Enantiodivergent Chemoenzymatic Synthesis of Codeine.

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Abstract

The present thesis describes our latest results in the chemistry of morphine alkaloids. An enantiodivergent synthesis of codeine utilizing a *cis*-cyclohexadiene diol derived from microbial whole cell oxidation of β-bromoethylbenzene, as starting material is discussed. The total synthesis of (+)-codeine in 14 steps featuring a Mitsunobu inversion and two intramolecular Heck cyclizations is presented. Investigation of a regioselective nucleophilic opening of a homochiral vinyl oxirane, which led to a total synthesis of the natural isomer of codeine, is detailed.

Furthermore, described herein are novel methodologies designed for the transformation of naturally occurring opiates into medicinally relevant derivatives. Two studies on the conversion of thebaine into the commercially available analgesic hydrocodone, two novel transition metal catalyzed *N*-demethylation procedures for opioids, and the development of a catalytic protocol for *N*-demethylation and *N*-acylation of morphine and tropane alkaloids are presented.

In addition, reactions of a menthol-based version of the Burgess reagent with epoxides are discussed. The synthetic utility of this novel chiral derivative of the Burgess reagent was demonstrated by an enantiodivergent formal total synthesis of balanol.

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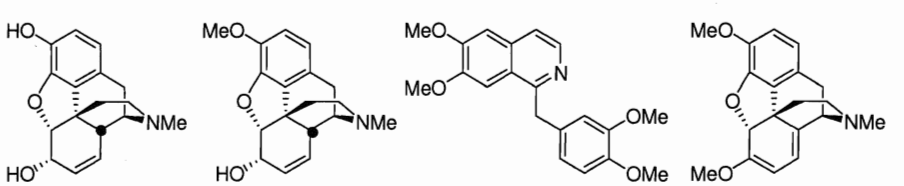
Ac	acetyl
Ac_2O	acetic acid anhydride
AcOH	acetic acid
AIBN	2,2'-azoisobutyronitrile
Al_2O_3	aluminum oxide
atm	atmosphere of pressure
BOC	*tert*-butyloxycarbonyl
$(BOC)_2O$	di-*tert*-butyl dicarbonate
BzCl	benzoyl chloride
CBz	carbobenzyloxy
$CDCl_3$	deutero-chloroform
CH_2Cl_2	dichloromethane
$CHCl_3$	chloroform
COD	cyclooctadiene
conc.	concentrated
CPM	cyclopropylmethyl
CSA	camphersulfonic acid
DBS	dibenzylsuberylamine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMAP	dimethylamino pyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMP	2,2-dimethoxypropane
DMSO	dimethyl sulfoxide

2,4-DNP	2,4-dinitrophenylhydrazine
dppf	1,1'-*bis*-(diphenylphosphino)ferrocene
Et_2O	diethyl ether
ee	enantiomeric excess
equiv	equivalent(s)
EDC	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride
EtOAc	ethyl acetate
FAB	fast atom bombardment
GC/MS	gas chromatography / mass spectrometry
h	hours
HBr	hydrobromic acid
HCl	hydrochloric acid
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
Hz	Hertz
IBX	2-iodoxybenzoic acid
i-Pr	isopropanol
IR	infrared spectroscopy
J	coupling constant
LAH	lithium aluminium hydride
LDA	lithium diisopropyl amide
*m*CPBA	*m*-chloroperoxybencoic acid
MeCN	acetonitrile
mp	melting point
MS	mass spectrometry
MsCl	mesityl chloride
NADPH	nicotinamide adenine dinucleotide phosphate
NBA	*N*-bromoacetamide
n-BuLi	*n*-butyl lithium
NEt_3	triethylamine

NMO	*N*-methyl-morpholine-*N*-oxide
NMP	*N*-methylpyrrolidone
NMR	nuclear magenetic resonance
PAD	potassium azodicarboxylate
Pd/C	palladium on charcoal
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
PPh_3	triphenylphosphine
ppm	parts per million
py	pyridine
quant.	quantitative
rec. SM	recovered starting material
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBSCl	tributyldimethylsilyl chloride
TBSOTf	tributyldimethylsilyl triflate
t-Bu	*tert*-butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THSCl	dimethyltexylsilyl chloride
TLC	thin layer chromatography
TMS	tetramethylsilane
TsCl	tosyl chloride
TsOH	*p*-toluenesulfonic acid

1. Introduction

Morphine alkaloids have been fascinating mankind since the days of antiquity. They are extensively used as medicines for the treatment of pain and are equally abused as illicit narcotics. In 2007 the estimated total amount of raw opium produced worldwide was 8200 tons,[1] with the major portion of it being used for illicit drug manufacturing. Raw opium contains varying amounts of morphine (**1**), codeine (**2**), narcotine, papaverin (**3**), and thebaine (**4**) (Figure 1).[2] Morphine, the most famous among the opiates, was first isolated in pure form by Friedrich Wilhelm Sertuerner in 1805,[3] its empirical formula was elucidated by Laurent in 1832,[4] and the structure was proposed by Robinson and Gulland in 1925.[5] Since the first reported total synthesis of morphine by Gates in 1952,[6] the alkaloid still remains a challenging target for synthetic organic chemists. Almost thirty total or formal syntheses of morphine alkaloids have been reported, of which none can be considered as a genuinely practical synthetic route, capable of competing with the natural supply. A practical synthesis would allow for the production of sufficient amounts of morphine to satisfy the world's demand for this valuable drug. It would therefore eliminate the uncertainty associated with the production of natural morphine in countries with



morphine **1** codeine **2** papaverine **3** thebaine **4**

Figure 1. Morphine alkaloids.

certain political instability such as Afghanistan, the country with the highest opium production in the world.

Over the last 20 years a major goal of the Hudlicky group has been the development of a practical synthesis of morphine alkaloids. The current thesis will discuss an enantiodivergent chemoenzymatic synthesis of codeine, combining strategies from Parker's,[7] as well as Trost's synthesis.[8] The approach to (+)-codeine (**2**) is envisioned by connecting allylic alcohol **6** with an aromatic fragment by a Mitsunobu reaction to yield a suitable precursor for subsequent intramolecular Heck cyclizations. The key step in the approach to (-)-codeine is based upon on a regioselective nucleophilic opening of vinyl oxirane **7**. This maneuver should allow for the formation of compound **9**, which is envisioned to be converted to (-)-codeine (**2**) by intramolecular Pd-catalyzed cyclizations similar to the (+)-codeine approach (Figure 2).

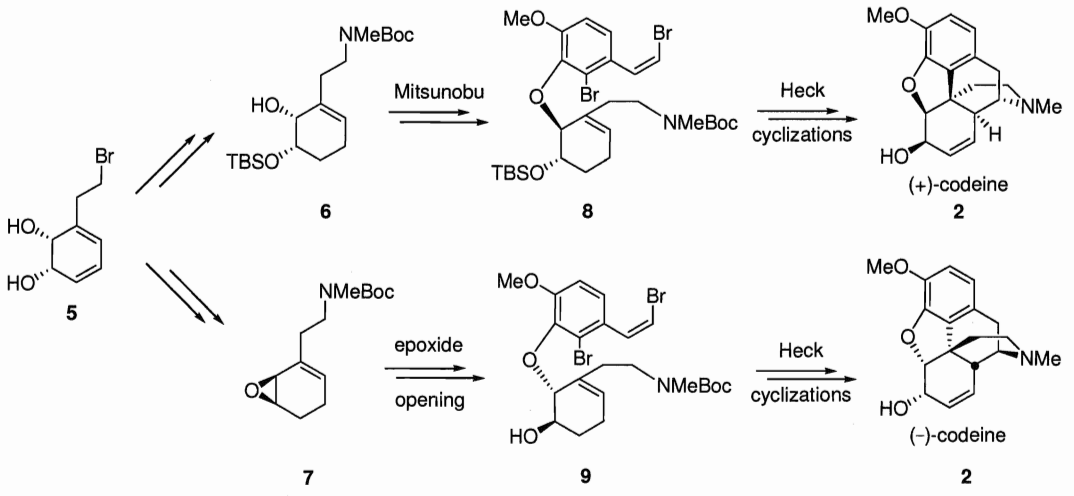
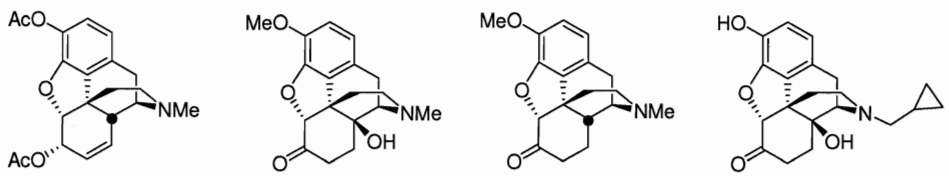


Figure 2. Design for the enantiodivergent synthesis of codeine (**2**).

Hudlicky's enantiodivergent synthetic strategy of morphine alkaloids presents a unique approach since chirality for both enantiomers is introduced by an enzymatic reaction, known to be enantiospecific.

Our interest in morphine alkaloids is not limited to their syntheses. Semi-synthetic drugs derived from opiates have affected society for more than 100 years. Diacetylmorphine, better known as heroin (**10**), was first synthesized by the English chemist Charles Robert Albert Wright[9] and was marketed by Bayer in 1898 as a non-addictive morphine substitute and cough suppressant. The even more addictive properties of heroin compared to those of morphine were realized years later and Bayer was forced to take heroin off the market in 1910.



diacetylmorphine **10** | oxycodone **11** | hydrocodone **12** | naltrexone **13**

Figure 3. Semi-synthetic opioids.

Two semi-synthetic opioids, oxycodone (**11**) and hydrocodone (**12**) (Figure 3), were discovered shortly after the mass production of heroin was stopped.[10] Both derivatives posses less addictive and euphoric properties than morphine and are still marketed as analgesics throughout the world. Naltrexone (**13**) is another semi-synthetic drug derived from thebaine (**4**) and is used for the treatment of alcohol and opioid dependence. The manufacturing of semi-synthetic opioids represents a prospering market. In cooperation with Noramco Inc., a subsidiary of Johnson &

Johnson, we became interested in the conversion of naturally occurring morphine alkaloids into more valuable derivatives utilizing economic and environmentally benign transformations. Thebaine (**4**), a minor constituent in the latex of *Papaver somniferum*, is an ideal starting material for the preparation of semi-synthetic analgesics. Tasmanian Alkaloids, in partnership with Noramco Inc., developed a genetically engineered poppy plant, the latex of which contains up to 30% thebaine (**4**).[11] Of special interest would be the conversion of thebaine (**4**) into neopinone ketal **14**, an alternative intermediate for the synthesis of 14-hydroxylated opiates.

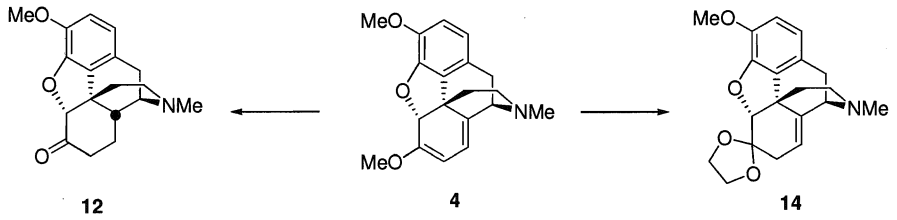


Figure 4. Functionalization of thebaine (**4**).

The potential advantage in the use of neopinone ketal **14** as starting material for 14-hydroxylated morphinans lies in the avoidance of α,β-unsaturated ketone intermediates, which frequently occur in the currently used commercial syntheses. This is of great importance since the ICH (International Conference on Harmonisation) have suggested strict limits in the amount of α,β-unsaturated carbonyl containing compounds in pharmaceutical preparations.[12]

Novel hydrogenation procedures for the conversion of thebaine (**4**) into the commercially available analgesic hydrocodone (**12**) will be investigated to provide for a catalytic and environmentally friendly procedure compared to the current

hazardous diimide reduction process. Further work, which will be presented in this thesis, will include investigations of an alternative approach to oxycodone (**11**) *via* the selective functionalization of the C-14 carbon of hydrocodone (**12**). A wide range of oxidative conditions, previously reported in the literature to effect the hydroxylation of tertiary carbons, will be tested.

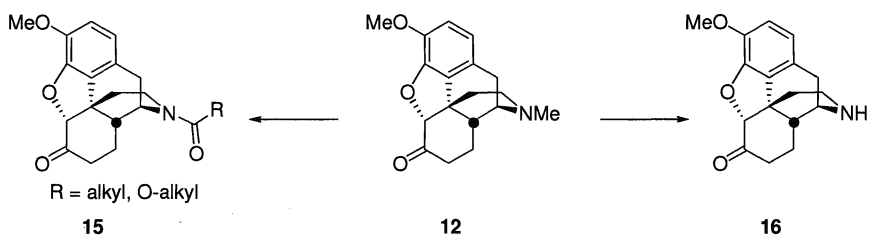


Figure 5. Functionalization of hydrocodone (**12**).

N-demethylation or *N*-demethylation / acylation reactions of morphine alkaloids represent key transformations in the synthesis of semi-synthetic opioids such as naltrexone (**13**). Our latest investigations in this field will be presented in Chapter 3.2.5 and 3.2.6.

In addition to the work related to morphine alkaloids, new reactive options of methyl *N*-(triethylammoniumsulfonyl)carbamate inner salt, more commonly known as the Burgess reagent **18**, with epoxides will be explored. Originally, the Burgess reagent was designed as a mild dehydrating agent for secondary and tertiary alcohols.[13] It found further application as the reagent of choice for the synthesis of urethanes from primary alcohols,[14] and dehydration of amides to nitriles.[15]

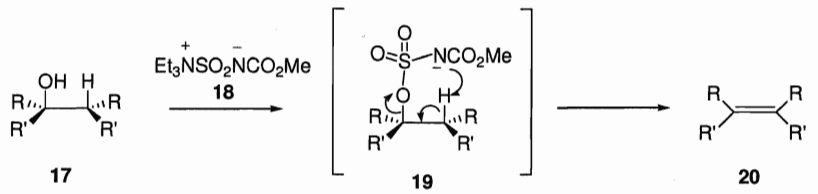


Figure 6. Proposed mechanism for the dehydration of alcohols.

Its polymer linked version was also employed in the synthesis of oxazolidines.[16] The Burgess reagent has been used in the preparation of α- and β-glycosylamines from carbohydrates,[17] sulfamidates from 1,2-diols,[18] sulfamidates from 2,3-epoxyalcohols,[19] and sulfamides from aminoalcohols.[20] In 2003, the Hudlicky group reported the reaction of epoxides with the Burgess reagent to yield 5- and 7-membered sulfamidates,[21] despite the fact that epoxides were thought to be inert to this reagent.[13b] Further investigations of the reaction of the Burgess reagent with epoxides and a possible mechanism of this transformation merit investigation.

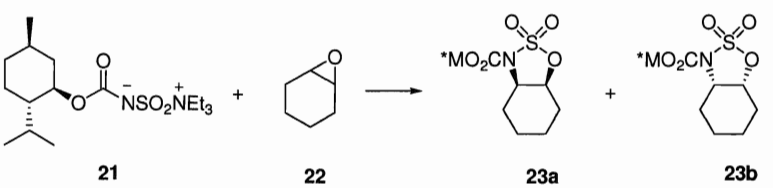


Figure 7. Chiral version of the Burgess reagent and its reaction with epoxides.

We envisioned that the reaction of a chiral version of the Burgess reagent, such as menthol-based reagent **21**, with epoxides might allow for the synthesis of both homochiral *cis*- and *trans*-amino alcohols, which are frequently used in the pharmaceutical sector.[22] Application of this novel methodology would also lead to an enantiodivergent approach to balanol, a fungal metabolite with significant inhibitory activities against protein kinase C isozymes.[23]

This thesis describes our results attained in the projects described above. A historical overview of all relevant areas is provided.

2. Historical

The following historical chapter is divided into two parts, and addresses the topic of the Burgess reagent as well as the chemistry of morphine alkaloids.

The Burgess reagent is a mild and selective dehydrating reagent for secondary and tertiary alcohols. The scope of the reagent has been broadened and its latest applications as well as a historical perspective is presented.

The isolation, structure determination, biosynthesis and pharmacology of the most relevant opiates is discussed, along with a review of selected total syntheses of morphine alkaloids.

2.1 Burgess Reagent

2.1.1 Dehydration of Alcohols

The first preparation of an alkyl *N*-(triethylammoniumsulfonyl)carbamate inner salt, the ethyl derivative **24**, was reported by George M. Atkins and Edward M. Burgess in 1968.[24] It was initially designed as an electrophilic *N*-sulfonylamine derivative and its reactions with amines, alcohols, allenes, and olefins were studied. The reaction of inner salt **24** with aniline gave *N*-carbethoxy-*N*'-phenylsulfamide (**25**) in nearly

quantitative yield, while the reaction with isopropanol afforded isopropyl carbethoxy sulfamate (**26**) in significant lower yield. Electrophilic addition of **24** to *N*-vinylpyrollidone was observed and *N*-(2-carbethoxyamidesulfonylvinyl) pyrrilidone (**27**) was isolated in 50% yield as shown in Figure 8. The application of the methyl derivative, methyl *N*- (triethylammoniumsulfonyl)carbamate inner salt, known as the Burgess reagent (**18**),[13] as a dehydrating reagent was first reported in 1970.[25] Burgess demonstrated that the reaction of compound **18** with secondary and tertiary alcohols yielded the corresponding olefins.

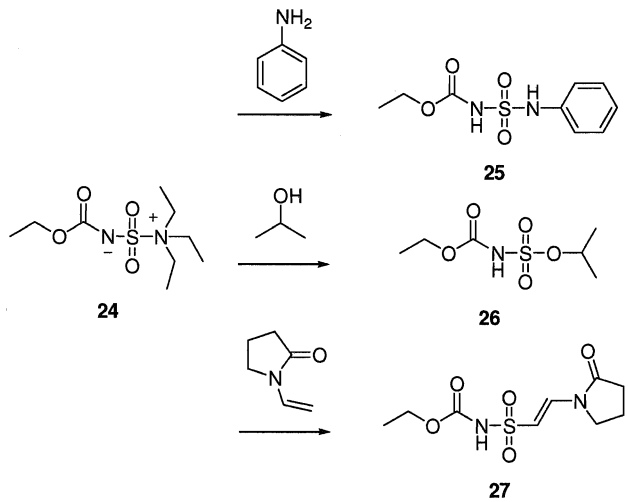


Figure 8. Reactions of ethyl *N*- (triethylammoniumsulfonyl)carbamate inner salt (**24**).

The same group conducted a kinetic study of the dehydration of *erythro*- and *threo*-2-deuterio-1,2-diphenyl ethanols. The results were consistent with rate limiting formation of an ion pair, followed by fast *syn*-β-proton transfer. Geometrical constraints require that the abstracted hydrogen is *syn* with respect to the leaving group. The mechanism is similar to the Chugaev elimination of dithiocarbonate (xanthate) esters and follows Saytzeff's rule.

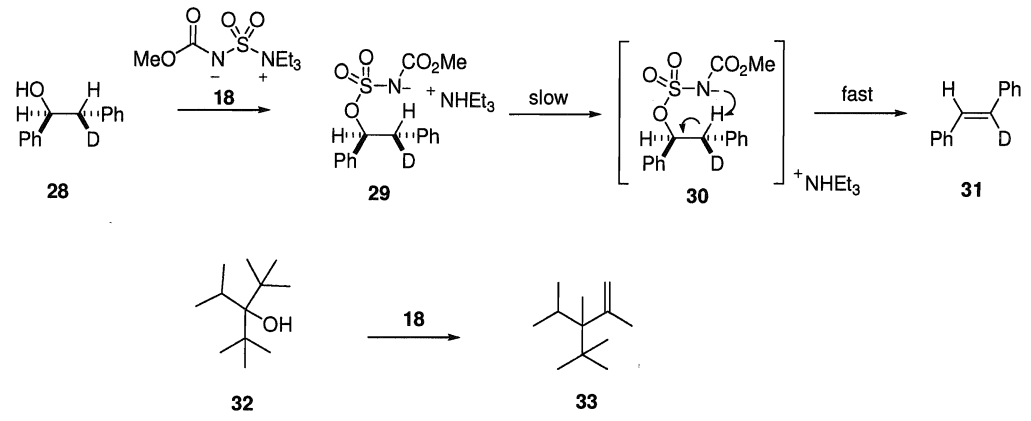


Figure 9. Proposed mechanism for the dehydration of alcohols with the Burgess reagent (**18**).

Based on this observation, the generality of the *cis* elimination was suggested. However, double bond formation can be less predictable, such as the case when a carbocation intermediate is highly stabilized. Reaction of tertiary alcohol **32** with the Burgess reagent (**18**) gives olefin **33** *via* a Wagner Meerwein rearrangement.

In contrast to the dehydration reaction of secondary and tertiary alcohols, primary alcohols react with the Burgess reagent to give carbamates. During the decomposition of the intermediate primary alkyl *N*-methoxycarbonylsulfamate salt, a S_N2 pathway is energetically more favourable than an elimination reaction and carbamates are isolated in high yield. Subsequent hydrolysis gives the primary amines and therefore this sequence represents an efficient two step synthesis of primary amines from alcohols.

Allylic alcohols can undergo either elimination or an S_N1 reaction and the outcome of the reaction can be tuned by the reaction conditions applied. Solvent free treatment of allylic alcohol **37** with the Burgess reagent provides carbamate **38** in nearly

quantitative yield, while the reaction in triglyme gives hexadiene **39** as the major product, as shown in Figure 10.

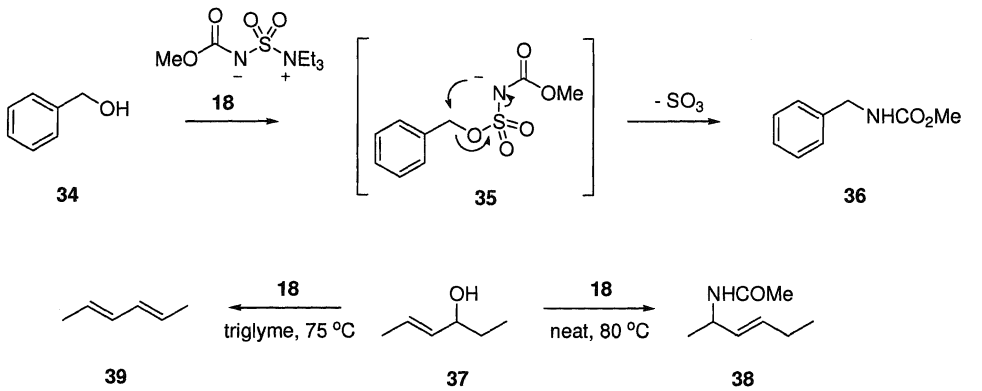


Figure 10. Formation of carbamates from primary alcohols.

2.1.2 Application of the Burgess Reagent as Dehydrating Reagent in Organic Synthesis

The Burgess reagent can effect the dehydration of secondary and tertiary alcohols to the respective olefins under mild conditions. Many alternative dehydration methods are acid-mediated and require elevated temperatures. This can result in rearrangements or alterations to acid and/or heat sensitive functionalities. In addition, the compatibility of the Burgess reagent with many functional groups makes it an attractive technique for the introduction of carbon-carbon double bonds into highly functionalized molecules.

The first application of the Burgess reagent in organic synthesis was reported by Crabbé and León only a few months after its initial discovery. Various steroidal secondary and tertiary alcohols such as 3α-hydroxy-5α-androstan-17-one (**40**) were

subjected to dehydration, with the corresponding olefins being isolated in satisfactorily yields.[26] In 1974 Caspi and coworkers reported one of the rare cases where the Burgess mediated dehydration reaction proceeded in an anti fashion, as shown in Figure 11. The unlikely possibility that *cis* elimination occurred first and was followed by a subsequent isomerisation was not ruled out.[27]

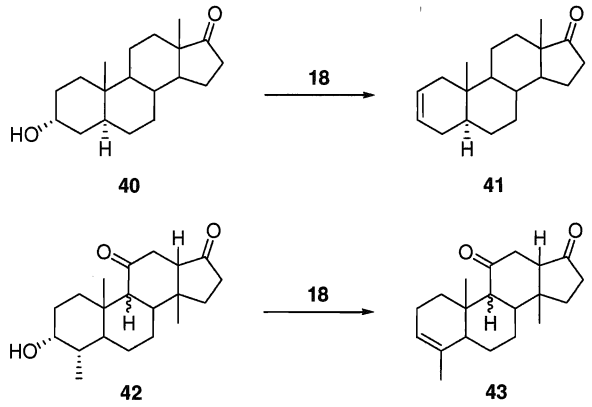


Figure 11. Application of the Burgess reagent in steroid chemistry.

The preparation of 3-keto-1,4-dienes provides for a useful entry to annulated cyclopentenones *via* the Nazarov cyclization. Burgess mediated dehydration of α'-hydroxy vinyl ketones, such as **44**, followed by acid treatment yielded the desired annulated cylopentenones in moderate to high yields as shown by Jacobson and Lahm.[28]

The Burgess reagent found further application in Stork's general approach to the tetracyclic 11-ketosteroid nucleus of several cortical hormones. Regioselective dehydration of **47** led to trienone **48**, which represented the precursor for an intramolecular Diels–Alder reaction. Stork employed this sequence for the concise syntheses of cortisone, adrenosterone (**49**), 11-ketoprogesterone, and 11-ketotestosterone.[29]

During Weyerstahl's total synthesis of the sesquiterpene isocanambrin, **51** and **52** were obtained with Burgess reagent in 90% yield, whereas attempted dehydration of this seven-membered ring with acidic reagents led mainly to ring contraction *via* cationic rearrangement.[30]

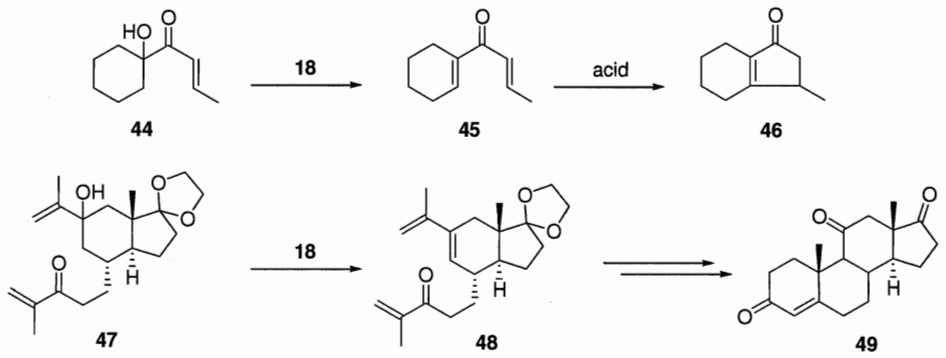


Figure 12. Preparation of Nazarov cyclization precursors with the Burgess reagent.

The synthetic value of the Burgess reagent as a dehydrating reagent is further underlined by its application in Rigby's syntheses of cedrene[31] and pancratistatin (**55**),[32] Paquette's synthesis of ikarugamycin,[33] Nicolaou's syntheses of efrontomycin[34] and thiostrepton,[35] Daniewski's synthesis of pravastatin (**58**),[36] Wovkulich's synthesis of mevinolin,[37] and Holton's syntheses of the C and D rings of paclitaxel.[38]

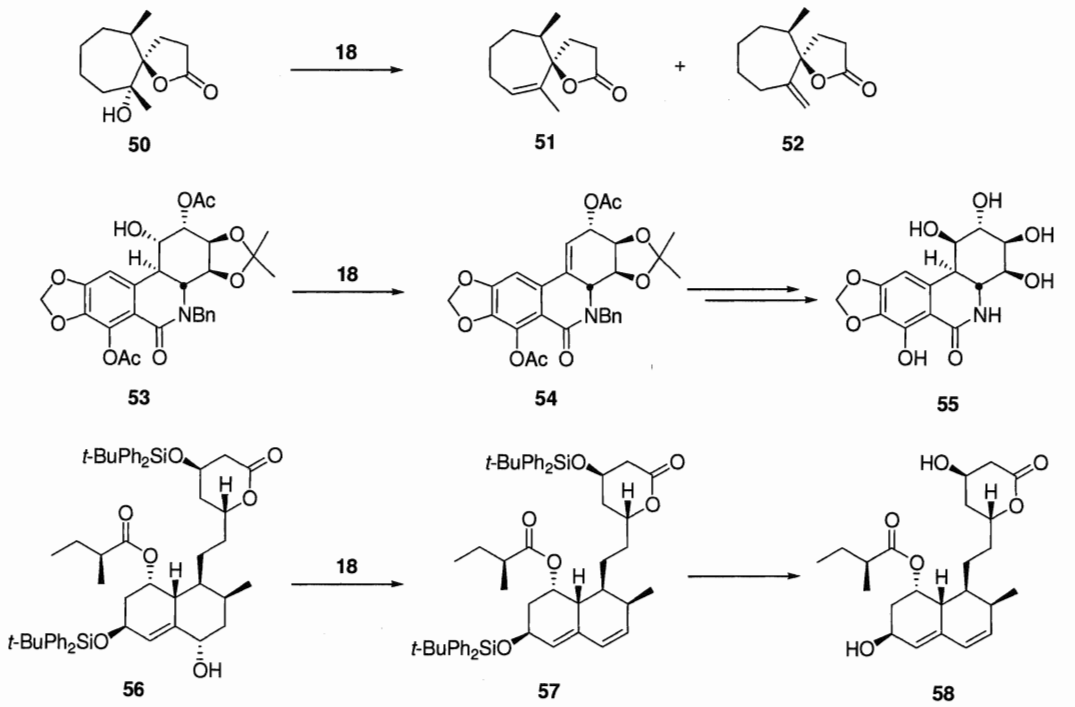


Figure 13. Application of the Burgess reagent in natural product syntheses.

2.1.3 Alternative Applications of the Burgess Reagent in Organic Synthesis

Formation of nitriles, isocyanides, carbodiimides, and nitro alkanes

The Burgess reagent can be effectively used for the dehydration of primary amides to nitriles at room temperature and was shown to be superior to other methods which are often incompatible with many functional groups.[15]

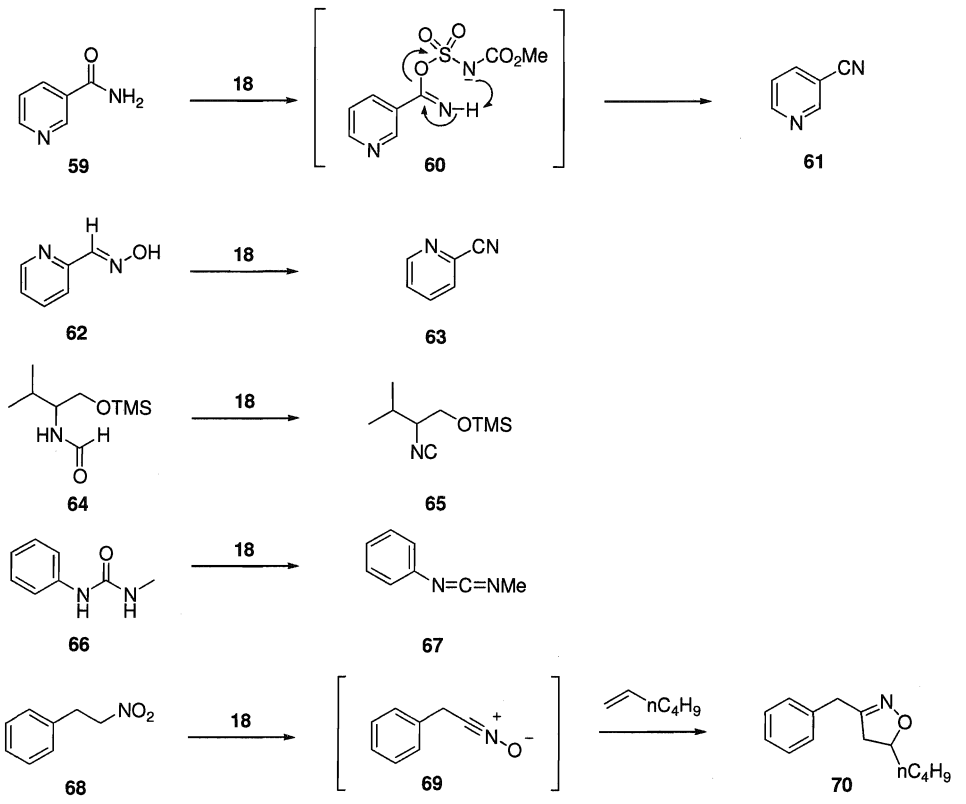


Figure 14. Formation of nitriles, isocyanides, carbodiimides, and nitro alkanes.

Prathapan and coworkers showed that *cis*-aldoximes are converted to nitriles by the Burgess reagent.[39] In a similar fashion, the Burgess reagent transforms formamides to isocyanides,[40] ureas to carbodiimides,[41] and primary nitro alkanes to nitrile oxides,[42] as shown in Figure 15.

Formation of heterocycles *via* cyclodehydration

The utility of the Burgess reagent was expanded by Wipf and coworkers, who applied inner salt **18** to the formation of oxazolines as well as thiazolines. In 1992, Wipf and Miller reported that the Burgess reagent promotes the formation of 4,5-

dihydrooxazole **72** from β-hydroxy-α-amino acid **71** (Figure 15).[43] As expected, cyclodehydration takes place with inversion of the configuration at the β-position. Common side products such as aziridines, dehydroamino acid side products, and β-lactams often obtained with other methods were not detected in the reaction mixture. Thioamides are converted to the corresponding thiazolines in a similar fashion.[44] This novel cyclodehydration method was found to be extremely useful for highly functionalized or sensitive substrates with epimerizable centers. A direct conversion of oxazolines to thiazolines can be achieved by thiolysis of oxazolines with hydrogen sulphide followed by cyclodehydration of the resulting thioamide with the Burgess reagent to yield the corresponding thiazolines.[45]

The scope of this novel cyclodehydration method was shown for example in Wipf's total syntheses of westiellamide[46], thiangazole,[47] and (+)-curacin A,[48] in Meyers's synthesis of (-)-bistatramide C,[49] and in Pattenden's synthesis of lissoclinamide.[50] Cyclodehydration promoted by the Burgess reagent is not limited to the synthesis of oxazolines and thiazolines. The formation of various other heterocyclic systems such as oxazoles from 2-acylamino carbonyl compounds,[51] 1,3,4-oxadiazoles from 1,2-diacylhydrazines,[52] 1,3-oxazines from γ-hydroxyamides,[53] 1,3-thiazines from γ-hydroxythiamides,[53] thiazepines from δ-hydroxythiamides,[53] as well as the syntheses of *N*-bridged 5,6-bicyclic pyridines from 2-substituted pyridines bearing a carbonyl group in the 3-position[54] have been reported.

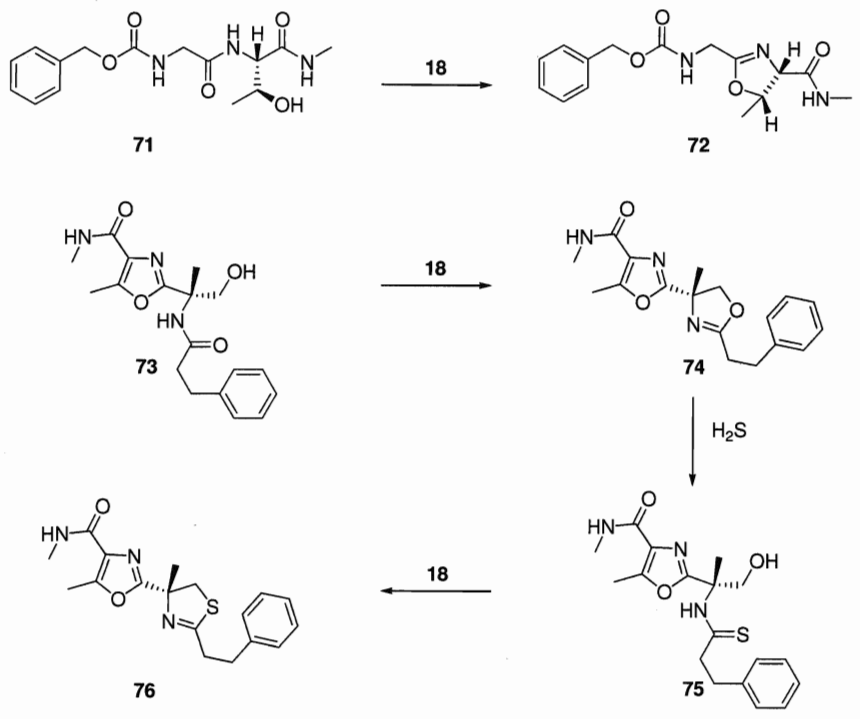


Figure 15. Formation of oxazolines and thiazolines.

Preparation of sulfamidates, sulfamides, and glycosylamines

Besides the application of the Burgess reagent as a mild and selective dehydrating reagent in total synthesis,[34,35] the Nicolaou group developed a novel regio- and stereoselective synthesis of sulfamidates from 1,2-diols. Treatment of such sulfamidates with aqueous acid led to the formation of β-amino alcohols. Therefore this sequence represents a two step conversion of diols to amino alcohols.[18] A mechanism for the formation of sulfamidates from 1,2-diols was proposed and is shown in Figure 16.

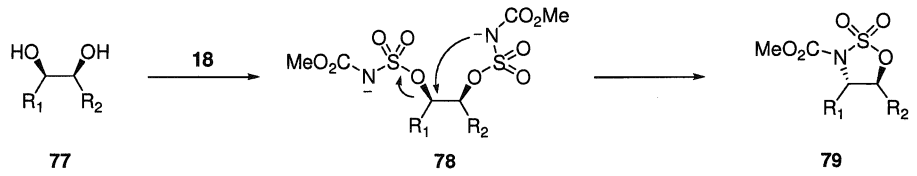


Figure 16. Proposed mechanism or the formation of sulfamidates from 1,2-diols.

Reaction of the diol with two equivalents of Burgess reagent (**18**) leads to the formation of bis-carbonylsulfamoyl intermediate **78**, which upon S_N2 displacement of the more activated leaving group, gives cyclic sulfamidates of the general structure **79**. Styrene derived diols were chosen as model substrates, because of their ease of preparation as single enantiomers *via* Sharpless asymmetric dihydroxylation.[55]

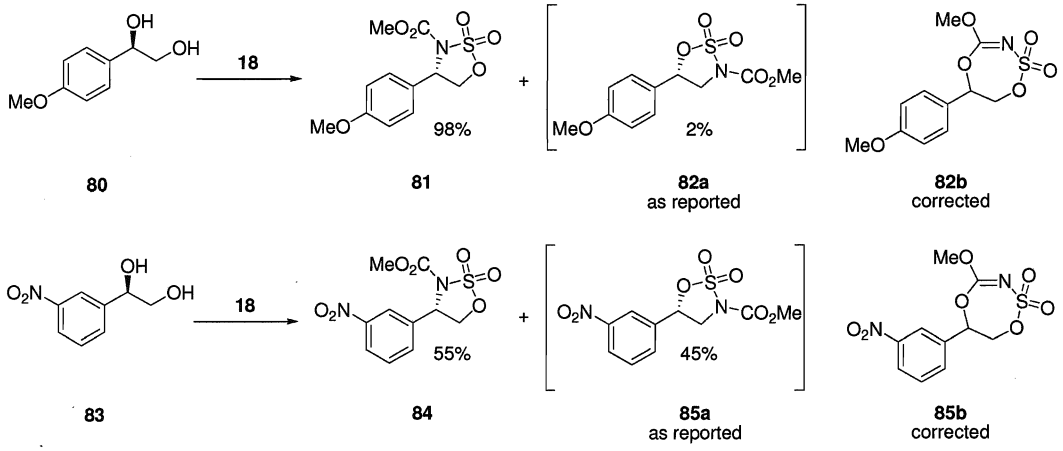


Figure 17. Formation of sulfamidates from 1,2-diols.

Burgess mediated sulfamidate synthesis followed the expected pattern for inductive influence in nucleophilic displacement at the benzylic position: electron-donating groups displayed excellent regioselectivity, whereas a poor selectivity was observed with electron-withdrawing groups as shown in Figure 17. It was later shown by the Hudlicky group that compounds **82a** and **85a**, assigned as regioisomers by the

Nicoleaou group are indeed 7-membered sulfamidates as shown in Figure 17 (see page 21 for more details).[21]

An application of this novel methodology can be found in the synthesis of (*S*)-α-trifluoromethylisoserine by Pergrina and coworkers.[56] Hydroxysulfamidates were reported to be prepared in a similar fashion by the reaction of the Burgess reagent with epoxyalcohols.[19]

Using the concept of sulfamidate formation from diols, the Nicolaou group applied the same strategy to the synthesis of sulfamides from amino alcohols.[20] The desired cyclic sulfamides were reported to be obtained in high yield, regardless of the nature of the group attached to the nitrogen. The Burgess reagent was shown to react with β- as well as γ-amino alcohols to yield 5- and 6-membered nonsymmetrical monoprotected sulfamides, respectively. Deprotection of the carbamate group is achieved under basic conditions, giving access to a wide range of sulfamides after substitution with appropriate electrophiles as demonstrated by Nicolaou and coworkers. Besides the formation of cyclic sulfamides, the syntheses of several linear sulfamides were presented in the same publication.[20] Further non-dehydrative utility of the Burgess reagent was discovered in the synthesis of both α- and β-glycosylamines from a wide range of carbohydrate scaffolds as shown in Figure 18. The reaction protocol was found to be tolerant to numerous protecting groups as well as applicable for scale-up.[17]

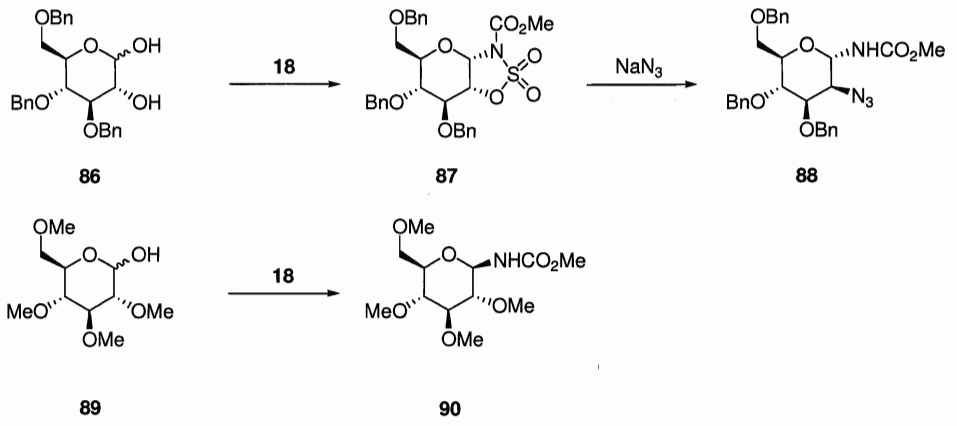


Figure 18. Synthesis of α- and β-glycosylamines.

Burgess-type reagents

The commercially available Burgess reagent is sensitive to oxidative conditions, moisture, and heat. It must be stored at low temperature and has a limited shelf life. Yields are therefore highest with freshly prepared reagent. Various groups have tried to improve the properties, the stability as well as the reactivity of the Burgess reagent (**18**). Wipf and Venkatramen reported the synthesis of polyethylene glycol (PEG) supported Burgess type reagents **91**, with molecular weight ranges from 750 to 2000.[16a] This PEG-supported reagent gave various oxazolines and thiazolines in 10-20% higher yields compared to the yields obtained from reactions with the regular reagent. In addition, the PEG supported Burgess reagent showed improved stability under wet and oxidative conditions and was readily separated from the reaction mixture, as highlighted in Wipf's publication.[16a]

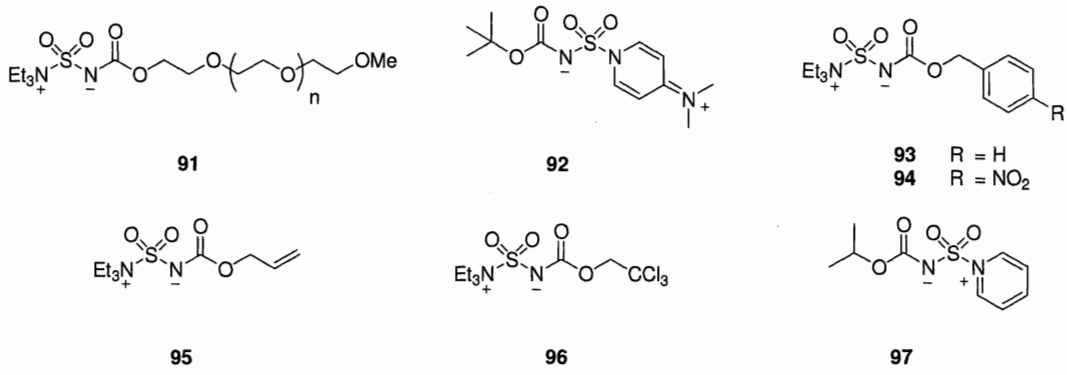


Figure 19. Burgess-type reagents.

The first Burgess type reagent, which had both the amine as well as the alcohol portion varied, was introduced by Montero and coworkers. *tert*-Butyl ester in in place of methyl and DMAP instead of triethylamine were the changes in this Burgess type reagent **92**. It allowed sulfamoylation of various amines under mild conditions to give sulfamide derivatives in good yields.[57]

The formation of carbamates from primary alcohols, rather than the dehydration product, was mentioned earlier in this chapter. This transformation has seen limited use due to the harsh conditions required for the removal of the methoxycarbamate protecting group. Modification of the methyl ester to a benzyl ester allowed for the preparation of benzyl Burgess reagent **93**.[58] Application of the benzyl Burgess reagent led to the smooth conversion of several primary alcohols to the corresponding CBz protected amines in good yields. In addition to the use of the Burgess reagent as a versatile reagent for the synthesis of sulfamidates and sulfamides, the Nicolaou group prepared four different Burgess type reagents **93**, **94**, **95**, and **96**, representing an orthogonal set of amine protecting groups (based on deprotection by hydrogenation, photolysis, exposure to palladium based catalysts, or treatment with

zinc).[18] They demonstrated that the reaction of the new reagents with several diols, amino alcohols and carbohydrates resulted in the formation of the desired products in comparable efficiency and selectivity as observed with the original Burgess reagent **18**.[17,18,19,20]

The group of Masui disclosed a one pot synthesis of *N*-acyl substituted sulfamides starting from chlorosulfonylisocyanate and isopropanol followed by addition of pyridine to the *N*-chlorosulfonylcarbamate intermediate to give Burgess type reagent **97**, which can be further reacted with aqueous or anhydrous amines to yield the desired substituted sulfamides in excellent yield.[59]

Miscellaneous Uses

The use of the Burgess reagent leads occasionally to unexpected products. Ring contraction of the neutral oleandrose sugar in the 14-membered macrolide antibiotic oleandomycin was observed, instead of the desired dehydration, by Nagel and coworkers.[60] The facile formation of organotin reagents like vinyltributyltin and tributyl isocyanate was reported by the application of the Burgess reagent.[61] Makara and coworkers published that carboxylic acids are converted to novel mixed sulfcarboxyanhydrides upon treatment with the Burgess reagent. Subsequent treatment of such mixed anhydrides with amines at elevated temperatures yields acyl ureas and amides.[62] Baylis-Hilmann adducts can be converted into carbamates of unsaturated β-amino acids in a one-pot reaction when treated with the Burgess reagent.[63] In addition, the oxidation of heterocyclic benzoin type compounds to the

corresponding benzil derivatives[64] as well as the preparation of sulfilimines from the corresponding sulfoxides have been achieved with the Burgess reagent.[65]

Formation of Sulfamidates from Epoxides

In 2003, the Hudlicky group published the first report on the reactivity of the Burgess reagent with epoxides.[21] Aliphatic epoxides yielded 5-membered sulfamidates upon treatment with 2.3 equivalents of Burgess reagent (**18**) whereas benzylic epoxides gave a separable mixture of 5- and 7-membered sulfamidates, as shown in Figure 20. This aspect of the Burgess reactivity is especially noteworthy because epoxides were believed to be inert to the action of the Burgess reagent as reported by Lamberth in 2000.[13b]

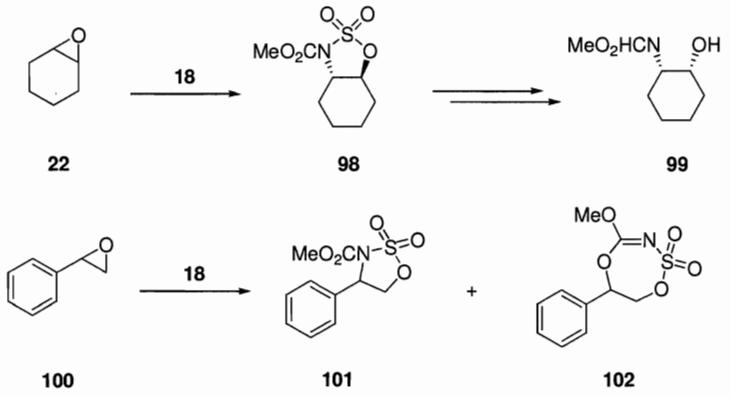


Figure 20. Formation of sulfamidates from epoxides.

Sulfamidates, derived from aliphatic epoxides, were further converted to their corresponding *cis*-β-amino alcohol derivatives. It was further suggested that treatment of the same sulfamidate intermediate under reductive conditions would lead to the corresponding *trans* amino alcohols. Comparison of the spectral data of the products derived from the reaction of styrene oxide (**100**) with the Burgess reagent (**18**), to

spectral data of the products derived from styrene diol, revealed that the minor products, reported by Nicolaou as regioisomers (see **82a** and **85a**, page 16), were actually 7-membered sulfamidates.[18] X-ray crystal structure analysis confirmed the structure of compound **102**. Hudlicky and coworkers proposed a mechanism to account for the formation of 7-membered sulfamidates from either epoxides or 1,2-diols and suggested that the latter compounds yield in some cases 7-membered sulfamidates, as shown in Figure 21.

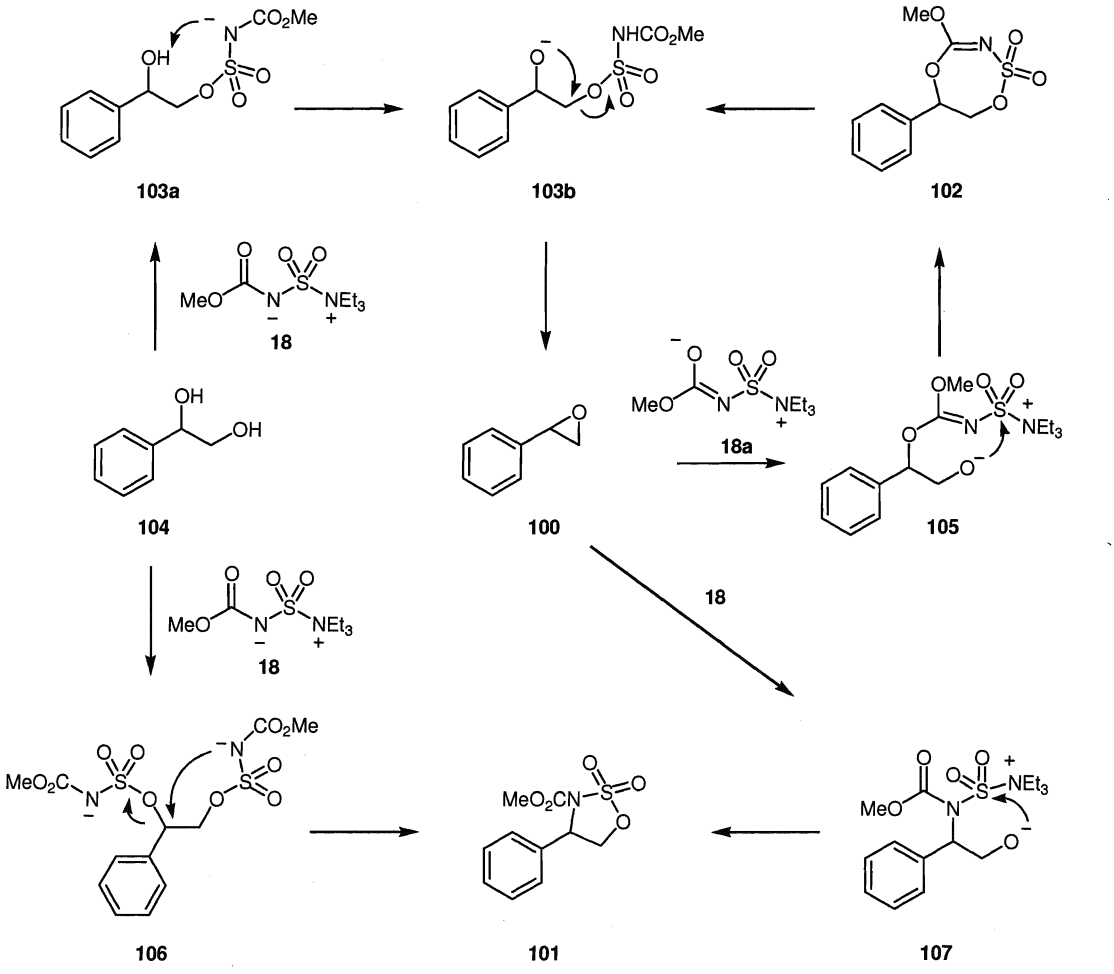


Figure 21. Proposed mechanism for the formation of 7-membered sulfamidates.

Interestingly, the hybrid resonance form of the Burgess reagent **18a** only plays a role in the reaction of benzylic epoxides and no 7-membered sulfamidates were detected in the reaction with aliphatic epoxides.

Further applications of the Burgess reagent and new reactive options are presented in the Discussion, Section 3.1.

2.2 Morphine Alkaloids

2.2.1 History of Morphine Alkaloids

Opium has been used to produce euphoria, analgesia, sleep, and relief from cough and diarrhoea for thousands of years. [66] The word "opium" has been postulated to be of Greek origin, deriving from "opos" (juice) and "opion" (poppy juice). The recorded history of opiates dates back to the times of the Sumerians 3400 years BC. It seems likely that the Summerians were aware of the mood elevating properties of the dried sap obtained from the unripe seed pod of the poppy flower, *Papaver Somniferum.*[67] In pre-Christian centuries opium was primarily used for its constipation effect and for its sleep-inducing properties, as noted by writers such as Homer, Hippocrates, Virgil, and Ovid.[66] In China and other oriental countries, where alcohol was prohibited because of religious beliefs, opium was commonly used as an intoxicant. The nearly bankrupt East Indian Company stabilized its financial situation with opium exports to China, which led to India becoming the main producer of opium. Chinese efforts to suppress the sale and use of opium failed because the British forced the Chinese to permit opium trade and consumption.[68] The invention of laudanum, an alcoholic herbal preparation of opium, by the Swiss physician Paracelsus established opium as a premium painkiller in Europe. One major drawback of opium was that the administration was difficult since the content of the active ingredients of the raw material was unknown to the physician.

The isolation of morphine (**1**) from opium was a seminal event in the development of the fields of chemistry and pharmacology. In 1805, Friedrich Wilhelm Sertürner, a young german pharmacist in Paderborn, isolated morphine (**1**) in its pure form from raw opium. He named the compound after Morpheus, the Greek God of Dreams.[3] The applied protocol for the isolation of the pure substance was rather simple and involved trituration of Indian opium with hot water until the filtrate became colorless. The filtrates were then concentrated, and saturated with ammonia. The semi crystalline material was then washed with water and triturated with ethanol. Sertürner identified morphine (**1**) as a potent active component of opium and recognized morphine (**1**) to be a base, marking the birth of alkaloid chemistry. Besides morphine (**1**), which accounts for 10-16% of weight, raw opium contains varying amounts of codeine (**2**) 1-3%, papaverine (**3**) 0.8-1%, thebaine (**4**) 0.5-2%, traces of oripavine (**108**), and narcotine (**109**) 1-7% as shown in Figure 22.

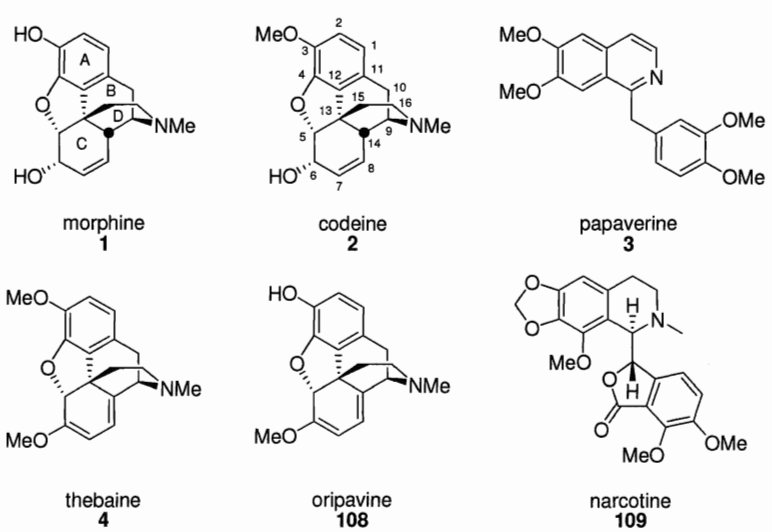


Figure 22. Natural occurring morphine alkaloids.

Structural elucidation began soon after the isolation of morphine (**1**) and early studies by Liebig were followed by those of Laurent, who correctly deduced the empirical formula for morphine as $C_{17}H_{19}NO_3$ in 1847.[4] Within a few years of its isolation, Heinrich Emmanuel Merck of Darmstadt began selling morphine as a painkiller, resulting in the development of an eponymous company. In 1853, the use of morphine proliferated with the invention of the hypodermic syringe, which provided a superior method of administration. The initial application of morphine for the treatment of alcohol and opium addiction was soon revised and research efforts were focused on the development of a less addictive derivative. Diacetylmorphine, known as heroin, was first synthesized by the English chemist Charles Robert Albert Wright and marketed by Bayer in 1898 as a non-addictive morphine substitute and cough suppressant.[9] Although heroin is metabolised to morphine in the human body and therefore has the same pharmacology as morphine, the semi-synthetic opioid has the ability to cross the blood brain barrier faster, which creates an euphoric rush. This property made the substance even more addictive and led to an immense illicit demand, which continues to this day. Besides the first synthesis of heroin, Wright also contributed to the elucidation of the oxygenation pattern in morphine.[69]

Numerous degradive experiments by Hofmann, Pschorr, and von Gerichten on morphine and codeine confirmed the presence of an oxygenated phenanthrene skeleton.[70] In 1925, Robinson and Gulland were able to propose the correct structure of morphine based on their own degradative studies as well as on the findings by Pschorr, Hofmann, Freund, and many others.[5] This proposal was ultimately confirmed by the first total synthesis by Gates in 1952.[6] The relative stereochemistry

of morphine was further confirmed by X-ray diffraction analysis by MacKay and Hodgkin in 1955.[71] The absolute stereochemistry was established by Jeger and coworkers by the chemical degradation of hydrocodone.[72] The structural elucidation of morphine represents one of the largest scientific efforts ever undertaken, spanning just over 150 years and was reviewed in an excellent publication by Butora and Hudlicky.[73]

2.2.2 Biosynthesis of Morphine Alkaloids

Morphine and codeine belong to a large group of secondary plant metabolites, more precisely to the group of benzylisoquinoline alkaloids. The biosynthetic pathway that produces all benzylisoquinoline alkaloids begins with the conversion of the amino acid tyrosine (**110**) into both dopamine (**111**) and 4-hydroxyphenylacetaldehyde (**112**) by four enzymes that catalyze hydroxylation, decarboxylation, as well as transamination reactions.[74]

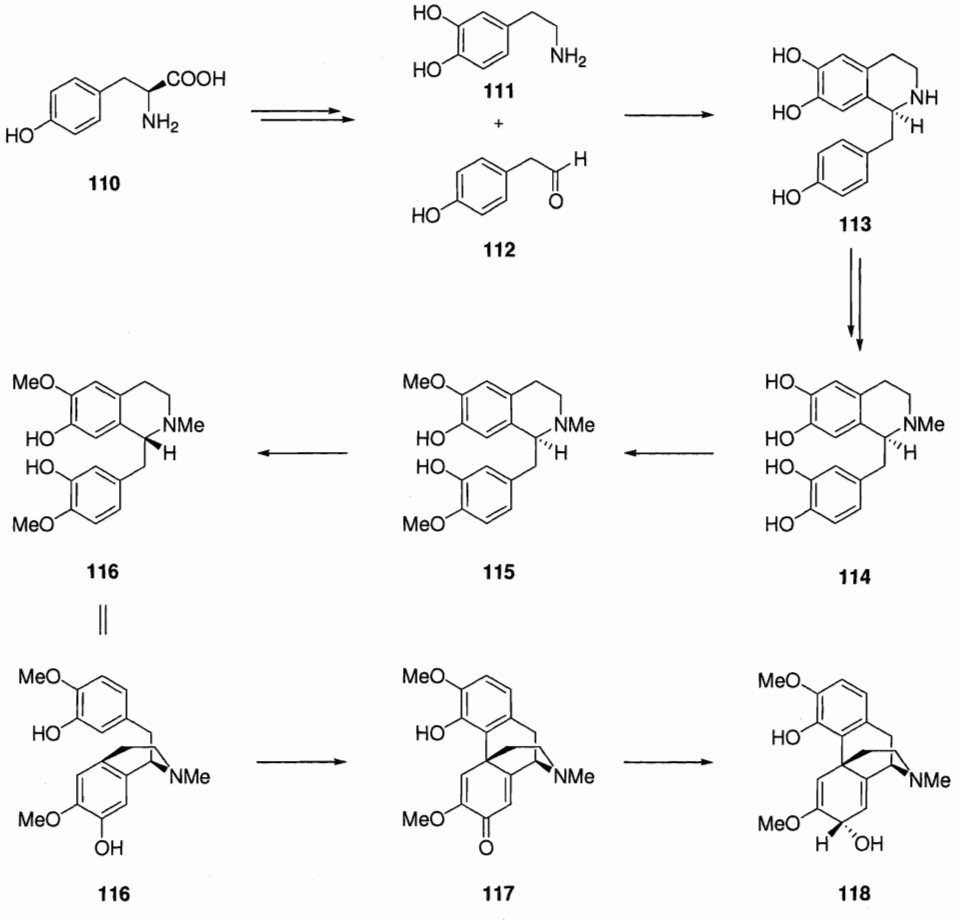


Figure 23. Biosynthesis of (*7S*)-salutaridinol (**118**).

The first step of the pathway towards morphine alkaloids involves the enzyme norcoclaurine synthase, which catalyzes the condensation of dopamine (**111**) and 4-hydroxyphenylacetaldehyde (**112**) in an asymmetric Pictet-Spengler reaction to form (*S*)-norcoclaurine (**113**), the central precursor to all benzylisoquinoline alkaloids in plants.[75] More recently the gene responsible for this transformation has been overexpressed in *Escherichia coli* and the protein has been purified.[76] Subsequent methylation catalyzed by a *N*-methyltransferase[77] and P-450 mediated hydroxylation give (*S*)-3´-hydroxy-*N*-methylcoclaurine (**114**),[78] which is further converted to (*S*)-reticuline (**115**), the precursor of more than 2500 benzylisoquinoline alkaloids. Interestingly, this substrate is not transformed into (+)-morphine, but is first converted into its enantiomer (*R*)-reticuline (**116**). Epimerization occurs *via* stereospecific reduction of its Schiff base catalyzed by the NADPH requiring enzyme 1,2-dehydroreticuline reductase.[79] Probably the most remarkable transformation of the morphine biosynthesis is the regioselective oxidative phenolic coupling catalyzed by the NADPH dependent cytochrome P450, salutaridine synthase.[80] Unlike most of the P-450 mediated reactions in alkaloid biosyntheses, salutaridine synthase represents an oxidase rather than a monooxygenase; this means no molecular oxygen is incorporated into the substrate. The ketone functionality of salutaridine (**117**) is reduced to (*7S*)-salutaridinol (**118**),[81] and the latter is then acylated by (*7S*)-salutaridinol-7-O-acetyltransferase.[82] The resulting allylic acetate **119** undergoes a non-enzymatic syn S_N2' displacement by the phenolic hydroxy group to yield thebaine (**4**).

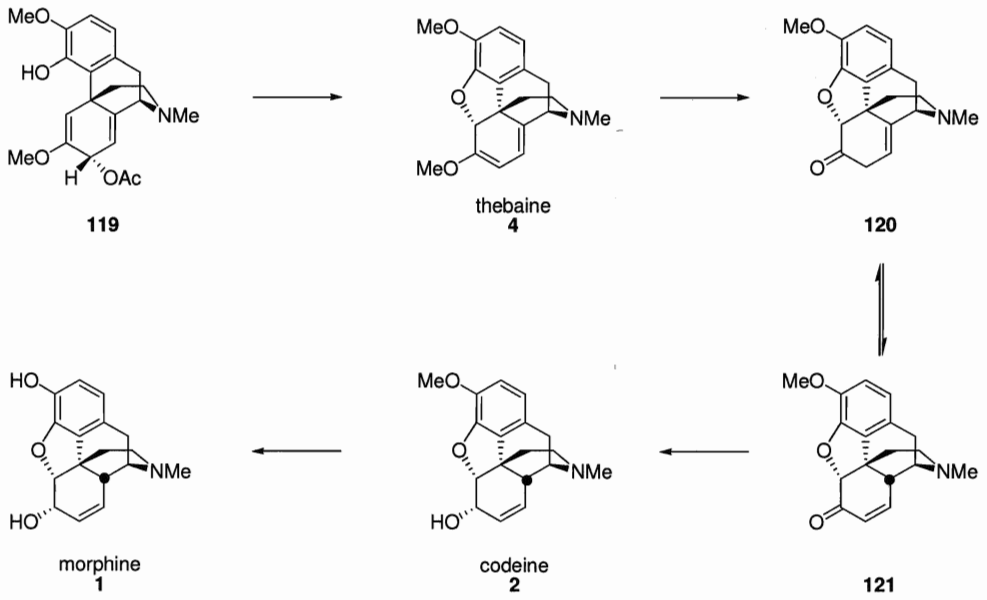


Figure 24. Biosynthesis of morphine.

Demethylation of the C-6 enol ether functionality by an as yet uncharacterized enzyme results in the formation of neopinone (**120**), which exists in equilibrium with its fully conjugated isomer, codeinone (**121**). Reduction of the C-6 keto group by codeinone reductase[83] and final demethylation of the phenolic ether yields morphine (**1**), as shown in Figure 24. Interestingly, an alternative pathway which leads to the formation of morphine (**1**) has been postulated and is shown in Figure 25.[84]

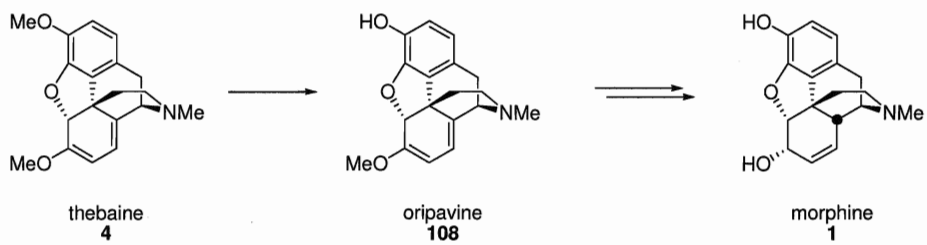


Figure 25. Alternative biosynthesis of morphine (**1**).

Experiments with radio-labelled morphine precursors revealed that oripavine (**108**) is formed from thebaine (**4**) by 3-*O*-demethylation. Subsequent enol-ether cleavage produces morphinone, which is further reduced by codeine reductase to yield morphine (**1**). This alternative biosynthetic pathway was further proven by the preparation of a poppy mutant known as *top1* (for 'thebaine oripavine poppy 1').[11] Commercial poppy cultivar were treated with a mutagen and then screened for progeny plants. The mutant *top1* was found to accumulate thebaine (**4**) and oripavine (**108**) but not morphine (**1**) and codeine (**2**). Feeding experiments with radioactive intermediates confirmed that there was a block in both arms of the bifurcated pathway at thebaine and oripavine. The authors suspected that a defect in the enzyme thebaine demethylase, which is responsible for the 6-*O*-demethylation of both thebaine and oripavine, caused the variation in the morphine biosynthesis.

The development of the *top1* mutant not only contributed to the understanding of the biosynthetic pathway of morphine alkaloids, but also provides for an agriculturally viable supply of thebaine (**4**) and oripavine (**108**), which are employed in the manufacturing of the vast majority of semi-synthetic opioids.

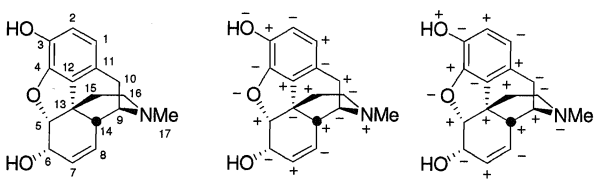
The current picture of the morphine biosynthesis in plants, involving 19 steps, is nearly complete.[85] However, recent studies have also provided evidence for the presence of morphine alkaloids in animals. Trace amounts have been detected in various tissues of mammals and lower animals.[86] The origin of the endogenous morphine has been a matter of controversy since morphine was also found in hay, lettuce, human milk, and cow milk as well as commercial rat and rabbit feed.[87] The group of Zenk could unambiguously demonstrate that human neuroblastoma cells are

capable of synthesizing morphine. On the basis of radiolabelled precursor feeding experiments, they provided a detailed picture of the biosynthesis of morphine in human cells starting from the amino acid tyrosine (**110**).[86,88]

The two main sources of morphine (**1**) for commercial applications are either opium or poppy straw. Both sources are obtained from processing the capsules of *Papaver somniferum*. Opium is the sun-dried sap obtained from incised capsules. Approximately 80 days after planting, the green capsule is incised and the released sap is collected and dried. Several lancings are combined and dried in special open air tanks until the moisture content is reduced to approximately 15%. The second commercial source for morphine alkaloids is poppy straw. Poppy straw consists of dried capsules which were freed from their seeds and milled. Although the alkaloid content of green, undried capsules would be considerably higher, the valuable seeds would be lost. Only the additional profit derived from the sale of the seeds makes the business of growing poppies lucrative, since the commercial value of the seeds is equal to the value of the alkaloids.[89]

2.2.3 Overview of Selected Morphine Synthesis

Since the first reported total synthesis of morphine by Gates and Tschudi in 1952, morphine has remained a challenging target for the synthetic community.[90] There are a number of unique structural features which contribute to its complexity as a synthetic target: the C-13 quarternary center, the C-4, C-5 ether linkage, five vincinal stereocenters, the pentacyclic framework and especially the dissonantly assembled 17 carbons of morphine, as shown in Figure 26. (The concept of consonance/dissonance was first introduced by Evans and was discussed in detail by Hudlicky and Reed. [91]) The following section summarizes a selection of synthetic efforts towards the total synthesis of morphine alkaloids which employ Diels-Alder, Grewe cyclization, radical cyclization, or palladium cyclizations as key strategies.



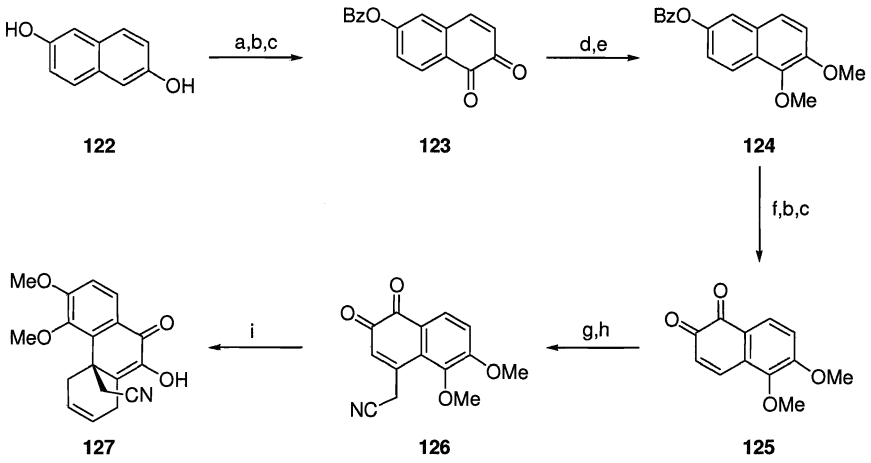
morphine
1

Figure 26. Dissonant relationships in morphine (**1**) connectivity.

