NEW SYNTHETIC APPROACHES TOWARDS THE SYNTHESIS OF MORPHINE

by Paul Grant Spoors

University of Southampton

1989

To my family

Corrigendum

Acknowledgements	line 5@6	should read Liz Tyrell
	line 7	should read Booker Milburn
page 3	line 17	should read $C_{17}H_{19}NO_3$
page 4	line 1	should read Robinson's
page 6	line 2	should read Meyer's
page 7	line 1	should read Tschudi
page 10	line 9	observations should be transformations
page 10	line 1	should read nitrite
page 12	line 5	should read aziridinium
page 18	line 18	should read syntheses
page 22	line 4,7,13	should read man's
page 23	line 9,12,16	should read endogenous
page 24	line 12	should read led
page 25	line 9	should read led
page 26	line 16	despatching should read dispensing
page 28	line 9	should read nalorphine
page 30	line 5	family should read member
page 30	line17	quarternary should read quaternary
page 30	line 10	should read respectively
page 32	line 2	should read interconvertible
page 38	line 3	should read Chandler's
page 43	line 7	should read O-4-methylphenyl
page 49	heading	should read Matthews
page 49	line 4	should read problems encounted by Matthews
page 51	line 4	should read are employed by the plant
page 52	line 7	should read sodium phenylselenide
page 78	line 1	should read Ziegler's conditions
page 88	line 2	should read predominantly
page 89	line 9	should read predominantly
page 109	line 6	should read complement
page 110	line 3	should read dominant
page 114	line 5	should read quaternary
page 116	line 10,20	should read Jeol
page 118	line 4	should read benzylalcohol
page 134	line 2	should read phenanthro
page 154	line 7	should read Isopropylenedioxypropyl
page 164	line 21	should read δ_C (90.6 MHz)
page 165	line 8	should read δ_C (90.6 MHz)
page 166	line 5	should read 2-cyclohexen-1-ol
page 166	line 7	should read 2-cyclohexen-1-one

CONTENTS

Chapter one.

Chapter two.

Chapter three.

Chapter four.

Chapter five.

Chapter six.

ACKNOWLEDGEMENTS

I would like to thank Phil Parsons for all his encouragement, support, kindness and above all friendship over the time I've known him. The people in the 'group' have also been a good laugh, especially Pete Stones, Helen Quillin, James Henshilwood and Liz Tyrrel. Special thanks are extended to David Cladingboel, Liz Tyrrel, James Henshilwood, Adrian Neary and Kevin Brooker-Milburn for their patient and concientious proof-reading. I wish to thank Richard Nichols, Yves Dory, Monique Blanken, Adrian Neary, Colin Streeter, Ian Tinsley, Tim Roberts, Richard Warburton, Sue Parsons and Iain Boyd for my memorable experiences in Southampton (not to mention the electrochem footballers and the 'Nob boys' of course!). I also appreciated the help of Joan Street and Dr. Langley. I gratefully acknowledge the receipt of a SERC award.

Abbreviations

Me	Methyl
NBA	*N*-Bromoacetamide
DNP	Dinitrophenylhydrazine
Ar	Aromatic
Δ	Heat
DMSO	Dimethyl sulphoxide
S_N2	Substitution Nucleophilic Bimolecular
DEAD	Diethylazodicarboxylate
DIBAL	Diisobutylaluminium hydride
TFA	Trifluoroacetic acid
Ac	Acetyl
TEOC	Trimethylsilylethoxy formate
DMF	*N,N*-Dimethylformamide
*m*CPBA	*meta*-Chloroperbenzoic acid
CNS	Central nervous system (the brain and the spinal cord)
THF	Tetrahydrofuran
PCC	Pyridinium chlorochromate
Cy	Cyclohexane
MVK	Methyl vinyl ketone
PyTs	Pyridinium tosylate
*p*NPBA	*para*-Nitroperbenzoic acid
OTf	Triflate
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
RT	Room temperature
Et	Ethyl
TLC	Thin layer chromatography

