in Scheme 2.38, the envisioned substrate variation involved the removal of a single methyl group at the specified position. This would help us in many ways if applied to the reactivity discovered earlier. The first advantage would be the absence of the hard-to-remove methyl substituent, leaving us with a secondary alcohol easily oxidized or eliminated to further functionalize the surrounding area. The second advantage would be the possible complete suppression of synthesis of **2.9a** and **2.9b** during the microwave portion of this synthetic step, therefore suggesting a high-yielding transformation leading to the exclusive synthesis of aldehyde **2.21**. Finally, the third and last advantage would be a simplified synthesis for the pericyclic cascade substrate, where synthesizing a methallyl pinacol boronic ester to custom fit our allylboration needs would not be necessary. A simple commercially available allyl pinacol boronic ester would suffice.

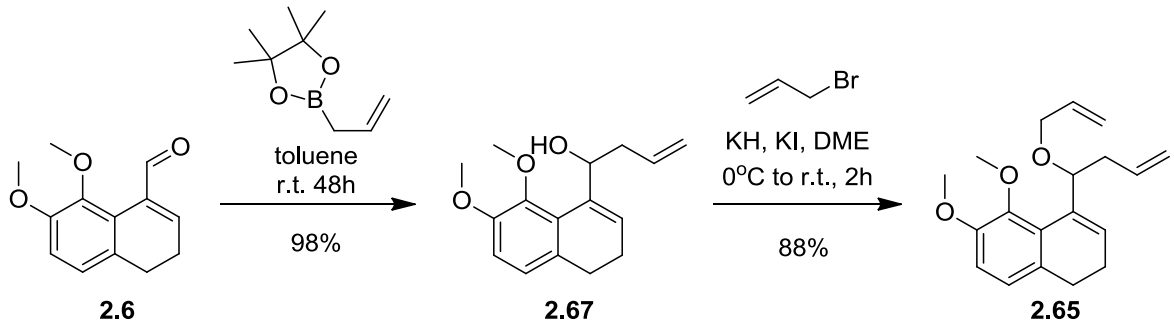
*Scheme 2.39 – Envisioned Reactivity with a Modified Substrate*




### 2.3.2 Substrate Variation

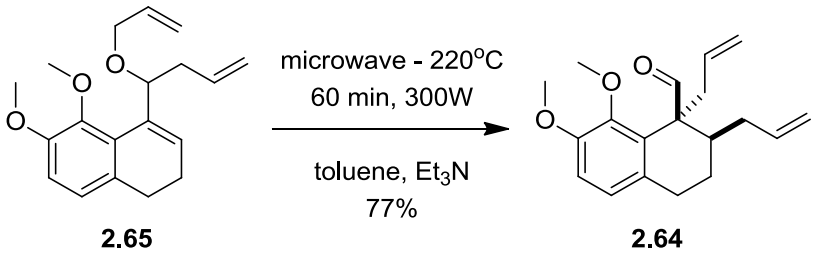
The synthesis of **2.65** was straightforward as mentioned earlier. Using the same *α,β* unsaturated aldehyde **2.6**, an allylboration was performed with the commercially available reagent and generated **2.67** in 98% yield. From there, a similar *O*-allylation protocol provided **2.65** in 88% yield (Scheme 2.40).

*Scheme 2.40 – Synthesis of the Modified Substrate **2.65***




The pericyclic reactions cascade also proceeded smoothly. As predicted, the reaction stopped at the Claisen transformation to furnish **2.64** in 77% yield after only 60 minutes in the microwave (Scheme 2.41). The reaction was surprisingly clean by TLC or NMR and no traces of **2.9a** or **2.9b**, the two diastereomers of the ene transformation, were detected. It is interesting to note the slightly diminished yield for this series of two pericyclic reactions when compared to the steady 85% of the oxy-Cope/Claisen/ene cascade with the standard substrate **2.8**.

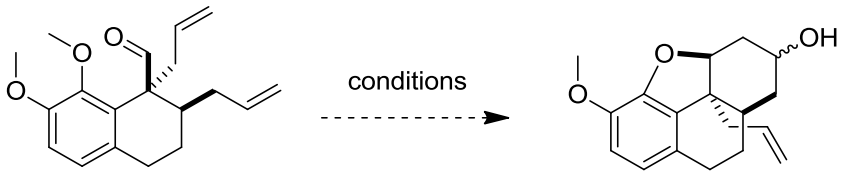
*Scheme 2.41 – Pericyclic Reaction Cascade with **2.65***




**2.65** **2.64**

With **2.64** in hands, attempts at the condensation/Prins-type cyclization were made. As can be seen in Table 2.7, the sought-after **2.66** was never isolated and/or characterized after several attempts. Initial conditions were similar to the ones successful with the methyl-bearing substrate **2.21** (entries **1** and **2**). The screening variables were further broadened to include other additives such as Brønsted acids (entry **3**) and boron or aluminum Lewis acids (entries **4,6,7,11,13** and **14**). Unfortunately none of these attempts yielded significant results. It was always either recovery of the starting material or slow but steady decomposition of the starting material (noticed by streaking on the TLC and multiplications of characteristic peaks by crude NMR). The only aluminum based attempt that yielded a significantly useful number of compounds was entry **13**, but an even number of methoxy signals by NMR and lack of a signal for the only hydrogen in the dihydrofuran ring in purified samples' NMR indicated that **2.66** was nowhere to be found. Finally, out of several indium triflate based attempts, one yielded a complex mixture containing a compound for which we could nearly match every H-NMR signal to our previously characterized **2.60**. Unfortunately, not enough material was isolated for proper characterization, and it is not without many efforts that we can state we were never able to reproduce that specific result.

*Table 2.7 – Attempts at Performing the Condensation/Prins Cyclization on Aldehyde **2.64***




**2.64** **2.66**

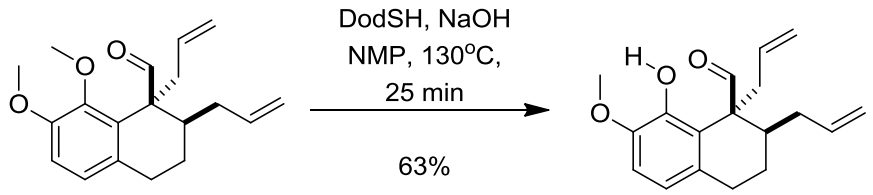
| Entry | Additive | Solvent | Result |
|---|---|---|---|
| **1** | $SnCl_4$ | Toluene | Rec. S.M. |
| **2** | $SnCl_4$(1 eq.) | DCM | Decomposition |
| **3** | TfOH | Toluene | Decomposition |
| **4** | $BBr_3$ | DCM | Decomposition |
| **5** | $In(OTf)_3$ | Toluene | Traces of Product[3] |
| **6** | $AlCl_3$-THF | Toluene | Rec. S.M. |
| **7** | $BF_3$-$Et_2O$ | Toluene | Decomposition |
| **8** | $In(OTf)_3$ (1 eq.) | Toluene | Complex Mixture |
| **9** | $In(OTf)_3$ | DCM | Complex Mixture |
| **10** | $In(OTf)_3$ (1 eq.) | DCM | Complex Mixture |
| **11** | $BCl_3$ | DCM | Decomposition |
| **12** | $InCl_3$ | DCM | Rec. S.M. |
| **13** | $AlBr_3$ | DCM | Complex Mixture |
| **14** | $AlMe_3$ | DCM | Rec. S.M. |

[1] If not specified, reaction was started at -78°C with 0.5 eq of additive and monitored by TLC.
[2] Entry 1,6,12 and 14 were kept at -78°C for at least 180min, then warmed-up to room temperature for 120 min until the reaction was stopped.
[3] Result could not be reproduced.

It seems that the modified substrate **2.64** would not undergo the same transformation. Several hypotheses were put forward as to why this would be the case. The most plausible explanation is that the formation of a previously tertiary carbocation was happening during the mechanism and without that extra methyl substituent, the carbocation has to be secondary, thus less stable and too energetically demanding to create. This would probably allow for the high-energy intermediate to undergo other transformation pathways which do not lead to the desired outcome. Breaking down the mechanism into its simpler parts might give us a better understanding of what was happening and better chances to solve the problem. It was envisioned that if the proximal aromatic methoxy group could be deprotected to a simple phenol, initial condensation on the aldehyde would be facilitated due to increased nucleophilicity from the aromatic oxygen. Unfortunately, common methods to demethylate aromatic oxygens were, by mere coincidence, already attempted during the

previous screening (Table 2.7), in this case $BBr_3$. Other methods which are compatible with an aldehyde lacking α-protons include anionic demethylation approache.[63] The first example attempted was the one of dodecylthiol and sodium hydroxide at high temperature in a sealed vial and high polarity solvent. It yielded the desired product **2.68** in 63% yield in a relatively clean reaction (Scheme 2.42). Although the desired outcome is a selective demethylation of the proximal phenol, it was clear that obtaining a mixture of deprotection products or even selective deprotection of the distal oxygen were real possibilities. Fortunately, precedents in anionic demethylation on similar phenanthrene-type substrates set by Gates[5] himself in his synthesis of morphine using hydrazine/KOH seemed to indicate that there is a preference for formation of the desired phenol **2.68**.

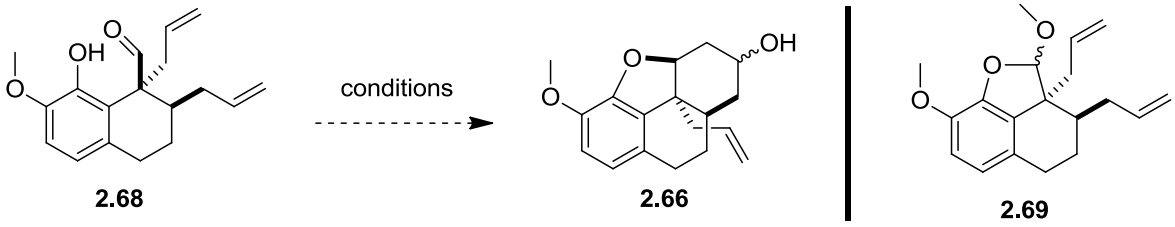
*Scheme 2.42 – Selective Demethylation of Proximal Aromatic Methoxy on **2.64***




**2.64** **2.68**

With **2.68** in hands, we envisioned that the use of a Lewis acid would eventually generate the sought-after oxonium intermediate **2.61** (Scheme 2.36) by condensation of the phenol on the aldehyde. This oxonium would then help stimulate the desired 6-exo-trig cyclization from *β*-allyl substituent, forming a secondary carbocation. Such carbocation could then be quenched either by elimination of a hydrogen or by the nucleophilic addition of a molecule of water/halide anion. Unfortunately again, only complete decomposition was observed in all cases but two (Table 2.8). In entry **8** and **7**, where TsOH as well as TsOH/trimethylorthoformate were used as additives respectively, what seemed like compound **2.69** (by characteristic NMR signals) and recovered starting material were isolated.

*Table 2.8 – Attempts for Condensation/Prins Cyclization on Deprotected **2.68***




**2.68** **2.66** **2.69**

| Entry | Additive | Solvent | Result |
|---|---|---|---|
| **1** | $SnCl_4$ | Toluene | Decomposition |
| **2** | $BBr_3$ | DCM | Decomposition |
| **3** | $In(OTf)_3$ | Toluene | Decomposition |
| **4** | $AlCl_3$-THF | DCM | Decomposition |
| **5** | TfOH | DCM | Decomposition |
| **6** | Amberlyst-15 | Toluene, r.t. | Decomposition |
| **7** | PTSA (1 eq), TMOF (2 eq) | MeOH r.t. | **2.69** |
| **8** | PTSA (1 eq) | Toluene, r.t. | Rec. S.M. |

[1] If not specified, reaction was started at -78°C with 0.3 eq of additive and monitored by TLC.

Much effort was put into this part of the project and again it seemed like an appropriate time to take a step back and look at the picture of what would be a viable synthesis using this approach. In other words it was a good time to adjust our expectations to reality.

Several characteristics seemed to diminish the expected scientific value of this approach. The first one was the increasing amount of steps. Initially it was supposed to be a one-pot/two steps process. With the possibility of solvent-change between the pericyclic cascade and the cyclization, as well as the added demethylation step and possible acetal formation, what should have been one synthetic step could become four. There was also the prospect of a long and tedious optimization where our initial hit with the original substrate had yields under 30%, and our current substrate for previously mentioned reasons, was a more difficult substrate to work with (tertiary vs secondary carbocation). By the same logic, a competition between two (almost) equivalent allyl groups appeared due to the performed substrate modification, (5-exo-trig cyclization vs desired 6-exo-trig cyclization). It is clear that this lack of differentiation between the two allyl groups would create many problems with unclear solutions. Finally, what was initially a three transformations reaction cascade, became a two transformation reaction cascade, essentially nullifying the publication value of the work done on attempting this methodology on simpler substrates during Kassandra's time in the lab (work that was performed by me

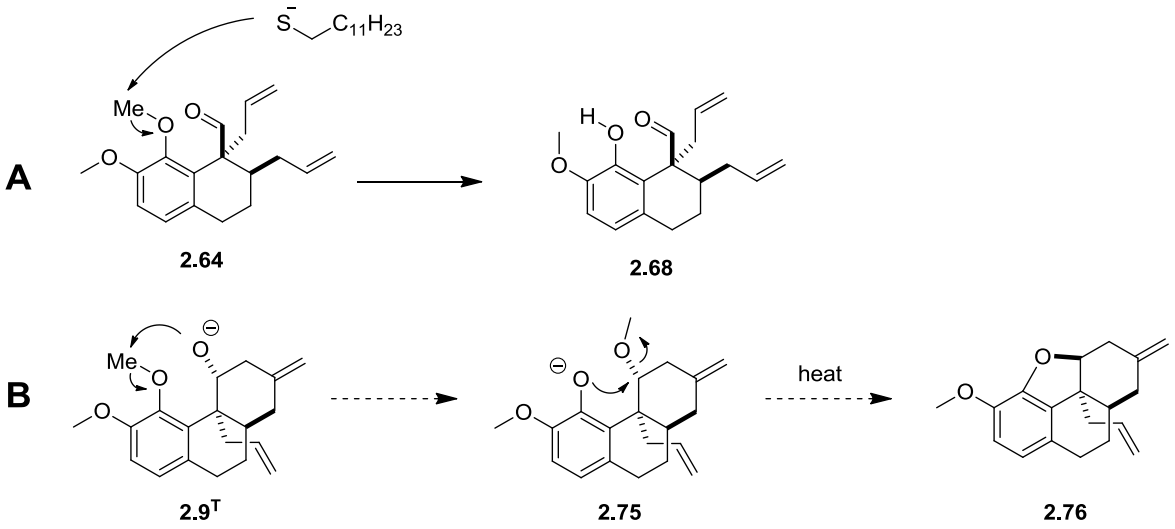
during my undergraduate studies). All these characteristics strongly indicated that there was a high probability that further efforts on this topic would be in vain. This approach was thus abandoned in favor of investigating other methods to push the synthesis forward.

## 2.4 EARLY FURAN SYNTHESIS AND END GAME

### 2.4.1 Demethylation-Cyclization

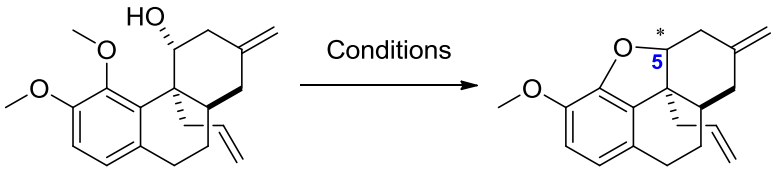
The previous foray into selective demethylation for the proximal aromatic methoxy group using anionic chemistry sparked our interest on alternative ways that the E-ring portion of morphine could be formed directly after the pericyclic reaction cascade. This would be followed by further functionalization of the molecule and late D-ring formation. As demonstrated in Scheme 2.43 **A**, usage of high energy anionic species can entice a demethylation of the sought methoxy group and form a more stable phenolate anion. Looking at a proposed mechanism in the same scheme (mechanism **B**), we hypothesized that a high energy alkoxyl anion could, if properly oriented, effect the same demethylation. Then, the formed phenolate could perform a nucleophilic attack on a near carbon to eject an equivalent of methoxide. Evidently, such a mechanism would require significant energy to place the entropy balance of the equation in favor of the product since a methoxide anion is a higher energy specie compared to a phenolate. Using a plastic model of the molecule, it also appeared that a significant amount of energy would be required to bend the molecule properly and obtain the right alignement in order to effect the demethylation in a $S_N2$ fashion. But such a demethylation-cyclization mechanism could potentially be done in a single step, and generate two considerable transformations (demethylation and cyclization) bringing us closer to the complete skeleton of morphine.

*Scheme 2.43 – Hypothesis on Demethylation-Cyclization Mechanism*




As can be seen in Table 2.9, our first attempt (entry **1**) was a success, where a molecule having the general structure of **2.77** was isolated. The use of potassium hydride was a deliberate choice, since the extrusion of hydrogen from the media would render the deprotonation of the initial alkoxyl group completely irreversible, and the energy that would be given to the reaction could then be used in a productive fashion (instead of being used to reprotonate the formed alkoxyde). Entry **2** confirms this fact by demonstrating that only 6% of **2.77** is isolated when using KHMDS as a base and mostly recovered starting material is obtained, even for a longer reaction time. Finally, it was thought that a solvent with more coordinating properties would be beneficial for this transformation for several reasons. These reasons include rendering the potassium alkoxyde more reactive, merely by elongating the potassium-oxygen bond, and increasing the solvation of the ejected potassium methoxyde. It was thus possible to increase the yield for this transformation to a consistent 80-83% by using dimethoxyethane instead of toluene.

*Table 2.9 – Attempts at an Anionic Demethylation-Cyclization Sequence*

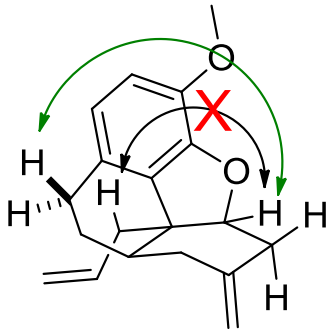



**2.9** **2.77**

| Entry | Conditions | Result |
|---|---|---|
| **1** | KH, toluene, reflux 2h | 70% **2.77** |
| **2** | KHMDS, toluene, reflux 3h | 6% **2.77**, 65% rec. S.M. |
| **3** | KH, DME, reflux 1h | 83% **2.77** |

Unfortunately, even though **2.77** was fully characterized, there was still ambiguous information in the NOESY spectrum that placed doubts in our mind about the specific configuration of carbon 5 in the E-ring (scheme of Table 2.9). Logically, if the mechanism in place was the predicted one, the correct configuration should be one where the hydrogen at C5 would be syn to the allyl chain.

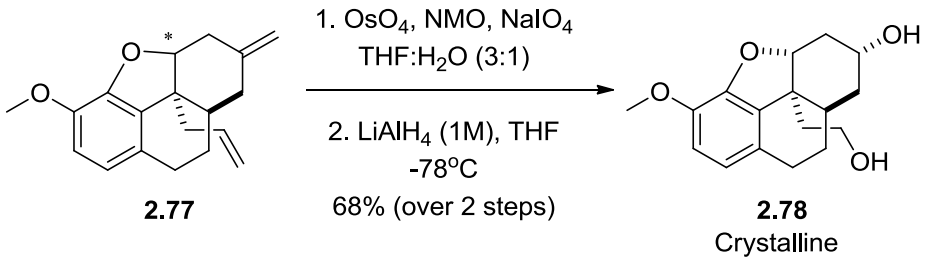
*Scheme 2.44 – Observable NOESY Interactions on **2.77***




Key NOESY interactions were missing such as the one shown in Scheme 2.44. Furthermore, an unexpected interaction between benzylic hydrogen and the relevant hydrogen in the E-ring could be observed. A crystal structure of **2.77** was thus required to confirm once and for all its exact configuration. Surprisingly, such a compact and rigid molecule was not crystalline. Chemical derivatization was therefore required. The goal was to increase the oxygen count in the molecule, to further increase the polarity of the compound and the chances of it being crystalline. As shown in Scheme 2.45, familiar reactions were performed; an oxidative cleavage of both olefins followed by lithium

aluminum hydride reduction of the two formed carbonyls. This yielded a crystalline **2.78** in 68% over two steps.

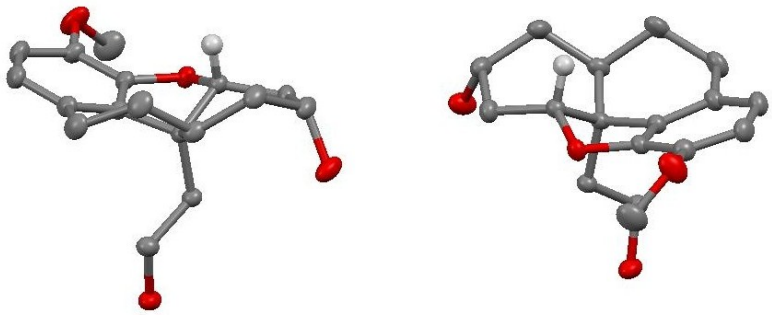
*Scheme 2.45 – Derivatization of **2.77** to Access a Crystalline Structure*




**2.77** **2.78** Crystalline

X-ray crystallography of **2.78** was then quickly performed after recrystallization and the resulting structure is shown in Figure 2.1. As can be observed, our doubts were correctly founded, as the opposite configuration at the relevant carbon was obtained through this supposed demethylation-cyclization sequence. Of note, this structure is surprisingly rigid when made in a plastic model. Undoubtedly this is due to its fused four ring systems which consists of two six-membered rings in boat conformations, an obviously planar aromatic ring and fused trans-dihydrofuran ring.

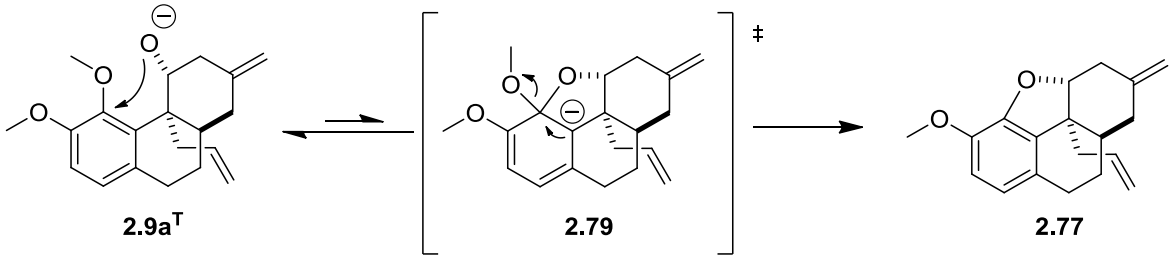
*Figure 2.1 – Crystal Structure of **2.78** in Two Orientations*



A revision of the proposed mechanism was necessary at this point. The most plausible explanation that was hypothesized is as follow (Scheme 2.46) where initial deprotonation yields the same alkoxyde **2.9a**$^{T}$. This alkoxyde then lacks the correct alignment that would allow the necessary $S_N2$ reaction to produce a phenoxyde anion and instead performs an aromatic nucleophilic addition on the π* system of the aromatic ring, ipso to the proximal methoxy substituent. The high energy intermediate **2.79** can either go back to form **2.9a**$^{T}$ or move forward in a productive manner by releasing an equivalent of

potassium methoxide. Once formed, high entropy prevents the reverse addition of the potassium methoxide onto the aromatic system. $S_NAr$ are usually performed on electron-deficient aromatic rings, it is thus surprising that it could occur on a ring as electron-rich as the one present in **2.9a**. It is probably merely the consequence of having a smaller energy barrier to reach transition state **2.79** than the one required to bend all the proper bonds in order to acquire the correct alignment for the demethylation event of the previously proposed mechanism.

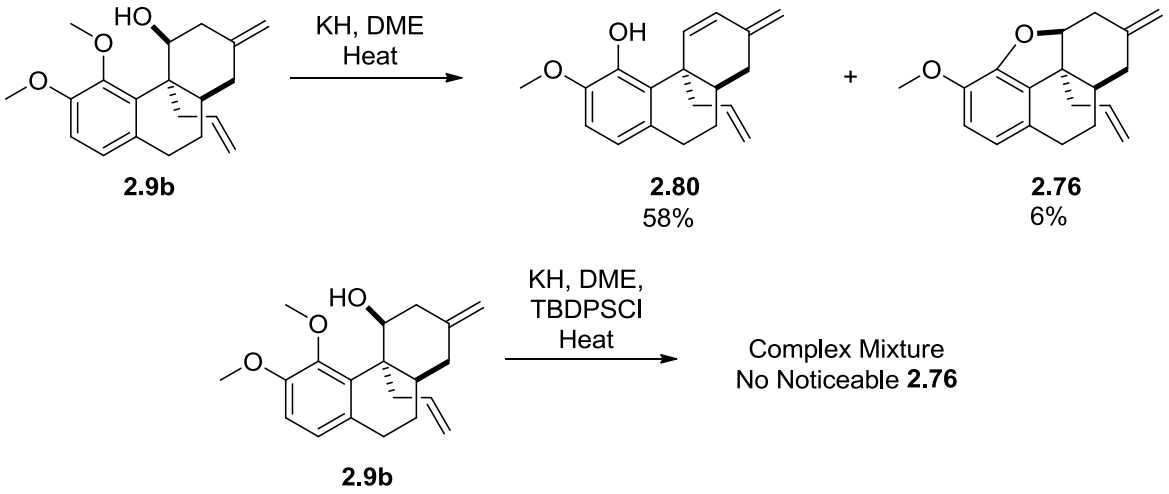
*Scheme 2.46 – Plausible Mechanism for the Synthesis of **2.77***




This knowledge combined with our access to the other diastereomer **2.9b** brings out the possibility of submitting it to identical reaction conditions in hope that it would undergo the same aromatic addition and yield the sought-after tetracyclic diastereomer. Upon submitting **2.9b** to the same reaction conditions, a mixture of triene **2.80** in 58% yield and the desired tetracyclic **2.76** in a very low 6% yield was obtained (Scheme 2.47). Interestingly, triene **2.80** has lost a methyl substituent on one of the aromatic oxygen. After thinking about a possible explanation, we settled on the fact that the desired reaction was occurring, but as the quantity of **2.76** was rising, so did the quantity of potassium methoxide in the media. Being a strong base, it has the capability to effect an intermolecular elimination reaction on **2.76** to form the third alkene and a lower energy phenolate anion. The possibility of a potassium hydride excess was considered, but the way the reaction was setup, as close as possible to one equivalent of potassium hydride is present in the reaction media and the alkoxyde anion is initially formed at room temperature for 10-15 minutes, then the vessel is sealed under argon and heated at refluxing temperature. In this manner, the chances of having leftover potassium hydride were minimized. A viable hypothesis to solve this problem included reducing the amount of potassium methoxide floating in the mixture by having it react with a third party once it is formed. That third party must not, however, react with the alkoxyde initially formed by the addition of the metal hydride. The addition of an excessively bulky silyl-protecting group to the mixture came to mind since

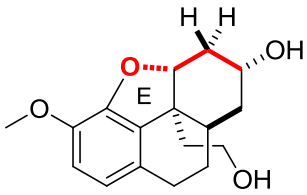
previous attempts at installing a simple TMS group on the hydroxyl of **2.9a** using TMSCl failed, probably due to the steric bulk of the nearby quaternary carbon. Using TBDPSCl should accomodate the characteristic of being unable to react with the initial alkoxyde, but still be able to react with any potassium methoxide that is formed, thus producing the corresponding methylated silanol and unreactive potassium chloride. Even though the rationale seemed logical, after several attempts, only complex mixture of compounds were obtained, from which no traces of **2.76** could be found by NMR.

*Scheme 2.47 – Attempts at a Demethylation-$S_NAr$ Addition using **2.9b***



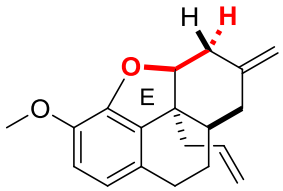

We pondered on why the production of triene **2.80** was observed in this case and not in the case of diastereomer **2.9a**. Looking at a model structure for **2.76** and comparing it to the obtained crystal structure for **2.78,** the following observations were made. In the case of **2.78**, there is no antiperiplanar hydrogens available; in fact it is the highlighted C-C bond that is antiperiplanar (Scheme 2.48) to the C-O bond. And for the possibility of a syn-elimination, even then, the two hydrogens on the *β* carbon each have a dihedral angle of about 40° to 70°. This means that the C-O bond is actually right in the middle of these two hydrogens and being such a rigid structure, no rotation is possible to allow a viable alignement for a syn-type elimination. In the case of **2.76**, both the antiperiplanar and syn-type elimination would be quite nicely accommodated by hydrogens on the *β* carbon. This characteristic is important to understand for the upcoming section. The tetracyclic **2.76** that is sought has two protons that can be readily removed to open the E-ring and form a molecule with a stable unsaturated system and a phenol.

*Scheme 2.48 – Possible Stereoelectronic Effects Explaining the Formation of **2.80***




**2.78**

C-C Bond Antiperiplanar
to C-O Bond



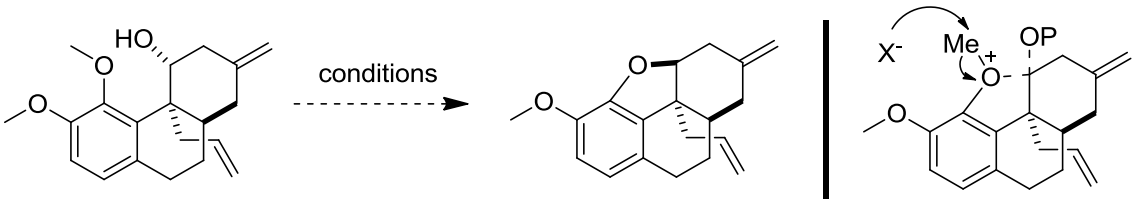

**2.76**

C-H Bond Antiperiplanar
to C-O Bond

### 2.4.2 Leaving-Group Promoted Cyclization

In the past section, the fact that the hydroxyl of **2.9a** could be used as an intramolecular nucleophile was discussed. Our initial intent was to, in the same reaction, transform the hydroxyl into a better leaving group (albeit, still a poor leaving group) by methylation and create a reactive phenoxide that could effect the necessary displacement. Even though this attempt failed, our goal stayed the same, to form ring E earlier in the synthesis. Screening a number of reaction conditions that could transform the hydroxyl into a good leaving group seemed a decent approach even if the methylated aromatic oxygen in this case would remain a relatively poor nucleophile (Table 2.10). One key aspect of the listed attempts is the presence of halide anions as by-products of initial leaving-group formation. This was a deliberate method to generate a potent nucleophile (halide anion) able to effect an aromatic demethylation reaction, shall such desired event be required in order to reach a stable compound (shown in scheme of Table 2.10).

*Table 2.10 – Attempts at a Leaving-Group Promoted Cyclization.*




**2.9a** **2.76** **2.81**

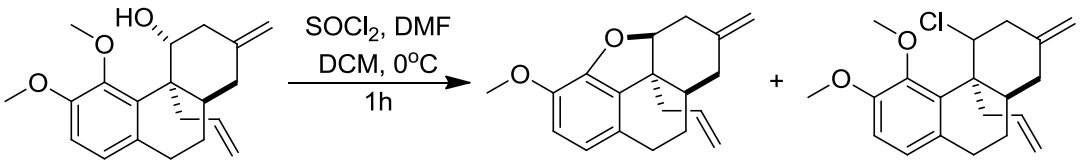
| Entry | Conditions | Result |
|---|---|---|
| **1** | $SOCl_2$, cat. DMF, DCM | **2.76** 70% |
| **2** | Cyanuric Chloride, cat. DMF, DCM | Degradation |
| **3** | $PBr_3$, cat. DMF, DCM | Degradation |
| **4** | Oxallyl Chloride, cat. DMF, DCM | Degradation |

[1]Entry 2,3 and 4 were also tried without catalytic DMF. Similar results were obtained

Entry **1** shows that surprisingly, the first attempt yielded the sought-after compound in 70% yield by treating **2.9a** with thionyl chloride in DCM at 0°C with a catalytic amount of DMF. The demonstrated formation of ring E is, to the best of our knowledge, unprecedented in morphine syntheses. Similar reaction conditions known to replace hydroxyls with a chloride atom (when no other nucleophiles are present) were attempted in order to estimate how broad this reactivity really is. With surprise, no **2.76** whatsoever was detected in entries **2**,**3** and **4** where cyanuric chloride, phosphorous tribromide and oxallyl chloride were used respectively. This meant that the reaction was very specific to thionyl chloride. Looking at the reaction products more carefully a side product was identified, chloro-compound **2.82** [4], formed in 21% yield. This compound is highly unstable and readily loses the chlorine atom in an elimination reaction leading to the corresponding triene in a matter of hours once isolated.

[4] Although a large coupling constant at C5 suggests that the chlorine is in axial position, its stereomeric identity is still unclear.

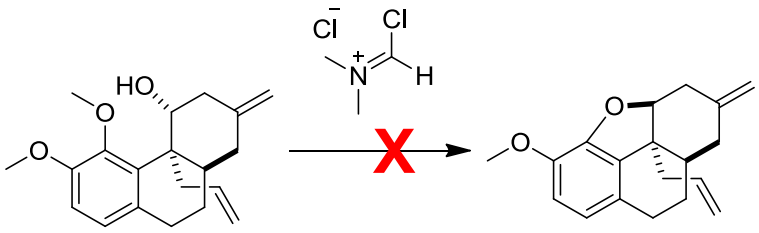
*Scheme 2.49 – Product Formation Profile of Thionyl Chloride Promoted Cyclization*




**2.9a** **2.76** 70% **2.82** 21%

The reaction was attempted with and without catalytic amounts of DMF and we noticed that the addition of DMF had the following impact: it decreased reaction time, increased yields, decreased the amount of visible degradation by TLC and overall gave a much smoother and robust reaction. One thing that was **not** impacted by DMF addition is the ratio of **2.76**:**2.82**. The next modification was temperature, and it seems that at higher temperatures the reaction is faster but leads to diminished yields of both **2.76** and **2.82**. Lower temperatures did not make any significant difference to yields and/or ratios of **2.76** and **2.82**. A very limited solvent screening of chloroform, dichloromethane, carbon tetrachloride and toluene did not change significantly the **2.76**/**2.82** ratio. Finally, the addition of pyridine completely stopped the formation of both compounds, and it is only after the addition of another equivalent of thionyl chloride that the reaction took place. It is known that thionyl chloride and dimethylformamide react together to form Villsemeier's reagent, but as a control experiment, this commercially available reagent was used with **2.9a** in similar conditions to the previous reaction and no formation of **2.76** was observed after a few hours. This suggested that although Villsmeier's reagent may be formed during the reaction, it is not its action alone that performs the sought-after transformation.

*Scheme 2.50 – Control Experiment with Villsmeier's Reagent*



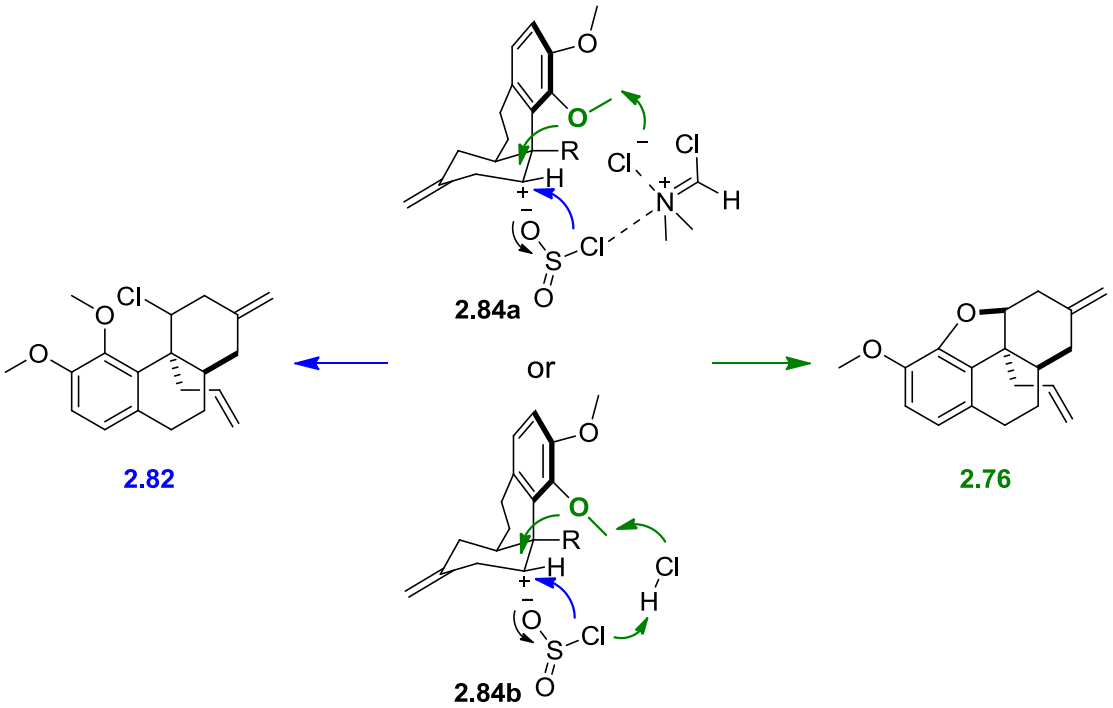

**2.9a** **2.76**

At that point, multiple mechanisms for this reactivity may be suggested using the observations collected above. Such mechanisms should account for some of the following factors.

1. Although Villsemeier's reagent is most-likely formed, it is not the principal actor of this transformation.
2. Similar to #1, the mechanism should be allowed to work in the absence of DMF, but its presence should definitely impact the reactivity.
3. The ratio of **2.76/2.82** is surprisingly stable, indicative of an unimolecular rate-limiting step that should account for the product distribution between these two compounds.
4. With thionyl chloride comes the possibility of a substitution nucleophilic internal ($S_Ni$) mechanism.[64,65] Such an intramolecular mechanism could be helped by anchimeric effects from the proximal aromatic methoxy substituent

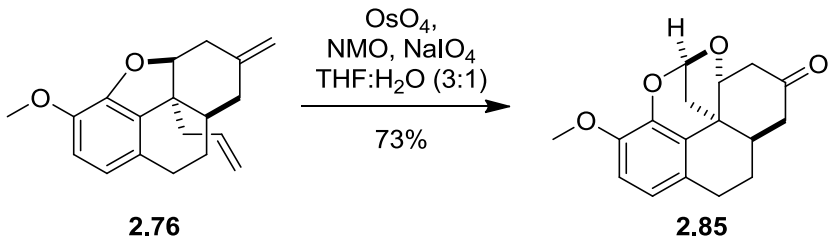
The mechanisms shown in Scheme 2.51 account for most of the aforementioned factors. The generated Villsmeier reagent in this case could act as a source of labile halide anions. Without it, the generated hydrochloric acid stands as the most available source. The competition between two intramolecular mechanisms is also hypothesized. A mechanism where a floating chloride anion acts as the nucleophile is still possible, but it seems likely that a change in concentration or solvent would affect the product distribution, since one displacement mechanism would be intramolecular and the other one intermolecular. We are aware that these are simply hypotheses and that successful 2D NMR experiments for compound **2.82** would be required to clarify its stereomeric identity, while helping to support or propose viable mechanisms.

*Scheme 2.51 – Modified Proposed Mechanisms for Production of **2.76** and **2.82**.*



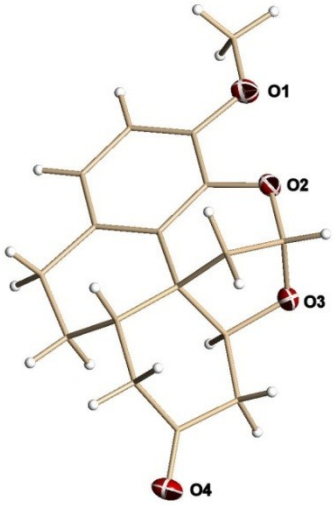

Nevertheless, the next step at this point was to cleave the alkenes present in tetracyclic **2.76** in a single step using the same Lemieux-Johnson protocol used thus far. As shown in Scheme 2.52, an unexpected outcome was obtained. During the reaction, the E-ring underwent a fragmentation, probably a consequence of E1cB-type elimination, which was followed by a collapsing of the aliphatic aldehyde and subsequent acetal formation to form compound **2.85**. Here again, the hydrogen alignment allowing a syn or anti elimination is undoubtedly an important factor in the observed reactivity, seeing as it was not observed upon oxidative cleavage of **2.78**. A crystal structure of **2.85** was acquired in order to confirm our suspicions on the exact structure, which is shown in Figure 2.2. Admittedly, this was helped by the necessary presence of water in the reaction mixture. A similar oxidative cleavage was attempted using ozone with the usual ozonide quench (triphenyl phosphine and dimethyl sulfide, in two separate attempts) as well as a reductive quench (sodium borohydride) in hope of gaining a direct access to the corresponding diol. Unfortunately all these attempts led to complete degradation of the starting material, which makes us believe that the formation of two parallel ozonide/molozonide functionality on this molecule is one of the problems faced with ozonolysis during this project.

*Scheme 2.52 – Outcome of a Lemieux-Johnson Protocol Using **2.76***




**2.76** **2.85**

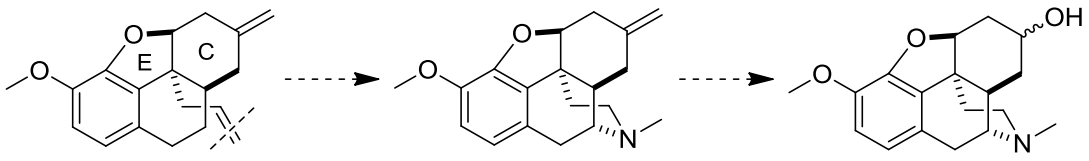
*Figure 2.2 – Crystal X-Ray Structure of **2.85***




Looking for alternative approaches that use **2.76** was relatively tedious at this point. As previously mentioned, there are few viable conditions in organic chemistry able to cleave alkenes and leave the rest of the molecule untouched. One of them (dihydroxylation / cleavage) was a very counter-productive step leading to the opening of the E-ring; ring which required considerate efforts to form. The other method, in this case ozonolysis, simply did not work. Time was starting to be an issue if I wanted to finish the synthesis, and solutions that included adding a few steps and/or sacrificing elegance had to be considered.

### 2.4.3 Epoxidation

*Scheme 2.53 – Hypothesis on Initial Ring D Formation.*




**2.76** **2.86** **2.87**

We hypothesized that one of the few ways that opening of the E-ring could be avoided was to slightly change the conformation of ring C. A slight change in conformation might affect a change in hydrogen alignment where the actual elimination occurs. One method to effect such conformational change is to close the nitrogen-bearing ring first (ring D). Although it won't change the conformation completely, it might diminish the chances of E-ring opening upon cleavage of the gem-disubstituted alkene. By nature of ring D being closed, there wouldn't be any aliphatic aldehyde present on the molecule to react in a similar fashion to the one demonstrated in Scheme 2.52. It was envisioned that selective oxidative cleavage of the allyl chain's double bond followed by some reductive amination would put us en route to obtain **2.86** (Scheme 2.53). Usually, selective oxidative cleavages are performed in a two steps sequence consisting of chemoselective epoxidation and *in situ* diol formation/oxidative cleavage using hypervalent iodine reagent such as periodic acid and sodium periodate.[66] The problem in this case was to selectively epoxidize an allylic mono-substituted alkene in the presence of a *gem*-disubstituted double bond.

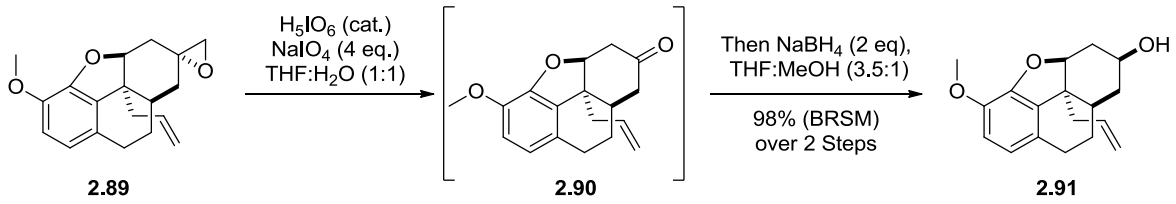
*Scheme 2.54 – Selective Epoxidation of the Gem-Disubstituted Double Bond*


**2.76** **2.89**

In the process of attempting known methods of epoxidation, *m*-CPBA was used. To our surprise, only epoxide **2.89** (Scheme 2.54) was isolated in high yield (90% product and 5% recovered starting material). Although the desired outcome was not obtained, we still had a good quantity of pure **2.89** on hands. Expected outcome of a treatment of **2.89** with periodic acid and/or sodium periodate in water would be a similar result than obtained

previously in Scheme 2.52 where E-ring opening occurred. Not knowing what to do with our sample of **2.89**, the *in situ* diol formation/oxidative cleavage was performed using conditions shown in Scheme 2.55. Upon isolation of the crude mixture, a proton NMR revealed that with the exception of noticeable starting epoxide, the mixture consisted almost exclusively of a compound corresponding to **2.90**. Immediately, the mixture was placed in a tetrahydrofuran/methanol mixture and sodium borohydride was rapidly added. In our best attempt, hydroxyl **2.91** could be isolated in 63% yield with recovery of about 33-35% of epoxide **2.89** (Scheme 2.55). It seems that the absence of the aldehyde prevents opening of the E-ring in this case, since the hydrogens alignement is evidently the same as in the previous case (**2.76**) where a Lemieux-Johnson protocol was used. This result effectively stopped our efforts toward selectively cleaving the mono-substituted alkene. In two short and high-yielding steps we were able to successfully "lock" ring E by getting rid of the problematic ketone and prevent its opening in most of the conditions required to finish the synthesis.

