UNIVERSITY OF SOUTHAMPTON

A New Synthetic Approach To The Morphinan Framework.

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Contents

ABSTRACT

FACULTY OF SCIENCE

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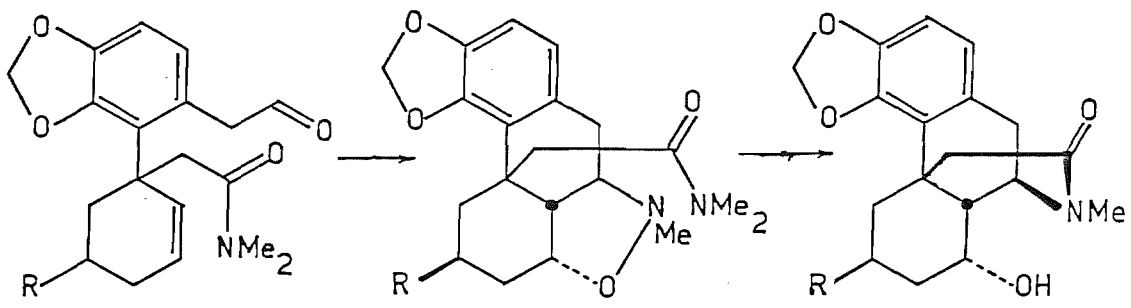
A NEW SYNTHETIC APPROACH TO THE MORPHINAN FRAMEWORK

by Ian Richard Matthews

A new synthetic approach to morphine has been investigated using an intramolecular nitrone cycloaddition reaction as the key step.

Coupling of 4-iodo-5-(2-propenyl)-1,3-benzodioxole with, alternately 3-methoxy-cyclohex-2-enone, and 3-methoxy-5-[(phenylmethoxy)methyl]-2-cyclohexen-1-one is described. Subsequent sodium borohydride reduction and a Claisen type rearrangement using N,N-dimethylacetamide dimethyl acetal followed by selective cleavage of the double bond afforded the aldehydes (1) and (2). When the nitrone cycloaddition reaction was performed for R=H a 1:1 ratio of *exo* : *endo* adducts was obtained. However for R=CH_2OCH_2Ph the *exo* : *endo* ratio was 1:4. In both cases the *exo* adduct was converted through to a morphinan structure and for R=H a number of steps were carried out towards producing a synthetic sample of morphine.



R=H	(1)	R=H	R=H
R=CH_2OCH_2Ph	(2)	R=CH_2OCH_2Ph	R=CH_2OH

A number of different methods for making 4-iodo-5-(2-propenyl)-1,3-benzodioxole are also discussed.

Acknowledgements

I am deeply indebted to my supervisor, Dr P. J. Parsons not only for his help and encouragement in the course of my studies but also for his friendship and consideration of my welfare throughout my stay in Southampton. The thoughts and assistance of Dr D. I. C. Scopes of Glaxo Group Research, Ware during my stay there, and on many other occasions were also gratefully received.

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Abbreviations

Δ	Heat
Ar	Aryl group
Bn	Benzyl
CNS	Central Nervous System
DEAD	Diethyl azodicarboxylate
DMAP	*N,N*-4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DIBAL	Di*iso*butylaluminium hydride
DMSO	Dimethyl sulphoxide
2,4 DNP	2,4-Dinitrophenylhydrazine
Ether	Diethyl ether
FMO	Frontier Molecular Orbital
HMPA	Hexamethylphosphorictriamide
HOMO	Highest occupied molecular orbital
LDA	Lithium di*iso*propylamide
LUMO	Lowest unoccupied molecular orbital
*m*CPBA	*meta*-Chloroperoxybenzoic acid
PCC	Pyridinium chlorochromate
Petrol	Petroleum ether (boiling range 40-60°C)
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMS	Tetramethylsilane
Ts	*p*-Toluenesulphonyl

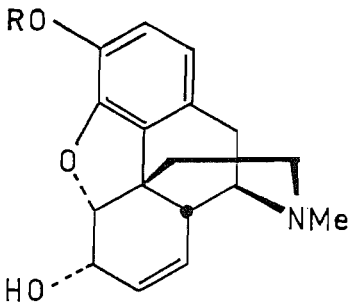
CHAPTER ONE

1.1 History[1]

The story of morphine began in the long distant past with its natural origins, the poppy plant *papaver somniferum*. The immature opium poppy capsules, where the plant manufactures its opiates, were known to have been given to small children to chew on some 3500 years ago, thereby no doubt, relieving their mothers of some of the pains of parenthood. Since then it has figured in all good apothecary shops and pharmacies in one form or another for the relief of both mental anguish and physical pain. No doubt it will be used for some more years to come.

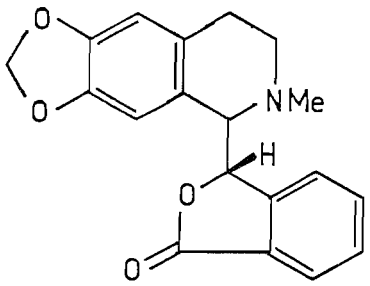
The incorrigible hand of science first came the way of morphine and the other opiates about 200 years ago when Derosne[2], in 1803, extracted opium to give a crystalline substance which he called 'salt of opium'. This is now believed to have been either morphine (1) or narcotine (2). In 1805 the pharmacist Serturner[3] in Hanover described the isolation of a pure alkaloid, which he named morphine after Morpheus the God of Sleep. This compound showed the same effects in dogs as opium. The report was shortly followed by the isolation and purification of a number of other alkaloids including narcotine[4](2) in 1817, codeine[5](3) in 1832, thebaine[6](4) in 1835 and papaverine[7](5) in 1848.

During the rest of the nineteenth century, work on the chemical and pharmacological properties of morphine was generally poor and qualitative in nature. The beginning of the twentieth century saw a great deal of research on the structural determination of morphine. This task was finally acceptably completed in 1925 by Gullard and Robinson[8] following extensive studies by both themselves and Hesse, Vongerichten, Knorr and Pschorr[9].



R=H 1

R=Me 3



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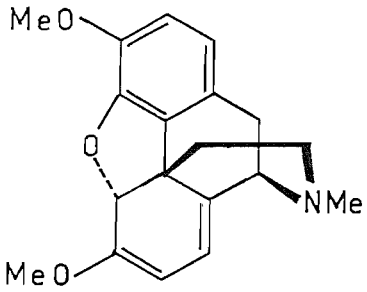

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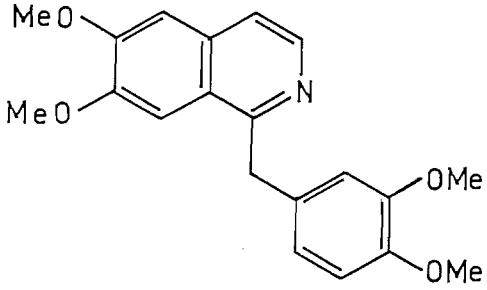

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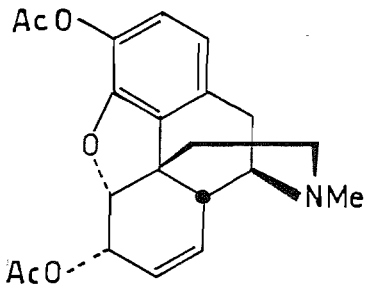
Opiate research was then directed towards other goals. Firstly a total synthesis of morphine was required to confirm the proposed structure and secondly work was required to try and obtain pain killing drugs without the physical dependence associated with the opiates. Whilst the first goal has now been completed by a number of workers using a variety of different approaches, the second objective has been only partially successful with the 'ideal' pain killer still awaiting discovery.

1.2 History of opiate analgesic research. Analgesics with similar structures to morphine[1,10]

The powerful analgesic action of morphine is not unique to this molecule, a fact that was realised early on in its use. As the malevolent side effects of morphine were also realised at an early

stage i.e. respiratory depression, induction of constipation, sedation and most importantly physical dependence, investigations to find other compounds which act as analgesics without showing the unwanted ancillary activities have a long history.

The first important compound to emerge from early searches for the 'ideal analgesic' was obtained by the diacetylation of morphine in 1874[11]. This compound, now known as heroin(6) or medically as diamorphine, was initially heralded as being significantly superior to morphine by virtue of its apparently lower depression of respiration and because it could be substituted for morphine without the patient suffering withdrawal symptoms, hence the addiction was 'cured'. The concept of a cross tolerance and the maintainance of dependance by a compound of similar pharmacological profile had not then been realised. How the greater respiratory depression of heroin(6) was missed now seems incredible. Despite the problems associated with heroin(6) it still finds use in hospitals, even today, with terminal cancer patients.



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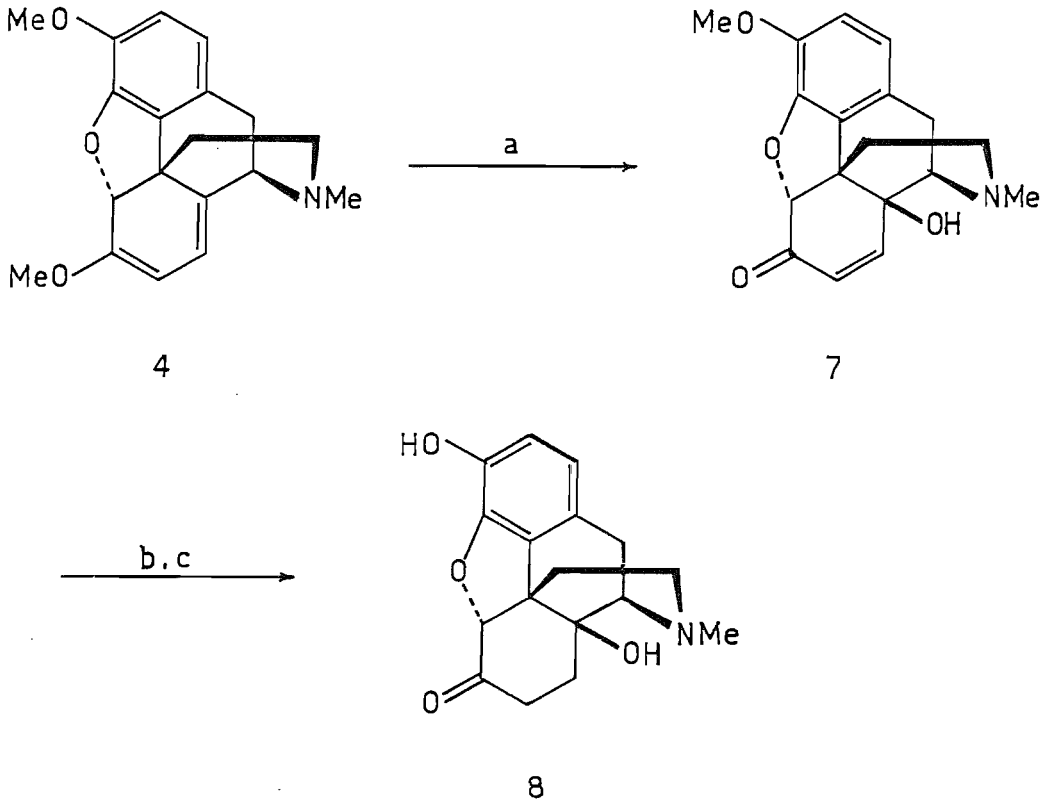
Much of the earlier work on morphine analogues was approached by degrading the naturally occurring opiates into new compounds which could then be screened. This early work was coordinated by the committee on Drug Addiction of the National Research Council (NRC) between 1929 and 1959 with financial support from the Rockefeller Foundation before being taken over by the National Institutes of Health.

Some of the most important modifications came from thebaine(4). Although this is only present in small amounts in *papaver somniferum*

the related poppy *papaver bracteatum* can yield up to 26% thebaine(4) from the dried latex. Treatment of thebaine(4) with acidic hydrogen peroxide yields the hydroxy ketone(7) which, upon reduction and demethylation, gives oxymorphone[12](8), an analgesic about 10 times as potent in man as morphine. It is, however still highly addictive.

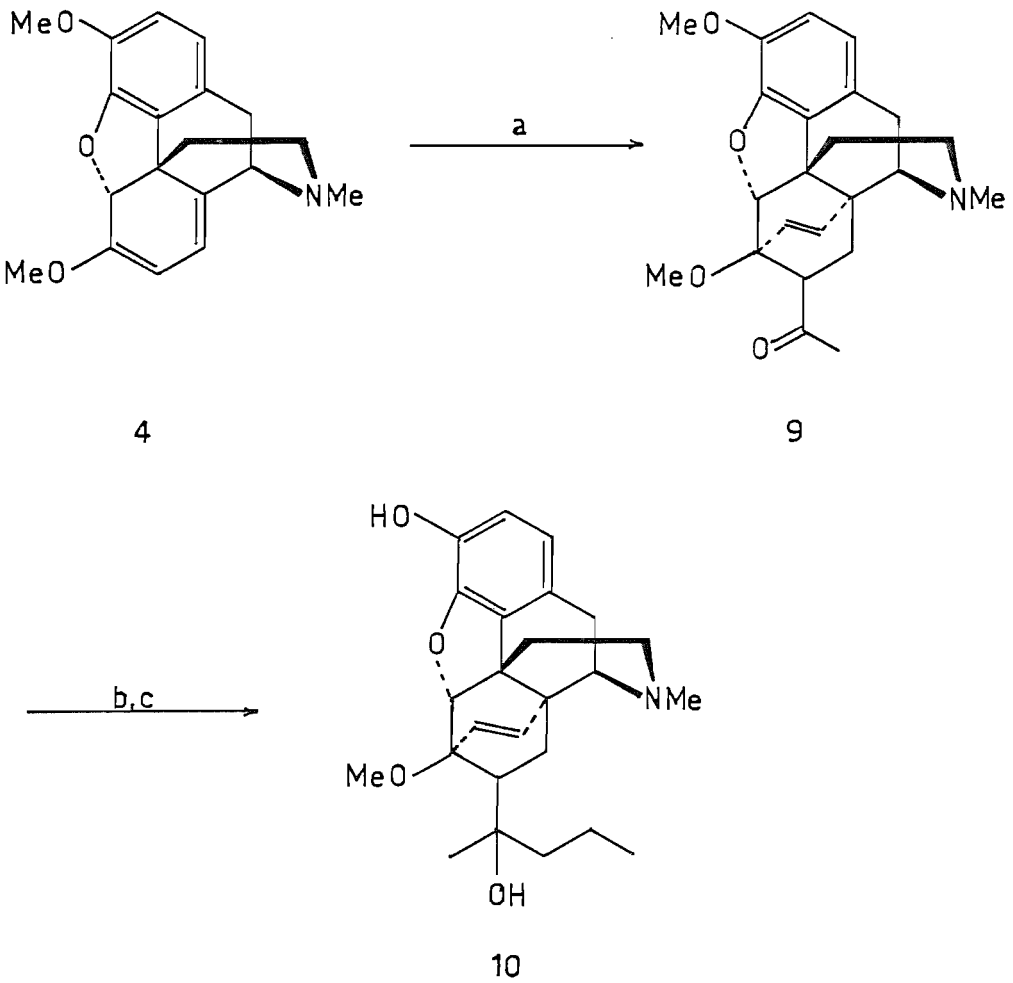


4 7 8

a H_2O_2, H_3O+ b H_2, catalyst c *O*-demethylation

Scheme 1.1

One of the most striking results to come from modification of the basic morphine framework follows the work of Bentley *et al*[13], who reasoned that a larger, more rigid structure might bind more selectively to the receptor site and hence show greater separation of analgesic action from dependence. Diels-Alder reaction between thebaine(4) and methyl vinyl ketone gave adduct(9) which upon treatment with *n*-propylmagnesium bromide and demethylation gave etorphine(10) an analgesic at least 2000 times more powerful than morphine. Again, however, it is highly addictive. Etorphine(10) has nonetheless found use in animal tranquillizer darts since only a very small dose, such as can be put on a dart fired from a crossbow, is required to bring even elephants to docility.

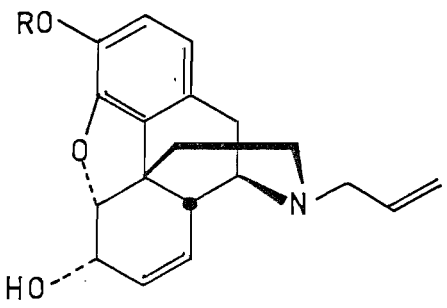


Scheme 1.2

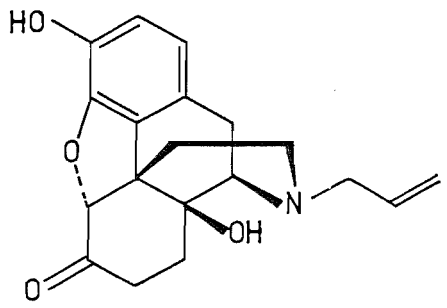
A methyl group on nitrogen had for a long time been considered essential for optimum analgesic activity as its removal, or substitution by ethyl, gave rise to reduced activity. A systematic study of the role of the tertiary nitrogen in morphine action in 1953[14] showed that activity was in fact restored with *n*-propyl and even increased with still larger groups, e.g. *n*-amyl, *n*-hexyl and phenethyl, but the most interesting group has proved to be allyl.

In 1915 Pohl[15] noticed that *N*-allylnorcodeine(11) was antagonistic to the respiratory depressant effect of morphine. It was another 30 years before the morphine analogue (*N*-allylnormorphine, nalorphine or Nalline(12)) was made[16] and the antagonistic action

confirmed. Nalorphine(12) represented a milestone in opiate based analgesic research as it was the first compound to show any real separation of analgesic action from addiction, and the other unwanted properties of morphine. Although nalorphine(12) has been shown to block many of the actions of morphine by acting as an antagonist it still retains analgesic activity similar to that of morphine. Unfortunately it also induces bizarre, disturbing, hallucinations which rendered it unsuitable for use as an analgesic in man. As a combination of this discovery and the previously described work which gave oxymorphone(8), the highly potent narcotic antagonist naloxone(13) was produced.



R=Me 11
R=H 12



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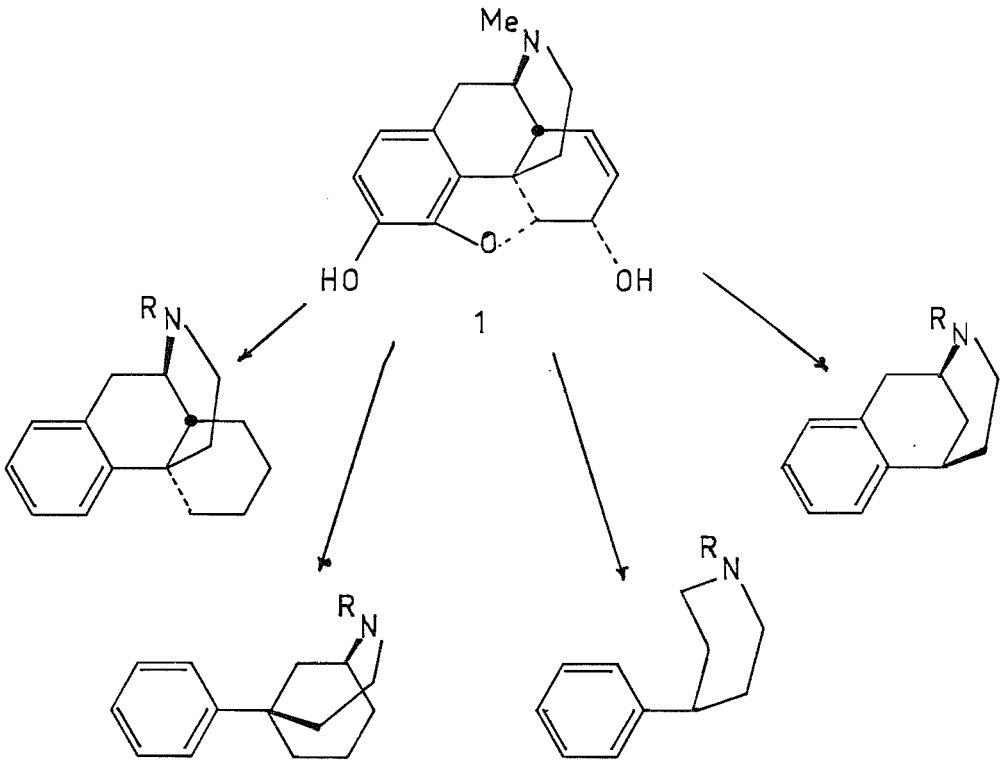
Analgesics based on morphine fragments[1,10]

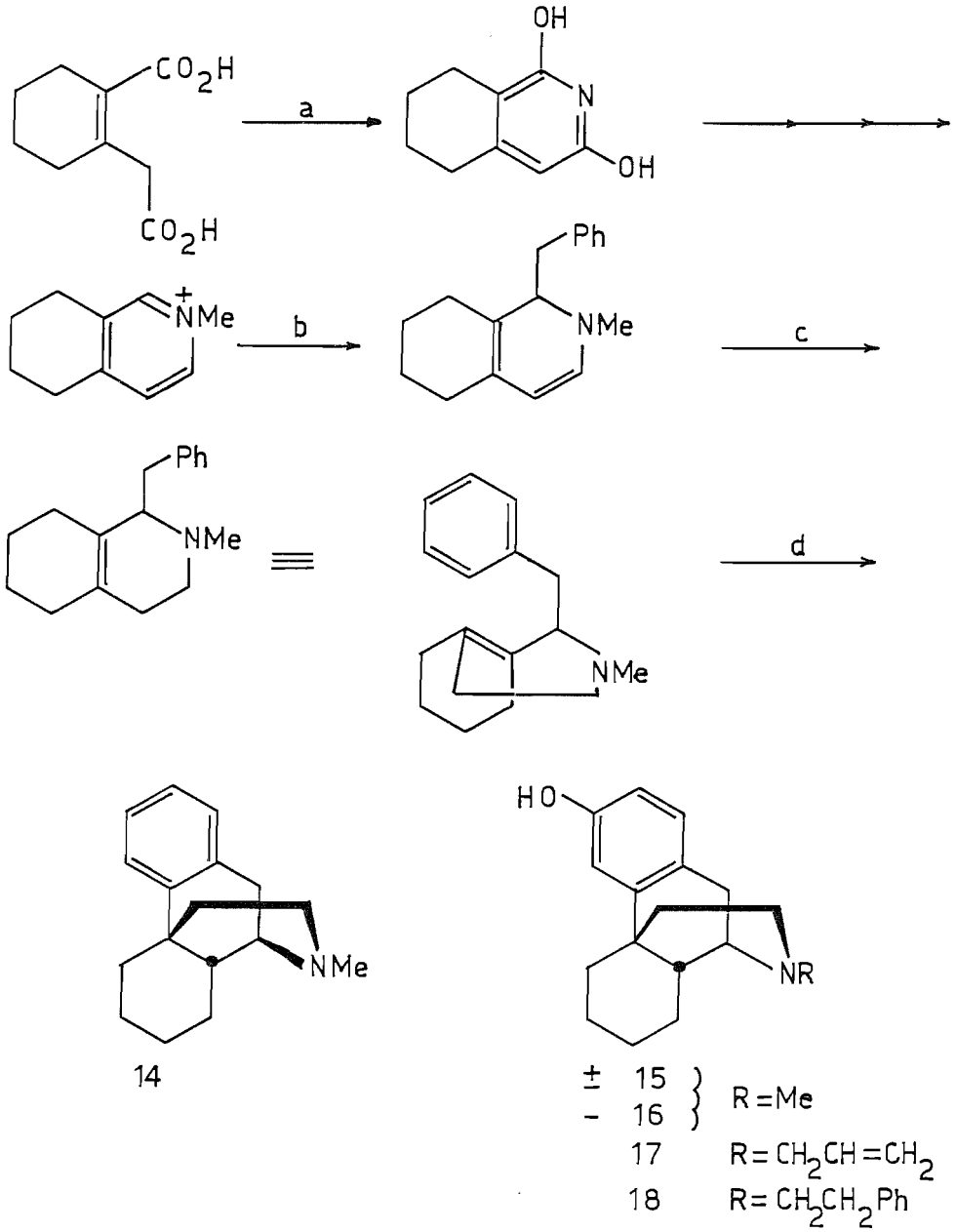
As morphine constitutes such a challenging synthetic target, considerable effort has gone into producing analgesics based on only part of the morphine skeleton. To this end the work has been successful, although the crucial separation of analgesic activity from dependence and the other detrimental side effects has still not been achieved. The basic fragments that have been studied and their relationships to morphine are illustrated in Scheme 1.3.



Scheme 1.3

During some of the earliest work directed towards the first total synthesis of morphine, Grewe[17] made the first morphinan fragment(14) by what is now known as the Grewe cyclisation.(Scheme 1.4). As an extension to this work Schnider *et al*[18] made the analogous 3-hydroxy morphinan(15). Resolution of this via the tartrate salt affords the analgesic levorphanol(16) which shows 6 to 8 times the analgesic potency of morphine with similar addictive properties. *N*-Demethylation of levorphanol(16), followed by treatment with allyl bromide affords the potent narcotic antagonist levallorphan(17) which shows similar pharmacological properties to nalorphine(12) whilst alkylation with 2-phenylethylbromide gives the antagonist phenomorphan(18).

Removal of another ring from the morphine structure gives the phenylmorphans. 5-(m-Hydroxyphenyl)-2-methylmorphan(19)[19] exhibits equivalent analgesic activity to morphine in animals. However little other work has been done on this class of compounds.



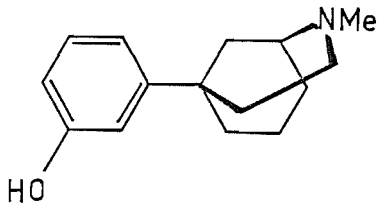
14

± 15 } R=Me
− 16 }
17 R= $CH_2CH=CH_2$
18 R= CH_2CH_2Ph

a $(NH_4)_2CO_3$ b $PhCH_2MgCl$ c H_2,H_3O^+, catalyst
d H_3PO_4

Scheme 1.4

A great deal more attention has been focussed on the benzomorphan[20] group of compounds. Two of these, pentazocine(20) and phenazocine(21), have found clinical use. The former is a mild analgesic with weak antagonistic activity and the latter a strong analgesic with no antagonistic activity. Another related compound, cyclazocine(22) which also shows good analgesic activity with reduced dependence potential is, however, hallucinogenic.



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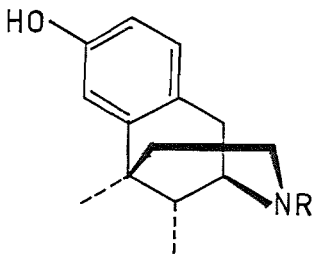
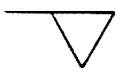
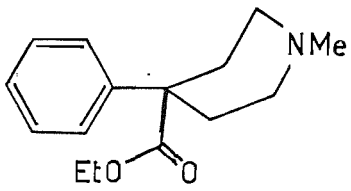


$R=CH_2CH=CMe_2$ 20

$R=CH_2CH_2Ph$ 21

$R=CH_2$  22



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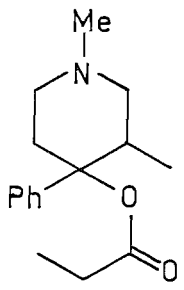
The final group of compounds to be discussed, which centre on part structures of morphine are the phenyl-piperidines. The origin of interest in these compounds is, like so many inventions, based on a chance discovery. In the late 1930's a German chemist-pharmacologist team were looking for a spasmolytic substitute for atropine. Pethidine(23) was tested for this purpose without success, but routine pharmacological screening revealed it to be an analgesic with other morphine-like properties, despite its apparent dissimilarity. Schaumann in 1940 rationalised this activity to three basic qualities - a benzene nucleus, a quarternary carbon attached and a tertiary amino group two aliphatic carbons removed. This can be seen to fit all the species discussed so far, indeed there are few exceptions. Pethidine(23) can replace morphine in many clinical situations and, like heroin(6), it was introduced with unjustified claims of non-addictiveness and greater safety. It was put under narcotics control in 1947 and is now generally recognised as requiring the same precautions in use as morphine.



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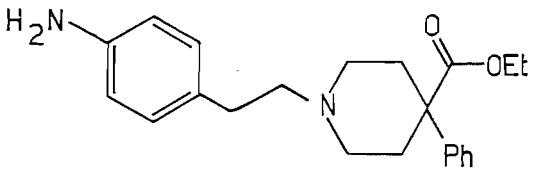

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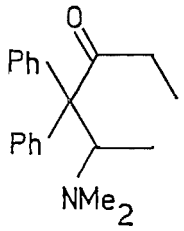

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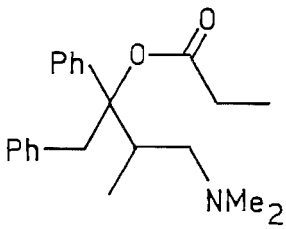

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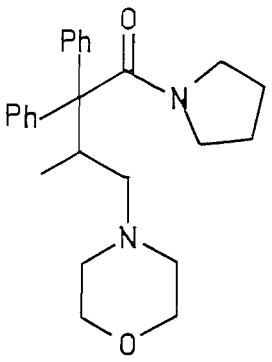

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Since then thousands of phenyl-piperidines have been synthesised, some showing greatly increased activity over morphine and a few have been used clinically e.g. alphaprodine(24) and anileridine(25). Sadly none of these molecules have shown any great separation of analgesic action from dependence.

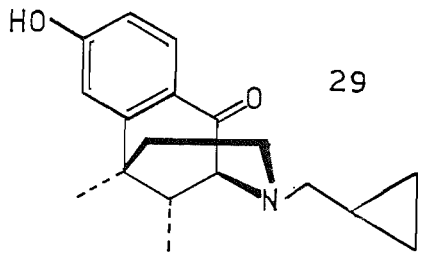
As a development from the pethidine studies the analgesic methadone(26) was introduced. This shows similar action to morphine but is more active and longer lasting when taken orally. It has found significant use for the treatment of addicts where it can be substituted for the physical dependence of a specific opiate. Withdrawal symptoms from methadone(26) are subsequently slower in onset, milder, and longer lasting than the original opiate. Other methadone(26) related compounds which have found use include dextropropoxyphene(27) and dextromoraninole(28). The former is a very popular mild analgesic with a very low abuse record whilst the latter is a highly effective analgesic with a similarly high abuse potential.

1.3 Recent developments in the search for better analgesics

The question why humans should show such profound sensitivity to a natural compound evolutionarily totally unrelated from themselves, with no known role in normal biochemical function, had bothered medicinal chemists for a long time. When reports of the existence of receptors for opiates in mammalian brains appeared in the literature the mystery deepened. Finally a pair of pentapeptides, called enkephalins, which bind tightly to opiate receptors, were identified[21]. These show analgesic activity when injected directly into the brain but show no activity by other routes, presumably because they are rapidly broken down by peptide cleaving enzymes in the body. Similarly fragments of the peptide hormone β-lipotropin, the endorphins, show binding to opiate receptors and have profound CNS activity in animals. Interestingly one of these fragments, β-endorphin, incorporates along its chain exactly the same sequence of amino acids as methionine enkaphalin. Correct folding of models of these peptides does indeed show similarities of structure with molecules like morphine. To date no analgesics have come out of these discoveries but they have provided a useful piece in the opiate-analgesic jig-saw puzzle.

The most significant advance in analgesic research of recent years has come in the field of pharmacology. For a long time it had been assumed that only one receptor was responsible for the effects of morphine. Recent studies[22] now indicate the presence of at least four different receptors[23]. These have been designated the μ, κ, δ and σ receptors. The μ receptor is the one associated with all the classical morphine-like effects e.g. analgesia, physical dependence etc. and is the site where drugs like morphine, normorphine, dihydromorphine and levorphanol bind as well as some of the synthetic enkephalins, specifically modified for μ character. The δ receptor is defined pharmacologically as the receptor which is found in peripheral tissues such as the mouse vas deferens as well as in the CNS. It exhibits a higher affinity for the naturally occurring enkephalins than for morphine and related compounds. Most μ and δ ligands cross react with μ and δ receptors although highly selective μ and δ ligands have been designed. However neither μ nor δ ligands generally exhibit

any great affinity for the κ or σ receptors. The κ receptor is that at which ketocyclazocine(29)-like opiates produce analgesia as well as ataxic and sedative effects. It has also been defined as the receptor showing high selectivity for dynorphin (a 17 amino acid opioid peptide).



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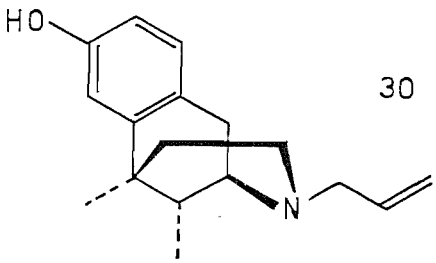

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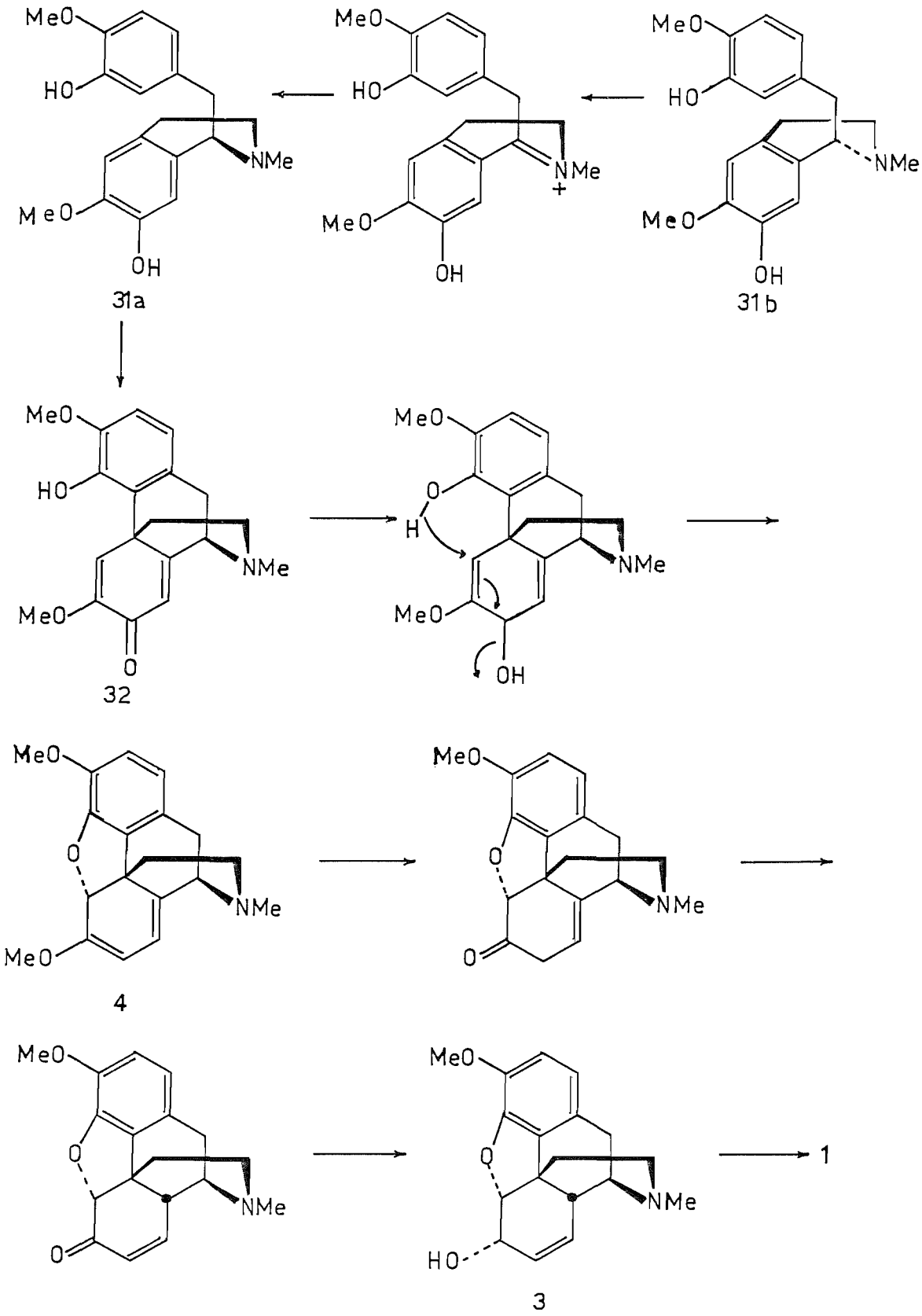
Actions at all three sites are reversible by the opiate antagonist naloxone(13), with increasing doses being required going from μ to δ to κ receptors. The fourth receptor, the σ receptor, which is not considered an opiate receptor by some as actions occurring there are not naloxone-reversible, shows a high affinity for certain benzomorphan opiates such as cyclazocine(22) and *N*-allylnor-cyclazocine(30) and acts to produce stimulant and psycotomimetic effects. Many opioids interact at more than one of these receptors.

The hope in opiate based analgesic research now stems from the possibility that a drug may be found which will bind strongly to some receptors, and less strongly to others to give an overall effect that is non-addictive, non hallucinogenic and does not show any great degree of sedation but is still a potent analgesic.

1.4 Biosynthesis of Morphine

Before considering the various synthetic routes man has used, and attempted to use to make morphine it is a good idea to consider the method used by the poppy plant itself. Work to determine the biosynthesis of morphine was carried out during the sixties principally by Battersby and Barton, and their co-workers[23] using ^{14}C and ^{3}H labelling studies. More recent studies by Rapoport *et al*[24] have also helped to confirm the later steps in the sequence.

The biogenetic relationship between the 1-benzylisoquinoline system and morphine had been recognised as early as 1925 by Robinson[8] and this has subsequently been shown to be the key coupling step in the biosynthesis. (R)-Reticuline(31a), made from the amino acid tyrosine, is thus cyclised by an oxidative phenolic coupling reaction to give salutoridine(32). (S)-Reticuline(31b) is also utilized by the



Scheme 1.5

plant through an epimerisation reaction. The details of the biosynthesis are illustrated in Scheme 1.5 and show how morphine is produced via both codeine(3) and thebaine(4).

1.5 Previous synthetic approaches to morphine

The synthetic approaches to morphine which have been investigated to date can best be classified by considering the key disconnections used in each of the routes pursued.

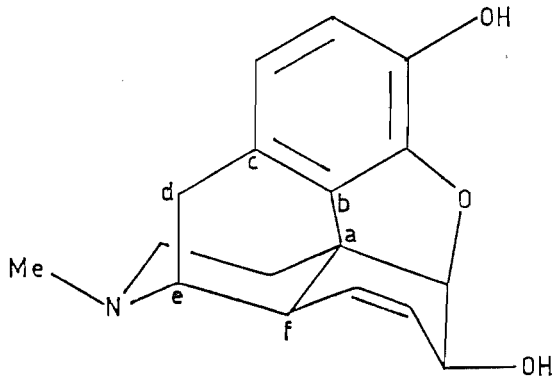


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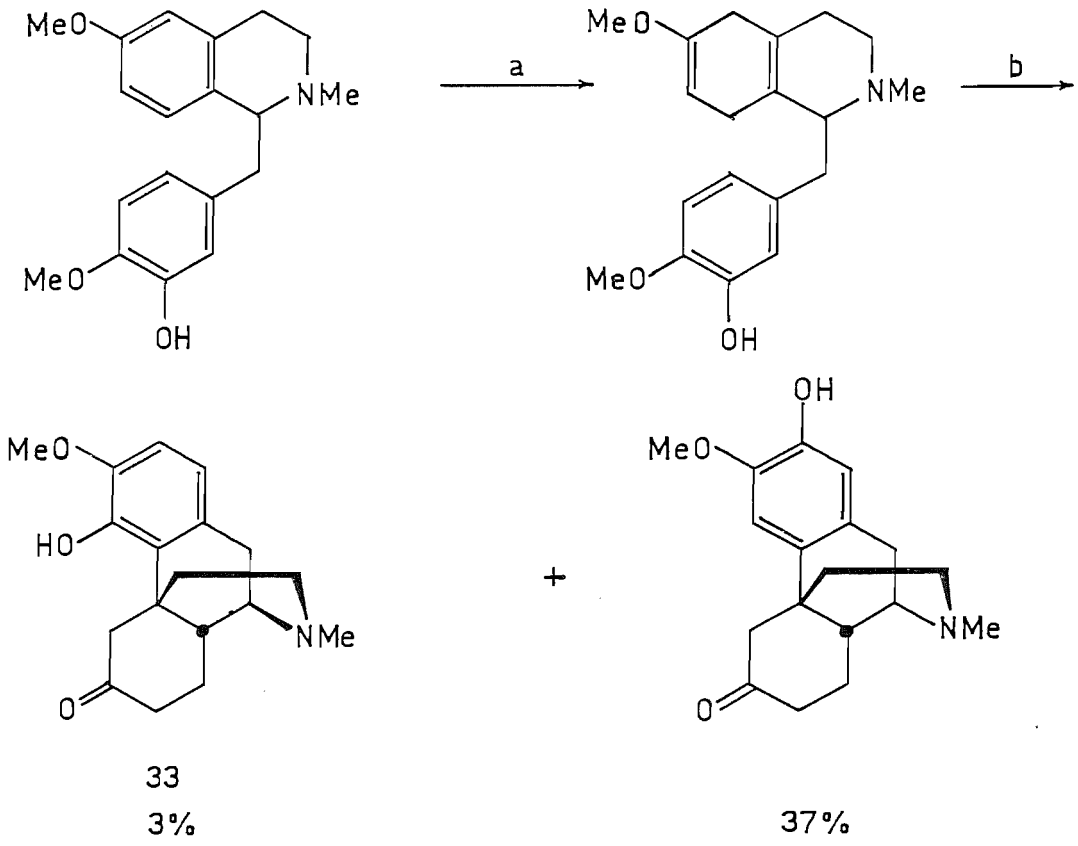
Diagram 1.1

The first successful route through to a morphinan fragment, the approach used by the plant, and the most studied route has been that which considers the a-b bond formation as the key step. This work was carried out by Grewe *et al*[17] in the late 1940's and gave the first purely synthetic morphinans. The key steps in this route are illustrated in Scheme 1.4. (page 8). Although this produced the first synthetic morphinans a total synthesis of morphine was not accomplished this way until 1967[25] using the following procedure (Scheme 1.6) where ketone(33) had previously been an intermediate in the first total synthesis of morphine. Since then a number of workers[26,27] have concentrated on improving the yield in the phenolic coupling step by using blocking groups to protect the aromatic ring (Scheme 1.7).