TBDMS	*tert*-Butyldimethylsilyl
TMEDA	*N,N,N',N'*,-Tetramethylethylenediamine
L	Ligand
MOM	Methoxy methyl
MEM	Methoxyethoxy methyl
THP	Tetrahydropyranyl
glc	Gas liquid chromatography
Bu	Butyl
Ts	*para*-Toluenesulphonyl
DME	1,2-Dimethoxyethane
Ph	Phenyl
Bz	Benzyl
cat	Catalytic
nmr	Nuclear magnetic resonance
ir	infra-red
TMS	Trimethylsilyl
ee	enantameric excess
E.I.	Electron impact
C.S.A.	Camphor sulphonic acid
ε	extinction coefficient

Terminology.

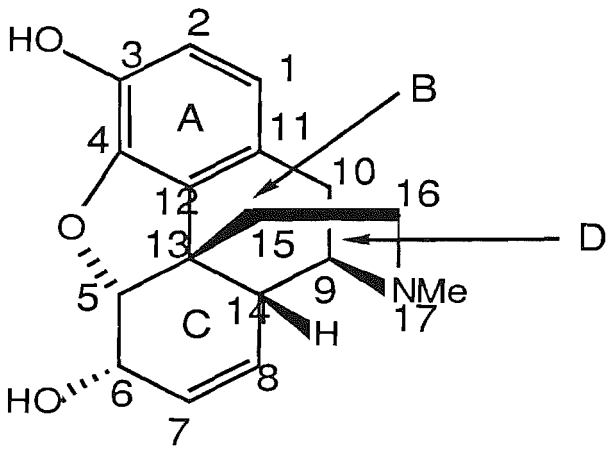
Addiction potential. The ability of a compound to elicit compulsory self-administration.

Agonist. A compound that elicits a biologic response by mimicking an endogenous substance.

Antagonist. A drug that blocks the biologic effects of an endogenous substance or exogenously

	applied drug.
Antitussive.	A drug that bocks the cough reflex.
Narcotic analgesic.	A drug that alleviates pain by interacting with the morphine receptor.
Narcotic antagonist.	A drug that selectively blocks the actions of morphine-like compounds.
Psychotropic.	Affecting the brain in such a way as to alter behavior.

The following diagram is intended to assist the reader in understanding the ring system of morphine.



ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

DOCTOR OF PHILOSOPHY

NEW SYNTHETIC APPROACHES TOWARDS

A SYNTHESIS OF MORPHINE

by Paul Grant Spoors

In the introduction, previous synthetic approaches to morphine are reviewed; a brief outline of the physiological properties of morphine and its analogues is also presented.

Chapter two describes the model studies conducted in our laboratories and then gives an account of the efforts to obtain a total synthesis. The key step, a 1,3-sigmatropic rearrangement, failed and the reasons for that are discussed briefly.

Chapter three gives an account of the efforts to secure the furan ring system of morphine by the opening of an epoxide. This was not achieved, however, some interesting reactions emerged from these studies. These included an intramolecular Alder-ene reaction, magnesium bromide initiated electrophilic cyclisation onto a aromatic ring, palladium catalysed alkyl substitution onto a aromatic ring as well as others.

Chapter four describes the efforts to secure the furan ring of morphine by an intramolecular radical cyclisation reaction. These were not clean reactions and were plagued by five and six membered ring formation as well as tandem cyclisations.

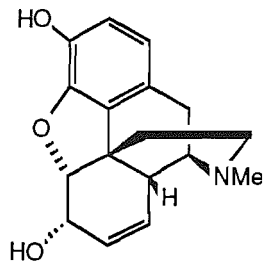
Chapter five concerns the possibility of utilising an intramolecular Heck reaction as a key step towards a total synthesis of morphine. Model studies were conducted which

indicate that that the proposed route is feasible.