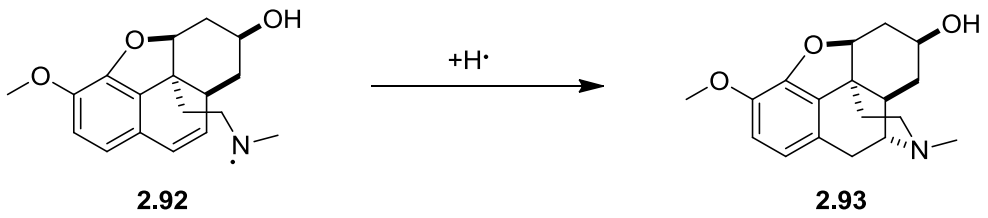
*Scheme 2.55 – Oxidative Cleavage / Reduction Sequence of Epoxide **2.89***




### 2.4.4 End Game

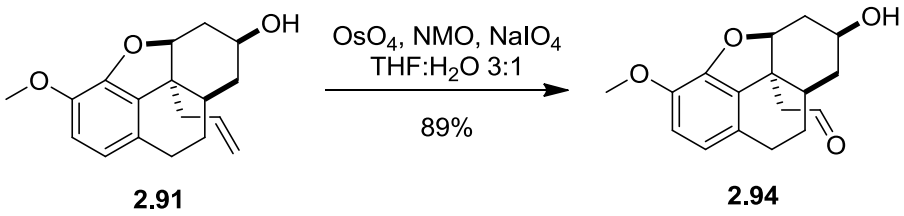
Most of the reactions required to finish the synthesis from this point on are relatively straightforward and/or previously documented. The fact that the structure of **2.91** highly resembles other structures in similar syntheses of morphine[25,31,29] is of key importance in choosing how to approach the subsequently required transformations.

*Scheme 2.56 – Required Transformation to Access the Five Rings of Morphine*



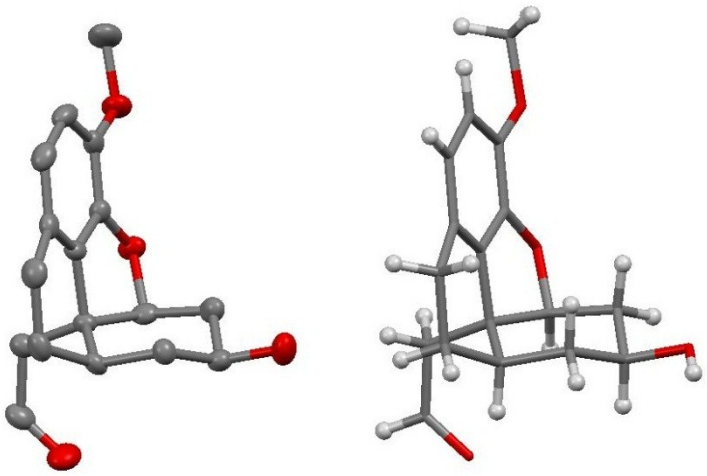
The key functionalization needed at this point is the formation of ring D. According to approaches put forward by Parker[23] and used by Ogasawara[29], with the proper styrenic unsaturation in place, the formation of a nitrogen-based radical should promote the necessary cyclization and yield the complete five rings that form morphine (Scheme 2.56). To access a compound such as **2.92**, the shortest route seemed to be oxidative cleavage of the last alkene present followed by reductive amination. As shown in Scheme 2.57, oxidative cleavage proceeded smoothly and yielded aldehyde **2.94** in 89% yield using the now familiar Lemieux-Johnson protocol. A crystal structure of **2.94** was obtained using X-ray crystallography and the resulting structure is presented in Figure 2.3. It can be noted that as witnessed in other publications regarding the synthesis of morphine, at this stage in the synthesis, ring C adopts a chair conformation. In this case for **2.94**, the hydroxyl group is in an equatorial position while rings A, B and E sit together almost in a single plane.

*Scheme 2.57 – Oxidative Cleavage of Terminal Olefin on **2.91***




**2.91** **2.94**

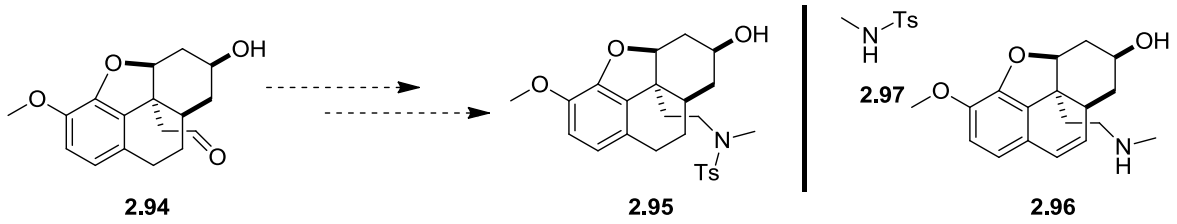
*Figure 2.3 – Crystal Structure of Aldehyde **2.94***



With an aldehyde functionality in place, obtaining tosylamine **2.95** required a reductive amination and subsequent tosylation. Even though there are some reports[67] of

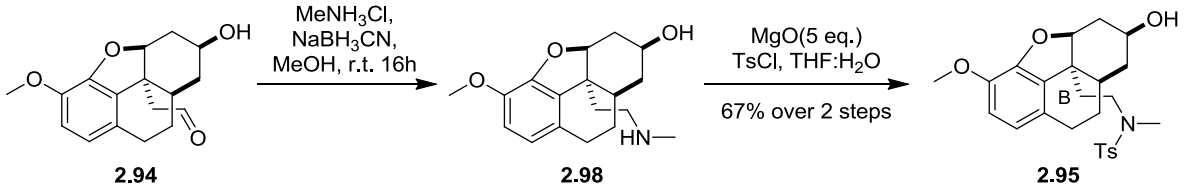
direct reductive amination with electron-deficient amines, none of those included highly deactivated nitrogens such as tosylamine **2.97** as the nucleophile. There has been some reported D-ring radical cyclization with an unprotected secondary amine similar to **2.96**[31,33], but those reports were either highly contested or low yielding.

*Scheme 2.58 – Synthesizing **2.95** from **2.94** and Related Compounds*




Therefore, the best course of action seemed to be the two step sequence (reductive amination/tosylation). Methylamine was used as the nucleophile and the reaction was performed using sodium cyanoborohydride in methanol overnight. Crude NMR showed complete conversion to secondary amine **2.98**. Using the crude mixture, a tosylation reaction was carried in a THF:water mixture, using *p*-toluenesulfonyl chloride and magnesium oxide. It yielded the desired tosylamine **2.95** in 67% over two steps (Scheme 2.59). This unique blend of conditions for the tosylation reaction is reported[68] for the nitrogen-selective tosylation of amino-alcohols. Such conditions were sought due to previous experiences at selectively tosylating a primary alcohol in the presence of a secondary alcohol. Assuming there would be similar competing pathways, a nitrogen selective tosylation method was researched, found and tried as our initial attempt. Upon noticing this successful result, and due to the very clean and easy work-up associated with this method, the need for alternative conditions for this transformation was never felt.

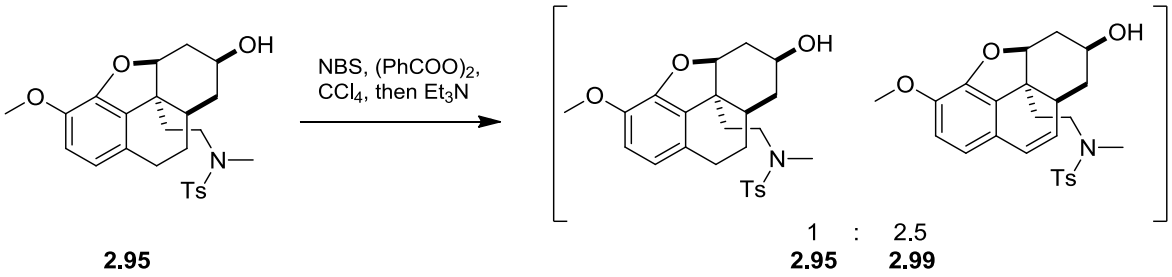
*Scheme 2.59 – Reductive Amination and Tosylation of Aldehyde **2.94***




The only functionalization required prior to the D-ring cyclization was the installation of an alkene on the benzylic carbons of ring B. Using an almost identical method to the one set forward by Mulzer and al.[25] a radical benzylic dehydrogenation using NBS and benzoyl peroxide in carbon tetrachloride at reflux, followed by triethylamine addition was performed

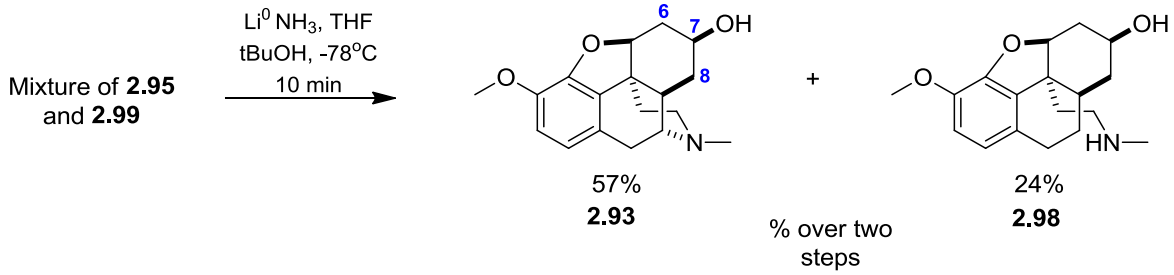
to install the required unsaturation. Such a transformation yielded an inseparable mixture of **2.99** and recovered **2.95** in a 2.5:1 ratio. In this regard, it is worthy to note that the group of Mulzer were purifying this mixture using preparative scale HPLC methods. Such methods were not used in this case due to the lack of material. Furthermore, it seemed possible to recover the corresponding secondary amine **2.98** in the following reductive detosylation.

*Scheme 2.60 – Radical Formation of Unsaturated **2.99***




A Birch reduction was used to accomplish the aforementioned D-ring heterocyclization and as hypothesized, a 57% yield of sought **2.93** and 24% yield of recovered **2.98** were obtained over two steps.

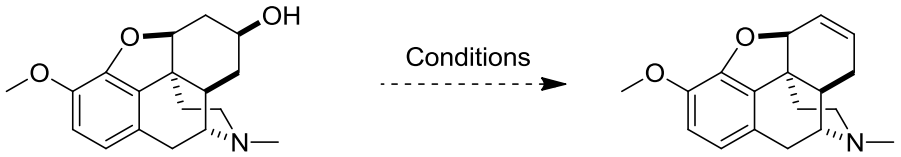
*Scheme 2.61 – Birch Reduction of a Mixture of **2.95** and **2.99***




With **2.93** in hands, the next logical step when looking at similar late C-ring functionalization[30,34,37] is to generate either a C6-C7 unsaturation, or C7-C8 unsaturation. We had crystallographic evidence (Figure 2.3) of the equatorial position of C7-hydroxyl. This meant that syn or anti-periplanar hydrogen alignment was most likely unavailable, therefore the elimination could prove somewhat difficult. It was also important to obtain selectively either a C6-C7 alkene or the C7-C8 isomer, but not a mixture of the two. It was envisioned that the electron-withdrawing nature of the E-ring oxygen could favor the C6-C7 unsaturation. However, it was also a possibility that depending on the conditions, a chelation-type effect on the nitrogen of ring D could favor a C7-C8 elimination. To be taken into consideration, the C7-C8 alkene was preferred due to estimations that three to four

additional steps were required in order to reach the total synthesis of morphine, whereas the C6-C7 alkene would require five to six additional steps.

*Table 2.11 – Attempts at Elimination of the Equatorial Hydroxyl Group*

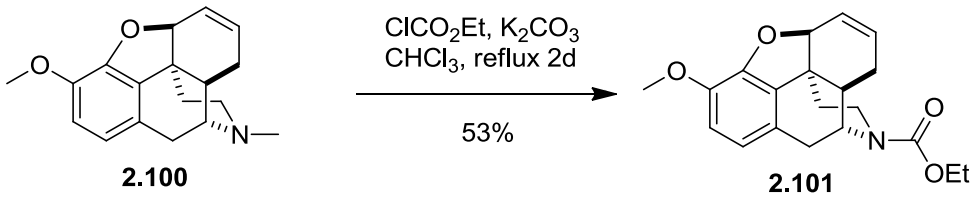



**2.93** **2.100**

| Entry | Conditions | Result |
|---|---|---|
| **1** | Burgess reagent, toluene, 80°C | Complex mixture |
| **2** | $Tf_2O$ (1.5 eq.), pyridine (3 eq.), 0°C, DCM | 69% |
| **3** | $Tf_2O$ (1.5 eq.), pyridine (3 eq.), -78°C, DCM | Degradation |
| **4** | $Tf_2O$ (1.1 eq.), pyridine (3 eq.), 0°C, DCM | 43% |
| **5** | $Tf_2O$ (1.7 eq.), pyridine (4 eq.), 0°C, DCM | 27% |

As shown in Table 2.11, we were able to perform the elimination reaction using trifluoromethanesulfonic anhydride and pyridine at 0°C. These conditions yielded isomer **2.100** selectively in 69% yield as our best attempt (usual yields rotate around 50-55%). Surprisingly, performing the reaction at -78°C led to degradation. It can be hypothesized that a longer-living triflate could engage in parallel pathways leading to the observed result. From **2.100**, several options were available; the most interesting one was epoxidation of the alkene. The main concern was the possible reactivity between the chosen epoxidation reagent and the tertiary amine. Looking at previous syntheses, it seems that many research groups decided to deactivate the nitrogen by forming a carbamate[17,30,32,37] which can easily be reduced later on in the synthesis. After some research, it appeared that a formal synthesis could be achieved by forming the ethyl carbamate at the corresponding position (Scheme 2.62). Carbamate **2.101** does indeed intersect the synthesis of codeine/morphine of Taber (2002)[30] and Magnus (2009).[37]

*Scheme 2.62 – Formation of Carbamate **2.101***

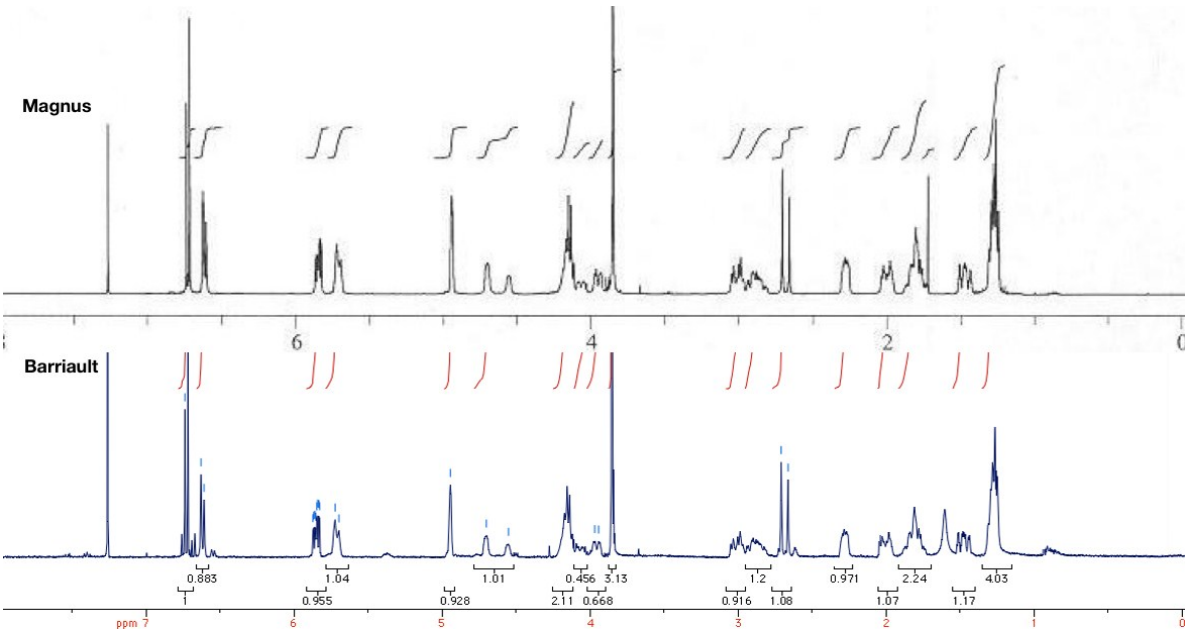



**2.100** **2.101**

**Formal Synthesis**

Formation of the methyl carbamate from the corresponding methyl amine is referenced in the synthesis of Rice (1980).[17] Similarly, it was performed by refluxing ethyl chloroformate and potassium carbonate in chloroform with tetracylic **2.100**. As seen in Scheme 2.62, we were able to obtain said carbamate in 53% yield, thus formally concluding the synthesis of (+/-) morphine by intersecting the synthesis of Douglass F. Taber (2002) and Philip D. Magnus(2009).

*Figure 2.4 – Comparison of Referenced Carbamate **2.101** H-NMR and the Obtained Sample*



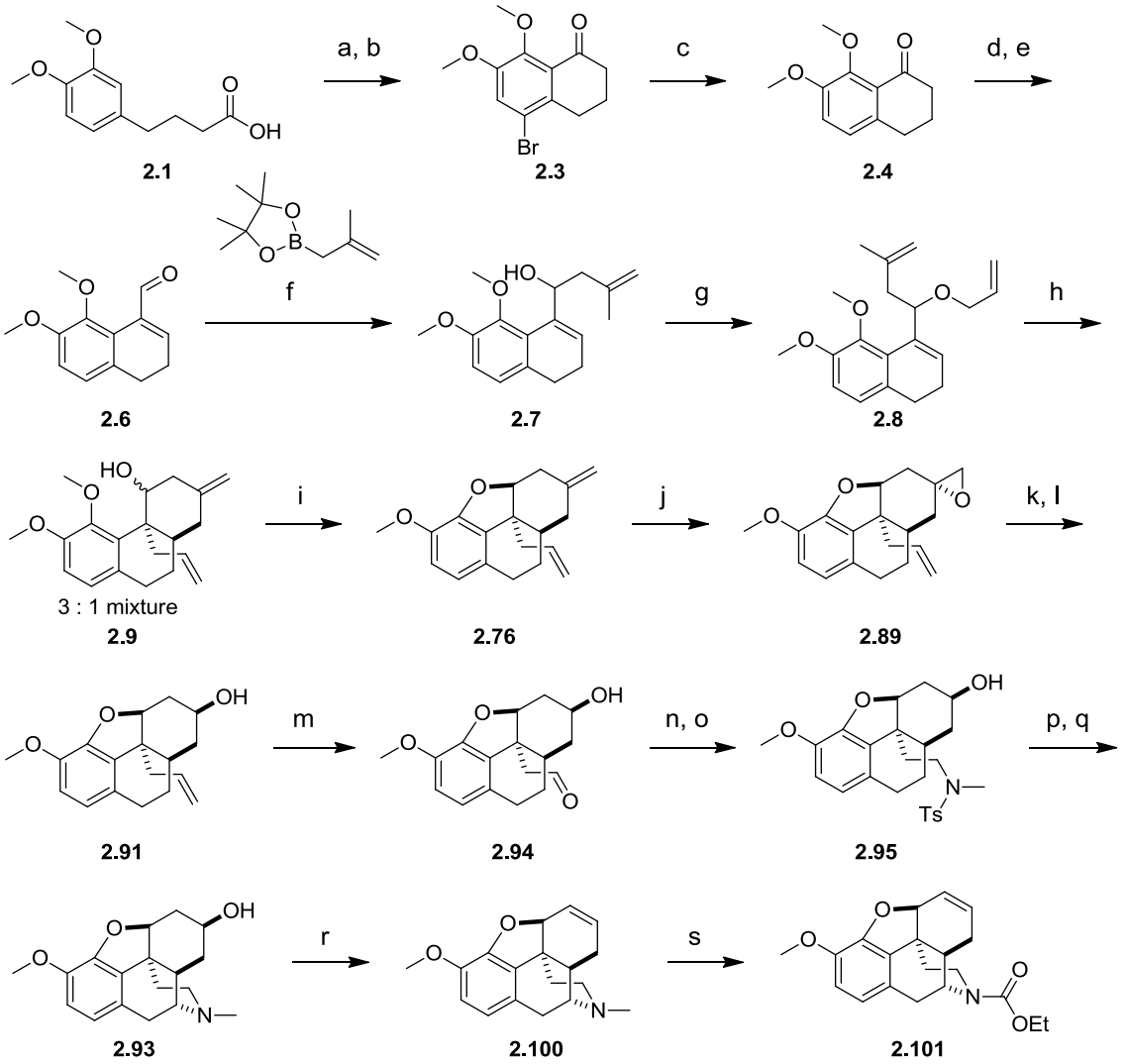

## 2.5 CONCLUSION

Unfortunately, a lack of time and material prevented us from completing the total synthesis of morphine. The sheer amount of work and efforts that the groups of Magnus and Taber put into realizing such accomplishment from the exact same **2.101** severely diminished our chances of bringing new relevant scientific input on this subject, and at the

same time diminished the value of such efforts should we have decided to pursue this goal further. Nevertheless, this does not by any mean lessen the value of this work as one can appreciate the uniqueness of this synthesis when looking at the landscape of morphinan alkaloids synthesis. The discussed approach demonstrates the impressive complexity added in a single pericyclic reaction cascade to a very simple substrate in a unique synthetic step. Although it is clear that there are still several weaknesses to this methodology before it can be broadly used to synthesize relevant decalin structures in pharmaceutically relevant molecules, this work clearly shows the potential of this reaction. To conclude, in this work we were able to synthesize ethyl carbamate **2.101** in 18 steps, formally concluding the synthesis of (+/-)-morphine with an overall yield of 1.0%[5] using a microwave-promoted oxy-Cope/Claisen/ene pericyclic reaction cascade. The approach taken included a unique and early E-ring formation, a selective alkene oxidative-cleavage sequence, followed by a radical D-ring heterocyclization and late C-ring functionalization.

[5] The overall yield accounts for recovery of starting material for four different steps, including the pericyclic reaction cascade.

*Scheme 2.63 – Complete Overview of the Synthesis*

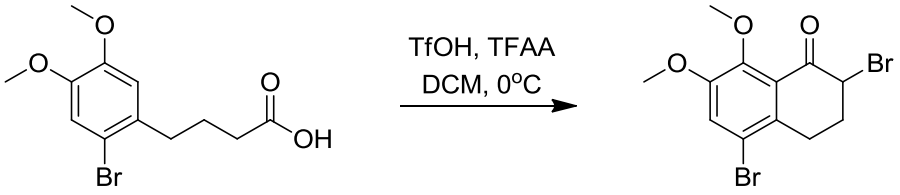



**a.** NBS, $AuCl_3$ (cat.), DCE, 45min.; **b.** TFAA, TfOH(cat.), DCM, 0°C (62%, 2 steps); **c.** Raney-Ni, EtOH, 5% $NaOH/H_2O$, 60 min, 90°C, 67%; **d.** trisylhydrazide, PPTS (cat.), THF, 12h; **e**. BuLi (2 eq.), THF, -78°C, then DMF (85%, 2 steps); **f. 2.18**, toluene, -78°C to r.t., 3h, 97%; **g**. allyl bromide, KH, NaI, DME, 0°C, 3h, 92%; **h**. $PhCF_3$-toluene(1:1), 220°C microwaves, $Et_3N$ (3 eq.), (30% 2.9a, 10% 2.9b or 80% 2.9 B.R.S.M); **i.** $SOCl_2$, DMF (cat.), DCM 70%; **j.** *m*-CPBA, DCM, 0°C, 12h, 95% B.R.S.M. **k.** periodic acid (cat.), sodium periodate (4 eq.), THF:$H_2O$ (1:1), 12-24h; **l.** $NaBH_4$ (2 eq.), THF:MeOH(3.5:1), (98%, 2 steps, B.R.S.M); **m.** $OsO_4$, NMO, $NaIO_4$, THF:$H_2O$ (3:1), 89%; **n.** $MeNH_3Cl$, $NaBH_3CN$, MeOH, r.t. 16h; **o.** MgO (5 eq.), TsCl, THF:$H_2O$, (67%, 2 steps); **p.** NBS, benzoyl peroxide (init.), $CCl_4$, reflux, then $Et_3N$; **q.** $Li^0$, $NH_3$, THF, tBuOH, -78°C, 10 min (57%, 2 steps); **r.** $Tf_2O$ (1.5 eq), pyridine (3 eq.), DCM, 69%; **s.** $ClCO_2Et$, $K_2CO_3$, $CHCl_3$, reflux, 48h, 53%.

# CHAPTER 3: EXPERIMENTAL AND REFERENCES

## 3.1 GENERAL EXPERIMENTAL

### 2,5-Dibromo-7,8-dimethoxy-3,4-dihydronaphthalen-1(2H)-one (2.13)

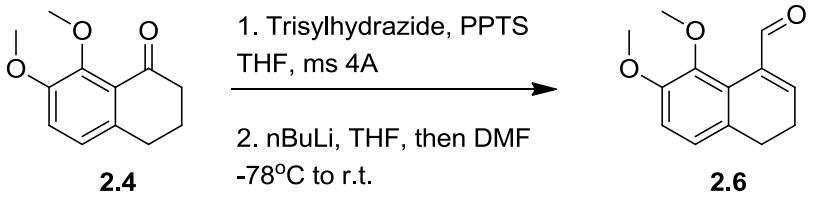



**2.2** **2.13**

**Procedure**: Carboxylic acid **2.2** (6.78 g, 22.4 mmol) was dissolved in anhydrous dichloromethane (15mL) in a flame-dried round-bottom flask and stirred at 0°C under argon. In a separate flame-dried flask, distilled trifluoromethanesulfonic acid (0.40 mL, 4.5 mmol), was added to trifluoroacetic anhydride (3.42 mL, 24.6 mmol) and stirred at 0°C under argon before being cannulated slowly into the main flask. The reaction was left to stir at 0°C for one hour until complete consumption of starting material could be observed by TLC. The reaction mixture was then slowly poured into ice-cold saturated sodium bicarbonate (20 mL). The layers were separated and the aqueous layer was extracted with ether (10 mL) three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vaccuo*. Flash chromatography (15 % ethyl acetate in hexanes) afforded ketone **2.13**, a side product of the main reaction (733 mg, 9 %) as a dark waxy-red solid.

**IR** (neat, $cm^{-1}$) 1694 (s), 1576 (w), 1471 (s), 1420(s), 1291(s), 1263(s);
**1H-NMR** (400 MHz; $CDCl_3$): δ 7.25 (s, 1H), 4.55 (dd, *J* = 5.4, 3.5 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.02-2.87 (m, 2H), 2.48-2.32 (m, 2H).
**13-C NMR** (100 MHz; $CDCl_3$): δ 189.3(C4), 152.5(C4), 150.3(C4), 133.3(C4), 125.8(C4), 121.5(CH), 118.1(C4), 61.3(CH), 56.4($CH_3$), 51.3($CH_3$), 30.5($CH_2$), 27.1($CH_2$)
**HRMS** (EI) m/z calculated for $C_{12}H_{12}Br_2O_3$ ($M^+$) 361.9153, found 361.9155.

## 7,8-Dimethoxy-3,4-dihydronaphthalene-1-carbaldehyde (2.6)



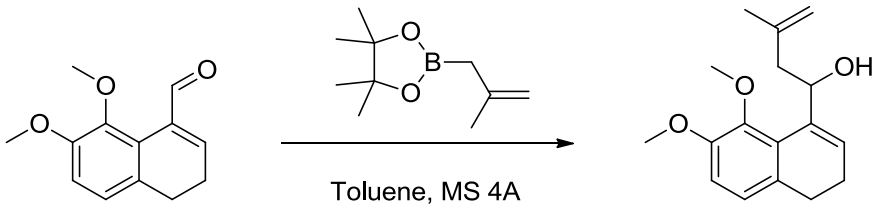

**2.4** **2.6**

**Procedure:** To a stirring solution of ketone **2.4** (3 g, 14.5 mmol) in THF (87 mL) under argon was added pyridinium p-toluenesulfonate (109.3 mg, 0.43 mmol) and trisylhydrazide (4.77 g, 15.9 mmol). The solution was left to stir for 24 hours before being filtered on celite and passed through a short plug of silica, which was washed with ethyl acetate. The solvent was evaporated *in vaccuo* to obtain an orange foamy solid (7 g, 14.4 mmol). The crude solid (3.5 g, 7.2 mmol) was dissolved in anhydrous THF (70 mL) and cooled to -78°C, to which was added BuLi (2.20 M, 6.7 mL, 14.7 mmol) dropwise by slow addition on the sides of the ice-cold flask. Upon addition of half of the buthyl lithium, the reaction should turn dark red. The reaction mixture was left to stir for 30 minutes at -78°C, and then warmed-up to 0°C for 25 minutes. To the black solution was added drop wise dry DMF (1.0 mL, 12.96 mmol) and the reaction was left to stir and warm up to room temperature slowly for 2.5 hours before cold water (~40 mL) was slowly added. The layers were separated and the aqueous phase was extracted three times with diethyl ether (50 mL). The combined organic extracts were dried on $MgSO_4$, filtered, and concentrated *in vaccuo*. Flash chromatography (20% ethyl acetate in hexanes) provided **2.6** (1.33 g, 6.12 mmol, 85%).

Based on the characterization data from Kassandra Lepack:

**1H-NMR** (400 MHz; $CDCl_3$): 9.94 (s, 1H), 6.92(d, *J*=8.27 Hz, 1H), 6.91 (t, *J*=4.86 Hz, 1H), 6.81 (d, *J*=8.19 Hz, 1H), 3.86 (s, 3H), 3.74 (s, 3H), 2.67 (t, *J*=7.50 Hz, 2 H), 2.35 (td, *J*=7.5 Hz, 5.20 Hz, 2H)
**13-C NMR** (100 MHz; $CDCl_3$): 192.2 (CH), 151.5 (C4), 145.6 (C4), 138.5 (CH), 137.8 (C4), 129.9 (C4), 125.0 (C4), 122.9 (CH), 111.8 (CH), 60.7 ($CH_3$), 55.9 ($CH_3$), 27.5 ($CH_2$), 23.5 ($CH_2$)
**HRMS** (EI) m/z calculated for $C_{13}H_{14}O_3$ $(M)^+$ 218.0943, found 218.0941

## 1-(7,8-Dimethoxy-3,4-dihydronaphthalen-1-yl)-3-methylbut-3-en-1-ol (2.7)



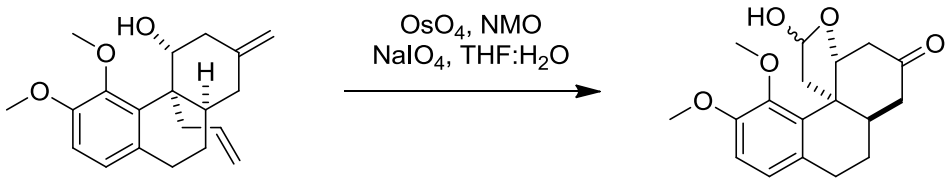

**2.6** **2.7**

**Procedure**: To a mixture of 2-methylallyl pinacol boronic ester (400 mg, 2.19 mmol) in anhydrous toluene (16 mL) at -78°C was added slowly a solution of aldehyde **2.6** (407 mg, 1.86 mmol) in toluene (16 mL). Reaction mixture was allowed to stir at -78°C for 1h, then allowed to warm up to room temperature. Reaction was monitored by TLC and upon noticing complete consumption of starting material, sodium hydroxide (1.0 M in water, 15 mL) was added and the mixture was stirred for 30 minutes. The layers were separated and the aqueous phase was extracted three times with toluene. The combined organic extract was dried ($MgSO_4$), filtered and concentrated in *vaccuo.* Flash chromatography (25% ethyl acetate in hexanes) provided **2.7** (582 mg, 2.12 mmol, 97%).

Based on the characterization data from Kassandra Lepack:

**1H-NMR** (400 MHz; $CDCl_3$): δ 6.90 (d, *J*=8.1 Hz, 1H), 6.74 (d, *J*=8.2 Hz, 1H), 6.46 (ddd, *J*=5.83 Hz, 4.31 Hz, 1.36 Hz, 1H), 5.07 (t, *J*=4.32 Hz, 1H) 4.86 (s, 1H), 4.77 (s, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 2.56 (m, 4H), 2.15 (m, 3H), 1.79 (s, 3H)
**13-C NMR** (100 MHz; $CDCl_3$): δ 151.8 (C4), 145.1 (C4), 143.5 (C4), 139.3 (C4), 131.8 (C4), 127.4 (C4), 126.7 (CH), 122.9 (CH), 113.1 ($CH_2$), 110.3 (CH), 68.9 (CH), 60.9 ($CH_3$), 55.9 ($CH_3$), 45.6 ($CH_2$), 29.0 ($CH_2$), 23.0 ($CH_2$), 22.3 ($CH_3$)
**HRMS** (EI) m/z calcd for $C_{17}H_{22}O_3$ ($M^+$) 274.1569, found 274.1584

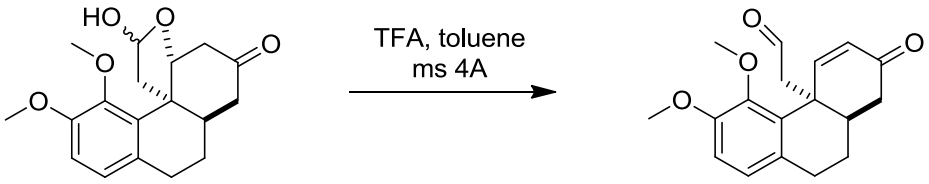
## 2-Hydroxy-11,12-dimethoxy-3a,4,6,6a,7,8-hexahydro-1H-phenanthro[4,4a-b]furan-5(2H)-one (2.10)




**2.9a** **2.10**

**Procedure**: **2.9** (76.2 mg, 0.24 mmol) was placed in a flask and a 3:1 THF:Water (4 mL) mixture was added. Osmium tetroxide (4% w/v in water, 0.15 mL, 0.1 eq) was added and the solution was stirred until it assumed a dark/black appearance. At that point, NMO (56 mg, 0.48 mmol) was added and the solution was stirred for 5h at room temperature. Upon noticing complete starting material consumption by TLC, sodium periodate (207 mg, 0.967 mmol) was added and the solution was stirred for 2h. A saturated solution of sodium sulfite (4 mL) was added and the mixture was extracted with diethyl ether (3 x 6 mL). The combination of organic phases was dried over magnesium sulfate and concentrated in vaccuo. A specific amount of pure naphthalene was added to the crude mixture, followed by deuterated chloroform. NMR spectrum comparison of naphthalene internal standard with the integrated sum of anomeric hydrogens and aldehyde hydrogen indicated a yield of approximately 92%. The compound is extremely unstable on silica and was thus used as the crude mixture.

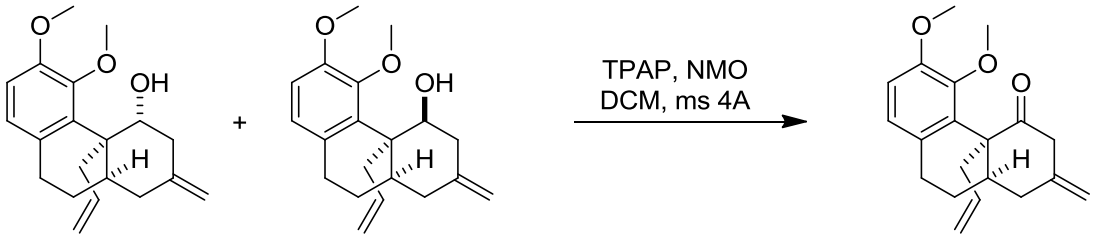
## 2-(5,6-Dimethoxy-2-oxo-1,2,4a,9,10,10a-hexahydrophenanthren-4a-yl)acetaldehyde (2.11)




**2.10** **2.11**

**Procedure:** Starting crude lactol **2.10** (23.2 mg, 0.24 mmol) was placed in a flame-dried flask and dry toluene (1 mL) was added, followed with ms. 4Å (~45 mg). The solution was stirred for a few minutes and TFA ( 0.02 mL, 0.26 mmol) was added. The solution was stirred overnight. Water was added and the phases were shaken and quickly separated. The aqueous phase was extracted three times with toluene (3x2 mL). Resulting organics were treated with magnesium sulfate, filtered and evaporated *in vaccuo*. Usually, the obtained crude mixture is used directly for any subsequent reaction. Upon chromatography, starting **2.10** is often reformed in significant amount.

## 4a-Allyl-5,6-dimethoxy-2-methylene-2,3,4a,9,10,10a-hexahydrophenanthren-4(1H)-one (2.22)




**2.9a** **2.9b** **2.22**

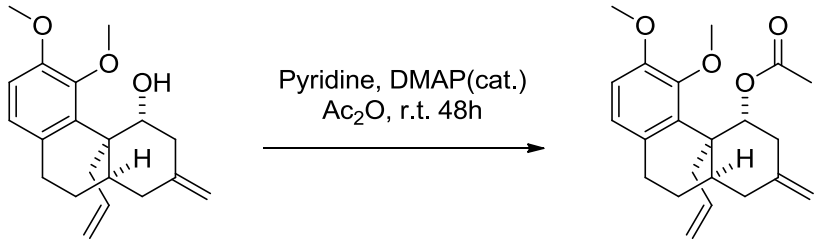
The reaction was carried in two separate flasks (one per alcohol) as to confirm the specific stereochemistry at the hydroxyl bearing carbon.

Example reaction for first diastereomer **2.9a**:

**Procedure**: The alcohol **2.9a** (15 mg, 0.047 mmol) was added to a flame-dried reaction vial under argon, to which was added dry DCM (2 mL) and 5 round molecular sieves (3A, ~25 mg). The solution was stirred at room temperature then *N*-methylmorpholine *N*-oxide (14 mg, 0.12 mmol) and tetrapropylammonium perruthenate (TPAP, 1.6 mg, 0.004 mmol) were added in succession. Upon noticing complete consumption of starting material by TLC (~2h), the reaction mixture was filtered on a small pad of silica then evaporated *in vaccuo*. Flash chromatography yielded a yellow oil (10.5 mg, 0.034 mmol, 72%)

**IR** (neat, $cm^{-1}$) 2838 (w), 1714 (vs), 1488 (s), 1447 (w), 1279(s), 1040(m);
**1-H NMR** (400 MHz; $C_6D_6$): δ 6.69 (dt, *J* = 8.4, 1.0, 1H), 6.51 (d, *J* = 8.4, 1H), 6.31 (dtd, *J* = 17.0, 10.0, 4.9, 1H), 4.99-4.93 (m, 2H), 4.60 (dd, *J* = 4.7, 2.9, 2H), 3.68 (d, *J* = 0.2, 3H), 3.34-3.28 (m, 4H), 3.19 (ddt, *J* = 14.2, 4.5, 1.9, 1H), 3.11 (dd, *J* = 12.1, 1.9, 1H), 2.71-2.50 (m, 2H), 2.28-2.22 (dd, *J* = 14.22, 9.72, 1H), 2.24-2.17 (m, 1H), 2.05-1.94 (m, 2H), 1.84 (ddd, *J* = 13.3, 3.8, 1.9, 1H), 1.31-1.25 (m, 1H)
**13-C NMR** (100 MHz; $C_6D_6$): δ 205.9(C4), 151.0(C4), 147.0(C4), 145.0(C4), 136.4(CH), 133.6(C4), 127.6(C4), 124.9(CH), 116.7($CH_2$), 112.1(CH), 109.4($CH_2$), 60.3($CH_3$), 55.4($CH_3$), 54.1(C4), 50.0($CH_2$), 42.6($CH_2$), 39.3(CH), 36.1($CH_2$), 23.6($CH_2$), 21.9($CH_2$)
**HRMS** (EI) m/z calcd for $C_{20}H_{24}O_3$ ($M^+$) 312.1725, found 312.17133.

## 4a-Allyl-5,6-dimethoxy-2-methylene-1,2,3,4,4a,9,10,10a-octahydrophenanthren-4-yl acetate (2.23a)

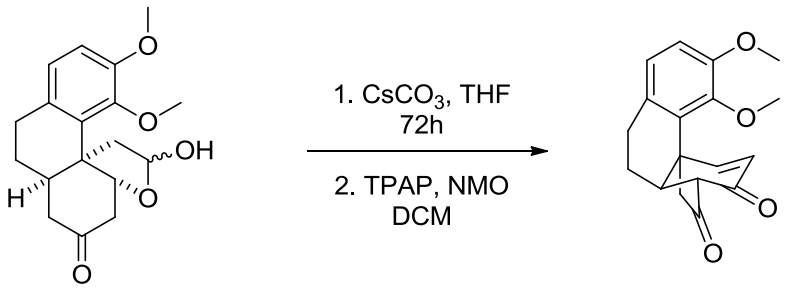



**2.9a** **2.23a**

**Procedure**: Alcohol **2.9a** (20 mg, 0.063 mmol) and acetic anhydride (0.5 mL, 5.3 mmol) were added to a solution of anhydrous pyridine (4 mL) and DMAP (1 crystal) and stirred at room temperature for 48 hours. Then, water (5 mL) was added and the solution was further diluted with dichloromethane (10 mL). The phases were separated and the aqueous was washed with DCM (5 mL) three times. After combining the organics, the mixture was dried on magnesium sulfate and evaporated *in vaccuo*. The product was passed on a small plug of silica using 20% ethyl acetate/hexanes and did not require any further purification. A yellow oil was obtained (17.5 mg, 0.05 mmol, 78%).

**IR** (neat, $cm^{-1}$) 3074(w), 1728(vs), 1474(m), 1371(m), 1280(s), 1246(s)
**1H-NMR** (400 MHz; $CDCl_3$): δ 6.81 (d, *J* = 8.4, 1H), 6.78 (d, *J* = 8.4, 1H), 6.46 (dd, *J* = 4.1, 2.0, 1H), 5.79-5.68 (m, 1H), 4.89 (s, 1H), 4.86 (d, *J* = 3.2, 1H), 4.67 (d, *J* = 1.8, 1H), 4.54 (d, *J* = 1.9, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 2.92 (dt, *J* = 18.2, 9.4, 1H), 2.73 (dd, J = 17.7, 7.1, 1H), 2.51-2.38 (m, 4H), 2.18-2.08 (m, 4H), 2.05 (s, 3H), 1.52 (m, 1H)
**13-C NMR** (100 MHz; $CDCl_3$): δ 170.7(C4), 151.0(C4), 148.9(C4), 145.0(C4), 136.4(CH), 132.3(C4), 129.5(C4), 125.1(CH), 115.7(CH), 111.6($CH_2$), 109.0(CH), 75.5(CH), 60.7($CH_3$), 56.0($CH_3$), 45.5(C4), 45.0($CH_2$), 37.0(CH), 36.32($CH_2$), 36.23($CH_2$), 24.8($CH_2$), 22.5($CH_2$), 21.7(C4)
**HRMS** (EI) m/z calcd for $C_{22}H_{28}O_4$ ($M^+$) 356.1988 found 356.1991

## 5,6-Dimethoxy-10,10a-dihydro-1H-1,4a-ethanophenanthrene-2,12(9H)-dione (2.41)

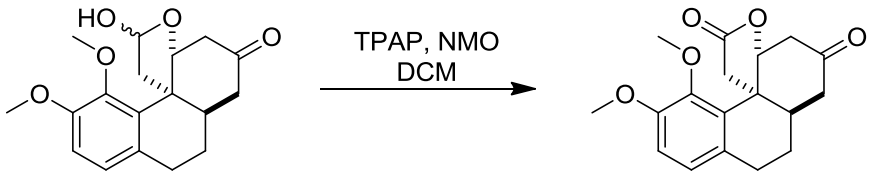



**2.10** **2.41**

**Procedure**: Crude lactol **2.10** (35 mg, 0.11 mmol) was placed in a flamed-dried flask under argon. Cesium carbonate (90 mg, 0.27 mmol) and THF (1.5 mL) were added followed by some 4 Å molecular sieves (~75 mg). The solution was left to stir at room temperature for 3 days. Water was then added (2 mL) and the mixture was extracted with diethyl ether (3 x 2 mL). The organics were combined, dried over magnesium sulfate, and concentrated *in vaccuo*. The obtained crude was placed in a flask to which was added dry DCM(1 mL), TPAP (3.8 mg, 0.011 mmol) and NMO (32 mg, 0.273 mmol). The solution was stirred for 2hrs and then filtered on a silica/celite pad. Flash chromatography (35% ethyl acetate/hexanes) yielded a white dust (8.1 mg, 0.027 mmol, 25% over 2 steps).

**IR** (neat, $cm^{-1}$) 2932(m), 2834(m), 1678(vs), 1522(s), 1272(s), 1031(m)
**1H-NMR** (400 MHz; $CDCl_3$): δ 7.00 (dd, *J* = 9.8, 2.2, 1H), 6.87 (s, 2H), 5.90 (dd, *J* = 9.8, 1.5, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.45 (d, *J* = 4.8, 1H), 3.36 (d, *J* = 17.8, 1H), 2.97-2.89 (m, 2H), 2.80 (dtd, *J* = 10.0, 4.9, 2.6, 1H), 2.61 (d, *J* = 17.3, 1H), 2.06 (tdd, *J* = 12.8, 11.3, 6.3, 1H), 1.96 (ddt, *J* = 12.9, 6.0, 2.9, 1H)
**13-C NMR** (100 MHz; $CDCl_3$): δ 209.1(C4), 190.1(C4), 158.2(CH), 151.0(C4), 147.2(C4), 132.3(C4), 129.7(C4), 126.3(CH), 124.7(CH), 112.7(CH), 68.9(CH), 60.9(CH), 56.0($CH_3$), 53.1($CH_3$), 48.9($CH_2$), 45.6(C4), 29.2($CH_2$), 19.8 ($CH_2$)
**HRMS** (EI) m/z calcd for $C_{18}H_{18}O_4$ ($M^+$) 298.1205, found 298.1190.

