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

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Chemistry

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Master of Science

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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

First and foremost I must extend my gratitude to Professor Tomas Hudlicky for providing the funds and equipment required to complete this work. I would like to acknowledge my committee members, Dr. Stuart Rothstein, Dr. Travis Dudding, and Dr. Jeffrey Atkinson for their intellectual input.

My appreciation is extended to Tim Jones for performing all of the mass spectrometry analysis. I also thank Razvan Simionescu for performing some of the NMR analysis and taking the time to help me interpret difficult spectra. I am forever indebted to members of Professor Hudlicky’s research group, both past and present, for their support. In particular, I would like to thank Bradford Sullivan and Hannes Leisch for their assistance during the balanol and codeine projects respectively.
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<td>dppp</td>
<td>1,3-bis(diphenylphosphino)propane</td>
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<tr>
<td>ee</td>
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<td>EDC</td>
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<tr>
<td>EI</td>
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<td>equiv.</td>
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<td>G protein-coupled receptor</td>
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<tr>
<td>LAH</td>
<td>lithium aluminium hydride</td>
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<td>LDA</td>
<td>lithium diisopropylamide</td>
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<td>M</td>
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<td>PPTS</td>
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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](image)

1. Introduction (continued)

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](image)
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).

![Image of balanol (3) and codeine (4)](image)

**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). 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.

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.
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. 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. In 1957, Haccius and Helfrich reported the isolation of pyrocatechol from the fermentation of benzene by *Nocardia coralline*. Soon after, Marr and Stone proposed that trans-1,2-dihydroxycyclohexa-3,5-dienes were the intermediates in catechol formation and not phenols. 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. 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](image)

**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-dihydriodiols. 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). At the time, all of the available evidence indicated that both mammalian and microbial metabolism of aromatic substrates went through the trans-diol intermediate. It was believed that the trans stereochemistry arose from the hydrolysis of a cis-epoxide. 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](image)

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_. 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 values17 established the absolute stereochemistry of 16 as 1S,2R (as depicted in Figure 6).

![Figure 7](image-url)  
**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, 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. Another possibility is a [3+2] cycloaddition between an iron peroxide species and the aromatic substrate (Figure 8). 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.

![Figure 8. Plausible mechanism for TDO-catalyzed dihydroxylations.](image)

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 (RS) will enter the binding pocket in preference to larger substituents (RL) (Figure
Boyd demonstrated that larger differences in relative size between $R_S$ and $R_L$ yield higher enantiomeric excess values.

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

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). 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). This method can supply multigram quantities of enantiopure cyclohexadienediols for use in synthesis.

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). In 1987, Ley reported the synthesis of (+/−)-pinitol (31) from the same diol. This marked the first exploitation of the stereochemistry contained in the cis-dihydrodiol metabolites.
The first enantioselective application of the cis-dihydrodiols was Hudlicky’s formal total synthesis of PGE$_{2a}$ (32) in 1988. Prostanoid synthon 33, which was previously converted to 32 by Johnson, 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$_2$S, 0°C; (iii) Al$_2$O$_3$ (neutral), DME, reflux

Scheme 1. Hudlicky’s enantioselective formal total synthesis of PGE$_{2a}$ (32)

Since Gibson’s initial isolation of cis-dihydrodiols in 1968, over 400 different metabolites of TDO have been identified. 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), Ley has also constructed both the (+)- and (-)-enantiomers of conduritol F (36) from cis-cyclohexa-3,5-diene-
1,2-diol (13). 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, MeONa⁺, MeOH; (ii) mCPBA, DCM; (iii) (R)-(+-)sec-phenethyl alcohol, HBF₄·OEt₂, DCM; (iv) Na/NH₃(l), Et₂O, -78°C

Scheme 2. Ley’s enantiodivergent synthesis of (+)- and (-)-conduritol F (36).

Boyd has developed routes to several pyranose carbasugars (pseudosugars) all originating from the iodobenzene derived cis-dihydrodiol 39. 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/Al₂O₃, 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 LiAlH₄ and aqueous trifluoroacetic acid catalyzed the acetonide deprotection.
Reagents and conditions: (i) 2,2-dimethoxypropane, p-TsOH; (ii) OsO₄, NMO, Me₂CO, H₂O; (iii) Pd(OAc)₂, CO (1 atm), NaOAc·3H₂O, MeOH; (iv) 5% Rh/Al₂O₃, EtOH, H₂ (55 psi); (v) BzCl, pyridine; (vi) LiAlH₄, THF, reflux; (vii) TFA-THF-H₂O (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 acid³⁰ 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 LiAlH₄ 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-butylin 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 \((-\text{-})\)-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\(_3\)SnH, 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\(_2\)CO; (xi) \(n\)-Bu\(_3\)SnH, AIBN, PhH, r.t.; (xii) NaBH\(_4\), MeOH; (xiii) NaH, THF, CS\(_2\), MeI; (xiv) \(n\)-Bu\(_3\)SnH, AIBN, PhMe, reflux; (xv) PPTS, \(r\)-BuOH, reflux; (xvi) PCC, DCM, r.t.; (xvii) \(CH_3\)\(^+\)PPh\(_3\)Br, KHMDS, toluene.

**Scheme 4.** Banwell’s synthesis of \((-\text{-})\)-hirsutene (44).\(^{30}\)

Hudlicky has utilized *cis*-dihydropyridols derived from the TDO-mediated dihydroxylation of halogenated aromatic substrates in the synthesis,\(^{32}\) of several Amaryllidaceae alkaloids.\(^{32}\) Included is the first total synthesis of \((+\text{-})\)-pancratistatin (52) from \((1S\text{-}cis\text{-})\)-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 dimethyl amide 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).

![Scheme 5](image)

Reagents and conditions: (i) 2,2-dimethoxypropane, $p$-TsOH, DCM; (ii) PhI=NTs, Cu(acac)$_2$, CH$_3$CN; (iii) nBu$_3$SnH, AIBN, THF, PhMe, reflux; (iv) a) s-BuLi, TMEDA, THF, -90°C; b) CuCN, -90°C to -20°C; c) 55, BF$_3$-Et$_2$O, -78°C to r.t.; (v) a) s-BuLi, THF; b) (Boc)$_2$O; (vi) Na/anthracene, DME, -78°C; (vii) TBAF, THF, 0°C; (viii) SMEAH, THF, morpholine, -45°C; (ix) BnBr, K$_2$CO$_3$, DMF; (x) a) NaClO$_2$, KH$_2$PO$_4$, 2-methyl-2-butene, $t$-BuOH, H$_2$O; b) CH$_2$N$_2$, Et$_2$O; (xi) AcOH, THF, H$_2$O, 60°C; (xii) $t$-BuOOH, VO(acac)$_2$, PhH, 60°C; (xiii) H$_2$O, BzO Na$^+$ (cat), 100°C; (xiv) Pd(OH)$_2$/C, H$_2$ (1 atm), 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\textsuperscript{35} and in 2009\textsuperscript{1} by Hudlicky. Also available is a more complete compilation of the known metabolites of TDO.\textsuperscript{36}

2.2 Balanol

2.2.1 Discovery of Balanol

The compound now named balanol (3) was originally isolated from \textit{Cordyceps ophioglossoides} in the 1970's by researchers at the Universit"at T"ubingen in Germany.\textsuperscript{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).\textsuperscript{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 \textit{Fusarium merismoides} Corda and \textit{Fusarium aquaeductuum} Lagh.\textsuperscript{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 \textit{Verticillium balanoides}.\textsuperscript{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.\textsuperscript{40} It was concluded that they were indeed the same molecule and that the structure assigned by the Sphinx group was the correct one.
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.\textsuperscript{43}

Analogs of balanol have been synthesized and screened for activity against PKCs and other kinases.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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, although the first completed total synthesis belongs to the Sphinx Pharmaceutical group.

Lampe and Hughes (1994)

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$_2$CO$_3$; (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$_4$NMnO$_4$, pyr; (xi) BnBr, K$_2$CO$_3$; (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.
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(1pc)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)\(_2\)O, NaOH, 1,4-dioxane, H\(_2\)O, 0-25 °C; (ii) K\(_2\)CO\(_3\), MeI, DMF, 0-25°C; (iii) TPSCI, imidazole, DMF, 25°C; (iv) DIBALH, toluene, -78°C; (v) Allyl-B(\(^{13}\)PC\(_2\))\(_2\), Et\(_2\)O, -78°C, ethanolamine; (vi) 2,2-dimethoxypropane, CSA, CH\(_2\)Cl\(_2\), 25°C; (vii) 9-BBN, THF; then NaOH, H\(_2\)O\(_2\); (viii) MsCl, Et\(_3\)N, CH\(_2\)Cl\(_2\), 0°C; (ix) NaN\(_3\), DMF, 25°C; (x) H\(_2\), Pd/C, THF; (xi) Benzyl chlorocarbonate, NaOH, 1,4-dioxane, H\(_2\)O, 0°C; (xii) TBABF, THF, 25°C; (xiii) MsCl, Et\(_3\)N, CH\(_2\)Cl\(_2\), 0°C; (xiv) KOrBu, THF, 25°C; (xv) TFA, CH\(_2\)Cl\(_2\), 25°C; (xvi) p-(benzyloxy) benzoyl chloride, Et\(_3\)N, 0-25°C; (xvii) 67, 2-chloro-1-methylpyridinium iodide, DMAP, NEt\(_3\), DCM; (xviii) H\(_2\), Pd black, THF, H\(_2\)O, 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.

\[
\begin{align*}
\text{MeO} & \text{COCl} + \text{Br} & \rightarrow & \text{OMe} \\
80 & 81 & 82 \\
\text{ii-iv} & \rightarrow & \text{OH} & \text{CO}_2\text{H} \\
84 & 83 & 85
\end{align*}
\]

Reagents and conditions: (i) Mg, THF; (ii) KMnO₄, pyridine (aq.); (iii) SOCl₂, MeOH; (iv) BBr₃, DCM; (v) SOCl₂, MeOH; (vi) NaH, BnBr, DMF; (vii) BBr₃, DCM; (viii) NaH, BnBr, DMF; (ix) Na₂CO₃ (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.\textsuperscript{50,53} Separation of (-)- and (+)-balanol (3) was accomplished through use of an HPLC protocol.

\[ \begin{align*}
\text{Reagents and conditions:} & \quad (i) \ N_2 CHCO_2 Et, BF_3-Et_2 O, DCM; (ii) HCl, dioxane; (iii) NaN_3, AcOH, DMF; (iv) NaBH_4, EtOH; (v) LiAlH_4, THF; (vi) HBr (aq.); (vii) NEt_3, DCM, 18-crown-6, benzyl chloroformate; (viii) p-(benzyloxy) benzoyl chloride, Et_3 N, DCM; (ix) 85, 2-chloro-1-methylpyridinium iodide, DMAP, NEt_3, DCM; (x) H_2, Pd black, EtOAc, H_2O, AcOH; (xi) HPLC separation. \\
\text{Scheme 10. Vicker's synthesis of} & \quad (-)- \text{ and} \quad (+)-\text{balanol.} \textsuperscript{54}
\end{align*} \]

Tanner (1995)\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 \textit{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.

