The synthesis of morphine-6-glucuronide analogues as potential analgesics

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THE SYNTHESIS OF MORPHINE-6-GLUCURONIDE ANALOGUES AS POTENTIAL ANALGESICS

by

Anna M.A. Di Pretoro

A Doctoral Thesis

Submitted in partial fulfilment for the requirements for the award of DOCTOR OF PHILOSOPHY of the LOUGHBOROUGH UNIVERSITY OF TECHNOLOGY October 1996

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ACKNOWLEDGEMENTS

I would like to thank Professor B.A. Marples and Dr. J.R. Traynor for their advice and assistance during the course of this project. I am extremely grateful to Dr. J.R. Traynor for his hard work in initiating the project, and securing funding.

I am indebted to The British Technology Group for their funding of this research project, and I would like to thank Dr. T. Smith for making it all possible.

I am grateful to all the technical staff Mr. J. Greenfield (mass spectroscopy); Mr. J. Kershaw (NMR spectroscopy); Mr. A. Daley, Mr. P. Hartopp and Mr. A. Kowalski, for all their hard work.

Many thanks to those who kept me sane over the years Dinesh, Ed, Catrina, Jase, Samina, Hank, Jim, Sue, Catherine, Mandy, Liz, Noeleen, Tara, Dave Corser, Dave Clark, Dave Price, Jon, Gi, Kevin, Mark, Moharem, Bob and Violetta.

Special thanks to two life long friends I have made during this time, Phil Naylor and Dr. C. Hinde. They looked after me, gave me constant encouragement when the going got tough and never gave up on me. Friends such as these are very rare indeed.

Love to my Mom and Dad who were so patient with me over the years. Thanks Mom not only for being an excellent mother but for being a good friend too, I could not have done this without you! My dad was so proud when I started this PhD my only regret is that he is not here to see its conclusion, though I am sure he is watching over me.

Finally lots of love to Paul who has never known me not writing a thesis, I hope things do not change too much.
SYNOPSIS

It is known that morphine-6-glucuronide is more potent than morphine, but it is difficult and expensive to produce. Our aim was to synthesise an analogue(s) of morphine-6-glucuronide which would have similar or enhanced properties, but that could be obtained via a simple synthetic route. It is hoped that such a compound could be used to treat terminally ill cancer patients. Due to the enhanced potency a smaller dose of the drug would be required to effect the same analgesic effect as morphine, and this may help to reduce the effect of morphine tolerance.

Initially the demethylation of codeine to yield morphine was examined. Investigations first involved the use of diisobutylaluminium hydride, but success was found using boron tribromide in chloroform.

Hydroxyl group protection was investigated using acetyl, benzyl, t-butyldimethylsilyl and methoxymethyl protecting groups. Selective protection of the phenolic function of morphine as opposed to the secondary alcohol was achieved in all cases.

A number of codeine-6-O-ester were synthesised using the reaction of an acid chloride or an acid anhydride on the secondary alcohol, or the coupling of a carboxylic acid with the secondary alcohol using 1,3-dicyclohexylcarbodiimide and 4-N,N-dimethylaminopyridine as a catalyst. A parallel series of morphine-6-O-ester derivatives was then completed. The phenol function in morphine was protected with the t-butyldimethylsilyl group before esterification, as in the codeine series, and later removed by fluoride ions. Tetrabutylammonium fluoride was used as the source of fluoride ions except in the case of the 6-O-phthalate ester where hydrogen fluoride in pyridine was used. The products isolated were essentially aromatic esters encompassing a variety of functional groups: acetyl, carboxylate, halogens, hydroxyl, methoxy and nitro.

The preparation of a series of 6-O-benzyl ethers of morphine was attempted, but was largely unsuccessful due to quaternisation at the amine function.
The synthesis of codeine-6-glucuronide and morphine-6-glucuronide was successfully completed. The glucuronic acid residue was introduced by use of the acetobromoderivative of glucuronic acid, via the Koeings-Knorr reaction. Deacetylation of the sugar moiety was effected using sodium methoxide and hydrolysis of the ester function was performed using pig liver esterase, rather than barium hydroxide and oxalic acid as previously reported in the literature.
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<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>BBr₃</td>
<td>boron tribromide</td>
</tr>
<tr>
<td>BF₃Et₂O</td>
<td>boron trifluoride etherate</td>
</tr>
<tr>
<td>BnBr</td>
<td>benzyl bromide</td>
</tr>
<tr>
<td>C-6-G</td>
<td>codeine-6-glucuronide</td>
</tr>
<tr>
<td>CHCl₃</td>
<td>chloroform</td>
</tr>
<tr>
<td>CuSO₄</td>
<td>copper (II) sulphate</td>
</tr>
<tr>
<td>DCC</td>
<td>1,3-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(N,N)-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>(N,N)-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>FAB</td>
<td>fast atom bombardment</td>
</tr>
<tr>
<td>HCl</td>
<td>hydrochloric acid</td>
</tr>
<tr>
<td>K₂CO₃</td>
<td>potassium carbonate</td>
</tr>
<tr>
<td>KOH</td>
<td>potassium hydroxide</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>M-3-G</td>
<td>morphine 3-glucuronide</td>
</tr>
<tr>
<td>M-6-G</td>
<td>morphine 6-glucuronide</td>
</tr>
<tr>
<td>MgSO₄</td>
<td>magnesium sulphate</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>Na₂SO₄</td>
<td>sodium sulphate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PTSA</td>
<td>p-toluenesulphonic acid</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBDMS</td>
<td>t-butyldimethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
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INTRODUCTION

What is pain? Pain is one of the most fundamental and important human experiences, and also one of the most complex. It is a warning signal of physiological disorder for which man has evolved a system of producing and sending nonciceptive ('pain receptor') messages to the central nervous system (CNS) for decoding. Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life. Though pain is a familiar experience it only becomes a clinical problem if it becomes chronic or reaches a severity that restricts normal activity.

Pain maybe broadly divided into acute and chronic according to duration. Acute pain can arise through a number of physical causes such as tissue damage, inflammation or muscle spasm, or physiological processes such as labour. Pain arising through physical causes can vary in intensity from mild to severe but is nearly always transient and self-resolving. It is considered a normal physiological response to guard the integrity of the organism and allow healing of damaged tissues.

Chronic pain generally arises through disease processes which lead to long lasting inflammation, or through inappropriate signals originating in the brain or peripheral nerves. In some patients pain can become so severe as to be intolerable without medical intervention.

Severe pain relievers such as the opiates have a strong narcotic action, are centrally acting and are termed analgesics. Minor pain relievers such as aspirin are non narcotic, act peripherally and are termed analgetic. They all act by diminishing pain perception.
1.1 Morphine

The power to alleviate severe pain has been one of man's foremost aspirations for many centuries. The world's first relief being in the form of opium, the dark sun-dried latex exuded from the fruit of the poppy, *Papaver somniferum*. References to the use of opiates have been found dating back to about 3000 BC. Opium itself is a resinous material that contains at least 40 different alkaloids, but the most important active constituent, isolated and identified in 1803 by Derosne\(^1\), is morphine (1). It was purified for pharmaceutical use a year later by Seguin\(^2\).

![Morphine structure](1)

Many chemists tried to elucidate its structure over the years but it was Robinson and Galland's\(^3\) proposal in 1925 that gave the correct structure for the alkaloid. However, a further 30 years elapsed before a successful total synthesis was determined by Gates and Tschudi\(^4\) in 1956.

Since its discovery morphine has been and still remains the foremost analgesic in the world. It is readily available, relatively inexpensive, a powerful sedative and its analgesic action is rapid in onset, reliable and long lasting. However, it is by no means ideal and its clinical use is greatly restricted by a number of unwanted side effects. Prolonged use can result in physical dependence on the drug. Ceasing administration of the alkaloid at this stage results in dangerous and painful withdrawal symptoms which can only be alleviated by recommencing morphine administration, or that of certain related compounds. Allied to physical dependence is the phenomenon of tolerance whereby a greater and greater dose of morphine is required to achieve the
desired result. Another severe consequence is that it causes respiratory depression, serious at low dosage but often fatal at higher doses. In addition to the problems of clinical usage, the euphoric effect induced by morphine has led to its large-scale world-wide abuse, both in its natural form and, more often, as its easily produced diacetyl derivative heroin (2).

Heroin is three times as potent as morphine and its increased solubility in lipids leads to faster penetration through the blood brain barrier, producing an intense 'rush' when injected intravenously.

1.2 Synthetic Analgesics

These side effects have made the development of other analgesics lacking such properties a highly desirable objective. Thus for many years there has been intensive research into the chemistry of the opium alkaloids and related compounds. This work can be categorised into 3 main areas:

a) the synthesis of similar compounds possessing only part of the morphine skeleton.
b) the construction of molecules more complex than morphine by altering the peripheral shape.
c) modifications of morphine itself, retaining the pentacyclic system.
1.2.1 Compounds possessing part of the morphine skeleton

A large proportion of the early work consisted of the preparation of simple fragments of the morphine molecule. In this way it was hoped to separate the features of the molecule responsible for its analgesic action from those responsible for the unwanted side-effects.

Several groups of compounds which can be regarded as fragments of the morphine skeleton have been synthesised.

i) Morphinans

The morphinans contain the complete carbon-nitrogen skeleton of morphine but lack the dihydrofuran oxygen.

\[
\text{N-Methyl morphinan (3) has about one fifth the analgesic activity of morphine, though the introduction of a hydroxyl group at the 3-position leads to a substantial rise in potency, (-) levorphanol (4) being four times as active as morphine. The (+) isomer, dextrorphan, is totally devoid of analgesic activity because its 3-D shape prevents it from binding to the receptor. Variations of the N-substituent in (-) levorphanol produced changes of activity similar to those in the morphine series},
\]

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ii) Benzomorphans

May\textsuperscript{6} further dissected the morphinan skeleton producing the 6,7-benzomorphans (5). In addition to the dihydrofuran oxygen the alicyclic ring is also lost leaving the A, B and E rings of morphine.

![Diagram (5)](image)

To indicate ring C, two methyl groups were retained on ring B, leading to the metazocine (6) series, which are non addictive analgesics.

![Diagram (6)](image)

Generally compounds in which the two non cyclic alkyl substituents on ring B are \textit{cis} are powerful analgesics but they cannot relieve withdrawal symptoms in addicted animals, meaning they are not addictive. The \textit{trans} isomers, however, while also potent analgesics, will relieve withdrawal.

Numerous metazocines have been evaluated for pharmaceutical use. The most useful so far is probably pentazocine (7), N-(3,3-dimethylallyl)benzomorphan, an analgesic of less potency than morphine but showing greatly diminished physical dependence\textsuperscript{7} and respiratory depression. When administered to morphine dependent people, it usually precipitates a withdrawal syndrome, because it displaces the more potent opioids from the receptors. Hence it is known as a mixed agonist-antagonist opioid.
Further development has lead to bremazocine (8), a powerful kappa agonist of long
duration which is devoid of addictive properties and respiratory depressant activity.
On the basis of receptor binding, it is about 200 times more active than morphine.

iii) Piperidine Derivatives

The 4-phenylpiperidines constitute the oldest class of synthetic morphine like
analgesics. The first important member, pethidine (9), 1-methyl-4-carbethoxy-4-
phenylpiperidine,9 was discovered in 1939. This class of compounds retains the A
and E rings of morphine.

Pethidine has 10-12% of the overall activity of morphine, though it takes effect more
quickly and has a shorter duration of action. It has moderate antispasmodic as well as
sedative properties, but also possesses many similar side-effects to morphine.

The addition of a 3-OH group results in the bemidone series, while modification of the
ester group to a ketone gives the ketobemidones (10), which have more than six times
the activity of pethidine.
Perhaps the most successful modification of the 4-phenylpiperidine derivatives of morphine are the 4-anilino compounds, like fentanyl (11).

This drug is 50-100 times more active than morphine, owing to its accelerated transport across the blood brain barrier and into the CNS, as a result of its high lipophilicity. Spectacular activities (~5000 times that of morphine) have been achieved by introducing ether or keto substituents e.g. sufentanil (12).

All fentanyl derivatives are very fast acting and of short duration.
iv) Methadone

Further reduction in the morphine skeleton leads to methadone (13), 6-dimethylamino-4,4-diphenyl-3-heptanone. Its pharmacological activity is very similar to morphine but it has an extended duration of action, is less emetic or constipating and leads to little euphoria. It is used clinically to ease the effects of heroin withdrawal, as withdrawal symptoms are less severe than other addictive narcotics. The methadone molecule has been modified in hundreds of ways leading to a number of effective analgesics, such as dextromoramide (14). Though all these compounds can be abused with resulting dependence liability.

\[ \text{(13)} \]

\[ \text{(14)} \]

1.2.2 Compounds having structures more complex than morphine

Bentley\textsuperscript{10} postulated that compounds with a more elaborate structure than morphine, particularly in regard to peripheral shape and rigidity, may fit the part of the receptor concerned with analgesia, but not those concerned with undesirable side effects. He thus developed a series of bridged opiates.

These oripavine derivatives are derived from thebaine (15), a naturally occurring alkaloid which is not a narcotic analgesic but a convulsant, via Diels-Alder and Grignard reactions. Attack of the dienophile, in particular vinyl ketones and alkyl acrylates,\textsuperscript{11,12} occurs on the outer face of the conjugated diene, from the same side as the nitrogen bridge, and hence the resultant adducts have the etheno bridge located on the opposite side of the molecule compared to the nitrogen bridge. This gives rise to
the 6,14-endo-etheno-6,7,8,14-tetrahydro-thebaine series (16). The dienophile adds regiospecifically at C-7, however stereoisomers can be produced depending on the position of the dieneophile relative to the diene.

![Diagram of molecular structure](image)

The presence of the etheno bridge adds greater rigidity to the molecule and the new centre at C-19 offers the opportunity for tangible changes to be made in both peripheral shape and polarity. A number of carbinol (17) compounds have been prepared via Grignard reaction with the methyl ketone derivative, which are all highly potent analgesics. Grignard addition occurs stereoselectively via a co-ordination complex.

![Diagram of molecular structure](image)

Hydrolysis of the 3-methoxy group to the phenolic hydroxyl results in a large increase in analgesic strength. Catalytic reduction of the etheno bridge increases activity further still. Etorphine (18) is 2000 times as potent as morphine. It is active in doses as small as 0.1 mg for an adult. However, it has only about 30-40 times the affinity of morphine for the opiate receptor. Its enormous activity is due to its great
lipophilicity and thus great ease at penetrating the blood brain barrier. It is used in veterinary medicine for the immobilisation of wild game. Buprenorphine (19) is a powerful analgesic in man, which interestingly at higher doses begins to antagonise itself.\textsuperscript{13}

![Morphine and Buprenorphine Structures](image)

1.2.3 Modifications of morphine retaining the pentacyclic system

Alkylation of the phenolic hydroxyl group on C-3 in morphine decreases analgesic activity, illustrated by codeine (20), which shows about one tenth the potency of morphine, if given parenterally. Its activity is due to the fact that it is partially demethylated in the liver and thus transformed to morphine, the active component. If it is given intracerebrally it is totally inactive as an analgesic. It is widely used as an antitussive (cough suppressant) drug.

Weakening of the electron density at the 3-OH position by the introduction of electron withdrawing substituents (e.g. NO\textsubscript{2}) is deactivating. Shifting the phenolic group to position 2 or 4 results in total loss of activity.

![Codeine and Buprenorphine Structures](image)
Hydrogenation of the 7,8 double bond to give dihydromorphine (21), results in a compound with increased activity but reduced duration of action.

The N-methyl substituent is not absolutely essential to analgesic activity, it is more attributed to lipid solubility. N-Normorphine (22), the secondary amine, has only one eighth of the central activity of morphine, though \textit{in vitro} it is equiactive with morphine,\textsuperscript{14} indicating that it can not cross the blood brain barrier, because of its high polarity. Higher alkyl substituents at the nitrogen render the molecule less active, though if the side chain carries an aromatic ring activity is increased. N-Furylmethyl-normorphine (23) and N-phenylethyl-normorphine (24) derivatives and their analogues can be up to 50 times more active than morphine, due to the involvement of auxiliary binding sites. Substituting N-allyl, nalorphine (25), or N-cyclopropylmethyl, naletrexone (26), shows a dramatic change to antagonist properties.

\begin{align*}
R = & -H \quad (22) \\
= & -\text{CH}_2-\text{CH}_2-\text{O} \quad (23) \\
= & -\text{CH}_2-\text{CH}_2-\text{O} \quad (24) \\
= & \text{C} - \quad (25) \\
= & -\text{CH}_2- \quad (26)
\end{align*}

14-Hydroxy derivatives, such as oxymorphone (27), show increased potency up to five times that of morphine, believed to be the result of additional hydrogen bonding to the receptor.

\begin{center}
\includegraphics[width=0.2\textwidth]{image}
\end{center}
Many modifications can also be performed at the alcoholic hydroxyl group at C-6. Both the 6-keto derivative and the 6-methylene derivative are active analgesics. Heterocodeine, which contains no C-6 hydroxyl group, is about five times as active as morphine.

1.3 The Opiate Receptor

The opiate receptor is generally believed to be composed of protein combined with membrane lipids, though its absolute configuration remains a mystery. The drug has its effect by binding to the receptor and provoking a signal where none was wanted.

Opioid receptors are located in specific areas of the brain, spinal cord and gastro-intestinal tract. They are not all identical, several distinct types exist, and each one has a different affinity for binding with various opioid analgesics. The major categories of receptors have been identified and they have been designated as mu, kappa, delta and sigma receptors. Additionally sub-types of these receptors have also been identified e.g. mu-1 and mu-2.\textsuperscript{15}

As we lack specific agonists and antagonists at each of the opiate receptors, the role of each receptor is not entirely clear.

The mu receptor seems to be the main receptor involved in pain suppression, since all the compounds that are the most effective pain killers do have a preference for this receptor.\textsuperscript{16} Mu receptors are located mostly at supraspinal sites. Activation of receptors in these areas seems to underlie the analgesic, respiratory depressant, miotic, euphoric and physical dependence properties of opiates. It is thought that the mu-1 subtype modulates analgesia and euphoria primarily while the mu-2 subtype modulates respiratory depression. As yet no specific mu-1 or mu-2 analgesics are clinically available. Thus, all analgesics that stimulate mu receptors also induce euphoria and can cause drug dependence. Some mu receptors are also located in the
spinal cord, and help modulate part of the spinal analgesia that is induced by morphine.

Kappa receptors are located principally within the dorsal horn of the spinal cord. They are responsible for inducing analgesia by depressing the initial relay site of pain transmission. Other kappa receptors are located in the brain stem and produce miosis and sedation. Euphoria, physical dependence, and respiratory depression are not mediated by kappa receptors.

Delta receptors are poorly delineated as yet, but they may be involved at brain stem and spinal levels in the production of certain aspects of analgesia.

Sigma receptors appear to be located primarily in the limbic system of the brain. Activation of these receptors results in psychotomimetic, hallucinogenic, and dysphoric responses to certain opioids.

Any drug which elicits a positive response on binding to a receptor is called an agonist. A drug that binds to a receptor but does not elicit a response is called an antagonist. A few drugs exhibit modest analgesic activity in isolation, but can have antagonistic properties in the presence of morphine, and are known as mixed agonist-antagonists.

Snyder and his group published a series of papers characterising the receptor and proposed that it is an allosteric lipoprotein modulated by sodium ions. In the presence of Na\(^+\), the receptor preferentially binds an antagonist, whereas in the absence of Na\(^+\) the agonist binding form of the receptor predominates. Lithium ions can replace sodium, but potassium is inactive. The binding of an agonist can be increased by Cu\(^{2+}\), Mg\(^{2+}\), Mn\(^{2+}\) and Ni\(^{2+}\), whereas the binding capacity is destroyed by reagents which bind to -SH groups, like N-ethylmaleimide, indicating the presence of an essential -SH group near the binding site.
1.4 Endogenous Peptides

It is inconceivable that man has developed receptors to distinguish alkaloids derived from plants, thus neuropharmacologists surmised that opiate receptors serve to detect endogenous regulators of pain perception rather than respond to a plant product. According to this view the opiates exert their pharmacological effects by mimicking molecules that are normally present in the bodies of vertebrates. The breakthrough came in 1975 when a natural morphine like substance was discovered in the brain of pigs. The substance isolated termed 'enkephalin' (Greek for "in the head"), was soon found to be a mixture of two pentapeptides methionine-enkephalin and leucine-enkephalin, in the ratio of 3:1 respectively. Structurally they are very alike differing only in the carboxyl terminus. These peptides interacted selectively with opioid receptors in vitro and were shown to be analgesic on intracerebroventricular administration, although the effects were brief due to rapid metabolism.

A year later longer opiate peptides were isolated from the intermediate lobe of the pituitary gland and termed endorphins. Endorphins are about as potent as morphine on a molecular basis in relieving pain. It is interesting that Met-enkephalin forms the amino terminus of the endorphins, which in turn represents residues 61-91 at the carboxyl terminus of the pituitary hormone, β-lipotrophin, although β-lipotrophin itself does not possess any opiate properties.

A further 17 amino acid peptide was isolated in 1977 and named dynorphin. Dynorphin is leu-enkephalin with an extension of twelve amino acid residues at the carboxyl terminus.

That these peptides are endogenous ligands for the opiate receptor was shown early on since they closely mimic the action of morphine and could be antagonised by the morphine antagonist naloxone.
The endogenous ligands are not absolutely specific for the different types of opioid receptor. β-Endorphin appears to bind equally well to mu and kappa receptors but has no affinity for delta. Leu-enkephalin, on the other hand binds preferentially to the delta receptor but less well to the mu. Morphine itself favours the mu receptor but still has measurable affinity at kappa and delta.\textsuperscript{22}

A large number of peptide analogues have been prepared but only a relatively small number have shown any activity, usually of short duration of action. Rapid hydrolysis between Tyr-Gly deactivates enkephalins and removing Tyr\textsuperscript{1} or interfering with its phenolic hydroxyl or amino group abolishes any activity. Replacement of the Gly\textsuperscript{2} residue with D-Ala renders the peptide resistant to hydrolysis. D-Ala\textsuperscript{2} analogues combined with modifications of Met\textsuperscript{5} have produced the most potent derivatives e.g. [D-Ala\textsuperscript{2}, MePhe\textsuperscript{4}, Met(O)ol\textsuperscript{5}]enkephalin, which showed 1000 times the activity of morphine in the mouse tailflick test.\textsuperscript{23} Unfortunately this activity did not extend to clinical trials,\textsuperscript{24} being limited by various pharmacological drawbacks.

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Amino acid sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met-enkephalin</td>
<td>Tyr\textsuperscript{1}-Gly\textsuperscript{2}-Gly\textsuperscript{3}-Phe\textsuperscript{4}-Met\textsuperscript{5}</td>
</tr>
<tr>
<td>Leu-enkephalin</td>
<td>Tyr-Gly-Gly-Phe-Leu</td>
</tr>
<tr>
<td>α-endorphin</td>
<td>Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu</td>
</tr>
</tbody>
</table>
The intrathecal administration of β-endorphin directly into the cerebrospinal fluid has provided rapid and long lasting (33 h) pain relief in cancer patients with otherwise intractable pain. Synthetic β-endorphins have also been prepared and found to give prolonged and long lasting analgesia when given intrathecally for pain due to disseminated cancer. Unfortunately, all synthetic opioids produce tolerance and addiction.

It may be that individual variations in sensitivity to pain depend on levels of endogenous opioids. In addition, it is believed that in acupuncture there is a release of these natural substances into cerebrospinal fluid. Direct measurement has shown a rise in β-endorphin but not met-enkephalin levels, after acupuncture for recurrent pain.

Ectopic β-endorphin and met-enkephalin have been found in tumour tissue. If this is a common finding these substances may automatically subdue pain in certain malignant diseases and these or other unknown substances may cause physiological changes in the sufferer.

1.5 Morphine 6-glucuronide

Morphine is metabolised in man mainly within human liver microsomes, by glucuronidation at the 3 or 6-position. The major metabolites are morphine 3-glucuronide (M-3-G) (28) and morphine 6-glucuronide (M-6-G) (29), occurring in the ratio 5:1. Small amounts of morphine 3,6-diglucuronide, normorphine, and normorphine 6-glucuronide are also formed.
The M-3-G and M-6-G metabolites accumulate in the plasma in higher levels than that of the parent compound morphine, after chronic oral dosing, and are still present in substantial amounts several hours later.

Traditionally conjugation was thought to terminate the pharmacological activity of a compound and many pharmacologists still believe conjugation means detoxification. Indeed morphine is excreted via the urinary tract as its glucuronides, but it has been shown that M-6-G is pharmacologically more active than morphine.

M-3-G shows no significant binding to any receptor subtype and is devoid of analgesic activity, although it may antagonise some pharmacological effects of morphine. In contrast M-6-G shows a similar binding profile to mu (3H-DAGO), delta (3H-DPDPE) and kappa (3H-EKC) receptors, as morphine.

<table>
<thead>
<tr>
<th>IC50 Value (nM)</th>
<th>Mu</th>
<th>Delta</th>
<th>Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-3-G</td>
<td>&gt;500</td>
<td>&gt;1000</td>
<td>&gt;250</td>
</tr>
<tr>
<td>M-6-G</td>
<td>7.3 + 1.4</td>
<td>&gt;150</td>
<td>&gt;250</td>
</tr>
<tr>
<td>Morphine</td>
<td>4.3 + 1.1</td>
<td>&gt;150</td>
<td>&gt;250</td>
</tr>
</tbody>
</table>

These binding studies indicated that M-6-G is a mu selective opioid with a potency similar to morphine. However on comparing analgesic properties, when injected into rats intracerebroventricularly or into the periaqueductal gray, M-6-G elicited a
profound analgesia, in tailflick tests. In fact M-6-G appeared to be 20-45 times more potent than morphine.\textsuperscript{29} Increasing the dose of M-6-G increased the peak latency and duration of analgesia.

