Chemoenzymatic Total Synthesis of Morphine alkaloids: Synthesis of Dihydrocodeine and Hydrocodone *via* a Double Claisen Strategy and *ent*-Hydromorphone *via* an Oxidative Dearomatization/intramolecular [4+2] Cycloaddition

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ABSTRACT

This thesis describes the chemoenzymatic synthesis of three morphine alkaloids. The total synthesis of dihydrocodeine and hydrocodone was accomplished starting from bromobenzene in 16 and 17 steps, respectively. The key steps included a microbial oxidation of bromobenzene by *E. coli* JM109 (pDTG601A), a Kazmaier-Claisen rearrangement of glycinate ester to generate C-9 and C-14 stereo centers, a Johnson-Claisen rearrangement to set the C-13 quaternary center, and a C-10/C-11 ring closure *via* a Friedel-Crafts reaction.

In addition, the total synthesis of *ent*-hydromorphone starting from β-bromoethylbenzene in 12 steps is also described. The key reactions included the enzymatic dihydroxylation of β-bromoethylbenzene to the corresponding *cis*-cyclohexadienediol, a Mitsunobu reaction, and an oxidative dearomatization followed by an intramolecular [4+2] cycloaddition.

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Ac	acetyl
Boc	tert-butyloxycarbonyl
$(Boc)_2O$	di-tert-butyl dicarbonate
$CDCl_3$	deutero-chlorofornn
CSA	camphorsulfonic acid
DBU	1,8-Diazabicyclo[5 .4.0]undec-7 -ene
DCC	dicyclohexylcarbodiimide
DCE	1,2 dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIPEA	diisopropylethylamine
DMAP	dimethylamino pyridine
DME	dimethoxyethane
DMF	N,N-dimethylfornnamide
DMSO	dimethyl sulfoxide
dppf	1,1 ' -*bis-(* diphenylphosphino)ferrocene

Et_2O	diethylether
Et_3N	triethylamine
EtOAc	ethyl acetate
HBTU	*O*-benzotriazol-1-yl-*N*,*N*,*N ‘*,*N’* -tetramethyluronium hexafluorophosphate
HCl	hydrochloric acid
IBX	2-iodoxybenzoic acid
i-Pr	isopropyl
IR	infrared spectroscopy
J	coupling constant
aq.	aqueous
Bu	butyl
CbzCl	benzyl chloroformate
d	days
DMF	dimethyl formamide
dr	diastereomeric ratio
DIBAL-H	diisobutylaluminium hydride

equiv.	equivalents
h	hours
IR	infrared
LDA	lithium diisopropylamide
LTMP	lithium 2,2,6,6-tetramethyl piperidine
min	minutes
n	normal
NMR	nuclear magnetic resonance
o	ortho
p	para
quant.	quantitative
Ph	phenyl
Pr	propyl
rt	room temperature
s	secondary
t	tertiary
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TS	transition state
TCDI	1,1'-thiocarbonyl diimidazole
DMAP	dimethylamino pyridine
DMP	Dess-Martin periodinane
MOM	methoxy methylether
DAIB	diacetoxy iodobenzene
LAH	lithium aluminum hydride
mp	melting point
n-BuLi	n-butyllithium
NADH	Nicotinamide adenine dinucleotide
NADPH	Nicotinamide adenine dinucleotide phosphate
PAD	potassium azodicarboxylate
PBu_3	tributyl phosphine
PEG	poly(ethylene glycol)

PMB	*p*-methoxybenzyl
PMP	p-methoxyphenyl
PPh_3	triphenyl phosphine
TBAF	tetrabutylammonium fluoride
TBS	tert-butyldimethylsilyl
TDS	thexyldimethylsilyl
t-Bu	*tert*-butyl
TDO	toluene dioxygenase
TIBAL	tri-isobutyl aluminum

1. Introduction

Morphine (**1),** Figure 1, is a naturally occurring alkaloid found in opium, which is the latex of the poppy plant, *Papaver somniferum*, and is one of the oldest drugs known to man. It is the most abundant alkaloid found in opium along with other related alkaloids such as codeine (**2**), thebaine (**3**) and others. Morphine, along with its congeners and semi-synthetic derivatives, is one of the most potent and commonly used analgesics, and all these compounds used in the medicinal field are obtained from natural sources followed by semi synthesis.[1]

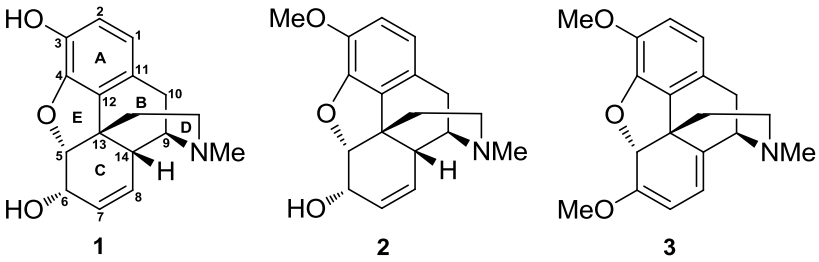


Figure 1: Naturally occurring opiate alkaloids.

More than 40 total and formal syntheses of morphinans are known so far but none of them meet the requirement of a truly practical synthesis. Although morphine does not present a highly complex structure, its unique pentacyclic core with five contiguous stereogenic centers makes it a challenging target for the synthetic chemist.[2] The development of a practical route for the synthesis of morphine alkaloids has been a long standing goal in the Hudlický group. Our current approach begins with the enzymatic dihydroxylation of substituted benzenes to obtain the chiral *cis*-cyclohexadienediols, Figure 2.

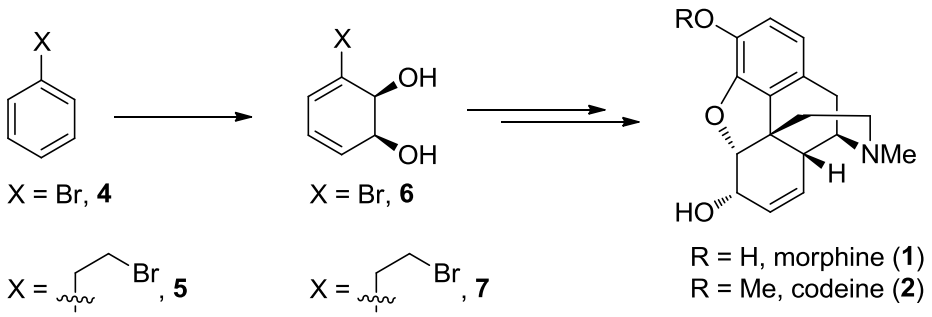


Figure 2: Chemoenzymatic approach to morphine alkaloids.

This thesis presents two approaches to these challenging targets. The first approach relies on two successive Claisen rearrangements: a Kazmaier-Claisen rearrangement[3] and Johnson-Claisen rearrangement[4]. The Kazmaier-Claisen rearrangement involves a [3,3]-sigmatropic rearrangement of a chelated enolate **8**, Figure 3, which will be useful to set the C-14 and C-9 stereocenters in morphine with remarkably high diastereoselectivity. A second Claisen rearrangement, the Johnson variant, will create the challenging C-13 quaternary center at **11** through intermediate **10**, Figure 3. This thesis presents the construction of this vital part of the molecule and further studies towards the completion of the synthesis of dihydrocodeine and hydrocodone.

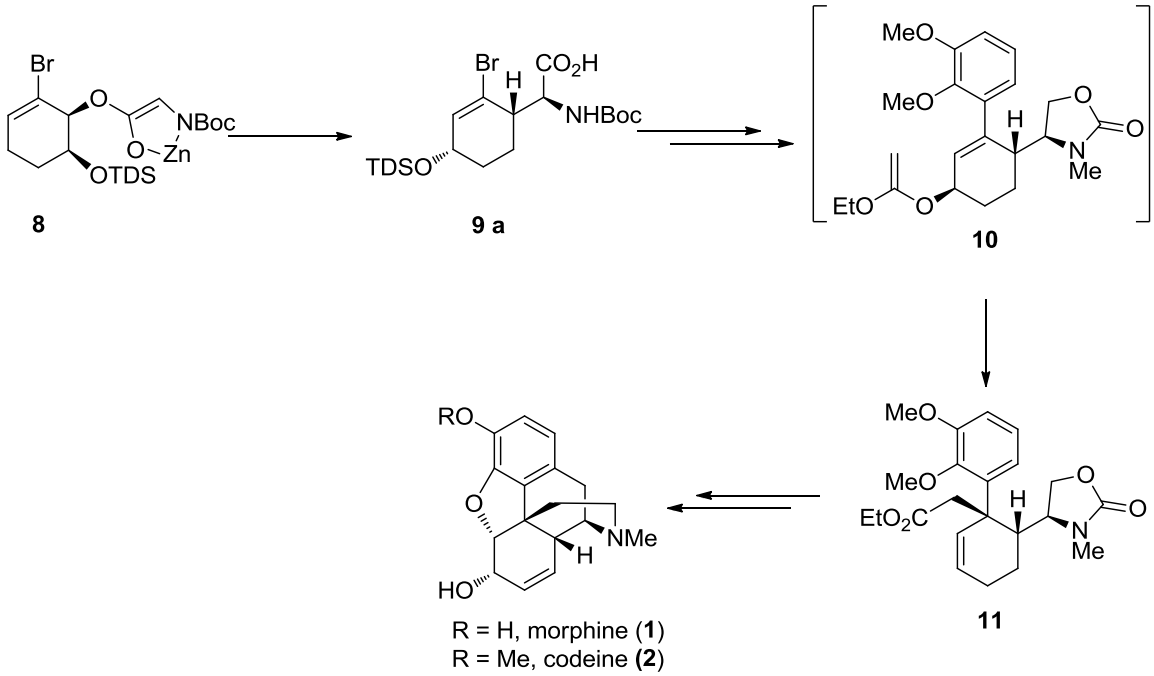


Figure 3: Double Claisen approach towards morphine alkaloids.

The second approach relies upon an unusual cycloaddition strategy, which involves an enzymatic dihydroxylation of the β-bromoethylbenzene **5,** to provide diene diol **7,** Figure 2, which will be tethered to the aromatic ring by a Mitsunobu reaction to access ether **13**, Figure 4. Dearomatization of ether **13** will provide dienone **14,** which will undergo a cycloaddition reaction to provide tetracycle **15**, Figure 4. The rapid construction of the tetracyclic core of morphine including A, B, C and E rings and the completion of the synthesis of *ent*-hydromorphone **16**, Figure 4, will be presented.

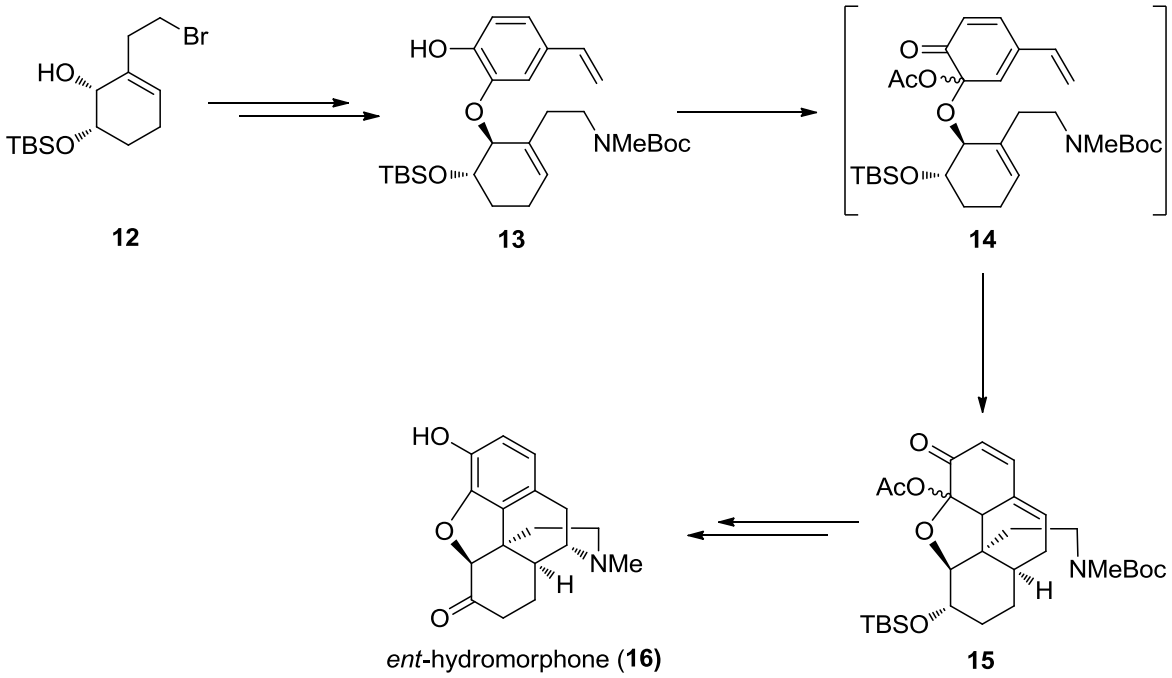


Figure 4: Dearomatization/cycloaddition approach towards morphine alkaloids.

2. Historical

2.1 Microbial Oxidation of Arenes

2.1.1 History of microbial oxidation of arenes

The process of fermentation for the production of different kinds of food has been known to mankind for many centuries. The earliest evidence of mankind using this process dates back to 5400–5000 BC. Analysis of a pottery jar found in Iran's northern Zagros mountains suggested that Neolithic man fermented grapes to make wine.[5] In 1857, Louis Pasteur identified yeast as the organism responsible for alcoholic fermentation;[6] he was successful in oxidising ethanol to acetic acid and was the first to show that the reason for this reaction is a living microorganism. The vital force behind these transformations was called 'ferments', which were active only in living organisms.[7] Later in 1886, based on Pasteur's observations, Brown devised a series of experiments and was able to oxidize different kinds of alcohols to the corresponding acids along with oxidation of dextrose to gluconic acid and mannitol to laevulose (fructose) using *Bacterium aceti*,[8] which is credited as the first use of biocatalysis.[9]

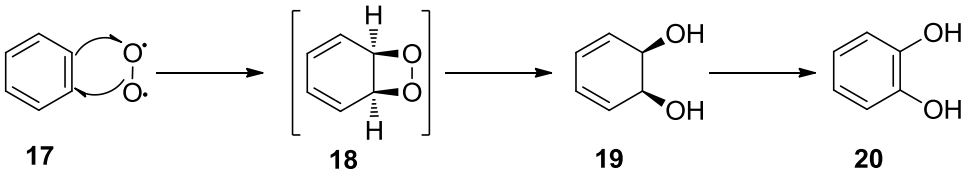
The study of enzymes dates back to 1833, when 'diastase' (a substance isolated from malt extract) was found to degrade starch.[10] The commonly used '-ase' suffix came from diastase, which is believed to be the first enzyme ever isolated. At the end of the 19th century, Fischer studied the metabolism of carbohydrates by yeast[11] and also came up with a new theory for the action of enzymes, which is now well-known as the "lock and key" model.[12] This model explains why enzymes can react specifically with some compounds, but this theory fails to explain the reactivity of the same functional group attached to different compounds with severe difference in size. Later in 1958, Daniel

Koshland amended this theory to an "induced fit" model, in which a conformational change was induced by the interaction between the enzyme and substrate.[13] The credit for the first use of an isolated enzyme in chemistry goes to Dakin for the kinetic resolution of racemic ethyl mandelate by crude pig liver lipase.[14]

The detailed study of the microbial metabolism of hydrocarbons started only in the beginning of the 20th century.[15] Consumption of toluene and xylene by the *Bacillus hexacarbavorum* bacterium was reported in 1908.[16] Later studies by Söhngen revealed a bacterium, *Bacillus pyocyaneum,* that can survive various concentrations of benzene.[17] In 1935, *trans*-1,2-dihydroxy-1,2-dihydroanthracene, a product of mammalian metabolism of anthracene was isolated, which was the first dihydrodiol metabolite isolated.[18] Subsequent studies by Haccius and Helfrich with the organism *Nocardia coralline* determined that catechol was the major product from the fermentation of benzene.[19] Initially, it was postulated that a phenol was formed as an intermediate during this process. However, Marr and Stone argued that the formation of a *trans*-l,2-dihydrocyclohexa-3,5-diene, resulting from hydrolysis of an epoxide is more favourable than the formation of a phenol intermediate. Their studies using two soil bacterial strains, *P. aeruginosa*and *Mycobacterium rhodochrous*, showed that both strains oxidized benzene to catechol, but did not oxidize phenols.[20] These results, along with the studies by Young on naphthalene degradation in rats, in which he reported the isolation of the 1,2-dihydronaphthalene-1,2-diol,[21] gave ample support to this hypothesis.

In eukaryotic organisms, cytochromes oxidize aromatics to the corresponding arene oxides, which can be opened by different nucleophiles.[9] However, in prokaryotic organisms, the dioxygen molecule bound to dioxygenase enzyme oxidises the aromatics

to the corresponding *cis*-dihydrodiols which are then further oxidised to catechols.[9] In 1968, Gibson reported the degradation of benzene, ethylbenzene and toluene by a strain of *Pseudomonas putida*.[22] His studies found that all these aromatic hydrocarbons were oxidized at the same rate by the cell-extracts obtained from the organism. The incubation of the organism with both *cis*- and *trans*-cyclohexa-3,5-diene-1,2-diols revealed that the *cis*-isomer was oxidized approximately six times faster than its *trans*-isomer. This successful oxidation of *cis*-benzene glycol to catechol along with the absence of a phenol during this process led them to the conclusion that the first step of the oxidation is not the formation of an epoxide. Gibson proposed a mechanism for the oxidation of aromatics which involves a dioxetane **18**, Figure 5.



17 **18** **19** **20**

Figure 5: Gibson's proposed pathway for aromatic oxidation.

Since the early 1950's a vast amount of research has been carried out on mechanistic studies aiming to elucidate the pathway(s) for the formation of diols and catechols from aromatic precursors. In 1960, Booth and co-workers incubated benzene and naphthalene with NADPH, $^{18}O_2$ and rat liver microsomes.[23] These studies showed incorporation of only one labelled atom of oxygen, which indicated the formation of an epoxide as an intermediate and the opening of the epoxide in a *trans*-diaxial fashion to obtain a *trans*-1,2-dihydrodiol **27**, Figure 7.

Gibson began to work on more diversely substituted intermediates to provide stronger evidence for the proposed dioxetane intermediate **18**. In 1968, he was able to isolate the first stable cis-dihydrodiol [(+)-cis-4-chloro-2,3-dihydroxy-1-methylcyclohexa-4,6-diene] **22**, Figure 6, from *p*-chlorotoluene by the action of soil bacteria *P. putida.*[24] The unknown compound obtained together with the catechol **23**, Figure 6, was treated with acid, which gave them a mixture of phenols, **24** and **25**, Figure 6. During these studies, he observed that the halogenated aromatics were metabolised at a slower rate with increasing size of the halogen, to give corresponding catechols.

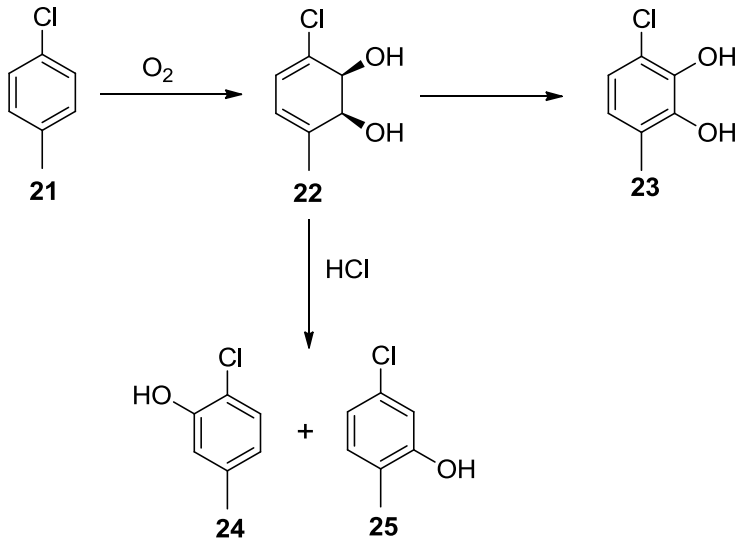


Figure 6: Degradation of *p*-chlorotoluene by soil bacteria *P. putida*.

In 1970, Gibson proposed an iron-mediated reaction of molecular oxygen with aromatics for the formation of *cis*-dihydrodiols. Incubation of *P. putida* with benzene and $^{18}O_2$ provided *cis*-l,2-dihydrocyclohexa-3,5-diene **30**, Figure 7, these isotopic labelling studies revealed that both oxygen atoms present in *cis*-dihydrodiol came from the same

molecule.[25] These studies showed that the mechanism for the oxidation of aromatic compounds in microbes differed from those in mammalian systems.

Cytochrome P450's are known to be responsible for the degradation of aromatic compounds in mammalian organism through an epoxide intermediate **26**, Figure 7.[26] This epoxide can be hydrolysed to yield an unstable *trans*-1,2-diydrodiol **27**, which undergoes a dehydration reaction to give phenols **28** and **29**. In dioxygenase enzymes[27] two oxygen atoms are incorporated from dioxygen and further oxidation by a second enzyme called catechol dehydrogenase results in the formation of the final product as a catechol **31**, Figure 7.

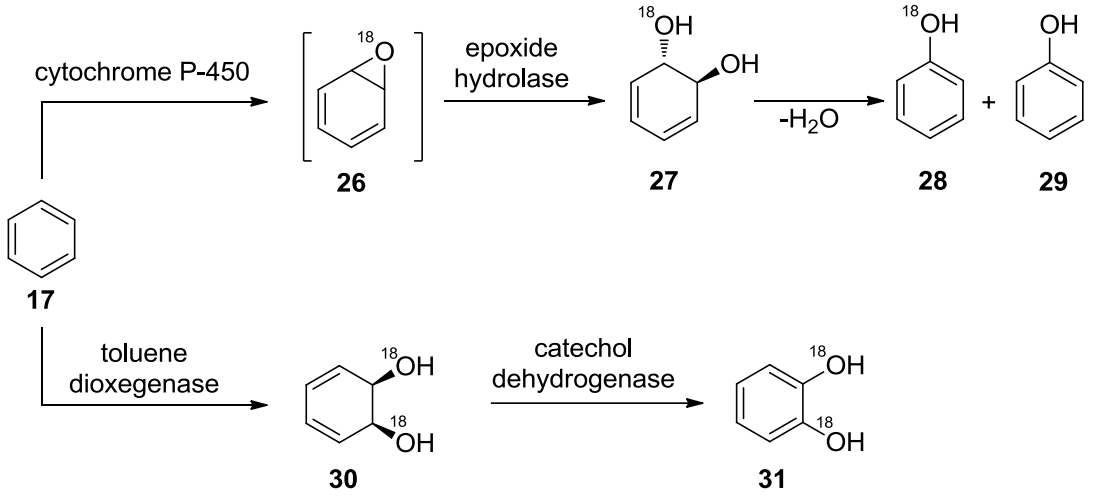


Figure 7: Divergent pathways for the degradation of aromatics in microbes and mammalian systems.

In 1970, Gibson reported the accumulation of *cis*-2,3-dihydroxy-l-methylcyclohexa-4,6-dien **33**, Figure 8, by the incubation of a mutant strain of *P. putida* 39/D with toluene. He

was able to generate the mutant strain of the parent organism by the incubation of the wild strains of the *Pseudomonas putida* with N-methyl-N-nitrosoguanidine. This mutant strain was devoid of the ability to carry out the second oxidation of the 1,2-dihydrodiene diol. The NMR data of 2,3-dihydroxy-l-methylcyclohexa-4,6-diene **33** was inconclusive, so a more rigid derivative was synthesized from the *cis*-dihydroarene diol **33,** Figure 8. Compound **33** was acetylated, and the diester underwent a Diels-Alder reaction with maleic anhydride to provide cycloadduct **35**, which was hydrogenated to obtain the saturated derivative **36**. NMR analysis of this derivative proved the *syn* relationship between vicinal protons H_a and H_b. The formation of *cis*-dihydroarene diol **33** was confirmed by this spectroscopic evidence and the acid catalyzed dehydration of **33** to form *o*-cresol.[28]

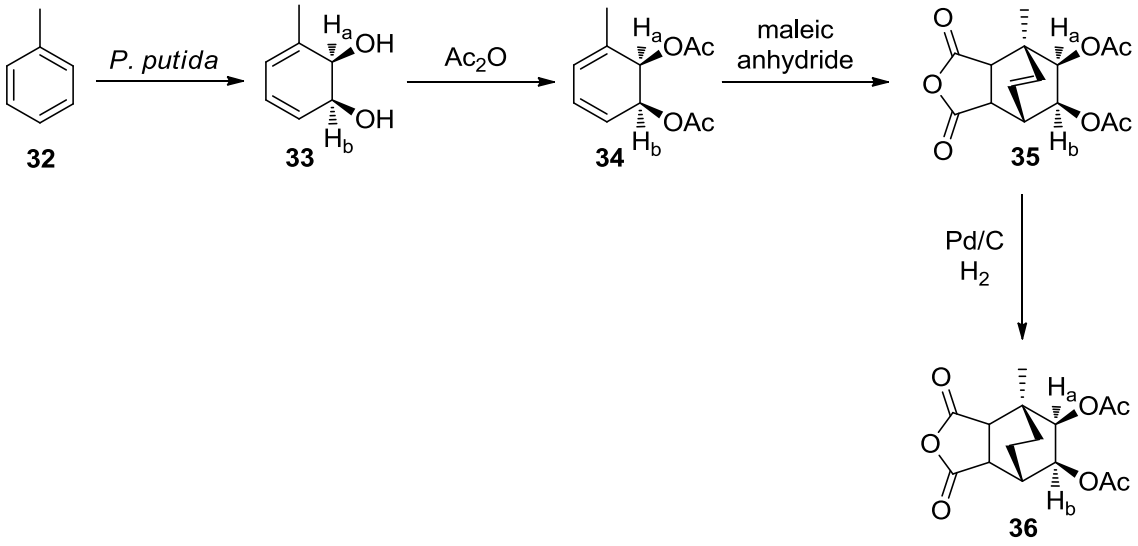


Figure 8: Degradation of toluene by mutant strain *P. putida* 39/D.

After establishing the relative stereochemistry of dihydrodiol **33**, Gibson and co-workers turned their attention to confirm the absolute stereochemistry of **33.** The absolute stereochemistry of the *cis*-dihydrodiol derived from naphthalene had already been confirmed by Gibson at that time by NMR studies and by conversion of the dihydrodiol to a known compound.[29] To confirm the absolute stereochemistry of *cis*-dihydrodiol **33,** it was hydrogenated to obtain a mixture of products **37**, Figure 9, which were separated by silica gel chromatography as protected mono benzoates. NMR analysis of the major product showed it to be *cis,cis*-3-methylcyclohexane-l,2-diol **39**, Figure 9. Further evidence was made available from the comparison between the minor isomer, *cis,trans*-3-methylcyclohexane-l,2-diol **38**, and a sample made from 3-methylcyclohexene **40**, Figure 9, *via* an oxidation using OsO_4–H_2O_2, which is well known for the oxidation from the least hindered side. The major isomer *cis,cis*-3-methylcyclohexane-l,2-diol **39,** was further oxidised to (-)-2(R)-methyladipic acid **41**, Figure 9, (a compound with known absolute stereochemistry) using Jones reagent. This experiment established the absolute stereochemistry of the metabolite 2,3-dihydroxy-l-methylcyclohexa-4,6-diene **33,** Figure 9**.**[30]

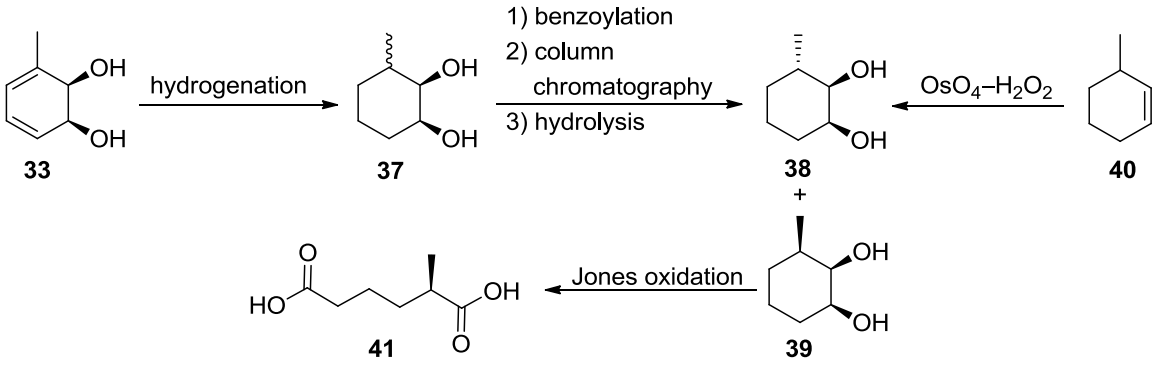


Figure 9: Gibson's experiments for absolute stereochemistry proof of metabolite of toluene.

Continuing research in the field of mutant strains resulted in determining the nucleotide sequence of the genes responsible for coding the toluene catabolic pathway.[31] The knowledge of this gene sequence was used in the preparation of clones of *Escherichia coli* JM109. The first part of the catabolic pathway was effectively over-expressed in a recombinant organism JMl09 (pDTG601), which enables the production of *cis*-dihydrodiols. Another recombinant organism JMl09 (pDTG602), which produces catechols from either arenes **42** or cis-dihydrodiols **43**, Figure 9, was also developed.[31] The recombinant organism *E. coli* JMl09 (pDTG601) and the mutant strain *P. putida* 39/D both lack the genes responsible for the oxidation of *cis*-dihydrodiols to the corresponding catechols. Toluene or chlorobenzene was required as an inducer for mutant strain *P. putida* 39/D, which resulted in the formation of mixture of products in the screening of new substrates. The recombinant organism JMl09 (pDTG601) uses isopropyl β-D-l-thiogalactopyranoside (IPTG) as an inducer, which solved the problem associated with the mutant strain *P. putida* 39/D. The third recombinant organism

developed, JMl09 (pDTG603), metabolized toluene to 2-hydroxy-6-oxo-2,4-heptadienoate **45** (R = Me), Figure 10, by overexpressing the 1,2-catechol dioxygenase.[31]

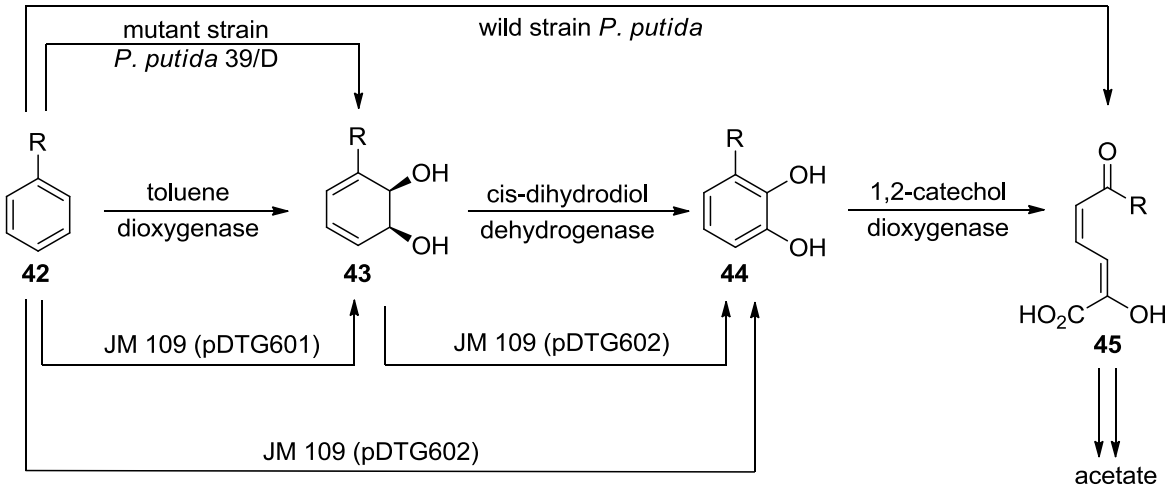


Figure 10: Comparison of the metabolism of aromatics by soil bacteria, blocked mutants, and recombinant strains.

The mechanism for dihydroxylation using tolune dioxygenase (TDO) still remains uncertain. The mechanism proposed by Gibson (Figure 5) is highly unlikely because of the presence of high energy intermediates.[9] Although the X-ray structure of naphthalene dioxygenase (NDO, an enzyme that metabolises fused aromatics) has been known since 2003,[32] the X-ray structure of TDO remains unknown. The exact mechanism is not known but some speculations are provided in Figure 11. The first mechanism postulated by Gibson to explain the cis-stereochemistry of addition proposed the formation of an intermediate dioxetane **46**, Figure 11, but the formation of such a species would require the considerably high-energy cycloaddition of a singlet oxygen species. Hence, another mechanism was suggested which involves a [3+2] cycloaddition of an iron (V) peroxide

57, Figure 11, to the aromatic substrate **42** to obtain **53**, followed by reduction and migration of a hydroxyl group as a possible pathway for the production of *cis*-dihydrodiols.[9, 33] The indole dihydroxylation by NDO through an indole C-3 peroxide species is already known from the work of Ramaswamy in 2000, which supports the iron mediated mechanism.[34]

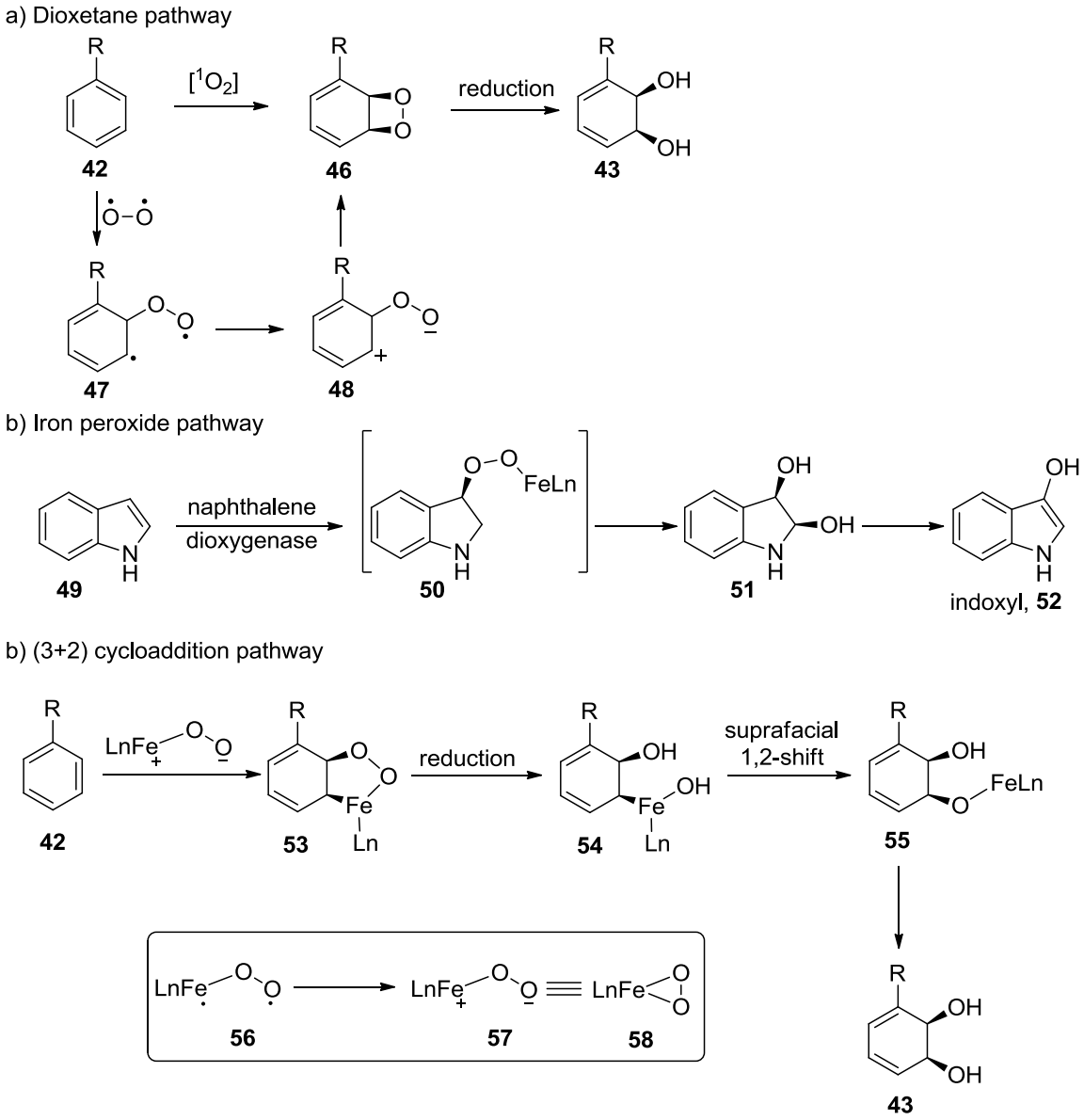


Figure 11: Postulated mechanisms for enzymatic dihydroxylation.

2.1.2 Application of aromatic metabolites in synthesis

A wide variety of *cis*-dihydrodiols can be obtained from different aromatics using toluene dioxygenase and related enzymes. These dihydroxylations are highly regio-, stereo-, and enantioselective. A model for predicting the regio- and stereoselectivity was developed by Boyd in 1993 based on the results obtained from the *cis*-dihydroxylation of a series of 1,4-disubstituted benzene.[35] This model proposed that as the size difference between the substituent increases, regioselectivity and enantioselectivity also improve.

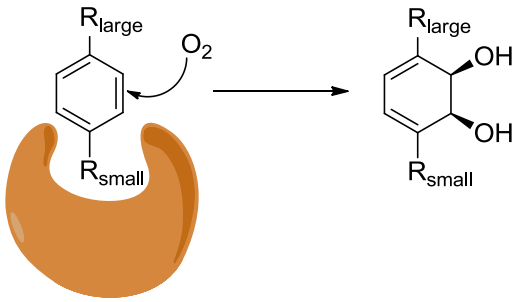


Figure 12: Boyd's model for predicting the regio- and stereoselectivity of the oxidation of single ring aromatics.

More than 400 substrates of toluene dioxygenase and related enzymes have been isolated so far, but only a few of these have been used by the synthetic community. The synthesis of polyphenylene **60**, Figure 13, from the benzene derived *cis*-dihydrodiol **19**, Figure 13, by researchers at Imperial Chemical Industries PLC in 1983 is the first known use of aromatic metabolites in synthesis.[36]

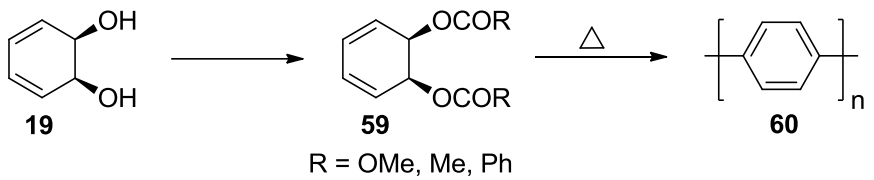


Figure 13: First application of an aromatic metabolite to synthesis.

Shortly after this, Gibson illustrated another example of synthetic use of *cis*-dihydrodiols by the synthesis of indigo **61** by the dihydroxylation of indole **49**, Figure 14, using NDO.[37]

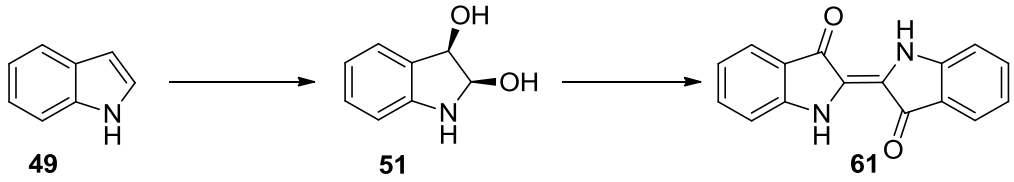
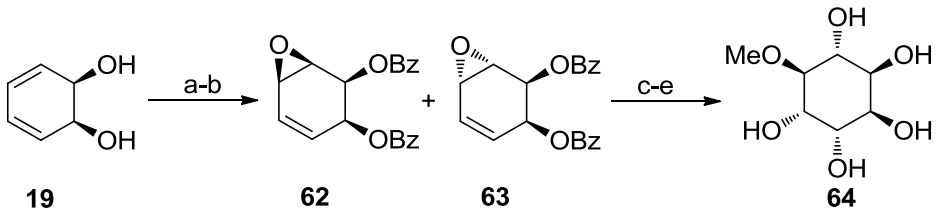


Figure 14: Synthesis of indigo.

Later in 1987, the synthesis of (±)-pinitol **64** from benzene derived diol **19**, Scheme 1, by Ley is considered to be the first true exploitation of aromatic metabolites in synthesis, which enticed the attention of many synthetic chemists.[38] Protection of the hydroxyl groups of **19** as benzoates and epoxidation leads to a mixture of vinyl oxiranes **62** and **63**, Scheme 1. Regioselective ring opening of epoxide **63** by MeOH, and a *cis*-dihydroxylation using OsO_4 followed by hydrolysis of the benzoate esters, provided (±)-pinitol **64**, Scheme 1.



Reagents and conditions: (a) BzCl, pyridine, DMAP, 0 °C; (b) *m*CPBA, DCE, phosphate buffer (pH 8); (c) MeOH, (+)-CSA; (d) OsO_4, NMO, t-BuOH/THF/H_2O (10:3:1); (e) Et_3N/MeOH/H_2O (1:5:1).

Scheme 1: Ley's synthesis of (±)-pinitol.

A year later, the same group reported a synthesis of the cellular secondary messenger inositol-1,4,5-trisphosphate (IP_3) **66**, starting from the benzene derived dihydrodiol **19**, Figure 15.[39]

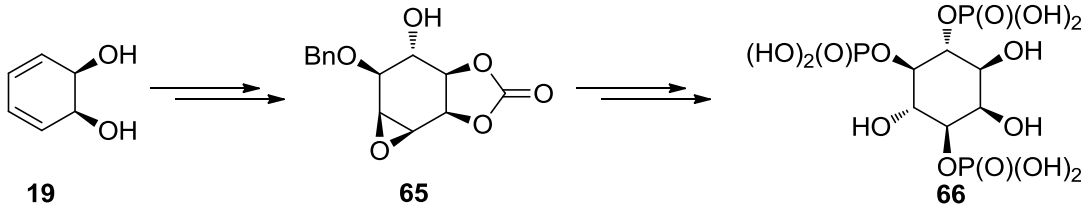
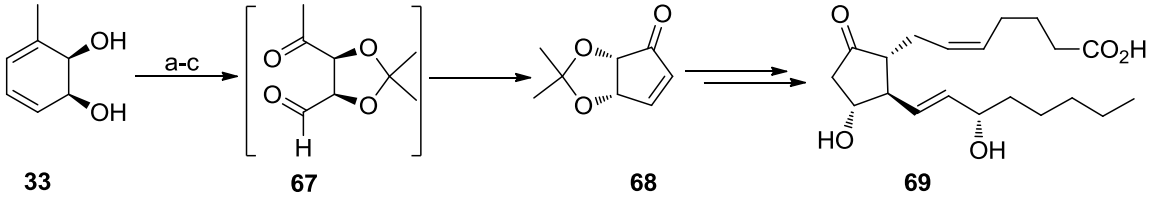


Figure 15: Synthesis of inositol-1,4,5-trisphosphate IP3.

In 1988, an enantioselective formal synthesis of $PGE_{2\alpha}$ was reported by the Hudlický group.[40] The *cis*-dihydrodiol **33** obtained from toluene was subjected to ozonolysis after protection of the diol functionality as an acetonide. Concomitant reductive work up and neutral alumina-mediated cyclization provided known intermediate **68**,[41] thus completing a formal synthesis of $PGE_{2\alpha}$, Scheme 2.

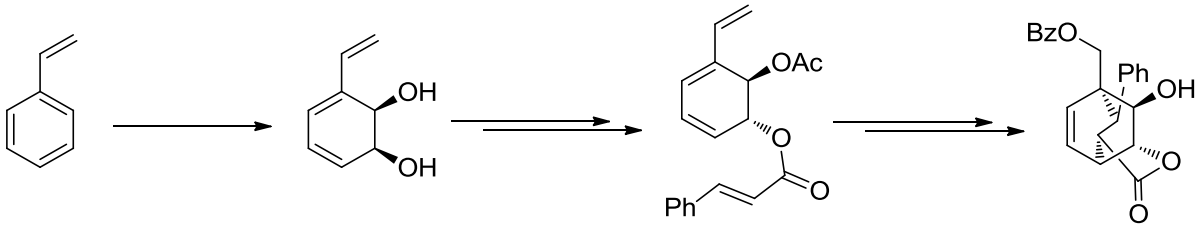


33 67 68 69

Reagents and conditions: (a) 2,2-dimethoxypropane, *p*-TsOH, rt; (b) i) O_3 (excess), EtOAc, –60 °C; ii) Me_2S, 0 °C; (c) Al_2O_3 (neutral), DME, reflux.

Scheme 2: Enantioselective formal total synthesis of PGE2α by Hudlický.

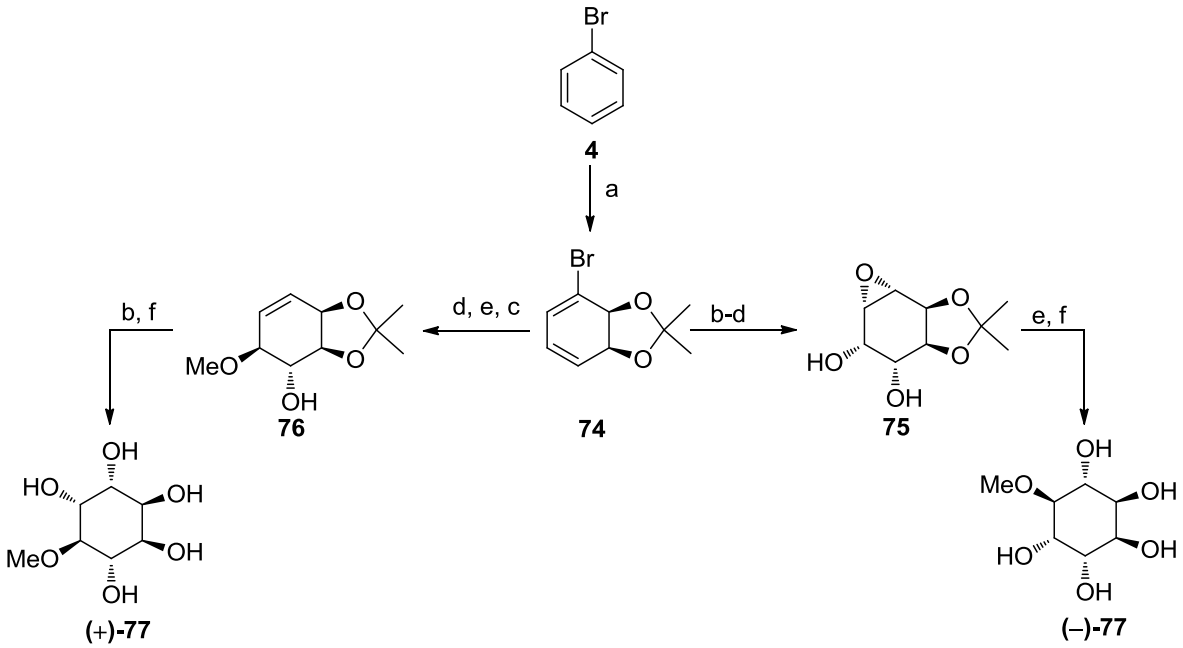
After the successful synthesis of $PGE_{2\alpha}$, Hudlický and co-workers reported an enantioselective synthesis of (–)-zeylena.[42] Enzymatic dihydroxylation of styrene **70**, Figure 16, provided the corresponding *cis*-dihydrodiol **71**, and a Mitsunobu inversion with cinnamic acid led to the intermediate **72**. An intramolecular cycloaddition followed by further manipulation completed the total synthesis of (–)-zeylena **73**, as shown in Figure 16.



70 71 72 73

Figure 16: Total synthesis of (–)-zeylena.

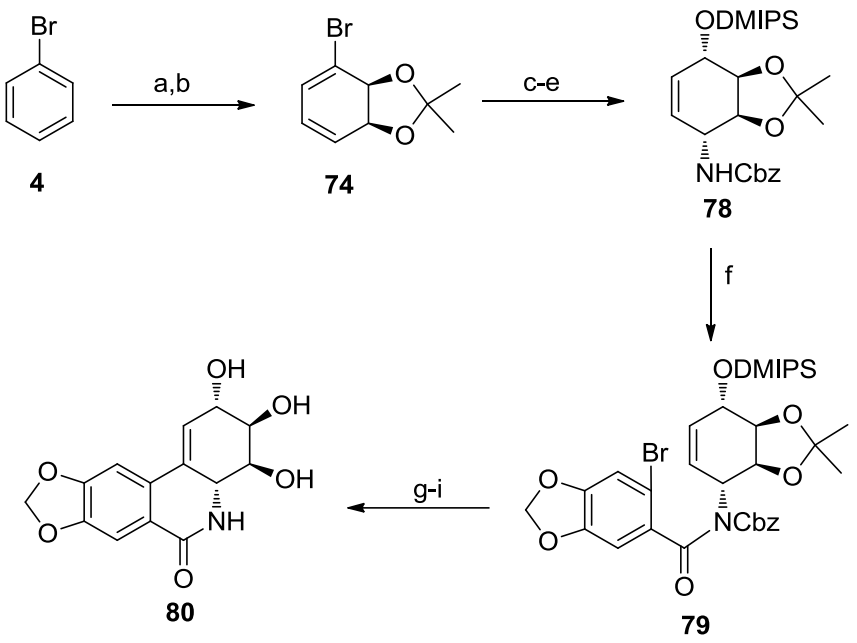
In 1990, Hudlický and co-workers completed an enantiodivergent synthesis of pinitol starting from bromobenzene **4**, Scheme 3. The bromo substituent at the C-1 position played a significant role in differentiating the double bonds in subsequent regioselective reactions.[43] Protection of the *cis*-dihydrodiol provided the acetonide **74**, which was followed by OsO_4-mediated *cis*-dihydroxylation, dehalogenation, and epoxidation to give epoxide **75**. The regioselective ring opening of the epoxide with MeOH and deprotection of the acetonide furnished (–)-pinitol **77**. In a similar fashion, epoxidation, ring opening and dehalogenation of **74** provided **76**; *cis*-dihydroxylation and deprotection of the acetonide yielded (+)-Pinitol **77**.



Reagents and conditions: (a) (i) *E. coli* JM 109 (*p*DTG601A); (ii) 2,2-dimethoxypropane, *p*-TsOH, rt; (b) OsO_4, NMO, H_2O, acetone; (c) $LiAlH_4$, THF; (d) *m*CPBA, CH_2Cl_2; (e) MeOH, Al_2O_3; (f) HCl, H_2O, acetone.

Scheme 3: Enantiodivergent synthesis of (+) and (–)-pinitol.

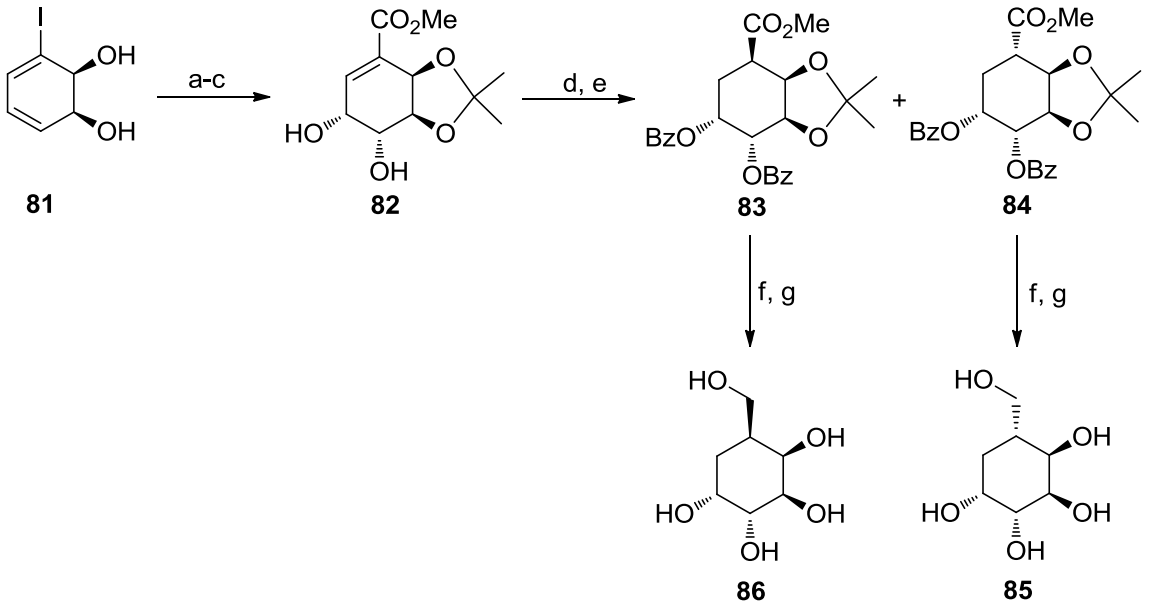
Since 1990, more than 50 natural products and their derivatives have been synthesized from the *cis*-dihydrodiol. The first few syntheses that used *cis*-dihydrodiols have been discussed; now only some noteworthy syntheses will be shown. A comprehensive listing of applications of *cis*-dihydrodiol in synthesis can be found in many reviews.[9, 44] Another important application of the biocatalytic method to synthesis was shown by the Hudlický group by the elegant synthesis of (+)-lycoricidine **80**, Scheme 4, in 1992.[45] Lycoricidine, pancratistatin, and narciclasine are members of the Amaryllidaceae family and show considerable potential medicinal activity. Even though several synthetic routes for these compounds were developed at that time none of them were shorter than 15 steps. Hudlický's synthesis started from halobenzene **4**, which underwent enzymatic dihydroxylation and protection of the diol functionality produced acetonide-protected diene **74**, which was subjected to a hetero-Diels-Alder cycloaddition with a hetero-dienophile, reduction of the N–O bond and protection of the alcohol functionality to yield compound **78**. Acylation of **78** with 6-bromobenzo(1,3)dioxole-5-carbonyl chloride delivered imide **79**; a modified Heck cyclization and global deprotection furnished (+)-lycoricidine **80**. Later in 1995, the first enantioselective synthesis of (+)-pancratistatin was accomplished by Hudlický.[46]



Reagents and conditions: (a) *E. coli* JM 109 (*p*DTG601A); (b) (ii) 2,2-dimethoxypropane, *p*-TsOH, rt; (c) benzyl hydroxycarbamate, Bu_4NIO_4, CH_2Cl_2; (d) Al(Hg), THF; (e) DMIPSCl, imidazole, CH_2Cl_2; (f) BuLi, THF, –78 °C, then 2-bromopiperonyloyl chloride; (g) Pd(OAc), Tl(OAc), DIPHOS, anisole; (h) Pd(C), cyclohexene, EtOH; (i) TFA, 0 °C.

Scheme 4: Hudlický's synthesis of (+)-lycoricidine.

Boyd has shown the versatility of *cis*-dihydrodiols by employing them in the synthesis of pseudosugars **85** and **86**, Scheme 5.[47] The metabolite of iodobenzene was converted to **82** by acetonide protection, *cis*-dihydroxylation and carbonylation. The hydrogenation of **82** afforded a mixture of diastereomers, which were separated as the benzoates to obtain **83** and **84**, Scheme 5. Reduction of esters and deprotection of acetonide provided carba-*β*-D-altropyranose **85** and carba-*α*-L-galactopyranose **86**, Scheme 5.



Reagents and conditions: (a) 2,2-dimethoxypropane, *p*TsOH*;* (b) OsO_4, NMO, Me_2CO, H_2O; (c) $Pd(OAc)_2$, CO (1 atm) , $NaOAc{\cdot}3H_2O$, MeOH; (d) 5% $Rh/A1_2O_3$, EtOH, H_2 (55 psi); (e) BzCI, pyridine; (f) $LiAIH_4$, THF, reflux; (g) TFA-THF-H_2O (1:8:2), 50 °C.

Scheme 5: Boyd's synthesis of pseudosugars.

In 2004, Banwell employed the *cis*-dihydrodiol obtained from toluene in the synthesis of (–)-hirsutene **89**, Figure 17.[48] His synthesis includes 17 steps, and he employed a high pressure-induced Diels-Alder cycloaddition and an oxa-di-π-methane rearrangement as key steps.

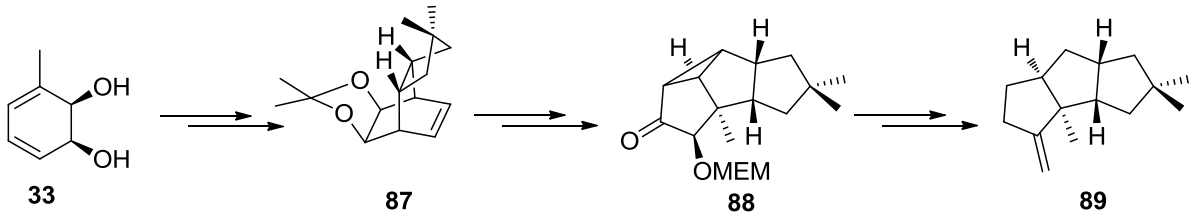
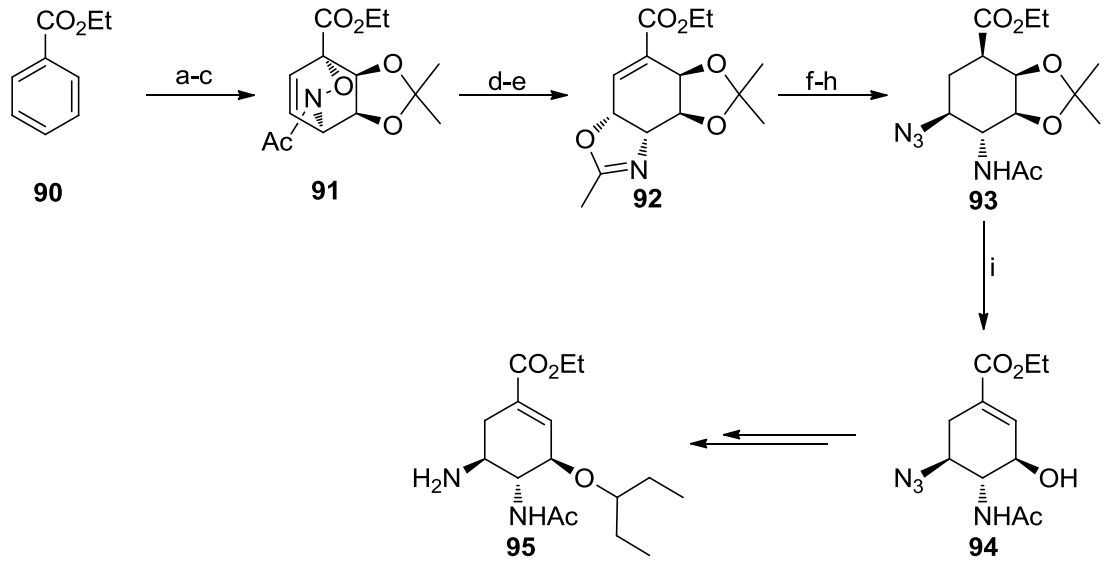


Figure 17: Banwell's synthesis of (–)-hirsutene.

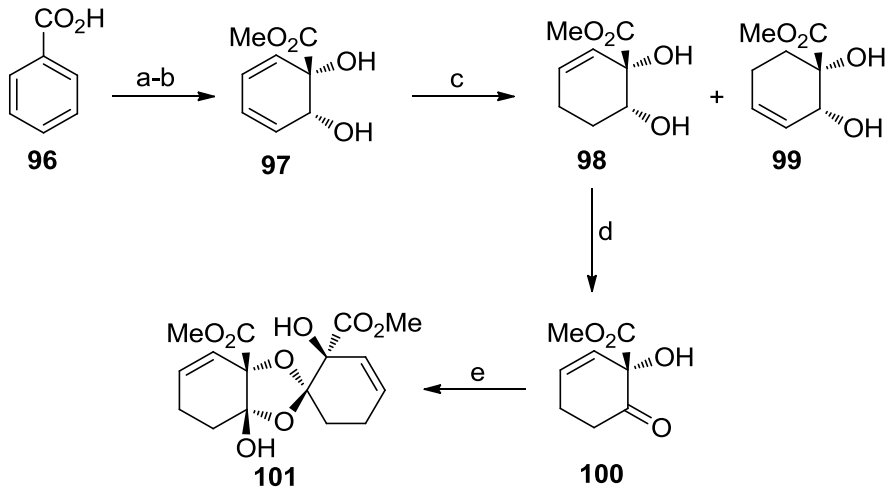
In 2009, Hudlický and co-workers provided another application of the chemoenzymatic approach with their formal synthesis of oseltamivir (Tamiflu®) starting from ethylbenzoate **90**, Scheme 6.[49] The metabolite of **90**, isolated after the biotransformation, was subjected to acetonide protection and then reacted with the *N*-hydroxy acetamide in the presence of $NaIO_4$ to provide the bicyclic oxazine **91** by a hetero-Diels-Alder cycloaddition. Reduction of the N–O bond and S_N2' substitution of the allylic alcohol led to oxazoline **92**. This was then hydrolysed to the acetamide and hydrogenation afforded the saturated ester that was then converted to azide **93**. A base-induced collapse of the acetonide completed the formal synthesis of oseltamivir (**95)** via Fang's intermediate **94**. In 2010, Hudlický reported a shorter, azide free synthesis of oseltamivir starting from the same starting material.[50]



Reagents and conditions: (a) *E. coli* JM 109 (*p*DTG601A); (b) 2,2-dimethoxypropane, *p*TsOH*;* (c) $CH_3CONHOH$, $NaIO_4$, MeOH, rt; (d) Mo(CO)6, CH_3CN/H_2O (15:1), Δ; (e) MsCl, Et_3N, DMAP, CH_2Cl_2, rt; (f) $CaCO_3$, $EtOH/H_2O$ (1:1), Δ; (g) Rh/Al_2O_3 (5 mlo%), 60 psi H_2, 85% $EtOH_{(aq)}$; (h) (i) Ms_2O, Et_3N, CH_2Cl_2, rt; (ii) NaN_3, acetone/H_2O, rt; (i) DBU, CH_2Cl_2, rt.

Scheme 6: Chemoenzymatic approach for the synthesis of oseltamivir.

Another application of enzymatic dihydroxylation by Hudlický was his synthesis of (–)-idesolide **101**, Scheme 7.[51] The synthesis began by converting benzoic acid **96** to the corresponding diol using a mutant strain *R. eutrophus* B9 developed by Reiner and Hegeman.[52] The dihydroxylated acid was reacted with diazomethane to obtain methyl ester **97**, which was reduced to a mixture of products, **98** and **99** with potassium azodicarboxylate (PAD). Oxidation and dimerization of the major isomer **98** led to the completion of the synthesis in five steps starting from benzoic acid.



Reagents and conditions: (a) *R. eutrophus* B9; (b) CH_2N_2, THF, 0 °C; (c) PAD, AcOH, MeOH, 0 °C; (d) IBX, DMSO; (e) $NaHCO_3$.

Scheme 7: Chemoenzymatic synthesis of (–)-idesolide from benzoic acid.

Another important application of aromatic metabolites involves the synthesis of morphine alkaloids and their derivatives. This topic will be covered in the following section. The aforementioned applications of metabolites constitute only a few of their many applications. These metabolites and their use in synthesis have been extensively reviewed.[9,44]

2.2 Morphine

2.2.1 History and isolation of morphine alkaloids

Opium has been used since ancient times; Sumerians were known to isolate opium from poppies 3000 years ago. They called opium "gill" which means "joy" and the poppy as "hul gill," the "plant of joy," [53] and it was used as a euphoriant in religious rituals. It is believed that opium spread from Sumaria to other parts of the world.[53] The word "opium" has been derived from the Greek word "opos" (juice) and "opion" (poppy juice). It has been used to produce euphoria, analgesia, sleep, and relief from cough and diarrhoea since ancient times.[54] Opium was brought to India and China by Arab traders in eighth century and it reached all parts of Europe by the tenth to thirteenth century. Later, it was used as a natural anaesthetic/analgesic agent to relieve pain during surgery. The use of opium as a medicinal drug was exploited by the Swiss physician Paracelsus (1493-1541), who called it "laudanum" (a mixture of opium and wine which means "something to be praised" in Latin) and was used for all kinds of medical ailments. British physician Sydenham (1624-1689) used opium in alcohol as a cough suppressant and sleep aid. Manuscripts from the sixteenth century reported the abuse of this drug and developing of drug tolerance in Europe, and smoking of opium became the greatest social problem in China during the mid-seventeenth century, after the banning of tobacco smoking. Attempts to suppress the sale of opium in China failed because of the actions of British East India Company. Export of opium from India to China provided a large revenue for the East India Company at that time, which made India the largest opium producer in the world.[55] Later, in 1913, British India stopped all opium shipments to China, after it had become less dependent on opium revenue.[56]

In the early nineteenth century (1805), the German pharmacist Friedrich Wilhelm Serturner isolated the active component of opium, which he named morphine (after Morpheus, the Greek God of dreams).[57] This event plays an important role in the development of the fields of organic chemistry and pharmacology. Serturner developed a simple procedure for the isolation of morphine; trituration of Indian opium with hot water until the filtrate became colorless, then the filtrate was concentrated and saturated with ammonia to get a semi crystalline solid. It was further washed with water and was triturated with ethanol to provid pure morphine.

The alkaloid content of crude opium constitutes more than forty different alkaloids. Raw opium contains 10-16% of morphine (**1)** by weight along with other alkaloids such as codeine (**2**) 1-3%, thebaine (**3**) 0.5-2%, papaverine (**102**) 0.8-1 %, traces of oripavine (**103**), and narcotine (**104**) 1-7%, as shown in Figure 18.

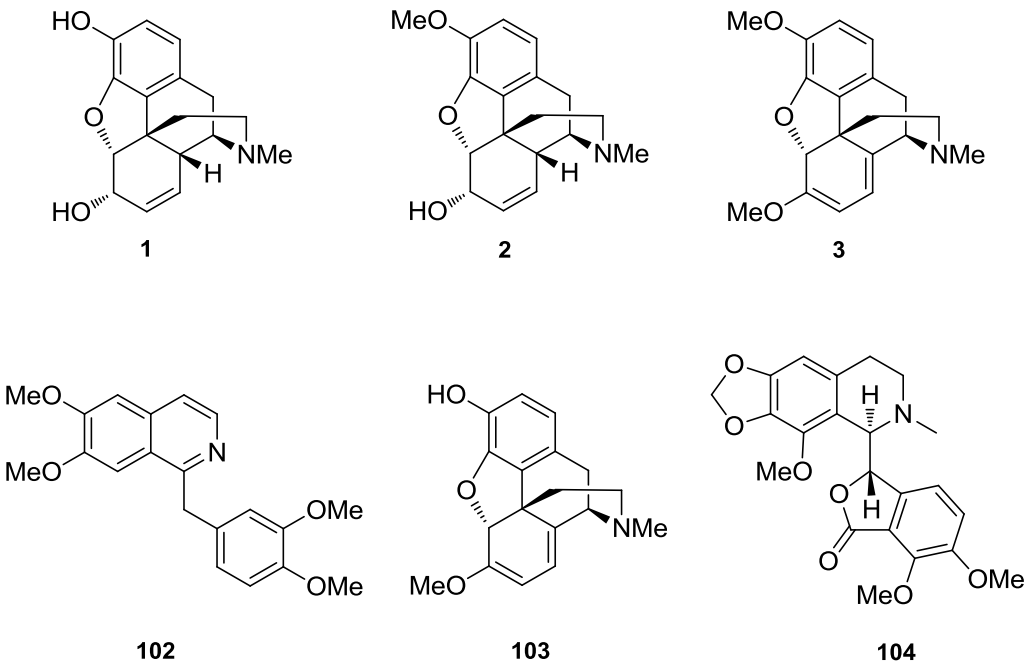


Figure 18: Naturally occurring morphine alkaloids.

Opium is isolated by cutting the unripened poppy seed pods of *Papaver somniferum* about 98 days after development. The latex leaks out and is scraped off and further dried to obtain raw opium. This harvesting process can be repeated on a single seed pod for several days. The timing of the opium harvesting is also important as the ripened seed pod stops the alkaloid production. Alkaloids are abundant in the seed pods but thebaine can also be found in the roots of the opium poppy.[56, 58]

In 1832, French chemist Robiquet isolated another naturally occurring opiate, codeine (**2)**, Figure 18. Thebaine **3** (1833) and papaverine **103** (1848) were later isolated from opium.[59] Structural elucidation of morphine began soon after its isolation. Initial work was carried out by Liebig and later in 1847 Laurent deduced the correct empirical formula for morphine as $C_{17}H_{19}NO_3$. [60] The use of morphine in minor surgeries and as an adjunct to general anaesthetics became common after the invention of the hypodermic syringe and hollow needle in 1853.[53] Morphine also eventually replaced crude opium as the analgesic of choice. But very soon the addiction profile of morphine was revealed, which led to the search for a less addictive but still potent analgesic. In 1874, a more potent semisynthetic drug named heroin (**105)**, Figure 19, was synthesized by an English chemist Wright at St. Mary's hospital in London by diacetylation of morphine (**1)**.[61] The name heroin came from "heroische", which in German means "powerful" or "extreme". Heroin was synthesised by refluxing morphine (**1)** and acetic anhydride to yield the bis-acetyl derivative of morphine. Later in 1898, Friedrich Bayer and Company marketed heroin as a non-addictive morphine substitute and cough suppressant. Heroin is much faster at passing through the blood-brain barrier and is then metabolised to morphine in

the body, so it in fact exhibits a more addictive profile than morphine. This led to the withdrawal of heroin from the market by Bayer. Also, the addictive property made heroin a potential target for illicit use. Wright also played an important role in the elucidation of the oxygenation pattern in morphine.[62]

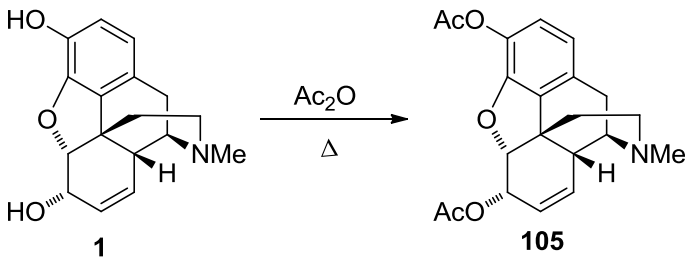
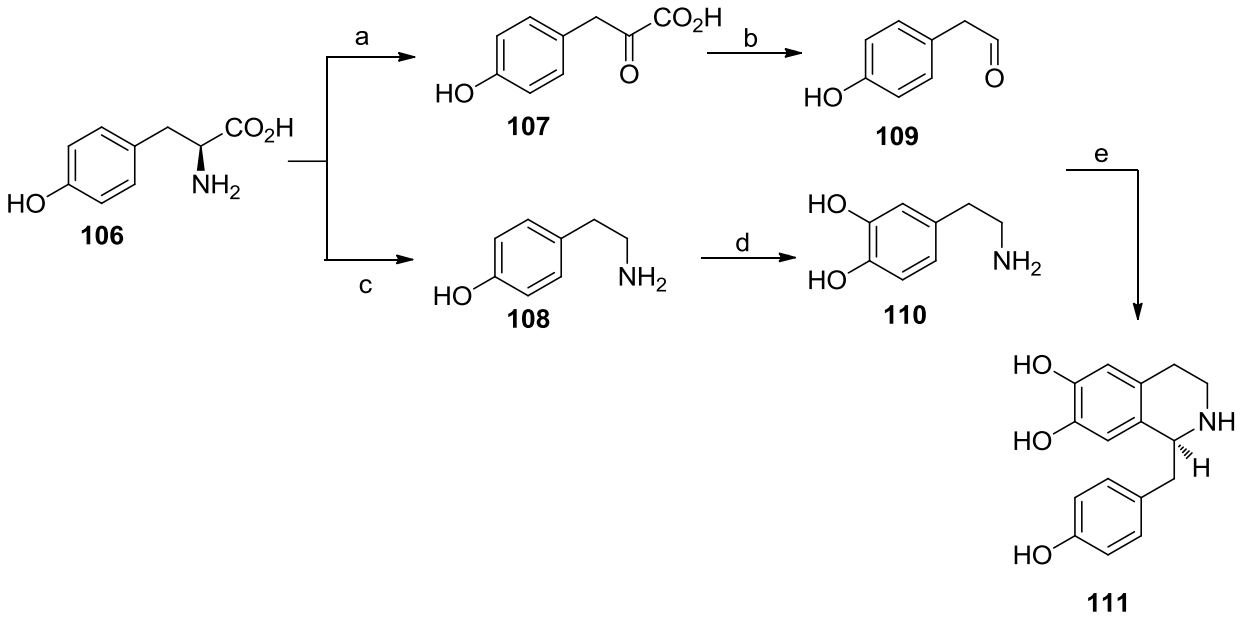


Figure 19: Synthesis of heroin from morphine.

The presence of the phenanthrene core in morphine was confirmed by von Gerichten in 1881.[63] About the same time, independent studies by Grimaux[64] and Hesse[65] proved the relationship between codeine and morphine by methylation of the phenolic hydroxyl group in morphine. After establishing the structural relationship between morphine and codeine, structural elucidation studies were performed on the more stable codeine. The presence of an oxygenated phenanthrene core was confirmed by experiments done by Hofmann, Knorr, and von Gerichten on morphine and codeine.[66] The structure of morphine was fully elucidated by Robinson and Gulland in 1925, 120 years after its isolation.[67] Later in 1952, the structure of morphine was confirmed by the first total synthesis by Gates.[68] Final structural evidence was given by X-ray analysis by Mackay and Hodgkin in 1955.[69] An excellent review by Hudlický and Butora covers the rich chemistry of structure elucidation of morphine.[70]

2.2.2 Biosynthesis of morphine alkaloids

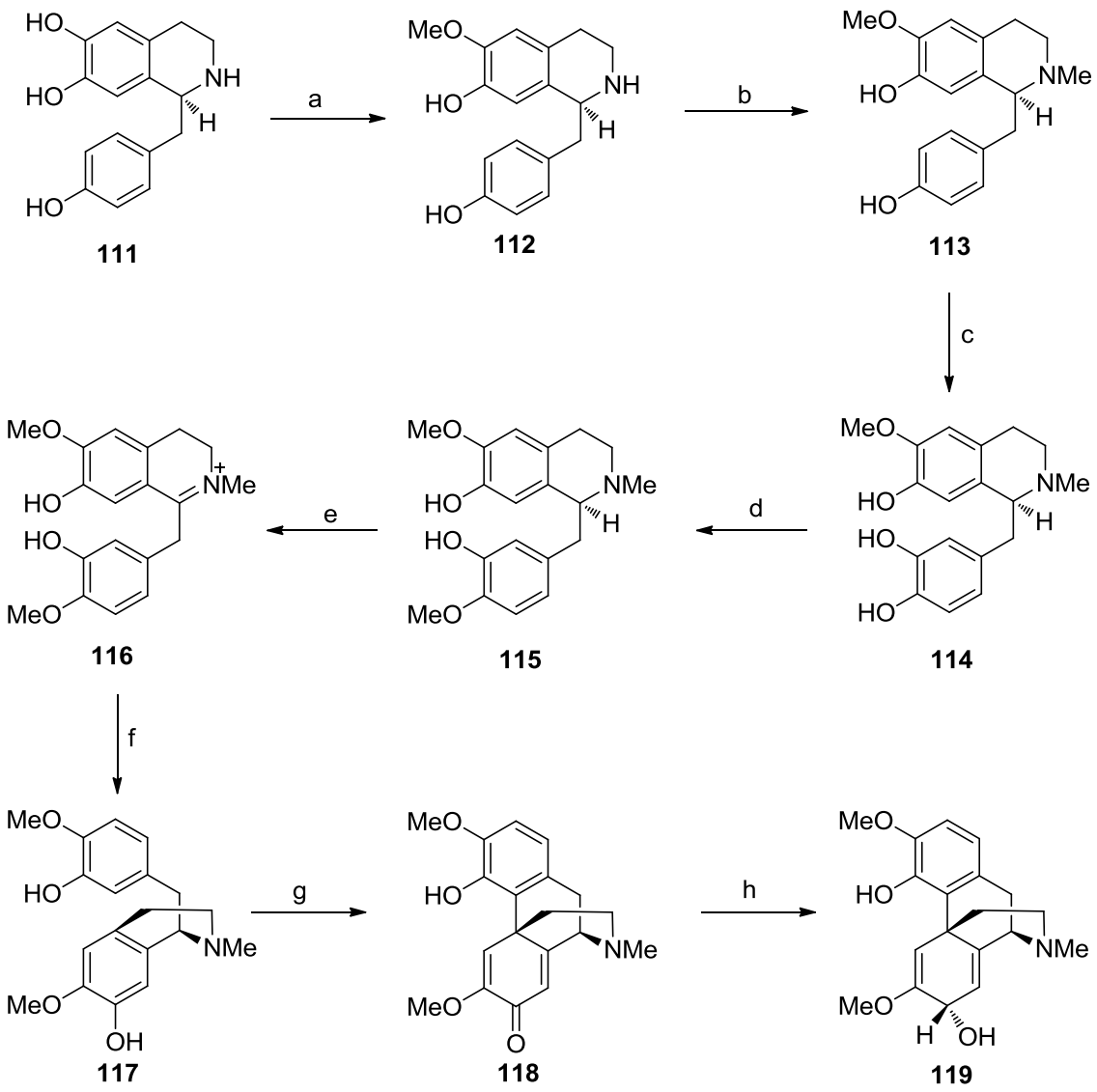
Morphine and related alkaloids are formed in *P. somniferum* through a series of benzylisoquinoline intermediates. The biosynthesis pathway begins with the conversion of L-tyrosine (**106)** to dopamine (**110)** and 4-hydroxyphenylacetaldehyde **109**, Scheme 8. First, **106** is converted to 4-hydroxyphenylpyruvic acid **107** by transamination and then decarboxylated to 4-hydroxyphenylacetaldehyde **109**. A second molecule of **106** is converted to dopamine **110** through an intermediate tyramine **108** by the action of two enzymes, L-tyrosine decarboxylase and phenolase. Condensation of **109** and **110** catalysed by (S)-norcoclaurine synthase provides (S)-norcoclaurine (**111)**, which is a common intermediate for the synthesis of many alkaloids.[71]



Enzymes: (a) L-tyrosine transaminase; (b) *p*-hydroxyphenylpyruvate decarboxylase; (c) L-tyrosine decarboxylase; (d) phenolase; (e) (S)-norcoclaurine synthase.

Scheme 8: Biosynthesis of (S)-norcoclaurine.

N-methyltransferase and norcoclaurine-6-*O*-methyltransferase-mediated[72] mediated methylation of (S)-norcoclaurine **111** and P-450 mediated hydroxylation delivers (S)-3′-hydroxy-*N*-methylcoclaurine **114**,[73] Scheme 9. It is converted to (S)-reticuline (**115)** by the 3′-hydroxy-*N*-methyl-(*S*)-coclaurine-4′-*O*-methyltransferase enzyme and is further transformed to its enantiomer (R)-reticuline (**117)** through a stereospecific reduction of an intermediate **116**. An enzyme called dehydroreticuline catalyzes the formation of **116,** Scheme 9, and the reduction involves the NADPH-dependent enzyme 1,2-dehydroreticuline reductase.[74] A regioselective oxidative phenolic coupling of **117** catalyzed by NADPH dependent cytochrome P450, salutaridine synthase provides **118**.[75] The ketone functionality in **118** is stereoselectively reduced by an enzyme called 7-oxidoreductase to provide (*7S*)-salutaridinol (**119)**.[76]

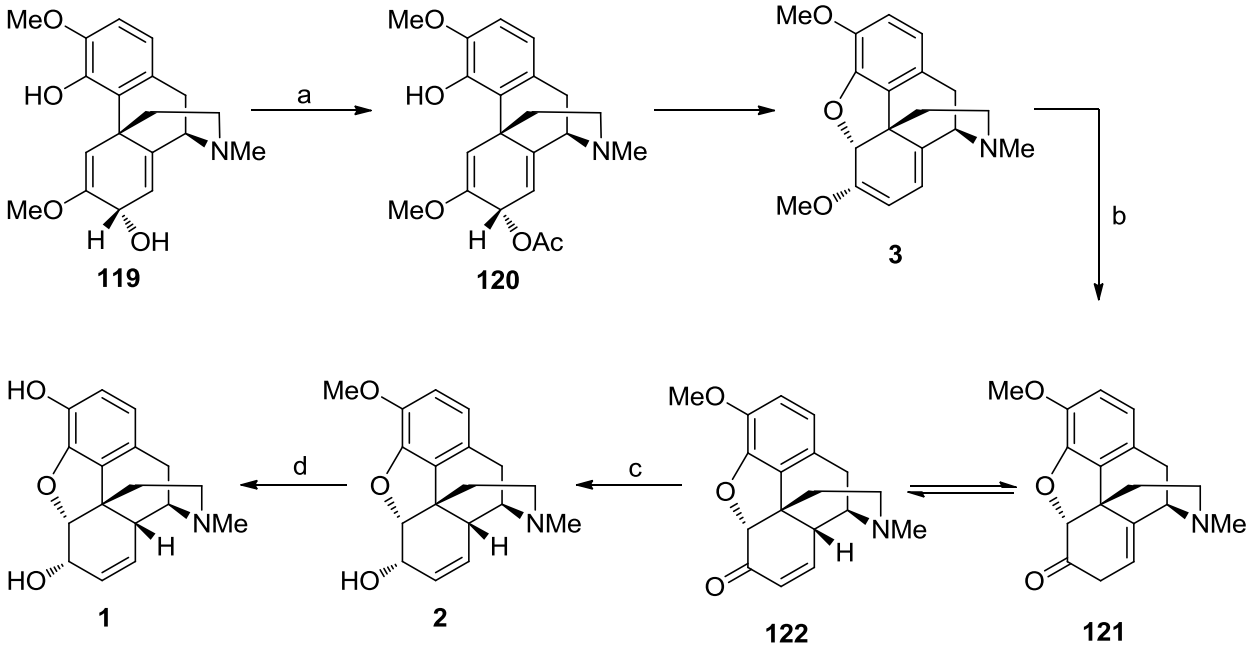


Enzymes: (a) norcoclaurine-6-*O*-methyltransferase (b) *N*-methyltransferase; (c) P-450-mediated hydroxylation; (d) 3′-hydroxy-*N*-methyl-(S)-coclaurine-4′-*O*-methyltransferase; (e) dehydroreticuline; (f) 1,2- dehydroreticuline reductase; (g) salutaridine synthase; (h) 7-oxidoreductase.

Scheme 9: Biosynthesis of (7*S*)-salutaridinol.

(*7S*)-salutaridinol **119** is then acylated by (*7S*)-salutaridinol-7-*O*-acetyltransferase to obtain **120**, Scheme 10.[77] A non-enzymatic S_N2' displacement of acetate by phenolic

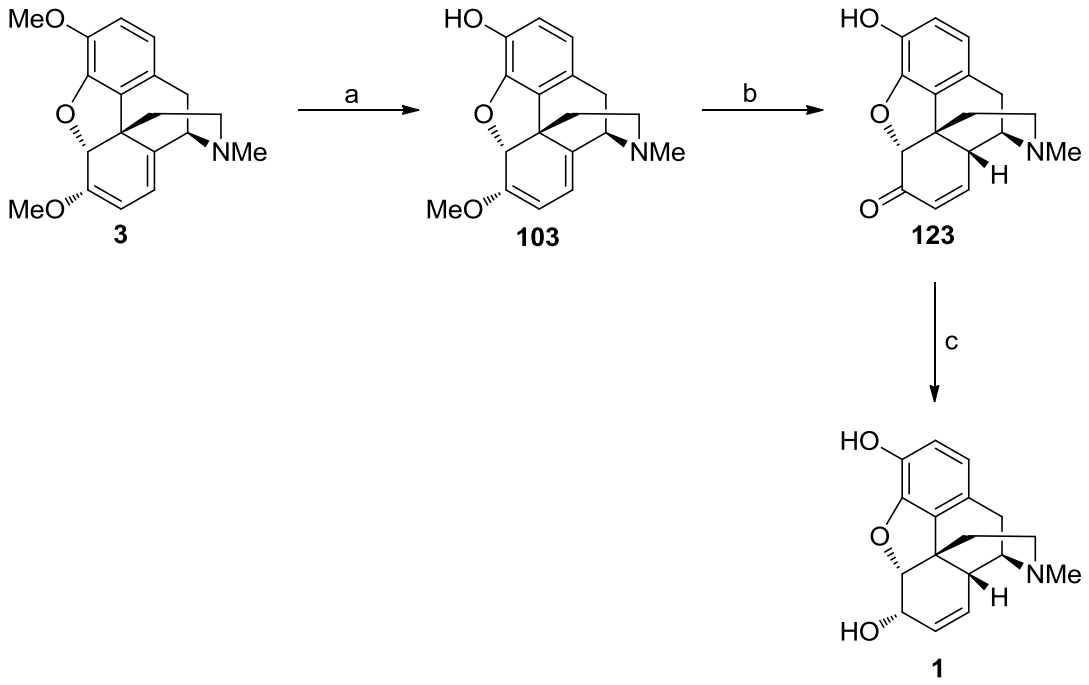
hydroxyl group yielded thebaine (**3**), as shown in Scheme 10. It is then converted to neopinone (**121)**, Scheme 10, by thebaine-6-*O*-demethylase *via* demethylation.[78] Neopinone (**121**) exists in equilibrium with its conjugated isomer codeinone (**122**), Scheme 10, which then undergoes a reduction at the C-6 keto group by codeinone reductase to yield codeine (**2**).[79] As a final step, demethylation of the phenolic ether by codeine-*O*-demethylase provides morphine (**1**), Scheme 10.[78]



Enzymes: (a) (*7S*)-salutaridinol-7-*O*-acetyltransferase; (b) thebaine-6-*O*-demethylase; (c) codeinone reductase; (d) codeine-*O*-demethylase.

Scheme 10: Biosynthesis of morphine.

An alternative pathway for the biosynthesis of morphine (**1**) from thebaine has been also proposed.[80] This pathway involves the phenolic ether demethylation to oripavine (**103**), Scheme 11, which then undergoes 6-*O*-demethylation to provide morphinone (**123**). Stereoselective reduction of morphinone (**123**) provides morphine (**1**), Scheme 11.[78]



Enzymes: (a) codeine-*O*-demethylase; (b) thebaine-6-*O*-demethylase; (c) codeinone reductase.

Scheme 11: Alternative biosynthesis of morphine.

2.2.3 Overview of selected morphine syntheses

The milestone of the first total synthesis of morphine (**1**) was achieved by Gates and Tschudi in 1952;[68] also, they confirmed the structure of morphine proposed by Robinson several years earlier.[81] To date, more than 40 total and formal syntheses of morphine alkaloids have been reported, but none of them meets the requirement of a truly practical

synthesis. Although, morphine is not a highly complex structure, its unique pentacyclic core with five contiguous stereogenic centers, a quarternary carbon at C-13, a C-4, C-5 ether linkage, and a completely dissonant relationship in morphine makes it a challenging target for synthetic chemists.[2] The concept of dissonance/consonance was first introduced by Evans in 1973 and it was discussed in detail and was applied in the disconnection studies of morphine by Hudlický.[82]

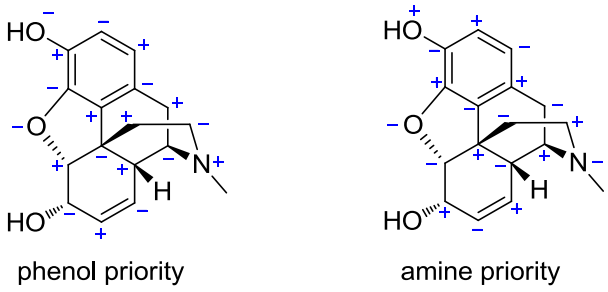


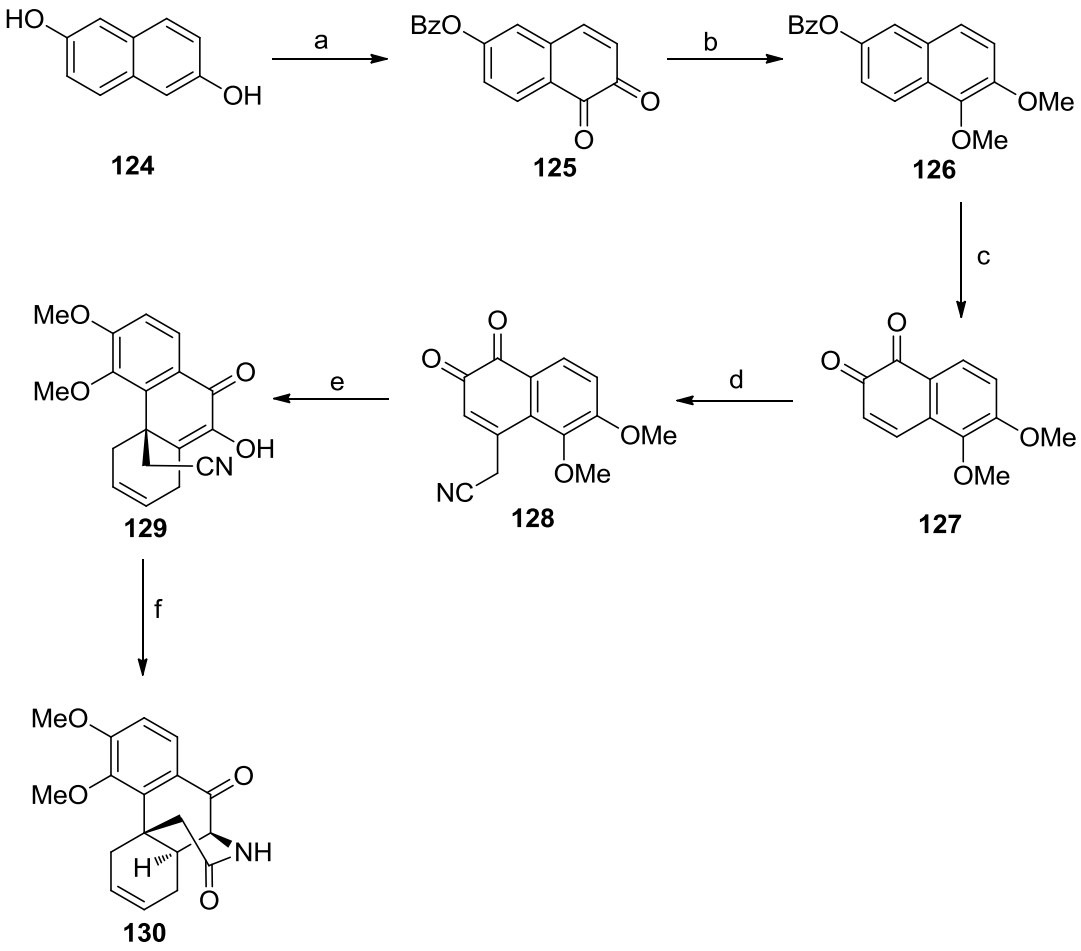
Figure 20: Dissonant relationship in morphine.

Some of the notable syntheses of morphine alkaloids will be mentioned here.

Gates (1952)

In 1952, the first total synthesis of morphine was achieved by Gates and Tschudi in 24 steps with an overall yield of 0.01%, starting from 2,6-dihydroxy naphthalene **124**, Scheme 12.[68, 83] The synthesis began with a nitrosation/reduction/oxidation sequence to yield intermediate **127**, which underwent Michael addition of ethyl cyanoacetate. Re-oxidation of the catechol and a decarboxylation reaction yielded intermediate **128**. A [4+2] cycloaddition reaction of butadiene with **128** provided **129** with correct C-13 stereochemistry as had been shown in earlier model studies.[84] The Diels-Alder cycloadduct **129** was converted to the keto lactam **130** through a reductive cyclization to

finish the D-ring. Unfortunately, this reaction led to the wrong stereochemistry at the C-14 carbon atom. The credit for developing this cyclization goes to Woodward and Gates.[85]

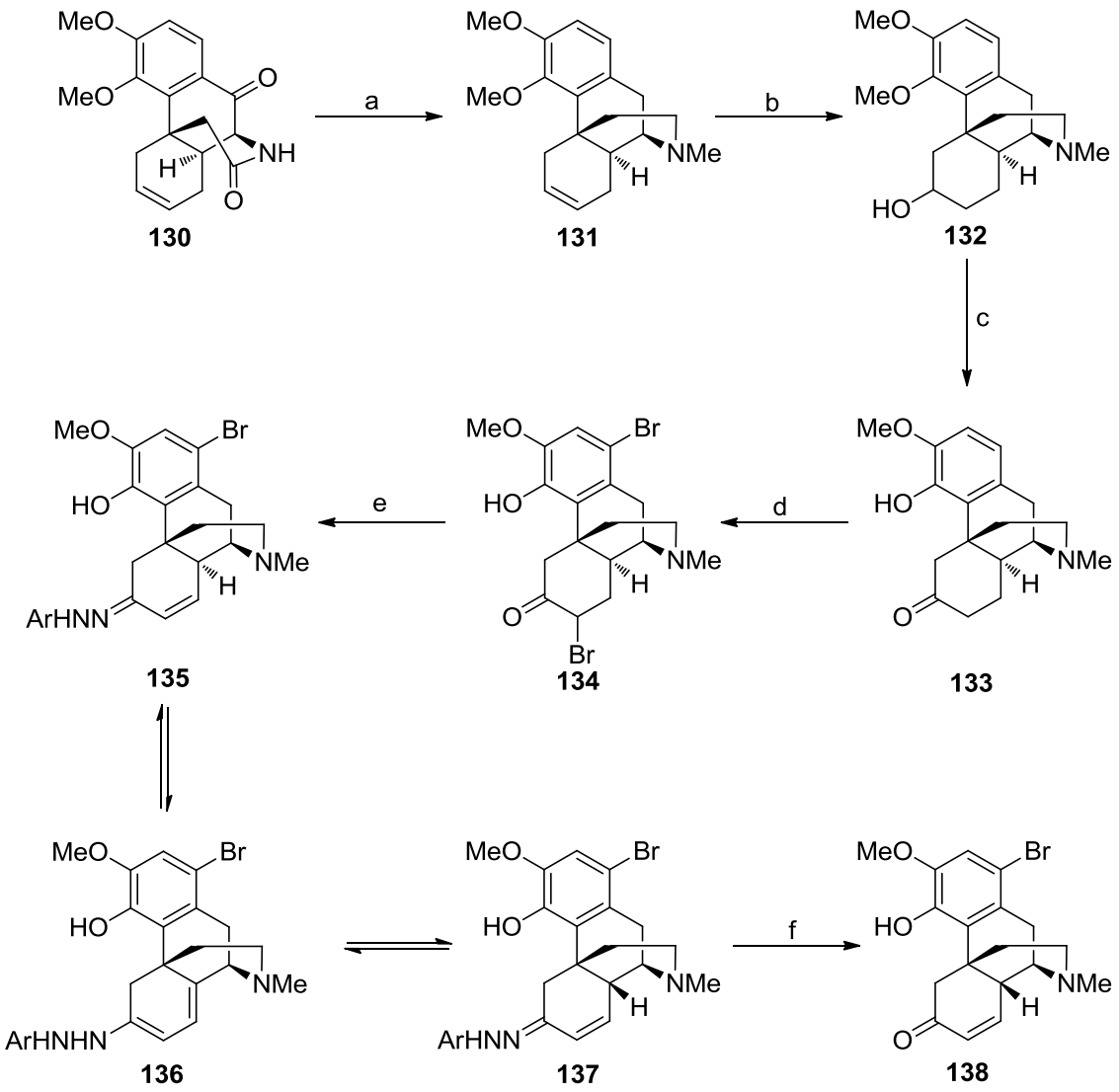


124 **125** **126** **127** **128** **129** **130**

Reagents and conditions: (a) (i) BzCl, pyridine, dioxane; (ii) $NaNO_2$, AcOH; (iii) Pd/C, H_2, AcOH, then $FeCl_3$; (b) (i) SO_2, MeOH; (ii) K_2CO_3, dimethylsulfite; (c) (i) KOH, MeOH; (ii) $NaNO_2$, AcOH; (iii) Pd/C, H_2, AcOH, then $FeCl_3$; (d) (i) ethyl cyanoacetate, NEt_3, then $K_3Fe(CN)_6$; (ii) KOH, MeOH, H_2O; (e) butadiene, AcOH; (f) CuO/Cr_2O, H_2, 150 °C.

