Investigations into Naloxone-Based Degradation Products in Suboxone® Sublingual Film

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Abstract

In the field of drug development, knowing the chemical composition of a pharmaceutical product is important to develop a process that will avoid the formation of unwanted compounds. The isolation and the chemical synthesis of impurities provides useful information.
Naloxone is an opioid derivative present in Suboxone® sublingual film. It has been demonstrated that naloxone-related impurities are formed during the storage of this pharmaceutical product. However, these compounds are unknown and therefore, synthesising them is the key to confirm their structure.

In this instance, the semi-synthesis of these impurities was attempted. Analysis showed that the majority of the impurities are oxidation products: Alcohols, carboxylic acid or lactones, *alpha*-hydroxy ketones, and products of rearrangements. In total, 17 impurities were found and needed to be prepared.

Various compounds were targeted. The benzylic oxidation of naloxone was first attempted. This compound is known as a naloxone-related impurity in Suboxone® sublingual film. *Chapter II* relates of the synthesis of the desired impurity following a literature procedure, and our attempts to obtain the desired product using other methods.

The second chapter of this report relates of the oxidation of the cyclohexanone ring of naloxone, in order to prepare a di-carboxylic acid, *alpha*-hydroxy ketone and lactone. A synthetic route to the dicarboxylic acid was designed. The key oxidation step – the dihydroxylation of an alkene – required a deallylation followed by the Boc protection of the amine. The diol is also an intermediate to the synthesis of the *alpha*-hydroxy ketone. The preferred route towards this compound involved the mono-protection followed by the oxidation of the diol. However, some work still needs to be done to provide the desired compound.
Another targeted impurity was a lactone, formed by Baeyer-Villiger oxidation of the parent ketone. However, the main reaction that seemed to happen was the oxidation of the basic nitrogen to form the corresponding *N*-oxide.

Finally, *Chapter IV* contains the initial work towards the opening of the furan ring, in order to form two *alpha*-hydroxyketone products. To this end, the formation of an alkene followed by oxidation was the attempted strategy. The opening of the E ring using a stepwise Wolff-Kishner approach provided the desired alkene between positions 5 and 6.

Acknowledgments

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Abbreviations

9-I-9-BBN	9-iodo-9-borabicyclo[3.3.1]nonane
Acac	Acetylacetone
AIBN	*α,α'*-Azoisobutyronitrile
Aq.	Aqueous
Ar	Aromatic
ax	Axial
BINAP	(1,1'-Binaphthalene-2,2'-diyl)bis(diphenylphosphine)
Boc	*tert*-Butyloxycarbonyl
BOP	(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
Br	Broad
CAN	Ceric ammonium nitrate
Cat.	Catalytic
cod	Cyclooctadiene
Conc.	Concentrated
CPM	Cyclopropylmethyl
dba	Dibenzylidene acetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminium
DIPEA	Diisopropylamine
DMAP	Dimethylaminopyridine
DMBA	Dimethylbarbituric acid
DMDO	Dimethyl dioxirane
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
DOR	Delta opioid receptor

dppf	1,1'-Ferrocenediyl-bis(diphenylphosphine)
dppp	1,3-Bis(diphenylphosphino)propane
Eq.	Equivalent
eq	Equatorial
FDA	Food and Drug Administration
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
IBX	2-Iodoxybenzoic acid
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IR	Infrared
KHMDS	Potassium bis(trimethylsilyl)amide
KOR	Kappa opioid receptor
LC-MS	Liquid chromatography-mass spectrometry
LDA	Lithium diisopropylamide
M	Molar
*m*CPBA	*meta*-Chloroperbenzoic acid
MMT	Methadone Maintenance Treatment
MOR	Mu opioid receptor
MPLC	Medium-pressure liquid chromatography
Ms	Methanesulfonate
MVK	Methyl vinyl ketone
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
Nu	Nucleophile
OMT	Opioid Maintenance Treatment
Piv	Pivaloyl
Quant.	Quantitative
Red-Al	Sodium bis(2-methoxyethoxy)aluminum hydride
RSM	Recovered starting material
rt	Room temperature
S_N2	Bimolecular nucleophilic substitution
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl

TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butylhydroperoxyde
TEAI	Tetraethylammonium iodide
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
Tf	Trifluoromethanesulfonate
TFE	Trifluoroethanol
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Tol	Tolyl
Troc	2,2,2-Trichloroethoxycarbonyl
Ts	Toluenesulfonate
UV	Ultra-violet

Chapter I : Introduction

Opium is extracted from the opium poppy *Papaver Somniferum*. The earliest evidence of the cultivation and use of opium date back to 3400 BC and it has been renowned for centuries for its psychoactive and analgesic effects, in medical and religious purposes by ancient Greeks, Persians and Egyptians.

Until the 17th century, opium was used in a mixture with alcohol. "Laudanum" was a commonly used analgesic, antitussive and antidiarrheal in Europe and America. A milder version of Laudanum was also available for children.

In 1805, Friedrich Sertürner, a German pharmacist, managed to isolate the active substance from opium, and gave its name from the Greek god of sleep and dreams, Morphine. He found that human consumption was safe and induced a feeling of happiness. At higher doses, morphine would cause drowsiness, confusion and somnolence.[1] A few years later, codeine was isolated by Pierre-Jean Robiquet (1832). Codeine was subsequently commercialised as a treatment against cough and diarrhoea.

The invention of the hypodermic needle at the start of the 19th century facilitated the use of morphine and codeine, even for addicts. The addictive character of morphine was rapidly recognised, which led scientists to look for new morphine derivatives. During his quest for new opioids, the chemist Charles Wright synthesised diacetylmorphine (heroin), which was supposed to be a less addictive version of morphine. Heroin was produced by the Bayer laboratories for 15 years, commercialised as an analgesic, cough treatment for tuberculosis, bronchitis and asthma, before its addictive potential was brought to light in 1913.

Nowadays, natural alkaloids such as morphine, codeine and thebaine are extracted from the poppy *Papaver Somniferum*, and are used in order to obtain semi-synthetic opioid derivatives such as oxycodone, oxymorphone or buprenorphine. So far, around 150 opioids have been synthesised.

I.1 Opioid receptors

Opioid receptors are a class of G protein-coupled receptors (also called seven transmembrane domain receptors). They are a big family of membrane proteins that, after extracellular activation by a ligand, pass the signal to the interior of the cell. Ligands include hormones, pheromones or neurotransmitters, with the size of a small molecule to a large peptide or protein.[2–4] Opioid receptors are activated by endogenous peptides (produced by the body), such as enkephalins, dynorphins or endorphins, or

exogenously (activated by species not produced by the body, comes from outside of the organism) by alkaloids (such as morphine).

The three main opioid receptors are called δ (OP_1 or DOR), κ (OP_2 or KOR) and μ (OP_3 or MOR). Other opioid receptors exist but have received less attention over the years: epsilon (ε), zeta (ζ) and lambda (λ). Those receptors, as well as the opioid receptor-like (ORL-1 or NOR-1) will not be discussed here.

The main structural similarity between these three receptors is the presence of a binding cavity. While large molecules such as norBNI (*Figure I.1*) fill all the space available in the cavity, smaller molecules (such as morphine) interact mostly with residues at the bottom of this binding cavity. It is thought that antagonists shift deeper in the cavity than agonists, thus creating the antagonist effect.[2] The activation of a receptor by an agonist leads to the inhibition of neurotransmitter release.[5]

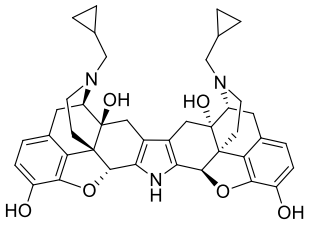


Figure I.1: Structure of norBNI

The μ receptor has been originally characterised by Martin and Kosterlitz,[6,7] and is named because of its high affinity for morphine. It is located along the neuraxis, with a higher density in the thalamus, among other locations.[8]

The functions regulated by the μ receptor include pain or analgesia, respiratory and cardiovascular functions, intestinal transit, feeding, mood, thermoregulation, hormone secretion and immune functions.[4]

Agonists at the MOR include morphine, codeine, fentanyl and methadone. Side-effects accompany the activation of the μ opioid receptor by opiates: the reduction of sensitivity of central receptors to hypercapnia (increase of the level of CO_2 in the bloodstream) leads to respiratory depression. Other reported side-effects include constipation.

The δ receptor is located in the central nervous system, with a highest density in the olfactory bulb. Analgesia, gastrointestinal mobility, mood and cardiovascular functions are regulated by the δ receptor however, its role is less clearly defined than for the μ receptor.[9,10]

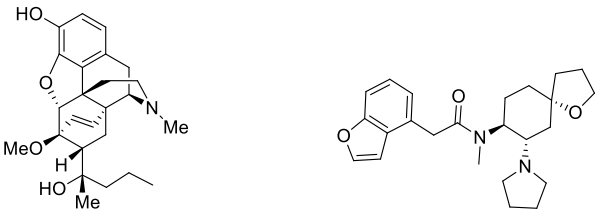
The DOR is activated by etorphine (*Figure I.2*) among other synthetic opioids, and is antagonised by naloxone or naltrexone.

The κ opioid receptor has been described based on studies in dogs with ketocyclazocine, and is located in the cerebral cortex.[7–9]

The KOR participates in the regulation of nociception (relates to the phenomenon that allow the perception of pain signals by the central nervous system), diuresis, feeding, neuroendocrine and immune system functions.

It is agonised by enadoline (*Figure I.2*) (among other synthetic opioids) and antagonised by naloxone, naltrexone or buprenorphine.

The activation of the KOR by opiates is also responsible for side-effects, such as the inhibition of the release of antidiuretic hormones that lead to increased urination. Unlike the MOR, the KOR seems to have little effects on respiratory functions.



Etorphine Enadoline

Figure I.2: Structure of etorphine and enadoline

I.2 Opioid ligands

DOR, KOR and MOR are agonised or antagonised by molecules called opioid ligands. An opioid is any substance which binds to any of the three available receptor and can be antagonised by naloxone, a synthetic compound that is structurally related to natural opioids (see later). Notorious opioid ligands include fentanyl, methadone and tramadol. The opioid category also includes peptides and are simply called opioid peptides. They can be agonists or antagonists at opioid receptors. This compound class will not be discussed in this report.

Opiates, however, are substances extracted from opium or any semi-synthetic substance derived from morphine or thebaine. These include codeine, oxycodone, and diacetylmorphine (heroin). The structure of these compounds is depicted in *Figure I.3*.

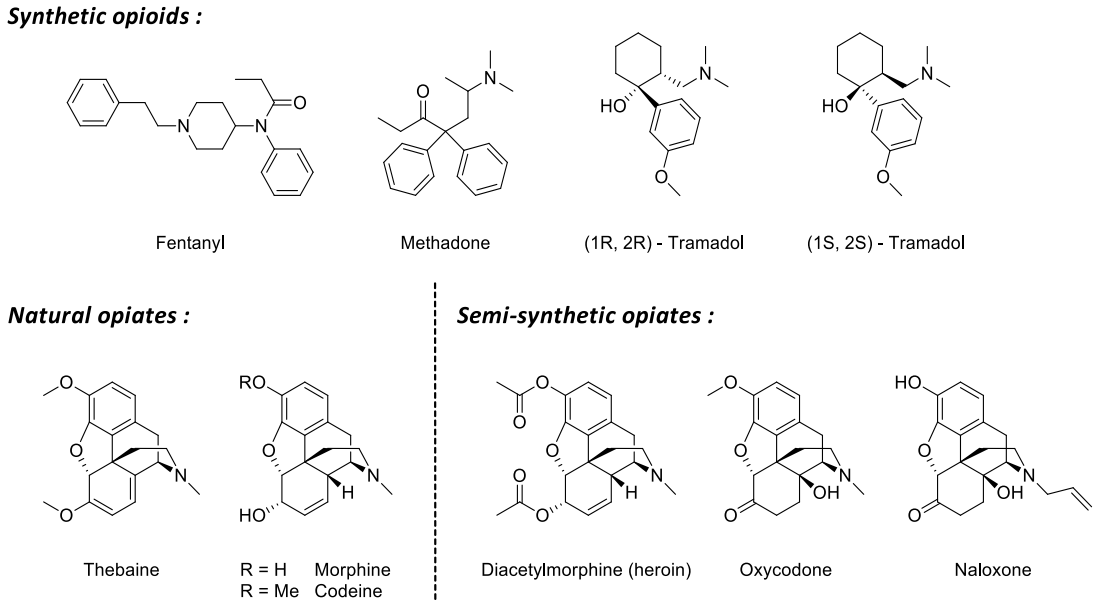


Figure I.3: Structure of opioids and opiates

Opioid receptors are localised throughout the nervous system and are responsible of the control of numerous functions in the body, such as nociception, respiration, intestinal transit or olfaction. Agonists at opioid receptors include morphine and oxycodone. Once the agonist is absorbed in the body, it will activate the receptor which, after the transmission of several signals in the brain, induce an effect: analgesia, sedation, euphoria, etc. Morphine was approved by the FDA in 1984 and is now commercialised under the branded name Avinza® or Morphine sulfate. Oxycodone, a semi-synthetic opiate, was FDA approved in 1950 and is commercialised under the branded name OxyContin®.

Naloxone and naltrexone (*Figure I.4*) are two antagonists at opioid receptors: they displace the agonist in the receptor. Naloxone is a non-selective antagonist but has a higher affinity with the MOR. Due to its strong and fast antagonist character, naloxone is used to reverse the effects of opiate-related overdose. It is also used as a treatment against opioid disorder (addiction) and was approved by the FDA in 1971 in America, under the name Narcan®. Naltrexone is an antagonist at the MOR and KOR to some extent. Its duration of action is longer that naloxone, which made it the best choice in terms of treatment, as it could be used only once a day. Although naltrexone was approved by FDA in 1984 for the treatment of opioid disorder (under the name Trexan®), the name was changed to ReVia® in 1995, and is now used as a treatment against alcohol dependence.

Along with pure agonists or pure antagonists, some opioid ligands can be agonists at a receptor and antagonist at another. That is the case for buprenorphine and nalorphine (*Figure I.4*). Nalorphine is a κ-agonist and a μ-antagonist. Buprenorphine, however, is a κ-antagonist and a partial μ-agonist, which means that it binds to the receptor but has a low activity. Buprenorphine has a high affinity for the μ receptor, which makes the duration of action longer (between 6 and 9 hours). Besides, the dissociation

of the ligand from the receptor is quite slow and allows buprenorphine to block the effects of other opioids taken afterwards. Buprenorphine exists under three different brand names: Buprenex® for the treatment of pain, Subutex® and Suboxone® (a buprenorphine and naloxone combination) for opioid addiction.

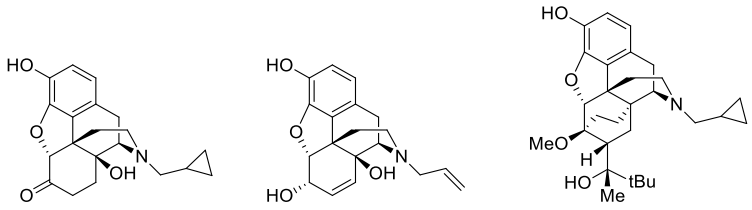


Figure I.4

Opioids are widely used for the treatment of pain however, they induce side effects such as constipation sedation, nausea, respiratory depression, tolerance, and dependence. The increase in opioid prescriptions in the last few years is believed to have resulted in the increase the number of opioid-related deaths. Moreover, the "opioid crisis" has been coined to convey the public health and societal impact on high-income countries.[11–13]

So far, hundreds of morphine derivatives have been synthesised, but the quest for the discovery of a better pain treatment continues.

I.3 Synthesis of opiates

Morphine, thebaine, oripavine and codeine are natural alkaloids extracted from opium poppy. The production of morphine, thebaine and oripavine is exclusively natural. Codeine, however, is present in much lower quantity than morphine, the latter serves as a precursor to synthetically derived codeine. Thebaine and oripavine are precursors for the semi-synthesis of other pharmacologically active opiates such as buprenorphine, naloxone or naltrexone.

The synthesis of morphine analogues (through semi-synthesis or total synthesis) is also an important area of pharmaceutical research.

I.3.1 Total synthesis of opiates

The structure of morphine was first proposed in 1925. It contains a pentacyclic scaffold, five contiguous stereogenic centres (C6, C5, C13, C14, C9) and a benzylic quaternary carbon (C13). The numbering of carbon atoms is depicted in *figure I.5*.

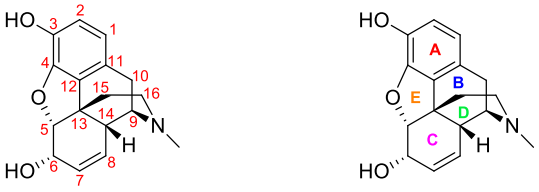


Figure I.5: Numbering of morphine scaffold

The synthesis of the morphine scaffold has been of interest for organic chemists for more than 70 years. Total synthesis has been a powerful tool for the synthesis of morphine derivatives or unnatural isomers. So far, an important effort has been made to develop a practical synthesis of morphine which would compete with the natural extraction from poppy straw: to date, at least 30 total and formal synthesis of morphine (asymmetric or racemic) and its derivatives have been published, highlighting different ways to connect the five rings together.[14–19] Synthetic strategies include an intramolecular Diels-Alder reaction,[20] Claisen rearrangement,[21] oxidative coupling[22] and others.

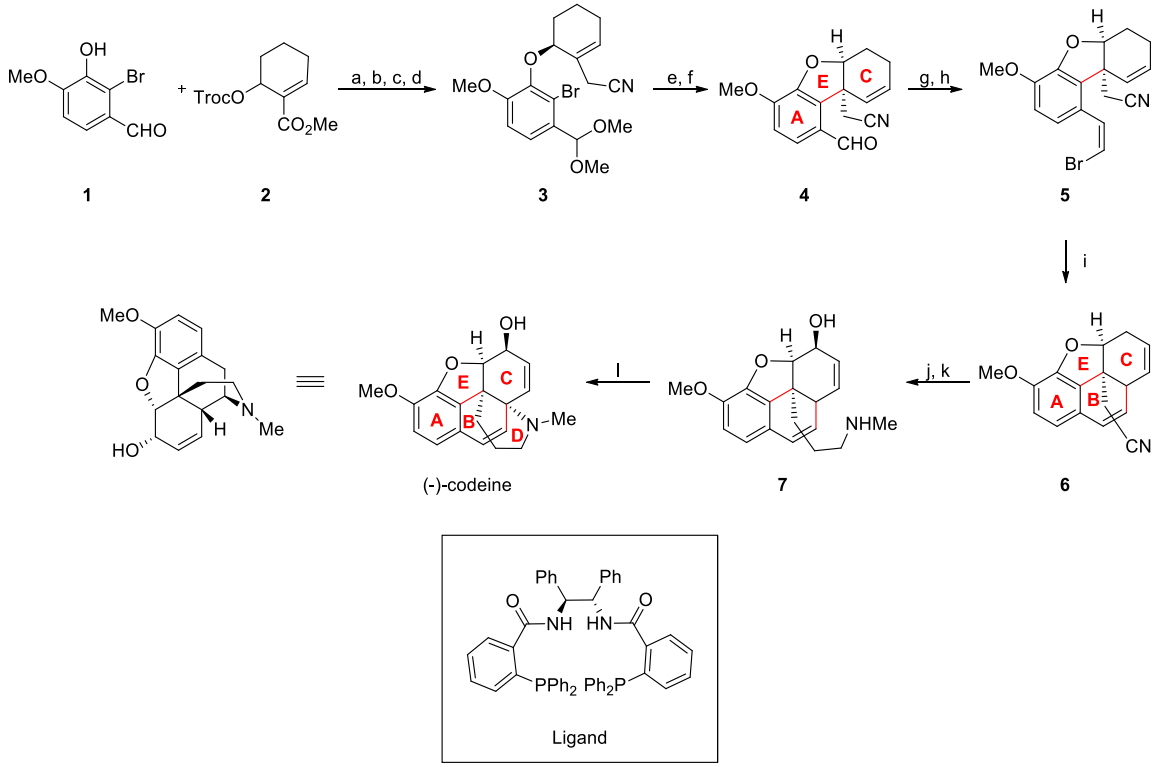
In this report, four total synthesis have been selected in order to highlight the diversity of synthetic plans for the preparation of the morphine scaffold: Trost's total synthesis of (-)-codeine, Parker's total synthesis of racemic dihydroisocodeine, White's synthesis of (+)-morphine and Opatz's total synthesis of (-)-dihydrocodeine.

I.3.1.1 Trost – Intramolecular Heck

Trost's enantioselective route to (-)-codeine is a 12-step synthesis, which gave the desired opiate in 6% overall yield. The synthesis is described below. Starting from bromovanillin **1** and the allylic ester **2**, rings A, E and C were connected after a six-step process involving a palladium-catalysed asymmetric allylic alkylation followed by protection of the aldehyde, reduction of the ester and Mitsunobu-type transformation to give the nitrile **3**. After deprotection of the acetal, an intramolecular Heck reaction afforded the tricyclic core AEC (*Scheme I.1*).[23,24] After converting the aldehyde **4** into the bromoalkene **5**, a second Heck reaction created the B ring. After allylic oxidation, a sequence of reduction-transamination-reduction converted the nitrile **6** to the secondary amine **7**. Visible light promoted

hydroamination provided (-)-codeine, which can be converted into (-)-morphine in one deprotection step.[25]

The key transformations in this synthesis are the two Heck reactions which allow the assembly of four of the five rings. Moreover, the hydroamination step permitted the formation of the fifth ring.



Scheme I.1: Trost total synthesis of (-)-codeine

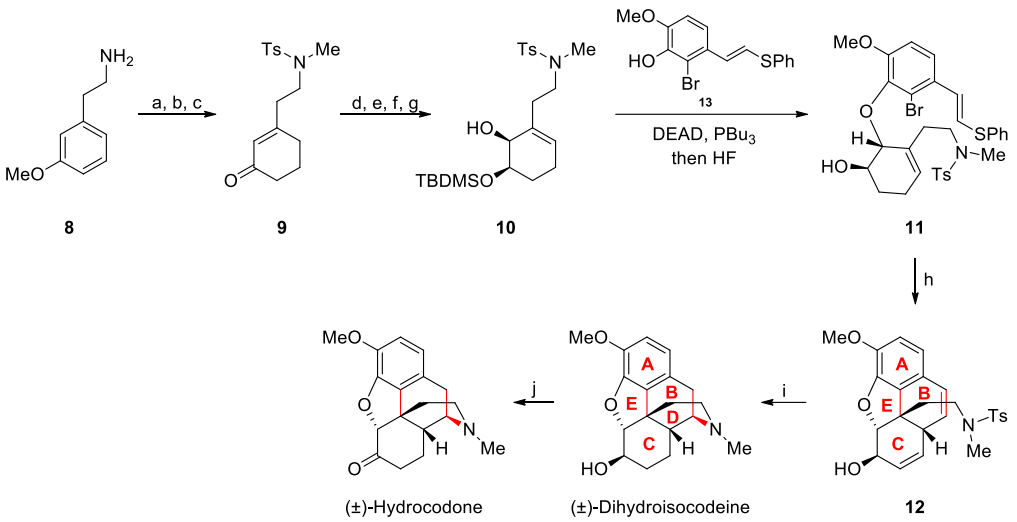
Reagents and conditions: a) $[\eta^3\text{-}C_3H_3PdCl]_2$, ligand, Et_3N, DCM, rt. b) TsOH, $CH(OMe)_3$, MeOH. c) Dibal-H, PhMe, -78 °C. d) Acetone cyanohydrin, PPh_3, DIAD, Et_2O. e) TsOH, THF/H_2O. f) $Pd(OAc)_2$, dppp, Ag_2CO_3, PhMe, 107 °C, 44% (6 steps). g) CBr_4, PPh_3, DCM, 91%. h) $Pd(PPh_3)_4$, *n*Bu_3SnH, PhMe, 88%. i) $Pd(OAc)_2$, dppp, Ag_2CO_3, PhMe, 65%. j) SeO_2, dioxane, sand, 75 °C then DMP, rt, 58%. k) Dibal-H, DCM/Et_2O then NH_4Br, $MeNH_2$ then, $NaBH_4$, 89%. l) LDA/THF, tungsten bulb, 57%.

I.3.1.2 Parker – Radical cyclisation

Parker's strategy is based on the formation of an aryl radical which would undergo a tandem cyclisation onto an alkene and therefore, bring together rings A, B, C and E.

The synthesis started with anisole **8** which was converted into allyl alcohol **10** in 7 steps (*Scheme I.2*): Reduction of the anisole moiety into a conjugated enol ether (which gave the corresponding ketone after keto-enol tautomerization), tosylation and methylation of the amine provided the α,β-unsaturated ketone **9**. Luche reduction, epoxidation of the alkene followed by regioselective isomerisation and protection gave the allylic alcohol **10**. Mitsunobu coupling with compound **13**

afforded the radical precursor **11**. Treatment with Bu_3SnH and AIBN gave the tetracyclic compound **12** which, after reductive detosylation, provided (±)-dihydroisocodeine.[26,27]

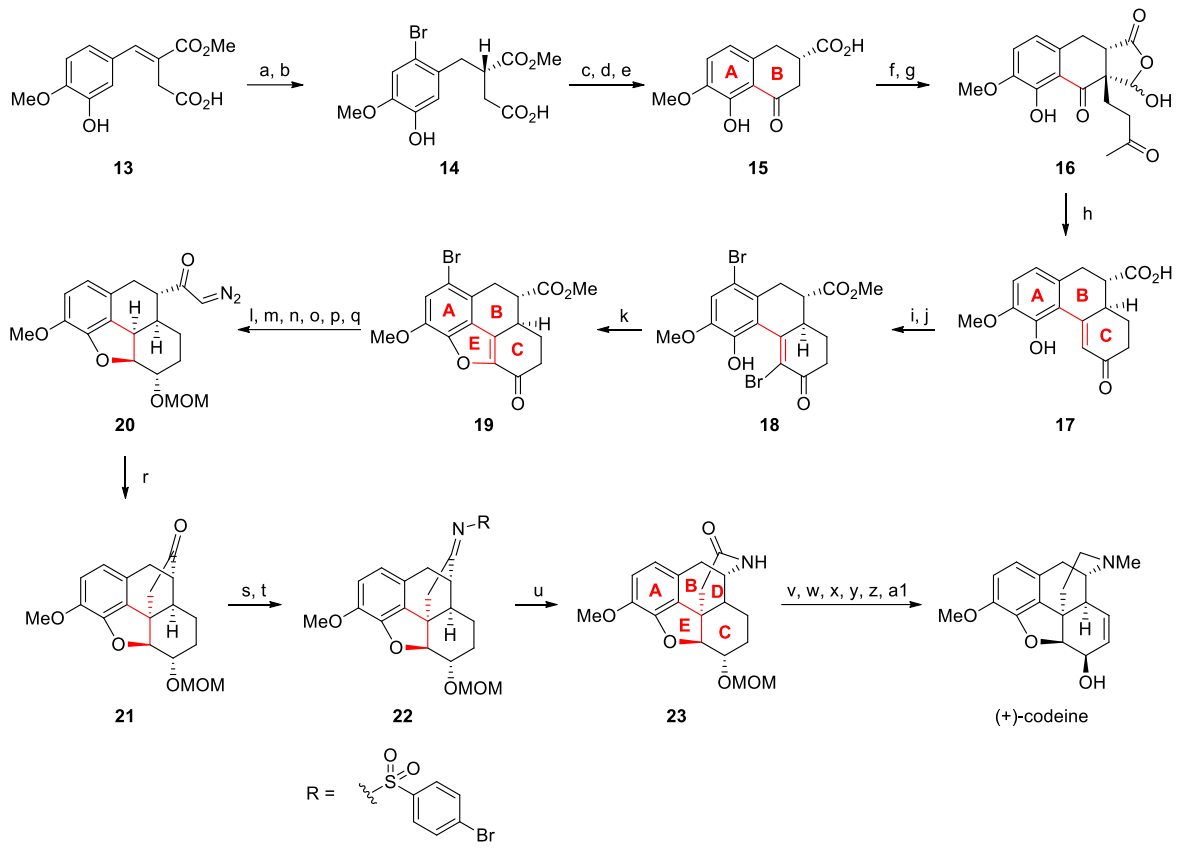


Scheme I.2: Parker formal synthesis of (±)-dihydroisocodeine

Reagents and conditions: a) Li/NH_3, *t*BuOH, -68 °C, 97%. b) TsCl, Et_3N, THF then 1M HCl, 81%. c) MeI, K_2CO_3, acetone, 96%. d) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 97%. e) *m*CPBA, DCM, 0 °C, 92%. f) Ti(O*i*Pr)$_4$, C_6H_6, 70 °C, 85%. g) TBDMSOTf, DIPEA, -78 °C, 82%. h) *n*Bu_3SnH, AIBN, C_6H_6, 130 °C, 35%. i) Li/NH_3, *t*BuOH, THF, -78 °C, 85%. j) $(COCl)_2$, DMSO, Et_3N, 0 °C to rt, 83%.

I.3.1.3 White – C-H insertion

White's asymmetric synthesis of the unnatural enantiomer (+)-morphine (*Scheme I.3*) relies on an asymmetric hydrogenation of alkene **13** and bromination to afford compound **14** in 93% yield and 94% ee. The presence of a bromide on the aromatic ring prevents cyclisation at this position. Intramolecular Friedel-Crafts acylation gave tetralone **15** (rings A and B). Treatment with methyl formate followed by methyl vinyl ketone produced lactol **16** which, under basic conditions, underwent a Robinson annulation to form ring C (compound **17**). Esterification and bromination afforded dibromophenantrenone **18** which, after treatment with DBU, closed ring E and gave tetracyclic compound **19**. Transformation of ester **19** to diazoketone **20** set the stage for the key C-H insertion, which allowed the formation of pentacyclic compound **21**. Oxime formation followed by Beckmann rearrangement gave the lactam **23**. Alkylation of the nitrogen, formation of an α,β-unsaturated ketone followed by reduction of both ketone and amide produced (+)-codeine which can then be demethylated using a known procedure to give (+)-morphine.[28]



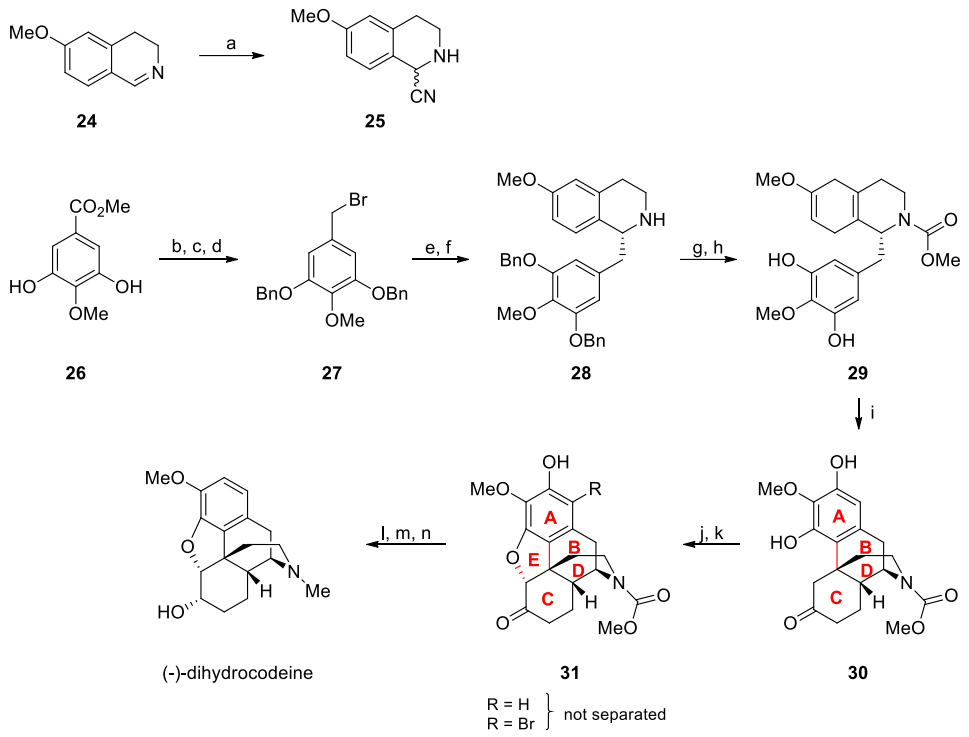
Scheme I.3: White's synthesis of (+)-codeine

Reagents and conditions: a) H_2, $[Rh(cod)Cl]_2$, (4*R*, 5*R*)-(-)-MOP-DIOP, 100%, 94% ee. b) Br_2, AcOH, 93%. c) MsOH, P_2O_5, 75%. d) H_2, Pd/C, $NaHCO_3$, 100%. e) LiOH, THF/H_2O, 100%. f) KH, HCO_2Me, DME, 0 °C, 85%. g) MVK, Et_3N, DCM, 95%. h) NaOH, H_2O/THF, 95%. i) CH_2N_2, Et_2O/DCM, 99%. j) Br_2, $NaHCO_3$, DCM, 80%. k) DBU, C_6H_6, 50 °C, 90%. l) $NaBH_4$, *i*PrOH/DCM, 99%. m) H_2, Pd/C, MeOH, 78%. n) $CH_2(OMe)_2$, P_2O_5, $CHCl_3$, 80%. o) LiOH, THF/H_2O, 99%. p) $(COCl)_2$, C_6H_6. q) CH_2N_2, 63%. r) $Rh_2(OAc)_4$, DCM, 50%. s) $NH_2OH.HCl$, NaOAc, MeOH, 90%. t) *p*-$BrC_6H_4SO_2Cl$, Et_3N. u) AcOH, rt, 62% (2 steps). v) NaH, MeI, C_6H_6, 95%. w) HBr, MeCN, 96%. x) DMP, $CHCl_3$, 99%. y) PhSeCl, MsOH, DCM. z) $NaIO_4$, 65% (2 steps). a1) $LiAlH_4$, THF, 90%.

I.3.1.4 Opatz – Grewe cyclisation

The enantioselective synthesis of (-)-dihydrocodeine (and the formal synthesis of (-)-thebaine, (-)-codeine and (-)-morphine) by Opatz is an 11 steps synthesis from the commercial dihydroisoquinoline **24**.[29] It involves a Noyori asymmetric transfer hydrogenation, which sets the stereochemistry at C1. The key step is a Grewe cyclisation which provides the morphinan skeleton (*Scheme I.4*).

The synthesis began with reaction of dihydroisoquinoline **24** with acetone cyanohydrin to give α-aminonitrile **25**. The ester **26** was converted into benzyl bromide **27** in a 3-step sequence: protection of the alcohols, reduction of the ester and bromination. α-Aminonitrile **25** was then alkylated with benzyl bromide **27**, subsequent asymmetric hydrogenation gave tetrahydroisoquinoline **28**. Alkoxycarbonylation of amine **28** followed by Birch reduction afforded carbamate **29** which, in the presence of acid, underwent a Grewe cyclisation. This step allowed the formation of the B ring in compound **30**. Bromination α to the ketone and subsequent basic treatment allowed the closure of ring E (compound **31**). Finally, reduction of the remaining phenol (transformed into a triflate) and reduction of the carbamate afforded (-)-dihydrocodeine. Those two compounds can be converted into (-)-codeine, (-)-morphine or (-)-thebaine using known procedures.[30–32]



Scheme I.4: Opatz's synthesis of dihydrocodeine

Reagents and conditions: a) acetone cyanohydrin, H_2O, rt, 92%. b) BnCl, K_2CO_3, DMF, 150 °C. c) $LiAlH_4$, THF, 60 °C, 91% (2 steps). d) NBS, PPh_3, THF, 0 °C to rt, 97%. e) **25**, KHMDS, THF, -78 °C to rt. f) RuCl[(S,S)-TsDPEN](*p*-cymene), HCO_2H/Et_3N 5:2, DMF, 0 °C, 68% (2 steps). g) $ClCO_2Me$, Et_3N, THF, quant. h) Li/NH_3, *t*BuOH, -78 °C. i) HCl/Et_2O, reflux, 88% (2 steps). j) $CuBr_2$, $CHCl_3$/EtOAc. k) 0.5 M NaOH, 93% (2 steps). l) Tf_2O, pyridine, 0 °C, 97%. m) $Pd(PPh_3)_4$, HCO_2H, Et_3N, DMF, 60 °C, 80%. n) Dibal-H, THF, 0 °C to rt, 81%.

I.3.2 Semi-synthesis of opiates

The semi-synthesis of morphine derivatives has been widely published and patented. The most common opiates (oxycodone, oxymorphone, hydrocodone, hydromorphone, buprenorphine) are prepared from thebaine, oripavine or morphine, extracted from the opium poppy straw. Several patents use oripavine as the starting material for the synthesis of hydromorphone, oxymorphone and noroxymorphone, whereas thebaine can be used for the synthesis of codeine, hydrocodone and oxycodone. But both thebaine and oripavine are suitable for the synthesis of those compounds and *N*-alkyl noroxymorphones such as naloxone and naltrexone, or buprenorphine.

The preparation of these compounds requires *O*-demethylation of thebaine, oxidation of position 14, hydrolysis of the enol ether to a ketone, *N*-demethylation and alkylation. Furthermore, most reported syntheses of buprenorphine engage the diene moiety of thebaine/oripavine in a Diels-Alder reaction. These key transformations will be discussed.

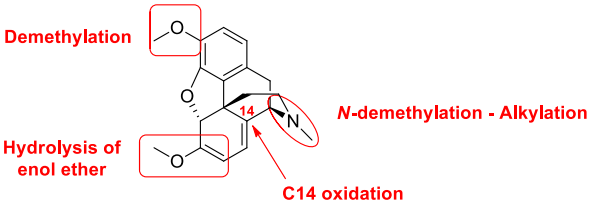
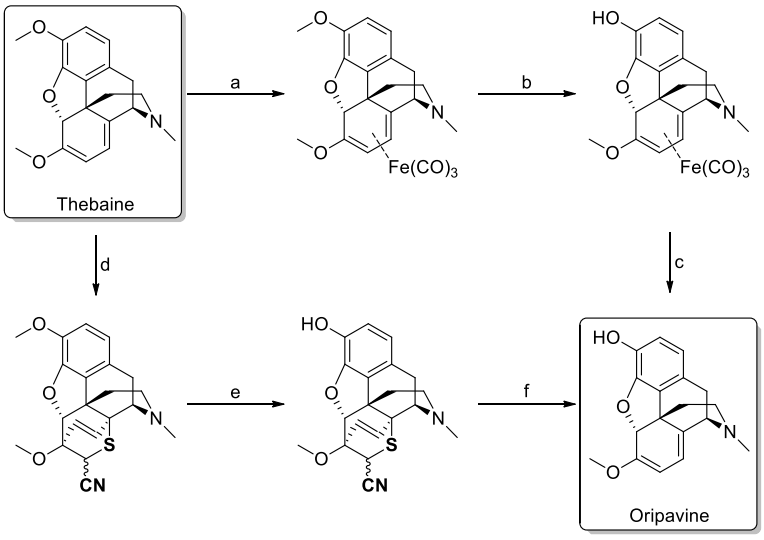


Figure I.6: Key transformations of thebaine in the semi-synthesis of opiates

I.3.2.1 *O-Demethylation*

The semi-synthesis of morphine derivatives from thebaine requires *O*-demethylation methods. However, this reaction is challenging, as the conjugated enol ether moiety is sensitive to most deprotection methods. Hudlicky reported the deprotection of the methyl ether of thebaine to oripavine, for the semi-synthesis of hydromorphone, after protecting the diene moiety as an iron tricarbonyl complex, following chemistry developed by Birch.[33] The use of iron (0) pentacarbonyl, under UV irradiation, modifies the reactivity of the diene and allows the use of reagents such as BBr_3 or $MeSO_3H$ to obtain the free phenol. Removal of the iron tricarbonyl complex by UV irradiation gave oripavine in a moderate 35% yield.[34] Another strategy is the protection of the diene as a bicyclic dihydrothiopyran-Diels-Alder adduct.[35] Thermal retro-Diels-Alder or oxidation of the sulfide to sulfoxide and subsequent elimination gave oripavine in 65% and 78% respectively (*Scheme I.5*). Oripavine was then converted into hydromorphone in a four-step sequence.

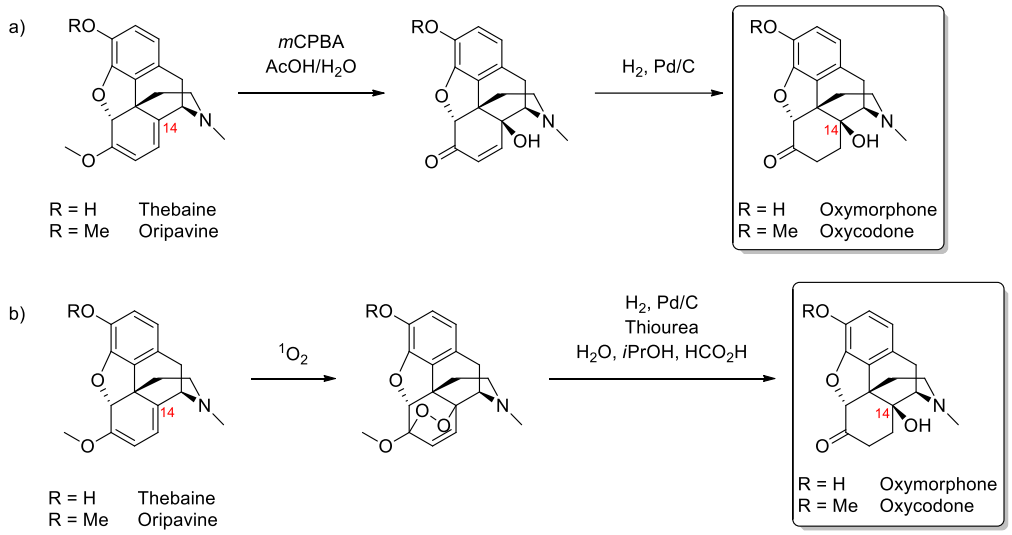


Scheme I.5: Hudlicky approach for the deprotection of thebaine

Reagents and conditions: a) $Fe(CO)_5$, UV, PhH, Quant. b) BBr_3, DCM, 0 °C, 83% *or* $BF_3.SMe_2$, DCM, 0 °C, 83% *or* $MeSO_3H$, methionine, 50 °C, 67% *or* 9-I-9-BBN, DCM, rt, 70%. c) UV, MeCN, 40 °C, 35%. d) Sodium S-(cyanomethyl)-sulfothioate, $CaCl_2$, Et_3N, PhH/MeOH, rt, 80 °C. e) BBr_3, DCM, 0 °C, 85% *or* $BF_3.SMe_2$, DCM, 0 °C, 50% *or* $MeSO_3H$, methionine, 50 °C, 51% *or* 9-I-9-BBN, DCM, rt, 72%. f) 2,3-Dimethylbutadiene, DMSO, 75 °C, 65% *or* *m*CPBA, DCM, rt then EtOH, reflux, 78%.

I.3.2.2 C14-Oxidation

The C14 oxidation of thebaine or oripavine have been reported by Lutz and Small[36] and more recently by Huang for the synthesis of oxymorphone from oripavine.[37] The use of peroxide or peracids in order to generate 14-hydroxymorphinone proceeds via epoxidation of the remote olefin, followed by hydrolysis to give the α,β-unsaturated ketone. The reduction of the double bond gives rise to oxymorphone (*Scheme I.6a*). Another reported method consists of reacting the diene with a source of singlet oxygen under irradiation with UV light, which gives an endoperoxide which is then hydrogenated to give oxycodone or oxymorphone, if the starting material is thebaine or oripavine (*Scheme I.6b*).[38]

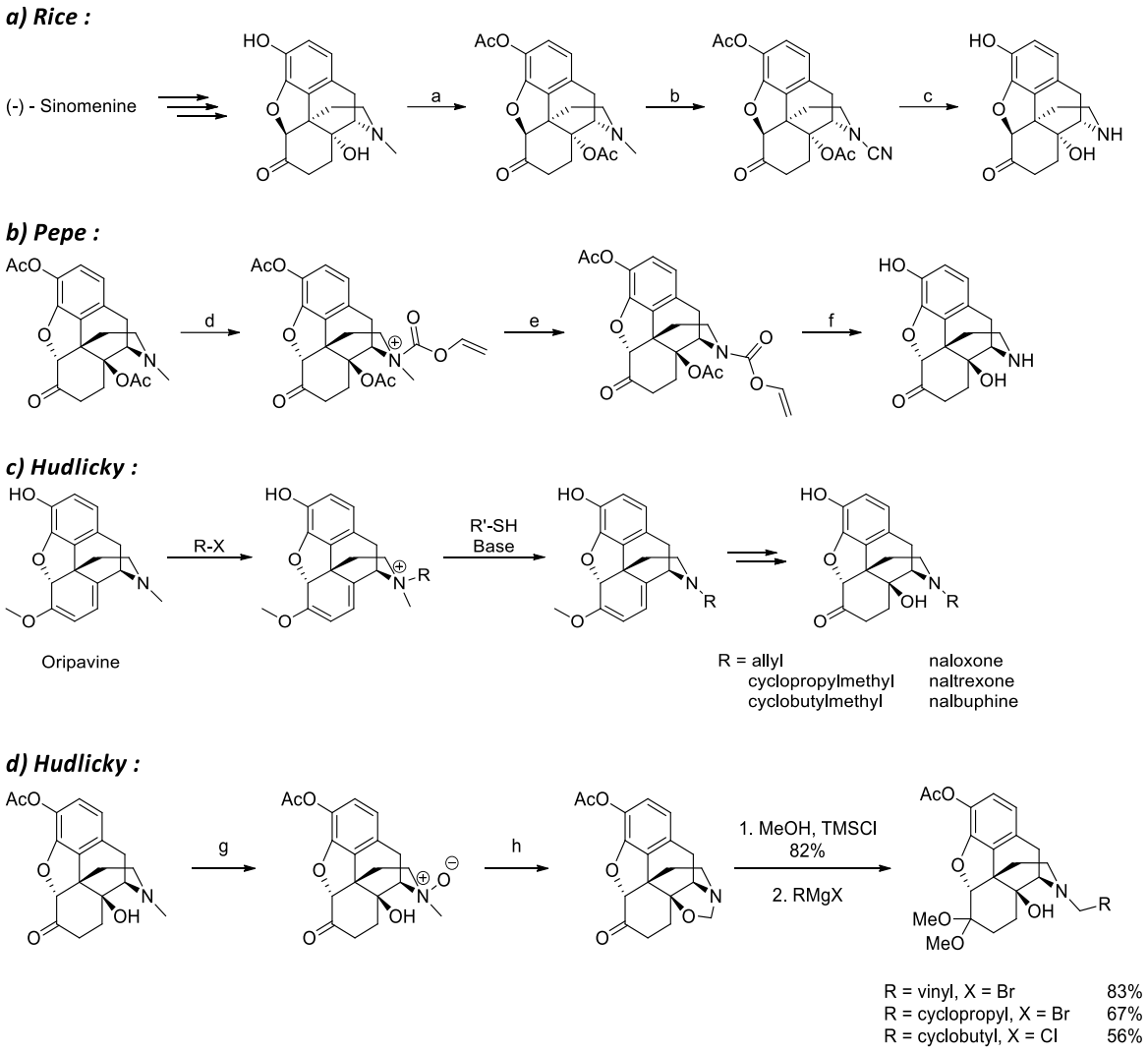


Scheme I.6: C14 oxidation

I.3.2.3 N-Demethylation

Naloxone, naltrexone and nalbuphine are oxymorphone derivatives, with different alkyl groups at the nitrogen in place of the methyl substituent (allyl, cyclopropylmethyl and cyclobutylmethyl, respectively). Therefore, the preparation of these compounds requires a *N*-demethylation step. Rice reported the synthesis of (+)-naloxone from (-)-sinomenine. This strategy relies on an actual demethylation step using cyanogen bromide to form a cyanamide (known as the von Braun reaction). The cyanamide is then hydrolysed in acidic conditions to release the secondary amine (*Scheme I.7*).[39,40] Alternatively, Pepe and Hudlicky have shown that demethylation of the ammonium salt is feasible upon heating or in the presence of a soft nucleophile. Indeed, an ammonium salt is formed when reacting vinyl chloroformate with 3,14-diacetyloxymorphone in refluxing DCE. The methyl group is then displaced by the chloride atom. The products from the reaction are methyl chloride and a vinyl

carbamate. Hydrolysis gives the secondary amine as a hydrochloride salt.[41,42] On the other hand, Hudlicky demonstrated that the *N*-alkylation of oripavine with different alkyl halides gives the corresponding ammonium salts. In the presence of a thiolate, the ammonium loses the methyl group to give the corresponding tertiary amine. As described above, *N*-alkyl nororipavine can then be oxidised by *m*CPBA or another peracid to give the desired *N*-alkyl opiate (*Scheme I.7*). This strategy was applied for the synthesis of various *N*-alkyl noroxymorphones such as naltrexone and nalbuphone.[38,43] Furthermore, Hudlicky has also shown that oxymorphone *N*-oxide reacts with Burgess reagent. The intermediate iminium ion is trapped to form an oxazolidine which then reacts with a Grignard to give the corresponding opiate (*Scheme I.7*).[44,45]



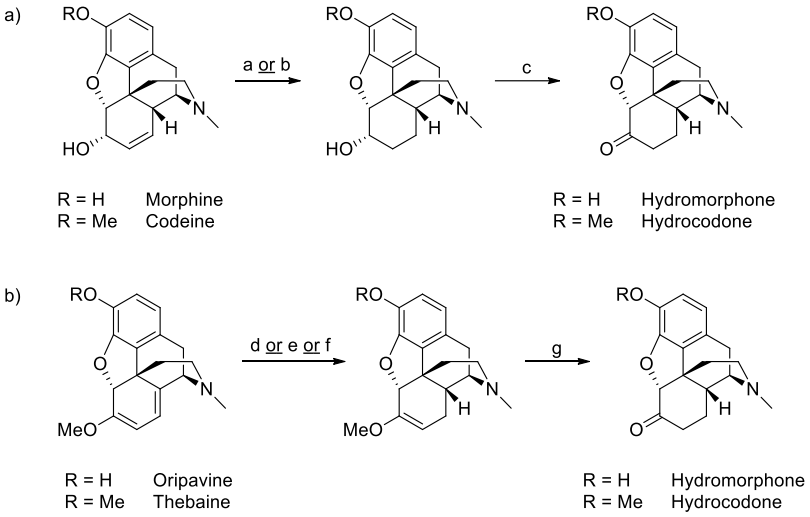
Scheme I.7: N-Demethylation of (+)-oxycodone

Reagents and conditions: a) Ac_2O, 100 °C, 90%. b) CNBr, $CHCl_3$ reflux, 91%. c) H_2SO_4 reflux, 95%. d) vinyl chloroformate, DCE. e) DCE, reflux. f) HCl, DCM then H_2SO_4, reflux, 98% overall yield. g) *m*CPBA, DCM, 0 °C. h) Burgess reagent, DCM, -20 °C to rt, 78% overall yield.

I.3.2.4 Reduction of the C ring: Hydrocodone and hydromorphone

Probably the most straightforward way to prepare hydrocodone and hydromorphone is to reduce codeine and morphine. This strategy was published by Rapoport in 1950; hydrogenation of morphine and codeine followed by Oppenauer oxidation gave hydromorphone and hydrocodone respectively (*Scheme I.8a*).[30,46]

The semi-synthesis of hydrocodone from thebaine as a starting material was patented in 1974. It involves the thermal decomposition of sulfonic acid hydrazides to diimide and sulfonic acid. In the presence of thebaine, diimide, a powerful reducing agent, will reduce the C8-C14 double bond to give 8,14-dihydrothebaine, which is then hydrolysed in the presence of acid to give hydrocodone (*Scheme I.8b*).[47] This strategy was also applied for the semi-synthesis of hydromorphone from oripavine.[48]



Scheme I.8: Synthesis of hydromorphone and hydrocodone

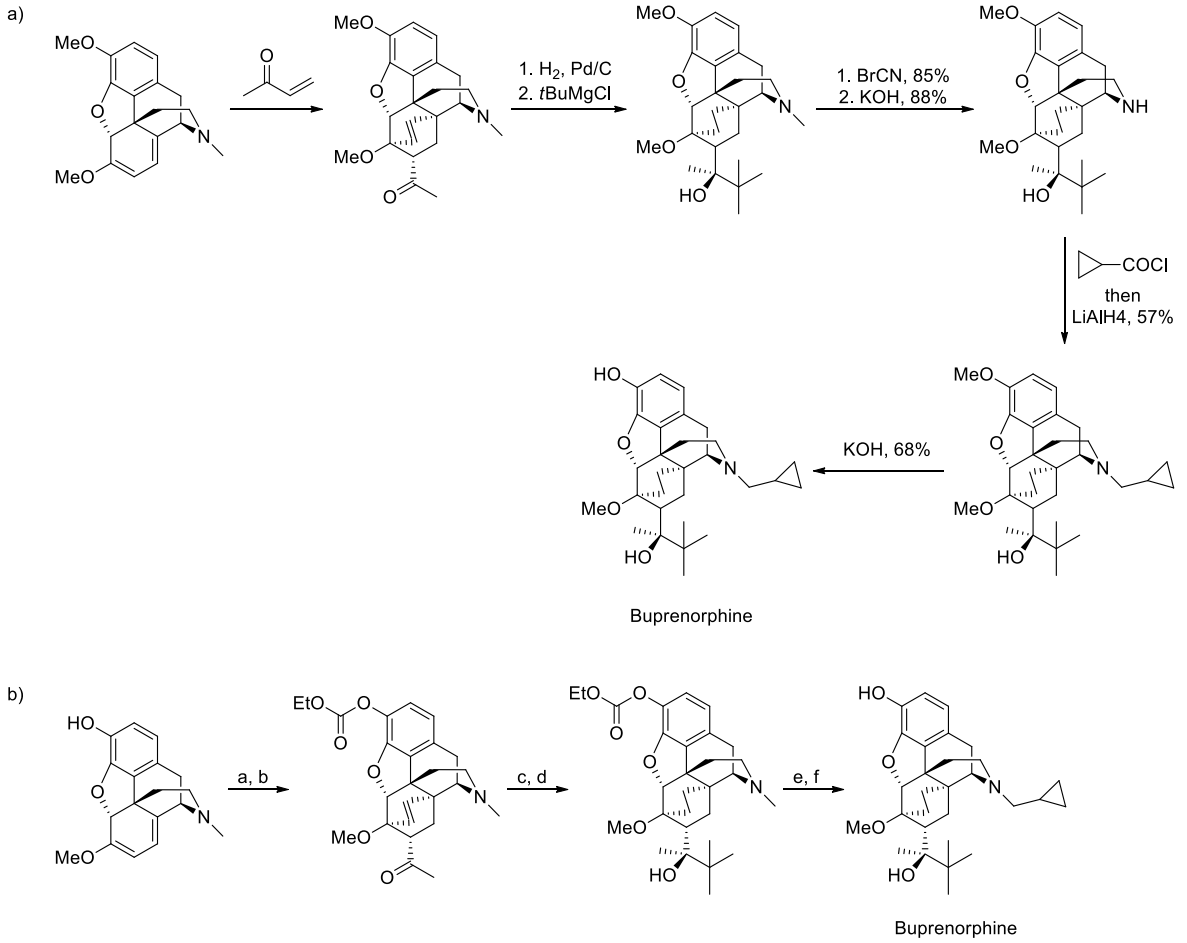
Reagents and conditions: a) H_2, Pd/C, EtOAc, 99%. b) H_2, Pd/Ba_2SO_4, AcOH, 97%. c) *t*BuOK, Ph_2CO, PhH, reflux, 71% to 99%. d) 2-methoxyethanol, ethanolamine, *p*-$TolSO_2NHNH_2$, reflux, 93%. e) *p*-$TolSO_2NHNH_2$, morpholine, reflux, 72%. f) *p*-$TolSO_2NHNH_2$, NaOH, H_2O/tBuOH 9.5:1, reflux, 87%. g) Aq. HCl, reflux, 82% to 88%.

I.3.2.5 Cycloaddition of thebaine and oripavine: Semi-synthesis of buprenorphine

Buprenorphine is a potent analgesic used for the management of post-operative pain.[49] Its synthesis is quite well established: Diels-Alder cycloaddition between thebaine and methyl vinyl ketone gives the hexacyclic buprenorphine scaffold. After reduction of the alkene of the Diels-Alder adduct, addition of a Grignard reagent on the ketone gives the tertiary alcohol in position 6. *N*-demethylation and alkylation afford buprenorphine (*Scheme I.9a*).[50]

Hudlicky and co-workers have reported an improved synthesis of buprenorphine that uses oripavine as a starting material, and avoids the use of cyanogen bromide. As mentioned earlier, alkylation of the

tertiary amine followed by treatment of the ammonium salt with a nucleophile (such as thiolate) demethylate the nitrogen to give the new tertiary amine (*Scheme I.7d*). Later, they published another synthesis of buprenorphine, avoiding the use of cyanogen bromide for the demethylation step. This new synthesis involves a transition-metal catalysed *N*-demethylation/acylation process (*Scheme I.9b*).[38,51,52]



Scheme I.9: Synthesis of buprenorphine

Reagents and conditions: a) $(EtO_2C)_2O$, DMAP, DCM, rt, 81%. b) MVK/H_2O 4:1, 80 °C, 81%. c) H_2, Pd/C, H_2O, tartaric acid, 80 °C, 84%. d) *t*BuMgCl, PhMe, rt, 71%. e) cyclopropane carboxylic acid anhydride, $Pd(OAc)_2$, $Cu(OAc)_2$, dioxane, 80 °C, 80%. f) Red-Al, THF, 80 °C, 81%.

I.4. Functionalisation of opiate ligands

Although morphine and its derivatives are efficient analgesics, as stated earlier, the administration of opiates induces severe side effects including respiratory depression, somnolence, nausea, and lead to tolerance and dependence. Therefore, there has been significant effort expended on the functionalisation of opiates to uncover medicines that are efficient for pain treatment, but that show reduced side effects. In order to reduce or supress the induced side effects, morphine derivatives with increased hydrophilicity have been designed to prevent the opioid crossing the blood-brain barrier that should block or attenuate access to the central nervous system.

4,5-Epoxymorphinans have several chemically interesting positions (highlighted in *Figure I.7*) that could be exploited in terms of derivatisation. Position 3 is a phenolic hydroxyl group (or a methoxy group in the case of thebaine or codeine). The transformation of a hydroxyl group into the corresponding ether is a simple procedure, moreover these ethers can be cleaved using Lewis or Brønsted acids, as described earlier. Position 5 is situated between an ether and a ketone, which makes this position difficult to functionalise, although methylation at position 5 has been reported. Moreover, the ketone in position 6 can be modified in a range of ways. Finally, the tertiary alcohol at C14, despite being congested, can be functionalised. Examples of the derivatisation of opiates are given in this chapter.

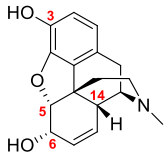
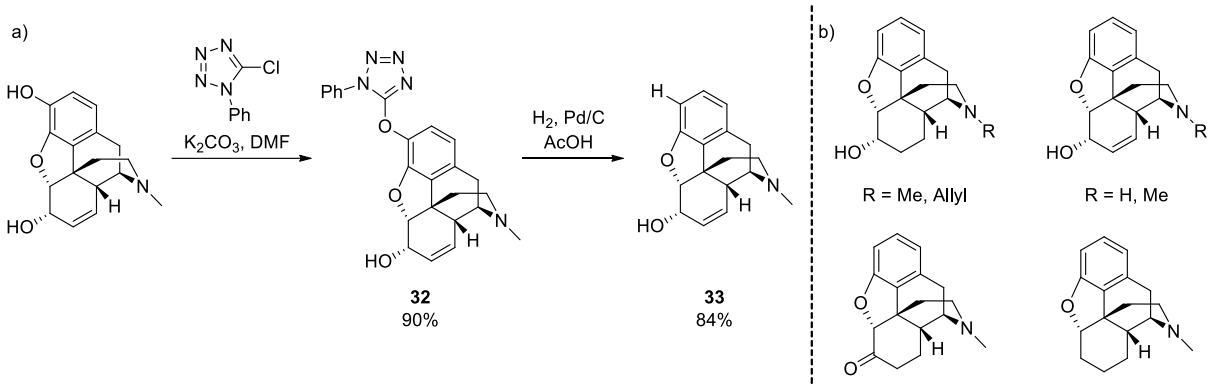


Figure I.7: Key positions for derivatisation (highlighted on morphine)

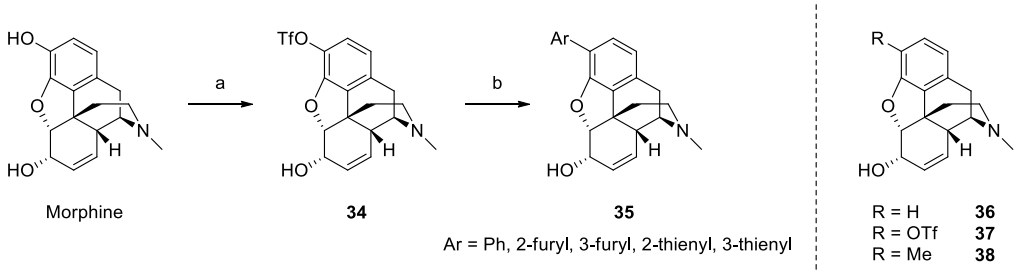
I.4.1 Functionalisation of opioid ligands in position 3

The strong biological activity of morphine is due in part to the presence of the phenolic 3-hydroxyl group, which facilitates the binding to the receptor by hydrogen bonding.[53] Studies have been undertaken in order to confirm the important role of the 3-hydroxyl group of morphine by comparison of the activities of the parent compound and the corresponding 3-deoxy derivatives.[54] 3-Deoxymorphine **33** is easily obtained in two steps from morphine, by hydrogenolysis of the corresponding tetrazolyl ether **32** (*Scheme I.10a*). Reden and co-workers synthesized several 3-deoxymorphine derivatives (*Scheme I.10b*) and tested their biological activity. They showed that the presence of the 3-hydroxyl group in the morphine series plays an important role in binding to the receptor, but not necessarily in the antinociception activity.[54]



Scheme I.10: Synthesis of 3-deoxydihydromorphine

Following on from this work, the 3-hydroxyl group was replaced by other functional groups, in order to compare the biological properties. Accordingly, a series of morphine derivatives have been synthesized, bearing aliphatic, aromatic or heteroaromatic groups at position 3 (*Scheme I.11*).[55]



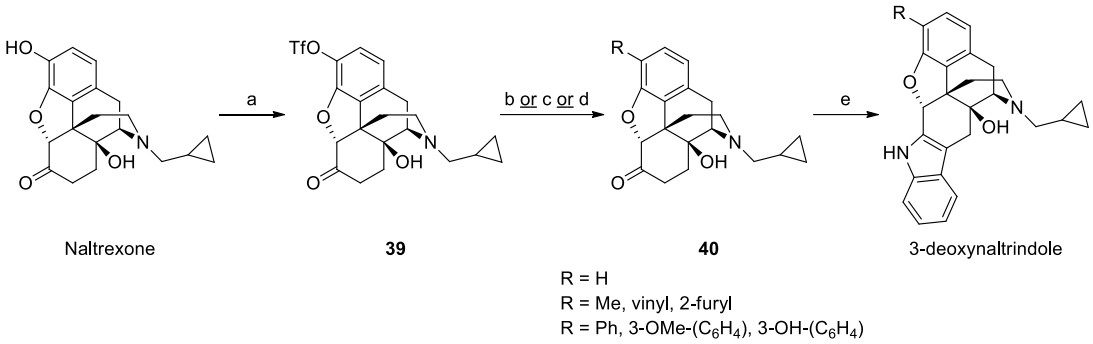
Scheme I.11: Synthesis of 3-arylmorphine and 3-acylmorphine

Reagents and conditions: a) $PhN(OTf)_2$, Et_3N, DCM, rt, 90%. b) $Ar(BOH)_2$, $Pd(PPh_3)_4$, LiCl, Na_2CO_3, EtOH, DME, 53-89%.

