Enantiodivergent Chemoenzymatic Synthesis of Balanol and Approaches to the Synthesis of (+)-Codeine

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Dedicated to my father

Abstract

The present thesis reviews the development of a formal enantiodivergent synthesis of the (+)- and (–)-isomers of balanol. This approach commences from a *cis*-dihydrodiol derived from the enzymatic dihydroxylation of bromobenzene. The stereochemistry of the diol is used to direct the synthesis of two different aziridines, each used in the formal synthesis of one enantiomer of balanol. Also described are several enantioselective approaches to (+)-codeine. Each strategy begins with the enzymatic dihydroxylation of β-bromoethylbenzene and involves a Mitsunobu inversion and intramolecular Heck reaction as key steps.

Acknowledgments

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List of Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
Å	angstroms
AAA	asymmetric allylic alkylation
Ac	acetyl
AD	Anno Domini
AIBN	azobisisobutyronitrile
alloc	allyloxycarbonyl
ATP	adenosine-5'-triphosphate
aq.	aqueous
BC	before Christ
BIPHEP	biphenylphosphine
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
Bu	butyl
Bz	benzoyl
cAMP	cyclic adenosine monophosphate
CAS	camphorsulfonic acid
CBz	carboxybenzyl
CDI	1,1'-carbonyldiimidazole
CNS	central nervous system
COD	cyclooctadiene
conc.	concentrated
COSY	correlation spectroscopy
dba	dibenzylideneacetone
DBS	dibenzosuberylamine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DCM	dichloromethane

DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DET	diethyl tartarate
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	2,2-dimethoxypropane
DMSO	dimethyl sulfoxide
DMT	bis-(4-methoxyphenyl)phenylmethyl
DPPA	diphenylphosphoryl azide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
ee	enantiomeric excess
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EI	electron ionization
equiv.	equivalent(s)
GC	gas chromatography
GPCR	G protein-coupled receptor
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
Hz	hertz
IBX	2-iodoxybenzoic acid
IPTG	isopropyl β-D-1-thiogalactopyranoside
IR	infrared spectroscopy
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide

LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
M	molar concentration
M*	(–)-menthyl
***m*CPBA**	*meta*-chloroperoxybenzoic acid
MEM	β-methoxyethoxymethyl
MHz	megahertz
MMPP	magnesium bis(monoperoxyphthalate) hexahydrate
MOM	methoxymethyl
MOP	2-methoxy-2-propyl
Moz	*p*-methoxybenzyl carbonyl
m.p.	melting point
Ms	methanesulfonyl
MS	mass spectroscopy
MTBE	methyl *tert*-butyl ether
NADH	nicotinamide adenine dinucleotide
NaHMDS	sodium bis(trimethylsilyl)amide
NBA	*N*-bromoacetamide
NBS	*N*-bromosuccinimide
NDO	naphthalene dioxygenase
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
PAD	potassium azodicarboxylate
PDC	pyridinium dichromate
PEG	poly(ethylene glycol)
PG	prostaglandin
Piv	pivaloyl
PKC	protein kinase C
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
ppm	part per million

PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
PS	phosphatidylserine
PSI	pounds per square inch
***p*-TSA**	*p*-toluenesulfonic acid
pyr	pyridine
RNA	ribonucleic acid
r.t.	room temperature
SAR	structure-activity relationship
SES	2-(trimethylsilyl)ethanesulfonyl
SM	starting material
SMEAH	sodium bis(2-methoxyethoxy)aluminum hydride
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TDO	toluene dioxygenase
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TPAP	tetrapropylammonium perruthenate
TMS	trimethylsilyl
Tr	triphenylmethyl (trityl)
Troc	2,2,2-trichloroethoxycarbonyl
Ts	*p*-toluenesulfonyl
TSA	*p*-toluenesulfonic acid

1. Introduction

Under normal physiological conditions, the chemical reactions required by a living organism proceed too slowly to be useful. Enzymes make life possible by catalyzing the reactions required to construct amino acids, nucleotides, carbohydrates, lipids, and other essential materials. They are also responsible for assembling the unessential compounds, collectively known as secondary metabolites. The ability to reproduce these natural products via synthesis was not realized until Wöhler's urea synthesis in 1828. Since that time, chemists have sought to mimic the reactions catalyzed by enzymes through the development of countless reagents and procedures.

One of the most impressive features of enzymes is their ability to carry out transformations in a stereo-, regio-, and chemoselective manner. Today, many of the reactions performed by enzymes have an equivalent in organic chemistry. Procedures to selectively reduce ketones, oxidize olefins, and form carbon-carbon bonds have all been accomplished. One exception is the selective dihydroxylation of aromatic substrates **1** (Figure 1). Catalyzed by the toluene dioxygenase (TDO) enzyme, this reaction yields *cis*-dihydrodiols **2**. The utility of these metabolites has been well established in the synthesis of many natural products by the Hudlicky group and others.[1]

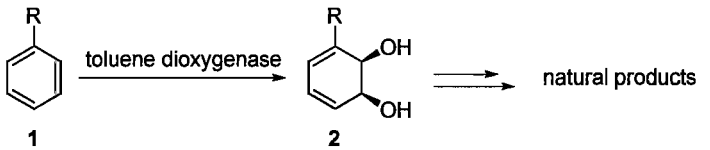
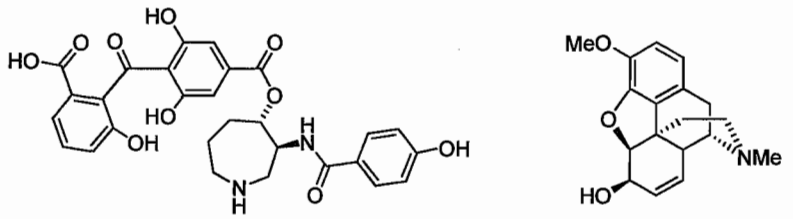


Figure 1. Stereoselective dihydroxylation of arene substrates by toluene dioxygenase

In the present study, the value of the *cis*-dihydrodiol metabolites will be demonstrated through their use in the synthesis of balanol (**3**), and codeine (**4**).



(+)-balanol (**3**) (+)-codeine (**4**)

Figure 2. (+)-balanol (**3**) and (+)-codeine (**4**)

Balanol (**3**) was first isolated from the fermentation broth of *Verticillium balanoides* by researchers at Sphinx Pharmaceuticals in 1993 while screening for inhibitors of protein kinase C (PKC).[2] PKC enzymes are involved in the signal transduction pathways that regulate thousands of processes in the body. Their overactivity has been implicated in a number of diseases, making antagonists of PKC an attractive drug lead.[3]

The synthetic strategy outlined in this thesis is enantiodivergent, with both the natural (–)- and the unnatural (+)-enantiomers of balanol (**3**) arising from a single compound. In each case a vinyl aziridine was fabricated from the *cis*-dihydrodiol **5** obtained in the fermentation of bromobenzene. The key step was the selective opening of the aziridines **6** and **7** with an oxygen nucleophile (Figure 3). This was followed by reduction of the vinyl halide and an oxidative cleavage/ reductive amination protocol to install the azepane ring.

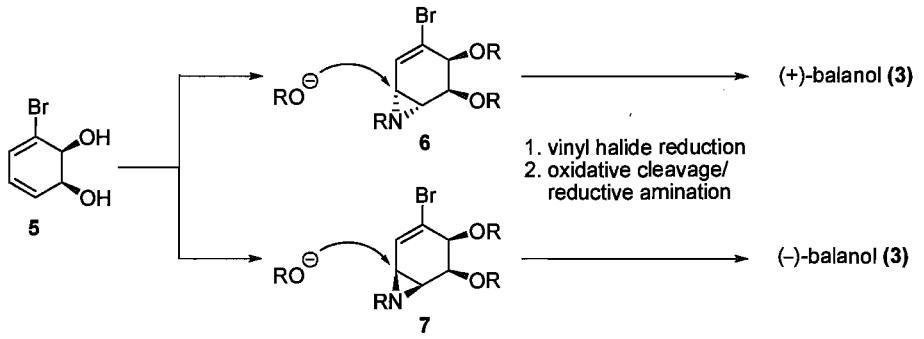


Figure 3. Enantiodivergent synthesis of (+)- and (–)-balanol from homochiral diol **5**

The analgesic and antitussive properties of opiate alkaloids have been known for thousands of years. Currently, codeine (**4**) is the most widely used opiate for the treatment of chronic pain and is one of the most widely prescribed drugs in the world.[4] Opiate alkaloids are harvested from the opium poppy species which grow predominantly in Asian countries, including Iran, Afghanistan, Turkey and India. In order to relieve the Western world's reliance on these countries, a fully synthetic route to opium alkaloids is required.

The Hudlicky group has long been focused on developing a practical synthesis of opium alkaloids. The current thesis will outline our application of the *cis*-dihydrodiol derived from the TDO-mediated dihydroxylation of (2-bromoethyl)benzene (**8**) to the synthesis of (+)-codeine (**4**). Conversion of diol **8** to vinyl β-ethylamine **9** setup a Mitsunobu inversion of the allylic oxygen by 5-bromovanilin derivative **10**. This was followed by a Heck cyclization to form advanced intermediate **12**. A large portion of the presented work focuses on the installation of the two remaining rings. These cyclizations, followed by inversion of the distal oxygen, provide access to (+)-codeine (**4**).

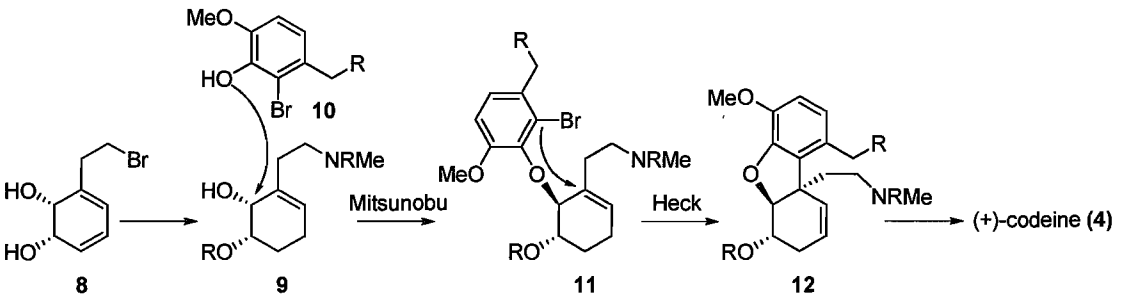


Figure 4. The synthetic strategy towards (+)-codeine (**4**)

2. Historical

2.1 Aromatic Ring-Hydroxylating Dioxygenases

2.1.1 History of Aromatic Dioxygenases

Research into the enzymatic processing of aromatic substrates began in the early twentieth century with Störmer's observation that the *Bacillus hexcarbavorum* species of bacteria could use xylene and toluene for growth.[5] In 1957, Haccius and Helfrich reported the isolation of pyrocatechol from the fermentation of benzene by *Nocardia coralline*.[6] Soon after, Marr and Stone proposed that *trans*-1,2-dihydroxycyclohexa-3,5-dienes were the intermediates in catechol formation and not phenols.[7] In 1968, Gibson demonstrated that *Pseudomonas putida* oxidized *cis*-cyclohexa-3,5-diene-1,2-diol (**13**) at rates far higher than the *trans* substrate.[8] He also established nicotinamide-adenine dinucleotide (NAD^+) and iron as required cofactors. These observations led directly to a proposed mechanism of pyrocatechol (**14**) formation during the microbial processing of benzene (**15**) (Figure 5).

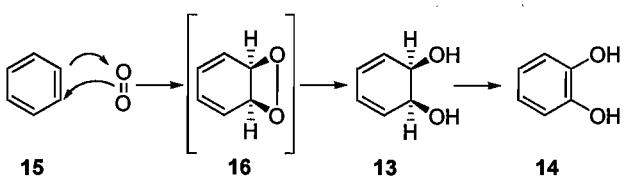


Figure 5. Gibson's proposed mechanism of pyrocatechol (**14**) formation from benzene (**15**).

Gibson also discovered that *P. putida* could process halogenated aromatic hydrocarbons into their corresponding *cis*-dihydrodiols.[9] The halocatechols were isolated in relatively low yields compared to their alkyl counterparts. It was theorized

that the halocatechols were chelating with the iron required for the initial oxygenation.

2.1.2 Stereochemistry of Enzymatic Dihydroxylations

In order to elucidate the method of oxygen fixation into aromatic substrates, Gibson developed a mutant strain (*P. putida* 39/D) which accumulated, what he believed to be, the (+)-*cis*-2,3-dihydroxy-1-methylcyclohexa-4,6-diene (**17**) intermediate during the fermentation of toluene (**18**).[10] At the time, all of the available evidence indicated that both mammalian and microbial metabolism of aromatic substrates went through the *trans*-diol intermediate.[11] It was believed that the *trans* stereochemistry arose from the hydrolysis of a *cis*-epoxide.[12] Unsure of the relative stereochemistry, Gibson condensed the acetylated derivative of **17** with maleic anhydride to form 1-methyl-2,3-diacetoxybicyclo(2,2,2)-7-hexene-5,6-dicarboxylic anhydride (**19**) which was hydrogenated to produce **20** (Figure 6).

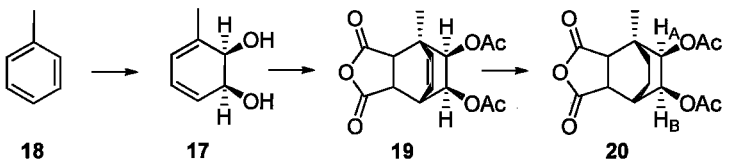


Figure 6. Relative stereochemistry proof of (+)-*cis*-2,3-dihydroxy-1-methylcyclohexa-4,6-diene (**17**)

Spectroscopic analysis revealed that the vicinal protons H_A and H_B in **20** are *cis* in relation to reach other, thus confirming the relative structure of **17**. In an ensuing publication Gibson incubated *P. putida* 39/D with benzene in the presence of $^{18}O_2$.[13] The mass spectra of the *cis*-1,2-dihydro-1,2-dihydroxybenzene metabolite indicated an incorporation of two isotopic oxygens, presumed to be from the same molecule.

This was strong evidence for the mechanism hypothesized by Gibson, which proceeds through a cyclic peroxide intermediate **16**.

The absolute stereochemistry of several *trans*-diols obtained from mono- and polycyclic aromatic substrates were established by 1971.[14,15] Gibson determined the absolute stereochemistry of the *cis*-dihydrodiol **17** shortly afterwards.[16] A palladium catalyzed hydrogenation of **17** produced *cis,trans*- and *cis,cis*-3-methylcyclohexane-1,2-diols, **21a** and **21b** respectively (Figure 7). The corresponding monobenzoate derivatives were prepared and found to be separable via chromatography on silica gel. Subsequent hydrolysis furnished pure samples of the two diastereomers **21a** and **21b**. Oxidation of the latter with Jones reagent yielded the known (–)-2(*R*)-methyladipic acid (**22**). Comparison to literature values[17] established the absolute stereochemistry of **16** as 1*S*,2*R* (as depicted in Figure 6).

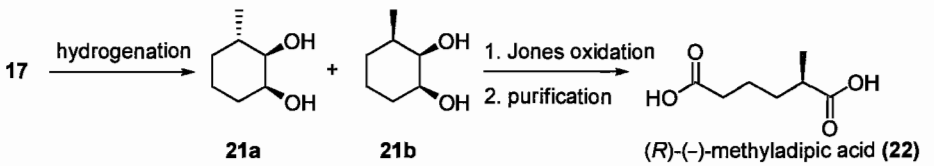


Figure 7. Absolute stereochemical proof of *cis*-dihydrodiol **17**.

The specific enzymes responsible for the aforementioned catabolism of toluene by *P. putida* were isolated and identified by Gibson in 1989.[18] Sequencing information was used to construct clones of *Escherichia coli* JM109 that overexpressed TDO (todC1C2BA). The implication of this work will be discussed in future sections of this thesis.

2.1.3 Mechanistic Views

Despite over 50 years of research, the exact mechanism of TDO catalyzed oxidations remains unsolved. The crystal structure of the closely related naphthalene dioxygenase (NDO), solved by Ramaswamy and Gibson in 2003,[19] has provided some valuable insight. Gibson's initial mechanism (Figure 5) involves the cycloaddition of singlet oxygen to the aromatic substrate. This high-energy process is considered unlikely. Research into the *cis*-dihydroxylation of indole has identified an iron bound peroxide species as a possible intermediate.[20] Another possibility is a [3+2] cycloaddition between an iron peroxide species **23** and the aromatic substrate **24** (Figure 8).[1] Following reduction of the peroxide linkage in **25**, a suprafacial migration of the iron- hydroxyl in **26** would form the last required carbon-oxygen bond. The lack of definitive evidence for, or against, a specific mechanism leaves this topic at the forefront of dioxygenase research.[21]

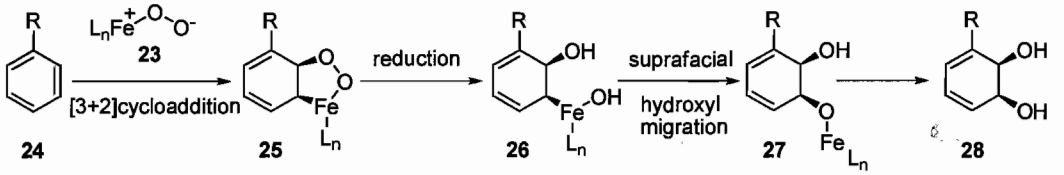


Figure 8. Plausible mechanism for TDO-catalyzed dihydroxylations.[1]

2.1.4 Application of *cis*-Dihydrodiols in Synthesis

Since its discovery, the TDO enzyme has been incubated with hundreds of compounds in an attempt to understand substrate specificity. The dihydroxylation reactions catalyzed follow a similar pattern of regio-, stereo- and enantioselectivity. A widely accepted model was developed by Boyd, and predicts that smaller substituents (R_S) will enter the binding pocket in preference to larger substituents (R_L) (Figure

9).[22] Boyd demonstrated that larger differences in relative size between R_S and R_L yield higher enantiomeric excess values.

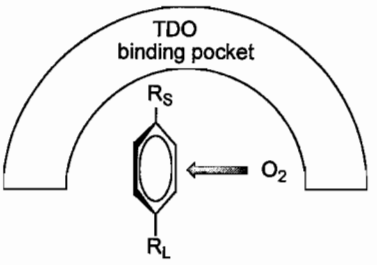


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Figure 9. Model for predicting the stereo- and regioselectivity of TDO dihydroxylations

In the 1970's, application of *cis*-dihydrodiols in the synthesis of more complex molecules seemed unreasonable. Gibson's mutant *P. putida* 39/D strain could only produce the desired metabolites in minute quantities (e.g. 243 mg/ L for the production of toluene derived diol **17**).[10] In contrast, the recombinant *E. coli* (pDTG601) expression system is controlled by the *tac* promoter, which expresses the TDO gene upon induction by isopropyl β-D-1-thiogalactopyranoside (IPTG).[18] This method can supply multigram quantities of enantiopure cyclohexadienediols for use in synthesis.[23]

Researchers at Imperial Chemical Industries Plc are credited with the first synthetic application of the *cis*-dihydrodiols. In 1983, they employed the diol derived from benzene **13** in the synthesis of polyphenylene (**30**) (Figure 10).[24] In 1987, Ley reported the synthesis of (+/–)-pinitol (**31**) from the same diol.[25] This marked the first exploitation of the stereochemistry contained in the *cis*-dihydrodiol metabolites.

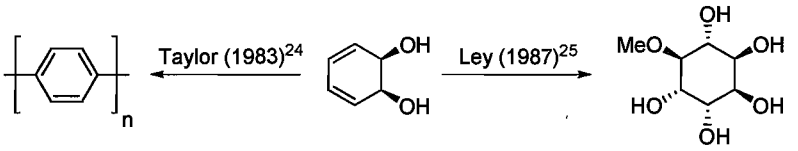
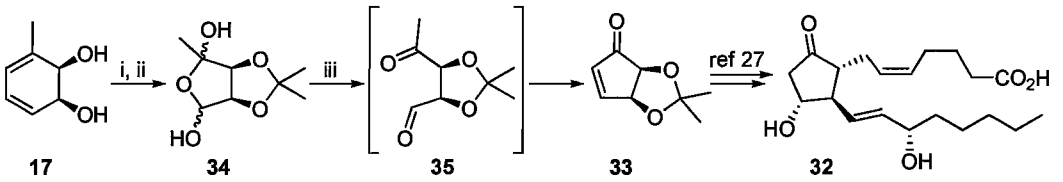


Figure 10. Preliminary applications of *cis*-dihydrodiols

The first enantioselective application of the *cis*-dihydrodiols was Hudlicky's formal total synthesis of $PGE_{2\alpha}$ (**32**) in 1988.[26] Prostanoid synthon **33**, which was previous converted to **32** by Johnson,[27] was prepared in only 3 steps from the *cis*-dihydrodiol diol **17** (Scheme 1). This synthesis was a drastic improvement over those previously reported, and demonstrated the remarkable value of the diol metabolites.



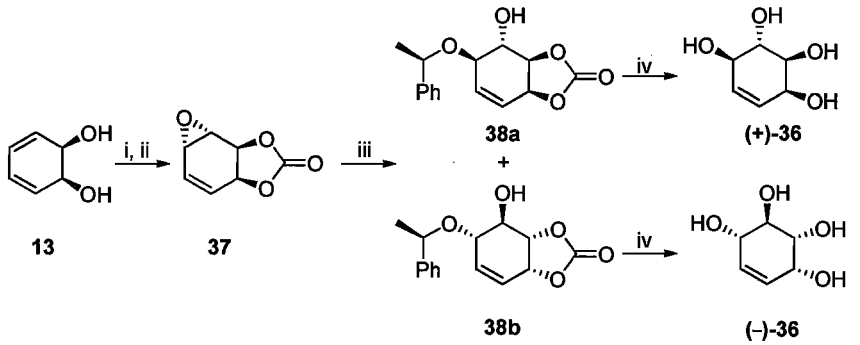
Reagents and conditions: (i) 2,2-dimethoxypropane, *p*TsOH, r.t.; (ii) a) O_2/O_3, EtOAc, -78°C; b) Me_2S, 0°C; (iii) Al_2O_3 (neutral), DME, reflux

Scheme 1. Hudlicky's enantioselective formal total synthesis of $PGE_{2\alpha}$ (**32**)[26]

Since Gibson's initial isolation of *cis*-dihydrodiols in 1968,[8,9] over 400 different metabolites of TDO have been identified.[1] However, only a small percentage have found applications in synthesis. The majority of natural products and other targets synthesized have originated from the dihydroxylation products of benzene, toluene, chlorobenzene or bromobenzene. Research into the applications of these and other *cis*-dihydrodiols has been led by Ley, Boyd, Banwell and Hudlicky. The most significant contributions of each researcher will be discussed in further detail.

In addition to the synthesis of (+/–)-pinitol (**31**),[25] Ley has also constructed both the (+)- and (–)-enantiomers of conduritol F (**36**) from *cis*-cyclohexa-3,5-diene-

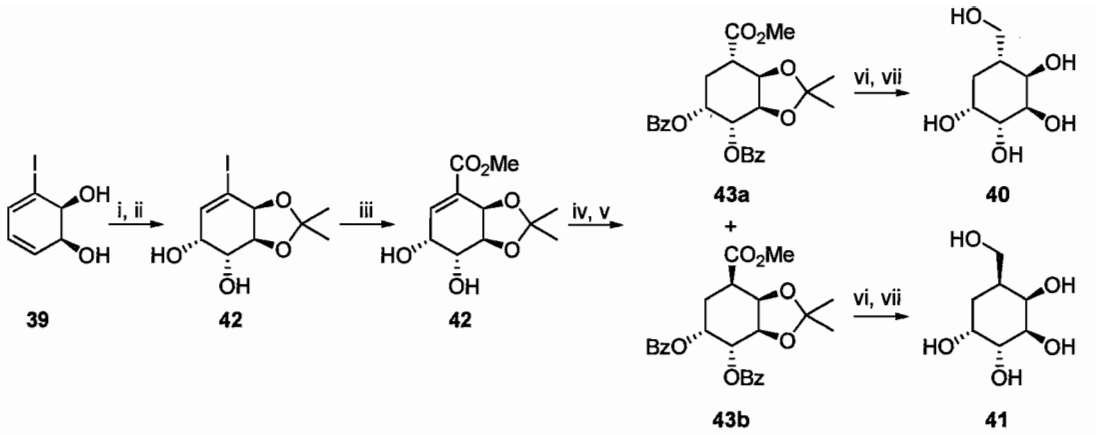
1,2-diol (**13**).[28] The synthesis begins with a one-pot procedure to form epoxy carbamate **37** in 47% overall yield from **13** (Scheme 2). Regioselective ring opening with (*R*)-(+)-*sec*-phenethyl alcohol in the presence of tetrafluoroboric acid-diethyl ether complex furnished separable diastereomers **38a** and **38b**. The final two deprotection reactions occurred during a single dissolving metal reduction.



Reagents and conditions: (i) $(MeO)_2CO$, MeO^-Na^+, MeOH; (ii) mCPBA, DCM; (iii) (*R*)-(+)-*sec*-phenethyl alcohol, $HBF_4{\cdot}OEt_2$, DCM; (iv) $Na/NH_3(l)$, Et_2O, -78°C

Scheme 2. Ley's enantiodivergent synthesis of (+)- and (–)-conduritol F (**36**).[28]

Boyd has developed routes to several pyranose carbasugars (pseudosugars) all originating from the iodobenzene derived *cis*-dihydrodiol **39**.[29] Two such examples are carba-β-D-altropyranose (**40**) and carba-α-L-galactopyranose (**41**). Protection of **39** as its acetonide followed by an osmium tetroxide-mediated dihydroxylation gave vinyl iodide **42** (Scheme 3). Installation of the methyl acrylate functionality was accomplished via a palladium(II)acetate catalyzed carbonylation in the presence of methoxide. Catalytic hydrogenation with 5% Rh/Al_2O_3, followed by treatment with excess benzoyl chloride provided diastereomers **43a** and **43b**, which were then separated via preparative layer chromatography (PLC). In each series, reduction of all three esters was achieved with $LiAlH_4$ and aqueous trifluoroacetic acid catalyzed the acetonide deprotection.

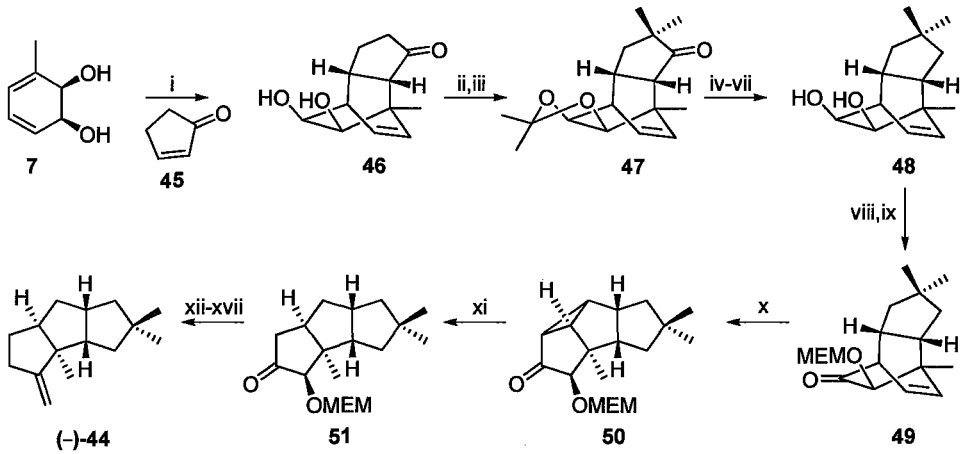


Reagents and conditions: (i) 2,2-dimethoxypropane, *p*-TsOH; (ii) OsO_4, NMO, Me_2CO, H_2O; (iii) $Pd(OAc)_2$, CO (1 atm), $NaOAc{\cdot}3H_2O$, MeOH; (iv) 5% Rh/Al_2O_3, EtOH, H_2 (55 psi); (v) BzCl, pyridine; (vi) $LiAlH_4$, THF, reflux; (vii) TFA-THF-H_2O (1:8:2), 50°C

Scheme 3. Boyd's synthesis of pyranose carbasugars **40** and **41**.[29]

Banwell has employed the toluene derived *cis*-dihydrodiol **7** in the synthesis of linear triquinane-type sesquiterpenoids, including (+)-hirsutic acid[30] and (–)-hirsutene (**44**).[31] Synthesis of the latter commenced with a Diels-Alder cycloaddition between **7** and 2-cyclopenten-1-one (**45**) to form the *syn*-addition product **46** with minimal contamination by the *anti*-isomer (Scheme 4). The acetonide derivative of **46** was treated sequentially with KHMDS, then methyl iodide to install the *gem*-methyl groups. Reduction of ketone **47** with $LiAlH_4$ setup a Barton-McCombie deoxygenation sequence which was followed by acidic hydrolysis of the acetonide. Selective oxidation of the less hindered alcohol with 4-acetamido-TEMPO and protection of the remaining alcohol as its β-methoxyethoxymethyl ether yielded ketone **49**. A subsequent triplet sensitized photolysis reaction on **49** gave the oxa-di-π-methane rearrangement product **50**. Reductive cleavage of the cyclopropyl group with tri-*n*-butyltin hydride produced triquinane **51**. Removal of the ketone functionality was accomplished with a similar reduction/ Barton-McCombie

procedure. Removal of the MEM group under acidic conditions followed by a PCC-promoted oxidation set up a Wittig reaction to produce (–)-hirsutene (**44**).

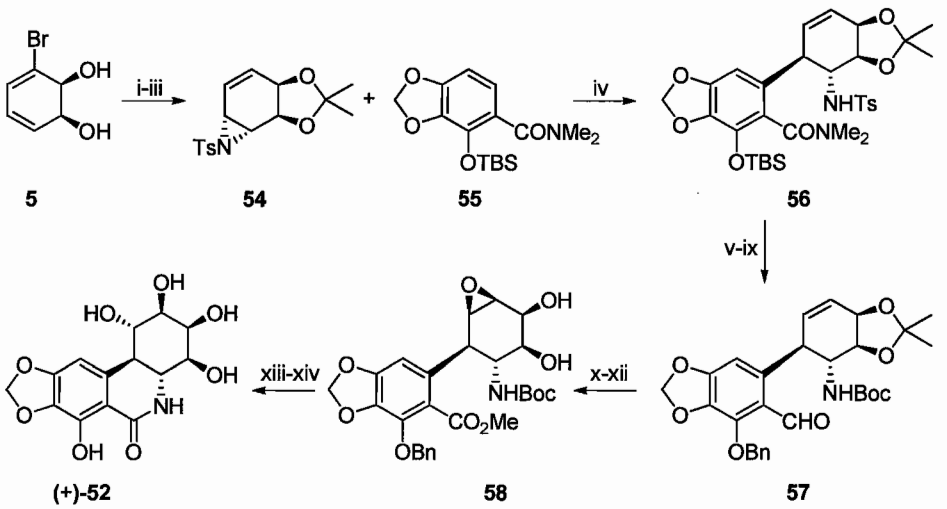


Reagents and conditions: (i) 19 kbar; (ii) 2,2-dimethoxypropane, *p*-TsOH, H_2O; (iii) LiHMDS, MeI, THF; (iv) $LiAlH_4$, THF, 0°C-50°C; (v) NaH, THF, CS_2, MeI; (vi) *n*-Bu_3SnH, AIBN, PhMe, reflux; (vii) AcOH, THF, H_2O, 60°C; (viii) 4-NAc-TEMPO, *p*-TsOH, DCM, 0°C; (ix) Hünig's base, MEM-Cl, DCM, r.t.; (x) *hv* (triplet), Me_2CO; (xi) *n*-Bu_3SnH, AIBN, PhH, r.t.; (xii) $NaBH_4$, MeOH; (xiii) NaH, THF, CS_2, MeI; (xiv) *n*-Bu_3SnH, AIBN, PhMe, reflux; (xv) PPTS, *t*-BuOH, reflux; (xvi) PCC, DCM, r.t.; (xvii) CH_3-$^+PPh_3$ ^-Br, KHMDS, toluene.

Scheme 4. Banwell's synthesis of (–)-hirsutene (**44**).[30]

Hudlicky has utilized *cis*-dihydrodiols derived from the TDO-mediated dihydroxylation of halogenated aromatic substrates in the synthesis of several Amaryllidaceae alkaloids.[32] Included is the first total synthesis of (+)-pancratistatin (**52**) from (1*S*-*cis*)-3-bromo-3,5-cyclohexadiene-1,2-diol (**5**).[33] The acetonide derivative of **53** was subjected to an copper-catalyzed aziridination procedure described by Evans,[34] before reducing the vinyl bromide with tri-*n*-butyltin hydride. Directed ortho metalation of amide **55**, followed by treatment with copper(I) cyanide, formed a lithium cyanocuprate species ($Ar_2Cu(CN)Li_2$) which selectively opened tosyl aziridine **54**. Conversion of **56** to its Boc derivative allowed for the removal of the tosyl group via a dissolving metal reduction. Removal of the silyl group with

TBAF was followed by reduction of the dimethylamide with sodium bis(methoxyethoxy) aluminum hydride. Benzyl protection of the phenol produced aldehyde **57** which was converted to its methyl ester via a diazomethane protocol. Acidic removal of the acetonide and $VO(acac)_2$-catalyzed epoxidation with di-*tert*-butyl peroxide produced oxirane **58**. Treatment with aqueous sodium benzoate at 100°C resulted in the stereoselective opening of the epoxide, thermal cleavage of the Boc carbamate, and cyclization to the δ-lactam. Finally, a palladium(II)hydroxide catalyzed hydrogenation removed the benzyl group to provide (+)-pancratistatin (**52**).



Reagents and conditions: (i) 2,2-dimethoxypropane, *p*-TsOH, DCM; (ii) PhI=NTs, $Cu(acac)_2$, CH_3CN; (iii) $n$$Bu_3SnH$, AIBN, THF, PhMe, reflux; (iv) a) *s*-BuLi, TMEDA, THF, -90°C; b) CuCN, -90°C to -20°C; c) **55**, $BF_3{\cdot}Et_2O$, -78°C to r.t.; (v) a) *s*-BuLi, THF; b) $(Boc)_2O$; (vi) Na/ anthracene, DME, -78°C; (vii) TBAF, THF, 0°C; (viii) SMEAH, THF, morpholine, -45°C; (ix) BnBr, K_2CO_3, DMF; (x) a) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O; b) CH_2N_2, Et_2O; (xi) AcOH, THF, H_2O, 60°C; (xii) *t*-BuOOH, $VO(acac)_2$, PhH, 60°C; (xiii) H_2O, BzO^-Na^+ (cat), 100°C; (xiv) $Pd(OH)_2/C$, H_2 (1atm), EtOAc

Scheme 5. Hudlicky's synthesis of (+)-pancratistatin (**52**).[33]

The preceding syntheses show only a fraction of the molecules made through use of arene *cis*-dihydrodiols. Comprehensive reviews on the subject have been

published in 1993[35] and in 2009[1] by Hudlicky. Also available is a more complete compilation of the known metabolites of TDO.[36]

2.2 Balanol

2.2.1 Discovery of Balanol

The compound now named balanol (**3**) was originally isolated from *Cordyceps ophioglossoides* in the 1970's by researchers at the Universität Tübingen in Germany.[37] They named their metabolite ophiocordin and demonstrated its antibiotic properties against several fungal strains. Derivatives of the **59** were made and subjected to standard analytic techniques (i.e. mass spectroscopy and NMR), allowing for a structure to be proposed (depicted in Figure 11 as **59**).[38] Thirteen years later, two independent research groups again isolated balanol (**3**) from three separate fungal species. A group at the Roche Nippon Research Center isolated a fungal metabolite from *Fusarium merismoides* Corda and *Fusarium aquaeductuum* Lagh.[39] They named their metabolite azepinostatin, but conceded that they were not the first group to isolate the compound. They credited a group from the Sphinx Pharmaceuticals for the initial isolation of balanol (**3**) from *Verticillium balanoides*.[2] In their publication, the Sphinx group noted that balanol (**3**) was a structural isomer of ophiocordin (**59**). For reasons not disclosed they obtained a sample of **59** and compared it to **3**.[40] It was concluded that they were indeed the same molecule and that the structure assigned by the Sphinx group was the correct one.

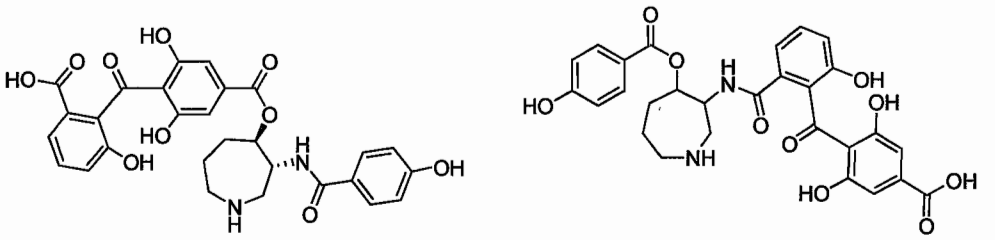


Figure 11. The structure of balanol (**3**) compared to the proposed structure of ophiocordin (**59**).

2.2.2 Activity of Balanol

Although the Sphinx Pharmaceutical group was not the first to isolate balanol, they were the first to demonstrate its nanomolar activity against the protein kinase C (PKC) family of enzymes.[2] Subsequent research has established that inhibition is a result of competition between balanol and ATP.[41] A solved crystal structure of balanol bound in the ATP binding site of a PKC enzyme has revealed details on the mechanism of inhibition.[42] The *p*-hydroxybenzamide group (A) occupies the adenine subsite, hexahydroazepine ring (B) occupies the ribose subsite and the benzophenone portion (C and D) mimics the triphosphate subsite (Figure 12).[43] Balanol has a nearly 3000 times greater affinity for the binding site compared to ATP.[44]

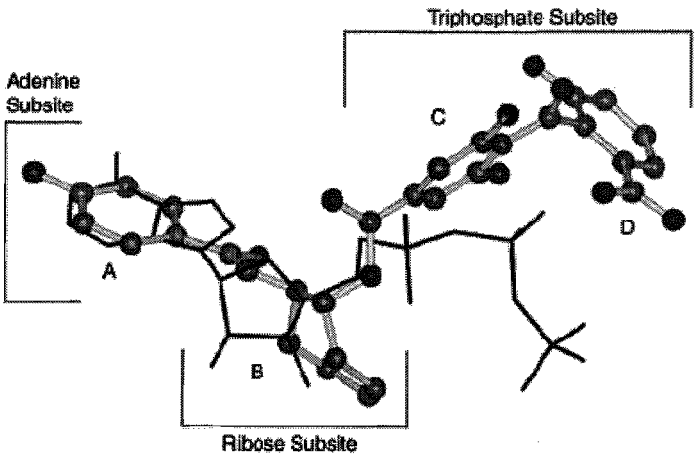


Figure 12. Balanol and ATP superposition.[43]

Analogs of balanol have been synthesized and screened for activity against PKCs and other kinases.[44,45] Some compounds containing the balanol core (hexahydroazepine ring) showed activity against members of the protein kinase A family of enzymes as well as PKCs. Any inhibitor of protein kinases (PK) is of interest to medicinal chemistry since kinases have broad biological effects in the cell.

Protein kinases are enzymes that catalyze the addition of a phosphate group on to another protein.[46] Typically, the addition of a phosphate changes the function of the target protein. The signal transduction pathways that convert external stimuli into cellular responses are under the control of this system. The addition of a phosphate to a protein can be compared to an on/off switch. An estimated 2% of the human genome codes for kinases, attesting to their importance in the body.[47] Disruptions in protein kinase activity have been linked to a myriad of diseases. It has been speculated that inhibitors of PKs would have wide ranging therapeutic value.[48] Currently, PK inhibitors are being investigated for their potential use in the treatment of asthma, Alzheimer's disease, arthritis, multiple sclerosis, diabetes, cancer, and

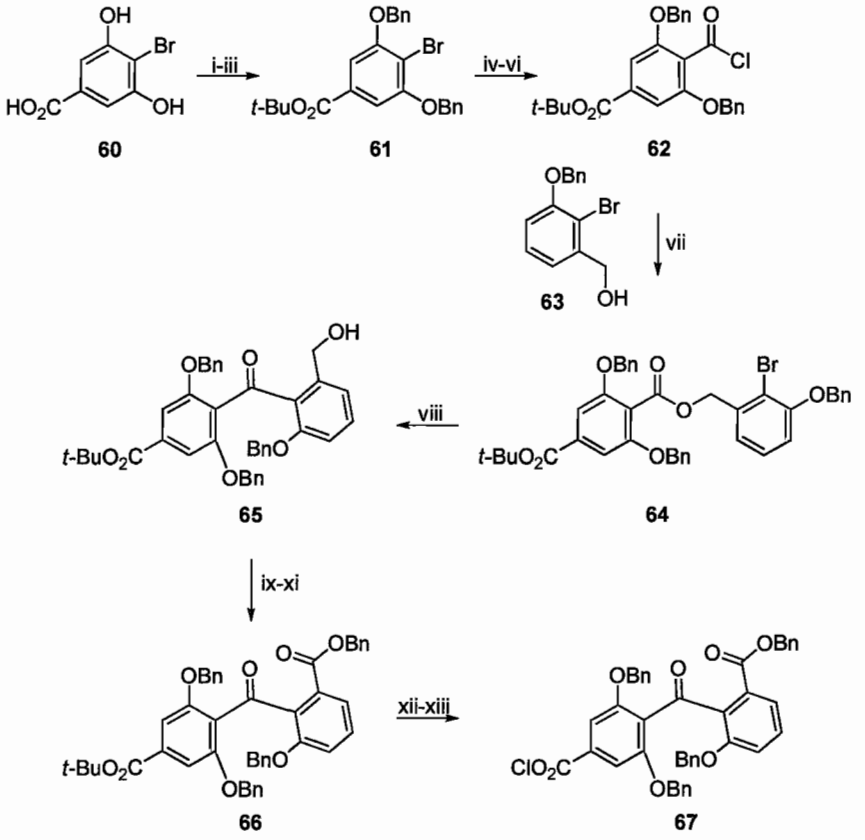
many other diseases.[49] The wide spread application of PK inhibitors, such as balanol, make their synthesis an important goal.

2.2.3 Selected Syntheses of Balanol

Synthesis of (–)-balanol, the natural enantiomer, and (+)-balanol have been an objective of researchers for over fifteen years. The following section will review a selection of the more than 30 formal and total syntheses accomplished to date. The first *published* total synthesis of balanol has been credited to the Nicolaou group,[50] although the first *completed* total synthesis belongs to the Sphinx Pharmaceutical group.[51]

Lampe and Hughes (1994)[51-2]

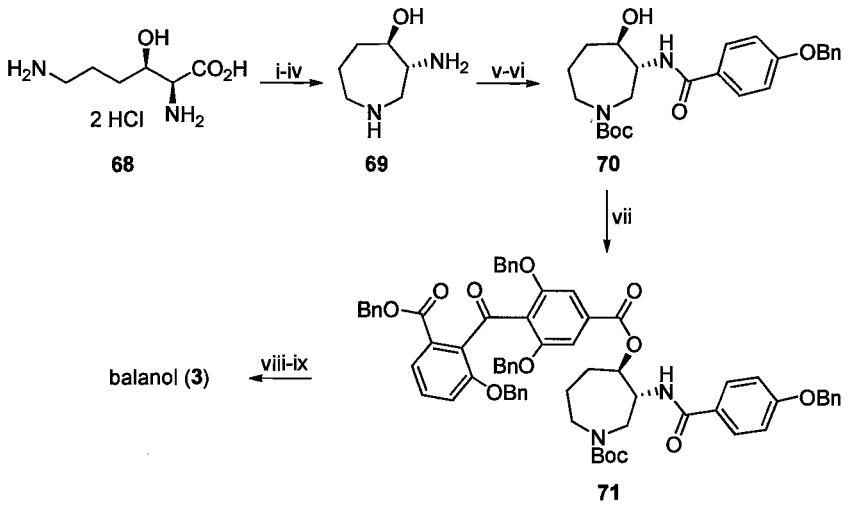
The Sphinx group, led by Lampe and Hughes, designed a synthesis in which the benzophenone and the hexahydroazepine portions would be generated separately and then coupled together later. Creation of the benzophenone segment began with the differential protection of arene **60** as its benzyl and *tert*-butyl esters (Scheme 6). Transmetalation of **61** followed by treatment with carbon dioxide gave a carboxylic acid species which was converted into acid chloride **62** with oxalyl chloride. Acylation of aryl bromide **63** with **62** and *tert*-butoxide yielded ester **64**. Subsequent transmetalation with *n*-butyllithium catalyzed a rearrangement to the ortho-substituted benzophenone **65**. A two-step oxidation, first pyridinium dichromate then tetra-*n*-butylammonium permanganate, converted the primary alcohol of **65** into the corresponding carboxylic acid. The last sequence was a benzyl protection, thermal hydrolysis of the *tert*-butyl ester, and conversion to its acid chloride **67**.



Reagents and conditions: (i) BnBr, K_2CO_3; (ii) NaOH; (iii) CDI, *t*-BuOH, DBU; (iv) *n*-BuLi, -78°C; (v) CO_2; (vi) $(COCl)_2$; (vii) *t*-BuOK, THF; (viii) *n*-BuLi, THF, -78°C; (ix) PDC, DMF; (x) Bu_4NMnO_4, pyr; (xi) BnBr, K_2CO_3; (xii) quinoline, 205°C; (xiii) $(COCl)_2$, DMF

Scheme 6. Lampe and Hughes' synthesis of the benzophenone portion of balanol.[51-2]

The synthesis of the azepane core of balanol was accomplished from hydroxylysine **68** (Scheme 7). Conversion to its lactam with hexamethyldisilazane in xylenes followed by the slow addition of isopropanol, set up a reduction which furnished azepane **69**. Selective protection of the secondary amine with Boc anhydride was followed by protection of the primary amine as an aryl ester to give amide **70**. Treatment with previously synthesized benzophenone **67** in triethylamine produced fully protected balanol derivative **71**. After hydrogenation of the benzyl groups and acidic hydrolysis of the Boc carbamate, balanol (**3**) was obtained.



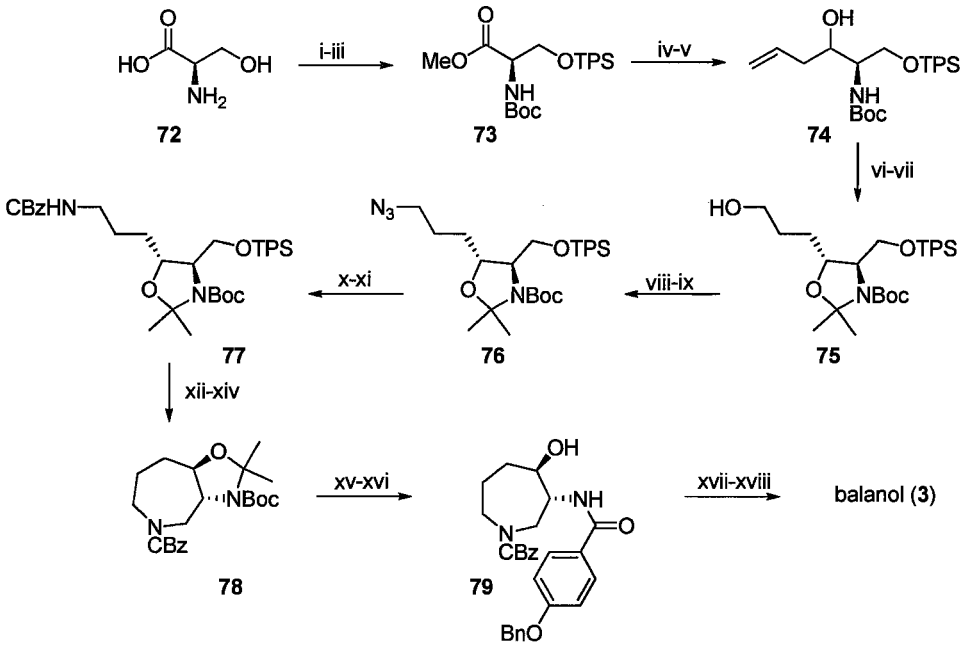
Reagents and conditions: (i) $(TMS)_2NH$, xylenes, reflux; (ii) isopropanol; (iii) 1N HCl; (iv) BH_3, THF; (v) $(Boc)_2O$, NaOH; (vi) *p*-$BnOC_6H_4COCl$, NaOH, DCM; (vii) **67**, NEt_3, DCM; (viii) H_2, $Pd(OH)_2/C$; (ix) TFA

Scheme 7. Lampe and Hughes synthesis of balanol.[51-2]

Nicolaou (1994)[50,53]

Nicolaou's synthesis of balanol followed the same strategy employed by Lampe and Hughes. They first synthesized the benzophenone portion and then coupled it to the azepane portion. Nicolaou used an almost identical approach to make benzophenone **67** and therefore it will not be reviewed. Preparation of the azepane core started from homochiral amino acid D-serine (**72**) which was differentially protected three times to yield ester **73** (Scheme 8). Reduction with DIBALH followed by treatment of the resulting amino aldehyde with Brown's diisopinocamphenylborane reagent (Allyl-B(^{l}Ipc)$_2$) gave alcohol **74**. Protection as its acetonide was followed by mesylation and displacement with azide to give **76**. Reduction, CBz protection and desilylation allowed for the key step, a 7-*exo-tet* cyclization initiated by treatment with *tert*-butoxide in THF which made azepane **78**. Removal of the protecting groups and derivatization with *p*-(benzyloxy)benzoyl

chloride was followed by a 2-chloro-1-methylpyridinium iodide mediated coupling reaction with the benzophenone fragment **67**. The synthesis was completed by removal of the last protecting groups to yield balanol (**3**).