\textbf{Scheme 11.} Two of Tanner's approaches to balanol.\textsuperscript{55,56}

\textit{Reagents and conditions:} (i) \textit{p}-TsCl, NEt\textsubscript{3}, DMAP, DCM; (ii) \textit{N}-tosylimidazole, \textit{Bu\textsubscript{4}}NF, THF; (iii) \textit{p}-\textit{TolSO\textsubscript{2}}NH\textsubscript{2}, \textit{Cs\textsubscript{2}}CO\textsubscript{3}, DMF, r.t.; (iv) LiN\textsubscript{3}, DMF, 90°C; (v) MsCl, NEt\textsubscript{3}, DCM; (vi) LiAlH\textsubscript{4}, THF, 50°C; (vii) \textit{p}-MeOC\textsubscript{6}H\textsubscript{4}COCl, NEt\textsubscript{3}, DCM; (viii) \textit{p}-TsCl, H\textsubscript{2}O, THF; (ix) BCl\textsubscript{3}, DCM; (x) Na(Hg), Na\textsubscript{2}HPO\textsubscript{4}, MeOH, reflux; (xi) \textit{BnN=C=O}, NEt\textsubscript{3}, DCM; (xii) NaH, THF, r.t.; (xiii) \textit{p}-TsCl, NEt\textsubscript{3}, DCM; (xiv) \textit{Bu\textsubscript{4}}NF, THF; (xv) \textit{p}-TsCl, NEt\textsubscript{3}, DMAP, DCM; (xvi) \textit{p}-\textit{TolSO\textsubscript{2}}NH\textsubscript{2}, \textit{Cs\textsubscript{2}}CO\textsubscript{3}, DMF, r.t.; (xvii) LiOH, THF, H\textsubscript{2}O, EtOH, reflux
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.

\[ \text{Reagents and conditions:} \]
\begin{itemize}
  \item[(i)] a) Na\(_2\)S\(_2\)O\(_4\), Bu\(_4\)NBr, THF, H\(_2\)O; b) 6N KOH, Me\(_2\)SO\(_4\), r.t.;
  \item[(ii)] O\(_2\)/hv, Et\(_2\)O, H\(_2\)SO\(_4\), acetone;
  \item[(iii)] NaH, MeI, DMF;
  \item[(iv)] NBS, AIBN, CCl\(_4\), reflux;
  \item[(v)] BBr\(_3\), DCM, r.t.;
  \item[(vi)] BnBr, K\(_2\)CO\(_3\), DMF;
  \item[(vii)] CaCO\(_3\), H\(_2\)O, dioxane, reflux;
  \item[(viii)] Pr\(_4\)NRuO\(_4\), NMO, MeCN;
  \item[(ix)] NaClO\(_2\), NaH\(_2\)PO\(_4\), 2-methyl-2-butene, THF, t-BuOH, H\(_2\)O.
\end{itemize}

\textbf{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.

\[ \text{Reagents and conditions: } (i) \text{ SmI}_2, \text{ HMPA, } t-\text{BuOH, } -78^\circ \text{C}; (ii) a) \text{ H}_2, \text{ Pto}_2, \text{ MeOH; b) } p-(\text{benzyloxy}) \text{ benzo} \text{yl chloride, } \text{NaHCO}_3, \text{ H}_2\text{O, DCM; (iii) immobilized lipase, vinyl acetate, } t-\text{BuOMe, } 45^\circ \text{C; (iv) a) TFA, DCM; b) CBz-Cl, Na}_2\text{CO}_3, \text{ H}_2\text{, acetone; (v) KOH, MeOH, r.t.; (vi) 85, 2-chloro-1-methylpyridinium iodide, DMAP, NEt}_3, \text{ DCM; (vii) H}_2, \text{ Pd black, HCO}_2\text{H, r.t.}} \]

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 Grubbs’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 % Grubbs’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 114⁶³ 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 (−)-
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) NH₄CO₂Ph, DMF, 50°C; b) H₂SO₄, THF, H₂O; (iii) 1N NaOH, MeOH; (iv) NaH, THF, reflux; (v) 4-benzyloxybenzoyl chloride, DCM, DMAP, NEt₃; (vi) OsO₄, NMO, DCM; (vii) a) NaIO₄, acetone-H₂O (8:2); b) BnNH₂, MeOH, AcOH, NaCNBH₃, 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 core⁶⁴-⁸⁴ 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. 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. 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. The conquest of Assyria by the Persians sparked the spread of opium (which they called theriac, malideh and afium) 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”. 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. 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. 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. 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.

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). 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. 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”. 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. A more detailed account on the structural elucidation of opium alkaloid has been published by Butora and Hudlicky.
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).\textsuperscript{100} (S)-Noracoc1aurine synthase catalyzes a Pictet-Spengler-type condensation reaction between 125 and 126 to produce (S)-noracoc1aurine (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.\textsuperscript{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\textsubscript{N}2' (or possibly a S\textsubscript{N}1) 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. 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.\textsuperscript{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 \textit{O}-demethylation of codeine to morphine by cytochrome P450 2D6 (CYP2D6).\textsuperscript{104} Approximately 10\% of codeine undergoes \textit{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.\textsuperscript{105} They found that people who lack the CYP450 2D6 enzyme for the \textit{O}-demethylation are still able to experience the effect of codeine.
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

**Figure 15. Metabolism of codeine (4).**
former having appreciable activity (Figure 16). Both metabolites can be further hydrolyzed to morphine itself.

![Chemical structures of metabolites](image)

**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.\(^9\) 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.

![Chemical structures of opioids](image)

**Figure 17. Opioid receptor ligands.**
The first significant attempt to explain opioid receptor binding was postulated by Beckett and Casy in 1954.\textsuperscript{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.\textsuperscript{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,\textsuperscript{108} 2. Simon, Hiller and Edelman,\textsuperscript{109} and 3. Terenius\textsuperscript{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 (\textsuperscript{145}) (an opioid receptor antagonist).\textsuperscript{111} Ultimately Kosterlitz identified the agents responsible as pentapeptides Tyr-Gly-Gly-Phe-Met (Met-enkephalin (\textsuperscript{146})) and Try-Gly-Gly-Phe-Leu (Leu-enkephalin (\textsuperscript{147})). The term "enkephalin" is derived from the Greek meaning "in the head", their location in the body.\textsuperscript{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*). 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). 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.

![Figure 18. Proposed pharmacophore of opioid agonists.](image)
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. The opioid receptors are G-protein coupled receptors found imbedded the cell membranes of neurons. They are widely, but unevenly, distributed throughout the CNS.

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 etorphine (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 \( \kappa \)-receptor agonist could be developed. Such a compound could be the safe, potent, and non-addictive pain killer researchers have been searching for.

\[
\begin{align*}
\text{etorphine (149)} & \quad \text{naltrexone (150)} & \quad 7\text{-spiroindanyloxymorphone (151)} & \quad \text{naltirindole (152)}
\end{align*}
\]

**Figure 19.** Selective opioid receptor ligands.

The delta (\( \delta \)) receptors are located in the brain (pontine nucleus, amygdala, olfactory bulbs, and deep cortex). Agonist activation of the \( \delta \)-receptors produces analgesia, euphoria, physical dependence, and possibly seizures and respiratory depression. When an agonist binds, the \( \delta \)-receptor changes conformation and initiates the fragmentation of a messenger \( G_\text{i} \)-protein. The \( \alpha_\text{i} \)-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 \( \delta \)-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 \( \delta \)-receptor is a result of specific interaction with the indane ring off C-7. Similarly, antagonists such as naltirindole (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.\cite{6} 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.\cite{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".\cite{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.][1]

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.\textsuperscript{118-122}

**Gates (1952)\textsuperscript{123}**

Gates published the first total synthesis of morphine (120) as a brief two page communication in 1952.\textsuperscript{123} Four years later, a detailed account of this seminal work was disclosed.\textsuperscript{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.

\begin{align*}
\text{HO} & \rightarrow \text{BzO} \\
153 & \quad \text{i-iii} \\
\text{BzO} & \rightarrow \text{BzO} \\
154 & \quad \text{iv} \\
\text{BzO} & \rightarrow \text{BzO} \\
155 & \quad \text{v-vii} \\
\text{MeO} & \rightarrow \text{MeO} \\
156 & \quad \text{x} \\
\text{CN} & \rightarrow \text{CN} \\
158 & \quad \text{viii-ix} \\
\end{align*}

**Scheme 16.** Gates' synthesis of Diels-Alder product 159.\textsuperscript{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 H₂, CuO, Cr₂O₃, EtOH, 135°C; (ii) N₂H₄, KOH; (iii) a) Mel, NaH; b) LiAlH₄; (iv) H₂SO₄, H₂O; (v) KOH, (HOCH₂CH₂)₂O; (vi) KOtBu, Ph₂CO; (vii) a) Br₂; b) 2,4-DNPH; (viii) HCl; (ix) H₂, PtO₂; (x) a) Br₂; b) 2,4-DNPH; (xi) HCl; (xii) LiAlH₄, THF; (xiii) pyridine-HCl, 220°C.

Scheme 17. Gates’ synthesis of morphine.¹²³
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) NaHSO₃; (ii) KCN, H₂SO₄; (iii) 166, 200°C; (iv) POCl₃, MeCN; (v) NaCNBH₃, MeOH; (vi) Li, NH₃, THF, t-BuOH, -55 to -65°C; (vii) PhOCHO, EtOAc; (viii) (CH₂OH)₂, THF, MeSO₃H, r.t.; (ix) CH₃CONHBr, 0°C; (x) HCO₂H-H₂O (5:1), r.t.; (xi) NH₄²HF, CF₃SO₃H, 0°C; (xii) a) MeOH, HCl, reflux; b) NH₂-H₂O, iPrOH; (xiii) H₂, Pd/C, AcOH, HOCH; (xiv) Br₂, AcOH; (xv) NaOH, CHCl₃; (xvi) H₂, AcOH-HCHO; (xvii) CICO₂Et; (xviii) PhSeCl; (xix) NaIO₄; (xx) NaBH₄; (xxi) BBr₃, CHCl₃.