More importantly, M-6-G was 1-4 times more active than morphine when the two compounds were administered subcutaneously, suggesting that it can penetrate into the brain despite its 'high polarity'. M-6-G has been shown by reverse phase HPLC to be far more lipophilic than predicted, in fact not much less lipophilic than morphine itself. Carrupt\textsuperscript{30} postulated that in aqueous media the structure of M-6-G is extended to expose maximally the polar groups for interaction with water. However, that a folded form was also possible, in which the polar groups were shielded, enabling membrane passage of the conjugate.

1.6 Morphine 6-O-esters

A thorough search of the literature has revealed a number of 6-O substituted esters. Here we attempt to outline some of their uses, and properties in comparison to morphine.

Morphine 6-succinate (30) has been prepared to assist in the investigation of the structure of the opioid receptor, using affinity chromatography. It exhibited no difference in peak effect or duration of analgesia compared to morphine, though the lethality of morphine was 1.7 times that of morphine 6-succinate. Its magnitude of dependence was also very similar to morphine.\textsuperscript{31}

\[
\begin{align*}
\text{O} & \quad \text{R} = \text{H} \quad (30) \\
\text{O} & \quad \text{R} = \text{Me} \quad (31)
\end{align*}
\]

3,6-Dipropanoylmorphine (DPM) (32), 3,6-dibutanoylmorphine (DBM) (33) and 3,6-dihexanoylmorphine (DHM) (34) have been prepared as prospective long-acting analgesics. In aqueous solution the stability of the HCl salts of these compounds
decreased with increasing alkyl chain length, so that DHM underwent rapid hydrolysis to 6-monohexanoylmorphine (MHM). Comparison studies using electrically stimulated guinea pig ileum revealed similar potencies and efficacies for all compounds, but marked differences in the onset of drug action i.e. morphine>heroin>MHM>DPM>DBM. DBM and MHM however were found to be five times longer acting than morphine.\textsuperscript{32}

Further 6-O-alkyl ester and 3,6-O-alkyl diester derivatives have been prepared using the fatty acids. These compounds tend to induce changes in thermal sensitivity and motor activity less than the parent compound i.e. reduced potency. They also tended to show a higher water and lipid solubility and were much more lipophilic than the parent drug in terms of octanol-buffer partition coefficients.

\[
\begin{align*}
R=R_1 & = \begin{array}{c}
\text{O} \\
\text{O}
\end{array} \text{C-Et} \\
\text{O} & = \begin{array}{c}
\text{O} \\
\text{O}
\end{array} \text{C-Pr} \\
\text{O} & = \begin{array}{c}
\text{O} \\
\text{O}
\end{array} \text{C-(CH}_2\text{)}_4\text{Me}
\end{align*}
\]

Further 6-O-alkyl ester and 3,6-O-alkyl diester derivatives have been prepared using the fatty acids. These compounds tend to induce changes in thermal sensitivity and motor activity less than the parent compound i.e. reduced potency. They also tended to show a higher water and lipid solubility and were much more lipophilic than the parent drug in terms of octanol-buffer partition coefficients.

\[
\begin{align*}
-n & = 3, 7, 8, 10, 12, 14, 16, 20
\end{align*}
\]

Codeine phosphate has been found to react with citric and tartaric acid, in experimental tablet formulations with paracetamol, forming citrate and tartrate esters,\textsuperscript{33} though no morphine analogue is documented. The structures and absolute configurations have been elucidated but there is no discussion of pharmacological properties.
A number of perfluoracylated compounds have been used to assist in the
determination of impurities in heroin and to identify morphine, using capillary GC and
mass spectrometry techniques. The trifluoroacetate derivative is formed by injecting
the free base with N-methylbistrifluoroacetamide directly onto the GC column. The
pentafluoropropanoate and heptfluorobutanoate derivatives are prepared using
pentafluorobenzoyl chloride or heptafluorobutyric anhydride in pyridine. Reaction with
morphine gives the disubstituted fluoro esters and reaction with 3-O-alkyl derivatives
gives the 3-O-alkyl 6-O-fluoro esters, but selective substitution at position-6 in
morphine has not been achieved.

\[-\text{O}^\ominus \text{C} = \text{C} - \text{CF}_3 \quad -\text{O}^\ominus \text{C} = \text{C} - \text{CF}_2\text{CF}_3 \quad -\text{O}^\ominus \text{C} = \text{C} - \text{CF}_2\text{CF}_2\text{CF}_3\]

Amino acids have also been attached to the morphine skeleton at position-6, in the
search for polysaccharidic prodrugs for enzymatically controlled release. Research
has mainly been carried out on pholcodine (35), being attached to cellulose via an
amino acid spacer arm. The drug is immobilised by the ester function formed between
the hydroxyl at position-6 and the carboxylic group of the C-terminal aromatic
\(\alpha\)-amino acid (Phe or Tyr). Significant release of the drug was only observed in the
presence of \(\alpha\)-chymotrypsin. There is no release if the C-terminal amino acid has
D-configuration.

![Diagram of the morphine skeleton with attached amino acids](image)

The spacer arm which gave the maximum duration for controlled release was the
dipeptide Ile and Tyr.
Oligoethylene glycol esters of codeine have been produced. In this case the ethylene glycol forms an ether bridge between two codeine molecules at their six positions.

\[
\text{codeine} \xrightarrow{O^6} \text{C} = \text{O} \xrightarrow{\text{Me}} \text{CHNHCOCHCHCH}_2\text{Me} \xrightarrow{\text{OH}} \text{codeine}
\]

1.7 Research Aims

The majority of research into the opium alkaloids has been in the search for an analgesic with a potency equivalent to that of morphine but without the addictive side effects. This project, however, is concerned with the potency and tolerance. The hope is to synthesise a drug more potent than morphine though not necessarily non-addictive, such that smaller doses of the drug would be required to effect the same result as morphine, in the hope that the effects of tolerance could be reduced. Also that this may provide more predictable kinetics.

Due to the high potency of M-6-G it has been chosen as our model. Unfortunately, it is very difficult to produce, the published procedure being via the Koenigs Knorr reaction, a quite lengthy and tedious pathway, giving a relatively low total yield. Our hope is to produce compounds with a similar or enhanced activity via a more effective route.
Initially we hoped to introduce a six membered ring connected through the oxygen at position-6 and we have decided to start with a simple aromatic ring. It was further proposed to introduce a number of functional groups to assess their effect on potency, hoping to incorporate carboxyl and hydroxyl functionalities as are present in M-6-G.

A limiting factor throughout the course of this research has been the high cost of morphine ~£250 per g. For this reason much of the work has been directed towards codeine, considerably cheaper at ~£20 per g, derivatives of codeine being successfully synthesised before moving to the morphine series.
DEMETHYLATION OF CODEINE

2.1 Introduction

Initially synthetic studies were directed towards the removal of the 3-methoxy group in codeine (20) to produce morphine (1). The strategy was to synthesise the 6-derivative of codeine and then to demethylate at the 3-position to give the morphine equivalent. A method is required that will successfully cleave the aromatic methyl ether but that will also preserve the labile oxygen bridge and the newly synthesised 6-derivative. The exposure of codeine or morphine to strong acid or alkali conditions at higher temperatures is known to promote substantial decomposition of these alkaloids. Thus, conventional procedures for ether cleavage have been unsuccessful when applied to the conversion of codeine to morphine.

Treatment of codeine with pyridine hydrochloride at elevated temperature was the first successful method employed. It was used by Rapoport\(^3\) for the O-demethylation of \(^14\)C-labelled codeine, by Gates\(^4\) in his total synthesis of (−)-morphine, and by Goto\(^3\) in the preparation of (+)-morphine. Practical difficulties though were encountered in isolation and purification, and yields were low (15-34%). Next Takeda utilised lithium diphenylphosphide to convert B/C trans-codeine and B/C trans-isocodeine\(^3\) to the corresponding morphines, in up to 61% yield. Later DeGraw\(^3\) reported a comparatively mild method, where codeine was treated with an excess of sodium propylmercaptide in dimethylformamide at elevated temperatures to afford morphine in 80% yield. It was Rice\(^4\) however, who produced the most simple, efficient and high yielding conversion of codeine to morphine (91%), using boron tribromide. More recently Andre\(^3\) has replaced this reagent with the methane sulfonic acid - methionine system, known as hard acid - soft nucleophile, reacting by a push-pull mechanism. Me\(^+\) has an appreciable affinity with sulphur because of its softness, thus methionine acts as an alkyl acceptor forming methionine S-methyl. Although some sulphides other than methionine may accept alkyl groups in this reaction,
methionine is preferable because of its biofunctionality, which makes isolation of the phenolic product convenient. This method overcomes problems with toxicity at an industrial scale, but has sacrificed the high yields (69%).

2.2 DIBAL-H

It has been reported that the aromatic steroidal ethers of the estrone series are split by alkylaluminium derivatives. Demethylation of these ethers could not be conducted under acid or Lewis acid catalysed conditions because of side reactions involving rearrangements. The only previous acceptable method was a high temperature process using a Grignard reagent to prepare the magnesium salts of the corresponding phenols. These ethers are, however, smoothly cleaved at 70-80°C with diisobutylaluminium hydride or triisobutylaluminium, to generate the corresponding phenol in high yield.

\[
\text{DIBAH}
\]

\[
\text{MeO} \rightarrow \text{HO}
\]

95%

It was decided to utilise this procedure for the demethylation of the aromatic ether in codeine. Unfortunately the treatment of codeine with DIBAH in toluene at 70°C, did not lead to the isolation of morphine. Instead an orange powder believed to be an aluminium salt, because of its abnormally high melting point (>300°C), was obtained. Similar unsuccessful results were obtained using thebaine. This failure meant a different approach was required.

2.3 Boron Tribromide

Of the methods outlined earlier, that of Rice appeared to be the simplest and gave the highest yields. The procedure consists of addition of a chloroform solution of codeine
to an excess of boron tribromide in chloroform, at room temperature. Brief stirring is followed by quenching the reaction mixture with ice-ammonium hydroxide and simply filtering off the morphine hydrate which results. Initial reactions afforded very low yields (28%) but a study of reaction times and dilution soon allowed high yields to be repeatedly reproduced. The optimum reaction time was found to be 1 h and the optimum dilution 80% of that quoted by Rice, this giving yields of 95%. Morphine was identified by its NMR spectrum which showed no methoxy singlet when compared to that of codeine.

\[
\text{MeO} \quad \text{Me} \\
\text{N-Me} \quad \text{N-Me}
\]

The reaction probably proceeds via a complex formed between the reagent and the ethereal oxygen atom. The reaction grade chloroform was used in this procedure, as stated in the original method. Using dry, distilled chloroform gave very low yields. It is thought that the ethanol impurity acts as a catalyst initiating the reaction, possibly by removing bromide from the intermediate complex, thus driving the reaction forward.
2.4 Application to Codeine Esters

The first 6-O-ester derivative to be synthesised was codeine 6-O-phthalate (36). This was easily prepared by refluxing codeine with phthalic anhydride in pyridine. See Chapter 4.

To obtain the morphine analogue of this compound it was proposed to demethylate using boron tribromide. Unfortunately the product isolated from the demethylation was found to lack the phthalate moiety. Initially it was thought that morphine had been regenerated but the product isolated was soluble in CHCl₃, where morphine is totally insoluble. A close inspection of NMR data showed significant differences in the fine structure, in comparison to morphine. Fig 1.

In the proton spectrum the 1 and 2-H ABₜ remained unchanged at δ 6.60. The 16-H₂ and 15-H₂ splitting patterns remain unchanged but shifted slightly upfield. The 10-H₂ splitting patterns also remain unchanged with the 10β-H remaining at δ 3.03, but the 10α-H is shifted downfield. These results suggest that the morphine structure itself remains intact. Subtle differences in the rest of the fine structure suggest some type of rearrangement. The double bond protons appear shifted downfield, by 0.4 ppm, and the further downfield doublet loses much of its resolution, suggesting reduced coupling effects. The 5-H doublet suffers a similar fate, losing resolution and being shifted 0.2 ppm downfield. The 6-H multiplet at δ 4.19 is shifted little, but a distinct doublet is observed. The 9-H quartet remains but again is shifted downfield, by 0.2 ppm. The 14-H is also shifted downfield, but now appears as a distinct doublet.
Morphine
β-Isomorphine
Examining the COSY spectra of morphine and this new compound (Fig 2 and 3) help to highlight these changes. Both the double bond protons are now coupled to the 5-H whereas only the further downfield one was in the morphine case. The 14-H also shows apparent loss of coupling to the double bond protons but enhanced coupling to the 6-H proton. The 5-H shows no coupling to the 6-H proton, suggesting that they are no longer neighbouring groups. The 9-H shows the same coupling pattern in both cases, as do the 10-H₂.

It is concluded from this information that β-isomorphine (37), the 8-OH isomer of morphine, has been isolated. The shifts in fine structure and resolution differences being accounted for by this structure. References to this compound do occur in the literature, but there is no apparent documented NMR data for comparison.

![Chemical Structure](image)

(37)

It is certain that the reaction conditions are too strongly acidic and are removing the ester functionality. There are therefore two possible avenues open. Firstly, find a new process of demethylation which will leave the ester function intact. This could be a difficult task since the conditions required for cleaving a methyl ether are most likely to cleave the ester. Secondly introduce a protecting group at the phenolic position on morphine to prevent reaction during esterification of the 6-hydroxyl group, and which would be able to be removed in the presence of an ester, (e.g. benzyl or TMS).
SELECTIVE PROTECTION OF 3-OH

The use of protective groups is a very important tool in synthetic methodology and has been a rapidly expanding field over recent years. The requirements for a good protecting group are:

a) it must react selectively in good yield to give a protected compound.
b) it must be selectively removed in good yield.
c) it should preferably be non-toxic.
d) it forms a crystalline derivative that is easily isolated from unwanted side products.
e) it gives minimum additional functionality to avoid further sites of reaction.

In the case of morphine, we need to protect a phenol in the presence of a secondary alcohol.

3.1 Acetylation

One of the earlier protecting groups used selectively at the phenolic function in morphine was the acetate function. It is easily introduced by the method of Welsh, treating a basic suspension of morphine in water with acetic anhydride. Unfortunately 3-O-acetylmorphine (38) has a tendency to be amorphous, existing with occluded solvent which is difficult to remove. Welsh chose to isolate his compound as the sulfamate. Carrupt chose to avoid any isolation procedure and to conduct his reactions in situ. We did manage to isolate a relatively clean crude product but found the acetate group to be highly labile in nature and decided against its continued use, on the basis that this could lead to reduced selectivity. The high stability of the phenoxide anion and the acetate carbocation leads to rapid hydrolysis of phenylacetates under mild conditions.
Ethers now tend to be more widely used for protecting phenols and there are a number of protecting groups documented in this area that could be utilised in this situation.

### 3.2 Benzylation

The methyl ether, as already seen, requires rather drastic conditions for removal but the benzyl group can easily be removed under much milder conditions i.e. hydrogenolysis.

The preparation of 3-O-benzylmorphine has been described by Merck\(^4\) and Rodionow.\(^5\) Benzylation is performed by refluxing in DMF with potassium carbonate and benzyl chloride. Attempting to repeat this reaction proved unsuccessful, a multi-benzylated compound being obtained.

Brands\(^6\) et al also found difficulties in trying to prepare 3-O-benzylmorphine. They suggest that dibenzylation occurs, at the phenolic position and at the nitrogen, producing a quaternary ammonium salt. **Scheme 1.** They propose that this compound then undergoes a Hofmann degradation under alkaline conditions, and on rearrangement produces the diene (41).
The IR spectrum of the compound we isolated showed a broad band at $\nu_{\text{max}}$ 3364 cm$^{-1}$, suggesting the presence of an OH group, and the ferric chloride test for a phenol proved negative, so this must be due to the hydroxyl group. The $^1$H NMR data showed certain similarities to the diene isolated by Brands, but we have isolated a tribenzylated rather than a dibenzylated product. The spectrum shows the presence of 3xABq in the region $\delta$ 4.60 - 5.31 which would represent three benzyl CH$_2$ groups. It is believed that 3-O-benzylation did occur highlighted by the 0.15 ppm downfield shift of the 1- and 2-H ABq, compared to morphine. The spectrum also shows three olefinic signals at $\delta$ 5.72, 6.16 and 6.45 suggesting conjugation, and consistent with Brands' structure. The downfield shift of the N-Me to $\delta$ 2.95, however, suggests a quaternary nitrogen. If the D-ring has been broken to produce the diene then this must be due to the addition of two benzyl groups. This could also explain the location of the ABq relating to the benzyl group attached to the nitrogen, which we would expect to find in the region $\delta$ 3.40. Instead both are located downfield at $\delta$ 4.60-5.09. The presence of a quaternary nitrogen could produce a
significant electron withdrawing effect compared to the amine, and thus produce this
downfield shift. From this information we can surmise that the compound we have
isolated is a Hofmann degradation product, which has been further benzylated before
isolation, possibly having the structure shown below.

![Chemical Structure](image1)

(42)

The reaction was repeated using different bases (i.e. NaH, NaOH and KOH) and in
different solvents (i.e. EtOH, DMF and DMSO) but where reaction did occur the
results remained the same.

Brands overcame this problem in selectivity by using cesium carbonate, and isolated
3-O-benzyl-morphine in 97% yield. These results were attributed to two properties of
cesium cations. First that they are poorly solvated in DMF due to their relatively large
ionic radii, and therefore, caesium salts exist as intimate ion pairs in solution. Second
that they are capable of forming so-called triple ions due to their high polarisability,
thus allowing the formation of a transition state as depicted below.

![Chemical Structure](image2)
We proceeded by moving to the more reactive reagent, benzyl bromide. Reacting with potassium carbonate in DMF was unsuccessful, even after adding a little KI in an attempt to initiate the reaction. Using a different solvent, acetone, gave similar results. However, on choosing a more powerful base, potassium hydroxide in a finely divided form, 3-O-benzylmorphine (43) was finally obtained, albeit in low yield, 30%.

```
\[ \text{K}_2\text{CO}_3 / \text{BnBr} \rightarrow \text{acetone} \]
```

The \(^1\text{H}\) NMR spectrum showed a broad multiplet at \(\delta 7.36-7.44\) corresponding to the benzyl aromatic protons. The benzylic ABq was observed at \(\delta 5.05-5.19\), with a coupling constant of \(J 12\) Hz. The N-Me singlet located at \(\delta 2.4\) showed no N-benzylation. The remainder of the fine structure showed the same spin–spin coupling as in morphine and signals occurred at similar chemical shifts.

The main disadvantage in using the benzyl ether protecting group is that when it is removed by hydrogenolysis, the morphine double bond in the C-ring is also lost. It is known that the double bond does not contribute to the analgesic properties of morphine, but we have also investigated a silylation procedure which would allow the retention of the double bond.

### 3.3 Silylation

Initial silylation reactions centred on the trimethylsilyl (TMS) group, which is easily removed in aqueous conditions. The reaction involves heating to 30-35°C with TMSCI in pyridine.\(^{48}\) Unfortunately even though the reaction was seen to progress by TLC, isolation of a product proved fruitless, only morphine was recovered. It is
thought that the highly labile TMS group is being removed during the work up. We cannot, however, conduct the reaction in situ as we do not know at which position the TMS group has been incorporated, if indeed at only one position. It was decided to use a silyl protecting group that was more stable, and the highly popular tert-butylidimethylsilyl (TBDMS) group was chosen. It is easily introduced with a variety of reagents, is relatively stable to a variety of organic reactions and is readily removed under conditions that do not attack other functional groups. It is approximately $10^4$ times more stable to hydrolysis than the TMS group. It has excellent stability towards base but is relatively sensitive to acid.

The most common method for the introduction of the TBDMS group is reacting with TBDMSCl and imidazole in DMF at 25°C. Utilising this procedure to protect morphine we managed to isolate the disilyl derivative (44).

\[
\begin{align*}
\text{HO} & \quad \text{N-Me} \\
\text{O} & \quad \text{TBDMSCl} \\
\text{HO} & \\
\text{imidazole / DMF} & \quad \text{OH} \\
\end{align*}
\]

The IR spectrum lacked any OH stretching bands suggesting silylation at both the phenol and secondary alcohol. The $^1$H NMR spectrum showed the N-Me singlet at $\delta$ 2.49 comparable to morphine. Two singlets were observed at $\delta$ 0.92 and 0.98 corresponding to the two t-butyl groups ($2x\text{SiCMe}_3$) and four singlets were observed in the region $\delta$ 0.10 - 0.21 corresponding to the four methyl groups ($4x\text{SiMe}_2$). The remainder of the fine structure appearing similar to that in morphine. The reaction was repeated altering the equivalents of reagents used and reaction times, but a monosilylated product could not be obtained.
The solution to this problem must be to make the phenol more susceptible to electrophilic attack than the secondary alcohol, and it was decided, as in the benzyl case, to use a strong base to produce the phenoxide anion, and enhance reactivity at that position. Thus the reaction of morphine with NaH and TBDMSCl in THF allowed isolation of the desired monosilylated product (45). Yields were relatively low at 50%, but unreacted morphine was recovered.

The IR spectrum exhibited a broad OH band at 3552 cm⁻¹ and, as the ferric chloride test for a phenol proved negative, this must be due to the hydroxyl group. The ¹H NMR spectrum as expected, showed the N-Me singlet at δ 2.54 comparable to morphine, a singlet at δ 0.98 and two singlets at δ 0.20 and 0.16 corresponding to one t-butyldimethylsilyl group. The remainder of the fine structure was comparable to that of morphine.

This morphine 3-O-TBDMS ether compound has been used extensively in our research.

3.4 Methoxymethyl (MOM) Ether

Morphine 3-O-MOM ether (46) was prepared in a similar manner to morphine 3-O-TBDMS ether, using NaH to produce the phenoxide anion and then utilising chloromethyl methyl ether (MOM-Cl) to effect a substitution reaction. Unfortunately in this case the reaction was found to be less selective. The morphine 3-O-MOM ether
was isolated but in very low yield (20%), and the disubstituted product (47) was identified as the major product (26%)

\[ \text{N-Me}\text{3-O-MOM} \]

The NMR spectrum of morphine 3-O-MOM ether showed the appearance of a 3 H singlet at \( \delta \) 3.46 and a 2 H doublet at \( \delta \) 4.97, signifying the presence of the MOM group. The 1- and 2-H ABq was shifted 0.2 ppm downfield compared to morphine, suggesting substitution at the 3-position. The 5-, 16- and 15a-H were also shifted downfield to \( \delta \) 5.56, 3.16 and 2.71 respectively, probably due to their close proximity to the MOM group. The remainder of the fine structure was very similar to morphine.

It was suggested that lack of reactivity at the phenolic function may be caused by solubility problems with the morphine anion in non-polar solutions. It was decided to use a phase transfer catalyst and a biphasic system. A similar procedure has been successfully used to protect phenolic functions in complex chalcones.\(^{50}\) Chloromethyl methyl ether was added to a mixture of morphine, aqueous sodium hydroxide and tetrabutylammonium hydrogen sulphate in DCM, at room temperature. Unfortunately no reaction was observed.

Rall\(^{51}\) also encountered problems in methoxymethylating phenol functions in certain chalcones. A solution was found by using 18-Crown-6, probably due to the ability of crown ethers to dissolve alkali metal salts in non-polar solvents. Chloromethyl methyl ether was added to a mixture of 18-Crown-6 and the potassium salt of morphine in dry acetonitrile, at room temperature. Unfortunately no reaction was observed.
Thus a high yielding process for the preparation of morphine 3-O-MOM ether has, as yet, eluded us.
ESTERIFICATION

The first linkage to be investigated for the introduction of our substituents was the ester. Much of the research conducted during the course of this project has been towards the production of a number of substituted morphine esters. Initially for pharmacological comparison purposes and to assess the viability of each esterification reaction, the codeine analogue was first prepared in each case. Aromatic esters were chosen as a starting point with the view to incorporate carboxyl and hydroxyl functions as in M-6-G.

4.1 Codeine Esters

The first ester to be synthesised was codeine 6-O-phthalate (36), prepared in high yield by refluxing codeine with phthalic anhydride in pyridine. The IR spectrum showed two carbonyl stretches at 1713 and 1608 cm\(^{-1}\), the first signifies the presence of an ester group and the second that of a carboxylic acid group. In the NMR spectrum the N-Me singlet of codeine was apparent at \(\delta 2.70\) and the O-Me singlet at \(\delta 3.85\). The upfield fine structure was very similar to that of codeine. The 5- and 6-H protons, however were shifted downfield to \(\delta 5.44\) and overlaid the 8-H double bond proton, an observation later found to be apparent in all 6-substituted esters. Two 1 H triplets were observed at \(\delta 7.37\) and 7.51 and two 1 H doublets at \(\delta 7.67\) and 8.04, corresponding to the four phthalic protons. A mass spectrum obtained by FAB showed the molecular ion (M+H\(^{+}\)) at 448.1752 consistent with the formula C\(_{26}\)H\(_{26}\)NO\(_{6}\). Data shows that the ester has indeed been prepared but a few abnormalities are apparent. The carbonyl stretch relating to a carboxylic acid is generally observed at ca 1700 cm\(^{-1}\), in the IR spectrum, here its appearance is much lower than expected. This may be explained by the existence of the carboxylate anion (COO\(^{-}\)) which is generally apparent at ca 1600 cm\(^{-1}\). The NMR data also showed an unusually high shift for the N-Me singlet, 0.6 ppm relative to codeine. The addition of a phthalic group at position-6 could not influence such a large chemical shift alone.
It is known, however, that quaternary nitrogen is shifted downfield compared to its tertiary counterpart, suggesting that such a group is present here. This leads us to conclude that codeine 6-O-phthalic ester must exist as a zwitterion.

![Chemical structure of codeine 6-O-phthalate](image)

Codeine 6-O-succinate (48) was prepared in the same way as the 6-O-phthalate derivative using succinic anhydride, though it was isolated in lower yields. Again the IR spectrum showed two carbonyl stretches at 1720 and 1632 cm⁻¹, corresponding to the ester and carboxylic acid functions respectively. The N-Me and O-Me singlets were easily identifiable in the NMR spectrum, appearing at δ 2.62 and 3.86 respectively. The 5 and 6-H's were shifted downfield, as in the case of codeine 6-O-phthalate, and overlaid with the 8-H doublet at δ 5.28, signifying ester formation at the 6-position. The mass spectrum showed the molecular ion at 399 consistent with the formula C₂₅H₂₆NO₆. Again the carbonyl stretch for the carboxylic acid functionality in the IR spectrum is low, suggesting carboxylate anion formation. The N-Me singlet in the NMR spectrum is also shifted downfield, suggesting quaternisation. Thus we can conclude that codeine 6-O-succinate must also exist as a zwitterion.