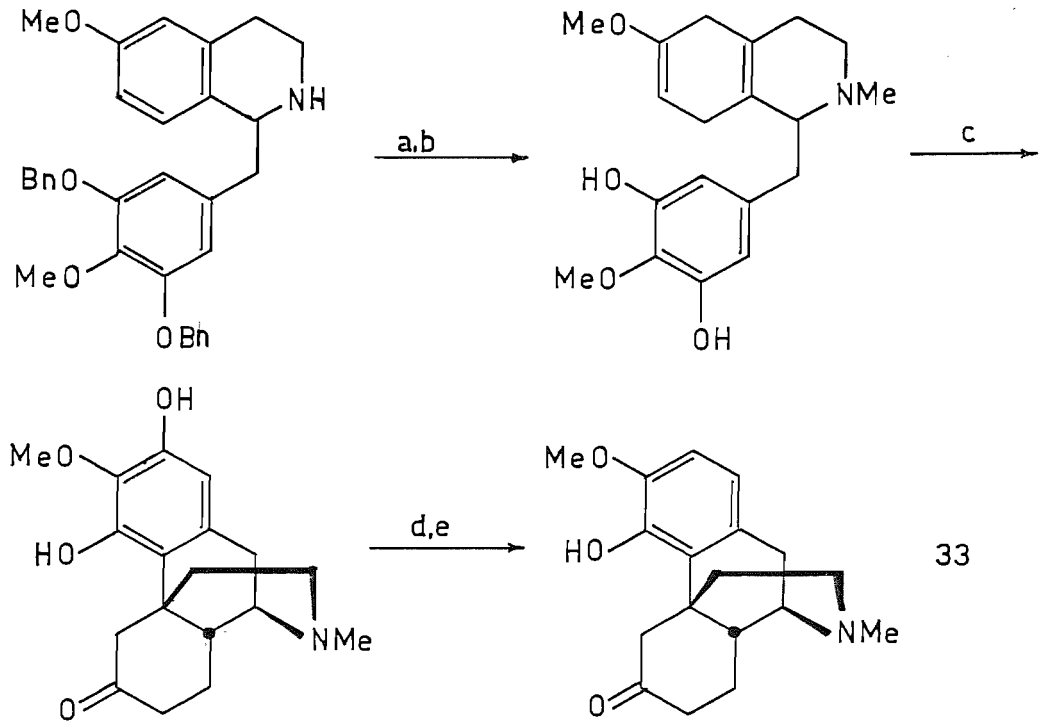


33
3%

37%

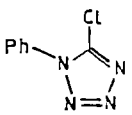
a Na, NH_3, *t*-BuOH b HCl, Ether

Scheme 1.6



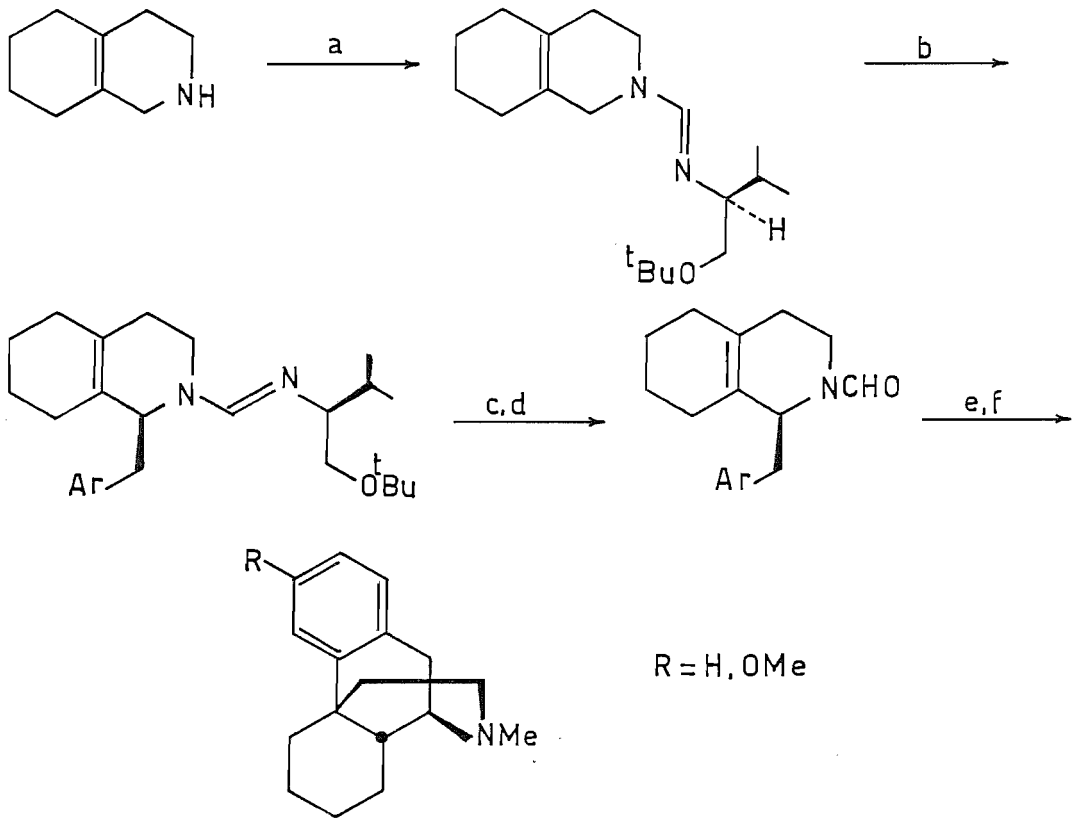
33

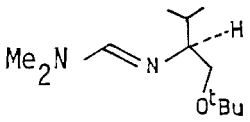
a H_2, Catalyst, CH_2O b Li, NH_3, *t*-BuOH c HCl, Ether

d  , K_2CO_3 e H_2, Pd

Scheme 1.7

The Grewe cyclisation route is the only approach which has been used to produce chiral morphinans synthetically. Meyers[28] has produced morphinans in 98%ee by an asymmetric alkylation of octahydroisoquinoline (Scheme 1.8).

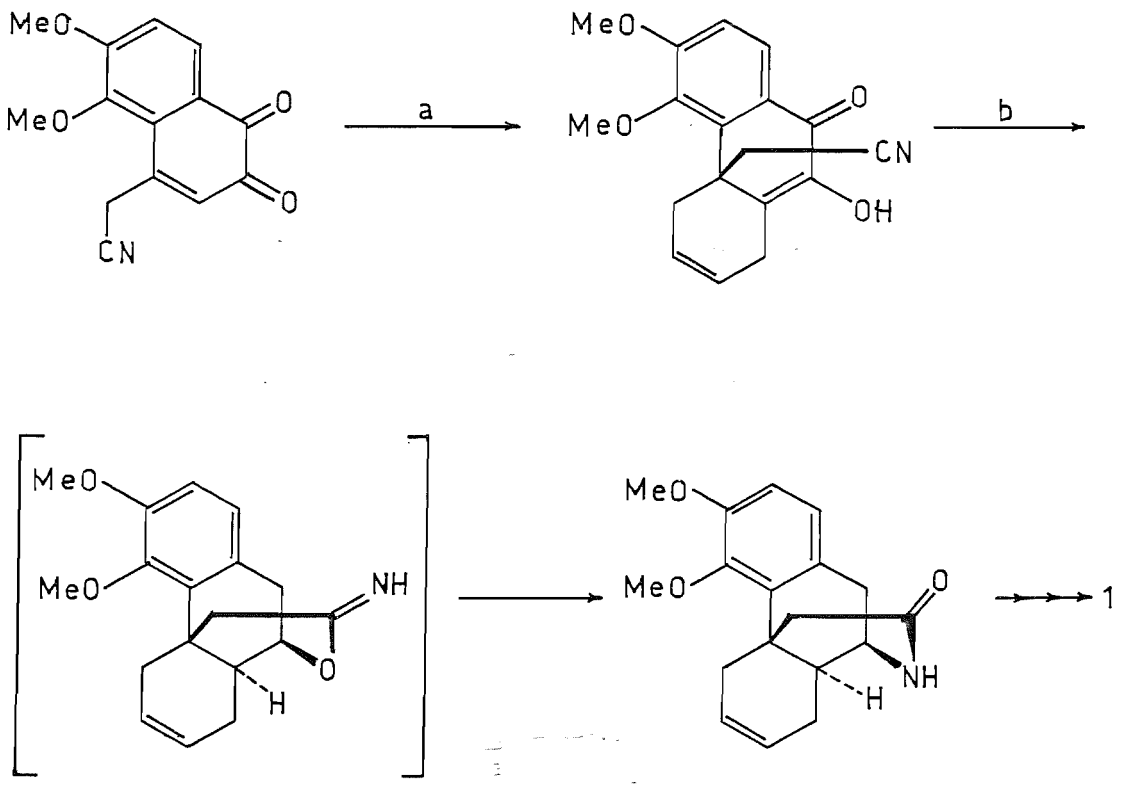


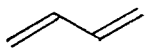
a Me_2N  b *n*-BuLi, $ArCH_2Cl$

c NH_2NH_2, EtOH, AcOH d HCO_2Et, Δ e $LiAlH_4$
f H_3PO_3

Scheme 1.8

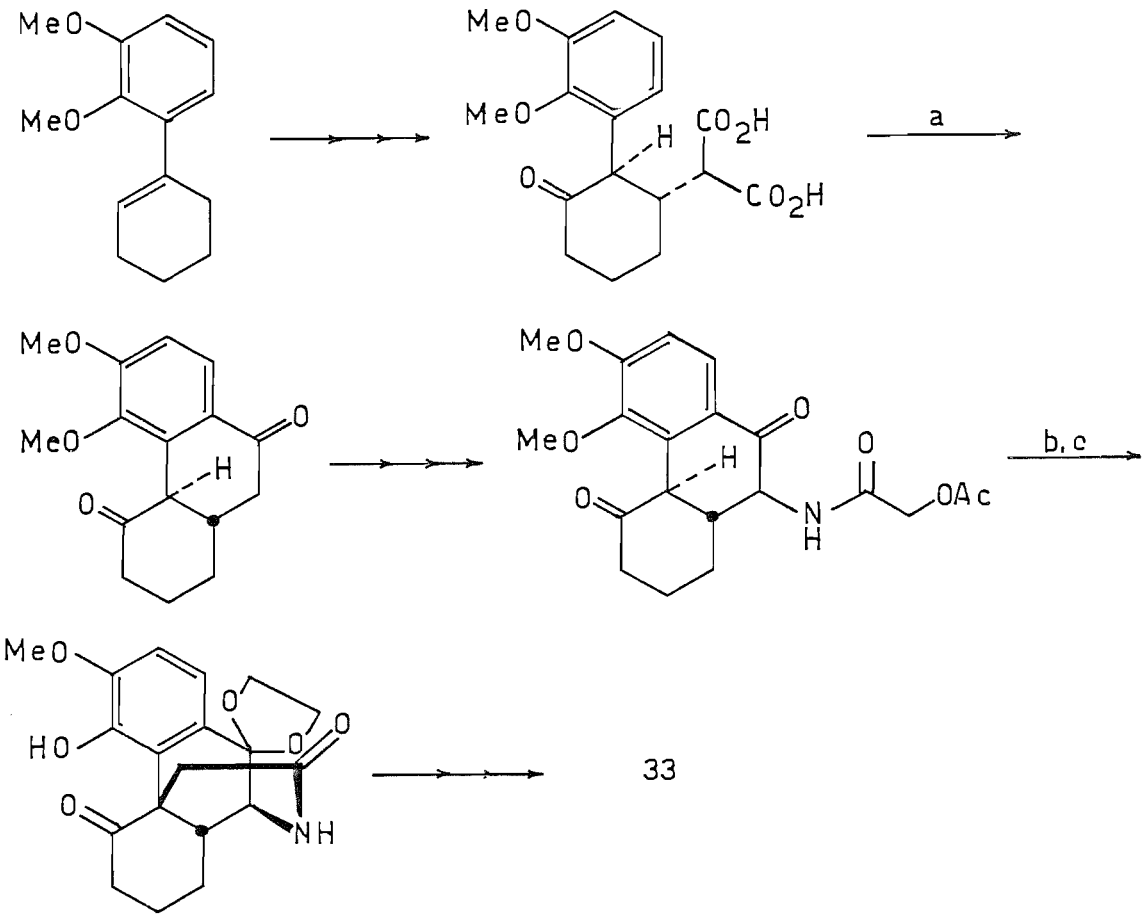
The approach taken in the first total synthesis of morphine by Gates *et al* used a Diels-Alder reaction, followed by a copper chromite hydrogenation to give the basic morphinan skeleton. Elaboration of this by a further 16 steps led to codeine(3) and thence, by demethylation, morphine.



a  , Δ b H_2, copper chromite, 27 bar, 130°C

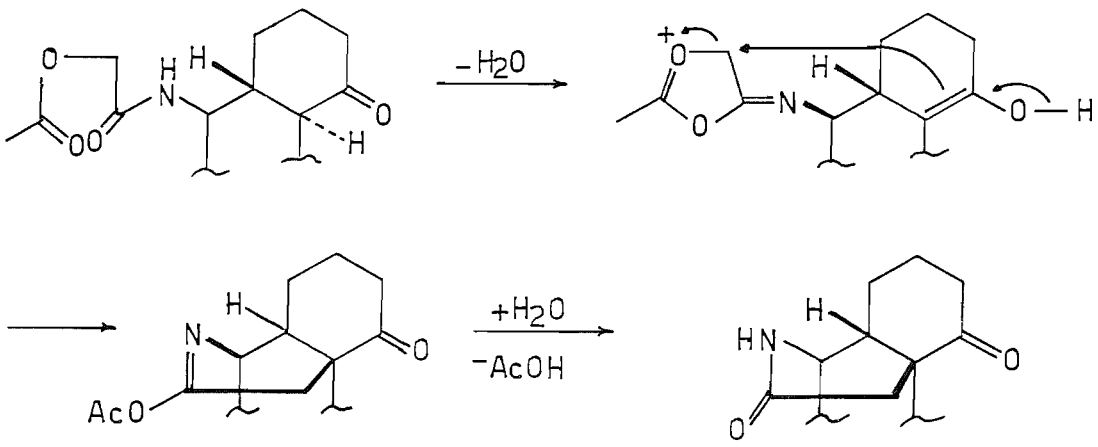
Scheme 1.9

This route was quickly followed by an entirely different approach from Elad and Ginsburg[30]. They constructed 1-dihydrothebainone(33), which had been previously converted by a number of workers[31] through to morphine, as outlined in Scheme 1.10. A possible mechanism for the formation of the amide bridge has been postulated by Stork[31]. (Scheme 1.11).



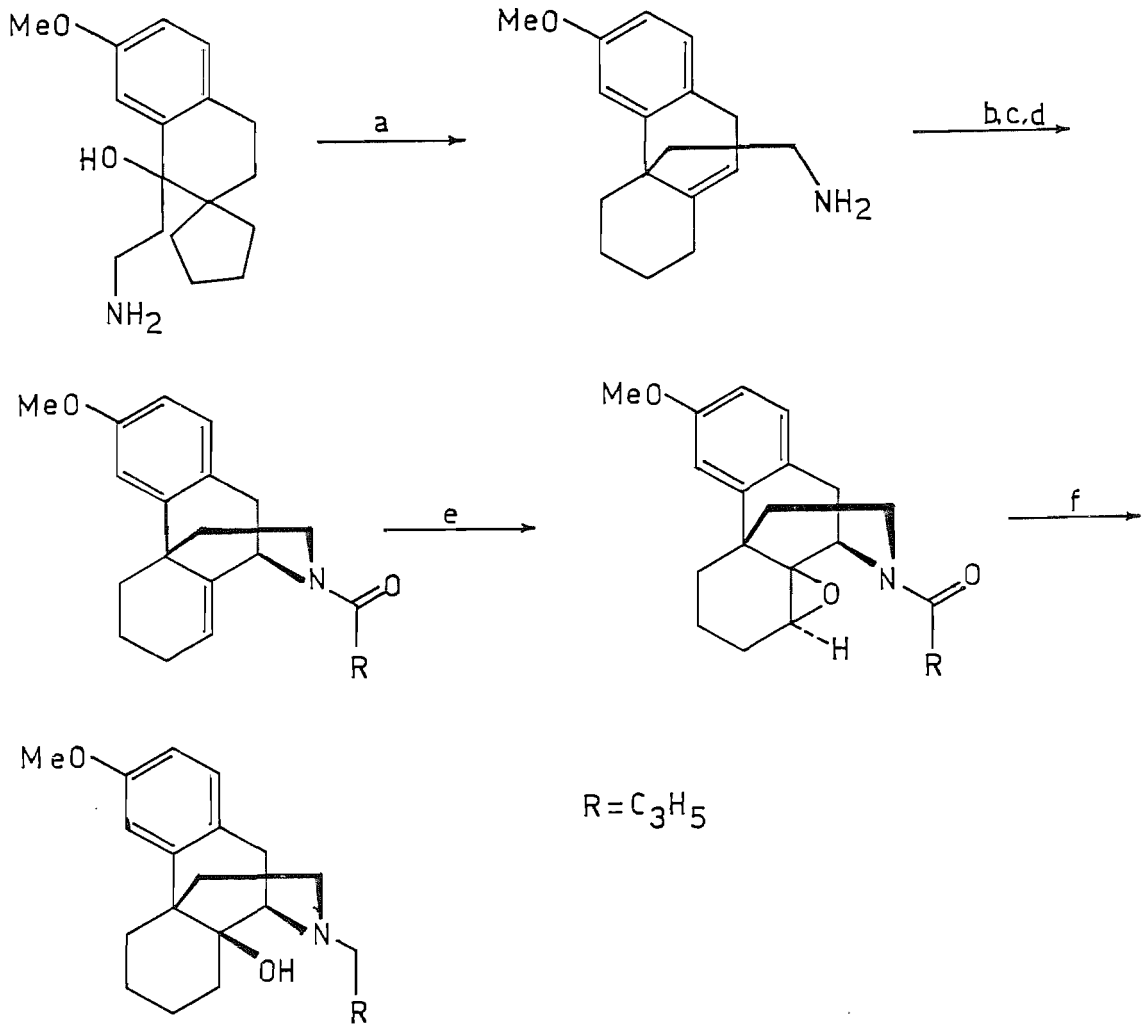
a HF b TsOH, $(CH_2OH)_2$ c Δ

Scheme 1.10



Scheme 1.11

Since the early work on morphine syntheses relatively few other approaches to this important natural product have been investigated. In 1973 a group of workers[32] illustrated the use of a different approach to the morphinan framework, which readily facilitated the incorporation of a 14-hydroxy group into the molecule (something not possible using the Grewe cyclisation approach) to give a number of oxymorphone(8) analogues. The key steps in their approach, which uses a rearrangement to give the quaternary carbon, are illustrated below. (Scheme 1.12).

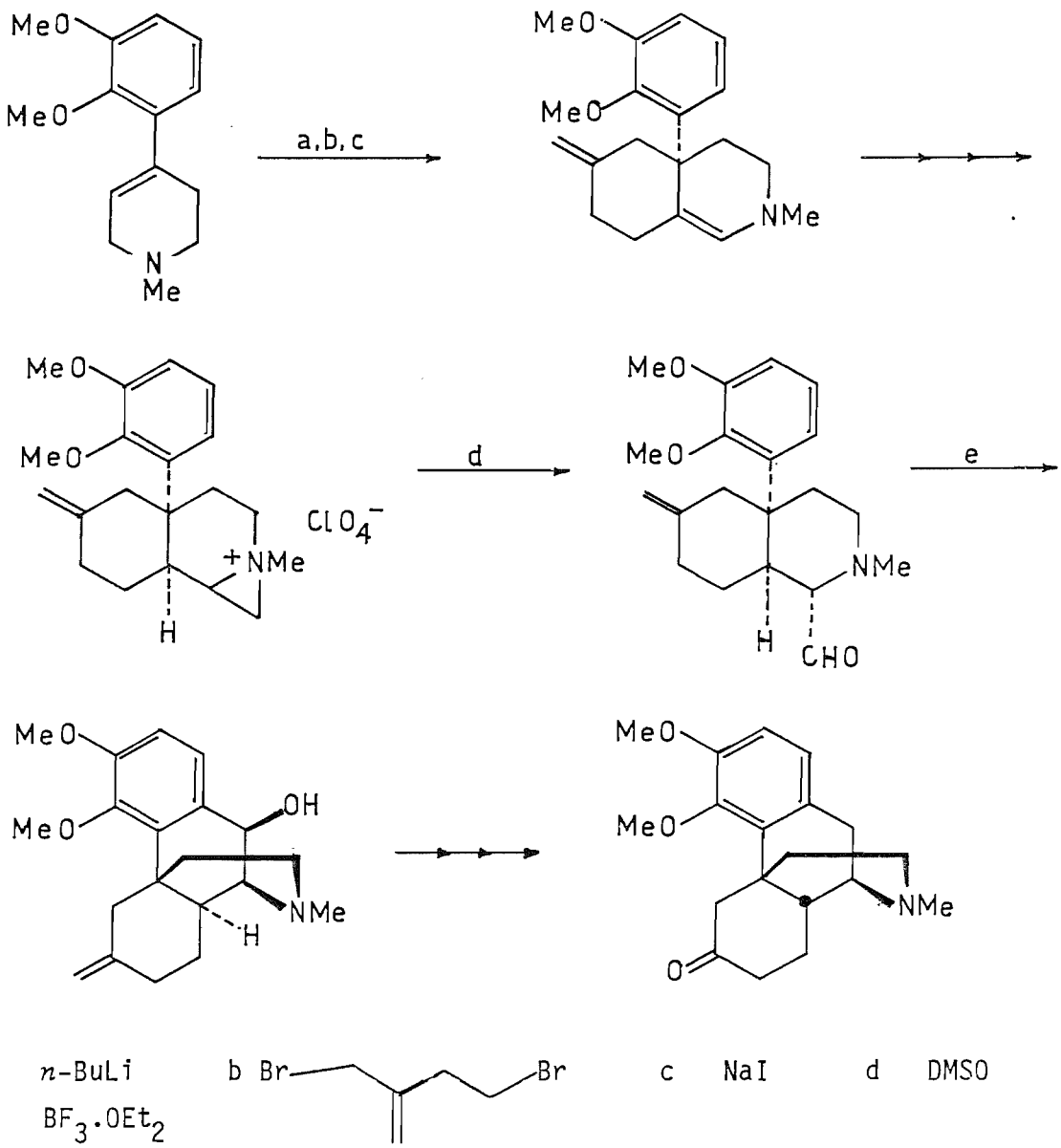


a HCl, ether b Br_2, $CHCl_3$ c $NaHCO_3$, DMF
d $(C_3H_5CO)_2O$ e *m*CPBA f $LiAlH_4$

Scheme 1.12

A recent disconnection considered concurrently by Evans[33], Rapoport[34] and McMurry[35] uses the c-d bond formation as the key

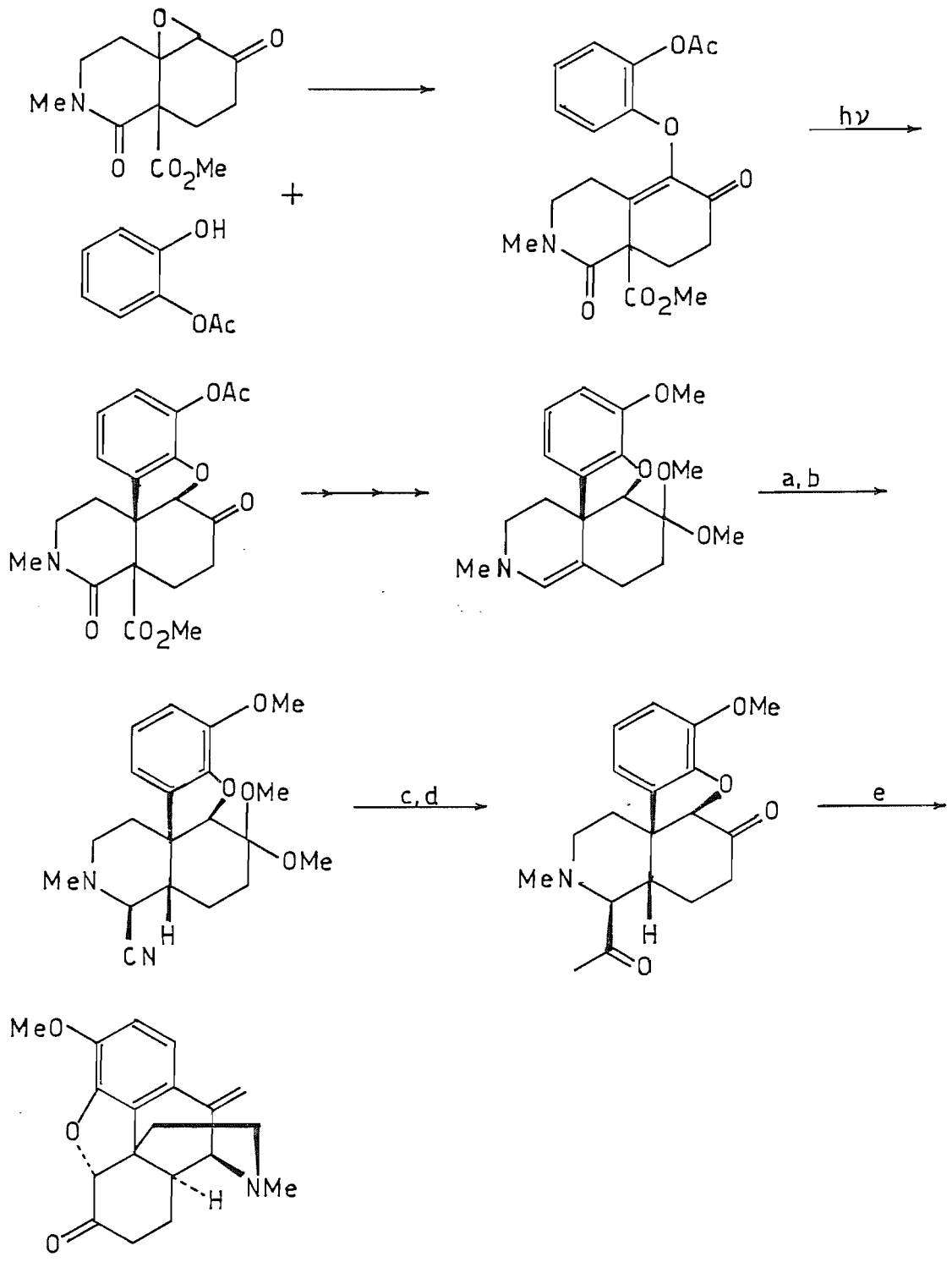
disconnection. The reconnection is achieved by the opening of an azidinium ion to give the required intermediate(35) for cyclization and is illustrated for Evans chemistry in Scheme 1.13.



a *n*-BuLi b Br—⟨—Br c NaI d DMSO
e $BF_3.OEt_2$

Scheme 1.13

The only other successful disconnection applied to the synthesis of the morphinan framework, apart from the one discussed in this work, has been that of Schultz *et al*[36]. His approach forms the a-b bond and furan ring early in the synthesis by a photochemical reaction and the c-d bond last to give the morphinan framework. (Scheme 1.14).

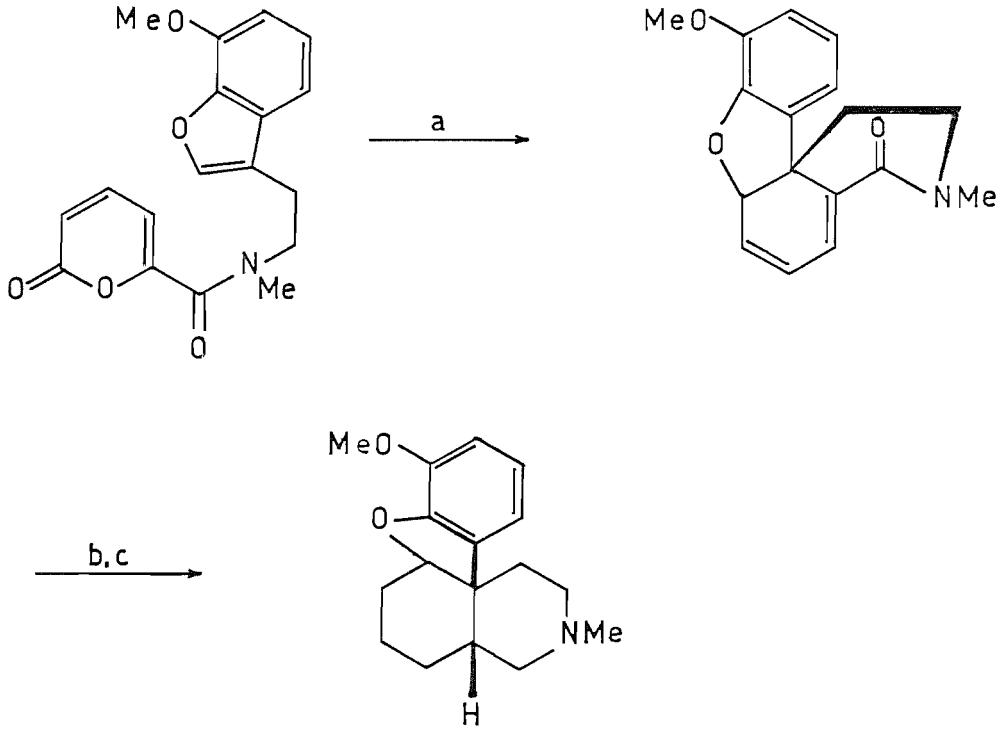


a $HClO_4$ b KCN c MeLi d H_3O+ e CF_3SO_3H

Scheme 1.14

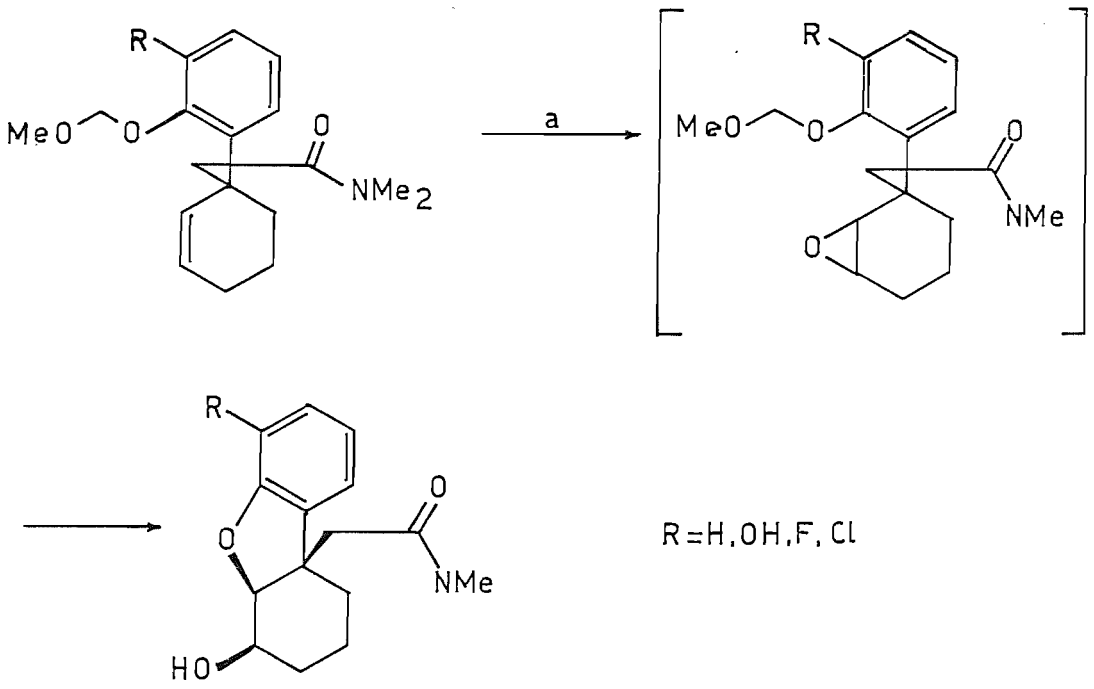
Two other approaches to morphine, which have not to date produced total syntheses, but nonetheless represent significantly different and interesting approaches, have been described by Ciganek[37] and Moskowitz[38] *et al*. Ciganek has used a Diels-Alder reaction to give a

very similar intermediate to that obtained later by Schultz. (Scheme 1.15). Whilst Moskowitz *et al* formed a tricyclic system using the opening of an epoxide (Scheme 1.16).



a 215°C, $-CO_2$ b H_2, Pd-C c $BH_3.SMe_2$

Scheme 1.15



R=H,OH,F,Cl

a CCl_3CN, CH_2Cl_2, $KHCO_3$, H_2O_2

Scheme 1.16

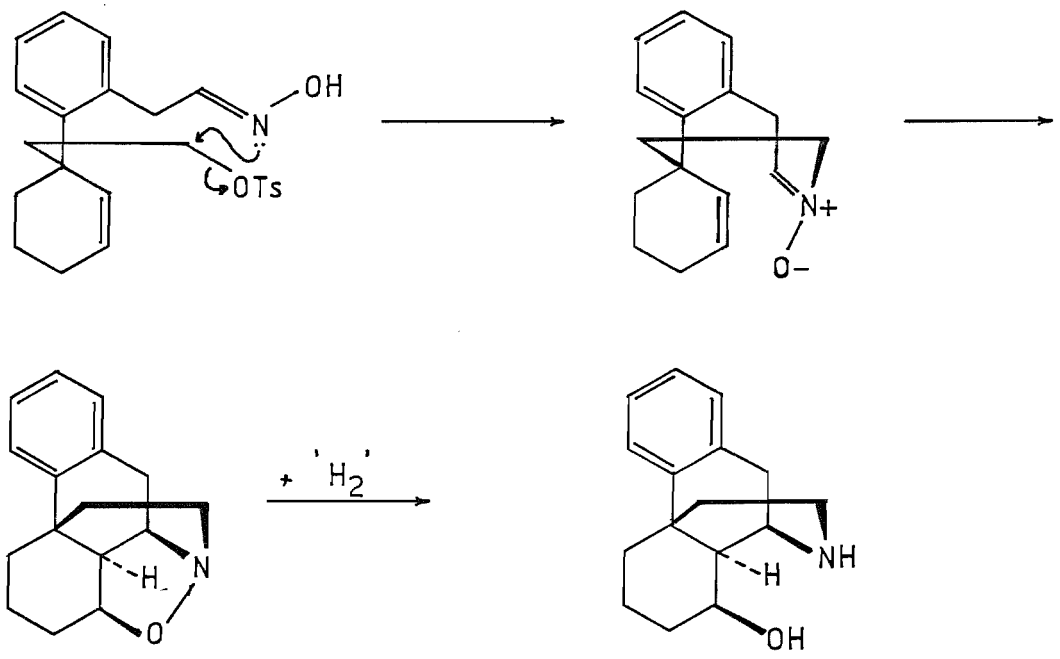
From this survey of synthetic approaches to morphine it can be seen that the variety in the routes investigated has been surprisingly limited. Although a number of new schemes have appeared since this review was produced, the work discussed in the following script still represents a radically different approach from those described elsewhere.

CHAPTER TWO

2.1 Introduction

The recent advances in pharmacological research[21,22] on the mode of action of the opiate based drugs have produced a commensurate increase in research into synthetic approaches to morphine. In considering a new synthetic approach to morphine it is important to take into account the requirements of such an undertaking. As to date no hard underlining trends have come from research to indicate the likely structural features an ideal analgesic will have, a new route needs to be flexible for the construction of analogues, as well as short and efficient. Ideally the route needs to be suitable for large scale preparations. This would enable sufficient quantities of the later intermediates to be produced for thorough pharmacological screening. Ultimately large scale commercial production of a suitable analgesic would free the medical profession from dependence on certain capricious foreign governments for its supply of important pain killers. This could help to reduce the growing heroin addiction epidemic by making the legal growth of the poppy *papaver somniferum* unnecessary. To this end we hoped to be able to produce a new and totally different synthesis which would give active compounds quickly, using some interesting chemistry.

The initial idea for this work revolved around the possibility that intramolecular alkylation of an oxime might give a nitrone. This intermediate could undergo an intramolecular 3+2 cycloaddition reaction to give the morphinan framework (Scheme 2.1).

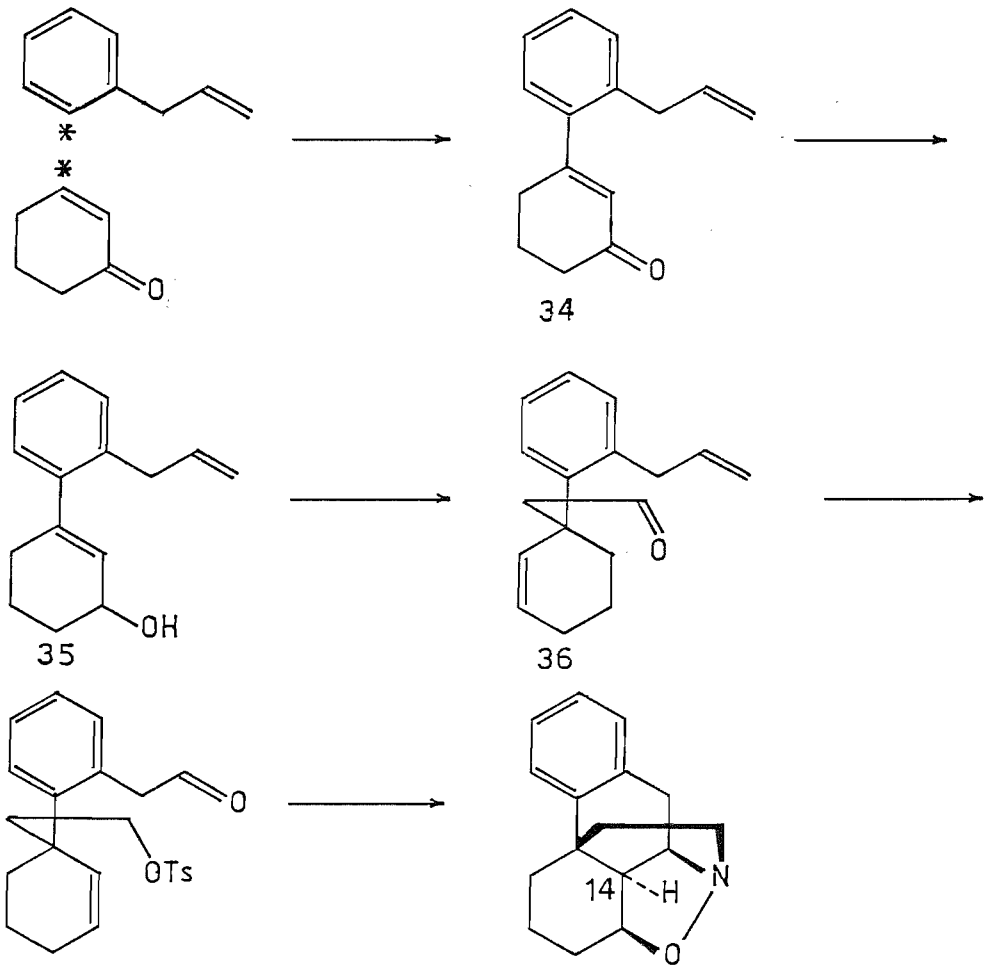


Scheme 2.1

This approach, which utilizes the e-f bond formation (diagram 1.1) as the key step, makes a significant deviation from all previous syntheses, where formation of either the a-b bond or the c-d bond to the aromatic ring has been the key step.

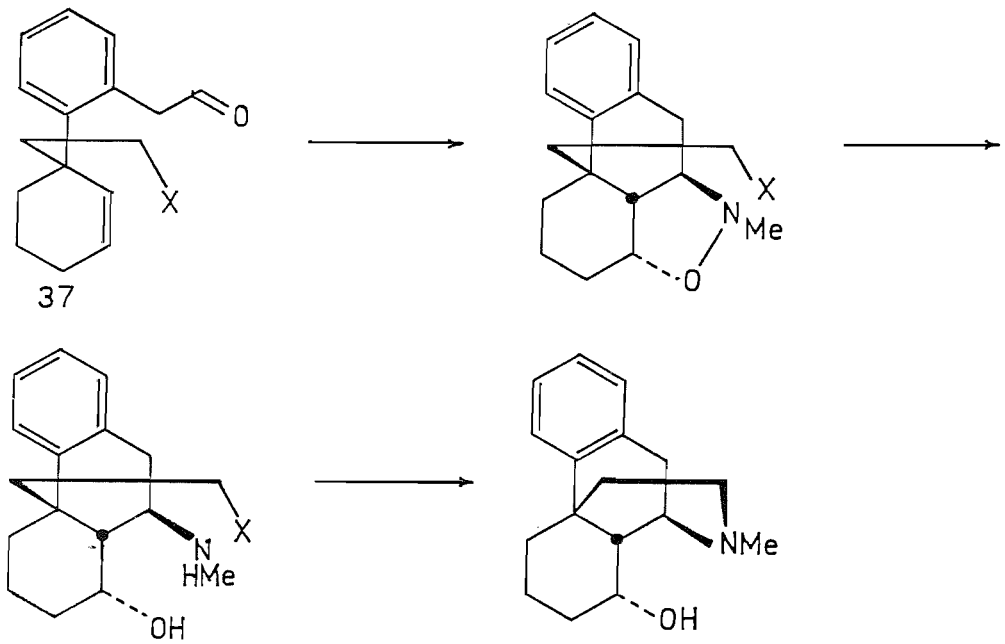
2.2 Design of a suitable model system

To examine the feasibility of the nitrone cycloaddition chemistry, it was prudent to investigate the reaction in a model system before attempting an outright total synthesis. To this end the following scheme was devised (Scheme 2.2).



Scheme 2.2

Inspection of a model of the intermediate nitrone species indicated that such a scheme would lead to the incorrect sterochemistry for a morphinan at carbon 14. Although this is not catastrophic, as epimeration at a later stage is well precedented[29,33], it would obviously be more satisfactory if this were not necessary. To this end an analogues approach was envisaged. This involved formation of a nitrone by reaction of the aldehyde with *N*-methylhydroxylamine and cleavage of the N-O bond. Subsequent intramolecular alkylation of the amine should then give the morphinan frame work. (Scheme 2.3). These two potential synthetic routes have the advantage of a common intermediate in the form of aldehyde(37).

