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New Chemistry to Support the Search for More Effective Opioids

Thesis submitted to the University of Nottingham for the degree of MSc Chemistry (by Research)

By

Ruoyan Yang

Supervisor: Professor Hon Wai Lam

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Declaration

I hereby declare that, except for where specific reference is made to other sources, the work contained within this thesis is the original work of my own research and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification. I confirm that the work submitted is my own, except work which has formed part of jointly-authored publications. The contributions of myself and other authors to this work have been specifically indicated where relevant. I confirm that appropriate credit has been given with the thesis where references has been made to the work of others.

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Thanks for the unforgettable experience in this wonderful University.

Contents

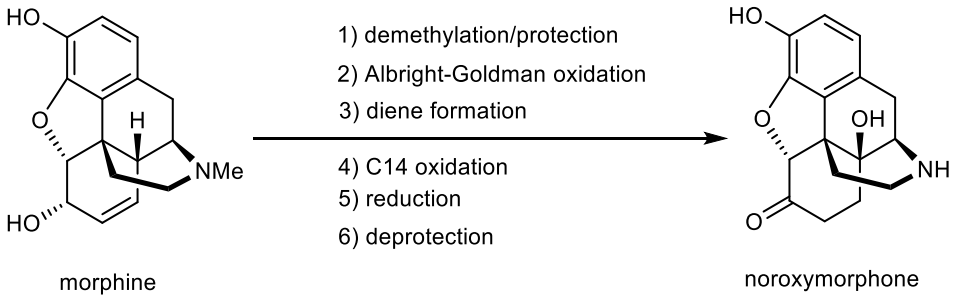
Abbreviations

Ac	acetyl
Ac_2O	acetic anhydride
acac	acetylacetonate
app.	apparent
Ar	aryl
ca.	*circa*
Cat.	catalyst
CN	cyano
d	doublet
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DOR	δ-opioid receptor
equiv	equivalents
Et	ethyl
g	gram
HRMS	high-resolution mass spectrometry
Hz	hertz
IR	infrared
IPA	isopropyl alcohol
i-Pr	*iso*-propyl
J	coupling constant
kg	kilogram
KOR	κ-opioid receptor
log P	partition coefficient
M	molar
m	multiplet
Me	methyl

mg	milligram
MHz	megahertz
min	minute(s)
mL	millilitres
mmol	millimole
MOR	μ-opioid receptor
m.p.	melting point
nM	nanomolar
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Pd/C	palladium on carbon
q	quartet
R_f	retention factor
r.t.	room temperature
s	singlet
t	triplet
TBS	*tert*-butyldimethylsilyl
t-Bu	tertiary butyl
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

Abstract

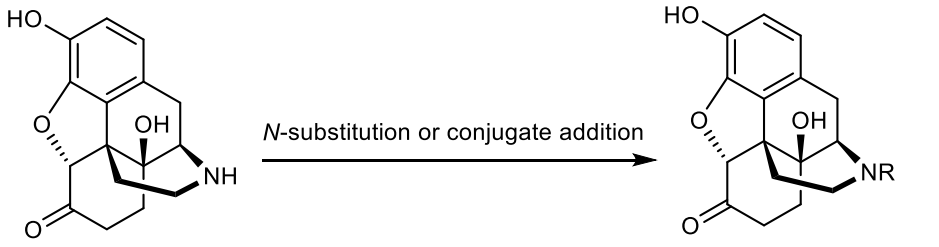
Herein is presented a synthesis route to obtain noroxymorphone, a vital intermediate in the manufacture of opioid medicines, using the major ingredient in opium – morphine as the starting material. Two steps of Albright-Goldman oxidation and the formation of diene are combined in one pot to enhance the efficiency of the whole route. The overall 14% yield is still impractical for industry. However, further optimization of Albright-Goldman oxidation can increase the yield to near 30% in total.



morphine noroxymorphone

14% overall yield

Noroxymorphone is employed as a starting material to access new opioid derivatives by *N*-substitution or conjugate addition of amines onto electron-deficient alkenes.



noroxymorphone potential opioid derivatives

5 examples (4 new substrates)

1. Introduction

1.1 History of Opiates

The poppy flower, or specifically *Papaver somniferum*, was widespread in Asia and Europe far before opium, the product derived from poppy plants was discovered to be capable of relieving pain. Therefore, opium was a very popular medical commodity during ancient times. Since 3400 BC, the Sumerians of Mesopotamia were obtaining opium from the poppy flower as a medical and recreational drug, as proven by their historical records that mentioned the medical use of the poppy plant with the name "joy flower". However, opiates, the compounds obtained from opium, leads to many side effects such as depression, constipation, excitation, addiction, euphoria, nausea, vomiting, itching and tolerance. These side effects were not considered seriously enough as a widely recognized problem until the 16th century, likely due to the lower life expectancy at that time.[1]

Figure 1.1: Dried poppy flower (picture taken at Beeston, Nottingham by the author)

Historical documents and pharmacopeias mention that people paid great attention to opium. Both the Ebers Papyrus, a record from ancient Egypt, and the Odyssey written by Homer, described opium as a drug that could help to

relieve physical pain and mental sorrow. After the 8th century, opium was traded by Arab merchants and widely spread all around Asia and Europe.[1]

In 17th century, Thomas Sydenham, the father of English medicine, invented laudanum which is the first tincture of opium as brown pills. Laudanum was very popular among sailors to make them more comfortable in harsh environments during days at sea.[2]

Morphine was used in the World War I and the American Civil War to relieve pain and inspire soldiers. It resulted in a great number of addicts and one original reason for the expansion of non-medical use of morphine.

Another huge issue caused by opiates were the Opium Wars during 1839-1860. When the British set foot on the Indian Peninsula and began colonial trade with the East India Company in order to produce tea and opium, to the Qing government for delivering the opium before it became one of the reasons for the first Opium War during 1839 to 1842. Some historians argue that the main reason for the Anglo-Chinese conflict was to battle for "free trading", which was presented in the Treaty of Nanjing, the first unequal treaty that let the opium trade continue legally in China.[3]

Regardless of what caused the Opium Wars, the consequences were too heavy for Chinese and Asian people to carry – nowadays, the previous colonies of Great Britain in Southeast Asia are called the Golden Triangle, the area covered the borders of Thailand, Laos, and Myanmar, here a large amount of opioid drugs were produced and exported to the whole world.

While the Chinese people were suffering during this nationwide drug problem, migration to South Asia, Europe and America also occurred. In the later 19th century in London, opium dens were very popular around Limehouse. This phenomenon was not only due to the highly addictive opium itself, but also because of their oriental decor, as Charles Dickens, Oscar Wilde and Arthur Conan Doyle described in their literatures.[4]

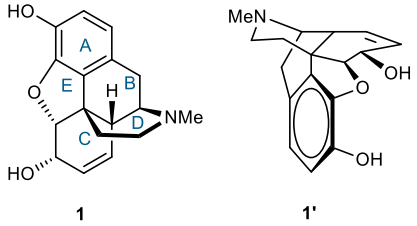
1.1.1 History of Using Morphine

Morphine (**1**) was isolated by Friedrich Sertürner in 1804, which proved to be the active ingredient of opium. However, several generations of chemists were unable to determine the precise structure of morphine because of the lack of scientific tools for analysing the structures of unknown chemical substances at those times.[2]

The experiments that Sertürner performed on himself gave disappointing results, as he found out that morphine was six times stronger and more addictive than opium, which degraded his health due to severe drug addiction.[5]

In 1827, the Merck company bought the patent from Sertürner and marketed morphine as a painkiller and a treatment for the addiction of opium and alcohol. Despite the health risks, morphine is still used in pain-relieving therapies until now. Morphine was adulterated with many other drugs in 19th century to reduce its actual dose. With a good water solubility and the capability to be transported efficiently around the body in the bloodstream, the consumption of morphine rose significantly after the hypodermic injection was developed in 1855.[2]

The structure of morphine was discovered by Sir Robert Robinson in 1925, deduced from various structural studies by Hesse, Vongerichten, Freund, Pschorr and Knorr.[6] Morphine has five rings: Phenol ring A and six-membered ring B, six-membered ring C, *N*-methylpiperidine ring D and dihydrofuran ring E, was presented in Figure 1.2. In 1968, Fridrichsons[7] reported the X-ray crystal structure of morphine, which showed it to possess a T-shape structure (**1'**) of morphine as shown in Figure 1.2.



1 **1'**

Figure 1.2: The structure of morphine (**1**), the T-shape structure of morphine (**1'**)

1.1.2 History of Using Heroin

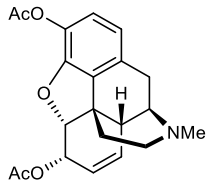


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Figure 1.3: The structure of diacetylmorphine/heroin (**2**)

As morphine had become a double-edged sword to society in the 19th century, chemists paid more attention to organic synthesis, aiming to create better opiates medicines based on morphine. In 1874, the English chemist C. R. Alder Wright boiled morphine in acetic anhydride at 100 °C and obtained diacetylmorphine (**2**) presented in Figure 1.3. However, this invention was not taken seriously after Wright obtained the biological report of the effect of this compound on rabbits and young dogs, which suggested it had significant side-effects.[8]

The revival of diacetylmorphine happened 23 years later when Felix Hoffmann synthesized it for the Bayer pharmaceutical company. Diacetylmorphine was marketed with a commercial name Heroin as a non-addictive morphine substitute and cough suppressant.

Marketing and advertising did not change the nature of heroin. After entering human bodies, diacetylmorphine is quickly metabolized into 6-monoacetylmorphine and then morphine, causing euphoria, ambition, dry mouth and long-term damage to the nervous system.

1.2 Pharmacological Effects of Opioids

1.2.1 Opioid Receptors and Their Function

Opiates derivatives and the other chemicals such as Fentanyl that can bind with opioid receptors are called opioids. Opioids cause their biological effects by binding to receptors in the central nervous system (CNS) called the opioid receptors, which are G-protein-coupled receptors (GPCRs). There are three

major types of opioid receptors, the μ-opioid receptor (MOR), κ-opioid receptor (KOR) and δ-opioid receptor (DOR). The most pronounced biological effects are triggered by binding to MOR, which causes both excitation and relaxation, but also long-term opioid addiction. The crystal structure of MOR is presented in Figure 1.4,[9] while KOR and DOR are presented in Figure 1.5.[10]

It normally takes 6-30 minutes for morphine to show its effects and has an average half-life of 2-3 hours. After morphine is absorbed orally, it undergoes metabolic inactivation in the liver and forms two major metabolites, not significantly active morphine-3-glucuronide and pharmacologically active morphine-6-glucuronide. The activity of morphine-6-glucuronide contributes the greatest part for the effects of morphine. This metabolite from morphine can also cross the blood-brain barrier and works as an agonist of MOR and KOR with twice the potency of morphine.[10]

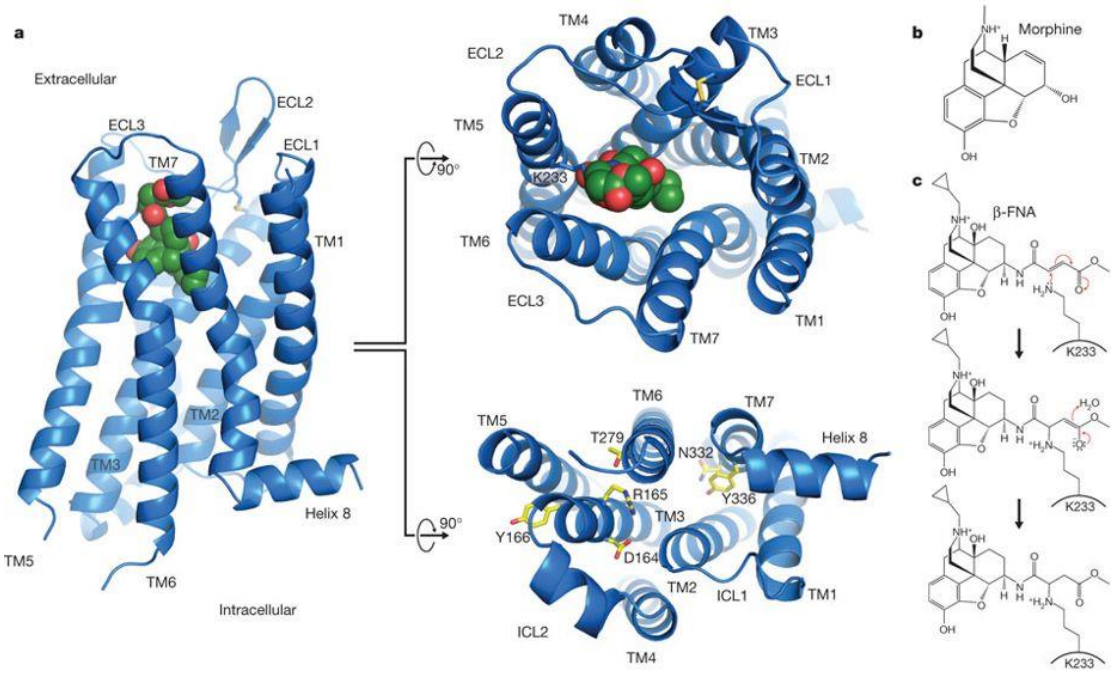


Figure 1.4[9]: (a) Crystal structure of MOR (μ-opioid receptor) observed from different angle: from within the membrane plane (left), from outside (top), from inside (bottom) The ligand (β-FNA) is shown in green spheres; (b) Chemical structure of morphine; (c) The chemical structure of β-FNA and the chemical reaction with the side chain of protein K233 in receptor.

There is still not enough scientific information in this area to precisely confirm how KOR and DOR works in human bodies. But animal experiments indicated that these receptors might have further medical potential.

In animal studies on κ-opioid receptor knockout mice, KOR binding is suggested to cause fewer side effects and potential for misuse than with MOR, but KOR seems to still be involved in the perception of visceral pain.[11] Animal behaviorists found it is very interesting that KOR can lead to stress and depression in mice, both acute[12] and long-term stress. [13]

As for DOR, it has a similar crystal structure as MOR and KOR, but it cannot be triggered as easily as MOR. Some experiments have been done to bring DOR agonists into the clinic; however, they still require improvements.[14]

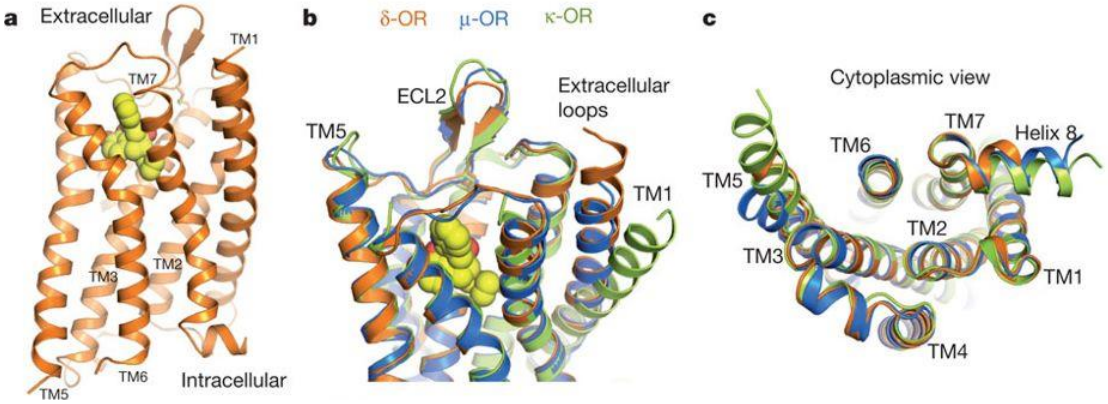
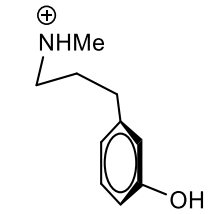


Figure 1.5[10]: (a): The mouse δ-OR, orange, exhibits a typical seven-pass transmembrane architecture common to other GPCRs. (b), (c), This fold is highly conserved among all three classical members of the opioid receptor family. δ-OR, orange; μ-OR, blue; κ-OR, green.

1.2.2 Opioids Pharmacophore

Opioids need to form chemical bonds in order to bind with the receptors. The phenolic OH group can be involved in H-bonding; van der Waals force and π-stacking are given of the phenol ring, and the ionic bond is from the tertiary amine. Synthetic derivatives without all these groups are less capable to bind with the opioid receptors. This fact indicates the skeletal pharmacophore of opioids [8] presented in Figure 1.6. Chemists and pharmacologists can design

and synthesize new chemical substances that lead to the development of new opioid medicines.[15]



Skeletal pharmacophore

Figure 1.6: Pharmacophore structures of opioids

Before binding with the opioid receptors in central nervous system (CNS), opioid molecules firstly need to cross the blood-brain barrier, which is a semipermeable membrane that can selectively separate the CNS from the circulating blood. Some molecules such as noroxymorphone cannot cross the blood-brain barrier, which makes it hard to present physiological characteristics of agonists in human bodies. Therefore, the methyl group in the skeletal pharmacophore of morphine is playing an important role in morphine chemical structure. [16]

1.3 Current Use of Opioids

1.3.1 Painkiller

Morphine is used as a painkiller, more specifically the agonist of mu opioid receptor. For now, it is a highly controlled medicine only for relieving severe or chronic pain on terminal diseases. For example, morphine sulfate, usually as immediate release tablets or blue-green solutions, are suggested to be used for severe pain in controlled lower dose. The reason for using lower dose since morphine was usually taken with other opioid medications, or the dose needs to be increased after general treatments.

Side effects like nausea, vomiting, constipation, lightheadedness, dizziness, drowsiness, or sweating may occur. Opioid agonists can also cause mental

depression, as well as physical and psychological addiction.

Besides, synthetic opioid drugs like fentanyl (**3**) shown in Figure 1.7 has potency at approximately 100 times higher than morphine. It only be used in the circumstances when other opioids pain medicines do not treat pain well enough. However, it can be produced in illicit laboratories without waiting for the harvest of poppy plants, which makes fentanyl a new threat to human health and social stability.