3-Arylmorphine analogues were synthesized by Suzuki cross-coupling. These compounds were tested for μ, κ and δ-opioid receptor affinity, as well as the 3-deoxy compound **36**, the triflate **37** and methyl derivative **38** (prepared according to a reported procedure[56]). Unfortunately, these compounds were found to be less potent than morphine. This result shows that the 3-hydroxyl group is essential for affinity to the receptor.

Modification in position 3 has been reported on other opiate derivatives. For example, the strategies described above were used on naltrexone in order to obtain naltrindole derivatives, modified in position 3 of the morphinan-6-one moiety (*Scheme I.12*).[57] These modifications were detrimental for both affinity to the μ or δ receptors and the selectivity μ/δ. This decrease of activity might be due to

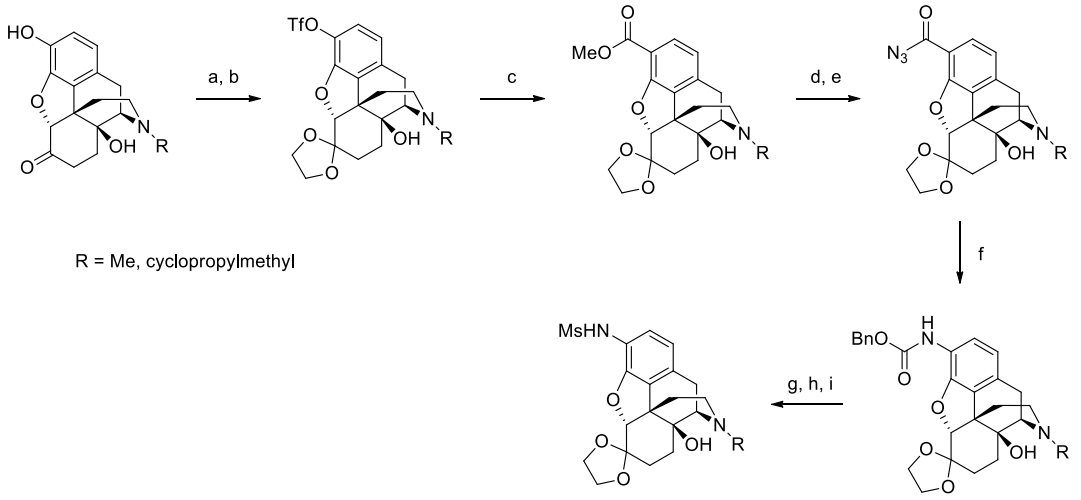
steric hindrance, or the inability for the compound to create hydrogen bonding in the receptor, compared to naltrindole (R = OH).



Scheme I.12: Synthesis of 3-deoxynaltrindole derivatives

Reagents and conditions: a) Tf_2O, Et_3N, DCM, 0 °C, 76%. b) *n*Bu_3N, HCO_2H, $Pd(PPh_3)_2Cl_2$, dppp, DMF, 80 °C, 68%. c) Me_4Sn or $RSnBu_3$, $Pd(PPh_3)_2Cl_2$, LiCl, PPh_3, DMF, 120 °C, 39-83%. d) $ArB(OH)_2$, $Pd(PPh_3)_4$, LiCl, Na_2CO_3, EtOH, DME, reflux, 80-85%. e) $PhNHNH_2$.HCl, *p*TsOH.H_2O, EtOH, reflux, 22-72%.

In 2000, Portoghese and co-workers synthesized naltrexone and oxymorphone derivatives in order to study the bioisosterism of the hydroxyl group and a sulfonamide (*Scheme I.13*).[58] The synthesis of the corresponding sulfonamide from naltrexone and oxymorphone is a nine-step sequence. After protection of the C-6 ketone, the free 3-OH was turned into a triflate. The intermediate was then transformed into an ester which was converted to a hydrazide. The hydrazide was oxidized to the corresponding acyl azide which underwent a Curtius rearrangement to provide the benzylcarbamate product. The benzylcarbamate was subjected to catalytic hydrogenolysis to give the corresponding aniline, which was converted into the sulfonamide (*Scheme I.13*).

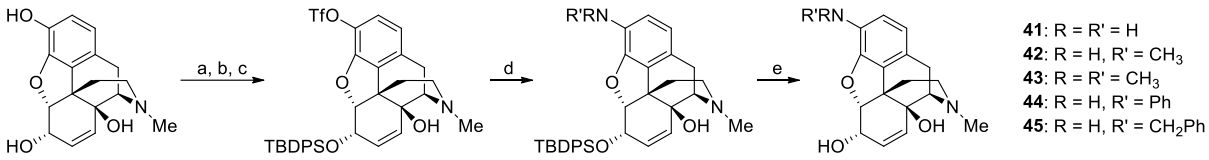


Scheme I.13: Synthesis of sulfonamide from naltrexone and oxymorphone

Conditions: a) Ethylene glycol, *p*TsOH. b) $PhNTf_2$, Et_3N. c) $Pd(OAc)_2$, dppf, CO. d) N_2H_4. e) HCl, *t*$BuNO_2$. f) $PhCH_2OH$. g) H_2, Pd/C. h) MsCl, Et_3N. i) HCl.

The underlying hypothesis was that changing the phenol to an alternative functional group that had a similar acidity would maintain the biological activity. Unfortunately, they did not observe any binding between the ligand and the receptor in the case of naltrexone or oxymorphone analogues, probably because of the steric hindrance of the sulfonamide.

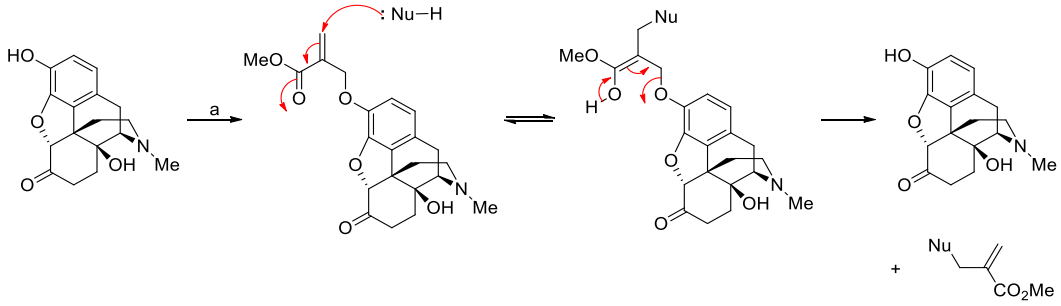
The hydroxyl group has also been subjected to diverse transformations in order to obtain amines. As for the previous example, the aim was to compare the biological activity to morphine.[59] To do so, the phenolic hydroxyl group was transformed into the corresponding triflate after protection and deprotection steps. The triflate was then subjected to palladium-catalysed Buchwald-Hartwig amination.[60,61] Five compounds have been synthesized using this method (*Scheme I.14*). The affinity of these compounds for the three receptors μ, δ and κ were measured and compared to that of morphine. The affinity of compounds **45**, **41**, **44** and **42** for the μ receptor was found to be 30 to 60-fold less than morphine (morphine μ receptor: K_i = 0.88 nM). However, their affinity for the μ receptor was still good: K_i values were 33, 53, 59 and 63 nM, respectively. Compound **43**, although 12-fold less active towards κ receptor (K_i = 290 nM) than morphine (K_i = 24 nM), had the best affinity for this receptor amongst the analogues. Concerning the δ receptor, compound **44** showed the strongest binding (K_i = 1500 nM), compared to the other amino derivatives, even if the affinity was 10-fold less than morphine (K_i= 140 nM). Overall, the general trend for these compounds was that they were less potent than morphine in terms of affinity to the receptors. The selectivity of the 3-amino derivatives for binding to the three opioid receptors has also been investigated. In all cases, the selectivity was found to decrease in the order: μ > κ > δ.



Scheme I.14: Pd-catalyzed amination

Reagents and conditions: a) TBDPSCl, imidazole, DCM, quant. b) 0.25eq. TBAF, THF, H_2O, 84%. c) Tf_2O, pyridine, DCM, quant. d) Pd_2dba_3/dppf or $Pd(OAc)_2$/BINAP, RR'NH, NaO*t*Bu, PhMe, 80 °C, 26-84%. e) 1.5eq. TBAF, THF/H_2O, 79-96%.

Another example of modification in position 3 of epoxymorphinans is the transformation of the hydroxyl group into carbomethoxyallyl ether (*Scheme I.15*).[62] This transformation was carried out under phase-transfer conditions. Unfortunately, this type of derivative may not be stable because of the possible nucleophilic attack on the double bond, which can regenerate the starting phenol.



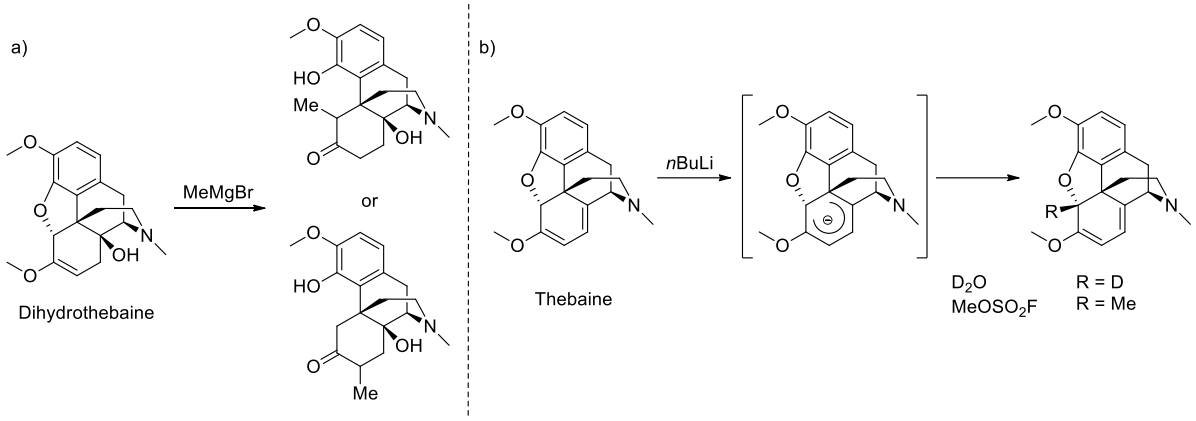
Scheme I.15: Formation of carbomethoxyallyl ether of oxymorphone and hydrolysis

Reagents and conditions: a) Methyl 2-(bromomethyl)acrylate, TBABr, NaOH, DCM/H_2O

Carbomethoxyallyl ether of several 4,5-epoxymorphinans (e.g. oxymorphone, naltrexone and naloxone) were synthesized in order to compare the biological activity with the parent compound. These were found to be two-fold less potent than the parent compound. Moreover, the stability of naltrexone 3-carbomethoxyallyl ether only was tested. This compound is not stable under thermal conditions.

I.4.2 Functionalisation of opioid ligands in position 5

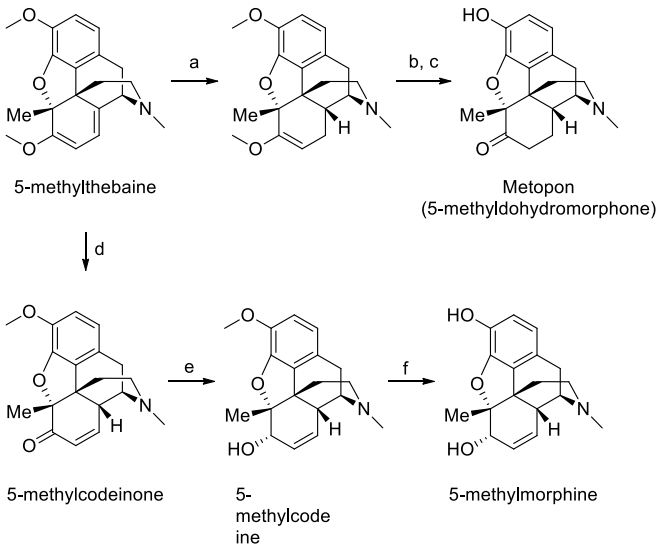
Alkylation in position 5 has been studied by Small and co-workers. They reported the preparation of thebaine derivatives bearing a methyl group in position 5. However, they noticed that the addition of methylmagnesium bromide on dihydrothebaine led to the ring-opening of the 4,5-epoxy bridge (*Scheme I.16a*).[63,64]



Scheme I.16**:** a) Grignard addition to dihydrothebaine. b) Preparation of 5-methylthebaine.

Boden and co-workers explored the treatment of thebaine with *n*-butyllithium at -78 °C and quenching with deuterium oxide. Under these conditions, the proton in position 5 was replaced by a deuterium. When the anion is treated with methyl fluorosulfonate, 5-methylthebaine was obtained (*Scheme I.16b*) and no ring opening was observed.[65]

This procedure was then used for the synthesis of metopon (5-methyldihydromorphone, *scheme I.17*), which has been administered as an analgesic. Its duration of action is longer than hydromorphone and it induces less severe side effects than morphine. Its synthesis is a three-step process from 5-methylthebaine: hydrogenation produces 5-methyldihydrothebaine, which is hydrolysed to 5-methyldihydrocodeinone after acidic treatment. The last step is the deprotection of the 3-methyl ether using HBr or sodium thioethoxide (*Scheme I.17*).



Scheme I.17: Synthesis of Metopon and related compounds

Reagents and conditions: a) H_2, Pd/C. b) HCl. c) HBr or NaSEt. d) $Hg(OAc)_2$. e) $NaBH_4$. f) NaSEt.

The synthesis of 5-methylthebaine led to an interest in accessing further related compounds. The treatment of 5-methylthebaine with mercury acetate gave 5-methylcodeinone, as shown by Dauben and co-workers.[66] The reduction of this compound generated 5-methylcodeine, which could be demethylated in position 3 to afford 5-methylmorphine (*Scheme I.17*). Biological tests on 5-methylcodeine and 5-methylmorphine revealed that these compounds may be more active than morphine and codeine.[67]

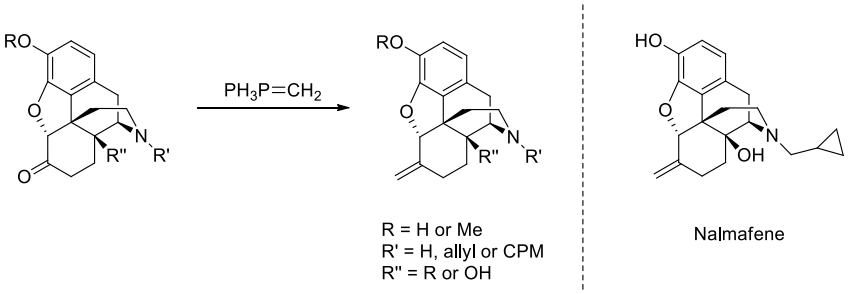
I.4.3 Functionalization of opioid ligands in position 6

The presence of the ketone at C6 allows several transformations of the 4,5-epoxymorphinan skeleton to be undertaken at this site. Some of the 6-modified opiate derivatives have interesting biological activity and are used in therapy for the treatment of narcotic addiction. The functionalization of position 6 is a well-established route to analogue generation. Some examples are described below.

I.4.3.4 Methylene substitution

The preparation of 6-methylene-6-desoxymorphine and codeine has been reported by Rapoport and co-workers.[68] The ketone can be transformed into a methylene group by treatment with triphenylphosphinemethylene, in a Wittig reaction (*Scheme I.18*).

6-Methylene derivatives of naloxone, naltrexone, oxymorphone and oxycodone have also been synthesized using this procedure.[69] Nalmafene (*Scheme I.18*) has been authorized in Japan for the treatment of opioid side effects, such as respiratory depression.[70]



Scheme I.18**:** Formation of the 6-methylene derivatives

I.4.3.2 Amino substitution

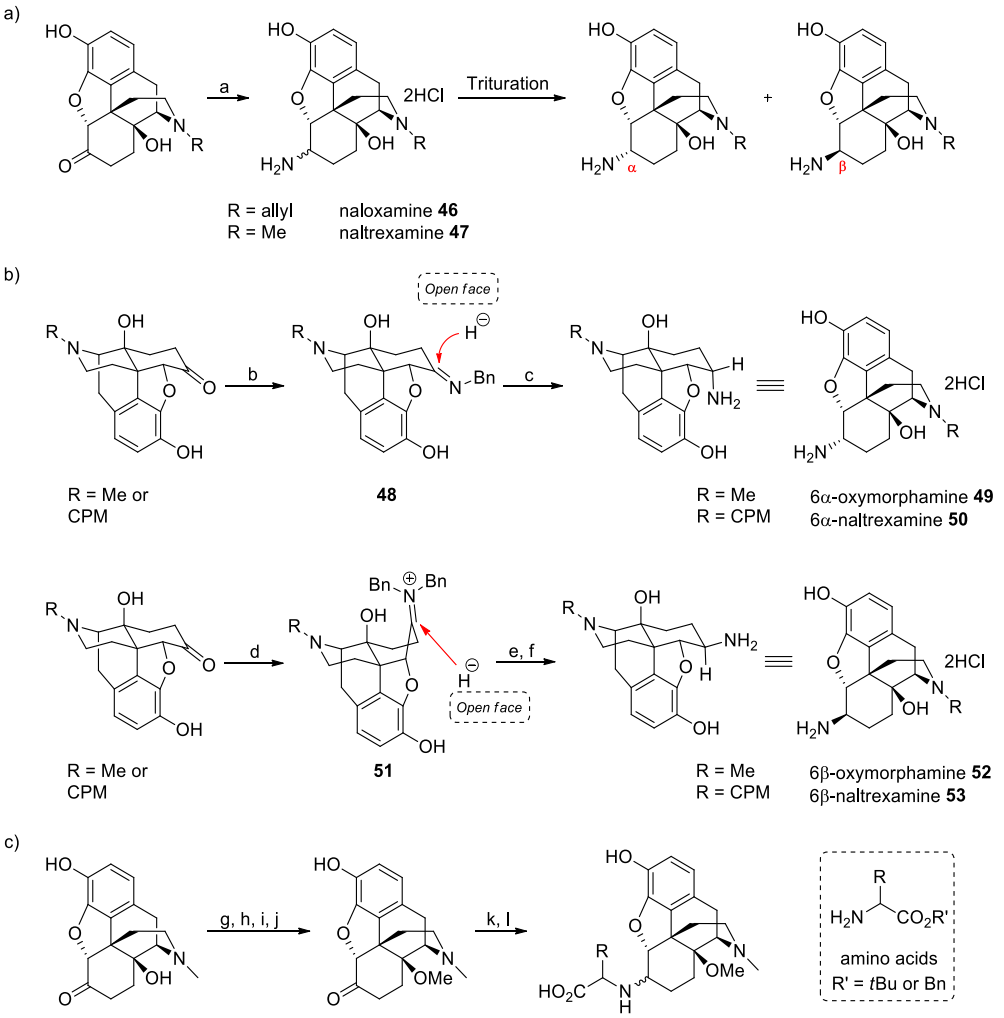
6-Amino derivatives of naloxone and naltrexone are known to have relatively modest antagonist activity against the effects of morphine. However, it has been shown that naloxamines 6α-**46** and 6β-**47** have a longer duration of action than naloxone, and could be good candidates for long-acting

antagonists.[71] 6-Amino-naloxone and -naltrexone have been prepared by reductive amination of the parent compound, and the two epimers 6α and 6β have been obtained in a 2:1 mixture, and separated by trituration (*Scheme I.19a*).

The 6-amino derivatives of naltrexone and oxymorphone have been synthesized stereoselectively by Portoghese and co-workers. 6α-Oxymorphamine **49** and 6α-naltrexamine **50** were prepared by reductive amination of oxymorphone or naltrexone using benzylamine and sodium borohydride as the reducing agent. 6β Amines however (compounds **52** and **53**), required the formation of the dibenzyliminium **51** followed by reduction with sodium cyanoborohydride (*Scheme I.19b)*.[72]

The stereoselectivity of the reaction is dictated by the steric hindrance of the α and β faces: attack of the imine **48** by a hydride occurs on the β face, which is the most accessible, and therefore, affords 6α amines. The formation of the 6β-amines, however, proceeds via a dibenzyliminium ion **51**. The C ring sits then in a boat conformation to avoid steric hindrance between the oxygen (ring E) and the benzyl group. The α face becomes the most accessible. Attack of the iminium by the hydride gives the 6β-amines (*Scheme I.19b*).

More recently, Schmidhammer reported the synthesis of a library of compounds derived from oxymorphone, containing an amine functionality at C6. These compounds are prepared by reductive amination of the starting ketone with various amino acids (*Scheme I.19c*). The two epimers from the reductive amination step were separated by MPLC (medium-pressure liquid chromatography), which allowed the preparation of 80 compounds in total. Both natural and unnatural amino acids were used, along with dipeptides. The R group contains alcohol, amine, amide, ester functionalities, as well as alkyl and aryl moieties (phenyl, indole).[73,74]

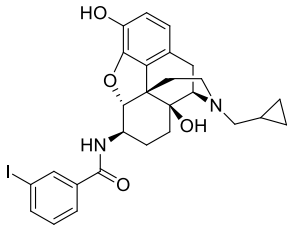


Scheme I.19

Reagents and conditions: a) NH_4OAc, $NaBH_3CN$, MeOH then HCl. b) $BnNH_2$, cat. *p*TsOH, C_6H_6, reflux, Dean-Stark then $NaBH_4$, EtOH. c) H_2, Pd/C, HCl, MeOH, 57-76% (2 steps). d) $PhCO_2Ag$, $MeOH/H_2O$, 40 °C then $PhCO_2H$, Bn_2NH, cat. *p*TsOH, PhMe, reflux, Dean-Stark. e) $NaBH_3CN$, EtOH, 3Å MS, 60-75% (2 steps). f) H_2, Pd/C, HCl, MeOH, 95%. g) BnBr, K_2CO_3, DMF, 83%. h) NaH, Me_2SO_4, DMF, 0 °C to RT, 80%. i) HCl, MeOH, reflux, then HBr, 68%. j) H_2, Pd/C, MeOH, 91%. k) Amino acid, $NaBH_3CN$, MeOH. l) HCl, Dioxane, 38-98% (2 steps).

I.4.3.3 Amide substitution

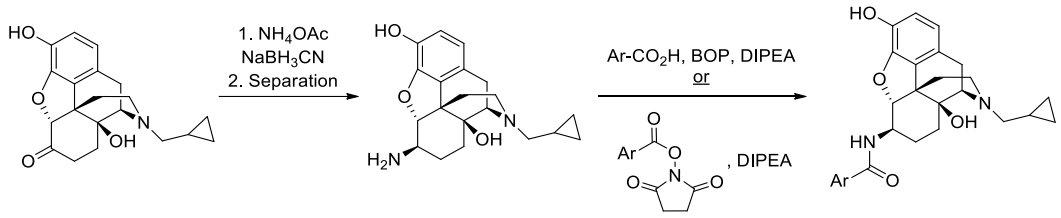
The synthesis of amide-substituted opiate analogues has been dominated by benzamide derivatives. Pasternak and co-workers developed a 6-amido naltrexone derivative IBNtxA **54** which shows 10 fold greater activity than morphine in terms of antinociceptive properties, and does not have the associated side effects (*Figure I.8*).[75]



IBNtxa **54**

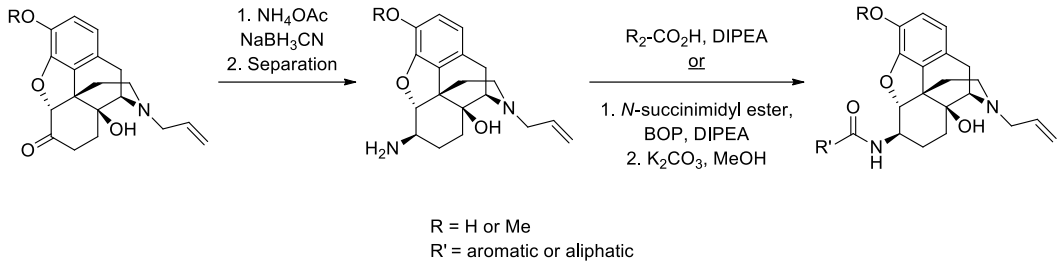
Figure I.8: Structure of IBNtxA

The synthesis of 6-amido-substituted opiates involves a two-step procedure. The first step consists of a reductive amination of the ketone which generates two epimers (6α/6β 2:1) of the amino opiate. These diastereomers are separated, as only the β epimer has good affinity for the receptor. The amino opiate is then condensed with the corresponding carboxylic acid in the presence of a coupling agent (such as BOP). An alternative route to these amides consists of the conversion of a carboxylic acid into the corresponding *N*-succinimidyl ester, using *N*-hydroxysuccinimide and DCC. The activated ester can be added to the 6-amino opiate in order to obtain the corresponding amide (*Scheme I.20*).[76,77]



Scheme I.20**:** Synthesis of 6-amido opiates

In order to determine the structure-activity relationship of IBNtxA-type drugs in the opioid series, amide derivatives of naloxone or naloxone-3-methyl ether have been prepared (*Scheme I.21*).[78] The R' group is a phenyl group substituted with halogens, electron-donating groups or electron-withdrawing groups, naphthalene and aliphatic group such as *n*-hexyl or cyclohexyl.

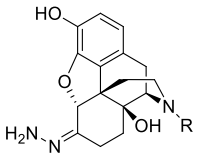


Scheme I.21: Synthesis of 6-amido naloxone derivatives

As 6-amido naltrexone derivative IBNtxA is a potent antagonist of the opioid receptor, Ghirmai and co-workers reported the preparation of different amides of the naltrexone skeleton, in which the amide is aromatic, heteroaromatic or a carbohydrate derivative.[79] The procedure for the synthesis of the amine group was slightly different from the method described previously. Specifically, the reduction of the corresponding oxime to amine was used instead of reductive amination.

I.4.3.4 Other substitution

The synthesis of naloxazone, naltrexazone and oxymorphazone (*Figure I.9*) has been reported by Pasternak and co-workers.[80] These compounds were obtained by treating naloxone, naltrexone and oxymorphone with anhydrous hydrazine.



Naloxazone	R = allyl
Naltrexazone	R = CPM
Oxymorphazone	R = Me

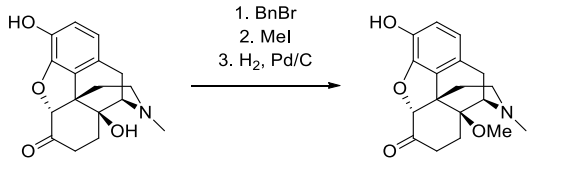
Figure I.9: Structure of hydrazones

Some biological results of oxime, semicarbazones and azines of epoxymorphinans have been reported, although the syntheses of these compounds have not been reported.[81–83]

I.4.4 Functionalisation of opioid ligands in position 14

I.4.4.1 14-Alkoxy substitution

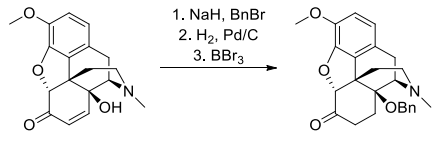
In their investigations of a new and potent opioid analgesic, Schmidhammer and co-workers were interested in the biological properties of 14-substituted derivatives of oxymorphone.[84] Indeed, they found that 14-methoxymorphone has a greater affinity for the three receptors, compared to morphine and oxymorphone. However, these derivatives were found to display side-effects, just like morphine.
The synthesis of 14-methoxymorphone starts from oxymorphone, which was first benzylated in position 3, then alkylated in position 14 using methyl iodide or dimethyl sulfate in the presence of sodium hydride.[85,86] This intermediate was then hydrogenated to provide 14-methoxymorphone (*Scheme I.22*).



Oxymorphone 14-O-methyloxymorphone

Scheme I.22: Synthesis of 14-*O*-methyloxymorphone

During the investigation on 14-alkoxymorphinans, 14-benzyloxymorphone was found to have a similar affinity to the μ receptor, compared to 14-methoxymorphone, and a lower affinity to the κ and δ receptors. However, 14-benzyloxymorphone was found to induce fewer side effects than 14-methoxymorphone, oxymorphone and morphine.
14-Benzyloxymorphone is prepared in three steps from 14-hydroxycodeinone (*Scheme I.23*). The starting material was 14-*O*-benzylated, then catalytic hydrogenation of the 7-8 double bond afforded 14-*O*-benzyloxycodone. The 3-methyl ether was removed using boron tribromide to give 14-*O*-benzyloxymorphone.[84]

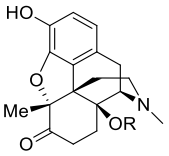


14-hydroxycodeinone 14-O-benzyloxymorphone

Scheme I.23: Synthesis of 14-*O*-benzyloxymorphone

In the metopon series, the 14-methoxy derivative (*Figure I.8*) has similar affinity for μ receptor, and affinity for κ and δ which is slightly better than 14-methoxymorphone. Moreover, the antinociception property of this compound is enhanced.

14-Arylalkyl metapons have also been developed by Schmidhammer and co-workers (*Figure I.10*). It was shown that for 14-benzyloxymetapon, the affinity of the ligand for κ and δ receptors is increased.



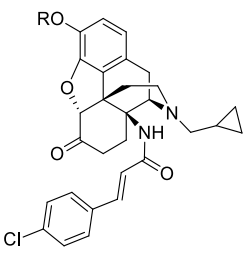
R = Me 14-methoxymetopon
R = Bn 14-benzyloxymetopon

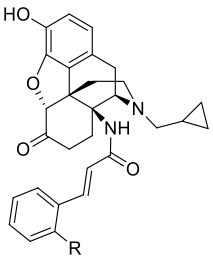
Figure I.10**:** Synthesis of 14-alkoxymetopon

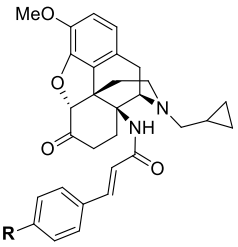
I.4.4.2. 14-amido substitution

In the past few decades, clocinnamox (C-CAM, compound **55**) and methoclocinnamox (MC-CAM, compound **56**) (*Figure I.11*) were found to be as potent as morphine or buprenorphine. C-CAM has μ-antagonist properties, and no agonist activity. MC-CAM has a partial μ-agonist activity. Because of its long duration of action, MC-CAM is called a pseudo-irreversible agonist.

In order to investigate the importance of the substitution pattern of the cinnamoyl ring, 2'-methyl **57**, 2'-chloro **58**, 4'-fluoro **59** and 4'-nitro **60** have been prepared and tested for biological activity (*Figure I.9*).[87]







R = H Clocinnamox (C-CAM) **55**
R = Me Methoclocinnamox (MC-CAM) **56**

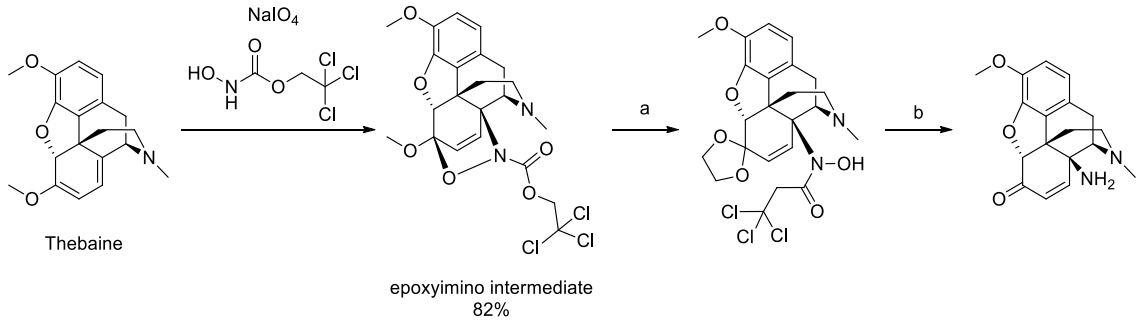
R = Me **57**
R = Cl **58**

R = F **59**
R = NO_2 **60**

Figure I.11

It has been shown that these four compounds have a potent agonist effect, better than morphine. However, 4'-nitro derivative seems to be a short term agonist.[88]

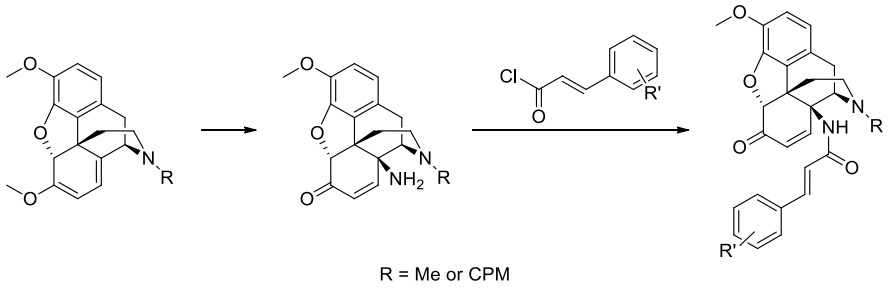
The synthesis of such compounds starts with the transformation of thebaine into 14β-aminocodeinone, using the method developed by Kirby and McLean, as described in *scheme I.24*.[89] Thebaine reacts with 2,2,2-trichloroethyl *N*-hydroxycarbamate in the presence of sodium periodate to give an epoxyimino intermediate. This intermediate is then converted to an acetal, using hydrochloric acid in dry ethylene glycol. Reduction of the *N*-hydroxycarbamate using zinc and ammonium chloride, followed by hydrolysis of the acetal gave 14β-aminocodeinone.



Scheme I.24: Synthesis of 14-aminocodeinone

Conditions: a) HCl, ethylene glycol, 95%. b) Zn, NH_4Cl then HCl, MeOH, 64% (2 steps).

14-Aminoepoxymorphinan can then, be transformed into the corresponding cinnamoyl amide by reaction with the corresponding cinnamoyl chloride (*Scheme I.25*).



Scheme I.25: Synthesis of 14-cinnamoyl amides

I.5 Treatment of opioid addiction

The different transformations described above are an attempt to respond to the need of analgesics with the potency of morphine, but without the induced side effects such as sedation, respiratory depression, tolerance and addiction. The increase of opioid use in the past few years then results in the increase of the number of deaths due respiratory issues in an overdosing individual.
According to a report from the World Health Organisation, in 2016, 27 million people suffered from opioid disorder, and more than 63,000 deaths have been observed in the US due to opioid overdoses.

In the 1970s, a treatment for the opioid disorder management known as OMT (opioid maintenance treatment) or MMT (methadone management treatment) was introduced in the US and in Australia and it still applies to heroin or opioid dependant patients. In the case of heroin-dependant patients, this treatment consists of substituting the heroin by methadone, or another opioid agonist, in a controlled environment. Taken orally, methadone has a long duration of action and can eliminate the withdrawal symptoms for at least 24 h, and up to 36 h. At higher dose, methadone can efficiently reduce cravings and block the euphoric effects from injected heroin. Other opioid agonists can be used as an OMT; among them, buprenorphine is as effective as methadone, and decreases the withdrawal symptoms quicker, probably due to its mixed agonist-antagonist nature. However, there is still a risk of misuse of buprenorphine (or methadone in the case of MMT).[90] Suboxone®, a 4:1 mixture of buprenorphine and naloxone (see below), proved to be as effective as buprenorphine for OMT, as it presents less risk of diversion.[91]

Suboxone® is a combination treatment comprising Buprenorphine.HCl and Naloxone.HCl. It is an FDA approved drug for the treatment of opioid addiction. Existing formulations include sublingual tablet and film. Buprenorphine, a partial μ-agonist, has a strong binding affinity for the receptor, therefore it will displace other lower-binding opioids without activating the receptor to a comparable degree. Administration of buprenorphine to an opioid-dependant patient will cause a state of “precipitated withdrawal”, characterised by a rapid start of the withdrawal symptoms such as nausea, anxiety, tachycardia, etc. Because buprenorphine is less potent and the dissociation from the receptor is lower than in other agonists, opioid-dependant patients do not experience sedation and euphoria at the same rate as they would if they took another agonist. The role of naloxone in Suboxone® is to prevent the misuse of buprenorphine. Taken orally, naloxone (a non-selective antagonist at opioid receptors) has a lower availability but would still displace buprenorphine from the receptor if the latter was taken intravenously.

Aim of the project

This work, conducted in collaboration with Indivior UK Limited, is related to the study of the stability of the drug substance Suboxone®.

The purity criteria of an active pharmaceutical ingredient can be altered by environmental factors such as humidity, light or temperature, which might lead to the formation of impurities or degradation products.[92,93] The study of the stability of a drug product includes heating the product at high temperatures, exposition to acidic, basic or oxidative media: the utility of forced degradation is to understand the reactions (and their mechanisms) that produce degradation products. Long-term storage is another stage of the degradation study.

With regard to Suboxone®, analysis of the sublingual film highlighted that degradation of one of the active components naloxone appeared to take place during the casting of the film, and over time during storage. Analysis of a non-commercial heavily degraded sample of sublingual film showed the presence of several naloxone related impurities close or above the identification threshold defined by the ICH guidelines. Forced-degradation studies using metabisulfite, base, peroxide, radical initiators, etc, were attempted to generate the impurities. Accurate mass directed preparative HPLC would permit the isolation of small amount of each compound (between 10 and 20 µg) for extensive NMR studies. This method allowed the identification of 6 compounds: *impurities 2, 4, 7, 9, 10* and *11* (Compounds **II**, **IV**, **VII**, **IX**, **X**, **XI**, *Figure I.12*). The numbering of each impurity relates to the order in which the different peaks appear on the HPLC chromatogram.[94]

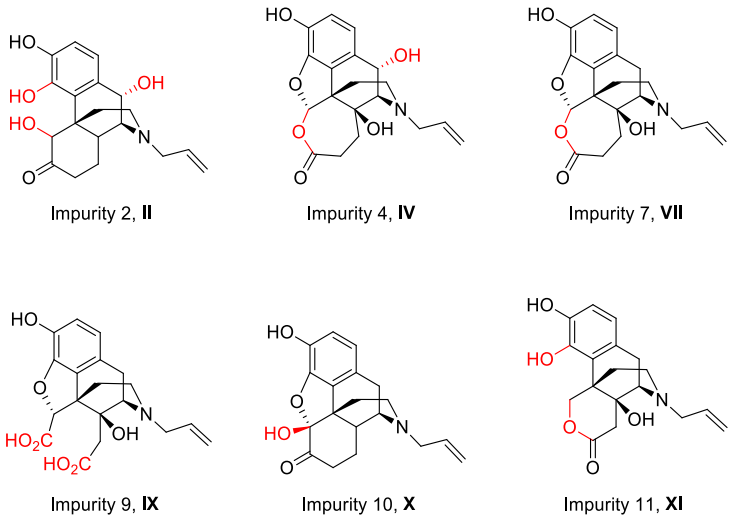


Figure I.10

Analysis of an aged film allowed *impurities 1* and *6* (Compounds **I** and **VI**, *Figure I.11*) to be isolated, as they were found to be present in the film in sufficient quantities. *Impurity 14* (Compound **XIV**) was recovered by applying an electrochemical current to an aqueous solution of naloxone. Interestingly, the analysis of the film at different time points identified the α-hydroxyketone **Va** as a potential intermediate in the formation of other degradants (*Figure I.11*). Indeed, the maximum concentration of this compound is reached at t= 3 weeks but it was found to significantly decrease by t=3 months.[94]

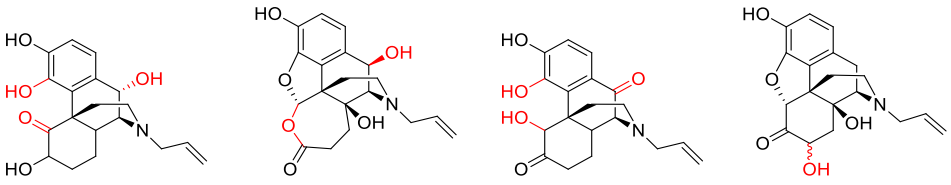


Figure I.12

The structure of some degradation products has been elucidated, and an authentic sample is available either because it has been synthesised or because the impurity has been isolated. This is the case for the benzylic alcohols and ketone **III**, **VIIIa** and **XIIa** (*impurities 3*, *8a*, *12a*), as well as secondary amine **V** (*Impurity 5*, noroxymorphone), *N*-oxide **XIII** and hydroxylamine ether **XV** (*Impurities 13* and *15*, *Table I.1*). For the rest of the degradants, a synthetic route is needed for the preparation of the impurities to confirm their structure and to provide a direct means for their access for HPLC assay purposes.

The main objective is to design synthetic routes for the synthesis of the impurities for which no authentic sample is available. This concerns *impurities 1*, *2*, *4*, *5a*, *6*, *7*, *9*, *10* and *11*. A procedure is available for the synthesis of *impurities 3* and *12a* however, the oxidation step proceeds to generate the benzylic alcohol in low yield.[95] An improved method is then needed in this instance.

The degradation products have been classified for clarity (*Table I.1*). This helped identifying the chemical transformations that will need to be done in order to access the impurities. The first category of compounds involves the oxidation at C5 (*impurity 10*), C10 (*impurities 3, 8a* and *12a*) or both C5 and C10 (*impurities 1* and *2*) with a cleavage of the E ring. The second class of impurities involves a benzylic oxidation (*impurities 4* and *6*) along with the expansion of the C ring. The next class concerns modification of the allylamine moiety: Deallylation to give noroxymorphone (*impurity 5*), 5-*exo* trig cyclisation to form the hexacyclic compound **XII** (*impurity 12*), oxidation of the nitrogen atom (*impurity 13*) and rearrangement to the hydroxylamine ether **XV** (*impurity 15*). This class of compounds will not be discussed in this report, as they have already been identified as naloxone-related impurities. The last three classes are made of one compound each: Ring opening of the C ring to provide *impurity 9*,

ring opening of the E ring and oxidation of the ketone (*impurity 11*) and finally, oxidation α to the ketone to give compound **Va**.

This report shows the investigations on the benzylic oxidation, cleavage of the E ring, expansion of the C ring and α-hydroxyketone formation. Moreover, the synthesis of the *impurity 9* will be reported.

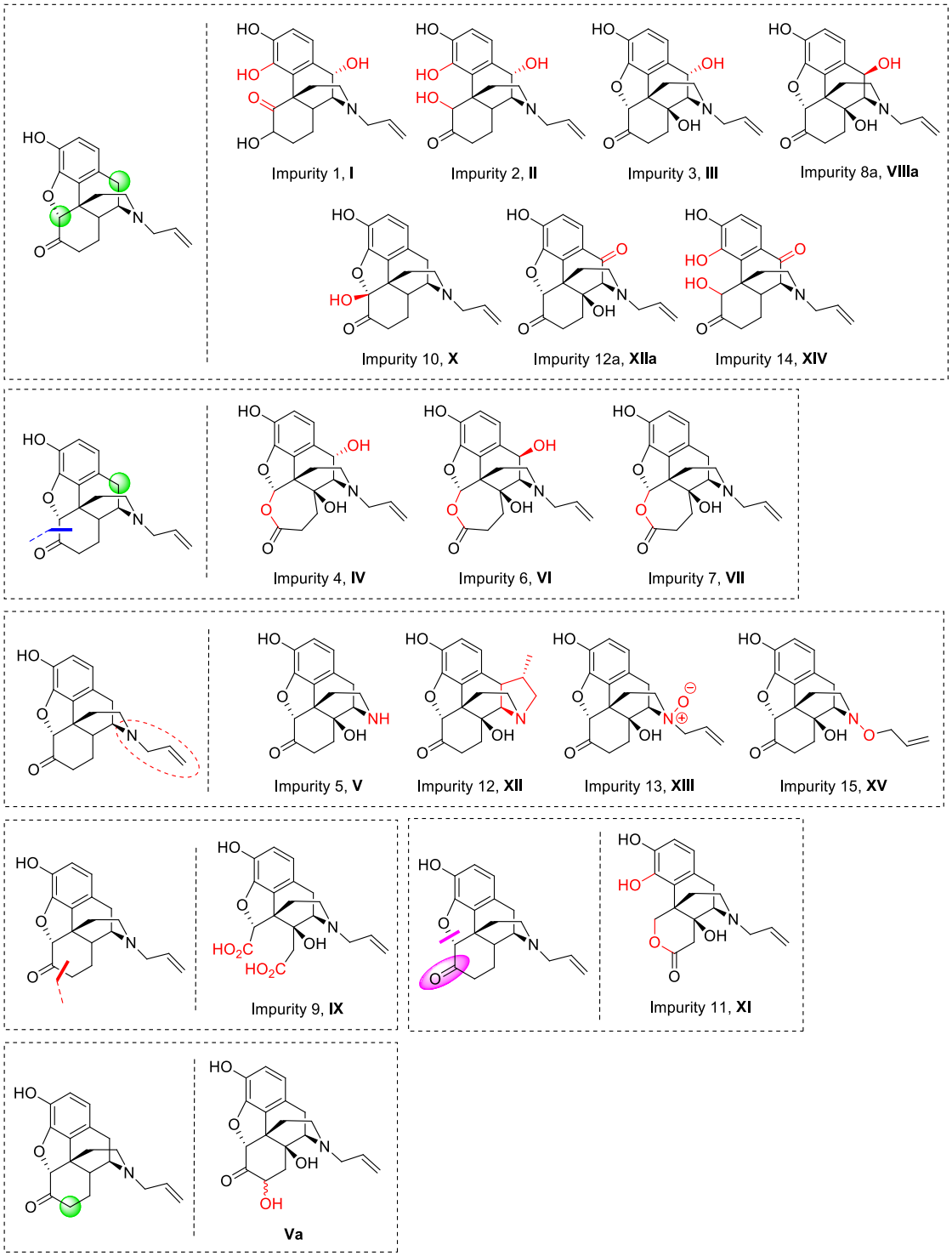


Table I.1: Classification of naloxone degradants

Chapter II: Benzylic oxidation of naloxone – Synthesis of *impurity 3*

The library of degradation products derived from naloxone shows a high degree of structural diversity. Therefore, deciding on a start point for our studies proved somewhat challenging. Fortuitously, the benzylic C10 oxidation of opioid skeleton has been reported previously in the literature, thus we decided to begin our investigation by preparing the benzylic alcohol **III** (*Figure II.1*). Furthermore, as this compound has already been identified as a degradant, this was a good way to understand how stable those compounds are, and to become more familiar with the purification techniques and spectral data.

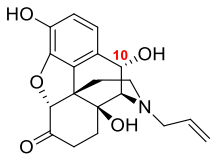
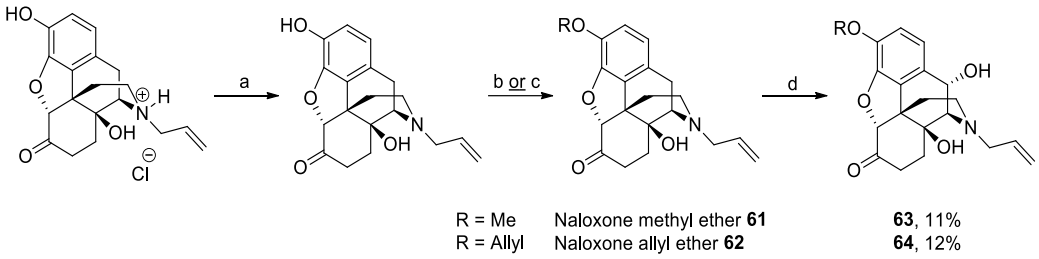


Figure II.1: Structure of 10- α-hydroxynaloxone **III** (*impurity 3*)

II.1 Benzylic oxidation of 3-protected naloxone

Naloxone, obtained from Indivior as a hydrochloride salt, was first free-based and the phenolic -OH was protected as a methyl or allyl ether, providing naloxone methyl ether **61** and naloxone allyl ether **62** in 84% and 63% yield, respectively (*Scheme II.2*). We continued the synthesis of *impurity 3* with the reported benzylic oxidation procedure, using ceric ammonium nitrate (CAN) as the oxidizing agent. CAN has been used for the benzylic oxidation of erythrinan alkaloids, for the total synthesis of (±)-erythristemine and (+)-erythrartine. The authors reported that the use of alcohols or acetic acid as solvent provided the corresponding benzylic ether or acetate in good yield.[96] In the case of naloxone, the reaction was performed in acetonitrile and water was used as co-solvent to generate the benzylic alcohol, albeit in a low yield. Following this literature procedure describing the benzylic oxidation of naloxone system, using 4 equivalents of CAN and 9 equivalents of sodium bicarbonate in acetonitrile containing 5% water, we were pleased to isolate the desired alcohol product **63**, albeit in low yield. This reaction was also successful when applied to naloxone-3-allyl ether **64**, but again a low yield was obtained (*Scheme II.2*). The two major drawback of this method are 1) the use of 4 equivalents of the oxidizing agent, 2) the low mass return of crude material and 3) the incomplete conversion of starting material: the product/starting material ratio (determined on the crude NMR) is 4:1.

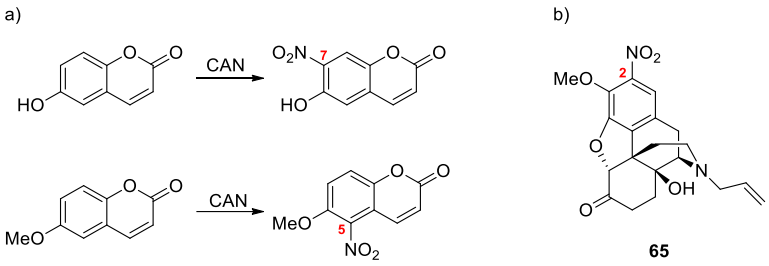


Scheme II.2: Benzylic oxidation of naloxone 3-methyl ether and naloxone 3-allyl ether

Reagents and conditions: a) NH_4OH, DCM/H_2O 2:1, rt, 1H, 90%. b) MeI, K_2CO_3, acetone, 50°C, 84%. c) AllylBr, K_2CO_3, acetone, 50°C, 63%. d) CAN, Na_2CO_3, MeCN/H_2O 95:5, 0°C to rt.

In order to increase the yield of the benzylic oxidation reaction, some optimisation studies were performed. When one or two equivalents of CAN were used, the conversion of starting material decreased significantly to 10% and 30% respectively. If the reaction mixture was diluted (0.02 M instead of 0.1 M), the conversion was adversely affected again (~30%). Finally, when the amount of water co-solvent was increased to 50%, ^{1}H NMR spectroscopy of the crude mixture showed only traces of oxidized product among a complex mixture.

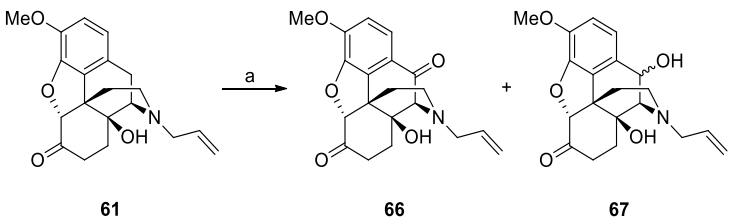
During these studies, we were able to isolate and identify one of the by-products of the reaction as the nitrated side-product **65**. In 2003, Ganguly and co-workers reported the nitration of 6-hydroxy and 6-methoxycoumarin using CAN.[97] In the case of 6-hydroxycoumarin, the nitrated product in position 7 is the major product, while the nitration of 6-methoxycoumarin occurs selectively in position 5 (*Scheme II.3a*), both by a radical mechanism. It should be noted that, in both cases, the nitration occurs on the carbon next to the methoxy or hydroxyl group, which might play the role of directing group. Based on this result and the mechanism provided in literature, it is reasonable to suppose that the nitration of naloxone occurs in position 2 (*Scheme II.3b*).



Scheme II.3: Nitration of coumarin and naloxone methyl ether

Although the CAN oxidation of naloxone allowed us to isolate the product, a better method for the benzylic oxidation of this compound was desirable. A number of different methods for the C-10 oxidation of morphinans and epoxymorphinans have been demonstrated in the literature. The use of selenium dioxide has been reported for the synthesis of naltrexone derivatives.[98,99] Molecular oxygen[100] and electrochemical oxidation[101] are non-selective methods of benzylic oxidation of morphinans. Furthermore, oxidation using chromic acid has been developed by Rapoport, in the preparation of 10-hydroxycodeines.[102,103] Thus, we attempted the benzylic oxidation of naloxone using different conditions. The results are summarised in *Table II.1*.

We began our studies by employing Rapoport's chromic acid conditions, with naloxone methyl ether **61** as the starting material, for the synthesis of ketone **66**. Analysis of the crude mixture by ^{1}H NMR and LC-MS showed a mixture of starting material, and a small amount of what appeared to be 10-hydroxynaloxone **67** and 10-ketonaloxone **66**, in a 16:4:1 ratio (*Table II.1*, entry 1, *Scheme II.4*).



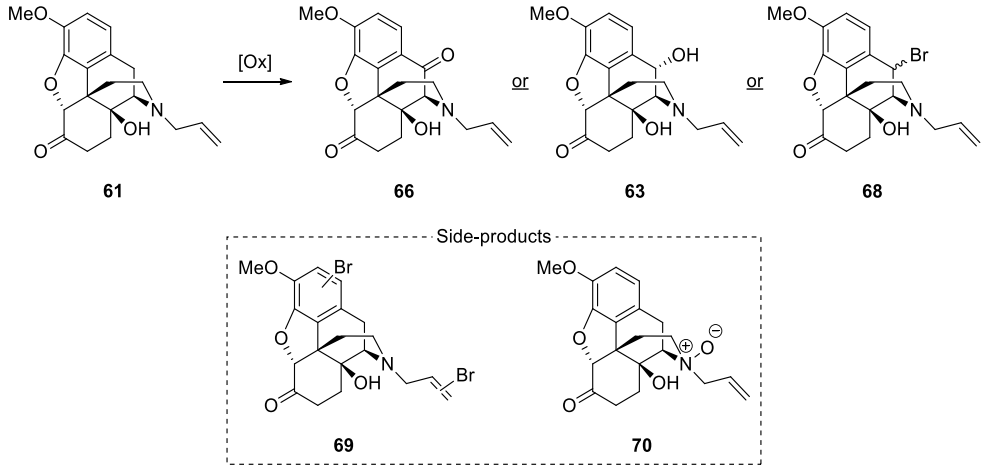
61 **66** **67**

Scheme II.4: Chromic acid oxidation

Reagents and conditions: CrO_3, 10% aq. H_2SO_4, rt.

Most oxidation methods employed gave a mixture of unidentified compounds or starting material. We noted that the use of oxidizing reagents such as *m*CBPA or potassium persulfate formed naloxone methyl ether *N*-oxide **70** as side-product, or major product, respectively (*Table II.1*, entries 2 and 3).

As the benzylic oxidation seemed difficult to achieve, we turned our attention to the benzylic bromination of naloxone methyl ether. Subjecting **61** to NBS and analysis of the crude ^{1}H NMR spectrum allowed us to confirm that the bromination occurred on both the aromatic ring and the allyl group (entries 9 and 10).



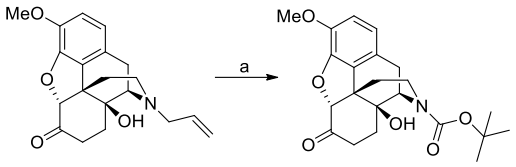
Entry	Targeted compound	Conditions	Outcome
1	**66**	CrO_3, H_2SO_4	16:4:1 **61**/**63**/**66**
2	**66**	*m*CPBA, $PhI(OAc)_2$, TBHP, TFE, rt	**70** + complex mixture
3	**66**	$K_2S_2O_8$, pyridine, MeCN, 70 °C	**70**
4	**66**	IBX, DMSO, 90°C	RSM
5	**63**	WO_3, 70% aq. TBHP, 40% aq. NaOH, 80 °C	Complex mixture
6	**66**	CrO_3, $NaIO_4$, MeCN/H_2O 25 °C	RSM
7	**66**	MnO_2, TBHP, MeCN, 80 °C	Complex mixture
8	**68**	NBS, AIBN, DCM, rt, W lamp	**69**
9	**68**	NBS, benzoyl peroxide, CCl_4, reflux	**69**

Table II.1: Attempted oxidation or naloxone methyl ether **61**

In general, we found that the chemoselective oxidation of the naloxone ring in the presence of the allylamine is very difficult or impossible in some cases. This observation, combined with the result of the attempted transformations described above, led us to conclude that the presence of a basic nitrogen and alkene, which are both prone to oxidation, needed to be removed (see Chapter III). Therefore, we assumed that changing allyl to a carbonyl protecting group on the nitrogen would lead to better results. The protecting group had to be inert towards oxidative conditions and be free of any activated C-H bonds (such as benzylic or allylic methylenes). We therefore decided to protect the nitrogen with a Boc group. Indeed, the nitrogen lone pair is no longer available for oxidation because of the delocalisation into the carbonyl group.

II.2 Benzylic oxidation of *N*-Boc noroxycodone

The palladium-catalysed deallylation of naloxone methyl ether and subsequent Boc protection afforded *N*-Boc noroxycodone **71** in 62% yield (*Scheme II.5*).



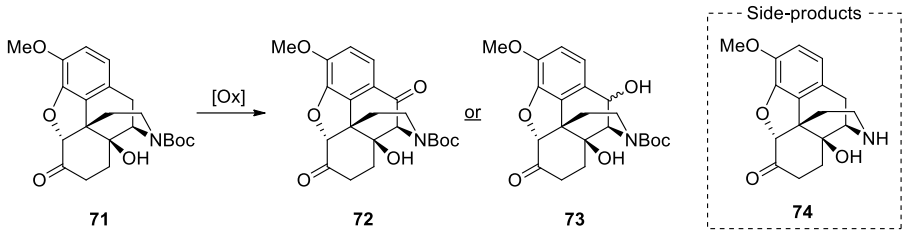
Naloxone methyl ether **61** **71**

Scheme II.5: Deallylation – Boc protection of naloxone methyl ether

Reagents and conditions: a) $Pd(PPh_3)_4$, DMBA, DCM, 40°C then Boc_2O, 1,4-dioxane, 60°C, 62%.

With the hope that this protecting group strategy would give better results, a variety of benzylic oxidation methods were tested on the carbamate **71**, including the CAN oxidation previously described (*Table II.2*, entry 1). In this first case, the oxidised product was detected by LC-MS analysis, although among a mixture of unidentified compounds. Moreover, the mass balance was quite low. The chromic acid method mentioned above gave a 4:1 mixture of starting material and product, but once again, the mass balance was low (entry 2). The Boc group is known to be acid sensitive, and so we attributed the low mass balance to the deprotection of the carbamate, and loss of the free amine in the aqueous phase.

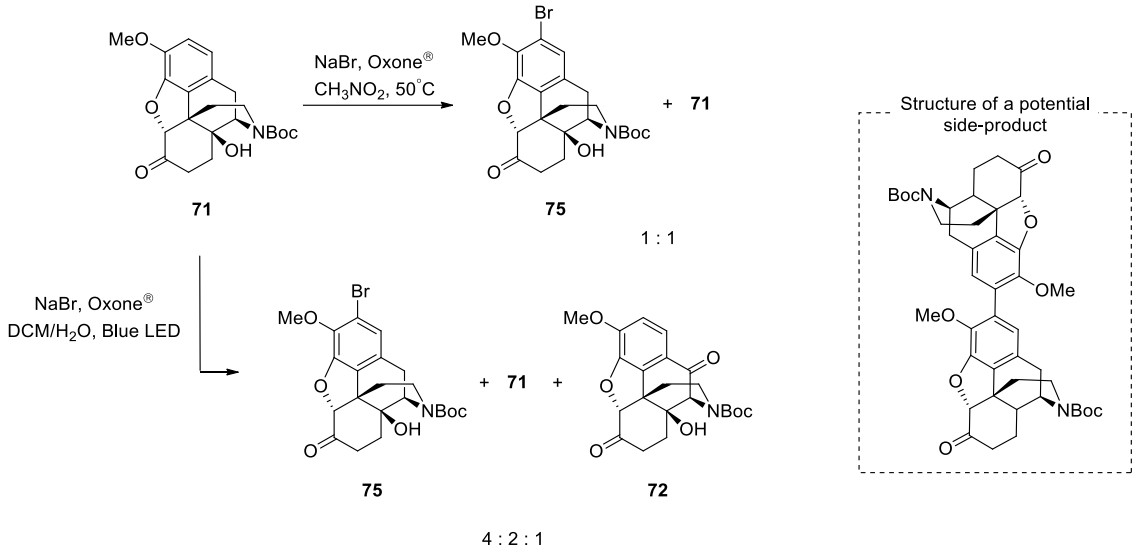
2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is known to be a powerful oxidising agent. A few years ago, the aerobic benzylic oxygenation of various aromatic compounds has been achieved in the presence of DDQ and *tert*-butyl nitrite, under visible-light irradiation. This set of conditions were unsuccessful when naloxone was used as the substrate: The aromatic protons were not detectable on the crude NMR spectrum, which may be due to overoxidation of naloxone, or extensive decomposition of the product during the reaction (entry 3).



Entry	Targeted compound	Conditions	Outcome
1	**73**	CAN, Na_2CO_3, MeCN/H_2O 95:5	Low mass return, complex mixture
2	**72**	CrO_3, H_2SO_4, 8 h, rt	4:1 **71**/**72**
3	**72**	DDQ, *t*BuONO, MeCN, rt, Blue LED	Decomposition
4	**72**	DDQ, AcOH, 120°C, 8 h	100% **74**

Table II.2: Benzylic oxidation of *N*-Boc noroxycodone **71**

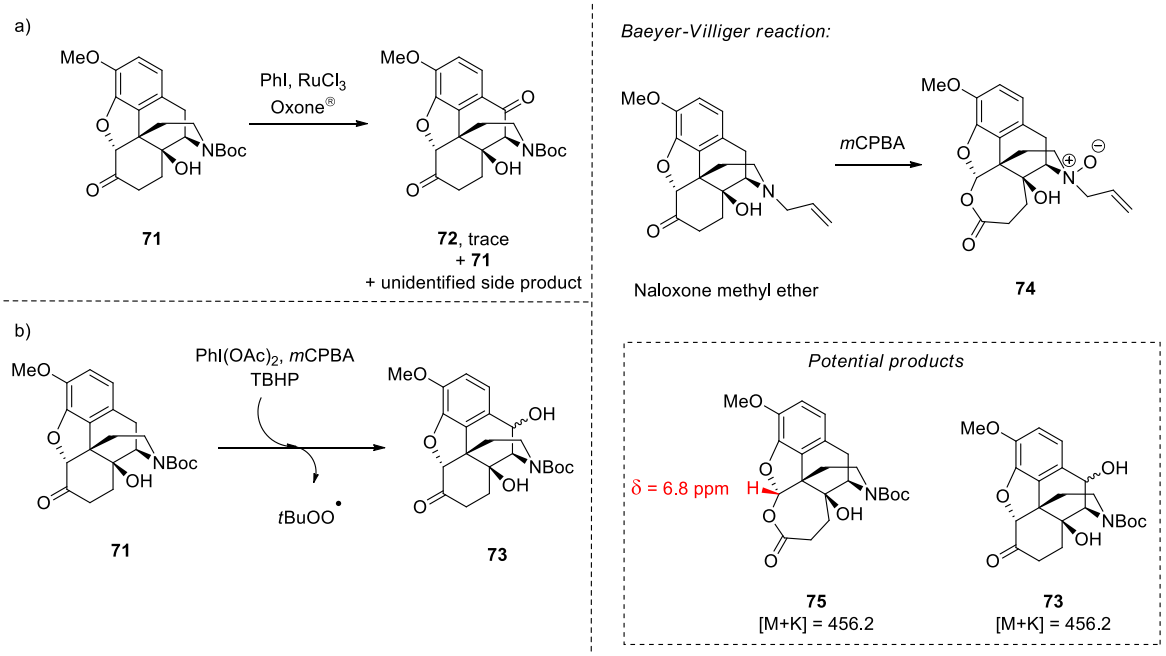
As a further alternative, both thermal and photochemical oxidation of sodium bromide with Oxone® were tried on *N*-Boc noroxycodone **71** (*Scheme II.6*).[104] In the photochemical reaction, the product was detected by ^{1}H NMR analysis of the crude product however, a side product was formed in this set of conditions. The authors reported the bromination of the aromatic ring when 2 equivalents of bromide source were used. It is likely that the side-product formed in this reaction, although only 0.5 equivalent have been used, is the brominated compound **75** (*Scheme II.6*). The thermal reaction led to incomplete conversion of the starting material to the brominated side-product **75**. Although it would make sense to conclude that the side-product is formed by bromination of the benzene ring, dimerization of epoxymorphinans has been documented in the literature. In terms of characterisation, the dimerization of naloxone methyl ether (or the bromination) would result in the formation of a singlet on the ^{1}H NMR, which was the case in those two examples. Unfortunately, the side-product was not further characterised, it is then not possible to accurately conclude about the nature of the side-product.