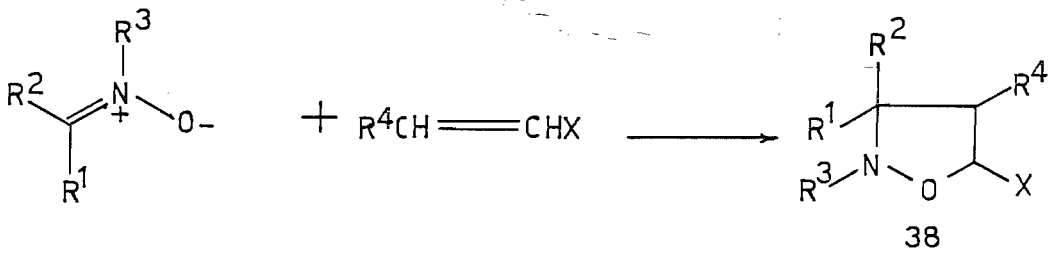


Scheme 2.3

2.3 The Chemistry of the Nitrone Cycloaddition Reaction[39-45]

Although nitrones have been known about for a long time, it is only in recent years that they have received the greatest attention. Since the early work of Huisgen[43] *et al* on 1,3-dipolar cycloadditions was carried out in the early 1960's the interest in nitrones has escalated, resulting in the application of cycloaddition reactions to many natural product syntheses.

The 3+2 cycloaddition reaction is simple to carry out, as it generally involves heating the nitrone and an alkene together in an inert solvent. This usually gives rise to the high yield of an isoxazolidine(38) (Scheme 2.4). There is often a high degree of regiochemical and stereochemical control exhibited by the nitrone cycloaddition addition. Some of the reasons for this will be discussed in due course. Besides alkenes nitrones have also been shown to undergo 1,3 dipolar cycloaddition reactions with a number of other double bonds[44] including isocyanates, isothiocyanates, thiocarbonyl compounds, phosphoranes, sulphenes and sulphinyl groups as well as alkynes.



38

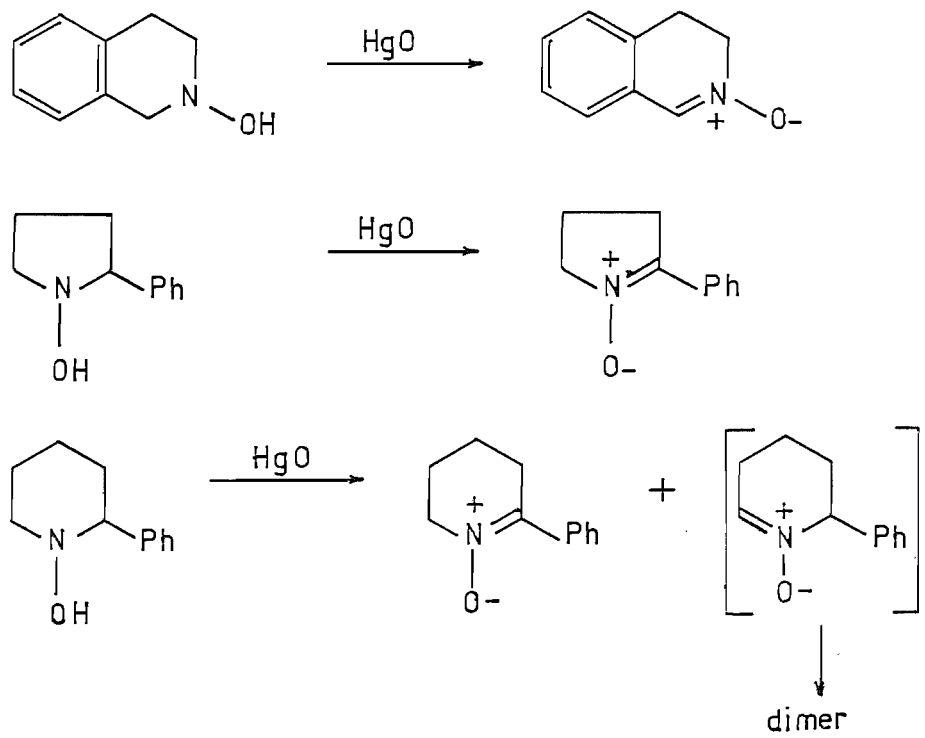
Scheme 2.4

Preparation

A number of methods are available for the formation of nitrones[45]. Of these the two most commonly used are:

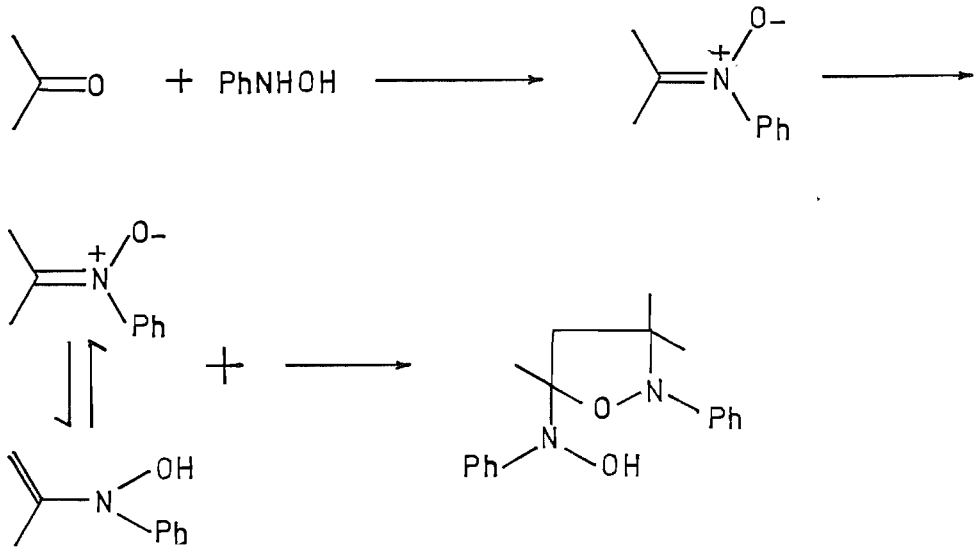
1. Oxidation of an *N,N*-disubstituted hydroxylamine, typically with mercuric oxide;
2. Condensation of an aldehyde with an *N*-substituted hydroxylamine.

The first method works well for systems where one regioisomer is favoured or where the hydroxylamine is symmetrical, but leads to a mixture of regioisomers in the majority of other cases. (Scheme 2.5)[46]. The second procedure is the most commonly used method as the condensation between an aldehyde or ketone and *N*-alkylhydroxylamines takes place very readily. The *N*-alkylhydroxylamines are readily prepared either by the reduction of the corresponding oxime with sodium cyanoborohydride[47] or by reduction of the nitro compound.



Scheme 2.5

With some reactive nitrones dimerisation can present a problem (Scheme 2.6). Four structures were originally assigned to the dimer formed by the condensation of *N*-phenylhydroxylamine and acetone before the structure was unequivocally assigned by X-ray crystallography[48]. From scheme 2.6 it can be seen that dimerisation in fact occurs between a tautomer of the nitrone and itself.

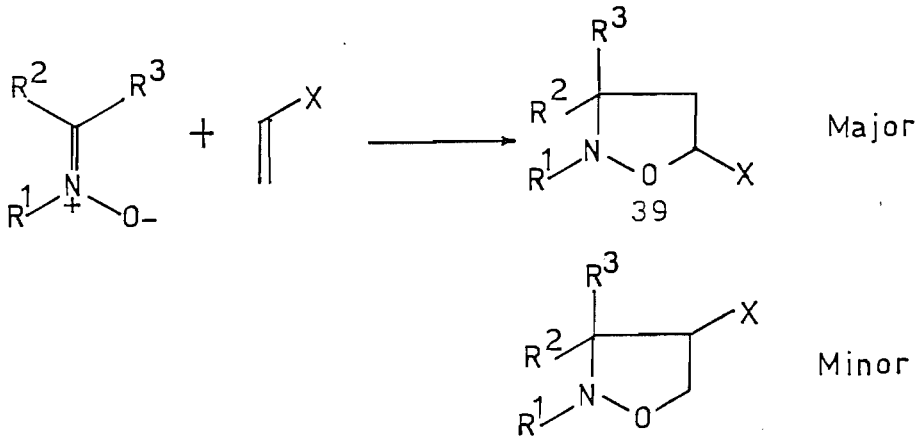


Scheme 2.6

Stereochemistry of Reactions

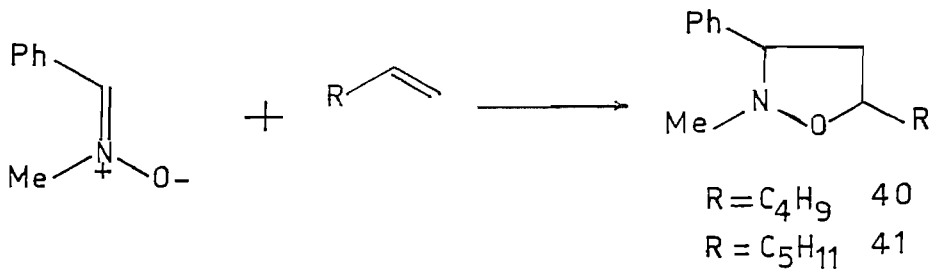
For the nitrone cycloaddition reaction to find use in synthetic organic chemistry it was obviously necessary to be able to predict, with some degree of accuracy, the likely regio and stereochemical outcome of the reaction. A great deal of the early work on nitrone cycloaddition reactions was therefore spent investigating the trends seen in the products formed. A rationalization of these results has come from FMO theory following the work of Houk *et al* in the field of 1,3-dipolar cycloadditions[49] and is presented in due course.

For the purposes of predicting the regiochemical outcome of these reactions the alkene can be classified into one of six main types, nonactivated, electron-deficient, electron-rich, 1,1-disubstituted, 1,2-disubstituted and tri- or tetrasubstituted. For the case of nonactivated alkenes, those where X is alkyl, aryl, vinyl or acetylenic, it was clear from the early investigations that the 5-substituted isoxazolidine(39) was the preferred product. (Scheme 2.7).



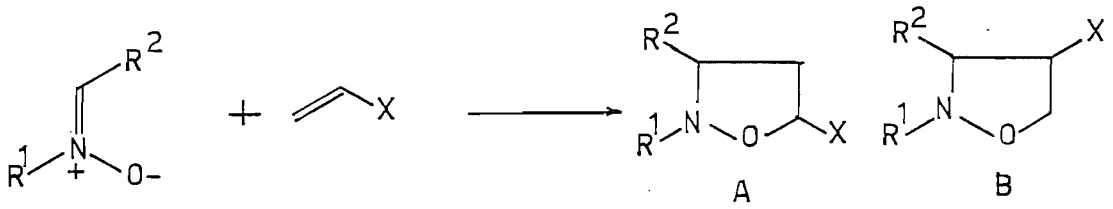
Scheme 2.7

Thus *N*-methyl-*C*-phenyl nitrone reacts with 1-hexene and 1-heptene to give isoxazolidines(40) and (41) respectively in excellent yield[50]. (Scheme 2.8).



Scheme 2.8

When X is an electron withdrawing group the selectivity for 5-substituted isoxazolidines tends to diminish with decreasing electron density on the alkene. This effect can be seen from Table 2.1.[41]

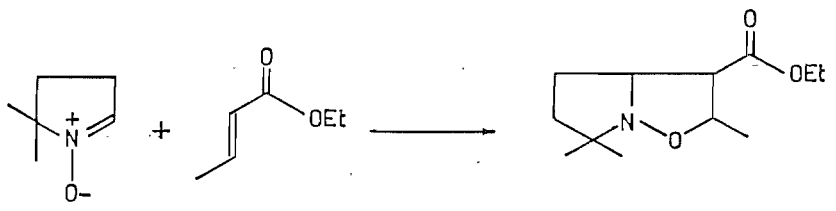


R^1	R^2	X	A/%	B/%
Ph	Ph	Ph	100	0
Ph	Ph	CO_2Me	70	30
Me	Ph	SO_2Ph	32	68
Me	Ph	NO_2	0	100
Ph	Ph	$PO(Ome)_2$	0	100

Table 2.1

Relatively few studies have been done on electron rich alkenes, but for those examples known the 5-substituted isoxazolidine has been the major product.

The regiochemistry observed in the addition of nitrones to disubstituted alkenes follows the same trends as those observed for mono substituted alkenes. Thus non activating 1,1 disubstituted alkenes give rise to the 5,5-disubstituted isoxazolidines whilst 1,1 disubstituted alkenes where both groups are electron withdrawing lead to the 4,4-disubstituted product. In between these extremes a range of ratios is observed, the 5,5-disubstituted product generally being favoured. With 1,2 disubstituted alkenes control is less pronounced, but as might be expected the more electron withdrawing group tends to occupy the 4-position. Hence 5,5-dimethyl-1-pyrroline 1-oxide(42) adds to ethyl crotonate[51] to give one isoxazolidine(43) exclusively (Scheme 2.9).



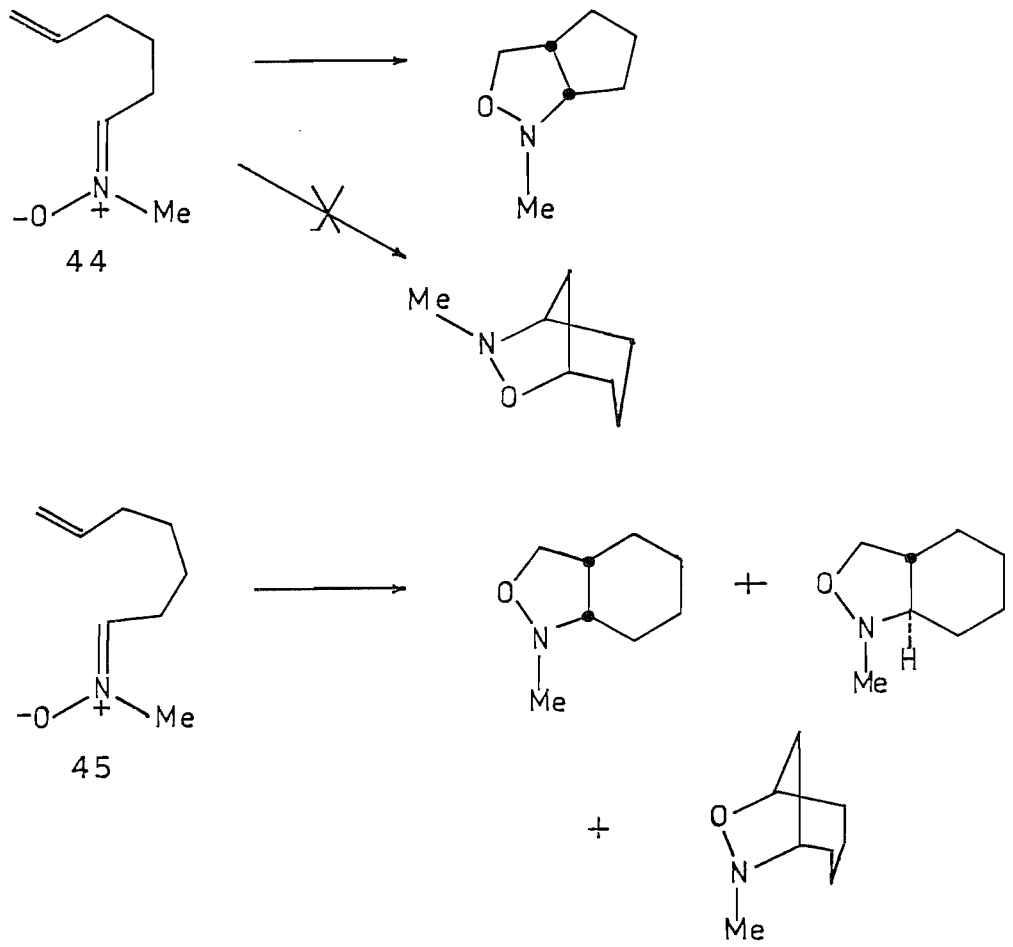
42 43

Scheme 2.9

When tri- and tetrasubstituted alkenes are considered the situation obviously becomes much harder to predict. Despite this electron withdrawing groups continue to show a preference for the 4-position with other groups preferring the 5 position.

Intramolecular cycloaddition reactions

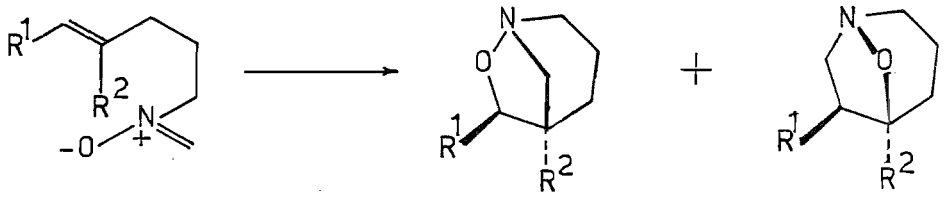
Like the Diels-Alder reaction the nitrone cycloaddition reaction readily occurs intramolecularly. As a consequence of the favourable nature of the entropic factors the intramolecular form of this reaction generally proceeds under milder conditions than is required for the intermolecular case. In certain cases, where the reaction has to pass through a highly strained transition state this is not, however the case. Many of the early investigation into this area of work can be attributed to LeBel and his co-workers[52]. They quickly established the tendency of intramolecular nitrone cycloadditions to give fused rather than bridged structures (Scheme 2.10)[53].



Scheme 2.10

Whilst the *C*-(4-pentenyl) nitrones(44) afford *cis*-fused products exclusively, the *C*-(5-hexenyl) nitrones(45) generally give a mixture of *cis* and *trans* fused adducts. Under conditions of kinetic control the *trans* fused adducts predominate whereas thermodynamic conditions lead to a preponderance of the *cis* adduct. This can be rationalised as a result of the ability of isoxazolidines to undergo a cycloreversion reaction back to the original nitrone at high temperature and hence reach a state of equilibrium where the most stable, thermodynamic product is formed.

The presence of substituents on the double bond effect the regiochemistry in the same way as for intermolecular cycloadditions, the oxygen of the nitrone preferring to bond to the most substituted end of the alkene. The results in Table 2.2 illustrate[54] this preference for *N*-(4-alkenyl) nitrones to give the 5-substituted isoxazolidine.



(46) (47)/% (48)/%

R1	R2		
Me	H	95	0
Ph	H	87	0
H	H	47	23
H	Ph	0	82

Table 2.2

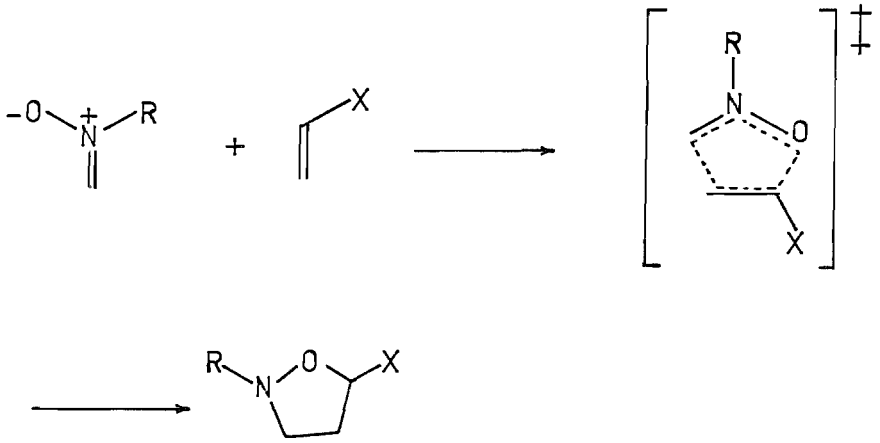
Intramolecular nitrone cycloaddition reactions tend to follow these trends to a much smaller degree than intermolecular reactions. This is due to the greater steric restraints that often exist in the

transition state and are thereby imposed on the products produced in the reaction. The trends seen for both inter- and intramolecular reactions can however be rationalised by considering the mechanistic processes involved in the reaction.

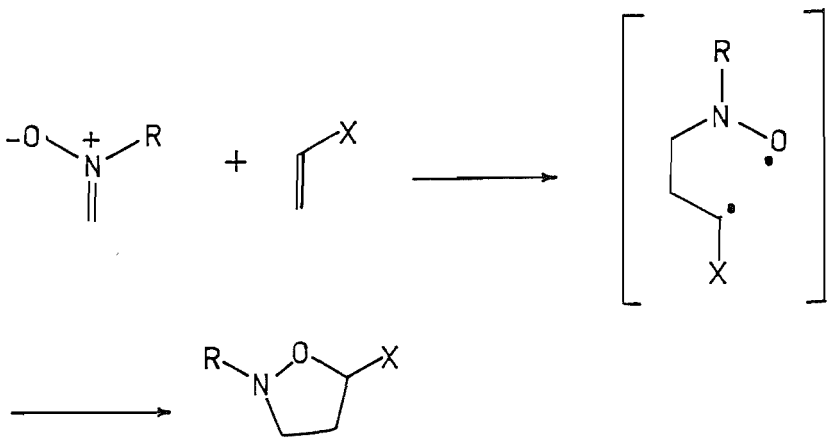
Mechanism

In order to postulate a particular mechanistic explanation for the nitrone cycloaddition reaction it is important to know the observations that have to be rationalised. At present the merits of a concerted mechanism over a stepwise diradical process are a matter of debate[55,56]. The exact details of these contrasting viewpoints will not be discussed here but a summary of the two pathways along with the possible zwitterionic mechanism are illustrated in Scheme 2.11.

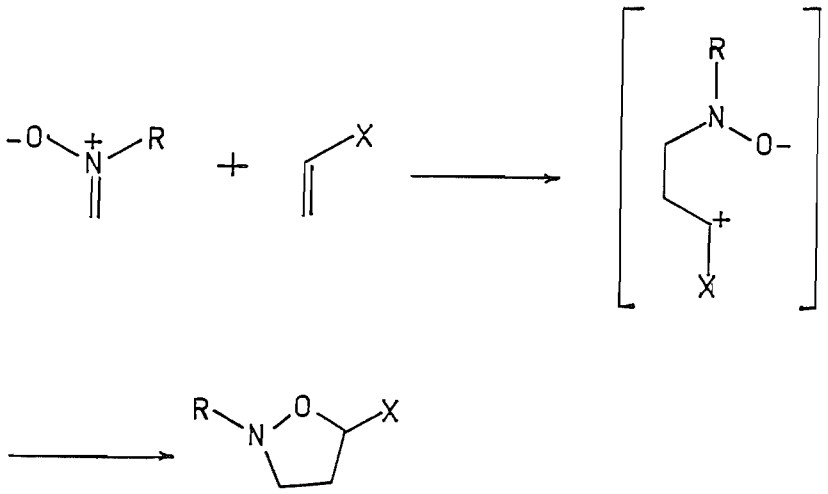
Concerted:



Diradical

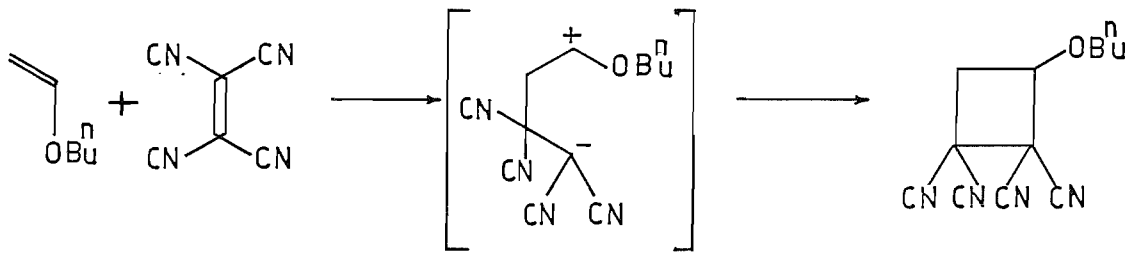


Zwitterionic mechanism



Scheme 2.11

The existence of a zwitterionic intermediate has been discounted due to the lack of any solvent effect on the rate of the nitrone cycloaddition reaction. As an illustration the reaction of *N*-methyl-*C*-phenylnitrone with ethyl acrylate occurs only 2.6 times faster in toluene than in DMSO[57]. In comparison the ratio for the rate of reaction of tetracyanoethylene with *n*-butyl vinyl ether on passing from cyclohexane to acetonitrile is 2600. (Scheme 2.12).



Scheme 2.12

Just as electron donating and electron withdrawing groups on the dipolarophile exerted an effect on the sterochemistry of the product formed, these groups also work to enhance the rate of reaction. What is unusual is that the rate enhancement is seen for either of these types of substituent relative to a simple alkene like 1-heptene. Table 2.3 compares the rate of reaction of a number of

dipolarophiles[55,58] with *N*-methyl-*C*-phenylnitrone(49) in toluene at 120°C. Electron withdrawing groups enhence the rate to the greatest extent. However steric crowding of the transition state, by the addition of alkyl groups (as in the case of ethyl trimethylacrylate) acts to greatly retard the reaction rate. Electron donating groups also enhance the reaction rate, but to a much smaller extent. These results have been rationalised by the diradical mechanism on the grounds that both electron-donating and electron-withdrawing groups can stabilise the radical intermediates formed in the transition states.

Dipolarophile	K_{rel}
Methyl acrylate	145
Acrylonitrile	106
Allyl acetate	2.7
1-Heptene	1.00
Methyl vinyl ether	2.8
Methyl methacrylate	49
Ethyl trimethylacrylate	0.04
Maleic anhydride	2523
Diethyl maleate	86
Diethyl fumarate	229
Styrene	4.4
p-Nitrostyrene	19
Methyl Propiolate	576

Table 2.3

Frontier Molecular Orbital Theory

An explanation for the observed facts has come from the application of FMO theory to the nitrone cycloaddition reaction. Cycloaddition reactions have been classified into 3 basic types by Sustmann[59], as illustrated in diagram 2.1.

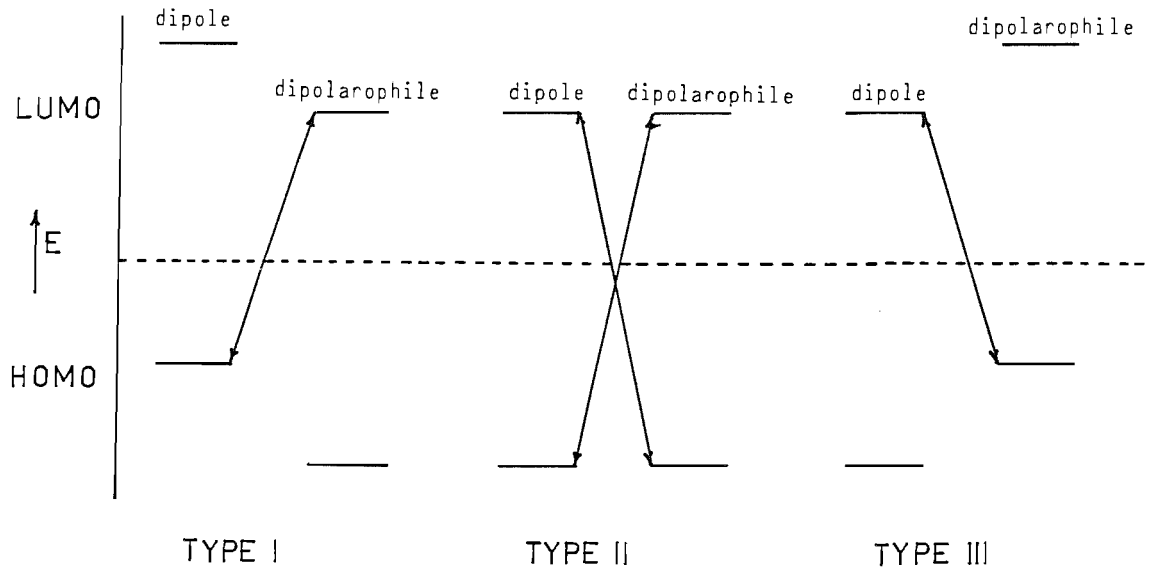


Diagram 2.1

For a type I process the dominant interaction comes from the dipole HOMO and the dipolarophile LUMO. In a type III process the case is reversed and the dominant interaction is that between the dipole LUMO and the dipolarophile HOMO. This is the situation generally seen for the ozonization of an alkene. In the final class, a type II process, the interaction of the dipole LUMO with the dipolarophile HOMO and the dipole HOMO, dipolarophile LUMO interaction both play an important part in the reaction.

Second order perterbation theory states that the stabilisation of the HOMO as the two species interact is inversely proportional to the difference in energy between the HOMO of one species and LUMO of the other. Hence, as nitrone cycloadditions are thought to be type II processes, the interaction that takes place will depend on the relative energies of the HOMO's and LUMO's on both the nitrone and the alkene. The dominant interaction for the reaction of *N*-methyl-*C*-phenylnitrone(49) with a number of alkenes is illustrated in diagram 2.2, based on measurements of the energies of the HOMO's and LUMO's in each case.

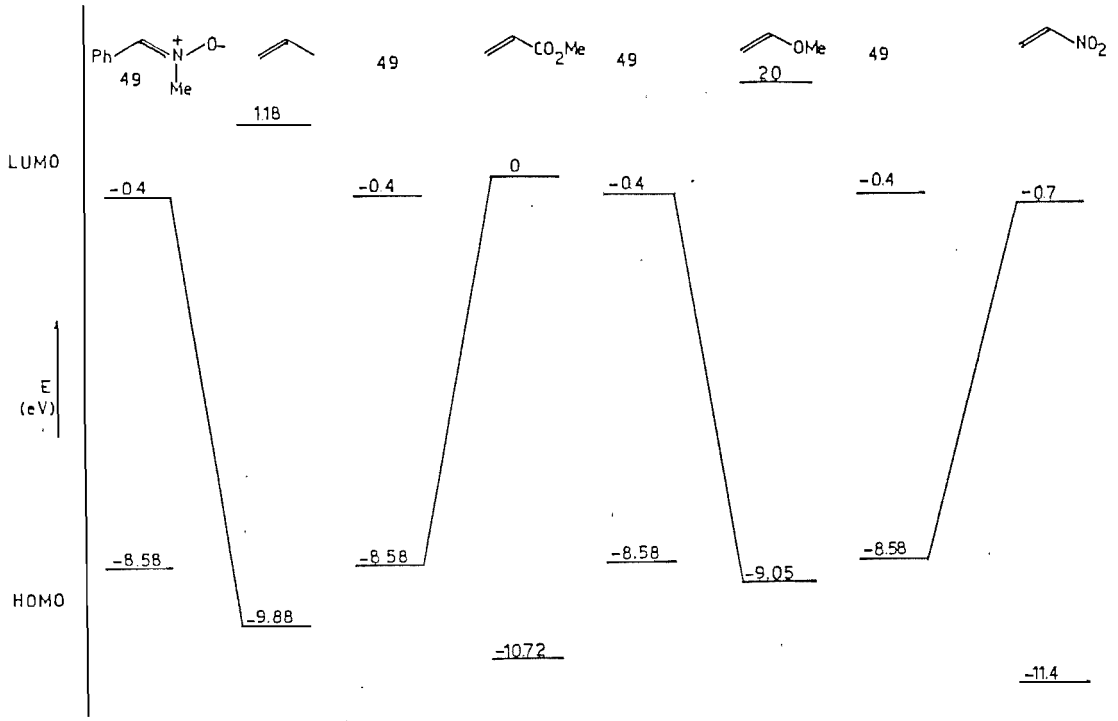


Diagram 2.2

It can be seen from this that the interaction will be strongest for reaction with nitroethylene and weakest for propene, this is borne out in their relative rates of reactions. It is also clear that for the case of an electron deficient alkene the reaction goes via a dipole HOMO-dipolarophile LUMO process whilst for the electron rich alkene the reverse is true.

To see how this might effect the regiochemical course of these reactions it is necessary to consider the coefficients of the various atomic orbitals that participate in the reactions. The dominant interaction will be between the largest atomic orbitals on each of the alkene and the nitrone. Diagram 2.3 summarises these interaction, and illustrates their effect on regiochemistry for the two cases of electron rich and electron poor alkenes.

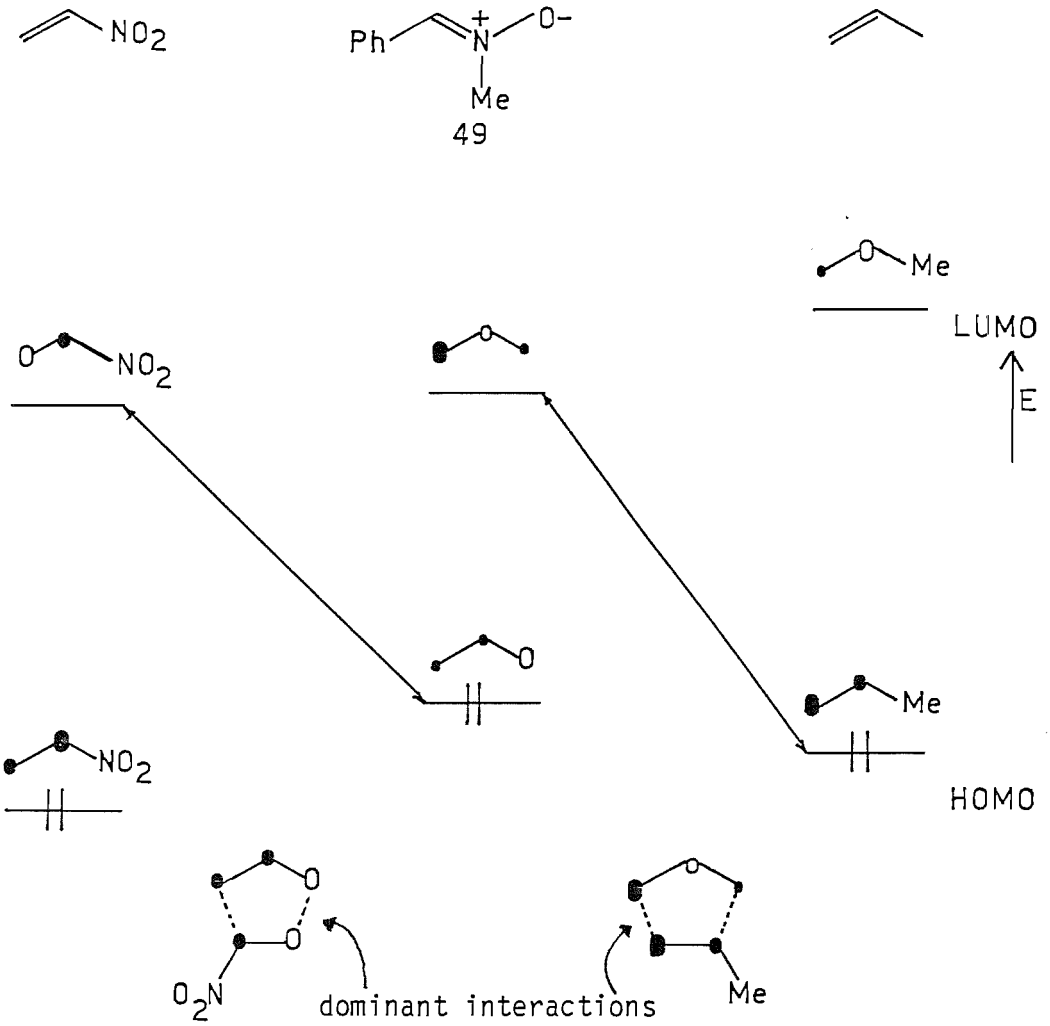


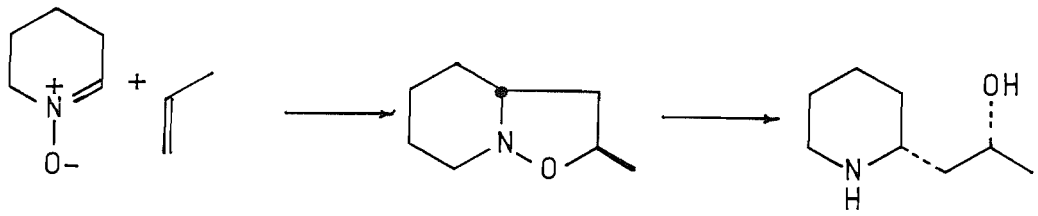
Diagram 2.3

Thus it can be seen that the products predicted by this application of FMO theory are in excellent agreement with the experimental observations. At some point the two extreme cases can be expected to cross over. This point is apparently approached for the cases of ester, keto and cyano groups. With these compounds mixtures of 4- and 5-substituted isoxazolidines are often isolated.

Sadly none of these factors can be expected to shed any light on the likely products to be gained from the cycloaddition reaction proposed in the course of our work. In our case steric factors are likely to be the dominant forces on the reaction since the alkene is disubstituted with similar groups at each terminus and there is no possibility of secondary orbital interactions effecting the stability of the transition state.

Applications of Nitrone Cycloaddition Reactions

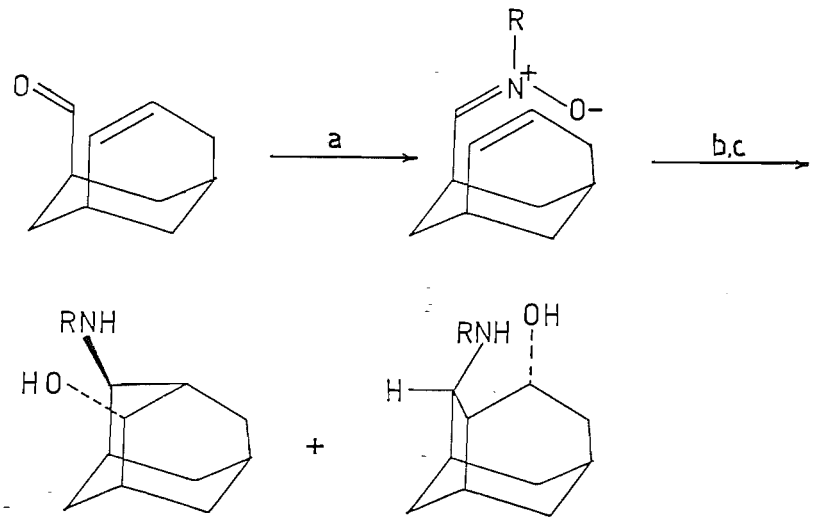
The recent advances in the understanding of the mechanisms of nitrone cycloaddition reactions has led to an enhanced activity in applications of this reaction. The ability of this transformation to form a carbon-carbon bond and a carbon-oxygen bond in the presence of a carbon-nitrogen bond has lent it particularly to use in the field of alkaloid synthesis. In a simple example *dl*-sedridine(50) was synthesised[60] in just two steps with full regiochemical and stereochemical control (Scheme 2.13).



Scheme 2.13

50

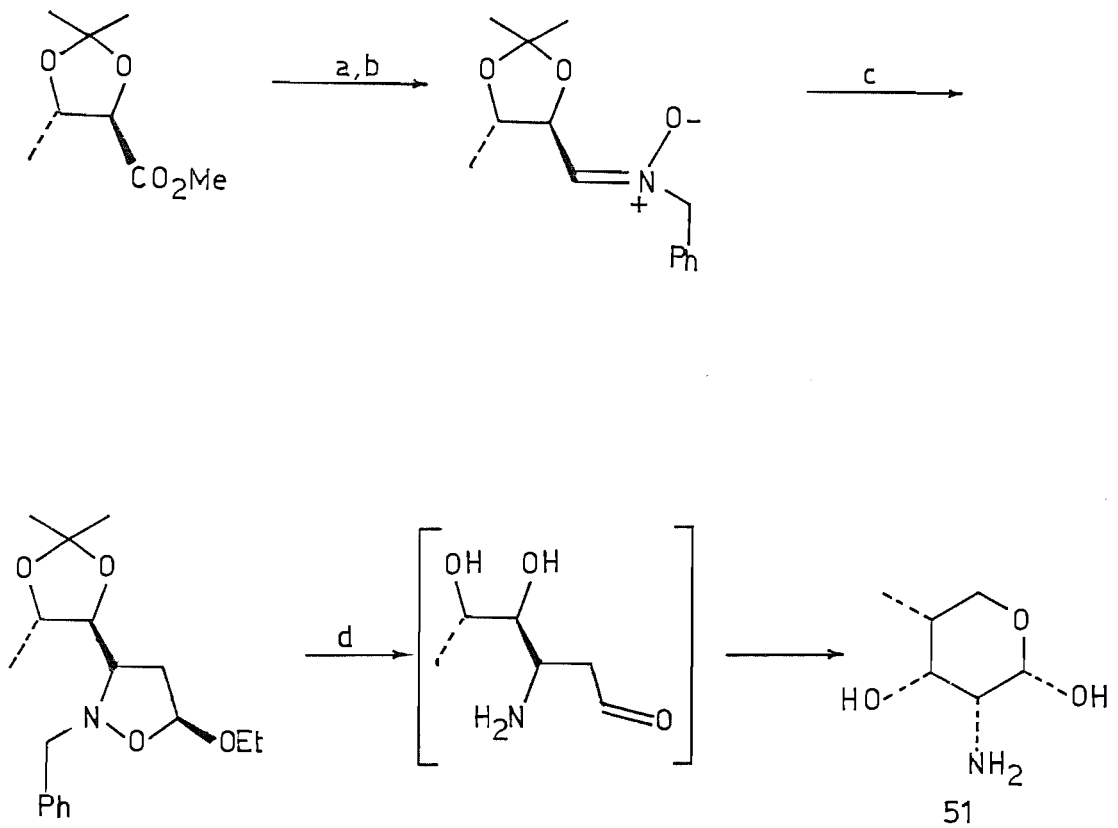
More elaborate schemes incorporating a nitrone cycloaddition reaction have appeared across a wide range of differing types of natural and unnatural products. T. Sasaki[61] *et al* have used the nitrone cycloaddition reaction to give a number of adamantane derivatives (Scheme 2.14).

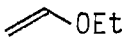


a RNHOH b Δ c H_2, Cat.