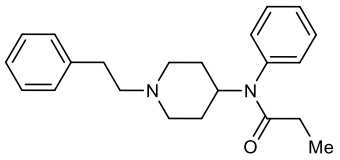


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Figure 1.7: Fentanyl (**3**)

1.3.2 Antagonists

Antagonists are pharmaceutical substances that bind to receptors, without triggering any biological activity. Regarding opioid antagonists, three of the most commonly used products are naloxone (**4**), naltrexone (**5**) and nalmefene (**6**). To access these MOR antagonists, semi-syntheses starting from noroxymorphone and originally from opiates such as thebaine (**7**) and oripavine (**8**) in Figure 1.8. They are in a similar structure with different *N*-substituted alkyl groups, which can help the compound to cross the blood-brain barrier by making the compound more lipophilic.[17]

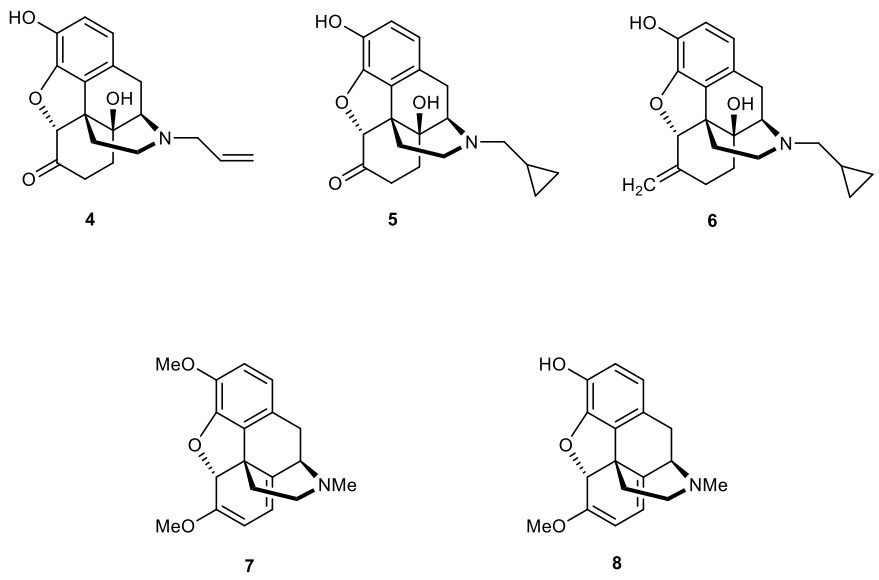


Figure 1.8: Naloxone (**4**), Naltrexone (**5**), Nalmefene (**6**), Thebaine (**7**), and Oripavine (**8**)

These antagonists are used to treat opioid overdose and alcohol dependence. Also, some opioid medications contain partial agonist/antagonist such as buprenorphine (**9**) and pentazocine (**10**) in Figure 1.9, whose functions are blocking MOR but activating the KOR.

Opioid antagonists typically reverse CNS depression, the effects leading to slower brain activities after taking opioids, in 30 to 60 minutes. For long-term administration to opioid addicts, it might take months or even years to overcome the effects of opioid withdrawal. However, even opioid antagonists can cause side effects such as liver damage, headache, anxiety, trouble sleeping, and blockage of the endorphin system.

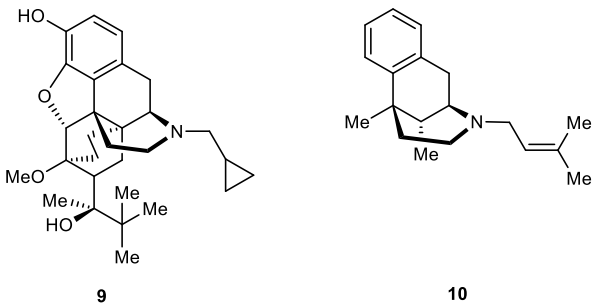


Figure 1.9: buprenorphine (**9**), and pentazocine (**10**)

1.3.3 Relieve Shortness of Breath and Acute Alcoholism

There are some other treatments that use opioids as enhancements in treating other diseases. One good example is decreasing the term of chronic breathlessness with lower dose of morphine than controlling pain. Codeine (**32**) and oxycodone (**27**) are also added in some cough medications and cold syrups. However, it is still not clear whether opioids are vital in these treatments, due to the lack of clinical experiences for using low-dose opioids for long-term respiratory diseases.[18]

Combined with Chinese traditional medical formula Xingnaojing, a herbal medication usually used in alcoholism treatments, the antagonist naloxone (**4**) can also be used in curing acute alcoholism.[19] Based on previous research and compared with Xingnaojing in clinical environment, naloxone (**4**) was proved to give majority contribution on decreasing Glasgow coma scale, which is a general index to measure the level of consciousness of patients with an acute brain injury.

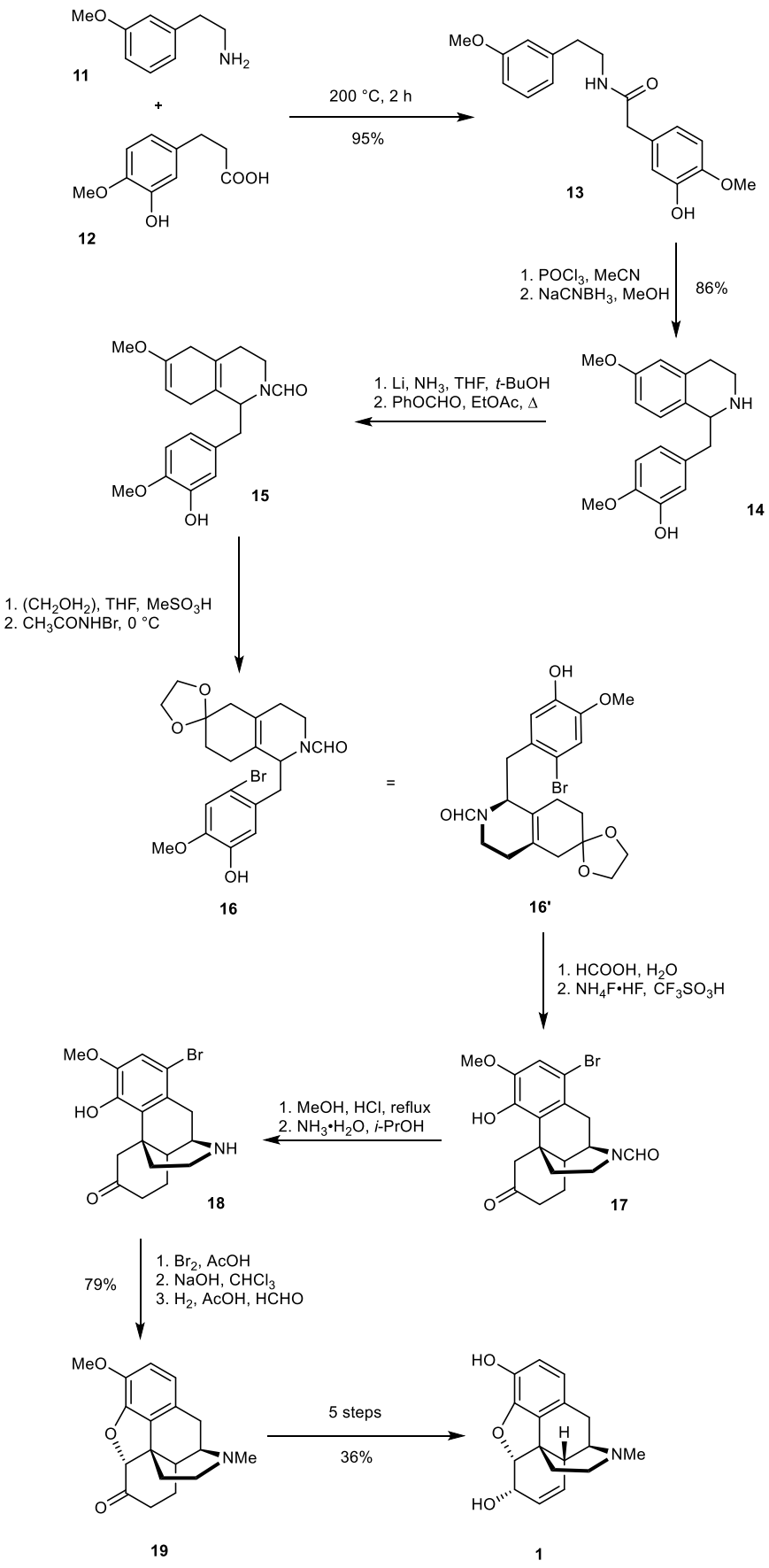
1.4 Chemical Syntheses of Opiate Alkaloids

The discovery of morphine arguably accelerated the development of organic chemistry and synthesis through the desire to determine its structure and to create more effective opiate medicines through total synthesis and semi-synthesis. Although the chemical total synthesis of morphine is highly challenging and impractical for obtaining morphine on scale, many academic groups have achieved it, resulting in many new developments in organic synthesis. In 1952, Gates [20]published the first total synthesis of morphine, which started with naphthalene-2,6-diol and gave morphine after 31 steps. It is obvious that this total synthesis had a very low overall yield, however, still is a milestone in this research area. Since that time, there have been various of great works from Ginsberg (1954), Grewe (1967), Evans (1982), Mulzer (1996), Magnus (2009), Fukuyama (2006, 2010), and Hudlicky (2007, 2009). These total syntheses will not be covered in this introduction. However, the one

exception is that of Rice and co-workers published in 1980, their biomimetic synthesis pathway has the highest possibility to be used in industry for its high efficiency and almost 30% overall yield. [21]

1.4.1 Rice's Total Synthesis Work

Rice's route published in 1980[22] was the shortest and the most efficient total synthesis of morphine (Scheme 1.1). The most important step was a Grewe cyclization, a biomimetic approach that led to **17**. The amidation of **11** and **12** to give **13** was achieved by heating at 200 °C for 2 hours, followed by a Bischler-Napieralski reaction and a sodium cyanoborohydride reduction gave the alkaloid **14**. Birch reduction and using phenyl formate for a *N*-formylation gave **15** as a starting material for the Grewe cyclization as they published in 1967. The reaction residue was treated with formic acid to give the ketone which was aiming reacted with $NH_4F \cdot HF$ in TfOH. Morphinan **17** was deformylated by heating at reflux in MeOH and HCl solution. Subsequent reductive amination gave amine **18**. After a bromination on the α-position of ketone and deprotonation of the phenol ring, the dihydrofuran ring was formed. A hydrogenation followed to remove the aryl bromide and formed dihydrocodeinone (**19**). This was used as an intermediate to morphine (**1**) and codeine in Rice's previous paper in 1977.[23]



Scheme 1.1: Total synthesis by K. C. Rice

1.4.2 Semi-synthesis of Opiate Medicines *via* Noroxymorphone

Although the total syntheses of morphine and related compounds inspired the development of new synthetic methods and strategies, they are largely academic exercises rather than truly practical manufacturing procedures that can be employed in industry. However, chemists have made significant accomplishments in semisynthetic routes to new opiate derivatives starting from other alkaloid starting materials obtained from poppy plants, such as thebaine (**7**) and oripavine (**8**). Compared with morphine (**1**), thebaine (**7**) and oripavine (**8**) are less abundant in the opium latex obtained from the poppy. Nevertheless, opiates derived from these compounds are therapeutically important compounds used in the clinic today.[24] For example, compounds such as naloxone (**4**), naltrexone (**5**), nalmefene (**6**) and their derivatives are effective opioid antagonists (Figure 1.10**)**.

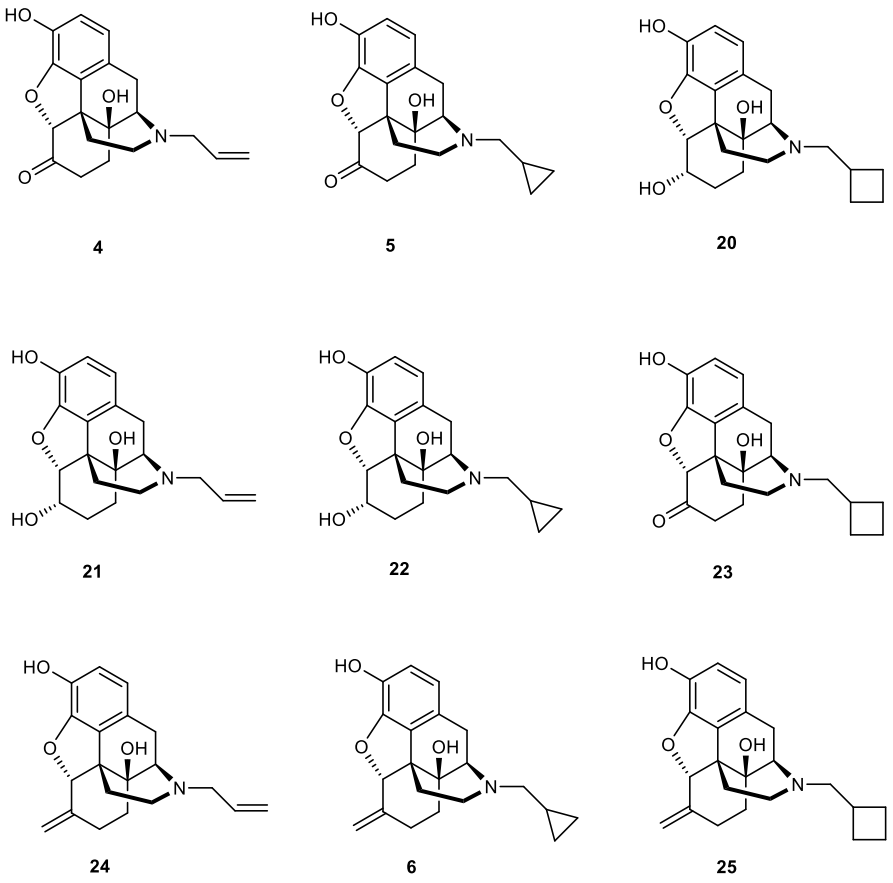


Figure 1.10: the noroxymorphone derivatives (**4-6**), **20-25**

An important intermediate in the synthesis of these opiates is noroxymorphone (**26**) in Figure 1.11. Noroxymorphone itself is not as effective as many other agonists that bind to the μ-opioid receptor. This phenomenon can be explained by consideration of the blood-brain barrier. The secondary amine of noroxymorphone renders it too polar to cross the blood-brain barrier easily compared with tertiary amine derivatives which are more lipophilic as a result of the *N*-alkyl groups.

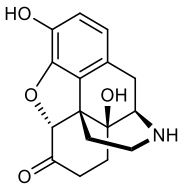


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Figure 1.11: Noroxymorphone (**26**)

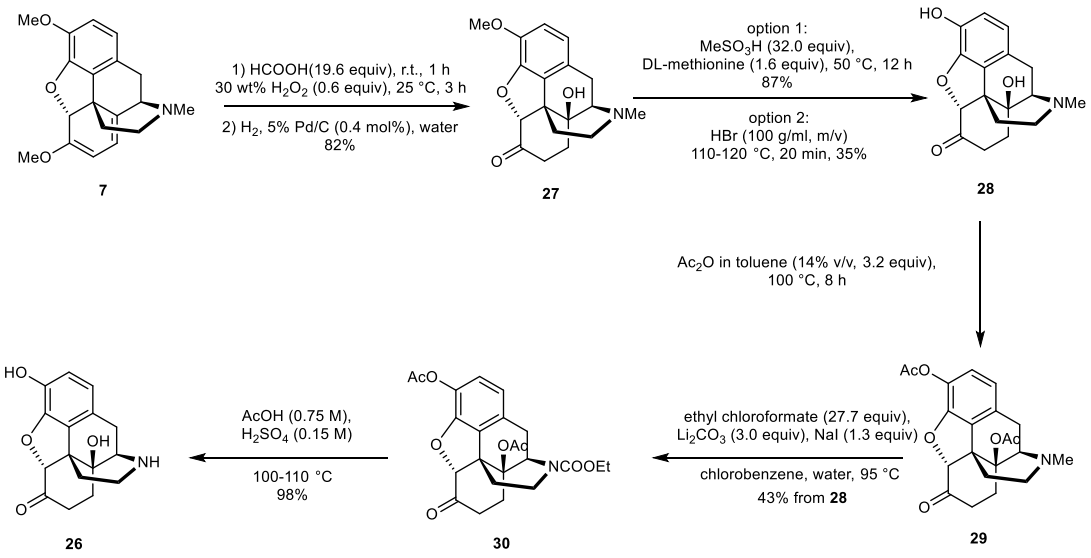
1.4.3 Synthesis of Noroxymorphone

From Thebaine

Compared with morphine (**1**), thebaine (**7**) is a minor constituent of the mixture of alkaloids obtained from the poppy plant. Although thebaine (**7**) does not have favourable bioactivity, it is an important starting material in the production of noroxymorphone (**26**), an important intermediate in the synthesis of several opiate medicines.