Scheme 12: Gates's synthesis of tetracyclic core of morphine *via* amide intermediate **130.**

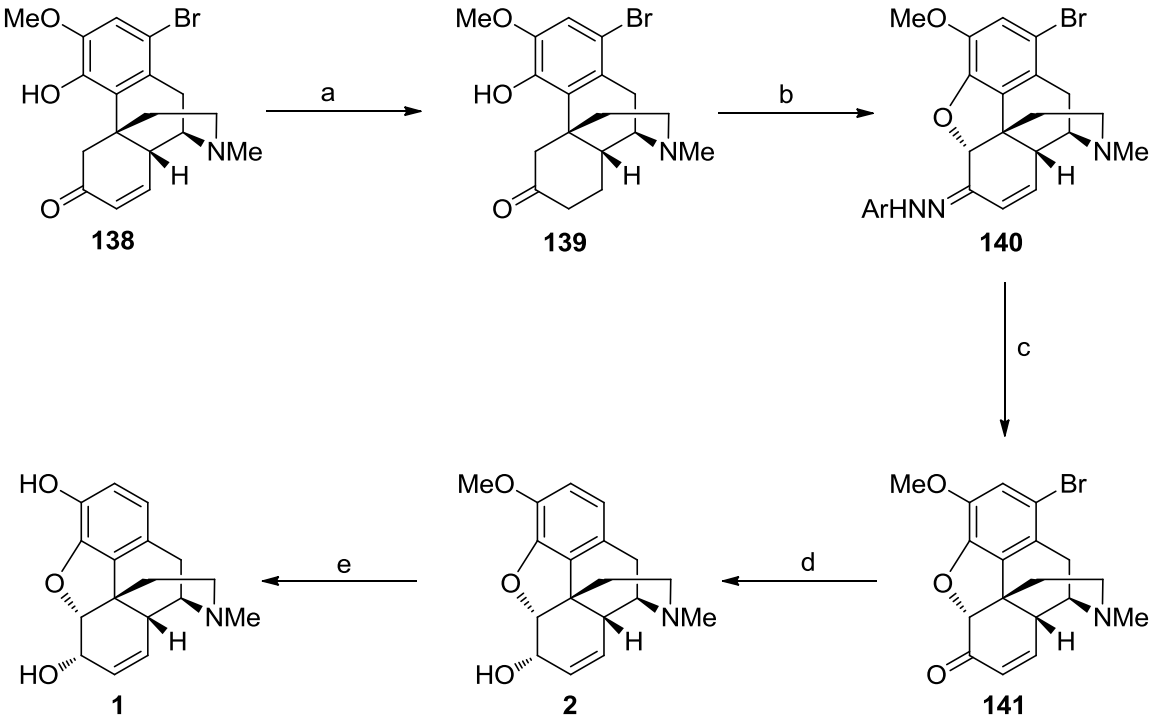
A modified Wolff-Kishner reaction was used to reduce the keto group, followed by methylation of nitrogen and reduction of amide functionality provided *d*-*β*-Δ^6-dihydrodesoxycodeine (**131**), Scheme 13. At this stage, a resolution of **131** by crystallization of the tartrate salt of **131** provided the natural enantiomer which is epimeric at C-14. The hydroxyl group at C-6 was introduced by an acid-mediated hydration. The methyl ether at C-4 position was selectively removed followed by oxidation at C-6 delivered compound **133**. After finishing compound **131**, Gates turned his attention to epimerize the C-14 stereo centre. An *α*,*β*-unsaturated ketone intermediate was created by bromination and elimination of HBr, which was converted to hydrazone **135**.



Reagents and conditions: (a) (i) KOH, N_2H_4; (ii) NaH, MeI; (iii) $LiAlH_4$; (b) dil. H_2SO_4; (c) (i) KOH, ethylene glycol; (ii) *t*BuOK, Ph_2CO; (d) Br_2, AcOH; (e) 2,4-DNP; (f) HCl.

Scheme 13: Epimerization of the C-14 stereocenter *via* hydrazone intermediate.

The hydrazone formation led to the equilibration at C-14 stereogenic centre to provide **137** through an intermediate **136**, Scheme 13, because of the formation of the more stable *cis*-fused ring system. The hydrazone was then hydrolysed using acid to obtain **138**.



Reagents and conditions: (a) H_2, PtO_2; (b) (i) Br_2, AcOH; (ii) 2,4-DNP; (c) HCl, acetone; (d) (i) $LiAlH_4$; (ii) H_2, Pd/C; (e) Py·HCl, 220 °C.

Scheme 14: Completion of the synthesis of (–)-morphine (**1**).

The *α,β*-unsaturated ketone in **138** was hydrogenated and the final ring of morphine was constructed using a diphenyl furan ring formation between C-4 and C-5 carbon atoms to provide **140**, Scheme 14. It was achieved by applying similar conditions that were used in the epimerization of C-14 stereo centre, which also led to the formation of unsaturation between C-7 and C-8. Acid-mediated hydrolysis of hydrazone and reduction of ketone functionality provided codeine (**2**). The first synthesis of morphine (**1**) was completed by demethylation of C-3 methyl ether using Rappoport's conditions.[86]

Rice (1980)

Rice's synthesis of hydrocodone is known as the shortest and highest yielding synthesis of any morphine alkaloid to date. This biomimetic approach towards morphine alkaloid involves the isolation of only six intermediates and no column chromatography, and the final product was isolated in an overall yield of 29%.[87] Rice's approach was inspired by the reports on Grewe-type electrophilic cyclization of benzylhexahydroisoquinoline **142**, Figure 21.[88] This reaction managed to provide dihydrothebainone **143**, a precursor for codeine, in lower yields where the formation of isomeric compound **144** predominates in the reaction.

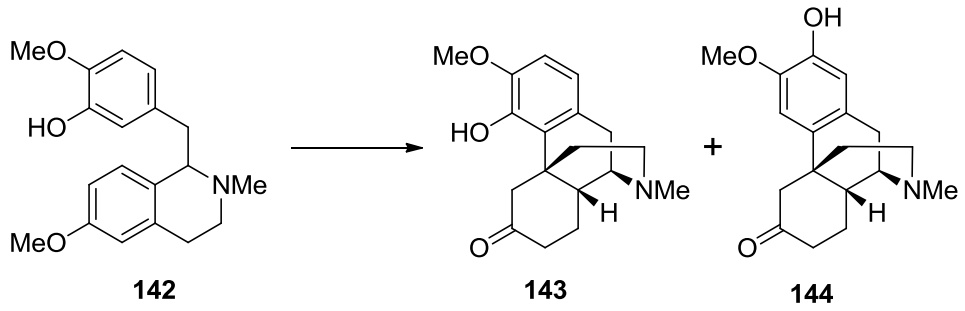
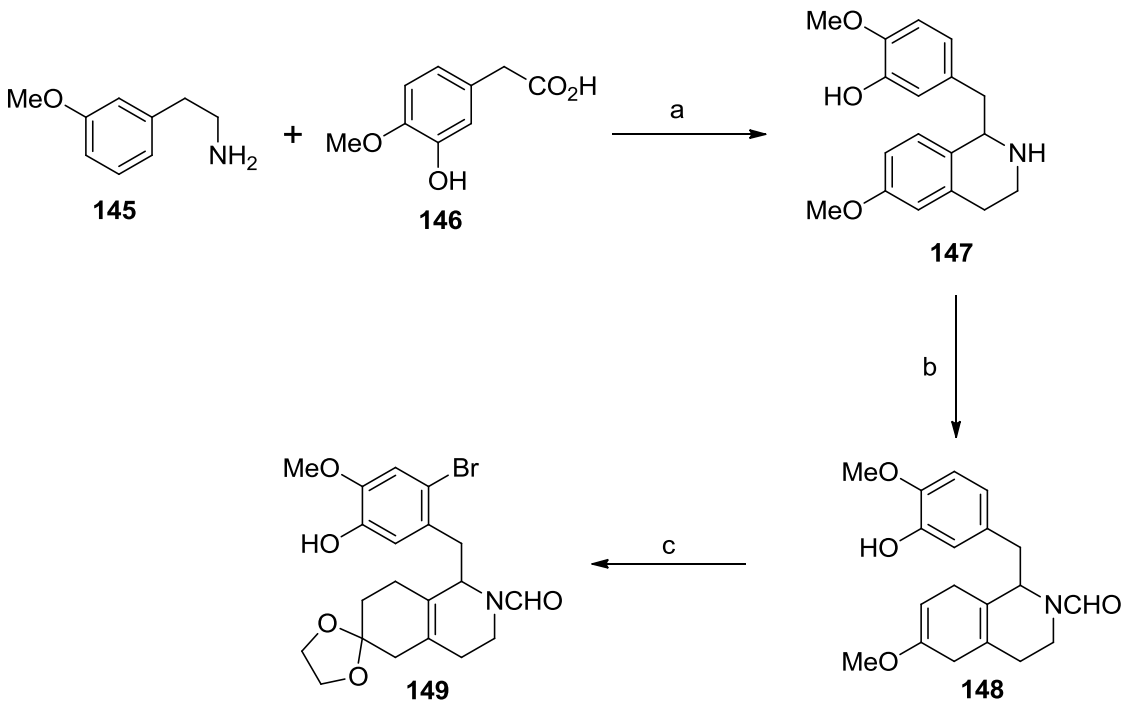


Figure 21: Formation of dihydrothebainone via Grewe-type electrophilic cyclization.

A mixture of amine **145**, and acid **146**, was heated to yield an amide intermediate, which underwent a Bischler-Napieralski cyclization to provide **147**, Scheme 15. Formylation and Birch reduction of the more electron deficient aromatic ring provided intermediate **148**. A one pot reaction involving ketalization and regeoselective bromination provided **149**.

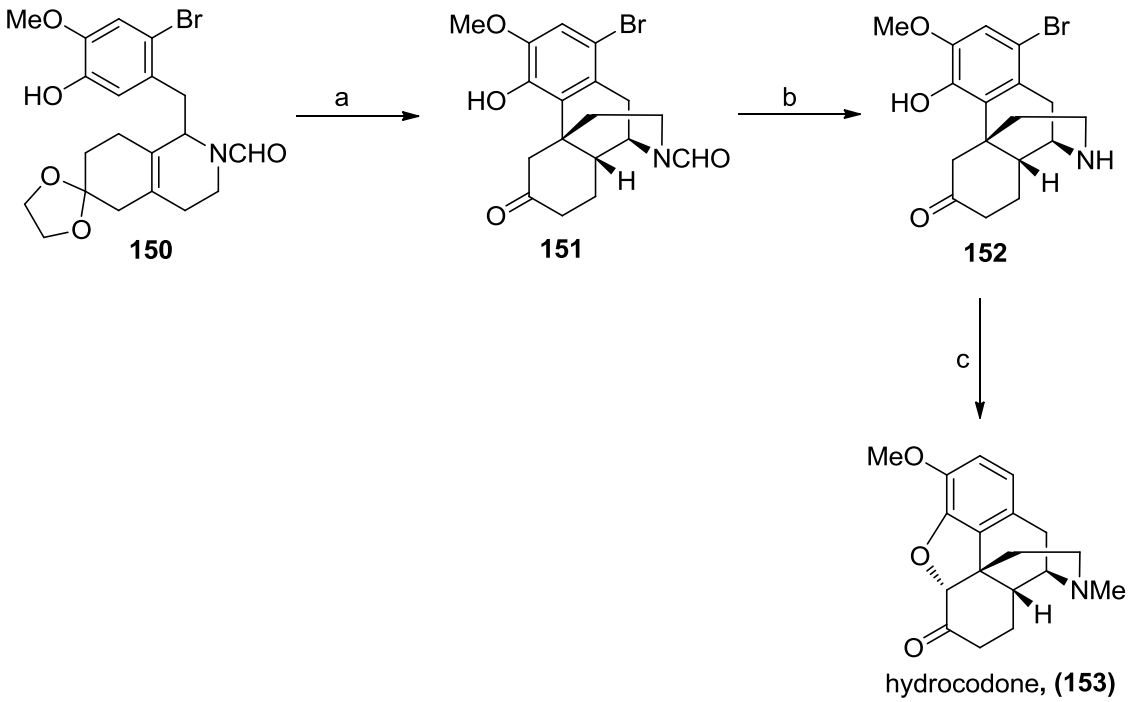


Reagents and conditions: (a) (i) 200°C; (ii) $POCl_3$, CH_3CN; (iii) $NaCNBH_3$, MeOH (86%); (b) (i) Li, NH_3, THF, *t*BuOH; (ii) PhOCHO, EtOH; (c) (i) ethylene glycol, $MeSO_3H$, THF; (ii) *N*-bromoacetamide (NBA).

Scheme 15: Rice's synthesis of tricyclic core of morphine alkaloid.

Acid-catalyzed hydrolysis of ketal followed by hydrogen fluoride-mediated Grewe-type cyclization provided dihydrothebainone derivative **151**, Scheme 16. Amide **151** was hydrolysed under acidic conditions to obtain **152** and the bromine atom at C-1 was then removed by hydrogenation. Bromination at C-5 and base induced cyclization completed the pentacyclic core of morphine alkaloid. The synthesis of hydrocodone (**153**) was completed by the removal of the aryl bromide and methylation of nitrogen. Rice also

developed a method for resolution of compound **147**, Scheme 15, which allowed access to both natural and unnatural series of morphine alkaloids.



Reagents and conditions: (a) (i) HCO_2H, H_2O; (ii) NH_4F, HF, CF_3SO_3H; (b) HCl, MeOH; (c) (i) H_2, Pd/C, AcOH, HCHO; (ii) Br_2, AcOH; (iii) NaOH, $CHCI_3$; (iv) H_2, Pd/C, AcOH, HCHO.

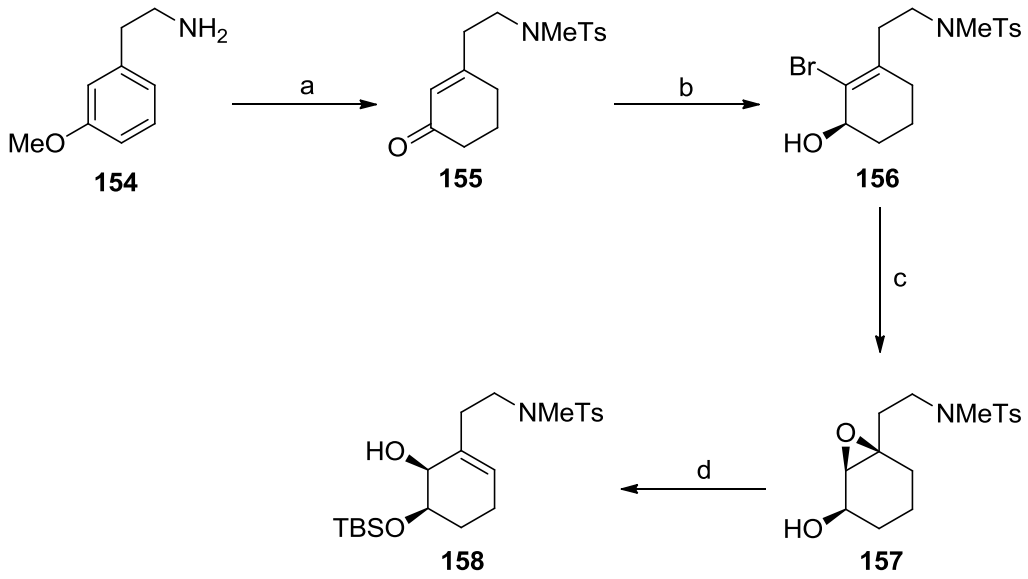
Scheme 16: Completion of synthesis of hydrocodone.

Parker (1992, 2006)

Parker and Fokas completed the racemic synthesis of dihydroisocodeine in 1992.[89] The synthesis was completed in 11 steps and constituted a formal synthesis of morphine. Their approach to the construction of the morphine ring system was based on the tandem

cyclization of an ortho allyloxy aryl radical. Later, in 2006, the original synthesis was modified to result in an asymmetric synthesis of hydrocodone.[90]

The synthesis started from commercially available *m*-methoxyphenethylamine **154**, Scheme 17. Birch reduction of **154** followed by tosylation of amino functionality and hydrolysis of enol ether followed by methylation provided the enone **155**. All attempts to perform an asymmetric reduction of **155** proved to be unsuccessful. This failure led to the bromination of **155** to obtain the 2-bromocyclohexenone derivative and the asymmetric reduction of this with (*S*)-oxazaborolidine -catechol borane reagent (CBS)[91] provided the desired alcohol **156** in good yield and acceptable enantiomeric excess. Then the removal of halogen from the ring system and peroxy acid mediated epoxidation delivered the *cis*-epoxy alcohol **157**, Scheme 17. Treatment of the epoxy alcohol **157** with titanium isopropoxide resulted in the formation of cyclohexene diol which was silylated to obtain the compound **158**, Scheme 17, C-ring fragment of morphine.

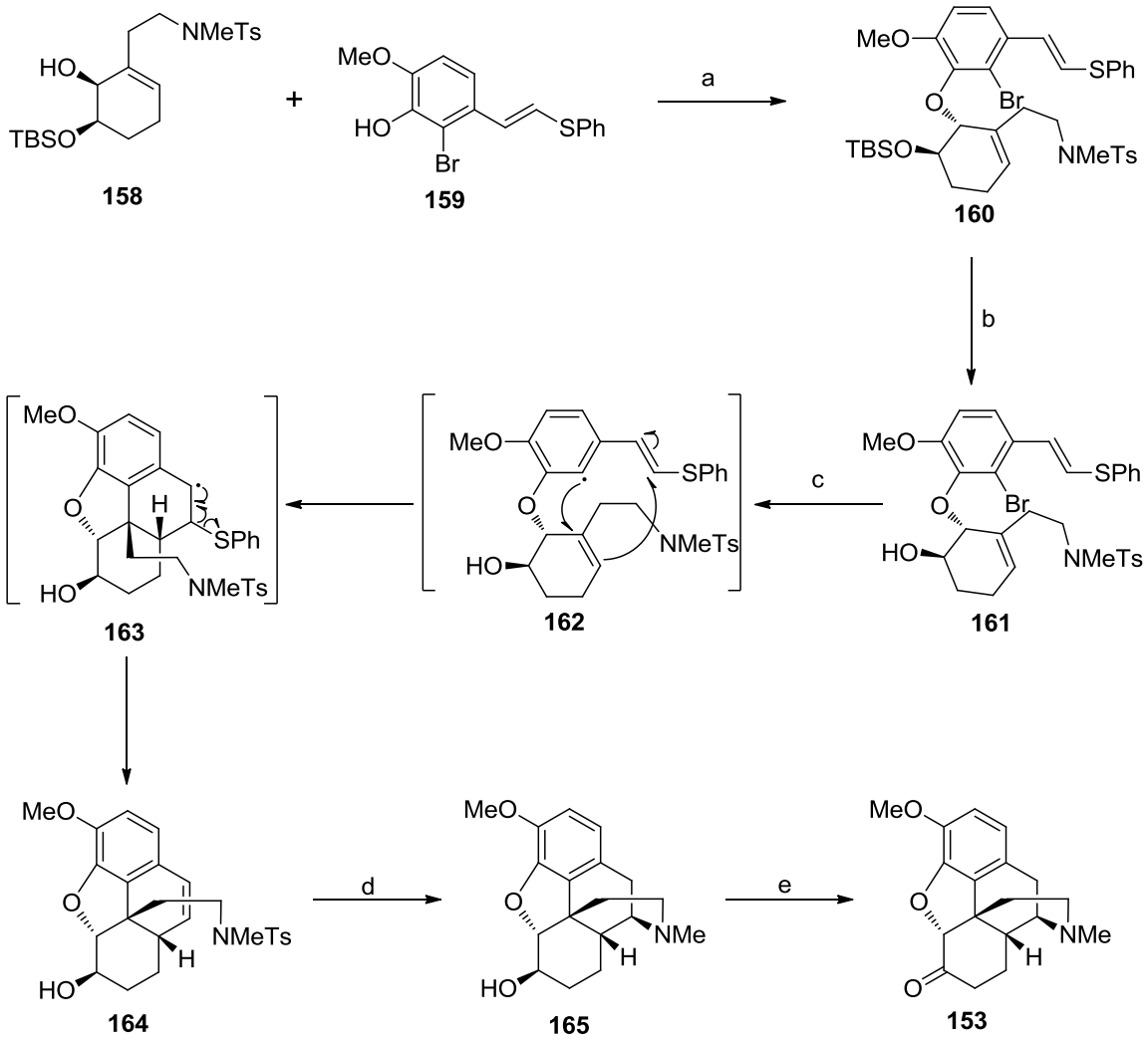


Reagents and conditions: (a) (i) Li, NH_3, *t*BuOH; (ii) TsCI, NEt_3, HCl; (iii) MeI, K_2CO_3, acetone; (b) (i) Br_2, NEt_3; (ii) CBS, catechol borane; (c) (i) Na(Hg); THF-MeOH; (ii) *m*CPBA; (d) (i) $Ti(OiPr)_4$; (ii) TBSCl, imidazole, DMF.

Scheme 17: Synthesis of C-ring fragment.

The key intermediate in the synthesis is compound **160**, Scheme 18, which is the precursor for the radical cyclization reaction. It was formed through a Mitsunobu reaction between alcohol **158** and a highly substituted phenol **159**, which was synthesized from isovanillin in two steps.[92] The silyl protecting group was removed to obtain intermediate **160**; tributyltin hydride mediated homolytic cleavage of carbon halogen bond in **161** generated the aryl radical **162**. The dihydrofuran ring was generated by the radical cyclization of the aforementioned species, which led to the formation of another radical at the C-14 carbon atom. This unstable radical was trapped by the styrene bond to form a stabilized benzylic radical and also connected the C-14 and C-9 carbon atoms as shown

in intermediate **163**, Scheme 18. Then, phenylthiolate radical was eliminated to afford **164** as a single diastereomer with the correct configuration at C-13 and C-14 stereocenters.



Reagents and conditions: (a) (i) PBu_3, DEAD; (b) 10% HF, CH_3CN; (c) $n$$Bu_3SnH$, AIBN, toluene; (d) Li, NH_3, tBuOH; (e) DMSO, $(COCI)_2$, NEt_3.

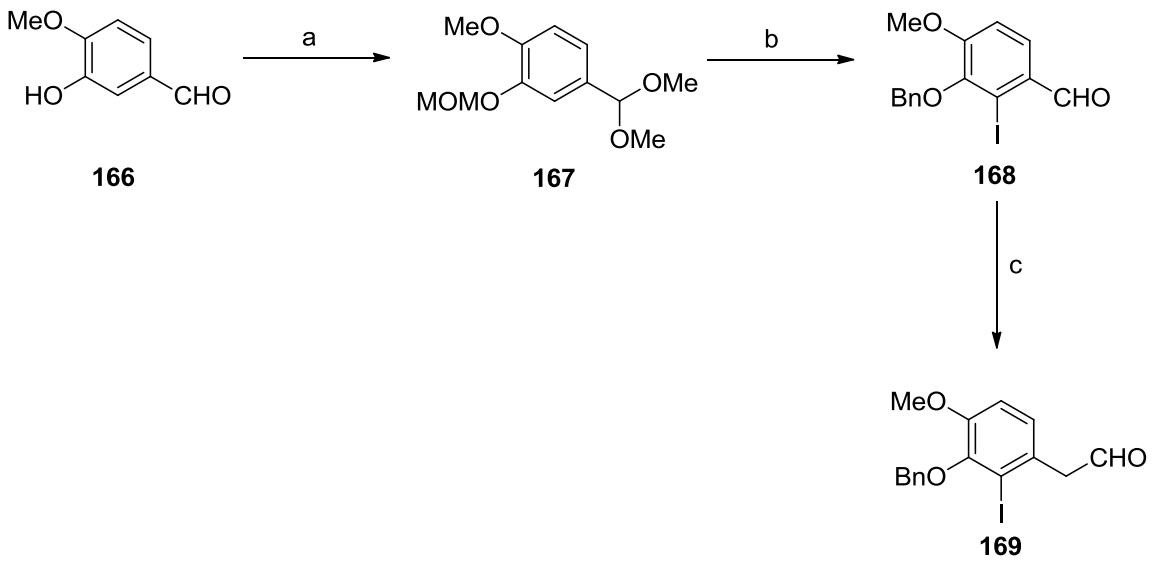
Scheme 18: Synthesis of hydrocodone via radical cyclization approach.

A reductive desulfonation using lithium in ammonia led to the cyclization of the final ring to obtain dihydroisocodeiene (**165**), Scheme 18, and Swern oxidation of the C-6 hydroxy group effected the completion of the synthesis of hydrocodone (**153**), Scheme 18.

Overman (1993)

The first published enantiodivergent synthesis of morphine is Overman's approach which involves no resolution of intermediates. [93] An iminium ion-allylsilane cyclization and a Heck reaction were the key reactions in his approach.

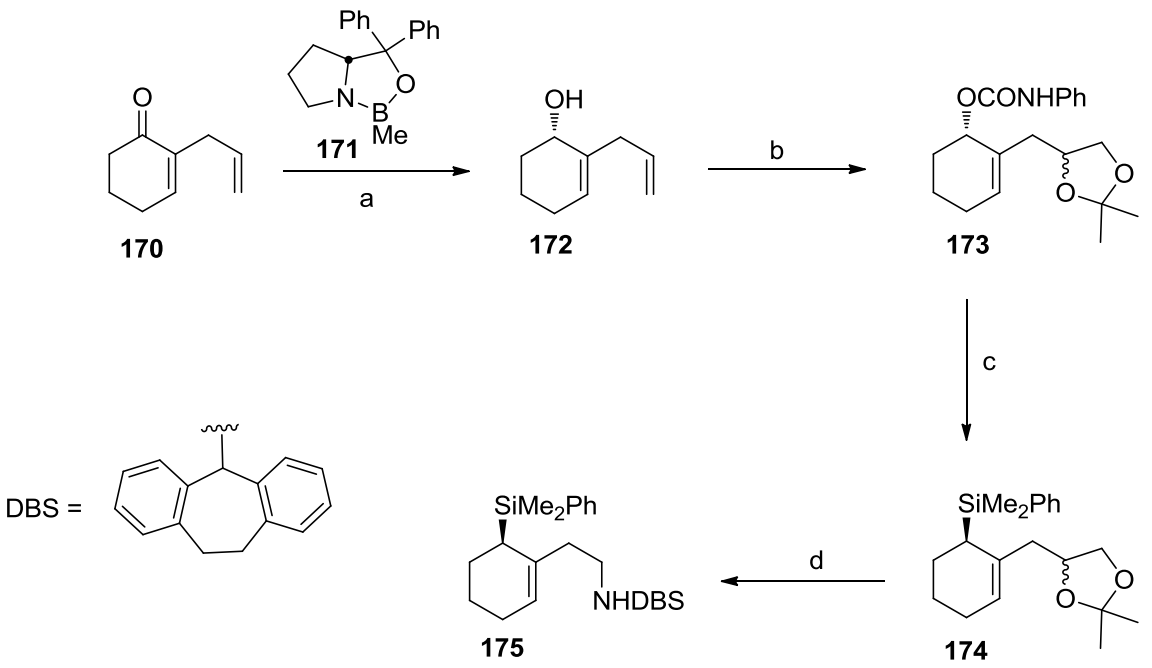
The synthesis started from isovanillin by the protection of the phenol and aldehyde to obtain ketal **167**, Scheme 19. *Ortho*-lithiation of **167** with *n*-BuLi and quenching the aryllithium with iodine followed by protecting group hydrolysis and reprotection of the phenol with a benzyl group provided compound **168**. Homologation of the aldehyde was effected using dimethylsulfonium methylide and Lewis acid catalyzed rearrangement of the corresponding epoxide to provide the A-ring fragment **169**.



Reagents and conditions: (a) (i) $HC(OMe)_3$, HCl; (ii) NaH, $ClCH_2OMe$; (b) (i) *n*BuLi, I_2; (ii) 6N HCl; (iii) BnBr, K_2CO_3; (c) (i) CH_2SMe_2; (ii) $BF_3{\cdot}OEt_2$, THF.

Scheme 19: Overman's synthesis of A-ring fragment.

The synthesis of the C-ring fragment was started by enantioselective reduction of 2-allylcyclohex-2-enone **170**, Scheme 20, using catecholborane in the presence of a chiral catalyst to obtain **172**. Condensation of this alcohol with phenyl isocyanate and dihydroxylation of the terminal olefin followed by protection provided the acetonide **173**. S_N2' displacement of this allylic carbamate provided the allyl silane **174**. Deprotection of the acetonide led to the formation of an aldehyde which was treated with dibenzosurberylamine (DBS-NH_2) followed by reduction to provid the C-ring fragment **175**, Scheme 20.

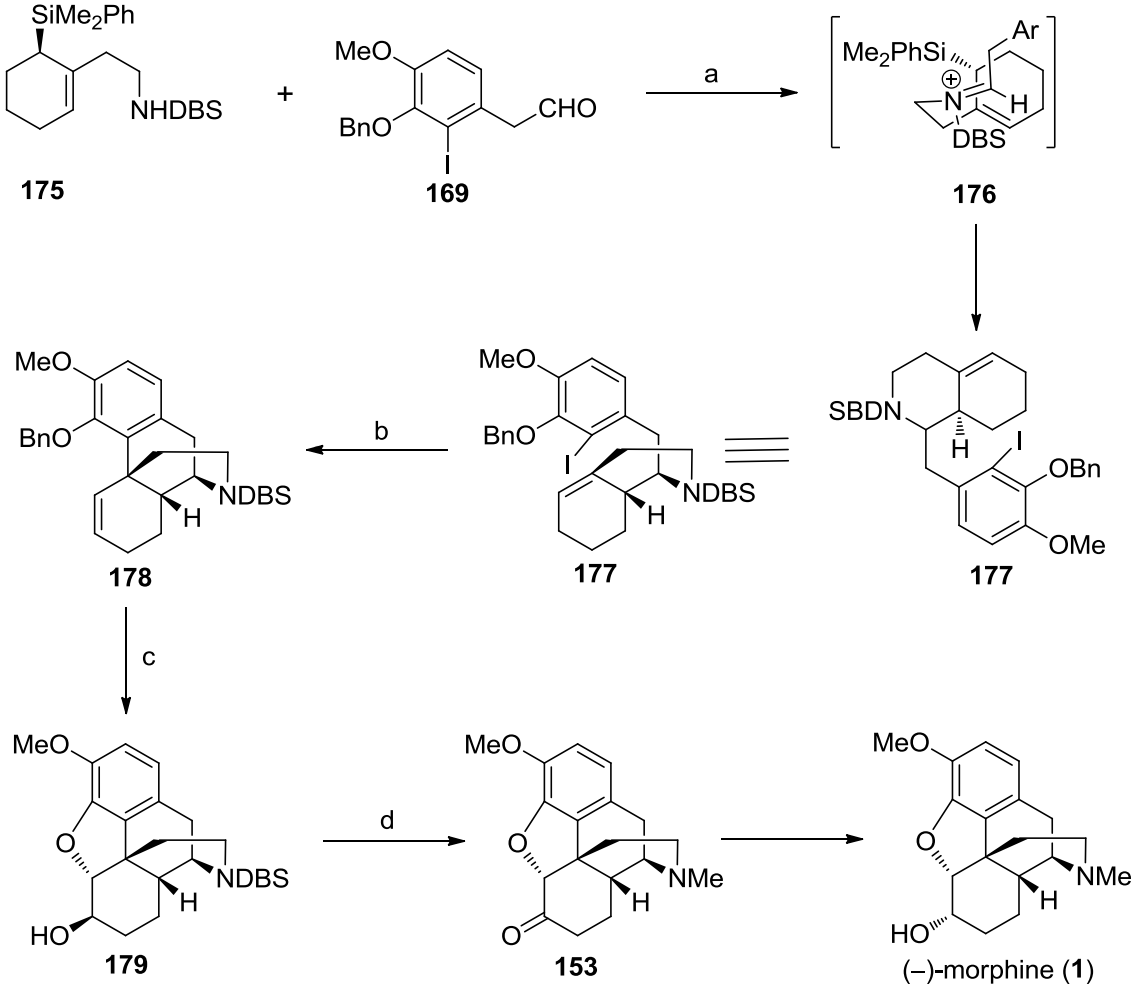


Reagents and conditions: (a) (i) **171**, catechol borane; (b) (i) PhNCO; (ii) OsO_4, acetone, HCI; (c) (i) *n*BuLi, THF, –30 °C; (ii) CuI $(PPh_3)_2$, 0 °C; (iii) $PhMe_2SiLi$, 0 °C; (d) (i) *p*TsOH, MeOH, $NaIO_4$; (ii) DBS-NH_2, $NaCNBH_3$.

Scheme 20: Synthesis of C-ring fragment.

Condensation of amine **175** and aldehyde **169** in the presence of ZnI_2 led to the formation of iminium ion **176**, which underwent an allylsilane cyclization to generate compound **177**, Scheme 21. An intramolecular Heck cyclization provided the tetracycle **178**, Scheme 21, in which the crucial C-13 quaternary carbon center was established. Deprotection of the benzyl ether group and a tandem epoxidation etherification reaction resulted in the formation of the final ring of the morphine alkaloid to provide **179**. Overman's synthesis was finished by oxidation of the C-6 alcohol to a ketone and hydrogenolysis of the DBS group in the presence of formaldehyde to provide

hydrocodone (**153)**, Scheme 21. Hydrocodone was then converted to morphine as using the conditions described by Rice.[94]



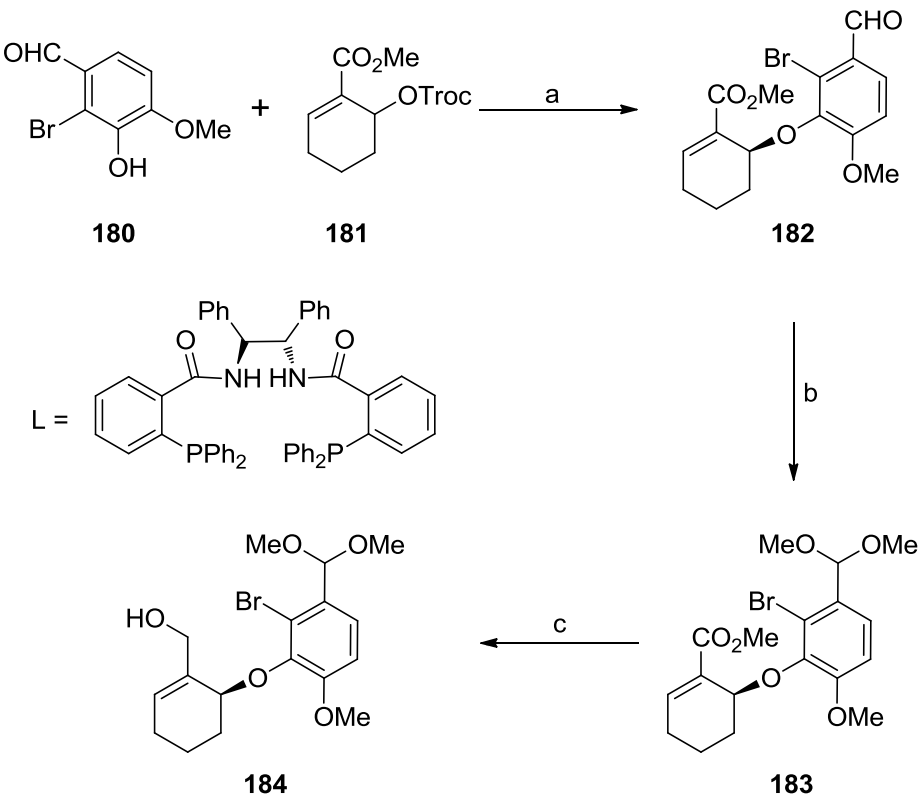
Reagents and conditions: (a) (i) ZnI, EtOH, 60°C; (b) $Pd(TFA)_2(PPh3)_2$, 1,2,2,6,6-pentamethylpiperidine, toluene; (c) (i) $BF_3{\cdot}OEt_2$, EtSH; (ii) CSA, 3,5-dinitroperoxybenzoicacid; (d) (i) TPAP, NMO; (ii) H_2 $Pd(OH)_2$, HCHO.

Scheme 21: Overman's synthesis of hydrocodone.

Trost (2002, 2005)

Enantioselective synthesis of (–)-codeine (**2**) and morphine (**1**) was reported by Trost in 2002. [95] Trost's synthesis involves an asymmetric allylic alkylation as a key step which connects the A and C rings of morphine in an enantioselective manner. Later, the dihydrofuran ring and B ring were created using two Heck cyclization sequence.

The synthesis started with the asymmetric allylic alkylation of 2-bromoisovanillin **180** and allylic ester **181**, Scheme 22, leading to the formation of ether linkage between the top A ring and bottom C ring of the morphine alkaloids to provide compound **182**, Scheme 22. The ester group was reduced to alcohol **184** after protection of the aldehyde functionality.

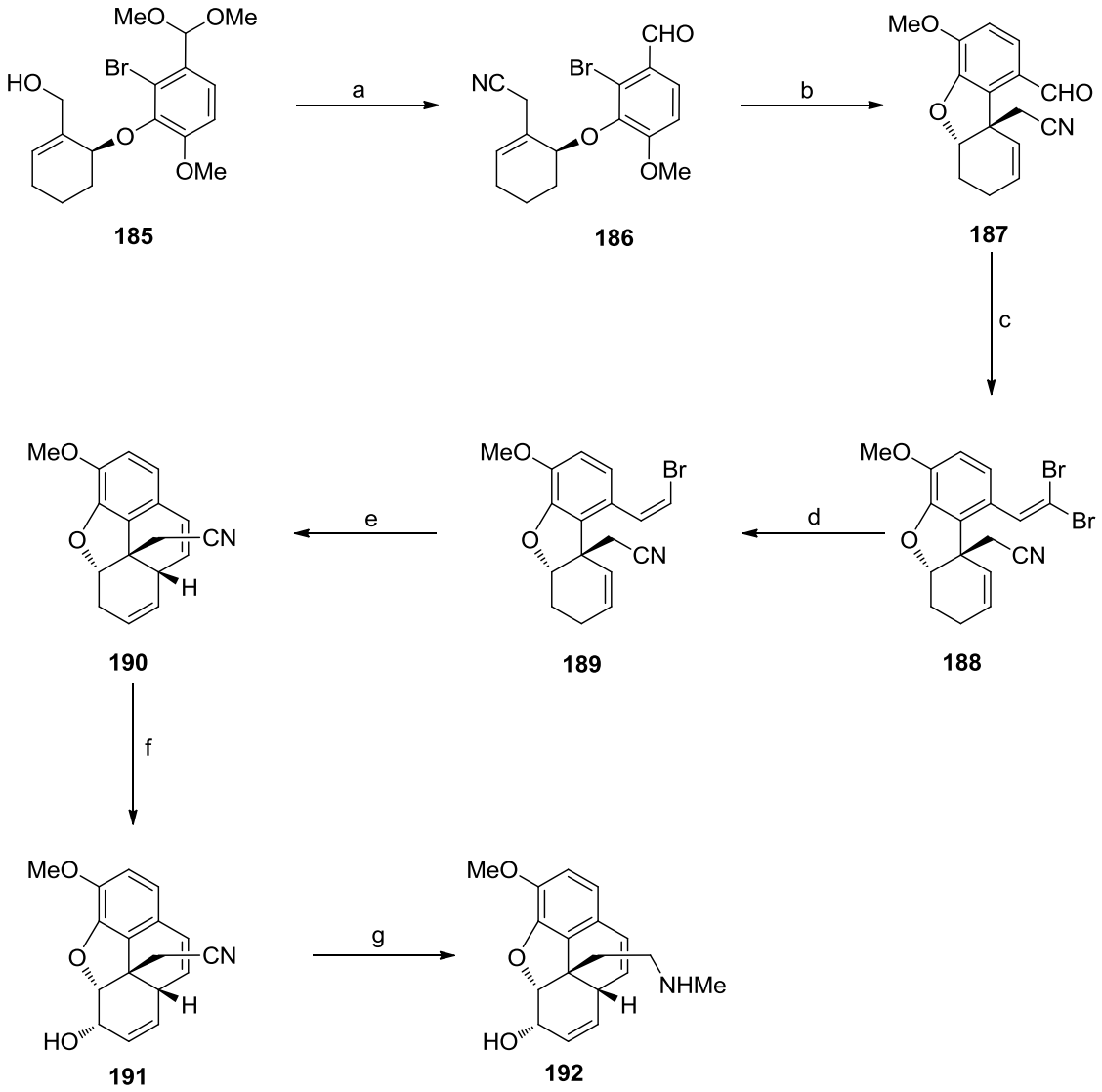


Reagents and conditions: cat. PdL, NEt_3, CH_2Cl_2; b) *p*-TsOH, $CH(OMe)_3$, MeOH; c) DIBALH, toluene, –78 °C.

Scheme 22: Trost's synthesis of intermediate **184.**

A modified Mitsunobu reaction followed by acid mediated deprotection led to the formation of aldehyde **186**, Scheme 23. The dihydrofuran ring and the quaternary C-13 carbon center were generated in one step *via* an intramolecular Heck cyclization to provide the tricyclic intermediate **187**. Aldehyde **187** was converted to **188** using a Corey-Fuchs homologation and a chemoselective reduction of the *trans*-vinyl bromide led to the formation of intermediate **189**. This underwent a second intramolecular Heck cyclization to create the B ring in **190**. Tetracycle **191** was generated *via* a selenium

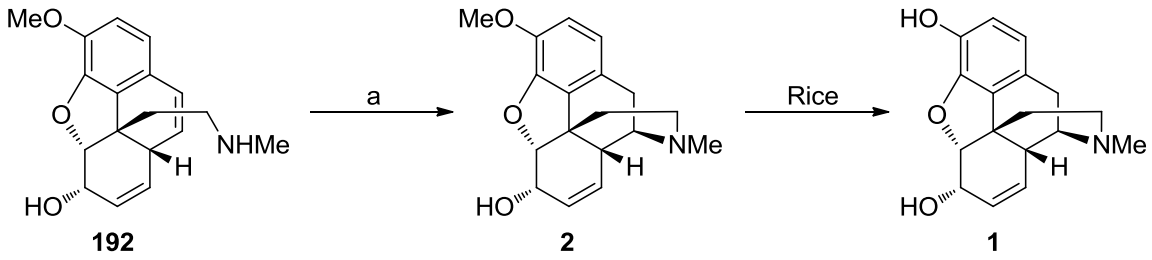
dioxide mediated allylic oxidation and reduction of the corresponding enone. The nitrile group was then converted to an amine and it was immediately methylated to obtain **192**, Scheme 23.



Reagents and conditions: (a) (i) PPh_3, acetonecyanohydrin, DIAD; (ii) *p*-TsOH, THF, H_2O; (b) $Pd(OAc)_2$, dppf, Ag_2CO_3, toluene; (c) CBr_4, PPh_3, CH_2Cl_2; (d) *n*-Bu_3SnH, toluene; (e) $Pd(OAc)_2$, dppp, Ag_2CO_3, toluene; (f) (i) SeO_2, dioxane, sand; (ii) DIBALH, THF, Et_2O; (g) DIBALH, CH_2Cl_2, Et_2O, then NH_4Br, $MeNH_2$ followed by $NaBH_4$.

Scheme 23: Trost's synthesis of intermediate **192**.

The pentacyclic core of morphine was made by generating the D ring through a hydroamination reaction to provide codeine (**2**) as shown in Scheme 24. Codeine (**2**) was then converted morphine (**1)** using Rice's existing method. [96]

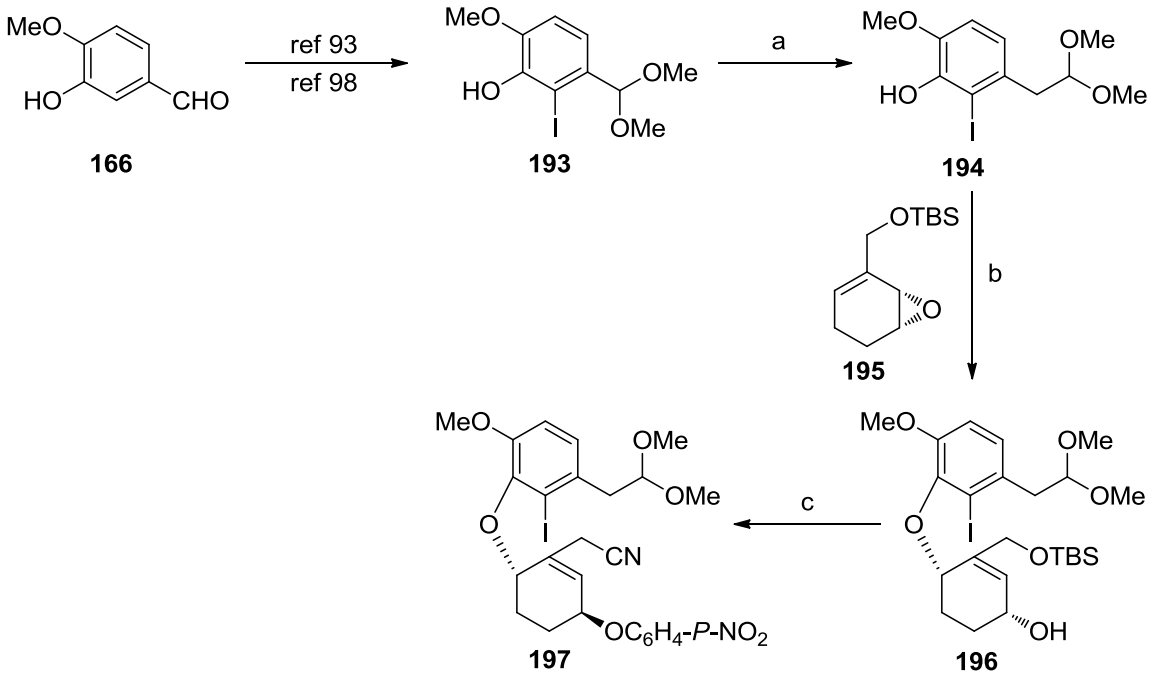


Reagents and conditions: (a) LDA, THF, 150-W tungsten bulb.

Scheme 24: Completion of synthesis of codeine.

Fukuyama (2006, 2010)

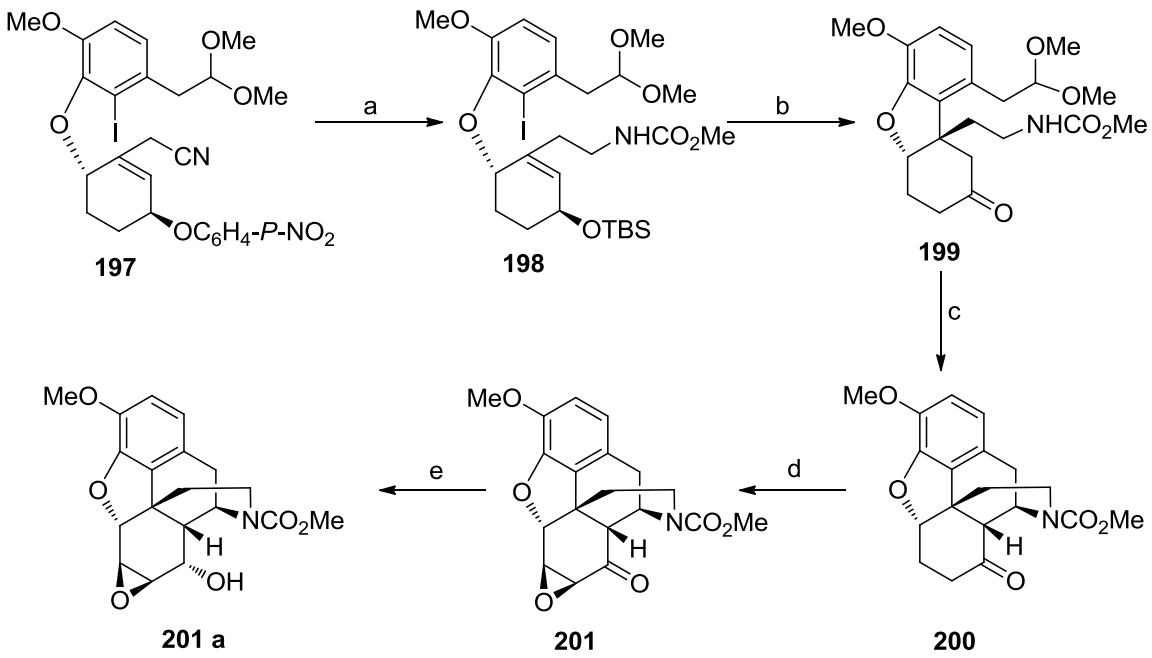
A racemic synthesis of morphine was reported by Fukuyama in 2006;[97] his synthesis started with the convertion of isovanillin into the 2-iodo derivative using known protocols.[93, 98] The acetal **193**, Scheme 25, was hydrolysed under acidic conditions followed by a Wittig reaction and treatment with camphorsulfonic acid in MeOH provided the homologated phenol **194**. One of the key steps in this synthesis was the coupling of phenol **194** with epoxide **195** by means of a Tsuji-Trost coupling.[99] A Mitsunobu inversion of alcohol **196** followed by deprotection of the silyl ether and another Mitsunobu reaction provided the nitrile **197**.



Reagents and conditions: (a) (i) AcOH, THF-H_2O, 0 °C to rt; (ii) $MeOCH_2PPh_3Cl$, NaHMDS, THF, 0 °C to rt; (iii) HCl, MeOH, rt; (b) $Pd_2(dba)_3$, P(2-furyl)$_3$, CH_3CN, rt; (c) (i) *p*-nitrobenzoic acid, DEAD, PPh_3, toluene, 0 °C; (ii) CSA, MeOH; (iii) 2-hydroxy-2-methylpropanenitrile, DEAD, PPh_3, toluene, 0 °C.

Scheme 25: Synthesis of ether **197**.

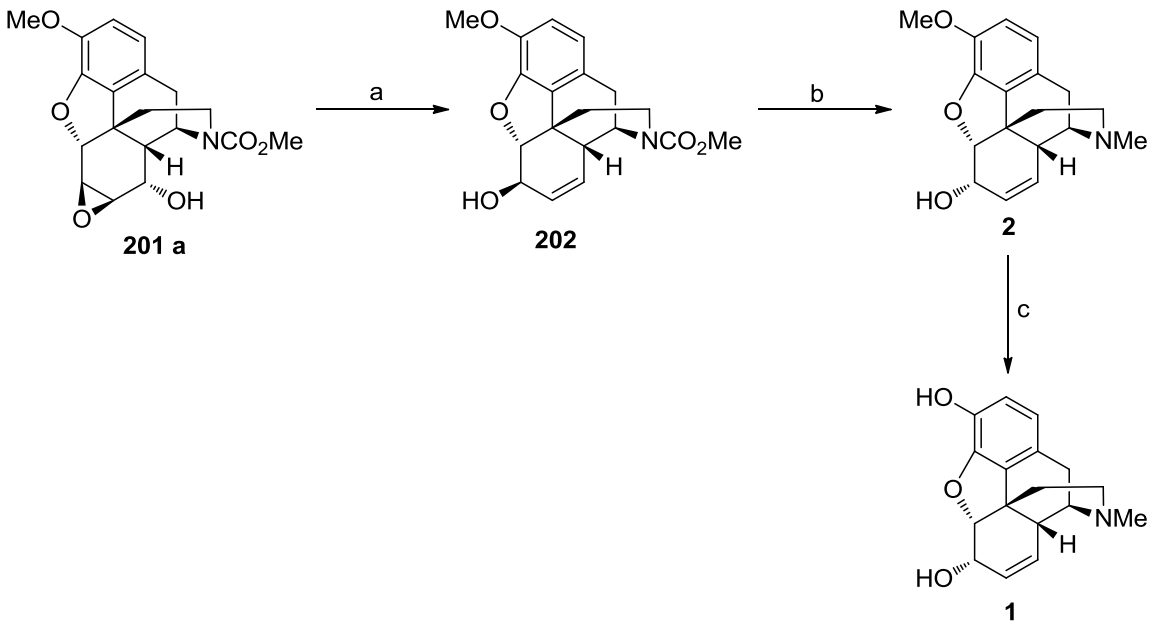
Reduction of nitrile **197** followed by protection delivered carbamate **198**, Scheme 26. An intramolecular Heck reaction was designed for the completion of tricyclic core to obtain a silyl enol ether which upon desillylation yielded ketone **200**. The double cyclization was achieved under acidic condition *via* an intramolecular Mannich type reaction. The endgame involved the conversion of ketone to enone by the Ito-Saegusa method[100] and epoxidation to obtain epoxide **201**, Scheme 26.



Reagents and conditions: (a) (i) $LiBH_4$, Et_2O, MeOH, 0 °C; (ii) TBSCI, imidazole; (iii) DIBALH, CH_2Cl_2, -78 °C; (iv) $ClCO_2Me$, K_2CO_3; (b) (i) $Pd_2(dba)_3$, P(o-tolyl)$_3$, NEt_3, MeCN; (ii) TBAF; (c) HCI, MeOH, reflux; (d) (i) TMSCI, LiHMDS, THF, 0 °C; (ii) $Pd(OAc)_2$, MeCN; (iii) H_2O_2, H_2O, NaOH, MeCN, 0 °C; (e) $NaBH_4$, MeOH, CH_2Cl_2, 0 °C.

Scheme 26: Synthesis of intermediate **201**.

The ketone in **201**, Scheme 26, was reduced from the less hindered face and the resulting alcohol **201 a** was converted to thiocarbamate, which upon exposure to radical conditions resulted in the allylic alcohol **202,** Scheme 27. C-6 stereochemistry was adjusted by a oxidation reduction sequence and the cleavage of the methyl ether was achieved following a known protocol to obtain racemic morphine (**1**).[96]

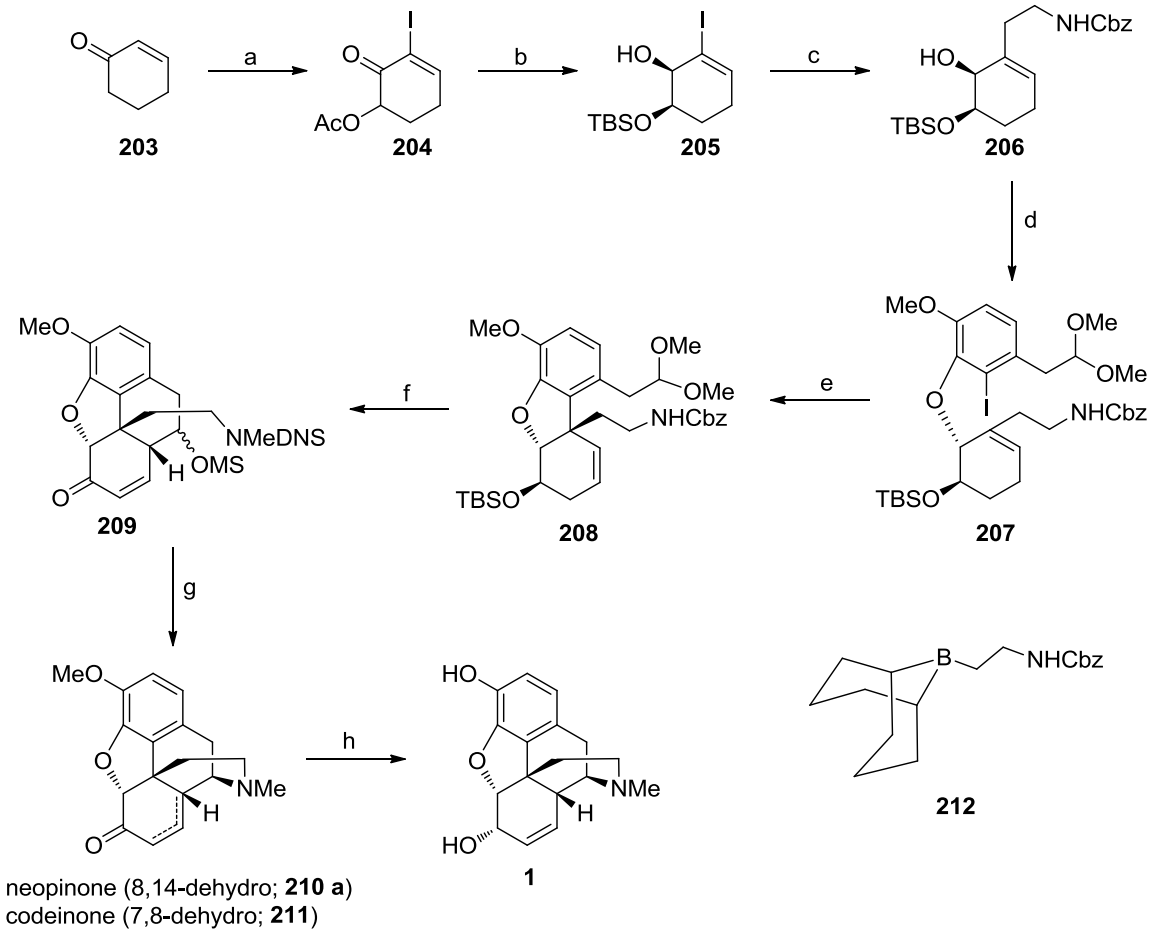


Reagents and conditions: (a) (ii) 1,1′-thiocarbonyl diimidazole, DMAP, $ClCH_2CH_2Cl$, 60 °C; (ii) Et_3B, *n*-Bu_3SnH, THF; (b) (i) Dess-Martin periodinane, CH_2Cl_2; (ii) $LiAlH_4$, THF; (c) BBr_3, CH_2Cl_2.

Scheme 27: Completion of synthesis of morphine.

Later in 2010, the same group reported an enantioselective synthesis of morphine based on the same approach.[101] α-Acetoxylation of cyclohexenone **203** followed by iodination provided iodoketone **204**, Scheme 28. Enzyme-mediated chiral resolution and protection of the alcohol as silyl ether followed by Luche reduction yielded alcohol **205**. Alcohol **206** was prepared by the palladium-catalyzed Suzuki-Miyaura coupling of **205** and **212**. A Mitsunobu reaction followed by intramolecular Heck cyclization delivered (+) or (-)-**208**. The carbamate was reduced and the secondary amine was protected using 2,4-dinitrobenzene-sulfonyl chloride (DNSCl). After deprotection of the silyl ether, the alcohol was oxidised to enone and the C-9 hydroxyl was mesylated to **209**.Treatment

with base led to substitution of the mesyl group for β-isomer and decomposition under much harsh conditions. DNS group was cleaved using mercapto acetic acid and Et_3N which led to the formation of neopinone (**210**) and codeinone (**211**), Scheme 28. These mixtures were converted to pure codeinone under acid mediated conditions and reduction and cleavage of the methyl ether provided morphine (**1**), Scheme 28.

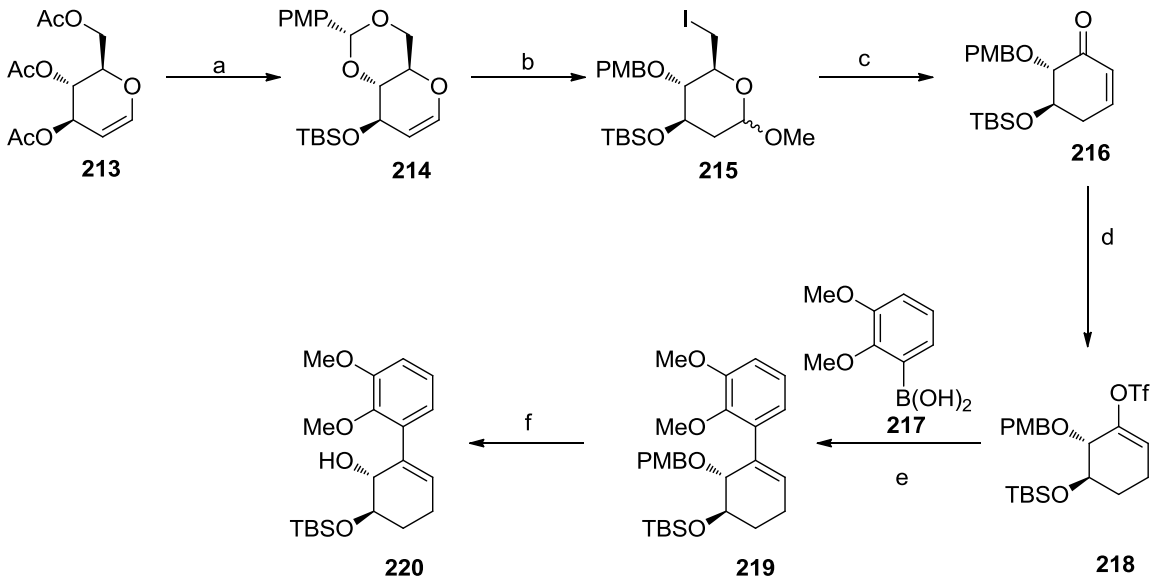


Reagents and conditions: (a) (i) Pb(OAc)4, toluene, rt; (ii) I_2, DMAP, py, CCl_4; (b) (i) lipase AK, THF, phosphate buffer (pH 7.41); (ii) TBSOTf, 2, 6-lutidine; (iii) $NaBH_4$, $CeCl_3$, MeOH (c) **212**, [$PdCl_2$(dppf)], aq. NaOH, THF; (d) **194,** *n*-Bu_3P,DEAD, THF; (e) [$Pd_2(dba)_3$], P(*o*-tolyl)$_3$, NEt_3, CH_3CN, rt; (f) (i) $LiAlH_4$, THF, rt; (ii) aq. NaOH, DNsCl; (iii) CSA, MeOH; (iv) Dess-Martin periodinane; (v) aq. TFA, toluene, 50 °C; (vi) MsCl, *i*Pr_2NEt, 0 °C; (g) $HSCH_2CO_2H$, *i*Pr_2NEt, 0 °C; (h) (i) HCl, dioxane, CH_2Cl_2; (ii) $NaBH_4$, MeOH; (iii) BBr_3, CH_2Cl_2.

Scheme 28: Fukuyama's synthesis of codeinone.

Chida (2008, 2013)

In 2008, Chida reported a formal synthesis of morphine by intercepting dihydroisocodeine.[102] The highlight of the synthesis was a cascade of Johnson-Claisen rearrangements to establish the C-13 and C-14 stereocenters. He had already employed this strategy in the synthesis of the Amaryllidaceae alkaloid galanthamine in 2007.[103] Synthesis of dihydroisocodeine started from commercially available tri-*O*-acetyl-D-glucal **213**, Scheme 29. The acetate group was hydrolysed under basic condition and was treated with *p*-anisaldehyde dimethylacetal before the C-6 hydroxyl group was protected as its silyl ether to provide **214**. The primary alcohol was generated by DIBALH mediated reductive cleavage of **214**, which was converted into the corresponding methyl glycoside and the primary alcohol was replaced by iodine to obtain compound **215**. The resulting iodide was eliminated under basic condition's to generate the corresponding olefin that underwent a Ferrier's carbocyclization. A subsequent *β*-elimination provided olefin **216**, followed by 1,4-reduction and trapping of the intermediate enolate using Comin's reagent completed the synthesis of C-ring by delivering vinyl triflate **218**. Suzuki coupling of vinyl triflate **218** with boronic acid **217** followed by clevage of the PMB ether provided allylic alcohol **220**.



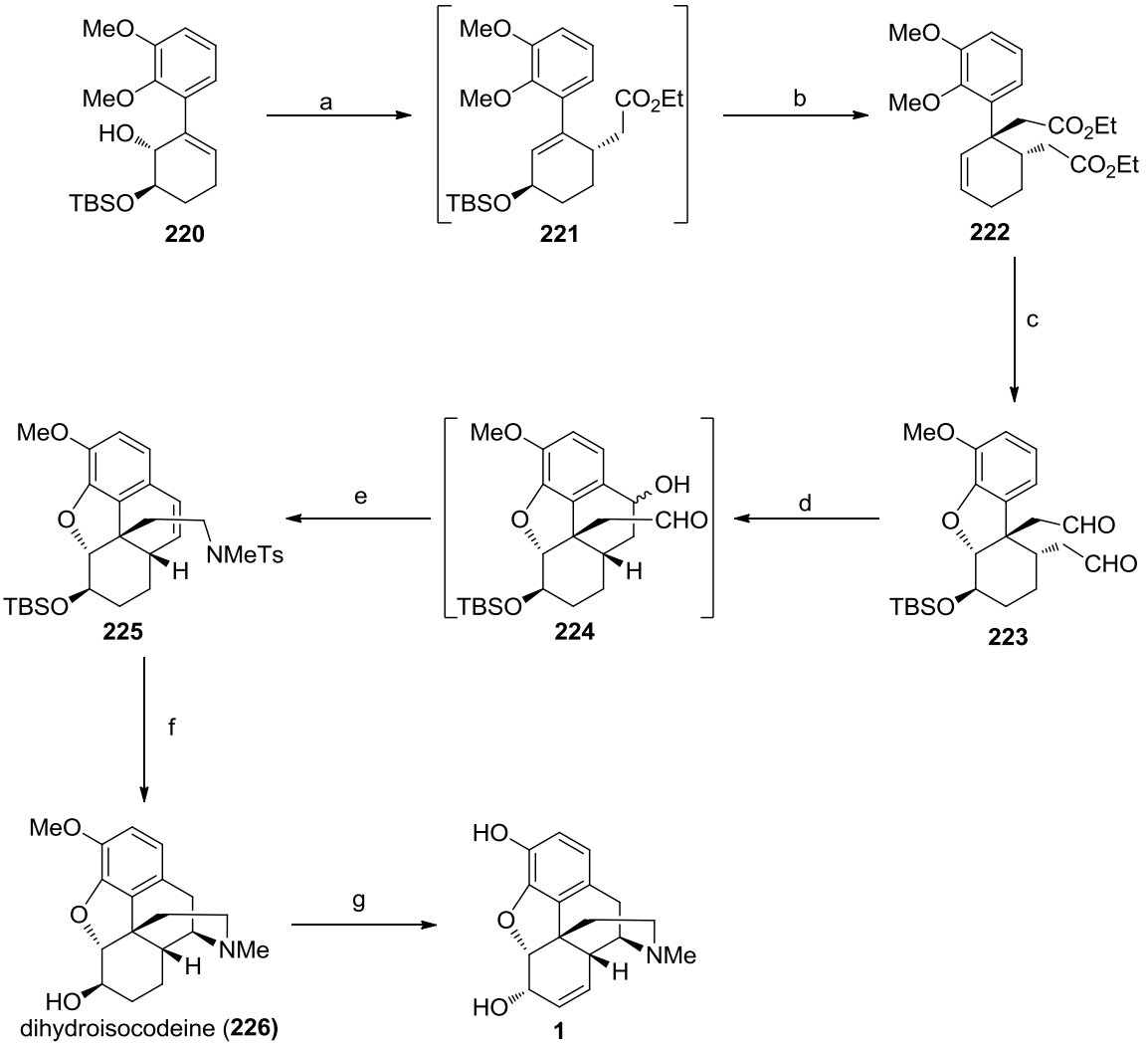
Reagents and conditions: (a) (i) NaOMe, MeOH; (ii) *p*-anisaldehyde dimethylacetal, PPTS, DMF, 45 °C; (iii) TBSCl, imidazole; (b) (i) DIBALH, toluene, –20 °C; (ii) Ph_3P, HBr, MeOH, NaBr, DME, 0 °C; (iii) I_2, imidazole, Ph_3P; (c) (i) *t*BuOK, THF; (ii) $Hg(OCOCF_3)_2$, acetone, buffer; (iii) MsCl, NEt_3, DMAP; (d) (i) L-Selectride, –78 °C; (ii) Comins' reagent; (e) $Pd(OAc)_2$, Ph_3P, aq .Na_2CO_3, 1, 4-dioxane; (f) DDQ.

Scheme 29: Synthesis of intermediate **220**.

Allylic alcohol **220** was subjected to Johnson-Claisen conditions to provide ester **221**, Scheme 30, with the requisite stereochemistry at C-14, in 87% yield. Removal of silyl protecting group and a second Claisen rearrangement provided the *bis*-ester **222**, with the correct C-13 stereochemistry in 55% yield. A cascade Claisen rearrangement route is also possible after removing the silyl protecting group of the allylic alcohol **220**. This reaction led to the product **222** in 36% yield.

An epoxidation etherification reaction and protection of alcohol as silyl ether followed by reduction of esters provided tricycle **223**, Scheme 30. Friedel-Crafts type cyclization

under acidic condition provided tetracycle **224**, Scheme 30. Dehydration followed by reductive amination and protection delivered **225** that underwent a hydroamination reaction to provide dihydroisocodeine **226**, Scheme 30. This formalised the synthesis as the conversion of **226** to morphine is already known.



Reagents and conditions: (a) EtCOOH, $CH_3C(OEt)_3$, 140 °C, 24 h; (b) Bu_4NF, 2-nitrophenol, $CH_3C(OEt)_3$, 140 °C, 120 h; (c) (i) *m*-CPBA; (ii) TBSCl, imidazole, CH_2Cl_2; (iii) DIBAL-H; (d) (i) montmorillonite K-10; (ii) TBSOTf, 2, 6-lutidine; (e) (i) $MeNH_2$, $MeNH_3Cl$, MS 3Å, 0 °C, then $LiBH_4$; (ii) TsCl, DMAP, py, 80 °C; (f) (i) Bu_4NF, THF; (ii) Li, *t*BuOH, NH_3,THF, –78 °C; (g) (i) Swern oxidation; (ii) $LiAlH_4$.

Scheme 30: Chida's formal synthesis of morphine.

Later in 2013, Chida group published another paper on the second generation synthesis of morphine using the same strategy.[104]

Hudlický (1992-present)

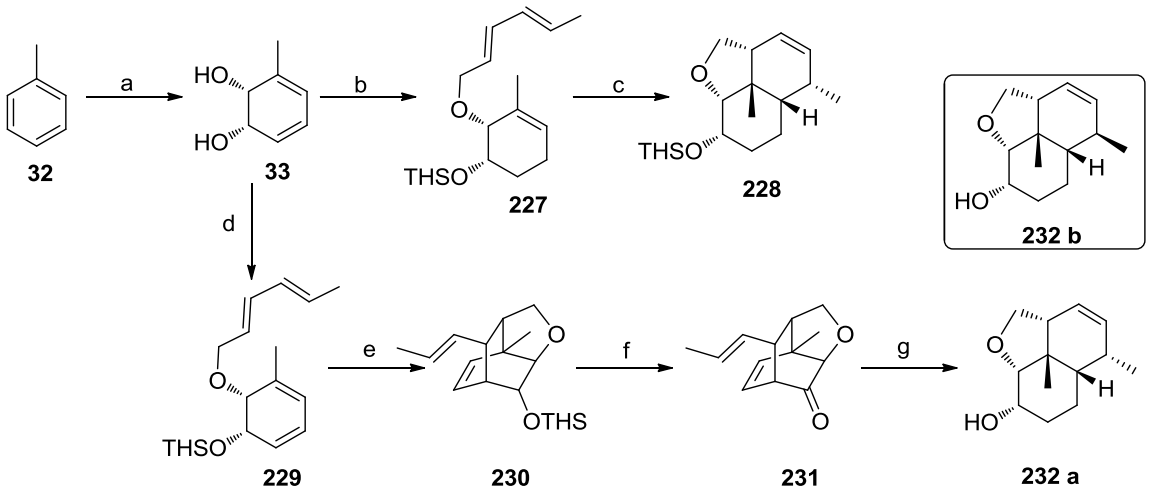
One of the long standing goals in the Hudlický group is the synthesis of morphine and a wide range of unique strategies have been applied to the synthesis of morphine alkaloids over the last 20 years. All these approaches relied on the successful implementation of enzymatically derived *cis*-cyclohexadiene diols. A short discussion of Hudlický's approaches toward morphine alkaloids will be presented.

Cycloaddition strategy

One of the first approach towards morphine alkaloids from Hudlický group relied on the successful construction of the morphine core through an intramolecular 4+2 cycloaddition. Both halves of morphine can be derived from *cis*-cyclohexadiene diol. These two subunits can be tethered and undergo cyclization to deliver the morphine core in a short sequence. To test this approach a series of model reactions was designed.

The first model study aims the formation of tricyclic core of morphine ring with all asymmetric centers, lacking only the aromatic ring and ethylamino bridge.[105] This study started by preparing enantiomerically pure *cis*-cyclohexadiene diol **33** by the biotransformation of toluene **32**, Scheme 31. Selective protection of the less hindered hydroxyl group as silyl ether and the diene functionality was attached by treatment with sorbyl bromide under basic conditions led to the formation of **229**. An intramolecular cycloaddition of **229** can lead to two different products, but heating in CCl_4 resulted in only in adduct **230** as observed in the synthesis of zeylena.[42] A Cope rearrangement of this molecule can lead to the desired structure **228,** but all attempts to carry out this reaction with **230** were unsuccessful. Deprotection of silyl ether followed by oxidation provided **231**, which underwent the Cope rearrangement and delivered the expected

product after reduction of ketone to obtain **232 a**, Scheme 31. A second approach was carried out that involved a diimide reduction and the aforementioned transformations to obtain **227**, which underwent an intramolecular cycloaddition to deliver **228**, Scheme 31, without any regiochemical issues.

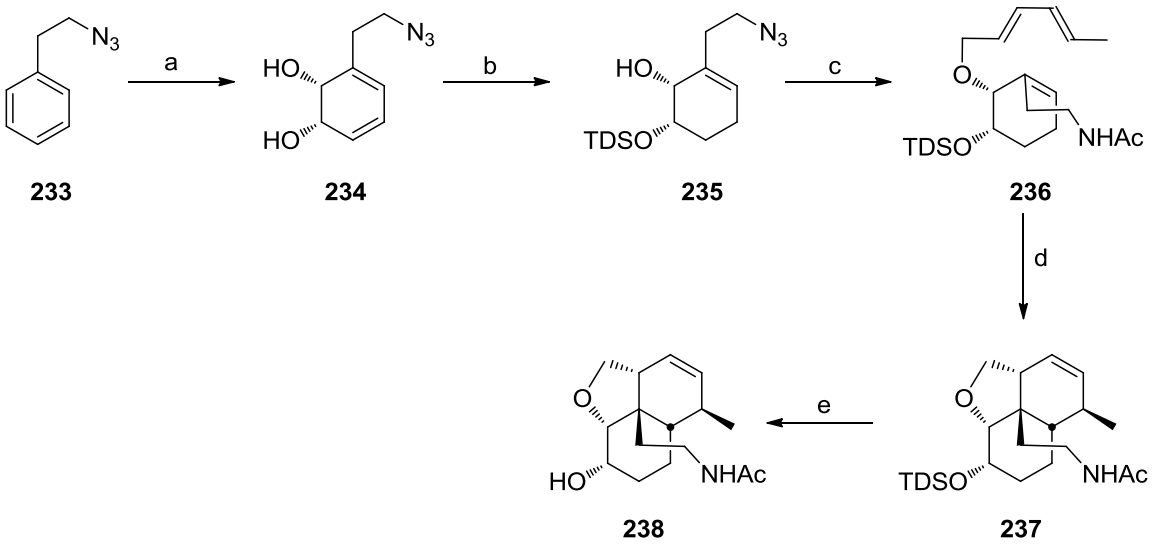


Reagents and conditions: (a) *Pseudomaonas putida* 39D; (b) (i) PAD, AcOH, MeOH; (ii) THSCl, imidazole, DMF, 0 °C, 18 h; (iii) NaH, sorbyl bromide, THF, 0 °C→rt, 30 h; (c) toluene, 210 °C, 24 h; (d) (i) THSCl, imidazole, DMF, 0 °C, 18 h; (ii) NaH, sorbyl bromide, THF, 0 °C→rt, 30 h; (e) CCl_4, 77 °C, 7 h; (f) (i) $Bu_4NF{\cdot}H_2O$, THF; (ii) PCC, CH_2Cl_2, rt, 21 h; (g) (i) xylene, 250 °C, 22 h; (ii) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, rt, 15 min.

Scheme 31: Cycloaddition approach towards the synthesis of tricyclic core of morphine.

Later in 1998, a more advanced model study for the synthesis of the morphine core was published by Hudlický group.[106] This work comprised the installation of ethylaminobridge and the stereochemical correction of previously reported compound **228** to **232b**, Scheme 31. The absolute stereochemistry of **232b** was determined by X-ray

crystallography. Azidoethyl benzene **233**, Scheme 32, was synthesised from commercially available bromoethyl benzene. Biooxidation of **233** afforded *cis*-cyclohexadiene diol **234**. Applying the same chemistry as discussed in previous synthesis, led to the formation of **235**. Reaction with sorbyl bromide followed by reduction of the azide and protection as acetate provided **236**, which is the key intermediate for the intramolecular [4+2] cycloaddition. The cyclization provided a single stereoisomer **237** in moderate yield. The stereochemistry was confirmed through X-ray crystallographic analysis that suggested an *exo* transition state for the cycloaddition.

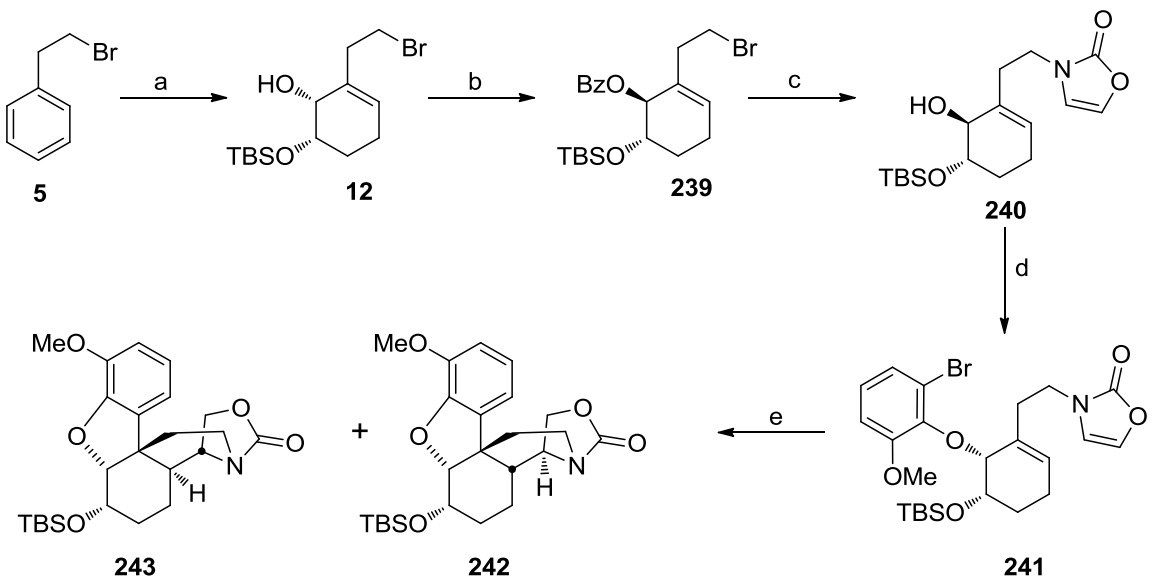


Reagents and conditions: (a) *E. coli* JM109 (pDTG601); (b) (i) PAD, AcOH, MeOH, 0 °C-rt, 14 h; (ii) THSCl, imidazole, DMF, 0 °C, 13 h; (c) (i) NaH, sorbyl bromide, THF, 0 °C-rt, 14 h; (ii) PPh_3, 0.4% H_2O/THF, 45 °C, 18 h; (iii) Ac_2O, pyridine, rt, 2 h; (d) toluene, sealed tube, 230 °C, 20 h; (e) HF/MeCN (5:95), rt, 3.5 h.

Scheme 32: Modified approach with revised stereochemistry.

Radical cyclizations

Hudlický's work on radical cyclization approach was inspired by the work of Parker and he designed several generations of radical cyclization approaches. His first generation approach involved β-bromoethylbenzene as the starting material; enzymatic dihydroxylation generated the *cis*-cyclohaxadiene diol that underwent a diimide reduction followed by selective protection of distal hydroxyl group delivered **12**, Scheme 33. Stereochemistry of C-5 hydroxyl group (morphine numbering) was inverted using Mitsunobu reaction and alkylation using oxazolidone followed by hydrolysis provided **240**. A second Mitsunobu installed the aromatic moiety of morphine also provided the correct C-5 stereocenter to deliver **241**. It was subjected to radical cyclization conditions that gave a complex mixture, from which upon chromatography **243** was isolated as major product along with **242**.



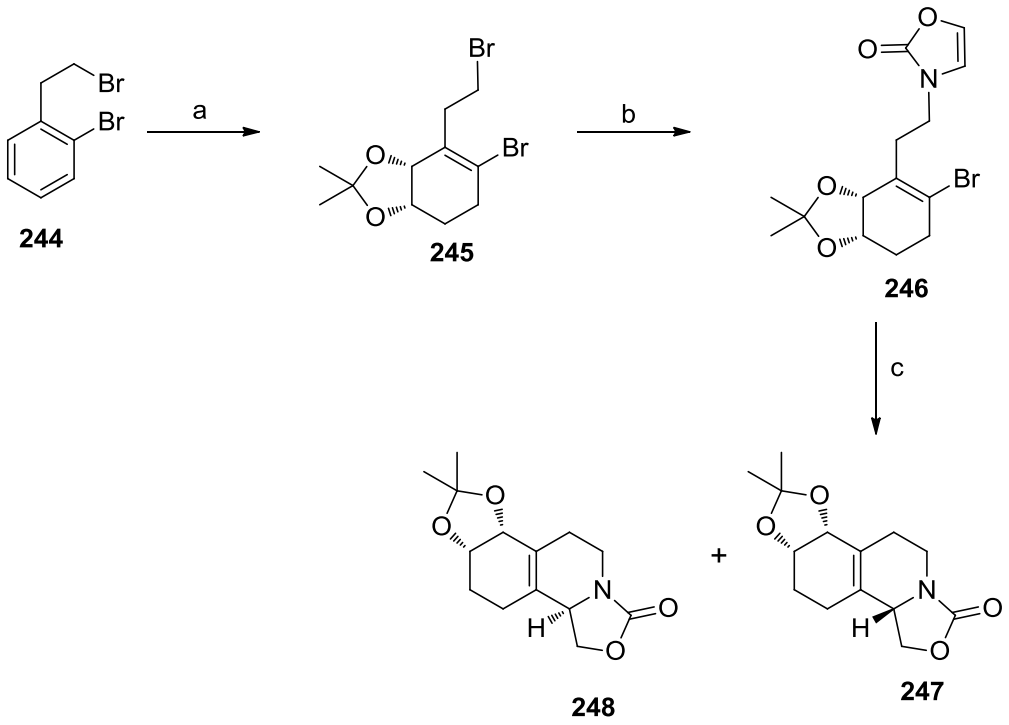
5 **12** **239** **240** **243** **242** **241**

Reagents and conditions: (a) (i) *Escherichia coli* JM109 (pDTG601) (10g/L); (ii) PAD, AcOH, MeOH; (iii) TBSOTf, Hunig's base, CH_2Cl_2; (b) BzOH, *n*-Bu_3P, DEAD, THF; (c) (i) NaOH; (ii) 2-oxazolidone, NaH, DMSO; (d) 2-bromo-6-methoxy phenol, *n*-Bu_3P, DEAD, THF; (e) $(TMS)_3SiH$, AIBN, benzene, 140 °C, sealed tube.

Scheme 33: Hudlický's radical cyclization approach towards morphine.

The second generation approach relied on two independent radical cyclization reactions that addressed the low yields and the lack of stereoselectivity of radical cyclization approach in the first synthesis.[107] This approach used *o*-bromo-β-bromoethylbenzene **244**, Scheme 34, as the substrate for biooxidation. Key intermediate **246** for the first radical cyclization was synthesised in straightforward steps. Exposure of **246** to radical cyclization conditions provided a mixture of diastereomers **247** and **248**, in a ratio 1:2 favouring *epi*-C9 configuration. After completing the synthesis of isoquinoline, the

chemistry was pursued with more abundant **248** that will lead to enantiomeric series of morphine.

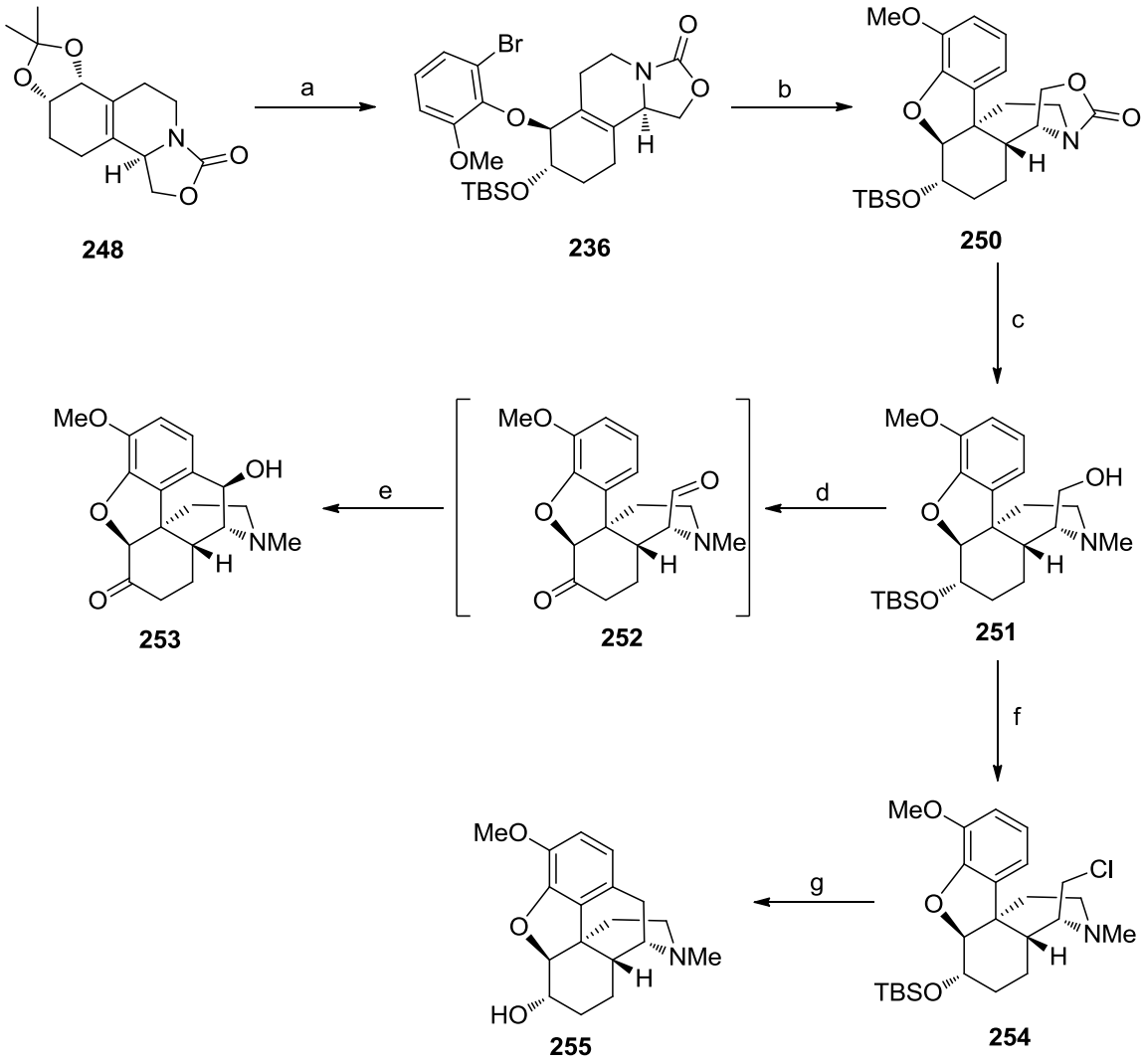


Reagents and conditions: (a) (i) *Escherichia coli* JMI09 (pDTG601) (0.2g/L); (ii) PAD, AcOH, MeOH; (iii) 2,2-dimethoxypropane, *p*-TsOH; (b) 2-oxazolidone, NaH, DMSO; (c) *n*-Bu_3SnH, AIBN, benzene, reflux.

Scheme 34: Second generation radical cyclization approach.

The second part of the synthesis was started by removing the acetonide, protecting the distal hydroxyl and was subjected to a Mitsunobu reaction to provide **236**, Scheme 35. It was subjected to radical cyclization conditions to provide **250** as a single diastereomer in 49% yield. Reduction of oxazilidinone moiety provided **251** that upon oxidation and a Freidel-Crafts type cyclization furnished pentacyclic morphine core **253**. The primary

alcohol in **251** was also transformed to a halide **254** and a C-10 to C-11 ring closure under Friedel-Crafts conditions provided morphinan **255**.

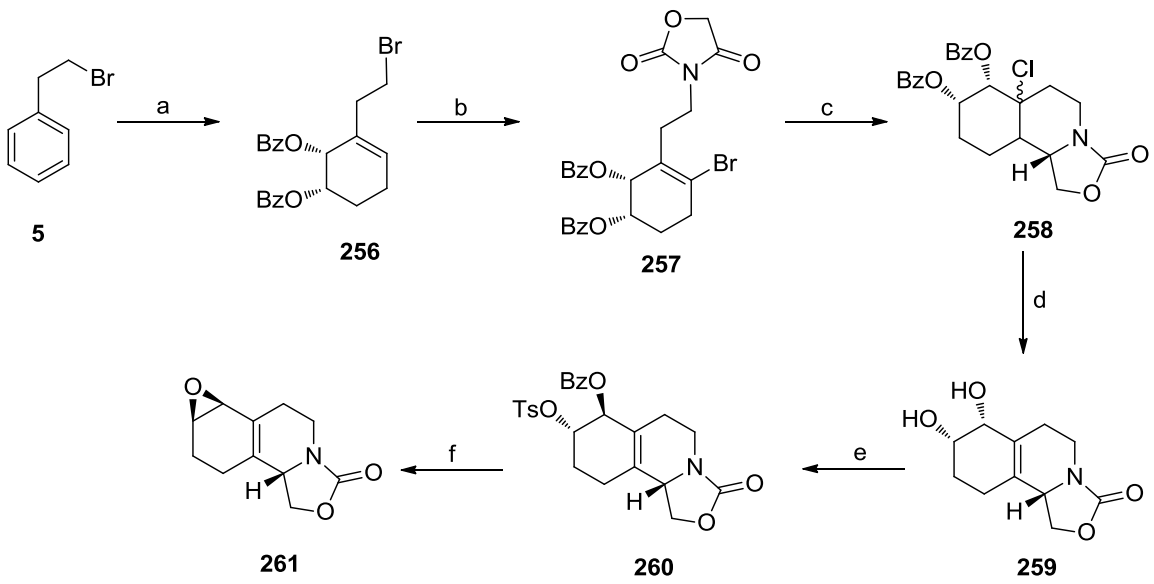


Reagents and conditions: (a) (i) Dowex 50X8-100, MeOH; (ii) TBSOTf, Hunig's base, CH_2Cl_2; (iii) 2-bromo-6-methoxy phenol, *n*-Bu_3P, DEAD, THF; (b) *n*-Bu_3SnH, AIBN, benzene,reflux; (c) DIBAL-H, DCM; (d) (i) TBAF, THF; (ii) $(COCI)_2$, DMSO, NEt_3, CH_2Cl_2; (e) CF_3SO_3H; (f) MsCI, NEt_3; (g) $AICl_3$, benzene.

Scheme 35: Completion of synthesis of morphinan **255.**

Heck cyclization

Radical cyclization studies resulted in the wrong stereochemistry at C-14 carbon that prompted Hudlický's group to design another approach based on Heck cyclization reaction. This approach also used an isoquinoline system similar to radical cyclization approach. *β*-Bromoethylbenzene **5**, Scheme 36, was used as the starting material for biooxidation, selective reduction and protection of both hydroxyl groups delivered **256**. Displacement of bromine with oxazolidine-1,4-dione completed the synthesis of **257**. More reactive amide carbonyl was selectively reduced and N-acyliminium ion–olefin cyclization provided **258**, elimination of halide followed by hydrolysis of benzoate esters afforded **259**. Tosylation of distal hydroxyl group followed by Mitsunobu inversion generated **260** that upon hydrolysis of benzoate delivered the epoxide **261**.



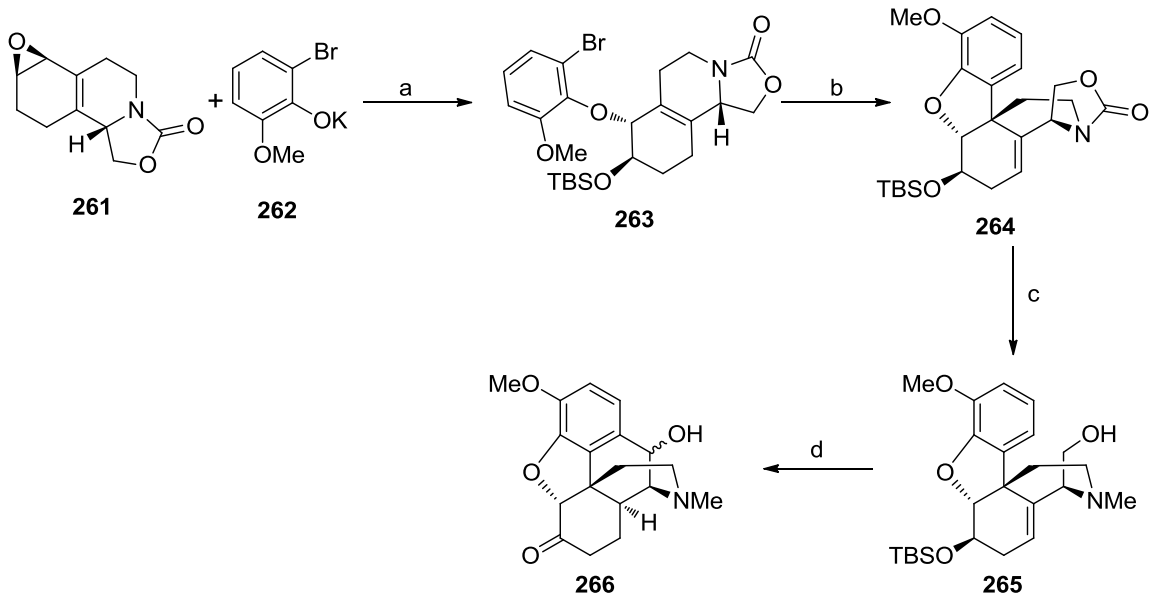
5 256 257 258 259 260 261

Reagents and conditions: (a) (i) *Escherichia coli* JM109 (pDTG601) (10g/L); (ii) PAD, AcOH, MeOH; (iii) benzoic acid, DCC, CH_2Cl_2; (b) oxazolidine-1,4-dione, tetramethylguanidine, THF; (c) (i) $NaBH_4$, MeOH, THF; (ii) $AlCl_3$, CH_2Cl_2 (*cis: trans* = 3.7 : 1); (d) (i) DBU, DMSO; (ii) NaOMe, THF; (e) (i) TsCl, py, DMAP; (ii) benzoic acid, PPh_3, DEAD, THF; (f) NaOMe, MeOH, THF.

Scheme 36: Synthesis of epoxide **261**.

A regio- and stereoselective ring opening of **261** using the potassium salt of guaicol **262** generated **263**, Scheme 37 that already contains all carbon atoms of morphine with correct stereochemistry at C-5 and C-9. An intramolecular Heck cyclization was designed as the key step to generate the furan ring with a concomitant closure of the C-13 stereo center. A similar strategy was already known from previously reported procedures.[95, 108] Heck cyclization furnished pentacyclic carbamate **264** in good yield. Reduction of oxazilidinone using DIBAL-H furnished **265.** Desilylation and hydrogenation followed by Swern oxidation provided aldehyde that underwent a Friedel-Crafts type cyclization to

obtain morphinan **266**.[109] The only problem encountered in this synthesis was the generation of *epi*-C-14 stereo center that originated from the hydrogenation of C-8/C-14 olefin.