Gates (1952, full disclosure 1956)[6,92]

The first total synthesis of morphine was published by Gates and Tschudi in 1952 requiring 24 steps to construct morphine (**1**) from 2,6-dihydroxynaphthalene (**122**) in an overall yield of 0.01%.

The symmetry of the starting material allowed Gates to synthesize intermediate **125** in an iterative fashion by employing a nitrosation/reduction/oxidation sequence. This sequence allowed for the installation of the two different 1,2-dioxygenation functionalities on both rings in a very efficient way. A Michael-type reaction of compound **125** and ethyl cyanoacetate, followed by re-oxidation and base-catalyzed decarboxylation provided the precursor for the subsequent Diels-Alder reaction. Earlier model studies had shown that the C-13 quaternary center of morphine could be constructed *via* cycloaddition of compound **126** and butadiene. [93]

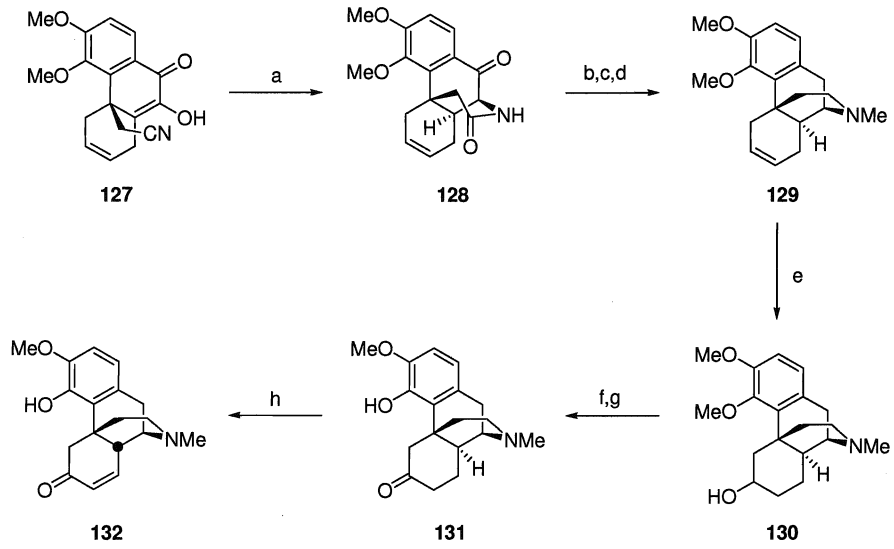


Reagents and Conditions: a) BzCl, py, dioxane (72%); b) $NaNO_2$, AcOH (88%); c) Pd/C, H_2, AcOH, then $FeCl_3$ (85%); d) SO_2, MeOH (91%); e) K_2CO_3, dimethyl sulfite (82-86%); f) KOH, MeOH (80%); g) ethyl cyanoacetate, NEt_3, then $K_3Fe(CN)_6$ (84%); h) KOH, MeOH, H_2O (97%); i) butadiene, AcOH (66%).

Scheme 1. Gates synthesis of Diels-Alder product **127**.

Diels-Alder adduct **127** underwent reductive cyclization through what the authors described as relatively "mild conditions" (130 °C, 27 atm of H_2) to give keto lactam **128**. This unusual cyclization was discovered by Gates and Woodward in an earlier series of model studies, two years before the first total synthesis of morphine was

reported.[94] The course of this reductive cyclization "was far from clear" as stated by Gates in his 1956 publication. Nevertheless, it produced the tetracyclic carbon-nitrogen skeleton stereoisomeric of that of morphine (**1**) very efficiently.



127 **128** **129** **130** **131** **132**

Reagents and Conditions: a) Cu-Cr, H_2 (50%); b) KOH, N_2H_4 (90%); c) NaH, MeI; d) LAH (54%); e) dilute H_2SO_4 (28%); f) KOH, ethylene glycol (54%); g) *tert*-BuOK, Ph_2CO (89%); h) Br_2, AcOH, 2,4-DNP (41%).

Scheme 2. Gate's synthesis of intermediate **132**.

The keto functionality was reduced using a modified Wolff-Kishner protocol, followed by methylation and lithium aluminium hydride reduction to give *d*-*β*-Δ^6-dihydrodesoxycodeine (**129**), which represents the entire carbon skeleton of morphine. The infrared spectrum of compound **129** was identical to that of natural *d*-*β*-Δ^6-dihydrodesoxycodeine methyl ether, which was obtained by degradation of *β*-dihydrothebainone. In addition, the resolution of morphinan **129** into its enantiomers was easily effected by crystallization with dibenzoyltartaric acid and provided the natural enantiomer in this series, but epimeric at C-14. The stereochemical

assignment of compound **129** is based on comparison with products obtained from degradation of naturally occurring morphine alkaloids. Acid mediated hydration of C-6 followed by selective cleavage of the proximal anisole methyl ether furnished compound **131**. The remaining challenge in Gates' synthesis, the epimerization of the C-14 center, was solved in an elegant manner. Ketone **131** was treated with two equivalents of bromine followed by hydrazone formation with 2,4-dinitrophenylhydrazine as shown in Figure 27.

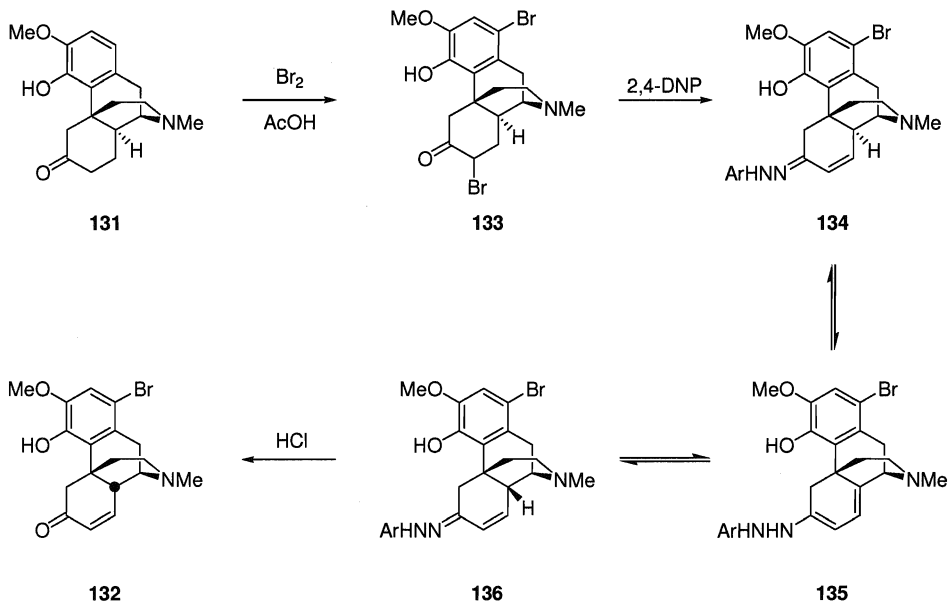
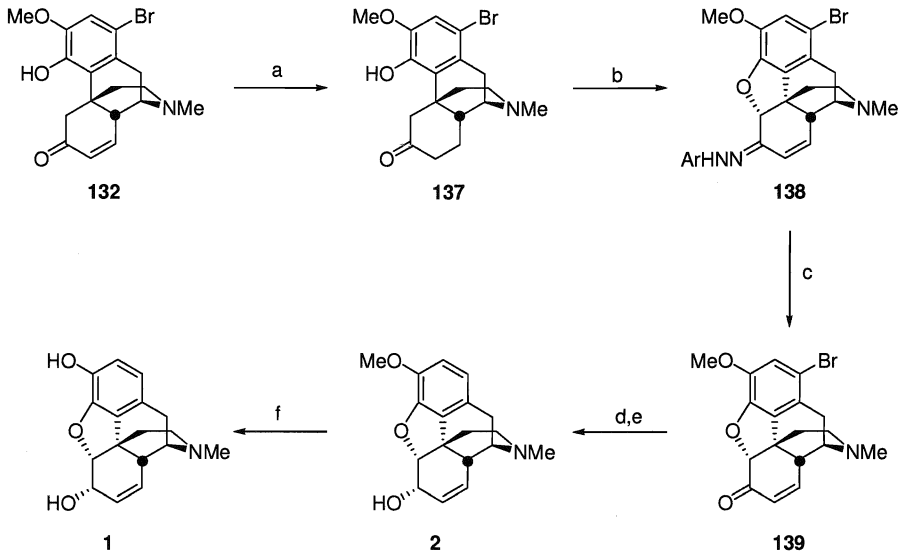


Figure 27. C-14 epimerization *via* hydrazone formation.

The introduction of the α,β-unsaturation in compound **134** allowed for the equilibration of the C-14 hydrogen, because of the formation of the more stable *cis* fused ring system of compound **136**. It has to be mentioned that Gates' sequence is still the method of choice for the equilibration of C-14 center in morphine alkaloid synthesis.



Reagents and Conditions: a) H_2, PtO_2; b) Br_2, AcOH, 2,4-DNP (26%); c) HCl, acetone (27%); d) LAH (quant); e) H_2, Pd/C; f) Py•HCl (34%).

Scheme 3. Gate's final transformation to (-)-morphine (**1**).

Acid mediated hydrolysis of the hydrazone, followed by hydrogenation gave the precursor for the C-4, C-5 dihydrobenzofuran closure **137**. The construction of the complete morphine pentacyclic core was achieved by applying the same remarkable conditions which addressed the problem of the C-14 epimerization. Treatment of ketone **137** with bromine in the presence of 2,4-2,4-dinitrophenylhydrazine effected the C-4, C-5 ether closure as well as introduced the $\Delta_{7\text{-}8}$ unsaturation unit. Cleavage of the phenylhydrazone unit with hydrochloride acid followed by treatment with lithium aluminium hydride furnished codeine (**2**) in 27% over two steps. Repetition of the conditions reported by Rapoport and coworkers for the demethylation of codeine completed the first synthesis of morphine (**1**).[95]

Rice (1980)[96]

Rice's work in opiate total synthesis was initiated by two events, the world-wide opium shortage of 1973-1975, as well as the discovery of morphine receptors and the resulting need of unnatural enantiomers for affinity studies.

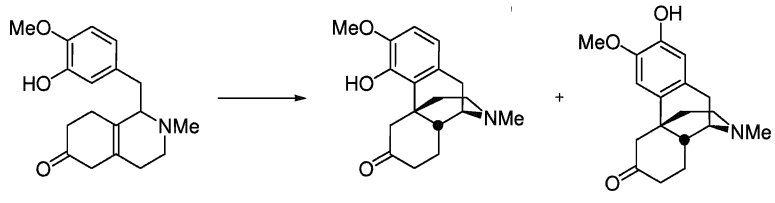
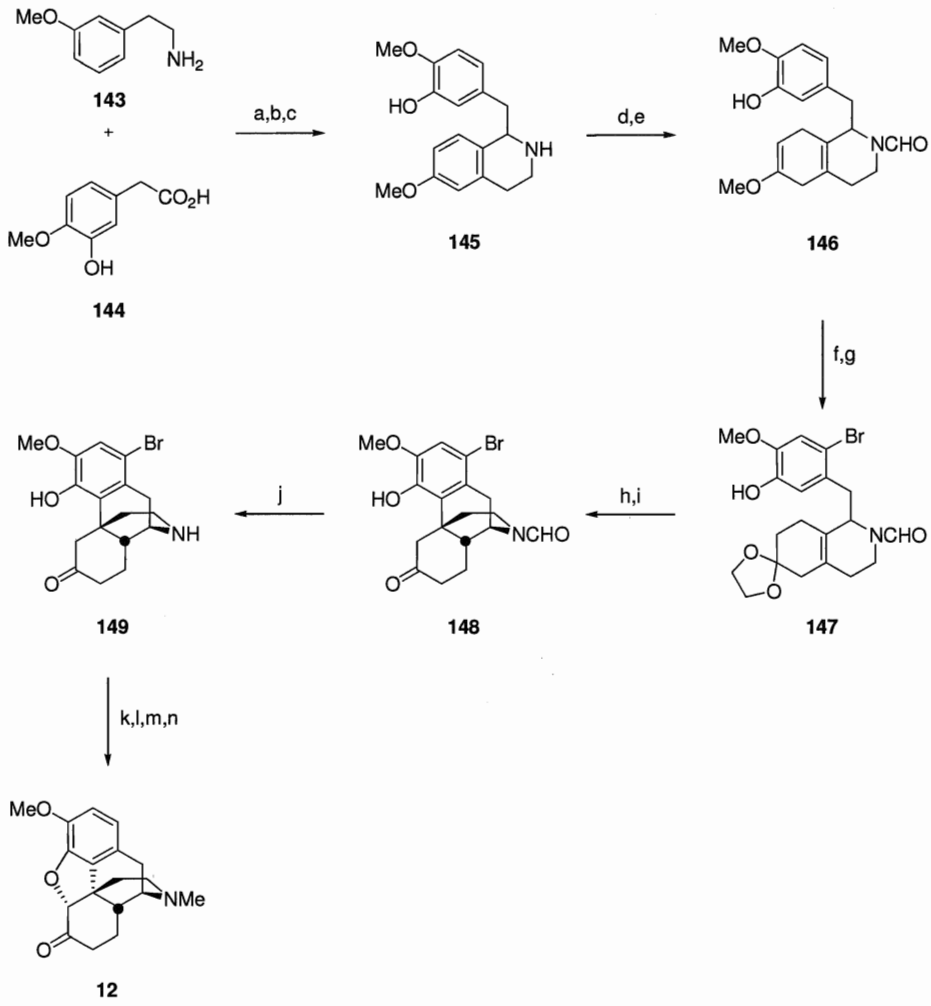


Figure 28. Cyclization of benzylhexahydroisoquinoline **140**.

Rice's strategy was presumably inspired by previous reports that described a Grewe-type electrophilic cyclization of *rac*-1-benzylhexahydroisoquinoline (**140**), which gave dihydrothebainone (**141**) in 3% yield with isomeric **142** as the predominant cyclization product (Figure 28).[97] Those studies were followed by the work of Beyerman and coworkers who utilized a blocking group (a methyl group at the C-1) of the benzoyl moiety in order to direct cyclization to the desired oxygenation pattern.[98]

Rice's synthesis starts with the preparation of amine **145** by condensation of amine **143** and acid **144**, followed by Bischler-Napieralski cyclization. Birch reduction of the more electron deficient aromatic ring gave amide **146** after formylation. Ketalisation and regioselective bromination of **146** was carried out consecutively in a one pot reaction.



Reagents and Conditions: a) 200 °C (95%); b) $POCl_3$, MeCN; c) $NaCNBH_4$, MeOH (86%); d) Li, NH_3, THF, *tert*-BuOH (90%); e) PhOCHO, EtOH (94%); f) ethylene glycol, $MeSO_3H$, THF; g) NBA (88%); h) HCO_2H-H_2O (90%); i) NH_4•HF, CF_3SO_3H (60%); j) MeOH, HCl (92%); k) H_2, Pd/C, AcOH, HCHO; l) Br_2, AcOH ; m) NaOH, $CHCl_3$; n) H_2, AcOH, HCHO (79% over 4 steps).

Scheme 4. Rice's synthesis of hydrocodone **12**.

Careful hydrolysis of compound **147**, followed by hydrogen fluoride mediated Grewe cyclization furnished dihydrothebainone derivative **148** in a remarkable 60% yield. The pentacyclic framework of morphine alkaloids was completed by mild hydrolysis of amide **148** followed by α-bromination to the ketone and base induced ring closure.

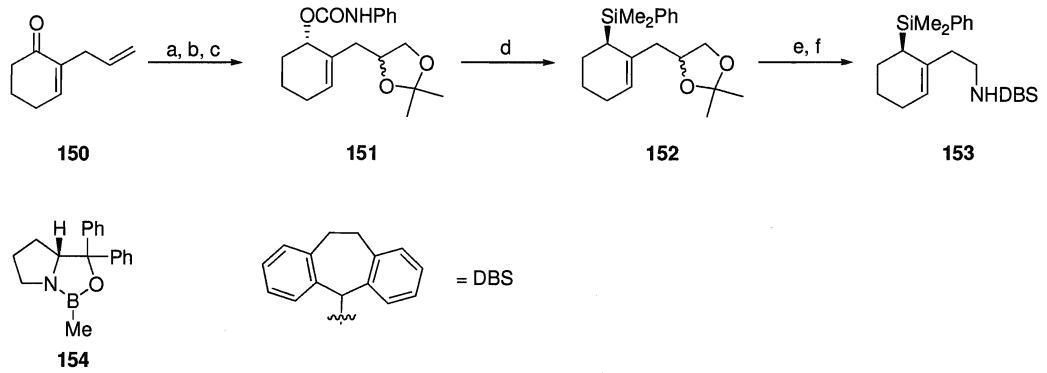
Removal of the aryl bromide and methylation of the secondary amine were achieved by hydrogenation over palladium in a mixture of acetic acid and formalin. Rice's synthesis of racemic hydrocodone **12** involves the isolation of only six intermediates, which required no chromatographic purification and proceeded in 29% overall yield. In addition Rice reported the resolution of compound **145** and therefore allowed access to both the natural as well as the unnatural series of morphine alkaloids. Rice's biomimetic route represents the most practical synthesis of morphine alkaloids to date and would be amenable to commercial production of a wide variety of opiates.

Despite the efficiency of Rice's synthesis, the isolation of opiates from natural sources remains more cost effective and therefore the need for an even more practical synthesis still exists.

Overman (1993)[99]

The first genuinely asymmetric synthesis of morphine was reported by Overman in 1993. All of the previously published syntheses were either racemic or involved a classic resolution strategy. Inspired by the previous synthesis of Grewe and Rice, [96, 97a] Overman employed an iminium ion-allylsilane cycliczation as well as an intramolecular Heck reaction of an enantioenriched octahydroisoquinoline derivative to construct the morphine skeleton. Chirality was incorporated in the first step of the synthesis *via* enantioselctive reduction of 2-allylcyclohexenone derivative **150** with catecholborane in the presence of (*R*)-oxazaborolidine catalyst **154** to give the corresponding alcohol in 96% ee.[100] Condensation of this intermediate with phenylisocyanate, followed by selective dihydroxylation of the terminal double bond

and protection resulted in the formation of compound **151**. A copper mediated suprafacial S_N2' displacement of the allylic carbamate with lithium dimethyl silane was achieved with minimal stereochemical erosion.



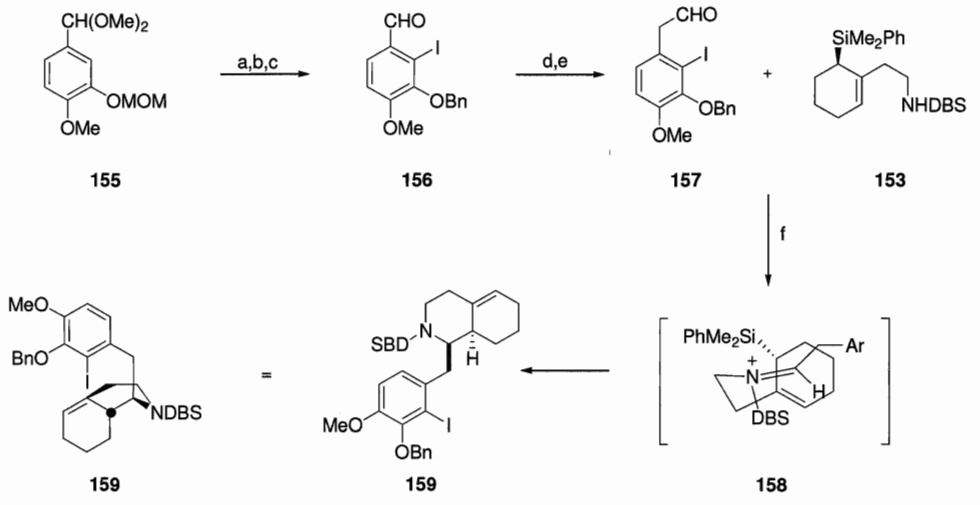
Reagents and Conditions: a) **154**, catechol borane (93%); b) PhNCO (93%); c) OsO_4, acetone, HCl (78%); d) *n*-BuLi, $CuI(Ph_3P)_2$, $PhMe_2SiLi$ (81%); e) *p*-TsOH, MeOH, $NaIO_4$; f) DBS-NH_2, $NaCNBH_3$ (88%).

Scheme 5. Overman's preparation of chiral intermediate **153**.

Deprotection of the acetonide group, followed by sodium periodate cleavage of the diol unit gave the corresponding aldehyde which yielded compound **153**, upon condensation with dibenzosuberylamine (DBS-NH_2) as shown in Scheme 5.

The second component of the iminium ion-allylsilane cyclization was prepared from isovanillin derivative **155** as shown in Scheme 6. Lithiation of compound **155** (available in two steps from isovanillin), followed by treatment with elemental iodine and subsequent cleavage of the acetal group provided aldehyde **156**. Reaction of this intermediate with dimethylsulfonium methylide followed by Lewis acid catalyzed rearrangement of the resulting epoxide gave compound **157** in excellent yield. Condensation of amine **153** and aldehyde **157** in the presence of ZnI_2, followed by

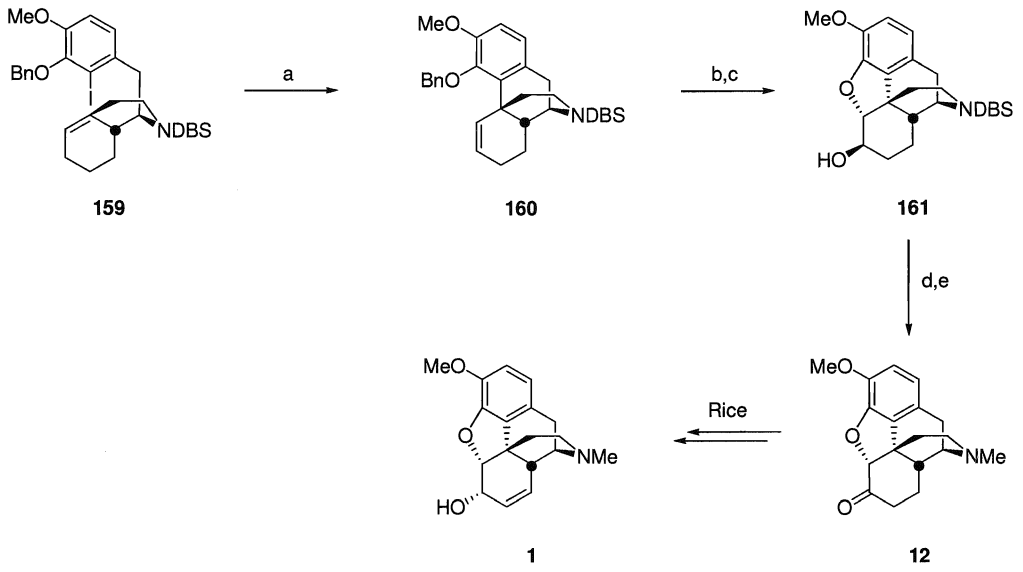
iminium ion-allylsilane cyclization yielded the desired octahydroisoquinoline **159** in high diasteroselectivity.



Reagents and Conditions: a) *n*-BuLi, I_2 (80%); b) 6N HCl; c) BnBr, K_2CO_3 (97%); d) CH_2SMe_2 (91%); e) $BF_3 \cdot OEt_2$, THF (92%); f) ZnI_2, EtOH, 60 °C (82%).

Scheme 6. Overman's synthesis of Heck cyclization precursor **159**.

The crucial C-13 quaternary center of the morphine skeleton was forged by intramolecular Heck cyclization of **159** catalyzed by 10 mol% $Pd(TFA)_2(Ph_3P)_2$ in the presence of four equivalents of 1,2,2,6,6-pentamethylpiperidine. After cleavage of the benzyl ether, the final ring of the opioid skeleton was formed by reaction of the camphersulfonate salt of the free phenol with three equivalents of 3,5-dinitrobenzoic acid. Oxidation of **161**, followed by hydrogenolysis of the DBS group in the presence of formaldehyde provided hydrocodone (**12**), which was further converted to morphine (**1**) as described by Rice.[101]



Reagents and Conditions: a) $Pd(TFA)_2(Ph_3P)_2$, 1,2,2,6,6-pentamethylpiperidine, toluene (60%); b) BF_3•OEt_2, EtSH (79%); c) CSA, 3,5-dinitroperoxybenzoic acid (60%); d) TPAP, NMO (86%); e) H_2, $Pd(OH)_2$, HCHO (80%).

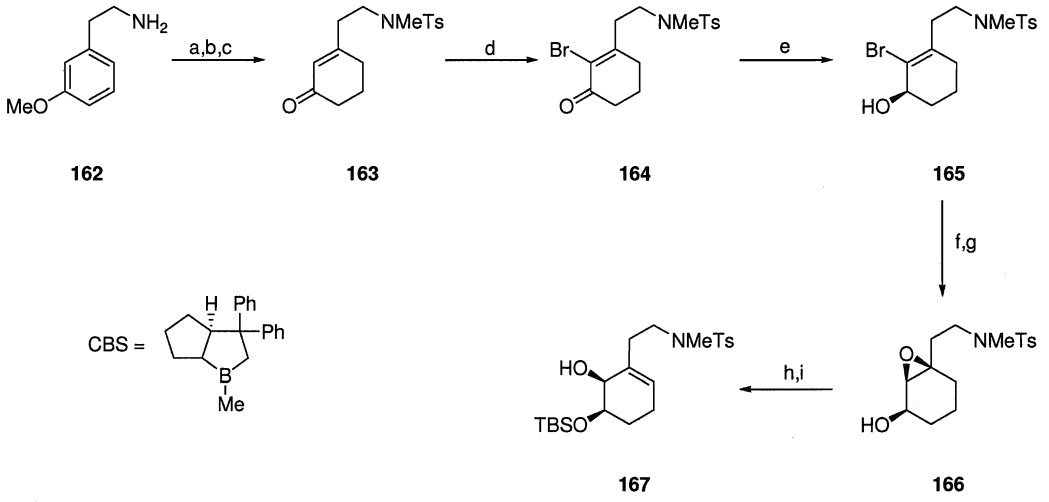
Scheme 7. Overman's final transformation to hydrocodone (**12**).

It is noteworthy that application of the (*S*) enantiomer of the oxazaborolidine reagent gives the opposite enantiomer of allylic alcohol **151** in comparable enantioselectivity.[100] In identical fashion as described for the synthesis of (-)-morphine, Overman was able to prepare (+)-hydrocodone, as well as (+)-morphine.

Parker (1992, 2006)[7]

Parker's approach to the morphine ring system was based on a tandem cyclization of an ortho allyloxy radical. In 1992 Parker and Fokas reported the racemic synthesis of dihydroisocodeine in 11 steps, which constitutes a formal synthesis of morphine. Fourteen years later the original synthesis was modified resulting in an asymmetric synthesis of (-)-hydrocodone (**12**).

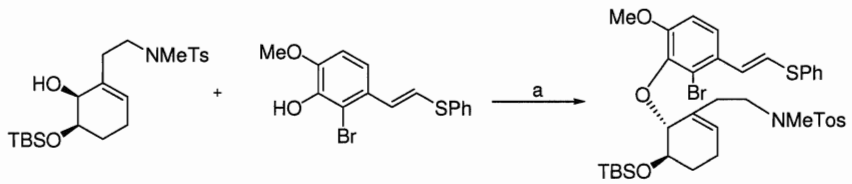
The key intermediate in Parker's synthesis represents an aryl cyclohexenyl ether, which was prepared by a Mitsunobu reaction. The synthesis of the cyclohexenyl portion, the C-ring synthon, started with the Birch reduction of commercially available *m*-methoxyphenethylamine (**162**), followed by tosylation of the amino group and hydrolysis of the enol ether unit.



Reagents and Conditions: a) Li, NH_3, *tert*-BuOH (97%); b) TsCl, NEt_3, then HCl (81%); c) MeI, K_2CO_3, acetone (96%); d) Br_2, NEt_3 (91%); e) CBS, catechol borane (84%); f) Na(Hg); THF-MeOH (90%); g) *m*-CPBA (92%); h) $Ti(OiPr)_4$ (85%); i) TBSCl, imidazole, DMF (78%).

Scheme 8. Parker's synthesis of C-ring fragment of morphine **167**.

Since the development of an appropriate protocol for the asymmetric reduction of compound **163** could not be accomplished, Parker resorted to an indirect strategy based on the asymmetric reduction of a 2-bromocyclohexenone derivative. Reduction of compound **164** with the Corey-Bakshi-Shibata (*S*)-oxazaborolidone-catechol borane reagent (CBS)[100] afforded alcohol **165** in excellent yield with enantiomeric excess ranging from 82% to 96%. Removal of the bromine from alcohol **165** by metal halogen exchange was not successful, but reduction with sodium amalgam proved to be suitable. Peracid-mediated epoxidation yielded the *cis*-epoxy alcohol intermtediate **166**, which was further treated with titanium isopropoxide to furnish the desired cyclohexenediol **167**, as shown Scheme 8.



167 **168** **169**

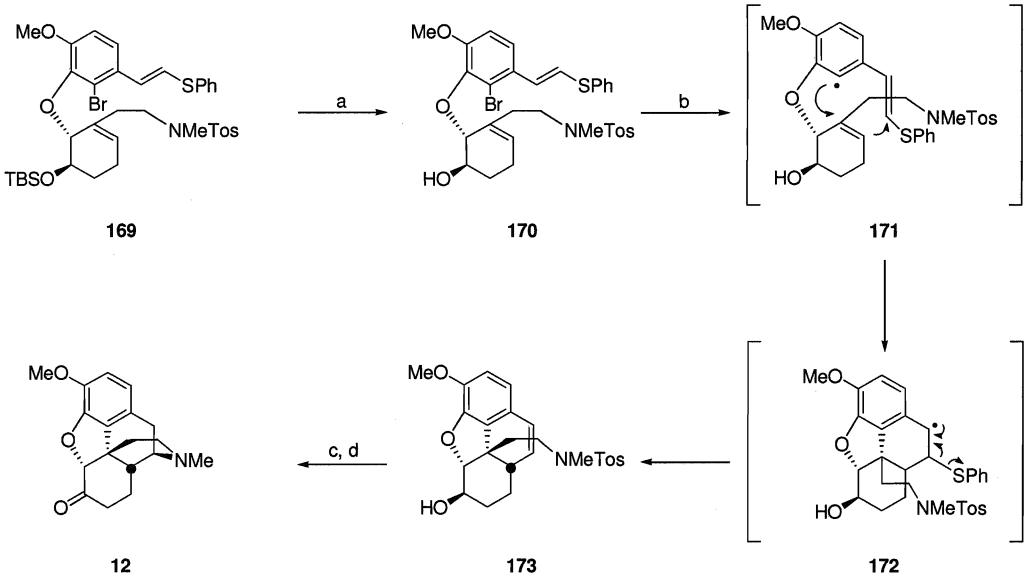
Reagents and Conditions: a) PBu_3, DEAD (83%).

Scheme 9. Parker's preparation of radical cascade precursor **169**.

The key intermediate **169** was successfully assembled by Mitsunobu reaction of C-ring fragment **167** and bromoisovanillin derivative **168** (A ring fragment) as shown in Scheme 9.

Removal of the silyl protecting group afforded compound **170**, which proved to be a suitable substrate for the radical-initiated tandem cyclization reaction. Homolytic cleavage of the carbon halogen bond in **170** mediated by tributyltin hydride and 2,2'-

azoisobutyronitrile afforded aryl radical **171**. This first species underwent a radical closure to form the dihydrofuran ring and generated a new radical at the C-14 carbon, which was trapped by the β-carbon of the styrene unit to give a resonance stabilized benzylic radical intermediate. Elimination of the phenylthiolate radical afforded intermediate **173** as a single diastereomer with correct configuration at the newly formed carbon centers. It was previously shown in various model studies that only the vinylthiophenol functionality gave excellent stereoselectivity in the radical mediated closures, whereas other radical acceptors failed to produce a single diastereomer.[7b,7c]



Reagents and Conditions: a) 10% HF, CH_3CN (78%); b) *n*-Bu_3SnH, AIBN, toluene (30%); c) Li, NH_3, *tert*-BuOH (85%); d) DMSO, $(COCl)_2$, NEt_3 (80%).

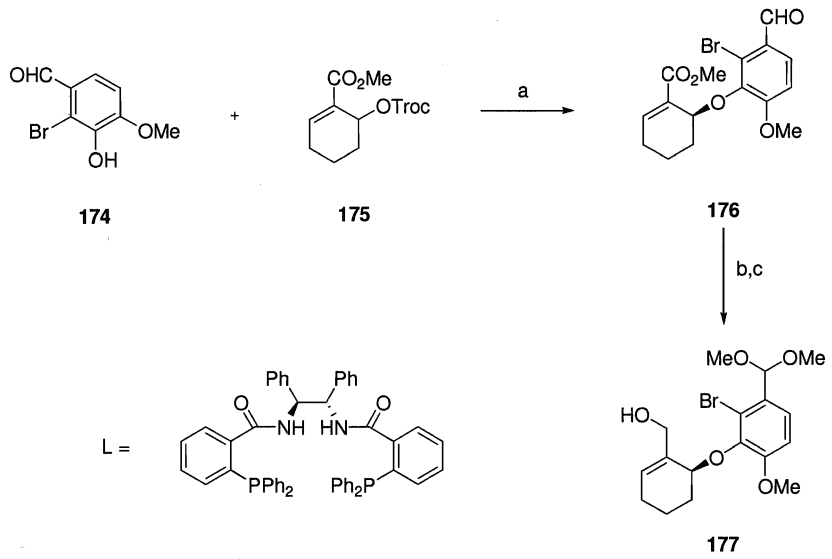
Scheme 10. Parker's final transformation to hydrocodone (**12**).

Although the reductive desulfonation of olefinic sulfonamides had not previously been reported to affect ring closure, dihydroisocodeine was obtained after treatment of tosylamine **173** with lithium and ammonia. Swern oxidation of the C-6 hydroxy

group completed this creative synthesis of hydrocodone (**12**) in thirteen steps from *m*-methoxyphenethylamine.

Trost (2002, 2005)[8]

In 2002, Trost and Tang reported the enantioselective synthesis of (-)-codeine (**2**) and morphine (**1**). The key strategies include an asymmetric allylic alkylation (AAA) to connect the A and C rings of morphine alkaloids in an enantioslective fashion, and two sequential Heck cyclizations to form the furan heterocycle, as well as the B ring of morphine alkaloids.

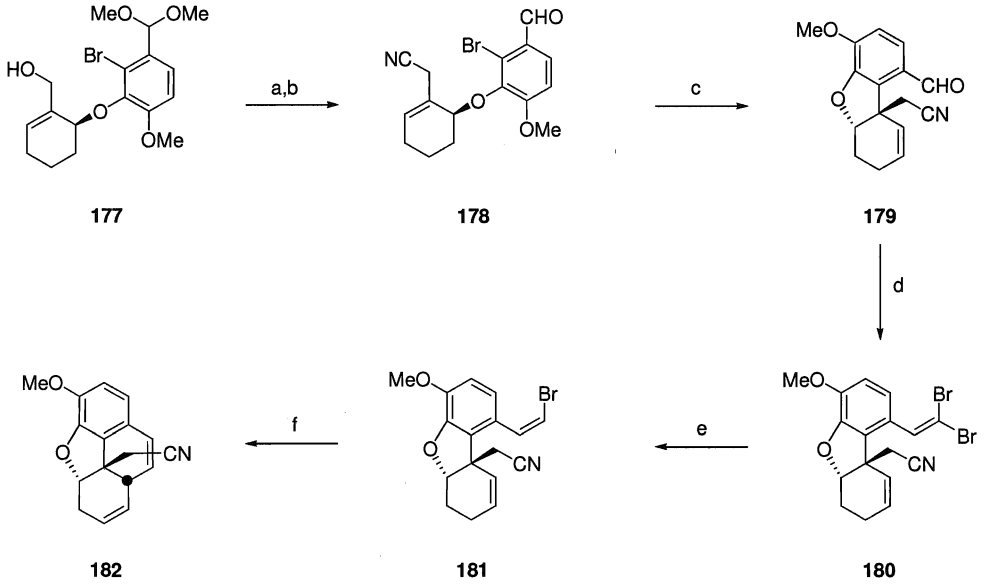


Reagents and Conditions: a) cat. PdL, NEt_3, DCM (72%); b) *p*-TsOH, $CH(OMe)_3$, MeOH; c) DIBAL-H, toluene, - 78 °C (85% over two steps).

Scheme 11. Trost's asymmetric allylic alkylation of compound **175**.

The synthesis began with the palladium catalyzed AAA of bromoisovanillin (**174**) and allylic ester **175** (available in two steps from glutaraldehyde) to give aryl ether **176** in 88% enantiomeric excess. Protection of the aldehyde, followed by reduction of

the ester functionality afforded alcohol **177**. The α,β-unsaturated nitrile was prepared by applying a modified Mitsunobu protocol with acetone cyanohydrin followed by liberation of the aldehyde under acidic conditions.

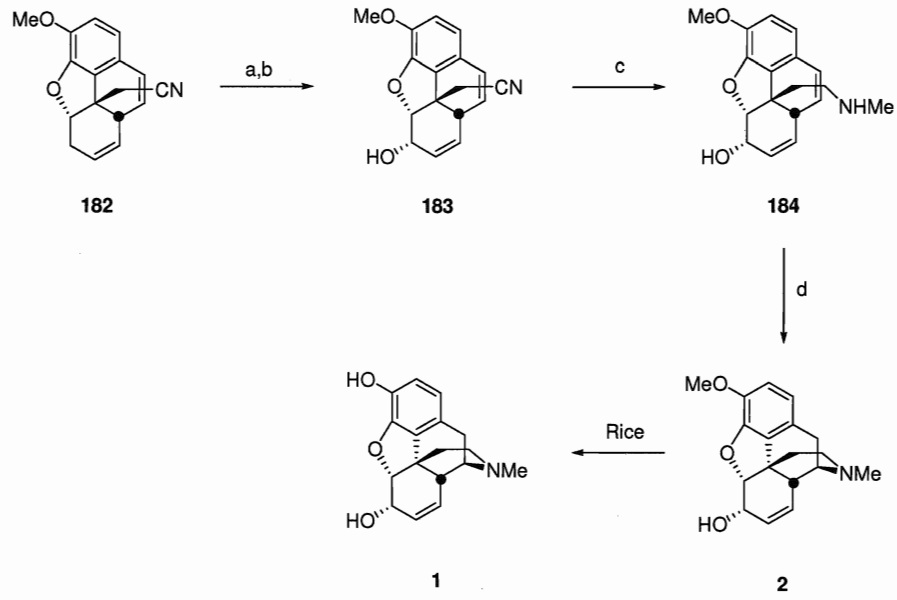


177 **178** **179** **180** **181** **182**

Reagents and Conditions: a) PPh_3, acetonecyanohydrin, DIAD; b) *p*-TsOH, THF, H_2O (76% over two steps); c) $Pd(OAc)_2$, dppf, Ag_2CO_3, toluene (91%); d) CBr_4, PPh_3, DCM (91%); e) *n*-Bu_3SnH, toluene (88%); f) $Pd(OAc)_2$, dppp, Ag_2CO_3, toluene (65%).

Scheme 12. Trost's synthesis of nitrile intermediate **182**.

Intramolecular Heck cyclization produced the quaternary C-13 center of the morphine skeleton in excellent yield. Corey-Fuchs homologation of aldehyde **179**, followed by chemoselective reduction of the *E*-vinyl bromide provided precursor **181** for the second Heck cyclization. Palladium catalyzed closure of the B-ring of the morphine skeleton gave compound **182** in 65%. Selenium dioxide mediated oxidation of the allylic carbon of the C-ring and subsequent DIBAL-H reduction of the enone in THF gave allylic alcohol **183** with the correct stereochemistry at C-6.

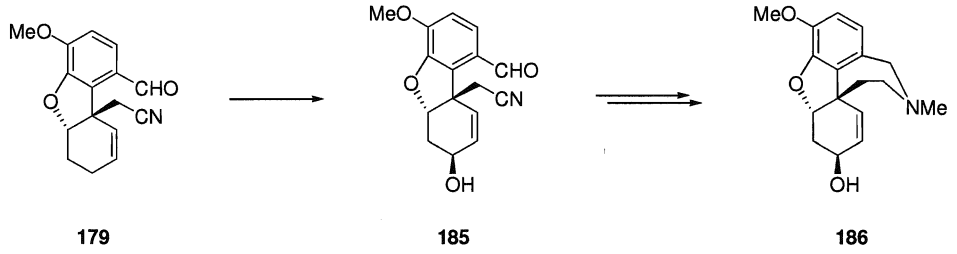


Reagents and Conditions: a) SeO_2, dioxane, sand (75%); b) DIBAL-H, THF, Et_2O (99%); c) DIBAL-H, DCM, Et_2O, then NH_4Br, $MeNH_2$ followed by $NaBH_4$ (quant.); LDA, THF, 150-W tungsten bulb (57%).

Scheme 13. Trost's final transformation to codeine (**2**).

Nitrile **183** was converted to amine **184** in a one pot transformation as follows: DIBAL-H mediated nitrile reduction was accomplished by switiching the solvent from THF to DCM, which afforded an imine aluminium complex. Addition of ammonium bromide to the reaction mixture destroyed excess DIBAL-H, as well as freeing the primary imine functionality. Subsequent treatment with methylamine furnished the more stable secondary imine, which was immediately treated with sodium borohydride to yield compound **184** in quantitative yield. The closure of the remaining D-ring is probably the most remarkable step in Trost's synthesis. Subjecting a solution of compound **184** to six equivalents of LDA to irradiation with a commercial 150-W tungsten light bulb led to intramolecular amination of the styrene to form (-)-codeine (**2**). Demethylation of codeine (**2**) with boron tribromide

as reported by Rice,[102] finished the synthesis of (-)-morphine in 16 steps from commercially available materials.



179 **185** **186**

Figure 29. Enantioselective synthesis of (-)-galanthamine (**186**).

Trost also applied compound **179** to the total synthesis of (-)-galanthamine (**186**) and therefore his strategy allowed for the synthesis of two different classes of alkaloids, morphine as well as amaryllidaceae alkaloids (Figure 29).

Hudlicky (1992 to present)

Over the last 20 years the Hudlicky group has explored various approaches to morphine alkaloids based on a wide range of strategies. The common feature of all approaches is the application of starting materials generated by enzymatic transformations. In 1968 Gibson and coworkers reported the isolation of a soil bacterium *Pseudomonas putida* which utilized ethylbenzene or toluene as its only carbon source.[103] Subsequent studies by the Gibson group led to the isolation of a mutant strain designated *Pseudomonas putida* F39/D, which converted aromatic compounds to their corresponding enantiomerically pure *cis*-cyclohexadienediols.[104] In order to improve the efficiency of this remarkable enzymatic transformation

Gibson prepared a genetically engineered *Escherichia coli*, which provided synthetically useful amounts of the metabolites from fermentation.[105]

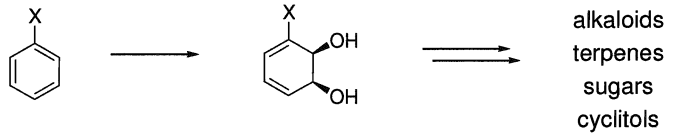


Figure 30. Application of *cis*-cyclohexadienediols to natural product synthesis.

Since Gibson's initial discovery in 1968 over 400 different homochiral cyclohexadienediols derived from microbial oxidation have been reported in literature.[106]

The synthetic utility of dihydroxylated metabolites from arenes was first shown in Ley's racemic synthesis of pinitol in 1987,[107] followed by Hudlicky's creative syntheses of prostaglandin intermediates in 1988.[108] Many applications followed with the group of Hudlicky being very active in the field reporting the total syntheses of a wide variety of natural products, such as alkaloids, terpenes, cyclitols and sugars.[106]

A brief review of Hudlicky's efforts towards a practical synthesis of morphine alkaloids utilizing *cis* cyclohexadienediol derivatives as starting materials will be presented on the following pages.

Intramolecular Diels Alder Cyclization Strategy[109]

The natural 1,2-disposition of the diol functionality makes the metabolites derived from dihydroxylation perfect synthons for the C-ring fragment of morphine alkaloids. Closer inspection of the morphine skeleton reveals that the entire morphine skeleton

could be assembled by two metabolites linked together at the C-5 postion. Intramolecular Diels-Alder reaction, followed by rearomatization of the A-ring would furnish the phenanthrene core of morphine alkaloids as shown in Figure 31.

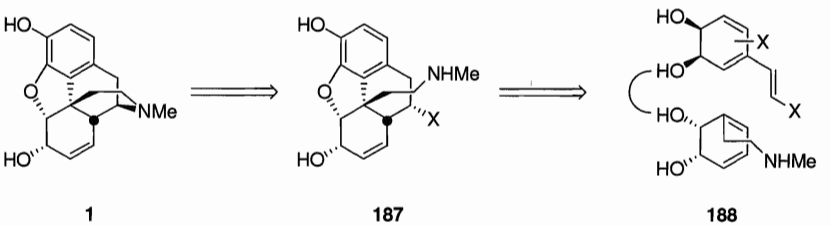


Figure 31. Retrosynthetic analysis of Hudlicky's intramolecular Diels - Alder approach to morphine alkaloids.

In 1992 Hudlicky and coworkers published a model study, which employed a Diels-Alder cyclization or a Diels-Alder and Cope rearrangement sequence to obtain tricycles **192** and **196**.

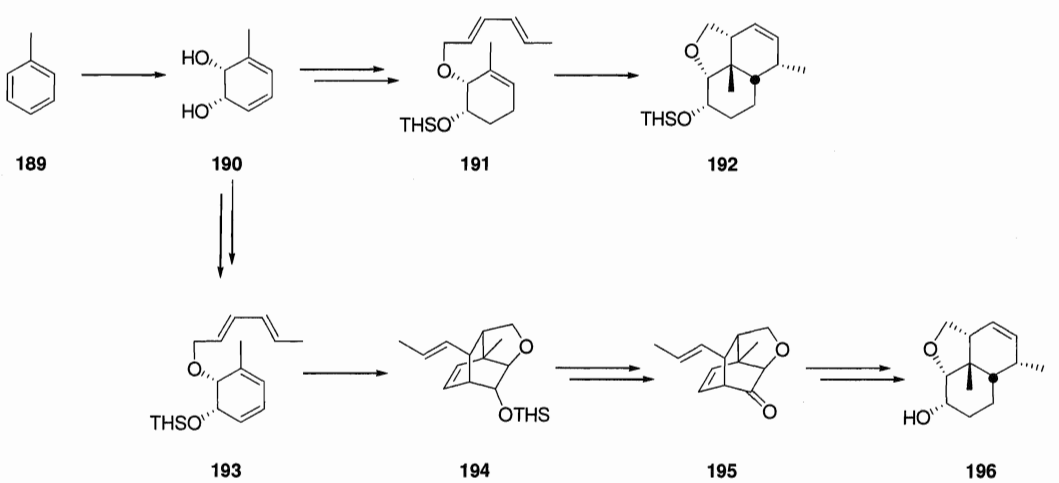
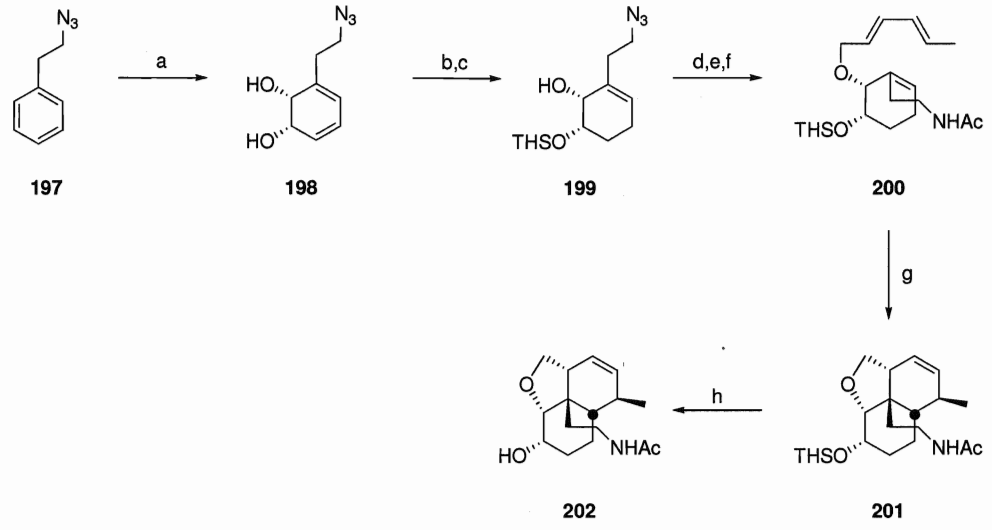


Figure 32. Hudlicky's Diels-Alder model studies towards the synthesis of morphine alkaloids.

Dienediol **190**, obtained by whole-cell mediated dihydroxylation of toluene served as starting material for both studies. Intramolecular Diels-Alder reaction of tetraene **193** gave compound **194**. The proposed Cope rearrangement could only be effected after deprotection of the alcohol functionality followed by oxidation. Heating of compound **195** in xylenes to 250 °C gave a single diasteremore, which was further reduced to give alcohol **196**, which possess four stereocenters of the morphine skeleton in the correct configuration.

In a similar model study triene **191** was rapidly assembled from toluene diol **190** and intramolecular Diels-Alder cyclization gave tricyclic compound **192**. The assignment of the stereochemistry of compound **192** was based on NOE-correlations and was revised in 1998, after a more advanced model study was conducted. Incorporation of the ethylamino bridge in the more advanced study was easily achieved by substitution of the starting material for whole cell fermentation from toluene to (2-azidoethyl)benzene (**197**). Selective reduction of the unsubstituted double bond, followed by protection of the distal hydroxyl group as its silyl ether led to the isolation of azide **199**. The precursor for the intramolecular Diels-Alder reaction compound **200** was rapidly assembled by reaction with sorbyl bromide, followed by Staudinger reduction and protection of the resulting primary amine. Heating compound **200** in toluene in a sealed tube to 230 °C for 20 hours gave the tricyclic intermediate **201**, which was further deprotected by TBAF treatment to yield compound **202**.



Reagents and Conditions: a) *Escherichia coli* JM109 (pDTG601); b) potassium azodicarboxylate (PAD), AcOH, MeOH (72%); c) THS-Cl, imidazole, DMF (99%); d) NaH, sorbyl bromide, THF (62%); e) PhP_3, H_2O (66%); f) Ac_2O, py (quant.); g) toluene, sealed tube. 230 °C (62%); h) TBAF, THF.

Scheme 14. Hudlicky's synthesis of tricyclic compound **202**.

X-ray single crystal structure analysis of free alcohol **202** revealed that the intramolecular Diels-Alder reaction had proceeded through an *exo*-transition state and not through an *endo*-transition state as originally assumed. At this point, repetition of the previously reported cyclization of intermediate **191**, followed by liberation of the free hydroxyl group, allowed for the isolation of crystalline compound **204**. X-ray crystal structure analysis of compound **204** revealed that the cyclization proceeded through the expected *exo*-transition state, in analogous fashion to amide **200**.

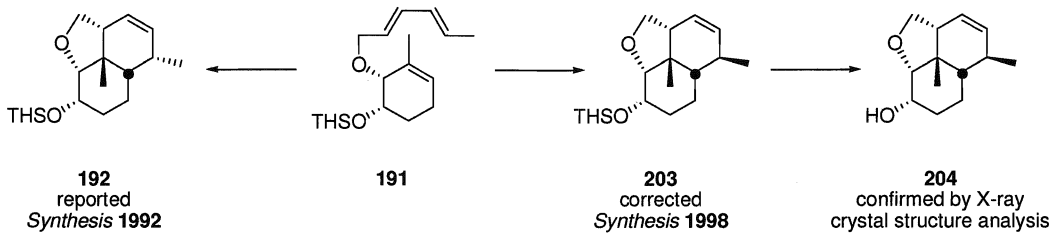
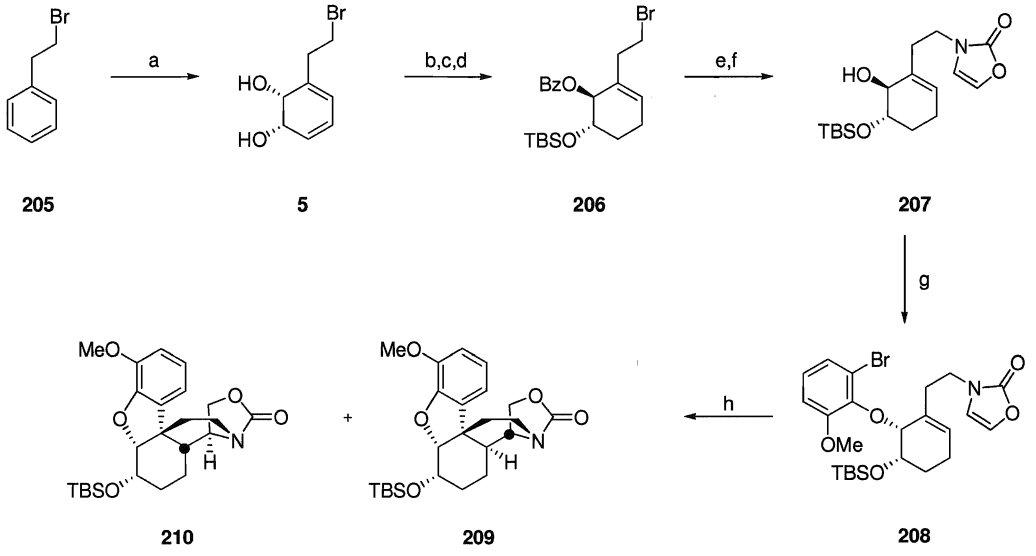


Figure 33. Structural revision of compound **192**.

Although this approach did not allow for the total synthesis of morphine, it highlights the efficient combination of enzymatic and traditional organic transformations to produce tricyclic compound **201**, which contains all of the five stereocenter of morphine alkaloids in their correct absolute configuration.

Radical cyclizations

Inspired by Parker's strategy, the Hudlicky group designed a tandem radical cyclization approach to morphine alkaloids. The homochiral diol **5**, available from whole cell fermentation of β-bromoethylbenzene (**205**), was chosen as the starting material because the configuration of each hydroxyl group can be easily manipulated by Mitsunobu reactions. Diimide reduction and selective protection of the distal hydroxyl group followed by Mitsunobu inversion of the allylic hydroxyl group furnished compound **206**. Alkylation of this material with oxazolidone and hydrolysis of the benzoate group gave the C-ring fragment of the morphine alkaloid. The aromatic portion was installed by a low yielding second Mitsunobu reaction to set the stereochemistry of the C-5 center. Treatment of compound **208** under radical conditions gave a complex mixture of more than six compounds.



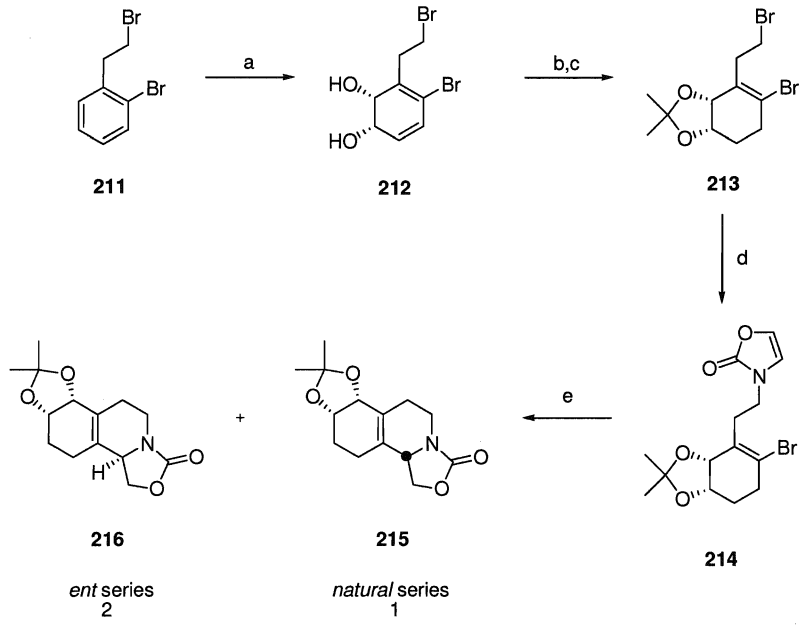
Reagents and Conditions: a) *Escherichia coli* JM109 (pDTG601) (10g/L); b) PAD, AcOH, MeOH (80%); c) TBSOTf, Hünig's base, DCM (47%); d) BzOH, *n*-Bu_3P, DEAD, THF (84%); e) NaOH; f) 2-oxazolidone, NaH, DMSO (71%); g) 2-bromo-6-methoxy phenol, *n*-Bu_3P, DEAD, THF (28% over two steps); h) $(TMS)_3SiH$, AIBN, benzene, 140 °C, sealed tube (15%).

Scheme 15. Hudlicky's first generation radical cyclization approach.

Separation of the mixture by chromatography gave predominantly diastereomer **209** in modest yield, whose *epi*-C-14 configuration was established by NMR analysis. The presence of a second diastereomer **210** was also detected, however the minute amounts did not allow for an unambiguous identification.

A second generation approach was designed which addressed the problems of stereoselectivity as well as the low yield of the tandem radical cyclization closure. The approach relied on two independent radical cyclizations. The first radical cyclization was designed to give an advanced isoquinoline intermediate, which was further reacted with an appropriate aromatic portion to allow for the second radical based ring closure. *o*-Bromo-β-bromoethylbenzene (**211**) was subjected to biodihydroxylation and was further converted to the precursor for the first radical

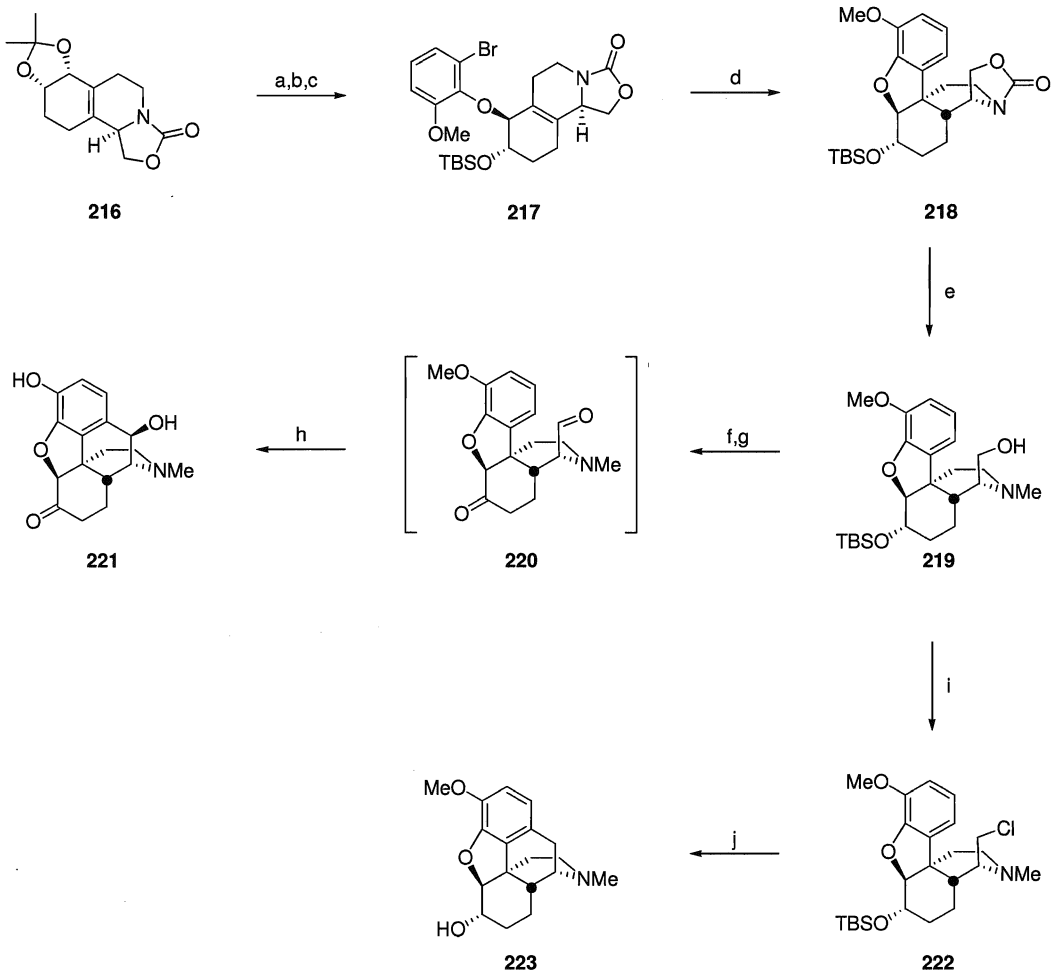
cyclization **214** in three steps. Exposure of compound **214** to *n*-Bu_3SnH and AIBN provided two octahydroisoquinolines **215** and **216**, in a ratio of 2 : 1 in favour of the isomer possessing the *epi*-C9 configuration.



Reagents and Conditions: a) *Escherichia coli* JM109 (pDTG601) (0.2g/L); b) PAD, AcOH, MeOH (50%); c) 2,2-dimethoxypropane, *p*-TsOH (90%); d) 2-oxazolidone, NaH, DMSO (38%); e) *n*-Bu_3SnH, AIBN, benzene, reflux (87%).

Scheme 16. Hudlicky's second generation radical cyclization approach.

The lack of stereocontrol was attributed to the negligible steric effect of the acetonide moiety. Because of the greater availability of the *epi*-isomer **216**, Hudlicky and coworkers decided to pursue the synthesis of *ent*-morphine.



Reagents and Conditions: a) Dowex 50X8-100, MeOH (94%); b) TBSOTf, Hünig's base, DCM (85%); c) 2-bromo-6-methoxy phenol, *n*-Bu_3P, DEAD, THF (94%); d) *n*-Bu_3SnH, AIBN, benzene, reflux (47%); e) DIBAL-H, DCM, (87%); f) TBAF, THF (quant.); g) $(COCl)_2$, DMSO, NEt_3, DCM (66%); h) TFA (58%); i) MsCl, NEt_3 (87%); j) $AlCl_3$, benzene.

Scheme 17. Hudlicky's syntheses of *ent*-morphinans **221** and **223**.

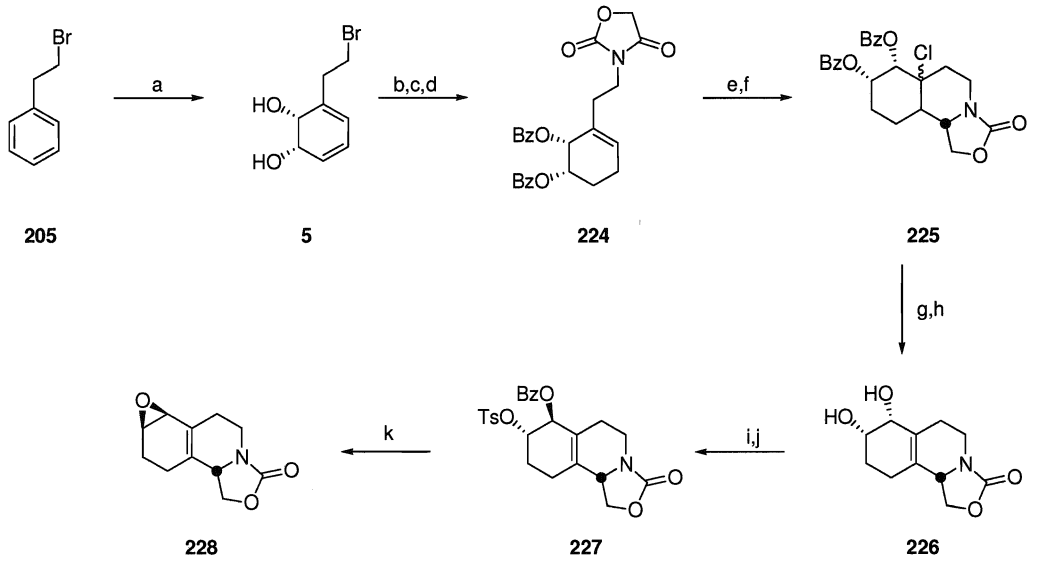
The A-ring fragment was installed *via* Mitsunobu alkylation to furnish the precursor for the second radical cyclization, ether **217**. As expected, exposure of aryl bromide **217** to *n*-Bu_3SnH and AIBN provided a single diastereomer in 47% yield. It has to be mentioned that the combined yields of both ring closures were higher than those of the radical cascade from the first generation and the second cyclization proceeded

stereospecifically to give a single diastereomer. The synthesis of the complete *ent*-morphinan skeleton was achieved by reduction of the oxazilidinone unit to give the required amino methyl group, as well as a primary alcohol at C-10. Double Swern oxidation of the diol intermediate yielded the ketoaldehyde **220**, which was treated with trifluoromethane sulfonic acid to induce Friedel-Crafts closure of the C-10 - C-11 bond. Alternatively, the C-10 - C-11 bond closure was affected by mesylation with *in situ* chloride displacement to give compound **222**, which upon treatment with aluminium trichloride in benzene gave a mixture of morphinan **223** and the corresponding free phenol.

Heck-cyclizations[110]

Since the results of the radical based approach showed that intermediates already containing the C-9 - C-14 bond did not give the correct stereochemistry at C-14 center, the Hudlicky group investigated a Heck cyclization strategy. Similar to the radical cyclization approaches, the B- and C- ring of the morphine skeleton were envisioned to be derived from an isoquinoline synthon. Cyclohexadiene diol **5** derived from microbial dihydroxylation of β-bromoethylbenzene (**205**) was chosen as the starting material. It was readily converted to heterocycle **224** by reduction, esterification of both hydroxyl groups, and displacement of the bromine with oxazolidine-1,4-dione. Selective reduction of the more reactive amide carbonyl followed by treatment of aluminium trichloride afforded the isoquinoline derivative **225** through an iminium ion cycloaddition. DBU mediated elimination of the alkyl

chloride afforded diol **226**, upon deprotection of the benzoate groups, as shown in Scheme 18.

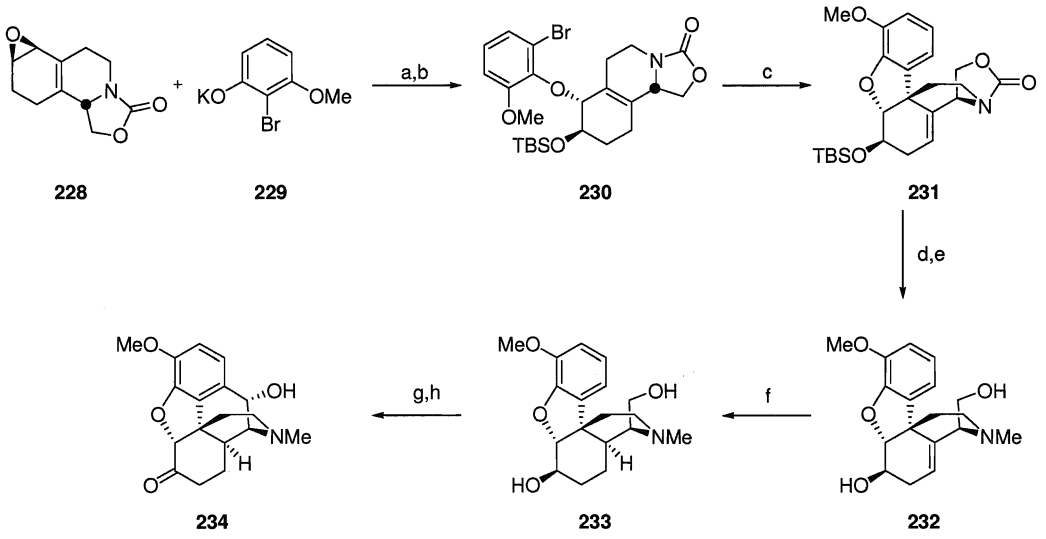


Reagents and Conditions: a) *Escherichia coli* JM109 (pDTG601) (10g/L); b) PAD, AcOH, MeOH (80%); c) benzoic acid, DCC, DCM (83%); d) oxazolidine-1,4-dione, tetramethylguanidine, THF (77%); e) $NaBH_4$, MeOH, THF (quant.); f) $AlCl_3$, DCM (57%, *cis* : *trans* = 3.7 : 1); g) DBU, DMSO (25%); h) NaOMe, THF (85%); i) TsCl, py, DMAP (45%); j) benzoic acid, PPh_3, DEAD, THF (84%); k) NaOMe, MeOH, THF (65%).

Scheme 18. Hudlicky's Heck cyclization approach.

Bis-protected *trans* diol **227** was generated by tosylation of the distal alcohol followed by Mitsunobu inversion of the allylic hydroxyl group. This protocol allowed for the efficient synthesis of β-epoxide **228** upon treatment of compound **227** under basic conditions. The attachment of the A-ring fragment was achieved by regio and stereoselective opening of epoxide **228** with the potassium salt of bromoguaicol **229** to give ether **230**, which contains all the necessary carbons in the morphine skeleton with the correct stereochemistry at C-5 and C-9. Intramolecular Heck cyclization furnished pentacyclic carbamate **231** in good yield. DIBAL-H reduction followed by

treatment with TBAF gave compound **232**, which was then subjected to hydrogenation.



Reagents and Conditions: a) DME, 18-crown-6 (80%); b) TBSOTf, Hünig's base, DCM (74%); c) $Pd(PPh_3)_4$, Proton Sponge™, toluene (74%); d) DIBAL-H, DCM (69%); e) TBAF, THF, H_2O (77-86%); f) H_2, PtO_2, AcOH (64%); g) $(COCl)_2$, DMSO, NEt_3, DCM; h) TFA (30% over two steps).

Scheme 19. Hudlicky's synthesis of 10-hydroxy-14-*epi*-hydrocodone (**234**).

Contrary to the expected sterochemical outcome, compound **233** was obtained with the α-configuration at C-14 carbon. To complete the synthesis of the morphine skeleton, the same protocol used for the final steps in the second generation radical cyclization approach, was applied to compound **233**. Double Swern oxidation followed by treatment with trifluoromethanesulfonic acid finished the synthesis of 10-hydroxy-14-*epi*-hydrocodone **234** in 14 steps from diene diol **5**.

2.2.4 Pharmacology of Morphine Alkaloids

Classification of Opioid Analgesics

Classification of opioids is usually made according to the receptors (μ-, κ-, and δ-receptors) to which they bind, the consequences of the binding (agonist, partial agonist, mixed agonist-antagonist, and antagonist) and their way of production (opiates, semi-synthetic, and fully synthetic opioids).