The synthesis of noroxymorphone (**26**) from thebaine (**7**) proceeds via oxycodone (**27**) in many literature routes.[25] [26] [27] [28] For example, one way to obtain oxycodone (**27**) is by treating thebaine (**7**) with performic acid, followed by a reduction with palladium on carbon and hydrogen gas (Scheme 1.2).[28] To achieve *O*-demethylation of oxycodone (**27**) to oxymorphone (**28**), **27** was heated with methanesulfonic acid and DL-methionine to give **28** in 87% yield. This demethylation can also be achieved with hydrogen bromide as described by Weiss in 1955.[29] Protection of the hydroxyl groups of oxymorphone (**28**) was accomplished by reaction with acetic anhydride in toluene to give 3,14-diacetyloxymorphone (**29**). Treatment of crude **29** with ethyl

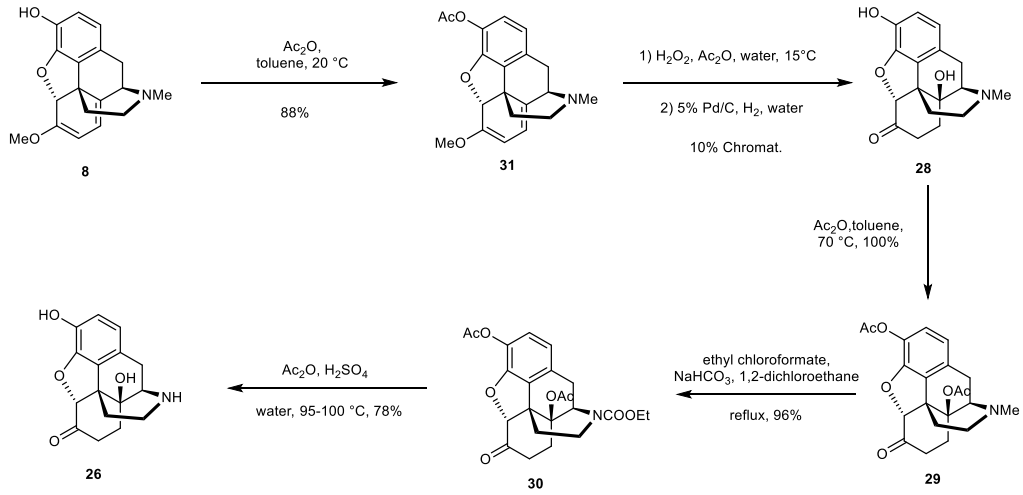
chloroformate, NaI and Li_2CO_3 in a mixture of chlorobenzene and water at 95-105 °C for 12 hours resulted in *N*-demethylation and carbamate formation to give **30**. Finally, noroxymorphone (**26**) was obtained after deprotection of **30** with sulfuric acid and acetic acid at 100 to 110 °C.[28]



Scheme 1.2: Synthesis of noroxymorphone from thebaine (**7**) *via* oxycodone (**27**)

From Oripavine

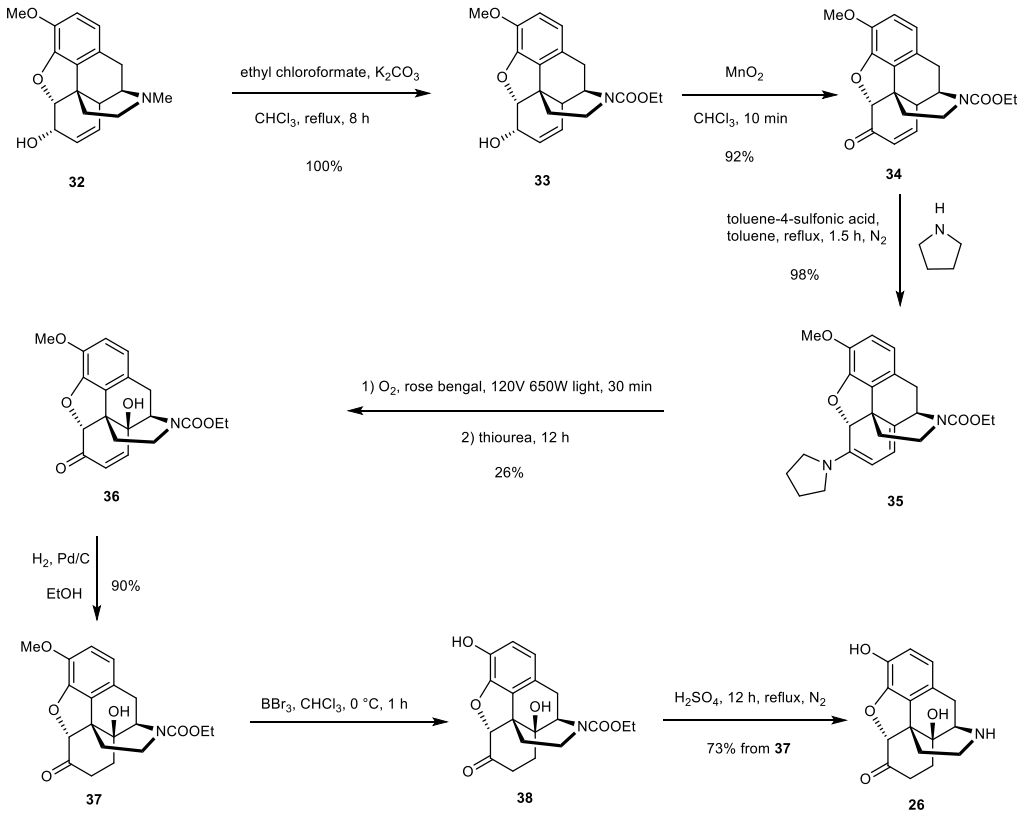
Noroxymorphone can also be synthesized from oripavine (**8**).[30] As shown in Scheme 1.3, mono-protection of oripavine (**8**) can be achieved using acetic anhydride in toluene. The resulting compound **31** can be directly reacted with hydrogen peroxide aqueous solution dropwise to install the C14 hydroxyl group. Acetyl anhydride is employed as a solvent. Palladium on carbon and hydrogen gas were added into the mixture to reduce the resulting enone to give oxymorphone (**28**). Diacetylation of **28** gives 3,14-diacetyloxymorphone (**29**), which reacts with ethyl chloroformate and Na_2CO_3 in dichloroethane to give **30**. Noroxymorphone (**26**) is obtained after deprotection of **30** in boiling water.



Scheme 1.3: Patent work WO 2017/207519, 2017, A1[30]

From Codeine

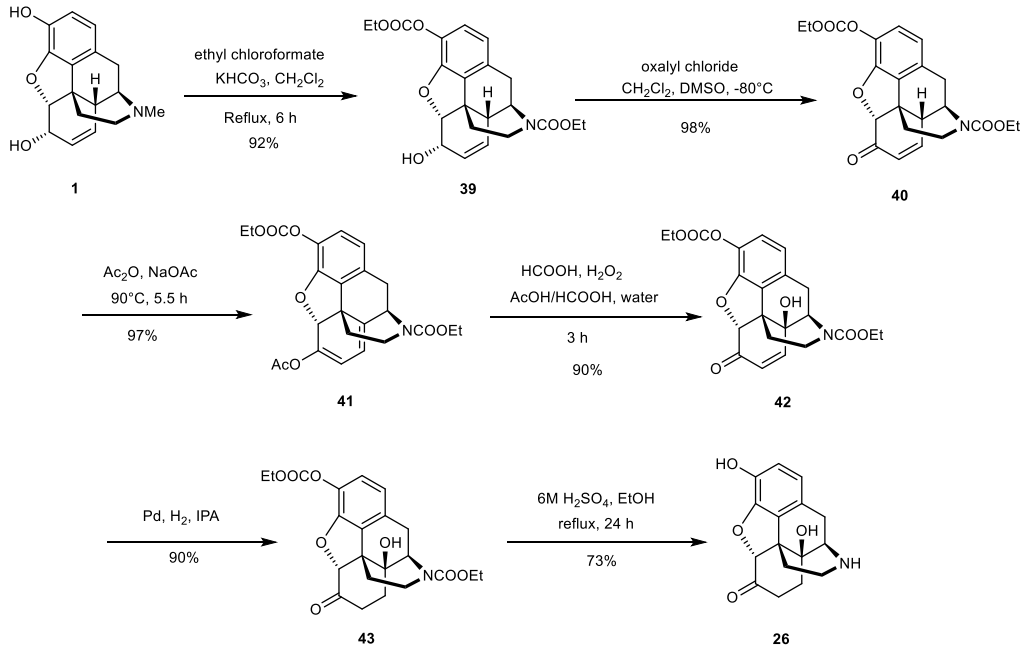
Schwartz and co-workers synthesized noroxymorphone (**26**) from codeine (**32**) in 1981.[31] The seven-step synthesis shown in Scheme 1.4 starts with the *N*-demethylation on codeine (**32**) using ethyl chloroformate and K_2CO_3. After refluxing in chloroform for 8 hours, the resulting *N*-substituted norcodeine **33** was treated with MnO_2 in chloroform to obtain the oxidized product **34**. The formation of diene is catalysed by toluene-4-sulfonic acid and pyrrolidine to give substance **35** after the treatment of oxygen and thiourea, photochemically generated by Rose Bengal sensitization for 30 minutes. This reaction only yields in 6% directly; however, further recovery and transformation can give desired compound **36** with a combined 26% yield. The reduction is achieved by treating with hydrogen and Pd/C, following by a demethylation reaction on aromatic methoxy group to give *N*-ethoxycarbonyl compound **38**. The crude product **38** can be directly employed in the deprotection to give noroxymorphone (**26**) in 73% yield from **37**.



Scheme 1.4: Route from codeine (**32**) to noroxymorphone (**26**)

1.4.4 Patent WO2015011131 from Morphine to Noroxymorphone

In this patent[32] presented in Scheme 1.5, the demethylation and protection is achieved by using ethyl chloroformate and K_2CO_3 in CH_2Cl_2 to give **39** in 92% yield after 6 hours. The resulting compound **39** is oxidized to ketone **40** by a Swern oxidation at -80 °C. The ketone **40** is treated with acetic anhydride and EtOAc at 90 °C for 5.5 hours, giving dienol acetate **41** in 97% yield. The C14 oxidation is achieved by adding **41** to performic acid in a mixture of organic acid (HCOOH: AcOH = 3:1) at room temperature for 3 hours. The resulting **42** is added to a reduction led by palladium on carbon and hydrogen gas to obtain **43** in 90% yield. The final step was the *O,N*-deprotection of **43** in refluxing EtOH and 6 M sulfuric acid, which finally give noroxymorphone (**26**) in 64% overall yield from morphine (**1**).



Scheme 1.5: Route from WO 2015/011131 2015, A1[32]

1.4.5 Conclusion

Noroxymorphone (**26**) is an important intermediate in the synthesis of a variety of opiate medicines. Although current manufacturing routes to noroxymorphone employ thebaine (**7**) or oripavine (**8**) as the starting materials, it can also be produced starting from codeine (**32**) or morphine (**1**). Since

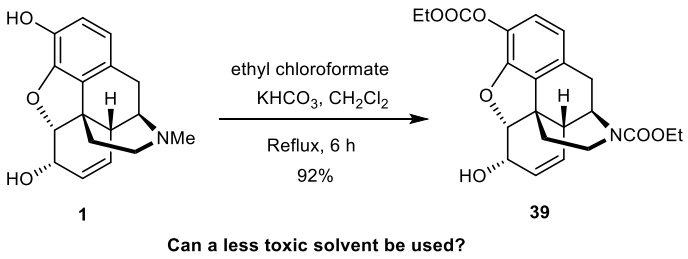
morphine is the major constituent of the mixture of alkaloids obtained from the poppy plant, and therefore of lower cost, there is a financial incentive to prepare noroxymorphone from morphine rather than thebaine (**7**) or oripavine (**8**). Recent patents describing the synthesis of noroxymorphone from morphine show this approach to have promise on laboratory scale. Increasing the efficiency of this overall transformation and translation into manufacturing scale is therefore a worthwhile objective.

2. Synthesis Noroxymorphone from Morphine

2.1 Aims and Objectives

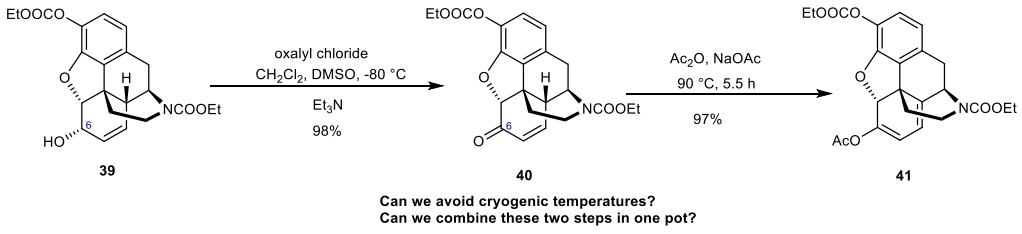
Using morphine, the major constituent isolated from opium, as the starting material may provide a more economical process to produce noroxymorphone (**26**) rather than using minor opium constituents such as thebaine (**7**) or oripavine (**8**). In search for a better approach to noroxymorphone (**26**) from morphine (**1**), the patent WO2015011131 (EP3024835B1) presented in Scheme 1.5 looked to be a good starting point.[32] However, it takes 6 steps in total to obtain noroxymorphone from morphine according to this patent route, compared to 5 steps when starting with thebaine (**7**) or oripavine (**8**). The reported 64% overall yield is reasonable, but several steps in this route could be improved with better conditions that may be more suitable for industrial application.

One example is the use of dichloromethane employed in the *O*,*N*-protection from WO2015011131 (EP3024835B1) as shown in Scheme 2.1. Dichloromethane is a toxic solvent, classified as Class 2 according to the European Medicines Agency's Q3C (R4) Guideline for Residual Solvents. However, Class 2 solvents are normally non-genotoxic animal carcinogens or possibly show irreversible toxicity such as neurotoxicity or teratogenicity. Dichloromethane has a low boiling point and a reasonable tolerable residual concentration limit (600 ppm) according to the Q3C (R4) Guideline. However, there are much better potential solvents for this reaction such as acetone and EtOAc (Class 3 solvents), which are less toxic and cheaper with higher residual concentration limits (up to 5000 ppm) in the resulting products.



Scheme 2.1: *O*, *N*-protection in WO2015011131 (EP3024835B1)

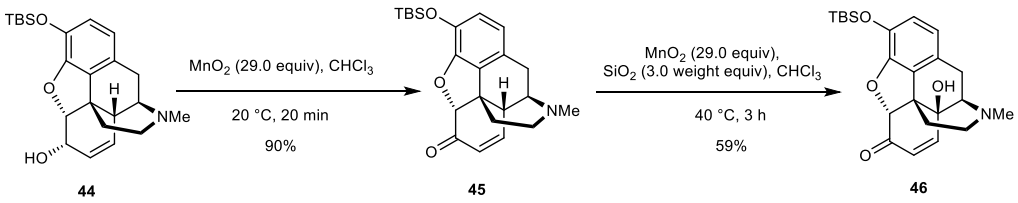
For the oxidation of alcohol **39** to the ketone **40** a Swern oxidation was employed which uses oxalyl chloride, a toxic and corrosive reagent that is also sensitive to water. A Swern oxidation requires low-temperature conditions (*ca.* –80 °C) to minimize side reactions, which can lead to technical difficulties and additional costs to reach this temperature in an industrial application. An alternative to the Swern oxidation is the Albright-Goldman oxidation, which uses acetic anhydride to activate DMSO instead of oxalyl chloride and works at ambient temperature. [33] In addition, the same reagent acetic anhydride is also used in the next step to form the dienol acetate **41** (Scheme 2.2). After the oxidation of **39** to give **40** is complete, raising the temperature to 90 °C and adding sodium acetate could potentially allow these two steps to be combined into a one-pot procedure, further increasing the efficiency of the route.



Scheme 2.2: route from **39** to **41** in WO2015011131 (EP3024835B1)

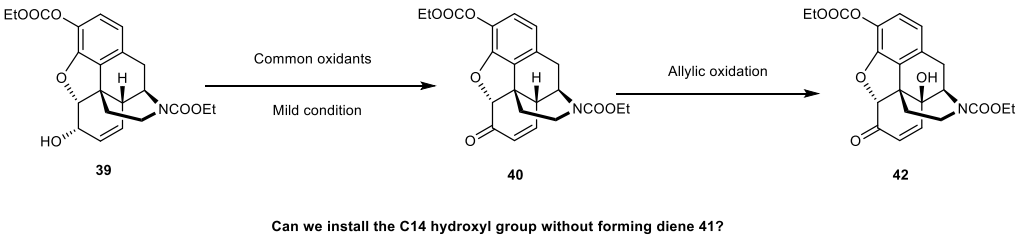
Compound **41** is then used as a substrate to install the C14 hydroxyl group by treatment with performic acid generated *in situ* from formic acid and hydrogen peroxide (Scheme 1.5). However, there are other potential methods to install the C14 hydroxyl group. For example, in 1992, the Sainsbury group reported the overall conversion of TBS-protected morphine (**44**) into tertiary

alcohol **46** using manganese (IV) oxide (Scheme 2.3).[34] First, oxidation of the allylic alcohol **44** into enone **45** was achieved using excess MnO_2 in $CHCl_3$ at room temperature. Next, addition of further MnO_2 along with 3 weight equivalents of silica gel followed by heating at 40 °C led to allylic oxidation to install the C14 hydroxyl group, giving **46** in 59% yield from **45**.



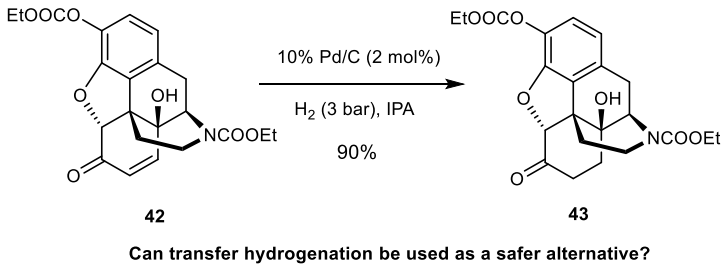
Scheme 2.3: Sainsbury's allylic oxidation to install the C14 hydroxyl group

Apart from the protecting groups on the phenol and the amine, compounds **44**, **45** and **46** are quite similar to those of **39**, **40** and **42**, respectively, which suggested that it might be possible to convert **40** or even **39** to give **42**, without the intermediary of dienol acetate **41** (Scheme 2.4). Therefore, the overall step-count would be decreased from 6 to 5, which would be advantageous.



Scheme 2.4: Proposed oxidation route to install the C14 hydroxyl group

In the patent route, reduction of enone **42** to give ketone **43** is achieved using palladium catalysis and hydrogen gas (Scheme 2.5). This reaction is efficient and suitable for industrial synthesis; however, handling large quantities of hydrogen gas is potentially hazardous and explosive, particularly when using pyrophoric Pd/C or under high pressure environments.



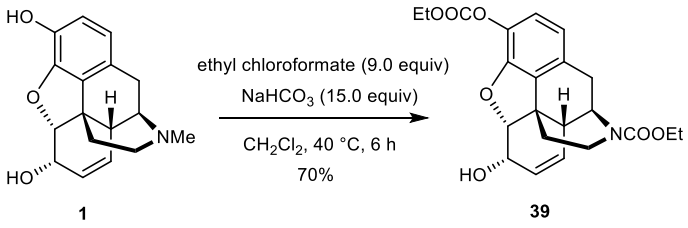
Scheme 2.5: Hydrogenation in WO2015011131 (EP3024835B1)

To avoid these safety problems, transfer hydrogenation could potentially be applied to avoid hydrogen gas. Handling liquid reagents is usually easier and safer than handling hydrogen gas on an industrial scale.

2.2 Result and Discussion

2.2.1 *O*, *N*-Protection

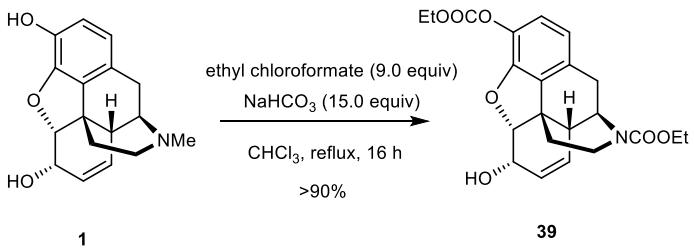
Dichloromethane was employed in the demethylation/protection of morphine according to patent WO2015011131 (EP3024835B1). However, several reactions replicating the patent route to form **39** in our lab did not give yields as good as the reported 92% in the patent. One such result shown in Scheme 2.6 only gave desired product **39** in 70% yield.