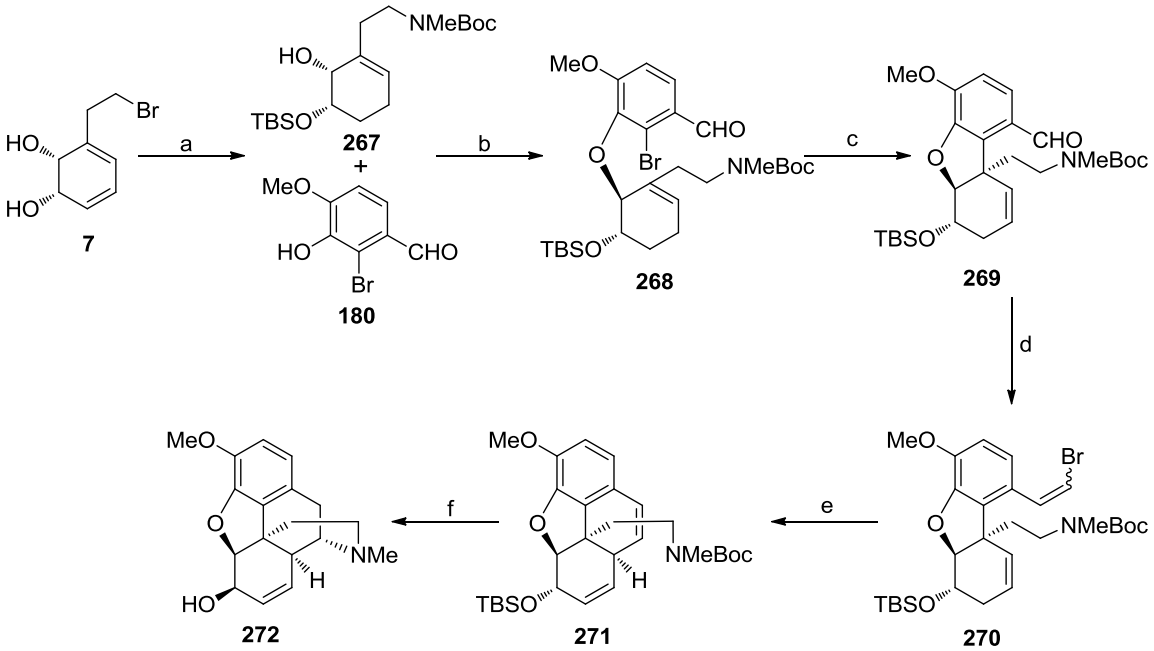


Reagents and conditions: (a) (i) DME, 18-crown-6; (ii) TBSOTf, Hunig's base, CH_2Cl_2; (b) $Pd(PPh_3)_4$, Proton Sponge™, toluene; (c) DIBAL-H, CH_2Cl_2; (d) (i) TBAF, THF, H_2O; (ii) H_2, PtO_2, AcOH; (iii) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; (iv) CF_3SO_3H.

Scheme 37: Synthesis of morphinan **266**.

In 2007, Hudlický designed an enantiodivergent route towards the synthesis of codeine.[110] Setting the stereochemistry at C-5 carbon was the key part in this design as it controls all the subsequent bond-forming processes. The starting material chosen for both approaches is homochiral diene diol **7**, Scheme 38, generated by the enzymatic oxidation of β-bromoethyl benzene. The diol was converted to Boc-protected amine **267** and was coupled with phenol **180** via a Mitsunobu reaction to provide **268** that has C-5

configuration opposite to the natural isomer. Intramolecular Heck cyclization was occurred *syn* to the C-5 substituent to provide **269**. Vinyl bromide **270** was made *via* a Wittig reaction of aldehyde **269** and a second Heck cyclization using Trost's condition delivered **271** in low yields (44%) to complete the phenanthrene skeleton. Stereocenter at C-6 carbon was adjusted by an oxidation reduction sequence after deprotection of the silyl group. Oxymercuration of the styrene bond and an intramolecular trapping of the mercurium ion with amino group after removal of Boc-protecting group followed by reduction produced *ent*-codeine (**272**) to complete the synthesis in 14 steps from β-bromoethylbenzene. The final transformation was plagued with low yields but all attempts to use Trost's photo stimulated protocol[95a] were unsuccessful.



Reagents and conditions: (a) (i) PAD, AcOH, MeOH; (ii) Ac_2O, NEt_3, DMAP; (iii) $MeNH_2$, K_2CO_3, –40 °C; (iv) $(Boc)_2O$, NEt_3, MeOH; (v) TBSCl, imidazole, –78 °C; (b) *n*-Bu_3P, DIAD, THF, 0 °C; (c) $Pd(OAc)_2$, Ag_2CO_3, dppf, toluene, 110 °C; (d) $PPh_3CH_2Br_2$, *t*-BuOK, THF, –60 °C; (e) $Pd(OAc)_2$, Ag_2CO_3, dppp, toluene, 110 °C; (f) (i)

TBAF, THF; (ii) IBX, DMF; (iii) $NaBH_4$, $CeCl_3$, MeOH; (iv) TFA, CH_2Cl_2; (v) $Hg(OAc)_2$, NEt_3, THF; $LiAlH_4$

Scheme 38: Second generation synthesis of *ent*-codiene *via* Heck cyclization reaction.

Later in 2009, synthesis of natural codeine was completed using this enantiodivergent approach.[110-111] A double Mitsunobu inversion was designed for the installation of the natural configuration at C-5 carbon center, but this route always led to poor yields. A modified approach was implemented in the synthesis of ether-bridge in **274**, Figure 17; a regio and stereoselective opening of the epoxide **273** with a phenoxide delivered ether **274**; the completion of the synthesis was achieved by following the same sequences as those leading to the unnatural series.

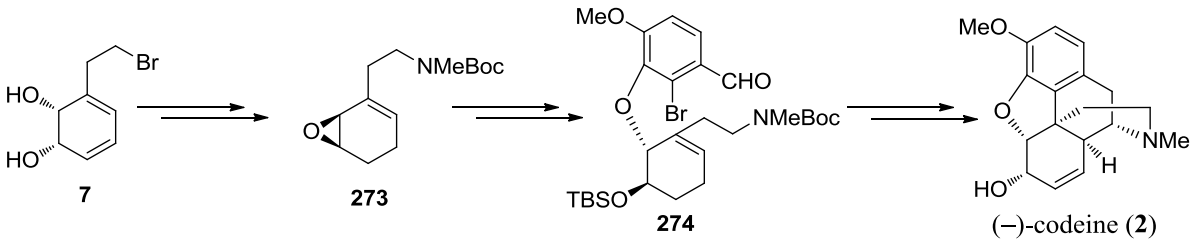


Figure 22: Enantiodivergent synthesis of (–)-codeine.

A third generation approach for the synthesis of opiate alkaloids were designed based on similar Heck cyclization approach. A major variation in this route was the generation of B and D-rings. Three different routes were designed to attain these rings that include an aldol, Mannich or aza-Prins cyclization.

The synthesis of A-ring started from commercially available isovanillin **275**, Figure 22, which was converted to acetal protected phenol **277** in 4 steps with an overall yield of 48%.

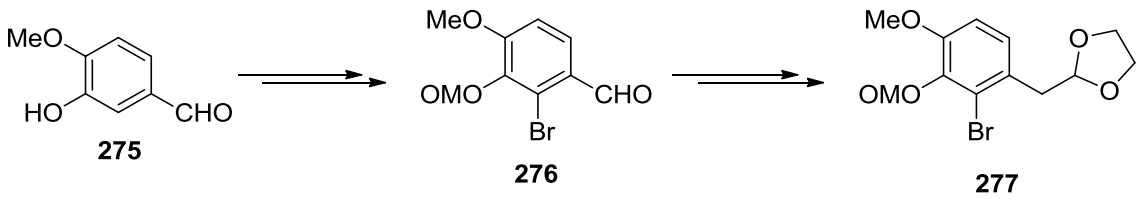


Figure 23: Synthesis of A-ring fragment.

Synthesis of C-ring started from β-bromoethylbenzene **5**, Figure 24, biooxidation and subsequent protection led to the formation of **278** that underwent displacement of halogen with amine functionality and further protection delivered allylic alcohol **279**. Mitsunobu coupling of A and C-ring fragments and an intramolcular Heck cyclization as seen earlier, accomplished the synthesis of tricycle **280**.

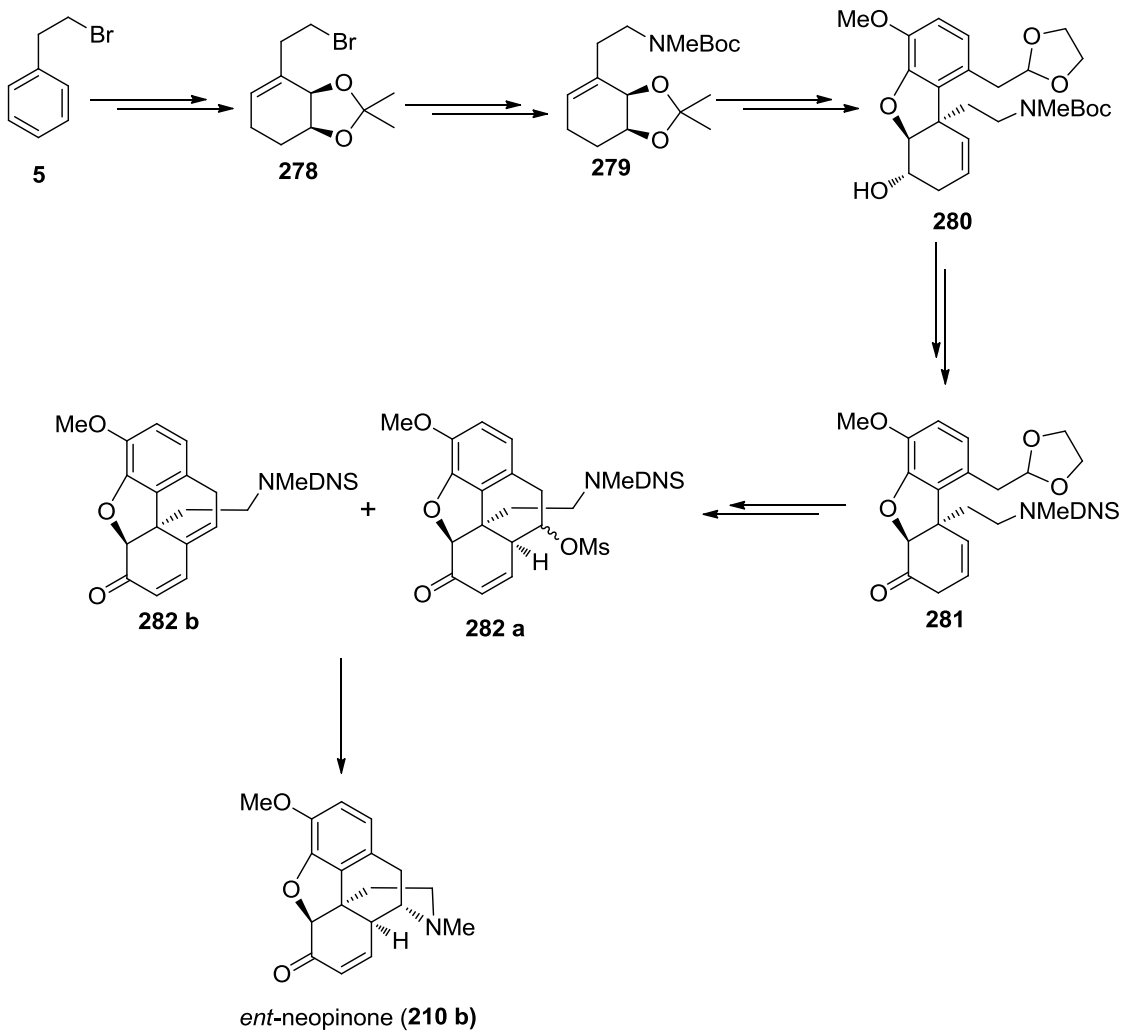


Figure 24: Synthesis of *ent*-neopinone.

Initial attempts to generate the B-ring were unsuccessful. At this point a similar approach was published by Fukuyama;[101] following his protocol, Boc-protecting group in **280**, Figure 24, was removed and the amine was reprotected with 2,4-dinitrobenzenesulfonyl group and oxidation provided **281**. Under acidic conditions, it underwent cyclization and the alcohol was protected with MsCl, generated mesylate **282a** and dienone **282b**. Removal of the protecting group with thioglycolic acid, 1,6-conjugate addition furnished the final molecule *ent*-neopinone (**210b**).[112]

Recent synthesis: A nitrone cycloaddition/radical cyclization approach

A recent synthesis from Hudlický group studied the stereochemical outcomes of a nitrone cycloaddition or a radical cyclization.[113] Previous work suggested that an intramolecular nitrone cycloaddition can be used to control the relative stereochemistry of C-9/C-14.[114]

The proposed synthesis begins with the biooxidation of 1-phenyl-2-acetoxyethane **283**, Figure 25; following the same chemical sequences as in earlier mentioned syntheses led to the formation of allylic alcohol **284**. Mitsunobu inversion with a suitable aromatic partner accessed **285**, a Heck cyclization attained tricycle **286**.

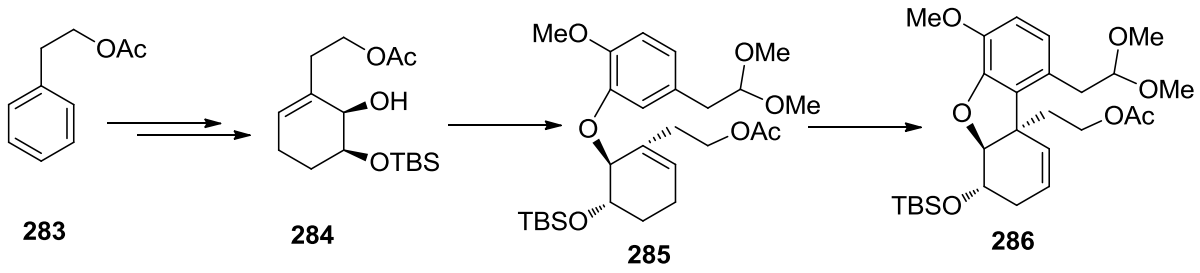
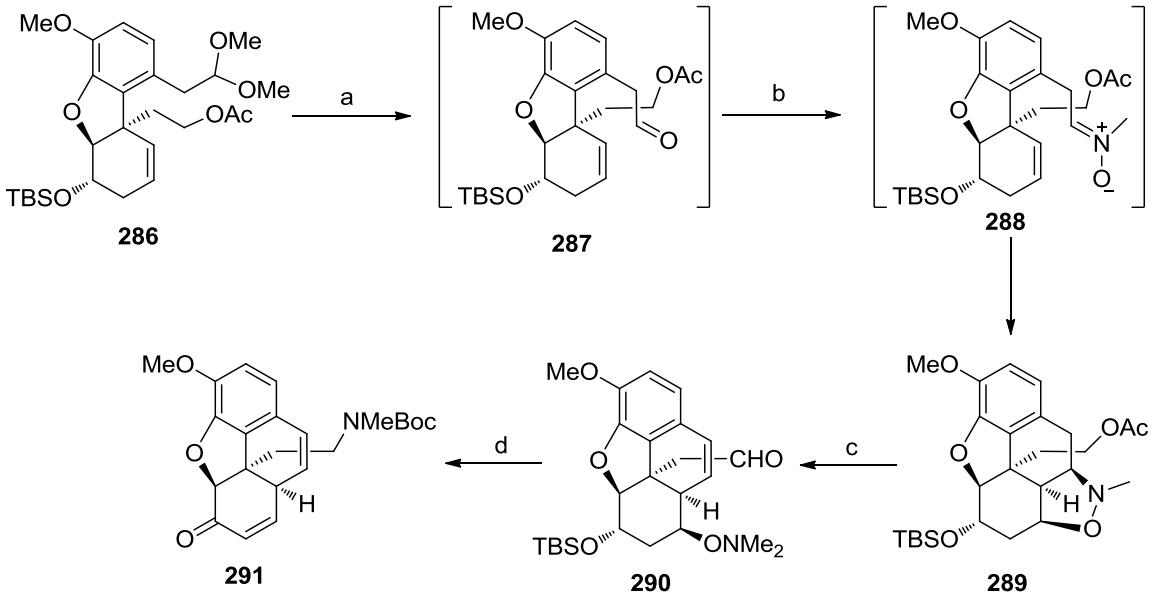


Figure 25: Synthesis of tricycle **286.**

Acid hydrolysis led to the formation of aldehyde **287**, Scheme 39, and the in situ generated nitrone **288** underwent [2+3] cycloaddition to adduct **289**. Surprisingly, the stereochemical outcome from the cycloaddition gave incorrect C-9/C-14 relationship. Hence, adduct **289** was converted to styrene **290** through a Hoffmann elimination of trialkyl ammonium salt resulted from treatment of **289** with Meerwein salt and $LiAlH_4$. Oxidation of the primary alcohol and a reductive amination followed by Boc-protection resulted in the formation of ethyl amino side chain. Desilylation and oxidation with

concomitant elimination of amino alcohol delivered tetracycle **291**; a known intermediate for the synthesis of *ent*-codienone and *ent*-codeiene. The [2+3] cycloadditon was repeated with nitrile oxide, but provided the same stereochemical outcome.

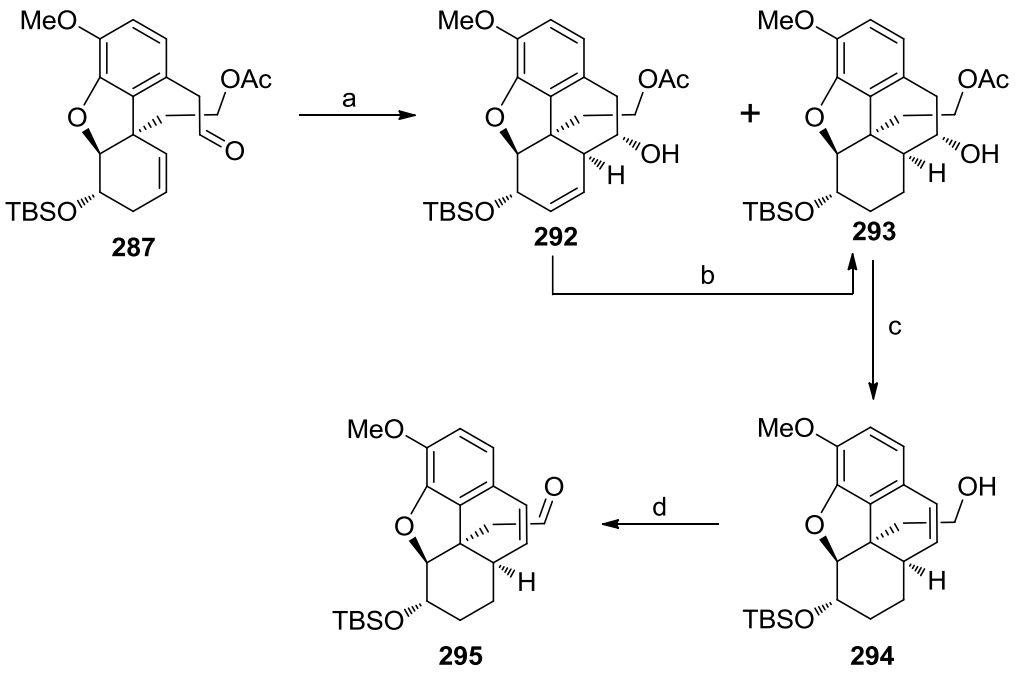


Reagents and conditions: (a) 50% aqueous TFA, toluene, 50 °C, 92%; (b) NHMeOH·HCl, Hunig's base, toluene, reflux, 38%; (c) (i) Meerwein salt, CH_2Cl_2, then $LiAlH_4$, THF, 76% over 2 steps; (ii) Dess–Martin periodinane, CH_2Cl_2, 75%; (d) (i) $NH_2Me·HCl$, NEt_3,$Ti(i\text{-}PrO)_4$, MeOH, then $NaBH_4$; (ii) $(BOC)_2O$, EtOH, 66% over 3 steps; (iii) TBAF, THF; (iv) Dess–Martin periodinane, CH_2Cl_2, 51% over 2 steps.

Scheme 39: Nitrone cycloaddition approach for the formal synthesis of *ent*-codeine.

A radical cyclization approach using SmI_2 was also investigated; aldehyde **287**, Scheme 40, underwent radical cyclization to generate tetracycles **292** and **293**. This mixture was hydrogenated to convert **292** to **293**, which led to styrene **294** in two steps. An oxidation

of primary alcohol provided aldehyde **295**, an intermediate that is already known, thus formalizing the synthesis of *ent*-hydrocodone.



Reagents and conditions: (a) SmI_2, HMPA, THF, 50%; (b) H_2, Pd/C, MeOH, 92%; (c) (i) MsCl, NEt_3, CH_2Cl_2 ; (ii) NaOH $_{(aq)}$, MeOH, 69% over 2 steps; (d) Dess–Martin periodinane, CH_2Cl_2, 72%.

Scheme 40: Formal synthesis of *ent*-hydrocodone *via* a radical cyclization reaction.

3. Discussion

3.1 Introduction

Morphine is one of the oldest drugs known to man and it plays an important role as an analgesic for pain relief. All the unnatural derivatives of morphine alkaloids currently used in medicine are obtained by the semi synthesis of morphine alkaloids isolated from natural sources. Morphine is the principal constituent of opium (latex isolated from the poppy plant *Pappaver somniferum*) along with other alkaloids such as codeine, thebaine, papaverine etc.[56, 58] A brief history of morphine has already been discussed in chapter two of this dissertation. The history of total synthesis of morphine alkaloids spans over 60 years since the first synthesis of morphine by Gates in 1952.[68] The quest for a practical synthetic route that can compete with isolation from natural sources remains an unsolved problem. More than 40 total and formal syntheses of morphinans are known so far, but none of them meets the requirement of a truly practical synthesis. As we discussed earlier, it can result from a complete "dissonant relationship" present in morphine. [82a] The only notable synthesis was accomplished by Rice in 1980 that comes close to a practical synthesis of morphine.[87]

One of the long standing goals in Hudlický's group is to develop an efficient route to morphine alkaloids. All of his approaches are based on the utilization of chiral *cis*-cyclohexadienediols as the starting materials obtained by the enzyme mediated dihydroxylation of aromatics. This strategy has been effectively applied in many syntheses of morphine alkaloids by Hudlický and co-workers as discussed in the historical section of this thesis.

This chapter describes two different approaches to morphine alkaloids. The first section involves the synthesis of dihydrocodeine and hydrocodone starting from bromobenzene. The key steps involved in this synthesis are two Claisen rearrangements, an intramolecular amidation reaction, a Friedel-Crafts type cyclization and an etherification reaction through the opening of an epoxide.[115] The second section describes the synthesis of *ent*-hydromorphone starting from β-bromoethyl benzene. A dearomatizive intramolecular cycloaddition/amination strategy was utilized for this efficient synthesis.[116]

3.2 Total synthesis of dihydrocodeine and hydrocodone

The pentacyclic core of the morphine alkaloid (**1**), Figure 26, can be generated through an intramolecular etherification reaction that resulted from the opening of an epoxide. The B-ring of the alkaloid can be generated form a Friedel-Crafts type ring closure reaction. Hydrolysis of oxazilidinone **11** and an intramolecular amidation followed by an oxidation will generate the aldehyde **297**. The most difficult part of the synthesis is the installation of C-13 quaternary carbon center that can be formed through a [3,3]-sigmatropic rearrangement of alcohol **298**, which can be generated through a coupling reaction between A- and C-ring fragments **299** and **9a** respectively. Synthesis of C-ring fragment and the installation of C-9 and C-14 stereocenters can be attained through another [3,3]-sigmatropic rearrangement of an intermediate derived from cyclohexadienediol **6** that can be obtained from bromobenzene **4** through enzymatic dihydroxylation.

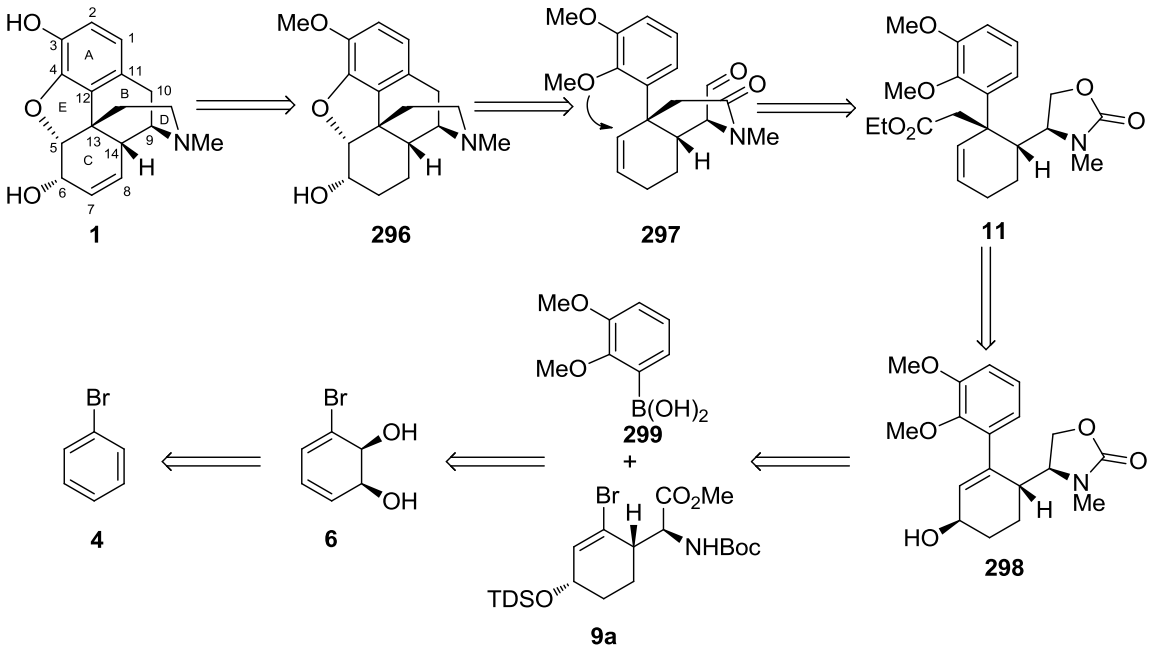


Figure 26: Retrosynthetic analysis for the synthesis of morphine alkaloids.

One of the key strategies in this approach is the generation of the key intermediate **9a,** Figure 26, using Claisen rearrangement along with C-9 and C-14 stereo centers. Claisen reaction or [3,3]-sigmatropic rearrangement was reported by Ludwig Claisen in 1912 where he described the transformation of phenylallyl ether **300**, Figure 27, to 2-allyl phenol **303** through an intermediate **302.**[117] The oxygen can be replaced by its sulfur or nitrogen analogues. Many versions of Claisen rearrangements have been reported since the discovery made by Ludwig Claisen. These reactions can be effectively catalyzed under different conditions; these topics have been extensively reviewed in many publications.[118]

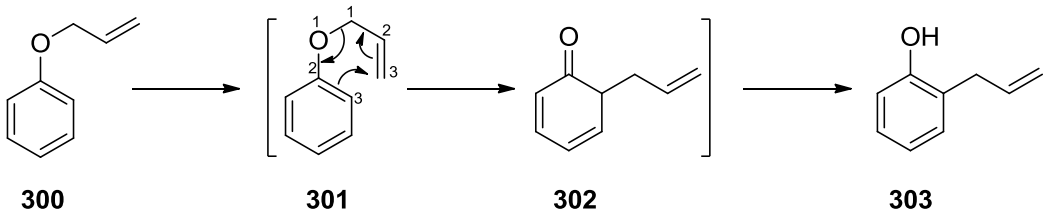


Figure 27: First reported [3,3]-sigmatropic rearrangement by Ludwig Claisen.

[3,3]-Sigmatropic rearrangements of lithium enolates of allyl esters at lower temperatures were reported by Robert E. Ireland in 1972.[119] He was able to prepare γ,δ-unsaturated acid **307**, Figure 28, of corresponding allyl ester **304** under mild conditions. He also reported quenching of lithium enolates like **305** with trimethylsilyl chloride as advantageous for these reactions to obtain silylenol ethers of the type **306** that showed better stability compared to enolate ethers of the type **305**. He also described the stereochemical control of [3,3]-sigmatropic rearrangement through stereoselective enolate formation.[120]

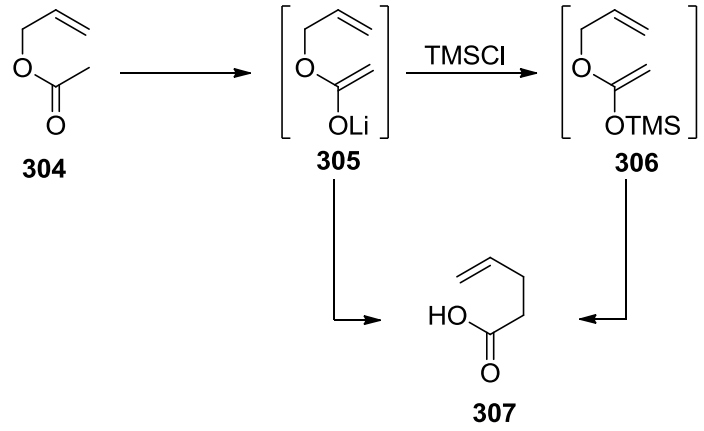


Figure 28: [3,3]-sigmatropic rearrangement of lithium enolates.

The first synthesis of an amino acids by Claisen rearrangement was reported by Steglich in 1975.[121] In 1982, Ireland-Claisen rearrangement of glycine allylic esters was reported by Bartlett and co-corkers.[122] Another variation of the Ireland-Claisen reaction was reported by Uli Kazmaier in 1994, where he prepared γ,δ-unsaturated acids **309** and **310**, Figure 29, from glycine allylester **308**. This rearrangement occurs with high diastereoselectivity; *trans*-substituted allyl esters led to *syn* as the major product and *cis*-allyl esters produced *anti* as major products. He proposed formation of a chelate-bridged metal enolate **311**, which can undergo [3,3]-sigmatropic rearrangement at low temperatures.[3] Addition of metal salts that would lead to chelation resulted in the formation of stable enolates that cannot decompose at higher temperatures. Stability and reactivity of these metal salts vary among which $ZnCl_2$ provided best results. Kazmaier proposed the formation of a chelate-bridged stabilized carboxylate intermediate rather than the formation of a high energy ester enolate as the reason for the accelerated rearrangement. Replacement of the acidic amide proton with a methyl group resulted in complete loss of reactivity. Later, Kazmaier and co-workers developed chiral versions of these reactions by incorporating chiral ligands.[123]

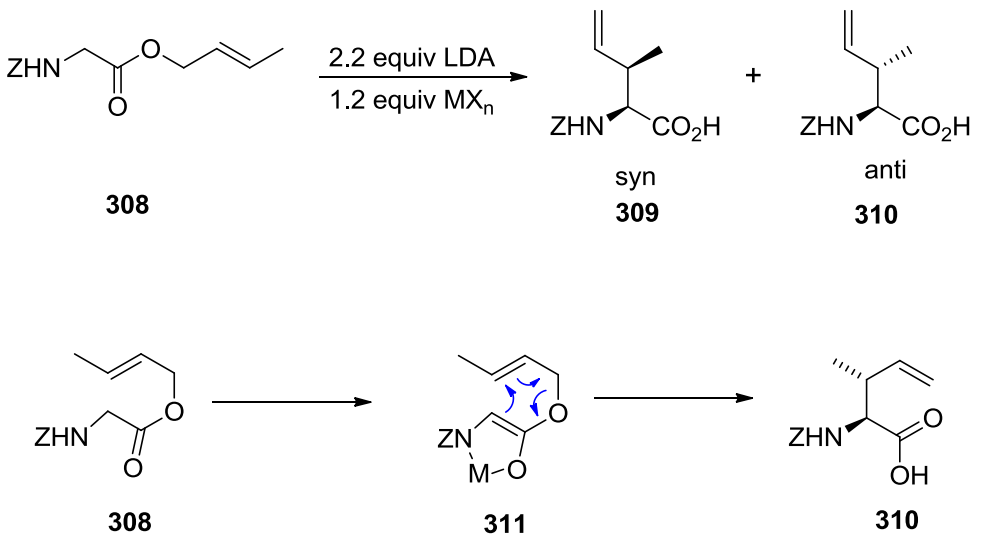


Figure 29: Kazmaier-Claisen rearrangement.

The early work by Hudlický group focused on the synthesis of **312**, Figure 30, from **313**, through a Kazmaier-Claisen rearrangement. The amino acid generated contains C-9 and C-14 stereocenters in the right configuration, and was the key intermediate for the synthesis of morphine. In order to test the viability of this methodology, different model compounds were prepared from enzymatically derived *cis*-cyclohexadienediols of the type **43**.

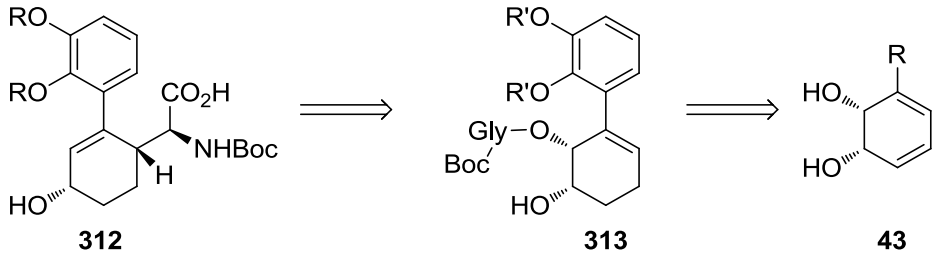


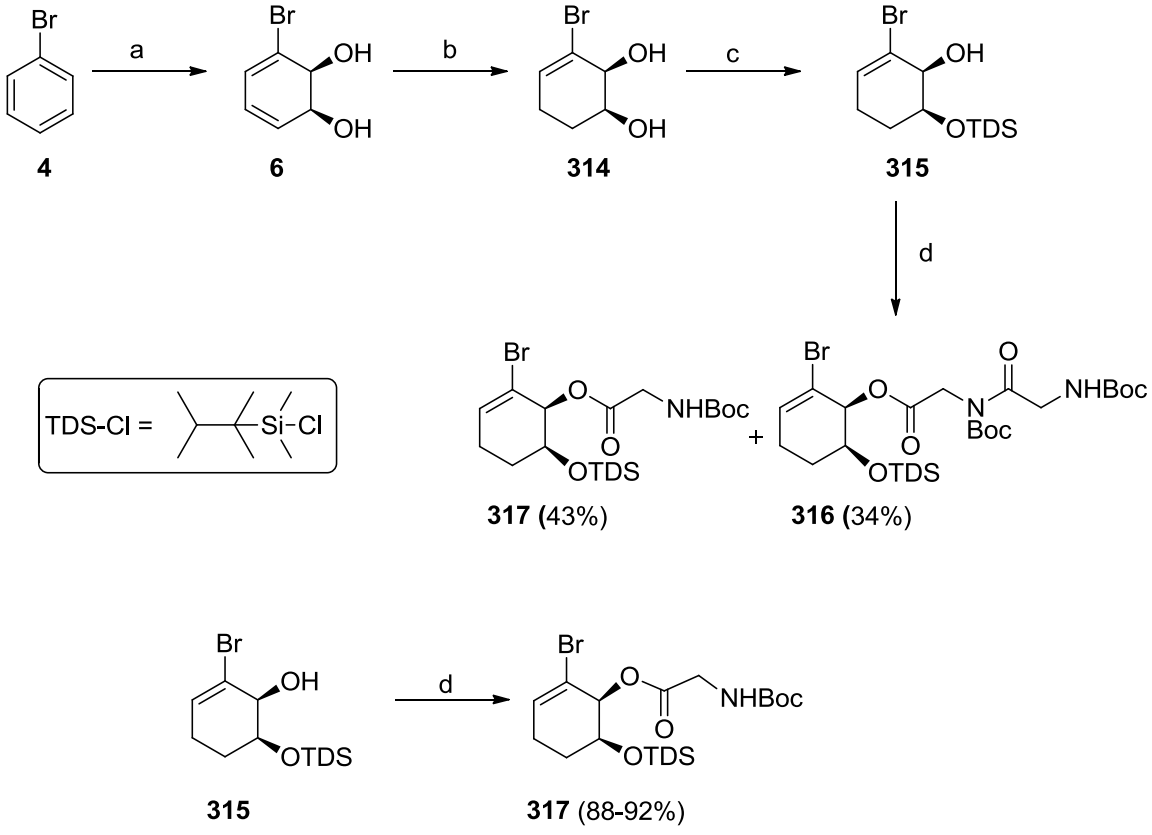
Figure 30: Synthesis of key intermediate from enzymatically derived cyclohexadienediols.

Different gycinate esters were prepared from diols (R = Cl, Me, aryl) and were tested for Kazmaier-Claisen rearrangement.[124] Even though Kazmaier-Claisen rearrangement is known to proceed with high diastereoselectivity, this rearrangement provided a mixture of diastereomers at C-9 (morphine numbering) presumably because the rearrangement proceeded through both chair and boat transition states despite the fact that only the *Z*-enolate species was generated from glycinates. It is known form Ireland's work that cyclohexenyl derivatives containing substituents on the ring frequently undergo the Ireland-Claisen rearrangement through both chair and boat transition states and therefore result in isomeric mixtures.[125] During these model studies, formation of the undesired isomer predominates but still it was a proof of concept that Kazmaier-Claisen rearrangement can be used to set the C-9 and C-14 stereocenters. Also, the undesired isomer can be equilibrated to the required isomer under base catalyzed conditions.

3.2.1 Synthesis of A and C-ring fragments

Our synthetic studies started from the enzymatic dihydroxylation of bromobenzene **4**, Scheme 41, with *E. coli* JM109 (pDTG601a)[31, 126] to obtain diol **6** (X = Br).[43] These biotransformations provide 15 g/L diol and each run provided 200-250 g product. The distal double bond that is less substituted was selectively reduced with diimide generated from potassium azodicarboxylate (PAD) to obtain compound **314** in 75-80% yield. Then the distal hydroxyl group was protected as silyl ether **315** with 93% yield. Then the proximal hydroxyl group was coupled with Boc-protected glycinate ester. Following a procedure that was already known,[127] mixing Boc-glycine, DCC and DMAP before

adding the alcohol **315**, led to mixture of compounds **316** and **317** that proved to be tedious in terms of separation. The ^{13}C NMR spectra of **316** exhibited four carbonyl signals, a signal at δ 171.8 ppm corresponding to the ester carbonyl, a signal at δ 167.7 ppm corresponding to the amide carbonyl, and two signals at δ 155.7 ppm, and δ 151.5 ppm corresponding to the Boc carbamate groups; instead of two carbonyl signals (δ 169.6 ppm, δ 155.3 ppm) exhibited by **317**. This problem was solved by adding the alcohol before mixing Boc-glycine, DCC and DMAP to obtain the desired product **317** in yields ranging from 88-92%. All these reactions described in this scheme proved to be efficient and scalable.

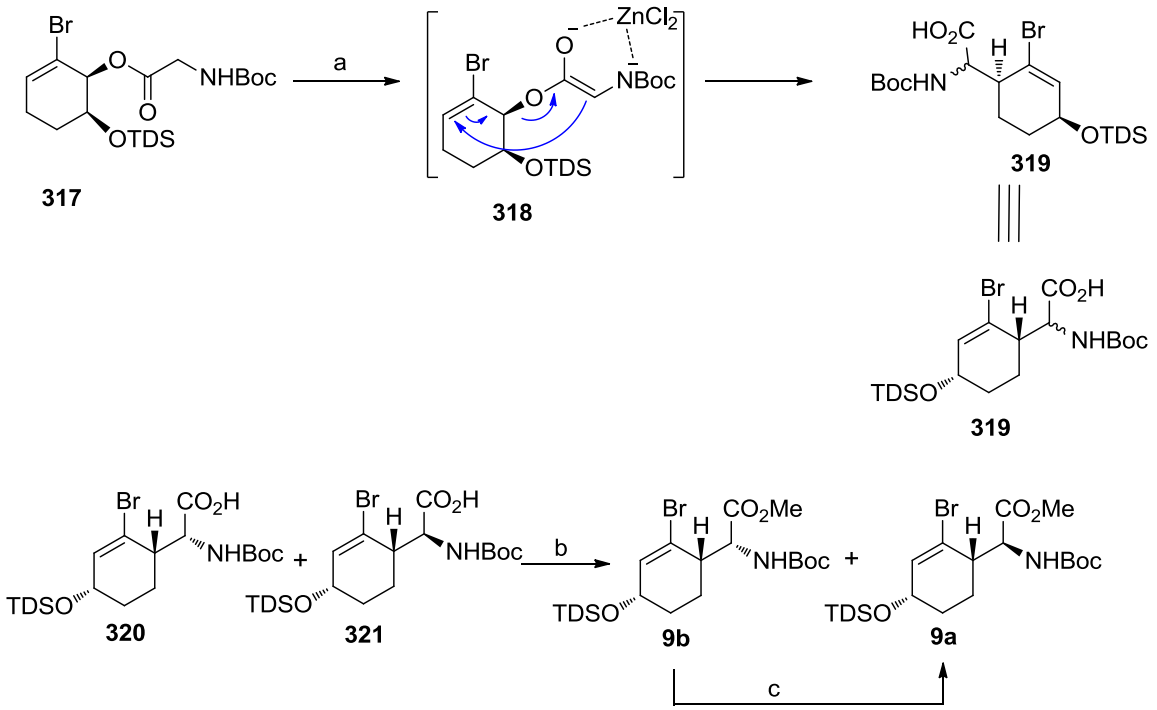


Reagents and conditions: (a) *E.coli* JM109 (pDTG 601a), 15 g/L; (b) PAD, AcOH, MeOH, 75-80%; (c) TDS-Cl, CH_2Cl_2, –78 °C → rt, 93%; (d) CH_2Cl_2, Boc-Gly, DCC, DMAP, 88-92%.

Scheme 41: An efficient route for the synthesis of glycinate ester.

The Boc-protected glycinate ester **317**, Scheme 42, was subjected to Kazmaier-Claisen rearrangement conditions; two diastereomers of amino acid **319** were obtained *via* intermediate **318**. It proved to be difficult to separate the amino acid diastereomers **320** and **321**, so the acid functionality in **319** was converted to methyl esters **9 a** and **9 b** with diazomethane. This reaction proved to be very challenging as slight variation in temperature led to inconsistent results. Best results were obtained when the reaction mixture was kept at –78 °C during the addition of LDA and then slowly warmed to room temperature over a period of 18 hours. Dropwise addition of LDA to a solution of glycinate ester **317** and $ZnCl_2$ in THF at –78 °C followed by esterification resulted in the formation of amino acid with 44% yield and 3.4:1 isomeric ratio favoring the undesired diastereomer. Reversing the addition of reagents, namely dropwise addition of a solution of glycinate ester **317** and $ZnCl_2$ to LDA in THF at –78 °C followed by esterification resulted in the formation of diastereomers **9 a** and **9 b** with 65% yield and 1.8:1 isomeric ratio favoring the undesired diastereomer. The undesired diastereomer **9 b** was subjected to base-catalyzed equilibration to eventually provide pure **9 a** with the correct absolute configuration at C-9 (morphine numbering). The separation of diastereomers was not economical in terms of the amount of silica gel, solvent, and time. This tedious column

chromatography problem was solved by using suction column chromatography as described by Hudlický.[128]

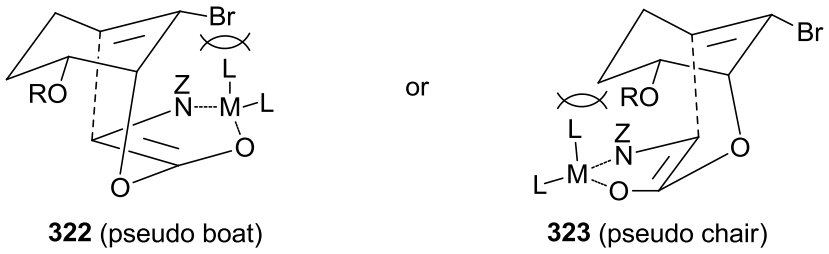


Reagents and conditions: (a) $ZnCl_2$, LDA, THF, –78 °C → rt; then quench with 1N HCl; (b) CH_2N_2, Et_2O, 0 °C, 65% with 1.8:1 isomeric ratio after two steps; (c) DBU, THF, reflux, 39%.

Scheme 42: Kazmaier-Claisen rearrangement of glycinate ester **294**.

The stereochemical outcome from the Kazmaier-Claisen rearrangement depends on the fixed enolate geometry arising from the chelation with the metal. The rearrangement can proceed through a chair or a boat like transition state. Six-membered rings are known to prefer a boat like transition state during similar reactions.[129] This is preferentially due to the steric interactions between the cyclohexenyl ring and the solvated metal in the chair

like transition state. But, studies by Ireland showed that rearranged product can be generated through both chair and boat transition state in silylketene acetals.[125] Many previous results pointed out that the effect of bulky silylether is negligible in this rearrangement.[130] As depicted in Figure 31, the bromine atom at the α-position in the allylic carbon can lead to unfavourable interactions with the solvated metal in a boat like transition state **322**, Figure 31, and the cyclohexenyl ring in a chair like transition state **323**. Because of these two steric interactions, both transition states have a very small energy difference. This led to the product formation by both pathways, therefore giving a mixture of diastereomers.[124]



322 (pseudo boat) **323** (pseudo chair)

Figure 31: Origin of diastereomers in the Kazmaier-Claisen rearrangement of glycinate ester **317**.

The equilibration of the undesired isomer **324**, Figure 32, to the desired isomer **325** stopped after reaching 1:1 ratio. Such equilibration is possible because of a more stable, hydrogen bonded conformation in cases where X = Br, Cl, as shown in Figure 32. The ester functionality is axial in **326 a** and equatorial in **326 b**. In both orientations, it experiences steric hindrance (cyclohexene methylene in **326 a** and Boc-group in **326 b**) and hence equilibration of either diastereomer yields ~1:1 mixture, with eventual production of the required isomer by recycling. The corresponding isomeric mixtures

where X = methyl or aryl were not responsive to base catalyzed equilibration[131] due to the absence of a hydrogen bonded conformation. This leads to a rigid conformation and a sterically crowded environment that reduces the availability of C-9 proton.

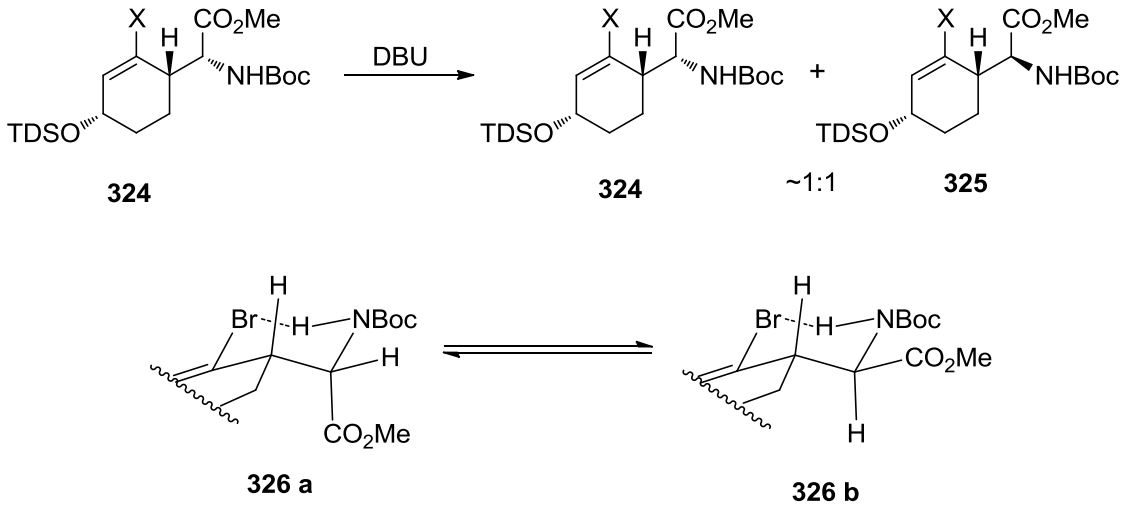
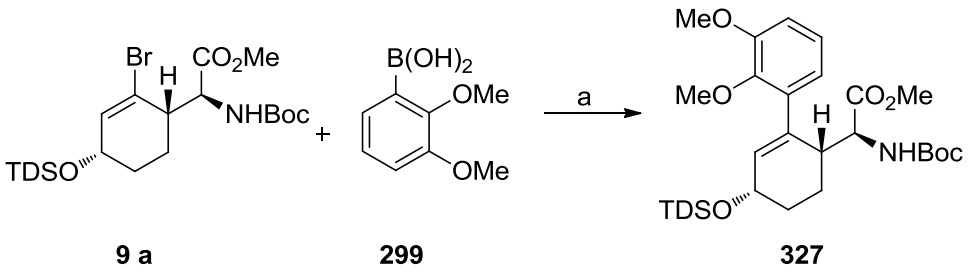


Figure 32: Base-catalyzed equilibration of undesired isomer.

3.2.2 Synthesis of tetracyclic core of morphine

After successfully establishing the C-9 and C-14 stereocenters we turned our attention to connect the A- and C-ring fragments of morphine alkaloid. The A-ring fragment; 2,3-dimethoxyboronic acid **299**, Scheme 43, was synthesized starting from 2,3-dimethoxy benzene using a known procedure.[132] Ester **9 a,** Scheme 43, was subjected to Suzuki coupling with 2,3-diemthoxyboronic acid to produce cleanly compound **327,** Scheme 43. No attempts were made at this point to elicit the C-10/C-11 closure of carboxylate **327** to a complete phenanthrene skeleton by creating the B-ring.

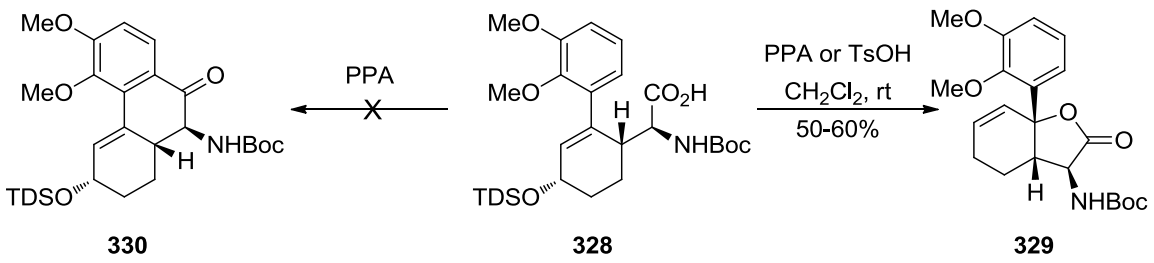


9 a **299** **327**

Reagents and conditions: (a)$Pd(dppf)_2Cl_2$, Cs_2CO_3, THF, reflux, 94-96%.

Scheme 43: Coupling of A and C-rings.

Studies by Gonzalez showed that attempts at the cyclization in **328**, Figure 33, using either TsOH or PPA failed and resulted in acylation of C-13 to provide **329** instead of **330**.[124, 131]



330 **328** **329**

Figure 33: Previous attempts for the synthesis of B-ring *via* Friedel-Crafts cyclization.

These results prompted us to focus on the installation of C-13 quaternary carbon before attempting the C-10/C-11 closure. Another [3,3]-sigmatropic rearrangement (Johnson-Claisen rearrangement) was planned for the installation of this stereocenter that involves the chirality transfer from the C-6 carbon center.

In 1970, Johnson developed another version of [3,3]-sigmatropic rearrangement which involved the formation of an olefinic ester from the allylic alcohol.[133] Heating allylic

alcohol **334**, Figure 34, with excess of ethyl orthoacetate **331** in the presence of a catalytic amount of acid resulted in mixed orthoacetate **335**, which loses ethanol to form the ketene acetal **336**. This acetal undergoes rearrangement to obtain the γ, δ-unsaturated ester **337**. These reactions have been widely used in the synthesis of many natural and unnatural products since their discovery and are covered in many reviews.[118b, 118e, 134]

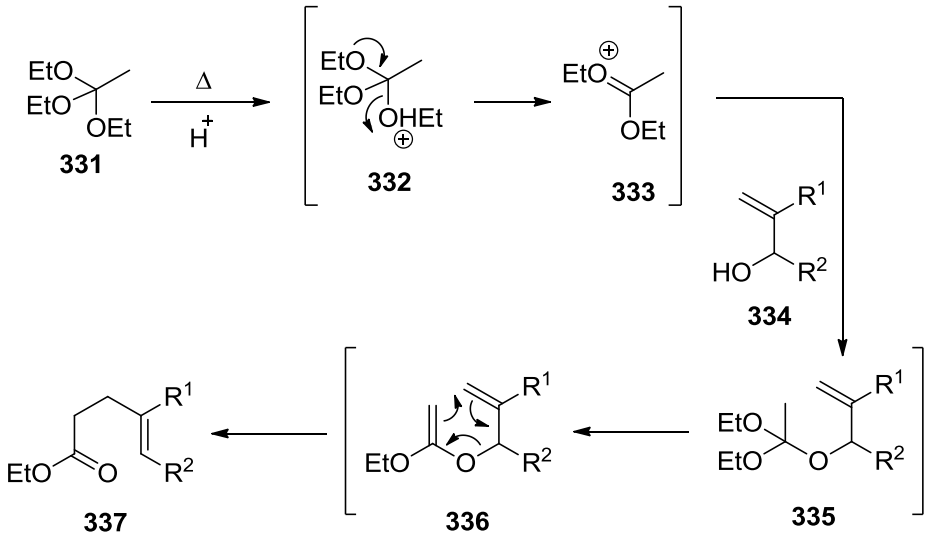
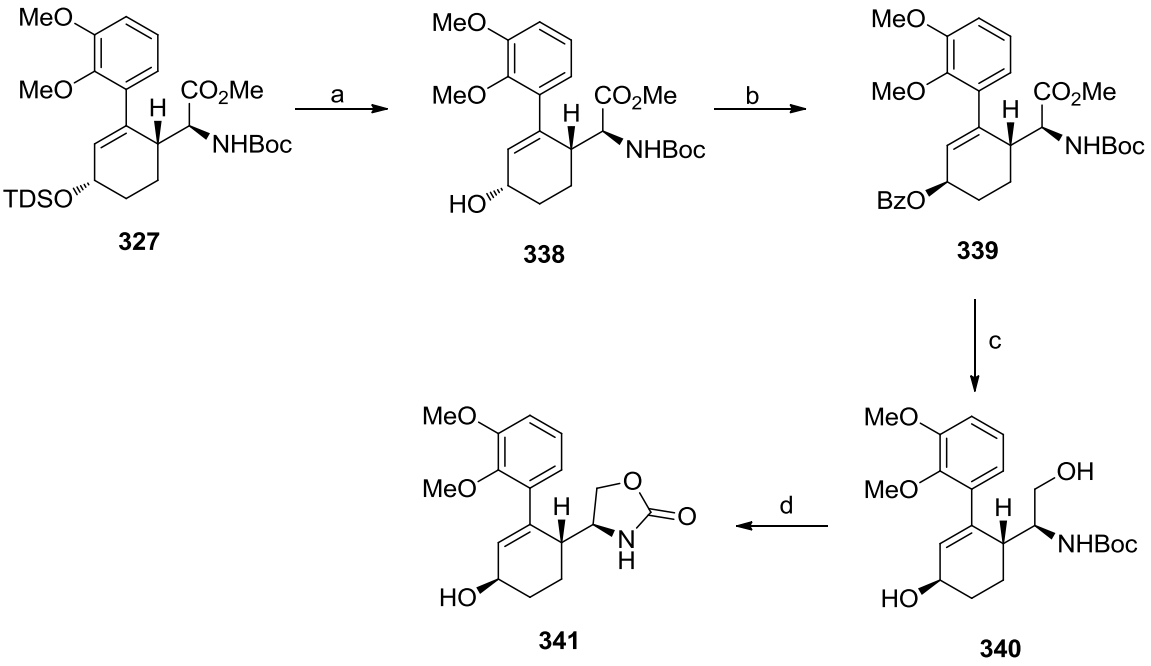


Figure 34: Johnson-Claisen rearrangement for the synthesis of olefinic ester from allylic alcohol.

In order to establish the correct stereochemistry, we decided to remove the silyl protecting group in **327**, Scheme 44, and the C-6 hydroxyl group in alcohol **338** was subjected to the Mitsunobu inversion to obtain the benzoate ester **339.** Earlier studies from our group showed that the hydrolysis of a benzoate ester to an alcohol and attempts to carry out Johnson-Claisen reaction were not fruitful.[127] Reduction of benzoate ester

339 with $LiAlH_4$ provided alcohol **340** in 74% yields over three steps. The primary alcohol in **340** was converted to oxazilidinone **341** *via* an intramolecular cyclization.



327 **338** **339** **340** **341**

Reagents and conditions: (a) Bu_4NF, THF, 92%; (b) *n*-Bu_3P, DEAD, BzOH, THF, 0 °C→rt, 95%; (c) $LiAlH_4$, THF, 0 °C→rt, 84%; (d) NaH, DMF, 0 °C→rt, >95%.

Scheme 44: Synthesis of oxazilidinone **341**.

After synthesizing the oxazilidinone, we turned our attention towards the installation of C-13 quaternary carbon through Johnson-Claisen rearrangement. Our studies started by treating the alcohol **341,** Table 1, with triethyl orthoacetate **332**, Figure 34, under acid-catalyzed conditions. Variety of acids was used for this purpose, but none of the reactions led to any satisfactory results. The results of several attempts are shown in Table 1. Mixing alcohol with large excess of triethyl orthoacetate and catalytic amount of propionic acid in sealed- tube and heating for 18 hours resulted in the formation of

propionate ester **342**, Table 1. It prompted us to change the catalyst to *o*-nitro phenol in order to avoid the unwanted side reaction. But the reaction mixture was complex with no indication of product formation. Attempts to increase the temperature of the reaction mixture to 160 °C with a catalytic amount of propionic acid resulted in the formation of bridged compound **343** in low yields. These reactions were carried out on a small scale and only a milligram of compound **343** was isolated, making the complete characterization very difficult. Similar results were observed when the reactions were carried out in presence of phenol[135] or I_2-SiO_2 as catalyst.[136]

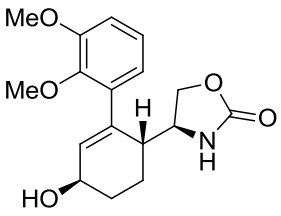
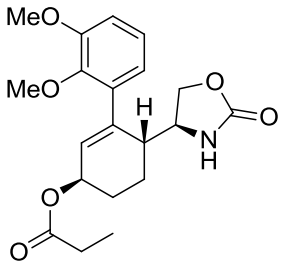
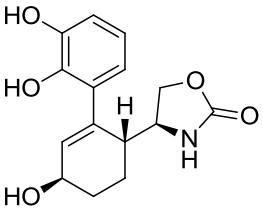
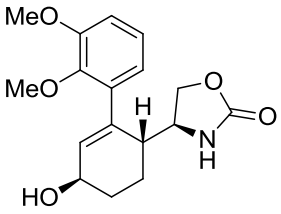
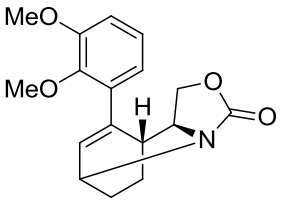
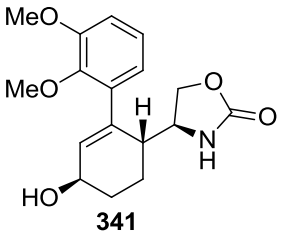
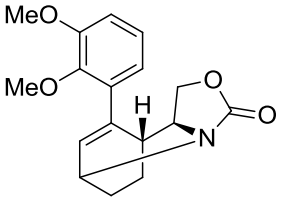
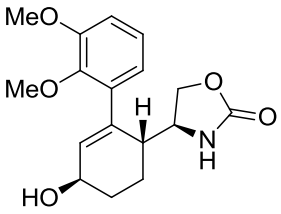
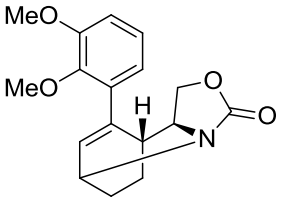
 **341**	$CH_3C(OEt)_3$, 140 °C propionic acid	 **342**
 **341**	$CH_3C(OEt)_3$, 140 °C *o*-nitophenol	Complex mixture with no characteristic product
 **341**	$CH_3C(OEt)_3$, 160 °C propionic acid	 **343**
 **341**	$CH_3C(OEt)_3$, 140 °C phenol	 **343**
 **341**	$CH_3C(OEt)_3$, 140 °C I_2-SiO_2	 **343**

Table 1: Screening of different conditions in Johnson-Claisen rearrangement.

We also investigated a modified version of Johnson-Claisen reaction that involved the formation of mixed orthoester **345**, Figure 35, *via* the reaction of alcohol **341** and excess of diethylketene acetal **344** to obtain the intermediate **346**. After formation of this intermediate, excess ketene acetal was evaporated and triisiobutylaluminium (TIBAL) was added to effect the [3,3]-sigmatropic rearrangement at room temperature.[137] To our surprise, the resulting reaction mixture was quite complex and only alcohol **341** was recovered in 34% yield.

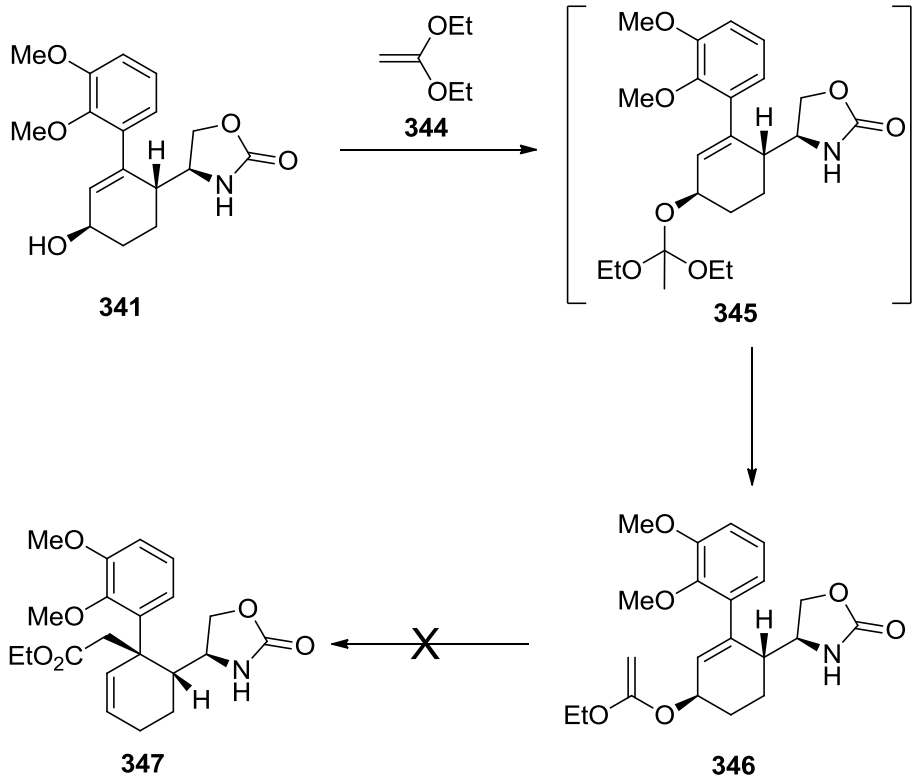


Figure 35: A modified version of Johnson-Claisen reaction.

The unsuccessful results obtained from the aforementioned reactions prompted us to investigate possibilities of other types of Claisen rearrangements for installing the C-13

quaternary carbon center. We decided to investigate Ireland-Claisen rearrangement; hence alcohol **341** was converted to acetate **348** and was subjected to Ireland-Claisen reaction conditions.[119-120, 138] This reaction only resulted in the formation of alcohol **341** possibly through an intermediate **348 a** as shown in Figure 36.

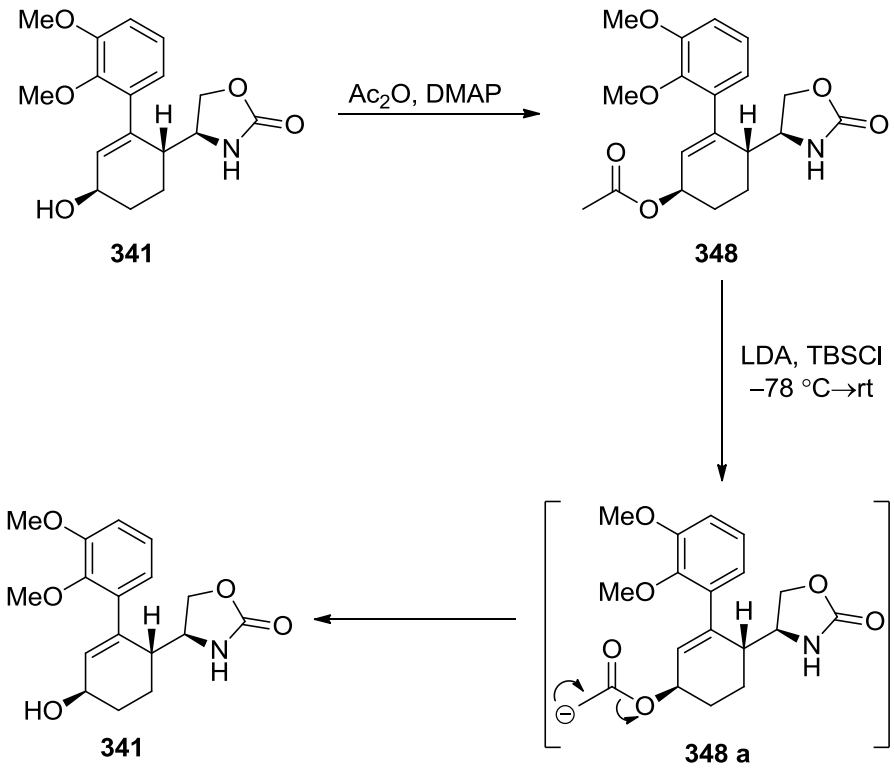


Figure 36: Attempts to generate the C-13 stereocenter *via* Ireland-Claisen reaction.

The Eschenmoser-Claisen rearrangement[139] was also investigated as an alternative to Johnson-Claisen rearrangement. Alcohol **341,** Figure 37, was stirred with N,N-dimethylacetamide dimethyl acetal **349** and was heated to reflux for several hours following a known protocol.[140] This reaction also resulted in the formation of bridged product **343** in low yield in a complex mixture.

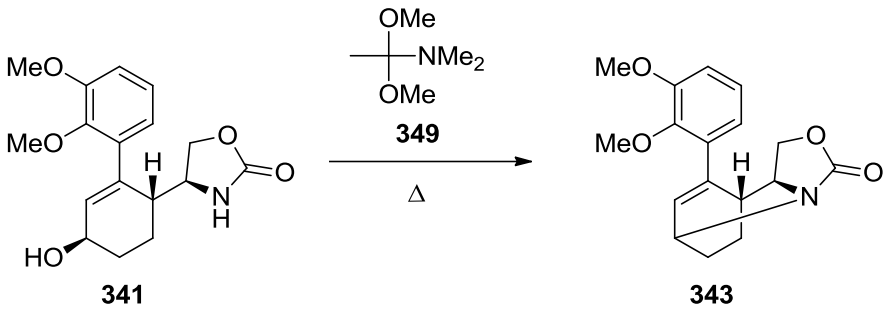


Figure 37: Eschenmoser-Claisen approach for the installation of C-13 quaternary carbon.

At this point, we turned our attention to a different strategy to install the C-13 quaternary carbon center. This approach relied on a cycloaddition reaction of a diene **351**, Figure 38, with a ketene dimethylacetal **352** to obtain **353** that can be eventually converted to the desired molecule **354**. Burgess reagent[141] is known as a mild reagent for effecting dehydration reactions; we decided to take advantage of this process that worked well in other projects in our group.[142] Surprisingly, this reaction led to the formation of a bicyclic compound **350** in 77% yields. The IR spectrum of **350** did not exhibit any -NH or -OH streach, indicating a new C-N bond formation. ^{1}H NMR signal exhibits only one alkene signal at δ 4.89 ppm. ^{13}C NMR showed two carbonyl signals corresponding to ester carbonyl and amide carbonyl. This result along with our previous observations from Johnson-Claisen rearrangement confirmed that the nucleophilic character of the secondary amide nitrogen causing problems in installing the C-13 quaternary carbon center.

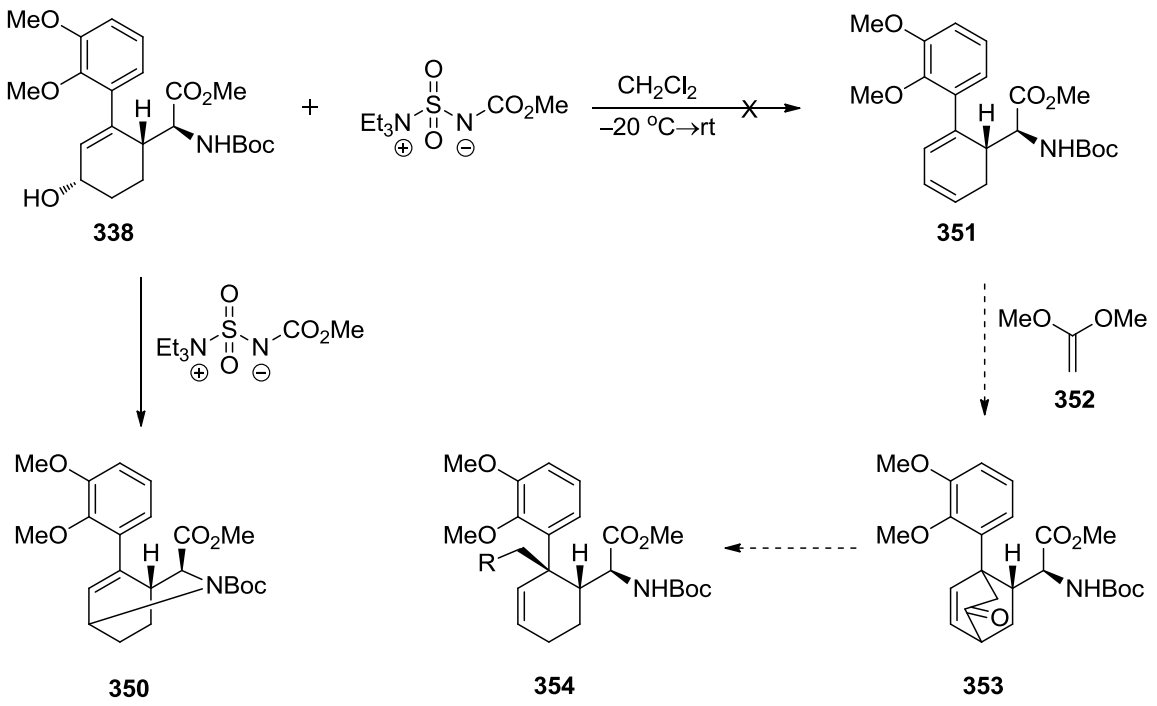
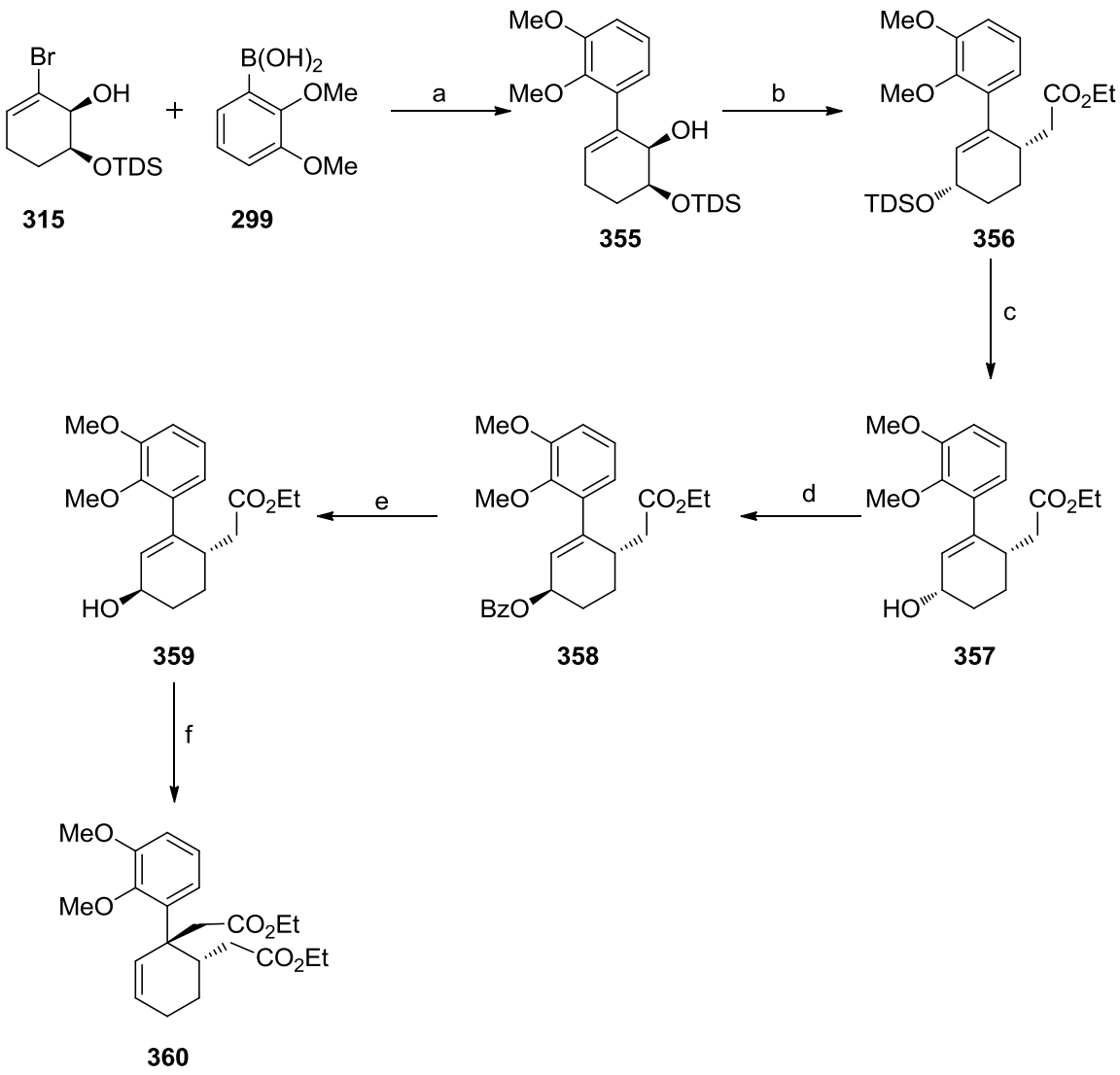


Figure 38: Unexpected formation of bicycle **350**.

Meanwhile, we decided to repeat Johnson-Claisen chemistry on a compound that was already known to give a successful result. In 2008, Chida and co-workers reported a formal synthesis of morphine.[102, 104] There key strategy was a cascade Johnson-Claisen rearrangement to install both C-13 and C-14 stereocenters as we discussed in earlier chapter.[102, 104] Repeating Chida's chemistry to install C-13 quaternary carbon center can be helpful to correct any technical errors associated with these reactions. In order to obtain the key intermediate to study the [3, 3]-sigmatropic rearrangement, we decided to proceed through a different route, much shorter than the one reported by Chida and co-workers as shown in Scheme 45. Starting from the allylic alcohol **315**, Scheme 45, which we have already used in the synthesis of our key intermediate, a Suzuki coupling with

boronic acid **299** attached both A- and C- ring fragments to produce **355**. The alcohol **355** was then treated with triethyl orthoacetate and catalytic amount of propionic acid to obtain the ester **356** through a [3,3]-sigmatropic rearrangement that set the C-14 stereocenter. Deprotection of silyl protecting group delivered alcohol **357**, a Mitsunobu inversion followed by selective hydrolysis of benzoyl group led to the formation of key intermediate **359**. Then we decided to employ Chida's conditions for Johnson-Claisen rearrangement, led to the formation of diester **360** with the installation of C-13 quaternary carbon center.

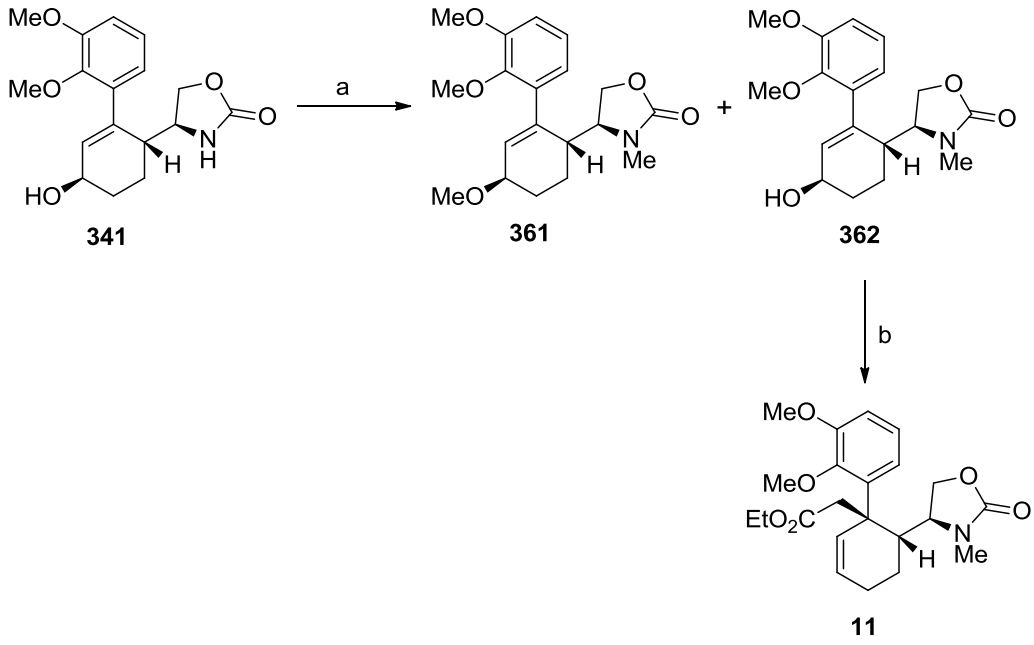


Reagents and conditions: (a) $Pd(dppf)_2Cl_2$, Cs_2CO_3, THF, reflux, 80%; (b) $CH_3C(OEt)_3$, propionic acid (cat.), 140 °C, 52%; (c) Bu_4NF, THF, 86%; (d) *n*-Bu_3P, DEAD, BzOH, THF, 0 °C→rt, 62%; (d) NaOMe/MeOH, 0 °C→rt, 42%; (e) $CH_3C(OEt)_3$, *o*-nitro phenol (cat.), 140 °C, 33%.

Scheme 45: Model reaction for installing C-13 and C-14 stereocenters.

Chida's experience along with our previous results confirmed that the side reactions at either C-13 or C-6 emanating from the nucleophilic character of the secondary amide

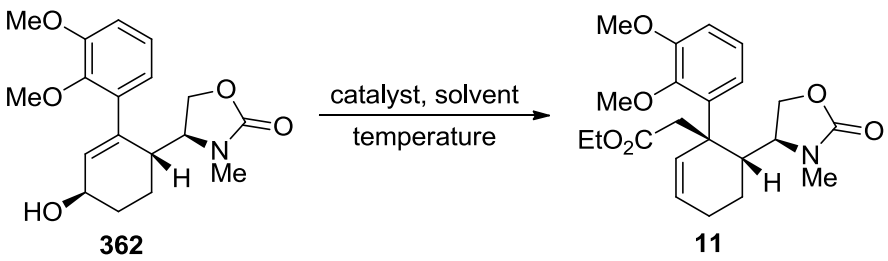
nitrogen was causing difficulties in installing the C-13 quaternary carbon center and displacing the C-6 group. In order to avoid these side reactions, we decided to protect the amide nitrogen in **341**, Scheme 46, with a methyl group that was planned to be installed at a later stage to provide **362** (56%) and **361** (31%). The formation of **361** was a result of the methylation of secondary alcohol along with amide nitrogen. We were quite excited to obtain the Claisen rearranged product **11** in 34% yields after heating the alcohol **362** with triethyl orthoactate and catalytic amount of *o*-nitro phenol for seven days.



Reagents and conditions: (a) NaH, MeI, THF, 0 °C, 56%; (b) $CH_3C(OEt)_3$, *o*-nitro phenol (cat.), 140 °C, 51%.

Scheme 46: Successful implementation of Johnson-Claisen rearrangement for the installation of C-13 stereocenter.

The orthoester Claisen rearrangement was studied under different reaction conditions and the results are summarised in Table 2 shown below. Entry 2 was found to give the best results among different conditions studied. When ethanol formed in the reaction mixture was continuously removed from the reaction mixture, the yield was improved up to 51% and the reaction time was reduced substantially to four days.



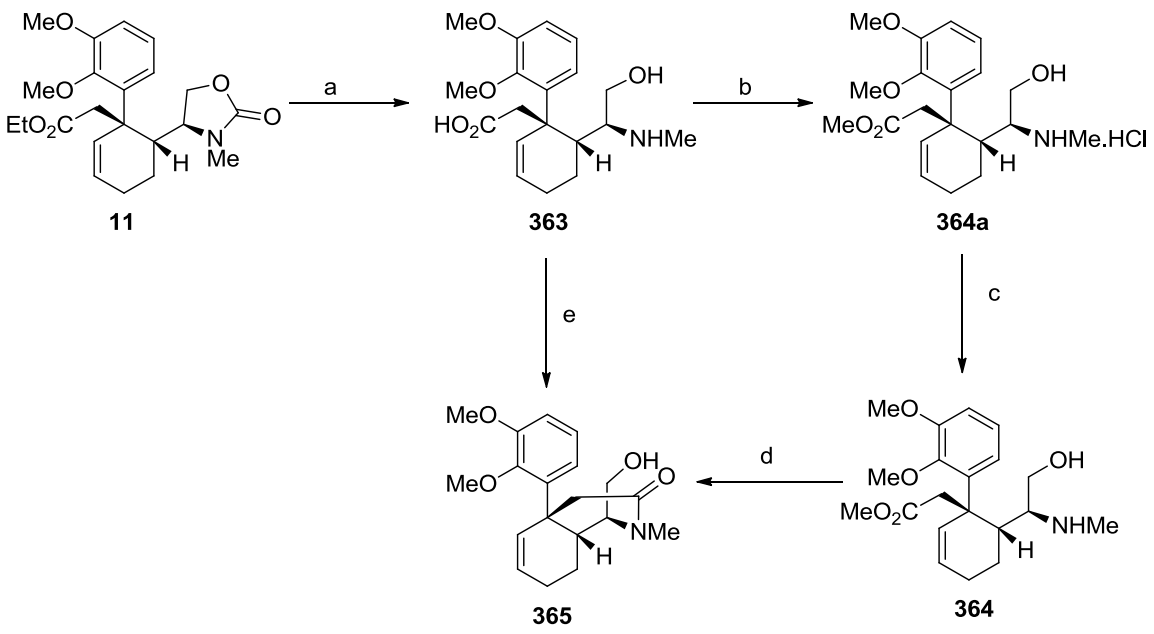
362 11

Entry	catalyst	solvent	temperature
1	—	$CH_3C(OEt)_3$	140 °C
2	2-nitrophenol	$CH_3C(OEt)_3$	140 °C
3	propionic acid	$CH_3C(OEt)_3$	140 °C
4	phenol	$CH_3C(OEt)_3$	140 °C
5	2-nitrophenol	$CH_3CH(OEt)_3$ + xylene	140 °C
6	propionic acid	$CH_3CH(OEt)_3$ + xylene	140 °C
7	trimethyl benzoic acid	$CH_3C(OEt)_3$	140 °C
8	2-nitrophenol	$CH_3C(OEt)_3$	160 °C

Table 2: Screening of Johnson-Claisen reaction conditions for the generation of a C-13 stereocenter.

Compound **11**, Scheme 47, was hydrolysed to acid **363** and was converted to the methyl ester **364** using a modified Fischer esterification protocol.[143] The B-ring in **365** was formed through a cyclization reaction that involved an acid catalyzed intramolecular amidation. This two-step process was later modified to a single step operation by using

the coupling reagent O-benzotriazol-1-yl-N,N,N′,N′-tetramethyluronium hexafluorophosphate (HBTU).[144]

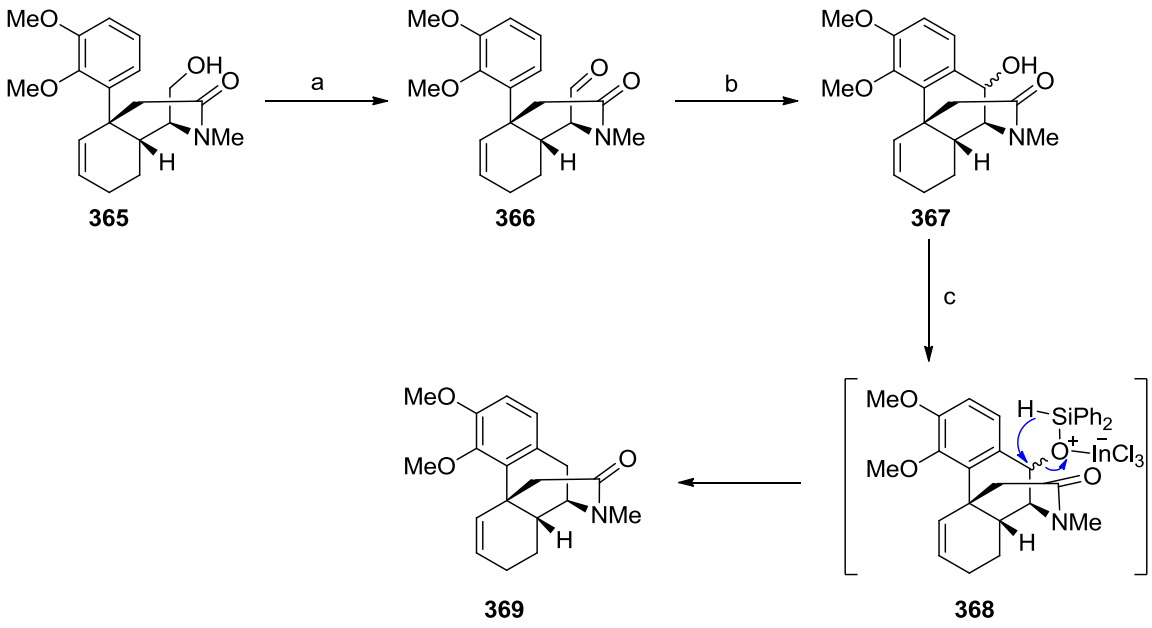


Reagents and conditions: (a) 50% aq NaOH, MeOH, 80 °C; (b) TMSCl, MeOH; (c) Na_2CO_3; (d) cat. AcOH, EtOH, 39%; (e) HBTU, DIPEA, CH_2Cl_2, r.t., 76%.

Scheme 47: Synthesis of D-ring *via* an intramolecular amidation reaction.

Oxidation of the primary alcohol in **365** furnished the crucial substrate for the C-10/C-11 closure, namely aldehyde **366,** Scheme 48, in 58% yields over three steps. The C-10/C-11 closure was studied using different conditions and we were pleased to obtain the desired cyclization product **367** under conditions employed by Evans.[145] We employed a known protocol for the reduction of the benzylic hydroxyl to furnish **369** in 50% over two steps.[146] The one step deoxygenation proceeds through the initial formation of a

hydrodiphenylsilyl ether and generation of the oxonium complex **368** by the Lewis acid, followed by desiloxylation through the donation of a hydrogen atom.

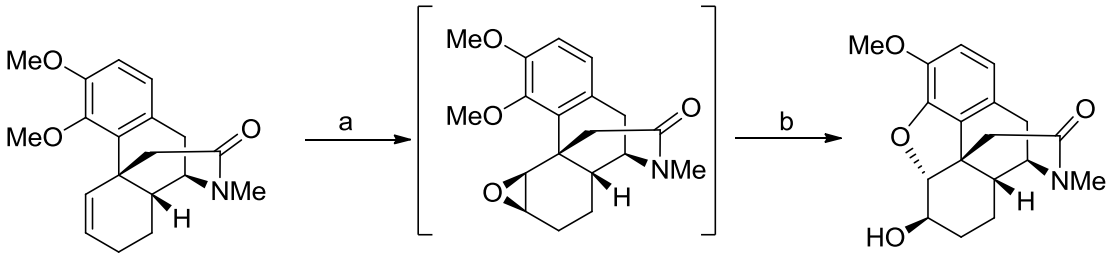


Reagents and conditions: (a) DMP, CH_2Cl_2, 82%; (b) $BF_3{\cdot}OEt_2$, CH_2Cl_2, –20 °C→r.t., 76%; (c) Ph_2SiHCl, cat.$InCl_3$, DCE, reflux, 67%.

Scheme 48: Synthesis of tetracyclic core of morphine.

3.2.3 Completion of the synthesis

Tetracycle **369**, Scheme 49, was subjected to epoxidation and an intramolecular opening of epoxide **370** established the C-5 stereocenter in **371** with 54% overall yield according to the method previously published by Overman.[108a, 147] Mulzer[148] and Chida[102] also used a similar strategy in their approaches towards morphine core.

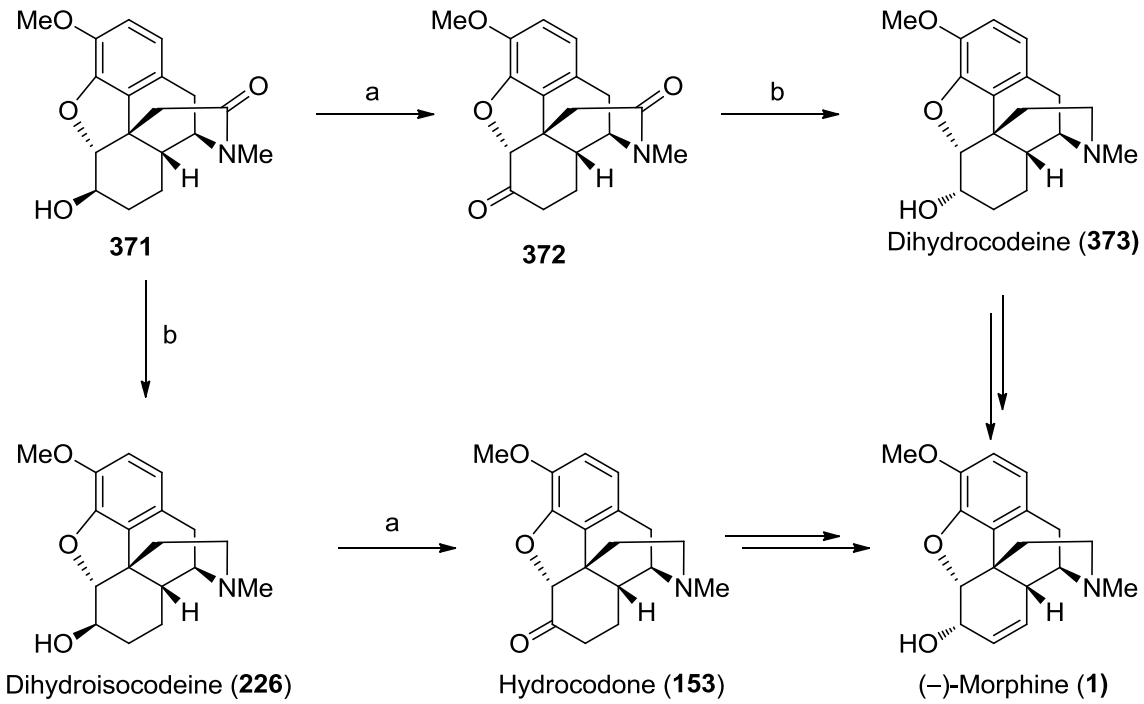


369 **370** **371**

Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C→r.t.; (b) CSA, THF, reflux, 54% after two steps.

Scheme 49: Synthesis of pentacyclic core of morphine *via* an intramolecular epoxide opening reaction.

Alcohol **371**, Scheme 50, was oxidized in 84% yield to ketoamide **372**, from which several morphinan derivatives would be easily attained. Thus the full reduction of **372** gave dihydrocodeine (**373**) in 71% yield with the correct absolute stereochemistry at C-6, which is known to result from the reduction of C-6 ketones already containing the dihydrofuran bridge.[94] Such a process is used frequently to adjust C-6 stereochemistry.[90, 97, 111, 149] Finally, reduction of the amide moiety in **371** delivered dihydroisocodeine (**226**) followed by oxidation at the C-6 alcohol provided hydrocodone (**153**) in 58% yield over two steps. Thus our synthetic efforts resulted in the total synthesis of dihydrocodeine (**374**) and hydrocodone (**153**), which formalized the synthesis of morphine.



Reagents and conditions: (a) DMP, CH_2Cl_2, 84%; (b) $LiAlH_4$, dioxane, reflux, 71%.

Scheme 50: Completion of the synthesis.

3.3 Total Synthesis of *ent*-Hydromorphone: An Oxidative Dearomatization/Intramolecular [4+2] Cycloaddition/Amination Sequence

3.3.1 Introduction

Diels-Alder reaction is one of the most widely used reactions in organic chemistry. Since its discovery in 1928,[150] Diels-Alder reaction plays an important role in building complexity and in the synthesis of fused polycyclic natural products. In 1951, Stork and co-workers published a synthesis of cantharidin using Diels-Alder reaction.[151] A few months later, first total synthesis of morphine[68] was reported by Gates which also utilised Diels-Alder reaction. Later, Woodward's work demonstrated the potential of this reaction by employing it in the synthesis of many complex natural products.[152]

The application of Diels-Alder reaction is further demonstrated in intramolecular versions, which are known as the intramolecular Diels-Alder (IMDA) reactions. This can be further subdivided in to Type 1 and Type 2 IMDA reactions depending on the position that the dienophile is tethered (See Figure 39).

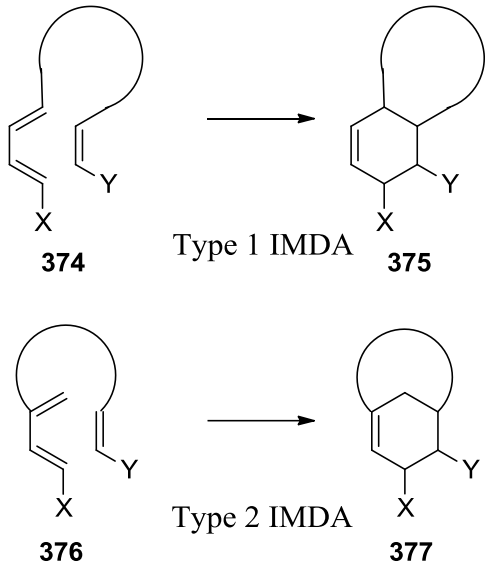


Figure 39: Type 1 and Type 2 IMDA reactions.

The aforementioned reactions are widely studied and have been a topic for many reviews over the years. [153]

The second approach involves an advanced strategy to construct the morphine skeleton by an intramolecular [4+2] cycloaddition of dienone **380,** Figure 40, produced by oxidative dearomatization of a phenol such as **379**. Previous studies have demonstrated that the configuration at C-5 carbon controls the stereochemical outcome in subsequent cyclization reaction.[95, 111] A toluene dioxygenase-mediated dihydroxylation of an appropriate arene will generate the homochiral portion **378** and a Mitsunobu reaction can be used to couple the phenolic fragment. An amine functionality at C-9 and a suitable leaving group at C-16 will lead to the incipient closure of the ethylamino bridge in **381** (or its aromatized equivalent), as shown in Figure 40. Completion of the synthesis can be achieved by a deprotection and oxidation sequence to obtain *ent*-hydromorphone **(16)**.