Scheme 18. Rice’s synthesis of morphine.

Evans (1982)

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\textsuperscript{124} to the natural isomer and thus complete a formal synthesis.

Reagents and conditions: (i) BH\textsubscript{3}, THF; (ii) PBr\textsubscript{3}, HBr, DCM; (iii) ZnBr\textsubscript{2}, PhH, 80°C; (iv) a) nBuLi, THF, -10°C; b) 175, Et\textsubscript{2}O, -78°C; (v) NaI, K\textsubscript{2}CO\textsubscript{3}, MeCN, 80°C; (vi) a) HClO\textsubscript{4}, Et\textsubscript{2}O; b) MeOH; (vii) CH\textsubscript{3}N\textsubscript{2}, Et\textsubscript{2}O; (viii) DMSO, r.t.; (ix) BF\textsubscript{3}Et\textsubscript{2}O, PhMe, -10°C; (x) MsCl, NEt\textsubscript{3}; (xi) LiEt\textsubscript{3}BH; (xii) OsO\textsubscript{4}, NaIO\textsubscript{4}.

Scheme 19. Evans’ formal synthesis of morphine.\textsuperscript{127}
Parker (1992)\textsuperscript{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-butylidimethylsilyl 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 $\beta$-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) Mel, K$_2$CO$_3$, 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$_2$NEt, -78°C; (viii) PBu$_3$, DEAD, THF, 0°C; (ix) 10% HF, MeCN; (x) n-Bu$_3$SnH, 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) Br₂, NEt₃; (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(PPh₃)₂, and then treated with PhMe₂SiLi to provide allylisilane 201. Acidic hydrolysis of the acetonide and subsequent reductive amination with dibenzosuberylamine (DBS-NH₂) and sodium cyanoborohydride provided coupling partner 202.

Reagents and conditions: (i) HC(OMe)₃, HCl; (ii) NaH, ClCH₂OMe; (iii) n-BuLi, I₂; (iv) 6N HCl; (v) BnBr, K₂CO₃; (vi) CH₂SMe₂; (vii) BF₃·Et₂O, THF; (viii) 198, catechol borane; (ix) PhN=C=P; (x) OsO₄, NMO, (CH₃)₂CO, H⁺; (xi) a) n-BuLi, THF, -30°C; b) CuI(PPh₃)₂, 0°C; c) PhMe₂SiLi, 0°C; (xii) p-TsOH, NaIO₄, MeOH; (xiii) DBS-NH₂, NaCNBH₃.

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 $\text{Pd(OCOCF}_3\text{)}_2(\text{PPh}_3)_2$ 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.

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-trichloethoxycarbonate. 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$_2$CO$_3$, H$_2$O; (ii) Troc-Cl, pyridine, 0°C; (iii) Br$_2$, AcOH, NaOAc, r.t.; (iv) 109, % [{(η$^3$-C$_3$H$_5$)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 forged 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\textsuperscript{136} to give morphine.

Scheme 25. Trost’s synthesis of morphine.\textsuperscript{133}

**Fukuyama (2006)\textsuperscript{137}**

In a similar manner to Overman,\textsuperscript{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).\textsuperscript{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.

Reagents and conditions: (i) AcOH, THF, H2O, 0°C; (ii) MeOCH2PPh3Cl, NaHMDS, THF; 0°C; (iii) HCl, MeOH, 40°C; (iv) Pd(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\textsuperscript{136} to give morphine.

\begin{align*}
\text{Reagents and conditions:} & & (i) & p\text{-nitrobenzoic acid, DEAD, PPh}_3, \text{PhMe, THF, 0°C; (ii) CSA, MeOH;} \\
& & (iii) & 2\text{-hydroxy-2-methylpropanenitrile, DEAD, PPh}_3, \text{PhMe, 0°C; (iv) LiBH}_4, \text{Et}_2\text{O, MeOH, 0°C; (v)} \\
& & & \text{TBS-Cl, imidazole, DMF, r.t.; (vi) a) DIBAL-H, DCM, -78°C; b) NaBH}_4, \text{MeOH, -78°C; (vii)} \\
& & & \text{ClCO}_2\text{Me, K}_2\text{CO}_3; (viii) a) \text{Pd}_2(\text{dba})_3, \text{P(o-toly)}_3, \text{NEt}_3, \text{MeCN, reflux; b) TBAF, r.t.; (ix) HCl, MeOH,} \\
& & & \text{reflux; (x) TMS-Cl, LHMDMS, THF, 0°C; (xi) Pd(OAc)}_2, \text{MeCN, r.t.; (xii) H}_2\text{O}_2, \text{H}_2\text{O, NaOH, MeCN,} \\
& & & \text{0°C; (xiii) NaBH}_4, \text{MeOH, DCM; (xiv) TCDI, DMAP, ClCH}_2\text{CH}_2\text{Cl, 60°C; (xv) Et}_3\text{B, n-Bu}_3\text{SnH,} \\
& & & \text{THF, r.t.; (xvi) Dess-Martin periodinane, DCM, r.t.; (xvii) LiAlH}_4, \text{THF; (xviii) BBr}_3, \text{DCM, r.t.}} \\
\end{align*}

\textbf{Scheme 27.} Fukuyama’s synthesis of morphine.\textsuperscript{137}
Hudlicky’s Radical Cyclization Approach (1996)\textsuperscript{140-3}

In parallel to Parker’s efforts,\textsuperscript{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\textsuperscript{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-Bu₃SnH, AIBN, PhH, reflux; (vi) Dowex 50X8-100, MeOH, H₂O; (vii) TBDMS-OTf, i-Pr₂NEt, THF, -78°C; (viii) 233, DEAD, n-Bu₃P, THF, 0°C; (ix) n-Bu₃SnH, AIBN, PhH, reflux; (x) TBAF, THF; (xi) DIBAL-H, DCM, 0°C; (xii) ClCOCOCl, DMSO, NEt₃, DCM, -78°C to 0°C; (xiii) CF₃SO₂H; (xiv) MsCl, NEt₃, THF; (xv) AlCl₃, 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 azobisobutyronitrile 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-Pr₂NEt, THF, -78°C; (iv) PhCO₂H, n-Bu₃P, DEAD, THF; (v) oxazol-2(3H)-one, NaH, DMSO; (vi) NaOH, H₂O; (vii) 233, n-Bu₃P, 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.

![Chemical structure and reactions](image)

**Reagents and conditions:** (i) PhCO₂H, DCC, DCM; (ii) oxazolidine-2,4-dione, tetramethylguanidine, THF, reflux; (iii) NaBH₄, MeOH; (iv) AlCl₃, 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) PhCO₂H, PPh₃, DEAD, THF; (iii) MeONa, MeOH, THF; (iv) 251, DME, 18-crown-6; (v) TBS-OTf, i-Pr₂NEt, DCM; (vi) Pd(PPh₃)₄, Proton Sponge™, PhMe; (vii) DIBAL-H, DCM; (viii) TBAF, THF; (ix) H₂, PtO₂, AcOH; (x) (COCl)₂, DMSO, NEt₃, DCM; (xi) CF₃SO₃H.

**Scheme 31.** Hudlický’s third approach to morphine skeleton.¹⁴⁸

In 2007, Hudlický 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) Ac₂O, NEt₃, DMAP, DCM, 0°C; (ii) a) MeNH₂, K₂CO₃, THF, -40°C to r.t.; b) (Boc)₂O, NEt₃, MeOH; (iii) TBS-Cl, imidazole, DCM, -78°C to r.t.; (iv) n-Bu₃P, DIAD, THF, 0°C; (v) Pd(OAc)₂, Ag₂CO₃, dppf, PhMe, 110°C; (vi) PPh₃CH₂Br₂, t-BuOK, THF, -60°C; (vii) Pd(OAc)₂, Ag₂CO₃, dipp, PhMe, 110°C; (viii) TBAF, THF, r.t.; (ix) IBX, DMF, r.t.; (x) NaBH₄, CeCl₃·7H₂O, MeOH, 0°C; (xi) TFA-DCM (1:4), 0°C; (xii) a) Hg(OAc)₂, NEt₃, THF; b) LiAlH₄, 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.

\[
\begin{align*}
\text{Reagents and conditions:} & \\
(i) & \text{Ac}_2\text{O}, \text{NEt}_3, \text{DMAP}, \text{DCM}, 0^\circ\text{C}; \\
(ii) & \text{a) MeNH}_2, \text{K}_2\text{CO}_3, \text{THF, -40}^\circ\text{C to r.t.}; \\
& \text{b) (Boc)}_2\text{O}, \text{NEt}_3, \text{MeOH}; \\
(iii) & \text{TsCl, NEt}_3, \text{DMAP, DCM, 0}^\circ\text{C to r.t.}; \\
(iv) & 4\text{-nitrobenzoic acid, DIAD, PPh}_3, \text{THF, 0}^\circ\text{C}; \\
(v) & \text{NaOMe, MeOH, 0}^\circ\text{C}; \\
(vi) & \text{268, 18-crown-6, DME-DMF (1:1); 80}^\circ\text{C}; \\
(vii) & \text{TBSCI, imidazole, DCM.}
\end{align*}
\]

\textbf{Scheme 33.} Hudlicky's synthesis of (-)-codeine.\textsuperscript{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. The synthesis intercepted the bis-benzyl-protected intermediates 119a and 119b from the Lampe and Hughes route. Although several formal syntheses employing these intermediates have been published, none reported optical data. Our own samples of 119a and 119b were in ~95% enantiomeric excess, as determined by the Mosher ester/19F 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. The optical purity of this compound has been confirmed through its use in several enantioselective syntheses of naturally occurring products. 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.

\[
\text{(+)-balanol (3) } \rightarrow \text{ 119b}
\]

\[
\text{(-)-balanol (3) } \rightarrow \text{ 119a}
\]

**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.
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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Equiv. AcOH</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OTf)₂</td>
<td>DCM</td>
<td>1</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>BF₃·OEt₂</td>
<td>DCM</td>
<td>1</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>TMSOTf</td>
<td>DCM</td>
<td>1</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>TMSOTf</td>
<td>DCM</td>
<td>5</td>
<td>77</td>
</tr>
</tbody>
</table>

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.