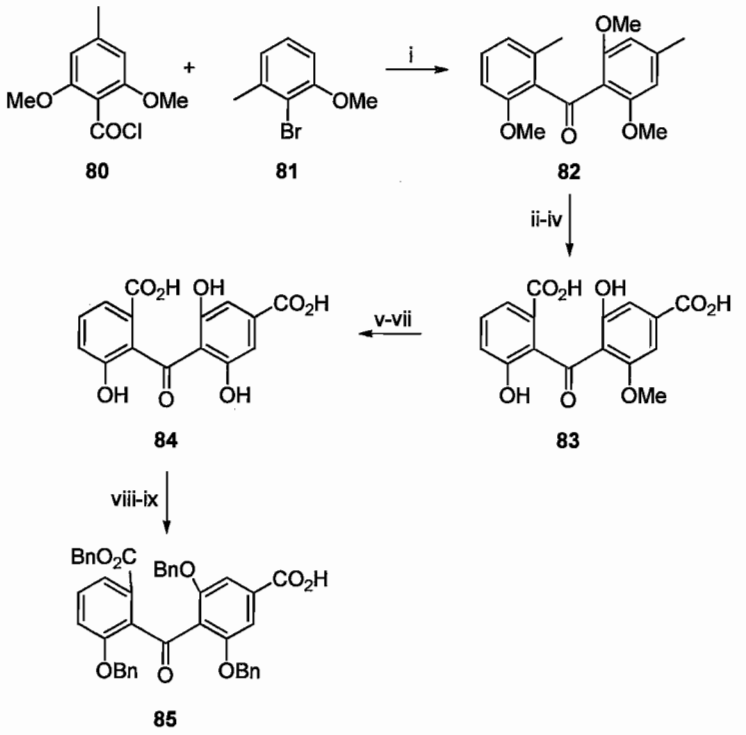
Reagents and conditions: (i) $(Boc)_2O$, NaOH, 1,4-dioxane, H_2O, 0-25 °C; (ii) K_2CO_3, MeI, DMF, 0-25°C; (iii) TPSCl, imidazole, DMF, 25°C; (iv) DIBALH, toluene, -78°C; (v) Allyl-B(^{l}Ipc)$_2$, Et_2O, -78°C, ethanolamine; (vi) 2,2-dimethoxypropane, CSA, CH_2Cl_2, 25°C; (vii) 9-BBN, THF; then NaOH, H_2O_2; (viii) MsCl, Et_3N, CH_2Cl_2, 0°C; (ix) NaN_3, DMF, 25°C; (x) H_2, Pd/C, THF; (xi) Benzyl chlorocarbonate, NaOH, 1,4-dioxane, H_2O, 0°C; (xii) TBAF, THF, 25 °C; (xiii) MsCl, Et_3N, CH_2Cl_2, 0°C; (xiv) KO*t*Bu, THF, 25°C; (xv) TFA, CH_2Cl_2, 25°C; (xvi) *p*-(benzyloxy) benzoyl chloride, Et_3N, 0-25°C; (xvii) **67**, 2-chloro-1-methylpyridinium iodide, DMAP, NEt_3, DCM; (xviii) H_2, Pd black, THF, H_2O, AcOH.

Scheme 8. Nicolaou's synthesis of balanol.[50,53]

Vicker (1995)[54]

Vicker's preparation of the benzophenone portion of balanol began with the formation of the Grignard reagent of **81** followed by its reaction with acid chloride **80** (Scheme 9).[54] Oxidation of the methyl groups of **82** with permanganate and

manipulation of the two phenol groups gave **83**. Removal of the remaining methyl furnished **84** which was benzyl protected to yield benzophenone **85**.

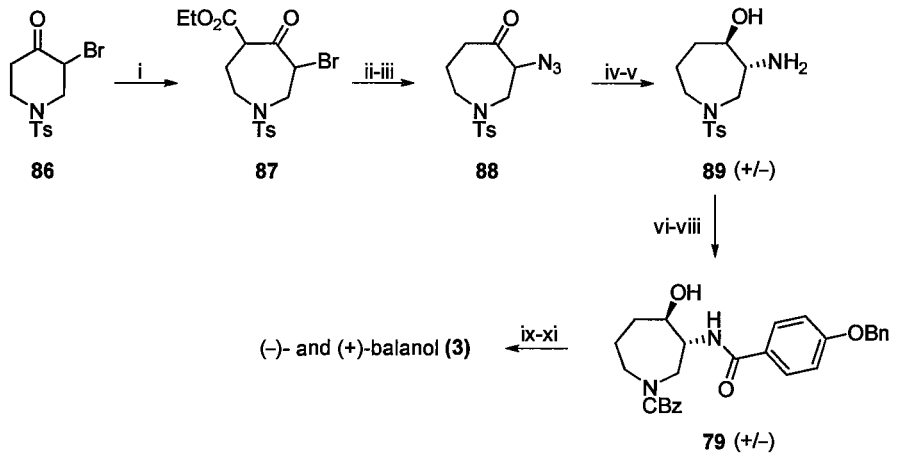


Reagents and conditions: (i) Mg, THF; (ii) $KMnO_4$, pyridine (aq.); (iii) $SOCl_2$, MeOH; (iv) BBr_3, DCM; (v) $SOCl_2$, MeOH; (vi) NaH, BnBr, DMF; (vii) BBr_3, DCM; (viii) NaH, BnBr, DMF; (ix) Na_2CO_3 (aq.), EtOH

Scheme 9. Vicker's synthesis of the benzophenone portion of balanol.[54]

Vicker's preparation of the hexahydroazepine portion of balanol began from ketone **86**, which was treated with ethyl diazoacetate under Lewis acid conditions to initiate a methylene insertion on the unhindered side to create ester **87** (Scheme 10). Acidic hydrolysis and decarbonylation was followed by displacement of the bromide with azide to furnish ketone **88**. Selective reduction with sodium borohydride produced a 2.4:1 ratio of *trans*- and *cis*-isomers, which were separated via column chromatography. Azide reduction and formation of the *p*-(benzyloxy) benzoyl amide derivative allowed for the completion of the synthesis through a similar coupling

method employed by Nicolaou.[50,53] Separation of (–)- and (+)-balanol (**3**) was accomplished through use of an HPLC protocol.



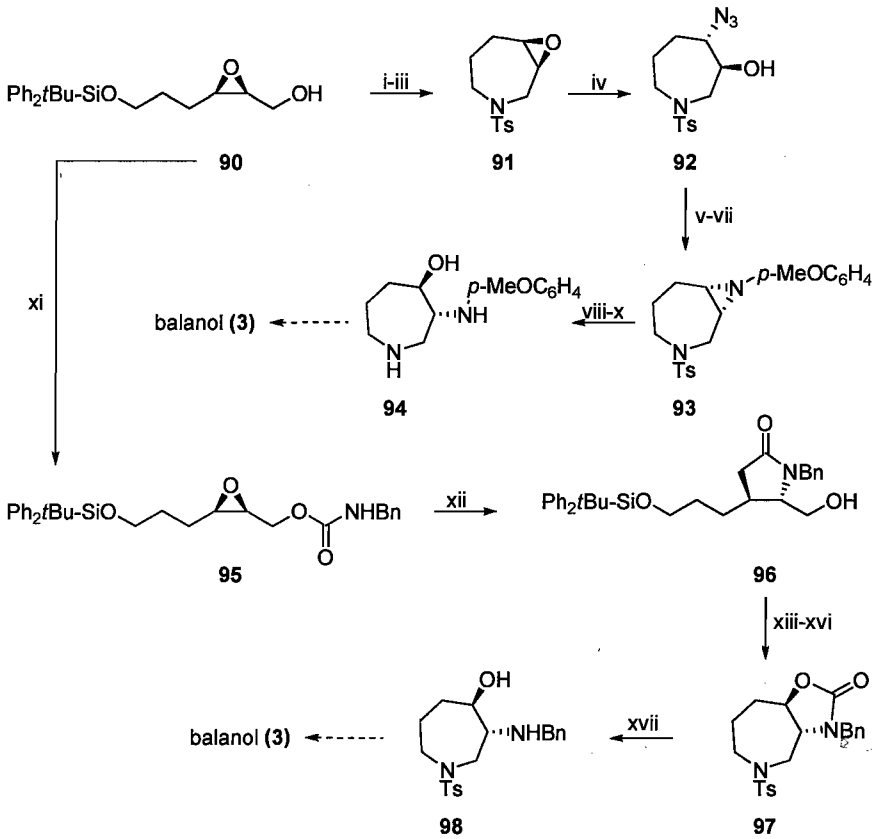
Reagents and conditions: (i) N_2CHCO_2Et, BF_3-Et_2O, DCM; (ii) HCl, dioxane; (iii) NaN_3, AcOH, DMF; (iv) $NaBH_4$, EtOH; (v) $LiAlH_4$, THF; (vi) HBr (aq.); (vii) NEt_3, DCM, 18-crown-6, benzyl chloroformate; (viii) *p*-(benzyloxy) benzoyl chloride, Et_3N, DCM; (ix) **85**, 2-chloro-1-methylpyridinium iodide, DMAP, NEt_3, DCM; (x) H_2, Pd black, EtOAc, H_2O, AcOH; (xi) HPLC separation.

Scheme 10. Vicker's synthesis of (–)- and (+)-balanol.[54]

Tanner (1995)[55-6]

Tanner has published several approaches to balanol through selective epoxide and aziridine openings. The two examples presented both start with epoxide **90**, obtained in 90% e.e. via a previously described Sharpless asymmetric epoxidation.[57] In the first route, compound **90** was converted into its ditosylate in a two step procedure and then cyclized in the presence of cesium carbonate (Scheme 11). The selective epoxide opening of **91** was intensely studied by Tanner.[56] When LiN_3 was used, a 97:3 ratio of separable isomers was obtained. Mesylation of **92** followed by reduction of the azide functionality with $LiAlH_4$ formed aziridine **93** upon protection with *p*-methoxybenzyl chloride. Opening of the aziridine **93** with aqueous *p*-TsOH

gave a 98:2 ratio of regioisomers in favour of **94**, a known degradation product of balanol. The second approach used an *in situ* acyl transfer reaction to transform alcohol **90** into cyclic-carbamate **96** in two steps. Alcohol **96** was converted to its ditosylate and then cyclized in similar manner to the first approach. Hydrolysis of **97** furnished alcohol **98**, a compound Tanner argues could be converted to balanol.

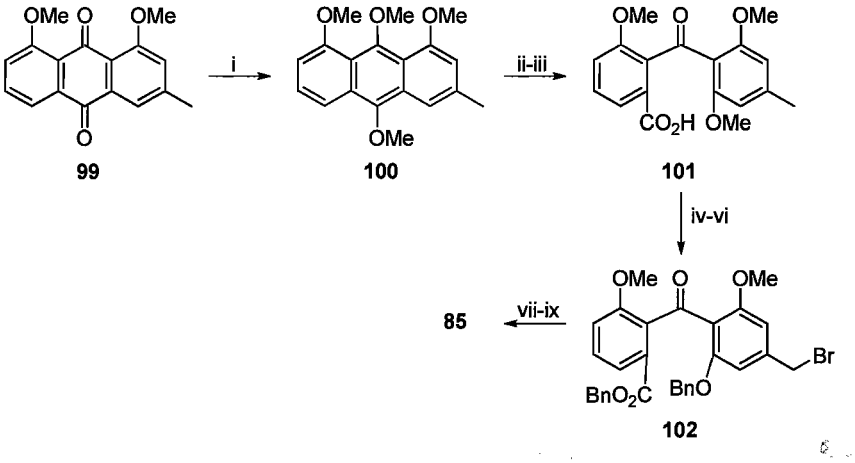


Reagents and conditions: (i) *p*-TsCl, NEt_3, DMAP, DCM; (ii) *N*-tosylimidazole, Bu_4NF, THF; (iii) *p*-$TolSO_2NH_2$, Cs_2CO_3, DMF, r.t.; (iv) LiN_3, DMF, 90°C; (v) MsCl, NEt_3, DCM; (vi) $LiAlH_4$, THF, 50°C; (vii) *p*-$MeOC_6H_4COCl$, NEt_3, DCM; (viii) *p*-TsCl, H_2O, THF; (ix) BCl_3, DCM; (x) Na(Hg), Na_2HPO_4, MeOH, reflux; (xi) BnN=C=O, NEt_3, DCM; (xii) NaH, THF, r.t.; (xiii) *p*-TsCl, NEt_3, DCM; (xiv) Bu_4NF, THF; (xv) *p*-TsCl, NEt_3, DMAP, DCM; (xvi) *p*-$TolSO_2NH_2$, Cs_2CO_3, DMF, r.t.; (xvii) LiOH, THF, H_2O, EtOH, reflux

Scheme 11. Two of Tanner's approaches to balanol.[55,56]

Naito (1997)[58-9]

Naito's synthesis of the benzophenone portion begins with the methylated derivative of chrysophanic acid **99**. Reductive methylation furnished anthracene derivative **100**, which was irradiated as an ether solution with a halogen lamp in the presence of oxygen (Scheme 12). The resulting oxygen adduct was treated with sulfuric acid to yield carboxylic acid **101**. Bromination and subsequent treatment with boron tribromide introduced the desired carboxylic acid functionality. The final manipulations and benzyl protections produced intermediate **85**, a commonly employed coupling partner in the synthesis of balanol.

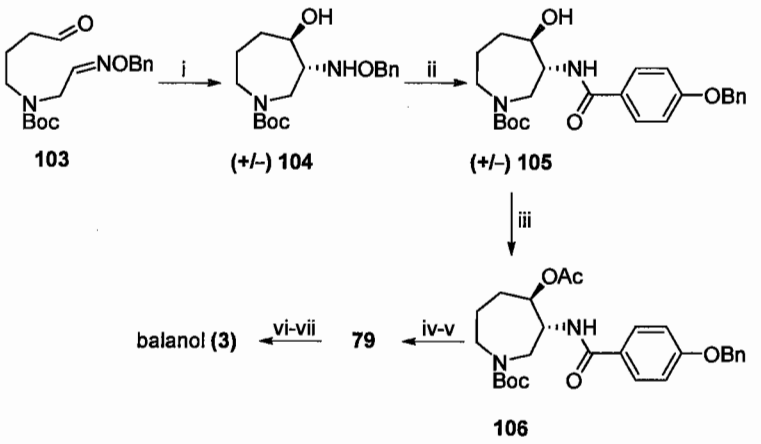


Reagents and conditions: (i) a) $Na_2S_2O_4$, Bu_4NBr, THF, H_2O; b) 6N KOH, Me_2SO_4, r.t.; (ii) O_2/ *hv*, Et_2O, H_2SO_4, acetone; (iii) NaH, MeI, DMF; (iv) NBS, AIBN, CCl_4, reflux; (v) BBr_3, DCM, r.t.; (vi) BnBr, K_2CO_3, DMF; (vii) $CaCO_3$, H_2O, dioxane, reflux; (viii) Pr_4NRuO_4, NMO, MeCN; (ix) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF, *t*-BuOH, H_2O.

Scheme 12. Naito's synthesis of the benzophenone portion of balanol.[58,59]

Naito's synthesis of the hexahydroazepine ring begins with the SmI_2-catalyzed cyclization of aldehyde **103** (Scheme 13). Removal of the benzyl group and replacement with the *p*-(benzyloxy) benzoyl group fashioned racemic **105**. Immobilized lipase and vinyl acetate was used to selectively esterify **105**, resulting in

96% e.e. of the desired isomer **106**. Conversion to known intermediate **79**, followed by coupling with the previously described benzophenone portion **85**, gave the target molecule.

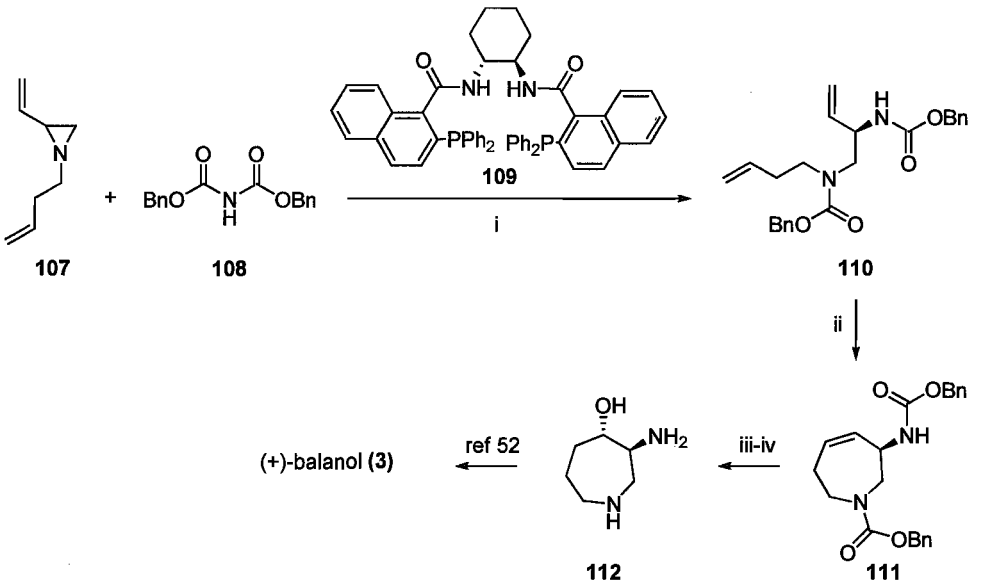


Reagents and conditions: (i) SmI_2, HMPA, *t*-BuOH, -78°C; (ii) a) H_2, PtO_2, MeOH; b) *p*-(benzyloxy) benzoyl chloride, $NaHCO_3$, H_2O, DCM; (iii) immobilized lipase, vinyl acetate, *t*-BuOMe, 45°C; (iv) a) TFA, DCM; b) CBz-Cl, Na_2CO_3, H_2), acetone; (v) KOH, MeOH, r.t.; (vi) **85**, 2-chloro-1-methylpyridinium iodide, DMAP, NEt_3, DCM; (vii) H_2, Pd black, HCO_2H, r.t.

Scheme 13. Naito's synthesis of balanol.[58,59]

Trost (2007)[60]

Trost completed a formal synthesis of (+)-balanol (**3**) through use of a dynamic kinetic asymmetric allylic amination and acyl migration of vinyl aziridine **107** with imido carboxylate **108**.[60] The stereochemistry of this palladium-catalyzed reaction was controlled by diphosphine ligand **109** and produced dicarbamate **110** with an e.e. of 88% (Scheme 14). Ring closing metathesis with Grubb's II catalyst provided tetrahydroazepine **111**, which was selectively oxidized with a hydroboration-oxidation procedure. Global deprotection furnished β-amino alcohol **112** which has previously been converted to (+)-balanol (**3**) by Lampe and Hughes.[52]



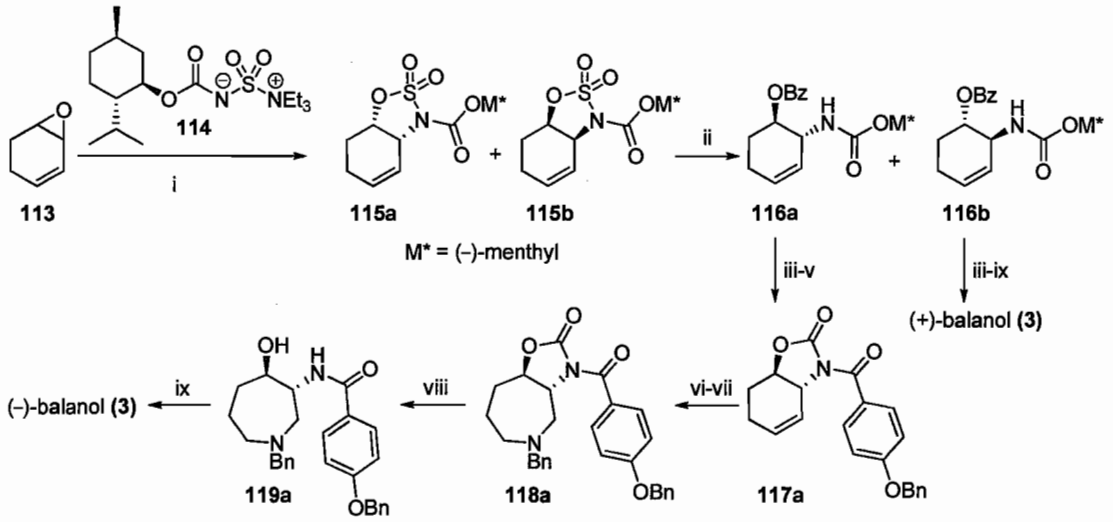
Reagents and conditions: (i) 6 mol % **109**, 2 mol % [{(η^3-C_3H_5)PdCl}$_2$], 10 mol % Et_3N, CH_2Cl_2, 35°C; (ii) 5 mol % Grubb's II catalyst, CH_2Cl_2, 35°C; (iii) a) BH_3·THF; b) $NaBO_3$·H_2O, 0°C; (iv) H_2, $Pd(OH)_2$, MeOH, then HCl.

Scheme 14. Trost's synthesis of (+)-balanol.[60]

Hudlicky (2008)[61-2]

Hudlicky has disclosed an enantiodivergent synthesis of (–)- and (+)-balanol from a single achiral starting material.[61,62] Reaction of vinyl epoxide **113** with a (–)-menthol version of the Burgess reagent **114**[63] produced a diastereomeric pair of *cis*-cyclic sulfamidates **115a** and **115b** (Scheme 15). Their reaction with ammonium benzoate produced a separable mixture of *trans*-amino alcohols **116a** and **116b**, precursors to (–)- and (+)-balanol respectively. Basic ester hydrolysis followed by treatment with sodium hydride furnished a cyclic carbamate, resulting from displacement of chiral auxiliary group, which was then reacted with 4-benzyloxybenzoyl chloride to produced carbamate **117**. Azepane **118** was formed via an osmium-tetroxide dihydroxylation, periodate cleavage and reductive amination sequence. Mild hydrolysis gave alcohol **119**, a compound previously converted to (–)-

balanol.[52] An identical sequence was also carried out on **116b** to produce a formal intermediate in the synthesis of (+)-balanol.



Reagents and conditions: (i) **114**, THF, 70°C; (ii) a) NH_4CO_2Ph, DMF, 50°C; b) H_2SO_4, THF, H_2O; (iii) 1N NaOH, MeOH; (iv) NaH, THF, reflux; (v) 4-benzyloxybenzoyl chloride, DCM, DMAP, NEt_3; (vi) OsO_4, NMO, DCM; (vii) a) $NaIO_4$, acetone-H_2O (8:2); b) $BnNH_2$, MeOH, AcOH, $NaCNBH_3$, 3Å MS, -78°C to r.t.; (viii) 1N NaOH, THF, -20°C; (ix) ref 52.

Scheme 15. Hudlicky's enantiodivergent synthesis of (–)- and (+)-balanol.[61,62]

A number of other formal syntheses of balanol have been published; some target the azepane core[64-84] while others the benzophenone fragment.[85-93]

2.3 Opiate alkaloids

2.3.1 History

It is impossible to determine the exact time and place opium poppy (*Papaver somniferum*) was first cultivated, although it is generally accepted that the Sumerians were among the first.[94] The Sumerians flourished from 4000 to 3000 BC between the Tigris and Euphrates rivers in modern day Iraq, and it was here where the earliest record of opium poppy was found. While excavating the ancient city of Nippur, a Sumerian spiritual centre, researchers from the University of Pennsylvania discovered several tablets inscribed in Cuneiform.[95] They describe the collection of poppy juice in the early morning from plants they called "Gil Hul" meaning "joy plant". The ancient Assyrians were also known to gather and use the secretions of poppy plants. They named the juice collected "arat-pa-pal" and some have speculated that the Latin word "Papaver" is derived from this term.[96] The conquest of Assyria by the Persians sparked the spread of opium (which they called *theriac*, *malideh* and *afiun*) out of Mesopotamia. In ancient Egypt opium use was generally associated with religious ceremonies although it appears to be used in medicine as well. The Ebers papyrus (ca. 1553-1550 BC) is a medical text that describes the use of opium as a "remedy to prevent excessive crying".[94] Thoth, the god of letters, was believed to have invented opium and to have taught mortals how to cultivate and use it. Furthermore, the ancient city of Thebes is the inspiration for the name of the opiate alkaloid "thebaine".

Ancient Greece is the source for most of the modern terminology associated with opium. The word "opium" is derived from either "opos" or "opion" meaning

juice and poppy juice respectively.[96] Many of the ancient Greek gods were associated with opium, including Hypos (sleep), Nyx (night), Thanatos (death), and Morpheus (dreams) the source of the name "morphine". Ancient Greeks regarded opium as a symbol for consolation and oblivion. Thus, they depicted all their nocturnal gods wearing a wreath of poppy blossoms. In Homer's "The Iliad" and "The Odyssey" opium is mentioned as an intoxicating and pain-relieving substance. The deadly effects were also known, opium in combination with hemlock were used to execute condemned individuals in ancient Greece.

The Arabs are credited with spreading opium throughout most of the ancient world. They called opium poppy "Abou-el-noum" meaning father of sleep. The famous Arabian physician Avicenna (10th century) wrote a thesis about opium and its effects; he later died from opium abuse. Arab traders brought opium to China somewhere between the 11th and 13th centuries AD.[95] It was initially used by only the socially elite for the control of dysentery. Soon after, European traders brought the habit of tobacco smoking from the Americas to China, where it quickly gained popularity. The last Ming emperor Tsung Chen viewed tobacco as an evil from the New World and banned its use in 1644.[94] In response, the Chinese people began the practice of smoking opium with tobacco in gradually increasing amounts. The problem grew quickly and soon 25% of the population was smoking pure opium.

Much of the opium used in China originated from the Bengal region of India where it was produced and traded by the East India Company. This British company had a complete monopoly on trade in the region and made opium one of most prevalent commercial crops by the end of the 18th century. The Chinese tried to cure

the problem by banning the sale and importation of opium. The East India Company circumvented the ban by purchasing tea on credit from China. The Chinese merchants would then go to Calcutta and receive opium as payment. Opium was also smuggled into China via Canton by British traders aboard "opium clipper fleets". In response, the emperor replaced the corrupt viceroy of Canton with Lin Tse-Hsu, who confiscated and destroyed an estimated 2.6 million pounds of opium belonging to British merchants in 1839. This infuriated the British and sparked the first Opium War from 1839 to 1842. The war ended with a decisive British victory, leading to the Treaty of Nanking, which lowered Chinese tariffs and gave control of Hong Kong island to the British. In 1856, the second Opium war began, which also allowed French traders to operate in China. The grip of opium on the Chinese people would remain strong until the conclusion of World War II and the formation of the People's Republic of China.

In order to control opium production, the International Opium Commission was founded in 1909. In 1924, a Commission composed of 62 countries met and passed laws to regulate the production and trade of opium. Currently, opium cultivation is regulated by the International Narcotics Control Board of the United Nations. India is the only country that produces significant amounts of opium for legal use.[97]

2.3.2 Opium Alkaloids

Opium is the air-dried exudate obtained from lacerating the immature capsules of *Papaver somniferum L.* or its variety *album* De Candolle (Fam. Papaveraceae).[96] Opium contains numerous non-alkaloidal constituents including various sugars and

several simple organic acids (e.g. fumaric acid, lactic acid, oxaloacetic acid and meconic acid). The alkaloid content is 10-20% by weight with more than 40 different compounds present. However, only 5 of these alkaloids account for the majority of weight; the morphinans (morphine (**120**), codeine (**4**) and thebaine (**121**)), the benzylisoquinoline papaverine (**122**) and the phthalide isoquinoline noscapine (**123**) (Figure 13).

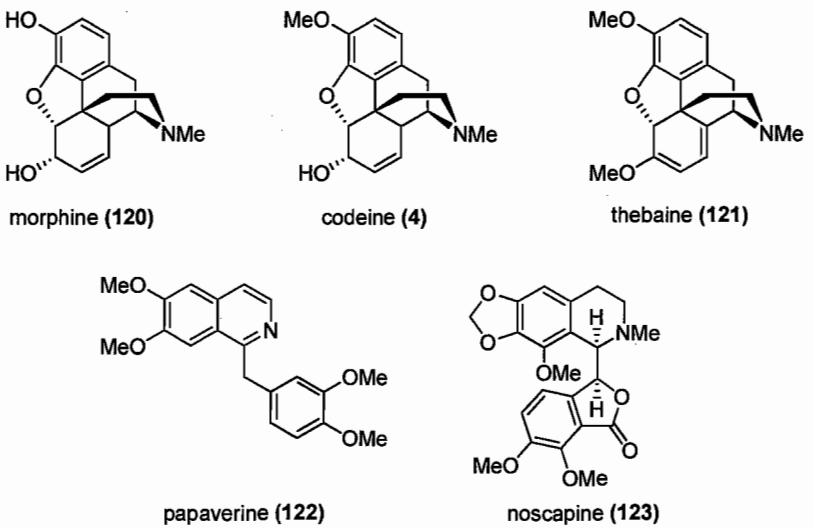


Figure 13. The major alkaloids of opium.

The identification of opium alkaloids began in concert with modern chemistry in the early 1800's. The Parisian Derosne described the isolation of a "salt of opium" in 1803, although the identity of the compound is unclear. A year later, Seguin also described such a salt, but it too has never been identified. In 1803, the German pharmacist Friedrich Wilhelm Adam Sertürner began his work on opium, initially dealing with the isolation of meconic acid. In 1806, he published a detailed account on the isolation of the narcotic component of opium, "principium somniferum". Sertürner described the substance as a member of a new class of organic bases that were "salifyable" (able to form salts with both organic and inorganic acids).[96]

Another German pharmacist, Karl Friedrich Wilhelm Meissner, called these bases "alkaloid" meaning "alkali-like". In 1817, Sertürner wrote a review on his research, and it was in this publication that the name 'morphine' was first used, named after Morpheus the god of dream. Sertürner believed morphine to be composed of carbon, oxygen, hydrogen and nitrogen, although the exact structure was not predicted. In 1833, Macfarlane and Co. (now Macfarlane-Smith) developed a method for commercial scale isolation of morphine.[103] Soon after, morphine became a popular drug for the treatment of pain. Its use as an immediate analgesic began after the invention of the hypodermic needle in 1853, previously opium pills and tincture were used.

The structural elucidation of morphine began soon after its isolation. In 1831, Liebig proposed the formula of morphine as $C_{34}H_{36}O_6N_2$. The correct formula, $C_{17}H_{19}O_3N$, was determined by Laurent in 1847. Many researchers tried to determine the structure through derivatization, resulting in the synthesis of heroin by Wright in 1874 and codeine by Grimaux in 1881. For decades it was believed that morphine contained an oxazine functionality; in fact this is the origin of the common name for tetrahydro-1,4-oxazine, "morpholine". [96] The correct structure was proposed in 1925 by Gulland and Robinson through a series of degradations. Their work led directly to the characterization of codeine, which was first isolated in 1833 by Robiquet. The correct structure of morphine was confirmed by x-ray crystallography in 1955 by Mackay and Hodgkin.[98] A more detailed account on the structural elucidation of opium alkaloid has been published by Butora and Hudlicky.[99]

2.3.3 Biosynthesis of Opium Alkaloids

All opium alkaloids produced in poppy plants originate from the amino acid tyrosine (**124**), which is first converted into dopamine (**125**) and 4-hydroxyphenylacetaldehyde (**126**) (Figure 14).[100] (*S*)-Norcoclaurine synthase catalyzes a Pictet-Spengler-type condensation reaction between **125** and **126** to produce (*S*)-norcoclaurine (**127**). Phenolic and nitrogen methylations, catalyzed by *S*-adenosylmethionine-dependant methyltransferases, afford (*S*)-reticuline (**128**) which is epimerized into (*R*)-reticuline (**129**) through a stereoselective reduction of its iminium ion after oxidation.[101] (*R*)-reticuline (**129**) is converted into salutaridine (**130**) by an oxidative coupling between the *ortho* position of one phenol ring and the *para* position of the other. Briefly, formation of phenoxide ions and abstraction of a nonbonding electron from each oxygen atom occurs to give two radicals which couple before a keto-enol tautomerization. Salutaridine (**130**) is selectively reduced by the NADPH-dependant salutaridine reductase to give salutaridinol (**131**) which is converted into acetate derivative **132**. Spontaneous (non-enzymatic) elimination of the acetate in a S_N2' (or possibly a S_N1) process gives thebaine (**121**). Demethylation of the C-6 enol ether is performed by an unknown enzyme(s). This provides neopinone (**133**), which is in equilibrium with codeinone (**134**). Codeinone reductase produces the C-6 alcohol in codeine (**4**), while a demethylation reaction gives morphine (**120**).

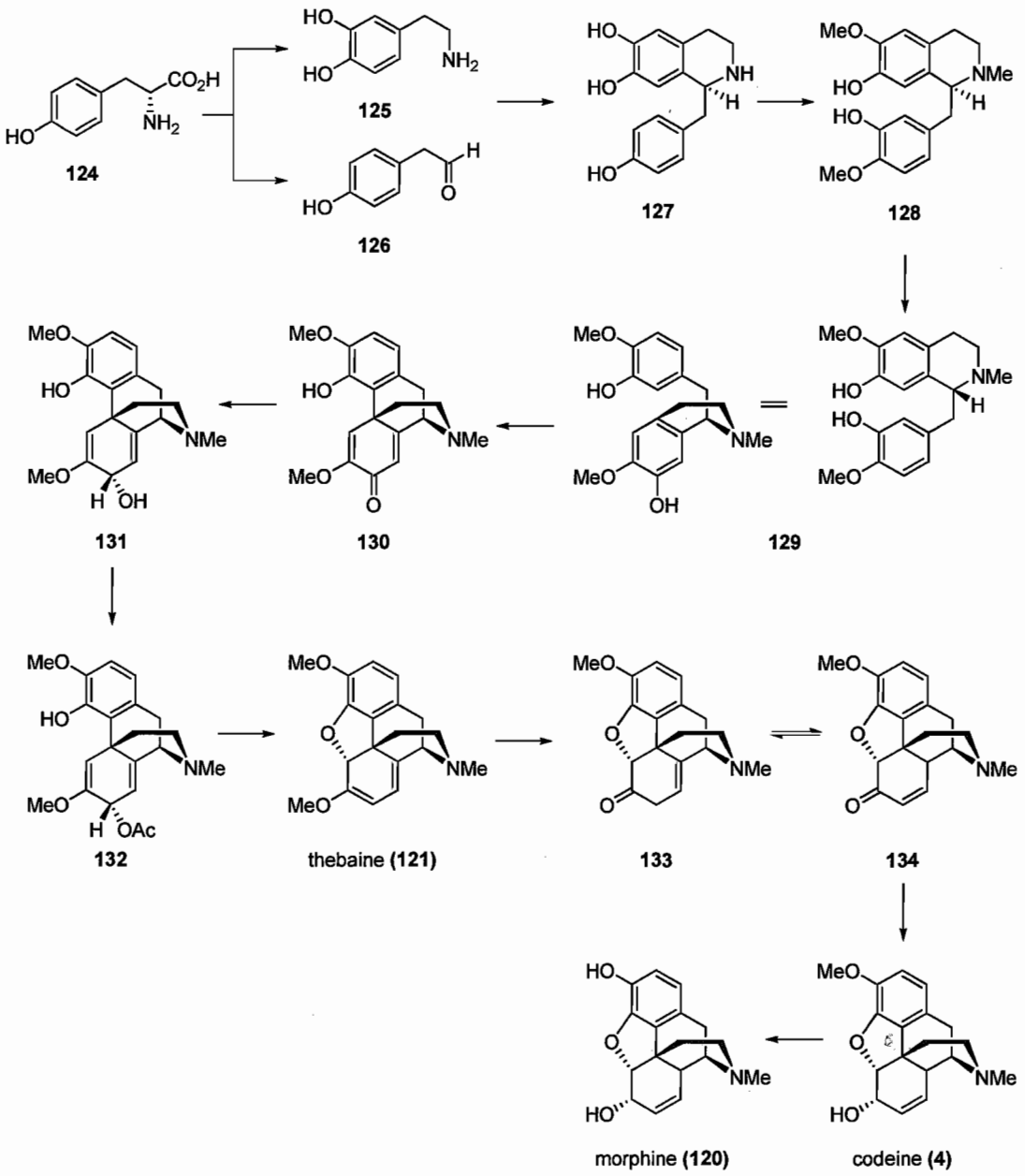


Figure 14. Biosynthesis of opium alkaloids.

2.3.4 Pharmacology

Morphine is still one of the most effective treatments available for pain relief. It is especially useful for dull, constant pain rather than sharp, periodic pain.[103] In general, morphine works by lowering the brain's awareness of pain. Unfortunately,

the side effects can often outweigh the benefits. These include; depression of the respiratory system, constipation, nausea, pupil constriction, hallucinations, memory loss and physical dependence, just to name a few. Some of the worst effects occur when a chronic addict stops using, resulting in chills, excessive sweating, abdominal cramps, muscle spasms, irritability, tremors, and increased heart rate.

Codeine is one of the most widely used drugs in the world, with the majority produced semi-synthetically from morphine.[103] It is typically administered orally as a salt (sulfate or phosphate) in combination with a non-narcotic analgesic (e.g. aspirin, ibuprofen). It is used for the relief of mild to moderate pain (arthralgia, back pain, dental pain, headaches, myalgia, surgical pain), for the treatment of non-productive coughing, and diarrhea. Codeine is approximately 60% as effective orally as parenterally, resulting from less first-pass metabolism in the liver. Codeine itself has a relatively low affinity for opioid receptors (~0.1% of morphine). The effects are attributed to the *O*-demethylation of codeine to morphine by cytochrome P450 2D6 (CYP2D6).[104] Approximately 10% of codeine undergoes *O*-demethylation, while most (~80%) is glycosylated to codeine-6-glucuronide (**135**). The remainder is converted to norcodeine (**136**) (Figure 15). Morphine is metabolized into two glycosylated products, morphine-6-glucuronide (**137**) and morphine-3-glucuronide (**138**), the former having relevant opioid activity. Researchers in Holland have suggested that codeine-6-glucuronide (**135**) is actually responsible for the analgesic effects of codeine.[105] They found that people who lack the CYP450 2D6 enzyme for the *O*-demethylation are still able to experience the effect of codeine.

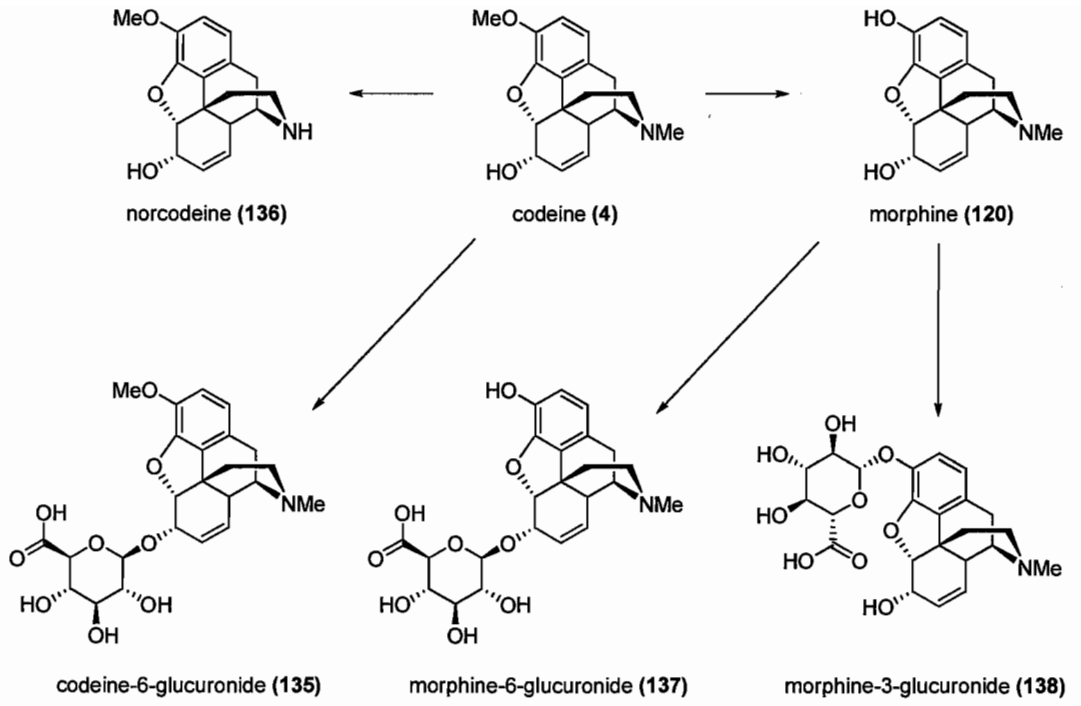


Figure 15. Metabolism of codeine **(4)**.

The adverse effects of morphine and codeine were recognized soon after their isolation. This led researchers to try and develop a safer, more efficacious, and non-addictive opiate. In 1897, a chemist at Bayer pharmaceuticals named Felix Hoffmann acetylated morphine to produce diacetylmorphine **(139)**. This transformation was first performed by C. R. Alder Wright in 1874, but was not considered significant at the time. Bayer named the morphine derivative "heroin" after the German word "heroisch", meaning heroic. Up until 1910, Bayer marketed heroin as a cough suppressant and as a non-addictive substitute for morphine. Eventually it was discovered that the increased lipophilic character of heroin results in better transport throughout the body, particularly across the blood-brain barrier. Heroin is metabolized into 6-monoacetylmorphine **(140)** or 3-monoacetylmorphine **(141)**, the

former having appreciable activity (Figure 16). Both metabolites can be further hydrolyzed to morphine itself.

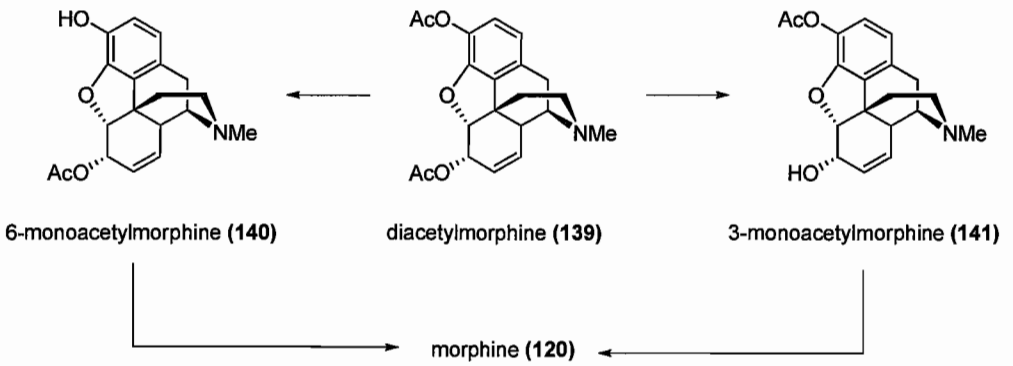


Figure 16. Metabolism of diacetylmorphine.

In 1939, while trying to develop a substitute for atropine, researchers synthesized meperidine (Demerol) (**142**). This was the first opiate discovered with a structure drastically different from morphine.[94] This led to the development of methadone (**143**), another non-opium alkaloid with activity at opioid receptors. The effects of methadone start slower, last longer and are not as intense as morphine. This, along with its oral activity, has made it a popular drug to treat morphine addiction. In 1942, Weijlard and Erikson synthesized nalorphine (**144**) and found it could reverse the respiratory depression produced by morphine, making it the first opiate antagonist ever developed. Nalorphine is actually a mixed agonist-antagonist, a detailed description of this property will be discussed later.

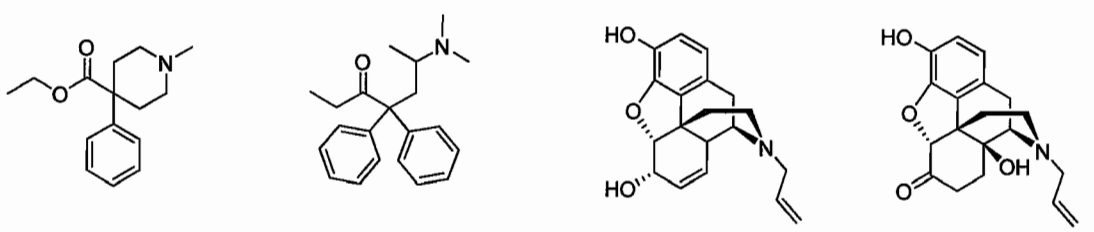


Figure 17. Opioid receptor ligands.

The first significant attempt to explain opioid receptor binding was postulated by Beckett and Casy in 1954.[106] It was assumed that morphine and its analogs required the following binding interactions for activity; 1. a positively charged nitrogen (ionized at physiological pH), 2. correctly oriented aromatic ring in relation to the nitrogen (making specific van der Waals interactions), 3. C-3 phenol group (hydrogen bonded in the binding site), and 4. an empty binding pocket which allows the ethylene bridge fit tightly so to properly orient the rest of the molecule.

In 1971, Goldstein suggested that the different activities of opioid agonists, antagonists, and mixed agonists-antagonists resulted from the existence of multiple opiate receptors.[107] It was theorized that radiolabeled drugs could demonstrate the existence of multiple receptors, unfortunately none could be obtained with high/ specific activity. However, subsequent research proved that Goldstein was in fact correct. Simultaneously, three separate research groups (1. Pert and Snyder,[108] 2. Simon, Hiller and Edelman,[109] and 3. Terenius[110]) identified multiple opioid receptors in the CNS through use of radiolabeled opioid ligands.

Soon it was theorized that morphine was not the natural ligand of the opioid receptors. In 1975, Kosterlitz observed that the brain extracts of guinea pigs contained a substance that inhibits acetylcholine release from nerves and that this inhibition is blocked by naloxone (**145**) (an opioid receptor antagonist).[111] Ultimately Kosterlitz identified the agents responsible as pentapeptides Tyr-Gly-Gly-Phe-Met (Met-enkephalin (**146**)) and Try-Gly-Gly-Phe-Leu (Leu-enkephalin (**147**)). The term "enkephalin" is derived from the Greek meaning "in the head", their location in the body.[103] At least 15 endogenous peptides (5 to 33 amino acids in length) have been

documented, each a member of the enkephalin, endorphine or dynorphin class of opioid peptides. A fourth class (deltorphins) have been isolated from the skin of the giant leaf frog (*Phyllomedusa bicolor*).[113] These opioid heptapeptides are unusual in that they contain the D-isomer of tyrosine. Researchers started to recognize a common structural feature required for relevant activity in opium alkaloids, opioid peptides and other compounds which induce analgesic activities. The pharmacophore appears to be the combination of an aromatic ring, and the specific 3-dimensional disposition of a nitrogen either 3 or 4 atoms away (Figure 18).[102] In addition to the phenyl and amino functionalities, the remaining portion of the molecule makes favorable interactions within the binding site. Although not fully understood, additional H-bonding is believed to partially account for the increased activity of more 'flexible' compounds such as carfentanil (**148**), which is approximately 10,000 more potent than morphine.[114]

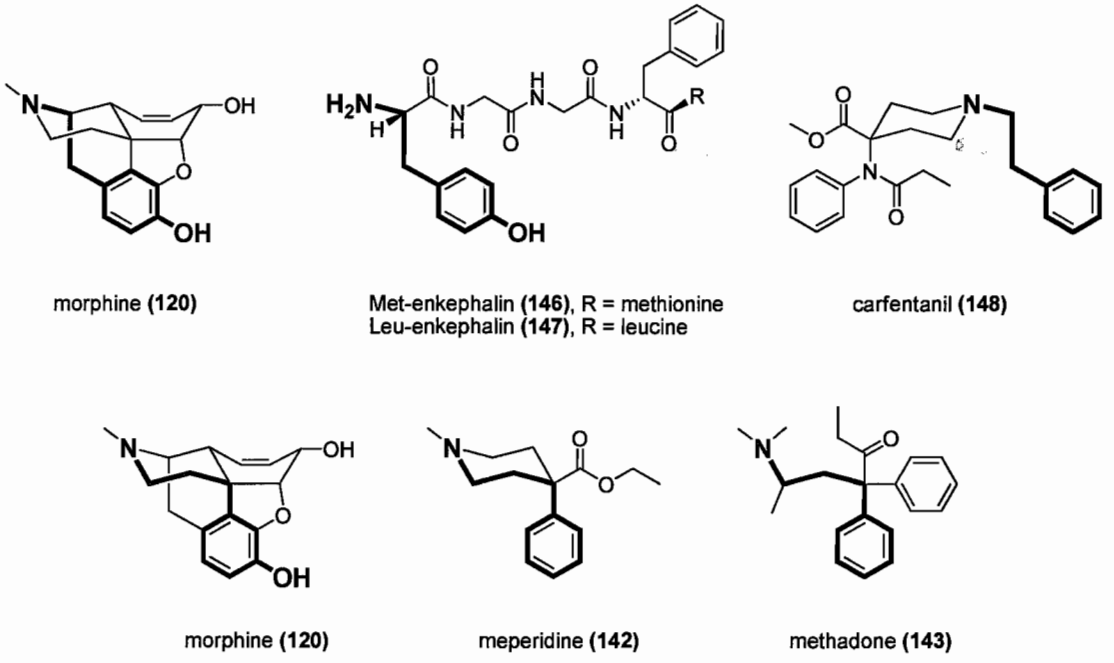


Figure 18. Proposed pharmacophore of opioid agonists.

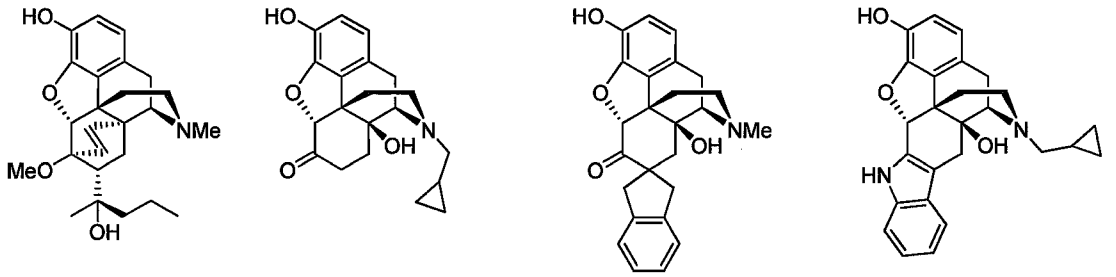
This proposed pharmacophore model helps explain the activity of opioid agonists, but fails to account for the antagonists. Nalorphine (**144**) and morphine (**120**) differ only in the substituent on the piperidine ring (*N*-allyl vs. *N*-methyl) yet have drastically different effects. As mentioned earlier, there are multiple opioid receptors in the CNS, which accounts for the discrepancy. Three main opioid receptors are now known; mu (μ), delta (δ), and kappa (κ). It was once believed that the sigma (σ) receptors were also a type of opioid receptor. However, pharmacological testing demonstrated that compounds structurally unrelated to opioids activated sigma receptors and isolation/ cloning experiments revealed drastic structural differences.[115] The opioid receptors are G-protein coupled receptors found imbedded the cell membranes of neurons. They are widely, but unevenly, distributed throughout the CNS.[116]

The mu (μ) receptors are located in the brain (laminae III and IV of the cortex, thalamus, periaqueductal gray), and spinal cord (substantia gelatinosa). Agonist activation of the μ-receptors produce analgesia, euphoria, respiratory depression, miosis, decreased gastrointestinal motility, and physical dependence. Upon binding of an agonist, the μ-receptor changes conformation opening up an ion channel across the cell membrane. Potassium ions flow out of the cell, hyperpolarizing the membrane potential, and thus disrupting the action potential. Another consequence is the decreased influx of calcium ions into the nerve terminal, resulting in the release of fewer neurotransmitters. Both events disrupt the transmission of pain signals throughout the CNS. The endogenous μ-receptor agonists are the enkephalins and β-endorphin, while morphine is the classic exogenous agonist. In the 1960's K.W.

Bentley developed a series of bridged oripavines (Diels-Alder adducts of thebaine) that became known as the 'super-potent' μ-receptor agonists.[117] This class includes etrophine (**149**) whose high hydrophobicity and affinity for the μ-receptor makes this compounds unsuitable for humans; it is currently used to immobilize large animals (e.g. elephants and bears). Antagonists of the μ-receptor include naloxone (**145**) and naltrexone (**150**), both of which treat opioid abuse. The former is use as an emergency room antidote, while the latter is used for long-term care.