An attempt was made to prepare codeine 6-O-maleate, by refluxing with maleic anhydride in pyridine. The reaction, however, was unsuccessful, resulting in a brown solid which was insoluble in all common solvents.
4.1.1 Codeine Benzoate Esters

Substituted benzoate esters had been highlighted as the main compounds of interest, the aim being to see which substituents would enhance analgesic activity the most, if at all.

The first compound of this series to be synthesised was codeine 6-O-benzoate (49). Preparation was first effected by stirring codeine with benzoyl chloride in pyridine, at room temperature. The reaction solution was dissolved in ethyl acetate and the pyridine solvent was removed by complexation with copper sulphate solution. The product was isolated in good yield.

Codeine 6-O-benzoate (49) was also prepared using a 1,3-dicyclohexylcarbodiimide (DCC) coupling reaction. This procedure offers a convenient method for the esterification of carboxylic acids with alcohols, under mild conditions. Its success depends on the high efficiency of 4-dialkylaminopyridines as nucleophilic catalysts in group transfer reactions. The esterification proceeds without the need of a preformed, activated carboxylic acid derivative, at room temperature, under non acidic, mildly basic conditions, in an aprotic solvent. Thus codeine and benzoic acid were stirred together in the presence of 4-N,N-dimethylaminopyridine (DMAP), in DCM. The addition of DCC followed by prolonged stirring, allowed on work up, the isolation of codeine 6-O-benzoate. The product was isolated in a slightly lower yield compared with the reaction employing benzoyl chloride. The IR and NMR spectra were identical in each case. The IR spectrum exhibited a carbonyl stretch at 1717 cm\(^{-1}\) corresponding to the ester functionality. The NMR spectrum contained the characteristic codeine N-Me and O-Me singlets at δ 2.48 and 3.72, the fine structure was clearly identifiable and comparable to codeine with the 5- and 6-H's being shifted downfield to δ 5.20 and 5.47, as expected with ester substitution at the 6-position. The benzoate protons were located farthest downfield, a doublet was observed at δ 8.09 integrating for two protons, consistent with the two aromatic hydrogens...
Scheme 2

Reagents:  i, phthalic anhydride, pyridine, reflux; ii, succinic anhydride, pyridine, reflux; iii, benzoyl chloride, pyridine; iv, benzoic acid, DCC, DMAP, DCM; v, p-x-benzoyl chloride, pyridine; vi, piperonylic acid, DCC, DMAP, DCM.
located next to the ester functionality. Two triplets were observed at δ 7.43 and 7.45, the upfield triplet integrating for two protons. The upfield triplet represents the two identical hydrogens meta to the ester functionality and the downfield triplet the single para hydrogen. The accurate mass was found to be 403.1795 consistent with the formula C25H25NO4.

Codeine 6-O-p-nitrobenzoate (50) was the next ester to be synthesised. Initial attempts at preparation centred on a transesterification procedure, using methyl p-nitrobenzoate. Refluxing codeine with methyl p-nitrobenzoate and PTSA, in benzene, with dry molecular sieves to remove any methanol produced, proved unsuccessful. Initial production of the morphine anion with NaH before reaction with methyl p-nitrobenzoate in THF did show some limited success with codeine 6-O-p-nitrobenzoate being produced in 18% yield. Reaction with concentrated sulphuric acid in benzene, to promote the loss of methanol as the leaving group, however, proved unsuccessful.

The failure of the transesterification procedure led to the use of the highly reactive acid chlorides. Reaction of codeine with p-nitrobenzoyl chloride in pyridine, at room temperature, allowed the successful isolation of codeine 6-O-p-nitrobenzoate. The ester carbonyl stretch was seen in the IR spectrum at 1722 cm⁻¹. The NMR spectrum showed the codeine N-Me and O-Me singlets at δ 2.46 and 3.71 respectively, the 5- and 6-H's were as usual shifted downfield to δ 5.20 and 5.47, and the four benzoate protons were located together at δ 8.27. The accurate mass was found to be 448.1607 consistent with the formula C25H24N2O6.

This successful procedure was applied to the preparation of further codeine esters. The p-fluorobenzoate derivative (52) was next prepared, followed by the p-chlorobenzoate (53) and p-bromobenzoate (54) derivatives so that the effect of increasing size and electronegativity of the substituent could be investigated. The p-fluorobenzoate derivative was easily prepared in quantitative yield from codeine and p-fluorobenzoyl chloride. The IR spectrum showed a carbonyl stretch at 1717 cm⁻¹.
The NMR spectrum showed the characteristic codeine N-Me and O-Me singlets at δ 2.52 and 3.72 respectively. The 5- and 6-H's were shifted downfield to δ 5.19 and 5.43 as expected for 6-substituted esters. The benzoate protons were seen as two doublets at δ 7.11 and 8.10, each integrating for two protons. The accurate mass was found to be 421.1689 consistent with the formula C_{25}H_{24}NFO_4.

The p-chlorobenzoate derivative was subsequently prepared in quantitative yield from codeine and p-chlorobenzoyl chloride. The IR spectrum showed a carbonyl stretch at 1719 cm\(^{-1}\). The NMR spectrum showed the characteristic codeine N-Me and O-Me singlets at δ 2.49 and 3.72 respectively. The 5- and 6-H's were shifted downfield to δ 5.19 and 5.43 as expected for 6-substituted esters. The benzoate protons were seen as two doublets at δ 7.41 and 8.02, each integrating for two protons. Two accurate mass ions were apparent in the mass spectrum at 439.1364 and 437.1394, in the ratio 3:1 and consistent with the formula C_{25}H_{24}ClO_4.

Unfortunately in repeating the reaction to prepare the p-bromobenzoate derivative using p-bromobenzoyl chloride, the yield fell drastically to ~50%. This was attributed to the relative deactivating effect of the bromo substituent on the acid chloride, but the problem was overcome by using DMAP to drive the reaction. The IR spectrum showed a carbonyl stretch at 1719 cm\(^{-1}\). The NMR spectrum showed the characteristic codeine N-Me and O-Me singlets at δ 2.48 and 3.72 respectively. The 5- and 6-H's were shifted downfield to δ 5.19 and 5.42 as expected for 6-substituted esters. The benzoate protons were seen as two doublets at δ 7.58 and 7.94, each integrating for two protons. Two accurate mass ions were apparent in the mass spectrum at 483.0887 and 481.0716, in the ratio 1:1 and consistent with the formula C_{25}H_{24}NBrO_4.

Further variations were to include benzoate esters containing oxygen substitution. The p-methoxybenzoate derivative (51) was successfully prepared by the reaction of codeine with p-methoxybenzoyl chloride in pyridine. The IR spectrum exhibited an ester carbonyl stretch at 1711 cm\(^{-1}\). The NMR contained the characteristic codeine
N-Me and O-Me singlets at $\delta$ 2.48 and 3.74 respectively, with the benzoate O-Me singlet observed at $\delta$ 3.44. The 5- and 6-H's were as usual shifted downfield to $\delta$ 5.18 and 5.41, with two doublets being observed for the benzoate protons at $\delta$ 6.92 and 8.04. The accurate mass was found to be 433.1915 consistent with the formula $\text{C}_{26}\text{H}_{27}\text{NO}_5$.

The 3,4 methylenedioxybenzoate derivative (55) was successfully prepared by the reaction of codeine with piperonylic acid and DCC, in DCM. The IR spectrum exhibited an ester carbonyl stretch at 1711 cm$^{-1}$. The NMR contained the characteristic codeine N-Me and O-Me singlets at $\delta$ 2.46 and 3.76 respectively, the 5- and 6-H's were as usual shifted downfield to $\delta$ 5.17 and 5.41, and as expected a singlet integrating for two protons was also observed at $\delta$ 6.03 representing the methylene protons. The accurate mass was found to be 447.1679 consistent with the formula $\text{C}_{26}\text{H}_{25}\text{NO}_6$.

Consideration was given to converting the esters (51) and (55) to the corresponding hydroxybenzoates of morphine. However it was decided that the conditions required for cleavage would probably cause the breakdown of the ester linkage.

### 4.2 Morphine Esters

The selective protection of the 3-position in morphine has been achieved with a variety of groups, benzyl and TBDMS giving the highest yields. It was decided to utilise morphine 3-O-TBDMS ether in further reactions, due to the fact that its removal with fluoride ions would leave the remainder of the morphine structure untouched. Benzyl groups are generally removed by hydrogenation which would also reduce the double bond in the C-ring of the morphine skeleton.

It was decided to initially prepare a very simple ester, morphine 6-O-acetate (57), to define a standard procedure for the preparation of all morphine esters. Morphine 3-O-TBDMS ether was stirred with acetic anhydride in pyridine, at room temperature,
to give the protected acetate (56) in good yield. The IR spectrum showed an absence of hydroxyl, and the appearance of an ester carbonyl stretch at 1736 cm\(^{-1}\). The NMR spectrum showed the appearance of a singlet at \(\delta 2.14\) corresponding to the acetate, with the morphine N-Me singlet apparent at \(\delta 2.45\). The 5- and 6-H's were clearly distinguishable and shifted downfield to \(\delta 5.04\) and \(5.17\), as observed in the codeine series for the introduction of an ester functionality at position-6. The remaining step was to remove the TBDMS protecting group, leaving the ester functionality unaffected.

Selective removal of the silyl ether was readily accomplished by treatment with tetrabutylammonium fluoride (TBAF), in THF,\(^5\) to give morphine 6-O-acetate (57). The TBDMS singlets at \(\delta 0.1\) were absent from the NMR spectrum, signifying its removal. The acetate singlet remained at \(\delta 2.15\). The 5- and 6-H's were again located at \(\delta 5.06\) and \(5.14\), suggesting the ester still remains at the 6-position, and the morphine N-Me singlet at \(\delta 2.45\) suggesting that the morphine skeleton also remains intact. The IR spectrum exhibited a carbonyl stretch at \(1732\) cm\(^{-1}\), but also the presence of a hydroxyl group was noted by a broad band at \(3368\) cm\(^{-1}\). Thus a viable route to the synthesis of morphine esters has been achieved.
Progressing in a parallel series to the codeine derivatives morphine 6-O-succinate-3-O-TBDMS ether (58) was initially prepared by refluxing morphine 3-O-TBDMS ether with succinic anhydride in pyridine. The IR spectrum showed two carbonyl stretches at 1735 and 1628 cm⁻¹, consistent with the presence of both ester and acid functionalities. Three singlets were observed in the NMR spectrum at 0.15, 0.20 and 0.98 representing respectively the two methyl groups and the t-butyl group of the TBDMS protecting group. The characteristic morphine N-Me singlet was observed at 2.82. Four aliphatic protons were apparent, as expected, in the region 2.52 - 2.72. The accurate mass was found to be 499.2388 consistent with the formula C₂₇H₃₇N₀₆Si. Close examination of the spectra again reveals that our compound exists as a zwitterion. The carbonyl stretch of the carboxylic acid group in the IR spectrum is lower than expected, suggesting the presence of the carboxylate anion. The N-Me singlet in the NMR spectrum is shifted downfield, suggesting quaternisation.

Morphine 6-O-phthalate-3-O-TBDMS ether (59) was prepared similarly using phthalic anhydride in pyridine. The IR spectrum showed two carbonyl stretches at 1714 and 1602 cm⁻¹, consistent with the presence of both ester and acid functionalities. The NMR spectrum showed the characteristic pattern of three singlets for the TBDMS group at 0.04, 0.06 and 0.88. The morphine N-Me singlet was observed at 2.91. Two 1 H triplets were observed at 7.38 and 7.52 and two 1 H doublets at 7.66 and 7.92, following the same pattern as the codeine 6-O-phthalic ester. Again we find that morphine 6-O-phthalate-3-O-TBDMS ether exists as a zwitterion. The carbonyl stretch of the carboxylic acid group in the IR spectrum is lower than expected, suggesting the presence of the carboxylate anion. The N-Me singlet in the NMR spectrum is shifted downfield, suggesting quaternisation. The elemental analysis obtained was consistent with the molecular formula C₃₁H₃₇N₀₆Si.
Scheme 3

Reagents: i, succinic anhydride, pyridine, reflux; ii, phthalic anhydride, pyridine, reflux; iii, p-x-benzoyl chloride, pyridine; iv, TBAF, THF; v, HF in pyridine; vi, TBAF, THF.
The morphine 6-O-benzoate 3-O-TBDMS ethers were prepared in the same way as their codeine analogues, from morphine 3-O-TBDMS ether and the corresponding substituted benzoyl chloride in pyridine, using DMAP as a catalyst where required. **Scheme 3.** In all cases the IR spectra exhibited a carbonyl stretch at \(~ 1715\) cm\(^{-1}\). NMR spectra all contained the characteristic TBDMS singlets in the region \(\delta 0 - 1\), and the N-Me singlet of the morphine skeleton at \(\sim \delta 2.45\). The same splitting patterns were observed for the substituted ester groups compared to the codeine compounds in the region \(\delta 6.90 - 8.05\). In all cases the 5- and 6-H's were shifted downfield as expected. Mass spectroscopy results gave the expected molecular ion for the benzoate, \(p\)-nitrobenzoate, \(p\)-methoxybenzoate, and \(p\)-fluorobenzoate derivatives. The \(p\)-chlorobenzoate spectrum showed two molecular ions in the ratio 3:1 and the \(p\)-bromobenzoate spectrum showed two molecular ions in the ratio 1:1. See Table 1.

**Table 1.**

<table>
<thead>
<tr>
<th>Compound</th>
<th>IR</th>
<th>TBDMS</th>
<th>N-Me</th>
<th>5-H</th>
<th>6-H</th>
<th>benzoate</th>
<th>mass ion</th>
</tr>
</thead>
<tbody>
<tr>
<td>benzoate (60)</td>
<td>1717</td>
<td>0.02, 0.04, 0.84</td>
<td>2.53</td>
<td>5.21</td>
<td>5.40</td>
<td>7.42, 7.56, 8.09</td>
<td>503.2446</td>
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<tr>
<td>p-nitrobenzoate (61)</td>
<td>1718</td>
<td>0.03, 0.06, 0.85</td>
<td>2.47</td>
<td>5.20</td>
<td>5.43</td>
<td>8.29</td>
<td>548.2331</td>
</tr>
<tr>
<td>p-methoxybenzoate (62)</td>
<td>1710</td>
<td>0.04, 0.06, 0.87</td>
<td>2.46</td>
<td>5.17</td>
<td>5.38</td>
<td>6.90, 8.06</td>
<td>533.2602</td>
</tr>
<tr>
<td>p-fluorobenzoate (63)</td>
<td>1717</td>
<td>0.01, 0.04, 0.84</td>
<td>2.58</td>
<td>5.19</td>
<td>5.39</td>
<td>7.07, 7.11, 8.08, 8.12</td>
<td>521.2413</td>
</tr>
<tr>
<td>p-chlorobenzoate (64)</td>
<td>1719</td>
<td>0.01, 0.05, 0.85</td>
<td>2.45</td>
<td>5.16</td>
<td>5.39</td>
<td>7.41, 8.01</td>
<td>539.2070</td>
</tr>
<tr>
<td>p-bromobenzoate (65)</td>
<td>1719</td>
<td>0.01, 0.04, 0.84</td>
<td>2.47</td>
<td>5.17</td>
<td>5.38</td>
<td>7.56, 7.95</td>
<td>583.1641</td>
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</table>

TBDMS deprotection was easily effected in most cases using TBAF in THF, though isolation and purification of the morphine 6-O-benzoates proved extremely difficult.
due to their insolubility in virtually all common solvents. Recrystallisations were eventually accomplished from CHCl₃/MeOH as solvent, though no compound was soluble in either of these solutions alone. In the case of morphine 6-O-p-nitrobenzoate (69) recrystallisation was effected from a DMSO/water solution. All IR spectra were comparable to their morphine 3-O-TBDMS ether counterparts, with carbonyl stretches at ~ 1715 cm⁻¹, but broad stretching was also apparent in the region 3400 cm⁻¹ due to the presence of the aromatic hydroxyl group. All NMR spectra were comparable with their morphine 3-O-TBDMS ether counterparts except that they lacked the TBDMS singlets in the region 80 - 1. Mass spectroscopy results were comparable with the morphine 3-O-TBDMS ether derivatives giving the expected molecular ion for the benzoate, p-nitrobenzoate, and p-fluorobenzoate derivatives. The p-chlorobenzoate spectrum showed two molecular ions in the ratio 3:1 and the p-bromobenzoate spectrum showed two molecular ions in the ratio 1:1. See Table 2.

**Table 2**

<table>
<thead>
<tr>
<th>Compound</th>
<th>IR</th>
<th>N-Me</th>
<th>5-H</th>
<th>6-H</th>
<th>benzoate</th>
<th>mass ion</th>
</tr>
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<tbody>
<tr>
<td>benzoate (68)</td>
<td>1713</td>
<td>2.44</td>
<td>5.21</td>
<td>5.41</td>
<td>7.45, 7.59,</td>
<td>389.1623</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.10</td>
<td></td>
</tr>
<tr>
<td>p-nitrobenzoate (69)</td>
<td>1719</td>
<td>2.31</td>
<td>5.12</td>
<td>5.43</td>
<td>8.22, 8.36</td>
<td>434.1479</td>
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<tr>
<td>p-fluorobenzoate (70)</td>
<td>1713</td>
<td>2.45</td>
<td>5.18</td>
<td>5.40</td>
<td>7.11, 7.15,</td>
<td>407.1593</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.09, 8.11</td>
<td></td>
</tr>
<tr>
<td>p-chlorobenzoate (71)</td>
<td>1719</td>
<td>2.46</td>
<td>5.22</td>
<td>5.41</td>
<td>7.39, 7.42,</td>
<td>425.1227</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>7.98, 8.01</td>
<td>423.1268</td>
</tr>
<tr>
<td>p-bromobenzoate (72)</td>
<td>1718</td>
<td>2.46</td>
<td>5.18</td>
<td>5.40</td>
<td>7.60, 7.95,</td>
<td>469.0544</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.95</td>
<td>467.0583</td>
</tr>
</tbody>
</table>

Morphine 6-O-phthalate-3-O-TBDMS ether (59) was found to be resistant to TBAF/THF deprotection. The use of acetic acid and water in THF also proved fruitless. It is obvious that quite vigorous conditions are required in this case in order
to remove the protecting group. The difficulty was to find conditions which would leave the ester and the morphine skeleton unaffected. It was decided to use hydrogen fluoride (HF) and pyridine. This reagent was used by Nicolaou for the removal of silyl protecting groups. The reaction proved extremely successful for our purposes. Again though, purification proved rather difficult, owing to the insolubility of morphine 6-O-phthalate (67). However recrystallisation was finally effected from a CHCl₃/MeOH solution. The IR spectrum contained two carbonyl stretches at 1716 and 1601 cm⁻¹ corresponding to the ester and acid functionalities, and a broad OH band was observed at 3398 cm⁻¹. The NMR spectrum lacked the TBDMS singlets, showing successful removal of the protecting group. The N-Me singlet was apparent at δ 3.01 and the 5- and 6-H's were as usual shifted downfield to δ 5.66 and 5.50 respectively. The phthalate protons had similar chemical shifts and splitting patterns to the codeine and morphine 3-O-TBDMS ether derivatives, appearing at δ 7.40, 7.56 and 7.92. A mass spectrum obtained by FAB showed the molecular ion (M+H⁺) at 434.1604 consistent with the formula C₂₅H₂₃NO₆. Close examination of the spectra again reveals that our compound exists as a zwitterion. The carbonyl stretch of the carboxylic acid group in the IR spectrum is lower than expected, suggesting the presence of the carboxylate anion. The N-Me singlet in the NMR spectrum is shifted downfield, suggesting quaternisation.

4.3 p-Hydroxy Esters

The preparation of benzoate esters with hydroxy substituents has proved a rather difficult task. It was first decided to prepare a morphine 6-O-benzoate ester with the introduction of a single hydroxyl group in the para position. The obvious reagent to be utilised is 3-hydroxybenzoic acid (73). Studying the reaction pathway, however, it is noted that the carboxylate centre can react with not only the free hydroxyl group at position-6 on the morphine skeleton, but also with the free hydroxyl group on other molecules of the reagent. Thus the first priority is to protect the hydroxyl group to prevent this occurrence.
It was decided to protect the hydroxyl function of the reagent with the TBDMS group, so that later in the preparation of morphine 6-O-p-hydroxybenzoate from morphine 3-O-TBDMS ether, all deprotections could be effected together in one simple step.

4.3.1 Transesterification

It is known that carboxylic acids can be protected using silyl ethers, under similar conditions to those required for the protection of a phenol group, and it was feared that we would be unable to selectively protect the hydroxyl function in the presence of the carboxylic acid. It was thought that this problem could be avoided by selectively modifying the carboxylic acid group making it insusceptible to reaction with TBDMS-Cl, but still able to react with the morphine 6-hydroxyl function.

Thus the carboxylic acid group was initially converted to the methyl ester, which may be further utilised in a transesterification procedure, to introduce the required functionality. The methyl ester (74) was prepared, in high yield, from the free acid by refluxing with concentrated sulphuric acid in methanol. A carbonyl stretch was observed in the IR spectrum at 1724 cm⁻¹ and the NMR spectrum showed the appearance of a methyl singlet at δ 3.90, indicating the presence of a methyl ester.

Protection of the hydroxyl functionality with the TBDMS group proved a little more difficult. The use of NaH and TBDMS-Cl in THF was unsuccessful, rather the sodium salt of the methyl ester was isolated. Moving to a slightly more polar solvent, DMF, did not alleviate this problem. Reacting methyl 3-hydroxybenzoate with imidazole and TBDMS-Cl in DMF however, did allow the isolation of our reagent (75). The O-Me singlet was still apparent in the NMR spectrum at δ 3.87 with the appearance of the two TBDMS singlets in the region δ 0-1.
The transesterification procedure was attempted using codeine, with the hope of progressing to morphine if successful. Reacting codeine with methyl \( p \)-TBDMS-oxy benzoate, in the presence of PTSA, in refluxing toluene proved fruitless. Repeating the reaction using a DMAP catalyst in refluxing toluene was again unsuccessful, as was using NaH to produce the codeine anion before proceeding with the transesterification reaction.

### 4.3.2 DCC Coupling

Using DCC to couple the hydroxyl group of codeine with a carboxylic acid group has previously been successful in the preparation of codeine 6-O-benzoate. It was decided to use the same procedure here, but using \( p \)-TBDMS-oxy benzoic acid (76), as the reagent.

It was attempted to prepare the \( p \)-TBDMS-oxy benzoic acid by the demethylation of methyl \( p \)-TBDMS-oxy benzoate (75). Using potassium carbonate in a methanolic solution, followed by an acidic work up did not give the \( p \)-TBDMS-oxy benzoic acid, but rather methyl \( p \)-hydroxybenzoate. It is believed that the reaction itself is unsuccessful and that the silyl protecting group is lost during the work up. Using potassium hydroxide in ethanol was also unsuccessful, but in this case all protecting groups were removed to give \( p \)-hydroxybenzoic acid.

The protection of \( p \)-hydroxybenzoic acid with TBDMS-Cl, in DMF with imidazole, as previously predicted, did protect both the acid and phenolic functions. Modifying this reaction by using NaH in THF, in an attempt to make the phenolic group more
reactive by forming the anion, did however have its benefits. The reaction was found to initially favour reaction at the phenolic position, so that if reaction times were kept to a minimum the hydroxy protected acid could be isolated, albeit in low yield.

\[
\begin{align*}
&\text{COOH} \\
&\text{TBDMS-Cl} \\
&\text{NaH, DMF} \\
&\text{OH} \quad \text{(73)} \\
&\text{COOH} \\
&\text{OTBDMS} \quad \text{+} \quad \text{OTBDMS} \\
&\text{COOTBDMS} \quad \text{(76)} \quad \text{(77)}
\end{align*}
\]

The IR spectrum of (76) contained a carbonyl stretch at 1678 cm\(^{-1}\). The NMR spectrum contained two TBDMS singlets at \(\delta 0.22\) and 0.98 and two aromatic doublets at \(\delta 6.87\) and 6.98, each integrating for two protons. The IR of the disubstituted product (77) contained a carbonyl stretch at 1700 cm\(^{-1}\) and the NMR spectrum contained five singlets at \(\delta 0.22, 0.24, 0.36, 0.98,\) and 1.02 indicating the presence of two silyl groups.

DCC coupling with codeine in the presence of DMAP however was unsuccessful. It is thought the \(p\)-TBDMS-oxy group is having a strongly deactivating effect on the benzene ring and thus the carboxylate function. A more reactive form of the carboxylic acid is required.

### 4.3.3 Acid Chloride Reaction

The traditional way to prepare acid chlorides is from the free acid using thionyl chloride (SOCl\(_2\)).\(^{57}\) Thus \(p\)-TBDMS-oxybenzoic acid was reacted with SOCl\(_2\) in pyridine as solvent, to mop up any HCl produced. The reaction appeared to proceed by TLC but the acid chloride could not be isolated. Thus it was decided to prepare the acid chloride and react it \textit{in situ}. Reaction with codeine in pyridine did appear successful by TLC, but no codeine derivative could be isolated, rather a TBDMS
product, indicating that the acid chloride had not been formed and that the initial reaction had removed the protecting group.