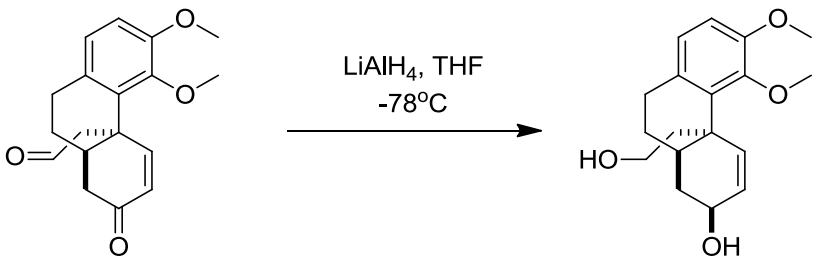
## 11,12-Dimethoxy-3a,4,6,6a,7,8-hexahydro-1H-phenanthro[4,4a-b]furan-2,5-dione (2.33)




**2.10** **2.33**

**Procedure**: Crude lactol **2.10** (10.8 mg, 0.034 mmol) was placed in a flask to which was added dry DCM (1.5 mL), TPAP (1 mg, 0.003 mmol) and NMO (9.9 mg, 0.084 mmol). The solution was stirred for 2hrs and then filtered on a celite pad. Flash chromatography (30% ethyl acetate/hexanes) yielded what appears to be a mixture of lactone **2.33** and the corresponding opened enone/carboxylic acid.

## 4a-(2-Hydroxyethyl)-5,6-dimethoxy-1,2,4a,9,10,10a-hexahydrophenanthren-2-ol (2.38)

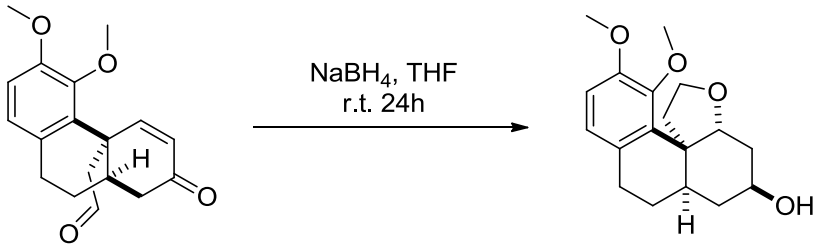



**2.11** **2.38**

**Procedure**: Enone **2.11** (63.8 mg, crude, 0.212 mmol) was placed in a dry flask and THF (7 mL) was added. The flask was placed at -78°C and lithium aluminum hydride (0.46 mL, 1M in THF, 0.46 mmol) was added dropwise. After stirring for 30 minutes, a solution of sodium L-tartrate in water was added (10 mL) and the solution was left to stir and warm-up to room temperature for 15 minutes. The mixture was then extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over magnesium sulfate and concentrated in vaccuo. Flash chromatography of the resulting crude mixture (90% ethyl acetate/hexanes) yielded a transparent liquid (38 mg, 0.125 mmol, 59%).

**IR** (neat, $cm^{-1}$) 3363 (br), 2941(m, br), 1480 (vs), 1273 (s), 1048(s)
**1H-NMR** (400 MHz; $CDCl_3$): δ 6.79 (d, *J* = 8.4, 1H), 6.74 (d, *J* = 8.4, 1H), 6.57 (dd, *J* = 10.3, 1.7, 1H), 5.73 (dt, *J* = 10.3, 1.9, 1H), 4.32 (ddt, *J* = 9.3, 6.5, 2.5, 1H), 3.82 (s, 3H), 3.82 (s, 3H), 3.72-3.61 (m, 2H), 2.85 (ddd, *J* = 17.3, 12.5, 5.7, 1H), 2.66 (dd, *J* = 16.0, 5.3, 1H), 2.20 (ddd, *J* = 14.0, 7.7, 6.2, 1H), 2.12-1.96 (m, 4H), 1.90 (ddt, *J* = 12.2, 6.0, 1.8, 1H), 1.70-1.50 (m, 2H), 1.25 (s, 1H)
**13-C NMR** (100 MHz; $CDCl_3$): δ 151.4(C4), 148.4(C4), 137.7(CH), 136.5(C4), 130.5(CH), 128.1(C4), 124.9(CH), 111.1(CH), 68.2($CH_3$), 60.4($CH_3$), 60.1($CH_2$), 55.9(CH), 42.47(C4), 42.30($CH_2$), 35.2($CH_2$), 29.8(CH), 25.4($CH_2$), 24.4 ($CH_2$)
**HRMS** (EI) m/z calcd for $C_{18}H_{24}O_4$ ($M^+$) 304.1675 found 304.1697

## 11,12-Dimethoxy-2,3a,4,5,6,6a,7,8-octahydro-1H-phenanthro[4,4a-b]furan-5-ol (2.42)

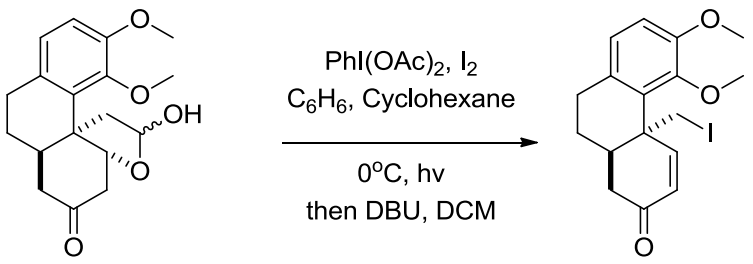



**2.11** **2.42**

**Procedure**: Aldehyde **2.11** (crude, 36.3 mg, 0.12 mmol) was dissolved in anhydrous THF (1 mL) in a flame-dried flask and stirred at room temperature. Sodium borohydride (18.3 mg, 0.48 mmol) was added in a single portion and the solution was stirred at room temperature for 24h. Upon noticing starting material consumption, dilute HCl (0.5M, 1mL) was added dropwise and the mixture was extracted four times with diethyl ether (1 mL) and the organic phases were combined. The combined organic mixture was then dried on $MgSO_4$ and evaporated *in vaccuo*. Flash chromatography of the resulting crude mixture (35% ethyl acetate in hexanes) afforded the alcohol (26.2 mg, 72%, 0.86 mmol)

**IR** (neat, $cm^{-1}$) 2929.7 (br), 1480.9 (s), 1409.4(m), 1276.8 (vs)
**1H-NMR** (400 MHz; $CDCl_3$): δ 6.82 (d, *J* = 8.4, 1H), 6.79 (d, *J* = 8.4, 1H), 5.28 (t, *J* = 2.9, 1H), 4.06 (d, *J* = 10.0, 1H), 4.04 (q, *J* = 7.8, 1H), 3.98-3.92 (m, 2H), 3.83 (s, 3H), 3.83 (s, 3H), 2.91 (ddd, *J* = 17.1, 13.3, 5.9, 1H), 2.62 (dd, *J* = 17.1, 4.4, 1H), 2.37-2.17 (m, 4H), 1.98 (tdd, *J* = 13.4, 5.8, 3.4, 1H), 1.69-1.54 (m, 3H), 1.49 (dt, *J* = 15.2, 3.0, 1H)
**13-C NMR** (100 MHz; $CDCl_3$): δ 151.2(C4), 149.0(C4), 131.1(C4), 130.4(C4), 124.9(CH), 111.4(CH), 79.7(CH3), 66.8($CH_3$), 65.2($CH_2$), 60.3(CH), 55.9(CH), 47.6(C4), 40.5($CH_2$), 34.3($CH_2$), 31.5($CH_2$), 29.0(CH), 25.5($CH_2$), 24.0($CH_2$)
**HRMS** (EI) m/z calcd for $C_{18}H_{24}O_4$ ($M^+$): 304.1675 found 304.1652.

## 4a-(Iodomethyl)-5,6-dimethoxy-1,9,10,10a-tetrahydrophenanthren-2(4aH)-one (2.49)

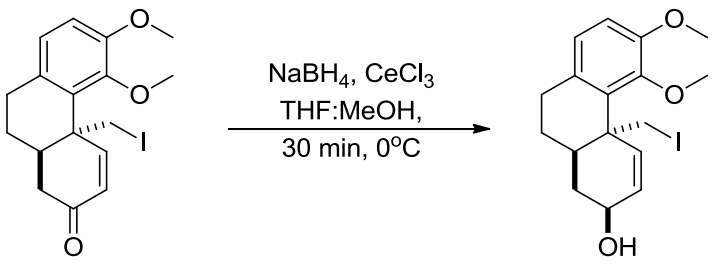



**2.10** **2.49**

**Procedure**: The starting lactol **2.10** (crude, 15.1 mg, 0.047 mmol) was placed in a flame-dried reaction vial. Dry benzene (1.75 mL) and dry cyclohexane (3 mL) were added to the vial. Then phenyliodonium diacetate (PIDA, 17.8 mg, 0.055 mmol) and iodine (12 mg, 0.047 mmol) were added to the solution in the absence of light. The vial's bottom half was placed in an ice-cold water bath (so that half the solution is in the water) and placed in front of 2 x 100W tungsten lamps (within 5 cm of each bulb). The solution was stirred in front of the light sources for 90 min. Upon noticing reaction completion by TLC (50% ethyl acetate/hexanes) saturated $Na_2S_2O_3$ was then added to quench the reaction and the vial was stirred until the solution turned pale. The mixture was extracted with diethyl ether (3 x 5 mL), dried over magnesium sulfate, filtered and concentrated *in vaccuo*. DCM (2 mL) was then added, the mixture was placed in an ice-cold water bath and 2 drops of DBU were added. The solution was stirred 5 min. at 0°C and 5 min. at room temperature. Ice-cold water was then added (5 mL), the phases were separated and the aqueous phase was extracted with diethyl ether (3 x 3mL). The organic phases were combined, dried over magnesium sulfate, filtered and concentrated *in vaccuo*. Flash chromatography of the resulting crude mixture (20% ethyl acetate/hexanes) provided the product as clear oil (10.2 mg, 0.0256 mmol, 54%).

**IR** (neat, $cm^{-1}$) 2933(m), 2834(m), 1675(vs), 1481(s), 1270(s)
**1H-NMR** (400 MHz; $CDCl_3$): δ 7.46 (d, *J* = 10.3, 1H), 6.84 (s, 2H), 6.02 (dd, *J* = 10.3, 0.8, 1H), 3.86 (d, *J* = 10.2, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.52 (d, *J* = 10.2, 1H), 2.86-2.69 (m, 3H), 2.55 (dd, *J* = 16.9, 12.2, 1H), 2.40 (dd, *J* = 16.9, 4.1, 1H), 1.92 (dddd, *J* = 14.4, 10.8, 7.1, 3.6, 1H), 1.64 (dddd, *J* = 14.2, 6.9, 4.1, 3.0, 1H)
**13-C NMR** (100 MHz; $CDCl_3$): δ 199.3(C4), 157.8(CH), 151.4(C4), 148.1(C4), 130.7(C4), 128.5(C4), 127.6(CH), 125.2(CH), 112.7(CH), 60.5($CH_3$), 56.0($CH_3$), 43.2(C4), 39.6($CH_2$), 38.8(CH), 25.1($CH_2$), 22.8($CH_2$), 17.0($CH_2$)
**HRMS** (EI) m/z calcd for $C_{17}H_{19}IO_3$ ($M^+$) 398.0379, found 398.0372.

## 4a-(Iodomethyl)-5,6-dimethoxy-1,2,4a,9,10,10a-hexahydrophenanthren-2-ol (2.50)

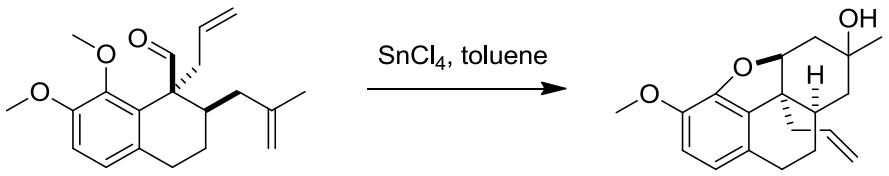



**2.49** **2.50**

**Procedure**: Enone **2.49** (30 mg, 0.075 mmol) was place in a vial and a 2:1 THF:MeOH (1 mL) mixture was added, the flask was then placed in an ice-cold water bath. Cerium trichloride (35.10 mg, 0.094 mmol) was added and the mixture was stirred for 5 min at 0°C. Sodium borohydride (3.5 mg, 0.094 mmol) was then added in one portion and the solution was stirred for 30 minutes at 0 deg. HCl (0.5M, 2 mL) was added and the mixture was extracted with dichloromethane (3 x 2 mL). The combined organic extract was dried over magnesium sulfate, filtered and evaporated *in vaccuo*. Flash chromatography of the crude mixture (20% ethyl acetate/hexanes) provided a yellow oil (26.1 mg, 0.065 mmol, 87%).

**IR** (neat, $cm^{-1}$) 2933(br, m), 2830 (w), 1481(s), 1287(m), 1272(s)
**1H-NMR** (400 MHz; $CDCl_3$): δ 6.82-6.77 (m, 2H), 6.34 (dd, *J* = 10.2, 1.8, 1H), 5.83 (dt, *J* = 10.3, 1.9, 1H), 4.36 (ddt, *J* = 9.6, 6.1, 2.0, 1H), 3.91 (d, *J* = 9.9, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.45 (d, *J* = 9.9, 1H), 2.81 (ddd, *J* = 17.1, 12.6, 6.3, 1H), 2.62 (ddd, *J* = 17.0, 6.1, 2.1, 1H), 2.35 (dq, *J* = 12.3, 2.9, 1H), 1.96-1.85 (m, 2H), 1.66-1.57 (m, 3H)
**13-C NMR** (100 MHz; $CDCl_3$): δ 151.5(C4), 148.9(C4), 136.8(CH), 132.2(C4), 131.6(CH), 128.7(C4), 125.1(CH), 112.0(CH), 67.8(CH), 60.4($CH_3$), 56.0($CH_3$), 43.0(C4), 36.4(CH), 34.6($CH_2$), 25.6($CH_2$), 23.8($CH_2$), 19.9 ($CH_2$)
**HRMS** (EI) m/z calcd for $C_{17}H_{21}IO_3$ ($M^+$) 400.0535, found 400.05445

## 2a1-Allyl-7-methoxy-4-methyl-1,2,2a,2a1,3,4,5,5a-octahydrophenanthro[4,5-bcd]furan-4-ol (2.60)

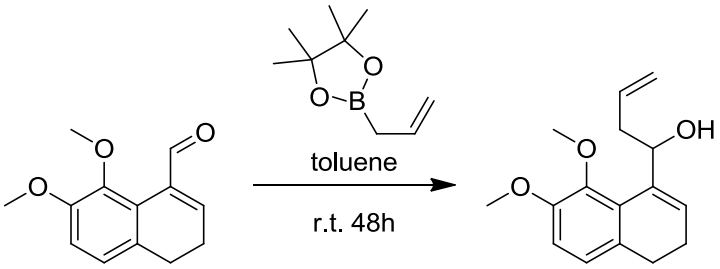



**2.21** **2.60**

**Procedure**: Aldehyde **2.21** (53.0 mg, 0.168 mmol) was placed in a flame-dried flask and dry toluene (1 mL) was added. The flask was cooled to -78°C and $SnCl_4$ (0.17 mL, 1M, 0.17 mmol) was added dropwise. The solution was left to stir for 2h at -78°C and quenched with saturated $NaHCO_3$ (3mL). The mixture was then left to warm up to room temperature and stirred (approx. 10 min). Diethyl ether was used (3 x 4 mL) during the extraction. The combined organic layers were dried over magnesium sulfate and concentrated *in vaccuo.* Flash chromatography of the resulting crude mixture (5% to 30% EtOAc/Hexanes) provided the **2.60** as transparent oil, (14.4 mg, 0.048 mmol, 28%).

**IR** (neat, $cm^{-1}$) 2929 (br), 2849 (s), 1633 (s), 1458(s), 1432(m), 1276(m) ;
**1H-NMR** (400 MHz; $CDCl_3$): δ 6.72 (d, *J* = 8.2, 1H), 6.62 (d, *J* = 8.2, 1H), 5.96-5.85 (m, 1H), 5.13 (s, 1H), 5.10 (d, *J* = 5.8, 1H), 5.03 (dd, *J* = 9.4, 7.3, 1H), 3.85 (s, 3H), 2.74 (dd, *J* = 17.6, 7.5, 1H), 2.53 (m, *J* = 6.0, 2H), 2.43 (dd, *J* = 14.5, 6.8, 1H), 2.30 (dd, *J* = 14.4, 7.7, 1H), 2.25-2.17 (m, 1H), 2.07 (ddd, *J* = 13.7, 7.3, 2.5, 1H), 1.62 (dddd, *J* = 14.5, 7.2, 2.6, 1.1, 1H), 1.44 (ddd, *J* = 13.6, 5.1, 2.7, 1H), 1.25 (s, 1H), 1.20-1.10 (m, 5H)
**13-C NMR** (100 MHz; $CDCl_3$): δ 144.8(C4), 143.6(C4), 134.4(CH), 131.9(C4), 126.1(C4), 120.2(CH), 118.0($CH_2$), 113.3(CH), 88.1(CH), 70.6(C4), 56.6($CH_3$), 44.6(C4), 41.8($CH_2$), 40.4($CH_2$), 38.5($CH_2$), 31.5(CH), 29.5($CH_3$), 23.2($CH_2$), 21.1($CH_2$).
**HRMS** (EI) m/z calcd for $C_{19}H_{24}O_3$ ($M^+$) 300.1725, found 300.1752

## 1-(7,8-Dimethoxy-3,4-dihydronaphthalen-1-yl)but-3-en-1-ol (2.67)

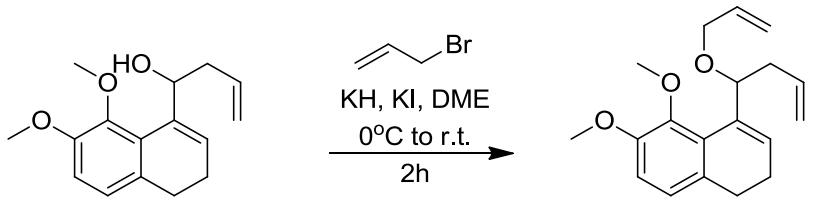



**2.6** **2.67**

**Procedure**: To a mixture of allyl pinacol boronic ester(202 mg, 1.20 mmol), molecular sieves (4 Å, <150 mg) in anhydrous toluene(9 mL) at 0°C was added slowly a solution of aldehyde **2.6** (200 mg, 0.91 mmol) in toluene(8 mL). The reaction mixture was allowed to stir at 0°C for 20min, then allowed to warm up to room temperature and stirring was continued until no more starting material was visible by TLC (48 h). Sodium hydroxide (1.0 M in water, 8 mL) was then added and the mixture was stirred for 30 minutes. The layers were separated and the aqueous phase was extracted three times with toluene. The combined organic extract was dried ($MgSO_4$), filtered and concentrated in *vaccuo.* Flash chromatography (20% ethyl acetate in hexanes) provided the homoallylic alcohol **2.67** (231 mg, 98%) as a transparent oil.

**IR** (neat, $cm^{-1}$) 2941 (br), 2830(w), 1474(vs), 1261(vs)
**1H-NMR** (400 MHz; $C_6D_6$): δ 6.77 (d, J = 8.1, 1H), 6.46 (d, J = 8.1, 2H), 5.97 (ddt, J = 17.1, 10.2, 7.0, 1H), 5.19 (s, 1H), 5.08-5.04 (dm, 1H), 5.03 (d, J = 1.1, 1H), 3.61 (s, 3H), 3.32 (s, 3H), 2.68-2.61 (m, 1H), 2.46-2.41 (m, 3H), 2.21 (OH, 1H), 2.01-1.97 (m, 2H)
**13-C NMR** (100 MHz; $CDCl_3$): δ 151.7(C4), 145.1 (C4), 139.0 (C4), 135.5 (CH), 131.8(C4), 127.4 (C4), 127.0(CH), 122.9 (CH), 117.6 ($CH_2$), 110.3 (CH), 70.7(CH), 61.0($CH_3$), 55.9 ($CH_3$), 41.1 ($CH_2$), 29.0 ($CH_2$), 23.1 ($CH_2$)
**HRMS** (EI) m/z calcd for $C_{16}H_{20}O_3$ ($M^+$) 260.1412 M+ found = 260.1415.

## 4-(1-(Allyloxy)but-3-enyl)-5,6-dimethoxy-1,2-dihydronaphthalene (2.65)

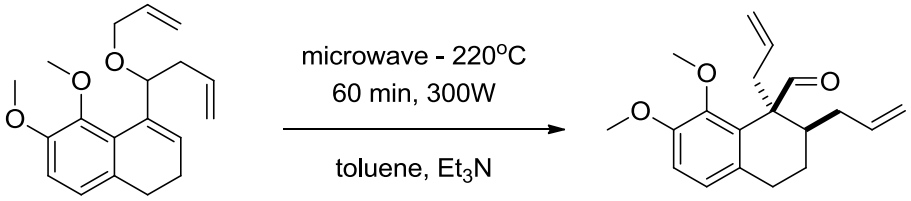



**2.67** **2.65**

**Procedure**: Potassium hydride (1.10 g, 30% w/w, 8.24 mmol) was added to a flame-dried round-bottom flask under an atmosphere of argon and was then washed twice with hexanes. The leftover hexane was removed under vacuum and freshly $LiAlH_4$-distilled DME (80 mL) was added to the reaction flask. The solution was stirred and cooled to 0°C and a premixed solution of the alcohol **2.67** (537.8 mg, 2.06 mmol), KI (33 mg, 0.20 mmol) and DME (20 mL) was cannulated to the main reaction flask, which was then left to stir for 15 minutes. Freshly distilled allyl bromide (0.370 mL, 4.37 mmol) was then added dropwise to the reaction flask and the solution was left to stir and warm-up to room temperature slowly. After two hours, or upon noticing reaction completion by TLC (best viewed at 10% EtOAc/Hexanes), the reaction flask was cooled again to 0°C and water (25 mL) was added. The layers were separated and the aqueous phase was extracted three times with diethyl ether (30 mL). The organic layers were combined, dried using magnesium sulfate, filtered and evaporated *in vaccuo.* Flash chromatography (5% EtOAc/Hexanes) yielded the allyloxy compound **2.65** as a clear oil (541.6 mg, 1.80 mmol, 87.6%).

**IR** (neat, $cm^{-1}$) 2830 (m), 1474 (s), 1299(w), 1261(s),1055(m);
**1H-NMR** (400 MHz; $CDCl_3$): δ 6.88 (d, *J* = 8.1, 1H), 6.72 (d, *J* = 8.1, 1H), 6.41 (ddd, *J* = 5.9, 4.3, 1.4, 1H), 5.98 (dddd, *J* = 17.2, 10.4, 5.7, 5.2, 1H), 5.90 (ddt, *J* = 17.1, 10.3, 6.9, 1H), 5.30 (dq, *J* = 17.2, 1.7, 1H), 5.16 (dq, *J* = 10.4, 1.6, 1H), 5.03-4.99 (m, 1H), 4.99-4.96 (m, 1H), 4.93 (ddt, *J* = 6.0, 3.2, 1.5, 1H), 4.13 (ddt, *J* = 12.9, 5.2, 1.5, 1H), 3.95 (ddt, *J* = 12.9, 5.8, 1.4, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 2.61-2.55 (m, 2H), 2.53-2.44 (m, 1H), 2.23-2.11 (m, 3H)
**13-C NMR** (100 MHz; $CDCl_3$): δ 152.0(C4), 145.7(C4), 137.6(C4), 136.1(CH), 135.7(CH), 131.8(C4), 128.0(C4), 126.2(CH), 122.8(CH), 116.4($CH_2$), 116.2($CH_2$), 110.3(CH), 78.1(CH), 70.3($CH_2$), 60.8($CH_3$), 56.0($CH_3$), 40.9($CH_2$), 29.2($CH_2$), 23.1($CH_2$)
**HRMS** (EI) m/z calcd for $C_{19}H_{24}O_3$ ($M^+$) 300.1725, found 300.1723

## 1,2-Diallyl-7,8-dimethoxy-1,2,3,4-tetrahydronaphthalene-1-carbaldehyde (2.64)

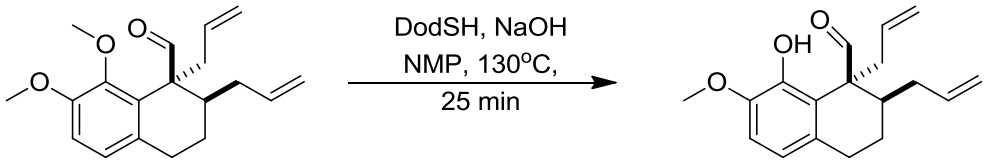



**2.65** **2.64**

**Procedure**: The allylated product **2.65** (100 mg, 0.33 mmol) was placed in a microwave-vessel. Toluene (3 mL), triethylamine (0.2 mL) and a carboflon were added and the solution was degassed by bubbling argon for 10 minutes. The mixture was submitted to micro-wave irradiation for 60 minutes (300W @ 220 deg.). The solution was evaporated in vaccuo to obtain a crude mixture. Flash chromatography (10% ethyl acetate/hexanes) provided a yellow oil (77 mg, 0.25 mmol, 77%)

**IR** (neat, $cm^{-1}$) 2937 (m), 1722(vs), 1489(s), 1451(m), 1279(s)
**1H-NMR** (400 MHz; $CDCl_3$): δ δ 9.73 (s, 1H), 6.84 (m, 2H), 5.79-5.68 (m, 1H), 5.53 (dddd, *J* = 17.0, 10.2, 8.1, 6.6, 1H), 5.07-4.93 (m, 4H), 3.83 (s, 3H), 3.76 (s, 3H), 2.91 (dd, *J* = 14.3, 6.5, 1H), 2.77-2.57 (m, 3H), 2.38 (ddddd, *J* = 9.8, 5.7, 3.9, 2.1, 1.7, 1H), 2.05-1.83 (m, 3H), 1.49 (dtd, *J* = 13.5, 8.9, 4.6, 1H)
**13-C NMR** (100 MHz; $CDCl_3$): δ 205.4(CH), 150.5(C4), 147.3(C4), 137.2(CH), 135.4(CH), 132.0(C4), 130.5(C4), 124.1(CH), 117.7($CH_2$), 116.8($CH_2$), 112.2(CH), 60.5($CH_3$), 56.0($CH_3$), 54.2(C4), 40.7(CH), 38.7($CH_2$), 34.1 ($CH_2$), 27.8($CH_2$), 24.1 ($CH_2$)
**HRMS** (EI) m/z calcd for $C_{19}H_{24}O_3$ ($M^+$) 300.1725, found 300.1699

## 1,2-Diallyl-8-hydroxy-7-methoxy-1,2,3,4-tetrahydronaphthalene-1-carbaldehyde (2.68)




**2.64** **2.68**

**Procedure**: In a small pressure vial, the starting aldehyde **2.64** (30 mg, 0.1 mmol), dodecanethiol (30.3 mg, 0.15 mmol), as well as sodium hydroxide (12 mg, 0.3 mmol) were added successively. NMP(1 mL) was then added, the vial was sealed and placed in a an oil bath at 130°C while stirring for 25 minutes. The solution was cooled down to room temperature and the content was added to a vial containing water (2 mL). At that point, 10% HCl was added (2 mL) followed by sodium bicarbonate until a pH of 7 was reached. The mixture was extracted with diethyl ether (3 x 3 mL). The combination of organic extracts was dried over magnesium sulfate and concentrated *in vaccuo*. Flash chromatography of the crude mixture (10% ethyl acetate / hexanes) yielded **2.68** as a transparent oil (18.2 mg, 0.063 mmol, 63%).

**IR** (neat, $cm^{-1}$) 3515 (v br), 3074 (s), 2933 (m br), 1722 (vs), 1491 (vs), 1279 (vs)
**1H-NMR** (400 MHz; $CDCl_3$): δ 9.76 (s, 1H), 6.76 (d, *J* = 8.3, 1H), 6.68 (d, *J* = 8.2, 1H), 5.81 (s, 1H), 5.74 (m, J = 6.9, 1H), 5.52-5.42 (m, 1H), 5.07-5.03 (m, 2H), 4.97 (m, 2H), 3.86 (s, 3H), 3.24 (ddt, *J* = 14.4, 6.0, 1.4, 1H), 2.75 (dt, *J* = 16.2, 4.7, 1H), 2.65 (dt, *J* = 10.4, 5.7, 2H), 2.43-2.38 (m, 1H), 2.02-1.95 (m, 2H), 1.86-1.77 (m, 1H), 1.48 (td, *J* = 11.9, 5.9, 1H)
**13-C NMR** (100 MHz; $CDCl_3$): δ 204.7(CH), 144.7(C4), 143.9(C4), 137.3(CH), 135.3(CH), 132.9(C4), 122.0(C4), 120.1(CH), 117.6($CH_2$), 116.7($CH_2$), 109.8(CH), 56.3($CH_3$), 54.5(C4), 40.6(CH), 35.8($CH_2$), 34.4($CH_2$), 28.9($CH_2$), 25.0 ($CH_2$)
**HRMS** (EI) m/z calcd for $C_{18}H_{22}O_3$ ($M^+$) 286.1569 found 286.1556

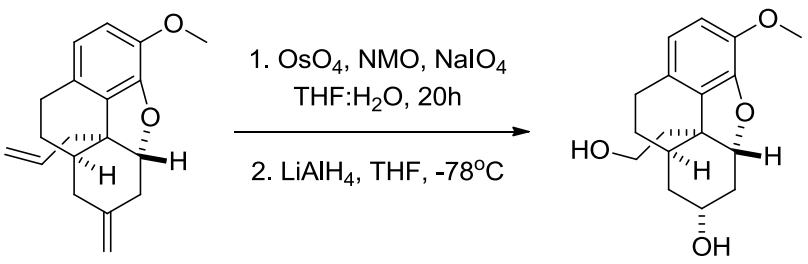
## 2a1-Allyl-7-methoxy-4-methylene-1,2,2a,2a1,3,4,5,5a-octahydrophenanthro[4,5-bcd]furan (2.77)


**2.9a** **2.77**

**Procedure**: To a flame-dried round bottom flask under argon was added hydroxyl **2.9a** (26.1 mg, 0.083 mmol) followed by 5 mL of dry DME. Then, one drop of potassium hydride powder in oil (approximated on the scale to be 19 mg, 0.14 mmol, on average) was added to the solution while stirring at room temperature. The solution was left to stir for 10 minutes before adding a condenser and being placed in an oil bath at 90°C. The reaction mixture was left to stir at this temperature (at reflux) for 90 minutes, at what point TLC showed complete consumption of starting material. The mixture was cooled to 0°C before water (2 mL) and diethyl ether (3 mL) were added successively. The layers were separated and the aqueous phase was extracted three times with diethyl ether (2 mL). The organic layers were combined, dried using magnesium sulfate, filtered, and evaporated *in vaccuo.* Flash chromatography (2% EtOAc/Hexanes) yielded a clear oil (19.5 mg, 0.069 mmol, 83%).

**IR** (neat, $cm^{-1}$) 2928 (s), 2845 (m), 1497(s), 1420(s), 1438 (s), 1269(s), 1255(s);
**1H-NMR** (400 MHz; $C_6D_6$): δ 6.69 (d, *J* = 8.1, 1H), 6.61 (dd, *J* = 8.1, 0.8, 1H), 5.56-5.46 (m, 1H), 4.94 (d, *J* = 1.3, 1H), 4.92-4.89 (m, 2H), 4.71 (quintet, *J* = 1.9, 1H), 4.13 (dd, *J* = 13.1, 7.4, 1H), 3.69 (s, 3H), 2.79-2.71 (m, 2H), 2.61 (ddq, *J* = 15.4, 7.4, 2.4, 1H), 2.40 (td, *J* = 13.5, 2.3, 1H), 2.29 (dt, *J* = 14.8, 3.2, 1H), 2.05 (td, *J* = 13.2, 8.0, 2H), 1.96-1.87 (m, 1H), 1.69-1.61 (m, 2H), 0.71 (qd, *J* = 12.4, 3.3, 1H)
**13-C NMR** (100 MHz; $C_6D_6$): δ 148.5 (C4), 144.6 (C4), 143.7(C4), 136.6(C4), 134.8(CH), 130.7(C4), 120.1(CH), 118.0(C4), 114.2(CH), 112.9(C4), 90.0(CH), 57.0($CH_3$), 43.9(C4), 38.1($CH_2$), 36.5($CH_2$), 35.5(CH), 32.7($CH_2$), 29.3($CH_2$), 28.0($CH_2$)
**HRMS** (EI) m/z calcd for $C_{19}H_{22}O_2$ ($M^+$) 282.1620, found 282.1611.

## 3a1-(2-Hydroxyethyl)-5-methoxy-1,2,3,3a,3a1,8,9,9a-octahydrophenanthro[4,5-bcd]furan-2-ol (2.78)

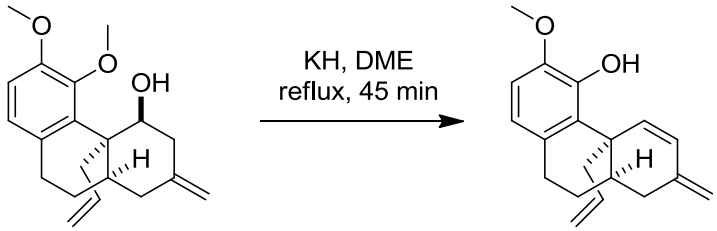



**2.77** **2.78**

**Procedure**: **2.77** (50.8 mg, 0.24 mmol) was placed in a flask and a 3:1 THF:Water (2 mL) mixture was added. Osmium tetroxide (4% w/v in water, 0.15 mL, 0.1 eq) was added and the solution was stirred until it assumed a dark/black appearance. At that point, NMO (82 mg, 0.7 mmol) was added and the solution was stirred for 5h at room temperature. Upon noticing complete starting material consumption by TLC, sodium periodate (140 mg, 0.65 mmol) was added and the solution was stirred overnight. A saturated solution of sodium sulfite (2 mL) was added and the mixture was extracted with diethyl ether (3 x 3 mL). The combination of organic phases was dried over magnesium sulfate and concentrated in vaccuo. The crude mixture was placed in a flame-dried flask, THF (2 mL) was added and the flask was placed in an acetone/dry ice bath. Lithium aluminum hydride (1M in THF, 0.5mL, 0.5 mmol) was then added dropwise and the solution was stirred for 5 minutes. A solution of sodium tartrate (3 mL) in water was then added and the solution was warmed up to room temperature. The mixture was extracted with diethyl ether (3 x 3 mL). The combination of organic extracts was dried over magnesium sulfate and concentrated *in vaccuo*. Flash chromatography (ethyl acetate) of the crude mixture provided a single white solid (47 mg, 0.16 mmol, 68%).

**IR** (neat, $cm^{-1}$) 3241 (br), 2922 (br), 1435 (s), 1253(s), 1200(s);
**1H-NMR** (400 MHz; $CDCl_3$): δ 6.67 (d, *J* = 8.1, 1H), 6.64 (d, *J* = 8.1, 1H), 4.47-4.43 (m, 1H), 4.09 (dd, *J* = 14.0, 6.4, 1H), 3.88 (s, 3H), 3.59 (s, 1H), 3.49-3.43 (m, 1H), 2.54 (dd, *J* = 7.9, 2.8, 2H), 2.50 (dd, *J* = 8.0, 5.2, 1H), 2.42 (tt, *J* = 11.8, 6.0, 1H), 2.35-2.23 (m, 2H), 2.17-2.11 (m, 1H), 2.09-2.03 (m, 1H), 1.92 (ddd, *J* = 15.0, 6.6, 2.9, 1H), 1.77-1.74 (m, 1H), 1.34 (ddd, *J* = 14.7, 11.2, 3.2, 1H), 1.28-1.24 (m, 1H), 1.03-0.93 (m, 1H)
**13-C NMR** (100 MHz; $CDCl_3$): δ 147.3(C4), 138.7(C4), 136.4(C4), 130.1(C4), 120.4(CH), 112.2(CH), 91.4(CH), 67.6($CH_3$), 60.2($CH_2$), 56.7($CH_3$), 41.7(C4), 37.2($CH_2$), 34.5($CH_2$), 34.1(CH), 33.3($CH_2$), 31.3($CH_2$), 27.8($CH_2$)
**HRMS** (EI) m/z calcd for $C_{17}H_{22}O_4$ ($M^+$) 290.1518, found 290.1488

## 4b-Allyl-3-methoxy-7-methylene-4b,7,8,8a,9,10-hexahydrophenanthren-4-ol (2.80)



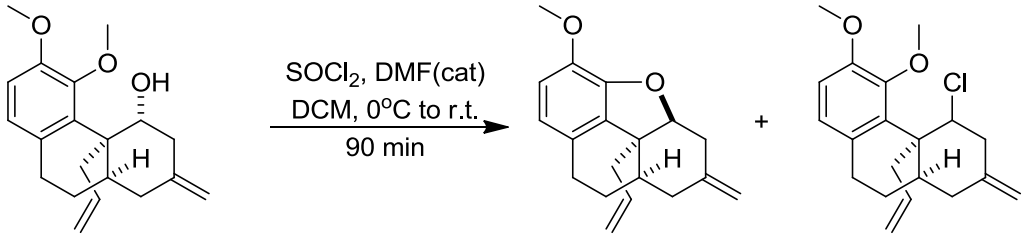

**2.9b** **2.80**

**Procedure**: To a flame-dried round bottom flask under argon was added alcohol **2.9b** (30.0 mg, 0.095 mmol) followed by 4 mL of dry DME. Then, one drop of potassium hydride (30% wt, approximated on the scale to be 19 mg each on average, 0.14 mmol total) was added to the solution while stirring at room temperature. The solution was left to stir for 10 minutes before adding a condenser and being placed in an oil bath at 90°C. The reaction mixture was left to stir at this temperature (under reflux condition) for 45 minutes, at what point TLC showed complete consumption of starting material. The mixture was cooled to 0°C before water (2mL) and diethyl ether (3 mL) were added successively. The layers were separated and the aqueous phase was extracted three times with diethyl ether (2 mL). The organic layers were combined, dried using magnesium sulfate, filtered, and evaporated *in vaccuo.* Flash chromatography (10% EtOAc/Hexanes) yielded a clear oil (15.6 mg, 0.055 mmol, 58%).

Of note: This is not the way we performed the experiment mentioned in this document, this is only a very slightly modified protocol that was used to make enough **2.80** for characterization.

**IR** (neat, $cm^{-1}$) 3522 (br), 2926 (s), 1485 (s),1458(s), 1436(s), 1275(s) , 1235(m)
**1-H NMR** (400 MHz; $C_6D_6$): δ 6.87 (d, *J* = 10.1, 1H), 6.63 (d, *J* = 8.2, 1H), 6.46 (d, *J* = 8.3, 1H), 6.33 (d, *J* = 10.1, 1H), 6.02 (s, 1H), 5.80 (ddt, *J* = 17.2, 10.0, 7.2, 1H), 5.14 (ddt, *J* = 17.0, 2.5, 1.3, 1H), 5.05 (ddt, *J* = 10.1, 2.4, 1.1, 1H), 4.98 (s, 1H), 4.92 (s, 1H), 3.51 (dd, *J* = 14.3, 6.8, 1H), 3.23 (s, 3H), 2.90 (dd, *J* = 14.3, 7.6, 1H), 2.75 (m 2H), 2.72-2.68 (m, 1H), 2.35 (dd, *J* = 14.7, 6.8, 1H), 2.27 (tt, *J* = 7.5, 3.8, 1H), 1.75 (m, 2H)
**13-C NMR** (400 MHz; $C_6D_6$): δ 145.1(C4), 144.8(C4), 142.1(C4), 136.46(CH), 136.45(CH), 131.1(C4), 127.6(CH), 127.4(CH), 120.4(CH), 116.7($CH_2$), 111.0($CH_2$), 108.9(CH), 55.6($CH_3$), 43.9(C4), 41.8($CH_2$), 36.5(CH), 33.6($CH_2$), 29.0($CH_2$), 25.5($CH_2$)
**HRMS** (EI) m/z calcd for $C_{19}H_{22}O_2$ ($M^+$) 282.1620, found 282.1612.

## 3a1-Allyl-5-methoxy-2-methylene-1,2,3,3a,3a1,8,9,9a-octahydrophenanthro[4,5-bcd]furan (2.76)




**2.9a** **2.76** **2.82**

**Procedure**: To a flame-dried reaction vessel was added alcohol **2.9** (150 mg, 0.477 mmol), dry DCM (10 mL) and 3 drops of dry DMF. The flask was stirred and cooled to 0°C. At that point, $SOCl_2$ (0.045 mL, 0.62 mmol) was added slowly. The solution was left to stir for 60 min at 0°C. TLC (30% EtOAc/Hexanes) is optimal to notice the consumption of starting material, but using benzene as elution solvent shows two products/spots (since EtOAc/Hexanes shows only one spot, which in fact contains 2 products having the same Rf), the most polar one being the wanted tetracyclic **2.76**. Upon noticing reaction completion by TLC a saturated solution of $NaHCO_3$ was added slowly (10 mL) and the two layers are separated in a separatory funnel. The aqueous phase was washed three times with DCM (5 mL). The organics are combined, dried over $MgSO_4$ then evaporated *in vaccuo*. A Flash chromatography of the crude mixture (40% - 50% benzene/hexanes) yielded a clear oil (94.8 mg, 0.336 mmol, 70%) as the tetracyclic compound and another clear oil(33.5 mg, 0.100 mmol, 21%).

**Tetracyclic 2.76**

**IR** (neat, $cm^{-1}$) 2933 (br), 2838 (m), 1500(s), 1439(s), 1340(m), 1277(s), 1259(s)

**1-H NMR** (400 MHz; $CDCl_3$): δ 6.74 (d, *J* = 8.2, 1H), 6.64 (d, *J* = 8.2, 1H), 5.80 (ddt, *J* = 17.1, 10.0, 7.2, 1H), 5.12-5.07 (m, 2H), 4.81 (dd, *J* = 8.9, 7.7, 1H), 4.71 (d, *J* = 7.7, 2H), 3.86 (s, 3H), 2.75 (dd, *J* = 17.3, 7.4, 1H), 2.66-2.55 (m, 2H), 2.39 (dd, *J* = 14.4, 7.1, 1H), 2.28-2.11 (m, 3H), 2.08-2.03 (m, 1H), 1.91 (dd, *J* = 12.7, 9.5, 1H), 1.77 (t, *J* = 12.6, 1H), 1.72-1.67 (m, 1H).

**13-C NMR** (100 MHz; $CDCl_3$): δ 144.7(C4), 143.77(C4), 143.60(C4), 134.1(CH), 132.0(C4), 126.0(C4), 120.4(CH), 118.4($CH_2$), 113.4(CH), 110.1($CH_2$), 89.3($CH_3$), 56.6(CH), 46.2(C4), 41.9($CH_2$), 38.0($CH_2$), 35.8(CH), 35.2($CH_2$), 23.9($CH_2$), 21.1($CH_2$)

**HRMS** (EI) m/z calcd for $C_{19}H_{22}O_2$ ($M^+$) 282.1620, found 282.1600.

**Chloro 2.82**

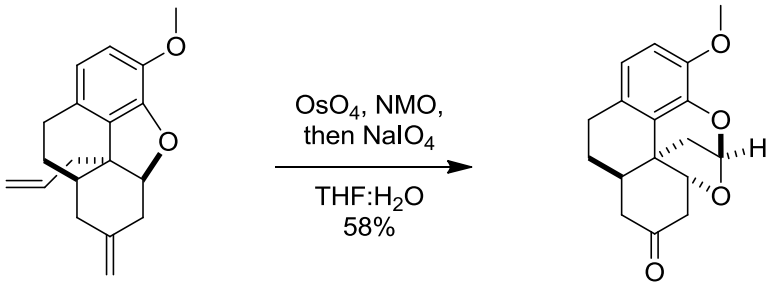
**IR** (neat, cm-1) 2937 (s, br), 2834(m), 1573(m), 1477(s), 1408(s), 1341(m), 1286(vs)

**1H-NMR** (400 MHz; $CDCl_3$): δ 6.83 (d, *J* = 8.4, 1H), 6.79 (d, *J* = 8.4, 1H), 5.99 (t, *J* = 3.2, 1H), 5.67 (dq, *J* = 17.2, 8.6, 1H), 5.00 (dq, *J* = 17.0, 1.9, 1H), 4.94 (dd, *J* = 10.1, 1.1, 1H), 4.79 (d, *J* = 1.8, 1H), 4.68 (d, *J* = 1.9, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 2.91 (dt, *J* = 18.7, 9.5, 1H), 2.75 (dd, *J* = 18.2, 7.7, 1H), 2.64 (dd, *J* = 14.3, 7.1, 1H), 2.57-2.44 (m, 4H), 2.25-2.15 (m, 1H), 2.12-2.04 (m, 2H), 1.53-1.47 (m, 1H).

**13-C NMR** (100 MHz; $CDCl_3$): δ 150.7(C4), 148.9(C4), 143.8(C4), 136.0(CH), 131.6(C4), 129.8(C4), 125.1(CH), 116.7($CH_2$), 111.6(CH), 110.3($CH_2$), 67.5($CH_3$), 61.0(CH), 56.0($CH_3$), 47.0(C4), 46.3($CH_2$), 40.3($CH_2$), 37.0(CH), 36.4(CH2), 24.8($CH_2$), 22.4($CH_2$)

**HRMS** (EI) m/z calcd for $C_{20}H_{25}O_2Cl(M^+)$ 332.1543 found 332.15417

## 8-Methoxy-3,4,5,6,12,12a-hexahydro-1H-4,6-epoxynaphtho[1,2-de]chromen-2(11H)-one (2.85)

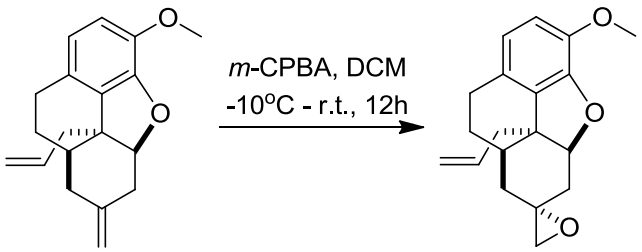



**2.76** **2.85**

**Procedure**: **2.76** (27.2 mg, 0.096 mmol) was placed in a flask and a 3:1 THF:Water mixture was added (2 mL). Osmium tetroxide in water (4% w/w, 0.06 mL, 0.096 mmol) was added dropwise and the solution was left to stir until the solution turned brown-black. At that point, NMO (28.25 mg, 0.241 mmol) was added and the solution was stirred until complete starting material consumption by TLC (80% ethyl acetate/hexanes). Then, sodium periodate was added (103 mg, 0.482 mmol) and the solution was stirred until complete consumption of the polyol by TLC (80 min in this case). The reaction was quenched with a $Na_2SO_3$ sat. solution (2 mL) and extracted with diethyl ether (4 x 2 mL). The combined mixture of organics was dried on magnesium sulfate and concentrated *in vaccuo*. Rapid flash chromatography of the obtained crude (80% ethyl acetate/hexanes) yielded a white solid (15.9 mg, 0.055 mmol, 58%).