Scheme II.6: Sodium bromide-Oxone® oxidation

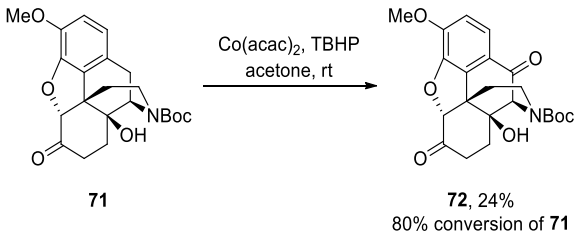
Hypervalent iodine reagents are commonly used for the oxidation of alcohols to carbonyl compounds however, strategies have also been developed for the oxidation of alkyl benzene to acetophenone derivatives: Zhdankin and co-workers developed an iodine(V)/Ru(III) co-catalysed oxidation of hydrocarbons, with Oxone® as stoichiometric oxidant. When these conditions were applied to naloxone, oxidation partially occurred on the aromatic ring: A 1.3:1 mixture of an unidentified side-product and starting material were recovered, along with traces of 10-oxo compound **72** (*Scheme II.7a*).

A related benzylic oxidation method employing (diacetoxy)iodobenzene ($PhI(OAc)_2$), *m*CPBA and *tert*-butyl hydroperoxide (TBHP) was also examined. This method is proposed to involve the *tert*-butylperoxy radical $tBuOO^{\bullet}$ that undertakes the benzylic oxidation. In the event, the desired compound was detected on the NMR spectrum of the crude product, but the LC-MS analysis showed several peaks with the same molecular ion of 456.2, presumed to be $[M + K]^+$ for the product of addition of one O-atom. In another study, we showed that naloxone can react with peracids such as *m*CPBA to form the Baeyer-Villiger product **74**. It is reasonable to think that one of the products in the mixture is the lactone **75**. Indeed, on the ^1H NMR spectrum of the crude material, the deshielded H5 proton of the lactone product (δ = 6.8 ppm) was evident. It can also be argued that the oxidised product might be the benzylic alcohol **73**, as the two compounds lactone **75** and alcohol **73** have the same molecular weight (*Scheme II.7*). The complexity of the crude NMR spectrum did not allow any accurate conclusion.



Scheme II.7

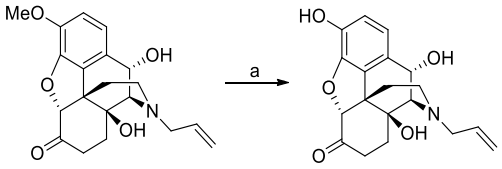
We terminated the C-10 oxidation study by a cobalt-catalysed benzylic oxidation, using $Co(acac)_2$ as the catalyst and TBHP as oxidant. Pleasingly, the crude NMR spectrum showed 80% conversion of the starting material to the desired product however, the purification by column chromatography on silica proved to be difficult: some new impurities appeared after the purification, and only 24% of impure product was recovered. This result led us to conclude that the product was unstable under these conditions of purification (*Scheme II.8*).



Scheme II.8: Cobalt-catalysed benzylic oxidation

II.3 End of the synthesis – Deprotection of the methyl ether

Overall, the replacement of the *N*-allyl with a Boc group did not significantly improve the benzylic oxidation step under the conditions that have been tested. The low yielding CAN oxidation proved to be the most expedient route, and so we then decided to proceed to the deprotection of the methyl ether, in order to accomplish the synthesis of the *impurity 3*. Boron tribromide was used in order to perform this transformation (*Scheme II.9*). The reaction proceeded smoothly and afforded *impurity 3* in 60% yield.



63 III

Scheme II.9: Deprotection of the methyl ether

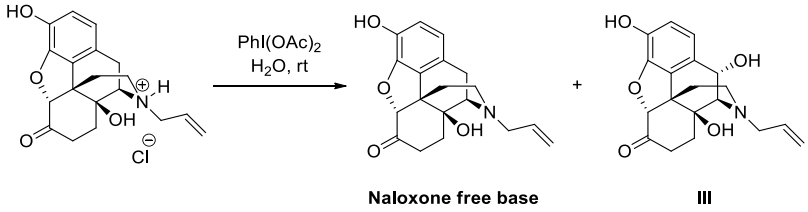
Reagent and conditions: BBr_3, DCM, 0°C to rt

II.4 Conclusion – Future outlook

Various attempts were made for the synthesis of *impurity 3*. However, none of them were promising, as most reactions did not produce the desired product. The CAN oxidation, although low yielding, is the only sequence that was able to provide the desired benzylic alcohol. The cobalt-catalysed benzylic oxidation provided the product in low yield because of the probable decomposition of the desired compound on silica during the purification step. Moreover, this reaction requires several protection and deprotection steps: Protection of the phenol, deallylation, Boc protection, followed by Boc deprotection, allylation, and deprotection of the methyl ether.

As mentioned earlier, hypervalent iodine reagents are versatile reagent for oxidative transformations. In an ultimate attempt to achieve the benzylic oxidation, naloxone hydrochloride was used as the substrate for the benzylic oxidation using (diacetoxy)iodobenzene. The choice of this starting material instead of naloxone methyl ether was motivated by the desire to achieve the transformation without playing with protection and deprotection steps, which might lower the overall yield. The reaction was performed in water, at room temperature using 1.2 equivalents of $PhI(OAc)_2$. After five hours, although the mass balance was only 50%, LC-MS analysis of the crude mixture showed that the major product was the desired benzylic alcohol **III**, along with naloxone (*Scheme II.10*). The release of an acetate

during the course of the reaction, which can deprotonate the hydrochloride salt to form the free base, prevents further oxidation of the naloxone core.



Naloxone free base **III**

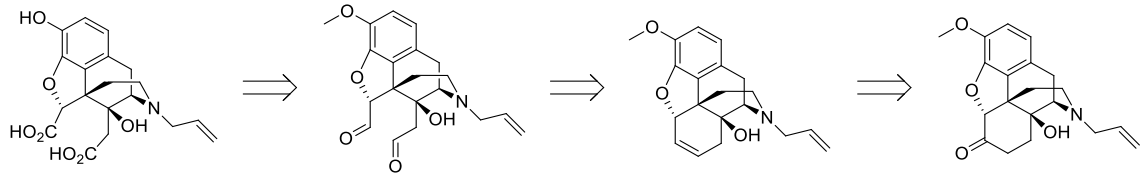
Scheme II.10: Benzylic oxidation of naloxone hydrochloride

Chapter III: Oxidative strategies involving the cyclohexanone ring

III.1 Semi-synthesis of *impurity 9*

As mentioned above, the *impurity 9* (diacid **XI**, *figure III.1*) is one of the major impurities in Suboxone® sublingual film. Therefore, we attempted the synthesis of this compound from naloxone methyl ether **61**.

The retrosynthetic analysis of the diacid is depicted in *figure III.1*. We envisaged that the diacid would be the result of the oxidation of the dialdehyde **76**, obtained by oxidative cleavage of the 6,7-alkene **77**, which would be obtained in a few steps from naloxone methyl ether **61**.

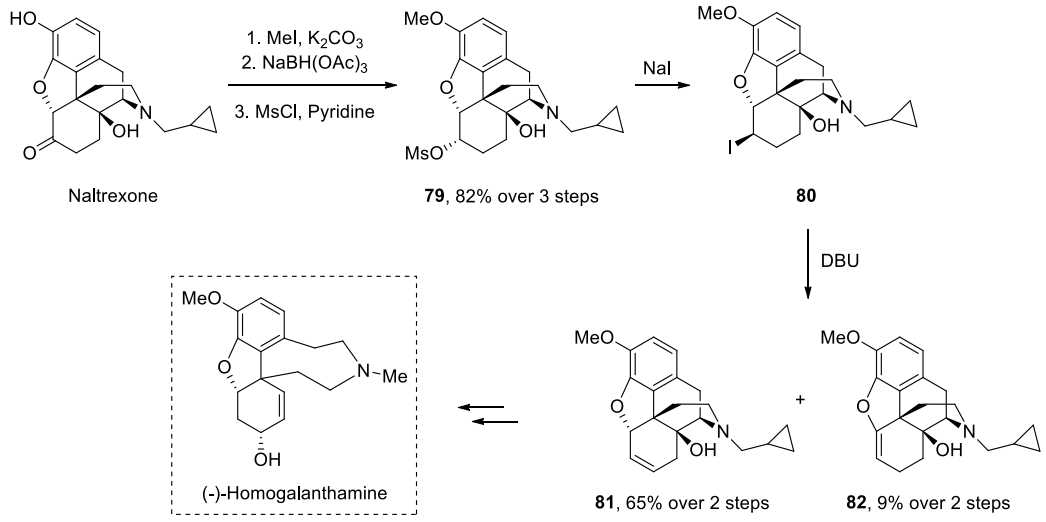


IX, impurity 9 **76** **77** **Naloxone methyl ether 61**

Figure III.1: retrosynthesis of *impurity 9*

III.1.1 Preparation of the alkene

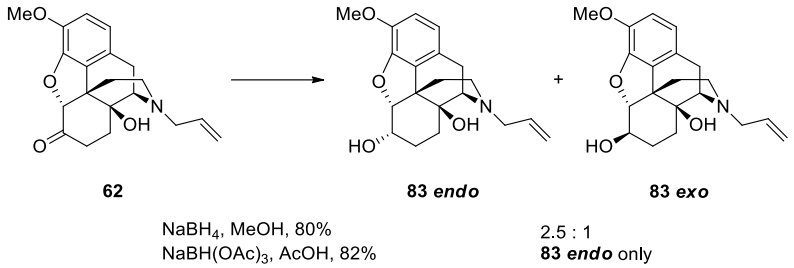
The synthesis of the 6,7-alkene has been inspired by the work of Nagase and co-workers, who reported the synthesis of (-)-homogalanthamine from naltrexone.[105] The first steps of this synthesis are represented in *scheme III.1*. After protection of the phenol, reduction of the ketone gave the 6-*endo* alcohol **78** which was transformed into a mesylate **79**. Reaction with sodium iodide provided the 6-*exo* iodo derivative **80**, which was eliminated using DBU as a base, to afford the 6,7-alkene **81** derived from naltrexone, along with the corresponding enol ether **82** as a minor side-product (*Scheme III.1*). This route appeared to be amenable to generating the required intermediate to study the oxidative cleavage process, and so we decided to employ this sequence on the derivatisation of naloxone.



Scheme III.1: First steps in the synthesis of (-)-homogalanthamine

Reduction of the ketone

We began by studying the ketone reduction step, using sodium borohydride and sodium (triacetoxy)borohydride for this transformation (*Scheme III.2*). Using sodium borohydride, a mixture of the two alcohol diastereoisomers was obtained in 80% yield and a 2:1 to 2.5:1 *endo/exo* ratio. Interestingly however, using sodium (triacetoxy)borohydride resulted in a very stereoselective reaction and only the *endo* isomer **83 *endo*** was obtained in 82% yield.



Scheme III.2: Reduction of the ketone

The ratio *endo/exo* was determined after analysis of the crude material by ^{1}H NMR spectroscopy, by comparison of the coupling constant of the H5 doublet (*cis* vicinal H5-H6, *J*=5.0 Hz and *trans* vicinal H5-H6, *J*=6.0 Hz): as shown on *figure III.2a*, the *exo* face of the C ring is the most accessible for the attack of the hydride, which explains the selectivity of the reduction using a bulkier reagent. It can also be argued that the tertiary alcohol at C14 coordinates to the boron, the attack of the hydride at C6 is then directed (*Figure III.2b*).

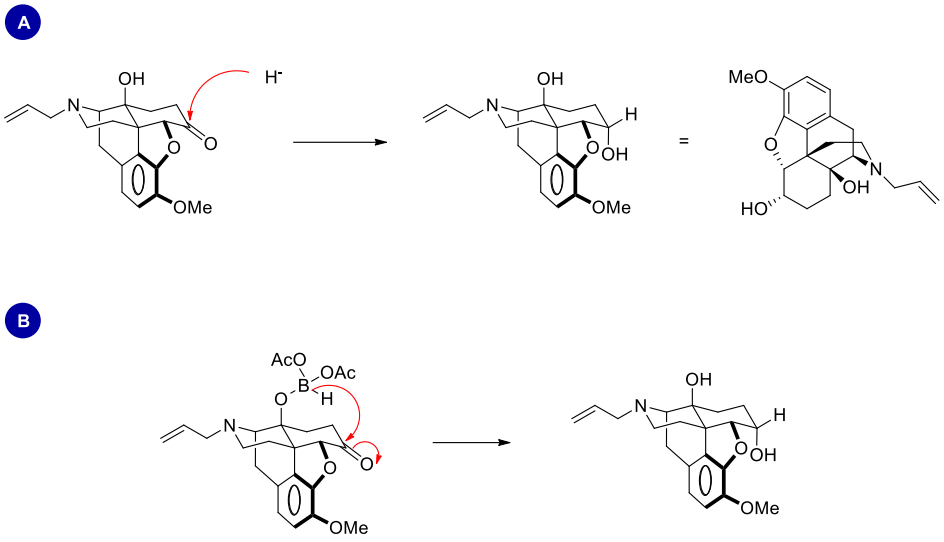
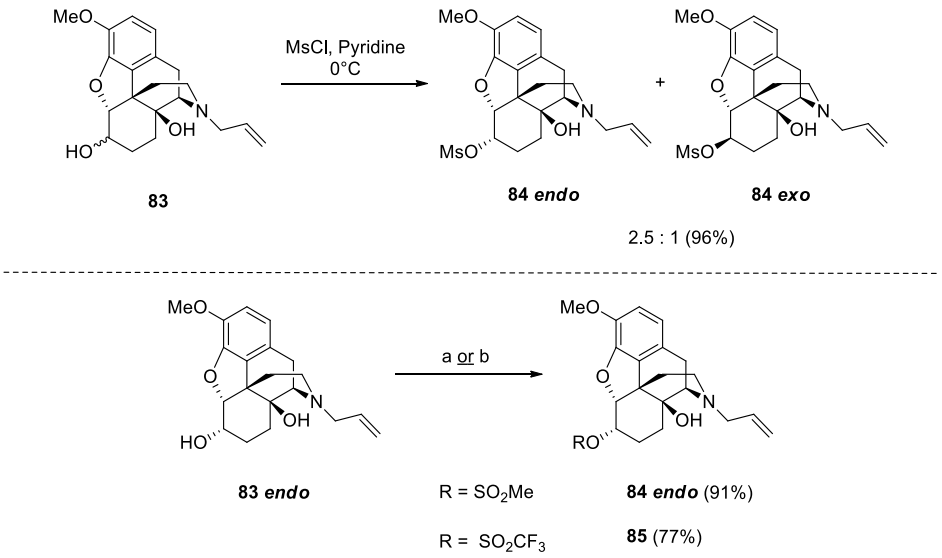


Figure III.2

Mesylation

The next step of the sequence transforms the newly formed alcohol into a leaving group. Indeed, using methanesulfonyl chloride, the mesylate was obtained in 96% yield in the case of the mixture of diastereoisomers (2:1 to 2.5:1 *endo/exo*), and 91% yield for the endo isomer only (*Scheme III.3*). Alternatively, the *endo* alcohol was converted into the corresponding triflate **85** in 77% yield, using trifluoromethanesulfonic anhydride.



Scheme III.3: Mesylation step

Reagents and conditions: a) MsCl, pyridine, 0°C, 91%. B) Tf_2O, 4-methylmorpholine, $CHCl_3$, -30°C to 0°C, 77%.

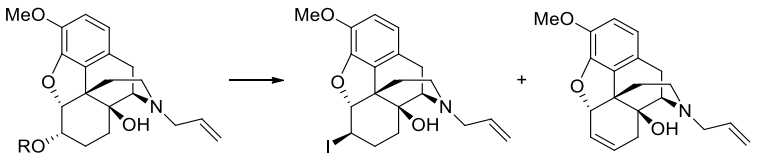
Displacement of the mesylate

In considering the elimination reaction according to Nagase's route, it is interesting to note that they decided to undertake a substitution of the mesylate by iodide, rather than carrying out the elimination reaction directly. The apparent reason for this was that it accelerated the rate of the elimination, while avoiding an intramolecular nucleophilic substitution by the 14-OH. Thus, this sequence was repeated with our naloxone derivative. A large excess of sodium iodide (30 equivalents) was used as the iodide source for the substitution. The results of the substitution reaction are summarised in *Table III.1*.

When the substitution was carried out on the *endo* mesylate **84** only, a mixture of 6-iodo compound **86** and alkene **77** was obtained in a 10:1 ratio (based on the ^{1}H NMR analysis of the crude material) (entry 1). On the other hand, the substitution of the triflate **85** using 2 equivalents of tetraethylammonium iodide as the iodide source afforded the *exo* iodide **86** as the only product, in 80% yield (entry 3).

The displacement with sodium iodide was performed in DMF at 100 °C whereas the reaction with TEAI is in acetonitrile took place at -10 °C to room temperature. The formation of the alkene during the substitution step in the former reaction can be explained by the high temperature of the reaction. Indeed, when the conversion of the triflate is performed with NaI at 100 °C, a mixture of 6-iodo product **86** and alkene **77** is obtained, in a 1:1 ratio (entry 4). The conversion of the mesylate at lower temperature, however, failed to provide the product, and the starting material was recovered (entry 2). These experiments allow us to conclude about the stability of the mesylate compared to that of the triflate. Indeed, when the triflate **85** was heated in the absence of iodide at 100 °C in DMF, 20% of the alkene **77** was detected in the crude mixture.

The mixture of alkene **77** and 6-iodo product **86** arising from the substitution of the mesylate could be used as a crude mixture in the next step, without altering the efficiency of the reaction.



R = SO_2Me (**84**)

R = SO_2CF_3 (**85**)

86

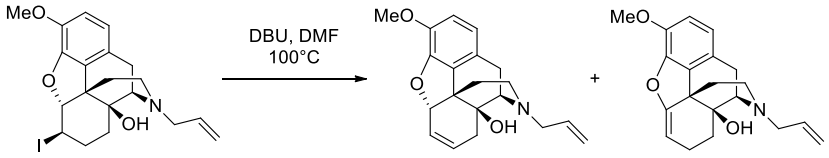
77

Entry	Starting material	Conditions	Conversion to 6-I 86
1	*endo* 6-OMs **84**	NaI (30eq.), DMF, 100°C, 18H	77%
2	*endo* 6-OMs **84**	TEAI (2eq.), MeCN, -10°C to rt	0%
3	*endo* 6-OTf **85**	TEAI (2eq.), MeCN, -10°C to rt	Complete conversion
4	*endo* 6-OTf **85**	NaI (30eq.), DMF, 100°C, 18H	50%

Table III.1

Elimination

The elimination step was carried out using DBU as the base. The 6-iodonaloxone derivative **86** was treated with an excess of DBU (18eq.). As expected, the elimination reaction produced a mixture of alkene **77** in 74% yield, along with the isomeric enol ether **87** in 10% yield over two steps (*Scheme III.4*).

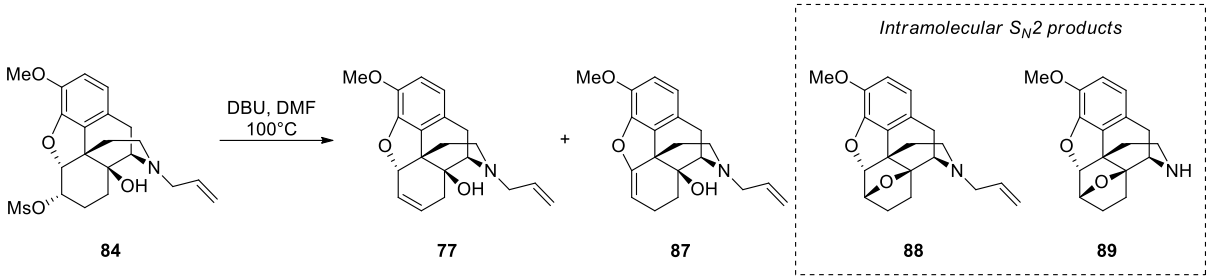


86 **77 (74%)** **87** (10%)

Scheme III.4: Elimination of the iodide

We were interested to see if this four-step sequence could be shortened and investigated the elimination of the *endo* mesylate instead of the *exo* iodide. Thus, the *endo* mesylate **84** was subjected to the elimination conditions (DBU, DMF, 100 °C). Surprisingly, a mixture of enol ether **87** and alkene **77** was recovered, in a 1.5:1 ratio (*Table III.2*, entry 1). We attempted to optimise the reaction, in order to increase the ratio of alkene to enol ether; the results are summarised in *table III.2*. None of the attempted optimisations led to a satisfactory result, as the conversion of starting material was low or because side-products were obtained. Decreasing the temperature to room temperature or 50 °C had no effect on the reaction and starting material was recovered (Entries 2 and 3). The solvent was also investigated. More polar solvents such as DMSO or acetonitrile resulted in approximately 1:1 mixture of alkene and enol ether detected in the crude mixture however, the conversion of mesylate **84** to

product was lower in acetonitrile. THF only gave trace amount of enol ether. Although the conversion of mesylate was higher in toluene, this was accompanied by the formation of a chlorinated side product (see below). Reaction without any solvent resulted in a higher conversion again, due to the formation of the chlorinated side product (entry 8). Finally, DBU was replaced by sodium ethoxide, which failed to promote the elimination reaction (entry 9). On the other hand, potassium *tert*-butoxide resulted in an intramolecular nucleophilic substitution reaction, and the hexacyclic compound **88** was isolated in 39% yield. Deallylation also occurred during this step, and the secondary amine **89** was isolated in 30% yield (entry 10).



Entry	Conditions	Conversion of starting material 84
1	DBU (18 eq.), DMF (0.2 M), 100°C, 24H	100%
2	DBU (18 eq.), DMF (0.2 M), 50°C, 24H	0%
3	DBU (18 eq.), DMF (0.2 M), rt, 24H	0%
4	DBU (18 eq.), DMSO (0.2 M), 100°C, 24H	53%
5	DBU (18 eq.), MeCN (0.2 M), 100°C, 24H	16%
6	DBU (18 eq.), THF (0.2 M), 60°C, 24H	4%
7	DBU (18 eq.), PhMe (0.2 M), 100°C, 24H	34%
8	Neat DBU (18 eq.), 100°C, 24H	65%
9	EtONa (5 eq.), DMF (0.2 M), 100°C, 36H	0%
10	*t*BuOK (5 eq.), THF (0.1 M), 60°C, 5H	100% (**88** 39%[a], **89** 30%[a])

Table III.2: Attempted optimisation of the elimination reaction. [a] Yield of isolated compound after column chromatography

Isolation of a chlorinated side-product

An unexpected side-product was detected by ^{1}H NMR analysis of the crude material in the case of the elimination of the mesylate in toluene and in neat DBU. This compound formed an inseparable mixture with the enol ether **87** and was isolated by preparative HPLC. Regarding the characterisation of this impurity, we observed a doublet at 4.63 ppm on the ^{1}H NMR spectrum with a coupling constant of 7.5

Hz, similar to the one observed for the H5 in the 6-exo iodide compound **86**. Therefore, we assumed that the impurity had a functional group at position 6, *anti* to proton H5. Analysis of the impurity by X-ray crystallography revealed it to be the 6-chloro derivative **90** (*Figure III.3*). We hypothesised that, given that the mesylate is not purified, a chloride might substitute the mesylate to provide compound **90**. Indeed, elemental analysis confirmed the presence of 4.89% of chlorine atom in the sample.

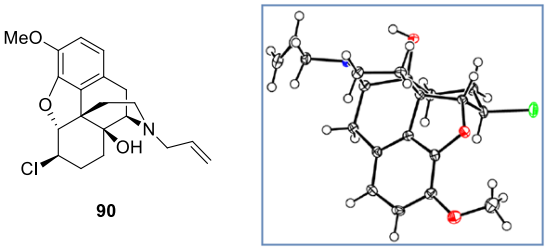


Figure III.3: Structure of the impurity

Elimination of the iodide *vs* elimination of the mesylate

Although the 6-iodo naloxone derivative **86** has an *anti* proton relative to the iodide (highlighted in red, *figure III.4*), the elimination to the alkene **77** cannot proceed via an E2 mechanism, as it requires *trans*-diaxial protons. Furthermore, the H5 proton (highlighted in blue) is not *anti* to the iodide, which rules out the possibility of an E2 elimination for the formation of the enol ether. An E1 elimination seems more likely for the elimination of the iodide.

The mesylate **84**, however, is axial and has *anti* protons at both C5 and C7. The E2 elimination of the mesylate could explain why the alkene and the enol ether are produced in a similar proportion, even if the conversion of starting material to product is low.

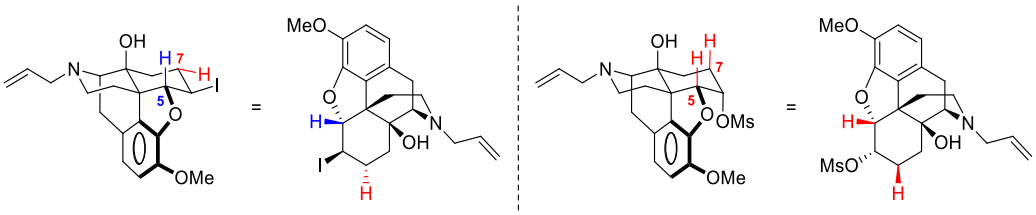
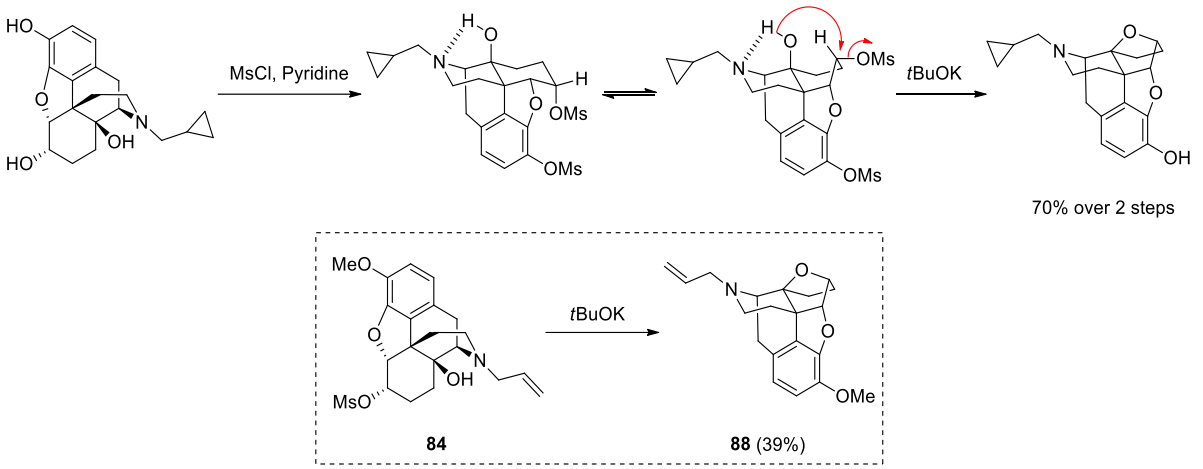


Figure III.4

Formation of the 6,14-epoxy-bridged product

Maloney-Huss and Portoghese reported the synthesis of 6,14-bridged epoxymorphinans.[106] According to the authors, the driving force of this reaction would be the anchimeric assistance of the nitrogen for the deprotonation of the 14-OH group by a base. The alkoxide can then rapidly substitute the axial leaving group at C6, in an intramolecular nucleophilic substitution process (*Scheme III.5*).

In our attempt to optimise the elimination of the mesylate, the starting material was treated with potassium *tert*-butoxide. As mentioned above, the substitution product **88** was obtained instead of the expected elimination product.

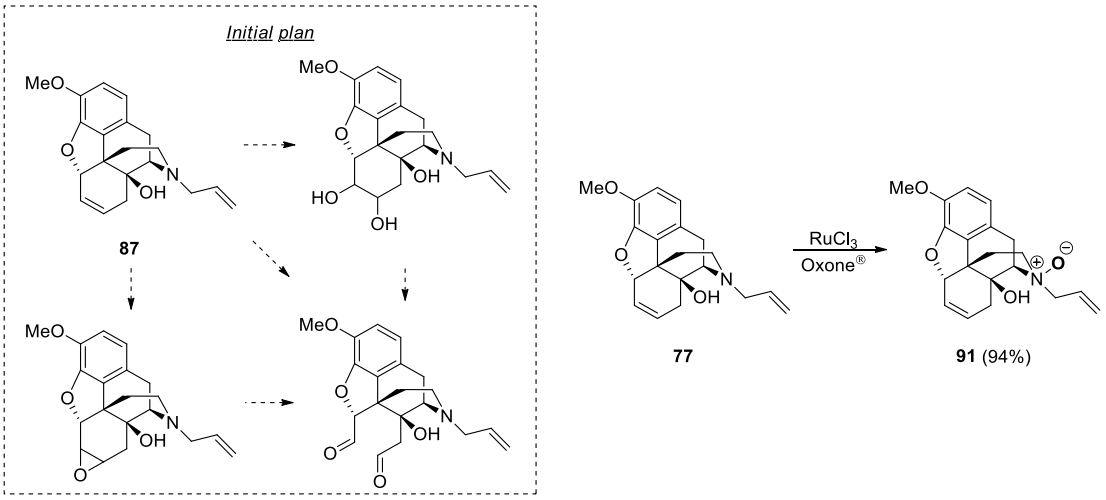


Scheme III.5: Formation of 6,14-epoxy bridged opiates

After studying the elimination of these various leaving groups, we concluded that the original sequence (alcohol→mesylate→iodide→alkene) was the best approach.

III.1.2 Oxidation of the alkene

After the successful synthesis of the alkene **77**, we pursued the synthesis of the *impurity 9* with the oxidation of the alkene. Different options were envisaged: the direct oxidative cleavage, a dihydroxylation and subsequent oxidative cleavage, or alternatively, the epoxidation of the alkene (*Scheme III.6*). We began with the oxidative cleavage of the alkene by an ozonolysis followed by treatment with dimethyl sulfide, in order to obtain the dialdehyde. Unfortunately, this reaction did not give the expected result, and the starting material was recovered in 49% yield together with unidentified materials. We attempted to cleave the alkene using ruthenium (III) chloride and Oxone® as the oxidant. Once again, we did not observe the formation of the dialdehyde, however the corresponding *N*-oxide **91** was formed in 94% yield.



Scheme III.6

We then turned our attention to the dihydroxylation of the alkene. Treatment of the starting material with osmium tetroxide and 4-methylmorpholine *N*-oxide as the oxidant was not promising. The proton NMR spectrum of the crude material showed the presence of starting material along with another compound that exhibited a multiplet containing the 6,7-alkene protons and the allyl H18 proton. The combined integration of the 6,7,18-alkene protons and the allyl H19 olefin peaks and those at C5 suggested that the allyl proton integration was significantly reduced (*Figure III.5*). We concluded that the dihydroxylation had not taken place at the 6,7-olefin as hoped, but instead it had partially occurred at the allyl group. We therefore abandoned this approach at this stage.

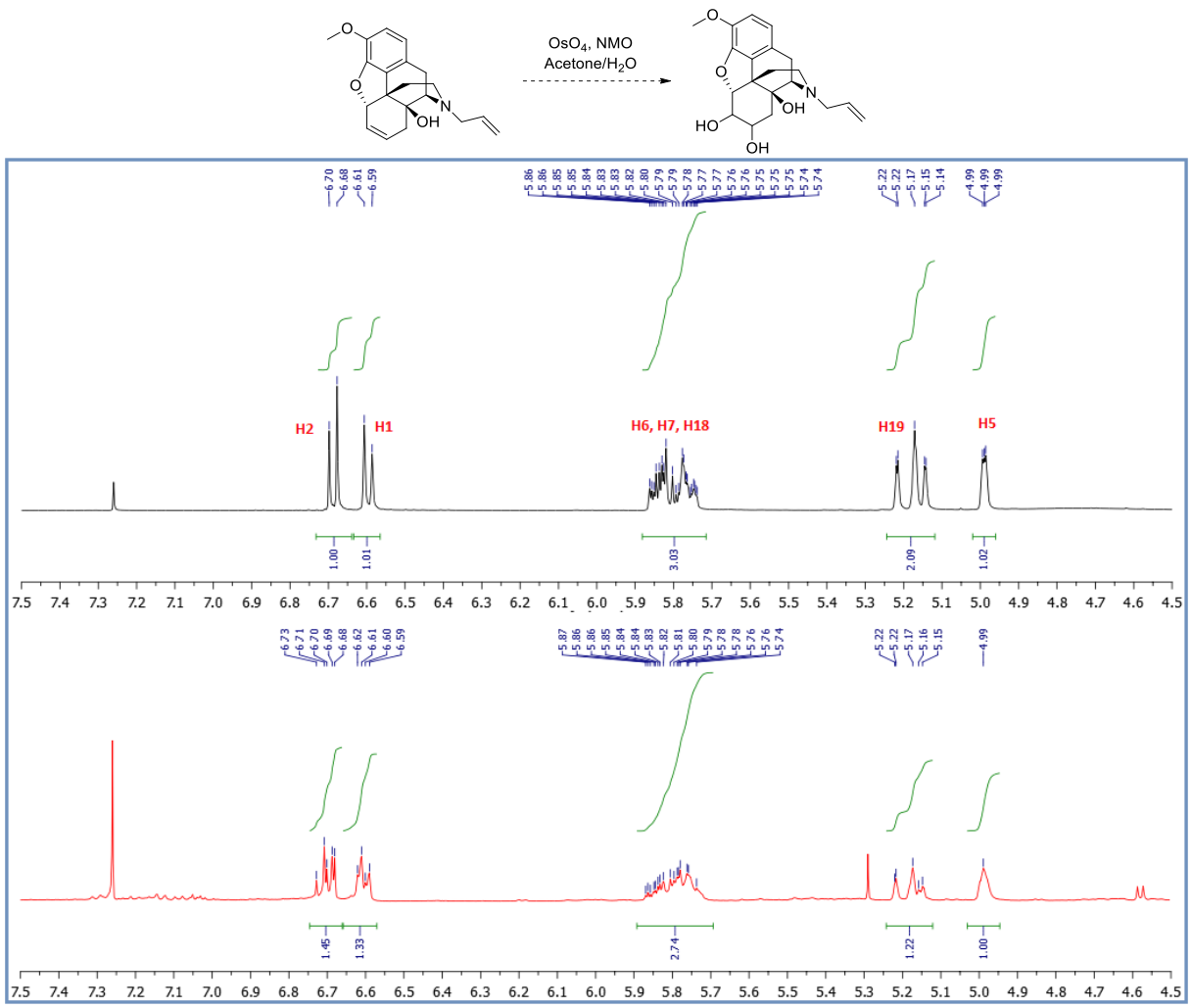
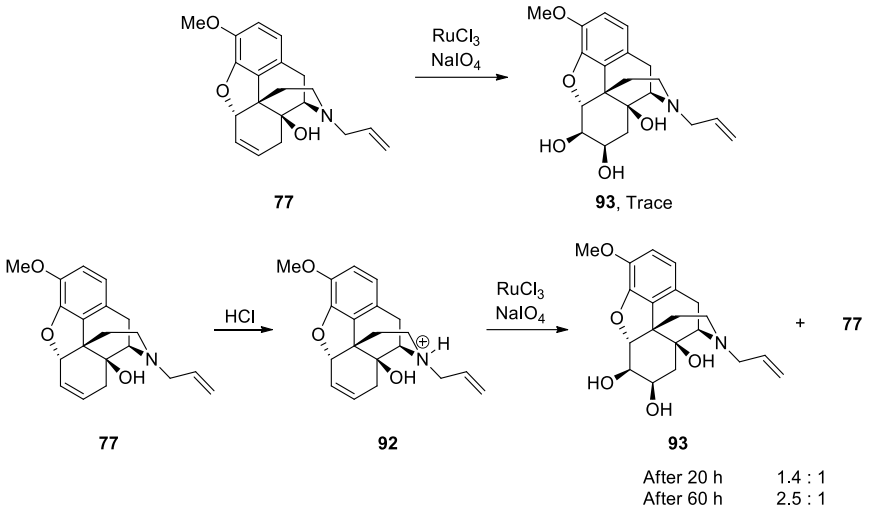


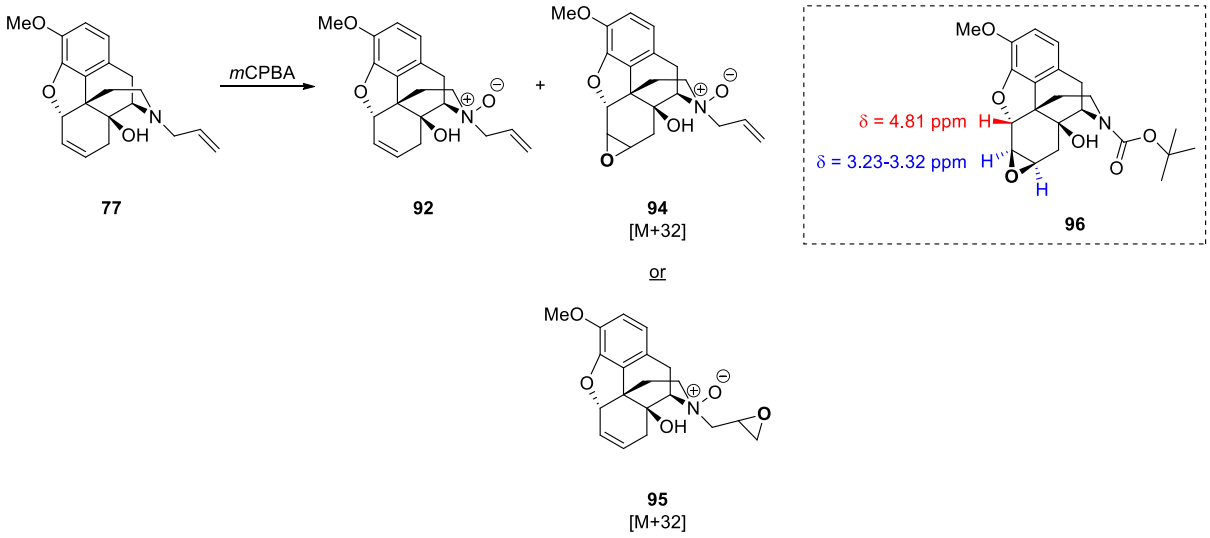
Figure III.5: Top – NMR spectrum of the starting material. Bottom – Crude NMR spectrum of the OsO_4 reaction

Alternatively, the sodium periodate/ruthenium (III) chloride dihydroxylation was investigated. Using 7 mol% of catalyst and 1.5 equivalents of oxidant gave mostly starting material, along with a dihydroxylated product in a 14:1 ratio (based on crude NMR analysis). The presence of a doublet at 4.59 ppm, with a coupling constant of 6 Hz indicated that the oxidised product was the diol **93**. We hypothesised that, in acidic conditions, a proton would play the role of a temporary protecting group (compound **92**, *Scheme III.7*) of the nitrogen and therefore, avoid *N*-oxide formation, as mentioned above. The alkene **77** was then stirred in a solution of hydrochloric acid in diethyl ether and, after evaporation of the solvent, the HCl salt was used as starting material for the oxidation reaction. After 20 h however, only 50% of the initial mass was recovered, and we detected a 1.4:1 ratio of diol **93** and starting material **77**. We were pleased to notice an increase of the ratio diol **93**/alkene **77** when the reaction time was increased to 60 h, however the mass balance was lower than expected (34% of the initial mass, *Scheme III.7*).



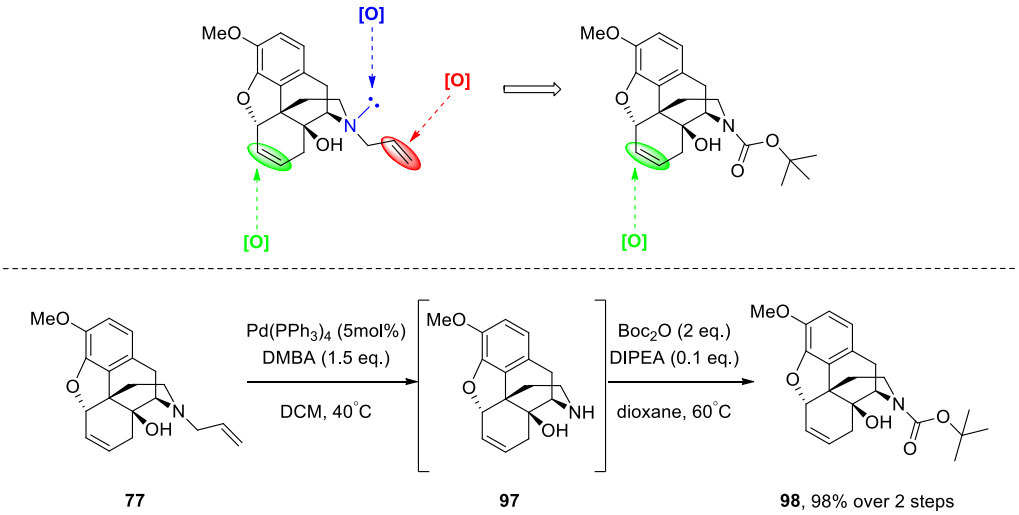
Scheme III.7: Attempted dihydroxylation

An epoxidation was attempted using *m*CPBA as the oxidising agent. Two compounds were formed in this reaction, in a 1:0.2 ratio (determined by analysis of the crude mixture by ^{1}H NMR spectroscopy). The major compound was identified as the alkene *N*-oxide **91** (*Scheme III.8*). LC-MS analysis revealed a mass ion of [M+32] for the minor compound. We then assumed that the minor compound had two more oxygens, compared to the starting material. The chemical shift of the H18 signal (allylic CH), at 6.45-6.53 ppm, showed the presence of an *N*-oxide functionality in the product. The second oxygen would then come from either the epoxidation of the 6,7-alkene (compound **94**), or the epoxidation of the allyl group (compound **95**), as shown in *scheme III.8*. We noticed the presence of a singlet at 5.02 ppm, and a doublet at 3.53 ppm with the same integration on the crude ^{1}H NMR spectrum. Those two signals could be H5 and H6 respectively, of epoxide **94**. Later on, we have been able to prepare the *N*-Boc epoxide **96** (see below for discussion). We then compared the ^{1}H NMR spectra of the crude mixture and compound **96**. Compound **96** shows a singlet at 4.81 ppm (H5), along with a multiplet at 3.23-3.32 ppm (H6-H7). Based on these observations, but keeping in mind that the compared structures have a different substituent on the nitrogen, we assumed that the minor component of crude mixture is the epoxide **94**.



Scheme III.8

The *N*-oxide **92**, which appeared to be really easy to make, was then subjected to oxidation conditions (dihydroxylation and epoxidation), however the starting material was recovered, and the alkene remained untouched in both cases. Finally, in order to see if functionalisation of the 6,7-alkene was at all viable in this compound, we added one equivalent of bromine to a solution of alkene **77**. Surprisingly, bromination of the aromatic ring and the allyl group occurred, while the 6,7-alkene remained untouched. These experiments led us to conclude that oxidation of the nitrogen in this substrate prevents the oxidation of the alkene. Moreover, the attempted bromination showed that this alkene is inactive towards oxidation. We then decided to convert the tertiary amine into a carbamate to make the nitrogen less basic and therefore, avoid the *N*-oxide formation. Furthermore, a *tert*-butyl carbamate (Boc) is easy to install and remove. Accordingly, a palladium-catalysed deallylation followed by a Boc protection was performed that afforded the *N*-Boc alkene **98** in 98% yield (*Scheme III.9*).

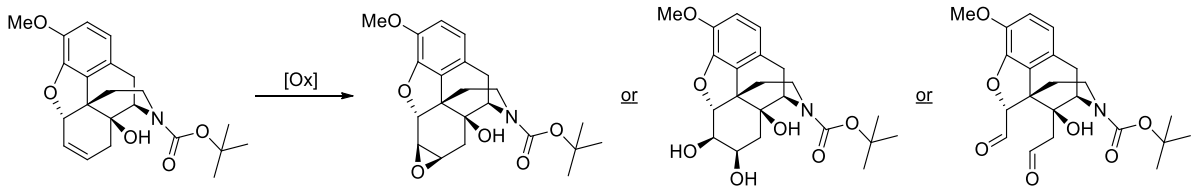


Scheme III.9: Deallylation and Boc protection of alkene **77**

We then reinvestigated the oxidation of the alkene under different conditions (*Table III.3*). Dihydroxylation with osmium tetroxide did not provide the product, and unreacted starting material was recovered. The same outcome was observed when we attempted the oxidative cleavage using ruthenium (III) chloride and Oxone® (entries 1 and 2). Attempted ozonolysis was not promising either (entry 3): although two potential aldehyde peaks were detected on the crude NMR spectrum, the two aromatic protons disappeared, which led us to conclude about extensive degradation of the substrate. Several sets of conditions for epoxidation were tested on the alkene **98**. The idea was to carry out the oxidation stepwise, as the direct cleavage of the double bond did not give satisfactory results. As mentioned above, *m*CBPA is the reagent of choice for this reaction. Unfortunately, only 21% of starting material was recovered when this reagent was employed (entry 4). Vanadyl acetylacetonate ($VO(acac)_2$), in combination with *tert*-butyl hydroperoxide, is a known epoxidizing agent for homoallylic alcohols. In the presence of this reagent combination, we were pleased to detect a 1:1 mixture of starting material and epoxide **96** (entry 5). Alternatively, in their total synthesis of (-)-morphine, Taber and co-workers reported the use of a (diperoxotungsto)phosphate catalyst with hydrogen peroxide.[107] The use of this system, along with the synthesis of the catalyst, was first reported by D'Aloisio for the epoxidation of various olefins.[108] Using these conditions, the epoxide **96** was obtained in 48% yield. For this reaction, an excess of hydrogen peroxide was used, and the reaction mixture was stirred in refluxing DCE for an extended period (40H). It resulted in the formation of an overoxidized product (or the dimer of the epoxide), as the aromatic disappeared to become a singlet. We found that the amount of hydrogen peroxide added could be decreased to 3 equivalents, and the reaction time to 7 h when the concentration of the reaction was increased. The product of this reaction was isolated in 81% and the overoxidized product (or dimer) was not detected (entry 6).

Having found conditions to selectively oxidise the required olefin, we decided to re-investigate the dihydroxylation reaction. Pleasingly, the alkene **98** was dihydroxylated with sodium periodate in the presence of ruthenium (III) chloride. The diol **99** was obtained in 72% yield.

The protecting group switch was successful and allowed the oxidation of the double bond in good yield. As we were able to synthesise the diol **99**, we decided to continue the synthesis of *impurity 9* from this compound instead of the epoxide.



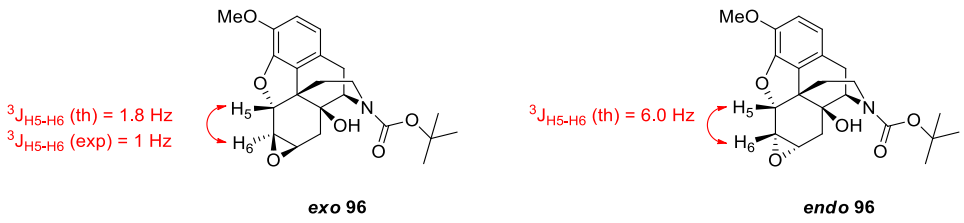
98 **96** **99** **100**

Entry	Transformation	Conditions	Outcome
1	Dihydroxylation	Cat. OsO_4, NMO	100% RSM
2	Oxidative cleavage	$RuCl_3$ (1mol%), Oxone®	83% RSM
3	Oxidative cleavage	O_3	Degradation/overoxidation
4	Epoxidation	*m*CPBA	21% RSM
5	Epoxidation	$VO(acac)_2$ (30mol%), TBHP	50% conversion to epoxide **96**
6	Epoxidation	Tungsten catalyst (20mol%), H_2O_2	81% epoxide **96**
7	Dihydroxylation	$RuCl_3$ (7mol%), $NaIO_4$	72% diol **99**

Table III.3: Oxidation of *N*-Boc alkene. Tungsten catalyst = $[(C_8H_{17})_3NCH_3]_3^+[PO_4[W(O)(O_2)_2]_4]^{3-}$

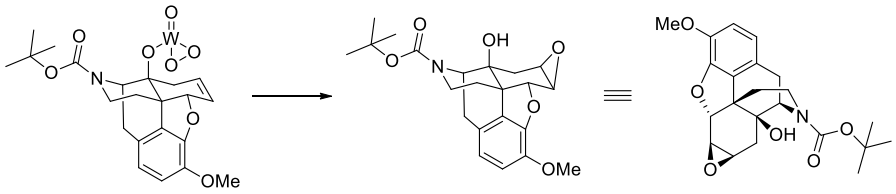
Stereochemistry of epoxide **96**

All the dihedral angles in compound **96** were generated using Chem3D. The theoretical coupling constant between protons H5 and H6 was then calculated using the Karplus equation and compared to the experimental coupling constant. Chem3D gave a value of 65.3° for dihedral angle H5-C5-C6-H6, which corresponds to a theoretical coupling constant of 1.8 Hz. Experimental results are in accordance with this result. Indeed, ^{1}H NMR analysis of the epoxide **96** shows that the proton H5 appears as a triplet with a coupling constant of 1 Hz: a coupling of 1 Hz with H6 and a long-range coupling of 1 Hz with H7 (*Scheme III.10*). For comparison, the dihedral angles of the diastereomer *endo* **96** were generated and the theoretical coupling constant was calculated. The dihedral angle H5-C5-C6-H6 has a value of 38.8° and thus, a coupling constant of 6 Hz. Based on these calculations, the stereochemistry of **96** was assigned as the *exo* epoxide.



Scheme III.10

Kamata and co-workers have been studying the catalytic epoxidation of olefins using a dinuclear peroxotungstate catalyst. They demonstrated that, in the course of the epoxidation of allylic alcohols, the first step of the mechanism would be the substitution of a molecule of water on the metal centre by the alcohol functionality.[109] In the case of naloxone, it can be argued that the tertiary alcohol at C14 coordinates to the catalyst and then plays the role of directing group for the epoxidation, which could explain the formation of the *exo* epoxide (*Scheme III.11*).



Scheme III.11: Formation of epoxide **96**

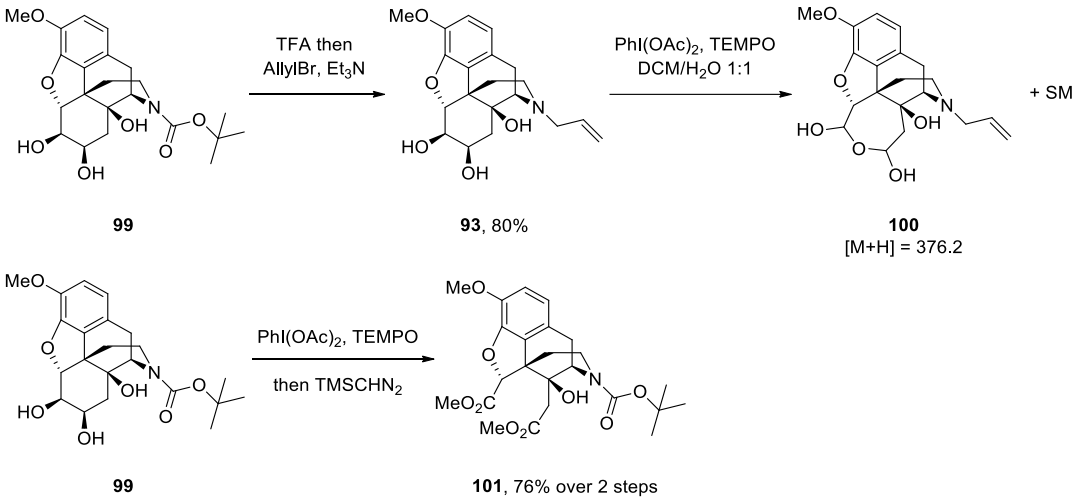
The second peroxide bridge on the tungsten atom has been removed for clarity

III.1.3. Oxidative cleavage – End of the synthesis

In 2012, Iwabuchi and co-workers reported the oxidative cleavage of vicinal diols into the corresponding dicarboxylic acids using (diacetoxy)iodobenzene ($PhI(OAc)_2$) as the oxidant and 1-methyl-2-azaadamantane *N*-oxyl (1-Me-AZADO) as the catalyst, in a biphasic solvent system (DCM/H_2O 1:1).[110] They were able to convert a range of cyclic and acyclic diols into (di)carboxylic acids. As we managed to obtain the diol derived from naloxone, we decided to try this method on two different substates: the *N*-allyl diol **93** (obtained in 85% yield after Boc deprotection and allylation of the secondary amine with allyl bromide, *scheme III.12*), and the *N*-Boc diol **99**. In the case of the *N*-allyl diol **93**, after 90 min, LC-MS analysis showed mostly starting material and another compound with a mass ion of 376.2. From a mechanistic point of view, Iwabuchi proposed that the oxidative cleavage might proceed via the oxidation of the diol to the corresponding dialdehyde or diketone, which would be then oxidised into two carboxylic acids. As shown in *scheme III.10*, in the presence or water, the dialdehyde would be able to form the hydrate **100** ([M+H] = 376.2). However, this compound was formed in low yield and could not be isolated and characterised, and so its identity remains

unconfirmed. After extending the reaction time to 20H, the conversion of the starting material did not increase and so we abandoned this route.

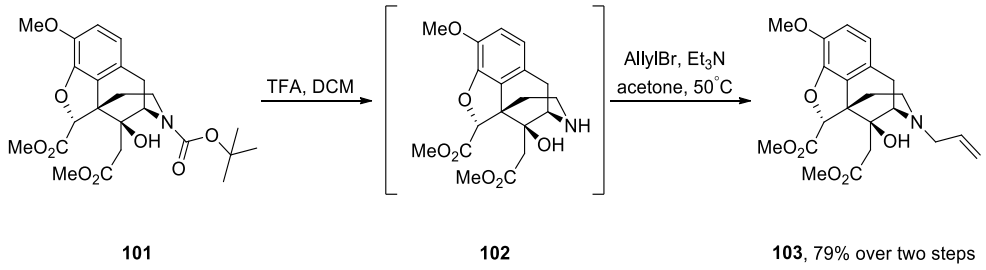
We then turned our attention to the oxidative cleavage of the *N*-Boc diol **99**. In this case, the product was detected by LC-MS, but it could not be isolated, probably due to its high water solubility. In order to avoid this problem, we treated the crude mixture with an excess of (trimethylsilyl)diazomethane and the corresponding *N*-Boc diester **101** was isolated in 76% yield (*Scheme III.12*).



Scheme III.12: Oxidative cleavage of diols **93** and **99** and allyl protection

At this point of the synthesis, we had achieved three key transformations: the synthesis of the alkene from the ketone, the oxidation of the alkene and finally, the oxidative cleavage. From the *N*-Boc diester **101**, the synthesis of the *impurity 9* required only four further steps: Boc deprotection and allylation, hydrolysis of the esters and deprotection of the methyl ether.

Compound **101** was treated with an excess of trifluoroacetic acid at room temperature. The secondary amine was then treated with allyl bromide to give the *N*-allyl diester **103** in 79% yield (*Scheme III.13*).

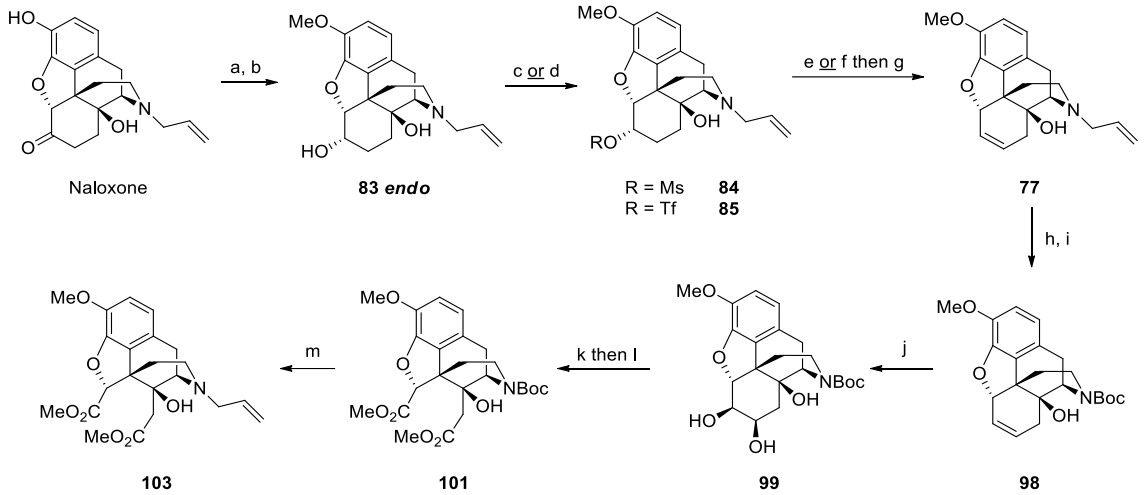


Scheme III.13: Boc deprotection and allylation steps

Regarding the deprotection of the esters and the methoxy group, we first used a combination of aqueous HBr with a phase transfer catalyst (trioctylmethylammonium chloride, Aliquat® 336). These conditions had been reported for the deprotection of aryl methyl ethers in the past.[111] LC-MS analysis showed that the major compound was the diacid **IX** (*impurity 9*), with some minor compounds containing a bromine atom. The ^{1}H NMR of the crude mixture showed an almost clean compound, however, the integration of the different signals implied that a mixture of compounds was present. Indeed, the ratio between one of the aromatic protons and the allyl CH_2 was 1:1.5 instead of 1:2. The mixture was sent to Indivior for analysis, in order to confirm the presence of this impurity in the degraded sample. HPLC analysis revealed that the diacid **IX** was actually a minor component in this mixture and, according to mass spectrometry, the other compounds were only partially deprotected **103**.

We assumed that the partial deprotection of the starting material was due to its low solubility in aqueous HBr, therefore the same reaction was performed in a mixture of acetonitrile and water. Unfortunately, starting material was recovered. We then attempted to fully deprotect the *N*-allyl diester **103** by treating it with an excess of aqueous HBr, without including the phase transfer catalyst. This reaction led to a mixture of compounds containing bromide atoms (according to LC-MS analysis). Finally, the diester **103** was hydrolysed using a solution of potassium hydroxide in methanol. This reaction was successful and the conversion of the diester to the corresponding diacid was complete. We decide to attempt the deprotection of the methyl ether using boron tribromide (BBr_3), unfortunately, the starting material was recovered, probably due to the low solubility of the diacid in organic solvents.

At this final stage of the synthesis, we realised that a methyl ether was probably not the right protecting group for the phenol. Given that the last step of the synthesis is the deprotection of the two esters, we wondered if the sequence could be repeated with a more acid- or base-sensitive protecting group at the 3 position. Even though we failed to provide a clean sample of the *impurity 9*, we designed a synthetic route for the preparation of the *N*-allyl diester **103** from naloxone, obtained in 19% overall yield over 11 synthetic steps (*Scheme III.14*).



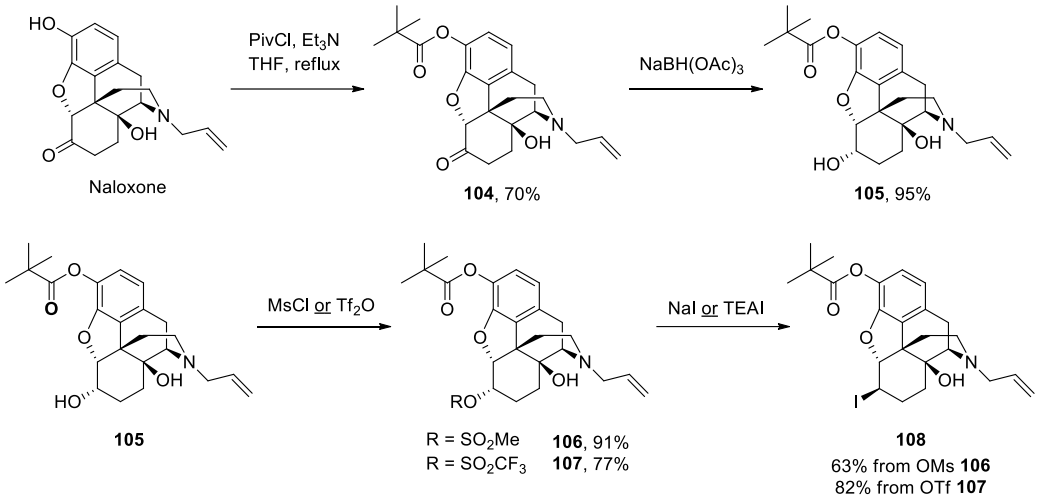
Scheme III.14: Semi-synthesis of *N*-allyl diester **103** from naloxone

Reagents and conditions: a) MeI, K_2CO_3, acetone, 50°C, 84%. B) $NaBH(Oac)_3$, AcOH, rt, 82%. C) MsCl, pyridine, 0°C, 91%. D) Tf_2O, 4-methylmorpholine, $CHCl_3$, -30°C to 0°C, 80%. E) NaI, DMF, 100°C. f) TEAI, MeCN, -10°C to rt, 80% (from OTf **85**). G) DBU, DMF, 100°C, 74% (from OMs **84**). H) $Pd(PPh_3)_4$, DMBA, DCM, 40°C. i) Boc_2O, DIPEA, 1,4-dioxane, 60°C, 98% (from alkene **87**). J) $RuCl_3$, $NaIO_4$, EtOAc/MeCN/H_2O, 0°C, 72%. K) $PhI(Oac)_2$, TEMPO, DCM/H_2O 1:1, 0°C. l) $TMSCHN_2$, PhMe/MeOH 4:1, rt, 76% (from diol **99**). M) TFA then AllylBr, Et_3N, acetone, 50°C, 79%. TEAI = tetraethylammonium iodide. DMBA = 1,3-dimethylbarbituric acid

III.1.4. Synthesis of *impurity 9* using an ester as the phenol protecting group

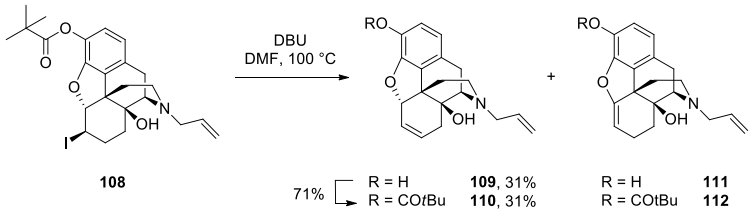
We decided to repeat the above-described sequence with a pivalate ester as protecting group of the phenol, as we assumed this protecting group would be robust enough in the different steps of this synthesis.

Using pivaloyl chloride, naloxone was transformed into the corresponding pivaloyl ester **104** in 70% yield. The following reduction of the ketone afforded the corresponding alcohol **105** in 95%. Mesylation followed by substitution with sodium iodide provided the iodide **108** in 52% yield over two steps. Alternatively, the yield of these two steps could be improved by preparing the iodide via the triflate **107** (*Scheme III.15*). Using this route, the iodide was then obtained in 63% after two steps.



Scheme III.15

The elimination step proved to be more problematic with the pivalate derivative, compared to the corresponding methoxy compound; a mixture of enol ethers **111** and **112** and alkenes **109** and **110** was detected by NMR spectroscopy, which led to difficult separation on column chromatography. The alkene **110** was isolated in 31% yield, along with the deprotected alkene **109** (also isolated in 31%). The rest of the material, which includes the enol ether 3-OPiv **111** and 3-OH **112**, was not isolated. The phenol moiety in alkene **109** can be protected by treatment of the alcohol with potassium carbonate and pivaloyl chloride and provided an additional 22% of the protected alkene **110** (*Scheme III.16*).