Opioid Receptors

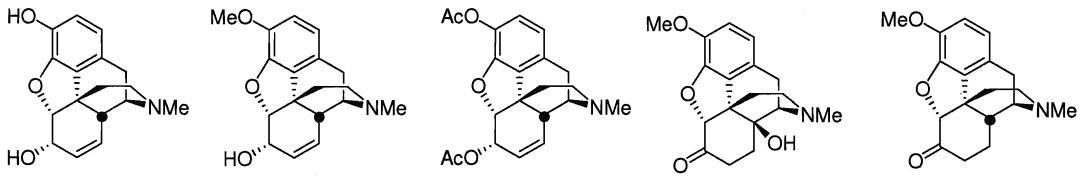
Opioids cause their biological response by binding to specific receptors in the human body. Through careful structure-action analysis, the British medicinal chemist Arnold Beckett postulated in the mid 1950s that morphine-like analgesics worked through "analgesic receptors".[111] By the mid-1960s Goldstein and coworkers suggested that the different actions of opioid agonists, antagonists, and mixed agonist-antagonists could be best explained by their action with different opioid receptors. Their efforts to prove this hypothesis failed because of the unavailability of radio-labelled ligands with high enough specific activity.[112] In 1973 three groups succeeded almost simultaneously in proving the existence of different opioid binding sites in the central nervous system.[113] The suspicion that morphine (**1**) was not a natural opioid receptor ligand and only mimicked endogenous analgesic compounds was confirmed by Kosterlitz and coworkers in 1975.[114] They could show that extracts of mammalian brain tissue contained factors that inhibited acetylcholine release from nerves innervating the guinea pig ileum. The factors responsible for this action were

identified as two peptidic enkephalins; met-enkephalin (Tys-Gly-Gly-Phe-Met) and leu-enkephalin (Tys-Gly-Gly-Phe-Leu). Morphine (**1**) showed similar inhibition rates in this study and the effect could be reversed by the addition of a known morphine anatagonist such as naloxone (**13**). Soon after the discovery of the two enkephalins other peptidic endogenous opioid receptor ligands could be identified. There are three families of endogenous opioid peptides; enkephalins, dynorphins, and β-endorphins. These peptides are known as endorphins, a shortened form of endogenous morphinoids.[115] In contrast, an opioid is any exogenous drug (natural or synthetic) that binds to an opioid receptor and produces morphine-like effects. The analgesic potency of the various opioids or endorphins correlates with the affinity of the substance for the opioid receptor. There is general agreement on the existence of at least three different types of opioid receptors: μ, κ, and δ-receptors.[116] All of the opioid receptors were isolated, purified, sequenced and cloned in the mid 1990s.[117] The comparison of the amino acid sequences of the three opioid receptors revealed that they show high structural homology with each other. Pain relief effects are mediated by all three receptor types but to a different degree.[118] Overall, it seems that the μ-receptor agonists display not only the best and strongest analgesic actions but also the highest abuse liability. μ-Receptor ligands, such as morphine, exert powerful effects on the brain, the brain stem (where it slows respiration) and the spinal cord (where it exerts a strong analgesic action). In contrast, the δ-receptors are thought to modulate the activity of μ-receptors and have a lower efficiency in mediating pain relief. κ-Receptors are known to mediate analgesic effects in peripheral tissues.[66]

All opioid receptors belong to a superfamily of G protein-coupled receptors, all of which posses seven membrane-spanning regions. The primary action of opioid receptor activation is reduction or inhibition of neurotransmission, which occurs largely through opioid-induced-presynaptic inhibition of neurotransmitter release. Gutstein and coworkers demonstrated that opioids strongly activate important intracellular cascades, which induce changes in cellular function to the level of nuclear proteins. Changes were different for each receptor type and that may explain the differences in receptor function.[119]

Agonists

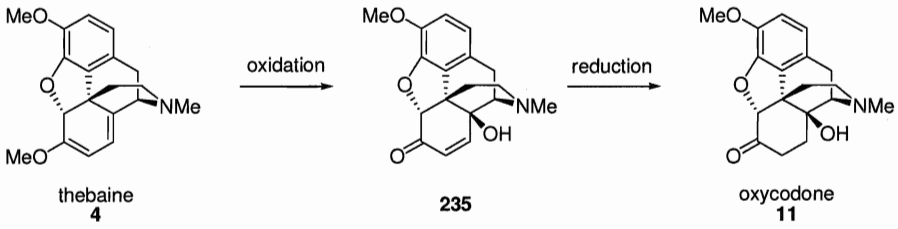
Substances which bind to a receptor and induce changes in the cell characteristic of the natural ligand for the receptor are called agonists. All strong opioid analgesics, morphine representing the prototype, have agonistic effects on the μ-receptor. Despite the desired analgesic effects, μ-receptor agonism results in respiratory depression, euphoria, sedation, nausea, addiction, and constipation. Examples of opioid agonists are the naturally occurring opiates morphine (**1**) and codeine (**2**), as well as the semi-synthetic opioids diacetylmorphine (**10**), oxycodone (**11**), and hydrocodone (**12**).



morphine **1** | codeine **2** | diacetylmorphine **10** | oxycodone **11** | hydrocodone **12**

Figure 34. Opioid agonists.

Oxycodone (**11**) was first synthesized by Freund and Speyer in 1916.[10a] Treatment of thebaine (**4**) with hydrogen peroxide under acidic conditions led to the isolation of oxycodeinone (**235**), which was further subjected to hydrogenation to give oxycodone (**11**) in two steps, as shown in Scheme 20. The original protocol has been exhaustively optimized by academic as well as industrial research groups and numerous oxidative conditions have been reported.[120] Similar to morphine (**1**), oxycodone (**11**) is used for the treatment of medium to severe pain.[121]



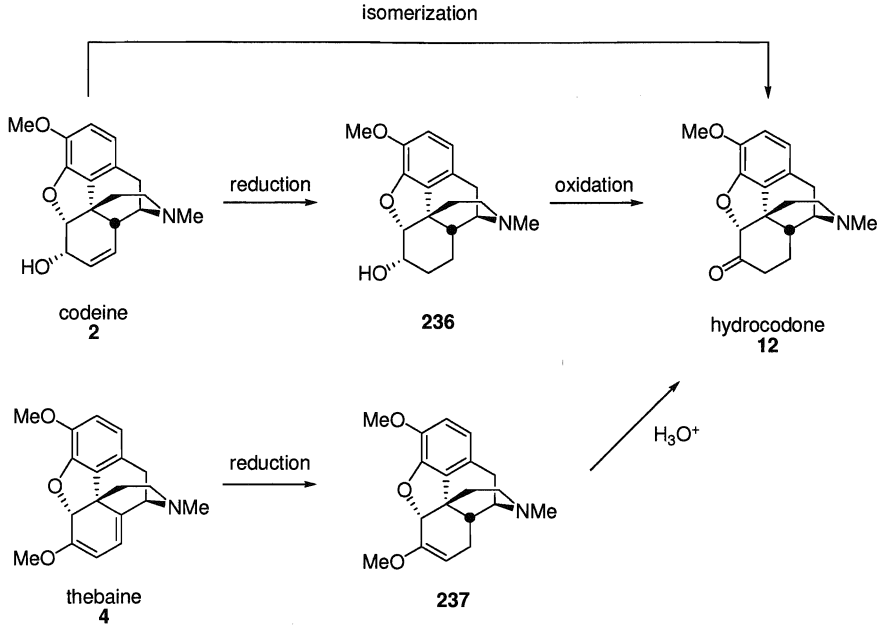
thebaine
4

235

oxycodone
11

Scheme 20. Synthesis of oxycodone (**11**) from thebaine (**4**).

The first synthesis of hydrocodone (**12**) was reported by Mannich and Löwenheim in 1920.[10b] Nowadays hydrocodone is mainly manufactured by three different routes. Reduction of codeine (**2**) to dihydrocodeine (**236**) followed by oxidation of the alcohol functionality yields hydrocodone (**12**).[122] Alternatively codeine can be isomerized to hydrocodone upon treatment with transition metal catalysts.[123] The third approach utilizes thebaine (**4**) as starting material. Diimide reduction, followed by hydrolysis of the enol ether functionality of 8,14-dihydrothebaine (**237**) yields hydrocodone (**12**),[124] as shown in Scheme 21.



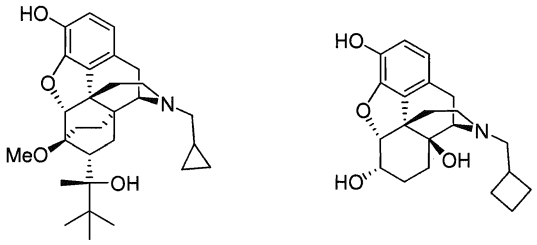
Scheme 21. Synthesis of hydrocodone (**12**).

Partial Agonists and Mixed Agonist-Antagonist

In contrast to pure agonists, which have a strong activity at the μ-receptor, partial opioid agonists have a lower activity at the same receptor and therefore lower analgesic activity. Buprenorphine, the prototype of a partial opioid agonist, has limited stimulation of the μ-receptor, binds very strongly to the receptor and has a very long duration of action. As a partial agonist there is a ceiling to its analgesic effectiveness as well as to its potential for inducing euphoria and respiratory depression. Buprenorphine (**238**) preparations are mainly used for the treatment of opioid dependency.[125]

A mixed agonist-antagonist opioid produces an agonistic effect at one receptor and an antagonistic effect at another. Preferable for clinical purposes are μ-receptor antagonists and κ-receptor agonists, such as the semi-synthetic opioid nalbuphine

(**239**), as drugs for opioid-dependent individuals. The problems associated with mixed agonist-antagonist opioids are the incidences of adverse psychotomimetic side effects, such as dysphoria, anxiety reactions, and hallucinations, limiting their therapeutic use but increasing their attraction for illicit use.[66]



buprenorphine
238

nalbuphine
239

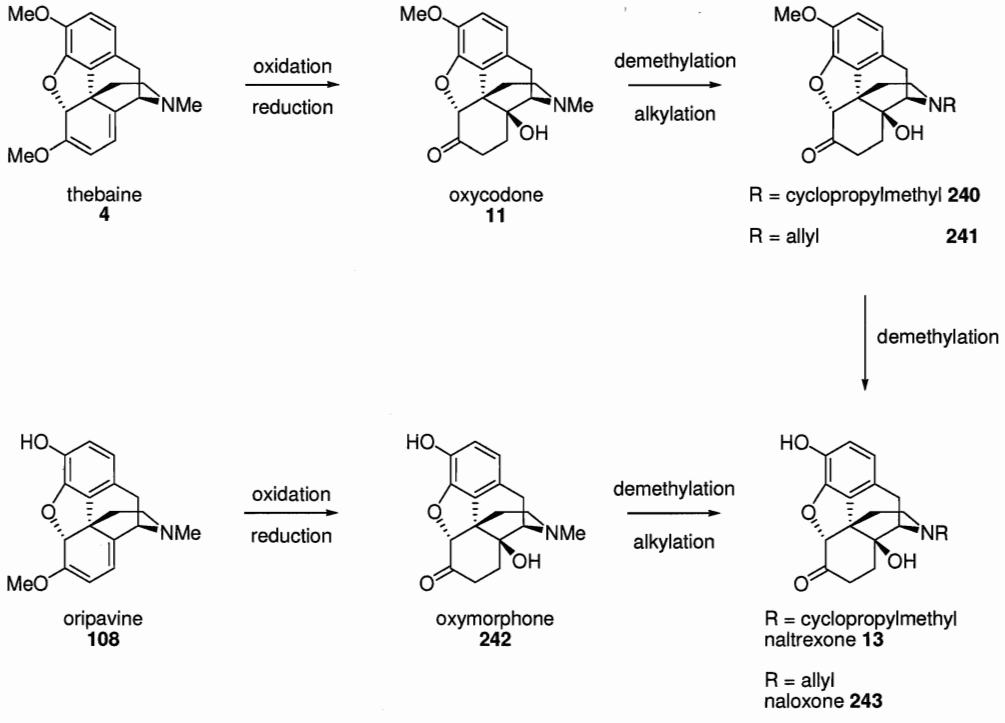
Figure 35. Partial agonists and mixed agonist-antagonist opioids.

Antagonists

Pure antagonists have high affinity for a receptor but after binding they elicit no change in cellular functioning. In the case of opioids, the antagonist, such as the semi-synthetic opioids naltrexone (**13**) and naloxone (**243**), competes with the μ-agonist for the receptor, precipitating withdrawal in an opioid-dependent person and reversing any analgesia caused by the agonist.[66]

The syntheses of naltrexone (**13**) and naloxone (**243**) follow the same strategy since only the *N*-substituents differ in both semi-synthetic opioid antagonists. Various protocols have been reported and generally thebaine (**4**) or oripavine (**108**) are chosen as starting materials.[126] They are further transformed to the corresponding 14-hydroxylated analogues oxycodone (**11**) or oxymorphone (**242**). Demethylation of the

tertiary amine followed by alkylation furnishes the *N*-alkyl 14-hydroxylated opioids. In the case of the *N*-alkyl noroxycodone derivatives **240** and **241** an additional step, the 3-*O*-demethylation is necessary for the synthesis of the opioid antagonists, as shown in Scheme 22.

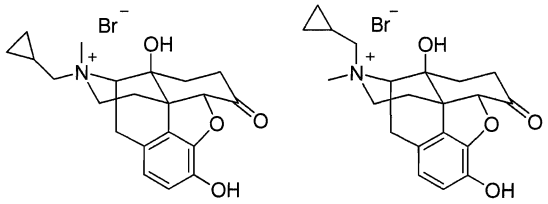


Scheme 22. Syntheses of naltrexone **13** and naloxone **243**.

Naloxone (**243**) is the prototype opioid antagonist with only effects on opioid-dependent people. Naloxone is neither an analgesic nor subject to abuse. Its duration of action is very brief (in the range of 15 to 20 minutes), therefore it must be administered at short intervals. Naloxone is predominantly used for the treatment of acute opioid intoxication (overdoses) to reverse the opioid-induced respiratory depression.

The actions of naltrexone (**13**) resemble those of naloxone, but it has a long duration of action as well as being absorbed well orally. Naltrexone is used for the treatment of heroin dependency as well as alcoholism.[66]

Goldberg and coworkers and, more recently, Cantrell and coworkers reported the syntheses of methylnaltrexone from naltrexone (**13**) with appropriate methylating reagents such as methyl iodide or methyl bromide.[127,128] Although quaternized morphine alkaloids occur as two diastereomers (the quaternized nitrogen represents an additional chiral center) both groups remained silent about the possible diastereomeric salts and reported a single isomer. In 2006, the first two "diastereoselective" syntheses of (*R*)- and (*S*)-methylnaltrexone were reported. [129] The reaction of naltrexone with methylbromide yielded predominantly (*R*)-methylnaltrexone (**244**),[126a] presumably the same compound as reported by Chantrell and Goldberg and the addition of cyclopropylmethylbromide to oxymorphone gave the (*S*)-isomer **245**.[126b]



(*R*)-methylnaltrexone **244** (*S*)-methylnaltrexone **245**

Figure 36. (*R*)- and (*S*)-methylnaltrexone.

Not surprisingly, the (*S*)-isomer of methylnaltrexone exhibited different activities than those reported previously in the literature. These findings are in accordance with Bianchetti and coworkers, who studied the *in vivo* as well *in vitro* activity of three pairs of diastereoisomers of quaternary opioid antagonists derived from levallorphan,

nalorphine, and naloxone.[130] Only the diastereomers prepared by methylation of the alkylated morphine derivative showed antagonistic activities.

As a quaternary amine, methylnaltrexone has restricted ability to cross the blood-brain barrier[131] and therefore reverses the undesired side effects of opioids that are mediated by receptors located in the periphery, without compromising centrally mediated effects of opioid analgesia or precipitating withdrawal.[132]

3. Discussion

Presented here are our latest efforts in the exploration of the reactivity of the Burgess reagent with epoxides as well as our most recent accomplishments in the synthesis of morphine alkaloids and derivatives. Additional novel methodologies, especially designed for the synthesis of opioids, will be discussed.

3.1 Burgess Reagent

3.1.1 Introduction

The Hudlicky group was able to propose a mechanism to account for the formation of 7-membered sulfamidates from the reaction of the Burgess reagent with either epoxides or 1,2-diols[21] and suggested that the latter compounds yield, in some cases, 7-membered sulfamidates and not regioisomeric pairs of 5-membered sulfamidates, as has been erroneously reported.[18]

In the case of 1,2-diols derived from various styrenes, the 7-membered sulfamidates are minor products, but their relative amounts increase with deactivation of the aromatic ring.[18] The discrepancies in the initial structural assignments are shown in Figure 37. It was proposed that 7-membered sulfamidates may be derived from epoxides and not from the starting diols. That the *in situ* formed epoxides may indeed be the intermediates has been proven by performing the reaction on optically active

styrene oxide as well as on the optically pure diol derived from styrene.[21] In each case, an inversion of configuration occurred at the benzylic center.

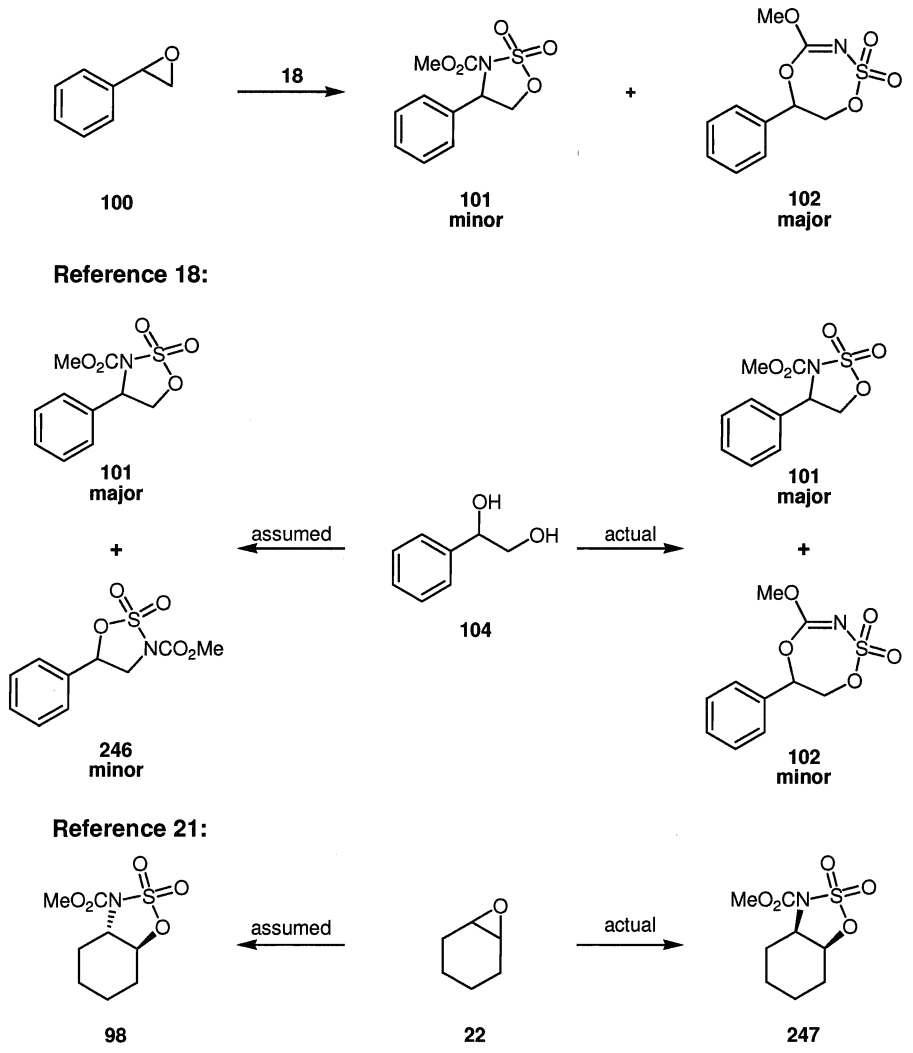
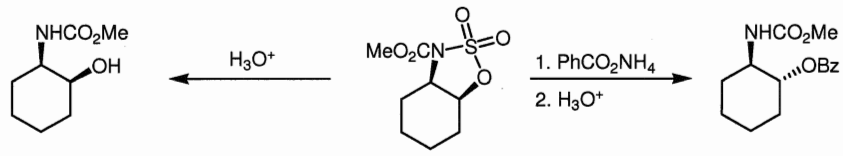


Figure 37. Sulfamidate formation from oxiranes and 1,2-diols. Assumed (reported) and actual (corrected) products.

3.1.2 Reactive Options of the Burgess Reagent with Epoxides

The reaction of the Burgess reagent with oxiranes derived from cyclic compounds was of special interest because it could serve as a source of both *cis*- and *trans*-amino alcohols (Figure 38).[22] As sulfamidates possess similar reactivity to cyclic sulfates[133] at the oxygenated center, we reasoned that such a transformation would provide for eventual access to homochiral amino alcohols in both diastereomeric series.

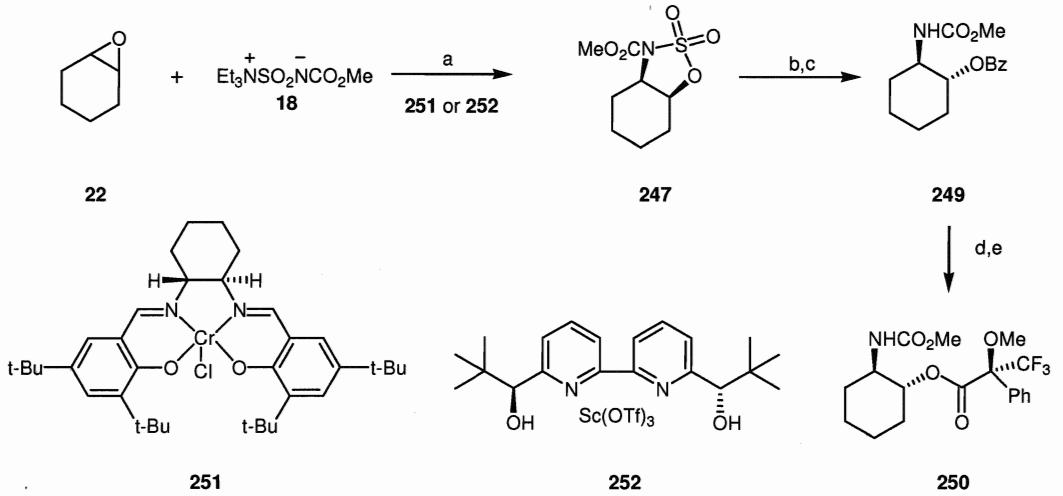


248 (+) and (-) **247** **249** (+) and (-)

Figure 38. Proposed syntheses of *cis*- and *trans*-amino alcohols from cyclic sulfate.

In order to study the extent of asymmetric induction, we tested Jacobsen's[134] salen catalyst (**251**) as well as the scandium chelate of the C_2-symmetric bipyridine[135] **252** reported to act as an activating Lewis acid in reactions with epoxides. The use of 0.1 equivalents of Jacobsen's catalyst (**251**) along with Burgess reagent (**18**) and cyclohexene oxide in THF or diethyl ether at either room temperature or reflux led to low yields (20%) of racemic sulfamidates, with no sign of asymmetric induction. Similar results were obtained when cyclohexene oxide was reacted with the Burgess reagent in the presence of 0.1 equivalents of Bolm's catalyst (**252**) in either THF or DCM at room temperature. In order to determine the enantiomeric excess of the products, cyclic sulfamidate **247** was treated with ammonium benzoate in DMF,

followed by acid hydrolysis to yield protected amino alcohol **249**. Basic hydrolysis of the benzoate ester followed by EDC mediated esterification with (*R*)-(+)-Mosher's acid gave a mixture of diastereomers (1:1) as assessed by ^{19}F-NMR and GC/MS analysis.

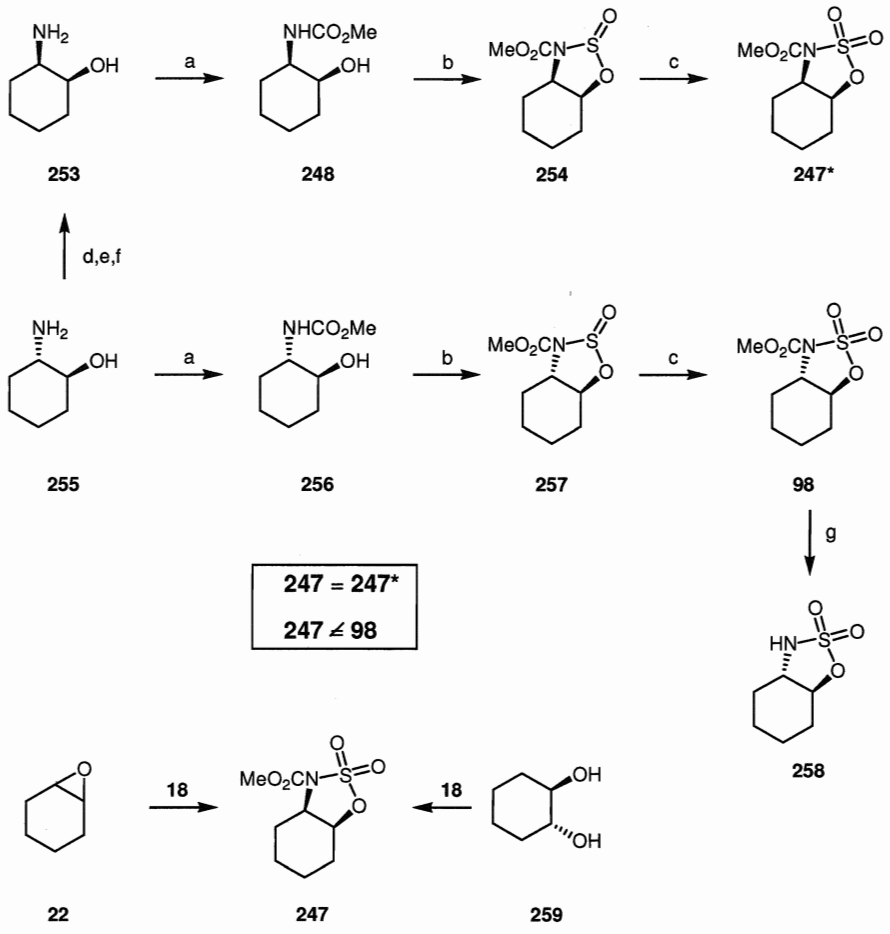


Reagents and Conditions: a) THF, 48 hrs; b) $PhCO_2^- NH_4^+$, DMF, 45 °C, 12 hrs; c) THF, H_2O, conc. H_2SO_4, rt, 6 hrs; d) 1M NaOH in MeOH, 2 hrs; e) (*R*)-(+)- Mosher's acid, EDC, DMAP, DCM, 0 °C to rt, 18 hrs.

Scheme 23. C_2-symmetric catalysts **251** and **252**.

One possible explanation for the complete lack of asymmetric induction in this reaction may be that the Burgess reagent itself acts as a Lewis acid, competing with and displacing the actual catalyst from the activated epoxide. Since 2.3 equivalents of the reagent are used and the concentration of the catalyst is only 10 mole percent, it is easy to see how the probability of developing a chiral substrate-catalyst complex is reduced, leading to the racemic product mixture which we observe.

At this stage of the project we have determined that the sulfamidates **247** are *cis*, not *trans* fused as originally reported in Hudlicky's 2003 publication.[21] The proof of the *cis* configuration of the cyclic sulfamidates derived from the reaction of the Burgess reagent with epoxides was easily achieved by preparing both authentic samples of *cis* and *trans* fused cyclic sulfamidates. The synthesis was straightforward and is shown in Scheme 24. *cis*-Sulfamidate **247*** was prepared from *cis*-aminoalcohol **253**, generated from the commercially available *trans*-isomer using Jacobsen's protocol.[136] Protection of the amine with methylchloroformate followed by reaction with thionylchloride and oxidation with ruthenium (III) chloride and sodium periodate, furnished *cis*-sulfamidate **247***. The *trans*-isomer **98**, was generated from commercially available **255** in a similar fashion. It became clear that **247** (Scheme 24) was identical to **247*** and not **98**. This argument eliminates the possibility of direct intramolecular sulfonation, which we have studied by dilution experiments and by varying substrate to reagent ratios. In all cases, it was the *cis*-isomer of sulfamidate that was formed from epoxides and not the expected *trans*-isomer. Thus the mechanism operating on epoxides is similar in concept but not the same as that operating on diols. *trans*-Cyclohexane diol **259** yielded exclusively *cis*-sulfamidate **247**, whereas *cis*-cyclohexane diol did not give the corresponding cyclic sulfamidate since the bis-sulfonated intermediate cannot undergo a S_N2 displacement. Two other observations are worth noting: First, the *trans*-sulfamidate yielded **258** upon treatment with ammonium benzoate and not the expected "inverted" *cis*-disposed benzoate. Second, methylamine in acetonitrile also provided the free sulfamidate **258** under very mild conditions.



Reagents and Conditions: a) methylchloroformate, $NaHCO_3$, $CHCl_3/H_2O$; b) $SOCl_2$, CH_3CN, -40 °C; c) $RuCl_3 \cdot H_2O$, $NaIO_4$, CH_3CN/H_2O; d) Ac_2O; e) $SOCl_2$; f) 10% HCl; g) $PhCO_2^- NH_4^+$, DMF, 45 °C, 12 hrs, then THF, H_2O, conc. H_2SO_4, rt.

Scheme 24. Preparation of standards **98** and **247***.

Possible mechanistic options for the reaction of the Burgess reagent with epoxides are shown in Figure 39. Two different pathways of the reaction of oxiranes with the Burgess reagent are possible.

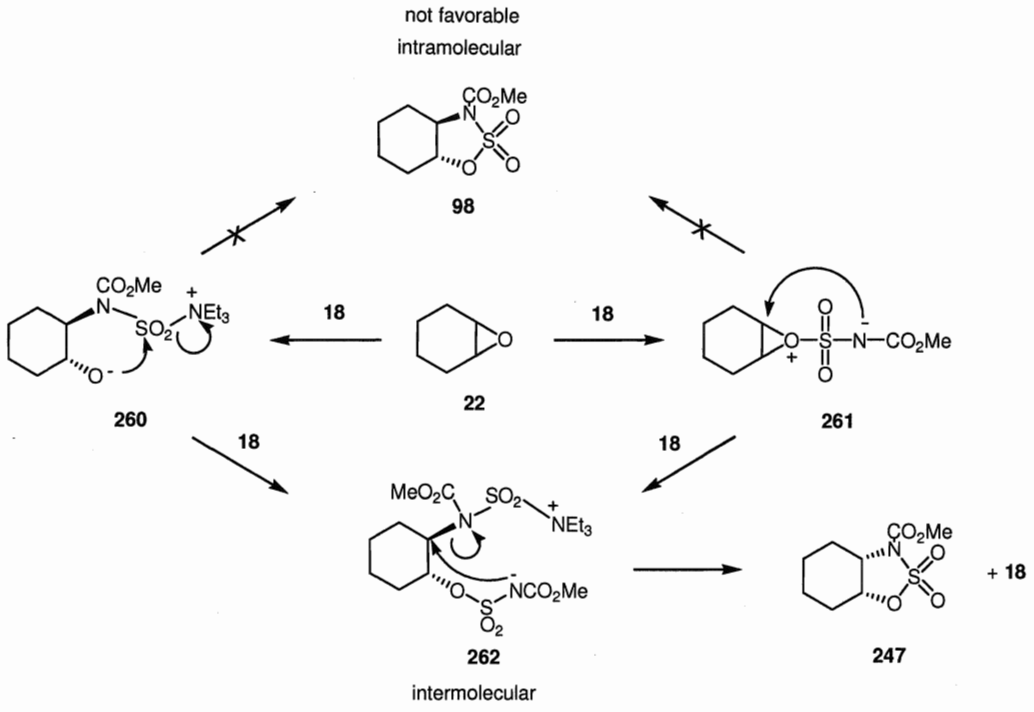


Figure 39. Possible mechanistic options for the formation of *cis*-sulfamidates from epoxides.

The activation of the epoxide to give compound **261** is likely and supported by preliminary calculations.[137] Another option is the direct nucleophilic attack of the Burgess reagent yielding compound **260**, although this process has a higher activation energy than the formation of **261**. In both cases, an intramolecular attack is rather unlikely; instead a second equivalent of the Burgess reagent reacts to give intermediate **262**. Rather than ejecting triethylamine by an intramolecular sulfonation, alkoxide **260** reacts with the second equivalent of the reagent to produce **262**, formed also from the opening of activated epoxide **261**. Displacement of the Burgess reagent then occurs from the site of initial oxirane opening. A similar mechanism has also been proposed for the reaction of **18** with diols and Hudlicky and coworkers have shown that epoxides may be intermediates in these reactions.[21] A study of

concentration and stoichiometry dependence indicated that indeed at least two equivalents of **18** are essential; with one equivalent of the reagent the yields were halved.

3.1.3 Chiral Version of the Burgess Reagent and its Reactions with Epoxides[138]

After finding that the two C_2-symmetric catalysts proved to be completely ineffective in the asymmetric synthesis of five membered sulfamidates from epoxides, we turned to the chiral-auxiliary-based approach, recognizing that in this fashion both enantiomers of the products could be obtained and converted to valuable amino alcohol derivatives (both *cis* and *trans*).[22]

Several chiral auxiliary versions of the Burgess reagent have been prepared, such as the menthol analogue **21**, as well as the camphor-derived carbamate **263** and the two cyclic forms **265** and **266** prepared from diene diol **264** (Figure 40).[139] However, the reaction of the Burgess variants derived from diene diol **264** with oxiranes proved erratic and we therefore focused on the investigations of reactions of the menthyl as well as camphor derivatives of the Burgess reagent. Both versions of the Burgess reagent **21** and **263** were reacted with cyclohexene oxide producing a 1:1 mixture of diastereomers of *cis*-fused sulfamidates (Scheme 25). The separation of diastereomers at this stage, derived from either the menthol or camphor version of the Burgess reagent was arduous, and the mixtures were converted to their benzoate derivatives, because the sulfamidates resemble cyclic sulfates in their reactivity.[133]

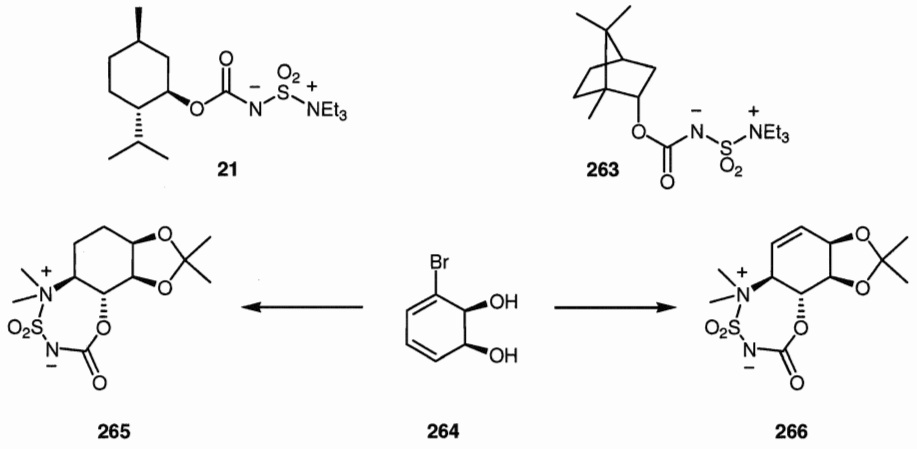
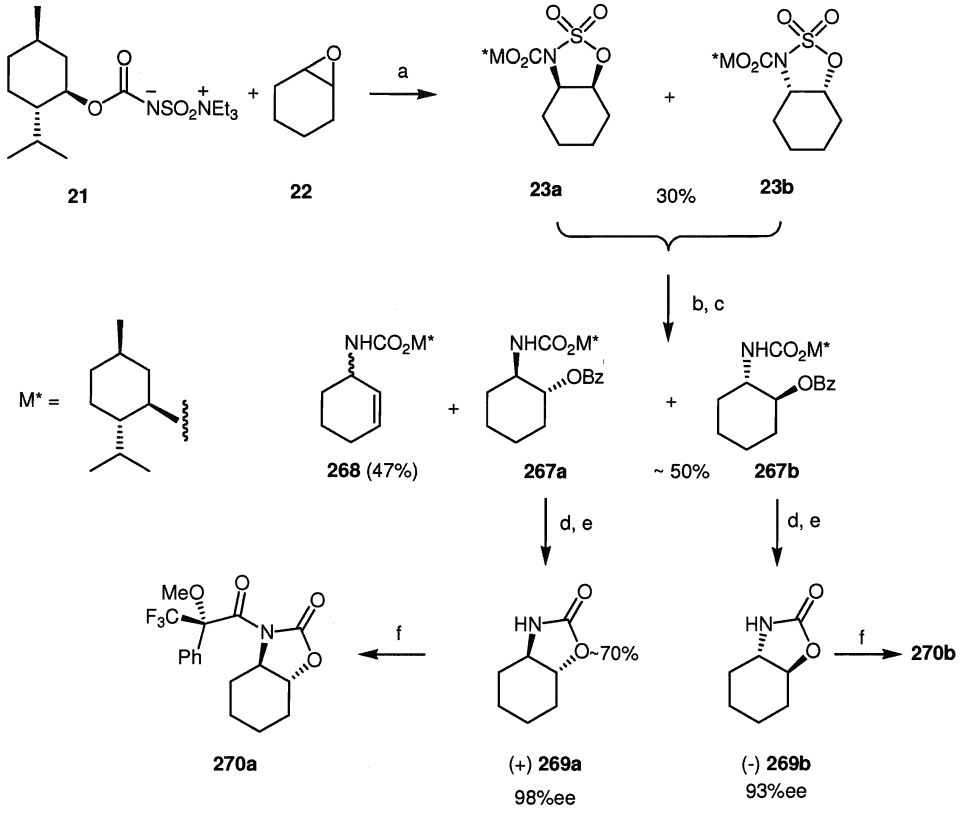


Figure 40. Chiral versions of the Burgess reagent.

No suitable conditions could be found for the separation of the benzoates bearing the camphor auxiliary group, however separation of benzoates **267a** and **267b** bearing the menthol auxiliary group was achieved by flash column chromatography. Conversion of **267a** and **267b** to the known cyclic carbamates **269a** and **269b** provided evidence of excellent enantiomeric excess in both amino alcohol products (optical rotations of **269a** and **269b** were higher than reported literature values). [140] Accurate determinations of enantiomeric purity were made by ^{19}F NMR evaluation of Mosher amides **270a** and **270b** and comparison with Mosher amide data obtained for the racemate of **269**. A moderate yield of the allylic amine derivative **268** was obtained from the reaction of sulfamidates **23a** and **23b** with ammonium benzoate. Simply heating a mixture of **23a** and **23b** in DMF at 45 °C for 18 hours provided **268** in moderate yield (55%) along with recovered starting material.

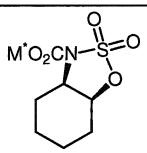
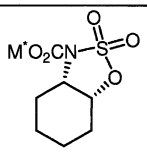
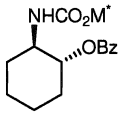
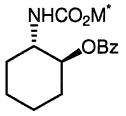
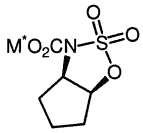
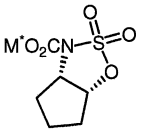
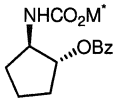
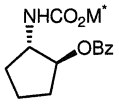
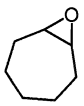
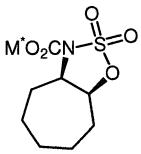
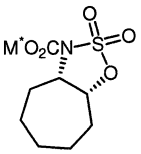
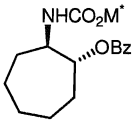
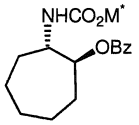
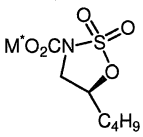
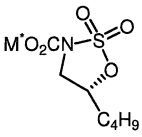
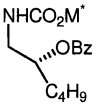
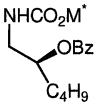
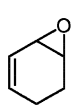
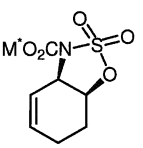
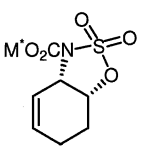
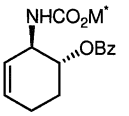
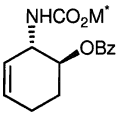


Reagents and Conditions: a) THF reflux, 1.5 hrs; b) $PhCO_2^-NH_4^+$, DMF, 45 °C, 12 hrs; c) THF, H_2O, conc. H_2SO_4, rt, 6 hrs; d) 1M NaOH in MeOH, 2 hrs; e) NaH, THF reflux, 18 hrs, f) *n*-BuLi, 0 °C, 30 min, (*S*)-(+)- Mosher's acid chloride, -78 °C to rt.

Scheme 25. Reaction of the menthol based Burgess-type reagent with cyclohexene oxide.

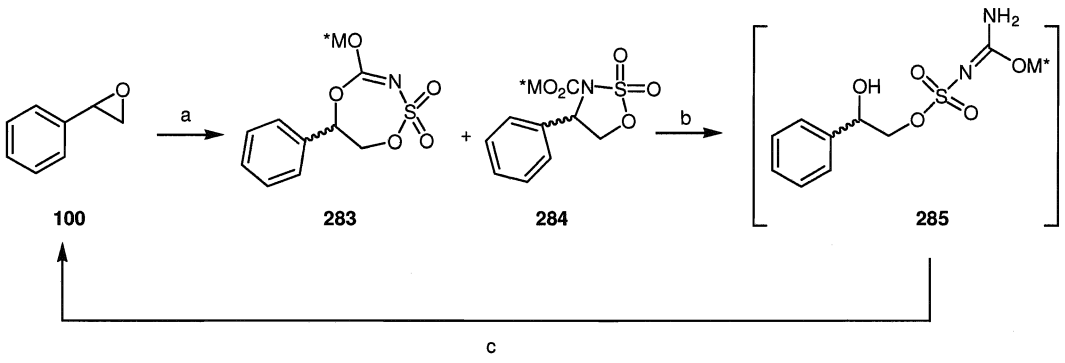
A more detailed study of this reaction revealed that treatment of **23a** and **23b** under strongly acidic conditions (6N HCl : dioxane; 1:1) led to the isolation of racemic **268** in nearly quantitative yield. This is another useful result as it allows for the direct conversion of epoxides to derivatives of allylic amines. In cases where the diastereomers are more easily separated, both enantiomers of allylic amine carbamates should therefore become available. The results from the reactions of other oxiranes with menthyl Burgess reagent **21** are summarized in Table 1.

Table 1. Reactions of various oxiranes with the menthyl chiral-auxiliary version of the Burgess reagent.

Oxirane	Sulfamidates[a]		Benzoates		ee(%)[b] or de(%)[c]
					(+) 98 and (-) 93[b]
22	**23a** 30%	**23b**	**267a** 49%	**267b**	
					98 and 93[c]
271	**272a** 37%	**272b**	**273a** 52%	**273b**	
					93 and 92[c]
274	**275a** 35%	**275b**	**276a** 75%	**276b**	
					—
277	**278a** 22%[d]	**278b**	**279a**[d] 36%	**279b**[d]	
					(+) 94 and (-) 84[e]
280	**281a** 36%	**281b**	**282a** 51%	**282b**	

a) yields are isolated and unoptimized; b) enantiomeric excess determined by Mosher's amide formation of cyclic carbamates, derived from the corresponding benzoates by hydrolysis and cyclization; c) diastereomeric excess determined by GC/MS of benzoates after separation by flash column chromatography; d) not separable by flash column chromatography; e) diastereomeric excess determined by GC/MS of separated benzoates after hydrogenation.

The moderate isolated yields of *cis*-sulfamidates reflect the difficulty of isolation and separation of the diastereomers, not an uncommon problem in auxiliary group-mediated resolutions. In all cases, the *cis*-sulfamidates were converted to *trans*-benzoates *via* inversion with ammonium benzoate at the oxygenated carbon and the enantiomeric or diastereomeric excess were determined after separation by column chromatography. Benzoates **282a** and **282b** were hydrogenated (Pd/C, MeOH, 3 atm of H_2) to **267a** and **267b**, respectively, and their identity as well as their optical purity evaluated by direct comparison with benzoates **267a** and **267b**, establishing also that no allylic mode of the oxirane opening had occurred. The products **279a** and **279b** from the reactions of *n*-butyl oxirane proved inseparable from each other.

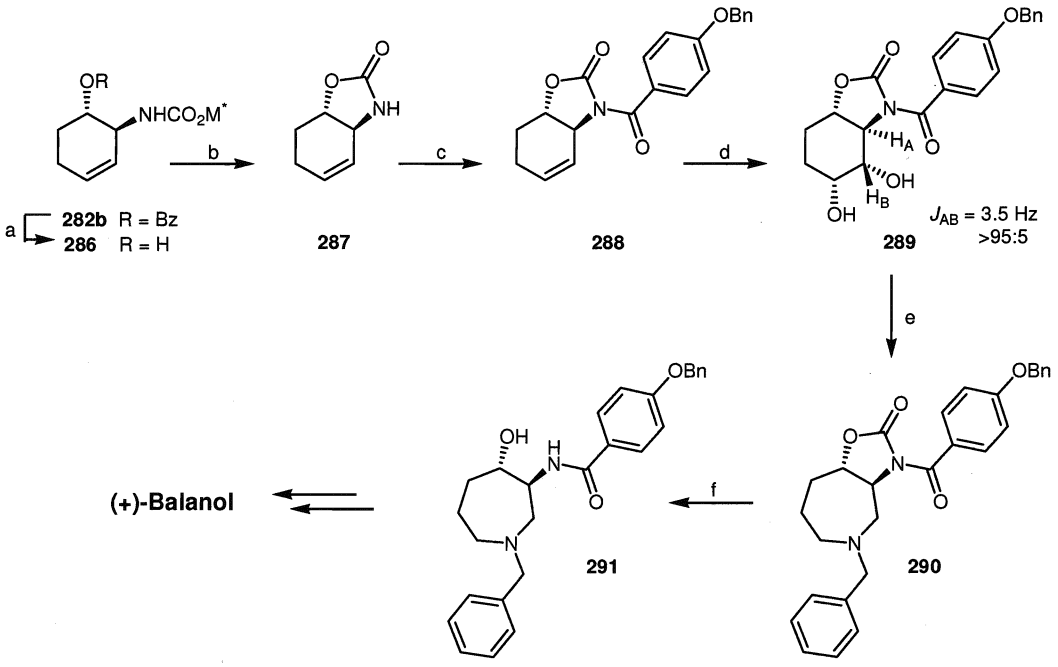


Reagents and Conditions: a) Burgess reagent (**21**), THF reflux, 1.5 hrs; b) $PhCO_2^- NH_4^+$, DMF, 45 °C, 12 hrs; c) 50% KOH.

Scheme 26. Formation of sulfonyl urea derivative **285**.

As expected, the reaction of styrene oxide and Burgess-type reagent **21** yielded predominately the seven-membered sulfamidate **283**, which was treated with ammonium benzoate to yield a mixture of two diastereomers identified by 2D-NMR

tentatively as **285**, produced by protonation of sulfimidate **283** and displacement with ammonia. Attempts to hydrolyze the sulfonyl group under basic conditions resulted in the formation of racemic styrene oxide **100**, in agreement with previous results.[21]



Reagents and Conditions: a) 1 N NaOH, MeOH; b) NaH, THF, reflux; c) *p*-benzyloxy benzoyl chloride, NEt_3, DMAP, DCM, 0 °C - rt; d) OsO_4, NMO, H_2O, DCM, rt; e) $NaIO_4$, acetone, H_2O, rt; then $BnNH_2$, MeOH, $NaCNBH_3$, AcOH, 3Å mol. sieves, -78 °C; f) 0.3 N NaOH, MeOH, -20 °C.

Scheme 27. Formal synthesis of (+)-balanol.

Encouraged by the ease with which the *trans*-amino alcohol derivatives were obtained, two other members of the group, Bradford Sullivan and Jacqueline Gilmet, under the guidance of Professor Hudlicky, applied this methodology to the formal synthesis of both (-)- and (+)-balanol. Benzoates **282a** and **282b** possess the absolute stereochemistry of (-)- and (+)-balanol, respectively and only oxidative cleavage of the olefin followed by reductive amination is required to produce the balanol core.

Diastereomer **282b** was converted to the cyclic carbamate **287** by treatment with 1N NaOH followed by sodium hydride in THF, as shown in Scheme 27.

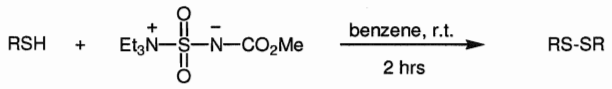
Osmium tetraoxide-mediated oxidation generated the *cis* diol **289** in a >95:5 ratio of diastereomers. Oxidative cleavage with sodium periodate was successful in furnishing the dialdehyde species (not shown) which was immediately transformed into hexahydroazepine derivative **290** under reductive amination conditions in the presence of benzylamine. Mild basic hydrolysis provided free alcohol **291**, whose preparation equates a formal synthesis of (+)-balanol. The same strategy was applied to the formal synthesis of (-)-balanol, which was was recently published.[141]

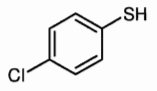
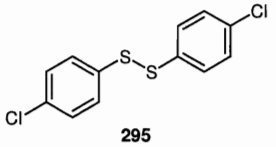
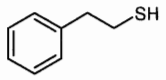
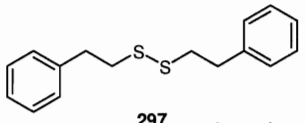
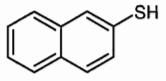
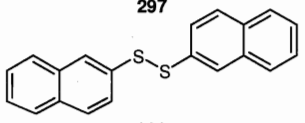
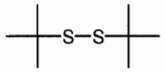
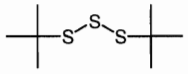
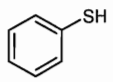
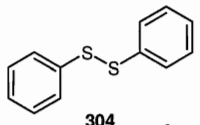
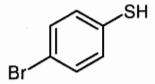
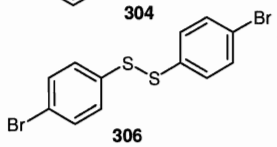
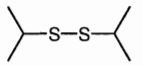
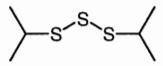
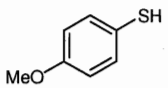
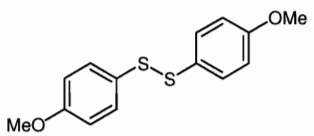
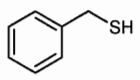
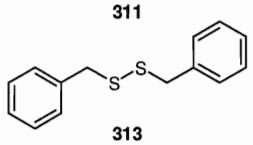
3.1.4 Reactivity of the Burgess Reagent with Thiols[142]

Our interest in the exploration of the reactivity of the Burgess reagent continued and the next step was to study the reactivity of the Burgess reagent (**18**) with thiols, as a means of forming alkenes from such compounds, suggested to us by a visiting speaker[143] We were, however, surprised to find no evidence of olefin or thiocarbamate formation when we reacted decane-1-thiol (**292**) with one equivalent of the Burgess reagent. Instead, a nearly quantitative yield of disulfide **293** was isolated. Examination of other thiols (

Table **2**) revealed the reaction to be a general and high yielding method for primary thiols and thiophenol derivatives. In contrast, the reaction of the Burgess reagent with branched aliphatic thiols (entries 5 and 8) afforded a mixture of both symmetrical disulfides[144] and trisulfides[145] in moderate yields.

Table 2. Burgess reagent-promoted disulfide formation.



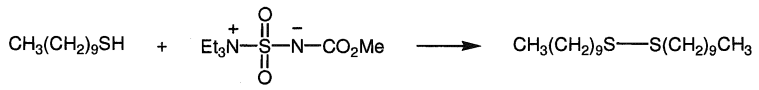
Entry	Thiol	Product	Yield (%)
1	$CH_3(CH_2)_9SH$ **292**	$CH_3(CH_2)_9S\text{-}S(CH_2)_9CH_3$ **293**	95
2	 **294**	 **295**	93
3	 **296**	 **297**	92
4	 **298**	 **299**	90
5	 **300**	 **301** (3 : 1)  **302**	39
6	 **303**	 **304**	96
7	 **305**	 **306**	95
8	 **307**	 **308** (3 : 1)  **309**	85
9	 **310**	 **311**	90
10	 **312**	 **313**	93

The reaction of decane-1-thiol (**292**) was optimized, as shown in Table 3 and we attempted to determine the mechanism of the reaction and to identify the reduced component in the sequence.

Although the oxidation proceeded cleanly at 50 °C in one hour, we found that higher yields were obtained at room temperature in the same time. The reaction was further accelerated by first forming the thiolate anion (entries 5-8, Table 3). The order of addition of either the Burgess reagent or the thiol was shown to be inconsequential, as long as there was a slight excess of the Burgess reagent present in the reaction mixture. The use of polar solvents, such as DMF (entry 4, Table 3), considerably hindered the rate of oxidation.

A speculative mechanism for this transformation is shown in Figure 41. Initially, the thiol reacts with the Burgess reagent either in an acid-base reaction to form thiolate **314** or *via* substitution to form inner salt **316**. Intermediates **316** or **317**, required for intramolecular E_2 elimination, are likely to be protonated by mercaptans to generate thiosulfonyl carbamate **318**. The difference in acidity between alcohols (pKa ~ 16), aliphatic thiols (pKa ~ 11) and aromatic thiols (pKa ~6) would not, at a first glance, lead to an assumption that the sulfamidate anion **317** would be completely protonated. This is not the case as is demonstrated by the high yields of disulfides obtained. Although it is possible for the E_2 pathway to proceed even with 1% relative concentration of the active intermediate **317**, this pathway appears unfavorable.

Table 3. Optimization study for decane-1-thiol.



Entry	Thiol (equiv)	Burgess (equiv)	Conditions	Addition Order[a]	Result[b]
1	1	1.05	Benzene, rt then 50 °C	Standard	72% isolated yield (1 h)
2	1	1.05	Benzene, rt	Standard	95% isolated yield (1 h)
3	2	1	Benzene, rt	Standard	67% conversion (60 hrs)
4	1	1.05	DMF, rt	Standard	50% conversion (24 hrs)
5	1	1.05	NaH, benzene, rt	Standard	>95% conversion (30 min)
6	1	1.05	NaH, benzene, rt	Inverse	>95% conversion (30 min)
7	1	1.05	NaH, benzene, 50 °C	Standard	>95% conversion (30 min)
8	1	1.05	NaH, benzene, 50 °C	Inverse	>95% conversion (30 min)

a) Standard addition: thiol added dropwise to Burgess reagent; Inverse addition: Burgess reagent added dropwise to thiol; b) GC/MS was used to measure % conversion.

Even when a large excess of NaH (10 equiv) was used in the reaction media, ensuring a higher relative concentration of **317**, no alkenes were detected when aliquots were monitored by GC/MS. Instead, it is likely that thiosulfonyl carbamate **318** is attacked by either the thiol or its conjugate base to form the disulfide and intermediate **320** or its tautomer **321**. We attempted to isolate compound **321** but were only able to characterize the triethylammonium salt **322** (in crystalline form), probably resulting from the immediate air oxidation of the labile intermediate **320**. NMR experiments in

d_6-benzene showed the formation of a new species, which did not correspond to either the Burgess reagent or compound **322**. As the compound disappeared upon exposure to air, the formation of triethylammonium salt **322** was observed.

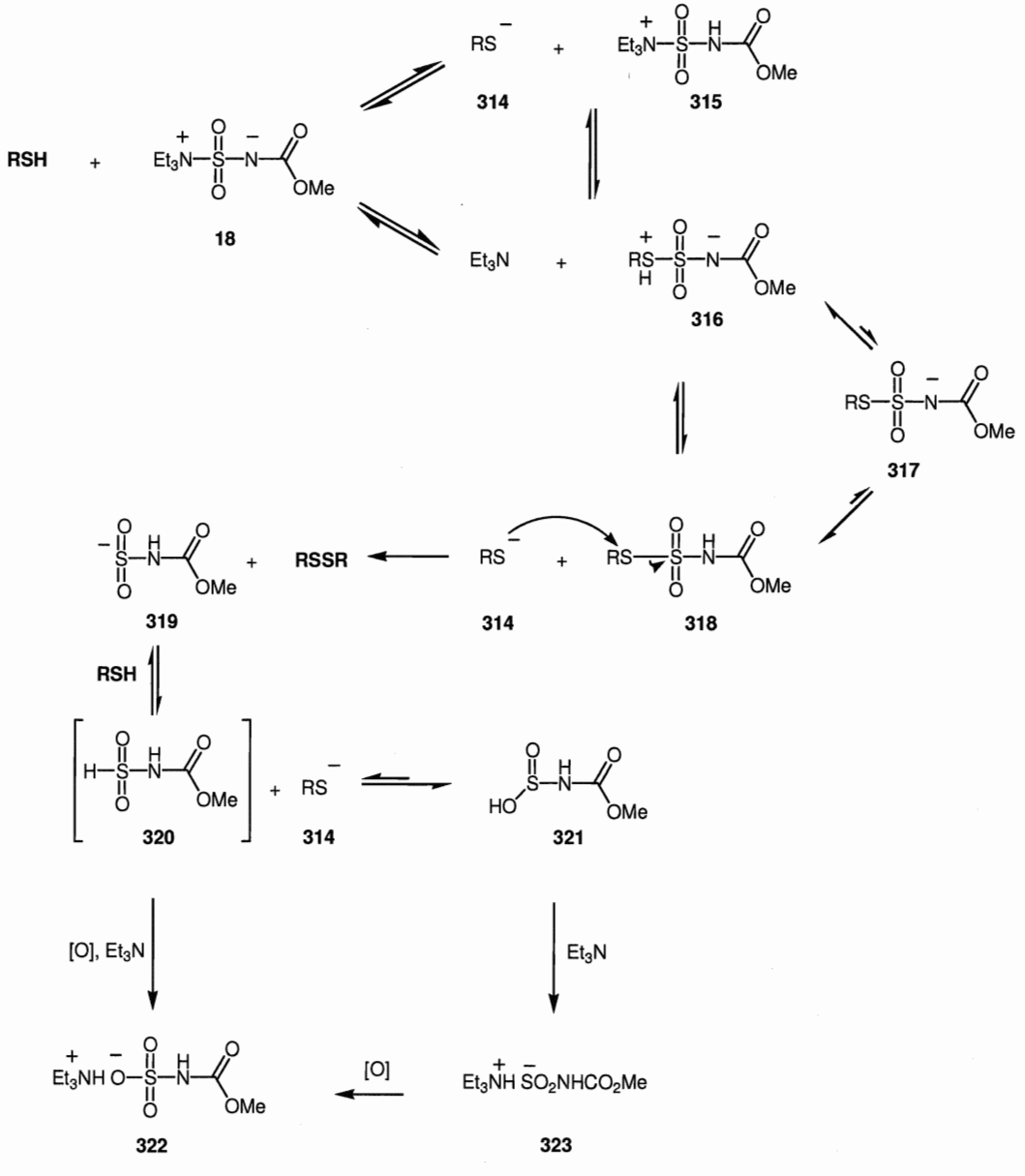


Figure 41. Suggested mechanistic options for the oxidation of thiols to disulfides with the Burgess reagent.

Various methods for the synthesis of symmetrical and unsymmetrical trisulfides have been developed by Harpp.[145a-d] Typical procedures include the alkoxide decomposition of sulfenylthiocarbonates;[145a] the reaction of thiols with sulfur dichloride to yield an intermediate thiosulfenyl chloride which reacts further with thiol to afford trisulfides;[145b] the reaction of disulfides with triphenylmethanesulfenyl chlorides with disulfides;[145c] and the reaction of thiols with triphenylmethanethiosulfenyl chloride to yield unsymmetrical trisulfides.[145d] By analogy with the mechanism proposed by Harpp,[145a-d] it is feasible that the sulfur atom of the newly formed disulfide is free to attack thiosulfonyl carbamate **318** to form a sulfonium salt. Loss of a stable carbocation by solvolysis (as in the case of 2-propanethiol and 2-methyl-2-propanethiol) would then lead to a symmetrical trisulfide, see Figure 42.

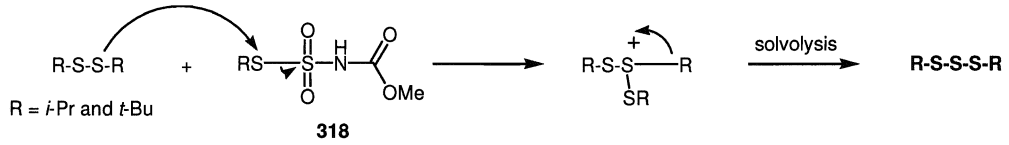


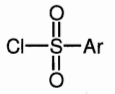
Figure 42. Suggested mechanistic options for the oxidation of disulfides to trisulfides with the Burgess reagent.

That thiosulfamidates react rapidly with mercaptans is surprising, although a similar reaction has been observed for thiosulfonates. In 1988, Fuchs[146] reported the formation of disulfides from thiols and thiosulfonates. The reaction only took place when thiosulfonate formation was sufficiently slow, compared to the reaction of excess mercaptan with the thiolsulfonate. When the more reactive sulfonyl bromides

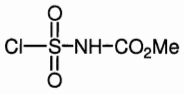
were used, the rate of sulfonylation was sufficiently fast and subsequent substitution leading to disulfides was not observed.

The electrophilic character of the Burgess reagent resembles that of a sulfuryl chloride. As it was difficult to compare the reactivity of sulfonyl chlorides, such as **324** with sulfamidyl chlorides **325**, and sulfuryl chloride **326**, we conducted a comparative study with decanethiol.

Table 4. Reactivity comparison of various substituted sulfuryl chlorides and the Burgess Reagent in benzene at room temperature.



324



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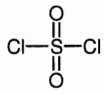


326

Entry[a]	Reagent	Time (hrs)	Conversion[b]
1	Burgess Reagent **18**	1	100%
2	**324**	24	0%
3	**325**	24	10%
4	**326**	1	40%

a) decane-1-thiol was used as substrate; b) GC/MS was used to measure % conversion.

Whereas the yield of disulfide is quantitative when Burgess reagent is used, it is formed in only 40% yield with sulfuryl chloride **326** after one hour (Table 4). Leino[144f] reported the formation of symmetrical disulfides with sulfuryl chloride in methylene chloride and slower reactivity when the reaction was conducted in benzene. Although sulfonyl chlorides such as **324**[146] have been reported to oxidize thiols to disulfides, these reactions require the addition of a stoichiometric amount of a base such as triethylamine. The Burgess reagent requires no external base in its

reactions with thiols to produce disulfides. The ease of preparation and the high yield of disulfides by this method compare favorably with other procedures in the literature.[144]

3.2 Morphine Alkaloids

3.2.1 Introduction

The supply of morphine and morphine-derived products depends on the isolation of major constituents from the opium poppy. Quite surprisingly, usable amounts of the morphine alkaloids can only be harvested from plants grown in a few specific geographic areas. Many of the countries situated in these geographic areas suffer from serious political turmoil, making the steady supply of morphine alkaloids uncertain. One of the long-standing goals of the Hudlicky group is the development of an efficient synthesis of morphine alkaloids which would rival the cost of its isolation from natural sources. Professor Hudlicky's strategy towards the synthesis of morphine alkaloids is unique since starting materials are obtained by an enzyme-mediated reaction. Cyclohexadiene diols derived from microbial dihydroxylation have been successfully employed in the synthesis of the morphine skeleton by the Hudlicky group, as discussed in the historical chapter of the current thesis.

The presented research discusses an enantiodivergent synthesis of codeine that combines strategies from previously reported syntheses by the Hudlicky, Parker and Trost groups. The unification of these three distinct approaches led to a total synthesis of (+)-codeine in 14 steps from commercially available β-bromoethylbenzene, featuring a Mitsunobu inversion and two intramolecular Heck cyclizations. A formal

synthesis of (-)-codeine will also be presented, which intercepts an intermediate in the (+)-codeine approach. The key step in the synthesis of the natural isomer of codeine represents a regioselective nucleophilic opening of a homochiral epoxide (Figure 43).

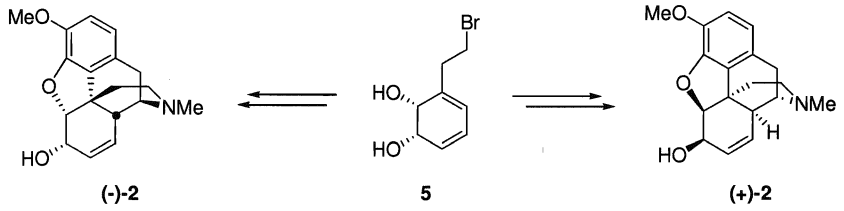


Figure 43. Enantiodivergent syntheses of codeine (**2**).

Professor Hudlicky's research interest in morphine alkaloids is not limited to their total synthesis. The highly addictive properties, as well as the undesired side effects of morphine (**1**) prompted researchers to investigate the medicinal properties of structural derivatives. Efforts aimed at increasing the analgesic potency, while decreasing addiction liability, have had mixed outcomes. The first reported semi-synthetic opioid diacetylmorphine, better known as heroin, was first marketed as a non-addictive morphine substitute.. Subsequent research led to the discovery of more useful semi-synthetic opioids, such as the μ-receptor agonists hydrocodone and oxycodone, μ-receptor antagonists naltrexone and naloxone, and the mixed agonist-antagonist opioid nalbuphine. In cooperation with Noramco Inc., a subsidiary of Johnson & Johnson, the Hudlicky group initiated a program directed toward the development of novel methodologies suitable for the conversion of opiates into higher value products.

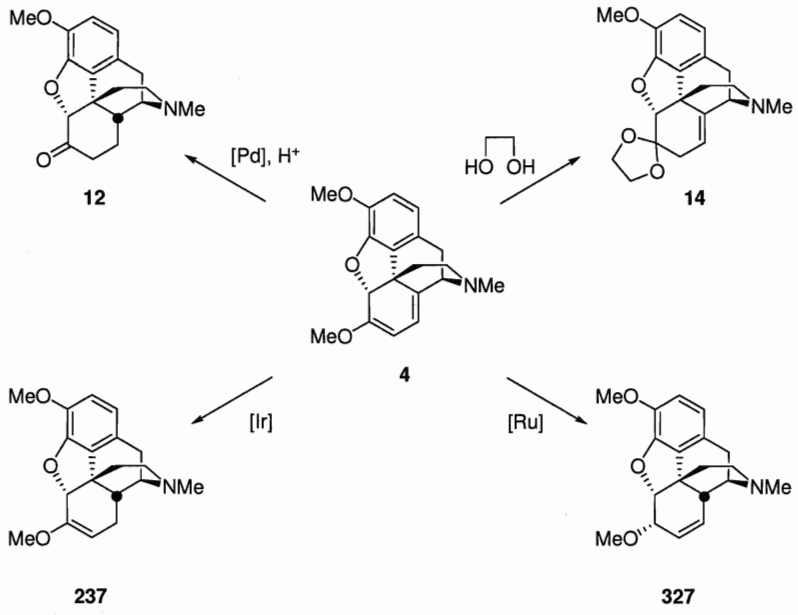


Figure 44. Functionalization of thebaine (**4**).

Progress towards the development of a regioselective hydrogenation of the C-8/C-14 olefin of thebaine (**4**) will be presented. A one-pot procedure for the conversion of thebaine (**4**) to neopinone ketal (**14**) was achieved and subsequent research has led to a one-step conversion of thebaine (**4**) to hydrocodone (**12**).

In addition to our investigations of the chemistry of thebaine, a novel demethylation/acylation procedure of hydrocodone (**12**) was developed. Alongside this, two novel demethylation procedures of hydrocodone (**12**) will be discussed.

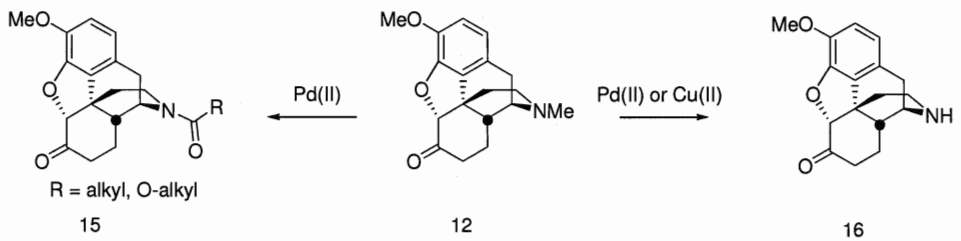


Figure 45. Functionalization of hydrocodone (**12**).

3.2.2 Enantiodivergent Synthesis of Codeine[147]

The failure to deliver chiral synthons in both enantiomeric series is said to be the common disadvantage in chemoenzymatic synthesis. The synthesis presented here will highlight the versatility of enzymatically derived dienediols in natural product synthesis, as well as the ease of preparation of both enantiomers of codeine (**2**) from a single metabolite derived from microbial dihyroxylation.

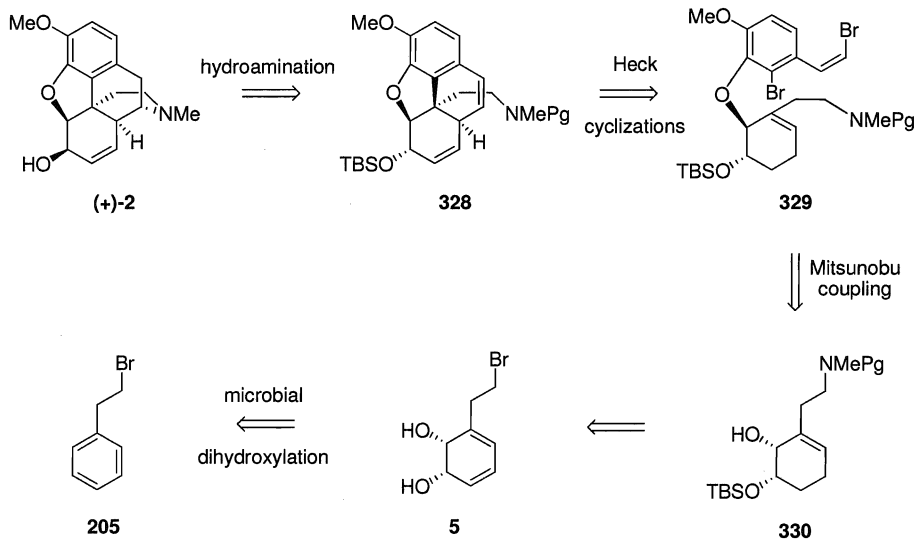
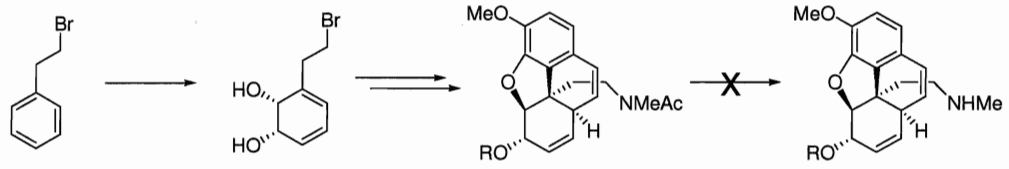


Figure 46. Retrosynthetic analysis of (+)-codeine (**2**) approach.

The strategy for the total synthesis of (+)-codeine is based on the formation of homochiral monoprotected diol **330**, whose source would be the microbial dihydroxylation of β-bromoethylbenzene and subsequent installation of the *N*-methyl amine unit *via* S_N2 reaction. Mitsunobu coupling with bromoisovanillin should provide **329**, the precursor for the first Heck cyclization upon transformation of the aldehyde to a vinyl bromide. This is anticipated to furnish the phenanthrene core of

the morphine alkaloids *via* a second Heck coupling. Adjustment of the stereochemistry of the hydroxyl group at C-6 by an oxidation-reduction sequence should give Trost's intermediate for the final visible light-promoted hydroamination reaction.

The combination of Trost's Heck cyclization strategy and Parker's Mitsunobu coupling procedure will allow for an efficient and short synthesis of (+)-codeine. In contrast to Parker's synthesis, our precursor for the Mitsunobu reaction will be enantiomerically pure, since it will be derived from microbial dihydroxylation. In addition, our C-ring fragment will already have the *N*-methyl amine unit and the hydroxyl functionality in place, making it more efficient than Trost's, who had to generate both functional groups in additional reactions later in the synthesis.

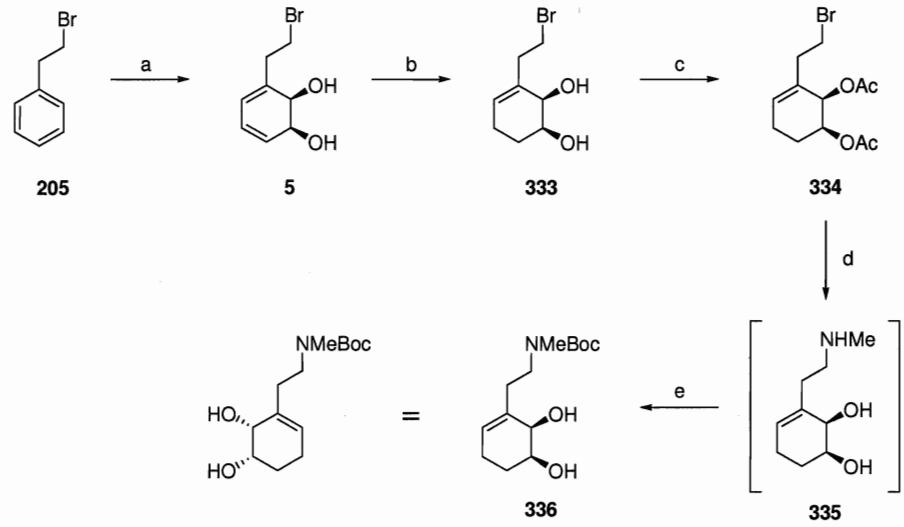


205 **5** **331** **332**

Figure 47. Initial approach to (+)-codeine.

The proposed approach to (+)-codeine was initially started by fellow group members Dr. Kevin Finn and Dr. Alvaro Takeo Omori. They successfully established an efficient route to advanced intermediates of structure **331**, however deprotection of the acetyl group proved to be unsuccessful, as shown in Figure 47, and the approach was aborted a few steps before the end.[148]

The obvious solution to this problem was the utilization of an alternative protecting group. In the second generation approach to (+)-codeine, Dr. Alvaro Takeo Omori, Dr. Robert Carroll and I, under the guidance of Professor Hudlicky, chose to protect the *N*-methyl amine functionality as its Boc carbamate (Scheme 28).