Scheme 2.14

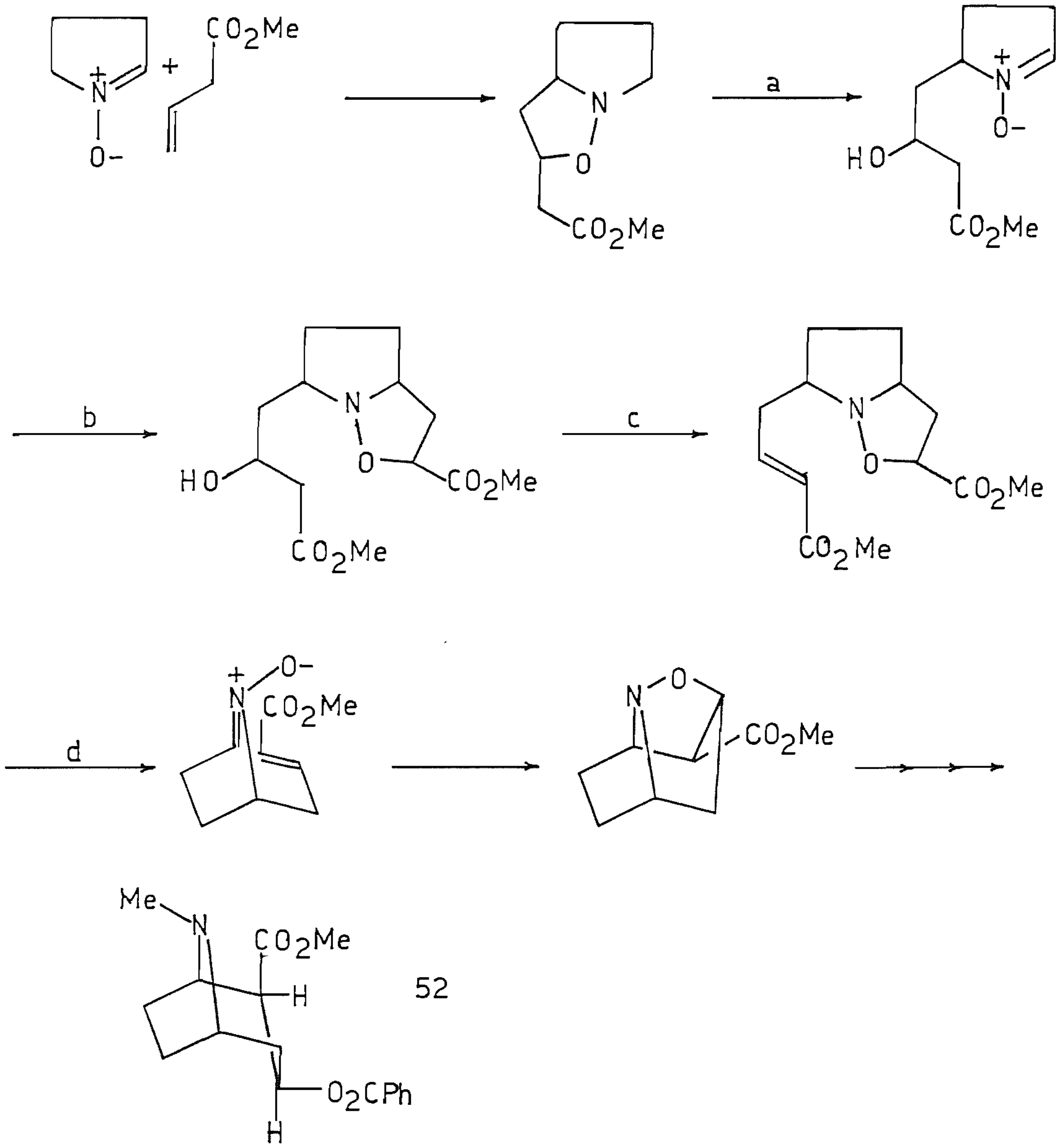
By starting with chiral materials DeShong[62] *et al* have been able to produce amino sugars synthetically by the use of nitrone cycloaddition reactions. This chemistry is illustrated for the synthesis of daunosamine(51) in Scheme 2.15.



a DIBAL b $PhCH_2NHOH$ c  d H_2Cat,HCl

Scheme 2.15

Tufariello[63] has utilised a number of the attributes of nitrone cycloaddition addition chemistry in his synthesis of *dl*-cocaine(52) (Scheme 2.16). In this work he makes use of three separate nitrone cycloaddition reactions and a retro-nitrone reaction to give the tropane required for functionalisation through to the natural product.



52

a *m*CPBA b $CH_2=CH-CO_2Me$ c dehydration d Δ

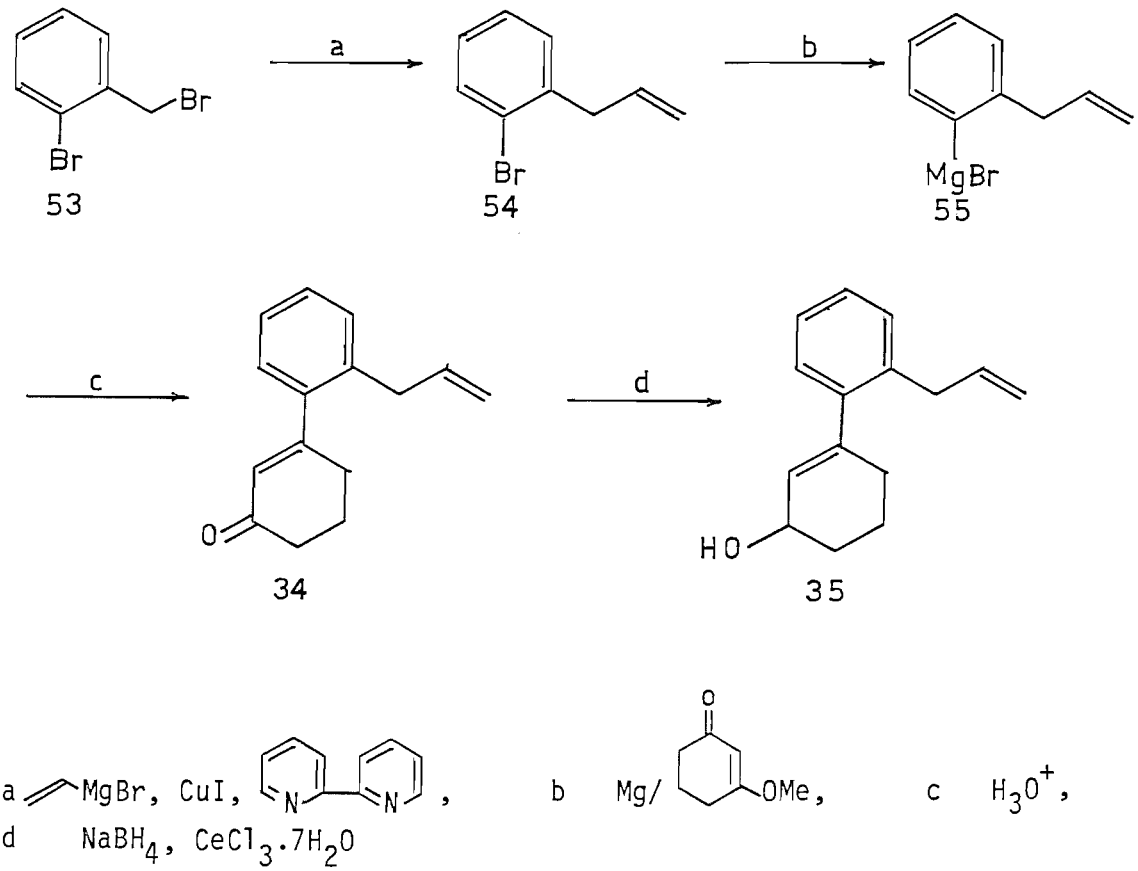
Scheme 2.16

A whole range of other natural products have similarly been produced using the nitrone cycloaddition and a number of these have been extensively reviewed[41] elsewhere.

2.4 Results and Discussion on the Model Study

The work carried out by Parsons and Chandler[64] on the model study is presented below. Some of the problems which they encountered and their eventual solutions are discussed, resulting in production of the desired morphinan framework.

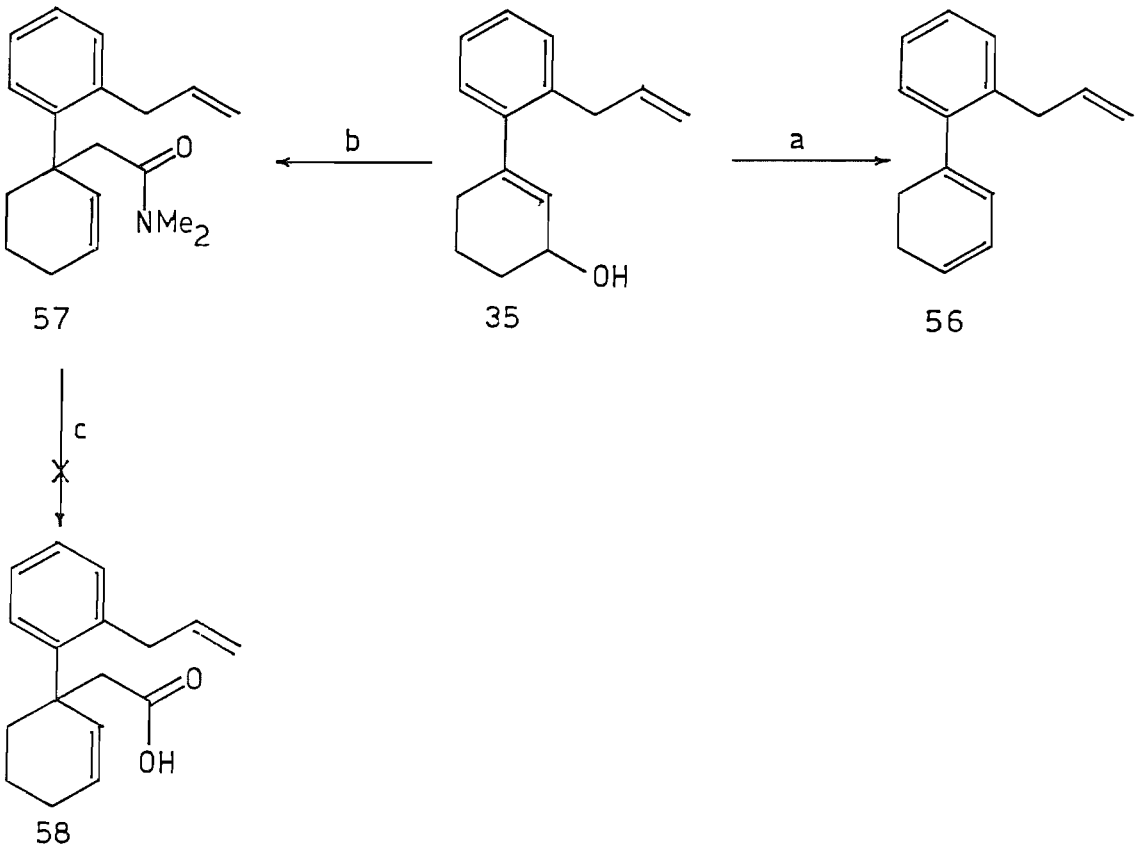
The first task to be tackled in the model work was the coupling of the aromatic ring with what would ultimately be the C ring in a morphinan structure. This was accomplished by formation of a Grignard reagent(55) in THF and treating it with 3-methoxycyclohex-2-enone. Hydrolysis of the resulting alcohol lead to the required enone system(34). The bromide(54) required for formation of the Grignard, was made in one step by treating commercially available *o*-bromobenzyl bromide(53) with vinylmagnesium bromide in the presence of equal quantities of catalytic amounts of copper (I) iodide and 2,2'-dipyridyl in THF. In this manner 1-(2-bromophenyl)-prop-2-ene(54) was produced in up to 65% yield (Scheme 2.17).



Scheme 2.17

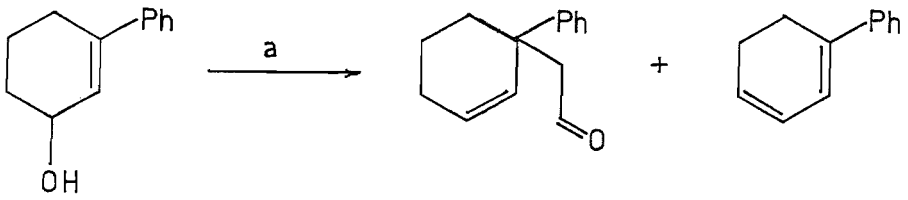
Reduction of the enone(34) with sodium borohydride in THF/water was performed in the presence of cerium (III) chloride[65], to prevent 1,4-reduction, and gave the allylic alcohol(35) in quantitative yield.

Attempts to affect the Claisen rearrangement (Scheme 2.18) with ethyl vinyl ether failed completely under various conditions, the only product isolated was the diene(56). Interestingly when the Claisen rearrangement was attempted with the simple aromatic analogue(59) at 120°C the expected aldehyde(60) was formed in 70% yield, with the diene(61) being formed in only 30%. However when the temperature was raised to 180°C the yield of the aldehyde(60) fell to only 10% and 90% of the diene(61) was produced. Presumably the added steric restraints imposed by the allyl group must be making the loss of acetaldehyde more favourable(57). When an Ireland-Claisen[66] reaction procedure was attempted a large mixture of identified products only were isolated. Similarly a Johnson-Claisen[67] reaction procedure was attempted with triethyl orthoacetate and also led to a mixture of products. Fortunately when Eschenmoser's Claisen[68] procedure was studied by heating the alcohol in toluene at reflux with *N,N*-dimethylacetamide dimethyl acetal the required amide(57) was formed in 60% yield.



57 35 56

58



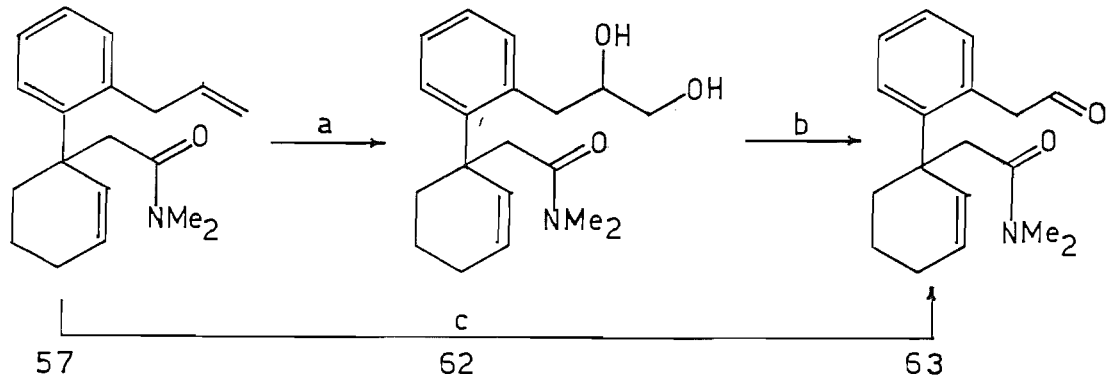
59 60 61

a ⟋OEt, b MeO OMe, NMe$_2$, Δ, c KOH

Scheme 2.18

Treatment of the amide(57) with aqueous hydroxide failed to give the desired carboxylic acid(58). They then decided to cleave the double bond in the allyl group to the aldehyde required for the nitrone addition.

The amide(57) was therefore treated with one equivalent of a standardised solution of ozone in dichloromethane at -95°C. Reductive work up gave the desired aldehyde(63), but only in 53% yield. To try to improve this yield alternative oxidation procedures were investigated. The use of osmium tetroxide and sodium periodate in THF/water/acetic acid resulted in only a 30% yield of the aldehyde(63). However when the oxidation was performed in two steps, by oxidizing to the diol(62) with osmium tetroxide and trimethylamine-*N*-oxide and then cleaving the resulting diol(62) with sodium periodate in acetic acid a quantitative yield of the aldehyde(63) was obtained. This may be rationalised in terms of the osmium tetroxide step proceeding very slowly and the periodate cleavage occurring quickly. Hence, as the aldehyde(63) is not very stable, it tends to decompose during the course of the reaction if both steps are performed together. When they are conducted separately the aldehyde is in acidic solution only for the time it takes the periodate reaction to go to completion (approximately 30 min.) and not the length of time taken by the osmium tetroxide reaction (approximately 24 h) to reach completion.



a OsO_4/Me_3NO b $NaIO_4$, H+ c O_3

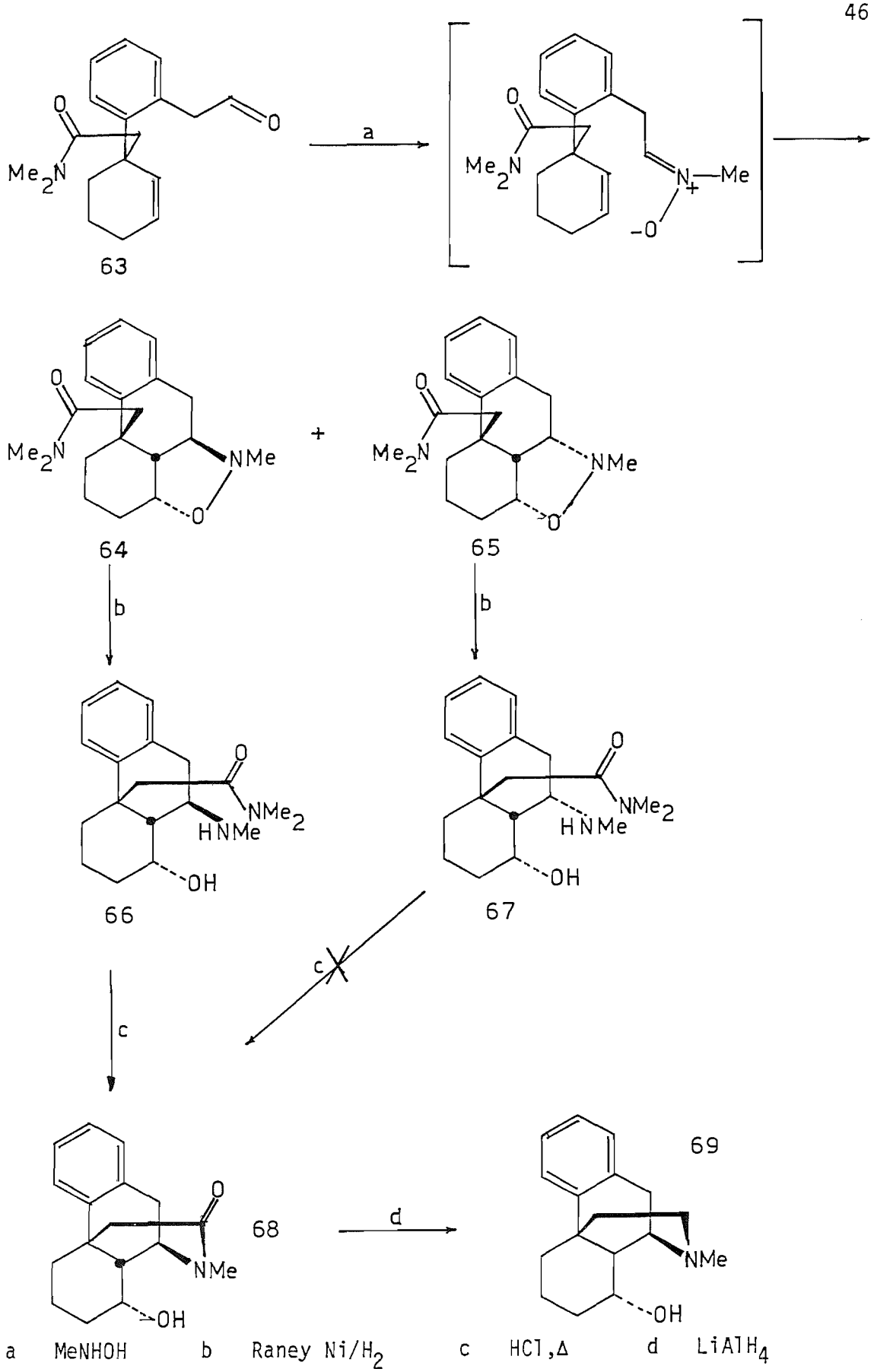
Scheme 2.19

With aldehyde(63) in hand Parsons and Chandler turned their attention to the crucial nitrone cycloaddition reaction. This was carried out by simply adding excess *N*-methylhydroxylamine to a boiling solution of the aldehyde(63) in benzene, in the presence of 4A molecular sieves. From this two compounds were isolated, corresponding to the two possible adducts formed through *exo*(64) and *endo*(65) addition, in a 1:1 ratio. (Scheme 2.20).

Although it was not possible to tell which isomer was required by n.m.r spectroscopy, it was reasoned that as only one product would cyclise to give a morphinan skeleton it should be possible to identify the correct isomer after only two further steps.

Reduction of both isomers using Raney nickel in acetic acid under an atmosphere of hydrogen at 3.1 bar proceeded smoothly to give the expected amino alcohols(66) and (67). After some experimentation it was found that one isomer was converted to the desired morphinan(68) simply by heating its anhydrous hydrochloride salt to approximately 180°C, causing it to melt and dimethylamine hydrochloride to sublime out of the flask. Treatment of the resulting lactam(68) with lithium aluminium hydride in boiling THF then gave the simple 8-hydroxy morphinan(69) (Scheme 2.21).

Once the correct isomer had been identified it was reasoned that by changing the reaction conditions a better yield of the desired adduct might be obtained. Sadly this was not found to be possible as, whilst reducing the temperature increased the yield of the unwanted *endo* adduct(65), increasing the temperature gave rise to a lower yield through decomposition of the aldehyde(63).



Scheme 2.20

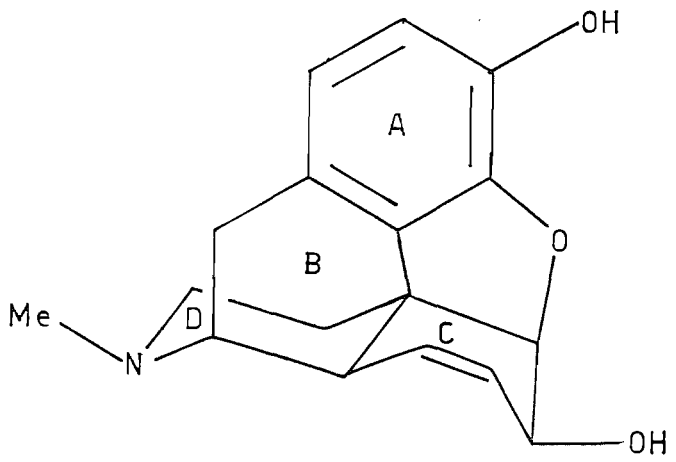
2.5 Conclusions from the Model Study

The model study illustrated that the proposed route to morphine was viable and helped to indicate where problems could occur if the route were to be developed to a total synthesis. Although the yield of the correct isomer from the nitrone cycloaddition reaction was rather disappointing, it was still obtained in a workable yield and there was hope that the slightly different steric features which would be encountered in a full synthesis could possibly tilt the isomer ratio in favour of the desired adduct.

CHAPTER THREE

3.1 Introduction

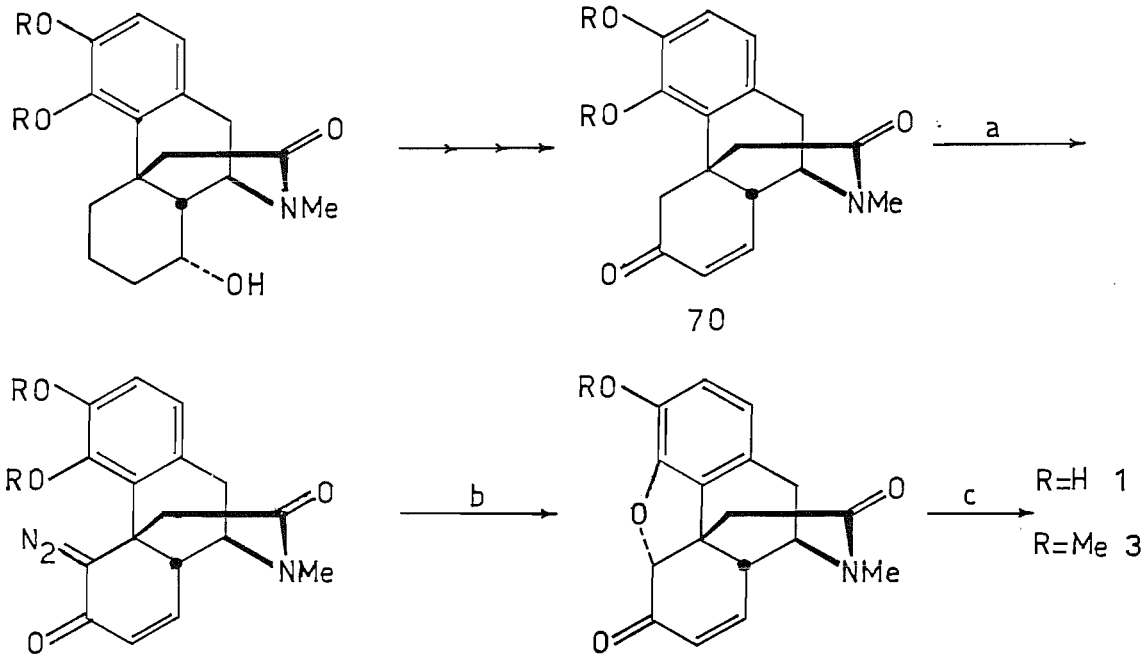
The principle difference between the model study and our proposed total synthesis was in the substitution pattern of the aromatic ring. To enable the phenol moiety and furan ring to be incorporated it was necessary to start in the first instance with a protected catechol functionality, this could then be released in the final stages of the synthesis and developed into morphine. The protecting group would need to be stable to the majority of commonly encountered experimental conditions and yet easily removed at the appropriate time. Another consideration to be taken into account was the size of the phenolic protecting groups. As the Claisen rearrangement had been shown in the model studies to be particularly sensitive to substituents on the aromatic ring, it was reasoned that a large protecting group might give an increased yield of the unwanted diene side product. With these factors in mind, and availability of starting materials, the two most promising candidates were either a dimethoxy protected catechol or a methylenedioxy group. Although there has been a greater volume of literature already published on the dimethoxy morphinans, the methylenedioxy group seemed likely to be less sterically demanding, and initially appeared to have advantages in the proposed early steps of the work. The majority of the work presented has been carried out with the methylenedioxy protecting group.



1

Scheme 3.1

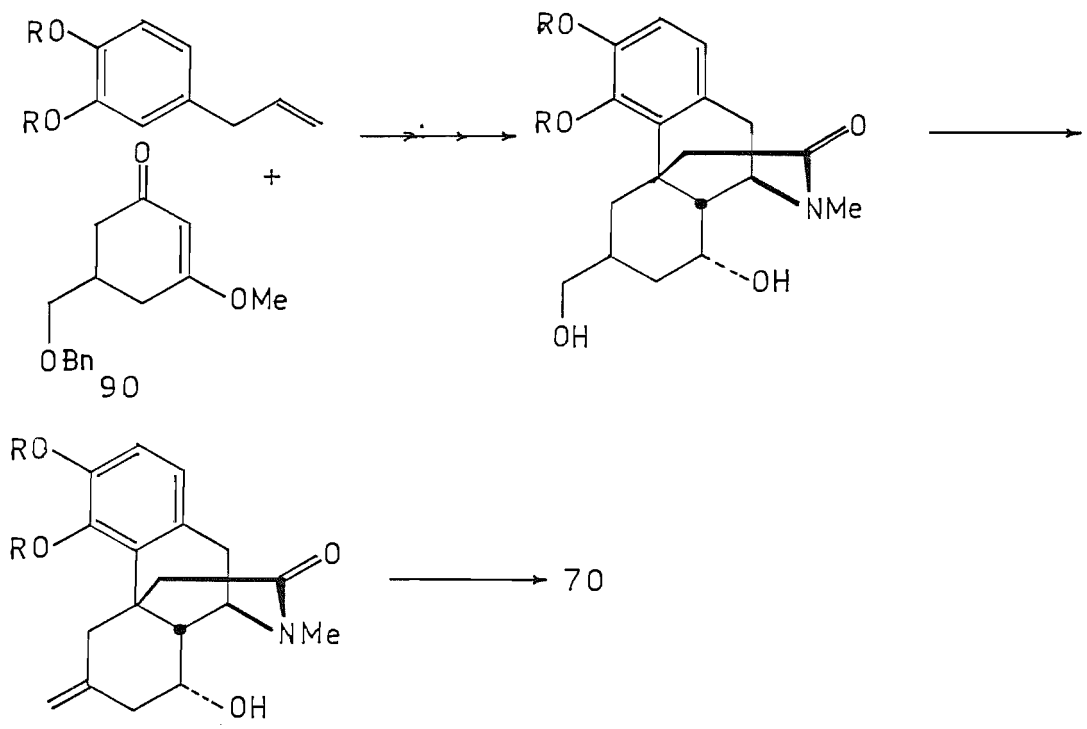
To develop the model study into a total synthesis of morphine it was also necessary to consider the options available for producing the required functionality in the C ring of the natural product. (Scheme 3.1). Two strategies were investigated during the course of our work. The first involved attempting to use the alcohol functionality produced from cleavage of the isoxazolidine ring as a handle for elaboration to an enone(70). This could then be used to form the ether linkage. (Scheme 3.2).



a TsN_3 b $Rh(OAc)_2$ c $LiAlH_4$

Scheme 3.2

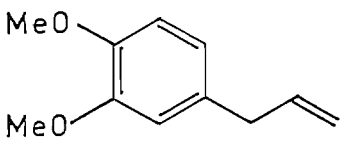
The second strategy aimed to prevent potential problems in the later stages of the synthesis by incorporating a substituent into what would become ring C of morphine. This could then be converted by standard chemistry, when required, to give the enone(70) needed to complete the synthesis. The substituent chosen for this purpose was a methyl alcohol group protected as its benzyl ether. Therefore the substituted methoxycyclohexenone(90) shown was required for coupling to the aromatic moiety to give the correct substitution pattern (Scheme 3.3). The details of the construction of this enone(90) will be discussed later.



Scheme 3.3

3.2 Approaches to the Aromatic Moiety

The first task in our proposed total synthesis was the production and coupling of the aromatic portion with what would become the C ring. To produce the required aromatic it was initially hoped that a method could be found whereby either eugenol methyl ether(71) or safrole(72) could be functionalised at the 2 position to give an organometallic analogue of the Grignard reagent(55) used in the model series.



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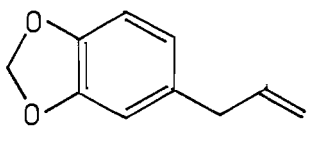
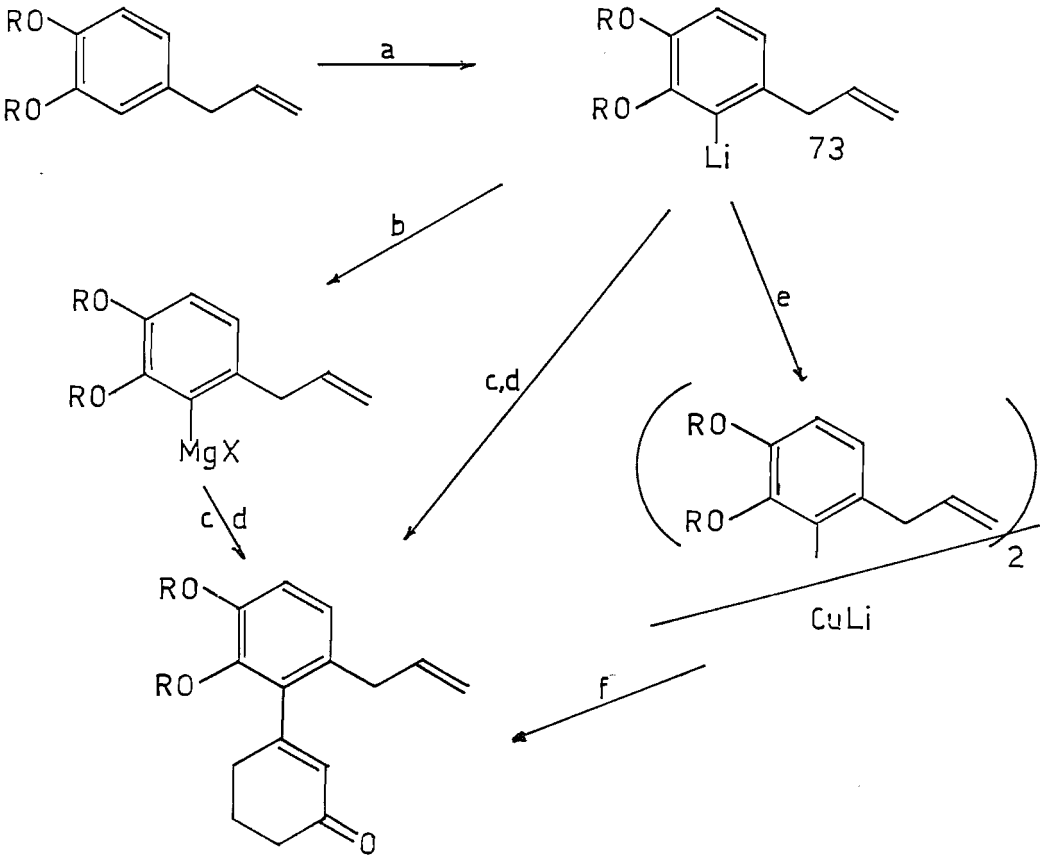


72

The process used to attempt this transformation was an orthometalation procedure using a lithium alkyl in various solvents or solvent mixtures. The resulting lithium aryl could then be quenched by the addition of iodine such that the Grignard reagent could be formed in two steps. Similarly the lithium aryl could be treated

directly with a magnesium halide to give the Grignard reagent *in situ* and then treated with 3-methoxycyclohex-2-enone to go straight through to the final product. Alternatively a copper (I) salt could be added and the resulting cuprate reacted with 3-chlorocyclohex-2-enone to again give the final product, by way of an addition-elimination process (Scheme 3.4).

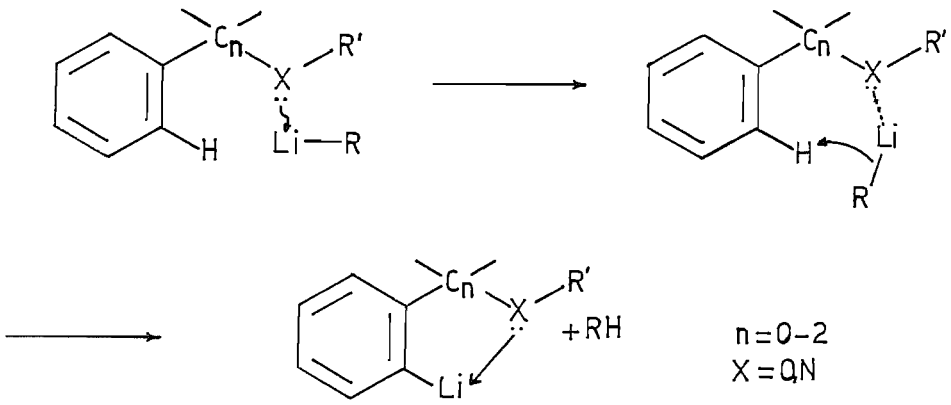


Scheme 3.4

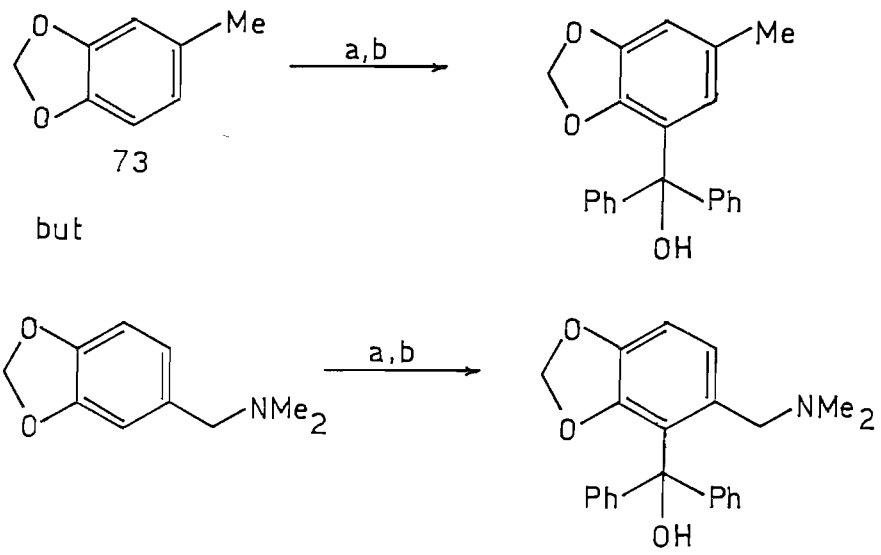
The Grignard reagent may have certain advantages over the more basic lithium aryl by favouring nucleophilic addition to 3-methoxycyclohex-2-enone over deprotonation of it.

Metalation reactions are well documented in the literature[69] and many examples are known, especially with aromatic systems. Their greatest attribute is generally their high degree of regioselectivity in attack on the aromatic ring. This often occurs at completely different positions from more conventional electrophilic attack. The basis for this regiochemical control stems from the initial approach

of the lithium alkyl reagents. It is generally believed that, in the absence of complexing agents like TMEDA, the lithium ion will coordinate with oxygen or nitrogen substituents, via their lone pairs, and so lead the base into specific positions on the ring, (Scheme 3.5). In this way attack is directed at one position preferentially. Other substituents can exert a steric influence on the site of attack, as seen in the case of 5-methyl 1,3 benzodioxole[70](73) (Scheme 3.6).



Scheme 3.5

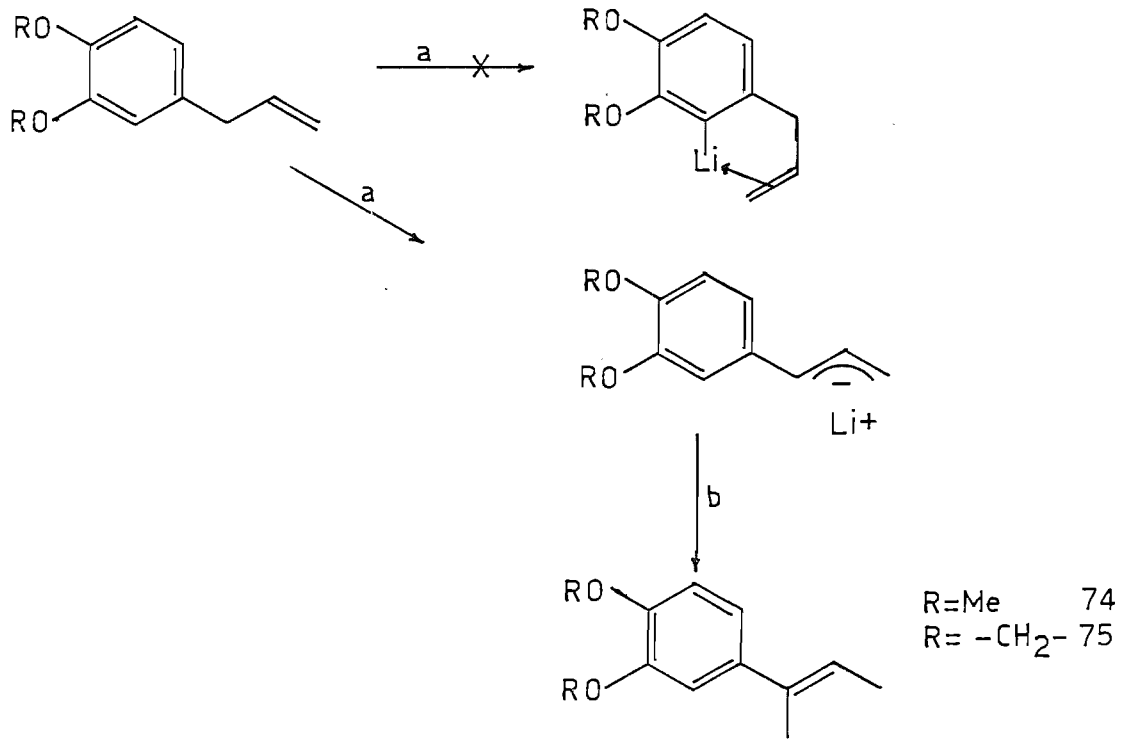


a *n*-BuLi b Ph_2CO

Scheme 3.6

The addition of an agent which can complex with the lithium ion has been shown to greatly enhance the reactivity of alkyl lithium reagents. Thus, whilst the deprotonation of benzene with *n*-butyllithium in hexane at 25°C is negligible over 3 hours, the addition of TMEDA allows the reaction to go to completion in 3 hours at this temperature. The function of the TMEDA is to depolymerise the normally hexameric[71] *n*-butyllithium aggregate in hexane to a monomer. The resulting smaller species can then attack the substrate more rapidly. Analogously the choice of solvent can effect the reactivity of the alkyl lithium. *n*-Butyllithium has been shown to be dimeric in THF[72] and tetrameric in ether[71], this being reflected by its generally greater reactivity in the former solvent.

With these factors in mind it was hoped that the π electrons on the double bond in either safrole(72) or eugenol methyl ether(71) might coordinate with the lithium ion along with the lone pair of electrons on oxygen and so lead attack of the alkyl lithium on to the desired position (Scheme 3.7).



a *n*-BuLi b MeI

Scheme 3.7

This notion proved unfounded as none of the desired product could be produced. The conditions used and results that were obtained are summarised in Table 3.1. The problem appears to be one of deprotonation at the benzyl position in preference to the aromatic ring, or deprotonation of the methylene acetal[73], leading to decomposition in the case of safrole(72). The studies carried out on eugenol methyl ether(71) were similarly unsuccessful.