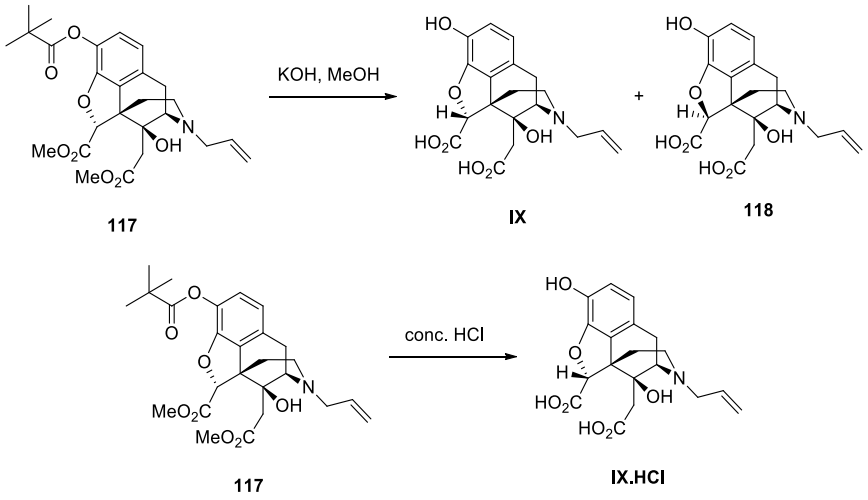


Scheme III.16: Elimination step

The deallylation and Boc protection steps proceeded smoothly to give the *N*-Boc alkene **113** in 92% yield over two steps. The following dihydroxylation step, using only 7 mol% of the catalyst, provided a mixture of starting material and product. The catalyst loading had to be increased to 14 mol% to ensure a complete conversion of the starting alkene, and the corresponding diol **114** was isolated in 59% yield. Then, treatment of the diol with $PhI(OAc)_2$ and a catalytic amount of TEMPO provided the di-carboxylic acid **115**. The esterification was carried out on the crude material, using TMS-diazomethane, and afforded the *N*-Boc diester **116** in 90% yield over two steps. The Boc group was then deprotected by

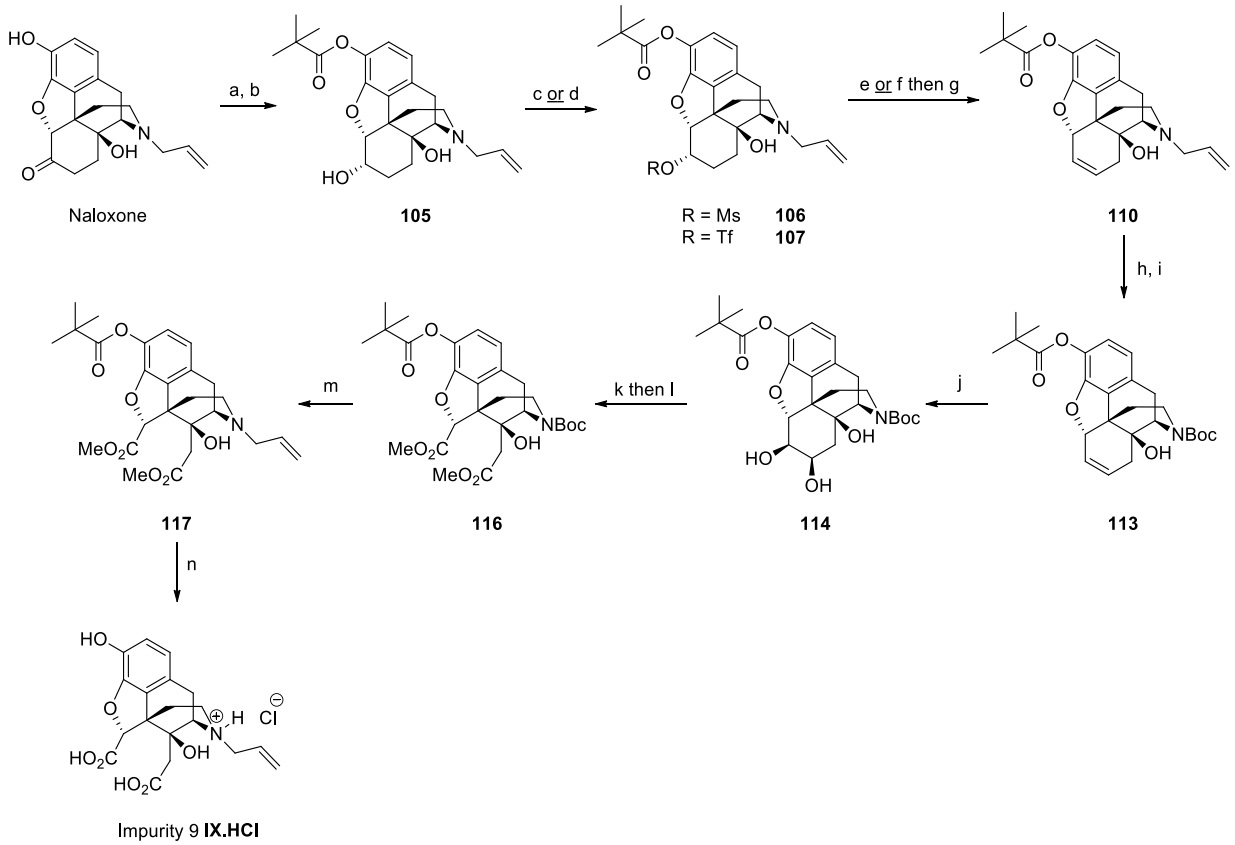
preparing a 0.1 M solution of diester **116** in trifluoroacetic acid, and rapidly gave a secondary amine. The residue was directly converted to the *N*-allyl diester **117**, obtained in 61% yield.

This sequence finally led us to the last step, the hydrolysis of the three esters. First, we attempted a saponification of the esters with potassium hydroxide in methanol. The reaction can be easily monitored by TLC analysis, as the starting material migrates on silica unlike the product, due to its high polarity. After three hours, although the conversion of the starting material was complete, a compound was detected by TLC analysis with a similar (but not identical) R*f* to the starting material, indicating a potential partial deprotection. When adding an excess of base, although LC-MS analysis showed a clean compound with the expected mass ion, a mixture of two compounds was detected by NMR spectroscopy in a 2.5:1 ratio. We concluded that, in basic conditions, the H5 proton can be deprotonated, which would lead to epimerisation of carbon C5. The two compounds might be the two epimers at C5 of the diacid **IX** and **118** (*Scheme III.17*). Pleasingly however, the acidic hydrolysis of the esters led to the formation of the hydrochloride salt of diacid **IX** in quantitative yield, as a single compound.



Scheme III.17: Deprotection of the diester **117**

In summary, we applied the aforementioned synthesis to the 3-OPiv series, for the synthesis of the *impurity 9*. This sequence afforded this compound in 5.5% overall yield after 12 steps (6.6% using the triflate **107**) (*Scheme III.18*).



Scheme III.18: Semi-synthesis of *impurity 9* **IX**

Reagents and conditions: a) PivCl, Et_3N, THF, 60°C, 70%. B) $NaBH(OAc)_3$, AcOH, rt, 95%. C) MsCl, pyridine, 0°C, 83%. D) Tf_2O, 4-methylmorpholine, $CHCl_3$, -30°C to 0°C, 77%. E) NaI, DMF, 100°C, 63% (from OMs **106**). F) TEAI, MeCN, -10°C to rt, 82% (from OTf **107**). G) DBU, DMF, 100°C, 53%. H) $Pd(PPh_3)_4$, DMBA, DCM, 40°C. i) Boc_2O, DIPEA, 1,4-dioxane, 60°C, 92% (from alkene **110**). J) $RuCl_3$, $NaIO_4$, EtOAc/MeCN/H_2O, 0°C, 59%. K) $PhI(OAc)_2$, TEMPO, DCM/H_2O 1:1, 0°C. l) $TMSCHN_2$, PhMe/MeOH 4:1, rt, 90% (from diol **114**). M) TFA then AllylBr, Et_3N, acetone, 50°C, 61%. N) conc. HCl, 100°C, quant.

III.1.5. Analysis of the diacid IX

The diacid **IX** was then analysed by Indivior, in order to confirm the presence of this impurity in the degraded sample of Suboxone and more importantly, confirm the structure of the impurity. First, the NMR data of compound **IX** were compared to the data that were obtained after analysis of the compound extracted from the degraded sample, by preparative HPLC. The chemical shift as well as coupling constants were similar although some differences have been noticed. This may be attributed to the fact that the synthesised substance is a salt, whereas the compound that have been extracted is a free base. The retention time and low-resolution mass spectroscopy of compound **IX** was compared to the one in the degraded sample. *Figure III.6* shows the HPLC traces of the degraded sample and compound **IX** separately, and *Figure III.7* shows the HPLC trace of the degraded sample

alone (unspiked sample) and the HPLC trace of compound **IX** added to the degraded sample (spiked sample). The increased peak at 9.54 minutes shows an increase in the concentration of *impurity 9* in the mixture, which confirm the presence of this impurity in the degraded sample. Finally, the fragmentation pattern of the diacid **IX** has been compared to the one of the *impurity 9* in the degraded sample of Suboxone®. As shown in *figure III.8*, mass ions of the major fragments are found in the degraded sample.

These analysis show that the diacid **IX** is one of the degradation products of naloxone in the Suboxone® sublingual film.

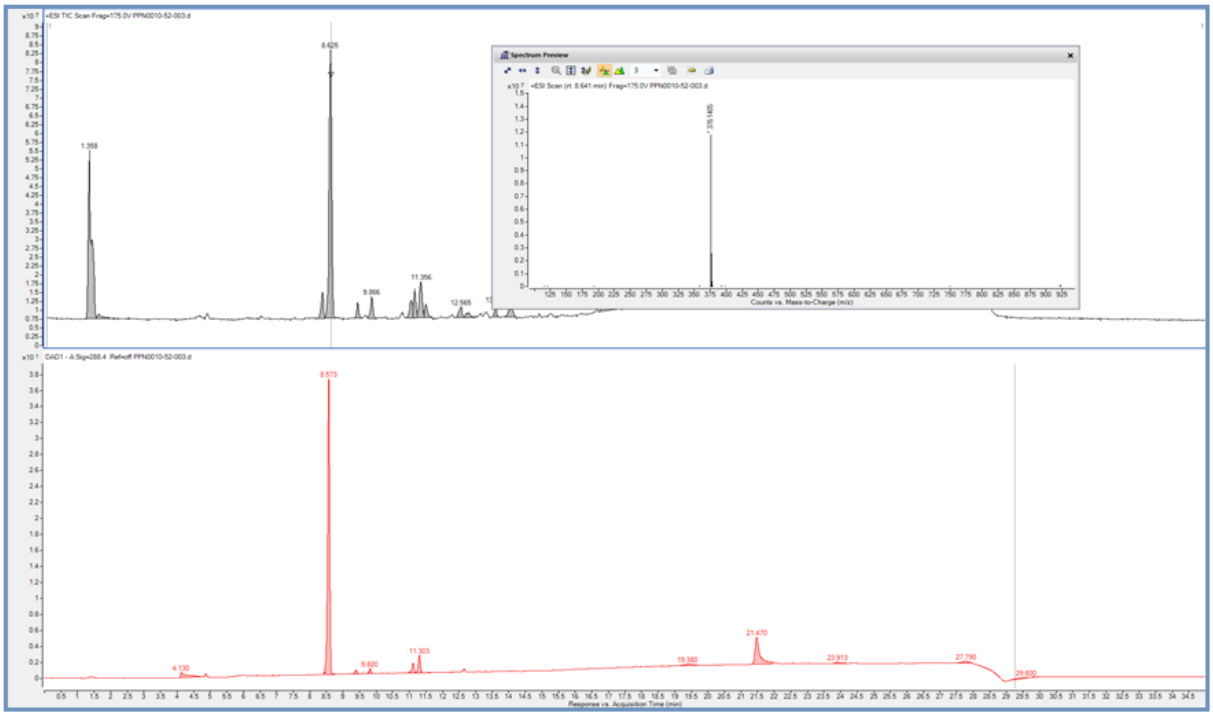


Figure III.6: HPLC traces of the degraded sample (top) and synthesised compound **IX** (bottom)

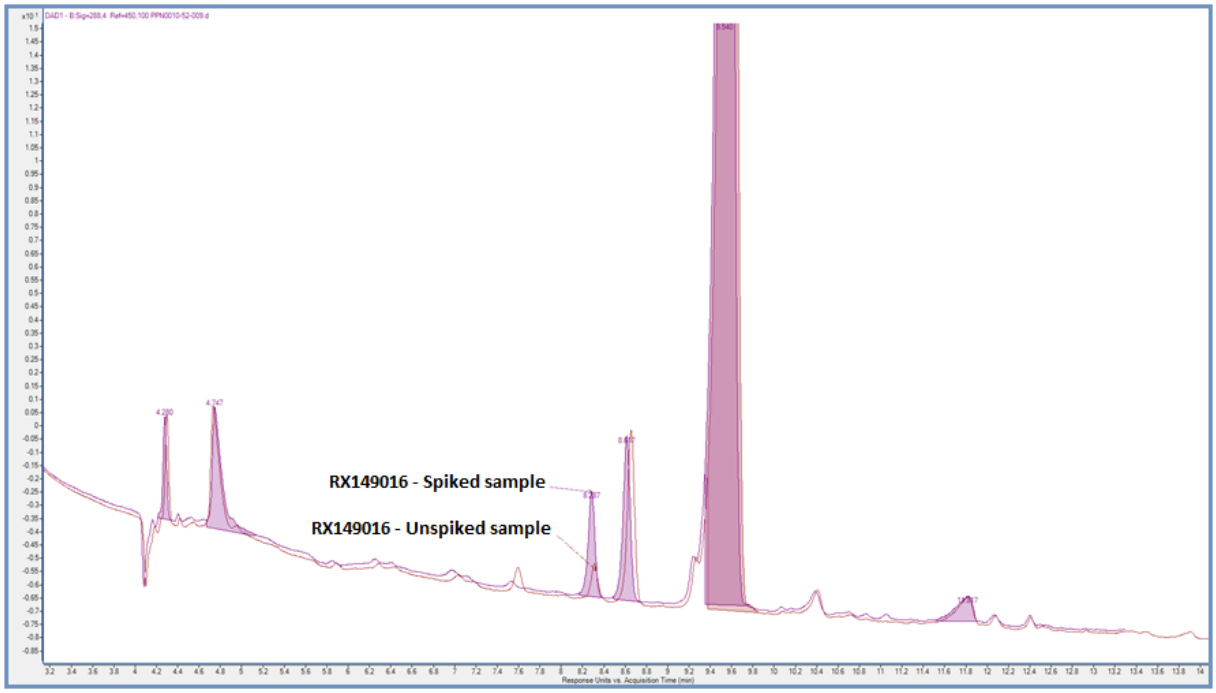


Figure III.7: HPLC trace of the degraded sample and degraded sample + *impurity 9*

Peak Name	File name	Sample	RT (min) MS	m/z (MS)	m/z (MS^2)
Peak 9	8275089_23oct12_02 (Full Scan) 8275089_23oct12_04 (MS^2)	Suboxone NDC 12496-1208-1 100mL 0.1%TFA Suboxone NDC 12496-1208-1 10mL 0.1%TFA	9.18	376.13859 ($C_{19}H_{22}O_7N$)	340.11729($C_{19}H_{18}O_5N$), 330.13298($C_{18}H_{20}O_4N$), 314.13805($C_{18}H_{20}O_4N$), 299.11466($C_{17}H_{17}O_4N$), 296.09121($C_{17}H_{14}O_4N$), 284.09112($C_{16}H_{14}O_4N$), 272.09116($C_{15}H_{14}O_4N$), 254.11694($C_{16}H_{16}O_2N$), 214.08563($C_{13}H_{12}O_2N$), 154.08588($C_8H_{12}O_2N$) 231.06475($C_{13}H_{11}O_4$), 185.05891($C_{12}H_9O_2$), 171.04361($C_{11}H_7O_2$).
	8275089_10dec12_13	Suboxone NDC 12496-1208-1	9.23	376.13890	
	8275089_10dec12_11	S1488A EDEN 2/0.5mg A08DW104-028	9.23	376.13837	
	8275089_10dec12_12	S1488B EDEN 8/2mg A08EJ102-025	9.24	376.13831	

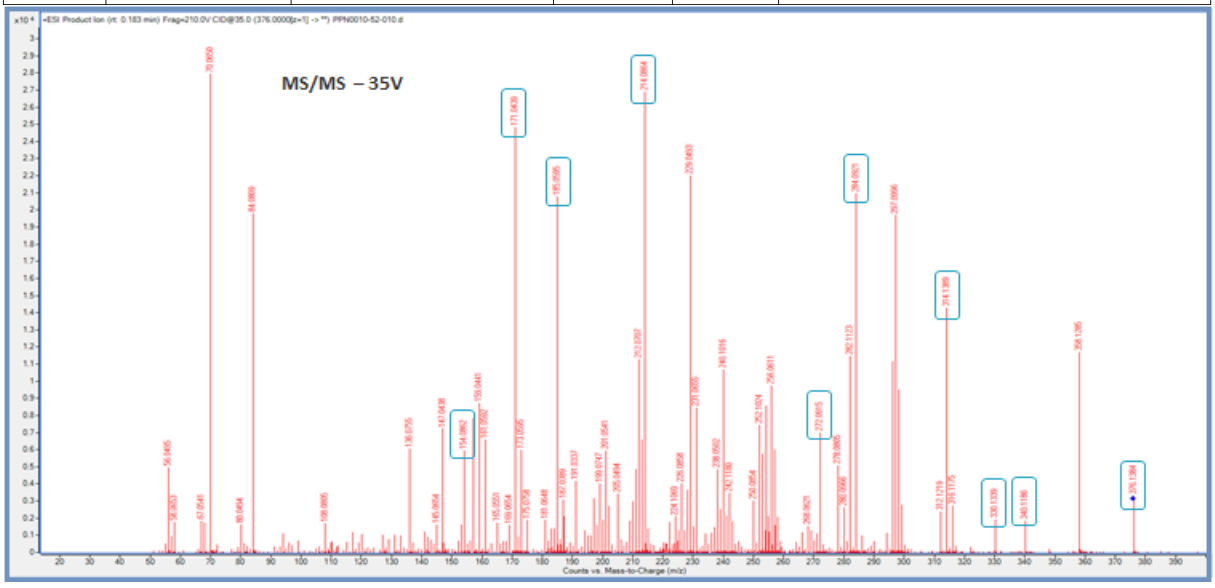


Figure III.8: Fragmentation pattern of impurity 9 in the degraded sample (top) and compound **IX** (bottom)

III.1.6. Conclusion

The synthesis of the *impurity 9* has been designed using naloxone methyl ether **61** as the starting material. The first intermediate shown in the retrosynthetic analysis was the alkene **77**, and was obtained in 55% yield, after a four-step sequence. The direct oxidation of **77** resulted only in the formation of the corresponding *N*-oxide, which is the consequence of the basicity of the nitrogen atom. The allyl group was replaced by a Boc group (compound **98**), and the oxidation of the resulting alkene allowed both epoxidation and dihydroxylation. The diester **103** was then obtained after three steps from the diol **99**, in 60% yield. Although attempts of the deprotection were not successful, it was found that the synthesis could be repeated when naloxone methyl ether was replaced by the corresponding 3-pivalate ester **104**. Eventually, compound **IX** was obtained in 5.5-6.6% overall yield after 12 steps.

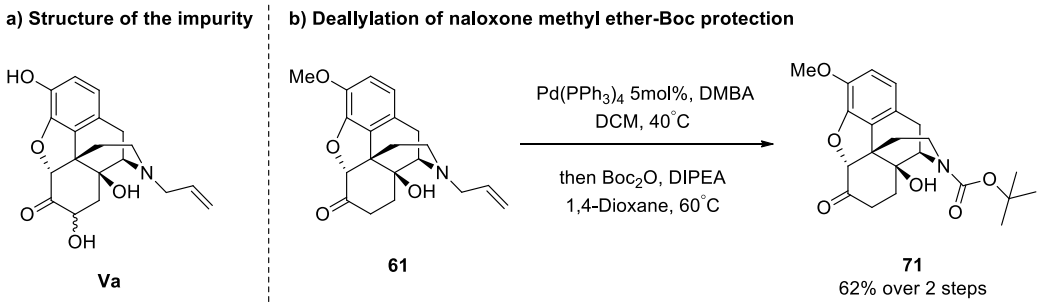
The structure of the impurity was confirmed by NMR spectroscopy and mass spectrometry. Indeed, several identical fragments were found when both compound **IX** and the impurity isolated from the degraded sample were analysed.

Finally, the presence of compound **IX** in the degraded sample was confirmed by HPLC analysis.

III.2 Investigation into the synthesis of *alpha*-hydroxy ketone Va

Acyloin containing compounds are of great interest, as this motif is present in numerous biologically active compounds.[112–114] Therefore, methods for the preparation of α-hydroxy ketones have been developed over the years, such as the Rubottom oxidation involving the epoxidation of a silyl enol ether, or the reductive coupling of esters, known as the acyloin condensation.

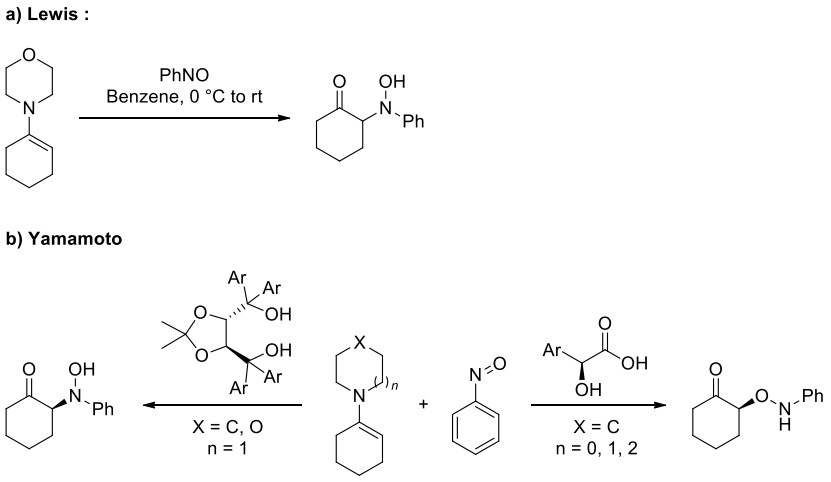
This section describes the results of the investigation into the synthesis of the *α*-hydroxy ketone **Va**, another potential impurity derived from naloxone (*Scheme III.16a*). In order to achieve the successful synthesis of this compound, a range of oxidation conditions has been screened, using naloxone methyl ether **61** or *N*-Boc noroxycodone **71** as the substrate. Compound **71** was prepared using the same deallylation-Boc protection sequence described in *Chapter II* and was obtained in 62% yield after two steps (*Scheme III.16b*).



Scheme III.16

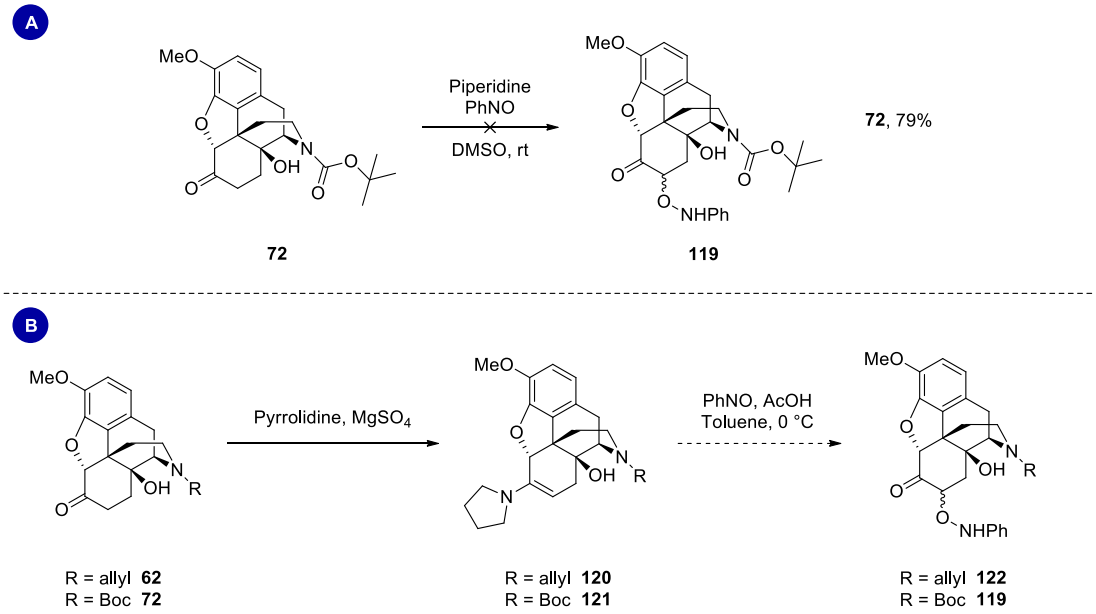
III.2.1 *Alpha*-hydroxylation at C7

The initial idea was the transformation of the ketone into a nucleophile, which would react with an oxygen electrophile to form the corresponding α-oxygenated ketone. We therefore decided to investigate the reaction of an enamine with nitrosobenzene. The nitroso-aldol reaction was first demonstrated by Lewis in 1972, for the synthesis of *alpha*-amino ketones (*Scheme III.17a*).[115] Since then, this protocol has been optimised to allow the synthesis of *alpha*-hydroxy ketones by using carboxylic acids as an additive. On the other hand, as exemplified by Yamamoto and co-workers, the use of alcohols promotes the synthesis of the α-amino product (*Scheme III.17b*).[116]



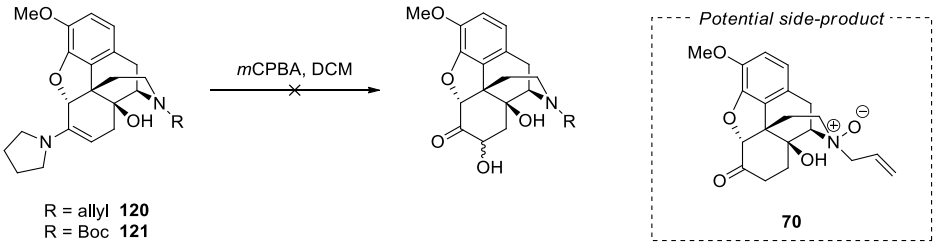
Scheme III.17

To test the feasibility of this reaction on our substrate, we began with the reaction of ketone **71** with piperidine and nitrosobenzene in DMSO (*Scheme III.18a*). Unfortunately, this reaction was not successful, and the starting material was recovered in 79% yield. Assuming that the initial formation of the enamine had failed, we decided to repeat the reaction in a stepwise manner, and the preparation of the enamine was first attempted. Ketones **61** and **71** were treated with a large excess of pyrrolidine in the presence of magnesium sulfate; enamines **120** and **121** were isolated by filtration and evaporation of the solvent. Both enamines were subjected to Yamamoto's conditions, namely one equivalent of nitrosobenzene, one equivalent of acetic acid in toluene, at 0 °C (*Scheme III.18b*). In both cases, the starting ketone was recovered, among a mixture of unidentified compounds, and the desired compound was not detected by LC-MS.



Scheme III.18: *α*-oxidation of ketone via enamines (1)

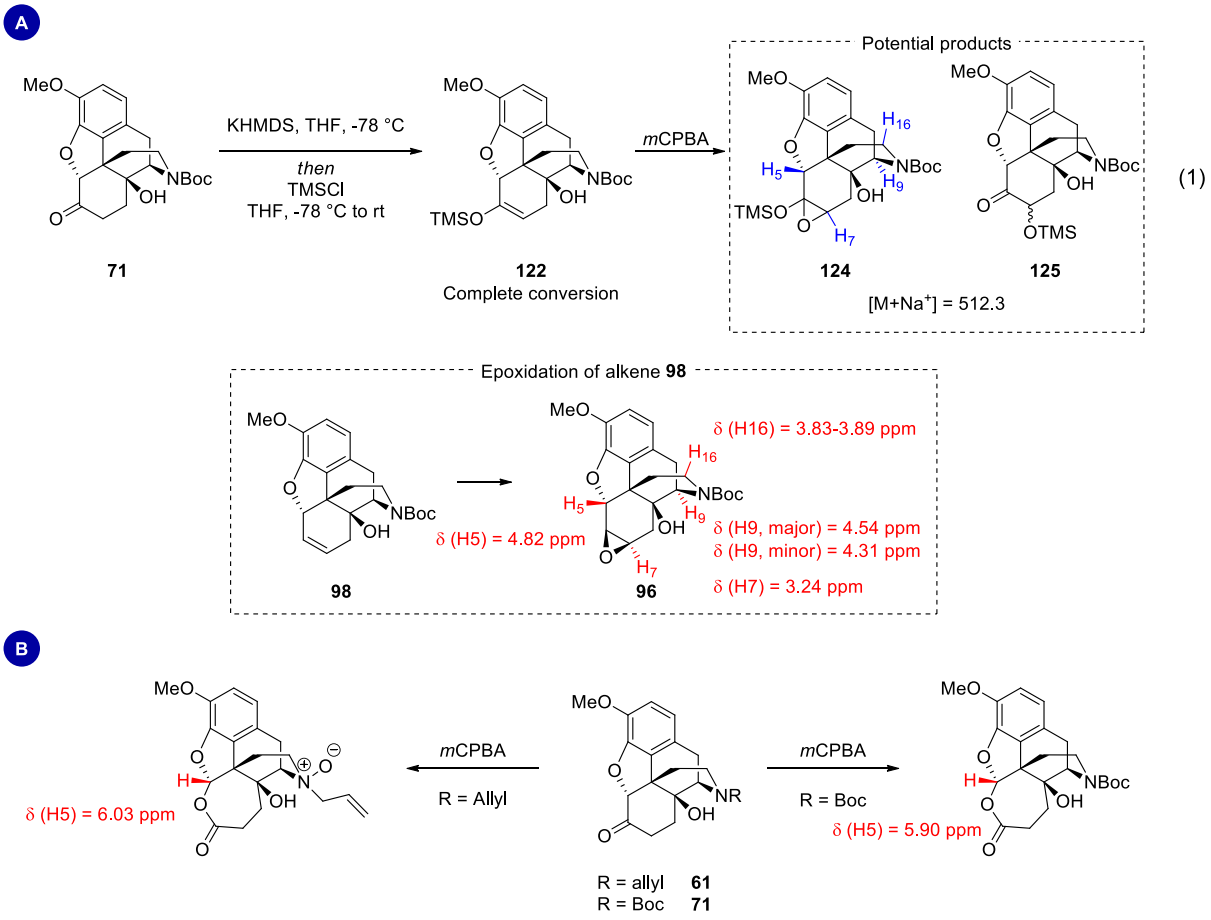
We then turned our attention to the oxidation of the enamine with *m*CPBA which, once again, led to the hydrolysis of the enamine to give the starting ketone (*Scheme III.19*). In the case of the reaction of enamine **121** with *m*CPBA, a mixture of ketone **71** and other compounds was detected by LC-MS. Another singlet (which could be the H5 of the desired product) was even noticeable on the ^{1}H NMR spectrum of the crude material. However, the corresponding methoxy and aromatic signals could not be clearly discerned. *m*CPBA is a 77% pure reagent, which contains small amount of 3-chlorobenzoic acid and water which could explain the propensity for the enamine to undergo hydrolysis. Moreover, in the case of the *N*-allyl enamine **120**, although it had not been clearly identified as a side-product of the reaction, it is reasonable to consider the potential formation of the *N*-oxide **70** as the oxidation of the basic nitrogen atom by *m*CPBA had already been observed (see *Section III.1*).



Scheme III.19: *α*-oxidation of ketone via enamines (2)

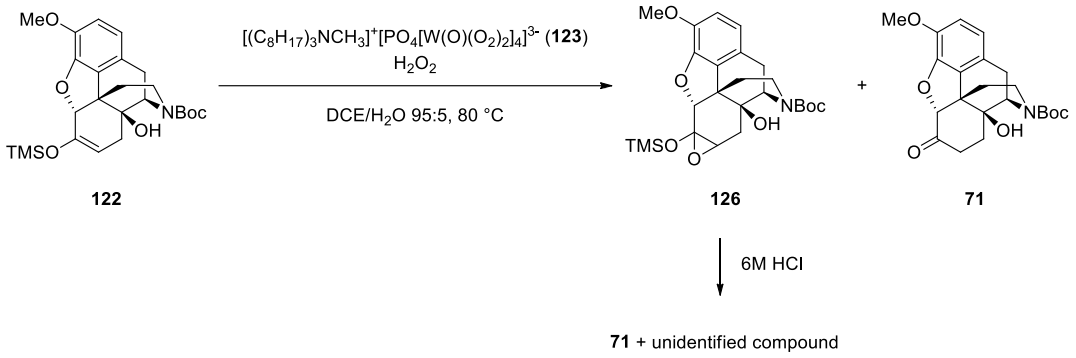
We then attempted the Rubottom oxidation of *N*-Boc noroxycodone **71** following a literature procedure.[117] Compound **71** was first transformed into the corresponding silyl enol ether **122** by

treatment with potassium bis(trimethylsilyl)amide (KHMDS) as the base and trimethylsilyl chloride. The subsequent oxidation step was performed using *m*CPBA or the (diperoxotungsto) phosphate catalyst **123** mentioned in section *III.1*.2. Although the conversion of the silyl enol ether was complete, the *m*CPBA reaction gave a mixture of several compounds. LC-MS analysis of the crude mixture revealed the presence of the desired product however, there was insufficient material for it to be detected in the ^{1}H NMR spectrum of the crude material. Moreover, we noticed the presence of a compound with a mass ion of [M+Na^{+}] = 512.3, which could correspond to the mass of the epoxide **124** or the *alpha*-oxygenated ketone **125** (*Scheme III.20a*, top). Purification was attempted, and a small amount of the "MW = 512.3" compound was isolated. We hypothesised that, if the isolated compound was the epoxide **124**, some ^{1}H NMR signals should be similar to those from the epoxide **96** (*Scheme III.20a*, bottom). In particular, we focused our attention on four signals: H5, H7 (epoxide proton), H9 and one H16; these protons are highlighted in blue in the case of epoxide **124**, and in red for the epoxide **96**. In the case of epoxide **96** (prepared during the investigation into the oxidation of the 6,7-alkene **98**, see section *III.1.2*), the H16 proton comes between 3.83 and 3.89 ppm, the chemical shift of the two rotameric H9 signals are at 4.31 and 4.54 ppm, H7 comes at 3.24 ppm and finally, H5 comes at 4.82 ppm. In the case of the epoxide **124**, which is potentially a product of the reaction (1) (*Scheme III.20a*, top), one proton is detected between 3.82 and 3.88 ppm, which matches with H16, the two signals at 4.33 and 4.50 ppm are potentially the rotameric H9 protons. Concerning H7, a doublet of doublets was detected at 3.09 ppm, which is slightly upfield compared to epoxide **96**. Unexpectedly, the H5 singlet was detected at 5.88 ppm, which is too far downfield for this compound. This change in chemical for the H5 proton has only been observed in the case of the Baeyer-Villiger oxidation of naloxone methyl ether **61** and *N*-Boc noroxycodone **71** to the corresponding lactones, where the H5 signal shifted to 5.95 and 5.91 ppm respectively (*Scheme III.20b*). In conclusion therefore, although some NMR signals confirm the presence of the epoxide in the molecule, this possibility in not entirely supported by the ^{1}H NMR data.



Scheme III.20

The second attempted oxidation using the (diperoxotungsto) phosphate catalyst **123** resulted in the complete conversion of the TMS-enol ether to give a mixture of *N*-Boc noroxycodone **71** (isolated in 8% yield) and epoxide **126**, among a mixture of unidentified compounds. Due to the complex mixture obtained in this reaction, purification of the epoxide by column chromatography was difficult and only a small fraction of mostly clean **126** was recovered. Unlike compound **124** mentioned above, chemical shifts for H5, H7, H9 and H16 are close to those found in epoxide **96**. These observations led us to propose the structure of compound **126** as the desired epoxide. The epoxide **126** was then treated with an excess of 6 M HCl in order to deprotect the TMS group and convert the epoxide to the desired *α*-hydroxy ketone. Unfortunately, less than 10% of the initial mass was recovered, and a 2:1 mixture of compounds was isolated. The major compound has been identified as *N*-Boc noroxycodone **71** but in the case of the minor component, the integration of the different signals on the ^{1}H NMR spectrum did not match with the desired product (*Scheme III.21*). Moreover, basifying the aqueous phase did not improve the mass balance.

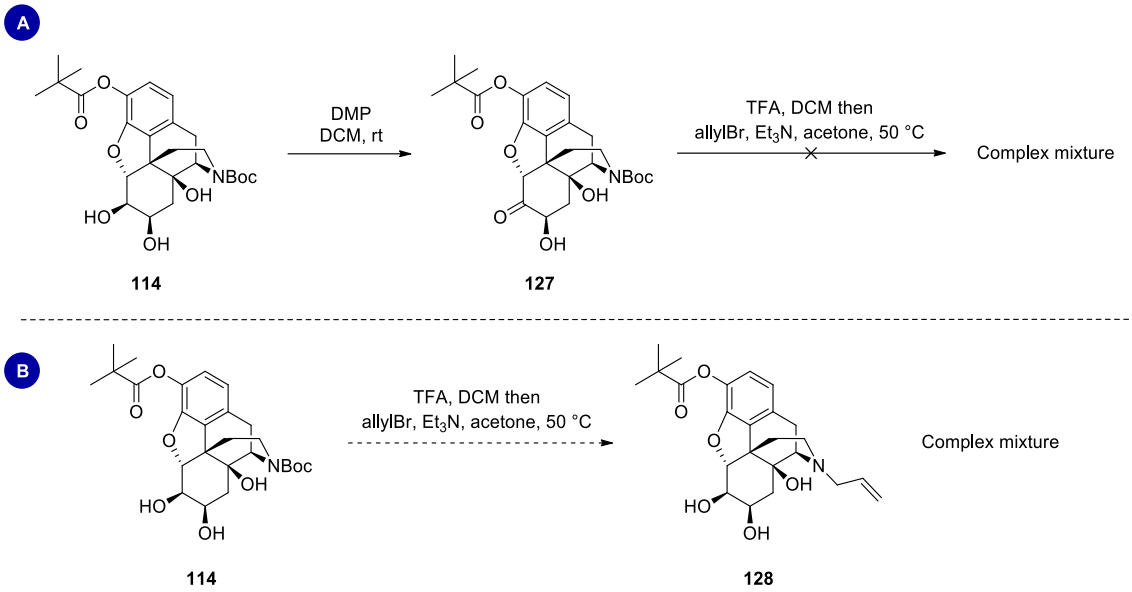


Scheme III.21

The oxidation of enol ether or enamine is a direct method for generating α-hydroxyketones from ketones, however this approach was not successful and gave the starting ketone as major product of the reaction in most cases. Therefore, we decided to try another approach for the synthesis of the desired impurity.

III.2.2 Oxidation of the diol 114

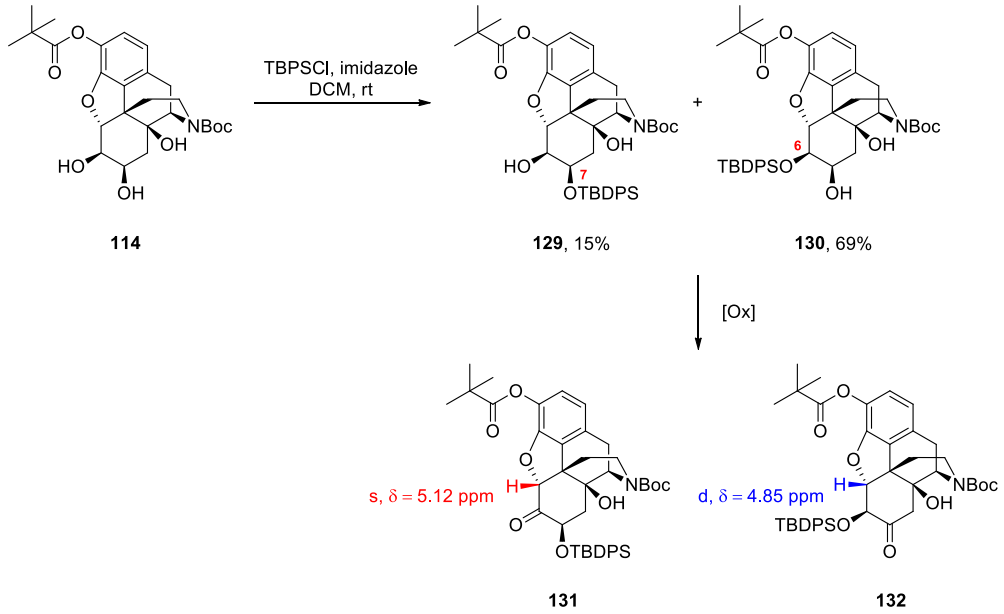
In the course of the synthesis of *impurity 9*, we have designed a route for the preparation of the diol **114** (*Scheme III.22*). With this compound in hand, we decided to test the direct oxidation of the diol. Several reaction conditions were attempted: DMDO (dimethyldioxirane), IBX (2-iodoxybenzoic acid) and DMP (Dess-Martin periodinane). The IBX oxidation was first attempted using DCM as the solvent, and the starting material remained untouched. Literature investigations revealed that dimethyl sulfoxide (DMSO) is the only solvent suitable for such reactions, as IBX is not soluble in other organic solvents. The reagent has to be stirred in the solvent for a few minutes, to ensure its dissolution. However, only benzoic acid residues were recovered when the solvent was changed. DMDO failed to provide the product and the starting material was recovered. On the other hand, DMP successfully converted the diol **114** into the ketone **127** in 74% conversion. The structure of the product was determined using ^{1}H NMR analysis: the presence of a H5 singlet at 4.79 ppm indicated the oxidation of the C6-alcohol to the corresponding ketone, instead of the C7. Although the formation of the ketone was not complete, it was decided to use the crude mixture in the next step (Boc deprotection and allylation of the resulting secondary amine) to test the feasibility of this approach (*Scheme III.22a*). Unfortunately, a mixture of unidentified products was recovered. The Boc deprotection followed by allylation seems to be a problem in the 3-OPiv derivatives. Indeed, in the case of the Boc deprotection and allylation of the diol **114**, a low mass balance was recovered (less than 40%), and the ^{1}H NMR analysis showed a mixture of unidentified products (*Scheme III.22b*).



Scheme III.22: Oxidation of the diol **114**

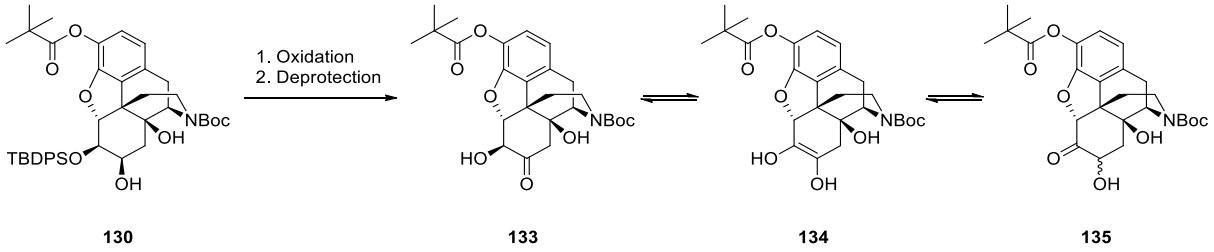
III.2.3 Regioselective mono-protection of diol **114**

Finally, it was decided to investigate the mono-protection of diol **114**. As our motivation was to achieve regiocontrol in the protection, a hindered protecting group was chosen, and the diol was treated with 2 equivalents of *tert*-butyldiphenylsilyl chloride (TBDPSCl) in the presence of imidazole. Pleasingly, a mixture of the two protected alcohols was recovered in a 4.3:1 ratio (determined by analysis of the crude ^{1}H NMR spectrum). After separation by column chromatography, the major compound was isolated in 69% yield and the minor compound, in 15%. It was not possible to distinguish between the two compounds by analysing the NMR spectra at this stage; indeed, for each alcohol the H5 signal is a doublet (with a different chemical shift). However, this H5 signal would become a singlet after the oxidation of the alcohol **129** to the corresponding ketone, whereas it would still be a doublet if alcohol **130** was oxidised (*Scheme III.23*). The oxidation of compounds **129** and **130** (see below for details) allowed us to conclude that the major compound in the protection step is the 6-silyloxy alcohol **130** and the minor is the 7-silyloxy alcohol **129** (*Scheme III.23*).



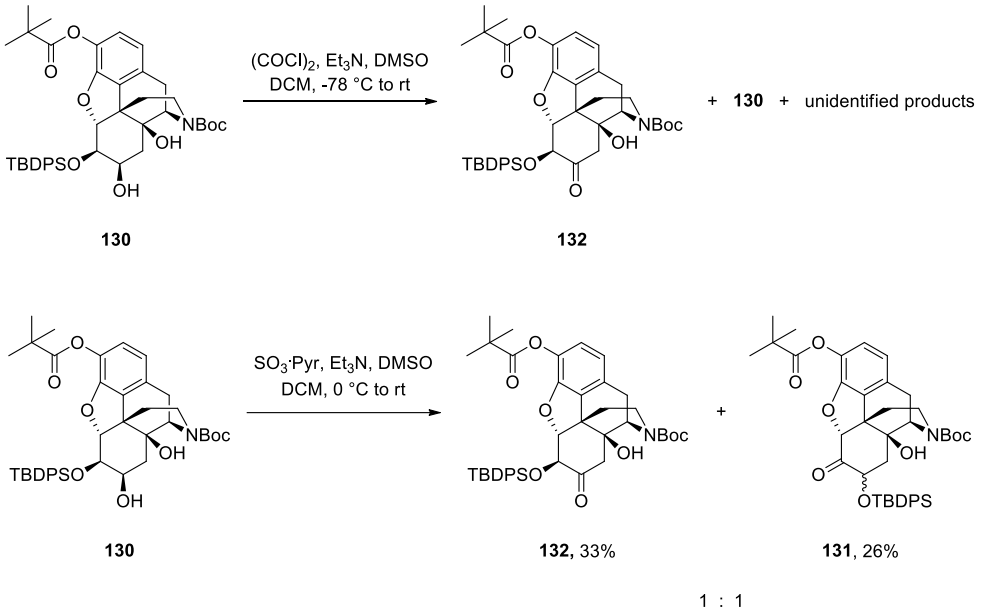
Scheme III.23: Protection of the diol **114**

Although the major silyl ether was the undesired regioisomer, we decided to press on with the conversion of this intermediate to the corresponding 6-hydroxy 7-keto isomer in the hope that this compound would tautomerise to the desired product (*Scheme III.24*). These studies were conducted in parallel with the oxidation of **129**.



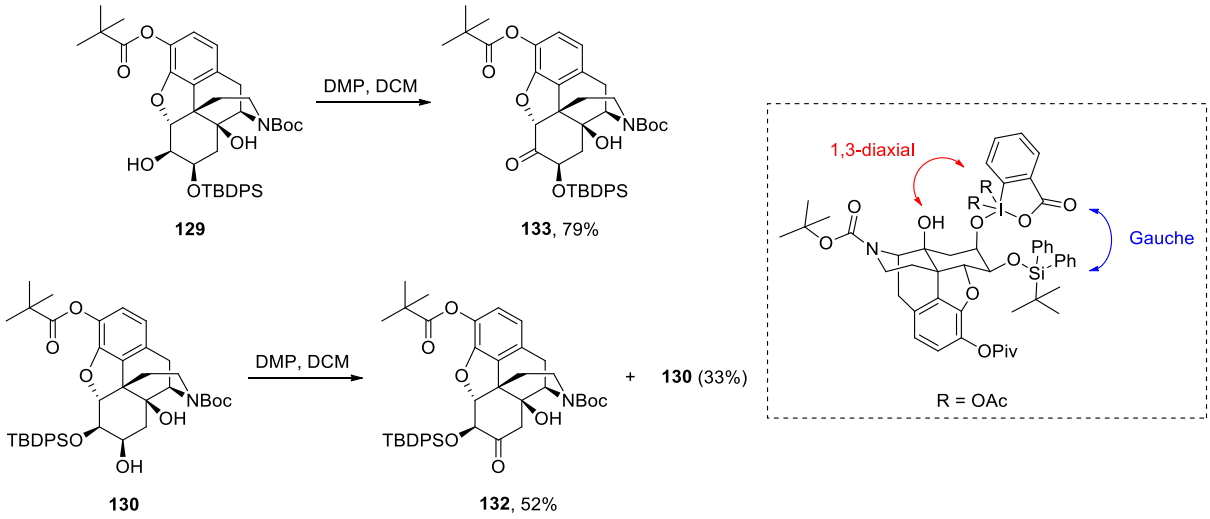
Scheme III.24

We began the oxidation of alcohol **130** with DMSO-based oxidations. Swern oxidation provided a 1:1 mixture of starting material and oxidised product, among other unidentified products (*Scheme III.25*, top). However, when a Parikh-Doering oxidation was performed on the same compound, the starting material was totally consumed and a 1:1 mixture of ketones **131** and **132** was recovered. The two compounds were isolated in 26% and 33% respectively, however the idea was to undertake the synthesis of both α-hydroxy ketones separately, this approach was then not pursued (*Scheme III.25*, bottom). The formation of ketone **131** can be explained by a silyl migration from the alcohol at C6 to the alcohol at C7 during the reaction.



Scheme III.25: DMSO-based oxidation of alcohol **130**

Hypervalent iodine reagents were also investigated in the oxidation reaction. Surprisingly, IBX did not provide the desired product when either **129** or **130** were subjected to oxidation with this reagent and again, only iodobenzoic acid residues were recovered. On the other hand, Dess-Martin periodinane successfully converted each alcohol into the corresponding ketone (*Scheme III.26*). Oxidation of alcohol **129** provided ketone **133** in 79% yield however, the conversion of alcohol **130** did not exceed 52%. The ketone **132** was isolated in 52% yield, along with the starting material **130**, in 33%. This difference in conversion between the two reactions can be explained by the steric hindrance of the alcohol in position 7 (compound **130**), even though it is not obvious on a two-dimensional drawing. As depicted in *scheme III.26*, the approach of the oxidant to position 7 is blocked on one side because of 1,3 diaxial interaction with the tertiary alcohol at C14, and on the other side, the bulky TBDPS group on the oxygen also blocks the approach of the oxidant because of gauche interaction, which leads to incomplete oxidation of the alcohol. Despite the incomplete conversion of alcohol **130**, the corresponding ketone was obtained in useful yield and we were then able to investigate the end of the synthesis.

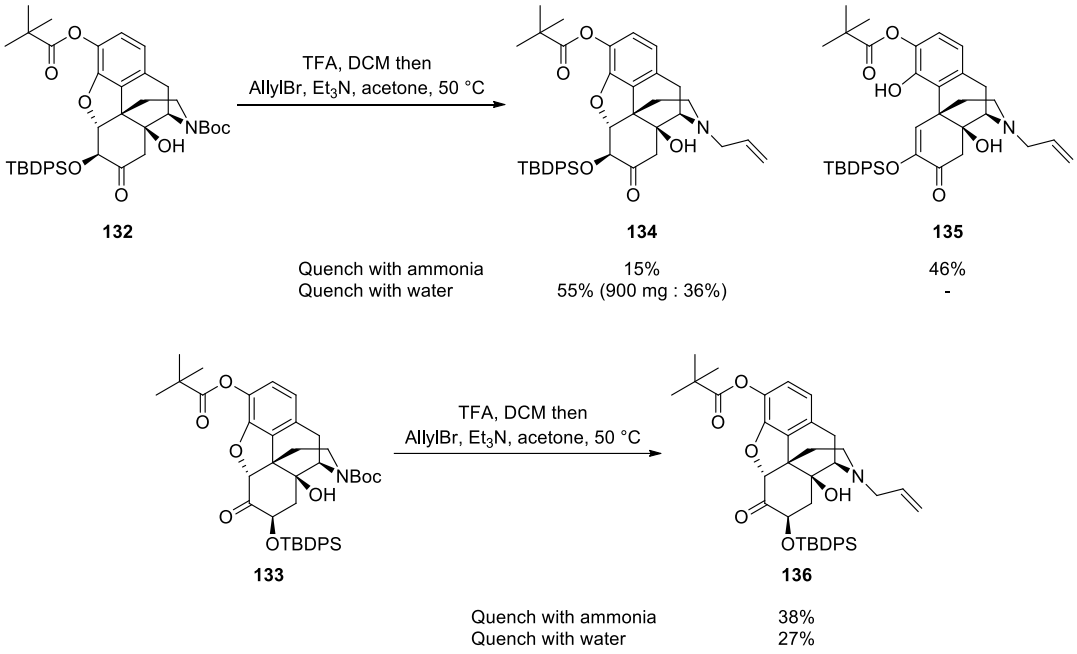


Scheme III.26: Oxidation of alcohols **129** and **130**

At this stage of the synthesis, the remaining steps were the Boc deprotection-allylation sequence, and the deprotection of the different protecting groups on the secondary alcohol and phenol. The deprotection of the Boc group followed by allylation of the nitrogen atom was then investigated for each ketone **132** and **133** (*Scheme III.27*).

Starting with the deprotection-allylation of ketone **132**, the corresponding *N*-allyl product **134** was obtained in only 15% yield, along with what appeared to be the elimination product **135** in 46% yield. In this case, the allylation reaction was quenched with aqueous ammonia solution. However, when the reaction mixture was quenched instead with water, the desired product was isolated in 55% yield and the elimination product **135** was not detected by ^{1}H NMR. However, only 54% of the mass of the crude was recovered after purification. Disappointingly, when the reaction was scaled up to 900 mg, the yield decreased to 36%.

In the case of ketone **133**, compound **136** was isolated in 38% yield when the allylation reaction was quenched with ammonia, and this decreased to 27% when quenched with water. Although the yields were moderate for the *N*-allyl derivatives **134** and **136**, we decided to carry on the synthesis of the α-hydroxyketone **Va** with the remaining deprotection steps.

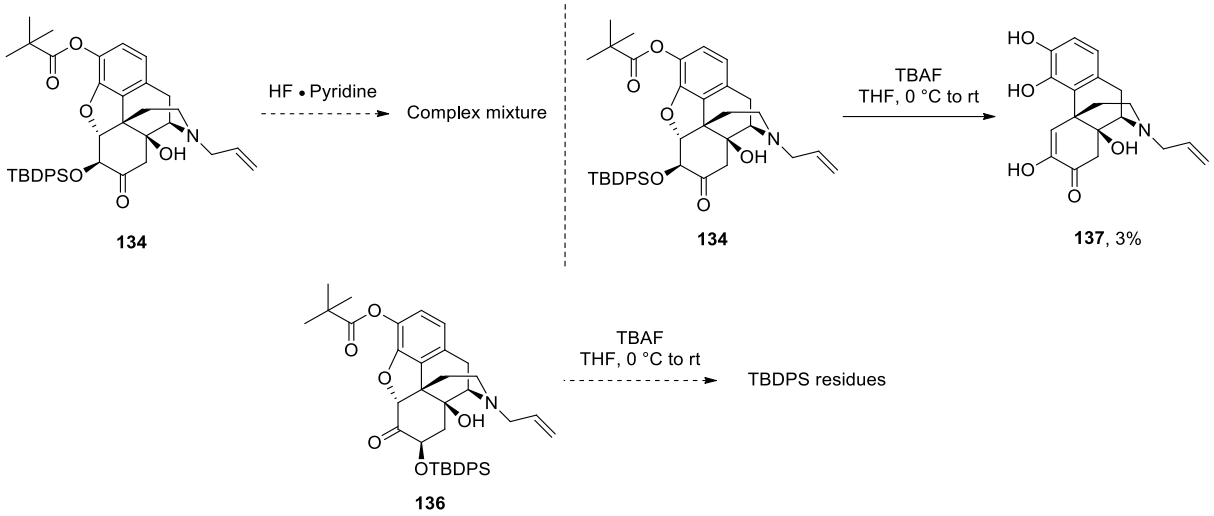


Scheme III.27: Boc deprotection – allylation of ketones **132** and **133**

We began by investigating the deprotection of the silyl ether by using HF•pyridine on the ketone **134**. We were hopeful that the acidity of this reagent would also offer the opportunity to deprotect the ester at C3, which is acid sensitive. Unfortunately, this reaction was not efficient, and the presence of multiple aromatic signals showed a mixture of compounds in the crude material. Moreover, the low mass recovery led us to abandon this idea. The stepwise deprotection of the silyl group followed by deprotection of the ester was then investigated.

When ketone **134** was treated with 1 M solution of tetrabutylammonium fluoride, the fully deprotected compound **137** was obtained in 3% yield (*Scheme III.28*). In the synthesis of the *impurity 9*, we experienced the deprotection of the pivaloyl group in basic conditions (excess of DBU). A plausible explanation for the deprotection here is that TBAF is basic enough to hydrolyse the pivaloyl group. Moreover, it is apparently basic enough to promote the elimination of the phenolate (ring opening of the E ring), which was also observed after the allylation step (see above).

In the case of ketone **136** however, employing identical conditions only resulted in TBDPS residues being isolated after workup. We hypothesised that a better control of the pH of the aqueous phase would allow the isolation of the desired compound.

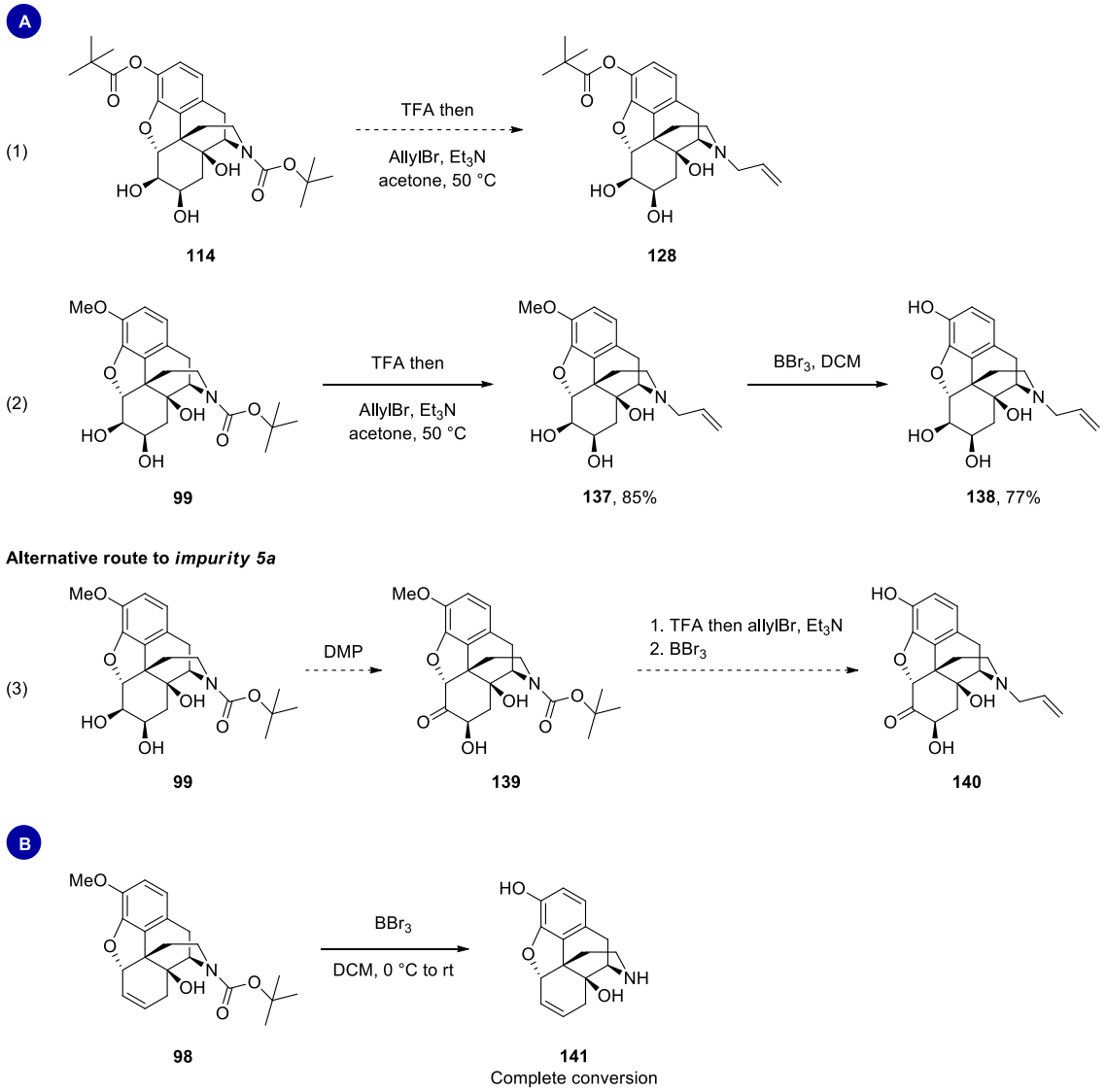


Scheme III.28

III.2.4 Future outlook

Progress has been made in the synthesis of *α*-hydroxy ketone derived from naloxone. Although the direct oxidation of enamine/enol ether was unsuccessful, the synthesis of a precursor to *impurity 5a* was achieve in a few steps from the diol **114**, which is a common intermediate in the synthesis of both *α*-hydroxy ketone **Va** and *impurity 9*.

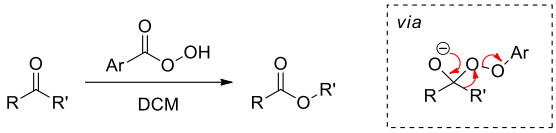
In *section II.2*, the challenging Boc deprotection and allylation of the nitrogen has been mentioned (*Scheme III.29a*, eq. (1)). Unlike the deprotection of the 3-OPiv derivative (compound **114**), the same sequence on the 3-OMe derivative (compound **99**) was successful. Moreover, the deprotection of the methyl ether was successful and provided the diol **138** in 65% yield after two steps, from the *N*-Boc diol **99** (*Scheme III.29a*, eq. (2)). An alternative approach to the protection of the diol would be the oxidation of diol **99** to the *α*-hydroxy ketone **139**, followed by Boc deprotection-allylation, and methyl ether deprotection (*Scheme III.29a*, eq. (3)). Moreover, the deprotection of the methoxy and Boc groups with BBr_3 is feasible in a one-pot process. Indeed, when the alkene **98** was treated with 3 equivalents of BBr_3 in DCM, NMR analysis of the crude mixture showed complete conversion to the secondary amine **141** (*Scheme III.29b*). Going forward then, it may be advantageous to reinvestigate the use of the methyl ether as a phenol protecting group.



Scheme III.29

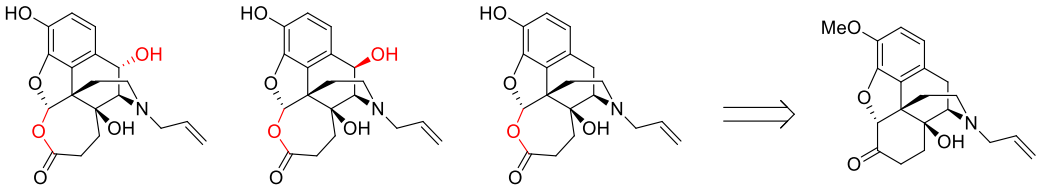
III.3. Expansion of the C ring: Baeyer-Villiger strategy for the synthesis of *impurity 4*, *6* and *7*

The Baeyer-Villiger reaction is the most straightforward way of converting a cyclic or acyclic ketone to an ester (or lactone in the case of cyclic ketone).[118,119] This reaction requires the use of a peroxyacid or hydrogen peroxide and a Lewis acid. Mechanistically, this reaction involves the migration of a group adjacent to the carbonyl to form the ester (*Scheme III.30*). The ability of a group to migrate compared to the other depends on its ability to stabilise a partial positive charge: for instance, a tertiary alkyl group will be more likely to migrate compared to a methyl group.[119]



Scheme III.30: Baeyer-Villiger oxidation

Impurities 4, 6 and *7* are seven-membered lactones; The Baeyer-Villiger reaction seems to be the most direct way to prepare these compounds from naloxone (*Figure III.9*). In this section, we focused on the feasibility of this reaction with naloxone methyl ether **61** as the substrate.