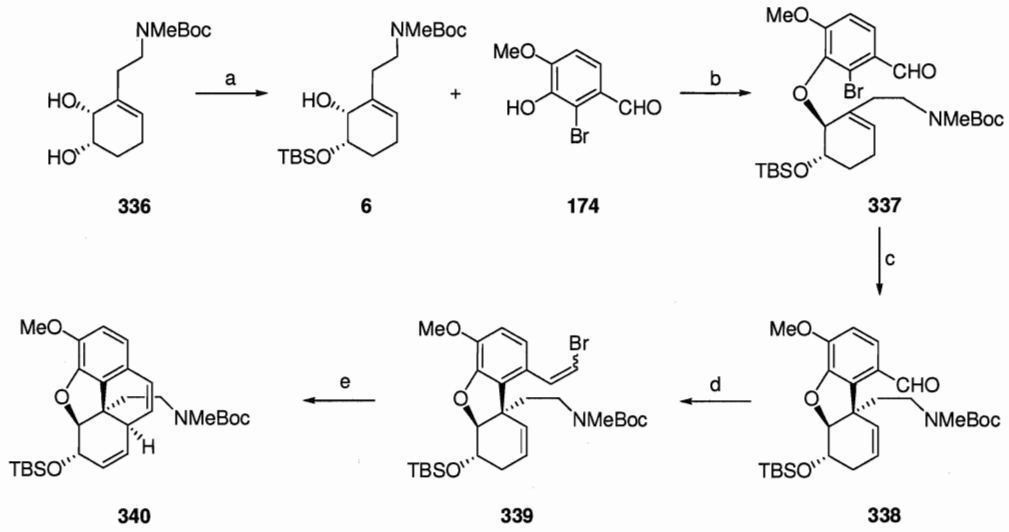
Reagents and Conditions: a) *E. coli* JM 109 (pDTG601A) (10 g/L); b) potassium azodicarboxylate, AcOH (60%); c) Ac_2O, NEt_3, DMAP, 0 °C (52%); d) $MeNH_2$ (g), K_2CO_3, THF, sealed tube; e) $(Boc)_2O$, NEt_3, DMAP, 0 °C (56% over two steps).

Scheme 28. Preparation of diol **336**.

The synthesis started with the microbial dihydroxylation of β-bromoethylbenzene using *E. coli* strain JM109 (pDTG601A),[105] which gave the homochiral diol **5** in 10 g per litre cell broth. Potassium azodicarboxylate mediated reduction of the distal double bond furnished intermediate **333** in 60% yield, which was treated with acetic anhydride and triethylamine to give bisacetate **334**.

Treatment of compound **334** with methylamine, in the presence of potassium carbonate, yielded the secondary amine with concomitant hydrolysis of the acetate

groups. The crude reaction mixture was treated with Boc anhydride to give the Boc protected amine **336** in 56% yield after flash column chromatography.

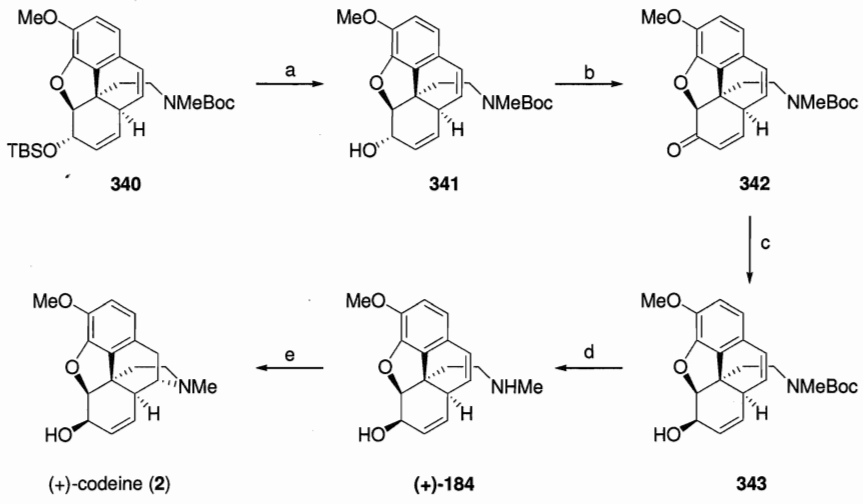


Reagents and Conditions: a) TBSCl, imidazole, DCM, -78 °C to rt (88%); b) DIAD, *n*-Bu_3P, bromoisovanillin, THF, 0 °C (55%); c) $Pd(OAc)_2$, Ag_2CO_3, dppf, toluene, 110 °C (82%); d) PPh_3CHBr_2, *t*BuOK, THF, -30 °C (49%); e) $Pd(OAc)_2$, Ag_2CO_3, dppp, toluene, 110 °C (44%).

Scheme 29. Mitsunobu coupling and Heck cyclizations towards the synthesis of (+)-codeine (**2**).

Protection of the distal hydroxyl group of compound **336** with TBSCl gave the precursor for the Mitsunobu reaction. Bromoisovanillin (**174**) was reacted with compound **6** in the presence of tri-*n*-butyl phosphine and DIAD to give aryl ether **337** in 55% yield. Palladium (II)-catalyzed Heck cyclization furnished aldehyde **338** in good yield, which was converted to vinyl bromide **339** by a Wittig type reaction (approximately 1 : 1 ratio of cis to trans isomer). The second Heck cyclization gave the complete phenanthrene core in moderate yield. Adjustment of the stereochemistry of the C-6 hydroxyl group was accomplished by deprotection of the alcohol

functionality with TBAF followed by an oxidation-reduction sequence. Removal of the *N-tert*-butyl carbamate was easily achieved using TFA in methylene chloride. This sequence allowed for the interception of Trost's intermediate **184** in the opposite enantiomeric configuration. Application of Trost's reported experimental procedure (LDA deprotonation of the amine, followed by light-mediated hydroamination of the styrene bond) to produce (+)-codeine (**2**) failed in our hands despite numerous attempts and in spite of receiving detailed protocols and advice from Dr. Tang, who conducted the synthesis while in Trost's group.



Reagents and Conditions: a) TBAF, THF, rt (88%); b) IBX, DMF, rt (92%); c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C (89%); d) TFA-DCM (1 : 4), 0 °C to rt (88%); e) $Hg(OAc)_2$, Et_3N, THF, 48 h then LAH, 2h, rt (18%).

Scheme 30. Final steps in the synthesis of (+)-codeine (**2**).

Further experimental details provided by Dr. Tang, a former coworker of Professor Trost, still did not lead to any success in the formation of the desired product. Unable to repeat Trost's procedure, we employed an oxymercuration reaction of the styrene

double bond to yield an oxymercurium ion, which was trapped intramolecularly by the ethyl amino side chain. This procedure gave (+)-codeine as well as a mixture of two diastereomeric C-10 acetates. The acetates were easily reduced by LAH at room temperature and this procedure allowed for the completion of the synthesis of (+)-codeine in 14 steps from β-bromoethylbenzene.

Total synthesis of (-)-codeine (2)

Having accomplished the synthesis of (+)-codeine, we were set to employ the same key intermediate **6** in the total synthesis of (-)-codeine. The strategy is outlined in Figure 48.

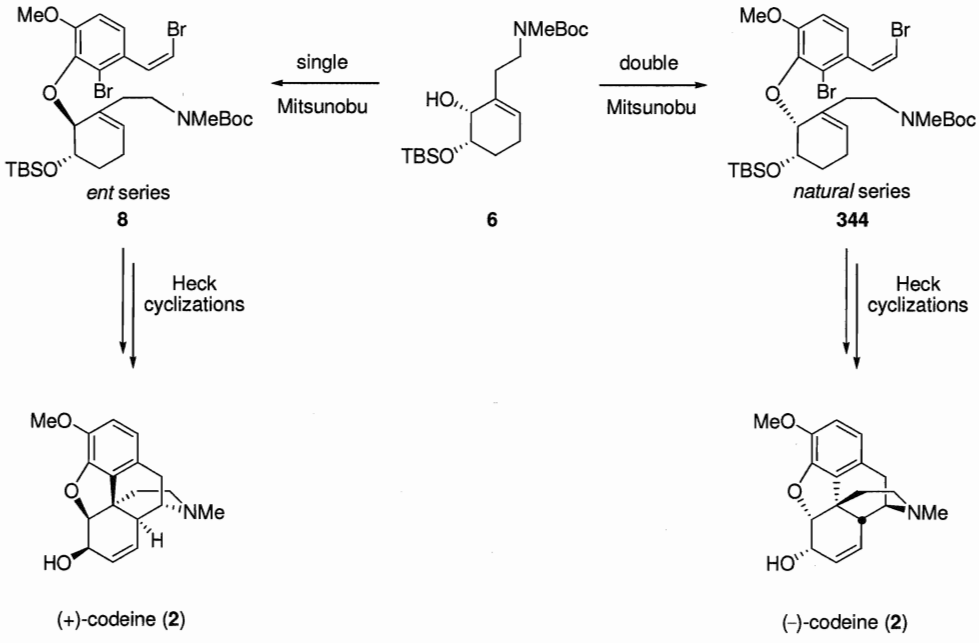
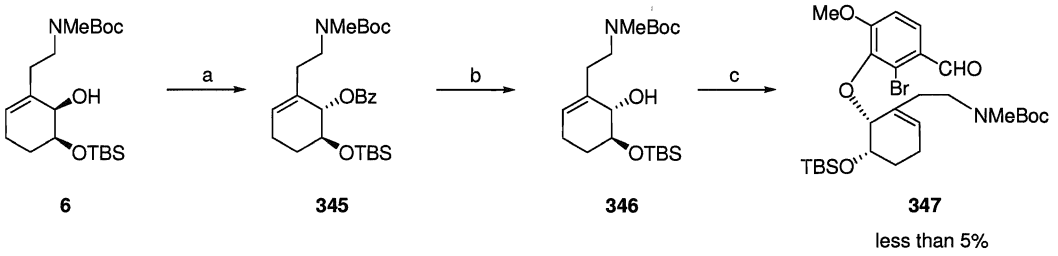


Figure 48. Initial strategy towards the enantiodivergent syntheses of codeine (**2**).

As demonstrated before, a single Mitsunobu inversion of the allylic alcohol led to the enantioselective synthesis of the *ent*-isomer of codeine; a double Mitsunobu inversion

strategy therefore should lead to precursor **344**, which would allow for the synthesis of (-)-codeine. The synthesis of the naturally occurring isomer was envisioned to be more efficient than the synthesis of the (+)-isomer, since the stereochemistry of the C-6 hydroxyl group would not have to be adjusted later in the synthesis.



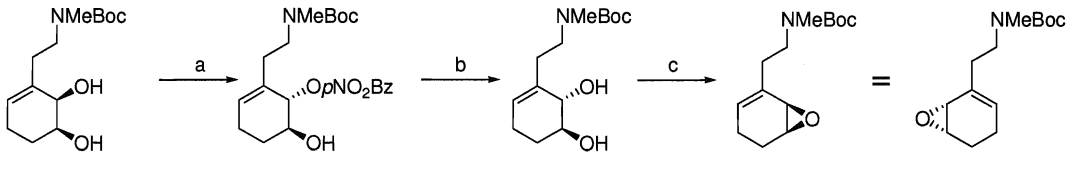
6 **345** **346** **347**

less than 5%

Reagents and Conditions: a) DIAD, nBu$_3$P, benzoic acid, THF, 0 °C (83 %); b) NaOMe, MeOH, 0 °C (55%); c) bromoisovanillin, various conditions.

Scheme 31. Double Mitsunobu sequence.

The allylic alcohol of compound **6** was inverted using benzoic acid under standard Mitsunobu conditions. Cleavage of the ester functionality gave precursor **346** for the second Mitsunobu coupling, which provided the desired product in less than 5% yield.



336 **348** **349** **(+)-7**

Reagents and Conditions: a) DIAD, Ph_3P, p-nitrobenzoic acid, toluene, 0 °C to rt (71%); b) NaOMe, MeOH, 0 °C (76%); c) DIAD, nBu$_3$P, bromoisovanillin, THF, 0 °C to rt (45%).

Scheme 32. Preparation of epoxide (+)-**7**.

This result was not entirely unexpected since the steric bulk of the TBS protecting group prevents the nucleophile from attacking the allylic carbon. As an alternative approach we envisioned a double Mitsunobu inversion, without the use of any protecting groups, as shown in Scheme 32.

Regioselective inversion of the allylic alcohol was achieved following a procedure by Banwell and coworkers[149] which gave the monoprotected diol **348** in good yield without further optimization. Saponification of the benzoate ester using sodium methoxide in methanol yielded *trans*-diol **349**, which was further subjected to Mitsunobu conditions, applying bromoisovanillin as a nucleophile. Unfortunately, no aryl ether was detected in the reaction mixture, but epoxide (+)-**7** was isolated in 45% yield. The formation of epoxides from 1,2-*trans*-diols has been reported previously.[150]

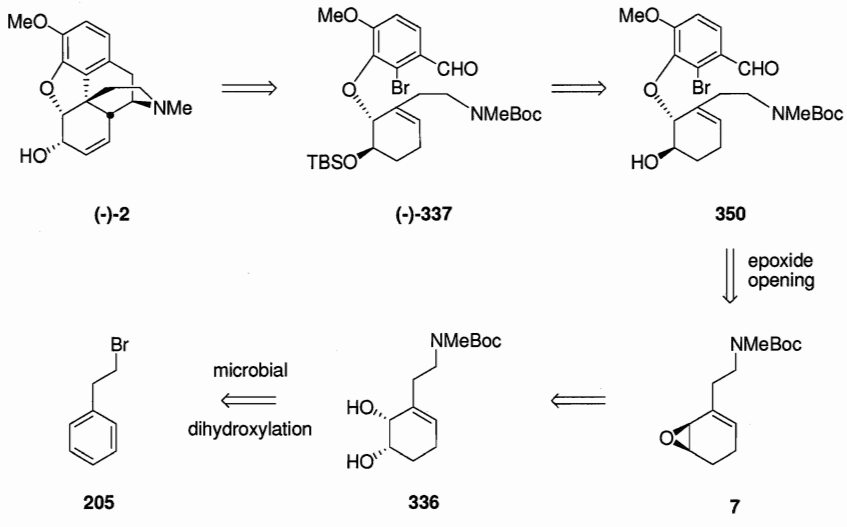
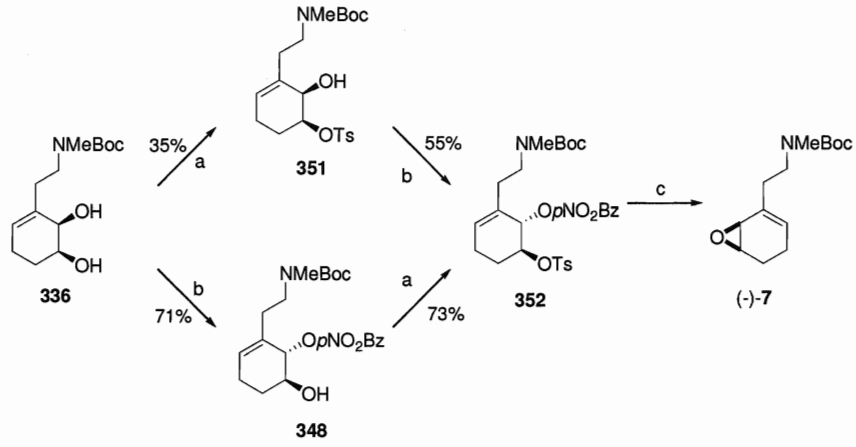


Figure 49. Retrosynthetic analysis of (-)-codeine (**2**) approach.

Although the formation of epoxide (+)-**7** was not anticipated, its preparation gives access to the synthesis of (+)-codeine. The regioselective opening of epoxide (+)-**7** with an appropriate aromatic nucleophile would allow for the connection of the unsaturated C-ring fragment and the aromatic A-ring fragment of morphine alkaloids. It has to be mentioned that a similar strategy was applied previously in Professor Hudlicky's synthesis of 10-hydroxy-14-*epi*-hydrocodone (**234**).[110] With that in mind, we revised our initial strategy for the synthesis of (-)-codeine and the alternative route is shown in Figure 49.

The major difference from the first generation approach is the alternative connection of the A-ring fragment to the C-ring fragment *via* a 1,2-trans diaxial epoxide opening instead of the previously envisioned second Mitsunobu inversion.

In order to synthesize epoxide (-)-**7**, two different routes were investigated. First, diol **336** was treated with tosylchloride in the presence of DMAP and triethylamine in DCM. After extensive optimization, the reaction yielded a rather disappointing 35% yield of the desired distal protected diol **351**, with 45% starting material recovered and small amounts of the proximally protected diol. In order to validate the new route, compound **351** was subjected to Mitsunobu conditions and bisprotected diol **352** was isolated in moderate yield.



Reagents and Conditions: a) TsCl, NEt_3, DMAP, DCM, 0 °C to rt; b) DIAD, PPh_3, benzoic acid, THF, 0 C; c) NaOMe, MeOH, 0 °C (88%).

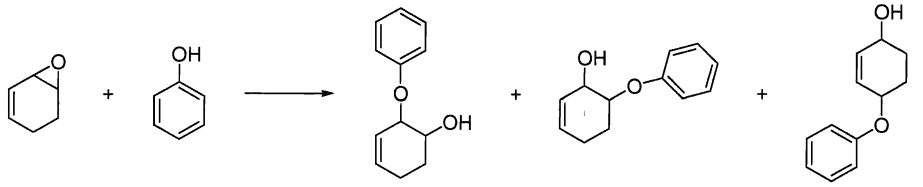
Scheme 33. Synthesis of epoxide (-)-**7**.

Treatment of benzoate **352** under basic conditions led to the saponification of the benzoate with concomitant formation of epoxide (-)-**7**. The overall yield for the formation of epoxide (-)-**7** could be dramatically increased by first performing the Mitsunobu inversion (71% yield) followed by protection of the distal alcohol (73% yield).

Having established a high yielding route to epoxide (-)-**7**, we were in a position to perform the key reaction of the synthesis. We decided to focus our attention on a model study which would allow us to quickly assess the feasibility of the regioselective 1,2-*trans* diaxial opening of vinyl oxiranes. We chose cyclohexadiene oxide (**280**), which can be easily prepared from commercial available cyclohexadiene, as the vinyl oxirane and phenol as the nucleophile. The results are summarized in Table 5. The results clearly show that the desired regioselective epoxide opening can be achieved under basic conditions. The best results were obtained when compound **280** was treated with phenol in the presence of potassium

carbonate or basic alumina or when treated with potassium phenolate (entries 3-6, Table 5).

Table 5. Model study for the reaction of vinyloxirane **280**.



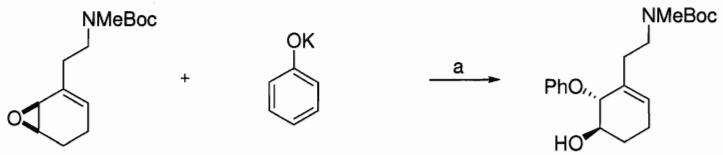
280 **353** **354** **355** **356**

Entry	Conditions [a]	Yield **354**	Yield **355**	Yield **356**
1	3 equiv phenol, melt, rt	10% [b]	20% [b]	45% [b]
2	3 equiv phenol, acidic Al_2O_3, Et_2O, reflux	43% [b]	traces [b]	-
3	3 equiv phenol, basic Al_2O_3, Et_2O, reflux	85% [c]	-	-
4	3 equiv phenol, neutral Al_2O_3, Et_2O, reflux	82% [c]	traces [c]	-
5	3 equiv phenol, SiO_2, Et_2O, reflux	55% [c]	6% [c]	23% [c]
6	3 equiv potassium phenolate, DME, 80 °C, 18-crown-6	95% [c]	-	-
7	3 equiv phenol,K_2CO_3, Et_2O, reflux	89% [c]	-	-

a) Reaction time was 18 hours; b) Isolated yield by flash column chromatography; c) Yield determined by GC/MS.

Having established suitable conditions for the regioselective epoxide opening of compound **280** with phenol, we focused our attention on the reaction of homochiral epoxide (-)-**7** and bromoisovanillin (**174**). Unfortunately, applying the previously successful reaction conditions from our model study (entries 3, 6 and 7, Table 5) did

not allow for the isolation of any aryl ether derivative, until we applied potassium phenolate (**357**) instead of the potassium salt of bromoisovanillin as nucleophile.

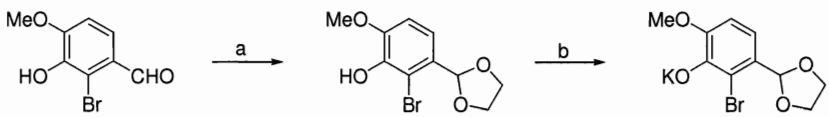


(-) - **7** **357** **358**

Reagents and Conditions: a) 18-crown-6, DME, 80 °C (78%).

Scheme 34. Regioselective opening of epoxide (-)-**7** with potassium phenolate.

We speculated that the electron withdrawing effect of the aldehyde of bromoisovanillin reduced the nucleophicility of the potassium salt of bromoisovanillin. To remedy this, we prepared acetal-protected potassium phenolate **360** as shown in Scheme 35.



174 **359** **360**

Reagents and Conditions: a) ethylene glycol, TsOH, THF, reflux (65%); b) KOH, EtOH (quant.).

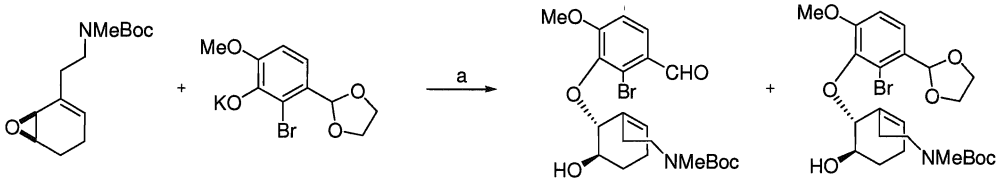
Scheme 35. Preparation of potassium salt **360**.

Various conditions for the reaction of epoxide (-)-**7** and potassium salt **360** were screened and led finally DME and DMF (1:1) as solvent and a reaction temperature of 90 °C. These conditions effected the aryl ether formation in low yield. To our

surprise, expected compound **361** was isolated only as minor product, along with compound **350**, as shown in

Table **6**.

Table 6. Reaction of epoxide (-)-7 with potassium salt **360**.



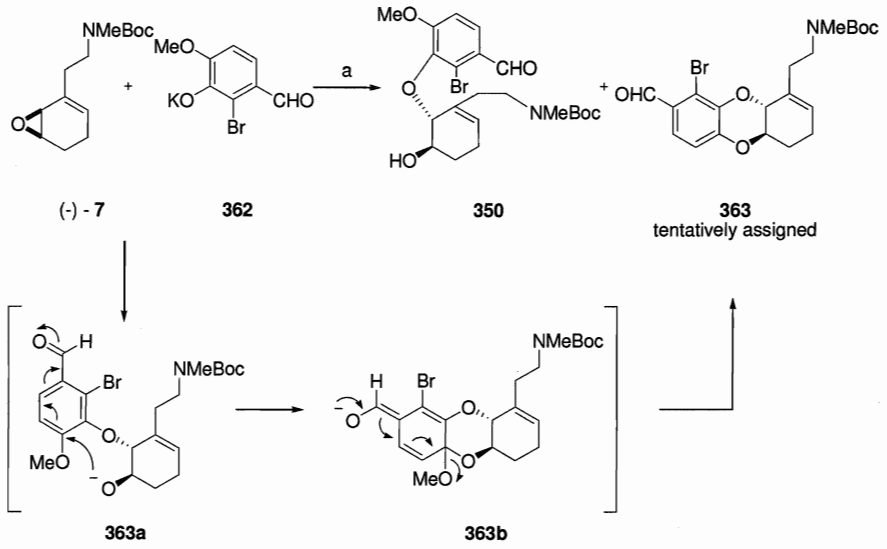
(-) - **7** **360** **350** **361**

Entry	Conditions[a]	Yield **350**	Yield **361**	recovered SM (-)-**7**
1	DME, 18-crown-6, 80 °C, 7 days	traces	traces	85%[b]
2	DME-DMF 1:1, 90 °C, 4 days	21%[b]	7%[b]	45%[b]
3	DMF, 90 °C, 5 days	10%[c]	13%[c]	-
4	DMF-HMPA 1:1, 90 °C, 5 days	6%[c]	8%[c]	-
5	DME-HMPA 1:1, 90 °C, 5 days	-	-	-
6	HMPA, 90 °C, 5 days	-	-	-

a) two equivalents of **360** were used in all reactions; b) isolated yield by flash column chromatography; compounds **350** and **361** were inseparable by flash column chromatography; c) determined by ^{1}H NMR of crude reaction mixture after work up.

Since compounds **350** and **361** proved to be inseparable by flash column chromatography and an additional deprotection step would be necessary to finish the synthesis of (-)-codeine, we reinvestigated the reaction of epoxide (-)-**7** and potassium salt **362**. Optimization of the previously applied conditions led to the aryl

ether **350** in 75 % yield, along with compound **363**, tentatively assigned as shown. It was observed that compound **363** is formed exclusively at higher reaction temperatures and a mechanism which accounts for the formation of compound **363** is proposed in Scheme 36.

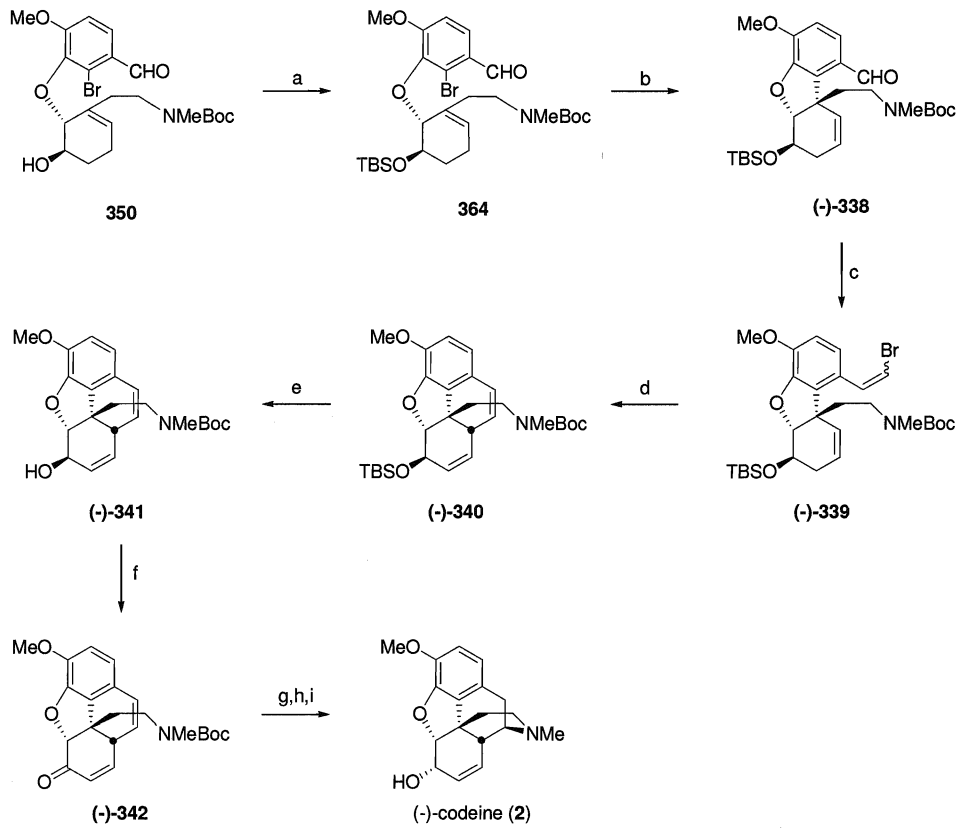


Reagents and Conditions: a) 18-crown-6, DME-DMF 1:1, 80 °C, 48 hours (75%); b) TBSCl, imidazole, DCM (61%).

Scheme 36. Preparation of aryl ether **350** and proposed mechanism for the formation of compound **363**.

Subsequent protection of the hydroxyl functionality of compound **350** with *tert*-butyldimethylsilyl chloride gave the protected ether **364** in 61% yield (Scheme 37). Analytical data (^{1}H and ^{13}C NMR, IR, MS) of compound **364** were found to be identical to those of compound **337**, only differing in the sign of their optical rotation (compound **364** α_D^{21} = -55.8 (c 0.325, $CHCl_3$), compound **337** α_D^{22} = +59.1 (c 0.35, $CHCl_3$)). Having matched an enantiomer of one of the intermediates of the route to (+)-codeine, the total synthesis of (-)-codeine was completed by repetition of the steps reported for the synthesis of (+)-codeine. Pd-catalyzed Heck-cyclization of

compound **364** gave furan (-)-**338** in 91% yield followed by Wittig reaction to give compound (-)-**339** in similar yield to the (+)-codeine route.



Reagents and Conditions: a) TBSCl, imidazole, DCM (61%); b) $Pd(OAc)_2$, Ag_2CO_3, dppf, toluene, 110 °C (91%); c) PPh_3CHBr_2, *t*BuOK, THF, -30 °C (40%); d) $Pd(OAc)_2$, Ag_2CO_3, dppp, toluene, 110 °C (45%); e) TBAF, THF, rt (72%); f) IBX, DMF, rt; g) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C; h) TFA-DCM (1 : 4), 0 °C to rt; i) $Hg(OAc)_2$, Et_3N, THF, 48 h then LAH, 2h, rt (8% over four steps).

Scheme 37. Synthesis of (-)-codeine (**2**).

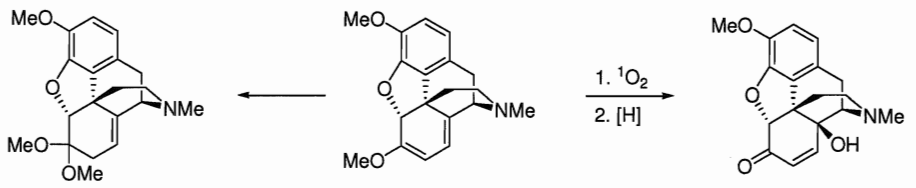
Alcohol (-)-**341** was prepared in comparable yield to the (+)-codeine route by previous established conditions with the Heck cyclization of vinyl bromide (-)-**339** in 45% yield and the deprotection of the alcohol functionality of intermediate (-)-**340** in 72% yield. In contrast to the oxidation of alcohol **341**, which proceeded in nearly

quantitative yield, the IBX-mediated oxidation of (-)-**341** gave a mixture of two compounds (ratio of 1:1). The discrepancy between these two experiments is explained by the use of an additional 0.3 equivalents of IBX for the oxidation of intermediate (-)-**341**, which reaction was not complete employing one equivalent of oxidizing reagent. No suitable conditions were found to effectively separate these two compounds and the identification of compound (-)-**342** is based on a small amount of purified product. In order to complete the synthesis, the mixture was first subjected to reductive conditions followed by treatment with trifluoroacetic acid. In both experiments an inseparable mixture of compounds was isolated with nearly quantitative mass recovery. Oxymercuration of the mixture, followed by treatment with lithium aluminium hydride allowed for the synthesis of (-)-codeine (**2**) (8% yield for the last four steps) after elaborative purification of the final reaction mixture.

The total synthesis of (-)-codeine (**2**) was achieved in 17 steps from β-bromoethylbenzene compared to 14 steps for the synthesis of the (+)-isomer. The synthesis of both isomers of codeine highlights the versatility of enzymatically derived dienediols in enantiodivergent natural product synthesis.

3.2.3 Regioselective Hydrogenation of Thebaine[151]

The conversion of thebaine into valuable morphinane derivatives, such as oxycodone (**11**) or hydrocodone (**12**) has attracted much attention from the chemical community over the last 100 years. Freud and Speyer discovered the conversion of thebaine (**4**) to 14-hydroxycodeinone (**235**) by simple treatment of thebaine (**4**) with formic acid and hydrogen peroxide (Figure 50).[10a] An alternative approach to 14-hydroxycodeinone (**235**) is the addition of singlet oxygen to yield an opioid endoperoxide, whose reduction yields the desired intermediate for the production of oxycodone **11**.[152] The dienol ether unit in thebaine has been transformed to neopinone ketal **365** by Rapoport[153] and by Dauben (Figure 50).[154] As the diene unit in thebaine is polarized, we reasoned that it could be possible to effect a regioselective reduction of the C-8 C-14 olefin through a directed catalytic hydrogenation of thebaine[155] under various conditions, in order to provide for a direct conversion of thebaine to hydrocodone (**12**) *via* 8,14-dihydrothebaine **237**, as shown in Scheme 38.



365
neopinone ketal

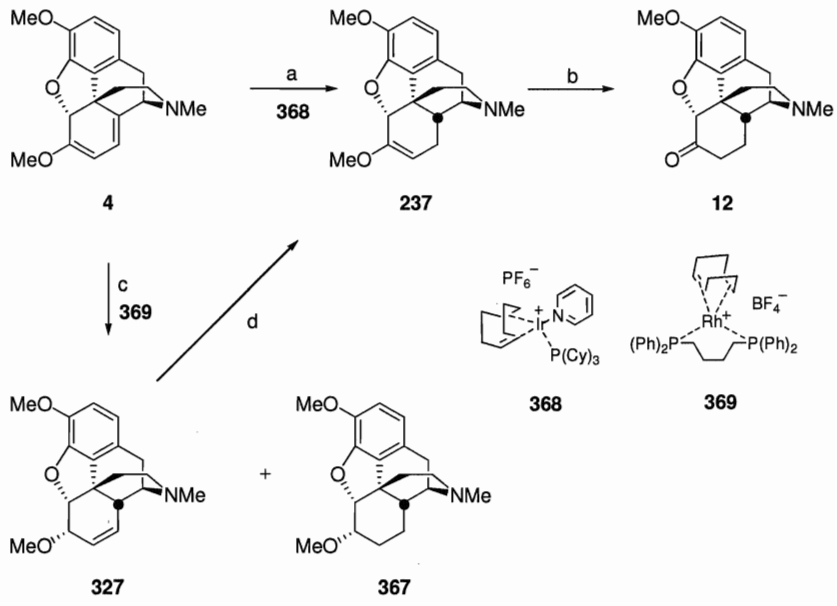
4

235
14-hydroxycodeinone

Figure 50. Functionalization of thebaine (**4**).

Although 8,14-dihydrothebaine can be obtained from thebaine by reduction with diimide (generated from hydrazine and oxygen) in 79% yield without

chromatography on a 0.1 mole scale,[124] the need for an environmentally-benign catalytic method, as well as a safer process, still exists. A regioselective hydrogenation of thebaine to **237** would provide a more convenient alternative for the conversion of thebaine to hydrocodone (**12**).



Reagents and Conditions: a) H_2, MeOH (45%); b) 2N HCl (82%); c) H_2, MeOH (38%); d) $RhCl(PPh_3)_3$, EtOH (20%).

Scheme 38. Hydrogenation of thebaine (**4**).

Hydrogenation of thebaine, using Crabtree catalyst (5 mol%) **368**[156] in methanol at 55 psi hydrogen pressure, led to the regioselective saturation of the C-8 C-14 olefin to produce enol ether **237** in 45% yield. Improved yields were achieved at lower pressure, as indicated in Table 7 (entries 1 - 4). Ratios were determined by ^{1}H-NMR in $CDCl_3$, by comparison of the intensities of H-5 protons of the morphine alkaloids (thebaine (**4**), 5.29 ppm (s); 8,14-dihydrothebaine (**237**), 4.84 ppm (s); codeine

methylether (**327**), 4.99 ppm (d, J = 5.8 Hz); and tetrahydrothebaine (**367**), 4.68 ppm (d, J = 5.0 Hz)), as well as separation of the relevant morphinans by HPLC.

Table 7. Hydrogenation of thebaine (**4**) with Crabtree's catalyst **368** in methanol.

Entry	**368** mol %	H_2	Time	Conversion[a]	Yield of **237**[a]	Yield of **367**[a]
1	5	55 psi	16 hrs	19%	9%	5%
2	5	55 psi	96 hrs	75%	43%	25%
3	10	55 psi	192 hrs	85%	44%	27%
4	**15**	**55 psi**	**288 hrs**	**95%**	**45%**	**27%**
5	5	150 psi	16 hrs	10%	3%	2%
6	5	400 psi	64 hrs	78%	24%	18%

[a] Conversion and yields were determined by ^{1}H-NMR and HPLC.

The use of rhodium catalyst **369**[157] provided an interesting contrast to the results obtained with Crabtree's catalyst **368**, in the regioselectivity of hydrogen addition, as shown in Table 8. Up to 38% yield of allylic ether **327** was obtained in addition to the fully saturated natural isomer tetrahydrothebaine (**367**), which in our hands were inseparable by column chromatography. The enol ether **327** was isomerised in preliminary experiments using Wilkinson's catalyst in refluxing ethanol to yield **237** in 20% yield with 80% recovery of unreacted starting material. A similar method for the isomerisation of codeine to hydrocodone has previously been published.[123] Hydrolysis of **237** using 2 *N* HCl yielded hydrocodone (**12**) in 82 % isolated yield after flash column chromatography. Tetrahydrothebaine (**367**) is a significant

byproduct produced by over-reduction of thebaine under most of the conditions that were tried and is likely to be formed in any process developed in the future that uses catalytic hydrogenation. Rice described a practical method for the conversion of tetrahydrothebaine to dihydromorphine with hydrobromic acid in acetic acid, thereby converting this byproduct into a valuable compound.[158]

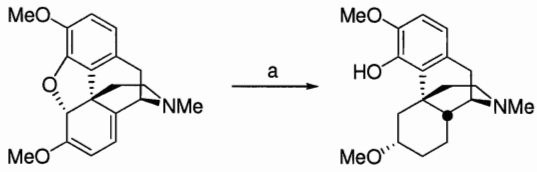
Table 8. Hydrogenation of thebaine over rhodium catalyst **369**.

Entry	H_2	Solvent	Time	Conversion[a]	Yield of **327**[a]	Yield of **367**[a]
1	1 atm	EtOH	18 hrs	100%	0%	60%
2	**1 atm**	**DCM**	**18 hrs**	**100%**	**0%**	**90%**
3	1 atm	$CHCl_3$	18 hrs	80%	0%	0%
4	**1 atm**	**MeOH**	**18 hrs**	**40%**	**38%**	**0%**
5	1 atm	MeOH	27 hrs	85%	33%	30%
6	1 atm	MeOH	36 hrs	100%	0%	85%
7	2 atm	MeOH	5 hrs	10%	8%	0%
8	1 atm	MeOH, 30 °C	5 hrs	9%	7%	0%
9	1 atm	MeOH, 30 °C	18hrs	100%	0%	60%
10	1 atm	MeOH, 0 °C	5 hrs	0%	0%	0%

a) The conversion and the yields were determined by ^{1}H-NMR.

Other catalysts investigated during these studies include $RhCl(PPh_3)_3$ (Wilkinson's catalyst), $RuCl_2(PPh_3)_3$, $Pd_2(dba)_3$, $PdCl_2(PPh_3)_2$, Lindlar's catalyst, and 5 % Rh/Al. In the case of Wilkinson's catalyst and $RuCl_2(PPh_3)_3$, no conversion was obtained in methanol at atmospheric pressure of hydrogen after 18 hours. The use of other

catalysts under the same conditions led (after 18 hours) to complete consumption of starting materials, yielding compounds not structurally related to **237**, **327** or **367**. Tetrahydrothebaine **367** was obtained in 8% yield with $Pd_2(dba)_3$, in 10% yield for $PdCl_2(PPh_3)_3$, and in 26 % yield with Rh/Al. With Lindlar's catalyst, dihydrothebaine **237** was obtained in 8% yield along with 10 % of tetrahydrothebaine **367**. In addition, the combination of $PdCl_2$ and sodium borohydride led to the isolation of phenolic compound **370** in 40% yield.



4 **370**

Reagents and Conditions a) $NaBH_4$, $PdCl_2$, MeOH (40%).

Scheme 39. Formation of compound **370** from thebaine (**4**).

In conclusion, some level of regioselectivity in hydrogenation of the C-8 C-14 olefin was demonstrated by using catalysts capable of coordinating to the nitrogen atom of thebaine.

3.2.4 Conversion of Thebaine to Neopinone Ketal and Direct Synthesis of Hydrocodone[159]

Thebaine is an ideal precursor to all C-14 hydroxylated derivatives and is easily transformed to 14-hydroxycodeinone by treatment with formic acid/hydrogen peroxide.[10a] Most C-14 hydroxylated derivatives are accessible through this and other procedures. The ICH (International Conference on Harmonisation) suggested to strictly limit the amount of α,β-unsaturated ketone containing compounds in pharmaceutical preparations. Therefore the development of new routes to active pharmaceutical ingredients that avoid the production of such intermediates and/or impurities are of high interest to the chemical community.[12] A logical alternative intermediate for C-14 hydroxylations would be the β, γ-unsaturated species such as neopinone and its derivatives, which still offer the potential to functionalize C-14 *via* selective transformations of the C-8 C-14 olefin. We investigated the transformation of thebaine (**4**) to neopinone ketal derivative **14** and its further transformation into valuable morphine derivatives.

4 14

Figure 51. Preparation of neopinone ketal derivative **14**.

The conversion of thebaine to neopinone ketal **365** has been demonstrated by Rapoport[153] and Dauben[154] who used mercuric acetate to activate the dieneol ether at the kinetically favored α-position as shown in Figure 52.

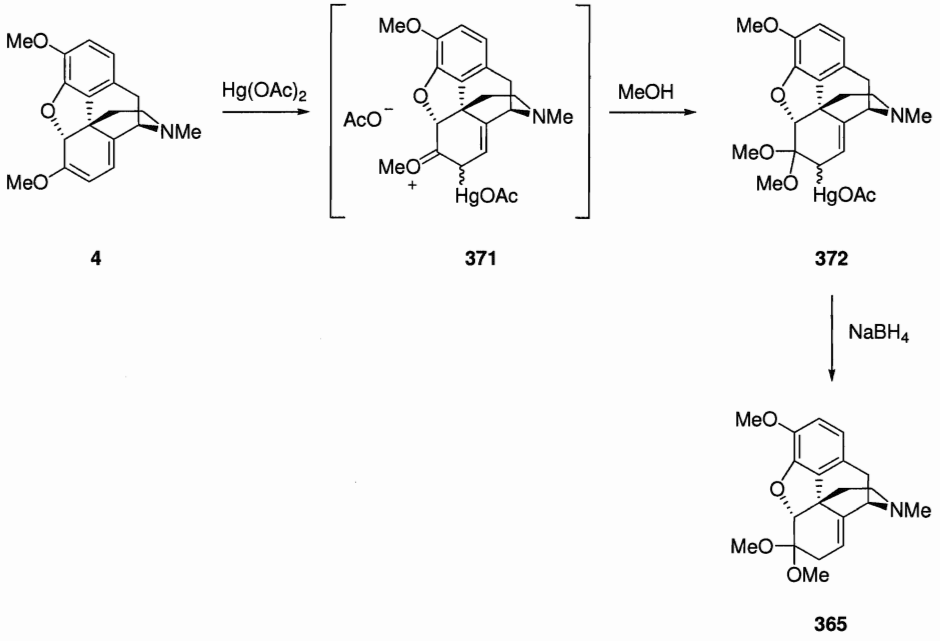
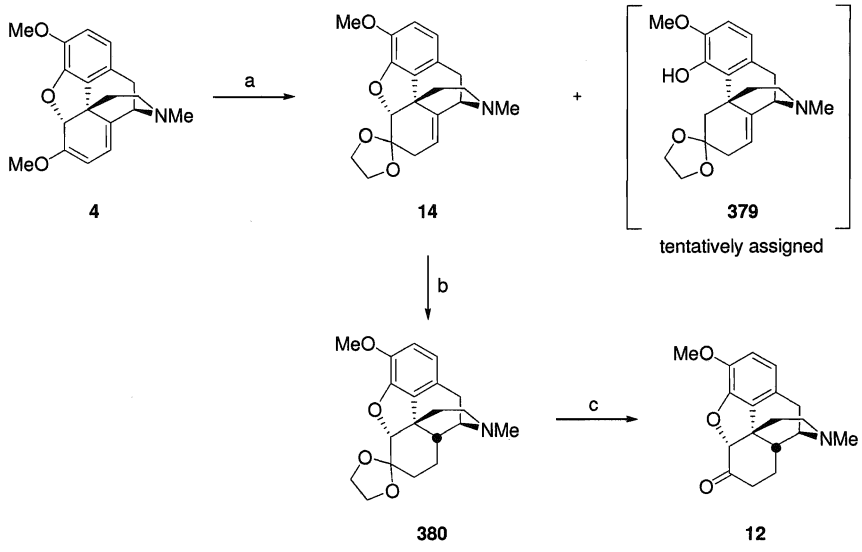


Figure 52. Formation of neopinone ketal derivative **365**.

It is well established that dienol ethers or α,β-unsaturated ketones may be converted to the corresponding β,γ-unsaturated ketals *via* kinetic protonation at the α-position and subsequent intra- or intermolecular trapping of the oxonium ion, as demonstrated by Heathcock's synthesis of α-bulnesene.[160]

To our knowledge, the unsaturated ethylene glycol ketal **14**, derived from neopinone has not been previously reported. A screening of various conditions revealed that exposure of thebaine (**4**) to ethylene glycol in chloroform in the presence of TsOH led

to the conversion to its corresponding ketal **14**, accompanied by a second species tentatively assigned as **379**, Scheme 40.



Reagents and Conditions: a) TsOH, ethylene glycol, $CHCl_3$ (45%); b) H_2, Pt/C (10%), $CHCl_3$ (quant.); c) H_2SO_4, MeOH (75%).

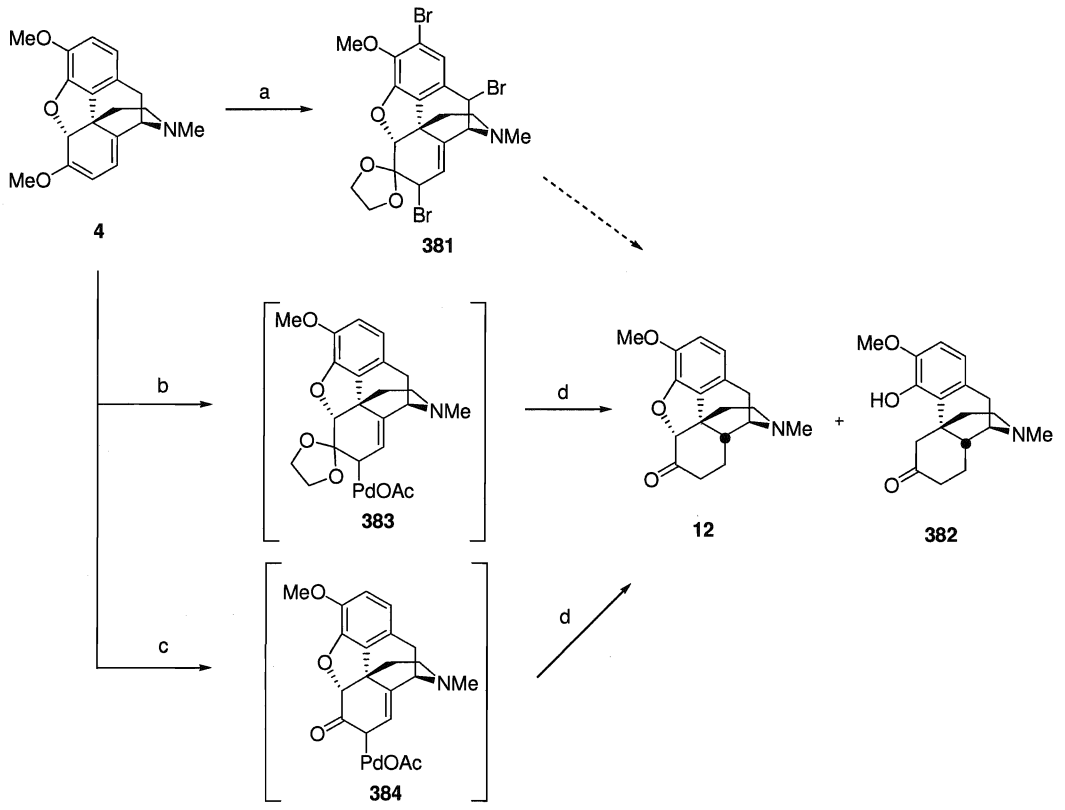
Scheme 40. Conversion of thebaine (**4**) to hydrocodone (**12**) *via* neopinone ketal **14**.

The $\Delta_{7\text{-}8}$ isomeric ketal was not detected in the reaction mixture. Encouraged by this result, we converted **14** to **380** by hydrogenation at atmospheric pressure, followed by acid catalysed hydrolysis to hydrocodone (**12**). Subsequent work demonstrated that **14** can be directly converted to **12** using a one-pot hydrogenation and hydrolysis procedure. The incompatibility of thebaine with strong protic acids is well documented,[161] as evident by the competing acid-induced pathways observed during the synthesis of **14**. We examined alternative conditions for the collapse of the enol ether of thebaine (**4**) in order to generate **14**. The use of bromine as a 'pseudo-proton', in the presence of ethylene glycol, led to the bromo ketal **381** (proposed structure),

which could be potentially be converted to hydrocodone (**4**) by hydrogenation and hydrolysis, Scheme 41.

Table 9. Reaction conditions for the formation of neopinone ketal **14**.

Entry	Conditions	Thebaine consumption (%)	Yield **14** (%) based on ^{1}H NMR
1	3.3eq TsOH (dry), 10eq glycol, $CHCl_3$	100	45 (isolated)
2	3.3eq TsOH.H_20, 10eq glycol, $CHCl_3$, 4Å MS	65	17
3	3.3eq polyphosphoric acid, 10eq glycol, $CHCl_3$	100	N/A
4	3.3eq oxalic acid.2 H_20, 10eq glycol, $CHCl_3$	0	N/A
5	3.3eq acetic acid (glacial), 10eq glycol, $CHCl_3$	0	N/A
6	3.3eq TsOH.H_20, 10eq glycol, EtOAc	100	16
7	3.3eq TsOH.H_20, 10eq glycol, EtOAc, 4Å MS	100	20
8	3.3eq TsOH.H_20, 10eq glycol, EtOAc, 4Å MS, 0.16M	100	21
9	3.3eq TsOH.H_20, 10eq glycol, EtOAc, 4Å MS, 5hrs, 0.04M	59	6
10	3.3eq TsOH.H_20, 10eq glycol, EtOAc, 4Å MS, 0.04M	100	8
11	3.3eq TsOH.H_20, 10eq glycol, PhMe, 40 °C	100	10
12	3.3eq TsOH.H_20, 10eq glycol, PhMe, 60 °C	100	12
13	3.3eq TsOH.H_20, 10eq glycol, PhMe, 120 °C	100	multiple products
14	3.3eq TsOH.H_20, 10eq glycol, 1,2-dichlorobenzene	100	8
15	5eq TsOH.H_20, 10eq glycol, $CHCl_3$	100	36
16	10eq TsOH.H_20, 10eq glycol, $CHCl_3$	100	17



Reagents and Conditions: a) Br_2, ethylene glycol, $CHCl_3$; b) $Pd(OAc)_2$, ethylene glycol, $CHCl_3$; c) $Pd(OAc)_2$, THF, H_2O; d) H_2 (4 hrs) then aq. H_2SO_4.

Scheme 41. One pot conversion of thebaine (**4**) to hydrocodone (**12**).

When $Pd(OAc)_2$, in the presence of ethylene glycol, was used with the dual purpose of acting initially as a proton surrogate and later as a hydrogenation catalyst, hydrocodone (**12**) was obtained in a one-pot sequence from thebaine in 17% yield, at the expense of the formation of phenol **382**. Since the formation of ketal intermediate **383** is not necessary for the conversion of thebaine (**4**) to hydrocodone (**12**), we reasoned that the hydrolysis step could be avoided if the reaction was performed under aqueous conditions. Indeed, treatment of thebaine in aqueous THF with stoichiometric amounts of $Pd(OAc)_2$ led rapidly to the same presumed intermediate

384, which was immediately treated with one atmosphere of hydrogen gas to yield hydrocodone (**12**) in 43% yield, with the attendant diminishment of byproduct **382**. Encouraged by the promising results with $Pd(OAc)_2$ in aqueous media, we started to screen conditions for an one-pot conversion of thebaine (**4**) to hydrocodone (**12**).[162] A wide series of common hydrogenation catalysts were screened and various acids were tested for the conversion of thebaine (**4**) to hydrocodone (**12**). Treatment of thebaine in 10 - 20% aqueous HCl under one atmosphere hydrogen in the presence of 5% w/w Pd/C (10%) provided, after extensive optimization, hydrocodone (**12**) in 63% yield. Also recovered from the reaction mixture was phenol **382** (20%) and tetrahydrothebaine (**367**) (8%). A detailed time study of this transformation is shown in Graph 1.

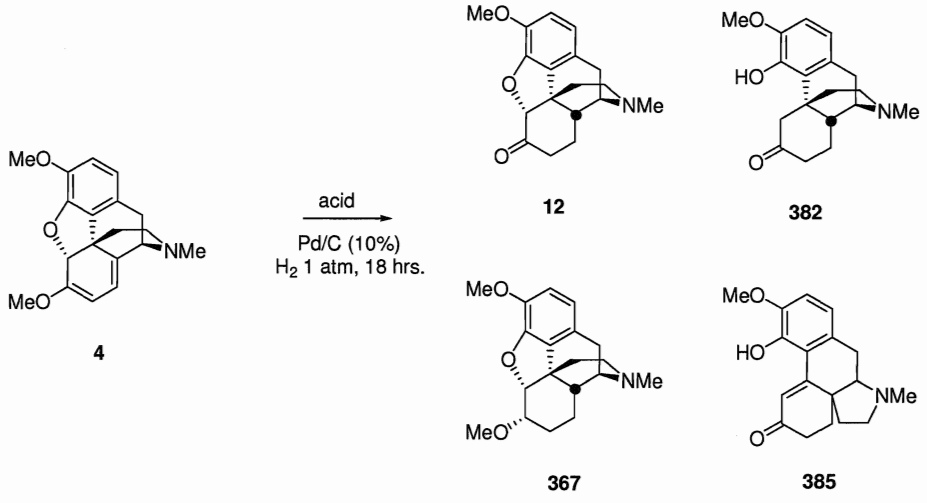
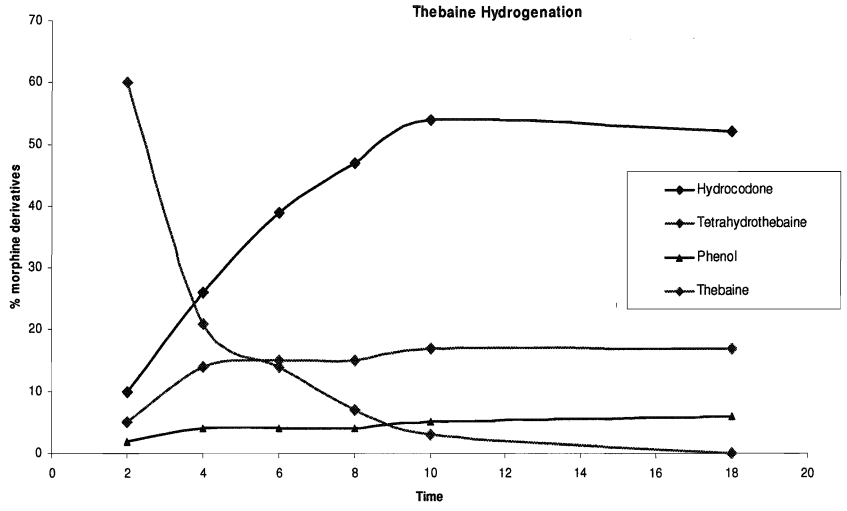


Figure 53. Hydrogenation of thebaine (**4**).



Graph 1. Hydrogenation of thebaine (**4**).

The graph shows that formation of tetrahydrothebaine (**367**) and phenol **382** only occured during the initial four hours of the reaction, after which time they have reached a maximum concentration. We suspected that one of the side-products formed during the reaction may modify the reactivity of the catalyst. Therefore we conducted several experiments, such as poisining of the catalyst with the observed sideproducts, tetrahydrothebaine **367** or phenol derivative **382**. In another set of experiments we conducted the hydrogenation with triethylamine, triphenyphosphine, or thiourea in attempts to modify the catalyst and get selective reduction. None of these variations improved the yield of hydrocodone (**12**).

Variation of the applied hydrogen pressure, as well as performing the reaction at higher temperature, decreased the yield of hydrocodone (**12**) in favour of the formation of tetrahydrothebaine (**367**). Delay of the addition of hydrogen gas (30

min, 60 min, 2 hours, or 6 hours) led to the formation of increased amounts of meta-thebainone **385**.

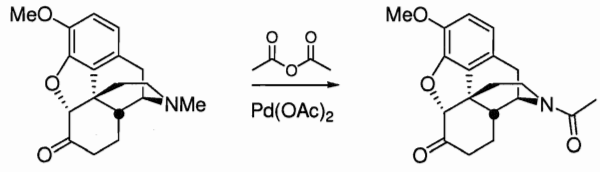
All these variations failed to improve the yield of hydrocodone, but led to the discovery of procedures which gave a wide range of morphine alkaloids in high purities (Table 10).

Table 10. Hydrogenation of thebaine (**4**).

Entry	Conditions	hydrocodone **12**	tetrahydro-thebaine **367**	phenol **382**	meta-thebainone **385**
1	Pd/C (10%), H_2 (1 atm), 20% aqueous. HCl, 18 hrs	63%	20%	8%	0%
2	Pd/C (10%), H_2 (1 atm), 20% aqueous. HCOOH, 18 hrs	0%	18%	73%	0%
3	$Rh(COD)(PPh_2C_4H_8PPh_2)^+ BF_4^-$, H_2 (1 atm), DCM, 18 hrs	0%	90%	0%	0%
4	Pt/C (1%), vanadium doped, 20% aqueous. HCl, H_2 (1 atm), 18hrs	15%	5%	0%	75%

3.2.5 Palladium-catalyzed *N*-demethylation / *N*-acylation of Morphine alkaloids[163]

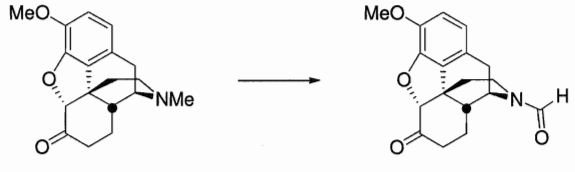
The direct conversion of hydrocodone to oxycodone would be of interest due to the higher commercial value of oxycodone. During the screening of oxidative conditions, we isolated a novel morphine derivative. The compound was identified as *N*-acetyl norhydrocodone **386**.



12 **386**

Figure 54. Formation of *N*-acetyl norhydrocodone **386**.

N-Demethylation and/or *N*-acylation reactions of morphine-type alkaloids have been extensively studied. The standard procedures for *N*-demethylation of substrates, including morphinan-derived compounds, include the use of cyanogen bromide (the von Braun reaction),[164] the reaction of a tertiary amine with chloroformates followed by hydrolysis,[165] as well as a photochemical demethylation procedure.[166] Other methods that have been used to effect demethylation include Polonovski-type reactions.[167,168]



12 **387**

Figure 55. Formation *N*-formyl norhydrocodone **387**.

Precedent for a Pd-catalysed oxidative demethylation procedure using stoichiometric amounts of Pd/C, appears in a single report by Chaudhuri,[169] however our repetition of this procedure with hydrocodone resulted only in the isolation of the *N*-formyl derivative **387** in 17% yield (Figure 55). We therefore decided to develop methodology that would be applicable to the *N*-demethylation / *N*-acylation of morphinans.

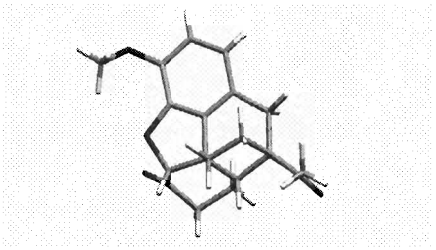


Figure 56. X-ray structure crystal structure of novel *N*-acetyl norhydrocodone **386**.

Initial experiments using stoichiometric amounts of palladium led to the use of benzene as solvent. Further investigation of reaction conditions demonstrated dioxane to be a superior solvent, with an optimum catalyst loading of 0.2 equivalents. Exhaustive experiments demonstrated that the influence of light, dissolved oxygen and moisture had no effect on the outcome of the reaction. Early attempts at optimization indicated that the use of coordinating solvents, such as acetonitrile and methanol, led to reduced yields. The use of $PdCl_2$ in place of $Pd(OAc)_2$ resulted in a dramatic decrease in yield. Less economical Pd (0) sources offered no further advantages. The most significant experiments are summarized in Table 11.

Table 11. Optimization of conditions for *N*-demethylation / *N*-acetylation of hydrocodone (**12**).

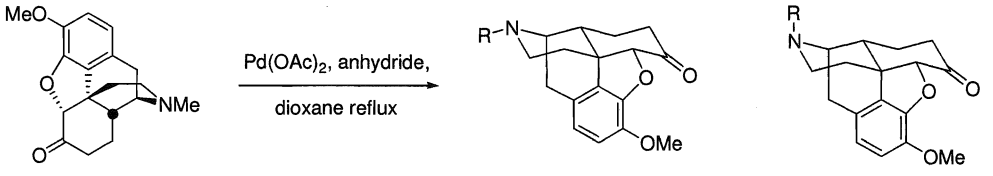
Entry	Conditions[a]	Yield of **386**[b]
1	$Pd(OAc)_2$ (1.2 equiv), MeCN, Ac_2O, 80° C	0%
2	$PdCl_2$ (1.2 equiv), benzene, Ac_2O, 80° C	50%
3	$Pd(OAc)_2$ (0.2 equiv), benzene, Ac_2O, 80° C	67%
4	$Pd(dba)_2$ (0.5 equiv), benzene, Ac_2O, 80° C	76%
5	**$Pd(OAc)_2$ (0.2 equiv), dioxane (dry), Ac_2O, 80° C**	**80%**
6	**$Pd(OAc)_2$ (0.2 equiv), dioxane (wet), Ac_2O, 80° C**	**80%**
7	$Pd(OAc)_2$ (0.2 equiv), toluene, Ac_2O, 80° C	67%
8	$Pd(OAc)_2$ (0.2 equiv), MeOH, Ac_2O, rt, 3 days	15%
9	$PdCl_2$ (0.2 equiv), Dioxane, Ac_2O, 80° C	17%
10	$Pd(PPh_3)_4$ (0.2 equiv), Dioxane, Ac_2O, 80° C	76%
11	$Pd(dba)_2$ (0.2 equiv), Dioxane, Ac_2O, 80° C	72%

a) reaction time 15 hrs, unless otherwise noted; b) yields refer to clean isolated material.

An interesting observation common to all conditions was the isolation of two conformers in a ratio of approximately 3:1 in favour of the natural, equatorially substituted isomer.

After the success of the *N*-demethylation acylation procedure using acetic anhydride, we explored the reactivity of a series of anhydrides that resulted in the isolation of a novel range of *N*-acylated norhydrocodone derivatives, as shown in Table 12.

Table 12. Synthesis of new *N*-acyl hydrocodone derivatives.



12

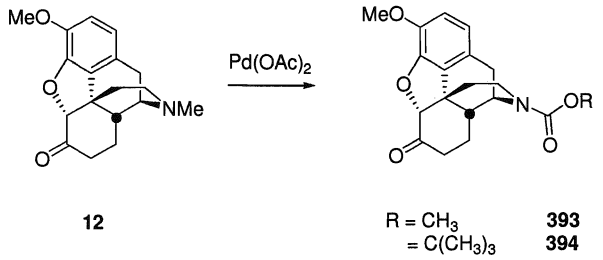
a
equatorial substitution
natural

b
axial substitution
unnatural

Entry	Anhydride	Product	R	Time (hrs)	Yield[a]	Ratio[b] a : b
1	acetic anhydride	**386**	Ac	15	80%	3 : 1
2	cyclopropylmethyl anhydride	**388**		24	76%	3 : 1
3	*iso*-butyric anhydride	**389**	$COCH(CH_3)_2$	24	13%	13 : 4
4	*n*-propyl anhydride	**390**	$COCH_2CH_3$	24	53%	3 : 1
5	decanyl anhydride	**391**	$CO(CH_2)_8CH_3$	120	36%	3 : 1
6	dodecanyl anhydride	**392**	$CO(CH_2)_{10}CH_3$	120	43%	7 : 2

a) Yields refer to clean isolated material; b) determined by NMR.

Substitution of an anhydride for a dicarbonate, such as dimethyldicarbonate, resulted in the isolation of the *N*-demethylated carbamate species **393**, in 33% yield as a mixture of two isomers (6:4 in favour of the equatorial isomer). We have also demonstrated that di-*tert*-butyldicarbonate (Boc-anhydride) can be used in this transformation (15% yield).



12

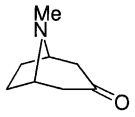
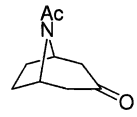
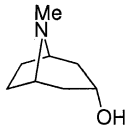
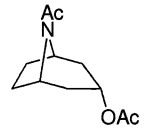
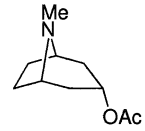
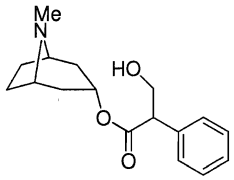
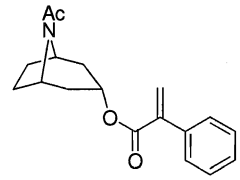
R = CH_3 **393**
= $C(CH_3)_3$ **394**

Figure 57. Formation of *N*-carbamate norhydrocodone derivatives.

In order to demonstrate the generality and the practicality of this methodology, we extended the study to include other *N*-methylated heterocycles, including atropine and its derivatives. We wished to demonstrate the compatibility of the method with a range of functional groups such as ketones and esters. The results of the demethylation / acylation sequence with tropane-type alkaloids are shown in Table 13.

The optimized conditions for the conversion of hydrocodone (**12**) to *N*-acetyl norhydrocodone **386** applied to tropane **395** gave only trace amounts of the acylated tropane derivative **396** and therefore more vigorous conditions were applied. The isolation of olefinic compound **403** can be explained by the elimination of the primary acetate formed under the reaction conditions.

Table 13. *N*-Demethylation / *N*-acylation of tropane alkaloids.

Entry	Substrate	Conditions $Pd(OAc)_2$ (0.2 equiv)	Yield[a] (conversion[b])
1	 **395**	a) Ac_2O neat, 80 °C, 14 hrs b) PhH, Ac_2O, 80 °C, 60 hrs c) MeOH, Ac_2O, rt, 3 days	 **396** a) 72% (100%) b) 48% (60 %) c) no reaction
2	 **397**	Ac_2O neat, 80 °C, 14 hrs	 **398** 70% (100%)
3	 **399**	Ac_2O neat, 80 °C, 14 hrs	 **400** 43%  **401** 35%
4	 **402**	PhH, Ac_2O, 80 °C, 60 hrs	 **403** 85%

a) Yields refer to pure isolated material; b) determined by GC/MS.

Speculative ideas on the mechanism of this reaction are outlined in Figure 58. Insertion of Pd (0), formed under the reaction conditions, into a molecule of acetic anhydride produces acyl-palladium species **404**, according to published precedent.[170]

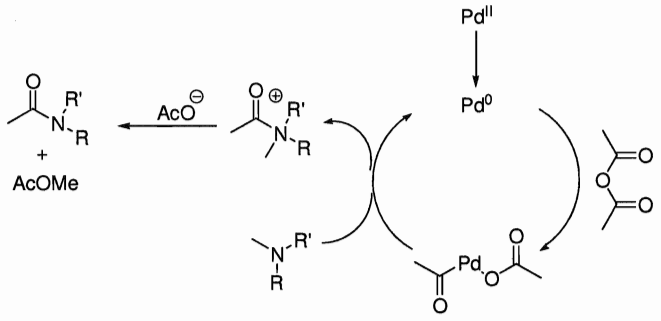
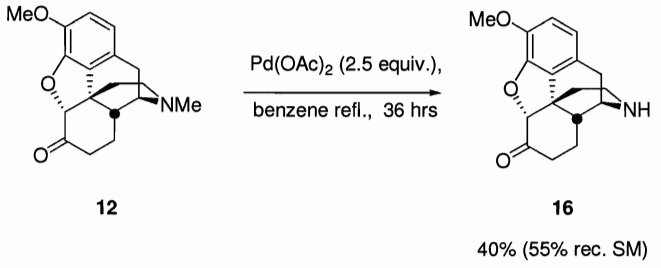


Figure 58. Suggested mechanism of *N*-demethylation using $Pd(OAc)_2$.

Quaternisation of the basic nitrogen and regeneration of a Pd (0) species is followed by release of acetate, which is subsequently methylated by the quaternized salt. Conducting the reaction in the absence of a palladium source yielded only starting material, while in the absence of anhydride and with stoichiometric amounts of $Pd(OAc)_2$, norhydrocodone (**8**) was obtained, Scheme 42. This demethylation reaction occurred only in the case of hydrocodone (**12**), and was unsuccessful if applied to other morphine derivatives such as morphine (**1**), codeine (**2**), or oxycodone (**11**).

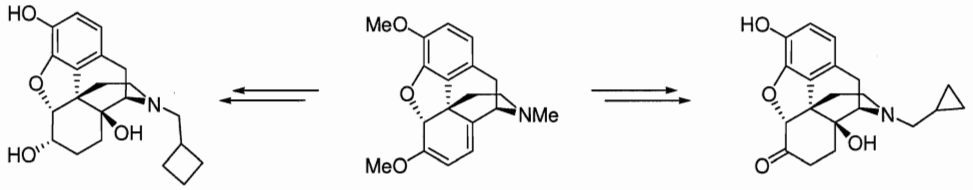


Scheme 42. *N*-demethylation of hydrocodone (**12**).

This result led to the investigation of novel procedures for the *N*-demethylation of morphine alkaloids and will be discussed in the following section.

3.2.6 Demethylation of Morphine Alkaloids[171]

The demethylation of morphine alkaloids holds immense commercial potential for the production of morphine-derived antagonists, such as naltrexone (**13**), nalbuphine (**239**), and other medicinally significant compounds. Semisynthesis of these derivatives from opium-derived natural products traditionally involve standard procedures for demethylation with subsequent formation of carbamate or acyl derivatives that then permit oxidative procedures for the introduction of a C-14 hydroxyl group. From this point, further functionalization can be achieved to yield the desired synthetic opioids.



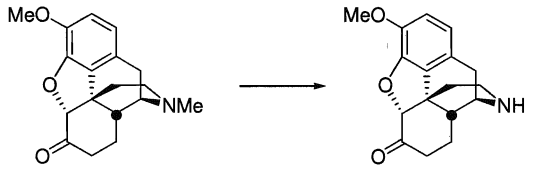
239 **4** **13**

Figure 59. Naltrexone (**13**) and nalbuphine (**239**).

We investigated alternative conditions for the synthesis of the *nor*-series of compounds, avoiding forcing and expensive conditions, such as those currently applied in industrial processes. During mechanistic studies of the novel one-pot demethylation / acylation procedure, we observed that treatment of hydrocodone (**12**) with catalytic amounts of palladium (II) salts resulted in the recovery of small amounts of the *N*-demethylated derivative **16**. Increasing the quantities of palladium

salt in the reaction resulted in elevated yields of the demethylated product **16**, as shown in Table 14.

Table 14. Demethylation of hydrocodone using $Pd(OAc)_2$ in benzene.



12 **16**

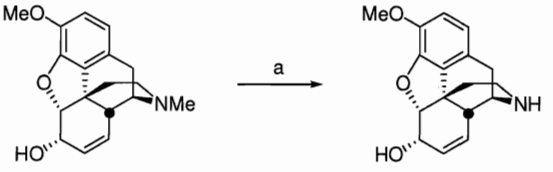
Entry	Conditions[a]	Norhydrocodone (**16**)[b]
1	$Pd(OAc)_2$ (0.2 equiv), 81° C, 15 hrs	3% (92% rec. SM)
2	$Pd(OAc)_2$ (1.2 equiv), 81° C, 36 hrs	20% (70% rec. SM)
3	$Pd(OAc)_2$ (2.5 equiv), 81° C, 36 hrs	40% (55% rec. SM)
4	$Pd(OAc)_2$ (1.0 equiv), PPh_3 (4 equiv), 81° C, 4 days	4% (90% rec. SM)
5	$Pd(OAc)_2$ (0.2 equiv), PPh_3 (0.8 equiv), 81° C, 4 days	3% (90% rec. SM)

a) benzene was used as solvent, b) isolated yield after flash column chromatography.