Figure 22. Reduction of vinyl bromide 274
Table 2. Reduction of vinyl bromide 274

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Ratio 275a:275b:276&lt;sup&gt;[a]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ru&lt;sub&gt;3&lt;/sub&gt;(CO)&lt;sub&gt;12&lt;/sub&gt;</td>
<td>-</td>
<td>MeOH</td>
<td>_&lt;sup&gt;[[b]]&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Raney Ni</td>
<td>-</td>
<td>MeOH</td>
<td>_&lt;sup&gt;[[b]]&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>5% Pd/C</td>
<td>-</td>
<td>MeOH</td>
<td>3:1:5</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-</td>
<td>MeOH</td>
<td>2:5:8</td>
</tr>
<tr>
<td>5</td>
<td>PtO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-</td>
<td>MeOH</td>
<td>7:3</td>
</tr>
<tr>
<td>6</td>
<td>PtO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-</td>
<td>EtOH</td>
<td>8:3</td>
</tr>
<tr>
<td>7</td>
<td>PtO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>EtOH</td>
<td>6:1:3</td>
</tr>
<tr>
<td>8</td>
<td>PtO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NEt&lt;sub&gt;3&lt;/sub&gt;</td>
<td>EtOAc</td>
<td>4:1:5</td>
</tr>
</tbody>
</table>

<sup>[a]</sup> approximate ratio determined from 1H NMR spectra; <sup>[[b]]</sup> 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.

Reagents and conditions: (i) SiO<sub>2</sub>, 50°C, 81%

**Scheme 35. Hydrogenation of vinyl bromide 274**
Table 3. Hydrogenation of vinyl bromide 277

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Ratio 278a:278b:279&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ru&lt;sub&gt;3&lt;/sub&gt;(CO)&lt;sub&gt;12&lt;/sub&gt;</td>
<td>-</td>
<td>MeOH</td>
<td>-&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Raney Ni</td>
<td>-</td>
<td>MeOH</td>
<td>-&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>5% Pd/C</td>
<td>-</td>
<td>MeOH</td>
<td>3:2:5</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-</td>
<td>MeOH</td>
<td>3:1:8</td>
</tr>
<tr>
<td>5</td>
<td>PtO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-</td>
<td>MeOH</td>
<td>3:1</td>
</tr>
<tr>
<td>6</td>
<td>PtO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-</td>
<td>EtOH</td>
<td>7:2</td>
</tr>
<tr>
<td>7</td>
<td>PtO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>EtOH</td>
<td>4:2:5</td>
</tr>
<tr>
<td>8</td>
<td>PtO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NEt&lt;sub&gt;3&lt;/sub&gt;</td>
<td>EtOAc</td>
<td>4:1:5</td>
</tr>
</tbody>
</table>

<sup>a</sup> approximate ratio determined from <sup>1</sup>H NMR spectra; <sup>b</sup> 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 280<sub>a</sub> 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.

Figure 23. Hydrolysis of acetate 274

Table 4. Hydrolysis of acetyl 274

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Yield</th>
<th>Ratio 280&lt;sub&gt;a&lt;/sub&gt;:280&lt;sub&gt;b&lt;/sub&gt;&lt;sup&gt;[a]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>MeOH</td>
<td>0°C – r.t.</td>
<td>82%</td>
<td>4:1</td>
</tr>
<tr>
<td>2</td>
<td>Na&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>MeOH</td>
<td>0°C – r.t.</td>
<td>88%</td>
<td>4:1</td>
</tr>
<tr>
<td>3</td>
<td>NaOH</td>
<td>MeOH</td>
<td>0°C – r.t.</td>
<td>67%</td>
<td>7:2</td>
</tr>
<tr>
<td>4</td>
<td>KOH</td>
<td>MeOH</td>
<td>0°C – r.t.</td>
<td>61%</td>
<td>8:3</td>
</tr>
</tbody>
</table>

<sup>[a]</sup> approximate ratio determined from <sup>1</sup>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).

![Figure 24. Radical debromination of 274](image)

**Table 5. Radical debromination of 274**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Concentration$^{[a]}$</th>
<th>Ratio 281a:281b$^{[b]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{Bu}_3\text{Sn-H, AIBN}$</td>
<td>THF</td>
<td>0.5 M</td>
<td>3:1</td>
</tr>
<tr>
<td>2</td>
<td>$\text{Bu}_3\text{Sn-H, AIBN}$</td>
<td>THF</td>
<td>1.0 M</td>
<td><strong>15:1</strong></td>
</tr>
<tr>
<td>3</td>
<td>$\text{Bu}_3\text{Sn-H, AIBN}$</td>
<td>THF</td>
<td>2.0 M</td>
<td>8:1</td>
</tr>
</tbody>
</table>

$^{[a]}$ concentration of $\text{Bu}_3\text{Sn-H};$ $^{[b]}$ approximate ratio determined from $^1\text{H}$ 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.
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).

Table 6. Radical debromination of 277

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Concentration[a]</th>
<th>Ratio 282a:282b[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu₃Sn-H, AIBN</td>
<td>THF</td>
<td>0.5 M</td>
<td>4:1</td>
</tr>
<tr>
<td>2</td>
<td>Bu₃Sn-H, AIBN</td>
<td>THF</td>
<td>1.0 M</td>
<td>8:1</td>
</tr>
<tr>
<td>3</td>
<td>Bu₃Sn-H, AIBN</td>
<td>THF</td>
<td>2.0 M</td>
<td>9:1</td>
</tr>
</tbody>
</table>

[a] concentration of Bu₃Sn-H; [b] approximate ratio determined from ^1^H NMR spectra

Table 7. Potassium azodicarboxylate reduction of olefin 281

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Equivalents[a]</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PAD, AcOH</td>
<td>MeOH</td>
<td>4</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>PAD, AcOH</td>
<td>MeOH</td>
<td>20</td>
<td>SM</td>
</tr>
</tbody>
</table>

[a] equivalents of PAD

Figure 25. Radical debromination of 277

Figure 26. Potassium azodicarboxylate reduction of olefin 281
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).

![Image of chemical structures](image)

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Equivalents(^{[a]})</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PAD, AcOH</td>
<td>MeOH</td>
<td>4</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>PAD, AcOH</td>
<td>MeOH</td>
<td>20</td>
<td>SM</td>
</tr>
</tbody>
</table>

\(^{[a]}\) 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\(_3\)-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.

![Diagram](Image)

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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Ratio (283a:283b)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OTf)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>DCM</td>
<td>r.t.</td>
<td>7:2</td>
<td>77%</td>
</tr>
<tr>
<td>2</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt; · OEt&lt;sub&gt;2&lt;/sub&gt;</td>
<td>DCM</td>
<td>r.t.</td>
<td>3:2</td>
<td>74%</td>
</tr>
<tr>
<td>3</td>
<td>TMSOTf</td>
<td>DCM</td>
<td>r.t.</td>
<td>5:1</td>
<td>82%</td>
</tr>
<tr>
<td>4</td>
<td>β-cyclodextrin</td>
<td>MeCN</td>
<td>r.t.</td>
<td>-</td>
<td>SM</td>
</tr>
<tr>
<td>5</td>
<td>β-cyclodextrin</td>
<td>MeCN</td>
<td>reflux</td>
<td>-</td>
<td>SM</td>
</tr>
<tr>
<td>6</td>
<td>(NH&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt; Ce(NO&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;6&lt;/sub&gt;</td>
<td>MeCN</td>
<td>r.t.</td>
<td>-</td>
<td>SM</td>
</tr>
<tr>
<td>7</td>
<td>(NH&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt; Ce(NO&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;6&lt;/sub&gt;</td>
<td>MeCN</td>
<td>reflux</td>
<td>-</td>
<td>SM</td>
</tr>
</tbody>
</table>

<sup>a</sup> approximate ratio determined from <sup>1</sup>H 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<sup>33</sup> afforded olefin 54 (Scheme 36). We sought to open this aziridine with a hydroxide anion. Our experiments with Cu(OTf)<sub>2</sub> 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.
Reagents and conditions: (i) Bu₃Sn-H, AIBN, THF

Scheme 36. Opening of vinyl aziridine 273

Table 10. Opening of vinyl aziridine 273

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OTf)₂</td>
<td>MeCN/ H₂O</td>
<td>r.t.</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>β-cyclodextrin</td>
<td>MeCN/ H₂O</td>
<td>reflux</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>β-cyclodextrin</td>
<td>acetone/ H₂O</td>
<td>reflux</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>(NH₄)₂Ce(NO₃)₆</td>
<td>acetone/ H₂O</td>
<td>r.t to reflux</td>
<td>decomposition[a]</td>
</tr>
<tr>
<td>5</td>
<td>KOH</td>
<td>DMSO</td>
<td>80°C</td>
<td>284 (27%)</td>
</tr>
<tr>
<td>6</td>
<td>KOH</td>
<td>DMSO</td>
<td>40°C</td>
<td>284 (93%)</td>
</tr>
</tbody>
</table>

[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.
Table 11. Hydrogenation of olefin 284

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5% Pd/ C</td>
<td>-</td>
<td>MeOH</td>
<td>44[a]</td>
</tr>
<tr>
<td>2</td>
<td>5% Pd/ C</td>
<td>NEt₃</td>
<td>MeOH</td>
<td>54[a]</td>
</tr>
<tr>
<td>3</td>
<td>PtO₂</td>
<td>NEt₃</td>
<td>MeOH</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>PtO₂</td>
<td>K₂CO₃</td>
<td>MeOH</td>
<td>92</td>
</tr>
</tbody>
</table>

[a] lower yield possibly a result of hydrogenolysis (¹H 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).

Table 12. Opening of tosyl aziridine 273 with hydroxide

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOH</td>
<td>DMSO</td>
<td>80°C</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>KOH</td>
<td>DMSO</td>
<td>40°C</td>
<td>94</td>
</tr>
</tbody>
</table>
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).

![Figure 31. Reduction of vinyl bromide 280a with Adams’ catalyst](image)

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PtO₂</td>
<td>NEt₃</td>
<td>MeOH</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>PtO₂</td>
<td>K₂CO₃</td>
<td>MeOH</td>
<td>77</td>
</tr>
</tbody>
</table>

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.