Scheme 2.6: Preparation of **39** in dichloromethane by Dmitry Gorbachev in the Lam group

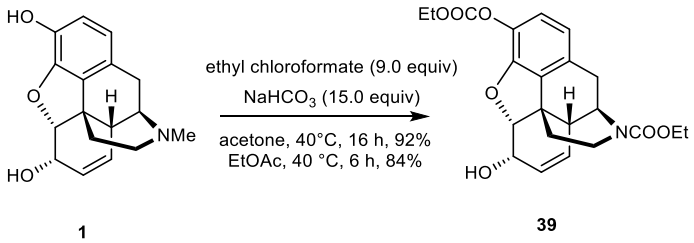
To enhance the reactivity and yield in this reaction, Dr. Rebecca. E. Ruscoe in the Lam group attempted to use chloroform as the solvent to reach a higher temperature under reflux (Scheme 2.7). This procedure gave **39** in over 90% yield on gram scale and became a reliable general procedure to make starting

material **39** for further reactions in our lab.



Scheme 2.7: *O,N*-protection in chloroform carried out by Dr. Rebecca. E. Ruscoe

However, considering the residual concentration limits in medical product of chloroform is 60 ppm, less toxic and safer solvents such as acetone and EtOAc would be more applicable for medical industry. [35]Both acetone and EtOAc were employed in the preparation of **39** as shown in Scheme 2.8. These two solvents, especially acetone, gave the desired product **39** in excellent yields under mild condition.

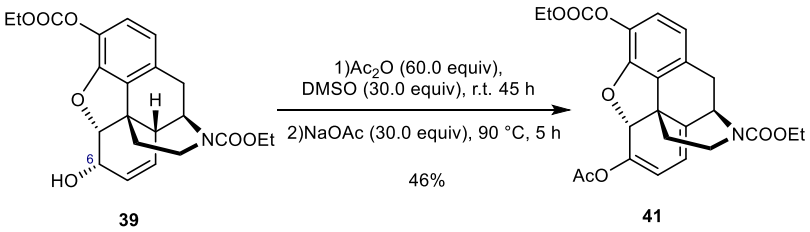


Scheme 2.8: *O,N*-protection in safer solvents to obtain **39**

2.2.2 One-Pot Albright-Goldman Oxidation and Diene Formation

In WO2015011131 (EP3024835B1), the inventors used a Swern oxidation to convert allylic alcohol **39** into ketone **40**. In the Swern oxidation and related reactions, DMSO reacts with oxalyl chloride or another activating agent to form a sulfonium ion, which can then react with **39** in the presence of a base to form ketone **40**. We wondered whether acetic anhydride, the reactant used in the next step to synthesize diene derivative **41** from **40**, can be employed as an activating agent for DMSO to achieve alcohol oxidation. In fact, this reagent

combination is already known in the literature as the Albright-Goldman oxidation,[33] and therefore this could potentially enable subsequent formation of the dienol acetate **41** in the pot.



39 **41**

Scheme 2.9: Albright-Goldman oxidation to obtain **41** in one pot by Dmitry Gorbachev

Presented in Scheme 2.9, my repetition of an Albright-Goldman oxidation of alcohol **39** which was contributed by Dmitry Gorbachev in the Lam group, the resulted ketone **40** can be detected by TLC analysis. After 45 hours, all of the alcohol **39** was consumed and then NaOAc was added into the flask. After heating at 90 °C for 5 hours, the desired dienol acetate **41** was obtained in 46% yield.

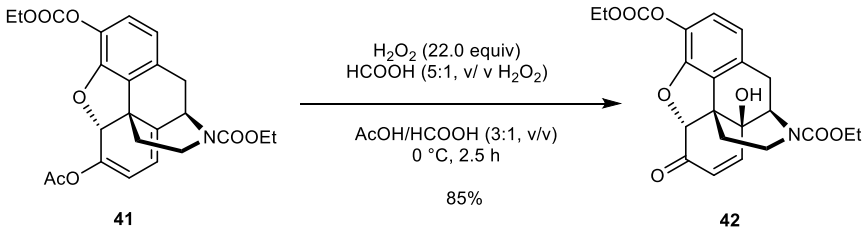
The Albright-Goldman oxidation using acetic anhydride was successful and could be combined to a one-pot process, especially given no requirement of cryogenic temperatures, which can be much better for application of the process from **39** to **41** in industrial circumstances. However, the yield is poor compared to the 95% yield over 2 steps as shown in the patent.

2.2.3 C14 Oxidation

The C14 oxidation in patent WO2015011131 (EP3024835B1) employed formic acid or acetic acid in a range of ratios between 1:20 to 20:1, organic acid: hydrogen peroxide. To reduce the amount of water used *via* the hydrogen peroxide and waste formed, which can make the reaction more economical and ecological friendly, hydrogen peroxide 50 wt.% was used to reduce the volume added for the same equivalents of oxidant added into the reaction. It was deduced experimentally that a 5:1 ratio (by volume) of formic acid to hydrogen

peroxide performed best. The peracid was easily prepared by the combination of formic acid and hydrogen peroxide at 0 °C which could be used in the C14 oxidation.

The resulting product **42** was formed in 85% yield from dienol acetate **41** (Scheme 2.10). However, the reaction gave no desired product when only acetic acid was used in the formation of peracid and as the solvent. The consequence on changing acid indicated that performic acid is a vital reactant in this C14 oxidation from dienol acetate **41** to **42**.

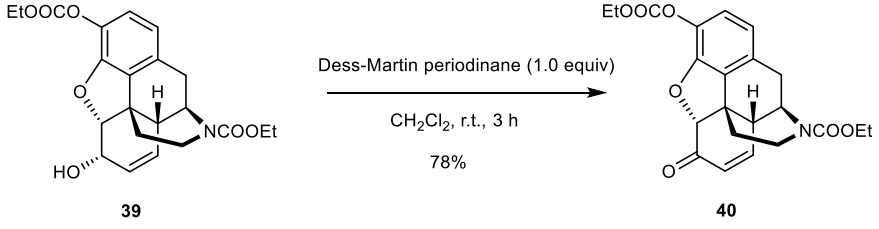


Scheme 2.10: C14 Oxidation

2.2.4 Oxidation Approaches to Install C14 Hydroxyl Group

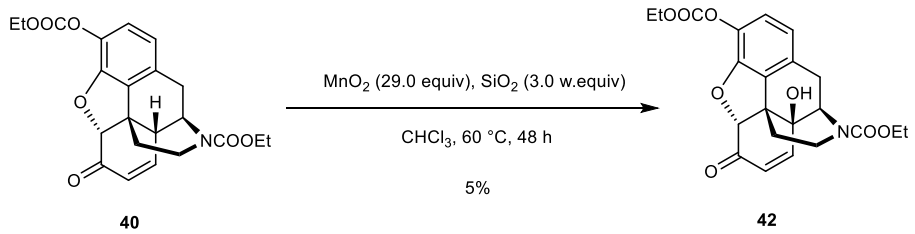
Although we have described a more efficient way to prepare dienol acetate **41**, a potentially more direct route is to oxidize **39** or **40** directly into **42**, which does not go through **41**. To test the feasibility of these approaches, both **39** and **40** were required.

Thanks to the previous work shown in Scheme 2.11 by Dr. Rebecca. E. Ruscoe in the Lam group, Dess-Martin periodinane (DMP) can be employed in the oxidation of **39** to give **40** at room temperature in yields up to 78% providing a convenient procedure to prepare **40** in the laboratory. However, Dess-Martin periodinane is more expensive than oxalyl chloride as an oxidant, and totally impractical for industrial use due to the difficulty of purification.



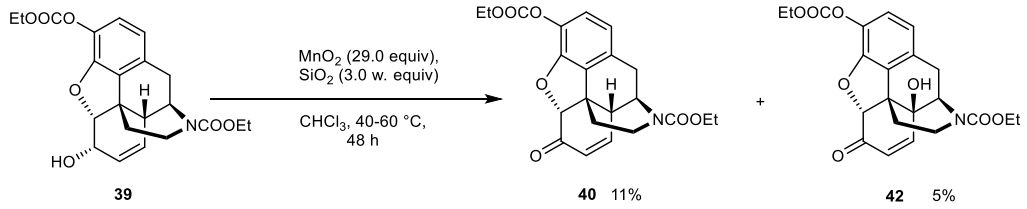
Scheme 2.11: Dess-Martin periodinane oxidation

Conversion of **40** into **42** by an allylic oxidation with MnO_2 in the presence of silica gel was attempted as described by the Sainsbury group.[34] Unfortunately, trace **42** was detected as shown in Scheme 2.12, only 10% of the mass recovered in the crude material which was a 1:1 mixture of **40** and **42** measured *via* crude ^{1}H NMR spectroscopy.



Scheme 2.12: Allylic oxidation to obtain **42** from **40**

For the attempted direct oxidation of **39** to **42**, 29 equivalents of MnO_2 and 3 weight equivalents of silica gel were used in $CHCl_3$ at 40-60 °C (Scheme 2.13). However, after purification by flash column chromatography or prep-TLC, only 5% of **42** was formed along with 11% of the intermediate ketone **40**.



Scheme 2.13: Direct oxidation of **39** to **42**

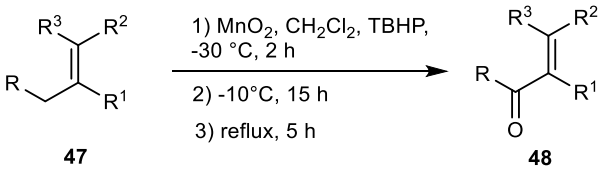
Unfortunately, not only was the yield poor but there were also difficulties in purification as repeated filtrations through silica or celite pads were acquired to remove excess MnO_2. An improved workup procedure is to dissolve MnO_2 using a mixed solution of acetic acid and hydrogen peroxide, which means filtration can be avoided during workup procedure. However, even though this direct oxidation can fully consume the starting material **39**, **42** was not obtained in more than 5% yield.

Although 29 equivalents of MnO_2 as the oxidant is not an ideal approach,

this section indicates that allylic oxidation can be achieved on ethoxycarbonyl-protected derivatives **39** and **40** ultimately forming **42**.

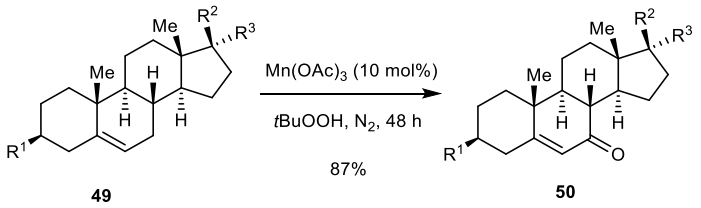
Metal-Catalysed Approaches

In Stefano Serra's allylic oxidation work (Scheme 2.14) alkenes **47** can be oxidized to enones **48** by catalytic manganese dioxide and stoichiometric *tert*-butyl hydrogen peroxide (TBHP). [36]



Scheme 2.14: Stefano Serra's allylic oxidation

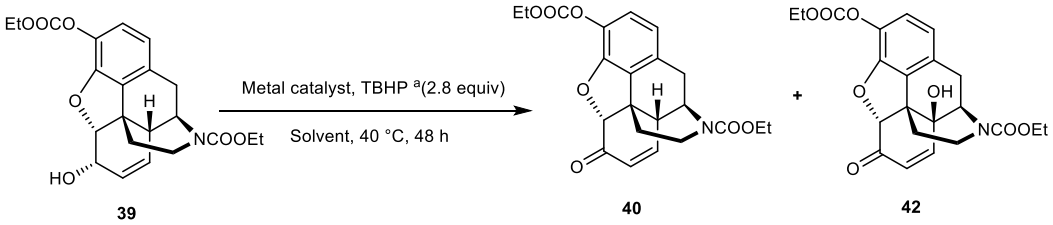
Manganese (III) acetate can also be applied on allylic oxidation with various of successful examples with TBHP at room temperature (Scheme 2.15) shown by Tony and co-workers.[37]



Scheme 2.15: Allylic Oxidation on cholesteryl acetate derivative **49** to 7-ketone **50**

Therefore, reactions were tested in entries (**1-4**) using **39** as the starting material as shown below in Table 2.1.

Table 2.1: Reaction conditions with TBHP



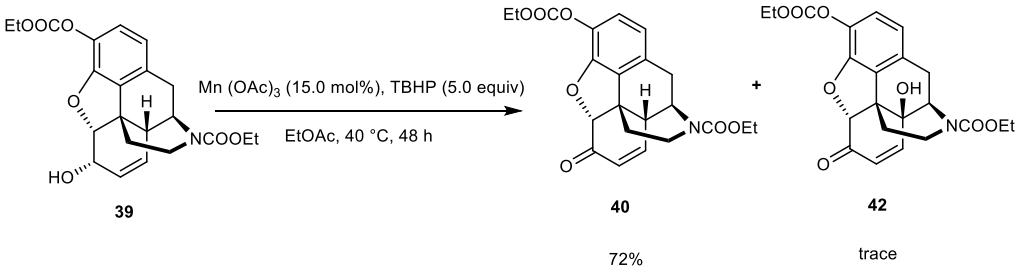
Entry	Metal Catalyst	Cat. Amount	Solvent	**39**	**40**	**42**[b]
1	**MnO_2**	**50 mol%**	**EtOAc**	**0**	**88%**[c]	**trace**
2	**$Mn(OAc)_3$**	**10 mol%**	**EtOAc**	**0**	**48%** [c]	**trace**
3	**$MnSO_4$**	**20 mol%**	**EtOAc**	**>99%** [c]	**trace**	**0**
4	**$Fe(acac)_3$**	**10 mol%**	**MeCN**	**55%** [c]	**34%** [c]	**0**

a) Same metal catalysts were also used in entries with 30 wt.% aq hydrogen peroxide solution as oxidant, gave no better result.

b) Trace **42** was detected by TLC analysis and Mass spectrometry.

c) Determined by crude ^{1}H NMR spectroscopy.

Similar conditions to entry **2** with 5 equivalents of TBHP were employed to give **40** in 72% yield (Scheme 2.16), but only trace **42** was detected by mass spectrometry.



Scheme 2.16: TBHP (5 equiv) allylic oxidation

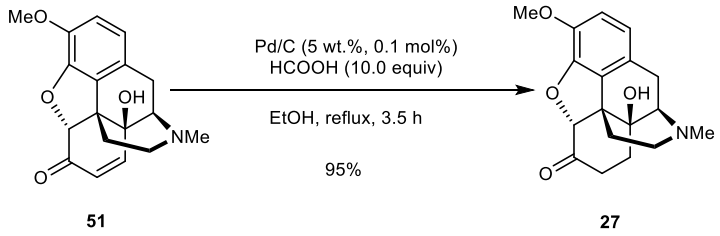
In conclusion, we investigated the direct conversion of either **39** or **40** into **42** with various oxidants and conditions. However, none of these attempts gave desired product **42** in good yield. Therefore, the original C14 oxidation *via*

dienol acetate **41** that is already described in section 2.2.3 remained the method of choice.

2.2.5 Reduction of Enone and Deprotection of Ethoxycarbonyl Groups

Large amount of hydrogen gas can be explosive in industrial scales, especially in contact with activated palladium on carbon. To avoid this issue and additional costs in controlling the pressure and utilization of hydrogen gas, formic acid was applied as a hydrogen transfer reagent to facilitate the reduction.

The hydrogen transfer reagent was used as shown in Scheme 2.17 for the reduction of 14-hydroxycodeine (**51**) to oxycodone (**27**) in 95% yield. The amount of activated palladium on carbon (5wt.%) was decreased from 50 mol% to 0.1 mol% to achieve this formal reduction. MeOH can also be employed as the solvent to give oxycodone (**27**) in 51% yield, which indicates that the efficiency of hydrogenation may be related to the reaction temperature due to the lower boiling point of MeOH than that of EtOH.

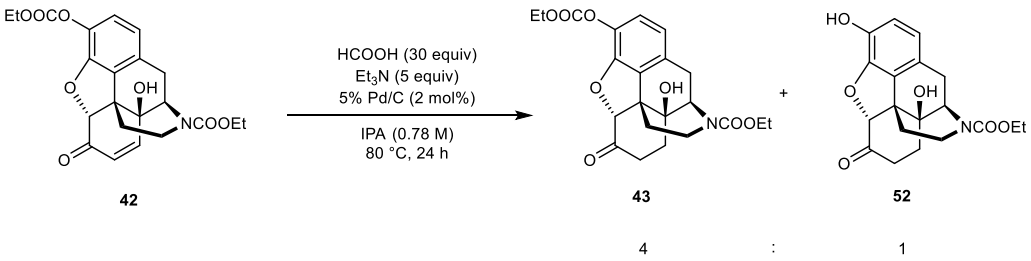


51 **27**

Scheme 2.17: Hydrogenation of 14-hydroxycodeine (**51**)

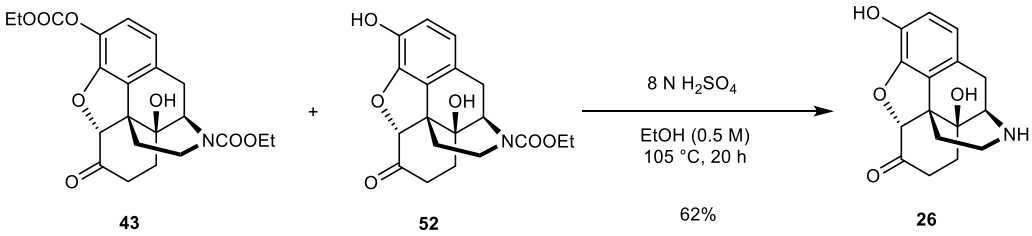
However, conditions that worked on 14-hydroxycodeine (**51**) met some difficulties on **42**, potentially because of the ethoxycarbonyl protecting group reducing the reactivity of the compounds. Dmitry Gorbachev in the Lam group applied similar condition as shown in Scheme 2.18 using more palladium on carbon (2 mol%) and formic acid in reduction along with triethyl amine to form triethyl ammonium formate, a more reactive hydrogen transfer reagent. The reaction gave both desired product **43** and its mono-deprotected compound **52** with a ratio of 4:1, measured by crude NMR spectra. In my repeated

experiment under same condition, the amount of side product **52** can be reduced by adding formic acid to pre-cooled triethyl amine in an ice bath to prevent the sudden exotherm of neutralization. However, the crude mixture of **43** and **52** can be used directly in the following deprotection as both compounds are deprotected to form the desired product, noroxymorphone (**26**).