Another milder method to for the preparation of acid chlorides, is to use an excess of oxalyl chloride in DCM. Thus \( p \)-TBDMS-oxybenzoic acid was reacted with oxalyl chloride in DCM, taking care only to use fresh oxalyl chloride, the reaction mixture effervesced indicating the formation of the acid chloride. Solvent and excess oxalyl chloride were easily removed on a rotor evaporator under reduced pressure, using a small amount of benzene to help remove the excess oxalyl chloride. The reagent was stored under nitrogen, without any further purification.

\[
\begin{align*}
\text{COOH} & \quad \text{oxalyl chloride} \quad \text{DCM} \\
\text{OTBDMS} & \quad \text{Cl} \quad \text{OTBDMS}
\end{align*}
\]

(76) (78)

4.3.4 Preparation of 6-O-\( p \)-hydroxybenzoates

To prepare codeine 6-O-\( p \)-hydroxybenzoate a pyridine solution of codeine was added to the freshly prepared acid chloride at room temperature, but after 6 h TLC indicated that the reaction was unsuccessful. However, on the further addition of a catalytic amount of DMAP the reaction did progress to completion and codeine 6-O-\( p \)-TBDMS-oxybenzoate was isolated (79). The IR spectrum exhibited a carbonyl stretch at 1709 cm\(^{-1}\). The NMR spectrum contained the characteristic codeine N-Me and O-Me singlets at \( \delta \) 2.56 and 3.73 respectively, the 5- and 6-H's were as expected shifted downfield to \( \delta \) 5.20 and 5.41. The silyl protecting group was observed as two singlets at \( \delta \) 0.22 and 0.98. The accurate mass was found to be 533.2597 consistent with the formula \( C_{31}H_{39}NO_5Si \).
The TBDMS protecting group was easily removed using TBAF/THF, to give the desired codeine 6-O-p-hydroxy benzoate (80). The loss of the silyl protecting group was noted by the appearance of an OH band in the IR spectrum at 3563 cm\(^{-1}\) and by the loss of the two characteristic singlets in the region \(\delta\) 0-1 in the NMR spectrum. The ester function remained present shown by the carbonyl stretch at 1712 cm\(^{-1}\) in the IR spectrum and the downfield shift of the 5- and 6-H's to \(\delta\) 5.19 and 5.39 in the NMR spectrum. The characteristic codeine N-Me and O-Me singlets were apparent at \(\delta\) 2.51 and 3.73. The accurate mass was found to be 419.1733 consistent with the formula C\(_{25}\)H\(_{24}\)NO\(_5\).

A similar route was followed in the preparation of morphine 6-O-p-hydroxybenzoate, but in this case morphine 3-O-TBDMS ether was used as the starting material. A pyridine solution of morphine 3-O-TBDMS ether was added to a solution of freshly
prepared p-TBDMS-oxybenzoyl chloride at room temperature, and the reaction proceeded without the use of a catalyst. Morphine 3-O-TBDMS-ether 6-O-p-TBDMS-oxybenzoate (81) was isolated as a colourless powder. The ester preparation was successful, shown by the carbonyl stretch in the IR spectrum at 1711 cm\(^{-1}\) and the downfield shift of the 5- and 6-H's to 5.13 and 5.31, in the NMR spectrum. The presence of two silyl protecting groups was indicated by the five upfield singlets at 0.02, 0.04, 0.17, 0.82 and 0.94. The characteristic morphine N-Me singlet was apparent at 2.42. The remainder of the fine structure was comparable to that of the codeine derivative.

**Scheme 5**

The two TBDMS protecting groups were easily removed in one step, using TBAF/THF and morphine 6-O-p-hydroxybenzoate (82) was finally prepared. The loss of the protecting groups was noted by the appearance of two OH bands in the IR
spectrum at 3640 and 3475 cm\(^{-1}\), and by the loss of all singlets in the region \(\delta 0-1\) in the NMR spectrum. The ester carbonyl stretch was apparent at 1736 cm\(^{-1}\) in the IR spectrum and the 5- and 6-H's were located, as expected for the presence of an ester, at 8 5.15 and 5.34 in the NMR spectrum. The characteristic morphine N-Me singlet was apparent at 8 2.43. The accurate mass was found to be 405.1569 consistent with the formula C\(_{24}\)H\(_{23}\)N\(_{1}\)O\(_{5}\).

Later a different approach to the synthesis of carboxylic acid chlorides was investigated. Acid chlorides can be prepared from \(t\)-butyldimethylsilyl esters using oxalyl chloride in the presence of a catalytic amount of DMF, under neutral conditions.\(^{59}\) Interestingly \(t\)-butyldimethylsilyl ethers are stable to oxalyl chloride under these conditions. Thus in the case of \(p\)-hydroxybenzoic acid both the hydroxyl and carboxylate moieties were silylated in a single step and then the silyl ester selectively converted to the acid chloride, giving the required \(p\)-TBDMS-oxybenzoyl chloride (78).

It has been shown that acid chloride formation proceeds extremely slowly in the absence of DMF, implicating it as the reactive species. The suggested mechanism involves the addition of DMF to the carboxyl group of the silyl ester to give an intermediate (83) which could undergo fragmentation to generate \(t\)-butyldimethylchlorosilane, DMF, and the carboxylic acid chloride.

\[
\text{HCON(CH}_3\text{)}_2 + \text{ClCOCOCl} \rightarrow \left[ \begin{array}{c} \text{Cl} \\ \text{H} \\ \text{N(CH}_3\text{)}_2 \\ \end{array} \right]^+ \quad \text{Cl}^- + \text{CO} + \text{CO}_2
\]
4.3.4 Future Work

This procedure could easily be extended to include the introduction of other hydroxy substituted benzoate esters, possibly culminating with gallic acid (84), allowing the introduction of three neighbouring hydroxyl groups, as found in M-6-G.
The next series of compounds to be investigated were the 6-O-benzyl ethers.

The Williamson synthesis is generally used for the preparation of ethers. It is important because of its versatility, being used to prepare both symmetrical and unsymmetrical ethers. During the synthesis an alkyl halide is allowed to react with an alkoxide ion, prepared from an alcohol or phenol.

5.1 Benzylation using a Base and an Alkyl Halide

Applying this to codeine, the function we hope to etherify is the secondary alcohol at position-6 on the codeine skeleton. It was hoped that using NaH to form the alkoxide ion and reacting with benzyl bromide (BnBr), in THF at room temperature, would lead to the isolation of codeine 6-O-benzyl ether (85).

\[
\begin{align*}
\text{MeO} & \quad \text{Q} \quad \text{N-Me} \\
\text{HO} & \quad \text{NaH, BnBr} \quad \text{THF} \quad \rightarrow \\
& \quad \text{MeO} \\
& \quad \text{Q} \\
& \quad \text{N-Me} \\
(20) & \quad \rightarrow & \quad (85)
\end{align*}
\]

The reaction was successful and codeine 6-O-benzyl ether (85) was isolated as a pale yellow powder. The NMR spectrum of the crude product exhibited the characteristic codeine O-Me and N-Me singlets at δ 3.85 and 2.67 respectively. A multiplet was observed at δ 7.38 integrating for five protons and thus representing the benzyl aromatic protons, indicating that benzylation has been successful. Two ABq's were observed one at δ 6.68 and 6.54 corresponding to the codeine aromatic protons, and one at δ 4.85 and 4.64 corresponding to the benzyl alkyl protons. The codeine double bond protons were identified, as expected, at δ 5.81 and 5.28. The remainder of the fine structure was comparable with that of codeine. The COSY spectrum exhibited couplings between
the 5- and 6- protons, also between the 9- and 10- protons and the 9- and 14- protons signifying that the codeine skeleton is unaltered. Also as the N-Me singlet shows no quaternisation, benzylation must be at the 6-hydroxyl position. The accurate mass was found to be 389.1995 consistent with the formula \(\text{C}_{25}\text{H}_{27}\text{N}_0\text{O}_3\).

The next codeine analogue to be prepared was the 6-O-p-nitrobenzyl ether (86). Codeine was reacted with NaH in THF to form the alkoxide ion, as previously. \(p\)-Nitrobenzyl bromide was added at room temperature to prepare codeine 6-O-\(p\)-nitrobenzyl ether. The NMR spectrum of the crude product showed that codeine 6-O-\(p\)-nitrobenzyl ether had been isolated but was still a little impure. The characteristic codeine O-Me and N-Me singlets were apparent at \(\delta\) 3.83 and 2.45 respectively. Two doublets were observed at \(\delta\) 8.21 and 7.62 each integrating for two protons and thus representing the benzyl aromatic protons, indicating that benzylation has been successful. Two ABq's were observed one at \(\delta\) 6.66 and 6.54 corresponding to the codeine aromatic protons, and one at \(\delta\) 5.33 and 4.73 corresponding to the benzyl alkyl protons. The codeine double bond protons were identified, as expected, at \(\delta\) 5.78 and 5.38. The remainder of the fine structure was comparable with that of codeine. The accurate mass was found to be 434.1846 consistent with the formula \(\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_5\).

Purification of these codeine analogues proved to be impossible. Column chromatography on silica and alumina, both neutral and basic, lead to degradation of the product with an apparent quaternised compound being isolated. Indicated by the downfield shift of the N-Me singlet. Recrystallisation was also unsuccessful. It is not understood why the 6-O-benzylated products are unstable under such a wide variety of conditions.
The reaction was repeated using morphine 3-O-TBDMS ether as the starting material to ascertain whether a 6-O-benzylated product could be prepared. Unfortunately, however, the reaction was unsuccessful. The reaction progress was followed by TLC but no clear product was identified, the plates being streaky. On work up a yellow/brown product was isolated. The NMR spectrum showed that the product was a morphine type compound, as much of the fine structure was apparent. Benzylation had occurred shown by a multiplet at δ 7.2 - 7.4 and a doublet at δ 7.7, possibly on the nitrogen as the characteristic N-Me singlet is shifted downfield to δ 3.3. The TBDMS singlets were still observed at δ 0.1, but the spectrum was generally impure with a considerable amount of background interference. Attempts at purification by column chromatography, on silica, failed to improve characterisation and it was decided that morphine 6-O-benzyl-3-O-TBDMS ether had not been obtained. Repeating the reaction in DMF as solvent gave the same results.

Repeating the reactions again but heating to reflux, was also unsuccessful as was attempting to use a different base, KOH, to form the alkoxide ion.

It had been suggested that maybe the large bulky TBDMS protecting group could be folded in such a way that it could hinder electrophilic attack at the alcohol function. It was initially thought that this could be solved by using a slightly more reactive benzyl species, the benzyl iodide. 3-O-TBDMS-morphine was initially stirred with NaH in DMF. Benzyl bromide was added followed by tetra-n-butyl ammonium iodide (Bu₄NI), to form the reactive benzyl iodide in situ. The reaction progress was monitored by TLC, but this was inconclusive, again being very streaky. Unfortunately on work up the reaction was found to be unsuccessful as the product isolated was a morphine compound with some ill defined benzylation, the NMR spectrum being comparable to that obtained from the NaH/BnBr reaction previously.

Maybe if the bulky TBDMS group was substituted for a smaller protecting group the problem of steric hindrance would not occur. It was hoped to investigate the use of the methoxy methyl ether protecting group. Morphine 3-O-MOM ether was successfully
prepared, but in a fairly low yield. See Chapter 3. It was then attempted to prepare morphine 3-0-MOM-6-0-benzyl ether. Morphine 3-0-MOM ether and NaH were reacted together in THF to form the alkoxide ion. Benzyl bromide was then added and the reaction left stirring at room temperature, overnight. Unfortunately on work up no satisfactory results were obtained.

5.2 Benzylation using a Silver Oxide Catalyst

Another common procedure for the preparation of ethers, under mild conditions, is to use silver oxide (Ag₂O) as a catalyst with an alkyl halide in DMF. Silver oxide was freshly prepared from an aqueous solution of silver nitrate treated with sodium hydroxide. The silver oxide precipitated immediately and was collected by filtration.

The reaction of morphine 3-0-TBDMS ether and benzyl bromide in DMF, in the presence of Ag₂O did allow the isolation of a colourless powder. The NMR spectrum was well defined. A two proton doublet was apparent at δ 7.76 and a three proton multiplet at δ 7.31-7.44, these are assigned to the benzyl aromatic protons and show that benzylation has occurred. The morphine aromatic ABq was apparent at δ 6.62 and 6.49 and the TBDMS singlets were clearly seen in the region δ 0-1. Another ABq was apparent at δ 5.96 and 5.79 representing the benzyl alkyl protons. The morphine double bond protons were observed at δ 5.53 and 4.92. The fine structure was all shifted downfield, the 5-H to δ 5.28, the 6-H to δ 4.81, the 9-H to δ 4.55 and the 14-H to δ 4.38. The COSY spectrum exhibited couplings between the 5- and 6- protons, also between the 9- and 10- protons and the 9- and 14- protons signifying that the morphine skeleton is unaltered. The characteristic N-Me singlet, however, was shifted downfield to δ 3.26, suggesting quaternisation. The mass spectrum did not exhibit a molecular ion at 489 as would be expected for morphine 3-0-TBDMS-6-O-benzyl ether, rather the molecular ion was found at 399, representing morphine 3-0-TBDMS ether. However the major ion was observed at m/z 91 which corresponds to the benzyl ion, suggesting that the parent compound is broken down in the mass spectrometer. It is concluded that
benzylation had occurred at the nitrogen rather than at the 6-hydroxyl position and that the quaternary benzyl product (87) had been isolated.

![Chemical Structure](image)

Repeating the reaction in THF as solvent gave the same results.

### 5.3 Benzylation using a Polar Aprotic Solvent

It was thought that the use of a polar aprotic solvent may increase the rate of alkylation at the oxygen atom rather than at the nitrogen atom. The more electronegative end of the nucleophile is thought to be freer from entanglement by both the solvent and the cation so that a change from aprotic to polar aprotic solvent increases the extent of attack by the more electronegative atom. Thus it was decided to incorporate N,N dimethylpropyleneurea\(^6\) (DMPU). Codeine and NaH were reacted together in THF, to form the alkoxide ion. DMPU was then added and the reaction stirred for a further 30 min before the addition of BnBr. After leaving overnight the reaction was quenched with water and the product isolated. \(^1\)H NMR data suggested the product was a mixture of O-benzylated and N-benzylated compounds. The benzyl protons were seen as a large multiplet at \(\delta 7.22-7.46\) but with two doublets apparent at \(\delta 7.79\) and 7.63 suggesting more than one benzyl substitution. Also two O-Me singlets were observed at \(\delta 3.84\) and 3.83 and two N-Me singlets were observed at \(\delta 3.61\) and 3.33. Attempts to separate the components by column chromatography on basic alumina were unsuccessful.
It was thought that a stronger base may allow selective O-benzylation and the above reaction was repeated using lithium diisopropylamide (LDA). The LDA was prepared just prior to use. To a stirred solution of diisopropylamine under nitrogen at -20°C was added butyllithium (2.5 M solution), with the formation of a thick yellow gel of LDA. (The reaction is unsuccessful if a solution is formed or if the product turns white). A codeine solution in THF was added to the freshly prepared LDA at -20°C, followed by stirring for 30 min. The reaction temperature was then allowed to rise to 0°C and stirring continued for a further hour. DMPU was then added and the reaction stirred overnight. Benzyl bromide was added and the reaction followed by TLC. Preliminary results were inconclusive with the TLC plates being very streaky. On work up, again an inseparable mixture of what seems to be N-benzylated and O-benzylated products was isolated.

5.4 Quaternisation

- Due to the problems arising from quaternisation of the nitrogen function it was decided to selectively prepare the methyl quaternary salt. Then having already protected the nitrogen function as the quaternary salt, it may then be possible to benzylate the hydroxyl function and then remove one of the methyl groups from the nitrogen to give the desired product.

The methyl quaternary salt of morphine 3-O-TBDMS ether was prepared by reacting the parent compound with potassium hydrogen carbonate (KHCO₃) in methanol. Then adding methyl iodide and stirring overnight.

Before performing a benzylation reaction upon the methyl quaternary salts it was decided to attempt to remove one of the methyl groups to assess the viability of the process. Quaternary methyl groups can be removed using the sodium salt of thiophenol. To prepare the reagent, sodium in dry, distilled toluene was treated with thiophenol. Gentle heating allowed the formation of the sodium salt as a white precipitate, which was collected by filtration in (85%) yield.
Then to a solution of morphine 3-O-TBDMS ether quaternary methyl salt dissolved in ethanol was added a solution of sodium thiophenoxide in ethanol. The reaction was stirred for 30 min at room temperature after which the solvent was removed under reduced pressure. The residue was dissolved in acetonitrile and heated to reflux. Unfortunately a black sludge was obtained from which morphine 3-O-TBDMS ether could not be isolated.

Time did not allow the exploration of any other methods for the removal of the quaternary methyl group, so we do not know whether the process would have been successful.
6.1 Introduction

Pharmacological tests were to be performed on isolated morphine-6-derivatives, but in order to complete a comparative binding profile a reference point was needed. Thus the preparation and isolation of morphine 6-O-glucuronide (M-6-G), the lead compound, was required.

For selective glycosidic linkage in an oligosaccharide synthesis, three fundamental procedures have proved to be particularly suitable...

a) ..the neighbouring group assisted procedure. An active substituent is required at C-2, e.g. an O-acetyl group. There then results via a carboxonium ion, a stabilised cyclic acyloxonium intermediate, that can be opened at the anomeric centre by a nucleophile approaching in a direction trans to the substituent at C-2. When a halide is present at C-1 mercury salts, silver perchlorate and silver triflate are suitable catalysts. When an acetate group is present at C-1 Lewis acids are used as catalysts.

b) ..the in situ anomerization procedure. A neighbouring group non-active substituent must be present at C-2. Use is made here of the possibility of producing an equilibrium, via suitable catalysts, between the $\alpha$ and $\beta$ forms of the glycoside, usually the glycoside halide. The glycosides are destabilised by the anomeric effect. Suitable catalysts are trialkylammonium halides, mercury salts, silver perchlorate and silver triflate.

c) ..the heterogeneous catalysis procedure. Generally an insoluble catalyst applied in the heterogeneous phase, under neutral conditions. Silver catalysts, particularly silver silicate, are suitable.
Elce, et al. have extended the heterogeneous catalysis procedure to incorporate the catalyst cadmium carbonate, successfully used in preparing glucuronide derivatives of estradiol. More recently Sasaki, et al. have shown that elevated pressures accelerate the condensation reaction of 2,3,6-tri-O-benzyl-α-D-glucopyranosyl bromide and various alcohols, in the presence of hindered amines. This also avoids the use of any heavy metal salts. Danishefsky has studied the usefulness of using oxiranes as glycosyl donors. The relevant glycal is epoxidised using dimethyldioxirane to produce the 1,2-anhydro sugar. Conjugation is performed in the presence of ZnCl₂ with stereospecific construction of the product glycoside.

6.2 Protection of Glucose

Firstly the required sugar moiety, glucose, needed to be manipulated into a form which could be utilised in further glycosylation reactions. Preparation of the tetraacetate derivative of glucuronic acid was effected from glucuronolactone (88), by the method of Bollenback. Initially the lactone was dissolved in methanol with a base catalyst, which causes a rearrangement to occur with the formation of a six membered ring.

![Chemical diagram]

Subsequent treatment with acetic anhydride in pyridine, leads to the selective isolation of both the α and β forms of tetra-O-acetyl-D-glucopyranuronate, (89) and (90) respectively.
The NMR spectra of tetra-O-acetyl-α-D-glucopyranuronate exhibited an O-Me singlet at δ 3.75 and acetyl groups at δ 2.00 - 2.20. The 1-H appeared as a doublet located the farthest downfield at δ 6.40. The 5-H appeared as a doublet located the farthest upfield. Two triplets were observed for the 3- and 4-H’s at δ 5.27 and 5.52 respectively, and a double doublet was observed for the 2-H at δ 5.12.

The NMR spectra of tetra-O-acetyl-β-D-glucopyranuronate exhibited an O-Me singlet at δ 3.75 and acetyl groups at δ 2.00 - 2.20, as in the α-case. The 1-H appeared as a doublet located the farthest downfield at δ 5.77. The remaining protons appeared as a multiplet at δ 5.11 - 5.35.

Melting points and optical rotation values in both cases were consistent with literature values.68

6.3 Glycosylation - Neighbouring Group Support

In peptide synthesis the glycosidation of secondary alcohols is known to progress by the neighbouring group assisted procedure.69 Good results are usually obtained if a β-D-1-O-acetate group is present. Thus in the case of glucuronide, the 2-O acetate group functions as the nucleophile pushing out the 1-O acetate leaving group to produce the cyclic acyloxonium intermediate (91).
The aim here was to utilise this procedure to glycosylate the secondary alcohol, at the 6-position, on the morphine skeleton. The reaction was initially conducted using codeine, with the hope of extending it to morphine if successful. Thus a solution of codeine in DCM was cooled to 0°C and boron trifluoride etherate added, the unusual formation of a precipitate was noted. Tetra-O-acetyl-β-D-glucopyranuronate was added in portions, keeping the reaction temperature below 10°C. Unfortunately no reaction was observed. Using a more polar solvent, DMF, the reaction was again unsuccessful, and the formation of a precipitate on addition of boron trifluoride etherate was again observed.

It was thought that the boron trifluoride could be forming an insoluble precipitate with codeine, preventing further reaction with the sugar. To overcome this problem it was decided to alter the sequence of addition for the reagents, such that codeine was added to the sugar. The sugar was dissolved in DMF and boron trifluoride etherate added, a homogeneous solution was noted. Codeine was slowly added in portions without the formation of a precipitate. Unfortunately the reaction was still unsuccessful, and it was decided to use a different approach.

6.4 Glycosylation - Koenigs Knorr

Casparis\textsuperscript{70} was the first to prepare a series of codeine glycosides, utilizing the Koenigs-Knorr procedure, but it was Yoshimura\textsuperscript{71} who extended this to condense codeine and morpine with the acetobromo derivative of glucuronic acid to produce the 6-O-glucuronides. It was decided to use this already successful procedure for the preparation of codeine-6-O-glucuronide (C-6-G) and M-6-G.
The acetobromo derivative of glucuronic acid (90) was prepared by reaction of the tetra-acetate derivative of glucuronic acid, with hydrobromic acid in acetic acid.68

![Chemical structure](image1)

The NMR spectrum contained similar splitting patterns to that of the α-tetra-acetyl glucopyranuronate. Two distinct triplets for the 3- and 4-H's were observed at δ 4.85 and 5.20 respectively, and a double doublet for the 2-H at δ 4.51 but all are shifted ~0.4 ppm upfield. The 5-H and 1-H doublets were also shifted slightly upfield to δ 4.18 and 6.31 respectively. An O-Me singlet was observed at δ 3.38 but there was a loss of an acetate singlet at δ 2.02. Melting points and optical rotation values were consistent with literature values.

Methyl(codein-6-yl-2,3,4-tri-O-acetyl-α-D-glucopyranosid)uronate (93) was next synthesised by the condensation of codeine with the acetobromo derivative of glucuronic acid in benzene, in the presence of silver carbonate. The reaction rate is very slow, requiring prolonged heating to complete the reaction. Slow concentration of the reaction solution, by the removal of benzene via distillation, also assisted in reactivity.
The NMR spectrum showed two methyl singlets at $\delta$ 3.76 and 3.78 corresponding to the methoxy group at C-3 and the carboxylic methyl ester. The acetate singlets were observed at $\delta$ 2.0 - 2.1, consistent with the original sugar. A carbonyl stretch was also observed in the IR spectrum at 1746 cm$^{-1}$, consistent with an ester group. The mass spectrum showed a molecular ion at 615 which was consistent with the molecular formula C$_{31}$H$_{37}$NO$_{12}$.

Removal of the protecting groups to yield C-6-G proved rather difficult. The procedure of Helfrich and Berger$^{72}$ reported the conversion of the methyl acetate derivative of codeine glucuronide (93) to the methyl derivative (94) on solvolysis with a catalytic amount of sodium methoxide. The ester functionality was then hydrolysed by an equivalent amount of aqueous barium hydroxide and C-6-G (95) was isolated after neutralisation with oxalic acid.

**Scheme 6**
Attempting to follow this procedure, the removal of the acetate groups with sodium methoxide appeared successful by TLC. The hydrolysis of the ester gave a white powder, which from TLC evidence was thought to be the required compound. However, spectra showed that this was not the case and the melting point was higher than expected. The NMR spectrum could not be clearly interpreted, although a morphine type structure was apparent, and mass spectroscopy showed a molecular ion at 551.

It is believed the problem lies in the isolation and purification of the extremely polar C-6-G, though we can not be certain that the reaction was successful. It was decided to attempt a new approach. A mild de-protection process was required that would leave the glucuronide attached to the morphine skeleton, and it was decided to utilise enzyme catalysed hydrolysis.

6.5 Esterases and Lipases

There are a wide range of esterases commercially available, but few have been widely used in organic transformations. The most commonly used esterases are pig liver esterase (PLE), porcine pancreatic lipase (PPL) and α-chymotrypsin.

Three main properties make enzymes exceptional catalysts...

1) They are extremely versatile and catalyse a broad spectrum of reactions. Reactions take place under mild conditions, often at room temperature and close to neutral pH, minimising isomerisation, racemisation, epimerisation and rearrangement.

2) They can be extremely efficient catalysts. The rates of enzyme promoted reactions can be faster than those of the corresponding uncatalysed reactions by factors of up to $10^{12}$. 
3) They are generally very selective in terms of the type of reaction catalysed and with respect to the structure and stereochemistry of the substrate and product. These properties collectively constitute the specificity of an enzyme and are its most important feature for selective and asymmetric synthetic exploitation.

There are six main groups of enzymes: oxidoreductases, transferases, hydrolyases, lyases, isomerases and ligases. The most useful enzymes for organic synthesis applications are those which accept a broad structural range of substrates while retaining the ability to operate stereospecifically on each.

Investigating hydrolytic enzymes\textsuperscript{73} we find that their abilities to catalyse selective hydrolyses have been widely exploited. e.g.

...the hydrolysis of nitriles to amides and subsequently carboxylic acids, under very mild conditions.

\[
\text{R-} \equiv \text{N} \xrightarrow{\text{nitrile hydratase}} \text{R-} \text{CONH}_2 \xrightarrow{\text{amidase}} \text{R-} \text{COOH}
\]

...using yeast of PPL to hydrolyse the methyl ester functions of highly sensitive prostaglandin precursors to the corresponding acids.

PLE is also a useful enzyme for prostaglandin methyl ester hydrolysis.
Examining further methyl ester hydrolysis reactions it was found that PLE and α-chymotrypsin have been used in the hydrolysis of C-3 substituted glutarate diesters and are generally pro-S ester group selective.

PLE exhibits a broad tolerance of structural variations in its meso-diester substrates.