![Scheme 37. Synthesis of cyclic carbamate 288](image)

*Reagents and conditions: (i) triphosgene, NEt₃, DCM, 0°C, 93%; (ii) Na/ naphthalene, DME, -78°C, 92%*
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](image)

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NEt₃</td>
<td>DCM</td>
<td>0°C - r.t.</td>
<td>20%[a]</td>
</tr>
<tr>
<td>2</td>
<td>pyridine</td>
<td>DCM</td>
<td>0°C - r.t.</td>
<td>25%[a]</td>
</tr>
<tr>
<td>3</td>
<td>NaH</td>
<td>THF</td>
<td>0°C - r.t.</td>
<td>91%</td>
</tr>
</tbody>
</table>

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

Acidic hydrolysis of acetonide 289 with AcOH/ THF/ H₂O 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/H₂O (9:3:1), reflux, 83%; (ii) NaIO₄, acetone/H₂O (8:2), r.t.; (iii) Bn-NH₂, AcOH, NaBH₃CN, 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). 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, SnBr4, MeCN, -30°C; (iii) KHMDS, n-BuNBr, DME, 0°C, 68% over three steps; (iv) AcOH, TMSOTf, DCM, r.t., 88%; (v) H2 (1 atm), PtO2, EtOAc, 84%; (vi) NaOMe, MeOH, reflux; (vii) methyl chloroformate, NEt3, DCM, DMAP, r.t., 73% over two steps; (viii) NaH, THF, reflux, 83%; (ix) p-BnOC6H4COCl, DCM, DMAP, NEt3, 0°C, 82%; (x) AcOH/THF/H2O (9:3:1), reflux, 88%; (xi) a) NaIO4, acetone/H2O (8:2), r.t.; b) Bn-NH2, AcOH, NaBH3CN, 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.](image)

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 K₂CO₃ 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) Ac₂O, NEt₃, DMAP, 0°C, 67%; (iv) a) NH₂Me, K₂CO₃, THF, sealed tube; b) Boc₂O, NEt₃, 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, CHCl₃, 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-Bu₃P, THF, 0°C – r.t., 55%; (ii) Pd(OAc)₂, Ag₂CO₃, 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Reagent(s)</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IBX</td>
<td>-</td>
<td>DMF</td>
<td>r.t.</td>
<td>decomposition(^{[a]})</td>
</tr>
<tr>
<td>2</td>
<td>IBX</td>
<td>-</td>
<td>DMSO</td>
<td>r.t.</td>
<td>decomposition(^{[a]})</td>
</tr>
<tr>
<td>3</td>
<td>TEMPO</td>
<td>KBr/HClO</td>
<td>DCM</td>
<td>r.t.</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>DMP</td>
<td>-</td>
<td>DCM</td>
<td>O°C-r.t.</td>
<td>decomposition(^{[a]})</td>
</tr>
<tr>
<td>5</td>
<td>TPAP</td>
<td>NMO</td>
<td>DCM</td>
<td>0°C-r.t.</td>
<td>SM</td>
</tr>
<tr>
<td>6</td>
<td>p-nitrobenzaldehyde</td>
<td>AlMe₃</td>
<td>toluene</td>
<td>reflux</td>
<td>SM</td>
</tr>
</tbody>
</table>

\(^{[a]}\) 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.

![Figure 37. Chromate oxidation of enol ether 304](image)

Table 16. Chromate oxidation of enol ether 304

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PCC</td>
<td>DCM</td>
<td>r.t.</td>
<td>305 (67%)</td>
</tr>
<tr>
<td>2</td>
<td>PDC</td>
<td>DCM</td>
<td>r.t.</td>
<td>305 (65%)</td>
</tr>
</tbody>
</table>

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.
Figure 38. Attempted oxidation of cyclohexenol 305

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IBX</td>
<td>-</td>
<td>DMF</td>
<td>r.t.</td>
<td>decomposition[a]</td>
</tr>
<tr>
<td>2</td>
<td>IBX</td>
<td>-</td>
<td>DMSO</td>
<td>r.t.</td>
<td>decomposition[a]</td>
</tr>
<tr>
<td>3</td>
<td>DMP</td>
<td>-</td>
<td>DCM</td>
<td>r.t.</td>
<td>decomposition[a]</td>
</tr>
<tr>
<td>4</td>
<td>PCC</td>
<td>-</td>
<td>DCM</td>
<td>r.t.</td>
<td>SM</td>
</tr>
<tr>
<td>5</td>
<td>PDC</td>
<td>-</td>
<td>DCM</td>
<td>r.t.</td>
<td>SM</td>
</tr>
<tr>
<td>6</td>
<td>p-nitrobenzaldehyde</td>
<td>AlMe3</td>
<td>toluene</td>
<td>reflux</td>
<td>SM</td>
</tr>
</tbody>
</table>

[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 NaCNBH₃ to obtain N-methyl piperidine 308 (Scheme 44). This was strong evidence for the formation of the iminium ion intermediate.
Reagents and conditions: (i) TFA, DCM, 0°C – r.t.; (ii) NaCNBH₃, 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.

Table 18. Attempted formation of iminium salt 309

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3% perchloric acid</td>
<td>DCM</td>
<td>0°C</td>
<td>decomposition[a]</td>
</tr>
<tr>
<td>2</td>
<td>TFA</td>
<td>DCM</td>
<td>0°C</td>
<td>decomposition[a]</td>
</tr>
</tbody>
</table>

[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.

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.

Figure 40. Attempted oxidation of cyclohexenol 311
Table 19. Attempted oxidation of cyclohexenol 311

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IBX</td>
<td>-</td>
<td>DMF</td>
<td>0°C - r.t.</td>
<td>decomposition[a]</td>
</tr>
<tr>
<td>2</td>
<td>IBX</td>
<td>-</td>
<td>DMSO</td>
<td>0°C - r.t.</td>
<td>decomposition[a]</td>
</tr>
<tr>
<td>3</td>
<td>TEMPO</td>
<td>KBr/HClO</td>
<td>DCM</td>
<td>0°C - r.t.</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>DMP</td>
<td>-</td>
<td>DCM</td>
<td>0°C - r.t.</td>
<td>decomposition[a]</td>
</tr>
<tr>
<td>5</td>
<td>PCC</td>
<td>-</td>
<td>DCM</td>
<td>0°C - r.t.</td>
<td>SM</td>
</tr>
<tr>
<td>6</td>
<td>PDC</td>
<td>-</td>
<td>DCM</td>
<td>0°C - r.t.</td>
<td>SM</td>
</tr>
</tbody>
</table>

[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).

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, H₂ (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.
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.

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).
Reagents and conditions: (i) 323, DIAD, n-Bu₃P, THF, 0°C – r.t., 78%

**Scheme 51.** Synthesis of ether 324

The Heck reaction conditions which had furnished tetrahydodibenzo[1]uran 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 tetrahydodibenzo[1]uran 310.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd Catalyst</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)₂</td>
<td>Ag₂CO₃, dppf</td>
<td>toluene</td>
<td>110°C</td>
<td>decomposition[^a]</td>
</tr>
<tr>
<td>2</td>
<td>Pd(dba)₂</td>
<td>P(o-tolyl)₃, NEt₃</td>
<td>MeCN</td>
<td>reflux</td>
<td>310 (27%)</td>
</tr>
<tr>
<td>3</td>
<td>Pd(dba)₂</td>
<td>P(o-tolyl)₃, NEt₃</td>
<td>toluene</td>
<td>110°C</td>
<td>310 (22%)</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)₂</td>
<td>P(o-tolyl)₃, NEt₃</td>
<td>toluene</td>
<td>110°C</td>
<td>310 (94%)</td>
</tr>
</tbody>
</table>

[^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.
Reagents and conditions: (i) TBAF, THF, 0°C – r.t.; (ii) 5% Pd/C, H₂ (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.

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.
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.

Figure 43. Acidic deprotection of ketal 320

Table 21. Acidic deprotection of ketal 320

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFA</td>
<td>DCM</td>
<td>reflux</td>
<td>328 (45%)</td>
</tr>
<tr>
<td>2</td>
<td>TFA</td>
<td>MeCN</td>
<td>reflux</td>
<td>328 (61%)</td>
</tr>
<tr>
<td>3</td>
<td>TFA</td>
<td>THF</td>
<td>reflux</td>
<td>328 (76%)</td>
</tr>
</tbody>
</table>

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).
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).

![Figure 44. Aqueous acidic deprotection of ketal 320](image)

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>aq. AcOH</td>
<td>MeCN</td>
<td>0°C</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>aq. AcOH</td>
<td>MeCN</td>
<td>40°C</td>
<td>329 (51%)</td>
</tr>
<tr>
<td>3</td>
<td>aq. HCl</td>
<td>MeCN</td>
<td>0°C</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>aq. HCl</td>
<td>MeCN</td>
<td>40°C</td>
<td>329 (77%)</td>
</tr>
</tbody>
</table>

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).
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.

![Chemical structure](attachment:image.png)

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) 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DIAD, nBu3P</td>
<td>THF</td>
<td>0°C - r.t.</td>
<td>decomposition[a]</td>
</tr>
<tr>
<td>2</td>
<td>DIAD, PPh3</td>
<td>THF</td>
<td>0°C - r.t.</td>
<td>decomposition[a]</td>
</tr>
<tr>
<td>3</td>
<td>DIAD, nBu3P</td>
<td>toluene</td>
<td>0°C - r.t.</td>
<td>decomposition[a]</td>
</tr>
</tbody>
</table>

[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.

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.

![Figure 47. Attempted enol ether deprotection with a Brønsted acid](image)

Table 24. Attempted enol ether deprotection with a Brønsted acid

<table>
<thead>
<tr>
<th>Entry</th>
<th>Brønsted acid</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3% HClO₄</td>
<td>THF</td>
<td>r.t.</td>
<td>decomposition[a]</td>
</tr>
<tr>
<td>2</td>
<td>3% HClO₄</td>
<td>THF</td>
<td>0°C</td>
<td>304 (63%)</td>
</tr>
</tbody>
</table>

[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. 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.

![Figure 48. Attempted enol ether deprotection with a Lewis acid](image)

**Table 25. Attempted enol ether deprotection with a Lewis acid**

<table>
<thead>
<tr>
<th>Entry</th>
<th>CuCl₂ Equiv.</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Degassed</th>
<th>Ratio (261:305:332:333)^[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>MeCN</td>
<td>40°C</td>
<td>no</td>
<td>1:2:1.2:2</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>MeCN</td>
<td>0°C</td>
<td>yes</td>
<td>_^[b]</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>MeCN</td>
<td>r.t.</td>
<td>yes</td>
<td>0:0:1:4</td>
</tr>
<tr>
<td>4</td>
<td>0.1</td>
<td>MeCN</td>
<td>40°C</td>
<td>yes</td>
<td>0:0:1:3</td>
</tr>
<tr>
<td>5</td>
<td>0.1</td>
<td>MeCN</td>
<td>80°C</td>
<td>yes</td>
<td>0:0:1:10</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>MeCN</td>
<td>40°C</td>
<td>yes</td>
<td>0:0:1:9</td>
</tr>
</tbody>
</table>

^[a] approximate ratio determined from 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).