**IR** (neat, cm-1) 2922 (br), 1723(s), 1497(s), 1435 (s), 1233(s), 1240(s)
**1-H NMR** (400 MHz; $C_6D_6$): δ 6.56 (d, *J* = 8.3, 1H), 6.48 (d, *J* = 8.3, 1H), 5.65 (d, *J* = 3.5, 1H), 4.35 (dd, *J* = 8.8, 7.5, 1H), 3.44 (s, 3H), 2.53-2.41 (m, 3H), 2.14 (dd, *J* = 14.1, 5.5, 1H), 1.87-1.80 (m, 2H), 1.77 (dd, *J* = 11.7, 3.6, 1H), 1.69-1.63 (m, 1H), 1.52 (d, *J* = 11.7, 1H), 1.28 (ddt, *J* = 13.4, 5.5, 2.8, 1H), 1.16-1.08 (m, 1H)
**13-C NMR** (100 MHz; $C_6D_6$): δ 205.1(C4), 147.3(C4), 141.9(C4), 127.9(C4), 126.3(C4), 120.5(CH), 112.7(CH), 99.2(CH), 87.1(CH), 56.0($CH_3$), 47.1($CH_2$), 43.0($CH_2$), 42.1(C4), 35.3 (CH), 33.9($CH_2$), 28.5 ($CH_2$), 28.1($CH_2$)
**HRMS** (EI) m/z calcd for $C_{17}H_{18}O_4Cl(M^+)$ 286.1205 found 286.1219

## 3a1'-Allyl-5'-methoxy-3',3a',3a1',8',9',9a'-hexahydro-1'H-spiro[oxirane-2,2'-phenanthro[4,5-bcd]furan] (2.89)

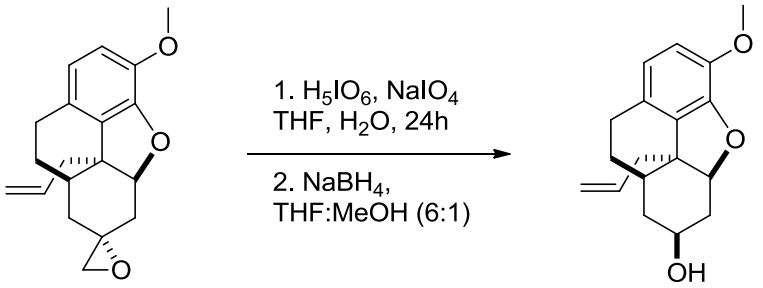



**2.76** **2.89**

**Procedure**: Tetracyclic **2.76** (132 mg, 0.47 mmol) was added to a flame-dried flask and placed under an atmosphere of argon. Dry dichloromethane (10 mL) was added; the solution was stirred and placed in a big salted-ice bath. The bath itself was covered and wrapped in aluminum paper to reduce the rate at which it would warm-up. *m*-CPBA was added in one portion (120 mg, 0.49 mmol, 70w/w%) and the solution was left to stir and very slowly warm-up overnight. In the morning, a $Na_2S_2O_4$ saturated solution (8 mL) was added and the solution was stirred for 5 minutes. The phases were separated and the organic phase was washed twice with saturated $NaHCO_3$ solution (5 mL). The aqueous phases were combined and back-extracted with DCM (10 mL). The combined organic mixture was dried over $MgSO_4$ and evaporated in *vaccuo*. Flash chromatography of the crude mixture (15% EtOAc/Hexanes) yielded a pale yellow oil (124.2 mg, 90%). It is possible to sometimes recover starting material during this chromatography.

**IR** (neat, $cm^{-1}$) 2937(m,br), 1497(s), 1439(s), 1277(s), 1258(s), 1189(m)
**1H-NMR** (400 MHz; $CDCl_3$): δ 6.74 (d, *J* = 8.2, 1H), 6.65 (d, *J* = 8.2, 1H), 5.91-5.89 (m, 1H), 5.17-5.11 (m, 2H), 5.06 (dd, *J* = 8.7, 7.8, 1H), 3.86 (s, 3H), 2.77 (dd, *J* = 17.6, 7.6, 1H), 2.58-2.52 (m, 4H), 2.45 (dd, *J* = 14.4, 7.0, 1H), 2.33 (dd, *J* = 14.3, 7.6, 1H), 2.24 (dddd, *J* = 14.9, 11.2, 7.5, 3.9, 1H), 1.80-1.62 (m, 4H), 1.07 (ddd, *J* = 13.6, 5.3, 2.0, 1H)
**13-C NMR** (100 MHz; $CDCl_3$): δ 144.7(C4), 143.7(C4), 133.9(CH), 131.5(C4), 125.9(C4), 120.6(CH), 118.6($CH_2$), 113.5(CH), 87.4(CH), 57.0(C4), 56.6($CH_3$), 53.0($CH_2$), 45.5(C4), 41.9($CH_2$), 35.3($CH_2$), 32.3($CH_2$), 30.9(CH), 23.3($CH_2$), 20.9($CH_2$)
**HRMS** (EI) m/z calcd for $C_{19}H_{22}O_3$ ($M^+$) 298.1569, found 298.1572.

## 3a1-Allyl-5-methoxy-1,2,3,3a,3a1,8,9,9a-octahydrophenanthro[4,5-bcd]furan-2-ol (2.91)

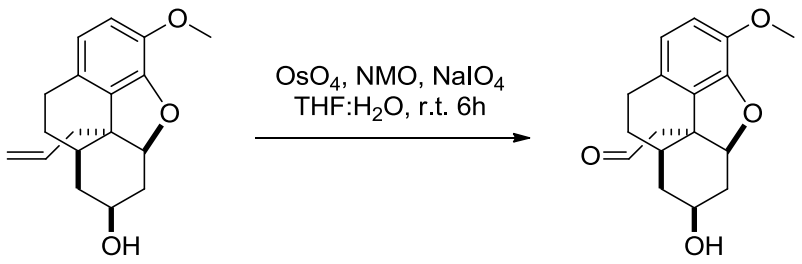



**2.89** **2.91**

**Procedure**: The epoxide **2.89** (67.5 mg, 0.226 mmol), was placed in a round-bottom flask and a THF-$H_2O$ mixture (2:1, 4.7 mL) was added, followed by a catalytic amount of $H_5IO_6$(3 mg), and sodium periodate (192.5 mg, 0.9 mmol). The solution was stirred overnight at room temperature. In the morning, 15 mg of sodium periodate were added and the solution was left to stir for another 5 hours. The solution was then diluted with $H_2O$ (5-7 mL) and extracted 3-4 times with diethyl ether (10 mL x 3). The organic phases were combined, dried on magnesium sulfate and evaporated *in vaccuo*. The obtained crude was placed in a vial and THF:MeOH (3.5:1, 5 mL) was added. To that mixture, sodium borohydride (17.1 mg, 0.450 mmol) was added in one portion and the solution was left to stir at room temperature for 2 hours. Dilute HCl (0.5 M-1M, 2 mL) was added and the solution was stirred for 3-5 minutes. More water (5 mL) was added and the whole mixture was extracted with diethyl ether 3 times (8 mL x 3). The combined organics were dried on magnesium sulfate and evaporated *in vaccuo*. Flash chromatography (~35% ethyl acetate/hexanes) yielded some recovered starting material **2.89** (23.8 mg, 0.077 mmol, 34%) and product **2.91** (41.0 mg, 0.143 mmol, 63%).

**IR** (neat, $cm^{-1}$) 2933(br), 1637(m), 1603(m), 1500(s), 1439(s), 1280(m)
**1H-NMR** (400 MHz; $CDCl_3$): δ δ 6.73 (d, *J* = 8.2, 1H), 6.63 (d, *J* = 8.2, 1H), 5.80 (ddt, *J* = 17.0, 9.9, 7.3, 1H), 5.12 (m, 2H), 4.88 (dd, *J* = 9.5, 7.4, 1H), 3.85 (s, 3H), 3.49 (tt, *J* = 11.7, 3.5, 1H), 2.74 (dd, *J* = 17.8, 7.4, 1H), 2.58 (m, 1H), 2.41-2.17 (m, 5H), 1.75-1.66 (m, 2H), 1.21-1.05 (m, 2H)
**13-C NMR** (100 MHz; $CDCl_3$): δ 144.5(C4), 143.7(C4), 133.9(CH), 131.5(C4), 125.8(C4), 120.5(CH), 118.7($CH_2$), 113.5(CH), 87.7(CH), 66.7(CH), 56.6($CH_3$), 45.5(C4), 41.4($CH_2$), 38.2($CH_2$), 35.8($CH_2$), 31.8(CH), 23.5($CH_2$), 21.1($CH_2$)
**HRMS** (EI) m/z calcd for $C_{18}H_{22}O_3$ ($M^+$) 286.1569, found 286.1558.

## 2-Hydroxy-5-methoxy-1,2,3,3a,3a1,8,9,9a-octahydrophenanthro[4,5-bcd]furan-3a1-yl)acetaldehyde (2.94)

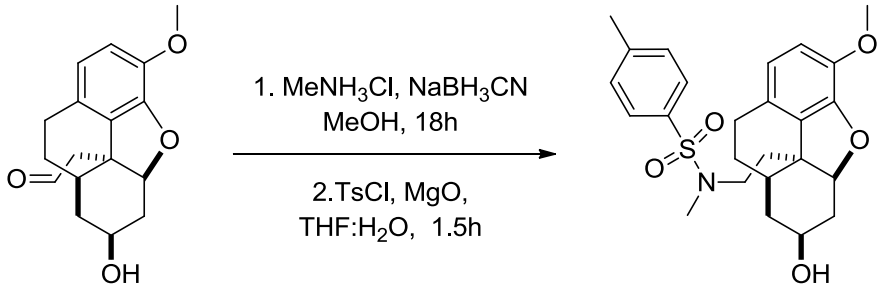



**2.91** **2.94**

**Procedure**: The alcohol **2.91** (42.1 mg, 0.14 mmol) was placed in a flask and a 3:1 THF:Water mixture was added (8 mL). Osmium tetroxide in water (4% w/w, 0.14 mL, 0.022 mmol) was added dropwise and the solution was left to stir until the solution did not get any darker (it should turn brown-black, and can take up to 20-30 min to do so). At that point, NMO (25.8 mg, 0.21 mmol) was added and the solution was stirred until complete starting material consumption by TLC (80% ethyl acetate/hexanes) (this can take between 3 to 5 hours). Then, sodium periodate was added (78 mg, 0.36 mmol) and the solution was stirred until complete consumption of the triol by TLC (around 40 minutes). It is important to not let the solution stir too long with sodium periodate, stop the reaction as soon as you notice disappearance of the triol, the solution should be beige-white at that point. The reaction was quenched with a $Na_2SO_3$ sat. solution (5 mL) and extracted with diethyl ether (4 x 10 mL). The combined mixture of organics was dried on magnesium sulfate and concentrated *in vaccuo*. Rapid flash chromatography of the obtained crude on a triethylamine treated silica column (80% ethyl acetate/hexanes) yielded a white solid (37.3 mg, 0.129 mmol, 88%).

**IR** (neat, $cm^{-1}$) 2933 (br), 1717 (vs), 1504 (s), 1439(m), 1276 (m)
**1H-NMR** (400 MHz; $CDCl_3$): δ 9.65 (s, 1H), 6.73 (d, *J* = 8.2, 1H), 6.63 (d, *J* = 8.2, 1H), 4.98 (dd, *J* = 9.6, 7.4, 1H), 3.83 (s, 3H), 3.69 (tt, *J* = 11.7, 3.5, 1H), 2.78-2.64 (m, 3H), 2.56 (ddd, *J* = 17.7, 11.5, 7.0, 1H), 2.32-2.27 (m, 2H), 2.09-1.99 (m, 1H), 1.80-1.64 (br, s, OH, 1H), 1.78-1.69 (m, 2H), 1.13 (tdd, *J* = 24.0, 11.4, 10.2, 2H)
**13-C NMR** (100 MHz; $CDCl_3$): δ 201.3(CHO), 144.7(C4), 143.9(C4), 129.5(C4), 126.0(C4), 121.0(CH), 114.1(CH), 89.1(CH), 66.3($CH_3$), 56.7(CH), 50.7($CH_2$), 44.0(C4), 37.9($CH_2$), 35.5($CH_2$), 33.2(CH), 24.0($CH_2$), 20.9 ($CH_2$)
**HRMS** (EI) m/z calcd for $C_{17}H_{20}O_4$ ($M^+$) 288.1362, found 288.1376.

## 2-Hydroxy-5-methoxy-1,2,3,3a,3a1,8,9,9a-octahydrophenanthro[4,5-bcd]furan-3a1-yl)ethyl)-N,4-dimethylbenzenesulfonamide (2.95)



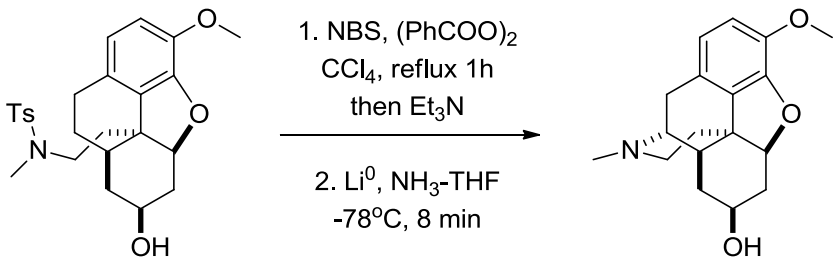

**2.94** **2.95**

**Procedure**: The aldehyde **2.94** (167.7 mg, 0.58 mmol) was placed in a dry flask. To this flask, methanol (12 mL), methyl amine hydrochloride (216 mg, 3.2 mmol) and sodium cyanoborohydride (182 mg, 2.9 mmol) were added in that order. The solution was stirred under argon at room temperature for 18hr. A solution of sodium hydroxide (6 mL, 0.5M) was added to quench the reaction and the solution was stirred for 5-10 min. The mixture was extracted 5 times with chloroform (8 mL). The organics were dried with magnesium sulfate and evaporated *in vaccuo*.

The crude mixture was then placed in a flask and a THF:Water (10 mL) solution was added. Powdered magnesium oxide was then added (MgO, 110mg, 2.7 mmol) followed by freshly recrystallized p-toluenesulfonyl chloride (104.7 mg, 0.55 mmol). The solution was stirred for 1.5h at room temperature. Upon reaction completion, the mixture was filtered on celite, sat. $NaHCO_3$ (5 mL) was added and extracted 3 times with ethyl acetate. The combined organic extract was dried on magnesium sulfate and evaporated *in vaccuo*. Flash chromatography of the resulting crude mixture (65% ethyl acetate/hexanes) yielded a yellow foam (160.7 mg, 0.35 mmol, 60% over 2 steps). If there is a problem obtaining the yellow foam, just adding a minimal amount of DCM and placing on high-vacuum might provoke its formation.

**IR** (neat, $cm^{-1}$) 2933(br, s), 1500(s), 1462(s), 1439(s), 1329(s), 1276(s), 1154(vs)
**1H-NMR** (400 MHz; $CDCl_3$): δ 7.63 (d, *J* = 8.3, 2H), 7.30 (d, *J* = 8.0, 2H), 6.72 (d, *J* = 8.2, 1H), 6.63 (d, *J* = 8.2, 1H), 4.92 (dd, *J* = 9.4, 7.4, 1H), 3.84 (s, 3H), 3.61 (tt, *J* = 11.6, 3.5, 1H), 3.20-3.13 (m, 1H), 2.96 (ddd, *J* = 13.6, 9.1, 6.0, 1H), 2.76-2.69 (m, 1H), 2.68 (s, 3H), 2.62-2.53 (m, 1H), 2.42 (s, 3H), 2.36-2.26 (m, 2H), 2.10 (dddd, *J* = 14.9, 11.3, 7.5, 3.9, 1H), 1.94-1.86 (m, 1H), 1.77-1.67 (m, 3H), 1.25 (s, 1H), 1.12 (tdd, *J* = 16.4, 11.5, 10.0, 2H)
**13-C NMR** (100 MHz; $CDCl_3$): δ 144.6(C4), 143.65(C4), 143.53(C4), 134.5(C4), 130.7(C4), 129.9(CH), 127.5(CH), 125.9(C4), 120.8(CH), 113.7(CH), 88.4(CH), 66.4(CH), 56.7(CH3), 46.6(CH2), 44.6(C4), 38.3($CH_2$), 35.7($CH_2$), 35.00($CH_3$), 34.85(CH2), 32.3($CH_3$), 23.9($CH_2$), 21.7(CH), 21.1($CH_2$)
**HRMS** (EI) m/z calcd for $C_{25}H_{31}NSO_5$ ($M^+$) 457.1922, found 457.1912

## 9-Methoxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro [3,2-e]isoquinolin-6-ol (2.93)




**2.95** **2.93**

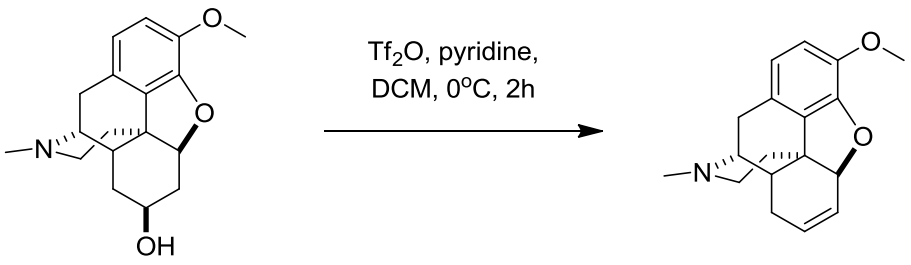
**Procedure**: Dry $CCl_4$ (21 mL, distilled over $CaH_2$) was refluxed for degassing during 10 min under argon. It was then taken out of the oil bath for 5 min. Tosylamine **2.95** (45.7 mg, 0.1 mmol), crystalline-white NBS (18.7 mg, 0.105 mmol) and wet benzoyl peroxide (75% w/w, 1.9 mg, 0.006 mmol) were added to the flask in that order. The flask was refluxed for 45 min, and more benzoyl peroxide (0.9 mg, 0.003 mmol) was added, followed by another 30 min of reflux. Then, triethylamine (6 ml) was added via the reflux condenser with a long needle right into the core of the flask over the solution. The reaction mixture was kept refluxing for 15 min (the solution should blurry at that point). The flask was taken out of the oil bath and allowed to cool down to room temperature. The solution was extracted with aqueous sat. $NaHCO_3$ (~10 mL), followed by aqueous sat. $Na_2S_2O_3$ (~10mL). The aqueous phases were combined and back extracted with chloroform (3 x 10 mL). The organics (chloroform and $CCl_4$) were combined, dried over magnesium sulfate, and evaporated *in vaccuo*. The resulting crude was purified by flash chromatography (60% ethyl acetate/ hexanes) and yielded 40 mg of an inseparable mixture of the wanted unsaturated product **2.99** and starting material **2.95** (2.5:1).

Using a cold-finger and dry-ice, ammonia (~5 mL) was condensed into a flame-dried flask at -78°C. A mixture of dry THF and tert-butanol (22 mg of tBuOH, 0.30 mmol in 5 mL of THF) was syringed in the flask and it was stirred and allowed to mix with the liquid ammonia. Lithium metal was then added (~5.5 mg, or 1 granule/cube) and the solution was vigorously stirred at -78°C until it assumed a deep blue color. At that point, a solution of a portion of this 3:1 mixture isolated above in THF (18mg in 0.5mL THF, container A) was added drop-wise slowly via the side-neck of the flask, followed by an extra 0.5mL of THF used to clean the original container A of all the starting material left. The blue color should discharge somewhat rapidly to assume a clear appearance during the addition. As soon as the addition is complete, one granule of Lithium metal was added via the side-neck and the solution was stirred vigorously until it regained a deep blue colour (Depending on the scale of the reaction, it might take several minutes (3-10) and several granules (2-4) of lithium for the solution to regain its blue color. If done on at least three times this scale, the lithium granules can be shortly submerged in methanol to clear their metal coating before being added to the reaction flask). As soon as the reaction has regained its blue colour, let it stir for between 5 and 8 minutes (depending on the amount of time it took to reach lithium saturation. More than that amount of time has shown product of aromatic over-reduction). The reaction was then quenched very rapidly at -78°C with 10 mL of a 1:1 mixture of sat. $NH_4Cl$:MeOH. The solution was left to warm-up to room-temperature (be careful of built up pressure due to ammonia). The solution was extracted with DCM(4 x 20mL) and evaporated *in vaccuo* to get rid of the methanol. DCM was then added, the solution was dried with magnesium sulfate, filtered and evaporated *in vaccuo* again to obtain a crude mixture. Flash chromatography of this crude mixture (10% MeOH in DCM with 1% of

fresh undiluted ammonium hydroxide) on a short column with a fast flow provided the pentacyclic product(7.7 mg, 0.026 mmol, 57% over 2 steps) as a white foam and some recovered methyl-amine **2.98** (3.3 mg, 0.011 mmol, 24%).

**IR** (neat, $cm^{-1}$) 3378(vb, m), 2930 (b, s), 1607(w), 1505(s), 1440(s), 1272(s)
**1H-NMR** (400 MHz; $CDCl_3$): δ 6.72 (d, *J* = 8.2, 1H), 6.64 (d, *J* = 8.2, 1H), 4.70 (dd, *J* = 8.8, 7.7, 1H), 3.86 (s, 3H), 3.61 (tt, *J* = 11.6, 3.6, 1H), 3.10 (s, 1H), 3.03 (d, *J* = 18.4, 1H), 2.53 (d, *J* = 9.9, 1H), 2.41 (s, 3H), 2.41-2.36 (m, 2H), 2.24-2.14 (m, 2H), 1.80-1.66 (m, 3H), 1.25 (td, *J* = 12.5, 9.1, 1H), 1.00 (q, *J* = 12.2, 1H)
**13-C NMR** (100 MHz; $CDCl_3$): δ 144.01(C4), 143.91(C4), 129.8(C4), 126.9(C4), 119.2 (CH), 113.6 (CH), 89.2(CH), 66.8($CH_3$), 59.8($CH_3$), 56.6(CH), 47.6 ($CH_2$), 42.9(CH), 42.1(C4), 40.6 (CH), 38.8 ($CH_2$), 35.0 ($CH_2$), 34.5 ($CH_2$), 20.2 ($CH_2$)
**HRMS** (EI) m/z calcd for $C_{18}H_{23}NO_3$ ($M^+$) 301.1678, found 301.16797.

## 9-Methoxy-3-methyl-2,3,4,4a,5,7a-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinoline (2.100)

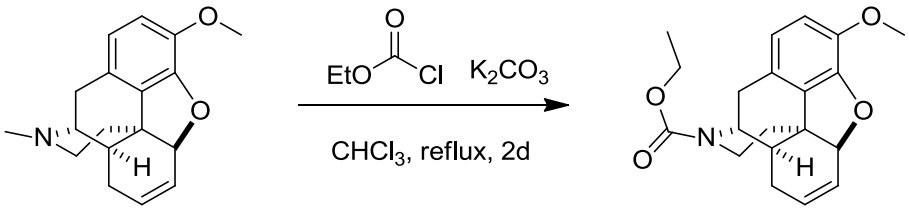



**2.93** **2.100**

**Procedure**: To the starting amine **2.93** (16.1 mg, 0.053mmol) in a flame-dried flask was added dry dichloromethane (1 mL) and distilled pyridine (12.7 mg, 0.16 mmol). The mixture was placed in an ice-cold bath and stirred for 5 min. Trifluoromethanesulfonic anhydride (13.5 uL, 0.08 mmol) was added dropwise and the mixture was left to stir under argon at 0°C for 2 hours. Ice cold water and sat. $NaHCO_3$ solution were then added successively (both ~ 1 mL) and the mix was left to stir for 5 min. The layers were separated and the aqueous was extracted with dichloromethane (3x2 mL). The organics solution was dried over magnesium sulfate, filtered and evaporated in vaccuo. Flash chromatography of the resulting crude (9% MeOH:DCM) yielded a viscous yellow oil (10.5 mg, 0.037 mmol, 70%).

**IR** (neat, $cm^{-1}$) (vs) 2925, (s)2838, (s)2796, (s)1629, (s)1603, (v)1504, (v)1440, (s) 1275, (s) 1151
**1H-NMR** (400 MHz; $CDCl_3$): δ 6.70 (d, *J* = 8.2, 1H), 6.62 (d, *J* = 8.2, 1H), 5.85 (ddd, *J* = 10.3, 5.7, 2.0, 1H), 5.70 (dtd, *J* = 10.3, 3.3, 0.9, 1H), 4.96 (s, 1H), 3.85 (s, 3H), 3.14 (dd, *J* = 6.1, 2.8, 1H), 3.02 (d, *J* = 18.6, 1H), 2.57 (dd, *J* = 12.1, 4.0, 1H), 2.47-2.42 (m, 1H), 2.43 (s, 3H) 2.30 (td, *J* = 12.2, 3.7, 1H), 1.98-1.89 (m, 3H), 1.81 (ddd, *J* = 12.5, 3.7, 1.8, 1H), 1.53 (dddt, *J* = 14.4, 11.6, 5.6, 2.8, 1H)
**13-C NMR** (100 MHz; $CDCl_3$): δ 144.9 (C4), 143.4(C4), 132.2(CH), 129.7(C4), 127.1(C4), 124.8(CH), 118.7(CH), 113.1(CH), 87.8(CH), 59.4($CH_3$), 56.5(CH), 47.1($CH_2$), 43.2(CH), 40.9(C4), 39.0($CH_3$), 35.6($CH_2$), 24.5($CH_2$), 20.1($CH_2$)
**HRMS** (EI) m/z calcd for $C_{18}H_{21}NO_2$ ($M^+$) 283.1572 found 283.1556

## Ethyl 9-methoxy-4,4a,5,7a-tetrahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinoline-3(2H)-carboxylate (2.101)



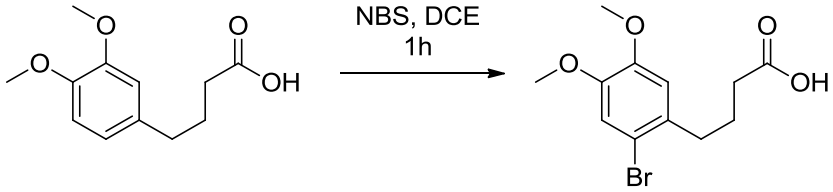

**2.100** **2.101**

**Procedure**: Starting amine **2.100** (9 mg, 0.031 mmol) was placed in a flame dried sealable vial under argon and dry chloroform (1 mL) was added. This was followed by the addition of potassium carbonate (27.5 mg, 0.19mmol), and ethyl chloroformate(10.8 mg, 0.093 mmol). The vial was sealed and placed at reflux in an oil bath for 48hours. Water (1mL) was added and the layers were separated. The aqueous layer was extracted with chloroform (2x 1 mL) and the organics were combined, dried over magnesium sulfate, filtered and evaporated *in vaccuo.* Flash chromatography (30% EtOAc:Hexanes) provided a clear yellow oil (5.5 mg, 0.016mmol, 52%).

**IR** (neat, $cm^{-1}$) (br) 2979, (br, s)2931, (m)2838, (w)2820 (vs) 1694
**1H-NMR** (400 MHz; $CDCl_3$): δ 6.73 (1H, d, *J* = 8 Hz), 6.62 (1H, d, *J* = 8 Hz), 5.85 (ddd, *J* = 10.3, 5.6, 1.9, 1H), 5.71 (1H, d, *J* = 10 Hz)), 4.95 (1H, s), 4.71 (major rotamer 0.58 H), 4.56 (minor rotamer 0.42 H), 4.15 (2H, m), 4.1-3.93 (1H, m), 3.85 (3H, s), 3.05-2.85 (2H, m), 2.68 (1H, d, J = 18 Hz), 2.30-2.25 (1H, m), 2.00 (1H, m), 1.90-1.70 (2H, m), 1.53-1.40 (1H, m), 1.26 (3H, m).
**13-C NMR** (100 MHz; $CDCl_3$): δ **Major rotamer**: δ 155.4, 144.9, 143.4, 131.8, 128.5, 125.8, 124.4, 118.9, 113.3, 87.4, 61.4, 56.2, 50.2, 41.1, 37.9, 37.8, 35.0, 28.8, 24.1, 14.7. **Minor rotamer**: δ 155.1, 144.7, 143.4, 131.6, 128.5, 125.6, 124.7, 118.9, 113.3, 87.4, 61.4, 56.2, 50.7, 41.1, 37.9, 37.8, 34.7, 29.0, 24.2, 14.6.
**HRMS** (EI) m/z calcd for $C_{20}H_{23}NO_4$ ($M^+$) 341.1627 found 341.1648
Data identical to previously reported characterization from Magnus (2009) and Taber (2002)

## 3.2 KASSANDRA LEPACK RELEVANT EXPERIMENTAL

### 3-(2-Bromo-4,5-dimethoxyphenyl)butyric acid (2.2)

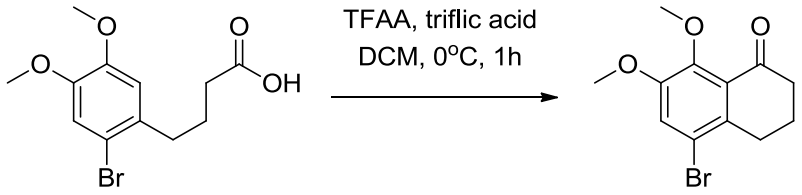



**2.1** **2.2**

**Procedure:** NBS (19.7g, 110.73 mmol) and $AuCl_3$ (100 mg, 0.33 mmol) were weighed in a round bottom flask. DCE (75.00 mL) and 4-(3,4-dimethoxyphenyl)butyric acid (24.6 g, 109.69 mmol) were added in succession. The mixture was left to stir for 45-1hr minutes at room temperature. The reaction was monitored by NMR analysis. The reaction mixture was then evaporated *in vaccuo* to afford a mixture of product and NHS in quantitative yield.

Based on the characterization data from Kassandra Lepack:
**1H-NMR** ($CDCl_3$, 400 MHz) $\delta$ ppm 7.00 (s, 1H), 6.71 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.73 (t, *J*=7.49 Hz, 2 H), 2.42 (t, *J*=7.45 Hz, 2 H)
**HRMS** (EI) m/z calculated for $C_{12}H_{15}O_4Br_1$ $(M)^+$ 302.0154, found 302.0290.

## 5-Bromo-7,8-dimethoxy-3,4-dihydronaphthalen-1(2H)-one (2.3)




**2.2** **2.3**

**Procedure :** To a stirred solution of **2.2** (1.00 g, 3.30 mmol) in dry DCM (5.00 mL, 78.30 mmol) at 0 °C was cannulated a dropwise mixture of trifluoroacetic anhydride (0.50 mL, 3.63 mmol) and freshly distilled triflic acid (0.29 mL, 3.30 mmol ) also cooled to 0 °C. The dark red solution was left to stir at 0 °C for one hour and then brought to room temperature and monitored by TLC. An ice-cold saturated aqueous $NaHCO_3$ solution (10 mL) was added to the reaction mixture and left to quench for one hour. The aqueous layer was then extracted with ether (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated in *vaccuo* to provide a dark yellow oil. Purification by flash chromatography (15 % ethyl acetate in hexanes) afforded the brominated tetralone as a light yellow solid (580.7 mg, 2.04 mmol, 62%).

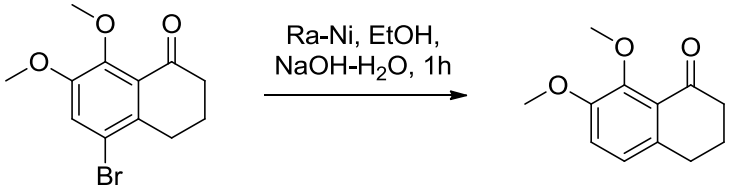
Based on the characterization data from Kassandra Lepack:

**1H-NMR** ($CDCl_3$, 400 MHz) $\delta$ 7.28 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.90 (t, *J*=6.30 Hz, 2 H), 2.61 (t, *J*=6.37 Hz, 2 H), 2.08 (quin, *J=6.50* Hz, 2 H)

**13C-NMR** (100 MHz; $CDCl_3$): δ 197.1 (C4), 152.5 (C4), 149.3 (C4), 135.4 (C4), 128.8 (C4), 120.9 (CH), 118.1 (C4), 61.4 ($CH_3$), 56.4 ($CH_3$), 40.1($CH_2$), 30.3 ($CH_2$), 22.3($CH_2$)

**HRMS** (EI) m/z calculated for $C_{12}H_{13}O_3Br_1$ $(M)^+$ 284.0048, found 284.0045.

## 7,8-Dimethoxy-3,4-dihydronaphthalen-1(2H)-one (2.4)

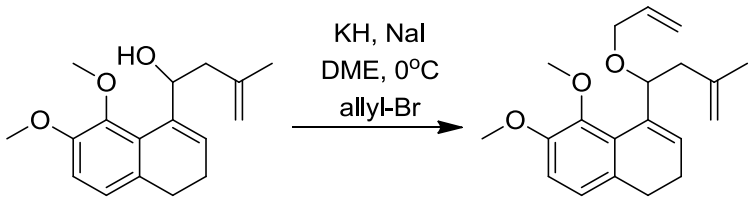



**2.3** **2.4**

**Procedure :** Raney-Ni (7.00 g, 119.24 mmol) was gradually added to a mixture of **2.3** (1.00 g, 3.51 mmol) in ethanol (20 mL, 342.52 mmol) and a 5% aqueous solution of NaOH (56 mL). The reaction mixture was left to stir for 30 minutes at 90°C and then cooled to room temperature for an additional 30 minutes. The solution was then filtered through celite and washed with EtOAc. After extraction with 3 x 40 mL of EtOAc, the organic phase was dried over $MgSO_4$ and evaporated in *vaccuo*. Purifaction of the greenish solid by flash chromatography in 18% EtOAc/hexanes yielded 67% of the white solid tetralone (0.49 g, 2.36 mmol).

Matches previously reported characterization[44]

## 4-(1-(Allyloxy)-3-methylbut-3-enyl)-5,6-dimethoxy-1,2-dihydronaphthalene (2.8)




**2.7** **2.8**

**Procedure**: In a flask was placed KH (30 % in oil, 126.5 mg, 0.95 mmol) which was washed with hexanes to remove the oil then dried under high vacuum. NaI (3.5 mg, 0.02 mmol) was placed in a separate flask and flame dried. The solids were suspended in DME (10.5 mL) and NaI was canulated to the KH containing flask. This suspension was cooled to 0 °C after which was added a solution of **2.7** (64.9 mg, 23.7 mmol) in DME (3.1 mL). The resulting mixture was stirred for 10 minutes whereupon it was treated with allyl bromide (0.04 mL, 4.97 mmol). This final mixture was stirred at 0 °C for 1 hour then for 2 hour at room temperature. The reaction was quenched by the addition of water and the layers were separated. The aqueous phase was extracted with $Et_2O$ (3 × 10 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography in 20% EtOAc : hexanes gave **2.8** (69.2 mg, 0.22 mmol) as a colorless oil with a 92% yield.

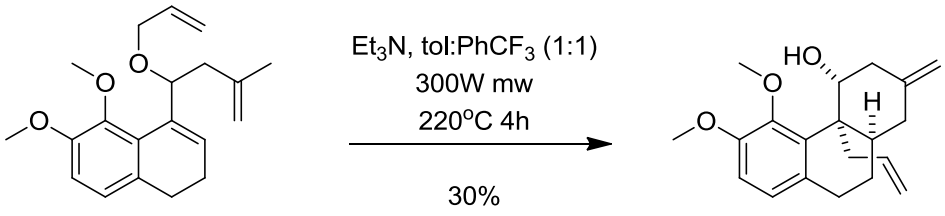
**IR** (neat, $cm^{-1}$) 3075.5 (m), 2935(s, br), 2833(s br), 1645(s), 1569(vs), 1472(vs), 1418(s), 1261(s).

**1H-NMR** (400 MHz; $CDCl_3$): δ 6.89 (d, *J* = 8.1, 1H), 6.72 (d, *J* = 8.1, 1H), 6.44 (ddd, *J* = 5.7, 4.4, 1.2, 1H), 5.97 (dddd, *J* = 17.2, 10.4, 5.8, 5.2, 1H), 5.28 (dq, *J* = 17.2, 1.8, 1H), 5.14 (dq, *J* = 10.4, 1.6, 1H), 5.05 (dd, *J* = 8.2, 1.2, 1H), 4.76 (dt, *J* = 6.3, 1.0, 2H), 4.12 (d, *J* = 5.2, 1H), 3.94 (d, *J* = 5.9, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 2.60-2.56 (m, 2H), 2.40 (d, *J* = 14.7, 1H), 2.23-2.09 (m, 3H), 1.80 (s, 3H)

**13-C NMR** (100 MHz; $C_3D_6O$): δ 153.0 (C4), 146.7 (C4), 144.6 (C4), 139.3 (C4), 136.9 (CH), 132.1 (C4), 128.4 (C4), 126.1 (CH), 123.5 (CH), 115.7 ($CH_2$), 112.1 ($CH_2$), 111.7 (CH), 78.4 (CH), 70.59 ($CH_2$), 60.7 ($CH_3$), 56.1 ($CH_2$), 45.7 ($CH_2$), 29.7 ($CH_2$), 23.6($CH_2$), 23.3 ($CH_3$)

**HRMS** (EI) m/z calcd for $C_{20}H_{26}O_3$ ($M^+$) 314.1882, found 314.1872.

## 4a-Allyl-5,6-dimethoxy-2-methylene-1,2,3,4,4a,9,10,10a-octahydrophenanthren-4-ol (2.9a)




**2.8** **2.9a**

**Procedure**: A sample of **2.8 (**100 mg, 0.31 mmol) was dissolved in toluene: trifluorotoluene (1:1) (3 mL) and placed in a microwave vessel for the CEM Corporation Discover microwave reactor, and $Et_3N$ (0.1 mL, 0.71 mmol) was added. The reaction mixture was then degassed for 15 minutes by bubbling with a stream of argon gas. The mixture was then irradiated with microwaves and heated to 220°C over 10 minutes, then for 4 hours at 220 °C. Upon cooling, the reaction mixture was concentrated and the product was recovered by flash chromatography in 15 % EtOAc/hexanes, affording **2.9** (30 mg, 0.095 mmol, 30 %) as a white waxy solid.

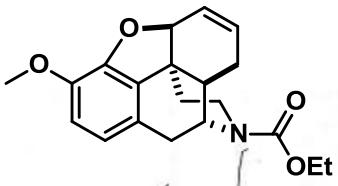
Based on the characterization data from Kassandra Lepack:

**1H-NMR** (400 MHz; $C_6D_6$): $\delta$ ppm 6.69 (dt, J=8.40 Hz, 0.89 Hz, 1H), 6.50 (d, J=8.33 Hz, 1H), 5.83 (m, 1H), 5.04 (t, J=1.32 Hz, 0.78 Hz, 1H) 4.96 (dddd, J=2.40 Hz, 1.62 Hz, 0.88 Hz, 2H), 4.92 (br s, 1H), 4.75 (dd, J=7.25 Hz, 0.88 Hz, 2H), 3.67 (s, 3H), 3.28 (s, 3H), 3.19 (dd, J=14.55 Hz, 5.34 Hz, 1H) 2.76 (dd, J=14.94 Hz, 8.38 Hz, 1H), 2.66 (m, 2H), 2.57 (dd, J=13.37 Hz, 3.48 Hz, 1H), 2.41 (dd, J=13.42 Hz, 7.64 Hz, 1H), 2.22 (m, 1H), 2.14 (tt, J=7.74 Hz, 3.87 Hz, 1H), 1.94 (dd, J=13.18 Hz, 7.59 Hz, 1H)

**13-C NMR** (100 MHz; $C_6D_6$): $\delta$ ppm 151.4(C4), 149.1(C4), 145.2(C4), 137.5(CH), 134.1(C4), 130.8(C4), 125.6(CH), 116.4($CH_2$), 112.1(CH), 110.4(CH2), 73.7(CH), 60.4($CH_3$), 55.6($CH_3$), 47.3(C4), 40.7($CH_2$), 38.0(CH), 37.0($CH_2$), 28.39($CH_2$), 28.33($CH_2$), 24.4($CH_2$)

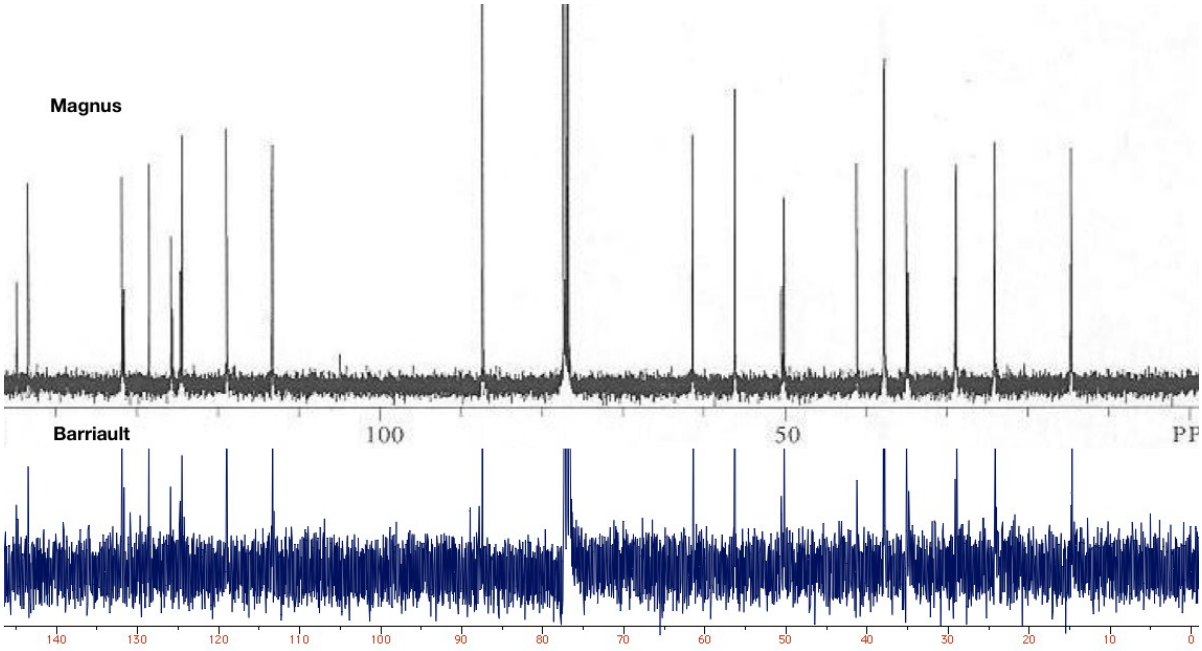
**HRMS** (EI) m/z calculated for $C_{20}H_{26}O_3$ $(M)^+$ 314.1882, found 314.1865.