CHAPTER ONE

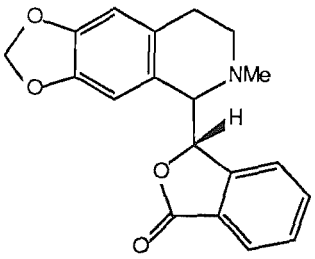
1.1 BACKGROUND

Nearly two hundred years has elapsed since Serturner,[1] a pharmacist of Einbeck in Hanover described the isolation of a crystalline substance from opium , which he called morphine (1) after Morpheus, the god of sleep.

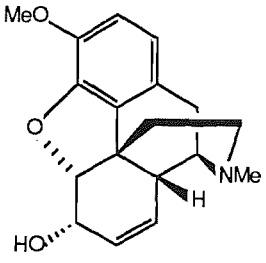


(1)

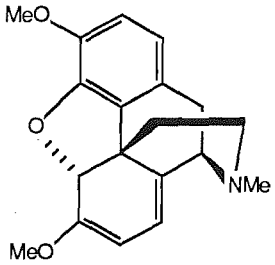
Recognised as the first organic base to be isolated, this early landmark in organic chemistry was the result of an increasing interest in a systematic study of plant materials that seemed to possess pharmacological activity. The documentation of other alkaloids soon followed- for example, narcotine (2) in 1817[2]; codeine (3) in 1832[3]; thebaine (4) in 1835[4]; and papaverine (5) in 1848[5].



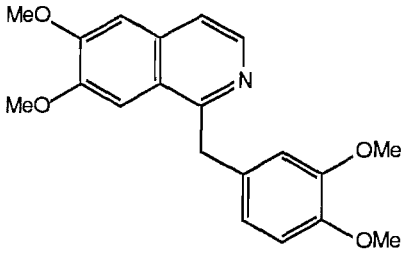
(2)



(3)



(4)



(5)

1.2 OCCURRENCE AND EXTRACTION

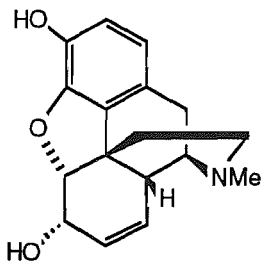
Morphine occurs principally in opium (36 days after the sprouting of the seed), which is the dried juice of unripe seed capsules of *papaver somniferum* (a species of poppy bearing white or bluish purple flowers and much larger than the European red poppy). The average content of morphine in opium is variable but normally about 10% can be extracted along with 24 other alkaloids[6]. A morphine content of 21.8% in the sap of *papaver somniferum* two hours after cutting has been reported, but this falls to 12% in one day as a result of atmospheric oxidation[7]. For many years the alkaloid was isolated by the "Gregory process"[8] in which the concentrated opium extract is treated with a concentrated solution of calcium chloride. The resulting mixture is filtered and concentration of the filtrate deposits the "Gregory salt", a mixture of codeine and morphine hydrochlorides. This is purified, dissolved in water and the morphine precipitated with ammonia (codeine

remains in solution and can be extracted with benzene). Morphine as its monohydrate is obtained as small rhombic crystals often resembling needles on crystallisation from aqueous methanol[9]or it can be obtained in anhydrous form by crystallisation from anisole[10]. It is sparingly soluble in most organic solvents, but it readily dissolves in benzyl alcohol. More modern methods are now avalaible for extraction[11].

Once the alkaloids present in opium had been established, the opium research program took two new routes. The questions to be addressed were:

1. What were the chemical and structural formulae of these compounds?.
2. By chemical modification is it possible to influence the profile of their pharmocological activity ?.

In the case of morphine, elemental analysis has a history of constant revision[12,13,14] until the correct formulae was accepted to be $C_{17}H_{34}O_3$[15]. As regards the chemical structure of morphine, extensive studies were conducted by Hesse, Vorgerichten, Knorr, and Schorr[16] and in 1925 Gulland and Robinson[17] proposed the structure for morphine shown below.