![Figure 49. Attempted Prins reaction on phenylacetaldehyde 332](image)
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.

\[ \text{MeO} \quad \text{i} \quad \text{TBSO'}^+ \]

Table 26. Attempted Prins reaction on phenylacetaldehyde 332

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AlMe₃</td>
<td>DCM</td>
<td>0°C</td>
<td>SM</td>
</tr>
<tr>
<td>2</td>
<td>ScOTf₃</td>
<td>DCM</td>
<td>0°C</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>ScOTf₃</td>
<td>DCM</td>
<td>r.t.</td>
<td>SM</td>
</tr>
</tbody>
</table>

Reagents and conditions: (i) AlMe₃, 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]_D^T \text{ } ^\circ \text{C} (c = \text{g/}100 \text{ mL, solvent}). ¹H 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 (CDCl₃: 7.24 ppm, acetone-d₆: 2.05 ppm, DMSO-d₆: 2.50, CD₃OD: 3.31 ppm, D₂O: 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 ¹³C NMR spectra were recorded at 150 or 75 MHz and are reported in ppm using solvent as an internal standard (CDCl₃: 77.23 ppm, acetone-d₆: 206.68 ppm, DMSO-d₆: 39.51 ppm, CD₃OD: 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

\[
\text{(3aR,8aR)-5-benzyl-3-[4-(benzyloxy)benzoyl]octahydro-2H-[1,3]oxazolo[4,5-c]azepin-2-one (118a)}
\]

To a stirred solution of 296 (58 mg, 0.151 mmol) in acetone (3 mL) was added a suspension of NaI04 (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 (4S,5R)-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 N2 bath. To this solution was added 3 Å molecular sieves (150 mg), followed by NaCNBH3 (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 NaHCO3 (1 x 3 mL). The organic layer was washed with brine (3 mL), then dried
with Na$_2$SO$_4$ 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) v 3029, 2835, 1783, 1679, 1604, 1300, 1253, 1119 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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 (El) 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$_2$O$_2$ 412.2151, found 412.2151; Anal. calcd: C 73.66, H 6.18, found C 73.55, H 6.20.

\[ \text{118b} \]

(3aS,7aS)-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$_2$O) 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 × 1 mL) and CHCl₃ (2 × 1 mL), filtered through a plug of SiO₂ then recrystallized from CHCl₃ to yield (3aS,4S,5R,7aS)-3-(4-Benzylxoy-benzoyl)-4,5-dihydroxy-hexahydro-benzooxazol-2-one (290) (15 mg, 83%) as a white solid: mp 166-167 °C (hexanes-ethyl acetate); Rf 0.31 (1:1 hexanes-ethyl acetate); [α]D²³ +80.2 (c 0.47, CHCl₃); IR (film) ν 3684, 3091, 1794, 1604, 1511, 1422, 1303, 1215, 1029 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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; ¹³C NMR (75 MHz, CDCl₃) 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 C₂₁H₂₁NO₆ 383.1369, found 383.1369.

To a stirred solution of (3aS,4S,5R,7aS)-3-(4-Benzylxoy-benzoyl)-4,5-dihydroxy-hexahydro-benzooxazol-2-one (290) (58 mg, 0.151 mmol) in 10:1 acetone-H₂O (2 mL) was added NaIO₄ (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-Benzylxoy-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 N₂ bath. To this solution was added 3 Å
molecular sieves (100 mg), followed by NaCNBH3 (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 x 2 mL) and washed with NaHCO3 (1 x 2 mL). The organic layer was washed with brine (1 mL), then dried over Na2SO4. 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): Rf 0.68 (2:1 hexanes-ethyl acetate); [α]D23 +31.1 (c 0.9, CHCl3); IR (film) ν 3029, 2835, 1783, 1679, 1604, 1300, 1253, 1119 cm⁻¹; ¹H NMR (300 MHz, CDCl3) 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; ¹³C NMR (75 MHz, CDCl3) 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–CO2), 44(20), 91(100), 160(76), 161(10); HRMS (M–CO2) calcd for C27H28N2O2 412.2151, found 412.2151.
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 Na₂SO₄. The crude product was subjected to flash column chromatography (3:1 hexanes-ethyl acetate) to yield 119a (9 mg, 81%) as yellow oil. Rf 0.19 (1:3 ethyl acetate-hexanes); [α]D²³ -4.7 (c 0.02, CHCl₃); IR (film) ν 3407, 3377, 2955, 1638, 1611, 1298, 1140 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (150 MHz, CDCl₃) 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 C₂₇H₃₁N₂O₃ 431.2310, found 431.2312.
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 H2O (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 Na2SO4. 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: Rf 0.31 (3:2, hexane-ethyl acetate); [α]D23 + 5.77 (c 0.75, CHCl3); IR (film) ν 3407, 3377, 2955, 1638, 1611, 1298, 1140 cm⁻¹; 1H NMR (600 MHz, CDCl3) 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); 13C NMR (150 MHz, CDCl3) 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 C27H31N2O3 431.2310, found 431.2312.
(3aS,4R,5S,7aS)-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. NaHCO₃ (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); Rf 0.64 (1:1 hexanes-ethyl acetate); [α]D²³ -119.5 (c 0.1, CHCl₃); IR (film) ν 3684, 3271, 3019, 2928, 1746, 1649, 1430, 1375, 1334, 1216, 1161, 1093 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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; ¹³C NMR (150 MHz, CDCl₃) 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 C₁₈H₂₃BrNO₆S 460.0429, found 460.0462.
(3aS,4R,5S,7aR)-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), NEt₃ (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 H₂. The reaction was stirred at room temperature and 1 atm for 12 h before filtering through a plug of SiO₂ 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; Rᵥ 0.61 (1:2 hexanes-ethyl acetate); ¹H 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, 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), 1.10-1.02 (m, 1H), 1.03 (s, 3H) ppm; ¹³C NMR (150 MHz, CDCl₃) 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 (El) 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 C₁₈H₂₅NO₆S 383.1403, found 383.1401
N-[(3aS,4R,7aR)-2,2-dimethylhexahydro-1,3-benzodioxol-4-yl]-4-methylbenzenesulfonamide (276)

To a stirred solution of 274 (50 mg, 0.153 mmol) and NEt₃ (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 H₂. The reaction was stirred at room temperature with 1 atm of H₂ for 12 h before being filtered through a plug of SiO₂ 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, CDCl₃) 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), 4.00 (s, 3H), 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; ¹³C NMR (150 MHz, CDCl₃) 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 (El) m/z (%): 325 (M), 41 (20), 43 (51), 84 (26), 91 (98), 96 (20), 112 (100), 155 (66), 170 (27), HRMS calcd for C₁₆H₂₃NO₄S 325.1348, found 325.1348.
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 SiO₂ (200 mg. The resulting slurry was stirred at 50 °C for 12 h, then filtered, triturated (benzene then Et₂O) and concentrated. Recrystallization from CHCl₃-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); [α]D²³ -62.61 (c 0.145, MeOH); ¹H 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; ¹³C 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 C₁₅H₁₉BrNO₆S 420.0116, found 420.0119.
N-[(1R,2S,3R)-2,3-dihydroxycyclohexyl]-4-methylbenzenesulfonamide (279)

To a stirred solution of 277 (50 mg, 0.120 mmol), NEt₃ (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 H₂. The reaction was stirred at room temperature and 1 atm for 12 h before filtering through a plug of SiO₂ 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); Rᶠ 0.22 (1:4, hexanes-ethyl acetate); ¹H 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; ¹³C NMR (75 MHz, CDCl₃) 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 C₁₃H₁₉NO₄S 286.1035, found 286.1035.
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. NH₄Cl. The crude mixture was extracted into ethyl acetate (3 x 5 mL), and the combined organic layers were dried over Na₂SO₄. 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); [α]_D²³ –22.7 (c 0.7, CHCl₃); IR (film) ν 3445, 2993, 2087, 1646, 1216, 1065 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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; ¹³C NMR (75 MHz, CDCl₃) 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-CH₃⁺), 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 C₁₅H₁₇BrNO₅S 402.0011, found 402.0004; Anal. calcd C 45.94, H 4.82, found C 45.88, H 4.80.
(3aS,4R,5S,7aR)-2,2-dimethyl-4-[(4-methylphenyl)sulfonyl]amino]-3a,4,5,7a-tetrahydro-1,3-benzodioxol-5-yl acetate (281a)

(3aS,4R,5R,7aR)-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-Bu3SnH (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: 1H 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; 13C 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-CH3), 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 C18H23NO6S 366.1011, found 325.134366.1011.
**281b:** $^1$H NMR (600 MHz, MeOD) $\delta$ 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) $\delta$ 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$_6$S 366.1011, found 325.13466.1011.

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

(1R,4R,5S,6S)-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$_3$SnH (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) v 3684, 3019, 1731, 1599, 1522, 1426, 1374, 1330, 1215, 1046 cm$^{-1}$, $^1$H NMR (600 MHz, MeOD) $\delta$ 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) $\delta$ 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$_6$S 341.0933.1348, found 341.0933.