Scheme 2.18: Reduction carried out by Dmitry Gorbachev in the Lam group

After the reduction, crude mixture of both **43** and **52** were added in a deprotection using 0.5 M EtOH with 8N (4M) H_2SO_4, and the resulting mixture was stirred at 105 °C for 20 hours then neutralized to give a brown precipitate. Thanks to further purification from Dmitry Gorbachev, this precipitate was collected by filtration and washed with cold water, to give crude noroxymorphone (**26**) as a brown solid in 62% yield. (Scheme 2.19)

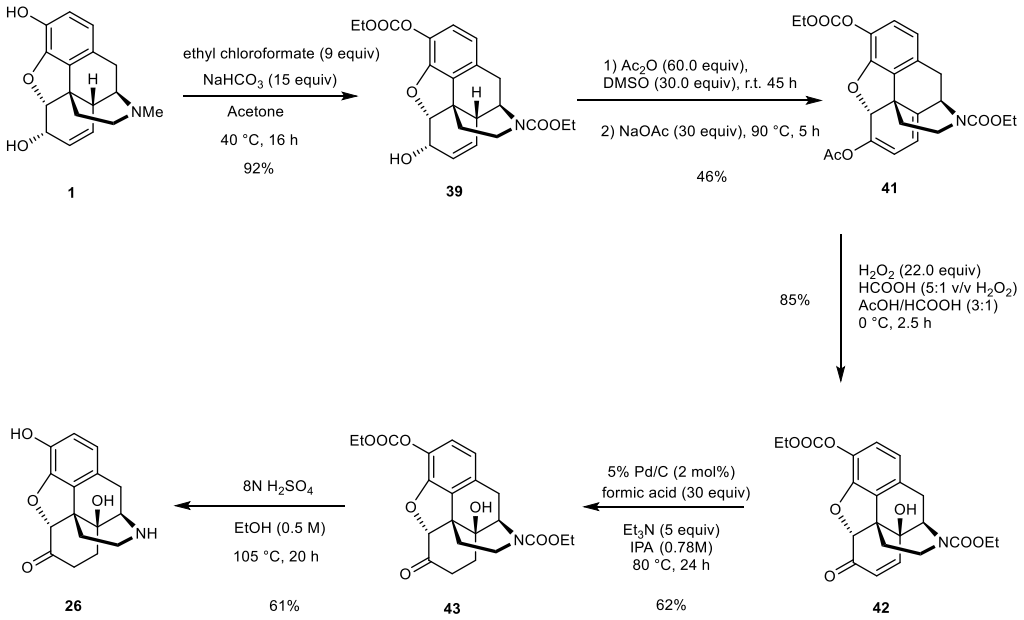


Scheme 2.19: Deprotection of the crude mixture of **43** and **52**

2.3 Conclusion

The formal synthesis route of noroxymorphone is presented in Scheme 2.20. The demethylation and *O,N*-protection of morphine with ethyl chloroformate in acetone gave **39** in 92% yield. The Albright-Goldman oxidation using acetic anhydride to activate DMSO is combined with the acetylation of the alcohol to give dienol acetate **41** in 46% yield. The resulting dienol acetate **41** is treated

with performic acid to install the C14 hydroxyl group and gives the desired product **42** in an 85% yield. Triethyl ammonium formate is employed as a hydrogen transfer reagent for the 1,4-reduction with 2 mol% of activated palladium on carbon (5wt.%), to obtain **43** which finally gives noroxymorphone (**26**) in a 14% overall yield after deprotection.



Scheme 2.20: The formal synthesis route from morphine to noroxymorphone

3. *N*-Alkylation of Noroxymorphone

3.1 *N*-Substituted Opiates

The *N*-substituted antagonists are a huge family of opioid derivatives. These compounds play vital roles in current clinical treatments (Figure 3.1). Naloxone (**4**) injection is used to treat opioid overdose in an emergency and to help diagnose whether a person has had an overdose of an opioid. Naltrexone (**5**) can help suppress opioid and alcohol addictions. These two antagonists block μ-opioid receptor (MOR) to prevent effects of opioids such as depression and euphoria.[38] Nalbuphine (**20**) is an agonist-antagonist primarily a KOR agonist and partial MOR antagonist, being used as a common opioid painkiller.[39] Buprenorphine (**9**) is usually used to treat addiction with its oral forms but can present as an MOR agonist in the injection form.[40]

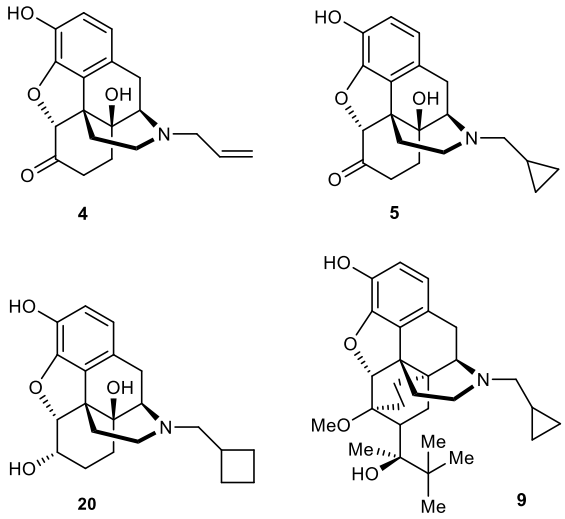


Figure 3.1: MOR antagonists: naloxone (**4**), naltrexone (**5**), nalbuphine (**20**), buprenorphine (**9**)

Recently, the consumption of these medications is increasing leading to a growing number of opiate addiction cases.[1] The industrial production of these derivatives are often still using thebaine (**7**) or oripavine (**8**) as their raw materials, which are the minority ingredients in natural poppy extractions.

Since naloxone (**4**) was invented in 1960s, no other opioid antagonists

have been developed which have replaced its common usage in medicine. On the contrary, further opiates have been developed for pain relief however many have addictive properties.

In 2016, 42,249 people died of opioid overdose in the United States, which sharply increase to 70,237 recorded deaths in 2017.[41] This significant rise can be attributed to the rapid diffusion of illicitly fentanyl and its highly potent synthetic derivatives.

3.2 Fentanyl and Its Derivatives

Fentanyl (**3**) is a synthetic opioid first synthesized by Belgian chemist Dr. Paul Janssen in 1960. It was around 100 times more potent than morphine with LD50 of 0.03 mg/kg in monkeys. Fentanyl has a similar binding affinity (1.346 nM) to MOR as morphine (1.168 nM), but is more lipophilic (4.28 log P) than morphine (1.07 log P).[42] It also takes less than 10 min for fentanyl to start onset and analgesic effects to be felt. Meanwhile, fentanyl is distributed to other tissues in large doses and has a longer duration which required multiple doses of naloxone (**4**) to reverse its effects.

After the invention, fentanyl (**3**) was used in clinics to replace morphine during 1970s to 1980s, until the misuse and abuse became an unignorable issue, which finally made fentanyl a schedule II prescription drug. [43]

However, the illicit use and production of fentanyl (**3**) and its derivatives (Figure 3.2) like carfentanil (**56**), a chemical that is 100 times potent than fentanyl, is currently a significant societal problem. In 2017, the Centers for Disease Control in the US suggested approximately 72,000 Americans died from drug overdoses. The death toll is higher than the peak yearly death totals from HIV, car crashes, or gun deaths.

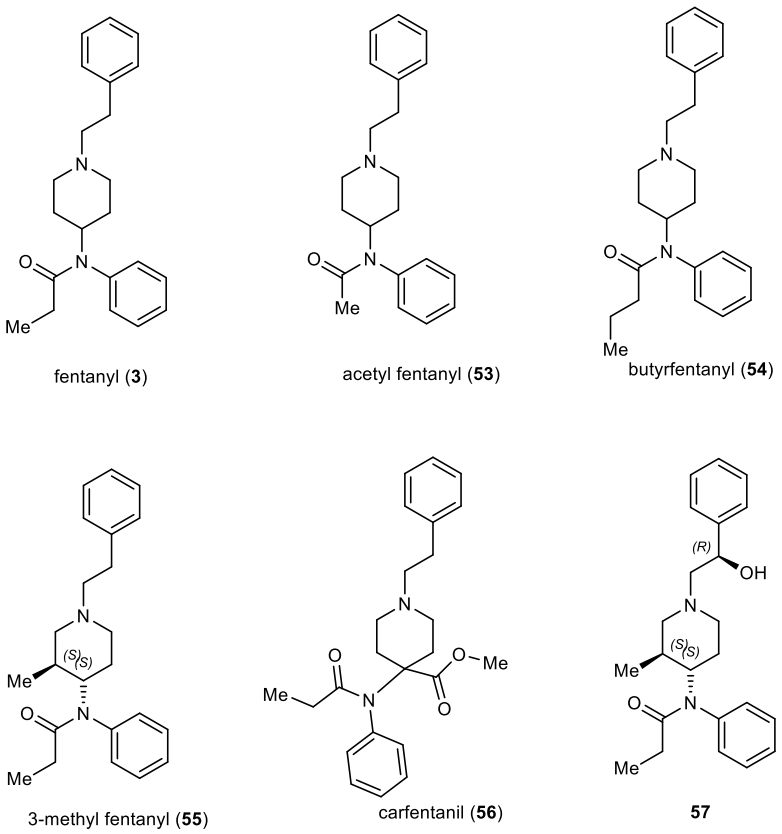


Figure 3.2: Fentanyl (**3**) and its derivatives (**53-57**)

The more potent an agonist is, the more doses of antagonists have to be given. Naloxone (**4**) is an antagonist with high efficiency to reverse the effects caused by morphine at 0.15 mg/kg, which means a single low dose of naloxone can be sufficient as an opioid antagonist. However, the Schemes of redosing in New Jersey Emergency Medical System from 2014 to 2016 showed overall 9% of naloxone (**4**) treatments on opioid overdose needed a second dose, with 2% requiring a third dose. A study presented 83% of patients required two or more doses of naloxone (**4**) in 2mg/mL before a response was observed in suspected fentanyl (**3**) cases.[42] It is obvious that currently used antagonists in their average dose are not enough to treat the addiction of fentanyl. Therefore, to synthesize more efficient antagonists is of interests to chemists and the medical industry.

3.3 Aims and Objectives

Noroxymorphone (**26**) is the starting material for the preparation of three common MOR antagonists, naloxone (**4**), naltrexone (**5**), and nalmefene (**6**), which are all produced by *N*-alkylation. *N*-alkylation of noroxymorphone (**26**) is a straightforward method to prepare a range of new lead structures for investigation of opioid antagonist activity.

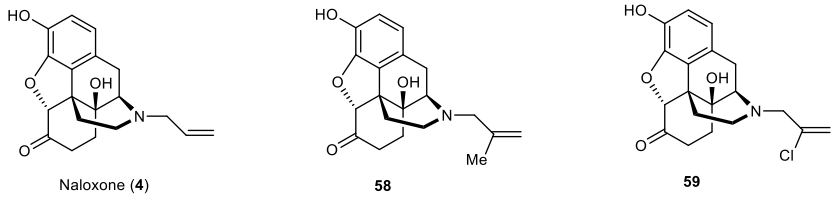
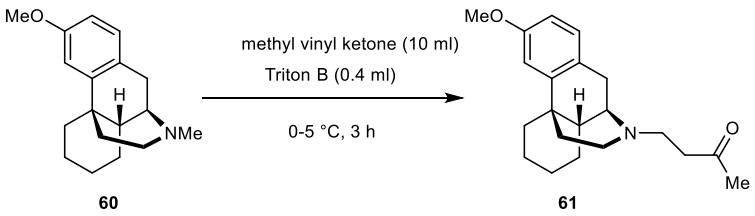


Figure 3.3: Comparison of structure between substances **58**, **59** and naloxone

Since naloxone (**4**) is the most efficient MOR antagonist in current clinical use, we looked into the investigated compounds **58** and **59** with an additional group on the β-position as shown in Figure 3.3. Compound **58** is known in the publication by Rice[44] and his group, but the characterization and bioactivity of **58** has not been reported yet.

The conjugate addition of amines onto electron-deficient alkenes is an effective method for amine alkylation. This reaction has been widely applied but is not very common in forming opioid derivatives. Therefore, our research intended to apply simple conjugate additions in *N*-substitution of noroxymorphone (**26**).

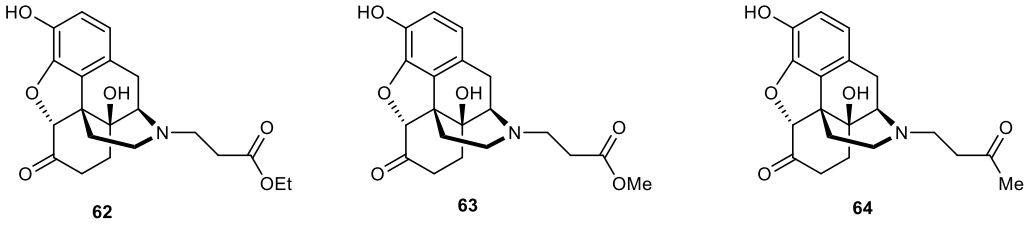
In 2014, Krzysztof Jozwiak and colleagues[45] published their study on *N*-substituted morphinan derivatives. 3-Methoxymorphinan (**60**), methyl vinyl ketone and Triton B were cooled down and maintained at 0-5 °C for 3 hours to give *N*-formyl-ethyl derivative **61**. (Scheme 3.1)



60 61

Scheme 3.1: *N*-substitution *via* conjugate addition on morphinan

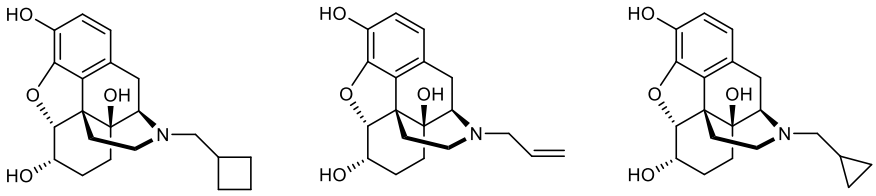
Therefore, similar conjugate addition of amines to obtain derivatives **62, 63** and **64** are expected to be achieved with ethyl acrylate, methyl acrylate and methyl vinyl ketone, respectively. (Figure 3.4)



62 63 64

Figure 3.4: Derivatives **63, 64** and **65** can be synthesized *via* conjugate addition

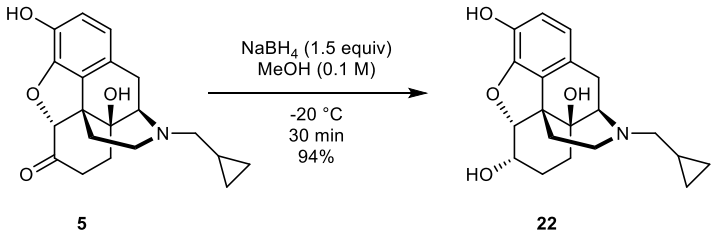
Furthermore, derivatives resulting from reduction of the ketone, such as nalbuphine (**20**), compound **21** from naloxone (**4**) and **22** from naltrexone (**5**), also have antagonism effects to μ-opioid receptor. (Figure 3.5)



Nalbuphine (**20**) 21 22

Figure 3.5: Nalbuphine (**20**) and reduced derivatives **21** and **22**

In 2004, Uwai Koji[46] and co-workers reported a reduction of naltrexone (**5**) HCl salt to give **22** in 94% yield (Scheme 3.2). As a common reductant, $NaBH_4$ can be applied on general ketones to form alcohols, opioid derivatives are included.



Scheme 3.2: Reduction of naltrexone (**5**)

Therefore, reductions on **58**, **59**, **62** and **63** might be able to give reduced products (**65-68**) as shown in Figure 3.6.

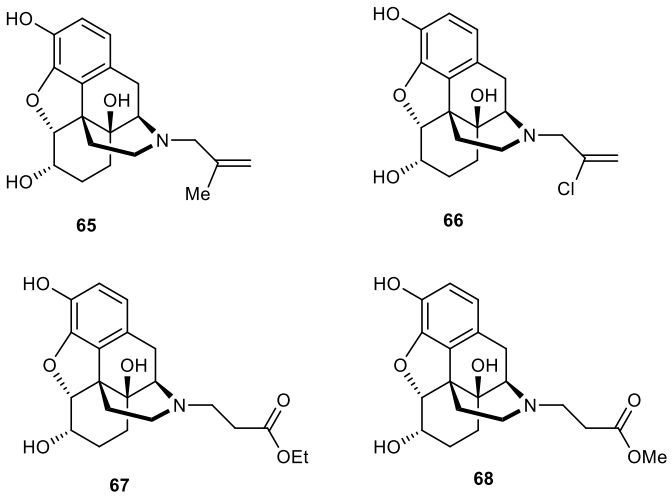
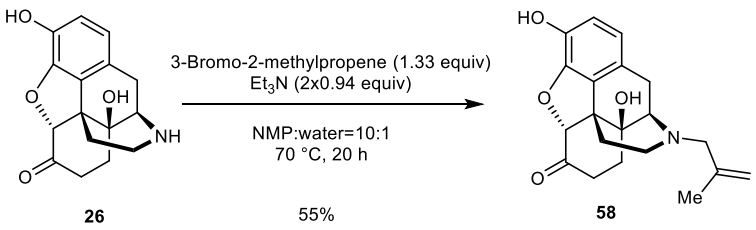


Figure 3.6: Reduced derivatives (**65-68**) targeted in this study

3.4 Result and Discussion

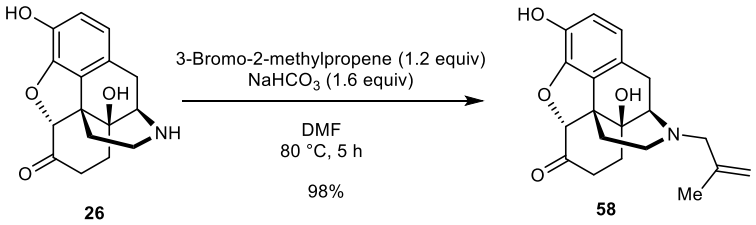
3.4.1 *N*-Substitution with Halogenated Hydrocarbon

Substance **58** was made by reacting noroxymorphone with 3-bromo-2-methylpropene and triethylamine in NMP and water at 70 °C, to give the product in 55% yield after 20 hours. (Scheme 3.3) This reaction has reasonable yield and mild conditions, but with some difficulties encountered during purification due to the NMP, which is a widely used solvent in a lot of reactions but not preferred in extraction and chromatography. Therefore, another approach to desired product **58** should be proposed.