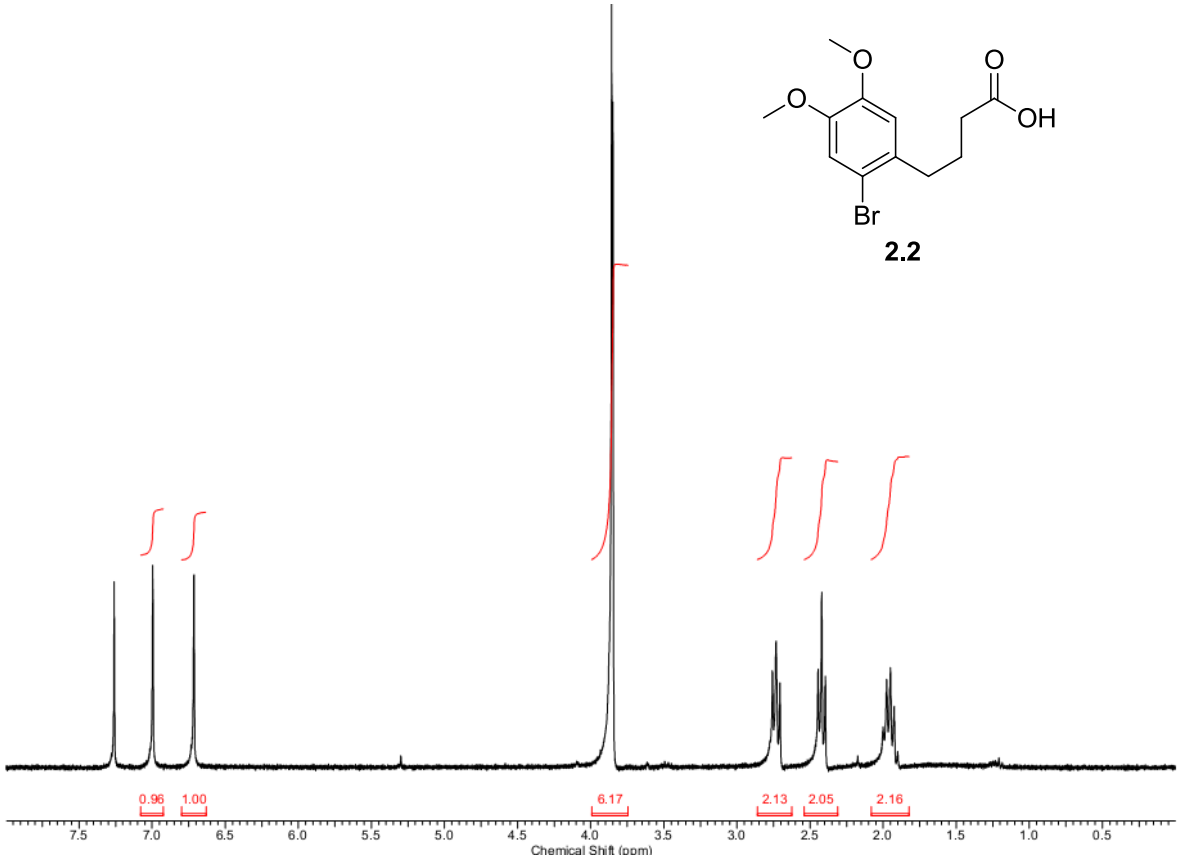
## 3.3 SPECTROSCOPIC DATA







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6.17
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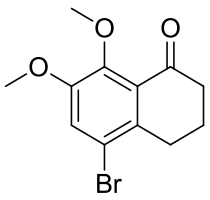
2.05
2.16
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

**2.2**


O
O
O
Br

**2.3**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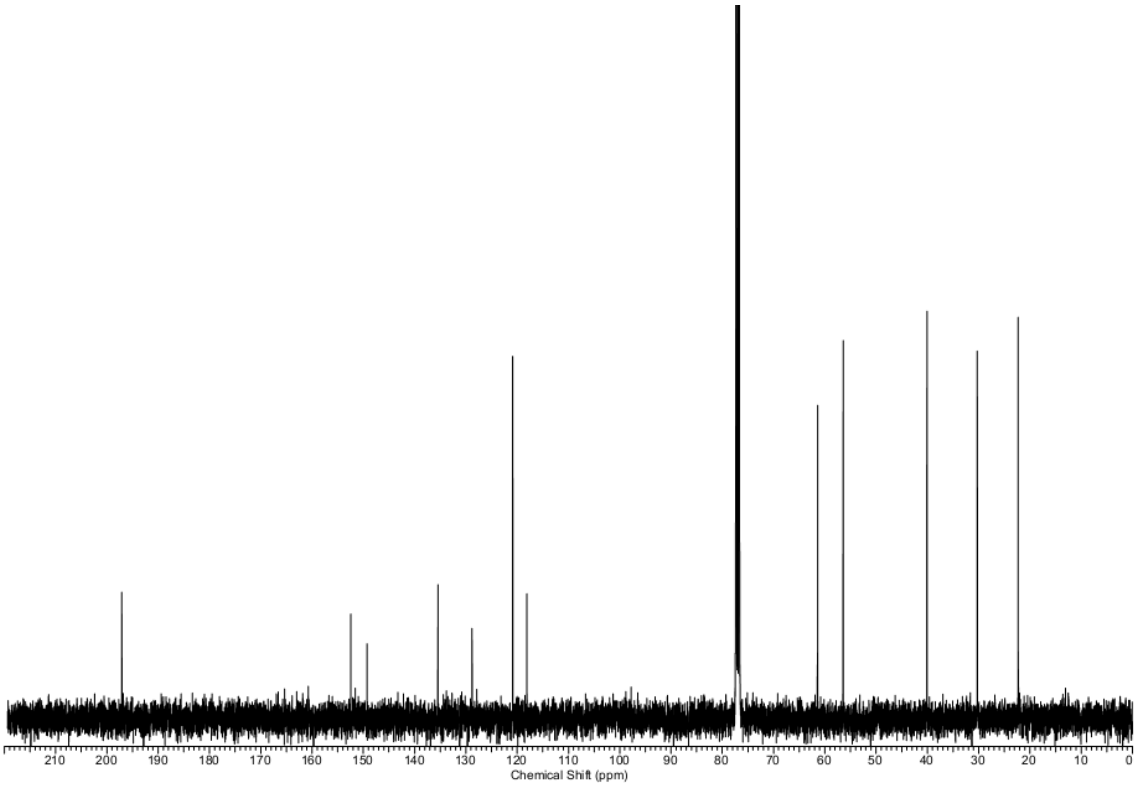
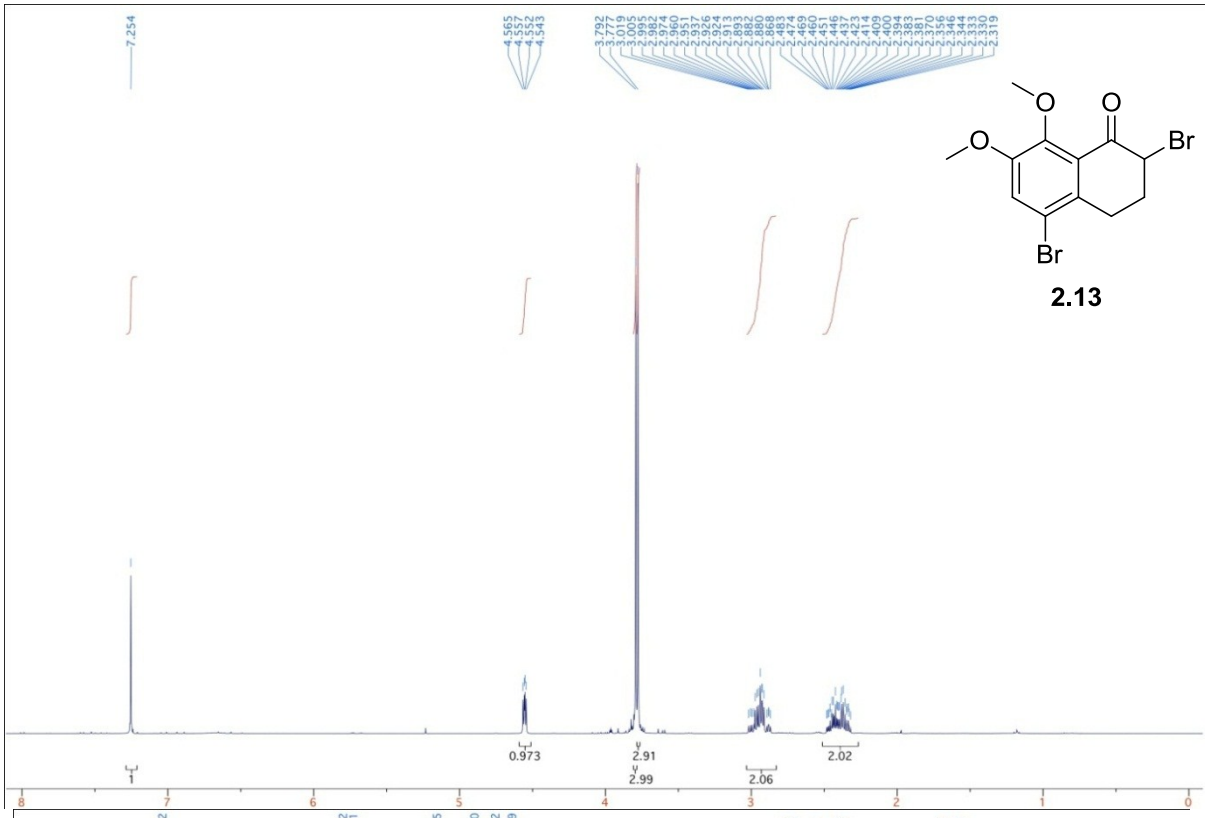
6.11
2.02
2.02
2.04
Chemical Shift (ppm)


Chemical Shift (ppm)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3.792
3.777
3.019
3.005
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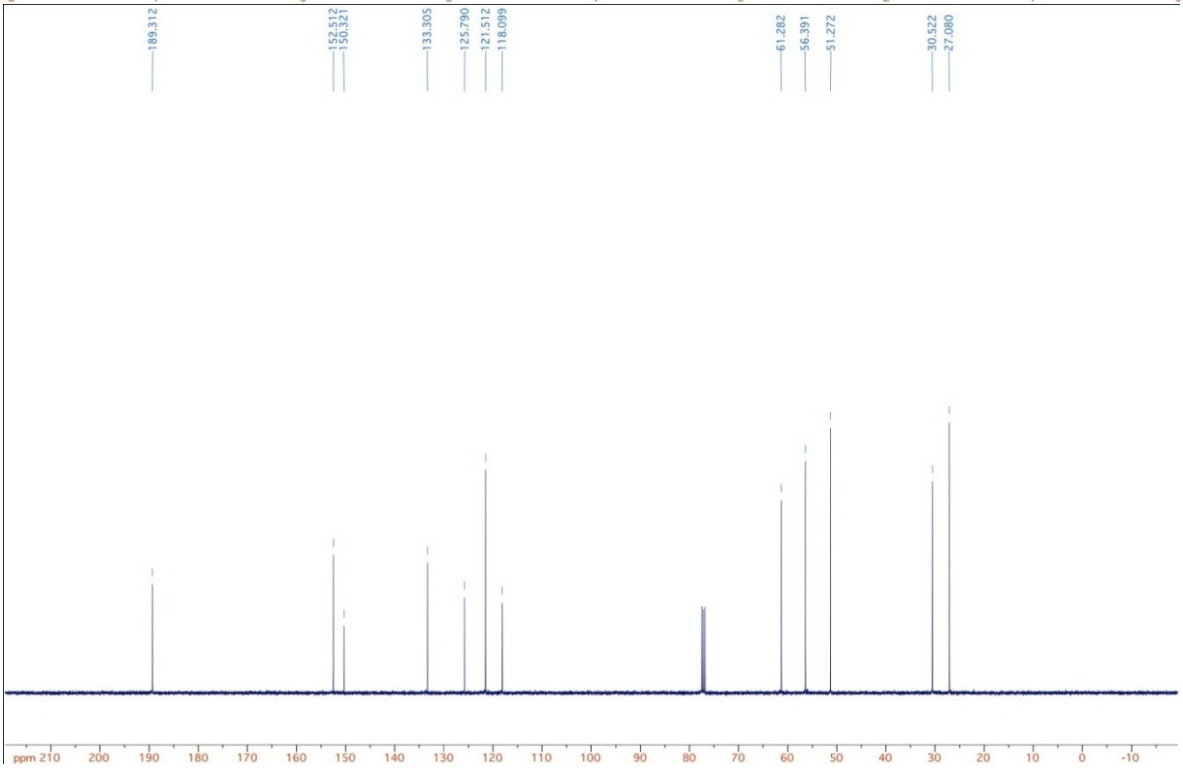
2.951
2.937
2.926
2.924
2.913
2.893
2.882
2.880
2.868
2.863
2.474
2.469
2.460
2.451
2.446
2.437
2.423
2.414
2.409
2.400
2.394
2.383
2.381
2.370
2.356
2.346
2.344
2.333
2.330
2.319
O
O
O
Br
Br
0.973
2.91
2.99
2.06
2.02
1
8
7
6
5
4
3
2
1
0

**2.13**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150.321
133.305
125.790
121.512
118.099
61.282
56.391
51.272
30.522
27.080
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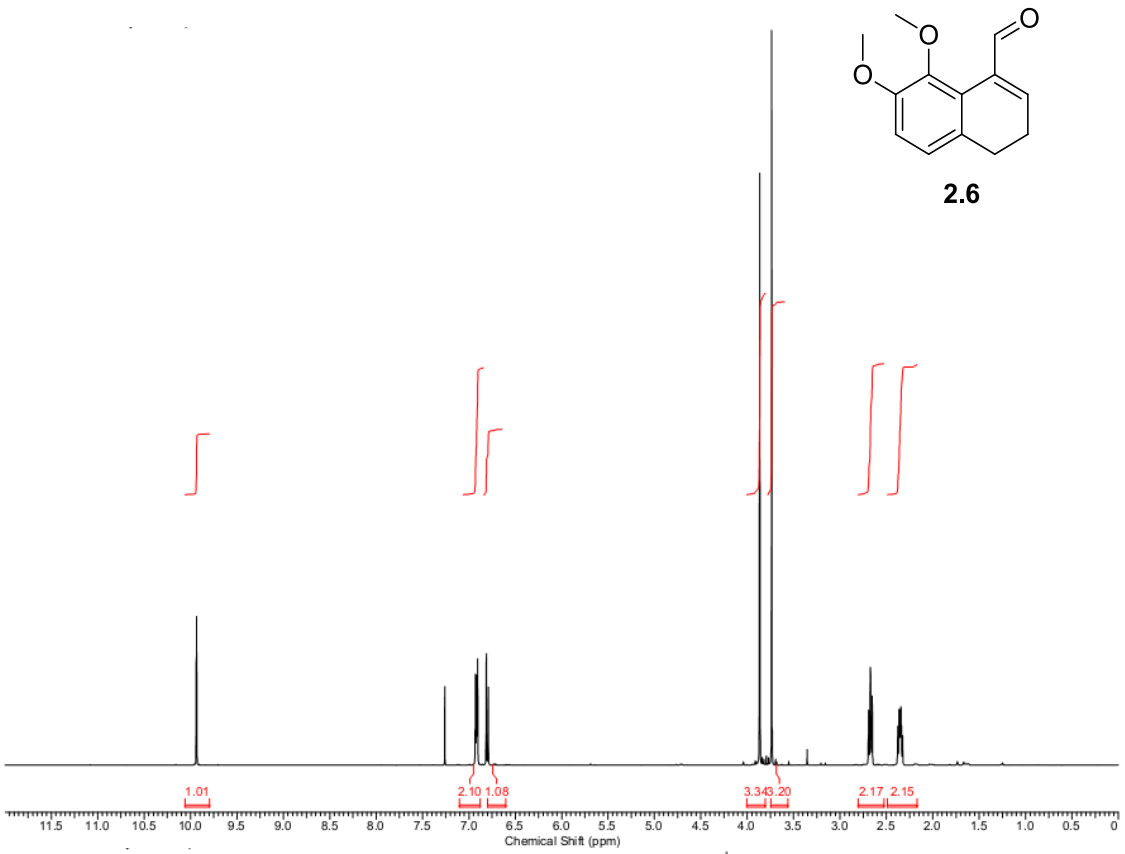
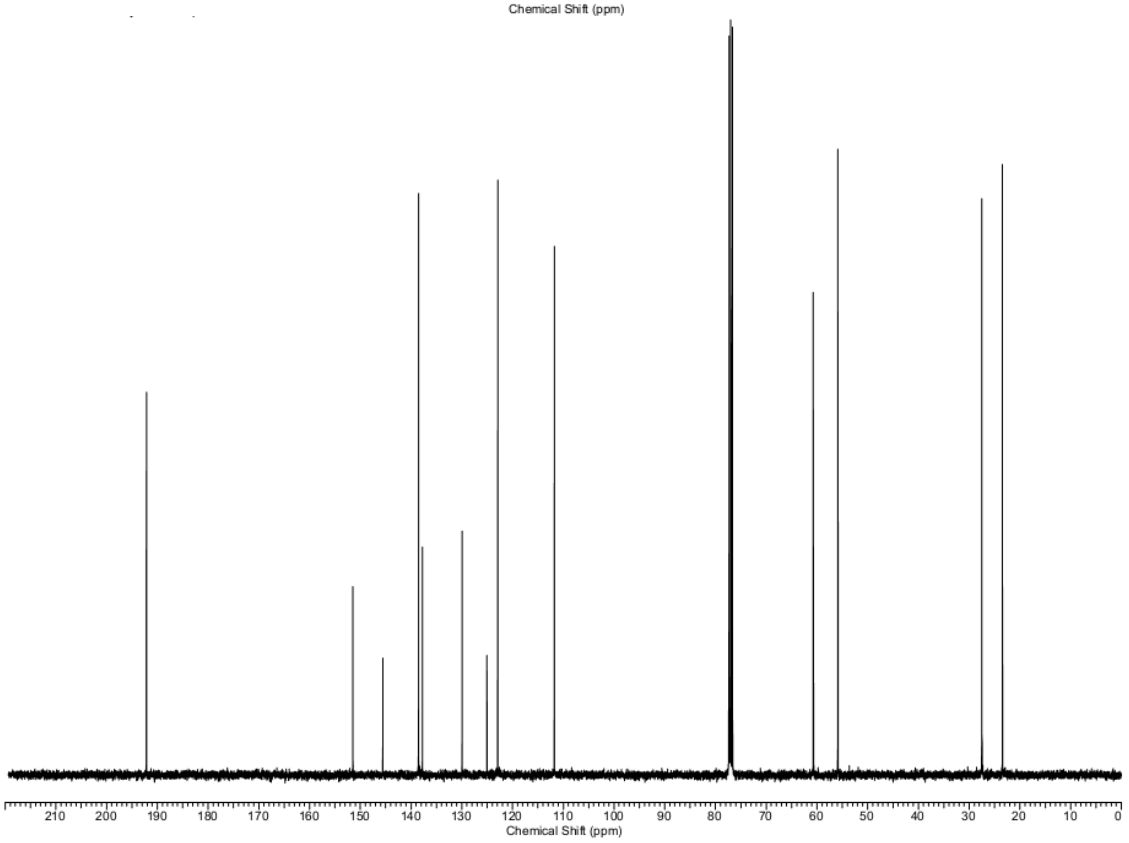
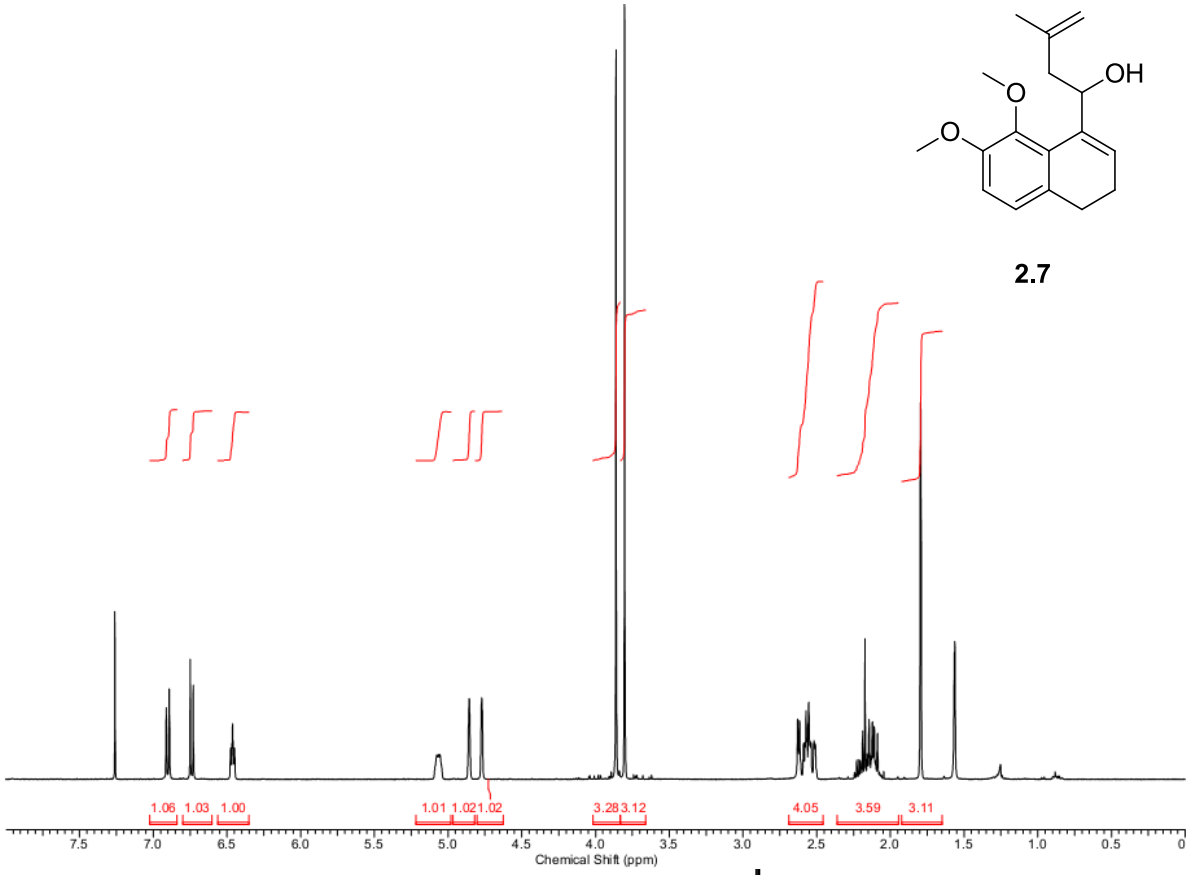
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


1.01
2.10
1.08
3.34
3.20
2.17
2.15
Chemical Shift (ppm)

**2.6**


Chemical Shift (ppm)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O
O
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1.00
1.01
1.02
1.02
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3.12
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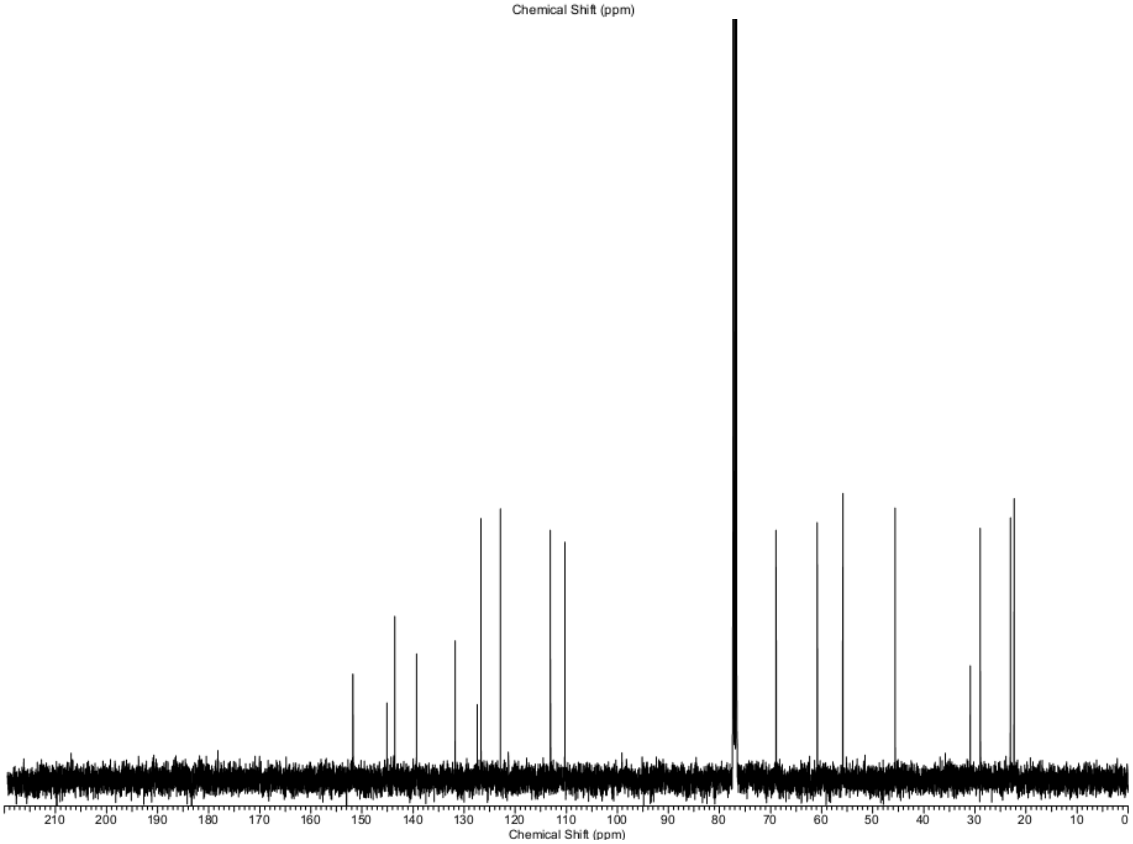
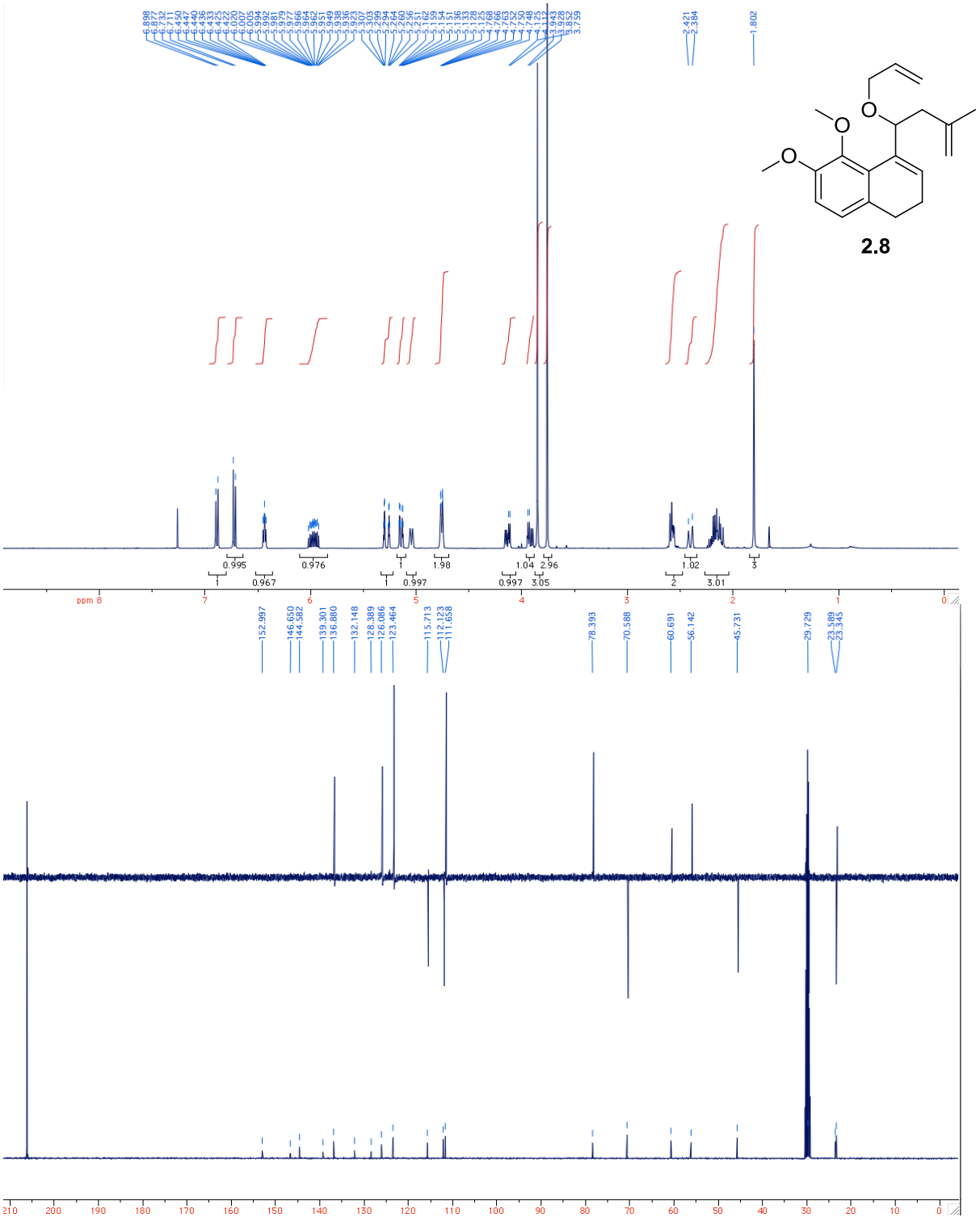
3.59
3.11
Chemical Shift (ppm)

**2.7**


Chemical Shift (ppm)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6.447
6.440
6.436
6.433
6.430
6.422
6.020
6.007
6.005
5.994
5.992
5.981
5.979
5.977
5.966
5.964
5.962
5.951
5.949
5.938
5.936
5.933
5.303
5.299
5.294
5.264
5.260
5.256
5.251
5.162
5.159
5.154
5.151
5.146
5.133
5.128
5.125
4.768
4.766
4.763
4.752
4.750
4.748
4.744
4.172
4.170
3.943
3.928
3.922
3.759
2.421
2.384
1.802
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O
O
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0.967
0.976
1
0.997
1.98
0.997
1.04
3.05
2.96
1.02
3.01
3
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7
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5
4
3
2
1
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136.880
132.148
128.389
126.086
123.464
115.713
112.123
111.658
78.393
70.588
60.691
56.142
45.731
29.729
23.589
23.345
210
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150
140
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70
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30
20
10
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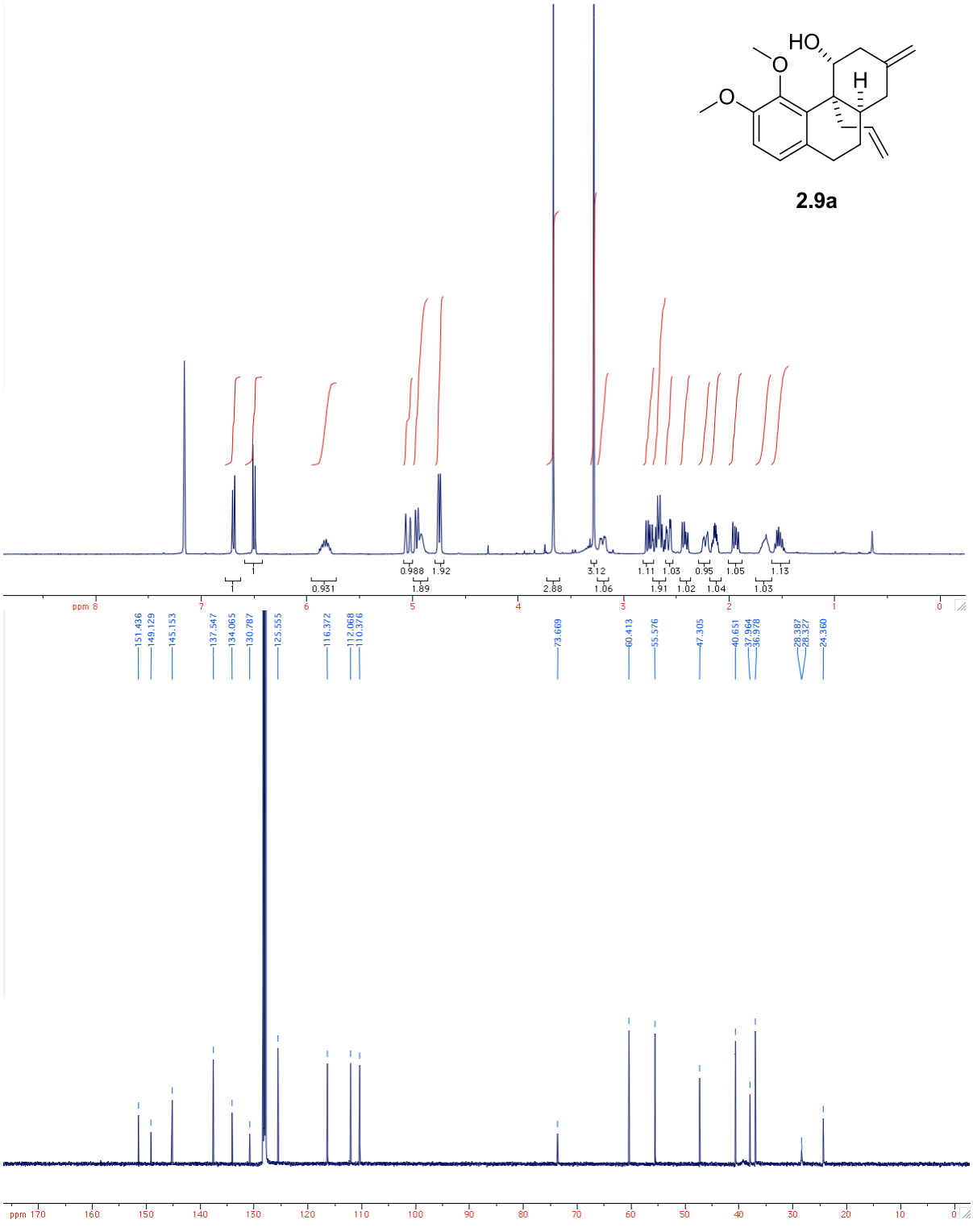
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O
H
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3.12
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0.95
1.05
1.13
1
0.931
1.89
2.88
1.06
1.91
1.02
1.04
1.03
ppm 8
7
6
5
4
3
2
1
0
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149.129
145.153
137.547
134.065
130.787
125.555
116.372
112.068
110.376
73.669
60.413
55.576
47.305
40.651
37.964
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28.327
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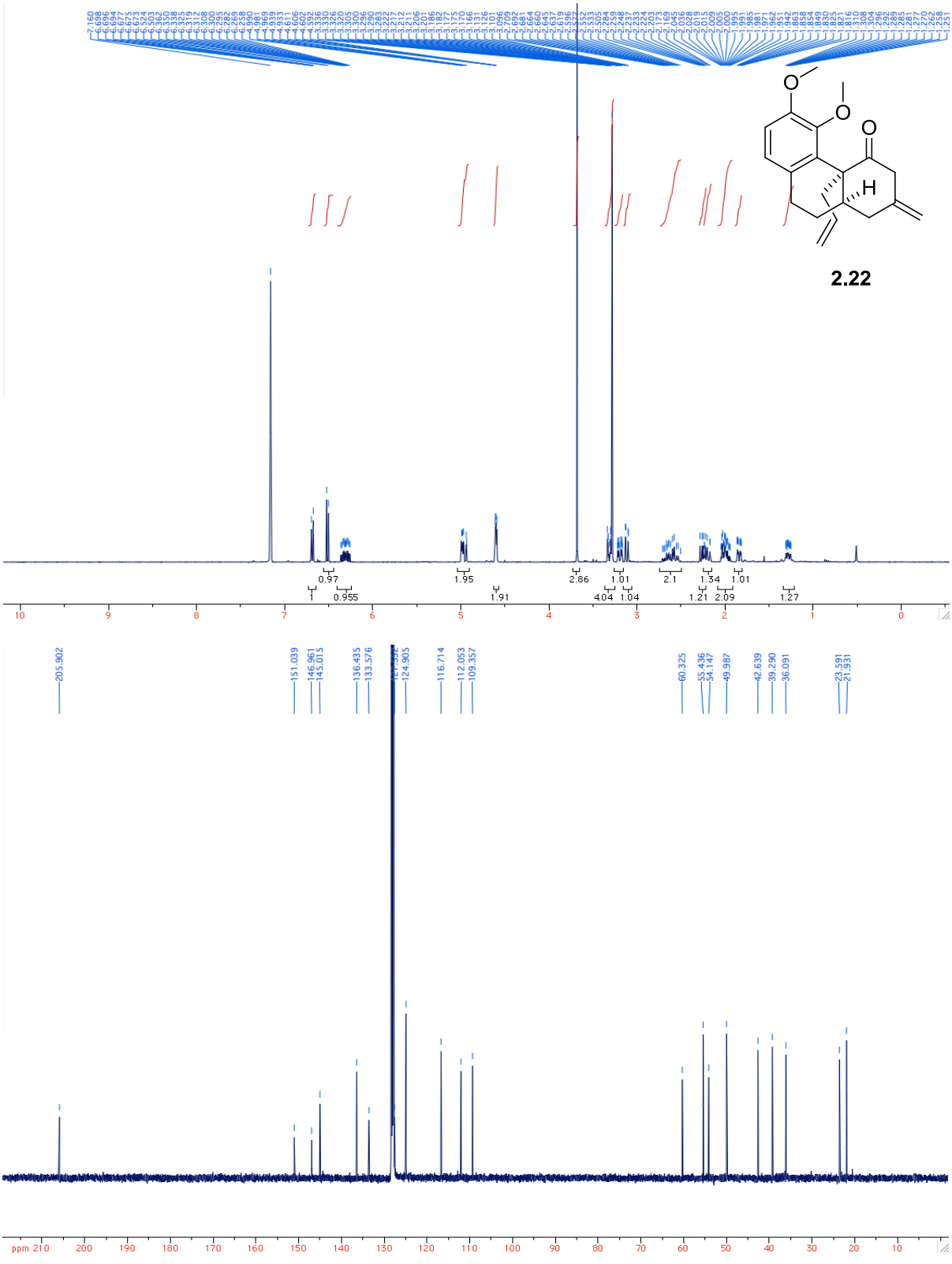
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133.576
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54.147
49.987
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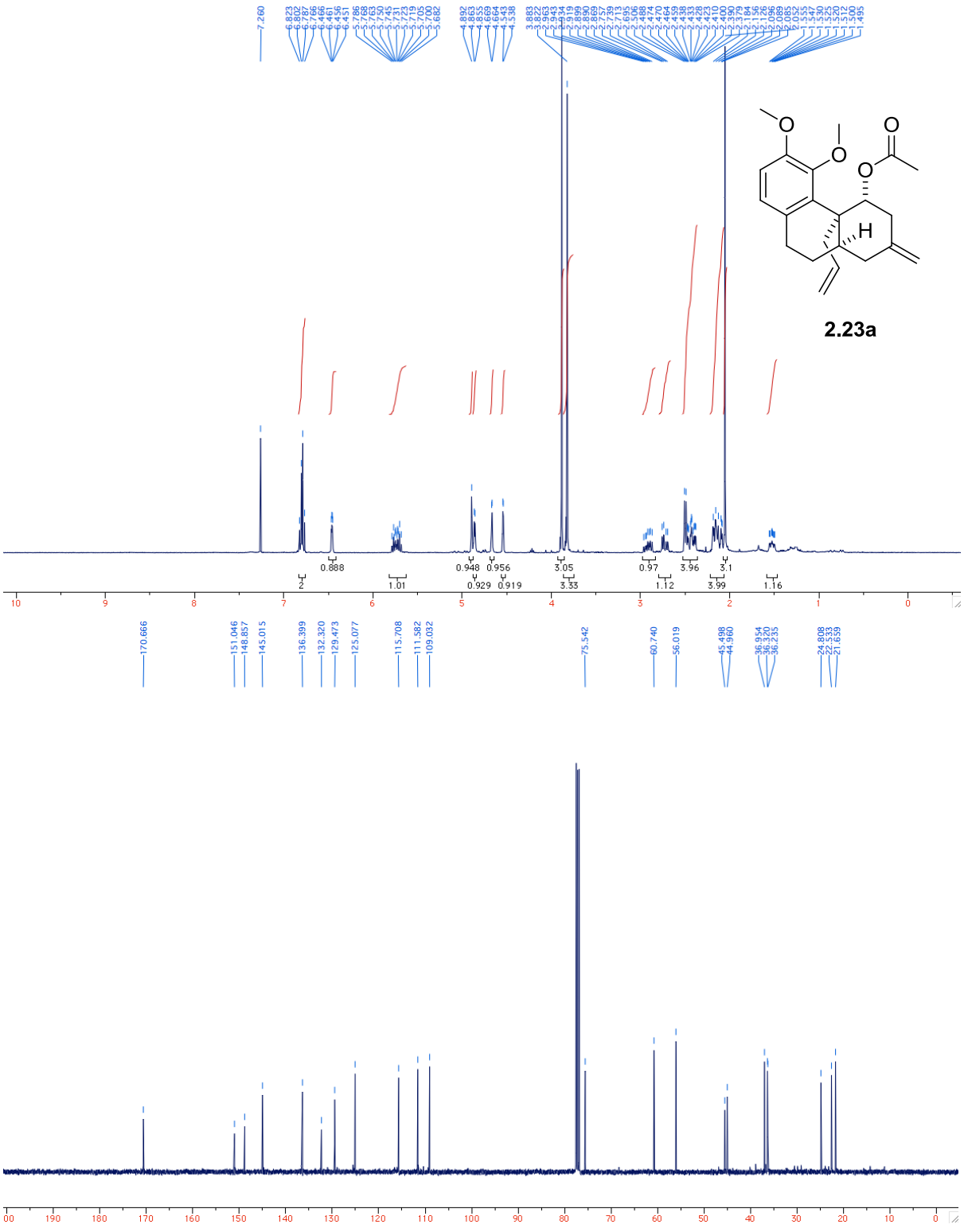
39.290
36.091
23.591
21.931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O
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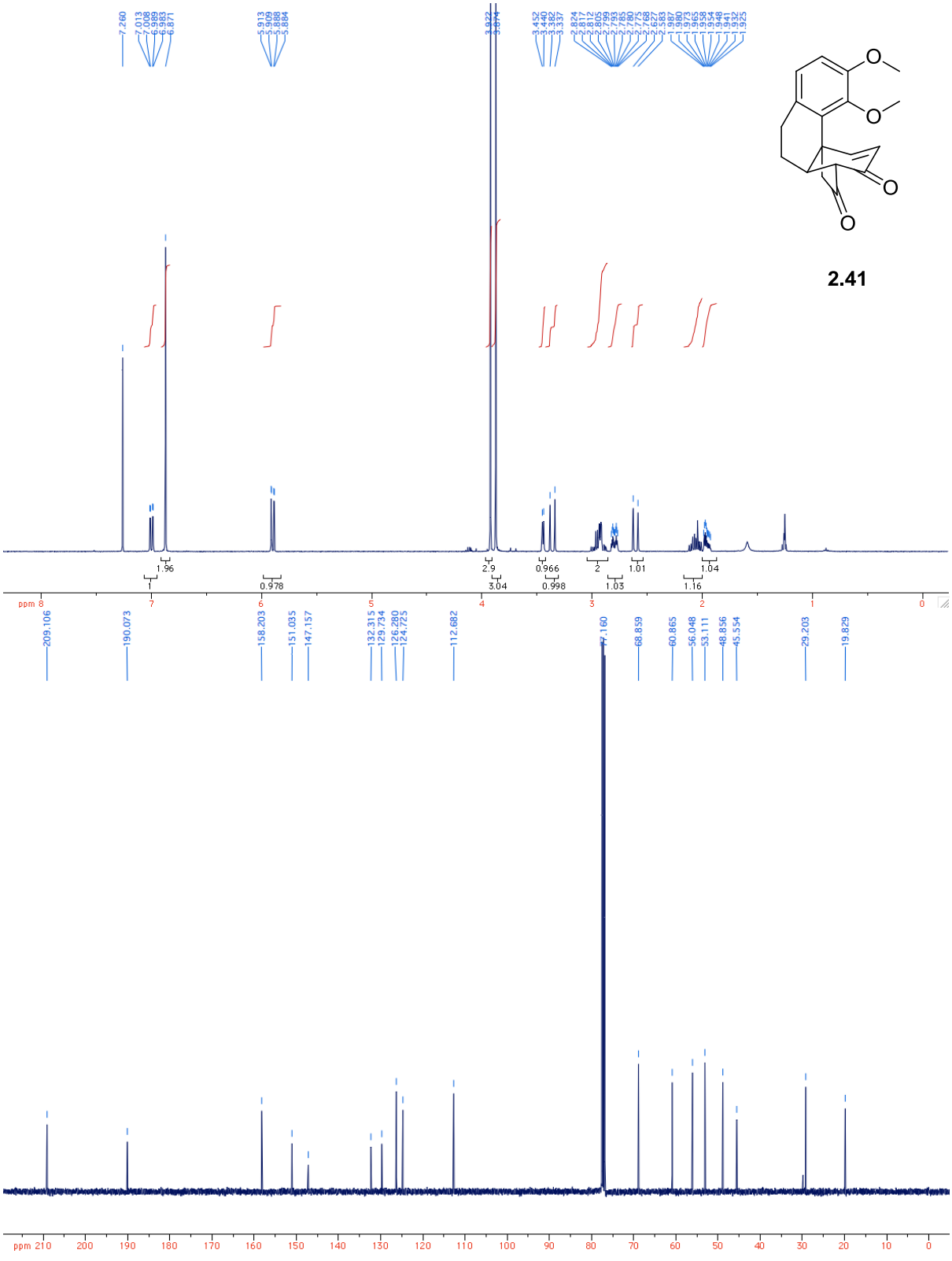
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3.874
3.452
3.440
3.382
3.337
2.824
2.817
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2.793
2.783
2.780
2.775
2.768
2.627
2.583
1.987
1.980
1.973
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1.934
1.948
1.941
1.932
1.925
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O
O
O
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1.96
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2.9
3.04
0.966
0.998
2
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1.01
1.16
1.04
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6
5
4
3
2
1
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129.734
126.280
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112.682
77.160
68.859
60.865
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10
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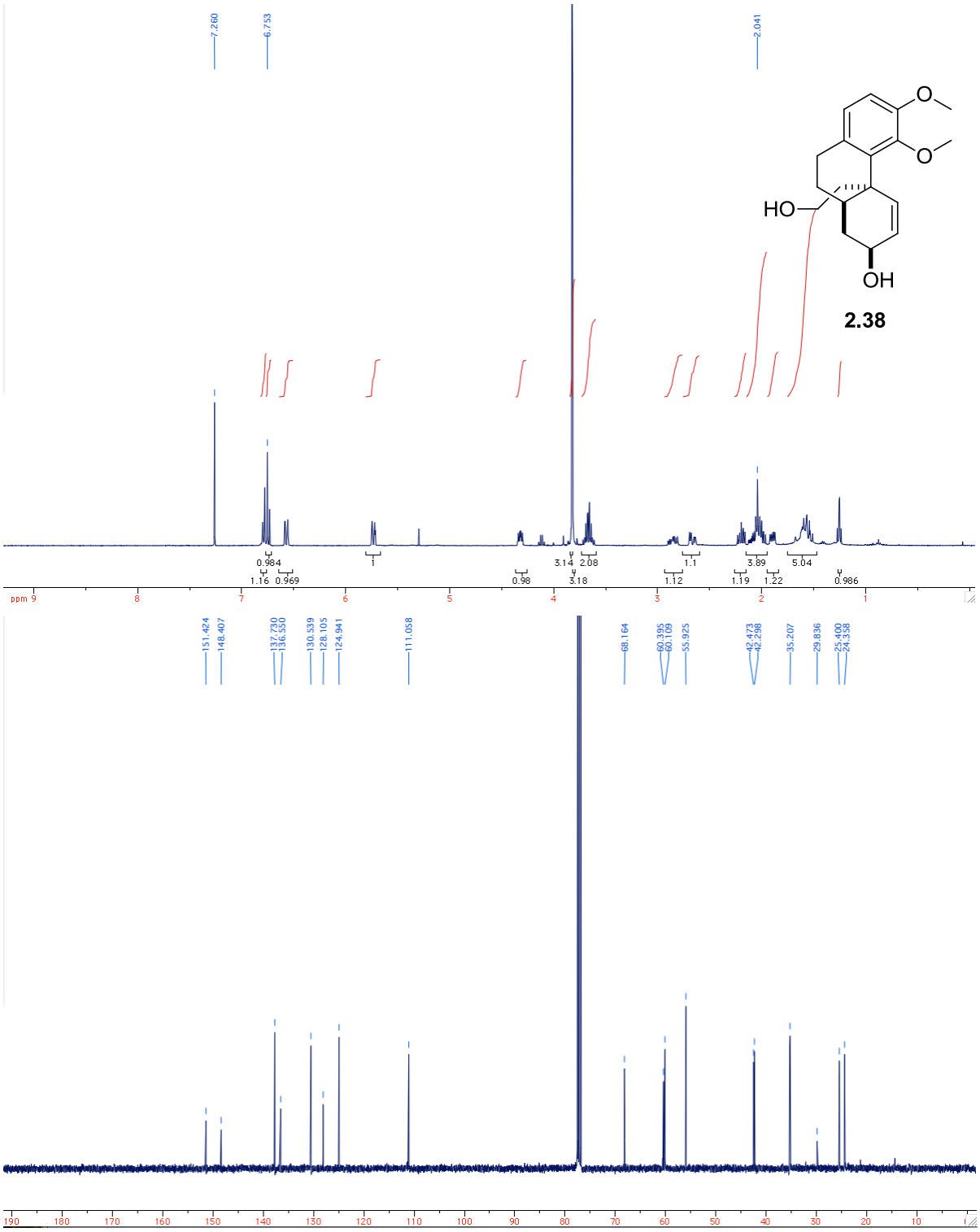
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OH
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3.18
0.98
1.1
1.12
3.89
1.19
1.22
5.04
0.986
ppm 9
8
7
6
5
4
3
2
1
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136.550
130.539
128.105
124.941
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68.164
60.395
60.109
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42.298
35.207
29.836
25.400
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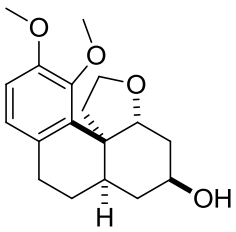
10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O
O
OH
H