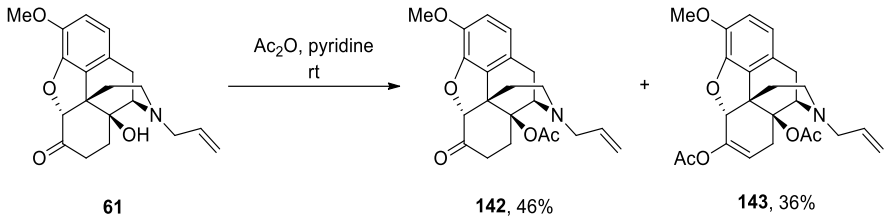
Impurity 4, **IV** *Impurity 6*, **VI** *Impurity 7*, **VII** **61**

Figure III.9: Structure of *impurities 4*, *6* and *7*

III.3.1 Baeyer-Villiger oxidation of 14-acetoxy naloxone methyl ether 142

Our investigations into the synthesis of this class of impurity began indirectly. In *section III.1*, we discussed the synthesis of the *α*-hydroxy ketone **61**. In this context, we became interested in the oxidation of the enol acetate **143**. The formation of the enol acetate from the corresponding epoxymorphinan was carried out according to Nagase and Portogese's work: stirring naloxone methyl ether **61** at room temperature in the presence of an excess of acetic anhydride in pyridine gave the protected alcohol **142** and the enol acetate **143** in 46% and 36% yield respectively (*Scheme III.31*).[120] This reaction was performed on a gram scale and then, provided enough material for a few test

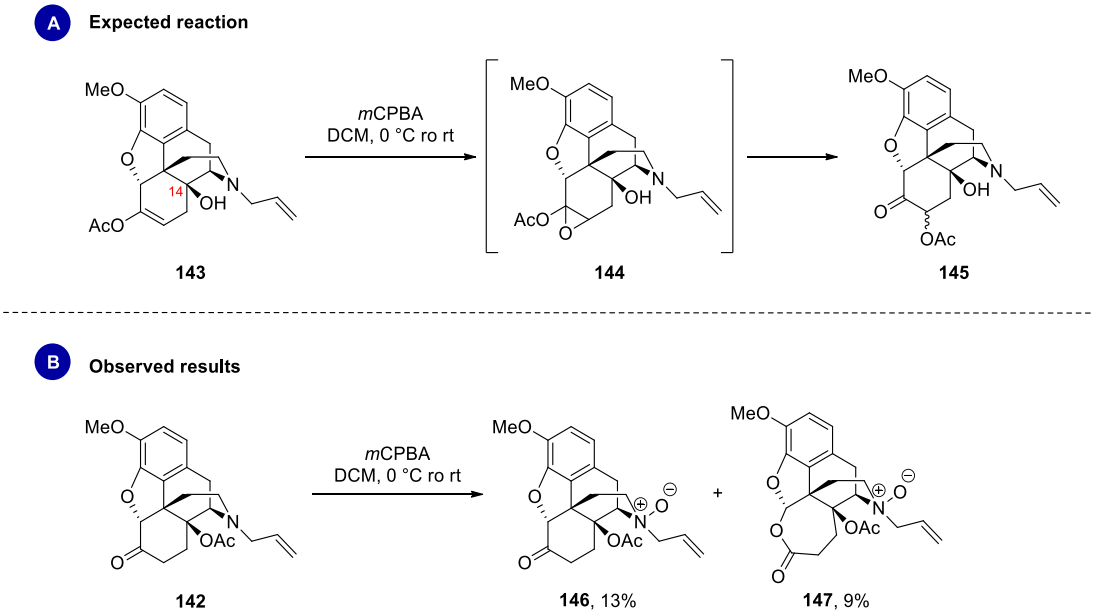
reactions. However, these test reactions did not provide the expected result therefore the enol acetate formation was not optimised.



61 **142**, 46% **143**, 36%

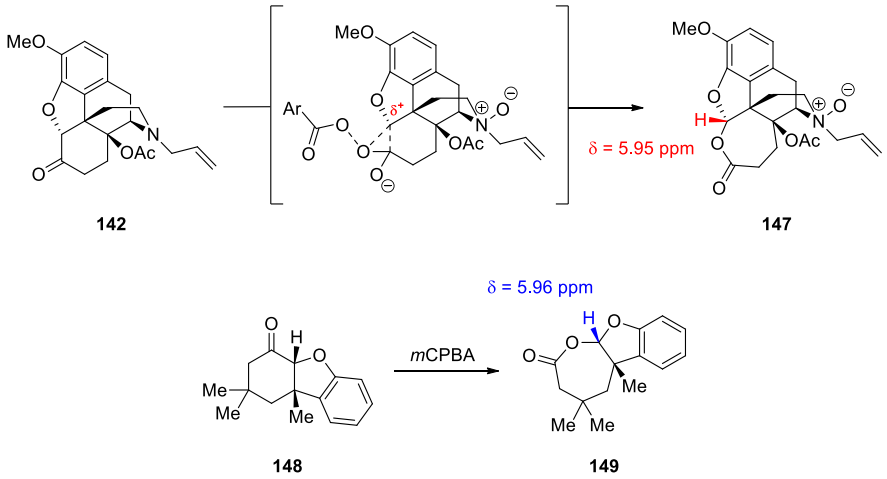
Scheme III.31: Enol acetate formation

During our studies on the epoxidation of the enol acetate **143** towards the corresponding *alpha*-acetoxy ketone **144** (*Scheme III.32a*), we carried out the epoxidation of **143** with two equivalents of *m*CPBA for 5 h, but the outcome of the reaction was unexpected. Not only a mixture of several compounds was obtained, but the shift of the H5 proton to 5.95 ppm was also observed. This shift was not really a surprise, given that the use of *m*CPBA in the presence of a basic nitrogen atom results in the oxidation of the nitrogen and then, the shift of several signals on the ^{1}H NMR spectrum, as discussed previously. Analysis of the ^{13}C and 2D NMR spectra of the two compounds revealed that the starting material was not the enol acetate we wanted, moreover, IR analysis revealed the absence of the tertiary O-H signal at C14. We concluded that the substrate was actually the 14-acetoxy naloxone derivative **142** (*Scheme III.32b*). Regarding the oxidation reaction, analysis of the two isolated compounds by LC-MS revealed that one compound had a molecular weight of [SM+16], and the other one, [M+32], which corresponds to one and two more oxygens, respectively. We concluded from this experiment that the two isolated compounds were the lactone **147**, isolated in 9% yield, and the *N*-oxide **146**, isolated in 13% yield (*Scheme III32b*). Therefore, this reaction had a positive outcome regarding the synthesis of the lactone containing impurities, as it confirmed the feasibility of this reaction, even on a substrate like naloxone.



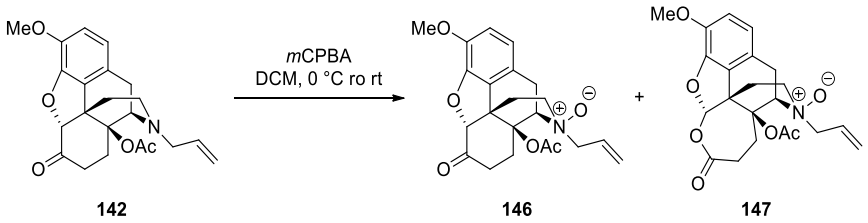
Scheme III.32

We rationalised the reaction regioselectivity in the following way. Given the structure of the substrate, we can predict the migration of the C5-C6 bond to form the lactone; the partial positive charge at C5 is tertiary and stabilised by the oxygen atom, which makes this bond more likely to migrate, compared to the C6-C7 bond. Moreover, the chemical shift of proton H5 (a singlet at 5.95 ppm, highlighted in red in *Scheme III.33*) is in accordance with literature data. Specifically, compound **149** is the product of a Baeyer-Villiger reaction of the keto-dihydrofuran **148**. The proton situated between the two oxygen atoms (highlighted in blue) has a chemical shift of 5.96 ppm in this case.[121]



Scheme III.33

We next attempted to optimise the Baeyer-Villiger reaction conditions, and the influence of reaction time and quantity of reagent used was investigated. The results are summarised in *Table III.4*. When the ketone **142** reacted with one equivalent of *m*CPBA for one hour, the ^{1}H NMR spectrum of the crude mixture revealed a 4.4:1 ratio between the *N*-oxide **146** and the lactone **147**. Purification of the crude mixture by column chromatography afforded **146** in 47% and **147** in 6% yield (Entry 1). Increasing the quantity of *m*CPBA to 2 equivalents gave a 1:1 ratio between **146** and **147**, which were isolated in 26% and 18% respectively (Entry 2). However, a longer reaction time was detrimental for the reaction. Indeed, the yield decreased to 23% for **146** and 14% for **147** (Entry 3). Although this difference in yield is negligible, some additional signals appeared on the ^{1}H NMR spectrum of the crude material. A side-product has a singlet at 6.04 ppm, which allowed us to determine a ratio between the desired compound **147** and the impurity. In this case, the ratio was 5:1 (**147** is the major product). However, when the reaction was left overnight, the ratio between **147** and the side-product became 1:5 (Entry 4). Furthermore, when 5 equivalents of *m*CPBA were used and the reaction left overnight, the ratio between the lactone and the side-product became close to 1:1 (Entry 5). This series of experiments pointed us towards an equilibrium between two lactones (the singlet at 6.04 ppm indicates the presence of an acetal-type proton), or the decomposition of the desired product into an unknown species (the side-product of the reaction has not been isolated). Finally, we decided to repeat the reaction in optimum conditions (2 equivalents of *m*CPBA, reaction time of 1 H) and determine the NMR yield using DMF as the internal standard: 53% for the *N*-oxide **146** and 28% for the lactone **147**. After a purification by column chromatography on Florisil®, the two compounds were isolated in 45% and 2%, respectively (Entry 6), the low yield of the latter compound is likely to be due to the decomposition of the lactone **147** during the purification.



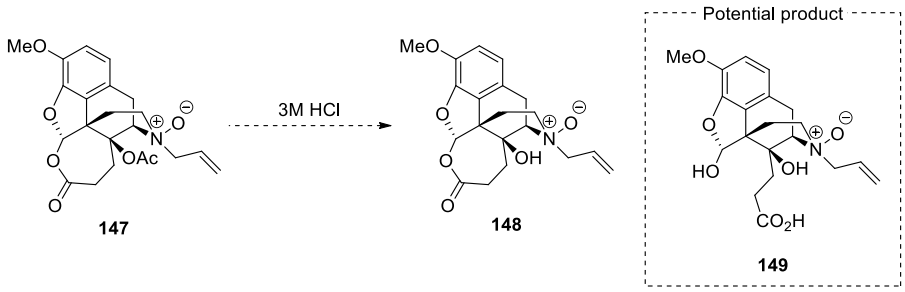
142 146 147

Entry	Conditions	Yield 146	Yield 147	Ratio 147 / side-product (NMR)
1	1eq. *m*CPBA, 1 H	47%	6%	NA
2	2eq. *m*CPBA, 2 H	26%	18%	NA
3	2eq. *m*CPBA, 2.5 H	23%	14%	5 : 1
4	2eq. *m*CPBA, overnight	-	-	1 : 5
5	5eq. *m*CPBA, overnight	-	-	1 : 1
6	2eq. *m*CPBA, 1 H	53%[a] (45%)[b]	28%[a] (2%)[b]	NA

Table III.4: Baeyer-Villiger oxidation of 14-acetoxy naloxone methyl ether **142**

[a] NMR yield using DMF as internal standard. [b] yield of isolated compound after purification by chromatography on Florisil®.

We attempted the acidic hydrolysis of the acetyl group, which gave a mixture of several compounds. Although the different components of this mixture have not been isolated, it is likely that the lactone hydrolysed during the reaction (*Scheme III.34*).



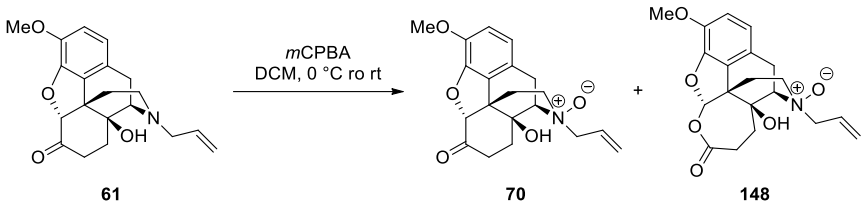
147 148 149

Scheme III.34: Hydrolysis of the acetyl group

III.3.2 Baeyer-Villiger oxidation of naloxone methyl ether 61

Despite the low yield of the lactone and the formation of the *N*-oxide, we decided to pursue this work with the Baeyer-Villiger reaction of naloxone methyl ether **61**. The results are summarised in *Table III.5*. When using two equivalents of *m*CPBA for an hour, the *N*-oxide **70**, and the lactone **148** were formed in a 2:1 ratio (determined by ^{1}H NMR analysis of the crude material, Entry 1). Increasing the reaction time to 4.5 H gave a 1.3:1 ratio in favour of the lactone **148** (Entry 2). However, a 10 H reaction

gave a decreased ratio to 1.6:1 in favour of the *N*-oxide **70**, which was isolated in 30% yield. The lactone **148** was obtained in 13% yield (Entry 3).



Entry	Conditions	Ratio 70 / 148 (NMR)
1	2eq. *m*CPBA, 1 H	2 : 1
2	2eq. *m*CPBA, 4.5 H	1 : 1.3
3	2eq. *m*CPBA, 10 H	1.6 (30%)[a] : 1 (13%)[a]

Table III.5: Baeyer-Villiger oxidation of naloxone methyl ether **61**

[a] yield of isolated compound after purification by chromatography on silica gel.

Lactone **148** and *N*-oxide **70** were identified by mass spectrometry and ^{1}H NMR analysis. Mass analysis showed that one or two oxygen atoms were added to the mass of naloxone methyl ether to form the *N*-oxide **70** and the lactone **148**, respectively.

Regarding the lactone **148**, a ratio between **148** and **70** has been determined by comparison of the chemical shift of the proton H5. Indeed, H5 moved from 4.63 ppm in naloxone methyl ether to 6.03 ppm in the lactone.

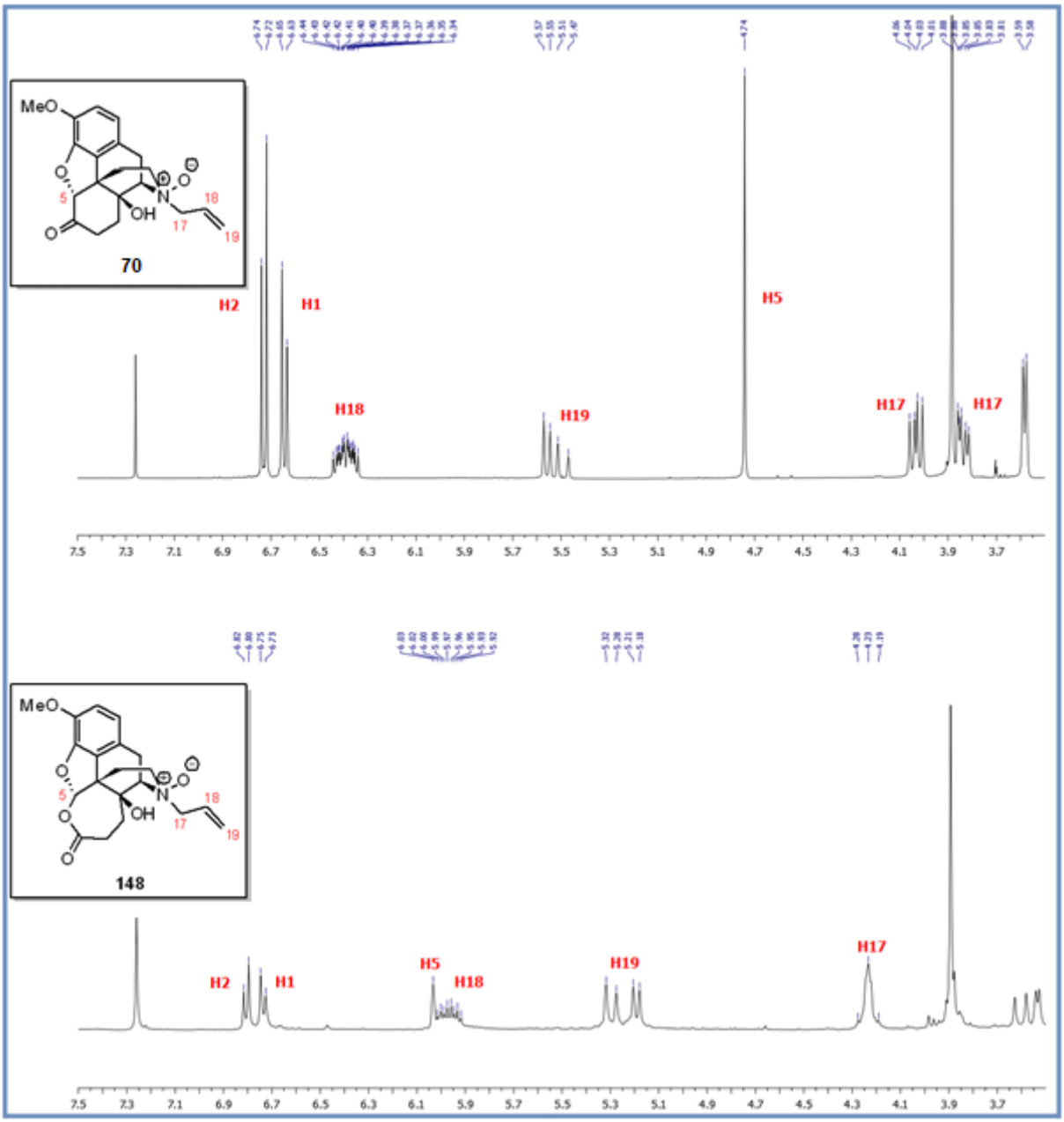
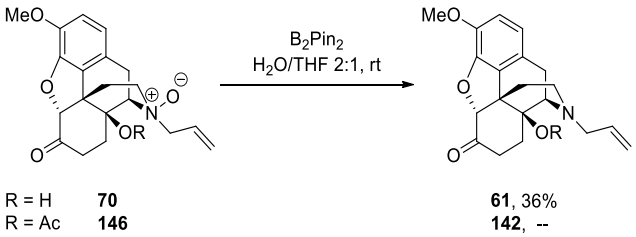


Figure III.10: 1H NMR spectra of compounds 148 and 150. The spectra have been extended between 7.5 and 3.5 ppm

Characterising compound **148** proved to be difficult. After purification by column chromatography, ^{1}H NMR analysis showed broaden signals. Several parameters were considered: The concentration of the NMR sample, the solvent, and the temperature. ^{1}H NMR spectra were then recorded in DMSO, D_2O and $CDCl_3$, however the resolution of the spectra did not improve. Changing the temperature to 5 °C and 40 °C had no effect on the quality of the spectrum. Only a concentration of 0.02 M seemed to slightly sharpen the signals. The proton H5 however, could not be seen on the various spectra

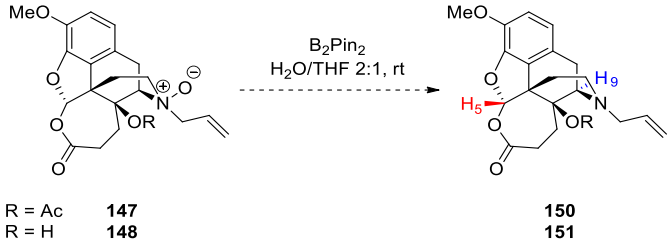
recorded, and a signal at 9.8 ppm appeared. It would seem reasonable to conclude that the lactone decomposes during the purification, or that a rearrangement of the lactone occurs.

Before going further in the optimisation of this reaction, the reduction of the *N*-oxide was attempted. In 2011, Lakshman and co-workers demonstrated that bis(pinacolato)-diboron (B_2Pin_2) could be used for the reduction of pyridine *N*-oxides and trialkylamine *N*-oxides to the corresponding pyridines or tertiary amines.[122] Naloxone methyl ether *N*-oxide **70** and the 14-acetoxy derivative **146** were used as model substrates to test the reaction. In the case of compound **70**, after 50 minutes at room temperature, the conversion of the starting material was complete and, according to TLC analysis, the desired product was formed, which was confirmed by ^{1}H NMR analysis. Although a mixture of unidentified compounds was obtained, naloxone methyl ether **61** was isolated from the rest of the mixture in 36% yield (*Scheme III.35*). Compound **146** however, showed no conversion to the desired product. Heating the reaction mixture to reflux did not improve the efficiency of the reaction and the starting material remained untouched.



Scheme III.35: *N*-oxide reduction with B_2Pin_2

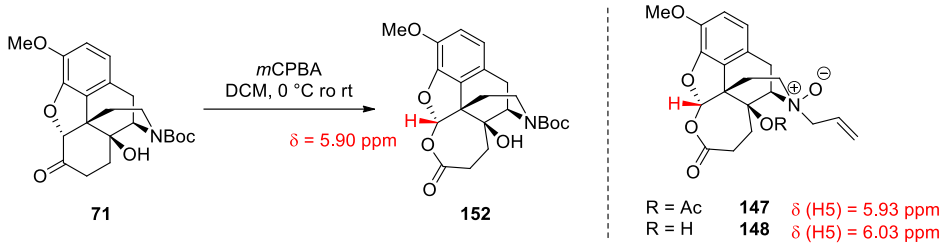
We applied the same reaction conditions to lactones **147** and **148**. In the case of lactone **147**, the aromatic protons shifted on the ^{1}H NMR spectrum, as well as H9 (highlighted in blue, *Scheme III.36*). H5 however (highlighted in red), was not detected on the crude NMR spectrum. We attempted the purification of this compound by column chromatography. Unfortunately, only BPin residues were recovered. The attempted reduction of the *N*-oxide **148** gave mostly BPin residues on the ^{1}H NMR spectrum of the crude material.



Scheme III.36

III.3.3 Baeyer-Villiger oxidation of *N*-Boc noroxycodone 71

In order to avoid the *N*-oxide formation, we performed the Baeyer-Villiger oxidation on the *N*-Boc noroxycodone **71**. The synthesis of this compound is described in *Chapter II*. The attempted epoxidation of different alkenes with *m*CPBA was inefficient in all cases (*Section III.1.2*). Therefore, with regards to the lactone formation, we decided to perform a test reaction with only one equivalent of *m*CPBA for 10 H. Pleasingly, 16% of the starting material was converted to the desired lactone **152** (*Table III.6*, entry 1). The compound was assigned by comparison of the chemical shift of proton H5 (highlighted in red) with lactones **147** and **148**. Using two equivalents of *m*CPBA, and after a prolonged reaction time of 48 H, the conversion only increased to 36% (Entry 2). As a long reaction time was not useful, the reaction was repeated using two equivalents of reagent, and the conversion was measured after 15 minutes, 30 minutes, 1 H and the reaction was stopped after a reaction time of 1.5 H (Entry 3-6). The formation of product increased from 37% after 15 minutes to 47% after 1.5 H. As described in *Table III.6*, the conversion after 30 minutes and 1.5 H suggest that the reaction is fast and does not evolve further when the reaction time is longer.



Entry	Conditions	Conversion of SM 71[a]
1	1eq. mCPBA, 10 H	16%
2	2eq. mCPBA, 48 H	36%
3	2eq. mCPBA, 0.25 H	37%
4	2eq. mCPBA, 0.5 H	45%
5	2eq. mCPBA, 1 H	28%
6	2eq. mCPBA, 1.5 H	47%

Table III.6: Baeyer-Villiger oxidation of *N*-Boc noroxycodone **71**

[a] conversion measured by comparison of starting material and product

III.3.4 Conclusion

The chemistry described in this section highlights the feasibility of the Baeyer-Villiger reaction on a complex molecule such as naloxone. The use of *m*CPBA however, led to the oxidation of the nitrogen atom, which was previously discussed. The instability of the seven-membered lactone on the *N*-allyl substrate makes it difficult to isolate. This approach for the synthesis of *impurity 4, 6* and *7*, although direct, requires more attention to the choice of protecting groups. Indeed, the carbamate, the acetate and the lactone are acid-sensitive functional groups. Moreover, the methyl ether deprotection involves the use of boron tribromide. We already observed a detrimental effect of acid on the lactone, and at this stage, we cannot confirm that the lactone would survive the BBr_3 conditions.

Although improvements need to be made, this unfinished work is a start point in the synthesis of these naloxone-related impurities.

Chapter IV - Cleavage of E ring via a Wolff-Kishner approach – Investigation into the synthesis of *impurity 1*, *2* and *14*

Impurities 1, *2* and *14* have several common features: They are oxidised in position 10 (discussed in Chapter I), and they all contain a catechol moiety, which comes from a cleavage of the E ring, and a *α*-hydroxyketone functionality at position 5-6 (*Figure IV.1a*). We envisaged that the acyloin motif could be installed by oxidation of the parent alkene **153**. In order to form this compound, a method would be needed to form the alkene selectively between C5 and C6, and to eliminate the phenoxide (*Figure IV.1b*).

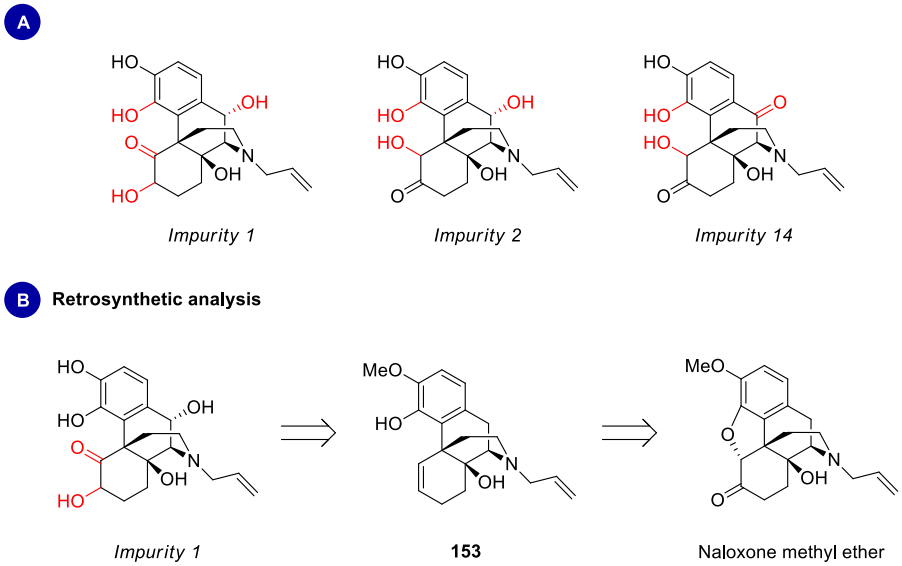
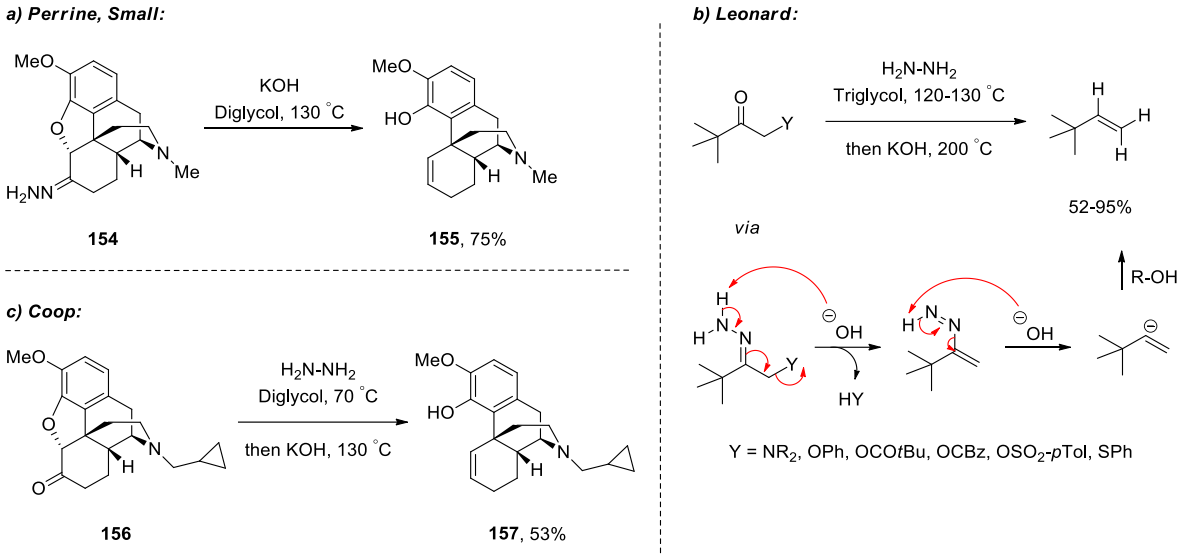


Figure IV.1

IV.1 Formation of the alkene

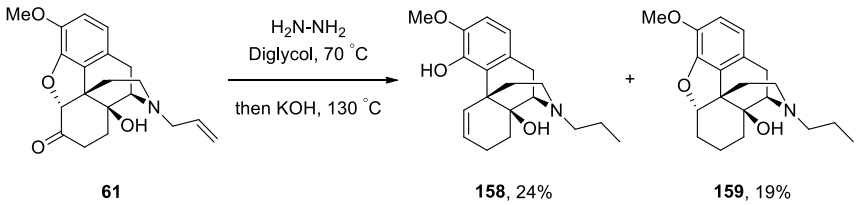
Back in 1952, Perrine and Small found that treating the hydrazone **154** with potassium hydroxide at elevated temperature led to the formation of dehydrodesoxycodeine **155** in 75% yield (*Scheme IV.1a*).[123] Indeed, Leonard demonstrated that, under Wolff-Kishner conditions, a leaving group *alpha* to the hydrazone would eliminate to form the corresponding alkene. This reaction is applicable to a variety of ketones bearing heteroatoms on the adjacent carbon, such as amine, ether, ester, thiolate, etc (*Scheme IV.1b*).[124] The Kishner-Leonard elimination has been exemplified by Coop and co-workers, whose initial work was to demonstrate that *L*-selectride can demethylate hindered phenolic methyl

ethers.[125] They showed that, by treating naltrexone methyl ether **156** under Wolff-Kishner conditions, the elimination product **157** was obtained in 53% yield (*Scheme IV.1c*).



Scheme IV.1

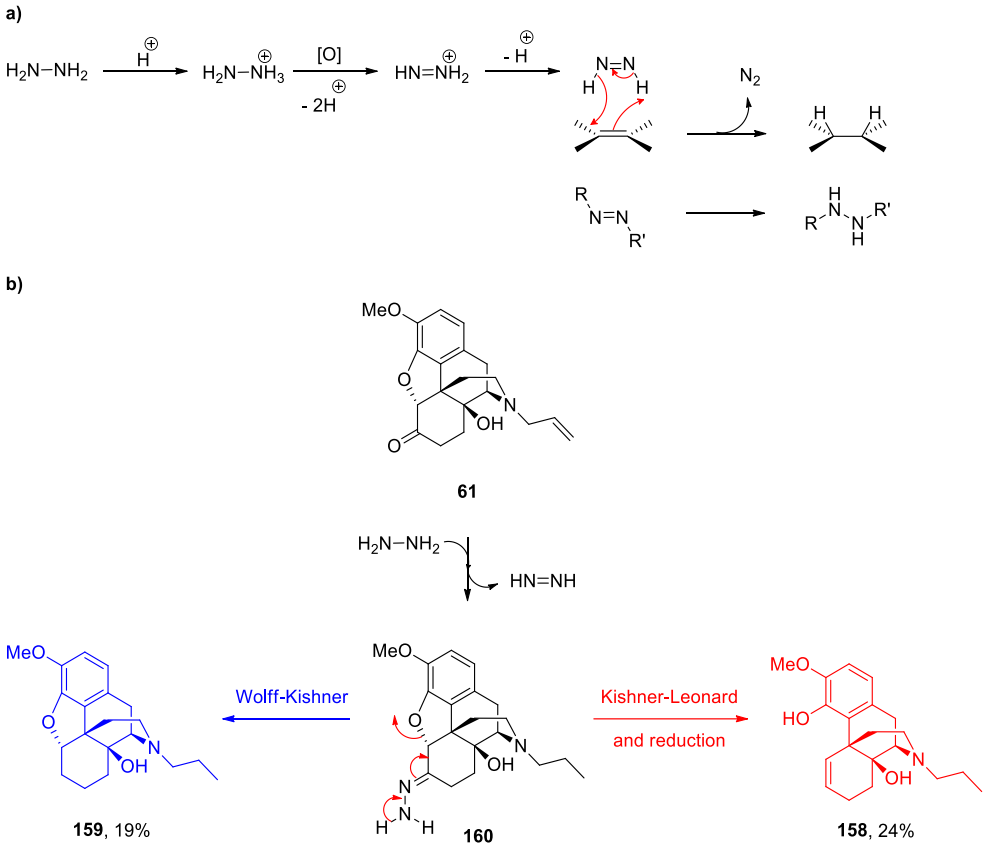
We then began our investigation into the cleavage of the furan ring by testing the Wolff-Kishner reduction of naloxone methyl ether **61**. The starting material was treated with 5 equivalents of hydrazine monohydrate and heated at 70 °C in order to form the corresponding hydrazone *in situ*. The hydrazone was not isolated, and 7 equivalents of potassium hydroxide were added to the reaction mixture and heated at 130 °C. Although we were pleased to see that the phenoxide had eliminated to form the 5-6 alkene, the allyl group was also reduced to a propyl group to form compound **158** in 24% yield. The deoxo-derivative **159** resulted in the reduction of both the allyl group and the hydrazone, without elimination of the phenoxide, and was isolated in 19% yield (*Scheme IV.2*).



Scheme IV.2

Diimide HN=NH is a powerful reducing agent, used as an alternative to catalytic hydrogenation, especially when polar groups such as nitrile, carbonyl or imine are present in the substrate. It can

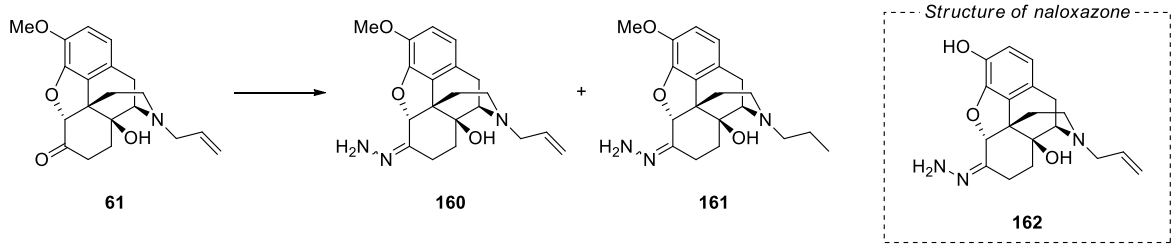
reduce carbon-carbon multiple bonds into the corresponding alkane, and nitrogen-nitrogen double bonds into azines. Diimide reduction involves *in situ* preparation of the reagent, as this species is unstable above 120 K. Existing methods for the generation of diimide include the oxidation of hydrazine. In aqueous or alcoholic solutions (or in the presence of a source of protons), hydrazine can be oxidised by oxygen or other oxidising agents to form diimide, which is then involved in a pericyclic reaction with an alkene, alkyne or diazo compound, producing nitrogen gas N_2 and the alkane/alkene or azine (*Scheme IV.3a*).[126,127] With regards to our attempted Kishner-Leonard elimination, we assumed that several processes occurred in the reaction of naloxone methyl ether **61** with hydrazine and potassium hydroxide. Once the hydrazone **160** is formed, the excess of hydrazine can be oxidised to diimide and reduce the allyl group. The hydrazone can also be reduced to a methylene to form compound **159** or eliminate the phenoxide to give the alkene **158** (*Scheme IV.3b*).



Scheme IV.3

In order to avoid the reduction of the allyl group and the formation of other side-products, the Kishner-Leonard reaction was attempted in a stepwise manner, and the formation of the hydrazone was first optimised; the results are shown in *Table IV.1*. We began the optimisation by using the conditions described above, as a control reaction (entry 1): When naloxone methyl ether **61** was treated with 5

equivalents of hydrazine in diethylene glycol at 70 °C for an hour, a 2.5:1 mixture of the desired hydrazone **160** and *N*-propyl hydrazone **161** was obtained (ratio determined by analysis of the ^{1}H NMR spectrum of the crude mixture). A similar result was obtained when the reaction was performed under nitrogen atmosphere (entry 2). The nature of the solvent was investigated in the formation of the hydrazone. As stated above, a polar solvent or weak proton source were thought to assist the reduction of the *N*-allyl group by hydrazine, therefore attempts were made using toluene - an aprotic and non-polar solvent. In this case, trace amount of the reduced product was observed on the ^{1}H NMR spectrum of the crude material (entry 4). Pasternak and co-workers were previously able to achieve the synthesis of naloxazone **162** using ethanol as the solvent. However, no improvement was observed, and a 2:1 mixture of *N*-allyl and *N*-propyl hydrazones was detected (entry 3). We then decided to degas the solvent by bubbling nitrogen through the solution before heating the reaction mixture, in order to remove oxygen from the solution and thus, avoiding the formation of diimide. The hydrazone was isolated in 89% yield in a 5:1 mixture of *E* and *Z* isomers (entry 5), which was in agreement with literature observations.[128]



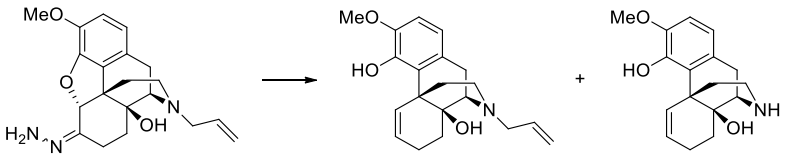
Entry	Solvent	Atmosphere	Outcome
1	Diethylene glycol	Air	2.5:1 **160** / **161**
2	Diethylene glycol	Nitrogen	2.5:1 **160** / **161**
3	Ethanol	Nitrogen	2:1 **160** / **161**
4	Toluene	Nitrogen	10:1 **160** / **161**
5	Degassed ethanol	Nitrogen	89% **160**

Table IV.1: Optimisation of the hydrazone formation

Reagent and conditions: Hydrazine monohydrate 5 eq., solvent 0.15 M, 70 °C, 1 H

With the hydrazone in hand, the optimisation of the elimination reaction was attempted, as shown in *Table IV.2*. We began with treating the hydrazone with an excess of aqueous potassium hydroxide in

diethylene glycol, at 130 °C for 16 H. When carried out under air, a low mass balance was obtained, and a mixture of unidentified compounds was recovered, although the desired product was detected after analysis of the crude mixture by LC-MS (entry 1). Performing the reaction under nitrogen atmosphere failed to produce the desired compound (entry 2). We then investigated the solvent of the reaction. The temperature the reaction had to be adjusted to 70 °C when ethanol was used (entry 3). This resulted in only 20% conversion to the desired product. Pleasingly, toluene provided the desired compound in 79% yield and purification of the product by column chromatography was not necessary (entry 4). It is worth mentioning that the ^{1}H NMR spectrum of the product did not show the presence of any of the starting hydrazone; we can then conclude that the stereochemistry of the hydrazone does not have any influence on the elimination reaction. Finally, DMSO was investigated in this reaction. Surprisingly, although the reaction had reached 100% conversion of the starting material, two different compounds were detected. The ^{1}H NMR spectrum of the crude material shows the presence of two doublet of triplets at 6.32 and 6.38 ppm, which are both alkene protons. However, the integration of the two signals was 4 and 1, respectively. Moreover, the integration of the allyl CH_2 suggested that it was not likely that both compounds contained the allyl group. Finally, LC-MS analysis revealed that the minor compound has a mass ion of 328, whereas the major compound has a mass ion of 288, which corresponds to the loss of the allyl group on the nitrogen atom. Based on these observations, we concluded that the minor component of the mixture is the desired product **163**, and the major compound is the secondary amine **164** depicted below (entry 5).



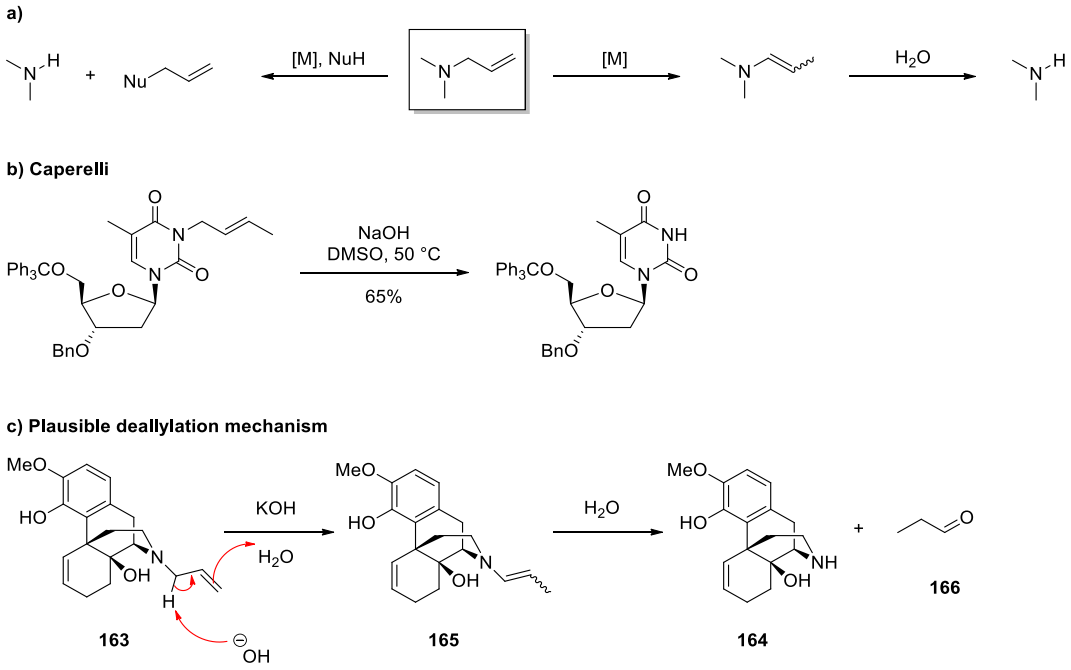
160 **163** **164**

Entry	Solvent	Atmosphere	Outcome
1	Diethylene glycol	Air	Complex Mixture
2	Diethylene glycol	Nitrogen	Complex Mixture
3	Ethanol	Nitrogen	20% conversion to **163**
4	Toluene	Nitrogen	79% yield (**163** only)
5	DMSO	Nitrogen	1:4 ratio **163** / **164**

Table IV.2

Literature examples describe the use of Pd, Ni or Ru as suitable transition-metal catalysts for the cleavage of allylic C-N bonds. The deprotection of allylamines relies on two strategies: in the presence

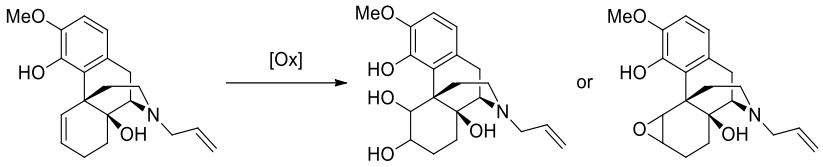
of a nucleophile, the secondary amine becomes a leaving group and is displaced by the nucleophile. On the other hand, the double bond can isomerise to form the enamine, which is then hydrolysed (*Scheme IV.4a*).[129–131] However, the use of base for the deallylation of tertiary amines has already been reported in the past; Caperelli used sodium hydroxide in DMSO for the deprotection of allylic amine in a thymidine derivative in good yield (*Scheme IV.4b*).[132] Therefore, a plausible mechanism for the deprotection of the allyl group would be the isomerisation of the double to form the enamine **165**. Hydrolysis gives the secondary amine **164** and the propionaldehyde **166** (*Scheme IV.4c*), which is eliminated from the crude material during the evaporation of the solvent, given its low boiling point (48 °C).



Scheme IV.4

IV.2 Oxidation of the alkene

With the alkene in hand, we then attempted the oxidation of this substrate for the preparation of the corresponding diol **167** or epoxide **168** (*Scheme IV.5*). In the case of the epoxide **168**, the idea was to open the ring with an oxygen-based nucleophile in order to obtain an *alpha*-oxygenated ketone.

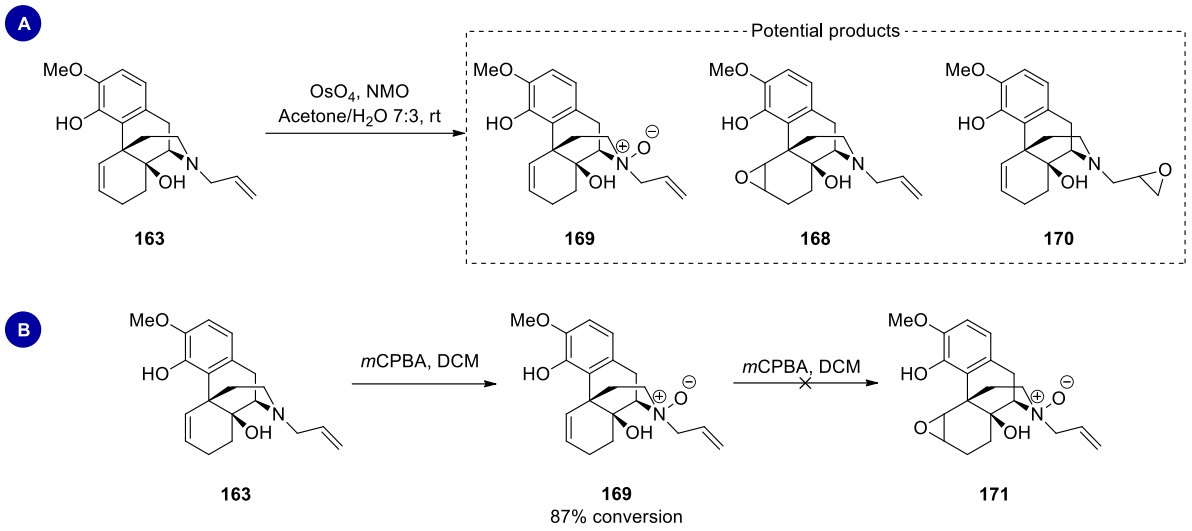


163 **167** **168**

Scheme IV.5

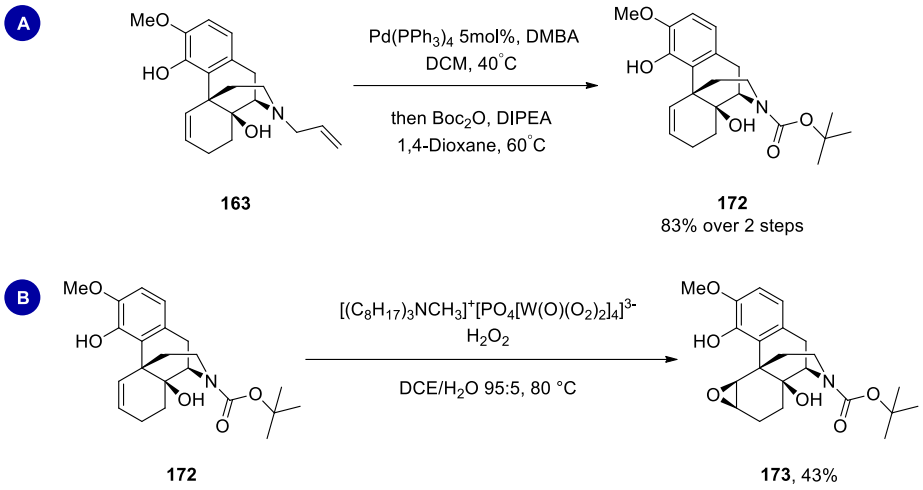
We began the study of the oxidation of the alkene by the use of osmium tetroxide, which is a usual reagent for the dihydroxylation of alkenes. The use of a catalytic amount of OsO_4 and 4-methylmorpholine *N*-oxide did not provide the desired product. Instead, a compound with a mass ion of 343 was identified as the major product by LC-MS analysis. This mass ion corresponds to the mass of an oxygen atom added to the mass of the starting material, which leaves us with three possibilities: The *N*-oxide **169**, or the epoxides **168** or **170** (Scheme IV.6a). Given that the alkene and allyl protons were still detectable on the ^{1}H NMR spectrum of the crude material, we assumed the major product of this reaction might be the *N*-oxide **169**. However, the aromatic signals did not match with those from the *N*-oxide synthesised in another reaction (see below). The products of this reaction might be either of the epoxides in a mixture with starting material. Nonetheless, as only ~20% of the initial mass was recovered, further purification was not attempted.

Epoxidation using *m*CPBA led to 87% conversion to the corresponding *N*-oxide **169** (*Scheme IV.6b*). The chemical shift of the allyl protons helped assigning this compound; the allylic CH comes between 6.38 and 6.47 ppm, as we already observed in another study (see Chapter II). Furthermore, when the *N*-oxide was treated with an excess of *m*CPBA, a low mass of benzoic acid residues was recovered. Basifying the aqueous phase followed by an extraction had no effect on the outcome of the reaction. It was then decided to move forward and try another approach.



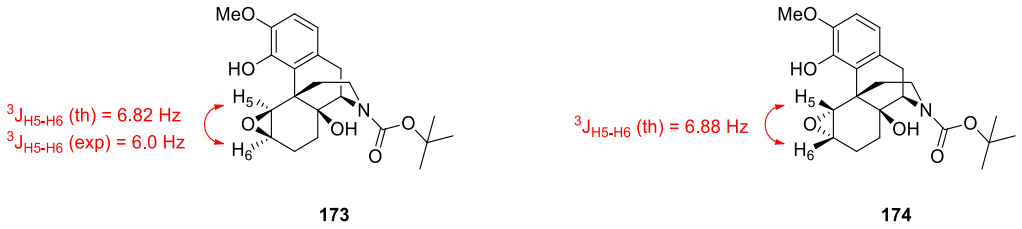
Scheme IV.6

As the formation of the *N*-oxide had already been observed in the formation of the *impurity 9* (*Section III.1.2*), it was decided to remove the allyl group and protect the nitrogen atom as a carbamate in order to avoid the oxidation. As described in *Chapter I* and *II*, the alkene **163** was treated with $Pd(PPh_3)_4$ and dimethylbarbituric acid to form the secondary amine, which was then protected as a *tert*-butylcarbamate. The *N*-Boc alkene **172** was then produced in 83% yield (*Scheme IV.7a*). Several oxidations method have been employed for the subsequent oxidation. The epoxidation with *m*CPBA was again attempted, and the desired product was detected by analysis of the crude mixture by LC-MS, among several other unidentified compounds. On the other hand, osmium tetroxide gave a complex mixture, without formation of the diol. Finally, the use of ruthenium chloride in combination with Oxone® or sodium periodate was inefficient in this reaction: in the first case, only the starting material was recovered, in the latter case, a mixture containing starting material and other unidentified compounds was recovered. The conversion of the alkene to an oxidised form was eventually achieved using the (diperoxotungsto)phosphate catalyst mentioned in *Section III.1.2*, which provided the epoxide **173** in 43% yield (*Scheme IV.7b*).



Scheme IV.7

The stereochemistry of the epoxide **173** was assigned based on the assumption that the epoxidation is directed by the tertiary alcohol in position 14 (see *Section III.1.2*). The Karplus equation, for the calculation of coupling constants from dihedral angles, does not give any indication in this case. Indeed, the dihedral angles between H5 and H6 have been calculated using Chem3D for both epoxides **173** and the other diastereoisomers **174**: 1.96 ° and 2.90 ° respectively, which gives a vicinal coupling constant of 6.82 Hz for **173** and 6.88 Hz for **174** (*Scheme IV.8*). The coupling between H5 and H6, in both cases, is too close to the experimental value of $^{3}J_{(H5\text{-}H6)}$ in compound **173** to allow us to make any conclusion. In this example, the use of the Karplus equation is then not helpful. The assignment of compound **173** is, at the moment, hypothetical.



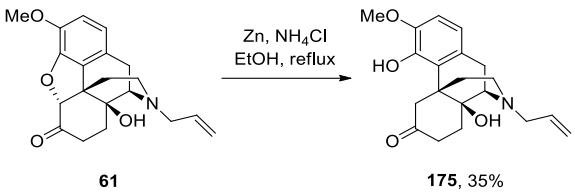
Scheme IV.8: Chemical shift of epoxide protons

At this stage, other oxidation methods or ring opening of the epoxide were not attempted.

IV.3 Conclusion – Future outlook

The Wolff-Kishner reaction provided the tetracyclic morphinan skeleton derived from naloxone in two steps in good yield. In order to achieve the oxidation in position 5 and 6, oxidation of the alkene using common reagents was attempted, but did not result in a positive outcome. Epoxidation of the *N*-Boc derivative **172** however, provided the desired product in moderate yield. The epoxide can potentially be opened by oxygenated nucleophiles to form diol precursors, or *alpha*-hydroxy species.

An alternative method to the Wolff-Kishner reaction is the use of zinc metal and ammonium chloride in refluxing ethanol for the opening of the E ring, to provide the ketone **175** (*Scheme IV.8*).



61 **175**, 35%

Scheme IV.8

This method of cleavage of the furan ring could also be exploited in the synthesis of *impurity 1, 2* and *14*. Indeed, the *alpha*-functionalisation of ketone could be attempted. Alternatively, the reduction-mesylation-elimination-dihydroxylation sequence could be performed on the *N*-Boc system. However, regioselectivity issues could arise with this approach.

Conclusion and perspectives

1. General conclusion

Long-term analysis of Suboxone® sublingual film revealed the formation of impurities over time, some of them reaching the identification threshold determined by the ICH guidelines. During the course of preliminary work (carried out by Indivior), the use of MS-directed preparative HPLC allowed the isolation of very small quantities of material. Various analytical methods were used to obtain the molecular weight as well as the molecular formula of these compounds, and a structure was assigned to the various compounds. The aim of this research work was to synthesise them from naloxone, in order to confirm their structure.

We focused on ways to install a particular functional group at a specific position; the work reported in the previous pages is a partial answer to three questions: can we find other ways to perform a benzylic oxidation on the naloxone system, is the oxidation of an alkene in the presence of other functionalities possible, is the ring expansion of a pentacyclic molecule feasible. During the course of this work, the side products formed during various reactions allowed us to make observations that are a partial answer to these questions.

Impurity 3 was prepared according to a literature procedure (*Chapter I*). The oxidation step provided the desired product in a low 11% yield therefore better conditions were needed for this step. The direct oxidation of naloxone methyl ether using various method failed to provide the desired product, furthermore the formation of naloxone methyl ether *N*-oxide as a side product helped us realise that it would be optimistic to keep the allylamine. The benzylic oxidation of *N*-Boc noroxycodone did not provide better results and only trace amount of the desired compound was detected.

Chapter II describes the synthesis of compounds with modification of the cyclohexanone ring of naloxone. During the course of the synthesis of *impurity 9*, we were facing similar issues with the oxidation of the 6,7-alkene, which only resulted in the formation of the corresponding *N*-oxide. Dihydroxylation of the corresponding *N*-Boc derivative was successful and after four more steps, the precursor of the *impurity 9* could be isolated in 19% overall yield. As the methyl ether at position 3 could not be removed, the protecting group has been replaced with a pivalate ester, which was supposed to facilitate the final deprotection step. Indeed, the *impurity 9* has been isolated after 12 steps in 5.5 to 6.6% yield (depending on the use of the triflate or the mesylate after the reduction step). Analysis of the synthesised *impurity 9* revealed a similar retention time by HPLC, as well as various similar fragments after mass spectroscopy analysis. This led us to conclude that the synthesised compound is an impurity found in the degraded sample of Suboxone®.

The synthesis of this compound is a clear answer to the second question. It is not possible to oxidise an alkene in the presence of other functionalities in this system, as demonstrated in *Chapter II*. An experiment with bromine showed that the 6,7-alkene was inactive towards oxidation.

Moving on to the synthesis of the impurity **Va**, classical methods for *alpha*-hydroxylation of ketones failed to provide the desired compound, as the intermediate enamine or enol ether hydrolysed in the reaction. However, the protection and oxidation of the diol **114**, which is also an intermediate in the synthesis of *impurity 9*, provided the precursor to *alpha*-hydroxy ketone **Va** in 4.5% yield after 4 steps.

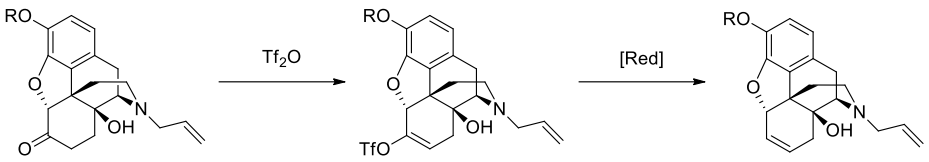
Finally, three impurities containing a seven membered lactone were investigated. This section focused on the possible ring expansion of the naloxone system, and the benzylic oxidation was not considered. It was found that naloxone methyl ether can react with peracids to undergo a Baeyer-Villiger reaction, providing the desired lactone. However, peracids can also oxidise nitrogen atoms into the corresponding *N*-oxide, and it was found that the isolated compound also contains the *N*-oxide functionality. Unlike the previous examples, the Baeyer-Villiger oxidation of *N*-Boc noroxycodone might not solve the issue, as the lactone might not survive the Boc deprotection step.

In Chapter IV, the cleavage of the E ring was discussed, and once again, the benzylic oxidation was not considered. The successful Wolff-Kishner reduction provided the alkene **163** which could then be used in the oxidation step. Although the dihydroxylation proved to be difficult, the epoxidation of the *N*-Boc derivative provided the desired compound. The work performed on this class on impurity is quite short however it establishes a good start point for further investigation.

2. Perspectives

Considering the benzylic oxidation of naloxone, the oxidative dearomatisation strategy of naloxone hydrochloride seems promising. Indeed, analysis of the crude material revealed the presence of desired product, despite the low mass balance. This would allow the synthesis of *impurity 3* in a single step.

The semi-synthesis of *impurity 9* is currently a 12 steps synthesis which could potentially be shortened. The formation of the 6,7-alkene is a four-step process from that involves reduction of the ketone, mesylation, displacement of the mesylate and elimination. This sequence could be improved if the formation of an enol triflate and reduction were successful (*Scheme 1*).[133,134]



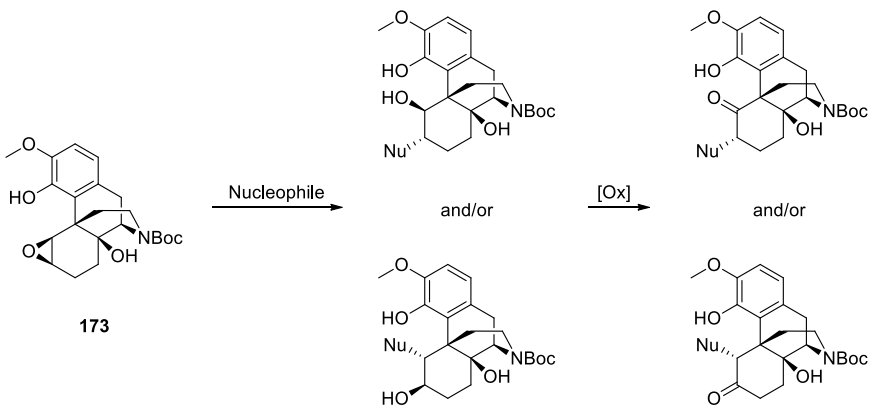
R = Me or CO*t*Bu

Scheme 1: Enol triflate reduction

If the synthesis of *alpha*-hydroxy ketone **Va** *via* the protection of the diol-oxidation approach is investigated, the final deprotection should be looked at more carefully. Indeed, it has been reported above that the TBDPS deprotection using TBAF only gave TBPS residues. The pH of the aqueous layer must be controlled before extraction in order to lose as little material as possible.

Improving the synthesis of *impurities 4*, *6* and *7* containing a lactone will be challenging. First, the *N*-oxide formation is problematic. The reduction of the *N*-oxide using B_2Pin_2 (discussed in *section III.3*) was inefficient when the lactone was used as the substrate. Furthermore, *N*-Boc noroxycodone would not be a good alternative substrate either because of the acid-sensitivity of both the Boc group and the lactone, as described in *section III.3*. Alternatively, the nitrogen could be temporarily protected as a salt. Indeed, in *section III.1*, we discussed the dihydroxylation of the 6,7-alkene in the presence of the allylamine. The conversion was not complete, but the formation of the diol was supported by ^{1}H NMR analysis and mass spectrometry.

The cleavage of the E ring was performed using the Wolff-Kishner strategy, which provides the alkene between positions 5 and 6. What needs to be done next is the ring opening of the epoxide, followed by oxidation in order to install the *alpha*-hydroxy ketone motif (*Scheme 2*).[135–139]



Nucleophile = H_2O, alcohol, carboxylic acid

Scheme 2: Ring-opening of epoxide **173**

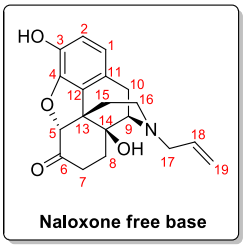
Chapter V: Experimental

V.1 General considerations

All reactions were carried out in flame-dried glassware under high vacuum, unless stated otherwise. For reactions carried out under an inert atmosphere, solvents were purified using a PureSolv MD purification system and transferred under nitrogen. Infrared (IR) spectra were recorded on a Perkin Elmer Paragon FTIR spectrometer (vmax in cm^{-1}). Samples were recorded neat as thin films. ^{1}H NMR spectra were recorded on a Bruker AVIII HD 400 (400 MHz), Bruker AVI 400 (400 MHz) or DPX-400 (400 MHz) supported by an Aspect 3000 data system. Chemical shifts are reported in parts per million (ppm) from tetramethylsilane, using the residual protic solvent resonance as the internal reference: ($CDCl_3$: δ 7.26, D_2O: δ 4.79, MeOD: δ 3.31). Data are reported as follows: chemical shift (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (Hz), integration, assignment). ^{13}C-NMR spectra were recorded on a Bruker AVIII HD 400 (101 MHz) using DEPTQ pulse sequences, with broadband proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference ($CDCl_3$: δ 77.16). High resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on either a Micromass LCT operating in electrospray mode (TOF, ES^+) or a Micromass Prospec operating in FAB (FAB^+), EI (EI^+) or CI (CI^+) mode. Thin layer chromatography (TLC) was performed on aluminium-backed plates pre coated with silica (0.2 mm, Merck 60 F254) which were developed using standard visualizing agents: UV light and potassium permanganate. Flash chromatography were performed on silica gel (Merck 40-63 µm). Melting points were recorded on Gallenkamp melting point apparatus and are uncorrected.

V.2 Procedures

Naloxone free base

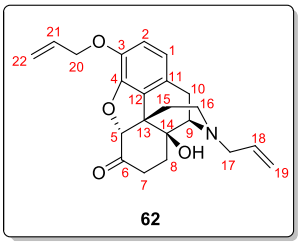


Naloxone hydrochloride dihydrate (6 g, 15.0 mmol) was dissolved in water (60 mL) and DCM (120 mL). A 5% aqueous solution of ammonia (15.6 mL, 15.8 mmol) was added and the mixture was stirred at

room temperature for 0.5 h under air. The two layers were separated and the aqueous layer was extracted with DCM. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure to afford naloxone free base (4.01 g, 82%) as a white solid. The compound showed satisfactory spectroscopic data in comparison to literature.[140]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, *J* = 8.0 Hz, 1H, **H2**), 6.60 (d, *J* = 8.0 Hz, 1H, **H1**), 5.82 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.26 – 5.16 (m, 2H, **H19**), 4.69 (s, 1H, **H5**), 3.21 – 3.13 (m, 2H, **H17**), 3.09 (d, *J* = 18.5 Hz, 1H, **H10eq**), 3.04 (td, *J* = 14.0, 5.0 Hz, 1H, **H7ax**), 3.01 (d, *J* = 6.0 Hz, 1H, **H9**), 2.59 (dd, *J* = 12.5, 5.0 Hz, 1H, **H16eq**), 2.55 (dd, *J* = 18.5, 6.0 Hz, 1H, **H10ax**), 2.40 (td, *J* = 12.5, 5.0 Hz, 1H, **H15ax**), 2.31 (dt, *J* = 14.0, 3.0 Hz, 1H, **H7eq**), 2.17 (td, *J* = 12.5, 3.5 Hz, 1H, **H16ax**), 1.96 (br s, **OH**), 1.87 (ddd, *J* = 14.0, 5.0, 3.0 Hz, 1H, **H8eq**), 1.64 (td, *J* = 14.0, 3.0 Hz, 1H, **H8ax**), 1.57 (dd, *J* = 12.5, 3.5 Hz, 1H, **H15eq**).
^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0 (**C6**), 143.6 (**C4**), 139.0 (**C3**), 135.3 (**C18**), 129.1 (**C12**), 124.4 (**C11**), 120.1 (**C2**), 118.3 (**C1**), 118.1 (**C19**), 90.7 (**C5**), 70.5 (**C14**), 62.4 (**C9**), 57.8 (**C17**), 51.1 (**C13**), 43.4 (**C16**), 36.3 (**C7**), 31.4 (**C8**), 30.6 (**C15**), 22.8 (**C10**).
m. p. 179-181 °C
IR (neat, cm^{-1}) 3328, 2927, 2828, 1725, 1618, 1457, 1243, 941.