The use of Pd (0) sources or addition of excess phosphine ligands, in an attempt to support the catalytically-active species, proved unsuccessful and resulted in almost complete inhibition of the reaction. Extending the reaction time resulted in no increase of yield beyond that observed after 36 hours.

The application of the $Pd(OAc)_2$ demethylation procedure proved to be unsuccessful for other morphine alkaloids, such as morphine (**1**), codeine (**2**), or thebaine (**4**). In all cases, decomposition of the starting material was observed. For this reason, we set about finding a more general set of reaction conditions that would also avoid the

stoichiometric quantities of palladium required by the initial reaction. We envisioned that oxidizing conditions would allow for the demethylation of morphine alkaloids. One obvious choice was the use of Fenton's reagent, iron sulfate and hydrogen peroxide.[172] Various variations of the originally reported conditions proved unsuitable for this conversion.



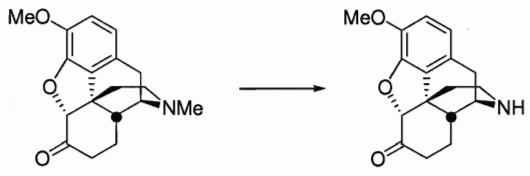
2 **405**

Reagents and Conditions: a) $Cu(OAc)_2$, $(NH)_4S_2O_8$, CH_3CN : H_2O; 5 :1, rt, 16 hrs (22%).

Scheme 43. *N*-Demethylation of codeine **2**.

Exhaustive screening of metal salts known to have been applied previously to oxidative demethylation-type reactions proved discouraging, until we applied a combination of copper acetate and ammonium peroxysulfate in a mixture of acetonitrile and water as solvent. These conditions were successful for the demethylation of hydrocodone (**12**), as well as codeine (**2**). Norhydrocodone (**16**) was isolated in 64% yield from **12** after optimisation (Table 15), whereas norcodeine (**405**) was obtained in 22% yield from **2** (Scheme 43).

Table 15. Optimization of the copper-mediated demethylation of hydrocodone 12.



12 16

Entry	$Cu(OAc)_2$	$(NH_4)_2S_2O_8$	Norhydrocodone (**16**)	Hydrocodone (**12**) (recovered SM)
1	0.5 equiv	2 equiv	20%	64%
2	1 equiv	2 equiv	36%	46%
3	0.5 equiv	4 equiv	24%	55%
4	1 equiv	4 equiv	36%	38%
5	2 equiv	4 equiv	64%	10%

All reactions were carried out at room temperature under an atmosphere of air, utilizing CH_3CN : H_2O 5 : 1 as solvent with nine hours of reaction time.

Optimisation of these conditions involved testing of various solvent mixtures, screening various copper salts (CuCl, CuI, $CuCl_2.2H_2O$, $CuCO_3$, $CuSO_4.5H_2O$, CuO) as well as varying the equivalents of both copper acetate and ammonium peroxysulfate.

Further variation of reaction conditions included conducting the reaction under oxygen as well as inert gas atmosphere, variation of the oxidant, alteration of the reaction temperature, as well as changing the catalyst and oxidant. Unfortunately, none of these variations showed beneficial effects (Table 16).

Table 16. Variation of the *N*-demethylation procedure.

Entry	Variable[a]	Norhydrocodone (**16**)[b]	Hydrocodone (**12**)[b]
1	Air	64%	10
2	Oxygen atmosphere	53%	15%
3	Argon atmosphere	50%	18%
4	H_2O_2 (10 equiv) as oxidant	Hydrocodone *N*-oxide **405**	
5	Reaction temperature 50 °C	42%	32%
6	Reaction temperature 60 °C	37%	51%

a) Reaction conditions: 2 equiv $Cu(OAc)_2$, 4 equiv $(NH)_4S_2O_8$, CH_3CN : H_2O; 5 :1, rt, 16 hrs; b) isolated yield after flash column chromatography.

Unlike the conditions reported by Scammels,[167] which require the initial formation and isolation of the corresponding *N*-oxide before its subsequent demethylation, the present process is a one-pot procedure. In fact, we found that prior formation of the corresponding *N*-oxide **406** and subsequent treatment with $Cu(OAc)_2$ and $(NH_4)_2S_2O_8$ resulted in no reaction, indicating that perhaps our process follows a different mechanism.

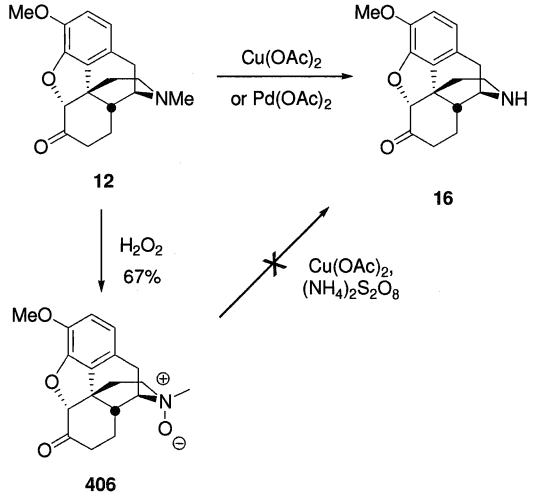


Figure 60. Probing the mechanism of the copper mediated demethylation procedure.

In summary, we developed convenient conditions for the demethylation of hydrocodone, which may also be applied to codeine. The true advantage of this method is the elimination of toxic and expensive reagents, while at the same time providing a one-pot, one-step conversion using cheap and easily accessible reagents.

4. Conclusions and Future Work

In the course of the studies summarizes in this dissertation, we were able to design an enantiodivergent synthesis of codeine (**2**). The common feature of these syntheses is the use of a cyclohexadiene diol derivative, obtained from microbial *cis*-dihydroxylation of β-bromoethylbenzene. In both cases, the homochiral C-ring fragment of codeine was constructed efficiently with the methyl amine and hydroxyl functionalities in place. The connection of the aromatic part to the C-ring fragment was achieved by Mitsunobu coupling, in the case of the (+)-codeine synthesis, and by the conversion of the *cis*-diol to a β-epoxide and its regioselective epoxide opening for the synthesis of (-)-codeine. The complete phenanthrene core of morphine alkaloids was constructed by Heck cyclizations similar to Trost's approach.[8] Unable to repeat Trost's procedure for the closure of the D-ring, we successfully designed an oxymercuration reduction sequence to obtain the complete core of morphine alkaloids. Optimization of this final transformation will be required in order to increase the overall yield of both syntheses.

In addition to the syntheses of codeine (**2**), novel methodologies were investigated directed towards the conversion of naturally-occurring opiates into more valuable opioids. Initial studies on the hydrogenation of thebaine revealed that the use of Crabtree's catalyst led to the regioselective hydrogenation of the C8/C14 olefin, whereas hydrogenation with a commercially available rhodium catalyst gave codeine methyl ether in acceptable yield. Furthermore, we were successful in developing a one pot procedure for the conversion of thebaine (**4**) into a novel neopinone ketal

derivative. Subsequent studies led to a one pot conversion of thebaine to the commercially available analgesic hydrocodone (**12**).

Studies directed towards the conversion of hydrocodone to oxycodone led to the isolation of *N*-acetyl norhydrocodone (**386**). Optimization of the *N*-demethylation / *N*-acylation reaction conditions and substitution of acetic anhydride by a wide range of anhydrides and dicarbonates led to the isolation of novel *N*-acyl and *N*-carbamate norhydrocodone derivatives. We could demonstrate the generality and practicality of this novel methodology by the conversion of other *N*-methylated heterocycles, including atropine, to their corresponding acylated derivatives. A novel palladium-catalyzed demethylation procedure for hydrocodone was discovered while studying the mechanism of the *N*-demethylation / *N*-acylation reaction. Further investigations on the demethylation of morphine alkaloids led to the discovery of a copper-based procedure, which was successful when applied to hydrocodone, as well as codeine. Future work in this area should focus on the application of these novel methodologies to the syntheses of opioid antagonists, such as naltrexone (**13**), naloxone (**243**), or nalbuphine (**239**).

In addition, we have shown that the reaction of the Burgess reagent with aliphatic epoxides gives *cis*-fused cyclic sulfamidates and not *trans*-fused sulfamidates as originally reported. We successfully prepared the first chiral version of the Burgess reagent and demonstrated that homochiral derivatives of both *cis*- and *trans*-amino alcohols can be obtained from epoxides in an enantiodivergent fashion. Application of the asymmetric version of the Burgess reagent allowed for the design of an enantiodivergent synthesis of balanol.

5. Experimental Section

5.1 General Experimental Details

All non-aqueous reactions were carried out in an argon atmosphere using standard Schlenk techniques for the exclusion of moisture and air. DCM and acetonitrile were distilled from calcium hydride. THF, benzene, dioxane, toluene, diethyl ether, and DME were distilled from sodium with benzophenone ketyl as indicator immediately before use. Methanol and ethanol were distilled from magnesium turnings and iodine under nitrogen, either directly into the reaction vessel, or stored over activated 3Å molecular sieves. Liquid reagents were distilled prior to use, and commercial solids were used as supplied. Analytical thin-layer chromatography was performed on Silicycle 60 Å 250 μm TLC plates with F-254 indicator. Flash column chromatography was performed using Natland 200-400 mesh silica gel. Melting points were recorded on a Hoover Unimelt apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer One FT-IR spectrometer. Optical rotation was measured on a Perkin Elmer 341 polarimeter. ^{1}H-, ^{19}F- and ^{13}C-NMR spectra were recorded on a Bruker (300 MHz or 600 MHz) spectrometer. All chemical shifts are referenced to TMS or residual undeuterated solvent ($CHCl_3$, DCM). 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. Separation by HPLC was either performed on a Hitachi L-6000 HPLC using a Hitachi L-4000H UV detector (254 nm) with a Phenomenex primespher 5 C18 HC

250 x 10 mm column; 2 ml/min flow; 5 mM KH_2PO_4, 0.1% NEt_3, pH = 2.8 adjusted with 2N HCl : MeOH (80:20) or performed on an Agilent 1100 series HPLC using a Phenomenex primesphere 5 C18 HC, 150 x 4.6 mm column and 1.3 ml/min flow. Compounds were detected at 280 nm and opioids were eluted with a gradient of 5 mM KH_2PO_4, 0.1% NEt_3, pH = 2.8 adjusted with 2N HCl and MeOH. Combustion analyses were performed by Atlantic Microlabs, Norcross, GA. Mass spectra were recorded on Kratos/MsI Concept 1S mass spectrometer at Brock University.

5.2 Experimental Procedures

General procedure for the reaction of oxiranes with Burgess reagent.

To a stirred solution of oxirane (4.0 mmol) in THF (20 mL) was added (methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt (**18**) (2.38 g, 9.2 mmol) at rt in a single portion. The resulting reaction mixture was immediately brought to reflux by submerging it into a preheated oil bath (70 °C). The reaction mixture was stirred until complete consumption of the oxirane (TLC), then cooled to rt and filtered through a plug of silica to remove salts formed during the reaction. The reaction solution was then concentrated and the resulting residue was purified by flash column chromatography using an appropriate solvent gradient (hexanes : ethyl acetate) to yield the corresponding sulfamidate product(s).

General procedure for the reaction of oxiranes with menthyl Burgess reagent 21.

To a stirred solution of oxirane (2.0 mmol) in THF (5 mL) was added **21** (4.60 mmol) at rt in a single portion. The resulting reaction mixture was immediately brought to reflux by submerging it into a preheated oil bath (70 °C). The reaction mixture was stirred until complete consumption of the oxirane (TLC), then cooled to rt and filtered through a plug of silica to remove salts formed during the reaction. The reaction mixture was then concentrated and the resulting residue was purified by flash column chromatography using an appropriate solvent gradient (hexanes : ethyl acetate) to afford a 1:1 mixture of diastereomers.

General procedure for the syntheses of benzoates from sulfamidates.

To a stirred solution of sulfamidate (1.25 mmol) in dry DMF (5 mL) was added ammonium benzoate (346 mg, 2.50 mmol). The solution was heated at 55 °C and stirred for 18 hrs before the solvent was evaporated, and the resulting residue was dissolved in THF (3 mL). Three drops of water and three drops of conc. H_2SO_4 were added, and the reaction mixture was stirred at rt for 12 hrs. The reaction mixture was diluted with water and the pH was adjusted to 9, using a saturated aqueous solution of $NaHCO_3$, before the layers were separated. The aqueous layer was extracted with DCM (3 x 5 mL), then the organic layers were combined and washed with brine (1 x 5 mL), dried over anhydrous sodium sulfate, filtered, and the solvent was evaporated. The resulting diastereomers were separated by flash column chromatography (hexanes : ethyl acetate) using an appropriate solvent system.

General procedure for the formation of disulfides.

To a solution of Burgess reagent (**18**) (1.05 equiv) in benzene (1 molar) was added dropwise the corresponding thiol (1 equiv) dissolved in benzene at rt The progress of the reaction was followed by GC/MS. After complete conversion of the starting material (approximately 30 min to 1 hour) the reaction mixture was filtered through a plug of silica (hexanes). The crude product was either triturated with hexanes or purified by flash column chromatography.

General procedure for *N*-demethylation / acylation reaction.

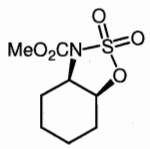
To the tertiary amine (0.1 mmol, 1.0 equiv) dissolved in an appropriate anhydride (1 mL) and dioxane (1 mL) was added $Pd(OAc)_2$ (0.01 mmol, 0.1 equiv). The mixture was heated at 80 °C for 18 h, cooled to room temperature and filtered through a plug of silica with DCM : MeOH: NH_4OH, 80:20:1 as eluent. The volatiles were removed *in vacuo,* and the residue was suspended in saturated aqueous $NaHCO_3$. The aqueous phase was extracted with DCM (three times), and the organic extracts were combined and washed with 1M aqueous HCl and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and the volatiles were removed under reduced pressure to yield the crude product, which was subjected to flash column chromatography (DCM : MeOH, gradient) to give the pure acylated compound.

General procedure for $Pd(OAc)_2$-mediated demethylation.

To a solution of the tertiary amine (0.1 mmol, 1.0 equiv) in benzene (1 mL) was added $Pd(OAc)_2$ (0.25 mmol, 2.5 equiv). The mixture was heated at reflux for 36 h, cooled to room temperature, and filtered through a plug of silica with DCM : MeOH : NH_4OH, 80:20:1 as eluent. Following the removal of volatiles under reduced pressure, the residue was suspended in aqueous $NaHCO_3$, then extracted with $CHCl_3$. The organic layer was dried over magnesium sulfate and filtered, then the volatiles removed *in vacuo*. Flash column chromatography (silica gel; $CHCl_3$: MeOH : NH_4OH, 96:4:1) of the crude material affords analytically pure demethylated product.

General procedure for $Cu(OAc)_2$-mediated demethylation.

To the tertiary amine (0.1 mmol, 1.0 equiv) dissolved in CH_3CN : H_2O; 5 : 1 (1 mL), was added $Cu(OAc)_2$ (0.2 mmol, 2.0 equiv) and $(NH_4)_2S_2O_8$ (0.4 mmol, 4.0 equiv). The mixture was stirred at room temperature for 12 h, then. the reaction was quenched with aqueous 10% $Na_2S_2O_3$. The organic solvent was removed under reduced pressure, the residue was basified to pH 9 with concentrated aqueous NH_4OH, then extracted three times with DCM. After combining the organic layers, drying over anhydrous magnesium sulfate, and filtration, the volatiles were removed *in vacuo*. Flash column chromatography (silica gel; $CHCl_3$: MeOH : NH_4OH, 96:4:1) of the crude material afforded analytically pure demethylated product.



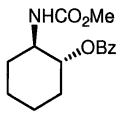
247

***cis*-Hexahydro-2,2-dioxide-3H-1,2,3-benzoxathiazole-3-carboxylic acid methyl ester (247).**

Compound **247** was prepared in 64 % yield (604 mg) as colorless crystals following the general procedure for reactions of oxiranes with the Burgess reagent **18**, using cyclohexene oxide as starting material. mp 97 - 98 °C (ethyl acetate/hexanes); R_f 0.49 (hexanes : ethyl acetate, 1:1); IR (film) ν_{max}: 2943, 1743, 1385, 1183 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.00 (bs, 1H), 4.22 (bs, 1H), 3.90 (bs, 3H), 2.33 (bs, 2H), 1.45 - 1.85 (m, 4H), 1.16 - 1.33 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.4, 80.0, 58.3, 54.7, 27.4, 27.2, 22.0, 19.1 ppm; HRMS (FAB) ($M+H^+$) calcd for $C_8H_{14}O_5NS$:

236.0593, found 236.0608; Anal calcd for $C_8H_{13}O_5NS$: C 40.84% H 5.70%, found C 40.98% H 5.70%.

Alternatively, compound **247** was prepared by following procedure. To a solution of oxathiazolidine **254** (300 mg, 1.37 mmol) in CH_3CN (5 mL) was added sequentially, ruthenium(III)chloride hydrate (catalytic amount), sodium periodate (439 mg, 2.05 mmol) and water (5 mL) at 0 °C. The reaction mixture was warmed to rt and was stirred at ambient temperature for an additional 3 hrs. The reaction mixture was extracted three times with Et_2O. The organic layers were combined, washed with water, then brine, and dried over anhydrous magnesium sulfate. Filtration, evaporation of the solvent, and purification by flash column chromatography (hexanes : ethyl acetate, 4:1) afforded 287 mg (82%) of compound **247*** as white solid after recrystallization from hexanes/ethyl acetate. The analytical data obtained for compound **247*** is identical to data of compound **247**.

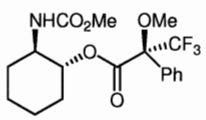


249

***trans*-2-Methylcarbonylamino-cyclohexylester benzoic acid (249).**

To a solution of benzoxathiazole **247** (550 mg, 2.34 mmol) in dry DMF (10 mL) was added ammonium benzoate (651 mg, 4.68 mmol). The solution was heated at 55 °C until TLC analysis indicated full conversion of the starting material (18 hrs). The solvent was evaporated and the residue was dissolved in THF (6 mL), three drops of water and three drops of conc. H_2SO_4 were added. The reaction mixture was stirred at

rt for 3 hrs, before the pH was adjusted to 8, using saturated aqueous $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted three times with DCM. The organic layers were combined, washed with water and brine. The solution was dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (hexanes : ethyl acetate, 9:1) affording 265 mg (41%) of compound **249** as colorless oil. R_f 0.55 (hexanes : ethyl acetate, 2:1); IR (film) ν_{max}: 3339, 3064, 2940, 2861, 1714, 1538, 1452, 1320, 1279, 1235, 1115, 713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.04 (d, *J* = 7.5 Hz, 2H), 7.50 - 7.58 (m, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 4.83 (m, 2H), 3.71 - 3.88 (m, 1H), 3.53 (s, 3H), 2.02 - 2.24 (m, 2H), 1.69 - 2.02 (m, 2H), 1.49 - 1.68 (m, 1H), 1.18 - 1.48 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.0, 156.8, 133.2, 130.3, 129.9, 128.5, 75.9, 54.5, 52.2, 32.6, 31.3, 24.6, 24.2 ppm; HRMS (FAB) ($M+H^+$) calcd for $C_{15}H_{20}NO_4$: 278.1392, found 278.1382.

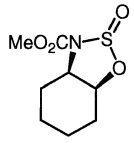


250

***trans*-2-((*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyloxy) cyclohexylmethyl-carbamate (250).**

To a solution of carbamic acid methyl ester **256** (40 mg, 0.23 mmol) dissolved in DCM (3 mL) were added sequentially 1-ethyl-3-(-3'dimethylaminopropoyl) carbodiimide·HCL (49 mg, 0.25 mmol), 4-dimethylaminopyridin (3 mg, 0.02 mmol), and (*R*)-(+)-Mosher's acid (54 mg, 0.23 mmol) at 0 °C. The reaction mixture was cooled for one additional hour and the solution was stirred at rt for two days until

TLC analysis indicated full consumption of starting material. The reaction mixture was diluted with DCM and washed with saturated aqueous solution of NH_4Cl, saturated aqueous solution of $NaHCO_3$, and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated under reduced pressure. Flash column chromatography (hexanes : ethyl acetate, 2:1) of the residue afforded 31 mg (40%) of compound **250** as colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.47 - 7.56 (m, 2H), 7.34 - 7.42 (m, 3H), 4.53 - 4.97 (m, 2H), 3.43 - 3.78 (m, 7H), 1.91 - 2.17 (m, 2H), 1.17 - 1.86 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.6, 156.5, 132.6, 129.93, 129.90, 128.8, 127.6, 125.5, 55.7, 54.2, 52.5, 52.3, 33.0, 32.8, 31.3, 30.9, 30.1, 29.3, 24.4, 24.2, 24.1 ppm; ^{19}F (282 MHz, $CDCl_3$) δ: -72.08 (3F), -72.42 (3F).

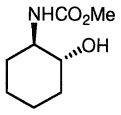


254

***cis*-Hexahydro-2-oxide-3H-1,2,3-benzoxathiazole-3-carboxylic acid methyl ester (254).**

To a solution of thionylchloride (0.83 mL, 11.41 mmol) in CH_3CN (60 mL) was added a solution of carbamic acid methyl ester **248** (0.79 g, 4.56 mmol) in CH_3CN (20 mL) dropwise at -35 °C over 10 min. The reaction mixture was stirred at -35 °C for 5 min, before pyridine (1.84 mL, 22.82 mmol) was added dropwise. The reaction mixture was warmed to rt over 3 hrs. The solvent was evaporated and the residue was triturated with Et_2O. The suspension was filtered and the filtrate was concentrated under reduced pressure. Purification of the residue by flash column chromatography

(hexanes : ethyl acetate, 5:1) afforded 0.63 g (63%) of compound **254** as colorless oil. R_f 0.75 (hexanes : ethyl acetate, 1:1); IR (film) ν_{max}: 2943, 2867, 1730, 1442, 1359, 1328, 1288, 1187, 1148 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (two rotamers) δ: 5.24 - 5.31 (bs, 0.66H), 4.66 (q, J = 4.0 Hz, 0.33H), 3.94 - 4.12 (m, 1H), 3.84 (s, 1H), 3.82 (s, 2H), 2.09 - 2.34 (m, 2H), 1.54 - 2.45 (m, 4H), 1.33 - 1.52 (m, 1H), 1.08 - 1.31 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) (two rotamers) δ: 152.9, 85.0, 80.0, 55.6, 54.1, 53.7, 53.6, 28.8, 28.4, 27.9, 26.8, 22.6, 22.2, 19.6, 19.5 ppm; MS (EI) *m/z* (%): 219 (12), 171 (16), 155 (29), 154 (26), 140 (65), 127 (44), 126 (13), 124 (16), 77 (100), 75 (16), 64 (33); HRMS (EI) calcd for $C_8H_{13}NO_4S$: 219.0565, found 219.0561.

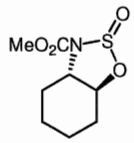


256

***trans*-[2-Hydroxycyclohexyl]- carbamic acid methyl ester (256).**

Methyl chloroformate (0.3 mL, 3.94 mmol) was added dropwise to a vigorously stirred solution of *trans*-2-aminocyclohexanol hydrochloride (**255**) (0.5 g, 3.30 mmol) and $NaHCO_3$ (0.83 g, 9.9 mmol) in a 1:1 mixture of $CHCl_3$ and water (30 mL). The mixture was stirred at rt for 1 hour, before the reaction mixture was neutralized with 1N HCl. The aqueous layer was extracted three times with DCM. The organic layers were combined, washed with brine, and dried over anhydrous magnesium sulfate. Filtration, evaporation of the solvent and recrystallization from hexanes/ethyl acetate furnished the title compound as colorless solid (498 mg, 87%). mp 109 - 111°C (hexanes/ethyl acetate); IR (film) ν_{max}: 3436, 3156, 2942, 2863, 2253, 1708, 1517, 1452, 1517, 1452, 1384 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 4.75 - 5.15 (bs, 1H),

3.66 (s, 3H), 3.21 - 3.46 (m, 1H), 2.98 - 3.18 (bs, 1H), 1.91 - 2.12 (m, 2H), 1.60 - 1.79 (m, 2H), 1.05 - 1.41 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.4, 75.6, 57.5, 52.9, 34.6, 32.2, 25.1, 24.5 ppm; MS (EI) *m/z* (%): 173 (1), 141 (18), 114 (75), 112 (22), 102 (12), 98 (100), 88 (42), 69 (26), 56 (51), 51 (66); HRMS (EI) calcd for $C_8H_{15}NO_3$: 173.1052, found 173.1053; Anal calcd for $C_8H_{15}NO_3$: C 55.47% H 8.73%, found C 55.16% H 8.73%.

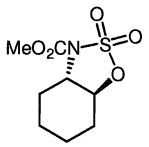


257

***cis*-Hexahydro-2-oxide-3H-1,2,3-benzoxathiazole-3-carboxylic acid methyl ester (257).**

To a solution of thionylchloride (0.84 mL, 11.55 mmol) in CH_3CN (60 mL) was added a solution of compound **256** (0.80 g, 4.62 mmol) in CH_3CN (20 mL) dropwise at - 35 °C over 10 min. The reaction mixture was stirred at the same temperature for 5 min, before pyridine (1.8 mL, 23.11 mmol) was added dropwise. The reaction mixture was warmed to rt over 3 hrs. The solvent was evaporated and the residue was triturated with Et_2O. The suspension was filtered and the filtrate was concentrated under reduced pressure. Flash column chromatography (hexanes : ethyl acetate, 5:1) of the residue afforded the title product **257** as colorless solid (0.79 g, 78%). mp 51 - 54 °C (hexanes/ethyl acetate); R_f 0.52 (hexanes : ethyl acetate, 2:1); IR (film) ν_{max}: 3368, 2954, 2254, 1733, 1572, 1444, 1384, 1328, 1300 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 4.71 (dt, J = 11.2, 4.1 Hz, 1H), 3.83 (s, 3H), 3.13 (dt, J = 13.4, 3.1 Hz, 1H),

2.61 - 2.74 (m, 1H), 2.20 - 2.34 (m, 1H), 1.79 - 2.02 (m, 2H), 1.69 (dq, J = 11.9, 4.2 Hz, 1H), 1.19 - 1.54 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.7, 86.8, 63.2, 54.0, 29.8, 29.5, 24.3, 23.9 ppm; MS (EI) *m/z* (%): 219 (5), 140 (10), 114 (100), 81 (12), 59 (24), 44(17); HRMS (EI) calcd for $C_8H_{13}NO_4S$: 219.0565, found 219.0565; Anal calcd for $C_8H_{13}NO_4S$: C 43.82% H 5.98%, found C 44.12% H 6.05%.

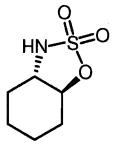


98

***trans*-Hexahydro-2,2-dioxide-3H-1,2,3-benzoxathiazole-3-carboxylic acid methyl ester (98).**

To a solution of oxathiazolidine **257** (140 mg, 0.64 mmol) in CH_3CN (3 mL) was added sequentially, ruthenium(III)chloride hydrate (catalytic amount), sodium periodate (205 mg, 0.96 mmol) and water (3 mL) at 0°C. The reaction mixture was warmed to rt and stirred at ambient temperature for an additional three hrs. The reaction mixture was extracted three times with Et_2O. The organic layers were combined and washed with water and brine, then dried over anhydrous magnesium sulfate. Filtration, evaporation of the solvent and purification by flash column chromatography (hexanes : ethyl acetate, 5:1) afforded 130 mg (87%) of the title compound **98** as colorless oil. R_f 0.55 (hexanes : ethyl aceate, 2:1); IR (film) ν_{max}: 3367, 2958, 2870, 2255, 1746, 1444, 1384, 1329, 1299, 1193 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.39 (dt, J = 11.1, 4.2 Hz, 1H), 3.88 (s, 3H), 3.73 - 3.84 (m, 1H), 2.59 - 2.73 (m, 1H), 2.19 - 2.31 (m, 1H), 1.81 - 2.05 (m, 2H), 2.05 (dq, J = 12.2, 4.1

Hz, 1H), 1.30 - 1.58 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.6, 84.6, 64.7, 54.9, 29.0, 28.3, 23.7, 23.5 ppm; MS (EI) *m/z* (%): 235 (1), 155 (37), 150 (100), 140 (12), 124 (13), 114 (19), 101 (52), 98 (26), 95 (22), 81 (44), 69 (24), 59 (53); HRMS (EI) calcd for $C_8H_{13}NO_5S$: 235.0514, found 235.0519. Anal calcd for $C_8H_{13}NO_5S$: C 40.84% H 5.57%, found C 41.18% H 5.84%.

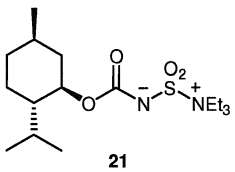


258

***trans*-Hexahydro-2,2-dioxide-3H-1,2,3-benzoxathiazole (258).**

To a solution of benzoxathiazole **98** (640 mg, 2.72 mmol) in DMF (5 mL) was added ammonium benzoate (757 mg, 5.44 mmol) in one portion. The reaction mixture was heated at 75 °C until full conversion of starting material was indicated by TLC (24 hrs). The solvent was evaporated and the residue was dissolved in THF (3 mL). Three drops of water and conc. H_2SO_4 were added and the reaction was allowed to stir at 60 °C for 3 hrs. The mixture was cooled to rt and the pH of the reaction mixture was adjusted to pH 9 using a saturated aqueous solution of $NaHCO_3$. The reaction mixture was extracted three times with DCM. The organic layers were combined, washed with brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (hexanes : ethyl acetate, 4:1) affording 440 mg (91%) of the title compound **258**. mp 94 - 97 °C (hexanes/ethyl acetate); R_f 0.60 (hexanes : ethyl acetate, 1:1); IR (film) ν_{max}: 3256, 2953, 2869, 1794, 1642, 1458, 1448, 1406, 1364, 1342, 1331, 1278, 1231,

1192, 1138, 1101, 1074, 1052, 1001, 950 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 4.91 (d, *J* = 9.0 Hz, 1 H), 4.30 (dq, *J* = 10.0, 5.2 Hz, 1H), 3.41 - 3.47 (m, 1H), 2.20 - 2.27 (m, 1H), 2.09 - 2.18 (m, 1H), 1.84 - 1.97 (m, 2H), 1.70 (dq, *J* = 12.0, 4.0 Hz, 1H), 1.36 - 1.44 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 90.1, 63.2, 28.5, 27.7, 23.8, 23.4; HRMS (EI) calcd for $C_6H_{11}NO_3S$: 177.0456, found 177.0454.

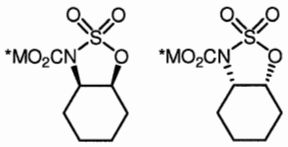


21

***N,N*-Diethyl-*N*-[[[[[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl) cyclohexyl]oxy] carbonyl] amino]sulfonyl]-ethanaminium, inner salt (21).**

To a stirred solution of chlorosulfonyl isocyanate (5.21 g, 36.8 mmol) in benzene (15 mL) was added a solution of (-)-menthol (5.00 g, 32 mmol) in benzene (15 mL) dropwise over 30 min while keeping the internal temperature between 25 - 30 °C, using an ice-water bath. The reaction mixture was then stirred at rt for an additional 30 min, before ice cold hexane (40 mL) was added while cooling the reaction mixture to 0 - 5 °C. The product was filtered and washed with ice cold hexanes (2 x 20 mL) and dried under reduced pressure to yield 8.29 g (87%) of (-)-menthol sulfamoyl chloride as colorless crystals (87%). mp 86 - 88 °C (hexanes); $[\alpha]_D^{23}$ -64.5 (*c* 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.38 - 8.55 (bs, 1H), 4.81 (td, *J* = 11.2, 4.6 Hz, 1H), 2.07 - 2.16 (m, 1H), 1.83 - 2.01 (m, 1H), 1.61 - 1.77 (m, 2H), 1.39 - 1.58 (m, 2H), 1.04 - 1.22 (m, 2H), 0.93 (t, *J* = 6.8 Hz, 6H), 0.83 (d, *J* = 6.8 Hz, 3H) ppm. (-)-Menthol sulfamoyl chloride was used without further purification for the next step.

To a stirred solution of triethylamine (6.53 mL, 47.0 mmol) in benzene (20 mL) was added a solution of (-)-menthol sulfamoyl chloride (7.00 g, 23.5 mmol) in benzene (40 mL) dropwise over 1 hour, keeping the internal temperature between 10 - 15 °C, using an ice-water bath. The reaction mixture was stirred at rt for an additional 30 min and then filtered to remove the triethylamine hydrochloride salt. The filtrate was evaporated under reduced pressure, then dissolved in THF (50 mL) at 30 °C and cooled to 0 - 5 °C and treated with hexanes (50 mL) to precipitate out 7.24 g (85%) of the title compound **21** as a colorless solid. mp 87 - 89 °C (THF/hexanes); $[\alpha]_D^{23}$ -48.7 (*c* 0.48, $CHCl_3$); IR (film) ν_{max}: 3426, 3020, 2958, 2872, 1682, 1457, 1389, 1369, 1340, 1285, 1253, 1216, 1105, 982, 922, 891 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 4.51 (td, *J* = 11.0, 4.6 Hz, 1H), 3.45 (q, *J* = 7.7 Hz, 6H), 3.14 - 3.26 (m, 1H), 1.93 - 2.08 (m, 2H), 1.65 (d, *J* = 11.9 Hz, 2H), 1.30 - 1.44 (m, 11H), 0.92 - 1.03 (m, 2H), 0.87 (t, *J* = 7.7 Hz, 6H), 0.76 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.7, 76.4, 50.7, 47.3, 46.7, 41.3, 34.6, 31.8, 26.4, 23.7, 21.2, 16.6, 9.8, 8.8 ppm.

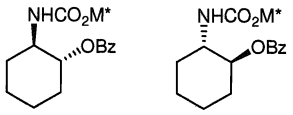


23a **23b**

(3a*R*,7a*S*)-*rel*-2,2-Dioxide-3H-1,2,3-benzoxathiazole-3-carboxylic acid hexahydro-5-methyl-2-(1-methylethyl)cyclohexyl ester (23a and **23b).**

Following the general procedure for the reaction of oxiranes with menthyl Burgess reagent using cyclohexene oxide (196 mg, 2.00 mmol) as starting material gave 215 mg (30%) of a 1:1 mixture of diastereomers **23a** and **23b** after purification by flash

column chromatography (hexanes : ethyl acetate, 15:1 to 3:1) as colorless oil. R_f 0.65 (hexanes : ethyl acetate, 3:1); $[\alpha]_D^{23}$ -52.2 (*c* 1.00, $CHCl_3$); IR (film) ν_{max}: 3401, 2958, 2873, 2254, 1728, 1457, 1383, 1314, 908, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 4.98 - 5.04 (bs, 1H), 4.73 (dt, *J* = 10.7, 4.5 Hz, 1H), 4.15 - 4.27 (m, 1H), 2.28 - 2.40 (m, 2H), 1.97 - 2.17 (m, 2H), 1.43 - 1.89 (m, 9H), 1.02 - 1.37 (m, 4H), 0.94 (d, *J* = 3.1 Hz, 3H), 0.92 (d, *J* = 3.1 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.9, 79.7, 79.3, 58.2, 58.1, 47.2, 47.1, 41.0, 40.9, 34.3, 31.8, 27.6, 27.5, 27.4, 26.1, 23.5, 23.4, 22.30, 22.25, 21.3, 21.2, 19.3, 16.4, 16.3 ppm; HRMS (EI) calcd for $C_{17}H_{29}NO_5S$: 359.1766, found 359,1761; Anal calcd for C 56.80% H 8.12%, found C 57.12% H 8.30%.

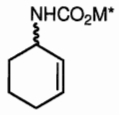


267a **267b**

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl ester, [(1*R*,2*R*)-2-(benzoyloxy)cyclohexyl]-carbamic acid (16a) and **(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexylester,[(1*S*,2*S*)-2-benzoyloxy)cyclohexyl]-carbamic acid (16b).**

Following the general procedure for the syntheses of benzoates using a mixture of **23a** and **23b** (449 mg, 1.25 mmol) as starting materials gave a mixture of two diastereomers 246 mg (49%), which was separated by flash column chromatography (DCM : MeOH, 200:1). **Compound 267a:** mp 111 - 113 °C (ethyl acetate/hexanes); R_f 0.50 (DCM : methanol, 100:1); $[\alpha]_D^{20}$ -77.8 (*c* 1.05, $CHCl_3$); IR (film) ν_{max}: 3434, 3368, 3019, 2954, 2868, 1711, 1603, 1585, 1513, 1452, 1370, 1318, 1279, 1216,

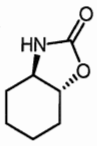
1115, 1038, 1028, 757, 712, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.07 (d, *J* = 7.7 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 4.83 (dt, *J* = 10.6, 4.5 Hz, 1H), 4.59 (d, *J* = 9.3 Hz, 1H), 4.34 - 4.46 (m, 1H), 3.76 - 3.90 (m, 1H), 2.07 - 2.19 (m, 2H), 1.73 - 1.93 (m, 3H), 1.13 - 1.69 (m, 10H), 0.91 - 1.06 (m, 1H), 0.86 (d, *J* = 10.0 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H), 0.46 - 0.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 156.5, 133.4, 130.6, 130.2, 128.7, 76.6, 74.7, 54.3, 47.5, 41.2, 34.6, 32.8, 31.5, 26.6, 25.0, 24.5, 23.8, 22.2, 21.1, 16.8; HRMS (EI) calcd for $C_{24}H_{35}NO_4$: 401.2566, found 401.2579; Anal calcd for $C_{24}H_{35}NO_4$: C 71.79% H 8.79%, found C 71.82% H 8.80%. **Compound 267b:** mp 138 - 141 °C (ethyl acetate/hexanes); R_f 0.45 (DCM : MeOH, 100:1); $[\alpha]_D^{20}$ -15.8 (*c* 1.05, $CHCl_3$); IR (film) ν_{max}: 3685, 3435, 3020, 2956, 2869, 1711, 1515, 1452, 1318, 1279, 1216, 1115, 1039, 929, 759, 714, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.05 (d, *J* = 7.7 Hz, 2H), 7.55 (t, *J* = 7.1 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 4.86 (dt, *J* = 10.6, 4.5 Hz, 1H), 4.69 (d, *J* = 9.3 Hz, 1H), 4.35 - 4.49 (m, 1H), 3.73 - 3.90 (m, 1H), 2.12 (d, *J* = 12.5 Hz, 2H), 1.98 (d, *J* = 11.9 Hz, 1H), 1.73 - 1.88 (m, 2H), 1.08 - 1.68 (m, 10H), 0.79 - 0.97 (m, 5H), 0.55 (d, *J* = 6.4 Hz, 3H), 0.30 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.2, 156.3, 133.3, 130.4, 130.1, 128.7, 76.0, 74.6, 54.4, 47.6, 41.8, 34.6, 33.2, 31.7, 31.6, 26.5, 24.9, 24.5, 23.9, 22.4, 20.7, 16.3 ppm; HRMS (EI) calcd for $C_{24}H_{35}NO_4$: 401.2566, found 401.2575; Anal calcd for $C_{24}H_{35}NO_4$: C 71.79% H 8.79%, found C 71.84% H 8.76%.



268

[(1*R*,2*R*)-2,3-Cyclohexenyl]-carbamic acid menthol ester (268).

Additionally to the isolation of compounds **267a** and **267b**, a 1:1 mixture of two diastereomers (164 mg, 47%) of compound **268** was obtained as colorless oil. R_f 0.55 (hexanes : ethyl acetate, 5:1); $[\alpha]_D^{20}$ (+/-) 0 (*c* 1.00, $CHCl_3$); IR (film) ν_{max}: 3323, 3026, 2938, 2838, 1699, 1529, 1450, 1310, 1241, 1193 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.75 (d, *J* = 9.5 Hz, 1H), 5.54 (d, *J* = 9.5 Hz, 1H), 4.35 - 4.59 (m, 2H), 4.00 - 4.17 (m, 1H), 1.76 - 2.04 (m, 5H), 1.51 - 1.65 (m, 4H), 1.34 - 1.50 (m, 2H), 1.15 - 1.29 (m, 1H), 0.77 - 1.07 (m, 9H), 0.73 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.1, 130.9, 128.4, 74.4, 47.8, 46.5, 41.9, 34.7, 31.7, 30.2, 26.7, 26.6, 25.2, 24.0, 23.9, 22.4, 21.2, 20.0, 16.9 ppm; HRMS (EI) calcd for $C_{17}H_{29}NO_2$: 279.2198, found 279.2194.



(+)-269a

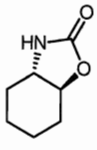
(*3aR,7aR*)-3H-Hexahydrobenzoxazolidin-2-one (269a).

Benzoic acid 2-menthylcarbonylamino-cyclohexylester **267a** (260 mg, 0.65 mmol) was dissolved in 1M NaOH in MeOH (30 mL) and the reaction mixture was stirred at rt for 10 hrs. The reaction mixture was diluted with water (30mL) and extracted three times with DCM. The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated. Flash column

chromatography (hexanes : ethyl acetate, 4:1) of the residue afforded [(1*R*,2*R*)-2-hydroxycyclohexyl]-carbamic acid menthol ester as colorless solid (152 mg, 79%). mp 130 - 132 °C (hexanes/ethyl acetate); R_f 0.15 (hexanes : ethyl acetate, 1:1); $[\alpha]_D^{20}$ -53.7 (c 1.35, $CHCl_3$); IR (film) ν_{max}: 3685, 3620, 3020, 2870, 2401, 1693, 1510, 1477, 1451, 1423, 1215, 1046, 1024, 929 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 4.60 - 4.79 (bs, 1H), 4.53 (dt, *J* = 11.2, 4.0 Hz, 1H), 3.21 - 3.44 (m, 2H), 3.00 - 3.21 (bs, 1H), 1.79 - 2.09 (m, 4H), 1.54 - 1.75 (m, 2H), 1.38 - 1.53 (m, 2H), 0.66 - 1-38 (m, 17H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.1, 75.8, 75.4, 57.2, 47.7, 41.7, 34.6, 34.5, 32.2, 31.7, 26.6, 25.0, 24.4, 23.8, 22.4, 21.2, 16.8 ppm; MS (EI) *m/z* (%): 297 (1), 158 (10), 139 (27), 138 (17), 115 (19), 114 (28), 98 (100), 97 (21), 96 (19), 95 (23), 83 (90), 82 (14), 81 (43), 71 (21), 70 (10), 69 (46), 67 (13); HRMS (EI) calcd for $C_{17}H_{31}NO_3$: 279.2304, found 297.2298; Anal calcd for $C_{17}H_{31}NO_3$: C 68.65% H 10.51%, found C 68.65% H 10.81%.

[(*1R,2R*)-2-Hydroxycyclohexyl]- carbamic acid menthyl ester (140 mg, 0.47 mmol) was dissolved in THF (5 mL) and sodium hydride (42 mg, 1.04 mmol) was added in one portion. The reaction mixture was heated at reflux for 12 hrs until TLC indicated complete conversion of starting material. The reaction mixture was quenched by the addition of an aqueous saturated solution of NH_4Cl. The aqueous layer was extracted three times with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, filtered, and the solvent was evaporated. Flash column chromatography (hexanes : ethyl acetate, 2:1 to 1:1) of the residue afforded (+)-**269** as colorless solid (55 mg, 83%). mp 133 - 134 °C (hexanes/ethyl actate); $[\alpha]_D^{22}$ +7.5 (c 1.0, EtOH); R_f 0.45 (hexanes : ethyl acetate, 1:1); IR (film)

ν_{max}: 3684, 3622, 3020, 1757, 1521, 1476, 1423, 1215, 1034, 929 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.96 - 6.19 (bs, 1H), 3.81 (dt, *J* = 11.1, 4.3 Hz, 1H), 3.16 - 3.33 (m, 1H), 2.05 - 2.20 (m, 1H), 1.93 - 2.05 (m, 1H), 1.67 - 1.90 (m, 2H), 1.49 - 1.65 (m, 1H), 1.14 - 1.47 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.2, 84.2, 61.3, 29.5, 28.9, 24.1, 23.9 ppm; MS (EI) *m/z* (%): 141 (32), 140 (11), 99 (6), 96 (5), 69 (42), 57 (15), 56 (100), 54 (8), 43 (40); HRMS (EI) calcd for $C_7H_{11}NO_2$: 141.0790, found 141.0788.



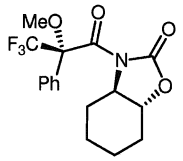
(-)-**269b**

(*3aS,7aS*)-3H-Hexahydrobenzoxazolidin-2-one (269b).

Benzoic acid 2-menthylcarbonylamino-cyclohexylester **267b** (270 mg, 0.67 mmol) was dissolved in 1M NaOH in MeOH (30 ml) and the reaction mixture was stirred at rt for 10 hrs. The reaction mixture was diluted with water (30 mL) and extracted three times with DCM. The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate and the solvent was evaporated. Flash column chromatography (hexanes : ethyl acetate, 4:1) of the residue afforded [(1*S*,2*S*)-2-hydroxycyclohexyl]- carbamic acid menthol ester as colorless solid (179 mg, 89%). mp 151 - 153 °C (hexanes/ethylacetate); R_f 0.15 (hexanes : ethyl acetate, 1:1); $[\alpha]_D^{20}$ -58.2 (c 1.2, $CHCl_3$); IR (film) ν_{max}: 3684, 3621, 3437, 3020, 2939, 2869, 2400, 1693, 1510, 1477, 1451, 1424, 1389, 1215, 1046, 1023, 929 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 4.62 - 4.85 (bs, 1H), 4.55 (dt, *J* = 11.1, 4.2 Hz, 1H), 3.21 - 3.42 (m, 2H),

2.98 - 3.21 (bs, 1H), 1.81 - 2.14 (m, 4H), 1.56 - 1.80 (m, 2H), 1.39 - 1.55 (m, 2H), 0.60 - 1.39 (m, 17H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.2, 75.8, 75.5, 57.3, 47.9, 41.8, 34.6, 34.5, 32.1, 31.8, 26.6, 25.0, 24.4, 23.8, 22.4, 21.2, 16.8 ppm; MS (EI) *m/z* (%): 297 (1), 160 (8), 159 (8), 158 (9), 139 (24), 138 (17), 115 (19), 114 (28), 98 (100), 97 (22), 96 (23), 95 (30), 83 (96), 82 (18), 81 (49), 71 (29), 70 (13), 69 (54), 67 (17); HRMS (EI) calcd for $C_{17}H_{31}NO_3$: 279.2304, found 297.2303; Anal calcd for $C_{17}H_{31}NO_3$: C 68.65% H 10.51%, found C 68.82% H 10.79%.

Following the same procedure as for the preparation of compound (+)-**269a** using [(*1S,2S*)-2-hydroxycyclohexyl]-carbamic acid menthol ester (160 mg, 0.54 mmol) and sodium hydride (32 mg, 1.33 mmol) as starting materials, gave 62 mg (82%) of compound (-)-**269b** as colorless crystals. mp 131 - 133 °C (hexanes/ethyl acetate); $[\alpha]_D^{22}$ -7.4 (c 1.1, EtOH); HRMS (EI) calcd for $C_7H_{11}NO_2$: 141.0790, found 141.0785.

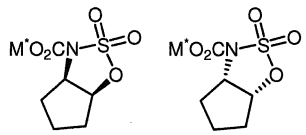


270a

(*3aR,7aR*)-3-((*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyl)-hexahydrobenzo[d]oxazol-2(3H)-one (270a).

To a solution of cyclic carbamate **269a** (20 mg, 0.14 mmol) in THF (2 mL) at 0 °C was added *n*-BuLi (2M in THF, 78 μL, 0.16 mmol) and the reaction mixture was stirred at the same temperature for one hour, before it was cooled to -78 °C. (*S*)-(+)-Mosher's chloride (43 mg, 0.17 mmol) was added and the reaction mixture was

warmed to rt over 14 hrs. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted three times with ethyl acetate. The organic layers were combined, washed with brine and dried over anhydrous sodium sulfate. The organic layer was filtered and the solvent was evaporated. The crude residue was analyzed by ^{19}F NMR (282 MHz, $CDCl_3$) δ: - 72.61 (1F), - 69.31 (0.035F). Compound **270b** as well as a racemic standard were prepared in the same manner, using **269b** and a racemate of **269** as starting materials. Compound **270b**: ^{19}F NMR (282 MHz, $CDCl_3$) δ: - 72.61 (not detected), - 69.30 (1F), Compound **270**: - 72.61 (1F), - 69.30 (1F). The results were confirmed by GC/MS analysis.

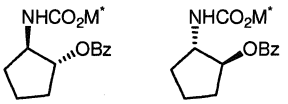


272a **272b**

(3a*R*,6a*S*)-*rel*-2,2-Dioxide-3(3aH)-cyclopent-1,2,3-oxathiazolecarboxylic acid tetrahydro-5-methyl-2-(1-methylethyl)cyclohexyl ester (272a and **272b).**

Following the general procedure for the reaction of oxiranes with menthyl Burgess reagent **21**, using cyclopentene oxide (168 mg, 2.00 mmol) as starting material gave 305 mg (37%) of a 1:1 mixture of diastereomers after purification by flash column chromatography (hexanes : ethyl acetate, 15:1 to 3:1). colorless oil; R_f 0.81 (hexanes : ethyl acetate, 2:1); $[\alpha]_D^{23}$ -79.2 (*c* 1.02, $CHCl_3$); IR (film) ν_{max}: 3400, 3019, 2962, 2400, 1731, 1522, 1423, 1383, 1307, 1030, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.21 (t, *J* = 5.3 Hz, 1H), 4.74 (dt, *J* = 10.9, 4.4 Hz, 1H), 4.55 - 4.63 (m, 1H), 2.08 - 2.15 (m, 5H), 1.81 - 1.89 (m, 2H), 1.66 - 1.74 (m, 2H), 1.42 - 1.50 (m, 2H), 1.10 -

1.18 (m, 2H), 0.88 - 0.95 (m, 7H), 0.76 - 0.85 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.1, 83.8, 79.1, 78.3, 71.2, 61.4, 61.3, 46.7, 40.6, 40.5, 33.9, 32.75, 32.7, 32.3, 31.4, 31.4, 26.2, 26.0, 25.6, 23.3, 23.2, 22.9, 22.6, 21.9, 20.8, 20.8 ppm; HRMS (FAB) ($M+H^+$) calcd for $C_{16}H_{27}NO_5S$: 346.1688, found 346.1659.

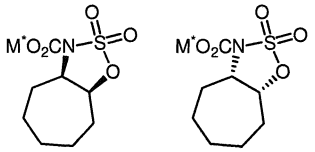


273a **273b**

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl ester *trans*-2-(benzoyloxy)cyclopentyl]-carbamic acid (273a and **273b).**

Following the general procedure for the syntheses of benzoates using a mixture of **272a** and **272b** (433 mg, 1.25 mmol) as starting material gave a mixture of two diastereomers (252 mg, 52%), which were separated by flash column chromatography (DCM : MeOH, 200:1). **Diastereomer 1:** mp 85 - 86 °C (ethyl acetate/hexanes); R_f 0.73 (DCM: MeOH; 400:1); $[\alpha]_D^{23}$ -99.6 (*c* 1.00, $CHCl_3$); IR (film) ν_{max}: 3684, 3019, 2961, 2400, 1711, 1512, 1424, 1031, 929, 669, 627 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.03 (d, J = 7.2 Hz, 2H), 7.42 - 7.52 (m, 3H), 5.16 (q, J = 5.8 Hz, 1H), 4.91 (bs, 1H), 4.40 - 4.48 (m, 1H), 4.03 - 4.12 (m, 1H), 2.19 - 2.23 (m, 2H), 1.73 - 1.85 (m, 5H), 1.51 - 1.58 (m, 7H), 1.20 - 1.25 (m, 2H), 0.67 - 0.85 (m, 7H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.0, 132.9, 130.2, 129.7, 128.3, 80.4, 75.0, 47.3, 41.3, 34.2, 31.3, 26.2, 22.0, 20.8 ppm; HRMS (FAB) ($M+H^+$) calcd for $C_{23}H_{33}NO_4$: 388.2488, found 388.2474. **Diastereomer 2:** mp 86 - 89 °C (ethyl acetate/hexanes); R_f 0.70 (DCM : MeOH, 400:1); $[\alpha]_D^{23}$ -5.59 (*c* 1.05, $CHCl_3$); IR (film) ν_{max}: 3436, 3019, 2960, 2400, 1711, 1512, 1037, 929, 669 cm^{-1}; ^1H NMR (300

MHz, $CDCl_3$) δ: 8.02 (d, J = 6.9 Hz, 2H), 7.50 - 7.57 (m, 3H) 5.11 - 5.19 (m, 1H), 4.78 - 4.82 (m, 1H), 4.52 - 4.57 (m, 1H), 4.11 - 4.14 (m, 1H), 2.11 - 2.21 (m, 2H), 1.80 - 1.83 (m, 1H), 1.72 - 1.79 (m, 4H), 1.46 - 1.58 (m, 6H), 1.38 - 1.45 (m, 4H), 0.80 - 1.25 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.0, 132.9, 130.2, 129.7, 128.3, 80.1, 74.7, 47.3, 41.4, 34.2, 31.3, 29.7, 26.2, 23.5, 22.0, 20.7, 16.3 ppm; HRMS (FAB) ($M+H^+$) calcd for $C_{23}H_{33}NO_4$: 388.2488, found 388.2481.

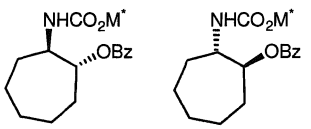


275a **275b**

(3a*R*,8a*S*)-*rel*- 2,2-Dioxide-cyclohept-1,2,3-oxathiazole-3(3aH-)carboxylic acid hexahydro-5-methyl-2-(1-methylethyl)cyclohexyl ester (275a and **275b).**

Following the general procedure for the reaction of oxiranes with menthyl Burgess reagent **21**, using cycloheptеneoxide (224 mg, 2.00 mmol) as starting material gave 211 mg (35%) of a 1:1 mixture of diastereomers after purification by flash column chromatography (hexanes : ethyl acetate, 15:1 to 4:1). colorless oil; R_f 0.57 (hexanes : ethyl acetate, 4:1); $[\alpha]_D^{23}$ -60.5 (*c* 0.75, $CHCl_3$); IR (film) ν_{max}: 2958, 2931, 1729, 1457, 1381, 1332, 1307, 1190 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.00 - 5.17 (m, 1H), 4.72 (dt, J = 11.0, 4.5 Hz, 1H), 4.21 - 4.36 (m, 1H), 2.20 - 2.37 (m, 1H), 1.63 - 2.18 (m, 10H), 1.35 - 1.58 (m, 4H), 1.03 - 1.33 (m, 3H), 0.85 - 1.00 (m, 8H), 0.71 - 0.84 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.8, 149.8, 81.6, 81.6, 79.1, 79.0, 63.1, 63.0, 46.8, 46.7, 40.6, 40.5, 33.9, 31.5, 31.4, 30.2, 30.2, 29.2, 28.6, 28.5, 26.0, 25.9, 25.6, 23.3, 22.9, 22.6, 21.9, 21.6, 20.9, 20.8, 15.8 ppm; MS (FAB) *m/z*

(%) 374 ($M+H^+$): 139 (52), 137 (22), 97 (19), 95 (44), 83 (100), 81 (37), 79 (11), 77 (12), 69 (46), 67 (21), 57 (36), 55 (62), 53 (14); HRMS (FAB) ($M+H^+$) calcd for $C_{18}H_{33}NO_5S$: 374.2001, found 374.2018.

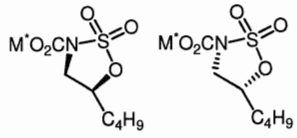


276a **276b**

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl ester *trans*-2-(benzoyloxy)cycloheptyl]-carbamic acid (276a and **276b).**

Following the general procedure for the syntheses of benzoates using a mixture of **275a** and **275b** (468 mg, 1.25 mmol) as starting materials gave a mixture of two diastereomers **276a** and **276b** 389 mg (75%), which were separated by flash column chromatography (DCM : MeOH, 200:1). **Diastereomer 1:** mp 89 - 91 °C (ethyl acetate/hexanes); R_f 0.55 (DCM : MeOH, 100:1); $[\alpha]_D^{23}$ -105.1 (*c* 0.8, $CHCl_3$); IR (film) ν_{max}: 3363, 2930, 2867, 1714, 1602, 1585, 1526, 1452, 1370, 1316, 1279, 1239,1179, 1117, 1070, 1028 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.98 (d, *J* = 7.5 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 2H), 4.91 (dt, *J* = 9.0, 3.4 Hz, 1H), 4.63 (d, *J* = 9.2 Hz, 1H), 4.28 - 4.36 (m, 1H), 3.83 - 3.93 (m, 1H), 1.85 - 1.94 (m, 2H), 1.74 - 1.93 (m, 2H), 1.47 - 1.71 (m, 10H), 1.36 - 1.44 (m, 1H), 1.16 - 1.27 (m, 1H), 0.89 - 1.02 (m, 1H), 0.81 - 0.88 (m, 2H), 0.77 (d, *J* = 7.0 Hz, 3H), 0.67 (d, *J* = 6.8 Hz, 3H), 0.56 - 0.61 (m, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 166.5, 155.9, 132.9, 130.3, 129.8, 128.3, 127.8, 78.4, 74.4, 56.2, 47.2, 40.9, 34.2, 32.0, 31.2, 26.2, 25.9, 23.9, 23.5, 22.4, 21.9, 20.7, 16.5 ppm; MS (EI) *m/z* (%): 415 (1), 137 (13), 123 (11), 111 (20), 105 (100), 97 (11), 95 (27), 83 (44), 82 (11), 81 (20), 77 (23), 71

(25), 69 (26), 67 (10), 57 (29), 56 (26), 55 (30); HRMS (EI) calcd for $C_{25}H_{37}NO_4$: 415.2723, found 415.2715. **Diastereomer 2:** mp 121 - 124 °C (ethyl acetate/hexanes); R_f 0.50 (DCM : MeOH, 100:1); $[\alpha]_D^{23}$ -37.6 (*c* 0.75, $CHCl_3$); IR (film) ν_{max}: 3369, 2928, 2866, 1714, 1524, 1452, 1369, 1315, 1279, 1180, 1116, 1070, 1028 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.96 (d, *J* = 7.4 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 2H), 4.93 (dt, *J* = 8.7, 3.7 Hz, 1H), 4.69 - 4.77 (m, 1H), 4.29 - 4.40 (m, 1H), 3.85 - 3.94 (m, 1H), 1.77 - 1.93 (m, 4H), 1.64 - 1.74 (m, 2H), 1.43 - 1.62 (m, 8H), 1.31 - 1.41 (m, 1H), 1.04 - 1.11 (m, 1H), 0.76 - 0.88 (m, 5H), 0.66 - 0.73 (m, 1H), 0.49 (d, *J* = 5.3 Hz, 3H), 0.27 (d, *J* = 0.48 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 166.6, 155.8, 132.9, 130.3, 129.7, 128.3, 127.8, 78.2, 74.3, 56.5, 47.3, 41.5, 34.3, 32.2, 31.3, 27.5, 26.2, 24.0, 23.6, 22.4, 22.0, 20.4, 16.1 ppm; MS (EI) *m/z* (%): 415 (1), 155 (10), 138 (18), 137 (14), 123 (16), 111 (20), 105 (100), 97 (11), 96 (12), 95 (43), 94 (10), 83 (47), 82 (16), 81 (31), 77 (23), 71 (28), 69 (34), 67 (14), 57 (32), 56 (25), 55 (37); HRMS (EI) calcd for $C_{25}H_{37}NO_4$: 415.2723, found 415.2720.

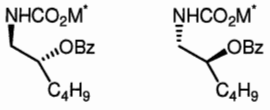


278a **278b**

2,2-Dioxide-1,2,3-oxathiazolidine-3-carboxylic acid 5-butyl-(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl ester (278a and **278b).**

Following the general procedure for the reaction of oxiranes with menthyl Burgess reagent using 2-butyloxirane (200 mg, 2.00 mmol) as starting material gave 159 mg (22%) of a 1:1 mixture of diastereomers **278a** and **278b** after purification by flash

column chromatography (hexanes : ethyl acetate, 20:1 to 5:1). colorless oil; R_f 0.68 (hexanes : ethyl acetate, 5:1); $[\alpha]_D^{23}$ -51.7 (*c* 2.3, $CHCl_3$); IR (film) ν_{max}: 3019, 2961, 2400, 1730, 1384, 1316, 1215, 1046, 928, 724, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 4.71 - 4.84 (m, 1H), 4.58 - 4.71 (m, 1H), 3.90 - 4.09 (m, 1H), 3.57 - 3.71 (m, 1H), 2.10 (m, 3H), 1.52 - 1.77 (m, 4H), 1.25 - 1.53 (m, 6H), 1.16 - 1.23 (s, 3H), 0.92 - 1.12 (m, 2H), 0.85 - 0.91 (m, 6H), 0.70 - 0.74 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.8, 79.9, 79.2, 50.6, 46.7, 40.5, 33.9, 32.1, 31.4, 29.7, 26.6, 25.8, 23.1, 22.1, 21.9, 20.8, 16.0, 13.7 ppm; MS (EI) *m/z* (%) 361 (1), 176 (44), 83 (88), 42 (60), 43 (39), 54 (31), 55 (61); HRMS (EI) calcd for $C_{17}H_{31}NO_5S$: 361.1923, found 361.1920.

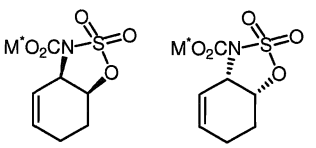


279a **279b**

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl ester [2-(benzoyloxy)hexyl]-carbamic acid (279a and **279b).**

Following the general procedure for the syntheses of benzoates using a mixture of **278a** and **278b** (451 mg, 1.25 mmol) as starting materials gave a mixture of two diastereomers (181 mg, 36%), which were inseparable by flash column chromatography. **Mixture of two diastereomers:** colorless solid; mp 121 - 124 °C (ethyl acetate/hexanes); R_f 0.50 (DCM : MeOH, 100:1); $[\alpha]_D^{23}$ -37.6 (*c* 0.75, $CHCl_3$); IR (film) ν_{max}: 3684, 3401, 3019, 2961, 2400, 1713, 1517, 1423, 1215, 1046, 929, 641, 669, 627 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.97 (d, *J* = 7.3, 2H), 7.46 - 7.54 (m, 1H), 7.33 - 7.43 (m, 2H), 5.03 - 5.20 (m, 1H), 4.70 - 4.86 (m, 1H), 4.35 - 4.54 (m,

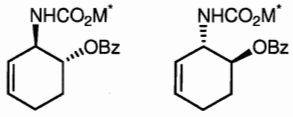
1H), 3.33 - 3.49 (m, 2H), 1.88 - 2.01 (m, 1H), 1.72 - 1.88 (m, 2H), 1.46 - 1.73 (m, 6H), 1.23 - 1.44 (m, 6H), 1.08 - 1.22 (m, 2H), 0.90 - 1.06 (m, 2H), 0.77 - 0.88 (m, 3H), 0.64 - 0.75 (m, 4H), 0.58 (d, J = 6.9 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.9, 154.0, 130.6, 127.2, 125.9, 72.2, 71.7, 44.9, 41.9, 38.9, 31.8, 29.0, 28.9, 28.8, 24.9, 23.8, 21.1, 20.1, 19.6, 18.3, 13.9, 13.9, 11.5 ppm; MS (EI) *m/z* (%) 403 (1), 221 (15), 176 (13), 55 (61), 54 (31), 43 (37); HRMS (EI) calcd for $C_{24}H_{37}NO_4$: 403.2723, found 403.2720.



281a **281b**

(3a*R*,7a*S*)-*rel*-2,2-Dioxo-3a,6,7,7a-tetrahydro-2λ^6-1,2,3-benzoxathiazole-3-carboxylic acid-(1*R*,2*S*,5*R*)-2-isopropyl-5-methyl-cyclohexyl ester (281 and **281b).** Following the general procedure for the reaction of oxiranes with menthyl Burgess reagent using cyclohexadiene oxide (192 mg, 2.00 mmol) as starting material gave 257 mg (36%) of a 1:1 mixture of diastereomers **281a** and **281b** after purification by flash column chromatography (hexanes : ethyl acetate, 15:1 to 3:1). white solid; mp 115 - 118 °C (hexanes/ethyl acetate); R_f 0.55 (hexanes : ethyl acetate, 4:1); $[\alpha]_D^{23}$ - 54.5 (*c* 1.25, $CHCl_3$); IR (film) ν_{max}: 3443, 3031, 2959, 2930, 2873, 1731, 1599, 1457, 1432, 1371, 1331, 1307, 1241, 1217, 1189, 1170, 1125 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) (two rotamers) δ: 6.02 - 6.28 (m, 1H), 5.56 - 5.85 (m, 1H), 5.13 - 5.33 (m, 1H), 4.66 - 4.84 (m, 2H), 1.82 - 2.44 (m, 5H), 1.39 - 1.75 (m, 5H), 1.00 - 1.31 (m, 3H), 0.87 - 0.96 (m, 6H), 0.74 - 0.85 (m, 3H), ppm; ^{13}C NMR (75 MHz, $CDCl_3$) (two

rotamers) δ: 147.9, 135.0, 129.5, 119.0, 117.9, 81.7, 81.6, 79.2, 75.5, 75.3, 75.1, 74.6, 72.9, 72.8, 53.2, 53.2, 51.5, 45.2, 44.9, 44.8, 44.7, 38.6, 37.9, 37.7, 32.0, 29.5, 29.3, 29.3, 24.2, 23.9, 23.7, 22.6, 22.1, 21.2, 20.3, 19.9, 18.9 18.8, 18.7 ppm; HRMS (EI) calcd for $C_{17}H_{27}NO_5S$: 357.1610, found 357.1593.

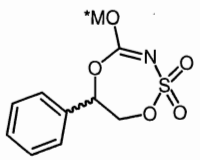


282a **282b**

(1*S*,6*R*)-(6-Hydroxy-cyclohex-2-enyl)-carbamic acid (1*R*,2*S*,5*R*)-2-isopropyl-5-methyl-cyclohexyl ester (282a) and **(1*R*,6*S*)-(6-hydroxy-cyclohex-2-enyl)-carbamic acid (1*R*,2*S*,5*R*)-2-isopropyl-5-methyl-cyclohexyl ester (282b).**

Following the general procedure for the syntheses of benzoates using a mixture of **281a** and **281b** (446 mg, 1.25 mmol) as starting materials gave a mixture of two diastereomers 254 mg (51%), which were separated by flash column chromatography (DCM : MeOH, 400:1). **Compound 282a:** mp 103 - 105 °C (ethyl acetate/hexanes); R_f 0.67 (DCM : MeOH, 400:1); $[\alpha]_D^{23}$ -100.8 (*c* 0.25, $CHCl_3$); IR (film) ν_{max}: 3436, 3019, 2962, 1713, 1602, 1511, 1424, 1277, 1117, 1048, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.07 (d, *J* = 7.4 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 5.85 (d, *J* = 10.2 Hz, 1H), 5.69 (dd, *J* = 9.5, 1.5 Hz, 1H), 5.04 - 5.11 (m, 1H), 4.66 (d, *J* = 9.2 Hz, 1H), 4.52 - 4.62 (m, 1H), 4.46 (dt, *J* = 10.7, 3.9 Hz, 1H), 2.25 - 2.28 (m, 2H), 2.08 - 2.11 (m, 1H), 1.96 - 2.00 (m, 1H), 1.88 - 1.93 (m, 1H), 1.59 - 1.72 (m, 4H), 1.26 - 1.42 (m, 2H), 1.21 - 1.25 (m, 1H), 0.98 - 1.04 (m, 1H), 0.87 (d, *J* = 7.1 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H), 0.72 (d, *J* = 5.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.5, 156.2, 133.0, 130.2, 129.8, 129.5, 128.4, 128.3, 126.8, 77.2,

74.8, 73.9, 51.7, 47.2, 41.0, 34.2, 31.2, 26.4, 26.3, 24.0, 23.5, 21.9, 20.8, 16.5 ppm; HRMS (EI) calcd for $C_{24}H_{33}NO_4$: 399.2410, found 399.2403; Anal calcd for $C_{24}H_{33}NO_4$: C 72.15% H 8.33%, found C 72.42% H 8.44%. **Compound 282b:** mp 107 - 109 °C (ethyl acetate/hexanes); R_f 0.62 (DCM : MeOH, 400:1); $[\alpha]_D^{23}$ +16.2 (*c* 0.4, $CHCl_3$); IR (film) ν_{max}: 3369, 3033, 2954, 2928, 2869, 1714, 1523, 1277, 1241, 1116, 1027 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 8.06 (d, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 5.84 (d, *J* = 8.6 Hz, 1H), 5.59 (dq, *J* = 9.8, 2.2 Hz, 1H), 5.04 - 5.12 (m, 1H), 4.70 (d, *J* = 9.5 Hz, 1H), 4.55 - 4.61 (m, 1H), 4.49 (td, *J* = 10.8, 3.7 Hz, 1H), 2.23 - 2.29 (m, 2H), 2.06 - 2.13 (m, 1H), 1.91 - 2.03 (m, 2H), 1.54 - 1.71 (m, 3H), 1.41 - 1.49 (m, 1H), 1.21 (t, *J* = 11.5 Hz, 1H), 0.85 - 0.97 (m, 6H), 0.65 (d, *J* = 6.6 Hz, 3H), 0.42 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.5 156.0, 132.9, 130.1, 129.8, 129.3, 128.3, 127.0, 74.5, 73.7, 51.7, 47.3, 41.4, 34.2, 31.3, 26.6, 26.2, 24.0, 23.5, 22.0, 20.5, 16.1 ppm; HRMS (EI) calcd for $C_{24}H_{33}NO_4$: 399.2410, found 399.2410.

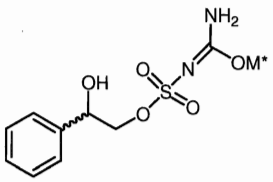


283

Compound 283.

Styrene oxide (500 mg, 4.16 mmol) and menthyl Burgess Reagent **21** (2.85 g, 9.57 mmol) were dissolved in THF (15 mL) and heated at reflux for two hrs. The reaction mixture was filtered through a plug of silica to remove salts formed during the reaction. The solvent was removed under reduced pressure and the residue was

purified by flash column chromatography (hexanes : ethyl acetate, 9:1) affording 495 mg (31%) of colorless solid as a 1:1 mixture of two diastereomers **283**. mp 47 - 50 °C (pentane); R_f 0.72 (hexanes : ethyl acetate, 3:1); IR (film) ν_{max}: 3362, 2961, 2929, 2873, 1794, 1727, 1598, 1585, 1496, 1458, 1398, 1371, 1336, 1304, 1195, 1181, 1165, 1131, 1097, 1079, 997, 962, 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.30 - 7.52 (m, 5H), 6.07 (dd, *J* = 11.1, 4.2 Hz, 1H), 4.75 (bs, 1H), 4.57 - 4.68 (m, 1H), 4.46 - 4.55 (m, 1H), 2.11 - 2.25 (m, 1H), 1.79 - 1.98 (m, 1H), 1.69 (d, *J* = 11.4 Hz, 2H), 1.37 - 1.58 (m, 2H), 0.73 - 1.16 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.4, 158.1, 132.7, 132.6, 130.52, 130.50, 129.6, 129.1, 129.0, 127.2, 127.1, 127.0, 84.8, 84.7, 82.9, 82.8, 72.8, 72.7, 47.5, 47.1, 40.2, 40.0, 34.2, 31.8, 31.69, 31.66, 26.6, 26.4, 23.6, 23.5,22.3, 21.1, 21.0, 16.7, 16.4 ppm; MS (EI) *m/z* (%): 163 (5), 139 (30), 138 (83), 137 (9), 123 (24), 121 (9), 120 (24), 119 (7), 105 (16), 104 (99), 103 (27), 97 (19), 96 (17), 95 (65), 91 (34), 84 (8), 83 (100), 82 (20), 81 (51), 77 (12), 71 (20), 69 (45), 68 (9), 67 (14), 65 (9), 57 (36), 56 (11), 55 (49).

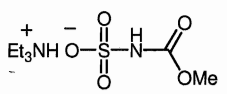


285

2-Hydroxy-2-phenylethylamino(menthyloxy)methylenesulfamate (285).