The kappa (κ) receptors are located in the brain (hypothalamus, periaqueductal gray, claustrum), and spinal cord (substantia gelatinosa). Agonist activation of a κ-receptor initiates a shape change that closes a calcium channel, normally open in an active nerve. This prevents the release of neurotransmitters and thus prevents pain signaling. The nerves controlled by κ-receptors are those induced by non-thermal stimuli. Conversely, the μ-receptors are associated with all forms of pain stimuli. The endogenous ligands for the κ-receptors are the dynorphin class of opioid peptides. Agonist activation of the κ-receptors produces analgesia, miosis, respiratory depression, dysphoria, urinary retention, delayed digestion and some psychomimetic effects (i.e. disorientation and/or depersonalization). However, κ-receptor agonists do not induce dangerous side effects such as addiction and physical dependence. Many believe that the κ-receptor provides the best hope for a safe analgesic. This theory is based on the results obtained from some mixed agonist-antagonist compounds. As mentioned earlier, naloxone (**145**) and naltrexone (**150**) are μ-receptor antagonists and thus do not provide any analgesic effects. A related compound, nalorphine (**144**), is a μ-receptor antagonist but is also a mild κ-receptor agonist. Unfortunately, nalorphine

also induces hallucinations by interacting with the sigma-receptor. However, there still remains the possibility that a highly selective κ-receptor agonist could be developed. Such a compound could be the safe, potent, and non-addictive pain killer researchers have been searching for.



etrophine **(149)** naltrexone **(150)** 7-spiroindanyloxymorphone **(151)** naltrindole **(152)**

Figure 19. Selective opioid receptor ligands.

The delta (δ) receptors are located in the brain (pontine nucleus, amygdala, olfactory bulbs, and deep cortex). Agonist activation of the δ-receptors produces analgesia, euphoria, physical dependence, and possibly seizures and respiratory depression. When an agonist binds, the δ-receptor changes conformation and initiates the fragmentation of a messenger G_i-protein. The α_i-subunit of the G-protein inhibits adenylate cyclase, a membrane-bound enzyme responsible for the production of cAMP. The transmission of pain throughout the CNS requires cAMP to act as a secondary messenger, thus its absence explains activity of δ-receptor agonists. The endogenous agonists are the enkephalins (Met and Leu). An example of an exogenous agonist is 7-spiroindanyloxymorphone (**151**), whose excellent selectivity for the δ-receptor is a result of specific interaction with the indane ring off C-7. Similarly, antagonists such as naltrindole (**152**) are highly selective due to hydrophobic interactions between the extra rings on the opiate skeleton, indole in this case.

2.3.5 Selected Syntheses

Opium has been utilized in medicinal and spiritual preparations for at least 5000 years.[96] Interest in preparing opium alkaloids began shortly after the isolation and characterization of morphine in 1806. Chemists sought to synthesize morphine even before the structure had been confirmed. In fact, the first reported synthesis by Gates and Tschudi in 1952 assisted in the structural elucidation.[99] Since that time, numerous racemic and enantioselective syntheses have been disclosed, as well as synthetic approaches to the morphinan skeleton.

Despite years of accumulated knowledge, morphine still represents a formidable challenge to synthetic chemists. In particular, the pentacyclic framework, five continuous stereogenic centres, and C-13 quaternary centre are challenging to construct. Hudlicky has suggested that the difficulty does not come from its complexity, but rather its "total dissonance".[118] The polarization of morphine cannot be assigned in a way which avoids an incorrect sign on a electronegative atom (Figure 20).

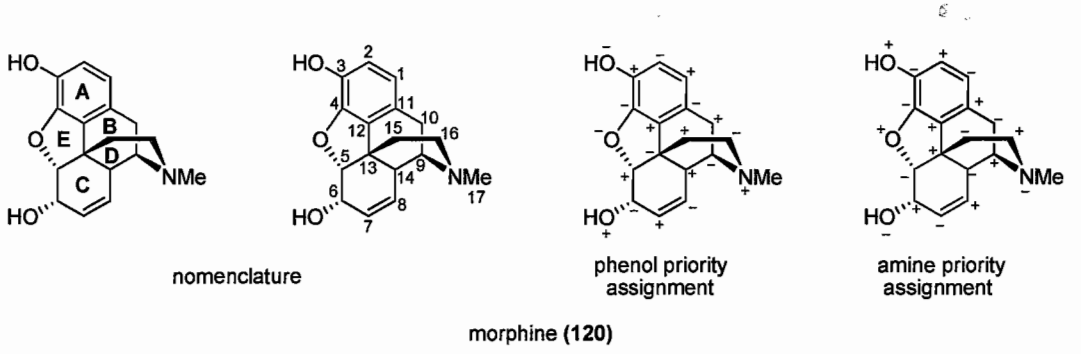


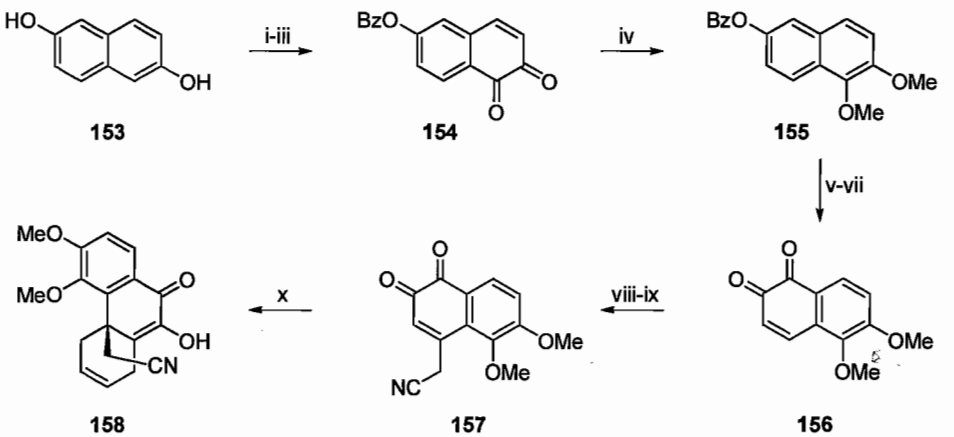
Figure 20. Morphine nomenclature and polarization assignments.[118]

The following section highlights some of the most important syntheses published to date. Several comprehensive reviews have been recently written

covering all formal, total, and synthetic approaches to morphine and its derivatives.[118-122]

Gates (1952)[123]

Gates published the first total synthesis of morphine **(120)** as a brief two page communication in 1952.[123] Four years later, a detailed account of this seminal work was disclosed.[124] The synthesis begins with the conversion of 2,6-dihydronaphthalene **(153)** into ortho quinone **156** via a nitrosation/ reduction/ oxidation protocol (Scheme 16). Conjugate addition of ethyl cyanoacetate to **156** was followed by an oxidation-decarbonylation procedure to yield nitrile **157**. A Diels-Alder reaction with 1,3-butadiene formed **158**.



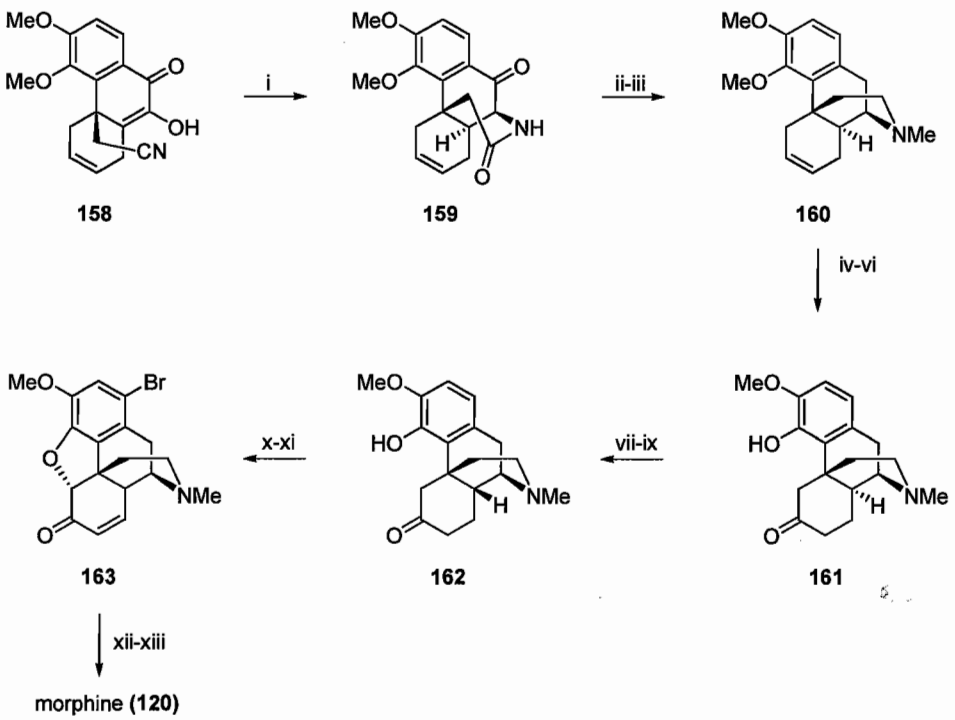
153 154 155 156 157 158

Reagents and conditions: (i) BzCl, pyridine, dioxane; (ii) $NaNO_2$, AcOH; (iii) a) Pd/C, H_2, AcOH; b) $FeCl_3$; (iv) a) SO_2; b) $(MeO)_2SO_2/K_2CO_3$; (v) KOH; (vi) $NaNO_2$, AcOH; (vii) a) Pd/C, H_2; b) $FeCl_3$; (viii) a) $NCCH_2CO_2Et$, EtOH, NEt_3; b) $K_3Fe(CN)_6$; (ix) KOH, MeOH; (x) 1,3-butadiene, AcOH.

Scheme 16. Gates' synthesis of Diels-Alder product **159**.[123]

Gates used a copper chromite reductive amination procedure to close the heterocyclic D-ring. Keto amide **159** was reduced using Wolf-Kishner conditions, and then methylated to give *N*-methyl piperidine **160**. Resolution of **160** was accomplished via a crystallization protocol employing D-dibenzoyltartaric acid. At

this stage, the undesired stereochemistry at the C-14 position needed to be corrected. Bromination of ketone **161**, followed by treatment with 2,4-dinitrophenylhydrazine, acidic isomerisation, and hydrogenation provided **162**. Closure of the E-ring proceeded by bromination of **162** followed by treatment with 2,4-dinitrophenylhydrazine, which activated the C-5 position for attack by the phenolic hydroxyl. The synthesis was completed by hydrolysis, hydrogenation of the aryl halide and enone reduction.

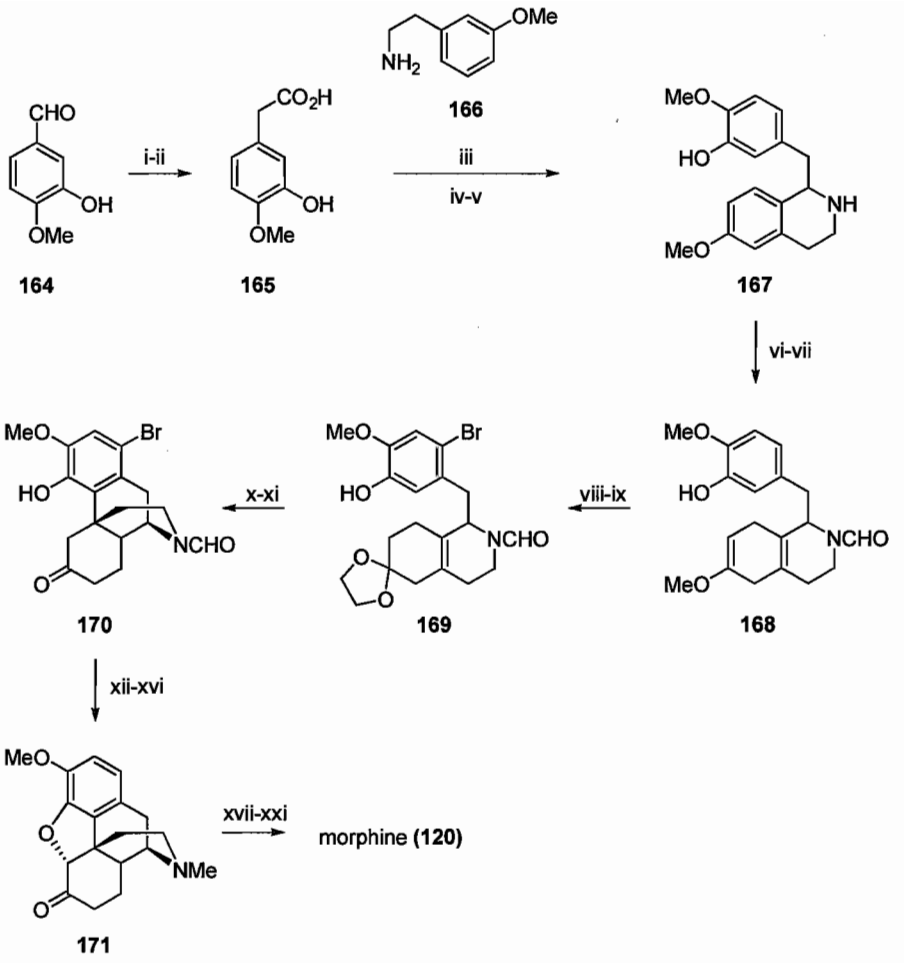


Reagents and conditions: (i) 68-98 atm H_2, CuO, Cr_2O_3, EtOH, 135°C; (ii) N_2H_4, KOH; (iii) a) MeI, NaH; b) $LiAlH_4$; (iv) H_2SO_4, H_2O; (v) KOH, $(HOCH_2CH_2)_2O$; (vi) KO*t*Bu, Ph_2CO; (vii) a) Br_2; b) 2,4-DNPH; (viii) HCl; (ix) H_2, PtO_2; (x) a) Br_2; b) 2,4-DNPH; (xi) HCl; (xii) $LiAlH_4$, THF; (xiii) pyridine-HCl, 220°C.

Scheme 17. Gates' synthesis of morphine.[123]

Rice (1980)[125-6]

Rice completed arguably the most practical synthesis of morphine in 1980 using a biomimetic approach. Carboxylic acid **165** and amine **166** (Scheme 18) are structurally similar to dopamine (**125**) and 4-hydroxyphenylacetaldehyde (**126**), the two coupling partners in the biosynthesis of morphine (Figure 14). Condensation between **165** and **166** provided an amide which was cyclized using a Bischler-Napieralski reaction. Reduction of the resulting cyclic imine with sodium cyanoborohydride was followed by a dissolving metal reduction and treatment with phenyl formate to provide formamide **168**. Bromination of the aryl ring was followed by ketal formation to afford olefin **169**. Grewe cyclization and acidic hydrolysis provided ketone **170**, an intermediate with four of the five rings installed. Acidic deformylation in the presence of methanol yielded the *N*-methyl piperidine ring, while bromination of the cyclohexanone ring initiated closure of the dihydrofuran ring. Hydrogenation of the aryl bromide provided dihydrocodeinone (**171**) a formal product in the synthesis of morphine and other opium alkaloids.



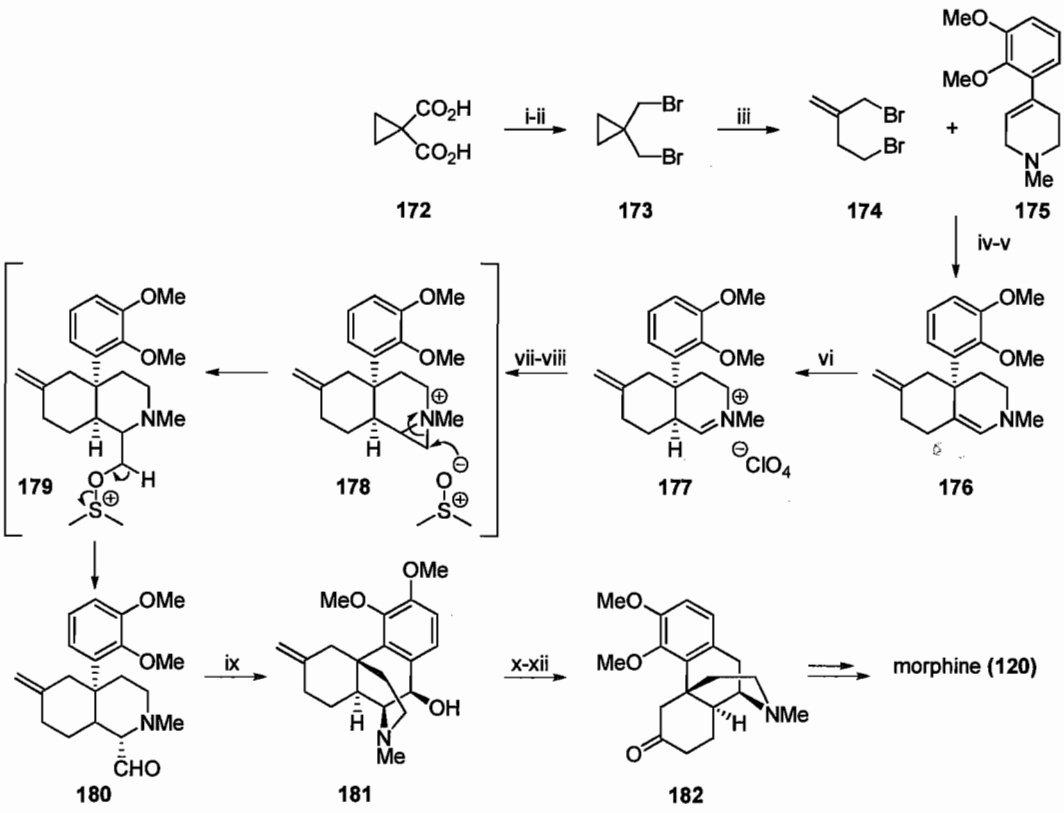
Reagents and conditions: (i) $NaHSO_3$; (ii) KCN, H_2SO_4; (iii) **166**, 200°C; (iv) $POCl_3$, MeCN; (v) $NaCNBH_3$, MeOH; (vi) Li, NH_3, THF, *t*-BuOH, -55 to -65°C; (vii) PhOCHO, EtOAc; (viii) $(CH_2OH)_2$, THF, $MeSO_3H$, r.t.; (ix) $CH_3CONHBr$, 0°C; (x) HCO_2H-H_2O (5:1), r.t.; (xi) NH_4·HF, CF_3SO_3H, 0°C; (xii) a) MeOH, HCl, reflux; b) NH_3-H_2O, *i*PrOH; (xiii) H_2, Pd/C, AcOH, HCOH; (xiv) Br_2, AcOH; (xv) NaOH, $CHCl_3$; (xvi) H_2, AcOH-HCHO; (xvii) $ClCO_2Et$; (xviii) PhSeCl; (xix) $NaIO_4$; (xx) $NaBH_4$; (xxi) BBr_3, $CHCl_3$.

Scheme 18. Rice's synthesis of morphine.[125-126]

Evans (1982)[127]

Evans completed one of the more creative syntheses of morphine in 1982. The synthesis begins with the bromination of diacid **172** and is followed by a cyclopropyl rearrangement to furnish the terminal olefin **174** (Scheme 19). Treatment of the tetrahydropyridine **175**, which was prepared in 2 steps from 1-methylpiperidin-4-one,

with *n*-butyl lithium provided a lithiated species which condensed with dibromide **174** to yield isoquinoline derivative **176**. The corresponding perchlorate salt **177** reacted with diazomethane to form aziridinium **178**, which underwent a Kornblum-type oxidation with dimethyl sulfoxide to afford aldehyde **180**. The B-ring was formed via a Lewis acid catalyzed ring closure and provided alcohol **181**. The hydroxyl was removed by a mesylation/ hydride elimination procedure, while a Lemieux-Johnson oxidation installed the ketone functionality. The resulting tetracycle **182** can be epimerized using a Gates procedure[124] to the natural isomer and thus complete a formal synthesis.

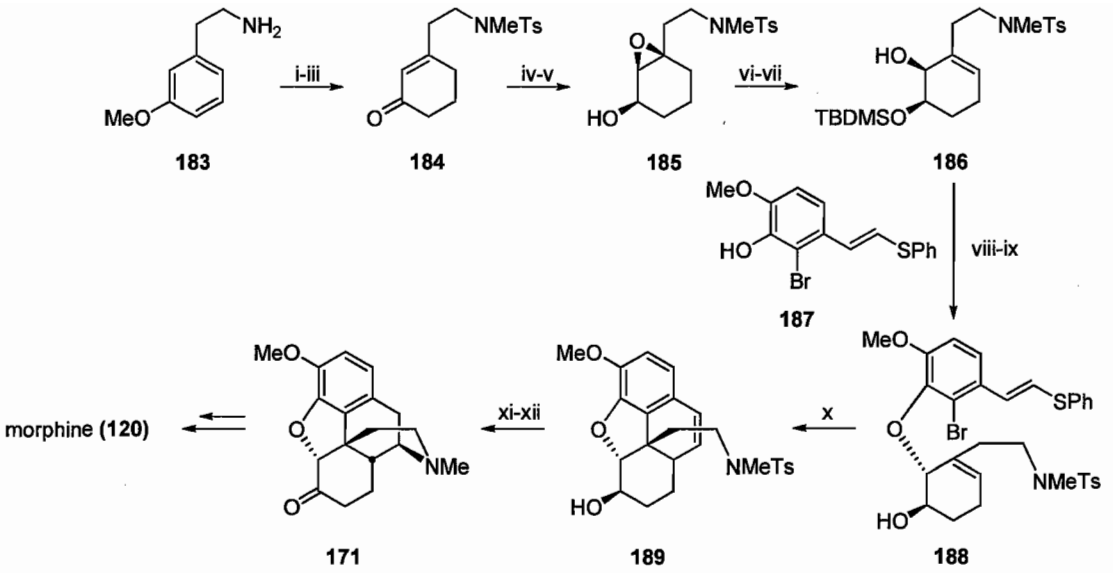


Reagents and conditions: (i) BH_3, THF; (ii) PBr_3, HBr, DCM; (iii) $ZnBr_2$, PhH, 80°C; (iv) a) *n*BuLi, THF, -10°C; b) **175**, Et_2O, -78°C; (v) NaI, K_2CO_3, MeCN, 80°C; (vi) a) $HClO_4$, Et_2O; b) MeOH; (vii) CH_2N_2, Et_2O; (viii) DMSO, r.t.; (ix) $BF_3{\cdot}Et_2O$, PhMe, -10°C; (x) MsCl, NEt_3; (xi) $LiEt_3BH$; (xii) OsO_4, $NaIO_4$.

Scheme 19. Evans' formal synthesis of morphine.[127]

Parker (1992)[128-9]

In 1992, Parker disclosed a formal synthesis of morphine by a tandem radical cyclization strategy. Birch reduction of *m*-methoxyphenethylamine **(183)** and tosylation of the primary amine was followed by acidic hydrolysis of the enol ether (Scheme 20). Treatment with methyl iodide effected the formation of enone **184.** Luche reduction of the ketone provided an allylic alcohol which directed the epoxidation of the olefin. Epoxy alcohol **185** was treated with titanium isopropoxide to provide an allylic diol, whose distal hydroxyl was protected as its *tert*-butyldimethylsilyl ether. Mitsunobu coupling of alcohol **186** with phenol **187** and desilylation with hydrofluoric acid afforded advanced intermediate **188.** Treatment of **188** with tri-*n*-butyltin hydride at 130°C in a sealed tube resulted in a tandem cyclization followed by fragmentation/ elimination of the thiophenyl radical. This remarkable sequence links the aryl and cyclohexene rings and forms the B-ring with the desired stereochemistry at C-13 and C-14. A dissolving metal reduction removed the tosyl group and generated a nitrogen radical, or anion, which attacked the β-carbon of the styrene moiety thus providing the piperidine ring. A Swern oxidation completes the formal synthesis by producing (+/–)-dihydrocodeinone **(171).**

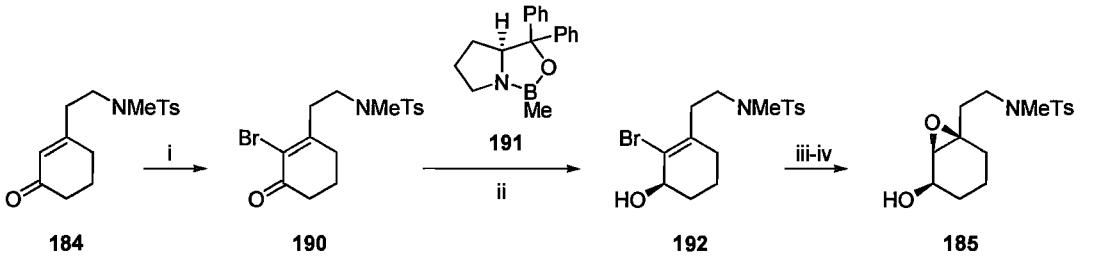


Reagents and conditions: (i) Li/NH_3, *t*-BuOH, -68°C; (ii) a) TsCl, NEt_3, THF; b) 1N HCl; (iii) MeI, K_2CO_3, $CO(Me)_2$; (iv) $NaBH_4$, $CeCl_3$, MeOH; (v) *m*-CPBA, DCM, 0°C; (vi) $Ti(OiPr)_4$, PhH, 70°C; (vii) TBDMSOTf, *i*-Pr_2NEt, -78°C; (viii) PBu_3, DEAD, THF, 0°C; (ix) 10% HF, MeCN; (x) *n*-Bu_3SnH, AIBN, PhH, 130°C, sealed tube; (xi) Li/NH_3, *t*-BuOH, THF, -78°C; (xii) $(COCl)_2$, DMSO, 0°C to r.t.

Scheme 20. Parker's formal synthesis of morphine.[128]

Parker has also described an asymmetric route to morphine through the preparation of a single isomer of chiral epoxy alcohol **185**.[130] The most obvious methods are a chiral reduction of enone **184** or a Sharpless kinetic resolution of the racemic allylic alcohol. Parker notes that these methods are not ideal for 3-substituted-2-cyclohexanones and therefore attempted to use Terashima's reagent instead. The poor selectivity (e.e. ~5%) of this method led to the development of the route shown in Scheme 21. Bromination of enone **184** in the presence of triethylamine yielded bromo-enone **190**, a suitable substrate for a Corey-Bakshi-Shibata reduction. Reduction with the (*S*)-isomer of the oxazaborolidine reagent afforded alcohol **192** with an e.e. of >82%. Reduction of C-Br bond with a sodium-mercury amalgam was followed by *meta*-chloroperoxybenzoic acid-mediated

epoxidation to give the chiral morphine intermediate **185** with an 80% e.e. (Mosher's ester analysis).



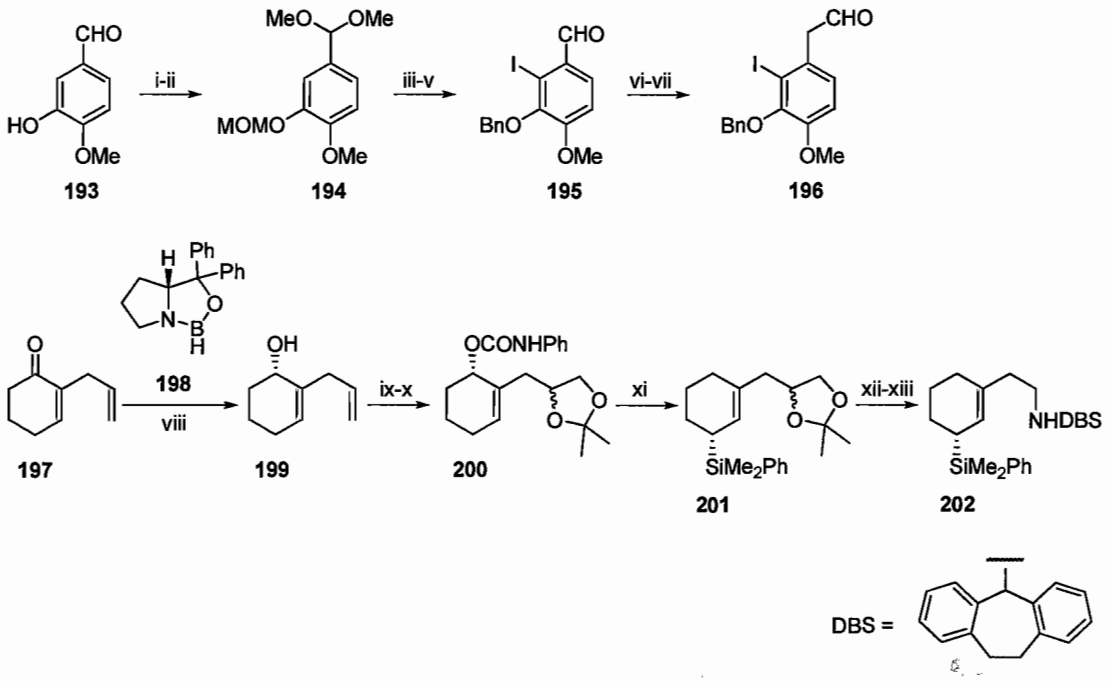
Reagents and conditions: (i) Br_2, NEt_3; (ii) **191**, catechol borane; (iii) Na(Hg), THF, MeOH; (iv) *m*-CPBA

Scheme 21. Parker's asymmetric synthesis of epoxide **185**.[130]

Overman (1993)[131]

Overman published an enantiodivergent approach to both morphine and dihydrocodeinone in 1993. As with many other syntheses, Overman coupled together the aryl A-ring with C-ring early in the synthesis. The aryl portion started from aldehyde **193**, which was converted in two steps to ketal **194** (Scheme 22). Lithiation and exposure to iodine, followed by acidic hydrolysis and phenol protection afforded aldehyde **195**. Reaction with dimethylsulfonium methylide formed an epoxide which underwent a Lewis acid-catalyzed rearrangement to construct homologous aldehyde **196**. Overman formed the coupling partner **202** using an asymmetric Mannich reaction which he developed in 1993.[132] First, the commercially available 2-allylcyclohex-2-enone (**197**) was selectively reduced using catecholborane (*R*)-oxazaborolidine **198** to afford alcohol **199**, an intermediate in the synthesis of (–)-morphine (natural isomer). The (*S*)-isomer of oxazaborolidine **198** could just as easily been used to provide an intermediate in the synthesis of (+)-morphine (unnatural isomer). Alcohol **199** was condensed with phenyl isocyanate, and the resulting

intermediate was oxidized with osmium tetroxide to provide a diol which was then protected as its acetonide. Carbamate **200** was reacted with *n*-butyl lithium in the presence of $CuI(PPh_3)_2$, and then treated with $PhMe_2SiLi$ to provide allylsilane **201**. Acidic hydrolysis of the acetonide and subsequent reductive amination with dibenzosuberylamine (DBS-NH_2) and sodium cyanoborohydride provided coupling partner **202**.

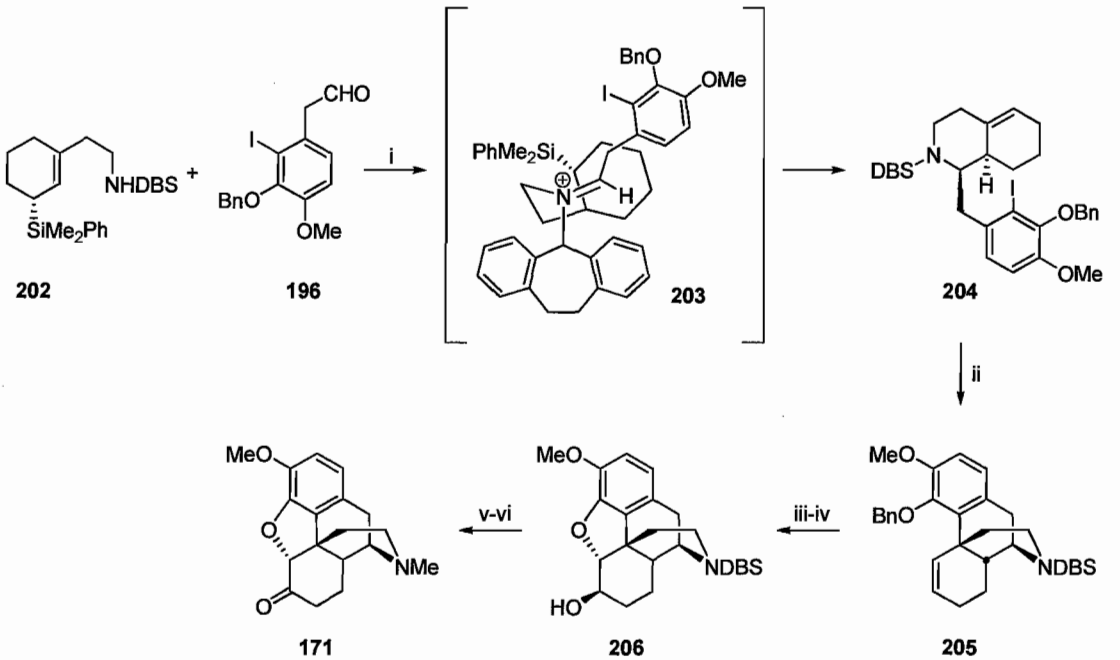


Reagents and conditions: (i) $HC(OMe)_3$, HCl; (ii) NaH, $ClCH_2OMe$; (iii) *n*-BuLi, I_2; (iv) 6N HCl; (v) BnBr, K_2CO_3; (vi) CH_2SMe_2; (vii) $BF_3{\cdot}Et_2O$, THF; (viii) **198**, catechol borane; (ix) PhN=C=P; (x) OsO_4, NMO, $(CH_3)_2CO$, H^+; (xi) a) *n*-BuLi, THF, -30°C; b) $CuI(PPh_3)_2$, 0°C; c) $PhMe_2SiLi$, 0°C; (xii) *p*-TsOH, $NaIO_4$, MeOH; (xiii) DBS-NH_2, $NaCNBH_3$.

Scheme 22. Overman's synthesis of morphine precursors **196** and **202**.[131]

Reaction between aldehyde **196** and homoallylic amine **202** in the presence of zinc(II)iodide gave octahydroisoquinoline **204** as a 20:1 mixture of diastereomers. The selectivity of the reaction results from a preferential approach of an (*E*)-iminium ion intermediate **203** to the cyclohexenylsilane ring from the face opposite to the silyl

group. Heck cyclization using $Pd(OCOCF_3)_2(PPh_3)_2$ gave the unsaturated morphinan **205**. Removal of the benzyl ether, followed by treatment of the resulting phenol with camphorsulfonic acid and 3,5-dinitroperoxybenzoic acid, afforded **206**. Oxidation and hydrogenolysis of the DBS group provided dihydrocodeinone (**171**) a formal product in the synthesis of morphine and other opium alkaloids.



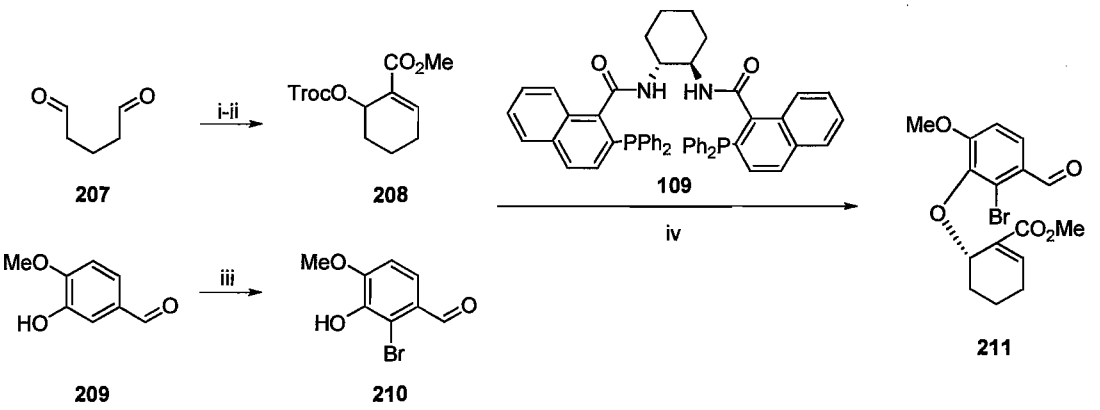
Reagents and conditions: (i) ZnI_2, EtOH, 60°C; (ii) $Pd(OCOCF_3)_2(PPh_3)_2$, PMP, PhMe, 120°C; (iii) $BF_3{\cdot}Et_2O$, EtSH; (iv) $3,5\text{-}(NO_2)_2PhCO_3$, $campSO_3H$, DCM, 0°C; (v) TPAP, NMO; (vi) H_2, $Pd(OH)_2$, HCHO.

Scheme 23. Overman's formal synthesis of morphine.[131]

Trost (2002)[133]

Trost's asymmetric allylic alkylation (AAA) procedure has been extensively used in the synthesis of many natural products.[134] In 2002, Trost applied this methodology to the synthesis of morphine. The synthesis begins with the reaction of glutaraldehyde (**207**) with a Horner-Wadsworth-Emmons reagent to provide a cyclohexenol derivative which was protected as its 2,2,2-trichlorethoxycarbonate. The

palladium-catalyzed AAA reaction between acrylate **208** and phenol **210** was performed in the presence of diphosphine ligand **109**. This method provided the coupled product **211** with an e.e. of 96%.

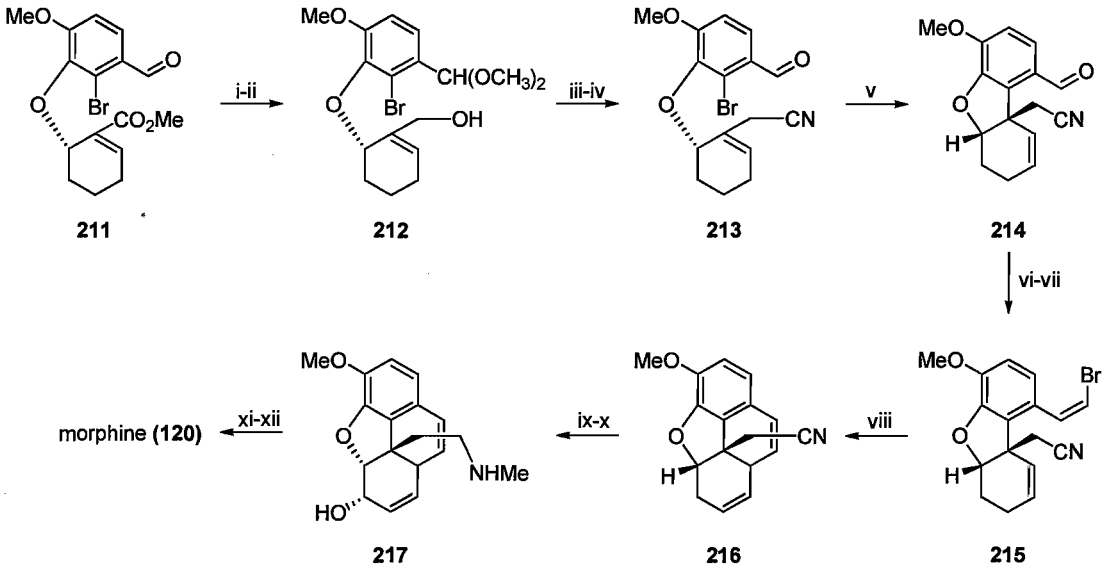


Reagents and conditions: (i) methyl 2-(dimethoxyphosphoryl)acetate, K_2CO_3, H_2O; (ii) Troc-Cl, pyridine, 0°C; (iii) Br_2, AcOH, NaOAc, r.t.; (iv) **109**, % $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$, NEt_3, DCM, r.t.

Scheme 24. Trost's synthesis of codeine intermediate **211**.[133, 135]

Aldehyde **211** was protected as a dimethoxy ketal prior to ester reduction with diisobutylaluminum hydride. Allylic alcohol **212** was reacted with acetone cyanohydrin in a modified Mitsunobu reaction to afford nitrile **214** after acidic hydrolysis of the ketal. A palladium(II)acetate catalyzed Heck reaction formed the C-13/ C-14 bond and three of the rings in morphine. The synthetic route to benzaldehyde **214** had been previously described by Trost when it was used in the synthesis of (–)-galanthamine.[135] Olefination of benzaldehyde **214**, followed by chemoselective reduction of the (*E*)-vinyl bromide, produced cyclization substrate **215**. A second Heck reaction, also catalyzed by palladium(II)acetate, formed the D-ring. Allylic oxidation with selenium dioxide proceeded at the least hindered position (C-6) to provide a ketone. Treatment with diisobutylaluminum hydride and then methylamine was followed by a sodium borohydride reduction. This sequence

furnished the *N*-methyl amine and allylic alcohol functionalities in advanced intermediate **217**. Irradiation with a 150W tungsten lamp effected the closure of the piperidine ring and completed the synthesis of codeine, which can be demethylated using a procedure developed by Rice[136] to give morphine.



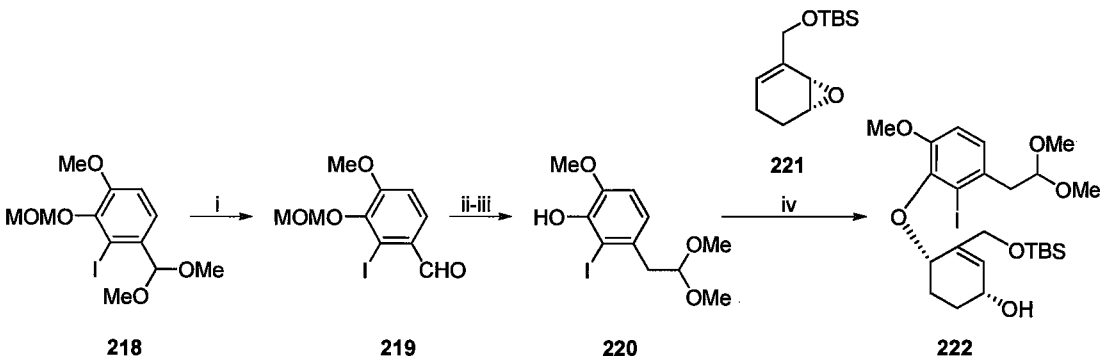
Reagents and conditions: (i) *p*-TsOH, $CH(OMe)_3$, MeOH; (ii) DIBAL-H, PhMe, -78°C; (iii) PPh_3, acetone cyanohydrin, DIAD, Et_2O; (iv) *p*-TsOH, THF, H_2O; (v) $Pd(OAc)_2$, dppp, Ag_2CO_3, PhMe, 107°C; (vi) CBr_4, PPh_3, DCM; (vii) $Pd(PPh_3)_4$, *n*-Bu_3SnH, $PhCH_3$; (viii) $Pd(OAc)_2$, dppp, Ag_2CO_3, PhMe; (ix) a) SeO_2, dioxane, sand, 75°C; b) DMP, r.t.; (x) a) DIBAL-H, DCM, Et_2O; b) NH_4Br, $MeNH_2$; c) $NaBH_4$; (xi) LDA, THF, 150W tungsten bulb; (xii) BBr_3, DCM, r.t.

Scheme 25. Trost's synthesis of morphine.[133]

Fukuyama (2006)[137]

In a similar manner to Overman,[131] Fukuyama employed a Mannich-type reaction in the synthesis of morphine. The synthesis begins with the preparation of two coupling pieces, **220** and **221**. The former was prepared in a three step procedure from ketal **218**, while the latter was previously synthesized by Fukuyama (Scheme 26).[138] This preliminary study employed racemic **221**, although a chiral version has

also been prepared. Treatment of phenol **220** with a palladium-ligand complex initiated its 1,4-addition to epoxide **221** and provided ether **222.**



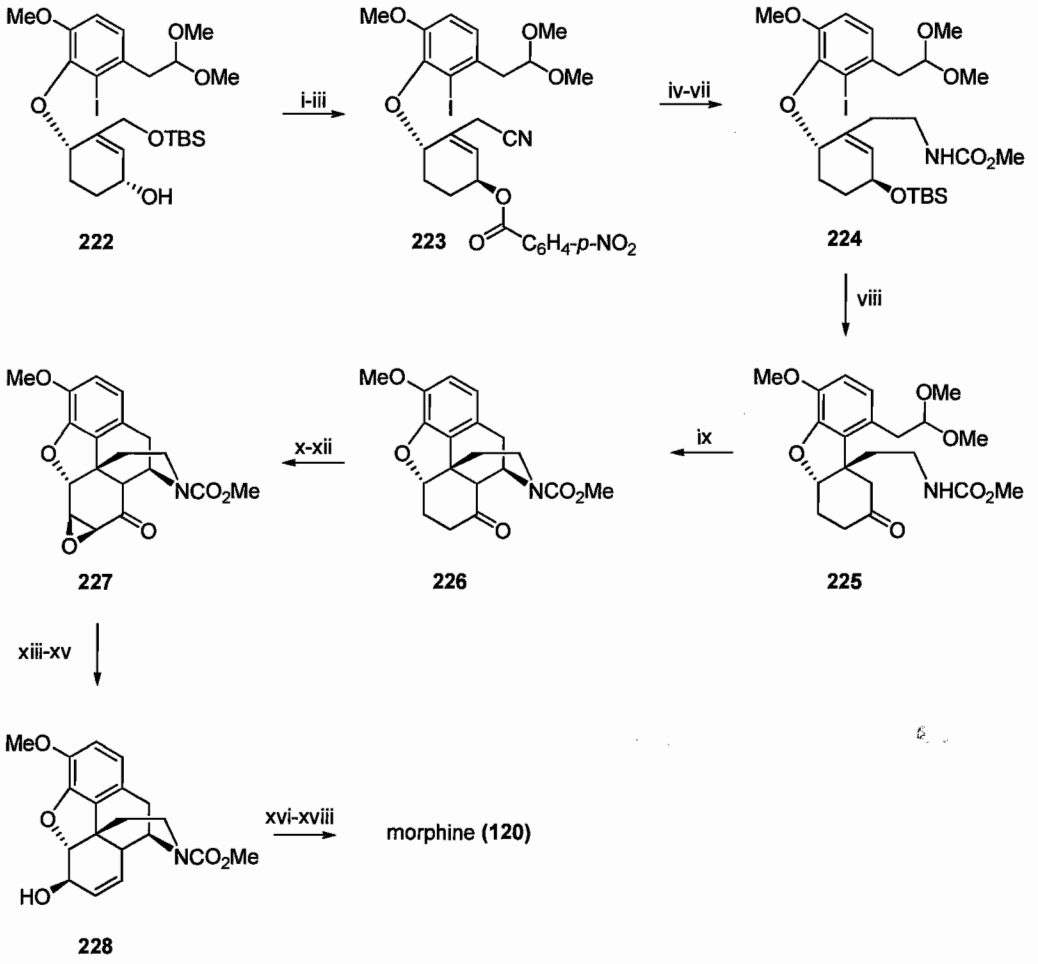
218 **219** **220** **222**

Reagents and conditions: (i) AcOH, THF, H_2O, 0°C; (ii) $MeOCH_2PPh_3Cl$, NaHMDS, THF; 0°C; (iii) HCl, MeOH, 40°C; (iv) $Pd_2(dba)_3$, P(2-furyl)$_3$, MeCN, r.t.

Scheme 26. Fukuyama's synthesis of morphine intermediate **222.**[137-138]

A Mitsunobu reaction between *p*-nitrobenzoic and allylic alcohol **222,** desilylation and a second Mitsunobu with 2-hydroxy-2-methylpropanenitrile provided nitrile **223** (Scheme 27). Ester hydrolysis and silylation of the resulting hydroxyl were performed prior to nitrile reduction and methyl carbamate formation. The next step was an intramolecular Heck coupling which provided a silyl enol ether that was immediately treated with tetra-*n*-butylammonium fluoride under basic conditions to afforded ketone **225**. Closure of the B and D-rings was accomplished in a single step by heating ketal **225** in methanolic hydrogen chloride; a transformation which Fukuyama believed to proceed through a Mannich-type reaction. Using a procedure developed by Itoh and Saegusa,[139] ketone **226** was converted to its silyl enol ether derivative and then treated with palladium(II)acetate. The resulting enone was oxidized with hydrogen peroxide to produce epoxide **227.** Treatment with sodium borohydride yielded an alcohol which was converted into its thiocarbamate derivative. Exposure to radical conditions induced an epoxide opening reaction and

Barton-McCombie deoxygenation to yield allylic alcohol **228**, which was then oxidized with Dess-Martin periodinane. Treatment with lithium aluminum hydride reduced both the ketone and methyl carbamate functionalities to provide codeine, which was easily demethylated using Rice's boron(III) bromide procedure[136] to give morphine.