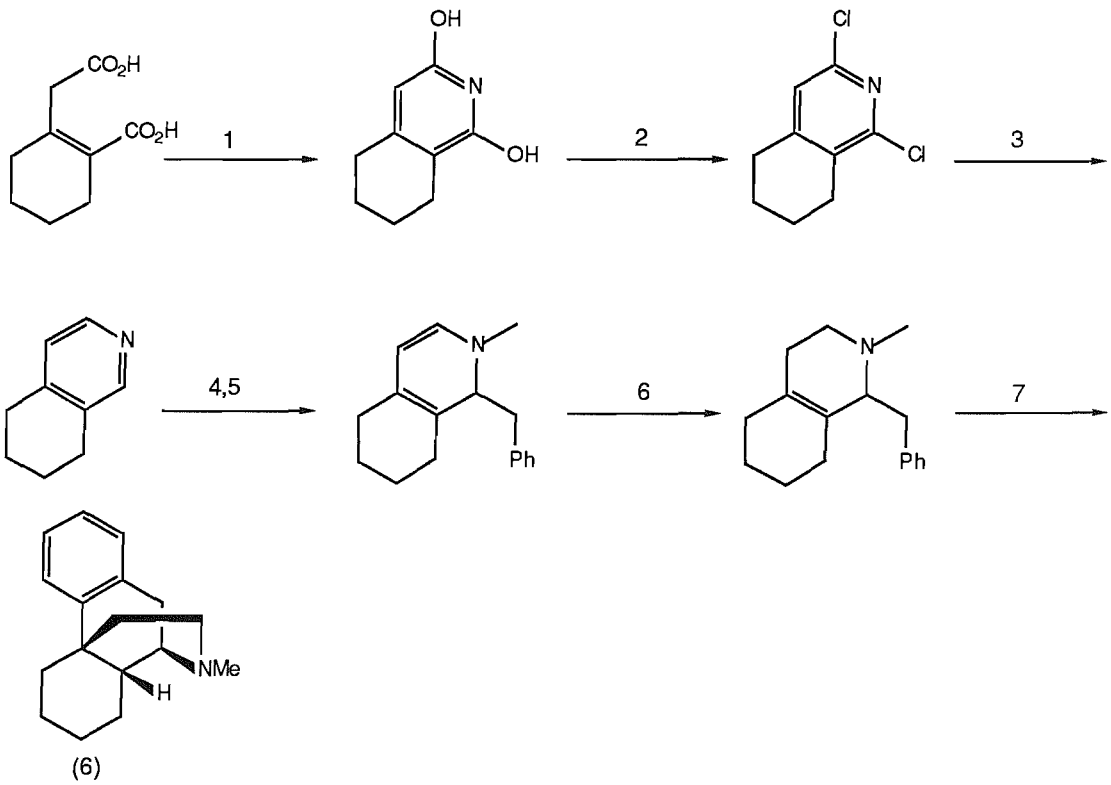


(1)

1.3 THE GREWE CYCLISATION

For the unequivocal verification of Robinsons structure, a total synthesis was required, or failing that, synthetic versions of known degradative products of morphine (or codeine), whose mode of construction would be totally unambiguous would suffice. Gates and Tschudi[18] achieved the former whilst as regards the latter, work carried out by Grewe[19]in the 1940's produced the first synthetic morphinan (6). This early milestone in the chemistry of morphine was interesting because Grewe's cyclisation involved a carbon-carbon bond formation (scheme 1.1 step 7) akin to the biogenetic mode employed by the plant itself (see section 1.6).