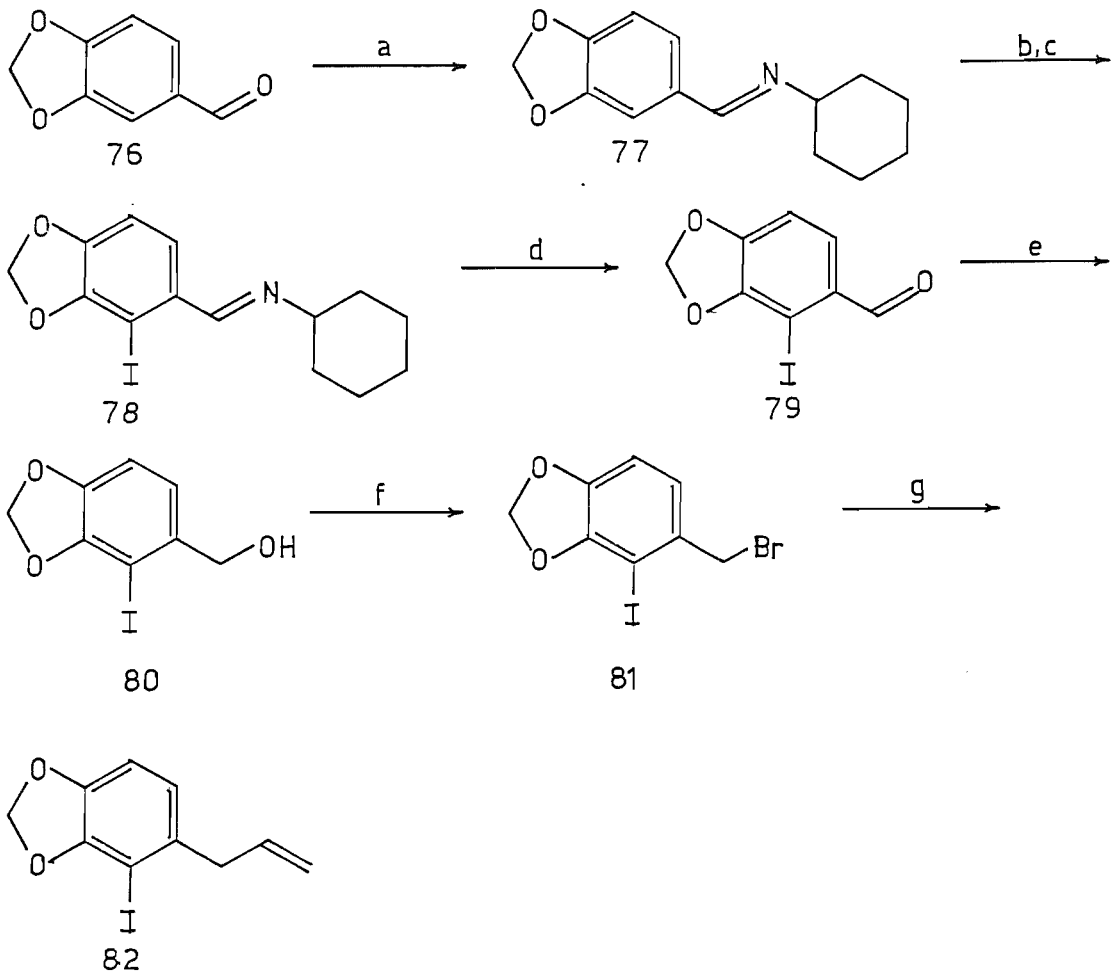
R^1,R^2	Solvent	Temp/°C	RLi	Time/h	Product
$-CH_2-$	THF	-78	*n*-Bu	2	Starting material
"	Ether	0	*n*-Bu	2	" "
"	*n*-Pentane	35	*n*-Bu	4	" "
"	THF	-78	Me	2	" "
"	THF+TMEDA	-78	*n*-Bu	2	" "
"	Ether	20	*n*-Bu	48	Tar
"	THF+HMPA	-78	*n*-Bu	2	(75)
"	THF+$KOBu^t$	-78	*n*-Bu	2	Tar
"	THF	-78	*t*-Bu	2	Starting material
"	Ether	20	*t*-Bu	2	" "
Me	THF	-78	*n*-Bu	1	" "
Me	THF	-30	*n*-Bu	1	" "
Me	Ether	20	*n*-Bu	2.5	(74)
Me	THF+TMEDA	0	*n*-Bu	2	(74)
Me	Hexane	20	*n*-Bu	1	(74)

Table 3.1

Methyl iodide was used to quench these reactions such that interpretation of the n.m.r. spectra obtained from the products was straightforward. The more usual electrophile for investigating these reactions, deuterium oxide, was not considered suitable as the aromatic protons in both eugenol methyl ether(71) and safrole(72) appear as a clean singlet at 60MHz.

To circumvent these initial problems we decided to try the metalation on a more reactive aromatic species and trap the resulting anion with iodine. The allyl group could then be formed from a

suitable precursor and the anion regenerated as a Grignard reagent with magnesium. A survey of the literature revealed that piperonal(76) had been converted to its cyclohexylimine(77). Metalation[74] of this followed by treatment with iodine had given incorporation of iodine onto the aromatic ring in the desired position. We hoped that after hydrolysis, the resulting aldehyde(79) could be taken through to the required aromatic(82) using the route outlined in Scheme 3.8.



a $\bigcirc$-NH_2, $-H_2O$. b *n*-BuLi. c I_2 d H_3O^+.

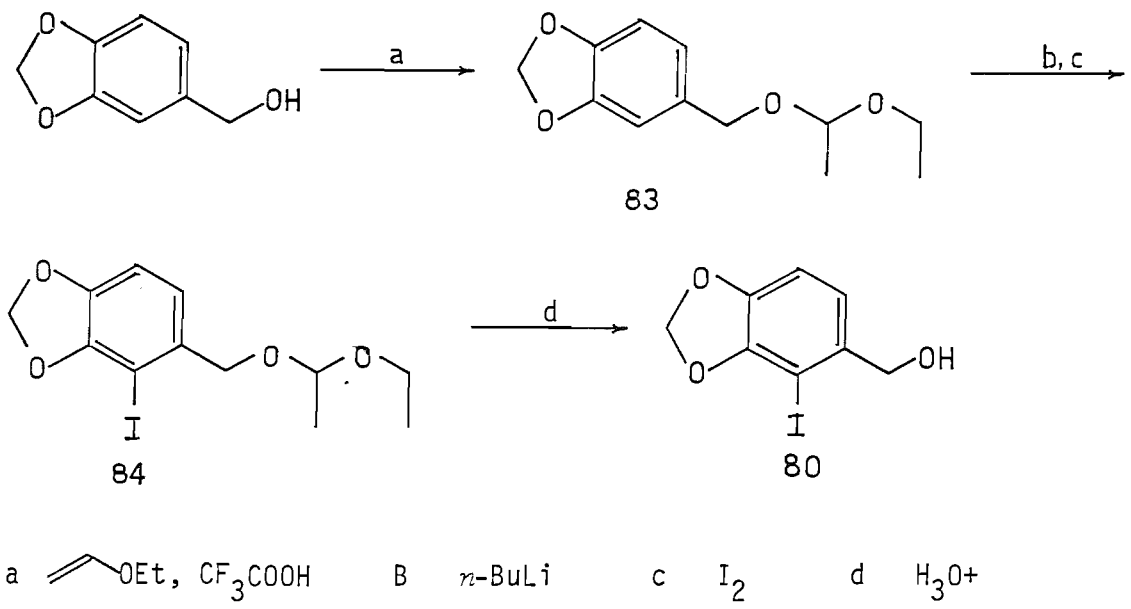
e $NaBH_4$. f PBr_3. g $\nearrow$MgBr, CuI, 2,2'dipyridyl.

Scheme 3.8

Consequently the aldehyde(79) was produced using the method described by Ziegler and Fowler[74] and reduced with sodium borohydride

to give the expected alcohol(80) in 85% yield. This was brominated with phosphorus tribromide in dichloromethane to give the bromide(81) in 91% yield. Coupling of this with vinylmagnesium bromide using copper (I) iodide and 2,2'-dipyridyl as catalysts proceeded more smoothly than for the model study, where the reaction was sometimes dangerously exothermic, to yield the desired aromatic system(82) in an overall yield of 20%. Whilst a 20% yield was quite satisfactory for producing the aromatic moiety in the early stages of our work, as the synthesis progressed it became increasingly desirable to produce large quantities of this material. To this end a number of variations on the synthesis were considered, in the hope of reducing the number of steps and thereby decreasing the man-hours required to make the aromatic intermediate(82).

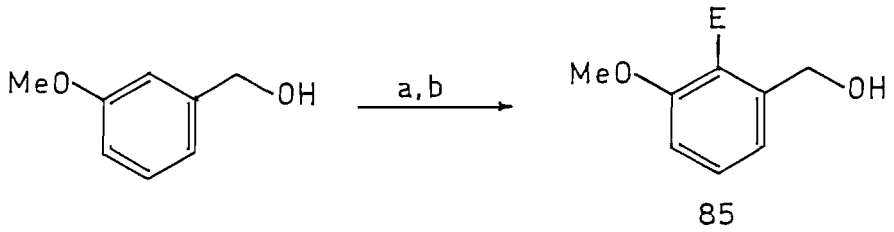
Initial hope that improvements would be possible came from the publication of work by Napolitano *et al*[75] on the orthometalation of the ethoxyethyl acetal of 3,4-methylenedioxy benzyl alcohol(83). Although in their work the anion was trapped with carbon dioxide or ethyl chloroformate it seemed reasonable to us that we could trap the anion with iodine and then hydrolyse the acetal to obtain the iodo-alcohol(80) in one less step than the original scheme. (Scheme 3.9.)



Scheme 3.9

This chemistry was successful and the alcohol(80) was obtained in an overall yield of 51%, compared to 32% for the original synthesis.

In an effort to improve the synthesis one stage further, direct metalation of 3,4-methylenedioxy benzyl alcohol was attempted. This idea was based on the reported[76] metalation of 3-methoxybenzyl alcohol(85) (Scheme 3.10).

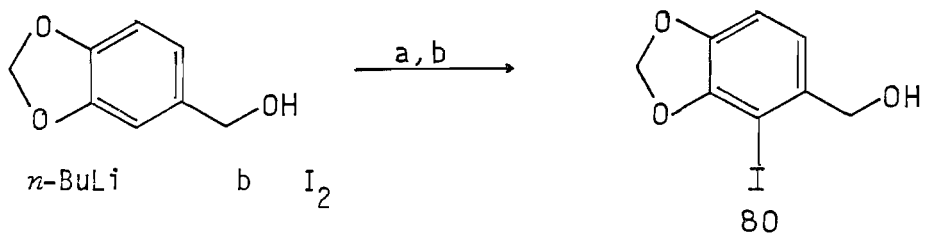


85

a *n*-BuLi b E^+

Scheme 3.10

A variety of conditions were investigated in order to carry out the transformation depicted in Scheme 3.11. Initially these experiments failed. Strangely, when one of the experiments was repeated with fresh *n*-butyllithium (from a different supplier) the reaction did give the desired product. The reason for this discrepancy remains a mystery but the reaction has been found to be repeatable on a large scale, with the alcohol(80) being isolated in 44% yield. Although this is lower than the route using an ethoxyethyl protecting group (as shown in Scheme 3.9), it requires significantly less work to carry out and consequently has become the preferred route. In summary the required aromatic moiety(82) can now be produced in just three steps with an overall yield of 28%.



a *n*-BuLi b I_2

80

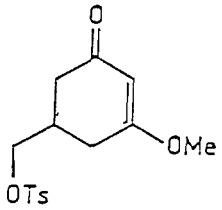
Scheme 3.11

3.3 Construction of the aldehyde required for the nitrone cycloaddition reaction.

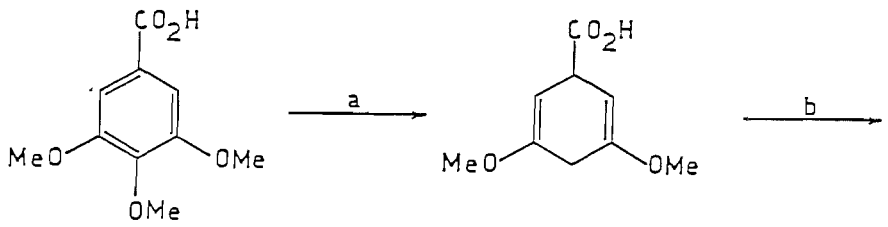
In this section a comparison is drawn between the two strategies adopted for the functionalisation of what would be the C ring in morphine. The chemistry was initially adapted from the model study for the simple unsubstituted series (Scheme 3.2) and then further developed for the substituted series (Scheme 3.3).

To proceed along either course it was first necessary to construct the methoxycyclohexenones required for coupling. In the first case this proved to be a simple task. Treatment of 1,3-cyclohexanedione in dichloromethane with methanol and a catalytic amount of acid, in the presence of a dehydrating agent gave 3-methoxycyclohex-2-enone[77] in 90% yield, after workup and distillation.

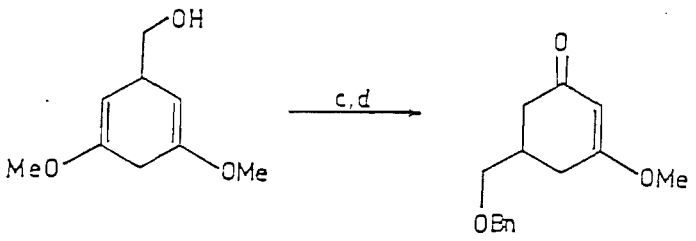
For the substituted compound(90) a straightforward three step synthesis was devised, based on an analogous synthesis[78] of the tosylate(86). (Scheme 3.12).



86



87 88



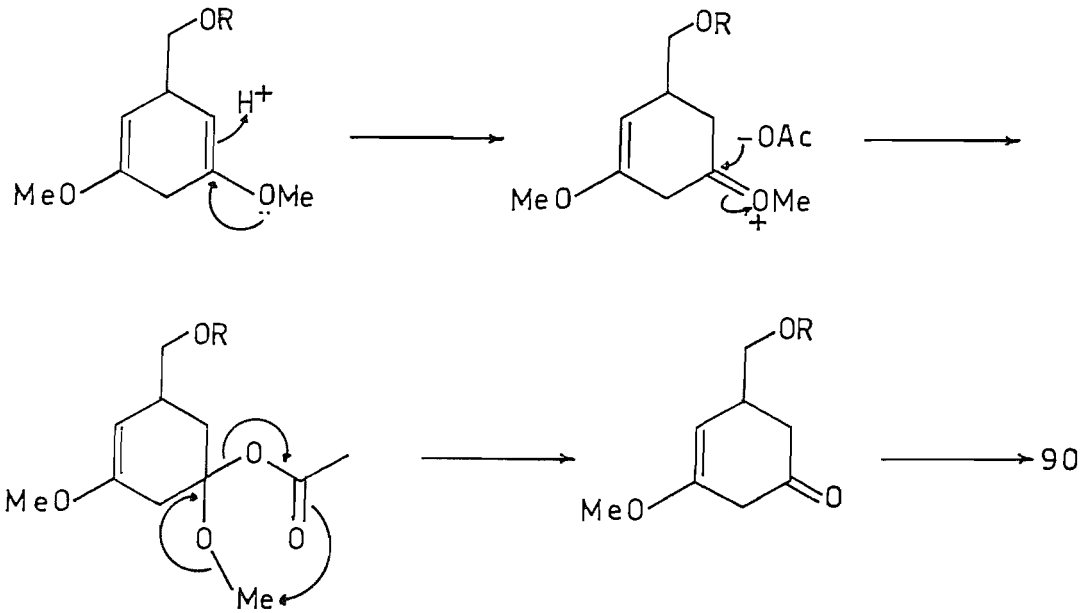
89 90

a Na,NH_3(l), MeOH B $LiAlH_4$ C NaH, $PhCH_2Br$
d NaOAc/Ac_2O/AcOH

Scheme 3.12

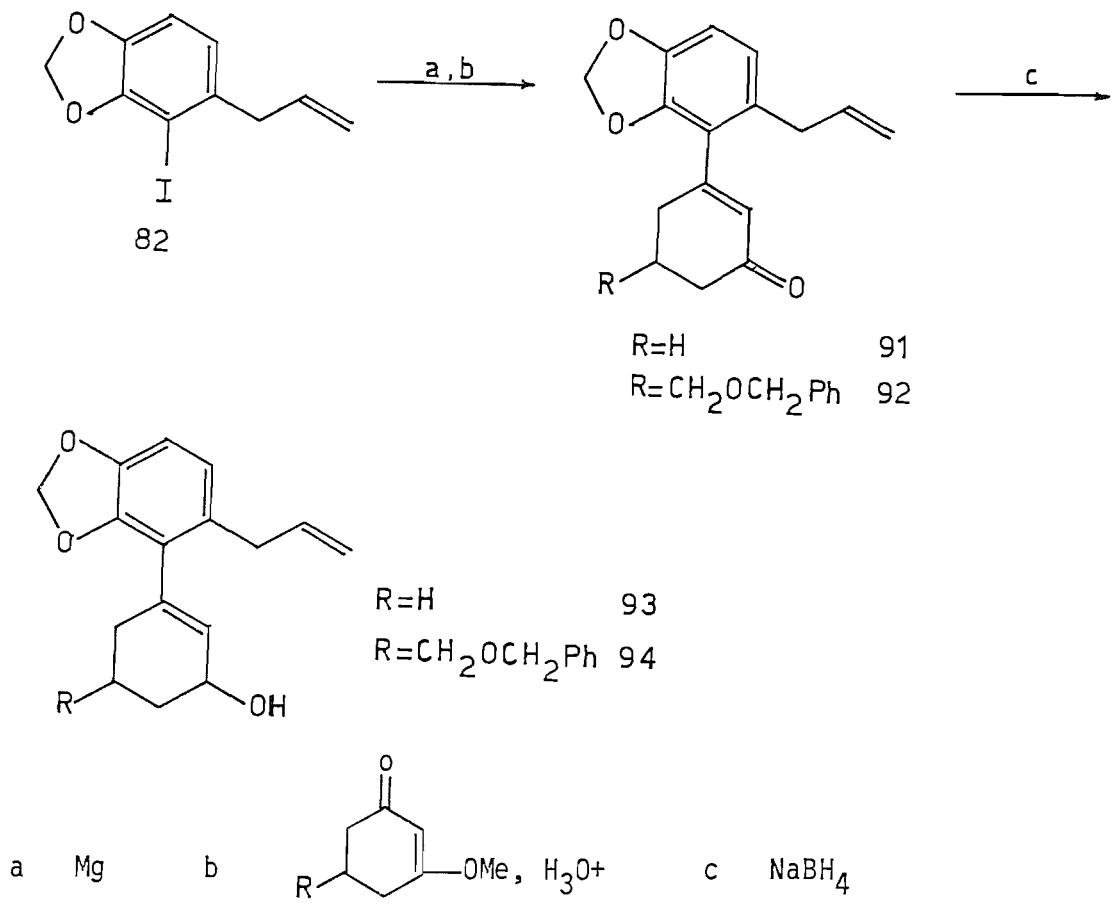
Birch reduction[78,79] of 3,4,5-trimethoxybenzoic acid with excess sodium in liquid ammonia afforded the diene(88) with loss of one methoxy group as well as reduction of the aromatic ring.

The crude acid(88) was reduced with lithium aluminium hydride in ether to the alcohol(89), as described by Chapman and Fitton[78]. This was then converted to the benzyl ether by heating it under reflux with sodium hydride and benzyl bromide. The concentrated crude reaction mixture was then hydrolysed with a mixture of sodium acetate, acetic acetate and acetic anhydride to afford the required product(90) in an overall yield of 42%. The mechanism for the hydrolysis step is of some interest and Chapman and Fitton[78] have postulated the following processes. (Scheme 3.13).



Scheme 3.13

Our attention was then turned to converting the aromatic moiety(82) into an organometallic reagent and reacting it with 3-methoxycyclohex-2-enone (Scheme 3.14). This was initially attempted in THF with magnesium turnings, catalysed by a crystal of iodine. Although a little of the magnesium appeared to react after prolonged heating, the majority remained unaffected. After addition of 3-methoxycyclohex-2-enone, and hydrolysis of the products with dilute acid approximately 5% of the required product(91) was isolated, but the majority of the material was a 3:2 mixture of starting material(82) and safrole(72) respectively. This was presumably due firstly to incomplete formation



Scheme 3.14

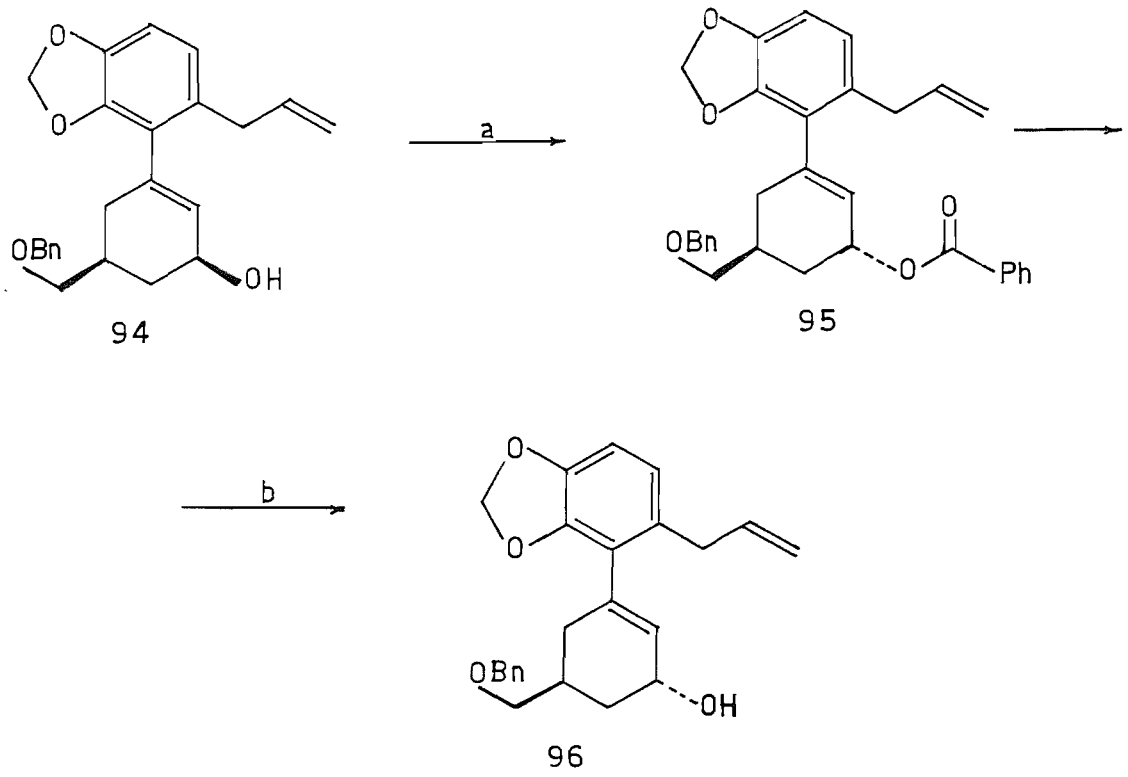
of the Grignard reagent and secondly to deprotonation of the 3-methoxycyclohex-2-enone by the Grignard that had formed, in preference to nucleophilic attack. In an attempt to remedy these problems the solvent was changed to ether and the reaction mixture placed in an ultrasonic bath for approximately 20 minutes. This caused essentially all the magnesium turnings to dissolve and when the 3-methoxycyclohex-2-enone was added a vigorous reaction took place. After hydrolysis with dilute hydrochloric acid, analysis of the products revealed a 47% yield of the desired product(91) along with 40% of safrole(72). Although this constituted a marked improvement on the original procedure, it still fell short of the sort of yield we were looking for. For this reason a number of other experimental conditions were investigated. The results obtained are presented in Table 3.2, all reactions were initiated by the use of ultrasound. Addition of the Grignard reagent to 3-methoxycyclohex-2-enone was also investigated with no discernable difference in yield for a given solvent system.

Solvent	Additional Co-solvent (1:1)	Temperature	Yield
THF	-	reflux	39%
Ether	Benzene	reflux	54%
Ether	Toluene	reflux	20%
Ether	Cyclohexane	reflux	66%

Table 3.2

Repetition of the experiment with the analogues methoxycyclohexenone containing the methoxybenzyl ether substituent(90) using the ether/cyclohexane procedure gave a 75% yield of the expected enone(92) (Scheme 3.14).

Reduction of the enone(91) using sodium borohydride in methanol, in the presence of cerium (III) chloride, gave the desired allylic alcohol(93) in 93% yield. When the same reduction procedure was used on the substituted enone(92), where two possible diasteromeric products can be formed, the yield of allylic alcohol(94)was 91%. Interestingly the ratio of diasteroisomers obtained from this reaction was approximately 7:1. Analysis of the high field proton n.m.r. spectrum revealed the *cis* isomer to be the major adduct. This was confirmed by inverting the alcoholic centre using a mitsunobu[80] reaction to give the benzoate ester(95). Hydrolysis of the ester(95) gave the *trans* substituted isomer(96) and analysis of the high field proton n.m.r. again confirmed the substitution pattern (Scheme 3.15).

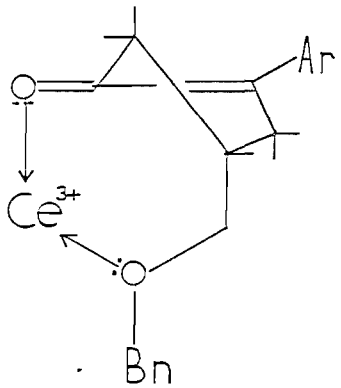


94 95 96

a $PhCO_2H$, PPh_3, DEAD b K_2CO_3

Scheme 3.15

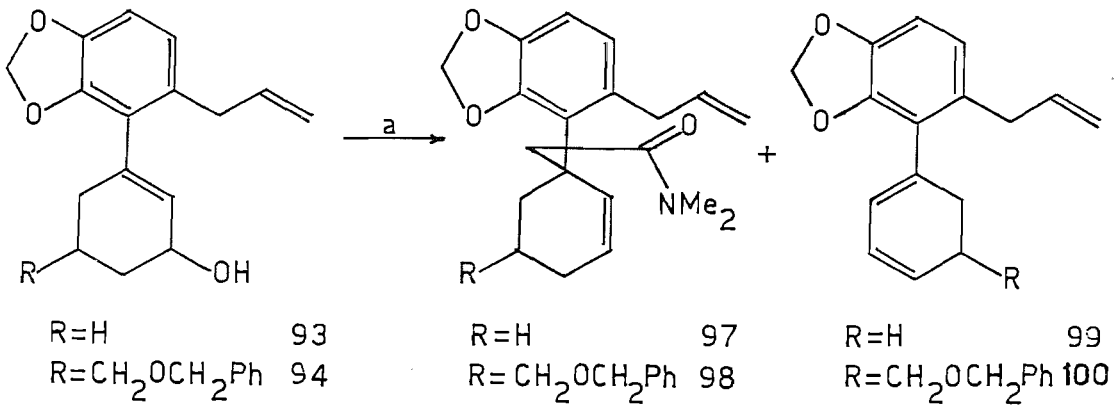
As ultimately one of the chiral centres is removed from the molecule this mixture does not present a problem. It is nonetheless interesting to consider what might cause such diasteroselectivity. Initially it was assumed that coordination of a cerium ion to the carbonyl group, and the oxygen in the methoxybenzyl ether side chain would make attack of the hydride species more favourable from the exposed face (Scheme 3.16).

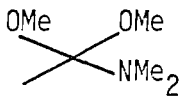


Scheme 3.16

In an effort to confirm this hypothesis the reduction was performed in the absence of the cerium (III) chloride. This resulted in the same ratio of diasteromers as had been obtained in the initial reduction procedure and has thereby disfavoured this hypothesis. It is possible that a sodium ion may be coordinating in a similar way with the oxygen atoms but no attempt has been made to investigate this.

Application of Eschenmoser's Claisen rearrangement[68] procedure to the allylic alcohol(93) by boiling it overnight in toluene with *N*,*N*-dimethylacetamide dimethyl acetal afforded only a 38% yield of the expected amide(97) product. The majority of the remaining material was isolated as the analogous diene(99) to that obtained in the model studies (Scheme 3.17).



a 

Scheme 3.17

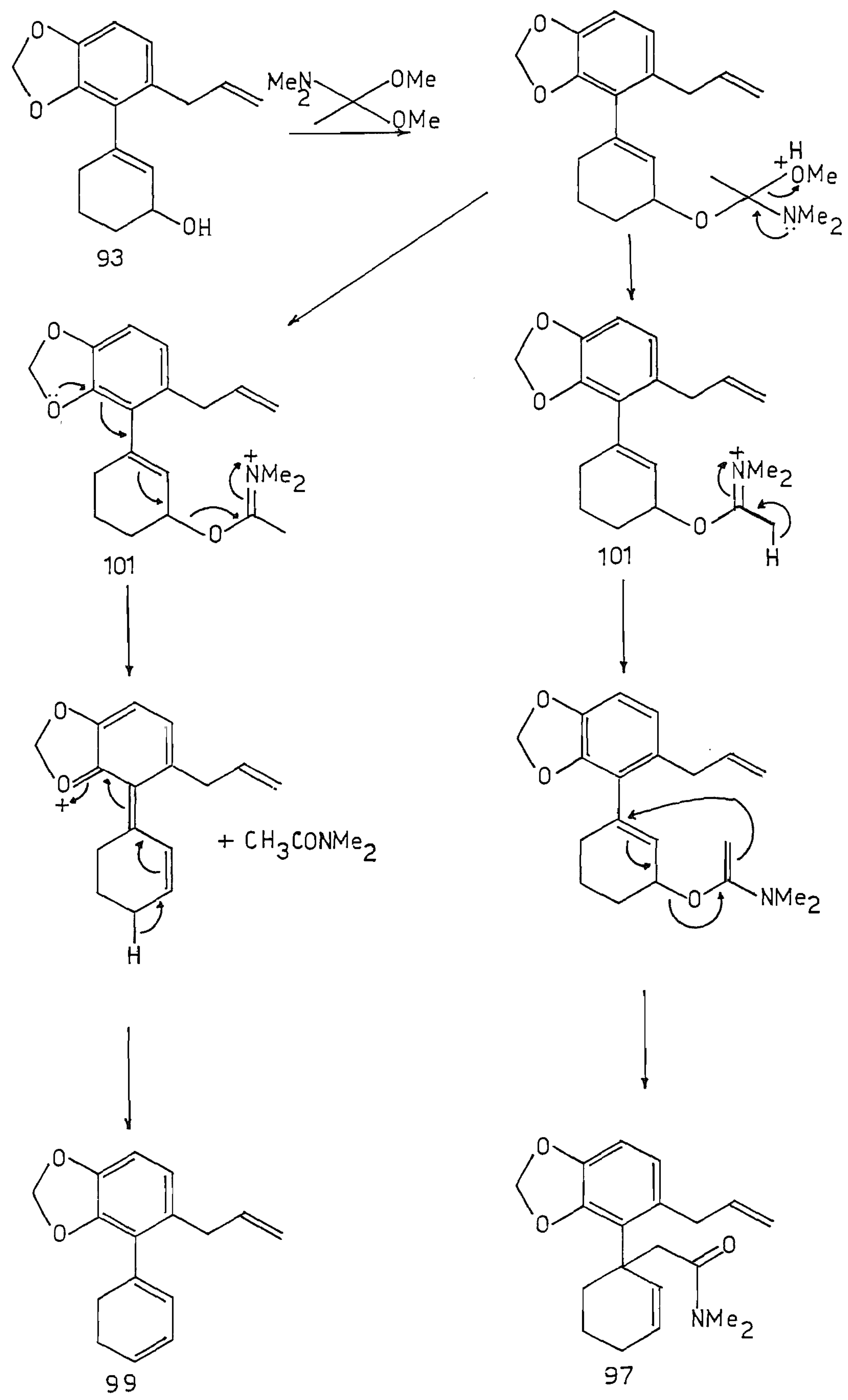
To improve this yield a variety of different conditions were tried, the results obtained are presented in Table 3.3.

Solvent	Temperature/ °C	Time taken to consume starting material/h	Yield of amide(97)/%
Benzene	80	24	22
Benzene/toluene 2.3:4.2	100 (reflux)	22	22
Toluene	111	20	38
Xylene	142	15	29
Toluene + DMAP (catalytic)	111	4	30
Toluene*	111	20	44

* *N*,*N*-Dimethylacetamide dimethyl acetal carefully fractionated prior to use.

Table 3.3

Whilst these results indicate toluene to be the solvent of choice, the yield was still disappointing. It seemed to us however, that an additional factor was at play, as the yield in toluene was very inconsistent, tending to decrease dramatically with large scale preparations. In an effort to track down this extra factor we investigated removing methanol from the reaction mixture. This was accomplished by passing the distillate through 4A molecular sieves before allowing it to return to the reaction vessel. With this simple modification a 58% yield of the amide(97) could repeatably be obtained, even on very large scale preparations. This experimental observation may be rationalised by assuming that the presence of methanol acts to increase the effective polarity of the solvent. This would favour the loss of *N*,*N*-dimethylacetamide from intermediate(101) by stabilising the resultant carbonium ion (Scheme 3.18).



Scheme 3.18

When the experimental procedure was applied to the allylic alcohol with a methoxybenzyl ether substituent(94) the yield of the required amide(98) was only 39%. (Scheme 3.17).

This was not suitable for our purposes and so further studies were performed on this reaction. Initially a number of sealed tube experiments were carried out at 115°C, in a variety of solvents, to see what effect this had on amide production. In one case propene oxide was also added to the reaction in order to scavange the methanol produced. The results obtained are shown in Table 3.4.

Solvent	Temp/°C	Yield of amide(98)/%
[1]MeCN	115	12
[1]THF	115	8
[1]THF + $CH_3\overline{CHCH_2}O$	115	8
[1]Benzene	115	14
[2]Petrol (B.P 105°C)	105	39
[2]Ethylcyclohexane	130	30
[2]Ethylcyclohexane/ methylcyclohexane (1:1)	115	48

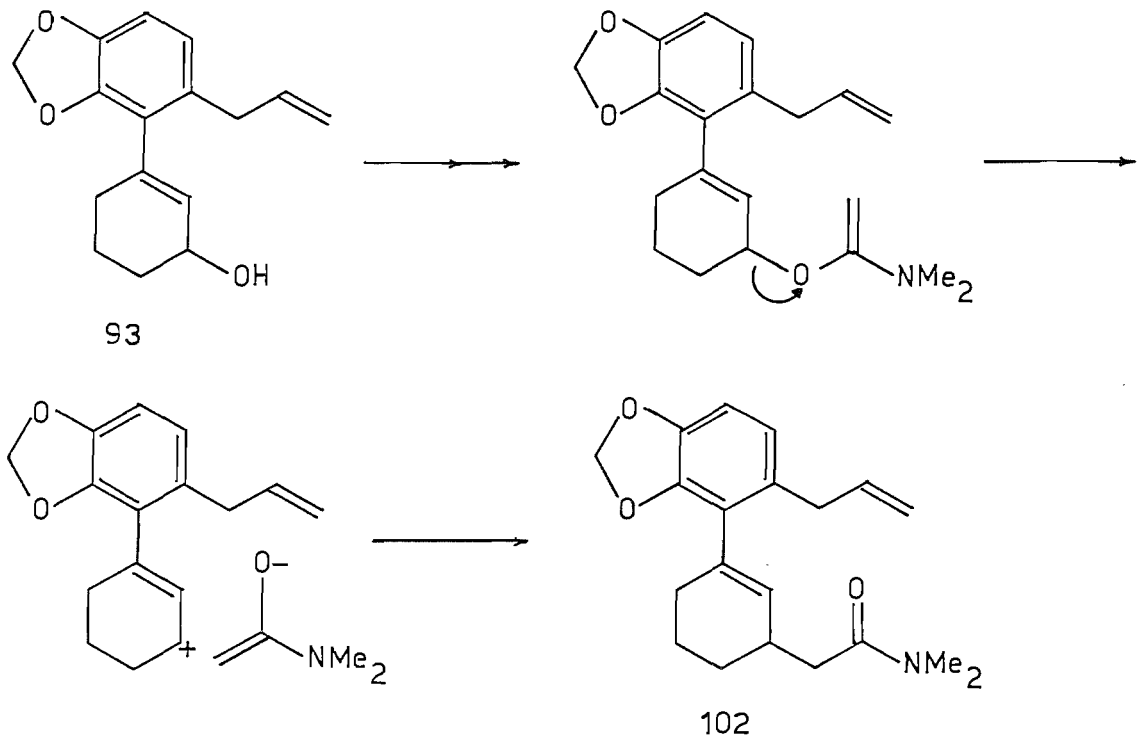
1. Performed in a sealed tube
2. Carried out at atmospheric pressure with methanol removed from the distillate.

Table 3.4

As can be seen the 1:1 mixture of methyl- and ethylcyclohexanes gave by far the best yield. Since there seemed little hope of improving the 48% yield no further studies were performed on this reaction. When the ethylcyclohexane/methylcyclohexane solvent system was used with the unsubstituted allylic alcohol(93) the yield of the amide(97) was only 49%.

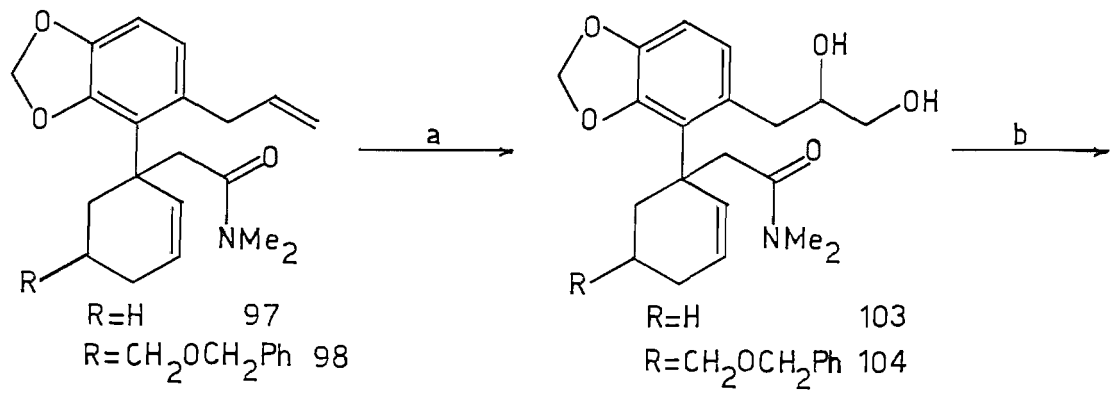
In the course of studies on this reaction removal of methanol was attempted by adding 4A molecular sieves to the reaction mixture itself. To our surprise a different product altogether was isolated from the reaction. Although it showed a consistent infrared and proton n.m.r. for the correct amide(97), its movement on TLC was much slower than the desired product. Carbon 13 n.m.r. showed there to be

the same number of each type of carbon present (CH_3, CH_2 etc.) however in the aliphatic region a quaternary had been replaced by a 'CH' carbon, whilst in the unsaturated region a 'CH' carbon had become a quaternary carbon. This led us to postulate the following structure for this compound, and mechanism for its formation (Scheme 3.19); the reason why this should be the preferred product in the presence of molecular sieves remains a mystery.



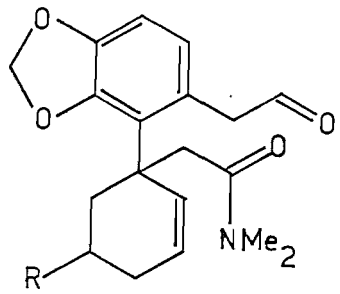
Scheme 3.19

With the amide in hand there remained only the cleavage of the allyl group to an aldehyde before work on the nitrone cycloaddition could begin. The osmium tetroxide procedure used in the model studies gave the requisite diols(103)and(104) for both series of work without any problems (Scheme 3.20). When the unsubstituted diol(103) was subjected to the reaction conditions used in the model study for forming the aldehyde(63) (sodium periodate in acetic acid) a 2,4-DNP active spot on the baseline of the TLC plate was obtained, of unidentified structure. When the solvent was changed to THF/H_2O containing a catalytic amount of CF_3COOH the reaction proceeded in quantitative yield to the required aldehyde(105) The same conditions also gave the substituted aldehyde(106) in quantitative yield.(Scheme 3.20).



R=H 97
R=CH_2OCH_2Ph 98

R=H 103
R=CH_2OCH_2Ph 104



R=H 105
R=CH_2OCH_2Ph 106

a OsO_4/Me_3NO b $NaIO_4$ c CF_3CO_2H

Scheme 3.20

3.4 Nitrone cycloaddition chemistry

Having produced the required aldehydes(105) and (106) everything rested on the ability of the nitrone cycloaddition reaction to give a good yield of the required *exo* adduct. The experiments used to investigate this reaction are presented below followed by a brief section which discusses and attempts to rationalise the results obtained.

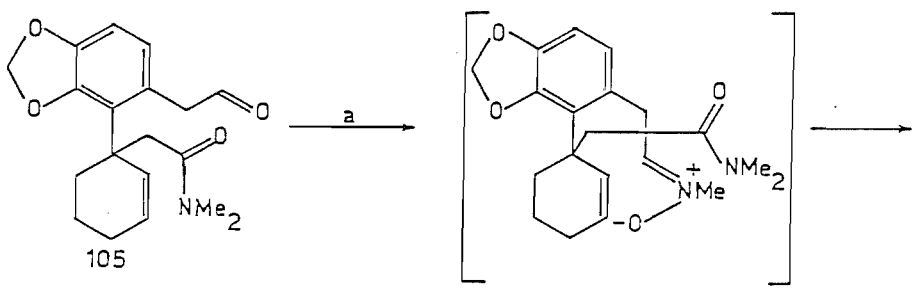
Firstly the unsubstituted aldehyde(105) was treated with freshly prepared *N*-methylhydroxylamine in boiling benzene, in the presence of 4A molecular sieves. This gave rise to two products which were readily separated on silica. Characterisation showed them to be products of cycloaddition, however no evidence could be gleaned to suggest which was the required product. Before work could begin on studying ways of increasing the yield of the desired isomer it was obviously necessary to ascertain which adduct was required. To this end each isomer in turn was reduced with palladium (II) chloride in

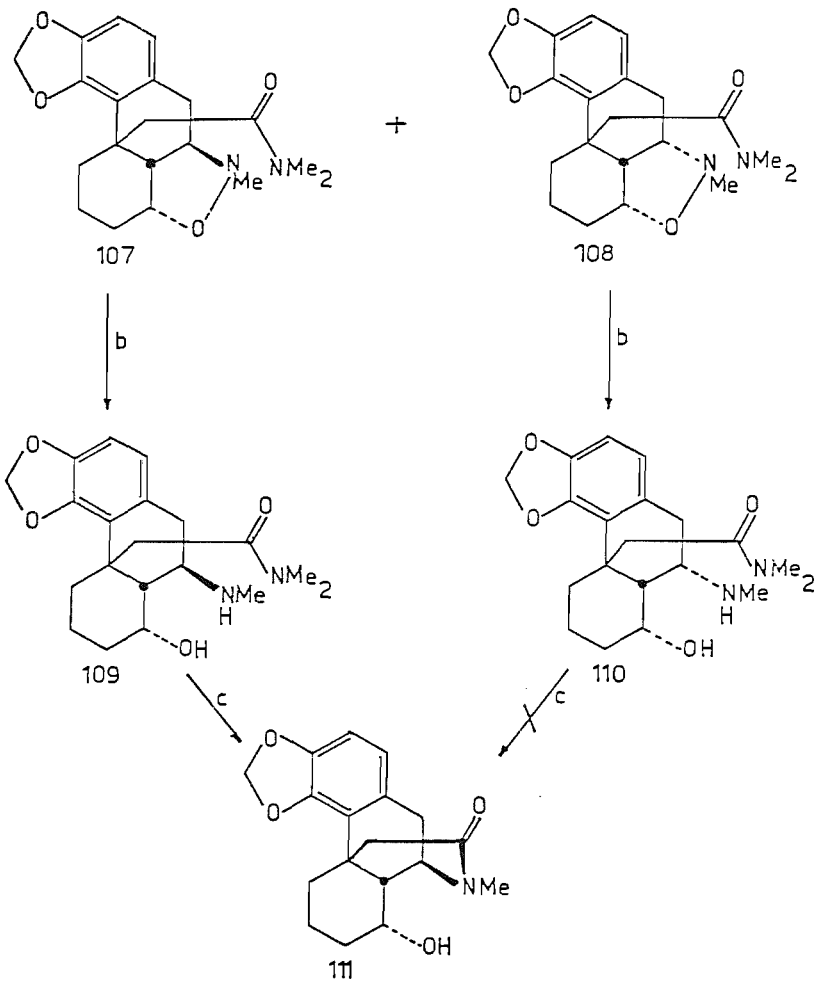
methanol under an atmosphere of hydrogen at 3.1 bar to give the amino-alcohols(109) and (110). The reduced products were converted to their hydrochloride salts and heated to 180°C under vacuum. As expected this caused one to cyclise and the other to simply decompose. (Scheme 3.21). Having ascertained which isomer was required a small temperature study was conducted on the cyclisation. The results are presented in Table 3.5 and show that the ratio of isomers is rather erratic but the best system seems to be boiling benzene.