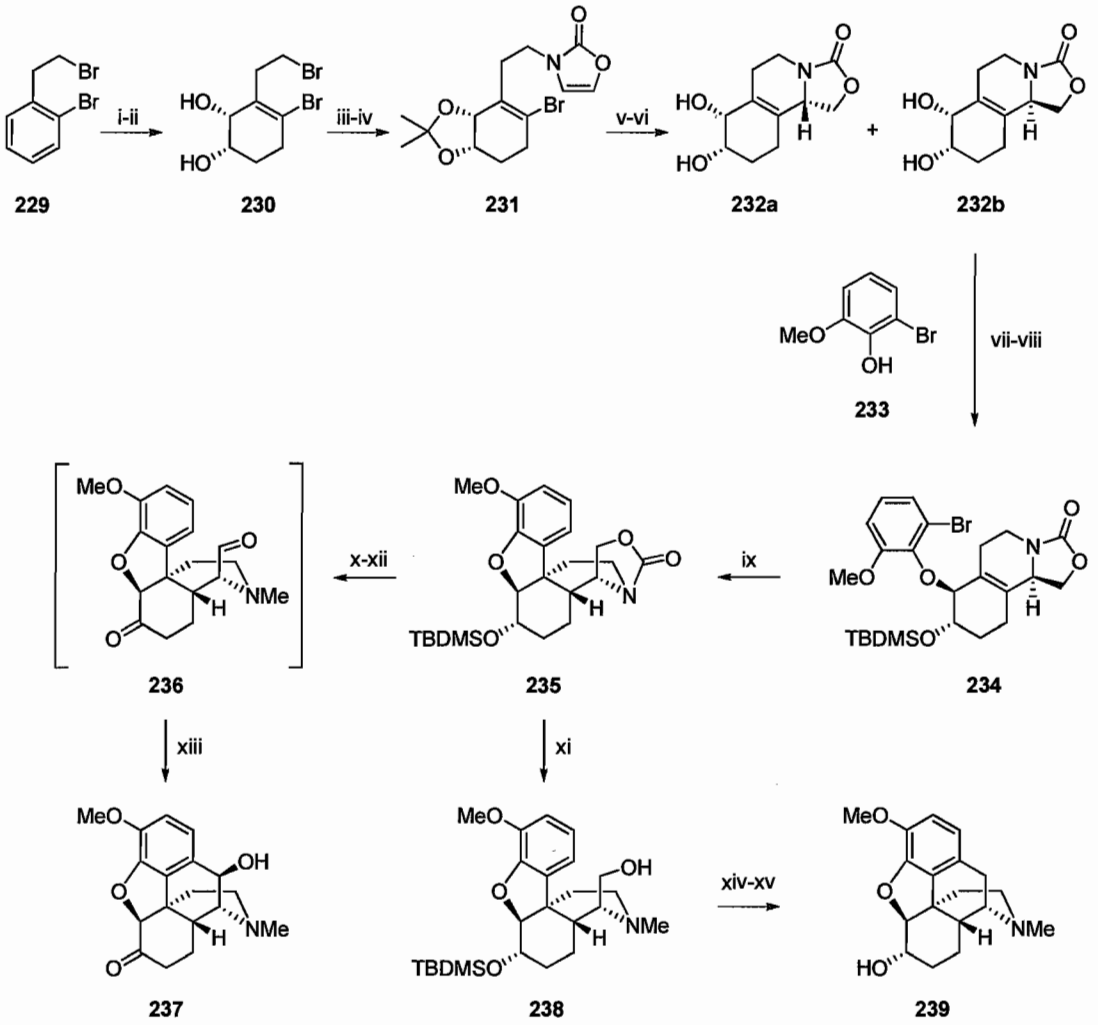


Reagents and conditions: (i) *p*-nitrobenzoic acid, DEAD, PPh_3, PhMe, THF, 0°C; (ii) CSA, MeOH; (iii) 2-hydroxy-2-methylpropanenitrile, DEAD, PPh_3, PhMe, 0°C; (iv) $LiBH_4$, Et_2O, MeOH, 0°C; (v) TBS-Cl, imidazole, DMF, r.t.; (vi) a) DIBAL-H, DCM, -78°C; b) $NaBH_4$, MeOH, -78°C; (vii) $ClCO_2Me$, K_2CO_3; (viii) a) $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, NEt_3, MeCN, reflux; b) TBAF, r.t.; (ix) HCl, MeOH, reflux; (x) TMS-Cl, LHMDS, THF, 0°C; (xi) $Pd(OAc)_2$, MeCN, r.t.; (xii) H_2O_2, H_2O, NaOH, MeCN, 0°C; (xiii) $NaBH_4$, MeOH, DCM; (xiv) TCDI, DMAP, $ClCH_2CH_2Cl$, 60°C; (xv) Et_3B, *n*-Bu_3SnH, THF, r.t.; (xvi) Dess-Martin periodinane, DCM, r.t.; (xvii) $LiAlH_4$, THF; (xviii) BBr_3, DCM, r.t.

Scheme 27. Fukuyama's synthesis of morphine.[137]

Hudlicky's Radical Cyclization Approach (1996)[140-3]

In parallel to Parker's efforts,[128-30] Hudlicky has developed several approaches to the morphine skeleton via a radical cyclization. In each instance, the chirality of the starting materials arose from the enzymatic *cis*-dihydroxylation of an aryl substrate. The first approach discussed employs the 1,2-diol metabolite of 1-bromo-2-(2-bromoethyl)benzene (**229**) (Scheme 28). Selective reduction of the unsubstituted olefin using potassium azodicarboxylate (PAD) under acidic conditions provides diol **230**. Acetonide protection was followed by displacement of the alkyl bromide with oxazol-2(3H)-one. Exposure of vinyl bromide **231** to *n*-tributyltin hydride, and then an acidic Dowex resin (50X8-100), afforded a 2:1 mixture of **232a** and **232b**. The synthesis continued with the latter because of its relative abundance to the former, even though it contains the unnatural stereochemistry seen in morphine. Protection of the homoallylic hydroxyl with *tert*-butyldimethylsilyl trifluoromethanesulfonate was followed by a Mitsunobu coupling reaction with the allylic hydroxyl and phenol **233**. An intramolecular radical cyclization between the aryl bromide and olefin of **234** proceeded with excellent stereospecificity providing only diastereomer **235**. Reduction of the dihydrooxazolone ring with DIBAL-H, desilylation, and Swern oxidation afforded a ketoaldehyde intermediate **236** which was immediately treated with trifluoromethanesulfonic acid to initiate closure of the D-ring. Reduction of ketone **237** and epimerization of the C-14 position[144] would provide ent-codeine or ent-morphine upon demethylation. If carbamate **235** is reduced directly, the resulting hydroxyl **238** serves as another means of forming the C10-C11 bond after mesylation and displacement.

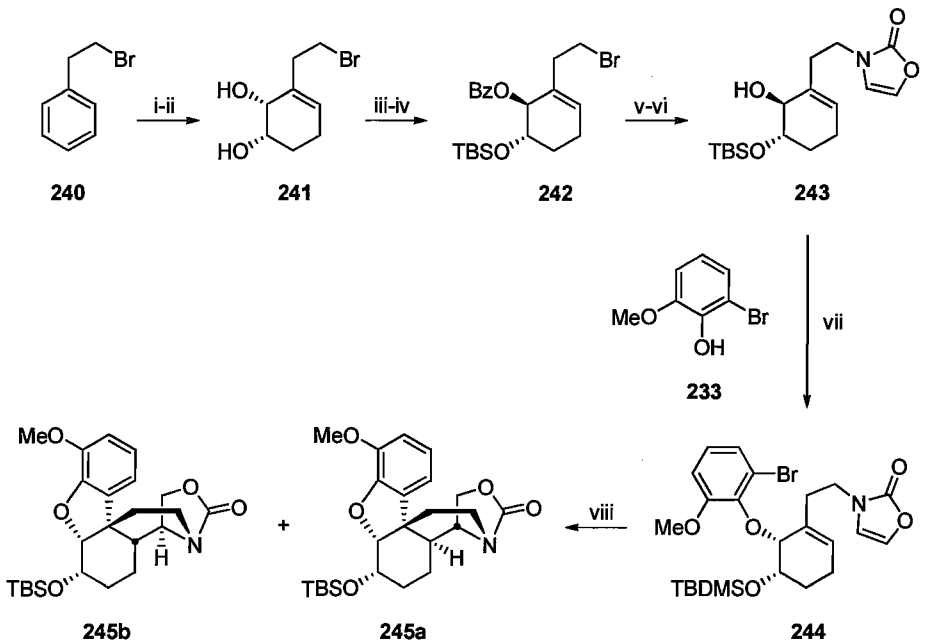


Reagents and conditions: (i) *E. coli* JM109 (pDTG602); (ii) PAD, AcOH, MeOH; (iii) 2,2-DMP, *p*-TsOH; (iv) oxazol-2(3H)-one, NaH, DMSO; (v) *n*-Bu_3SnH, AIBN, PhH, reflux; (vi) Dowex 50X8-100, MeOH, H_2O; (vii) TBDMS-OTf, *i*-Pr_2NEt, THF, -78°C; (viii) **233**, DEAD, *n*-Bu_3P, THF, 0°C; (ix) *n*-Bu_3SnH, AIBN, PhH, reflux; (x) TBAF, THF; (xi) DIBAL-H, DCM, 0°C; (xii) ClCOCOCl, DMSO, NEt_3, DCM, -78°C to 0°C; (xiii) CF_3SO_3H; (xiv) MsCl, NEt_3, THF; (xv) $AlCl_3$, PhH, reflux.

Scheme 28. Hudlicky's approach to the morphine skeleton.[140]

Hudlicky's second radical cyclization approach began with the toluene dioxygenase mediated dihydroxylation of (2-bromoethyl)benzene **(240)** (Scheme 29). As with the first approach, diazene reduction occurs on the unsubstituted alkene to provide 1,2-diol **241**. Silylation of the homoallylic alcohol and Mitsunobu inversion of the allylic hydroxyl with benzoic acid afforded **242**. Displacement of the alkyl

halide with oxazol-2(3H)-one and basic ester hydrolysis produced allylic alcohol **243**. A second Mitsunobu reaction with phenol **233** provided ester **244**. Radical cyclization was effected with tris(trimethylsilyl)silane and azobisisobutyronitrile to afford pentacycle **245a**, and evidence for the formation of **245b**. The method to close the D-ring previously employed by Hudlicky would complete the morphine skeleton.



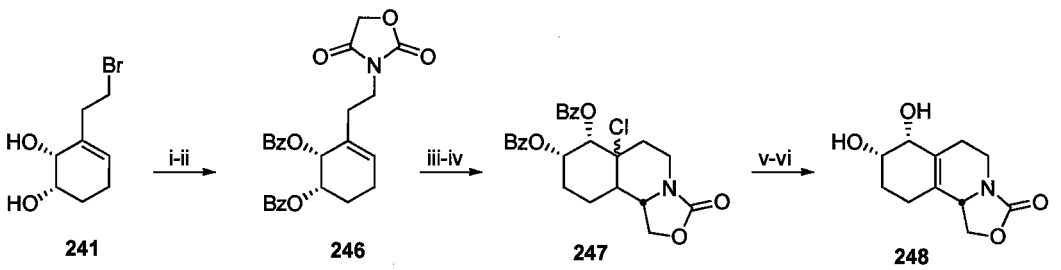
Reagents and conditions: (i) *E. coli* JM109 (pDTG602); (ii) PAD, AcOH, MeOH; (iii) TBS-OTf, *i*-Pr_2NEt, THF, -78°C; (iv) $PhCO_2H$, *n*-Bu_3P, DEAD, THF; (v) oxazol-2(3H)-one, NaH, DMSO; (vi) NaOH, H_2O; (vii) **233**, *n*-Bu_3P, DEAD, THF; (viii) $(TMS)_3SiH$, AIBN, PhH, 140°C, sealed tube.

Scheme 29. Hudlicky's second approach to morphine skeleton.[142]

Hudlicky's Heck Cyclization Approach (1999)[143, 145-9]

In addition to the radical cyclization approach, Hudlicky also explored the possibility of an analogous Heck reaction to form the C12-C13 bond. The first route discussed begins with the *cis*-dihydrodiol obtained from the oxidation of (2-bromoethyl)benzene (Scheme 30). Olefin reduction provided 1,2-diol **241** which was first treated with *N,N'*-dicyclohexylcarbodiimide/ benzoic acid and then oxazolidine-

2,4-dione to furnish alkene **246**. Selective reduction with sodium borohydride and treatment with aluminum chloride effected a cyclization reaction to provide carbamate **247**. Chloride elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene and basic ester hydrolysis yielded diol **248**.

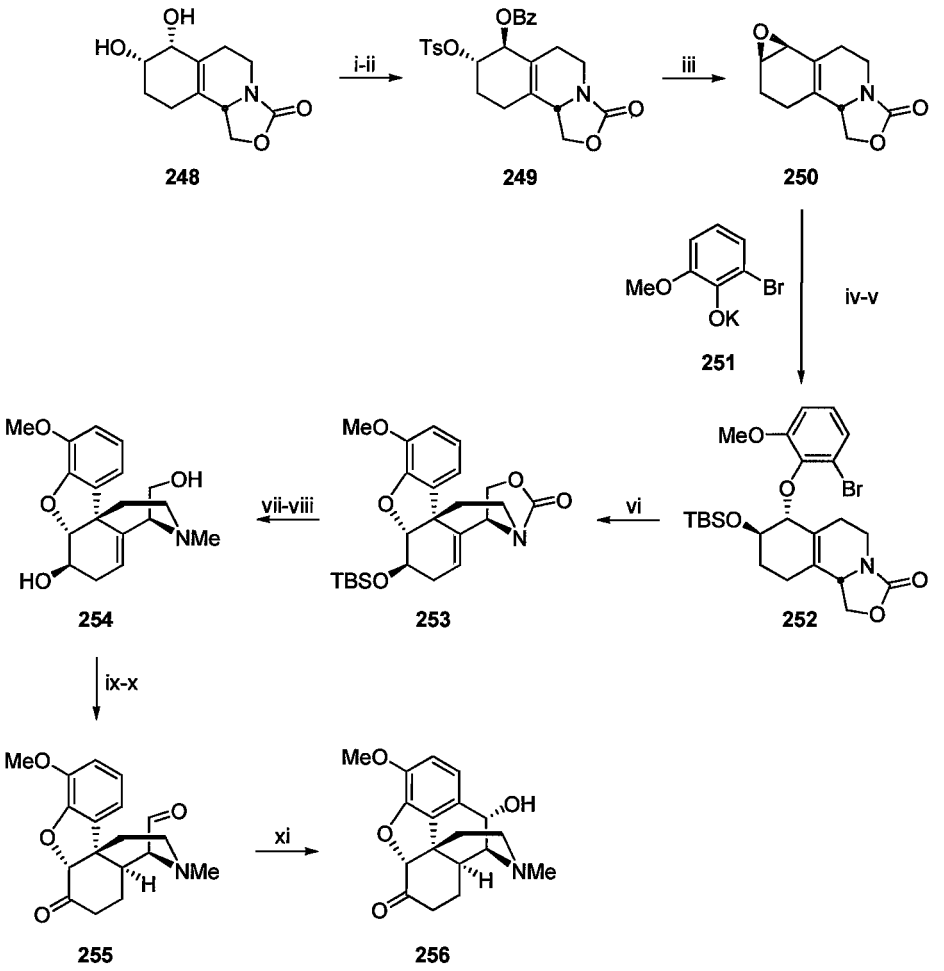


241 **246** **247** **248**

Reagents and conditions: (i) $PhCO_2H$, DCC, DCM; (ii) oxazolidine-2,4-dione, tetramethylguanidine, THF, reflux; (iii) $NaBH_4$, MeOH; (iv) $AlCl_3$, DCM; (v) DBU, DMSO, reflux; (vi) LiOH, MeOH.

Scheme 30. Hudlicky's synthesis of isoquinoline derivative **248**.[143,145]

The homoallylic hydroxyl of **248** was protected with 4-toluenesulfonyl chloride and a Mitsunobu inversion of the allylic hydroxyl with benzoic acid provided **249** (Scheme 31). Basic hydrolysis with sodium methoxide initiated the formation of vinyl epoxide **250**. Regioselective opening with potassium salt **251**, and protection of the resulting hydroxyl as its *tert*-butyldimethylsilyl ether, afforded **252**. A Heck reaction catalyzed by tetrakis(triphenylphosphine)palladium(0) provided pentacyclic carbamate **253**. Reduction with diisobutylaluminum hydride and desilylation furnished dihydroxyl **254**. Hydrogenation with Adams' catalyst and double hydroxyl oxidation with Swern conditions provided aldehyde **255**. Treatment with trifluoromethanesulfonic acid closed the D-ring and produced hydroxyl **256**. As previously described, this compound can be easily converted (–)-morphine.

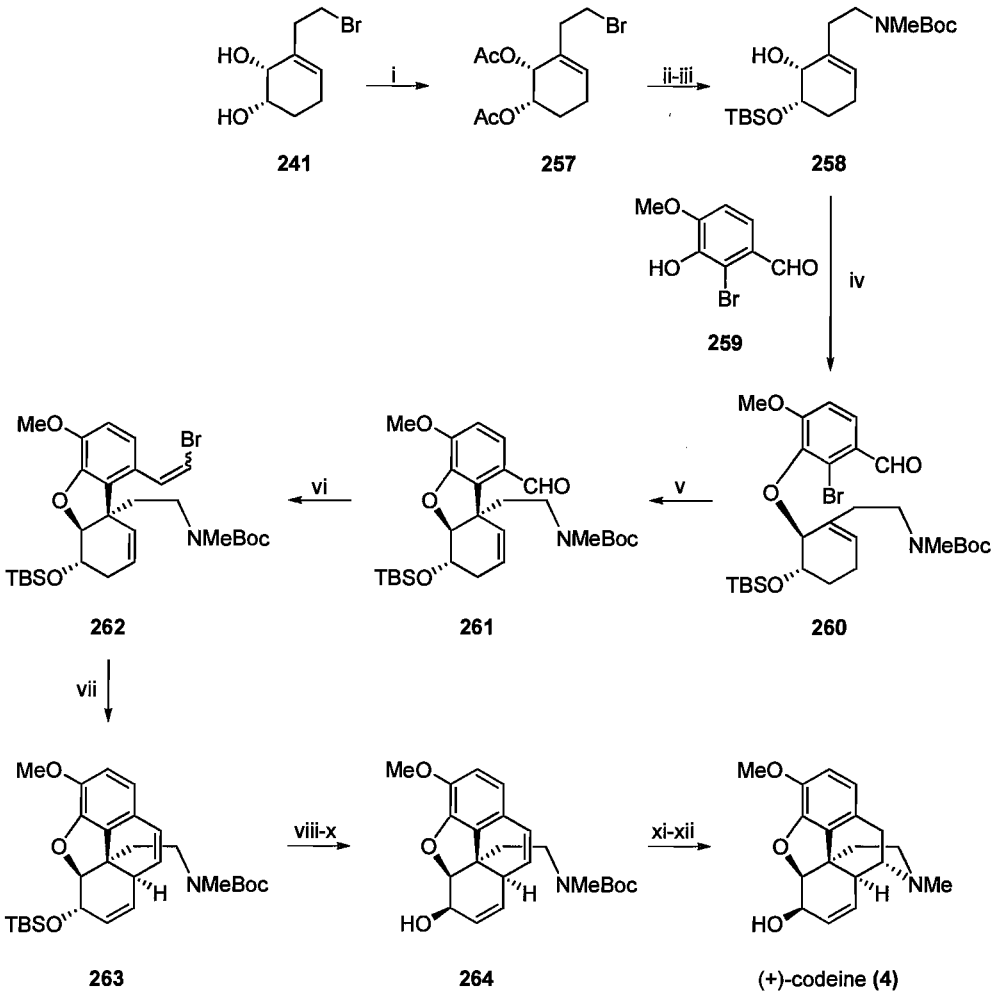


Reagents and conditions: (i) TsCl, pyridine, DMAP; (ii) $PhCO_2H$, PPh_3, DEAD, THF; (iii) MeONa, MeOH, THF; (iv) **251**, DME, 18-crown-6; (v) TBS-OTf, , *i*-Pr_2NEt, DCM; (vi) $Pd(PPh_3)_4$, Proton Sponge™, PhMe; (vii) DIBAL-H, DCM; (viii) TBAF, THF; (ix) H_2, PtO_2, AcOH; (x) $(COCl)_2$, DMSO, NEt_3, DCM; (xi) CF_3SO_3H.

Scheme 31. Hudlicky's third approach to morphine skeleton.[148]

In 2007, Hudlicky employed two intramolecular Heck cyclizations in the total synthesis of (+)-codeine.[147] This synthesis exploits the same 1,2-diol **241** discussed in previous approaches (Scheme 32). The diacetate derivative **257** was treated with methylamine and then di-*tert*-butyl dicarbonate. This sequence displaced the bromide, protected the resulting secondary amine and hydrolyzed the acetates. Silylation of the distal hydroxyl provided allylic alcohol **258**, which was reacted with phenol **259**

under Mitsunobu conditions to afford aryl bromide **260**. The first Heck reaction, catalyzed by palladium(II)acetate, formed the dihydrofuran E-ring. The resulting aldehyde **261** was converted to vinyl bromide **262** via a Wittig reaction. The second Heck cyclization closed the B-ring and provided tetrahydrophenanthrene derivative **263**. Removal of the silyl group revealed a hydroxyl which was inverted by a 2-iodoxybenzoic acid oxidation/ borohydride reduction procedure. Hydrolysis of the *tert*-butyl carbamate **264** provided a secondary amine suitable for the final ring closure. Oxymercuration of the styrene olefin produced a mercurium ion which was quenched by attack of the ethylamino group on the C-9 position. Subsequent reduction with LAH completed the total synthesis of (+)-codeine **(4)**.

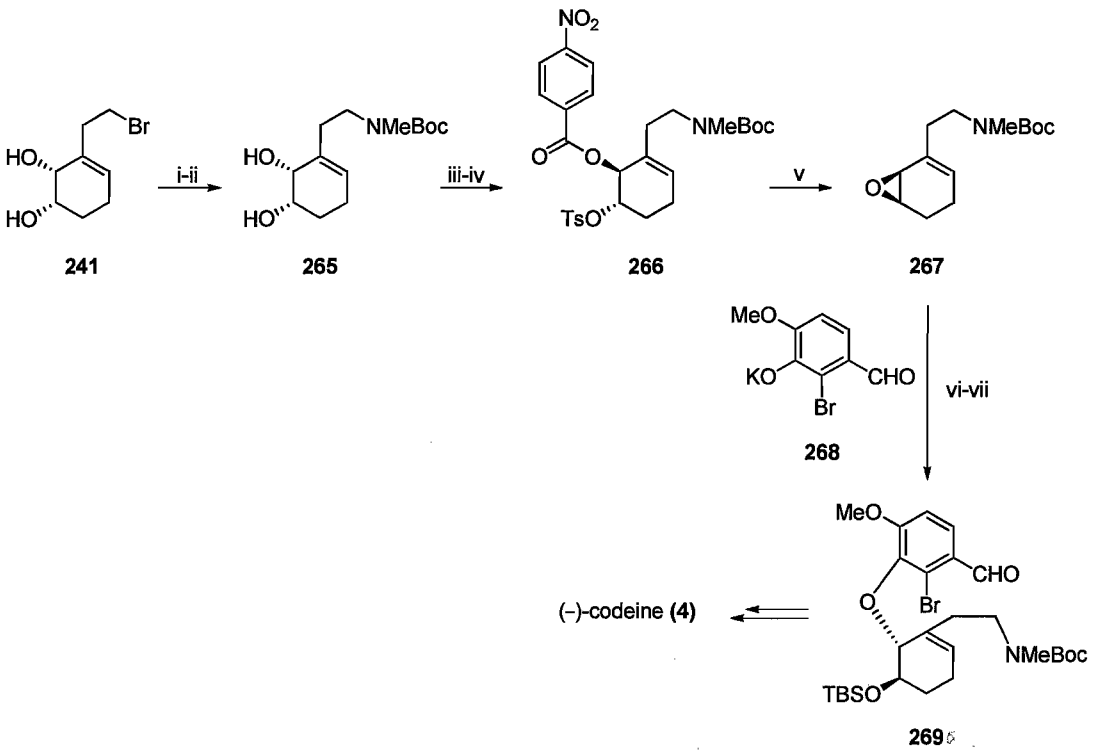


Reagents and conditions: (i) Ac_2O, NEt_3, DMAP, DCM, 0°C; (ii) a) $MeNH_2$, K_2CO_3, THF, -40°C to r.t.; b) $(Boc)_2O$, NEt_3, MeOH; (iii) TBS-Cl, imidazole, DCM, -78°C to r.t.; (iv) *n*-Bu_3P, DIAD, THF, 0°C; (v) $Pd(OAc)_2$, Ag_2CO_3, dppf, PhMe, 110°C; (vi) $PPh_3CH_2Br_2$, *t*-BuOK, THF, -60°C; (vii) $Pd(OAc)_2$, Ag_2CO_3, dppp, PhMe, 110°C; (viii) TBAF, THF, r.t.; (ix) IBX, DMF, r.t.; (x) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0°C; (xi) TFA-DCM (1:4), 0°C; (xii) a) $Hg(OAc)_2$, NEt_3, THF; b) $LiAlH_4$, r.t.

Scheme 32. Hudlicky's synthesis of (+)-codeine.[147]

Hudlicky also synthesized the natural (–)-isomer of codeine from the same 1,2-diol **241**, demonstrating the enantiodivergent character of this approach. In this synthesis, displacement of the bromide with methylamine and subsequent *tert*-butyl carbamate protection provided diol **265** (Scheme 33). Protection of the distal hydroxyl with 4-toluenesulfonyl chloride and Mitsunobu inversion of the allylic

hydroxyl with 4-nitrobenzoic acid yielded ester **266**. Exposure to sodium methoxide hydrolyzed the ester and formed vinyl epoxide **267**. Regioselective ring opening with potassium salt **268** and subsequent silylation of the C-6 hydroxyl afforded ether **269**. This compound is identical to **260** (Scheme 32) except for the sign of its optical rotation.



Reagents and conditions: (i) Ac_2O, NEt_3, DMAP, DCM, 0°C; (ii) a) $MeNH_2$, K_2CO_3, THF, -40°C to r.t.; b) $(Boc)_2O$, NEt_3, MeOH; (iii) TsCl, NEt_3, DMAP, DCM, 0°C to r.t.; (iv) 4-nitrobenzoic acid, DIAD, PPh_3, THF, 0°C; (v) NaOMe, MeOH, 0°C; (vi) **268**, 18-crown-6, DME-DMF (1:1); 80°C; (vii) TBSCl, imidazole, DCM.

Scheme 33. Hudlicky's synthesis of (–)-codeine.[149]

3. Results and Discussion

3.1 Formal Enantiodivergent Synthesis of Balanol

3.1.1 Formal Synthesis of (+)-Balanol

In 2008, the Hudlicky group published a formal enantiodivergent synthesis of (+)-and (–)-balanol (**3**) from 1,3-cyclohexadiene oxide.[61,2] The synthesis intercepted the bis-benzyl-protected intermediates **119a** and **119b** from the Lampe and Hughes route.[65] Although several formal syntheses employing these intermediates have been published,[65-7, 81] none reported optical data. Our own samples of **119a** and **119b** were in ~95% enantiomeric excess, as determined by the Mosher ester/ ^{19}F NMR method. Each suffered from cross contamination of the opposite enantiomer, resulting from the incomplete separation of benzoate diastereomers **116a** and **116b** near the beginning of the synthesis (see Section 2.2.3, Scheme 15). Hence, we sought to design a second enantiodivergent synthesis of balanol, one which would provide accurate optical data for the intermediates in question. The synthesis will make use of the *cis*-dihydrodiol **5** obtained from the chemoenzymatic dihydroxylation of bromobenzene by the toluene dioxygenase enzyme.[18] The optical purity of this compound has been confirmed through its use in several enantioselective syntheses of naturally occurring products.[1] We envisioned an enantiodivergent route to (+)- and (–)-balanol (**3**) proceeding thorough vinyl aziridines **6** and **7** respectively (Figure 21). Opening of each aziridine with an oxygen nucleophile will generate the necessary *trans*-stereochemistry seen in the targets. Reduction of the vinyl bromide moiety and

an oxidative cleavage/ reductive amination protocol with benzylamine provides access to the formal compounds **119a** and **119b**.

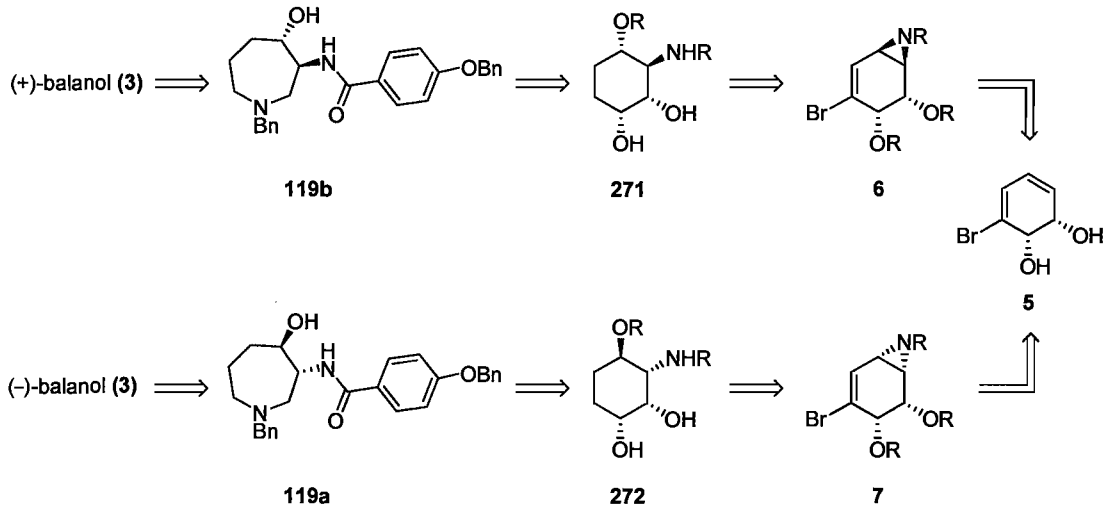
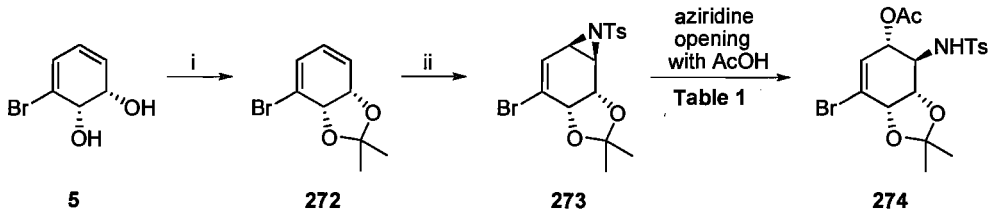


Figure 21. Retrosynthetic analysis of an enantiodivergent route to (+)- and (–)-balanol (**3**)

Our approach to the (+)-balanol intermediate **119a** began with the preparation of tosyl-aziridine **273**, a compound utilized by the Hudlicky group in the enantioselective synthesis of (+)-pancratistatin.[33] Our first attempts to open the aziridine used acetic acid as the oxygen nucleophile (Scheme 34). We found that copper(II) trifluoromethanesulfonate and boron trifluoride etherate did provide the desired *trans*-product **274**, albeit in modest yields (Table 1). The best results were seen when trimethylsilyl trifluoromethanesulfonate was used as the catalyst. A slight increase in yield was observed when five equivalents of acetic acid were used instead of one.



5 272 273 274

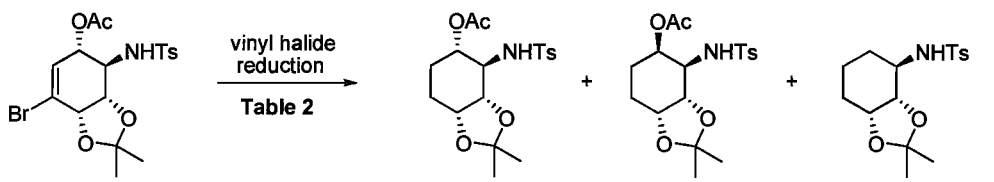
Reagents and conditions: (i) 2,2-DMP, *p*-TsOH, acetone, r.t.; (ii) PhI=NTs, $Cu(acac)_2$, MeCN, 0°C, 77% over 2 steps

Scheme 34. Opening of aziridine **273** with acetic acid

Table 1. Opening of aziridine **273** with acetic acid

Entry	*Catalyst*	*Solvent*	*Equiv. AcOH*	*Yield (%)*
1	$Cu(OTf)_2$	DCM	1	63
2	$BF_3{\cdot}OEt_2$	DCM	1	55
3	TMSOTf	DCM	1	74
4	**TMSOTf**	**DCM**	**5**	**77**

We sought to reduce the vinyl bromide functionality through use of a hydrogenation protocol (Figure 22). Several catalysts were screened with the hope of obtaining the saturated product **275a**. The first attempts (Table 2, Entries 1 and 2) did not reduce the vinyl halide, but did epimerize the *O*-acetyl functionality. All other catalysts screened reduced the vinyl bromide. Unfortunately, each provided a mixture of *cis* and *trans*- *O*-acetyl products, **275a** and **275b**. We observed the formation of a third compound, hydrogenolysis product **276**, for all but two experiments (Table 2, Entries 5 and 6). Complete separation of the compounds via flash column chromatography proved difficult. Hence, we decided to explore other options.



274 275a 275b 276

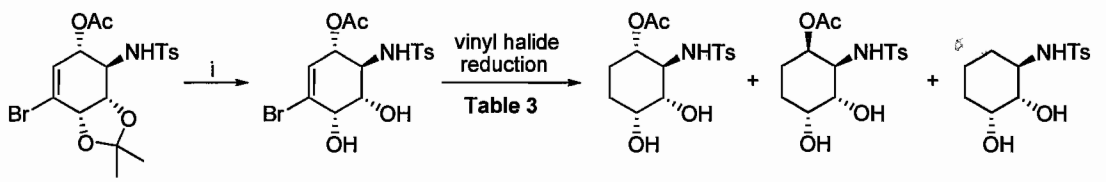
Figure 22. Reduction of vinyl bromide **274**

Table 2. Reduction of vinyl bromide **274**

Entry	*Catalyst*	*Reagent*	*Solvent*	*Ratio 275a:275b:276*[a]
1	$Ru_3(CO)_{12}$	-	MeOH	–[b]
2	Raney Ni	-	MeOH	–[b]
3	5% Pd/ C	-	MeOH	3:1:5
4	$Pd(OAc)_2$	-	MeOH	2:5:8
5	PtO_2	-	MeOH	7:3
6	**PtO_2**	**-**	**EtOH**	**8:3**
7	PtO_2	K_2CO_3	EtOH	6:1:3
8	PtO_2	NEt_3	EtOAc	4:1:5

[a] approximate ratio determined from ^1H NMR spectra; [b] recovered starting with epimerized OAc

We questioned whether the steric and/ or electronic affects of the acetonide attributed to the unfavourable results. Deprotection was accomplished by loading acetonide **274** on silica gel, then removing the solvent and heating to 50°C; a reaction easily performed on a rotary evaporator (Scheme 35). We tested the resulting 1,2-diol substrate **277** against the same conditions used for acetonide-protected product **274** with remarkably similar results (Table 3). The most favourable result, a 7:3 ratio of diastereomers, was achieved with Adams' catalyst in ethanol. Once again, complete separation of the mixture proved troublesome.



274 **277** **278a** **278b** **279**

Reagents and conditions: (i) SiO_2, 50°C, 81%

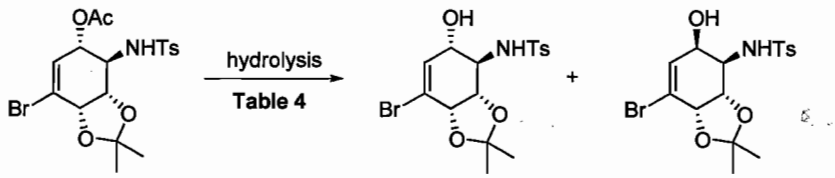
Scheme 35. Hydrogenation of vinyl bromide **274**

Table 3. Hydrogenation of vinyl bromide **277**

Entry	*Catalyst*	*Reagent*	*Solvent*	*Ratio* ***278a:278b:279***[a]
1	$Ru_3(CO)_{12}$	-	MeOH	_[b]
2	Raney Ni	-	MeOH	_[b]
3	5% Pd/ C	-	MeOH	3:2:5
4	$Pd(OAc)_2$	-	MeOH	3:1:8
5	PtO_2	-	MeOH	3:1
6	**PtO_2**	**-**	**EtOH**	**7:2**
7	PtO_2	K_2CO_3	EtOH	4:2:5
8	PtO_2	NEt_3	EtOAc	4:1:5

[a] approximate ratio determined from ^{1}H NMR spectra; [b] recovered starting with epimerized OAc

We speculated that the acetyl group hydrolysis product of **274** might be a better substrate for our hydrogenation procedures. We screened a series of basic hydrolysis procedures with the hope that allylic alcohol **280a** could be isolated (Figure 23). Hydrolysis with potassium or sodium carbonate salts occurred smoothly, but epimerized the hydroxyl group to a 4:1 ratio of *trans*- and *cis*-products (Table 4, Entries 1 and 2). The isolated yields of the sodium and potassium hydroxide experiments were lower, and also epimerized the allylic alcohol group.



274 **280a** **280b**

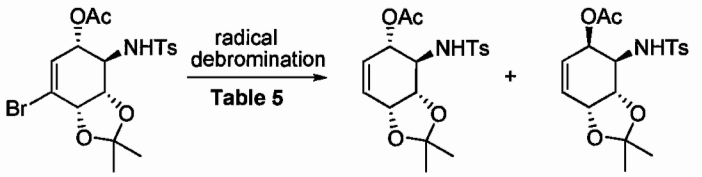
Figure 23. Hydrolysis of acetate **274**

Table 4. Hydrolysis of acetyl **274**

Entry	*Reagent*	*Solvent*	*Temp.*	*Yield*	*Ratio* **280a:280b**[a]
1	K_2CO_3	MeOH	0°C – r.t.	82%	4:1
2	Na_2CO_3	MeOH	0°C – r.t.	88%	4:1
3	NaOH	MeOH	0°C – r.t.	67%	7:2
4	**KOH**	**MeOH**	**0°C – r.t.**	**61%**	**8:3**

[a] approximate ratio determined from ^{1}H NMR spectra

At this stage we chose to pursue a two-step reduction route. Specifically, reduce the carbon-bromide bond and then reduce the olefin. We selected a radical debromination procedure to accomplish the first step (Figure 24). Our procedure used tributyltin hydride in the presence of the radical initiator azobisisobutyronitrile (AIBN). We ran three experiments, differing only in concentration (Table 5). Each afforded a mixture of the *trans*- and *cis*-isomers, **281a** and **281b** respectively. A concentration of 1.0 M provided an excellent ratio of 15:1 in favour of the *trans*-isomer. However, we were unable to completely separate the isomers (GC/MS analysis).



274 281a 281b

Figure 24. Radical debromination of **274**

Table 5. Radical debromination of **274**

Entry	*Reagents*	*Solvent*	*Concentration*[a]	*Ratio **281a:281b*** [b]
1	Bu_3Sn-H, AIBN	THF	0.5 M	3:1
2	**Bu_3Sn-H, AIBN**	**THF**	**1.0 M**	**15:1**
3	Bu_3Sn-H, AIBN	THF	2.0 M	8:1

[a] concentration of Bu_3Sn-H; [b] approximate ratio determined from ^1H NMR spectra

In order to rule out the steric and/ or electronic effects of the acetonide, we tested our radical debromination procedures on the free 1,2-diol **277**. Once again, three experiments were run with varying concentrations of hydride reagent (Table 6). Once again we obtained an inseparable mixture of isomers.

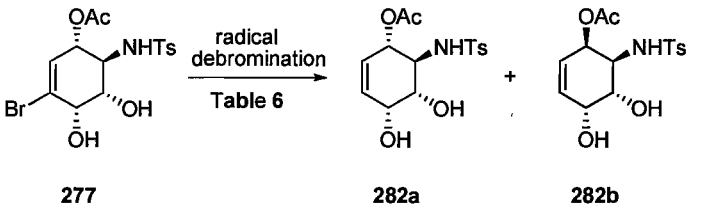


Figure 25. Radical debromination of **277**

Table 6. Radical debromination of **277**

Entry	*Reagents*	*Solvent*	*Concentration*[a]	*Ratio 282a:282b* [b]
1	Bu_3Sn-H, AIBN	THF	0.5 M	4:1
2	Bu_3Sn-H, AIBN	THF	1.0 M	8:1
3	**Bu_3Sn-H, AIBN**	**THF**	**2.0 M**	**9:1**

[a] concentration of Bu_3Sn-H; [b] approximate ratio determined from ^1H NMR spectra

Before continuing with the two-step reduction, we questioned whether the olefin functionality could be reduced without the use of a hydrogenation procedure. The mixture of diastereomers **281a** and **281b**, obtained from our first radical debromination experiments, were subjected to a reduction procedure using potassium azodicarboxylate (PAD) (Figure 26). Only starting material was isolated from these experiments, even when a large excess of PAD was used (Table 7).

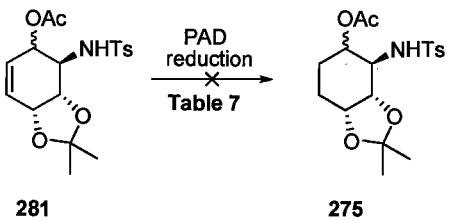


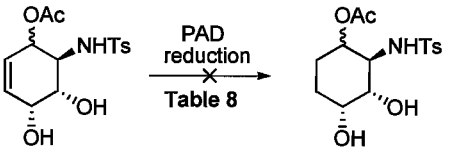
Figure 26. Potassium azodicarboxylate reduction of olefin **281**

Table 7. Potassium azodicarboxylate reduction of olefin **281**

Entry	*Reagents*	*Solvent*	*Equivalents*[a]	*Result*
1	PAD, AcOH	MeOH	4	SM
2	PAD, AcOH	MeOH	20	SM

[a] equivalents of PAD

We also tested the mixture of diastereomers **282a** and **282b**, obtained from our radical debromination experiments on 1,2-diol **277** (Figure 27). Once again, the experiments did not provide any new products (Table 8).



282 **278**

Figure 27. Potassium azodicarboxylate reduction of olefin **282**

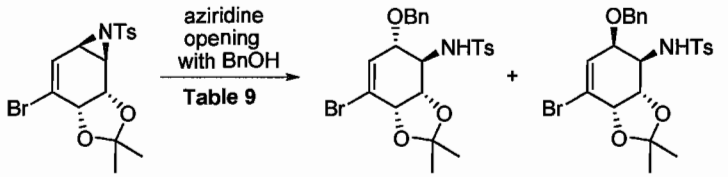
Table 8. Potassium azodicarboxylate reduction of olefin **282**

Entry	*Reagents*	*Solvent*	*Equivalents*[a]	*Result*
1	PAD, AcOH	MeOH	4	SM
2	PAD, AcOH	MeOH	20	SM

[a] equivalents of PAD

Frustrated with the aforementioned results, we decided to abandon any routes that would proceed through *O*-acetyl product **274**. Our next strategy was to open tosyl aziridine **273** with benzyl alcohol (Figure 28). In principle, the *O*-benzyl functionality could be deprotected during a hydrogenation procedure which simultaneously reduces the vinyl halide moiety. We screened different catalysts for their ability to selectively open the vinyl tosyl aziridine. Our first trials, using $Cu(OTf)_2$, $BF_3{\cdot}OEt_2$, and TMSOTf, were capable of facilitating the regioselective opening of aziridine **273** (Table 9, Entries 1 to 3). However, in each instance a mixture of *trans*- and *cis*-*O*-benzyl diastereomers were obtained. As with our experiments using acetic acid, TMSOTf offered the most favourable ratio (5:1) of epimers. We found complete separation of these diastereomers difficult, and thus impractical for a multi-step synthesis. We also tried two non-conventional catalysts, namely β-cyclodextrin and

cerium ammonium nitrate (Table 9, Entries 6 and 7). In each case, no new products were formed.



273 283a 283b

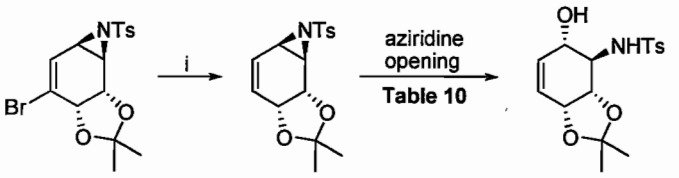
Figure 28. Opening of tosyl aziridine **273** with benzyl alcohol

Table 9. Opening of tosyl aziridine **273** with benzyl alcohol

Entry	*Catalyst*	*Solvent*	*Temp.*	*Ratio (283a:283b)*[a]	*Result*
1	$Cu(OTf)_2$	DCM	r.t.	7:2	77%
2	$BF_3{\cdot}OEt_2$	DCM	r.t.	3:2	74%
3	**TMSOTf**	**DCM**	**r.t.**	**5:1**	**82%**
4	β-cyclodextrin	MeCN	r.t.	-	SM
5	β-cyclodextrin	MeCN	reflux	-	SM
6	$(NH_4)_2Ce(NO_3)_6$	MeCN	r.t.	-	SM
7	$(NH_4)_2Ce(NO_3)_6$	MeCN	reflux	-	SM

[a] approximate ratio determined from ^1H NMR spectra

At this stage, we questioned whether the tosyl-aziridine functionality could be opened after the carbon-bromide bond had been reduced. Treatment of vinyl bromide **273** to a tributyltin hydride radical debromination protocol, first reported in Hudlicky's synthesis of (+)-pancratistatin,[33] afforded olefin **54** (Scheme 36). We sought to open this aziridine with a hydroxide anion. Our experiments with $Cu(OTf)_2$ and β-cyclodextrin were unsuccessful, as only starting material was isolated (Table 10, Entries 1 to 3). Ceric ammonium nitrate did not produce any new compounds at ambient temperature, while elevated temperatures decomposed the starting material. Ultimately, we found that an excess of potassium hydroxide in dimethyl sulfoxide provided allylic alcohol **284**. The reaction is high yielding so long as the temperature does not exceed 40°C.



273 54 284

Reagents and conditions: (i) Bu_3Sn-H, AIBN, THF

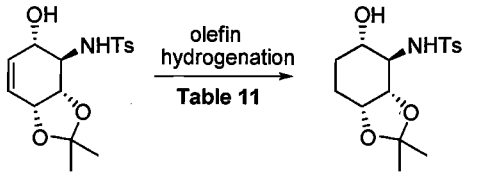
Scheme 36. Opening of vinyl aziridine **273**

Table 10. Opening of vinyl aziridine **273**

Entry	*Reagents*	*Solvent*	*Temp.*	*Result*
1	$Cu(OTf)_2$	MeCN/ H_2O	r.t.	SM
2	β-cyclodextrin	MeCN/ H_2O	reflux	SM
3	β-cyclodextrin	acetone/ H_2O	reflux	SM
4	$(NH_4)_2Ce(NO_3)_6$	acetone/ H_2O	r.t to reflux	decomposition[a]
5	KOH	DMSO	80°C	**284** (27%)
6	**KOH**	**DMSO**	**40°C**	**284 (93%)**

[a] no new products observed at r.t. (TLC monitoring), while multiple spots (<10) observed at elevated temperatures (i.e. > 50°C)

Our next goal was to study the reduction of the olefin functionality. Previously, we had hypothesized that a free hydroxyl group would prevent epimerization during a hydrogenation reaction. Now we could test our theory using allylic alcohol **284** as a substrate (Figure 29). Our first experiments used 5% palladium on carbon, either in the presence or absence of triethylamine (Table 11, Entries 1 and 2). Our hypothesis proved correct, as we were able to isolate the saturated product **285** without any evidence of its epimer. Our last two experiments used Adams' catalyst and either triethylamine or potassium carbonate as the basic additive. We observed a substantial increase in isolated yield, particularly when the latter base was used.



284 285

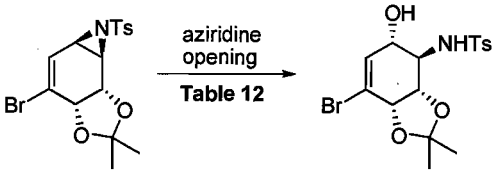
Figure 29. Hydrogenation of olefin **284**

Table 11. Hydrogenation of olefin **284**

Entry	*Catalyst*	*Reagent*	*Solvent*	*Yield (%)*
1	5% Pd/ C	-	MeOH	44[a]
2	5% Pd/ C	NEt_3	MeOH	54[a]
3	PtO_2	NEt_3	MeOH	86
4	**PtO_2**	**K_2CO_3**	**MeOH**	**92**

[a] lower yield possibly a result of hydrogenolysis (^{1}H NMR evidence)

We were pleased with these results, but questioned whether we could avoid the radical debromination step and thus reduce the route to **285**. We decided to test our KOH aziridine opening procedure on the vinyl bromide substrate **273** (Figure 30). One again, we varied the temperature in different experiments and concluded that a lower temperature offered a higher yield (Table 12).



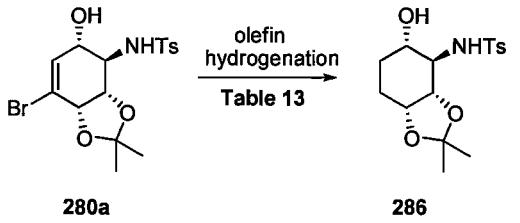
273 280a

Figure 30. Opening of tosyl aziridine **273** with hydroxide

Table 12. Opening of tosyl aziridine **273** with hydroxide

Entry	*Reagents*	*Solvent*	*Temp.*	*Yield (%)*
1	KOH	DMSO	80°C	40
2	**KOH**	**DMSO**	**40°C**	**94**

Finally, we employed our Adams' catalyst hydrogenation procedures to vinyl bromide **280a** (Figure 31). As with the unsubstituted olefin **284**, the addition of potassium carbonate afforded the highest isolated yield (Table 13).



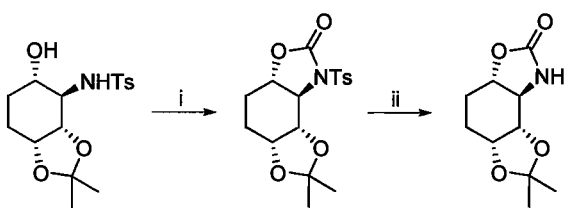
280a **286**

Figure 31. Reduction of vinyl bromide **280a** with Adams' catalyst

Table 13. Reduction of vinyl bromide **280a** with Adams' catalyst

Entry	*Catalyst*	*Reagent*	*Solvent*	*Yield (%)*
1	PtO_2	NEt_3	MeOH	75
2	**PtO_2**	**K_2CO_3**	**MeOH**	**77**

Our group's first generation formal synthesis of (+)- and (–)-balanol employed a cyclic carbamate moiety as a means of simultaneously protecting both the oxygen and nitrogen atoms.[61-2] Hence, we sought to use a similar strategy in our second generational approach. Exposure of cyclohexanol derivative **286** to triphosgene furnished *N*-tosyl carbamate **287** (Scheme 37). A dissolving metal reduction with Na/ naphthalene removed the tosyl functionality and provided cyclic carbamate **288**.



286 **287** **288**

Reagents and conditions: (i) triphosgene, NEt_3, DCM, 0°C, 93%; (ii) Na/ naphthalene, DME, -78°C, 92%

Scheme 37. Synthesis of cyclic carbamate **288**

The next step in the synthesis involved the derivatization of cyclic carbamate **288** with 4-(benzyloxy)benzoyl chloride (Figure 32). Experiments utilizing nitrogenous bases, specifically triethylamine and pyridine, were troublesome (Table 14, Entries 1 and 2). In those instances, a large excess of acid chloride was required to obtain relatively low amounts of product. Fortunately, sodium hydride in tetrahydrofuran with 1 equivalent of acid chloride provided the desired amide **289** in excellent yield.