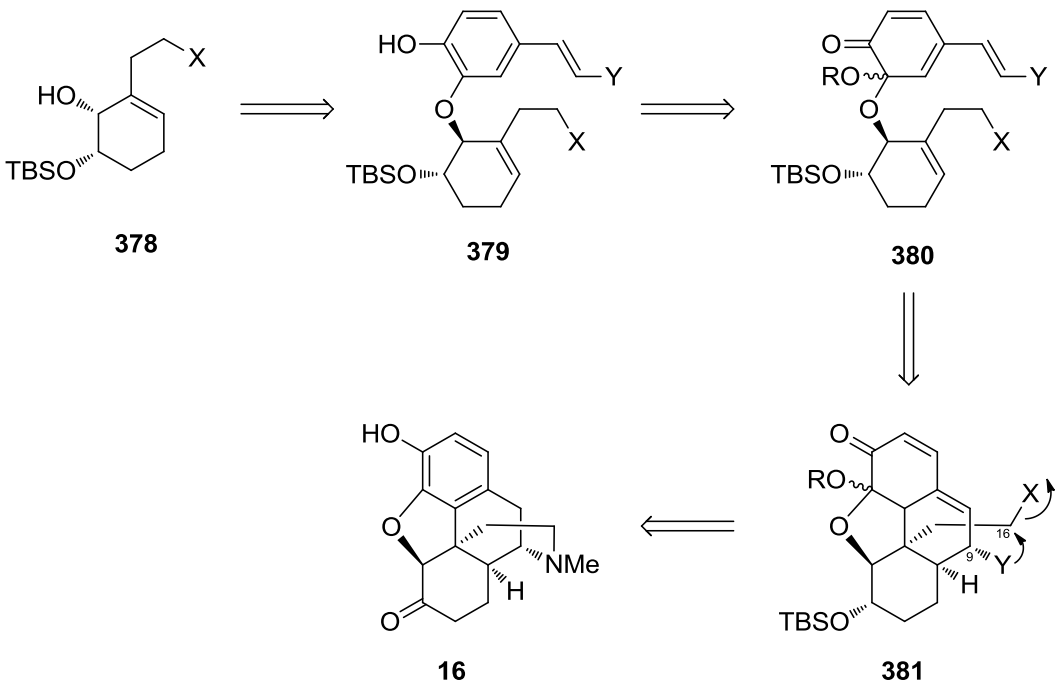


Figure 40: Advanced strategy to access morphinans by cycloaddition protocol.

A model study was designed to test the viability of this cycloaddition approach. Instead of using an advanced species, we decided to start our studies using simpler molecule such as **384**, Figure 41, which did not contain the nucleophilic group Y or a leaving group X as in **380**, Figure 40. The expected [4+2] cycloaddition would generate **383,** then the known hydroamination methodology[95, 110-111] would be used to set C-9 late in the synthesis.

The retrosynthetic analysis involves an enzymatic dihydroxylation of the *β*-bromoethylbenzene **5,** Figure 41, which undergoes further chemical manipulations to provide allylic alcohol **12**. This can be tethered to the phenolic ring *via* a Mitsunobu reaction to access ether **13;** dearomatization of **13** to dienone **384** and a [4+2] cycloaddition reaction provides tetracycle **383** as shown in Figure 41. A late stage introduction of C-9 stereochemistry can be attained *via* a hydroamination reaction of a

rearomatized substrate such as **382** and a deprotection-oxidation sequence completes the synthesis of *ent*-hydromorphone (**16**).

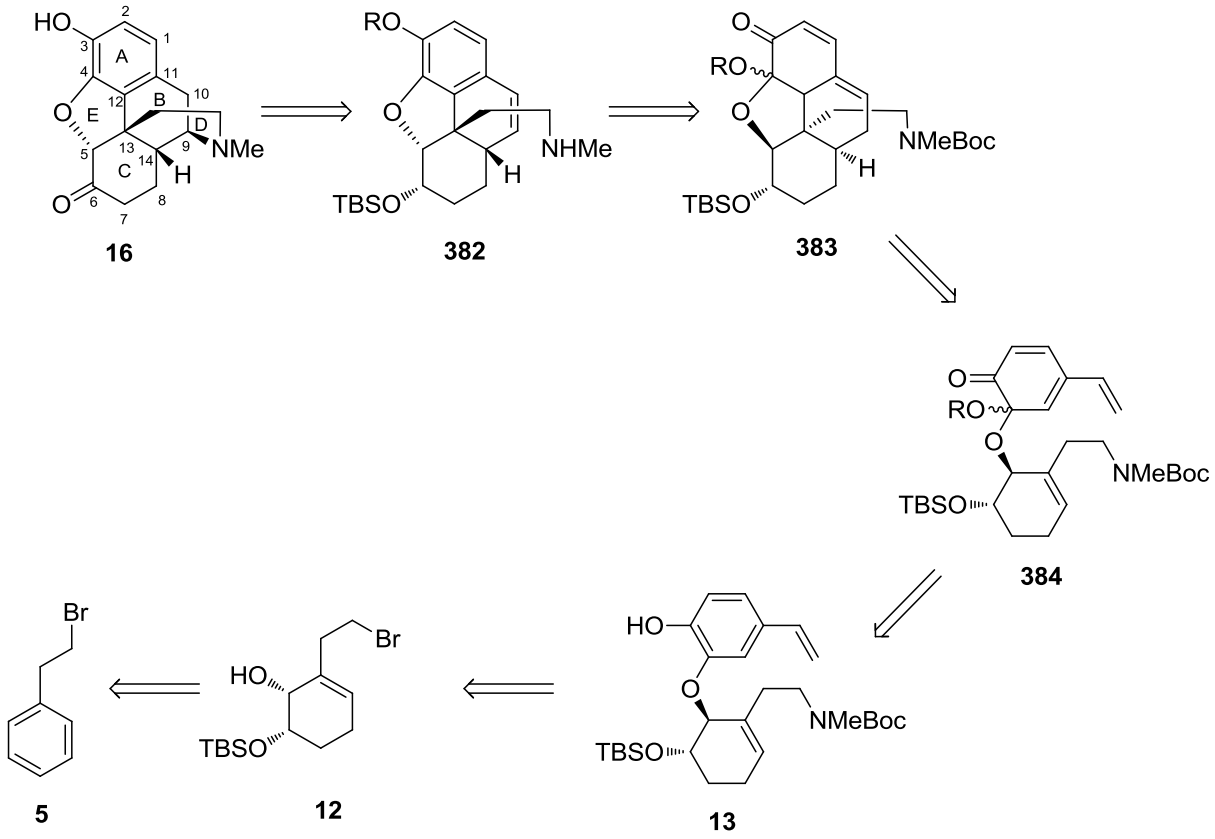


Figure 41: Retrosynthetic analysis for the synthesis of *ent*-hydromorphone.

Only a few syntheses of opiate alkaloids utilized Diels-Alder reactions to construct the complexity in the morphine core. The first reported synthesis of morphine by Gates demonstrated the power of [4+2] cycloaddition reaction by constructing the C-ring.[68] In 2009, Stork reported the construction of B and D-rings through the application of IMDA reaction.[154] But it has been used only once in a direct construction of ring B of morphine skeleton, namely in an intermolecular [4+2] approach by Tius.[155] They envisioned an

intermolecular cycloaddition between a substituted benzoquinone **387**, Figure 42, and a styrene **386** to develop the phenanthrene core of morphine (**1**) through the formation of B-ring as evidenced in **385**.

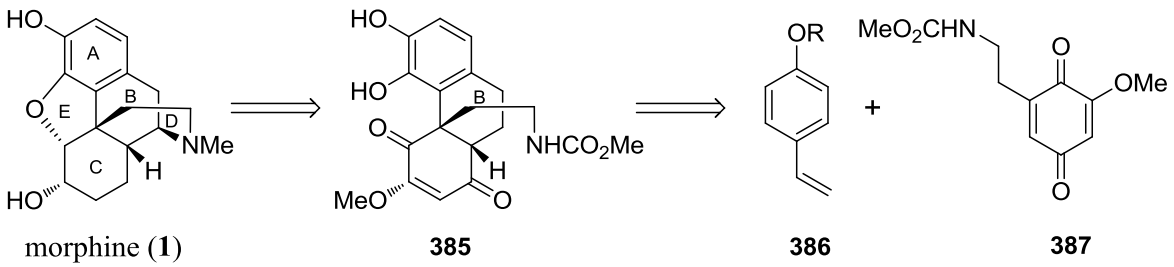
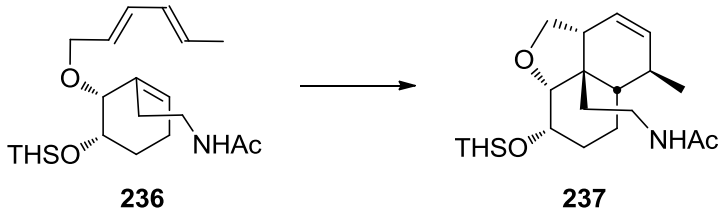


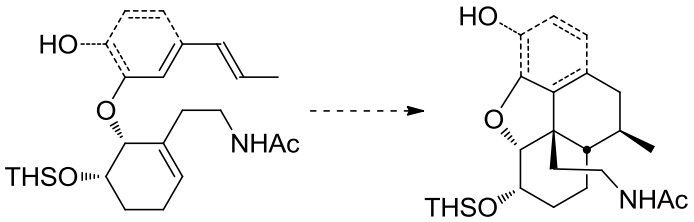
Figure 42: Diels-Alder approach for the construction of B-ring by Tius.

Earlier work from our group demonstrated the construction of B-ring leading to morphinan substructure *via* an intramolecular Diels-Alder reaction.[105-106] It has been already discussed in the historical section of this thesis. Even though the tricyclic core which contains B-C-E rings of morphine with five stereocenters was created, the installation of aromatic part still provided a challenging task (See Figure 43). An enantiomerically pure substrate like **388**, Figure 43, is easily available by taking advantage of enzymatically derived *cis*-cyclohexadiene diol. But the construction of B-ring *via* an IMDA reaction is rather difficult process in such a system due to the fact that high energy conditions is required to overcome the aromatic stabilization energy.



236 **237**

Known work from Hudlicky group

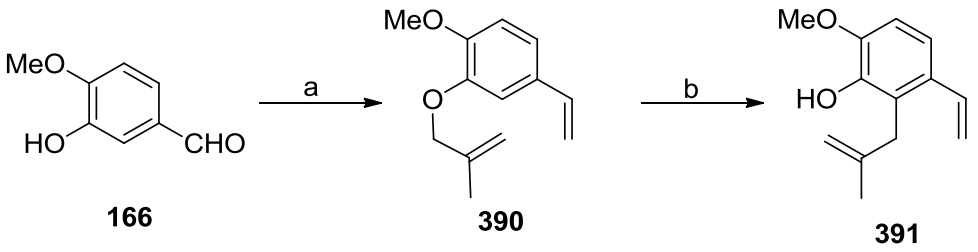


388 **389**

Construction of phenanthrene core

Figure 43: Initial ideas for the synthesis of phenanthrene core.

The aforementioned statement is well evidenced from our initial model reactions to effect such a cycloaddition reaction. All attempts led to [3,3]-sigmatropic rearrangement to provide **391**, Scheme 51, no evidence for the cycloaddition product was obtained. These results turned our attention to destroy the aromaticity of A-ring to generate a reactive diene moiety to effect the [4+2] cycloaddition. Many methods are available for the preparation of a dearomatized intermediate to effect the cycloaddition. The dearomatization reaction and its application in synthesis of complex natural products have been extensively reviewed.[156]



166 390 391

Reagents and conditions: (a) (i) 3-bromo-2-methylprop-1-ene, K_2CO_3, DMF, 76%; (ii) CH_3PPh_3Br, *n*-BuLi, THF, –78 °C → 0 °C then reflux for 4 h, 95%; (b) *m*-xylene, sealed tube, reflux, 9 days, 18%.

Scheme 51: Model reactions to effect a [4+2] intramolecular cycloaddition.

A Diels-Alder/Cope sequence similar in concept to our model studies was published by Rodrigo in 1998.[157] His studies include oxidative dearomatization of phenols[158] and subsequent cycloaddition on structurally different substrates to various natural products. A recent work from his group showed a more advanced dearomatization/cyclization strategy to synthesize partial morphine skeleton that includes rings A-B-C-E.[159] His synthetic studies involve dearomatization of phenol **392**, Figure 44, led to a mixture of many products. One drawback of this approach was the quinone generated by dearomatization can act as a dienophile or diene to provide **393** or **394** successively. The formation of dimer (24%) was also observed during this process. The mixture of **393** and **394** (obtained in 64% yield) can undergo Cope rearrangement to generate the required product. The tetracycle **393** is further elaborated to the natural product (–)-indolinocodeine in six steps.

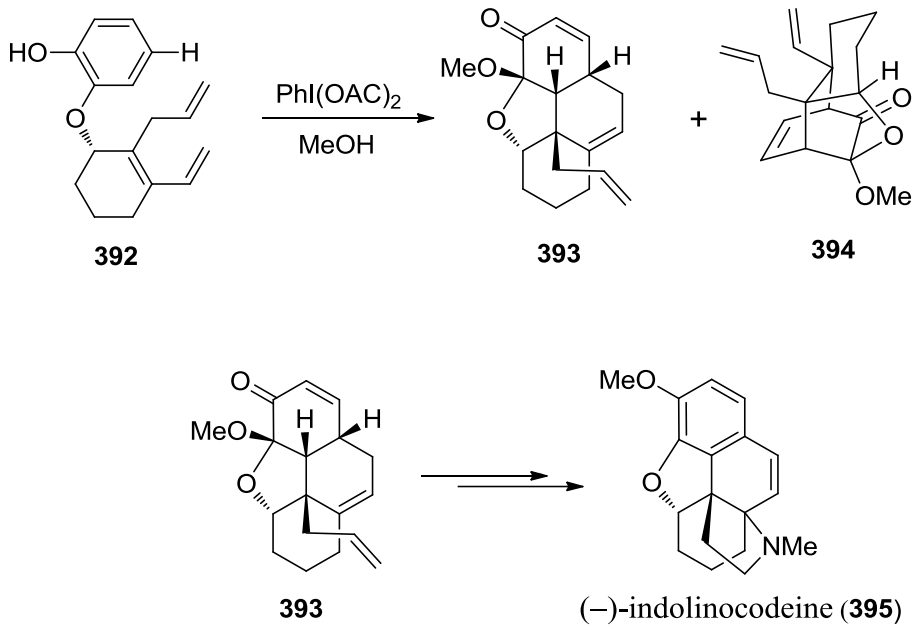
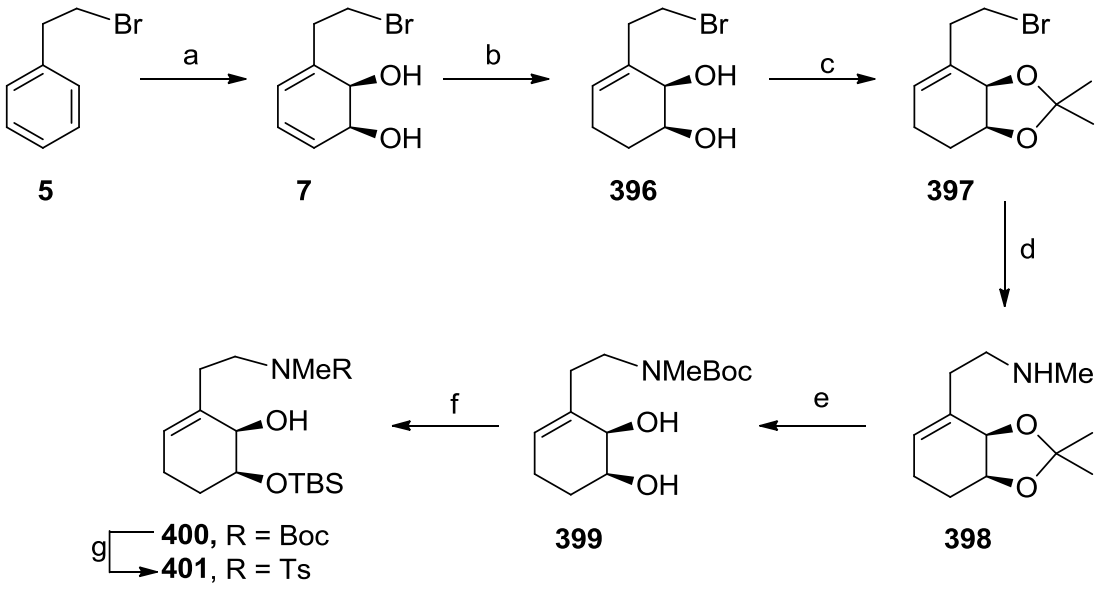


Figure 44: Rodrigo's synthesis of indolinocodeine.

3.3.2 Synthesis of dearomatizive cyclization precursor

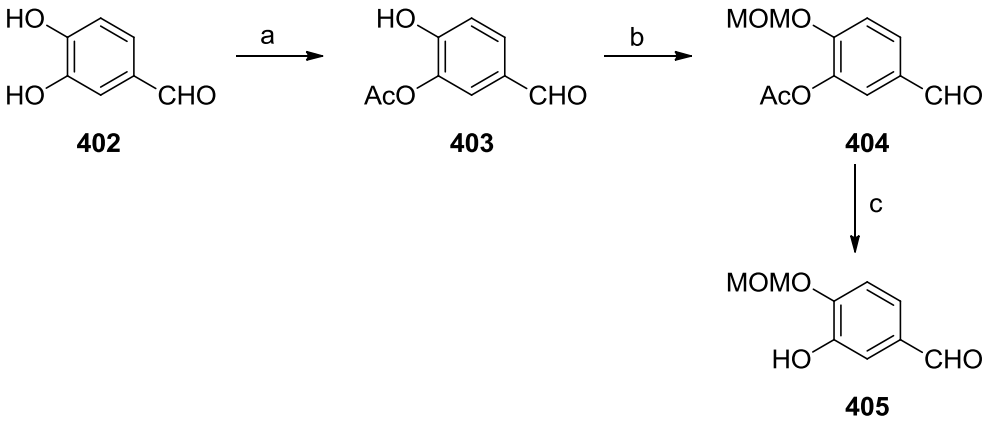
The above precedents bode well for a successful approach, which we began with the synthesis of the two subunits required to join together. Our synthetic efforts began with synthesizing **400**, Scheme 52, following a known protocol.[112] The first step of the synthesis was the generation of homochiral diol **7** by dihydroxylation of **5** by whole-cell fermentation with E. *coli* JM 109 (pDTG601A).[31] It was immediately subjected to a selective reduction with potassium azodicarboxylate to obtain **396**, followed by protection of the diol to give acetonide **397**. The amine functionality was introduced by displacement of bromine in **397** with methylamine to provide **398**. A one-pot operation that includes hydrolysis of the acetonide and protection of the secondary amine as a Boc-carbamate delivered **399**. A regioselective silylation of the distal hydroxyl group completed the synthesis of C-ring fragment **400**.



Reagents and conditions: (a) *E. coli* JM 109 (pDTG601A), 10–15 gL^{-1}; (b) potassium azodicarboxylate, AcOH, MeOH, 0 °C, 83%; (c) 2,2-dimethoxypropane, acetone, TsOH, 80%; (d) $MeNH_2$, K_2CO_3, THF, sealed tube, 93%; (e) (i) 3M HCl, EtOH; (ii) Boc_2O, $NaHCO_3$, EtOH, 74% (2 steps); (f) TBSCl, imidazole, CH_2Cl_2, –78 °C → RT, 92%; (g) (i) TFA, CH_2Cl_2; (ii) TsCl, Et_3N, CH_2Cl_2, 0 °C →RT.

Scheme 52: Synthesis of C-ring fragment.

The arene coupling partner **405**, Scheme 53, was synthesized from 3,4-dihydroxybenzaldehyde **402** by adjustment of a known protocol.[160] A regioselective acetylation of 3,4-dihydroxybenzaldehyde **402** produced the mono-acetylated derivative **403**. Protection of the *p*-hydroxyl phenol with MOMCl under mild basic conditions afforded aldehyde **404**; the required phenol **405** was attained after the hydrolysis of the acetyl group.

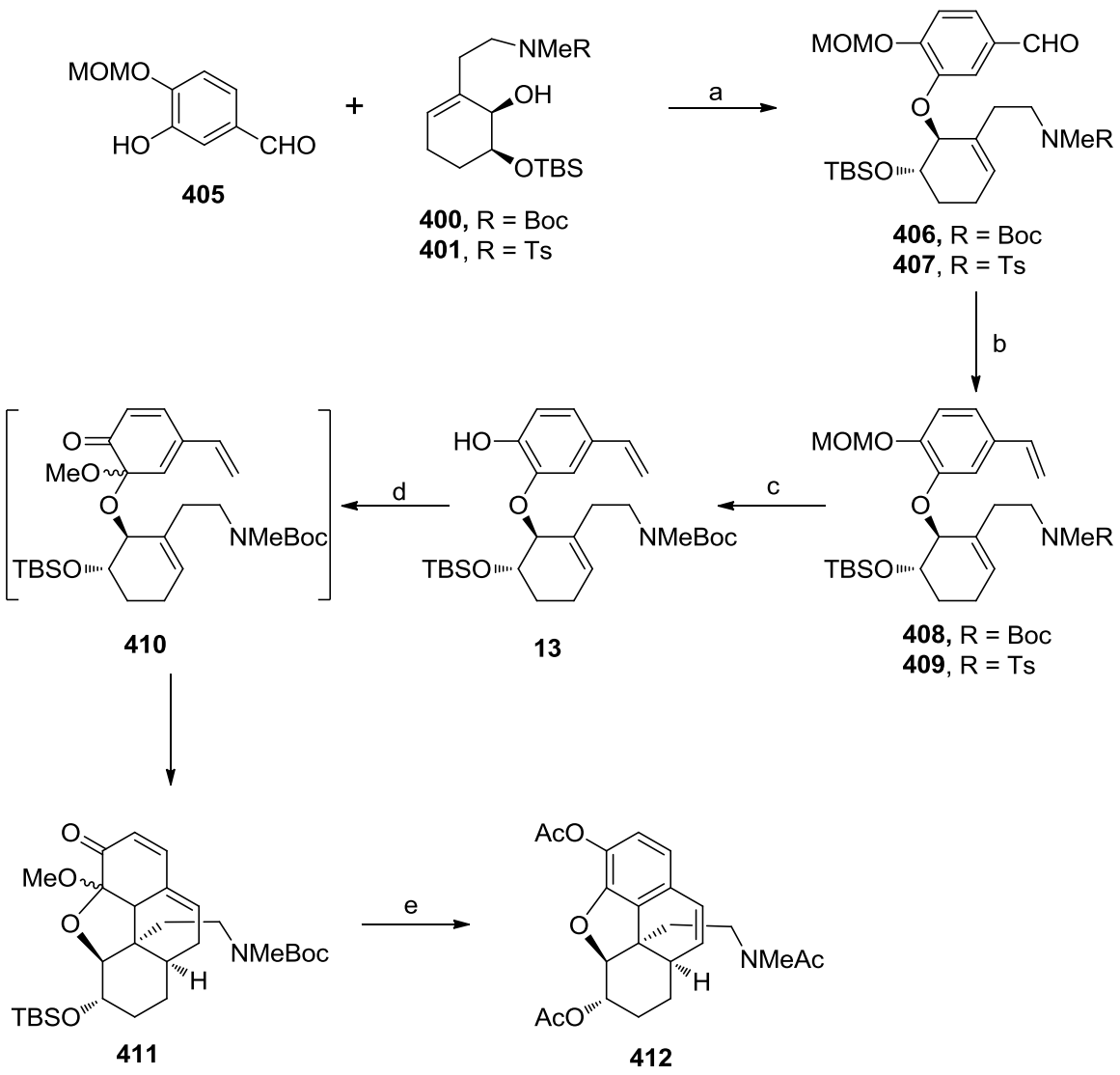


Reagents and conditions: (a) Ac_2O, NaOH, THF, 0 °C, 82–85%; (b) MOMCl, K_2CO_3, DMF, 0 °C → RT, 76–80%; (c) K_2CO_3, MeOH, RT, 88–90%.

Scheme 53: Synthesis of A-ring fragment.

3.3.3 Synthesis of tetracyclic core through an intramolecular cycloaddition

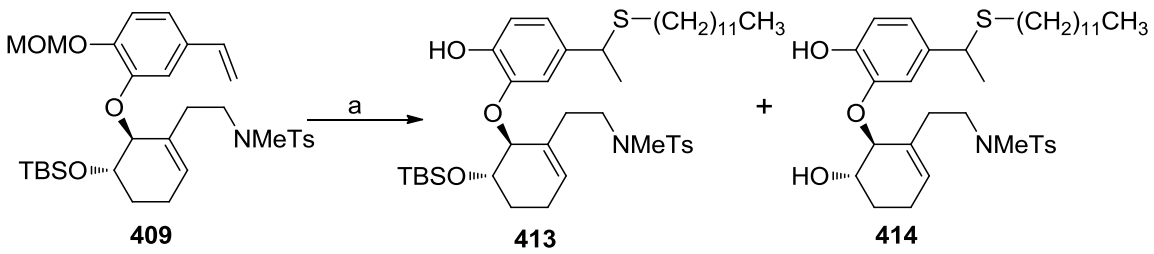
After successfully synthesizing the A and C-ring fragments, our next goal was to connect both fragments. We performed a Mitsunobu reaction between the phenol **405** and alcohol **400**, Scheme 54, which gave access to the ether **406**; a Wittig reaction completed the synthesis of styrene **408**. Next challenge in the synthesis was the selective removal of MOM-protecting group in the presence of other acidic labile protecting groups. It was achieved by applying a known protocol employed by Rawal and co-workers;[161] under mild conditions phenol **13** was produced, and this is the key intermediate required for the cyclization studies.



Reagents and conditions: (a) TMAD, PBu_3, THF, 0 °C → RT, 81–85%; (b) CH_3PPh_3Br, *n*-BuLi, THF, –78 °C → 0 °C then reflux for 4 h, 82–88%; (c) $ZnBr_2$, $CH_3(CH_2)_{10}CH_2SH$, CH_2Cl_2, RT, 10 min, 92%; (d) $PhI(OAc)_2$, MeOH, reflux, 16 h, 50%; (e) TFA, CH_2Cl_2, Ac_2O, 0 °C, 15 min.

Scheme 54: Intramolecular [4+2] cycloaddition approach towards the synthesis of tetracyclic core of morphine.

Applying similar conditions to remove MOM group from tosylated compound **409**, Scheme 55, did not provide any evidence of required product rather than undesired side products **413** (46%) and **414** (37%).



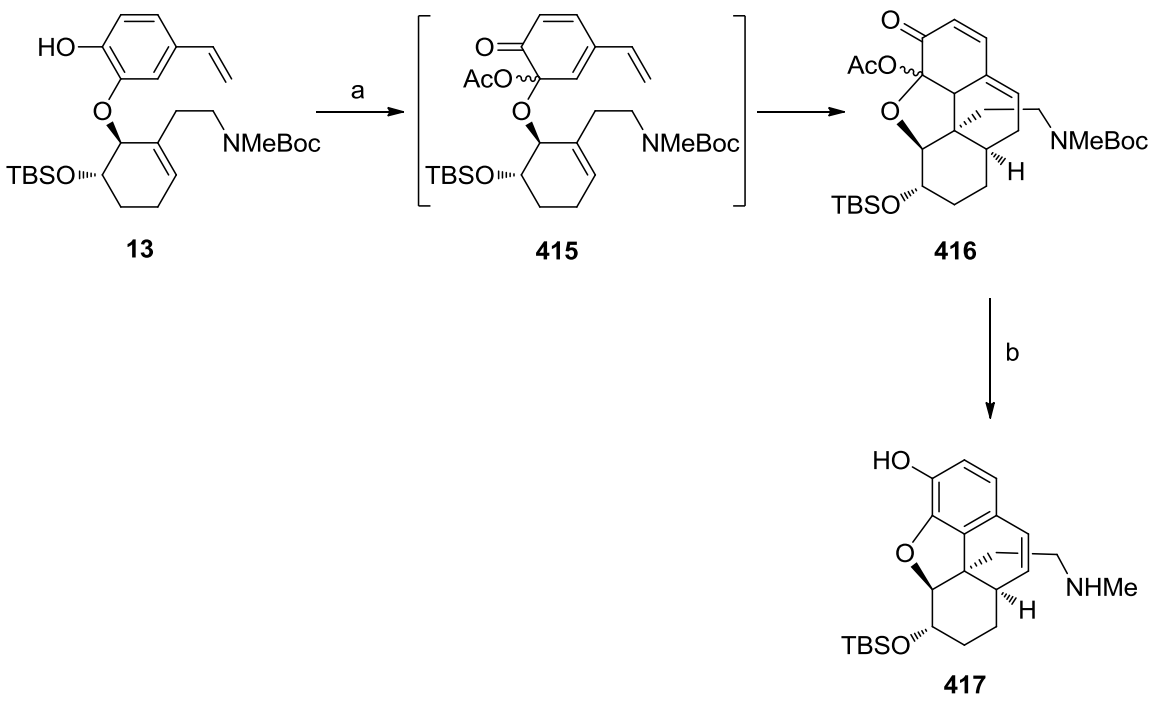
Reagents and conditions: (a) $ZnBr_2$, $CH_3(CH_2)_{10}CH_2SH$, CH_2Cl_2, RT.

Scheme 55: Attempts to cleave MOM group in **409**.

Our dearomatization studies began with the exposure of phenol **13**, Scheme 54, to diacetoxy iodobenzene (DAIB) in MeOH at room temperature and then under reflux conditions, led to tetracycle **411** *via* an intermediate **410**. The intermediate **410** is supposed to be very reactive species but we did not observe any cyclized product without heating the reaction mixture. Even though, this result was exciting, re-aromatization of **411** was proved to be a little challenging. Acid-mediated conditions can lead to a deprotection of Boc-group before re-aromatization, which can result in conjugate addition to dienone to produce unwanted side product. Following Rodrigo's protocol,[159] treating **411** with TFA in presence of acetic anhydride provided acetamide **412**. Unfortunately this route led to the formation of acetamide; all our attempts to hydrolyze the acetamide were unsuccessful.

These results prompted us to investigate other reagents for the dearomatization reaction. Introducing a better leaving group than –OMe group can solve the problem of re-aromatization reaction. Exposure of **13**, Scheme 56, to lead tetraacetate in refluxing dichloroethane provided [4+2] adduct **416** in 50% isolated yield *via* an intermediate dienone **415**. The reason for low yields of this reaction can be formation of two diastereomers during the generation of intermediate dienone **415** with only one diastereomer undergoing the cycloaddition.

As only one cycloaddition product was observed in the reaction seems to indicate that dienone **415** underwent the cycloaddition exclusively at the site of the exocyclic diene; none of the dimerization product was observed in this reaction. The endocyclic cycloaddition product was detected only once in about 3-4% yield. Even though the endocyclic diene is quite reactive, the exclusive formation of **416** can be attributed to steric reasons, which deny the dienophile the proximity of the endocyclic diene. The ^{13}C NMR spectrum of **416** exhibited three carbonyl signals; a signal at δ 188.2 corresponding to the enone, signal at δ 170.9 showed the presence of the ester carbonyl from the acetyl group, and the amide carbonyl appeared at δ 155.4. Even though **416** obtained as a single stereoisomer, assignment of stereochemistry at C-4/C-12 was complicated by the presence of rotamers. Also these stereocenters were immediately destroyed by re-aromatization reaction.



13 415 416 417

Reagents and conditions: (a) $Pb(OAc)_4$, DCE, reflux, 4 h, 50%; (b) TFA, CH_2Cl_2, 0 °C, 15 min.

Scheme 56: Synthesis of tetracycle **414** *via* re-aromatization.

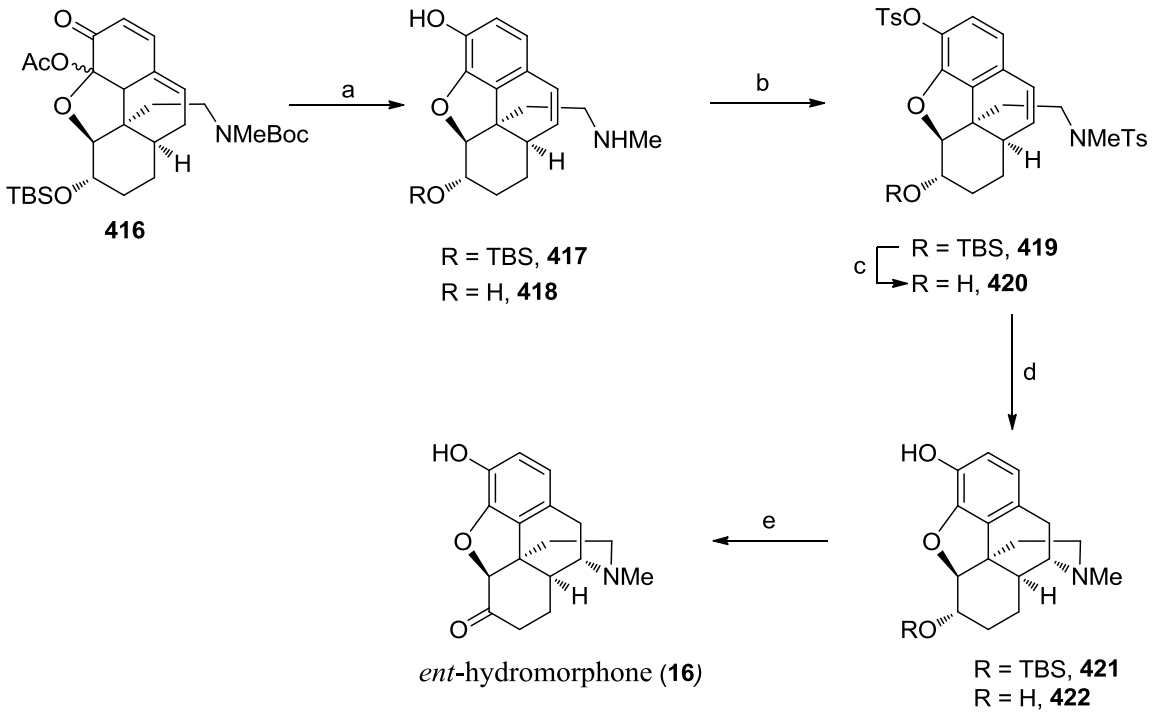
Dienone **416** was treated with trifluoroacetic acid to afford phenol **417** *via* re-aromatization and the concomitant hydrolysis of the Boc carbamate.

3.3.4 Synthesis of D-ring and completion of the synthesis

Our next aim was to construct the D-ring to complete the synthesis. A hydroamination reaction of **417**, Scheme 56, was designed; however, all our attempts failed to install the ethylamino bridge through an aminomercuration were unsuccessful. A similar strategy was successfully employed in our previous work;[110-111] $Hg(OAc)_2$ mediated oxymercuration and subsequent reductive work up with lithium aluminium hydride constructed D-ring successfully. Analysis of the crude reaction mixture suggested some

evidence of hydroamination under the aforementioned conditions but the isolation of pure products from these reactions was not possible. The failure of the aminomercuartion was likely due to the instability of phenol **417**.

We also observed the formation of **418**, Scheme 57, produced by the treatment of **416** with trifluoroacetic acid for longer period of time. Both **417** and **418** converted to the corresponding tosyl amides **419** and **420** by treatment with excess tosyl chloride. This resulted in concomitant tosylation of the phenolic hydroxyl along with the amine in 45% yield, over two steps. Removal of the silyl group from **419** delivered **420** in good yields. The establishment of the ethylamino bridge was accomplished by a nitrogen-centered radical cyclization enabled by a dissolved-metal reduction of the tosyl amide according to conditions adapted from the work of Parker[89a] and Chida.[104] This reaction worked very efficiently on both protected (**419)** and unprotected (**420)** compounds. The reductive cyclization approach was superior to hydroamination conditions that previously employed in our group. Hydroamination of **419** produced pentacycle **421** in 82-86% yields. To our surprise, cyclization of free alcohol **420** gave **422** in 93% yields.



Reagents and conditions: (a) TFA, CH_2Cl_2, 0 °C, 15 min; (b) TsCl, Et_3N, CH_2Cl_2, 0 °C →RT, 45% over two steps; (c) TBAF, THF, RT, 86%; (d) Li, tBuOH, NH_3(liq), THF, –78 °C, 10 min [82–86% for **419** to **421**; 93% for **420** to **422**]; (e) tBuOK, PhCOPh, $PhCH_3$/DME, 85 °C, 8 h, 44%.

Scheme 57: Completion of the synthesis of *ent*-hydromorphone.

Oxidation of **422**, Scheme 57, to *ent*-hydromorphone **(16)** was accomplished with benzophenone and tBuOK in 44% yield (83% based on recovered starting material) using a modified procedure from Woodward and Rapoport.[162] Because of poor solubility of **422** in most of the solvents, the reaction did not proceed to completion, and starting material (53%) was recovered from the reaction. Another explanation for the low yield is the trans relationship between the C-5 and C-6 positions in the *ent*-dihydroisomorphine **422.**

Rapoport has provided a reasonable explanation based on the pseudo-six-membered ring conformation involved in such oxidations.[162b]

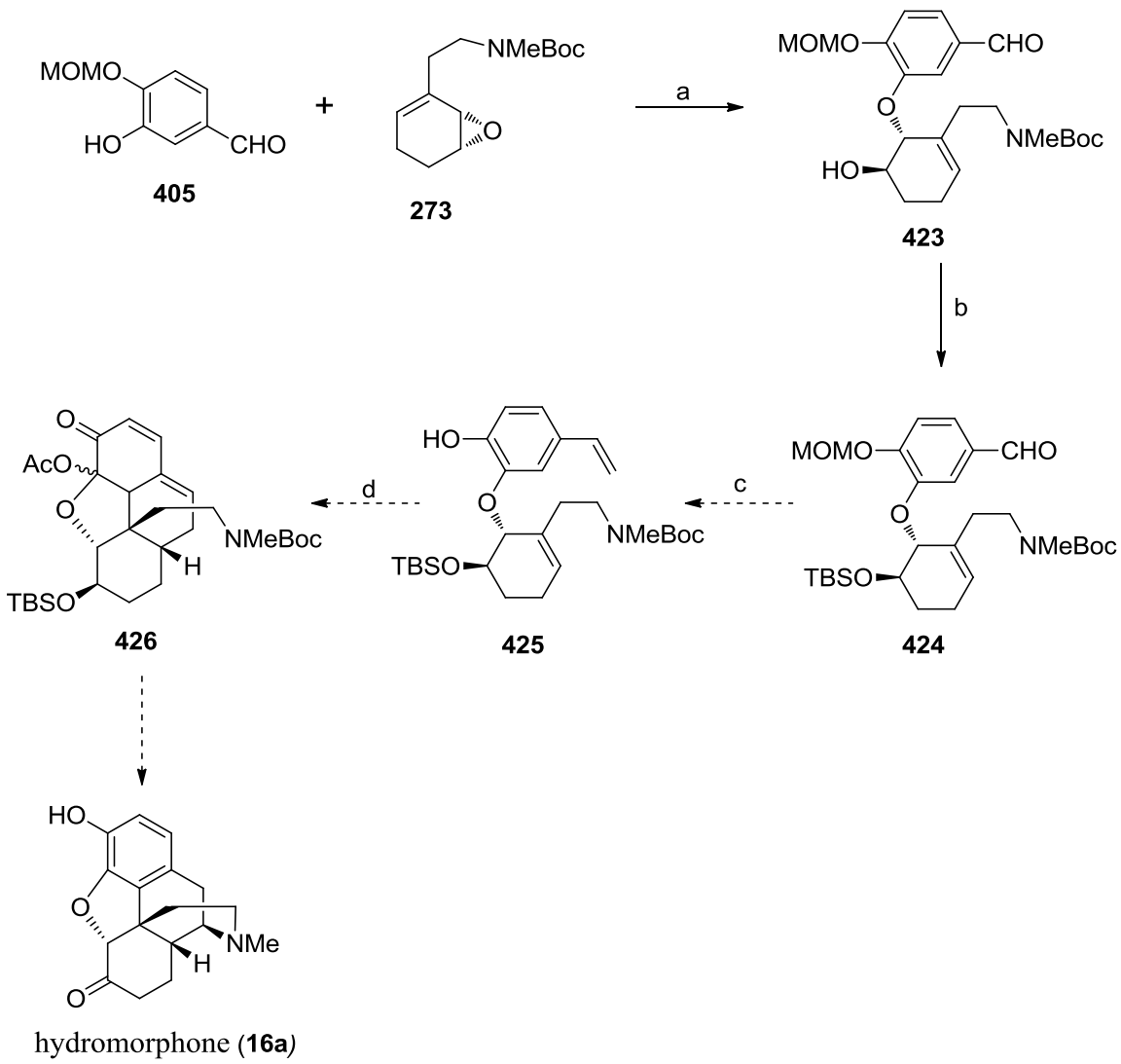
Thus we were able to synthesize *ent*-hydromorphone in 12 steps from β-bromoethylbenzene **5** making it one of the shortest syntheses of a morphinan.

4. Conclusions and Future Work

In the course of the present study, the total syntheses of dihydrocodeine, hydrocodone, and *ent*-hydromorphone were accomplished using chemoenzymatic methods. A [3,3]-Sigmatropic rearrangement was effectively used to set the C-9, C-14, and C-13 stereocenters in the synthesis of dihydrocodeine and hydrocodone. A successful oxidative dearomatization and cycloaddition strategy was developed to accomplish the first total synthesis of *ent*-hydromorphone in 12 steps starting from β-bromoethylbenzene.

Future work may be divided in to two categories:

a) Optimized synthesis of natural hydromorphone: An enantiodivergent synthesis is achievable through the modification of stereocenter at C-5 carbon, as this stereocenter controls the rest of the stereochemical outcomes in the subsequent reaction sequences. Control of the stereocenter at C-5 carbon has already been accomplished by previous work from our group.[111] Epoxide **273**, Scheme 58, was synthesised following a known protocol. This epoxide **273** was opened with phenol **405** to set the C-5 stereocenter in **423** that gave C-5 configuration of natural series. Protection of the alcohol with a silyl group provided **428**, which is the enantiomer of **406**, Scheme 54. Following the same sequences as in the *ent*-series would deliver the natural hydromorphone (**16a**), thus completing the enantiodivergent syntheses. The oxidative dearomatization and subsequent cycloaddition can be also achieved through an anodic oxidation by electrochemistry as evidenced from Quideau's work.[163]

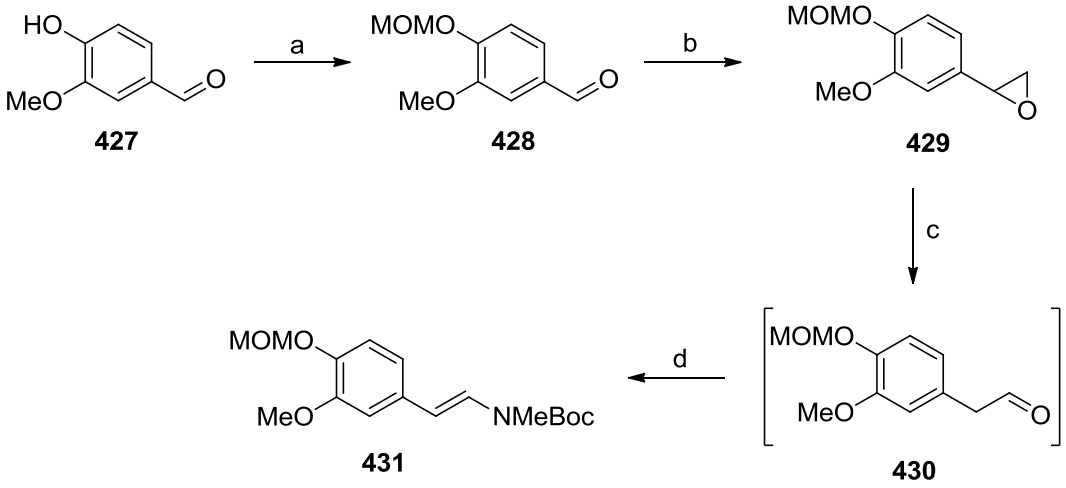


Reagents and conditions: (a) DME-DMF (1:1), 18-crown-6, 80 °C, 24 h, 68%; (b) TBSCl, imidazole, CH_2Cl_2, –78 °C → RT.

Scheme 58: Proposed synthesis of natural hydromorphone.

b) Advanced strategies for the synthesis of hydromorphone: An advanced approach towards hydromorphone is proposed *via* an enamine intermediate as discussed earlier in chapter 3. The viability of this approach was tested through a model synthesis of enamine

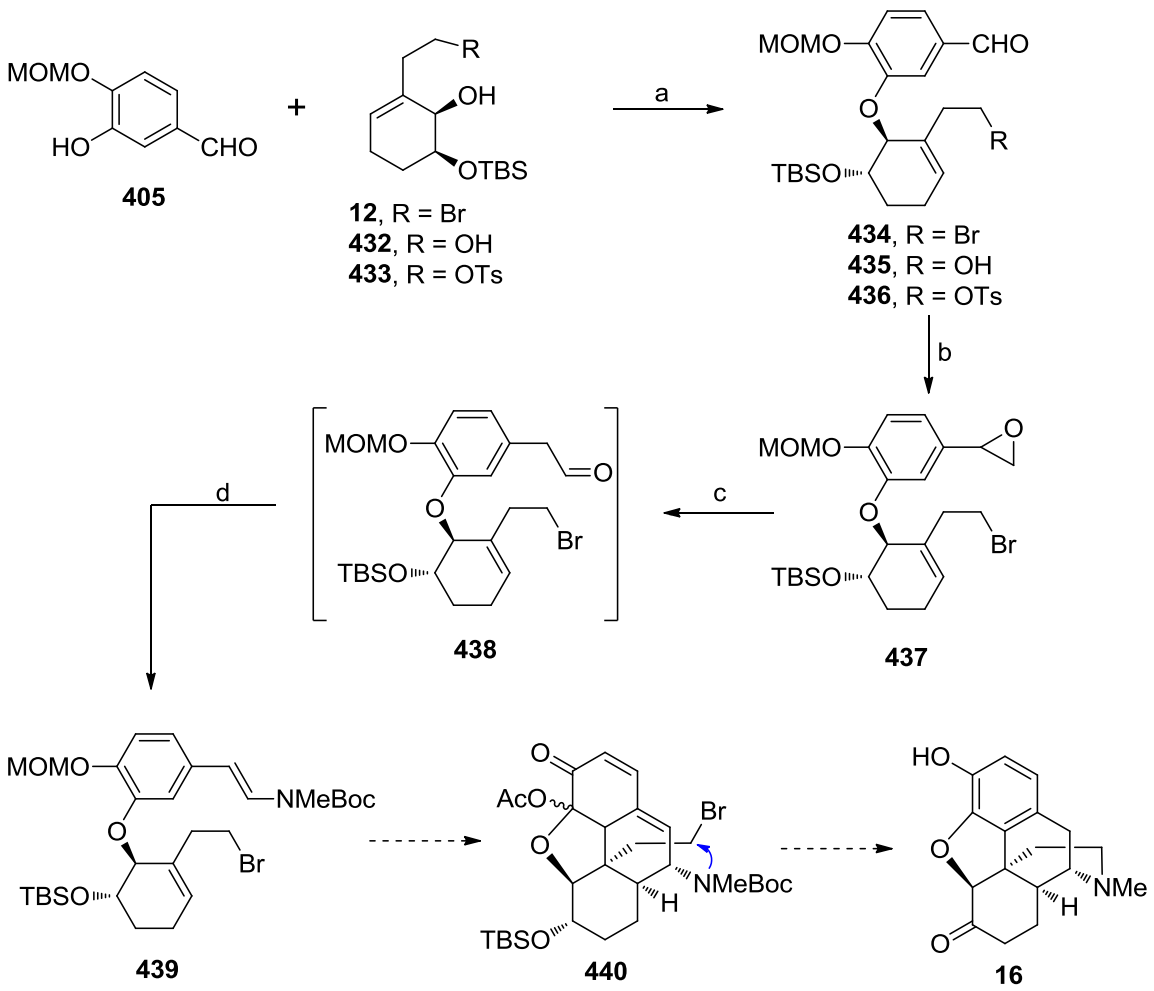
431, Scheme 59, in a simple system as shown in Scheme 59. Starting from vanillin **427**, Scheme 59, enamine **431** was prepared in a four step, three pot operation.



Reagents and conditions: (a) MOMCl, Hunig's base, CH_2Cl_2, 65%; (b) trimethylsulfonium methyl sulfate; 50% NaOH $_{(aq)}$, CH_2Cl_2, 87%; (c) BF_3OEt_2, CH_2Cl_2; (d) MeNHBOc, *n*-BuLi, THF, –78 °C → RT, 45% over two steps.

Scheme 59: Model reactions for the synthesis of enamine.

Following the successful outcome of the model reaction, we focused in synthesizing advanced enamine intermediate. Mitsunobu coupling of phenol **405**, scheme 60, with various alcohols were studied, ether **434** was subjected to Corey-Chaykovsky reaction to obtain the epoxide **437.** Rearrangement of epoxide **437** provided aldehyde **438** which was converted to enamine **439** without isolation of the aldehyde **438**. Enamine **439** was isolated in low yield, but all our attempts to reproduce this step was unsucdessful. This reaction needs to be studied in more detail to optimize this step.



Reagents and conditions: (a) TMAD, PBu_3, THF, 0 °C → RT; (b) trimethylsulfonium methyl sulfate; 50% NaOH $_{(aq)}$, CH_2Cl_2, 87%; (c) BF_3OEt_2, CH_2Cl_2; (d) MeNHBoc, *n*-BuLi, THF, –78 °C → RT, 9% over two steps.

Scheme 60: Approach towards *ent*-hydromorphone *via* an advanced enamine intermediate.

Future work towards hydromorphone also includes oxidative dearoamtization of an ester **441**, Figure 45; cycloaddition followed by a Curtius rearrangement would install the

amine functionality as shown in **443**. This approach will serve as an alternate route, if the enamine approach does not work.

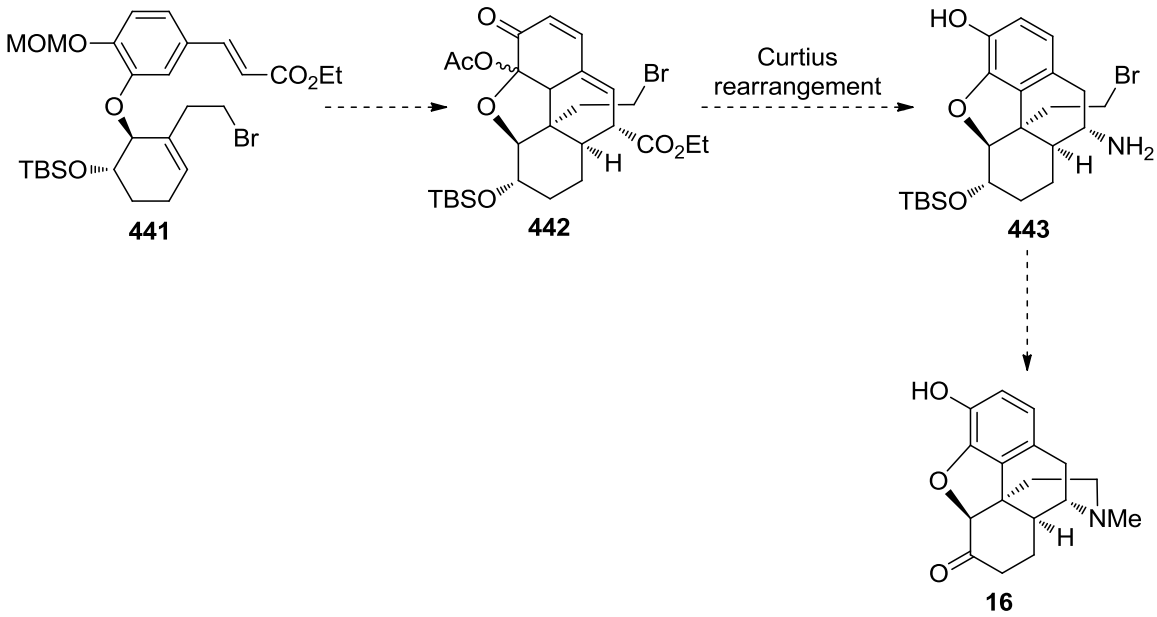


Figure 45: Proposed synthesis of hydromorphone from ester **441**.

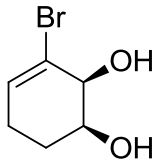
5. Experimental Section

5.1 General Experimental Details

All reagents were purchased from Aldrich, Fisher Scientific, Acros or Oakwood chemicals and used as received unless otherwise indicated. Reactions were carried out under inert atmosphere in flame dried glassware unless stated otherwise. Solvents were distilled: CH_2Cl_2, DMF, *i*Pr_2EtN, DCE and pyridine from CaH_2; MeOH from magnesium methoxide; THF from Na/benzophenone; toluene from Na. All alkyllithium and lithium amide bases were titrated against *N*-benzylbenzamide[164] to a blue endpoint. QualitativeTLC was done with pre-coated silica gel aluminium sheets (EMD silica gel 60 F254); detection by UV or by spraying with "CAM" solution (5 g of $(NH_4)_6Mo_7O_{24}.4H_2O$, 1 g of $Ce(SO_4)_2$, 100 ml of 10% H_2SO_4) or 0.5% aqueous $KMnO_4$ solution followed by heating. Column chromatography was performed using silica gel SiliaFlash P60 from Silicycle (40-66 μm). Optical rotation was measured in a 1dm cell at 18-22 °C and 589 nm; concentration *c* in g/100 ml. FT-IR spectra were obtained as *ca*. 2% solutions in $CHCl_3$ and on Bruker ALPHA platinum ATR spectrometer as neat material. NMR spectra were obtained on a Bruker Avance 300, 400 or 600 MHz instrument and are referenced to the residual proton signal of the deuterated solvent for ^1H spectra, and to the carbon multiplet of the deuterated solvent for ^{13}C spectra according to published values.[165] The chemical shifts are reported in ppm and the spectroscopic data are reported as follows: (multiplicity, number of protons, coupling constant), where s = singlet, d = doublet, t = triplet, q = quartet and dd = doublet of doublets. Mass spectra were recorded on Kratos/MsI Concept lS mass spectrometer at Brock University. Combustion analyses were performed by Atlantic Microlabs, Norcross, GA.

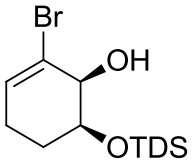
5.2 Detailed Experimental Procedures

(–)-(1*S*,2*S*)-3-Bromocyclohex-3-ene-1,2-diol (314).



A 3L three neck flask was charged with diol **6** (203 g, 1.06 mol) in MeOH (1L) and was cooled in freezing mixture. Potassium azodicarboxylate (PAD) (318 g, 1.59 mol) was added in four portions over 20 minutes followed by slow addition of AcOH (424 mL, 7.42 mol) in MeOH (1.2 L). Reaction mixture was stirred for 18 h and the pH of the reaction mixture was neutralized with sat. $NaHCO_3$. Product was extracted with EtOAc, washed with brine, dired over Na_2SO_4, and was evaporated under reduced pressure to obtain **314** as a white solid (198 g, 1.02, 96%). Data was matched with reported procedure.[127, 166]

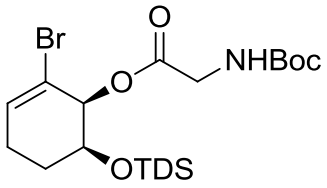
(–)-(1*S*,6*S*)-2-Bromo-6-(((2,3-dimethylbutan-2-yl)dimethylsilyl)oxy)cyclohex-2-enol (315).



Diol **314** (112 g, 0.58 mol) and imidazole (47g, 0.69 mol) was dissolved in CH_2Cl_2 (400 mL) and this mixture was cooled to –78 °C. A solution of TDSCl (114 g, 0.64 mol) in

CH_2Cl_2 (300 mL) was added to the raction mixture over a period of 15 min. The reaction mixture was allowed to warm to room temperature and was stirred for 48 h. White precipitate formed was dissolved in water and the organic phase was separated. It was then washed with 10% $CuSO_4$ solution (200 mLx3), brine, dried over Na_2SO_4, and was evaporated under reduced pressure to obtain **315** (166 g**,** 0.49 mol, 85%) as a thick colorless oil. It was taken to next step without further purification.

(–)-(1*S*,6*S*)-2-Bromo-6-(((2,3-dimethylbutan-2-yl)dimethylsilyl)oxy)cyclohex-2-en-1-yl 2-((tert-butoxycarbonyl)amino)acetate (317).

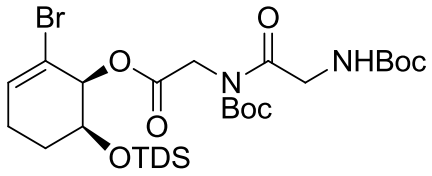


A solution of alcohol, **315** (125 g, 0.37 mol), DCC (84.6 g, 0.41 mol) and DMAP (4.5 g, 0.037 mol) in CH_2Cl_2 (350 mL) was cooled to –20 °C under argon atmosphere and a solution of Boc-glycine (72.0 g, 0.41 mol) in CH_2Cl_2 (350 mL) was cannulated to this reaction mixture over a period of 15 minutes. The reaction mixture was stirred for 14 hours warming to room temperature. Then the reaction mixture was diluted with Et_2O (200 mL) to preciptate dicyclohexyl urea, which was removed by filtration. Then the solvent was removed under reduced pressure, and the resulting crude mixture was subjected to silica gel chromatography with hexanes/EtOAc (90:10) as eluent to isolate the product **317** (167 g, 0.34 mol, 92%) as colorless oil.

317: R_f = 0.31 [hexane/EtOAc (90:10)]; $[\alpha]_D^{20}$ = –64.0 (*c* = 1.0, MeOH); IR (neat) *v* 3445, 2958, 1755, 1715, 1511 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.27 (dd, *J* = 5.2, 3.1 Hz,

1H), 5.59 (d, *J* = 3.9 Hz, 1H), 5.00 (bs, 1H), 3.97 (m, 3H), 2.39-2.19 (m, IH), 2.15-2.09 (m, IH), 1.85-1.62 (m, 2H), 1.43 (s, 9H), 0.84 (s, 3H), 0.82 (s, 3H), 0.77 (d, *J* = 1.9 Hz, 6H), 0.07 (d, *J* = 4.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 155.3, 134.8, 117.0, 79.6, 73.9, 69.2, 42.3, 34.0, 28.2, 25.5, 24.7, 22.6, 20.0, 18.5, −3.10, −3.15; LRMS (EI) *m/z* (%) 171 (7), 157 (9), 136 (34), 121 (9), 79 (10), 28 (100); HRMS (EI) calcd for $C_{21}H_{39}NSiBrO_5$: 492.1781. Found 492.1806; Anal. Calcd for $C_{21}H_{39}NSiBrO_5$: C, 51.21; H, 7.78. Found C, 51.41; H, 7.75.

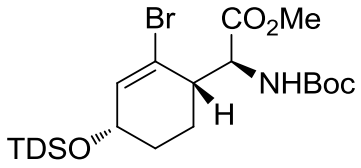
(1*S*,6*S*)-2-Bromo-6-(((2,3-dimethylbutan-2-yl)dimethylsilyl)oxy)cyclohex-2-en-1-yl 2-(*N*-(tert-butoxycarbonyl)-2-((tert-butoxycarbonyl)amino)acetamido)acetate (316).



A solution of alcohol, **315** (16.0 g, 47.7 mmol), DCC (17.7 g, 85.9 mmol) and DMAP (0.9 g, 7.16 mmol) in CH_2Cl_2 (30 mL) was cooled to –20 °C under argon atmosphere and a solution of Boc-glycine (13.4 g, 76.3 mmol) in CH_2Cl_2 (30 mL) was cannulated to this reaction mixture over a period of 15 minutes. The reaction mixture was stirred for 14 hours warming to room temperature. Then the reaction mixture was diluted with Et_2O (100 mL) to preciptate dicyclohexyl urea, which was removed by filtration. Then the solvent was removed under reduced pressure, resulting crude mixture was subjected to silica gel chromatography using hexanes/EtOAc (90:10) as eluent to isolate the product **316** (9.8 g, 15.1 mmol, 34%) as colorless oil.

316: R_f = 0.28 [hexane/EtOAc (90:10)]; $[\alpha]_D^{20}$ = –75.0 (*c* = 1.0, MeOH); IR (neat) *v* 3448, 2955, 1755, 1715, 1684, 1511 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.28 (dd, *J* = 4.8, 3.3 Hz, 1H), 5.56 (d, *J* = 3.6 Hz, 1H), 5.30-5.27 (m, 1H), 4.70 (d, *J* = 17.4 Hz, 1H), 4.51 (d, *J* = 5.1 Hz, 2H), 4.39 (d, *J* = 17.4 Hz, 1H), 3.99-3.94 (m, 1H), 2.32-2.23 (m, 1H), 2.12-2.04 (m, 1H), 1.86-1.63 (m, 2H), 1.62-1.55 (m, 1H), 1.52 (s, 9H), 1.45 (s, 9H), 0.88 (d, *J* = 2.4 Hz, 3H), 0.85 (d, *J* = 2.4 Hz, 3H), 0.82 (s, 3H), 0.81 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 167.7, 155.7, 151.5, 134.7, 117.1, 84.4, 79.2, 74.0, 69.2, 46.7, 45.0, 33.9, 28.3, 27.8, 25.8, 25.6, 24.8, 20.1, 20.0, 18.5, 18.4, –3.0, –3.1;

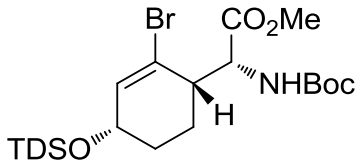
(–)-(*S*)-Methyl 2-((1*S*,4*S*)-2-bromo-4-(((2,3-dimethylbutan-2-yl)dimethylsilyl)oxy) cyclohex-2-en-1-yl)-2-((tert-butoxycarbonyl)amino)acetate (9a).



A solution of glycinate ester **317** (55 g, 0.11 mol) in THF (200 mL) along with a solution of $ZnCl_2$ (18.3 g, 0.13 mol) in THF (200 mL) was added dropwise to freshly prepared LDA (0.31 mol) in THF (400 mL) at –78 °C over a period of 2 hours. The reaction mixture was slowly warmed to room temperature and stirred for 18 hours. The reaction mixture was then diluted with Et_2O (800 mL), quenched with H_2O (25 mL), and the pH value was adjusted to approximately 2.5 using 1 N HCl at 0 °C. The organic layer was separated, aqueous layer was washed with Et_2O (3 x 500 mL), combined organic washes were dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to provide amino acid **319** as a mixture of two diastereomers. A solution of excess of

diazomethane in Et_2O (generated from *N*,*N*-nitrosomethylurea and 50% aqueous KOH solution) was treated with the crude amino acid solution in Et_2O at 0 °C, and the resulting diastereomeric mixture of esters was separated by column chromatography on silica gel with hexane/EtOAc (95:5) as eluent to yield **9a** and **9b** (36 g, 1:1.8 ratio, 0.07 mol, 65% combined yield) as a colorless oil.

9a: R_f = 0.14 [hexane/EtOAc (95:5)]; $[\alpha]_D^{20}$ = –27.7 (*c* = 1.0, $CHCl_3$); IR ($CHCl_3$) *v* 3443, 2956, 2868, 1749, 1715, 1503 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.27 (dd, *J* = 5.6, 1.3 Hz, 1H), 4.81-4.73 (m, 2H), 4.12-4.09 (m, 1H), 3.71 (s, 3H), 2.96 (bs, 1H), 1.86-1.76 (m, 1H), 1.63-1.50 (m, 4H), 1.40 (s, 9H), 0.86 (d, *J* = 6.9 Hz, 6H), 0.80 (s, 6H), 0.06 (d, *J* = 5.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 155.4, 135.5, 127.9, 79.7, 65.4, 55.2, 52.2, 43.7, 34.1, 29.5, 28.2, 24.8, 20.2, 19.9, 18.5, –2.6, –3.0; LRMS (EI) *m/z* (%) 370 (13), 366 (38), 364 (37), 348 (16), 346 (15), 231 (24), 229 (24), 162 (95), 75 (100); HRMS (EI) calcd for $C_{22}H_{41}NSiBrO_5$: 506.1920. Found 506.1937; Anal. Calcd for $C_{22}H_{41}NSiBrO_5$: C, 52.16; H, 7.96. Found C, 52.34; H, 8.01.

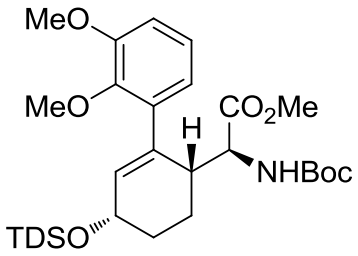


9b: colorless liquid; R_f = 0.16 [hexane/EtOAc (95:5)]; $[\alpha]_D^{20}$ = –55.7 (*c* = 1.0, $CHCl_3$); IR ($CHCl_3$) *v* 3439, 2955, 2867, 1753, 1720, 1498, 1365, 1251, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.30 (dd, *J* = 5.6, 1.3 Hz, 1H), 5.21 (d, *J* = 8.6 Hz, 1H), 4.68 (dd, *J* = 8.7, 2.3 Hz, 1H), 4.11-4.09 (m, 1H), 3.71 (s, 3H), 3.05 (bs, 1H), 1.86-1.78 (m, 2H), 1.63-1.50 (m, 3H), 1.43 (s, 9H), 0.84 (d, *J* = 6.9 Hz, 6H), 0.80 (s, 6H), 0.05 (d, *J* = 5.3 Hz,

6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 155.4, 136.3, 125.5, 80.0, 66.7, 55.9, 52.3, 45.1, 34.1, 29.2, 28.3, 25.8, 24.7, 23.4, 20.2, 18.6, -2.7, -2.9; HRMS (EI) calcd for $C_{20}H_{36}NSiBrO_5$: 506.1920. Found 506.1937; Anal. Calcd for $C_{20}H_{36}NSiBrO_5$: C, 52.16; H, 7.96. Found C, 52.28; H, 8.06.

To a solution of pure **9b** (26.5 g, 0.52 mol) in THF (250 ml), DBU (4.01 g, 0.26 mol) was added and the reaction mixture was heated to reflux for 36 hours. Chromatographic separation on silica gel using hexane/EtOAc (95:5) as eluent yielded **9a** as a colorless liquid (10 g, 0.02 mol, 39%) along with **9b** (colorless liquid, 12.8 g, 0.025 mol, 49%). After separation (as above) this process was repeated to convert all of **9b** into **9a**.

(+)-(*S*)-Methyl 2-((tert-butoxycarbonyl)amino)-2-((2*R*,5*S*)-5-(((2,3-dimethylbutan-2-yl)dimethylsilyl)oxy)-2',3'-dimethoxy-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-yl)acetate (337).

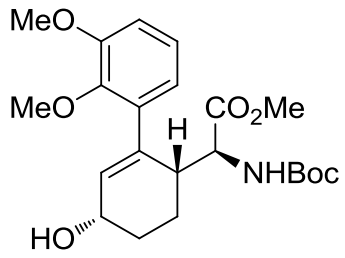


Methyl ester **9a** (8.2 g, 16.2 mmol) was taken in a flame dried flask with boronic acid[132] (3.54 g, 19.42 mmol), Cs_2CO_3 (7.92 g, 24.3 mmol) and $Pd(dppf)_2Cl_2$ (1.3 g, 1.62 mmol) was added and was immediately evacuated under vacuum for 20 minutes after connecting to a reflux condenser. The reaction flask was purged with argon, THF (100 mL) was added and the reaction mixture was heated to reflux for 12 hours. Then the reaction mixture was cooled to room temperature and was filtered through a pad of celite, washed

several times with CH_2Cl_2 and the dark brown solution obtained was evaporated under reduced pressure to obtain the crude product as black dense oil. Chromatographic separation of crude product on silica gel using [hexane/EtOAc (90:10) → hexane/EtOAc (80:20)] as eluent yielded **337** (9 g, 15.9 mmol, 98%) as a colorless liquid.

337: R_f = 0.24 [hexane/EtOAc (80:20)]; $[\alpha]_D^{20}$ = +14.7 (*c* = 0.57, $CHCl_3$); IR (neat) *v* 3449, 3019, 2956, 2401, 1748, 1716 cm^{-1}; ^{I}H NMR (300 MHz, $CDCl_3$) δ 6.97 (t, *J* = 7.9 Hz, 1H), 6.82 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 5.77 (dd, *J* = 3.9, l.5 Hz, 1H), 5.71 (d, *J* = 9.7 Hz, 1H), 4.33 (dd, *J* = 9.7, 2.3 Hz, 1H), 4.24 (m, 1H), 3.85 (s, 6H), 3.23 (s, 1H), 1.74 (m, 2H), 1.74 (q, *J* = 6.9 Hz, 1H), 1.55 (bs, 4H), 1.42 (s, 9H), 0.91 (dd, *J* = 6.8, 0.9 Hz, 6H), 0.85 (s, 7H), 0.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 155.2,152.3, 146.2, 139.5, 134.6, 132.5, 124.1, 122.0, 11l.8, 79.3, 63.4, 60.6, 55.7, 54.7, 52.1, 38.4, 34.4, 30.1, 28.4, 24.9, 20.5, 18.7, 17.9, -2.3, -2.8; LRMS (FAB + NBA matrix) *m/z* (%) 404 (10), 375 (17), 287 (68), 227 (55); HRMS (FAB + NBA matrix) calcd for $C_{30}H_{49}NO_7Si$: 506.2574. Found 506.2538.

(+)-(*S*)-Methyl 2-((tert-butoxycarbonyl)amino)-2-((2*R*,5*S*)-5-hydroxy-2',3'-dimetho-xy-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-yl)acetate (338).

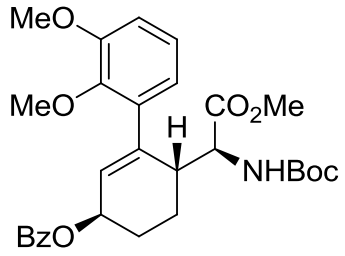


To a stirred solution of silylether **327** (9 g, 15.9 mmol) in THF (100 mL) was added tetra-*n*-butylammonium fluoride (TBAF) (19.6 mL, 19.6 mmol, 1M solution in THF) dropwise

at room temperature. The resulting solution was stirred for 16 h and the solvent was evaporated under reduced pressure to obtain the crude product, which was separated by column chromatography on silica gel with hexane/EtOAc (50:50) as eluent to yield free alcohol **338** (6.2 g, 14.7 mmol, 92%) as a white solid.

338: R_f = 0.30 [hexane/EtOAc (50:50)]; mp 65-68 ^{o}C (EtOAc/hexane); $[\alpha]_D^{20}$ = +39.2 (*c* = 1.0, $CHCl_3$); IR (neat) *v* 3354,3015,2938, 1709, 1523 cm^{-1}; ^{I}H NMR (300 MHz, $CDCl_3$) δ 6.98 (t, *J* = 7.9 Hz, 1H), 6.83 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.68 (d, *J* = 7.5 Hz, 1H), 5.89 (dd, *J* = 3.9, 1.4 Hz, 1H), 5.56 (d, *J* = 9.7 Hz, 1H), 4.3 (dd, *J* = 9.7, 2.5 Hz, 1H), 4.28 (m, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.47 (q, *J* = 7.0 Hz, 1H), 3.37 (bs, 1H), 3.30 (s, 3H), 1.92 (m, 4H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.7, 155.2, 152.2, 146.1, 141.7, 134.4, 131.0, 124.0, 122.1, 112.0, 76.6, 63.5, 60.6, 55.8, 54.9, 52.1, 39.1, 30.0, 28.3, 18.8; LRMS (EI) *m/z* (%) 303 (13), 216 (100), 200 (24), 185 (9); HRMS (EI) Calcd. for $C_{22}H_{31}NO_7$: 421.2101. Found: 421.2077. Anal. Calcd for $C_{22}H_{31}NO_7$: C, 62.69; H, 7.41. Found: C, 62.65; H, 7.46.

(+)-(3*R*,6*R*)-6-((*S*)-1-((*tert*-Butoxycarbonyl)amino)-2-methoxy-2-oxoethyl)-2',3'-dimethoxy-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl benzoate (339).

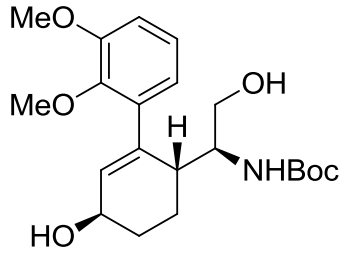


Mitsunobu reagent was prepared by the addition of diethyl azodicarboxylate (DEAD) (3.5 mL, 22.1 mmol) to PBu_3 (5.5 mL, 22.1 mmol) in THF at 0 °c and was stirred for 15

minutes. It was then cannulated to a stirred solution of alcohol **338** (6.2 g, 14.7 mmol) and benzoic acid (2.2 g, 17.7 mmol) in THF at 0 °c and was stirred for 4 hours while the reaction mixture was allowed to warm to room temperature. Then the solvent was removed under reduced pressure and the resulting oil was separated by column chromatography on silica gel using hexane/EtOAc (80:20) as eluent to yield the product **339** as a white solid (7.3 g, 13.9 mmol, 95%).

339: R_f = 0.27 [hexane/EtOAc (70:30)]; mp 57-60 °C (EtOAc/hexane); $[\alpha]_D^{20}$ = +130.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* =7.2 Hz, 2H), 7.54 (t, *J* =7.4 Hz, 1H), 7.42 (t, *J* = 5.6 Hz, 2H), 6.98 (t, *J* = 7.9 Hz, 1H), 6.83 (dd, *J* = 1.5, 8.0 Hz, 1H) 6.70 (dd, *J* = 1.1, 7.2 Hz, 1H), 5.9 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.53 (s, 1H), 3.26 (s, 3H), 2.22 (m, 2H), 1.86 (m, 2H), 1.55 (s, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 166.3, 156.2, 152.8, 146.2, 139.2, 135.1, 133.0, 129.7, 128.4, 123.8, 122.2, 112.1, 61.4, 56.0, 51.8, 40.9, 28.5, 26.9, 24.8; LRMS (EI) *m/z* (%) 525 (3), 403 (8), 303 (21), 260 (50), 216 (100); HRMS (EI) calcd for $C_{29}H_{35}NO_5$: 525.2363. Found 525.2369; Anal. Calcd for $C_{29}H_{35}NO_5$: C, 66.27; H, 6.71. Found C, 65.76; H, 6.88.

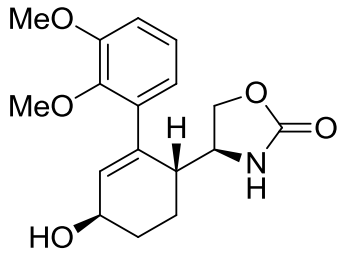
(+)-*tert*-Butyl ((*S*)-2-hydroxy-1-((2*R*,5*R*)-5-hydroxy-2',3'-dimethoxy-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-yl)ethyl)carbamate (340).



To a suspension of lithium aluminum hydride (1.7 g, 45.66 mmol) in THF (200 mL) at 0 °C was added a solution of ester **339** (7.3 g, 13.8 mmol) in THF (200 mL) in a dropwise manner. The reaction mixture was slowly warmed to room temperature and was stirred for 2 hours. The reaction mixture was again cooled to 0 °C and 1.5 mL of H_2O was added followed by 1.5 mL of 15% of aqueous NaOH solution and 4.5 mL of H_2O. The reaction mixture was filtered through a pad of Celite and washed several times with CH_2Cl_2. Solvent was evaporated under reduced pressure to provide the crude product, which was chromatographed on silica gel with [hexane/EtOAc (50:50) → EtOAc (100)] as eluent to yield the product **340** as a white solid (4.6 g, 11.7 mmol, 84%).

340: R_f = 0.21 [hexane/EtOAc (20:80)]; mp 61-65 °C (EtOAc/hexane); $[\alpha]_D^{20}$ = +91.0 (*c* = 1.0, $CHCl_3$); IR (neat) *v* 3384, 2938, 1696, 1577, 1472 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.89 (s, 2H), 6.54 (dd, *J* = 6.4, 1.8 Hz, 1H), 6.00 (d, *J* = 8.7 Hz, 1H), 5.56 (s, 1H), 4.70 (d, *J* = 5.3 Hz, 1H), 4.54 (t, *J* = 5.4 Hz, 1H), 4.18 (d, *J* = 3.7 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.16 (m, 4H), 1.97 (m, 1H), 1.74 (m, 1H), 1.32 (s, 9H), 1.12 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 152.1, 146.0, 139.9, 136.6,.135.4, 124.0, 122.3, 111.7, 77.7, 66.0, 61.5, 60.2, 56.0, 53.0, 37.1, 32.0, 28.7, 20.2; LRMS (EI) *m/z* (%) 321 (5), 264 (20), 244 (15), 216 (100); HRMS (EI) calcd for $C_{21}H_{29}NO_5$: 375.2046. Found 375.2039; Anal. calcd for $C_{21}H_{29}NO_5$: C, 64.10; H, 7.94. Found C, 63.83; H, 8.24.

(–)-(*S*)-4-((2*R*,5*R*)-5-Hydroxy-2',3'-dimethoxy-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-yl)oxazolidin-2-one (341).

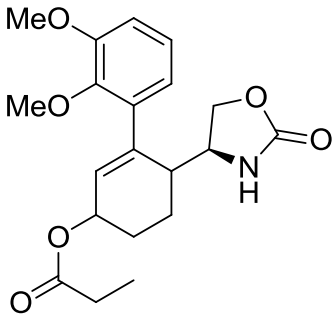


A solution of NaH (0.7 g, 29.23 mmol) in DMF (30 mL) was cooled to 0 °C and a solution of alcohol **340** (4.6 g, 11.7 mmol) in DMF (30 mL) was added *via* a cannula. The reaction mixture was stirred for 30 minutes at 0 °C and was taken to room temperature and was stirred for 14 hours. The reaction mixture was diluted with brine solution (50 mL) and washed with a mixture of $CHCl_3$/EtOH (3:1). The organic layer was then dried over Na_2SO4 and the solvent was evaporated under reduced pressure to provide the crude product. Silica gel column chromatography of crude mixture using EtOAc provides the product **341** (3.7 g, 11.6 mmol) as an off white solid.

341: R_f = 0.29 [EtOAc]; mp 63-65 °C (CH_2Cl_2/hexane); $[\alpha]_D^{20}$ = –46.2 (*c* = 1.8, $CHCl_3$); IR (neat) *v* 3368, 2936, 1747, 1576 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (t, *J* = 7.9 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.67 (dd, *J* = 7.6, 1.2 Hz, 1H), 5.87 (m, 1H), 4.41 (m, 1H), 4.16 (m, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.55 (t, *J* = 4.7 Hz, 1H), 2.76 (bs, 1H), 2.27 (m, 1H), 1.67 (m, 1H), 1.59 (m, 1H), 1.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 152.9, 145.7, 134.7, 124.8, 121.0, 111.7, 71.6, 71.1, 67.3, 67.0, 61.9, 61.4, 55.8, 53.3, 42.1, 31.7, 31.2, 19.3, 14.2; LRMS (EI) *m/z* (%) 301 (4), 216 (49), 200 (14), 87 (87);

HRMS (EI) calcd for $C_{17}H_{21}NO_5$: 301.1314. Found 301.1310; Anal. calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63. Found C, 62.21; H, 6,87 [$(C_{17}H_{21}NO_5)_2$.EtOAc].

3-(2,3-Dimethoxyphenyl)-4-((*S*)-2-oxooxazolidin-4-yl)cyclohex-2-enylpropionate (342).

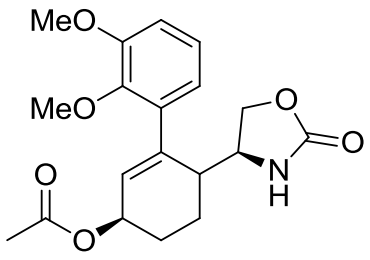


A solution of alcohol **341** (100 mg, 0.31 mmol) and propanoic acid (0.20 mL) in triethyl orthoacetate (2 mL) was heated at 140 °C for 18 h under argon atmosphere. The solvent was removed *in vacuo* by heating in an oil bath, the crude reaction mixture obtained was purified by column chromatography on silica gel hexane/EtOAc/Et_3N (70:29:1) to obtain **342** (25 mg, 0.07 mmol, 21%) as a colorless oil.

342: R_f = 0.46 [hexane/EtOAc (70:30)]; IR ($CHCl_3$) ν 3456, 3005, 2942, 2829, 1755, 1472 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 (t, J = 8.1 Hz, 1H), 6.88 (dd, J = 8.1, 1.2 Hz, 1H), 6.63 (dd, J = 7.5, 1.2 Hz, 1H), 5.93 (dd, J = 4.5, 1.8 Hz, 1H), 5.39 (d, J = 3.3 Hz, 1H), 5.31 (t, J = 3.9 Hz, 1H), 4.25 (t, J = 9.0 Hz, 1H), 4.11 (dd, J = 9.0, 5.1 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 1H), 3.75 (s, 3H), 2.65 (s, 1H), 2.36 (dd, J = 15.0, 7.5 Hz, 2H), 2.04-2.01 (m, 1H), 1.90-1.85 (m, 2H), 1.69 (bs, 1H), 1.16 (t, J = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.3, 159.1, 152.9, 145.5, 141.6, 135.2, 130.6, 128.4, 124.9, 124.8,

120.9, 120.8, 111.9, 67.6, 66.2, 61.3, 55.8, 53.3, 53.1, 42.1, 41.9, 42.21, 41.9, 27.9, 26.7, 17.1, 9.3; HRMS (EI) calcd for $C_{20}H_{25}NO_6$: 375.1682. Found 375.1679.

(1*R*)-3-(2,3-Dimethoxyphenyl)-4-((*S*)-2-oxooxazolidin-4-yl)cyclohex-2-enyl acetate (348).

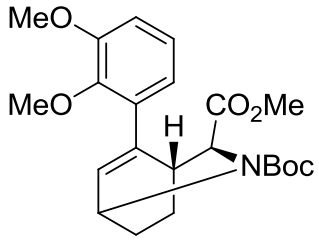


Alcohol **341** (210 mg, 0.66 mmol) and acetic anhydride (0.08 mL, 0.79 mmol) were taken in pyridine (4 mL) and DMAP (8.6 mg, 0.07 mmol) was added and stirred for 18 h. Then the raction mixture was diluted with CH_2Cl_2 and was washed with dilute acid. The organic layer was washed with sat. $NaHCO_3$ solution, brine, and dried over Na_2SO_4. Solvent was evaporated under reduced pressure and was purified by silica gel column chromatography hexane/EtOAc (50:50) to obtain **348** (127 mg, 0.35 mmol, 53%) as a white solid.

348: R_f = 0.20 [hexane/EtOAc (50:50)]; mp 66-68 $^{\circ}$C (EtOAc/hexane); $[\alpha]_D^{20}$ = +12.3 (*c* = 1.0, $CHCl_3$); IR ($CHCl_3$) ν 3454, 3027, 3008, 2937, 2871, 2838, 1753, 1469 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (t, *J* = 8.1 Hz, 1), 6.85 (dd, *J* = 8.4, 1.5 Hz, 1H), 6.66 (dd, *J* = 7.5, 1.2 Hz, 1H), 5.79 (d, *J* = 9.9 Hz, 1H), 5.41-5.37 (m, 1H), 4.19-4.01 (m, 2H), 3.85 (s, 3H), 3.77 (s, 3H), 3.75-3.72 (m, 1H), 2.79 (bs, 1H), 2.21 (t, *J* = 4.5 Hz, 1H), 2.05 (m, 4H), 1.72-1.66 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 159.2, 152.9, 145.6, 139.6, 135.0, 130.5, 124.8, 120.9, 111.9, 69.3, 67.3, 61.4, 55.8, 53.3, 41.8, 27.0, 21.3,

19.3; HRMS (EI) calcd for $C_{19}H_{23}NO_6$: 361.1525. Found 361.1526; Anal. Calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41. Found C, 60.74; H, 6.39 [$(C_{19}H_{23}NO_6)_{7}.CHCl_3$].

(3*S*)-2-*tert*-Butyl 3-methyl 5-(2, 3-dimethoxyphenyl)-2-azabicyclo [2.2.2] oct-5-ene-2, 3-dicarboxylate (350).

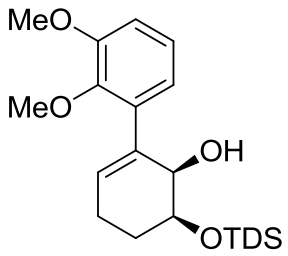


Compound **338** (50 mg, 0.12 mmol) was dissolved in CH_2Cl_2 (3 mL) and the temperature was lowered to −20 ^{0}C. Then Burgess reagent (34 mg, 0.14 mmol) was added and then the reaction was allowed to warm to room temperature. The reaction was stirred for 20h and then washed with $NaHCO_3$, brine and dried with Na_2SO_4. Solvent was evaporated under reduced pressure to obtain crude product and pure product was separated by column chromatography on silica gel with hexane/EtOAc (50:50) as eluent to yield **350** (37 mg, 0.09 mmol, 77%) as a white dense oil.

350: R_f = 0.50 [hexane/EtOAc (50:50)]; IR ($CHCl_3$) ν 3007, 2976, 2940, 2873, 2837, 1749, 1684, 1470, 1400 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, rotameric) δ 7.01 (t, J = 7.8 Hz, 1H) 6.89-6.86 (m, 1H), 6.81-6.78 (m, 1H), 6.56-6.53 (m, 1H), 4.89 (dd, J = 6.0, 3.0 Hz, 0.7H), 4.75 (m, 0.3H), 4.11 (s, 0.3H), 4.05 (s, 0.7H), 3.87 (s, 3H), 3.81 (s, 3H), 3.74 (s, 3H), 3.34 (s, 0.3H), 3.28 (s, 0.7H), 2.21-2.16 (m, 1H), 1.07-1.1.67 (m, 1H), 1.54-1.48 (m, 2H), 1.38 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.2, 171.7, 154.5, 154.1, 152.9, 146.6, 146.5, 144.4, 144.3, 133.4, 130.5, 130.1, 124.0, 123.9, 121.1, 112.1, 79.9, 79.8,

60.6, 59.4, 58.9, 55.9, 52.0, 51.9, 47.2, 45.7, 38.7, 38.4, 30.9, 29.7, 28.5, 28.3, 25.8, 18.9, 18.8; HRMS (EI) calcd for $C_{22}H_{29}NO_6$: 403.1995. Found 403.1991.

(–)-(1*R*,6*S*)-2-(2,3-Dimethoxyphenyl)-6-((2,3-dimethylbutan-2-yl)dimethyl silyloxy)-cyclohex-2-enol (355).

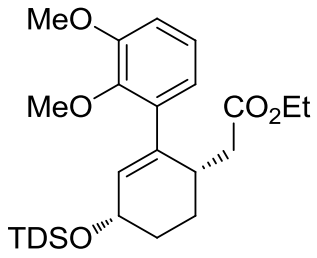


Compound **315** (1 g, 2.98 mmol), boronic acid (1.09 g, 5.96 mmol), Cs_2CO_3 (1.94 g, 5.96 mmol) and $Pd(dppf)_2Cl_2$ (0.49 g, 0.60 mmol) were taken in THF (15 mL) and purged with argon and was heated to reflux. Reaction was stirred for 5 h and then solvent was evaporated on a rotary evaporator. Reaction mixture was diluted with CH_2Cl_2 and was passed through a pad of celite. Solvent was evaporated under educed pressure to obtain the crude product. Pure product was separated by column chromatography on silica gel with hexane/EtOAc (80:20) as eluent to yield **355** (0.87 g, 2.2 mmol, 80%) as a colorless oil.

355: R_f = 0.37 [(hexane/EtOAc (80:20)]; $[\alpha]_D^{20}$ = −74.6 (*c* = 1.0, $CHCl_3$); IR ($CHCl_3$) ν 3544, 3004, 2956, 2866, 2838, 1424 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (t, *J* = 8.1 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 2H), 5.88 (t, *J* = 3.6 Hz, 1H), 4.47 (t, *J* = 3.6 Hz, 1H), 4.04-3.98 (m, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 2.65 (d, *J* = 3.9 Hz, 1H), 2.39-2.18 (m, 2H), 2.02-1.89 (m, 1H), 1.73-1.60 (m, 2H), 0.92-0.87 (m, 12H), 0.17 (d, *J* = 5.4 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.6, 146.4, 136.4, 136.0, 129.7, 123.9, 122.4, 11.4, 70.9,

69.3, 60.6, 55.8, 34.3, 25.5, 24.9, 24.3, 20.4, 20.2, 18.7, 18.6, -2.5, -2.9; HRMS (EI) calcd for $C_{22}H_{36}O_4Si$: 392.2383. Found 392.2379; Anal. Calcd for $C_{22}H_{36}O_4Si$: C, 67.30; H, 9.24. Found C, 67.29; H, 9.27.

(+)-Ethyl 2-((1*S*,4*S*)-2-(2,3-dimethoxyphenyl)-4-((2,3-dimethylbutan-2-yl)dimethyl silyloxy)cyclohex-2-enyl)acetate (356).

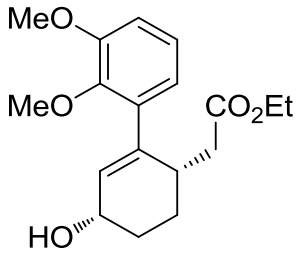


Compound **355** (40 mg, 0.10 mmol) was taken in triethyl ortho acetate (5 mL) and micro spatula of activated 4A^o molecular sieves were added along with catalytic amount of propionic acid (5 μL). The mixture was heated at 150 ^{o}C in a sealed tube filled with argon for two days. Then the reaction mixture was passed through a pad of celite and washed with EtOAc, 2 drops of triethyl amine was added to the filtrate and was evaporated. Solvent was removed by azeotropic distillation with toluene, product was separated by column chromatography on silica gel with hexane/EtOAc (90:10) as eluent afforded **356** (23 mg, 0.05 mmol, 52%) as a colorless oil.

356: R_f = 0.27 [hexane/EtOAc (90:10)]; $[\alpha]_D^{20}$ = +9.2 (*c* = 1.0, $CHCl_3$); IR ($CHCl_3$) ν 3026, 2957, 2867, 2842, 1725, 1470 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (t, *J* = 7.8 Hz, 1H), 6.83 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.71 (dd, *J* = 7.8, 1.5 Hz, 1H), 5.69 (dd, *J* = 3.0, 1.5 Hz, 1H), 4.32-4.27 (m, 1H), 4.02 (q, *J* = 7.2 Hz, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 3.11 (dd, *J* = 10.5, 5.1 Hz, 1H), 2.33-2.08 (m, 2H), 1.89-1.59 (m, 5H), 1.18 (t, *J* = 7.2 Hz, 3H),

0.89 (d, J = 6.9 Hz, 6H), 0.85 (s, 6H), 0.11 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.9, 152.7, 146.5, 140.4, 135.9, 131.9, 123.8, 122.2, 111.4, 66.5, 60.7, 60.1, 55.8, 38.2, 34.3, 29.1, 24.9, 24.8, 20.4, 20.3, 18.6, 14.2, -2.5, -2.6; HRMS (EI) calcd for $C_{26}H_{42}O_5Si$: 462.2802. Found: 462.2798; Analysis Calcd for $C_{26}H_{42}O_5Si$: C, 67.49; H, 9.15. Found C, 67.61; H, 9.15.

(+)-Ethyl 2-((1*S*,4*S*)-2-(2,3-dimethoxyphenyl)-4-hydroxycyclohex-2-enyl)acetate (357).

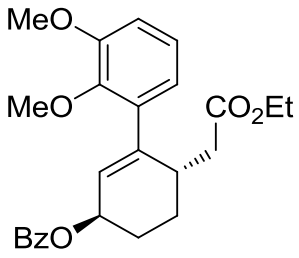


TBAF (0.24 mL, 0.24 mmol) in THF (1.5 mL) was added to a solution of **356** (88 mg, 0.19 mmol) in THF (1.5 mL) at room temperature and was stirred for 18 h. Solvent was evaporated under reduced pressure and the product was purified by silicagel column chromatography using hexane/EtOAc (70:30) as eluent to yield **357** (52 mg, 0.16 mmol, 86%) as a pale yellow oil.

357: R_f = 0.45 [hexane/EtOAc (30:70)]; $[\alpha]_D^{20}$ = +50.2 (c = 1.0, $CHCl_3$); IR ($CHCl_3$) ν 3607, 3007, 2935, 2868, 2837, 1723, 1467 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (t, J = 7.8 Hz, 1H), 6.83 (dd, J = 8.4, 1.5 Hz, 1H), 6.68 (dd, J = 7.5, 1.5 Hz, 1H), 5.79 (dd, J = 3.9, 1.5 Hz, 1H), 4.30 (d, J = 4.2 Hz, 1H), 4.00 (q, J = 7.2 Hz, 2H), 3.84 (s, 3H), 3.77 (s, 3H), 3.16-3.11 (m, 1H), 2.33-2.10 (m, 3H), 1.94-1.85 (m, 2H), 1.79-1.69 (m, 2H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7, 152.5, 146.2, 142.7, 135.7, 130.1,

123.9, 122.2, 111.6, 65.5, 60.7, 60.2, 55.8, 37.9, 34.2, 29.1, 24.2, 14.2; LRMS (EI) *m/z* (%) 320 (14), 289 (12), 232 (44), 215 (33), 214 (100), 199 (18), 160 (16), 175 (30); HRMS (EI) calcd for $C_{18}H_{24}O_5$: 320.1624. Found 320.1618.

(3*R*,6*S*)-6-(2-Ethoxy-2-oxoethyl)-2',3'-dimethoxy-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl benzoate (358).

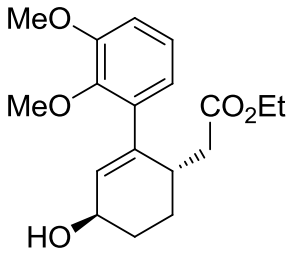


Mitsunobu reagent was prepared by the addition of diethyl azodicarboxylate (0.21 mL, 1.30 mmol) to PBu_3 (0.24 mL, 1.3 mmol) in THF (4 mL) at 0 °C and was stirred for 15 minutes. It was then cannulated to a stirred solution of alcohol **357** (284 mg, 0.89 mmol) and benzoic acid (130 mg, 1.06 mmol) in THF (4 mL) at 0 °C and stirred for 2 hours during which the reaction mixture was allowed to warm to room temperature. The solvent was removed under reduced pressure and the resulting oil was purified by silica gel column chromatography using hexane/EtOAc (80:20) as eluent to yield the product **358** (235 mg, 0.55 mmol, 62%) as colorless oil.

358: R_f = 0.37 [hexane/EtOAc (80:20)]; $[\alpha]_D^{20}$ = +147.2 (*c* = 1.0, $CHCl_3$); IR (neat) *v* 3025, 3004, 2939, 2870, 2836, 1711, 1600, 1578, 1470, 1270 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04-8.02 (m, 2H), 7.57-7.51 (m, 1H), 7.45-7.39 (m, 2H), 7.00 (t, *J* = 8.1 Hz, 1H); 6.85 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.72 (dd, *J* = 7.8, 1.5 Hz, 1H), 5.87-5.85 (m, 1H), 5.67-5.63 (m, 1H), 4.03 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 3.36-3.31 (m, 1H),

2.37-2.32 (m, 1H), 2.26-2.08 (m,1H), 1.95-1.86 (m, 1H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 166.2, 152.6, 146.2, 144.4, 135.6, 132.8, 130.6, 129.6, 128.4, 128.3, 126.6, 124.0, 122.1, 111.8, 69.5, 60.8, 60.2, 55.8, 37.9, 34.3, 26.0, 25.1, 14.2; LRMS (EI) *m/z* (%) 424 (2), 215 (21), 214 (74), 200 (11), 122 (15), 105 (100)77 (20); HRMS (EI) calcd for $C_{25}H_{28}O_6$: 424.1886. Found 424.

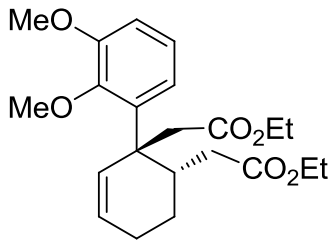
Ethyl 2-((2S,5R)-5-hydroxy-2',3'-dimethoxy-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-yl)acetate (359).