Cyclic sulfimidate **283** (mixture of two diastereomers in a ratio of 1:1, 150 mg, 0.39 mmol) was dissolved in dry DMF (1.5 mL) and ammonium benzoate (109 mg, 0.78 mmol) was added. The reaction mixture was heated at 50 °C until complete conversion of starting material (TLC, 18 hrs), before it was diluted with diethyl ether

(25 mL). The organic layer was extracted ten times with water (0.5 mL), then washed two times with a saturated aqueous solution of Na_2CO_3, and brine. The organic layer was dried over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (hexanes : ethyl acetate, 8:1 to 2:1) affording 125 mg (80%) of the title compound **285** as colorless oil. R_f 0.12 (hexanes : ethyl acetate, 1:1); $[\alpha]_D^{23}$ - 48.5 (*c* 0.275, $CHCl_3$); IR (film) ν_{max}: 3448, 3340, 2956, 2926, 2871, 1631, 1548, 1496, 1446, 1372, 1322, 1173, 1097, 986, 954, 917, 863, 815, 759, 700, 661, 609, 541 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.28 - 7.46 (m, 5H), 7.06 (bs, 1H), 5.76 (bs, 1H), 5.06 (dt, *J* = 9.3, 2.2 Hz, 1H), 4.80 (td, *J* = 11.0, 4.6 Hz, 1H), 4.24 (ddd, *J* = 10.6, 8.8, 2.8 Hz, 1H), 4.13 (ddd, *J* = 18.2, 10.3, 9.2 Hz, 1H), 2.68 (bs, 1H), 2.08 (d, *J* = 12.5 Hz, 1H), 1.83 - 1.91 (m, 1H), 1.67 (d, *J* = 12.1 Hz, 2H), 1.32 - 1.51 (m, 2H), 0.99 (q, *J* = 11.6 Hz, 1H), 0.91 (d, *J* = 5.8 Hz, 3H), 0.89 (dd, *J* = 6.8, 1.0 Hz, 3H), 0.81 - 0.92 (m, 1H), 0.76 (t, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 160.3, 138.5, 129.1, 128.7, 126.5, 79.5, 75.0, 72.1, 47.1, 40.7, 34.1, 31.5, 26.4, 23.3, 22.4, 21.2, 16.8 ppm; HRMS (FAB) ($M+H^+$) calcd for $C_{19}H_{30}N_2O_5S$: 398.1875, found 398.1855.

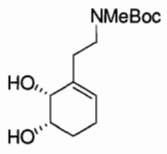


322

Sulfo-methylester carbamic acid triethlylammonium salt (322).

Compound **322** was isolated by diluting the crude reaction mixture with diethyl ether, after following the general procedure for the formation of disulfides. A white precipitate was formed, which was filtered and dried under reduced pressure. mp 93 -

95 °C (diethyl ether); IR (film) ν_{max}: 3483, 3237, 2989, 2711, 2499, 1723, 1647, 1476, 1421, 1341, 1225, 1044, 948, 838 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.20 (bs, 1H), 7.15 (bs, 1H), 3.69 (s, 3H), 3.15 - 3.31 (m, 6H), 1.39 (t, J = 7.2 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.7, 52.2, 46.4, 8.4; HRMS (FAB) ($M+H^+$) calcd for ($C_2H_5NO_5S$ • 2 $C_6H_{15}N$ + H)$^+$: 358.2376, found 358.2379; Anal calcd for $C_2H_5NO_5S$ • $C_6H_{15}N$: C 37.49% H 7.86% N 10.96%, found C 37.67% H 7.83% N 10.76%.

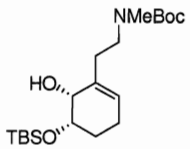


336

(*5S,6R*)-[2-(5,6-Dihydroxy-cyclohex-1-enyl)-ethyl]-methyl-carbamic acid *tert*-butyl ester (336).

Compound **334** (6.34 g, 20.8 mmol) was dissolved in THF (20 mL) and transferred to a 50 mL thick-walled reaction vessel containing K_2CO_3 (1.61 g, 11.6 mmol) and a magnetic stirring bar. The reaction vessel was cooled to - 40 °C, and the solution was saturated with methylamine by bubbling gaseous methylamine from a lecture bottle through the solution for 15 min. The reaction vessel was sealed, and the mixture stirred at rt for 48 hrs. The vessel was cooled to -40 °C before it was carefully opened. Potassium salts were removed by filtration and rinsed with DCM (20 mL). The solvent was removed and the residue was dissolved in DCM (50 mL). Boc anhydride (8.53 g, 37.4 mmol) was added to the solution and the reaction mixture was cooled to 0 °C. Triethylamine (5.20 mL, 37.4 mmol) and DMAP (0.24 g, 2.0 mmol) were added to the reaction mixture, which was warmed to rt over 24 hrs. A saturated

aqueous solution of NH_4Cl was added and the layers were separated. The aqueous layer was extracted with DCM and the organic extracts were combined. The organic layer was washed three times with a saturated aqueous solution of Na_2CO_3, brine, and then dried over anhydrous sodium sulfate. The solution was filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (hexanes : ethyl acetate, 6:1 to 1:2) afforded the title compound **336** as colorless oil. (2.51 g, 45%). R_f 0.20 (hexanes : ethyl acetate, 1:1); IR (film) ν_{max}: 3383, 2974, 2930, 1693, 1672 , 1396, 1158, 988 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.43 (bs, 1H), 4.87 (bs, 1H), 3.96 (bs, 2H), 3.56 (bs, 1H), 2.99 (d, *J* = 8.8 Hz, 1H), 2.91 (bs, 1H), 2.86 (s, 3H), 2.42 - 2.30 (m, 1H), 2.18 (d, *J* = 13.4 Hz, 1H), 2.03 (bs, 2H), 1.74 - 1.63 (m, 1H), 1.60 - 1.45 (m, 1H), 1.43 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CHCl_3$) δ: 157.0, 133.9, 128.8, 79.9, 70.0, 69.8, 48.3, 34.8, 34.0, 28.3, 25.4, 24.8 ppm; MS (EI) *m/z* (%): 144 (12), 110 (110), 57 (71), 44 (100). HRMS (EI) (M^+-57) calcd for $C_{14}H_{25}NO_4$: 271.1784, found 271.1787.

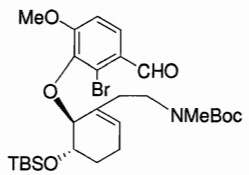


6

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

To a solution of diol **336** (656 mg, 2.0 mmol) in DCM (8 mL) at -78 °C was added imidazole (272 mg, 4.0 mmol) followed by the addition of TBDMS-chloride (330 mg, 2.2 mmol). The reaction mixture was warmed to rt over 14 hrs and then

quenched by the addition of a saturated aqueous solution of NH_4Cl. The layers were separated, and the aqueous layer was extracted twice with DCM. The organic layers were combined and washed with cold 2% aqueous HCl, saturated aqueous solution of $NaHCO_3$, then dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crude oil, which was purified by flash column chromatography (hexanes : ethyl acetate, 1:1 to 0:1) to give the mono-silyl derivative **6** as a clear and colorless oil (678 mg, 88%). R_f 0.47 (DCM : ethyl acetate, 96:4); $[\alpha]_D^{24}$ -22.6 (*c* 0.5, $CHCl_3$); IR (film) ν_{max}: 3556, 3475, 2953, 2857, 1692, 1472, 1392, 1253, 1085 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) (mixture of rotamers) δ: 5.54 (s, 1H), 5.52 (s, 1H), 3.98 (s, 1H), 3.90 (s, 1H), 3.79 (s, 1H), 3.77 (s, 1H), 3.26 - 3.20 (m, 2H), 2.85 (s, 3H), 2.82 (s, 3H), 2.39 - 2.32 (m, 2H), 2.30 - 2.23 (m, 2H), 2.13 (bs, 2H), 1.98 (bs, 2H) 1.80 - 1.72 (m, 2H), 1.54 (s, 2H), 1.44 (s, 18H), 0.9 (s, 18H), 0.11 (s, 6H), 0.10 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 155.7, 134.8, 126.6, 79.0 (br), 71.0, 68.8, 48.4, 47.2, 34.1, 33.3, 32.8, 28.4, 25.8, 25.4, 25.3, 24.3, 24.1, 18.1, - 4.4, - 4.8 ppm; MS (EI) *m/z* (%): 228 (21), 197 (21), 136 (12), 74 (22), 73 (15), 57 (63), 44 (100); HRMS (EI) (M^+-57) calcd for $C_{12}H_{30}NO_4Si$: 328.1944, found 328.1946; Anal calcd for $C_{20}H_{39}NO_4Si$: C 62.10% H 10.22%, found C 62.29% H 10.19%.

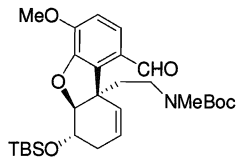


337

***N*-[2-[(5*S*,6*S*)-6-(2-Bromo-3-formyl-6-methoxyphenoxy)-5-[[(1,1-dimethylethyl) dimethylsilyl]oxy]-1-cyclohexen-1-yl]ethyl]-*N*-methyl carbamic acid 1,1-dimethylethylester (337).**

To a solution of DIAD (1.02 mL, 5.21 mmol) in THF (10 mL) at -10 °C, was added tributyl phosphine (1.69 mL, 5.21 mmol) dropwise. The solution was stirred at -10 °C for 10 min, then it was transferred dropwise to a solution of bromoisovanillin **174** (0.93 g, 4.01 mmol) and monoprotected diol **6** (1.39 g, 3.61 mmol) in THF (2 mL) at -78 °C. Once the addition was completed, the reaction vessel was warmed to rt and stirred at ambient temperature for 48 hrs. The solvent was removed under reduced pressure and the crude mixture was subjected to column chromatography (DCM : ethyl acetate, 100:0 to 98:2). Compound **337** was isolated as colorless oil (1.19 g, 55%). R_f 0.81 (DCM:EtOAc, 96:4); $[\alpha]_D^{22}$ +59.1 (*c* 0.35, $CHCl_3$); IR (film) ν_{max}: 3007, 2952, 2929, 2857, 1688, 1578, 1481, 1275, 1252, 1173, 1085, 1028, 1005, 836 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) (two rotamers) δ: 10.30 (s, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 5.79 - 5.90 (m, 1H), 4.57 (bs, 1H), 3.94 - 4.04 (m, 4H), 3.40 - 3.65 (m, 1H), 3.22 (bs, 1H), 2.85 (s, 3H), 2.37 - 2.57 (m, 2H), 2.17 - 2.28 (m, 2H), 2.02 - 2.10 (m, 1H), 1.65 - 1.74 (m, 1H), 1.46 (s, 9H), 0.76 (s, 9H), - 0.12 (s, 3H), -0.17 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 191.3, 157.9, 155.8, 144.6, 130.9, 130.3, 127.7, 125.9, 123.5, 110.9, 80.3, 79.1, 67.7, 56.1, 48.9, 48.3, 41.5, 35.0, 33.4, 32.7, 28.5, 25.6, 25.4, 20.8, 18.0, -4.9, -5.1 ppm; MS (EI) *m/z* (%): 312 (28),

269 (10), 268 (45), 237 (24), 136 (31), 109 (14), 75 (27), 73 (33), 57 (47), 44 (100); HRMS (EI) (M^+-73) calcd for $C_{24}H_{35}NO_5BrSi$: 524.1468, found 524.1464; Anal calcd for $C_{28}H_{44}NO_6BrSi$: C 56.18% H 7.41%, found C 56.09% H 7.65%.

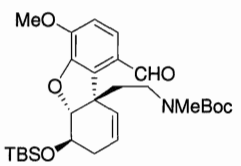


338

(*5S,6S,9aR*)-{2-[6-(*tert*-Butyl-dimethyl-silanyloxy)-1-formyl-4-methoxy-6,7-dihydro-5a*H*-dibenzofuran-9a-yl]-ethyl}-methyl-carbamic acid *tert*-butyl ester (338).

To aryl bromide **337** (205 mg, 0.34 mmol) dissolved in degassed (N_2) toluene (5 mL) were added sequentially silver carbonate (283 mg, 1.03 mmol), diphenylphosphino ferrocene (57 mg, 0.10 mmol), and $Pd(OAc)_2$ (12 mg, 0.05 mmol). The reaction mixture was heated to 110 °C (preheated oil bath) in a Teflon-sealed Schlenk tube (10 mL) for 1 hour, before it was cooled to rt. The remaining black reaction mixture was filtered through Celite and washed with several portions of $CHCl_3$. The filtrate was concentrated and adsorbed onto a mixture of silica gel and charcoal. Purification by flash column chromatography (DCM : ethyl acetate, 4:1) gave 146 mg (82%) of the title compound as colorless oil. R_f 0.80 (DCM : ethyl acetate, 96:4); $[\alpha]_D^{24}$ +12.5 (*c* 0.6, $CHCl_3$); IR (film) ν_{max}: 3008, 2953, 2930, 2856, 2734, 1692, 1610, 1571, 1436, 1366, 1285, 1250, 1170, 1155, 1046, 837 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) (two rotamers) δ: 9.90 (s, 1H), 9.89 (s, 1H), 7.38 (d, *J* = 8.2 Hz, 2H), 6.86 - 6.93 (m, 2H), 6.40 - 6.49 (m, 1H), 6.32 - 6.40 (m, 1H), 5.65 - 5.72 (m, 2H), 4.54 - 4.80 (m, 2H),

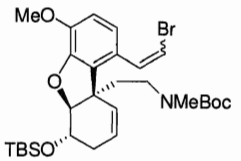
3.95 (s, 6H), 3.91 (bs, 2H), 3.32 (bs, 1H), 3.16 - 3.25 (m, 1H), 2.93 - 3.03 (m, 2H), 2.78 (s, 6H), 2.01 - 2.29 (m, 8H), 1.43 (s, 18H), 0.91 (s, 18H), 0.14 (s, 6H), 0.04 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) (two rotamers) δ: 190.6, 155.5, 150.2, 147.5, 133.6, 130.4, 129.8, 129.2, 126.5, 124.1, 110.4, 90.9, 89.9, 79.5, 68.8, 68.4, 56.0, 55.9, 51.8, 45.3, 44.6, 36.4, 35.5, 34.7, 34.6, 34.1, 31.6, 30.5, 29.1, 28.4, 25.8, 25.7, 25.3, 22.7, 20.7, 18.1, 14.1, 11.4, -4.7, -5.2 ppm; MS (EI) *m/z* (%): 162 (12), 144 (17), 136 (12), 118 (13), 117 (18), 92 (32), 91 (38), 88 (11), 75 (46), 73 (38), 57 (87), 44 (100); HRMS (EI) (M^+-57) calcd for $C_{24}H_{34}NO_6Si$: 460.2155, found 460.2150; Anal calcd for $C_{28}H_{43}NO_6Si$: C 64.96% H 8.37%, found C 64.87% H 8.46%.



(-)-338

(*5R,6R,9aS*)-{2-[6-(*tert*-Butyl-dimethyl-silanyloxy)-1-formyl-4-methoxy-6,7-dihydro-5a*H*-dibenzofuran-9a-yl]-ethyl}-methyl-carbamic acid *tert*-butyl ester (-)-(338).

Following the same procedure as for the preparation of compound **338**, using compound **364** (380 mg, 0.64 mmol), $Pd(OAc)_2$ (22 mg, 0.10 mmol), dppf (105 mg, 0.19 mmol), and Ag_2CO_3 (533 mg, 1.91 mmol) as starting materials, gave 301 mg (91%) of compound (-)-**338**. Data for (-)-**338** (^1H NMR spectra, R_f value) are identical to those of compound **338**; $[\alpha]_D^{22}$ -8.5 (*c* 0.6, $CHCl_3$).

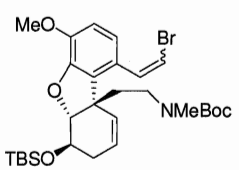


339

(*5S,6S,9aR*)-{2-[6-(*tert*-Butyl-dimethyl-silanyloxy)-1-(2-bromovinyl)-4-methoxy-6,7-dihydro-5a*H*-dibenzofuran-9a-yl]-ethyl}-methyl-carbamic acid *tert*-butyl ester (339).

Potassium *tert*-butoxide (2.91 g, 26.0 mmol) was added to a solution of ylide (prepared by refluxing a solution of triphenylphosphine (15 g, 57.0 mmol) and methylene bromide (22.3 g, 115 mmol) in toluene (100 mL) for 24 hrs. The mixture was cooled to 0 °C, the precipitate was collected by filtration, washed with toluene and dried under reduced pressure) (12.2 g, 28.0 mmol) in THF (100 mL) at -30 °C. The solution was stirred for 5 min at - 30 °C and then benzaldehyde **338** (4.05 g, 7.8 mmol) was added. The mixture was stirred at - 30 °C until TLC analysis indicated full conversion (20 min). The reaction mixture was quenched with brine (40 mL) and the aqueous layer was extracted twice with ethyl acetate (50 ml). The organic layers were combined, dried over anhydrous magnesium sulfate, and filtered. The concentrated residue was purified by flash column chromatography (hexanes : ethyl acetate, 9:1 to 4:1) to give the title compound as colorless oil (2.25. g, 49%). R_f 0.56 (hexanes : ethyl acetate, 4:1); $[\alpha]_D^{21}$ +46.6 (*c* 1.2, $CHCl_3$); IR (film) ν_{max}: 2952, 2929, 2855, 1691, 1620, 1502, 1366, 1282, 1156, 1122, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (two isomers, ratio 2:1) δ: 7.10 (d, *J* = 8.4 Hz, 1H), 6.70 - 6.86 (m, 3H), 6.56 (d, *J* = 13.9 Hz, 1H), 6.52 (d, *J* = 7.9 Hz, 1H), 5.86 - 5.99 (m, 2H), 5.66 - 5.81 (m, 2H), 4.46 - 4.60 (m, 2H), 3.94 - 4.03 (m, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.18 - 3.48 (bs, 2H),

2.89 - 3.04 (m, 2H), 2.80 (s, 3H), 2.76 (s, 3H), 2.31 (t, J = 4.5 Hz, 1H), 2.25 (t, J = 2.8 Hz, 1H), 2.03 - 2.18 (m, 2H), 1.80 - 2.03 (m, 4H), 1.43 - 1.48 (m, 20H), 0.92 (s, 18H), 0.15 (s, 3H), 0.14 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) (two isomers, ratio 2:1) δ: 155.5, 147.1, 145.3, 145.0, 130.2, 129.0, 128.6, 124.7, 122.5, 119.5, 111.7, 110.9, 108.6, 106.7, 89.8, 89.1, 79.5, 68.9, 68.3, 65.9, 55.9, 55.8, 55.7, 51.0, 50.9, 45.2, 37.1, 34.2, 30.4, 30.3, 29.7, 28.5, 28.5, 25.8, 25.7, 25.7, 18.1, 15.3, -3.5, -4.7, -5.2 ppm; MS (EI) *m/z* (%): 536 (4), 436 (7), 144 (8), 118 (6), 88 (14), 86 (29), 84 (44), 75 (21), 73 (38), 59 (33), 57 (61), 47 (10), 44 (100), 41 (18), MS (ES- pos) *m/z* (%): 618 (100), 616 (92), 553 (20), 477 (14), 476 (52); HRMS (EI) (M^+-57) calcd for $C_{25}H_{35}NO_5BrSi$: 536.1467, found 536.1461; Anal calcd for $C_{29}H_{44}NO_5BrSi$: C 58.57% H 7.46%, found C 59.48% H 7.87%.

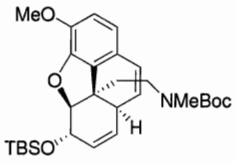


(-)-339

(*5R,6R,9aS*)-{2-[6-(*tert*-Butyl-dimethyl-silanyloxy)-1-(2-bromovinyl)-4-methoxy-6,7-dihydro-5a*H*-dibenzofuran-9a-yl]-ethyl}-methyl-carbamic acid *tert*-butyl ester (-)-(339).

Following the same procedure as for the preparation of compound **339**, using compound (-)-**338** (0.75 g, 1.45 mmol), ylide (prepared by refluxing a solution of triphenylphosphine (15 g, 57.0 mmol) and methylene bromide (22.3 g, 115 mmol) in toluene (100 mL) for 24 hrs. The mixture was cooled to 0 °C, the precipitate was collected by filtration, washed with toluene and dried under reduced pressure) (1.26

g, 2.90 mmol), and potassium *tert*-butoxide (0.31 g, 2.76 mmol), gave 344 mg (40%) of compound (-)-**339**. Data for (-)-**339** (^{1}H NMR spectra, R_f value) are identical to those of compound **339**; $[\alpha]_D^{21}$ -37.1 (*c* 1.30, $CHCl_3$).

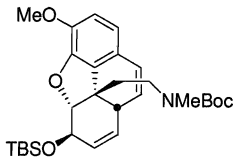


340

(3a*S*,3*S*,9a*R*,9b*R*)-[2,[3-(*tert*-Butyl-dimethylsilanyloxy)-5-methoxy-3,8,9,9a-tetrahydro-3aH-phenanthro[4,5-bcd]furan-9b-yl]-ethyl]-methyl-carbamic acid tert-butyl ester (340).

Vinyl bromide **339** (788 mg, 1.33 mmol) was dissolved in degassed (N_2) toluene (20 mL) and transferred to a 50 mL Teflon-sealed Schlenk tube containing a magnetic stirring bar. Silver carbonate (1.10 g, 4.0 mmol), diphenylphosphino propane (164 mg, 0.4 mmol), and $Pd(OAc)_2$ (45 mg, 0.2 mmol) were added sequentially. The tube was flushed with nitrogen, sealed, and placed in a pre-heated oil bath at 110 ºC for 3 hrs. The black reaction mixture was filtered through Celite and washed with several portions of $CHCl_3$. The filtrate was adsorbed onto a mixture of silica gel and charcoal and loaded onto a silica gel column. Elution with DCM : ethyl acetate, 4:1 gave compound **340** as a yellow oil (300 mg, 44%). R_f 0.55 (hexanes : ethyl acetate, 4:1); IR (film) ν_{max}: 2954, 2929, 2856, 1697, 1507, 1438, 1391, 1365, 1279, 1162, 1094, 865 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) (two rotamers) δ: 6.69 (d, *J* = 8.0 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 6.40 - 6.48 (m, 1H), 5.85 (dd, *J* = 9.2, 5.8 Hz, 1H), 5.59 - 5.73 (m, 1H), 5.55 (d, *J* = 9.8 Hz, 1H), 4.64 - 4.74 (m, 1H), 4.04 - 4.15 (m, 1H), 3.90

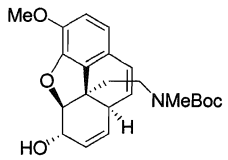
(s, 3H), 3.16 - 3.28 (m, 1H), 3.05 - 3.14 (m, 2H), 2.68 - 2.80 (m, 3H), 1.92 - 2.01 (m, 1H), 1.80 - 1.91 (m, 1H), 1.38 - 1.46 (m, 10H), 0.92 (s, 9H), 0.16 (s, 3H), 0.07 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) (two rotamers) δ: 155.5, 144.7, 141.7, 129.6, 128.2, 128.0, 127.7, 124.1, 117.8, 113.0, 102.1, 95.0, 85.7, 79.3, 68.8, 56.5, 45.1, 38.8, 36.4, 34.7, 34.2, 28.4, 25.8, 25.3, 18.1, -4.7, -4.9 ppm; MS (EI) *m/z* (%): 440 (2), 370 (10, 356 (11), 355 (12), 299 (10), 281 (8), 238 (18), 225 (17), 224 983), 223 (14), 158 (9) 117 (8), 102 (54), 75 (41), 73 (63), 59 (38), 58 (59), 57 (99), 44 (100), 41 (22); HRMS (EI) (M^+-73) calcd for $C_{25}H_{34}NO_4Si$: 440.2257, found 440.2250.



(-)-340

(3a*R*,3*R*,9a*S*,9b*S*)-[2,[3-(*tert*-Butyl-dimethylsilanyloxy)-5-methoxy-3,8,9,9a-tetrahydro-3aH-phenanthro[4,5-bcd]furan-9b-yl]-ethyl]-methyl-carbamic acid tert-butyl ester (-)-(340).

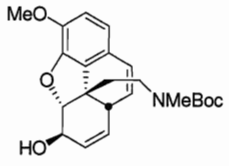
Following the same procedure as for the preparation of compound **340**, using compound (-)-**339** (325 mg, 0.55 mmol), $Pd(OAc)_2$ (31 mg, 0.14 mmol), dppp (111 mg, 0.27 mmol), and Ag_2CO_3 (451 mg, 1.64 mmol) as starting materials, gave 127 mg (45%) of compound (-)-**340**. Data for (-)-**340** (^1H NMR spectra, R_f value) are identical to those of compound **340**; $[\alpha]_D^{22}$ 22.1 (*c* 0.3, $CHCl_3$).



341

(3a*S*,3*S*,9a*R*,9b*R*)-[2,[3-Hydroxy-5-methoxy-3,8,9,9a-tetrahydro-3aH-phenanthro[4,5-bcd]furan-9b-yl]-ethyl]-methyl-carbamic acid tert-butyl ester (341).

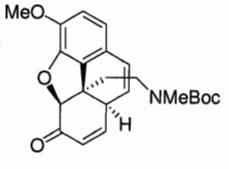
To compound **340** (278 mg, 0.54 mmol) dissolved in THF (3 mL) was added TBAF (0.6 mL, 1M in THF) and the reaction mixture was stirred at ambient temperature for one hour. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (DCM : MeOH, 95:5) to give the title compound as colorless oil (190 mg, 88%). R_f 0.50 (DCM : MeOH, 95:5); $[\alpha]_D^{21}$ -80.5 (*c* 1.2, $CHCl_3$); IR (film) ν_{max}: 3417, 2974, 2933, 1675, 1633, 1507, 1438, 1366, 1280, 1162, 1051, 878 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) (two rotamers) δ: 6.68 (d, *J* = 9.1 Hz, 1H), 6.64 (d, *J* = 6.0 Hz, 1H), 6.40 - 6.50 (m, 1H), 5.83 (bs, 1H), 5.75 (d, *J* = 9.91 Hz, 1H), 5.61 (bs, 1H), 4.70 - 4.82 (m, 1H), 4.14 (bs, 1H), 3.89 (s, 3H), 3.21 - 3.42 (m, 1H), 3.05 - 3.20 (m, 2H), 2.72 - 2.80 (m, 3H), 2.38 - 2.65 (m, 1H), 1.90 - 2.08 (m, 1H), 1.75 - 1.90 (m, 1H), 1.35 - 1.50 (m, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) (two rotamers) δ: 155.5, 145.4, 144.1, 128.3, 128.0, 127.6, 127.2, 123.9, 123.3, 118.1, 117.9, 112.5, 95.2, 79.4, 68.7, 68.6, 56.2, 44.9, 44.4, 43.2, 43.0, 39.3, 38.6, 36.1, 37.0, 34.2, 28.4 ppm; MS (EI) *m/z* (%): 399 (1), 256 (10), 242 (21), 241 (47), 238 (21), 225 (25), 224 (89), 223 (23), 213 (11), 209 917), 181 (12), 152 (10), 102 (30), 88 (11), 85 (14), 83 (20), 59 (27), 58 (35), 57 (100), 44 (27); HRMS (EI) calcd for $C_{23}H_{29}NO_5$: 399.2046, found 399.2043.



(-)-341

(3a*R*,3*R*,9a*S*,9b*S*)-[2,[3-Hydroxy-5-methoxy-3,8,9,9a-tetrahydro-3aH-phenanthro[4,5-bcd]furan-9b-yl]-ethyl]-methyl-carbamic acid tert-butyl ester (-)-(341).

Following the same procedure as for the preparation of compound **341**, using compound (-)-**340** (125 mg, 0.24 mmol) and TBAF (0.27 ml, 1M in THF) as starting materials, gave 72 mg (72%) of compound (-)-**341**. Data for (-)-**341** (^{1}H NMR spectra, R_f value) are identical to those of compound **341**; $[\alpha]_D^{21}$ 68.5 (*c* 0.65, $CHCl_3$).

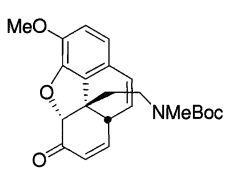


342

***(3aS,9aR,9bR)*-[2,[3-on-5-Methoxy-3,8,9,9a-tetrahydro-3aH-phenanthro[4,5-bcd]furan-9b-yl]-ethyl]-methyl-carbamic acid tert-butyl ester (342).**

To compound **341** (157 mg, 0.39 mmol) dissolved in DMF (2 mL) was added IBX (110 mg, 0.42 mmol) at room temperature. After completion consumption of starting material (TLC) the reaction mixture was quenched with water (20 mL). The phases were separated and the aqueous phase was extracted with DCM (3 x 20 mL). The organic layers were combined, washed with a saturated aqueous solution of $NaHCO_3$,

then dried over anhydrous sodium sulfate. Filtration and removal of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography (DCM : ethyl acetate, 4:1) to afford the title product as colorless oil (142 mg, 92%). R_f 0.68 (DCM : ethyl acetate, 90:10); $[\alpha]_D^{21}$ +61.4 (*c* 1.4, $CHCl_3$); IR (film) ν_{max}: 2928, 1683, 1508, 1438, 1393, 1366, 1281, 1153, 1050, 808 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) (two rotamers) δ: 6.70 (bs, 1H), 6.58 - 6.66 (m, 1H), 6.58 (dd, *J* = 11.8, 1.3 Hz, 1H), 6.08 - 6.18 (m, 1H), 5.87 (t, *J* = 7.5 Hz, 1H), 4.90 (s, 1H), 3.91 (s, 3H), 3.68 - 3.74 (br s, 1H), 3.28 - 3.77 (m, 2H), 3.05 - 3.23 (m, 1H), 2.78 (s, 3H), 1.86 - 2.04 (m, 2H), 1.37 - 1.48 (m, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) (two rotamers) δ: 194.0, 155.4, 146.1, 145.7, 145.0, 144.7, 129.0, 128.6, 127.8, 126.3, 124.6, 124.2, 122.1, 119.2, 119.0, 113.9, 87.3, 79.6, 56.6, 45.0, 44.8, 44.4, 38.5, 37.6, 35.2, 34.2, 29.7, 28.4 ppm; MS (EI) *m/z* (%): 397 (1), 254 (23), 241 (14), 240 (77), 239 (38), 238 (12), 225 (17), 211 (14), 149 (12), 102 (21), 97 (13), 85 (27), 83 (35), 71 (20), 70 (10), 69 (18), 59 (24), 58 (23), 57 (100), 56 (13), 55 (23), 44 (31), 43 (38), 41 (31); HRMS (EI) calcd for $C_{23}H_{27}NO_5$: 397.1889, found 397.1895.

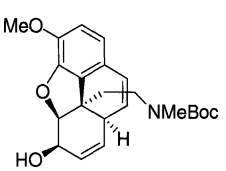


(-)-342

(*3aR,9aS,9bS*)-[2,[3-on-5-Methoxy-3,8,9,9a-tetrahydro-3aH-phenanthro[4,5-bcd]furan-9b-yl]-ethyl]-methyl-carbamic acid tert-butyl ester (-)-(342).

To compound (-)-**341** (70 mg, 0.18 mmol) dissolved in DMF (2 mL) was added IBX (49 mg, 0.18 mmol) at room temperature. The reaction mixture was stirred at room

temperature for 2 hours (TLC indicated unreacted starting material) and additional IBX (15 mg, 0.05 mmol) was added. After completion consumption of starting material (TLC) the reaction mixture was quenched with water (20 mL). The phases were separated and the aqueous phase was extracted with DCM (3 x 20 mL). The organic layers were combined, washed with a saturated aqueous solution of $NaHCO_3$, then dried over anhydrous sodium sulfate. Filtration and removal of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography (DCM : ethyl acetate, 9:1 to 4:1) to afford 60 mg of a mixture of two compounds. Exhaustive purification by flash column chromatography gave 7 mg in 90% purity of compound (-)-**342** and 50 mg of a 1:1 mixture of compounds ((-)-**342** and a yet unidentified byproduct). Data for (-)-**342** (^{1}H NMR spectra, R_f value) are nearly identical to those of compound **342**; $[\alpha]_D^{22}$ -59.2 (*c* 0.35, $CHCl_3$).

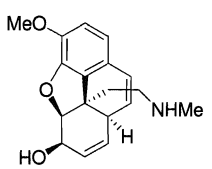


343

(*3aS,3R,9aR,9bR*)-[2,[3-Hydroxy-5-methoxy-3,8,9,9a-tetrahydro-3aH-phenanthro[4,5-bcd]furan-9b-yl]-ethyl]-methyl-carbamic acid tert-butyl ester (343).

To ketone **342** (123 mg, 0.31 mmol) dissolved in methanol (3 mL), was added $CeCl_3 \cdot 7H_2O$ (182 mg, 0.62 mmol). The reaction mixture was stirred at ambient temperature for 5 min and then cooled to 0 °C. $NaBH_4$ (13 mg, 0.34 mmol) was added portion-wise and the mixture was stirred at 0 °C for 20 min. The solvent was removed

under reduced pressure and the residue was suspended in DCM (15 mL). The organic layer was washed with a saturated aqueous solution of NH_4Cl (15 mL), dried over anhydrous sodium sulfate, filtered and the volatiles were removed under reduced pressure. The residue was purified by flash column chromatography (DCM : MeOH, 95:5) to give 110 mg (89%) of alcohol **343**. R_f 0.48 (DCM : MeOH, 95:5); $[\alpha]_D^{22}$ +98 (*c* 0.5, $CHCl_3$); IR (film) ν_{max}: 3449, 2973, 2932, 1690, 1637, 1507, 1457, 1393, 1366, 1269, 1160, 1089, 1051, 798 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.63 (d, *J* = 8.0 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 6.51 (d, *J* = 9.3 Hz, 1H), 6.00 (dd, *J* = 9.3, 6.2 Hz, 1H), 5.81 (d, *J* = 10.0 Hz, 1H), 5.28 (dd, *J* = 10.0, 2.3 Hz, 1H), 5.15 (bs, 1H), 4.17 - 4.28 (m, 1H), 3.85 (s, 3H), 3.22 - 3.45 (m, 1H), 2.80 - 2.99 (m, 2H), 2.76 (s, 3H), 2.05 - 2.22 (m, 1H), 1.76 - 1.99 (m, 1H), 1.42 (s, 9H) ppm; MS (EI) *m/z* (%): 399 (14), 343 (12), 246 (43), 242 (34), 241 (87), 240 (11), 252 (13), 224 (12), 223 (11), 213 (16), 209 (16), 181 (16), 88 (23), 86 (56), 84 (56), 59 (25), 58 (33), 57 (100), 55 (12); HRMS (EI) calcd for $C_{23}H_{29}NO_5$: 399.2046, found 399.2044.

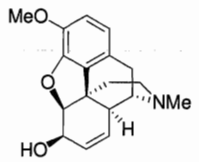


(+)-184

(*2aS,5R,5R,5aS*)-2a,5,5,5a-tetrahydro-7-Methoxy-5-(2-(methylamino)ethyl) phenanthro[4,5-bcd]furan-5-ol (+)-(184).

To compound **343** (105 mg, 0.26 mmol) dissolved in DCM (3 mL) was added trifluoroacetic acid (0.5 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 hrs and then the solvent was removed under reduced pressure. The residue

was suspended in $CHCl_3$ and washed with a saturated aqueous solution of Na_2CO_3 and brine. The aqueous layers were combined and extracted with $CHCl_3$. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered and then the solvent was evaporated. The crude product was purified by flash column chromatography (DCM : MeOH, 4:1) to give 69 mg (88%) of amine (+)-**184**. $[\alpha]_D^{22}$ +112.5 (*c* 0.4, $CHCl_3$); IR (film) ν_{max}: 3583, 3311, 3032, 2931, 2851, 1635, 1573, 1506, 1457, 1381, 1270, 1194, 1161, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.64 (d, *J* = 7.9 Hz, 1H), 6.58 (d, *J* = 7.9 Hz, 1H), 6.50 (d, *J* = 9.0 Hz, 1H), 6.00 (dd, *J* = 9.3, 6.4 Hz, 1H), 5.77 - 5.85 (m, 1H), 5.29 (dt, *J* = 10.1, 2.5 Hz, 1H), 5.16 (d, *J* = 6.1 Hz, 1H), 4.19 - 4.26 (m, 1H), 3.85 (s, 3H), 2.78 - 2.86 (m, 1H), 2.71 (td, *J* = 5.2, 2.9 Hz, 1H), 2.31 - 2.49 (m, 2H), 2.36 (s, 3H), 2.06 - 2.19 (m, 2H), 1.78 - 1.92 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.2, 143.8, 132.0, 129.2, 127.6, 125.1, 123.7, 117.8, 112.0, 90.5, 66.0, 56.0, 57.9, 45.4, 37.7, 36.4, 35.9, 25.8 ppm; MS (EI) *m/z* (%): 299 (9), 242 (53), 240 (16), 225 (24), 197 (13), 152 (10), 59 (100), 44 (54); HRMS (EI) calcd for $C_{18}H_{21}NO_3$: 299.1521, found 299.1517.

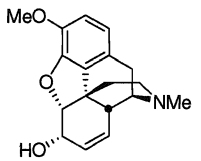


(+) - **2**

(+)-Codeine (2).

Amine (+)-**184** (50 mg, 0.17 mmol) dissolved in THF (5 mL) was added to a mixture of $Hg(OAc)_2$ (80 mg, 0.25 mmol) and triethylamine (60 μL, 0.40 mmol) in THF (2 mL). The mixture was stirred for 48 hrs and then a solution of LAH in THF (0.46 mL

(1M THF), 0.46 mmol) was added dropwise. The reaction mixture was stirred for 2 hrs and then quenched with saturated aqueous solution of Na_2CO_3 (2 mL). The aqueous phase was extracted with $CHCl_3$ (3 x 3 mL). The organic layers were combined and dried over anhydrous sodium sulfate. The mixture was filtered and the solvent was evaporated under reduced pressure. The concentrated product was purified by flash column chromatography (DCM : MeOH : NH_4OH, 80:20:1) affording (+)-codeine (10 mg, 0.03 mmol, 17.6%). R_f 0.75 (DCM : MeOH, 4:1); $[\alpha]_D^{22}$ +130 (*c* 0.3, EtOH) (Lit.[173] +137.5 (*c* 0.16, EtOH). IR (film) ν_{max}: 3402, 2930, 2839, 1634, 1603, 1504, 1452, 1277, 1254, 1121, 1054, 942 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 6.69 (d, *J* = 8.2 Hz, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 5.74 (m, 1H), 5.31 (m, 1H), 4.93 (d, *J* = 6.5 Hz, 1H), 4.20 - 4.23 (m, 1H), 3.87 (s, 3H), 3.72 (m, 1H), 3.41 - 3.46 (m, 1H), 3.08 (d, *J* = 18.5 Hz, 1H), 2.74 - 2.81 (m, 1H), 2.65 - 2.72 (m, 1H), 2.51 (s, 3H), 2.44 - 2.50 (m, 1H), 2.34 - 2.42 (m, 1H), 2.11 - 2.21 (m, 1H), 1.92 (d, *J* = 12.4 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 146.3, 142.3, 133.7, 130.8, 127.9, 119.7, 112.9, 91.2, 66.3, 59.0, 56.3, 46.5, 42.9, 42.8, 40.4, 35.4, 29.9, 20.6 ppm; MS (EI) *m/z* (%): 300 (21), 299 (100), 298 (14), 229 (19), 188 (13), 162 (23), 124 (22), 115 (12), 59 914), 42 (13); HRMS (EI) calcd for $C_{18}H_{21}NO_3$: 299.1521, found 299.1520.



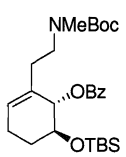
(-)-2

(-)-Codeine (2).

To a mixture of compounds (1:1, (-)-**342** and unidentified byproduct) (50 mg) dissolved in methanol (1 mL), was added $CeCl_3 \bullet 7H_2O$ (70 mg, 0.19 mmol). The reaction mixture was stirred at ambient temperature for 5 min and then cooled to 0 °C. $NaBH_4$ (5 mg, 0.14 mmol) was added in one portion and the mixture was stirred at 0 °C for 20 min. The solvent was removed under reduced pressure and the residue was suspended in DCM (10 mL). The organic layer was washed with a saturated aqueous solution of NH_4Cl (10 mL), dried over anhydrous sodium sulfate, filtered and the volatiles were removed under reduced pressure. The residue was purified by flash column chromatography (DCM : MeOH, gradient and DCM : ethyl acetate, gradient) to give 38 mg of a mixture of compounds (1.25:1).

To this mixture of compounds (38 mg) dissolved in DCM (1 mL) was added trifluoroacetic acid (0.25 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 hrs and then the solvent was removed under reduced pressure. The residue was suspended in $CHCl_3$ and washed with a saturated aqueous solution of Na_2CO_3 and brine. The aqueous layers were combined and extracted with $CHCl_3$. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered and then the solvent was evaporated. The crude product was purified by flash column chromatography (DCM : MeOH, 4:1) to give 28 mg of a mixture of compounds (1.25:1).

This mixture of compounds (28 mg) dissolved in THF (1 mL) was added to a mixture of $Hg(OAc)_2$ (45 mg, 0.14 mmol) and triethylamine (33 μL, 0.23 mmol) in THF (1 mL). The mixture was stirred for 48 hrs and then a solution of LAH in THF (10 mg, 0.25 mmol in 1 mL of THF) was added dropwise. The reaction mixture was stirred for 2 hrs and then quenched with saturated aqueous solution of Na_2CO_3 (2 mL). The aqueous phase was extracted with $CHCl_3$ (3 x 3 mL). The organic layers were combined and dried over anhydrous sodium sulfate. The mixture was filtered and the solvent was evaporated under reduced pressure. The concentrated product (26 mg) was purified by flash column chromatography (DCM : MeOH : NH_4OH, 100:0:0 to 90:10:1) affording (-)-codeine (4.2 mg, 0.014 mmol, 8% over four steps). Data for (-)-codeine (**2**) (^1H NMR spectra, R_f value) are identical to those of (+)-codeine (**2**); $[\alpha]_D^{20}$ -124.6 (*c* 0.15, EtOH), (Lit.[92] $[\alpha]_D^{27}$ - 137 (*c* 1.15, EtOH)).

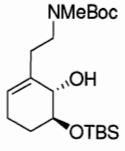


345

{2-[5-(*tert*-Butyl-dimethyl-silanyloxy)-6-benoyloxy-cyclohex-1-enyl]-ethyl}-methyl-carbamic acid *tert*-butyl ester (345).

To a stirred solution of alcohol **6** (360 mg, 0.94 mmol) and benzoic acid (171 mg, 1.40 mmol) in THF (12 mL) at 0 °C, was added a solution of the Mitsunobu reagent [previously prepared by addition of DIAD (568 mg, 2.81 mmol) to a stirred solution of freshly distilled tributylphosphine (736 mg, 2.81 mmol) in THF (10 mL) at 0 °C], and the mixture was warmed to rt After 16 hrs, silica gel was added to the reaction

mixture and the solvent was removed under reduced pressure. The crude residue was subjected to flash column chromatography (hexanes : ethyl acetate, 15:1 to 1:1) to give compound **345** as a clear and colorless oil (380 mg, 83 %). R_f 0.55 (hexanes : ethyl acetate, 1:1); $[\alpha]_D^{23}$ -5.6 (*c* 0.8, $CHCl_3$); IR (film) ν_{max}: 3030, 2956, 2859, 1718, 1692, 1472, 1392, 1253, 1085 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 8.08 (d, *J* = 7.8 Hz, 2H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 5.79 - 5.68 (m, 1H), 5.52 (bs, 1H), 4.03 (bs, 1H), 3.18 - 3.35 (m, 2H), 2.69 - 2.81 (m, 3H), 2.20 - 2.29 (m, 2H), 2.09 - 2.20 (m, 2H), 1.81 - 1.91 (m, 1H), 1.71 -1.80 (m, 1H), 1.45 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 166.2, 155.7, 133.0, 131.5, 130.3, 129.7, 129.1, 128.7, 128.4, 79.3, 74.6, 74.3, 69.9, 48.2, 47.7, 34.8, 34.4, 32.4, 31.6, 31.5, 28.5, 27.9, 25.7, 22.7, 22.5, 17.9, 14.2, - 4.76, - 4.82 ppm; HRMS (EI) (M^+-57) calcd for $C_{27}H_{43}NO_5Si$: 489.2911, found 428.2916.

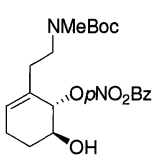


346

{2-[5-(*tert*-Butyl-dimethyl-silanyloxy)-6-hydroxy-cyclohex-1-enyl]-ethyl}-methyl-carbamic acid *tert*-butyl ester (346).

To a solution of compound **345** (370 mg, 0.76 mmol) in MeOH (5 mL) was added 1M NaOH (2.3 mL, 2.3 mmol) and the resulting reaction mixture was stirred at rt for 18 hrs. Brine was added and MeOH was removed on the rotary evaporator. The aqueous layer was extracted five times with ethyl acetate and the organic layers were combined and dried over anhydrous sodium sulfate. The solution was filtered and the

solvent was removed under reduced pressure to yield a colorless oil, which was purified by flash column chromatography (hexanes : ethyl acetate 8:1 to 5:1) to yield compound **346** as a colorless oil (160 mg, 55%). R_f 0.62 (hexanes : ethyl acetate, 2:1); $[\alpha]_D^{23}$ -12.6 (*c* 0.8, $CHCl_3$); IR (film) ν_{max}: 3584, 2976, 2931, 1698, 1482, 1393, 1365, 1162 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 5.42 (bs, 1H), 3.87 - 4.11 (m, 1H), 3.69 - 3.87 (m, 2H), 2.88 (s, 3H), 2.25 - 2.45 (m, 1H), 2.08 - 2.22 (m, 2H), 1.85 - 2.01 (m, 1H), 1.65 - 1.79 (m, 1H), 1.58 - 1.62 (m, 2H), 1.44 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 155.5, 129.3, 122.0, 80.1, 75.9, 75.6, 49.9, 48.4, 34.3, 33.5, 32.6, 28.2, 25.4, 25.2, 25.2, 24.3, 24.0, 17.9, -4.6, -4.8 ppm; MS (EI) *m/z* (%): 367 (1), 272 (16), 228 (55), 197 (35), 185 (19), 153 (13), 144 (24), 136 (22), 127 (12), 88 (20), 75 (60), 73 (36), 57 (87), 45 (11), 44 (100); HRMS (EI) (M^+-18) calcd for $C_{20}H_{37}NO_3Si$: 367.2543, found 367.2542.

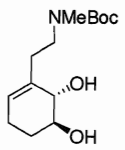


348

{2-[5-Hydroxy-6-(4-nitro-benzoyloxy)-cyclohex-1-enyl]-ethyl}-methyl-carbamic acid *tert*-butyl ester (348).

A magnetically stirred suspension of *cis* diol **336** (200 mg, 0.74 mmol) in toluene (5 mL) at 0 °C was treated with *p*-nitrobenzoic acid (369 mg, 2.21 mmol) and triphenylphosphine (291 mg, 1.11 mmol). DIAD (209 mg, 1.04 mmol) was added dropwise and the reaction mixture was warmed to rt and stirred for 18 hrs. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$.

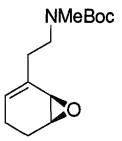
The layers were separated and the aqueous layer was extracted with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated and the residue was purified by flash column chromatography (hexanes : ethyl acetate, 12:1 to 1:1) to give the title compound **348** as a colorless oil (220 mg, 71%). R_f 0.38 (hexanes : ethyl acetate, 1:1); $[\alpha]_D^{22}$ -41.6 (*c* 0.6, $CHCl_3$); IR (film) ν_{max}: 3424, 2977, 2931, 1722, 1692, 1529, 1396, 1270, 1161, 1102 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) (two rotamers) δ: 8.39 (d, *J* = 8.4 Hz, 4H), 8.32 (d, *J* = 8.4 Hz, 4H), 5.64 - 5.81 (m, 4H), 4.38 (bs, 1H), 4.24 (bs, 1H), 4.02 (bs, 2H), 3.60 (bs, 1H), 3.41 (bs, 1H), 3.23 (bs, 1H), 3.08 (bs, 1H), 2.88 (bs, 1H), 2.82 (s, 3H), 2.76 (s, 3H), 2.12 - 2.39 (m, 8H), 1.88 - 1.99 (m, 2H), 1.71 - 1.82 (m, 2H), 1.46 (s, 18H) ppm; ^{13}C NMR (150 MHz, aceton-d_6) (two rotamers) δ: 164.6, 156.3, 150.7, 130.90, 130. 86, 129.1, 123.6, 78.4, 76.5, 75.3, 69.2, 68.8, 68.3, 47.7, 46.6, 33.6, 33.4, 31.6, 31.4, 27.6, 27.5, 22.7, 22.5, 21.9 ppm; MS (EI) *m/z* (%): 420 (1), 167 (14), 144 (35), 120 (14), 118 (11), 110 (29), 109 (13), 103 (43), 88 (10), 76 (51), 65 (15), 59 (17), 57 (83), 45 (13), 44 (100); HRMS (EI) calcd for $C_{21}H_{28}N_2O_7$: 420.1897, found 420.1901; Anal calcd for $C_{21}H_{27}N_2O_7$: C 59.99% H 6.71%, found C 60.02% H 7.24%.



349

[2-(5, 6-Dihydroxy-cyclohex-1-enyl)-ethyl]-methyl-carbamic acid *tert*-butyl ester (349).

To a solution of compound **348** (200 mg, 0.48 mmol) in MeOH (3 mL) was added 1M NaOH (1.43 mL, 1.43 mmol) and the resulting reaction mixture was stirred at rt for 18 hrs. Brine was added and MeOH was removed on the rotary evaporator. The aqueous layer was extracted five times with ethyl acetate and the organic layers were combined and dried over anhydrous sodium sulfate. The solution was filtered and the solvent was removed under reduced pressure to yield a colorless oil, which was purified by flash column chromatography (hexanes : ethyl acetate, 4:1 to 1:3) to yield compound **349** as a colorless oil (98 mg, 76%). R_f 0.10 (hexanes : ethyl acetate, 1:1); $[\alpha]_D^{23}$ +17.6 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3430, 2975, 2929, 1695, 1673, 1484, 1397, 1366, 1158, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.34 (bs, 1H), 3.96 - 4.06 (m, 1H), 3.62 - 3.78 (m, 2H), 3.58 (bs, 2H), 2.98 - 3.18 (m, 1H), 2.82 (s, 3H), 2.31 - 2.43 (m, 1H), 2.20 - 2.31 (m, 1H), 1.95 - 2.20 (m, 2H), 1.82 - 1.95 (m, 1H), 1.55- 1.71 (m, 1H), 1.45 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.7, 134.6, 126.7, 79.8, 74.7, 73.2, 47.8, 34.1, 32.6, 28.5, 28.3, 27.2, 23.7 ppm; HRMS (EI) calcd for $C_{14}H_{25}NO_4$: 271.1784, found 271.1782.

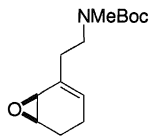


(+)-7

***tert*-Butyl-2-(7-oxa-bicyclo[4.1.0]hept-2-en-2-yl)ethylmethylcarbamate (7).**

From *trans*-diol 349: (+)-(7).

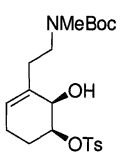
A solution of *trans* diol **349** (80 mg, 0.30 mmol) in THF (1 mL) at 0 °C was treated with bromoisovanillin (205 mg, 0.89 mmol) and triphenylphosphine (116 mg, 0.44 mmol). DIAD (89 mg, 0.44 mmol) was added dropwise and the reaction mixture was warmed to rt and stirred for 18 hrs. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$. The layers were separated and the aqueous layer was extracted with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated and the residue was purified by flash column chromatography (hexanes : ethyl acetate, 5:1 to 1:1) to give the title compound (+)-**7** as a colorless oil (30 mg, 45%). R_f 0.40 (hexanes : ethyl acetate, 2:1); $[\alpha]_D^{22}$ +20.6 (*c* 0.25, $CHCl_3$); IR (film) ν_{max}: 2976, 2931, 1692, 1482, 1393, 1365. 1134 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 5.63 (d, *J* = 6.6 Hz, 1H), 3.54 (bs, 1H), 3.38 - 3.53 (m, 1H), 3.12 - 3.30 (m, 2H), 2.89 (bs, 3H), 2.32 - 2.48 (m, 2H), 2.16 - 2.28 (m, 1H), 1.88 - 2.04 (m, 2H), 1.52 - 1.60 (m, 1H), 1.48 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 155.7, 132.1, 127.3, 79.7, 55.4, 50.2; 48.4, 47.8, 34.8, 34.5, 34.2, 28.5, 20.8, 20.2 ppm; MS (EI) *m/z* (%): 253 (1), 144 (34), 110 (24), 88 (10), 57 (94), 44 (100); HRMS (EI) calcd for $C_{14}H_{23}NO_3$: 253.1678, found 253.1680; Anal calcd for $C_{14}H_{23}NO_3$: C 66.37% H 9.15%, found C 66.37% H 9.09%.



(-)-**7**

From compound 352: (-)-(7).

Compound **352** (1.70 g, 2.96 mmol) was dissolved in THF (30 mL) and 0.5 M sodium methoxide solution in MeOH (7.1 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for one hour, before it was quenched by the addition of a saturated aqueous solution of NH_4Cl (50 mL). The organic solvent was removed under reduced pressure and the aqueous layer was extracted five times with ethyl acetate. The organic extracts were combined and dried over anhydrous sodium sulfate. The solution was filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (hexanes : ethyl acetate, 9:1 to 3:1) to give the title compound **(-)-7** as colorless oil (0.66 g, 88%). $[\alpha]_D^{22}$ - 21.0 (*c* 0.25, $CHCl_3$).

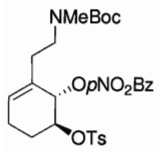


351

[2-[6-Hydroxy-5-(4-methylbenzenesulfonyl)-cyclohex-1-enyl]-ethyl]-methyl-carbamic acid *tert*-butyl ester (351).

To a solution of diol **336** (2.0 g, 7.4 mmol) and tosylchloride (2.5 g, 13.3 mmol) in DCM (20 mL) were added triethylamine (1.9 g, 18.5 mmol) and DMAP (catalytic amount) at 0 °C. The reaction mixture was warmed to rt and was stirred until

complete consumption of starting materials (TLC, 18 hrs). The solution was diluted with DCM (20 mL) and washed three times with a saturated aqueous solution of Na_2CO_3, three times with a saturated aqueous solution of NH_4Cl, and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography afforded the tile compound **351** as colorless oil (1.1 g, 35%) and 0.9 g (45%) of recovered starting material. R_f 0.48 (hexanes : ethyl acetate, 1:1); $[\alpha]_D^{22}$ +107.1 (*c* 0.10, $CHCl_3$); IR (film) ν_{max}: 3400, 2918, 2849, 1689, 1672, 1599, 1483, 1453, 1395, 1364, 1180, 1123, 1098 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) (two rotamers) δ: 7.78 - 7.92 (m, 2H), 7.31 - 7.39 (m, 2H), 5.38 - 5.59 (m, 1H), 4.56 - 4.69 (m, 1H), 4.00 - 4.23 (m, 2H), 3.58 - 3.70 (m, 1H), 3.18 - 3.39 (m, 1H), 3.00 - 3.13 (m, 1H), 2.82 (s, 3H), 2.45 (s, 3H), 2.26 - 2.37 (m, 1H), 2.08 - 2.19 (m, 2H), 1.95 - 2.07 (m, 2H), 1.41 (bs, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ (two rotamers): 156.4, 144.5, 134.3, 134.0, 129.8, 127.8, 127.4, 81.4, 79.6, 68.1, 47.6, 34.0, 33.8, 28.3, 24.3, 23.9, 22.5, 21.7 ppm; HRMS (EI) (M^+-73) calcd for $C_{17}H_{22}NO_5S$: 352.1219, found 352.1228; Anal calcd for $C_{21}H_{31}NO_6S$: C 59.27% H 7.34%, found C 59.34% H 7.18%.

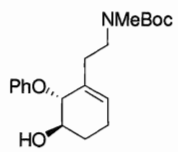


352

(*5S,6S*)-[2-[5-(4-Methylbenzenesulfonyl)-6-(4-nitro-benzoyloxy)-cyclohex-1-enyl]-ethyl]-methyl-carbamic acid *tert*-butyl ester (352).

To a solution of nitrobenzoate **348** (2.3 g, 5.5 mmol) in DCM (30 mL) were added tosylchloride (5.2 g, 27.4 mmol), triethylamine (7.6 mL, 54.8 mmol) and DMAP (60 mg) at 0 °C. The reaction mixture was warmed to rt and stirred for 22 hrs, before it was quenched by the addition of water (20 mL). The layers were separated and the aqueous layer was extracted three times with DCM (20 mL). The organic extracts were combined, washed three times with a saturated aqueous solution of Na_2CO_3, three times with a saturated aqueous solution of NH_4Cl, and brine. The organic layers were dried over anhydrous sodium sulfate, filtered and the solvent was evaporated under reduced pressure. Purification of the crude residue by flash column chromatography (hexanes : ethyl acetate, 9:1 to 1:1) gave the title compound **352** as colorless solid (2.5 g, 78%). mp 135 - 136 °C (hexanes/ethyl acetate); R_f 0.48 (hexanes : ethyl acetate, 2:1); $[\alpha]_D^{23}$ +81.6 (c 0.9, $CHCl_3$); IR (film) ν_{max}: 3112, 3054, 2976, 2931, 1730, 1691, 1599, 1529, 1454, 1350, 1266, 1190, 1101, 914 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) (two rotamers) δ: 8.28 (d, *J* = 7.9 Hz, 2H), 8.10 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 7.9 Hz, 2H), 7.11 - 7.18 (m, 2H), 5.80 - 5.88 (m, 1H), 5.73 - 5.76 (m, 1H), 4.88 - 4.93 (m, 1H), 3.28 - 3.45 (m, 1H), 3.08 - 3.16 (m, 1H), 2.70 - 2.78 (m, 3H), 2.30 (s, 3H), 2.22 - 2.28 (m, 2H), 2.09 - 2.19 (m, 2H), 1.95 - 2.09 (m, 2H), 1.43 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) (two rotamers) δ: 164.0, 155.6,

150.6, 144.7, 134.0, 131.0, 130.9, 129.2, 129.7, 128.6, 127.6, 123.4, 79.9, 79.6, 79.2, 72.8, 72.4, 47.6, 47.0, 34.2, 31.3, 30.7, 28.5, 26.7, 23.2, 23.0, 21.6 ppm; HRMS (EI) (M^+-73) calcd for $C_{24}H_{25}N_2O_8S$: 501.1326, found 501.1330; Anal calcd for $C_{28}H_{34}N_2O_9S$: C 58.52% H 5.96%, found C 58.78% H 6.02%.

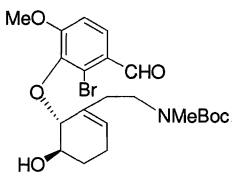


358

***tert*-Butyl-2-((5*R*,6*R*)-5-hydroxy-6-phenoxycyclohex-1-enyl)ethylmethylcarbamate (358).**

To a solution of epoxide (-)-**7** (50 mg, 0.20 mmol) in DME (0.5 mL) was added potassium phenoxide (52 mg, 0.40 mmol) followed by the addition of 18-crown-6-ether (catalytic amount). The reaction mixture was heated at reflux for 16 hrs, before it was cooled to rt and quenched by the addition of water (2 mL). The layers were separated and the aqueous layer was extracted three times with ethyl acetate. The organic layers were combined, washed three times with a saturated aqueous solution of Na_2CO_3 and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (hexanes : ethyl acetate, 5:1 to 1:1) and the title compound **358** was isolated as colorless oil (54 mg, 78%). R_f 0.35 (hexanes : ethyl acetate, 2:1); $[\alpha]_D^{23}$ -33.2 (*c* 0.59, $CHCl_3$); IR (film) ν_{max}: 3429, 2975, 2928, 1694, 1670, 1596, 1492, 1454, 1396, 1366, 1228, 1164, 1078 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.31 (t, *J* = 7.4 Hz, 2H), 7.07 (d, *J* = 7.4 Hz, 2H), 6.98 (t, *J* = 7.4 Hz,

1H), 5.70 - 5.73 (m, 1H), 4.69 - 4.72 (m, 1H), 4.15 - 4.19 (m,1H), 3.85 - 3.93 (m, 1H), 3.63 (d, J = 6.4 Hz, 1H), 2.86 (s, 3H), 2.73- 2.80 (m, 1H), 2.13 -2.32 (m, 3H), 2.04 - 2.11 (m, 1H), 1.77 - 1.85 (m, 2H), 1.46 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 158.6, 157.0, 130.6, 129.7, 121.1, 115.6, 79.9, 73.6, 66.0, 46.3, 34.0, 32.7, 28.5, 24.4, 20.7 ppm; HRMS (EI) calcd for $C_{20}H_{29}NO_4$: 347.2097, found 347.2084; Anal calcd for $C_{20}H_{29}NO_4$: C 69.14% H 8.41%, found C 68.85% H 8.49%.

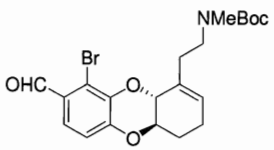


350

***N*-[2-[(5*R*,6*R*)-6-(2-bromo-3-formyl-6-methoxyphenoxy)-5-hydroxy-1-cyclohexen-1-yl]ethyl]-*N*-methyl carbamic acid 1,1-dimethylethylester (350).**

To a solution of epoxide (-)-**7** (90 mg, 0.375 mmol) in DME (0.5 mL) and DMF (0.5 mL) was added potassium phenoxide derivative **362** (260 mg, 1.126 mmol), followed by the addition of 18-crown-6-ether (catalytic amount). The reaction mixture was heated at 90 °C for 24 hrs, before it was cooled to rt and diluted with diethyl ether (20 mL). The organic layer was extracted three times with a saturated aqueous solution of Na_2CO_3 (10 mL), ten times with water (0.5 mL) and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes : ethyl acetate, 4:1 to 1:1) gave the title compound **350** (130 mg, 75%) and compound **363** (8 mg, 5%). Compound **350**: colorless oil; R_f 0.35 (hexanes : ethyl acetate, 3:2); $[\alpha]_D^{23}$ -93.0 (*c* 0.2, $CHCl_3$); IR (film) ν_{max}: 3428, 3088, 2975, 2931, 2869, 2741, 1678, 1579,

1482, 1440, 1367, 1276, 1253, 1164, 1029, 938 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 10.27 (s, 1H), 7.73 (d, *J* = 8.6 Hz, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 5.71 - 5.75 (m, 1H), 4.78 - 4.82 (m, 1H), 3.98 - 4.06 (m, 2H), 3.95 (s, 3H), 3.53 (bs, 1H), 2.89 (s, 3H), 2.80 - 2.87 (m, 1H), 2.65 - 2.79 (m, 1H), 2.22 - 2.37 (m, 2H), 2.03 - 2.21 (m, 2H), 1.80 - 1.89 (m, 1H), 1.42 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 191.3, 158.1, 157.1, 144.7, 130.9, 130.4, 127.6, 126.1, 123.4, 111.0, 80.0, 76.9, 66.4, 56.1, 46.3, 34.0, 32.8, 28.5, 28.5, 24.3, 20.7 ppm; HRMS (EI) (M^+-73) calcd for $C_{18}H_{21}NO_5$: 410.0603, found 410.0601; Anal calcd for $C_{22}H_{30}BrNO_6$: C 54.55% H 6.24%, found C 54.68% H 6.41%.

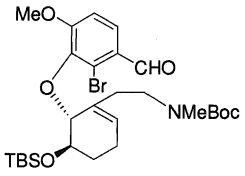


363

***tert*-Butyl-2-((4a*R*,10a*R*)-6-bromo-7-formyl-1,2,4a,10a-tetrahydrodibenzo [b,e][1,4] dioxin-4-yl)ethylmethylcarbamate (363).**

Colorless oil; R_f 0.42 (hexanes : ethyl acetate, 3:1); $[\alpha]_D^{22}$ +168.3 (*c* 0.5, $CHCl_3$); IR (film) ν_{max}: 2975, 2931, 2873, 1686, 1591, 1561, 1477, 1392, 1280, 1160, 1052, 969 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) (two rotamers) δ: 10.14 (s, 1H), 7.46 (d, *J* = 8.7 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 1H), 5.58 - 5.66 (m, 1H), 4.60 - 4.79 (m, 1H), 4.10 - 4.25 (m, 1H), 3.47 - 3.78 (m, 1H), 2.74 - 2.88 (m, 3H), 2.52 - 2.64 (m, 1H), 2.13 - 2.47 (m, 4H), 1.63 - 1.87 (m, 2H), 1.28 - 1.44 (s, 9H) ppm; ^{13}C NMR (600 MHz based on HSQC, DMSO-d_6) (two rotamers) δ: 190.7, 127.9, 123.9, 117.2, 76.5, 75.5, 40.3, 34.1, 30.1, 28.3, 25.7, 23.9 ppm; HRMS (EI) calcd for $C_{21}H_{26}BrNO_5$: 451.0994,

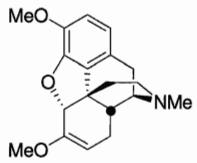
found 451.0995; Anal calcd for $C_{21}H_{26}BrNO_5$: C 55.76% H 5.79%, found C 56.51% H 5.96%.



364

***N*-[2-[(5*R*,6*R*)-6-(2-Bromo-3-formyl-6-methoxyphenoxy)-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-cyclohexen-1-yl]ethyl]-*N*-methyl carbamic acid 1,1-dimethylethylester (364).**

To a solution of compound **350** (15 mg, 0.03 mmol) in diethyl ether (0.5 mL) were added imidazole (8.2 mg, 0.12 mmol) and TBDMSCl (9.1 mg, 0.06 mmol) at -60 °C. The reaction mixture was warmed to rt and stirred at ambient temperature for 18 hrs. The reaction mixture was diluted with DCM (5 mL) and extracted three times with a saturated aqueous solution of NH_4Cl. The organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. Evaporation of the solvent and purification of the crude residue by flash column chromatography gave the title compound **364** as colorless oil (11 mg, 61%). Data for **364** is identical to data of **337** except $[\alpha]_D^{21}$ -55.8 (*c* 0.325, $CHCl_3$); **337** $[\alpha]_D^{22}$ +59.1 (*c* 0.35, $CHCl_3$).



237

8,14-Dihydrothebaine (237).

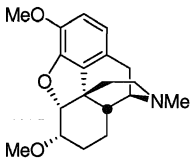
Thebaine (**4**) (30 mg, 0.10 mmol) was dissolved in MeOH (1 mL) and nitrogen was bubbled through the reaction mixture for five min. Crabtree's catalyst **368** (4 mg, 0.005 mmol) was added and the reaction vessel was evacuated and flushed with hydrogen. This cycle was repeated two more times. The reaction mixture was hydrogenated (55 psi H_2 pressure) for 12 days. Crabtree's catalyst (4 mg, 0.005 mmol) was added every fourth day. After each addition of catalyst the reaction vessel was evacuated and flushed with hydrogen as written before. The progress of the reaction was monitored by HPLC.

The reaction mixture was filtered through a plug of Celite and the filtrate was concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (DCM : MeOH : NH_4OH, 100:0:0 to 94:6:1) and a mixture of 8,14-dihydrothebaine (**237**) and tetrahydrothebaine (**367**) in a ratio of 5 :3 (72% combined yield) was recovered. Analyses are based on comparison of the data obtained on the mixture with analytical data of purified standards. 8,14-Dihydrothebaine (**237**) was prepared according to a procedure by Weller and Rapoport[174] to give compound **237** as colorless crystals. mp 163 - 165 °C ($CHCl_3$/MeOH) (lit. mp[174] 158 - 160 °C); R_f 0.60 (DCM : MeOH : NH_4OH, 92:8:1); IR (film) ν_{max}: 3030, 3005, 2923, 2848, 2793, 2771, 1658, 1633, 1605, 1501, 1446, 1374, 1215, 1150, 1057 cm^{-1}; ^1H NMR ($CDCl_3$, 600MHz) δ: 6.69 (d, J = 7.9 Hz, 1H),

6.60 (d, J = 7.9 Hz, 1H), 4.84 (s, 1H), 4.72 (d, J = 5.3 Hz, 1H), 3.83 (s, 3H), 3.48 (s, 3H), 3.11 - 3.14 (m, 1H), 3.01 (d, J = 18.5 Hz, 1H), 2.52 (dd, J = 12.1, 4.5 Hz, 1H), 2.41 (s, 3H), 2.35 - 2.40 (m, 1H), 2.29 - 2.34 (m, 1H), 2.25 (dt, J = 12.4, 4.0 Hz, 1H), 1.89 - 2.00 (m, 2H), 1.79 - 1.84 (m, 1H), 1.52 - 1.60 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 150MHz) δ: 152.3, 145.2, 143.1, 129.3, 127.0, 118.6, 113.5, 98.1, 88.6, 59.0, 56.5, 54.4, 46.5, 43.1, 42.5, 39.9, 35.8, 23.6, 20.2 ppm; HRMS (EI) calcd for $C_{19}H_{23}NO_3$: 313.1678, found 313.1664.

8,14-Dihydrothebaine (237) from codeine methyl ether (327).

Codeine methyl ether (**327**) (10 mg, 0.03 mmol) was dissolved in dry EtOH (0.1 mL) and Wilkinson's catalyst (0.1 mg) was added. The reaction mixture was heated at reflux for 14 hrs, before it was cooled to rt and filtered through a plug of silica. Evaporation of the solvent and analysis by NMR and HPLC showed a 20% conversion to 8,14-dihydrothebaine (**237**), besides unreacted starting material.

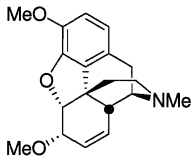


367

Tetrahydrothebaine (367).

A standard of tetrahydrothebaine (**367**) was prepared by following procedure. Thebaine (30 mg, 0.100 mmol) was dissolved in DCM (0.3 mL) and catalyst **369** (3.5 mg, 0.005 mmol) was added. The reaction vessel was evacuated and flushed with hydrogen. This cycle was repeated two more times. The reaction mixture was

hydrogenated (14 psi H_2 pressure) for 18 hrs, before it was filtered through a plug of silica. The solvent was removed under reduced pressure to yield the title compound after purification by flash column chromatography ((DCM : MeOH : NH_4OH, 100:0:0 to 94:6:1) as colorless oil (27 mg, 90%). Data for **367** are identical to those published in the literature.[175] R_f 0.60 (DCM : MeOH : NH_4OH, 96:4:1); IR (film) ν_{max}: 3429, 2933, 2835, 1635, 1609, 1504, 1440, 1337, 1277, 1258, 1152, 1105, 1057 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ: 6.71 (d, *J* = 8.2 Hz, 1H), 6.58 (d, *J* = 8.2 Hz, 1H), 4.68 (d, *J* = 5.0 Hz, 1H), 3.85 (s, 3H), 3.50 - 3.54 (m, 2H), 3.68 (s, 3H); 3.09 - 3.12 (m, 1H), 2.98 (d, *J* = 18.5 Hz, 1H), 2.51 - 2.57 (m, 1H), 2.39 - 2.45 (m, 4H), 2.21 - 2.32 (m, 2H), 1.89 (dt, *J* = 12.5, 4.9 Hz, 1H), 1.72 (dd, *J* = 11.3, 1.1 Hz, 1H), 1.37 - 1.54 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 147.1, 141.8, 129.9, 126.4, 118.4, 113.5, 89.3, 76.9, 59.9, 58.2, 56.5, 46.9, 42.9, 42.3, 39.9, 37.1, 24.3, 20.1, 19.4 ppm; MS (EI) *m/z* (%): 316 (18.3), 315 (87.3), 300 (42.5), 178 (15.0), 86 (68.8), 85 (75.8), 84 (97.1), 83 (100), 70 (18.3), 49 (30.5), 47 (53.5), 42 (19.9); HRMS (EI) calcd for $C_{19}H_{25}NO_3$: 315.1834, found 315.1831.

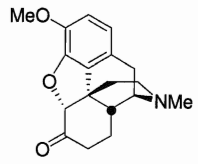


327

Codeine methyl ether (327).