In this instance it was decided to utilise PLE, a complex mixture of trimeric isoenzymes which can behave similarly or differently depending on reaction conditions.

Thus to prepare C-6-G the methyl acetate derivative of codeine glucuronide (93) was treated with a catalytic amount of sodium methoxide. The hydrolysis of the methyl derivative (94) was then carried out in phosphate buffer at pH 7, incubation at 25°C, using PLE suspended in ammonium sulphate. The pH was monitored continuously using a pH meter and base was automatically added during the course of the reaction to maintain a pH 7, to compensate for the production of the glucuronic acid. Acidification is generally used to destroy the enzyme at the end of the reaction but care
was needed here not to destroy the glycosidic bond. Thus the reaction mixture was slowly acidified to pH 5 using acetic acid. Again isolation of C-6-G proved difficult due to its high polarity. The products of most enzymatic reactions are isolated from the enzyme by extraction into an organic solvent. Unfortunately in this case C-6-G is insoluble in organic solvents but highly soluble in water. Thus isolation and purification was effected using HPLC with a reverse phase silica column, using aqueous methanol as the mobile phase. A white powder was isolated whose melting point was consistent with literature values for C-6-G. The NMR spectrum exhibited the characteristic codeine methoxy singlet at δ 3.81 and N-Me singlet at δ 2.51. The aromatic ABq and double bond protons were comparable to codeine. The glycosidic protons were apparent in the region δ 3.49 - 4.60. The 2', 3' and 4' protons appearing as a multiplet, and the 1' and 5' protons as doublets with the 1'-H being farthest downfield. An EI mass spectrum showed a molecular ion at 299, not at 475 as expected. This corresponds to the codeine ion and obviously conditions are causing early fragmentation of the C-6-G molecule. A different procedure such as fast atom bombardment (FAB) would be required to identify the molecular ion.

6.6 Morphine 6-O-glucuronide

Yoshimura prepared M-6-G (29) using 3-O-acetylmorphine\(^{71}\), for protection of the three position. This was condensed with the acetobromo derivative of glucuronic acid in benzene, in the presence of silver carbonate to give the protected sugar. Deprotection was reported using successively sodium methoxide and barium hydroxide solution, as in the codeine case.

Repeating this procedure proved unsuccessful, with the failure to isolate methyl(3-acetylmorphin-6-yl-2,3,4-tri-O-acetyl-β-D-glucopyranosid)uronate. As outlined earlier in the preparation of morphine 3-O-acetate the problem is probably due to the instability of this compound. This was overcome by utilising the much more stable morphine 3-O-TBDMS ether. The same glycosylation procedure was used, condensing morphine 3-O-TBDMS ether with the acetobromo derivative of
glucuronic acid in benzene, in the presence of silver carbonate, and the reaction proved successful, allowing the isolation and purification of methyl (3-O-TBDMS-morphin-6-yl-2,3,4-tri-O-acetyl-β-D-glucopyranosid) uronate (96). The IR spectrum exhibited a carbonyl stretch at 1758 cm⁻¹, suggesting an ester. The NMR spectrum showed TBDMS singlets at δ 0.14, 0.16 and 0.96 corresponding to 2xSiMe and SiCMe₃ respectively. Three acetate singlets were observed in the region δ 2.07, defining the presence of the sugar moiety. A singlet was apparent at δ 3.74, identifying the presence of a methyl ester. The remaining sugar protons were observed along with the morphine fine structure. The accurate mass was found to be 687.3264, by EI mass spectroscopy, which was consistent with the molecular formula C₃₆H₄₉NO₁₂.

It was decided that due to the problems arising in isolating the highly polar glucuronides the next step would be to remove the TBDMS group, before deprotection of the glucuronide sugar. This was easily effected using TBAF in THF.

- The NMR spectrum showed the loss of all singlets in the region δ 0-1, indicating the successful removal of the TBDMS group. The remainder of the spectrum was comparable with that of the protected compound. The IR spectrum still showed a carbonyl stretch at 1746 cm⁻¹, suggesting the remainder of the molecule is still intact and that methyl(morphin-6-yl-2,3,4-tri-O-acetyl-β-D-glucopyranosid)uronate (97) has been isolated. It also exhibited a carbonyl stretch at 1746 cm⁻¹ corresponding to an ester functionality. The NMR spectrum showed the characteristic N-Me singlet of morphine at δ 2.49 and the aromatic ABq at δ 6.47 - 6.64. The three acetate singlets were apparent at δ 2.01 - 2.18 and the methoxy singlet of the ester at δ 3.73. Elemental analysis was correct for C₃₀H₃₅NO₁₂.

The initial attempt at de-protection was, as for codeine, using the method of Helferich and Berger. Again the methyl derivative of morphine glucuronide seemed to be produced by TLC, on reaction with a catalytic amount of sodium methoxide in methanol. However, after hydrolysis of the ester functionality with an equivalent
amount of aqueous barium hydroxide and neutralisation with oxalic acid, M-6-G (29) could not be isolated.

Following the success of using PLE to hydrolyse the methyl ester, in the preparation of C-6-G, it was decided to repeat the procedure to isolate M-6-G. Thus treatment of the methyl acetate derivative of morphine glucuronide (97) with sodium methoxide in methanol and then incubation with PLE in phosphate buffer, at 25°C, afforded M-6-G (29). Isolation and purification was effected by HPLC using a reverse phase column and aqueous methanol as the mobile phase. The melting point was consistent with literature values. The NMR spectrum exhibited the characteristic N-Me singlet of morphine at δ 2.87. The aromatic ABq and the double bond protons were clearly identified. The methoxy and acetate singlets were no longer visible compared to the spectrum of the protected compound. The glycosidic protons were all shifted upfield, consistent with the removal of the acetate groups. A mass spectrum by FAB showed the molecular ion (M+H) at 462 consistent with the formula C_{23}H_{27}NO_{9}.

The preparation and isolation of M-6-G though far more difficult than expected has been accomplished. It is thought the method could be further utilised to prepare a series of morphine glycosides.
Scheme 7

(45) TBDMS-O

\[ \text{TBDMS-O} \]

\[ \text{COOMe} \]

\[ \text{AcO} \]

\[ \text{Br} \]

\[ \text{OAc} \]

\[ \text{benzene, Ag}_2\text{CO}_3 \]

\[ \text{TBDMS-O} \]

\[ \text{COOMe} \]

\[ \text{AcO} \]

\[ \text{OAc} \]

\[ \text{TBAF} \]

\[ \text{THF} \]

\[ \text{OH} \]

\[ \text{HO} \]

\[ \text{MeOH} \]

\[ \text{NaOMe} \]

\[ \text{PLE} \]

\[ \text{COOH} \]

\[ \text{COOH} \]

\[ \text{OH} \]

\[ \text{OH} \]

(29)
EXPERIMENTAL

7.1 General Procedures

All solvents were distilled before use. Chloroform (CHCl₃) and dichloromethane (DCM) were distilled from phosphorus pentoxide. Diethyl ether (Et₂O), ethyl acetate (EtOAc) and petroleum ether (40-60°C) were distilled from calcium chloride. Dimethylformamide (DMF) and dimethylsulphoxide (DMSO) were dried over calcium hydride, distilled under reduced pressure and stored over 4Å molecular sieves under nitrogen. Methanol (MeOH) was distilled from magnesium methoxide, and ethanol (EtOH) was distilled from magnesium ethoxide, both were stored over 4Å molecular sieves. Pyridine was distilled from and stored over potassium hydroxide pellets. Tetrahydrofuran (THF) was stored over sodium wire and distilled from the sodium-benzophenone ketyl immediately prior to use. Toluene and benzene were distilled from sodium hydride and stored over sodium wire. Glassware used in the reactions was generally flame dried under nitrogen and reactions were conducted under an inert atmosphere of nitrogen or argon.

Analytical TLC was carried out on aluminium backed plates coated with Merck Kieselgel 60 F₂₅₄ and compounds were visualised by staining with iodine, or under uv light (at 254 and / or 360 nm). Preparative TLC was performed on 20 cm by 20 cm glass plates coated with Merck Kieselgel 60 PF₂₅₄+366 (0.75 mm thickness). Flash chromatography was performed on Matrex® Silica 60 (35-70 micron).

Melting points were determined on a Kofler hot - stage apparatus and are uncorrected.

Infra red spectra were recorded in the range 4000 - 600 cm⁻¹, as nujol mulls or chloroform solutions using a Nicolet 205 FT-IR spectrophotometer, with internal calibration.
NMR spectra were recorded on a Bruker AC-250 spectrometer operating at 250 MHz for $^1$H NMR and at 62.9 MHz for $^{13}$C NMR. Chemical shifts are expressed in ppm relative to tetramethylsilane as internal standard. Coupling constants ($\textit{J}$) are quoted in hertz (Hz). The following abbreviations are used in the presentation of spectra: s = singlet, d = doublet, dd = double doublet, dt = double triplet, t = triplet, q = quartet, m = multiplet.

Electron impact mass spectra were recorded on a Kratos MS-80 spectrometer with an ionising potential of 70 eV. Chemical ionisation mass spectra were recorded on a Finnigan MAT-90 mass spectrometer.

Elemental analyses were initially sent to Medac Ltd, Department of Chemistry, Brunel University, Uxbridge, Middlesex and later performed on a Perkin Elmer 2400 Elemental Analyser.

HPLC was performed on a Fisons Spherisorb ODS-2 column, 300 mm x 25 mm. The solvents used were degassed, HPLC grade methanol and water.

7.2 Experimental

Preparation of Morphine (1)
To a well stirred solution of BBr$_3$ (25 g, 0.1 mol) in CHCl$_3$ (250 ml), was added dropwise a solution of codeine (5 g, 16.7 mmol) in CHCl$_3$ (35 ml), maintaining the solution at 25°C. The addition funnel was flushed with 10 ml of CHCl$_3$, and the resulting mixture stirred for 1 h. The reaction mixture was poured onto a well stirred mixture of ice (125 g) and concentrated ammonia (30 ml), and kept at -5-0°C for 30 min, with continuous stirring. This mixture was filtered and the resulting crystalline material washed thoroughly with small portions of cold CHCl$_3$ and water, and dried. Morphine, a white solid was obtained (4.615 g, 97%) m.p. 253-4°C (decomp) [lit 254-256°C$^{40}$]; $\nu_{\text{max}}$(nujol)/cm$^{-1}$ 3476 (OH); $\delta_H$ (CD$_3$OD) 1.91 (1 H, d, $J$ 11, 15e-H), 2.12 (1 H, dt, $J$ 12.5, 5, 5, 15a-H), 2.37 (1 H, dd, $J$ 18.5, 6,
Preparation of Morphin-6-yl-β-D-glucopyranosiduronic Acid (29)
To a solution of methyl(morphin-6-yl-2,3,4-tri-O-acetyl-β-D-glucopyranosid)uronate (150 mg, 0.21 mmol) in methanol (3 cm³), was added 0.01 M NaOMe solution (1 cm³) and the solution stirred overnight. On completion of the reaction, indicated by TLC, the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in phosphate buffer (10 cm³), at 25°C, and the pH adjusted to 7 using 0.05 M NaOH. PLE (0.45 cm³, 1 mg, ~200 units) as a suspension in 3.2 M (NH₄)SO₄ solution was added and the reaction left stirring overnight, maintaining the temperature at 25°C and the pH at 7, by using a pH-stat. The reaction mixture was adjusted to pH 6 using acetic acid, and evaporated under reduced pressure to give a concentrated solution. The crude solution was chromatographed on reverse phase silica (elution with 30% H₂O in MeOH). Final purification was by semi-prep HPLC, using a silica reverse phase column, to give colourless needles of M-6-G 29 (42 mg, 35%) m.p. 252-255°C (decomp) [lit 254-256°C⁷]; νmax(nujol)/cm⁻¹ (C=O); δH (D₂O) 1.98 (1 H, d, J 11, 15e-H), 2.25 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.87 (6 H, m, NMe, 10α, 14 and 16a-H), 3.17 (2 H, m, 10β and 16e-H), 3.70 (1 H, d, J 9, 22-H), 4.02 (1 H, q, J 4, 9-H), 4.51 (1 H, m, 6-H), 4.59 (1 H, d, J 8, 18-H), 5.17 (1 H, d, J 7, 5-H), 5.30 (1 H, d, J 10, 8-H), 5.66 (1 H, d, J 10, 7-H), 6.61 and 6.69 (2 H, ABq, 1 and 2-H); δC 24.18, 34.50, 40.20, 43.24 (NMe), 44.34, 49.05, 62.50, 74.20, 75.42, 75.54, 77.95, 78.72, 90.74, 103.92, 120.17, 122.79, 125.98, 129.05, 131.77, 135.58, 140.88, 148.15, 178.07; HPLC: Solvent - MeOH/H₂O (70:30), Flow rate - 0.5 ml/min, Elution time - 10.5 min.
Preparation of 6α-(2'-Carboxybenzyloxy)-7,8-didehydro-4,5α-epoxy-3-methoxy-17-methyl-morphinan (36)

A mixture of codeine (1 g, 3.34 mmol) and phthalic anhydride (2 g, 13.5 mmol) in pyridine (5 cm³) was refluxed for 1 h. The hot reaction mixture was poured onto ice and the resulting white precipitate collected on a filter. The precipitate was washed with cold water. Crystallisation from DCM-light petroleum gave the ester 36 (2.67 g, 88%) m.p. 227-8°C (decomp); νmax(nujol)/cm⁻¹ 3417 (OH), 1713 (C=O ester), 1608 (C=O acid); δH(CDCl₃) 1.98 (1 H, d, J 13.5, 15e-H), 2.68-2.97 (7 H, m, NMe, 10α, 15a, 16a-H and OH), 3.07 (1 H, d, J 18.5, 10β-H), 3.44 (1 H, d, J 7, 16e-H), 3.59 (1 H, t, J 2.5, 14-H), 3.85 (4 H, m, OMe and 9-H), 5.44 (3 H, m, 5, 6 and 8-H), 5.80 (1 H, d, J 8.5, 7-H), 6.61 and 6.74 (2 H, ABq, 1 and 2-H), 7.37 (1 H, t, J 7.5, 21-H), 7.51 (1 H, t, J 7.5, 22-H), 7.67 (1 H, d, J 7.5, 20-H), 8.04 (1 H, d, J 7.5, 23-H); δC 21.40, 32.09, 36.84, 40.80 (NMe), 40.96, 47.31, 56.99 (OMe), 60.11, 67.66, 87.38, 115.40, 119.88, 122.83, 126.79, 127.29, 127.90, 129.75, 129.98, 130.22, 131.16, 131.39, 132.07, 143.26, 146.81, 166.68, 175.83; m/z 447 (M⁺)

Preparation of 3-Acetyloxy-7,8-didehydro-4,5α-epoxy-17-methylmorphinan-6-ol (38)

To a stirred solution of sodium carbonate (10 g) in water (100 cm³) was added morphine (1 g, 3.5 mmol). To this suspension was added acetic anhydride (5.4 g, 5 cm³, 53 mmol) dropwise with constant stirring, at room temperature. After the mixture ceased to foam, it was poured onto ice / water and extracted into CHCl₃. The organic layer was dried (Na₂SO₄) and evaporated under reduced pressure to yield a white solid 38 (1.121 g, 97%); νmax(nujol)/cm⁻¹ 3400 (OH), 1690 (C=O); δH(CDCl₃) 1.96 (1 H, d, J 11, 15e-H), 2.29 (4 H, m, 10α-H and Ac), 2.58 (5 H, m, NMe, 10α and 16a-H), 2.95 (2 H, m, 14 and 16e-H), 3.08 (1 H, d, J 18.5, 10β-H), 3.70 (1 H, q, J 3.5, 9-H), 4.20 (1 H, m, 6-H), 4.96 (1 H, d, J 6.5, 5-H), 5.26 (1 H, d, J 10, 8-H), 5.79 (1 H, d, J 10, 7-H), 6.64 and 6.77 (2 H, ABq, 1 and 2-H).
Preparation of 3-Benzyloxy-7,8-didehydro-4,5α-epoxy-17-methylmorphinan-6-ol (43)

A solution of morphine (100 mg, 0.35 mmol) in dry DMF (5 cm³), with finely divided KOH (100 mg), was stirred, under nitrogen, at room temperature for 1 h. Benzyl bromide (0.05 cm³, 72 mg, 0.42 mmol) was added and the reaction stirred at room temperature overnight. The reaction mixture was dissolved in CHCl₃ washed with water, dried (Na₂SO₄) and evaporated under reduced pressure. A yellow solution was obtained which was purified by column chromatography (elution with 15% MeOH in DCM) to give a cream powder 43 (40 mg, 30%) m.p. 122-5°C [lit 125-6°C]; υmax(nujol)/cm⁻¹ 3540 (OH); δH (CDCl₃) 1.89 (1 H, d, J 11, 15e-H), 2.05 (1 H, dt, J 12.5, 5, 5, 15α-H), 2.28 (1 H, dd, J 18.5, 6, 10α-H), 2.43 (4 H, m, NMe and 16α-H), 2.56 (1 H, dd, J 12.5, 4, 16e-H), 2.65 (1 H, t, J 2.5, 14-H), 3.03 (1 H, d, J 18.5, 10β-H), 3.34 (1 H, q, J 3.5, 9-H), 4.15 (1 H, m, 6-H), 4.87 (1 H, d, J 6.5, 5-H), 5.13 (2 H, ABq, CH₂-Ph), 5.27 (1 H, d, J 10, 8-H), 5.66 (1 H, d, J 10, 7-H), 6.53 and 6.71 (2 H, ABq, 1 and 2-H), 7.36-7.44 (5 H, m, CH₂-Ph).

Preparation of 3,6-Di-t-butyldimethylsilyloxy-7,8-didehydro-4,5α-epoxy-17-methyl-morphinan (44)

Morphine (200 mg, 0.7 mmol), imidazole (120 mg, 1.75 mmol) and t-butyldimethylsilyl chloride (315 mg, 2.1 mmol) were shaken together in dry DMF (0.5 cm³), under nitrogen for 5 min. The reaction mixture was left stirring at room temperature overnight. The product was taken up in CHCl₃, washed with aq. NaHCO₃ and water, dried (Na₂SO₄) and evaporated to yield a cream solid. Crystallisation from DCM-light petroleum gave colourless crystals of 44 (133 mg, 37%) m.p. 116-8°C; υmax(nujol)/cm⁻¹ 1628; δH (CDCl₃) 0.13 (12 H, m, 2xSiMe₂), 0.92 (9 H, s, SiCMe₃), 0.98 (9 H, s, SiCMe₃), 1.86 (1 H, d, J 11.5, 15e-H), 2.03 (1 H, dt, J 12.5, 5, 5, 15α-H), 2.31 (1 H, dd, J 18.5, 6, 10α-H), 2.49 (4 H, m, NMe and 16α-H), 2.60 (2 H, m, 14 and 16e-H), 3.02 (1 H, d, J 18.5, 10β-H), 3.35 (1 H, q, J 3.5, 9-H), 4.21 (1 H, m, 6-H), 4.66 (1 H, d, J 6.5, 5-H), 5.22 (1 H, d, J 10, 8-H), 5.60 (1 H, d, J 10, 7-H), 6.41 and 6.56 (2 H, ABq, 1 and 2-H); m/z 513.
(M⁺, 15%) 456(54), 413(48), 335(12), 278(17), 238(9), 146(10), 73(100), 59(14), 41(17).

Preparation of 3-t-Butyldimethylsilyloxy-7,8-didehydro-4,5α-epoxy-17-methyl-morphinan-6-ol (45)

To a solution of morphine (2 g, 7 mmol) in THF, under nitrogen, was added NaH-60% dispersion in mineral oil (310 mg, 7.75 mmol) and the reaction stirred for 1 hr. t-Butyldimethylsilyl chloride (1.27 g, 8.45 mmol) was added and the reaction stirred overnight. The mixture was filtered and THF removed under reduced pressure. The residue was purified by column chromatography (elution with 15% MeOH in CHCl₃). A cream powder was obtained 45 (1.445 g, 52%) m.p. 121-22°C [lit. 122-123°C²]; νmax(nujol)/cm⁻¹ 3552 (OH), 1629; δH (CDCl₃) 0.16 (3 H, s, SiMe), 0.20 (3 H, s, SiMe), 0.98 (9 H, s, SiCMe₃), 1.89 (1 H, d, J 12, 15α-H), 2.21 (1 H, dt, J 12.5, 5, 15α-H), 2.43 (2 H, m, 10α and 16α-H), 2.55 (3 H, s, NMe), 2.75 (1 H, dd, J 12.5, 4, 16e-H), 2.89 (1 H, t, J 2.5, 14-H), 3.04 (1 H, d, J 18.5, 10β-H), 3.50 (1 H, q, J 3.5, 9-H), 4.19 (1 H, m, 6-H), 4.87 (1 H, d, J 6.5, 5-H), 5.26 (1 H, d, J 10, 8-H), 5.70 (1 H, d, J 10, 7-H), 6.50 and 6.60 (2 H, ABq, 1 and 2-H).

Preparation of 3-Methoxymethoxy-7,8-didehydro-4,5α-epoxy-17-methyl-morphinan-6-ol (46)

To a solution of morphine (500 mg, 1.75 mmol) in THF (50 cm³), under nitrogen, was added NaH-60% dispersion in mineral oil (77 mg, 1.92 mmol) and the reaction stirred for 1 h. Chloromethyl methyl ether (182 mg, 0.17 cm³, 2.27 mmol) in THF (10 cm³) was added dropwise and the reaction stirred overnight. TLC showed complete reaction of morphine. THF was removed under reduced pressure and the residue dissolved in DCM. The solution was washed with water, dried (Na₂SO₄), and evaporated under reduced pressure. A brown residue was obtained which was purified by column chromatography (elution with 5% MeOH in DCM) to give a beige powder 46 (118 mg, 20 %) m.p. 92-95°C. [lit. 91-93°C²]; νmax(CHCl₃)/cm⁻¹ 3536 (OH); δH (CDCl₃) 2.07 (1 H, d, J 12, 15ε-H), 2.56 - 2.90 (6 H, m, NMe, 10α-.
15a- and 16a-H), 2.95 (2 H, m, 10β- and 16e-H), 3.46 (4 H, m, OMe and 14-H),
3.87 (1 H, q, J 3.5, 9-H), 4.22 (1 H, m, 6-H), 4.97 (2 H, d, J 6.5, OCH2O), 5.21
(1 H, d, J 10, 8-H), 5.56 (1 H, d, J 6.5, 5-H), 5.79 (1 H, d, J 10, 7-H), 6.63 and
6.84 (2 H, ABq, 1 and 2-H); δC 21.87, 32.62, 37.57, 41.22, 41.68, 47.11, 56.31,
60.35, 65.34, 90.20, 95.23, 119.94, 120.70, 124.47, 124.59, 130.34, 135.65,
139.02, 146.52.

Preparation of 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methyl-6α-
succinyloxy-morphinan (48)
A mixture of codeine (1 g, 3.34 mmol) and succinic anhydride (2 g, 20 mmol) in
pyridine (5 cm³) was refluxed for 1 h. The hot reaction mixture was poured onto ice
and the resulting white precipitate collected on a filter. The precipitate was washed with
cold water. Crystallisation from DCM-petroleum ether gave the ester 48 (240 mg,
18%) m.p. 154-6°C; νmax(νujol)/cm⁻¹ 3432 (OH), 1720 (C=O ester), 1632 (C=O
acid); δH(CDCl₃) 1.89 (1 H, d, J 13.5, 15e-H), 2.39-2.79 (11 H, m, NMe, 16-H₂,
10a and 15a-H), 3.01 (1 H, d, J 19, 10β-H), 3.11 (1 H, t, J 2.5, 14-H), 3.76 (1 H, q, J 3, 9-H), 3.86 (3 H, s, OMe), 5.15 (1 H, d, J 6.5, 5-H), 5.28
(2 H, m, 6 and 8-H), 5.60 (1 H, d, J 10, 7-H), 6.55 and 6.68 (2 H, ABq, 1 and 2-H);
m/z 399 (M⁺ 13%) 299(100), 282(22), 229(29), 188(14), 162(31), 124(27), 70(17),
56(56), 42(49).

Preparation of 6α-Benzoyloxy-7,8-didehydro-4,5α-epoxy-3-methoxy-
17-methyl-morphinan (49)
To a solution of codeine (300 mg, 1 mmol) in pyridine (3 cm³), under nitrogen, was
added benzoyle chloride (0.35 ml, 1 mmol) and the reaction stirred at room temperature
for 4 h. DCM (10 ml) was added and the solution washed with a 5% CuSO₄ solution
and water, dried (Na₂SO₄) and evaporated under reduced pressure. The crude product
was purified by column chromatography (elution with 5% MeOH in DCM) to give the
ester 49 (295 mg, 73%).
A mixture of codeine (300 mg, 1 mmol), benzoic acid (122 mg, 1 mmol) and DMAP
(122 mg, 1 mmol) in DCM was stirred for 1 h at 0°C, the flask being fitted with a
calcium chloride guard tube. DCC (230 mg, 1.1 mmol) was added and the solution was stirred at 0°C for 5 min before being allowed to warm up to room temperature. After stirring for a further 3 h the reaction mixture was washed successively with dilute HCl / water / bicarbonate / water, dried (MgSO4) and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 5% MeOH in DCM) to give the ester 49 (275 mg, 68%). Recrystallisation in each case from DCM-petroleum ether gave colourless crystals m.p. 130-32°C; υmax(nujol)/cm⁻¹ 1717 (C=O ester); δH(CDCl₃) 1.91 (1 H, d, J 12.5, 15e-H), 2.12 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.37 (2 H, m, 10α and 16a-H), 2.48 (3 H, s, NMe), 2.65 (1 H, dd, J 12.5, 4, 16e-H), 2.86 (1 H, t, J 2.5, 14-H), 3.06 (1 H, d, J 18.5, 10β-H), 3.42 (1 H, q, J 3, 9-H), 3.72 (3 H, s, OMe), 5.20 (1 H, d, J 6.5, 5-H), 5.47 (2 H, m, 6 and 8-H), 5.78 (1 H, d, J 10, 7-H), 6.55 and 6.67 (2 H, ABq, 1 and 2-H), 7.43 (2 H, t, J 8, 21 and 23-H), 7.55 (1 H, t, J 8, 22-H), 8.09 (2 H, d, J 8, 20 and 24-H); δC 21.36, 35.09, 40.39, 42.50, 42.85 (NMe), 46.63, 56.79 (OMe), 59.08, 68.40, 87.95, 114.59, 119.13, 126.66, 128.13, 128.57, 129.31, 129.80, 130.63, 132.91, 142.10, 146.70, 165.92; m/z 403 (M⁺, 53%) 282(28), 266(23), 229(14), 155(15), 122(31), 105(100), 77(51). (Found M⁺, 403.1795. C25H25NO4 requires 403.1783).