Naloxone-3-allyl ether 62



62

Naloxone free base (0.6 g, 1.82 mmol) and potassium carbonate (0.38 g, 2.73 mmol) were dissolved in acetone (18 mL) under air. Allyl bromide (0.19 mL, 2.2 mmol) was added dropwise and the mixture was stirred at 50 °C for 18 h. After completion, the reaction mixture was cooled to room temperature. A 5% aqueous solution of ammonia was added, and the solution was stirred for an hour. The mixture was then poured into water, transferred into a separating funnel, and the crude product was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The crude material was purified by flash chromatography on Florisil (100% petroleum ether to 100% ethyl aetate) to afford naloxone-3-allyl ether **62** (450 mg, 67%) as a colourless oil.

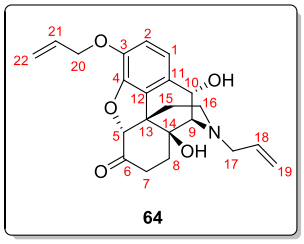
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (d, *J* = 8.0 Hz, 1H, **H2**), 6.57 (d, *J* = 8.0 Hz, 1H, **H1**), 6.03 (ddt, *J* = 17.0, 10.5, 5.5 Hz, 1H, **H21**), 5.78 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.35 (m, 1H, **H22**), 5.22 – 5.12 (m, 3H, **H19**, **H22**), 4.73 – 4.60 (m, 2H, **H20**), 4.63 (s, 1H, **H5**), 3.12 (m, 2H, **H17**), 3.05 (d, *J* = 18.5 Hz, 1H, **H10eq**), 2.97 (td, *J* = 14.5, 5.0 Hz, 1H, **H7ax**), 2.96 (d, *J* = 6.0 Hz, 1H, **H9**), 2.54 (dd, *J* = 12.5, 5.0 Hz, 1H, **H16eq**), 2.53 (dd, *J* = 18.5, 6.0 Hz,1H, **H10ax**), 2.35 (td, *J* = 13.0, 5.0 Hz, 1H, **H15ax**), 2.25 (dt, *J* = 14.5, 3.0 Hz, 1H, **H7eq**), 2.10 (td, *J* = 12.5, 3.0 Hz, 1H, **H16ax**), 1.83 (ddd, *J* = 13.5, 5.0, 3.0 Hz, 1H, **H8eq**), 1.59 (ddd, *J* = 14.5, 13.5, 3.0 Hz, 1H, **H8ax**), 1.52 (dd, *J* = 13.0, 3.0 Hz, 1H, **H15eq**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.4 (**C6**), 145.3 (**C4**), 141.6 (**C3**), 135.1 (**C18**), 133.8 (**C21**), 129.7 (**C12**), 125.4 (**C11**), 119.4 (**C1**), 118.1 (**C22**), 117.6 (**C19**), 117.6 (**C2**), 90.3 (**C5**), 70.9 (**C20**), 70.2 (**C14**), 62.2 (**C9**), 57.6 (**C17**), 50.6 (**C13**), 43.3 (**C16**), 36.1 (**C7**), 31.4 (**C8**), 30.5 (**C15**), 22.7 (**C10**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{22}H_{26}NO_4$ 368.1856 found 368.1872.

IR (neat, cm^{-1}) 3390, 2927, 2828, 1726, 1496, 940.

10-Hydroxy naloxone-3-allyl ether 64



64

Naloxone allyl ether **61** (0.3 g, 0.8 mmol) was dissolved in acetonitrile (8 mL) and water (0.4 mL) and cooled down to 0 °C. Ceric ammonium nitrate (1.8 g, 3.26 mmol) was added portion wise over 10 minutes. The mixture was allowed to warm to room temperature and was stirred for 20 h under air. After completion of the reaction, sodium carbonate (0.78 g, 7.3 mmol) and celite were added and the mixture was stirred at room temperature for 1 H. The resulting slurry was filtered through celite and washed with acetonitrile. The filtrate was evaporated to dryness and the residue was dissolved in ethyl acetate. The organic phase was washed with sodium hydroxide, the layers were separated, and the aqueous phase was extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with 30% ethyl acetate in petroleum ether to afford 10-hydroxynaloxone-3-allyl ether **64** (29 mg, 9%) as a colourless oil.

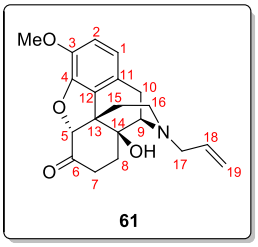
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, *J* = 8.5 Hz, 1H, **H2**), 6.82 (d, *J* = 8.5 Hz, 1H, **H1**), 6.06 (ddt, *J* = 17.0, 11.0, 5.5 Hz, 1H, **H21**), 5.86 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.43 – 5.35 (m, 1H, **H22**), 5.29 – 5.20 (m, 3H, **H19**, **H22**), 5.05 (s, 1H, **H10**), 4.79 – 4.68 (m, 2H, **H20**), 4.67 (s, 1H, **H5**), 3.35 (dd, *J* = 13.0, 6.5 Hz, 1H,**H17**), 3.25 (dd, J = 13.0, 6.5 Hz, 1H, **H17**), 3.04 (s, 1H, **H9**), 3.02 (ddd, *J* = 14.5, 11.5, 8.5 Hz, 1H, **H7ax**), 2.59 (dd, *J* = 12.0, 5.0 Hz, 1H, **H16eq**), 2.38 (td, *J* = 12.0, 5.0 Hz, 1H, **H15ax**), 2.28 (dt, *J* = 14.3, 3.0 Hz, 1H, **H7eq**), 2.03 (td, *J* = 12.0, 3.0 Hz, 1H, **H16ax**), 1.98 – 1.92 (m, *2*H, **H8**), 1.56 (dd, *J* = 12.0, 3.0 Hz, 1H, **H15eq**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.2 (**C6**), 145.0 (**C4**), 143.5 (**C3**), 134.9 (**C18**), 133.6 (**C21**), 129.9 (**C12**), 127.9 (**C11**), 119.8 (**C2**), 118.1 (**C1**), 118.0 (**C19**, **C22**), 90.6 (**C5**), 70.9 (**C20**), 69.8 (**C9**), 69.5 (**C14**), 64.0 (**C10**), 57.9 (**C17**), 51.5 (**C13**), 43.6 (**C15**), 36.6 (**C7**), 32.3 (**C8**), 30.5 (**C15**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{22}H_{26}NO_5$ 384.1805 found 384.1820.

IR (neat, cm^{-1}) 3402, 2926, 2825, 1722, 1276, 928.

Naloxone 3-methyl ether 61



61

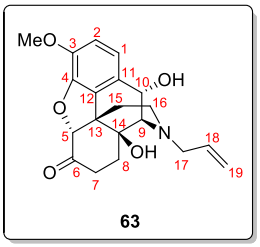
Naloxone free base (1 g, 3.05 mmol) and potassium carbonate (0.5 g, 3.66 mmol) were dissolved in acetone (31 mL). Methyl iodide (0.42 mL, 6.7 mmol) was added slowly and the mixture was stirred at 50 °C for 24 h under air. The reaction mixture was cooled down to room temperature. An aqueous solution of ammonia was added, and the solution was stirred for 0.5 h. The crude mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. Recrystallisation from ethanol afforded naloxone methyl ether **61** (0.88 g, 84%) as a light brown solid. The compound showed satisfactory spectroscopic data in comparison to literature.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (d, *J* = 8.0 Hz, 1H, **H2**), 6.60 (d, *J* = 8.0 Hz, 1H, **H1**), 5.79 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.25 – 5.12 (m, 2H, **H19**), 4.99 (br s, 1H, **OH**), 4.63 (s, 1H, **H5**), 3.86 (s, 3H, **OMe**), 3.15 – 3.11 (m, 2H, **H17**), 3.07 (d, *J* = 18.5 Hz, 1H, **H10eq**), 2.99 (td, *J* = 14.0, 6.0 Hz, 1H, **H7ax**), 2.98 (d, *J* = 6.0 Hz, 1H, **H9**), 2.60 – 2.52 (m, 1H, **H16eq**), 2.55 (dd, *J* = 18.5, 6.0 Hz, 1H, **H10ax**), 2.36 (td, *J* = 12.5, 5.0 Hz, 1H, **H15ax**), 2.26 (dt, *J* = 14.0, 3.0 Hz, 1H, **H7eq**), 2.11 (td, *J* = 12.5, 3.5 Hz, 1H, **H16ax**), 1.83 (ddd,

J = 13.5, 6.0, 3.0 Hz, 1H, **H8eq**), 1.59 (ddd, *J* = 14.0, 13.5, 3.0 Hz, 1H, **H8ax**), 1.54 (ddd, *J* = 12.5, 3.5, 1.5 Hz, 1H, **H15eq**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 208.7 (**C6**), 145.0 (**C4**), 143.0 (**C3**), 135.2 (**C18**), 129.5 (**C12**), 124.9 (**C11**), 119.5 (**C2**), 118.2 (**C19**), 114.9 (**C1**), 90.4 (**C5**), 70.3 (**C14**), 62.3 (**C9**), 57.7 (**C17**), 56.9 (**OMe**), 54.1 (**C13**), 43.4 (**C16**), 36.2 (**C7**), 31.5 (**C8**), 30.6 (**C15**), 22.8 (**C10**).

10-Hydroxynaloxone-3-methyl ether 63



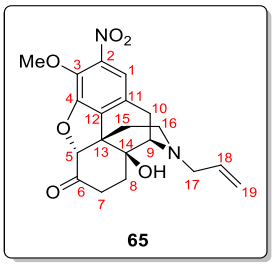
63

Naloxone methyl ether **61** (1.08 g, 3.2 mmol) was dissolved in acetonitrile (30 mL) and water (1.6 mL) and cooled down to 0 °C. Ceric ammonium nitrate (6.9 g, 12.7 mmol) was added portion wise over 10 minutes. The mixture was allowed to warm to room temperature and was stirred for 20 h under air. After completion of the reaction, sodium carbonate (3.02 g, 28.5 mmol) and celite were added and the mixture was stirred at room temperature for 1 h. The resulting slurry was filtered through celite and washed with acetonitrile. The filtrate was evaporated to dryness and the residue was dissolved in ethyl acetate. The organic phase was washed with sodium hydroxide, the layers were separated, and the aqueous phase was extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with 40% ethyl acetate to 80% ethyl acetate in petroleum ether, to afford 10-hydroxynaloxone-3-methyl ether **63** (0.17 g, 14%) as a white solid, and 2-nitronaloxone-3-methyl ether **65** as a yellow solid (19 mg, 2%). Compound **63** showed satisfactory ^{1}H NMR data in comparison to literature.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, *J* = 8.5 Hz, 1H, **H2**), 6.80 (d, *J* = 8.5 Hz, 1H, **H1**), 5.85 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.28 – 5.19 (m, 2H, **H19**), 5.05 (s, 1H, **H10**), 4.67 (s, 1H, **H5**), 3.92 (s, 3H, **OMe**), 3.34 (ddt, *J* = 13.5, 6.5, 1.0 Hz, 1H, **H17**), 3.24 (ddt, *J* = 13.5, 6.5, 1.0 Hz, 1H, **H17**), 3.02 (s, 1H, **H9**), 3.01 (td, *J* = 14.5, 8.0, 1H, **H7ax**), 2.58 (ddd, *J* = 12.0, 5.0, 1.0 Hz, 1H, **H15eq**), 2.37 (td, *J* = 12.0, 5.0 Hz, 1H, **H16ax**), 2.28 (dt, *J* = 14.5, 3.0 Hz, 1H, **H7eq**), 2.03 (td, *J* = 12.0, 3.5 Hz, 1H, **H15ax**), 1.97 – 1.91 (m, 2H, **H8**), 1.56 (ddd, *J* = 12.0, 3.5, 1.0 Hz, 1H, **H16eq**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.3 (**C6**), 144.8 (**C4**), 144.8 (**C3**), 135.0 (**C18**), 129.7 (**C12**), 127.6 (**C11**), 119.9 (**C2**), 118.6 (**C19**), 115.5 (**C1**), 90.7 (**C5**), 69.8 (**C9**), 69.5 (**C14**), 64.1 (**C10**), 57.9 (**C17**), 56.9 (**OMe**), 51.6 (**C13**), 43.6 (**C15**), 36.6 (**C7**), 32.4 (**C8**), 30.5 (**C16**).

2-Nitronaloxone-3-methyl ether 65



65

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H, **H1**), 5.81 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.29 – 5.19 (m, 2H, **H19**), 4.84 (s, 1H, **H5**), 3.95 (s, 3H, **OMe**), 3.58 (d, *J* = 20.0 Hz, 1H, **H10eq**), 3.20 – 3.16 (m, 2H, **H17**), 3.10 (dd, *J* = 6.0 Hz, 1H, **H9**), 3.05 (td, *J* = 14.5, 5.0 Hz, 1H, **H8ax**), 2.97 (dd, *J* = 20.0, 6.0 Hz, 1H, **H10ax**), 2.63 (dd, *J* = 13.0, 5.0 Hz, 1H, **H16eq**), 2.44 (td, *J* = 13.0, 5.0 Hz, 1H, **H15ax**), 2.35 (dt, *J* = 14.5, 3.0 Hz, 1H, **H8eq**), 2.06 (td, *J* = 13.0, 4.0 Hz, 1H, **H16ax**), 1.95 (ddd, *J* = 13.5, 5.0, 3.0 Hz, 1H, **H7eq**), 1.60 (ddd, *J* = 14.5, 13.5, 3.0 Hz, 1H, **H7ax**), 1.56 (dd, *J* = 13.0, 4.0 Hz, 1H, **H15eq**).

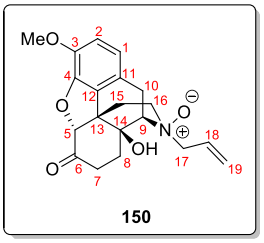
^{13}C NMR (101 MHz, $CDCl_3$) δ 206.9 (**C6**), 150.4 (**C4**), 143.3 (**C3**), 140.0 (**C2**), 134.75 (**C18**), 131.1 (**C12**), 123.9 (**C11**), 118.9 (**C19**), 111.9 (**C1**), 91.6 (**C5**), 69.4 (**C14**), 61.5 (**C9**), 57.7 (**C17**), 56.9 (**OMe**), 51.0 (**C13**), 42.8 (**C16**), 36.0 (**C8**), 31.5 (**C7**), 30.9 (**C15**), 23.9 (**C10**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{20}H_{23}N_2O_6$ 387.1551 found 387.1555.

m. p. 195-197 °C

IR (neat, cm^{-1}) 2930, 1728, 1522, 1323.

***N*-Oxide 70**



150

Naloxone methyl ether **61** (0.2 g, 0.57 mmol) was dissolve in chloroform (19 mL) under air. The solution was cooled down to 0 °C and *m*CPBA (0.27 g, 1.17 mmol) was added portion-wise. The reaction mixture was stirred from 0 °C to room temperature overnight. An aqueous solution of sodium thiosulfate was

added, and the mixture was stirred for 15 minutes. The layers were separated, and the crude product was extracted three times with DCM. The combined organic extracts were washed with an aqueous solution of sodium carbonate, water and brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with 1% to 10% MeOH in DCM to afford naloxone methyl ether *N*-oxide **70** (63.6 mg, 30%) as a light-brown foam and the lactone **148** (28 mg, 13%) as a pale beige foam.

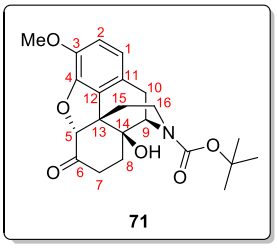
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, *J* = 8.0 Hz, 1H, **H2**), 6.64 (d, *J* = 8.0 Hz, 1H, **H1**), 6.39 (dddd, *J* = 16.0, 10.5, 8.0, 5.5 Hz, 1H, **H18**), 5.53 (m, 2H, **H19**), 4.74 (s, 1H, **H5**), 4.03 (dd, *J* = 13.0, 8.0 Hz, 1H, **H17**), 3.88 (s, 3H, **OMe**), 3.84 (dd, *J* = 13.0, 5.5 Hz, 1H, **H17**), 3.58 (d, *J* = 5.5 Hz, 1H, **H9**), 3.29 – 3.18 (m, 2H, **H15**, **H16**), 3.19 (d, *J* = 19.5 Hz, 1H, **H10eq**), 3.12 (td, *J* = 14.5, 5.0 Hz, 1H, **H7ax**), 3.06 – 3.00 (m, 1H, **H16**), 3.01 (dd, *J* = 19.5, 5.5 Hz, 1H, **H10ax**), 2.18 (dt, *J* = 14.5, 3.0 Hz, 1H, **H7eq**), 1.90 (ddd, *J* = 12.5, 5.0, 3.0 Hz, 1H, **H8eq**), 1.70 – 1.63 (m, 1H, **H15**), 1.55 (ddd, *J* = 14.5, 12.5, 3.0 Hz, 1H, **H8ax**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0 (**C6**), 145.4 (**C4**), 144.0 (**C3**), 129.6 (**C12**), 127.5 (**C18**), 124.2 (**C19**), 120.5 (**C11**), 120.1 (**C1**), 115.8 (**C2**), 90.0 (**C5**), 72.2 (**C14**), 71.9 (**C17**), 71.9 (**C9**), 60.8 (**C16**), 56.9 (**OMe**), 50.5 (**C13**), 35.0 (**C7**), 33.0 (**C8**), 28.0 (**C10**), 25.6 (**C15**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{20}H_{24}NO_5$ 358.1649 found 358.1656

IR (neat, cm^{-1}) 2961, 1724, 1505, 1439, 1280, 1173, 929.

***N*-Boc noroxycodone 71**



71

A solution of naloxone methyl ether **61** (1.5 g, 4.39 mmol) in anhydrous DCM (33 mL) was added to a solution of $Pd(PPh_3)_4$ (0.25 g, 0.22 mmol) and *N*,*N*-dimethylbarbituric acid (1.03 g, 6.6 mmol) in anhydrous DCM (33 mL). The resulting solution was heated at 40 °C for 20 h. The solvent was removed under reduced pressure and the residue was dissolved in 1,4-dioxane (44 mL). DIPEA (0.08 mL, 0.44 mmol) and Boc_2O (2.02 mL, 8.79 mmol) were added and the mixture was stirred at 60 °C overnight. After cooling to room temperature, the reaction mixture was poured into water and the crude product was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, and the solvent was removed under reduced pressure. The crude material was

purified by flash chromatography on silica gel eluting with 50% ethyl acetate in petroleum ether to afford *N*-Boc noroxycodone **71** (1.12 g, 63%) as a yellow foam.

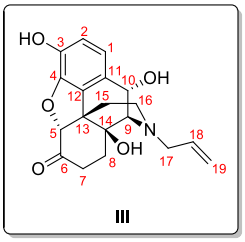
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, *J* = 8.0 Hz, 1H, **H2**), 6.64 (d, *J* = 8.0 Hz, 1H, **H1**), 4.66 (s, 1H, **H5**), 4.51 (br, **H9 major**), 4.34 (br, **H9 minor**), 3.90 (br, 1H, **H16**), 3.90 (s, 3H, **OMe**), 3.04 (dd, *J* = 18.5, 5.5 Hz, 1H, **H10ax**), 3.02 (td, *J* = 14.0, 4.5 Hz, 1H, **H7ax**), 2.90 (d, *J* = 18.5 Hz, 1H, **H10eq**), 2.72 (br, 1H, **H16**), 2.41 (br, 1H, **H15**), 2.29 (dt, *J* = 14.0, 3.0 Hz, 1H, **H7eq**), 1.91 (ddd, *J* = 14.0, 4.5, 3.0 Hz, 1H, **H8eq**), 1.67 (td, *J* = 14.0, 3.0 Hz, 1H, **H8ax**), 1.49 (s, 9H, **CH_3 *t*Bu Boc**), 1.48 (br, 1H, **H15**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.2 (**C6**), 156.2 (**C=O Boc**), 145.0 (**C4**), 143.1 (**C3**), 128.6 (**C12**), 124.0 (**C11**), 119.8 (**C1**), 115.1 (**C2**), 89.9 (**C5**), 80.4 (**C^{IV} *t*Bu Boc**), 70.6 (**C14**), 56.7 (**OMe**), 55.8 (**C9**), 50.3 (**C13**), 37.8 (**C16**), 35.6 (**C7**), 31.7 (**C8**), 31.4 (**C10**), 28.4 (**C15**), 28.3 (**CH_3 *t*Bu Boc**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{22}H_{28}NO_6$ 402.1911 found 402.1913.

IR (neat, cm^{-1}) 3432, 2930, 1726, 1684, 1162.

10-Hydroxynaloxone III



III

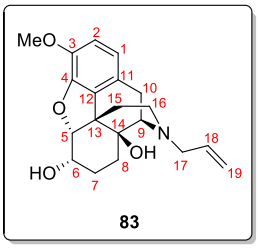
10-Hydroxynaloxone methyl ether **63** (0.13 g, 0.352 mmol) was dissolved in anhydrous DCM (3.5 mL) and the solution was cooled down to 0 °C. A solution of BBr_3 (1 M in DCM, 1.23 mL, 1.23 mmol) was added dropwise, the solution was warmed to room temperature and the reaction mixture was stirred for 18 h. The reaction mixture was cooled down to 0 °C, aqueous NaOH was added and the mixture was stirred for 1 h. The layers were separated, the aqueous layer was saturated with ammonium chloride and the crude product was extracted with DCM. The combined organic layers were wash with brine, dried and the solvent was removed under reduced pressure to afford a first sample of 10-hydroxynaloxone. The original DCM layer was wash with an aqueous solution of NaOH, this solution was then saturated with ammonium chloride and extracted with DCM. The solvent was evaporated to afford a second sample of 10-hydroxynaloxone. The two previous aqueous layers were combined, saturated with sodium chloride, and extracted with DCM. The combined organic layers were washed with brine, dried and the solvent was removed under reduced pressure to afford a third sample of 10-hydroxynaloxone. The three samples were combined, and the crude material was purified by flash chromatography on silica gel eluting with 30% ethyl acetate in DCM to afford 10-hydroxynaloxone **III**

(70 mg, 60%) as a pale-yellow foam. The compound showed satisfactory spectroscopic data in comparison to literature.[95]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, *J* = 8.0 Hz, 1H, **H2**), 6.81 (d, *J* = 8.0 Hz, 1H, **H1**), 5.85 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.28 – 5.18 (m, 2H, **H19**), 5.12 (s, 1H, **H10**), 4.68 (s, 1H, **H5**), 3.37 (dd, *J* = 13.5, 6.5 Hz, 1H, **H17**), 3.25 (dd, J = 13.5, 6.5 Hz, 1H, **H17**), 3.12 – 2.98 (m, 2H), 2.60 (dd, *J* = 12.0, 5.0 Hz, 1H), 2.39 (td, *J* = 12.6, 5.4 Hz, 1H), 2.30 (dt, *J* = 14.2, 2.9 Hz, 1H), 2.07 (td, *J* = 12.0, 3.5 Hz, 1H), 1.98 (m, 2H), 1.56 (dd, *J* = 13.0, 2.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.3, 143.3, 141.0, 135.0, 129.2, 127.0, 120.5, 119.2, 118.7, 90.8, 69.9, 69.6, 64.2, 58.0, 51.9, 43.5, 36.6, 32.2, 30.4.

Alcohol 83



83

Naloxone methyl ether **61** (2 g, 5.95 mmol) was dissolved in acetic acid (20 mL), under N_2 atmosphere. Sodium (triacetoxy)borohydride (3.8 g, 17.85 mmol) was added portion-wise at room temperature and the mixture was stirred for 1 h. Acetone (4 mL) was added and the mixture was stirred for one more hour. The solvent was evaporated, and the pH was adjusted to 9-10 using a 1 M solution of sodium hydroxide. The aqueous phase was extracted with DCM, the organic layer was washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure, to afford 6α-naloxol **83** (1.55 g, 77%) as a white foam.

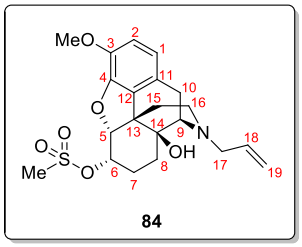
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (d, *J* = 8.0 Hz, 1H, **H2**), 6.58 (d, *J* = 8.0 Hz, 1H, **H1**), 5.77 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.21 – 5.10 (m, 2H, **H19**), 4.61 (d, *J* = 4.5 Hz, 1H, **H5**), 4.17 (dt, *J* = 10.0, 4.5 Hz, 1H, **H6**), 3.84 (s, 3H, **OMe**), 3.11 – 3.07 (m, 2H, **H17**), 3.07 (d, *J* = 19.0 Hz, 1H, **H10eq**) 2.88 (d, *J* = 6.5 Hz, 1H, **H9**), 2.58 (dd, *J* = 19.0, 6.5 Hz, 1H, **H10ax**), 2.54 – 2.48 (m, 1H, **H16**), 2.25 – 2.13 (m, 2H, **H7**, **H16**), 1.75 (td, *J* = 12.5, 4.2 Hz, 1H, **H15ax**), 1.59 (dt, J = 14.5, 8.0 Hz, 1H, **H8eq**), 1.53 – 1.49 (m, 1H, **H7**), 1.43 (ddd, *J* = 14.5, 8.0, 4.5 Hz, 1H, **H8ax**), 1.20 – 1.09 (m, 1H, **H15eq**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6 (**C4**), 141.7 (**C3**), 135.4 (**C18**), 131.5 (**C12**), 126.2 (**C11**), 118.9 (**C1**), 117.9 (**C19**), 113.7 (**C2**), 90.8 (**C5**), 70.0 (**C14**), 66.7 (**C6**), 62.4 (**C9**), 58.0 (**C17**), 56.5 (**OMe**), 54.2 (**C13**), 43.0 (**C16**), 33.3 (**C7**), 28.3 (**C8**), 23.7 (**C15**), 22.9 (**C10**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{20}H_{26}NO_4$ 344.1856 found 344.1861

IR (neat, cm^{-1}) 3340, 2925, 1724, 1428, 1275, 979.

Mesylate 84



Alcohol **83** (2.5 g, 7.32 mmol) was dissolved in pyridine (24 mL), under N_2 atmosphere and cooled down to 0 °C. Methanesulfonyl chloride (0.85 mL, 11 mmol) was added dropwise and the solution was stirred at 0 °C for 45 minutes. After completion, the reaction mixture was poured into crashed ice and the pH was adjusted to 9-10 with potassium carbonate. The aqueous phase was extracted with ethyl acetate. The organic phase was washed with an aqueous solution of copper sulfate, water, brine, dried over magnesium sulfate and the solvent was removed under reduced pressure to afford the mesylate **84** (2.3 g, 93%) as a green foam.

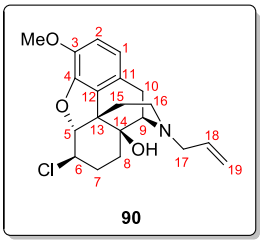
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (d, *J* = 8.0 Hz, 1H, **H2**), 6.52 (d, *J* = 8.0 Hz, 1H, **H1**), 5.68 (ddt, *J* = 12.5, 10.0, 6.5 Hz, 1H, **H18**), 5.13 – 4.98 (m, 3H, **H6**, **H19**), 4.80 (br s, 1H, **OH**), 4.62 (d, *J* = 5.0 Hz, 1H, **H5**), 3.73 (s, 3H, **OMe**), 3.13 – 3.06 (m, 2H, **H17**), 3.08 (d, *J* = 18.0 Hz, 1H, **H10eq**), 3.05 (s, 3H, **CH_3 OMs**), 2.80 (d, *J* = 6.0 Hz, 1H, **H9**), 2.49 (dd, *J* = 18.0, 6.0 Hz, 1H, **H10ax**), 2.44 – 2.37 (m, 1H, **H16**), 2.15 – 2.01 (m, 2H, **H15**, **H16**), 1.94 (ddd, *J* = 12.0, 6.5, 4.0 Hz, 1H, **H7eq**), 1.57 (td, *J* = 12.0, 6.0 Hz, 1H, **H7ax**), 1.49 – 1.41 (m, 2H, **H8**), 1.40 – 1.34 (m, 1H, **H15**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.4 (**C4**), 141.9 (**C3**), 135.3 (**C18**), 130.6 (**C12**), 125.7 (**C11**), 119.2 (**C1**), 118.1 (**C19**), 114.2 (**C2**), 86.6 (**C5**), 77.1 (**C6**), 69.9 (**C14**), 62.5 (**C9**), 57.9 (**C17**), 56.6 (**OMe**), 47.2 (**C13**), 43.4 (**C16**), 38.3 (**CH_3 OMs**), 32.4 (**C15**), 26.6 (**C8**), 23.2 (**C7**), 22.9 (**C10**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{21}H_{28}NO_6S$ 422.1632 found 422.164.

IR (neat, cm^{-1}) 3383, 2933, 2835, 1336, 1172, 948.

Chloride 90



90

The mesylate **84** (3.3 g, 7.8 mmol) was dissolved in anhydrous DMF (39 mL) under nitrogen atmosphere. DBU (21 mL, 141 mmol) was added slowly and the reaction mixture was stirred at 100 °C for 36 h. The crude mixture was poured into saturated aqueous $NaHCO_3$ and extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with 10% to 50% ethyl acetate in petroleum ether to afford an inseparable mixture of enol ether **87** and chloride **90** (0.42 g). 100 mg of the mixture were dissolved in acetonitrile/water 50:50 *v:v* and subjected to preparative HPLC, in six runs of 16 mg each. Compound **90** was isolated as a white solid.

HPLC (XBridge C18 250 x 4.6 mm, acetonitrile/water 70:30, flow rate 1.0 mL/min, λ = 240 nm, 23 °C) t_R (enol ether **88**) = 9.620 min, t_R(chloride **91**) = 10.403 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, *J* = 8.0 Hz, 1H, **H2**), 6.64 (d, *J* = 8.0 Hz, 1H, **H1**), 5.78 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.22 – 5.13 (m, 2H, **H19**), 4.64 (d, *J* = 7.5 Hz, 1H, **H5ax**), 3.89 (s, 3H, **OMe**), 3.68 (ddd, *J* = 12.7, 7.5, 5.1 Hz, 1H, **H6ax**), 3.12 (dt, *J* = 6.5, 1.0 Hz, 2H, **H17**), 3.06 (d, *J* = 18.5 Hz, 1H, **H10**), 2.90 (d, *J* = 5.5 Hz, 1H, **H9**), 2.58 (dd, *J* = 18.5, 5.5 Hz, 1H, **H10**), 2.53 (dd, *J* = 12.0, 4.5 Hz, 1H, **H16eq**), 2.37 – 2.25 (m, 1H, **H7ax**), 2.21 (td, *J* = 12.0, 4.5 Hz, 1H, **H15ax**), 2.08 (td, *J* = 12.0, 3.5 Hz, 1H, **H16ax**), 1.88 (ddt, *J* = 13.0, 5.0, 3.5 Hz, 1H, **H7eq**), 1.62 (dt, *J* = 13.0, 3.5 Hz, 1H, **H8eq**), 1.46 (dd, *J* = 12.0, 3.5 Hz, 1H, **H15eq**), 1.37 (td, *J* = 13.0, 3.0 Hz, 1H, **H8ax**).

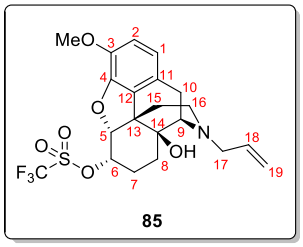
^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0 (**C4**), 143.7 (**C3**), 135.4 (**C18**), 131.3 (**C12**), 125.3 (**C11**), 119.1 (**C1**), 118.1 (**C19**), 114.8 (**C2**), 95.4 (**C5**), 70.0 (**C14**), 62.5 (**C9**), 61.4 (**C6**), 57.7 (**C17**), 57.0 (**OMe**), 48.6 (**C13**), 43.7 (**C16**), 31.4 (**C8**), 30.6 (**C15**), 28.8 (**C7**), 22.8 (**C10**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{20}H_{25}ClNO_3$ 362.1517 found 362.1525

m. p. 105-107 °C

IR (neat, cm^{-1}) 3390, 2924, 2833, 1499, 1277, 1045, 983.

Triflate 85



Alcohol **83** (0.5 g, 1.46 mmol) was dissolved in anhydrous chloroform (15 mL), under argon atmosphere. *N*-Methylmorpholine (0.64 mL, 5.83 mmol) was added and the solution was cooled down to -30 °C. Trifluoromethanesulfonic anhydride (0.49 mL, 2.92 mmol) was added dropwise and the solution was stirred from -30 to 0 °C for 1.5 h. The reaction mixture was, then, diluted with chloroform, washed with saturated aqueous solution of sodium hydrogen carbonate, water and brine. The organic phase was dried over magnesium sulfate and the solvent was removed under reduced pressure to afford the triflate **85** (537 mg, 77%) as a brown oil.

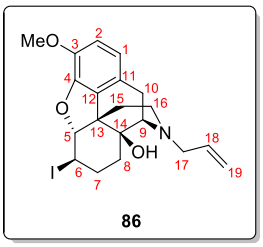
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, *J* = 8.0 Hz, 1H, **H2**), 6.62 (d, *J* = 8.0 Hz, 1H, **H1**), 5.84 – 5.69 (m, 1H, **H18**), 5.41 (dt, *J* = 9.0, 4.0 Hz, 1H), 5.23 – 5.12 (m, 2H), 4.82 (br s, 1H), 4.69 (d, *J* = 5.0 Hz, 1H), 3.85 (s, 3H, **OMe**), 3.15 – 3.03 (m, 3H), 2.92 (d, *J* = 6.0 Hz, 1H), 2.65 – 2.50 (m, 2H), 2.27 – 2.14 (m, 2H), 1.74 – 1.59 (m, 2H), 1.56 – 1.44 (m, 2H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -75.48 (**CF_3**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{21}H_{25}F_3NO_6S$ 476.1349 found 476.1359.

IR (neat, cm^{-1}) 3386, 2928, 1408, 1204, 910.

Iodide 86



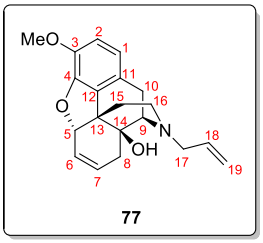
Method I: Sodium iodide (49 g, 327 mmol) was suspended in anhydrous DMF (20 mL). A solution of mesylate **84** (4.5 g, 10.9 mmol) in anhydrous DMF (16 mL) was added under nitrogen atmosphere and the reaction mixture was stirred at 100 °C for 20 h. After cooling to room temperature, the solid was dissolved in DCM and water and the organic solvent was evaporated. A saturated solution of sodium bicarbonate was added, and the crude product was extracted with diethyl ether. The combined organic

extracts were washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure to afford a 10:1 mixture of 6-iodo derivative **86** and alkene **77** (3.5 g). The crude mixture was used without further purification in the elimination step.

Method II: The triflate **85** (0.15 g, 0.32 mmol) was dissolved in dry acetonitrile (5.5 mL), under argon atmosphere. Tetraethylammonium iodide (0.16 g, 0.63 mmol) was added in one portion at -10 °C and the reaction mixture was stirred for 1 h. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was evaporated. The residue was dissolved in chloroform and washed with water. The organic layer was dried over magnesium sulfate and the solvent was evaporated to give the 6-iodo derivative **86** (114 mg, 80%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, *J* = 8.0 Hz, 1H, **H2**), 6.63 (d, *J* = 8.0 Hz, 1H, **H1**), 5.77 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.21 – 5.12 (m, 2H, **H19**), 4.91 (d, *J* = 8.0 Hz, 1H, **H5**), 3.89 (s, 3H, **OMe**), 3.86 (ddd, *J* = 8.0, 6.5, 3.0 Hz, 1H, **H6**), 3.14 – 3.09 (m, 2H, **H17**), 3.05 (d, *J* = 18.5 Hz, 1H, **H10eq**), 2.86 (d, *J* = 5.5 Hz, 1H, **H9**), 2.60 (td, *J* = 13.0, 3.0 Hz, 1H, **H8ax**), 2.52 (dd, *J* = 12.5, 5.0 Hz, 1H, **H16eq**), 2.56 (dd, *J* = 18.5, 5.5 Hz, 1H, **H10ax**), 2.20 (td, *J* = 12.5, 5.0 Hz, 1H, **H15ax**), 2.11 – 2.02 (m, 2H, **H8eq**, **H16ax**), 1.46 – 1.39 (m, 1H, **H15eq**), 1.43 (dd, J = 13.0, 3.0 Hz, 1H, **H7eq**), 1.33 (td, *J* = 13.0, 3.0 Hz, 1H, **H7ax**).
^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1 (**C4**), 143.6 (**C3**), 135.3 (**C18**), 131.0 (**C12**), 125.6 (**C11**), 119.2 (**C2**), 118.1 (**C19**), 115.3 (**C1**), 96.6 (**C5**), 69.9 (**C14**), 62.6 (**C9**), 57.7 (**C17**), 57.3 (**OMe**), 48.8 (**C13**), 43.9 (**C16**), 33.7 (**C7**), 31.8 (**C8**), 30.6 (**C15**), 29.3 (**C6**), 22.8 (**C10**).
HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{20}H_{25}INO_3$ 454.0874 found 454.0877.
m. p. 154-156 °C
IR (neat, cm^{-1}) 3391, 2920, 2832, 1498, 1277, 979.

Alkene 77



77

Iodide **86** (3.1 g, 6.86 mmol) was dissolved in dry DMF (34 mL), under nitrogen atmosphere. DBU (19 mL, 124 mmol) was added and the solution was stirred at 100 °C for 24 h. The crude mixture was poured into a saturated aqueous solution of sodium hydrogen carbonate, diluted with water, and extracted three times with DCM. The combined organic layers were washed with brine, dried over magnesium sulfate, and the solvent was removed under reduced pressure. The crude material was

purified by flash chromatography on silica gel, eluted with 10% to 20% ethyl acetate in petroleum ether, to afford the alkene **77** as a colourless oil (1.6 g, 74%) and enol ether **87** (231 mg, 10%) as a white solid.

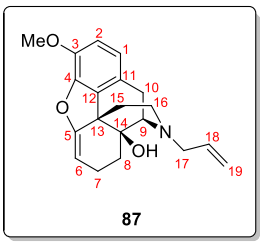
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (d, *J* = 8.0 Hz, 1H, **H2**), 6.56 (d, *J* = 8.0 Hz, 1H, **H1**), 5.82 – 5.68 (m, 3H, **H6**, **H7**, **H18**), 5.19 – 5.09 (m, 2H, **H19**), 4.95 – 4.92 (m, 1H, **H5**), 4.54 (br s, **OH**), 3.78 (s, 3H, **OMe**), 3.11 – 3.06 (m, 2H, **H17**), 3.07 (d, *J* = 17.5 Hz, 1H, **H10eq**), 2.90 (d, *J* = 6.5 Hz, 1H, **H9**), 2.61 (dd, *J* = 17.5, 6.5 Hz, 1H, **H10ax**), 2.55 – 2.50 (m, 1H, **H16**), 2.23 – 2.13 (m, 2H, **H15**, **H16**), 2.02 – 1.89 (m, 2H, **H8**), 1.62 – 1.53 (m, 1H, **H15**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7 (**C3**), 143.4 (**C4**), 135.4 (**C18**), 131.6 (**C12**), 129.8 (**C6**), 125.8 (**C11**), 124.2 (**C7**), 118.3 (**C1**), 117.9 (**C19**), 113.4 (**C2**), 87.2 (**C5**), 70.7 (**C14**), 61.9 (**C9**), 58.0 (**C17**), 56.4 (**OMe**), 45.2 (**C13**), 43.6 (**C16**), 31.9 (**C8**), 31.1 (**C15**), 22.9 (**C10**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{20}H_{24}NO_3$ 326.1751 found 326.1753.

IR (neat, cm^{-1}) 3401, 2922, 1504, 1280, 902.

Enol ether 87



87

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (d, *J* = 8.5 Hz, 1H, **H2**), 6.63 (d, *J* = 8.5 Hz, 1H, **H1**), 5.81 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.53 (dd, *J* = 8.5, 3.0 Hz, 1H, **H6**), 5.24 – 5.14 (m, 2H, **H19**), 3.91 (s, 3H, **OMe**), 3.21 – 3.16 (m, 2H, **H17**), 3.14 (d, *J* = 19.0 Hz, 1H, **H10eq**), 3.06 (d, *J* = 5.0 Hz, 1H, **H9**), 2.74 (ddt, *J* = 15.5, 12.0, 3.0 Hz, 1H, **H7ax**), 2.61 (dd, *J* = 12.0, 4.5 Hz, 1H, **H16eq**), 2.55 (dd, *J* = 19.0, 5.0 Hz, 1H, **H10ax**), 2.30 (td, *J* = 12.0, 4.5 Hz, 1H, **H15ax**), 2.19 (td, *J* = 12.0, 3.5 Hz, 1H, **H16ax**), 1.96 (dddd, *J* = 15.5, 8.5, 4.0, 3.0 Hz, 1H, **H7eq**), 1.61 (dt, *J* = 12.0, 3.0 Hz, 1H, **H8eq**), 1.48 (dd, *J* = 12.0, 3.5 Hz, 1H, **H15eq**), 1.14 (td, *J* = 12.0, 4.0 Hz, 1H, **H8ax**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1 (**C5**), 145.6 (**C4**), 142.0 (**C3**), 135.5 (**C18**), 133.6 (**C12**), 123.5 (**C11**), 118.6 (**C1**), 118.0 (**C19**), 113.6 (**C2**), 109.0 (**C6**), 70.5 (**C14**), 62.6 (**C9**), 57.8 (**C17**), 57.0 (**OMe**), 44.7 (**C16**), 31.1 (**C8**), 28.0 (**C15**), 23.3 (**C10**), 19.9 (**C7**).

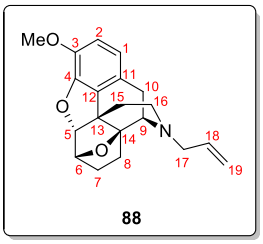
The quaternary carbon C13 was not detected.

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{20}H_{24}NO_3$ 326.1751 found 326.1756.

m. p. 128-130°C

IR (neat, cm^{-1}) 3355, 2921, 2833, 1502, 1279, 1053, 993.

Oxabicycle 88



The mesylate **84** (0.21 g, 0.5 mmol) and potassium *tert*-butoxide (0.28 g, 2.5 mmol) were dissolved in anhydrous THF (5 mL) under nitrogen atmosphere. The reaction mixture was heated at reflux for 4.5 h. After cooling to room temperature, water was added to the reaction mixture and the crude product was extracted three times with diethyl ether. The combined organic extracts were washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel to afford the hexacyclic compound **88** (64 mg, 39%) as a brown oil and the hexacyclic compound **89** (43 mg, 30%) as a brown foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (d, *J* = 8.0 Hz, 1H, **H2**), 6.58 (d, *J* = 8.0 Hz, 1H, **H1**), 5.92 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.27 – 5.08 (m, 2H, **H19**), 4.97 (t, *J* = 5.0 Hz, 1H, **H6**), 4.65 (d, *J* = 5.0 Hz, 1H, **H5**), 3.87 (s, 3H, **OMe**), 3.51 (d, *J* = 6.5 Hz, 1H, **H9**), 3.41 (d, *J* = 18.0 Hz, 1H, **H10eq**), 3.25 – 3.18 (m, 2H, **H17**), 2.77 – 2.62 (m, 2H, **H16**), 2.40 (dd, *J* = 18.0, 6.5 Hz, 1H, **H10ax**), 2.19 (td, *J* = 13.0, 7.0 Hz, 1H, **H15ax**), 1.75 (ddd, *J* = 13.0, 3.0, 1.5 Hz, 1H, **H15eq**), 1.62 (ddd, *J* = 12.0, 9.5, 5.0 Hz, 1H, **H7eq**), 1.47 (tt, *J* = 12.0, 5.0 Hz, 1H, **H7ax**) [a], 1.00 (td, *J* = 13.0, 5.0 Hz, 1H, **H8ax**), -0.18 (ddd, *J* = 13.0, 9.5, 5.0 Hz, 1H, **H8eq**).

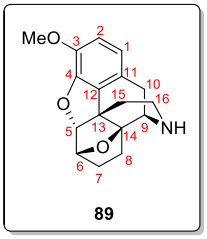
[a] The coupling of 12.0 Hz corresponds to the vicinal coupling with H8ax (^{3}J = 13.0 Hz) however the accuracy of the coupling is limited by the resolution of the spectrometer.

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2 (**C4**), 143.5 (**C3**), 136.2 (**C18**), 135.4 (**C12**), 130.7 (**C11**), 122.2 (**C1**), 117.7 (**C19**), 115.0 (**C2**), 92.3 (**C5**), 89.2 (**C14**), 86.7 (**C6**), 58.1 (**C17**), 57.3 (**C9**), 57.1 (**OMe**), 54.5 (**C13**), 43.2 (**C16**), 31.6 (**C8**), 31.0 (**C15**), 30.4 (**C10**), 21.6 (**C7**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{20}H_{24}NO_3$ 326.1751 found 326.1764.

IR (neat, cm^{-1}) 2916, 1491, 1434, 1254.

Oxabicycle 89



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, *J* = 8.0 Hz, 1H, **H2**), 6.61 (d, *J* = 8.0 Hz, 1H, **H1**), 5.01 (t, *J* = 5.0 Hz, 1H, **H6**), 4.63 (d, *J* = 5.0 Hz, 1H, **H5**), 3.87 (s, 3H, **OMe**), 3.72 (d, *J* = 7.0 Hz, 1H, **H9**), 3.57 (br s, 1H, **NH**), 3.32 (d, *J* = 18.0 Hz, 1H, **H10eq**), 3.16 (td, *J* = 13.5, 3.5 Hz, 1H, **H16ax**), 2.99 – 2.92 (m, 1H, **H15**), 2.93 (dd, J = 18.0, 7.0 Hz, 1H, **H10ax**), 2.12 – 2.01 (m, 1H, **H16eq**), 1.76 (dd, *J* = 13.5, 3.5 Hz, 1H, **H15eq**), 1.66 (ddd, *J* = 12.0, 9.5, 5.0 Hz, 1H, **H7eq**), 1.49 (tt, *J* = 12.0, 5.0 Hz, 1H, **H7ax**)[a], 0.99 (td, *J* = 13.0, 5.0 Hz, 1H, **H8ax**), -0.21 (ddd, *J* = 13.0, 9.5, 5.0 Hz, 1H, **H8eq**).

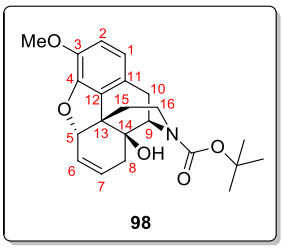
[a] The coupling of 12.0 Hz corresponds to the vicinal coupling with H8ax (^3J = 13.0 Hz) however the accuracy of the coupling is limited by the resolution of the spectrometer.

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.1 (**C4**), 143.5 (**C3**), 135.3 (**C12**), 130.6 (**C11**), 122.2 (**C1**), 115.0 (**C2**), 92.3 (**C5**), 89.3 (**C14**), 86.8 (**C6**), 57.1 (**OMe**), 56.0 (**C9**), 54.9 (**C13**), 41.3 (**C16**), 32.9 (**C10**), 31.5 (**C8**), 30.2 (**C15**), 21.6 (**C7**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{17}H_{20}NO_3$ 286.1438 found 286.1450.

IR (neat, cm^{-1}) 3385, 2943, 1610, 1492, 1434, 1256, 947.

***N*-Boc alkene 98**



A solution of alkene **77** (0.49 g, 1.504 mmol) in anhydrous DCM (7 mL) was added to a solution of $Pd(PPh_3)_4$ (87 mg, 0.075 mmol) and *N,N*-dimethylbarbituric acid (0.35 g, 2.256 mmol) in amhydrous DCM (8 mL), under nitrogen atmosphere. The solution was heated at 40 °C and stirred for 16 h. After completion, the solvent was evaporated. The crude mixture was dissolved in 1,4-dioxane (15 mL). Di-*tert*-butyl dicarbonate (0.66 g, 3 mmol) and *N,N*-diisopropylethylamine (0.026 mL, 0.15 mmol) were added and the solution was stirred at 60 °C for 5 h. After cooling down to room temperature, the solution was poured into water and extracted three times with ethyl acetate. The combined organic

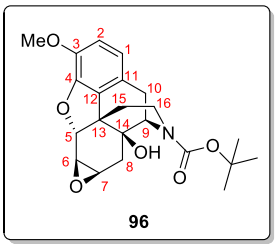
layers were washed with brine, dried over magnesium sulfate and the solvent was evaporated. The crude material was purified by flash chromatography on silica gel, eluting with 50% ethyl acetate in petroleum ether to afford the *N*-Boc alkene **98** (0.57 g, 98%) as a light-yellow foam, and as a 64:36 mixture of rotamers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, *J* = 8.0 Hz, 1H, **H2**), 6.60 (d, *J* = 8.0 Hz, 1H, **H1**), 5.86 – 5.75 (m, 2H, **H6**, **H7**), 5.00 – 4.94 (m, 1H, **H5**), 4.50 (br, **H9 major**), 4.32 (br, **H9 minor**), 3.91 (br, 1H, **H16**), 3.85 (s, 3H, **OMe**), 3.16 (dd, *J* = 18.5, 6.5 Hz, 1H, **H10ax**), 2.91 (d, *J* = 18.5 Hz, 1H, **H10eq**), 2.85 (br, 1H, **H16**), 2.51 (br s, **OH**), 2.27 (br, 1H, **H15**), 2.11 – 1.97 (m, 2H, **H8**), 1.57 (br, 1H, **H15**), 1.48 (s, 9H, **CH_3 *t*Bu**).
^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5 (**C=O Boc**), 144.8 (**C4**), 143.7 (**C3**), 130.8 (**C12**), 129.3 (**C7**), 125.0 (**C11**), 124.3 (**C6**), 118.7 (**C1**), 113.8 (**C2**), 86.8 (**C5**), 80.4 (**C^{IV} *t*Bu Boc**), 71.4 (**C14**), 56.4 (**OMe**), 55.4 (**C9**), 45.2 (**C13**), 38.1 (**C16**), 32.7 (**C8**), 32.3 (**C10**), 29.2 (**C15**), 28.5 (**CH_3 *t*Bu Boc (3C)**).
HRMS (ES) *m/z* $[M+Na]^+$ calculated for $C_{22}H_{27}NO_5Na$ 408.1781 found 408.1788.
IR (neat, cm^{-1}) 3443, 2974, 1687, 1421, 1267, 1161, 904.

Tungsten catalyst $[(C_8H_{17})_3NCH_3]^{3+}[PO_4[W(O)(O_2)_2]_4]^{3-}$ 123

Tungstic acid (1 g, 4.08 mmol) and 30% aqueous H_2O_2 (3 mL) were stirred at 60 °C for 15 minutes, until the disappearance of the yellow colour. The solid was filtered. Phosphoric acid (0.07 mL, 1.02 mmol) was added to the filtrate and the resulting solution was diluted with water (13.6 mL). The solution was stirred at room temperature. A solution of methyltrioctylammonium chloride (0.8 g, 2.04 mmol) in DCM (16.3 mL) was added over two minutes, and the reaction mixture was stirred at room temperature for 15 minutes. The layers were separated, the organic layer was dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure to afford the tungsten catalyst **123** (1.0 g) as a white gum. Compound **123** was directly used for the epoxidation of compound **98**.

Epoxide 96



96

A solution of tungsten catalyst **123** (0.19 g, 0.084 mmol) in DCE (4.2 mL) and water (0.2 mL) was added to a solution of alkene **98** (0.16 g, 0.42 mmol) and hydrogen peroxide (30% in water, 0.14 mL, 1.26

mmol). The reaction mixture was heated at 80 °C for 7 h. After cooling down to room temperature, a saturated solution of sodium thiosulfate was added, and the mixture was stirred for 15 minutes. The layers were separated, and the crude product was extracted three times with DCM. The combined organic extracts were washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with 40% to 50% ethyl acetate in petroleum ether to afford the epoxide **96** (0.14 g, 81%) as a white foam, and as a 58:42 mixture of rotamers.

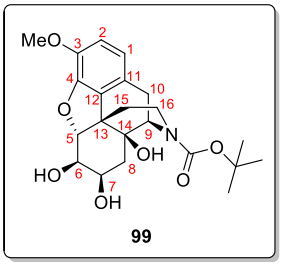
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.0 Hz, 1H, **H2**), 6.65 (d, *J* = 8.0 Hz, 1H, **H1**), 4.82 (t, *J* = 1 Hz, 1H, **H5**), 4.54 (d, *J* = 6.0 Hz, **H9 major**), 4.32 (d, *J* = 6.0 Hz, **H9 minor**), 4.04 – 3.97 (m, **H16a minor**), 3.87 (s, 3H, **OMe**), 3.92 – 3.82 (m, **H16a major**), 3.32 (dd, *J* = 3.0, 1 Hz, 1H, **H6**), 3.24 (t, *J* = 3.0 Hz, 1H, **H7**), 3.07 (dd, *J* = 18.5, 6.0 Hz, 1H, **H10ax**), 2.87 (d, *J* = 18.5 Hz, 1H, **H10eq**), 2.79 (td, *J* = 13.0, 3.5 Hz, **H16ax major**), 2.69 (td, *J* = 13.0, 3.5 Hz, **H16ax minor**), 2.34 (td, *J* = 13.0, 5.5 Hz, 1H, **H15ax**), 2.16 (dd, *J* = 15.5, 1.5 Hz, **H8a major**), 2.09 (dd, *J* = 15.5, 2.0 Hz, **H8a minor**), 1.69 (d, *J* = 15.5 Hz, 1H, **H8b**), 1.46 (s, 9H, **CH_3 *t*Bu**), 1.35 (dd, *J* = 13.0, 3.5 Hz, 1H, **H15eq**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (**C=O**), 144.8 (**C4**), 142.9 (**C3**), 129.1 (**C12**), 125.5 (**C11 major**), 125.3 (**C11 minor**), 119.7 (**C1**), 114.1 (**C2 minor**), 114.0 (**C2 major**), 85.2 (**C5**), 79.8 (**C^{IV} *t*Bu Boc**), 69.3 (**C14**), 56.5 (**OMe**), 55.7 (**C9 minor**), 54.2 (**C9 major**), 53.5 (**C6**), 52.7 (**C7**), 46.0 (**C13**), 37.7 (**C16 major**), 36.5 (**C16 minor**), 32.2 (**C10 minor**), 32.1 (**C10 major**), 30.2 (**C15**), 30.0 (**C8 minor**), 29.8 (**C8 major**), 28.5 (**CH_3 *t*Bu Boc (3C)**).

HRMS (ES) *m/z* $[M+Na]^+$ calculated for $C_{22}H_{27}NO_6Na$ 424.1731 found 424.1712

IR (neat, cm^{-1}) 3504, 2929, 1684, 1419, 1284, 1164, 1013.

***N*-Boc diol 99**



99

The alkene **98** (0.22 g, 0.575 mmol) was dissolved in ethyl acetate (3.6 mL), acetonitrile (3.6 mL) and water (1.2 mL) and the solution was cooled down to 0 °C. $RuCl_3.H_2O$ (21 mg, 0.04 mmol) and sodium periodate (0.18 g, 0.86 mmol) were successively added and the reaction mixture was stirred for 45 minutes. The reaction mixture was allowed to warm to room temperature, a saturated solution of sodium thiosulfate was added, and the mixture was stirred for 15 minutes. The crude product was

extracted three times with DCM. The combined organic extracts were washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by chromatography on silica gel eluting with 100% ethyl acetate to afford the diol **99** (0.19 g, 72%) as a white foam, and as a 60:40 mixture of rotamers.

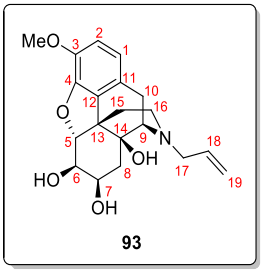
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, *J* = 8.0 Hz, 1H, **H2**), 6.63 (d, *J* = 8.0 Hz, 1H, **H1**), 4.61 (d, *J* = 6.0 Hz, 1H, **H5**), 4.51 (br, **H9 minor**), 4.30 (br, **H9 major**), 4.02 (br, 1H, **H7**), 3.87 (br, 1H, **H16**), 3.86 (s, 3H, **OMe**), 3.45 (br, 1H, **H6**), 3.03 (dd, *J* = 18.5, 5.5 Hz, 1H, **H10ax**), 2.87 (d, *J* = 18.5 Hz, 1H, **H10eq**), 2.67 (br, 1H, **H16**), 2.36 (td, *J* = 12.5, 5.5 Hz, 1H, **H15ax**), 2.07 (dd, *J* = 14.5, 4.0 Hz, 1H, **H8**), 1.60 (dd, *J* = 14.5, 3.0 Hz, 1H, **H8**), 1.47 (s, 9H, **CH_3 *t*Bu Boc**), 1.47 (br, 1H, **H15eq**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1 (**C=O Boc**), 144.2 (**C3**), 143.9 (**C4**), 131.3 (**C12**), 124.5 (**C11**), 119.6 (**C1**), 114.6 (**C2**), 93.9 (**C5**), 80.4 (**C^{IV} *t*Bu Boc**), 73.8 (**C6**), 72.1 (**C14**), 70.0 (**C7**), 56.7 (**OMe**), 55.4 (**C9**), 47.7 (**C13**), 38.1 (**C16**), 34.4 (**C8**), 31.6 (**C10**), 28.7 (**C15**), 28.6 (**CH_3 *t*Bu Boc (3C)**).

HRMS (ES) *m/z* $[M+Na]^+$ calculated for $C_{22}H_{29}NO_7Na$ 442.1836 found 442.1851.

IR (neat, cm^{-1}) 3383, 2926, 1664, 1417, 1163, 1058.

***N*-Allyl diol 93**



93

The *N*-Boc diol **99** (0.17 g, 0.4 mmol) was dissolved in DCM (4 mL) and TFA (4 mL) was added. The solution was stirred at room temperature for 0.5 h. The solvent was evaporated. The residue was then dissolved in acetone (4 mL). Allyl bromide (0.07 mL, 0.8 mmol) and triethylamine (0.17 mL, 1.2 mmol) were added and the reaction mixture was heated at 50 °C for 36 h. After cooling to room temperature, an aqueous solution of ammonia was added, and the reaction mixture was stirred for 1 h. The mixture was poured into water and the crude product was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with 5% MeOH in ethyl acetate to afford the *N*-allyl diol **93** (0.12 g, 85%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (d, *J* = 8.0 Hz, 1H, **H2**), 6.61 (d, *J* = 8.0 Hz, 1H, **H1**), 5.77 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.22 – 5.14 (m, 2H, **H19**), 4.58 (d, *J* = 6.0 Hz, 1H, **H5**), 3.86 (s, 3H, **OMe**), 3.87 –

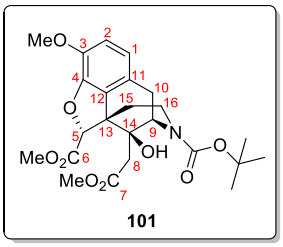
3.83 (m, 1H, **H7**), 3.38 (dd, *J* = 6.0, 3.5 Hz, 1H, **H6**), 3.10 (m, 2H, **H17**), 3.05 (d, *J* = 18.5 Hz, 1H, **H10eq**), 2.97 (d, *J* = 6.0 Hz, 1H, **H9**), 2.60 (dd, J = 18.5, 6.0 Hz, 1H, **H10ax**), 2.52 (ddd, *J* = 12.5, 4.0, 2.5 Hz, 1H, **H16eq**), 2.22 – 2.07 (m, 2H, **H15ax**, **H16ax**), 1.92 (dd, J = 14.5, 4.5 Hz, 1H, **H8**), 1.63 (dd, *J* = 14.5, 3.5 Hz, 1H, **H8**), 1.54 (dd, *J* = 12.5, 2.5 Hz, 1H, **H15eq**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1 (**C4**), 143.9 (**C3**), 135.1 (**C18**), 131.5 (**C12**), 124.9 (**C11**), 118.9 (**C1**), 118.4 (**C19**), 114.9 (**C2**), 94.3 (**C5**), 74.3 (**C6**), 72.1 (**C14**), 69.4 (**C7**), 62.1 (**C9**), 57.7 (**C17**), 56.9 (**OMe**), 47.2 (**C13**), 43.4 (**C16**), 34.7 (**C8**), 30.8 (**C15**), 22.7 (**C10**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{20}H_{26}NO_5$ 360.1805 found 360.1823.

IR (neat, cm^{-1}) 3371, 2923, 1502, 1439, 1276, 1135.

***N*-Boc diester 101**



The diol **99** (0.44 g, 1.05 mmol) was dissolved in DCM (2.6 mL) and water (2.6 mL) under air at room temperature. TEMPO (16 mg, 0.104 mmol) and $PhI(OAc)_2$ (1.67 g, 5.21 mmol) were added and the solution was stirred for 3 h. The solvent was evaporated. The residue was dissolved in anhydrous toluene (166 mL) and anhydrous methanol (42 mL) under nitrogen atmosphere. A solution of TMS-diazomethane (2M in diethyl ether, 3.1 mL, 6.25 mmol) was added at room temperature and the solution was stirred for 3 h. The solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel, eluting with 40% ethyl acetate in petroleum ether to afford the diester **101** (0.2 g, 60%) as a yellow oil, and as a 55:45 mixture of rotamers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, *J* = 8.0 Hz, 1H, **H2**), 6.68 (d, *J* = 8.0 Hz, 1H, **H1**), 4.92 (s, 1H, **H5**), 4.76 (d, *J* = 5.0 Hz, **H9 minor**), 4.62 (d, *J* = 5.5 Hz, **H9 major**), 4.04 (br, **H16a major**), 3.90 (s, 3H, **OMe**), 3.88 (br, **H16a minor**), 3.77 (br s, 3H, **CO_2Me (C6)**), 3.71 (br s, 3H, **CO_2Me (C7)**), 3.11 (br, 1H, **H10**), 2.87 (br, 1H, **H10**), 2.82 – 2.76 (m, **H16b minor**), 2.75 – 2.70 (m, **H16b major**), 2.70 – 2.64 (m, 1H, **H15**), 2.36 (d, *J* = 15.0 Hz, **H8a minor**), 2.35 (d, *J* = 15.0 Hz, **H8a major**), 2.22 (d, *J* = 15.0 Hz, **H8b major**), 2.19 (d, *J* = 15.0 Hz, **H8b minor**), 1.47 (m, 10H, **H15**, **CH_3 *t*Bu Boc**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2 (**C7**), 170.7 (**C6**), 145.7 (**C4**), 142.8 (**C3**), 127.6 (**C12**), 125.1 (**C11**), 119.9 (**C1**), 114.8 (**C2**), 89.5 (**C5**), 80.2 (**C^{IV} *t*Bu Boc**), 73.8 (**C14**), 56.8 (**OMe**), 55.1 (**C9 major**), 54.1 (**C9**

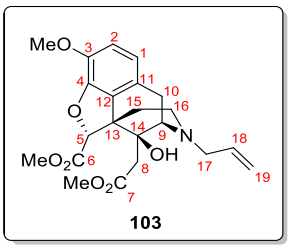
minor), 52.4 (**CO_2Me (C6)**), 52.2 (**CO_2Me (C7)**), 38.1 (**C8**), 37.7 (**C16 minor**), 36.4 (**C16 major**), 33.8 (**C15**), 31.9 (**C10**), 28.5 (**CH_3 *t*Bu Boc (3C)**).