A solution of NaOEt in EtOH (5 mL, 0.02 M) was added to a solution of benzoate **358** (86 mg, 0.20 mmol) in EtOH (2 mL) at room temperature. The reaction mixture was stirred for 2 hours and then the reaction mixture was made neutral pH with acidic resin. Filtration and purification using silica gel column chromatography using hexane/EtOAc (50:50) as eluent to yield the product **359** (27 mg, 0.08 mmol, 42%) as colourless oil and the data was matched with the reported compound. **359:** R_f = 0.28 [hexane/EtOAc (50:50)]; $[\alpha]_D^{20}$ = +101.4 (c = 1.40, $CHCl_3$) [lit[104] $[\alpha]_D^{23}$ = +94.4 (c = 1.37, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (t, J = 8.1 Hz, 1H), 6.84 (dd, J = 8.1, 1.2 Hz, 1H), 6.68 (dd, J = 7.8, 1.5 Hz, 1H), 5.77 (t, J = 2.4 Hz, 1H), 4.34 (bs, 1H), 4.01 (q, J = 7.2 Hz, 2H), 3.89 (s, 3H), 3.79 (s, 3H), 3.24-3.19 (m, 1H), 2.30 (dd, J = 15.6, 3.9 Hz, 1H), 2.10-1.99

(m, 3H), 1.67-1.47 (m, 2H), 1.17 (t, J = 7.2 Hz, 3H); HRMS (EI) calcd for $C_{18}H_{24}O_5$: 320.1614. Found 320.1618.

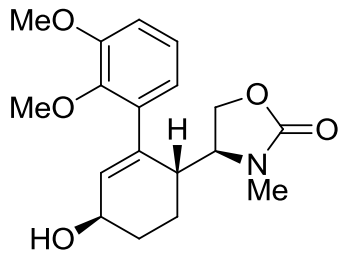
Diethyl 2,2'-((1R,2S)-2',3'-dimethoxy-1,2,3,4-tetrahydro-[1,1'-biphenyl]-1,2-diyl) diacetate (360).



Alcohol **359** (25 mg, 0.08 mmol) was dissolved in triethyl orthoacetate (7 mL) and 2-nitrophenol (0.5 mg, 0.004 mmol) was added in a sealed tube and was heated to 140 °C for 3 days. Then the reaction mixture was diluted with sat. $NaHCO_3$ solution and dried over Na_2SO_4. Triethyl orthoacetate was removed by azeotropy with toluene to get the crude product which was purified by silica gel column chromatography using [hexane/EtOAc (90:10) → hexane/EtOAc (30:70)] as eluent to yield the product **360** (10 mg, 0.03 mmol, 33%) as light yellow oil and the data was matched with the reported compound.[104]

360: R_f = 0.28 [hexane/EtOAc (70:30)]; $[\alpha]_D^{20}$ = –69.3 (c = 0.48, $CHCl_3$) [lit.[104] $[\alpha]_D^{27}$ = –53.5 (c = 0.61, $CHCl_3$); 6.96-6.81 (m, 3H), 6.13 (d, J = 10.5 Hz, 1H), 5.89-5.82 (m, 1H), 4.02 (q, J = 7.2 Hz, 2H), 3.96-3.90 (m, 5 H), 3.84 (s, 3H), 3.64 (d, J = 15.0 Hz, 1H), 2.89 (d, J = 15 Hz, 1H), 2.74-2.70 (m, 1H), 2.12-2.03 (m, 3H), 1.95-1.81 (m,1H), 1.58-1.52 (m, 1H), 1.18 (t, J = 7.2 Hz, 3H), 1.03 (t, J = 7.2 Hz, 3H); HRMS (EI) calcd for $C_{22}H_{30}O_6$: 390.2035. Found 390.2037.

(+)-(*S*)-4-((1*R*,4*R*)-2-(2,3-Dimethoxyphenyl)-4-hydroxycyclohex-2-enyl)-3-methyloxazolidin-2-one (362).

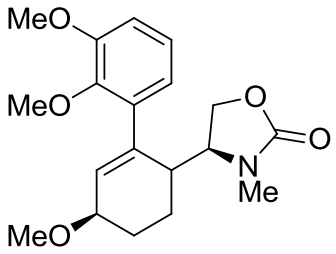


The alcohol **341** (2.2 g, 6.89 mmol) was added to a suspension of NaH (0.5 g, 20.67 mmol) in THF (30 mL) at room temperature and stirred for 1 hour. Then MeI (64.7mg, 0.46) was added in THF (30 mL) *via* an addition funnel and was stirred overnight. Then the reaction was quenched with water, acidified to neutral pH, extracted with CH_2Cl_2, dried over Na_2SO_4, evaporated on a rotary evaporator and dried under reduced pressure to obtain the crude product, which was purified by flash column chromatography (EtOAc) to provide **362** (1.28 g, 3.8 mmol, 56%) as a light yellow solid along with **361** (0.75 g, 2.16 mmol, 31%) as white solid.

362: R_f = 0.14 [hexane/EtOAc (70:30)]; mp 60-62 °C (EtOAc/hexane); $[\alpha]_D^{20}$ = +92.2 (*c* = 1.0, $CHCl_3$); IR ($CHCl_3$) *ν* 3603, 3012, 2961, 2939, 2866, 2836, 1744, 1576, 1473, 1451, 1264, 1236 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.05 (t, *J* = 8.1 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.73 (dd, *J* = 7.5, 1.2 Hz, 1H), 5.89 (s, 1H), 4.39-4.34 (m, 1H), 4.26 (t, *J* = 9.0 Hz, 1H), 4.00-3.95 (m, 1H), 3.87 (s, 3H), 3.78-3.72 (m, 1H), 3.69 (s, 3H), 3.19-3.15 (m, 1H), 2.63 (s, 3H), 2.18 (t, *J* = 5.4 Hz, 1H), 2.03-1.97 (m, 2H), 1.64-1.60 (m, 1H), 1.48-1.39 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.6, 152.6, 145.6, 140.1, 135.0, 134.4,

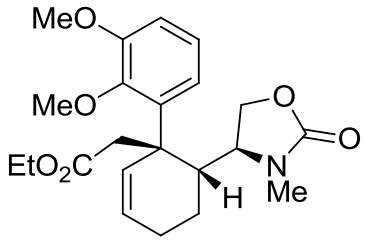
124.9, 121.9, 111.8, 67.5, 65.8, 60.4, 57.9, 55.8, 40.2, 31.4, 30.1, 20.3; LRMS (EI) *m/z* (%) 333 (4), 216 (19), 101 (16), 100 (100), 85 (50), 83 (74); HRMS (EI) calcd for $C_{18}H_{23}NO_5$: 333.1576. Found 333.1579; Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95. Found C, 64.67; H, 6.96.

(4*S*)-4-((4*R*)-2-(2,3-Dimethoxyphenyl)-4-methoxycyclohex-2-enyl)-3-methyloxazolidin-2-one (361).



361: R_f = 0.25 [hexane/EtOAc (70:30)]; mp 144-146 °C (CH_2Cl_2/hexane); $[\alpha]_D^{20}$ = +127.8 (*c* = 1.0, $CHCl_3$); IR ($CHCl_3$) ν 3008, 2931, 2866, 2827, 1744, 1468, 1267 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (t, *J* = 7.8 Hz, 1H), 6.88 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.75 (dd, *J* = 7.8, 1.5 Hz, 1H), 5.94 (d, *J* = 0.9 Hz, 1H), 4.26 (t, *J* = 9.0 Hz, 1H), 3.94-3.91 (m, 2H), 3.90 (s, 3H), 3.87-3.71 (m, 1H), 3.70 (s, 3H), 3.43 (s, 3H), 3.21-3.17 (m, 1H), 2.64 (s, 3H), 2.25-2.21 (m, 1H), 2.06-2.01 (m, 1H), 1.67-1.55 (m, 1H), 1.47-1.38 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 158.7, 152.5, 145.6, 140.3, 135.2, 132.1, 124.9, 121.9, 111.7, 76.2, 65.9, 65.8, 60.5, 57.9, 55.9, 55.8, 40.4, 30.1, 27.5, 20.2, 15.3; LRMS (EI) *m/z* (%) 347 (4), 210 (12), 179 (38), 100 (100), 56 (21); HRMS (EI) calcd for $C_{19}H_{25}NO_5$: 347.1733. Found 347.1728; Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25. Found C, 65.75; H, 7.11.

(+)-Ethyl2-((1*S*,6*R*)-1-(2,3-dimethoxyphenyl)-6-((*S*)-3-methyl-2-oxooxazolidin-4-yl)-cyclohex-2-enyl)acetate (11).

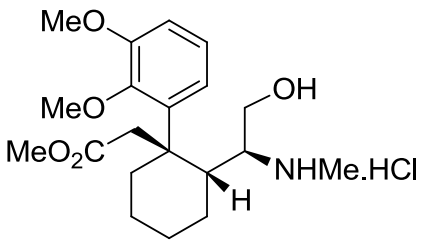


A solution of alcohol **362** (1 g, 2.99 mmol) and 2-nitrophenol (20 mg, 0.14 mmol) in triethyl orthoacetate (60 ml) was heated at 130 °C for 6 d under argon with continuous removal of EtOH. The reaction mixture was diluted with EtOAc, washed with 1N HCl, satd $NaHCO_3$ solution, brine, dried over Na_2SO_4 and solvent was evaporated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel [hexane/EtOAc (50:50) → hexane/EtOAc (30:70)] to obtain **11** (618 mg, 1.53 mmol, 51%) as a viscous yellow liquid.

11: R_f = 0.30 [hexane/EtOAc (40:60)]; $[\alpha]_D^{20}$ = +25.6 (*c* = 1.0, $CHCl_3$); IR ($CHCl_3$) *v* 3008, 2978, 2939, 2836, 1737, 1466, 1425, 1264, 1230 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.01-6.96 (m, 1H), 6.90-6.86 (m, 1H), 5.98-5.89 (m, 2H), 4.39 (t, *J* = 8.7 Hz, 1H), 4.13-4.08 (m, 1H), 4.03 (q, *J* = 7.2 Hz, 2H), 3.93-3.81 (m, 7H), 3.14 (dd, *J* = 19.2, 14.4 Hz, 2H), 2.4-2.36 (m, 1H), 2.20-2.09 (m, 2H), 2.02 (s, 3H), 1.79-1.69 (m, 1H), 1.58-1.45 (m, 1H), 1.16 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 159.8, 153.5, 148.4, 134.2, 133.1, 127.3, 123.9, 123.0, 112.0, 69.4, 60.7, 60.1, 56.9, 55.8, 47.9, 45.5, 45.2, 30.9, 24.7, 18.5, 14.2; LRMS (EI) *m/z* (%) 403 (2), 100 (22), 83 (100), 47 (34), 43

(29); HRMS (EI) calcd for $C_{22}H_{29}NO_6$: 403.1995. Found 403.2006; Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.49; H, 7.24. Found C, 65.78; H, 7.32.

Methyl2-((1*S*,6*R*)-1-(2,3-dimethoxyphenyl)-6-((*S*)-2-hydroxy-1-(methylamino)ethyl) cyclohe- x-2-enyl)acetate hydrochloride (364a).



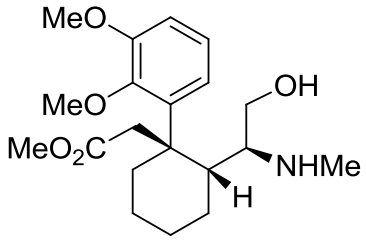
To a solution of **11** (115 mg, 0.29 mmol) in MeOH (6 mL), 50% NaOH (aq) (3 mL) was added and the reaction mixture was heated for 4 hours. It was cooled to room temperature and was diluted with brine solution; pH of the reaction mixture was adjusted to ca. 3 using con. HCl, and was extracted using $CHCl_3$: EtOH (3:1). The organic phase was dried with Na_2SO_4 and the solvent was evaporated under reduced pressure to obtain the crude product **363** (105 mg, 0.29 mmol) as a light brown solid. This crude product was taken to next step without further purification.

To a stirred solution of **363** (100 mg, 0.29 mmol) in MeOH (10 mL), TMSCl (156 mg, 1.43 mmol) was added. The reaction mixture was stirred 48 hours, then the solvent was evaporated on a rotary evaporator and was dried under vacuum to get **364a** (120 mg, 0.29 mmol) as light brown compound.

364a: R_f = 0.12 [CH_2Cl_2/MeOH (80:20)]; IR ($CHCl_3$) ν 3632, 3605, 3354, 3246, 2969, 2954, 2842, 1738, 1601, 1577, 1467, 1438, 1426, 1264, 1164 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 7.18-7.11 (m, 3H), 6.02 (d, J = 10.2 Hz, 1H), 5.95-5.88 (m, 1H), 3.90 (s, 3H),

3.88-3.80 (m, 5H), 3.68 (d, *J* = 5.4 Hz, 1H), 3.64 (s, 3H), 3.45 (d, *J* = 15.9 Hz, 1H), 3.12 (d, *J* = 15.9 Hz, 1H), 2.48 (d, *J* = 9.3 Hz, 1H), 2.37 (s, 3H), 2.19 (s, 2H), 1.72-1.69 (m, 1H), 1.55-1.48 (m, 1H); ^{13}C NMR (150 MHz, D_2O) δ 174.4, 153.2, 147.2, 132.7, 132.1, 127.8, 124.3, 123.9, 113.6, 60.9, 60.3, 55.9, 51.8, 48.8, 44.8, 43.7, 43.1, 32.9, 24.1, 17.9; HRMS (FAB/NBA matrix) calcd for $C_{20}H_{29}NO_5$: 363.2124. Found 364.2071.

Methyl 2-((1R,2R)-1-(2,3-dimethoxyphenyl)-2-((S)-2-hydroxy-1-(methylamino) ethyl)cyclohexyl)acetate (364).

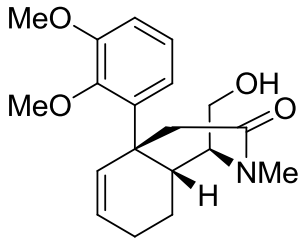


The hydrochloride salt **364a** (120 mg) was washed with saturated Na_2CO_3 (aq) solution and was extracted with CH_2Cl_2 at least three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and was evaporated to get the crude product **364** (109 mg, 0.29 mmol) as light yellow oil. It was taken to the next step without further purification.

364: R_f = 0.6 [CH_2Cl_2/MeOH (90:10)]; $[\alpha]_D^{20}$ = +39.0 (*c* = 0.15, $CHCl_3$); IR ($CHCl_3$) *v* 3369, 3250, 3075, 3009, 2951, 2838, 2803, 1736, 1596, 1579, 1466, 1265 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.03-6.96 (m, 2H), 6.86 (dd, *J* = 6.9, 2.7 Hz, 1H), 6.06 (d, *J* = 10.2 Hz, 1H), 5.96-5.90 (m, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.64 (bs, 1H), 3.56-3.52 (m, 4H), 3.43-3.35 (m, 2H), 3.13 (d, *J* = 15 Hz, 1H), 2.69 (d, *J* = 6.3 Hz, 1H), 2.36 (d, *J* = 4.2 Hz,

1H), 2.24-2.17 (m, 1H), 2.08-2.03 (m, 2H), 1.81 (s, 3H), 1.77-1.66 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.5, 153.1, 148.6, 135.0, 133.7, 127.7, 122.8, 122.7, 111.5, 62.5, 60.5, 60.4, 55.8, 51.1, 45.2, 45.0, 34.6, 25.1, 18.8; LRMS (EI) *m/z* (%) 332 (16), 227 (12), 88 (23), 86 (100), 84 (87), 74 (39); HRMS (EI) calcd for $C_{20}H_{31}NO_5$: 363.2046. Found 363.2037.

(+)-(1*S*,4a*S*,8a*R*)-4a-(2,3-Dimethoxyphenyl)-1-(hydroxymethyl)-2-methyl-1,4,4a,7,8, 8a-hexahydroisoquinolin-3(2H)-one (365).



The free amine **364** (10mg, 0.028 mmol) was heated to reflux with catalytic amount (0.12mg, 10 mol %) of acetic acid in EtOH. After 5 days of heating, solvent was evaporated, diluted with CH_2Cl_2 and was washed with sat. $NaHCO_3$ solution. The organic layer was dried with Na_2SO_4 and was evaporated to get the crude product. Column chromatography on silica gel with CH_2Cl_2/ MeOH (95:5) as eluent provided **365** (3.6mg, 0.011 mmol) as a light brown solid (39%), along with 20% recovered starting material.

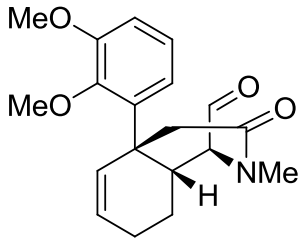
or

To a solution of amino acid 1 (784 mg, 2.24 mmol) and DIPEA (2.03 g, 15.68 mmol) in CH_2Cl_2/CH_3CN (3:1, 20 ml), HBTU (808.4 mg, 2.13 mmol) was added and stirred for 4 hours. Then the reaction mixture was diluted with CH_2Cl_2 (60 ml), washed with dil. HCl (3 x 15 ml), satd solution of $NaHCO_3$ (2 x 10 ml), brine (2 x 10 ml), dried over Na_2SO_4,

filtered and solvent evaporated to provide crude product. Column chromatography on silica gel using CH_2Cl_2/ MeOH (95:5) as eluent provided the amide **365** (567 mg, 1.7 mmol, 76%) as a light brown solid.

365: R_f = 0.39 [CH_2Cl_2/ MeOH (95:5)]; mp = 69-72 °C (CH_2Cl_2/hexane); $[\alpha]_D^{20}$ = +236 (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν 3625, 3028, 3007, 2964, 2941, 2839, 1620, 1578, 1464, 1423, 1310, 1225 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.98-6.83 (m, 3H), 5.83-5.77 (m, 1H), 5.55 (d, *J* = 9.9 Hz, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.34 (d, *J* = 3.9 Hz, 1H), 3.14 (bs, 1H), 3.08 (s, 3H), 3.04-2.92 (m, 3H), 2.42-2.34 (m, 4H), 1.96-1.93 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 125.4, 122.6, 111.7, 66.8, 61.3, 61.1, 55.9, 45.3, 34.7, 26.2, 20.7; LRMS (FAB/NBA matrix) *m/z* (%) 332 (100), 301 (21), 300 (46), 178 (21), 165 (30), 152 (35), 128 (29), 115 (39), 105 (33), 91 (49), 89 (69), 77 (90); HRMS (EI) calcd for $C_{18}H_{22}NO_3$ (M–CH_2OH): 300.1594. Found 300.1596; Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60. Found C, 68.07; H, 7.59.

(+)-(1S,4aS,8aR)-4a-(2,3-Dimethoxyphenyl)-2-methyl-3-oxo-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-1-carbaldehyde (366).

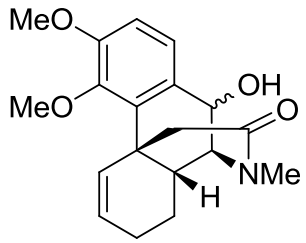


To a solution of amide **365** (224 mg, 0.67 mmol) in CH_2Cl_2 (5 ml), DessMartin periodinane (428 mg, 1.01 mmol) was added at 0 °C and was stirred for 30 minutes. Then the mixture was warmed up to room temperature and stirred for another 30 minutes. The

reaction mixture was diluted with CH_2Cl_2, stirred with 1:1 mixture of 10% $Na_2S_2O_3$ and saturatedd solution of $NaHCO_3$ for 10 minutes. Then organic layer was separated and washed with satd solution of $NaHCO_3$, brine and dried over Na_2SO_4. Solvent was evaporated under reduced pressure to yield **366** (181 mg, 0.55 mmol, 82%) as a white glassy solid. It was taken to next step without further purification.

366: R_f = 0.29 [CH_2Cl_2/ MeOH (95:5)]; $[\alpha]_D^{20}$ = +169 (*c* = 0.45, $CHCl_3$); IR ($CHCl_3$) *ν* 3006, 2962, 2929, 2875, 2855, 1721, 1633, 1579, 1465, 1441, 1424, 1398, 1302, 1262, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 9.02 (s, 1H), 6.94-6.86 (m, 3H), 5.84-5.80 (m, 1H), 5.57 (d, *J* = 9.9 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.53 (dd, *J* = 5.7, 1.8 Hz, 1H), 3.02 (s, 3H), 2.49-2.43 (m, 2H), 2.34-2.31 (m, 2H), 2.04-1.91 (m, 1H), 1.79-1.62 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$,) *δ* 201.4, 170.0, 153.9, 149.1, 136.1, 133.9, 132.7, 125.7, 124.8, 122.6, 112.3, 70.9, 61.2, 55.8, 47.4, 45.5, 41.9, 34.8, 29.7, 25.7, 19.9; LRMS (EI) *m/z* (%) 329 (19), 301 (20), 300 (100), 248 (10), 229 (38), 180 (45); HRMS (EI) calcd for $C_{18}H_{21}NO_4$: 329.1627. Found 329.1623.

(+)-(4b*S*,8a*R*,9*S*)-3,4-Dimethoxy-11-methyl-8,8a,9,10-tetrahydro-7H-9,4b-(epiminoethano)phenanthren-10-ol (367).

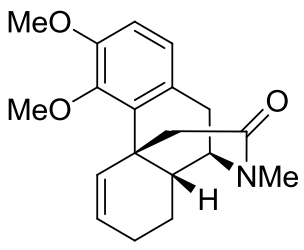


Aldehyde **366** (50 mg, 0.15 mmol) was dissolved in CH_2Cl_2 (2 ml) and cooled to –10 °C, then $BF_3{\cdot}OEt_2$ (54 mg, 0.38 mmol) was added. The reaction mixture was stirred for 3 h,

then quenched with water and diluted with CH_2Cl_2. The reaction mixture was then washed with H_2O, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel with CH_2Cl_2/MeOH (95:5) as eluent to furnish the intermediate alcohol **367** (38 mg, 0.12 mmol, 76%) as a colourless liquid.

367: R_f = 0.20 [CH_2Cl_2/MeOH (95:5)]; $[\alpha]_D^{20}$ = +48.7 (*c* = 1.5, $CHCl_3$); IR ($CHCl_3$) *v* 3583, 3004, 2940, 2840, 1626, 1484, 1415, 1399, 1320, 1279, 1096, 1054, 1029, 978 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 6.41 (d, *J* = 10.2 Hz, 1H), 5.69-5.65 (m, 1H), 4.89 (d, *J* = 3.9 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.61 (t, *J* = 1.8 Hz, 1H), 3.13 (s, 3H), 2.88 (d, *J* = 17.7 Hz, 1H), 2.40 (d, *J* = 17.7 Hz, 1H), 2.14-2.04 (m, 3H), 1.77-1.72 (m, 1H), 1.50-1.36 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 153.0, 147.4, 134.9, 133.9, 127.8, 125.7, 122.6, 112.0, 70.2, 63.0, 60.2, 55.8, 46.1, 41.5, 38.2, 38.0, 25.4, 23.0; LRMS (FAB) *m/z* (%) 330 (81), 270 (20), 226 (20), 165 (28), 115 (40), 89 (68), 77 (100); HRMS (EI) calcd for $C_{19}H_{23}NO_4$: 329.1627. Found 329.1627; Anal. Calcd for $C_{19}H_{23}NO_4$: C, 62.28; H, 7.04. Found C, 61.61; H, 7.66.

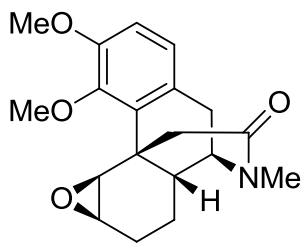
(+)-(4b*S*)-3,4-Dimethoxy-11-methyl-8,8a,9,10-tetrahydro-7H-9,4b- (epiminoethano) phenanthren-12-one (369).



To a solution of the intermediate alcohol **367** (40 mg, 0.12 mmol) in 1,2-dichloroethane (2 ml), chlorodiphenylsilane (66.4 mg, 0.3 mmol) was added and the mixture was heated for 1 h; then catalytic $InCl_3$ (5.3 mg, 0.02 mmol) was added and the mixture was heated to reflux for another 20 hours. After complete consumption of starting material (*vide* TLC), the reaction mixture was diluted with CH_2Cl_2, washed with H_2O, brine and dried over Na_2SO_4. Solvent was evaporated under reduced pressure to obtain the crude product and column chromatography on silica gel with EtOAc as eluent afforded amide **369** (25 mg, 0.08 mmol, 67%) as a white solid.

369: R_f = 0.24 [EtOAc]; mp 55–58 °C (EtOAc/hexane); $[\alpha]_D^{20}$ = +48.7 (*c* = 1.5, $CHCl_3$); IR ($CHCl_3$) *v* 3000, 2938, 2840, 1623, 1485, 1275, 1219, 1051 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.78-6.75 (m, 2H), 6.45 (d, *J* = 10.2 Hz, 1H), 5.67 (d, *J* = 9.9 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.58 (s, 1H), 2.99-2.94 (m, 4H), 2.83 (d, *J* = 16.8 Hz, 2H), 2.37 (d, *J* = 17.4 Hz, 1H), 2.09-2.04 (m, 3H), 1.69-1.66 (m, 1H), 1.57-1.43 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 151.9, 148.6, 134.7, 133.9, 125.5, 124.8, 123.7, 111.8, 60.1, 58.4, 55.9, 46.1, 40.2, 37.8, 33.4, 29.5, 25.2, 23.1; LRMS (EI) *m/z* (%) 313 (100), 240 (37), 225 (22), 192 (71), 85 (53), 83 (79); HRMS (EI) calcd for $C_{19}H_{23}NO_3$: 313.1677. Found 313.1673; Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40. Found C, 72.57; H, 7.46.

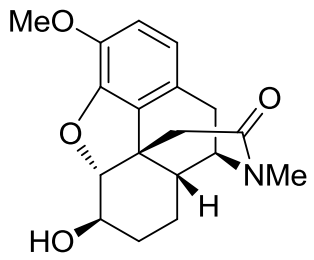
(–)-(1a*R*,3a*R*,4*R*,9b*S*,9c*S*)-8,9-Dimethoxy-12-methyl-2,3,3a,4,5,9c-hexahydro-1aH-4,9b-(epiminoethano)phenanthro[3,4-b]oxiren-11-one (370).



To a solution of **369** (40 mg, 0.13 mmol) in CH_2Cl_2 (2 ml) at 0 °C, *m*CPBA (26.4 mg, 0.15 mmol) was added in one portion and the reaction was warmed to room temperature. Stirring was continued for another 12 hours, then the reaction mixture was diluted with CH_2Cl_2, washed with a 1:1 mixture of 10% $Na_2S_2O_3$, satd solution of NH_4Cl, satd solution of $NaHCO_3$, brine and was dried over Na_2SO_4. Solvent was evaporated under reduced pressure to obtain crude product as a colourless liquid. It was taken to next step without further purification.

370: R_f = 0.30 [CH_2Cl_2/MeOH (95:5), double run]; $[\alpha]_D^{20}$ = –20.0 (*c* = 1.5, $CHCl_3$); IR ($CHCl_3$) ν 3023, 3003, 2937, 1626, 1483, 1416, 1277, 1261, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.85 (d, *J* = 4.2 Hz, 1H), 6.81 (d, *J* = 3.9 Hz, 1H), 4.55 (d, *J* = 1.5 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.49 (s, 1H), 3.28 (1H), 2.97-2.87 (m, 4H), 2.84-2.80 (m, 2H), 2.28 (d, *J* = 3.0 Hz, 1H), 2.04-1.94 (m, 2H), 1.37-1.34 (m, 1H), 1.34-1.22 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 151.8, 149.3, 130.1, 125.2, 125.1, 112.3, 60.7, 57.3, 56.6, 55.9, 54.9, 43.4, 38.6, 33.9, 33.4, 29.7, 29.4, 22.4, 21.6; LRMS (EI) *m/z* (%) 329 (14), 192 (8), 123 (10), 111 (18), 109 (15), 97 (23), 95 (20), 85 (28), 83 (26), 71 (38), 57 (54), 55 (36), 44 (100), 43 (49); HRMS (EI) calcd for $C_{19}H_{23}NO_3$: 329.16271 found 329.1633.

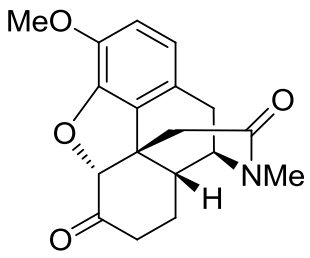
(–)-(4*R*,4a*R*,7*R*,7a*R*,12b*S*)-7-Hydroxy-9-methoxy-3-methyl-4,4a,5,6,7,7a-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-2(3H)-one (371).



The crude epoxide **370** (36 mg, 0.11) in THF (1ml) was treated with camphor sulphonic acid (CSA) (30.5 mg, 0.13) and heated to reflux for 24 hours. The reaction mixture was then diluted with CH_2Cl_2, washed with saturatedd solution of $NaHCO_3$, brine and was dried over Na_2SO_4.The solvent was evaporated under reduced pressure to provide the crude product. Column chromatography on silica gel using CH_2Cl_2/MeOH (95:5) as eluent afforded **371** (22 mg, 0.07 mmol, 54% after two steps) as a colourless oil. This data was matched with reported compound.[149a]

371: R_f = 0.16 [CH_2Cl_2/MeOH (95:5)]; $[\alpha]_D^{20}$ = –114.8 (*c* = 0.6, $CHCl_3$); IR ($CHCl_3$) ν 3592, 3004, 2932, 1633, 1504, 1440, 1400, 1323, 1282, 1266, 1124, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (d, *J* = 8.1 Hz, 1H), 6.62 (d, *J* = 8.1 Hz, 1H), 4.33 (d, *J* = 6.9 Hz, 1H), 3.86 (s, 3H), 3.74-3.71 (m, 1H), 3.42-3.34 (m, 1H), 2.99 (s, 3H), 2.97-2.92 (m, 1H), 2.72-2.52 (m, 4H), 2.38-2.33 (m, 1H), 1.89-1.74 (m, 2H), 1.45-1.32 (m, 1H), 1.11-1.00 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 144.5, 144.2, 130.3, 121.3, 121.2, 114.6, 96.8, 72.1, 58.8, 56.6, 44.7, 42.7, 39.0, 34.1, 29.2, 26.6, 22.9.

(–)-(7a*R*,12b*S*)-9-Methoxy-3-methyl-4,4a,5,6-tetrahydro-1H-4,12-methanobenzo furo[3,2-e]isoquinoline-2,7(3H,7aH)-dione (372).

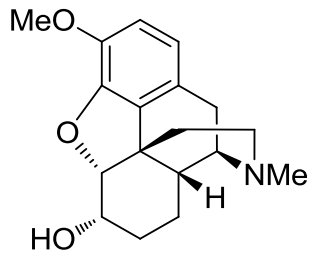


To a solution of **371** (12 mg, 0.038 mmol) in CH_2Cl_2 (1 ml), Dess-Martin periodinane (32 mg, 0.08 mmol) was added at 0 °C and the mixture was stirred for 30 minutes whereupon it was allowed to warm to room temperature and stirred for another 5 hours. The reaction mixture was diluted with CH_2Cl_2, stirred with a 1:1 mixture of 10% $Na_2S_2O_3$ and satd $NaHCO_3$ solution during 10 minutes. The organic layer was separated and washed with satd $NaHCO_3$ solution, brine and was dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel with CH_2Cl_2/MeOH (98:2) as eluent to provide **372** (10 mg, 0.03 mmol, 84%) as colorless oil.

372: R_f = 0.15 [CH_2Cl_2/MeOH (95:5)]; $[\alpha]_D^{20}$ = –178.0 (*c* = 0.17, $CHCl_3$); IR ($CHCl_3$) *v* 3005, 2933, 1735, 1636, 1507, 1439, 1400, 1279, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (d, *J* = 8.4 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 4.70 (s, 1H), 3.90 (s, 3H), 3.80-3.79 (m,1H), 3.04 (s, 3H), 3.01-2.95 (m, 1H), 2.80-2.77 (m, 3H), 2.62 (dd, *J* = 18.0, 3.9 Hz, 1H), 2.47-2.42 (m, 2H), 2.08-2.02 (m, 1H), 1.39-1.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 167.6, 146.1, 143.6, 127.1, 121.9, 121.1, 115.8, 91.5, 58.8, 57.2, 46.7, 44.5, 38.9, 34.3, 30.0, 26.8, 25.2; LRMS (EI) *m/z* (%) 313 (21), 248 (100), 231 (59),

203 (18), 156 (18), 149 (13), 139 (18), 127 (10), 111 (16), 105 (13); HRMS (EI) calcd for $C_{18}H_{19}NO_4$: 313.1314. Found 313.1308.

(–)-(4*R*,4a*R*,7*S*,7a*R*,12b*S*)-9-Methoxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-ol (373), dihydrocodeine.

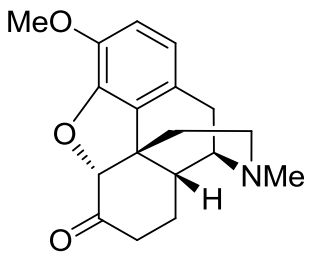


To a stirred suspension of $LiAlH_4$ (3 mg, 0.079 mmol) in dioxane (0.5 ml) was added a solution of **372** (5 mg, 0.016 mmol) in dioxane (0.5 ml), and the mixture was heated to reflux for 6 hours. Then the reaction mixture was cooled to room temperature, quenched by the addition of two drops of water followed by the addition of two drops of 15% NaOH solution and six more drops of water. The white suspension formed was filtered through a pad of celite, washed with CH_2Cl_2, solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel with EtOAc/Et_2NH (20:1) as eluent to provide **373** (3.4 mg, 0.011 mmol, 71%) as a white glassy solid which provided crystalline dihydrocodeine **373** upon trituration with CH_2Cl_2.

373: R_f = 0.16 [EtOAc/Et_2NH (20:1)]; mp 110-112 °C (CH_2Cl_2) [lit.[167] mp 111-112 °C]; $[\alpha]_D^{20}$ = –212 (*c* = 0.11, 1,4-dioxane) [lit.[168] $[\alpha]_D^{21}$ = –220 (*c* = 0.246, 1,4-dioxane)]; IR ($CHCl_3$) *v* 3590, 3010, 2936, 2909, 1504, 1449, 1440, 1322, 1278, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.73 (d, *J* = 8.1 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 4.61 (d, *J* = 5.4 Hz, 1H), 4.05 (bs, 1H), 3.87 (s, 3H), 3.14 (bs, 1H), 3.01 (d, *J* = 18.3 Hz, 1H), 2.55-2.52

(m, 1H), 2.32 (s, 4H), 2.32-2.28 (m, 2H), 2.05-1.84 (m, 2H), 1.73-1.69 (m, 1H), 1.60-1.54 (m, 1H), 1.51-1.40 (m, 2H), 1.18-1.12 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.2, 141.7, 130.0, 126.5, 119.2, 113.3, 90.3, 67.1, 60.0, 56.4, 47.0, 42.8, 41.9, 40.4, 37.0, 27.2, 20.2, 18.9; MS (EI) *m/z* (%) 301 (100), 286 (10), 244 (18), 242 (13), 199 (28), 185 (10), 164 (20), 91 (18), 73 (16), 60 (21), 58 (32), 45 (61), 44 (54); HRMS (EI) calcd for $C_{18}H_{23}NO_3$: 301.1678. Found 301.1674.

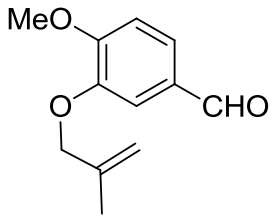
(–)-(4*R*,4a*R*,7a*R*,12b*S*)-9-Methoxy-3-methyl-2,3,4,4a,5,6-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7(7aH)-one (153), hydrocodone.



To a solution of **373** (3.5 mg, 0.012 mmol) in CH_2Cl_2 (0.6 ml), Dess-Martin periodinane (7.4 mg, 0.017 mmol) was added at 0 °C and the reaction mixture was stirred for 30 minutes whereupon it was allowed to warm to room temperature and stirred for another 2 h. The reaction mixture was diluted with CH_2Cl_2, stirred with a 1:1 mixture of 10% $Na_2S_2O_3$ and saturated $NaHCO_3$ solution during 10 min. Then organic layer was separated and washed with saturated $NaHCO_3$ solution, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel with EtOAc/Et_2NH (20:1) as eluent to provide **153** (2.9 mg, 0.01 mmol, 83%) as a white glassy solid. Trituration with ether provided crystalline hydrocodone (**153**).

153: R_f = 0.21 [EtOAc/Et_2NH (20:1)]; mp 191-194 °C (Et_2O) [lit.[169] mp = 194-197 °C]; $[\alpha]_D^{20}$ = –195 (*c* = 0.11, $CHCl_3$) [lit. $[\alpha]_D^{20}$ = –207 (*c* = 1.0, $CHCl_3$)]; IR ($CHCl_3$) *v* 3007, 2936, 1728, 1504, 1439, 1278, 1157, 1058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.70 (d, *J* = 8.1 Hz, 1H), 6.63 (d, *J* = 8.1 Hz, 1H), 4.66 (s, 1H), 3.90 (s, 3H), 3.20-3.17 (m, 1H), 3.03 (d, *J* = 18.3 Hz, 1H), 2.60-2.54 (m, 2H), 2.43-2.40 (m, 4H), 2.37-2.31 (m, 1H), 2.28-2.15 (m, 2H), 2.11-2.02 (m, 1H), 1.89-1.79 (m, 2H), 1.33-1.19 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8, 145.6, 142.9, 127.3, 126.3, 119.8, 114.6, 91.4, 59.2, 56.8, 46.9, 46.8, 42.9, 42.8, 40.2, 35.6, 25.6, 19.9; MS (EI) *m/z* (%) 299 (100), 284 (14), 256 (11), 243 (29), 242 (47), 214 (19), 212 (18), 161 (12), 188 (14), 185 (20), 96 (26), 86 (17), 84 (24), 70 (18), 59 (30), 42 (15); HRMS (EI) calcd for $C_{18}H_{21}NO_3$: 299.1521. Found 299.1518.

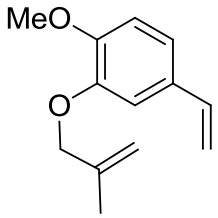
4-Methoxy-3-(2-methylallyloxy) benzaldehyde (390a).



To a suspension of **166** (5.0 g, 32.8 mmol) and K_2CO_3 (6.8 g, 49.3 mmol) in DMF (30 mL) was added 2-methyl bromo propene (3.6 mL, 39.4 mmol) at room temperature and was stirred for 5 hours. Then the reaction was quenched with water, diluted with ether and washed with water and extracted with ether. Then the organic layers were combined and washed with brine and dried over Na_2SO_4 and solvent was evaporated to get the pure product **390a** (5.0 g, 24.3 mmol, 76%).

390a: R_f = 0.50 [hexane/EtOAc (50:50)]; IR ($CHCl_3$) ν 3083, 3022, 2977, 2937, 2843, 2758, 2735, 1685, 1596, 1587, 1510, 1441, 1435, 1269, 1134 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.46 (dd, J = 8.1, 1.5 Hz, 1H), 7.39 (d, J = 1.5 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 5.07 (d, J = 3.2 Hz, 2H), 4.57 (s, 2H), 3.96 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.9, 154.9, 148.7, 140.1, 130.0, 126.8, 113.3, 111.2, 110.8, 72.5, 56.3, 19.4; LRMS (EI) calcd for $C_{12}H_{14}O_3$: 206. Found 206.

1-Methoxy-2-(2-methylallyloxy)-4-vinylbenzene (390).

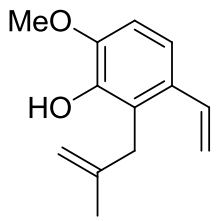


To a solution of Wittig salt (2.94 g, 7.3 mmol) in THF (30 mL) at −78 ^oC *n*-BuLi (3.01 ml, 6.78 mmol) was added drop wise and stirred for 15 minutes. Then the reaction mixture was warmed to 0 ^oC and **390a** (1 g, 4.8 mmol) was added in THF (10 mL) *via* a canula. Then the suspension was heated to reflux for 2 hours, cooled to room temperature, diluted with EtOAc, washed with water and re-extracted with EtOAc. Then the organic layers were combined and washed with brine and dried over Na_2SO_4 and solvent was evaporated to get the crude product. It was the purified by flash column chromatography on silica gel using [hexane/EtOAc (90:10) → (80:20)] to get **390** (0.95 g, 4.7 mmol, 95%) as a colorless oil.

390: R_f = 0.54 [hexane/EtOAc (70:30)]; IR ($CHCl_3$) ν 3088, 3012, 2980, 2935, 2913, 2840, 1512, 1261, 1137 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.99-6.94 (m, 2H), 6.83 (d, J = 8.1 Hz, 1H), 6.63 (dd, J = 17.4, 10.8 Hz, 1H), 5.58 (d, J = 17.4 Hz, 1H), 5.13 (d, J =

10.5 Hz, 2H), 5.00 (s, 1H), 4.54 (s, 2H), 3.88 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.6, 148.4, 140.9, 136.6, 130.7, 119.9, 112.9, 111.8, 111.7, 111.1, 72.8, 56.21, 19.5; LRMS (EI) **c**alcd for $C_{13}H_{16}O_2$: 204. Found 204.

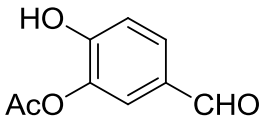
6-Methoxy-2-(2-methylallyl)-3-vinylphenol (391).



A solution of (100 mg, 0.49 mmol) was heated to reflux in *m*-xylene (2 mL) for 9 days under argon atmosphere in a sealed tube. It was then purified by column chromatography hexane/EtOAc (95:5) to obtain 391 (18 mg, 0.09 mmol, 18%) as a colorless oil. Only a part of the compound was isolated as pure product, rest came as a mixture of product with starting material.

391: R_f = 0.24 [hexane/EtOAc (90:10)]; IR ($CHCl_3$) ν 3541, 3086, 3011, 2972, 2943, 2843, 1650, 1614, 1579, 1489, 1462, 1441, 1278, 1246 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, J = 8.4 Hz, 1H), 6.88-6.75 (m, 2H), 5.69 (s, 1H), 5.54 (dd, J = 17.1, 1.2 Hz, 1H), 5.17 (dd, J = 11.1, 1.2 Hz, 1H), 4.77 (s, 1H), 4.44 (s, 1H), 3.89 (s, 3H), 3.44 (s, 2H), 1.82 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.9, 144.1, 143.7, 134.7, 131.6, 123.5, 116.9, 114.1, 110.6, 108.8, 56.1, 33.7, 23.2; LRMS (EI) calcd for $C_{13}H_{16}O_2$: 204. Found 204.

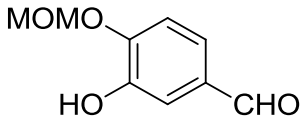
4-Formyl-2-hydroxyphenyl acetate (403).



Aldehyde **402** [1] (3.9 g, 28 mmol) was dissolved in THF (20 mL) and the solution was cooled to 0 °C. Then a solution of NaOH in water (2N, 70 mmol) was added dropwise followed by the addition of acetic anhydride (3.2 mL, 34 mmol).The reaction mixture was stirred for 20 minutes, diluted with EtOAc, made acidic with con. HCl (2.5 mL) and phosphate buffer (20 mL, pH = 2.5). Then it was filtered through a pad of Celite and organic phase was separated. The aqueous phase was washed 3 times with EtOAc, organic washes were combined, washed with brine, dried over Na_2SO_4 and solvent was evaporated under reduced pressure to obtain the crude product, which was purified by suction filtration chromatography on silica gel with [CH_2Cl_2/MeOH (98:2) → CH_2Cl_2/MeOH (95:5)] as eluent to provide **403** as a light yellow solid (4.2 g, 23.3 mmol, 84%). It was recrystallized from ether to provide colourless crystals.

403: R_f = 0.33 [CH_2Cl_2/MeOH (98:2)]; mp 88–91 °C (ether), [lit.[2] 87-89 °C (ether- light petrol)]; IR ($CHCl_3$) ν 3564, 3374, 3028, 2838, 2737, 1773, 1696, 1607, 1509, 1441, 1371, 1296, 1277, 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.69 (dd, J = 8.4, 1.8 Hz, 1H), 7.58 (d, J = 2.1 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 4.95 (bs, 1H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.8, 169.3, 155.4, 139.1, 129.6, 129.1, 124.0, 116.7, 19.2; LRMS (EI) *m/z* (%) 180 (11), 138 (65), 137 (55), 43 (100); HRMS (EI) calcd for $C_9H_8O_4$: 180.0423. Found 180.0427; Anal. Calcd for $C_9H_8O_4$: C, 60.00; H, 4.48. Found C, 60.24; H, 4.59.

3-Hydroxy-4-(methoxymethoxy)benzaldehyde (405).



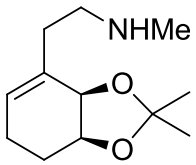
To a suspension of K_2CO_3 (2.3 g, 16.8 mmol) in DMF (30 mL) at 0 °C was added MOMCl (0.84 mL, 2 mmol) dropwise. Then a solution of **403** (1.0 g, 5.6 mmol) in DMF (30 mL) was added dropwise through an addition funnel. The reaction mixture was allowed to stir for another 30 minutes and was diluted with H_2O (100 mL). It was then extracted three times with Et_2O (75 mL), organic washes were combined, washed with brine solution, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to provide the crude acetate **404** which was taken to next step without further purification.

A saturated solution of K_2CO_3 in MeOH (15 mL) was added to a solution of acetate **404** in MeOH (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 40 minutes, then the pH of the reaction mixture was adjusted to 7 using 1 N HCl and NH_4Cl (sat.) solution. The aqueous layer was extracted with CH_2Cl_2 (3x100 mL), washed with brine, dried over Na_2SO_4, and the volatiles were removed *in vacuo* to provide crude product, which was filtered through a plug of silica using EtOAc to yield **405** (0.72 g, 3.95 mmol, 71% over two steps) as a colourless liquid.

405: R_f = 0.15 [hexane/EtOAc (80:20)]; IR ($CHCl_3$) ν 3615, 3028, 3007, 2964, 2740, 1705, 1578, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.79 (s, 1H), 7.42 (d, J = 1.8 Hz, 1H), 7.35 (dd, J = 8.4, 1.8 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 6.54 (s, 1H), 5.26 (s, 2H), 3.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.4, 149.8, 146.7, 131.4, 124.3, 114.9,

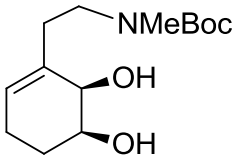
114.3, 95.2, 56.6; LRMS (EI) *m/z* (%) 182 (13), 45 (100); HRMS (EI) calcd for $C_9H_{10}O_4$: 182.0579. Found 182.0576.

(+)-2-((3a*R*,7a*S*)-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-yl)-N-methylethanamine (398).



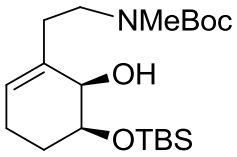
A solution of diol **396** (15 g, 67.8 mmol) in acetone (130 mL) was treated with 2,2,-dimethoxypropane (12.5 mL, 101.8 mmol) and pTsOH. The reaction was stirred for 4 h at room temperature, whereupon the solvent was evaporated. The residue was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with saturated aqueous Na_2CO_3 solution (2 × 10 mL), and brine, then dried (Na_2SO_4), filtered, and evaporated to yield bromide **397** (15.6 g) as a clear colorless oil, which was used without further purification. Bromide **397** (17.8 g, 68.2 mmol) was dissolved in THF (70 mL) and transferred to a 200 mL thick-walled reaction vessel containing K_2CO_3 (4.74 g, 34.1 mmol) and a magnetic stirring bar. The reaction vessel was cooled to –40 °C, and the solution was saturated with methylamine by passing gaseous methylamine from a lecture bottle through the solution for 15 min. The reaction vessel was sealed, and the mixture was stirred at 25 °C for 18 h. The mixture was cooled to –40 °C before the vessel was opened. Potassium salts were removed by filtration and rinsed with CH_2Cl_2. The solvent was evaporated to obtain amine **398** (13.6 g, 64.3 mmol, 94%) as a pale yellow oil, which was used without further purification. Data was matched with reported procedure.[112]

(–)-*tert*-Butyl (2-((5S,6R)-5,6-dihydroxycyclohex-1-en-1-yl)ethyl)(methyl)carbamate (399).



A solution of acetonide **398** (16.0 g, 75.7 mmol) in EtOH (91 mL) and H_2O (9 mL) was treated with 3 mol L^{-1} HCl (38.0 mL, 113.6 mmol). The reaction mixture was stirred for 4 h, treated with $NaHCO_3$ (96 g), and stirred vigorously for 1 h. Then Boc anhydride (24.8 g, 113.6 mmol) was added, reaction mixture was stirred for additional 4 h, filtered, and evaporated. The residue was diluted with H_2O (40 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with saturated aqueous NH_4Cl solution (2 × 10 mL), brine, dried (Na_2SO_4), filtered, and evaporated. Column chromatography on silica gel using [hexane/EtOAc (70:30) → hexane/EtOAc (30:70)] provided **399** (14.8 g, 54.8 mmol, 74%) as a light yellow oil. Data was matched with reported procedure.[112]

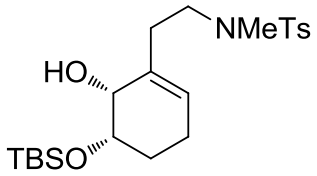
(–)-*tert*-Butyl (2-((5S,6R)-5-((tert-butyldimethylsilyl)oxy)-6-hydroxycyclohex-1-en-1-yl)ethyl)(methyl)carbamate (400).



A solution of carbamate **399** (15 g, 55.2 mmol) and imidazole (7.5 g, 110.4 mmol) in CH_2Cl_2 (75 mL) was treated with TBSCl (9.16 g, 60.7 mmol) at –78 °C, the reaction

mixture was left to warm slowly to 25 °C overnight and treated with saturated aqueous NH_4Cl solution (40 mL). After extraction with CH_2Cl_2 (3 × 100 mL), the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (50 mL), brine (50 mL), dried over Na_2SO_4, filtered, and evaporated. Column chromatography on silica gel using [hexane/EtOAc (90:10) → hexane/EtOAc (60:40)] provided **400** (19.5 g, 50.6 mmol, 92%) as a light yellow oil. Data was matched with reported procedure.[112]

(–)-N-(2-((5*S*,6*R*)-5-((tert-Butyldimethylsilyl)oxy)-6-hydroxycyclohex-1-en-1-yl)ethyl)-N,4-dimethylbenzenesulfonamide (**401**).

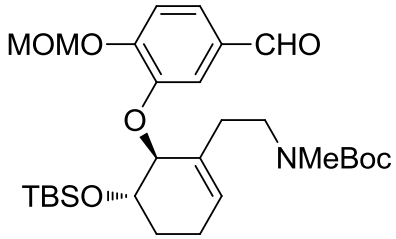


To a solution of **400** (1.0 g, 2.59 mmol) in CH_2Cl_2 at 0 °C was added TFA (4.0 mL, 32 mmol) and was stirred for 20 minutes. Then the reaction mixture was diluted with CH_2Cl_2 (60 mL), then saturated $NaHCO_3$ solution was added and pH was adjusted to ~9. Organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (3 x 30 mL), organic washes were combined and was washed with brine solution, dried over Na_2SO_4 and solvent was evaporated under reduced pressure to provide crude product (540 mg). Then the aqueous phase was saturated with NaCl and was washed with $CHCl_3$:EtOH (3:1) (3 x 30 mL), dried over Na_2SO_4 and solvent was evaporated under reduced pressure to provide another 200 mg of crude product. The crude material was taken to next step without further purification.

To a solution of crude product (740 mg, 2.6 mmol) in CH_2Cl_2 at 0 °C was added Et_3N (0.47 mL, 3.37 mmol) followed by TsCl (593 mg, 3.1 mmol). The reaction mixture was slowly warmed to room temperature and was stirred for 3 hours. Then the solvent was evaporated under reduced pressure and column chromatography on silica gel using [hexane/EtOAc (90:10) → hexane/EtOAc (70:30)] provided **401** (979 mg, 2.2 mmol, 86%) as a clear liquid.

401: R_f = 0.12 [hexane/EtOAc (70:30)]; $[\alpha]_D^{20}$ = –30.0 (*c* = 1.15, $CHCl_3$); IR ($CHCl_3$) *v* 3550, 3028, 3008, 2954, 2930, 2885, 2859, 1690, 1598, 1462, 1373, 1339, 1160, 1088 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 5.58 (bs, 1H), 3.92 (d, *J* = 3.6 Hz, 1H), 3.83-3.78 (m, 1H), 3.35-3.26 (m, 1H), 3.00-2.93 (m, 1H), 2.70 (s, 3H), 2.39 (s, 4H), 2.30-2.23 (m, 1H), 2.21-1.88 (m, 3H), 1.80-1.67 (m, 1H), 1.56-1.52 (m, 1H), 0.89 (s, 9H), 0.14-0.09 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.1, 134.8, 134.0, 129.6, 127.3, 127.2, 70.7, 68.7, 49.1, 34.6, 33.1, 25.8, 25.5, 23.9, 21.4, 18.0, −4.5, −4.9; LRMS (EI) *m/z* (%) 382 (4), 324 (8), 200 (10), 199 (25), 198 (100), 197 (86), 155 (67), 140 (21), 105 (15), 91 (58), 77 (13), 75 (81), 73 (30), 57 (16), 44 (35); HRMS (EI) calcd for $C_{22}H_{37}NO_4SSi$ (M^+–C_4H_9): 382.1508. Found 382.1496; Anal. Calcd for $C_{22}H_{37}NO_4SSi$: C, 60.10; H, 8.48. Found C, 59.92; H, 8.28.

(–)-tert-Butyl(2-((*5S,6S*)-5-((tert-butyldimethylsilyl)oxy)-6-(5-formyl-2-(methoxymethoxy)phenoxy)cyclohex-1-en-1-yl)ethyl)(methyl) carbamate (406).

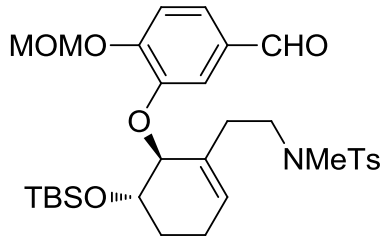


To a solution of alcohol **400** (3.19 g, 8.28 mmol) and phenol **405** (1.66 g, 9.11 mmol) in THF (30 mL) at −10 °C was added PBu_3 (2.9 mL, 11.59 mmol) followed by tetramethylazodicarboxamide (TMAD) (1.9 g, 10.76 mmol). The reaction mixture was slowly warmed to room temperature and was stirred for 18 hours. Solvent was evaporated under reduced pressure and purified by flash column chromatography on silica gel using [hexane/EtOAc (90:10)] as eluent to isolate product **406** (3.7 g, 6.7 mmol, 81%) as a clear oil.

406: R_f = 0.39 [hexane/EtOAc (70:30)]; $[\alpha]_D^{20}$ = –27.6 (*c* = 1.48, $CHCl_3$); IR ($CHCl_3$) ν 3681, 3009, 2931, 1726, 1682, 1582, 1506, 1394, 1271, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.86 (s, 1H), 7.70 (s, 1H), 7.44 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.28-7.24 (m, 1H), 5.69 (s, 1H), 5.29 (s, 2H), 4.75 (s, 1H), 4.11-4.06 (m, 1H), 3.49 (s, 3H), 3.25-3.17 (m, 2H), 2.72 (s, 3H), 2.35-2.04 (m, 4H), 1.93-1.86 (m, 1H), 1.79-1.70 (m, 1H), 1.41 (s, 9H), 0.81 (s, 9H), 0.00 (s, 3H), −0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, rotameric) δ 190.8, 155.7, 152.7, 149.8, 132.4, 131.1, 128.6, 125.8, 125.2, 115.5, 94.8, 80.3, 79.3, 70.4, 60.5, 56.5, 48.5, 34.5, 32.3, 31.7, 28.5, 25.8, 22.8, 18.0, −4.7, −4.8; LRMS (EI) *m/z* (%) 312 (37), 268 (50), 237 (29), 136 (34), 57 (51), 44 (100); HRMS (EI) calcd for $C_{29}H_{47}NO_7Si$:

549.3122. Found 549.3115; Anal. Calcd for $C_{29}H_{47}NO_7Si$: C, 63.36; H, 8.62. Found C, 63.02; H, 8.61.

(–)-N-(2-((5*S*,6*S*)-5-((Tert-butyldimethylsilyl)oxy)-6-(5-formyl-2- (methoxymethoxy) phenoxy) cyclohex-1-en-1-yl)ethyl)-N,4-dimethylbenzenesulfonamide (407).

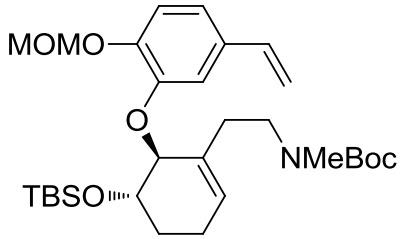


To a solution of alcohol **401** (190 mg, 0.43 mmol) and phenol **405** (102 mg, 0.56 mmol) in THF (6 mL) at −10 °C was added PBu_3 (0.15 mL, 0.65 mmol) followed by tetramethylazodicarboxamide (TMAD) (111 mg, 0.65 mmol). The reaction mixture was slowly warmed to room temperature and was stirred for 22 hours. Solvent was evaporated under reduced pressure and purified by flash column chromatography on silica gel using [hexane/EtOAc (80:20)→ hexane/EtOAc (50:50)] as eluent to isolate product **407** (130 mg, 0.22 mmol, 50%) as a clear oil.

407: R_f = 0.34 [hexane/EtOAc (70:30)]; $[\alpha]_D^{20}$ = –21.1 (c = 1.5, $CHCl_3$); IR ($CHCl_3$) ν 3028, 3009, 2954, 2930, 2857, 1688, 1596, 1584, 1505, 1463, 1339, 1264, 1160, 1126, 1084 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.87 (s, 1H), 7.69 (d, J = 1.2 Hz, 1H), 7.55-7.45 (m, 3H), 7.28-7.23 (m, 3H), 5.75 (s, 1H), 5.31-5.26 (m, 2H), 4.72 (d, J = 4.8 Hz, 1H), 4.14-4.05 (m, 1H), 3.48 (s, 3H), 3.05-3.01 (m, 1H), 2.94-2.88 (m, 1H), 2.62 (s, 3H), 2.50-2.40 (m, 4H), 2.36-2.26 (m, 1H), 2.19-2.13 (m, 2H), 1.89-1.87 (m, 1H), 1.85-1.83 (m, 1H), 0.80 (s, 9H), −0.00 (s, 3H), −0.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz,

rotameric) δ 190.9, 152.8, 150.1, 149.4, 143.1, 134.6, 131.8, 130.9, 129.6, 128.9, 127.3, 125.4, 115.4, 115.1, 94.8, 79.9, 70.2, 60.4, 56.5, 49.4, 34.9, 32.4, 28.0, 25.7, 22.7, 21.5, 17.9, −4.9, −5.0; LRMS (EI) *m/z* (%) 546 (2), 199 (12), 198 (100), 155 (44), 91 (47), 75 (67), 45 (77); HRMS (EI) calcd for $C_{31}H_{45}NO_7SSi$ (M^+–C_4H_9): 546.1982. Found 546.1976.

(–)-tert-Butyl(2-((*5S,6S*)-5-((tert-butyldimethylsilyl)oxy)-6-(2-(methoxy-methoxy)-5-vinylphenoxy)cyclohex-1-en-1-yl)ethyl)(methyl)carbamate (408).

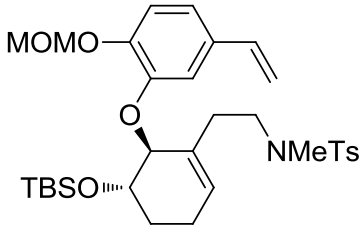


To a suspension of Wittig salt $CH_3P^+Ph_3Br^-$(2.26 g, 6.3 mmol) in THF (20 mL) at -78 °C, *n*BuLi (2.9 mL, 5.8 mmol) was added and the resulting yellow solution was stirred for 15 minutes. It was then warmed to 0 °C, and aldehyde **406** (1.58 g, 2.9 mmol) in THF (20 mL) was cannulated into the reaction mixture, which was stirred for another 10 minutes at 0 °C. The resulting yellow suspension was heated to reflux for 4 hours whereupon the solvent was evaporated under reduced pressure and column chromatography on silica gel using hexane/EtOAc (80:20) provided **408** (1.3 g, 2.37 mmol, 82%) as a colourless liquid.

408: R_f = 0.57 [hexane/EtOAc (70:30)]; $[\alpha]_D^{20}$ = –9.4 (*c* = 0.17, $CHCl_3$); IR ($CHCl_3$) ν 3009, 2954, 2930, 2898, 2857, 1683, 1601, 1577, 1506, 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, rotameric) δ 7.21-7.20 (m, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 7.01-6.93 (m, 1H), 6.67-

6.57 (m, 1H), 5.67-5.58 (m, 2H), 5.20-5.13 (m, 3H), 4.57 (bs, 1H), 4.08 (bs, 1H), 3.48 (s, 3H), 3.20-3.16 (m, 2H), 2.73 (bs, 3H), 2.36-2.04 (m, 4H), 1.89-1.86 (m, 1H), 1.74-1.67 (m, 1H), 1.42 (s, 9H), 0.83 (s, 9H), −0.01 (s, 3H), −0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, rotameric) δ 155.6, 149.2, 147.2, 136.3, 132.6, 132.3, 128.2, 127.8, 119.7, 114.2, 113.7, 116.9, 114.2, 113.7, 112.4, 95.3, 79.9, 79.0, 69.6, 60.3, 56.0, 48.4, 47.7, 34.4, 32.6, 31.8, 28.4, 27.6, 25.7, 22.4, 20.9, 17.9, −4.8, −4.9; LRMS (EI) *m/z* (%) 312 (35), 268 (72), 237 (28), 225 (17), 180 (24), 136 (57), 109 (30), 75 (77), 57 (57), 45 (100); HRMS (EI) calcd for $C_{30}H_{49}NO_6Si$: 547.3329. Found 547.3323; Anal. Calcd for $C_{30}H_{49}NO_6Si$: C, 65.78; H, 9.02. Found C, 65.52; H, 8.85.

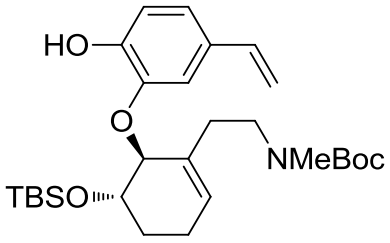
N-(2-((5*S*,6*S*)-5-((Tert-butyldimethylsilyl)oxy)-6-(2-(methoxymethoxy)-5-vinylphen-oxy) cyclohex-1-en-1-yl)ethyl)-N,4-dimethylbenzenesulfonamide (409).



To a suspension of Wittig salt $CH_3P^+Ph_3Br^-$(254 mg, 0.71 mmol) in THF (5 ml) at -78 °C, *n*-BuLi (0.28 ml, 0.64 mmol) was added and the resulting yellow solution was stirred for 15 minutes. It was then warmed to 0 °C, and aldehyde **407** (215 mg, 0.36 mmol) in THF (5 ml) was cannulated into the reaction mixture, which was stirred for another 10 minutes at 0 °C. The resulting yellow suspension was heated to reflux for 4 hours whereupon the solvent was evaporated under reduced pressure and column chromatography on silica gel using hexane/EtOAc (80:20) provided **409** (190 mg, 0.35 mmol, 89%) as a colorless liquid.

409: R_f = 0.46 [hexane/EtOAc (70:30)]; $[\alpha]_D^{20}$ = –2.6 (*c* = 0.65, $CHCl_3$); IR ($CHCl_3$) *v* 2981, 2950, 2930, 2891, 2857, 1577, 1506, 1462, 1339, 1254, 1159, 1129 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.55 (d, *J* = 8.1 Hz, 1H), 7.26-7.21 (m, 3H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.95 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.63 (d, *J* = 17.4, 10.8 Hz, 1H), 5.73 (s, 1H), 5.64 (d, *J* = 17.7 Hz, 1H), 5.17-5.12 (m, 3H), 4.62 (d, *J* = 3.9 Hz, 1H), 4.09-4.04 (m, 1H), 3.45 (s, 3H), 3.15-3.05 (m, 1H), 2.95-2.86 (m, 1H), 2.62 (s, 3H), 2.51-2.42 (m, 1H), 2.38 (s, 3H), 2.32-2.17 (m, 2H), 2.09-2.06 (m, 1H), 1.93-1.84 (m, 1H), 1.78-1.67 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.1, 147.3, 143.0, 136.2, 134.7, 132.4, 132.0, 129.5, 128.7, 127.3, 119.8, 116.9, 114.2, 112.6, 95.4, 79.6, 69.6, 56.1, 49.3, 34.9, 32.6, 27.5, 25.8, 22.4, 21.5, 18.0, −4.9, −5.0; LRMS (EI) *m/z* (%) 422 (18), 200 (11), 198 (100), 155 (72), 91 (68), 75 (72), 45 (48); HRMS (EI) calcd for $C_{32}H_{47}NO_6SSi$: 601.2893. Found 601.2877; Anal. Calcd for $C_{32}H_{47}NO_6SSi$: C, 63.86; H, 7.87. Found C, 64.00; H, 7.95.

(+)-*tert*-Butyl(2-((*5S,6S*)-5-((tert-butyldimethylsilyl)oxy)-6-(2-hydroxy-5-vinylphenoxy)cyclohex-1-en-1-yl)ethyl)(methyl)carbamate (13).

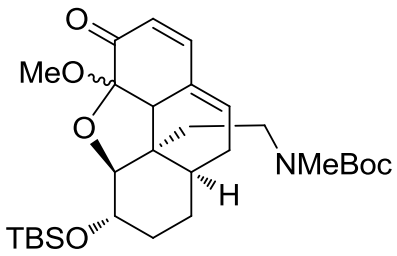


To a solution of **408** (1.3 g, 2.4 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added $ZnBr_2$ (0.59 g, 2.6 mmol) followed by 1-dodecane thiol (1.1 mL, 4.8 mmol). Then the reaction mixture was stirred for 10 minutes, diluted with CH_2Cl_2 (60 mL), then $NaHCO_3$ (sat) solution was added dropwise and the mixture was filtered through a pad of celite. The

aqueous layer was separated and further extracted with CH_2Cl_2. The combined organic solution was dried with Na_2SO_4, volatiles were removed *in vacuo* to provide crude product and column chromatography on silica gel using [hexane/EtOAc (90:10)] provided **13** (1.12 g, 2.22 mmol, 93%) as a clear liquid.

13: R_f = 0.27 [hexane/EtOAc (80:20)]; $[\alpha]_D^{20}$ = +1.0 (*c* = 3.15, $CHCl_3$); IR ($CHCl_3$) ν 3535, 3297, 2955, 2930, 2858, 1684, 1605, 1508, 1396, 1268, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, rotameric) δ 7.06 (s, 1H), 6.92-6.86 (m, 2H), 6.60 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.65 (s, 1H), 5.56 (d, *J* = 17.7 Hz, 1H), 5.09 (d, *J* = 10.8 Hz, 1H), 4.58 (s, 1H), 4.10-4.06 (m, 1H), 3.71 (bs, 0.6H), 3.15 (bs, 0.8H), 2.95-2.91 (m, 0.6H), 2.75 (s, 3H), 2.33-1.95 (m, 4H), 1.70-1.68 (m, 2H), 1.43 (s, 9H), 0.86 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, rotameric) δ 155.7, 146.8, 145.7, 136.7, 130.5, 129.2, 119.7, 115.3, 111.0, 109.8, 79.2, 78.7, 69.6, 68.7, 48.6, 47.6, 44.1, 33.8, 33.1, 31.2, 31.4, 29.6, 29.5, 29.3, 29.0, 28.4, 27.5, 26.7, 25.7, 22.7, 21.9, 17.9, −4.8; LRMS (EI) *m/z* (%) 312 (14), 268 (15), 237 (17), 228 (17), 136 (42), 109 (15), 105 (240), 83 (34), 75 (56), 57 (90), 44 (100); HRMS (EI) calcd for $C_{28}H_{45}NO_5Si$: 503.3067. Found 503.3073; Anal. Calcd for $C_{28}H_{45}NO_5Si$: C, 66.76; H, 9.00. Found C, 65.85; H, 9.07.

***tert*-Butyl (2-((3*S*,3a*S*)-3-((tert-butyldimethylsilyl)oxy)-4a-methoxy-5-oxo-1,2,3,3a, 3a1,4a,4a1,5,9,9a-decahydrophenanthro[4,5-bcd]furan-3a1-yl)ethyl)(methyl)carbamate (411)**.

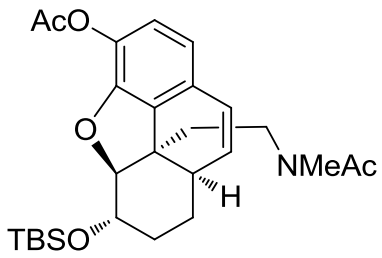


To a solution of **13** (110 mg, 0.22 mmol) in MeOH (5 ml) PIDA (84.4 mg, 0.26 mmol) in MeOH (5 ml) was added via a syringe pump over one hour. TLC analysis showed the complete consumption of starting material, then the reaction mixture was diluted with CH_2Cl_2, washed with $NaHCO_3$ (sat.) solution, dried over Na_2SO_4 and solvent was evaporated *in vacuo* to provide crude product. It was dissolved in toluene (3 ml) and was heated to reflux in a sealed tube for 18 hours. Then the reaction mixture was directly loaded to a silica column, toluene was eluted using hexanes, and the product **411** (29 mg, 0.05 mmol, 25%) was eluted using hexane/EtOAc (80:20).

411: R_f = 0.24 [hexane/EtOAc (70:30)]; $[\alpha]_D^{20}$ = +25 (*c* = 0.45, $CHCl_3$); IR ($CHCl_3$) ν 2959, 2927, 2858, 1681, 1622, 1482, 1462, 1393, 1266 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.07 (d, *J* = 9.9 Hz, 1H), 6.03 (t, *J* = 2.7 Hz, 1H), 5.95 (d, *J* = 9.9 Hz, 1H), 3.99-3.89 (m, 2H), 3.61-3.51 (m, 1H), 3.37 (s, 3H), 3.09 (s, 1H), 2.94 (bs, 1H), 2.71 (s, 4H), 2.25-2.02 (m, 3H), 1.84-1.72 (m, 3H), 1.42 (s, 9H), 1.25-1.12 (m, 2H), 0.89 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.4, 155.4, 143.2, 132.1, 125.7,

100.1, 88.4, 79.5, 72.7, 52.5, 50.5, 49.9, 34.1, 33.2, 32.6, 29.3, 28.4, 25.8, 17.9, −4.3, −4.5.

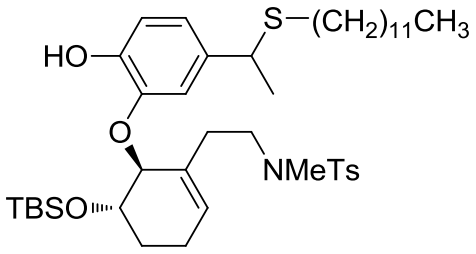
(3*S*,3a*S*)-3a1-(2-(*N*-Methylacetamido)ethyl)-1,2,3,3a,3a1,9a-hexahydrophenanthro [4,5-bcd]furan-3,5-diyl diacetate (412).



To a solution of **411** (5 mg, 0.01 mmol) in CH_2Cl_2 at room temperature Ac_2O (0.1 ml) and TFA (0.1 ml) was added and was stirred for 18 hours. Then the reaction mixture was neutralised with $NaHCO_3$ (sat) solution, organic layer was separated, dried over Na2SO4 and solvent was evaporated *in vacuo* to provide crude product. It was then passed through a silica gel pipette column using EtOAc as eluent to yield (1.7 mg, 0.004 mmol, 40%) as an yellow liquid.

412: R_f = 0.19 [EtOAc]; IR ($CHCl_3$) ν 3008, 2929, 2851, 2340, 1759, 1666, 1632 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.96-6.85 (m, 3H), 6.17-6.11 (m, 1H), 4.79 (d, J = 7.2 Hz, 1H), 4.45-4.48 (m, 1H), 3.76-3.71 (m, 1H), 3.51-3.47 (m, 1H), 3.13 (s, 3H), 2.86 (s, 1H), 2.62 (bs, 1H), 2.10 (s, 3H), 2.09 (s, 6H); LRMS (EI) *m/z* (%) 413 (2), 371 (5), 212 (14), 211 (13), 149 (17), 101 (100); HRMS (EI) calcd for $C_{23}H_{27}NO_6$: 413.1838. Found 413.1837.

(+)-*N*-(2-((5*S*,6*S*)-5-((Tert-butyldimethylsilyl)oxy)-6-(5-(1-(dodecylthio)ethyl)-2-hydroxyphenoxy)cyclohex-1-en-1-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide (413).

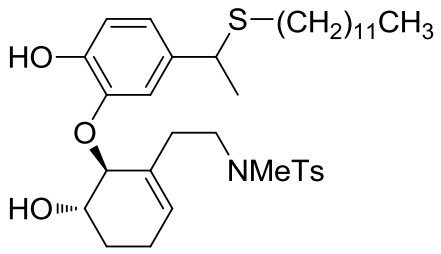


To a solution of **409** (190 mg, 0.35 mmol) in CH_2Cl_2 (4 ml) at 0 °C was added $ZnBr_2$ (86.0 mg, 0.38 mmol) followed by 1-dodecane thiol (0.16 ml, 0.7 mmol). Then the reaction mixture was stirred for 10 minutes, diluted with CH_2Cl_2 (15 ml), then $NaHCO_3$ (sat) solution was added dropwise and the mixture was filtered through a pad of celite. The aqueous layer was separated and further extracted with CH_2Cl_2. The combined organic solution was dried with Na_2SO_4, volatiles were removed *in vacuo* to provide crude product and column chromatography on silica gel using [hexane/EtOAc (90:10)→hexane/EtOAc (70:30)] provided **413** (122 mg, 0.16 mmol, 46%) and **414** (83 mg, 0.13 mmol, 37%) as clear liquids.

413: R_f = 0.45 [hexane/EtOAc (70:30)]; $[\alpha]_D^{20}$= +7.02 (*c* = 0.87, $CHCl_3$); IR ($CHCl_3$) ν 3536, 3456, 3030, 2923, 2853, 1686, 1598, 1505, 1436, 1341, 1305, 1152, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.60 (dd, *J* = 8.1, 1.8 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.86 (dd, *J* = 10.2, 8.1 Hz, 2H), 6.13-6.07 (m, 1H), 5.79 (s, 1H), 4.64-4.60 (m, 1H), 4.08 (d, *J* = 2.1 Hz, 1H), 3.92-3.84 (m, 1H), 3.04 (t, *J* = 7.2 Hz, 2H), 2.62 (s, 3H), 2.41 (s, 3H), 2.41-2.26 (m, 5H), 2.13-2.07 (m, 1H), 1.86-1.73 (m, 2H), 1.53-1.47 (m, 5H), 1.26-1.25 (m, 20H), 0.87 (s, 9H), 0.07-0.04 (m, 6H); ^{13}C NMR ($CDCl_3$, 75

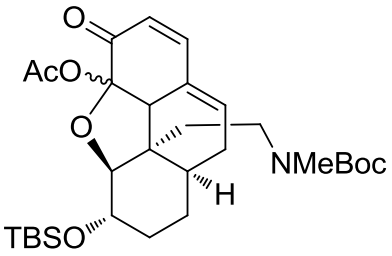
MHz) δ 145.5, 145.4, 145.2, 143.1, 136.2, 134.7, 131.1, 130.9, 129.6, 127.3, 120.6, 120.5, 114.8, 114.7, 112.4, 112.3, 78.9, 69.3, 69.1, 49.3, 44.1, 34.7, 32.5, 32.4, 31.9, 31.4, 29.6, 29.5, 29.4, 29.3, 29.0, 27.3, 27.1, 25.8, 23.2, 22.8, 22.7, 22.2, 22.1, 18.0, 14.1, −4.6, −4.7; HRMS (EI) calcd for $C_{42}H_{69}NO_5S_2Si$: 759.

_N_-(2-((5*S*,6*S*)-6-(5-(1-(Dodecylthio)ethyl)-2-hydroxyphenoxy)-5-hydroxycyclohex-1-en-1-yl)ethyl)-N,4-dimethylbenzenesulfonamide (414).



414: R_f = 0.19 [hexane/EtOAc (70:30)]; $[\alpha]_D^{20}$ = +18.2 (*c* = 0.87, $CHCl_3$); IR ($CHCl_3$) *v* 3447, 2921, 2851, 1597, 1507, 1435, 1336, 1265, 1201, 1155, 1117, 1088, 1003 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.62 (dd, *J* = 8.1, 2.7 Hz, 2H), 7.30-7.27 (m, 2H), 7.12 (s, 1H), 6.87 (s, 2H), 6.28 (bs, 1H), 5.81 (s, 1H), 4.77 (s, 1H), 4.16-4.11 (m, 1H), 3.90 (dd, *J* = 13.8, 6.9 Hz, 1H), 3.24-3.13 (m, 1H), 3.03-2.93 (m, 1H), 2.65 (s, 3H), 2.42 (s, 3H), 2.36-2.22 (m, 5H), 1.90-1.79 (m, 2H), 1.55-1.47 (m, 5H), 1.26 (d, *J* = 4.2 Hz, 19H), 0.91-0.87 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.4, 143.3, 136.3, 134.7, 131.0, 129.9, 129.7, 127.3, 121.0, 115.1, 113.2, 113.1, 79.2, 68.9, 49.1, 43.8, 34.5, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 26.4, 22.9, 22.7, 22.1, 21.5, 14.1; LRMS (EI) *m/z* (%) 202 (17), 198 (100), 155 (76), 136 (26), 111 (16), 99 (19), 98 (36), 91 (80), 83 (50), 69 (56), 55 (60), 43 (61); HRMS (EI) calcd for $C_{36}H_{55}NO_5S_2$: 645.3522. Found 645.3476.

(–)-(4a*S*,4a1*R*,5*S*,7a*R*)-4a1-(2-((*tert*-Butoxycarbonyl)(methyl)amino)ethyl)-5-((tert-butyldimethylsilyl)oxy)-3-oxo-3,3a,3a1,4a,4a1,5,6,7,7a,8-decahydrophenanthro[4,5-bcd]furan-3a-yl acetate (416).

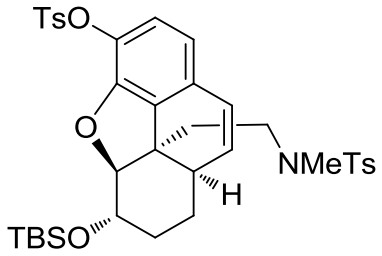


A solution of lead tetraacetate (37.9 mg, 0.08 mmol) in DCE (1 mL) was added dropwise to a refluxing solution of **13** (43 mg, 0.08 mmol) in DCE (1 mL). The reaction mixture was stirred for another 4 hours, cooled to room temperature, and then passed through a plug of celite and solvent was evaporated under reduced pressure to obtain the crude product which was purified by column chromatography on silica gel using [hexane/EtOAc (90:10) → hexane/EtOAc (70:30)] as eluent to provide **416** (24 mg, 0.04 mmol, 50%) as a colourless liquid.

416: R_f = 0.46 [hexane/EtOAc (70:30)]; $[\alpha]_D^{20}$ = –22.0 (c = 1.2, $CHCl_3$); IR ($CHCl_3$) ν 3024, 3009, 2951, 2931, 2858, 1730, 1686, 1625, 1462, 1368, 1252, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, rotameric) δ 7.06 (d, J = 9.9 Hz, 1H), 6.47 (bt, J = 3.6 Hz, 1H), 5.98 (d, J = 9.9 Hz, 1H), 4.15-4.05 (m, 1H), 3.42-3.10 (m, 4H), 2.87 (s, 3H), 2.27-2.22 (m, 2H), 2.16 (bs, 1H), 2.13 (s, 3H), 2.04-2.02 (m, 2H), 1.72 (bs, 1H), 1.53-1.51 (m, 1H), 1.47 (s, 9H), 1.14-1.05 (m, 2H), 0.84 (s, 9H), −0.01 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, rotameric) δ 188.2, 170.9, 155.4, 144.5, 139.0, 134.2, 122.7, 103.9, 90.6, 79.7, 74.2, 73.5, 52.0, 48.6, 45.9, 45.4, 40.7, 39.8, 38.6, 37.3, 34.4, 30.8, 29.4, 28.5, 25.8,

21.3, 20.6, 18.1, −4.6, −5.1; LRMS (EI) *m/z* (%) 388 (10), 345 (10), 313 (12), 287 (25), 171 (15), 83 (12), 75 (23), 73 (45), 59 (34), 57 (87), 44 (100); HRMS (EI) calcd for $C_{30}H_{47}NO_7Si$ (M^+–$C_2H_4O_2$): 501.2911. Found 501.2910; Anal. Calcd for $C_{30}H_{47}NO_7Si$: C, 64.14; H, 8.43. Found C, 64.03; H, 8.45.

(–)-(4a*S*,4a1*R*,5*S*,7a*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4a1-(2-(*N*,4-dimethylphenylsulfonamido)ethyl)-4a,4a1,5,6,7,7a-hexahydro phenanthro[4,5-bcd]furan-3-yl 4-methylbenzenesulfonate (419).



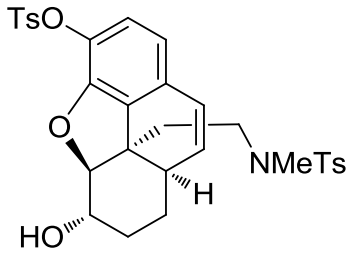
A solution of **416** (16 mg, 0.028 mmol) in CH_2Cl_2 (1.5 mL) was cooled in an ice bath and TFA (0.5 mL) was added dropwise. The reaction mixture was stirred for 10 minutes, diluted with CH_2Cl_2 (4.5 mL) and the pH of the reaction mixture was adjusted to ~7 using saturated Na_2CO_3 solution. The organic layer was separated, washed with water, dried over Na_2SO_4 and evaporated *in vacuo* to obtain the crude product (**417**) which was immediately taken to next step without further purification.

A solution of **417** in CH_2Cl_2 was cooled in an ice bath, was added Et_3N (6.3 µL, 0.045 mmol) and TsCl (8.6 mg, 0.045 mmol) and the resulting reaction mixture was stirred for 10 hours. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel using [hexane/EtOAc (90:10) →

hexane/EtOAc (80:20)] as eluent to provide **419** (9 mg, 0.013 mmol, 46% over two steps) as a light yellow oil.

419: R_f = 0.47 [hexane/EtOAc (70:30)]; $[\alpha]_D^{20}$ = –106.5 (*c* = 0.42, $CHCl_3$); IR ($CHCl_3$) *v* 3027, 2929, 2857, 1599, 1490, 1446, 1378, 1341, 1274, 1221, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.31-7.26 (m, 4H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.59 (d, *J* = 8.1 Hz, 1H), 6.35 (d, *J* = 9.6 Hz, 1H), 5.92 (dd, *J* = 9.6, 5.7 Hz, 1H), 4.36 (d, *J* = 6.9 Hz, 1H), 3.31-3.23 (m, 1H), 3.05-2.95 (m, 1H), 2.82-2.72 (m, 1H), 2.59 (s, 3H), 2.44 (s, 3H), 2.40 (s, 3H), 2.36-2.34 (m, 1H), 1.77-1.68 (m, 2H), 1.63-1.55 (m, 3H), 1.25-1.17 (m, 1H), 0.88 (s, 9H), 0.08 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.2, 145.3, 143.3, 134.6, 133.0, 132.8, 132.7, 129.7, 129.6, 129.2, 128.9, 128.8, 127.4, 124.1, 122.5, 117.7, 98.2, 73.9, 46.1, 44.7, 39.7, 35.8, 34.8, 29.8, 29.7, 26.6, 25.8, 21.7, 21.5, 18.1, −4.6, −5.0; LRMS (EI) *m/z* (%) 653 (3), 198 (34), 155 (12), 149 (19), 124 (28), 123 (13), 100 (42), 92 (17), 91 (58), 83 (16), 57 (35), 43 (100); HRMS (EI) calcd for $C_{37}H_{47}NO_7S_2Si$ (M^+–C_4H_9): 652.1859. Found 652.1852; Anal. Calcd for $C_{37}H_{47}NO_7S_2Si$: C, 62.59; H, 6.67. Found C, 62.52; H, 6.63.

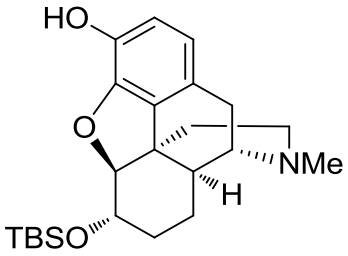
(–)-(4a*S*,4a1*R*,5*S*,7a*R*)-4a1-(2-(N,4-Dimethylphenylsulfonamido)ethyl)-5-hydroxy-4a,4a1,5,6,7,7a-hexahydrophenanthro[4,5-bcd]furan-3-yl 4-methylbenzenesulfonate (420).



To a mixture of **419** (141 mg, 0.19 mmol) and THF (5 mL) at room temperature was added tetrabutylammonium fluoride (TBAF) solution in THF (0.34 mL, 0.34 mmol). The resulting mixture was stirred for 6 hours and the solvent was evaporated under reduced pressure to provide the crude product, which was purified by column chromatography on silica gel using [hexane/EtOAc (70:30) → hexane/EtOAc (50:50)] as eluent to provide **420** (101 mg, 0.17 mmol, 86%) as a clear oil.

420: R_f = 0.29 [hexane/EtOAc (50:50)]; $[\alpha]_D^{20}$ = –20.4 (*c* = 0.55, $CHCl_3$); IR ($CHCl_3$) ν 3518, 3033, 2926, 2861, 1597, 1489, 1445, 1335, 1191, 1177, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.1 Hz, 2H), 7.33-7.26 (m, 4H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 6.35 (d, *J* = 9.6 Hz, 1H), 5.93 (dd, *J* = 9.6, 5.7 Hz, 1H), 4.48 (d, *J* = 7.2 Hz, 1H), 3.08-2.98 (m, 2H), 2.84-2.74 (m, 1H), 2.57 (s, 3H), 2.47-2.36 (m, 8H), 1.88-1.56 (m, 4H), 1.27-1.15 (m, 1H), 0.89-0.76 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 145.6, 143.4, 134.3, 133.0, 132.6, 129.7, 129.3, 129.1, 128.7, 127.4, 123.8, 122.5, 117.9, 98.0, 76.7, 72.9, 46.1, 44.7, 39.3, 35.2, 34.8, 27.8, 26.9, 21.7, 21.5; LRMS (EI) *m/z* (%) 595 (1), 440 (4), 384 (3), 229 (7), 198 (10), 155 (35), 139 (13), 124 (20), 97 (13), 92 (18), 91 (100), 69 (21), 57 (30); HRMS (EI) calcd for $C_{31}H_{33}NO_7S_2$: 595. 1698. Found 595. 1693.

(+)-(4*S*,4a*S*,7*S*,7a*S*,12b*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-9-ol (421).

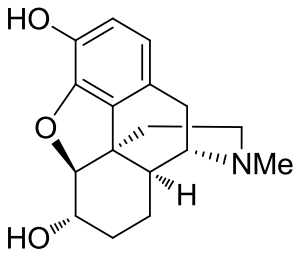


To a mixture of *t*BuOH (64 μL, 0.62 mmol) and THF (2 mL) at −78 °C was added liquid NH_3 (~15 mL) and Li wire (37 mg, 5.3 mmol). The resulted blue colour reaction mixture was stirred for five minutes and **419** (35 mg, 0.05 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred for another 10 minutes while it remained blue in colour. Then 2 g of NH_4Cl was added as a solid, followed by 10 mL of MeOH and 20 mL of saturated NH_4Cl solution. This mixture was then washed three times with CH_2Cl_2 (20 mL), the combined organic layers were washed with saturated NaCl solution, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to provide the crude product, which was purified by column chromatography on silica gel using [CH_2Cl_2/MeOH (95:5) → CH_2Cl_2/MeOH (90:10)] as eluent to provide **421** (16 mg, 0.04 mmol, 82%) as a colourless oil.

421: R_f = 0.24 [CH_2Cl_2/MeOH (90:10)]; $[\alpha]_D^{20}$ = +70.5 (*c* = 0.8, $CHCl_3$); IR ($CHCl_3$) ν 3688, 3586, 2953, 2931, 2858, 1624, 1604, 1505, 1455, 1220, 1119, 1098 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.70 (d, *J* = 8.4 Hz, 1H), 6.58 (d, *J* = 7.8 Hz, 1H), 4.91 (bs, 1H), 4.31 (d, *J* = 6.6 Hz, 1H), 3.39-3.35 (m, 1H), 3.25 (d, *J* = 2.4 Hz, 1H), 2.98 (d, *J* = 18.6 Hz, 1H), 2.68 (dd, *J* = 12, 4.2 Hz, 1H), 2.46 (s, 3H), 2.44-2.43 (m, 1H), 2.28-2.22 (m,

2H), 2.03 (s, 1H), 1.95-1.90 (m, 1H), 1.67-1.65 (m, 2H), 1.53-1.50 (m, 1H), 1.39-1.32 (m, 1H), 0.88 (s, 9H), 0.10 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.0, 139.9, 129.9, 124.5, 119.2, 117.0, 97.3, 73.7, 59.5, 46.9, 42.9, 42.2, 41.7, 34.7, 31.6, 25.8, 23.4, 20.4, 18.1, −4.5, −4.8; LRMS (EI) *m/z* (%) 401 (3), 120 (29), 118 (32), 87 (92), 85 (80), 83 (76), 60 (30), 47 (100), 43 (44); HRMS (EI) calcd for $C_{23}H_{35}NO_3Si$: 401.2386. Found 401.2375.

(+)-(4*S*,4a*S*,7*S*,7a*S*,12b*R*)-3-Methyl-2,3,4,4a,5,6,7,7a-octahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinoline-7,9-diol (422).

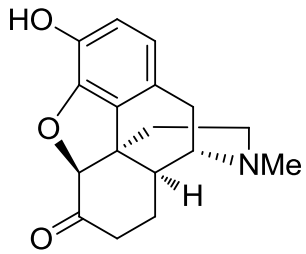


To a mixture of *t*BuOH (35 µL, 0.34 mmol) and THF (2 mL) at −78 °C was added liquid NH_3 (~15 mL) and Li wire (20 mg, 2.85 mmol). The resulted blue colour reaction mixture was stirred for five minutes and **420** (20 mg, 0.03 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred for another 10 minutes while the reaction mixture remained blue in colour. Then 2 g NH_4Cl was added as a solid, followed by 10 mL of MeOH and 20 mL of saturated NH_4Cl solution. This mixture was then washed three times with CH_2Cl_2 (20 mL), the combined organic washes were washed with saturated NaCl solution and was further dried over Na_2SO_4. The solvent was evaporated under reduced pressure to provide the crude product, which was purified by

column chromatography on silica gel using [CH_2Cl_2/MeOH (90:10) → CH_2Cl_2/MeOH (80:20) → MeOH] as eluent to provide **422** (9.1 mg, 0.03 mmol, 93%) as a white solid.

422: R_f = 0.15 [CH_2Cl_2/MeOH (80:20)]; mp >200 °C; $[\alpha]_D^{20}$ = +57.0 (*c* = 0.35, MeOH); IR ($CHCl_3$) ν 3311, 2923, 1599, 1462, 1313, 1255, 1084 cm^{-1}; ^1H NMR (600 MHz, MeOD) δ 6.71 (d, *J* = 7.8 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 4.33 (d, *J* = 6.6 Hz, 1H), 3.66 (s, 1H), 3.16 (d, *J* = 19.2 Hz, 1H), 3.02 (d, *J* = 11.4 Hz, 1H), 2.78 (s, 3H), 2.64-2.60 (m, 1H), 2.39 (d, *J* = 9.6 Hz, 1H), 2.10-2.05 (m, 1H), 1.81 (d, *J* = 10.6 Hz, 2H), 1.68-1.66 (m, 1H), 1.43-1.31 (m, 2H), 1.03-0.97 (m, 1H), 0.93–0.90 (m, 1H); ^{13}C NMR (150 MHz, MeOD) δ 142.9, 140.9, 128.5, 122.1, 119.3, 117.5, 95.5, 72.1, 60.9, 47.2, 42.1, 40.6, 40.4, 33.2, 30.1, 22.9, 20.8; MS (EI) *m/z* (%) 287 (92), 286 (23), 230 (22), 228 (10), 164 (17), 149 (15), 97 (17), 84 (26), 70 (32), 57 (53), 43 (100); HRMS (EI) calcd for $C_{17}H_{21}NO_3$: 287.1521. Found 287.1519.

(+)-(4*S*,4a*S*,7a*S*,12b*R*)-9-Hydroxy-3-methyl-2,3,4,4a,5,6-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7(7aH)-one (16).

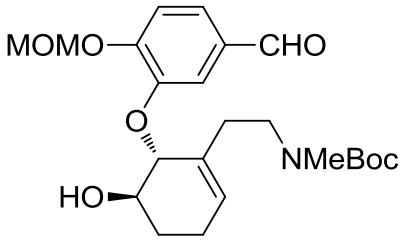


To a suspension of **422** (8.0 mg, 0.028 mmol) and benzophenone (10.2 mg, 0.056 mmol) in a mixture of toluene (1 mL) and DME (1 mL) was added potassium *tert*-butoxide (18 mg, 0.16 mmol) at room temperature. The resulting reaction mixture was heated at 85 °C for 8 hours and then the solvent was evaporated under reduced pressure to obtain the

crude reaction mixture, which was purified by column chromatography on silica gel using [CH_2Cl_2/MeOH (95:5) → CH_2Cl_2/MeOH (90:10)] as eluent to provide **16** (3.5 mg, 0.012 mmol, 44%) as a white solid along with unreacted starting material **422** (4 mg, 0.014 mmol, 53%). The physical and spectral properties of **16** were matched with those given in the literature.[3]

16: R_f = 0.41 [CH_2Cl_2/MeOH (80:20)]; mp >200 ^oC; [lit.[3] m.p. 266-267 °C (ethanol)]; $[\alpha]_D^{20}$ = +190.0 (*c* = 0.13, dioxane), [lit. [3] $[\alpha]_D^{20}$ = –194 (*c* = 0.98, dioxane); ^{1}H NMR (300 MHz, MeOD) δ 6.70 (dd, *J* = 14.1, 8.4 Hz, 2H), 4.61 (s, 1H), 3.56 (bs, 1H), 3.14 (d, *J* = 19.2 Hz, 1H), 2.95-2.89 (m, 1H), 2.77-2.72 (m, 4H), 2.60-2.52 (m, 1H), 2.36-2.32 (m, 1H), 2.00-1.87 (m, 1H), 1.80 (dd, *J* = 13.2, 2.7 Hz, 1H), 1.68 (dd, *J* = 13.2, 2.4 Hz, 1H), 1.45-1.40 (m, 1H), 1.14-1.05 (m, 1H), 0.92-0.89 (m, 1H).

***tert*-Butyl (2-((5*R*,6*R*)-6-(5-formyl-2-(methoxymethoxy)phenoxy)-5-hydroxycyclohex-1-en-1-yl)ethyl)(methyl)carbamate (423).**

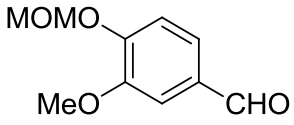


Potassium phenoxide (196 mg, 0.89 mmol) and epoxide **273** (75 mg, 0.30 mmol) were taken in a mixture of DMF (0.8 mL0 and DME (0.8 mL) in a sealed tube and was purged vigorously with argon. Then catalytic amount of 18-crown-6 was added and was heated at 80 °C for 24 hours. Then the reaction mixture was cooled to room temperature and Et_2O (20mL) was added, washed with sat. Na_2CO_3 solution (5 mL), and with water (1

mLx6). The organic layer was dried over Na_2SO_4 and slvent was evaporated under reduced pressure to obtain 115 mg of crude product. Pure product was separated by column chromatography on silica gel with [hexane/EtOAc (90:10) → hexane/EtOAc (50:50)] as eluent to yield **423** (88 mg, 0.20 mmol, 68%) as light yellow oil.