Solvent	Temperature /°C	Yield of (108)/%	Yield of (107)/%
Benzene	50	43	19
Benzene[1]	80	34	27
Toluene	100	63	12
Toluene	111	40	15
Xylene	142	32	7
Benzene + DMAP[2]	80	31	15

1. Average for five separate experiments.
2. DMAP (3eq) added to produce *N*-methylhydroxylamine in solution from *N*-methylhydroxylamine hydrochloride.

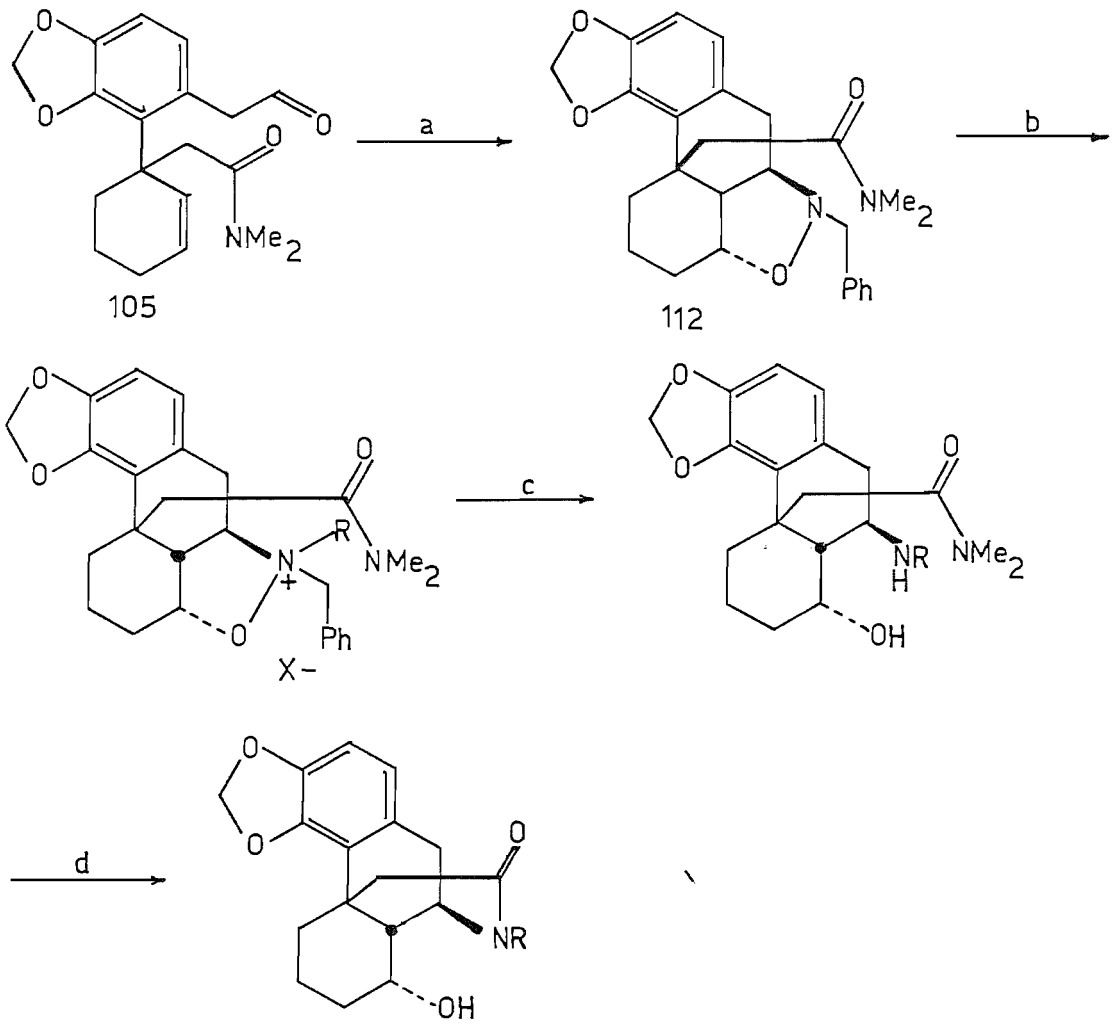
Table 3.5





Scheme 3.21

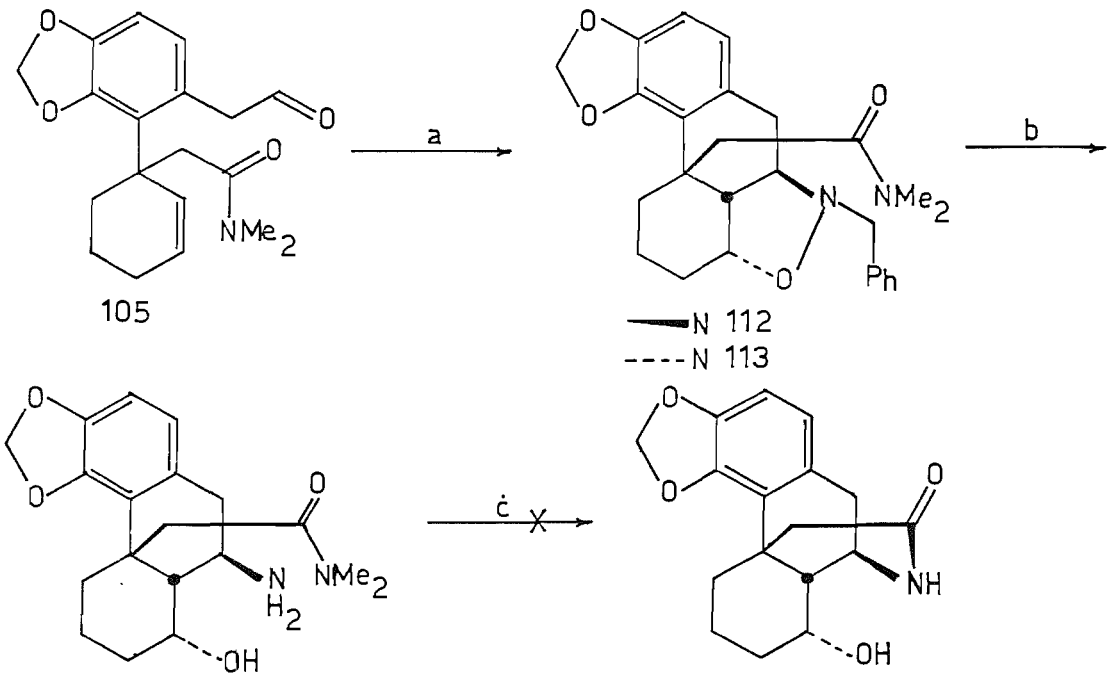
From a study of molecular models it seemed likely that a larger group on the nitrogen of the nitrone might help to make an *exo* transition state more favourable. In order to investigate this hypothesis an *N*-benzyl group appeared to be the most suitable. The ability to remove it by hydrogenation at the same time as cleaving the N-O bond would negate the requirement for a separate deprotection step. This also gave the possibility of incorporating a wide range of different alkyl substitutes on nitrogen, such as would be particularly useful for pharmacological studies. Thus the following scheme was proposed, based on analogous work by Sasaki *et al* [61] used to produce adamantane derivatives by nitrone cycloaddition chemistry. (Scheme 3.22).



a $PhCH_2NHOH$ b RX c $H_2/PdCl_2$ d HCl, Δ

Scheme 3.22

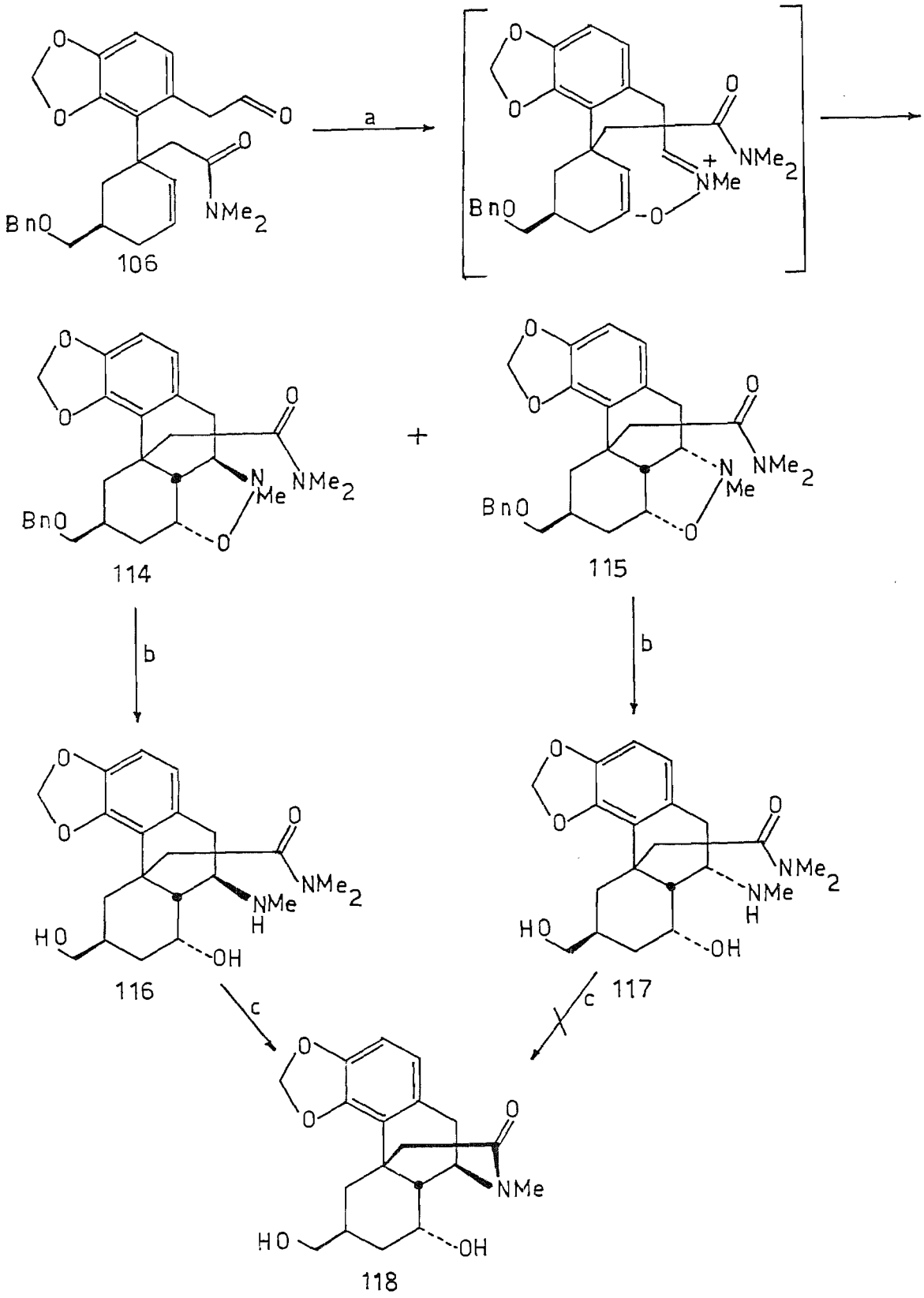
Preparation of the required *N*-benzylhydroxylamine was carried out using the procedure of Borch *et al*[47]. This involves the reduction of the oxime of benzaldehyde with sodium cyanoborohydride in a buffered methanolic solution. Treatment of the aldehyde(105) with *N*-benzylhydroxylamine in boiling benzene, using a Dean-Stark apparatus to remove water, gave a mixture of the two epimeric isoxazolidines(112) and (113) in a 6:1 ratio. Comparison of the proton n.m.r. spectrum of each isomer with those for isoxazolidines(107) and (108) strongly indicated that the minor product was again the *exo* adduct. To confirm this each isomer was reduced in turn and the resulting primary amino-alcohols subject to the cyclisation procedure used for the *N*-methyl compounds. Unfortunately in neither case could any of the desired morphinan be isolated (Scheme 3.23).



a $PhCH_2NHOH$ b $H_2/PdCl_2$ c HCl, Δ

Scheme 3.23

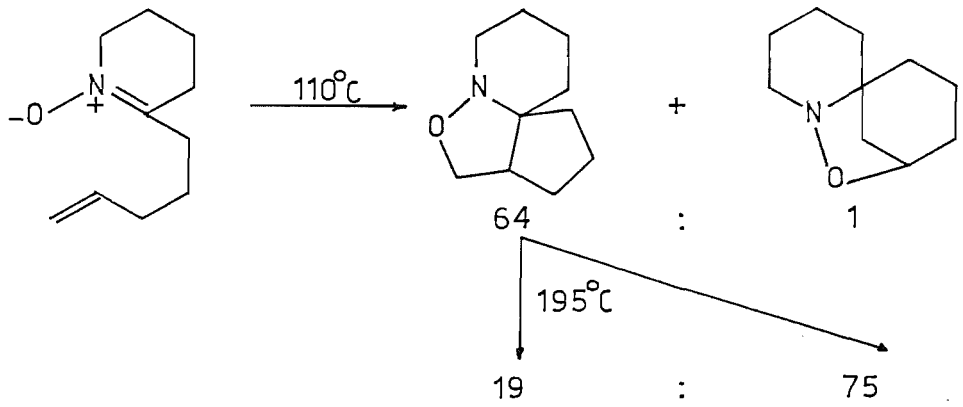
In an effort to obtain a better yield of the correct isomer the methoxybenzyl ether substituted aldehyde(106) was treated with *N*-methylhydroxylamine in boiling benzene, using a Dean-Stark apparatus. Once again a mixture of isomers(114) and (115) was obtained, this time in an 8:1 ratio. There was less similarity between the proton n.m.r.'s of each isomer in this case and those obtained previously, consequently the two isomers were in turn reduced to give amine-diols(116) and (117), and each subjected to the conditions of the cyclisation reaction. This led to the minor adduct from the nitrone cycloaddition(114) being converted through to a morphinan skeleton(118) whilst the major product failed to react (Scheme 3.24).



a MeNHOH b $H_2/PdCl_2$ c HCl, Δ

Scheme 3.24

A review of the literature (see Chapter Two) revealed that the nitrone cycloaddition reaction has been shown to be reversible. In the most dramatic example, a model study on the synthesis of histrionicotoxin[81], it has been found that the isomer ratios obtained from the cycloaddition reaction conducted in toluene at 100°C could be changed from a 64:1 ratio to a 19:75 ratio simply by heating the products in a sealed tube in toluene at 195°C for 48 hours. (Scheme 3.25).



Scheme 3.25

With this in mind a sample of the incorrect isomer(115) was heated in a sealed tube in toluene at 250°C for 48 hours before being analysed. Whilst this gave rise to a small yield of the correct isomer(114), it was barely significant and the transformation was not pursued further.

In another series of experiments which set out to improve the yield of the required adduct, the cycloaddition reaction was performed in a range of different solvents, all at reflux. Although acetonitrile, dichloromethane, ethanol, cyclohexane, trichloroethylene and dichloroethane all gave essentially the same ratio of the adducts as benzene had (despite their differing boiling points), chloroform showed a slightly improved yield of the required product(114). Further to this when the cycloaddition reaction was conducted in chloroform, in an ultrasonic bath, the yield of the correct isomer(114) rose to 20% representing a 4:1 ratio of isomers. This may be explained on the basis of localised 'hot spots' created by the ultrasonic waves. The high temperature sealed tube experiment and the ultrasonic bath work lead us to believe that the *exo* adduct(114)

represents the thermodynamic product, whilst the undesired *endo* product(115) exists as the kinetic product.

The effect of the methoxybenzyl ether substituent on the product ratios can be rationalised by considering the conformation of the cyclohexene ring in the transition state. With the aromatic ring in a pseudo axial position it is hard to align the nitrone up in a suitable position for it to undergo cycloaddition through an *exo* transition state, whilst the *endo* transition state lends itself more readily to reaction. If the cyclohexene ring exists in the other conformation, with the aromatic ring equitorial it then becomes feasible for the *exo* adduct to be formed readily, the *endo* transition state appearing much less favourable. With this hypothesis in mind it can be seen that the addition of a group *cis* to the amide group is going to make the aromatic ring more likely to take the pseudo axial position and so disfavour the *exo* transition state. Therefore the much lower yield of the desired product in this series of compounds can be justified. This hypothesis can only really be appreciated by studying Dreiding models as a diagram fails to show the strain imposed by the bond angles on the transition state.

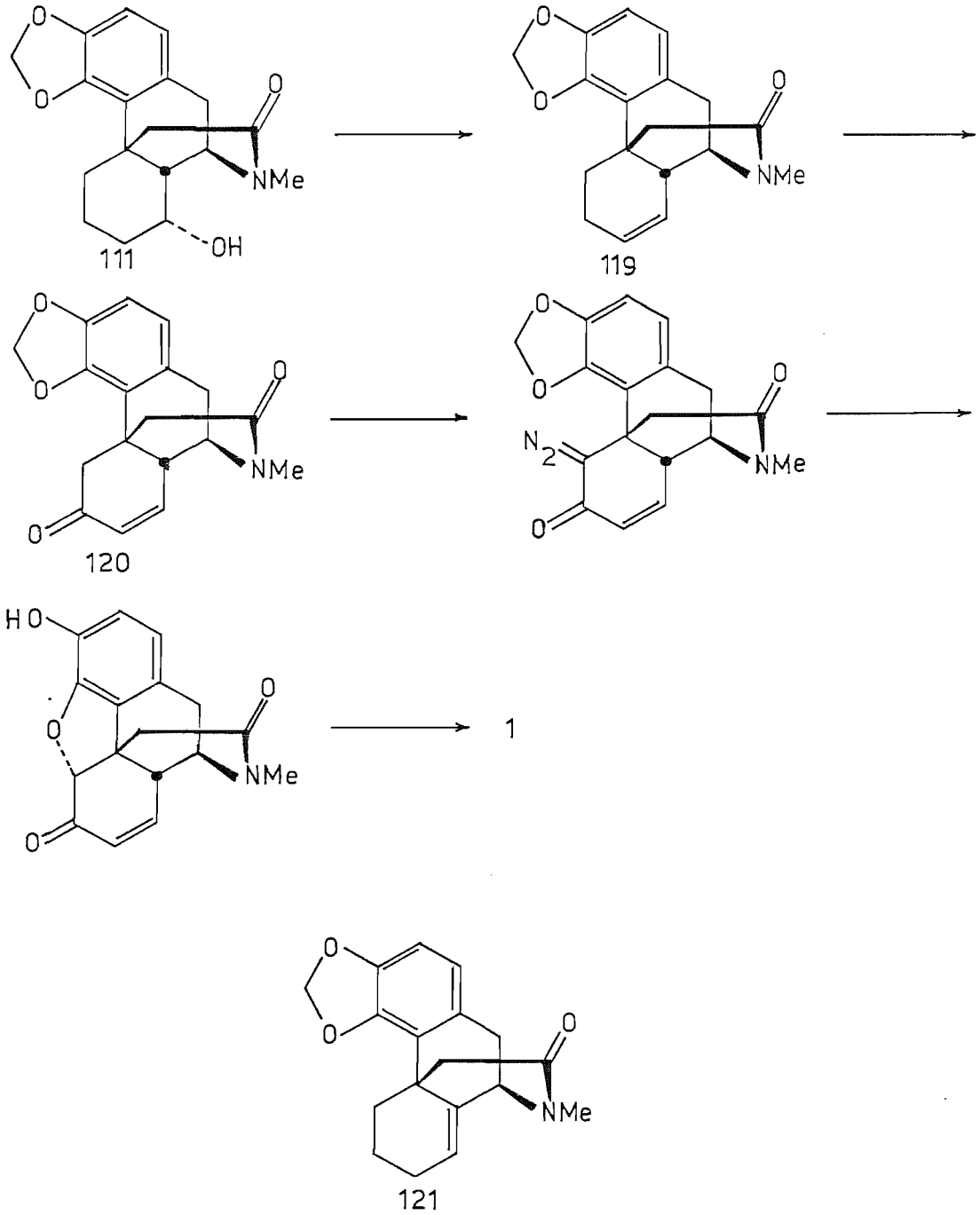
The results obtained from the use of *N*-benzylhydroxylamine remains an enigma. This was expected to give an improvement in the yield of the desired isomer as steric factors seen in molecular models seem to predict a preference for the *exo* transition state, where the benzyl group is out of the way of the axial protons on the cyclohexene ring.

In conclusion, the nitrone cycloaddition has proved to be something of a disappointment as it has failed to give a reasonable yield of the correct isomer for either series of compounds under investigation. Despite this being the case we were still left with two potential routes to finish the synthesis of morphine. However, owing to the poor yield of the correct isomer(114) obtained for the series of compounds containing a methoxybenzyl ether substituent from the nitrone cycloaddition reaction, only the unsubstituted route has been investigated further.

3.5 Manipulations of the morphinan framework

Our initial plan to complete the synthesis of morphine is illustrated in Scheme 3.25. The first task was to dehydrate the alcohol(111) to give the least substituted alkene(119). From the

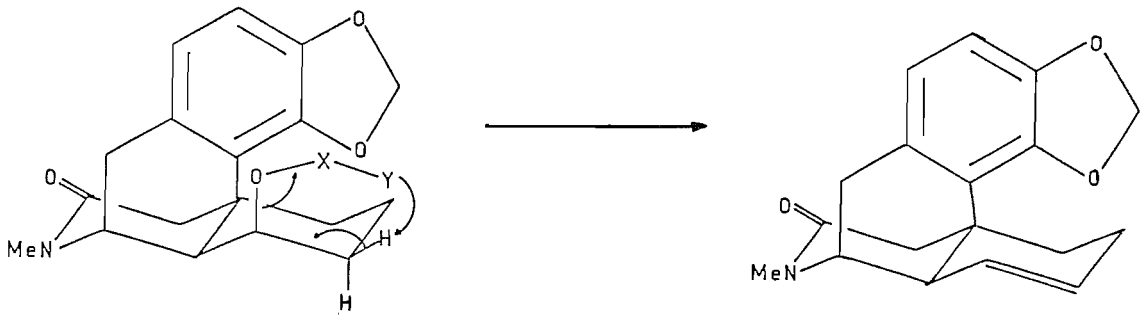
study of models we hoped that the most substituted alkene(121) would be strained and therefore unfavoured. Consequently the first method



Scheme 3.26

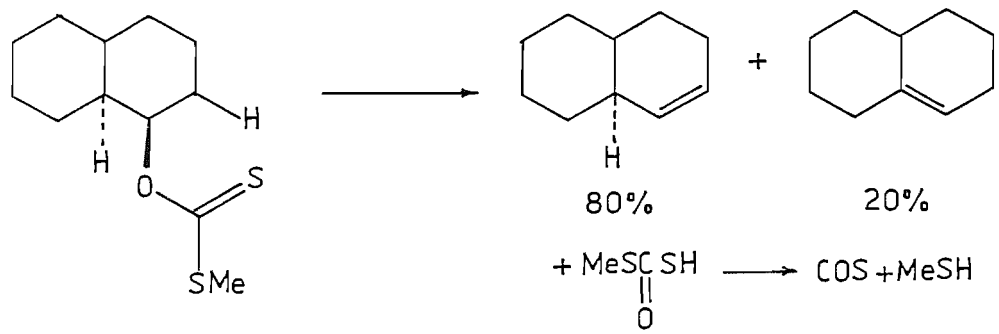
used to attempt this transformation was a simple dehydration procedure with phosphorus oxychloride in pyridine[82]. This proved to be a clean reaction giving a 68% yield of one product. High field n.m.r. showed this to be the undesired Saytzeff product of elimination(121), exhibiting the highest degree of substitution onto the double bond. In order to obtain the desired product we envisaged that a suitable

syn elimination procedure would be successful. From models it is quite obvious that the proton at the ring junction could not be removed in a concerted mechanism (Scheme 3.27), going via a six membered transition state.



Scheme 3.27

The reaction studied for this purpose was the Chugaev reaction[83]. This relies on the formation of a xanthate, which upon heating typically in the vapour phase, decomposes by elimination of the mercaptothioacid to give an alkene. (Scheme 3.28).



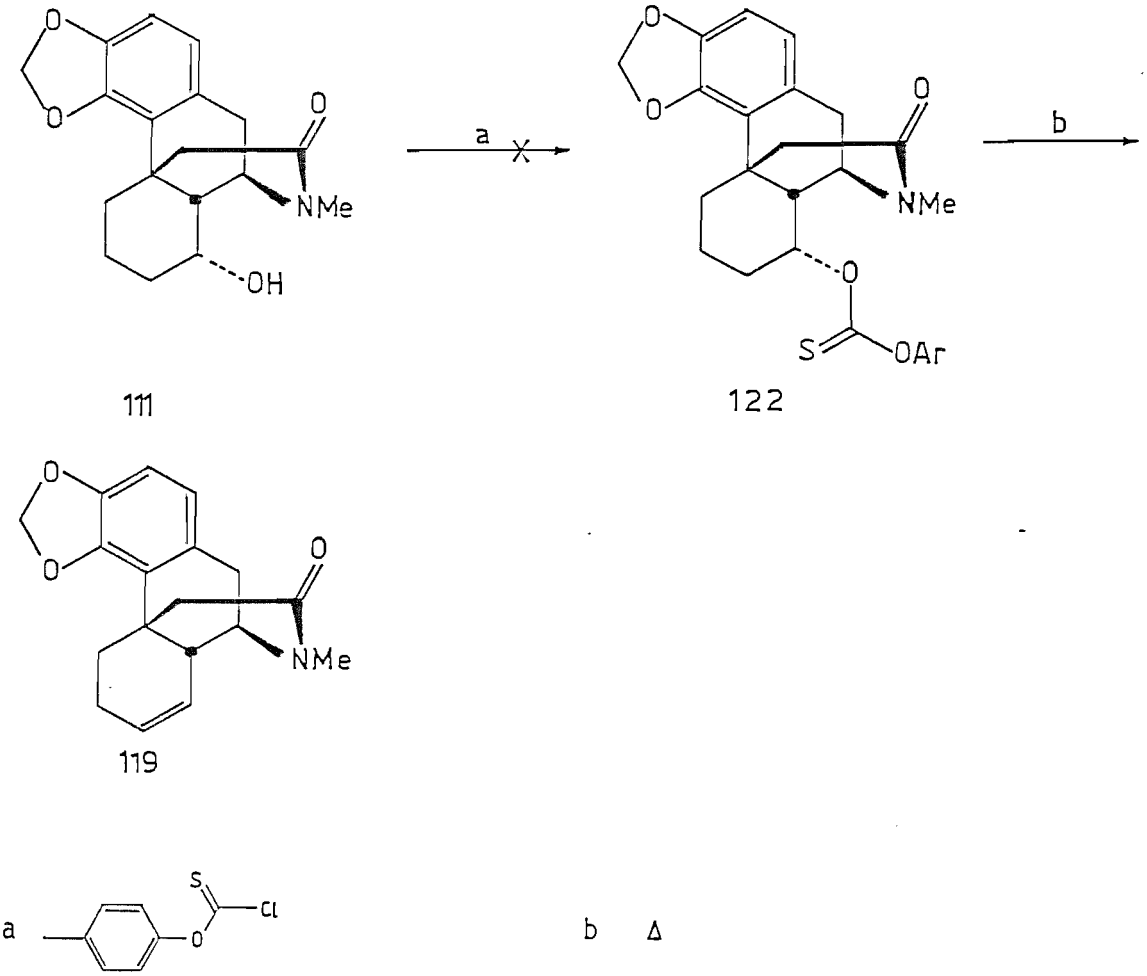
Scheme 3.28

Although we found no examples in the literature where a Chugaev reaction had been performed in the presence of an amide we still attempted this reaction. Treatment of the alcohol(111) with sodium hydride followed by carbon disulphide and methyl iodide gave a mixture of a large number of unidentified products. This may be due in part to deprotonation of the amide functionality and subsequent substitution on to the carbon α to the carbonyl by the carbon disulphide.

In a variation on the Chugaev reaction Gerlach *et al*[84] have treated alcohols with *O*-4-methylphenyl chlorothionoformate to give the

thiocarbonates in good yield. When these are heated to >135°C an analogous *syn* elimination reaction occurs, resulting in the formation of an alkene.

Hence the morphinan alcohol(111) was treated with commercially available *O*-4-methylphenyl chlorothionoformate in order to obtain the thiocarbonate(122) (Scheme 3.29). Unfortunately under none of the reaction conditions investigated could the desired thiocarbonate(122) be produced. Table 3.6 shows the conditions used to attempt this transformation and the results obtained. It is evident from these results that alkylation of the hydroxyl group is not a facile process. The production of the most substituted alkene, with DMF as solvent, represented something of a surprise, but led us to believe that there was no point in pursuing this reaction further.

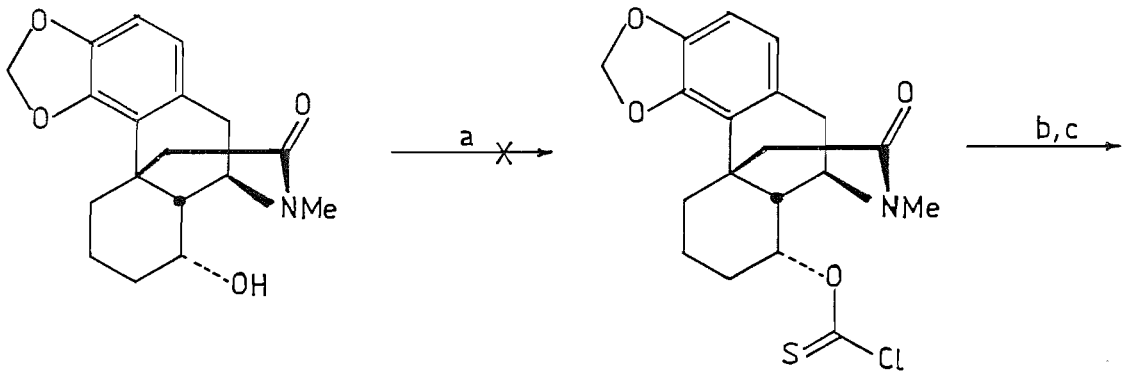


Scheme 3.29

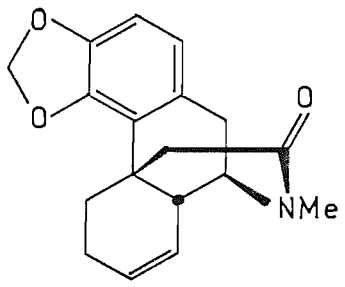
Solvent/Conditions	Temperature/°C	time/h	Product
Pyridine/THF	ambient	2	(111)
THF/DMAP	"	18	(111)
Dichloromethane/DMAP	"	48	(111)
Acetonitrile/DMAP	81	35	(111)
DMF/DMAP	60	2	(121)

Table 3.6

Next our attention was attracted to the idea that the alcohol(111) may be treated with firstly thiophosgene and then ethanethiol to give the xanthate needed for pyrolysis (Scheme 3.30). When the procedure was attempted using boiling acetonitrile as solvent a mixture of the most substituted alkene(121) and the starting alcohol(111) only were isolated. Repetition of the experiment in dichloromethane containing triethylamine as base at ambient temperature overnight gave the same result.



111

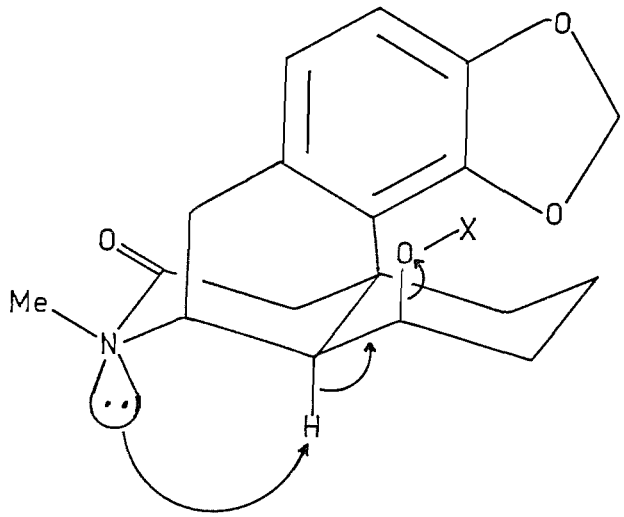


119

a ClCSCl b EtSH c Δ

Scheme 3.30

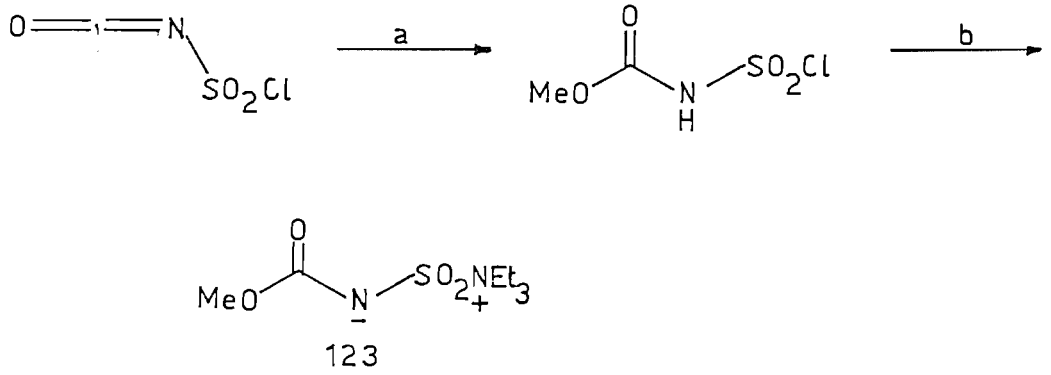
With this result we decided to seek another procedure for affecting the desired transformation. The failure of these experiments may be rationalised by postulating neighbouring group participation from the nitrogen atom of the amide. Although this is obviously far less basic than an amine, its close proximity to the proton at the ring junction may significantly weaken the bond. Hence as soon as any sort of leaving group is formed from the hydroxyl group, the ring is ideally set up to undergo a trans, *anti* elimination in preference to other possible reaction routes. (Scheme 3.31).



Scheme 3.31

In order to accomplish the desired transformation a number of other ideas were considered. Firstly it was thought that if the alcohol(111) was converted to its mesylate and then treated with a strong bulky base at low temperature, deprotonation would occur from the least hindered side thereby giving the desired alkene(119). However in accordance with the ideas discussed above when the alcohol(111) was treated with methanesulphonyl chloride in dichloromethane containing triethylamine, the only product isolated was the unwanted olefin(121).

Another reagent reported to promote elimination via an Ei mechanism is 'Burgess's Salt'[85](123). When this salt is added to alcohols in warm acetonitrile dehydration takes place smoothly to give an alkene. The salt itself is readily prepared by the action of methanol on chlorosulphonyl isocyanate, followed by treatment of the resulting crystals with triethylamine in toluene (Scheme 3.32).



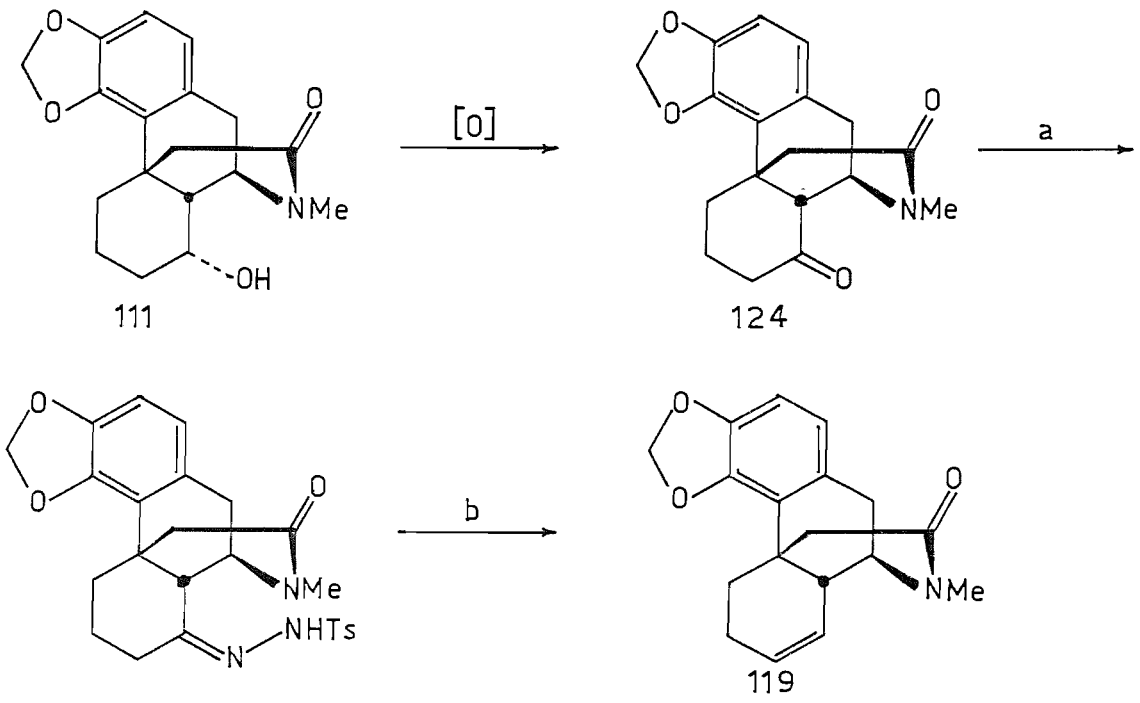
123

a MeOH b Et_3N.

Scheme 3.32

Addition of this salt(123) to the alcohol(111) in acetonitrile at 50°C and stirring for 1 hour gave, upon workup, mainly the most substituted alkene(121) once again. We can only assume that participation of the nitrogen lone pair is promoting decomposition of the intermediate again, before the desired elimination mechanism can take place.

In final attempt to obtain the elusive alkene(119) we considered oxidising the alcohol(111) to a ketone and converting it to the tosyl hydrazone derivative such that a Shapiro[18] reaction could be attempted (Scheme 3.33). To produce the required ketone(124) the alcohol(111)

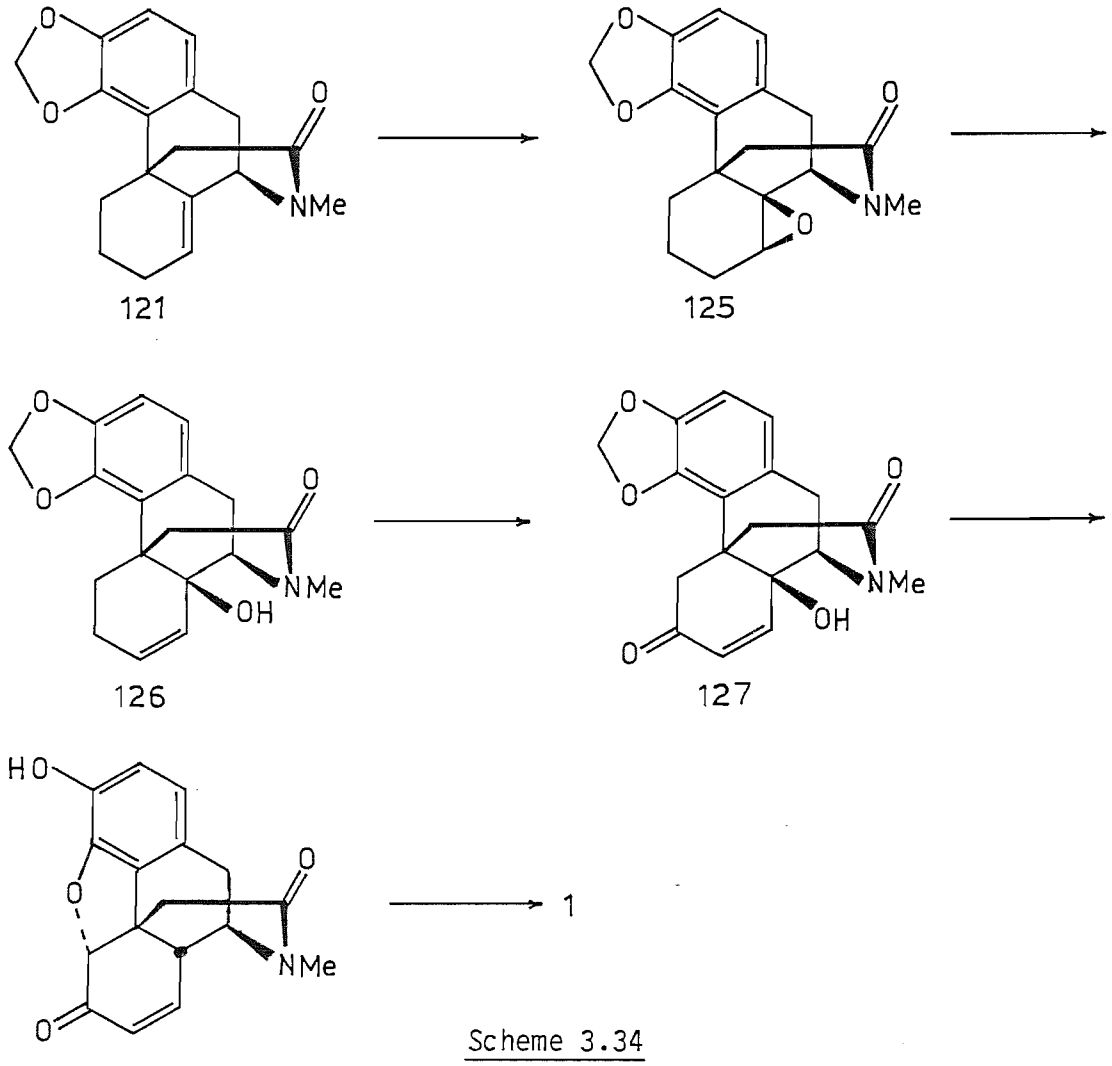


111 124 119

Scheme 3.32

was first treated with Jones reagent, which unfortunately rapidly gave a black tar. Consequently the milder PCC oxidation procedure was attempted in dichloromethane, this again produced a black tar. A literature survey revealed that some work had been carried out by Rapoport *et al*[87] on the oxidation of hydroxyl groups in this position on other morphinans. Their work used an Oppenauer oxidation procedure and gave a 40% yield of the ketone. Unfortunately when an Oppenauer oxidation was used on our alcohol(111) no oxidation took place and the starting material was recovered.