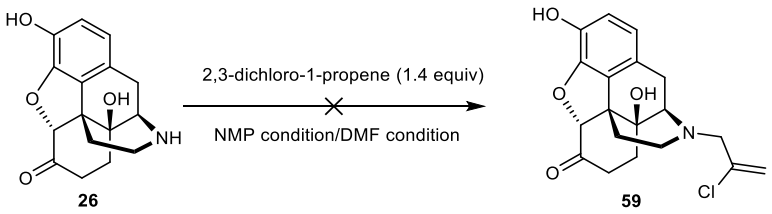
Scheme 3.3

Interestingly, Rice and his group [44] mentioned compound **58** as an intermediate in their semi-synthesis route of a delta opioid receptor agonist, which also starts from noroxymorphone (**26**) and its derivatives. Although they did not give the general procedure of this reaction in detail, the formal preparation of compound **58** in 98% yield as presented in Scheme 3.4.



Scheme 3.4: Preparation of **58** as reported by Rice and his group

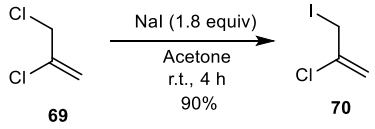
To obtain compound **59**, both NMP and DMF conditions shown in Scheme 3.3 and Scheme 3.4 were applied on the substitution using 2,3-dichloro-1-propene as the alkyl reactant. However, due to chloroalkane usually are less reactive than similar bromoalkane, no compound **59** was detected when using either of the two conditions. (Scheme 3.5)



Scheme 3.5: NMP/DMF approaches to **59**

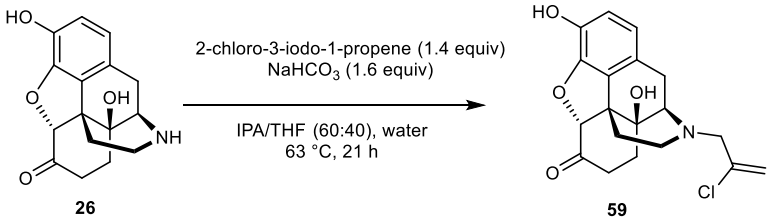
To increase the reactivity of starting material in the *N*-substitution, 2,3-dichloro-1-propene (**69**) was made into 2-chloro-3-iodo-1-propene (**70**) as

shown in Scheme 3.6. [47]



Scheme 3.6: Preparation of starting material **70**

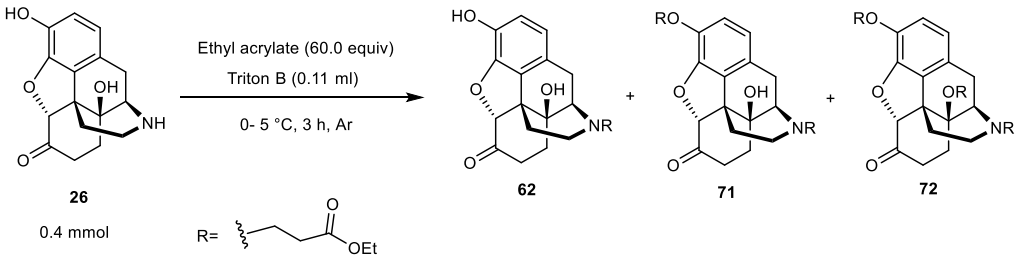
As described in patent WO2016005923, a 30 wt.% solution of noroxymorphone (**26**) in IPA/THF (60:40 v/v) was prepared, and was then employed in an alkylation to obtain naltrexone (**5**).[48] This reaction was applied with 2-chloro-3-iodo-1-propene (**70**) and gave desired product **59** in 71% yield. (Scheme 3.7)



Scheme 3.7: Application of WO2016005923 condition to obtain **59**

3.4.2 *N*-Substitution by Conjugate Addition of Amines

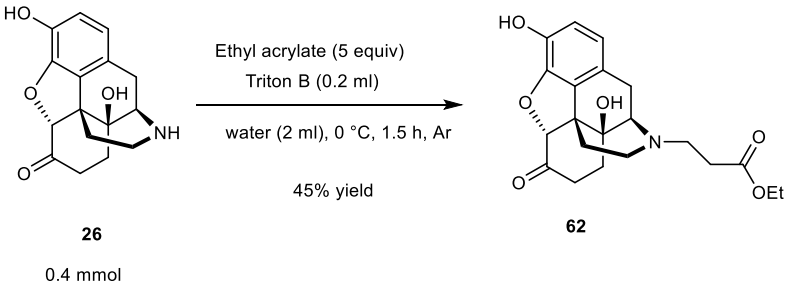
Triton B is a phase transfer catalyst as well as a base in conjugate addition of amines as shown in Scheme 3.1. The formation of morphinan derivatives indicated that the similar reaction might be capable to be applied on the free amine of noroxymorphone (**26**). In Scheme 3.8, the resulting product **62** and side products **71** and **72** were detected by TLC analysis, mass spectrometry and crude NMR spectrum, which suggested that multiple substitution happened under these conditions.



Schemes 3.8: Triton B conjugate addition on amine of noroxymorphone (**26**)

Noroxymorphone has lower solubility in ethyl acrylate than in protonated solvents such as MeOH and EtOH, therefore, the resulting mixture from this reaction had starting material in majority. Besides, literature reported that free OH group can slowly participate in this conjugate addition with a strong base[49] such as Triton B, which essentially lead to the formation of multi-substituted side products **71** and **72**.

The optimization of this condition was to reduce the amount of ethyl acrylate (5 equivalents) and the addition of water. Noroxymorphone (**26**) has a better solubility in water (13.2 g/L), which also provides an aqueous environment for Triton B to show its phase transfer catalytic function to give desired product **62** in 45% yield. (Scheme 3.9)



Scheme 3.9: Triton B employed in the conjugate addition of **62**

Similar conjugate additions were run at room temperature, but only gave a mixture of **63** and **73**, detected by prep-TLC analysis, mass spectrometry, and crude NMR analysis. Formation of side products might originate from migration of the methyl group from Triton B (40% solution in MeOH), and the ethyl group in desired product **62**. Potentially, this migration can give both methoxy side product **63** and the acidic side product **73**. (Figure 3.7)

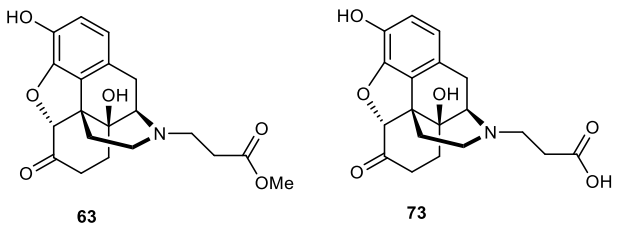
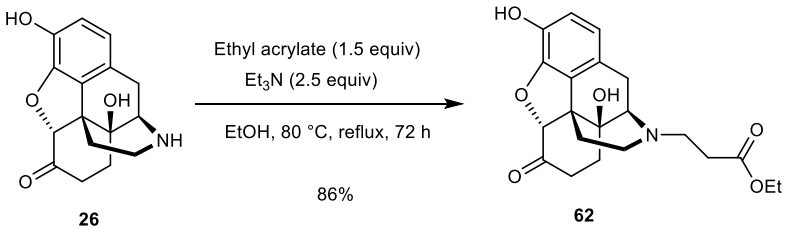


Figure 3.7: Side products of migration

To avoid the migration, strong bases such as Triton B are not applied in conjugate addition ideally. Mild organic base triethylamine was employed in the conjugate addition in EtOH, to give desired compound **62** in 86% yield. (Scheme 3.10)



Scheme 3.10

Compound **63** and **64** can be synthesized in MeOH at room temperature, with methyl acrylate or methyl vinyl ketone as the starting material, yield in 93% and 82%, separately. (Figure 3.8)

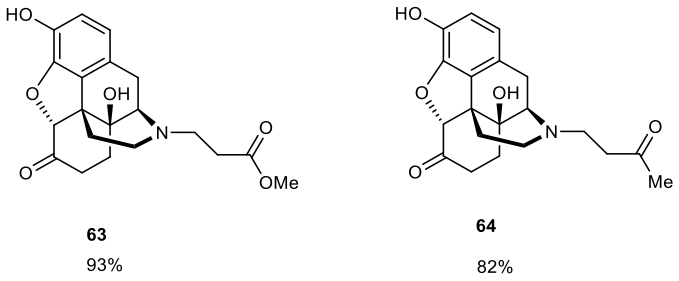
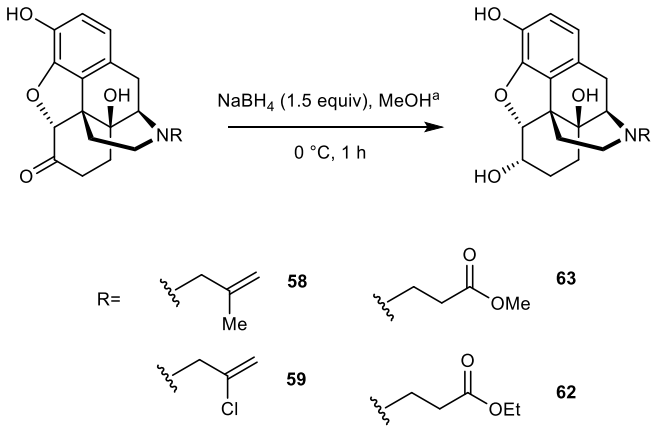


Figure 3.8: 63 and **64** were obtained in excellent yields

3.5 Reduction of Ketone

$NaBH_4$ was applied in the reduction of ketone derivatives **58, 59, 62,** and **63**, to give reduced compounds **65-68**. (Scheme 3.11)



Scheme 3.11: Reduction of ketone derivatives;

a) EtOH was used in reduction of **62**

These reduced products were detected by mass spectrometry and crude ^{13}C-NMR spectroscopy. However, isolation of the pure compound has not currently been achieved, with purification by column chromatography a target in the future work. The impurities might be trimethyl borate, triethyl borate or boric acid.

3.6 Conclusion

To obtain new opioid derivatives by *N*-alkylation, a known compound **58** and 4 new compounds **59, 62, 63** and **64** were formed by *N*-substitution and conjugate addition on amine. 4 reduced compounds **65-68** were detected by HRMS during this project. Since the initial idea of searching new *N*-alkylated opioid derivatives from noroxymorphone was to find new chemical substrates with medical effects, further biological tests need to be carried out on these compounds.

4. Future Work

By now, the Lam group is still optimizing the formal synthesis route to get a better overall yield. The combined steps to obtain dienol acetate **41** from **39** now only takes 4 hours in total, using one-pot Albright-Goldman oxidation and diene formation with triethyl amine to give desired product **41** in 89% yield. This improvement can sharply increase the overall yield from 14% to 27%.

The samples of *N*-alkylated compounds will be sent to the School of Pharmacy for biological testing to define their potential value in medical use. These results from this project might be an inspiration to investigate new MOR antagonists in the future. The application of conjugate addition on tertiary amine of noroxymorphone, also provides successful examples that can be employed to similar opioids or other natural products.

Derivatives **74** and **75** are also obtained from similar alkylation as shown in Figure 4.1. Alkyne **74** is a potential intermediate compound to form various ethyl cyclopropane opioid derivatives using Lindlar catalyst.[50] The alkyl phenyl derivative **75** has similar pharmacophore structure as fentanyl, which is known to have high agonistic potency.[51]

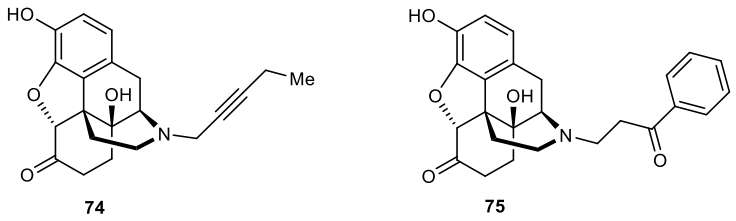


Figure 4.1: derivatives **74** and **75**

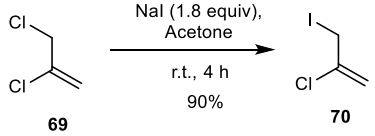
5. Experimental

5.1 General Information

All air-sensitive reactions were carried out under an inert atmosphere using oven-dried apparatus. All commercially available reagents were used as received unless otherwise stated. Petroleum ether refers to Sigma-Aldrich product 24587 (petroleum ether boiling point 40-60 °C). Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien 60F254 0.2 mm precoated plates. Compounds were visualized by exposure to UV light or by dipping the plates into solutions of potassium permanganate or vanillin followed by gentle heating. Flash column chromatography was carried out using silica gel (Fisher Scientific 60 Å particle size 35-70 micron or Fluorochem 60 Å particle size 40-63 micron). Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. The solvent of recrystallization is reported in parentheses. Infrared (IR) spectra were recorded on Bruker platinum alpha FTIR spectrometer on the neat compound using the attenuated total reflectance technique. NMR spectra were acquired on Bruker Ascend 400 spectrometers. ^{1}H and ^{13}C NMR spectra were referenced to external tetramethylsilane via the residual protonated solvent (^{1}H) or the solvent itself (^{13}C). All chemical shifts are reported in parts per million (ppm). For $CDCl_3$, the shifts are referenced to 7.26 ppm for ^{1}H NMR spectroscopy and 77.16 ppm for ^{13}C NMR spectroscopy. For DMSO-*d*6, the shifts are referenced to 2.50 ppm for ^{1}H NMR spectroscopy and 39.52 ppm for ^{13}C NMR spectroscopy. Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High-resolution mass spectra were recorded using electrospray ionization (ESI) techniques.

5.2 Preparation of substrates

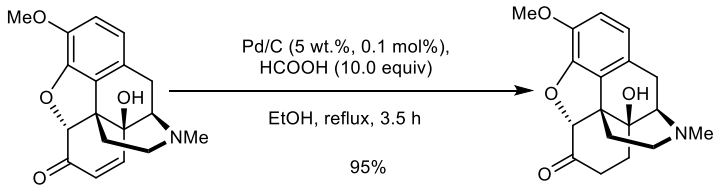
Preparation of 2-chloro-3-iodo-1-propene (70)



69 **70**

Sodium iodide (2.92 g, 19.5 mmol) was added to a solution of 2,3-dichloro-1-propene (**69**) (1.00 mL, 10.8 mmol) in acetone (11 mL) and refluxed at 60 °C for 3.5 hours. The reaction mixture was allowed to cool to room temperature and quenched with water (20 mL) and diethyl ether (20 mL). The mixture was washed with 2 M $Na_2S_2O_3$ aqueous solution (2 x 10 mL) and extracted with diethyl ether (2 x 20 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated in *vacuo* to give the title product (**70)** as a brown liquid (1.97 g, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (1H, d, J = 1.8 Hz, C=C**H**$_2$), 5.32 (1H, d, J = 1.8 Hz, C=C**H**$_2$), 4.09 (2H, s, C**H**$_2$I); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4 (CH_2), 115.4 (CH), 7.4 (C); The analytical data were consistent with those reported previously.[52]

Oxycodone (27)

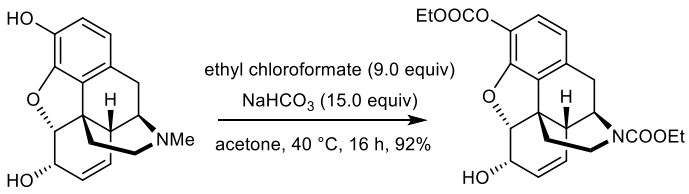


51 **27**

To a solution of 14-hydroxycodeinone (**51**) (157 mg, 0.50 mmol) in EtOH (5 mL), was added activated palladium on carbon (5 wt. %, 1.1 mg, 0.0005 mmol) and formic acid (0.19 mL, 5.0 mmol) under stirring. The reaction was heated at 90 °C. After 3.5 hours, the reaction was quenched with saturated aq. $NaHCO_3$ solution and extracted with dichloromethane. The organic layers were combined and dried with magnesium sulfate and the solvent was removed in *vacuo* to give title product **27** as white solid (150 mg, 95% yield). ^{1}H NMR

(500 MHz, $CDCl_3$) δ 6.70 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.65-6.62 (1H, m, Ar**H**), 4.66 (1H, s, OC**H**), 3.90 (3H, s, OC**H**$_3$), 3.15 (1H, d, *J* = 18.5 Hz, C**H**$_2$), 3.02 (1H, td, *J* = 14.4, 5.1 Hz, C**H**$_2$), 2.86 (1H, d, *J* = 5.9 Hz, NC**H**), 2.56 (1H, ddd, *J* = 18.5, 5.9, 1.0 Hz, C**H**$_2$), 2.49-2.41 (2H, m, 2H from 2 different C**H**$_2$), 2.40 (3H, s, NC**H**$_3$), 2.30 (1H, dt, *J* = 14.3, 3.2 Hz, C**H**$_2$), 2.17 (1H, td, *J* = 11.6, 3.9 Hz, C**H**$_2$), 1.87 (1H, ddd, *J* = 13.3, 5.1, 3.0 Hz, C**H**$_2$), 1.63 (1H, ddd, *J* = 14.6, 13.3, 3.4 Hz, C**H**$_2$), 1.59-1.55 (1H, m, C**H**$_2$); HRMS (ESI) Exact mass calculated for $[C_{18}H_{22}NO_4]^+$ $[M+H]^+$: 316.1543, found: 316.1537. The analytical data were consistent with those reported previously.[53]

Ethyl(4*R*,4a*R*,7*S*,7a*R*,12b*S*)-9-[(ethoxycarbonyl)oxy]-7-hydroxy-1,2,4,4a,7, 7a-hexahydro-3*H*-4,12-methanobenzofuro(3,2-e) isoquinoline-3-carboxylate (39)