To a solution of thebaine (30 mg, 0.10 mmol) in MeOH (0.5 mL) was added catalyst **369** (3.5 mg, 0.005 mmol). The reaction vessel was evacuated and flushed with hydrogen. This cycle was repeated twice. The reaction mixture was hydrogenated (14

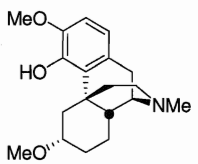
psi H_2 pressure) for 18 hrs. The reaction mixture was filtered through a plug of silica and the filtrate was concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (DCM : MeOH : NH_4OH, 100:0:0 to 94:6:1) and a mixture of codeine methyl ether (**327**) and thebaine (**4**) in a ratio of 2 :3 (98% combined yield) was recovered. Analyses are based on comparison of the data obtained on the mixture with analytical data of purified standards. Codeine methyl ether was prepared according to a procedure by Barber and Rapoport[176] to give compound **327** as colorless crystals. mp 135 - 136 °C (EtOH) (lit. mp[176] 138 - 139 °C); R_f 0.60 (DCM : MeOH : NH_4OH, 92:8:1); IR (film) ν_{max}: 2930, 2837, 1635, 1603, 1504, 1443, 1389, 1351, 1278, 1254, 1121, 1104, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ: 6.63 (d, J = 8.1 Hz, 1H), 6.51 (d, J = 8.1 Hz, 1H), 5.73 (d, J = 9.8 Hz, 1H), 5.30 - 5.34 (m, 1H), 4.99 (d, J = 5.8 Hz, 1H), 3.82 (s, 3H), 3.76 - 3.80 (m, 1H), 3.53 (s, 3H); 3.35 - 3.38 (m, 1H), 3.04 (d, J = 18.5 Hz, 1H), 2.65 - 2.68 (m, 1H), 2.56 - 2.61 (m, 1H), 2.44 (s, 3H), 2.39 - 2.43 (m, 1H), 2.31 (dd, J = 18.5, 6.0 Hz, 1H), 2.05 (dt, J = 11.4, 3.5 Hz, 1H), 1.88 - 1.93 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 150MHz) δ: 147.6, 142.1, 130.8, 130.6, 128.8, 126.9, 118.8, 89.4, 76.9, 76.2, 58.9, 57.2, 56.4, 46.5, 43.5, 43.2, 41.3, 36.1, 20.5 ppm; HRMS calcd for $C_{19}H_{23}NO_3$: 313.1678, found 313.1678.



12

Hydrocodone (12).

A solution of 8,14-dihydrothebaine (**237**) (20 mg, 0.06 mmol) in 2N HCl (0.2 mL) was heated at reflux for 30 min (according to a published procedure).[155g] The reaction mixture was cooled to rt and poured into 15% aqueous solution of NaOH (1 mL). The aqueous layer was extracted three times with $CHCl_3$ (3 mL). The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and filtered. Evaporation of the solvent and purification by flash column chromatography (DCM : MeOH : NH_4OH, 100:0:0 to 94:6:1) yielded 16 mg (82%) of the title compound **12**. Analytical data generated for hydrocodone synthesized in this manner is identical with that of an authentic sample of hydrocodone (**12**).

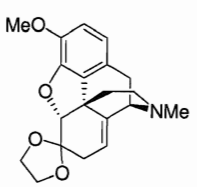


370

Dihydro-O-methyl-thebainol A (370).

Thebaine **8** (60 mg, 0.19 mmol) was dissolved in MeOH (4 mL) and $PdCl_2$ (67 mg, 0.38 mmol) was added. The suspension was cooled to 0 °C and $NaBH_4$ (72 mg, 1.93 mmol) was added portionwise. The reaction mixture was allowed to stir at rt for 4 hrs, before it was filtered through a plug of silica. The filtrate was quenched by the addition of 15% NaOH (4 mL). MeOH was carefully removed under reduced

pressure and the aqueous solution was extracted three times with $CHCl_3$. The organic layer were combined and washed with brine, dried over anhydrous magnesium sulfate, filtered, and the solvent was evaporated. The residue was purified by flash column chromatography ($CHCl_3$: MeOH : NH_4OH, 100:0:0 to 85:15:1) to give 24 mg (40 %) of compound **370** as colorless oil. R_f 0.33 (DCM : MeOH : NH_4OH, 92:8:1); IR (film) ν_{max}: 3517, 2997, 2933, 2850, 1606, 1581, 1277, 1234, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 600MHz): 6.69 (d, *J* = 8.2 Hz, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 6.02 (bs, 1H), 3.90 (dt, *J* = 14.9, 2.6 Hz, 1H), 3.87 (s, 3H), 3.51 - 3.55 (m, 1H), 3.19 (s, 3H), 2.85 - 2.95 (m, 2H), 2.76 (dd, *J* = 17.7, 5.3 Hz, 1H), 2.46 - 2.52 (m, 1H), 2.40 (s, 3H), 2.05 (td, *J* = 11.7, 2.0 Hz, 1H), 1.86 - 1.93 (m, 2H), 1.74 - 1.82 (m, 1H), 1.52 - 1.67 (m, 3H), 1.26 - 1.31 (m, 1H), 1.21 (dd, *J* = 14.7, 2.4 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): 144.6, 130.2, 127.3, 118.6, 108.2, 108.0, 76.6, 58.1, 56.7, 56.3, 47.8, 46.5, 42.6, 38.7, 37.0, 35.8, 31.3, 24.2, 22.5 ppm; HRMS calcd for $C_{19}H_{27}NO_3$: 317.1991, found 317.1986.

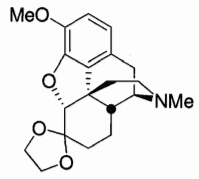


14

(5α)-Cyclic-1,2-ethanediyl acetal-8,14-didehydro-4,5-epoxy-3-methoxy-17-methyl-morphinan-6-one (14).

Thebaine (0.5 g, 1.6 mmol) was dissolved in $CHCl_3$ (0.9 mL) and freshly distilled ethylene glycol (1.0 g, 16.1 mmol) was added. To this biphasic mixture was added $TsOH•H_2O$ (1.0 g, 5.3 mmol) under vigorous stirring. The reaction mixture was

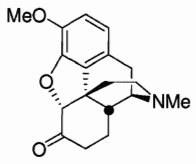
heated at reflux for 45 min, cooled to 0 °C and the pH was adjusted to 11, using a saturated aqueous solution of K_2CO_3. The reaction solution was extracted three times with $CHCl_3$ (5 mL) and the organic layers were combined. Drying over anhydrous sodium sulfate, filtration and evaporation of the solvent provided a dark yellow residue, which was purified by flash column chromatography ($CHCl_3$: MeOH : NH_4OH, 98:2:1) to give the title compound **14** as a pale yellow oil in 38% yield. R_f 0.55 (DCM : MeOH : NH_4OH, 96:4:1); IR (film) ν_{max}: 3407, 3031, 2924, 2903, 2833, 2791, 1634, 1603, 1504, 1448, 1325, 1277, 1258, 1165, 1050, 1035, 825 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ: 6.74 (d, *J* = 8.2 Hz, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 5.56 (d, *J* = 5.6 Hz, 1H), 4.70 (s, 1H), 4.28 (q, *J* = 6.2 Hz, 1H), 3.93 (q, *J* = 6.8 Hz, 1H), 3.86 - 3.90 (m, 4H), 3.81 (q, *J* = 6.2 Hz, 1H), 3.64 (d, *J* = 3.64 Hz, 1H), 3.26 (d, *J* = 18.1 Hz, 1H), 2.67 - 2.78 (m, 2H), 2.61 (dd, *J* = 12.6, 4.6 Hz, 1H), 2.50 (d, *J* = 1.1 Hz, 1H), 2.47 (s, 3H), 2.14 (dd, *J* = 16.2, 6.4 Hz, 1H), 2.06 (td, *J* = 12.5, 5.0 Hz, 1H), 1.85 (dd, *J* = 12.3, 1.9 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 145.6, 142.1, 138.4, 131.8, 127.2, 119.4, 113.8, 113.2, 108.1, 93.1, 66.7, 65.4, 61.2, 56.8, 45.9, 45.8, 42.2, 36.2, 32.7, 26.8 ppm; MS (EI) *m/z* (%): 342 (23), 341 (100), 326 (10), 269 (11), 268 (21), 255 (18), 254 (52), 240 (10), 226 (15), 212 (11), 85 (22), 83 (34), 42 (18); HRMS (EI) calcd for $C_{20}H_{23}NO_4$: 341.1627, found 341.1621.



380

(5α)-Cyclic-1,2-ethanediyl acetal-4,5-epoxy-3-methoxy-17-methyl-morphinan-6-one (380).

A solution of **14** (100 mg, 0.3 mmol) in $CHCl_3$ (1 mL) was treated with Pt/C (10%) under 1 atm of H_2 for 16 hrs. Filtration through a plug of silica and elution with $CHCl_3$: MeOH : NH_4OH, 92:8:1 gave the title compound **380** in quantitative yield. Data for **380** are identical to those published in the literature.[177] R_f 0.55 (DCM : MeOH : NH_4OH, 96:4:1); IR (film) ν_{max}: 2941, 2926, 2889, 1636, 1611, 1502, 1441, 1325, 1275, 1258, 1190, 1155, 1060, 922 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ: 6.67 (d, *J* = 8.2 Hz, 1H), 6.55 (d, *J* = 8.2 Hz, 1H), 4.42 (s, 1H), 4.12 (q, *J* = 6.5 Hz, 1H), 3.97 (q, *J* = 5.0 Hz, 1H), 3.78 - 3.85 (m, 5H), 3.72 (q, *J* = 6.3 Hz, 1H), 3.01 - 3.05 (m, 1H), 2.93 (d, *J* = 18.3 Hz, 1H), 2.44 (dd, *J* = 12.1, 4.3 Hz, 1H), 2.33 (s, 3H), 2.27 (dd, *J* = 18.2, 5.4 Hz, 1H), 2.09 - 2.17 (m, 2H), 1.79 (dt, *J* = 12.3, 4.9 Hz, 1H), 1.56 - 1.66 (m, 1H), 1.41 - 1.50 (m, 2H), 1.08 (td, *J* = 12.7, 2.2 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 146.6, 142.1, 129.2, 126.5, 118.6, 113.4, 108.6, 94.4, 66.4, 64.9, 59.5, 56.5, 47.1, 43.6, 42.9, 42.6, 36.5, 33.4, 22.3, 20.1 ppm; MS (EI) *m/z* (%): 344 (23), 343 (100), 342 (13), 329 (14), 256 (11), 244 (17), 198 (11), 99 (87), 59 (17), 55 (12); HRMS (EI) calcd for $C_{20}H_{25}NO_4$: 343.1784, found 343.1777.



12

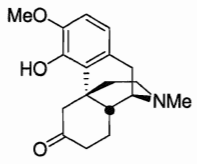
Hydrocodone (12) (One pot procedure from 14)

A solution of **14** (45 mg, 0.13 mmol) in MeOH (90 μL) was treated with Pt/C (10%) (1 mg) under 1 atm of H_2 for 12 hrs. 25% v/v H_2SO_4/MeOH (0.5 mL) was added to the reaction solution, which was stirred for 3 hrs. The pH of the solution was adjusted to >11 with saturated aqueous K_2CO_3 and extracted three times with $CHCl_3$ (5 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated and the crude material was purified by flash column chromatography ($CHCl_3$: MeOH : NH_4OH, 98:2:1) to yield hydrocodone **12** in 75% yield. Analytical data generated for hydrocodone synthesized in this manner was identical with those of an authentic sample of hydrocodone (**12**).

Hydrocdone (12) (One pot procedure from 4)

Thebaine (**4**) (100 mg, 0.32 mmol) was dissolved in THF (1 mL) and water (1 mL) added. To this solution $Pd(OAc)_2$ (72 mg, 0.32 mmol) was added. After two hrs at rt the orange/red reaction solution contains no thebaine as evidenced by TLC. H_2 was added to the reaction vessel by use of a balloon on the reaction stirred for a further 4 hrs. Removal of the balloon and filtration of the reaction mixture through a plug of silica ($CHCl_3$: MeOH : NH_4OH, 92:8:1) gave the crude products **12** and **20** in a ratio of 3:4. Purification of the crude material was achieved by column chromatography ($CHCl_3$: MeOH : NH_4OH, 98:2:1) to yield **12** in 43% and **382** in 52% yield. All

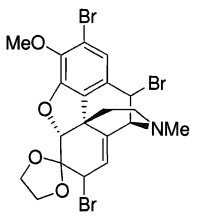
analytical data generated for hydrocodone synthesized in this manner was identical with those of an authentic sample of hydrocodone. Data for **382** are identical to those published in the literature.[178]



382

4-Hydroxy-3-methoxy-17-methyl-morphinan-6-one (382).

R_f 0.35 (DCM : MeOH : NH_4OH, 96:4:1); IR (film) ν_{max}: 3401, 2935, 2839, 2243, 1710, 1604, 1583, 1483, 1439, 1277, 1228, 1062, 922 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ: 6.68 (d, *J* = 8.3 Hz, 1H), 6.60 (d, *J* = 8.3 Hz, 1H), 4.25 (dd, *J* = 13.3, 2.5 Hz, 1H), 3.82 (s, 3H), 3.13 - 3.16 (m, 1H), 2.98 (d, *J* = 18.5 Hz, 1H), 2.76 (dd, *J* = 18.5, 6.0 Hz, 1H), 2.60 - 2.64 (m, 1H), 2.46 (s, 3H), 2.41 - 2.45 (m, 1H), 2.31 (dt, *J* = 12.8, 3.2 Hz, 1H), 2.23 - 2.28 (m, 2H), 2.12 (td, *J* = 12.0, 4.1 Hz, 1H) 2.05 (s, 1H), 1.84 - 1.93 (m, 3H), 1.68 (qd, *J* = 13.2, 5.0 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 210.7, 145.1, 144.8, 129.7, 122.6, 118.5, 109.0, 57.0, 56.1, 50.4, 46.4, 44.3, 42.1, 41.0, 40.9, 38.0, 27.0, 23.8 ppm; MS (EI) *m/z* (%): 302 (12), 301 (56), 300 (18), 242 (10), 164 (53), 88 (11), 86 (64), 84 (100), 60 (19), 59 (17), 49 (20), 47 (24), 45 (25), 44 (13), 43 (35), 42 (18); HRMS (EI) calcd for $C_{18}H_{23}NO_3$: 301.1678, found 301.1671.



381

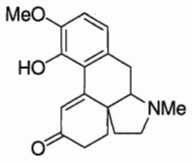
(5α)-1,7,10-Tribromo-cyclic-1,2-ethanediyl acetal-8,14-didehydro-4,5-epoxy-3-methoxy-17-methyl-morphinan-6-one (381).

Thebaine (**4**) (50 mg, 0.16 mmol) was dissolved in THF (1 mL) and freshly distilled ethylene glycol (100 mg, 1.61 mmol) was added. Br_2 (103 mg, 0.64 mmol) was added in a single portion and the reaction stirred for 10 hrs. A saturated aqueous solution of Na_2SO_3 was added to remove excess bromine. The reaction was cooled to 0 °C and the pH was adjusted to 11 using a saturated aqueous solution of K_2CO_3. The reaction solution was extracted five times with $CHCl_3$ (5 mL) and the organic extracts were combined, dried over anhydrous sodium sulfate. Filtration and evaporation of the solvent gave a crude mixture, which was further purified by flash column chromatography ($CHCl_3$: MeOH, 200:1) to provide the title compound **381** in 27% yield. R_f 0.60 (DCM : MeOH : NH_4OH, 96:4:1); IR (film) ν_{max}: 2391, 2937, 2891, 1654, 1632, 1611, 1487, 1435, 1287, 1203, 1160, 1125, 1089, 1051, 909 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ: 6.92 (s, 1H), 5.88 (d, *J* = 6.4 Hz, 1H), 5.25 (s, 1H), 4.61 (d, *J* = 6.4 Hz, 1H), 3.94 - 3.99 (m, 1H), 3.88 (s, 3H), 3.81 - 3.87 (m, 1H), 3.61 - 3.64 (m, 1H), 3.11 (d, *J* = 18.6 Hz, 1H), 3.04 (s, 3H), 2.70 - 2.79 (m, 1H), 2.56 - 2.68 (m, 2H), 2.50 (s, 3H), 2.37 - 2.43 (m, 1H), 1.76 (dd, *J* = 12.8, 2.3 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 145.2, 143.1, 132.3, 126.5, 117.0, 116.3, 112.0, 98.4, 92.0, 77.2, 64.4, 62.0, 60.1, 57.0, 49.5, 46.4, 45.3, 41.9, 35.1, 30.3 ppm; MS (EI) *m/z* (%): 531 (M^+-CH_2CH_2O), 451 (1), 435 (1), 420 (1), 407 (1), 301 (1), 217 (16), 216 (81),

188 (54), 187 (100), 171 (22), 145 (13), 118 (11), 117 (22), 90 (13), 86 (20), 84 (24), 78 (16), 71 (11), 57 (12), 55 (14), 47 (12), 44 (28), 43 (41), 42 (12), 41 (33).

Pd/C hydrogenation of thebaine (4).

Thebaine (**4**) (100 mg, 0.32 mmol) was dissolved in 20% HCl (0.5 mL) and Pd/C (10%, 5 mg) was added. The reaction mixture was stirred under 1 atm of H_2 at rt for 12 hrs, after which time the reaction mixture was basified with NH_4OH and extracted three times with DCM (2 mL). The organic layers were combined, dried over anhydrous sodium sulfate and filtered. Evaporation of the solvent gave a mixture of compounds, which was purified by flash column chromatography ($CHCl_3$: MeOH : NH_4OH, 98:2:1) to give hydrocodone (**12**) (63%), β-dihydro-thebainone (**382**) (20%), and tetrahydrothebaine (**367**) (8%).

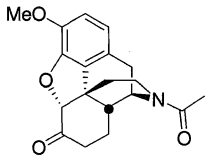


385

Metathebainone (385).

Thebaine (**4**) (100 mg, 0.32 mmol) was dissolved in an aqueous solution of 20% HCl (0.5 mL) and Pt/C (1%), vanadium doped (16 mg) was added. The reaction mixture was stirred under 1 atm of H_2 at rt for 12 hrs, after which time the reaction mixture was basified with NH_4OH and extracted three times with DCM (2 mL). The organic layers were combined, dried over anhydrous sodium sulfate and filtered. Evaporation of the solvent gave a mixture of compounds, which was purified by flash column

chromatography (DCM : MeOH, 200:1 to 200:4) to give 14 mg (15%) of hydrocodone (**12**) and 72 mg (75%, 90% purity) of metathebainone (**385**). Data for **385** are identical to those published in the literature.[179] R_f 0.50 (DCM : MeOH : NH_4OH, 96:4:1); IR (film) ν_{max}: 3306, 2927, 2851, 2782, 1727, 1650, 1601, 1479, 1441, 1349, 1266, 1183, 1092, 1002 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ: 6.83 (d, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.50 (s, 1H), 3.90 (s, 3H), 2.94 - 2.99 (m, 1H), 2.69 - 2.82 (m, 2H), 2.57 (dd, *J* = 14.9, 3.6 Hz, 1H), 2.50 - 2.55 (m, 1H), 2.33 (s, 3H), 2.22 - 2.29 (m, 2H), 2.05 - 2.15 (m, 2H), 2.00 (ddd, *J* = 13.3, 5.4, 2.1 Hz, 1H), 1.51 - 1.58 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 199.6, 158.4, 145.5, 131.4, 126.2, 120.4, 118.7, 113.9, 111.7, 73.1, 56.2, 55.3, 46.6, 40.4, 35.0, 33.9, 33.8, 30.6 ppm; HRMS (EI) calcd for $C_{18}H_{21}NO_3$: 299.1678, found 299.1521.

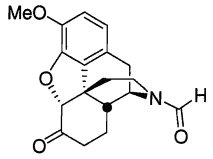


386

***N*-Acetyl-norhydrocodone 386.**

The title compound was isolated following the general procedure for *N*-demethylation acylation reaction as a mixture of two isomers in a ratio of 3:1 in 80% yield. mp 99 - 100 °C (DCM); R_f 0.3 (DCM : MeOH, 96:4); IR (film) ν_{max}: 2929, 1727, 1628, 1505, 1436, 1325, 1274, 1241, 1121, 1061, 1026 cm^{-1}; (major isomer) ^1H NMR ($CDCl_3$, 600 MHz) δ: 6.77 (d, *J* = 8.2 Hz, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 5.25 - 5.28 (m, 1H), 4.69 (s, 1H), 3.94 (s, 3H), 3.67 (dd, *J* = 13.8, 4.8 Hz, 1H), 3.09 (dt, *J* = 13.2, 4.0 Hz, 1H), 2.91 (dd, *J* = 18.6, 6.1 Hz, 1H), 2.67 (d, *J* = 18.5 Hz, 1H), 2.32 - 2.51 (m, 3H),

2.14 (s, 3H), 1.91 - 2.02 (m, 3H), 1.20 - 1.32 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 206.8, 169.0, 145.6, 143.2, 126.0, 124.9, 120.4, 115.1, 91.0, 56.8, 47.6, 47.3, 41.2, 40.5, 39.9, 35.5, 28.4, 25.3, 22.1 ppm; (minor isomer) ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 6.77 (d, *J* = 8.2 Hz, 1H), 6.67 (d, *J* = 8.2 Hz, 1H), 4.70 (s, 1H), 4.56 (dt, *J* = 14.2, 3.1 Hz, 1H), 4.27 - 4. 31 (m, 1H), 3.94 (s, 3H), 3.67 (dd, *J* = 13.8, 4.8 Hz, 1H), 3.09 (dt, *J* = 13.2, 4.0 Hz, 1H), 2.97 (dd, *J* = 18.2, 5.8 Hz, 1H), 2.76 (d, *J* = 18.1 Hz, 1H), 2.53 - 2.61 (m, 1H) 2.32 - 2.51 (m, 2H), 2.14 (s, 3H), 1.91 - 2.02 (m, 2H), 1.20 - 1.32 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 206.7, 168.7, 145.6, 143.6, 126.0, 123.9, 120.3, 115.3, 91.0, 56.8, 53.8, 47.2, 42.1, 39.7, 35.4, 34.7, 29.2, 25.5, 21.9 ppm; MS (EI) *m/z* (%) 327 (24), 241 (23), 117 (10), 87 (68), 86 (21), 85 (72), 84 (31), 83 (100), 57 (12), 49 (13), 48 (12), 47 (28), 43 (23), 41 (10); HRMS (EI) calcd for $C_{19}H_{21}NO_4$: 327.1470, found 327.1483; Anal calcd for $C_{19}H_{21}NO_4$: C 69.71% H 6.47%, found C 69.38% H 6.47%.

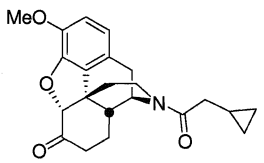


387

***N*-Formyl-norhydrocodone 387.**

Hydrocodone (50 mg, 0.17 mmol) was dissolved in MeOH (1 mL) and Pd on charcoal (89 mg, 0.08 mmol) was added at 0 °C. The reaction mixture was stirred open to air at rt for three days. The reaction mixture was filtered through a plug of Celite. The solvent was evaporated and the residue was purified by flash column chromatography ($CHCl_3$: MeOH : NH_4OH, 100:0:0 to 85:15:1) to give 10 mg (17 %)

of the title compound **387** as a mixture of 2 isomers in a ratio of 4:3 as colorless oil. R_f 0.53 (DCM : MeOH, 92:8); IR (film) ν_{max}: 3007, 2932, 1728, 1660, 1609, 1505, 1438, 1276, 1108 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) (two isomers) δ: 8.23 (s, 1H), 8.06 (s, 1H), 6.78 (d, *J* = 8.3 Hz, 2H), 6.67 - 6.72 (m, 2 H), 5.01 - 5.05 (m, 1H), 4.71 (s, 1H), 4.70 (s, 1H), 4.35 (dd, *J* = 14.1, 5.1 Hz, 1H), 4.07 - 4.10 (m, 1H), 3.94 (s, 6H), 3.87 - 3.99 (m, 2 H), 3.45 - 3.50 (m, 1H), 3.10 - 3.17 (m, 1H), 2.91 - 3.04 (m, 2H), 2.77 (d, *J* = 18.1 Hz, 1H), 2.71 (d, *J* = 19.3 Hz, 1H), 2.63 (td, *J* = 13.1, 4.3 Hz, 1H), 2.45 - 2.52 (m, 2H), 2.33 - 2.44 (m, 3H), 1.90 - 2.02 (m, 5H), 1.22 - 1.35 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) (two isomers) δ: 206.5, 206.4, 160.7, 160.5, 145.7, 143.5, 143.4, 126.0, 125.9, 124.5, 123.9, 120.5, 120.3, 115.4, 115.2, 91.1, 56.80, 56.77, 54.3, 48.1, 48.0, 46.8, 42.6, 41.3, 40.7, 39.7, 39.6, 35.5, 34.5, 34.3, 29.8, 28.2, 25.2, 25.1 ppm; HRMS (EI) calcd for $C_{18}H_{19}NO_4$: 313.1314, found 313.1308.

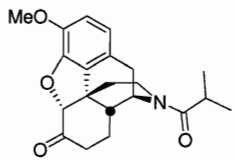


388

***N*-Cyclopropylmethyl-norhydrocodone 388.**

The title compound **388** was isolated following the general procedure for *N*-demethylation acylation reaction as a mixture of two isomers in a ratio of 3:1 in 76% yield. R_f 0.28 (DCM : MeOH, 96:4); IR (film) ν_{max}: 3448, 3007, 2929, 1728, 1631, 1505, 1438, 1327, 1275, 1115, 960, 753 cm^{-1}; (major isomer) ^1H NMR ($CDCl_3$, 600 MHz) δ: 6.76 (d, *J* = 8.2 Hz, 1H), 6.64 - 6.70 (m, 1H), 5.22 - 5.26 (m, 1H), 4.69 (s,

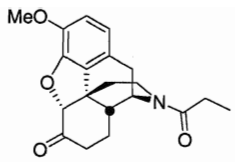
1H), 4.09 (dd, *J* = 13.7, 4.6 Hz, 1H), 3.92 (s, 3H), 3.12 (dt, *J* = 13.2, 3.7 Hz, 1H), 2.89 (dd, *J*=18.3, 6.2 Hz, 1H), 2.65 (d, *J* = 18.5 Hz, 1H), 2.31 - 2.63 (m, 5H), 2.04 (dt, *J* = 12.5, 5.1 Hz, 1H), 1.89 - 2.00 (m, 1H), 1.70 - 1.78 (m, 1H), 1.18 - 1.36 (m, 1H), 0.96 - 1.09 (m, 1H), 0.74 - 0.92 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 207.1, 172.0, 145.6, 143.3, 126.2, 125.1, 120.4, 115.1, 91.1, 67.1, 56.7, 48.3, 47.4, 42.1, 39.9, 36.2, 29.7, 28.4, 11.5, 8.8, 7.6 ppm; (minor isomer) ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 6.76 (d, *J* = 8.2 Hz, 1H), 6.64 - 6.70 (m, 1H), 4.73 - 4.77 (m, 1H), 4.70 (s, 1H), 4.50 (dd, *J* = 13.9, 3.6 Hz, 1H), 3.92 (s, 3H), 2.99 (dd, *J* = 18.0, 5.7 Hz, 1H), 2.80 (d, *J* = 18.1 Hz, 1H), 2.31 - 2.63 (m, 5H), 2.04 (dt, *J* = 12.5, 5.1 Hz, 1H), 1.89 - 2.00 (m, 1H), 1.81 - 1.83 (m, 1H), 1.57 - 1.65 (m, 1H), 1.18 - 1.36 (m, 1H), 0.96 - 1.09 (m, 1H), 0.74 - 0.92 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 206.9, 171.9, 145.5, 143.1, 126.2, 125.1, 120.2, 114.9, 91.0, 67.1, 56.7, 48.3, 47.4, 41.2, 39.7, 35.7, 29.4, 25.3, 11.5, 7.5, 7.3 ppm; MS (EI) *m/z* (%): 354 (17), 353 (66), 301 (28), 300 (11), 242 (30), 241 (57), 240 (14), 213 (11), 199 (11), 185 (19), 164 (30), 141 (10), 129 (16), 128 (12), 127 (10), 115 (15), 114 (11), 113 (61), 112 (82), 111 (28), 109 (11), 99 (11), 98 (73), 97 (11), 88 (23), 87 (19), 86 (48), 85 (89), 84 (80), 83 (100), 82 (18), 72 (13), 71 (21), 70 (25), 69 (81), 68 (14), 60 (12), 59 (18), 58 (22), 57 (37), 56 (13), 55 (31), 49 (21), 48 (13), 47 (36), 45 (22), 44 (28), 43 (40), 42 (32), 41 (77) HRMS (EI) calcd for $C_{21}H_{23}NO_4$: 353.1627, found 353.1612.



389

***N-iso*-Butyricacetyl-norhydrocodone 389.**

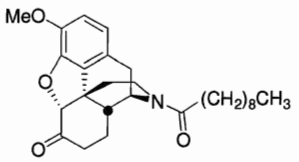
The title compound was isolated following the general procedure for *N*-demethylation / acylation reaction as a mixture of two isomers in a ratio of 13:4 in 13% yield. R_f 0.32 (DCM : MeOH, 96:4); IR (film) ν_{max}: 3444, 2970, 2933, 1728, 1643, 1634, 1505, 1435, 1327, 1276, 1260, 1177, 1156, 1032, 958, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (major isomer) δ: 6.77 (d, *J* = 8.2 Hz , 1H), 6.68 (d, *J* = 8.6 Hz, 1H), 5.26 - 5.33 (m, 1H), 4.68 (s, 1H), 3.94 (s, 3H), 3.74 - 3.84 (m, 1H), 2.73 - 3.12 (m, 3H), 2.62 (d, *J* = 18.5 Hz, 1H), 2.28 - 2.51 (m, 3H), 1.87 - 2.06 (m, 3H), 1.20 - 1.30 (m, 1H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 7.0 Hz , 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 206.9, 175.4, 145.6, 143.2, 126.2, 125.1, 120.4, 115.1, 91.0, 56.8, 47.6, 47.4, 41.4, 39.9, 39.4, 35.9, 30.5, 28.5, 25.4, 19.6, 19.1 ppm; MS (EI) *m/z* (%): 355 (35), 242 (13), 241 (34), 115 (99), 100 (13), 88 (13), 87 (16), 86 (66), 84 (100), 72 (24), 55 (11), 49 (20), 47 (24), 43 (53), 41 (15); HRMS (EI) calcd for $C_{21}H_{25}NO_4$: 355.1784, found 355.1777.



390

***N*-*n*-Propylacetyl-norhydrocodone 390.**

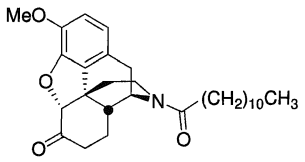
The title compound **390** was isolated following the general procedure for *N*-demethylation / acylation reaction as a mixture of two isomers in a ratio of 3:1 in 53% yield. R_f 0.32 (DCM : MeOH, 96:4); IR (film) ν_{max}: 3436, 2918, 2849, 1727, 1634, 1505, 1437, 1276, 1118, 1031, 971 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) (major isomer) δ: 6.68 (d, *J* = 8.2 Hz, 1H), 6.59 (d, *J* = 8.3 Hz, 1H), 5.17 - 5.22 (m, 1H), 4.60 (s, 1H), 3.85 (s, 3H), 3.62 (dd, *J* = 13.4, 5.0 Hz, 1H), 2.96 (dt, *J* = 13.0, 3.8 Hz, 1H), 2.83 (dd, *J* = 18.6, 6.0 Hz, 1H), 2.56 (d, *J*=8.5 Hz, 1H), 2.20 - 2.47 (m, 6H), 1.81 - 1.93 (m, 3H), 1.10 (t, *J* = 7.7 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 206.9, 172.3, 145.6, 143.3, 126.2, 125.2, 120.5, 115.2, 91.1, 56.8, 47.9, 47.3, 41.4, 40.1, 39.5, 35.9, 28.5, 27.2, 25.4, 9.7 ppm; MS (EI) *m/z* (%): 341 (33), 242 (12), 241(31), 188 (11), 185 (11), 167 (11), 149 (28), 129 (13), 113 (10), 102 (11), 101 (100), 72 (18), 71 (14), 70 (14), 57 (85), 56 (11), 55 (19), 43 (18), 41 (14); HRMS (EI) calcd for $C_{20}H_{23}NO_4$: 341.1627, found 341.1628.



391

***N-n*-Decanylacetyl-norhydrocodone 391.**

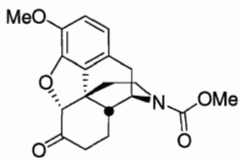
The title compound **391** was isolated following the general procedure for *N*-demethylation / acylation reaction as a mixture of two isomers in a ratio of 3:1 in 36% yield. R_f 0.35 (DCM : MeOH, 96:4); IR (film) ν_{max}: 3435, 2926, 2850, 1726, 1626, 1505, 1436, 1155, 1030, 892, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) (major isomer) δ: 6.68 (d, *J* = 8.2 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 5.18 - 5.21 (m, 1H), 4.60 (s, 1H), 3.84 (s, 3H), 3.62 (dd, *J* = 13.5, 4.6 Hz, 1H), 3.38 (m, 1H), 2.96 (dt, *J* = 13.1, 3.8 Hz, 1H), 2.83 (dd, *J* = 18.6, 6.1 Hz, 1H), 2.55 (d, *J* = 18.4 Hz, 1H), 2.34 - 2.40 (m, 1H), 2.20 - 2.33 (m, 3H), 1.81 - 1.93 (m, 2H), 1.59 - 1.65 (m, 2H), 1.49 - 1.58 (m. 2H), 1.13 - 1.33 (m, 12H), 0.81 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 207.3, 171.9, 145.6, 143.4, 126.2, 124.9, 120.7, 115.1, 91.3, 56.7, 47.4, 41.3, 39.9, 39.7, 35.7, 34.0, 33.8, 31.9, 31.7, 29.5, 29.4, 28.4, 25.6, 25.4, 25.0, 22.7, 14.1 ppm; MS (EI) *m/z* (%): 439 (1), 224 (42), 172 (10), 143 (36), 100 (16), 99 (57), 98 (37), 83 (18), 82 (11), 70 (21), 67 (10), 61 (52), 57 (19), 56 (100), 55 (43), 44 (14), 43 (46), 41 (43); HRMS (EI) calcd for $C_{27}H_{37}NO_4$: 439.2723, found 439.2719.



392

***N-n*-Dodecanylacetyl-norhydrocodone 392.**

The title compound **392** was isolated as a mixture of two isomers in a ratio of 7:2 in 43% yield. R_f 0.35 (DCM : MeOH, 96:4); IR (film) ν_{max}: 3334, 2926, 2852, 1729, 1627, 1575, 1505, 1438, 1275, 1031, 965 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (major isomer) δ: 6.77 (d, *J* = 8.2 Hz, 1H), 6.67 (d, *J* = 8.5 Hz, 1H), 5.24 - 5.32 (m, 1H), 4.69 (s, 1H), 3.93 (s, 3H), 3.66 - 3.76 (m, 1H), 3.42 - 3.58 (m, 1H), 2.98 - 3.11 (m. 1H), 2.91 (dd, *J* = 18.6, 6.1 Hz, 1H), 2.63 (d, *J* = 18.5 Hz, 1H), 2.23 - 2.52 (m, 3H), 1.87 - 2.04 (m, 4H), 1.54 - 1.79 (m, 4H), 1.20 - 1.47 (m, 12H), 1.01 - 1.20 (m, 3H), 0.89 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 207.2, 171.8, 145.9, 143.3, 126.2, 125.2, 120.5, 115.2, 91.1, 56.8, 49.4, 47.6, 47.4, 41.4, 39.8, 35.9, 35.7, 34.2, 34.0, 32.1, 32.0, 29.7, 29.6, 29.5, 25.8, 25.4, 25.0, 22.8, 14.3; MS (EI) *m/z* (%): 467 (3), 224 (21), 143 (18), 100 (10), 99 (27), 98 (17), 61 (23), 56 (100), 55 (20), 43 (21), 41 (19); HRMS (EI) calcd for $C_{29}H_{41}NO_4$: 467.3036, found 467.3037.

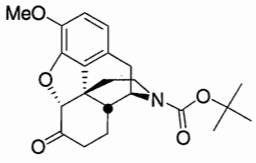


393

5α-4,5-Epoxy-3-methoxy-6-oxo-morphinan-17-carboxylic acid methyl ester (393).

Hydrocodone bitartrate (100 mg, 0.22 mmol) was suspended in a mixture of benzene (1 mL) and dimethyldicarbonate (1 mL), and $Pd(OAc)_2$ (2 mg, 0.01 mmol) were added. The reaction mixture was heated at 80 °C for 18 hrs, before it was cooled to rt and filtered through a plug of Celite. The solvent was evaporated and the residue was taken up in $CHCl_3$ and the organic layer was washed with 1N HCl. The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated. The residue was purified by flash column chromatography ($CHCl_3$: MeOH, 100:0 to 90:10) to give 25 mg (33%) of compound **393** as mixture of two isomers in a ratio of 3:2 as colorless oil. Analytical data for the major isomer are identical to those published in the literature.[180] R_f 0.55 (DCM : MeOH, 92:8); IR (film) ν_{max}: 3019, 2955, 2934, 2842, 2806, 1744, 1637, 1610, 1506, 1441, 1325, 1263, 1164, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) (two isomers) δ: 6.75 (d, J = 8.2 Hz, 2H), 6.63 - 6.68 (m, 2H), 4.77 - 4.81 (m, 1H), 4.67 - 4.70 (m, 2H), 4.60 - 4.64 (m, 1H), 4.10 (dd, J = 13.5, 5.0 Hz, 1H), 3.93 - 3.98 (m, 1H), 3.92 (s, 6H), 3.80 - 3.88 (m, 2H), 3.76 (s, 3H), 3.73 (s, 3H), 2.83 - 2.91 (m, 2H), 2.75 - 2.82 (m, 2H), 2.68 - 2.74 (m, 2H), 2.42 - 2.48 (m, 4H), 2.34 - 2.41 (m, 2H), 1.82 - 2.00 (m, 4H), 1.18 - 1.28 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 207.2, 155.9, 155.5, 145.5, 143.1, 126.1, 124.9, 124.7, 120.4, 120.3, 114.9, 114.8, 91.2, 56.7, 52.9, 52.8, 50.9, 50.6, 47.24, 47.17, 41.5, 41.4, 40.7,

39.9, 39.8, 38.01, 37.97, 35.0, 34.8, 28.9, 28.5, 25.4, 25.3 ppm; HRMS (EI) calcd for $C_{19}H_{21}NO_5$: 343.1420, found 343.1421; Anal calcd for $C_{18}H_{21}NO_3$•1/6 H_2O: C 69.07% H 6.51%, found C 69.07% H 6.41%.

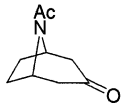


394

5α-4,5-Epoxy-3-methoxy-6-oxo-morphinan-17-carboxylic acid *tert*-butyl ester (394).

Hydrocodone bitartrate (100 mg, 0.22 mmol) was suspended in a mixture of benzene (1 mL) and di-*tert*-butyl dicarbonate (1 mL), followed by the addition of $Pd(OAc)_2$ (2 mg, 0.01 mmol). The reaction mixture was heated at 80 ºC for 18 hrs, before it was cooled to rt and filtered through a plug of Celite. The solvent was evaporated and the residue was taken up in $CHCl_3$. The organic layer was washed with 1N HCl, dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated. The residue was purified by flash column chromatography ($CHCl_3$: MeOH, 100:0 to 90:10) to give 19 mg (15 %) of compound **394** as mixture of two isomers in a ratio of 3:2 as colorless oil. R_f 0.60 (DCM : MeOH, 92:8;); IR (film) ν_{max}: 3366, 2975, 2932, 1728, 1683, 1505, 1366, 1259, 1165, 1126 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) (major isomer) δ: 6.74 (d, J = 8.1 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 4.67 (s, 1H), 4.48 (bs, 1H), 3.91 (s, 3H), 2.73 - 2.89 (m, 2H), 2.69 (d, J = 17.8 Hz, 1H), 2.32 - 2.48 (m, 3H), 1.78 - 1.99 (m, 3H), 1.47 - 1.54 (m, 10H), 1.13 - 1.16 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 207.3, 156.3, 154.8, 145.5, 143.1, 126.2, 120.3, 114.8, 114.8,

91.2, 80.0, 56.7, 51.2, 49.9, 41.4, 39.9, 38.3, 35.1, 28.6, 25.4, 24.3 ppm; HRMS (EI) calcd for $C_{22}H_{27}NO_5$: 385.1892, found 385.1879.



396

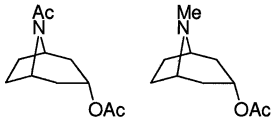
8-Acetyl-8-aza-bicyclo[3.2.1]octan-3-one (396).

Tropane (100 mg, 0.72 mmol) was dissolved in neat acetic anhydride (2 mL) and $Pd(OAc)_2$ (32 mg, 0.14 mmol) was added. The reaction mixture was heated at 80 °C for 14 hrs. The reaction mixture was filtered through a plug of Celite and the solvent was removed under reduced pressure. The pH of the residue was adjusted to 9 using a 50% aqueous solution of NaOH. The aqueous layer was extracted three times with $CHCl_3$ (5 mL). The organic layers were combined, washed three times with 1N HCl and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (DCM : MeOH, 98:2) to yield 86 mg (72%) of the title compound **396** as colorless oil. Data for **396** are identical to those published in the literature.[181] R_f 0.65 (DCM : MeOH, 96:4); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.90 - 4.99 (m, 1H), 4.39 - 4.47 (m, 1H), 2.67 - 2.82 (m, 1H), 2.33 - 2.64 (m, 3H), 2.19 (s, 3H), 2.00 - 2.21 (m, 2H), 1.65 - 1.87 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 207.2, 167.0, 54.4, 50.8, 49.7, 48.8, 29.9, 28.0, 21.6 ppm; HRMS (EI) calcd for $C_9H_{13}NO_2$: 167.0946, found 167.0942.

398

1-(8-Aza-bicyclo[3.2.1]octan-8-yl)ethanone (398).

Compound **398** was prepared by following the procedure for the preparation of compound **396** using tropane (200 mg, 1.60 mmol), $Pd(OAc)_2$ (72 mg, 0.32 mmol) and acetic anhydride (2 mL) as starting materials. The crude product was purified by flash column chromatography (DCM : MeOH, 98:2) to yield 172 mg (70%) of the title compound **398** as colorless oil. Data for **398** are identical to those published in the literature.[182] R_f 0.70 (DCM : MeOH, 96:4); ^1H NMR ($CDCl_3$, 300 MHz) δ: 4.48 - 4.59 (m, 1H), 3.93 - 4.04 (m, 1H), 1.96 (s, 3H), 1.32 - 1.94 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 165.9, 55.7, 51.7, 32.3, 30.6, 28.5, 27.0, 21.5, 16.6 ppm; HRMS (EI) calcd for $C_9H_{15}NO_2$: 153.1154, found 153.1153.



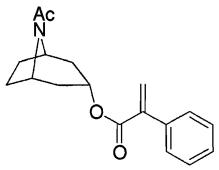
400 401

8-Acetyl-8-aza-bicyclo[3.2.1]octan-3-yl acetate (400) and **8-methyl-8-aza-bicyclo[3.2.1]octan-3-yl acetate (401).**

Tropine (200 mg, 1.42 mmol) was dissolved in acetic anhydride (2 mL) and $Pd(OAc)_2$ (64 mg, 0.28 mmol) was added. The reaction mixture was heated at 80 °C for 14 hrs. The reaction mixture was cooled to rt, water (5 mL) was added and the pH was adjusted to 9, using a 50% aqueous solution of NaOH. The aqueous layer was extracted three times with $CHCl_3$ (5 mL). The organic layers were combined, washed

three times with 1N HCl and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent was evaporated to yield 129 mg (43%) of compound **400**. Data for **400** are identical to those published in the literature.[183] R_f 0.56 (DCM : MeOH, 96:4); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.04 (t, *J* = 5.8 Hz, 1H), 4.57 - 4.66 (m, 1H), 4.03 - 4.13 (m, 1H), 2.04 - 2.18 (m, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.70 - 2.00 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 170.1, 166.1, 67.5, 54.2, 50.1, 37.2, 35.5, 28.7, 27.0, 21.5, 21.4 ppm; HRMS (EI) calcd for $C_{11}H_{17}NO_3$: 211.1208, found 211.1205.

In addition, the acidic extracts were combined and basified to pH 9 (50% aqueous solution of sodium hydroxide). The aqueous layer was extracted three times with $CHCl_3$ (5 mL). The organic layers were combined, washed with brine, and dried over anhydrous sodium sulfate, filtered and the solvent was evaporated. The crude product was purified by flash column chromatography (DCM : MeOH : NH_4OH, 98:2) to yield 91 mg (35%) of compound **401** as colorless oil. Data for **401** are identical to those published in the literature.[184] R_f 0.32 (DCM : MeOH, 96:4;); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.97 (t, *J* = 5.3 Hz, 1H), 3.08 - 3.17 (m, 1H), 2.30 (s, 3H), 2.16 (td, *J* = 15.2, 4.2 Hz, 2H), 1.90 - 2.07 (m, 7H), 1.71 (d, *J* = 15.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 170.3, 67.3, 59.9, 40.3, 36.4, 25.5, 21.6 ppm.

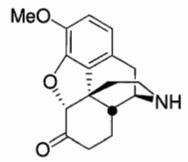


403

8-Acetyl-8-aza-bicyclo[3.2.1]octan-3-yl 2-phenylacrylate (403).

Atropine (100 mg, 0.35 mmol) was dissolved in benzene (1 mL) and acetic anhydride (1 mL) followed by the addition of $Pd(OAc)_2$ (16 mg, 0.07 mmol). The reaction mixture was heated at 80 °C for 16 hrs, before it was cooled to rt and filtered through a plug of Celite. The solvent was evaporated and the residue was taken up in $CHCl_3$ and the organic layer was washed with 1N HCl. The organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography ($CHCl_3$: MeOH, 100:0 to 90:10) to give 85 mg (82%) of compound **403** as colorless solid. R_f 0.45 (DCM : MeOH, 96:4); mp 104 - 107 °C (DCM / hexanes); IR (film) ν_{max}: 2953, 2922, 1714, 1635, 1495, 1445, 1424, 1327, 1196, 1167, 1076, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.29 - 7.42 (m, 5H), 6.37 (s, 1H), 5.89 (s, 1H), 5.25 (t, J = 4.8 Hz, 1H), 4.59 - 4.68 (m, 1H), 4.04 - 4.13 (m, 1H), 2.22 (dt, J = 15.3, 4.3 Hz, 1H), 2.05 (s, 3H), 1.78 – 2.15 (m, 7H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 166.1, 165.8, 141.8, 136.7, 123.3, 128.2, 128.1, 127.0, 68.3, 54.2, 50.1, 37.3, 35.6, 28.6, 26.9, 21.5 ppm; MS (EI) *m/z* (%) 299 (18), 257 (16), 168 (15), 152 (28), 151 (32), 136 (18), 126 (10), 111 (14), 110 (100), 109 (38), 108 (17), 103 (38), 97 (10), 86 (27), 84 (44), 83 (15), 82 (19), 81 (25), 80 (29), 77 (22), 71 (11), 69 (33), 68 (35) 67 (28), 57 (19), 55 (18), 47 (10), 43 (68), 41 (26); HRMS (EI) calcd for $C_{18}H_{21}NO_3$: 299.1521, found

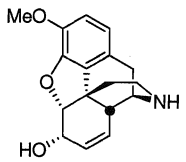
299.1518; Anal calcd for $C_{18}H_{21}NO_3 \bullet 1/3\ H_2O$: C 70.80 % H 7.15%, found C 70.84% H 7.18%.



16

Norhydrocodone (16).

The title compound **16** was isolated following the general procedure for $Cu(OAc)_2$ mediated demethylation in 64% yield as colorless solid. In addition the compound was isolated following the general procedure for $Pd(OAc)_2$ mediated demethylation in 40% yield along with 55% recovered starting material. Data for **16** are identical to those published in the literature.[185] mp 149 - 151 °C (MeOH/diethyl ether); R_f 0.25 (DCM : MeOH : NH_4OH, 98:2:1); IR (film) ν_{max}: 3369, 2928, 1725, 1636, 1609, 1504, 1439, 1274, 1061 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ: 6.74 (d, *J* = 8.2 Hz, 1H), 6.67 (d, *J* = 8.2 Hz, 1H), 4.66 (s, 1H), 3.93 (s, 3H), 3.48 - 3.52 (m, 1H), 2.85 - 2.95 (m, 2H), 2.79 (d, *J* = 18.5 Hz, 1H), 2.71 - 2.77 (m, 1H), 2.55 (dt, *J* = 12.6, 3.2 Hz, 1H), 2.45 (dt, *J* = 13.8, 4.6 Hz, 1H), 2.40 (td, *J* = 13.8, 4.6 Hz, 1H), 1.97 (td, *J* = 12.3, 4.8 Hz, 1H), 1.82 - 1.91 (m, 2H), 1.22 (qd, *J* = 13.3, 3.2 Hz, 1H); ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 207.6, 145.5, 142.9, 127.3, 126.3, 119.9, 114.7, 91.6, 56.8, 52.4, 47.7, 43.0, 40.3, 39.0, 36.0, 30.8, 25.8 ppm; MS (EI) *m/z* (%) 285 (9), 87 (11), 86 (21), 85 (65), 84 (35), 83 (100), 49 (14), 48 (13), 47 (33); HRMS (EI) calcd for $C_{17}H_{19}NO_3$: 285.1365, found 285.1364.

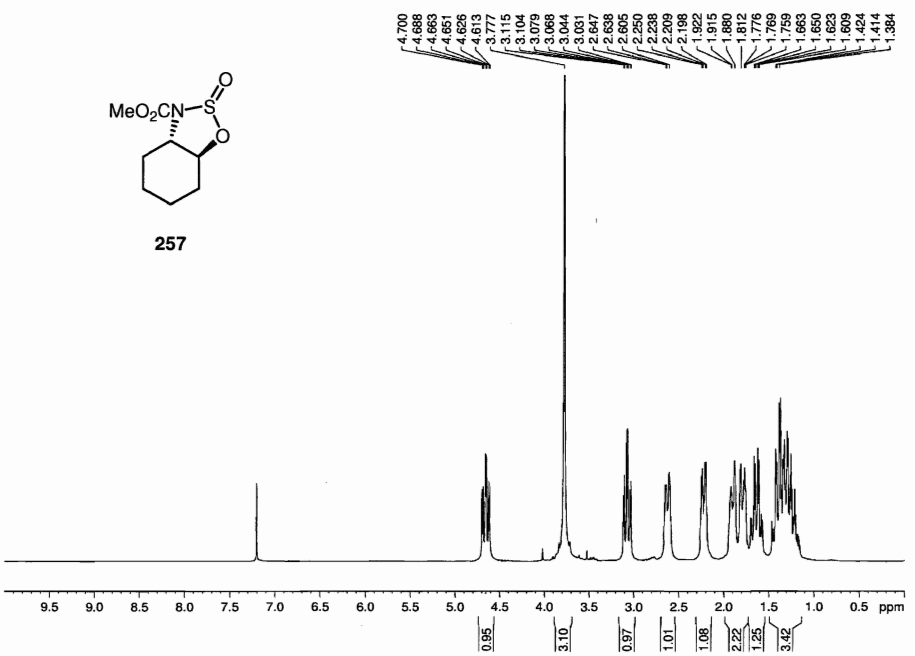


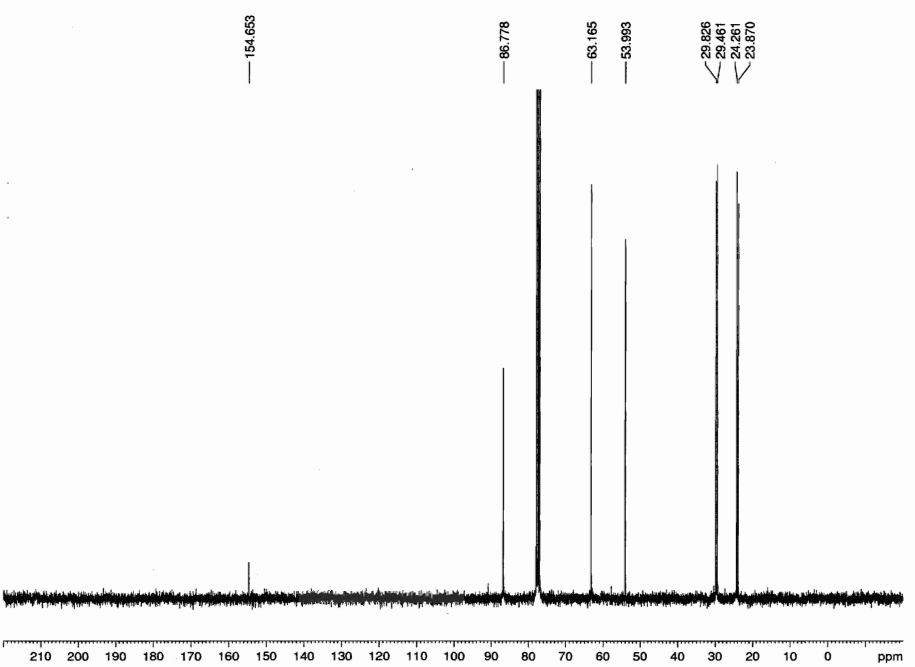
405

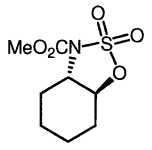
Norcodeine (405).

The title compound **405** was isolated following the general procedure for $Cu(OAc)_2$ mediated demethylation in 64% yield as colorless solid. Data for **405** are identical to those published in the literature.[167] mp 182 - 183 °C (MeOH/diethyl ether); R_f 0.22 (DCM : MeOH : NH_4OH, 98:2:1); IR (film) ν_{max}: 3309, 3000, 2935, 2837, 1635, 1603, 1504, 1453, 1282, 1127, 943 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ: 6.70 (d, J = 8.2 Hz, 1H), 6.60 (d, J = 8.2 Hz, 1H), 5.72 - 5.76 (m, 1H), 5.28 (dt, J = 9.9, 2.5 Hz, 1H), 4.89 (d, J = 6.4 Hz, 1H), 4.17 - 4.22 (m, 1H), 3.87 (s, 3H), 3.65 - 3.69 (m, 2H), 2.98 (td, J = 12.1, 4.4 Hz, 1H), 2.86 - 2.93 (m, 2H), 2.83 (d, J = 18.7 Hz, 1H), 2.59 - 2.63 (m, 1H), 1.88 - 1.98 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 146.4, 142.2, 133.7, 131.1, 128.2, 127.4, 119.6, 112.8, 91.9, 66.3, 56.3, 52.0, 43.9, 41.3, 38.5, 36.6, 31.4 ppm; MS (EI) *m/z* (%) 285 (39), 87 (13), 86 (17), 85 (70), 84 (25), 83 (100), 82 (10), 59 (34), 49 (11), 47 (25), 45 (13), 44 (29), 43 (19), 42 (12) HRMS (EI) calcd for $C_{17}H_{19}NO_3$: 285.1365, found 285.1368.

6. Selected Spectra



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O
O

98

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3.638
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3.603
3.592
2.528
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2.108
2.079
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1.833
1.825
1.792
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1.690
1.682
1.597
1.584
1.558
1.544
1.303
1.291
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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3.00
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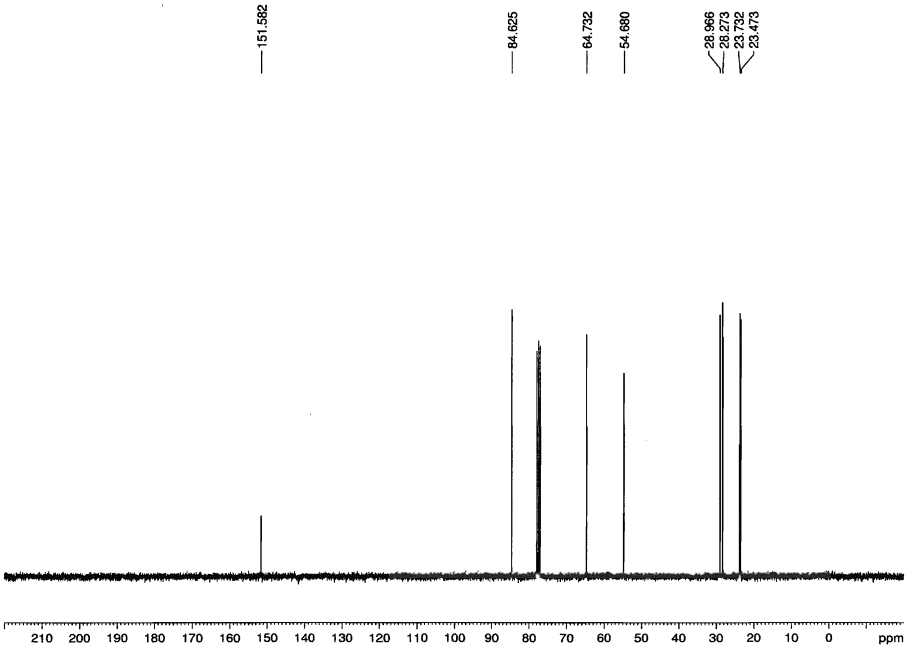
1.13
1.13
1.22
1.18
1.27
3.41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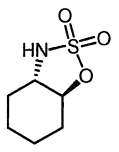
28.273
23.732
23.473
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



258

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3.443
2.247
2.240
2.223
2.208
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2.136
2.109
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1.871
1.859
1.848
1.768
1.755
1.728
1.715
1.688
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1.636
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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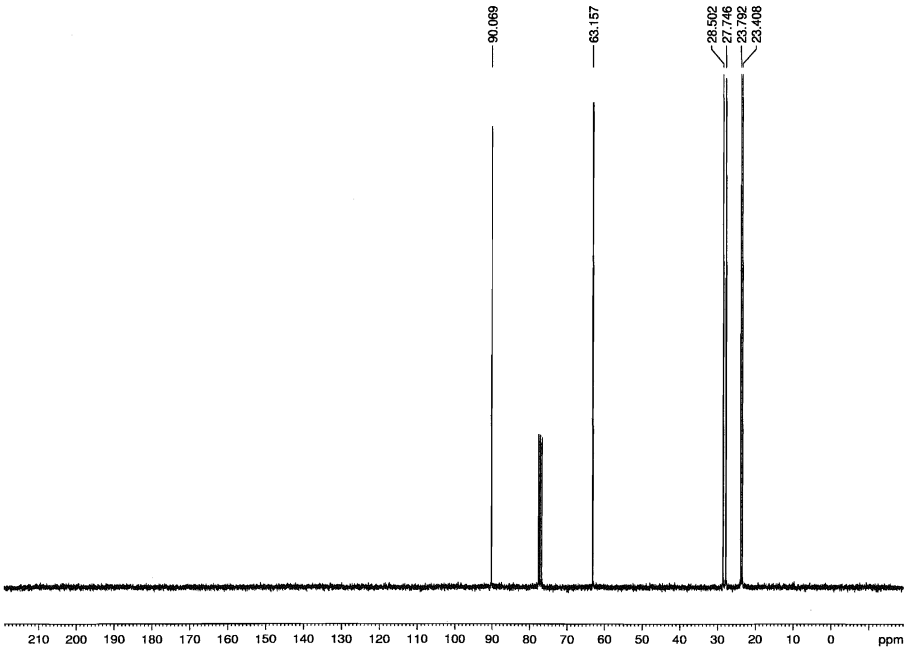
1.00
1.03
1.01
2.08
1.09
3.06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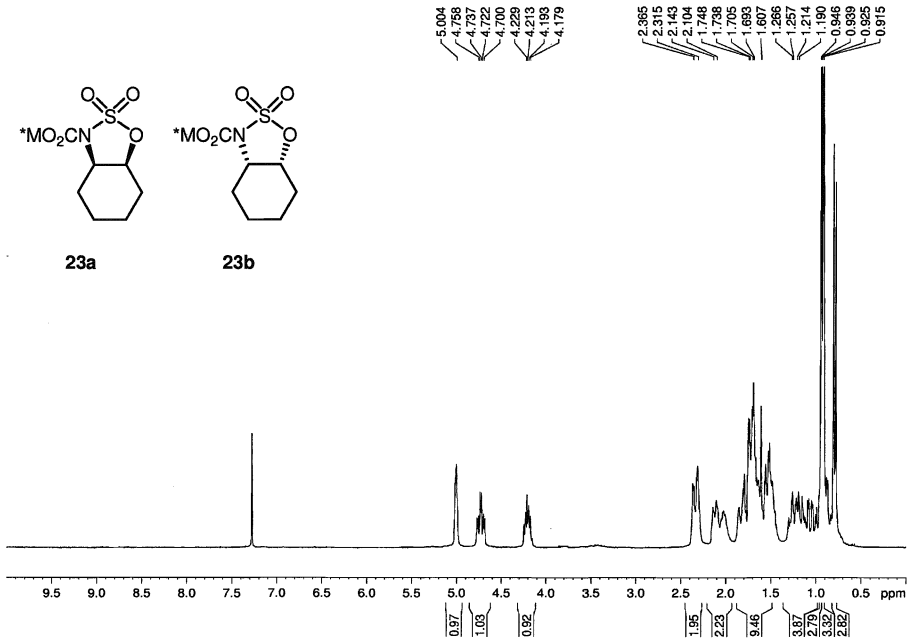
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1.748
1.738
1.705
1.693
1.607
1.266
1.257
1.214
1.190
0.946
0.939
0.925
0.915
*MO2CN
*MO2CN
23a
23b
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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1.03
0.92
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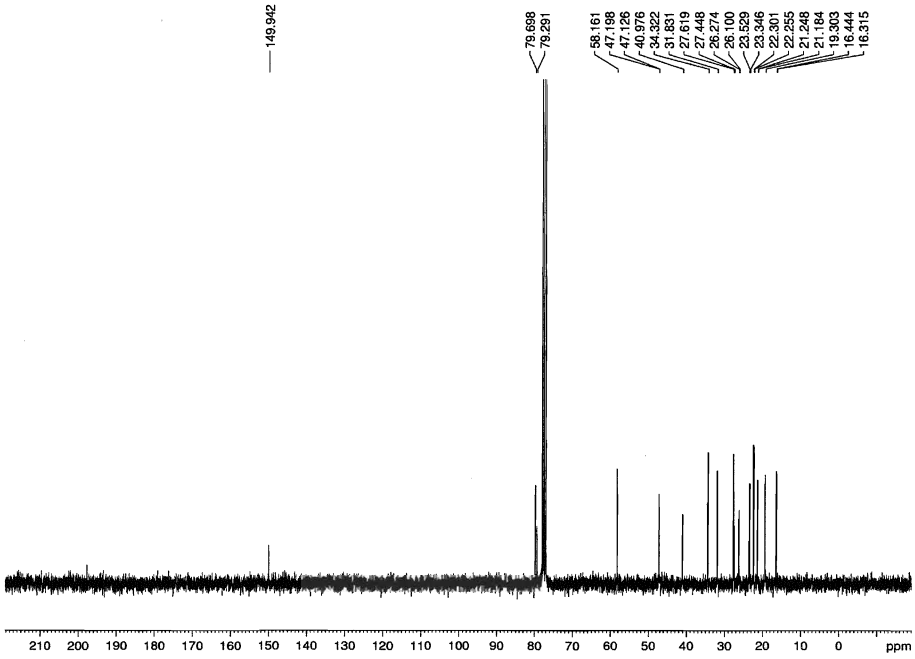
2.23
9.46
3.87
2.79
3.32
2.82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47.126
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26.100
23.529
23.346
22.301
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21.248
21.184
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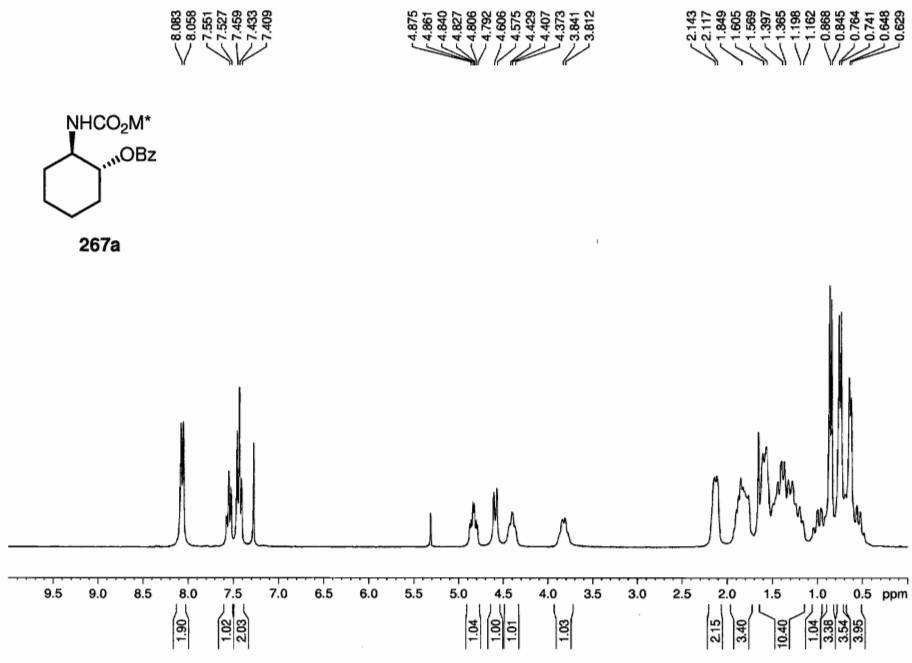
16.315
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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4.827
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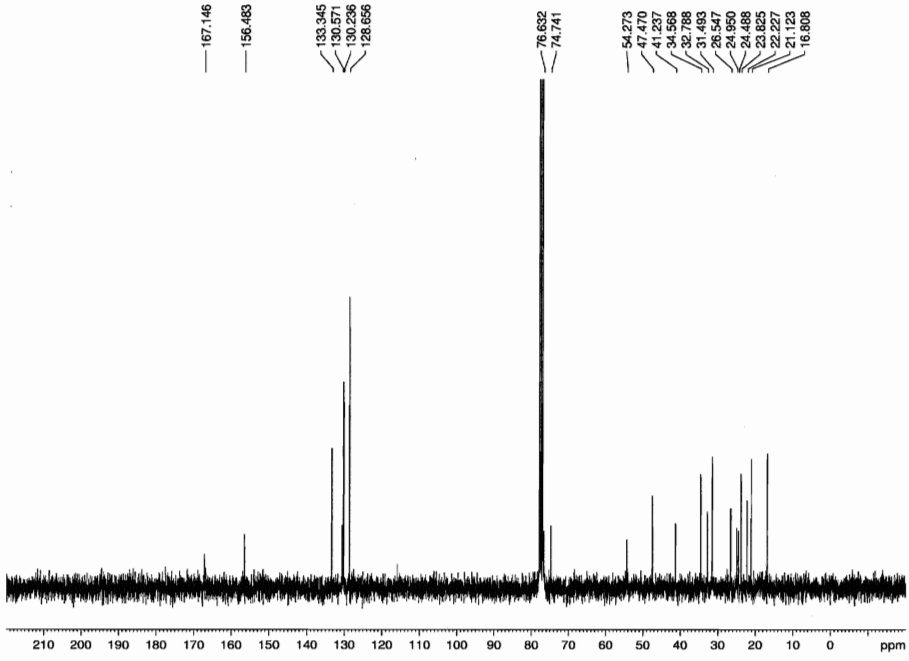
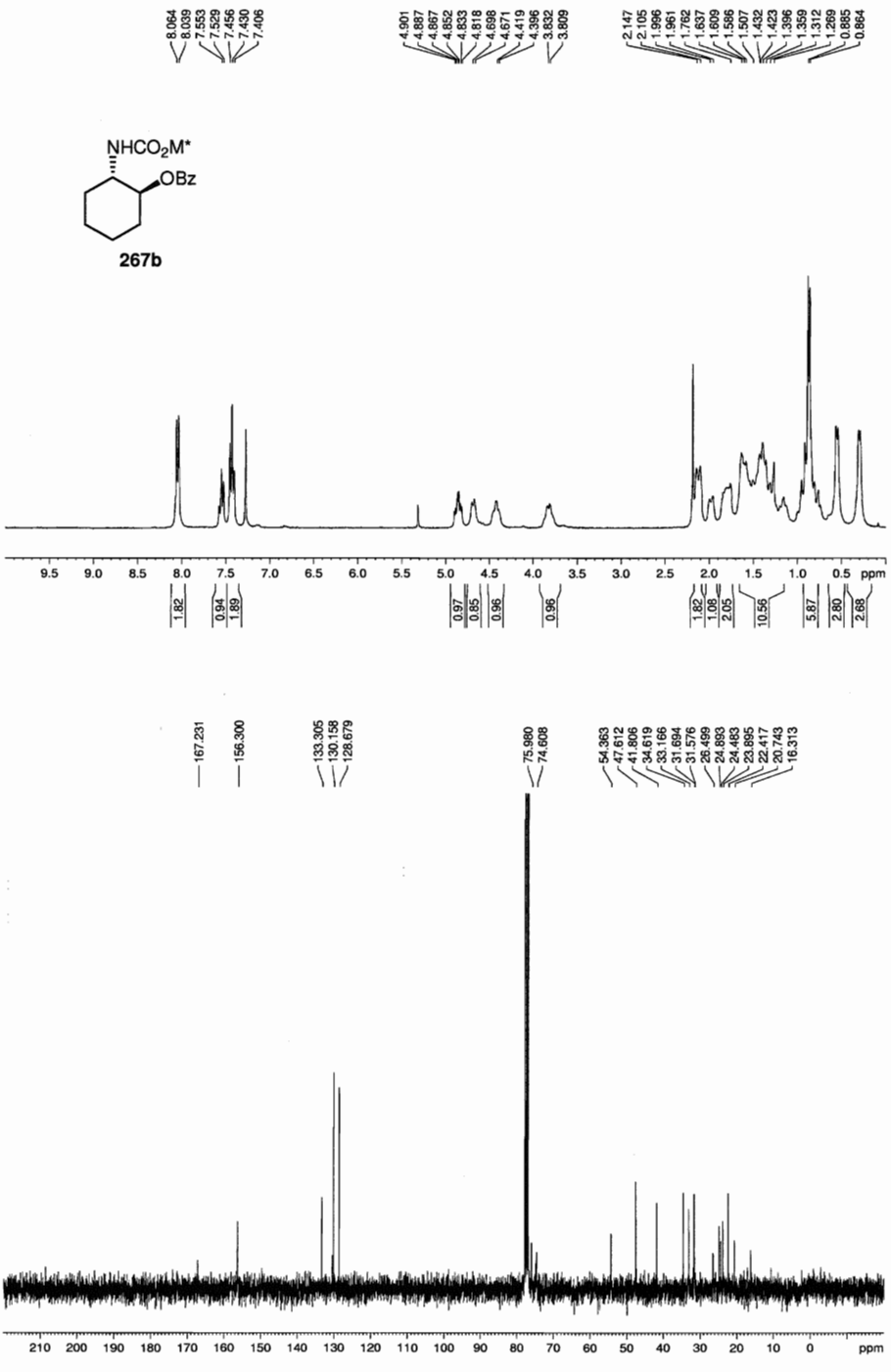
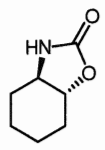
2.143
2.117
1.849
1.605
1.569
1.397
1.365
1.198
1.162
0.868
0.845
0.764
0.741
0.648
0.629
NHCO2M*
OBz
267a
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.90
1.02
2.03
1.04
1.00
1.01
1.03
2.15
3.40
10.40
1.04
3.38
3.54
3.95