282b: *R*$_f$ 0.27 (1:4 hexanes-ethyl acetate); IR (film) v 3684, 3019, 1731, 1599, 1522, 1426, 1374, 1330, 1215, 1046 cm$^{-1}$, $^1$H NMR (600 MHz, MeOD) $\delta$ 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) $\delta$ 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$_6$S 341.0933.1348, found 341.0933.
N-[(3aS,4R,5S,7aR)-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$_2$SO$_4$, 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); [α]$_D^{23}$ -39.509 (c 1.10, CHCl$_3$); IR (film) v 3479, 3227,
2986, 2884, 1455, 1380, 1320, 1219, 1090, 1065, 748, 666 cm$^{-1}$; $^1$H NMR (300 MHz,
CDCl$_3$) $\delta$ 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, $J_c = 7.80$ 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) $\delta$ 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$_5$S 324.0905, found 324.0905
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 K₂CO₃ (10 mg), and platinum(IV)oxide (catalytic amount) before purging the reaction flask with H₂. The reaction mixture was stirred at room temperature and 1 atm of H₂ for 36 h before being filtered through a plug of SiO₂. 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); [α]D²³ −105.2 (c 1.32, CHCl₃); IR (film) ν 3381, 3255, 2985, 2934, 2893, 2765, 1597, 1155, 1088, 753 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.81 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 5.48 (d, J = 69 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; ¹³C NMR (75 MHz, CDCl₃) 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 (El) 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 C₁₆H₂₃NO₅S 341.1297 found 341.1297; Anal. calcd: C 56.29, H 6.79, found C 56.21, H 6.70.
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 Na₂SO₄, 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); Rf 0.58 (1:1 hexanes-ethyl acetate); [α]D²³ −2.56 (c 0.56, CHCl₃); IR (film) ν 3557, 3027, 2987, 2890, 1797, 1597, 1495, 1438, 1379, 1180, 1153 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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; ¹³C NMR (75 MHz, CDCl₃) 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 C₁₇H₂₁NO₆S 367.1089, found 367.1089; Anal. calcd: C 55.57, H 5.76, found C 55.67, H 5.60.
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. NH₄Cl (5 mL). The crude mixture was extracted into diethyl ether (3 x 10 mL), and the combined organic layers were dried over Na₂SO₄, 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); Rf 0.31 (1:1 hexanes-ethyl acetate); [α]D²³ −89.2 (c 2.9, CHCl₃); IR (film) ν 3450, 3305, 2987, 2938, 2894, 1860, 1855, 1647, 1547, 1466, 1383, 1239, 1061 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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; ¹³C NMR (150 MHz, CDCl₃) δ 160.1, 109.4, 77.9, 77.7, 73.3, 62.9, 28.4, 25.9, 24.7, 24.0 ppm; MS (El) 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 C₁₀H₁₅NO₄ 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. NH₄Cl (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 Na₂SO₄, 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); Rₖ 0.62 (1:1 hexanes-ethyl acetate); [α]D₂₃ + 0.72 (c 2.1, CHCl₃); IR (film) v 3682, 3531, 3379, 3066, 3019, 2989, 2937, 2889, 2587, 1952, 1786, 1697, 1603, 1382, 1256, 1216 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) 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; ¹³C NMR (150 MHz, CDCl₃) 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 (El) m/z (%): 423 (M), 43(67), 65(20), 83(24), 85(68), 91(100),
92(25), HRMS calcd for C_{24}H_{25}N_{6}O_{6} 423.1682, found 423.1682; Anal. calcd: C 68.07, H 5.95, found C 68.14, H 5.96.

5.3 Codeline Project Experimental Procedures

(1R,6S)-Acetic acid 6-acetoxycyclohex-2-enyl ester (257)

Dial 241 (2 g, 9 mmol) was dissolved in CH_{2}Cl_{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: [α]^{23}_{D} -120.5 (c 0.9, CH_{2}Cl_{2}); R_{f} 0.5 (hexanes-ethyl acetate, 3:1); IR (film) v 2947, 1738, 1434 cm^{-1}; ^{1}H 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_{4}Br 304.0310, found 304.0317; Anal. calcd: C, 47.23; H, 5.62, found C, 47.42, H, 5.67.
{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 CH₂Cl₂ 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 H₂O (15 mL). The layers were separated, and the aqueous layer extracted with CHCl₃ (2 x 10 mL). The combined organic phase was washed with cold 2% aq. HCl, sat. NaHCO₃, and then dried over MgSO₄. 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: Rₚ 0.47 (DCM:EtOAc, 96:4); [α]D²⁴ -22.6 (c 0.5, CHCl₃); IR (film) ν 3556, 3475, 2953, 2857, 1692, 1472, 1392, 1253, 1085 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) 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; ¹³C NMR (150 MHz, CDCl₃) 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 (El) m/z (%): 228 (21), 197 (21), 136 (12), 74 (22), 73 (15), 57 (63), 44 (100) HRMS-EI (M⁺-57) calcd for C₁₂H₃₀NO₄Si 328.1944, found 328.1946; Anal. calcd. for C₂₀H₃₉NO₄Si C 62.10, H 10.22, found C 62.29, H 10.19.
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 H₂O 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 Mg₂SO₄ to yield 259 (58.5 g, 75%) as a white solid: Rᵢ 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, CDCl₃) 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; ¹³C NMR (150 MHz, CDCl₃) 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) C₇H₇BrO₃ 229.9579, found 229.9578.
(2-[6-(2-Bromo-3-formyl-6-methoxy-phenoxy)-5-(tert-butyl-dimethyl-silanyloxy)-cyclohex-1-etyl]-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: Rf 0.81 (DCM:EtOAc, 96:4); [α]D 23 +75.7 (c 0.7, CHCl₃); IR (film) v 3007, 2952, 2929, 2857, 1688, 1578, 1481, 1275, 1252, 1173, 1085, 1028, 1005, 836 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) 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; ¹³C NMR (150 MHz, CDCl₃) 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_{6}BrSi 597.2121, found 597.2140; Anal. Calcd. for C_{28}H_{44}NO_{6}BrSi C 56.18, H 7.41, found C 56.09, H 7.65.

{2-[6-(tert-butyl-dimethyl-silanyloxy)-1-formyl-4-methoxy-6,7-dihydro-5aH-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 ^1H 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_{2}Cl_{2}-EtOAc, 4:1) gave 261 (146 mg, 82%) as a semi-crystalline brown solid: Rf 0.79 (DCM:EtOAc, 96:4); [α]_{D}^{23} +12.5 (c 0.6, CHCl_{3}); IR (film) v 3008, 2953, 2930, 2856, 2734, 1692, 1610, 1571, 1436, 1366, 1285, 1250, 1170,
1155, 1046, 837 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) mixture of rotamers \(\delta\) 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\(_3\)) \(\delta\) 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\(_6\)Si 460.2155, found: 460.2150; Anal. calcd. for C 64.96, H 8.37, found C 64.87, H 8.46

![Chemical Structure](image)

[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\(_2\)CO\(_3\) (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 Na₂SO₄. 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); Rf 0.07 (ethyl acetate-hexanes, 2:1); IR (film) ν 3383, 2974, 2930, 1693, 1672, 1396, 988 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) 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; ¹³C NMR (150 MHz, CDCl₃) 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 C₁₄H₂₅NO₄ 271.1784, found 271.1785
*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$^{-1}$; $^1$H 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, $J = 6$Hz, 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,
tert-butyl \{2-[(5aS,6S,9aR)-6-hydroxy-4-methoxy-1-[(\textit{E})-2-methoxyvinyl]-6,7-
dihydrodibenzob[\textit{b,d}]furan-9a(5aH)-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 \textit{E} & \textit{Z} isomers, 225 mg, 74%) as an oil: R$_f$ 0.2 (hexanes-ethyl acetate, 1:1); IR (film) v 3426, 2933, 1682, 1572, 1504, 1483, 1423, 1399, 1366, 1282, 1215, 1156, 1098, 1046, 1015, 882 cm$^{-1}$; $^1$H 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.

![Chemical Structure](image)

**305**

*tert*-butyl-[2-[(5aS,6S,9aR)-1-formyl-6-hydroxy-4-methoxy-6,7-dihydrodibenzo[b,d]furan-9a(5aH)-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 SiO₂ 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$_2$SO$_4$, 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) v 3684, 3608, 3019, 2978, 2933, 1688, 1612, 1571, 1436, 1285, 1215 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) two rotamers $\delta$ 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 $\delta$ 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$_{34}$N$_2$O$_6$Si 460.2155, found 460.2150.

(4a$S,5S,8aR$)-3-methoxy-11-methyl-5,6,10,11,12,13-hexahydro-4aH,9H-

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
CHCl₃ (3 x 4 mL). The combined organic layers were dried with Na₂SO₄, filtered and concentrated. The resulting enamine 307 was dissolved in dry MeOH (0.3 mL) and cooled to 0 °C before the addition of NaCNBH₃ (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. NaHCO₃ (2 mL). The MeOH was removed under reduced pressure and the aqueous layer extracted with CHCl₃ (3 x 3 mL) dried with Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography (DCM-ethyl acetate, 4:1) gave 308 (146 mg, 41%) as colourless oil: R₇ 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, CDCl₃) 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; ¹³C NMR (150 MHz, CDCl₃) 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 C₁₈H₂₅NO₃ 301.1678, found 301.1678.
tert-butyl \[2-\{(5aS,6S,9aR)-6-\{\text{tert}-\text{butyl(dimethyl)silyl)oxy}\}-1-(1,3-dioxolan-2-ylmethyl)-4-methoxy-6,7-dihydrodibenzo[b,d]furan-9a(5aH)-yl]ethyl\]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 \(p\text{TsOH}\). 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 \(\text{Na}_2\text{SO}_4\) 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. \(P(\rho\text{-tolyl})_3\) (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); \(^1\text{H NMR (300 MHz, CDCl}_3\) \(\delta\) 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$_{49}$N$_{2}$O$_{7}$Si 575.3278, found 575.3288.

![Chemical structure of compound 311](image)

**tert-butyl-{2-[(5aS,6S,9aR)-1-(1,3-dioxolan-2-ylmethyl)-6-hydroxy-4-methoxy-6,7-dihydrodibenzo[b,d]furan-9a(5aH)-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$_2$SO$_4$ 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), 3.84 (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$_{49}$N$_{2}$O$_{7}$Si 575.3278, found 575.3288.
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$_{35}$N$_{7}$O$_{7}$: 461.2414, found 461.2414.

$^{13}$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$_{35}$N$_{7}$O$_{7}$: 461.2414, found 461.2414.

$\text{MeO} \quad \text{O}$

$\text{HO}^-$

313

$\text{MeO}$

$\text{O}$

$\text{NMeBoc}$

313

tert-butyl-\{2-[(5aS,6S,9aS)-6-hydroxy-4-methoxy-1-methyl-6,7,8,9-tetrahydrodibenzo[\text{b,d]}furan-9a(5aH)-y]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) $\delta$ 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$_{33}$NOS 391.2359, found 391.2359.