Preparation of 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methyl-6α-(4'-nitrobenzoyloxy)-morphinan (50)

To a solution of codeine (300 mg, 1 mmol) in pyridine (3 cm³), under nitrogen, was added p-nitrobenzoyl chloride (560 mg, 3 mmol) and the reaction stirred at room temperature for 4 h. EtOAc was added and the solution washed with 5% CuSO₄ solution / water, dried (MgSO₄), and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 15% MeOH in CHCl₃) and TLC plates (run in CHCl₃/MeOH/NH₄OH) to give the ester 50 (283 mg, 63%). Recrystallisation from DCM-petroleum ether gave yellow crystals m.p. 186-87°C; υmax(CHCl₃)/cm⁻¹ 1722 (C=O ester); δH(CDCl₃) 1.90 (1 H, d, J 12.5, 15e-H), 2.08 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.34 (2 H, m, 10α and 16a-H), 2.46 (3 H, s, NMe), 2.61 (1 H, dd, J 12, 4, 16e-H), 2.83 (1 H, t, J 2.5, 14-H), 3.07 (1 H, d, J 18.5, 10β-H), 3.40 (1 H, q, J 3, 9-H), 3.71 (3 H, s, OMe), 5.20 (1 H, d, J 6.5, 5-H), 5.47
(1 H, m, 6-H), 5.55 (1 H, d, J 10, 8-H), 5.76 (1 H, d, J 10, 7-H), 6.58 and 6.67
(2 H, ABq, 1 and 2-H), 8.27 (4 H, m, 20, 21, 23 and 24-H); δC 20.30, 35.35,
40.66, 42.59, 43.09 (NMe), 46.74, 56.49 (OMe), 59.13, 69.17, 87.57, 113.86,
119.46, 123.40, 127.03, 127.80, 130.20, 130.60, 131.07, 142.18, 146.44, 150.59,
164.22; m/z 448 (M+, 84%), 311(20), 282(82), 229(25), 152(16), 104(44), 92(20),
76(42), 59(39), 50(100), 44(58). (Found M+, 448.1607 C25H24N2O6 requires
448.1634).

Preparation of 7,8-Didehydro-4,5α-epoxy-3-methoxy-6α-(4'-methoxy
benzoyloxy)-17-methyl-morphinan (51)

To a solution of codeine (300 mg, 1 mmol) in pyridine (3 cm³), under nitrogen, was
added p-anisoyl chloride (0.45 ml, 513 mg, 3 mmol) and the reaction stirred at room
temperature for 10 min. EtOAc was added and the solution washed successively with
dilute HCl / water / bicarbonate / water, dried (MgSO₄), and evaporated under reduced
pressure. The crude product was purified by column chromatography (elution with 5%
MeOH in DCM) to give the ester 51 (426 mg, 98%). Recrystallisation from DCM-
petroleum ether gave colourless crystals m.p. 174-76°C; νmax(CHCl₃)/cm⁻¹ 1711
(C=O ester); δH(CDCl₃) 1.90 (1 H, d, J 12.5, 15e-H), 2.09 (1 H, dt, J 12, 5, 5,
15a-H), 2.36 (2 H, m, 10α and 16a-H), 2.48 (3 H, s, NMe), 2.62 (1 H, dd, J 12, 4,
16e-H), 2.83 (1 H, t, J 2.5, 14-H), 3.06 (1 H, d, J 18.5, 10β-H), 3.42 (1 H, q, J 3,
9-H), 3.44 (3 H, s, OMe), 3.74 (3 H, s, OMe), 5.18 (1 H, d, J 6.5, 5-H), 5.41 (1 H,
m, 6-H), 5.48 (1 H, d, J 10, 8-H), 5.76 (1 H, d, J 10, 7-H), 6.55 and 6.66 (2 H,
ABq, 1 and 2-H), 6.92 (2 H, d, J 9, 21 and 23-H), 8.04 (2 H, d, J 9, 20 and 24-H);
δC 20.49, 35.28, 40.54, 42.69, 42.94 (NMe), 46.63, 55.42 (OMe), 57.02 (OMe),
59.05, 68.34, 88.32, 114.82, 119.19, 122.41, 126.97, 128.85, 129.42, 130.90,
131.98, 142.16, 146.78, 163.47, 165.77; m/z 433 (M⁺, 43%), 282(20), 229(12),
152(14), 135(100), 77(16), 44(11). (Found M⁺, 433.1915 C26H27NO5 requires
433.1889).
Preparation of 7,8-Didehydro-4,5α-epoxy-6α-(4'-fluorobenzoyloxy)-3-methoxy-17-methyl-morphinan (52)

To a solution of codeine (300 mg, 1 mmol) in pyridine (3 cm³), under nitrogen, was added p-fluorobenzoyl chloride (0.35 cm³, 477 mg, 3 mmol) and the reaction stirred at room temperature for 10 min. CHCl₃ was added and the solution washed successively with dilute HCl / water / bicarbonate / water, dried (MgSO₄), and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 5% MeOH in CHCl₃) to give the ester 52 (403 mg, 95%). Recrystallisation from DCM-petroleum ether gave colourless crystals m.p. 136-39°C; \( \nu_{\text{max}} \) (nujol)/cm⁻¹ 1717 (C=O ester); \( \delta_{\text{H}} \) (CDCl₃) 1.92 (1 H, d, \( J \) 12.5, 15e-H), 2.16 (1 H, dt, \( J \) 12.5, 5, 5, 15a-H), 2.42 (2 H, m, 10α and 16a-H), 2.52 (3 H, s, NMe), 2.75 (1 H, dd, \( J \) 12.5, 4, 16e-H), 2.92 (1 H, t, \( J \) 2.5, 14-H), 3.08 (1 H, d, \( J \) 18.5, 10β-H), 3.53 (1 H, q, \( J \) 3, 9-H), 3.72 (3 H, s, OMe), 5.20 (1 H, d, \( J \) 6.5, 5-H), 5.43 (1 H, m, 6-H), 5.51 (1 H, d, \( J \) 10, 8-H), 5.77 (1 H, d, \( J \) 10, 7-H), 6.58 and 6.68 (2 H, ABq, 1 and 2-H), 7.11 (2 H, m, 21 and 23-H), 8.10 (2 H, m, 20 and 24-H); \( \delta_{\text{C}} \) 20.63, 34.82, 39.98, 42.41, 42.60 (NMe), 46.60, 56.74 (OMe), 59.04, 68.41, 87.85, 114.49, 115.24, 115.59, 119.37, 126.36, 128.69, 129.26, 130.49, 132.43, 132.58, 142.30, 146.76, 165.05, 167.88; m/z 421 (M⁺, 53%) 282(28), 266(23), 229(14), 155(15), 122(31), 105(100), 77(51). (Found M⁺, 421.1689. C₂₅H₂₄NFO₄ requires 421.1725).

Preparation of 6α-(4'-Chlorobenzoyloxy)-7,8-didehydro-4,5α-epoxy-3-methoxy-17-methyl-morphinan (53)

To a solution of codeine (300 mg, 1 mmol) in pyridine (3 cm³), under nitrogen, was added p-chlorobenzoyl chloride (0.38 ml, 527 mg, 3 mmol). The reaction mixture was stirred at room temperature for 10 min. EtOAc was added and the solution washed successively with dilute HCl / water / bicarbonate / water, dried (MgSO₄), and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 10% MeOH in CHCl₃) to give the ester 53 (315 mg, 72%). Recrystallisation from DCM-petroleum ether gave colourless crystals m.p. 165-67°C; \( \nu_{\text{max}} \) (CHCl₃)/cm⁻¹ 1719 (C=O ester); \( \delta_{\text{H}} \) (CDCl₃) 1.91 (1 H, d, \( J \) 12.5, 15e-H), 2.11 (1 H, dt, \( J \) 12.5, 5, 5, 15a-H), 2.38 (2 H, m, 10α and 16a-H), 2.49
Preparation of 6α-(4'-Bromobenzoyloxy)-7,8-didehydro-4,5α-epoxy-3-methoxy-17-methyl-morphinan (54)

To a solution of codeine (300 mg, 1 mmol) in pyridine (3 cm³), under nitrogen, was added p-bromobenzoyl chloride (1.1 g, 5 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 10 min. CHCl₃ was added and the solution washed successively with dilute HCl / water / bicarbonate / water, dried (MgSO₄), and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 5% MeOH in CHCl₃) to give the ester 54 (441 mg, 92%). Recrystallisation from DCM-petroleum ether gave colourless crystals m.p. 177-80°C; υₘₐₓ(CHCl₃)/cm⁻¹ 1719 (C=O ester); δₛ(CHCl₃) 1.90 (1 H, d, J 12.5, 15e-H), 2.11 (1 H, dt, J 12.5, 5, 5, 15α-H), 2.37 (2 H, m, 10α and 16α-H), 2.48 (3 H, s, NMe), 2.65 (1 H, dd, J 12.5, 4, 16e-H), 2.85 (1 H, t, J 2.5, 14-H), 3.07 (1 H, d, J 18.5, 10β-H), 3.44 (1 H, q, J 3, 9-H), 3.72 (3 H, s, OMe), 5.19 (1 H, d, J 6.5, 5-H), 5.42 (1 H, m, 6-H), 5.51 (1 H, d, J 10, 8-H), 5.76 (1 H, d, J 10, 7-H), 6.57 and 6.67 (2 H, ABq, 1 and 2-H), 7.58 (2 H, d, J 8, 21 and 23-H), 7.94 (2 H, d, J 8, 20 and 24-H); δₛ 20.46, 35.14, 40.38, 42.54, 42.88 (NMe), 46.68, 56.74 (OMe), 59.10, 68.62, 87.84, 114.38, 119.34, 126.72, 128.16, 128.42, 128.92, 129.60, 130.63, 131.46, 131.60, 142.23, 146.66, 165.31; m/z 483 and 481 (M⁺, 80 and 90%), 282(100), 346 and 344(25 and 27), 229(42), 185 and 183(76 and 90%).
Preparation of 7,8-Didehydro-4,5α-epoxy-3-methoxy-6α-(3',4'-methylene dioxybenzoyloxy)-17-methyl-morphinan (55)

To a solution of codeine (200 mg, 0.67 mmol) in DCM (2 cm³) at 0°C, under nitrogen, was added piperonylic acid (333 mg, 2 mmol) and DMAP (82 mg, 0.67 mmol) and the solution was stirred for 30 min. DCC (152 mg, 0.74 mmol) was added and the reaction flask fitted with a calcium chloride guard tube. After stirring for 5 min at 0°C, the reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was filtered, washed with water / bicarbonate, dried (MgSO₄) and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 10% MeOH in CHCl₃) to give the ester 55 (195 mg, 65%). Recrystallisation from DCM petroleum ether gave colourless crystals m.p. 63.5°C; $\nu_{\text{max}}$(CHCl₃)/cm⁻¹ 1711 (C=O ester);

$\delta_{\text{H}}$(CDCl₃) 1.90 (1 H, d, $J_{12.5}$, 15e-H), 2.11 (1 H, dt, $J_{12}$, 5, 5, 15a-H), 2.37 (2 H, m, 10α and 16a-H), 2.46 (3 H, s, NMe), 2.64 (1 H, dd, $J_{12}$, 4, 16e-H), 2.84 (1 H, t, $J_{2.5}$, 14-H), 3.06 (1 H, d, $J_{18.5}$, 10β-H), 3.44 (1 H, q, $J_{3}$, 9-H), 3.76 (3 H, s, OMe), 5.17 (1 H, d, $J_{6.5}$, 5-H), 5.41 (1 H, m, 6-H), 5.50 (1 H, d, $J_{10}$, 8-H), 5.75 (1 H, d, $J_{10}$, 7-H), 6.03 (2 H, s, CH₂), 6.56 and 6.67 (2 H, ABq, 1 and 2-H), 6.84 (1 H, d, $J_{8}$, 23-H), 7.52 (1 H, d, $J_{1.5}$, 20-H), 7.70 (1 H, dd, $J_{8}$, 1.5, 24-H); $\delta_{\text{C}}$ 20.54, 35.08, 40.30, 42.57, 42.82 (NMe), 46.64, 56.86 (OMe), 59.07, 68.34, 88.12, 101.75, 107.90, 109.86, 114.57, 119.26, 124.00, 124.91, 125.79, 126.68, 128.80, 129.32, 130.72, 142.24, 147.64, 151.70, 165.38; $m/z$ 447 (M⁺, 40%), 310(17), 282(25), 229(13), 165(29), 149(100), 121(20), 91(8), 65(25), 42(21). (Found M⁺, 447.1679. C₂₆H₂₅NO₆ requires 447.1682).
Preparation of 6α-Acetyloxy-3-t-butyldimethylsilyloxy-7,8-didehydro-4,5α-epoxy-17-methyl-morphinan (56)

To a solution of morphine 3-0-TBDMS ether 45 (200 mg, 0.5 mmol), in pyridine (2 cm³), was added acetic anhydride (1 cm³, 1.1 g, 10 mmol), and the reaction stirred overnight. The reaction mixture was dissolved in DCM and washed three times with a 5% CuSO₄ solution. The organic layer was dried (Na₂SO₄), and evaporated under reduced pressure to give a white solid. Re-crystallisation from DCM-petroleum ether afforded the ester 56 (195 mg, 85%) m.p. 145-8°C (decomp); (Found: C, 66.2; H, 7.75; N, 2.95. C₂₅H₃₅NO₄Si requires C, 66.6; H, 8.0; N, 3.1%): νmax(nujol)/cm⁻¹ 1736 (C=O ester); δH(CDCl₃) 0.16 (3 H, s, SiMe), 0.19 (3 H, s, SiMe), 0.98 (9 H, s, SiCMe₃), 1.83 (1 H, d, J 12.5, 15e-H), 2.05 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.14 (3 H, s, Ac), 2.30 (1 H, dd, J 12.5, 6, 10α-H), 2.44 (4 H, m, NMe and 16α-H), 2.59 (1 H, dd, J 12.5, 4, 16e-H), 2.72 (1 H, t, J 2.5, 14-H), 3.02 (1 H, d, J 18.5, 10β-H), 3.36 (1 H, q, J 3, 9-H), 5.04 (1 H, d, J 6, 5-H), 5.17 (1 H, m, 6-H), 5.41 (1 H, d, J 8.5, 8-H), 5.58 (1 H, d, J 8.5, 7-H), 6.45 and 6.58 (2 H, ABq, 1 and 2-H); δC -4.18, -4.66, 18.26, 20.54, 20.94, 25.68, 35.52, 40.87, 43.04 (N-Me), 43.17, 46.52, 58.94, 68.91, 88.08, 119.03, 121.27, 127.36, 128.26, 129.83, 130.68, 137.12, 148.96, 170.48 (C=O).

Preparation of 6α-Acetyloxy-7,8-didehydro-4,5α-epoxy-17-methyl-morphinan-3-ol (57)

To a stirred solution of morphine 3-O-TBDMS ether 6-O-acetate 56 (165 mg, 0.37 mmol) in THF, at 0°C, under an inert atmosphere, was added TBAF (0.33 cm³, 300 mg, 1.15 mmol). The reaction mixture was stirred at 0°C for 5 min, then allowed to warm up to room temperature and left stirring for a further 6 h. EtOAc was added and the solution washed with water, dried (Na₂SO₄), and evaporated under reduced pressure. The crude product was purified by preparative TLC to give the ester 57 (77 mg, 63%) m.p. 106-9°C (decomp); νmax(nujol)/cm⁻¹ 3368 (OH), 1732 (C=O ester); δH(CDCl₃) 1.84 (1 H, d, J 12.5, 15e-H), 2.06 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.15 (3 H, Ac), 2.31 (1 H, dd, J 12.5, 6, 10α-H), 2.44 (4 H, m, NMe and 16α-H), 2.62 (1 H, dd, J 12.5, 4, 16e-H), 2.75 (1 H, t, J 2.5, 14-H), 3.03 (1 H, d,
J 18.5, 10β-H), 3.39 (1 H, q, J 3, 9-H), 5.06 (1 H, d, J 6, 5-H), 5.14 (1 H, m, 6-H), 5.42 (1 H, d, J 8.5, 8-H), 5.59 (1 H, d, J 8.5, 7-H), 6.50 and 6.63 (2 H, ABq, 1 and 2-H).

Preparation of 3-t-Butyldimethylsilyloxy-7,8-didehydro-4,5α-epoxy-17-methyl-6α-succinloyloxy-morphinan (58)

A mixture of morphine 3-0-TBDMS ether 45 (300 mg, 0.75 mmol) and succinic anhydride (375 mg, 3.75 mmol) in pyridine (5 cm³), under nitrogen, was refluxed for 1 h. The hot reaction mixture was poured onto ice and the resulting white precipitate collected on a filter. The precipitate was washed with cold water. Crystallisation from DCM-petroleum ether gave the ester 58 (225 mg, 60%) m.p. 144-7°C; νmax(CHCl₃)/cm⁻¹ 1735 (C=O ester), 1628 (C=O acid); δH (CDCl₃) 0.15 (3 H, s, SiMe), 0.20 (3 H, s, SiMe), 0.98 (9 H, s, SiCMe₃), 1.86 (1 H, d, J 12, 15e-H), 2.41-2.82 (10 H, m, NMe, 2xCH₂, 10α, 15a, and 16-H), 3.00 (1 H, d, J 18.5, 10β-H), 3.10 (2 H, m, 14 and 16-H), 3.79 (1 H, q, J 3.5, 9-H), 5.09 (1 H, d, J 6, 5-H), 5.28 (2 H, m, 6 and 8-H), 5.56 (1 H, d, J 10, 7-H), 6.47 and 6.61 (2 H, ABq, 1 and 2-H); δC -4.78, -4.55, 18.15, 21.19, 25.66, 30.18, 30.95, 33.20, 37.63, 40.92 (NMe), 42.01, 46.16, 58.66, 68.08, 88.18, 119.19, 122.01, 124.45, 127.71, 129.60, 129.94, 137.80, 148.62, 172.70, 172.85; m/z 499 (M⁺, 3%) 456(5), 382(9), 324(11), 267(12), 215(29), 105(24), 73(100), 41(94) (Found M⁺, 499.2388. C₂₇H₃₇N0₆Si requires 499.2390).

Preparation of 3-t-Butyldimethylsilyloxy-6α-(2'-carboxybenzoyloxy)-7,8-didehydro-4,5α-epoxy-17-methyl-morphinan (59)

A mixture of morphine 3-0-TBDMS ether 45 (250 mg, 0.63 mmol) and phthalic anhydride (500 mg, 3.38 mmol) in pyridine (2 cm³), under nitrogen, was refluxed for 1 h. The hot reaction mixture was poured onto ice and the resulting white precipitate collected on a filter. The precipitate was washed with cold water. Crystallisation from DCM-petroleum ether gave the ester 59 (237 mg, 69%) m.p. 193-5°C (decomp); νmax(CHCl₃)/cm⁻¹ 1714 (C=O ester), 1602 (C=O acid); δH (CDCl₃) 0.04 (3 H, s, SiMe), 0.06 (3 H, s, SiMe), 0.88 (9 H, s, SiCMe₃), 1.97 (1 H, d, J 11, 15e-H), 94
2.78-2.88 (3 H, m, 10α, 15a and 16-H), 2.91 (3 H, s, NMe), 3.08 (1 H, d, J 18.5, 10β-H), 3.45 (1 H, dd, J 12, 4, 16-H), 3.59 (1 H, t, J 2.5, 14-H), 4.03 (1 H, q, J 3.5, 9-H), 5.32 (1 H, d, J 6.5, 5-H), 5.40 (1 H, d, J 10, 8-H), 5.55 (1 H, m, 6-H), 5.80 (1 H, d, J 10, 7-H), 6.54 and 6.66 (2 H, ABq, 1 and 2-H), 7.38 (1 H, t, J 7.5, 22-H), 7.52 (1 H, t, J 7.5, 23-H), 7.66 (1 H, d, J 7.5, 21-H), 7.92 (1 H, d, J 7.5, 24-H).

Preparation of 6α-Benzoyloxy-3-t-butyldimethylsilyloxy-7,8-didehydro-4,5α-epoxy-17-methyl-morphinan (60)

To a solution of morphine 3-0-TBDMS ether 45 (300 mg, 0.75 mmol) in pyridine (3 cm³) with a catalytic amount of DMAP, under nitrogen, was added benzoyl chloride (0.5 cm³, 317 mg, 2.25 mmol) and the reaction stirred at room temperature for 10 min. CHCl₃ was added and the solution washed successively with 5% CuSO₄ solution / water, dried (MgSO₄), and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 3% MeOH in DCM) to give the ester 60 (336 mg, 89%) m.p. 133-35°C; νmax(CHCl₃)/cm⁻¹ 1717 (C=O); δH (CDCl₃) 0.02 (3 H, s, SiMe), 0.04 (3 H, s, SiMe), 0.82 (9 H, s, SiCMe₃), 1.88 (1 H, d, J 11, 15a-H), 2.16 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.44 (2 H, m, 10α and 16-H), 2.53 (3 H, s, NMe), 2.72 (1 H, dd, J 12.5, 4, 16-H), 2.88 (1 H, t, J 2.5, 14-H), 3.07 (1 H, d, J 18.5, 10β-H), 3.51 (1 H, q, J 3.5, 9-H), 5.21 (1 H, d, J 6, 5-H), 5.40 (1 H, m, 6-H), 5.51 (1 H, d, J 10, 8-H), 5.76 (1 H, d, J 10, 7-H), 6.49 and 6.60 (2 H, ABq, 1 and 2-H), 7.42 (2 H, t, J 7.5, 21 and 23-H), 7.56 (1 H, t, J 7.5, 22-H), 8.09 (2 H, d, J 7, 20 and 24-H); δC -4.93, -4.90, 18.05, 20.71, 25.47, 35.11, 40.33, 42.62 (NMe), 43.03, 46.36, 58.80, 69.34, 88.10, 119.04, 121.35, 126.81, 128.16, 128.52, 129.57, 130.03, 130.47, 131.40, 133.01, 137.25, 149.07, 166.02; m/z 503 (M⁺, 15%) 446(10), 324(6), 266(9), 122(8), 105(100), 77(27), 57(16), 41(35). (Found M⁺, 503.2446. C₃₀H₃₇N₀₄Si requires 503.2492).
Preparation of 3-t-Butyldimethylsilyloxy-7,8-didehydro-4,5α-epoxy-17-methyl-6α-(4'-nitrobenzoyloxy)-morphinan (61)

To a solution of morphine 3-O-TBDMS ether 45 (150 mg, 0.37 mmol) in pyridine (5 cm³) with a catalytic amount of DMAP, under nitrogen, was added p-nitrobenzoyl chloride (210 mg, 1.13 mmol) and the reaction stirred overnight. EtOAc was added and the solution washed with 5% CuSO₄ solution / water, dried (Na₂SO₄) and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 10% MeOH in CHCl₃) to give the ester 61 (162 mg, 78%) m.p. 129-31°C; \( \nu_{\text{max}} \) (nujol)/cm⁻¹ 1718 (C=O ester); \( \delta_{\text{H}} \) (CDCl₃) 0.03 (3 H, s, SiMe), 0.06 (3 H, s, SiMe), 0.85 (9 H, s, SiCMe₃), 1.89 (1 H, d, J 11, 15e-H), 2.13 (1 H, dt, J 12.5, 5, 15a-H), 2.40 (2 H, m, 10α and 16-H), 2.47 (3 H, s, NMe), 2.65 (1 H, dd, J 12.5, 4, 16-H), 2.85 (1 H, t, J 2.5, 14-H), 3.10 (1 H, d, J 18.5, 10β-H), 3.44 (1 H, q, J 3, 9-H), 5.20 (1 H, d, J 6.5, 5-H), 5.43 (1 H, m, 6-H), 5.54 (1 H, d, J 10, 8-H), 5.75 (1 H, d, J 10, 7-H), 6.49 and 6.59 (2 H, ABq, 1 and 2-H), 8.29 (4 H, s, 20, 21, 23 and 24-H); \( \delta_{\text{C}} \) -4.92, 17.96, 20.36, 25.35, 35.43, 40.71, 42.87, 42.95 (NMe), 46.51, 58.91, 69.85, 87.37, 119.19, 121.23, 123.29, 127.27, 127.49, 130.27, 130.43, 131.01, 135.29, 137.06, 148.42, 150.48, 163.98; \( m/z \) 548 (M⁺, 52%) 491(38), 382(25), 266(21), 137(18), 122(14), 104(40), 92(20), 77(45), 50(79), 41(100). (Found M⁺, 548.2331. C₃₀H₃₆N₂O₆Si requires 548.2342).