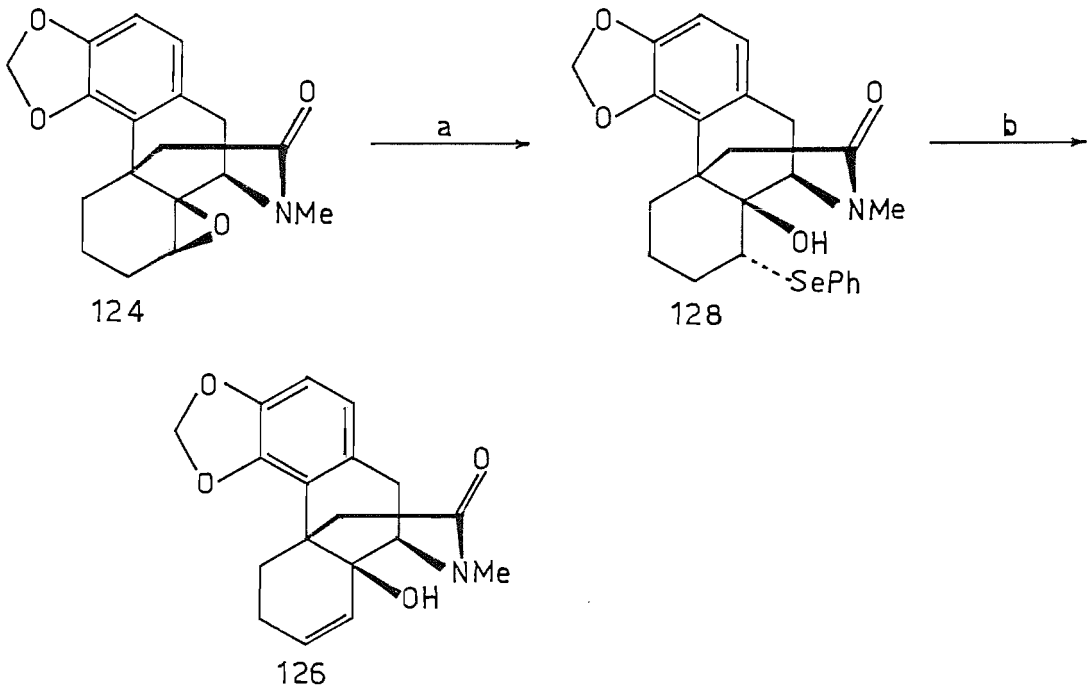
A further consideration of the merits of this route, particularly with respect to the problems likely to be encountered attempting a Shapiro reaction using *n*-butyllithium in the presence of an amide and the problems already encountered attempting to oxidize the alcohol(111) to the required ketone(124), led us to consider a different route through to morphine. The revised scheme is illustrated below (Scheme 3.34) and uses the known transformation to the previously unwanted alkene(121).



Scheme 3.34

Of the numerous dehydration procedures attempted which had led to the formation of the most substituted alkene(121) the cleanest and highest yielding process had used phosphorus oxychloride in pyridine. Subsequent epoxidation was carried out using *m*CPBA in dichloromethane, based on the precedent of Monkovic *et al* [32] in their synthesis of 14-hydroxy morphinans (Scheme 1.12), and gave a 58% yield of the epoxide. In the first instance our attempts to open the epoxide were directed to the use of lithium diethylamide[88,89] in ether/HMPA. This procedure led only to a large number of unidentified products and was particularly difficult to carry out effectively on the small quantities of material at our disposal.

Our attention was then directed towards using an organoselenium reagent[90]. Thus treatment of the epoxide(125) with sodium phenyl selenide in boiling *n*-propanol gave the dialkyl selenide(128). Oxidation of this *in situ* with hydrogen peroxide in THF gave the selenoxide which eliminates spontaneously at room temperature to the allylic alcohol(126). (Scheme 3.35).



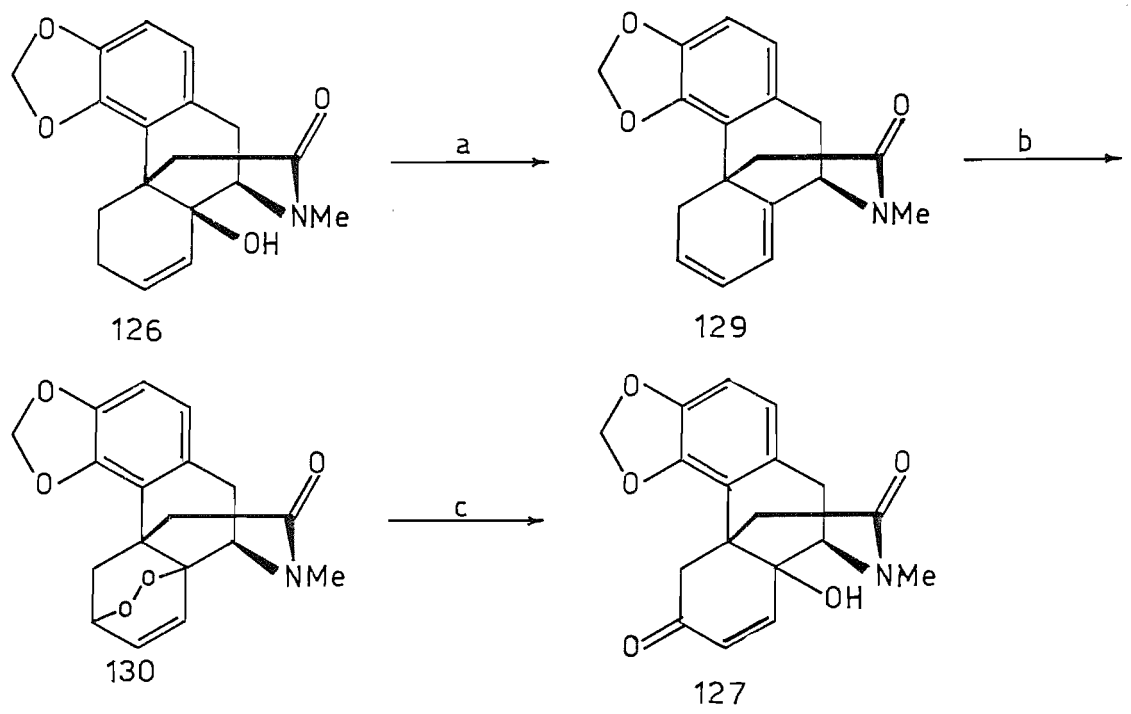
124 128 126

a PhSeNa b H_2O_2

Scheme 3.35

To convert the allylic alcohol(126) through to the required enone(127) we hoped to make use of work carried out by Pearson[91] *et al* on the oxidation of alkenes with *t*-butyl hydroperoxide catalysed by chromium (0) hexacarbonyl in acetonitrile. However when our system was subjected to the described conditions only a large number of unrecognisable products could be detected. In their work Pearson *et al* had reported particularly low yields in the presence of tertiary alcohols. This combined with the possibility of forming a chromium complex with the aromatic ring and subsequent benzylic oxidations persuaded us not to pursue the reaction further.

Still wishing to end up with the enone system(127) we considered the possibility of converting the allylic alcohol(126) to a diene(129). It was envisaged that this would undergo a Diels-Alder reaction with singlet oxygen to give the endoperoxide(130). This could then be opened with base to give the enone(127). (Scheme 3.36).

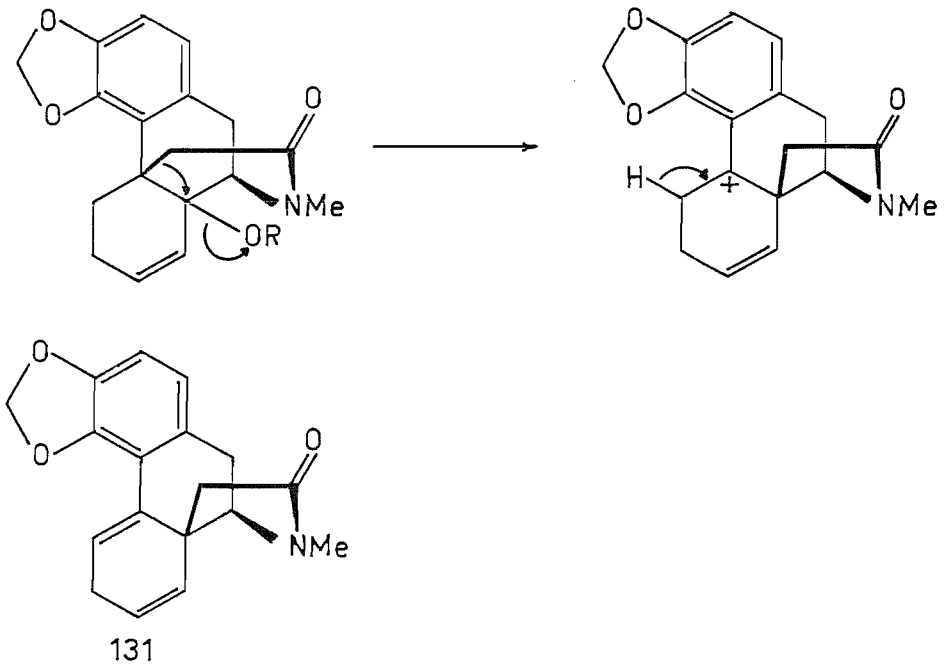


a dehydrate b O=O c Et_3N

Scheme 3.36

To convert the allylic alcohol(126) into the required diene(129) we envisaged using a simple dehydration procedure. The only proton that could be removed in such a procedure would be the one α to the double bond. The proton next to nitrogen would give rise to an 'anti

Brett' alkene and would not be favourable. Hence the allylic alcohol(126) was subjected to the same dehydration procedure as had been used previously with phosphorus oxychloride in pyridine. This led to the isolation of a single fast moving material which initially appeared to be the required product. Therefore we attempted a singlet oxygen Diels-Alder reaction using the procedure developed by Barton *et al*[92]. This led only to the recovery of the starting material. Use of the conventional photolysis procedure with rose bengal as a photo sensitizer also led only to the isolation of starting material. On closer inspection of the spectral data for the proposed diene it was noticed that the carbonyl stretch in the infra red was not consistent with the other morphinan that we had made. Whilst all the previous morphinans had the lactam carbonyl stretch in the range 1635-1650 cm^{-1}, our material gave a carbonyl stretch at 1680 cm^{-1}. This, and a closer inspection of the complexed olefinic signals in the proton n.m.r. led us to propose the structure shown in Scheme 3.36 for the material.



Scheme 3.37

Sadly by this stage nearly all our material had been used up, and more importantly all the available time had been used, therefore the work has had to halt here to await new hands, new ideas and new material.

CHAPTER FOUR

EXPERIMENTAL

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected.

I.r. spectra were recorded in cm^{-1} on a Perkin Elmer 298 spectrometer and calibrated using the 1603 cm^{-1} peak of a polystyrene film as reference. U.v. spectra were performed by Glaxo Group Research, Ware in pure ethanol.

Proton n.m.r spectra were recorded either, at 100 MHz on a Varian Associates XL100/12 Spectrometer, at 250 MHz on a Bruker AM 250 or WM 250 spectrometer, or at 360 MHz on a Bruker AM 360 Spectrometer. All spectra were recorded in $CDCl_3$ with TMS as internal standard equal to 0δ.

Carbon 13 n.m.r were recorded either on a Varian Associates XL100/12 spectrometer at 25.5 MHz or on a Bruker AM 360 spectrometer at 90.56 MHz, using $CDCl_3$ as solvent and TMS as internal standard equal to 0δ, except where otherwise stated.

Mass spectra were recorded on a Kratos A.E.I. MS30 spectrophotometer using 70eV electron impact ionisation and a DS 55s data system.

Elemental analyses were performed by Glaxo Group Research, Ware.

Chromatographic separations were performed either on Kiesegel 60 using the method of Still[93] for samples of less than 0.5 g or on Kieselgel 60H using the method of Harwood[94] for samples greater than 0.5g. Solvents for chromatography were used as supplied with the exception of petrol which was distilled from calcium hydride prior to use.

TLC was conducted with Kiesegel on precoated glass plates using U.v. light (254 nm) and then aqueous potassium permanganate for visualization.

Except where otherwise stated all reactions were performed under an atmosphere of nitrogen in solvents freshly distilled from the following drying agents, also under an atmosphere of nitrogen.

THF, Ether	sodium in the presence of benzophenone
Methanol	magnesium methoxide
chloroform, carbon tetrachloride	phosphorus pentoxide
All other solvents	calcium hydride

Reagents were used as supplied expect where otherwise stated.

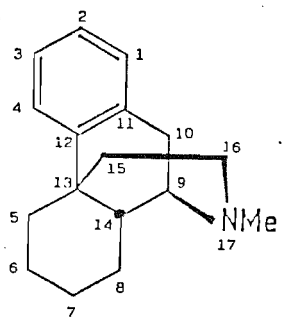
Dilute aqueous inorganic solutions were used at the following strengths:

Hydrochloric acid	2M
Brine	saturated solution of sodium chloride at 20°C
Sodium hydroxide	2M
Sodium carbonate	saturated at 20°C
Sodium bicarbonate	saturated at 20°C
Sodium thiosulphate	1M
Sodium metabisulphite	1M
Sodium sulphite	1M
Sodium sulphate	saturated at 20°C
Ammonium chloride	saturated at 20°C
Copper (II) sulphate	1M

Alkyllithiums were supplied by Aldrich Chemical Company in the following solvents and strengths, and were all titrated prior to use.

n-Butyllithium	2.5M in hexanes
t-Butyllithium	1.7M in pentane
Methyllithium	1.4M in ether (halide content 0.05M)

Throughout the following text compounds are named by the system used in Chemical Abstracts. The numbering system adopted for the morphinan system is illustrated below.



N-(1,3-Benzodioxol-5-ylmethylene)-cyclohexanamine (77). Piperonal(76) (150g, 1 mol) and cyclohexylamine (140 ml, 1.2 mol) were heated under reflux in benzene (700 ml). Water was removed with a Dean-Stark apparatus over 24 h and the reaction allowed to cool. The solvent was removed *in vacuo* and the resulting solid recrystallised (petrol) to

yield the imine(77) (225g, 98%) as white needles.

Physical properties and spectroscopic data were in agreement with the literature[95].

4-Iodo-1,3-benzodioxole-5-carboxaldehyde (79). To a solution of the imine(77) (222g, 0.97 mol) in THF (2.5l) at -78°C was added *n*-butyllithium solution (1 mol) with mechanical stirring. After 40 min iodine (254g, 1 mol) in THF (270 ml) was added, dropwise with stirring at such a rate that the temperature did not exceed -60°C. The reaction mixture was then left to reach ambient temperature overnight before addition to dilute hydrochloric acid (3l). This mixture was stirred vigorously for 24 h before the organic material was extracted into ether (3 x 1.5l). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give a crude solid product. Recrystallisation twice from ethanol gave the aldehyde(79) as white needles (102.7g, 39%). Physical properties and spectroscopic data were in agreement with the literature[74].

4-Iodo-1,3-benzodioxole-5-methanol (80) (Method A). Sodium borohydride (6.9g, 0.18 mol) in water (250 ml) was added to a stirred solution of the aldehyde in methanol (1.1l). Stirring was continued for 1h before dilute hydrochloric acid was added until effervescence ceased. The reaction was concentrated to 20% of its original volume *in vacuo* and the resulting residue partitioned between brine (500 ml) and ether (3 x 1l). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude solid product. Recrystallisation from cyclohexane gave the *alcohol*(80) as white needles (81.3g, 85%). M.p. = 93-95°C. A sample was sublimed in a Kugelrohr (oven temperature 80°C, 0.03 mmHg) to give a white amorphous solid. (Found: C, 34.5; H, 2.4%. $C_8H_7IO_3$ requires C, 34.6; H, 2.5%.)

I.r.

$\nu_{max.}(CH_2Cl_2)$. 3950m (OH), 1460s, and 1050s.

N.m.r.

(δ_H, 250 MHz) 2.16 (1H, t, *J* 5 Hz, O*H*), 4.6 (2H, d, *J* 5 Hz, CH_2OH), 6.04 (2H, s, OCH_2O), 6.74 (1H, d, *J* 8 Hz, *aryl proton*), and 6.92 (1H, d, *J* 8 Hz, *aryl proton*).

Mass spectrum

m/z (%) 277 (100, M^+), and 260 (14).

5-Bromomethyl-4-iodo-1,3-benzodioxle (81). Freshly distilled phosphorus tribromide (16 ml, 0.17 mol) was added to a stirred solution of the benzyl alcohol(80) (30g, 0.11 mol) in dichloromethane (800 ml) at 0°C. The reaction was allowed to attain room temperature over 1 h, with stirring before being poured into aqueous sodium bicarbonate (1l) in a large vessel. The organic layer was separated and the aqueous layer washed with dichloromethane (2 X 250 ml). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude solid product. Recrystallisation from cyclohexane gave the *bromide*(81) as white needles (33.6g, 91%). M.p. 122-125°C. A sample was sublimed in a Kugelrohr (oven temperature 70°C, 0.03 mmHg) to give a white amorphous solid. (Found: C, 28.2; H, 1.8%. $C_8H_6BrIO_2$ requires C, 28.2; H, 1.8%.)

I.r.

ν_{max} (CH_2Cl_2) 1562s, 1050s, and 941s.

N.m.r.

(δ_H, 250 MHz) 4.60 (2H, s, CH_2Br), 6.05 (2H, s, OCH_2O), 6.72 (1H, d, *J* 8 Hz, *aryl proton*), and 7.08 (1H, d, *J* 8 Hz, *aryl proton*).

(δ_C, 25.2 MHz) 38.2 (CH_2Br), 76.9 (*C*I), 101.0 (OCH_2O), 108.2 (*C*H), 124.1 (*C*H), 133.0 (*C*) 146.2 (*C*), and 150.3 (*C*).

Mass Spectrum

m/z(%) 341 (6,M^+), 339(6,M^+), and 261 (100, *M*-Br).

4-Iodo-5-(2-propenyl)-1,3-benzodioxole (82). To a well stirred solution of the benzyl bromide(81) (20g, 58.6 mmol), copper (I) iodide (1.12g, 588 mmol), and 2,2'dipyridyl (0.92g, 5.89 mmol) in THF (120 ml) at 0°C was added vinylmagnesium bromide solution (59 ml of a 1M solution in THF, 59 mmol). After stirring for 2h at ambient temperature ammonium chloride (15g) was added followed by wet ether (150 ml) and concentrated aqueous ammonia solution (300 ml). The reaction mixture was stirred vigorously until a deep blue aqueous phase was produced and the organic layer was then separated. The organic layer was washed with dilute hydrochloric acid (250 ml) and sodium bicarbonate solution (200 ml). After drying (Na_2SO_4) the

solvent was removed *in vacuo* to give the crude product. Trituration with petrol and concentration of the triturant *in vacuo* gave a pale yellow oil which was distilled (b.p. 100-102°C, 0.035 mmHg) to give the *iodide*(82) as a colourless oil (11.64g, 69%).

I.r. (film)

ν_{max}	2900s, 1638m (C=C), and 1410s.

N.m.r.

(δ_H, 100 MHz)	3.24-3.60 (2H, m, $CH_2CH=CH_2$), 4.91-5.25 (2H, m, $CH=CH_2$), 5.73-6.20 (1H, m, $CH=CH_2$), 6.02 (2H, s, OCH_2O), and 6.72 (2H, s, *aryl protons*).
(δ_C, 90.6 MHz),	43.3 ($CH_2CH=CH_2$), 77.9 (*C*I), 100.8 (OCH_2O), 108.2 (*C*H), 116.7 ($CH=CH_2$), 122.3 (*C*H), 135.7 (*C*), 136.5 ($CH=CH_2$), 144.7 (*C*), and 149.9 (*C*).

Mass Spectrum

High Resolution:	287.9628; calculated for $C_{10}H_9IO_2$ 287.9648.
m/z (%)	288 (100, M^+), 261 (9, M-CH=CH_2), 131 (26), and 103 (34).

1,3-Benzodioxole-5-[(1-ethoxyethoxy)methyl] (83). Piperonyl alcohol (90g, 0.59 mol) and trifluoroacetic acid (1 ml) were dissolved in ethyl vinyl ether (500 ml) and stirred at ambient temperature until none of the alcohol remained by TLC (approximately 48h). Ether (500 ml) was added and the reaction mixture washed with dilute sodium hydroxide solution. The organic layer was dried (K_2CO_3) and concentrated *in vacuo* to give the crude product. Distillation gave the pure product as a colourless oil (126g, 95%). Physical properties and spectroscopic data were in agreement with the literature[75].

4-Iodo-1,3-benzodioxole-5-methanol (Method B). To the acetal(83) (70g, 0.313 mol) in ether (1.5l) at 0°C was added dropwise, with mechanical stirring, *n*-butyllithium solution (0.344 mol) such that the temperature did not exceed 0°C. The reaction was stirred at 0°C for a further 2h before cooling to -78°C. Iodine (90g, 0.345 mol) in THF (220 ml) was added dropwise whilst the temperature was maintained below -60°C. When the addition was complete the cooling bath was removed and the reaction allowed to warm to 0°C. Sodium thiosulphate solution (500 ml) was added followed by sodium bicarbonate solution (500 ml). The ether layer was separated and the aqueous phase washed

with ether (2 X 300 ml). The combined ethereal layers were dried (Na_2SO_4) and the solvent removed *in vacuo* to give a brown oil. This was added to methanol (2.5l) and the resulting solution stirred with concentrated hydrochloric acid (100 ml) for 40 min. Sodium carbonate solution was added until all the acid had been neutralised and the solvent removed *in vacuo*. The residue was then partitioned between water (500 ml) and dichloromethane (1l). The organic phase was separated and the aqueous layer washed with dichloromethane (2 X 300 ml). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude alcohol as a brown solid. This was recrystallised twice from cyclohexane to give white needles (51.3g, 59%) which exhibited the same spectroscopic properties as noted above for the alcohol(80).

4-Iodo-1,3-benzodioxole-5-methanol (Method C). *n*-Butyllithium solution (0.123 mol) was added dropwise to a mechanically stirred solution of piperonyl alcohol (8.5g, 55.9 mmol) in THF (160 ml) at 0°C, at such a rate that the temperature remained between -5°C and 0°C. The reaction was stirred for a further 2h at 0°C before being cooled to -70°C. A solution of iodine (14.2g, 55.9 mmol) in THF (50 ml) was added dropwise to the reaction mixture such that the temperature did not exceed -60°C. The cooling bath was removed and when the reaction mixture had reached 0°C ammonium chloride solution (100 ml) was added. The organic phase was separated and the aqueous layer washed with ether (2 X 50 ml). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Recrystallisation twice from cyclohexane gave the benzyl alcohol(80) (6.9g, 44%) showing the same physical properties noted above.

3-Methoxycyclohex-2-enone 1,3-cyclohexanedione (31g, 0.28 mol), methanol (75 ml), concentrated sulphuric acid (1 ml) magnesium sulphate (55g) and dichloromethane (800 ml) were stirred together overnight at ambient temperature. The reaction mixture was then poured into sodium bicarbonate solution (300 ml) and the organic layer separated. The aqueous layer was washed with dichloromethane (2 X 100 ml) and the combined organic layers dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil. Distillation

(b.p.89°C, 0.02 mmHg) gave 3-methoxycyclohex-2-enone[77] as a colourless oil which solidified in the fridge to a low melting colourless solid (31.5g,90%).

I.r.

ν_{max} (film)	2960s, 1660s (C=O), and 1610s (C=C).

N.m.r.

(δ_H, 360 MHz)	1.97 (2H, quintet, J 6 Hz, CH_2), 2.29 (2H, t, J 6 Hz, CH_2), 2.42 (2H, t, J 6 Hz, CH_2), 3.71 (3H, s, OCH_3), and 5.33 (1H, s, CH).
(δ_C, 90.6 MHz)	21.5 (CH_2), 28.9 (CH_2), 36.9 (CH_2), 55.7 (CH_3), 102.3 (CH), 178.5 ($COCH_3$), and 198.6 (CO).

3,5-Dimethoxy-2,5-cyclohexadiene-1-methanol (89). Small pieces of sodium metal (75g, 3.24 mol) were added to a mechanically stirred solution of 3,4,5-trimethoxybenzoic acid (125g, 0.589 mol) in methanol (750 ml)/liquid ammonia (2.5l) at reflux. After the addition was complete ammonium chloride (300g) was added in portions and the ammonia allowed to evaporate overnight. Iced water (2l) was added such that all the solid material went into solution. Dilute hydrochloric acid was then added in portions and the aqueous layer extracted with dichloromethane until it reached pH 3. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude acid. This was dissolved/suspended in ether (700 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (30g) in ether (300 ml) so as to maintain a steady reflux. After stirring for a further 20 min sodium sulphate solution was added dropwise with stirring until all the excess hydride had been destroyed. The solution was filtered and the filtrate concentrated *in vacuo* to give a pale yellow oil. Distillation gave the alcohol as a viscous oil (36.8g, 37%). Physical properties and spectroscopic data were in accordance with the literature[78].

3-Methoxy-5-[(phenylmethoxy)methyl]-2-cyclohexen-1-one (90). Sodium hydride (15g as a 60% dispersion in oil, 0.38 mol) was added with stirring to a solution of 3,5-dimethoxy-2,5-cyclohexadiene-1-methanol(89)[78] (36.5g, 0.21 mol) in THF (600 ml). After the evolution of hydrogen had ceased the reaction was brought to reflux and benzyl bromide (30 ml, 0.25 mol) was added dropwise over 5 min.

Heating was continued for a further 1h before the reaction was allowed to cool to ambient temperature. Sodium hydroxide solution (50 ml) was added dropwise with stirring followed by water (150 ml) and ether (200 ml). The aqueous layer was separated and washed with ether (2 X 50 ml). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil. The oil was mixed with acetic acid (700 ml), acetic anhydride (70 ml) and anhydrous sodium acetate (70g), and stirred at 30°C for 2h before removing the majority of the solvent *in vacuo*. The residue was added to a water (2l)/ether (500 ml) mixture and excess acid destroyed by the addition of solid sodium carbonate. The ether layer was separated and the aqueous layer washed with ether (3 X 300 ml). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil. Chromatography (ether) gave the required *enone*(90) (39.8g, 75%). A sample was distilled in a Kugelrohr (oven temperature 200°C, 0.1 mmHg) to give a colourless oil which solidified on standing. M.p. 33-35°C. (Found: C, 73.5; H, 7.5%. $C_{15}H_{18}O_3$ requires C, 73.2; H, 7.4%.)

I.r.

ν_{max} ($CHBr_3$)	2860m, 1640s (C=O), and 1600s (C=C).

N.m.r.

(δ_H, 250 MHz)	2.1-2.55 (5H, m, CH_2CHCH_2), 3.44 (2H, m, OCH_2CH), 3.70 (3H, s, OCH_3), 4.52 (2H, s, $PhCH_2O$), 5.38 (1H, s, C=CH), and 7.33 (5H, m, Ph).
(δ_C, 90.6 MHz)	32.3 (CH_2), 34.5 (CH), 40.2 (CH_2), 45.9 (OCH_3), 73.3 (CH_2O), 73.4 (CH_2O), 102.4 (C=CH), 127.8 (CH), 127.9 (CH), 128.7 (CH), 138.6 (C), 177.9 (C=COMe), and 198.6 (CO).

Mass Spectrum

High resolution:	246.1255; calculated for $C_{15}H_{18}O_3$ 246.1256.
m/z (%)	246 (2.4, *M*+), 215 (4, *M*-OMe), 155 (4, *M*-CH_2Ph), 125 (100, *M*-CH_2OCH_2Ph), and 91 (97, $PhCH_2$).

3-[5-(2-Propenyl)-1,3-benzodioxol-4-yl]-2-cyclohexen-1-one (91). A flask charged with a mixture of the aromatic iodide(82) (10.1g, 35 mmol) and magnesium turnings (0.84g, 35 mmol) in boiling ether (30 ml) was heated in an ultrasonic cleaning bath for 24 min. Cyclohexane (30 ml) was added to give a two phase solution which was brought to reflux, with vigorous stirring. 3-Methoxycyclohex-2-enone (6.1g,

48 mmol) in hot cyclohexane (30 ml) was added at such a rate as to maintain a vigorous reflux. After the addition was complete the reaction was allowed to cool. Dilute hydrochloric acid (50 ml) was added and the reaction stirred until all the gummy residue had dissolved. The aqueous layer was separated and washed with ether (2 X 20 ml). The combined organic layers were then washed with sodium bicarbonate solution, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Chromatography (petrol:ether, 1:1) gave the *enone*(91) as an almost colourless viscous oil (5.53 g, 62%). A sample was distilled in a Kugelrohr (oven temperature 180°C, 0.1 mmHg) to give a very pale yellow oil. (Found: C, 74.7; H, 6.4%. $C_{16}H_{16}O_3$ requires C, 74.4; H 6.3%.)

U.V.

λ_{max} (EtOH) 235 (ε 14,000 $dm^3\ mol^{-1}cm^{-1}$), and 268 nm (ε 7920).

I.r.

ν_{max} (film) 2890m, 1669s (C=O), 1640m, and 1450s.

N.m.r.

(δ_H, 100 MHz). 1.96-2.70 (6H, m, $CH_2CH_2CH_2$), 3.21-3.38 (2H, m, $CH_2CH{=}CH_2$), 4.92-5.17 (2H, m, $CH{=}CH_2$), 5.60-6.08 (2H, m, $CH{=}CH_2$ and $COCH{=}C$), 5.96 (2H, s, OCH_2O), and 6.75 (2H, s, *aryl protons*).

(δ_C, 25.2 MHz) 22.9 (CH_2), 30.3 (CH_2), 36.8 (CH_2), 37.4 (CH_2), 101.2 (OCH_2), 108.1 (CH), 116.0 (C), 122.7 (CH), 123.0 (CH), 129.9 ($CH{=}CH_2$), 130.0 (CH), 137.6 (C), 144.3 (C), 145.9 (C), 157.5 (C), and 199.0 (CO).

Mass Spectrum

High resolution: 256.1081; calculated for $C_{16}H_{16}O_3$ 256.1099.

m/z (%) 256 (61, M^+) 228 (100, M-CO), 200 (46), and 185 (44).

5-[Phenylmethoxy)methyl]-3-[5-(2-propenyl)-1,3-benzodioxol-4-yl]-2-cyclohexen-1-one. The *enone*(92) was produced by the same procedure as the enone(91) from the aromatic iodide(82) and 3-methoxy-5-[(phenylmethoxy) methyl]-2-cyclohexen-1-one(90) in 75% yield as a gel, without distillation. (Found: C, 76.7; H, 6.4%. $C_{24}H_{24}O_4$ requires C, 76.6; H, 6.4%.)

U.V.

λ_{max} (EtOH) 235 (ε 13800 $dm^3mol^{-1}cm^{-1}$), and 268 nm (ε 7430).

I.r.

ν_{max} (film). 2890m, 1670s (C=O), 1645m, and 1495s.

N.m.r.

(δ_H, 250 MHz), 2.4 (1H, m, CH_2CHCH_2), 2.6 (4H, m, CH_2CHCH_2), 3.26 (2H, d, *J* 6 Hz, $CH_2CH{=}CH_2$), 3.48 (2H, d, *J* 4 Hz, $CHCH_2O$), 4.53 (2H, s, OCH_2Ph), 4.93 (1H, dq, *J* 17 and 1.6 Hz, CH=CHH), 5.03 (1H, dq, *J* 10.4 and 1.6Hz, CH=CHH), 5.85 (1H, m, $CH{=}CH_2$), 5.94 (2H, s, OCH_2O), 6.05 (1H, s, COCH=C), 6.69 (1H, d, *J* 8 Hz, *aryl proton*), 6.74 (1H, d, *J* 8 Hz, *aryl proton*), and 7.32 (5H, m, Ph).

(δ_C, 90.6 MHz) 33.4 (CH_2), 35.7 (CH), 36.7 (CH_2), 40.4 (CH_2), 73.1 (CH_2), 73.2 (CH_2), 101.1 (CH_2O), 108.1 (CH), 115.9 ($CH{=}CH_2$), 122.5 (C), 122.9 (CH), 127.4 (CH), 127.5 (CH), 128.3 (CH), 129.78 (CH), 129.81 (C), 137.5 (CH), 138.3 (C), 144.2 (C), 145.8 (C), 156.0 (C), and 198.2 (CO).

Mass Spectrum

High resolution: 376.1647; calculated for $C_{24}H_{24}O_4$ 376.1674.

m/z (%) 376 (5, M^+), 285(31, M-CH_2Ph), 255 (20, M-CH_2OCH_2Ph), and 91 (100, CH_2Ph).

3-[5-(2-Propenyl)-1,3-benzodioxol-4-yl]-2-cyclohexen-1-ol (93). Sodium borohydride (2.5g, 66 mmol) was added in portions over 10 min to a stirred solution of the enone(91) (16.7g, 65 mmol) and cerium (III) chloride (24.1g, 65 mmol) in methanol (100 ml). After stirring for 1.5h dilute hydrochloric acid was added slowly, until effervescence ceased, and the solvent removed *in vacuo*. The residue was partitioned between sodium bicarbonate solution (100 ml) and ether (200 ml) and the organic phase separated. The aqueous phase was washed with ether (2 X 100 ml) and the combined organic layers dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Chromatography (ether) followed by distillation (b.p. 166-170°C, 0.06 mmHg) gave the *alcohol*(93) as a colourless viscous oil (15.58g, 93%). (Found: C, 74.2; H 7.2%. $C_{16}H_{18}O_3$ requires C, 74.4; H, 7.0%.)

U.V.

λ_{max} (EtOH) 289 nm (ε 3190 $dm^3\ mol^{-1}cm^{-1}$)

I.r.

ν_{max} (CCl_4) 3400br (OH), 2940s and 1640m (C=C).

N.m.r.

(δ_H, 100 MHz) 1.37-2.60 (7H, m, $CH_2CH_2CH_2$ and OH), 3.08-3.34 (2H, m, $CH_2CH{=}CH_2$), 4.32 (1H, m, CHOH), 4.70-5.10 (2H, m, $CH{=}CH_2$), 5.33-6.08 (2H, m, $CH{=}CH_2$ and CH=CAr), 5.87 (2H, s, OCH_2O), and 6.66 (2H, s, *aryl protons*).

(δ_C, 25.2 MHz) 19.4 (CH_2), 29.3 (CH_2), 31.5 (CH_2), 36.5 (CH_2), 65.5 (CHOH), 100.7 (OCH_2O), 107.0 (CH), 115.5 ($CH{=}CH_2$), 122.4 (CH), 124.8 (C), 130.5 (CH), 131.1 (C), 135.9 (C), 138.3 (CH), 144.7 (C), and 145.4 (C).

Mass Spectrum

High resolution: 258.1258; calculated for $C_{16}H_{18}O_3$; 258.1256.

m/z (%) 258 (100, M^+) , 240 (39, M-H_2O), 227 (63), 185 (76), and 115 (97).

cis-*5-[(Phenylmethoxy)methyl]-3-[5-(2-propenyl)-1,3-benzodioxol-4-yl]-2-cyclohexen-1-ol* (94). Sodium borohydride (3g, 79.4 mmol) was added in portions to a stirred solution of the enone(92) (26.8g, 71.3 mmol) in methanol (160 ml) at 0°C. After the addition was complete the reaction was stirred for a further 30 min before dilute hydrochloric acid was added until effervescence ceased. The solvent was removed *in vacuo* and the residue partitioned between water (150 ml) and ether (200 ml). The organic layer was separated and the aqueous phase washed with ether (2 X 100 ml). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Chromatography (ether) gave the pure *alcohol* (94) as a colourless syrup (24.5g, 91%) (Found: C, 75.8; H, 6.9%. $C_{24}H_{26}O_4$ requires C, 76.15; H, 6.9%).

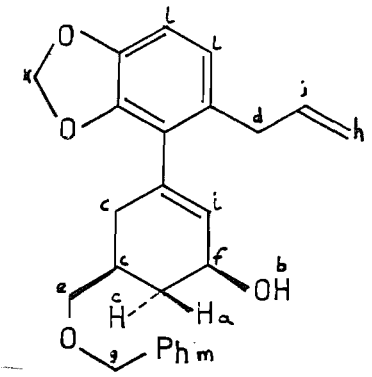
U.V.

λ_{max} (EtOH) 289 nm (ε 3180 $dm^3\ mol^{-1}cm^{-1}$).

I.r.

ν_{max} (film). 3400br (OH), 2780s, 1445s, and (C=C).

N.m.r.



(δ_H, 250 MHz) 1.37 (1H, q, *J* 11 Hz, *a*), 1.72 (1H, d, *J* 7 Hz, *b*), 2.0-2.4 (4H, m, *c*), 3.3 (2H, d, *J* 6 Hz, *d*), 3.46 (2H, d, *J* 6 Hz, *e*), 4.48 (1H, m, *f*), 4.53 (2H, s, *g*), 4.9-5.1 (2H, m, *h*), 5.69 (1H, s, *i*), 5.9 (1H, m, *j*), 5.95 (2H, s, *k*), 6.66 (1H, d, *J* 9 Hz, *l*), 6.70 (1H, d, *J* 9 Hz, *m*), and 7.3 (5H, m, *m*).

Mass Spectrum

High resolution: 378.1854; calculated for $C_{24}H_{26}O_4$ 378.1831.

m/z (%) 378 (2, *M*+), 360 (3, *M*-H_2O), 287 (4, *M*-CH_2Ph), 269 (6), and 91 (100, CH_2Ph)

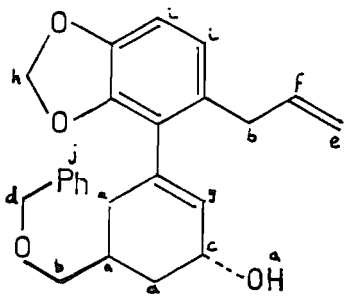
Trans-*5-[(Phenylmethoxy)methyl]-3-[5-(2-propenyl)-1,3-benzodioxol-4-yl]-2-cyclohexen-1-ol* (96). A solution of freshly distilled diethyl azodicarboxylate (3.9 ml, 24.8 mmol) in THF (25 ml) was added dropwise to a stirred mixture of the allylic alcohol(94) (4.65g, 12.3 mmol), triphenylphosphine (6.48g, 24.7 mmol) and benzoic acid (3g, 24.6 mmol) in THF (120 ml). After stirring overnight the solvent was removed *in vacuo* and the residue partitioned between ether (200 ml) and water (100 ml). The aqueous layer was separated and the ether layer dried (Na_2SO_4) before being concentrated *in vacuo* to give an oil. The resulting benzoate ester was separated from the unwanted products by chromatography (petrol: ether, 1:1) to give a colourless oil. It was then mixed with aqueous methanol (160 ml, 10% v/v water) and stirred overnight with potassium carbonate (3.4g, 24.6 mmol) at ambient temperature. The solvent was then removed *in vacuo* and the residue taken up in ether (150 ml) and water (100 ml). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo* to give an oil. Chromatography (petrol:ether, 3:7) gave the *allylic alcohol*(96) as a

viscous, colourless oil (3.12g, 67%). (Found: C, 76.3; H 7.1%; $C_{24}H_{26}O_4$ requires C, 76.2; H, 6.9%.)

I.r.

ν_{max} (film) 3400br (OH), 2910s, 1638m (C=C), and 1445s.

N.m.r.



(δ_H, 360 MHz) 1.5-2.4 (6H, m, *a*), 3.2-3.5 (4H, m, *b*), 4.39 (1H, m, *c*), 4.53 (2H, s, *d*), 4.9-5.1 (2H, m, *e*), 5.8-6.0 (2H, m, *f* and *g*), 5.9 (2H, s, *h*), 6.68 (2H, s, *i*), and 7.2-7.5 (5H, m, *j*).

Mass Spectrum

High resolution: 378.1857; calculated for $C_{24}H_{26}O_4$ 378.1831

m/z (%) 378 (9 M^+)360 (4, *M*-H_2O), 287 (18, *M*-CH_2Ph), and 91 (100, CH_2Ph).

N,N-*Dimethyl-1-[5-(2-propenyl)-1,3-benzodioxol-4-yl]-2-cyclohexene-1-acetamide* (97). Freshly distilled *N,N*-dimethylacetamide dimethyl acetal (21.2 ml, 145 mmol) was added to a solution of the allylic alcohol(93) (10.3g, 40 mmol) in toluene (300 ml) at reflux. Heating was continued for a further 16 h (during which time methanol was removed from the system by passing the distillate through a pressure equalising dropping funnel charged with 4A molecular sieves) before the reaction was allowed to cool. The reaction mixture was washed with dilute hydrochloric acid (100 ml) followed by sodium bicarbonate solution (100 ml) and dried (Na_2SO_4). The solvent was removed *in vacuo* to give an oil which solidifed on standing. Chromatography (ether) gave a white solid which was recrystallised from petrol (boiling range 80-100°C) to give white needles of the *amide*(97) (7.57g, 58%) M.p. 99-101°C. (Found: C, 73.1; H, 7.5; N, 4.3%. $C_{20}H_{25}NO_3$ requires C, 73.35; H, 7.7; N, 4.3%.)

I.r.

ν_{max} (CCl_4) 2930m, 1662s (C=O), and 1430m.

N.m.r.

(δ_H, 100 MHz) 1.32-2.04 (6H, m, $CH_2CH_2CH_2$), 2.61 (1H, d, *J* 17 Hz, CHHCON), 2.85 (3H, s, NCH_3CH_3), 2.97 (3H, s, NCH_3CH_3), 3.51 (1H, d, *J* 17 Hz, CHHCON), 3.57-3.76 (2H, m, $CH_2CH=CH_2$), 4.80-5.10 (2H, m, $CH=CH_2$), 5.55-6.17 (2H, m, $CH=CH_2$ and $CH=CHCH_2$), 5.74 (1H, d, J 1.5 Hz, OCHHO), 5.85 (1H, d, J 1.5 Hz, OCHHO), 6.53 (1H, t, *J* 2 Hz, $CH=CHCH_2$), and 6.65 (2H, s, *aryl protons*).