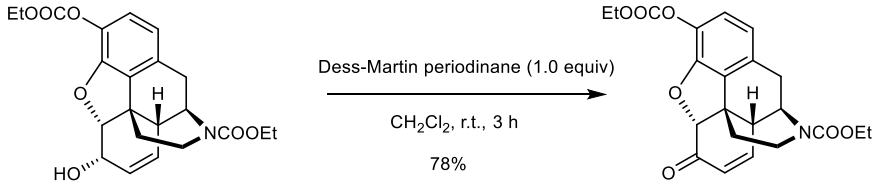


1 **39**

Ethyl chloroformate (3.00 mL, 31.5 mmol) was added to a solution of morphine (**1**) (1.00 g, 3.50 mmol) and $NaHCO_3$ (4.42 g, 52.5 mmol) in acetone (50 mL), which was heated to 40 °C for 16 hours. Once cooled the mixture was filtered and the resulting solution was concentrated in *vacuo* to give the title product **39** as a white solid (1.34 g, 92% yield). As a 1:1 mixture of rotamers (only seen at room temperature) R_f = 0.31 (50% EtOAc/Petroleum ether); m.p. 157 - 159 °C (EtOAc); $[\alpha]_D^{25}$ –176 (c 1.000, $CHCl_3$); IR 3516 (OH), 2981 (CH), 1747 (C=O), 1689 (C=O), 1615, 1450, 1238, 829, 579, 457 cm^{-1}; ^1H NMR (400 MHz, 70 °C, DMSO-d_6) δ 6.85 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.59 (1H, d, *J* = 8.2 Hz, Ar**H**), 5.63 (1H, dddd, *J* = 9.8, 3.1, 2.1, 1.2 Hz, HO-C-C**H**=CH), 5.34 (1H, dt, *J* = 9.8, 2.7 Hz, HO-C-CH=C**H**), 4.83 (2H, m, O-C**H** and N-C**H**), 4.63 (1H, d, *J* = 6.8 Hz, O**H**), 4.26 (2H, q, *J* = 7.1 Hz, OCOOC**H**$_2$CH$_3$), 4.18

(1H, appdq, *J* = 6.3, 3.1 Hz, C**H**OH), 4.12 (2H, q, *J* = 7.1 Hz, NCOOC**H**$_2$CH$_3$), 3.95 (1H, dd, *J* = 14.0, 5.2 Hz, N-C**H**$_2$), 2.97-2.82 (2H, m, 1H from N-C**H**$_2$ and Ar-C**H**$_2$), 2.69 (1H, d, *J* = 18.9 Hz, Ar-C**H**$_2$), 2.53 (1H, q, *J* = 2.8 Hz, solvent peak and CH=CH-C**H**), 2.00 (1H, td, *J* = 12.9, 5.4 Hz, N-CH$_2$-C**H**$_2$), 1.76 (1H, ddd, *J* = 13.0, 3.9, 1.6 Hz, N-CH$_2$-C**H**$_2$), 1.30 (3H, t, *J* = 7.1 Hz, OCOOCH$_2$C**H**$_3$), 1.23 (3H, t, *J* = 7.1 Hz, NCOOCH$_2$C**H**$_3$); ^{13}C NMR (101 MHz, 70 °C, DMSO) δ 155.0 (C), 152.9 (C), 150.1 (C), 134.9 (CH), 132.3 (C), 132.3 (C), 131.9 (C), 127.4 (CH), 121.9 (CH), 119.5 (CH), 93.4 (CH), 66.3 (CH), 65.2 (CH$_2$), 61.3 (CH$_2$), 50.3 (CH), 43.9 (C), 39.9 (CH), 37.5 (CH$_2$), 35.0 (CH$_2$), 29.9 (CH$_2$), 15.0 (CH$_3$), 14.4 (CH$_3$); Because of a hidden peak (δ 2.53), CDCl$_3$ NMRs are added below; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.86 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.69-6.56 (1H, m, *J* = 8.2 Hz, Ar**H**), 5.86-5.75 (1H, m, HO-C-C**H**=CH), 5.34-5.23 (1H, m, HO-C-CH=C**H**), 4.96 (2H, dd, *J* = 7.0, 1.1 Hz, O-C**H** and N-C**H**), 4.34 (2H, qd, *J* = 7.1, 1.3 Hz, OCOOC**H**$_2$CH$_3$), 4.26-4.12 (3H, m, NCOOC**H**$_2$CH$_3$ and C**H**OH), 4.09-3.99 (1H, m, N-C**H**$_2$), 3.46 (1H, dd, *J* = 11.8, 3.6 Hz, O**H**), 3.00 (1H, dd, *J* = 16.6, 8.1 Hz, N-C**H**$_2$), 2.92-2.82 (1H, m, Ar-C**H**$_2$), 2.76 (1H, dt, *J* = 18.8, 1.1 Hz, Ar-C**H**$_2$), 2.58 (1H, p, *J* = 2.9 Hz, CH=CH-C**H**), 1.97 (2H, dd, *J* = 11.0, 5.4 Hz, N-CH$_2$-C**H**$_2$), 1.39 (3H, t, *J* = 7.1 Hz, OCOOCH$_2$C**H**$_3$), 1.34-1.26 (3H, m, NCOOCH$_2$C**H**$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 155.4 (C), 153.0 (C), 148.7 (C), 135.3 (CH, minor), 135.0 (CH, major), 132.6 (C), 131.9 (C), 131.6 (C), 126.5 (CH, major), 126.4 (CH, minor), 121.5 (CH), 120.29 (CH), 92.3 (CH), 65.6 (CH), 65.4 (CH$_2$), 61.6 (CH$_2$), 50.4 (CH, major), 50.1 (CH, major), 43.1 (C), 39.4 (CH, minor), 39.3 (CH, major), 37.4 (CH$_2$, major), 37.3 (CH$_2$, minor), 34.9 (CH$_2$, major), 34.5 (CH$_2$, minor), 29.9 (CH$_2$, minor),29.7 (CH$_2$, major), 14.7 (CH$_3$, major), 14.2 (CH$_3$, major); HRMS (ESI) Exact mass calculated for $[C_{22}H_{25}NO_7Na]^+$ $[M+Na]^+$: 438.1328, found: 438.1108;

Ethyl(4*R*,4a*R*,7*S*,7a*R*,12b*S*)-9-((ethoxycarbonyl)oxy)-7-hydroxy-1,2,4,4a,7, 7a-hexahydro-3*H*-4,12-methanobenzofuro[3,2-e] isoquinoline-3-carboxylate (40) (carried out by Dr. Rebeca Ruscoe)

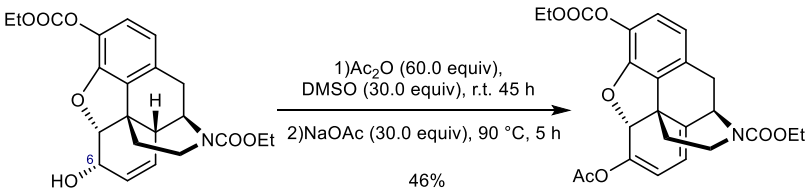


39 **40**

A solution of Dess-Martin periodinane (1.02 g, 2.40 mmol) in CH_2Cl_2 (2 mL) was added to a solution of **39** (1.00 g, 2.40 mmol) in CH_2Cl_2 (10 mL) at room temperature. Thin layer chromatography (CH_3Cl: MeOH = 9:1) showed complete consumption of starting material after 3 hours. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with a 1:1 mixture of saturated aqueous sodium thiosulfate (5 x 10 mL) and saturated $NaHCO_3$ solutions (10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in *vacuo* to give the title product (**40**) as an off-white solid (581 mg, 59% yield). As a 1:1 mixture of rotamers (only seen at room temperature). R_f = 0.32 (57% EtOAc/Petroleum ether); m.p. 174 - 179 °C (EtOAc); $[\alpha]_D^{25}$ –164 (c 1.000, $CHCl_3$); IR 2988 (CH_3), 1768 (C=O), 1675 (C=O), 1624 (C=O), 1494, 1421, 1121, 1090, 808, 485 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.90 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.65 (2H, m, 1H from Ar**H** and O=C-C**H**=CH), 6.12 (1H, dd, *J* = 10.3, 2.9 Hz, O=C-CH=C**H**), 5.08-4.87 (1H, m, N-C**H**), 4.76 (1H, s, O-C**H**), 4.28 (2H, q, *J* = 7.1 Hz, OCOOC**H**$_2$CH$_3$), 4.16-3.97 (3H, m, NCOOC**H**$_2$CH$_3$ and 1H from N-C**H**$_2$), 3.05 (1H, td, *J* = 3.1, 2.1 Hz, CH=CH-C**H**), 2.84 (3H, d, *J* = 3.4 Hz, Ar-C**H**$_2$ and 1H from N-C**H**$_2$), 1.97 (2H, dq, *J* = 15.8, 10.4, 7.8 Hz, N-CH$_2$-C**H**$_2$), 1.34 (3H, t, *J* = 7.1 Hz, OCOOCH$_2$C**H**$_3$), 1.35-1.19 (3H, m, NCOOCH$_2$C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9 (C), 155.5 (C), 152.7 (C), 147.8 (C), 147.1 (CH, major), 146.9 (CH, minor), 133.3 (CH, minor), 133.3 (CH, major), 133.0 (C), 130.6 (C), 128.9 (C), 122.8 (CH), 120.5 (CH), 88.4 (CH), 65.2 (CH_2), 61.9 (CH_2), 50.5 (CH, minor), 50.1 (CH, major), 43.6 (C), 40.2 (CH), 37.8 (CH_2, major), 37.8 (CH_2, minor), 33.5 (CH_2, major), 33.2

(CH_2, minor), 29.7 (CH_2, minor), 29.4 (CH_2, major), 14.6 (CH_3), 14.1 (CH_3); ^{1}H NMR (400 MHz, 70 °C, DMSO-d_6) δ 6.99-6.89 (2H, m, 1H from Ar**H** and O=C-C**H**=CH), 6.74 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.04 (1H, dd, *J* = 10.3, 2.8 Hz, O=C-CH=C**H**), 4.95 (1H, d, *J* = 4.4 Hz, N-C**H**), 4.92 (1H, s, O-C**H**), 4.25 (2H, q, *J* = 7.1 Hz, OCOOC**H**$_2$CH$_3$), 4.13 (2H, qq, *J* = 7.1, 3.9 Hz, NCOOC**H**$_2$CH$_3$), 3.96 (1H, dd, *J* = 13.8, 5.2 Hz, N-C**H**$_2$), 3.18 (1H, q, *J* = 2.8 Hz, CH=CH-C**H**), 2.88 (1H, dd, *J* = 18.8, 5.6 Hz, N-C**H**$_2$), 2.82-2.66 (2H, m, Ar-C**H**$_2$), 2.10 (1H, td, *J* = 12.8, 5.5 Hz, N-CH$_2$-C**H**$_2$), 1.75-1.65 (1H, m, N-CH$_2$-C**H**$_2$), 1.27 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$), 1.21 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (101 MHz, 70 °C, DMSO) δ 193.1 (C), 155.2 (C), 152.5 (C), 149.4 (CH), 147.8 (C), 132.7 (CH), 132.5 (C), 131.7 (C), 130.1 (C), 122.8 (CH), 120.7 (CH), 89.1 (CH), 65.4 (CH_2), 61.5 (CH_2), 50.4 (CH), 43.6 (C), 40.2 (CH), 38.1 (CH_2), 33.1 (CH_2), 29.6 (CH_2), 15.0 (CH_3), 14.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{22}H_{24}NO_7]^+$ $[M+H]^+$: 414.1547, found: 414.1551.

Ethyl-(4*R*,7a*R*,12b*S*)-7-acetoxy-9-((ethoxycarbonyl)oxy)-1,2,4,7a-tetrahydro-3*H*-4,12-methanobenzofuro[3,2-e] isoquinoline-3-carboxylate (41) (reaction carried out by Dmitry Gorbachev)

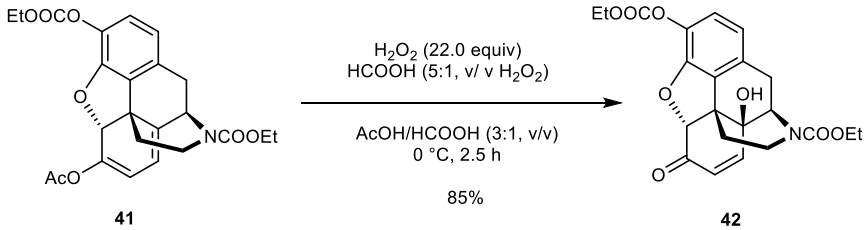


39 **41**

To a solution of **39** (500 mg, 1.20 mmol) in acetic anhydride (6.8 mL, 72.0 mmol), was added DMSO (2.6 mL, 36.0 mmol) and the reaction was stirred for 45 hours before the starting material **39** was all consumed. Sodium acetate (2.96 g, 36.0 mmol) was added and the reaction was heated to 90 °C and stirred for 5 hours. The reaction mixture was allowed to cool down to room temperature and quenched with water (10 mL), extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ (2 x 10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated in *vacuo* to give

a brown liquid. The crude was purified by column chromatography (1:1 EtOAc/ Petroleum ether), to give a white-yellow foam (250 mg, 46% yield). As a 1.4:1 mixture of rotamers. R_f = 0.48 (50% EtOAc/Petroleum ether); $[\alpha]_D^{25}$ – 152 (c 1.000, $CHCl_3$); IR 2036, 1724 (C=O), 1634 (C=O), 1543 (C=O), 1397, 1133, 1038, 827, 456 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.90 (1H, d, *J* = 8.2 Hz, C**H**), 6.64 (1H, d, *J* = 8.2 Hz, C**H**), 5.79 (1H, d, *J* = 6.2 Hz, C**H**), 5.69-5.58 (1H, m, C**H**), 5.55 (1H, m, C**H**), 5.29-5.07 (1H, m, C**H**), 4.32 (2H, app. qd, *J* = 7.1, 2.1 Hz, C**H**$_2$CH$_3$), 4.24-4.02 (3H, m, C**H**$_2$ and 1H from C**H**$_2$), 3.31-3.14 (2H, m, C**H**$_2$), 3.06 (1H, d, *J* = 18.4 Hz, C**H**$_2$), 2.25-2.15 (4H, m, C**H**$_3$ and 1H from C**H**$_2$), 1.85 (1H, d, *J* = 12.4 Hz, C**H**$_2$), 1.38 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$), 1.30-1.26 (3H, m, CH$_2$C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0 (C), 155.0 (C, major), 154.9 (C, minor), 153.0 (C), 147.6 (C), 143.8 (C, minor), 143.7 (C, major), 135.9 (C), 133.3 (C), 132.2 (C, major), 132.1 (C, minor), 122.2 (CH), 119.8 (CH), 115.4 (CH, major), 115.3 (CH, minor), 111.0 (CH, major), 110.9 (CH, minor), 88.3 (CH), 65.1 (CH_2), 61.7 (CH_2), 52.5 (CH, minor), 52.2 (CH, major), 47.3 (C), 38.0 (CH_2, minor), 37.7 (CH_2, minor), 37.64 (CH_2, minor), 37.59 (CH_2, major), 37.3 (CH_2, major), 37.1 (CH_2, minor), 21.1 (CH_3, major), 20.8 (CH_3), 14.7 (CH_3), 14.2 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{24}H_{29}N_2O_8]^+$ $[M+NH_4]^+$: 473.1926, found: 473.1926.

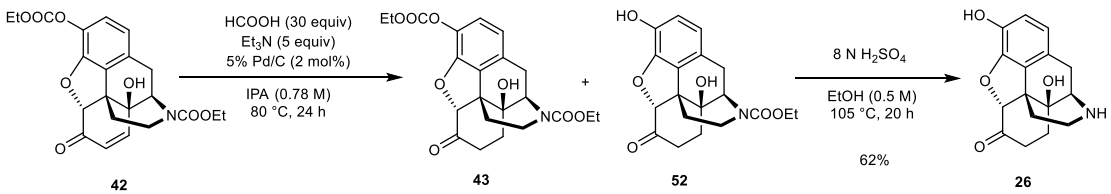
Ethyl(4*R*,4a*S*,7a*R*,12b*S*)-9-((ethoxycarbonyl)oxy)-4a-hydroxy-7-oxo-1,2,4,4a,7,7a-hexahydro-3*H*-4,12-methanobenzofuro[3,2-e] isoquinoline-3-carboxylate (42)



To a solution of **41** (100 mg, 0.22 mmol) in a cooled (0 °C) mixture of acetic acid (0.6 mL) and formic acid (0.2 mL), was added a pre-stirred (10 min at least) solution of H_2O_2 (50 wt.%, 14.7 M, 0.33 mL, 4.84 mmol) in formic acid

(1.65 mL, 5:1 v/v to H_2O_2) dropwise over 1.5 hours. The reaction was stirred at 0 °C for 2 hours and quenched with 2 M aq NH_4OH solution until pH = 7. The aqueous layer was extracted with $CHCl_3$ (3 x 30 mL), the combined organic layers were dried (Na_2SO_4) and concentrated in *vacuo* to give title product **42** as a pale-yellow solid (80.0 mg, 85% yield). R_f = 0.17 (50% EtOAc/Petroleum ether); m.p. 182 - 193 °C (EtOAc); $[\alpha]_D^{25}$ –128 (c 1.000, $CHCl_3$); IR 3339 (OH), 2981 (CH_3), 1762 (C=O), 1679 (C=O), 1371, 1159, 1049, 887, 865, 488, 447 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.93 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.76 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.68 (1H, dd, *J* = 8.4, 1.0 Hz, C**H**=CH), 6.19 (1H, d, *J* = 10.0 Hz, CH=C**H**), 4.78 (1H, s, OC**H**), 4.65 (1H, d, *J* = 55.2 Hz, NC**H**), 4.30 (2H, qd, *J* = 7.1, 1.3 Hz, OCOOC**H**$_2$CH$_3$), 4.22-4.14 (2H, m, NCOOC**H**$_2$CH$_3$), 4.14-4.00 (1H, m, 1H from NC**H**$_2$), 3.34 (1H, s, O**H**), 3.12-2.95 (2H, m, C**H**$_2$), 2.89 (1H, t, *J* = 13.6 Hz, NC**H**$_2$), 2.50 (1H, d, *J* = 5.1 Hz, C**H**$_2$), 1.72 (1H, s, C**H**$_2$), 1.36 (3H, t, *J* = 7.1 Hz, OCOOCH$_2$C**H**$_3$), 1.30 (3H, t, *J* = 7.1 Hz, NCOOCH$_2$C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.5 (C), 156.5 (C), 152.1 (C), 147.5 (CH), 146.8 (C), 132.7 (CH), 130.3 (C), 129.4 (C), 122.6 (CH), 119.5 (CH), 87.0 (CH), 67.4 (C), 64.8 (CH_2), 61.7 (CH_2), 54.9 (C), 46.8 (C), 37.3 (CH), 36.9 (CH_2), 31.3 (CH_2), 27.0 (CH_2), 14.1 (CH_3), 13.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{22}H_{24}NO_8]^+$ $[M+H]^+$: 430.1496, found: 430.1507.