Preparation of 3-t-Butyldimethylsilyloxy-7,8-didehydro-4,5α-epoxy-6α-(4'-methoxybenzoyloxy)-17-methyl-morphinan (62)

To a solution of morphine 3-O-TBDMS ether 45 (100 mg, 0.25 mmol) in pyridine (3 cm³), under nitrogen, was added p-anisoyl chloride (0.1 cm³, 128 mg, 0.75 mmol) and the reaction stirred at room temperature for 30 min. EtOAc was added and the solution washed successively with dilute HCl / water / bicarbonate / water, dried (MgSO₄), and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 5% MeOH in CHCl₃) to give the ester 62 (82 mg, 61%) m.p.173-5°C; \( \nu_{\text{max}} \) (CHCl₃)/cm⁻¹ 1710 (C=O ester); \( \delta_{\text{H}} \) (CDCl₃) 0.04 (3 H, s, SiMe), 0.06 (3 H, s, SiMe), 0.87 (9 H, s, SiCMe₃), 1.88 (1 H, d, J 11,
Preparation of 3-t-Butyldimethylsilyloxy-7,8-didehydro-4,5α-epoxy-6α-(4'-fluorobenzoyloxy)-17-methyl-morphinan (63)

To a solution of morphine 3-O-TBDMS ether 45 (300 mg, 0.75 mmol) in pyridine (3 cm³), under nitrogen, was added p-fluorobenzoyl chloride (0.3 cm³, 360 mg, 2.25 mmol) and the reaction stirred at room temperature for 20 min. CHCl₃ was added and the solution washed successively with 5% CuSO₄ solution and water, dried (MgSO₄), and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 3% MeOH in DCM) to give the ester 63 (342 mg, 87%) m.p. 134-6°C; νmax(CHCl₃)/cm⁻¹ 1717 (C=O ester); δH (CDCl₃) 0.01 (3 H, s, SiMe), 0.04 (3 H, s, SiMe), 0.84 (9 H, s, SiCMe₃), 1.90 (1 H, d, J 11, 15e-H), 2.24 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.52 (2 H, m, 10α and 16-H), 2.58 (3 H, s, NMe), 2.85 (1 H, dd, J 12.5, 4, 16-H), 3.01 (1 H, t, J 2.5, 14-H), 3.08 (1 H, d, J 18.5, 10β-H), 3.66 (1 H, q, J 3, 9-H), 5.19 (1 H, d, J 6.5, 5-H), 5.39 (1 H, m, 6-H), 5.48 (1 H, d, J 10, 8-H), 5.76 (1 H, d, J 10, 7-H), 6.50 and 6.61 (2 H, ABq, 1 and 2-H), 7.07 and 7.11 (2 x 1 H, d, J 8.5, 21 and 23-H), 8.08 and 8.12 (2 x 1 H, d, J 8.5, 20 and 24-H); δC -4.85, -4.81, 18.06, 21.11, 25.51, 34.56, 39.55, 42.16 (NMe), 42.71, 46.39, 58.90, 69.16, 87.79, 115.24, 115.59, 119.31, 121.71, 126.11, 128.80, 129.04, 130.11, 131.96, 132.52, 132.67, 137.76, 149.03, 163.86, 168.12; m/z 521 (M⁺, 14%) 464(9), 382(5), 324(4), 284(5), 140(20), 123(100), 153.2602. C₃₁H₃₉NO₅Si requires 533.2598.
Preparation of 3-t-Butyldimethylsilyloxy-6α-(4'-chlorobenzoyloxy)-7,8-didehydro-4,5α-epoxy-17-methyl-morphinan (64)

To a solution of morphine 3-O-TBDMS ether 45 (300 mg, 0.75 mmol) in pyridine (3 cm³), under nitrogen, was added p-chlorobenzoyl chloride (0.3 cm³, 396 mg, 2.25 mmol) and the reaction stirred at room temperature for 5 min. CHCl₃ was added and the solution washed successively with 5% CuSO₄ solution and water, dried (MgSO₄), and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 3% MeOH in DCM) to give the ester 64 (381 mg, 94%) m.p. 119-21°C; \( \nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1} \) 1719 (C=O ester); \( \delta_{\text{H}} \) (CDCl₃) 0.05 (6 H, s, SiMe₂), 0.85 (9 H, s, SiCMe₃), 1.84 (1 H, d, J 11, 15ε-H), 2.05 (1 H, dt, J 12.5, 5, 15α-H), 2.34 (2 H, m, 10α and 16-H), 2.45 (3 H, s, NMe), 2.57 (1 H, dd, J 12.5, 4, 16-H), 2.77 (1 H, t, J 2.5, 14-H), 3.04 (1 H, d, J 18.5, 10β-H), 3.38 (1 H, q, J 3.5, 9-H), 5.16 (1 H, d, J 6.5, 5-H), 5.39 (1 H, m, 6-H), 5.48 (1 H, d, J 10, 8-H), 5.72 (1 H, d, J 10, 7-H), 6.47 and 6.58 (2 H, ABq, 1 and 2-H), 7.41 (2 H, d, J 8.5, 21 and 23-H), 8.01 (2 H, d, J 8.5, 20 and 24-H); \( \delta_{\text{C}} \) -4.84, -4.78, 18.10, 21.26, 25.49, 34.23, 39.17, 41.92 (NMe), 42.52, 46.40, 58.95, 69.08, 87.57, 119.39, 121.86, 125.67, 128.22, 128.63, 128.91, 129.95, 131.10, 131.43, 137.70, 139.60, 149.03, 165.12; m/z 539 and 537 (M⁺, 23 and 55%) 482(13), 480(34), 456(15), 413(13), 382(25), 324(18), 300(14), 266(14), 141(35), 139(91), 123(7), 94(10), 73(100), 59(36), 42(48). (Found M⁺, 539.2070 and 537.2123. C₃₀H₃₆NClO₄Si requires 539.2072 and 537.2102).

Preparation of 6α-(4'-Bromobenzoyloxy)-3-t-butyldimethylsilyloxy-7,8-didehydro-4,5α-epoxy-17-methyl-morphinan (65)

To a solution of morphine 3-O-TBDMS ether 45 (300 mg, 0.75 mmol) in pyridine (3 cm³) with a catalytic amount of DMAP, under nitrogen, was added p-bromobenzoyl chloride (825 mg, 3.75 mmol) and the reaction stirred at room temperature for 20 min.
CHCl₃ was added and the solution washed successively with 5% CuSO₄ solution and water, dried (MgSO₄), and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 3% MeOH in DCM) to give the ester 65 (315 mg, 72%) m.p. 137-8°C; ν_max(CHCl₃)/cm⁻¹ 1719 (C=O ester); δ_H (CDCl₃) 0.01 (3 H, s, SiMe), 0.04 (3 H, s, SiMe), 0.84 (9 H, s, SiCMe₃), 1.87 (1 H, d, J 11, 15e-H), 2.15 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.40 (2 H, m, 10α and 16-H), 2.47 (3 H, s, NMe), 2.72 (1 H, dd, J 12, 4, 16-H), 2.88 (1 H, t, J 2.5, 14-H), 3.06 (1 H, d, J 18.5, 10β-H), 3.50 (1 H, q, J 3, 9-H), 5.17 (1 H, d, J 6.5, 5-H), 5.38 (1 H, m, 6-H), 5.48 (1 H, d, J 10, 8-H), 5.73 (1 H, d, J 10, 7-H), 6.49 and 6.59 (2 H, ABq, 1 and 2-H), 7.56 (2 H, d, J 8.5, 21 and 23-H), 7.95 (2 H, d, J 8.5, 20 and 24-H); δ_C -4.84, -4.79, 18.09, 21.26, 25.48, 34.20, 39.16, 41.98 (NMe), 42.48, 46.50, 59.09, 69.05, 87.52, 119.40, 121.89, 125.56, 128.38, 128.65, 129.91, 131.24, 131.34, 131.63, 137.73, 149.01, 165.25; m/z 583 and 581 (M⁺, 22 and 22%) 527(15), 525(14), 382(19), 266(15), 202(29), 200(30), 185(96), 183(100), 155(31), 123(41), 105(33), 75(50), 73(62), 51(56), 41(58). (Found M⁺, 583.1641 and 581.1603. C₃₀H₃₆NBrO₄Si requires 583.1578 and 581.1597).

Preparation of 7,8-didehydro-4,5α-epoxy-17-methyl-6α-succinylloxy-morphinan-3-ol (66)

To a solution of the ester 58 (150 mg, 0.3 mmol) in THF (2 cm³) under nitrogen, at 0°C, was added TBAF (1 M solution in THF) (1 cm³). The reaction was stirred at 0°C for 5 min and then allowed to warm up to room temperature, with stirring continuing overnight. The reaction mixture was quenched with water. The resulting precipitate was collected on a filter giving the ester 66 (62 mg, 54%). Crystallisation was from CHCl₃/MeOH. m.p. 275-9°C (decomp); Found C, 60.9; H, 6.05; N, 3.20. C₂₁H₂₃NO₅ requires C, 61.2; H, 6.31; N, 3.39%; ν_max(nujol)/cm⁻¹ 3382 (OH), 1736 (C=O ester), 1605 (C=O acid); δ_H (CD₃OD/CDCl₃) 1.96 (1 H, d, J 12, 15e-H), 2.43-2.86 (10 H, m, NMe, 2xCH₂, 10α, 15a, and 16-H), 3.04 (1 H, d, J 18.5, 10β-H), 3.15 (2 H, m, 14 and 16-H), 3.83 (1 H, q, J 3.5, 9-H), 5.11 (1 H, d, J 6, 5-H), 5.30 (2 H, m, 6 and 8-H), 5.58 (1 H, d, J 10, 7-H), 6.57 and 6.61 (2 H, ABq, 1 and 2-H).
Preparation of 6a-(2'-Carboxybenzoyloxy)-7,8-didehydro-4,5\(\alpha\)-epoxy-17-methyl-morphinan-3-ol (67)

To a solution of the ester 59 (300 mg, 0.7 mmol) in pyridine (5 cm\(^3\)), under nitrogen, at 0°C, was added HF-pyridine (1 cm\(^3\)). The reaction was stirred at 0°C for 5 min and then allowed to warm up to room temperature, with stirring continuing overnight. The reaction mixture was quenched with water. The resulting precipitate was collected on a filter giving the ester 67 (135 mg, 57%). Crystallisation from CHCl\(_3\)/MeOH yielded colourless prisms. m.p. 259-64°C (decomp); (Found: C, 65.5; H, 5.35; N, 2.85. C\(_{25}\)H\(_{23}\)NO\(_6\) requires C, 65.2; H, 5.65; N, 3.05%); \(\nu_{\text{max}}\) (nujol)/cm\(^{-1}\) 3398 (OH), 1716 (C=O ester), 1601 (C=O acid); \(\delta_{\text{H}}\) (CD\(_3\)OD/CDCl\(_3\)) 2.03 (1 H, d, J 10, 15e-H), 2.90 (3 H, m, 10\(\alpha\), 15a and 16-H), 3.01 (3 H, s, NMe), 3.21 (1 H, d, J 18.5, 10\(\beta\)-H), 3.48 (1 H, d, J 8, 16-H), 3.86 (1 H, t, J 2.5, 14-H), 4.12 (1 H, q, J 3, 9-H), 5.53 (2 H, m, 6 and 8-H), 5.66 (1H, d, J 6.5, 5-H), 5.91 (1 H, d, J 10, 7-H), 6.59 and 6.63 (2 H, ABq, 1 and 2-H), 7.40 (1 H, m, 22-H), 7.56 (2 H, m, 21 and 23-H), 7.92 (1 H, d, J 7.5, 23-H); \(m/z\) (M\(^+\), 433) 285(100), 268(11), 215(21), 162(29), 124(17), 104(96), 76(79), 42(31).

Preparation of 6a-Benzoyloxy-7,8-didehydro-4,5\(\alpha\)-epoxy-17-methyl-morphinan-3-ol (68)

To a solution of the ester 60 (150 mg, 0.27 mmol) in dry THF (3 cm\(^3\)), under nitrogen, at 0°C, was added TBAF (1 M solution in THF) (1 cm\(^3\)). The reaction was stirred at 0°C for 5 min and then allowed to warm up to room temperature, with stirring continuing overnight. The reaction mixture was dissolved in EtOAc and washed with water, dried (Na\(_2\)SO\(_4\)) and evaporated under reduced pressure. The crude product was purified by TLC to give the ester 68, a white powder, (102 mg, 88%). Crystallisation was from CHCl\(_3\)/MeOH yielding colourless crystals m.p. 264-8°C (decomp); (Found: C, 73.25; H, 5.85; N, 3.65. C\(_{24}\)H\(_{23}\)NO\(_4\) requires C, 73.2; H, 5.95; N, 3.55%); \(\nu_{\text{max}}\) (nujol)/cm\(^{-1}\) 1713 (C=O ester); \(\delta_{\text{H}}\) (CD\(_3\)OD/CDCl\(_3\)) 1.88 (1 H, d, J 12.5, 15e-H), 2.08 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.37 (2 H, m, 10\(\alpha\) and 16-H), 2.44 (3 H, s, NMe), 2.61 (1 H, dd, J 12.5, 4, 16-H), 2.80 (1 H, t, J 2.5, 14-H), 3.04 (1 H, d, J 18.5, 10\(\beta\)-H), 3.38 (1 H, q, J 3, 9-H), 5.21 (1 H, d, J 6.5, 5-H), 5.41 (1 H, m,
6-H), 5.49 (1 H, d, J 10, 8-H), 5.76 (1 H, d, J 10, 7-H), 6.52 and 6.63 (2 H, ABq, 1 and 2-H), 7.45 (2 H, t, J 8, 21 and 23-H), 7.59 (1 H, t, J 7.5, 22-H), 8.10 (2 H, d, J 7, 20 and 24-H); δC 20.30, 34.92, 40.23, 42.71 (NMe), 46.58, 58.98, 68.74, 88.07, 116.69, 119.63, 125.34, 128.16, 128.35, 129.46, 129.58, 129.71, 129.92, 133.20, 138.27, 144.94, 166.24; m/z 389 (M+, 38%) 268(33), 215(13), 146(12), 122(11), 105(100), 94(6), 77(34). (Found M+, 389.1623. C_{24}H_{23}N_{2}O_{4} requires 389.1627).

**Preparation of 7,8-Didehydro-4,5α-epoxy-17-methyl-6α-(4'-nitro benzoyloxy)-morphinan-3-ol (69)**

To a solution of the ester 61 (300 mg, 0.18 mmol) in dry THF (5 cm³), under nitrogen, at 0°C, was added TBAF (1 M solution in THF) (1 cm³). The reaction was stirred at 0°C for 5 min and then allowed to warm up to room temperature, with stirring continuing overnight. The reaction mixture was evaporated under reduced pressure. The crude product was purified by TLC to give the ester 69, a yellow powder, (206 mg, 87%). Crystallisation was from DMSO / water yielding yellow prisms. m.p. 253-8°C (decomp); (Found: C, 64.0; H, 5.4; N, 5.95. C_{24}H_{22}N_{2}O_{6} requires C, 63.7; H, 5.35; N, 6.2%); v\(_{\text{max}}\)(nujol)/cm\(^{-1}\) 1719 (C=O ester); δ\(_{\text{H}}\)(DMSO-d\(_{6}\)) 1.62 (1 H, d, J 11, 15e-H), 2.06 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.21 (2 H, m, 10α and 16-H), 2.31 (3 H, s, NMe), 2.48 (1 H, m, 16-H), 2.76 (1 H, t, J 2.5, 14-H), 2.89 (1 H, d, J 18.5, 10β-H), 3.31 (1 H, q, J 3, 9-H), 5.12 (1 H, d, J 6.5, 5-H), 5.43 (1 H, m, 6-H), 5.55 (1 H, d, J 10, 8-H), 5.72 (1 H, d, J 10, 7-H), 6.41 and 6.47 (2 H, ABq, 1 and 2-H), 8.22 (2 H, d, J 9, 20 and 24-H), 8.36 (2 H, d, J 9, 21 and 23-H); δC 19.90, 34.85, 39.94, 42.12, 42.78 (NMe), 46.32, 58.27, 69.38, 86.84, 116.48, 119.16, 123.87, 125.18, 127.64, 130.46, 130.53, 130.98, 135.32, 138.88, 145.14, 150.36, 163.90; m/z 434 (M+, 14%) 268(15), 248(16), 136(11), 104(17), 91(21), 88(19), 44(100). (Found M+, 434.1479. C_{24}H_{22}N_{2}O_{6} requires 434.1478).
Preparation of 7,8-Didehydro-4,5α-epoxy-6α-(4'-fluorobenzoyloxy)-17-methyl-morphinan-3-ol (70)

To a solution of the ester 63 (150 mg, 0.29 mmol) in dry THF (3 cm³), under nitrogen, at 0°C, was added TBAF (1 M solution in THF) (1 cm³). The reaction was stirred at 0°C for 5 min and then allowed to warm up to room temperature, with stirring continuing overnight. The reaction mixture was dissolved in EtOAc and washed with water, dried (Na₂SO₄) and evaporated under reduced pressure. The crude product was purified by TLC to give the ester 70, a white powder, (96 mg, 82%). Crystallisation was from CHCl₃/MeOH. m.p. 279-83°C (decomp); (Found: C, 70.45; H, 5.4; N, 3.3. C₂₄H₂₂NF₃O₄ requires C, 70.75; H, 5.45; N, 3.45%); \( \nu_{\text{max}} \) (nujol)/cm⁻¹ 1713 (C=O ester); \( \delta_H \) (CD₂OD/CDCl₃) 1.88 (1 H, d, J 11, 15e-H), 2.06 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.37 (2 H, m, 10α and 16-H), 2.45 (3 H, s, NMe), 2.62 (1 H, dd, J 12.5, 4, 16-H), 2.80 (1 H, t, J 2.5, 14-H), 3.04 (1 H, d, J 18.5, 10β-H), 3.38 (1 H, q, J 3.5, 9-H), 5.18 (1 H, d, J 6.5, 5-H), 5.40 (1 H, m, 6-H), 5.50 (1 H, d, J 10, 8-H), 5.74 (1 H, d, J 10, 7-H), 6.51 and 6.62 (2 H, ABq), 1 and 2-H), 7.11 and 7.15 (2 x 1 H, d, J 8.5, 21 and 23-H), 8.09 and 8.11 (2 x 1 H, d, J 8.5, 20 and 24-H); \( \delta_C \) 21.28, 34.77, 40.06, 42.59 (NMe), 46.56, 58.95, 68.66, 87.84, 115.21, 115.56, 116.64, 119.53, 125.15, 128.10, 129.39, 129.86, 132.26, 132.41, 138.36, 145.03, 163.80, 165.32, 167.84; \( m/z \) 407 (M⁺, 30%) 284(17), 268(33), 215(14), 146(13), 123(100), 95(31), 84(21). (Found M⁺, 407.1593. C₂₄H₂₂NF₃O₄ requires 407.1533).

Preparation of 6α-(4'-Chlorobenzoyloxy)-7,8-didehydro-4,5α-epoxy-17-methyl-morphinan-3-ol (71)

To a solution of the ester 64 (150 mg, 0.28 mmol) in dry THF (3 cm³), under nitrogen, at 0°C, was added TBAF (1 M solution in THF) (1 cm³). The reaction was stirred at 0°C for 5 min and then allowed to warm up to room temperature, with stirring continuing overnight. The reaction mixture was dissolved in EtOAc and washed with water, dried (Na₂SO₄) and evaporated under reduced pressure. The crude product was purified by TLC to give the ester 71 (105 mg, 89%). Crystallisation was from CHCl₃/MeOH. m.p. 269-72°C (decomp); (Found: C, 67.7; H, 5.2; N, 3.25. C₂₄H₂₂NCI₄O₄ requires C, 68.0; H, 5.25; N, 3.3%); \( \nu_{\text{max}} \) (nujol)/cm⁻¹ 1719 (C=O ester);
\[ \delta_{H}(\text{CD}_{3}\text{OD/CDCl}_{3}) \] 1.95 (1 H, d, J 12.5, 15e-H), 2.29 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.57 (2 H, m, 10\alpha and 16-H), 2.66 (3 H, s, NMe), 3.04 (3 H, m, 10\beta, 14 and 16-H), 3.75 (1 H, q, J 3, 9-H), 5.22 (1 H, d, J 6.5, 5-H), 5.41 (1 H, m, 6-H), 5.51 (1 H, d, J 10, 8-H), 5.79 (1 H, d, J 10, 7-H), 6.55 and 6.65 (2 H, ABq, 1 and 2-H), 7.39 and 7.42 (2 x 1 H, d, J 8.5, 21 and 23-H), 7.98 and 8.01 (2 x 1 H, d, J 8.5, 20 and 24-H); \( m/z \) 423 and 425 (M\(^+\), 36 and 12%) 300(8), 268(54), 215(21), 141(34), 139(100), 111(32), 94(10), 81(17). (Found M\(^+\), 425.1207 and 423.1237. \( C_{24}H_{22}NClO_{4} \) requires 425.1227 and 423.1268).

**Preparation of 6\alpha-(4'-Bromobenzyloxy)-7,8-didehydro-4,5\alpha-epoxy-17-methyl-morphinan-3-ol** (72)

To a solution of the ester 65 (150 mg, 0.26 mmol) in dry THF (3 cm\(^3\)), under nitrogen, at 0°C, was added TBAF (1 M solution in THF) (1 cm\(^3\)). The reaction was stirred at 0°C for 5 min and then allowed to warm up to room temperature, with stirring continuing overnight. The reaction mixture was dissolved in EtOAc and washed with water, dried (Na\(_2\)SO\(_4\)) and evaporated under reduced pressure. The crude product was purified by TLC to give the ester 72, a white powder, (97 mg, 80%). Crystallisation was from CHCl\(_3\)/MeOH. m.p. 279-84°C (decomp); (Found: C, 61.25; H, 4.7; N, 3.05. \( C_{24}H_{22}NBrO_{4} \) requires C, 61.5; H, 4.7; N, 3.0%). \( \nu_{\text{max}}\) (nujol)/cm\(^{-1}\) 1718 (C=O ester); \( \delta_{H}(\text{CD}_{3}\text{OD/CDCl}_{3}) \) 1.88 (1 H, d, J 12.5, 15e-H), 2.08 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.37 (2 H, m, 10\alpha and 16-H), 2.46 (3 H, s, NMe), 2.62 (1 H, dd, J 12.5, 4, 16-H), 2.81 (1 H, t, J 2.5, 14-H), 3.04 (1 H, d, J 18.5, 10\beta-H), 3.40 (1 H, q, J 3, 9-H), 5.18 (1 H, d, J 6.5, 5-H), 5.40 (1 H, m, 6-H), 5.51 (1 H, d, J 10, 8-H), 5.74 (1 H, d, J 10, 7-H), 6.51 and 6.63 (2 H, ABq, 1 and 2-H), 7.60 (2 H, d, J 8.5, 21 and 23-H), 7.95 (2 H, d, J 8.5, 20 and 24-H); \( m/z \) 469 and 467 (M\(^+\), 39 and 42%) 268(95), 215(36), 185(92), 183(100), 155(42), 141(23), 94(17), 81(32). (Found M\(^+\), 469.0544 and 467.0583. \( C_{24}H_{22}NBrO_{4} \) requires 469.0713 and 467.0733).
Preparation of Methyl p-hydroxybenzoate (74)

p-Hydroxybenzoic acid 73 (8 g, 0.058 mol) was mixed with absolute methanol (25 ml). Concentrated H$_2$SO$_4$ was cautiously added with shaking to give a slightly yellow solution, which was refluxed for 6 h. Excess MeOH was evaporated under reduced pressure and the residue dissolved in EtOAc. The organic solution was washed with water and saturated NaHCO$_3$ solution, dried (Na$_2$SO$_4$), and evaporated under reduced pressure. The resulting white product was recrystallised from DCM to give colourless crystals of 74, (7.79 g, 88%) m.p. 125-127°C [Lit. 126-128°C$^{56}$]; $\nu_{\text{max}}$(CHCl$_3$)/cm$^{-1}$ 2800 (OH), 1724 (C=O ester); $\delta_H$(CDCl$_3$) 3.90 (3 H, s, OMe), 6.88 (2 H, d, J 8.8, 4 and 6-H), 7.92 (2 H, d, J 8.8, 3 and 7-H).

Silylation of Methyl p-hydroxybenzoate

To a mixture of methyl p-hydroxybenzoate 74 (5 g, 0.032 mol) and imidazole (5.6 g, 0.082 mol) in DMF was added t-butyldimethylsilylchloride (5.45 g, 0.036 mol) and the reaction stirred at 25°C overnight. The reaction mixture was dissolved in ether, washed with water, dried (Na$_2$SO$_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 25% EtOAc in petroleum ether) to give a colourless solution 75 (7.713 g, 88%); $\nu_{\text{max}}$(CHCl$_3$)/cm$^{-1}$ 1723 (C=O ester); $\delta_H$(CDCl$_3$) 0.22 (6H, s, 2xSiMe$_2$), 0.98 (9H, s, SiCMe$_3$), 3.87 (3 H, s, OMe), 6.85 (2 H, d, J 8.8, 4 and 6-H), 7.93 (2 H, d, J 8.8, 3 and 7-H).

Preparation of p-TBDMS-oxybenzoic acid (76)

To a solution of p-hydroxybenzoic acid (5 g, 0.036 mol) and NaH (1.6 g, 0.040 mol) in THF was added t-butyldimethylsilylchloride (7 g, 0.046 mol) and the reaction stirred for 2 h. The reaction was then quenched with water and the product extracted into ethyl acetate. The organic layer was dried (MgSO$_4$) and evaporated under reduced pressure. The crude product contained two components by TLC and these were separated by column chromatography (elution with 25% EtOAc in petroleum ether) to give colourless powders. The first fraction collected was the disubstituted product 77 (7.61 g, 58%) m.p. 57-59°C; $\nu_{\text{max}}$(CHCl$_3$)/cm$^{-1}$ 1700 (C=O ester); $\delta_H$(CDCl$_3$) 0.22 (3H, s,
SiMe₂), 0.24 (3H, s, SiMe₂), 0.36 (6H, s, 2xSiMe₂), 0.98 (9H, s, SiCMe₃), 1.02 (9H, s, SiCMe₃), 6.86 (2H, d, J 8.8, 4 and 6-H), 7.93 (2H, d, J 8.8, 3 and 7-H).

The second fraction collected was the hydroxy protected product 76 (2.06 g, 23%) m.p. 108-110°C; \( \nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1} \) 1678 (C=O ester); \( \delta_H(\text{CDCl}_3) \) 0.22 (6H, s, 2xSiMe₂), 0.98 (9H, s, SiCMe₃), 6.87 (2H, d, J 8.8, 4- and 6-H), 7.98 (2H, d, J 8.8, 3- and 7-H); \( \delta_C \) -4.74, -4.37, 18.25, 25.57, 119.81, 119.94, 122.27, 132.13, 132.32, 160.87, 172.22.