**2.42**


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1.97
1.01
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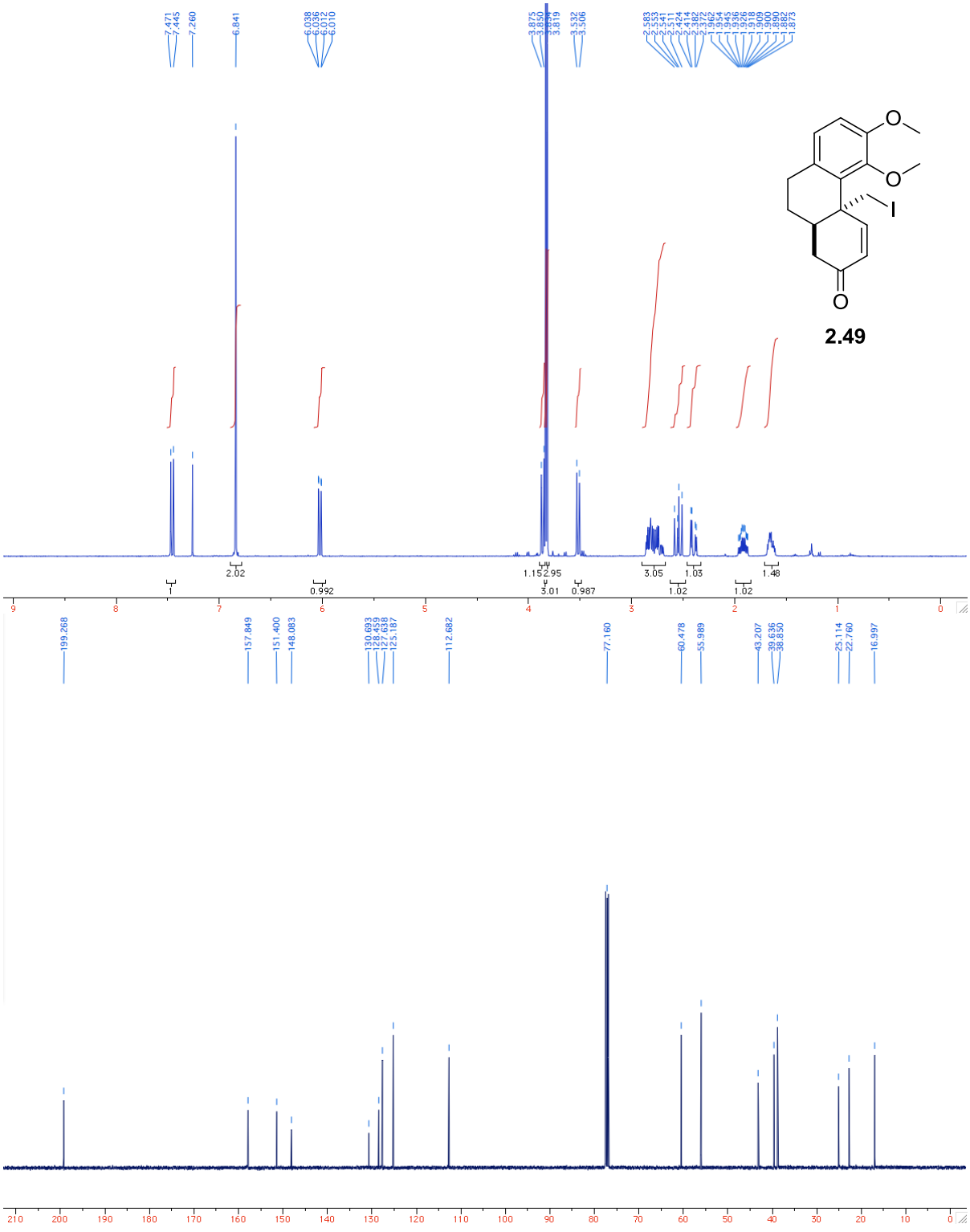
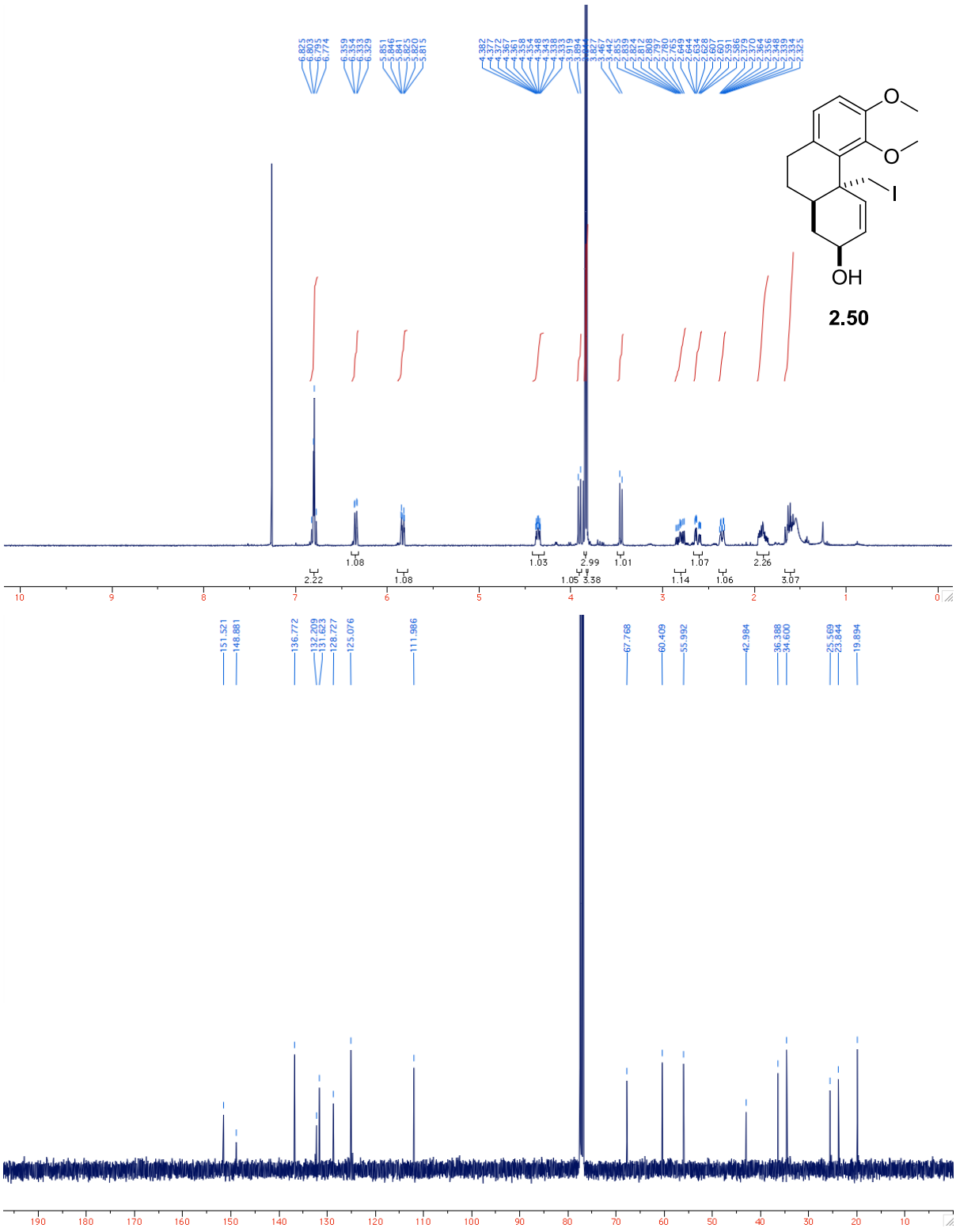
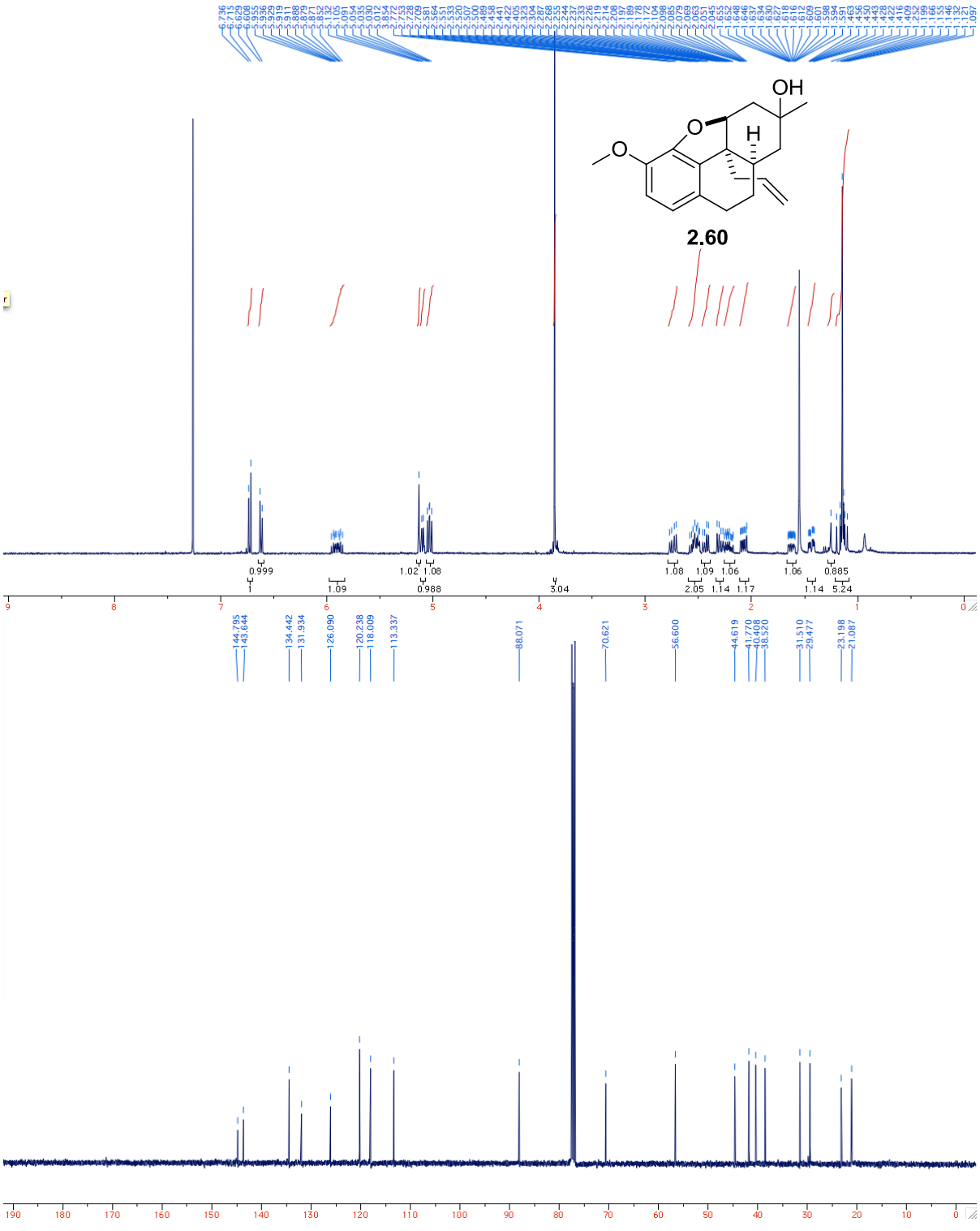
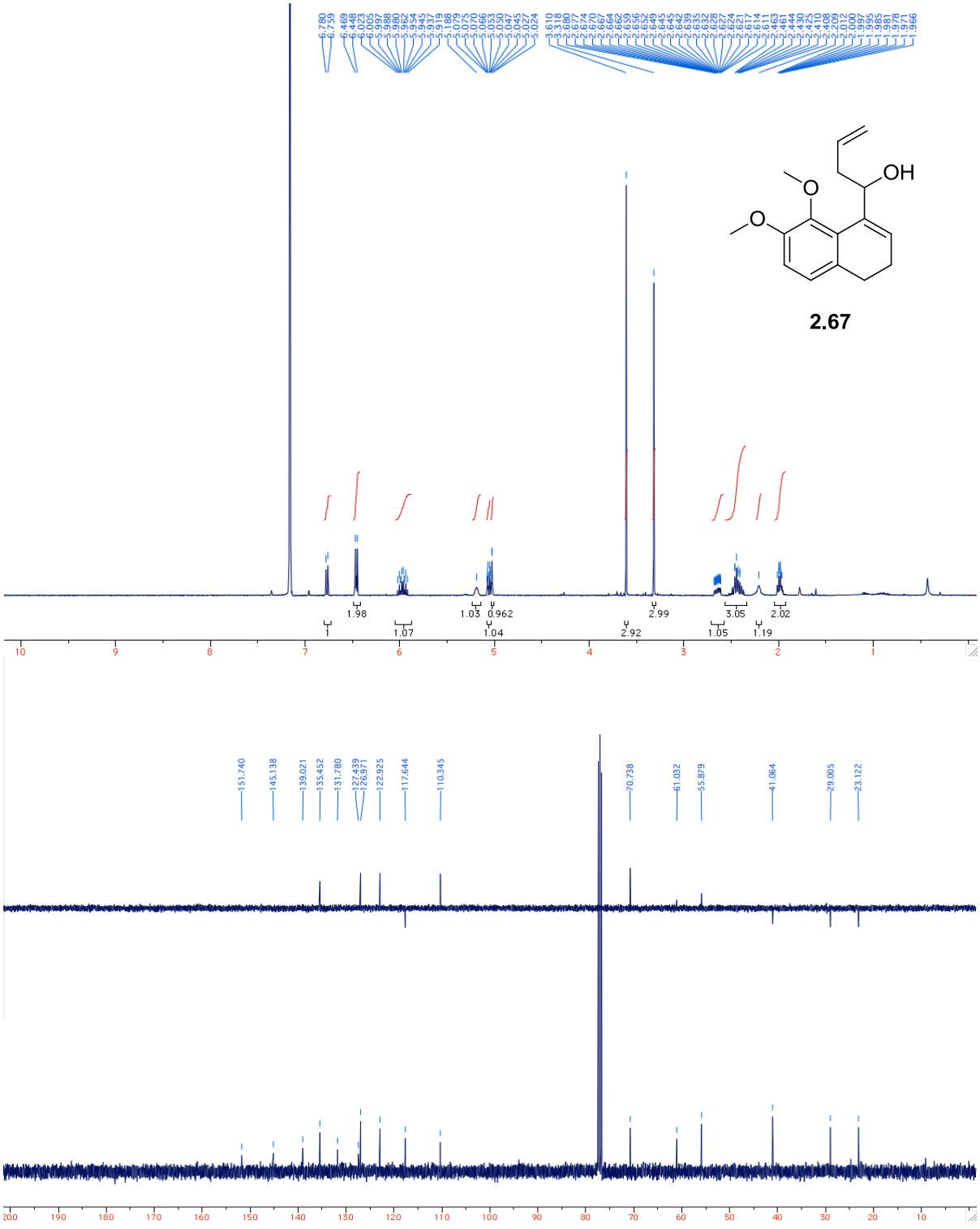
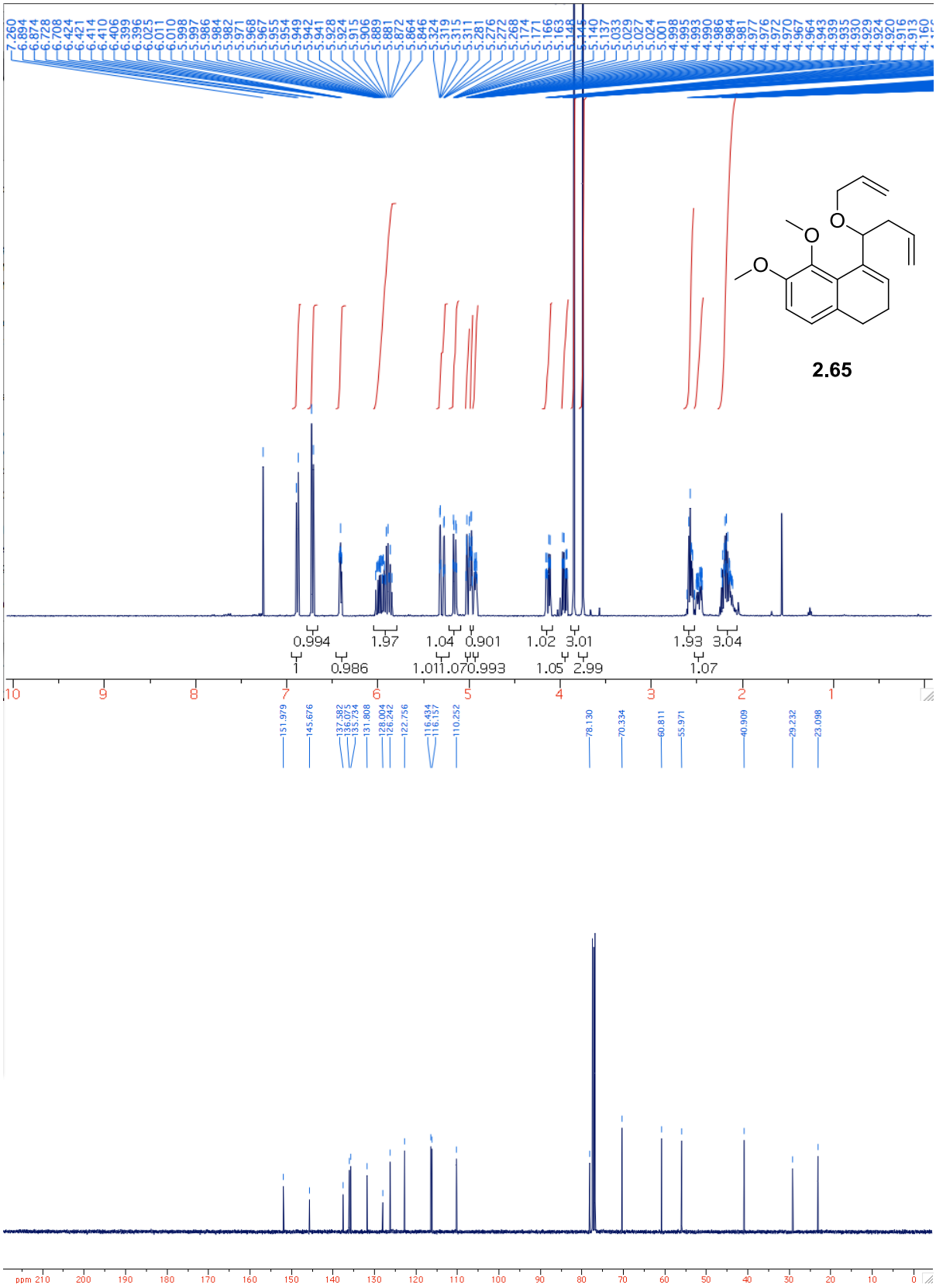
124.883
111.375
79.684
66.750
65.203
60.256
55.947
47.620
40.516
34.266
31.478
28.965
25.459
23.995

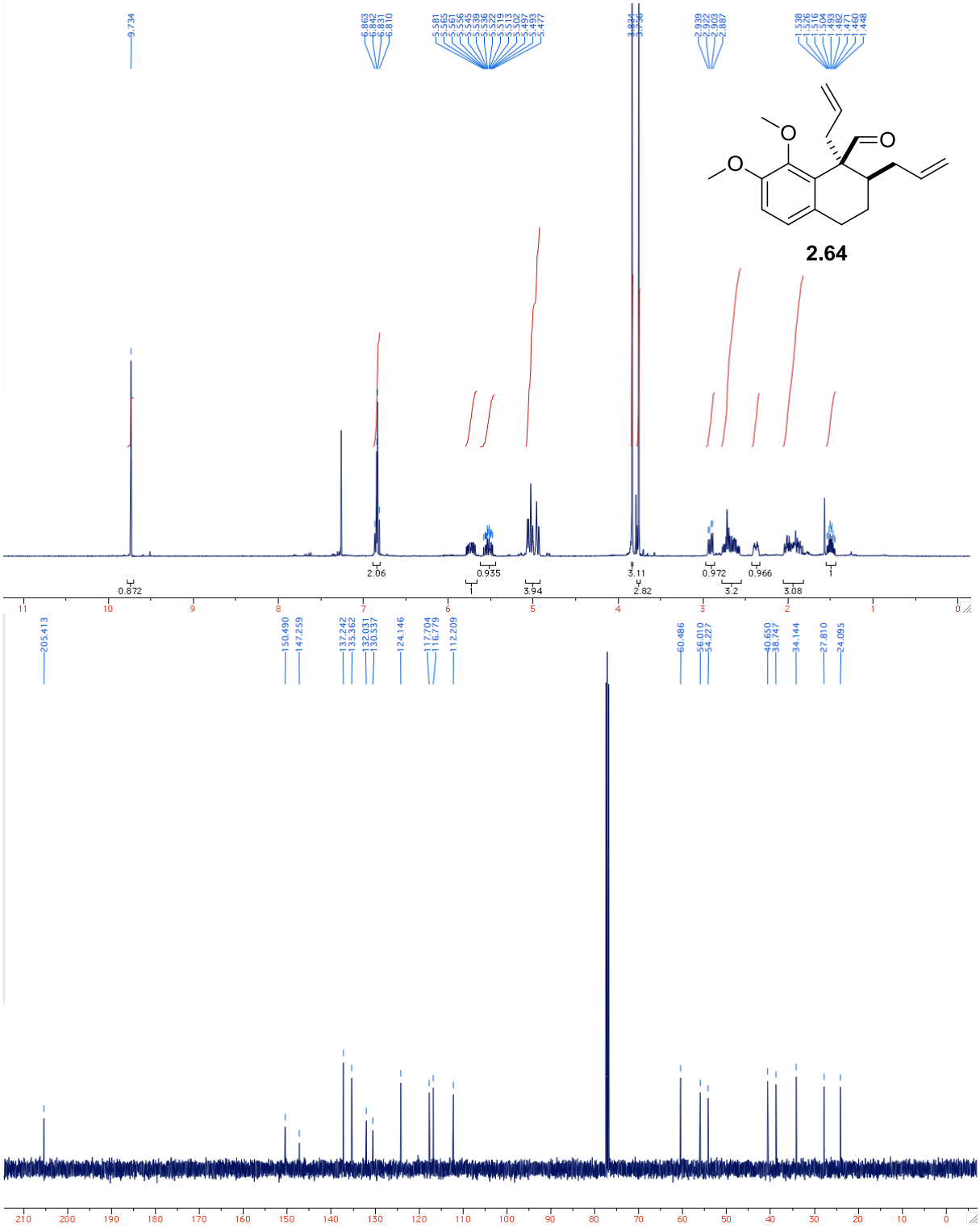

7.471
7.445
7.260
6.841
6.038
6.036
6.012
6.010
3.875
3.850
3.819
3.532
3.506
2.583
2.553
2.541
2.511
2.424
2.414
2.372
2.362
1.962
1.954
1.945
1.936
1.926
1.919
1.908
1.900
1.890
1.882
1.873
O
O
I
O
2.49
2.02
0.992
1.15
2.95
3.01
0.987
3.05
1.02
1.03
1.02
1.48
199.268
157.849
151.400
148.083
130.693
128.459
127.638
125.187
112.682
77.160
60.478
55.989
43.207
39.636
38.850
25.114
22.760
16.997

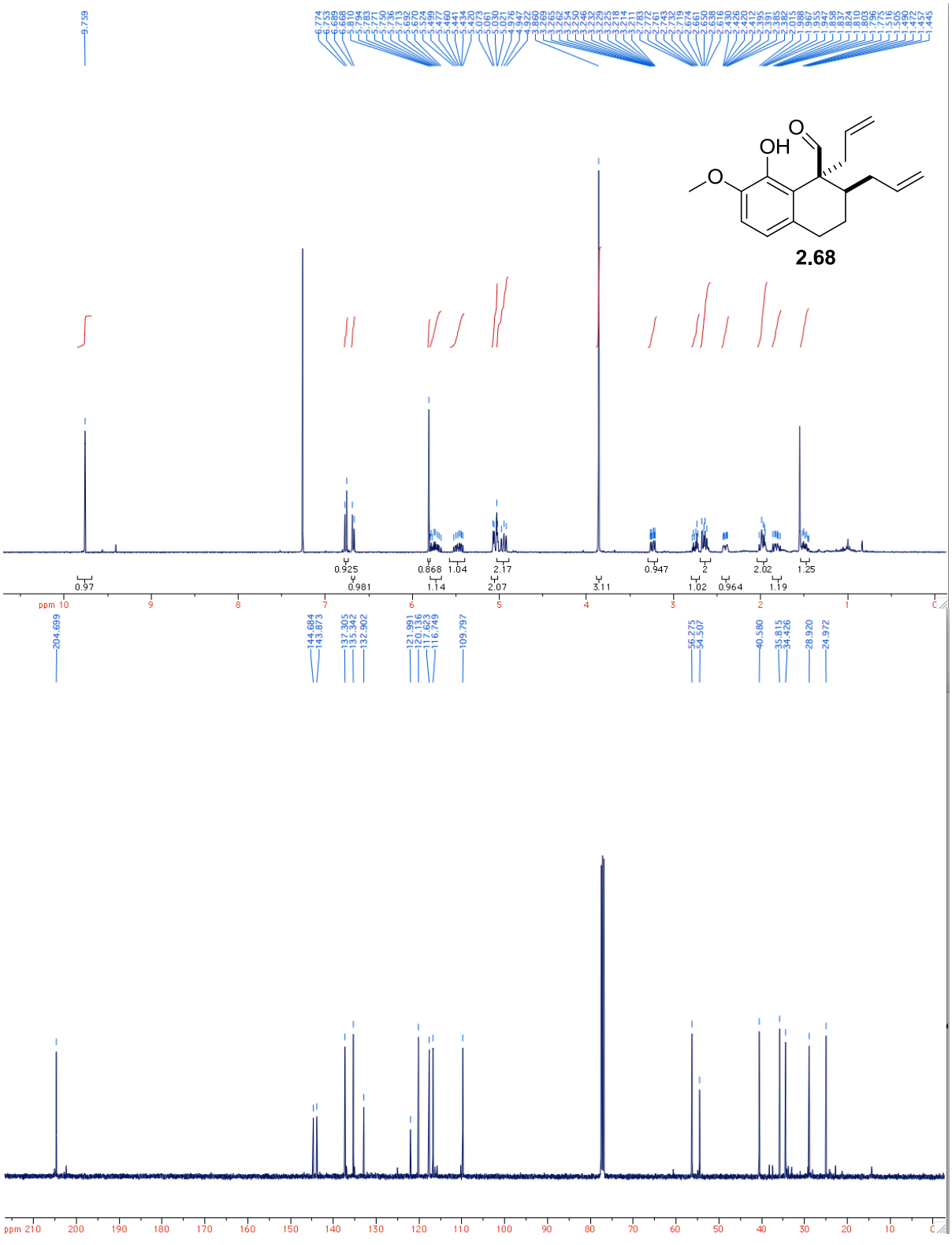

O
O
I
OH
2.50

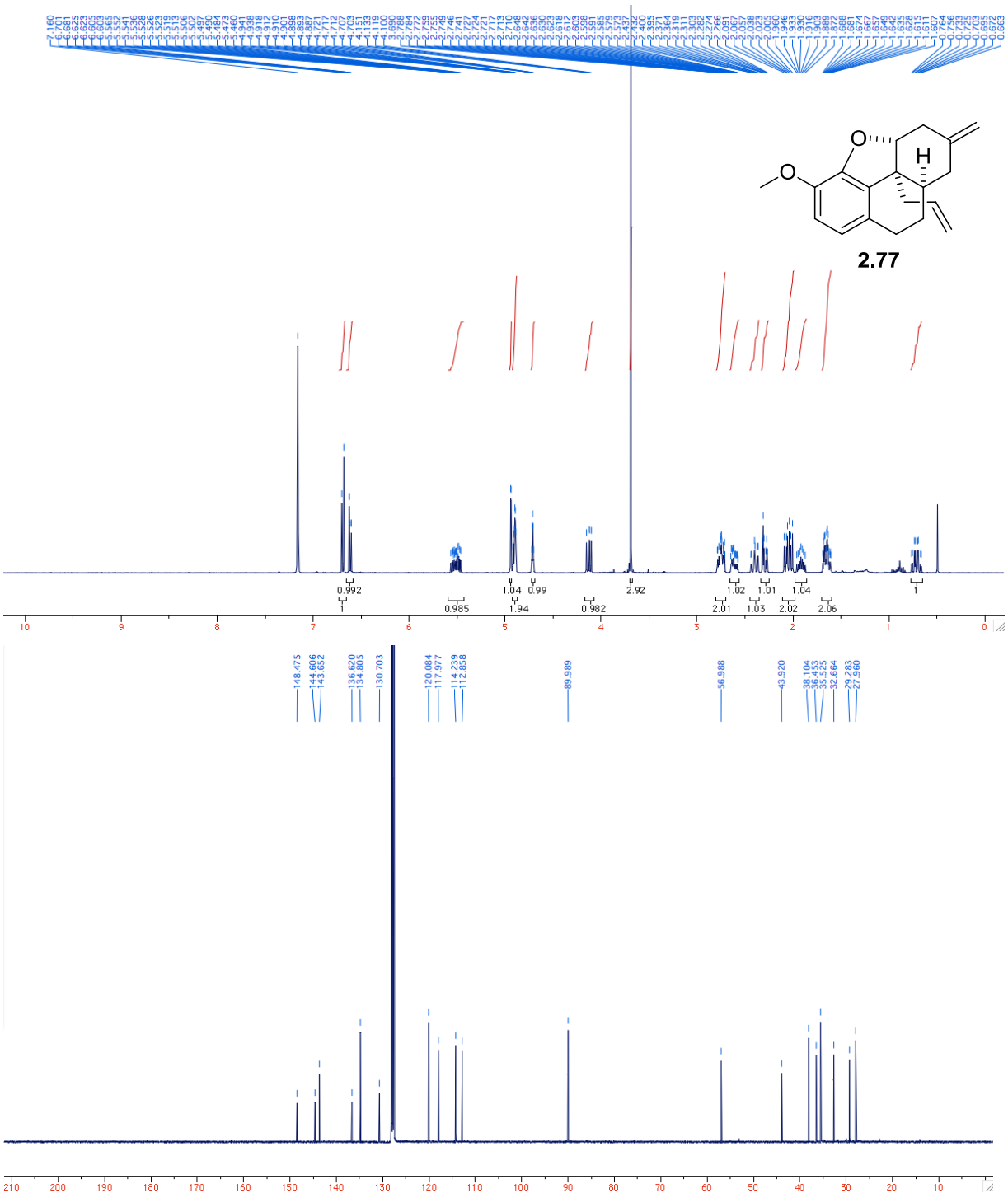

OH
O
O
H
2.60

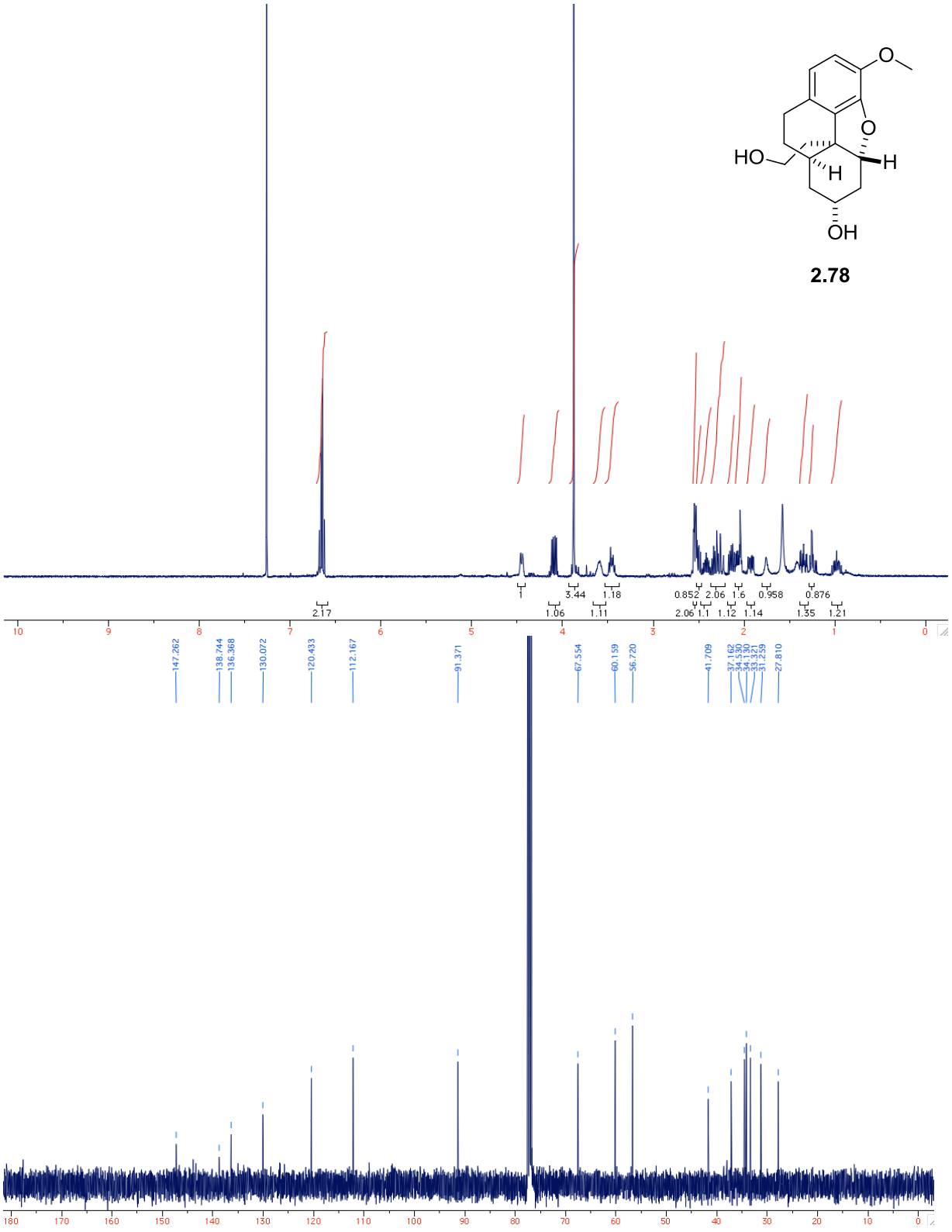

OH
O
O
2.67

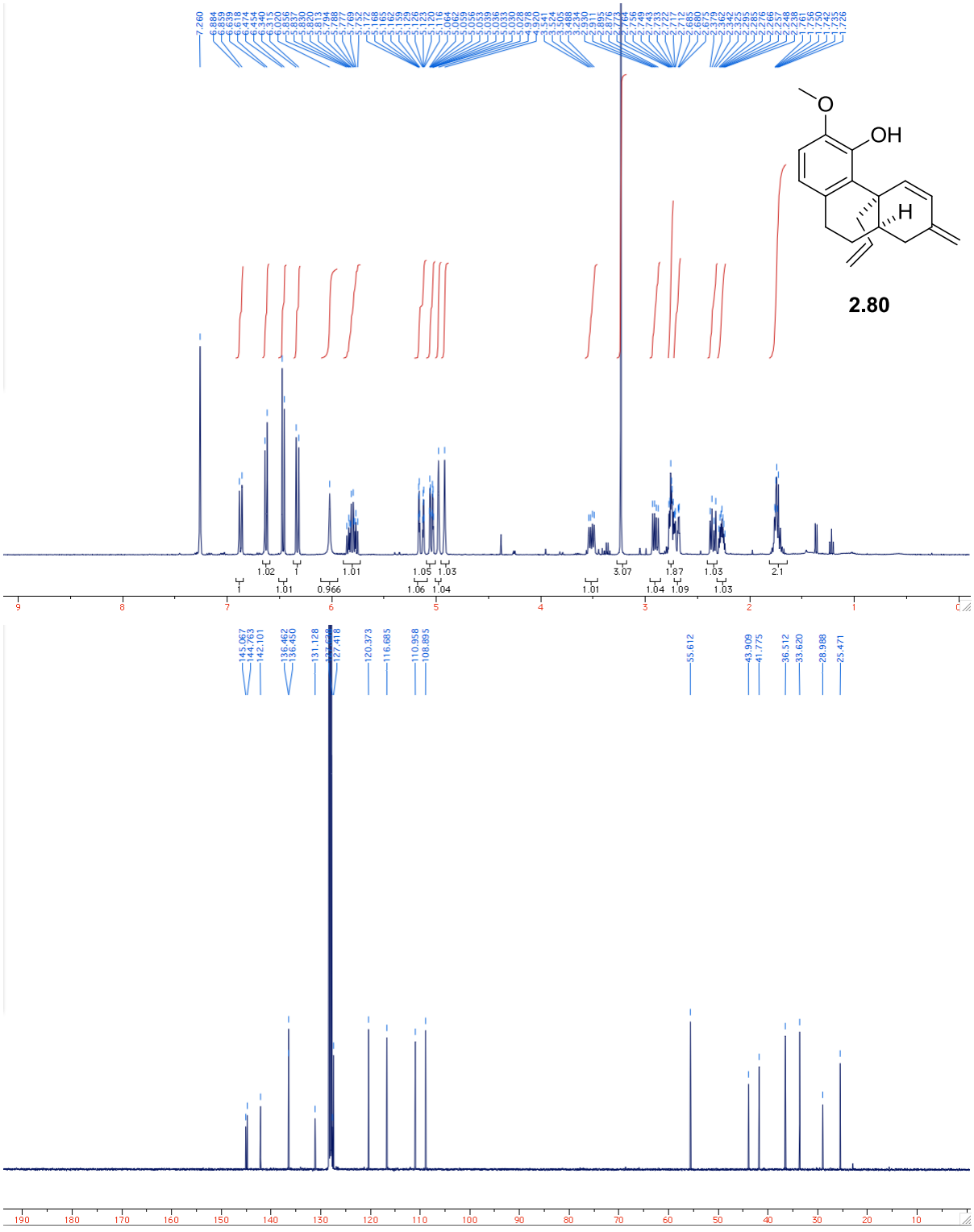

2.65

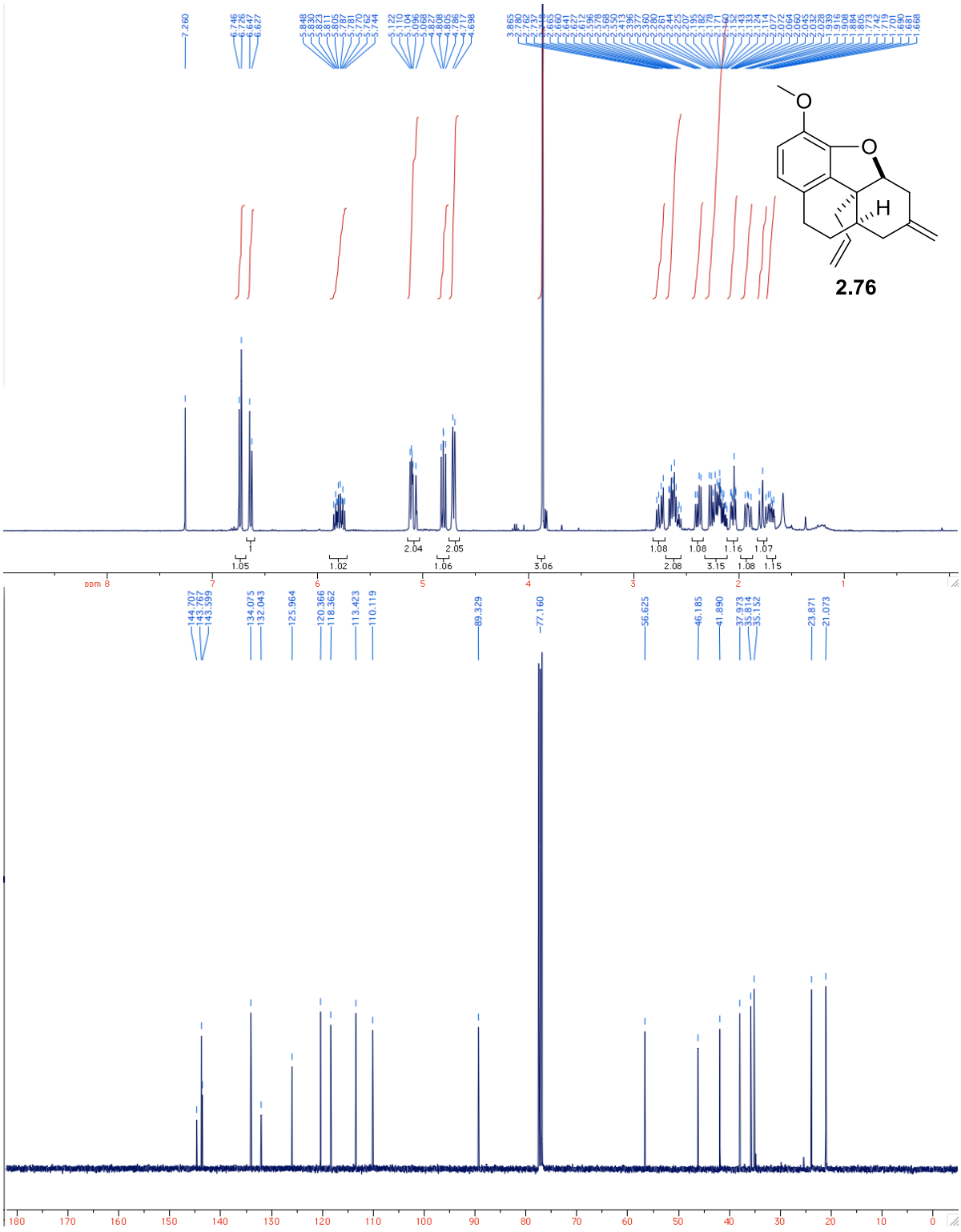

9.734
6.863
6.842
6.831
6.810
5.581
5.565
5.561
5.545
5.539
5.526
5.519
5.513
5.507
5.497
5.493
5.477
3.824
3.798
2.939
2.922
2.903
2.887
1.538
1.526
1.516
1.494
1.482
1.471
1.460
1.448
O
O
O
2.64
0.872
2.06
0.935
3.94
3.11
2.82
0.972
3.2
0.966
3.08
1
205.413
150.490
147.259
137.242
135.362
132.031
130.537
124.146
117.704
116.779
112.209
60.486
56.010
54.227
40.650
38.747
34.144
27.810
24.095