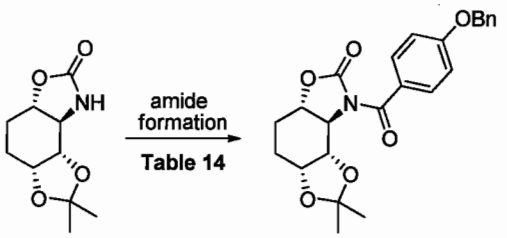


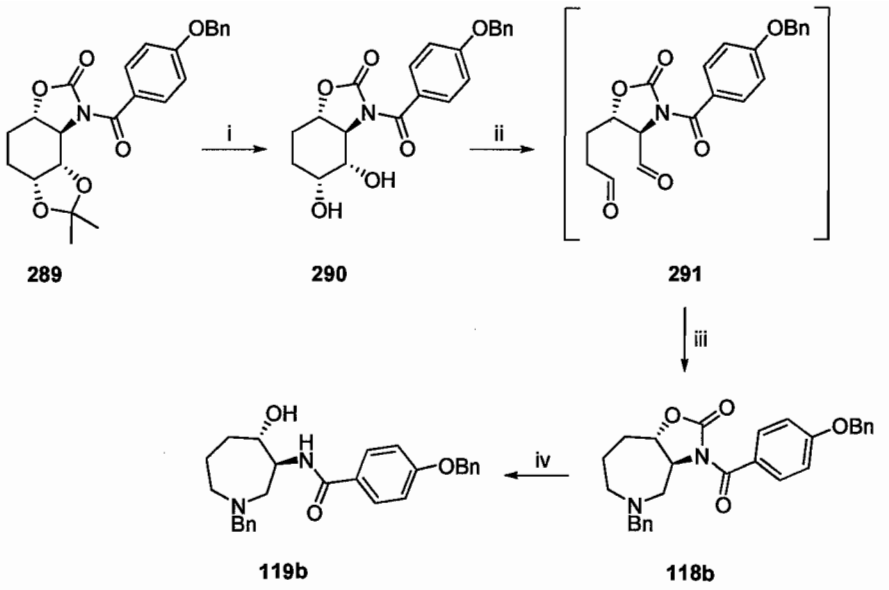
Figure 32. Derivatization of cyclic carbamate **288**

Table 14. Derivatization of cyclic carbamate **288**

Entry	*Base*	*Solvent*	*Temp*	*Result*
1	NEt_3	DCM	0°C – r.t.	20%[a]
2	pyridine	DCM	0°C – r.t.	25%[a]
3	**NaH**	**THF**	**0°C – r.t.**	**91%**

[a] low yield a consequence of high amounts of starting material recovered

Acidic hydrolysis of acetonide **289** with AcOH/ THF/ H_2O afforded 1,2-diol **290** (Scheme 38). Oxidative cleavage with sodium periodate provided a dialdehyde species which was used without purification. A reductive amination protocol with benzylamine constructed the azepane core of balanol. Mild basic hydrolysis of the cyclic carbamate moiety completed the formal synthesis of (+)-balanol.

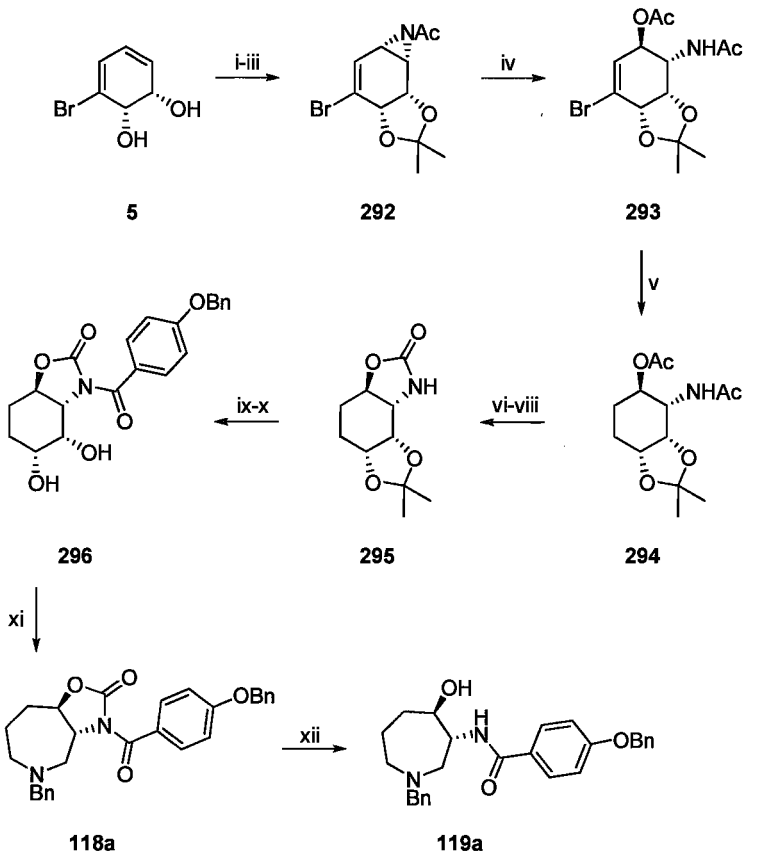


Reagents and conditions: (i) AcOH/THF/H_2O (9:3:1), reflux, 83%; (ii) $NaIO_4$, acetone/H_2O (8:2), r.t.; (iii) Bn-NH_2, AcOH, $NaBH_3CN$, 3Å mol. sieves, MeOH, -78°C to r.t., 60% over two steps; (iv) 1N NaOH, THF, -20°C, 56%

Scheme 38. Formal synthesis of (+)-balanol

3.1.2 Synthesis of (–)-Balanol

As mention previously, we sought to develop an enantiodivergent route to both isomers of balanol from *cis*-dihydrodiol **5**. The route to (–)-balanol intermediate **119b**, completed with Bradford Sullivan, begins with the aziridination of the acetonide derivative of diol **5** using a procedure developed by Corey (Scheme 39).[150] Opening of acetyl-aziridine **292** with acetic acid was followed by reduction of vinyl halide moiety with Adams' catalyst. Basic hydrolysis, and then sequential exposure to methyl chloroformate and then sodium hydride afforded cyclic carbamate **295**. Derivatization with 4-(benzyloxy)benzoyl chloride, acetonide hydrolysis and an oxidative cleavage/ reductive amination yielded azepane **118a**. Basic hydrolysis with sodium hydroxide completed the formal synthesis of (–)-balanol.



Reagents and conditions: (i) 2,2-DMP, acetone, *p*-TsOH; (ii) *N*-bromoacetamide, $SnBr_4$, MeCN, -30°C; (iii) KHMDS, *n*-BuNBr, DME, 0°C, 68% over three steps; (iv) AcOH, TMSOTf, DCM, r.t., 88%; (v) H_2 (1 atm), PtO_2, EtOAc, 84%; (vi) NaOMe, MeOH, reflux; (vii) methyl chloroformate, NEt_3, DCM, DMAP, r.t., 73% over two steps; (viii) NaH, THF, reflux, 83%; (ix) *p*-$BnOC_6H_4COCl$, DCM, DMAP, NEt_3, 0°C, 82%; (x) AcOH/THF/H_2O (9:3:1), reflux, 88%; (xi) a) $NaIO_4$, acetone/H_2O (8:2), r.t.; b) Bn-NH_2, AcOH, $NaBH_3CN$, 3Å mol. sieves, MeOH, -78°C to r.t., 64% over two steps; (xii) 1N NaOH, THF, -20°C, 86%

Scheme 39. Formal synthesis of (–)-balanol

The preceding work describes one of the few enantiodivergent routes to balanol. Differential aziridination of the acetonide derivative of *cis*-dihydrodiol **5** allowed access to both formal intermediates while avoiding the synthesis and separation of diastereomers seen in previous enantiodivergent strategies.

3.2 Synthetic Approaches to Codeine

Opium alkaloids are among the most commonly used and important pharmaceuticals in medicine. Unfortunately, only a few regions are able to grow the poppy plants which produce these drugs in significant amounts. This has left the Western world, the predominant users, reliant on only a few countries for their opium. One solution to this problem would be the development of a fully synthetic route to these drugs from readily available materials. Although many elegant syntheses of opium alkaloids have been developed, not one is practical enough to supplant the natural sources. One of the goals of the Hudlicky research group is to develop an economically viable and environmentally benign synthetic route to the opium alkaloids. The present thesis will outline the most current work by the Hudlicky group on the synthesis of (+)-codeine (Figure 33).

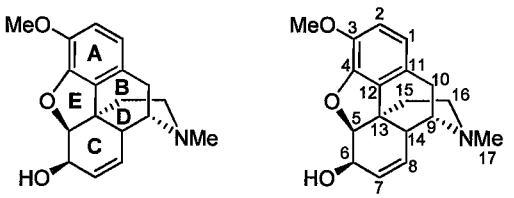


Figure 33. Carbon numbering and ring nomenclature of (+)-codeine.

All of the strategies discussed commence with the TDO-mediated dihydroxylation of β-bromoethylbenzene. This provides large quantities of enantiomerically pure *cis*-dihydrodiol **8**, the carbon source for the C and D-rings of (+)-codeine (Figure 34). A Mitsunobu reaction with an arene substrate can be used to fasten the A-ring and install the ether linkage. The C12 and C13 bond, and hence the E-ring, can be formed via an intramolecular Heck coupling reaction. The majority of

the research discussed in this thesis will focus on the closure of the B and D-rings from a cyclohexenone species **298**.

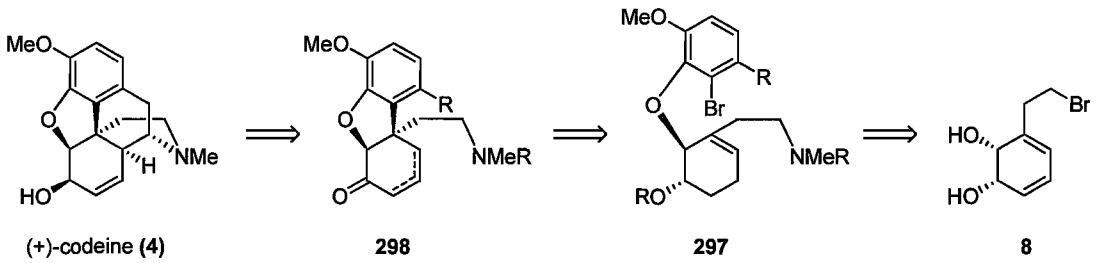
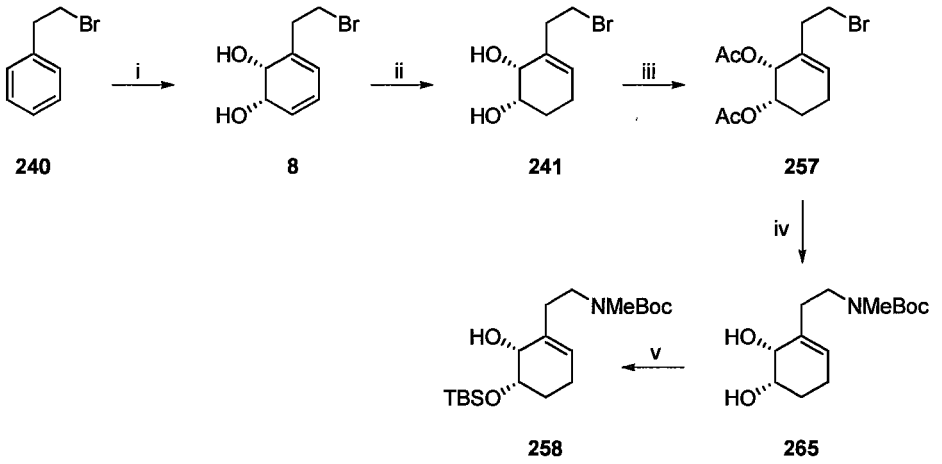


Figure 34. Retrosynthetic analysis of (+)-codeine

3.2.1 Enol Ether Approach

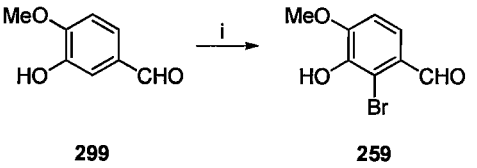
The first strategy explored utilizes a Mitsunobu coupling reaction between allylic alcohol **258** and arene **259**, originally described by Hudlicky in 2007.[147] Synthesis of the **258** commences with the PAD reduction and acetylation of *cis*-dihydrodiol **8** (Scheme 40). Treatment with methylamine and K_2CO_3 displaced the bromide and produced a secondary amine derivative and simultaneously hydrolyzed the acetates. Subsequent exposure to Boc anhydride and triethylamine protected the amine. Silylation of the homoallylic hydroxyl with TBS-Cl provided C-ring fragment **258**.



Reagents and conditions: (i) *E. coli* JM109 (pDTG602), 5g/L; (ii) PAD, AcOH, MeOH, -20°C, 60%; (iii) Ac_2O, NEt_3, DMAP, 0°C, 67%; (iv) a) NH_2Me, K_2CO_3, THF, sealed tube; b) Boc_2O, NEt_3, DCM, 0°C – r.t., 50% over two steps; (v) TBS-Cl, imidazole, DCM, -78°C – r.t., 88%

Scheme 40. Synthesis of C-ring fragment **258**

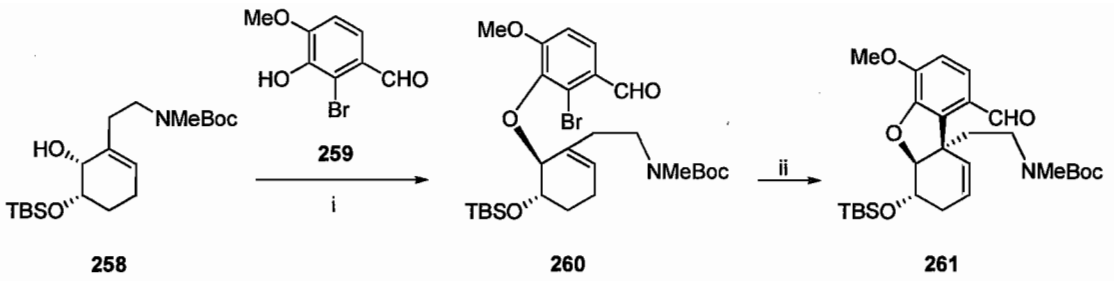
The arene fragment **259** was prepared through the NBS bromination of iso-vanillin (**299**) (Scheme 41).



Reagents and conditions: (i) NBS, $CHCl_3$, reflux

Scheme 41. Synthesis of A-ring fragment **259**

A Mitsunobu reaction between the A-ring and C-ring fragments afforded ether **260** (Scheme 42). A palladium(II) acetate catalyzed intramolecular Heck reaction closed the dihydrofuran ring and provided **261**, a common intermediate in Hudlicky's 2007 synthesis of (+)-codeine.[147]



Reagents and conditions: (i) **259**, DIAD, *n*-Bu_3P, THF, 0°C – r.t., 55%; (ii) $Pd(OAc)_2$, Ag_2CO_3, dppf, toluene, 110°C, 82%

Scheme 42. Synthesis of tetrahydrodibenzofuran **261**

We envisioned the final two rings of (+)-codeine closing from enol ether intermediate **300** (Figure 35). Treatment with acid should remove the Boc carbamate, hydrolyze the enol ether, and tautomerize the cyclohexenone ring. If the secondary amine condenses on the aldehyde, the resulting iminium could be attacked by the enol ring in order to form the C9-C14 bond and provide (+)-codeinone **(134)**, a precursor to (+)-codeine.[151]

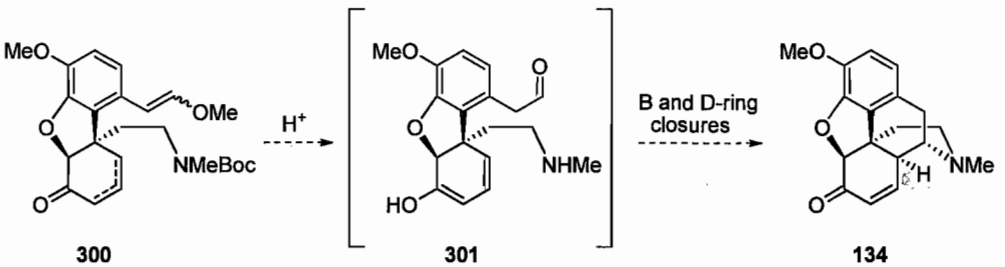
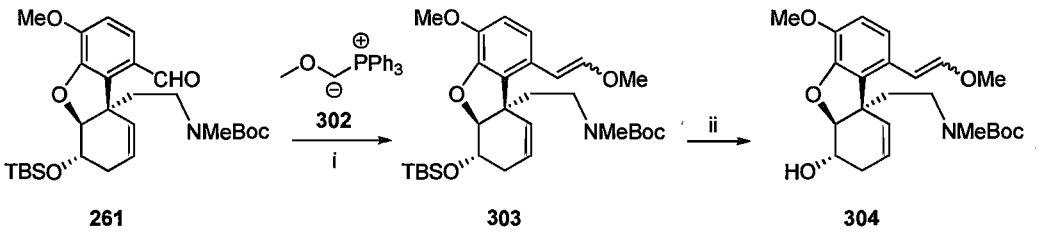


Figure 35. Proposed route to close the B- and D-rings from enol ether **300**

Our synthesis of enol ether **300** began by reacting Wittig reagent **302** with aldehyde **261** to produce **303** as a mixture of *cis* and *trans* enol ethers. Desilylation with TBAF revealed a cyclohexenol ring that is an oxidation away from our target molecule **300**.



Reagents and conditions: (i) chloride salt of **302**, *n*-BuLi, THF, -78°C – r.t., 70%; (ii) TBAF, THF, 0°C – r.t., 74%

Scheme 43. Synthesis of cyclohexenol **304**

We anticipated that the oxidation of hydroxyl **304** would give us the 2-cyclohexenone or 3-cyclohexenone (conjugated) product, or perhaps a mixture of the two. In Hudlicky's 2007 (+)-codeine synthesis, the C6 hydroxyl was oxidized using an 2-iodoxybenzoic acid (IBX) procedure. When cyclohexenol **304** was subjected to identical conditions (Table 15, Entry 1) the starting material was decomposed. We employed several different oxidation procedures without success. Either we recovered the starting material or obtained a complex mixture of compounds. Identification of products is complicated by the rotameric nature of the compounds, in addition to the presence of *cis* and *trans* isomers. Specifically, NMR analysis of a single compound would appear as four compounds; two conformational isomers (rotamers) of two geometric isomers (*cis* and *trans*).

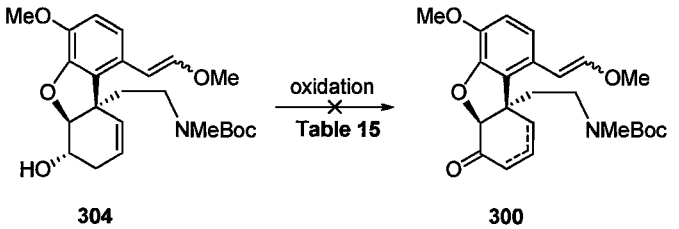


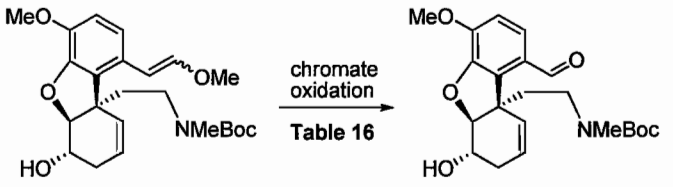
Figure 36. Attempted oxidation of cyclohexenol **304**

Table 15. Attempted oxidation of cyclohexenol **304**

Entry	*Oxidant*	*Reagent(s)*	*Solvent*	*Temp.*	*Result*
1	IBX	-	DMF	r.t.	decomposition[a]
2	IBX	-	DMSO	r.t.	decomposition[a]
3	TEMPO	KBr/HClO	DCM	r.t.	SM
4	DMP	-	DCM		decomposition[a]
5	TPAP	NMO	DCM	0°C-r.t.	SM
6	*p*- nitrobenzaldehyde	$AlMe_3$	toluene	reflux	SM

[a] complex mixture of unidentifiable compounds

When chromate oxidants (i.e. PCC and PDC) were used we isolated benzaldehyde **305**, with the loss of a carbon atom. Strangely, the hydroxyl was not oxidized, even when multiple equivalent of chromate was employed.



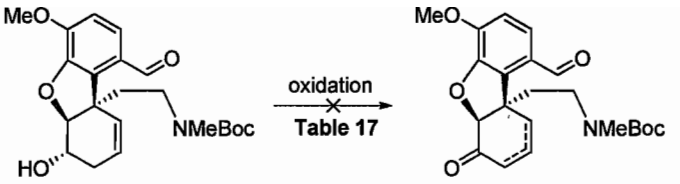
304 **305**

Figure 37. Chromate oxidation of enol ether **304**

Table 16. Chromate oxidation of enol ether **304**

Entry	*Oxidant*	*Solvent*	*Temp.*	*Result*
1	**PCC**	**DCM**	**r.t.**	**305 (67%)**
2	PDC	DCM	r.t.	**305** (65%)

We questioned whether the C6 hydroxyl of **305** could be oxidized to cyclohexenone **306**, understanding that the aldehyde could be preferentially homologated with Wittig reagent **302** over the ketone. The IBX and Dess–Martin periodinane (DMP) procedure we tested decomposed the starting material (Table 17, Entries 1 to 3). The chromate and modified Oppenauer oxidation protocols we screened did not produce any new products.



305 306

Figure 38. Attempted oxidation of cyclohexenol **305**

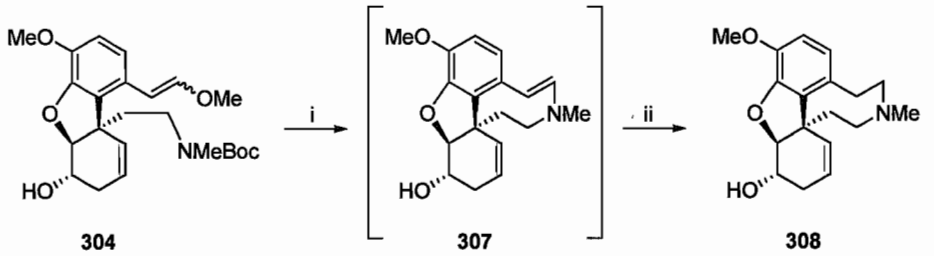
Table 17. Attempted oxidation of cyclohexenol **305**

Entry	*Oxidant*	*Reagents*	*Solvent*	*Temp.*	*Result*
1	IBX	-	DMF	r.t.	decomposition[a]
2	IBX	-	DMSO	r.t.	decomposition[a]
3	DMP	-	DCM	r.t.	decomposition[a]
4	PCC	-	DCM	r.t.	SM
5	PDC	-	DCM	r.t.	SM
6	*p*- nitrobenzaldehyde	$AlMe_3$	toluene	reflux	SM

[a] complex mixture of unidentifiable compounds

3.2.2 Aza-Prins Reaction Approach

The Prins reaction is an effective method for forming carbon-carbon bonds via an electrophilic addition between a carbonyl and an alkene. An aza-Prins replaces the electrophilic carbonyl with an iminium ion. We envisioned the exposure of enol ether **304** to TFA resulting in the formation of an iminium-trifluoroacetate salt which could be attacked by the C-ring olefin. When we tested our hypothesis, we did not isolate the aza-Prins product. However, upon workup we isolated the unstable enamine **307**, which we immediately reduced with $NaCNBH_3$ to obtain *N*-methyl piperidine **308** (Scheme 44). This was strong evidence for the formation of the iminium ion intermediate.

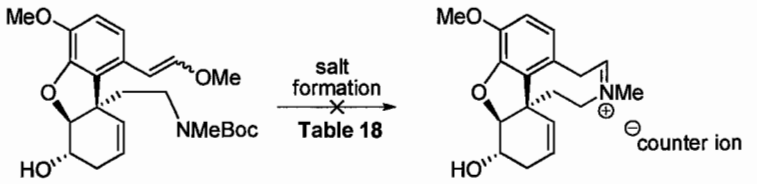


304 307 308

Reagents and conditions: (i) TFA, DCM, 0°C – r.t.; (ii) $NaCNBH_3$, AcOH, MeOH, 0°C – r.t., 41% over two steps

Scheme 44. Synthesis of *N*-methyl piperidine **308**

We speculated that if the iminium could be trapped as a salt, we could find conditions to promote the aza-Prins reaction. To this end, we reacted enol ether **304** with perchloric acid and trifluoroacetic acid (Table 18). Unfortunately, these conditions decomposed the starting material.



304 309

Figure 39. Attempted formation of iminium salt **309**

Table 18. Attempted formation of iminium salt **309**

Entry	*Acid*	*Solvent*	*Temp.*	*Result*
1	3% perchloric acid	DCM	0°C	decomposition[a]
2	TFA	DCM	0°C	decomposition[a]

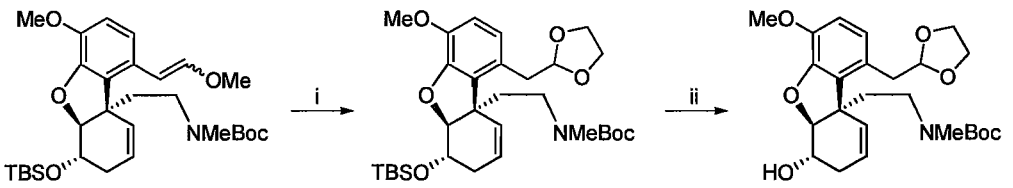
[a] complex mixture of unidentifiable compounds

3.2.3 Ketal Approach

At this stage of the project we elected to abandon the enol ether protected aldehyde **303** in favour of a ketal group. We hoped that the lack of *cis* and *trans* geometric isomers would simplify the identification of any new products produced.

Furthermore, the enol ether had undergone an undesired reaction with chromate oxidants (see Section 3.2.1). Exposure of enol ether **303** to excess ethylene glycol promoted the formation of ethylene ketal **310** (Scheme 45). The isolated yield of ketal **310** was very poor, a consequence of the acid labile Boc and TBS groups.

Desilylation with TBAF provided cyclohexenol **311.**

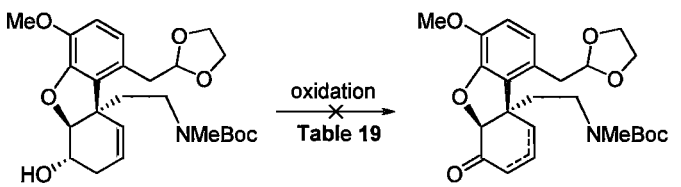


303 **310** **311**

Reagents and conditions: (i) ethylene glycol, *p*-TsOH, benzene, reflux, 18%; (ii) TBAF, THF, 0°C – r.t., 92%

Scheme 45. Synthesis of ethylene ketal **311**

We questioned whether replacement of the enol ether with an ethylene ketal would affect the outcome of the C6 hydroxyl oxidation procedures (Figure 40). We tried many of the same oxidation conditions tested on enol ether **304** (Table 19). Once again, the hypervalent iodine reagents (i.e. DMP and IBX) decomposed the starting material into an inseparable mixture of unidentifiable compounds. The chromate oxidants (i.e. PCC and PDC) and TEMPO did not react with the hydroxyl or the ketal.



311 **312**

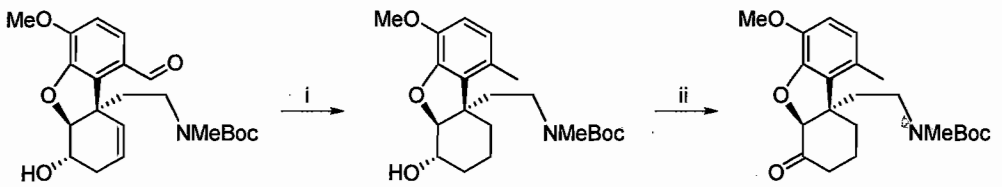
Figure 40. Attempted oxidation of cyclohexenol **311**

Table 19. Attempted oxidation of cyclohexenol **311**

Entry	*Oxidant*	*Reagents*	*Solvent*	*Temp.*	*Result*
1	IBX	-	DMF	0°C - r.t.	decomposition[a]
2	IBX	-	DMSO	0°C - r.t.	decomposition[a]
3	TEMPO	KBr/HClO	DCM	0°C - r.t.	SM
4	DMP	-	DCM	0°C - r.t.	decomposition[a]
5	PCC	-	DCM	0°C - r.t.	SM
6	PDC	-	DCM	0°C - r.t.	SM

[a] complex mixture of unidentifiable compounds

From the aforementioned results we concluded that the unsuccessful oxidations were, in part, caused by either the olefin or the protected aldehyde (ketal or enol ether). We elected to try and oxidize the C6 hydroxyl of a substrate lacking an oxygenated substituent at C11 and an alkene in the C-ring. We subjected benzaldehyde **305**, obtained from the chromate oxidation of enol ether **304**, to a palladium-catalyzed hydrogenation procedure. This reduced the C10 aldehyde and olefin functionalities to provide cyclohexanol **313**, which was easily oxidized to cyclohexanone **314** using IBX (Scheme 46).

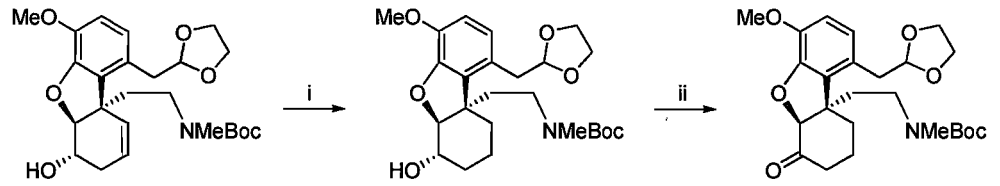


305 **313** **314**

Reagents and conditions: (i) 5% Pd/C, H_2 (1 atm), MeOH, 54%; (ii) IBX, DMF, 0°C – r.t., 77%.

Scheme 46. Synthesis of cyclohexanone **314**

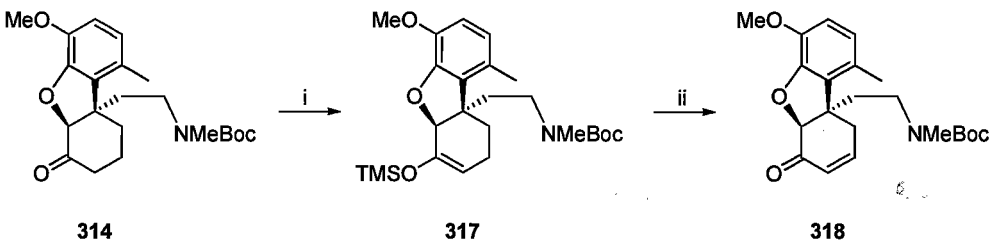
We attempted this newly developed synthetic route on ketal **311**, selected in favour of the hydrogenation-labile enol ether **304**. As anticipated, reduction of olefin **311** followed by exposure to IBX afforded cyclohexanone **316.**



Reagents and conditions: (i) 5% Pd/C, H_2 (1 atm), MeOH, 82%; (ii) IBX, DMF, 0°C – r.t., 85%

Scheme 47. Synthesis of cyclohexanone **316**

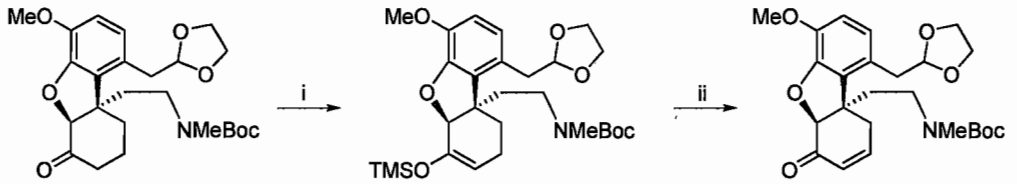
Pleased with these results, we sought to find a method to reintroduce the olefin functionality into the C-ring. For our preliminary study, we employed cyclohexanone **314**, simply because we had no other use for this compound. The obvious method for reintroduction of the alkene is the oxidation of a silyl enol ether derivative via a Saegusa oxidation. Sequential exposure of **314** to LDA and then TMS-Cl provided silyl enol ether **317** (Scheme 48). Its reaction with $Pd(OAc)_2$ produced enone **318** via an oxo-allyl palladium complex.



Reagents and conditions: (i) a) LDA, THF, -78°C; b) TMS-Cl; (ii) $Pd(OAc)_2$, MeCN, 76% over two steps

Scheme 48. Saegusa oxidation of cyclohexanone **314**

Fortunately, the Saegusa oxidation of cyclohexanone **314** proceeded as successfully as the test substrate. With **320**, we finally had an enone A-ring with a latent aldehyde at the C9 position. Unfortunately, this synthetic route to enone **320** is not trivial. As mentioned previously, the ketal formation from enol ether **303** is a poor yielding reaction.

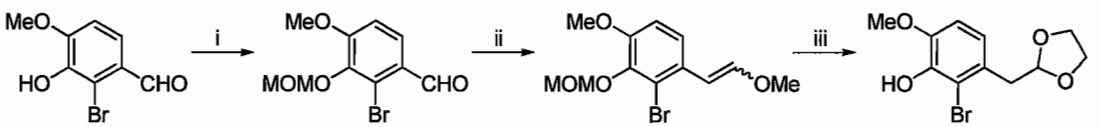


316 319 320

Reagents and conditions: (i) a) NaHMDS, THF, -78°C; b) TMS-Cl; (ii) $Pd(OAc)_2$, MeCN, 81% over two steps

Scheme 49. Saegusa oxidation of cyclohexanone **316**

In order to circumvent the ketal construction from enol ether **303**, we elected to develop an alternative route to enone **320**. Our first approach was to introduce the ethylene ketal moiety into the A-ring fragment prior to the Mitsunobu coupling step. Protection of 2-bromo iso-vanillin **(259)** as its methoxymethyl ether and subsequent Wittig reaction with **302** provided enol ether **322** (Scheme 50). Ketalization with ethylene glycol afforded arene **323** in a satisfactory yield.

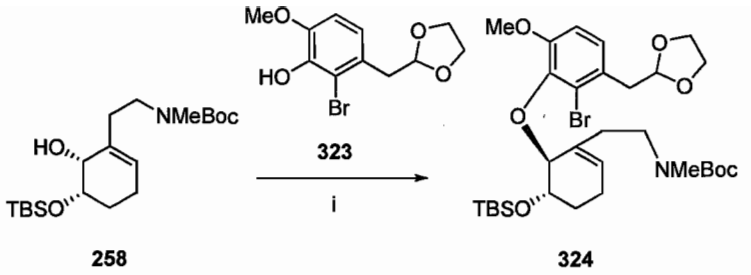


259 321 322 323

Reagents and conditions: (i) MOM-Cl, $EtN(iPr)_2$, DCM, 0°C; (ii) chloride salt of **302**, *n*-BuLi, THF, -78°C – r.t.; (iii) ethylene glycol, *p*-TsOH, 64% over three steps

Scheme 50. Synthesis of ethylene ketal **323**

A Mitsunobu coupling reaction between allylic alcohol **258** and arene **323** provided ether **324**, setting up an intramolecular Heck reaction to form the C12-C13 bond (Scheme 51).

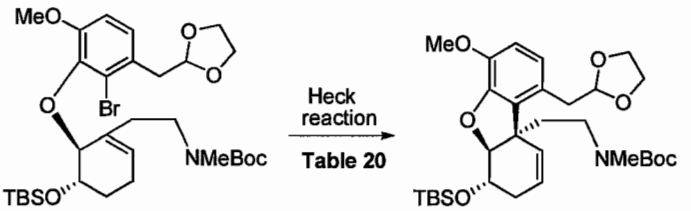


258 324

Reagents and conditions: (i) **323**, DIAD, *n*-Bu_3P, THF, 0°C – r.t., 78%

Scheme 51. Synthesis of ether **324**

The Heck reaction conditions which had furnished tetrahydodibenzofuran **261** decomposed ether **324** (Table 20, Entry 1). We screened conditions employing tris(dibenzylideneacetone)dipalladium(0) and obtained the desired product in modest yields. Ultimately, palladium(II) acetate in concert with P(*o*-tolyl)$_3$ gave us the best result, 94% of tetrahydodibenzofuran **310**.



324 310

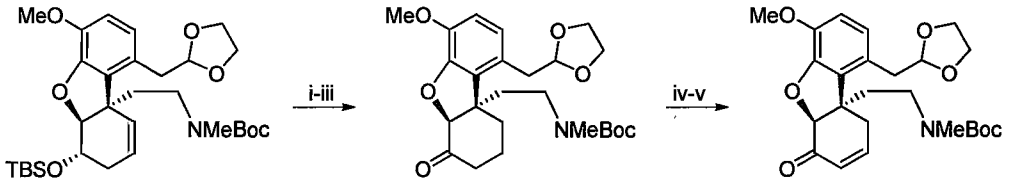
Figure 41. Intramolecular Heck reaction of ether **324**

Table 20. Intramolecular Heck reaction of ether **324**

Entry	*Pd Catalyst*	*Reagents*	*Solvent*	*Temp.*	*Result*
1	$Pd(OAc)_2$	Ag_2CO_3, dppf	toluene	110°C	decomposition[a]
2	$Pd(dba)_2$	P(*o*-tolyl)$_3$, NEt_3	MeCN	reflux	**310** (27%)
3	$Pd(dba)_2$	P(*o*-tolyl)$_3$, NEt_3	toluene	110°C	**310** (22%)
4	**$Pd(OAc)_2$**	**P(*o*-tolyl)$_3$, NEt_3**	**toluene**	**110°C**	**310 (94%)**

[a] complex mixture of compounds

Desilylation of **310**, hydrogenation with 5% Pd/C, and oxidation with IBX afforded cyclohexanone **316**. A Saegusa oxidation completed our efficient route to enone **320**.

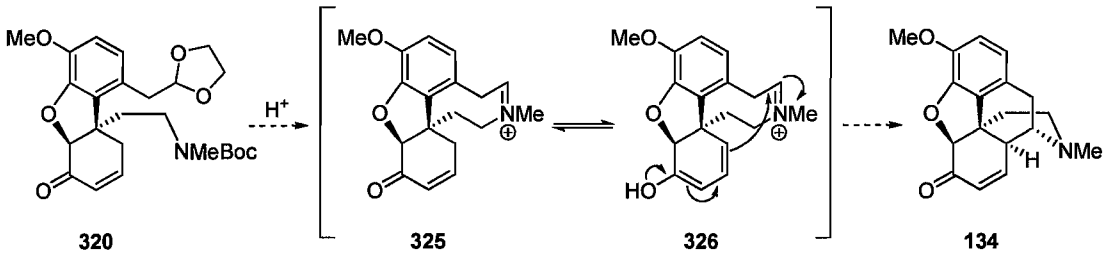


310 316 320

Reagents and conditions: (i) TBAF, THF, 0°C – r.t.; (ii) 5% Pd/C, H_2 (1 atm), MeOH; (iii) IBX, DMF, 0°C – r.t.; (iv) a) LDA, THF, -78°C; b) TMS-Cl; (v) $Pd(OAc)_2$, MeCN

Scheme 52. Synthesis of enone **320**

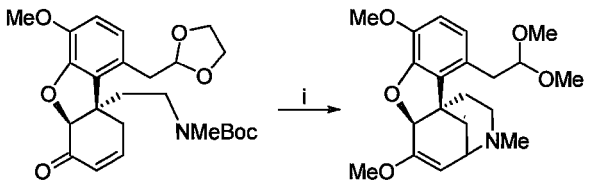
With enone **320** in hand, we sought to develop a method to close the two remaining rings of (+)-codeine. In principle, acidic conditions should reveal the aldehyde, remove the Boc carbamate, and promote the formation iminium **325** (Figure 42). Tautomerization of the enone, and subsequent attack of the resulting 1,3-dienol **326** should close the C14-C9 bond.



320 325 326 134

Figure 42. Theoretical acid-promoted closure of the B- and D-rings

In Fukuyama's 2006 synthesis of morphine,[137] the B- and D-rings were formed in a single step from a substrate similar to enone **320** (Section 2.3.5, compound **225** in Scheme 27). Fukuyama believed the closures proceeded through a Mannich-type reaction and not an aldol condensation/ Michael addition. When we employed identical conditions, **320** in refluxing methanolic hydrogen chloride, we obtained tetracycle **327** (Scheme 53). Clearly the favoured process is the 1,4 conjugate addition of the amine to the enone followed by enol ether formation.

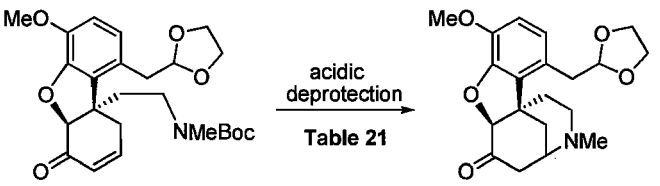


320 327

Reagents and conditions: (i) HCl, MeOH, reflux, 74%

Scheme 53. Synthesis of 1,4 conjugate addition product **327**

We began the search for acidic conditions that would deprotect the ketal/ Boc groups, and initiate closure of the B- and D-rings (Figure 43). All of our attempts employed trifluoroacetic acid and each afforded the Michael addition product **328**.



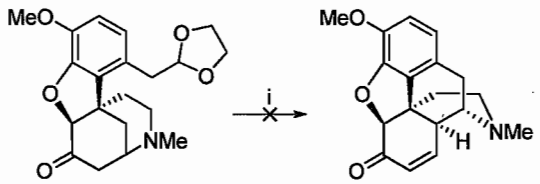
320 328

Figure 43. Acidic deprotection of ketal **320**

Table 21. Acidic deprotection of ketal **320**

Entry	*Acid*	*Solvent*	*Temp.*	*Result*
1	TFA	DCM	reflux	**328** (45%)
2	TFA	MeCN	reflux	**328** (61%)
3	**TFA**	**THF**	**reflux**	**328 (76%)**

We resubmitted piperidine **328** to acidic conditions (i.e. TFA in THF) in an attempt to promote a retro-Michael reaction/ iminium ion formation sequence (Scheme 54). However, we could not find evidence for the formation of (+)-codeinone (**134**).

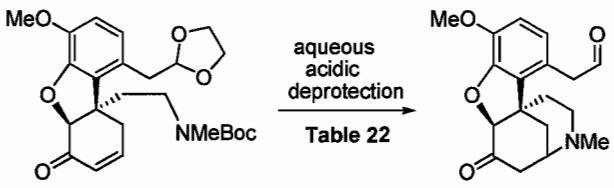


328 134

Reagents and conditions: (i) TFA, THF, reflux

Scheme 54. Attempted retro Michael reaction on piperidine **328**

We also attempted to selectively hydrolyze the ketal over the Boc carbamate using aqueous acidic conditions (Figure 44). We hoped that the free aldehyde would serve as a better electrophile and favour iminium ion formation over 1,4 conjugate addition. All of the conditions we evaluated did hydrolyze the ketal, nevertheless, the Michael addition product **329** was isolated (Table 22).



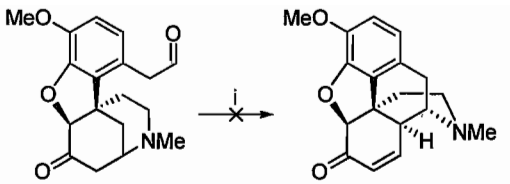
320 329

Figure 44. Aqueous acidic deprotection of ketal **320**

Table 22. Aqueous acidic deprotection of ketal **320**

Entry	*Acid*	*Solvent*	*Temp.*	*Result*
1	aq. AcOH	MeCN	0°C	SM
2	aq. AcOH	MeCN	40°C	**329** (51%)
3	aq. HCl	MeCN	0°C	SM
4	**aq. HCl**	**MeCN**	**40°C**	**329 (77%)**

We subjected piperidine **329** to conditions we hoped would promote a retro Michael reaction (Scheme 55). Once again, we were unable to find evidence for the formation of (+)-codeinone (**134**).

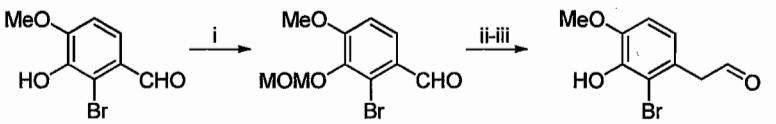


329 134

Reagents and conditions: (i) TFA, THF, reflux

Scheme 55. Attempted retro Michael reaction on piperidine **329**

We attempted to design a route which avoided the selective hydrolysis of a ketal or an enol ether in the presence of a *N*-Boc carbamate. To this end, we prepared A-ring fragment **330** by reacting the MOM-protected 2-bromo iso-vanillin derivative **321** with Wittig reagent **302**. Acidic hydrolysis provided aldehyde **330** in 24% yield over the three steps.



259 321 330

Reagents and conditions: (i) MOM-Cl, EtN(*i*Pr)$_2$, DCM, 0°C; (ii) chloride salt of **302**, *n*-BuLi, THF, -78°C – r.t.; (iii) *p*-TsOH, THF, reflux, 24% over three steps

Scheme 56. Synthesis of A-ring fragment **330**

When we tried our standard Mitsunobu conditions to couple allylic alcohol **258** with arene **330**, the starting materials were decomposed (Table 23, Entry 1). All other conditions we explored were also unsuccessful.

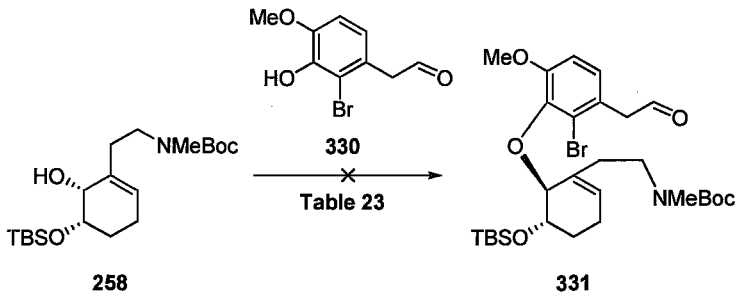


Figure 45. Attempted Mitsunobu coupling between allylic alcohol **258** and arene **330**

Table 23. Attempted Mitsunobu coupling between allylic alcohol **258** and arene **330**

Entry	*Reagents*	*Solvent*	*Temp.*	*Result*
1	DIAD, nBu$_3$P	THF	0°C – r.t.	decomposition[a]
2	DIAD, PPh$_3$	THF	0°C – r.t.	decomposition[a]
3	DIAD, nBu$_3$P	toluene	0°C – r.t.	decomposition[a]

[a] complex mixture of compounds

3.2.4 Prins Reaction Approach

The failure of the Mitsunobu coupling between arene **330** and allylic alcohol **258** necessitated an alternative approach. Hence, we attempted to develop a procedure to selectively deprotect the enol ether functionality of **303** over the acid labile Boc and TBS groups (Figure 46). We theorized that the resulting aldehyde, **332**, could undergo a Prins reaction to close the B-ring. A subsequent dehydration reaction would provide alkene **263**, an intermediate in Hudlicky's 2007 synthesis of (+)-codeine .[147]

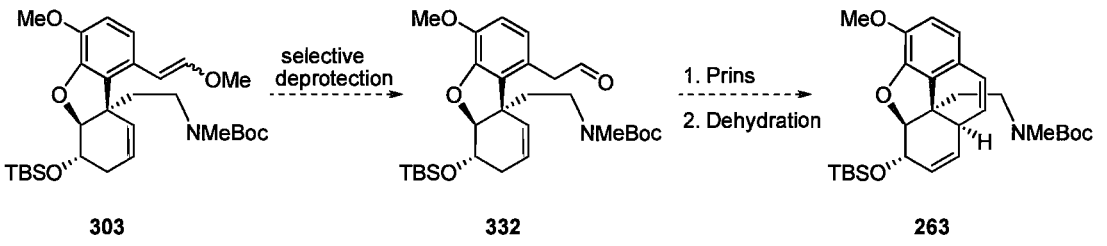
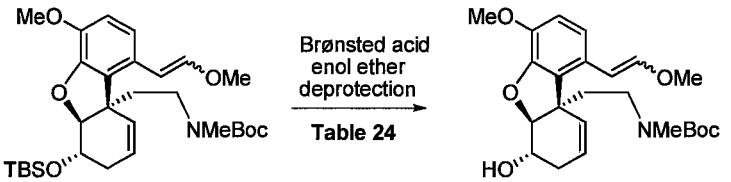


Figure 46. Selective enol ether deprotection

Our first strategy to selectively remove the enol ether functionality employed a Brønsted acid (Figure 47). Treatment of enol ether **303** with 3% perchloric acid at room temperature resulted in the decomposition of the starting material (Table 24). When the same reaction was performed at 0°C, the desilylation product **304** was isolated. The TBS ether appeared to be the most labile group under these conditions, hence we abandoned this approach.



303 **304**

Figure 47. Attempted enol ether deprotection with a Brønsted acid

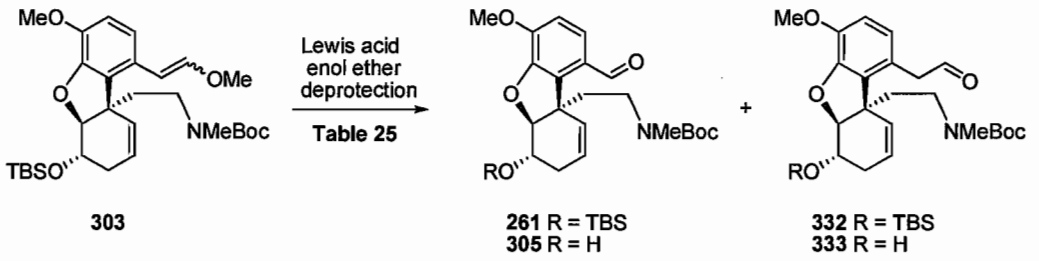
Table 24. Attempted enol ether deprotection with a Brønsted acid

Entry	*Brønsted acid*	*Solvent*	*Temp.*	*Result*
1	3% $HClO_4$	THF	r.t.	decomposition[a]
2	**3% $HClO_4$**	**THF**	**0°C**	**304 (63%)**

[a] complex mixture of compounds

Our second strategy was to attempt a Lewis acid-catalyzed enol ether deprotection (Figure 48). Tokunaga has successfully employed copper(II) chloride in the removal of enol ether groups.[152] When we treated enol ether **303** with 0.1 equivalents of copper(II) chloride in acetonitrile at 40°C we obtained a mixture of benzaldehyde derivatives **261** and **305** along with the phenylacetaldehyde derivatives **332** and **333** (Table 25, Entry 1). We speculated that the two former products were a result of aerobic benzylic oxidation. Hence, we began to purge the reaction mixture with argon. The degassed experiments proved more favourable, as we no longer observed the formation of benzaldehyde derivatives **261** and **305**. We ran the reactions at

various temperatures (0°C to 80°C) and found that 40°C provided the highest ratio of **332**. Before continuing, we exposed our 3:1 mixture to TBS-Cl to obtain only **332**.



303 | **261** R = TBS, **305** R = H | **332** R = TBS, **333** R = H

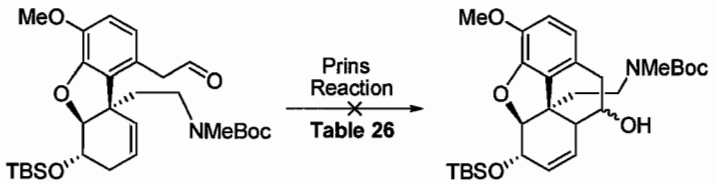
Figure 48. Attempted enol ether deprotection with a Lewis acid

Table 25. Attempted enol ether deprotection with a Lewis acid

Entry	*$CuCl_2$ Equiv.*	*Solvent*	*Temp.*	*Degassed*	*Ratio (**261:305:332:333**)*[a]
1	0.1	MeCN	40°C	no	1:2:1.2:2
2	0.1	MeCN	0°C	yes	_[b]
3	0.1	MeCN	r.t.	yes	0:0:1:4
4	**0.1**	**MeCN**	**40°C**	**yes**	**0:0:1:3**
5	0.1	MeCN	80°C	yes	0:0:1:10
6	1	MeCN	40°C	yes	0:0:1:9

[a] approximate ratio determined from ^{1}H NMR spectra; [b] recovered starting material

We subjected phenylacetaldehyde **332** to Lewis acid conditions in an effort to obtain cyclized product **334** (Figure 49). All of the conditions attempted, with either scandium(III) triflate or trimethylaluminium, did not produce any new compounds (Table 26).