Preparation of 6α-(4'-t-Butyldimethylsilyloxybenzoyloxy)-7,8-didehydro-4,5α-epoxy-3-methoxy-17-methyl-morphinan (79)

Freshly prepared p-TBDMS-oxybenzoic acid (500 mg, 1.98 mmol) in DCM (5 cm³), under nitrogen, was treated with oxalyl chloride (630 mg, 0.43 cm³, 5 mmol). Effervescence implied formation of the acid chloride. On completion of the reaction, after 20 min, benzene (5 cm³) was added and all solvents removed under reduced pressure. To the acid chloride residue, under nitrogen, was added a solution of codeine (200 mg, mmol) in pyridine (3 ml). The reaction mixture turned yellow and was stirred for 2 h. EtOAc was added and the solution washed with dilute HCl / water / bicarbonate / water, dried (MgSO₄) and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 5% MeOH in DCM) to give the ester 79 (293 mg, 82%) m.p. 102-5°C; \( \nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1} \) 1709 (C=O ester); \( \delta_H(\text{CDCl}_3) \) 0.22 (6H, s, SiMe₂), 0.98 (9H, s, SiCMe₃), 1.93 (1H, d, J 12.5, 15e-H), 2.21 (1H, dt, J 12.5, 5, 5, 15a-H), 2.47 (2H, m, 10α and 16a-H), 2.56 (3H, s, NMe), 2.83 (1H, dd, J 12, 4, 16e-H), 2.99 (1H, t, J 2.5, 14-H), 3.08 (1H, d, J 18.5, 10β-H), 3.60 (1H, q, J 3, 9-H), 3.73 (3H, s, OMe), 5.20 (1H, d, J 6, 5-H), 5.41 (1H, m, 6-H), 5.48 (1H, d, J 10, 8-H), 5.78 (1H, d, J 10, 7-H), 6.57 and 6.68 (2H, ABq, 1 and 2-H), 6.86 (2H, d, J 9, 21 and 23-H), 7.98 (2H, d, J 9, 20 and 24-H); \( \delta_C \) -4.36, -3.75, 18.16, 21.11, 25.67, 34.20, 39.28, 42.07, 42.21 (NMe), 46.83, 57.11 (OMe), 59.43, 67.98, 88.08, 115.09, 115.35, 119.60, 119.80, 125.74, 128.30, 129.60, 131.21, 132.26, 142.51, 146.96, 161.87, 166.33; \( m/z \) 533 (M⁺, 77%) 396(25), 282(57), 266(23), 235(100), 229(25), 195(52), 121(43), 73(59), 42(34). (Found M⁺, 533.2597. C₃₁H₃₉NO₅Si requires 533.2597).
Preparation of 7,8-didehydro-4,5α-epoxy-6α-(4'-hydroxybenzoyloxy)-3-methoxy-17-methyl-morphinan (80)

To a solution of the ester 79 (100 mg, 0.187 mmol) in dry THF (3 cm³), under nitrogen, at 0°C, was added TBAF (1 M solution in THF) (1 cm³). The reaction was stirred at 0°C for 5 min and then allowed to warm up to room temperature, with stirring continuing for 2 h. The reaction mixture was dissolved in EtOAc and washed with water, dried (Na₂SO₄) and evaporated under reduced pressure. The crude product was purified by column chromatography (elution with 5% MeOH in DCM) to give the ester 80. Crystallisation was from CHCl₃ / MeOH (48 mg, 61%), m.p. 132-5°C; v_max(CHCl₃)/cm⁻¹ 3563 (OH), 1712 (C=O ester); δ_H (CDCl₃) 1.91 (1 H, d, J 12.5, 15e-H), 2.15 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.41 (2 H, m, 10α and 16a-H), 2.51 (3 H, s, NMe), 2.68 (1 H, dd, J 12, 4, 16e-H), 2.89 (1 H, t, J 2.5, 14-H), 3.06 (1 H, s, J 18.5, 10β-H), 3.47 (1 H, q, J 3, 9-H), 3.73 (3H, s, OMe), 5.19 (1 H, d, J 6, 5-H), 5.39 (1 H, m, 6-H), 5.47 (1 H, d, J 10, 8-H), 5.78 (1 H, d, J 10, 7-H), 6.56 and 6.67 (2 H, ABq, 1 and 2-H), 6.83 (2 H, d, J 9, 21 and 23-H), 7.95 (2 H, d, J 9, 20 and 24-H); δ_C 20.85, 34.57, 39.73, 42.39, 42.54 (NMe), 46.80, 57.10 (OMe), 59.32, 68.08, 88.18, 114.99, 115.16, 119.42, 121.19, 126.18, 128.64, 129.35, 130.52, 132.23, 142.35, 146.90, 161.65, 166.18; m/z 419 (M⁺, 20%) 282(19), 162(40), 138(32), 121(80), 94(36), 73(21), 44(100). (Found M⁺, 419.1733. C₂₅H₂₅NO₅ requires 419.1749).

Preparation of 3-t-Butyldimethylsilyloxy-6α-(4'-t-butyldimethylsilyloxy benzoyloxy)-7,8-didehydro-4,5α-epoxy-17-methyl-morphinan (81)

Freshly prepared p-t-BDMS-oxy benzoic acid (500 mg, 1.98 mmol) in DCM (5 cm³), under nitrogen, was treated with oxalyl chloride (630 mg, 0.43 cm³, 5 mmol). On completion of the reaction, after 20 min, benzene (5 cm³) was added and all solvents removed under reduced pressure. To the acid chloride residue, under nitrogen, was added a solution of morphine 3-O-TBDMS ether 45 (250 mg, 0.63 mmol) in pyridine (3 cm³) and the reaction stirred at room temperature overnight. EtOAc was added and the solution washed with dilute HCl / water / bicarbonate / water, dried (Na₂SO₄) and evaporated under reduced pressure. The crude product was purified by column
chromatography (elution with 5% MeOH in DCM) to give the ester 81 (276 mg, 70\%)
m.p. 122-4°C; $\nu_{\text{max}}$(nujol)/cm$^{-1}$ 1711 (C=O ester); $\delta_H$(CDCl$_3$) 0.02 (3 H, s, SiMe),
0.04 (3 H, s, SiMe), 0.17 (6 H, s, SiMe$_2$) 0.82 (9 H, s, SiCMe$_3$), 0.94 (9 H, s,
SiCMe$_3$), 1.83 (1 H, d, J 11, 15e-H), 2.07 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.34 (2 H,
m, 10$\alpha$ and 16-H), 2.42 (3 H, s, NMe), 2.58 (1 H, dd, J 12, 4, 16-H), 2.78 (1 H, t,
J 2.5, 14-H), 3.00 (1 H, d, J 18.5, 10$\beta$-H), 3.39 (1 H, q, J 3, 9-H), 5.13 (1 H, d,
J 6.5, 5-H), 5.31 (1 H, m, 6-H), 5.40 (1 H, d, J 10, 8-H), 5.68 (1 H, d, J 10, 7-H),
6.42 and 6.53 (2 H, ABq, 1 and 2-H), 6.80 (2 H, d, J 9, 21 and 23-H), 7.94 (2 H, d,
J 9, 20 and 24-H).

**Preparation of 7,8-Didehydro-4,5$\alpha$-epoxy-6$\alpha$-(4$'$-hydroxy-
benzoyloxy)-17-methyl-morphinan-3-ol (82)**

To a solution of the ester 81 (500 mg, 0.79 mmol) in dry THF (5 cm$^3$), under
nitrogen, at 0°C, was added TBAF (1 M solution in THF) (2 cm$^3$). The reaction was
stirred at 0°C for 5 min and then allowed to warm up to room temperature, with stirring
continuing overnight. The reaction mixture was dissolved in EtOAc and washed with
water, dried (Na$_2$SO$_4$) and evaporated under reduced pressure. The crude product was
purified by TLC to give the ester 82. Crystallisation was from CHCl$_3$ / MeOH
(268 mg, 84\%), m.p. 178-82°C (decomp); (Found: C, 68.1; H, 5.65; N, 3.2.
C$_{24}$H$_{23}$NO$_5$ requires C, 68.1; H, 5.9; N, 3.3\%); $\nu_{\text{max}}$(nujol)/cm$^{-1}$ 3640, 3475, 1736
(C=O ester); $\delta_H$(CD$_3$OD/CDCl$_3$) 1.81 (1 H, d, J 11.5, 15e-H), 2.05 (1 H, dt, J 12.5,
5, 5, 15a-H), 2.34 (2 H, m, 10$\alpha$ and 16-H), 2.43 (3 H, s, NMe), 2.61 (1 H, dd,
J 12.5, 4, 16-H), 2.79 (1 H, t, J 2.5, 14-H), 3.02 (1 H, d, J 18.5, 10$\beta$-H), 3.38 (1 H,
q, J 3, 9-H), 5.15 (1 H, d, J 6, 5-H), 5.34 (1 H, m, 6-H), 5.46 (1 H, d, J 10, 8-H),
5.73 (1 H, d, J 10, 7-H), 6.50 and 6.63 (2 H, ABq, 1 and 2-H), 6.85 (2 H, d, J 9, 21
and 23-H), 7.95 (2 H, d, J 9, 20 and 24-H); $\delta_C$ 20.38, 34.68, 39.94, 42.48 (NMe),
42.62, 46.56, 58.94, 68.27, 88.15, 115.30, 116.78, 119.58, 120.47, 125.27,
128.48, 129.19, 129.97, 132.04, 138.28, 145.02, 162.06, 166.27; m/z 405 (M$^+$,
11\%) 285(14), 210(14), 155(15), 138(23), 121(84), 94(100), 65(42), 51(28), 44(49).
(Found M$^+$, 405.1569. C$_{24}$H$_{23}$NO$_5$ requires 405.1576).
Preparation of 6a-Benzylxyloxy-7,8-didehydro-4,5a-epoxy-3-methoxy-17-methyl-morphinan (85)
To a solution of codeine (300 mg, 1 mmol) in THF, under nitrogen, was added NaH-60% dispersion in mineral oil (4.4 mg, 1.1 mmol) and the reaction stirred for 2 h. Benzyl bromide (0.14 cm$^3$, 205 mg, 1.2 mmol) was added and the reaction stirred overnight. The reaction was quenched with water and extracted into EtOAc. The organic layer was washed with water dried (Na$_2$SO$_4$) and evaporated under reduced pressure to yield a light yellow product 85 (372 mg, 95%); $\delta_H (CDCl_3)$ 2.00 (1 H, d, J 11.5, 15e-H), 2.44 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.67 (5 H, m, NMe, 10a and 16-H), 3.03 (3 H, m, 10β, 14 and 16-H), 3.68 (1 H, q, J 3, 9-H), 3.84 (3 H, s, OMe) 4.01 (1 H, m, 6-H), 4.64 and 4.85 (2 H, ABq, CH$_2$-Ph), 5.03 (1 H, d, J 6, 5-H), 5.28 (1 H, d, J 10, 8-H), 5.81 (1 H, d, J 10, 7-H), 6.55 and 6.68 (2 H, ABq, 1 and 2-H), 7.36 (5 H, m, CH$_2$-Ph); $m/z$ 389 (M$^+$, 34%) 298(21), 282(13), 229(11), 178(9), 146(14), 91(100), 81(24), 65(15), 42(26). (Found M$^+$, 389.1995. C$_{25}$H$_{27}$N$_0$3 requires 389.1991).

Preparation of 7,8-Didehydro-4,5a-epoxy-3-methoxy-6a-(4'-nitrobenzylxyloxy)-17-methyl-morphinan (86)
To a solution of codeine (300 mg, 1 mmol) in THF, under nitrogen, was added NaH-60% dispersion in mineral oil (4.4 mg, 1.1 mmol) and the reaction stirred for 2 h. $p$-Nitrobenzyl bromide (260 mg, 1.2 mmol) was added and the reaction stirred overnight. The reaction was quenched with water and extracted into EtOAc. The organic layer was washed with water, dried (Na$_2$SO$_4$) and evaporated under reduced pressure to yield a yellow product 86 (391 mg, 90%); $\delta_H (CDCl_3)$ 1.91 (1 H, d, J 12.5, 15e-H), 2.02 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.37 (5 H, m, NMe, 10a and 16-H), 2.61 (1H, dd, J 12.5, 4, 16-H), 2.68 (1 H, t, J 2.5, 14-H), 3.05 (1 H, d, J 18.5, 10β-H), 3.37 (1 H, q, J 3, 9-H), 3.83 (3 H, s, OMe), 4.03 (1 H, m, 6-H), 4.72 and 4.97 (2 H, ABq, CH$_2$-Ph), 5.04 (1 H, d, J 6, 5-H), 5.38 (1 H, d, J 10, 8-H), 5.77 (1 H, d, J 10, 7-H), 6.54 and 6.66 (2 H, ABq, 1 and 2-H), 7.62 (2 H, d, J 8.5, 20 and 24-H), 8.17 (2 H, d, J 8.5, 21 and 23-H); $m/z$ 434 (M$^+$, 33%) 298(21),
Preparation of Methyl Tetra-O-acetyl-(α+β)-D-glucopyranuronate

NaOH (0.05 g) was dissolved in MeOH (115 ml) and to this was added glucuronolactone 88 (15 g, 0.085 mol) in small increments, making sure the pH did not fall below 8. The reaction mixture was stirred at room temperature for 2 h and the MeOH evaporated to yield β-D-glucopyranuronate, a yellow syrup. To this was added pyridine (38 ml) and acetic anhydride (60 ml, 65 g, 0.64 mol) dropwise, keeping the reaction temperature below 30°C. The solution was refrigerated overnight. The crystals that formed were separated from the mother liquor and washed with cold EtOH, to give clear white crystals. Recrystallisation was affected from hot EtOH yielding white needles of methyl tetra-O-acetyl-β-D-glucopyranuronate 89 (12.493 g, 43%). The mother liquor and EtOH washings were condensed and refrigerated overnight to give another crop of crystals 0.8 g. Total product (13.293 g, 45%) m.p. 174-8°C [lit 178°C68]; $^{23}[\alpha]_D +7.80$ (c1 in CHCl₃); $\delta_H$ (CDCl₃) 2.03 - 2.12 (12 H, m, 4xAc), 3.75 (3 H, s, OMe), 4.18 (1 H, d, $J$ 9, 5-H), 5.11 - 5.35 (3 H, m, 2, 3 and 4-H), 5.77 (1 H, d, $J$ 8, 1-H).

The mother liquor from the reaction was poured onto crushed ice and neutralised with aq. NaHCO₃. The mixture was filtered to remove excess NaHCO₃. The cake and filtrate were extracted thoroughly with CHCl₃, and the combined extracts dried (Na₂SO₄) and concentrated to a syrup. The syrup was taken up in hot isopropyl alcohol and refrigerated overnight. The white crystals that separated were collected and recrystallised from isopropyl alcohol yielding methyl tetra-O-acetyl-α-D-glucopyranuronate 90 (1.419 g, 5%). $^{23}[\alpha]_D +98^\circ$ (c1 in CHCl₃); $\delta_H$ (CDCl₃) 2.02-2.19 (12 H, m, 4xAc), 3.75 (3 H, s, OMe), 4.41 (1 H, d, $J$ 10, 5-H), 5.12 (1 H, dd, J 10, 3.5, 2-H), 5.27 (1 H, t, $J$ 10, 3-H), 5.52 (1 H, t, J 10, 4-H), 6.40 (1 H, d, J 3.5, 1-H).
Preparation of Methyl-2,3,4-tri-O-acetyl-1α-bromo-1-deoxy-D-gluco.pyranuronate (92)

Methyl tetra-O-acetyl-β-D-gluco.pyranuronate (5 g, 0.015 mol) was dissolved in 45% hydrobromic acid in acetic acid (20 ml, 20 g, 0.15 mol), and the mixture refrigerated overnight. The solvent was evaporated to give a brown syrup residue, which was dissolved in CHCl₃ (10 ml), washed with cold aq. NaHCO₃ and water, and dried (Na₂SO₄). The resulting pale yellow solution was evaporated under reduced pressure and the residual syrup dissolved in EtOH (15 ml). Crystals formed immediately but were dissolved on heating. The solvent was evaporated to give a white product which was recrystallised from EtOAc using petroleum ether, to yield white needles of the bromo acetate sugar 92 (3.384 g, 64%). m.p. 80-2°C [lit 104-105°C68]; [α]D +199° (c1 in CHCl₃); δH (CDCl₃) 1.71 (9 H, m, 3xAc), 3.38 (3 H, s, OMe), 4.18 (1 H, d, J 10, 5-H), 4.51 (1 H, dd, J 10, 4, 2-H), 4.85 (1 H, t, J 10, 3-H), 5.20 (1 H, t, J 10, 4-H), 6.31 (1 H, d, J 4, 1-H).

Preparation of Methyl (codein-6-yl-2,3,4-tri-O-acetyl-β-D-gluco.pyranosid) uronate (93)

Codeine (0.5 g, 1.67 mmol) was dissolved in sodium dried benzene (30 cm³), under nitrogen. Dry AgCO₃ (1.4 g, 8.4 mmol) was added, turning the clear solution grey. Methyl-2,3,4-tri-O-acetyl-1α-bromo-1-deoxy-D-gluco.pyranuronate (0.9 g, 2.27 mmol) was added in several portions, with constant stirring. The reaction mixture was heated to reflux, and benzene was gradually distilled off using a Dean Stark apparatus. Heating was continued for 13 h, with reaction progress being monitored by TLC. On completion the reaction mixture was filtered and washed with benzene. The filtrate was evaporated under reduced pressure to yield a brown residue (1.275 g). The crude product was purified by column chromatography (elution with 50% benzene in CHCl₃ and 5% MeOH in CHCl₃). A cream powder was obtained 93 (347 mg, 33%) m.p. 111-4°C (decomp) [lit. 112-4°C⁷¹]; νmax(nujol)/cm⁻¹ 1746 (C=O); δH (CDCl₃) 1.90 (1 H, d, J 12, 15e-H), 2.03 (6 H, s, 2xAc), 2.15 (4 H, m, Ac and 15a-H) 2.39 (1 H, dd, J 18.5, 6, 10α-H), 2.51 (4 H, m, NMe and 16a-H), 2.71 (1 H, d, J 18.5, 16e-H), 2.81 (1 H, s, 14-H), 3.04 (1 H, d, J 18.5, 10β-H),
3.47 (1 H, m, 9-H), 3.76 (3 H, s, OMe), 3.78 (3 H, s, OMe), 4.11 (1 H, d, J 9, 22-H), 4.39 (1 H, m, 6-H), 4.95 (2 H, m, 5 and 20-H), 5.09 (1 H, t, J 8, 21-H), 5.29 (3 H, m, 8, 18 and 19-H), 5.70 (1 H, d, J 9, 7-H), 6.52 and 6.64 (2 H, ABq, 1 and 2-H); m/z 615 (M+, 8%) 555(7), 298(18), 282(83), 229(13), 197(8), 155(32), 127(21), 43(100).

Preparation of Codein-6-y1-β-D-glucopyranosiduronate (95)

To a solution of methyl(codein-6-yl-2,3,4-tri-O-acetyl-β-D-glucopyranosid)uronate (150 mg, 0.24 mmol) in methanol (3 cm³), was added 0.01 M NaOMe solution (1 cm³) and the solution stirred overnight. On completion of the reaction indicated by TLC, the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in phosphate buffer (10 cm³), at 25°C, and the pH adjusted to 7 using 0.05 M NaOH. PLE (0.45 cm³, 1 mg, ~200 units) as a suspension in 3.2 M (NH₄)SO₄ solution was added and the reaction left stirring overnight, maintaining the temperature at 25°C and the pH at 7, by using a pH-stat. 2.6 cm³ of base were consumed. The reaction mixture was adjusted to pH 6 using acetic acid, and evaporated under reduced pressure to give a concentrated solution. The crude solution was chromatographed on reverse phase silica (elution with 30% H₂O in MeOH). Final purification was by semi-prep HPLC, using a silica reverse phase column, to give colourless needles of C-6-G 95 (48 mg, 41%) m.p. 272-276°C (decomp) [lit 276-278°C¹]; v_max(nujol)/cm⁻¹ (C=O); δ_H (CD₃OD) 1.89 (1 H, m, 15c-H), 1.98 (1 H, dt, J 12.5, 5, 5, 15a-H), 2.51 (5 H, m, NMe, 10α and 16a-H), 2.74 (2 H, m, 14 and 16e-H), 3.10 (1 H, d, J 18.5, 10b-H), 3.49 (3 H, m, 19, 20 and 21-H), 3.61 (1 H, d, J 9, 22-H), 3.81 (3 H, s, OMe), 4.53 (1 H, m, 9-H), 4.60 (1 H, d, J 8, 18-H) 4.88 (1 H, m, 6-H), 5.11 (1 H, d, J 7, 5-H), 5.32 (1 H, d, J 10, 8-H), 5.80 (1 H, d, J 10, 7-H), 6.58 and 6.72 (2 H, ABq, 1 and 2-H); HPLC: Solvent - MeOH/H₂O (70:30), Flow rate - 0.7 ml/min, Elution time - 4.5 min.

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Preparation of Methyl (3-t-Butyldimethylsilyloxy-morphin-6-yl-2,3,4-tri-O-acetyl-β-D-glucopyranosid) uronate (96)

Morphine 3-O-TBDMS ether 45 (0.4 g, 1 mmol) was dissolved in sodium dried benzene (20 cm³), under nitrogen. Dry AgCO₃ (1.12 g, 6.7 mmol) was added, turning the clear solution grey. Methyl-2,3,4-tri-O-acetyl-1α-bromo-1-deoxy-D-glucopyranuronate (0.75 g, 1.9 mmol) was added in several portions, with constant stirring. The reaction mixture was heated to reflux, and benzene was gradually distilled off using a Dean Stark apparatus. Heating was continued for 14 h, with reaction progress being monitored by TLC. On completion the reaction mixture was filtered and washed with benzene. The filtrate was evaporated under reduced pressure to yield a brown residue (0.93 g). The crude product was purified by column chromatography (elution with 15% MeOH in CHCl₃ and 5% MeOH in DCM). A cream powder was obtained 96 (240 mg, 33%) m.p. 81-83°C (decomp); \( \nu_{max}(\text{nujol})/\text{cm}^{-1} \) 1758 (C=O); \( \delta_H (\text{CDCl}_3) \) 0.14 (3 H, s, SiMe), 0.16 (3 H, s, SiMe), 0.96 (9 H, s, SiCMe₃), 1.83 (1 H, d, J 11, 15e-H), 2.07 (10 H, m, 3xAc and 15a-H), 2.36 (5 H, m, NMe, 10α and 16a-H), 2.60 (2 H, m, 14 and 16e-H), 3.02 (1 H, d, J 18.5, 10β-H), 3.37 (1 H, q, J 3, 9-H), 3.74 (3 H, s, OMe), 4.11 (1 H, d, J 9, 22-H), 4.28 (1 H, m, 6-H), 4.84 (1 H, d, J 6, 5-H), 5.01 (2 H, m, 19 and 21-H), 5.28 (3 H, m, 8, 18 and 20-H), 5.71 (1 H, d, J 10, 7-H), 6.42 and 6.56 (2 H, ABq, 1 and 2-H); \( \delta_C \) -4.73, -4.48, 18.37, 20.53, 20.65, 20.72, 20.84, 25.75, 35.83, 41.10, 43.02 (NMe), 43.73, 46.38, 52.87 (OMe), 69.26, 71.62, 72.21, 72.59, 74.15, 89.00, 99.36, 118.88, 121.45, 127.28, 128.77, 130.49, 130.63, 137.16, 149.45, 167.44, 169.43, 169.52, 170.15. (Found M⁺, 687.3264, C₃₆H₄₉NO₁₂ requires 687.3255).

Preparation of Methyl (morphin-6-yl-2,3,4-tri-O-acetyl-β-D-glucopyranosid) uronate (97)

Methyl(3-O-TBDMS-morphin-6-yl-2,3,4-tri-O-acetyl-β-D-glucopyranosid)urionate (0.2 g, 2.8 mmol) was dissolved in THF (10 cm³), under an inert atmosphere, and the solution cooled to 0°C. TBAF (1M solution in THF) (1 cm³) was added and the reaction mixture stirred at 0°C for 30 min, before being allowed to warm up to room
temperature. The reaction was stirred for a further 3 h, quenched with water and extracted into CHCl₃. The organic layer was dried (Na₂SO₄), and evaporated under reduced pressure. The residue was purified by column chromatography (elution with 5% MeOH in CHCl₃), to give a cream solid (139 mg, 83%) m.p. 106-9°C (decomp); (Found: C, 55.24; H, 6.2; N, 1.9. C₃₀H₃₅NO₁₂ requires C, 54.96; H, 6.3; N, 2.1%); ν_max(nujol)/cm⁻¹ 1746 (C=O); δ_H (CDCl₃/DMSO-d₆) 1.69 (1 H, d, J 11, 15e-H), 2.04 (7 H, m, 2xAc and 15a-H), 2.17(1 H, s, Ac), 2.44 (5 H, m, NMe, 10α and 16α-H), 2.69 (2 H, m, 14 and 16e-H), 3.00 (1 H, d, J 18.5, 10β-H), 3.41 (1 H, q, J 3, 9-H), 3.73 (3 H, s, OMe), 4.15 (1 H, d, J 9, 22-H), 4.32 (1 H, m, 6-H), 4.87 (2 H, m, 5 and 19-H), 5.11 (1 H, t, J 8, 21-H), 5.33 (3 H, m, 8, 18 and 20-H), 5.64 (1 H, d, J 10, 7-H), 6.49 and 6.65 (2 H, ABq, 1 and 2-H); δ_C 20.47, 20.57, 20.85, 21.55, 32.59, 37.69, 41.30 (NMe), 41.68, 47.30, 52.78 (OMe), 60.58, 69.32, 71.20, 71.79, 71.84, 77.69, 86.93, 98.74, 118.21, 119.64, 120.63, 125.24, 128.33, 131.91, 140.10, 146.42, 167.27, 169.37, 169.82, 170.26.

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42) German Patent (DBP) 2409 990, 1974, Schering AG.


Appendix 3.

[Diagram of a chemical structure with peaks labeled as 1, 2, 3, 4, 6+4, 7+3, and PPM values indicated.]

[Chemical structure image with labels COOH and OH.]