The quaternary carbon C13 was not detected.

HRMS (ES) *m/z* $[M+Na]^+$ calculated for $C_{24}H_{31}NO_9Na$ 500.1891 found 500.1905.

IR (neat, cm^{-1}) 3507, 2959, 1692, 1437, 1284, 1163, 749.

***N*-Allyl diester 103**



103

N-Boc diester **101** (103 mg, 0.22 mmol) was dissolved in DCM (2 mL) and TFA (2 mL) was added. The reaction mixture was stirred at room temperature for 0.5 h, and the solvent was evaporated. The residue was dissolved in acetone (2 mL). Triethylamine (0.09 mL, 0.65 mmol) and allyl bromide (0.04 mL, 0.43 mol) were added and the reaction mixture was heated at 50 °C for 20 h. The reaction mixture was allowed to cool to room temperature, an aqueous solution of ammonia was added, and the reaction mixture was stirred for 1 h. The mixture was poured into water and the crude product was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with 100% ethyl acetate to afford the *N*-allyl diester **103** (36 mg, 40%) as a brown oil.

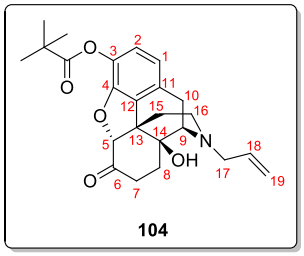
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, *J* = 8.0 Hz, 1H, **H2**), 6.67 (d, *J* = 8.0 Hz, 1H, **H1**), 5.77 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.21 – 5.13 (m, 2H, **H19**), 4.90 (s, 1H, **H5**), 3.89 (s, 3H, **OMe**), 3.82 (s, 3H, **CO_2Me (C6)**), 3.63 (s, 3H, **CO_2Me (C7)**), 3.45 (d, *J* = 6.5 Hz, 1H, **H9**), 3.16 – 3.03 (m, 2H, **H17**), 3.03 (d, *J* = 18.5 Hz, 1H, **H10eq**), 2.84 (dd, *J* = 18.5, 6.5 Hz, 1H, **H10ax**), 2.58 – 2.45 (m, 2H, **H15**, **H16**), 2.49 (d, *J* = 14.0 Hz, 1H, **H8**), 2.18 – 2.10 (m, 1H, **H16**), 2.07 (d, *J* = 14.0 Hz, 1H, **H8**), 1.67 – 1.60 (m, 1H, **H15**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0 (**C7**), 170.5 (**C6**), 145.5 (**C4**), 142.5 (**C3**), 135.1 (**C18**), 128.5 (**C12**), 126.1 (**C11**), 119.5 (**C1**), 118.1 (**C19**), 114.4 (**C2**), 89.3 (**C5**), 72.8 (**C14**), 61.5 (**C9**), 57.8 (**C17**), 56.7 (**OMe**), 54.6 (**C13**), 52.6 (**CO_2Me (C6)**), 51.8 (**CO_2Me (C7)**), 42.9 (**C16**), 37.7 (**C8**), 36.1 (**C15**), 22.8 (**C10**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{22}H_{27}NO_7$ 418.186 found 418.1861

IR (neat, cm^{-1}) 3395, 2951, 2837, 1737, 1506, 1438, 1280, 1196, 1053.

Ketone 104



104

Naloxone (7.37 g, 22.5 mmol) was dissolved in THF (28 mL). Et_3N (6.3 mL, 45 mmol) and PivCl (4.2 mL, 33.8 mmol) were added and the reaction mixture was heated at reflux for 45 minutes. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated. The residue was dissolved is ethyl acetate and filtered through a pad of silica. The solvent was evaporated. The solid was recrystallized from ethanol to afford the naloxone derivative **104** (6.47 g, 70%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (d, *J* = 8.0 Hz, 1H, **H2**), 6.67 (d, *J* = 8.0 Hz, 1H, **H1**), 5.81 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.26 – 5.14 (m, 2H, **H19**), 4.65 (s, 1H, **H5**), 3.17 – 3.14 (m, 2H, **H17**), 3.12 (d, *J* = 19.0 Hz, 1H,**H10eq**), 3.01 (d, *J* = 6.0 Hz, 1H, **H9**), 2.98 (td, *J* = 14.5, 5.0 Hz, 1H, **H7ax**), 2.60 (dd, *J* = 19.0, 6.0 Hz, 1H, **H10ax**), 2.61 – 2.57 (m, 1H, **H16eq**), 2.37 (td, *J* = 12.5, 5.0 Hz, 1H, **H15ax**), 2.28 (dt, *J* = 14.5, 3.5 Hz, 1H, **H7eq**), 2.14 (td, *J* = 12.5, 3.5 Hz, 1H, **H16ax**), 1.85 (ddd, *J* = 14.5, 5.0, 3.5 Hz, 1H, **H8eq**), 1.63 – 1.58 (m, 1H, **H15eq**), 1.66 – 1.54 (m, 1H, **H8ax**), 1.37 (s, 9H, **CH_3 *t*Bu**).

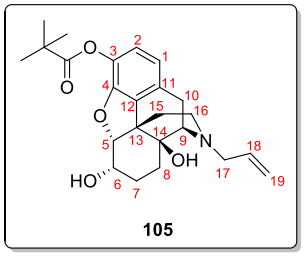
^{13}C NMR (101 MHz, $CDCl_3$) δ 207.5 (**C6**), 176.3 (**C=O Piv**), 148.0 (**C4**), 135.2 (**C18**), 133.1 (**C3**), 130.2, 130.0, 122.9 (**C2**), 119.3 (**C1**), 118.3 (**C19**), 90.5 (**C5**), 70.3 (**C14**), 62.2 (**C9**), 57.8 (**C17**), 50.6 (**C13**), 43.3 (**C16**), 39.2 (**C^{IV} *t*Bu**), 36.2 (**C7**), 31.2 (**C8**), 30.7 (**C15**), 27.3 (**CH_3 *t*Bu (3C)**), 23.1 (**C10**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{24}H_{30}NO_5$ 412.2118 found 412.2124.

m. p. 173-175 °C

IR (neat, cm^{-1}) 3398, 2972, 2932, 1754, 1728, 1443, 1111.

Alcohol 105



105

The ketone **104** (6.3 g, 15.3 mmol) was dissolved in acetic acid (51 mL). Sodium (triacetoxy)borohydride (9.0 g, 46 mmol) was added protionwise at room temperature and the reaction mixture was stirred under nitrogen atmosphere for 2 h. Acetone (3.4 mL, 46 mmol) was added and the mixture was stirred for 0.5 h. The pH of the solution was adjusted to 9-10 using an aqueous solution of potassium hydroxide, and the crude product was extracted with DCM. The combined organic extracts were washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure to afford the alcohol **105** (6.05 g, 95%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, *J* = 8.0 Hz, 1H, **H2**), 6.63 (d, *J* = 8.0 Hz, 1H, **H1**), 5.79 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.17 (m, 2H, **H19**), 4.64 (d, *J* = 5.0 Hz, 1H, **H5**), 4.20 – 4.13 (m, 1H, **H6**), 3.14 – 3.09 (m, 2H, **H17**), 3.08 (d, *J* = 18.5 Hz, 1H, **H10eq**), 2.91 (d, *J* = 6.0 Hz, 1H, **H9**), 2.64 (dd, *J* = 18.5, 6.0 Hz, 1H, **H10ax**), 2.54 (dd, *J* = 11.5, 3.5 Hz, 1H, **H15**), 2.27 – 2.12 (m, 2H, **H15**, **H16**), 1.95 – 1.85 (m, 1H, **H7**), 1.67 – 1.58 (m, 1H, **H8**), 1.53 – 1.42 (m, 3H, **H7**, **H8**, **H16**), 1.35 (s, 9H, **CH_3 *t*Bu**).

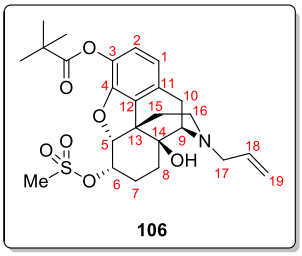
^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6 (**C=O Piv**), 148.8 (**C3**), 135.4 (**C18**), 133.2 (**C4**), 131.9 (**C12**), 130.8 (**C11**), 121.7 (**C2**), 118.9 (**C1**), 117.9 (**C19**), 91.7 (**C5**), 70.3 (**C14**), 66.7 (**C6**), 62.7 (**C9**), 57.9 (**C17**), 46.3 (**C13**), 43.4 (**C15**), 39.2 (**C^{IV} *t*Bu**), 32.1 (**C16**), 27.3 (**CH_3 *t*Bu (3C)**), 26.5 (**C8**), 24.1 (**C7**), 23.3 (**C10**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{24}H_{32}NO_5$ 414.2275 found 414.2281.

m. p. 168-170 °C

IR (neat, cm^{-1}) 3511, 3408, 2962, 2927, 1741, 1447, 1115, 925, 732.

Mesylate 106



The alcohol **105** (6.05 g, 14.7 mmol) was dissolved in pyridine (49 mL). The solution was cooled down to 0 °C. Methanesulfonyl chloride (1.7 mL, 22.1 mmol) was added dropwise and the reaction mixture was stirred for 2.5 h. The reaction mixture was poured into crashed ice and the pH was adjusted to 9-10 using potassium carbonate. The crude product was extracted with DCM. The combined organic extracts were washed with a 10% aqueous solution of copper sulfate, water and brine, dried over magnesium sulfate, and the solvent was removed under reduced pressure to afford the mesylate **106** (6.1 g, 82%) as a green foam.

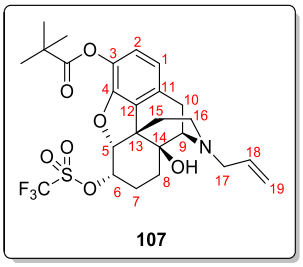
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (d, *J* = 8.0 Hz, 1H, **H2**), 6.65 (d, *J* = 8.0 Hz, 1H, **H1**), 5.78 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.23 – 5.12 (m, 3H, **H6**, **H19**), 4.77 (d, *J* = 5.0 Hz, 1H, **H5**), 3.15 – 3.06 (m, 2H, **H17**), 3.11 (d, *J* = 18.5 Hz, 1H, **H10eq**), 2.97 (s, 3H, **OMs**), 2.93 (d, *J* = 6.0 Hz, 1H, **H9**), 2.63 (dd, *J* = 18.5, 6.0 Hz, 1H, **H10ax**), 2.53 (dd, *J* = 10.5, 6.5 Hz, 1H, **H15**), 2.26 – 2.13 (m, 2H, **H15**, **H16**), 2.05 – 1.95 (m, 1H, **H7**), 1.72 – 1.48 (m, 4H, **H7**, **H8**, **H16**), 1.33 (s, 9H, **CH_3 *t*Bu**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2 (**C=O Piv**), 149.4 (**C3**), 135.2 (**C18**), 122.8 (**C2**), 119.1 (**C1**), 118.2 (**C18**), 87.3 (**C5**), 76.6 (**C6**), 69.8 (**C14**), 62.2 (**C9**), 57.9 (**C17**), 47.4 (**C13**), 43.1 (**C15**), 39.1 (**C^{IV} *t*Bu**), 38.5 (**OMs**), 32.3 (**C16**), 27.3 (**CH_3 *t*Bu (3C)**), 27.0 (**C8**), 23.2 (**C10**), 22.5 (**C7**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{25}H_{34}NO_7$ 492.205 found 492.2061.

IR (neat, cm^{-1}) 3391, 2972, 2929, 2825, 1751, 1355, 1339, 1174, 1107, 951, 856.

Triflate 107



The alcohol **105** (1.0 g, 2.42 mmol) was dissolved in anhydrous chloroform (24 mL) under nitrogen atmosphere. 4-Methylmorpholine (1.1 mL, 9.68 mmol) was added and the solution was cooled to -30 °C. Trifluoromethanesulfonic anhydride (0.8 mL, 4.84 mmol) was added dropwise and the reaction mixture was stirred from -30 °C to 0 °C for 4 h. The solution was allowed to warm to room temperature and washed with saturated aqueous sodium bicarbonate, water and brine. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel, eluting with a gradient 20% petroleum ether in DCM to 100% DCM to afford the triflate **107** (0.77 g, 59%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, *J* = 8.0 Hz, 1H, **H2**), 6.65 (d, *J* = 8.0 Hz, 1H, **H1**), 5.76 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.38 (dt, *J* = 9.0, 4.5 Hz, 1H, **H6**), 5.22 – 5.12 (m, 2H, **H19**), 4.82 (br s, 1H, **OH**), 4.73 (d, *J* = 4.5 Hz, 1H, **H5**), 3.11 (d, *J* = 18.5 Hz, 1H, **H10eq**), 3.11 – 3.05 (m, 2H, **H17**), 2.93 (d, *J* = 6.5 Hz, 1H, **H9**), 2.61 (dd, *J* = 18.5, 6.5 Hz, 1H, **H10ax**), 2.60 – 2.49 (m, 1H, **H16**), 2.26 – 2.15 (m, 2H, **H15**, **H16**), 2.04 – 1.93 (m, 1H, **H7**), 1.67 (m, 2H, **H7, H8**), 1.59 (m, 1H, **H15**), 1.50 – 1.41 (m, 1H, **H8**), 1.33 (s, 9H, **CH_3 *t*Bu**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2 (**C=O Piv**), 149.3 (**C4**), 135.3 (**C18**), 132.3 (**C3**), 130.8 (**C12**), 130.6 (**C11**), 123.0 (**C2**), 119.3 (**C1**), 118.5 (q, *J* = 319.5 Hz, **CF_3**), 118.2 (**C19**), 86.9 (**C5**), 84.2 (**C6**), 69.5 (**C14**), 61.8 (**C9**), 57.8 (**C17**), 48.2 (**C13**), 42.8 (**C16**), 39.0 (**C^{IV} tBu**), 32.7 (**C15**), 27.7 (**C8**), 27.1 (**CH_3 tBu (3C)**), 23.2 (**C10**), 21.3 (**C7**).

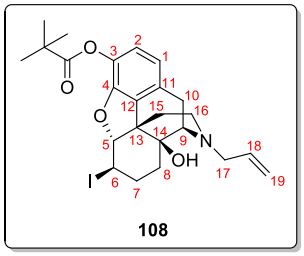
^{19}F NMR (377 MHz, $CDCl_3$) δ -75.65 (**CF_3**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{25}H_{31}F_3NO_7S$ 546.1768 found 546.1784.

m. p. 111-113 °C

IR (neat, cm^{-1}) 3396, 2974, 1754, 1410, 1205, 1109, 914, 609.

Iodide 108



108

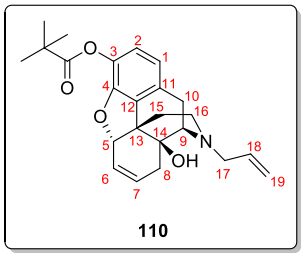
Method I: Sodium iodide (55.0 g, 370 mmol) was dissolved in anhydrous DMF (100 mL) under nitrogen atmosphere. A solution of mesylate **106** (6.06 g, 12.3 mmol) in anhydrous DMF (23 mL) was added and the reaction mixture was stirred at 100 °C for 20 h. After cooling to room temperature, the solid was dissolved in DCM and water and the organic solvent was evaporated. A saturated solution of sodium bicarbonate was added, and the crude product was extracted with diethyl ether. The combined organic extracts were washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with 100% DCM then 10% ethyl acetate in DCM to afford the 6-iodo derivative **108** (4.0 g, 63%) as a white solid.

Method II: A solution of triflate **107** (0.77 g, 1.4 mmol) in anhydrous acetonitrile (24 mL) under nitrogen atmosphere was cooled down to -10 °C. Tetraethylammonium iodide (0.73 g, 2.84 mmol) was added in one portion. The reaction mixture was stirred at -10 °C for 1 h, allowed to warm to room temperature and stirred at room temperature for 24 h. The solvent was removed under reduced pressure. The residue was dissolved in DCM (10 mL), the organic layer was washed with water and brine, dried over magnesium sulfate and the solvent was removed under reduced pressure to afford the 6-iodo derivative **108** (0.6 g, 82%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, *J* = 8.0 Hz, 1H, **H2**), 6.69 (d, *J* = 8.0 Hz, 1H, **H1**), 5.78 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.23 – 5.12 (m, 2H, **H19**), 4.93 (d, *J* = 8.0 Hz, 1H, **H5**), 3.84 (ddd, *J* = 13.0, 8.0, 5.0 Hz, 1H, **H6**), 3.13 – 3.10 (m, 2H, **H17**), 3.08 (d, *J* = 18.0 Hz, 1H, **H10eq**), 2.87 (d, *J* = 5.0 Hz, 1H, **H9**), 2.63 – 2.49 (m, 2H, **H7**, **H15ax**), 2.59 (dd, *J* = 18.0, 5.0 Hz, 1H, **H10ax**), 2.22 (td, *J* = 12.5, 4.5 Hz, 1H, **H16ax**), 2.12 (dd, *J* = 12.0, 4.5 Hz, 1H, **H15eq**), 2.08 – 2.00 (m, 1H, **H7**), 1.48 (dd, *J* = 12.5, 3.0 Hz, 1H, **H16eq**), 1.41 (dt, *J* = 13.5, 3.0 Hz, 1H, **H8eq**), 1.38 (s, 9H, **CH_3 *t*Bu**), 1.26 (ddd, *J* = 14.5, 13.5, 5.5 Hz, 1H, **H8ax**).
^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5 (**C=O**), 147.1 (**C4**), 135.3 (**C18**), 134.7 (**C3**), 131.6 (**C12**), 130.7 (**C11**), 122.6 (**C2**), 119.3 (**C1**), 118.2 (**C19**), 97.6 (**C5**), 70.0 (**C14**), 62.5 (**C9**), 57.7 (**C17**), 48.9 (**C13**), 43.8 (**C15**), 39.2 (**C^{IV} *t*Bu**), 33.6 (**C8**), 31.5 (**C7**), 30.4 (**C16**), 28.8 (**C6**), 27.3 (**CH_3 *t*Bu (3C)**), 23.1 (**C10**).
HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{24}H_{31}INO_4$ 524.1292 found 524.1304.
m.p. 123-125 °C

IR (neat, cm^{-1}) 3398, 2972, 2919, 2827, 1752, 1445, 1102, 921, 706.

Alkene 110



110

The iodide **108** (7.4 g, 14.22 mmol) was dissolved in anhydrous DMF (71 mL) under nitrogen atmosphere. DBU (38 mL, 256 mmol) was added slowly and the reaction mixture was stirred at 100 °C for 18 h. After cooling to room temperature, the reaction mixture was poured into a saturated solution of sodium bicarbonate and the crude product was extracted with diethyl ether. The combined organic extracts were washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with 20% ethyl acetate in petroleum ether to afford the phenol **109** (1.4 g, 31%) as a yellow solid, and the alkene **110** (1.7 g, 31%) as a pale-yellow oil.

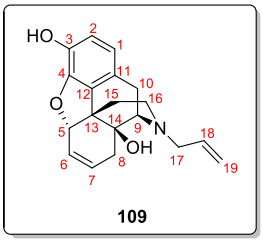
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.0 Hz, 1H, **H2**), 6.62 (d, *J* = 8.0 Hz, 1H, **H1**), 5.87 – 5.83 (m, 1H, **H7**), 5.81 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.71 (ddd, *J* = 10.5, 6.0, 1.0 Hz, 1H, **H6**), 5.24 – 5.13 (m, 2H, **H19**), 5.03 – 5.00 (m, 1H, **H5**), 3.12 (d, *J* = 19.0 Hz, 1H, **H10eq**), 3.14 – 3.10 (m, 2H, **H17**), 2.95 (d, *J* = 6.5 Hz, 1H, **H9**), 2.67 (dd, *J* = 19.0, 6.5 Hz, 1H, **H10ax**), 2.60 – 2.55 (m, 1H, **H16**), 2.25 – 2.20 (m, 2H, **H15**, **H16**), 2.04 – 1.97 (m, 2H, **H8**), 1.72 – 1.62 (m, 1H, **H15**), 1.34 (s, 9H, **CH_3 *t*Bu**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1 (**C=O Piv**), 147.9 (**C4**), 135.3 (**C18**), 133.5 (**C3**), 132.4 (**C12**), 130.8 (**C11**), 129.7 (**C7**), 124.1 (**C6**), 122.2 (**C2**), 118.3 (**C1**), 118.0 (**C19**), 87.7 (**C5**), 70.6 (**C14**), 61.8 (**C9**), 58.0 (**C17**), 45.1 (**C13**), 43.5 (**C16**), 39.1 (**C^{IV} *t*Bu**), 31.8 (**C8**), 30.9 (**C15**), 27.2 (**CH_3 *t*Bu Piv (3C)**), 23.3 (**C10**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{24}H_{30}NO_4$ 396.2169 found 396.2164.

IR (neat, cm^{-1}) 3416, 2969, 2919, 2822, 1753, 1447, 1156, 1110, 906.

Phenol 109



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (d, *J* = 8.0 Hz, 1H, **H2**), 6.56 (d, *J* = 8.0 Hz, 1H, **H1**), 5.89 – 5.85 (m, 1H, **H7**), 5.82 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.72 (ddd, *J* = 10.5, 6.5, 1.5 Hz, 1H, **H6**), 5.25 – 5.13 (m, 2H, **H19**), 5.06 – 4.99 (m, 1H, **H5**), 4.82 (br s, **OH**), 3.15 – 3.11 (m, 2H, **H17**), 3.10 (d, *J* = 18.0 Hz, 1H, **H10eq**), 2.95 (d, *J* = 5.5 Hz, 1H, **H9**), 2.64 (dd, *J* = 18.0, 5.5 Hz, 1H, **H10ax**), 2.60 – 2.56 (m, 1H, **H15**), 2.30 – 2.18 (m, 2H, **H8**, **H15**), 2.08 – 1.93 (m, 2H, **H16**), 1.69 – 1.56 (m, 1H, **H8**).

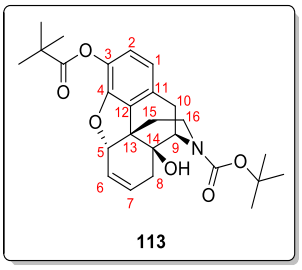
^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3 (**C4**), 139.2 (**C3**), 135.5 (**C18**), 131.5 (**C11**), 130.2 (**C7**), 125.5 (**C12**), 124.1 (**C6**), 118.8 (**C1**), 118.1 (**C19**), 116.7 (**C2**), 87.9 (**C5**), 70.9 (**C14**), 62.1 (**C9**), 58.1 (**C17**), 45.6 (**C13**), 43.7 (**C15**), 32.0 (**C16**), 31.1 (**C8**), 23.1 (**C10**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{19}H_{22}NO_3$ 312.1594 found 312.1607.

m. p. 196-198 °C

IR (neat, cm^{-1}) 3180, 2927, 1610, 1458, 1240, 905.

***N*-Boc alkene 113**



A solution *N*-allyl alkene **110** (1.5 g, 3.78 mmol) in anhydrous DCM (18 mL) was added to a solution of $Pd(PPh_3)_4$ (0.22 g, 0.19 mmol) and *N*,*N*-dimethylbarbituric acid (0.89 g, 5.67 mmol) in anhydrous DCM (20 mL) under nitrogen atmosphere. The solution was stirred at 40 °C overnight. After completion, DIPEA (0.07 mL, 0.38 mmol) and Boc_2O (1.74 mL, 7.56 mmol) were added, the temperature was increased to 60 °C and the reaction mixture was stirred for 7 h. The reaction mixture was allowed to cool to room temperature, poured into water and the crude product was extracted with DCM. The combined organic layers were washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica

gel eluting with 20% to 50% ethyl acetate in petroleum ether to afford the *N*-Boc alkene **113** (1.58 g, 92%) as a yellow oil, and as a 70:30 mixture of rotamers.

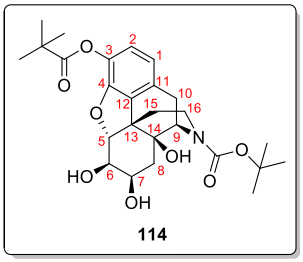
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (d, *J* = 8.0 Hz, 1H, **H2**), 6.64 (d, *J* = 8.0 Hz, 1H, **H1**), 5.82 (ddd, *J* = 10.5, 4.5, 3.0 Hz, 1H, **H7**), 5.76 – 5.70 (m, 1H, **H6**), 5.02 – 4.98 (m, 1H, **H5**), 4.51 (br, **H9 major**), 4.34 (br, **H9 minor**), 3.92 (br, 1H, **H16**), 3.18 (dd, *J* = 18.5, 6.5 Hz, 1H, **H10ax**), 2.93 (d, *J* = 18.5 Hz, 1H, **H10eq**), 2.86 (br, 1H, **H16**), 2.53 (br s, 1H, **OH**), 2.27 (br, 1H, **H15**), 2.07 – 2.02 (m, 2H, **H8**), 1.64 (br, 1H, **H15**), 1.48 (s, 9H, **CH_3 *t*Bu Boc**), 1.34 (s, 9H, **CH_3 *t*Bu Piv**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2 (**C=O Piv**), 148.0 (**C=O Boc**), 133.9 (**C3**), 131.7 (**C4**), 130.1 (**C11**), 129.3 (**C7**), 124.3 (**C6**), 122.8 (**C2**), 120.2 (**C12**), 118.7 (**C1**), 87.4 (**C5**), 80.6 (**C^{IV} *t*Bu Boc**), 71.6 (**C14**), 55.3 (**C9**), 45.2 (**C13**), 39.2 (**C^{IV} *t*Bu Piv**), 38.0 (**C16**), 32.6 (**C8**, **C10**), 29.1 (**C15**), 28.5 (**CH_3 *t*Bu Boc (3C)**), 27.3 (**CH_3 *t*Bu Piv (3C)**).

HRMS (ES) *m/z* $[M+Na]^+$ calculated for $C_{26}H_{33}NO_6Na$ 478.22 found 478.2223.

IR (neat, cm^{-1}) 3442, 2974, 1686, 1421, 1157, 1111.

Diol 114



114

N-Boc alkene **113** (0.93 g, 2.01 mmol) was dissolved in ethyl acetate (13 mL), acetonitrile (13 mL) and water (4 mL) under air and the solution was cooled down to 0 °C. $RuCl_3.H_2O$ (72 mg, 0.286 mmol) and sodium periodate (0.66 g, 3.06 mmol) were successively added and the reaction mixture was stirred from 0 °C to room temperature for 3 h. An aqueous solution of sodium thiosulfate was added, the mixture was stirred for 15 minutes. The layers were separated and the crude product was extracted with DCM. The combined organic layers were washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with 40% ethyl acetate in petroleum ether followed by 100% ethyl acetate, to afford the diol **114** (0.59 g, 59%) as a brown oil.

^{1}H NMR shows significant line broadening, likely due to the existence of rotamers.

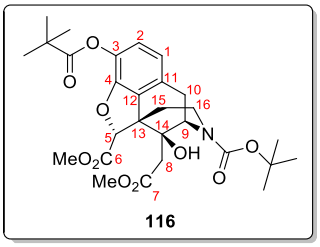
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.0 Hz, 1H, **H2**), 6.65 (d, *J* = 8.0 Hz, 1H, **H1**), 4.59 (d, *J* = 6.0 Hz, 1H, **H5**), 4.52 (br, 1H, **H9**), 3.99 (br, 1H, **H7**), 3.87 (br, 1H, **H16**), 3.44 (br, 1H, **H6**), 3.03 (dd, *J* = 18.5, 5.5 Hz, 1H, **H10ax**), 2.87 (d, *J* = 18.5 Hz, 1H, **H10eq**), 2.67 (br, 1H, **H16**), 2.38 (td, *J* = 12.5, 5.5 Hz, 1H, **H15ax**), 2.01 (dd, *J* = 14.5, 4.0 Hz, 1H, **H8**), 1.54 (dd, *J* = 14.5, 3.0 Hz, 1H, **H8**), 1.50 – 1.40 (m, 10H, **H15eq**, **CH_3 *t*Bu Boc**), 1.33 (s, 9H, **CH_3 *t*Bu Piv**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4 (**C=O Piv**), 156.0 (**C=O Boc**), 147.2 (**C4**), 134.2 (**C3**), 132.1 (**C12**), 129.7 (**C11**), 122.9 (**C2**), 119.4 (**C1**), 94.4 (**C5**), 80.2 (**C^{IV} *t*Bu Boc**), 73.4 (**C6**), 71.7 (**C14**), 69.9 (**C7**), 55.0 (**C9**), 47.6 (**C13**), 39.1 (**C^{IV} *t*Bu Piv**), 37.8 (**C16**), 34.4 (**C8**), 31.8 (**C10**), 28.5 (**CH_3 *t*Bu Boc (3C)**), 28.0 (**C15**), 27.2 (**CH_3 *t*Bu Piv (3C)**).

HRMS (ES) *m/z* $[M+Na]^+$ calculated for $C_{26}H_{35}NO_8Na$ 512.2255 found 512.226

IR (neat, cm^{-1}) 3403, 2974, 1664, 1418, 1111, 734

***N*-Boc diester 116**



116

Diol **114** (0.76 g, 1.56 mmol) was dissolved in a 1:1 mixture of DCM and water (7.8 mL) under air. TEMPO (24 mg, 0.156 mmol) and $PhI(OAc)_2$ (2.5 g, 7.83 mmol) were added and the reaction mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The residue was dissolved in anhydrous toluene (25 mL) and anhydrous methanol (6 mL, dried over 4 Å molecular sieves for 12 h) under nitrogen atmosphere. A solution of TMS-diazomethane (2 M in Et_2O, 4.7 mL, 9.33 mmol) was added and the reaction mixture was stirred at room temperature for 1.5 h. The solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with 20% diethyl ether in petroleum ether followed by 20% MeOH in DCM to afford the diester **116** (0.77 g, 90%) as a colourless oil, and as a 53:47 mixture of rotamers.

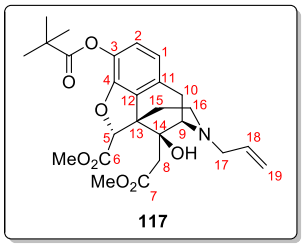
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, *J* = 8.0 Hz, 1H, **H2**), 6.71 (d, *J* = 8.0 Hz, 1H, **H1**), 4.91 (s, 1H, **H5**), 4.76 (d, *J* = 5.0 Hz, **H9 minor**), 4.61 (d, *J* = 5.0 Hz, **H9 major**), 4.03 (br, **H16a minor**), 3.86 (br, **H16a major**), 3.75 (s, 3H, **CO_2Me (C6)**), 3.71 (s, 3H, **CO_2Me (C7)**), 3.13 (dd, *J* = 18.0, 5.0 Hz, 1H, **H10ax**), 2.89 (d, *J* = 18.0 Hz, 1H, **H10eq**), 2.75 (br, **H16b major**), 2.64 (br, **H15, H16b minor**), 2.34 (br, 1H, **H8**), 2.18 (br, 1H, **H8**), 1.57 – 1.50 (m, 1H, **H15**), 1.46 (s, 9H, **CH_3 *t*Bu Boc**), 1.35 (s, 9H, **CH_3 *t*Bu Piv**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2 (**C=O Piv**), 172.1 (**C7**), 170.3 (**C6 major**), 170.2 (**C6 minor**), 155.9 (**C=O Boc minor**), 155.3 (**C=O Boc major**), 148.5 (**C4**), 132.9 (**C3**), 130.4 (**C11 minor**), 130.2 (**C11 major**), 128.3 (**C12**), 123.6 (**C2**), 119.7 (**C1**), 89.7 (**C5**), 80.23 (**C^{IV} *t*Bu Boc**), 73.7 (**C14**), 55.00 (**C9 minor**), 53.9 (**C13**), 53.8 (**C9 major**), 52.4 (**CO_2Me**), 52.3 (**CO_2Me**), 39.2 (**C^{IV} *t*Bu Piv**), 38.0 (**C8**), 37.5 (**C16 major**), 36.2 (**C16 minor**), 33.6 (**C15**), 32.2 (**C10**), 28.5 (**CH_3 *t*Bu Boc (3C)**), 27.3 (**CH_3 *t*Bu Piv (3C)**).

HRMS (ES) *m/z* $[M+Na]^+$ calculated for $C_{28}H_{37}NO_{10}Na$ 570.231 found 570.2328.

IR (neat, cm^{-1}) 3496, 2974, 1755, 1693, 1452, 1161, 1111, 749.

***N*-Allyl diester 117**



117

N-Boc diester **116** (0.77 g, 1.41 mmol) was dissolved in DCM (14 mL) under air. TFA (1.1 mL, 14.1 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated. The residue was dissolved in acetone (14 mL) under air. Et_3N (1.2 mL, 8.46 mmol) and allyl bromide (0.49 mL, 5.64 mmol) were added and the reaction mixture was heated at 50°C for 2.5 h. An aqueous solution of ammonia was added, and the solution was stirred for 10 minutes. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with 20% to 50% diethyl ether in petroleum ether to afford the *N*-allyl diester **117** (0.42 g, 61%) as a yellow oil.

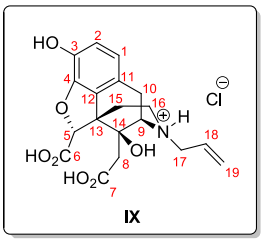
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, *J* = 8.0 Hz, 1H, **H2**), 6.69 (d, *J* = 8.0 Hz, 1H, **H1**), 5.75 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.20 – 5.12 (m, 2H, **H19**), 4.88 (s, 1H, **H5**), 4.72 (br s, 1H, **OH**), 3.79 (s, 3H, **CO_2Me (C6)**), 3.61 (s, 3H, **CO_2Me (C7)**), 3.44 (d, *J* = 6.0 Hz, 1H, **H9**), 3.10 – 3.05 (m, 2H, **H17**), 3.04 (d, *J* = 19.0 Hz, 1H, **H10eq**), 2.85 (dd, *J* = 19.0, 6.0 Hz, 1H, **H10ax**), 2.58 – 2.46 (m, 2H, **H15**, **H16**), 2.46 (d, *J* = 14.0 Hz, 1H, **H8**), 2.12 (td, *J* = 11.2, 2.5 Hz, 1H, **H16ax**), 2.03 (d, *J* = 14.0 Hz, 1H, **H8**), 1.65 (dd, *J* = 12.6, 2.5 Hz, 1H, **H15eq**), 1.33 (s, 9H, **CH_3 *t*Bu**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3 (**C=O Piv**), 170.8 (**C7**), 170.1 (**C6**), 148.4 (**C4**), 134.9 (**C18**), 132.4 (**C3**), 131.2 (**C11**), 129.1 (**C12**), 123.1 (**C2**), 119.3 (**C1**), 118.1 (**C19**), 89.5 (**C5**), 72.7 (**C14**), 61.2 (**C9**), 57.7 (**C17**), 54.4 (**C13**), 52.5 (**CO_2Me (C6)**), 51.8 (**CO_2Me (C7)**), 42.7 (**C16**), 39.1 (**C^{IV} *t*Bu**), 37.6 (**C8**), 36.0 (**C15**), 27.2 (**CH_3 *t*Bu (3C)**), 23.0 (**C10**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{26}H_{34}NO_8$ 488.2279 found 488.2287.

IR (neat, cm^{-1}) 3406, 2955, 1751, 1452, 1108.

Diacid IX



IX

Diester **117** (25.7 mg, 0.053 mmol) was dissolved in concentrated hydrochloric acid (0.53 mL) under air and heated at reflux for 45 minutes. The solvent was removed under reduced pressure to afford the diacid **IX** (22.3 mg) as a brown foam.

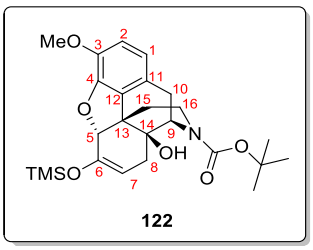
^{1}H NMR (400 MHz, D_2O) δ 6.88 (d, *J* = 8.0 Hz, 1H, **H2**), 6.79 (d, *J* = 8.0 Hz, 1H, **H1**), 5.90 (ddt, *J* = 16.5, 11.5, 7.0 Hz, 1H, **H18**), 5.67 – 5.58 (m, 2H, **H19**), 5.07 (s, 1H, **H5**), 4.22 (d, *J* = 7.0 Hz, 1H, **H9**), 3.90 – 3.84 (m, 2H, **H17**), 3.42 (d, *J* = 20.0 Hz, 1H, **H10eq**), 3.31 – 3.25 (m, 1H, **H16**), 3.15 (dd, *J* = 20.0, 7.0 Hz, 1H, **H10ax**), 2.97 – 2.79 (m, 2H, **H16**, **H15ax**), 2.75 (d, *J* = 15.5 Hz, 1H, **H8**), 2.19 (d, *J* = 15.5 Hz, 1H, **H8**), 1.92 (dd, *J* = 14.5, 2.5 Hz, 1H, **H15eq**).

^{13}C NMR (101 MHz, D_2O) δ 174.2 (**C6**), 173.4 (**C7**), 144.1 (**C4**) 138.2 (**C3**), 126.56 (**C19**), 126.4 (**C12**), 125.5 (**C18**), 122.4 (**C11**), 120.6 (**C1**), 118.7 (**C2**), 88.5 (**C5**), 72.9 (**C14**), 60.0 (**C9**), 55.9 (**C17**), 51.7 (**C13**), 45.0 (**C16**), 37.6 (**C8**), 32.8 (**C15**), 22.7 (**C10**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{19}H_{22}NO_7$ 376.1391 found 376.1398.

IR (MeOH, cm^{-1}) 3350, 2949, 2838, 2505, 1648, 1450, 1014.

TMS enol ether 122



122

N-Boc noroxycodone **71** (0.5 g, 1.246 mmol) was dissolved in anhydrous THF (6.2 mL) under nitrogen atmosphere and the solution was added dropwise to a solution of KHMDS (0.5 M in toluene, 5.5 mL, 2.74 mmol) at -78 °C. The reaction mixture was stirred for 0.5 h. Trimethylsilyl chloride (0.35 mL, 2.75

mmol) was added dropwise and the reaction mixture was stirred from -78 °C to room temperature for 16 h. The solvent was evaporated and the residue was dissolved in DCM, filtered through Celite and the solvent was removed under reduced pressure. The Crude material was purified by flash chromatography on silica gel eluting with 5% to 30% ethyl acetate in petroleum ether to afford the silyl enol ether **122** (100 mg, 17%) as a light-yellow oil, and as a 70:30 mixture of rotamers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, *J* = 8.0 Hz, 1H, **H2**), 6.60 (d, *J* = 8.0 Hz, 1H, **H1**), 4.91 (dd, *J* = 5.0, 3.0 Hz, 1H, **H7**), 4.70 (s, 1H, **H5**), 4.52 (br, **H9 major**), 4.34 (br, **H9 minor**), 3.93 (br, **H16**), 3.85 (s, 3H, **OMe**), 3.13 (dd, *J* = 18.5, 6.5 Hz, 1H, **H10ax**), 2.89 (d, *J* = 18.5 Hz, 1H, **H10eq**), 2.82 (br, **H16**), 2.30 (dt, *J* = 14.0, 3.0 Hz, 1H, **H15eq**), 2.12 – 1.99 (m, 2H, **H8**), 1.67 (td, *J* = 14.0, 3.0 Hz, 1H, **H15ax**), 1.48 (s, 9H, **CH_3 *t*Bu Boc**), 0.17 (s, 9H, **CH_3 TMS**).

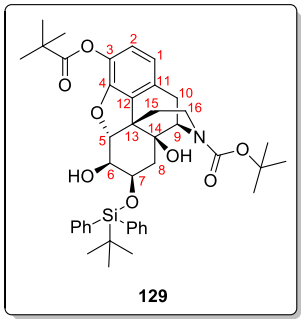
^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0 (**C4**), 143.8 (**C3**), 130.9 (**C12**), 125.4 (**C11**), 118.9 (**C1**), 114.5 (**C2**), 105.8 (**C7**), 88.9 (**C5**), 80.5 (**C^{IV} *t*Bu Boc**), 71.5 (**C14**), 56.7 (**OMe**), 55.8 (**C9 minor**), 55.3 (**C9 major**), 46.9 (**C13**), 37.7 (**C16**), 32.4 (**C10**), 31.5 (**C8**), 29.4 (**C15**), 28.6 (**CH_3 *t*Bu Boc (3C)**), 0.4 (**CH_3 TMS (3C)**).

The quaternary carbons C6 and Boc carbonyl were not detected.

HRMS (ES) *m/z* $[M+Na]^+$ calculated for $C_{25}H_{35}NO_6SiNa$ 496.2126 found 496.2148.

IR (neat, cm^{-1}) 3443, 2929, 1684, 1420, 1275, 1163.

7-Silyloxy alcohol 129



129

The diol **114** (1.09 g, 2.22 mmol) and imidazole (0.3 g, 4.45 mmol) were dissolved in anhydrous DCM (11 mL) under nitrogen atmosphere. *tert*-Butyldiphenylsilyl chloride (1.2 mL, 4.45 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was poured into water and the crude product was extracted three times with DCM. The combined organic extracts were washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with 20% ethyl acetate in petroleum ether then 100% ethyl acetate, to afford the 7-silyloxy alcohol **129** (0.25 g, 15%) as a white foam, and the 6-silyloxy alcohol **130** (1.1 g, 69%) as a white foam. Compound **129** and **130** were isolated as a 55:45 and 70:30 mixture of rotamers, respectively.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.51 (m, 4H, **Ph TBDPS**), 7.45 – 7.38 (m, 2H, **Ph TBDPS**), 7.38 – 7.30 (m, 4H, **Ph TBDPS**), 6.74 (d, *J* = 8.0 Hz, 1H, **H2**), 6.55 (d, *J* = 8.0 Hz, 1H, **H1**), 4.68 (d, *J* = 5.0 Hz, 1H, **H5**), 4.48 – 4.41 (br, **H9 minor**), 4.36 – 4.27 (br, **H9 major**), 3.99 (br, **H16b minor**), 3.85 (br, **H7 minor**, **H16b major**), 3.74 (br, **H7 major**), 3.57 (br, 1H, **H6**), 2.79 (br, 2H, **H10**), 2.70 (br, **H16a minor**), 2.60 (br, **H16a major**), 2.47 (td, *J* = 12.5, 5.0 Hz, 1H, **H15ax**), 1.81 (br, 1H, **H8**), 1.47 (s, 9H, **CH_3 *t*Bu Boc**), 1.55 – 1.42 (m, 1H, **H8**), 1.32 (s, 9H, **CH_3 *t*Bu Piv**), 1.31 – 1.24 (m, 1H, **H15**), 1.06 (s, 9H, **CH_3 *t*Bu TBDPS**).

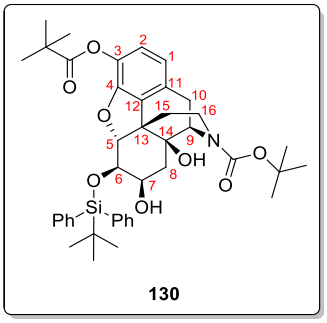
^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1 (**C=O Piv**), 155.9 (**C=O Boc**), 147.9 (**C4**), 136.0 (**CH Ph TBDPS (4C)**), 133.0 (**C3**), 130.1 (**CH Ph TBDPS**), 130.0 (**CH Ph TBDPS**), 127.9 (**CH Ph TBDPS (2C)**), 127.8 (**CH Ph TBDPS (2C)**), 122.9 (**C2**), 119.5 (**C1**), 93.2 (**C5**), 79.9 (**C^{IV} *t*Bu Boc**), 73.3 (**C6**), 71.4 (**C14**), 70.2 (**C7**), 56.3 (**C9 major**), 54.8 (**C9 minor**), 46.9 (**C13**), 39.1 (**C^{IV} *t*Bu Piv**), 37.8 (**C16 major**), 36.8 (**C16 minor**), 36.4 (**C8**), 32.0 (**C10**), 29.5 (**C15**), 28.6 (**CH_3 *t*Bu Boc**), 27.3 (**CH_3 *t*Bu Piv**), 27.2 (**CH_3 *t*Bu TBDPS**), 19.4 (**C^{IV} *t*Bu TBDPS**).

The quaternary carbons C11, C13 and two C^{IV} Ph TBDPS were not detected.

HRMS (ES) *m/z* $[M+Na]^+$ calculated for $C_{42}H_{53}NO_8SiNa$ 750.3433 found 750.3441.

IR (neat, cm^{-1}) 3384, 2962, 1689, 1426, 1110, 701.

6-Silyloxy alcohol 130



130

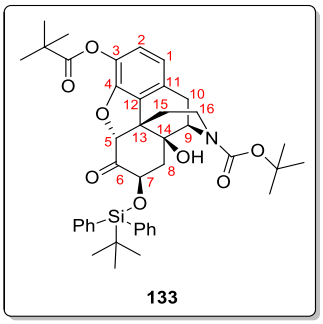
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.61 (m, 4H, **Ph TBDPS**), 7.42 – 7.32 (m, 6H, **Ph TBDPS**), 6.80 (d, *J* = 8.0 Hz, 1H, **H2**), 6.58 (d, *J* = 8.0 Hz, 1H, **H1**), 4.85 (d, *J* = 6.0 Hz, 1H, **H5**), 4.58 (br s, **OH**), 4.50 (br, **H9 major**), 4.30 (br, **H9 minor**), 3.96 (br, **H16a minor**), 3.85 (br, **H16a major**), 3.71 (br, 1H, **H7**), 3.44 (br, 1H, **H6**), 2.90 (dd, *J* = 18.5, 4.0 Hz, 1H, **H10ax**), 2.82 (d, *J* = 18.5 Hz, 1H, **H10eq**), 2.62 (br, **H16b major**), 2.54 – 2.42 (br, **H15**, **H16b minor**), 1.96 (br, 1H, **H8**), 1.46 (br s, 10H, **H15**, **CH_3 *t*Bu Boc**), 1.32 – 1.18 (m, 1H, **H8**), 1.23 (s, 9H, **CH_3 *t*Bu Piv**), 1.11 (s, 9H, **CH_3 *t*Bu TBDPS**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2 (**C=O Piv**), 155.9 (**C=O Boc**), 146.7 (**C4**), 135.8 (**CH Ph TBDPS (2C)**), 135.7 (**CH Ph TBDPS (2C)**), 133.8 (**C3**), 133.0 (**C11**), 132.9 (**C^{IV} Ph TBDPS**), 132.1 (**C12**), 130.1 (**CH Ph TBDPS**), 129.9 (**CH Ph TBDPS**), 129.5 (**C^{IV} Ph TBDPS**), 127.9 (**CH Ph TBDPS (2C)**), 127.7 (**CH Ph TBDPS (2C)**), 123.0 (**C2**), 119.2 (**C1**), 94.2 (**C5**), 79.8 (**C^{IV} *t*Bu Boc**), 75.9 (**C6**), 71.1 (**C7**), 70.8 (**C14**), 56.5 (**C9 minor**), 55.1 (**C9 major**), 48.3 (**C13**), 39.0 (**C^{IV} *t*Bu Piv**), 37.8 (**C16 major**), 36.8 (**C16 minor**), 33.5 (**C8**), 31.7 (**C10**), 28.6 (**CH_3 *t*Bu Boc (3C)**), 28.1 (**C15**), 27.2 (**CH_3 *t*Bu Piv (3C)**), 27.1 (**CH_3 *t*Bu TBDPS (3C)**), 19.4 (**C^{IV} *t*Bu TBDPS**).

HRMS (ES) *m/z* $[M+Na]^+$ calculated for $C_{42}H_{53}NO_8SiNa$ 750.3433 found 750.3444.

IR (neat, cm^{-1}) 3413, 2972, 1684, 1426, 1106, 702.

7-Silyloxy ketone 133



133

7-Silyloxy alcohol **129** (0.24 g, 0.329 mmol) was dissolved in DCM (3.3 mL) under air. DMP (0.28 g, 0.66 mmol) was added in one portion and the mixture was stirred at room temperature for 16 h. An aqueous solution of sodium thiosulfate was added, and the solution was stirred for 15 minutes. The crude product was extracted with DCM. The combined organic layers were washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with 30% ethyl acetate in petroleum ether to afford the 7-silyloxy ketone **133** (0.19 g, 79%) as a white foam, and as a 60:40 mixture of rotamers.

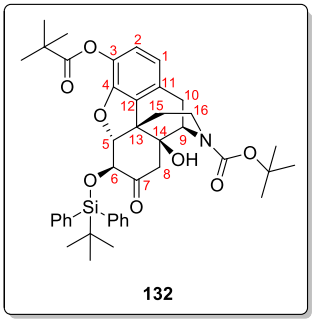
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.52 (m, 4H, **CH Ph TBDPS**), 7.48 – 7.33 (m, 6H, **CH Ph TBDPS**), 6.78 (d, *J* = 8.0 Hz, 1H, **H2**), 6.60 (d, *J* = 8.0 Hz, 1H, **H1**), 5.12 (s, 1H, **H5**), 4.56 (br, **H9 major**), 4.36 (br, **H9 minor**), 4.15 (br, 1H, **H7**), 4.05 (br, **H16a minor**), 3.92 (br, **H16a major**), 2.89 – 2.85 (m, 2H, **H10**), 2.75 (br, **H15**, **H16b major**), 2.63 (br, **H16b minor**), 2.17 (br, 1H, **H8**), 1.65 (br, 1H, **H8**), 1.61 (br, 1H, **H15**), 1.50 (br, 9H, **CH_3 *t*Bu Boc**), 1.35 (s, 9H, **CH_3 *t*Bu Piv**), 1.09 (s, 9H, **CH_3 *t*Bu TBDPS**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.9 (**C6**), 176.1 (**C=O Piv**), 156.0 (**C=O Boc**), 148.0 (**C4**), 135.9 (**CH Ph TBDPS (2C)**), 135.7 (**CH Ph TBDPS (2C)**), 133.5 (**C3**), 131.6 (**C^{IV} Ph TBDPS**), 131.2 (**C^{IV} Ph TBDPS**), 130.7 (**CH Ph TBDPS**), 130.6 (**CH Ph TBDPS**), 129.7 (**C11**), 129.3 (**C12**), 128.1 (**CH Ph TBDPS (2C)**), 128.1 (**CH Ph TBDPS (2C)**), 123.4 (**C2**), 120.1 (**C1**), 90.1 (**C5**), 80.2 (**C^{IV} *t*Bu Boc**), 75.7 (**C7**), 70.8 (**C14**), 56.6 (**C9 minor**), 55.1 (**C9 major**), 52.6 (**C13**), 38.8 (**C^{IV} *t*Bu Piv**), 38.2 (**C8**), 37.8 (**C16 major**), 36.8 (**C16 minor**), 31.9 (**C10**), 29.0 (**C15**), 28.6 (**CH_3 *t*Bu Boc (3C)**), 27.3 (**CH_3 *t*Bu Piv (3C)**), 27.0 (**CH_3 *t*Bu TBDPS (3C)**), 19.2 (**C^{IV} *t*Bu TBDPS**).

HRMS (ES) *m/z* $[M+Na]^+$ calculated for $C_{42}H_{51}NO_8SiNa$ 748.3276 found 748.3260.

IR (neat, cm^{-1}) 3475, 2971, 1746, 1666, 1427, 1112.

6-Silyloxy ketone 132



132

6-Silyloxy alcohol **130** (0.18 g, 0.246 mmol) was dissolved in DCM (2.5 mL) under air. DMP (0.3 g, 0.74 mmol) was added in one portion and the mixture was stirred at room temperature for 72 h. An aqueous solution of sodium thiosulfate was added, and the solution was stirred for 15 minutes. The crude product was extracted with DCM. The combined organic layers were washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with 10% ethyl acetate in DCM to afford the 6-silyloxy ketone **132** (93 mg, 52%) as a white solid.

^{1}H NMR shows significant line broadening, likely due to the existence of rotamers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.73 (m, 2H, **CH Ph TBDPS**), 7.66 – 7.61 (m, 2H, **CH Ph TBDPS**), 7.40 – 7.28 (m, 6H, **CH Ph TBDPS**), 6.84 (d, *J* = 8.0 Hz, 1H, **H2**), 6.67 (d, *J* = 8.0 Hz, 1H, **H1**), 4.94 (d, *J* = 5.0 Hz, 1H, **H5**), 4.46 (br, 1H, **H9**), 4.03 (d, *J* = 5.0 Hz, 1H, **H6**), 3.89 (br, 1H, **H16**), 3.00 (dd, *J* = 18.5, 5.5 Hz, 1H, **H10ax**), 2.91 (d, *J* = 18.5 Hz, 1H, **H10eq**), 2.71 (br, 1H, **H16**), 2.31 (br, 1H, **H15**), 2.29 (d, *J* = 13.5 Hz, 1H, **H8**), 2.24 (d, *J* = 13.5 Hz, 1H, **H8**), 1.59 (br, 1H, **H15**), 1.46 (s, 9H, **CH_3 *t*Bu Boc**), 1.25 (s, 9H, **CH_3 *t*Bu Piv**), 1.11 (s, 9H, **CH_3 *t*Bu TBDPS**).

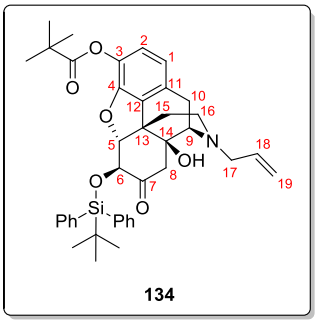
^{13}C NMR (101 MHz, $CDCl_3$) δ 201.3 (**C7**), 176.1 (**C=O Piv**), 152.1 (**C=O Boc**), 147.1 (**C4**), 136.2 (**CH Ph TBDPS (2C)**), 136.0 (**CH Ph TBDPS (2C)**), 134.1 (**C3**), 133.0 (**C^{IV} Ph TBDPS**), 132.8 (**C^{IV} Ph TBDPS**), 131.4 (**C12**), 129.7 (**CH Ph TBDPS (2C)**), 129.3 (**C11**), 127.6 (**CH Ph TBDPS (2C)**), 127.5 (**CH Ph TBDPS (2C)**), 123.7 (**C2**), 119.7 (**C1**), 99.4 (**C5**), 80.9 (**C^{IV} *t*Bu Boc**), 80.6 (**C6**), 74.2 (**C14**), 55.5 (**C9**), 47.8 (**C13**), 45.4 (**C8**), 39.0 (**C^{IV} *t*Bu Piv**), 37.7 (**C16**), 31.9 (**C10**), 29.1 (**C15**), 28.5 (**CH_3 *t*Bu Boc (3C)**), 27.2 (**CH_3 *t*Bu Piv (3C)**), 27.1 (**CH_3 *t*Bu TBDPS (3C)**), 19.9 (**C^{IV} *t*Bu TBDPS**).

HRMS (ES) *m/z* $[M+Na]^+$ calculated for $C_{42}H_{51}NO_8SiNa$ 748.3276 found 748.3284.

m. p. 144-146 °C

IR (neat, cm^{-1}) 3416, 2973, 2860, 1681, 1108.

***N*-Allyl 6-silyloxy ketone 134**



134

6-Silyloxy ketone **132** (0.38 g, 0.52 mmol) was dissolved in DCM (5.3 mL) under air. TFA (5.3 mL) was added and the solution was stirred at room temperature for 1.5 h. The solvent was evaporated. The residue was dissolved in acetone (5.3 mL) under air. Triethylamine (0.22 mL, 1.58 mmol) and allyl bromide (0.09 mL, 1.05 mmol) were added and the reaction mixture was stirred at 50 °C overnight. After cooling to room temperature, water was added, and the crude product was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with 10% ethyl acetate in DCM to afford the *N*-allyl 6-silyloxy ketone **134** (0.19 g, 55%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 7.5, 1.5 Hz, 2H, **CH Ph TBDPS**), 7.64 (dd, *J* = 7.5, 1.5 Hz, 2H, **CH Ph TBDPS**), 7.37 – 7.28 (m, 6H, **CH Ph TBDPS**), 6.81 (d, *J* = 8.0 Hz, 1H, **H2**), 6.66 (d, *J* = 8.0 Hz, 1H, **H1**), 5.76 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.22 – 5.14 (m, 2H, **H19**), 4.96 (d, *J* = 5.5 Hz, 1H, **H5**), 4.02 (d, *J* = 5.5 Hz, 1H, **H6**), 3.17 – 3.05 (m, 2H, **H17**), 3.10 (d, *J* = 18.5 Hz, 1H, **H10eq**), 2.92 (d, *J* = 5.5 Hz, 1H, **H9**), 2.55 (dd, *J* = 18.5, 5.5 Hz, 1H, **H10ax**), 2.58 – 2.51 (m, 1H, **H16eq**), 2.25 (d, *J* = 12.5 Hz, 1H, **H8**), 2.25 (td, *J* = 12.5, 5.0 Hz, 1H, **H15ax**), 2.16 (d, *J* = 12.5 Hz, 1H, **H8**), 2.10 (td, *J* = 12.5, 3.5 Hz, 1H, **H16ax**), 1.63 (dd, *J* = 12.5, 2.5 Hz, 1H, **H15eq**), 1.24 (s, 9H, **CH_3 *t*Bu Piv**), 1.11 (s, 9H, **CH_3 *t*Bu TBDPS**).

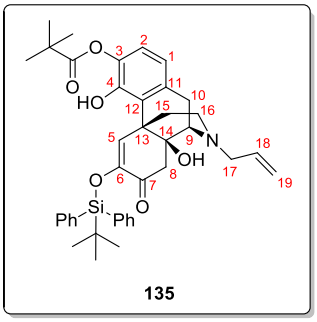
^{13}C NMR (101 MHz, $CDCl_3$) δ 201.7 (**C7**), 176.2 (**C=O Piv**), 147.0 (**C4**), 136.4 (**CH Ph TBDPS (2C)**), 136.1 (**CH Ph TBDPS (2C)**), 134.9 (**C18**), 134.0 (**C3**), 133.3 (**C^{IV} Ph TBDPS**), 133.0 (**C^{IV} Ph TBDPS**), 132.4 (**C12**), 129.9 (**C11**), 129.7 (**CH Ph TBDPS (2C)**), 127.6 (**CH Ph TBDPS (2C)**), 127.4 (**CH Ph TBDPS (2C)**), 123.3 (**C2**), 119.2 (**C1**), 118.4 (**C19**), 99.9 (**C5**), 80.9 (**C6**), 73.7 (**C14**), 61.9 (**C9**), 57.7 (**C17**), 48.1 (**C13**), 44.8 (**C8**), 43.2 (**C16**), 39.1 (**C^{IV} *t*Bu Piv**), 30.9 (**C15**), 27.2 (**CH_3 *t*Bu Piv (3C)**), 27.2 (**CH_3 *t*Bu TBDPS (3C)**), 23.1 (**C10**), 20.0 (**C^{IV} *t*Bu TBDPS**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{40}H_{48}NO_6SiNa$ 666.3245 found 666.3262.

m. p. 138-140 °C

IR (neat, cm^{-1}) 3396, 2930, 1742, 1105, 701, 509

Silyl enol ether 135



135

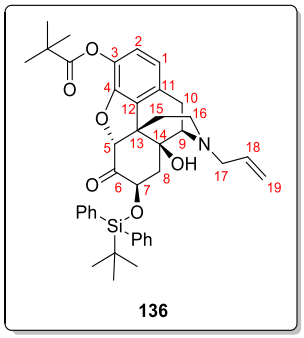
6-Silyloxy ketone **132** (0.2 g, 0.283 mmol) was dissolved in DCM (2.8 mL) and TFA (2.8 mL) under air at room temperature. The solution was stirred for 2 h and the solvent was removed under reduced pressure. The residue was dissolved in acetone (2.8 mL) under air. Et_3N (0.12 mL, 0.85 mmol) and allyl bromide (0.05 mL, 0.56 mmol) were added and the reaction mixture was stirred at 50 °C overnight. The reaction mixture was allowed to cool to room temperature. An aqueous solution of ammonia was added and the mixture was stirred for 1 h. The crude product was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with 10% ethyl acetate in DCM to afford the silyl enol ether **135** (107 mg, 56%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.70 (m, 4H, **CH Ph TBDPS**), 7.42 – 7.27 (m, 6H, **CH Ph TBDPS**), 6.89 (d, *J* = 8.5 Hz, 1H, **H2**), 6.66 (d, *J* = 8.5 Hz, 1H, **H1**), 6.40 (s, 1H, **H5**), 5.76 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.19 – 5.10 (m, 2H, **H19**), 3.09 – 3.03 (m, 2H, **H17**), 3.04 (d, *J* = 17.5 Hz, 1H, **H10eq**), 2.79 (dd, *J* = 17.5, 6.0 Hz, 1H, **H10ax**), 2.77 (d, *J* = 6.0 Hz, 1H, **H9**), 2.53 (d, *J* = 16.0 Hz, 1H, **H8**), 2.47 (dd, *J* = 12.0, 4.0 Hz, 1H, **H16ax**), 2.34 (d, *J* = 16.0 Hz, 1H, **H8**), 2.00 (dt, *J* = 12.0, 2.5 Hz, 1H, **H16eq**), 1.93 (td, *J* = 12.5, 4.5

Hz, 1H, **H15ax**), 1.44 (dd, *J* = 12.5, 2.5 Hz, 1H, **H15eq**), 1.37 (s, 9H, **CH_3 *t*Bu Piv**), 1.09 (s, 9H, **CH_3 *t*Bu TBDPS**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.3 (**C7**), 176.6 (**C=O Piv**), 144.9 (**C4**), 137.5 (**C3**), 135.8 (**CH Ph TBDPS (2C)**), 135.8 (**CH Ph TBDPS (2C)**), 135.4 (**C18**), 133.8 (**C^{IV} Ph TBDPS**), 133.6 (**C11**), 133.2 (**C^{IV} Ph TBDPS**), 132.1 (**C5**), 129.7 (**CH Ph TBDPS**), 129.6 (**CH Ph TBDPS**), 128.7 (**C12**), 127.5 (**CH Ph TBDPS**), 127.4 (**CH Ph TBDPS**), 120.3 (**C2**), 119.4 (**C1**), 118.0 (**C19**), 72.9 (**C14**), 59.2 (**C9**), 57.6 (**C17**), 45.4 (**C8**), 44.2 (**C16**), 43.1 (**C13**), 39.5 (**C^{IV} *t*Bu Piv**), 31.1 (**C15**), 27.3 (**CH_3 *t*Bu Piv (3C)**), 26.6 (**CH_3 *t*Bu TBDPS (3C)**), 25.6 (**C10**), 19.7 (**C^{IV} *t*Bu TBDPS**).

_N_-Allyl 7-silyloxy ketone 136



136

7-Silyloxy ketone **133** (0.19 g, 0.26 mmol) was dissolved in DCM (2.6 mL) and TFA (0.2 mL, 2.6 mmol) under air at room temperature. The solution was stirred overnight, and the solvent was removed under reduced pressure. The residue was dissolved in acetone (2.6 mL) under air. Et_3N (0.1 mL, 0.78 mmol) and allyl bromide (0.045 mL, 0.52 mmol) were added and the reaction mixture was stirred at 50 °C for 3.5 h. The reaction mixture was allowed to cool to room temperature. An aqueous solution of ammonia was added and the mixture was stirred for 1 h. The crude product was extracted with DCM. The combined organic layers were washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with 10% ethyl acetate in DCM to afford the *N*-allyl 7-silyloxy ketone **136** (65 mg, 38%) as a white foam.