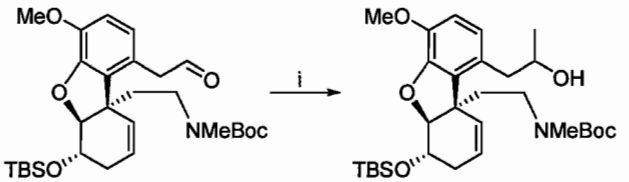
332 | **334**

Figure 49. Attempted Prins reaction on phenylacetaldehyde **332**

Table 26. Attempted Prins reaction on phenylacetaldehyde **332**

Entry	*Lewis Acid*	*Solvent*	*Temp.*	*Result*
1	$AlMe_3$	DCM	0°C	SM
2	$ScOTf_3$	DCM	0°C	SM
3	$ScOTf_3$	DCM	r.t.	SM

When we utilized trimethylaluminium in DCM at room temperature we isolated the methylated product **335** (Scheme 57). Although our efforts thus far have been unsuccessful, we remain optimistic that conditions to promote a Prins cyclization can be found.



332 **335**

Reagents and conditions: (i) $AlMe_3$, DCM, r.t.

Scheme 57. Methylation of phenylacetaldehyde **332**

4. Conclusions and Future Work

The preceding study reviewed our latest efforts in two areas of research; 1. the enantiodivergent synthesis of balanol, and 2. chemoenzymatic synthetic approaches to codeine. We have developed an enantiodivergent synthesis of the (+)- and (–)-isomers of balanol commencing from a single *cis*-dihydrodiol obtained through the TDO-mediated dihydroxylation of bromobenzene. We have explored various synthetic strategies to construct the unnatural isomer of codeine from the TDO-oxidation product of β-bromoethylbenzene. The majority of the research disclosed focused on the closure of the carbocyclic B-ring and the heterocyclic D-ring. Unfortunately, we were unable to find suitable conditions to promote this transformation. In the future, we plan to extensively investigate the Prins and aza-Prins approaches by screening Lewis and Brønsted acids.

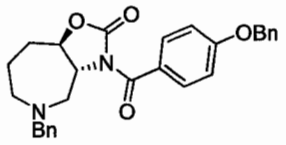
5. Experimental Section

5.1 General experimental procedures

All non-aqueous reactions were carried out in an argon atmosphere using standard Schlenk techniques for the exclusion of moisture and air. Methylene chloride was distilled from calcium hydride. Tetrahydrofuran and benzene were dried over sodium/benzophenone. Analytical thin-layer chromatography was performed on Silicycle 60 Å 250 μm TLC plates with F-254 indicator. Flash column chromatography was performed using 200-400 mesh silica gel. Melting points were recorded on a Hoover Unimelt apparatus and are uncorrected. IR spectra were recorded as thin films on NaCl plates and were obtained on a Perkin-Elmer One FT-IR spectrometer. Optical rotation was measured on a Perkin Elmer 341 polarimeter using a sodium (589, D line) lamp and are reported as follows: $[\alpha]_{\lambda}^{T\,^{\circ}C}$ (c = g/100 mL, solvent). ^{1}H NMR spectra were recorded on a Bruker (300 MHz or 600 MHz) spectrometer and are reported in ppm using tetramethylsilane (0.00 ppm) or solvent ($CDCl_3$: 7.24 ppm, acetone-d_6: 2.05 ppm, DMSO-d_6: 2.50, CD_3OD: 3.31 ppm, D_2O: 2.80) as an internal standard. Data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constant(s) in Hz, integration. Proton-decoupled ^{13}C NMR spectra were recorded at 150 or 75 MHz and are reported in ppm using solvent as an internal standard ($CDCl_3$: 77.23 ppm, acetone-d_6: 206.68 ppm, DMSO-d_6: 39.51 ppm, CD_3OD: 49.15 ppm). Combustion analyses were performed by Atlantic Microlabs, Norcross, GA. Mass spectra were recorded on Kreatus/MsI Concept 1S mass spectrometer at Brock University. The GC/MS data was obtained on

a Perkin-Elmer Clarus 500 Gas Chromatograph and Mass Spectrometer using a Perkin Elmer Elite-5MS column, 10 m, 0.25 mmID, 2 mL/min helium flow.

5.2 Balanol Project Experimental Procedures

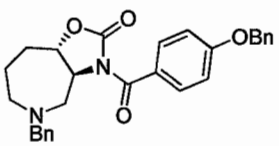


118a

(3a*R*,8a*R*)-5-benzyl-3-[4-(benzyloxy)benzoyl]octahydro-2*H*-[1,3]oxazolo[4,5-*c*]azepin-2-one (118a)

To a stirred solution of **296** (58 mg, 0.151 mmol) in acetone (3 mL) was added a suspension of $NaIO_4$ (322 mg, 1.51 mmol) in distilled water. The reaction was stirred at room temperature for 6 h, then the solvent was removed. The crude residue was triturated with ethyl acetate (3 x 5 mL), then washed with brine (2 x 5 mL). The resulting solution was filtered through a plug of silica gel and concentrated under reduced pressure to yield **(4*S*,5*R*)-3-[4-(benzyloxy)benzoyl]-2-oxo-5-(3-oxopropyl)-1,3-oxazolidine-4-carbaldehyde** which was used without further purification. The dialdehyde intermediate was dissolved in dry MeOH (3 mL) and cooled to −78 °C in an acetone and liquid N_2 bath. To this solution was added 3 Å molecular sieves (150 mg), followed by $NaCNBH_3$ (10 mg, 0.166 mmol) then AcOH (17.3 μL, 0.302 mmol) and finally benzylamine (18.2 μL, 0.166 mmol). The reaction was warmed to room temperature slowly over 24 h before concentrating under reduced pressure. The resulting residue was triturated with ethyl acetate (3 x 5 mL) and washed with $NaHCO_3$ (1 x 3 mL). The organic layer was washed with brine (3 mL), then dried

with Na_2SO_4 before concentrating. The crude material was recrystallized from ethyl ether-hexanes to yield 47 mg (68%) of the title compound as a pale yellow solid: mp 126-128 °C (ethyl ether-hexanes); R_f 0.68 (2:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ –17.9 (*c* 0.07, $CHCl_3$; IR (film) ν 3029, 2835, 1783, 1679, 1604, 1300, 1253, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.7 Hz, 2H), 7.37-7.43 (m, 4H), 7.32-7.37 (m, 2H), 7.29-7.32 (m, 4H), 6.98 (d, *J* = 8.7 Hz, 2H), 5.11 (s, 2H), 4.90 (td, *J* = 3.2, 10.5 Hz, 1H), 4.39 (td, *J* = 7.1, 9.6 Hz, 1H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.64 (d, *J* = 13.2 Hz, 1H), 3.44 (dd, *J* = 6.6, 11.1 Hz, 1H), 2.65-2.70 (m, 1H), 2.60-2.65 (m, 1H), 2.55-2.60 (m, 1H), 2.35-2.39 (m, 1H), 1.73-1.77 (m, 1H), 1.70-1.73 (m, 1H), 1.66-1.70 (m, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.7, 162.8, 154.1, 138.9, 136.1, 132.3, 128.7, 128.4, 128.2, 127.5, 125.2, 114.1, 78.0, 70.1, 63.0, 61.8, 55.3, 51.4, 31.2, 26.4 ppm; MS (EI) *m/z* (%): 412 ($M–CO_2$); 44(20), 91(100), 160(76), 161(10); HRMS ($M–CO_2$) calcd for $C_{27}H_{28}N_2O_2$ 412.2151, found 412.2151; *Anal.* calcd: C 73.66, H 6.18, found C 73.55, H 6.20.



118b

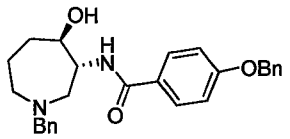
(3a*S*,7a*S*)-5-Benzyl-3-(4-benzyloxy-benzoyl)-octahydro-1-oxa-3,5-diaza-azulen-2-one (118b)

A stirred solution of amide **289** (20 mg, 0.047 mmol) in 1 mL of 9:3:1 (AcOH:tetrahydrofuran:H_2O) was brought to reflux for 16 h then cooled to room temperature and concentrated under reduced pressure. The resulting residue was

triturated with benzene (2 x 1 mL) and $CHCl_3$ (2 x 1 mL), filtered through a plug of SiO_2 then recrystallized from $CHCl_3$ to yield **(3aS,4S,5R,7aS)-3-(4-Benzyloxy-benzoyl)-4,5-dihydroxy-hexahydro-benzooxazol-2-one (290)** (15 mg, 83%) as a white solid: mp 166-167 °C (hexanes-ethyl acetate); R_f 0.31 (1:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ +80.2 (*c* 0.47, $CHCl_3$); IR (film) ν 3684, 3091, 1794, 1604, 1511, 1422, 1303, 1215, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.8 Hz, 2H), 7.29-7.44 (m, 5H), 6.98 (d, *J* = 8.8 Hz, 2H), 5.93 (br s, 1OH), 5.11 (s, 2H), 4.34 (dd, *J* = 9.7, 11.1 Hz, 1H), 4.07 (dd, *J* = 2.6, 5.5 Hz, 1H), 3.95-4.05 (m, 1H), 3.87 (dd, *J* = 3.1, 9.6 Hz, 1H), 3.10 (br s, 1OH), 2.26 (ddd, *J* = 0.1, 3.1, 14.7 Hz, 1H), 2.01-2.10 (m, 2H), 1.54-1.59 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 163.1, 153.6, 136.0, 132.1(2xC), 128.7, 128.3(2xC), 127.6(2xC), 124.6, 114.2(2xC), 77.6, 72.7, 70.2, 68.6, 64.6, 26.7, 22.2 ppm; MS (EI) *m/z* (%): 383 (M), 43(12), 83(20), 84(10), 85(13), 91(100), 211(15); HRMS calcd for $C_{21}H_{21}NO_6$ 383.1369, found 383.1369.

To a stirred solution of **(3aS,4S,5R,7aS)-3-(4-Benzyloxy-benzoyl)-4,5-dihydroxy-hexahydro-benzooxazol-2-one (290)** (58 mg, 0.151 mmol) in 10:1 acetone-H_2O (2 mL) was added $NaIO_4$ (600 mg, 3.00 mmol). The resulting suspension was stirred at room temperature for 6 h, before the solvent was removed under reduced pressure. The crude residue was triturated with ethyl acetate (3 × 5 mL), then washed with brine (2 × 5 mL). The resulting organic layers were filtered through a plug of silica gel and concentrated under reduced pressure to yield **(4R,5S)-3-(4-Benzyloxy-benzoyl)-2-oxo-5-(3-oxo-propyl)-oxazolidine-4-carbaldehyde (291)**, which was used without further purification. Dialdehyde **291** was dissolved in dry MeOH (2 mL) and cooled to –78 °C in an acetone and liquid N_2 bath. To this solution was added 3 Å

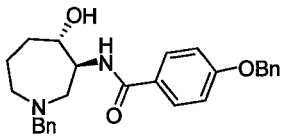
molecular sieves (100 mg), followed by $NaCNBH_3$ (10 mg, 0.166 mmol), then AcOH (17 μL, 0.302 mmol), and finally benzylamine (18 μL, 0.166 mmol). The reaction was warmed to room temperature slowly over 24 h before concentrating under reduced pressure. The resulting residue was triturated with ethyl acetate (3 × 2 mL) and washed with $NaHCO_3$ (1 × 2 mL). The organic layer was washed with brine (1 mL), then dried over Na_2SO_4. The crude material was recrystallized from ethyl ether-hexanes to yield **118b** (38 mg, 60% over 2 steps) as a pale yellow solid: mp 126-128 °C (ethyl ether-hexanes): R_f 0.68 (2:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ +31.1 (*c* 0.9, $CHCl_3$); IR (film) ν 3029, 2835, 1783, 1679, 1604, 1300, 1253, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.6 Hz, 2H), 7.28-7.44 (m, 10H), 6.98 (d, *J* = 8.6 Hz, 2H), 5.11 (s, 2H), 4.90 (t, *J* = 8.5 Hz, 1H), 4.39 (q, *J* = 8.7 Hz, 1H), 3.68 (q, *J* = 18.6 Hz, 2H), 3.40-3.47 (m, 1H), 2.50-2.73 (m, 3H), 2.33-2.45 (m, 1H), 1.69-1.78 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 162.8, 154.1, 138.9, 136.1, 132.5, 132.3(2xC), 128.8, 128.7, 128.4(2xC), 128.2, 127.5(2xC), 127.2, 125.2, 114.2(2xC), 114.1, 78.0, 70.1, 63.0, 61.8, 55.3, 51.4, 31.2, 26.3 ppm; MS (EI) *m/z* (%): 412 (M–CO_2), 44(20), 91(100), 160(76), 161(10); HRMS (M–CO_2) calcd for $C_{27}H_{28}N_2O_2$ 412.2151, found 412.2151.



119a

***N*-[(3*R*,4*R*)-1-benzyl-4-hydroxyazepan-3-yl]-4-(benzyloxy)benzamide (119a)**

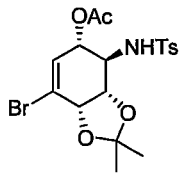
To a stirred solution of **118a** (12 mg, 0.0263 mmol) in freshly distilled THF (0.2 ml) was added 1 N NaOH (1 mL) at -20 °C. The reaction was warmed to room temperature slowly over 12 h before concentrating under reduced pressure. The reaction was concentrated, extracted into ethyl ether (5 x 1 mL), washed with brine and then dried over Na_2SO_4. The crude product was subjected to flash column chromatography (3:1 hexanes-ethyl acetate) to yield **119a** (9 mg, 81%) as yellow oil. R_f 0.19 (1:3 ethyl acetate-hexanes); $[\alpha]_D^{23}$ –4.7 (*c* 0.02, $CHCl_3$); IR (film) ν 3407, 3377, 2955, 1638, 1611, 1298, 1140 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55–1.99 (m, 4H), 2.50 (m, 1H), 2.73 (dd, *J* = 1.9, 14.3 Hz, 1H), 2.93 (dd, *J* = 2.0, 14.2 Hz, 1H), 3.00 (m, 1H), 3.42 (d, *J* = 13.2 Hz, 1H), 3.74–3.78 (m, 2H), 3.88 (m, 1H), 5.15 (s, 2H), 6.54 (d, *J* = 8.7 Hz, 1H), 6.99 (d, *J* = 6.8 Hz, 2H), 7.22–7.50 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.7, 31.5, 54.4, 58.0, 59.9, 64.2, 70.1, 77.5, 114.5, 126.4, 127.4, 127.5 (2x C), 128.2, 128.7 (2x C), 128.9 (2x C), 129.0, 129.5 (2x C), 136.4, 161.4, 167.8 ppm; MS (FAB) *m/z* (%) 431 ($M + H^+$); 41(34), 43(43), 57(51), 71(34), 91(71), 149(100); HRMS calcd for $C_{27}H_{31}N_2O_3$ 431.2310, found 431.2312.



119b

***N*-[(3S,4S)-hexahydro-4-hydroxy-1-(phenylmethyl)-1H-azepin-3-yl]-4-(phenylmethoxy)benzamido (119b)**

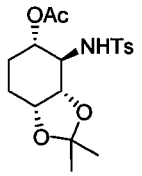
To a stirred solution of azepane **118b** (12 mg, 0.026 mmol) in tetrahydrofuran (0.3 mL) was added 1 N NaOH (1.5 mL) at –20 °C. The reaction mixture was allowed to warm to room temperature slowly over 12 h before concentrating under reduced pressure. The resulting residue was diluted with H_2O (1 mL) and extracted into ethyl acetate (5 x 1 mL), then the combined organic layers were washed with brine (1 mL) and dried over Na_2SO_4. The crude material was purified via flash column chromatography with a solvent system of 3:1 (hexanes-ethyl acetate) to yield **119b** (6.5 mg, 56 %) as a pale yellow oil: R_f 0.31 (3:2, hexane-ethyl acetate); $[\alpha]_D^{23}$ + 5.77 (*c* 0.75, $CHCl_3$); IR (film) ν 3407, 3377, 2955, 1638, 1611, 1298, 1140 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.22–7.50 (m, 12H), 6.99 (d, *J* = 6.8 Hz, 2H), 6.54 (d, *J* = 8.7 Hz, 1NH), 5.11 (s, 2H), 3.88 (m, 1H), 3.69–3.78 (m, 1H), 3.63 (d, *J* = 13.2 Hz, 1H), 3.42 (d, *J* = 13.2 Hz, 1H), 3.00 (m, 1H), 2.93 (dd, *J* = 2.0, 14.2 Hz, 1H), 2.73 (dd, *J* = 1.9, 14.3 Hz, 1H), 2.50 (m, 1H), 1.85-1.95(m, 2H), 1.60-1.85 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 161.4, 136.4(2xC), 129.5(2xC), 129.0, 128.9(2xC), 128.7(2xC), 128.2(2xC), 127.5(2xC), 127.4(2xC), 126.4, 114.5(2xC), 77.5, 70.1, 64.2, 59.9, 58.0, 54.4, 31.5, 29.7 ppm; MS (FAB) *m/z* (%): 431 ($M+H^+$), 41(34), 43(43), 57(51), 71(34), 91(71), 149(100); HRMS calcd for $C_{27}H_{31}N_2O_3$ 431.2310, found 431.2312.



274

(3a*S*,4*R*,5*S*,7a*S*)-7-bromo-2,2-dimethyl-4-{[(4-methylphenyl)sulfonyl]amino}-3a,4,5,7a-tetrahydro-1,3-benzodioxol-5-yl acetate (274)

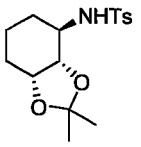
To a stirred solution of tosyl aziridine **273** (200 mg, 0.500 mmol), acetic acid (34 μL, 0.500 mmol) in DCM (2 mL) was added trimethylsilyl trifluoromethanesulfonate (9 μL, 0.0500 mmol). The reaction was stirred at r.t. for 8 h before being quenched with sat. $NaHCO_3$ (4 mL) and extracted into DCM (3 x 5 mL). The resulting crude material was recrystallized from hexanes-ethyl acetate to yield **274** (170 mg, 74%) as a white solid: mp 159-160 °C (hexanes-ethyl acetate); R_f 0.64 (1:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ -119.5 (*c* 0.1, $CHCl_3$); IR (film) ν 3684, 3271, 3019, 2928, 1746, 1649, 1430, 1375, 1334, 1216, 1161, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.1 Hz, 2H), 7.29(d, *J* = 6.3 Hz, 2H), 6.12 (s, 1H), 5.53 (d, *J* = 8.1 Hz, 1H), 5.27 (d, *J* = 7.4 Hz, 1H), 4.67 (d, *J* = 4.5 Hz, 1H), 4.25-4.17 (m, 1H), 3.70-3.60 (m, 1H), 2.41 (s, 3H), 1.95 (s, 3H), 1.33 (s, 3H), 1.30 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 143.2, 138.4, 131.8, 129.4 (2C), 127.2 (2C), 121.0, 111.2, 76.9, 75.8, 70.6, 55.5, 27.4, 26.0, 21.5, 20.8ppm; MS (FAB) *m/z* (%): 460 (M+1), 91 (82), 79 (20), 80 (30), 81 (18), 136 (26), 137 (29), 139 (40), 155 (100), 186 (26), 187 (42), 88 (32), 189 (43), 342 (23), 344 (23), 402 (28); HRMS-FAB calcd for $C_{18}H_{23}BrNO_6S$ 460.0429, found 460.0462.



275a

(3a*S*,4*R*,5*S*,7a*R*)-2,2-dimethyl-4-{[(4-methylphenyl)sulfonyl]amino}hexahydro-1,3-benzodioxol-5-yl acetate (275a)

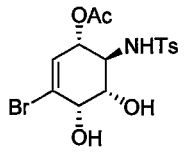
To a stirred solution of **274** (75 mg, 0.175 mmol), NEt_3 (0.17 mL, 1.25 mmol) in ethyl acetate (1 mL) was added platinum(IV)oxide (10 mg, 0.032 mmol) before evacuating the reaction flask with H_2. The reaction was stirred at room temperature and 1 atm for 12 h before filtering through a plug of SiO_2 and concentrating. The crude material was purified using flash column chromatography 2:1 (hexanes-ethyl acetate) and then recrystallized from hexanes-ethyl acetate to yield **275a** (22 mg, 32%) as a white solid: m.p. 155 °C; R_f 0.61 (1:2 hexanes-ethyl acetate); ^{1}H NMR (600 MHz, MeOD) δ 7.80 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 5.11 (d, J = 5.7 Hz, 1H), 4.22-4.16 (m, 1H), 3.67 (dd, J = 8.3, 4.86 Hz, 1H), 3.09-2.97 (m, IH), 2.40 (s 3H), 2.06-1.96 (m, 2H), 1.66-1.52 (m, 1H), 1.52-1.41 (m, 2H), 1.15 (s, 3H), 1.10-1.02 (m, 1H), 1.03 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.2, 137.2, 129.4, 127.5, 108.5, 78.2, 73.9, 56.0, 30.0, 27.5, 26.4, 26.2, 21.4, 19.0 ppm; MS (EI) *m/z* (%): 325 (M); 41(20), 43(51), 59(24), 84(25), 91(98), 96(20), 112(100), 170 (270, 155(66), HRMS calcd for $C_{18}H_{25}NO_6S$ 383.1403, found 383.1401



276

***N*-[(3a*S*,4*R*,7a*R*)-2,2-dimethylhexahydro-1,3-benzodioxol-4-yl]-4-methylbenzenesulfonamide (276)**

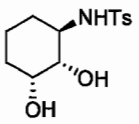
To a stirred solution of **274** (50 mg, 0.153 mmol) and NEt_3 (0.15 mL, 1.07 mmol) in ethyl acetate (2 mL) was added platinum(IV)oxide (12 mg, 0.043 mmol) before evacuating the reaction flask with H_2. The reaction was stirred at room temperature with 1 atm of H_2 for 12 h before being filtered through a plug of SiO_2 and concentrating. The crude material was purified via flash column chromatography 2:1 (hexanes-ethyl acetate) to yield **276** (23 mg, 48%) as a white solid: m.p. 149-148 °C (hexanes-ethyl acetate); R_f 0.40 (2:1 hexanes-ethyl acetate); IR (film) ν 3330, 2985, 2939, 1597, 1496, 1326, 1160, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H) 5.11 (d, *J* = 5.7 Hz, 1H), 4.22-4.16 (m, 1H), 3.76 (dd, *J* = 8.3, 4.8 Hz, 1H), 3.09-2.97 (m, 1H), 2.40 (s, 3H), 2.06-1.96 (m, 2H), 1.66-1.52 (m, 1H), 1.52-1.41 (m, 2H), 1.15 (s, 3H), 1.10-1.03 (m, 1H) 1.02 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.2, 137.2, 129.4 (2C), 127.5 (2C), 108.5, 78.2, 73.9, 56.0, 30.1, 27.5, 26.5, 26.2, 21.5, 19.0 ppm; MS (EI) *m/z* (%): 325 (M), 41 (20), 43 (51), 84 (26), 91 (98), 96 (20), 112 (100), 155 (66), 170 (27), HRMS calcd for $C_{16}H_{23}NO_4S$ 325.1348, found 325.1348.



277

(1*S*,4*S*,5*S*,6*S*)-3-bromo-4,5-dihydroxy-6-{[(4-methylphenyl)sulfonyl]amino}cyclohex-2-en-1-yl acetate (277)

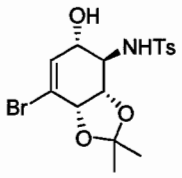
To a stirred solution of aziridine **273** (100 mg, 0.250 mmol), acetic acid (0.28 mL, 4.99 mmol) in DCM (1 mL) was added trimethylsilyl trifluoromethanesulfonate (4.5 μL, 0.0250 mmol). The reaction was stirred at room temperature for 8h before the addition of SiO_2 (200 mg. The resulting slurry was stirred at 50 °C for 12 h, then filtered, triturated (benzene then Et_2O) and concentrated. Recrystallization from $CHCl_3$-hexanes yielded **277** (86 mg, 81%) as a white solid: mp 195-197 °C (hexanes-ethyl acetate); R_f 0.46 (1:2 hexanes-ethyl acetate); $[\alpha]_D^{23}$ -62.61 (*c* 0.145, MeOH); ^{1}H NMR (600 MHz, MeOD) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 5.95 (d, *J* = 2.3 Hz, 1H), 5.10 (dd, *J* = 2.6, 9.0 Hz, 1H), 4.23 (d, *J* = 3.8 Hz, 1H), 3.70 (dd, *J* = 9.2, 11.1 Hz, 1H), 3.58 (dd, 3.9, 11.1, 1H), 2.41 (s, 3H), 1.64 (s, 3H) ppm; ^{13}C NMR (150 MHz, MeOD) δ 170.4, 142.9, 139.6, 129.5 (2xC), 129.1, 126.6 (2xC), 125.5, 73.2, 72.4, 69.5, 53.8, 19.9, 19.1 ppm; MS (FAB) *m/z* (%): 420 (M+1), 91 (82), 79 (20), 80 (30), 81 (18), 136 (26), 137 (29), 139 (40), 155 (100), 186 (26), 187 (42), 88 (32), 189 (43), 342 (23), 344 (23), 402 (28); HRMS calcd for $C_{15}H_{19}BrNO_6S$ 420.0116, found 420.0119.



279

***N*-[(1*R*,2*S*,3*R*)-2,3-dihydroxycyclohexyl]-4-methylbenzenesulfonamide (279)**

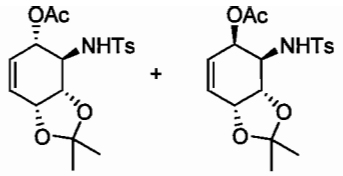
To a stirred solution of **277** (50 mg, 0.120 mmol), NEt_3 (0.12 mL, 0.874 mmol) in ethyl acetate (1 mL) was added platinum(IV)oxide (7 mg, 0.025 mmol) before evacuating the reaction flask with H_2. The reaction was stirred at room temperature and 1 atm for 12 h before filtering through a plug of SiO_2 and concentrating. The crude material recrystallized from hexanes-ethyl acetate to yield **279** (21 mg, 62%) as a white solid; m.p. 112°C (hexanes-ethyl acetate); R_f 0.22 (1:4, hexanes-ethyl acetate); ^{1}H NMR (300 MHz, MeOD) δ 7.78 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 4.00-3.90 (m, 1H), 3.40-3.26 (m, 4H), 2.44 (s, 3H), 2.04-2.02 (m, 3H), 1.79-1.67 (m, 3H), 1.79-1.67 (m, 2H), 1.67-1.56 (m, 1H), 1.56-1.43 (m, 1H), 1.42-1.30 (m, 1H), 1.23- 1.07 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 138.6, 129.2 (2C), 126.7 (2C), 73.6, 68.9, 53.8, 29.5, 20.0, 18.3 ppm; MS (FAB) *m/z* (%): 286 (M+1),69 (22), 89 (24), 90 (21), 91 (100), 95 (24), 96 (46), 97 (39), 105 (22), 107 (36), 112 (30), 113 (30), 128 (20), 136 (30), 137 (45), 138 (25), 139 (47), 149 (47), 155 (189), 172 (50), 286 (80); HRMS calcd for $C_{13}H_{19}NO_4S$ 286.1035, found 286.1035.



280a

***N*-((3aS,4R,5S,7aS)-7-Bromo-5-hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[1,3]dioxol-4-yl)-4-methyl-benzenesulfonamide (280a)**

To a stirred solution of *N*-tosyl aziridine **273** (200 mg, 0.499 mmol), in dimethyl sulfoxide (1.5 mL) was added 10% KOH (1.5 mL). The resulting reaction mixture was heated to 40 °C for 2 h before cooling and being neutralized with sat. NH_4Cl. The crude mixture was extracted into ethyl acetate (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4. The crude material was recrystallized from hexane-ethyl acetate to yield **280a** (196 mg, 94%) as white crystals: mp 155-156 °C (hexanes-ethyl acetate); R_f 0.43 (1:1, hexanes-ethyl acetate); $[\alpha]_D^{23}$ –22.7 (*c* 0.7, $CHCl_3$); IR (film) ν 3445, 2993, 2087, 1646, 1216, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.24 (d, *J* = 3.1 Hz, 1H), 5.48 (br s, 1NH), 4.58(d, *J* = 5.6 Hz, 1H), 4.17 (t, *J* = 6.7 Hz, 1H), 3.99 (br s, 1OH), 3.79 (d, *J* = 4.7 Hz, 1H), 3.33 (t, *J* = 6.8, 1H), 2.41 (s, 3H), 1.28 (s, 3H), 1.06 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 135.9, 134.1, 129.9, 127.6, 120.6, 111.4, 76.3, 75.9, 70.0, 56.7, 27.2, 25.9, 21.6 ppm; MS (EI) *m/z* (%): 402(M-CH_3^+), 43(40), 59(32), 65(30), 91(85), 92(16), 97(15), 98(48), 99(68), 139(30), 155(26), 254(100), 255(15); HRMS calcd for $C_{15}H_{17}BrNO_5S$ 402.0011, found 402.0004; *Anal.* calcd C 45.94, H 4.82, found C 45.88, H 4.80.



281a **281b**

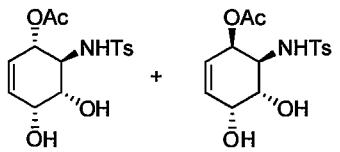
(3a*S*,4*R*,5*S*,7a*R*)-2,2-dimethyl-4-{[(4-methylphenyl)sulfonyl]amino}-3a,4,5,7a-tetrahydro-1,3-benzodioxol-5-yl acetate (281a)

(3a*S*,4*R*,5*R*,7a*R*)-2,2-dimethyl-4-{[(4-methylphenyl)sulfonyl]amino}-3a,4,5,7a-tetrahydro-1,3-benzodioxol-5-yl acetate (281b)

To a stirred solution of **274** (100 mg, 0.217 mmol) in toluene (2.2 mL) was added *n*-Bu_3SnH (86 μL, 0.326 mmol). The reaction was placed in a preheated oil bath (78 °C) before the addition of AIBN (catalytic amount). The reaction was heated at reflux for 5 h before being cooled to room temperature and concentrated. The crude reaction mixture was purified via flash column chromatography (1:1, 1:2, hexanes-ethyl acetate) to give **281a** and **281b** (15:1) as white solids (60 mg, 60%)

281a: ^{1}H NMR (600 MHz, MeOD) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.0.1 Hz, 2H) 5.92 (ddd, *J* = 10.1, 3.6, 2.2 Hz, 1H), 5.76 (d, *J* = 10.2 Hz, 1H), 5.24 (dd, *J* = 8.8, 0.8 Hz, 1H), 4.89 (s, 3H), 4.10 (s, 3H), 4.11 (dd, *J* = 9.7, 6.19 Hz, 1H), 3.46 (t, *J* = 9.74 Hz, 1H), 2.43 (s, 3H), 1.86 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H) ppm; ^{13}C NMR (300 MHz, MeOD) δ ppm; 170.8, 142.6, 139.9, 131.1, 128.9(2C), 126.7(2C), 124.6, 110.2, 75.7, 72.1, 70.8, 56.3, 26.7, 24.6, 19.9, 19.4, ppm; MS (EI) *m/z* (%): 366 (M-CH_3), 43 (100), 44 (20), 59 (23), 80 (36), 91 (75), 98 (32), 99 (48), 108 (45), 109 (28), 155 (21), 169 (25), 254 (29); HRMS calcd for $C_{18}H_{23}NO_6S$ 366.1011, found 325.134366.1011.

281b: ^{1}H NMR (600 MHz, MeOD) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H) 5.97 (dd, *J* = 10.1, 3.5 Hz, 1H), 5.16 (t, J = 4.1 Hz, 1H), 4.67-4.65 (m, 1H), 4.28 (dd, *J* = 6.9, 6.9 Hz, 1H), 3.58 (dd, *J* = 7.8, 3.9, 1H), 2.43 (s, 3H) , 1.91 (s, 3H) , 1.29 (s, 3H) , 1.14 (s, 3H) ppm; ^{13}C NMR (300 MHz, MeOD) δ 170.3, 143.1, 138.4, 129.2(2C), 128.8, 126.9, 126.8, 124.6, 109.3, 73.8, 71.3, 67.6, 53.9, 26.3, 24.5, 20.0, 19.2 ppm; MS (EI) *m/z* (%): 366 (M-CH_3), 43 (100), 44 (20), 59 (23), 80 (36), 91 (75), 98 (32), 99 (48), 108 (45), 109 (28), 155 (21), 169 (25), 254 (29); HRMS calcd for $C_{18}H_{23}NO_6S$ 366.1011, found 325.134366.1011.



282a **282b**

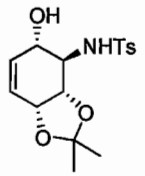
(1*S*,4*R*,5*S*,6*S*)-4,5-dihydroxy-6-{[(4-methylphenyl)sulfonyl]amino}cyclohex-2-en-1-yl acetate (282a)

(1*R*,4*R*,5*S*,6*S*)-4,5-dihydroxy-6-{[(4-methylphenyl)sulfonyl]amino}cyclohex-2-en-1-yl acetate (282b)

To a stirred solution of **277** (40 mg, 0.095 mmol) in toluene (0.95 mL) was added *n*-Bu_3SnH (41 μL, 0.143 mmol). The reaction was placed in a preheated oil bath (78 °C) before the addition of AIBN (catalytic amount). The reaction was heated at reflux for 4 h before being cooled to room temperature and concentrated. The crude reaction mixture was purified via flash column chromatography (1:1, 1:2, 1:4, hexanes-ethyl acetate) to give **282a** and **282b** (8:1 mixture) as an inseparable mixture of white solids (23 mg, 65%): mp 194-195 °C (hexanes-ethyl acetate):

282a: R_f 0.27 (1:4 hexanes-ethyl acetate); IR (film) ν 3684, 3019, 1731, 1599, 1522, 1426, 1374, 1330, 1215, 1046 cm^{-1}, ^1H NMR (600 MHz, MeOD) δ 7.7 (d, *J* = 7.7 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H) 5.87 (dd, *J* = 10.1, 3.9 Hz, 1H), 5.69-5.66 (m, 1H), 5.24 (t, *J* = 4.1 Hz, 1H), 4.89 (s, 3H), 4.28 (t, *J* = 3.8, 1H), 3.92 (dd, *J* = 8.5, 3.9, 1H), 3.84 (dd, *J* = 8.4, 4.5, 1H), 2.43 (s, 3H) ppm; ^{13}C NMR (150 MHz, MeOD) δ 170.6, 143.1, 139.5, 131.9, 129.1(2C), 126.5 (2C), 72.6, 69.7, 66.1, 54.6, 19.9, 19.2 ppm; MS (EI) *m/z* (%): 341 (M), 43 (81), 58 (54), 65 (29), 86 (29), 91 (100), 92 (27), 108 (22), 128 (27), 155 (43); HRMS calcd for $C_{15}H_{19}NO_6S$ 341.0933.1348, found 341.0933.

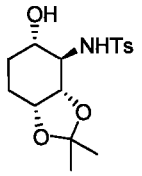
282b: R_f 0.27 (1:4 hexanes-ethyl acetate); IR (film) ν 3684, 3019, 1731, 1599, 1522, 1426, 1374, 1330, 1215, 1046 cm^{-1}, H NMR (600 MHz, MeOD) δ 7.7 (d, *J* = 7.7 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H) 5.87 (dd, *J* = 10.1, 3.9 Hz, 1H), 5.69-5.66 (m, 1H), 5.24 (t, *J* = 4.1 Hz, 1H), 4.89 (s, 3H), 4.28 (t, *J* = 3.8, 1H), 3.92 (dd, *J* = 8.5, 3.9, 1H), 3.84 (dd, *J* = 8.4, 4.5, 1H), 2.43 (s, 3H) ppm; ^{13}C NMR (300 MHz, MeOD) δ 170.3, 143.1, 138.5, 131.9, 129.2, 128.9(2C), 128.5(2C), 125.3, 68.6, 67.9, 65.3, 53.4, 20.0, 19.3 ppm; MS (EI) *m/z* (%): 341 (M), 43 (81), 58 (54), 65 (29), 86 (29), 91 (100), 92 (27), 108 (22), 128 (27), 155 (43); HRMS calcd for $C_{15}H_{19}NO_6S$ 341.0933.1348, found 341.0933.



284

***N*-[(3a*S*,4*R*,5*S*,7a*R*)-5-hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxol-4-yl]-4-methylbenzenesulfonamide (284)**

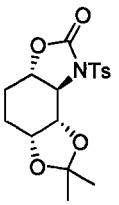
To a stirred solution of aziridine **54** (600 mg, 1.875 mmol), in DMSO (3 mL) was added 10% KOH (4 mL). The reaction mixture was heated to 40 °C for 2 h and then cooled and neutralized. The crude mixture was extracted with ethyl acetate (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude material recrystallized from hexanes-ethyl acetate to yield **284** (567 mg, 93%) as a white solid: m.p. 162-164 °C (hexanes-ethyl acetate); R_f 0.45 (1:2, hexanes-ethyl acetate); $[\alpha]_D^{23}$ -39.509 (*c* 1.10, $CHCl_3$); IR (film) v 3479, 3227, 2986, 2884, 1455, 1380, 1320, 1219, 1090, 1065, 748, 666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.01 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 5.93 (d, *J* = 10.20 Hz, 1H), 5.87-5.79 (m, 1H), 5.01 (s, br) 4.54 (t, *J* = 4.32 Hz, 1H), 4.11 (d, J_{ℓ}= 7.80 Hz, 1H), 3.98 (dd, 8.7, 6.0, 1H), 3.05 (t, *J* = 8.4 Hz, 3H), 2.44 (s, 3H), 1.27 (s, 3H), 0.88 (s, 3H) ppm; ^{13}C NMR (75 MHz, MeOD) δ 142.7, 139.2, 134.9, 128.8 (2C), 127.0 (2C), 122.8, 75.9, 72.1, 69.2, 59.2, 26.6, 24.6, 20.0 ppm; MS (EI) *m/z* (%): 324(M-CH_3), 41(31), 42(18), 43(86), 59(20), 65(26), 69(20), 81(31), 84(20), 91(100), 92(16), 97(16), 98(56), 99(59), 100(25), 109(18), 127(31), 139(37), 155(25), 253(16), 217(50), 255(24); HRMS calcd for $C_{15}H_{18}NO_5S$ 324.0905, found 324.0905



286

***N*-((3aS,4R,5S,7aR)-5-Hydroxy-2,2-dimethyl-hexahydro-benzo[1,3]dioxol-4-yl)-4-methyl-benzenesulfonamide (286)**

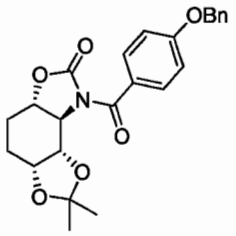
To a stirred solution of allylic alcohol **280a** (196 mg, 0.468 mmol), in MeOH (2 mL) was added K_2CO_3 (10 mg), and platinum(IV)oxide (catalytic amount) before purging the reaction flask with H_2. The reaction mixture was stirred at room temperature and 1 atm of H_2 for 36 h before being filtered through a plug of SiO_2. The crude material was purified via flash column chromatography (1:1 then 1:2, hexanes-ethyl acetate) to yield **286** (123 mg, 77%) as a white solid: m.p. 155-156 °C (hexanes-ethyl acetate); R_f 0.30 (1:2 hexanes-ethyl acetate); $[\alpha]_D^{23}$ –105.2 (*c* 1.32, $CHCl_3$); IR (film) ν 3381, 3255, 2985, 2934, 2893, 2765, 1597, 1155, 1088, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 5.48 (d, *J* = 6.9 Hz, 1H), 4.17-4.10 (m, 1H), 3.72 (dd, *J* = 8.4, 4.9 Hz, 1H), 3.51 (d, *J* = 3.0 Hz, 1H), 3.50-3.35 (m, 1H), 2.97, (q, *J*= 17.4, 8.3 Hz, 1H), 2.39 (s, 3H), 2.11-2.03 (m, 1H), 1.88-1.80 (m, 1H), 1.72-1.57 (m, 2H), 1.18 (s, 3H), 0.937 (s, 3H), ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 137.1, 129.7, 129.4, 127.8, 127.4, 108.9, 78.7, 73.6, 70.7, 63.0, 27.5, 27.4, 26.1, 23.2, 21.5 ppm; MS (EI) *m/z* (%): 341(M), 43(21), 59(34), 65(29), 82(35), 83(20), 91(100), 100(28), 128(65), 155(34), HRMS calcd for $C_{16}H_{23}NO_5S$ 341.1297 found 341.1297; *Anal.* calcd: C 56.29, H 6.79, found C 56.21, H 6.70.



287

(3aR,5aS,8aR,8bS)-2,2-dimethyl-8-(toluene-4-sulfonyl)-hexahydro-[1,3]dioxolo[4',5':3,4]benzo[2,1-d]oxazol-7-one (287)

To a stirred solution of sulfonamide **286** (600 mg, 1.76 mmol), in methylene chloride (5 mL) was added pyridine (1.42 mL, 17.6 mmol) then triphosgene (625 mg, 2.11 mmol). The reaction was stirred at 0 °C for 30 min before being quenched by the addition of water (10 mL) and extracted into methylene chloride (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude material was purified via flash column chromatography (2:1, 1:1 then 1:2, hexanes-ethyl acetate) to yield **287** (567 mg, 93%) as a white solid: m.p. 197-198 °C (hexanes-ethyl acetate); R_f 0.58 (1:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ –2.56 (*c* 0.56, $CHCl_3$); IR (film) ν 3557, 3027, 2987, 2890, 1797, 1597, 1495, 1438, 1379, 1180, 1153 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.59 (dd, *J* = 7.6, 5.5 Hz, 1H), 4.38-4.32 (m, 1H), 3.90 (td, *J* = 11.7, 3.5 Hz, 1H), 3.38 (dd, *J* = 11.6, 8.0 Hz, 1H), 2.42 (s, 3H), 2.32-2.22 (m, 1H), 2.06-1.97 (m, 1H), 1.90-1.74 (m, 1H), 1.73-1.65 (m, 1H) 1.46 (s, 3H), 1.40 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 145.6, 133.8, 130.1, 129.7, 128.8, 128.6, 108.9, 76.4, 76.1, 73.2, 68.4, 28.5, 25.9, 24.7, 22.4, 21.7 ppm; MS (EI) *m/z* (%): 367 (M), 41(23), 43(52), 65(29), 83(69), 85(45), 91(100), 155(47), 352(48) HRMS calcd for $C_{17}H_{21}NO_6S$ 367.1089, found 367.1089; *Anal.* calcd: C 55.57, H 5.76, found C 55.67, H 5.60.



289

(3aR,5aS,8aR,8bS)-8-(4-Benzyloxy-benzoyl)-2,2-dimethyl-hexahydro-[1,3]dioxolo[4',5':3,4]benzo[2,1-d]oxazol-7-one (289)

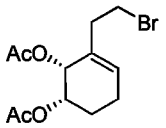
To a stirred solution of *N*-tosyl cyclic carbamate **287** (560 mg, 1.52 mmol), in tetrahydrofuran (2 mL) was added sodium naphthalide (0.5 M.) at –78 °C until a green colour persisted. The reaction mixture was stirred at –78 °C for 30 min before being quenched by the addition of sat. NH_4Cl (5 mL). The crude mixture was extracted into diethyl ether (3 x 10 mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude reaction mixture was purified via flash column chromatography (2:1, 1:1 then 1:2, hexanes-ethyl acetate) to yield **(3aR,5aS,8aR,8bS)-2,2-dimethyl-hexahydro[1,3]dioxolo[4',5':3,4]benzo[2,1-d]oxazol-7-one (288)** (300 mg, 92%) as a white solid: m.p. 134-136 °C (hexanes-ethyl acetate); R_f 0.31 (1:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ –89.2 (*c* 2.9, $CHCl_3$); IR (film) v 3450, 3305, 2987, 2938, 2894, 1860, 1855, 1647, 1547, 1466, 1383, 1239, 1061 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.16 (br s, 1H), 4.30-4.25 (m, 1H), 4.07 (dd, *J* = 8.8, 5.0 Hz, 1H), 3.81 (td, *J* = 11.5, 3.6 Hz, 1H), 3.48 (dd, *J* = 11.5, 9.1 Hz, 1H), 2.42-2.27 (m, 1H), 2.10-2.03 (m, 1H), 1.89-1.79 (m, 1H), 1.57 (br s, 1H), 1.47 (s, 3H), 1.32 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.1, 109.4, 77.9, 77.7, 73.3, 62.9, 28.4, 25.9, 24.7, 24.0 ppm; MS (EI) *m/z* (%): 213 (M), 41(31), 43(100), 55(28), 59(34), 67(48), 82(35), 83(21), 85(22), 98(23), 99(80), 127(22), 198(87),

HRMS calcd for $C_{10}H_{15}NO_4$ 213.1001, found 213.1001; *Anal.* calcd C 56.33, H 7.09, found C 56.23, H 7.02.

To a stirred solution of NaH (18.5 mg, 0.774 mmol) in THF (1 mL) was added **(3aR,5aS,8aR,8bS)-2,2-Dimethyl-hexahydro-[1,3]dioxolo[4',5':3,4]benzo[2,1-d]oxazol-7-one** (**288**) (110 mg, 0.516 mmol), in tetrahydrofuran (1 mL) dropwise at 0 °C. The reaction was allowed to warm to room temperature over 1 h before the addition of 4-benzyloxy benzoyl chloride (127 mg, 0.516 mmol) in four portions over 2 h. The reaction mixture was stirred for 12 h before being quenched by the addition of sat. NH_4Cl (2 mL). The tetrahydrofuran was removed under reduced pressure and the aqueous layer was extracted into ethyl acetate (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude reaction mixture was purified via flash column chromatography (4:1, 2:1 then 1:1, hexanes-ethyl acetate) to yield **289** (220 mg, 91%) as a white solid: m.p. 149-150 °C (hexanes-ethyl acetate); R_f 0.62 (1:1 hexanes-ethyl acetate); $[\alpha]_D^{23}$ + 0.72 (*c* 2.1, $CHCl_3$); IR (film) ν 3682, 3531, 3379, 3066, 3019, 2989, 2937, 2889, 2587, 1952, 1786, 1697, 1603, 1382, 1256, 1216 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.31-7.42 (m, 5H), 6.97 (d, *J* = 8.3 Hz, 2H), 5.10 (s, 2H), 4.29 (dd, *J* = 4.2, 7.9 Hz, 1H), 4.20-4.27 (m, 2H), 3.94 (dd, *J* = 3.8, 11.3 Hz, 1H), 2.31-2.36 (m, 1H), 2.15-2.20 (m, 1H), 1.93-1.97 (m, 1H), 1.88-1.93 (m, 1H), 1.68 (s, 3H), 1.34 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 163.3, 155.1, 136.1, 132.6(2xC), 128.7, 128.3(2xC), 127.6(2xC), 125.4, 114.3(2xC), 109.6, 78.2, 75.4, 73.7, 70.2, 63.8, 27.9, 25.9, 24.7, 23.5 ppm; MS (EI) *m/z* (%): 423 (M), 43(67), 65(20), 83(24), 85(68), 91(100),

92(25), HRMS calcd for $C_{24}H_{25}NO_6$ 423.1682, found 423.1682; *Anal.* calcd: C 68.07, H 5.95, found C 68.14, H 5.96.

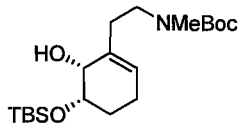
5.3 Codeine Project Experimental Procedures



257

(1*R*,6*S*)-Acetic acid 6-acetoxy-2-(2-bromoethyl)-cyclohex-2-enyl ester (257)

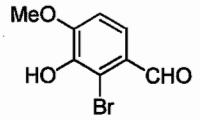
Diol **241** (2 g, 9 mmol) was dissolved in CH_2Cl_2 (20 mL) and transferred to a 100 mL round-bottomed flask. The flask was cooled externally in an ice bath before sequential addition of NEt_3 (3.6 mL, 27 mmol), acetic anhydride (1.85 mL, 20 mmol), and DMAP (244 mg, 2 mmol). The reaction mixture was allowed to warm to r.t. over 5 h. The mixture was cooled to 0 °C before being washed with 1 N HCl (2 x 10 mL), sat $NaHCO_3$ (1 x 10 mL), and brine (1 x 10 mL). The organic layer was dried over anhydrous $MgSO_4$, and the drying agent removed by filtration through a short column (ca 4 cm) of silica gel. Evaporation of the organic solvent furnished **257** (4.02, 67%) as a yellow oil: $[\alpha]^{23}_D$ -120.5 (*c* 0.9, CH_2Cl_2); R_f 0.5 (hexanes-ethyl acetate, 3:1); IR (film) ν 2947, 1738, 1434 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (t, *J* = 3.3 Hz, 1H), 5.47 (d, *J* = 3.3 Hz, 1H), 4.99 (dt, *J* = 11.7, 3.6 Hz, 1H), 3.39 (td, *J* = 7.2, 2.4 Hz, 2H), 2.53 (m, 2H), 2.24-2.20 (m, 2H), 2.08 (s, 3H), 1.99 (s, 3H), 1.90-1.83 (m, 1H), 1.77-1.71 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 170.2, 131.2, 130.4, 70.0, 67.3, 37.4, 30.6, 24.0, 22.2, 20.9, 20.9 ppm; HRMS-EI (M^+) Calcd for $C_{12}H_{17}O_4Br$ 304.0310, found 304.0317; *Anal.* calcd: C, 47.23; H, 5.62, found C, 47.42, H, 5.67.