423: R_f = 0.19 [hexane/EtOAc (70:30), three run]; $[\alpha]_D^{19}$ = –27.6 (*c* = 1.0, $CHCl_3$); IR (neat) *v* 3430, 3004, 2973, 2927, 2846, 2725, 1685, 1593, 1582, 1483, 1257, 1153 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, rotameric) δ 7.61 (bs, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 5.84 (bs, 1H), 5.25 (s, 2H), 4.67 (d, *J* = 3 Hz, 1H), 4.11-4.04 (m, 1H), 3.86-3.59 (m, 1H), 3.45 (s, 3H), 2.81 (s, 3H), 2.38-2.08 (m, 4H), 1.88-1.74 (m, 2H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, rotameric) δ 190.8, 171.1, 156.8, 153.4, 153.0, 148.9, 146.83, 131.1, 131.0, 130.4, 130.0, 127.5, 125.9, 117.4, 116.9, 115.8, 115.5, 94.9, 94.7, 92.5, 79.8, 66.2, 60.4, 56.5, 46.4, 34.0, 32.6, 28.4, 24.6, 21.0, 14.2.

3-Methoxy-4-(methoxymethoxy)benzaldehyde (427).

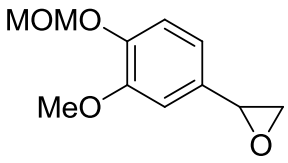


A solution of vanillin (2.0 g, 13.14 mmol) in CH_2Cl_2 at 0 °C was added Hunig's base (2.75 mL, 15.8 mmol) followed by MOMCl (1.19 mL, 15.8 mmoml). The resulting reaction mixture was stirred for 12 h. It was then diluted with H_2O (30 mL) and was extracted with CH_2Cl_2 (3x20 mL). Organic washes were combined and was washed with brine solution (20 mL), dried over Na_2SO_4 and solvent was evaporated under reduced pressure to provide crude product. Pure product was separated by column

chromatography on silica gel with hexane/EtOAc (80:20) as eluent to yield **427** (36 g, 1:1.8 ratio, 0.07 mol, 65%) as an oil.

427: R_f = 0.31 [hexane/EtOAc (70:30)]; IR (neat) *v* 2954, 2931, 2915, 2872, 2828, 1679, 1585, 1505, 1466, 1420, 1395, 1258, 1150, 1124, 1081 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.24-7.21 (m, 1H), 7.07 (d, *J* = 8.7 Hz, 1H), 5.13 (s, 2H), 3.74 (s, 3H), 3.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 151.8, 149.9, 130.9, 126.0, 114.6, 109.4, 94.8, 56.2, 55.7; LRMS (EI) *m/z* (%) 196 (100), 166 (34), 165 (20), 151 (17), 119 (15), 105 (13), 95 (13), 79 (19), 77 (20), 76 (18), 51 (12); HRMS (EI) calcd for $C_{10}H_{12}O_4$: 196.0736. Found 196.0738.

2-(3-Methoxy-4-(methoxymethoxy)phenyl)oxirane (429).

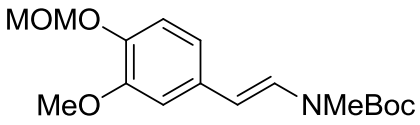


A 50% $NaOH_{(aq)}$ solution (2 mL) was added to a solution of trimethysulfonium methylsulfate (585 mg, 3.1 mmol) in CH_2Cl_2 (2 mL). Then a solution of aldehyde (508 mg, 2.8 mmol) in CH_2Cl_2 (2 mL) was added and the resulting yellow suspension was stirred for 18 hours. Then the reaction mixture was diluted with H_2O (50 mL) and the product was extracted with CH_2Cl_2 (3x25 mL). Organic washes were combined and was washed with brine solution (20 mL), dried over Na_2SO_4 and solvent was evaporated under reduced pressure to provide product **429** (514 mg, 2.4 mmol, 87%) as a colorless oil.

429: R_f = 0.28 [hexane/EtOAc (70:30)]; IR (neat) *v* 3050, 2991, 2937, 2902, 2828, 1607, 1592, 1514, 1463, 1423, 1393, 1262, 1200, 1153, 1132, 1075, 1034 cm^{-1}; ^1H NMR (300

MHz, $CDCl_3$) δ 7.06 (d, J = 8.1 Hz, 1H), 6.79 (dd, J = 8.4, 2.1 Hz, 1H), 6.73 (d, J = 2.1 Hz, 1H), 5.16 (s, 2H), 3.81 (s, 3H), 3.76 (dd, J = 3.9, 2.4 Hz, 1H), 3.45 (s, 3H), 3.05 (dd, J = 5.4, 3.9 Hz, 1H), 2.71 (dd, J = 5.7, 2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 146.4, 131.8, 118.3, 116.4, 108.4, 95.4, 56.1, 55.8, 52.2, 51.0; LRMS (EI) *m/z* (%) 210 (100), 180 (19), 165 (11), 157 (10), 151 (87), 135 (14), 105 (18), 91 (17), 77 (22), 65 (13); HRMS (EI) calcd for $C_{1l}H_{14}O_4$: 210.0892. Found 210.0891.

(E)-tert-Butyl 3-methoxy-4-(methoxymethoxy)styryl(methyl)carbamate (431).

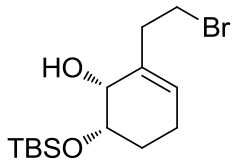


To a solution of MeNHBoc (129 mg, 0.98 mmol) in THF (4 mL) at –78 °C was added *n*-BuLi (0.41 mL, 0.98 mmol) and was stirred for 15 minutes. A solution of epoxide (173 mg, 0.82 mmol) in THF (4 mL) was cooled to –10 °C in a separate vessel and $BF_3.OEt_2$ was added and the reaction mixture from the first vessel was cannulated to it after 5 minutes. The resulting reaction mixture was stirred for 3 hours and was diluted with CH_2Cl_2 (25 mL), washed with H_2O (3x5 mL). Organic layer was washed with brine solution (8 mL), dried over Na_2SO_4 and solvent was evaporated under reduced pressure to provide crude product. Pure product was separated by column chromatography on neutral alumina with hexane/EtOAc (95:5) as eluent to yield **431** (118 mg, 0.36 mmol, 45%) as a colorless oil.

431: R_f = 0.45 [hexane/EtOAc (70:30)]; IR (neat) ν 2954, 2931, 2915, 2872, 2828, 1679, 1585, 1505, 1466, 1420, 1395, 1258, 1150, 1124, 1081 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, rotameric) δ 7.69 (d, J = 14.0 Hz, 0.5H), 7.47 (d, J = 13.6 Hz, 0.5H), 7.03 (d, J = 6.8 Hz,

1H), 6.88-6.78 (m, 2H), 5.70 (d, J = 14.8 Hz, 1H), 5.17 (s, 2H), 3.85 (s, 3H), 3.48 (s, 3H), 3.10 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, rotameric) δ 156.6, 153.4, 152.8, 149.9, 144.9, 132.1, 128.4, 128.0, 125.9, 121.9, 118.4, 117.6, 116.8, 116.7, 113.1, 109.2, 108.4, 108.0, 95.6, 81.4, 56.1, 55.8, 31.3, 30.6, 29.7, 28.2; LRMS (EI) *m/z* (%) 210 (32), 196 (27), 162 (16), 151 (37), 144 (11), 117 (27), 77 (12), 76 (16), 57 (100); HRMS (EI) calcd for $C_{17}H_{25}NO_5$: 323.1733. Found 323.1722.

(–)-(1*R*,6*S*)-2-(2-Bromoethyl)-6-((tert-butyldimethylsilyl)oxy)cyclohex-2-enol (12).

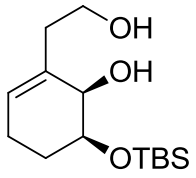


To a solution of alcohol (3.05 g, 13.8 mmol) in CH_2Cl_2 (35 mL) at –78 °C was added TBSCl (2.29 g, 15.2 mmol) followed by imidazole (1.03 g, 15.2 mmol). The resulting reaction mixture was stirred for 18 hours while it was slowly warmed to room temperature. Then it was diluted with CH_2Cl_2 (100 mL), washed with 10% $CuSO_4$ solution $_{(aq)}$ (3x30 mL), H_2O (30 mL), brine solution (20 mL), dried over Na_2SO_4 and solvent was evaporated under reduced pressure to provide crude product. Pure product was separated by column chromatography on silica gel with hexane/EtOAc (95:5) as eluent to yield **12** (3.7 g, 11.0 mmol, 80%) as a colorless oil.

12: R_f = 0.25 [hexane/EtOAc (95:5)]; $[\alpha]_D^{19}$ = –47.7 (c = 1.5, $CHCl_3$); IR (neat) ν 3553, 2951, 2928, 2883, 2856, 1470, 1462, 1387, 1252, 1080 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62 (t, J = 3.6 Hz, 1H), 3.87 (s, 1H), 3.79 (dt, J = 10.5, 3.6 Hz, 1H), 3.57-3.42 (m, 2H), 2.78-2.67 (m, 1H), 2.63 (s, 3H), 2.62-2.53 (m, 2H), 2.19-2.12 (m, 1H), 2.03-

1.95 (m, 1H), 1.82-1.69 (m, 1H), 1.58-1.50 m, 1H), 0.89 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.8, 127.8, 70.8, 68.7, 38.5, 32.0, 25.9, 25.5, 24.0, 18.1, –4.4, –4.8; LRMS (EI) *m/z* (%) 279 (15), 277 (15), 198 (28), 197 (100), 179 (13), 167 (19), 105 (29), 103 (13), 91 (21), 81 (15), 77 (16), 75 (62), 73 (14), 59 (13), 55 (13); HRMS (EI) calcd for $C_{14}H_{27}BrO_2Si$ (M^+-C_4H_9): 277.0260. Found 277.0255; Anal. Calcd for $C_{14}H_{27}BrO_2Si$: C, 50.14; H, 8.12. Found C, 50.33; H, 8.20.

(1*R*,6*S*)-6-((tert-Butyldimethylsilyl)oxy)-2-(2-hydroxyethyl)cyclohex-2-enol (432).

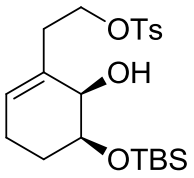


To a solution of acetate (1.24g, 3.96 mmol) in MeOH (6 mL) was added NaOMe/MeOH and was stirred at room temperature for 30 minutes. Then acidic Dowex-50 resin was added until the pH of the reaction mixture was changed to approximately 6-7. Then the solids were filtered off and the solvent was evaporated *in vacuo* to provide the product **432** (0.98 g, 3.62 mmol, 91%) as a colorless oil.

432: R_f = 0.27 [hexane/EtOAc (60:40)]; $[\alpha]_D^{19}$ = –39.6 (*c* = 0.54, $CHCl_3$); IR ($CHCl_3$) ν 3379, 2950, 2928, 2883, 2856, 1471, 1462, 1319, 1083 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5. 60 (s, 1H), 3.82 (d, *J* = 3.6 Hz, 1H), 3.76-3.53 (m, 3H), 3.36 (s, 3H), 2.60-2.50 (m, 1H), 2.41-2.33 (m, 1H), 2.22-1.87 (m, 4H), 1.79-1.65 (m, 1H), 1.52-1.48 (m, 1H), 0.85 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, rotameric) δ 134.8, 133.4, 128.3, 126.6, 71.0, 70.8, 69.3, 68.4, 62.0, 61.0, 50.3, 39.7, 36.1, 26.2, 25.8, 25.6, 24.9,

24.6, 21.5, 18.1, 18.0, −4.5, −4.9; Anal. Calcd for $C_{14}H_{28}O_3Si$: C, 61.72; H, 10.36. Found C, 61.57; H, 10.39.

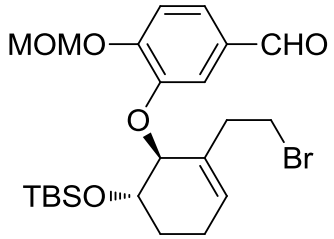
2-((5*S*,6*R*)-5-((tert-Butyldimethylsilyl)oxy)-6-hydroxycyclohex-1-en-1-yl)ethyl 4-methylbenzenesulfonate (433).



A solution of **432** (900 mg, 3.3 mmol) in CH_2Cl_2 was cooled in an ice bath, was added pyridine (0.53 mL, 6.6 mmol) and TsCl (756 mg, 3.96 mmol) and the resulting reaction mixture was stirred for 18 hours. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel using [hexane/EtOAc (90:10) → hexane/EtOAc (80:20)] as eluent to provide **433** (565 mg, 1.33 mmol, 40%) as an yellow oil.

433: R_f = 0.56 [hexane/EtOAc (60:40)]; $[\alpha]_D^{19}$ = –20.5 (c = 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, rotameric) δ 7.69 (d, J = 8.1 Hz, 2H), 7.26 (dd, J = 8.4, 2.4 Hz, 2 H), 5.45 (d, J = 12.6 Hz, 1H), 4.17-3.95 (m, 4H), 2.43-2.32 (m, 5H), 2.02-1.82 (m, 2H), 1.63-1.43 (m, 2H), 0.83 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, rotameric) δ 144.6, 144.5, 133.3, 133.1, 132.3, 129.8, 129.7, 128.0, 127.8, 127.7, 70.8, 70.6, 69.3, 69.2, 68.7, 67.9, 34.3, 32.3, 31.5, 26.1, 25.7, 25.4, 23.9, 21.5, 21.3, 18.0, 14.1, –4.4, –4.6; Anal. Calcd for $C_{23}H_{35}BrO_5Si$: C, 59.12; H, 8.03. Found C, 59.26; H, 6.84.

(–)-3-(((1*S*,6*S*)-2-(2-Bromoethyl)-6-((tert-butyldimethylsilyl)oxy)cyclohex-2-en-1-yl) oxy)-4-(methoxymethoxy)benzaldehyde (434).

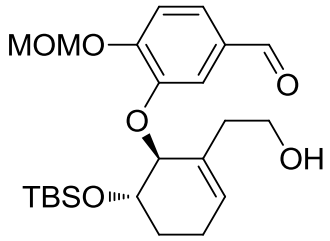


To a solution of PBu_3 (0.88 mL, 3.88 mmol) in THF (7 mL) at 0 °C was added TMAD (0.67 g, 3.88 mmol) and was stirred for 15 minutes. The orange solution formed was cannulated to a solution of alcohol **12** (1.00 g, 2.98 mmol) and phenol (0.71 g, 3.88 mmol) at 0 °C and was stirred for 18 hours. Then solvent was evaporated to provide crude product and was dissolved in CH_2Cl_2 and was adsorbed in silica. Pure product was separated by column chromatography on silica gel with [hexane/EtOAc (95:5) → hexane/EtOAc (80:20)] as eluent to yield **434** (0.67 g, 1.3 mmol, 45%) as colorless oil.

434: R_f = 0.18 [hexane/EtOAc (90:10)]; $[\alpha]_D^{19}$= –30.7 (*c* = 1.8, $CHCl_3$); IR (neat) *v* 2951, 2927, 2895, 2854, 2724, 1690, 1594, 1582, 1502, 1432, 1253, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.66 (d, *J* = 1.8 Hz, 1H), 7.45 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 5.78 (t, *J* = 3.3 Hz, 1H), 5.31 (s, 2H), 4.64 (d, *J* = 4.5 Hz, 1H), 4.10-4.05 (m, 1H), 3.50 (s, 3H), 3.48-3.26 (m, 2H), 2.82-2.72 (m, 1H), 2.61-2.51 (m, 1H), 2.27-2.20 (m, 1H), 2.13-2.06 (m, 1H), 1.94-1.84 (m, 1H), 1.80-1.69 (m, 1H), 0.80 (s, 9H), –0.02 (s, 3H), –0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 152.9, 149.3, 132.5, 130.9, 129.6, 126.1, 115.3, 94.8, 80.1, 69.8, 56.5, 37.7, 31.7, 27.8, 25.7, 22.6, 17.9, –4.8, –4.9; LRMS (EI) *m/z* (%) 319 (41), 318 (11), 317 (40), 239 (11), 194 (12), 193 (14),

179 (20), 105 (41), 95 (22), 91 (24), 81 (12), 79 (19), 78 (11), 77 (30), 75 (100), 73 (98), 57 (16), 56 (16); HRMS (EI) calcd for $C_{23}H_{35}BrO_5Si$ (M^+-C_4H_9): 441.0733. Found 441.0729; Anal. Calcd for $C_{23}H_{35}BrO_5Si$: C, 55.30; H, 7.06. Found C, 55.15; H, 7.08.

(–)-3-(((1*S*,6*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-2-(2-hydroxyethyl)cyclohex-2-en-1-yl)oxy)-4-(methoxymethoxy)benzaldehyde (435).

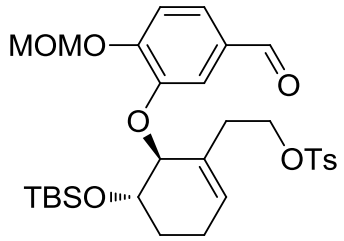


To a solution of acetate (63 mg, 0.13 mmol) in MeOH (1 mL) was added NaOMe/MeOH and was stirred at room temperature for 3 h. Then acidic Dowex-50 resin was added until the pH of the reaction mixture was changed to approximately 6-7. Then the solids were filtered off and the solvent was evaporated *in vacuo* to provide the product **15** (49.4 mg, 0.11 mmol, 86%) as a yellow liquid.

435: R_f = 0.36 [hexane/EtOAc (60:40)]; $[\alpha]_D^{19}$= –23.7 (*c* = 1.5, $CHCl_3$); IR ($CHCl_3$) ν 3610, 2950, 2927, 2896, 2855, 1690, 1594, 1582, 1503, 1462, 1432, 1389, 1254, 1155 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.64 (d, *J* = 1.5 Hz, 1H), 7.46 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 5.87 (bs, 1H), 5.30 (s, 2H), 4.62 (d, *J* = 3.9 Hz, 1H), 4.16-4.12 (m, 2H), 3.51 (s, 3H), 3.50-3.49 (m, 1H), 2.52-2.46 (m, 1H), 2.32-2.23 (m, 2H), 2.21-2.15 (m, 1H), 1.93-1.87 (m, 1H), 1.78-1.71 (m, 1H), 0.85 (s, 9H), 0.03 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 152.6, 148.8, 130.9, 130.8,

130.3, 126.0, 115.1, 113.8, 94.7, 78.9, 68.6, 61.3, 56.5, 37.9, 26.9, 25.7, 22.1, 17.9, −4.8, −4.9.

(–)-2-((5*S*,6*S*)-5-((tert-Butyldimethylsilyl)oxy)-6-(5-formyl-2-(methoxymethoxy)phenolxy)cyclohex-1-en-1-yl)ethyl 4-methylbenzenesulfonate (436).

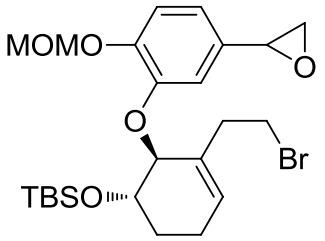


To a solution of alcohol **435** (540 mg, 1.27 mmol) and phenol (300 mg, 1.65 mmol) in THF (10 mL) at −10 °C was added PBu_3 (0.43 mL, 1.91 mmol) followed by tetramethylazodicarboxamide (TMAD) (328 mg, 1.91mmol). The reaction mixture was slowly warmed to room temperature and was stirred for 3 hours. Solvent was evaporated under reduced pressure and purified by flash column chromatography on silica gel using [hexane/EtOAc (90:10)→hexane/EtOAc (80:20)] as eluent to isolate product **436** (337 mg, 0.57 mmol, 45%) as an yellow oil.

436: R_f = 0.42 [hexane/EtOAc (60:40)]; $[\alpha]_D^{18}$ = –19.9 (*c* = 1.8, $CHCl_3$); IR ($CHCl_3$) *ν* 2952, 2928, 2897, 2855, 1737, 1691, 1594, 1582, 1503, 1470, 1253 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 9.87 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 1.5 Hz, 1H), 7.47 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.32-7.26 (m, 3H), 5.70 (bs, 1H), 5.29 (s, 2H), 4.53 (d, *J* = 4.8 Hz , 1H), 4.15-3.99 (m, 3H), 3.49 (s, 3H), 2.60-2.50 (m, 1H), 2.45-2.34 (m, 4H), 2.23-2.04 (m, 2H), 1.90-1.81 (m, 1H), 1.74-1.63 (m, 1H), 0.80 (s, 9H), –0.01 (s, 3H), –0.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 190.7, 152.7, 49.2, 144.6, 133.2, 130.8, 130.0, 129.8,

129.8, 127.8, 125.8, 115.2, 115.1, 94.7, 80.4, 70.1, 69.3, 56.5, 33.3, 28.0, 25.7, 22.7, 21.6, 17.9, −4.9, −5.0; Anal. Calcd for $C_{30}H_{42}O_8SSi$: C, 60.99; H, 7.17. Found C, 61.29; H, 6.98.

(+)-(((1*S*,2*S*)-3-(2-Bromoethyl)-2-(2-(methoxymethoxy)-5-(oxiran-2-yl)phenoxy)cyclohex-3-en-1-yl)oxy)(tert-butyl)dimethylsilane (437).

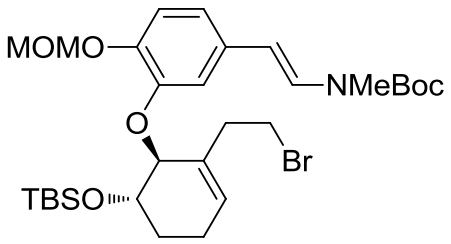


A 50% $NaOH_{(aq)}$ solution (2 mL) was added to a solution of trimethysulfonium methylsulfate (111 mg, 0.58 mmol) in CH_2Cl_2 (1 mL) and was stirred for 5 minutes. Then a solution of aldehyde **434** (240 mg, 0.48 mmol) in CH_2Cl_2 (3 mL) was added and the resulting suspension was stirred for 18 hours. Then the reaction mixture was diluted with H_2O (10 mL) and the product was extracted with CH_2Cl_2 (4x8 mL). Organic washes were combined and was washed with brine solution (8 mL), dried over Na_2SO_4 and solvent was evaporated under reduced pressure to provide product **437** (215 mg, 0.42 mmol, 87%) as a colorless oil.

437: R_f = 0.26 [hexane/EtOAc (90:10)]; $[\alpha]_D^{19}$= +5.3 (*c* = 1.2, $CHCl_3$); IR (neat) *ν* 3046, 2951, 2927, 2895, 2855, 1607, 1588, 1507, 1429, 1246, 1077 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 1.12 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.00 (dd, *J* = 6.0, 2.1 Hz, 1H), 6.89-6.83 (m, 1H), 5.78 (s, 1H), 5.20 (d, *J* = 1.2 Hz, 1H), 4.45 (s, 1H), 4.09-4.04 (m, 1H), 3.79 (t, *J* = 3.0 Hz, 1H), 3.49 (s, 3H), 3.47-3.30 (m, 2H), 3.11-3.07 (m, 1H), 2.84-2.71 (m, 2H), 2.63-

2.53 (m, 1H), 2.26-2.20 (m, 1H), 2.10-2.02 (m, 1H), 1.94-1.83 (m, 1H), 1.76-1.66 (m, 1H), 0.82 (s, 9H), –0.02 (d, J = 1.2 Hz, 3H), –0.08 (d, J = 3.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, rotameric) δ 149.0, 148.9, 147.7, 147.6, 132.4, 131.8, 131.7, 129.6, 129.5, 119.3, 119.0, 116.9, 116.8, 114.2, 114.1, 95.3, 79.6, 79.5, 69.0, 68.9, 56.2, 52.2, 52.1, 51.0, 38.0, 31.9, 27.0, 26.9, 25.7, 22.1, 18.0, –4.8, –4.9; LRMS (EI) *m/z* (%) 233 (27), 231 (27), 210 (18), 197 (28), 193 (33), 179 (29), 165 (12), 160 (16), 158 (14), 151 (27), 149 (24), 135 (15), 123 (13), 121 (14), 111 (14), 105 (29), 97 (22), 91 (19), 85 (19), 83 (24), 77 (30), 75 (100), 69 (29), 57 (50); HRMS (EI) calcd for $C_{24}H_{37}BrO_5Si$: 512.1594. Found 512.1572.

***tert*-Butyl (E)-3-(((1S,6S)-2-(2-bromoethyl)-6-((tert-butyldimethylsilyl)oxy)cyclohex-2-en-1-yl)oxy)-4-(methoxymethoxy)styryl(methyl)carbamate (439):**

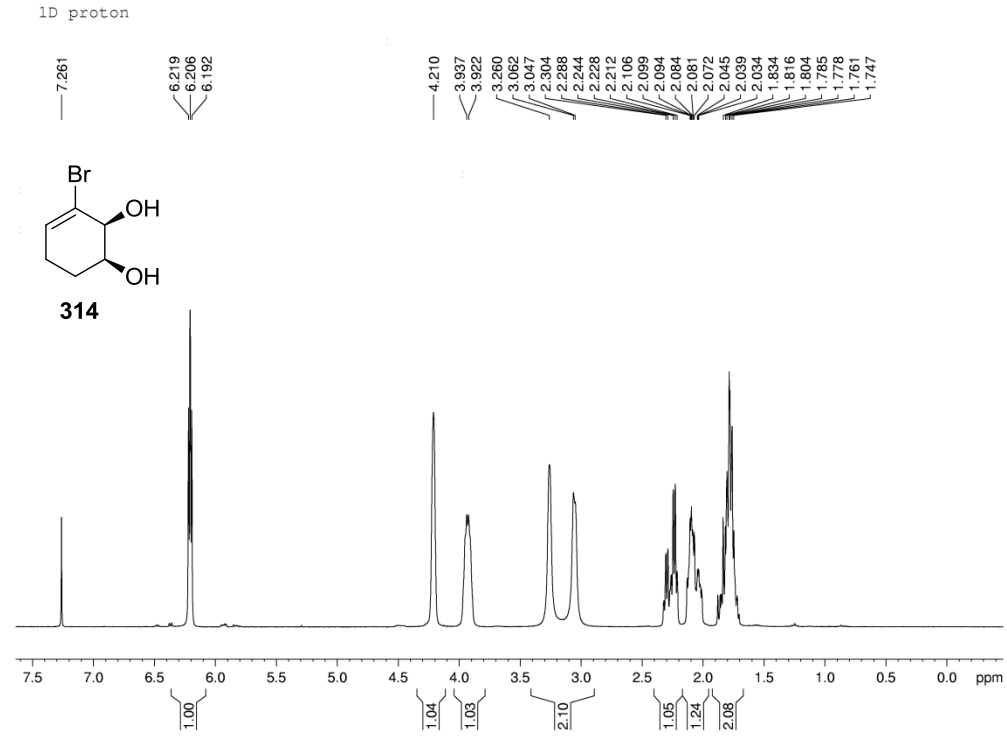


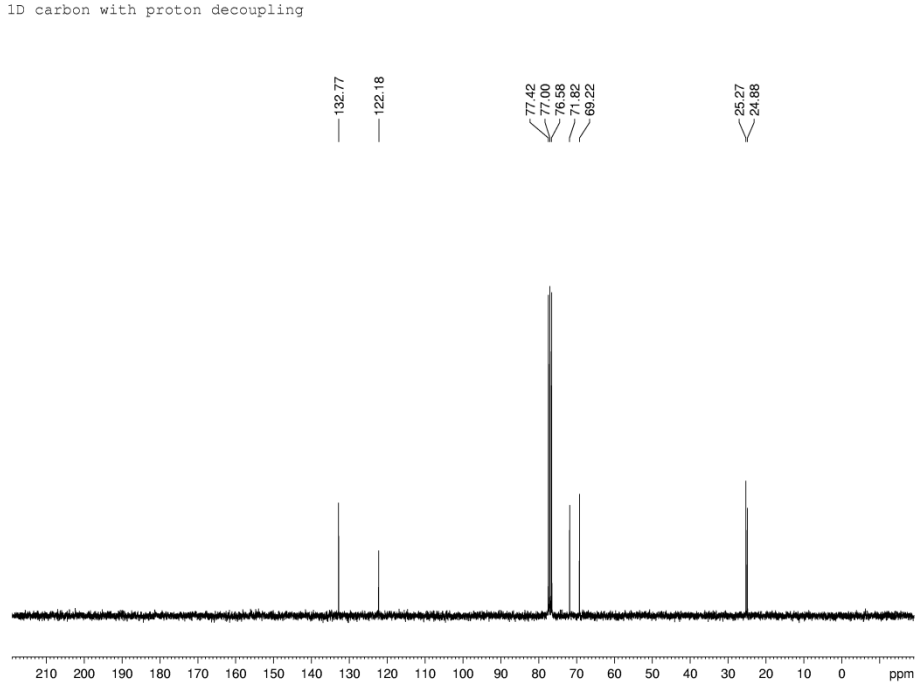
To a solution of MeNHBoc (36 mg, 0.27 mmol) in THF (4 mL) at –78 °C was added *n*-BuLi (0.14 mL, 0.26 mmol) and was stirred for 15 minutes. A solution of epoxide **437** (126 mg, 0.25 mmol) in THF (4 mL) was cooled to –10 °C in a separate vessel and $BF_3.OEt_2$ (0.03 mL, 0.25 mmol) was added and the reaction mixture from the first vessel was cannulated to it after 5 minutes. The resulting reaction mixture was stirred for 3 hours and was diluted with CH_2Cl_2 (25 mL), washed with H_2O (3x5 mL). Organic layer was washed with brine solution (8 mL), dried over Na_2SO_4 and solvent was evaporated under reduced pressure to provide crude product. Pure product was separated by column

chromatography on neutral alumina with hexane/EtOAc (95:5) as eluent to yield **439** (14 mg, 0.02 mmol, 9%) as colorless oil.

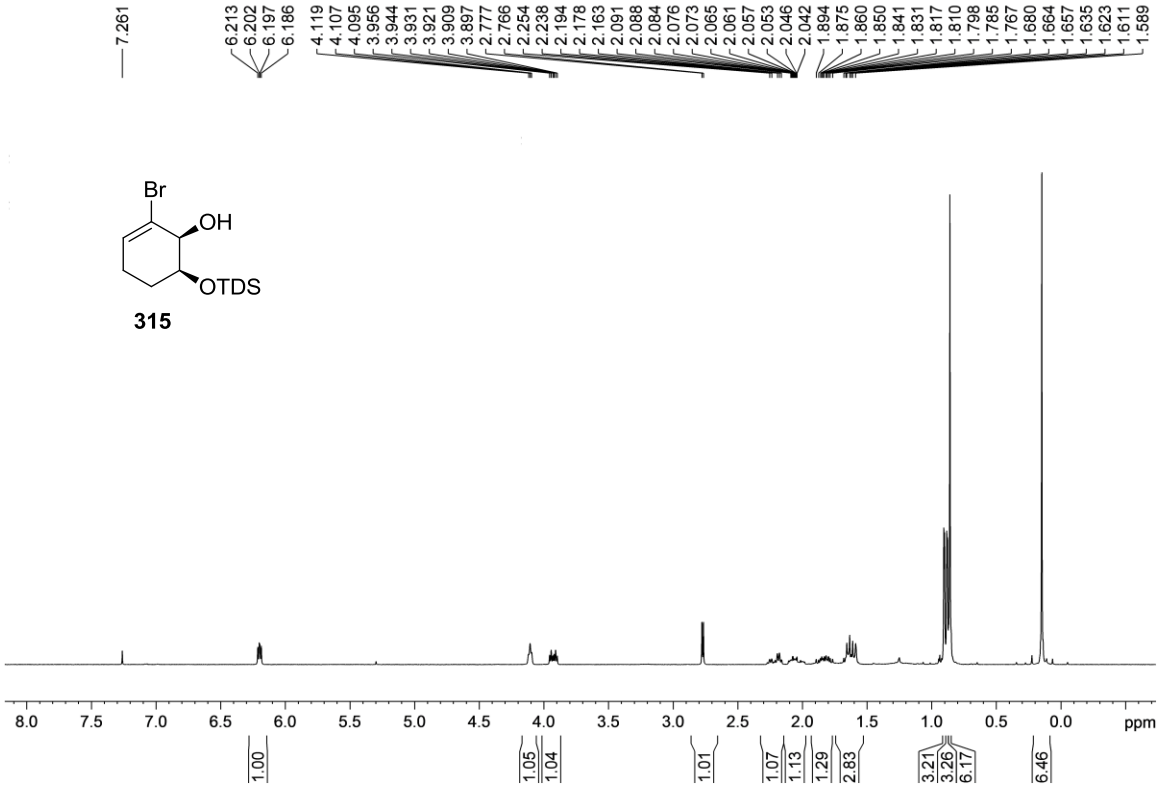
439: R_f = 0.26 [hexane/EtOAc (90:10)]; IR (neat) ν 3089, 3045, 2951, 2927, 2895, 2855, 1708, 1645, 1601, 1577, 1508, 1473, 1416, 1368, 1322, 1247, 1144 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, rotameric) δ 7.70-7.46 (m, 1H), 7.08-7.03 (m, 2H), 6.91 (bs, 1H), 5.78 (s, 1H), 5.68 (d, J = 14.4 Hz, 1H), 5.21-5.17 (m, 2H), 4.47 (bs, 1H), 4.11-4.06 (m, 1H), 3.50 (s, 3H), 3.49-3.44 (m, 4H), 3.12 (s, 3H), 2.89-2.77 (m, 1H), 2.65-2.55 (m, 1H), 2.27-2.20 (m, 1H), 2.11-2.03 (m, 1H), 1.94-1.88 (m, 1H), 1.76-1.68 (m, 1H), 1.53 (s, 9H), 0.83 (s, 9H), –0.03 (s, 3H), –0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 158.4, 146.1, 132.6, 132.1, 129.5, 128.4, 118.6, 117.2, 115.4, 95.5, 69.1, 56.2, 38.0, 32.0, 28.3, 27.1, 25.8, 22.1, 18.0, –4.8, –4.9; LRMS (EI) *m/z* (%) 319 (19), 317 (19), 279 (13), 179 (15), 178 (20), 167 (33), 149 (93), 129 (26), 105 (31), 95 (23), 91 (17), 83 (26), 77 (12), 57 (100); HRMS (EI) calcd for $C_{30}H_{48}BrNO_6Si$: 625.2434. Found 625.2449.

6. Selected Spectra





1D proton



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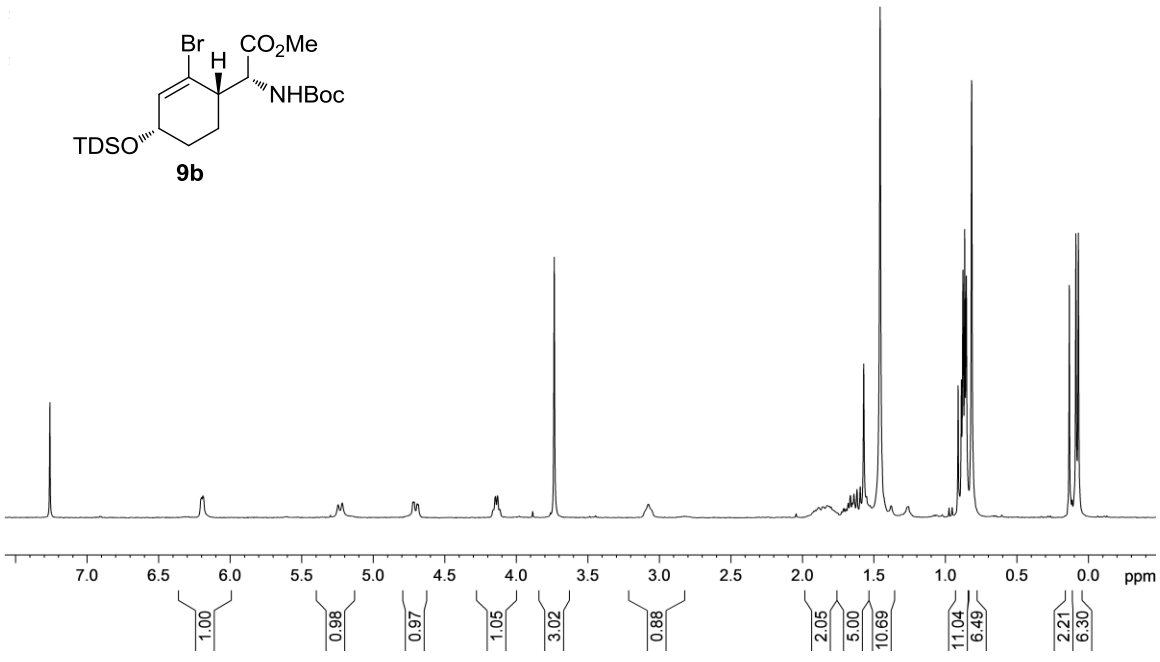

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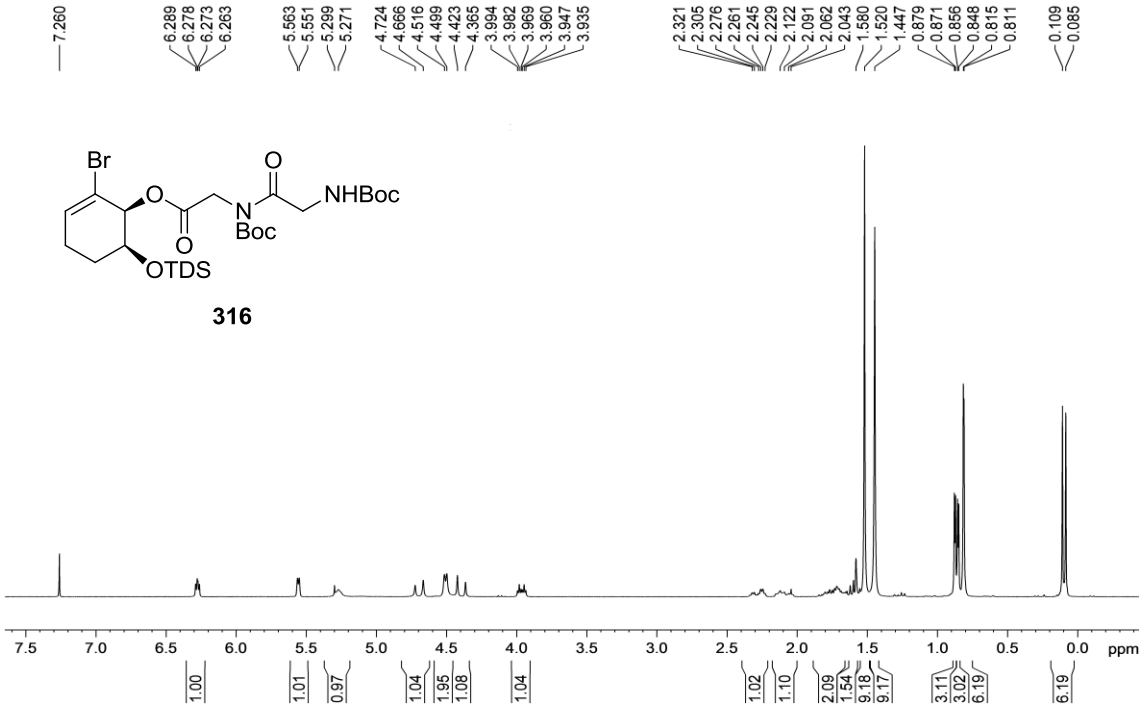

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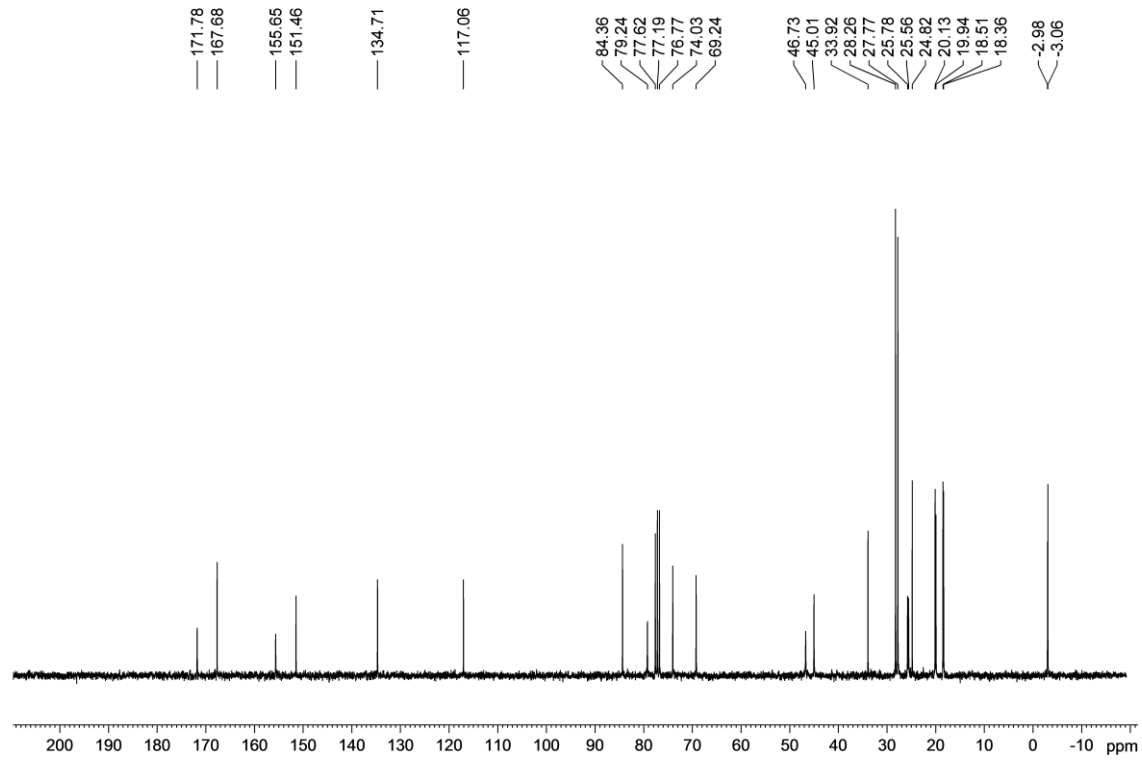
1D carbon with proton decoupling



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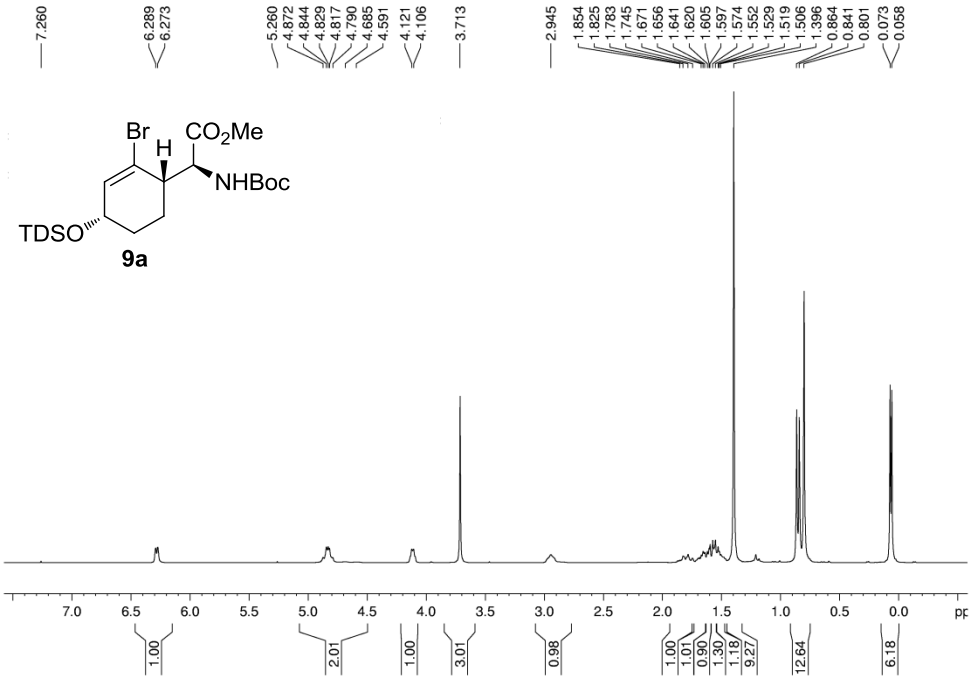

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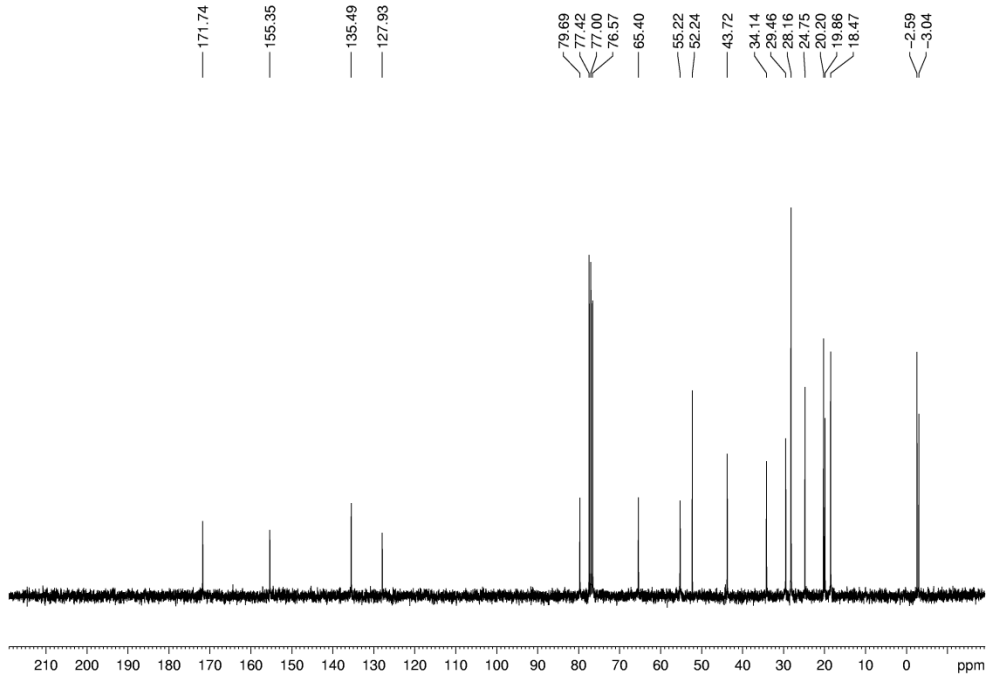

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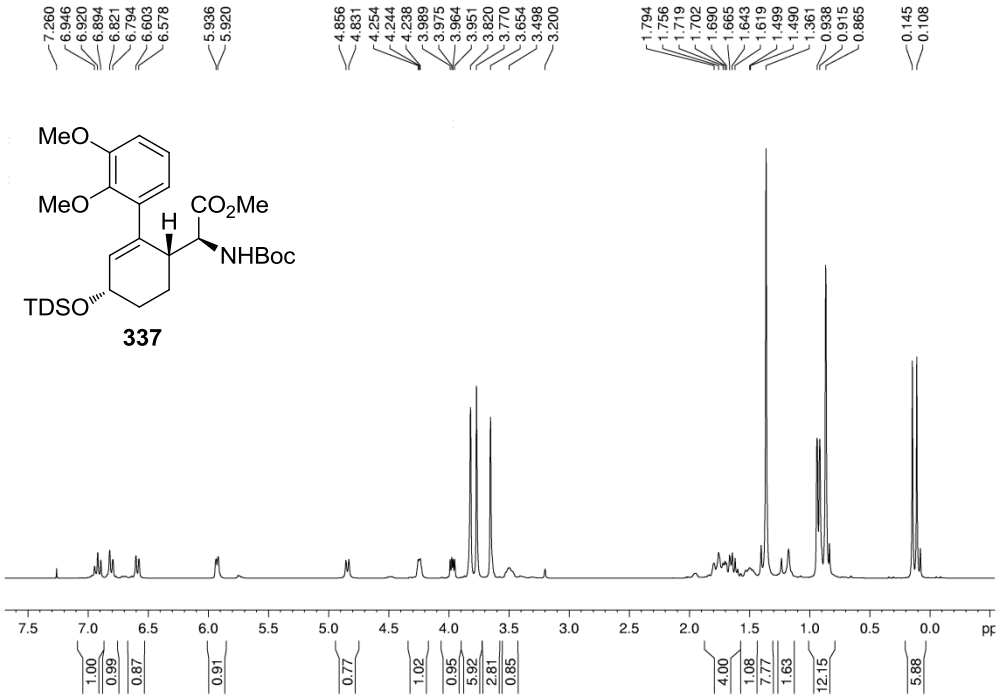
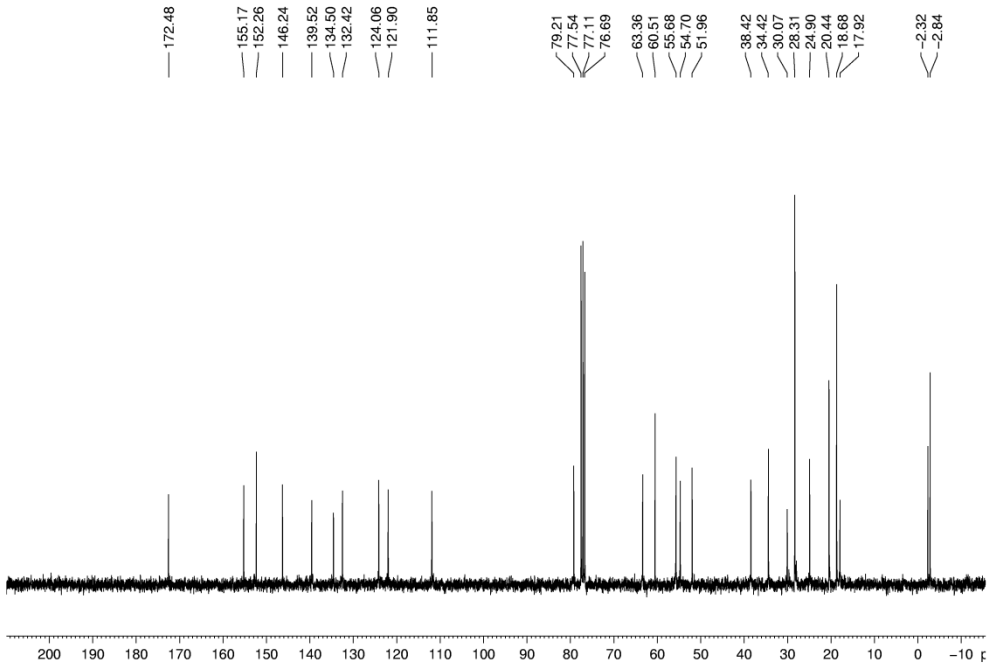


1D carbon with proton decoupling



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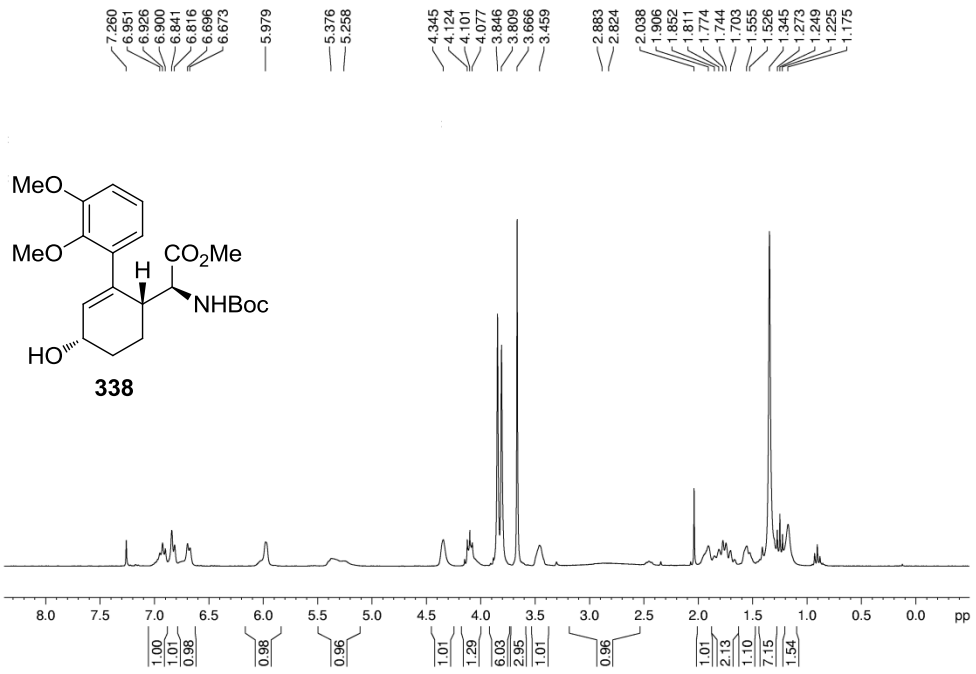
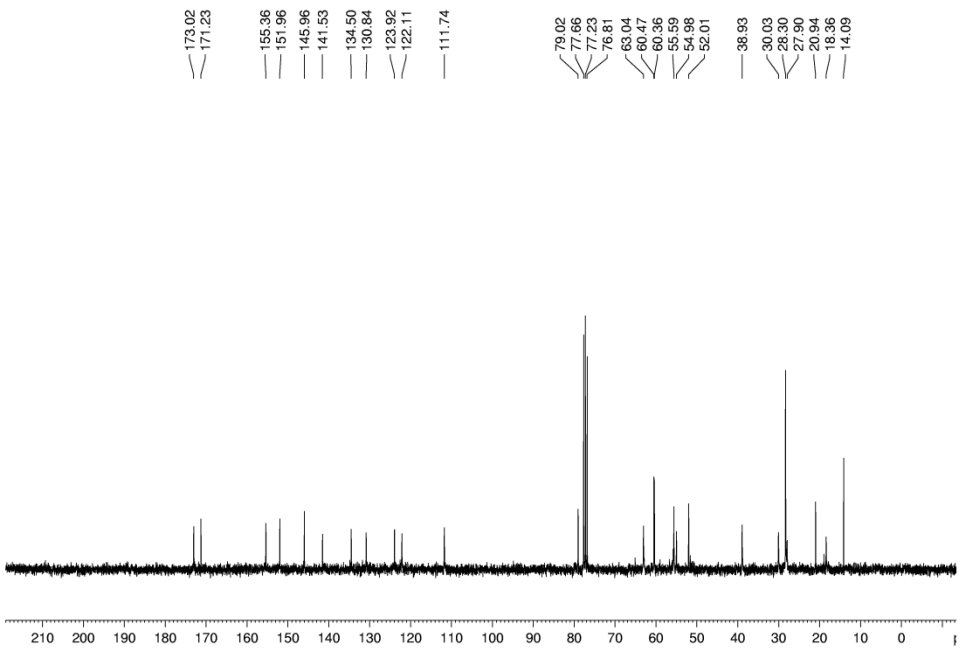


1D carbon with proton decoupling



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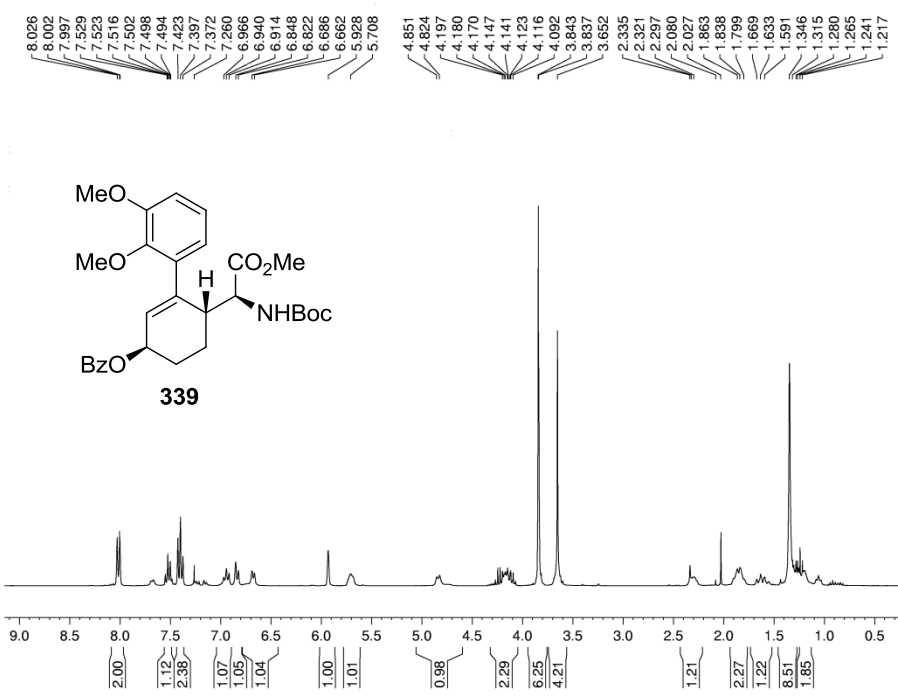
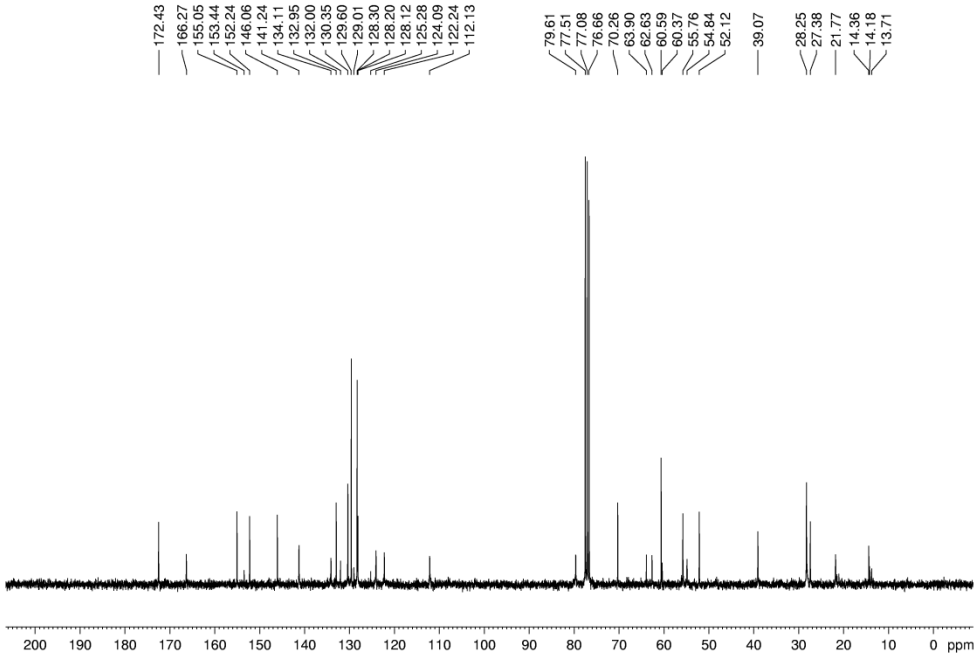


1D carbon with proton decoupling



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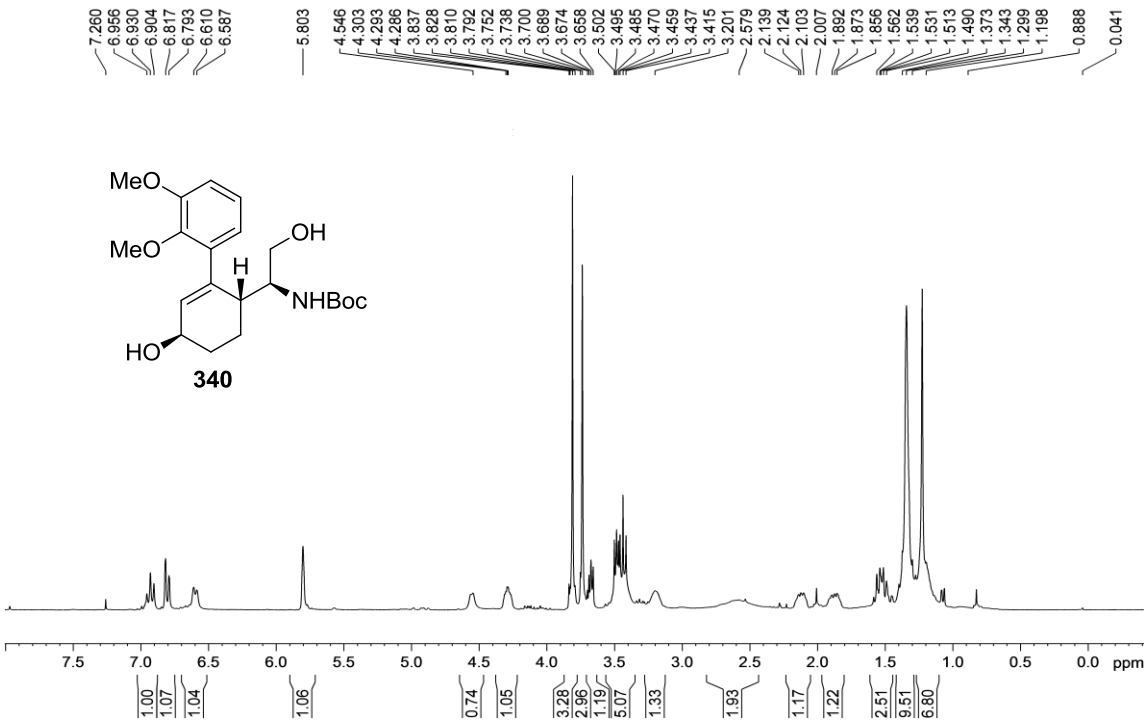

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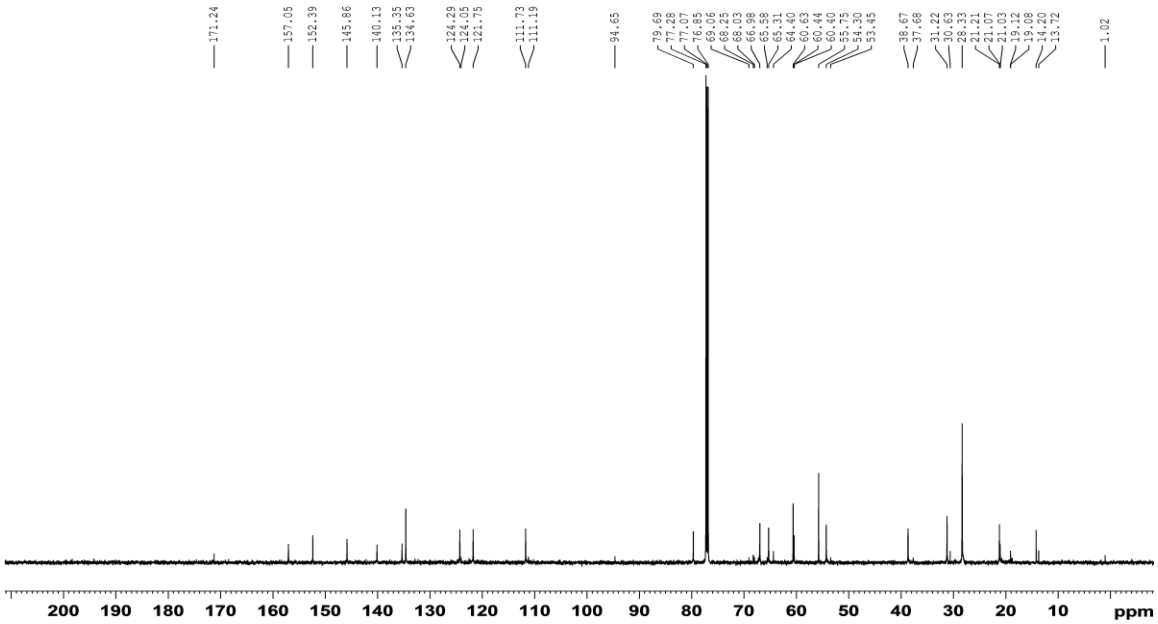

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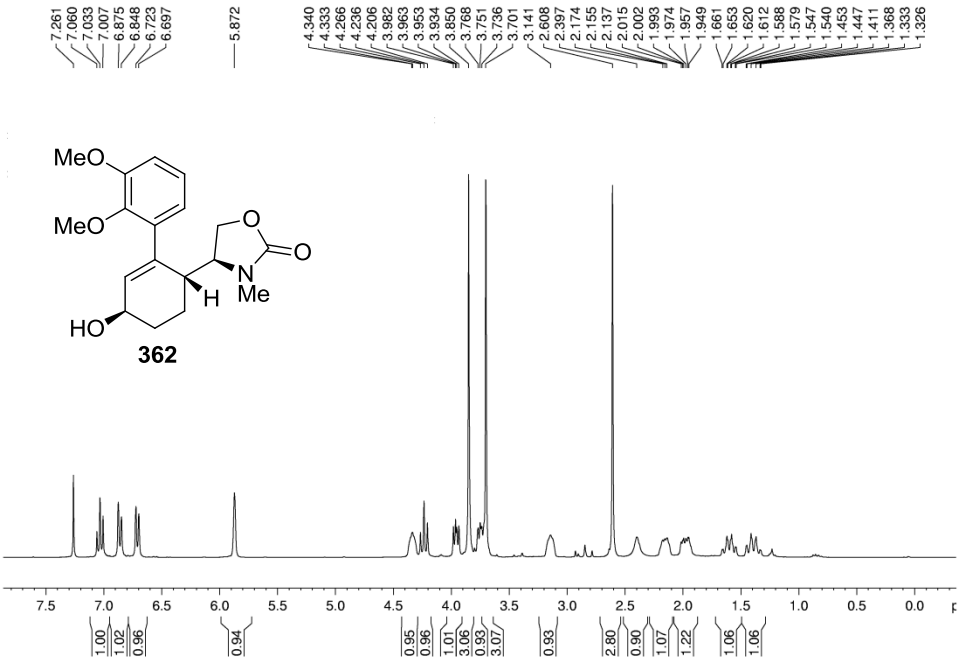
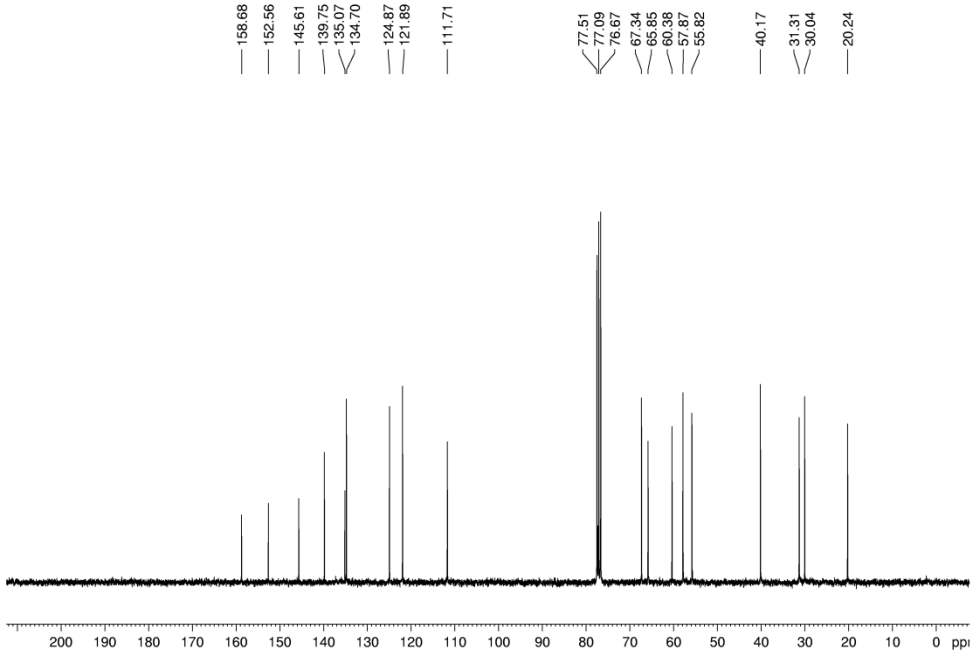


1D carbon with proton decoupling



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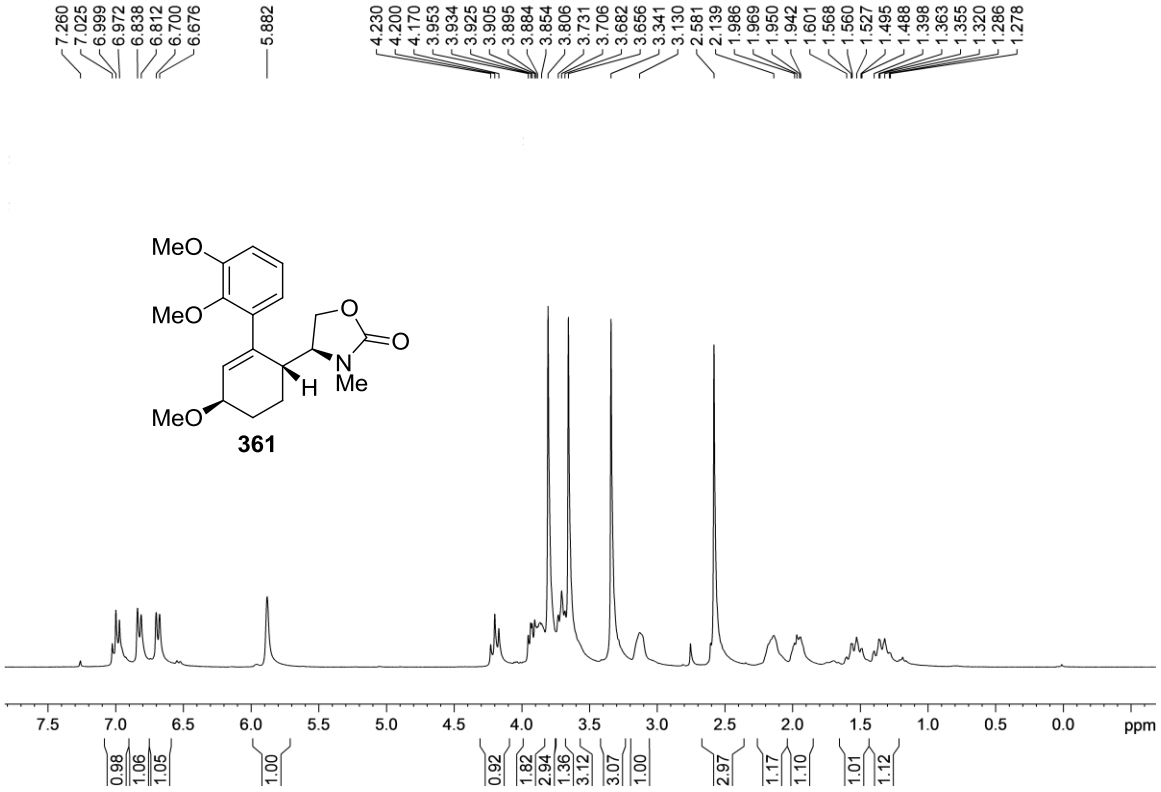
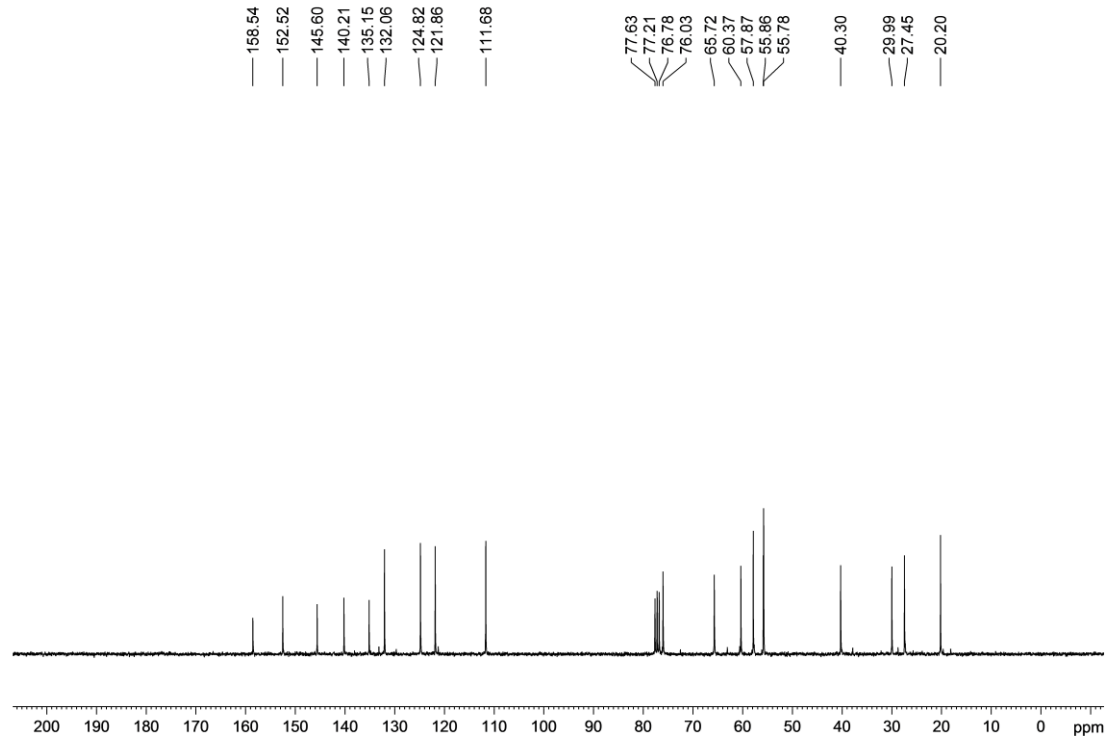
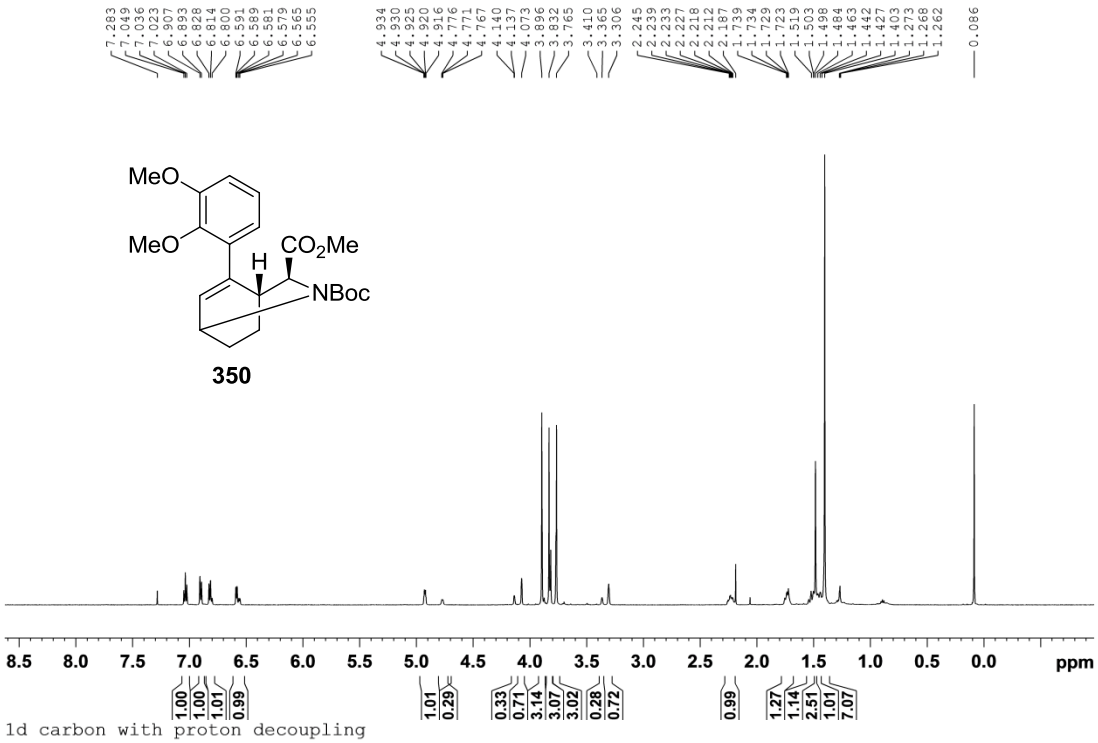


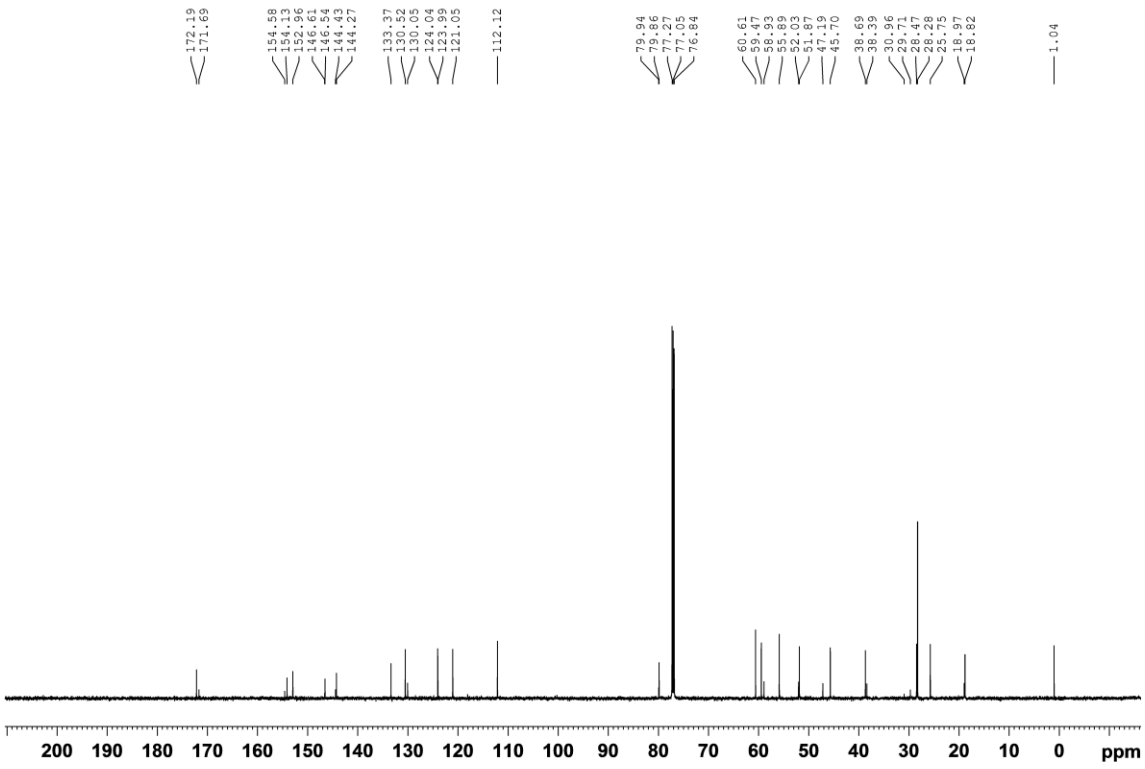
1D carbon with proton decoupling



1d proton



1d carbon with proton decoupling



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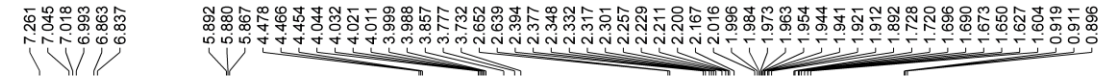
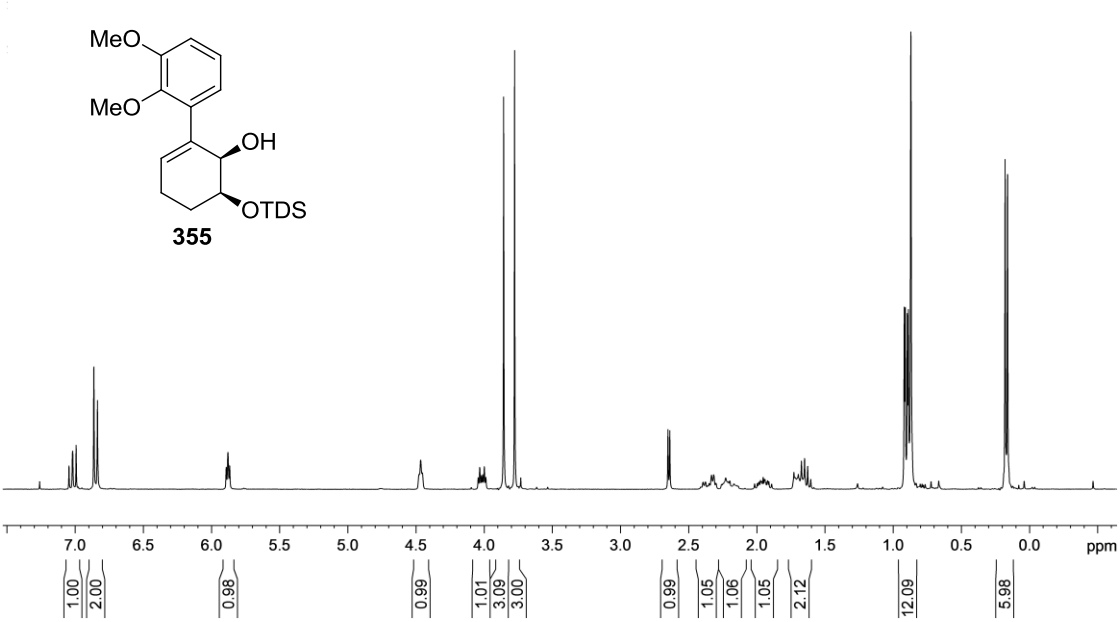
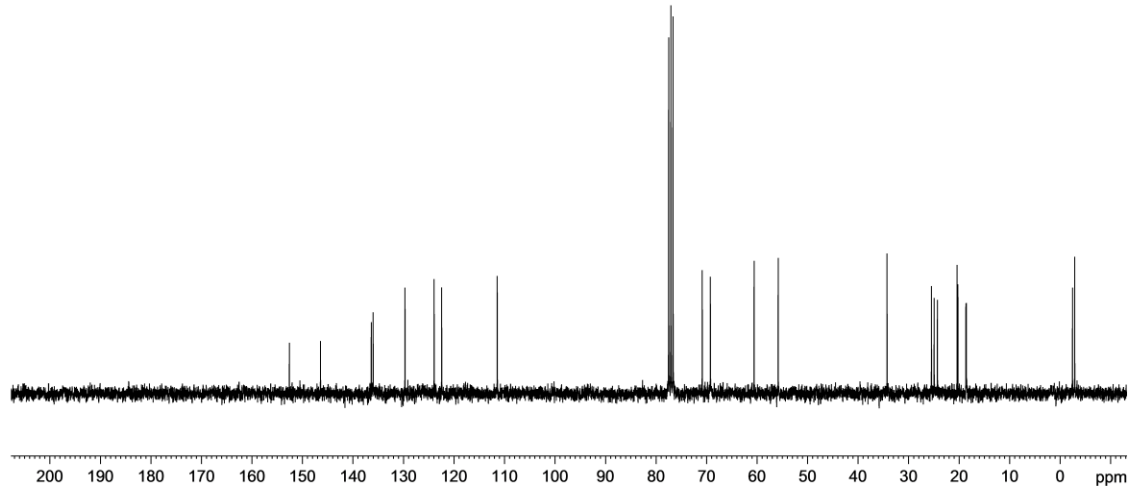
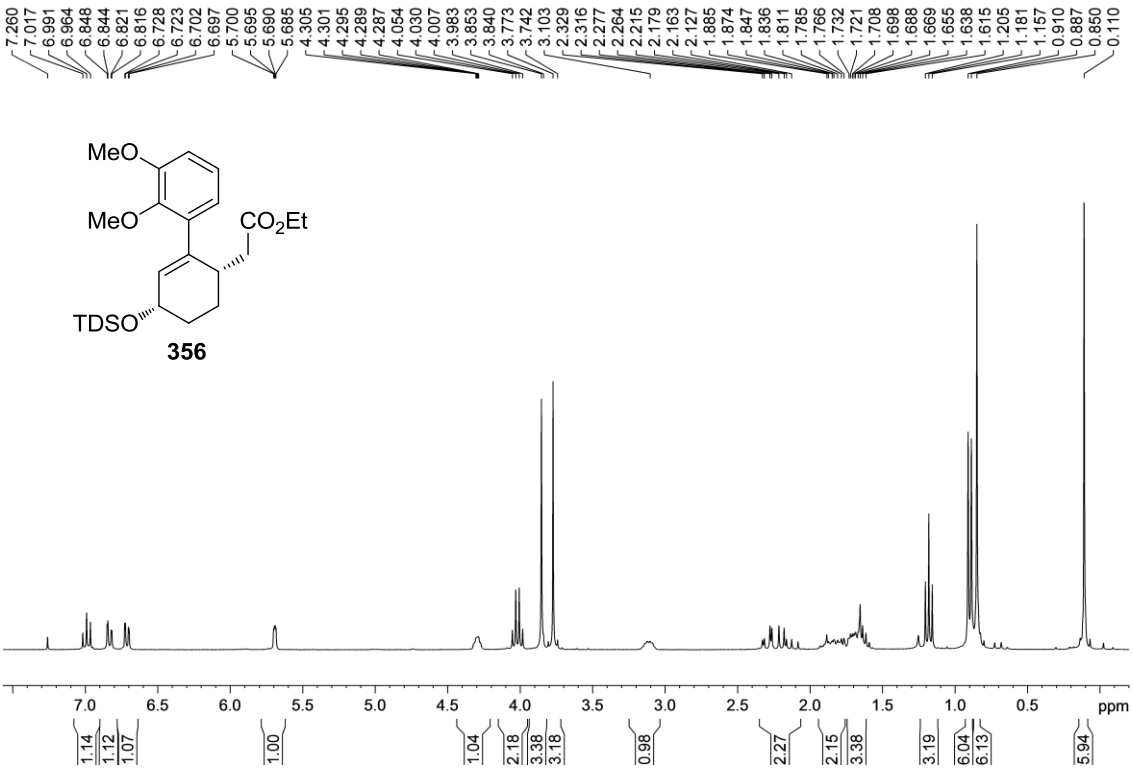




1D carbon with proton decoupling



1D proton



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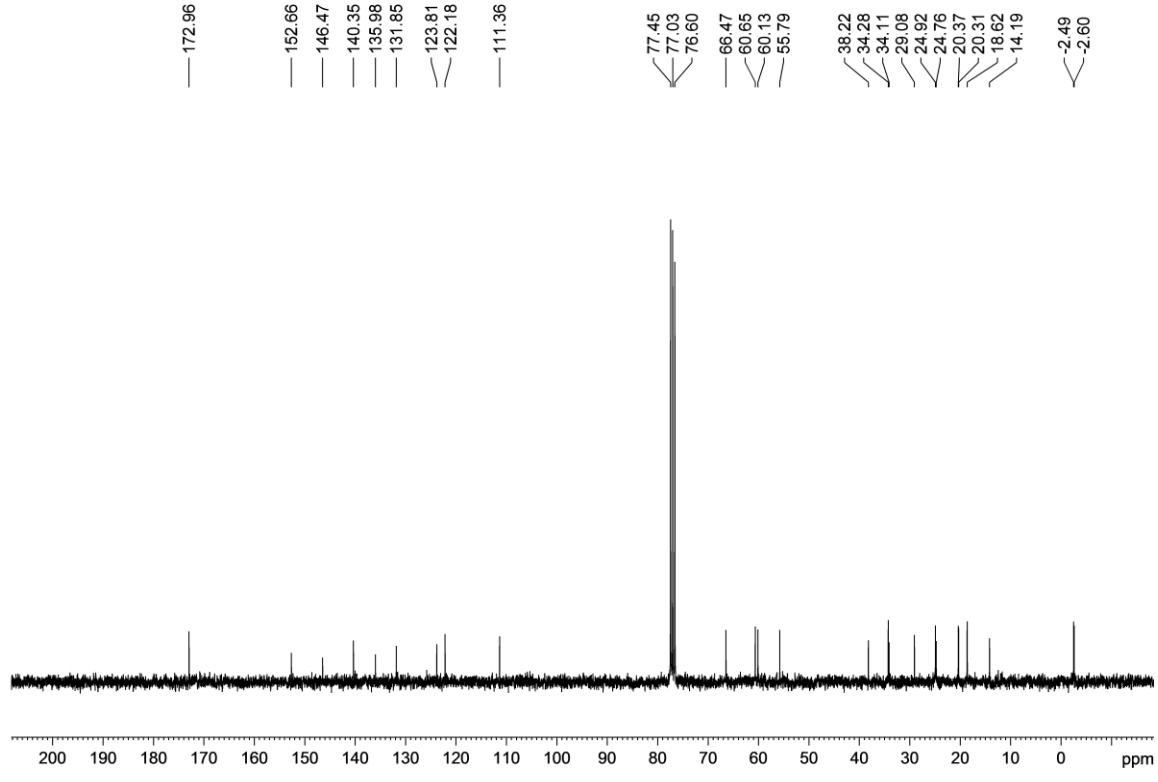

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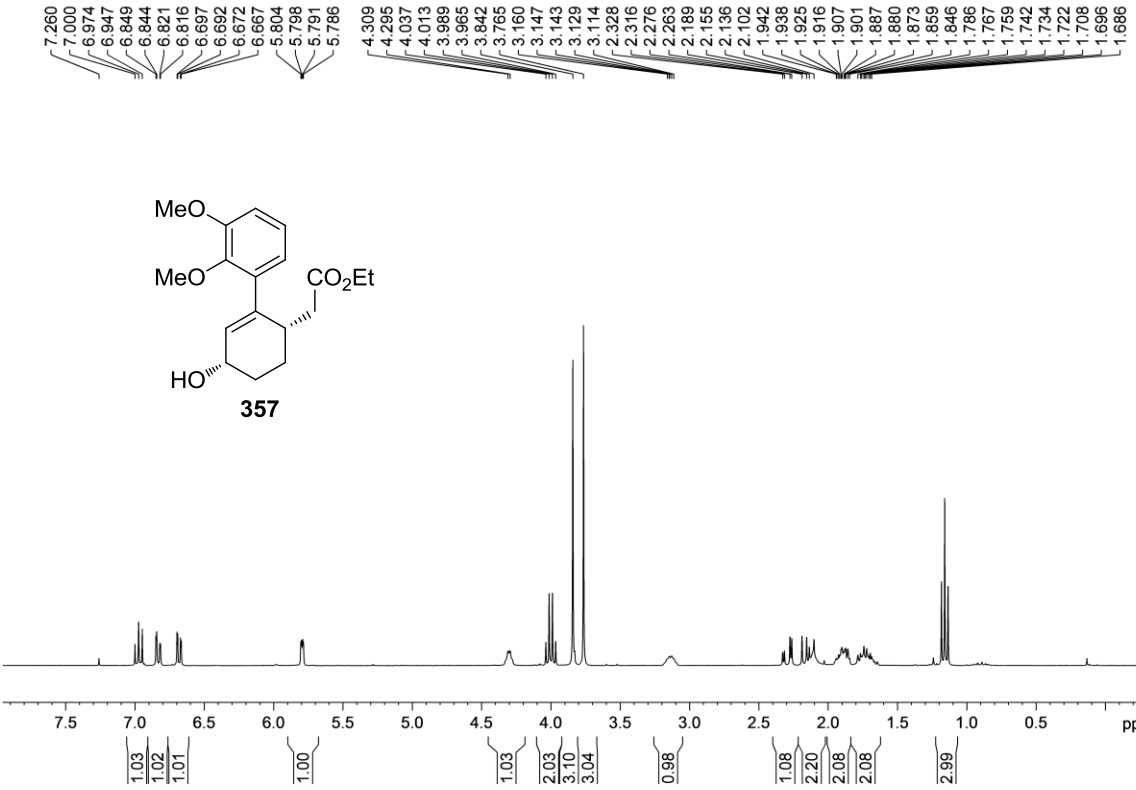

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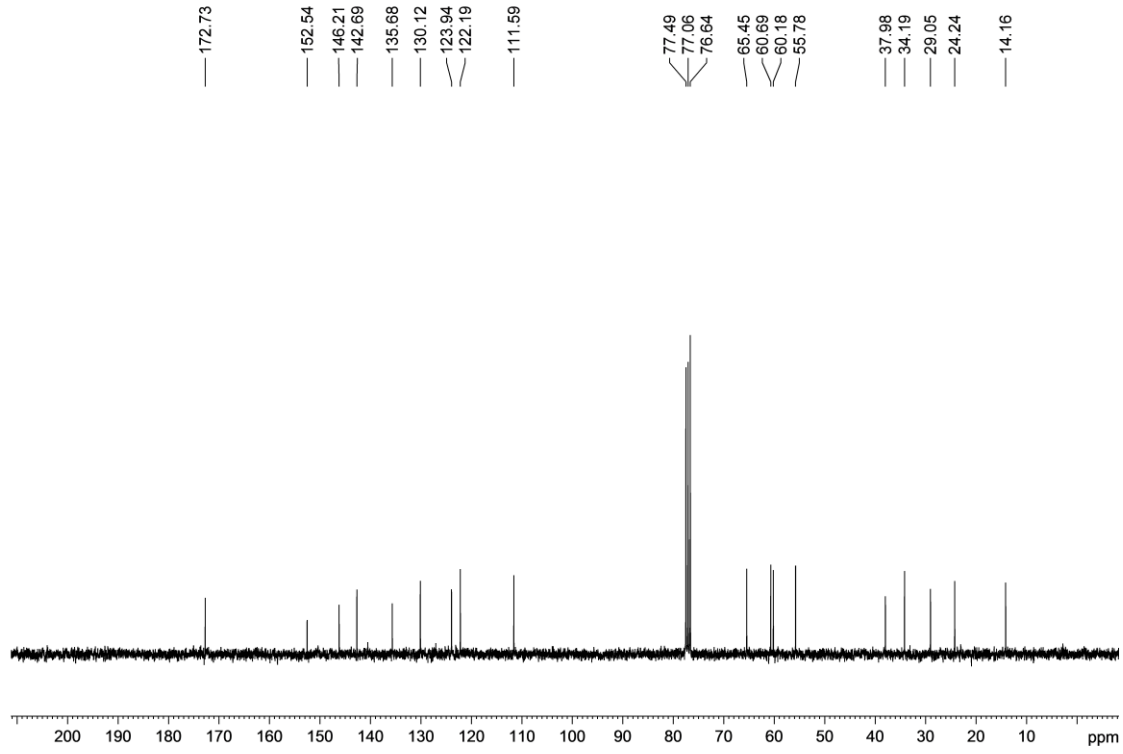

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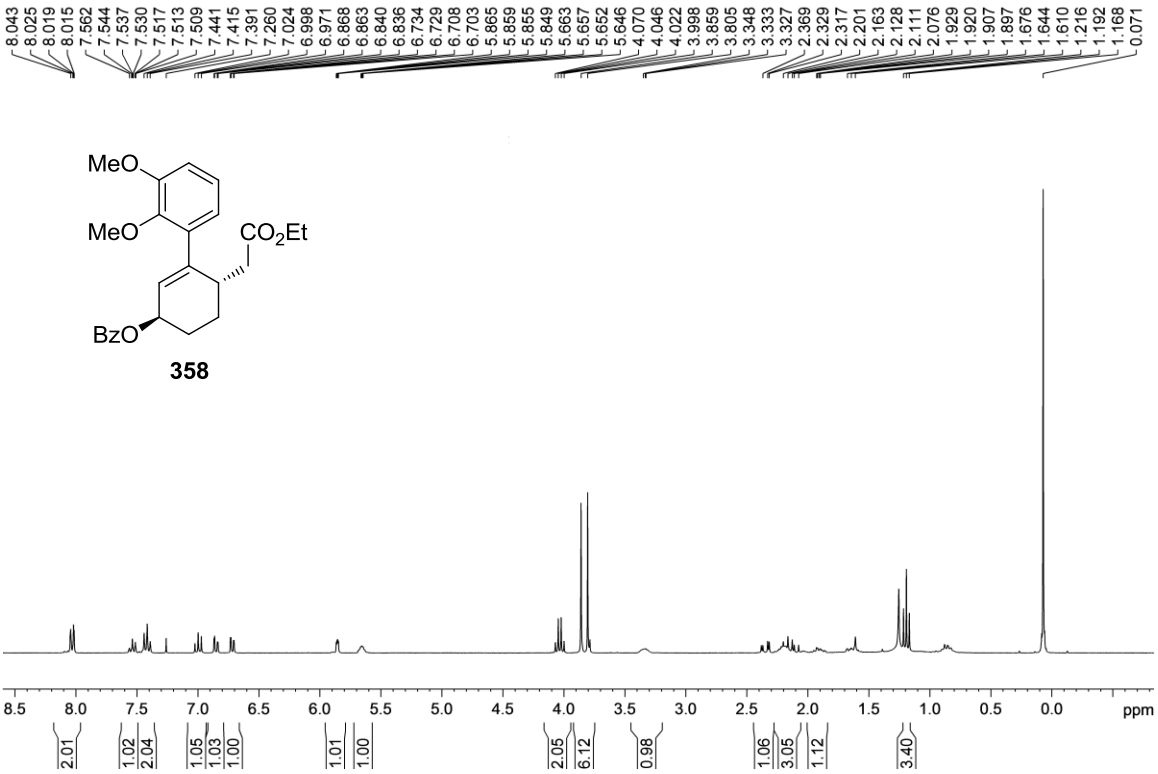