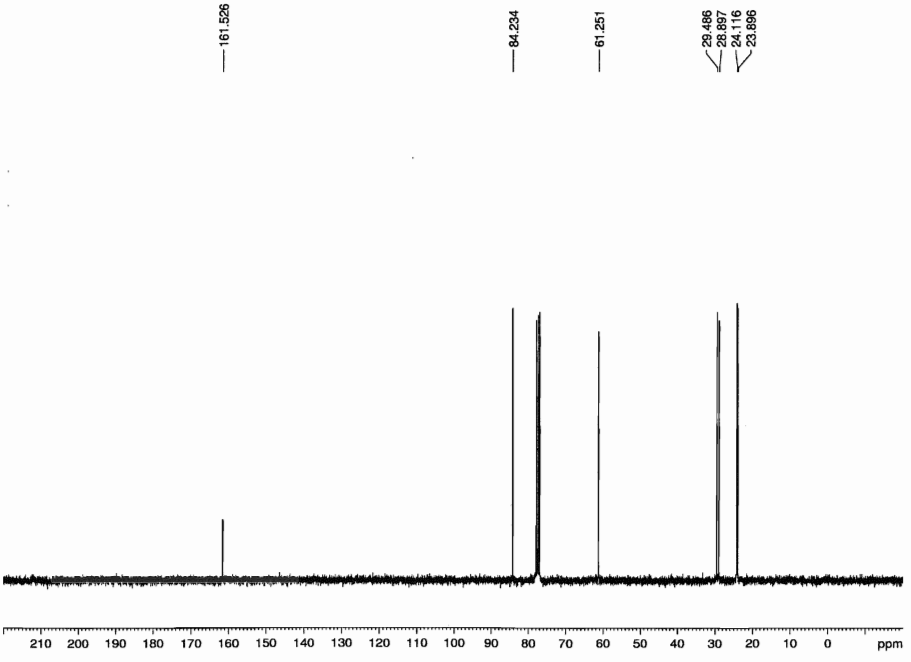

167.146
156.483
133.345
130.571
130.236
128.656
76.632
74.741
54.273
47.470
41.237
34.568
32.788
31.493
26.547
24.950
24.488
23.825
22.227
21.123
16.808
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

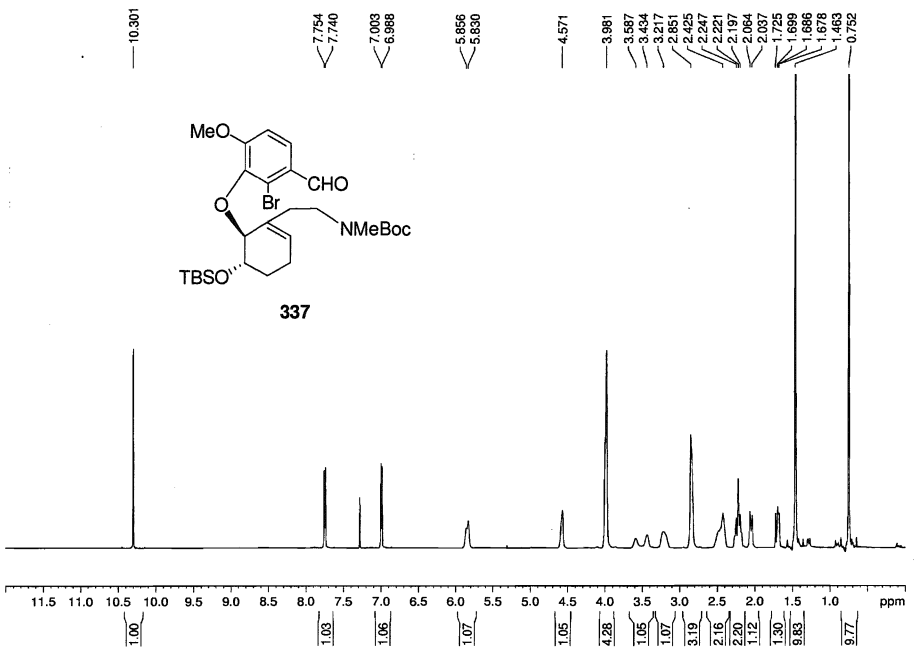

8.064
8.039
7.553
7.529
7.456
7.430
7.406
4.901
4.887
4.867
4.852
4.833
4.818
4.698
4.671
4.419
4.396
3.832
3.809
2.147
2.105
1.996
1.961
1.762
1.637
1.609
1.586
1.507
1.432
1.423
1.396
1.359
1.312
1.269
0.885
0.864
NHCO2M*
OBz
267b
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.82
0.94
1.89
0.97
0.85
0.96
0.96
1.82
1.06
2.05
10.56
5.87
2.80
2.68
167.231
156.300
133.305
130.158
128.679
75.980
74.608
54.363
47.612
41.806
34.619
33.166
31.694
31.576
26.499
24.893
24.483
23.895
22.417
20.743
16.313
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

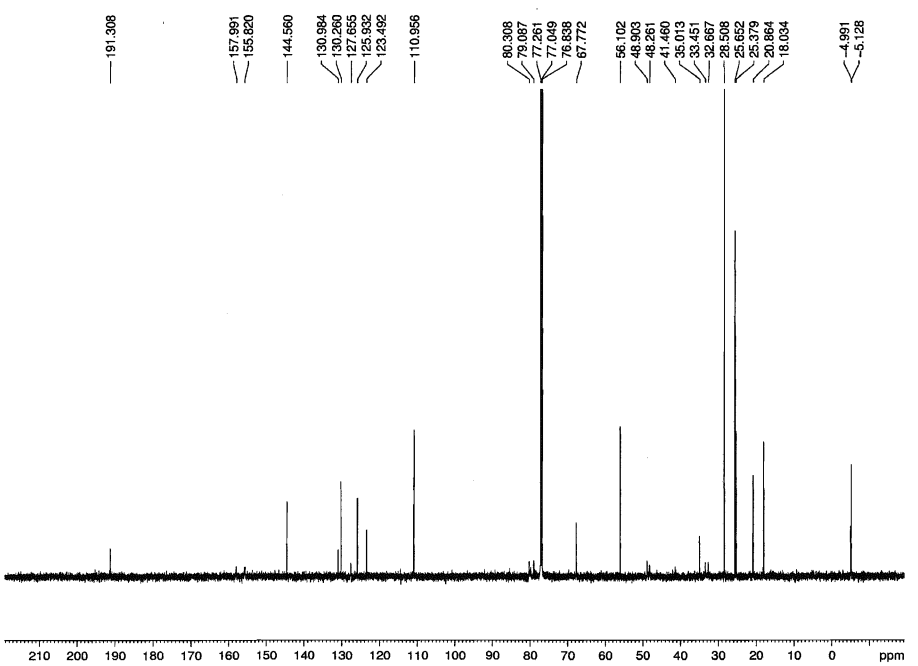

HN
O
O

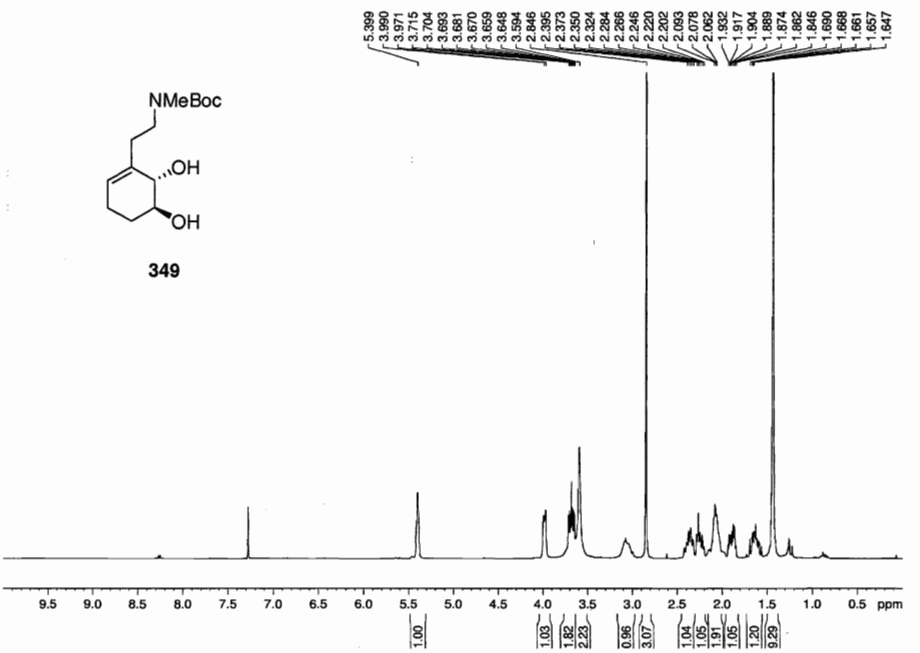
(+) **269a**

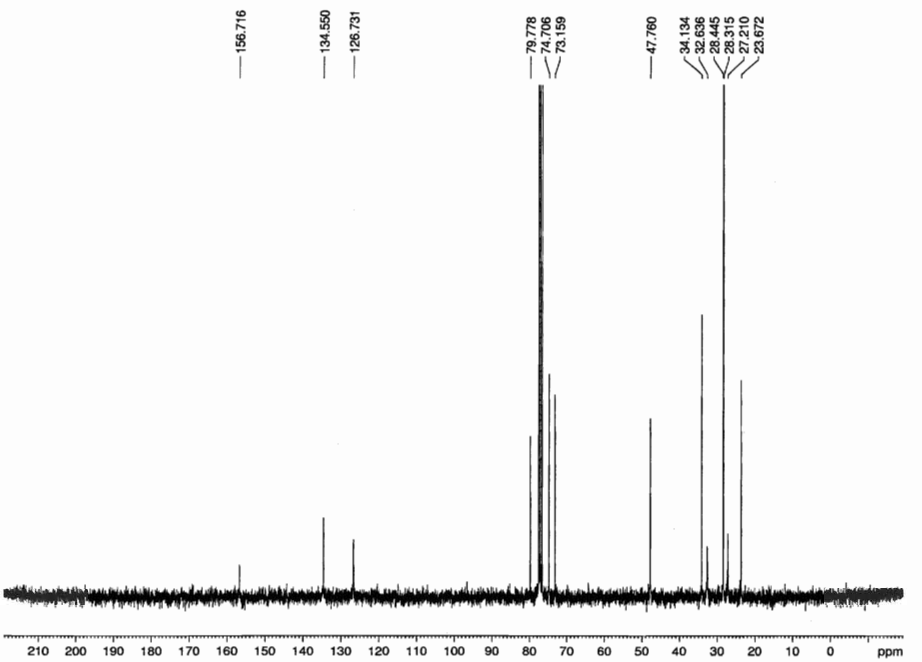
5.898
3.854
3.843
3.816
3.805
3.779
3.767
3.279
3.242
3.216
3.206
2.127
2.090
2.011
1.974
1.854
1.839
1.818
1.756
1.719
1.605
1.594
1.567
1.554
1.363
1.321
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.02
1.00
1.03
2.24
2.28
1.21
3.55

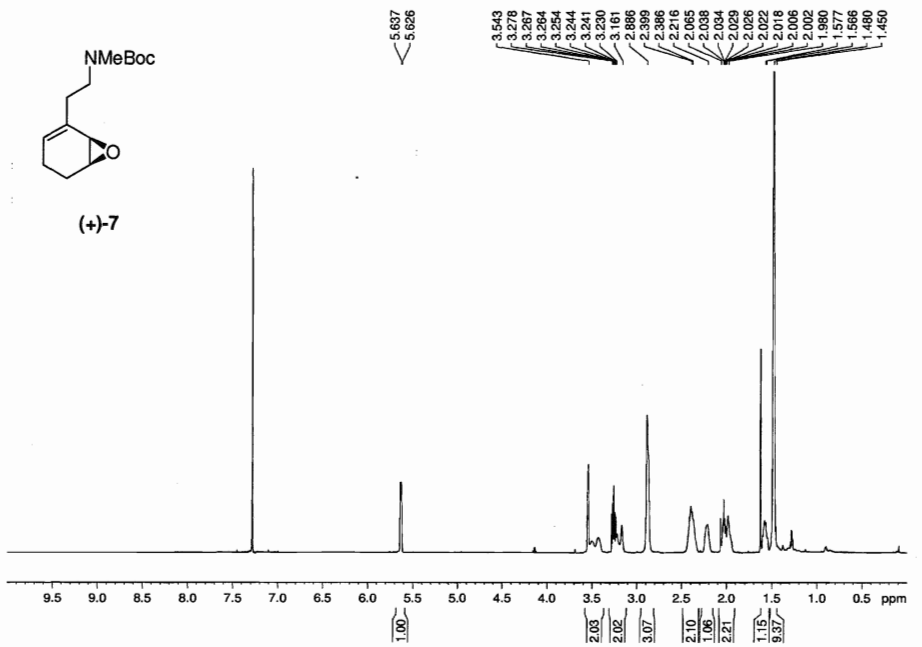

161.526
84.234
61.251
29.486
28.897
24.116
23.896
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

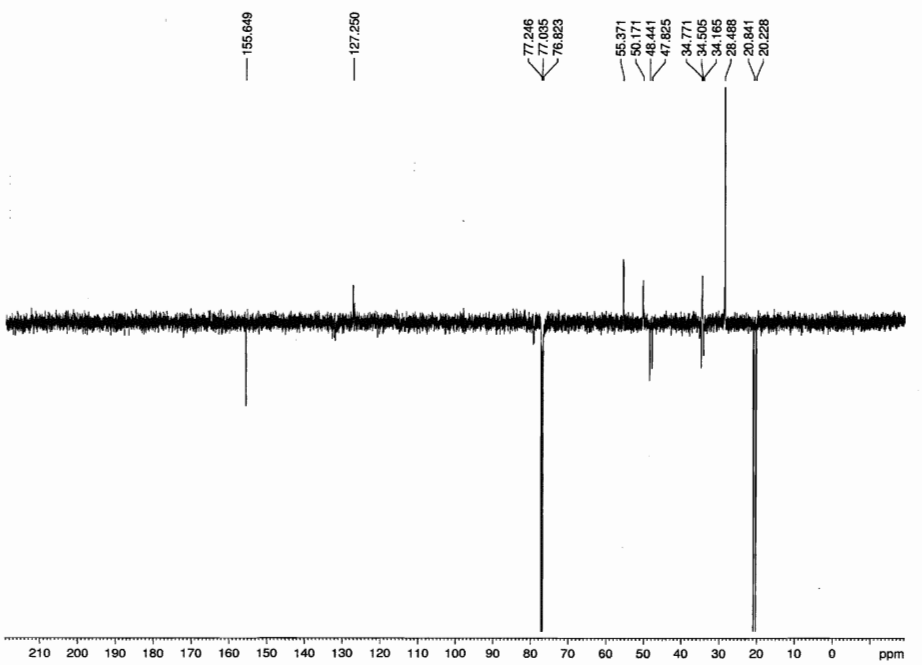

10.301
7.754
7.740
7.003
6.988
5.856
5.830
4.571
3.981
3.587
3.434
3.217
2.851
2.425
2.247
2.221
2.197
2.064
2.037
1.725
1.699
1.686
1.678
1.463
0.752
MeO
CHO
Br
O
NMeBoc
TBSO
337
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.03
1.06
1.07
1.05
4.28
1.05
1.07
3.19
2.16
2.20
1.12
1.30
9.83
9.77

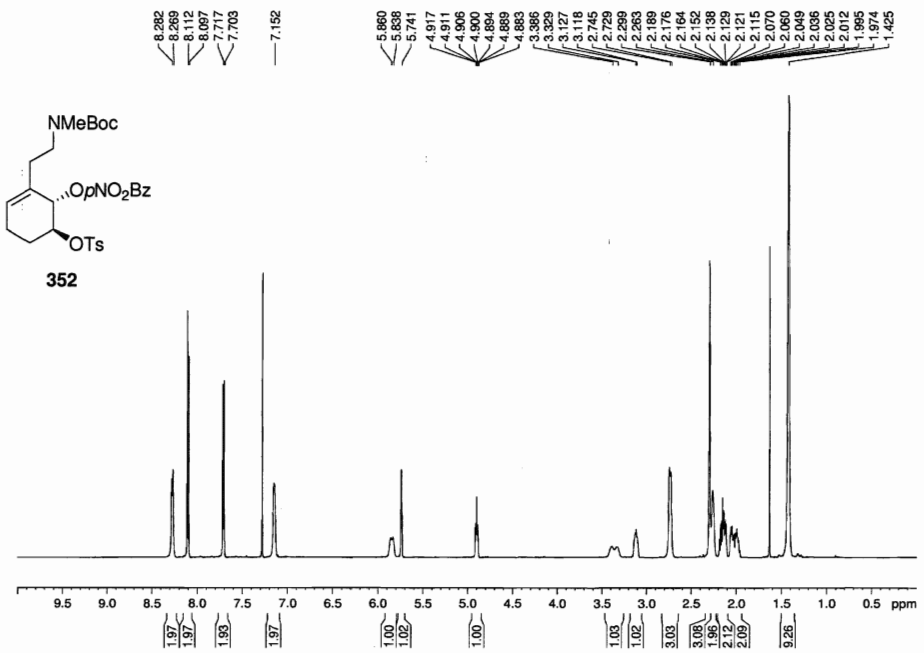

191.308
157.991
155.820
144.560
130.984
130.260
127.655
125.932
123.492
110.956
80.308
79.087
77.261
77.049
76.838
67.772
56.102
48.903
48.261
41.460
35.013
33.451
32.667
28.508
25.652
25.379
20.864
18.034
-4.991
-5.128
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

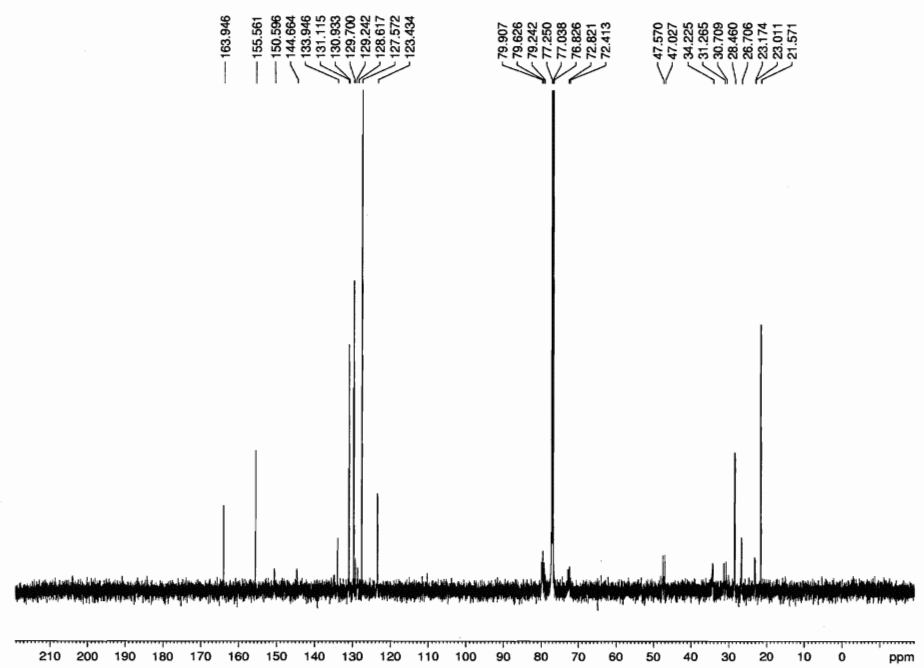

NMeBoc
OH
OH
349
5.399
3.990
3.971
3.715
3.704
3.693
3.681
3.670
3.659
3.648
3.594
2.846
2.395
2.373
2.350
2.324
2.284
2.266
2.246
2.220
2.202
2.093
2.078
2.062
1.932
1.917
1.904
1.889
1.874
1.862
1.846
1.690
1.668
1.661
1.657
1.647
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.03
1.82
2.23
0.96
3.07
1.04
1.05
1.91
1.05
1.20
9.29

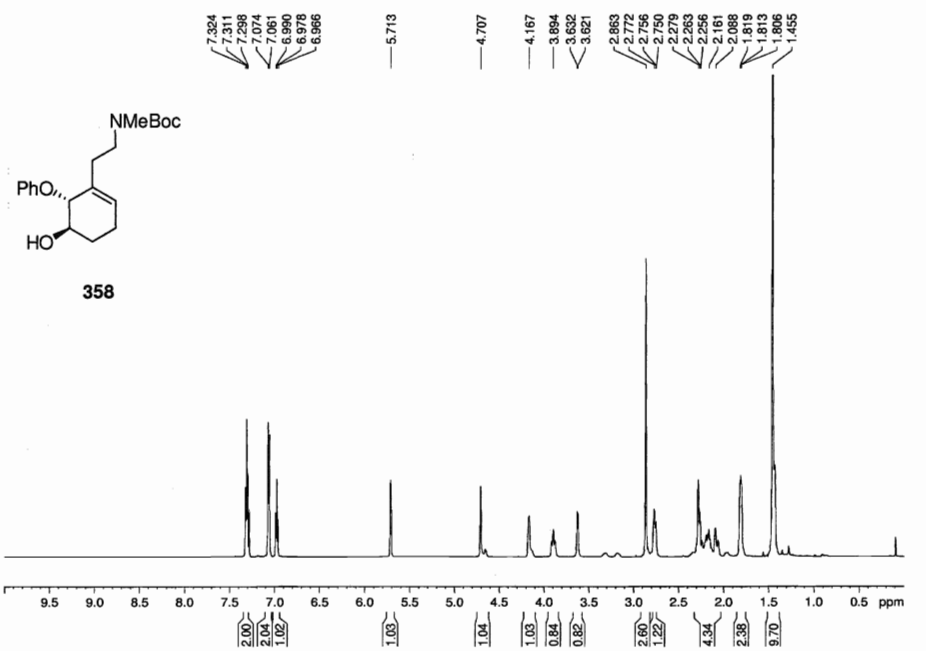

156.716
134.550
126.731
79.778
74.706
73.159
47.760
34.134
32.636
28.445
28.315
27.210
23.672
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

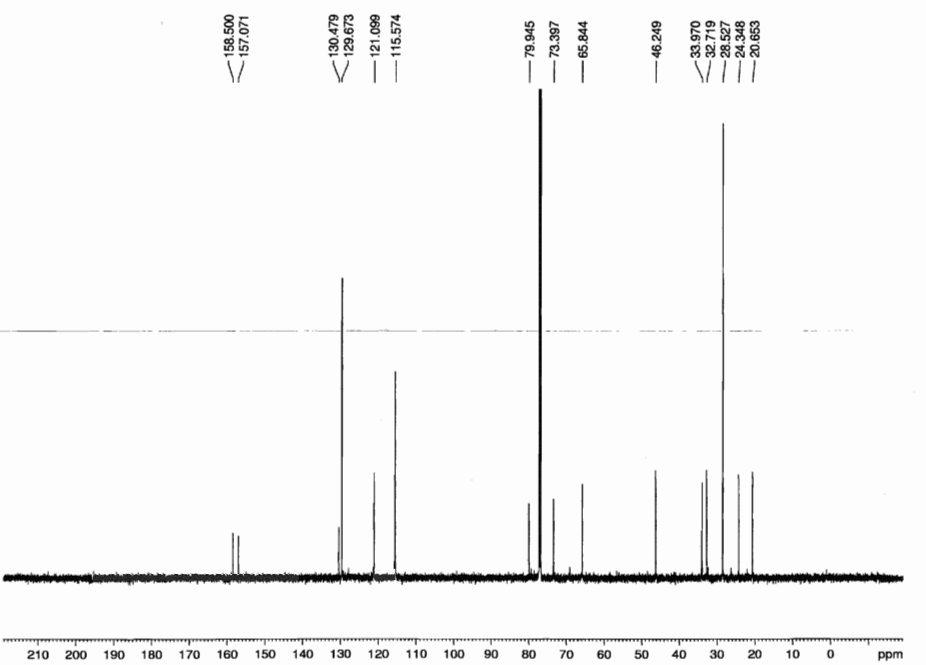

NMeBoc
O
(+)-7
5.637
5.626
3.543
3.278
3.267
3.264
3.254
3.244
3.241
3.230
3.161
2.886
2.399
2.386
2.216
2.065
2.038
2.034
2.029
2.026
2.022
2.018
2.006
2.002
1.980
1.577
1.566
1.480
1.450
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
2.03
2.02
3.07
2.10
1.06
2.21
1.15
9.37

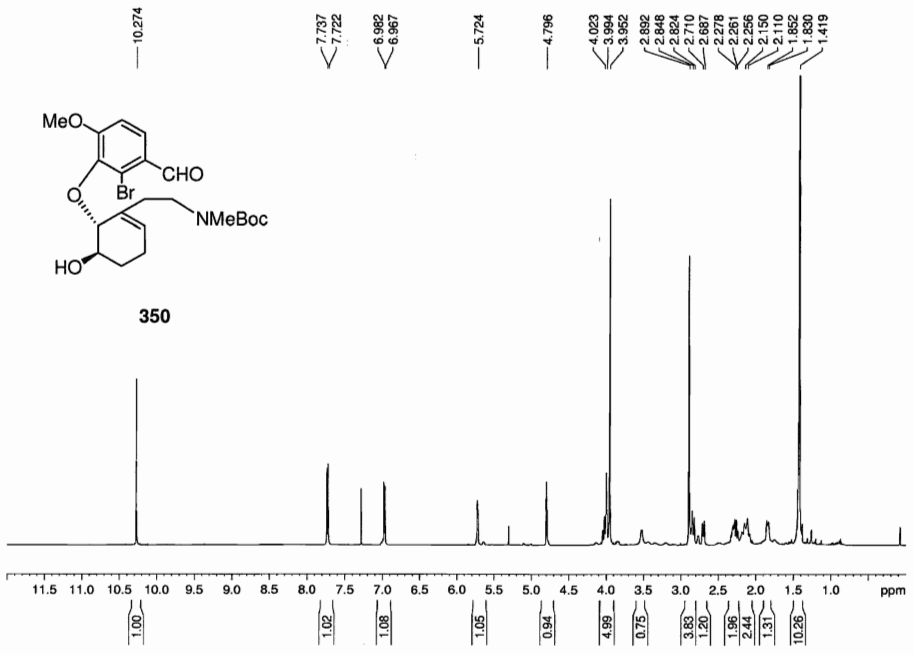

155.649
127.250
77.246
77.035
76.823
55.371
50.171
48.441
47.825
34.771
34.505
34.165
28.488
20.841
20.228
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

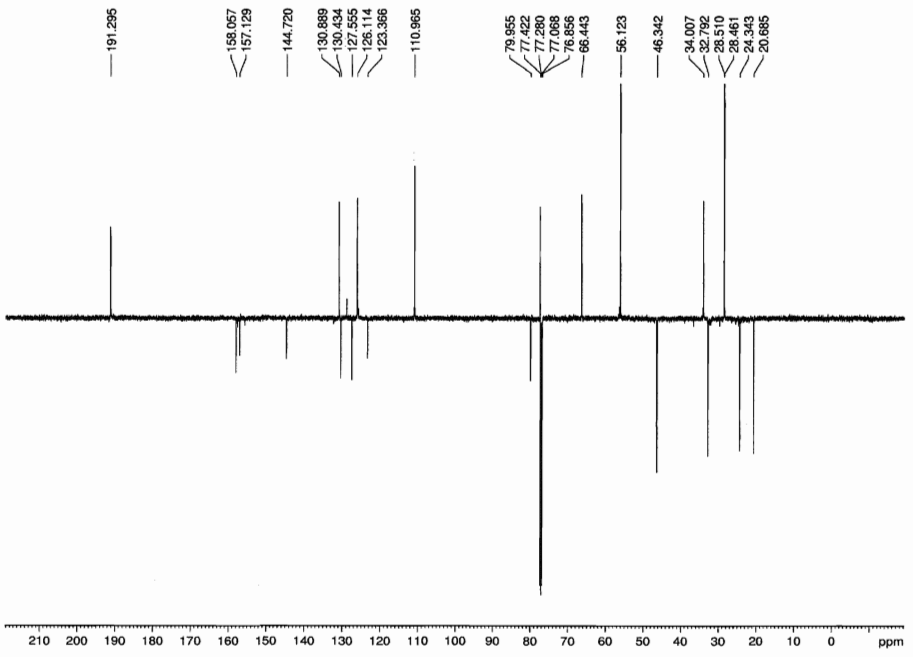

NMeBoc
OpNO2Bz
OTs
352
8.282
8.269
8.112
8.097
7.717
7.703
7.152
5.860
5.838
5.741
4.917
4.911
4.906
4.900
4.894
4.889
4.883
3.386
3.329
3.127
3.118
2.745
2.729
2.299
2.263
2.189
2.176
2.164
2.152
2.138
2.129
2.121
2.115
2.070
2.060
2.049
2.036
2.025
2.012
1.995
1.974
1.425
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.97
1.97
1.93
1.97
1.00
1.02
1.00
1.03
1.02
3.03
3.08
1.96
2.12
2.09
9.26

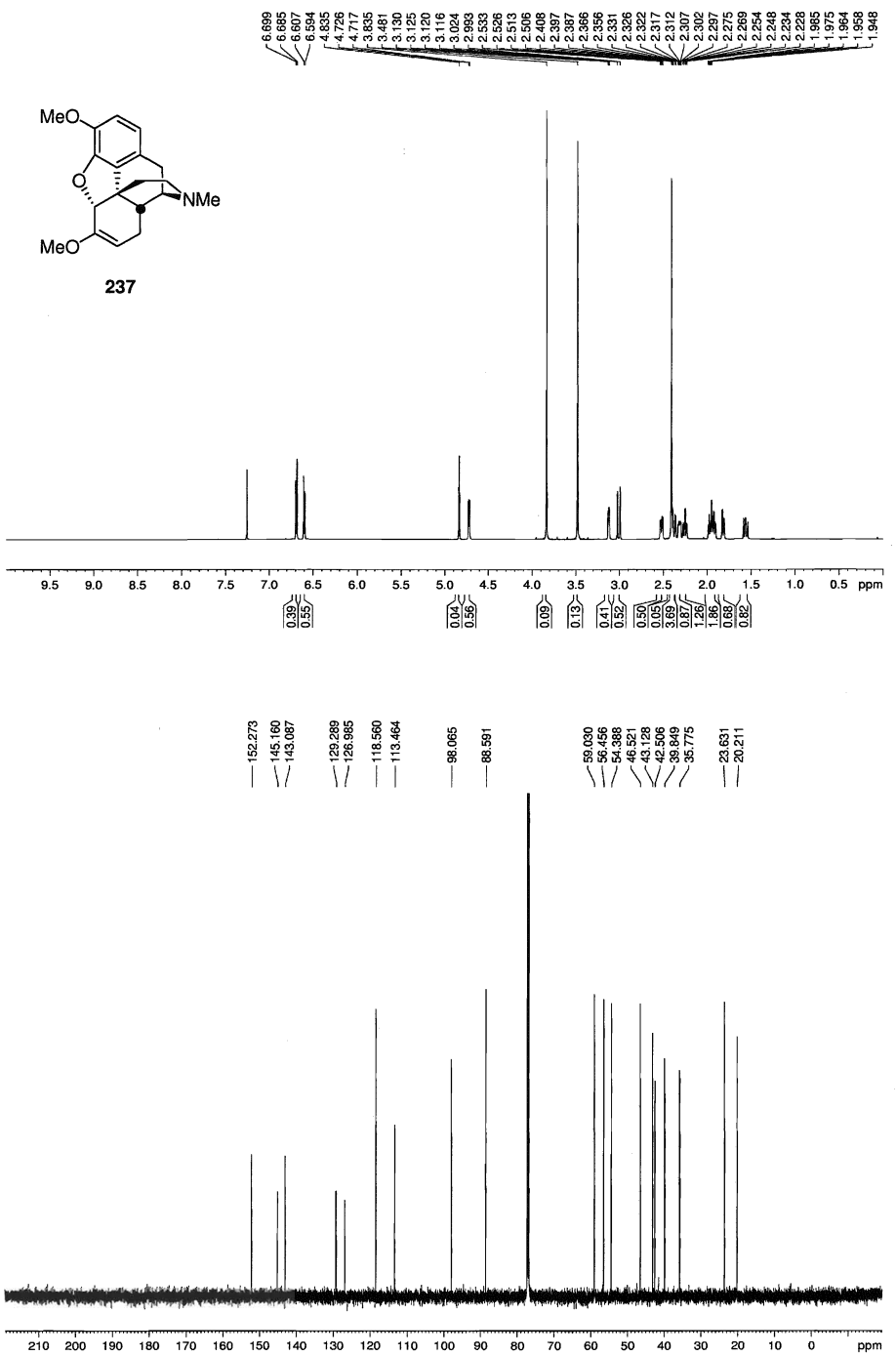

163.946
155.561
150.596
144.664
133.946
131.115
130.933
129.700
129.242
128.617
127.572
123.434
79.907
79.626
79.242
77.250
77.038
76.826
72.821
72.413
47.570
47.027
34.225
31.265
30.709
28.460
26.706
23.174
23.011
21.571
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

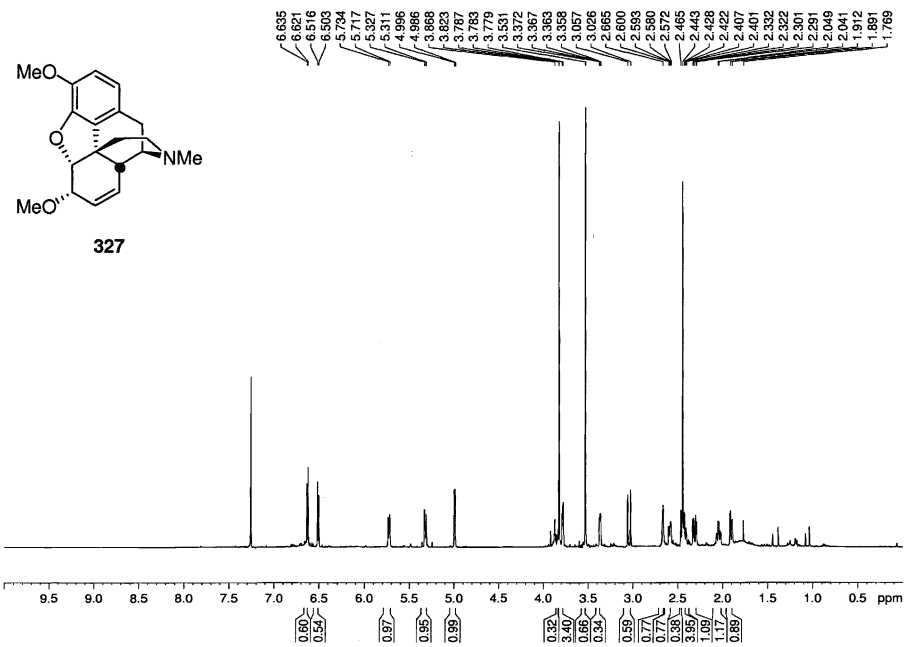

7.324
7.311
7.298
7.074
7.061
6.990
6.978
6.966
5.713
4.707
4.167
3.894
3.632
3.621
2.863
2.772
2.756
2.750
2.279
2.263
2.256
2.161
2.088
1.819
1.813
1.806
1.455
NMeBoc
PhO
HO
358
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.00 2.04 1.02 1.03 1.04 1.03 0.84 0.82 2.60 1.22 4.34 2.38 9.70


158.500
157.071
130.479
129.673
121.099
115.574
79.945
73.397
65.844
46.249
33.970
32.719
28.527
24.348
20.653
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

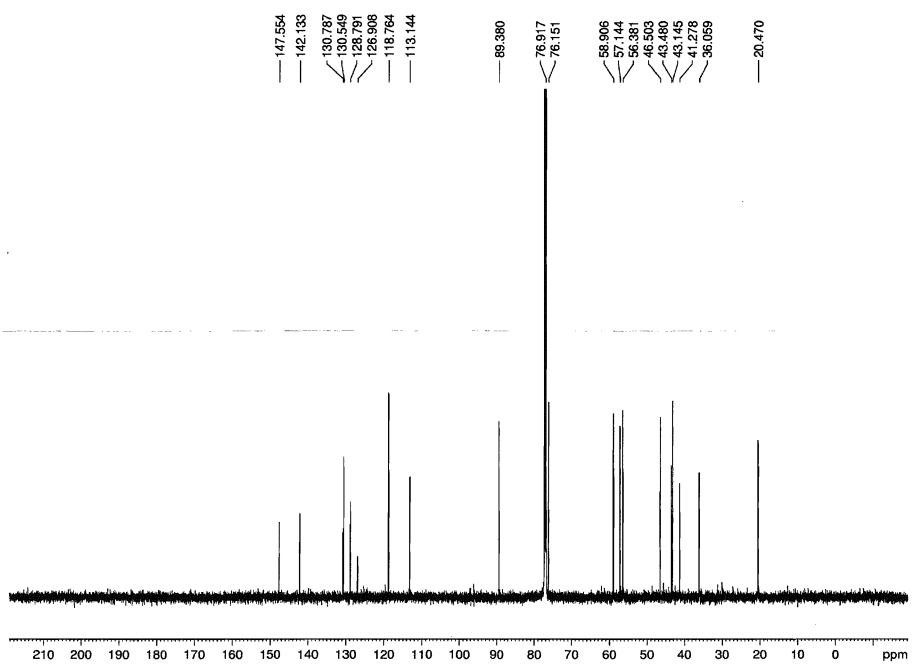

10.274
7.737
7.722
6.982
6.967
5.724
4.796
4.023
3.994
3.952
2.892
2.848
2.824
2.710
2.687
2.278
2.261
2.256
2.150
2.110
1.852
1.830
1.419
MeO
CHO
Br
O
NMeBoc
HO
350
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.02
1.08
1.05
0.94
4.99
0.75
3.83
1.20
1.96
2.44
1.31
10.26

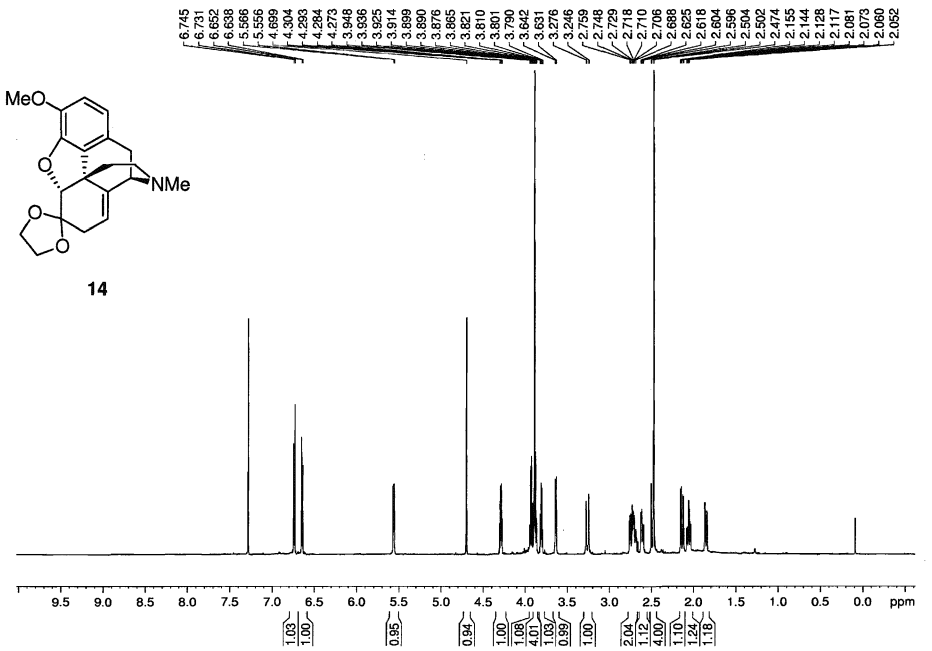

191.295
158.057
157.129
144.720
130.889
130.434
127.555
126.114
123.366
110.965
79.955
77.422
77.280
77.068
76.856
66.443
56.123
46.342
34.007
32.792
28.510
28.461
24.343
20.685
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

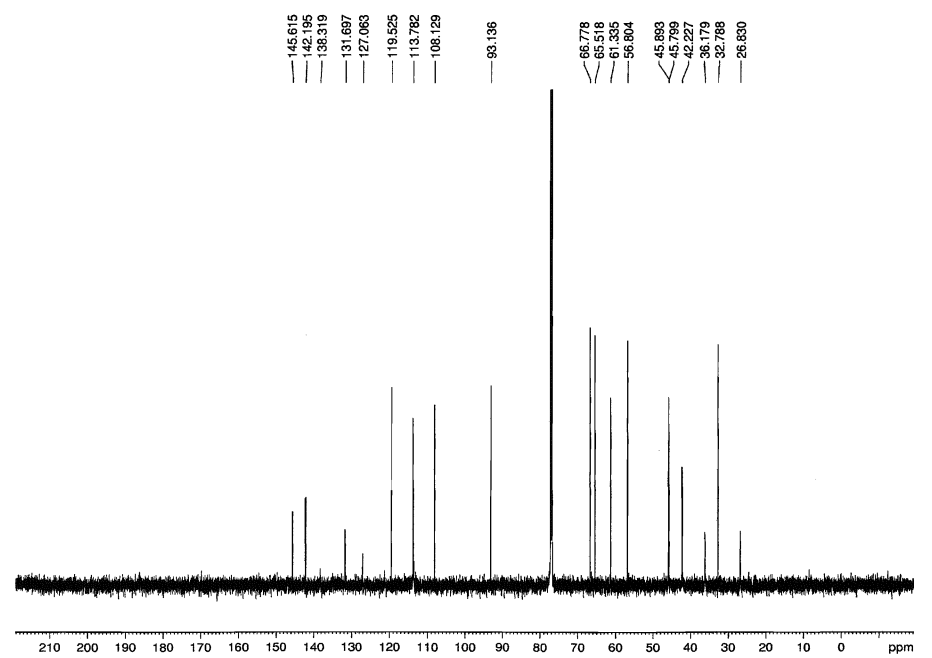

6.699
6.685
6.607
6.594
4.835
4.726
4.717
3.835
3.481
3.130
3.125
3.120
3.116
3.024
2.993
2.533
2.526
2.513
2.506
2.408
2.397
2.387
2.366
2.356
2.331
2.326
2.322
2.317
2.312
2.307
2.302
2.297
2.275
2.269
2.254
2.248
2.234
2.228
1.985
1.975
1.964
1.958
1.948
MeO
O
NMe
MeO
237
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.39
0.55
0.04
0.56
0.09
0.13
0.41
0.52
0.50
0.05
3.69
0.87
1.26
1.86
0.68
0.82
152.273
145.160
143.087
129.289
126.985
118.560
113.464
98.065
88.591
59.030
56.456
54.388
46.521
43.128
42.506
39.849
35.775
23.631
20.211
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

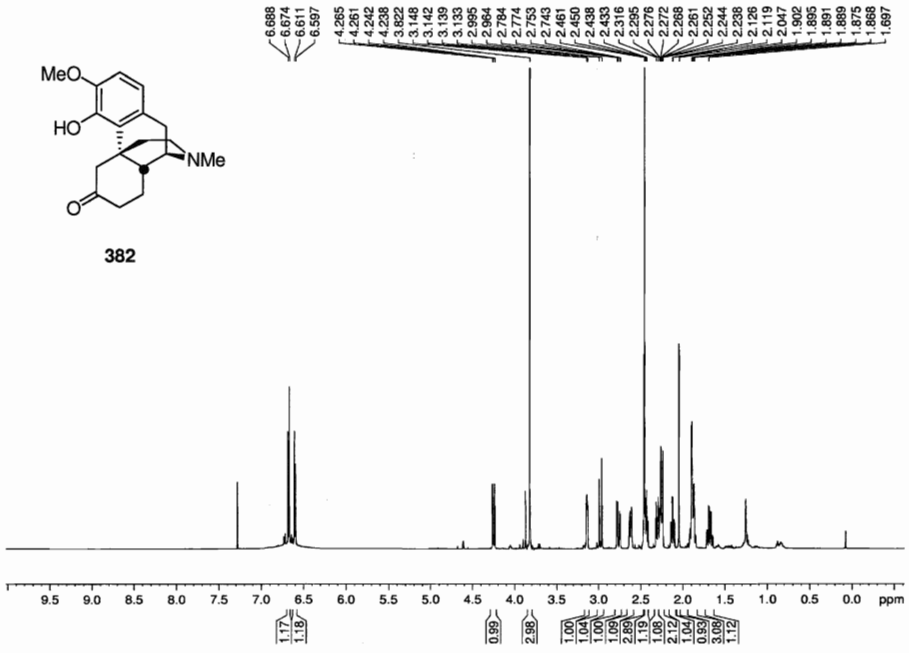

MeO
O
NMe
MeO
6.635
6.621
6.516
6.503
5.734
5.717
5.327
5.311
4.996
4.986
3.868
3.823
3.787
3.783
3.779
3.531
3.372
3.367
3.363
3.358
3.057
3.026
2.665
2.600
2.593
2.580
2.572
2.465
2.443
2.428
2.422
2.407
2.401
2.332
2.322
2.301
2.291
2.049
2.041
1.912
1.891
1.769
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.60
0.54
0.97
0.95
0.99
0.32
3.40
0.66
0.34
0.59
0.77
0.77
0.38
3.95
1.09
1.17
0.89

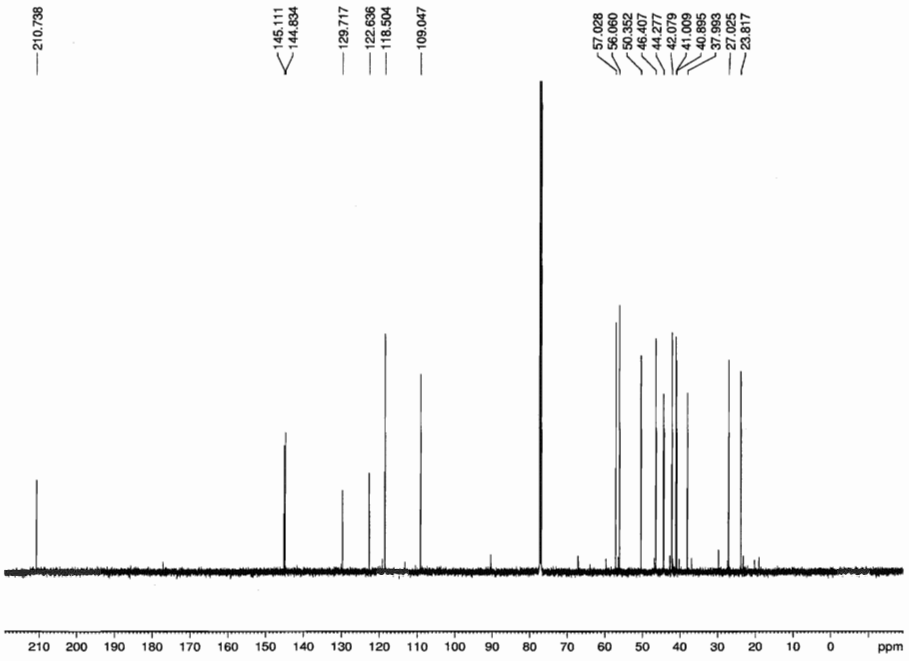
327


147.554
142.133
130.787
130.549
128.791
126.908
118.764
113.144
89.380
76.917
76.151
58.906
57.144
56.381
46.503
43.480
43.145
41.278
36.059
20.470
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


6.745
6.731
6.652
6.638
5.586
5.556
4.699
4.304
4.293
4.284
4.273
3.948
3.936
3.925
3.914
3.899
3.890
3.876
3.865
3.821
3.810
3.801
3.790
3.642
3.631
3.276
3.246
2.759
2.748
2.729
2.718
2.710
2.706
2.688
2.625
2.618
2.604
2.596
2.504
2.502
2.474
2.155
2.144
2.128
2.117
2.081
2.073
2.060
2.052
MeO
NMe
O
O
O
O
14
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.03
1.00
0.95
0.94
1.00
1.08
4.01
1.03
0.99
1.00
2.04
1.12
4.00
1.10
1.24
1.18


145.615
142.195
138.319
131.697
127.063
119.525
113.782
108.129
93.136
66.778
65.518
61.335
56.804
45.893
45.799
42.227
36.179
32.788
26.830
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


MeO
HO
NMe
O
382
6.688
6.674
6.611
6.597
4.265
4.261
4.242
4.238
3.822
3.145
3.142
3.139
3.133
2.995
2.964
2.784
2.774
2.753
2.743
2.461
2.450
2.438
2.433
2.316
2.295
2.276
2.272
2.268
2.261
2.252
2.244
2.238
2.128
2.119
2.047
1.902
1.895
1.891
1.889
1.875
1.868
1.697
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.17
1.18
0.99
2.98
1.00
1.04
1.00
1.09
2.85
1.19
1.08
2.12
1.04
0.93
3.09
1.12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145.111
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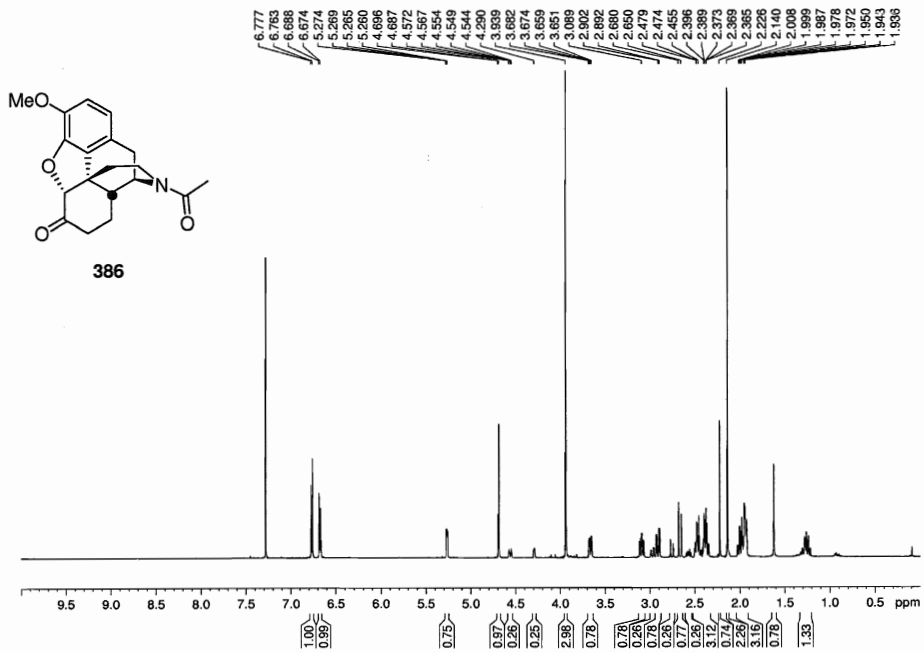
109.047
57.028
56.060
50.352
46.407
44.277
42.079
41.009
40.895
37.993
27.025
23.817
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


MeO
O
N
O
O
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6.763
6.688
6.674
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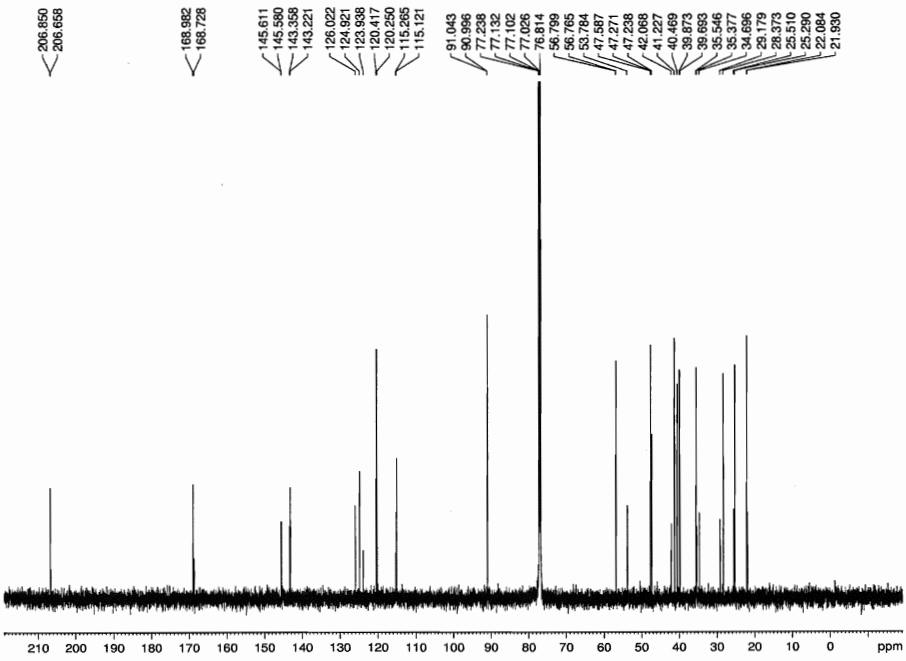
5.269
5.265
5.260
4.696
4.687
4.572
4.567
4.554
4.549
4.544
4.290
3.939
3.682
3.674
3.659
3.651
3.089
2.902
2.892
2.680
2.650
2.479
2.474
2.455
2.396
2.389
2.373
2.369
2.365
2.226
2.140
2.008
1.999
1.987
1.978
1.972
1.950
1.943
1.936
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
0.99
0.75
0.97
0.26
0.25
2.98
0.78
0.78
0.28
0.78
0.26
0.77
0.26
3.12
0.74
2.26
3.16
0.78
1.33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206.658
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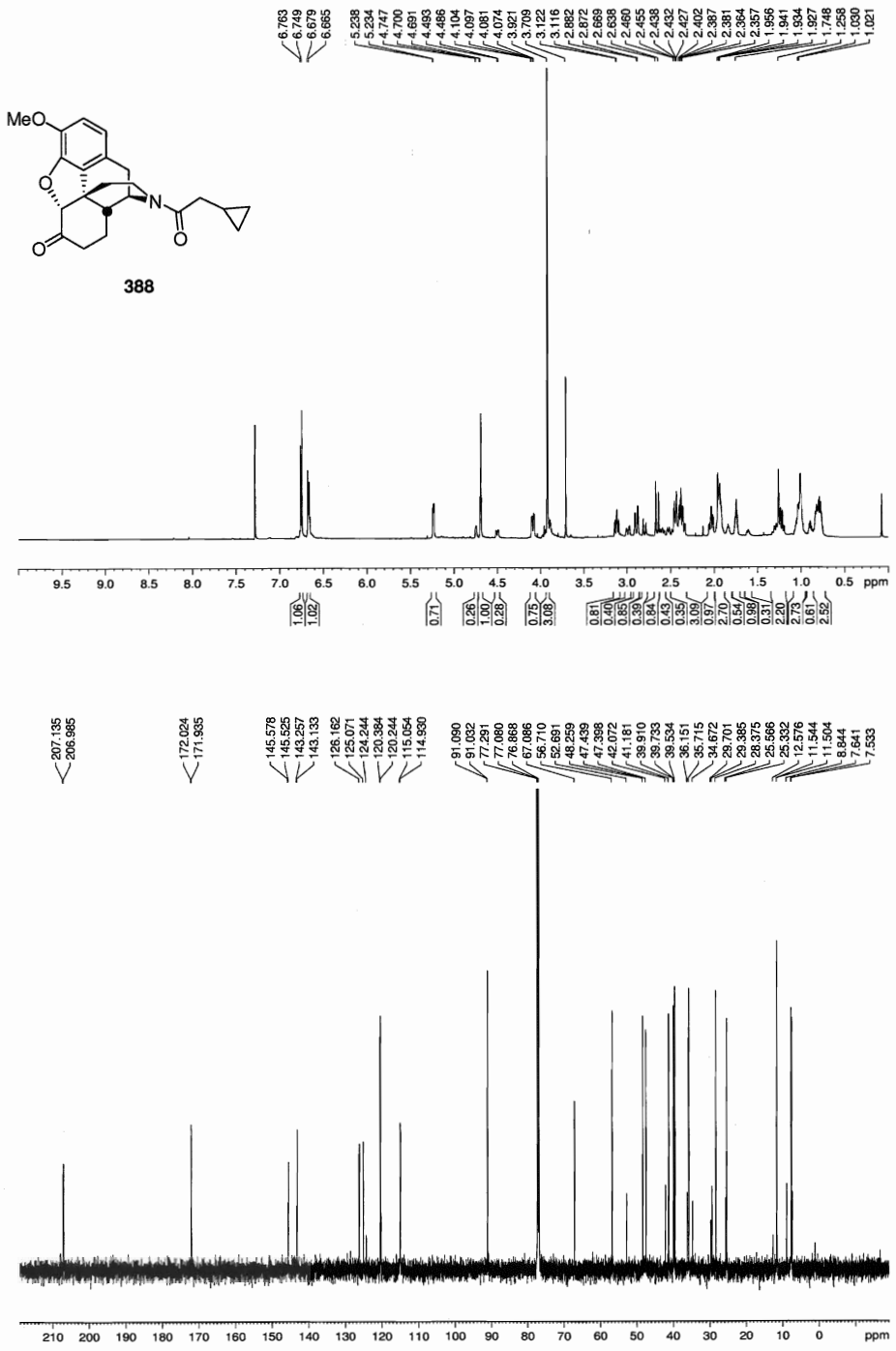
120.417
120.250
115.265
115.121
91.043
90.996
77.238
77.132
77.102
77.026
76.814
56.799
56.765
53.784
47.587
47.271
47.238
42.068
41.227
40.469
39.873
39.693
35.546
35.377
34.696
29.179
28.373
25.510
25.290
22.084
21.930
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


MeO
O
N
O
O
388
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6.749
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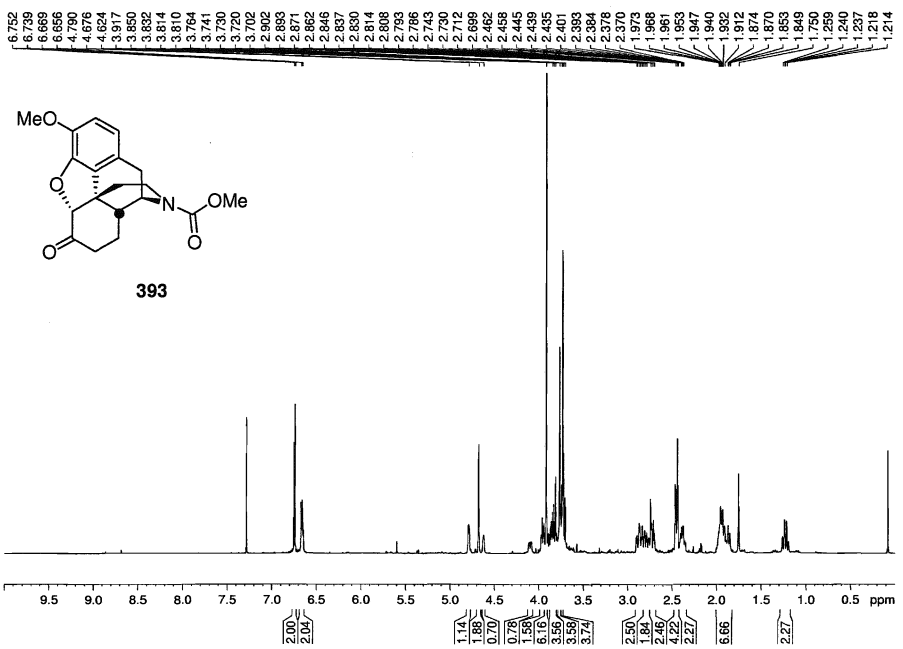
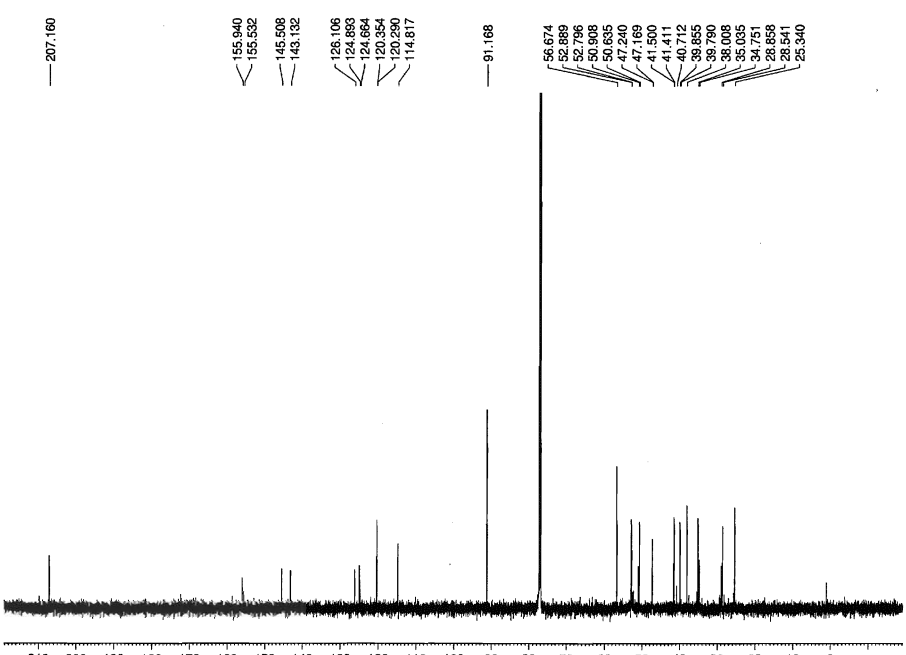
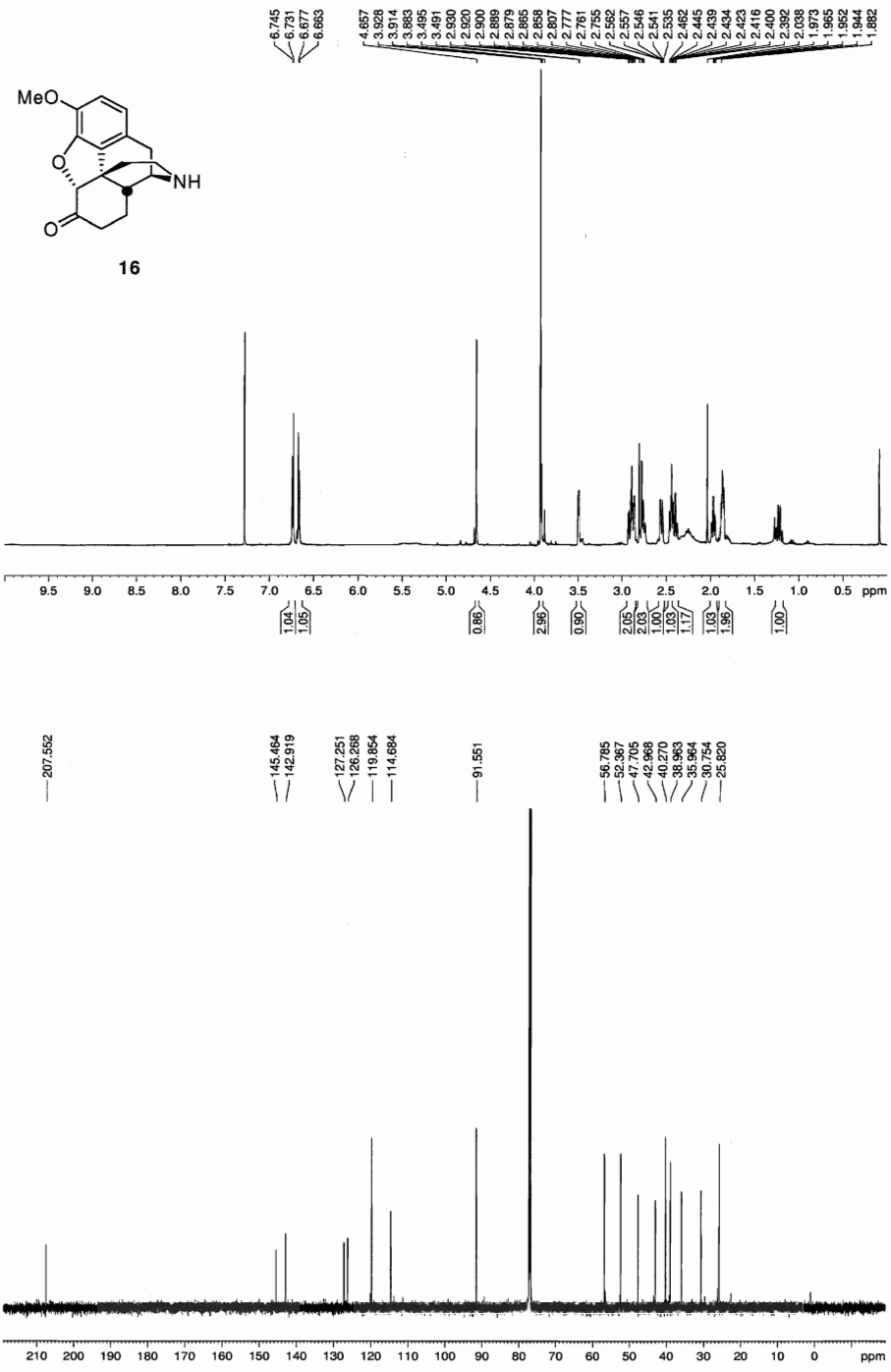
6.665
5.238
5.234
4.747
4.700
4.691
4.493
4.486
4.104
4.097
4.081
4.074
3.921
3.709
3.122
3.116
2.882
2.872
2.669
2.638
2.460
2.455
2.438
2.432
2.427
2.402
2.387
2.381
2.364
2.357
1.956
1.941
1.934
1.927
1.748
1.258
1.030
1.021
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.06
1.02
0.71
0.26
1.00
0.28
0.75
3.08
0.81
0.40
0.85
0.39
0.84
0.43
0.35
3.09
0.97
2.70
0.54
0.98
0.31
2.20
2.73
0.61
2.52
207.135
206.985
172.024
171.935
145.578
145.525
143.257
143.133
126.162
125.071
124.244
120.384
120.244
115.054
114.930
91.090
91.032
77.291
77.080
76.868
67.086
56.710
52.691
48.259
47.439
47.398
42.072
41.181
39.910
39.733
39.534
36.151
35.715
34.672
29.701
29.385
28.375
25.586
25.332
12.576
11.544
11.504
8.844
7.641
7.533
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

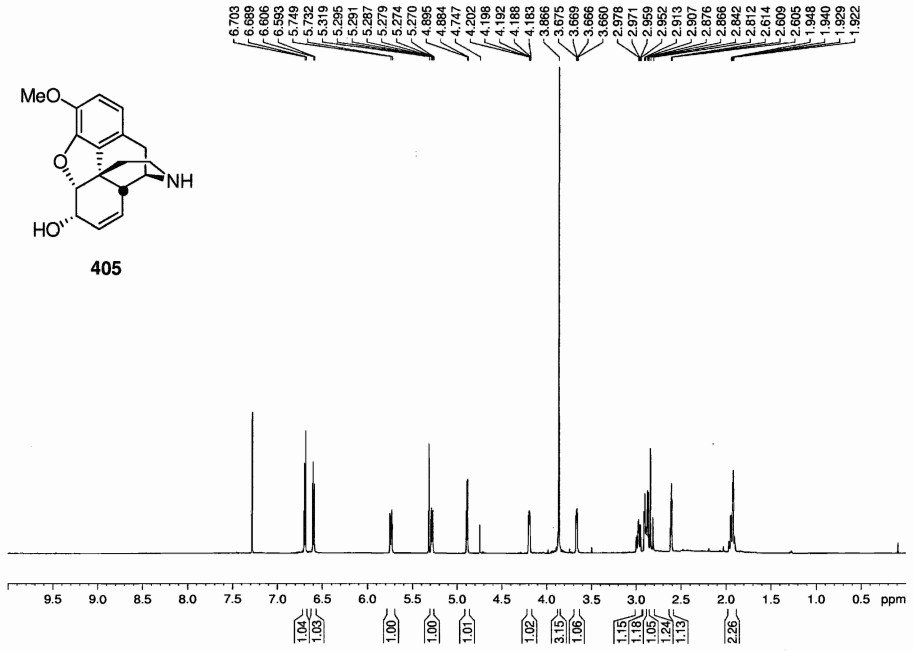

MeO
O
N
OMe
O
O

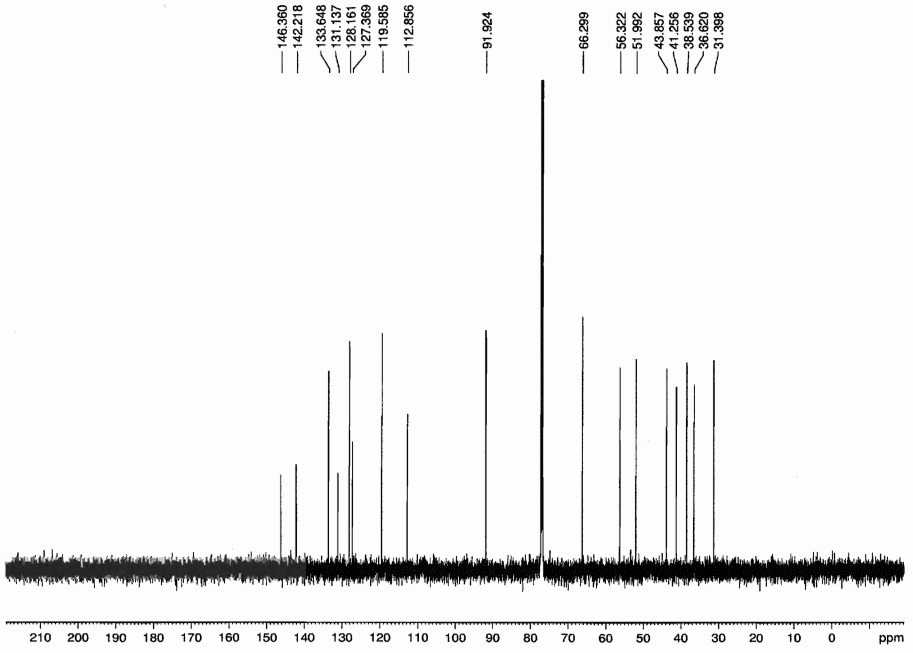
393

6.752
6.739
6.669
6.656
4.790
4.676
4.624
3.917
3.850
3.832
3.814
3.810
3.764
3.741
3.730
3.720
3.702
2.902
2.893
2.871
2.862
2.846
2.837
2.830
2.814
2.808
2.793
2.786
2.743
2.730
2.712
2.699
2.462
2.458
2.445
2.439
2.435
2.401
2.393
2.384
2.378
2.370
1.973
1.968
1.961
1.953
1.947
1.940
1.932
1.912
1.874
1.870
1.853
1.849
1.750
1.259
1.240
1.237
1.218
1.214
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.00
2.04
1.14
1.88
0.70
0.78
1.58
6.16
3.56
3.59
3.74
2.50
1.84
2.46
4.22
2.27
6.66
2.27


207.160
155.940
155.532
145.508
143.132
126.106
124.893
124.664
120.354
120.290
114.817
91.168
56.674
52.889
52.796
50.908
50.635
47.240
47.169
41.500
41.411
40.712
39.855
39.790
38.008
35.035
34.751
28.858
28.541
25.340
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


MeO
O
NH
O
16
6.745
6.731
6.677
6.663
4.657
3.928
3.914
3.883
3.495
3.491
2.930
2.920
2.900
2.889
2.879
2.865
2.858
2.807
2.777
2.761
2.755
2.562
2.557
2.546
2.541
2.535
2.462
2.445
2.439
2.434
2.423
2.416
2.400
2.392
2.038
1.973
1.965
1.952
1.944
1.882
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.04
1.05
0.86
2.96
0.90
2.05
2.03
1.00
1.03
1.17
1.03
1.96
1.00
207.552
145.464
142.919
127.251
126.268
119.854
114.684
91.551
56.785
52.367
47.705
42.968
40.270
38.963
35.964
30.754
25.820
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


6.703
6.689
6.606
6.593
5.749
5.732
5.319
5.295
5.291
5.287
5.279
5.274
5.270
4.895
4.884
4.747
4.202
4.198
4.192
4.188
4.183
3.866
3.675
3.669
3.666
3.660
2.978
2.971
2.959
2.952
2.913
2.907
2.876
2.866
2.842
2.812
2.614
2.609
2.605
1.948
1.940
1.929
1.922
MeO
O
NH
HO
405
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.04
1.03
1.00
1.00
1.01
1.02
3.15
1.06
1.15
1.18
1.05
1.24
1.19
2.26


146.360
142.218
133.648
131.137
128.161
127.369
119.585
112.856
91.924
66.299
56.322
51.992
43.857
41.256
38.539
36.620
31.398
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

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8. Vita

Hannes Leisch was born in Linz, Austria on March 9, 1979. He and his two brothers, Franz and Peter, were raised by their parents, Margot and Franz. He attended elementary school at Volksschule 48 and high school at Khevenhüller Gymnasium in Linz. As a child he has became fascinated with all kinds of sports, especially soccer, tennis, and, fencing. The highlight of his sports career was the participation at the Junior World Championship in Fencing in 1996. After graduation from high school in 1997 he moved to Vienna to study chemistry at the Vienna University of Technology. During his undergraduate studies he had the opportunity to spend one term at Trinity College Dublin, Ireland working under the supervision of Professor Thorfinnur Gunnlaugsson. After his return to Austria he joined the research group of Professor Marko Mihovilovic working in the field of biotransformations. In 2004 he finished his MSc in organic chemistry with distinction and moved to St. Catharines, Canada to pursue further graduate studies with Professor Tomas Hudlicky at Brock University. He is presently working towards completion of his PhD in chemical biotechnology. His research interests include the application of biotransformations in organic synthesis and the total synthesis of natural products.