258

{2-[5-(*tert*-butyl-dimethyl-silanyloxy)-6-hydroxy-cyclohex-1-enyl]-ethyl}-methyl-carbamic acid *tert*-butyl ester (258)

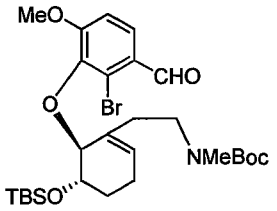
To a solution of diol **265** (426 mg, 2 mmol) in 30 mL of CH_2Cl_2 at -70 °C was added triethylamine (0.53 mL, 4 mmol) before the addition of TBS-triflate (0.50 mL, 2.2 mmol) was added dropwise over 3 min. The reaction stirred for 10 min before being quenched by addition of H_2O (15 mL). The layers were separated, and the aqueous layer extracted with $CHCl_3$ (2 x 10 mL). The combined organic phase was washed with cold 2% aq. HCl, sat. $NaHCO_3$, and then dried over $MgSO_4$. Evaporation of the solvent gave a crude oil, which was purified via flash column chromatography (1:1, hexanes-ethyl acetate,) to give **258** (435 mg, 66%) as a clear and colourless oil: R_f 0.47 (DCM:EtOAc, 96:4); $[\alpha]_D^{24}$ -22.6 (*c* 0.5, $CHCl_3$); IR (film) ν 3556, 3475, 2953, 2857, 1692, 1472, 1392, 1253, 1085 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) mixture of rotamers δ 5.54 (s, 1H), 5.52 (s, 1H), 3.98 (s, 1H), 3.90 (s, 1H), 3.79 (s, 1H), 3.77 (s, 1H), 3.26-3.20 (m, 2H), 2.85 (s, 3H), 2.82 (s, 3H), 2.39 – 2.32 (m, 2H), 2.30 – 2.23 (m, 2H), 2.13 (br s, 2H), 1.98 (br s, 2H) 1.80 – 1.72 (m, 2H), 1.54 (s, 2H), 1.44 (s, 18H), 0.9 (s, 18H), 0.11 (s, 6H), 0.10 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.7, 134.8, 126.6, 79.0 (br), 71.0, 68.8, 48.4, 47.2, 34.1, 33.3, 32.8, 28.4, 25.8, 25.4, 25.3, 24.3, 24.1, 18.1, -4.4, -4.8 ppm; MS (EI) *m/z* (%): 228 (21), 197 (21), 136 (12), 74 (22), 73 (15), 57 (63), 44 (100) HRMS-EI (M^+-57) calcd for $C_{12}H_{30}NO_4Si$ 328.1944, found 328.1946; *Anal.* calcd. for $C_{20}H_{39}NO_4Si$ C 62.10, H 10.22, found C 62.29, H 10.19.



259

2-Bromo-4-methoxy-3-hydroxybenzaldehyde, 259

To a solution of isovanillin **299** (51 g, 337 mmol) in chloroform (1.1 L) was added *N*-bromosuccinimide (72 g, 405 mmol) portion-wise under an atmosphere of nitrogen. The mixture was heated at reflux until total consumption of the starting material (TLC analysis). The reaction was quenched with H_2O and then concentrated. The crude mixture was washed with 3:1 ethyl acetate-methanol (150 mL) and 3:1 methanol: water (150 mL) and dried over Mg_2SO_4 to yield **259** (58.5 g, 75%) as a white solid: R_f 0.27 (2:1, hexanes-ethyl acetate); m.p. 202-204 °C (ethyl acetate); IR (film) ν 3188, 2922, 1666, 1561, 1493, 1278, 774 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 10.24 (s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.05 (s, 1H), 3.99 (s, 3H), 1.54 (s, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.9, 151.7, 143.2, 127.2, 122.8, 112.9, 109.3, 56.6 ppm; MS (EI) *m/z* (%) 232 (85), 231 (89), 230 (100), 229 (87), 228 (13), 80 (11), 79 (25), 51 (22), 50 (14); HRMS-EI (M) $C_8H_7BrO_3$ 229.9579, found 229.9578.

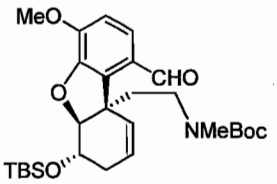


260

{2-[6-(2-Bromo-3-formyl-6-methoxy-phenoxy)-5-(*tert*-butyl-dimethyl-silanyloxy)-cyclohex-1-enyl]-ethyl}-methyl-carbamic acid *tert*-butyl ester (260)

To a stirred solution of DIAD (1.02 mL, 5.207 mmol) in 10 mL anhydrous THF at -10 °C was added freshly distilled tributyl phosphine (1.69 mL, 5.207 mmol) dropwise. The solution was stirred at -10 °C for 10 min, then transferred dropwise to an anhydrous THF (20 mL) solution of bromoisovanillin **259** (0.925 g, 4.005 mmol) and allylic alcohol **258** (1.39 g, 3.605 mmol) at -78 °C. Once the addition was completed, the reaction vessel was warmed to 0 °C and stirred for 1 h then stirred at r.t. for an additional 48 h. The solvent was removed under reduced pressure and the crude mixture was subjected to column chromatography (DCM-EtOAc, 100:0, 98:2) to yield **260** (1.01 g, 55%) as colourless oil: R_f 0.81 (DCM:EtOAc, 96:4); $[\alpha]_D^{23}$ +75.7 (*c* 0.7, $CHCl_3$); IR (film) ν 3007, 2952, 2929, 2857, 1688, 1578, 1481, 1275, 1252, 1173, 1085, 1028, 1005, 836 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) mixture of rotamers δ 10.30 (s, 2H), 7.75 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 5.85 (s, 1H), 5.83 (s, 1H), 4.57 (s, 2H), 3.98 (br s, 8H), 3.59 (s, 1H), 3.44 (s, 1H), 3.22 (br s, 2H), 2.85 (br s, 6H), 2.55 – 2.37 (m, 4H), 2.28 – 2.17 (m, 4H), 2.06 (s, 1H), 2.04 (s, 1H), 1.72 – 1.65 (m, 2H), 1.46 (s, 18H), 0.75 (s, 18H), -0.12 (s, 6H), -0.17 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.3, 157.9, 155.8, 144.6, 130.9, 130.3, 127.7, 125.9, 123.5, 110.9, 80.3, 79.1, 67.7, 56.1, 48.9, 48.3, 41.5, 35.0, 33.4, 32.7, 28.5,

25.6, 25.4, 20.8, 18.0, -4.9, -5.1 ppm; MS (EI) *m/z* (%): 312 (28), 269 910), 268 (45), 237 (24), 136 (31), 109 (14), 75 (27), 73 (33), 57 (47), 44 (100); HRMS-EI (M): calcd for $C_{28}H_{44}NO_6BrSi$ 597.2121, found 597.2140; *Anal.* Calcd. for $C_{28}H_{44}NO_6BrSi$ C 56.18, H 7.41, found C 56.09, H 7.65.

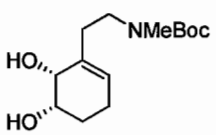


261

{2-[6-(*tert*-butyl-dimethyl-silanyloxy)-1-formyl-4-methoxy-6,7-dihydro-5a*H*-dibenzofuran-9a-yl]-ethyl}-methyl-carbamic acid *tert*-butyl ester (261)

Aryl bromide **260** (205 mg, 0.3424 mmol) was dissolved in 5 mL of degassed toluene and transferred to a 10 mL Teflon-sealed Schlenck tube containing a magnetic stirring bar. Silver carbonate (283.3 mg, 1.0272 mmol), diphenylphosphino ferrocene (57.00 mg, 0.1027 mmol) and palladium acetate (12 mg, 0.0514 mmol) were added sequentially. The tube was flushed with nitrogen, sealed, and placed in a pre-heated oil bath at 110 °C for 50 min. A small aliquot of the reaction mixture was filtered through Celite, and ^{1}H NMR analysis of this aliquot indicated complete conversion to the product. The remaining black reaction mixture was filtered through Celite and washed with several portions of chloroform. The filtrate was adsorbed onto a mixture of silica gel and charcoal and then filtered through a plug of silica gel. Column chromatography (CH_2Cl_2-EtOAc, 4:1) gave **261** (146 mg, 82%) as a semi-crystalline brown solid: R_f 0.79 (DCM:EtOAc, 96:4); $[\alpha]_D^{23}$ +12.5 (*c* 0.6, $CHCl_3$); IR (film) ν 3008, 2953, 2930, 2856, 2734, 1692, 1610, 1571, 1436, 1366, 1285, 1250, 1170,

1155, 1046, 837 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) mixture of rotamers δ 9.90 (s, 1H), 9.89 (s, 1H), 7.38 (d, J = 8.2 Hz, 2H), 6.93 – 6.86 (m, 2H), 6.49 -6.40 (m, 1H), 6.40 – 6.32 (m, 1H), 5.72 – 5.65 (m, 2H), 4.80 – 4.54 (m, 2H), 3.95 (s, 6H), 3.91 (br s, 2H), 3.32 (br s, 1H), 3.25 – 3.16 (m, 1H), 3.03 – 2.93 (m, 2H), 2.78 (s, 6H), 2.30 – 2.00 (m, 8H), 1.43 (s, 18H), 0.91 (s, 18H), 0.14 (s, 6H), 0.04 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.6, 155.5, 150.2, 147.5, 133.6, 130.4, 129.8, 129.2, 126.5, 124.1, 110.4, 90.9, 89.9, 79.5, 68.8, 68.4, 56.0, 55.9, 51.8, 45.3, 44.6, 36.4, 35.5, 34.7, 34.6, 34.1, 31.6, 30.5, 29.1, 28.4, 25.8, 25.7, 25.3, 22.7, 20.7, 18.1, 14.1, 11.4, -4.7, -5.2 ppm; MS (EI) *m/z* (%): 162 (12), 144 (17), 136 (12), 118 (13), 117 (18), 92 (32), 91 (38), 88 (11), 75 (46), 73 (38), 57 (87), 44 (100) HRMS-EI (M^+-57) Calcd for $C_{24}H_{34}NO_6Si$ 460.2155, found: 460.2150; *Anal.* calcd. for C 64.96, H 8.37, found C 64.87, H 8.46

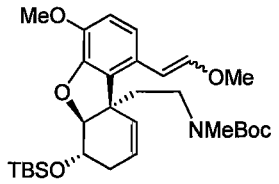


265

[2-(5, 6-Dihydroxy-cyclohex-1-enyl)-ethyl]-methyl-carbamic acid *tert*-butyl ester, 265

Bromide **257** (6.34 g, 20.8 mmol) was dissolved in 20 mL anhydrous THF and transferred to a 50 mL thick-walled reaction vessel containing K_2CO_3 (1.61 g, 11.6 mmol) and a magnetic stirring bar. The reaction vessel was cooled to -40 °C, and gaseous methylamine was passed through the solution for 15 min. The reaction vessel was sealed, and the mixture stirred at r.t. for 48 h. The vessel was cooled to -40 °C before it was carefully opened. Potassium salts were removed by filtration and rinsed

with 15 mL DCM. The solvent was removed and the residue taken up in 50 mL anhydrous DCM. Triethylamine (5.20 mL, 37.4 mmol) was added to the solution and the reaction mixture was cooled to 0 °C in an ice salt bath. Boc anhydride (8.53 g, 37.4 mmol) was added and the reaction mixture was stirred at r.t for 24 h. The reaction was washed with sat. ammonium chloride (3 x 100 mL) and sat. sodium carbonate (3 x 120 mL), brine (100 mL), and then dried with Na_2SO_4. The solvent was then removed under reduced pressure and the crude mixture was subjected to column chromatography (6:1, 1:2, hexanes ethyl acetate) to afford **265** (2.51g, 50% over two steps); R_f 0.07 (ethyl acetate-hexanes, 2:1); IR (film) ν 3383, 2974, 2930, 1693, 1672 , 1396, 1158, 988 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.43 (br s, 1H), 4.87 (br s, 1H), 3.96 (br s, 2H), 3.56 (br s, 1H), 2.99 (d, J = 8.8 Hz, 1H), 2.91 (br s, 1H), 2.86 (s, 3H), 2.42 – 2.30 (m, 1H), 2.18 (d, J = 13.4 Hz, 1H), 2.03 (br s, 2H), 1.74 – 1.63 (m, 1H), 1.60 – 1.45 (m, 1H), 1.43 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.0, 133.9, 128.8, 79.9, 70.0, 69.8, 48.3, 34.8, 34.0, 28.3, 25.4, 24.8 ppm; MS (EI) *m/z* (%): 144 (12), 110 (110), 57 (71), 44 (100); HRMS-EI (M^+) Calcd for $C_{14}H_{25}NO_4$ 271.1784, found 271.1785

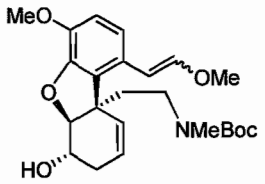


303

***tert*-butyl {2-[(5a*S*,6*S*,9a*R*)-6-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methoxy-1-[(*E*)-2-methoxyvinyl]-6,7-dihydrodibenzo[*b*,*d*]furan-9a(5a*H*)-yl]ethyl}methylcarbamate (303)**

(Methoxymethyl)triphenyl-phosphonium chloride (430 mg, 1.255 mmol) was suspended in anhydrous THF (4 mL) and cooled to -78 °C. *tert*-BuLi (1.40 M in THF, 900 μL, 1.255 mmol) was added dropwise. The reaction mixture was then stirred at -78 °C for 15 min. In a second flask, aryl aldehyde **261** (260 mg, 0.502 mmol) was dissolved in 8 mL anhydrous THF. The ylid/THF solution was cannulated into the aldehyde solution at r.t, and the resulting mixture was stirred for 3 h before being filtered through a plug of SiO_2 and concentrated. The crude material was purified via flash column chromatography with a solvent system of 5:1 (hexanes-ethyl acetate) to yield **303** (mixture of *E* & *Z* isomers, 183 mg , 70 %) as a clear oil: R_f 0.7 (hexanes-ethyl acetate, 1:1); IR (film) ν 2930, 2855, 1696, 1640, 1504, 1462, 1421, 1391, 1365, 1279, 1251, 1213, 1155, 1123, 1017, 837, 778, 666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) mixture of geometric isomers and rotamers δ 7.39 (d, *J* = 8.7 Hz, 1H), 6.85-6.60 (m, 4H), 6.15 (d, *J* = 6Hz, 1H), 6.10-5.80 (m, 3H), 5.80-5.60 (m, 2H), 5.35 (s, 1H), 4.50 (s, 2H), 4.10-3.90 (m, 2H), 3.90-3.75 (m, 7H), 3.75 (s, 3H), 3.74 (s, 3H), 3.50-3.10 (m, 2H), 3.10-2.85 (m, 2H), 2.78 (s, 7H), 2.35-2.20 (m, 2H), 2.20-1.75 (m, 9H), 1.71 (d, *J* = 6 Hz, 1H), 1.50-1.30 (m, 20H), 1.00-0.80 (m, 20H), 0.15 (s, 6H), 0.05 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 149.1, 147.4, 146.3, 143.7, 143.4, 129.2,

124.4, 124.3, 122.8, 118.7, 111.7, 111.4, 101.2, 68.4, 60.5, 60.4, 55.9, 55.8, 28.5, 28.4, 25.9, 21.0, 18.1, 14.2, -4.7, -5.2 ppm; MS (EI) *m/z* (%): 184 (50), 135 (15), 84 (80), 71 (19), 43 (100); Calcd for $C_{30}H_{47}NO_6Si$ 545.3173, found 545.3170.

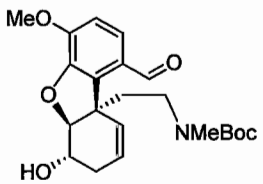


304

***tert*-butyl {2-[(5a*S*,6*S*,9a*R*)-6-hydroxy-4-methoxy-1-[(*E*)-2-methoxyvinyl]-6,7-dihydrodibenzo[*b*,*d*]furan-9a(5a*H*)-yl]ethyl}methylcarbamate (304)**

Enol ether **303** (384 mg, 0.7042 mmol) was dissolved in 6 mL of THF at 0 °C, and then TBAF (1.0 M in THF, 775 μL, 0.7746 mmol) was added. The reaction mixture was stirred at r.t for 3 h. A second portion of TBAF (352 μL) was added at r.t, and the reaction was allowed to stir for an additional 2 h. The reaction was quenched with water (10 mL) and extracted into DCM (3 x 15 mL). The organic phase was washed with brine and dried over sodium sulfate. The crude material was subjected to column chromatography (hexanes-ethyl acetate, 9:1, 4:1, 1:1) to afford **304** (mixture of *E* & *Z* isomers, 225 mg, 74%) as an oil: R_f 0.2 (hexanes-ethyl acetate, 1:1); IR (film) ν 3426, 2933, 1682, 1572, 1504, 1483, 1423, 1399, 1366, 1282, 1215, 1156, 1098, 1046, 1015, 882 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) mixture of geometric isomers and rotamers δ 6.79-6.65 (m, 3H), 6.20-6.05 (m, 1H), 6.00-5.85 (m, 1H), 5.85-5.70 (m, 1H), 4.70-4.25 (m, 1H), 4.00-3.80 (m, 5H), 3.76 (d, *J* = 3.6 Hz, 1H), 3.71 (s, 3H), 3.60-3.10 (m, 2H), 3.00-2.50 (m, 7H), 2.50-2.30 (m, 2H), 2.20-1.70 (m, 6H), 1.45 (s, 12H), 1.40-1.20 (m, 4H), 1.01-0.80 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ

155.5, 149.3, 147.6, 145.7, 145.4, 143.7, 143.4, 143.1, 130.1, 129.2, 127.6, 125.4, 124.7, 124.6, 124.4, 123.1, 119.3, 111.7, 111.6, 111.3, 111.2, 101.5, 101.3, 96.1, 90.3, 89.6, 79.5, 78.1, 77.3, 77.0, 76.8, 68.2, 67.8, 60.7, 60.6, 57.0, 56.1, 56.0, 55.9, 55.8, 53.5, 51.4, 51.3, 48.4, 45.2, 44.8, 37.1, 36.6, 36.1, 34.3, 32.0, 29.7, 29.4, 29.0, 28.5, 24.7, 22.7, 14.2, 13.7, 1.0 ppm; MS (EI) *m/z* (%): 142 (25), 84 (100), 71 (28), 57 (43), 43 (88); HRMS (EI) Calcd for $C_{24}H_{33}NO_6$ 431.2308, found 431.2308.



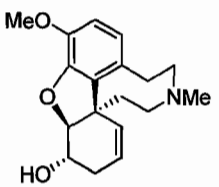
305

***tert*-butyl-{2-[(5a*S*,6*S*,9a*R*)-1-formyl-6-hydroxy-4-methoxy-6,7-dihydrodibenzo[*b*,*d*]furan-9a(5a*H*)-yl]ethyl}methylcarbamate (305)**

Method A: To a stirred solution of **304** (40 mg, 0.0927 mmol) in DCM (0.3 mL) was added sodium acetate (2.5 mg, 0.0278 mmol) and pyridinium chlorochromate (40 mg, 0.185 mmol) at 0 °C. The reaction was allowed to warm to room temperature before being filtered through SiO_2 and concentrated under reduced pressure. The crude material was purified via flash column chromatography with a solvent system of 3:1 (hexanes-ethyl acetate) to yield **305** (26 mg, 67 %) as a colourless oil.

Method B: To a solution of aryl bromide **261** (400 mg, 0.774 mmol) in THF (3 mL) was added TBAF in THF (1.2 mL, 1.161 mmol) at 0 °C. The resulting reaction mixture was warmed slowly to room temperature before being quenched with water (6 mL). The organic layer was removed under reduced pressure and the resulting aqueous layer was extracted with DCM (3 x 10 mL), washed with brine (1 x 5 mL),

dried with Na_2SO_4, filtered and concentrated. Purification by flash column chromatography (hexanes-ethyl acetate, 1:1) gave **305** (15 mg, 92%) as colourless oil: R_f 0.31 (hexanes-ethyl acetate, 1:1); $[\alpha]_D^{24}$ +22.5 (*c* 0.6, $CHCl_3$); IR (film) ν 3684, 3608, 3019, 2978, 2933, 1688, 1612, 1571, 1436, 1285, 1215 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) two rotamers δ 9.90 (s, 1H), 9.89 (s, 1H), 7.38 (d, *J* = 8.2 Hz, 2H), 6.86 - 6.93 (m, 2H), 6.40 - 6.49 (m, 1H), 6.32 - 6.40 (m, 1H), 5.65 - 5.72 (m, 2H), 4.54 - 4.80 (m, 2H), 3.95 (s, 6H), 3.91 (bs, 2H), 3.32 (bs, 1H), 3.16 - 3.25 (m, 1H), 2.93 - 3.03 (m, 2H), 2.78 (s, 6H), 2.01 - 2.29 (m, 8H), 1.43 (s, 18H), ppm; ^{13}C NMR (150 MHz, $CDCl_3$) two rotamers δ 190.6, 155.5, 150.2, 147.5, 133.6, 130.4, 129.8, 129.2, 126.5, 124.1, 110.4, 90.9, 89.9, 79.5, 68.8, 68.4, 56.0, 55.9, 51.8, 45.3, 44.6, 36.4, 35.5, 34.7, 34.6, 34.1, 31.6, 30.5, 29.1, 28.4, 25.8, 25.7, 25.3, 22.7, 20.7, 18.1, 14.1, 11.4, -4.7, -5.2 ppm; MS (EI) *m/z* (%): 162 (12), 144 (17), 136 (12), 118 (13), 117 (18), 92 (32), 91 (38), 88 (11), 75 (46), 73 (38), 57 (87), 44 (100); HRMS (EI) (M^+-57) calcd for $C_{24}H_{34}NO_6Si$ 460.2155, found 460.2150.

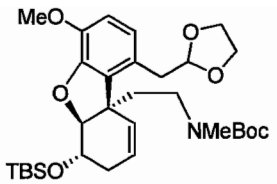


308

(4a*S*,5*S*,8a*R*)-3-methoxy-11-methyl-5,6,10,11,12,13-hexahydro-4a*H*,9*H*-[1]benzofuro[3a,3,2-*fg*][3]benzazocin-5-ol (308)

Enol ether **304** (23 mg, 0.34 mmol) was dissolved in a 4:1 mixture of DCM and TFA (0.5 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight before being quenched with cold sat. $NaHCO_3$ (2 mL) and extracted into

$CHCl_3$ (3 x 4 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated. The resulting enamine **307** was dissolved in dry MeOH (0.3 mL) and cooled to 0 °C before the addition of $NaCNBH_3$ (7 mg, 0.11 mmol) and AcOH (19 μL, 0.34 mmol). The reaction mixture was warmed to room temperature and stirred overnight before being quenched with cold sat. $NaHCO_3$ (2 mL). The MeOH was removed under reduced pressure and the aqueous layer extracted with $CHCl_3$ (3 x 3 mL) dried with Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (DCM-ethyl acetate, 4:1) gave **308** (146 mg, 41%) as colourless oil: R_f 0.49 (DCM-ethyl acetate, 96:4); IR (film) ν 3656, 3019, 2978, 2932, 2589, 1729, 1689, 1612, 1480, 1215 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) two rotamers δ 6.71 (d, *J* = 8.1 Hz, 1H), (d, *J* = 8.1 Hz, 1H), 5.74-5.68 (m, 1H), 4.32 (m, 1H), 4.00-4.93 (m, 1H), 3.87 (s, 3H), 3.13-3.05 (m, 1H), 2.85-2.76 (m, 1H), 2.74-2.65 (m, 1H), 2.59-2.52 (m, 2H), 2.46-2.38 (m, 2H), 2.31 (s, 3H), 2.17-2.11 (m, 1H), 2.01-1.96 (m, 1H), 1.83-1.75 (m, 1H) 1.32-1.25 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) two rotamers δ 143.8, 132.2, 129.6, 122.7, 122.1, 111.2, 96.1, 67.8, 60.5, 55.8, 52.6, 47.5, 33.0, 29.2 ppm; MS (EI) *m/z* (%): 42 (27), 43 (50), 44 (27), 57 (38), 58 (56), 70 (100), 71 (27), 83 (22), 149 (49), 179 (62), 301 (41); HRMS (EI) calcd for $C_{18}H_{23}NO_3$ 301.1678, found 301.1678.



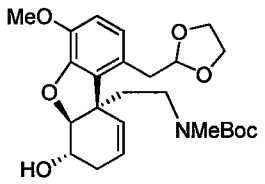
310

***tert*-butyl {2-[(5a*S*,6*S*,9a*R*)-6-{[*tert*-butyl(dimethyl)silyl]oxy}-1-(1,3-dioxolan-2-ylmethyl)-4-methoxy-6,7-dihydrodibenzo[*b*,*d*]furan-9a(5a*H*)-yl]ethyl}methylcarbamate (310)**

Method A: To enol ether **303** (30 mg, 0.055 mmol) dissolved in benzene (0.5 mL) and ethylene glycol (0.5 mL) was added 1 crystal of *p*TsOH. The resulting reaction mixture was refluxed overnight before being filtered through silica, washing with DCM. The organic layer was removed under reduced pressure and the resulting aqueous layer extracted with DCM (3 x 3 mL), dried over Na_2SO_4 filtered, and concentrated. Purification via flash column chromatography (hexanes-ethyl acetate, 1:1) gave **310** (6 mg, 18%) as colourless oil.

Method B: Aryl bromide **324** (2.75 g, 4.19 mmol) was dissolved in 40 mL of degassed toluene and transferred to a 150 mL Teflon-sealed Schlenck tube containing a magnetic stirring bar. P(*p*-tolyl)$_3$ (290 mg, 0.954 mmol), palladium acetate (213 mg, 0.954 mmol), and triethylamine (1.34 mL, 9.53 mmol) were added sequentially. The tube was flushed with nitrogen, sealed, and placed in a pre-heated oil bath at 110 °C for 48 h before being filtered through Celite and silica and washed with ethyl acetate. The resulting organics were dried under reduced pressure and purified via flash column chromatography (hexanes-ethyl acetate, 10:1) to give **310** (2.2 mg, 94%) as a clear oil: R_f 0.59 (hexanes-ethyl acetate, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (d, J = 8.3 Hz, 1H), 6.74 (d, J = 8.3 Hz, 1H), 6.04 – 5.98 (m, 1H), 5.75 - 5.71 (m, 1H),

5.11.5.08 (m, 1H), 4.57 - 4.43 (m, 2H), 4.03 (t, J = 5.3, 1H), 3.91-3.86 (m, 3H), 3.84 (s, 3H), 3.07 (dd, J = 14.4, 3.6, 1H), 3.00-2.88 (m, 2H), 2.79 (s, 3H), 2.76 (s, 1H), 2.28-2.22 (m, 1H), 2.01-1.93 (m, 1H), 1.45 (s, 9H), 0.91 (s, 9H), 0.15 (s, 3H), 0.03 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) (two rotamers) δ 155.5, 146.1, 143.9, 132.3, 129.4, 124.8, 123.1, 111.7, 104.7, 104.5, 89.8, 79.4, 68.4, 65.0, 64.9, 55.8, 51.4, 45.2, 37.5, 36.3, 35.4, 34.2, 30.8, 29.7, 28.4, 25.8, 25.7, 18.1 ppm; MS (EI) *m/z* (%): 41 (31), 43 (58), 44 (51), 45 (26), 57 (35), 59 (34), 73 (100), 83 (26), 189 (23); HRMS(EI) calcd for $C_{31}H_{49}NO_7Si$ 575.3278, found 575.3288.

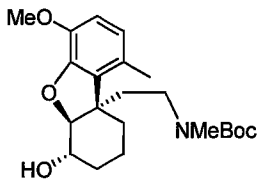


311

***tert*-butyl-{2-[(5a*S*,6*S*,9a*R*)-1-(1,3-dioxolan-2-ylmethyl)-6-hydroxy-4-methoxy-6,7-dihydrodibenzo[*b*,*d*]furan-9a(5a*H*)-yl]ethyl}methylcarbamate (311)**

To a solution of ketal **310** (20 mg, 0.035 mmol) in THF (0.5 mL) was added TBAF in THF (0.05 mL, 0.052 mmol) at 0 °C. The resulting reaction mixture was warmed slowly to room temperature before being quenched with water (1 mL). The organic layer was removed under reduced pressure and the resulting aqueous layer was extracted with DCM (3 x 2 mL), dried with Na_2SO_4 filtered and concentrated. Purification via flash column chromatography (hexanes-ethyl acetate, 1:1) gave **311** (15 mg, 92%) as colourless oil: R_f 0.3 (hexanes-ethyl acetate, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, J = 8.3 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 6.08 - 6.00 (m, 1H), 5.83 - 5.75 (m, 1H), 4.57 - 4.38 (m, 1H), 4.04-3.99 (m, 2H), 3.91-3.88 (m, 3H),

3.88 (s, 3H), 3.45-3.22 (m, 1H), 3.07 (dd, J = 14.4, 3.6, 1H), 2.90(dd, J = 14.4, 6.3, 1H), 2.78 (s, 3H), 2.47-2.33 (m, 1H), 2.19-2.06 (m, 1H), 2.00-1.90 (m, 3H), 1.44 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) two rotamers δ 155.4, 145.6, 144.0, 129.3, 124.9, 124.5, 123.7, 111.6, 104.6, 104.5, 90.5, 79.5, 68.0, 65.1, 64.9, 64.9, 55.8, 51.7, 45.2, 37.7, 36.4, 35.5, 34.2, 29.7, 29.2, 28.4 ppm; MS (EI) *m/z* (%): 41 (46), 43 (79), 44 (53), 45 (21), 49 (23), 55 (46), 56 (21), 57 (80), 59 (34), 69 (24), 73 (100), 83 (25), 84 (31), 103 (20), 142 (30), 149 (22); HRMS-EI calcd for $C_{25}H_{35}NO_7$: 461.2414, found 461.2414.

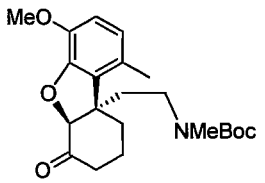


313

***tert*-butyl-{2-[(5a*S*,6*S*,9a*S*)-6-hydroxy-4-methoxy-1-methyl-6,7,8,9-tetrahydrodibenzo[*b*,*d*]furan-9a(5a*H*)-yl]ethyl}methylcarbamate (313)**

To aldehyde **305** (100 mg, 0.248 mmol) dissolved in MeOH (0.5 mL) was added 5% Pd/C (catalytic amount). The resulting reaction mixture was put under 1 atm H_2 gas and stirred overnight. The reaction mixture was then filtered through SiO_2 and concentrated. Purification via flash column chromatography (hexanes-ethyl acetate, 1:1) yielded **313** (52 mg, 54%) as a colourless oil: R_f 0.28 (hexanes-ethyl acetate, 1:1); IR (film) ν 3612, 3019, 2977, 1682, 1506, 1434, 1214 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) (two rotamers) δ 6.67 (d, J = 8.2 Hz, 1H), 6.58 (d, J = 8.2 Hz, 1H), 4.38-4.18 (m, 1H), 3.84 (s, 1H), 3.82-3.74 (m, 1H), 3.27-3.11 (m, 1H), 3.06-2.83 (m, 2H), 2.75 (s, 3H), 2.25-2.10 (m, 1H), 1.99-1.82 (m, 3H), 1.79-1.66 (m, 1H), 1.50-1.44 (m, 1H),

1.41 (s, 9H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) (two rotamers) δ 155.5, 146.1, 143.5, 126.2, 123.5, 111.3, 79.4, 70.5, 49.4, 45.2, 37.7, 34.2, 31.1, 28.4, 28.3, 18.1 ppm; MS (EI) *m/z* (%): 44 (28), 47 (25), 57 (32), 83 (100), 85 (69), 215 (59), 216 (20); HRMS (EI) (M, 391) calcd for $C_{22}H_{33}NO_5$ 391.2359, found 391.2359.

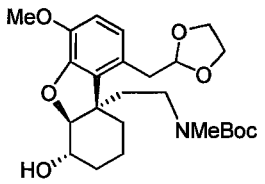


314

***tert*-butyl-{2-[(5a*S*,9a*S*)-4-methoxy-1-methyl-6-oxo-6,7,8,9-tetrahydrodibenzo[*b*,*d*]furan-9a(5a*H*)-yl]ethyl}methylcarbamate (314)**

To alcohol **313** (8 mg, 0.020 mmol) dissolved in DMF (0.5 mL) was added IBX (11 mg, 0.04 mmol) at 0 °C. The resulting reaction mixture was warmed to room temperature and stirred overnight before being quenched with water (2 mL) and extracted into $CHCl_3$ (3 x 4 mL). The combined organic layers were washed with $NaHCO_3$ (3 x 3 mL) and dried over Na_2SO_4. Purification by flash column chromatography (hexanes-ethyl acetate, 2:1) gave **314** (6 mg, 77%) as colourless oil: R_f 0.65 (hexanes-ethyl acetate, 1:2); ^1H NMR (300 MHz, $CDCl_3$) (two rotamers) δ 6.69 (d, *J* = 8.2 Hz, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 4.57 (s, 1H), 3.86 (s, 1H), 3.29-3.11 (m, 1H), 2.79 (s, 3H), 2.72-2.55 (m, 2H), 2.44-2.32 (m, 2H), 2.27 (s, 3H), 2.17-2.02 (m, 2H), 1.98-1.85 (m, 2H), 1.84-1.69 (m, 2H), 1.44 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) (two rotamers) δ 207.9, 155.4, 147.9, 143.2, 128.3, 125.1, 124.3, 113.3, 112.0, 89.7, 89.5, 79.7, 56.2, 56.0, 53.9, 45.1, 37.3, 37.0, 36.0, 35.6, 34.3, 32.6, 32.0,

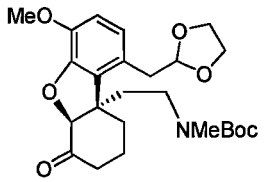
28.4, 19.5, 19.2, 17.6 ppm; MS (EI) *m/z* (%): 41 (29), 43 (45), 57 (56), 230 (35), 231 (100), 248 (44); HRMS-EI calcd for $C_{22}H_{31}NO_5$: 389.2202, found 389.2202.



315

***tert*-butyl-{2-[(5a*S*,6*S*,9a*S*)-1-(1,3-dioxolan-2-ylmethyl)-6-hydroxy-4-methoxy-6,7,8,9-tetrahydrodibenzo[*b*,*d*]furan-9a(5a*H*)-yl]ethyl}methylcarbamate (315)**

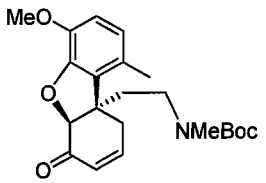
To a solution of ketal **311** (20 mg, 0.043 mmol) in MeOH (0.5 mL) was added 5% Pd/C (catalytic amount). The resulting reaction mixture was put under 1 atm H_2 gas and stirred overnight. The reaction mixture was then filtered through SiO_2 and concentrated. Purification by flash column chromatography (hexanes-ethyl acetate, 1:1) gave **315** (16 mg, 82%) as colourless oil: R_f 0.17 (hexanes-ethyl acetate, 1:1); IR (film) ν 3612, 3019, 2977, 1682, 1506, 1434, 1214 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (two rotamers) δ 6.81 (dd, *J* = 8.4 Hz, 1H), 6.73 (dd, *J* = 8.4 Hz, 1H), 5.06 (t, *J* = 4.6 Hz, 1H), 4.02-3.96 (m, 1H), 3.89-3.85 (m, 3H), 3.84 (s, 3H), 3.36-3.22 (m, 1H), 3.00 (dd, *J* = 14.5, 4.4 Hz, 1H), 2.95-2.84 (m, 2H), 2.73 (s, 3H), 2.28-2.11 (m,1H), 1.99-1.82 (m, 3H), 1.81-1.64 (m, 2H), 1.55-1.44 (m, 3H), 1.40 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) (two rotamers) δ 155.5, 146.8, 143.9, 124.9, 123.5, 111.7, 104.5, 92.4, 79.3, 70.5, 65.0, 64.9, 55.8, 38.6, 35.7, 28.4, 28.0 ppm; MS (EI) *m/z* (%): 44 (27), 47 (26), 49 (20), 73 (68), 84 (100), 86 (78); HRMS-EI calcd for $C_{25}H_{35}NO_7$ 463.2570, found 463.2570.



316

***tert*-butyl-{2-[(5a*S*,9a*S*)-1-(1,3-dioxolan-2-ylmethyl)-4-methoxy-6-oxo-6,7,8,9-tetrahydrodibenzo[*b*,*d*]furan-9a(5a*H*)-yl]ethyl}methylcarbamate (316)**

To a solution of ketal **315** (13 mg, 0.029 mmol) in DMF (0.5 mL) was added IBX (8 mg, 0.029 mmol) at 0 °C. The resulting reaction mixture was warmed to room temperature and stirred overnight before being quenched with water (2 mL) and extracted into $CHCl_3$ (3 x 4 mL). The combined organic layers were washed with $NaHCO_3$ (3 x 3 mL) and dried over Na_2SO_4. Purification via flash column chromatography (hexanes-ethyl acetate, 1:1) gave **316** (11 mg, 85%) as colourless oil: R_f 0.55 (hexanes-ethyl acetate, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (d, J = 8.3 Hz, 1H), 6.76 (d, J = 8.3 Hz, 1H), 5.07 (t, J = 4.7 Hz, 1H), 4.74-4.57 (m, 1H), 4.00-3.94 (m, 1H), 3.86 (s, 3H), 3.86-3.82 (m, 2H), 3.40-3.25 (m, 1H), 2.93-2.90 (m, 2H), 2.81-2.71 (m, 4H), 2.45-2.34 (m, 1H), 2.16-2.00 (m, 3H), 1.98-1.81 (m, 4H), 1.41-1.39 (m 2H), 1.43 (s, 9H) ppm; MS (EI) *m/z* (%): 44 (20), 47 (47), 49 (38), 56 (27), 73 (99), 86 (100), 88 (23), 303 (85); HRMS-EI calcd for $C_{25}H_{35}NO_7$ 461.2414, found 461.2414.

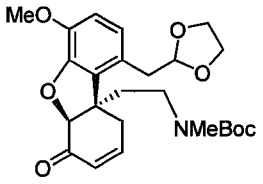


318

***tert*-butyl-{2-[(5a*S*,9a*S*)-4-methoxy-1-methyl-6-oxo-6,9-dihydrodibenzo[*b*,*d*]furan-9a(5a*H*)-yl]ethyl}methylcarbamate (318)**

Saturated ketone **314** (105 mg, 0.286 mmol) was dissolved in anhydrous THF (0.4 mL) and cooled to -78 °C before the addition of LDA in THF (0.268 mmol). After stirring for 10 min, TMS-Cl (37 uL, 0.295 mmol) was added dropwise. The resulting reaction mixture was warmed to 0 °C before being quenched with saturated NH_4Cl (2 mL) and extracted into EtOAc (3 x 3mL), washed with brine (1 x 2 mL), dried with Na_2SO_4, filtered, and concentrated. The organic layer was removed under reduced pressure and the resulting crude mixture was dissolved in MeCN (0.5 mL). $Pd(OAc)_2$ was added in one portion and the resulting reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with sat. $NaHCO_3$ (1 mL) extracted into EtOAc (3 x 3 mL), washed with brine (1 x 3 mL), dried with Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (hexanes-ethyl acetate, 1:1) gave **318** (78 mg, 76% over two steps) as colourless oil: R_f 0.31 (hexanes-ethyl acetate, 1:1); $[\alpha]_D^{24}$ +97.342 (*c* 1.7, $CHCl_3$); IR (film) ν 3019, 2979, 2931, 1683, 1596, 1508, 1426, 1215 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) (two rotamers) δ 6.947 (dt, *J* = 10.2, 4.5 Hz, 1H), 6.62 (dd, *J* = 15.8, 8.2 Hz, 2H), 6.19 (d, *J* = 10.2 Hz, 1H), 4.62 (s, 3H), 3.29-3.15 (m, 1H), 3.01-2.86 (m, 1H), 2.75 (s, 3H), 2.30 (s, 3H), 2.17-2.06 (m, 2H), 2.01-1.98 (m, 2H), 1.86 (s, 1H), 1.39 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) (two rotamers) δ 189.8, 189.4, 185.9, 155.4, 148.1, 147.1,

143.3, 129.2, 124.4, 112.3, 86.0, 79.7, 56.1, 49.4, 45.2, 37.0, 34.4, 33.4, 28.4, 23.2, 22.8, 22.4, 21.9, 18.9 ppm; MS (EI) *m/z* (%): 41 (19), 44 (19), 57 (36), 191 (22), 229 (100), 230 (25); HRMS-EI calcd for $C_{25}H_{29}NO_5$ 387.2046, found 387.2046.

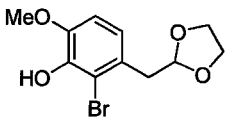


320

***tert*-butyl-{2-[(5a*S*,9a*S*)-1-(1,3-dioxolan-2-ylmethyl)-4-methoxy-6-oxo-6,9-dihydrodibenzo[*b*,*d*]furan-9a(5a*H*)-yl]ethyl}methylcarbamate (320)**

Ketone **316** (150 mg, 0.325 mmol) was dissolved in anhydrous THF (0.5 mL) and cooled to -78 °C before the addition of NaHMDS in THF (0.325 mmol). After stirring for 10 min, TMS-Cl (43 uL, 0.358 mmol) was added dropwise. The resulting reaction mixture was warmed to 0 °C before being quenched with sat. NH_4Cl (4 mL) and extracted into EtOAc (3 x 5 mL), washed with brine (1 x 2 mL), dried with Na_2SO_4, filtered, and concentrated. The organic layer was removed under reduced pressure and the resulting crude mixture was dissolved in MeCN (0.5 mL). $Pd(OAc)_2$ (109 mg, 0.487 mmol) was added in one portion and the resulting reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with saturated $NaHCO_3$ (3 mL) extracted into EtOAc (3 x 5 mL), washed with brine (1 x 3 mL), dried with Na_2SO_4, filtered, and concentrated. Purification via flash column chromatography (hexanes-ethyl acetate, 1:2) gave **320** (120 mg, 81% over two steps) as colourless oil: R_f 0.29 (hexanes-ethyl acetate, 1:2); $[\alpha]_D^{24}$ +91.57 (*c* 1.415, $CHCl_3$); IR (film) ν 2978, 2850, 1685, 1625, 1507, 1283 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)

(two rotamers) δ 6.99-6.89 (m, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 6.20 (d, J = 9.4 Hz, 1H), 5.05 (t, J = 4.4 Hz, 1H), 3.98-3.88 (m, 2H), 3.87-3.79 (m, 6H), 3.35-3.22 (m, 1H), 3.17-3.03 (m, 1H), 3.03-2.94 (m, 1H), 2.88-2.82 (m, 1H), 2.76 (s, 3H), 2.24-2.09 (m, 2H), 2.06 (m, 1H), 1.41 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) (two rotamers) δ 155.3, 148.6, 147.2, 143.7, 128.9, 124.5, 124.0, 112.5, 104.5, 86.3, 79.8, 65.0, 64.9, 60.4, 56.0, 49.6, 45.2, 38.4, 35.7, 34.2, 28.4, 21.0, 14.2 ppm; MS (EI) *m/z* (%): 41(24), 43(81), 57(33), 73(100), 84(20), 301(21); HRMS-EI calcd for $C_{25}H_{33}NO_7$ 459.2257, found 459.2206.

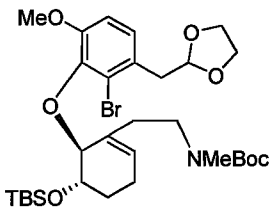


323

2-Bromo-3-[1,3]dioxolan-2-ylmethyl-6-methoxy-phenol (323)

To a solution of bromoisovanilin **259** (20 g, 86.6mmol) in DCM (600 mL) at 0 °C was added Et$N(i$Pr$)_2$ (30.1 mL, 173.1 mmol) under an atmosphere of nitrogen. Afterwards, MOM-Cl (9.8 mL, 129.84 mmol) was added via syringe over 3 min, and then the reaction was stirred for 3 h. The reaction mixture was washed with 200 mL of distilled water and the aqueous phase was extracted with ethyl acetate (3 x 80 mL). The combined organic phases were washed with brine (150 mL), and then dried over $MgSO_4$ to afford **321** (29 g) as white solid. The product was used in the next step without further purification. A solution of $Ph_3PCH_2OCH_2Cl$ (13.7 g, 39.9 mmol) in THF (75 mL) was cooled to –78 °C and *t*-butyl lithium (1.48 M in pentane, 24.5 mL, 36.4 mmol) was added over 3 min. The solution stirred at -78 °C for 10 min then warmed to 0 °C and bromoisovanillin methoxy-methyl ether **321** (10.0 g, 36.4 mmol)

in THF (10 mL) was added dropwise over 2 min. The reaction mixture was heated to reflux for 4 hr, and then cooled to r.t and 100 mL of ethyl acetate was added. To this mixture was added distilled water (80 mL) and the biphasic mixture was extracted with ethyl acetate (3 x 100 mL). The organic phase was collected and washed with brine, then dried over $MgSO_4$ to afford **322** (18.2 g), which was taken to the next step without further purification. To the Wittig product **322** (18.2 g, 0.06 mol) in THF (200 mL) was added ethylene glycol (16.7 mL, 0.3 mol) and *p*-TsOH (5.7 g, 0.03 mol). The mixture was heated at reflux for 2 h, cooled, and diluted with ethyl acetate and washed with water. The organic phase was dried with brine and then $MgSO_4$. The solvent was removed under reduced pressure. Column chromatography afforded **323** (6.74 g, 64% over three steps): R_f 0.39 (2:1, hexanes-ethyl acetate); IR (KBr) ν 3609, 3583, 3370, 2959, 2892, 1607, 1490, 1441, 1283, 1232, 1199, 1130, 1034, 986, 941, 820, 802, 645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.85 (d, J = 8.34 Hz, 1H), 6.76 (d, J = 8.34 Hz, 1H), 6.00 (s, 1H), 5.10 (t, J = 5.1 Hz, 1H), 3.97 (m, 2H), 3.84 (m, 5H), 3.07 (d, J = 5.0 Hz, 2H), 2.08 (s, 1H) ppm; ^{13}C NMR (75MHz, $CDCl_3$) δ 145.9, 143.1, 128.8, 122.0, 111.3, 109.6, 103.4, 65.0, 56.3, 40.1 ppm; MS (EI) *m/z* (%) 73 (100), 45 (14); HRMS-EI $C_{11}H_{13}BrO_3$ Calc. 287.9997, found 287.99936; *Anal.* calcd for $C_{11}H_{13}BrO_3$ C 45.70, H 4.53, found C 46.25, H 4.55.

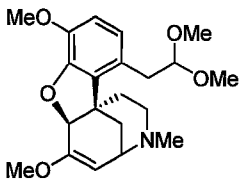


324

***tert*-butyl-[2-((5*S*,6*S*)-6-[2-bromo-3-(1,3-dioxolan-2-ylmethyl)-6-methoxyphenoxy]-5-{[*tert*-butyl(dimethyl)silyl]oxy}cyclohex-1-en-1-yl)ethyl]methylcarbamate (324)**

To a solution of DIAD (1.02 mL, 5.207 mmol) in 10 mL anhydrous THF at -10 °C was added freshly distilled tributyl phosphine (1.69 mL, 5.207 mmol).The resulting solution was allowed to stir at -10 °C for 10 min before transferring dropwise to an anhydrous THF (20 mL) solution of bromoisovanillin derivative **323** (0.925 g, 4.005 mmol) and protected diol **258** (1.39 g, 3.605 mmol) at -78 °C. Once the addition was completed, the reaction vessel was warmed to 0 °C and stirred for 1 h. Then the reaction mixture was allowed to warm to r.t and was stirred for an additional 48 h. The solvent was removed under reduced pressure and the crude mixture was subjected to column chromatography (DCM:EtOAc 100:0 to 98:2) to afford **324** (2.2 g, 78%) as colourless oil: R_f 0.81 (DCM:EtOAc, 96:4); $[\alpha]_D^{24}$ +75.7 (*c* 0.7, $CHCl_3$); IR (film) ν 3007, 2952, 2929, 2857, 1688, 1578, 1481, 1275, 1252, 1173, 1085, 1028, 1005, 836 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) mixture of rotamers δ 10.30 (s, 2H), 7.75 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 5.85 (s, 1H), 5.83 (s, 1H), 4.57 (s, 2H), 3.98 (br s, 8H), 3.59 (s, 1H), 3.44 (s, 1H), 3.22 (br s, 2H), 2.85 (br s, 6H), 2.55 – 2.37 (m, 4H), 2.28 – 2.17 (m, 4H), 2.06 (s, 1H), 2.04 (s, 1H), 1.72 – 1.65 (m, 2H), 1.46 (s, 18H), 0.75 (s, 18H), -0.12 (s, 6H), -0.17 (s, 6H) ppm; ^{13}C NMR (150 MHz,

$CDCl_3$) δ: 191.3, 157.9, 155.8, 144.6, 130.9, 130.3, 127.7, 125.9, 123.5, 110.9, 80.3, 79.1, 67.7, 56.1, 48.9, 48.3, 41.5, 35.0, 33.4, 32.7, 28.5, 25.6, 25.4, 20.8, 18.0, -4.9, -5.1; MS (EI) *m/z* (%): 312 (28), 269 910), 268 (45), 237 (24), 136 (31), 109 (14), 75 (27), 73 (33), 57 (47), 44 (100); HRMS-EI calcd for $C_{31}H_{50}BrNO_7Si$ 655.2540, found 655.2541; *Anal.* calcd. for C 56.70, H 7.67, found C 56.69, H, 7.65.

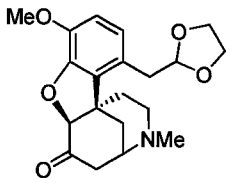


327

(6a*S*,11b*R*)-11-(2,2-dimethoxyethyl)-6,8-dimethoxy-3-methyl-2,3,4,6a-tetrahydro-1*H*-4,11b-methano[1]benzofuro[3,2-*d*]azocine (327)

To a solution of ketone **320** (20 mg, 8.6 mmol) in methanol (0.5 mL) was added conc. HCl (1 drop). The mixture was heated at reflux for 24 h before being cooled to 0 °C and quenched with $NaHCO_3$ (2 mL). The organic layer was separated, and the resulting aqueous layer was extracted with chloroform (3 x 5 mL). The combined organic layers were washed with brine and dried with $NaSO_4$. The solvent was removed under reduced pressure and subsequent flash column chromatogrpahy (95:5:1 $CHCl_3$:MeOH:NH_4OH) afforded **327** (12 mg, 74% yield) as a clear oil: R_f 0.72, (92:8:1 $CHCl_3$: MeOH: NH_4OH); IR (KBr) ν 3518, 3020, 2915, 1724, 1489, 1215 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.74 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 4.92 (d, J = 6.4 Hz, 1H), 4.92 (dd, J = 6.5, 4.3 Hz, 1H), 4.51 (s, 1H), 3.81 (s, 3H), 3.69 (s, 3H), 3.52-3.49 (m, 1H), 3.34 (s, 3H), 3.31 (s, 3H), 3.04 (dd, J = 14.4, 4.3 Hz, 1H), 2.90 (dd, J = 14.4, 6.6 Hz, 1H), 2.65-2.58 (m, 2H), 2.27 (s, 3H), 2.26-2.25

(m, 1H), 2.14-2.09 (m, 1H), 1.77-1.72 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.2, 143.4, 132.6, 125.6, 123.6, 110.9, 105.1, 92.1, 83.4, 77.2, 77.0, 76.8, 55.6, 54.8, 54.2, 53.7, 52.8, 45.8, 45.7, 43.0, 35.4, 34.7, 34.1 ppm; MS (EI) *m/z* (%) 75 (100), 255 (10), 375 (22); HRMS-EI calcd for $C_{21}H_{29}NO_5$ 375.2046, found 375.2046.