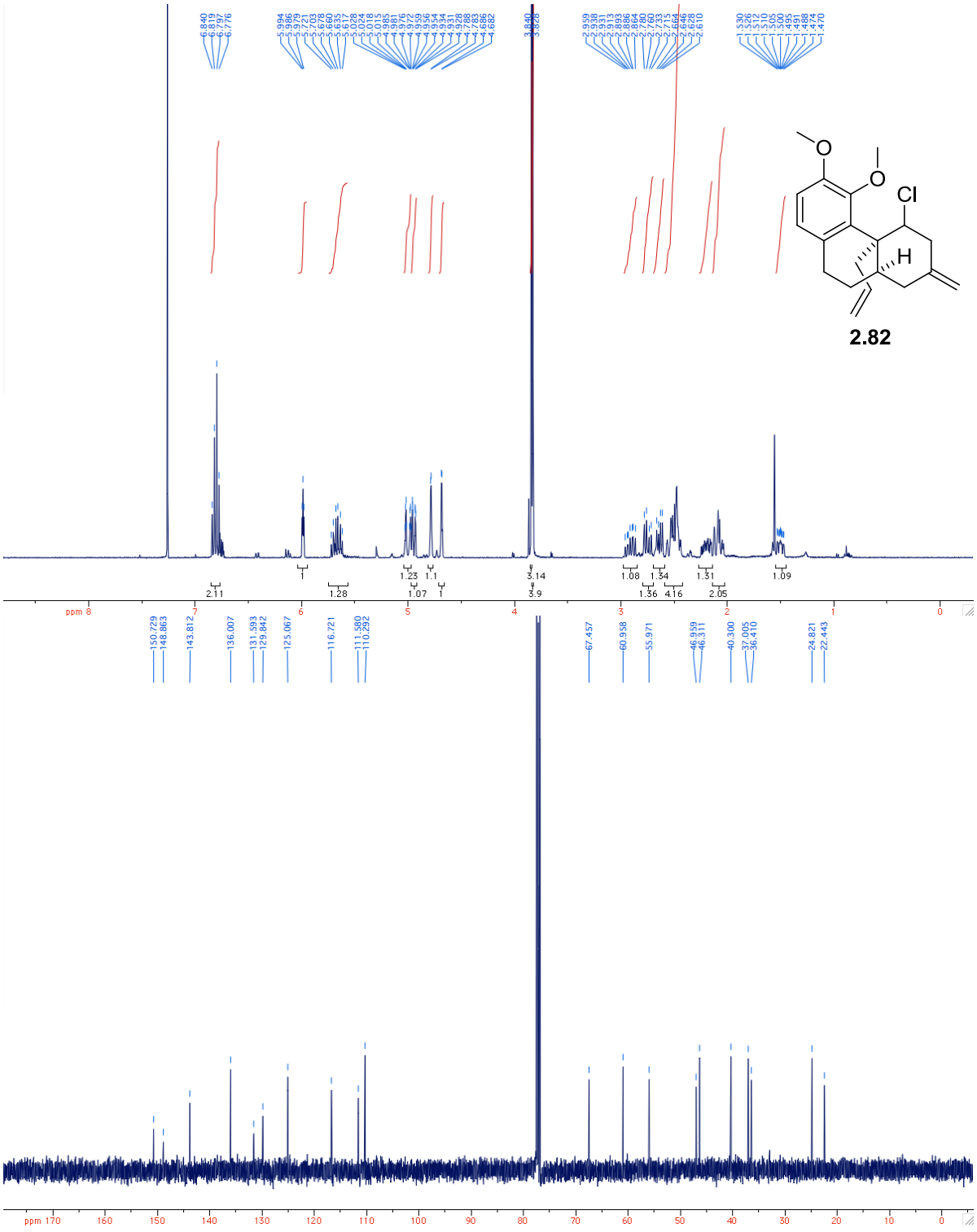

OH
O
O
2.68
ppm 10
9
8
7
6
5
4
3
2
1
0
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


O
O
H
2.77
0.992
0.985
1.04
1.94
0.99
0.982
2.92
1.02
2.01
1.01
1.03
1.04
2.02
2.06
1
148.475
144.606
143.652
136.620
134.805
130.703
120.084
117.977
114.239
112.858
89.989
56.988
43.920
38.104
36.455
35.525
32.664
29.283
27.960

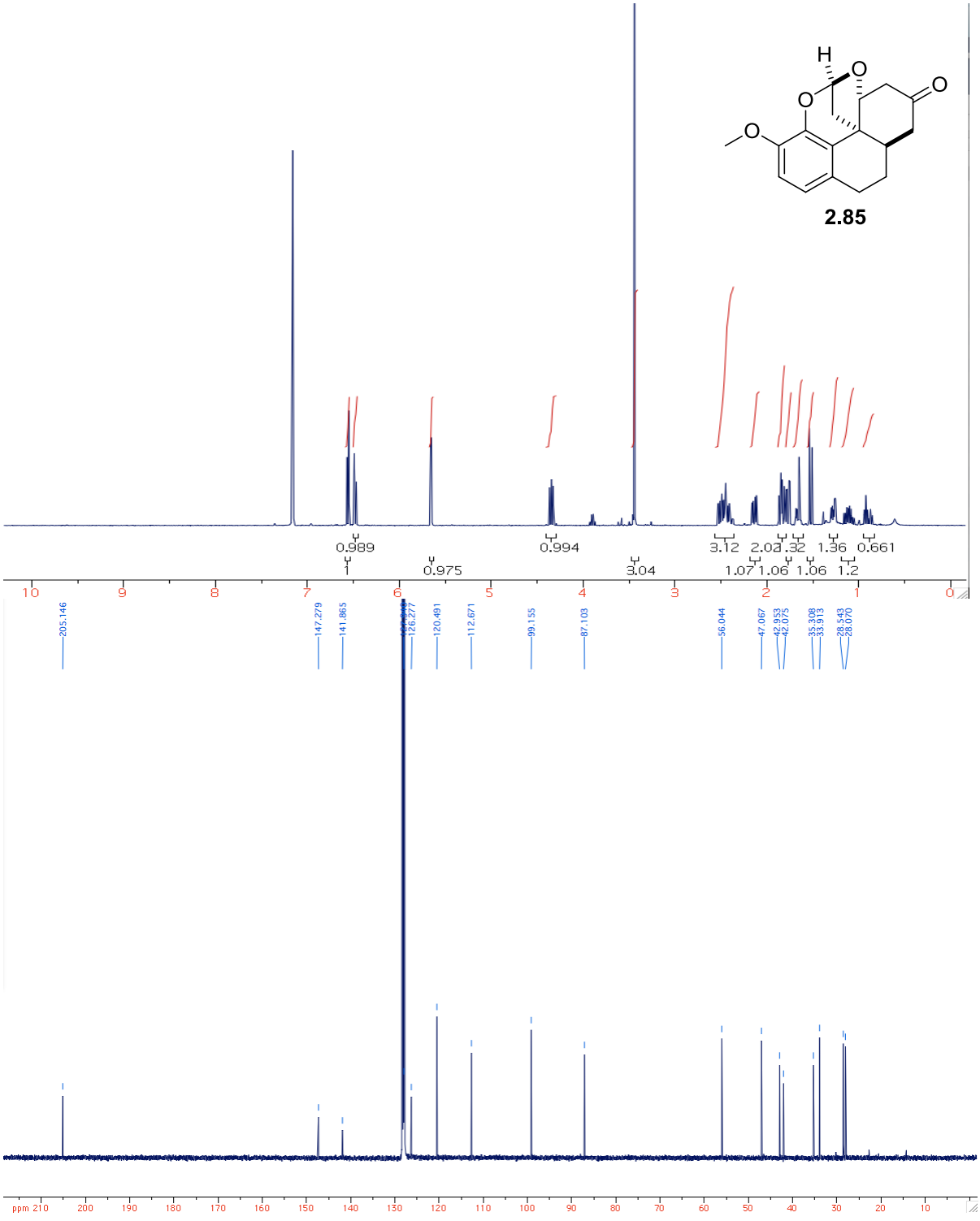

HO
O
O
H
H
OH
2.78
147.262
138.744
136.368
130.072
120.433
112.167
91.371
67.554
60.159
56.720
41.709
37.162
34.530
34.191
33.321
31.259
27.810

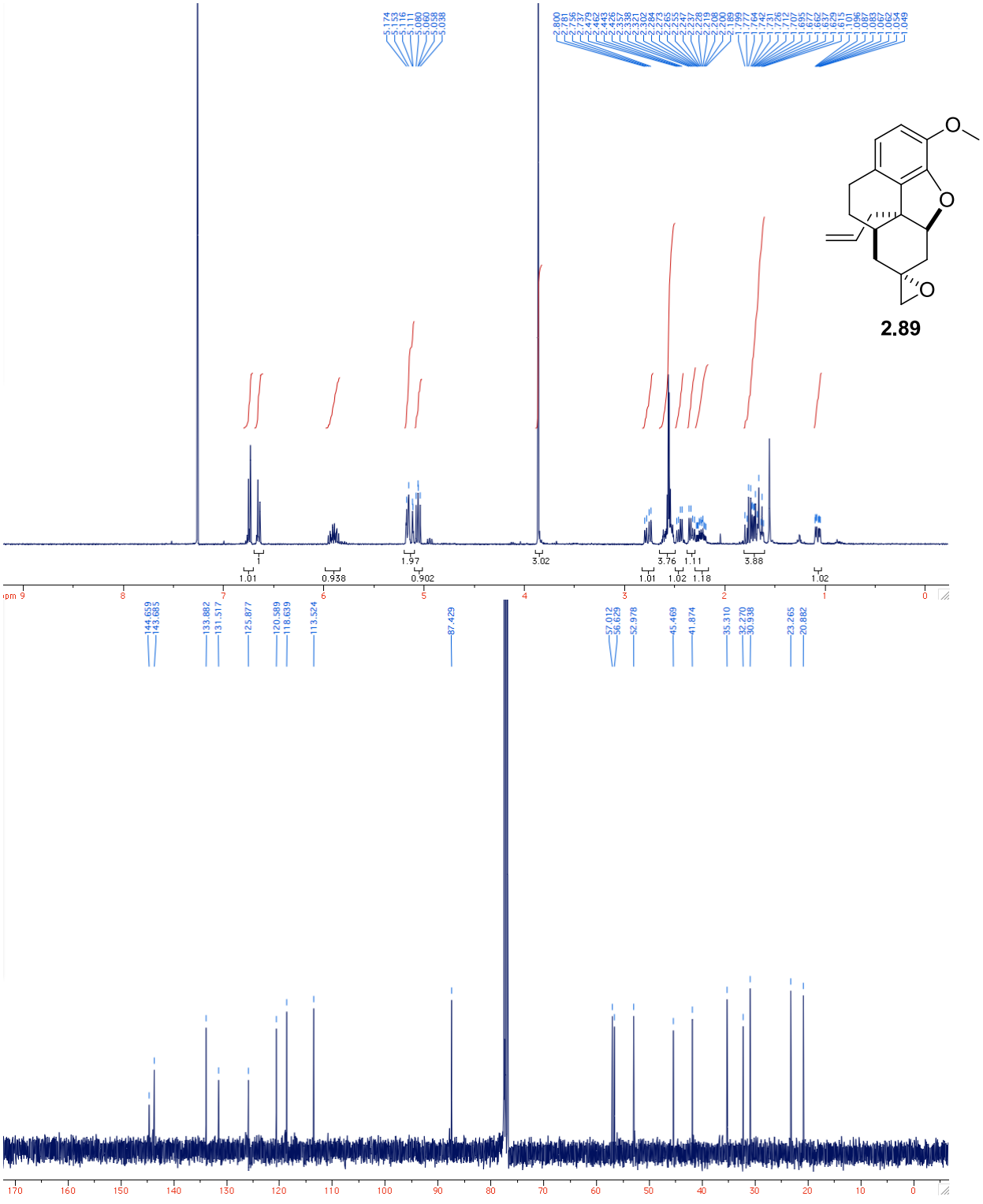

OH
H
2.80

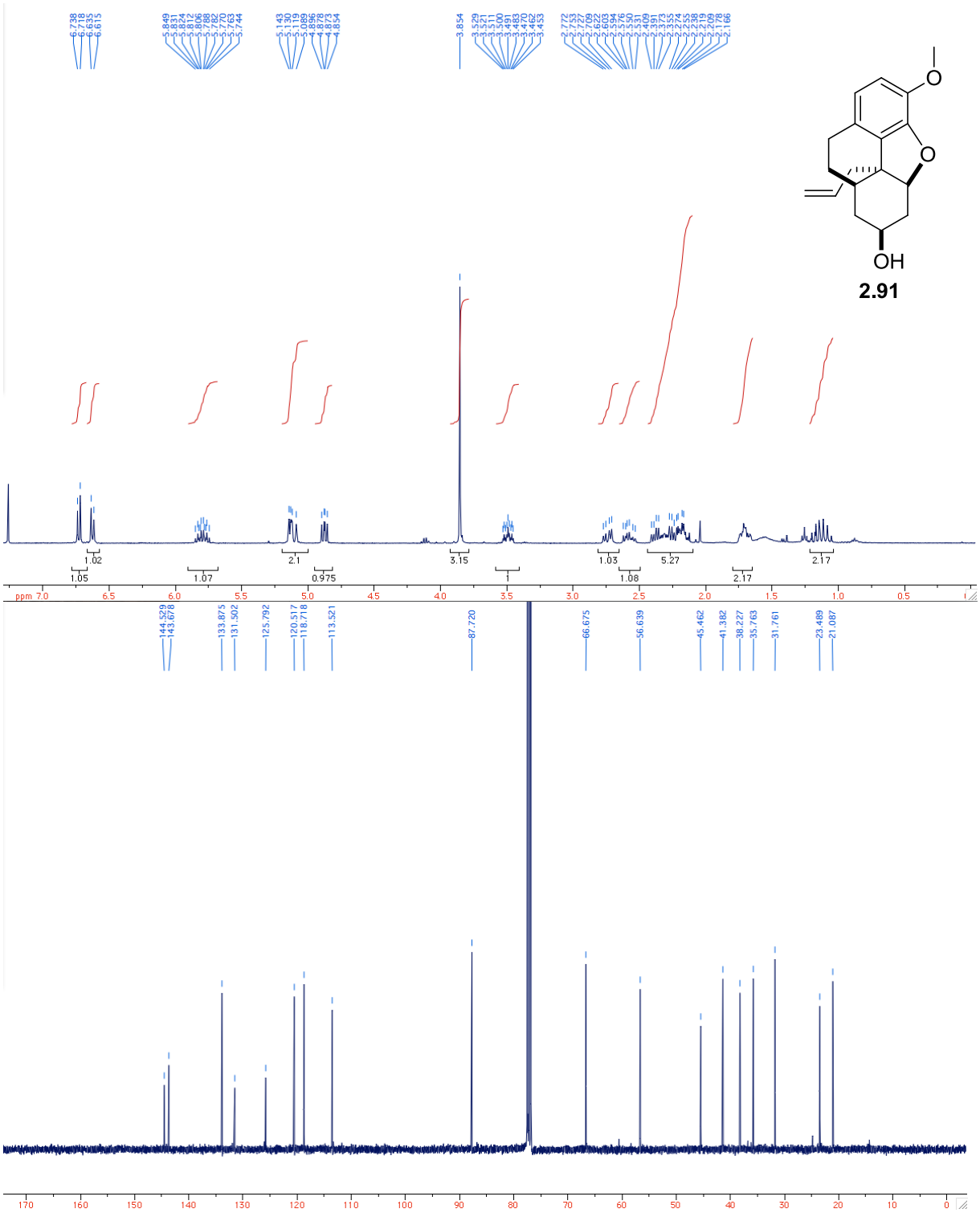

2.76

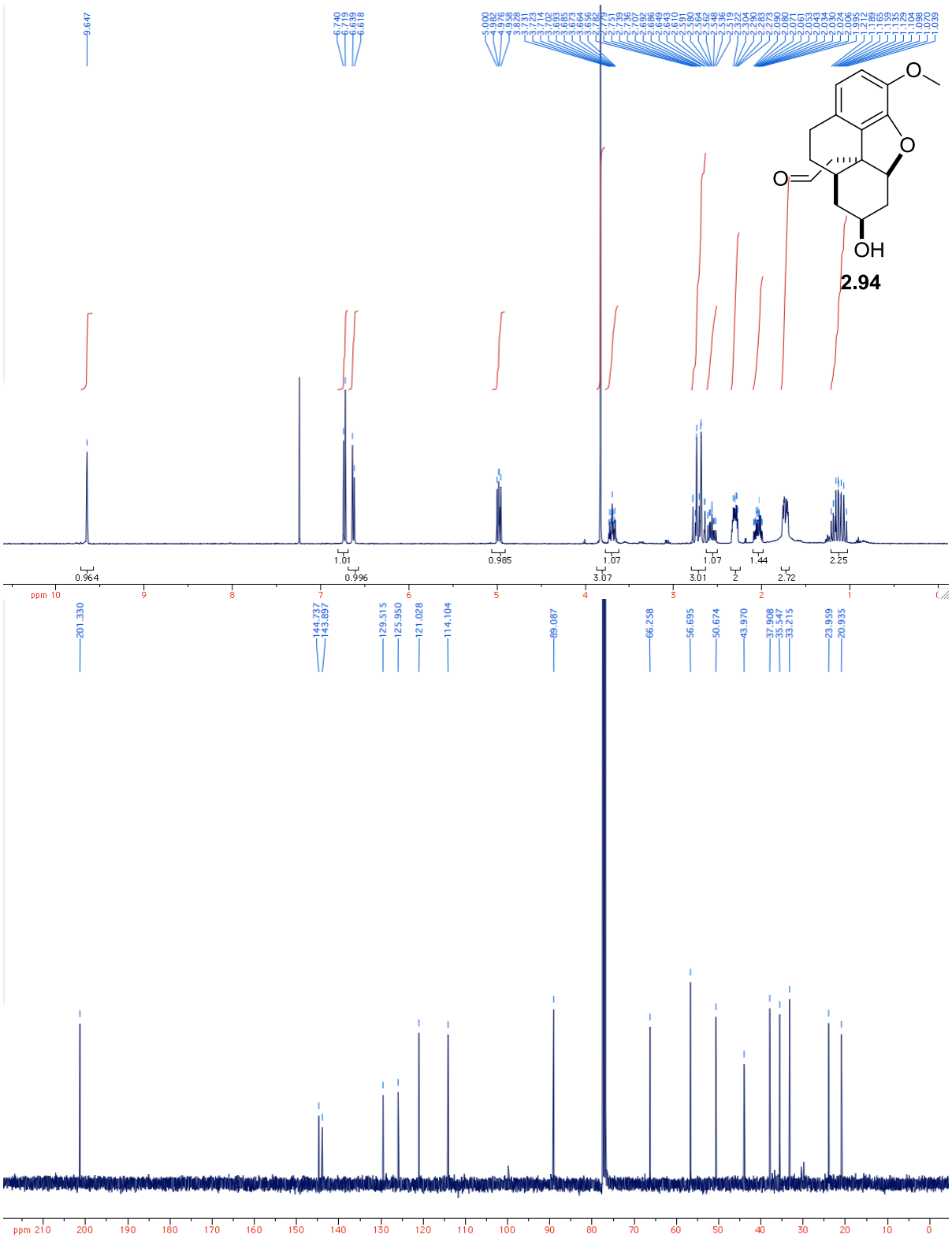


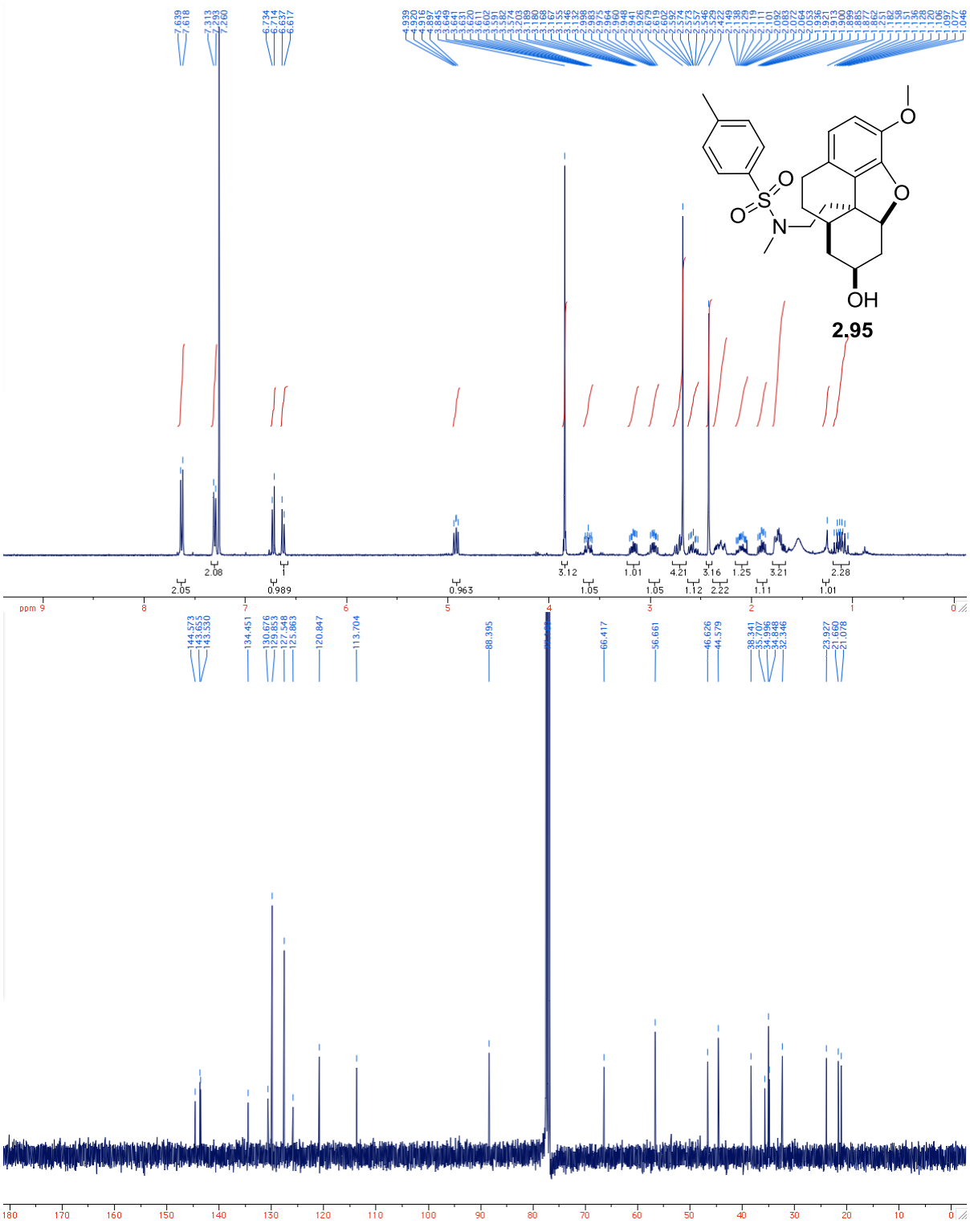

**2.82**

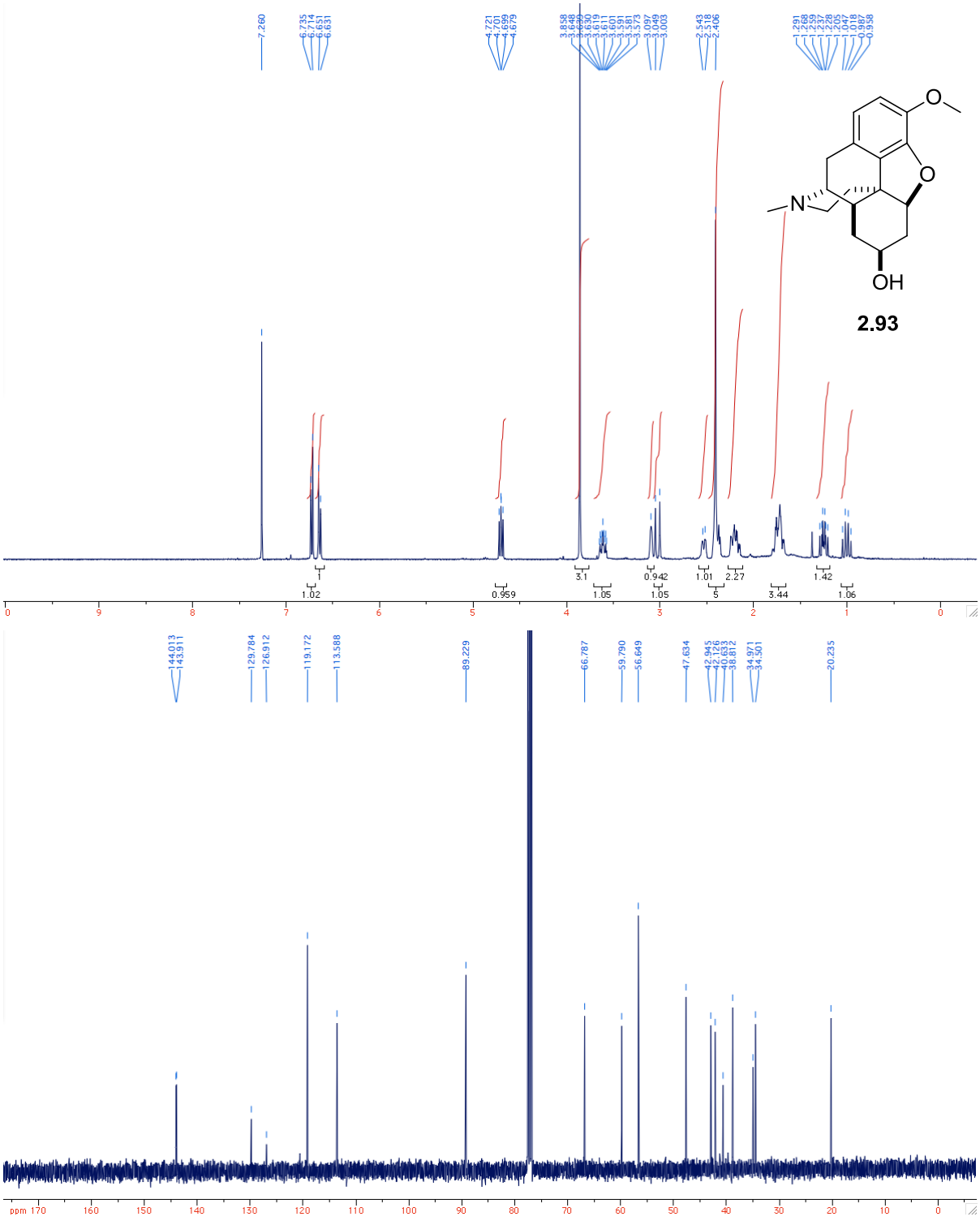

H
O
O
O
O
2.85
0.989
0.994
3.12
2.03
2.32
1.36
0.661
1
0.975
3.04
1.07
1.06
1.06
1.2
205.146
147.279
141.865
126.277
120.491
112.671
99.155
87.103
56.044
47.067
42.953
42.075
35.308
33.913
28.543
28.370

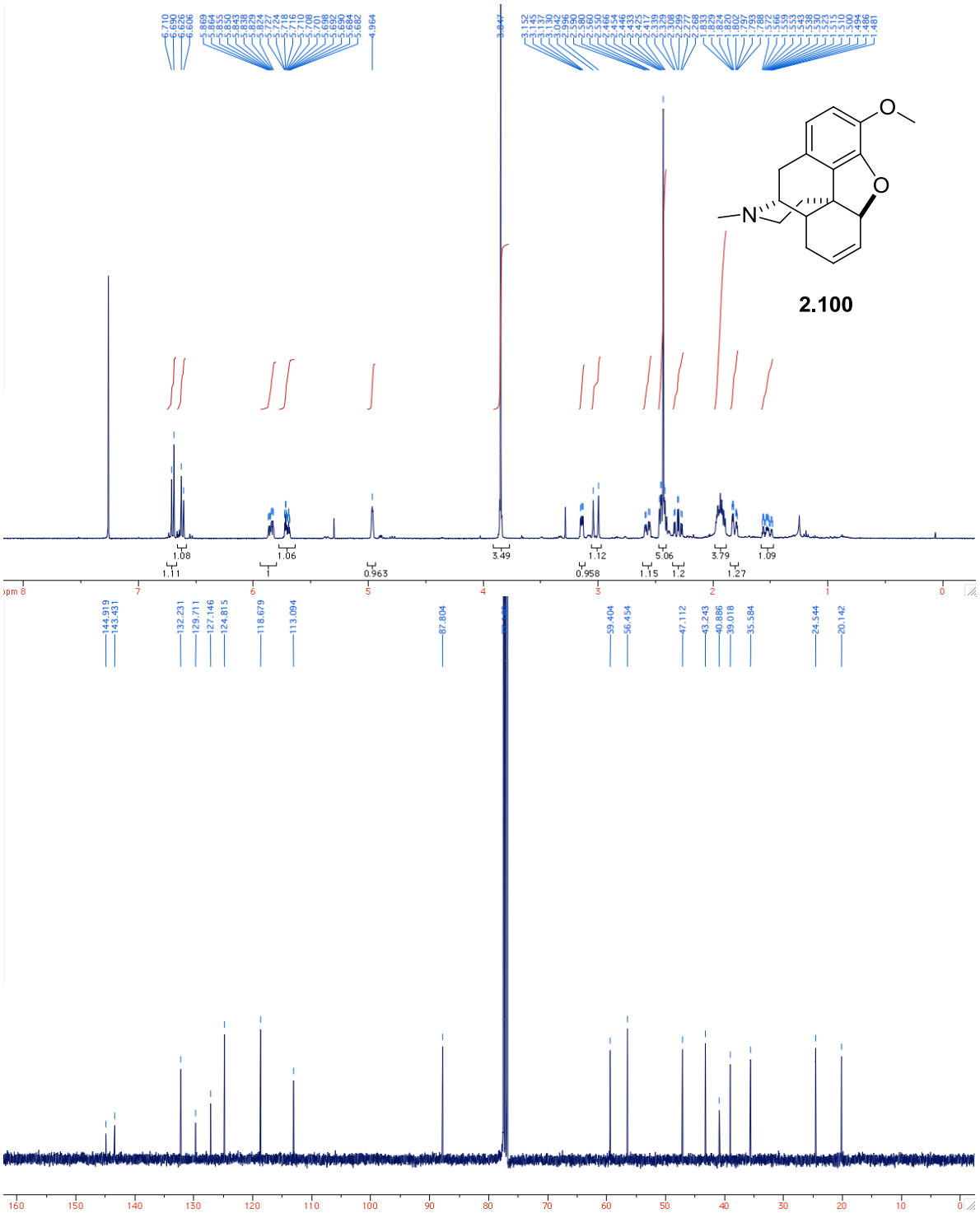

5.174
5.153
5.116
5.111
5.080
5.060
5.058
5.038
2.800
2.781
2.755
2.737
2.479
2.462
2.443
2.426
2.357
2.338
2.321
2.302
2.284
2.273
2.265
2.255
2.247
2.237
2.228
2.219
2.208
2.200
2.189
1.799
1.777
1.764
1.742
1.711
1.726
1.712
1.707
1.695
1.677
1.662
1.647
1.629
1.615
1.101
1.096
1.087
1.083
1.067
1.062
1.054
1.049
O
O
O
2.89
1
1.01
0.938
1.97
0.902
3.02
1.01
3.76
1.02
1.11
1.18
3.88
1.02
ppm 9
8
7
6
5
4
3
2
1
0
144.659
143.685
133.882
131.517
125.877
120.589
118.639
113.524
87.429
57.012
56.629
52.978
45.469
41.874
35.310
32.270
30.938
23.265
20.882
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

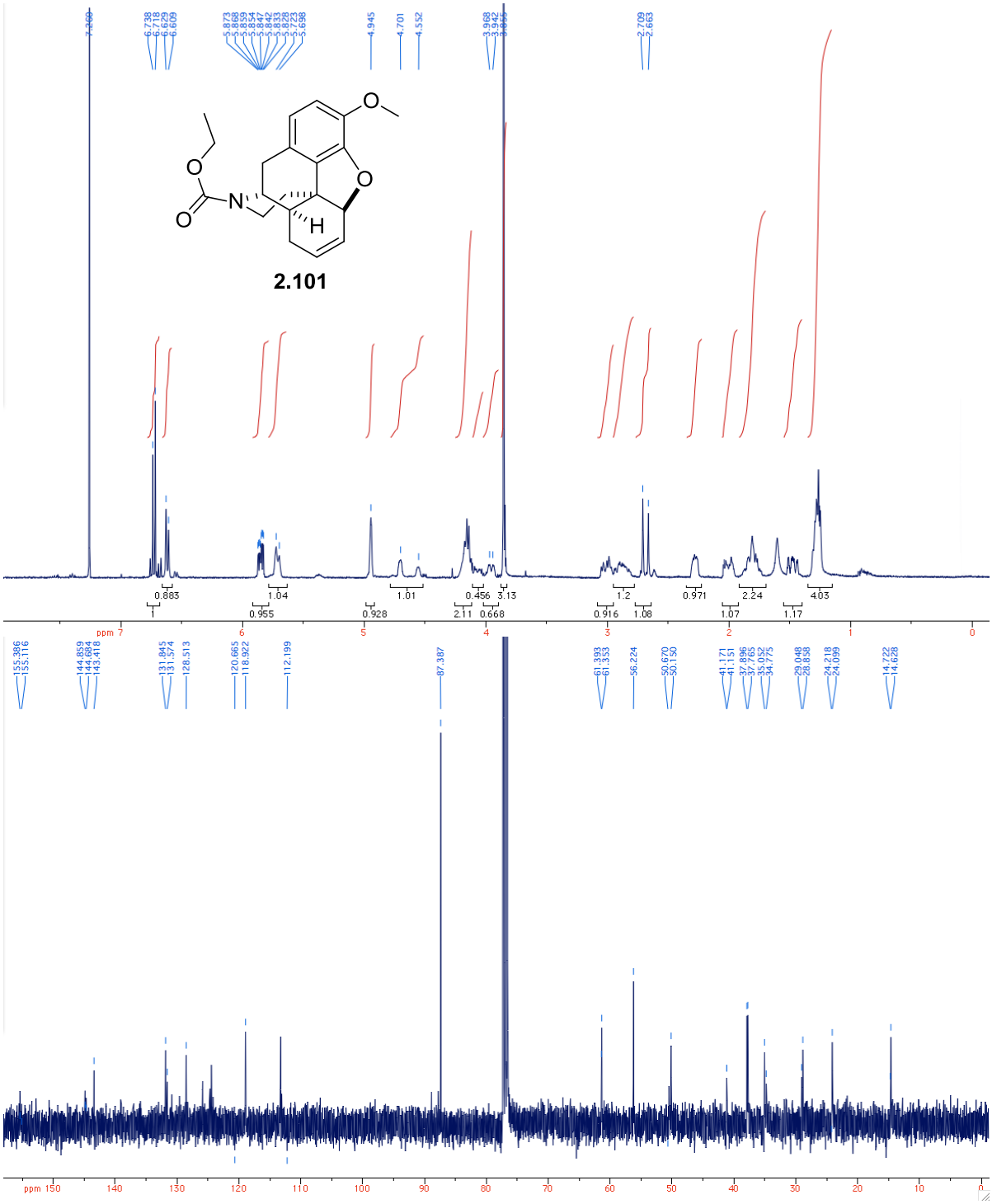

6.738
6.718
6.635
6.615
5.849
5.831
5.824
5.812
5.806
5.788
5.782
5.770
5.763
5.744
5.143
5.130
5.119
5.089
5.086
4.878
4.873
4.854
3.854
3.529
3.521
3.511
3.500
3.491
3.483
3.470
3.462
3.453
2.772
2.753
2.737
2.709
2.622
2.603
2.594
2.576
2.530
2.511
2.409
2.391
2.373
2.355
2.274
2.255
2.238
2.219
2.209
2.178
2.166
O
O
OH
2.91
1.02
1.05
1.07
2.1
0.975
3.15
1
1.03
1.08
5.27
2.17
2.17
ppm 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
144.529
143.678
133.875
131.502
125.792
120.517
118.718
113.521
87.720
66.675
56.639
45.462
41.382
38.227
35.763
31.761
23.489
21.087
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


9.647
6.740
6.719
6.639
6.618
O
O
O
OH
2.94
0.964
1.01
0.996
0.985
1.07
3.07
1.07
3.01
2
1.44
2.72
2.25
ppm 10
9
8
7
6
5
4
3
2
1
201.330
144.737
143.897
129.515
125.950
121.028
114.104
89.087
66.238
56.695
50.674
43.970
37.908
35.547
33.215
23.959
20.935
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


OH
2.95

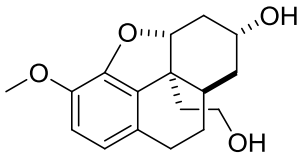

7.260
6.735
6.714
6.651
6.631
4.721
4.700
4.699
4.679
3.858
3.648
3.630
3.619
3.611
3.601
3.591
3.581
3.573
3.097
3.049
3.003
2.543
2.518
2.406
1.291
1.268
1.259
1.237
1.228
1.205
1.047
1.018
0.997
0.958
O
O
N
OH
2.93
1.02
0.959
3.1
1.05
0.942
1.05
1.01
5
2.27
3.44
1.42
1.06
144.013
143.911
129.784
126.912
119.172
113.588
89.229
66.787
59.790
56.649
47.634
42.945
42.126
41.683
38.812
34.971
34.501
20.235
ppm


2.100


7.260
6.738
6.718
6.629
6.609
5.873
5.866
5.859
5.854
5.847
5.842
5.833
5.828
5.723
5.698
4.945
4.701
4.552
3.968
3.947
3.942
3.663
2.709
2.663
0.883
1.04
1.01
0.456
3.13
1.2
0.971
2.24
4.03
0.955
0.928
2.11
0.668
0.916
1.08
1.07
1.17
ppm 7
6
5
4
3
2
1
0
155.386
155.116
144.859
144.684
143.418
131.845
131.574
128.513
120.665
118.922
112.199
87.387
61.393
61.333
56.224
50.670
50.150
41.171
41.151
37.896
37.765
35.052
34.775
29.048
28.838
24.218
24.099
14.722
14.628
ppm 150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

**2.101**

## 3.4 X-RAY DATA




**2.78**

**Datablock lb021** - ellipsoid plot

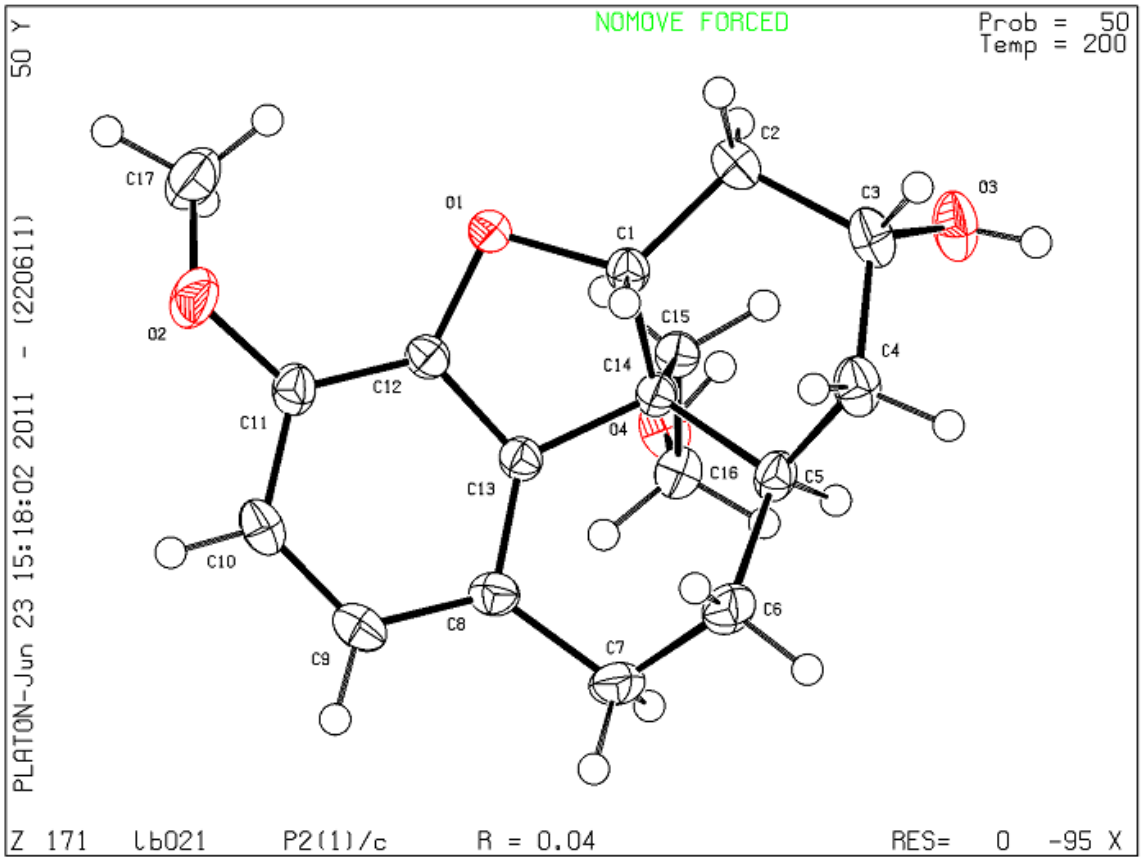


Table 1. Crystal data and structure refinement for lb021.

| | |
|---|---|
| Identification code | lb021 |
| Empirical formula | C17 H22 O4 |
| Formula weight | 290.35 |
| Temperature | 200(2) K |
| Wavelength | 0.71073 A |
| Crystal system, space group | Monoclinic, P2(1)/c |
| Unit cell dimensions | a = 14.0015(7) A alpha = 90 deg.<br>b = 7.3138(3) A beta = 105.776(2) deg.<br>c = 14.4994(7) A gamma = 90 deg. |
| Volume | 1428.87(12) A^3 |
| Z, Calculated density | 4, 1.350 Mg/m^3 |
| Absorption coefficient | 0.095 mm^-1 |
| F(000) | 624 |
| Crystal size | 0.21 x 0.18 x 0.16 mm |
| Theta range for data collection | 2.90 to 28.40 deg. |
| Limiting indices | -16<=h<=18, -9<=k<=9, -19<=l<=18 |
| Reflections collected / unique | 19447 / 3515 [R(int) = 0.0219] |
| Completeness to theta = 28.40 | 98.0 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.9850 and 0.9803 |
| Refinement method | Full-matrix least-squares on F^2 |
| Data / restraints / parameters | 3515 / 0 / 191 |
| Goodness-of-fit on F^2 | 1.006 |
| Final R indices [I>2sigma(I)] | R1 = 0.0362, wR2 = 0.1016 |
| R indices (all data) | R1 = 0.0420, wR2 = 0.1076 |
| Largest diff. peak and hole | 0.341 and -0.182 e.A^-3 |

Table 2. Atomic coordinates ( x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for lb021.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 3363(1) | 3278(1) | 7889(1) | 21(1) |
| O(2) | 4948(1) | 463(1) | 7872(1) | 37(1) |
| O(3) | 775(1) | 7492(1) | 7221(1) | 34(1) |
| O(4) | -58(1) | 742(1) | 6413(1) | 28(1) |
| C(1) | 2832(1) | 4884(1) | 7386(1) | 20(1) |
| C(2) | 2393(1) | 6201(1) | 7955(1) | 26(1) |
| C(3) | 1798(1) | 7639(1) | 7229(1) | 27(1) |
| C(4) | 1917(1) | 7455(1) | 6204(1) | 28(1) |
| C(5) | 1690(1) | 5545(1) | 5748(1) | 23(1) |
| C(6) | 2114(1) | 5292(2) | 4876(1) | 31(1) |
| C(7) | 2150(1) | 3279(2) | 4562(1) | 30(1) |
| C(8) | 2820(1) | 2213(1) | 5377(1) | 23(1) |
| C(9) | 3587(1) | 1007(2) | 5344(1) | 28(1) |
| C(10) | 4237(1) | 373(1) | 6187(1) | 28(1) |
| C(11) | 4200(1) | 987(1) | 7093(1) | 24(1) |
| C(12) | 3455(1) | 2216(1) | 7120(1) | 20(1) |
| C(13) | 2755(1) | 2688(1) | 6278(1) | 20(1) |
| C(14) | 2072(1) | 4071(1) | 6519(1) | 18(1) |
| C(15) | 1223(1) | 3101(1) | 6820(1) | 20(1) |
| C(16) | 551(1) | 1947(1) | 6037(1) | 24(1) |
| C(17) | 4688(1) | 109(2) | 8729(1) | 40(1) |

Table 3. Bond lengths [A] and angles [deg] for lb021.

| | |
|---|---|
| O(1)-C(12) | 1.3927(11) |
| O(1)-C(1) | 1.4728(11) |
| O(2)-C(11) | 1.3695(13) |
| O(2)-C(17) | 1.4106(14) |
| O(3)-C(3) | 1.4335(13) |
| O(4)-C(16) | 1.4333(11) |
| C(1)-C(2) | 1.5045(13) |
| C(1)-C(14) | 1.5297(13) |
| C(2)-C(3) | 1.5592(15) |
| C(3)-C(4) | 1.5447(15) |
| C(4)-C(5) | 1.5413(15) |
| C(5)-C(14) | 1.5406(12) |
| C(5)-C(6) | 1.5470(13) |
| C(6)-C(7) | 1.5457(16) |
| C(7)-C(8) | 1.5099(14) |
| C(8)-C(13) | 1.3790(13) |
| C(8)-C(9) | 1.4008(14) |

| | |
|---|---|
| C(9)-C(10) | 1.3902(16) |
| C(10)-C(11) | 1.4025(14) |
| C(11)-C(12) | 1.3851(13) |
| C(12)-C(13) | 1.3862(13) |
| C(13)-C(14) | 1.4970(12) |
| C(14)-C(15) | 1.5463(12) |
| C(15)-C(16) | 1.5184(14) |

| | |
|---|---|
| C(12)-O(1)-C(1) | 101.13(7) |
| C(11)-O(2)-C(17) | 117.08(8) |
| O(1)-C(1)-C(2) | 117.76(8) |
| O(1)-C(1)-C(14) | 103.98(7) |
| C(2)-C(1)-C(14) | 113.71(8) |
| C(1)-C(2)-C(3) | 106.52(8) |
| O(3)-C(3)-C(4) | 110.75(9) |
| O(3)-C(3)-C(2) | 107.66(8) |
| C(4)-C(3)-C(2) | 114.42(8) |
| C(5)-C(4)-C(3) | 115.37(8) |
| C(4)-C(5)-C(14) | 109.39(8) |
| C(4)-C(5)-C(6) | 112.30(8) |
| C(14)-C(5)-C(6) | 112.01(8) |
| C(7)-C(6)-C(5) | 113.91(9) |
| C(8)-C(7)-C(6) | 108.93(9) |
| C(13)-C(8)-C(9) | 116.07(9) |
| C(13)-C(8)-C(7) | 115.12(9) |
| C(9)-C(8)-C(7) | 128.13(9) |
| C(10)-C(9)-C(8) | 120.37(9) |
| C(9)-C(10)-C(11) | 122.29(9) |
| O(2)-C(11)-C(12) | 124.80(9) |
| O(2)-C(11)-C(10) | 117.89(9) |
| C(12)-C(11)-C(10) | 117.03(9) |
| C(11)-C(12)-C(13) | 119.64(9) |
| C(11)-C(12)-O(1) | 128.23(9) |
| C(13)-C(12)-O(1) | 111.61(8) |
| C(8)-C(13)-C(12) | 123.97(9) |
| C(8)-C(13)-C(14) | 127.03(9) |
| C(12)-C(13)-C(14) | 107.87(8) |
| C(13)-C(14)-C(1) | 96.21(7) |
| C(13)-C(14)-C(5) | 114.91(7) |
| C(1)-C(14)-C(5) | 110.56(8) |
| C(13)-C(14)-C(15) | 110.16(7) |
| C(1)-C(14)-C(15) | 111.29(7) |
| C(5)-C(14)-C(15) | 112.62(8) |
| C(16)-C(15)-C(14) | 114.30(8) |
| O(4)-C(16)-C(15) | 111.66(8) |

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Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for lb021.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [ h^2 a*^2 U11 + ... + 2 h k a* b* U12 ]

| | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|
| O(1) | 21(1) | 24(1) | 18(1) | 0(1) | 6(1) | 4(1) |
| O(2) | 24(1) | 54(1) | 33(1) | 10(1) | 7(1) | 17(1) |
| O(3) | 30(1) | 29(1) | 50(1) | 11(1) | 22(1) | 9(1) |
| O(4) | 25(1) | 22(1) | 41(1) | -1(1) | 14(1) | -3(1) |
| C(1) | 19(1) | 20(1) | 21(1) | 1(1) | 7(1) | 1(1) |
| C(2) | 27(1) | 24(1) | 28(1) | -4(1) | 11(1) | 1(1) |
| C(3) | 28(1) | 19(1) | 39(1) | 1(1) | 17(1) | 2(1) |
| C(4) | 32(1) | 21(1) | 37(1) | 8(1) | 17(1) | 4(1) |
| C(5) | 23(1) | 24(1) | 24(1) | 8(1) | 9(1) | 5(1) |
| C(6) | 36(1) | 35(1) | 23(1) | 11(1) | 12(1) | 6(1) |
| C(7) | 32(1) | 41(1) | 18(1) | 1(1) | 7(1) | 4(1) |
| C(8) | 24(1) | 27(1) | 20(1) | -2(1) | 8(1) | -1(1) |
| C(9) | 29(1) | 30(1) | 27(1) | -6(1) | 14(1) | 0(1) |
| C(10) | 26(1) | 26(1) | 34(1) | -2(1) | 14(1) | 5(1) |
| C(11) | 19(1) | 26(1) | 27(1) | 3(1) | 7(1) | 4(1) |
| C(12) | 19(1) | 22(1) | 20(1) | 0(1) | 8(1) | 0(1) |
| C(13) | 19(1) | 21(1) | 20(1) | 1(1) | 7(1) | 1(1) |
| C(14) | 17(1) | 20(1) | 19(1) | 3(1) | 7(1) | 2(1) |
| C(15) | 19(1) | 21(1) | 21(1) | 2(1) | 8(1) | 0(1) |
| C(16) | 22(1) | 22(1) | 27(1) | 3(1) | 6(1) | -2(1) |
| C(17) | 37(1) | 50(1) | 32(1) | 15(1) | 7(1) | 12(1) |

Table 5. Hydrogen coordinates ( x 10^4) and isotropic displacement parameters (A^2 x 10^3) for lb021.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(3B) | 470 | 8438 | 6975 | 41 |
| H(4C) | -337 | 1336 | 6763 | 34 |
| H(1A) | 3319 | 5590 | 7133 | 24 |
| H(2A) | 2924 | 6806 | 8454 | 31 |
| H(2B) | 1947 | 5550 | 8271 | 31 |
| H(3A) | 2037 | 8882 | 7474 | 33 |
| H(4A) | 1472 | 8352 | 5787 | 34 |
| H(4B) | 2607 | 7784 | 6220 | 34 |
| H(5A) | 952 | 5418 | 5514 | 28 |
| H(6A) | 1703 | 6001 | 4330 | 37 |
| H(6B) | 2794 | 5802 | 5036 | 37 |
| H(7A) | 1474 | 2749 | 4393 | 36 |
| H(7B) | 2407 | 3214 | 3991 | 36 |
| H(9A) | 3664 | 621 | 4743 | 33 |
| H(10A) | 4724 | -508 | 6148 | 33 |
| H(15A) | 1516 | 2307 | 7379 | 24 |

| | | | | |
|---|---|---|---|---|
| H(15B) | 814 | 4037 | 7028 | 24 |
| H(16A) | 121 | 2760 | 5552 | 28 |
| H(16B) | 962 | 1217 | 5716 | 28 |
| H(17A) | 5240 | -511 | 9184 | 60 |
| H(17B) | 4098 | -673 | 8592 | 60 |
| H(17C) | 4546 | 1266 | 9007 | 60 |

Table 6. Torsion angles [deg] for lb021.