![Chemical Structure](image)

**tert-butyl-[2-[(5aS,9aS)-4-methoxy-1-methyl-6-oxo-6,7,8,9-tetrahydrodibenzo[b,d]furan-9a(SaH)-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$_2$SO$_4$. 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); $^1$H NMR (300 MHz, CDCl$_3$) (two rotamers) $\delta$ 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) $\delta$ 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) \textit{m/z} (%): 41 (29), 43 (45), 57 (56), 230 (35), 231 (100), 248 (44); HRMS-EI calcd for C\textsubscript{22}H\textsubscript{31}NO\textsubscript{5}: 389.2202, found 389.2202.

\begin{center}
\includegraphics[width=0.3\textwidth]{315.png}
\end{center}

\textit{tert}-butyl-\{2-[(5aS,6S,9aS)-1-(1,3-dioxolan-2-ylmethyl)-6-hydroxy-4-methoxy-6,7,8,9-tetrahydrodibenzo[\textit{b,}\textit{d}]furan-9a(5a\textit{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\textsubscript{2} gas and stirred overnight. The reaction mixture was then filtered through SiO\textsubscript{2} and concentrated. Purification by flash column chromatography (hexanes-ethyl acetate, 1:1) gave 315 (16 mg, 82\%) as colourless oil: \textit{R}\textsubscript{f} 0.17 (hexanes-ethyl acetate, 1:1); IR (film) \nu 3612, 3019, 2977, 1682, 1506, 1434, 1214 cm\textsuperscript{-1}; \textit{\textsuperscript{1}}H NMR (300 MHz, CDCl\textsubscript{3}) (two rotamers) \delta 6.81 (dd, \textit{J} = 8.4 Hz, 1H), 6.73 (dd, \textit{J} = 8.4 Hz, 1H), 5.06 (t, \textit{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, \textit{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; \textit{\textsuperscript{13}}C NMR (150 MHz, CDCl\textsubscript{3}) (two rotamers) \delta 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) \textit{m/z} (%): 44 (27), 47 (26), 49 (20), 73 (68), 84 (100), 86 (78); HRMS-EI calcd for C\textsubscript{25}H\textsubscript{35}NO\textsubscript{7} 463.2570, found 463.2570.
tert-butyl-2-[(5aS,9aS)-1-(1,3-dioxolan-2-ylmethyl)-4-methoxy-6-oxo-6,7,8,9-tetrahydrodibenzo[b,d]furan-9a(5aH)-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 CHCl₃ (3 x 4 mL). The combined organic layers were washed with NaHCO₃ (3 x 3 mL) and dried over Na₂SO₄. Purification via flash column chromatography (hexanes-ethyl acetate, 1:1) gave 316 (11 mg, 85%) as colourless oil: Rₚ 0.55 (hexanes-ethyl acetate, 1:1); ¹H NMR (300 MHz, CDCl₃) 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 C₂₅H₃₅NO₇ 461.2414, found 461.2414.
**tert-butyl-{2-[(5aS,9aS)-4-methoxy-1-methyl-6-oxo-6,9-dihydrodibenzo[b,d]furan-9(5aH)-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 NH₄Cl (2 mL) and extracted into EtOAc (3 x 3mL), washed with brine (1 x 2 mL), dried with Na₂SO₄, 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. NaHCO₃ (1 mL) extracted into EtOAc (3 x 3 mL), washed with brine (1 x 3 mL), dried with Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography (hexanes-ethyl acetate, 1:1) gave 318 (78 mg, 76% over two steps) as colourless oil: Rᵣ 0.31 (hexanes-ethyl acetate, 1:1); [a]ᵣ⁺⁺⁴ = +97.34 (c 1.7, CHCl₃); IR (film) ν 3019, 2979, 2931, 1683, 1596, 1508, 1426, 1215 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) (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; ¹³C NMR (150 MHz, CDCl₃) (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_{23}H_{29}NO_5 387.2046, found 387.2046.

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

Ketone 316 (150 mg, 0.325 mmol) was dissolved in anhydrous THF (0.5 mL) and
cooled to -78 ºC 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 ºC 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); [α]_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; 13C NMR (150 MHz, CDCl₃) (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 (El) m/z (%): 41(24), 43(81), 57(33), 73(100), 84(20), 301(21); HRMS-EI calcd for C₂₅H₃₃N₀₇ 459.2257, found 459.2206.

![Chemical structure of 2-Bromo-3-[1,3]dioxolan-2-ylmethyl-6-methoxy-phenol (323)](image)

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

To a solution of bromoisovanilin 259 (20 g, 86.6 mmol) in DCM (600 mL) at 0 °C was added EtN(iPr)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 MgSO₄ to afford 321 (29 g) as white solid. The product was used in the next step without further purification. A solution of Ph₃PCH₂OCH₂Cl (13.7 g, 39.9 mmol) in THF (75 mL) was cooled to −78 °C and t-butyllithium (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 MgSO₄ 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 MgSO₄. The solvent was removed under reduced pressure. Column chromatography afforded 323 (6.74 g, 64% over three steps): Rᶠ 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, CDCl₃) 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; ¹³C NMR (75MHz, CDCl₃) δ 145.9, 143.1, 128.8, 122.0, 111.3, 109.6, 103.4, 65.0, 56.3, 40.1 ppm; MS (El) m/z (%) 73 (100), 45 (14); HRMS-EI C₁₁H₁₃BrO₃ Calc. 287.9997, found 287.99936; Anal. calcd for C₁₁H₁₃BrO₃ C 45.70, H 4.53, found C 46.25, H 4.55.
tert-butyl-[2-((5S,6S)-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: Rf 0.81 (DCM:EtOAc, 96:4); [α]D 24 +75.7 (c 0.7, CHCl3); IR (film) ν 3007, 2952, 2929, 2857, 1688, 1578, 1481, 1275, 1252, 1173, 1085, 1028, 1005, 836 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) 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; ¹³C NMR (150 MHz,
CDCl₃) 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 C₃₁H₅₀BrNO₇Si 655.2540, found 655.2541; Anal. calcd. for C 56.70, H 7.67, found C 56.69, H, 7.65.

(6aS,11bR)-11-(2,2-dimethoxyethyl)-6,8-dimethoxy-3-methyl-2,3,4,6a-tetrahydro-1H-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 NaHCO₃ (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 Na₂SO₄. The solvent was removed under reduced pressure and subsequent flash column chromatography (95:5:1 CHCl₃:MeOH:NH₄OH) afforded 327 (12 mg, 74% yield) as a clear oil: Rᵣ 0.72, (92:8:1 CHCl₃: MeOH: NH₄OH); IR (KBr) ν 3518, 3020, 2915, 1724, 1489, 1215 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) 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
(6aS,11bR)-11-(1,3-dioxolan-2-ylmethyl)-8-methoxy-3-methyl-2,3,4,5-tetrahydro-
1H-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 NaHCO₃ (4 mL). The crude
mixture was extracted into CHCl₃ (3 x 5 mL), washed with brine (1 x 2 mL), dried
with Na₂SO₄, filtered, and concentrated. Purification via flash column
chromatography (CHCl₃:MeOH:NH₄OH, 92:8:1) gave 328 (65 mg, 76%) as
colourless oil: R₇ 0.52 (CHCl₃:MeOH:NH₄OH, 92:8:1); [α]D²⁴ -58.108 (c 0.565,
CHCl₃); ¹H NMR (300 MHz, CDCl₃) (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; ¹³C NMR (150 MHz, CDCl₃) (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.

[(6aS,11bR)-8-methoxy-3-methyl-6-oxo-2,3,4,5,6,6a-hexahydro-1H-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_{2}O (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_{2}SO_{4}, filtered, and concentrated. Purification by flash column chromatography (CHCl_{3}:MeOH:NH_{4}OH, 92:8:1) gave 329 (135 mg, 77%) as colourless oil: R_{f} 0.37 (CHCl_{3}:MeOH:NH_{4}OH, 92:8:1); [α]_{D}^{24} -51.08 (c 0.43, CHCl_{3}); IR (film) ν 2927, 2870, 1722, 1624, 1506, 1436, 1283 cm\(^{-1}\); \(^{1}\)H 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 (El) m/z (%): 214 (20), 229 (18), 297 (100), 298 (20); HRMS-EI calcd for C\textsubscript{18}H\textsubscript{21}N\textsubscript{O}\textsubscript{4} 315.1471, found 315.1469.

![Chemical structure](image)

(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(iPr)\textsubscript{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\textsubscript{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\textsubscript{3}PCH\textsubscript{2}OCH\textsubscript{2}Cl (1.4 g, 4.0 mmol) in THF (10 mL) was cooled to -78 °C and t-butyllithium (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\textsubscript{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 MgSO₄. Flash column chromatography afforded 330 (0.53 g, 24% over 3 steps): Rf 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, CDCl₃) 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; ¹³C NMR (75 MHz, CDCl₃) 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 C₉H₉BrO₃ 243.9735, found 243.9735.

![Chemical Structure](image)

**tert-butyl-{2-[(5aS,6S,9aR)-6-\{tert-butyl(dimethyl)silyloxy\}-4-methoxy-1-(2-oxoethyl)-6,7-dihydrodibenz[bf]furan-9a(5aH)-yl]ethyl}methylcarbamate (332)**

A solution of 303 (180 mg, 0.33 mmol) in MeCN (2 mL) was degassed under an atmosphere of N₂ before the addition of CuCl₂ (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 SiO₂, washing with MeCN, and concentrated. Purification by flash column chromatography (hexanes-ethyl acetate, 6:1) gave 332 (33 mg, 20%) as colourless oil: Rf 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, CDCl₃) 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$_3$) $\delta$ 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$_9$H$_9$BrO$_3$ 243.9735, found 243.9735.

\[ \text{MeO} \]
\[ \text{O} \]
\[ \text{OH} \]
\[ \text{TBSO'} \]
\[ \text{NMeBoc} \]
\[ 335 \]

**tert-butyl-[2-[(5aS,6S,9aR)-6-[[tert-butyl(dimethyl)silyl]oxy]-1-(2-hydroxypropyl)-4-methoxy-6,7-dihydrobenzo[b,d]furan-9a(5aH)-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$_2$SO$_4$ 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$_3$) $\delta$ 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), 3.52-3.49 (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$_3$) $\delta$ 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.
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8. Vita

Jacqueline Danielle Gilmet was born on September 29th 1984 in Hamilton, Ontario, Canada. She spent her early childhood in St. Petersburg, Florida before living in Welland, Ontario. She attended Centennial Secondary School, graduating with her high school degree in 2003. She completed her BSc. (Honours) in Biology and Chemistry at Brock University in 2007. She began her graduate studies in January 2008 under the supervision of Prof. Tomas Hudlicky. She completed her Master of Chemistry degree in 2009.