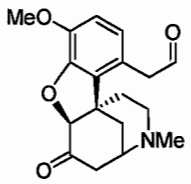


328

(6a*S*,11b*R*)-11-(1,3-dioxolan-2-ylmethyl)-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-4,11b-methano[1]benzofuro[3,2-*d*]azocin-6-one (328)

To a solution of α,β-unsaturated ketone **320** (110 mg, 0.24 mmol) in THF (1 mL) was added TFA (0.5 mL). The resulting reaction mixture was refluxed for 3 h before being cooled to 0 °C, and quenched with saturated $NaHCO_3$ (4 mL). The crude mixture was extracted into $CHCl_3$ (3 x 5 mL), washed with brine (1 x 2 mL), dried with Na_2SO_4, filtered, and concentrated. Purification via flash column chromatography ($CHCl_3$:MeOH:NH_4OH, 92:8:1) gave **328** (65 mg, 76%) as colourless oil: R_f 0.52 ($CHCl_3$:MeOH:NH_4OH, 92:8:1); $[\alpha]_D^{24}$ -58.108 (*c* 0.565, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) (two rotamers) δ 6.82 (d, *J* = 8.3 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 5.02 (t, *J* = 4.8 Hz, 1H), 4.72 (s, 1H), 3.99-3.91 (m, 2H), 3.86-3.81 (m, 6H), 3.51-3.44 (m, 1H), 3.01 (dd, *J* = 9.2, 4.8 Hz, 2H), 2.95-2.86 (m, 1H), 2.70-2.56 (m, 2H), 2.49-2.39 (m, 2H), 2.34 (s, 3H), 1.85 (dd, *J* = 11.9, 1.0 Hz, 1H), 1.75-1.66 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) (two rotamers) δ 205.7, 146.9, 143.5, 131.1, 124.6, 124.0, 111.8, 104.7, 89.0, 64.9, 55.8, 49.2, 46.8, 42.8, 36.1, 35.5,

34.1 ppm; MS (EI) *m/z* (%): 44 (41), 73 (100), 215 (21), 217 (21); HRMS-EI calcd for $C_{20}H_{25}NO_5$ 359.1733, found 359.1739.

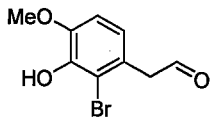


329

[(6a*S*,11b*R*)-8-methoxy-3-methyl-6-oxo-2,3,4,5,6,6a-hexahydro-1*H*-4,11b-methano[1]benzofuro[3,2-*d*]azocin-11-yl]acetaldehyde (329)

To a solution α,β-unsaturated ketone **320** (200 mg, 0.55 mmol) in MeCN (1 mL) and H_2O (1 mL) was added conc. HCl dropwise until a pH of 1 was reached. The resulting reaction mixture was heated at 45 °C for 24 h before being cooled to 0 °C, and quenched with saturated $NaHCO_3$ (4 mL). The crude mixture was extracted into $CHCl_3$ (3 x 5 mL), washed with brine (1 x 2 mL), dried with Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography ($CHCl_3$:MeOH:NH_4OH, 92:8:1) gave **329** (135 mg, 77%) as colourless oil: R_f 0.37 ($CHCl_3$:MeOH:NH_4OH, 92:8:1); $[\alpha]_D^{24}$ -51.08 (*c* 0.43, $CHCl_3$); IR (film) ν 2927, 2870, 1722, 1624, 1506, 1436, 1283 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (two rotamers) δ 9.67 (t, *J* = 1.9 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 4.73 (s, 1H), 3.71 (dd, *J* = 5.8, 2.1 Hz, 2H), 3.51-3.41 (m, 1H), 2.94-2.84 (m, 1H), 2.70-2.60 (m, 1H), 2.47-2.40 (m, 2H), 2.39-2.34 (m, 1H), 2.31 (s, 3H), 2.22-2.14 (m, 1H), 1.86-1.77 (m, 1H), 1.72-1.62 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) (two rotamers) δ 205.1, 199.0, 147.4, 144.3, 131.3, 124.6, 119.9, 112.2, 89.0, 60.3, 55.8, 55.6, 48.9, 46.4, 46.2, 42.6, 35.9,

35.3, 34.0, 21.0, 14.1 ppm; MS (EI) *m/z* (%): 214 (20), 229 (18), 297 (100), 298 (20); HRMS-EI calcd for $C_{18}H_{21}NO_4$ 315.1471, found 315.1469.

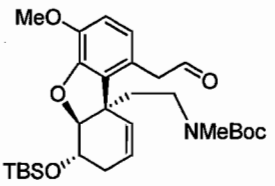


330

(2-bromo-3-hydroxy-4-methoxyphenyl)acetaldehyde (330)

To a solution of bromoisovanilin (**259**) (2.0 g, 8.6 mmol) in DCM (60 mL) at 0 °C was added EtN(*i*Pr)$_2$ (3.0 mL, 17.3 mmol), before the dropwise addition of MOM-Cl (0.98 mL, 12.9 mmol). The reaction was stirred for 3 h and then washed with 20 mL of distilled water, and extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure to provide MOM ether **321**, which was taken to the next step without further purification. A solution of $Ph_3PCH_2OCH_2Cl$ (1.4 g, 4.0 mmol) in THF (10 mL) was cooled to –78 °C and *t*-butyl lithium (1.4 M in pentane, 2.5 mL, 3.64 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 10 min before being warmed to 0 °C. Bromoisovanillin methoxy-methyl ether **321** (1.0 g, 3.64 mmol) in THF (2 mL) was added dropwise. The resulting reaction mixture was heated to reflux for 4 h before being cooled to r.t. and diluted with distilled water (10 mL). The resulting mixture was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. To this crude product in THF (20 mL) was added water (10 mL) and *p*-TsOH (0.57 g, 0.33 mmol). The mixture was heated at reflux for 2 h before being diluted with ethyl acetate. The organic layer was washed

with water, washed with brine, and dried over $MgSO_4$. Flash column chromatography afforded **330** (0.53 g, 24% over 3 steps): R*f* 0.61 (1:1, hexanes-ethyl acetate); m.p. 104 °C (hexanes-ethyl acetate); IR (KBr) ν 3518, 3020, 2915, 1724, 1489, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (t, *J* = 1.8 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.04 (s, 1H), 3.91 (s, 3H), 3.80 (d, *J* = 1.8 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 146.5, 143.7, 125.4, 122.0, 111.0, 109.7, 56.4, 49.9 ppm; MS (EI) *m/z* (%) 215 (100), 217 (100), 218 (11), 244 (32), 246 (32); HRMS-EI calcd for $C_9H_9BrO_3$ 243.9735, found 243.9735.

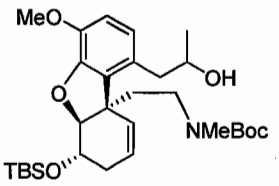


332

***tert*-butyl-{2-[(5a*S*,6*S*,9a*R*)-6-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methoxy-1-(2-oxoethyl)-6,7-dihydrodibenzo[*b*,*d*]furan-9a(5a*H*)-yl]ethyl}methylcarbamate (332)**

A solution of **303** (180 mg, 0.33 mmol) in MeCN (2 mL) was degassed under an atmosphere of N_2 before the addition of $CuCl_2$ (3 mg, 0.033 mmol). The resulting reaction mixture was placed immediately into an oil bath preheated to 40 °C and stirred for 2 h before being cooled to room temperature and filtered through SiO_2, washing with MeCN, and concentrated. Purification by flash column chromatography (hexanes-ethyl acetate, 6:1) gave **332** (33 mg, 20%) as colourless oil: R_f 0.37, (1:1, hexanes-ethyl acetate), m.p. 104 °C (hexanes-ethyl acetate); IR (KBr) ν 3518, 3020, 2915, 1724, 1489, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (t, *J* = 1.8 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.04 (s, 1H), 3.91 (s, 3H), 3.80 (d, *J*

= 1.8 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 146.5, 143.7, 125.4, 122.0, 111.0, 109.7, 56.4, 49.9 ppm; MS (EI) *m/z* (%) 215 (100), 217 (100), 218 (11), 244 (32), 246 (32); HRMS-EI calcd for $C_9H_9BrO_3$ 243.9735, found 243.9735.



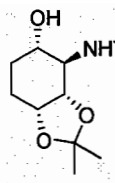
335

***tert*-butyl-{2-[(5a*S*,6*S*,9a*R*)-6-{[*tert*-butyl(dimethyl)silyl]oxy}-1-(2-hydroxypropyl)-4-methoxy-6,7-dihydrodibenzo[*b*,*d*]furan-9a(5a*H*)-yl]ethyl}methylcarbamate (335)**

To a solution of aldehyde **332** (10 mg, 0.019 mmol) in DCM (0.2 mL) at 0 °C was added $AlMe_3$ (19 μL, 0.19 mmol). The mixture was warmed slowly to room temperature and stirred for 30 min before being quenched with water and extracted into DCM (3 X 5mL) The combined organic layers were dried with Na_2SO_4 and the solvent was removed under reduced pressure. Column chromatography (10:1, hexanes-ethyl acetate) afforded **335** (4 mg, 35%) as a clear oil: R_f 0.42 (2:1, hexanes-ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, *J* = 8.4 Hz, 1H), 6.65 (t, *J* = 8.0 Hz, 1H), 6.07 (dd, *J* = 15.1, 10.0 Hz, 1H), 5.75-5.66 (m, 1H), 4.55 (dd, *J* = 24.2, 4.53 Hz, 1H), 4.37 (dd, *J* = 6.8, 1.2 Hz, 1H), 3.72 (s, 3H), 3.70-3.62 (m, 1H), 3.69 (s, 3H), 3.52-3.49 (m, 1H), 3.34 (s, 3H), 3.20-3.05 (m, 1H), 3.00-2.86 (m, 1H), 2.71 (s, 3H), 2.66-2.57 (m, 1H), 2.53-2.48 (m, 1H), 2.24-2.13 (m, 1H), 1.37 (s, 9H), 1.27-1.13 (m, 1H), 1.08 (m, 2H) 0.87 (s, 9H), 0.098 (s, 3H), -0.017 (s, 3H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 143.5, 143.4, 129.9, 129.7, 124.6, 124.3, 123.3, 112.5, 89.4, 78.9,

67.4, 67.2, 56.1, 51.9, 51.8, 44.9, 41.6, 41.1, 40.5, 40.3, 40.2, 40.1, 39.9, 39.6, 39.5, 34.2, 32.4, 31.2, 28.5, 26.2, 23.4, 18.3, -4.3, -4.9 ppm; MS (EI) *m/z* (%): 41 (51), 43 (29), 44 (100), 55 (28), 57 (89), 58 (27), 59 (94), 102 (22), 103 (88), 211 (22), 213 (75), 214 (23), 225 (21), 227 (21), 239 (87); HRMS-EI $C_{30}H_{49}NO_6Si$ calc. 547.7987, found 547.7987.

6. Selected Spectra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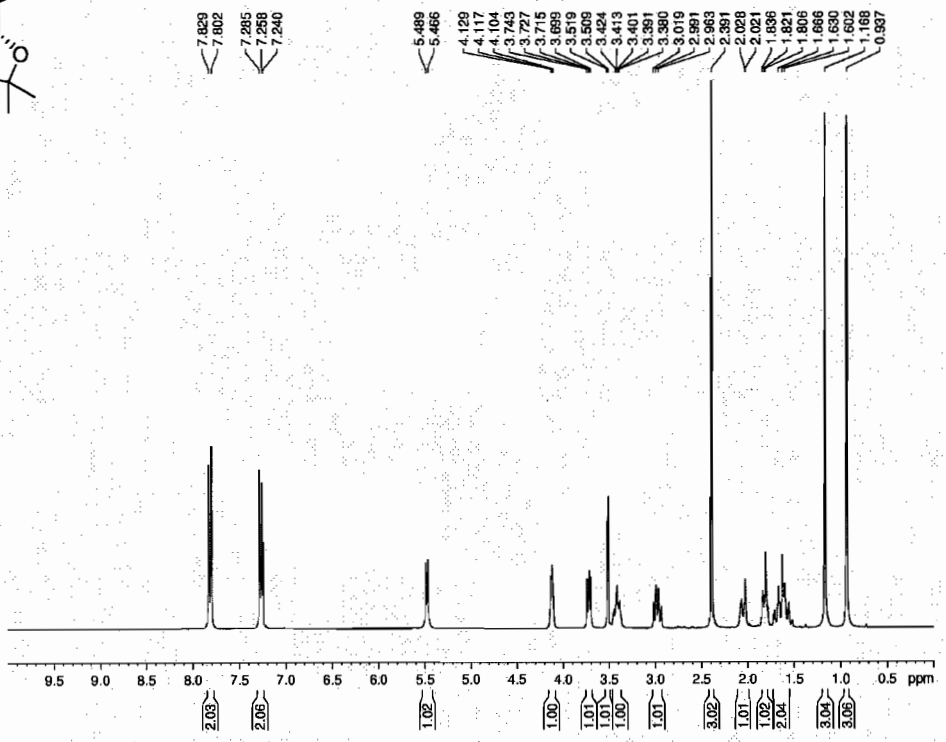
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2.391
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9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.03
2.06
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1.01
1.00
1.01
3.02
1.01
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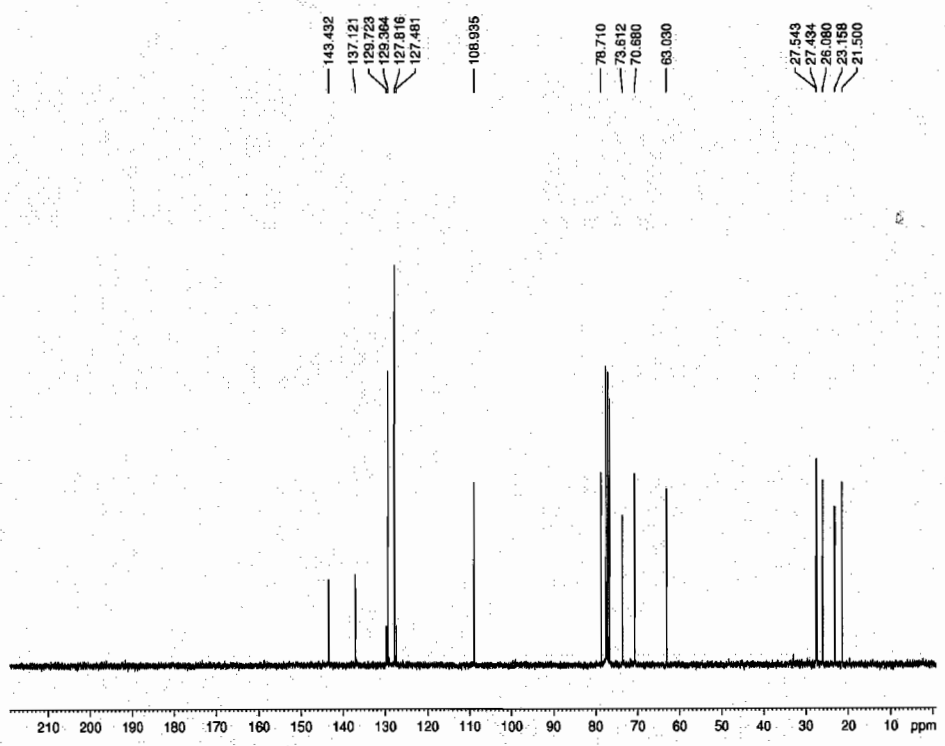
2.04
3.04
3.06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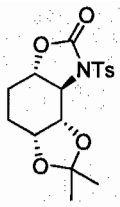
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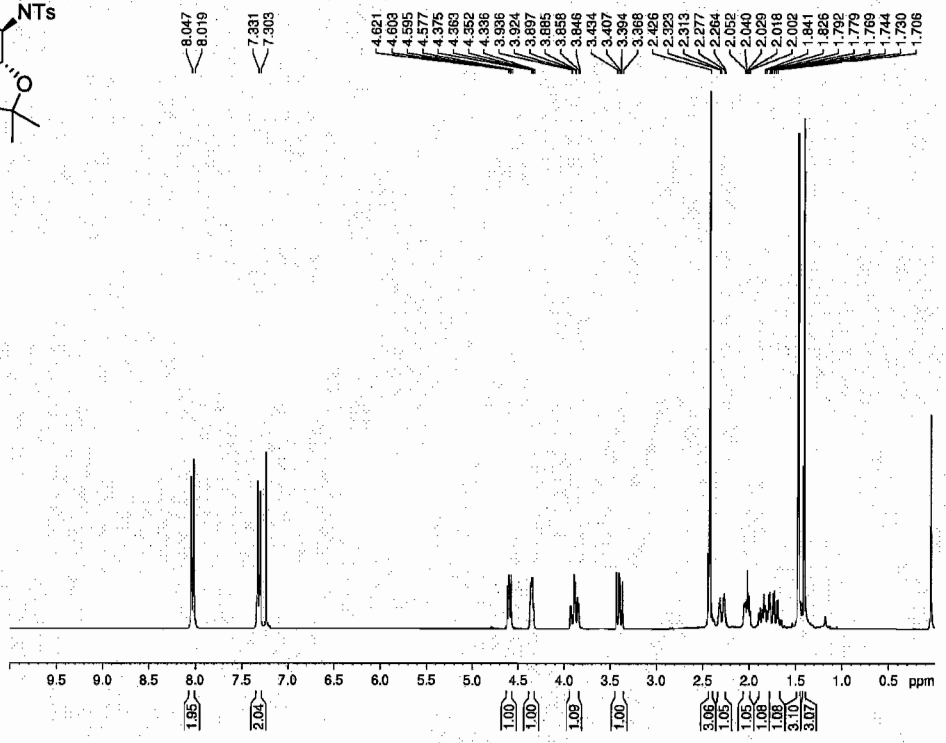
287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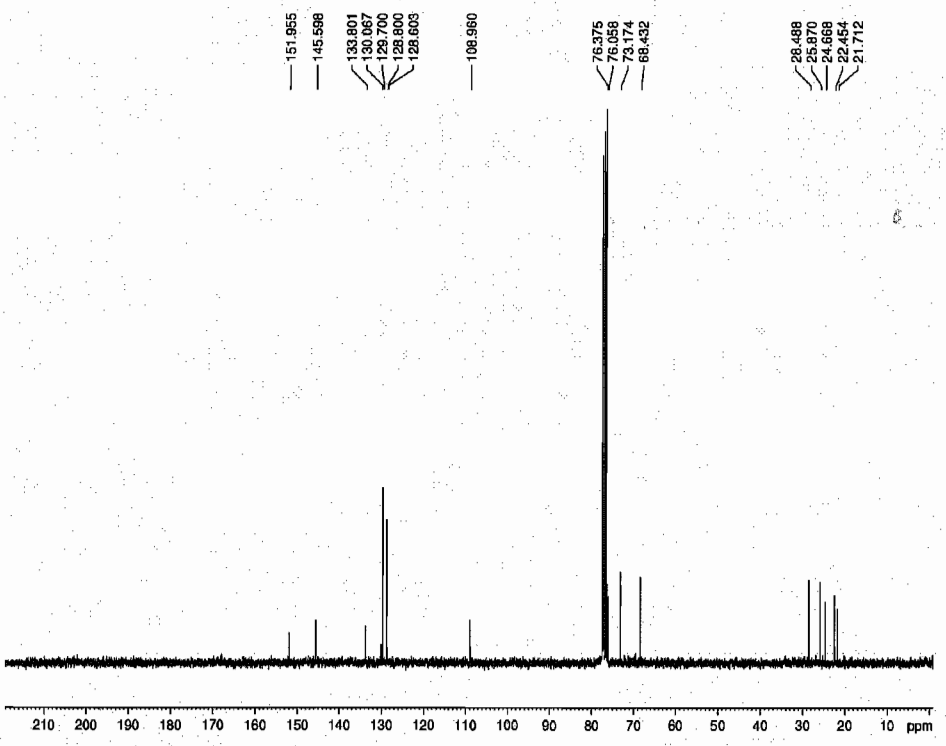
3.07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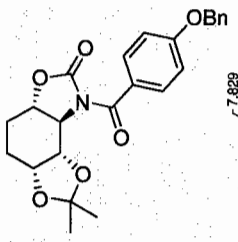
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289

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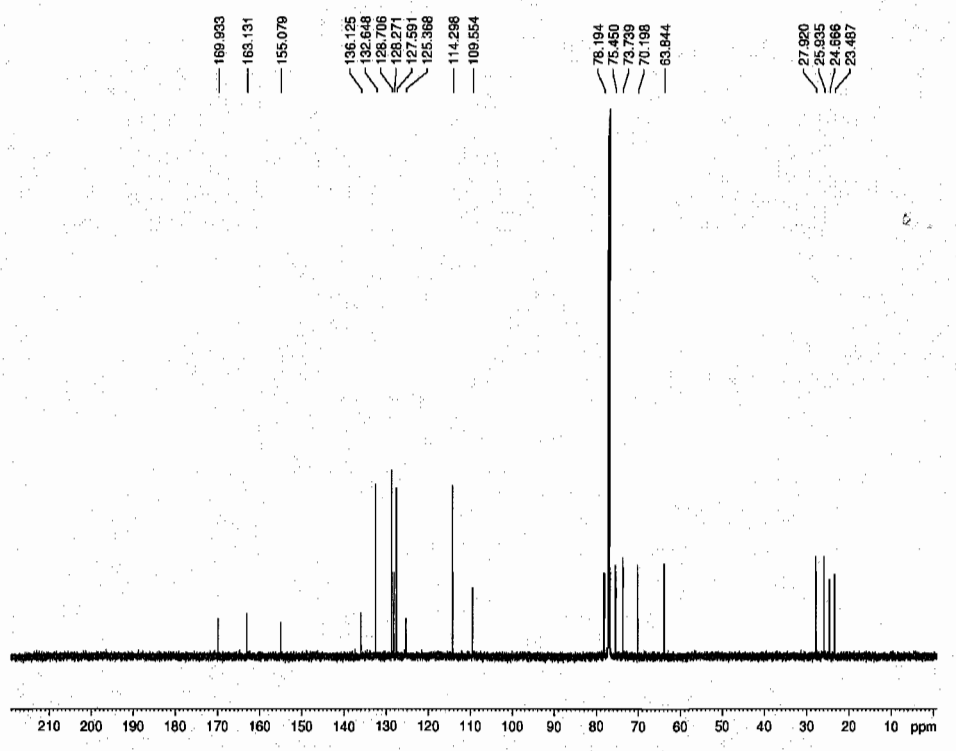
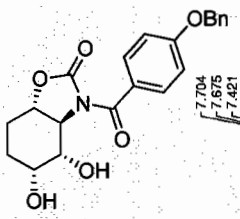
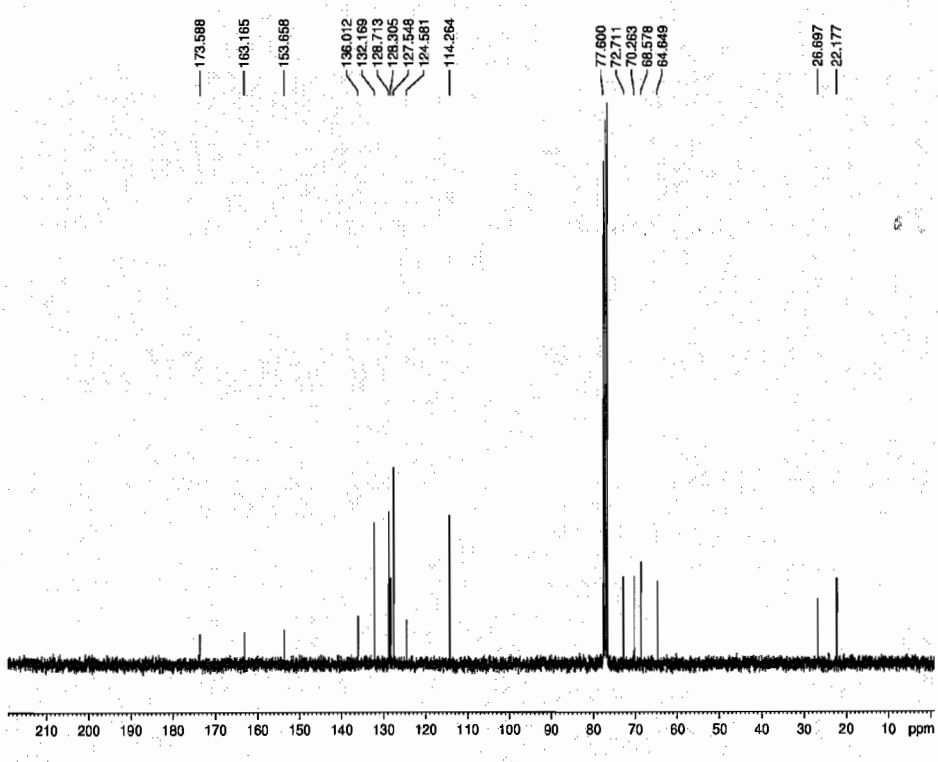
2.01
1.03
2.10
1.02
1.01
1.01
1.05
1.08
3.01
3.07

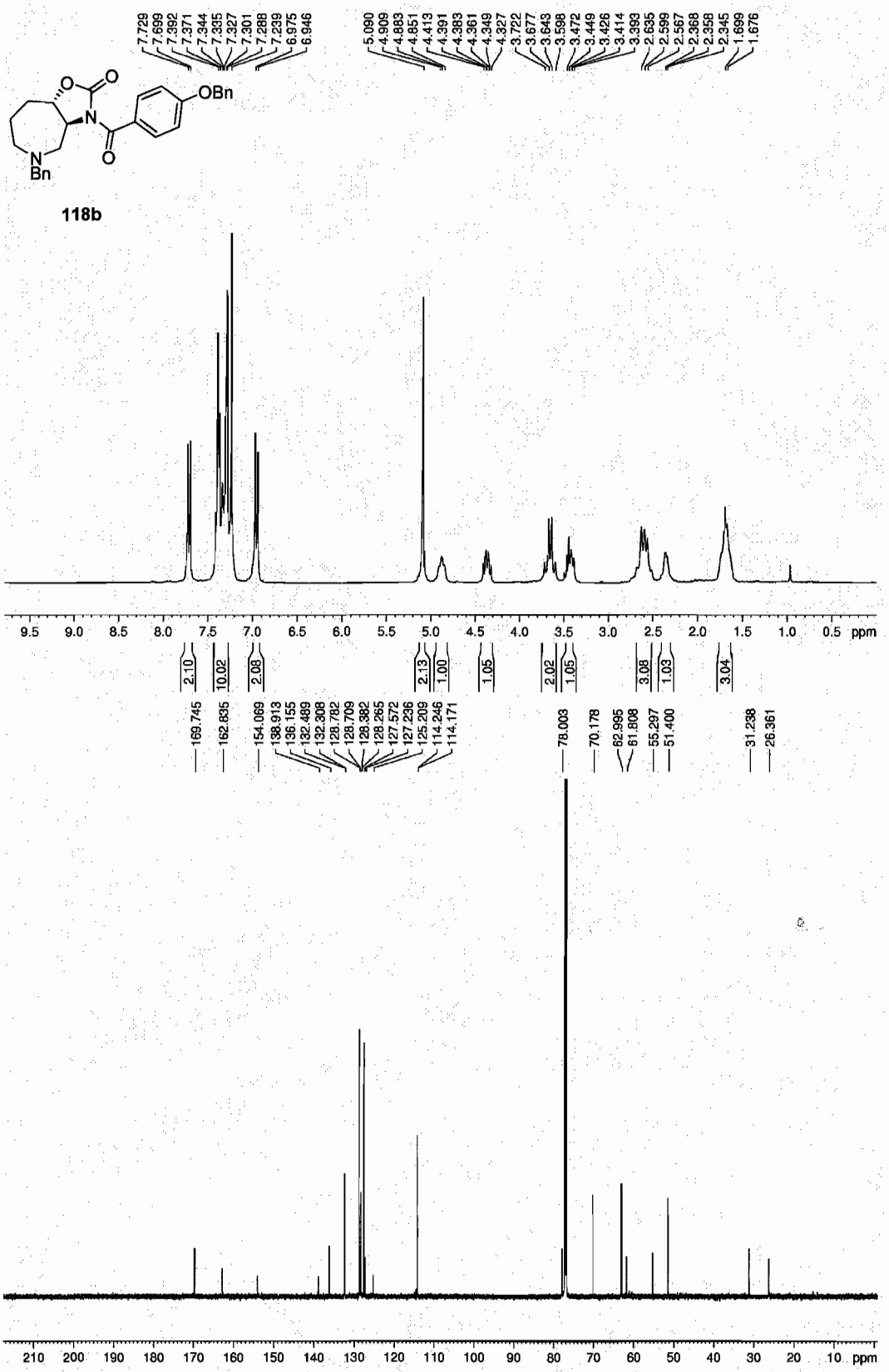

169.933
163.131
155.079
136.125
132.648
128.706
128.271
127.591
125.368
114.296
109.554
78.194
75.450
73.739
70.198
63.844
27.920
25.935
24.666
23.487
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

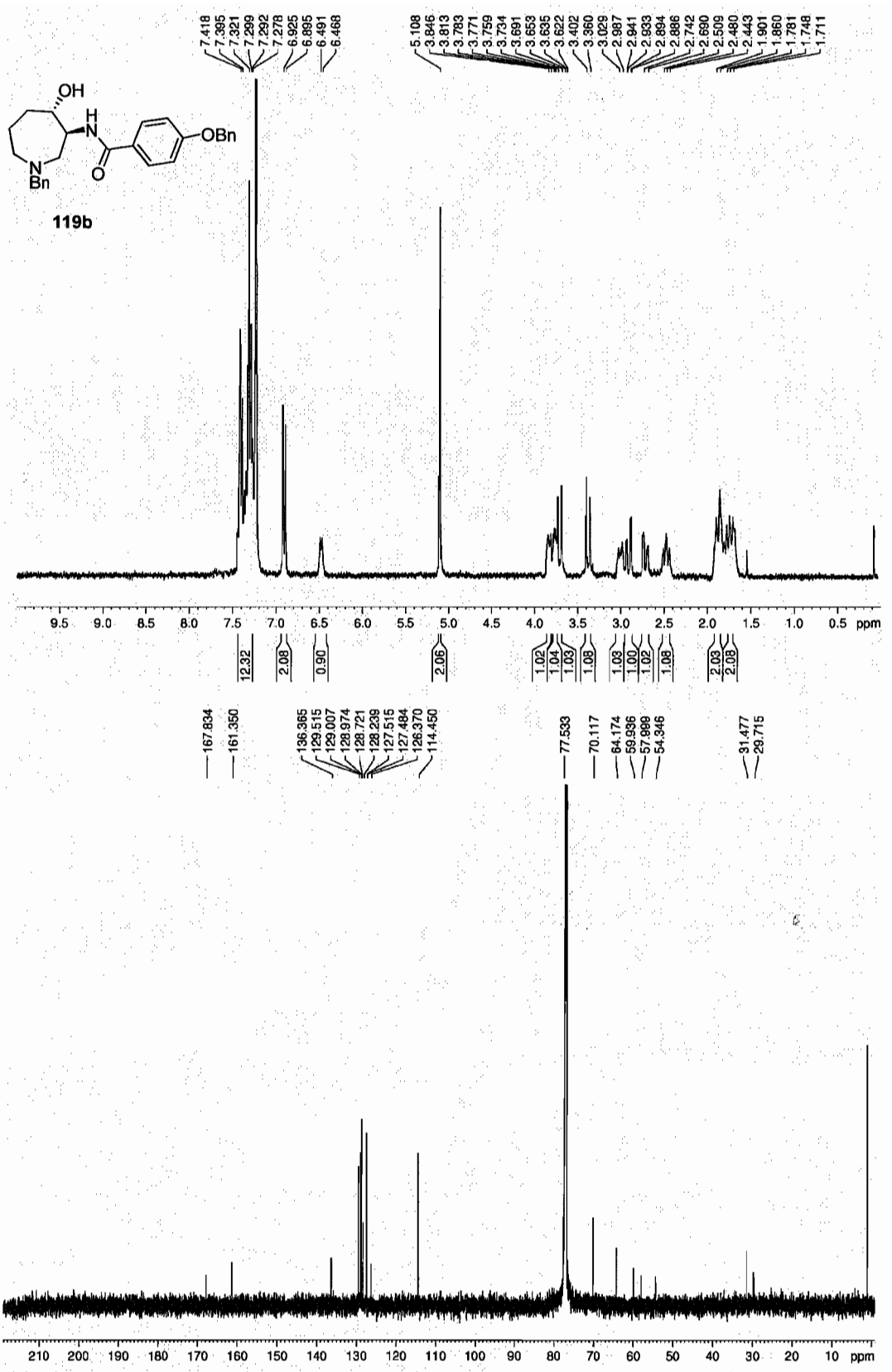

OBn
O
O
N
O
OH
OH

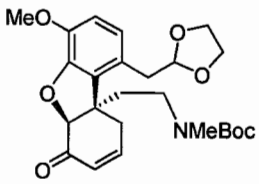
290

7.704
7.675
7.421
7.400
7.394
7.380
7.372
7.361
7.353
7.346
7.337
7.324
7.003
6.973
5.932
5.108
4.381
4.348
4.344
4.311
4.083
4.073
4.045
4.019
4.011
4.008
3.991
3.981
3.975
3.964
3.895
3.885
3.863
3.853
3.132
2.291
2.281
2.271
2.252
2.242
2.232
2.221
2.086
2.079
2.060
2.049
2.039
2.025
2.014
1.593
1.571
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 ppm
2.01
5.05
2.03
1.00
2.01
1.02
1.01
1.02
1.01
1.01
1.03
2.02
1.07

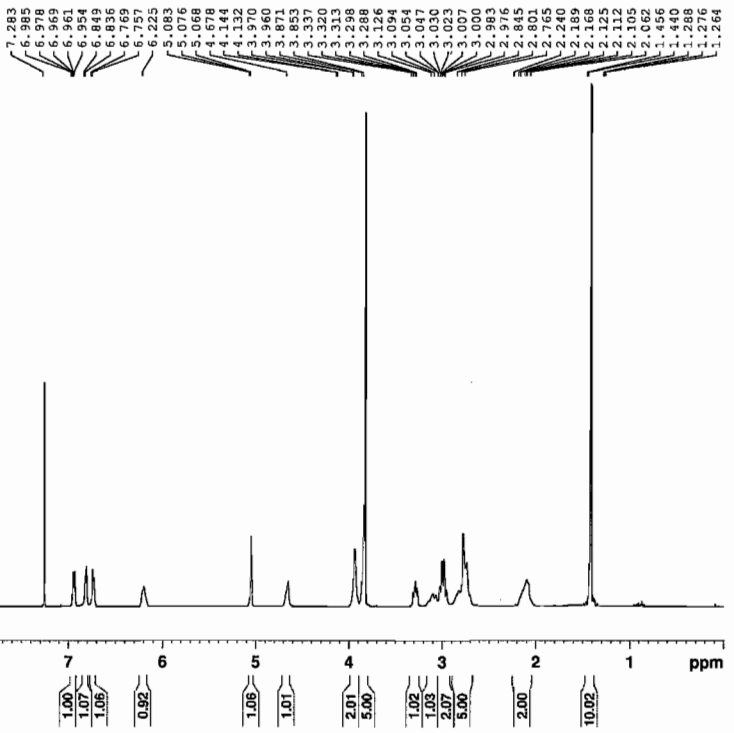

173.588
163.165
153.658
136.012
132.169
128.713
128.305
127.548
124.581
114.264
77.600
72.711
70.263
68.578
64.649
26.697
22.177
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

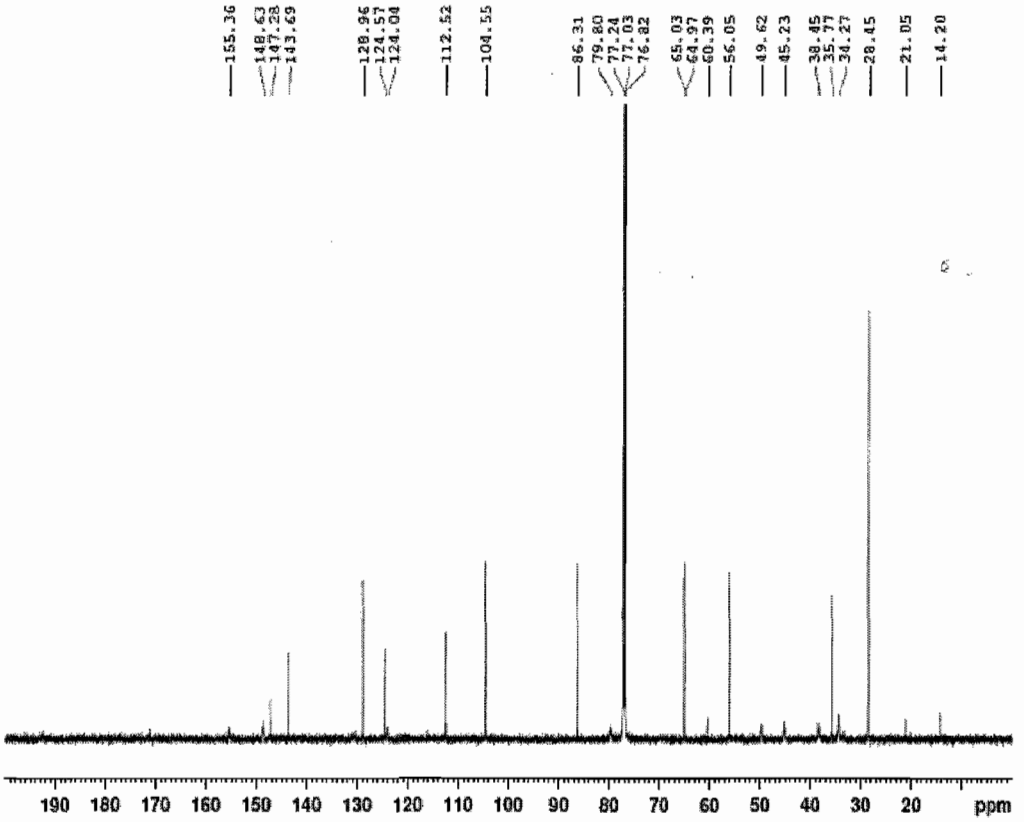

7.729
7.699
7.392
7.371
7.344
7.335
7.327
7.301
7.288
7.239
6.975
6.946
5.090
4.909
4.883
4.851
4.413
4.391
4.383
4.361
4.349
4.327
3.722
3.677
3.643
3.598
3.472
3.449
3.426
3.414
3.393
2.635
2.599
2.567
2.368
2.358
2.345
1.699
1.676
OBn
N
Bn
O
O
O
N
O
118b
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.10
10.02
2.08
2.13
1.00
1.05
2.02
1.05
3.08
1.03
3.04
169.745
162.835
154.069
138.913
136.155
132.489
132.308
128.782
128.709
128.382
128.265
127.572
127.236
125.209
114.246
114.171
78.003
70.178
62.995
61.808
55.297
51.400
31.238
26.361
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

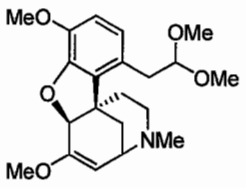

OH
H
N
OBn
N
Bn
O
119b
7.418
7.395
7.321
7.299
7.292
7.278
6.925
6.895
6.491
6.468
5.108
3.846
3.813
3.783
3.771
3.759
3.734
3.691
3.653
3.635
3.622
3.402
3.360
3.029
2.987
2.941
2.933
2.894
2.886
2.742
2.690
2.509
2.480
2.443
1.901
1.860
1.781
1.748
1.711
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
12.32
2.08
0.90
2.06
1.02
1.04
1.03
1.08
1.03
1.00
1.02
1.08
2.03
2.08
167.834
161.350
136.365
129.515
129.007
128.974
128.721
128.239
127.515
127.484
126.370
114.450
77.533
70.117
64.174
59.936
57.999
54.346
31.477
29.715
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


MeO
O
O
O
O
NMeBoc

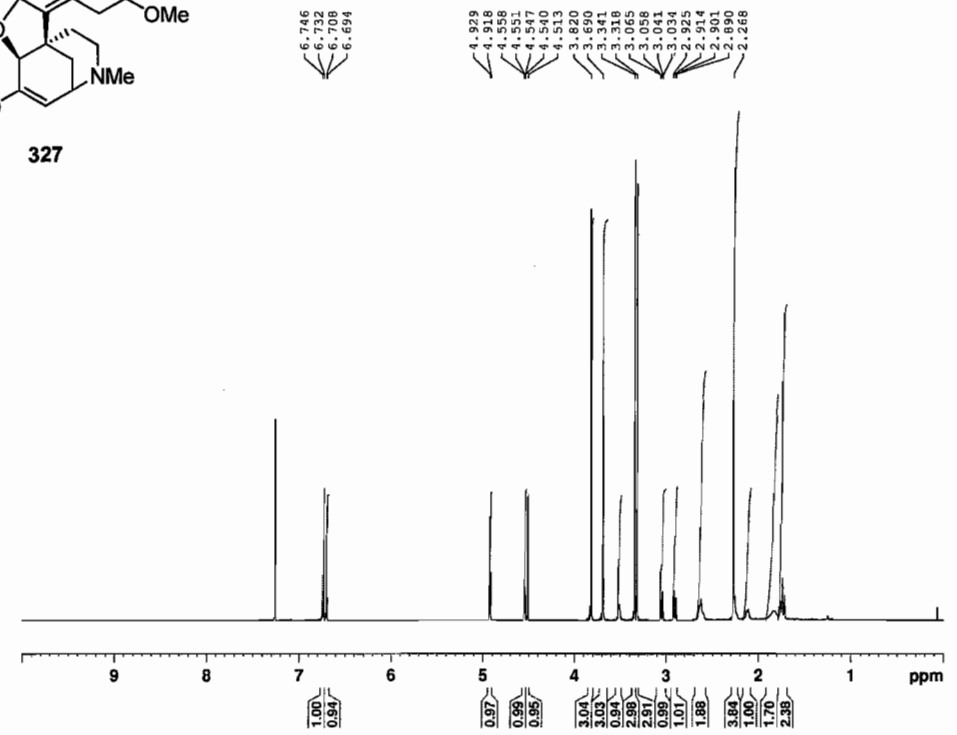
320

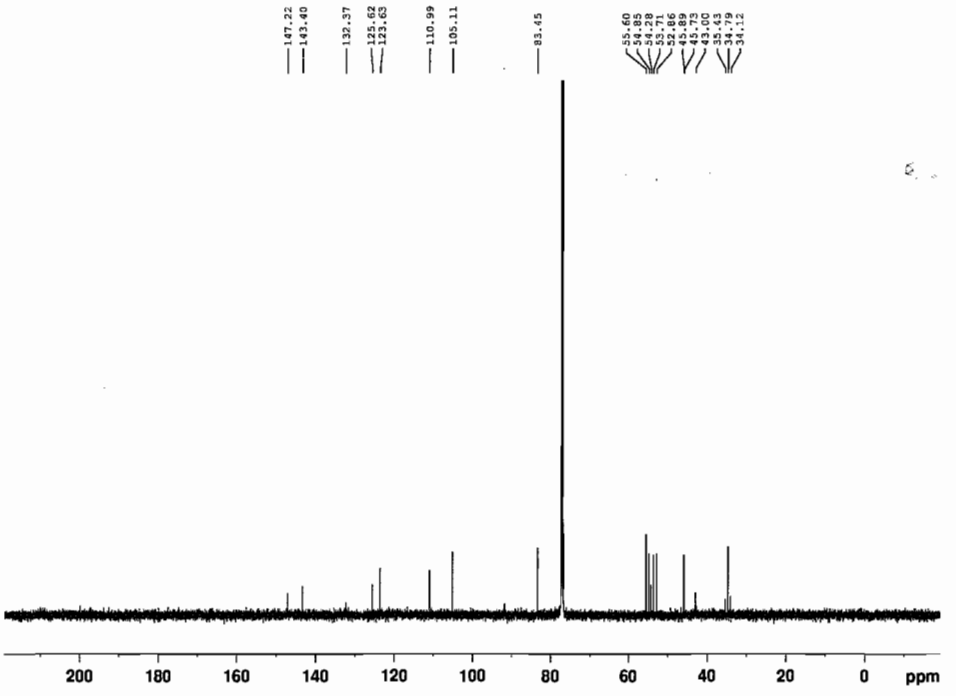

7.283
6.985
6.978
6.969
6.961
6.954
6.849
6.836
6.769
6.757
6.225
5.083
5.076
5.068
4.678
4.144
4.132
3.970
3.960
3.871
3.853
3.337
3.320
3.313
3.298
3.288
3.126
3.094
3.054
3.047
3.030
3.023
3.007
3.000
2.983
2.976
2.845
2.801
2.765
2.240
2.189
2.168
2.125
2.112
2.105
2.062
1.456
1.440
1.288
1.276
1.264
9
8
7
6
5
4
3
2
1
ppm
1.00
1.07
1.06
0.92
1.06
1.01
2.01
5.00
1.02
1.03
2.07
5.00
2.00
10.02

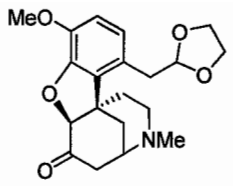

155.36
148.63
147.28
143.69
128.96
124.57
124.04
112.52
104.55
86.31
79.80
77.24
77.03
76.82
65.03
64.97
60.39
56.05
49.62
45.23
38.45
35.77
34.27
28.45
21.05
14.20
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


MeO
OMe
OMe
O
NMe
MeO

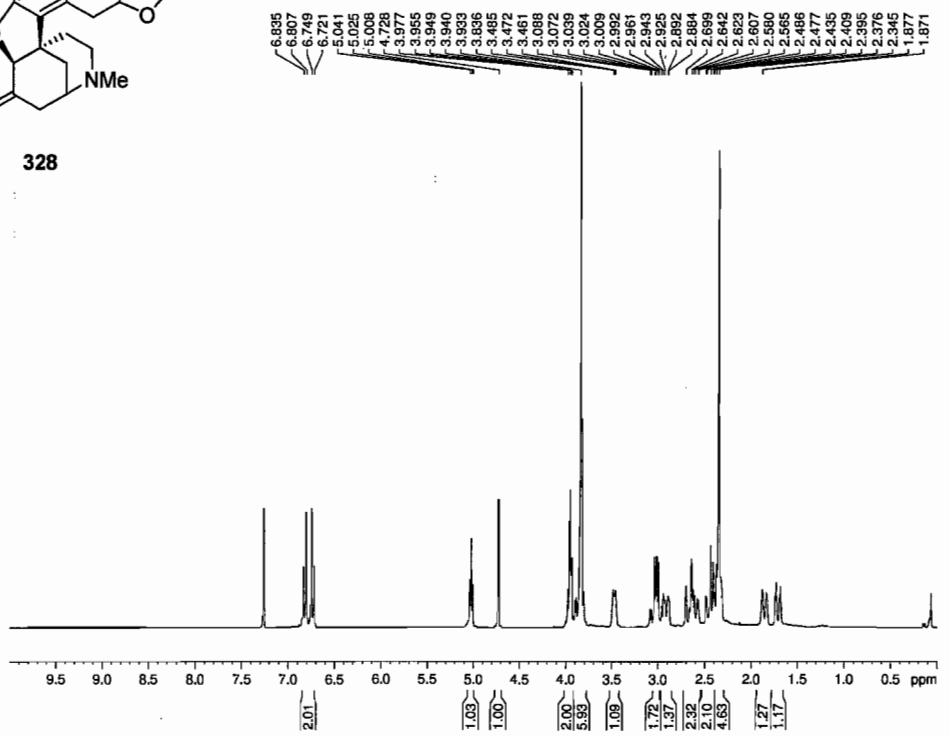
327


6.746
6.732
6.708
6.694
4.929
4.918
4.558
4.551
4.547
4.540
4.513
3.820
3.690
3.341
3.318
3.065
3.058
3.041
3.034
2.925
2.914
2.901
2.890
2.268
9
8
7
6
5
4
3
2
1
ppm
1.00
0.94
0.97
0.99
0.95
3.04
3.03
0.94
2.98
2.91
0.99
1.01
1.88
3.84
1.00
1.70
2.38


147.22
143.40
132.37
125.62
123.63
110.99
105.11
83.45
55.60
54.85
54.78
53.71
52.86
45.89
45.73
43.00
35.45
34.79
34.12
200
180
160
140
120
100
80
60
40
20
0
ppm


MeO
O
O
O
NMe
O

328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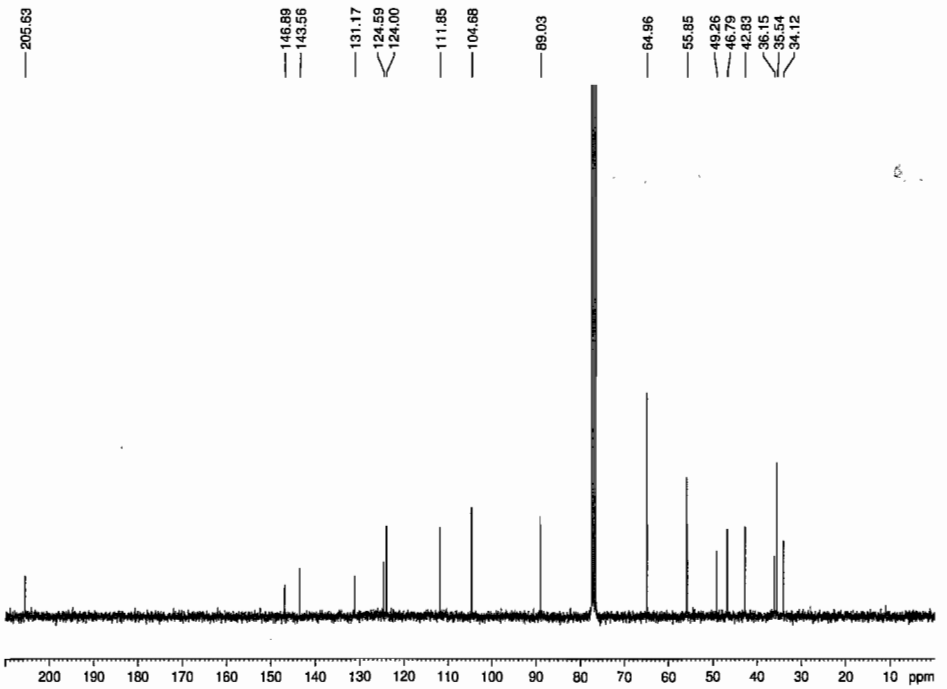
6.807
6.749
6.721
5.041
5.025
5.006
4.728
3.977
3.955
3.949
3.940
3.933
3.836
3.485
3.472
3.461
3.088
3.072
3.039
3.024
3.009
2.992
2.961
2.943
2.925
2.892
2.884
2.699
2.642
2.623
2.607
2.580
2.565
2.486
2.477
2.435
2.409
2.395
2.376
2.345
1.877
1.871
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.01
1.03
1.00
2.00
5.93
1.09
1.72
1.37
2.32
2.10
4.63
1.27
1.17


205.63
146.89
143.56
131.17
124.59
124.00
111.85
104.68
89.03
64.96
55.85
49.26
46.79
42.83
36.15
35.54
34.12
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

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8. Vita

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