(δ_C, 90.6 MHz), 19.3 (CH_2), 24.8 (CH_2), 35.3 (CH_3), 35.6 (CH_2), 37.5 (CH_3), 38.1 (CH_2), 42.8 (*C*), 44.7 (CH_2), 99.3 (OCH_2O), 106.5 (*C*H), 114.7 (CH_2=CH), 125.1 (*C*H), 125.6 (*C*H), 129.4 (*C*), 133.1 (*C*), 136.5 (*C*H), 139.7 (*C*H), 144.7 (*C*), 145.3 (*C*), and 171.2 (*C*O).

Mass Spectrum

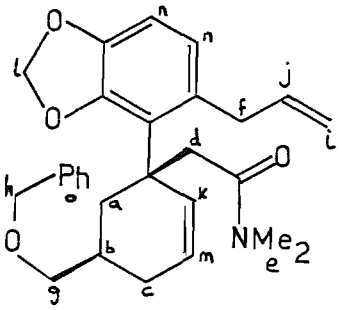
m/z (%) 327 (M^+, 7), 240 (60, M-CH_3CONMe_2), 166 (39), 87 (87, CH_3CONMe_2), and 72 (100).

cis-N,N-*Dimethyl-5-[(phenylmethoxy)methyl]-1-[5-(2-propenyl)-1,3-benzodioxol-4-yl]-2-cyclohexene-1-acetamide* (98). Freshly distilled *N,N*-dimethylacetamide dimethyl acetal (25 ml, 0.171 mol) was added to a solution of the allylic alcohol(94) (11.92g, 36.3 mmol) in methylcyclohexane/ethylcyclohexane at reflux. Heating was continued for a further 16 h (during this time methanol was removed from the reaction by passing the distillate through a pressure equalising dropping funnel charged with 4A molecular sieves) before the reaction was allowed to cool. The reaction mixture was washed with dilute hydrochloric acid followed by sodium bicarbonate solution and dried (Na_2SO_4). Concentration *in vacuo* gave a gum. Chromatography (ether) gave the desired amide (7.16 g, 49%) as a colourless gum. (Found C, 75.5; H, 7.6; N, 3.1%.) $C_{28}H_{33}NO_4$ requires C, 75.1; H, 7.4; N, 3.1%.)

I.r.

ν_{max} ($CHBr_3$) 2850s, 1635s (C=O), and 1451s.

N.m.r.



(δ_H, 250 MHz) 1.2-2.3 and 2.7-2.8 (5H, m, *a, b, c*), 2.54 (1H, d, *j* 15.5 Hz, *d*), 2.85 (3H, s, *e*), 2.92 (3H, s, *e*), 3.3 (3H, m, *f*), 3.4 (1H, d, *J* 15.5 Hz, d), 3.7 (2H, m, *g*), 4.39 (2H, s, *h*), 4.88 (1H, dq, *J* 17Hz, 2Hz, *i*), 4.97 (1H, dq, *J* 17Hz, 2Hz, *i*), 5.6 - 6.1 (2H, m, *j, k*), 5.73 (1H, d, *J* 1.5Hz, *l*), 5.82 (1H, d, *J* 1.5Hz, *l*), 6.53 (1H, d, *J* 10Hz, *m*), 6.58 (1H, d, *J* 8Hz, *n*), 6.65 (1H, d, *J* 8Hz, *n*), and 7.2-7.4 (5H, m, *o*).

Mass Spectrum

High Resolution: 447.2446; $C_{28}H_{33}NO_4$ requires 447.2410.

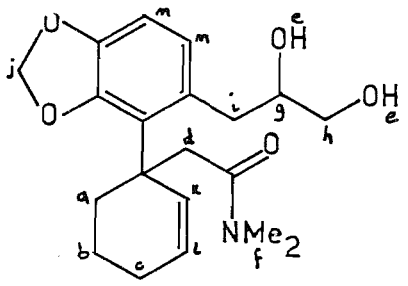
m/z(%) 447 (M^+, 0.3), 360 (1, *M*-$CH_3CON(CH_3)_2$), and 269 (2, 91 (100, -CH_2Ph)

N,N-*Dimethyl-1-[5-(propan-2,3-diol)-1,3-benzodioxol-4-yl]-2-cyclohexene-1-acetamide* (103). A solution of the amide(97) (4.52g, 13.8 mmol) in THF/H_2O/*t*-BuOH (30:4:1, 350 ml) was stirred for 25 h with osmium tetroxide (4 ml of a 0.5 w/v solution in *t*-butanol) and trimethylamine-*N*-oxide dihydrate (3.07g, 27.7 mmol). Sodium metabisulphite solution (50 ml) was added and the solvent volume reduced *in vacuo* to approximately 120 ml. The product was extracted into dichloromethane, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Chromatography (ethyl acetate) gave the *diol*(103) as a gum (4.59g, 92%).

I.r.

ν_{max}(CH_2Cl_2) 3400br (OH), 2940m, and 1636s (C=O).

N.m.r.



(δ_H, 360 MHz) 1.3-3.2 (10H, m, *a, b, c, d, e*), 2.82 (3H, s, *f*), 2.97 (3H, s, *f*), 3.4-4.1 (5H, m, *f, g, h, i*), 5.7-5.9 (3H, m, *j, k*), and 6.4-6.8 (3H, m, *l, m*).

Mass Spectrum

High Resolution: 361.1846; $C_{20}H_{27}NO_5$ requires 361.1889.

m/z (%) 361 (M^+, 3), 301 (10, *MH*-CHOH CH_2OH); 214 (85, *MH*-CHOH CH_2OH - $CH_3CON(CH_3)_2$), and 87 (100, $CH_3CON(CH_3)_2$).

cis-N,N-*Dimethyl-5-[(Phenylmethoxy)methyl]-1-[5-(Propan-2,3-diol)-1,3-benzodioxol-4-yl-2-cyclohexene-1-acetamide* (104). The amide(98) gave the *diol*(104) as a mixture of diastereomers in 83% yield, in the form of a gum, by the procedure used to give the diol(103).

I.r.

$\nu_{max}(CH_2Cl_2)$ 3420br (OH), 2880m, and 1635s (C=O).

N.m.r.

(δ_H, 360 MHz) 1.1-1.3 (1H, m), 1.7-4.6 (17H, m), 2.82 (3H, s, N*Me*), 2.96 (3H, s, N*Me*), 4.36 (2H, s, OCH_2O and C*H*=CH), 6.4-6.8 (3H, m, CH=C*H*, and *aryl protons*), and 7.2-7.4 (5H, m, *Ph*).

Mass Spectrum

High Resolution: 481.2500; $C_{28}H_{35}NO_6$ requires 481.2464.

m/z (%) 481 (*M*+, 0.3), 390 (9, *M*-CH_2Ph), 334 (14, *MH*-$CHOHCH_2OH$ - $CH_3CON(CH_3)_2$), 243 (20), and 91 (100, -CH_2Ph).

N,N-*Dimethyl-1-[5-(2-oxoethyl)-1,3-benzodioxol-4-yl]-2-cyclohexene-1-acetamide*. The diol(103) (7.31g, 20.2 mmol) and sodium periodate (7.5g, 35.1 mmol) were dissolved in THF/water (2:1, 210 ml) at ambient temperature and trifluoroacetic acid (0.5 ml) was added. The reaction was stirred for 30 min during which time a white precipitate formed. Sodium bicarbonate solution (50 ml) was added and the product extracted into ether (3 X 150 ml). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give the aldehyde(105) as a gum (6.67g, 100%).

I.r.

ν_{max} ($CHCl_3$)	2940s, 1718s (CHO), and 1639s (CON)

N.m.r.

(δ_H 360 MHz)	1.2-3.0 (6H, m, $CH_2CH_2CH_2$), 2.49 (1H, d, *J* 17Hz, C*H*HCON), 2.83 (3H, s, NCH_3CH_3), 2.97 (3H, s, NCH_3CH_3), 3.59 (1H, d, *J* 17Hz, CH*H*CON), 3.80 (1H, d, *J* 18Hz, C*H*HCHO), 4.27 (1H, d, *J* 18Hz, CH*H*CHO), 5.73 (1H, dt, *J* 10.3, 3.5 Hz, CH=C*H*CH_2), 5.82 (1H, s, OC*H*HO), 5.89 (1H, s, OCH*H*O), 6.46 (1H, d, *J* 10.3Hz, C*H*=$CHCH_2$), 6.52 (1H, d, *J* 8Hz, *aryl protons*), 6.65 (1H, d, *J* 8Hz, *aryl protons*) and 9.68 (1H, s, C*H*O).
(δ_C, 90.6 MHz)	19.1 (CH_2), 25.0 (CH_2), 35.3 (CH_3), 35.6 (CH_2), 37.4 (CH_3), 43.0 (*C*), 44.0 (CH_2), 49.7 (CH_2), 99.7 (OCH_2O), 106.6 (*C*H), 126.6 (*C*), 127.0 (*C*H), 127.3 (*C*H), 130.0 (*C*), 136.3 (*C*H), 145.0 (*C*), 146.6 (*C*), 171.0 (*C*ON), and 200.9 (*C*HO).

Mass Spectrum

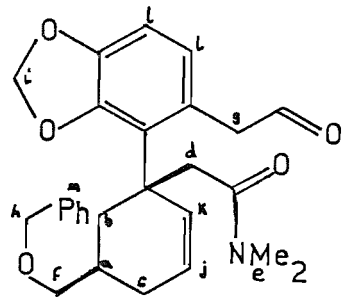
High Resolution:	329.1574; $C_{19}H_{23}NO_4$ requires 329.1627.
m/z (%)	329 (3, *M*+), 301 (15, *M*-CO), 242 (9, *M*-$CH_3CON(CH_3)_2$), 214 (34, *M*-$CH_3CON(CH_3)_2$-CO), and 87 (100, $CH_3CON(CH_3)_2$).

cis-N,N-*Dimethyl-5-[(phenylmethoxy)methyl]-1-[5-(2-oxoethyl)-1,3-benzodioxol-4-yl]-2-cyclohexene-1-acetamide* (106). Following the procedure used to give the aldehyde(105) described above, this *aldehyde*(106) was produced as a gum in 100% yield.

I.r.

ν_{max} (CH_2Cl_2) 2870m, 1720s (CHO), and 1646s (CON).

N.m.r.



(δ_H, 360 MHz) 1.1-2.1 (4H, m, *a, b, c*), 2.37 (1H, d, *J* 16.4Hz, *d*), 2.7-2.8 (1H, m, *a* or *b* or *c*), 2.82 (3H, s, *e*), 2.94 (3H, s, *e*), 3.2-3.35 (2H, m, *f*), 3.55 (1H, d, *J* 16.4Hz, *d*), 3.71 (1H, d, *J* 18.2Hz, *g*), 4.39 (2H, s, *h*), 4.44 (1H, d, *J* 18.2Hz, *g*), 5.74 (1H, d, *J* 1.2Hz, *i*), 5.77 (1H, dt, *J* 10.1Hz, 2.1Hz, *j*), 5.85 (1H, d, 1.2Hz, *i*), 6.45 (1H, d, *J* 10.1Hz, *k*), 6.52 (1H, d, *J* 8Hz, *l*), 6.67 (1H, d, *J* 8Hz, *l*), and 7.2-7.4 (5H, m, *m*).

Mass Spectrum

High Resolution: 449.2223; $C_{27}H_{31}NO_5$ requires 449.2202.

m/z (%) 449 (1, *M*+), 421 (4, *M*-CO), 358 (9, *M*-CH_2Ph), 334 (5, *M*-CO-$CH_3CON(CH_3)_2$), 330 (7) 243 (12), and 91 (100,-CH_2Ph).

General procedure for nitrone cycloaddition reaction.

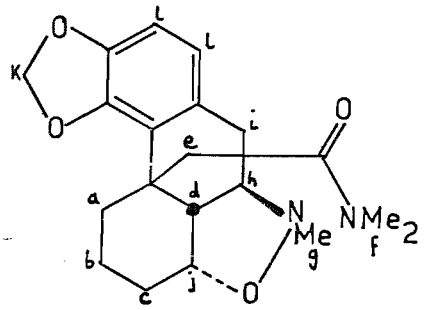
To the aldehyde (3.0 mmol) in benzene (35 ml) at reflux was added *N*-methylhydroxylamine (6.4 mmol). Water was removed from the reaction with a Dean-Stark apparatus over 2h. The reaction was then allowed to cool and the solvent removed *in vacuo*. Chromatography (acetone) gave the two adducts, the *endo* product in all cases being the faster moving material by TLC.

*(3aα,5aβ,11cα,11dα)-1,2,3,3a,5a,6-Hexahydro-*N,N,*5-trimethyl-[1,3]dioxolo[5,6]phenanthro[10,1-cd]isoxazole-11c(11dH)-acetamide* (107).

I.r.

ν_{max} (CH_2Cl_2) 2930s, 1640s (C=O), 1441m, and 1049m.

N.m.r.



(δ_H, 360 MHz) 1.2-1.7 (3H, m, *a, b, c, d*), 2.0-2.3 (2H, m, *a, b, c, d*), 2.7-3.3 (5H, m, *e, h, i*), 2.80 (3H, s, *f* or *g*), 2.86 (3H, s, *f* or *g*), 2.99 (3H, s, *f* or *g*), 3.24 (1H, m, *j*), 5.86 (1H, d, *J* 1.5Hz, *k*), 5.87 (1H, d, *J* 1.5Hz, *k*), and 7.26 (2H, s, *l*).

(δ_C, 90.6 MHz) 19.4 (CH_2), 32.2 (CH_2), 34.9 (CH_2), 34.9 (CH_2), 35.5 (CH_3), 37.5 (CH_3), 38.6 (CH_2), 40.5 (C), 46.5 (CH_3), 50.2 (CH), 63.9 (CHN), 73.7 (CHO), 100.2 (CH_2O), 106.6 (CH), 122.8 (CH), 127.7 (C), 128.8 (C), 144.3 (C), 145.9 (C), and 170.7 (CO)

Mass Spectrum

High resolution: 358.1928; $C_{20}H_{26}N_2O_4$ requires 358.1893.

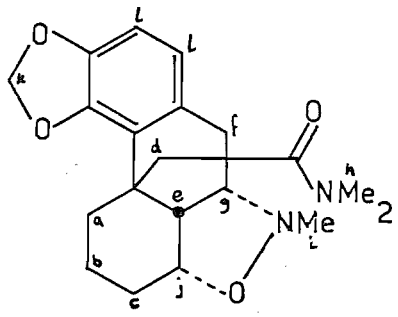
m/z (%) 358 (*M*+, 47), 254 (54) 242 (57) 224 (78), and 87 (100, $CH_3CON(CH_3)_2$).

*(3aα, 5aα, 11cα, 11dα)-1,2,3,3a,5a,6-Hexahydro-*N,N,*5-trimethyl[1,3]-dioxolo[5,6]phenanthro[10,1-cd]isoxazole-11c(11dH)-acetamide* (108).

I.r.

ν_{max}($CHCl_3$) 2940s, 1640s (C=O), 1446m, and 1054m.

N.m.r.



(δ_H, 360 MHz) 1.4-1.8 (6H, m, *a, b, c*), 2.2-3.5 (6H, m, *d, e, f ,g*), 2.74 (3H, s, *h* or *i*), 2.78 (3H, s, *h* or *i*), 2.86 (3H, s, *h* or *i*), 4.2-4.4 (1H, m, *j*), 5.80 (1H, d, *J* 1.2 Hz, *k*), 5.84 (1H, d, *J* 1.2 Hz, *k*), and 6.64 (2H, s, *l*)

(δ_C, 90.6 MHz) 17.5 (CH_2), 26.0 (CH_2), 32.3 (CH_2), 33.4 (CH_2), 35.5 (CH_3), 37.5 (CH_3), 39.6 (*C*), 43.0 (CH_2), 44.3 (CH_3), 48.5 (*C*H), 66.2 (*C*HN), 75.6 (*C*HO), 100.1 (CH_2O), 106.7 (*C*H), 122.2 (*C*H), 125.3 (*C*), 129.6 (*C*), 144.0 (*C*), 146.0 (*C*), and 170.9 (*C*O).

Mass Spectrum

High resolution: 358.1882; $C_{20}H_{26}N_2O_4$ requires 358.1893.

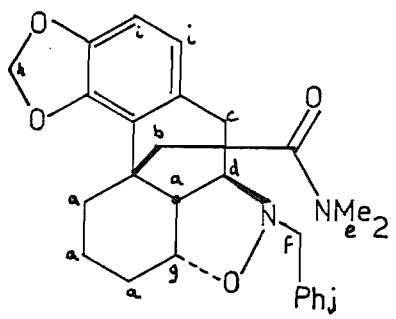
m/z (%) 358 (*M*+, 16), 254 (100, *M*-$CH_3CON(CH_3)_2$,-OH), 255 (49, *M*-$CH_3CON(CH_3)_2$,-OH,-NMe), and 87 (83, $CH_3CON(CH_3)_2$).

*(3aα,5aβ,11cα,11dα)-1,2,3,3a,5a,6-Hexahydro-*N,N*-dimethyl-5-phenylmethyl-[1,3]dioxolo[5,6]phenanthro[10,1-cd]isoxazole-11c(11dH)* (112).

I.r.

ν_{max} (CH_2Cl_2) 2940s, 1650s (C=O), 1443s, and 1058s.

N.m.r.



(δ_H, 360 MHz) 1.2-1.7 (5H, m, *a*), 1.95-2.1 (1H, m, *a*), 2.15-2.3 (1H, m, *a*), 2.6-3.3 (5H, m, *b, c, d*), 2.81 (3H, s, *e*), 2.98 (3H, s, *e*), 4.13 (1H, d, *J* 13.5 Hz, *f*), 4.18 (1H, d, *J* 13.5 Hz, *f*), 4.25-4.35 (1H, m, *g*), 5.868 (1H, d, *J* 1.6 Hz, *h*), 5.874 (1H, d, *J* 1.6 Hz, *h*), 6.55 (1H, d, *J* 7.8 Hz, *i*), 6.62 (1H, d, *J* 7.8 Hz, *i*), and 7.2-7.5 (5H, m, *j*).

Mass Spectrum

High resolution: 434.2188; $C_{26}H_{30}N_2O_4$ requires 434.2205.

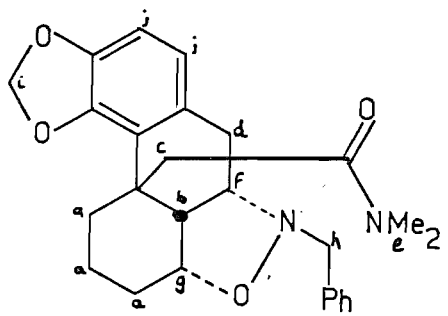
m/z (%) 434 (42, *M*+), 313 (38), 242 (87), and 87 (100, $CH_3CON(CH_3)_2$).

(3aα,5aβ,11cα,11dα)-1,2,3,3a,5a,6-Hexahydro-N,N-dimethyl-5-phenylmethyl-[1,3]dioxolo[5,6]phenanthro[10,1-cd]isoxazole-11c(11dH)-acetamide (113).

I.r.

ν_{max} (CH_2Cl_2) 2950s, 1640s (C=O), 1445s amd 1059s.

N.m.r.



(δ_H) 360 MHz) 1.2-1.9 (5H, m, *a*), 2.2-2.4 (1H, m, *a*), 2.55-2.8 (2H, m, *b, d*), 2.68 (1H, d, *J* 15 Hz, *c*), 2.78 (3H, s, *e*), 2.81 (1H, d, *J* 15 Hz, *c*), 2.86 (3H, s, *e*), 3.4-3.6 (2H, m, *d, f*), 3.99 (1H, d, *J* 13.2 Hz, *h*), 4.11 (1H, d, *J* 13.2 Hz, *h*), 4.3-4.4 (1H, m, *g*), 5.80 (1H, d, *J* 1.5 Hz, *i*), 5.84 (1H, d, *J* 1.5 Hz, *i*), 6.54 (1H, d, *J* 7.8 Hz, *j*), 6.63 (1H, d, *J* 7.8 Hz, *j*), and 7.2-7.45 (5H, m, *k*).

Mass Spectrum

High resolution: 434.2188; $C_{26}H_{30}N_2O_4$ requires 434.2205.

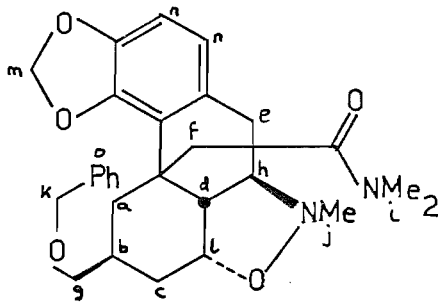
m/z (%) 434 (11, *M*+), 330 (20), 226 (10), and 91 (100).

(2β,3aα, 5aβ, 11cα, 11dα)-1,2,3,3a,5a,6-Hexahydro-N,N,5-trimethyl-2-[phenylmethoxy)methyl]-[1,3] dioxolo[5,6]phenanthro[10,1-cd]isoxazole-11c(11dH)-acetamide (114).

I.r.

ν_{max} (CH_2Cl_2) 2920s, 1650s (C=O), 1446s, and 1061s.

N.m.r.



(δ_H, 360 MHz) 1.1-3.5 (12H, m, *a–h*), 2.75 (3H, S, *I* OR *J*), 2.79 (3H, s, *i* or *j*), 2.92 (3H, S, *I* OR *J*), 4.4-4.6 (3H, m, *k*, *l*), 5.92 (1H, d, *j* 1 Hz, *m*), 5.93 (1H, d, *j* 1 Hz, *m*), 6.62 (1H, d, *j* 8 Hz, *n*), 6.65 (1H, d, *j* 8 Hz, *n*), and 7.2-7.4 (5H, m, *o*).

Mass spectrum

High resolution: 478.2475; $C_{28}H_{34}N_2O_5$ requires 478.2468.

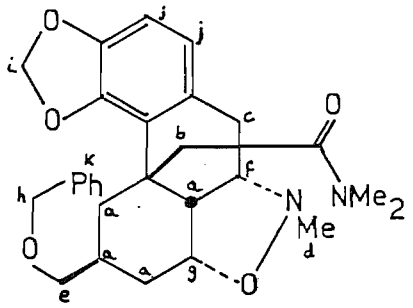
m/z (%) 478 (M^+, 16), 373 (18), 362 (22), 345 (43), 254 (50), and 91 (100, CH_2Ph).

(2β,3aα, 5aα, 11cα,11dα)-1,2,3,3a,5a,6-Hexahydro-2-[(phenylmethoxy)methyl]-N,N,5-trimethyl-[1,3]dioxolo[5,6]phenanthro[10,1-cd]isoxazole-11c(11dH)-acetamide (115).

I.r.

ν_{max} (CH_2Cl_2) 2870m, 1630s (CO), 1446s, and 1059s.

N.m.r.



(δ_H, 360 MHz) 1.3-1.7 (5H, m, *a*), 2.0-2.2 (1H, m, *a*), 2.5-3.1 (4H, m, *b, c*), 2.61 (3H, s, *d*), 2.71 (3H, s, *d*), 2.85 (3H, s, *d*), 3.25-3.45 (3H, m, *e, f*), 4.43 (1H, q, *J* 7.7 Hz, *g*), 4.48 (2H, s, *h*), 5.78 (1H, d, *J* 1.3 Hz, *i*), 5.84 (1H, d, *J* 1.3 Hz, *i*), 6.63 (1H, d, *J* 8 Hz, *j*), 6.67 (1H, d, *J* 8 Hz, *j*), and 7.2-7.4 (5H, m, *k*).

(δ_C), 90.6 MHz) 29.4 (CH_2), 30.4 (CH), 32.7 (CH_2), 35.5 (CH_2), 36.5 (CH_3), 38.6 (CH_3), 40.7 (C), 45.0 (CH_2), 45.2 (CH_3), 50.5 (CH), 66.6 (CH), 73.9 (CH_2), 75.6 (CH), 76.0 (CH_2), 101.1 (OCH_2O), 108.2 (CH), 123.4 (CH), 124.7 (C), 128.3 (CH), 128.4 (CH), 129.2 (CH), 131.2 (C), 139.8 (C), 147.1 (C), and 171.5 (CO).

Mass Spectrum

High resolution: 478.2478; $C_{28}H_{34}H_2O_5$ requires 478.2468.

m/z (%) 478 (12, *M*+), 373 (32, *M*-$CH_3CON(CH_3)_2$,-H_2O), 283 (29), and 91 (100-CH_2Ph).

General procedure for reduction of the isoxazolidine ring.

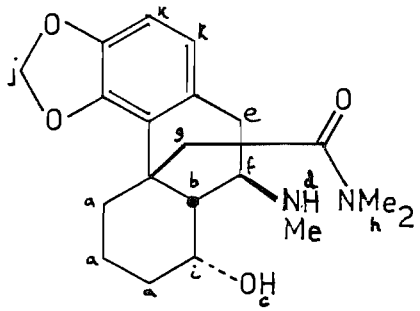
The isoxazolidine (0.7 mmol) in methanol (10 ml) was stirred overnight with a catalytic amount of palladium (II) chloride under an atmosphere of hydrogen (3.1 bar). The catalyst was removed by filtration and the filtrate concentrated *in vacuo*. The resulting material was partitioned between dichloromethane (10 ml) and sodium hydroxide solution (5 ml). The organic layer was separated, dried (K_2CO_3) and concentrated *in vacuo* to give the amino alcohol.

*(7α,8β,11aα)-6,7,8,9,10,11-Hexahydro-8-hydroxy-*N,N*-dimethyl-7-(methylamino) phenanthrd 3,4-d]-1,3-dioxole-11a(7aH)-acetamide* (109).

I.r.

ν_{max} ($CDCl_3$) 2940s, 1643s (CO), and 1444s.

N.m.r.



(δ_H, 250 MHz), 1.2-2.0 (9H, m, *a, b, c, d*), 2.6-3.2 (5H, m, *e, f, g*), 2.55 (3H, s, *h*), 2.82 (3H, s, *h*), 3.02 (3H, s, *h*), 4.0-4.2 (1H, m, *i*), 5.82 (1H, d, *J* 1.5 Hz, *j*), 5.86 (1H, d, *J* 1.5 Hz, *j*), 6.55 (1H, d, *J* 8 Hz, *k*), and 6.61 (1H, d, *J* 8 Hz, *k*).

Mass Spectrum

High resolution: 360.2046; $C_{20}H_{28}N_2O_4$ requires 360.2049.

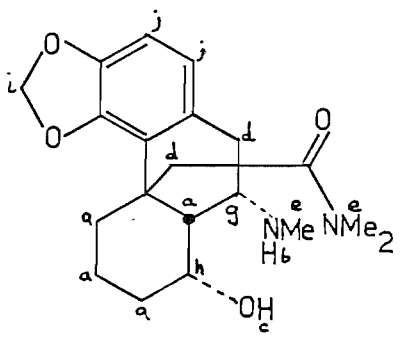
m/z (%) 360 (3, *M*+), 242 (100, *M*-$CH_3CON(CH_3)_2$,-NH_2Me), and 87 (69).

(7β,8β,11aα)-6,7,8,9,10,11-Hexahydro-8-hydroxy-N,N-dimethyl-7-(methylamino)phenanthrd 3,4-d]-1,3-dioxole-11a(7aH)-acetamide (110).

I.r.

ν_{max} (CH_2Cl_2) 2940s and 1645s (CO).

N.m.r.



(δ_H 360 MHz) 1.4-2.0 (6H, m, *a*), 2.2-3.3 (1H, m, *a*), 2.5-3.5 (6H, m, *b, c, d*), 2.73 (3H, s, *e*), 2.79 (3H, s, *e*), 2.88 (3H, s, *e*), 3.4-3.5 (1H, m, *g*), 4.2-4.4 (1H, m, *h*), 5.79 (1H, d, *J* 1.4 Hz, *i*), 5.84 (1H, d, *J* 1.5 Hz, *i*), and 6.6-6.7 (2H, m, *j*).

Mass Spectrum

High resolution: 360.2075; $C_{20}H_{28}N_2O_5$ requires 360.2049.

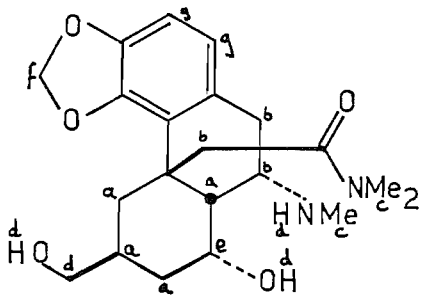
m/z (%) 360 (6, M^+), 242 (55), 224 (57), 87 (78), and 43 (100).

(6β,7α,8α,11aα)7,8,9,10,11-Hexahydro-8-hydroxy-6-methanol-N,N-dimethyl-7-(methylamino)phenanthro [3,4-d] -1,3-dioxole-11a(7aH)-acetamide (117).

I.r.

ν_{max} (CH_2Cl_2) 3430br (OH), 2940m, 1635s (C=O), and 1449s.

N.m.r.



(δ_H 360 MHz) 1.2-1.35 (2H, m, *a*), 1.6-1.8 (2H, m, *a*), 2.2-3.1 (7H, m, *a, b*), 2.44 (3H, s, NCH_3, *c*), 2.66 (3H, s, NCH_3, *c*), 3.1-3.5 (5H, m, *d*), 4.2-4.3 (1H, m, *e*), 5.81 (2H, s, OCH_2O, *f*), 6.55 (1H, d, *J* 8Hz, *g*), and 6.63 (1H, d, *J* 8Hz, *g*).

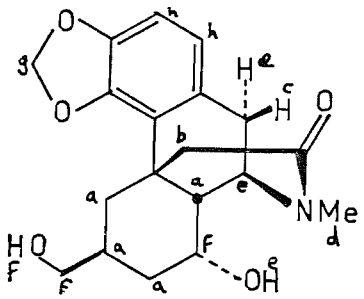
(δ_C 90.6 MHz) 32.4 (CH_3), 34.3 (CH_3), 35.2 (CH_2), 36.1 (CH_2), 36.7 (CH), 37.4 (CH_2), 38.6 (CH_3), 43.04 (C), 43.05 (CH_2), 44.1 (CH_2), 54.6 (CH), 67.5 (CH), 68.2 (CH_2), 101.1 (OCH_2O), 107.6 (CH), 122.8 (CH), 125.7 (C), 133.0 (C), 145.3 (C), 146.2 (C), and 171.4 (CO).

(±)(8α,6β)-8-Hydroxy-6-methanol-17-methyl-3,4-methylenedioxy-morphinan-16-one (118). A solution of the isoxazolidine(114) (60 mg, 0.13 mmol) in methanol (2 ml) was stirred overnight with a catalytic amount of palladium (II) chloride under an atmosphere of hydrogen at 3.1 bar. The catalyst was removed by filtration and the solvent concentrated *in vacuo* to give a glass. The product was dissolved in dichloromethane (2 ml) and a solution of anhydrous hydrogen chloride in ether (0.5 ml, 0.95 M) was added. The solvent was removed *in vacuo* and the resulting solid heated to 180°C under high vacuum (0.03 mmHg) for 1h. The resulting material was dissolved in dichloromethane (2 ml) and washed with hydrochloric acid solution (1 ml) and sodium bicarbonate solution before drying (Na_2SO_4) and concentrating *in vacuo* to a foam. The product was chromatographed (acetone) to give a colourless glass (25 mg, 55%).

I.r.

ν_{max} (CH_2Cl_2) 3400br (OH), 2930m, and 1630s (CO).

N.m.r.



(δ_H, 360 MHz) 0.8-2.2 (7H, m, *a*), 2.35 (1H, d, *J* 17Hz, *b*), 2.81 (1H, d, *J* 17Hz, *c*), 3.01 (3H, s, *d*), 3.15-3.9 (3H, m, *e*), 4.2-4.6 (4H, m, *f*), 5.86 (1H, d, *J* 1.5 Hz, *g*), 5.89 (1H, d, *J* 1.5 Hz, *g*), 6.56 (1H, d, *J* 8Hz, *h*), and 6.66 (1H, d, *J* 8Hz, *h*).

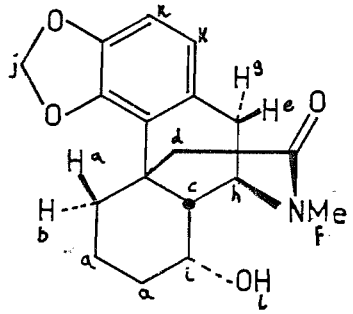
(±)(8α)-8-Hydroxy-17-methyl-3,4-methylenedioxy-morphinan-16-one (111). To a solution of the amino alcohol(109) (0.5g, 1.39 mmol) in dichloromethane (3 ml) was added a solution of anhydrous hydrogen chloride in ether (2.2 ml, 0.95 M). A white precipitate formed immediately and the solvent was removed *in vacuo* to give a hygroscopic white solid. This was heated to 250°C in a sublimation apparatus under high vacuum (0.03 mmHg). A white solid collected on the cold finger and was chromatographed (acetone) to give the pure alcohol as

white needles (0.38g, 87%). M.p. 249-252°C. (Found: C, 68.4; H, 7.0; N, 4.3%. $C_{18}H_{21}NO_4$ requires C, 68.6; H, 6.7; N, 4.4%.)

I.r.

ν_{max} (CH_2Cl_2) 3610w, 2940m, 1636s (CO), and 1443s.

N.m.r.



(δ_H, 360 MHz) 0.9-1.9 (6H, m, *a* and *l*), 2.02 (1H, t, *J* 3 Hz, *c*), 2.34 (1H, d, *J* 17.5 Hz, *d*), 2.58 (1H, d, *J* 17.5 Hz, *d*), 2.80 (1H, d, *J* 17 Hz, *e*), 2.98 (3H, s, *f*), 3.2-3.3 (1H, m, *b*), 3.63 (2H, dd, *J* 17 Hz, 5 Hz, *g*), 3.75 (1H, t, *J* 3.8 Hz, *h*), 4.1-4.2 (1H, m, *i*), 5.85 (1H, d, *J* 1.6 Hz, *j*), 5.92 (1H, d, *J* 1.6 Hz, *j*),6.55 (1H, d, *J* 8 Hz, *k*), and 6.67 (1H, d, *J* 8 Hz,

Mass Spectrum

High resolution: 315.1478; $C_{18}H_{21}NO_4$ requires 315.1471.

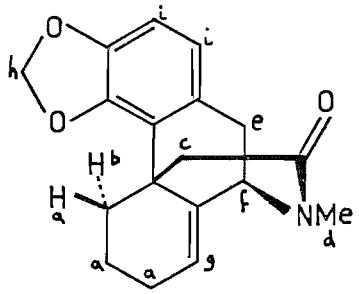
m/z (%) 315 (59, *M*+), 297 (10, *M*-H_2O), 254 (35), and 42 (100).

(±)*8,14-Didehydro-17-methyl-3,4-methyenedioxy-morphinan-16-one. (121)*
Phosphorus oxychloride (4 ml) was added to a stirred solution of the alcohol(111) (0.5g, 1.59 mmol) in pyridine (15 ml) at 5°C. The reaction was stirred overnight and then poured onto crushed ice (20g) (CARE!). The aqueous layer was extracted with ether (5 X 10 ml) and the ether layer then washed with dilute hydrochloric acid. The organic layer was washed with sodium bicarbonate solution and dried (Na_2SO_4) before concentrating *in vacuo*. Chromatography (ethyl acetate) gave the *alkene*(121) as a foam (0.32g, 68%). A sample was sublimed in a Kugelrohr (oven temperature 200°C, 0.1 mmHg) to give an amorphous solid. (Found C, 72.5; H, 6.5; N, 4.7%. C, 72.7; H, 6.4; N, 4.7%.)

I.r.

ν_{max} ($CDCl_3$) 2940m, 1625s (CO), 1446s, and 1274s.

N.m.r.



(δ_H, 360 MHz) 1.5-2.2 (5H, m, *a*), 2.50 (1H, dt, *J* 14 Hz, 3.4 Hz, *b*), 2.68 (2H, s, *c*), 2.90 (3H, s, *d*), 2.94 (1H, dd, *J* 16.3 Hz, 2.5 Hz, *e*), 3.11 (1H, dd, *J* 16.3 Hz, 2.5 Hz, *e*), 3.98 (1H, t, *J* 2.6 Hz, *f*), 5.82 (1H, dd, *J* 5.3 Hz, 2.2 Hz, *g*), 5.89 (1H, d, *J* 1.5 Hz, *h*), 5.93 (1H, d, *J* 1.5 Hz, *h*), 6.50 (1H, d, *J* 7.9 Hz, *i*), and 6.64 (1H, d, *J* 7.9 Hz, *i*).

(δ_C, 90.6 MHz) 19.4 (CH_2), 24.6 (CH_2), 31.7 (CH_2), 32.6 (CH_3), 36.3 (CH_2), 37.2 (*C*), 45.1 (CH_2), 61.3 (*C*H), 100.6 (OCH_2O), 107.4 (*C*H), 121.8 (*C*H), 122.2 (*C*H), 126.0 (*C*), 126.3 (*C*), 135.2 (*C*), 144.8 (*C*), 146.7 (*C*), and 169.9 (*C*O).

Mass Spectrum

High resolution: 297.1335; $C_{18}H_{19}NO_3$ requires 297.1365.

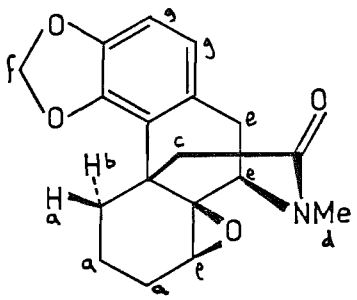
m/z (%) 297 (100, M^+), 254 (50), and 226 (13).

(±)*(8β,14β)-8,14-Epoxy-17-methyl-3,4-methlenedioxy-morphinan-16-one* (125). The alkene(121) (0.3g, 1.01 mmol) was stirred in dichloromethane (10 ml) for 48h at ambient temperature with *m*CPBA. Sodium sulphite solution (5 ml) was added and the organic layer separated and washed with sodium bicarbonate solution (5 ml). The organic phase was then dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Chromatography (ethyl acetate) gave the *epoxide*(125) as a foam (0.184g, 58%).

I.r.

ν_{max} (CH_2Cl_2) 2950m, 1643s (CO), 1448s, and 1243m.

N.m.r.



(δ_H, 360 MHz) 0.9-1.6 (3H, m, *a*), 1.7-2.2 (2H, m, *a*), 2.5-2.6 (1H, m, *b*), 2.65 (1H, d, *J* 16.8 Hz, *c*), 2.78 (1H, d, *J* 16.8 Hz, *c*), 2.89 (3H, s, *d*), 2.9-3.4 (4H, m, *e*), 5.87 (1H, d, *J* 1.5 Hz, *f*), 5.95 (1H, d, *J* 1.5 Hz, *f*), 6.58 (1H, d, *J* 8 Hz, *g*), and 6.70 (1H, d, *J* 8 Hz,

(δ_C, 90.6 MHz) 17.1 (CH_2), 23.0 (CH_2), 26.3 (CH_2), 32.6 (CH_3), 34.3 (CH_2), 37.6 (*C*), 43.1 (CH_2), 58.8 (*C*H), 60.9 (*C*H), 61.3 (*C*), 100.6 (CH_2), 108.0 (*C*H), 123.0 (*C*H), 126.6 (*C*), 129.8 (*C*), 144.7 (*C*), 146.6 (*C*), and 168.9 (*C*O).

Mass Spectrum

High resolution: 313.1316; $C_{18}H_{19}NO_4$ requires 313.1314.

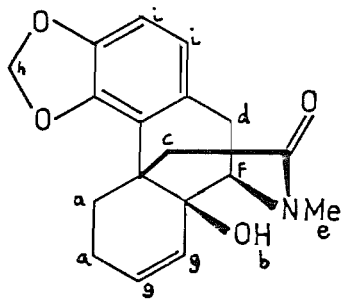
m/z (%) 313 (31, M^+), 242 (34), 205 (18) 83, and (100).

(±)(14β)-7,8-Didehydro-14-hydroxy-17-methyl-3,4-methylenedioxymorphinan-16-one (126). To the epoxide(125) (166 mg, 0.53 mmol) in *n*-propanol (4 ml) was added a solution of sodium phenyl selenide, prepared by the addition of sodium borohydride to diphenyl diselenide (120 mg, 0.38 mmol) in *n*-Propanol. The reaction mixture was brought to reflux and heating continued for 1.5h before cooling to 0°C. THF (1 ml) was added followed by the dropwise addition of hydrogen peroxide solution (30%, 0.65 ml). The mixture was stirred at less than 20°C for 1.5 h, water (2 ml) was added and the products extracted into ethyl acetate (4 X 2 ml). The ethyl acetate solution was then washed with sodium carbonate solution, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Chromatography (acetone:petrol, 2:1) gave the *allylic alcohol*(126) as a foam (88 mg, 53%).

I.r.

ν_{max} (CH_2Cl_2) 3680w (OH), 2920m, 1633s (CO), and 1447s.

N.m.r.



(δ_H, 360 MHz) 1.2-1.3 (1H, m, *a*), 1.5-2.2 (4H, m, *a*, *b*), 2.53 (1H, d, *J* 17.1 Hz, *c*), 2.6-2.7 (1H, m, *d*), 2.76 (1H, d, *J* 17.1 Hz, *c*), 2.9-3.1 (1H, m, *d*), 2.95 (3H, s, *e*), 3.58 (1H, t, *J* 2.9 Hz, *f*), 5.75 (1H, d, *J* 9.8 Hz, *g*), 5.84 (1H, d, *J* 9.8 Hz, *g*), 5.87 (1H, d, *J* 1.2 Hz, *h*), 5.93 (1H, d, *J* 1.2 Hz, *h*), 6.49 (1H, d, *J* 8 Hz, *i*), and 6.66 (1H, d, *J* 8 Hz, *i*).

(δ_C, 90.6 MHz)
$(CD_3)_2SO$ 22.3 (CH_2), 23.5 (CH_2), 30.8 (CH_2), 32.8 (CH_3), 39.6 (*C*), 41.4 (CH_2), 62.4 (*C*H), 65.7 (*C*), 100.2 (OCH_2O), 107.1 (*C*H), 122.0 (*C*H), 122.8 (*C*), 123.3 (*C*), 128.6 (*C*H), 130.1 (*C*H), 144.6 (*C*), 145.2 (*C*) and 168.1 (*C*).

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