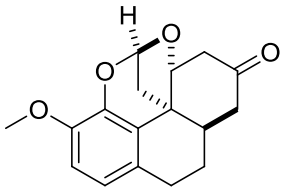
| | |
|---|---|
| C(12)-O(1)-C(1)-C(2) | 167.17(8) |
| C(12)-O(1)-C(1)-C(14) | 40.35(8) |
| O(1)-C(1)-C(2)-C(3) | -174.69(8) |
| C(14)-C(1)-C(2)-C(3) | -52.73(10) |
| C(1)-C(2)-C(3)-O(3) | 117.25(9) |
| C(1)-C(2)-C(3)-C(4) | -6.31(12) |
| O(3)-C(3)-C(4)-C(5) | -68.31(11) |
| C(2)-C(3)-C(4)-C(5) | 53.58(13) |
| C(3)-C(4)-C(5)-C(14) | -37.92(12) |
| C(3)-C(4)-C(5)-C(6) | -162.92(9) |
| C(4)-C(5)-C(6)-C(7) | 164.80(9) |
| C(14)-C(5)-C(6)-C(7) | 41.25(12) |
| C(5)-C(6)-C(7)-C(8) | -61.37(12) |
| C(6)-C(7)-C(8)-C(13) | 38.27(12) |
| C(6)-C(7)-C(8)-C(9) | -131.83(11) |
| C(13)-C(8)-C(9)-C(10) | -0.73(15) |
| C(7)-C(8)-C(9)-C(10) | 169.29(11) |
| C(8)-C(9)-C(10)-C(11) | -4.21(17) |
| C(17)-O(2)-C(11)-C(12) | 42.13(16) |
| C(17)-O(2)-C(11)-C(10) | -144.12(11) |
| C(9)-C(10)-C(11)-O(2) | -171.77(10) |
| C(9)-C(10)-C(11)-C(12) | 2.47(16) |
| O(2)-C(11)-C(12)-C(13) | 177.87(9) |
| C(10)-C(11)-C(12)-C(13) | 4.08(14) |
| O(2)-C(11)-C(12)-O(1) | 6.81(17) |
| C(10)-C(11)-C(12)-O(1) | -166.99(9) |
| C(1)-O(1)-C(12)-C(11) | 149.84(10) |
| C(1)-O(1)-C(12)-C(13) | -21.81(9) |
| C(9)-C(8)-C(13)-C(12) | 7.61(15) |
| C(7)-C(8)-C(13)-C(12) | -163.73(9) |
| C(9)-C(8)-C(13)-C(14) | 173.94(9) |
| C(7)-C(8)-C(13)-C(14) | 2.60(15) |
| C(11)-C(12)-C(13)-C(8) | -9.51(15) |
| O(1)-C(12)-C(13)-C(8) | 162.94(9) |
| C(11)-C(12)-C(13)-C(14) | -178.08(8) |
| O(1)-C(12)-C(13)-C(14) | -5.62(11) |
| C(8)-C(13)-C(14)-C(1) | -139.20(10) |
| C(12)-C(13)-C(14)-C(1) | 28.92(9) |
| C(8)-C(13)-C(14)-C(5) | -23.08(14) |
| C(12)-C(13)-C(14)-C(5) | 145.03(8) |
| C(8)-C(13)-C(14)-C(15) | 105.39(11) |
| C(12)-C(13)-C(14)-C(15) | -86.49(9) |

| | |
|---|---|
| O(1)-C(1)-C(14)-C(13) | -41.89(8) |
| C(2)-C(1)-C(14)-C(13) | -171.21(8) |
| O(1)-C(1)-C(14)-C(5) | -161.46(7) |
| C(2)-C(1)-C(14)-C(5) | 69.22(10) |
| O(1)-C(1)-C(14)-C(15) | 72.59(8) |
| C(2)-C(1)-C(14)-C(15) | -56.73(10) |
| C(4)-C(5)-C(14)-C(13) | -125.97(9) |
| C(6)-C(5)-C(14)-C(13) | -0.81(12) |
| C(4)-C(5)-C(14)-C(1) | -18.41(10) |
| C(6)-C(5)-C(14)-C(1) | 106.75(9) |
| C(4)-C(5)-C(14)-C(15) | 106.79(9) |
| C(6)-C(5)-C(14)-C(15) | -128.04(9) |
| C(13)-C(14)-C(15)-C(16) | -63.13(10) |
| C(1)-C(14)-C(15)-C(16) | -168.60(8) |
| C(5)-C(14)-C(15)-C(16) | 66.59(10) |
| C(14)-C(15)-C(16)-O(4) | 165.68(8) |

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for lb021 [A and deg.].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|




**2.85**

**Datablock lb022** - ellipsoid plot

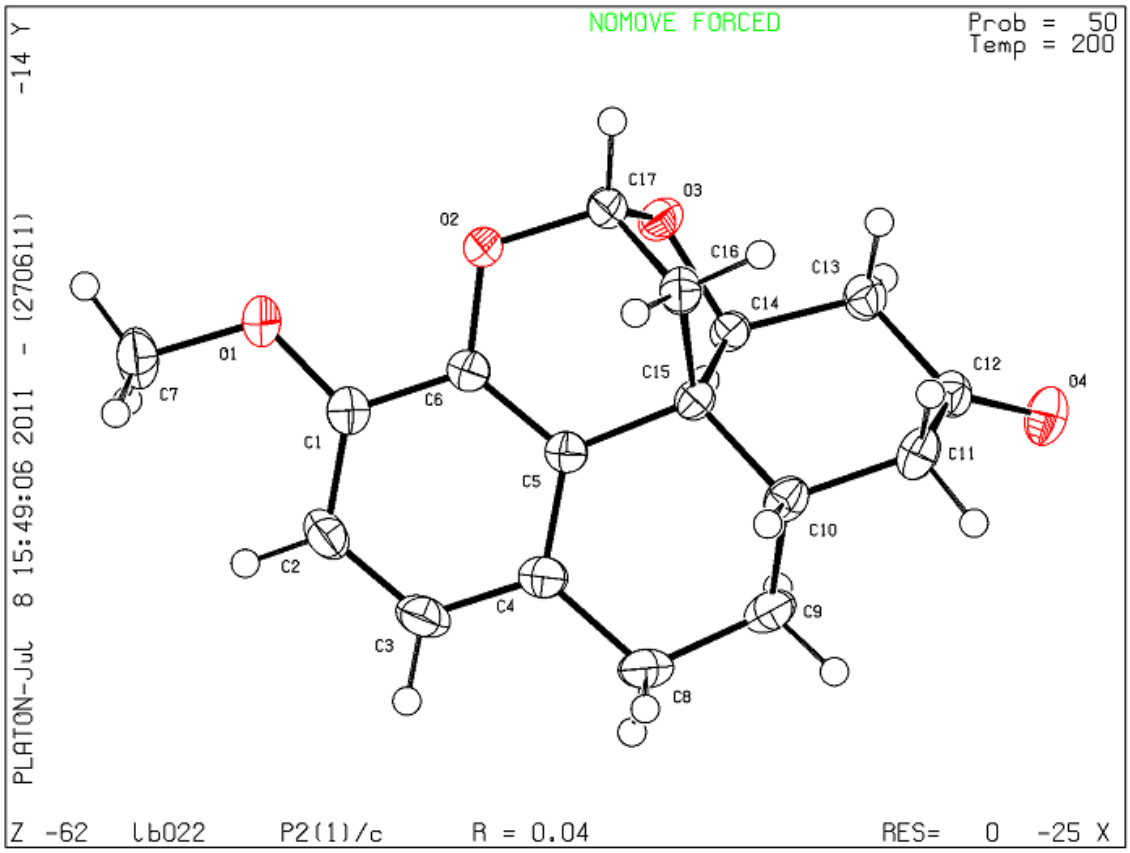


Table 1. Crystal data and structure refinement for lb022.

| | |
|---|---|
| Identification code | lb022 |
| Empirical formula | C17 H18 O4 |
| Formula weight | 286.31 |
| Temperature | 200(2) K |
| Wavelength | 0.71073 A |
| Crystal system, space group | Monoclinic, P2(1)/c |
| Unit cell dimensions | a = 8.75620(10) A alpha = 90 deg.<br>b = 14.2583(2) A beta = 107.4600(10) deg.<br>c = 11.3674(2) A gamma = 90 deg. |
| Volume | 1353.82(3) A^3 |
| Z, Calculated density | 4, 1.405 Mg/m^3 |
| Absorption coefficient | 0.099 mm^-1 |
| F(000) | 608 |
| Crystal size | 0.14 x 0.06 x 0.05 mm |
| Theta range for data collection | 2.36 to 28.29 deg. |
| Limiting indices | -11<=h<=11, -19<=k<=17, -15<=l<=15 |
| Reflections collected / unique | 21531 / 3332 [R(int) = 0.0256] |
| Completeness to theta = 28.29 | 99.0 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.9950 and 0.9862 |
| Refinement method | Full-matrix least-squares on F^2 |
| Data / restraints / parameters | 3332 / 0 / 190 |
| Goodness-of-fit on F^2 | 1.047 |
| Final R indices [I>2sigma(I)] | R1 = 0.0416, wR2 = 0.1008 |
| R indices (all data) | R1 = 0.0603, wR2 = 0.1086 |
| Largest diff. peak and hole | 0.314 and -0.210 e.A^-3 |

Table 2. Atomic coordinates ( x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for lb022.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 1352(1) | 5119(1) | -1372(1) | 31(1) |
| O(2) | 3827(1) | 4210(1) | -52(1) | 26(1) |
| O(3) | 5411(1) | 2935(1) | -190(1) | 27(1) |
| O(4) | 6175(1) | -167(1) | 1428(1) | 33(1) |
| C(1) | 1040(2) | 4261(1) | -955(1) | 25(1) |
| C(2) | -460(2) | 3869(1) | -1160(1) | 31(1) |
| C(3) | -615(2) | 2985(1) | -690(1) | 34(1) |
| C(4) | 710(2) | 2476(1) | -14(1) | 27(1) |
| C(5) | 2238(1) | 2870(1) | 208(1) | 21(1) |
| C(6) | 2381(1) | 3761(1) | -257(1) | 22(1) |
| C(7) | 19(2) | 5653(1) | -2086(1) | 38(1) |
| C(8) | 500(2) | 1534(1) | 528(2) | 34(1) |
| C(9) | 2040(2) | 971(1) | 938(1) | 30(1) |
| C(10) | 3404(2) | 1570(1) | 1740(1) | 24(1) |
| C(11) | 4889(2) | 969(1) | 2344(1) | 28(1) |
| C(12) | 5728(1) | 635(1) | 1450(1) | 24(1) |
| C(13) | 6099(2) | 1389(1) | 650(1) | 25(1) |
| C(14) | 4723(1) | 2072(1) | 95(1) | 21(1) |
| C(15) | 3770(1) | 2378(1) | 973(1) | 20(1) |
| C(16) | 4877(2) | 3162(1) | 1681(1) | 25(1) |
| C(17) | 5185(2) | 3657(1) | 593(1) | 25(1) |

Table 3. Bond lengths [A] and angles [deg] for lb022.

| | |
|---|---|
| O(1)-C(1) | 1.3683(16) |
| O(1)-C(7) | 1.4258(16) |
| O(2)-C(6) | 1.3744(14) |
| O(2)-C(17) | 1.4317(15) |
| O(3)-C(17) | 1.4140(16) |
| O(3)-C(14) | 1.4482(14) |
| O(4)-C(12) | 1.2115(15) |
| C(1)-C(2) | 1.3815(18) |
| C(1)-C(6) | 1.3993(17) |
| C(2)-C(3) | 1.392(2) |
| C(3)-C(4) | 1.3887(19) |
| C(4)-C(5) | 1.4028(17) |
| C(4)-C(8) | 1.5115(19) |
| C(5)-C(6) | 1.3959(17) |
| C(5)-C(15) | 1.5324(16) |
| C(8)-C(9) | 1.5171(19) |
| C(9)-C(10) | 1.5277(18) |

| | |
|---|---|
| C(10)-C(15) | 1.5361(17) |
| C(10)-C(11) | 1.5359(18) |
| C(11)-C(12) | 1.4983(18) |
| C(12)-C(13) | 1.5048(18) |
| C(13)-C(14) | 1.5306(17) |
| C(14)-C(15) | 1.5434(16) |
| C(15)-C(16) | 1.5389(16) |
| C(16)-C(17) | 1.5163(18) |

| | |
|---|---|
| C(1)-O(1)-C(7) | 117.37(10) |
| C(6)-O(2)-C(17) | 114.32(9) |
| C(17)-O(3)-C(14) | 109.35(9) |
| O(1)-C(1)-C(2) | 125.59(12) |
| O(1)-C(1)-C(6) | 115.51(11) |
| C(2)-C(1)-C(6) | 118.90(12) |
| C(1)-C(2)-C(3) | 119.92(12) |
| C(2)-C(3)-C(4) | 121.68(12) |
| C(3)-C(4)-C(5) | 118.87(12) |
| C(3)-C(4)-C(8) | 120.45(12) |
| C(5)-C(4)-C(8) | 120.60(12) |
| C(6)-C(5)-C(4) | 119.09(11) |
| C(6)-C(5)-C(15) | 117.92(10) |
| C(4)-C(5)-C(15) | 122.97(11) |
| O(2)-C(6)-C(5) | 122.84(11) |
| O(2)-C(6)-C(1) | 115.63(11) |
| C(5)-C(6)-C(1) | 121.52(11) |
| C(4)-C(8)-C(9) | 112.93(11) |
| C(8)-C(9)-C(10) | 110.59(11) |
| C(9)-C(10)-C(15) | 109.88(10) |
| C(9)-C(10)-C(11) | 111.15(10) |
| C(15)-C(10)-C(11) | 112.30(10) |
| C(12)-C(11)-C(10) | 113.30(10) |
| O(4)-C(12)-C(11) | 122.84(12) |
| O(4)-C(12)-C(13) | 122.08(12) |
| C(11)-C(12)-C(13) | 114.90(10) |
| C(12)-C(13)-C(14) | 114.73(10) |
| O(3)-C(14)-C(13) | 107.71(9) |
| O(3)-C(14)-C(15) | 104.26(9) |
| C(13)-C(14)-C(15) | 115.10(10) |
| C(10)-C(15)-C(5) | 111.66(10) |
| C(10)-C(15)-C(16) | 116.99(10) |
| C(5)-C(15)-C(16) | 105.73(9) |
| C(10)-C(15)-C(14) | 113.58(10) |
| C(5)-C(15)-C(14) | 108.29(9) |
| C(16)-C(15)-C(14) | 99.57(9) |
| C(17)-C(16)-C(15) | 98.59(10) |
| O(3)-C(17)-O(2) | 109.26(10) |
| O(3)-C(17)-C(16) | 105.52(10) |
| O(2)-C(17)-C(16) | 110.51(10) |

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Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for lb022.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [ h^2 a*^2 U11 + ... + 2 h k a* b* U12 ]

| | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|
| O(1) | 28(1) | 26(1) | 37(1) | 9(1) | 5(1) | 6(1) |
| O(2) | 20(1) | 19(1) | 35(1) | 4(1) | 5(1) | -1(1) |
| O(3) | 29(1) | 22(1) | 34(1) | 5(1) | 16(1) | 0(1) |
| O(4) | 43(1) | 21(1) | 33(1) | 1(1) | 10(1) | 6(1) |
| C(1) | 27(1) | 25(1) | 24(1) | 0(1) | 7(1) | 2(1) |
| C(2) | 21(1) | 36(1) | 33(1) | 1(1) | 2(1) | 5(1) |
| C(3) | 20(1) | 38(1) | 40(1) | -2(1) | 6(1) | -5(1) |
| C(4) | 24(1) | 27(1) | 31(1) | -3(1) | 10(1) | -3(1) |
| C(5) | 22(1) | 21(1) | 21(1) | -2(1) | 8(1) | 0(1) |
| C(6) | 21(1) | 22(1) | 22(1) | -2(1) | 7(1) | 0(1) |
| C(7) | 36(1) | 37(1) | 38(1) | 10(1) | 6(1) | 12(1) |
| C(8) | 27(1) | 32(1) | 45(1) | 1(1) | 14(1) | -8(1) |
| C(9) | 34(1) | 23(1) | 37(1) | 2(1) | 17(1) | -6(1) |
| C(10) | 31(1) | 22(1) | 24(1) | 1(1) | 13(1) | 1(1) |
| C(11) | 38(1) | 23(1) | 23(1) | 4(1) | 11(1) | 3(1) |
| C(12) | 23(1) | 21(1) | 22(1) | -1(1) | 0(1) | 1(1) |
| C(13) | 25(1) | 24(1) | 28(1) | 1(1) | 10(1) | 3(1) |
| C(14) | 22(1) | 18(1) | 22(1) | 1(1) | 8(1) | 0(1) |
| C(15) | 22(1) | 18(1) | 20(1) | -1(1) | 6(1) | -1(1) |
| C(16) | 26(1) | 21(1) | 24(1) | -2(1) | 2(1) | 0(1) |
| C(17) | 20(1) | 19(1) | 34(1) | 1(1) | 4(1) | 0(1) |

Table 5. Hydrogen coordinates ( x 10^4) and isotropic
displacement parameters (A^2 x 10^3) for lb022.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(2A) | -1385 | 4203 | -1620 | 37 |
| H(3A) | -1653 | 2723 | -836 | 40 |
| H(7A) | 398 | 6250 | -2323 | 57 |
| H(7B) | -709 | 5775 | -1596 | 57 |
| H(7C) | -548 | 5301 | -2829 | 57 |
| H(8A) | -316 | 1169 | -95 | 41 |
| H(8B) | 98 | 1633 | 1245 | 41 |
| H(9A) | 2321 | 747 | 205 | 36 |
| H(9B) | 1882 | 416 | 1412 | 36 |
| H(10A) | 3035 | 1850 | 2414 | 29 |
| H(11A) | 5648 | 1342 | 2998 | 33 |
| H(11B) | 4562 | 418 | 2741 | 33 |

| | | | | |
|---|---|---|---|---|
| H(13A) | 6404 | 1086 | -30 | 30 |
| H(13B) | 7035 | 1750 | 1148 | 30 |
| H(14A) | 3979 | 1800 | -676 | 25 |
| H(16A) | 4332 | 3574 | 2130 | 29 |
| H(16B) | 5873 | 2910 | 2261 | 29 |
| H(17A) | 6164 | 4058 | 875 | 30 |

Table 6. Torsion angles [deg] for lb022.

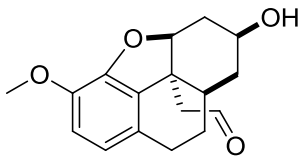
| | |
|---|---|
| C(7)-O(1)-C(1)-C(2) | -0.39(19) |
| C(7)-O(1)-C(1)-C(6) | -179.89(12) |
| O(1)-C(1)-C(2)-C(3) | 179.52(12) |
| C(6)-C(1)-C(2)-C(3) | -1.0(2) |
| C(1)-C(2)-C(3)-C(4) | -0.1(2) |
| C(2)-C(3)-C(4)-C(5) | 0.6(2) |
| C(2)-C(3)-C(4)-C(8) | 177.49(13) |
| C(3)-C(4)-C(5)-C(6) | 0.01(19) |
| C(8)-C(4)-C(5)-C(6) | -176.90(12) |
| C(3)-C(4)-C(5)-C(15) | 178.27(12) |
| C(8)-C(4)-C(5)-C(15) | 1.36(19) |
| C(17)-O(2)-C(6)-C(5) | 4.71(17) |
| C(17)-O(2)-C(6)-C(1) | -176.05(11) |
| C(4)-C(5)-C(6)-O(2) | 178.08(11) |
| C(15)-C(5)-C(6)-O(2) | -0.26(18) |
| C(4)-C(5)-C(6)-C(1) | -1.11(19) |
| C(15)-C(5)-C(6)-C(1) | -179.46(11) |
| O(1)-C(1)-C(6)-O(2) | 1.89(17) |
| C(2)-C(1)-C(6)-O(2) | -177.64(12) |
| O(1)-C(1)-C(6)-C(5) | -178.86(11) |
| C(2)-C(1)-C(6)-C(5) | 1.61(19) |
| C(3)-C(4)-C(8)-C(9) | 164.97(13) |
| C(5)-C(4)-C(8)-C(9) | -18.17(19) |
| C(4)-C(8)-C(9)-C(10) | 49.54(16) |
| C(8)-C(9)-C(10)-C(15) | -64.90(14) |
| C(8)-C(9)-C(10)-C(11) | 170.17(11) |
| C(9)-C(10)-C(11)-C(12) | 71.65(14) |
| C(15)-C(10)-C(11)-C(12) | -51.91(14) |
| C(10)-C(11)-C(12)-O(4) | -134.19(12) |
| C(10)-C(11)-C(12)-C(13) | 50.70(14) |
| O(4)-C(12)-C(13)-C(14) | 139.97(12) |
| C(11)-C(12)-C(13)-C(14) | -44.87(15) |
| C(17)-O(3)-C(14)-C(13) | -112.54(10) |
| C(17)-O(3)-C(14)-C(15) | 10.18(12) |
| C(12)-C(13)-C(14)-O(3) | 156.58(10) |
| C(12)-C(13)-C(14)-C(15) | 40.79(15) |
| C(9)-C(10)-C(15)-C(5) | 46.35(13) |
| C(11)-C(10)-C(15)-C(5) | 170.61(10) |
| C(9)-C(10)-C(15)-C(16) | 168.34(10) |
| C(11)-C(10)-C(15)-C(16) | -67.40(14) |
| C(9)-C(10)-C(15)-C(14) | -76.46(12) |
| C(11)-C(10)-C(15)-C(14) | 47.81(14) |

| | |
|---|---|
| C(6)-C(5)-C(15)-C(10) | 162.39(10) |
| C(4)-C(5)-C(15)-C(10) | -15.89(16) |
| C(6)-C(5)-C(15)-C(16) | 34.13(14) |
| C(4)-C(5)-C(15)-C(16) | -144.15(12) |
| C(6)-C(5)-C(15)-C(14) | -71.83(13) |
| C(4)-C(5)-C(15)-C(14) | 109.89(13) |
| O(3)-C(14)-C(15)-C(10) | -160.50(9) |
| C(13)-C(14)-C(15)-C(10) | -42.75(14) |
| O(3)-C(14)-C(15)-C(5) | 74.86(11) |
| C(13)-C(14)-C(15)-C(5) | -167.39(10) |
| O(3)-C(14)-C(15)-C(16) | -35.35(11) |
| C(13)-C(14)-C(15)-C(16) | 82.40(12) |
| C(10)-C(15)-C(16)-C(17) | 168.26(10) |
| C(5)-C(15)-C(16)-C(17) | -66.72(11) |
| C(14)-C(15)-C(16)-C(17) | 45.50(11) |
| C(14)-O(3)-C(17)-O(2) | -98.74(10) |
| C(14)-O(3)-C(17)-C(16) | 20.09(12) |
| C(6)-O(2)-C(17)-O(3) | 70.64(13) |
| C(6)-O(2)-C(17)-C(16) | -45.04(14) |
| C(15)-C(16)-C(17)-O(3) | -41.51(11) |
| C(15)-C(16)-C(17)-O(2) | 76.48(11) |

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for lb022 [A and deg.].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|




**2.94**

**Datablock lb067_5** - ellipsoid plot

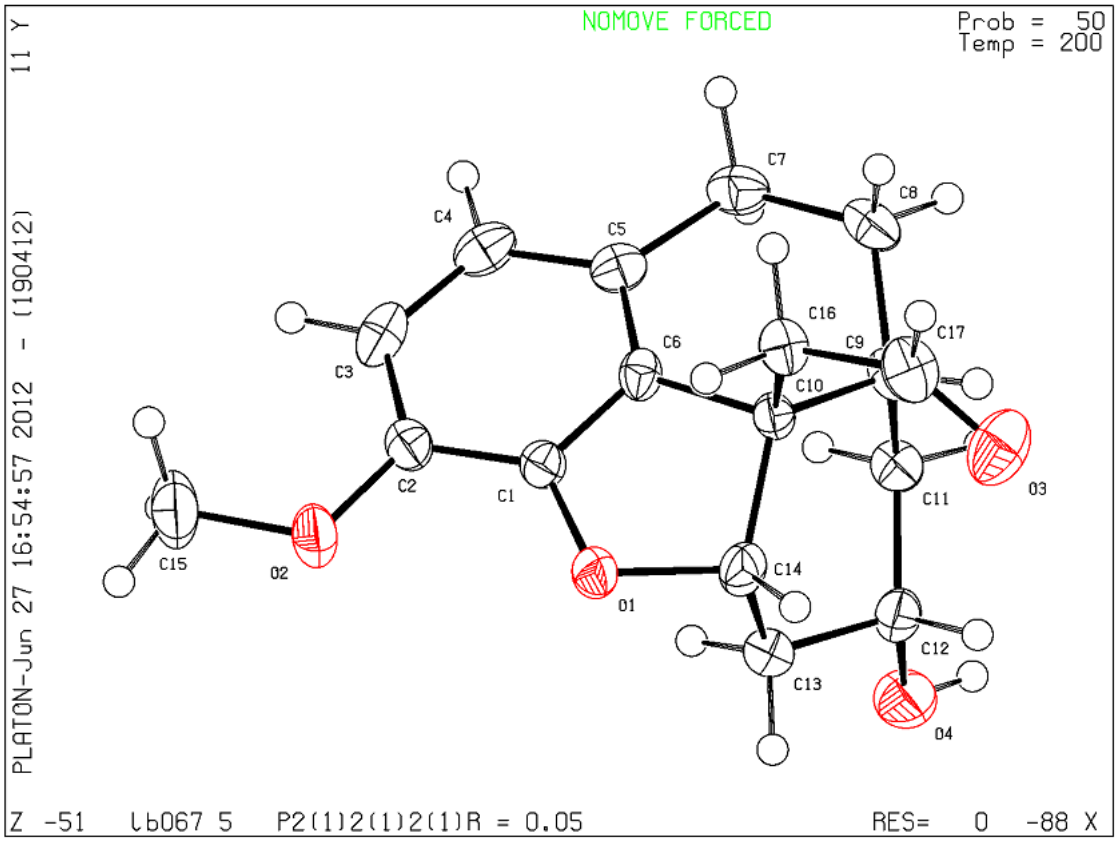


Table 1. Crystal data and structure refinement for lb067_5.

| | |
|---|---|
| Identification code | lb067_5 |
| Empirical formula | C17 H20 O4 |
| Formula weight | 288.33 |
| Temperature | 200(2) K |
| Wavelength | 0.71073 A |
| Crystal system, space group | Orthorhombic, P2(1)2(1)2(1) |
| Unit cell dimensions | a = 6.8347(4) A alpha = 90 deg.<br>b = 11.9375(7) A beta = 90 deg.<br>c = 17.2314(9) A gamma = 90 deg. |
| Volume | 1405.90(14) A^3 |
| Z, Calculated density | 4, 1.362 Mg/m^3 |
| Absorption coefficient | 0.096 mm^-1 |
| F(000) | 616 |
| Crystal size | 0.31 x 0.18 x 0.04 mm |
| Theta range for data collection | 2.08 to 28.39 deg. |
| Limiting indices | 0<=h<=9, 0<=k<=15, 0<=l<=23 |
| Reflections collected / unique | 5097 / 2687 [R(int) = 0.0000] |
| Completeness to theta = 28.39 | 98.4 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.9962 and 0.9708 |
| Refinement method | Full-matrix least-squares on F^2 |
| Data / restraints / parameters | 2687 / 0 / 191 |
| Goodness-of-fit on F^2 | 1.038 |
| Final R indices [I>2sigma(I)] | R1 = 0.0545, wR2 = 0.1227 |
| R indices (all data) | R1 = 0.0978, wR2 = 0.1458 |
| Absolute structure parameter | 2(2) |
| Largest diff. peak and hole | 0.259 and -0.254 e.A^-3 |

Table 2. Atomic coordinates ( x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for lb067_5.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 630(4) | 6124(2) | 533(1) | 28(1) |
| O(2) | -1629(4) | 5913(2) | -854(2) | 37(1) |
| O(3) | 6018(5) | 6703(2) | 1901(2) | 46(1) |
| O(4) | 1041(4) | 3059(2) | 2301(2) | 42(1) |
| C(1) | 1164(6) | 5485(3) | -103(2) | 23(1) |
| C(2) | 85(6) | 5316(3) | -776(2) | 26(1) |
| C(3) | 826(7) | 4552(3) | -1311(2) | 32(1) |
| C(4) | 2564(6) | 3977(3) | -1172(2) | 31(1) |
| C(5) | 3657(6) | 4161(3) | -503(2) | 26(1) |
| C(6) | 2921(6) | 4962(3) | -3(2) | 22(1) |
| C(7) | 5437(6) | 3506(3) | -264(2) | 32(1) |
| C(8) | 6438(6) | 3955(3) | 467(2) | 30(1) |
| C(9) | 5053(5) | 4404(3) | 1098(2) | 24(1) |
| C(10) | 3827(5) | 5360(3) | 752(2) | 21(1) |
| C(11) | 3765(6) | 3487(3) | 1436(2) | 27(1) |
| C(12) | 2228(6) | 3940(3) | 1989(2) | 29(1) |
| C(13) | 864(6) | 4727(3) | 1565(2) | 32(1) |
| C(14) | 1907(6) | 5704(3) | 1172(2) | 27(1) |
| C(15) | -2664(7) | 5823(4) | -1575(2) | 52(1) |
| C(16) | 5058(6) | 6408(3) | 572(2) | 28(1) |
| C(17) | 6152(6) | 6928(3) | 1228(2) | 34(1) |

Table 3. Bond lengths [A] and angles [deg] for lb067_5.

| | |
|---|---|
| O(1)-C(1) | 1.384(4) |
| O(1)-C(14) | 1.491(4) |
| O(2)-C(2) | 1.377(5) |
| O(2)-C(15) | 1.433(5) |
| O(3)-C(17) | 1.193(4) |
| O(4)-C(12) | 1.432(5) |
| C(1)-C(6) | 1.364(5) |
| C(1)-C(2) | 1.389(5) |
| C(2)-C(3) | 1.391(5) |
| C(3)-C(4) | 1.393(6) |
| C(4)-C(5) | 1.391(5) |
| C(5)-C(6) | 1.383(5) |
| C(5)-C(7) | 1.504(5) |
| C(6)-C(10) | 1.517(4) |
| C(7)-C(8) | 1.531(5) |

| | |
|---|---|
| C(8)-C(9) | 1.537(5) |
| C(9)-C(11) | 1.521(5) |
| C(9)-C(10) | 1.537(5) |
| C(10)-C(16) | 1.539(5) |
| C(10)-C(14) | 1.554(5) |
| C(11)-C(12) | 1.517(5) |
| C(12)-C(13) | 1.512(5) |
| C(13)-C(14) | 1.525(5) |
| C(16)-C(17) | 1.491(5) |

| | |
|---|---|
| C(1)-O(1)-C(14) | 104.2(3) |
| C(2)-O(2)-C(15) | 117.8(3) |
| C(6)-C(1)-O(1) | 112.5(3) |
| C(6)-C(1)-C(2) | 120.5(3) |
| O(1)-C(1)-C(2) | 127.0(3) |
| O(2)-C(2)-C(3) | 125.7(3) |
| O(2)-C(2)-C(1) | 117.3(3) |
| C(3)-C(2)-C(1) | 117.0(3) |
| C(2)-C(3)-C(4) | 121.3(3) |
| C(3)-C(4)-C(5) | 121.5(3) |
| C(6)-C(5)-C(4) | 115.5(4) |
| C(6)-C(5)-C(7) | 118.9(3) |
| C(4)-C(5)-C(7) | 125.4(3) |
| C(1)-C(6)-C(5) | 123.9(3) |
| C(1)-C(6)-C(10) | 109.0(3) |
| C(5)-C(6)-C(10) | 127.1(3) |
| C(5)-C(7)-C(8) | 113.9(3) |
| C(7)-C(8)-C(9) | 115.4(3) |
| C(11)-C(9)-C(10) | 111.6(3) |
| C(11)-C(9)-C(8) | 112.1(3) |
| C(10)-C(9)-C(8) | 108.7(3) |
| C(6)-C(10)-C(9) | 108.8(3) |
| C(6)-C(10)-C(16) | 107.8(3) |
| C(9)-C(10)-C(16) | 112.6(3) |
| C(6)-C(10)-C(14) | 97.9(3) |
| C(9)-C(10)-C(14) | 118.4(3) |
| C(16)-C(10)-C(14) | 109.9(3) |
| C(12)-C(11)-C(9) | 112.6(3) |
| O(4)-C(12)-C(13) | 106.8(3) |
| O(4)-C(12)-C(11) | 111.5(3) |
| C(13)-C(12)-C(11) | 110.2(3) |
| C(12)-C(13)-C(14) | 113.7(3) |
| O(1)-C(14)-C(13) | 108.1(3) |
| O(1)-C(14)-C(10) | 103.9(2) |
| C(13)-C(14)-C(10) | 113.6(3) |
| C(17)-C(16)-C(10) | 117.4(3) |
| O(3)-C(17)-C(16) | 127.2(4) |

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Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for lb067_5.

The anisotropic displacement factor exponent takes the form:
-2 pi^2 [ h^2 a*^2 U11 + ... + 2 h k a* b* U12 ]

| | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|
| O(1) | 27(2) | 32(1) | 25(1) | 0(1) | -3(1) | 8(1) |
| O(2) | 31(2) | 49(2) | 32(1) | 8(1) | -10(1) | 3(2) |
| O(3) | 61(2) | 43(2) | 34(1) | -7(1) | -8(2) | -13(2) |
| O(4) | 36(2) | 48(2) | 40(2) | 15(1) | 5(2) | 0(2) |
| C(1) | 23(2) | 23(2) | 23(2) | 5(1) | 0(2) | 1(2) |
| C(2) | 22(2) | 28(2) | 28(2) | 10(2) | -1(2) | -2(2) |
| C(3) | 45(3) | 30(2) | 21(2) | 2(2) | -5(2) | -11(2) |
| C(4) | 43(3) | 25(2) | 26(2) | -2(2) | 6(2) | -2(2) |
| C(5) | 28(2) | 22(2) | 28(2) | 3(1) | 5(2) | -6(2) |
| C(6) | 24(2) | 22(2) | 22(2) | 2(1) | -5(2) | -5(2) |
| C(7) | 32(2) | 30(2) | 35(2) | -2(2) | 7(2) | 6(2) |
| C(8) | 21(2) | 28(2) | 42(2) | 6(2) | 2(2) | 3(2) |
| C(9) | 18(2) | 24(2) | 30(2) | 4(2) | -4(2) | -2(2) |
| C(10) | 20(2) | 22(2) | 21(1) | -2(1) | -3(2) | 2(2) |
| C(11) | 26(2) | 24(2) | 30(2) | 2(2) | 0(2) | -1(2) |
| C(12) | 28(2) | 36(2) | 22(2) | 1(2) | -3(2) | -2(2) |
| C(13) | 24(2) | 44(2) | 27(2) | 2(2) | 1(2) | 4(2) |
| C(14) | 31(2) | 29(2) | 22(2) | -6(2) | -4(2) | 2(2) |
| C(15) | 41(3) | 71(3) | 42(2) | 17(2) | -18(2) | -5(3) |
| C(16) | 28(2) | 25(2) | 30(2) | 1(2) | -4(2) | -1(2) |
| C(17) | 33(2) | 28(2) | 43(2) | -2(2) | -7(2) | -6(2) |

Table 5. Hydrogen coordinates ( x 10^4) and isotropic displacement parameters (A^2 x 10^3) for lb067_5.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(4B) | 1762 | 2575 | 2508 | 50 |
| H(3A) | 132 | 4421 | -1780 | 38 |
| H(4A) | 3014 | 3447 | -1543 | 38 |
| H(7A) | 6391 | 3513 | -696 | 39 |
| H(7B) | 5051 | 2717 | -173 | 39 |
| H(8A) | 7340 | 4565 | 314 | 37 |
| H(8B) | 7239 | 3347 | 695 | 37 |
| H(9A) | 5868 | 4719 | 1527 | 29 |
| H(11A) | 3106 | 3084 | 1007 | 32 |
| H(11B) | 4598 | 2942 | 1716 | 32 |
| H(12A) | 2884 | 4350 | 2423 | 35 |
| H(13A) | -102 | 5029 | 1938 | 38 |
| H(13B) | 136 | 4298 | 1167 | 38 |
| H(14A) | 2170 | 6314 | 1555 | 33 |

| | | | | |
|---|---|---|---|---|
| H(15A) | -3845 | 6287 | -1554 | 77 |
| H(15B) | -3034 | 5040 | -1663 | 77 |
| H(15C) | -1822 | 6080 | -1999 | 77 |
| H(16A) | 6015 | 6209 | 164 | 34 |
| H(16B) | 4176 | 6984 | 352 | 34 |
| H(17A) | 7057 | 7501 | 1096 | 41 |

Table 6. Torsion angles [deg] for lb067_5.

| | |
|---|---|
| C(14)-O(1)-C(1)-C(6) | -16.9(4) |
| C(14)-O(1)-C(1)-C(2) | 160.6(3) |
| C(15)-O(2)-C(2)-C(3) | -6.0(5) |
| C(15)-O(2)-C(2)-C(1) | 174.5(3) |
| C(6)-C(1)-C(2)-O(2) | -177.0(3) |
| O(1)-C(1)-C(2)-O(2) | 5.7(5) |
| C(6)-C(1)-C(2)-C(3) | 3.4(5) |
| O(1)-C(1)-C(2)-C(3) | -173.9(3) |
| O(2)-C(2)-C(3)-C(4) | -179.0(3) |
| C(1)-C(2)-C(3)-C(4) | 0.6(5) |
| C(2)-C(3)-C(4)-C(5) | -1.6(5) |
| C(3)-C(4)-C(5)-C(6) | -1.3(5) |
| C(3)-C(4)-C(5)-C(7) | 173.7(3) |
| O(1)-C(1)-C(6)-C(5) | 170.9(3) |
| C(2)-C(1)-C(6)-C(5) | -6.8(5) |
| O(1)-C(1)-C(6)-C(10) | -6.2(4) |
| C(2)-C(1)-C(6)-C(10) | 176.2(3) |
| C(4)-C(5)-C(6)-C(1) | 5.5(5) |
| C(7)-C(5)-C(6)-C(1) | -169.8(3) |
| C(4)-C(5)-C(6)-C(10) | -178.0(3) |
| C(7)-C(5)-C(6)-C(10) | 6.7(5) |
| C(6)-C(5)-C(7)-C(8) | -9.8(5) |
| C(4)-C(5)-C(7)-C(8) | 175.4(3) |
| C(5)-C(7)-C(8)-C(9) | 37.1(4) |
| C(7)-C(8)-C(9)-C(11) | 64.8(4) |
| C(7)-C(8)-C(9)-C(10) | -59.1(4) |
| C(1)-C(6)-C(10)-C(9) | 148.6(3) |
| C(5)-C(6)-C(10)-C(9) | -28.3(5) |
| C(1)-C(6)-C(10)-C(16) | -89.0(3) |
| C(5)-C(6)-C(10)-C(16) | 94.1(4) |
| C(1)-C(6)-C(10)-C(14) | 24.9(3) |
| C(5)-C(6)-C(10)-C(14) | -152.0(3) |
| C(11)-C(9)-C(10)-C(6) | -73.4(4) |
| C(8)-C(9)-C(10)-C(6) | 50.8(4) |
| C(11)-C(9)-C(10)-C(16) | 167.2(3) |
| C(8)-C(9)-C(10)-C(16) | -68.6(4) |
| C(11)-C(9)-C(10)-C(14) | 37.0(4) |
| C(8)-C(9)-C(10)-C(14) | 161.2(3) |
| C(10)-C(9)-C(11)-C(12) | -51.0(4) |
| C(8)-C(9)-C(11)-C(12) | -173.2(3) |
| C(9)-C(11)-C(12)-O(4) | -179.8(3) |
| C(9)-C(11)-C(12)-C(13) | 61.9(4) |

| | |
|---|---|
| O(4)-C(12)-C(13)-C(14) | -178.2(3) |
| C(11)-C(12)-C(13)-C(14) | -57.0(4) |
| C(1)-O(1)-C(14)-C(13) | -88.6(3) |
| C(1)-O(1)-C(14)-C(10) | 32.3(3) |
| C(12)-C(13)-C(14)-O(1) | 157.0(3) |
| C(12)-C(13)-C(14)-C(10) | 42.3(4) |
| C(6)-C(10)-C(14)-O(1) | -33.8(3) |
| C(9)-C(10)-C(14)-O(1) | -150.2(3) |
| C(16)-C(10)-C(14)-O(1) | 78.4(3) |
| C(6)-C(10)-C(14)-C(13) | 83.4(3) |
| C(9)-C(10)-C(14)-C(13) | -33.0(4) |
| C(16)-C(10)-C(14)-C(13) | -164.4(3) |
| C(6)-C(10)-C(16)-C(17) | -178.0(3) |
| C(9)-C(10)-C(16)-C(17) | -57.9(4) |
| C(14)-C(10)-C(16)-C(17) | 76.4(4) |
| C(10)-C(16)-C(17)-O(3) | -9.2(6) |

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for lb067_5 [A and deg.].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|

## 3.5 REFERENCES


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