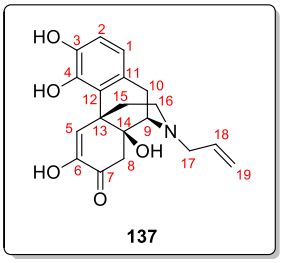
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 2H, **CH Ph TBDPS**), 7.48 – 7.44 (m, 2H, **CH Ph TBDPS**), 7.41 – 7.26 (m, 6H, **CH Ph TBDPS**), 6.74 (d, *J* = 8.0 Hz, 1H, **H2**), 6.53 (d, *J* = 8.0 Hz, 1H, **H1**), 5.76 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.21 – 5.12 (m, 2H, **H19**), 4.67 (s, 1H, **H5**), 3.97 (dd, *J* = 9.5, 7.5 Hz, 1H, **H7**), 3.12 – 2.99 (m, 2H, **H17**), 3.00 (d, *J* = 20.0 Hz, 1H, **H10eq**), 2.84 (d, *J* = 6.0 Hz, 1H, **H9**), 2.52 (dd, *J* = 12.0, 4.5 Hz, 1H, **H16eq**), 2.29 (dd, *J* = 20.0, 6.0 Hz, 1H, **H10ax**), 2.30 – 2.22 (m, 1H, **H15**), 2.11 (td, *J* = 12.0, 3.5

Hz, 1H, **H16ax**), 1.93 (dd, *J* = 14.5, 7.5 Hz, 1H, **H8**), 1.67 (dd, *J* = 14.5, 9.5 Hz, 1H, **H8**), 1.64 – 1.60 (m, 1H, **H15**), 1.29 (s, 9H, **CH_3 *t*Bu Piv**), 1.03 (s, 9H, **CH_3 *t*Bu TBDPS**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.0 (**C6**), 176.0 (**C=O Piv**), 148.1 (**C4**), 135.7 (**CH Ph TBDPS (2C)**), 135.7 (**CH Ph TBDPS (2C)**), 134.9 (**C18**), 132.7 (**C12**), 129.8 (**CH Ph TBDPS**), 129.8 (**CH Ph TBDPS**), 127.8 (**CH Ph TBDPS (2C)**, 127.7 (**CH Ph TBDPS (2C)**), 123.4 (**C2**), 119.9 (**C1**), 118.5 (**C19**), 91.6 (**C5**), 70.6 (**C7**), 69.9 (**C14**), 61.4 (**C9**), 57.9 (**C17**), 50.8 (**C13**), 43.2 (**C16**), 42.9 (**C8**), 39.1 (**C^{IV} *t*Bu Piv**), 31.9 (**C15**), 27.2 (**CH_3 *t*Bu Piv (3C)**), 26.9 (**CH_3 *t*Bu TBDPS (3C)**), 23.2 (**C10**), 19.4 (**C^{IV} *t*Bu TBDPS**).

The quaternary carbons C3, C11 and two C^{IV} Ph TBDPS were not detected.

Enol 137



137

N-Allyl 6-silyloxy ketone **134** (29 mg, 0.044 mmol) was dissolved in anhydrous THF (0.15 mL) under nitrogen atmosphere and the solution was cooled down to 0 °C. A solution of TBAF (1 M in THF, 0.66 mL, 0.065 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. Water was added, and the crude product was extracted with Et_2O. The combined organic layers were washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with 20% ethyl acetate in petroleum ether, followed by 100% ethyl acetate to afford the enol **137** (0.5 mg, 3%).

^{1}H NMR (400 MHz, MeOD) δ 6.68 (d, *J* = 8.0 Hz, 1H, **H2**), 6.52 (d, *J* = 8.0 Hz, 1H, **H1**), 6.31 (s, 1H, **H5**), 5.87 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, **H18**), 5.26 (ddd, *J* = 17.0, 3.0, 1.5 Hz, 1H, **H19*trans***), 5.20 (ddt, *J* = 10.0, 2.0, 1.0 Hz, 1H, **H19*cis***)[a], 3.84 (d, *J* = 5.0 Hz, 1H, **H9**), 3.27 – 3.18 (m, 3H, **H10eq**, **H17**), 2.98 (dd, *J* = 16.5, 5.0 Hz, 1H, **H10ax**), 2.71 (dd, *J* = 12.0, 3.4 Hz, 1H), 2.47 (dd, *J* = 12.0, 3.0 Hz, 1H), 2.43 – 2.36 (m, 1H), 1.66 (ddd, *J* = 12.5, 6.0, 3.0 Hz, 1H), 1.36 – 1.27 (m, 2H).

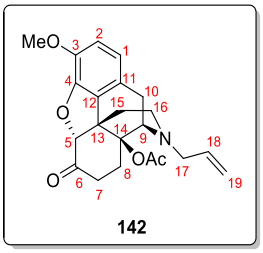
[a] The coupling constant of 2.0 Hz corresponds to the coupling to H19*trans* (^{3}J = 1.5 Hz) however the accuracy of the coupling is limited by the resolution of the spectrometer.

^{13}C NMR experiment was not recorded due to the low amount of product isolated.

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{19}H_{21}NO_5$ 344.1492 found 344.1506.

IR (neat, cm^{-1}) 3358, 2923, 1640, 1286, 1209.

14-Acetoxy naloxone methyl ether 142



Naloxone methyl ether **61** (250 mg, 0.73 mmol) was dissolved in dry pyridine (5 mL) under a nitrogen atmosphere. Acetic anhydride (10 mL, 105 mmol) was added and the solution was stirred at room temperature for four days. The solvent was evaporated under vacuum and the crude material was purified by flash chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether to afford 14-acetoxy naloxone methyl ether **142** (144 mg, 46%) as a white solid, and the enol acetate **143** (102 mg, 36%) as a pale-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (d, *J* = 8.0 Hz, 1H, **H2**), 6.64 (d, *J* = 8.0 Hz, 1H, **H1**), 5.72 (ddt, *J* = 16.5, 10.0, 6.0 Hz, 1H, **H18**), 5.20 – 5.07 (m, 2H, **H19**), 4.67 (s, 1H, **H5**), 4.27 (d, *J* = 5.5 Hz, 1H, **H9**), 3.89 (s, 3H, **OMe**), 3.11 (d, *J* = 19.0 Hz, 1H, **H10eq**), 3.17 – 3.05 (m, 2H, **H17**), 2.81 (ddd, *J* = 14.5, 5.0, 3.0 Hz, 1H, **H8eq**), 2.64 (td, *J* = 14.5, 5.0 Hz, 1H, **H7ax**), 2.62 – 2.49 (m, 2H, **H15**, **H16eq**), 2.48 (dd, *J* = 19.0, 5.5 Hz, 1H, **H10ax**), 2.28 (dt, *J* = 14.5, 3.0 Hz, 1H, **H7eq**), 2.18 (s, 3H, **CH_3 OAc**), 2.12 (td, *J* = 12.0, 4.0 Hz, 1H, **H16ax**), 1.62 (td, *J* = 14.5, 3.0 Hz, 1H, **H8ax**), 1.52 (dd, *J* = 12.0, 3.0 Hz, 1H, **H15**).

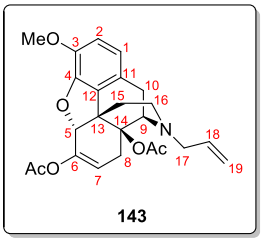
^{13}C NMR (101 MHz, $CDCl_3$) δ 207.4 (**C6**), 170.2 (**C=O OAc**), 145.1 (**C4**), 143.1 (**C3**), 136.3 (**C18**), 128.6 (**C12**), 125.8 (**C11**), 119.6 (**C1**), 116.9 (**C19**), 115.1 (**C2**), 90.1 (**C5**), 82.6 (**C14**), 58.0 (**C17**), 56.9 (**OMe**), 56.0 (**C9**), 51.1 (**C13**), 43.6 (**C16**), 35.8 (**C7**), 30.1 (**C15**), 27.2 (**H8**), 23.3 (**C10**), 22.3 (**CH_3 OAc**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{24}H_{28}NO_6$ 426.1911 found 426.1916

m. p. 126-128 °C

IR (neat, cm^{-1}) 2923, 2838, 1729, 1440, 1216, 1148, 909.

Enol acetate 143



143

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (d, *J* = 8.0 Hz, 1H, **H2**), 6.62 (d, *J* = 8.0 Hz, 1H, **H1**), 5.71 (ddt, *J* = 16.5, 10.0, 6.0 Hz, 1H, **H18**), 5.41 (dd, *J* = 6.5, 2.0 Hz, 1H, **H7**), 5.19 – 5.07 (m, 2H, **H19**), 5.03 – 5.00 (m, 1H, **H5**), 4.30 (d, *J* = 6.0 Hz, 1H, **H9**), 3.84 (s, 3H, **OMe**), 3.12 (d, *J* = 18.5 Hz, 1H, **H10eq**), 3.09 – 3.05 (m, 2H, **H17**), 3.05 (dd, *J* = 15.5, 6.5, 1H, **H8**) 2.60 – 2.54 (m, 1H, **H16**), 2.55 (dd, *J* = 18.5, 6.0 Hz, 1H, **H10ax**), 2.40 (td, *J* = 12.5, 5.0 Hz, 1H, **H15ax**), 2.21 – 2.18 (m, 1H, **H16**), 2.17 (s, 3H, **CH_3 OAc**), 2.09 (s, 3H, **CH_3 OAc**), 2.08 – 2.06 (m, 1H, **H8**), 1.56 (dd, *J* = 12.5, 2.1 Hz, 1H, **H15eq**).

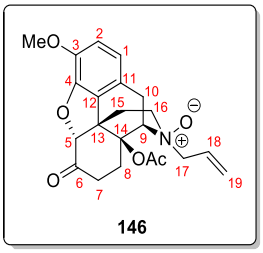
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9 (**C=O OAc**), 169.4 (**C=O OAc**), 144.1 (**C4**), 143.6 (**C3**), 136.2 (**C18**), 130.0 (**C12**), 126.3 (**C11**), 118.9 (**C1**), 116.9 (**C19**), 116.7 (**C7**), 114.4 (**C2**), 86.4 (**C5**), 81.6 (**C4**), 58.1 (**C17**), 56.7 (**OMe**), 55.5 (**C9**), 47.6 (**C13**), 43.4 (**C16**), 30.5 (**C15**), 27.3 (**C8**), 23.6 (**C10**), 22.4 (**CH_3 OAc**), 21.2 (**CH_3 OAc**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{22}H_{26}NO_5$ 384.1805 found 384.1808.

m. p. 155-157 °C

IR (neat, cm^{-1}) 2965, 2941, 2822, 1733, 1364, 1248, 1045.

14-Acetoxy *N*-oxide 146



146

14-Acetoxynaloxone methyl ether **142** (100 mg, 0.26 mmol) was dissolved in anhydrous chloroform (8.7 mL) under nitrogen atmosphere. The solution was cooled down to 0 °C and *m*CPBA (120 mg, 0.52 mmol) was added. The reaction mixture was stirred from 0 °C to room temperature for 2.5 h. An aqueous solution of sodium thiosulfate was added, and the mixture was stirred for 0.5 h. The layers were separated, and the product was extracted with DCM. The combined organic extracts were washed with aqueous $NaHCO_3$, water, brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica

gel eluting with 20% ethyl acetate in petroleum ether to afford the 14-acetoxy *N*-oxide **146** (17 mg, 16%) as a white solid, and the 14-acetoxy lactone **147** (22 mg, 20%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, *J* = 8.0 Hz, 1H, **H2**), 6.66 (d, *J* = 8.0 Hz, 1H, **H1**), 5.92 (ddt, *J* = 16.5, 10.5, 6.0 Hz, 1H, **H18**), 5.27 – 5.14 (m, 2H, **H19**), 4.75 (d, *J* = 5.5 Hz, 1H, **H9**), 4.65 (s, 1H, **H5**), 4.16 – 4.05 (m, 2H, **H17**), 3.89 (s, 3H, **OMe**), 3.53 (d, *J* = 17.5 Hz, 1H, **H10eq**), 3.05 – 2.95 (m, 1H, **H16**), 2.87 (ddd, *J* = 14.5, 5.0, 3.0 Hz, 1H, **H8eq**), 2.61 (td, *J* = 14.5, 5.0 Hz, 1H, **H7ax**), 2.59 – 2.53 (m, 3H, **H10**, **H15**, **H16**), 2.27 (dt, *J* = 14.5, 3.0 Hz, 1H, **H7eq**), 2.17 (s, 3H, **CH_3 OAc**), 1.65 (td, *J* = 14.5, 3.0 Hz, 1H, **H8ax**), 1.64 – 1.59 (br, 1H, **H15**).

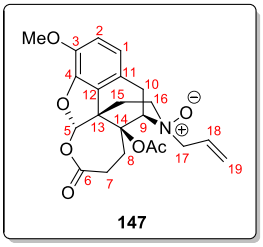
^{13}C NMR (101 MHz, $CDCl_3$) δ 207.1 (**C6**), 171.5 (**C=O OAc**), 144.9 (**C4**), 143.1 (**C3**), 134.9 (**C18**), 128.3 (**C12**), 119.9 (**C1**), 117.7 (**C19**), 115.3 (**C2**), 89.6 (**C5**), 73.3 (**C17**), 58.2 (**C9**), 56.9 (**OMe**), 46.6 (**C16**), 35.3 (**C7**), 30.1 (**C15**), 27.2 (**C8**), 23.9 (**C10**), 22.3 (**CH_3 OAc**).

The quaternary carbons C11, C13 and C14 were not detected.

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{22}H_{26}NO_6$ 400.1755 found 400.1771.

IR (neat, cm^{-1}) 2919, 1730, 1441, 1243, 1049.

14-Acetoxy lactone 147



147

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, *J* = 8.5 Hz, 1H, **H2**), 6.77 (d, *J* = 8.5 Hz, 1H, **H1**), 5.95 (s, 1H, **H5**), 5.90 (ddt, *J* = 17.0, 10.5, 6.0 Hz, 1H, **H18**), 5.26 – 5.13 (m, 2H, **H19**), 4.80 (d, *J* = 6.5 Hz, 1H, **H9**), 4.16 – 4.05 (m, 2H, **H17**), 3.90 (s, 3H, **OMe**), 3.58 (d, *J* = 18.5 Hz, 1H, **H10eq**), 3.04 (dd, *J* = 11.0, 4.0 Hz, 1H, **H16**), 2.75 – 2.53 (m, 4H, **H7**, **H10**, **H15**, **H16**), 2.27 (dt, *J* = 14.0, 5.5 Hz, 1H, **H8eq**), 2.16 – 2.11 (m, 1H, **H8ax**), 2.10 (s, 3H, **CH_3 OAc**), 1.68 (ddd, *J* = 15.5, 7.0, 5.5 Hz, 1H, **H7eq**), 1.54 – 1.45 (m, 1H, **H15**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (**C6**), 170.4 (**C=O OAc**), 144.6 (**C4**), 142.3 (**C3**), 134.7 (**C18**), 127.6 (**C12**), 120.9 (**C1**), 117.9 (**C19**), 115.1 (**C2**), 110.2 (**C5**), 85.8 (**C14**), 73.3 (**C17**), 59.4 (**C9**), 56.8 (**OMe**), 50.6 (**C13**), 46.3 (**C16**), 34.2 (**C15**), 31.4 (**C8**), 27.9 (**C7**), 24.9 (**C10**), 22.2 (**CH_3 OAc**).

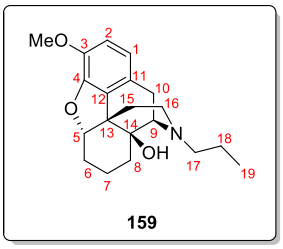
The quaternary carbon C11 was not detected.

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{22}H_{26}NO_7$ 416.1704 found 416.1707.

m. p. 152-154 °C

IR (neat, cm^{-1}) 2931, 1764, 1737, 1221, 926.

Deoxo-derivative 159

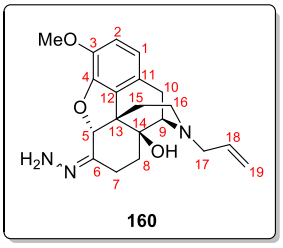


159

Naloxone methyl ether **61** (0.2 g, 0.59 mmol) was dissolved in diethylene glycol (2 mL). Hydrazine monohydrate (0.14 mL, 2.9 mmol) was added and the solution was stirred at 70 °C for 1 h. A solution of potassium hydroxide (0.23 g, 4.1 mmol) in water (0.1 mL) was added and the solution was stirred at 130 °C for 20 h. The reaction mixture was allowed to cool down to room temperature. Water was added and the mixture was extracted with diethyl ether. The organic phase was washed with brine, dried over magnesium sulfate and the solvent was evaporated. The crude mixture was purified by flash chromatography on silica gel, eluting with 2% to 4% methanol in DCM to afford the reduced compound **159** (26 mg, 19%) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, *J* = 8.0 Hz, 1H, **H2**), 6.61 (d, *J* = 8.0 Hz, 1H, **H1**), 4.71 (t, *J* = 8.0 Hz, 1H, **H5**), 3.85 (s, 3H, **OMe**), 3.08 (d, *J* = 18.5 Hz, 1H, **H10eq**), 2.81 (d, *J* = 5.5 Hz, 1H, **H9**), 2.64 (dd, *J* = 18.5, 5.5 Hz, 1H, **H10ax**), 2.54 – 2.47 (m, 1H), 2.48 – 2.38 (m, 2H, **H18**) 2.23 – 2.10 (m, 3H, **H6**), 1.84 – 1.71 (m, 1H, **H7**), 1.55 – 1.23 (m, 8H, **H6 (1H)**, **H7 (1H)**, **H8 (2H)**, **H17 (2H)**), 0.92 (t, *J* = 7.5 Hz, 3H, **H19**).
^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1 (**C3**), 118.3 (**C1**), 113.6 (**C2**), 89.2 (**C5**), 70.8 (**C14**), 63.5 (**C9**), 56.6 (**OMe**), 56.3 (**C18**), 44.3, 31.1, 30.9, 29.1 (**C6**), 23.1 (**C10**), 20.8 (**C17**), 17.4 (**C7**), 11.9 (**C19**).
The quaternary carbons C4, C11, C12 and C13 were not detected.
HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{20}H_{28}NO_3$ 330.2064 found 330.2068
IR (neat, cm^{-1}) 3391, 2933, 2832, 1609, 1505, 1438, 1283, 1052

Hydrazone 160



160

Naloxone methyl ether **61** (1.0 g, 2.93 mmol) was dissolved in ethanol (20 mL) under nitrogen atmosphere and hydrazine monohydrate (0.74 mL, 14.7 mmol) was added. Nitrogen was bubbled through the solution for 15 minutes, and the reaction mixture was heated at 70 °C for 1 h. The solution

was allowed to cool to room temperature, water was added and the crude product was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate and the solvent removed under reduced pressure to afford a 2:1 mixture of *E* and *Z* hydrazones **160** (960 mg, 92%) as a white solid. The compound showed satisfactory spectroscopic data in comparison with the literature.[41]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (d, *J* = 8.0 Hz, **H2 minor**), 6.66 (d, *J* = 8.0 Hz, **H2 major**), 6.60 (d, *J* = 8.0 Hz, **H1 minor**), 6.55 (d, *J* = 8.0 Hz, **H1 major**), 5.76 (ddt, *J* = 12.5, 10.0, 6.5 Hz, 1H, **H18**), 5.25 (s, **H5 minor**), 5.25 – 5.10 (m, 2H, **H19**), 4.89 (s, **H5 major**), 3.79 (s, 3H, **OMe**), 3.14 – 3.02 (m, 3H, **H10**, **H17**), 2.91 (d, *J* = 5.0 Hz, **H9 major**), 2.89 (d, *J* = 6.0 Hz, **H9 minor**), 2.60 – 2.46 (m, 2H, **H10**, **H16**), 2.35 (ddd, *J* = 17.5, 12.0, 7.0 Hz, 1H, **H7ax**), 2.28 – 2.11 (m, 3H, **H7eq**, **H15**, **H16**), 1.61 – 1.47 (m, 2H, **H8**, **H15**), 1.44 – 1.28 (m, 1H, **H8**).

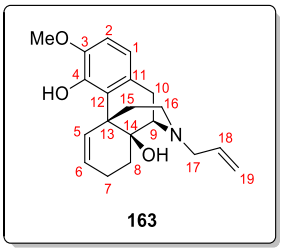
^{13}C NMR (101 MHz, $CDCl_3$) δ 147.3 (**C6**), 145.5 (**C4 minor**), 145.3 (**C4 major**), 142.8 (**C3 minor**), 142.4 (**C3 major**), 135.3 (**C18 major**), 135.2 (**C18 minor**), 131.2 (**C12 major**), 130.8 (**C12 minor**), 125.5 (**C11 major**), 125.4 (**C11 minor**), 119.2 (**C1 minor**), 118.4 (**C1 major**), 117.8 (**C19**), 114.1 (**C2 major**), 113.7 (**C2 minor**), 89.8 (**C5 major**), 87.1 (**C5 minor**), 70.1 (**C14 minor**), 70.0 (**C14 major**), 62.6 (**C9 minor**), 62.2 (**C9 major**), 57.7 (**C17 major**), 57.6 (**C17 minor**), 56.5 (**OMe major**), 56.4 (**OMe minor**), 47.9 (**C13 minor**), 47.1 (**C13 major**), 43.4 (**C16 minor**), 43.3 (**C16 major**), 32.2 (**C15 major**), 31.0 (**C15 minor**), 29.2 (**C8 minor**), 27.5 (**C8 major**), 22.9 (**C10 major**), 22.6 (**C10 minor**), 18.5 (**C7**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{20}H_{26}N_3O_3$ 356.1969 found 356.1973.

m. p. 155-157 °C

IR (neat, cm^{-1}) 3400, 2924, 2833, 1636, 1604, 1504, 1279, 1050, 905.

5,6-Alkene 163



163

Hydrazone **160** (0.83 g, 16.4 mmol) was dissolved in toluene (10 mL) under nitrogen atmosphere, and a solution of potassium hydroxide (0.92 g, 16.4 mmol) in water (0.6 mL) was added. Nitrogen was bubbled through the solution for 15 minutes, and the resulting mixture was stirred at 115 °C for 20 h. The reaction mixture was allowed to cool to room temperature, poured into water and extracted with

ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and the solvent removed under reduced pressure to afford the alkene **163** (0.71 g, 93%) as a light-yellow foam.

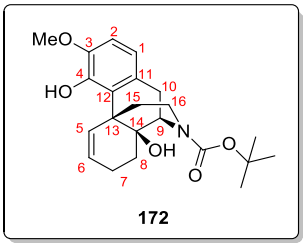
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (d, *J* = 8.5 Hz, 1H, **H2**), 6.57 (d, *J* = 8.5 Hz, 1H, **H1**), 6.37 (dt, *J* = 10.0, 2.0 Hz, 1H, **H5**), 5.80 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, **H18**), 5.73 (dt, *J* = 10.0, 3.0 Hz, 1H, **H6**), 5.20 – 5.08 (m, 2H, **H19**), 3.81 (s, 3H, **OMe**), 3.16 – 3.06 (m, 2H, **H17**), 3.00 (d, *J* = 16.5 Hz, 1H, **H10eq**), 2.87 – 2.79 (m, 2H, **H9**, **H10ax**), 2.55 – 2.50 (m, 1H, **H16**), 2.39 (dtd, *J* = 18.0, 7.0, 3.0 Hz, 1H, **H7eq**), 2.13 – 2.04 (m, 2H, **H15ax**, **H16**), 2.04 – 1.94 (m, 1H, **H7ax**), 1.79 (ddd, *J* = 13.0, 11.0, 7.0 Hz, 1H, **H8ax**), 1.65 (dd, *J* = 7.5, 3.5 Hz, 1H, **H15eq**), 1.51 (d, *J* = 13.0, 7.0 Hz, 1H, **H8eq**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0 (**C4**), 143.8 (**C3**), 136.1 (**C18**), 133.0 (**C5**), 129.5 (**C12**), 128.5 (**C11**), 124.7 (**C6**), 118.1 (**C1**), 117.4 (**C19**), 108.7 (**C2**), 69.1 (**C14**), 61.2 (**C9**), 57.7 (**C17**), 56.2 (**OMe**), 44.9 (**C16**), 41.7 (**C13**), 31.3 (**C15**), 28.3 (**C8**), 25.4 (**C10**), 21.6 (**C7**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{20}H_{26}NO_3$ 328.1907 found 328.1914.

IR (neat, cm^{-1}) 3390, 2933, 1608, 1504, 1438, 1283, 1052, 904.

***N*-Boc alkene 172**



172

A solution of 5,6-alkene **163** (2.25 g, 6.872 mmol) in DCM (30 mL) was added to a solution of $Pd(PPh_3)_4$ (0.4 g, 0.344 mmol) and *N*,*N*-dimethylbarbituric acid (1.6 g, 10.3 mmol) in DCM (39 mL) under nitrogen atmosphere. The reaction mixture was heated at 40 °C and stirred for 24 h. The mixture was cooled down to room temperature, the solvent was removed under reduced pressure and the residue was dissolved in 1,4-dioxane (69 mL).Di-*tert*-butyl dicarbonate (3.0 g, 13.75 mmol) and DIPEA (0.12 mL, 0.688 mmol) were added, the reaction mixture was heated at 65 °C and stirred for 24 h. After cooling down to room temperature, the reaction mixture was poured into water and the crude product was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude material was purified by automated flash chromatography on silica gel eluting with 20% to 30% ethyl acetate in heptane to afford the *N*-Boc alkene **172** (2.2 g, 83%) as a light-yellow foam, and as a 1:1 mixture of rotamers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (d, *J* = 8.5 Hz, 1H, **H2**), 6.56 (d, *J* = 8.5 Hz, 1H, **H1**), 6.35 (d, *J* = 10.0 Hz, 1H, **H5**), 5.94 (s, 1H, **OH**), 5.78 – 5.71 (m, 1H, **H6**), 4.37 (br, **H9a**), 4.20 (br, **H9b**), 3.90 (br, **H16a**), 3.83 (s, 3H, **OMe**), 3.81 (br, **H16b**), 3.22 (dd, *J* = 18.0, 5.0 Hz, 1H, **H10ax**), 2.79 (br, 1H, **H10eq**), 2.58 (br, 1H, **H16**), 2.38 – 2.22 (m, 1H, **H7**), 2.16 - 1.97 (m, 2H, **H7**, **H15**), 1.84 (ddd, *J* = 13.0, 11.5, 7.1 Hz, 1H, **H8ax**), 1.73 (br, **H15a**), 1.63 (br, **H15b**), 1.59 (dd, *J* = 13.0, 6.5 Hz, 1H, **H8eq**), 1.45 (br s, 9H, **CH_3 *t*Bu Boc**).

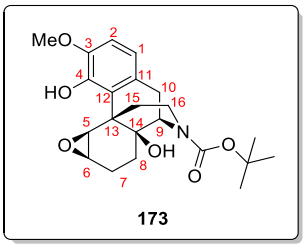
^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5 (**C=O Boc**), 145.2 (**C4**), 143.7 (**C3**), 132.4 (**C5**), 128.3 (**C12**), 125.1 (**C6**), 118.8 (**C1**), 109.0 (**C2**), 79.9 (**C^{IV} Boc**), 69.1 (**C14**), 56.2 (**OMe**), 55.7 (**C9b**), 54.3 (**C9a**), 46.9 (**C13**), 38.5 (**C16b**), 38.0 (**C16a**), 33.0 (**C10**), 29.1 (**C15**), 28.5 (**CH_3 *t*Bu Boc (3C)**), 28.4 (**C8**), 22.1 (**C7**).

The quaternary carbon C11 was not detected.

HRMS (ES) *m/z* $[M+Na]^+$ calculated for $C_{22}H_{29}NO_5Na$ 410.2046 found 410.1949.

IR (neat, cm^{-1}) 3461, 2970, 2929, 1685, 1280.

Epoxide 173



173

A solution of tungsten catalyst **123** (0.15 g, 0.065 mmol) in DCE (3.26 mL) was added to a suspension of *N*-Boc alkene **172** (122 mg, 0.326 mmol) and 30% aqueous hydrogen peroxide (0.1 mL, 0.98 mmol) in water (0.16 mL). The reaction mixture was heated at 80 °C and stirred for 2 h. The reaction mixture was cooled down to room temperature, aqueous sodium metabisulfite was added and the mixture was stirred for 15 minutes. The layers were separated, the organic layer was washed with brine, dried over magnesium sulfate, and the solvent was removed under reduced pressure. The crude material was purified by automated flash chromatography on silica gel eluting with 20 to 30% ethyl acetate in heptane to afford the 5-6 epoxide **175** (48 mg, 36%) as a yellow oil, and as a 59:41 mixture of rotamers.

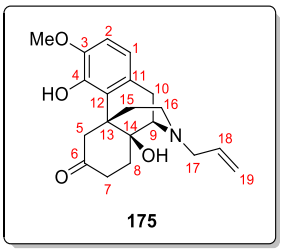
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, *J* = 8.0 Hz, 1H, **H2**), 6.63 (d, *J* = 8.0 Hz, 1H, **H1**), 4.46 (d, *J* = 6.0 Hz, 1H, **H5**), 4.43 (br, **H9 major**), 4.25 (br, **H9 minor**), 3.87 (s, 3H, **OMe**), 3.82 (br, 1H, **H16**), 3.56 (ddd, *J* = 11.0, 6.0, 5.0 Hz, 1H, **H6**), 3.05 (dd, *J* = 18.5, 5.5 Hz, 1H, **H10ax**), 2.88 (d, *J* = 18.5 Hz, 1H, **H10eq**), 2.70 (br, 1H, **H16**), 2.22 (br, 1H, **H15**), 1.95 (ddd, *J* = 15.0, 11.0, 3.0 Hz, 1H, **H7ax**), 1.73 – 1.55 (m, 2H, **H7**, **H8**), 1.47 (s, 9H, **CH_3 *t*Bu Boc**), 1.40 (br, 1H, **H8**), 1.28 (br, 1H, **H15**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (**C=O Boc**), 144.2 (**C4**), 143.9 (**C3**), 131.2 (**C12**), 124.4 (**C11**), 119.3 (**C1**), 114.1 (**C2**), 95.8 (**C5**), 80.7 (**C^{IV} *t*Bu Boc**), 72.4 (**C6**), 69.8 (**C14**), 56.6 (**OMe**), 56.5 (**C9**), 47.1 (**C13**), 37.7 (**C16**), 31.6 (**C10**), 29.8 (**C8**), 29.3 (**C15**), 28.5 (**CH_3 *t*Bu Boc (3C)**), 25.2 (**C7**).

HRMS (ES) *m/z* $[M+Na]^+$ calculated for $C_{22}H_{29}NO_6Na$ 426.1887 found 426.1907.

IR (neat, cm^{-1}) 3421, 2930, 1666, 1418, 1270, 1161.

Ketone 175



175

Naloxone-3-methyl ether **61** (0.25 g, 0.73 mmol) and ammonium chloride (0.39 g, 7.33 mmol) were dissolved in ethanol (4 mL). Zinc (0.29 g, 4.4 mmol) was added and the mixture was stirred at reflux for 8 h. After evaporation of the solvent, water was added, and the mixture was basified to pH 9-10 using an aqueous solution of ammonia. The crude product was then extracted with DCM. The combined organic layers were washed with water, brine and dried over magnesium sulfate, and the solvent was removed under reduced pressure. The crude product is purified by flash chromatography on silica gel eluting with 5% to 10% methanol in DCM to afford ketone **175** (46 mg, 19%) as a light brown foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (d, *J* = 8.5 Hz, 1H, **H2**), 6.57 (d, *J* = 8.5 Hz, 1H, **H1**), 5.81 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H, **H18**), 5.22 – 5.11 (m, 2H, **H19**), 3.91 (dd, *J* = 13.0, 2.0 Hz, 1H, **H5**), 3.81 (s, 3H, **OMe**), 3.12 (ddd, *J* = 6.0, 2.5, 1.5 Hz, 2H, **H17**), 3.02 (d, *J* = 18.5 Hz, 1H, **H10eq**), 2.94 (d, *J* = 6.0 Hz, 1H, **H9**), 2.93 (d, *J* = 13.0 Hz, 1H, **H5**), 2.83 (dd, *J* = 18.5, 6.0 Hz, 1H, **H10ax**), 2.77 (td, *J* = 13.5, 7.0 Hz, 1H, **H7ax**), 2.49 (dd, *J* = 7.5, 1.4 Hz, 1H, **H16**), 2.16 – 2.09 (m, 1H, **H7eq**), 2.05 – 2.00 (m, 2H, **H15**, **H16**), 1.94 (td, *J* = 13.5, 5.5 Hz, 1H, **H8ax**), 1.79 (ddd, *J* = 13.5, 7.0, 1.5 Hz, 1H, **H8eq**), 1.57 (dd, *J* = 9.4, 1.7 Hz, 1H, **H15**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.1 (**C6**), 145.1 (**C3**), 144.5 (**C4**), 135.8 (**C18**), 129.5 (**C11**), 124.8 (**C12**), 118.2 (**C1**), 117.7 (**C19**), 109.2 (**C2**), 69.2 (**C14**), 60.1 (**C9**), 57.8 (**C17**), 56.2 (**OMe**), 45.6 (**C13**), 45.2 (**C5**), 43.7 (**C16**), 37.7 (**C7**), 33.6 (**C15**), 32.1 (**C8**), 25.4 (**C10**).

HRMS (ES) *m/z* $[M+H]^+$ calculated for $C_{20}H_{26}NO_4$ 344.1856 found 344.1863

IR (neat, cm^{-1}) 3417, 2921, 2836, 1709, 1482, 1278, 1047.

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Appendix

X-ray analysis of 90

Table 1 Crystal data and structure refinement for ojh367v_0m.

Identification code	ojh367v_0m
Empirical formula	$C_{20}H_{24}ClNO_3$
Formula weight	361.85
Temperature/K	100.01
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	13.3149(7)
b/Å	18.2064(10)
c/Å	21.6254(12)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	5242.4(5)
Z	12
ρ_{calc}g/cm^3	1.375
μ/mm^{-1}	2.092
F(000)	2304.0
Crystal size/mm^3	0.15 × 0.1 × 0.04
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	6.346 to 133.51
Index ranges	-15 ≤ h ≤ 15, -21 ≤ k ≤ 21, -25 ≤ l ≤ 25
Reflections collected	85024
Independent reflections	9269 [R_{int} = 0.0553, R_{sigma} = 0.0306]
Data/restraints/parameters	9269/0/715
Goodness-of-fit on F^2	1.051
Final R indexes [I>=2σ (I)]	R_1 = 0.0257, wR_2 = 0.0611
Final R indexes [all data]	R_1 = 0.0278, wR_2 = 0.0622
Largest diff. peak/hole / e Å^{-3}	0.15/-0.26
Flack parameter	0.039(4)

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for ojh367v_0m. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
Cl1A	3347.7(4)	1845.8(3)	9271.6(3)	25.52(13)
O1A	3153.4(11)	-527.1(9)	8204.4(7)	19.4(3)

O2A	7444.3(12)	1688.9(9)	9023.9(7)	23.5(4)
O3A	5419.6(10)	899.9(8)	9260.2(7)	17.3(3)
N1A	4740.7(14)	-1373.5(10)	7924.1(8)	16.4(4)
C1A	3932.9(16)	1263.8(12)	8695.4(10)	17.9(5)
C2A	3177.3(16)	1036.6(12)	8207.3(11)	21.4(5)
C3A	3708.5(16)	561.8(12)	7720.3(10)	18.4(5)
C4A	4052.0(15)	-152.6(11)	8020.4(10)	14.4(4)
C5A	4744.9(16)	-0.5(12)	8573.5(9)	14.1(4)
C6A	4451.7(15)	623.4(11)	9023(1)	15.8(4)
C7A	4644.8(16)	-670.0(11)	7583.3(9)	14.3(4)
C8A	5638.3(16)	-334.8(12)	7334.3(10)	16.5(4)
C9A	6186.4(15)	149.1(12)	7789.5(9)	14.4(4)
C10A	7101.5(16)	503.1(12)	7677.7(10)	17.0(4)
C11A	7487.5(16)	993.5(12)	8108(1)	17.9(4)
C12A	6994.4(15)	1165.6(12)	8662.5(10)	16.5(4)
C13A	6088.4(15)	805.7(12)	8771.6(9)	14.9(4)
C14A	5727.2(15)	306.3(11)	8343.8(9)	13.6(4)
C15A	4945.1(17)	-725.6(12)	8919.7(10)	18.2(5)
C16A	5369.4(17)	-1303.7(12)	8480.2(10)	18.3(5)
C17A	7171(2)	1705.9(15)	9660.7(11)	29.6(6)
C18A	5087.6(17)	-1988.3(12)	7537.3(10)	18.6(5)
C19A	4360.6(17)	-2159.2(12)	7029.8(11)	21.3(5)
C20A	4582(2)	-2141.9(13)	6436.2(11)	25.8(5)
Cl1B	1669.3(4)	-2002.5(3)	7479.4(3)	23.79(13)
O1B	1923.7(11)	558.2(8)	6653.1(7)	16.5(3)
O2B	-2290.9(12)	-1815.0(9)	7278.6(8)	25.8(4)
O3B	-296.3(11)	-1021.9(8)	7575.7(6)	15.5(3)
N1B	303.0(13)	1395.8(9)	6427.6(8)	13.7(4)
C1B	1163.6(16)	-1310.8(12)	6965.3(10)	16.0(4)
C2B	1953.2(16)	-1017.1(12)	6522.2(10)	17.7(5)
C3B	1442.3(15)	-478.4(11)	6074.5(10)	15.3(4)
C4B	1047.9(15)	185.7(11)	6429.4(9)	12.0(4)
C5B	356.1(15)	-46.9(11)	6963.4(9)	12.4(4)
C6B	665.0(15)	-715.7(11)	7355.8(10)	13.3(4)
C7B	436.4(15)	731.7(11)	6033.5(10)	13.5(4)
C8B	-538.2(15)	407.4(11)	5752.6(10)	14.8(4)
C9B	-1076.2(15)	-132.2(11)	6166.6(9)	13.2(4)
C10B	-1984.8(15)	-484.4(11)	6028.2(10)	15.8(4)
C11B	-2350.1(16)	-1033.2(12)	6410.4(10)	17.9(4)
C12B	-1845.5(16)	-1262.2(11)	6949.2(10)	16.1(4)
C13B	-960.0(16)	-894.0(11)	7091.3(9)	14.2(4)
C14B	-613.5(15)	-344.4(11)	6704.8(9)	12.4(4)
C15B	132.1(16)	631.1(12)	7365.7(10)	15.4(4)
C16B	-315.1(16)	1249.1(11)	6976.3(10)	16.4(4)
C17B	-1693(2)	-2217.6(15)	7701.5(13)	38.2(7)

C18B	-85.8(16)	2036.1(12)	6087.8(10)	17.6(5)
C19B	609.6(17)	2260.4(11)	5578.3(10)	19.8(5)
C20B	405(2)	2177.2(12)	4986.2(11)	22.7(5)
Cl1C	-1713.4(4)	2992.4(3)	3939.9(3)	23.79(13)
O1C	-2095.9(11)	5232.8(9)	5238.4(7)	17.4(3)
O2C	2246.1(12)	3300(1)	4093.2(8)	31.7(4)
O3C	174.7(11)	4073.0(8)	3985.7(7)	18.7(3)
N1C	-548.3(13)	6071.8(9)	5589.2(8)	16.0(4)
C1C	-1214.4(16)	3559.2(12)	4554.5(10)	18.1(5)
C2C	-1975.8(16)	3671.0(12)	5065.4(11)	19.9(5)
C3C	-1468.8(16)	4097.1(11)	5591.4(10)	18.0(5)
C4C	-1170.9(15)	4860.0(11)	5365.8(10)	14.4(4)
C5C	-502.4(16)	4821.7(11)	4785.1(9)	14.0(4)
C6C	-792.4(15)	4264.6(11)	4277.8(10)	15.8(4)
C7C	-576.8(15)	5316.9(11)	5844.1(9)	15.0(4)
C8C	451.7(16)	4985.9(12)	6031(1)	17.0(4)
C9C	989.6(16)	4589.6(11)	5514.9(10)	15.2(4)
C10C	1922.0(16)	4240.5(12)	5570.2(10)	19.4(5)
C11C	2297.3(16)	3830.8(12)	5081.0(11)	21.5(5)
C12C	1786.2(17)	3743.5(12)	4519.7(11)	20.1(5)
C13C	864.8(16)	4099.3(11)	4467.3(10)	16.1(4)
C14C	506.5(15)	4514.1(11)	4956.9(10)	13.9(4)
C15C	-370.2(17)	5604.7(11)	4523.8(9)	16.9(4)
C16C	51.1(17)	6116.6(12)	5018.9(10)	17.4(5)
C17C	1721(2)	3118.5(15)	3541.8(11)	33.1(6)
C18C	-234.1(17)	6629.6(12)	6043(1)	19.3(5)
C19C	-592.7(17)	7372.4(12)	5853.3(11)	22.3(5)
C20C	2(2)	7900.3(14)	5656.5(12)	28.8(6)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for ojh367v_0m. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl1A	21.4(3)	21.6(2)	33.6(3)	-9.2(2)	6.6(3)	3.4(2)
O1A	12.9(8)	17.2(8)	28.2(8)	-4.3(6)	3.5(6)	-3.3(6)
O2A	20.1(8)	29.5(9)	20.9(8)	-6.7(7)	1.4(7)	-7.9(7)
O3A	11.8(7)	24.6(8)	15.5(7)	-6.5(6)	1.7(6)	-0.9(6)
N1A	16.6(9)	15.0(9)	17.6(9)	-0.6(7)	1.4(8)	1.2(7)
C1A	14.7(11)	17.3(10)	21.7(11)	-4.0(9)	3.1(9)	2.3(9)
C2A	14.1(11)	19.2(11)	31.0(12)	-1.6(9)	-4.2(10)	3.3(9)
C3A	15.9(11)	18.2(11)	21.0(11)	-1.1(9)	-5.0(9)	1.7(9)
C4A	10(1)	16.1(10)	17.1(10)	-1.2(9)	0.5(8)	-1.0(9)
C5A	12(1)	16.8(11)	13.4(10)	-0.4(8)	2.1(8)	0.8(8)
C6A	10.7(10)	19.3(10)	17.5(10)	-3.5(9)	0.4(8)	-1.6(9)

C7A	13.4(10)	15.5(10)	13.9(10)	-0.2(8)	-1.5(8)	-0.4(8)
C8A	16.9(11)	18.9(11)	13.6(10)	-0.7(8)	2.1(9)	0.1(9)
C9A	12.6(10)	15.7(10)	14.9(10)	1.8(8)	0.2(8)	2.2(9)
C10A	14.5(10)	20.7(11)	15.6(10)	2.1(9)	4.1(9)	3.1(9)
C11A	9.9(10)	21.1(11)	22.8(11)	3.2(9)	0.7(8)	-0.2(9)
C12A	12.3(10)	18.2(10)	19.0(11)	-1.7(9)	-3.1(8)	0.9(8)
C13A	11.8(10)	18.3(10)	14.5(10)	0.0(8)	-0.4(8)	2.4(8)
C14A	10.7(10)	14.7(10)	15.5(10)	2.0(8)	-0.2(8)	3.0(8)
C15A	19.5(11)	19.3(11)	15.8(11)	1.6(9)	1.2(9)	0.7(9)
C16A	21.0(11)	17.5(11)	16.3(11)	2.6(9)	-0.4(9)	4.5(9)
C17A	31.0(13)	41.1(15)	16.7(12)	-7.6(10)	-1.7(10)	-10.7(12)
C18A	17.6(11)	15.8(11)	22.3(11)	-2.0(9)	3.0(9)	2.9(9)
C19A	17.3(11)	17.1(11)	29.6(12)	-6.5(9)	2.5(10)	-0.1(9)
C20A	33.1(14)	17.7(11)	26.5(13)	-4.3(10)	-4.2(11)	3.3(11)
Cl1B	19.2(3)	19.4(3)	32.8(3)	12.3(2)	0.0(2)	4.3(2)
O1B	12.1(7)	13.8(8)	23.6(8)	2.5(6)	-3.6(6)	-2.6(6)
O2B	17.0(8)	26.3(9)	34.0(9)	11.5(7)	2.3(7)	-6.4(7)
O3B	12.9(7)	19.0(7)	14.5(7)	4.2(6)	0.6(6)	-1.1(6)
N1B	15.5(9)	10.7(8)	15.0(9)	1.3(7)	-0.5(7)	1.4(7)
C1B	13.9(10)	15.5(10)	18.6(11)	4.8(9)	-1.5(9)	3.2(9)
C2B	12.6(10)	16.7(10)	23.8(11)	2.1(9)	1.7(9)	2.0(9)
C3B	14.1(10)	15.2(10)	16.8(10)	1.8(8)	2.8(8)	0.2(8)
C4B	9(1)	13.7(10)	13.3(10)	0.5(8)	-0.9(8)	-2.7(8)
C5B	10.9(10)	14.3(10)	12.1(10)	0.6(8)	-1.4(8)	-0.1(8)
C6B	10.8(10)	15.8(10)	13.4(10)	2.8(8)	0.1(8)	-1.5(8)
C7B	13.7(10)	13.3(10)	13.4(10)	-0.2(8)	2.3(8)	-0.4(8)
C8B	15.9(10)	15.6(10)	12.9(10)	1.3(8)	-2.4(9)	0.4(8)
C9B	13.2(10)	12.7(10)	13.8(10)	-2.0(8)	0.0(8)	3.2(8)
C10B	13.3(10)	18.2(10)	16(1)	-3.1(8)	-3.2(8)	3.0(8)
C11B	9.8(10)	18.9(11)	24.8(11)	-5.4(9)	0.4(9)	-0.4(9)
C12B	12.4(10)	15.9(10)	20.0(11)	-0.1(8)	5.3(8)	-0.9(9)
C13B	13.8(10)	15.7(10)	13(1)	0.4(8)	0.6(8)	2.4(8)
C14B	9(1)	13.2(10)	15.1(10)	-2.3(8)	3.2(8)	1.3(8)
C15B	16.8(10)	16.9(11)	12.5(10)	-2.6(9)	0.6(8)	-0.9(8)
C16B	18.0(11)	14.5(10)	16.5(10)	-2.4(8)	3.4(9)	1.5(9)
C17B	36.8(15)	36.1(15)	41.7(15)	22.7(12)	-6.8(13)	-13.5(13)
C18B	15.0(11)	14.6(10)	23.3(11)	3.0(9)	0.1(9)	2.1(8)
C19B	17.1(11)	15(1)	27.3(12)	7.7(9)	-0.2(9)	-0.4(9)
C20B	27.1(13)	16.0(11)	25.0(12)	5.5(9)	3.0(11)	3(1)
Cl1C	19.6(3)	17.7(2)	34.0(3)	-9.9(2)	-4.2(2)	0.9(2)
O1C	12.7(7)	17.6(8)	21.7(8)	-3.1(7)	-2.8(6)	5.0(6)
O2C	19.1(8)	35.2(10)	40.8(11)	-18.0(8)	6.6(8)	3.6(7)
O3C	16.6(8)	21.4(8)	18.2(8)	-5.6(6)	2.6(6)	0.3(6)
N1C	19.6(9)	15.8(8)	12.6(9)	-1.4(7)	-2.1(7)	0.5(7)
C1C	15.1(10)	15.8(10)	23.3(11)	-3.4(9)	-4.5(9)	0.4(9)

C2C	13.4(10)	17.5(10)	28.7(12)	-0.1(9)	1.8(9)	-2.0(9)
C3C	15(1)	19.3(11)	19.7(11)	2.5(9)	3.0(9)	0.5(8)
C4C	11.9(10)	15.2(10)	16.1(10)	0.9(8)	-0.2(8)	3.2(8)
C5C	14.4(10)	14.3(10)	13.5(10)	-0.8(8)	-1.2(8)	1.0(8)
C6C	14.1(10)	16.4(10)	17(1)	-2.6(9)	0.6(9)	2.7(8)
C7C	15.2(10)	17.9(10)	11.8(10)	0.7(8)	-0.7(8)	2.1(8)
C8C	16.8(11)	20.6(11)	13.7(10)	2.7(8)	-1.8(9)	1.6(9)
C9C	12.9(10)	15.3(10)	17.5(11)	3.0(8)	0.1(8)	-2.1(8)
C10C	12.4(10)	22.0(11)	23.9(12)	3.9(9)	-1.9(9)	-1.6(9)
C11C	10.3(10)	20.8(11)	33.3(13)	3.6(10)	3.3(10)	0.4(9)
C12C	13.4(10)	17.7(10)	29.2(12)	-3.8(9)	7.4(9)	-1.3(9)
C13C	14.8(10)	15.4(10)	18.1(11)	-0.8(8)	2.8(8)	-3.8(8)
C14C	11.6(10)	12.2(9)	17.9(10)	2.5(8)	3.5(8)	-0.5(8)
C15C	23.0(11)	14.2(10)	13.3(10)	1.4(8)	-0.5(9)	0.5(9)
C16C	22.0(11)	16.4(11)	13.8(10)	1.1(9)	-0.1(9)	-2.0(9)
C17C	39.4(15)	36.0(14)	23.9(12)	-3.9(11)	11.1(12)	11.7(13)
C18C	23.1(12)	20.1(11)	14.8(11)	-2.9(9)	-0.9(9)	-0.6(9)
C19C	20.2(11)	21.2(11)	25.6(12)	-8.8(9)	-5.8(10)	3.4(10)
C20C	35.9(15)	20.4(12)	30.1(13)	-4.3(11)	-12.0(11)	-2.3(11)

Table 4 Bond Lengths for ojh367v_0m.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Cl1A	C1A	1.812(2)	C5B	C6B	1.540(3)
O1A	C4A	1.434(3)	C5B	C14B	1.508(3)
O2A	C12A	1.370(3)	C5B	C15B	1.539(3)
O2A	C17A	1.425(3)	C7B	C8B	1.550(3)
O3A	C6A	1.476(2)	C8B	C9B	1.510(3)
O3A	C13A	1.392(3)	C9B	C10B	1.402(3)
N1A	C7A	1.483(3)	C9B	C14B	1.372(3)
N1A	C16A	1.471(3)	C10B	C11B	1.385(3)
N1A	C18A	1.472(3)	C11B	C12B	1.408(3)
C1A	C2A	1.516(3)	C12B	C13B	1.391(3)
C1A	C6A	1.529(3)	C13B	C14B	1.383(3)
C2A	C3A	1.535(3)	C15B	C16B	1.526(3)
C3A	C4A	1.524(3)	C18B	C19B	1.496(3)
C4A	C5A	1.536(3)	C19B	C20B	1.318(3)
C4A	C7A	1.550(3)	Cl1C	C1C	1.809(2)
C5A	C6A	1.545(3)	O1C	C4C	1.433(2)
C5A	C14A	1.506(3)	O2C	C12C	1.370(3)
C5A	C15A	1.541(3)	O2C	C17C	1.421(3)
C7A	C8A	1.553(3)	O3C	C6C	1.476(2)
C8A	C9A	1.509(3)	O3C	C13C	1.390(3)
C9A	C10A	1.400(3)	N1C	C7C	1.481(3)

C9A	C14A	1.376(3)	N1C	C16C	1.471(3)
C10A	C11A	1.388(3)	N1C	C18C	1.473(3)
C11A	C12A	1.403(3)	C1C	C2C	1.513(3)
C12A	C13A	1.393(3)	C1C	C6C	1.524(3)
C13A	C14A	1.383(3)	C2C	C3C	1.533(3)
C15A	C16A	1.527(3)	C3C	C4C	1.525(3)
C18A	C19A	1.496(3)	C4C	C5C	1.541(3)
C19A	C20A	1.317(3)	C4C	C7C	1.545(3)
Cl1B	C1B	1.810(2)	C5C	C6C	1.543(3)
O1B	C4B	1.433(2)	C5C	C14C	1.502(3)
O2B	C12B	1.368(3)	C5C	C15C	1.544(3)
O2B	C17B	1.417(3)	C7C	C8C	1.550(3)
O3B	C6B	1.475(2)	C8C	C9C	1.510(3)
O3B	C13B	1.390(2)	C9C	C10C	1.400(3)
N1B	C7B	1.490(3)	C9C	C14C	1.374(3)
N1B	C16B	1.469(3)	C10C	C11C	1.388(3)
N1B	C18B	1.472(3)	C11C	C12C	1.401(3)
C1B	C2B	1.520(3)	C12C	C13C	1.392(3)
C1B	C6B	1.526(3)	C13C	C14C	1.385(3)
C2B	C3B	1.537(3)	C15C	C16C	1.526(3)
C3B	C4B	1.525(3)	C18C	C19C	1.492(3)
C4B	C5B	1.537(3)	C19C	C20C	1.316(4)
C4B	C7B	1.544(3)			

Table 5 Bond Angles for ojh367v_0m.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C12A	O2A	C17A	117.06(18)	C1B	C6B	C5B	111.88(17)
C13A	O3A	C6A	104.64(15)	N1B	C7B	C4B	105.55(16)
C16A	N1A	C7A	112.37(17)	N1B	C7B	C8B	115.70(17)
C16A	N1A	C18A	110.61(17)	C4B	C7B	C8B	114.43(16)
C18A	N1A	C7A	113.66(16)	C9B	C8B	C7B	114.38(16)
C2A	C1A	Cl1A	110.67(15)	C10B	C9B	C8B	125.49(18)
C2A	C1A	C6A	114.48(18)	C14B	C9B	C8B	118.23(18)
C6A	C1A	Cl1A	108.76(15)	C14B	C9B	C10B	116.09(19)
C1A	C2A	C3A	109.00(17)	C11B	C10B	C9B	120.4(2)
C4A	C3A	C2A	109.07(18)	C10B	C11B	C12B	122.7(2)
O1A	C4A	C3A	105.88(17)	O2B	C12B	C11B	116.21(19)
O1A	C4A	C5A	111.77(17)	O2B	C12B	C13B	127.4(2)
O1A	C4A	C7A	107.77(16)	C13B	C12B	C11B	116.40(19)
C3A	C4A	C5A	110.98(17)	O3B	C13B	C12B	128.66(19)
C3A	C4A	C7A	114.32(17)	C14B	C13B	O3B	111.38(18)
C5A	C4A	C7A	106.18(16)	C14B	C13B	C12B	119.88(19)
C4A	C5A	C6A	118.08(17)	C9B	C14B	C5B	126.72(18)

C4A	C5A	C15A	109.14(17)	C9B	C14B	C13B	124.50(19)
C14A	C5A	C4A	109.36(17)	C13B	C14B	C5B	108.75(18)
C14A	C5A	C6A	98.87(16)	C16B	C15B	C5B	110.79(17)
C14A	C5A	C15A	109.13(17)	N1B	C16B	C15B	111.17(17)
C15A	C5A	C6A	111.58(17)	N1B	C18B	C19B	111.47(17)
O3A	C6A	C1A	107.19(17)	C20B	C19B	C18B	123.8(2)
O3A	C6A	C5A	104.40(15)	C12C	O2C	C17C	118.81(18)
C1A	C6A	C5A	112.54(17)	C13C	O3C	C6C	104.35(15)
N1A	C7A	C4A	105.40(16)	C16C	N1C	C7C	112.17(16)
N1A	C7A	C8A	116.00(17)	C16C	N1C	C18C	111.48(17)
C4A	C7A	C8A	113.96(17)	C18C	N1C	C7C	113.52(16)
C9A	C8A	C7A	114.52(17)	C2C	C1C	Cl1C	111.54(15)
C10A	C9A	C8A	125.25(19)	C2C	C1C	C6C	114.85(18)
C14A	C9A	C8A	118.35(18)	C6C	C1C	Cl1C	109.13(15)
C14A	C9A	C10A	116.2(2)	C1C	C2C	C3C	108.35(17)
C11A	C10A	C9A	120.2(2)	C4C	C3C	C2C	109.76(17)
C10A	C11A	C12A	122.9(2)	O1C	C4C	C3C	105.63(16)
O2A	C12A	C11A	116.00(19)	O1C	C4C	C5C	111.18(16)
O2A	C12A	C13A	127.5(2)	O1C	C4C	C7C	108.28(16)
C13A	C12A	C11A	116.4(2)	C3C	C4C	C5C	111.71(17)
O3A	C13A	C12A	128.65(19)	C3C	C4C	C7C	114.18(17)
C14A	C13A	O3A	111.47(18)	C5C	C4C	C7C	105.91(16)
C14A	C13A	C12A	119.79(19)	C4C	C5C	C6C	117.68(17)
C9A	C14A	C5A	126.58(19)	C4C	C5C	C15C	108.81(16)
C9A	C14A	C13A	124.4(2)	C6C	C5C	C15C	112.04(17)
C13A	C14A	C5A	108.97(18)	C14C	C5C	C4C	109.39(17)
C16A	C15A	C5A	110.62(17)	C14C	C5C	C6C	98.88(16)
N1A	C16A	C15A	110.98(17)	C14C	C5C	C15C	109.45(17)
N1A	C18A	C19A	111.84(18)	O3C	C6C	C1C	106.89(16)
C20A	C19A	C18A	124.4(2)	O3C	C6C	C5C	103.97(16)
C12B	O2B	C17B	118.23(18)	C1C	C6C	C5C	111.53(18)
C13B	O3B	C6B	104.20(15)	N1C	C7C	C4C	105.28(16)
C16B	N1B	C7B	112.42(16)	N1C	C7C	C8C	115.80(17)
C16B	N1B	C18B	110.50(16)	C4C	C7C	C8C	114.68(17)
C18B	N1B	C7B	113.52(16)	C9C	C8C	C7C	114.34(17)
C2B	C1B	Cl1B	112.01(14)	C10C	C9C	C8C	125.07(19)
C2B	C1B	C6B	113.58(17)	C14C	C9C	C8C	118.35(19)
C6B	C1B	Cl1B	108.43(14)	C14C	C9C	C10C	116.4(2)
C1B	C2B	C3B	108.39(16)	C11C	C10C	C9C	119.9(2)
C4B	C3B	C2B	109.95(17)	C10C	C11C	C12C	123.1(2)
O1B	C4B	C3B	105.35(16)	O2C	C12C	C11C	115.7(2)
O1B	C4B	C5B	111.37(16)	O2C	C12C	C13C	127.8(2)
O1B	C4B	C7B	108.16(16)	C13C	C12C	C11C	116.5(2)
C3B	C4B	C5B	111.46(16)	O3C	C13C	C12C	128.88(19)
C3B	C4B	C7B	114.39(16)	C14C	C13C	O3C	111.34(18)

C5B	C4B	C7B	106.15(16)	C14C	C13C	C12C	119.7(2)
C4B	C5B	C6B	118.16(17)	C9C	C14C	C5C	126.75(19)
C4B	C5B	C15B	108.65(16)	C9C	C14C	C13C	124.4(2)
C14B	C5B	C4B	109.48(16)	C13C	C14C	C5C	108.80(18)
C14B	C5B	C6B	98.57(16)	C16C	C15C	C5C	110.42(17)
C14B	C5B	C15B	109.38(17)	N1C	C16C	C15C	110.78(17)
C15B	C5B	C6B	111.98(16)	N1C	C18C	C19C	110.55(18)
O3B	C6B	C1B	106.72(16)	C20C	C19C	C18C	124.0(2)
O3B	C6B	C5B	104.17(15)				

Table 6 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for ojh367v_0m.

Atom	*x*	*y*	*z*	U(eq)
H1AA	4465	1560	8485	21
H2AA	2886	1478	8009	26
H2AB	2625	754	8401	26
H3AA	3243	454	7375	22
H3AB	4295	829	7551	22
H6A	4026	431	9368	19
H7A	4206	-767	7217	17
H8AA	6090	-740	7209	20
H8AB	5485	-43	6960	20
H10A	7460	408	7306	20
H11A	8114	1223	8023	21
H15A	5428	-637	9260	22
H15B	4311	-908	9103	22
H16A	6060	-1164	8358	22
H16B	5403	-1783	8695	22
H17A	6493	1909	9703	44
H17B	7647	2014	9889	44
H17C	7185	1206	9829	44
H18A	5178	-2429	7799	22
H18B	5747	-1863	7355	22
H19A	3695	-2289	7143	26
H1BA	627	-1549	6712	19
H2BA	2260	-1427	6288	21
H2BB	2490	-763	6756	21
H3BA	1931	-315	5758	18
H3BB	879	-727	5861	18
H6B	1103	-566	7710	16
H7B	874	879	5679	16
H8BA	-1002	816	5655	18
H8BB	-368	159	5359	18
H10B	-2352	-346	5670	19

H11B	-2966	-1265	6305	21
H15C	-345	495	7697	19
H15D	761	803	7563	19
H16C	-1002	1111	6845	20
H16D	-363	1701	7230	20
H17D	-1083	-2389	7493	57
H17E	-2074	-2641	7854	57
H17F	-1509	-1901	8050	57
H18C	-174	2452	6378	21
H18D	-752	1915	5911	21
H19B	1235	2475	5688	24
H1CA	-636	3286	4739	22
H2CA	-2217	3190	5218	24
H2CB	-2560	3950	4907	24
H3CA	-1937	4141	5945	22
H3CB	-865	3829	5733	22
H6C	-1268	4485	3972	19
H7C	-995	5337	6228	18
H8CA	889	5386	6184	20
H8CB	346	4638	6377	20
H10C	2297	4284	5942	23
H11C	2931	3598	5129	26
H15E	93	5591	4166	20
H15F	-1027	5793	4379	20
H16E	755	5980	5110	21
H16F	46	6628	4863	21
H17G	2145	2806	3282	50
H17H	1554	3570	3317	50
H17I	1102	2855	3647	50
H18E	507	6632	6076	23
H18F	-513	6505	6454	23
H19C	-1293	7470	5876	27
H20A	5240(20)	-2006(15)	6286(12)	33(8)
H20E	740(20)	7804(16)	5642(13)	38(8)
H20F	-250(20)	8366(17)	5521(13)	41(8)
H20B	4120(20)	-2276(16)	6115(14)	41(8)
H20C	844(19)	2313(14)	4666(12)	23(7)
H20D	-230(20)	1977(14)	4869(12)	29(7)
H1B	1760(20)	1005(17)	6650(13)	37(8)
H1A	3290(20)	-973(18)	8177(14)	43(9)
H1C	-1990(20)	5669(17)	5320(14)	38(9)

Experimental

A suitable crystal was selected and mounted on a Mitigen tip in oil on a Bruker D8 Venture Photon 100 diffractometer. The crystal was kept at 100.01 K during data collection. Using Olex2 [1], the structure was solved with the XT [2] structure solution program using Intrinsic Phasing and refined with the XL [3] refinement package using Least Squares minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8.
3. Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

Crystal structure determination of ojh367v_0m

Crystal Data for $C_{20}H_{24}ClNO_3$ (M =361.85 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 13.3149(7) Å, b = 18.2064(10) Å, c = 21.6254(12) Å, V = 5242.4(5) Å^3, Z = 12, T = 100.01 K, μ(CuKα) = 2.092 mm^{-1}, *Dcalc* = 1.375 g/cm^3, 85024 reflections measured (6.346° ≤ 2Θ ≤ 133.51°), 9269 unique (R_{int} = 0.0553, R_{sigma} = 0.0306) which were used in all calculations. The final R_1 was 0.0257 (I > 2σ(I)) and wR_2 was 0.0622 (all data).

Refinement model description

Number of restraints - 0, number of constraints - unknown.

Details:

```
1. Fixed Uiso
 At 1.2 times of:
  All C(H) groups, All C(H,H) groups
 At 1.5 times of:
  All C(H,H,H) groups
2.a Ternary CH refined with riding coordinates:
 C1A(H1AA), C6A(H6A), C7A(H7A), C1B(H1BA), C6B(H6B), C7B(H7B), C1C(H1CA),
 C6C(H6C), C7C(H7C)
2.b Secondary CH2 refined with riding coordinates:
 C2A(H2AA,H2AB), C3A(H3AA,H3AB), C8A(H8AA,H8AB), C15A(H15A,H15B), C16A(H16A,
 H16B), C18A(H18A,H18B), C2B(H2BA,H2BB), C3B(H3BA,H3BB), C8B(H8BA,H8BB),
 C15B(H15C,H15D), C16B(H16C,H16D), C18B(H18C,H18D), C2C(H2CA,H2CB), C3C(H3CA,
 H3CB), C8C(H8CA,H8CB), C15C(H15E,H15F), C16C(H16E,H16F), C18C(H18E,H18F)
2.c Aromatic/amide H refined with riding coordinates:
 C10A(H10A), C11A(H11A), C19A(H19A), C10B(H10B), C11B(H11B), C19B(H19B),
 C10C(H10C), C11C(H11C), C19C(H19C)
2.d Idealised Me refined as rotating group:
 C17A(H17A,H17B,H17C), C17B(H17D,H17E,H17F), C17C(H17G,H17H,H17I)
```

This report has been created with Olex2, compiled on 2017.08.10 svn.r3458 for OlexSys. Please let us know if there are any errors or if you would like to have additional features.