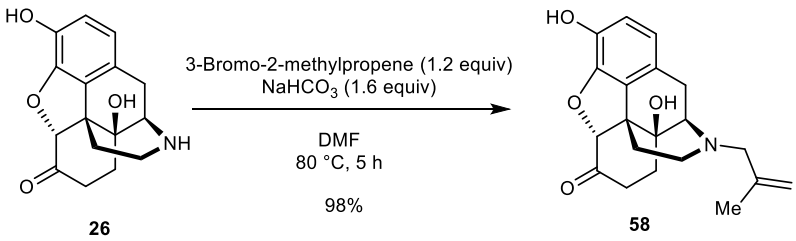
(4*R*,4a*S*,7a*R*,12b*S*)-4a,9-dihydroxy-2,3,4,4a,5,6-hexahydro-1*H*-4,12-metha nobenzofuro[3,2-e] isoquinolin-7(7a*H*)-one (26)



To a solution of **42** (250 mg, 0.60 mmol) in IPA (0.78 M, 2.5 mL, 1.95 mmol), was added triethylamine (0.42 mL) and 5% Pd/C (26.0 mg, 2.0 mol%) under nitrogen protection. The reaction was stirred at 0 °C and was added formic acid

(0.68 mL) dropwise before the reaction was stirred at 80 °C for 24 hours. The remaining product was quenched with water. The aqueous layer was extracted with $CHCl_3$ (3 x 30 mL), the combined organic layers were dried (Na_2SO_4) and concentrated in *vacuo* to give a crude mixture of **43** and **52**, which can be used directly in the next reaction to achieve **26**. The mixture of **43** and **52** (250 mg) in EtOH (0.5 M, 2.4 mL, 1.2 mmol), was added 8N H_2SO_4 (4.0 M, 2.4 mL, 9.6 mmol) at stirring. The reaction was stirred at 105 °C for 20 hours and neutralized with ammonia until pH = 9. The remained brown precipitate was collected by filtration to give crude noroxymorphone as a brown solid (106.8 mg, 62% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.56 (1H, d, *J* = 8.1 Hz, Ar**H**), 6.51 (1H, d, *J* = 8.1 Hz, Ar**H**), 4.67 (1H, s, OC**H**), 2.99-2.79 (4H, m, 2C**H₂**), 2.66-2.57 (1H, m, NC**H**), 2.46-2.23 (2H, m, C**H₂**), 2.06 (d, *J* = 14.3 Hz, C**H**$_2$), 1.72 (1H, d, *J* = 13.5 Hz, C**H**$_2$), 1.48 – 1.35 (1H, td, *J* = 14.0, 3.2 Hz, C**H**$_2$), 1.19 – 1.11 (1H, dd, *J* = 12.1, 3.2 Hz, C**H**$_2$); HRMS (ESI) Exact mass calculated for $[C_{16}H_{18}NO_4]^+$ $[M+H]^+$: 288.1230, found: 288.1231.

(4*R*,4a*S*,7a*R*,12b*S*)-4a,9-dihydroxy-3-(2-methylallyl)-2,3,4,4a,5,6-hexahydro-1*H*-4,12-methanobenzofuro[3,2-e] isoquinolin-7(7a*H*)-one (58)

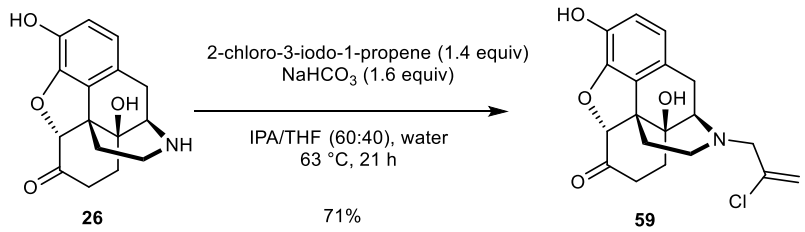


26 **58**

Noroxymorphone (500 mg, 1.74 mmol) and $NaHCO_3$ (234 mg, 2.78 mmol) were made in a mixture of DMF (1.8 mL), before 3-bromo-2-methylpropene (0.21 mL, 2.09 mmol) was added to the reaction vial. The reaction was stirred at 80 °C for 5 hours and finally turned to clear dark-brown solution, quenched with water (30 mL). Extracted with diethyl ether (3 x 20 mL) and the collected organic layers were washed with 5% aqueous LiCl solution (30 mL) and brine (20 mL), dried (Na_2SO_4) and concentrated in *vacuo* to give title product (**58**) as

a white solid (580 mg, 98% yield). R_f = 0.32 (50% EtOAc/Petroleum ether); m.p. 186 - 190 °C (EtOAc); $[\alpha]_D^{25}$ –180 (c 1.000, $CHCl_3$); IR 3169 (OH), 2980 (CH=CH_2), 2904 (CH=CH_2), 2837 (CH_3), 1732 (C=O), 1619 (C=C), 1456, 1238, 973, 480 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.72 (1H, d, *J* = 8.1 Hz, Ar**H**), 6.64-6.49 (1H, m, Ar**H**), 5.66 (1H, s, O**H**), 5.11 (1H, s, O**H**), 4.92 (2H, pd, *J* = 2.5, 1.6 Hz, C=C**H₂**), 4.69 (1H, s, OC**H**), 3.10 (3H, d, *J* = 19.6 Hz, 1H from C**H**$_2$ and NC**H₂**), 3.06-2.89 (2H, m, C**H₂**), 2.62-2.49 (2H, m, C**H₂**), 2.41 (1H, td, *J* = 12.5, 5.2 Hz, C**H**$_2$), 2.32 (1H, dt, *J* = 14.5, 3.1 Hz, C**H**$_2$), 2.15 (1H, td, *J* = 12.1, 3.8 Hz, C**H**$_2$), 1.98 (1H, s, C**H**$_2$), 1.88 (1H, ddd, *J* = 13.4, 5.2, 2.9 Hz, C**H**$_2$), 1.80 (3H, d, *J* = 1.2 Hz, C**H₃**), 1.69-1.53 (2H, m, 2H from different C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.4 (C), 143.4 (C), 141.6 (C), 138.7 (C), 129.0 (C), 124.4 (C), 119.9 (CH), 117.7 (CH), 114.3 (CH_2), 90.6 (C), 70.5 (C), 62.3 (CH), 61.4 (CH_2), 51.0 (C), 43.2 (CH_2), 36.1 (CH_2), 31.3 (CH_2), 30.6 (CH_2), 22.7 (CH_2), 20.7 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{20}H_{24}NO_4]^+$ $[M+H]^+$: 342.1700, found: 342.1699.

(4*R*,4a*S*,7a*R*,12b*S*)-3-(2-chloroallyl)-4a,9-dihydroxy-2,3,4,4a,5,6-hexahydro-1*H*-4,12-methanobenzofuro[3,2-e] isoquinolin-7(7a*H*)-one (59)

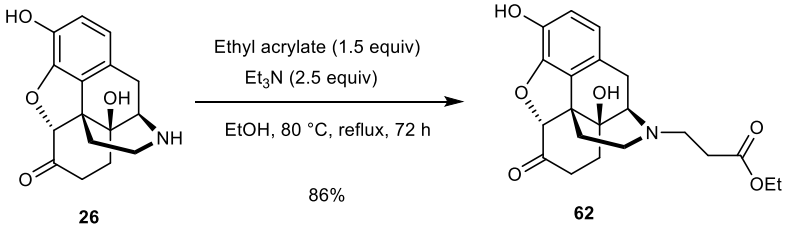


26 **59**

Noroxymorphone (144 mg, 0.500 mmol) and $NaHCO_3$ (67.2 mg, 0.800 mmol) were dissolved in a mixture of IPA: THF (0.57 mL, 3:2 v/v). Water (0.01 mL) was added to the reaction mixture to make a 30 wt.% solution of noroxymorphone (**26**) in solvent before 2-chloro-3-iodo-1-propene (**70**) (0.073 mL, 0.700 mmol) was added to the reaction vial. The reaction was stirred at 63 °C for 21 hours and finally turned to clear dark-brown solution. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ solution (5 mL), extracted with diethyl ether (3 x 10 mL) and the combined organic layers

were washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated in *vacuo*. The crude was purified with column chromatography (EtOAc: Petroleum ether = 1:1 to 2:1) to give title product (**59**) as a white solid (128 mg, 71% yield). R_f = 0.54 (50% EtOAc/Petroleum ether); m.p. 197-202 °C (EtOAc); $[\alpha]_D^{25}$ –184 (c 1.000, $CHCl_3$); IR 3165 (OH), 2971 ($CH=CH_2$), 2903 ($CH=CH_2$), 2838 (CH_2), 1729 (C=O), 1619 (C=C), 1456, 1239, 822, 477 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.73 (1H, d, *J* = 8.1 Hz, Ar**H**), 6.60 (1H, dt, *J* = 8.2, 0.9 Hz, Ar**H**), 5.68 (1H, s, C**H**$_2$-C-Cl), 5.38 (2H, d, *J* = 0.8 Hz, C=C**H₂**), 5.06 (1H, s, C**H**$_2$-C-Cl), 4.71 (1H, s, OC**H**), 3.37-3.25 (2H, m, NC**H₂**), 3.11-2.96 (3H, m, C**H₂** and NC**H**), 2.66 (2H, ddd, *J* = 18.2, 5.7, 1.1 Hz, C**H₂**), 2.65-2.55 (1H, m, C**H**$_2$), 2.47 (1H, td, *J* = 12.4, 5.2 Hz, C**H**$_2$), 2.37-2.22 (1H, m, C**H**$_2$), 1.99 (1H, s, O**H**), 1.90 (1H, ddd, *J* = 13.3, 5.0, 2.9 Hz, C**H**$_2$), 1.70-1.54 (2H, m, 2H from different C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.3 (C), 143.5 (C), 139.2 (C), 138.8 (C), 128.9 (C), 123.9 (C), 119.9 (CH), 117.8 (CH), 115.6 (CH_2), 90.6 (CH), 70.5 (C), 62.4 (CH), 61.0 (CH_2), 50.9 (C), 42.9 (CH_2), 36.1 (CH_2), 31.2 (CH_2), 30.4 (CH_2), 23.7 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{19}H_{21}NO_4Cl]^+$ $[M+H]^+$: 362.1159, found: 362.1154.

Ethyl-3-((4*R*,4a*S*,7a*R*,12b*S*)-4a,9-dihydroxy-7-oxo-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-e] isoquinolin-3-yl) propanoate (62)

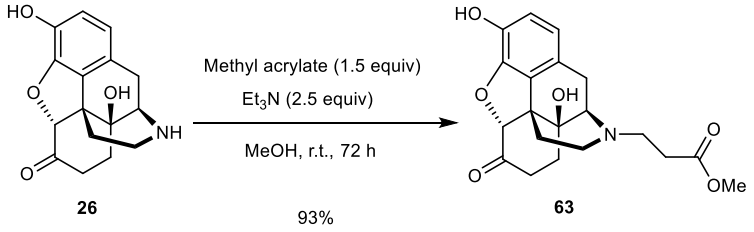


26 **62**

To a solution of Noroxymorphone (144 mg, 0.50 mmol) in EtOH (2.5 mL), was added triethylamine (0.18 mL, 1.25 mmol) and ethyl acrylate (0.083 mL, 0.75 mmol). The reaction was stirred at 80 °C and turned to dark-brown solution after 72 hours, that was diluted with diethyl ether (10 mL). The reaction mixture was washed with brine (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated

in *vacuo* to give title product (**62**) as a yellow foam (167 mg, 86% yield). R_f = 0.66 (EtOAc); $[\alpha]_D^{25}$ –148 (c 1.000, $CHCl_3$); IR 3168 (OH), 2980 (CH_2), 2919 (CH_3), 2838 (CH_2), 1722 (C=O), 1621 (C=O), 1465, 1246, 892, 497 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.48 (1H, s, O**H**), 6.74 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.62 (1H, d, *J* = 8.2 Hz, Ar**H**), 4.97 (1H, s, O**H**), 4.70 (1H, s, OC**H**), 4.21 (2H, q, *J* = 7.1 Hz, C**H₂**CH_3), 3.15-2.97 (3H, m, 2C**H**$_2$ and NC**H**), 2.89 (2H, dt, *J* = 12.9, 7.2 Hz, C**H₂**), 2.71-2.57 (2H, m, 2C**H**$_2$), 2.62-2.45 (2H, m, C**H₂**), 2.41 (1H, td, *J* = 12.4, 5.0 Hz, C**H**$_2$), 2.37-2.20 (2H, m, 2C**H**$_2$), 1.90 (1H, ddd, *J* = 13.4, 5.1, 2.9 Hz, C**H**$_2$), 1.70-1.54 (2H, m, 2C**H**$_2$), 1.32 (3H, t, *J* = 7.2 Hz, C**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.8 (C), 172.3 (C), 143.5 (C), 138.9 (C), 128.9 (C), 124.0 (C), 119.9 (CH), 118.0 (CH), 90.5 (CH), 70.3 (C), 63.6 (CH), 60.7 (CH_2), 50.8 (C), 50.2 (CH_2), 43.2 (CH_2), 36.1 (CH_2), 33.4 (CH_2), 31.3 (CH_2), 30.6 (CH_2), 23.7 (CH_2), 14.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{21}H_{26}NO_6]^+$ $[M+H]^+$: 388.1755, found: 388.1746.

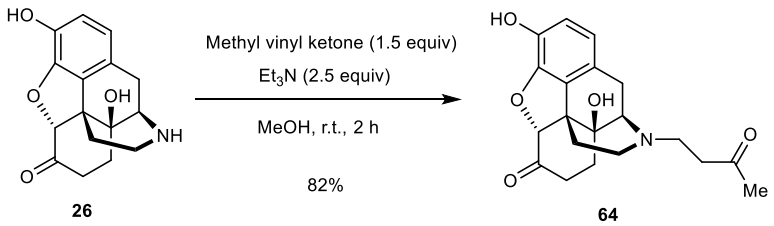
Methyl-3-((4*R*,4a*S*,7a*R*,12b*S*)-4a,9-dihydroxy-7-oxo-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-e] isoquinolin-3-yl) propanoate (63)



To a solution of noroxymorphone (144 mg, 0.50 mmol) in MeOH (2.5 mL), was added triethylamine (0.18 mL, 1.25 mmol) and methyl acrylate (0.068 mL, 0.75 mmol). The reaction was stirred at room temperature and turned to clear brown solution after 72 hours, diluted with diethyl ether (10 mL). The reaction mixture was washed with brine (10 mL), extracted with EtOAc (3 x 15 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in *vacuo* to give product (**63**) as white solid (175 mg, 93% yield). R_f = 0.52 (EtOAc); m.p. 174-176 °C (EtOAc); $[\alpha]_D^{25}$ –136 (c 1.000, $CHCl_3$); IR 3278 (OH), 2931 (CH_3), 2838 (CH_2), 1736 (C=O), 1638 (C=O), 1263, 890, 556 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.65-6.52 (1H, m, Ar**H**), 5.42-4.73 (2H, m, 2O**H**), 4.68 (1H, s, OC**H**), 3.72 (3H, s, OC**H₃**), 3.13-2.94 (3H, m, 2C**H**$_2$ and NC**H**), 2.92-2.73 (2H, m, C**H₂**), 2.70-2.56 (2H, m, 2C**H**$_2$), 2.52 (2H, ddt, *J* = 9.1, 5.5, 3.1 Hz, 2C**H**$_2$), 2.38 (1H, td, *J* = 12.5, 5.0 Hz, C**H**$_2$), 2.33-2.19 (2H, m, 2C**H**$_2$), 1.88 (1H, ddd, *J* = 13.4, 5.2, 2.9 Hz, C**H**$_2$), 1.67-1.52 (2H, m, 2C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.7 (C), 172.7 (C), 143.5 (C), 138.9 (C), 128.9 (C), 124.0 (C), 119.9 (CH), 117.9 (CH), 90.5 (CH), 70.3 (C), 63.7 (CH), 51.8 (CH_3), 50.8 (C), 50.2 (CH_2), 43.1 (CH_2), 36.1 (CH_2), 33.2 (CH_2), 31.3 (CH_2), 30.6 (CH_2), 23.7 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{20}H_{24}NO_6]^+$ $[M+H]^+$: 374.1598, found: 374.1594.

(4*R*,4a*S*,7a*R*,12b*S*)-4a,9-dihydroxy-3-(3-oxobutyl)-2,3,4,4a,5,6-hexahydro-1*H*-4,12-methanobenzofuro[3,2-e] isoquinolin-7(7a*H*)-one (64)



To a solution of noroxymorphone (144 mg, 0.50 mmol) in MeOH (2.5 mL), was added triethylamine (0.18 mL, 1.25 mmol) and methyl vinyl ketone (0.063 mL, 0.75 mmol). The reaction was stirred at room temperature and turned to clear brown solution after 2 hours, diluted with diethyl ether (10 mL). The reaction mixture was washed with brine (10 mL) and extracted with EtOAc (3 x 10 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in *vacuo* to give (**64**) as white solid (147 mg, 82% yield). R_f = 0.25 (EtOAc); m.p. 194 - 201 °C (EtOAc); $[\alpha]_D^{25}$ –188 (c 1.000, $CHCl_3$); IR 3381 (OH), 2980 (CH_3), 2841 (CH_2), 1705 (C=O), 1639 (C=O), 1237, 806, 522, 489 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.63-6.55 (1H, m, Ar**H**), 5.62-4.70 (2H, br, 2O**H**), 4.68 (1H, s, OC**H**), 3.17-2.95 (2H, m, C**H₂**), 2.95 (1H, d, *J* = 5.8 Hz, C**H**$_2$), 2.90-2.68 (2H, m, C**H₂**), 2.70-2.64 (1H, m, C**H**$_2$), 2.68-2.55 (2H, m, C**H₂**), 2.60-2.51 (1H, m,

C**H**$_2$), 2.37 (1H, td, *J* = 12.5, 5.0 Hz, C**H**$_2$), 2.30 (1H, dt, *J* = 14.5, 3.1 Hz, C**H**$_2$), 2.25-2.16 (1H, m, C**H**$_2$), 2.20 (3H, s, C**H**$_3$), 1.87 (1H, ddd, *J* = 13.4, 5.2, 2.9 Hz, C**H**$_2$), 1.70-1.51 (2H, m, 2H from 2 different C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5 (C), 207.2 (C), 143.4 (C), 138.8 (C), 128.8 (C), 124.1 (C), 120.0 (CH), 117.9 (CH), 90.5 (CH), 70.3 (C), 63.4 (CH), 50.8 (C), 48.9 (CH_2), 43.4 (CH_2), 42.1 (CH_2), 36.1 (CH_2), 31.2 (CH_2), 30.6 (CH_2), 30.3 (CH_3), 23.4 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{20}H_{24}NO_5]^+$ $[M+H]^+$: 358.1649, found: 358.1643.

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