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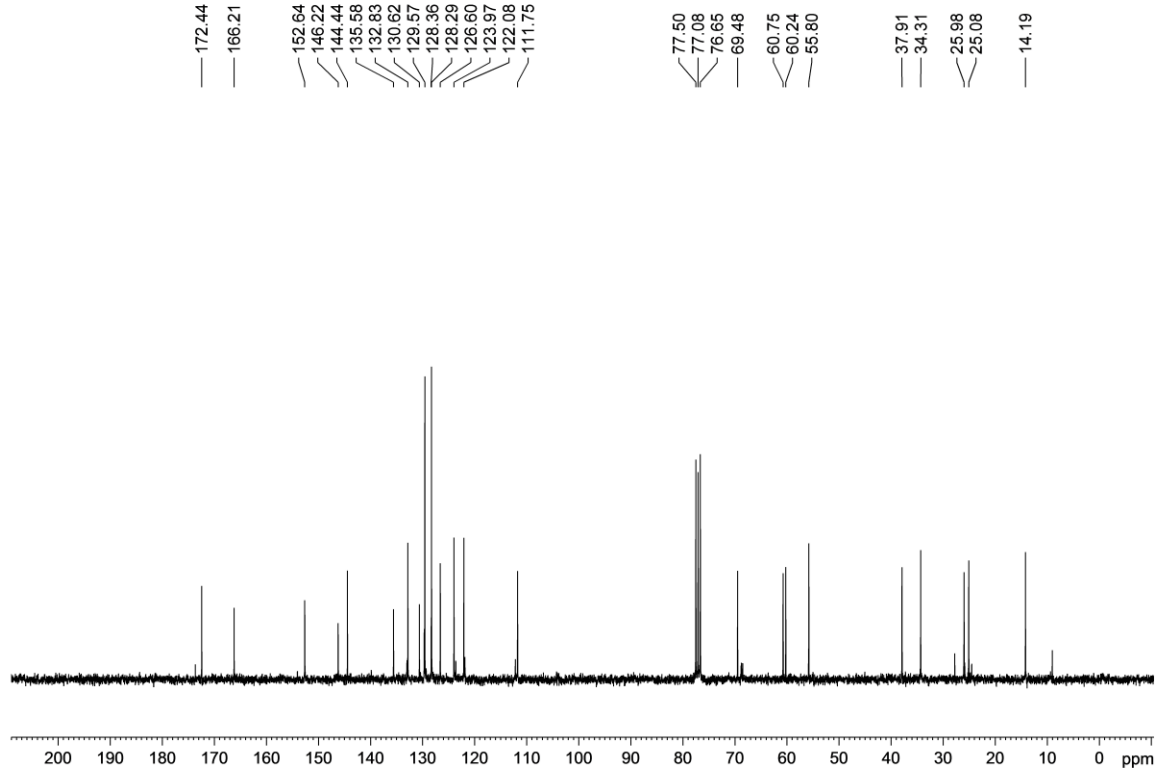

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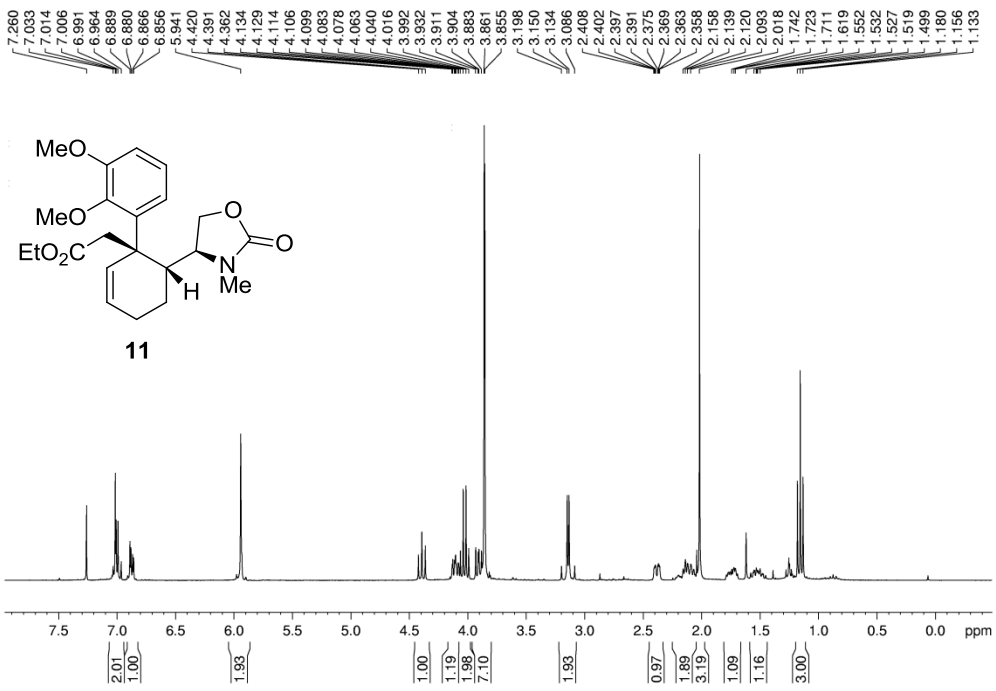

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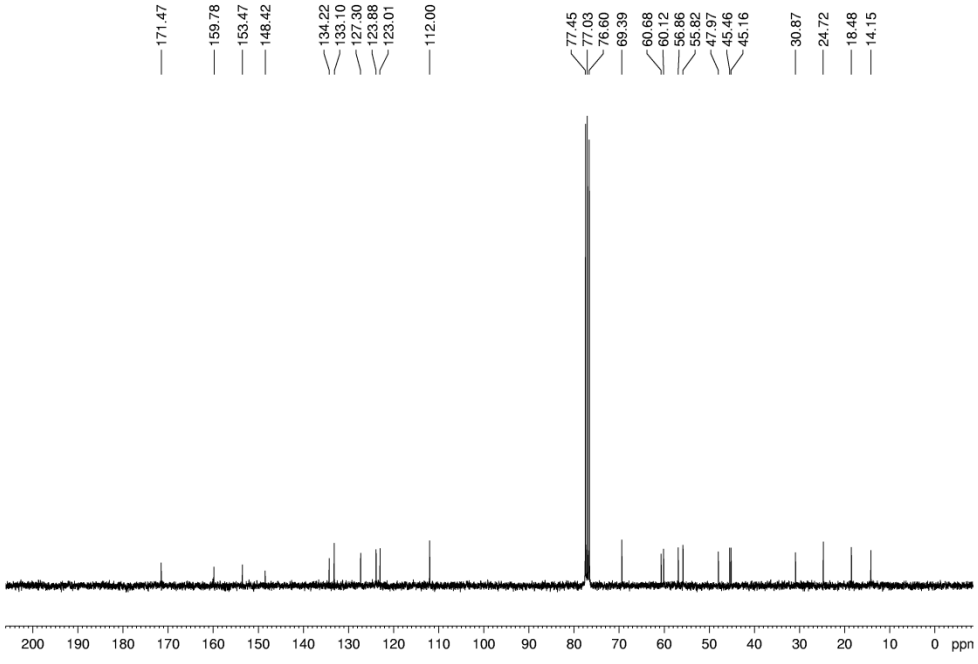

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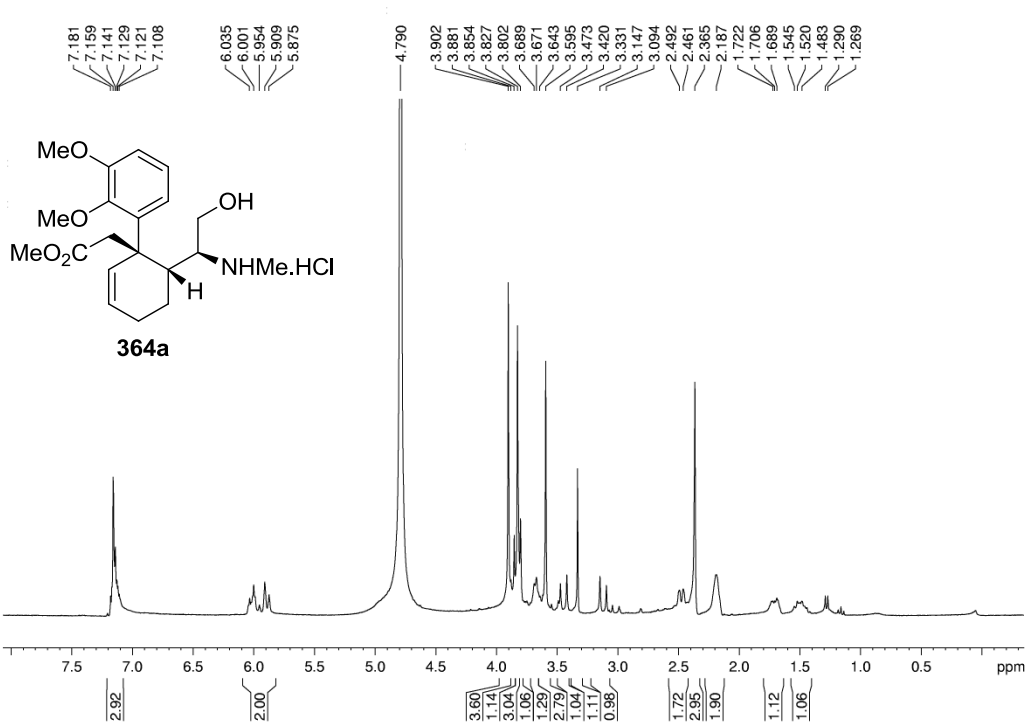
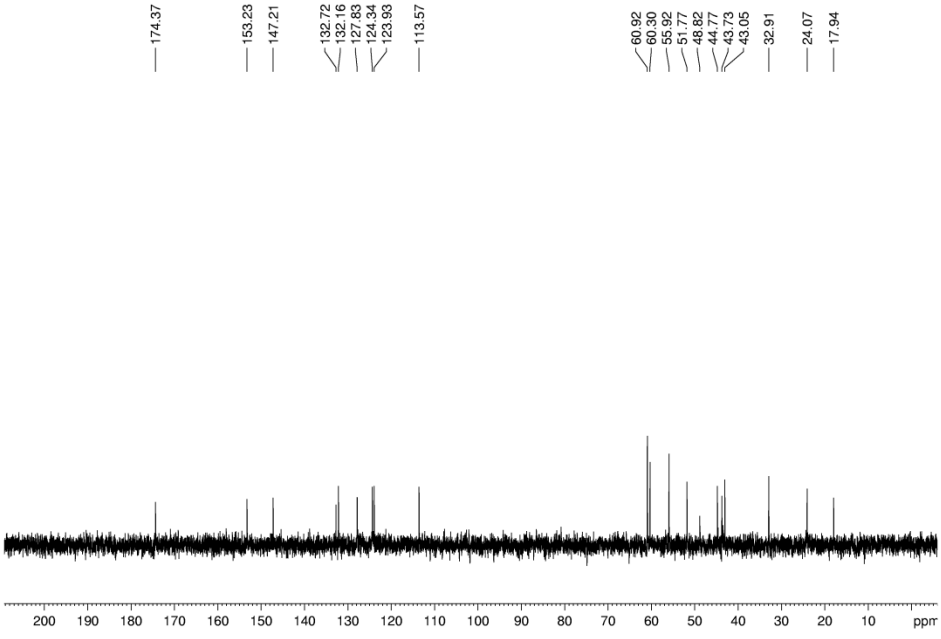


1D carbon with proton decoupling



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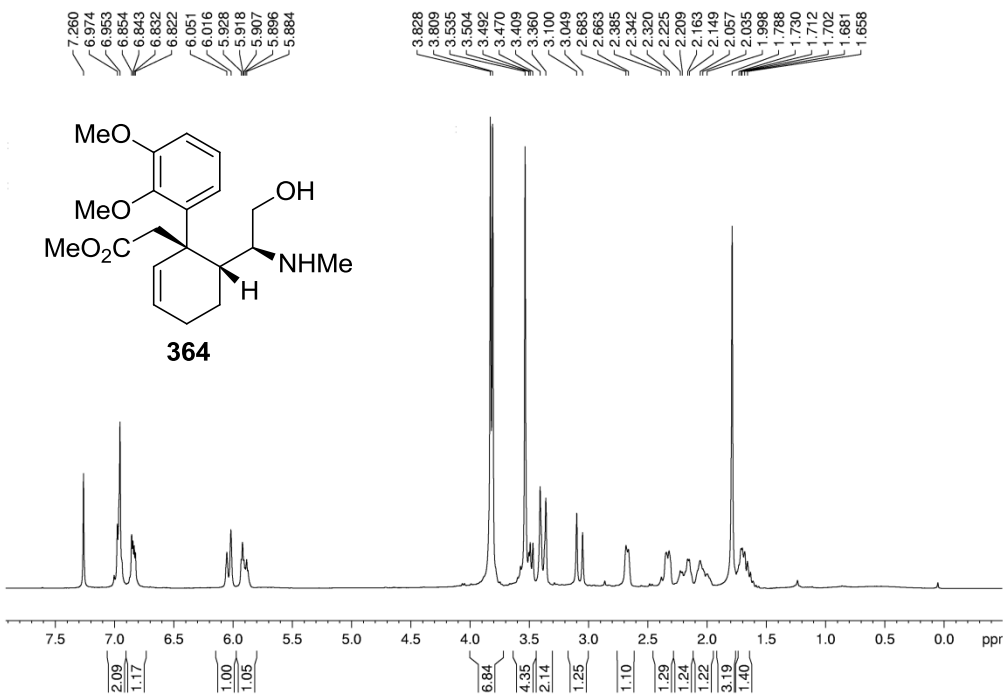
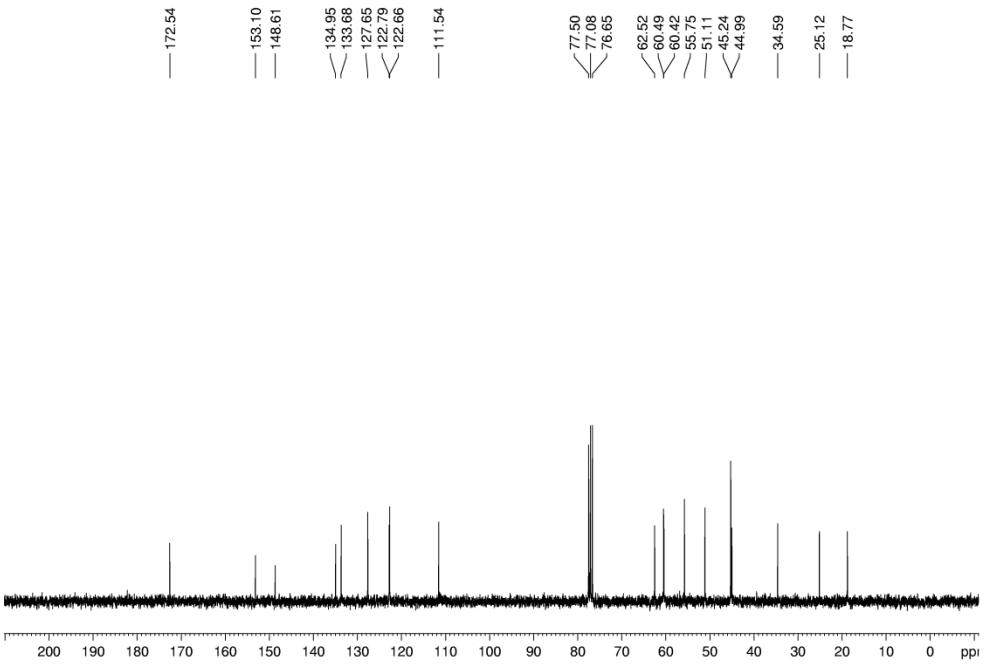
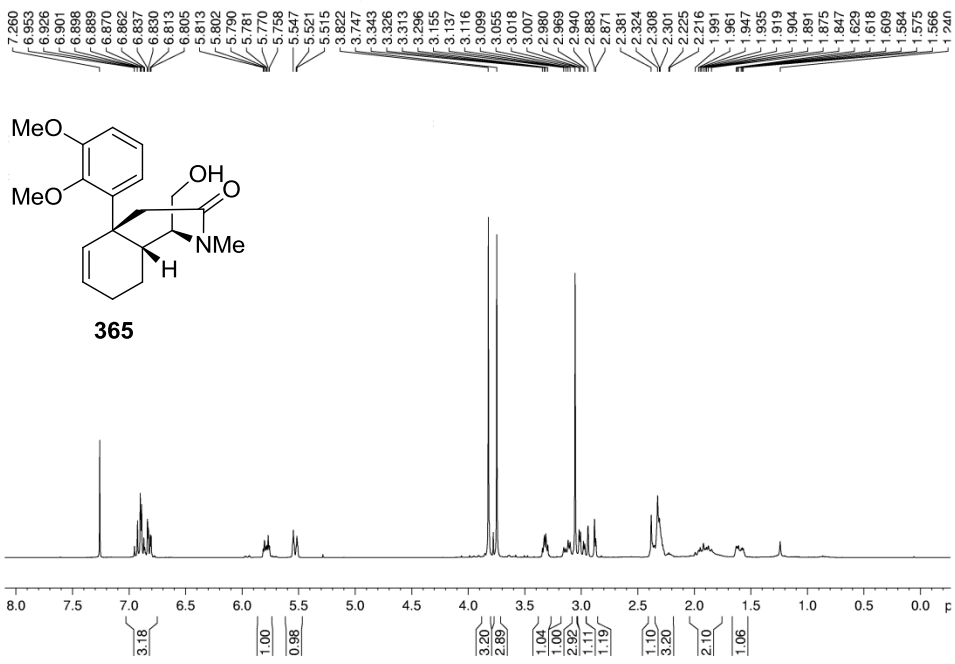


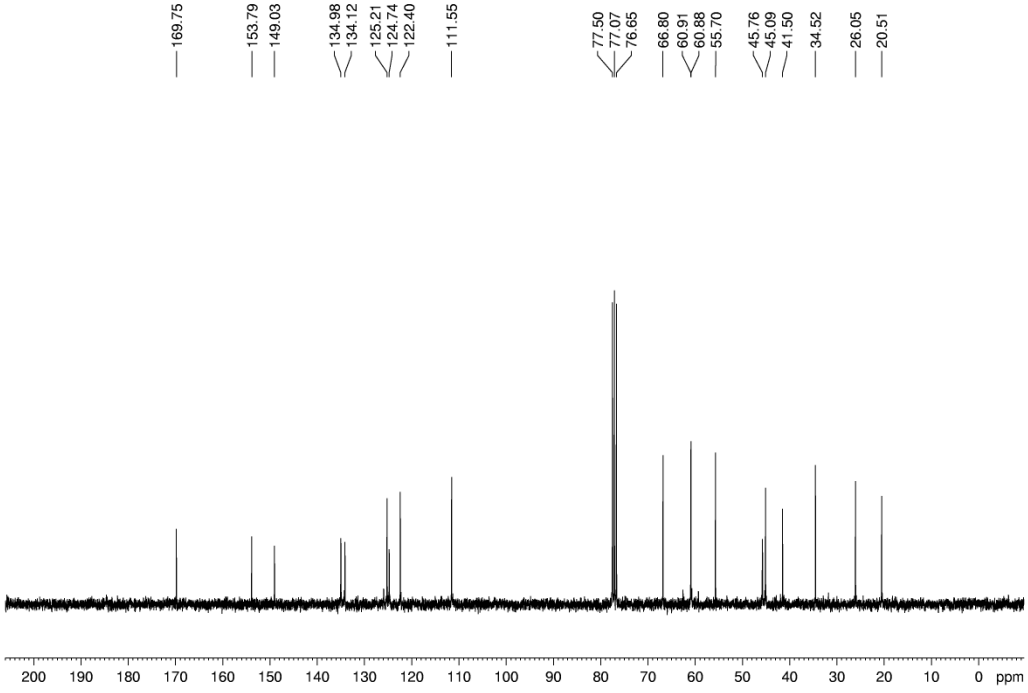
1D carbon with proton decoupling



1D proton



1D carbon with proton decoupling



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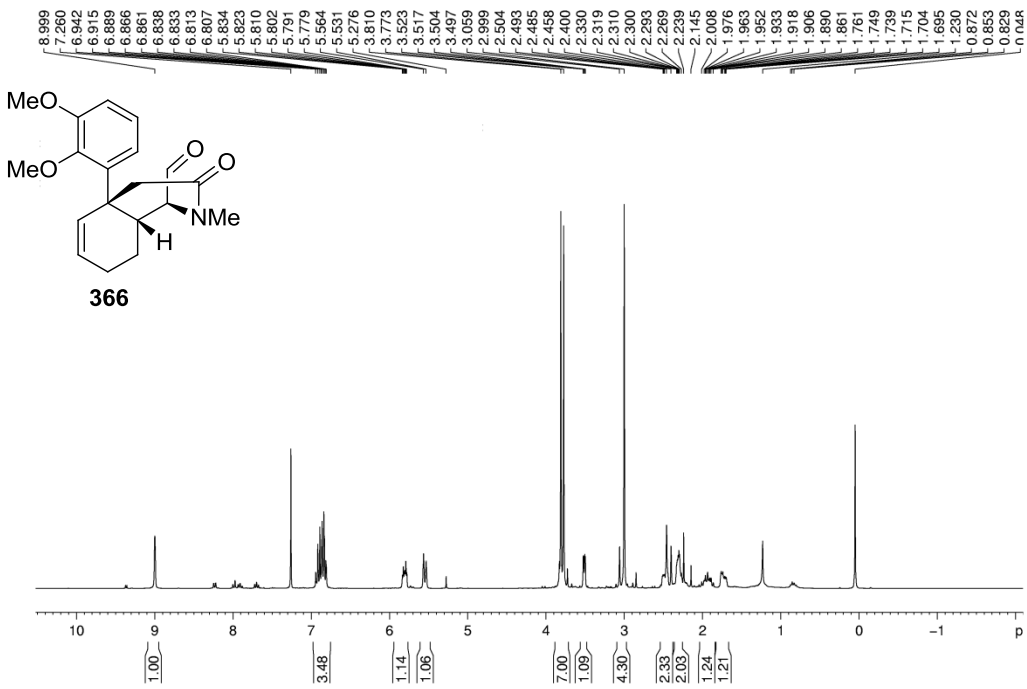

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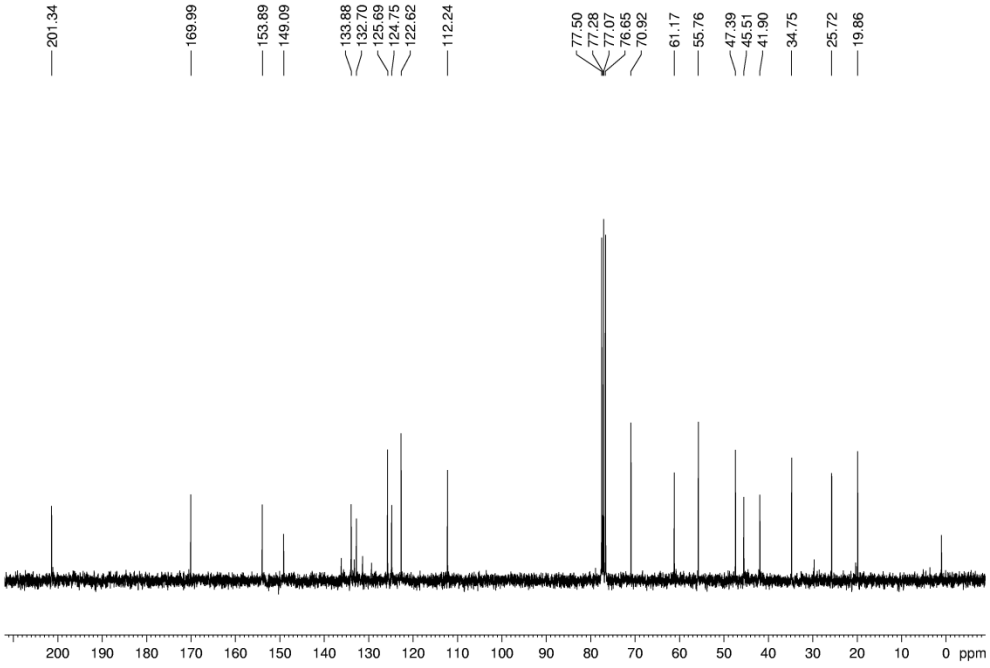

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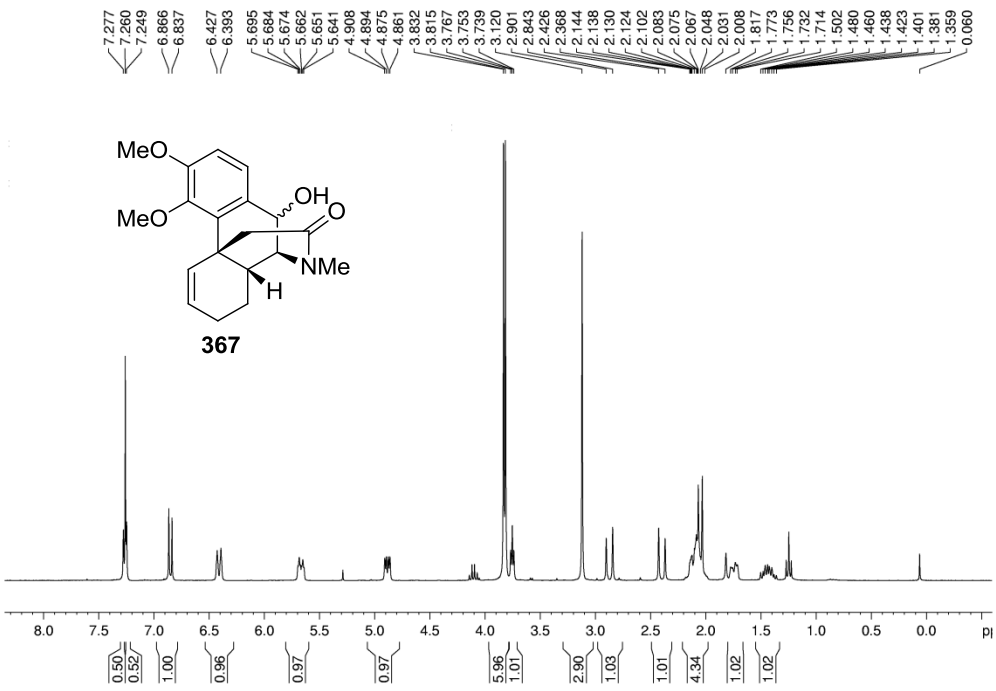
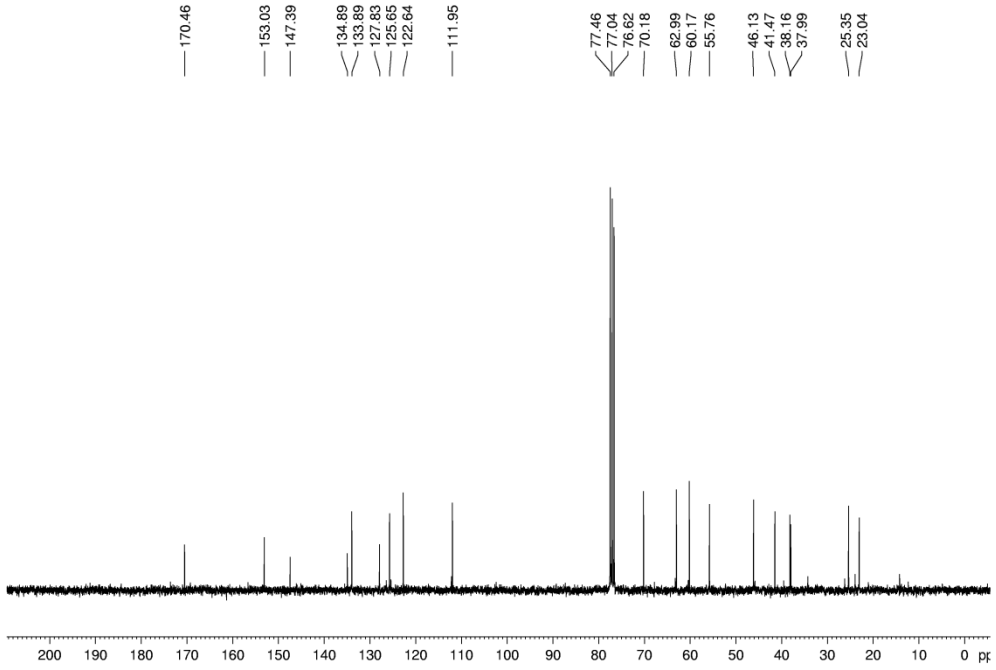


1D carbon with proton decoupling



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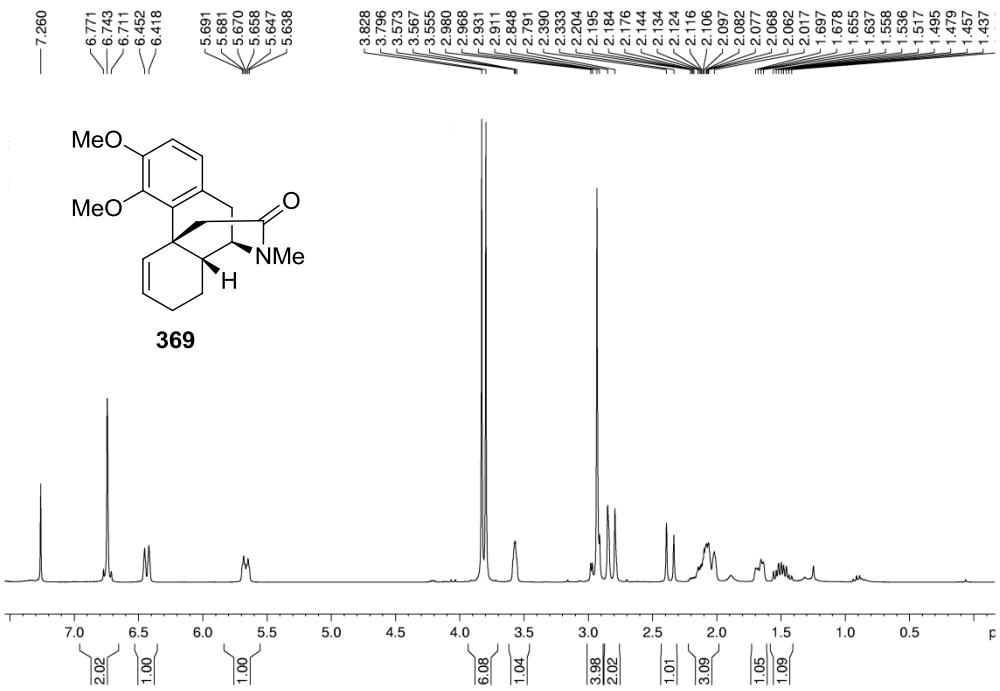
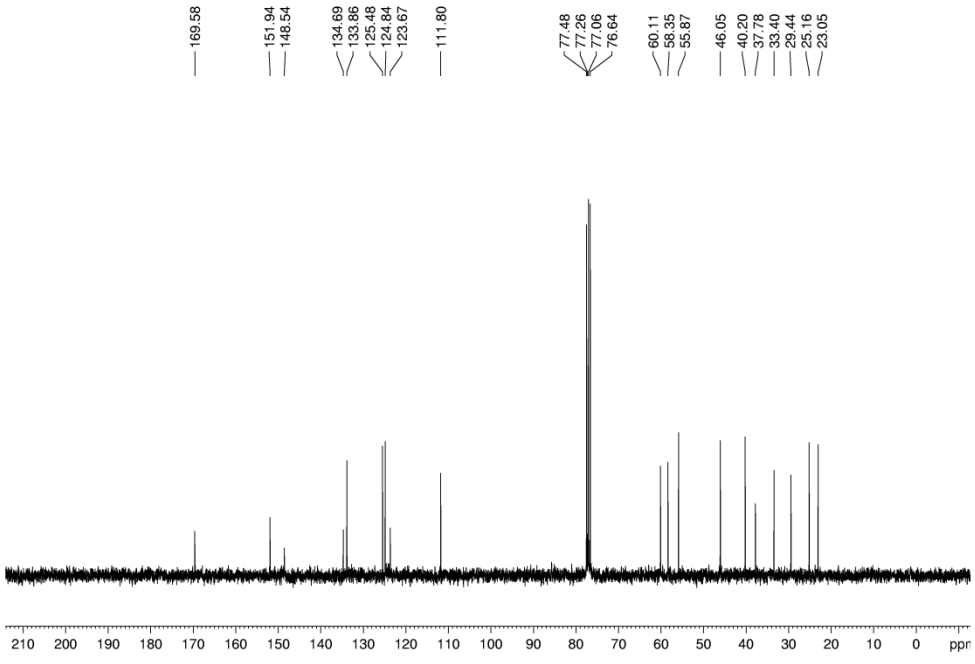
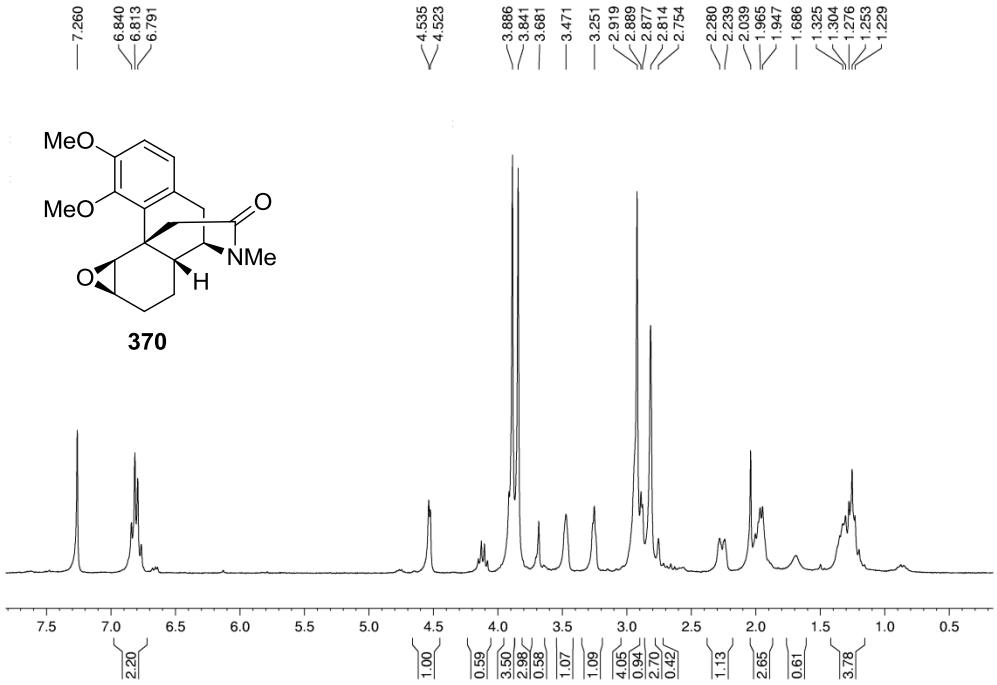


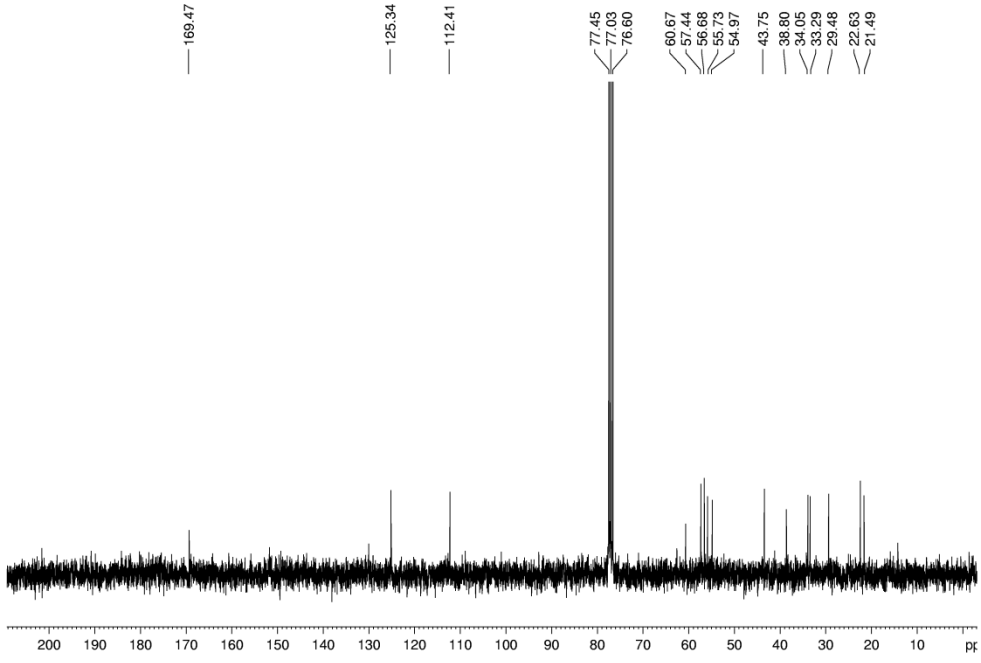
1D carbon with proton decoupling



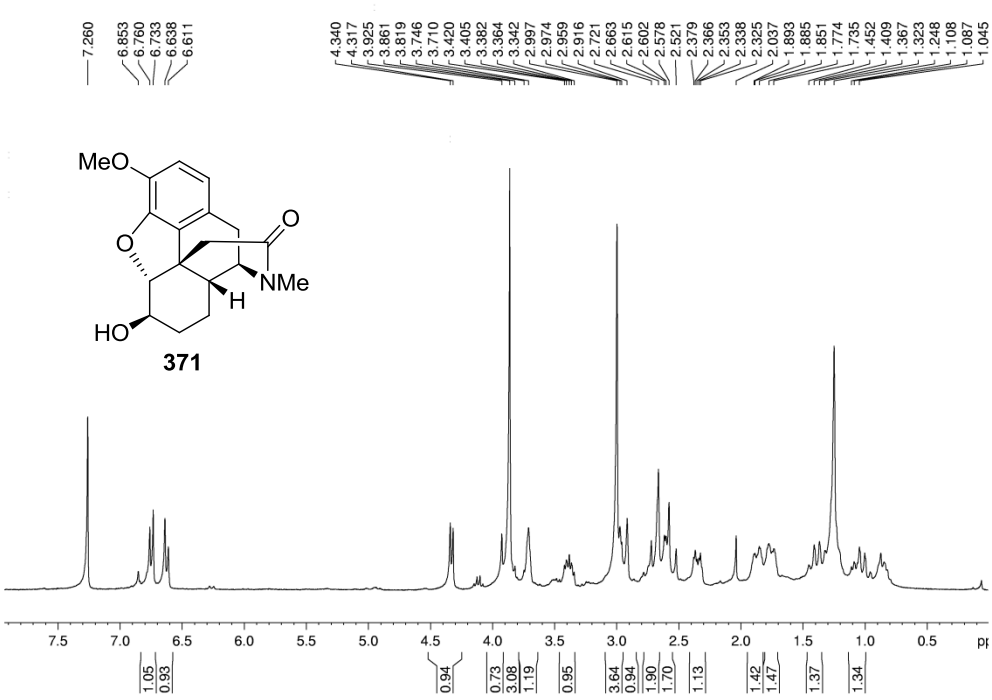
1D proton



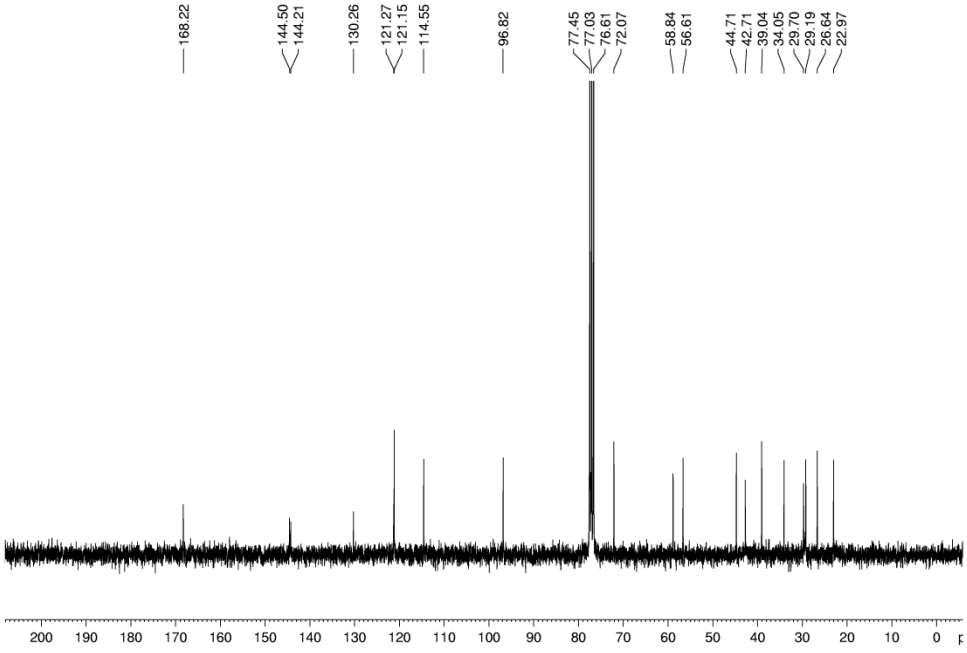
1D carbon with proton decoupling



1D proton



1D carbon with proton decoupling



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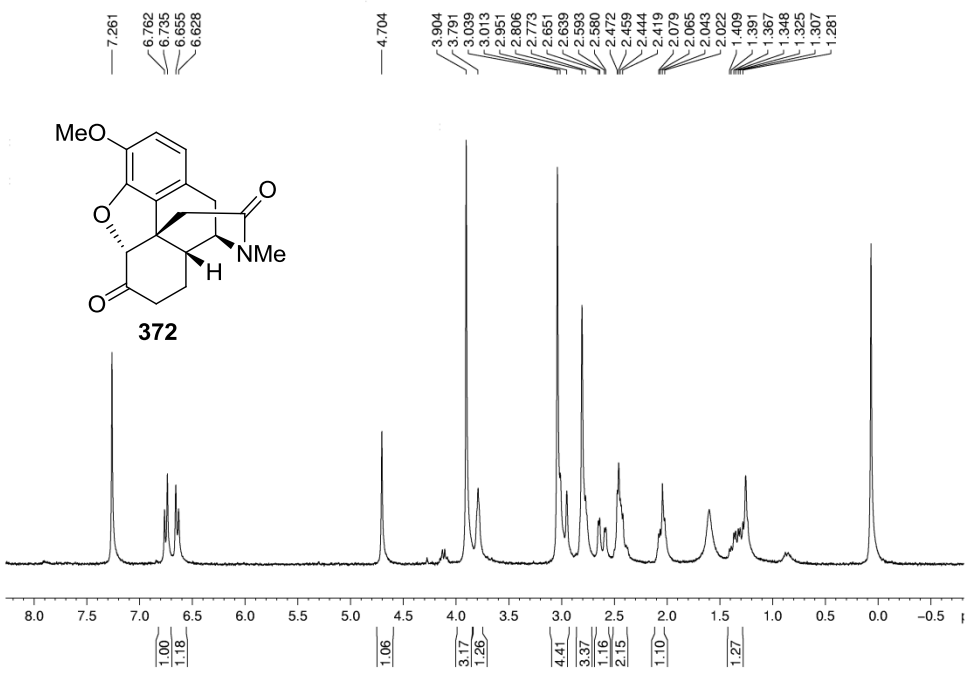

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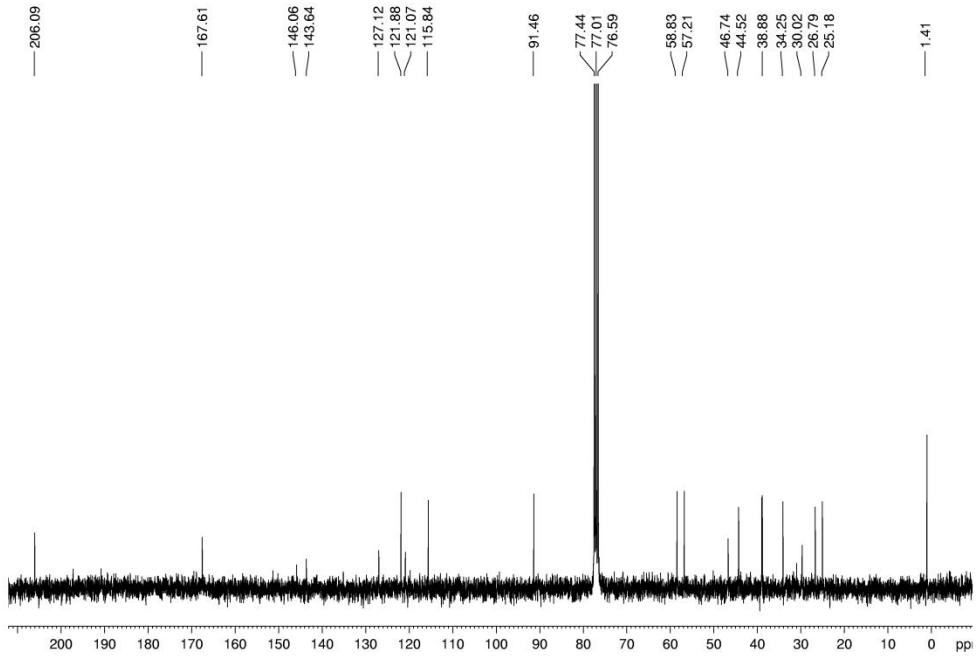

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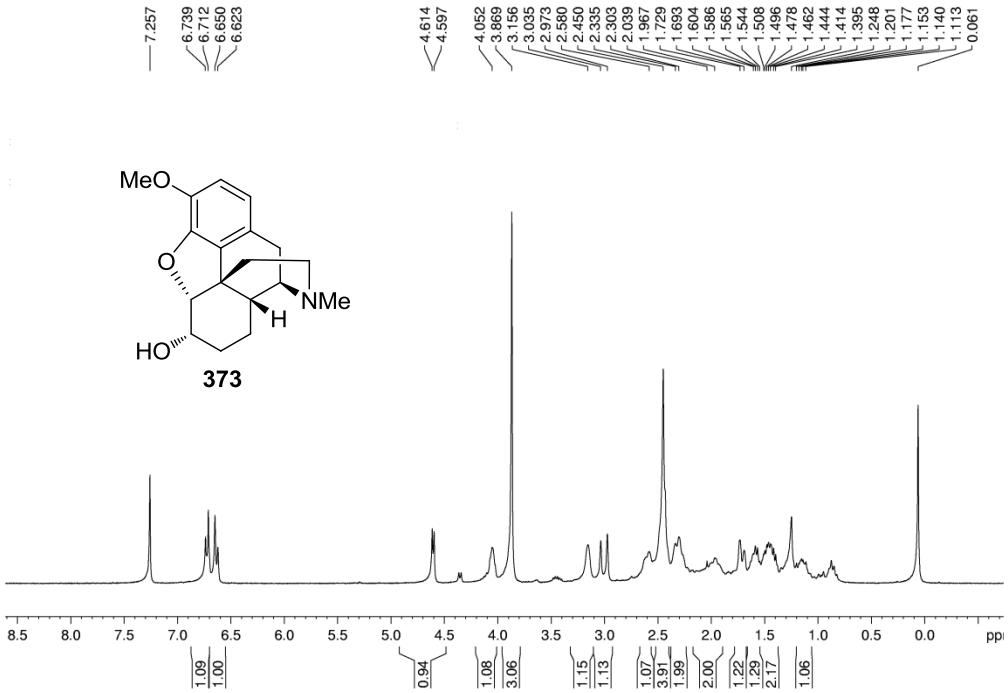
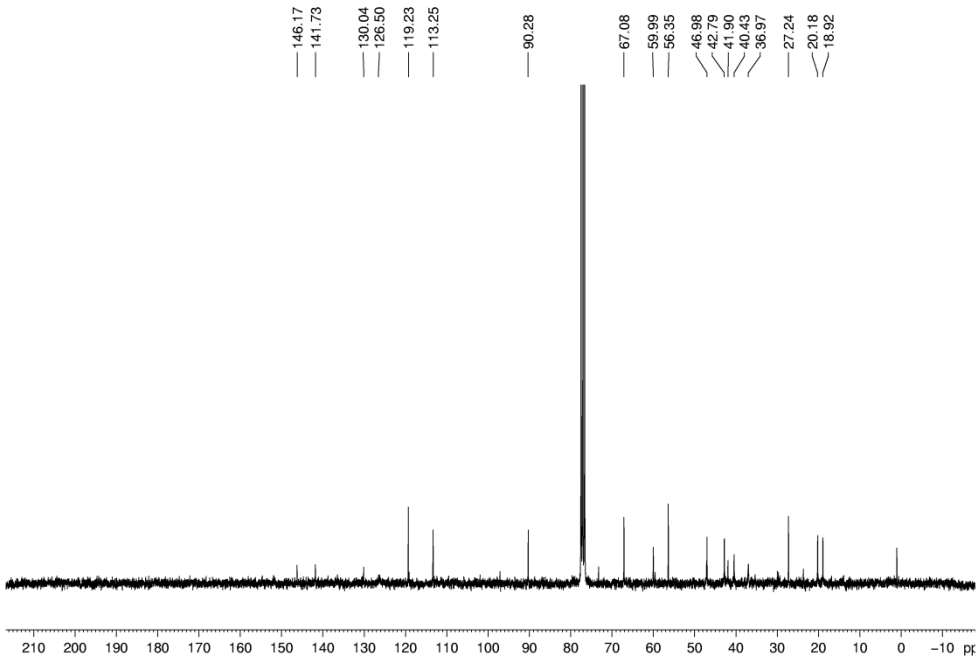
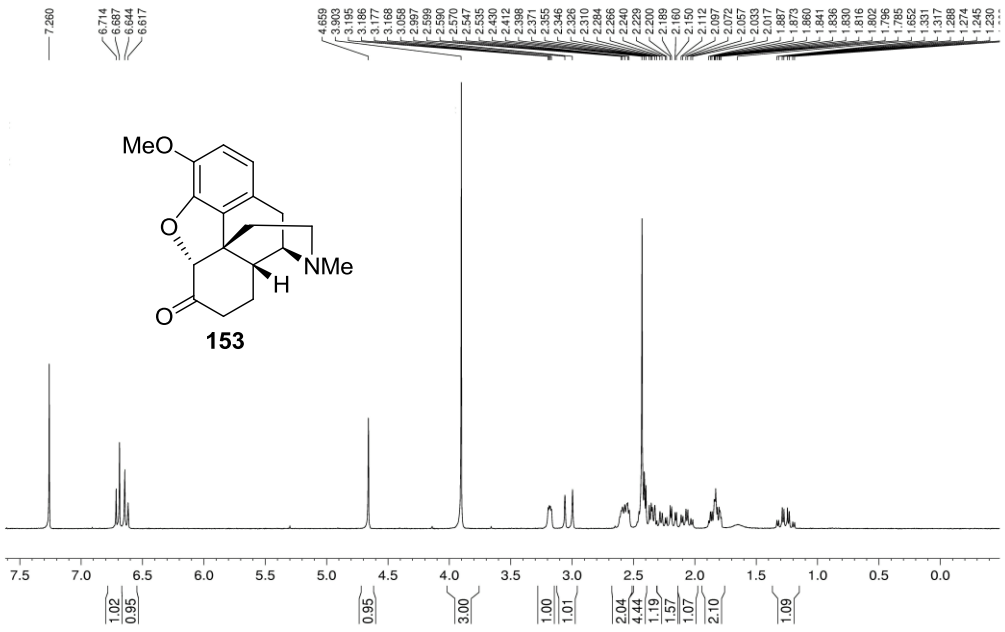


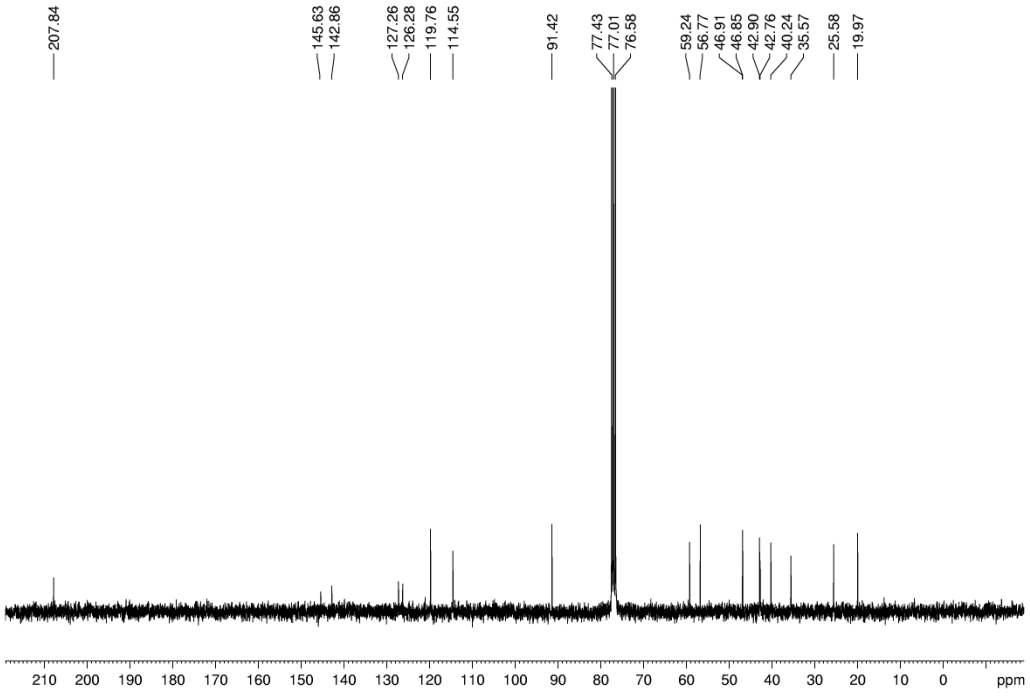
1D carbon with proton decoupling



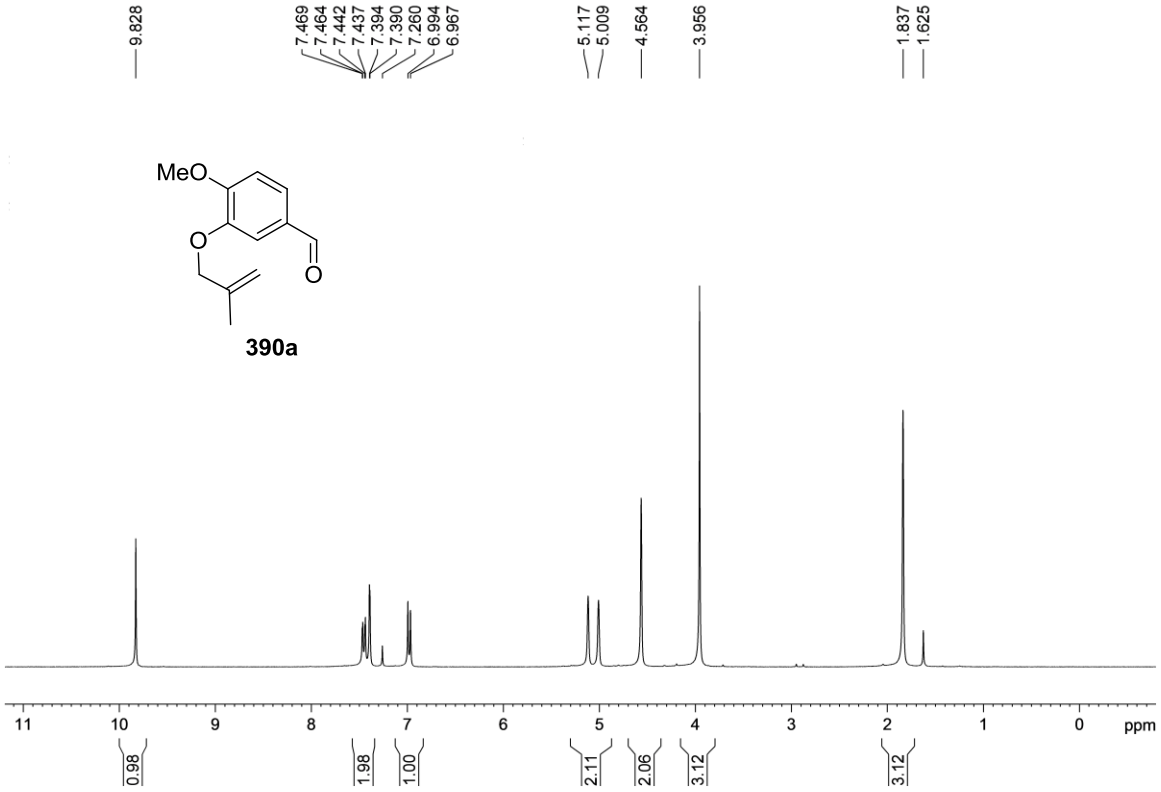
1D proton



1D carbon with proton decoupling



1D proton



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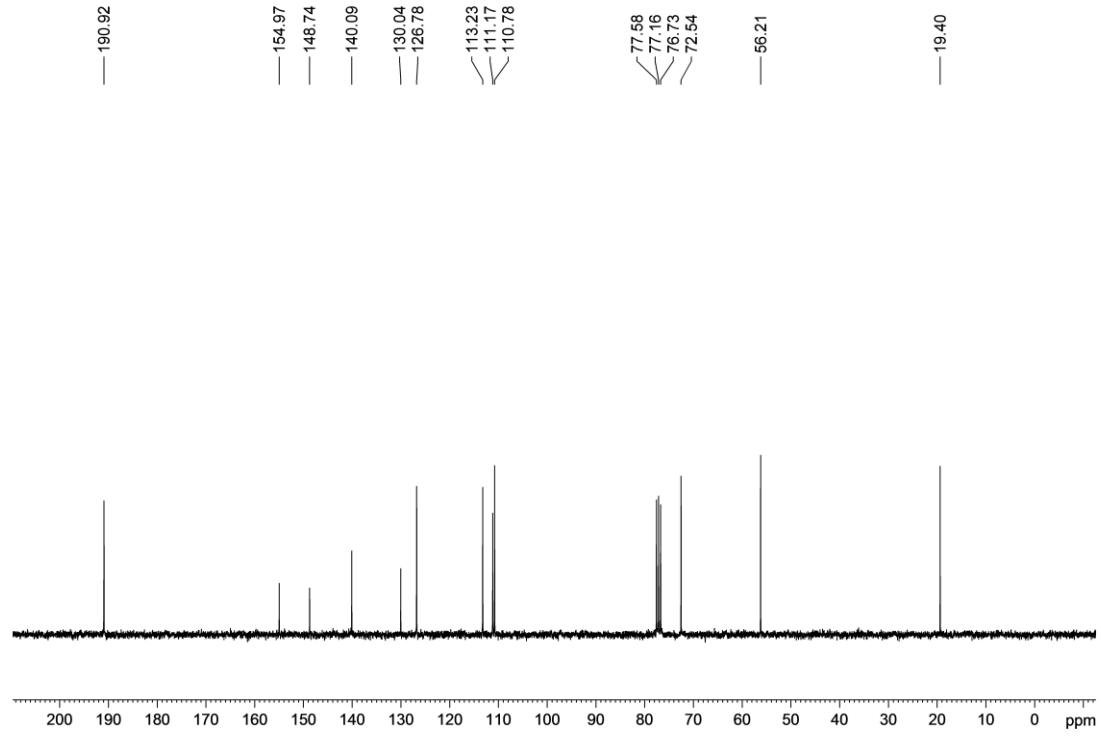
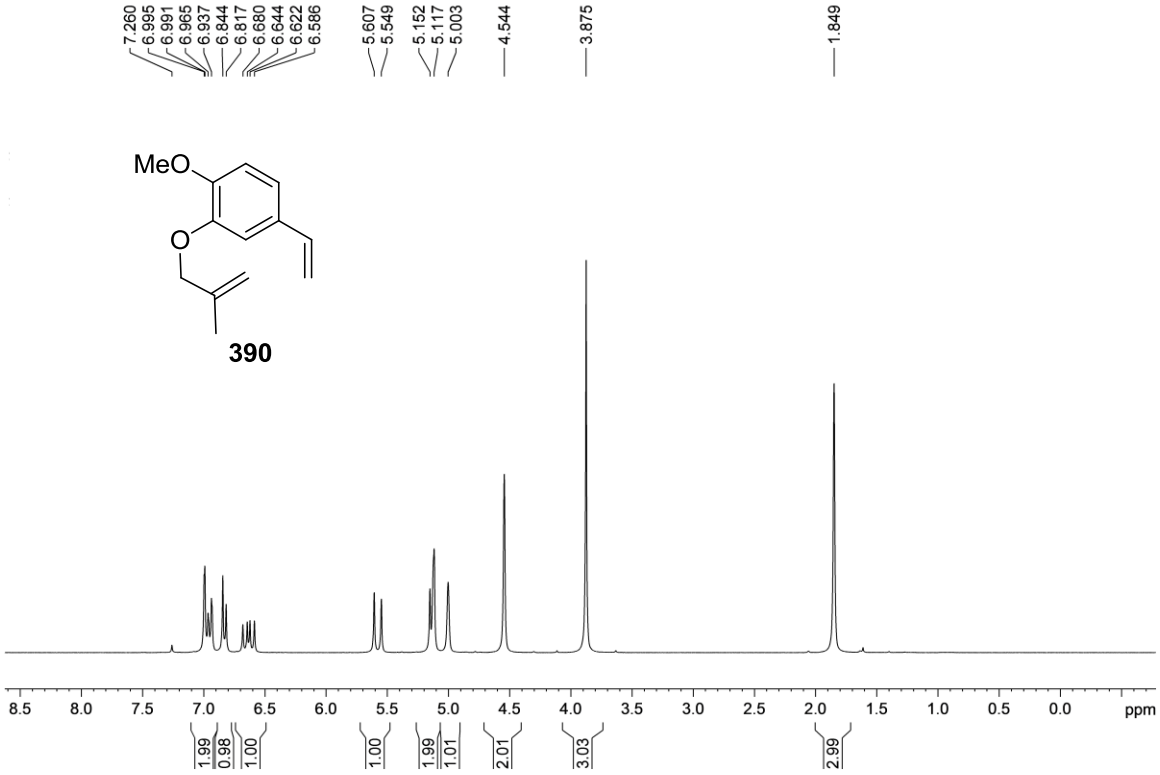
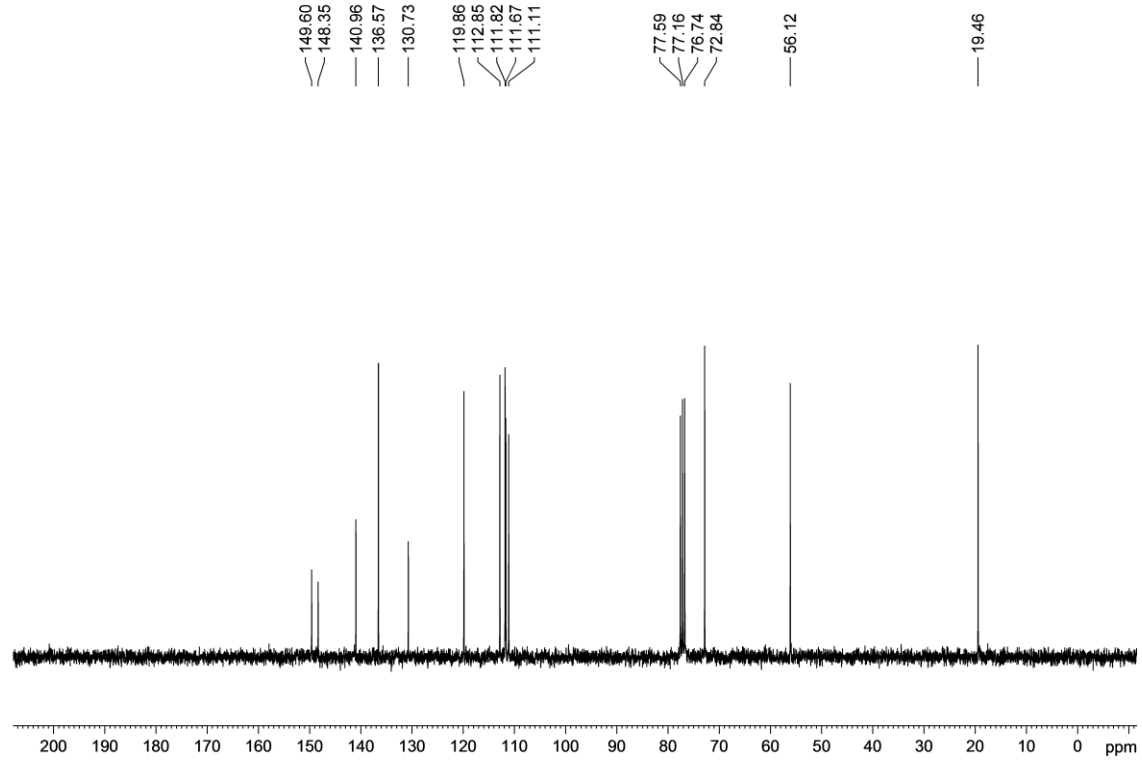
1D carbon with proton decoupling



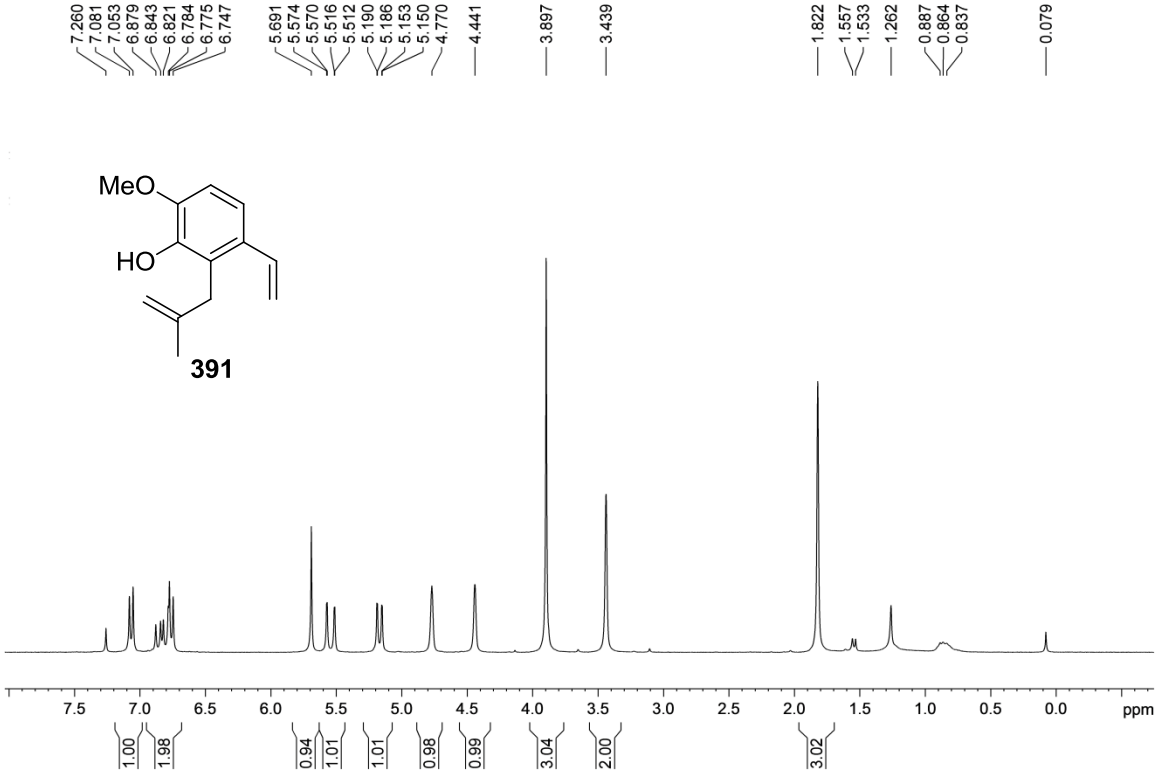
1D proton



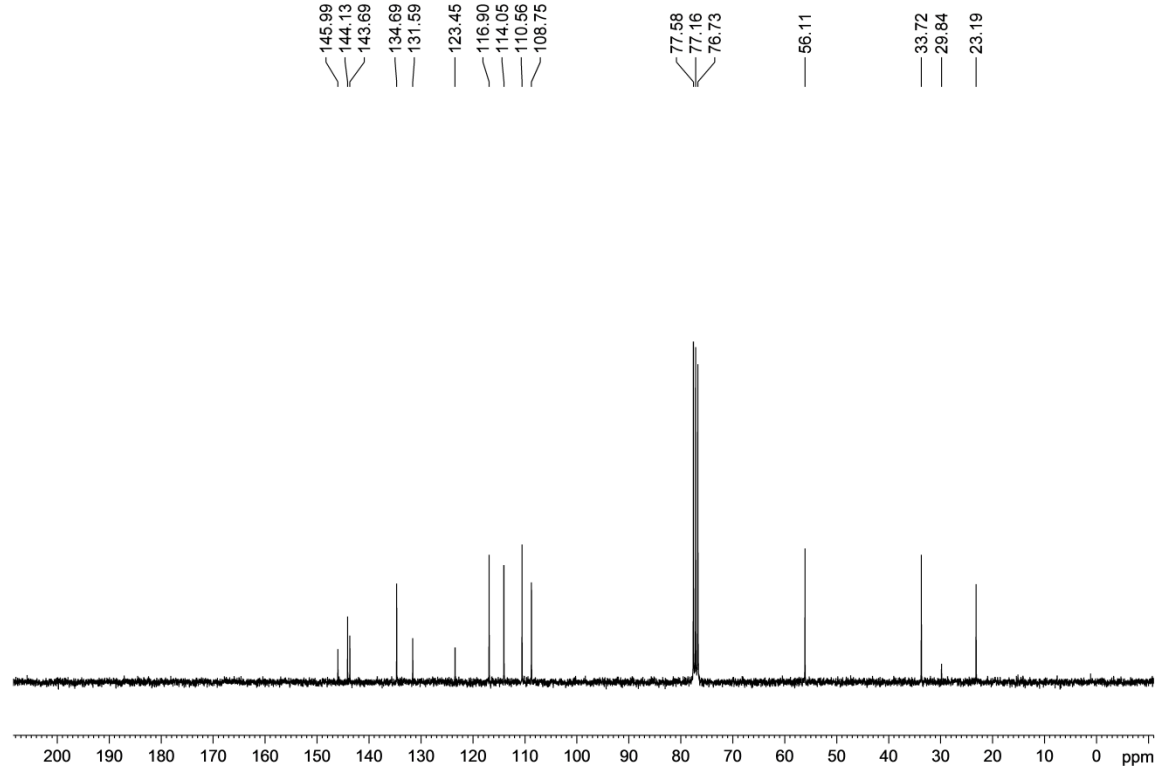
1D carbon with proton decoupling

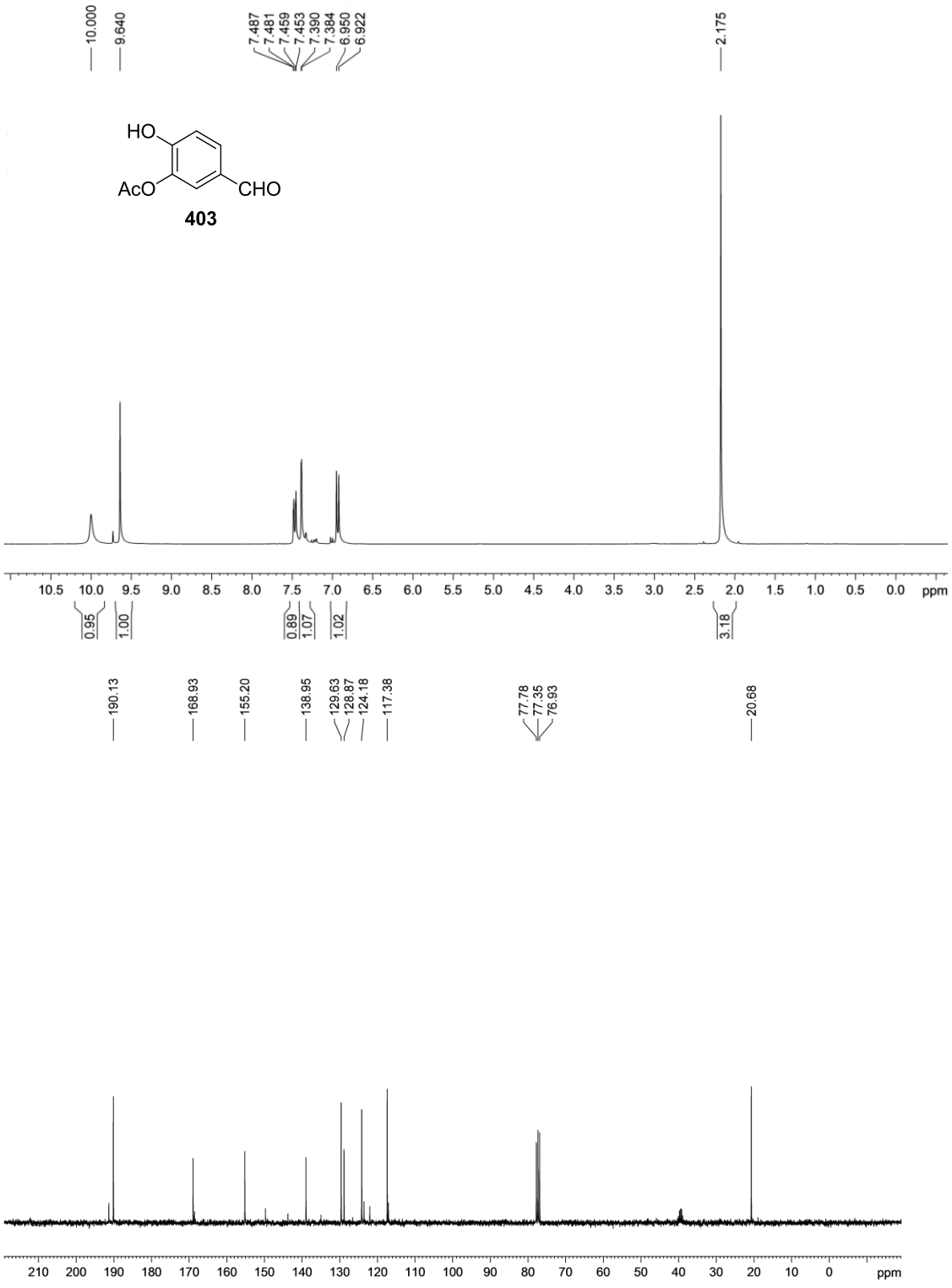


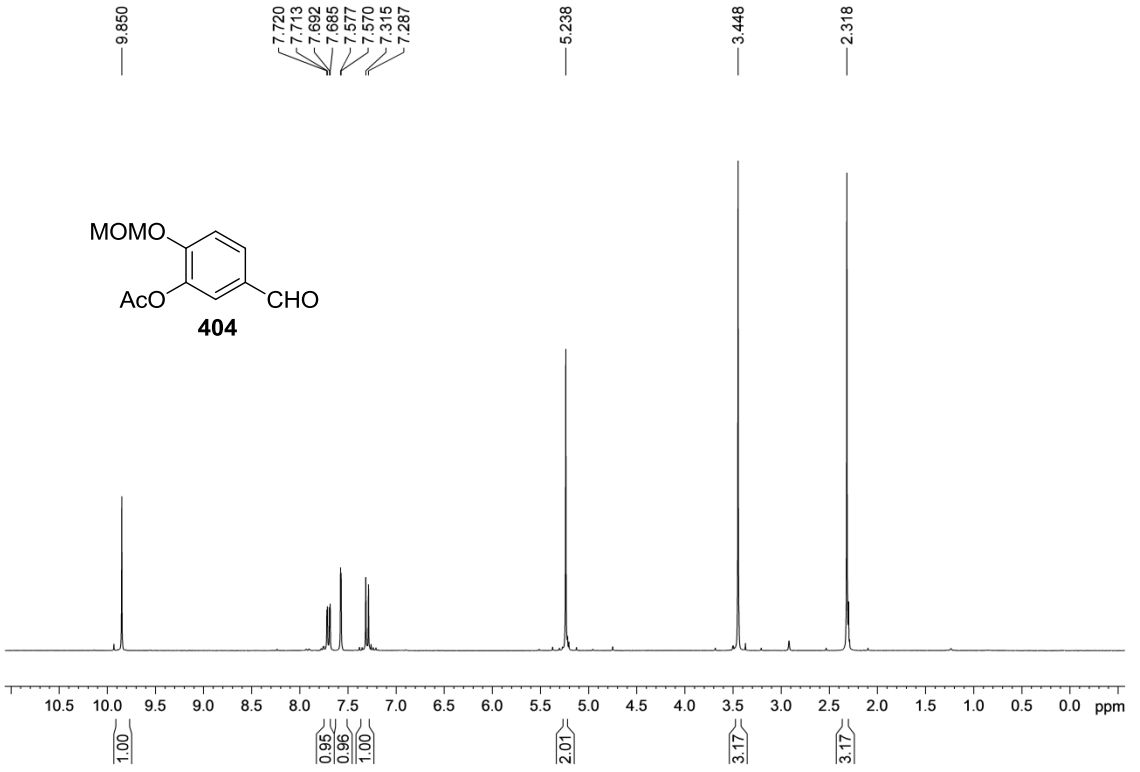
1D proton

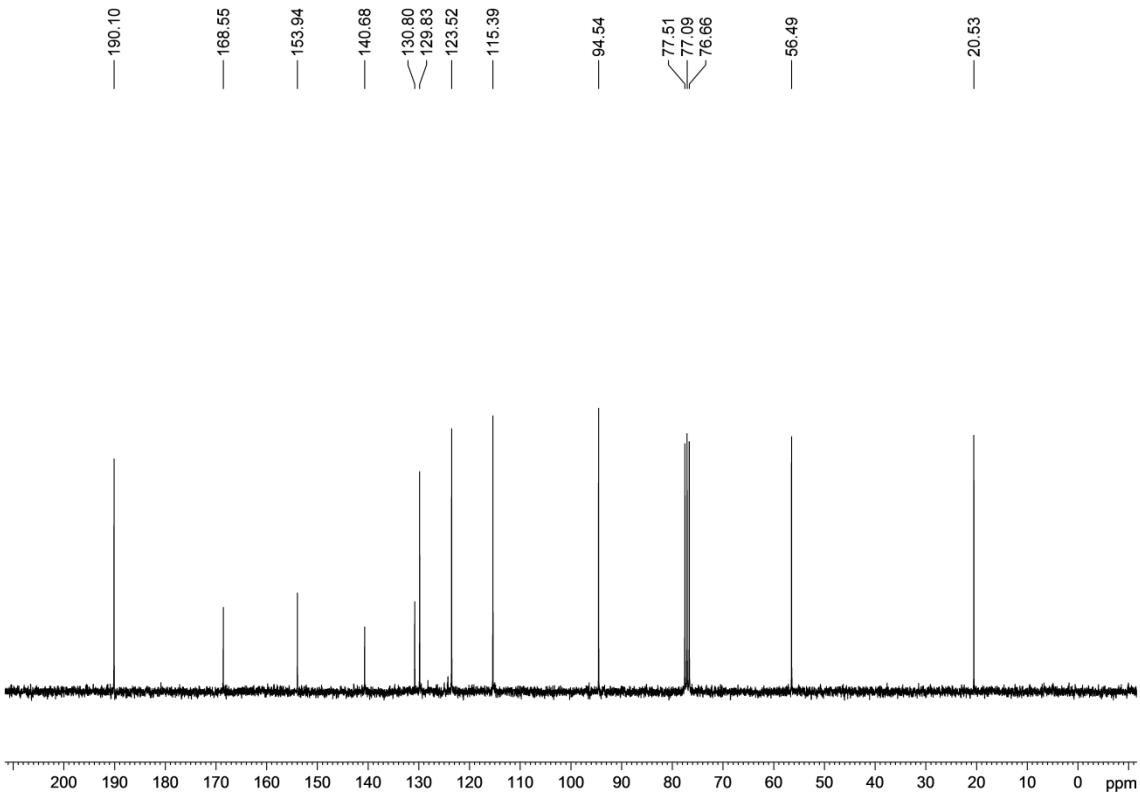


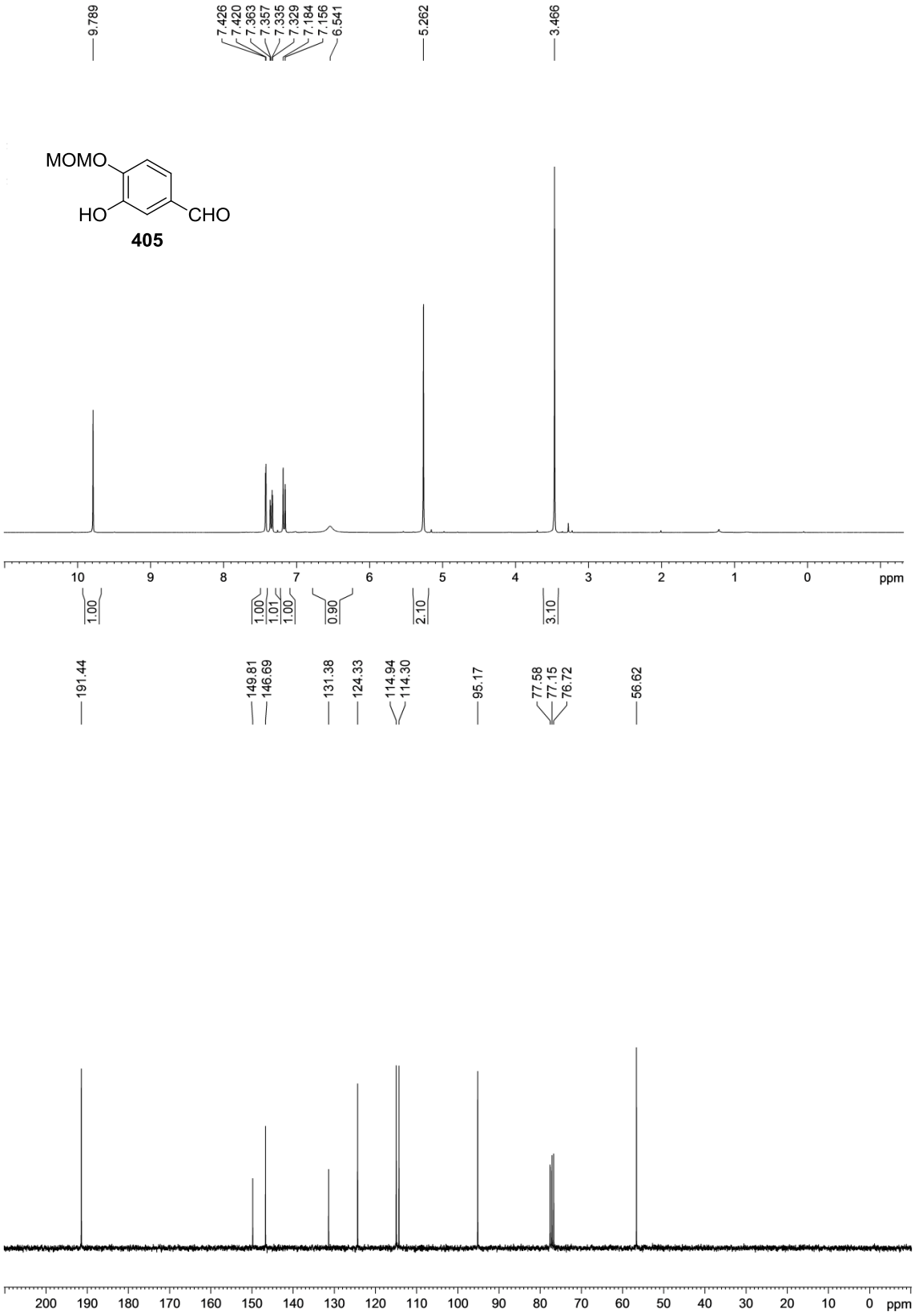
1D carbon with proton decoupling



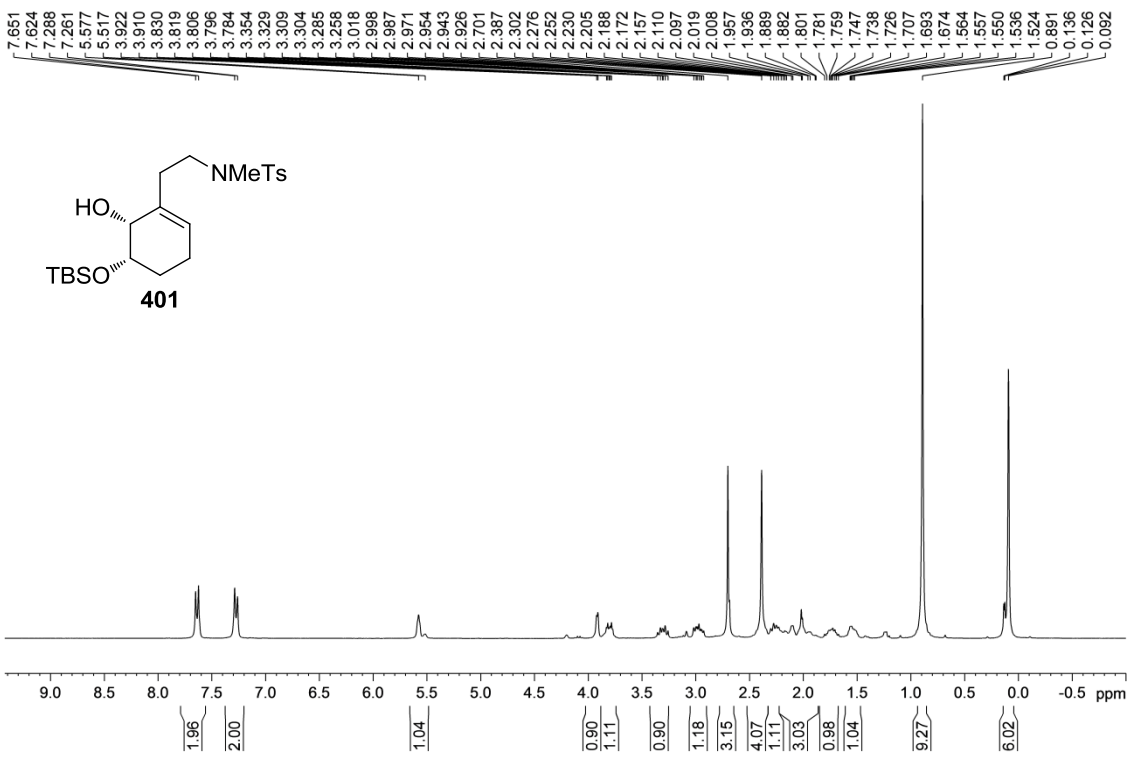

10.000
9.640
7.487
7.481
7.459
7.453
7.390
7.384
6.950
6.922
2.175
HO
AcO
CHO
403
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.95
1.00
0.89
1.07
1.02
3.18
190.13
168.93
155.20
138.95
129.63
128.87
124.18
117.38
77.78
77.35
76.93
20.68
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


9.850
7.720
7.713
7.692
7.685
7.577
7.570
7.315
7.287
5.238
3.448
2.318
MOMO
AcO
CHO
404
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00
0.95
0.96
1.00
2.01
3.17
3.17

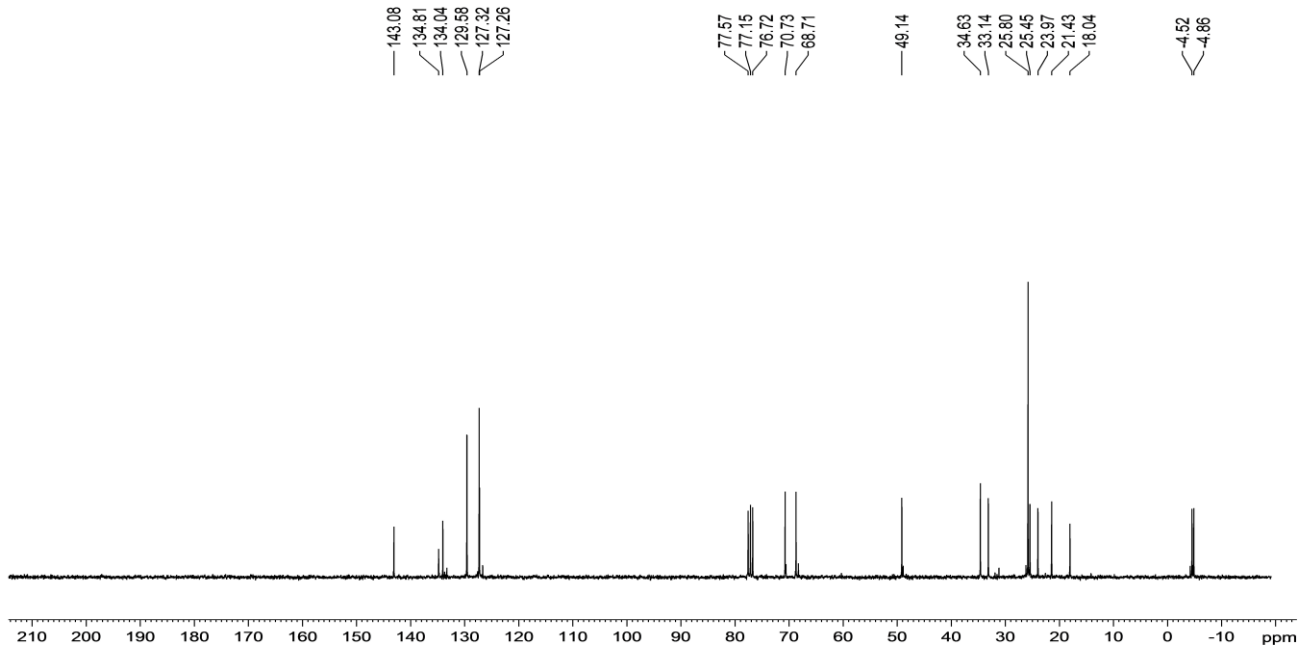

190.10
168.55
153.94
140.68
130.80
129.83
123.52
115.39
94.54
77.51
77.09
76.66
56.49
20.53
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

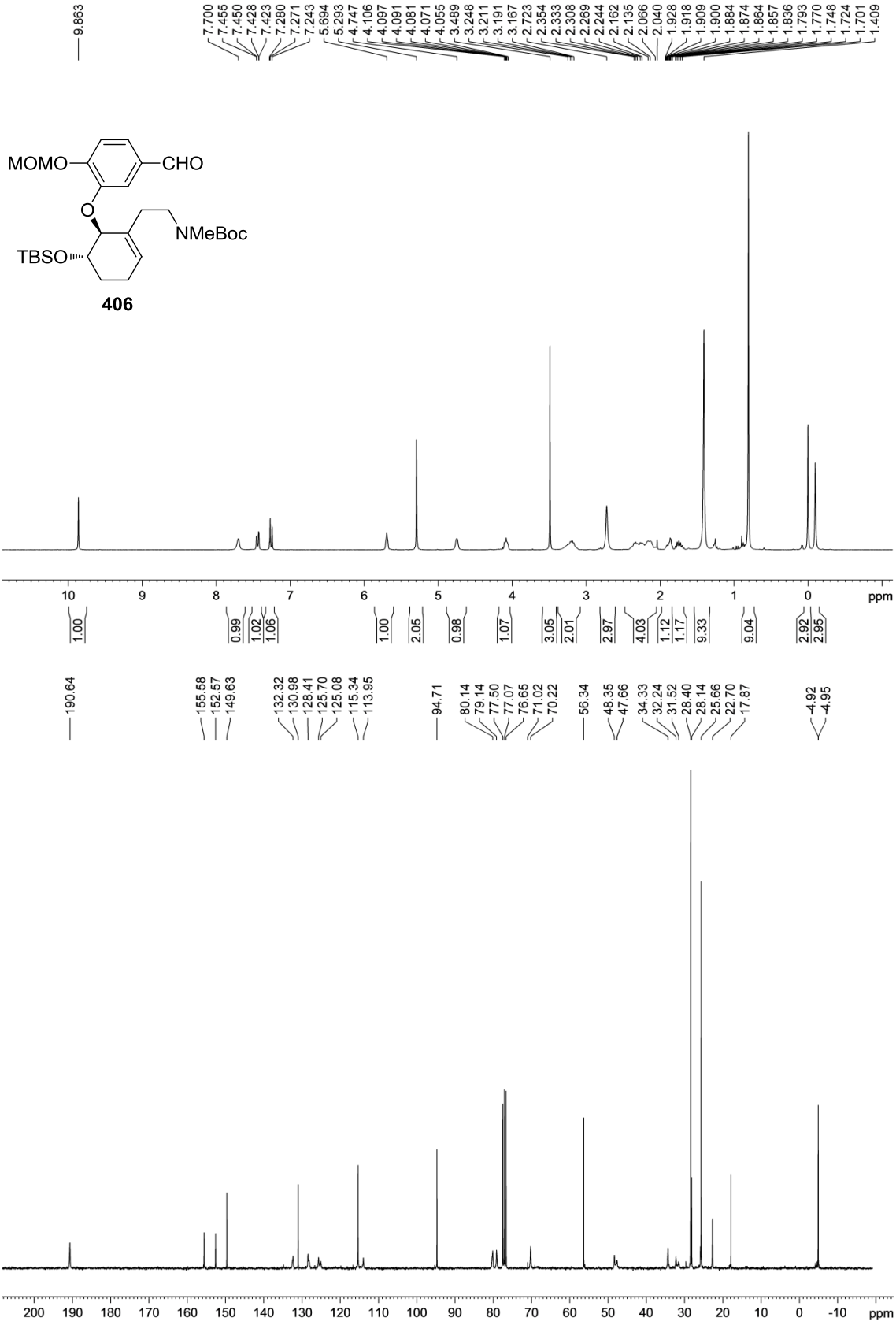

9.789
7.426
7.420
7.363
7.357
7.335
7.329
7.184
7.156
6.541
5.262
3.466
MOMO
HO
CHO
405
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.00
1.01
1.00
0.90
2.10
3.10
191.44
149.81
146.69
131.38
124.33
114.94
114.30
95.17
77.58
77.15
76.72
56.62
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

1D proton

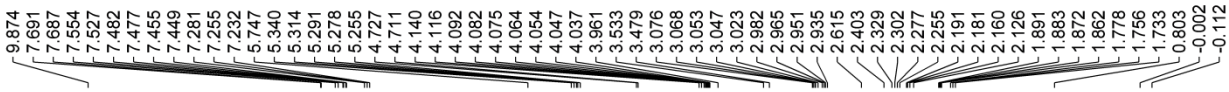


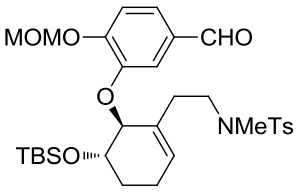
1D carbon with proton decoupling




9.863
7.700
7.455
7.450
7.428
7.423
7.280
7.271
7.243
5.694
5.293
4.747
4.106
4.097
4.091
4.081
4.071
4.055
3.489
3.248
3.211
3.191
3.167
2.723
2.354
2.333
2.308
2.269
2.244
2.162
2.135
2.066
2.040
1.928
1.918
1.909
1.900
1.884
1.874
1.864
1.857
1.836
1.793
1.770
1.748
1.724
1.701
1.409
MOMO
CHO
O
NMeBoc
TBSO
406
ppm
1.00
0.99
1.02
1.06
1.00
2.05
0.98
1.07
3.05
2.01
2.97
4.03
1.12
1.17
9.33
9.04
2.92
2.95
190.64
155.58
152.57
149.63
132.32
130.98
128.41
125.70
125.08
115.34
113.95
94.71
80.14
79.14
77.50
77.07
76.65
71.02
70.22
56.34
48.35
47.66
34.33
32.24
31.52
28.40
28.14
25.66
22.70
17.87
-4.92
-4.95
ppm

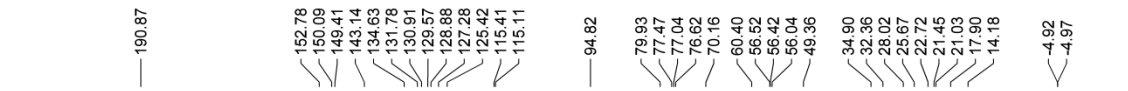
1D proton

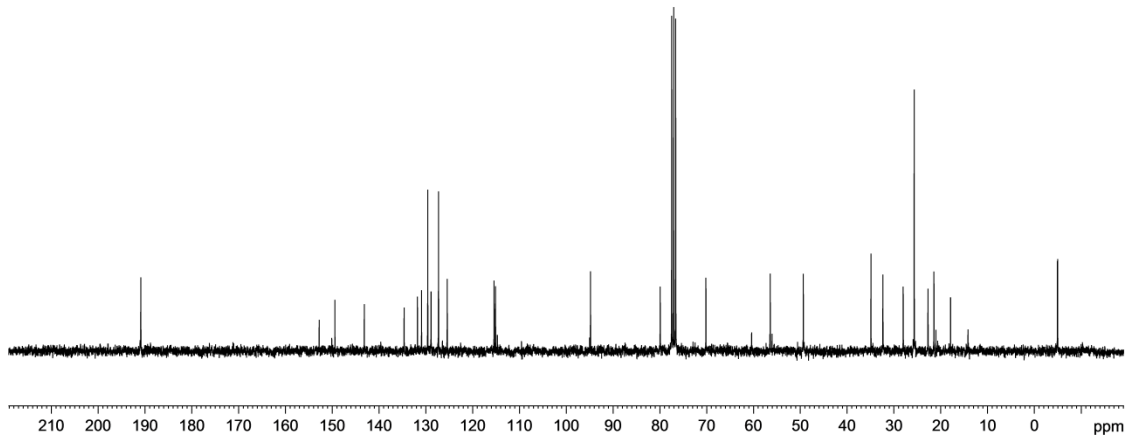


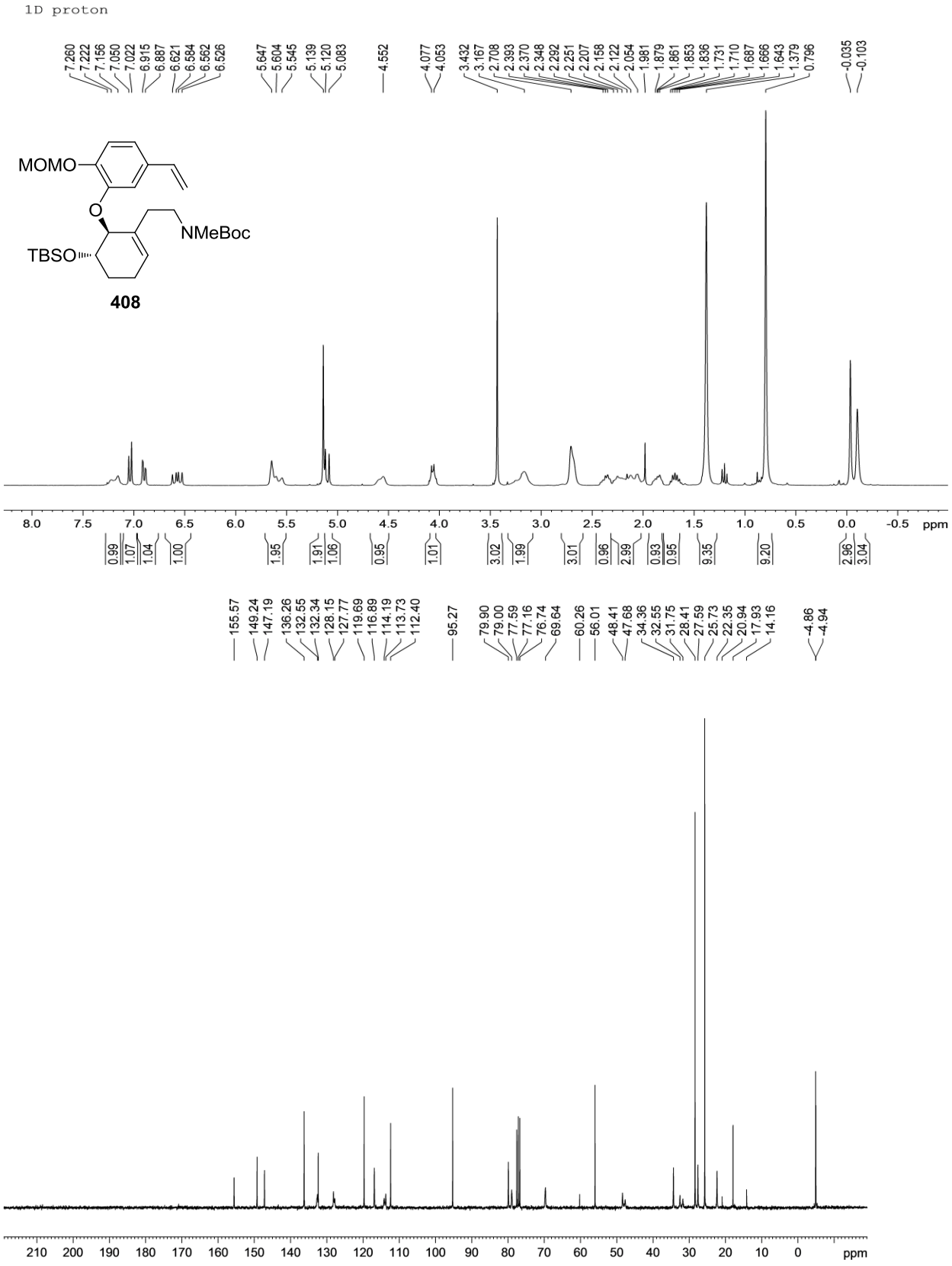


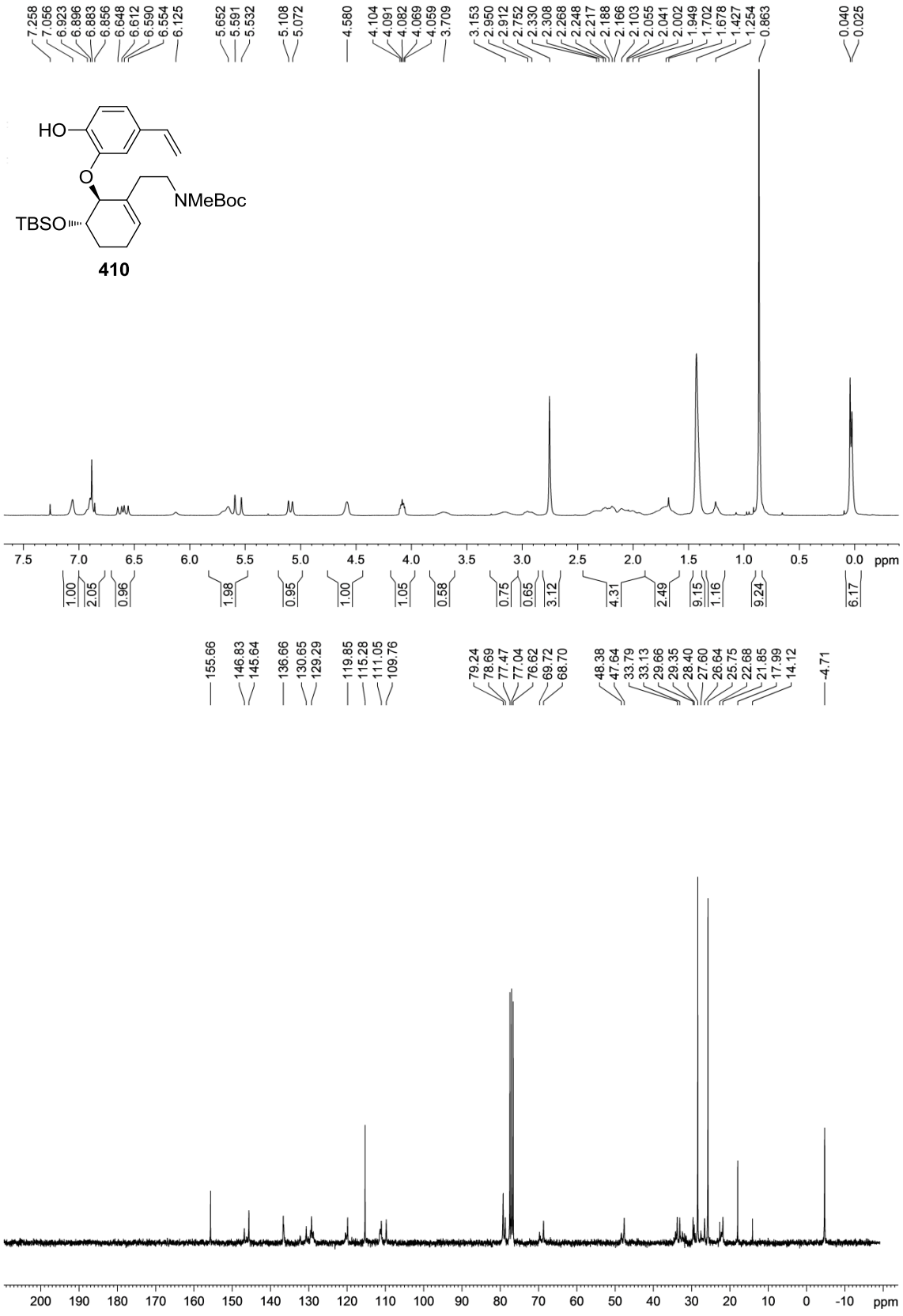
407

1D carbon with proton decoupling

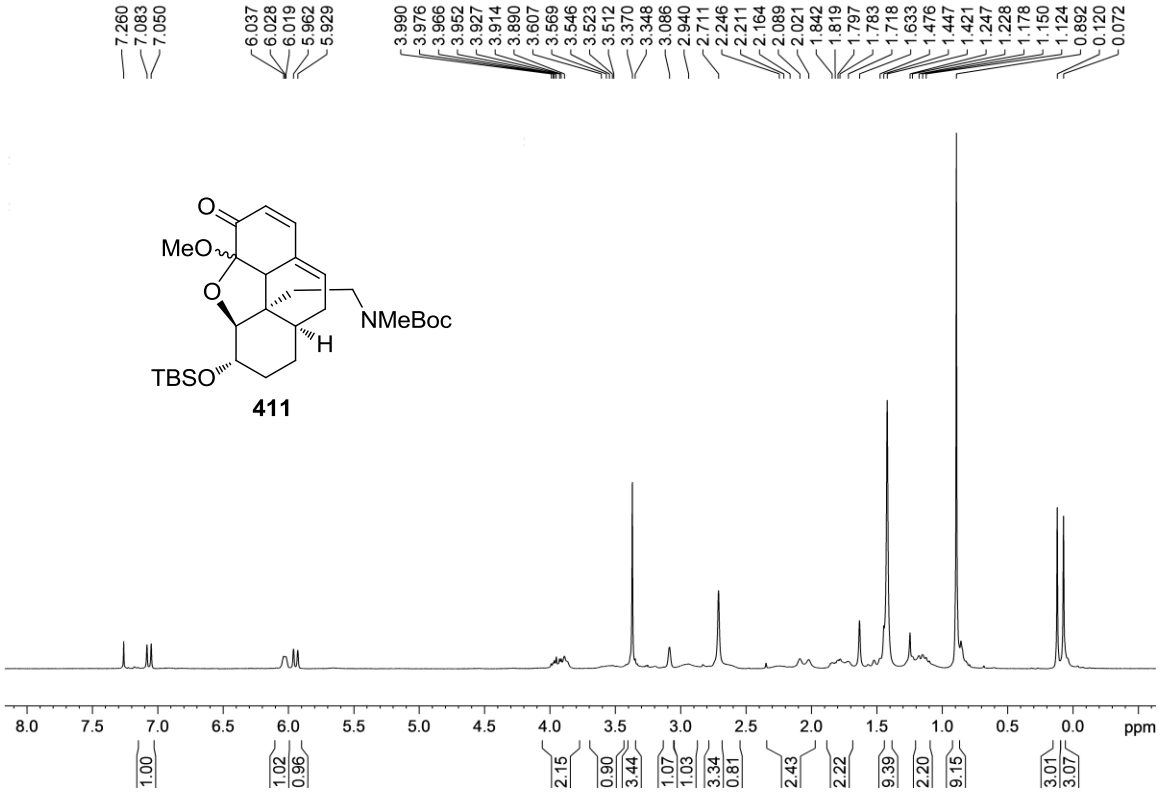




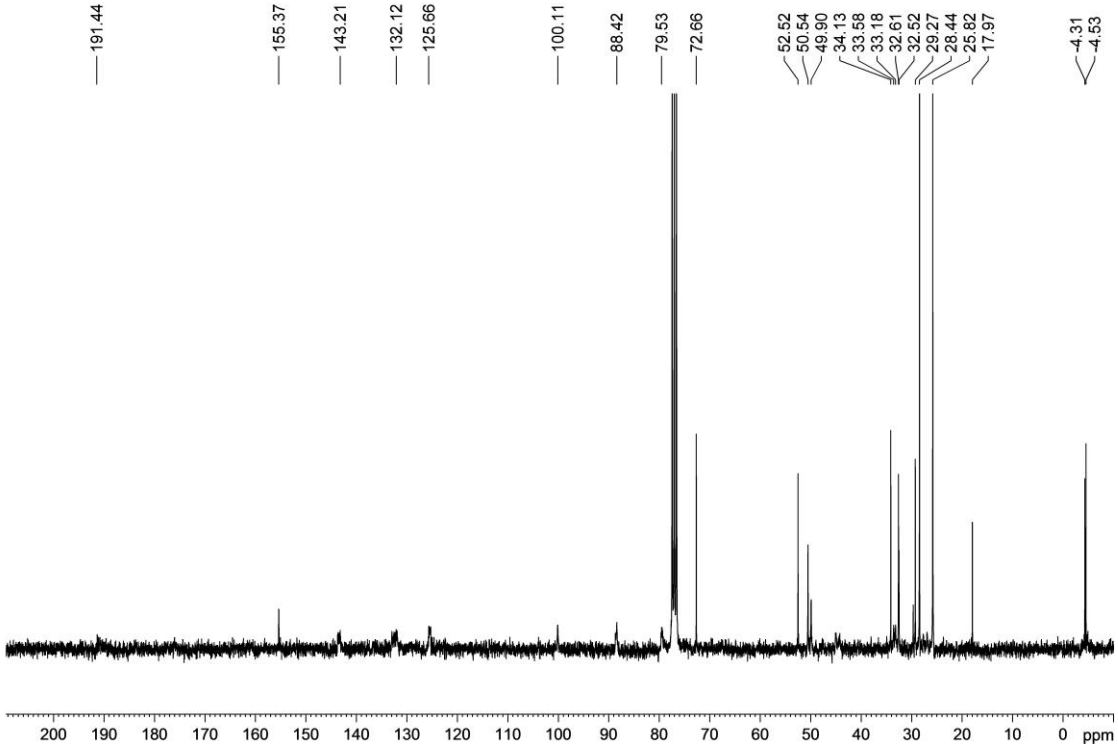

1D proton
7.260
7.222
7.156
7.050
7.022
6.915
6.887
6.621
6.584
6.562
6.526
5.647
5.604
5.545
5.139
5.120
5.083
4.552
4.077
4.053
3.432
3.167
2.708
2.393
2.370
2.348
2.292
2.251
2.207
2.158
2.122
2.054
1.981
1.879
1.861
1.853
1.836
1.731
1.710
1.687
1.666
1.643
1.379
0.796
-0.035
-0.103
MOMO
O
NMeBoc
TBSO
408
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
0.99
1.07
1.04
1.00
1.95
1.91
1.06
0.95
1.01
3.02
1.99
3.01
0.96
2.99
0.93
0.95
9.35
9.20
2.96
3.04
155.57
149.24
147.19
136.26
132.55
132.34
128.15
127.77
119.69
116.89
114.19
113.73
112.40
95.27
79.90
79.00
77.59
77.16
76.74
69.64
60.26
56.01
48.41
47.68
34.36
32.55
31.75
28.41
27.59
25.73
22.35
20.94
17.93
14.16
-4.86
-4.94
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

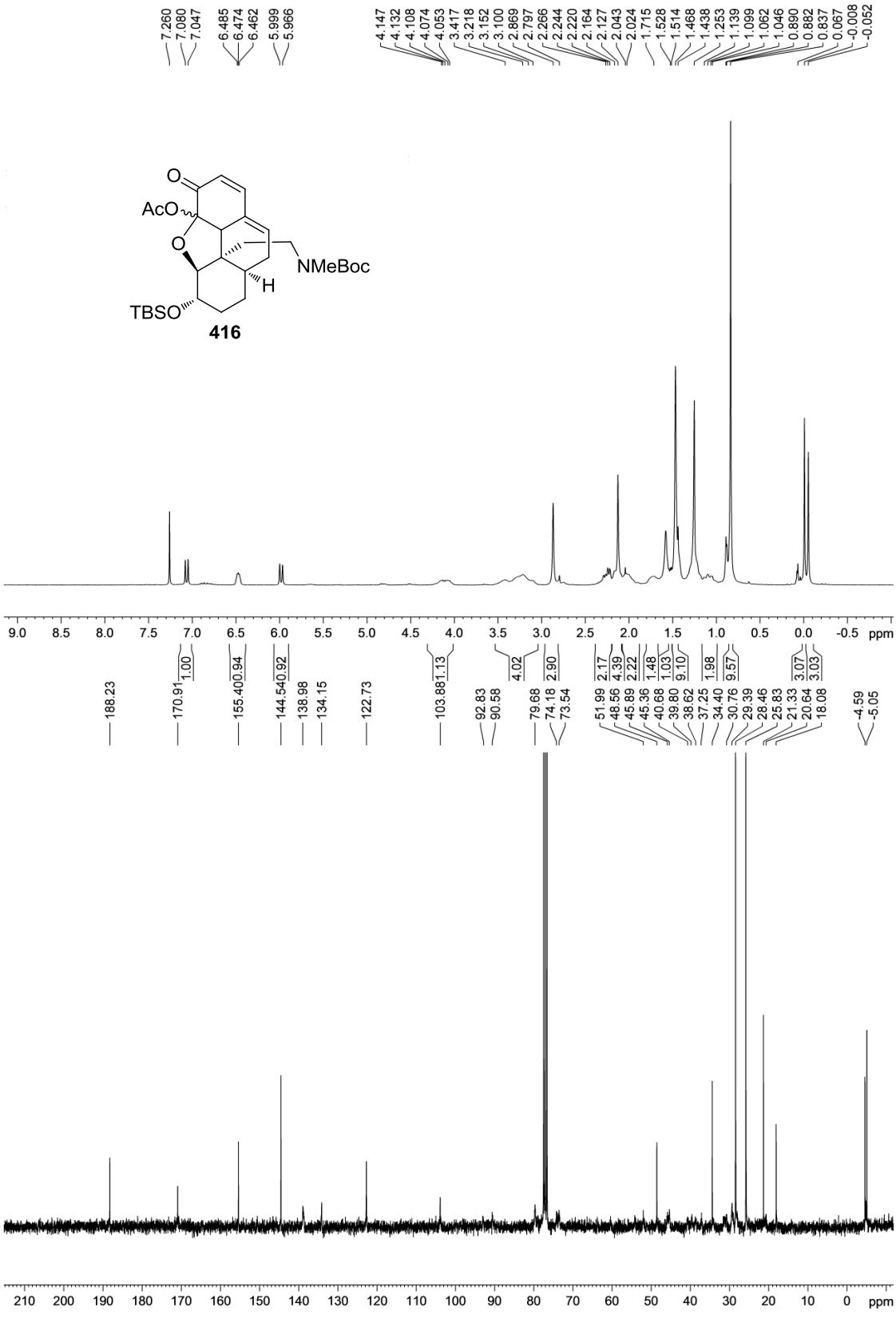

HO
O
NMeBoc
TBSO
410
7.258
7.056
6.923
6.896
6.883
6.856
6.648
6.612
6.590
6.554
6.125
5.652
5.591
5.532
5.108
5.072
4.580
4.104
4.091
4.082
4.069
4.059
3.709
3.153
2.950
2.912
2.752
2.330
2.308
2.268
2.248
2.217
2.188
2.166
2.103
2.055
2.041
2.002
1.949
1.702
1.678
1.427
1.254
0.863
0.040
0.025
ppm
155.66
146.83
145.64
136.66
130.65
129.29
119.85
115.28
111.05
109.76
79.24
78.69
77.47
77.04
76.62
69.72
68.70
48.38
47.64
33.79
33.13
29.66
29.35
28.40
27.60
26.64
25.75
22.68
21.85
17.99
14.12
-4.71

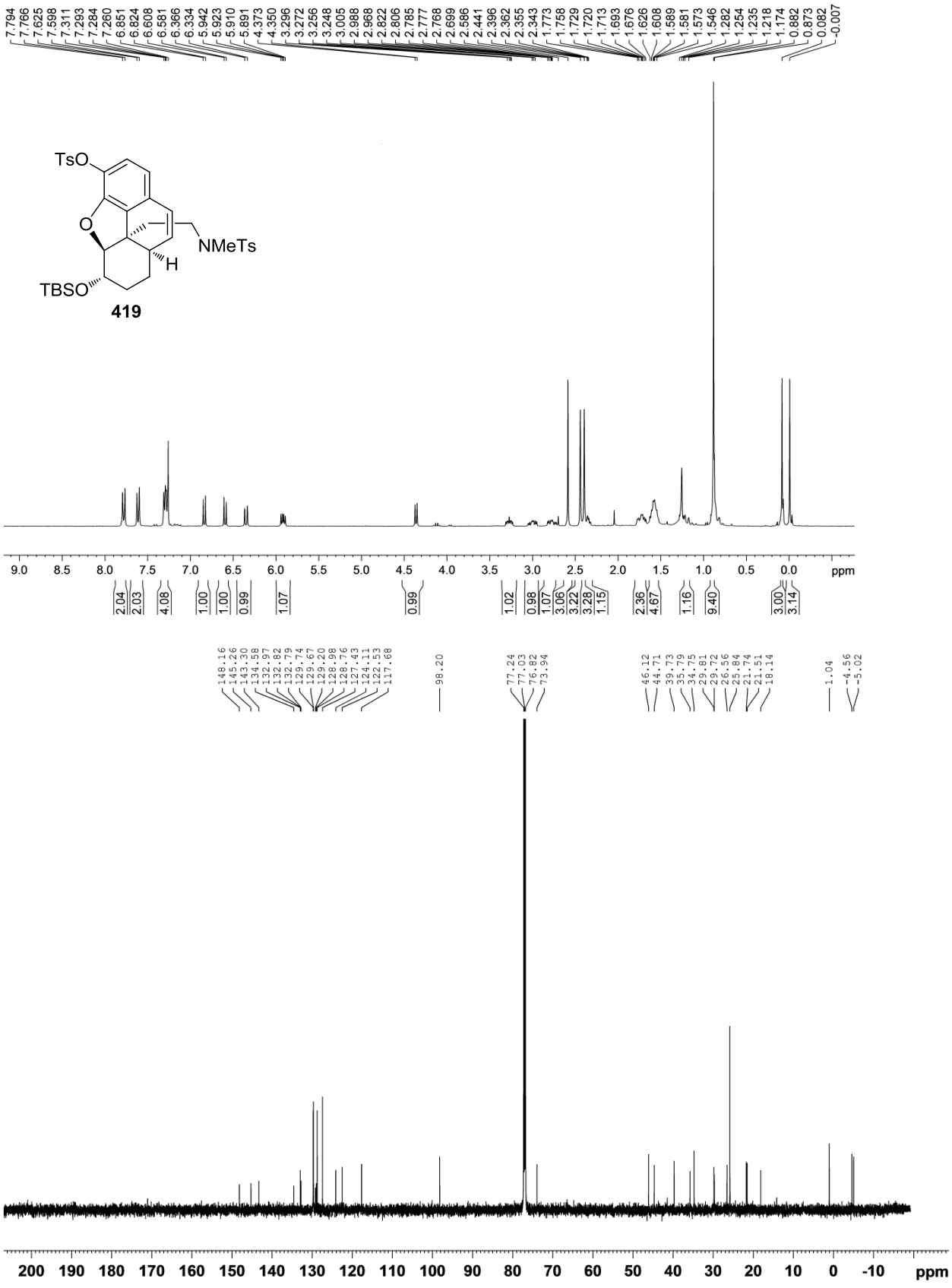
1D proton

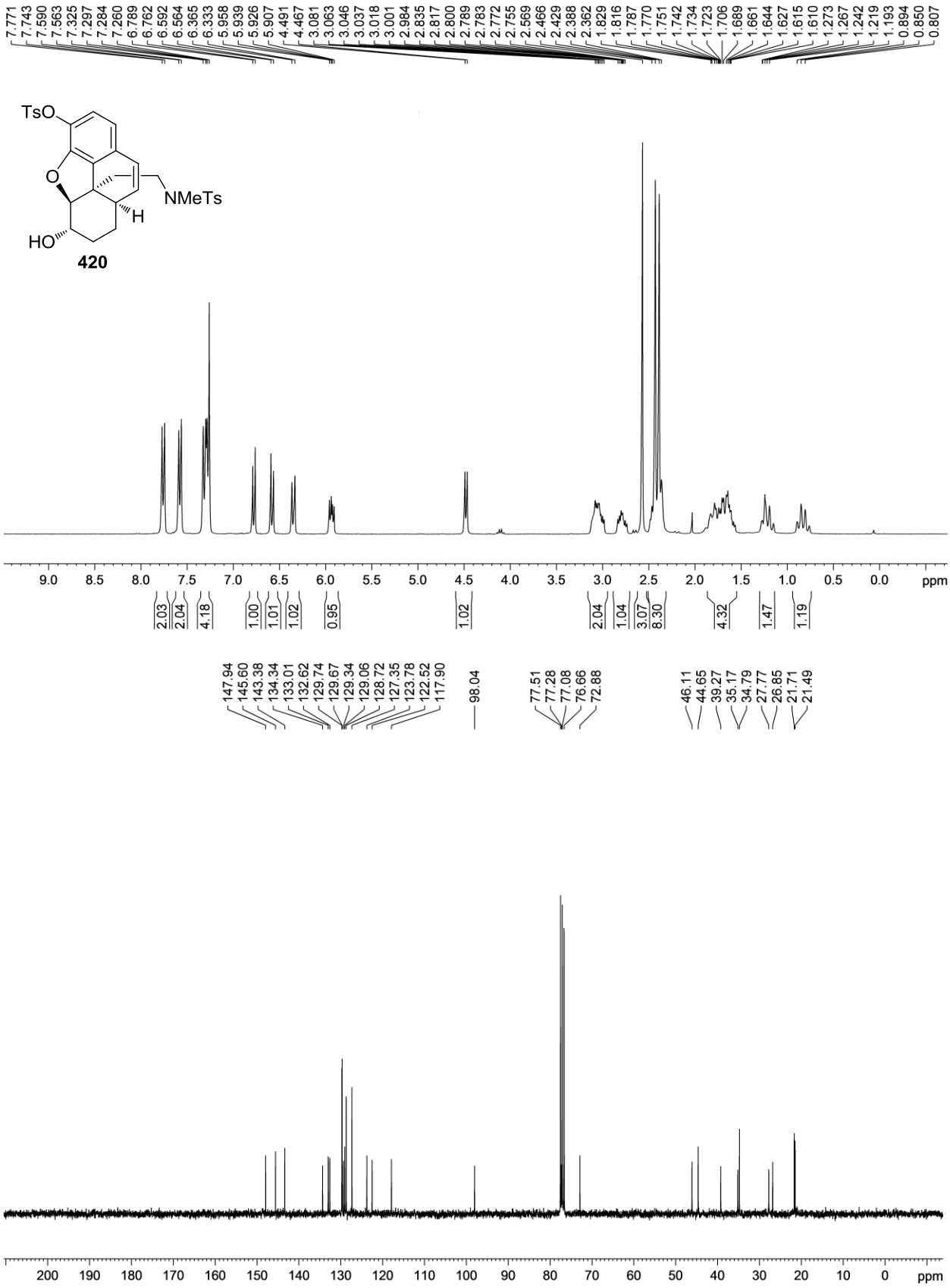


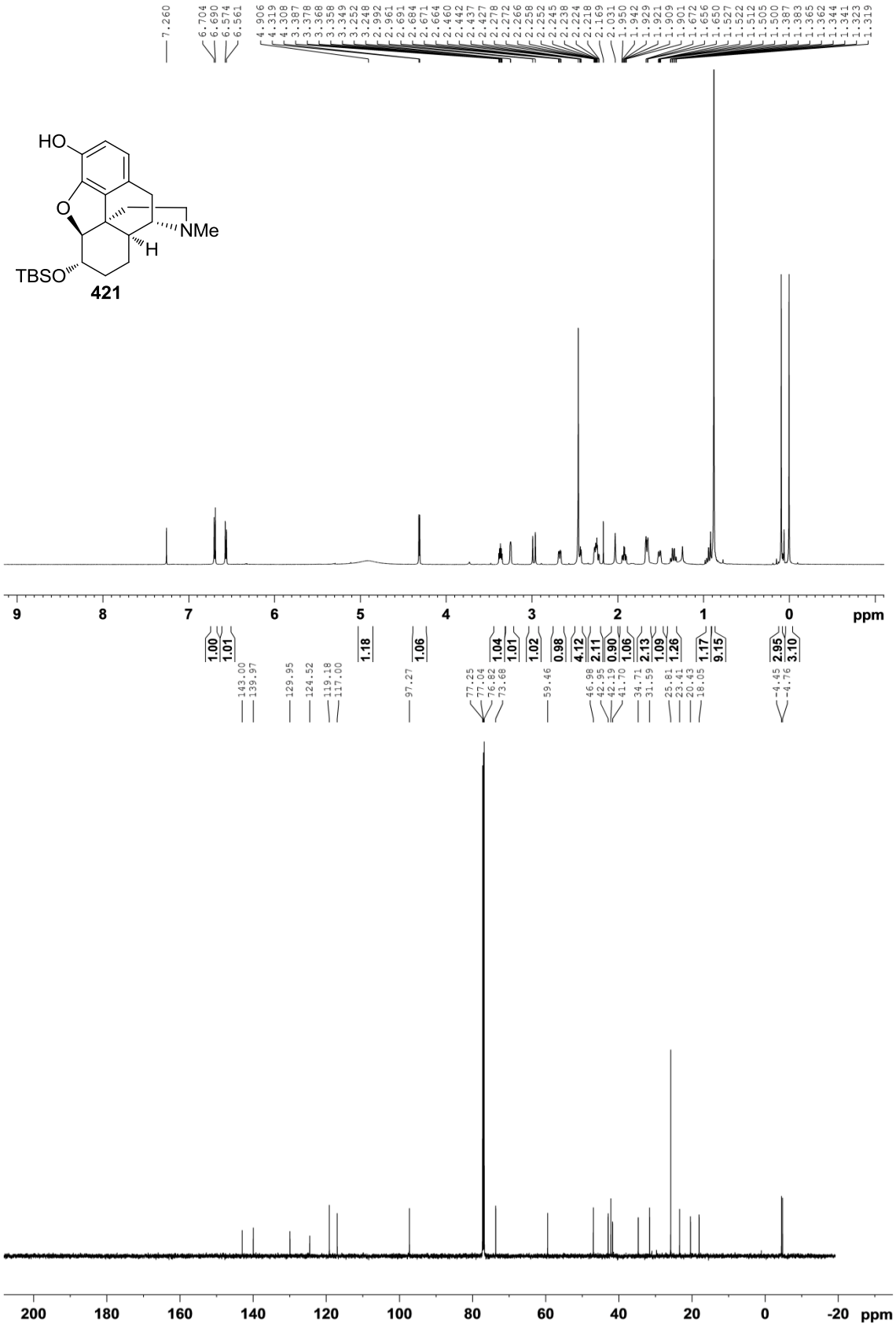
1D carbon with proton decoupling

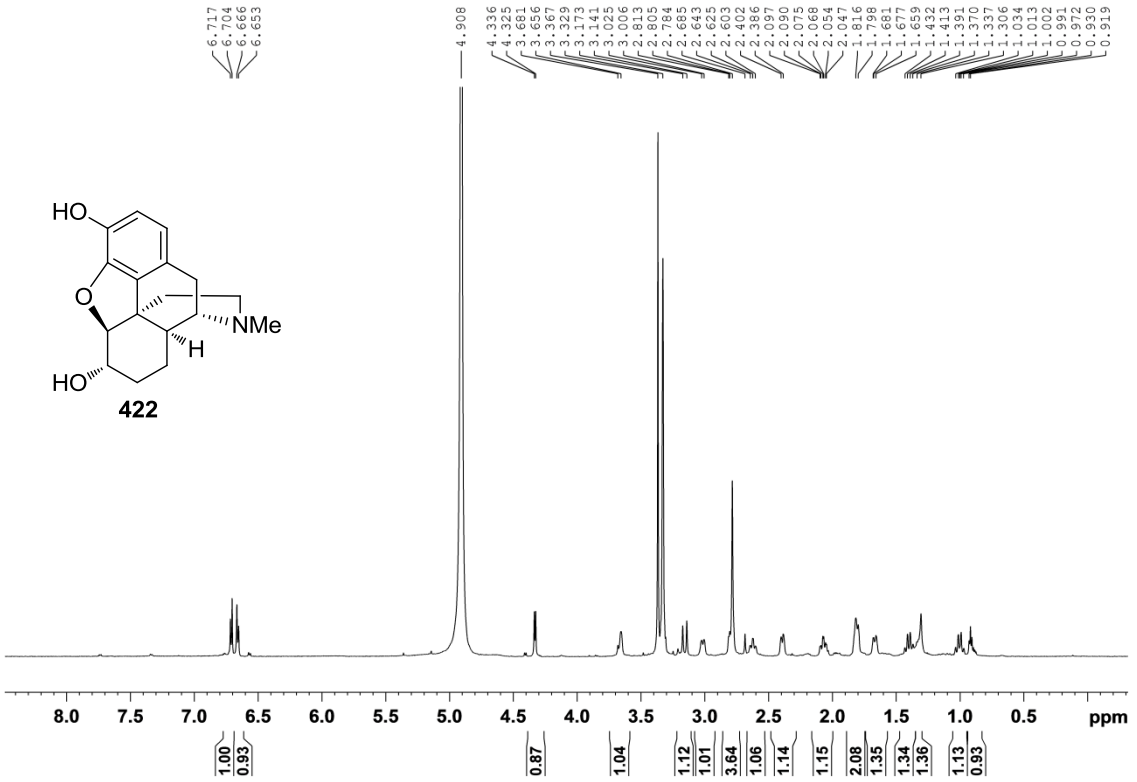


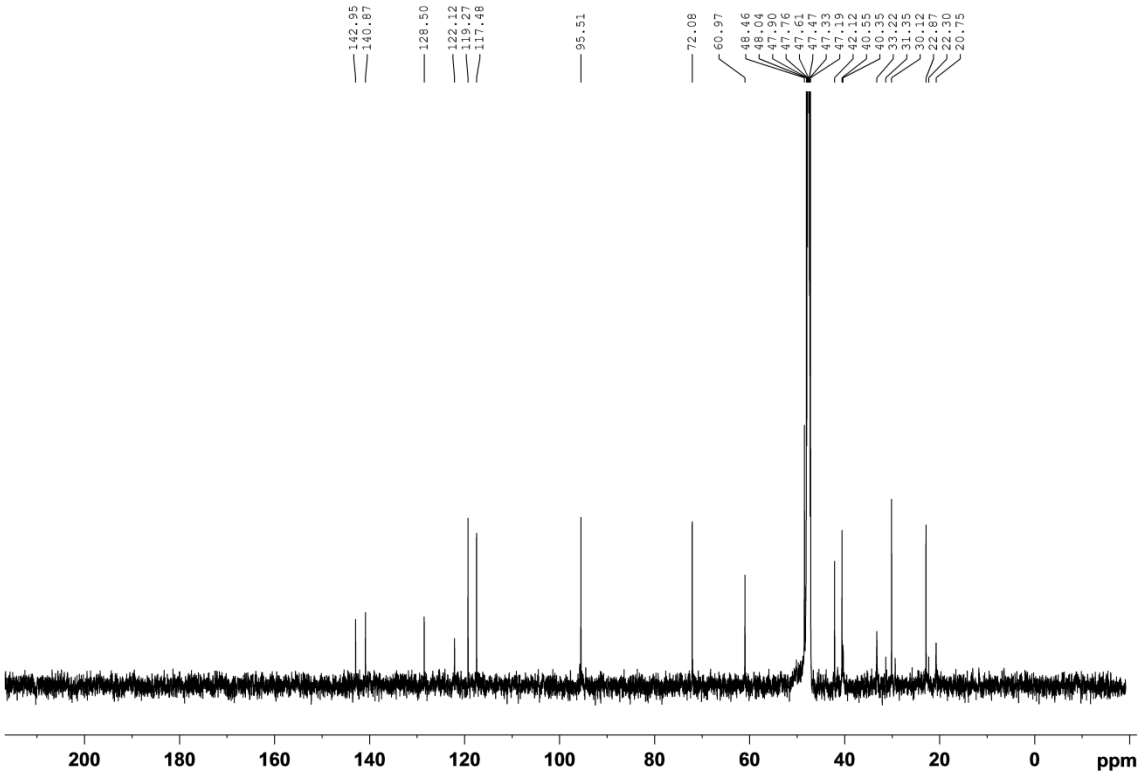

7.260
7.080
7.047
6.485
6.474
6.462
5.999
5.966
4.147
4.132
4.108
4.074
4.053
3.417
3.218
3.152
3.100
2.869
2.797
2.266
2.244
2.220
2.164
2.127
2.043
2.024
1.715
1.528
1.514
1.468
1.438
1.253
1.139
1.099
1.062
1.046
0.890
0.882
0.837
0.067
-0.008
-0.052
O
AcO
O
NMeBoc
H
TBSO
416
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm
1.00
0.94
0.92
1.13
4.02
2.90
2.17
4.39
2.22
1.48
1.03
9.10
1.98
9.57
3.07
3.03
188.23
170.91
155.40
144.54
138.98
134.15
122.73
103.88
92.83
90.58
79.68
74.18
73.54
51.99
48.56
45.89
45.36
40.68
39.80
38.62
37.25
34.40
30.76
29.39
28.46
25.83
21.33
20.64
18.08
-4.59
-5.05
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


TsO
O
NMeTs
H
TBSO
419
ppm
ppm

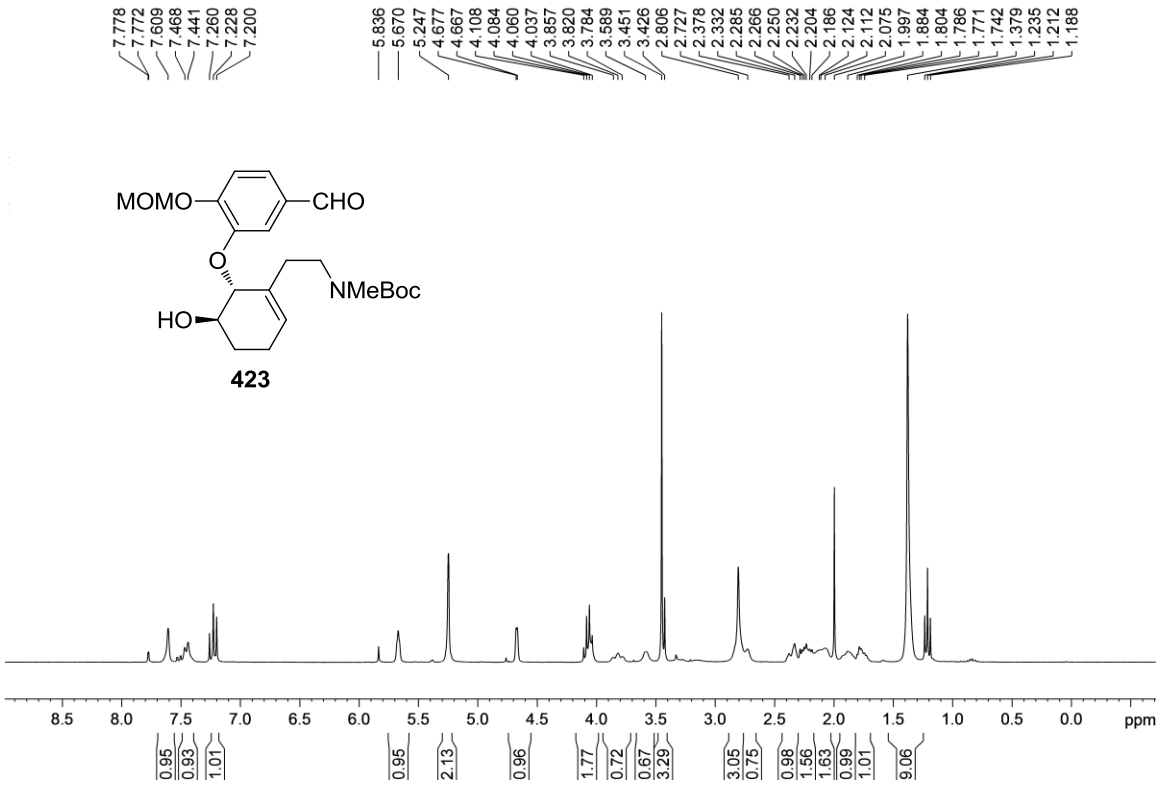

7.771
7.743
7.590
7.563
7.325
7.297
7.284
7.260
6.789
6.762
6.592
6.564
6.365
6.333
5.958
5.939
5.926
5.907
4.491
4.467
3.081
3.063
3.046
3.037
3.018
3.001
2.984
2.835
2.817
2.800
2.789
2.783
2.772
2.755
2.569
2.466
2.429
2.388
2.362
1.829
1.816
1.787
1.770
1.751
1.742
1.734
1.723
1.706
1.689
1.661
1.644
1.627
1.615
1.610
1.273
1.267
1.242
1.219
1.193
0.894
0.850
0.807
TsO
O
NMeTs
H
HO
420
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.03
2.04
4.18
1.00
1.01
1.02
0.95
1.02
2.04
1.04
3.07
8.30
4.32
1.47
1.19
147.94
145.60
143.38
134.34
133.01
132.62
129.74
129.67
129.34
129.06
128.72
127.35
123.78
122.52
117.90
98.04
77.51
77.28
77.08
76.66
72.88
46.11
44.65
39.27
35.17
34.79
27.77
26.85
21.71
21.49
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


HO
O
NMe
H
TBSO
421
ppm
ppm

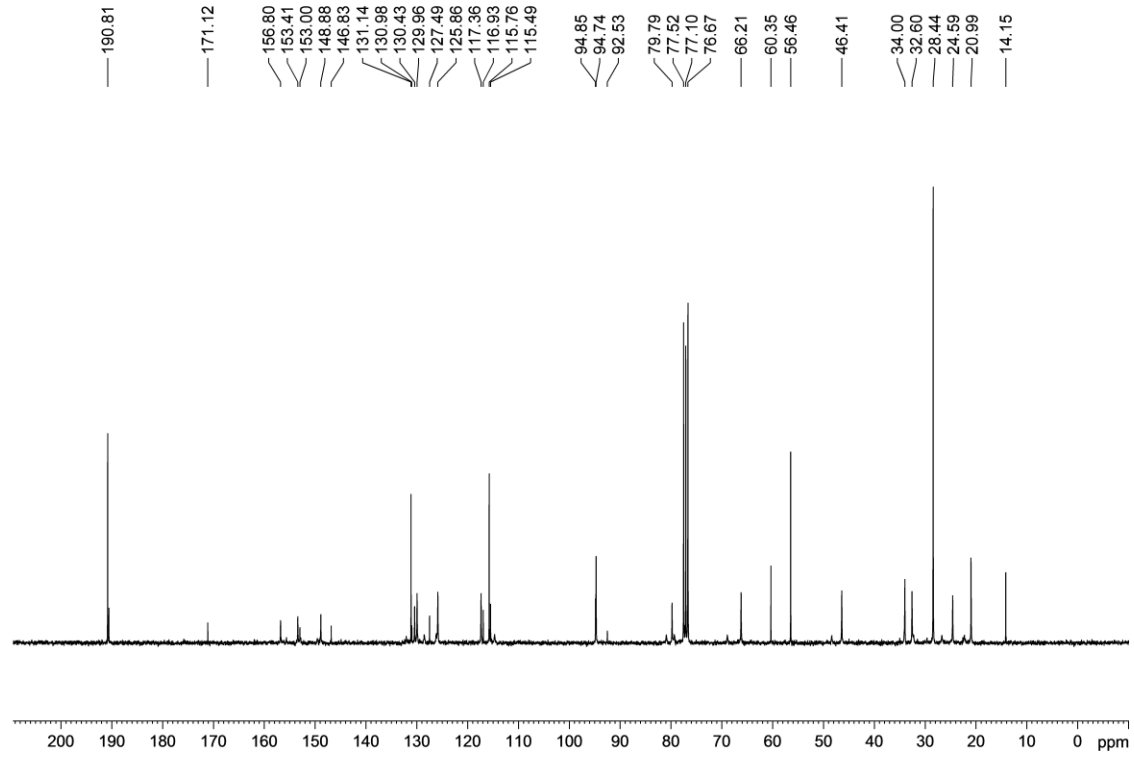

6.717
6.704
6.666
6.653
4.908
4.336
4.325
3.681
3.656
3.367
3.329
3.173
3.141
3.025
3.006
2.813
2.805
2.784
2.685
2.643
2.625
2.603
2.402
2.386
2.097
2.090
2.075
2.068
2.054
2.047
1.816
1.798
1.681
1.677
1.659
1.432
1.413
1.391
1.370
1.337
1.306
1.034
1.013
1.002
0.991
0.972
0.930
0.919
HO
O
NMe
H
HO
422
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
0.93
0.87
1.04
1.12
1.01
3.64
1.06
1.14
1.15
2.08
1.35
1.34
1.36
1.13
0.93


142.95
140.87
128.50
122.12
119.27
117.48
95.51
72.08
60.97
48.46
48.04
47.90
47.76
47.61
47.47
47.33
47.19
42.22
40.55
40.35
31.22
31.15
30.12
22.87
22.30
20.75
200
180
160
140
120
100
80
60
40
20
0
ppm

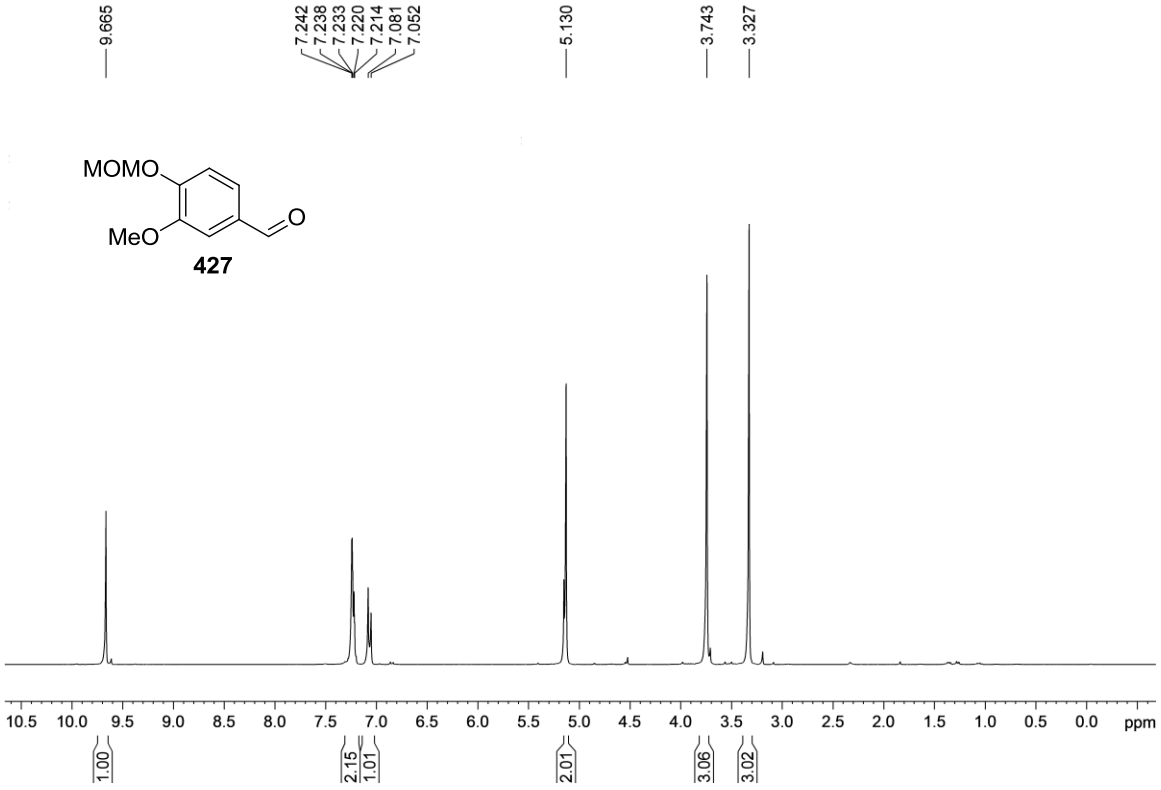
1D proton



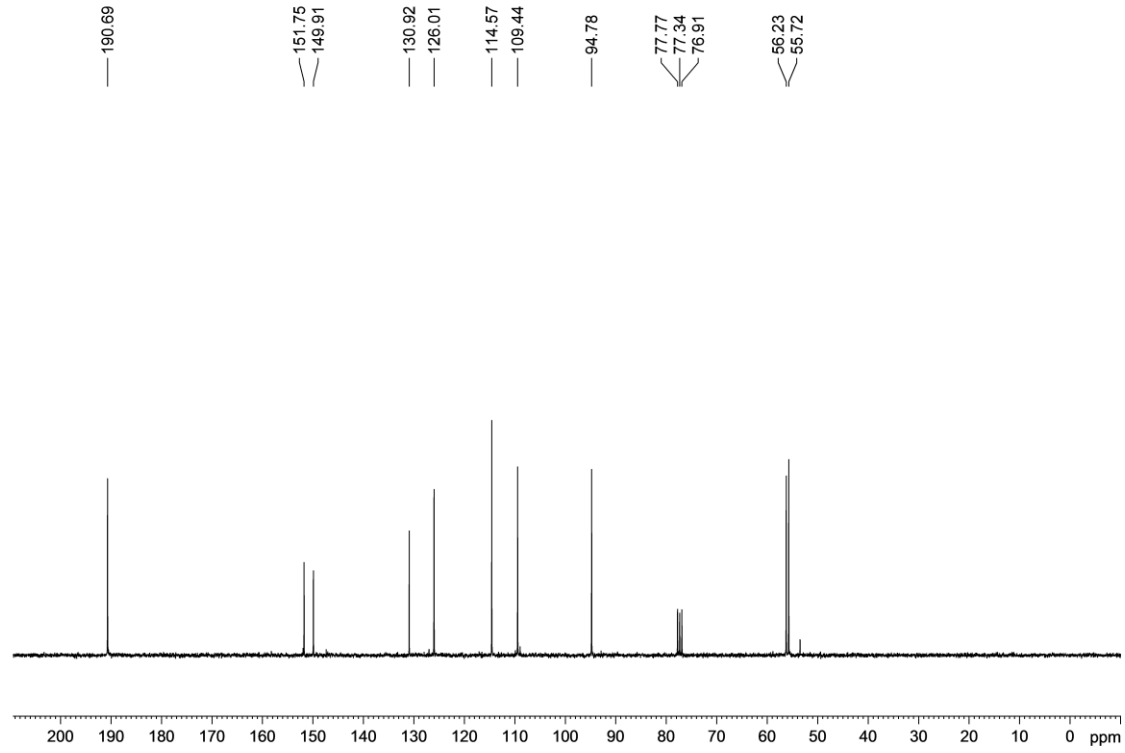
1D carbon with proton decoupling



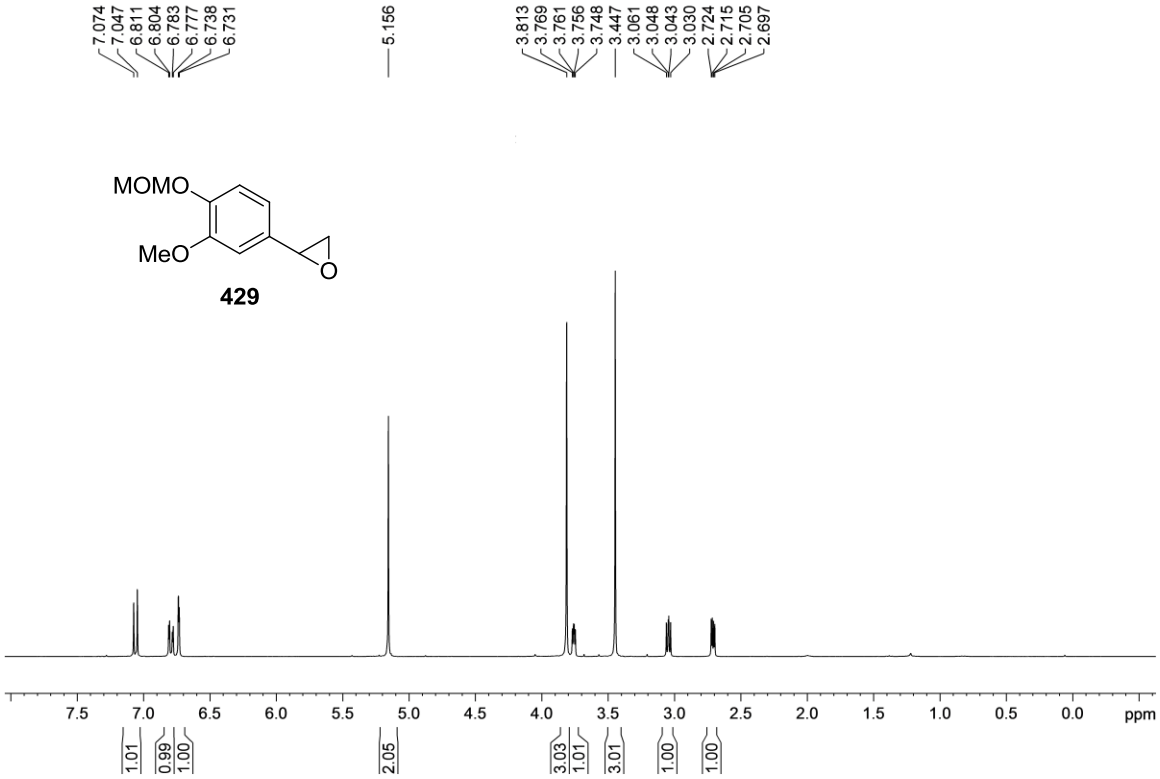
1D proton



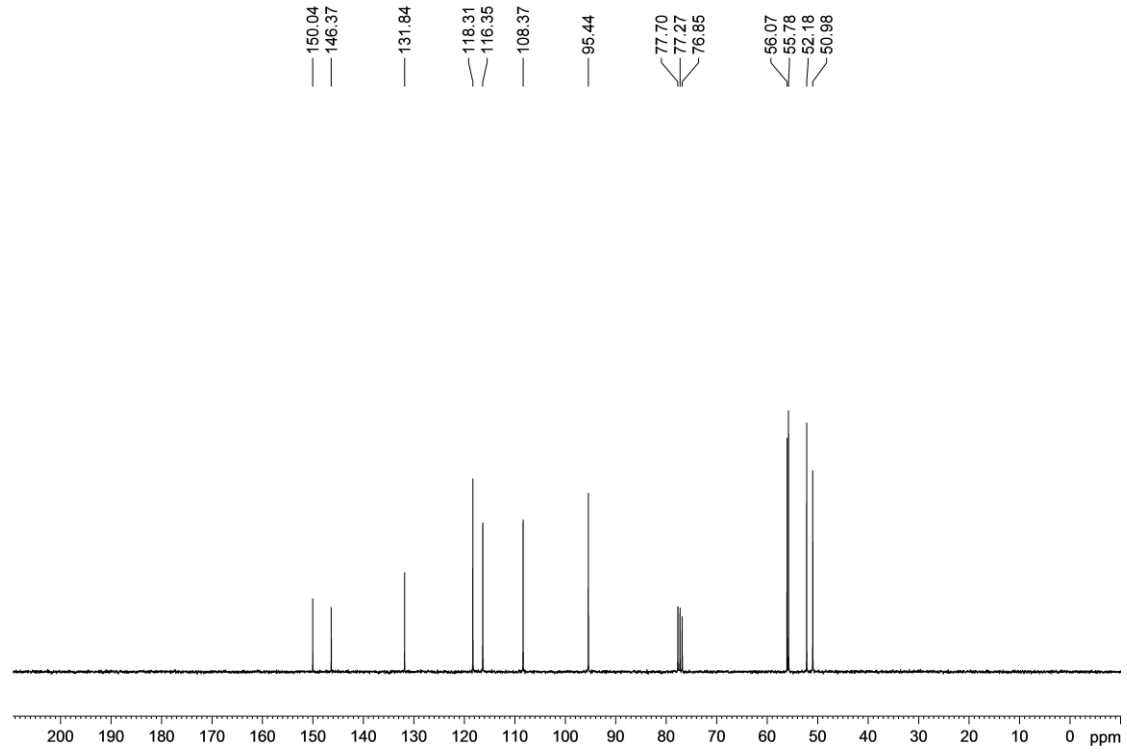
1D carbon with proton decoupling



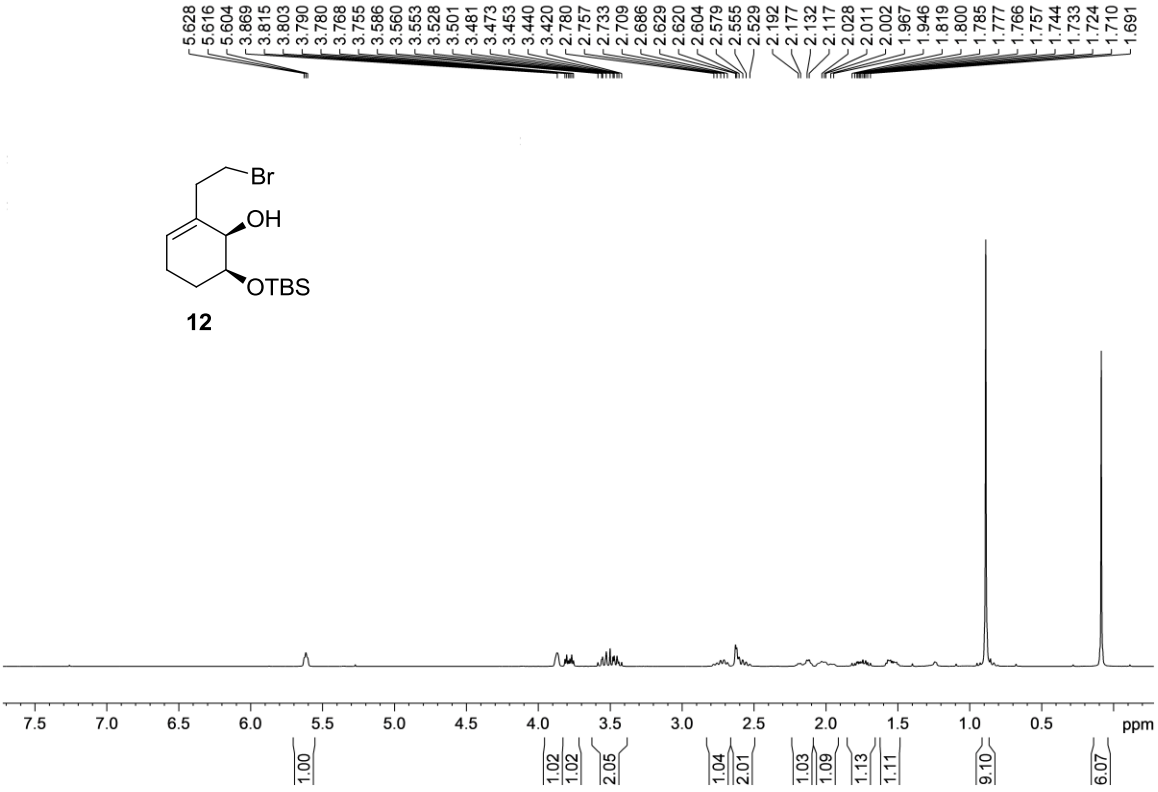
1D proton



1D carbon with proton decoupling



1D proton



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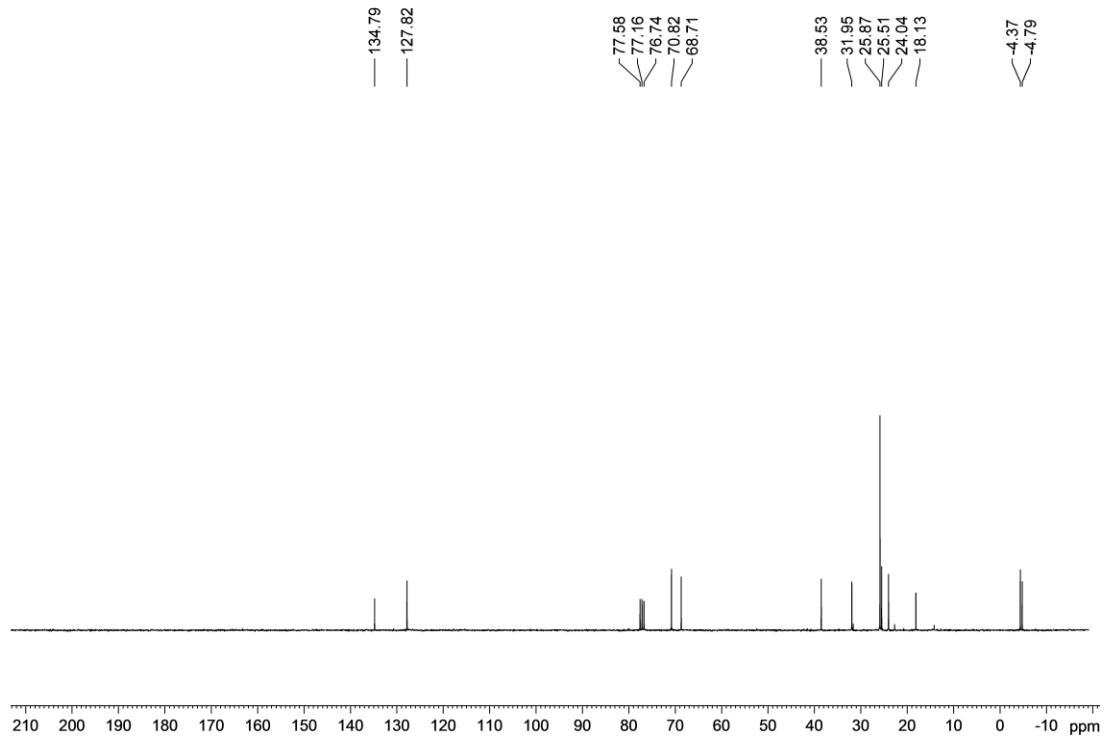

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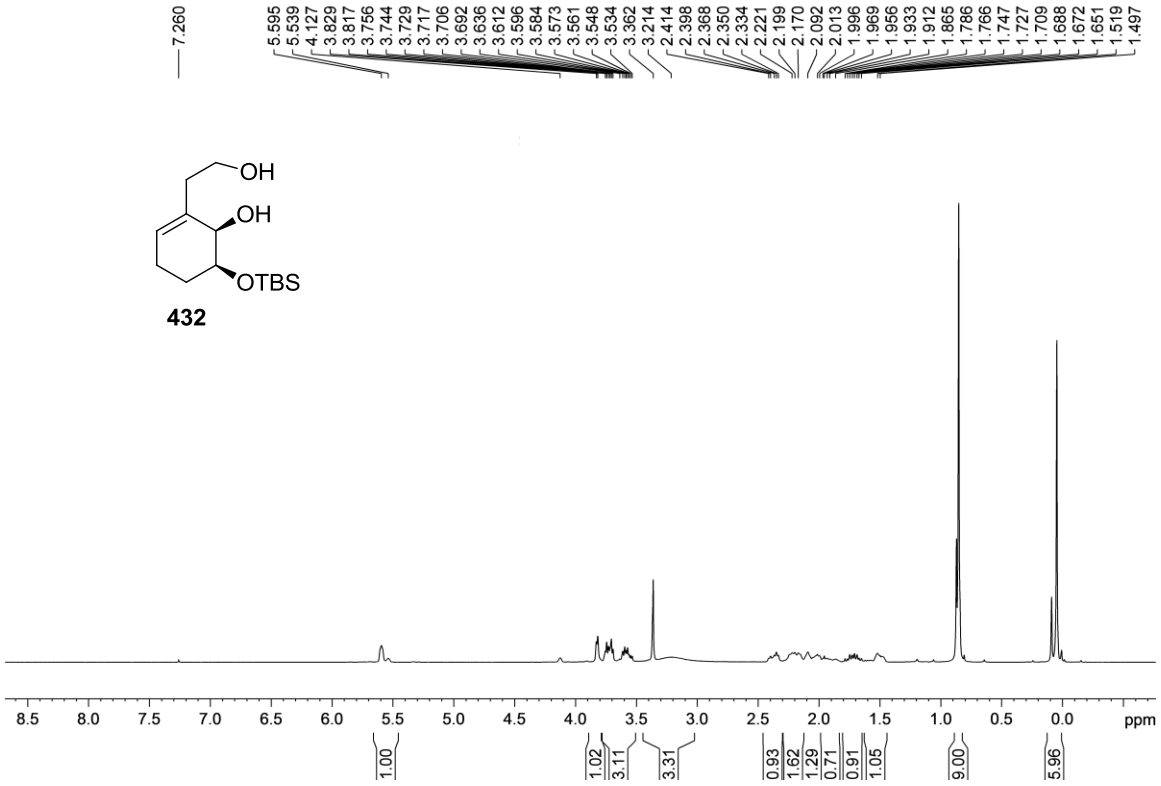

432

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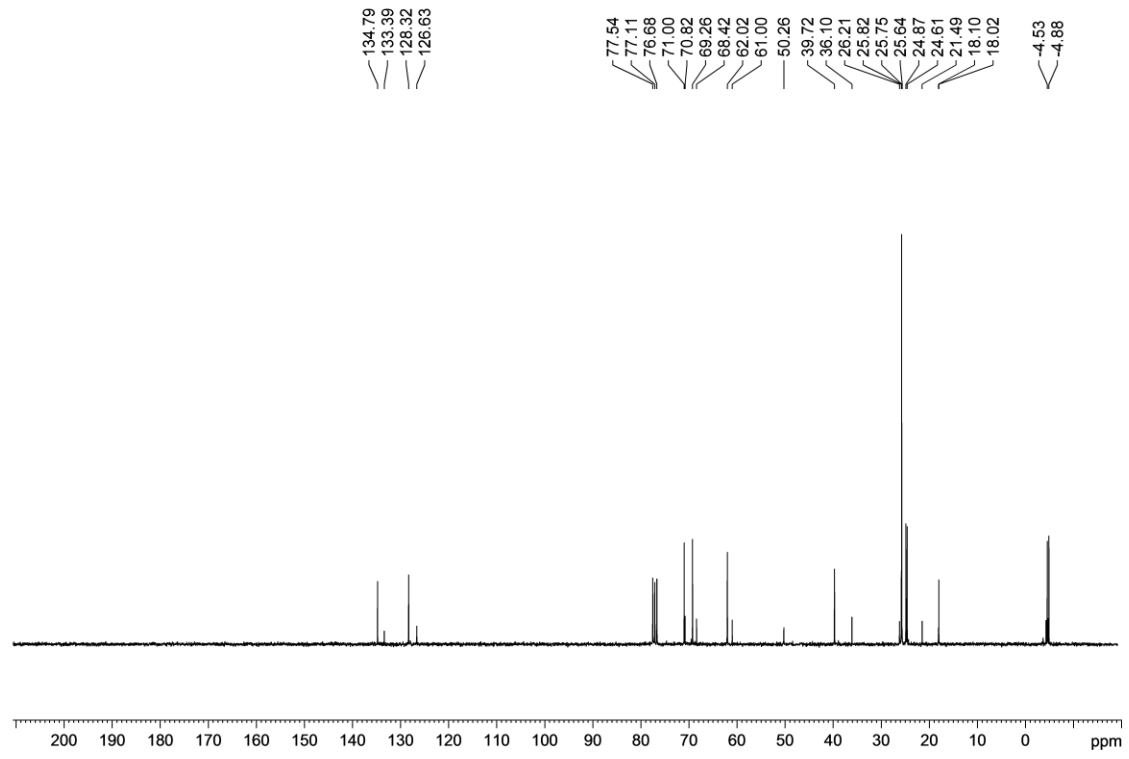

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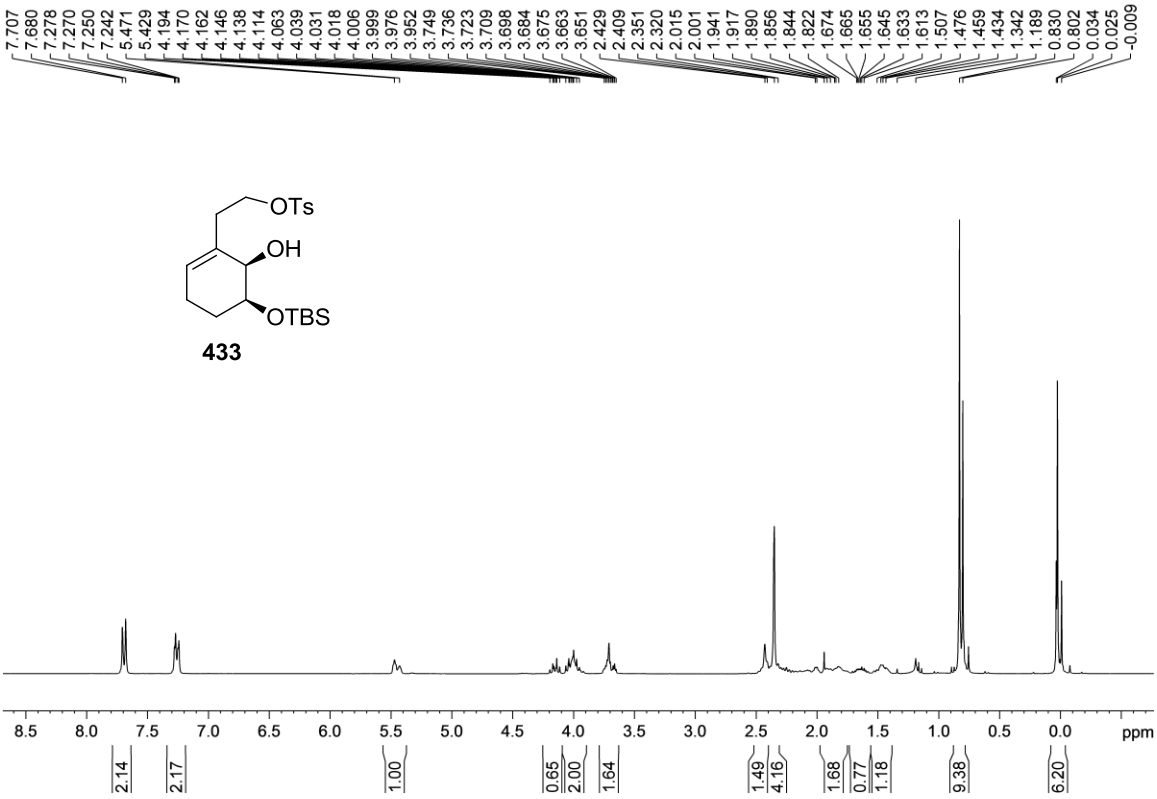

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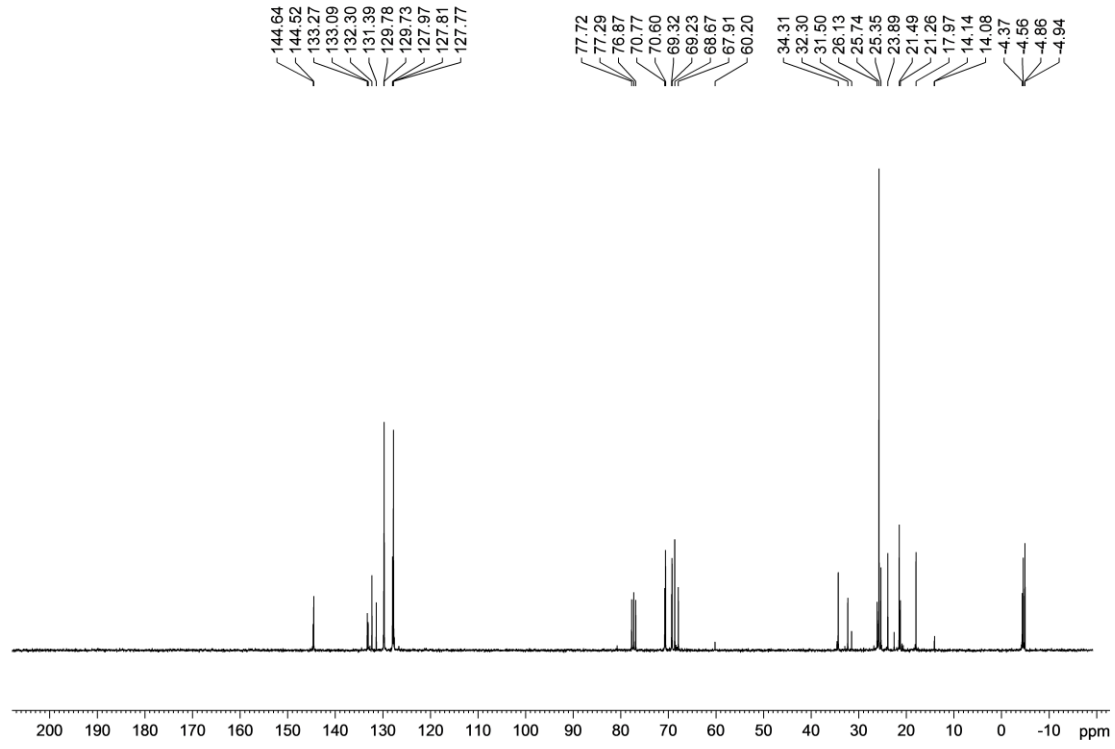

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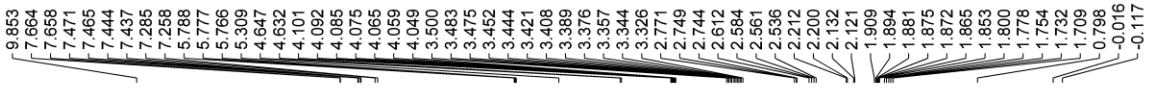

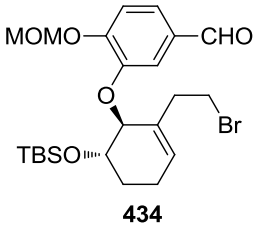

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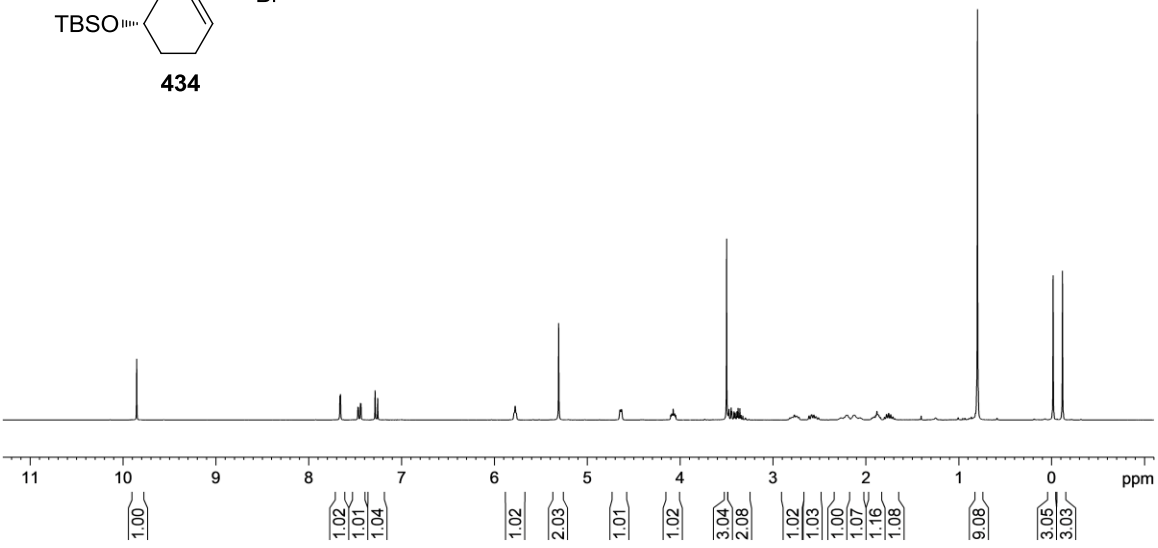

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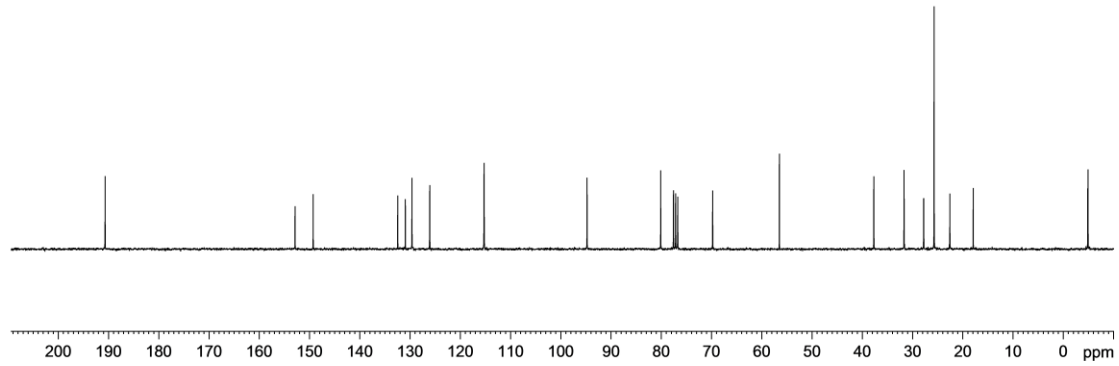

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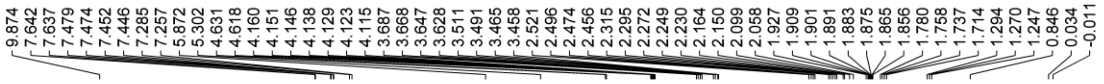

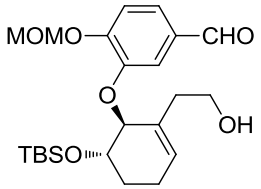

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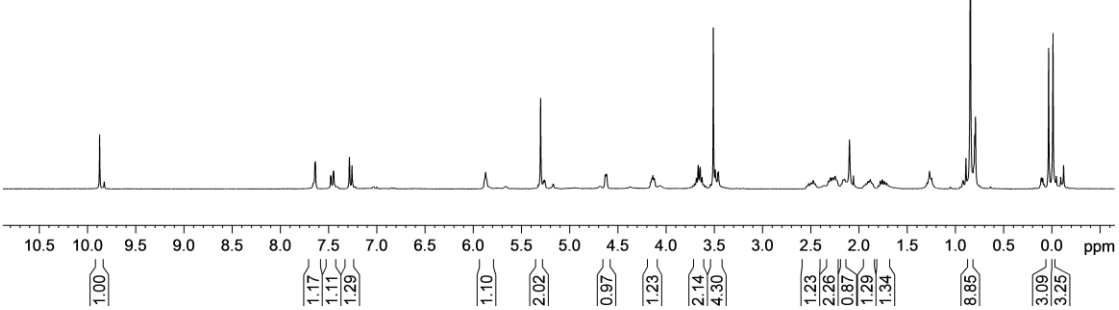

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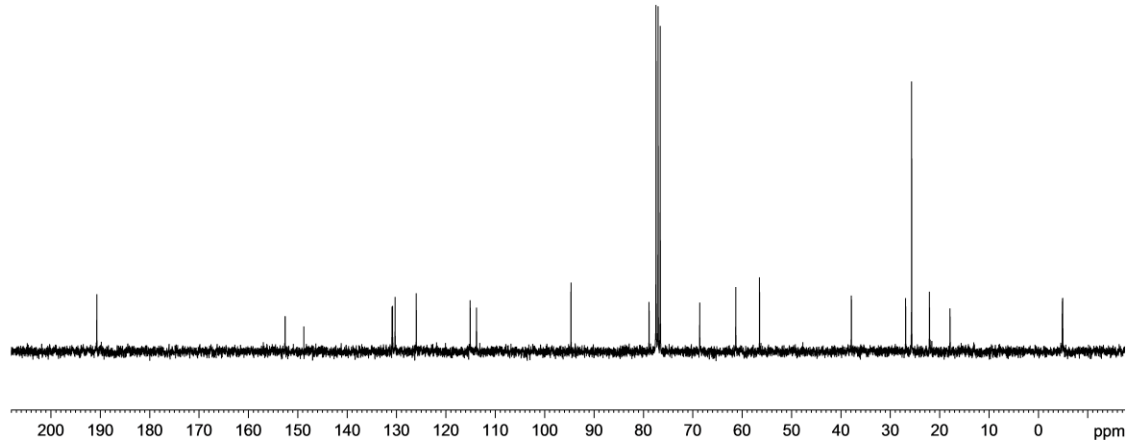
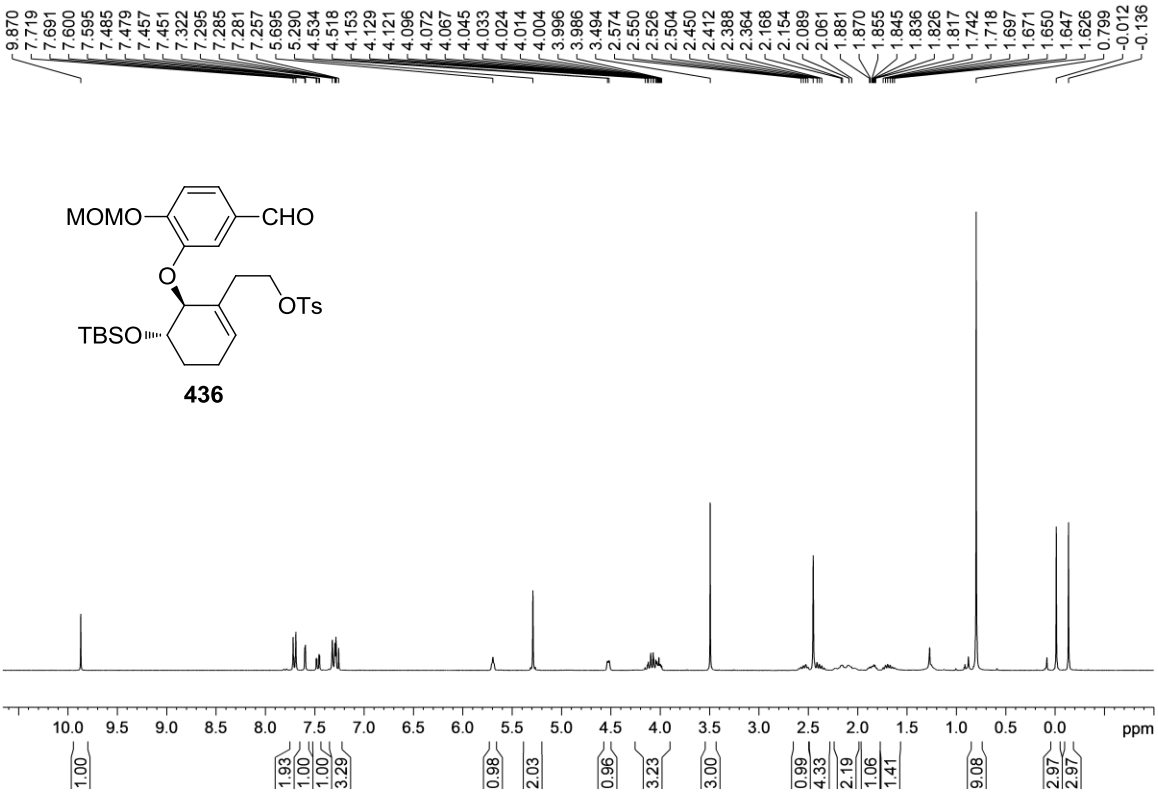


1D proton



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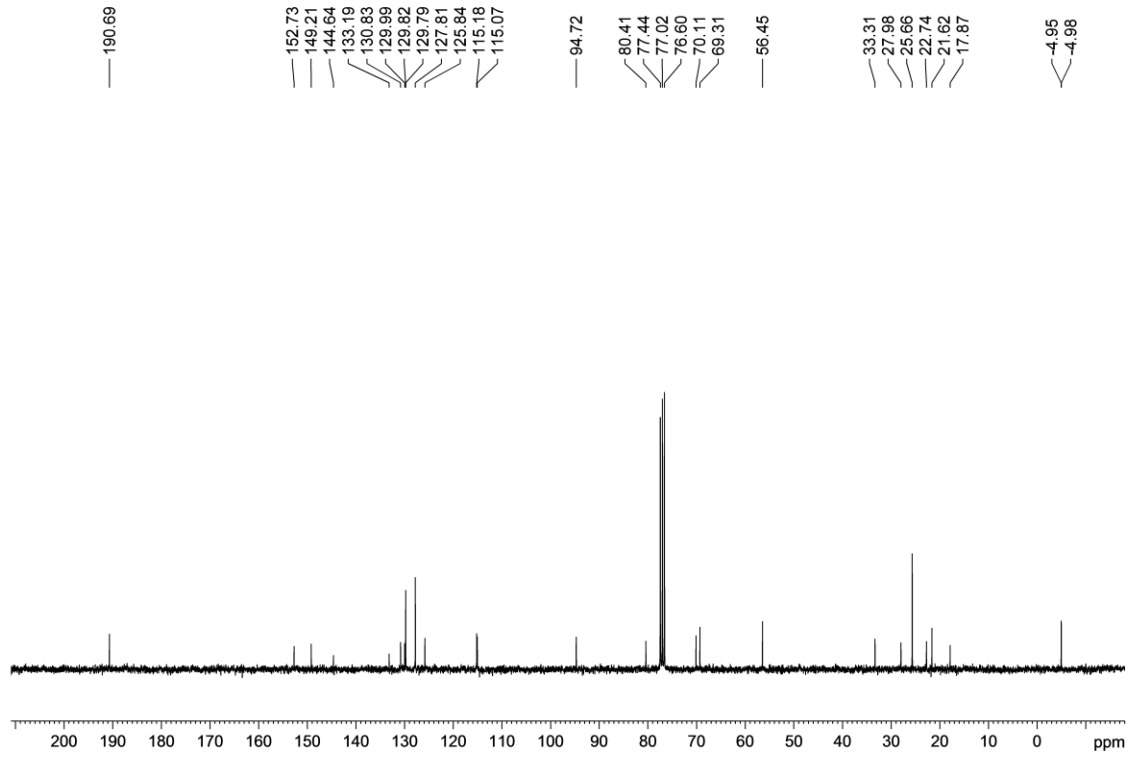

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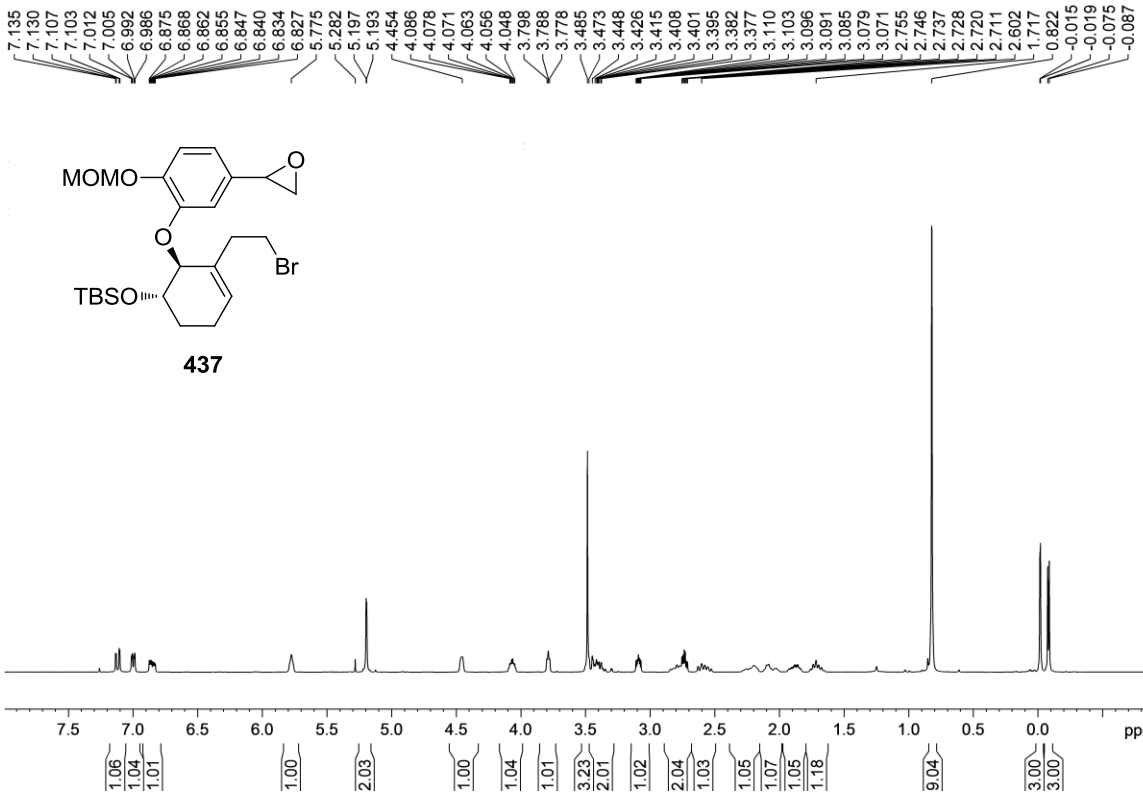
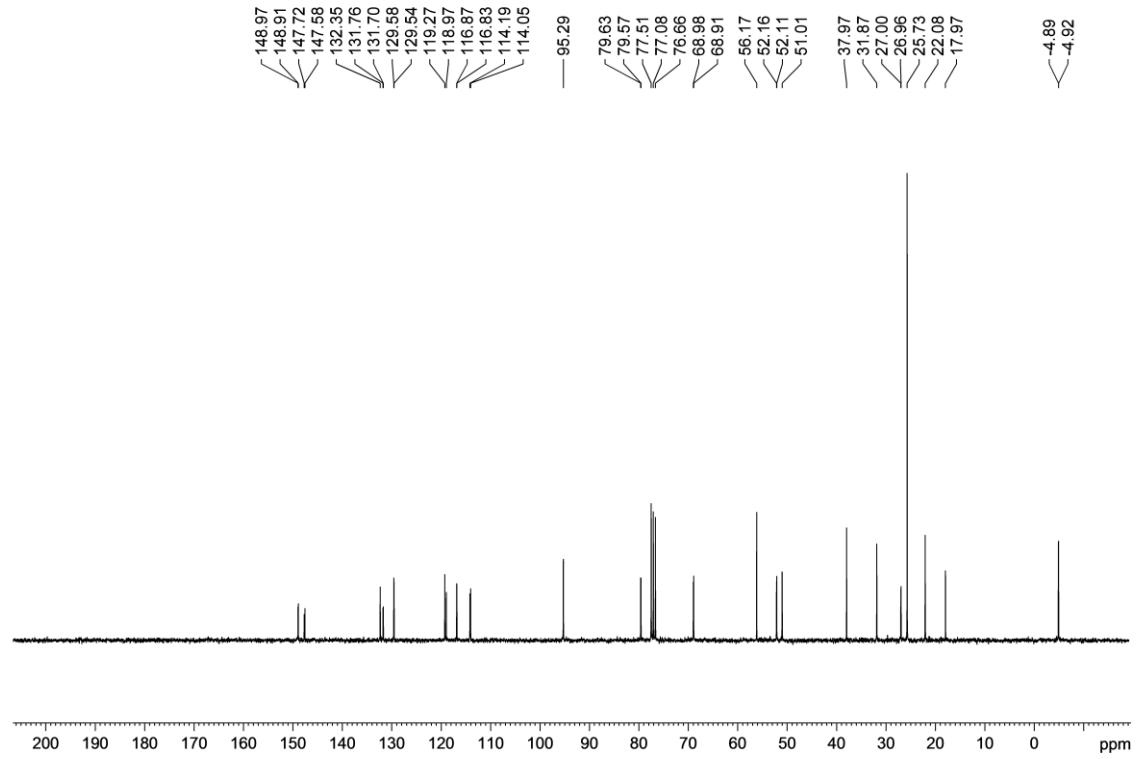
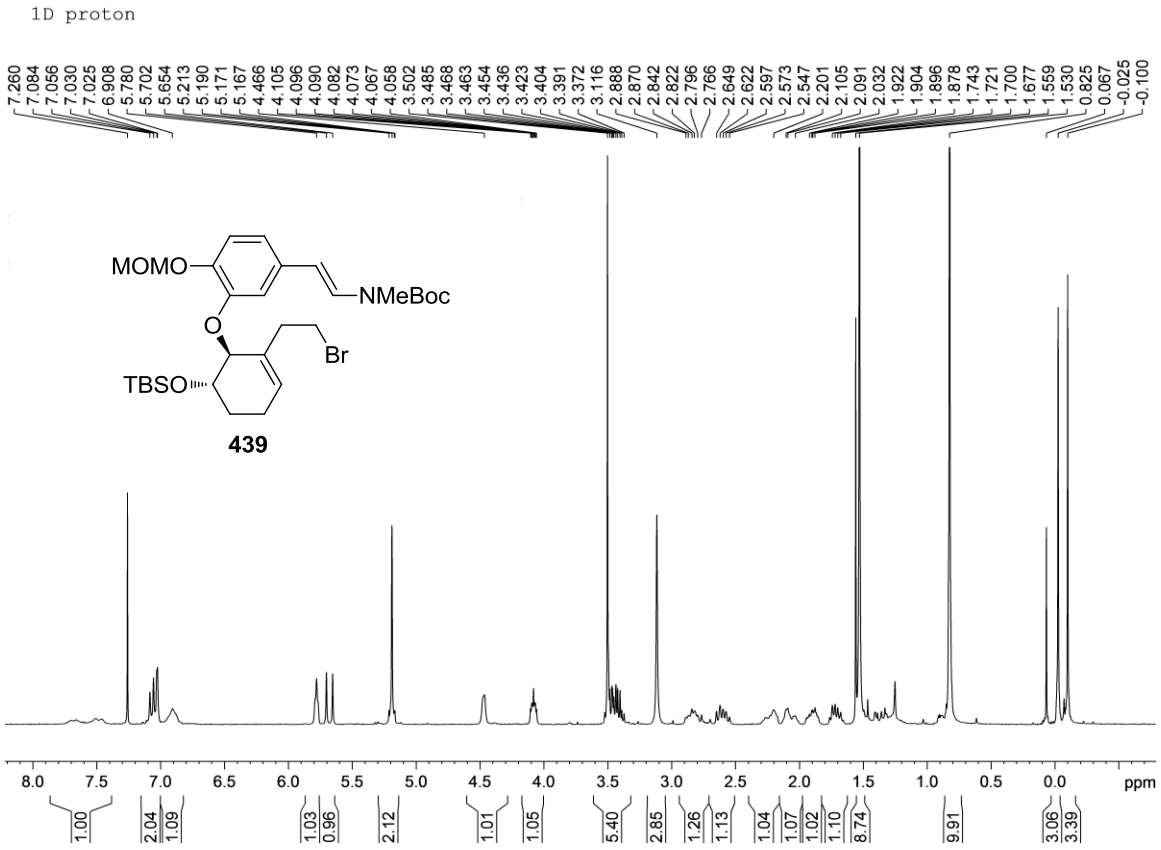


1D carbon with proton decoupling




1D proton
MOMO
NMeBoc
O
Br
TBSO
439
ppm

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8. Vita

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