Scheme 1.1

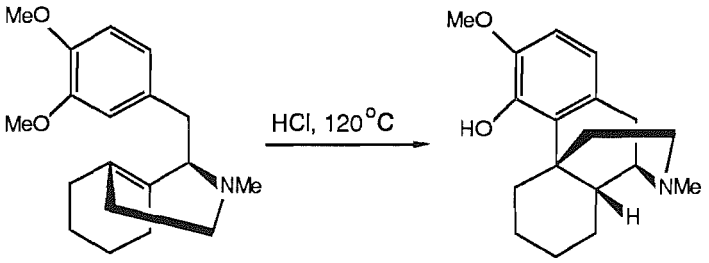


(6)

Reagents
1. NH_4Cl 2. $POCl_3$ 3. H_2, Ni, NaOEt 4. MeI 5. $PhCH_2MgI$ 6. H_2, PtO_2 7. H_3PO_4.

Scheme 1.1

In an analogous manner when 3,4-dimethoxy-N-methylmorphinane (7) was heated in the presence of hydrochloric acid, cyclisation and partial demethylation occurred. The resulting product *dl* -*tetra*-hydrodesoxycodeine (8) was identical in structure to the racemate prepared from the separate *dl* - isomers obtained from codeine (2). Scheme 1.2.

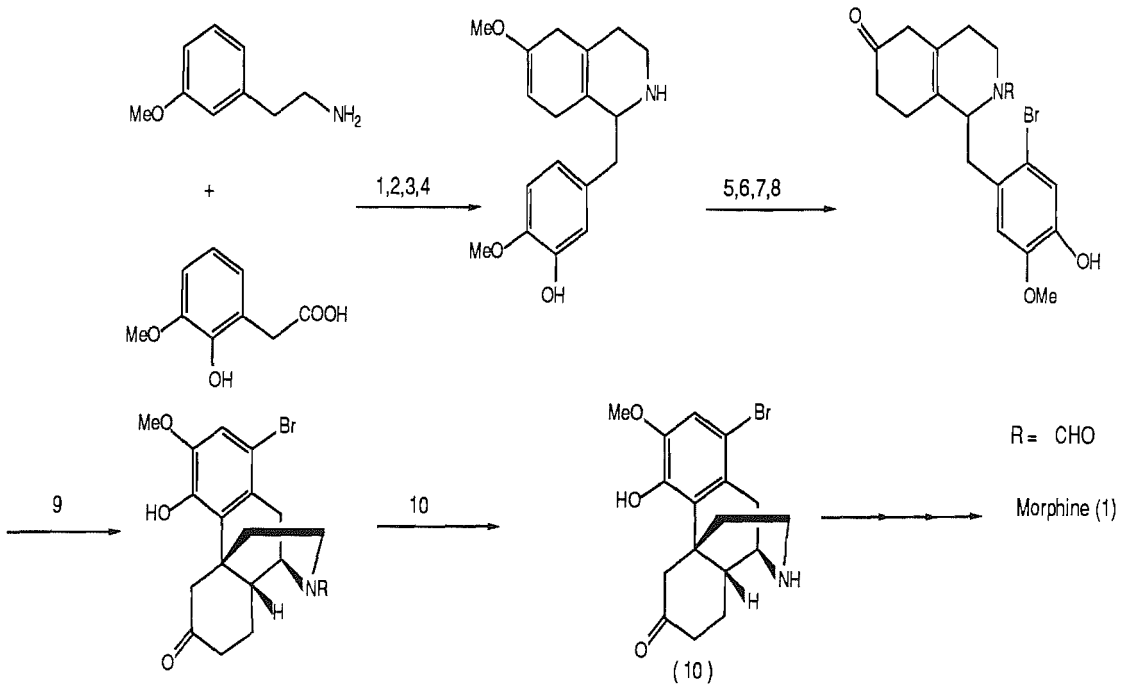


(7) (8)

Scheme 1.2

A synthesis of morphine was realised in 1967 using this cyclisation procedure[20] which went via an intermediate common to the Gates synthesis[18].

To utilise more effectively the Grewe type cyclisation towards a synthesis of morphine, a number of workers have put blocking groups on the aromatic ring to make the cyclisation more regioselective[21]. By incorporating a bromine atom, Rice and coworkers[22] effected an efficient Grewe type cyclisation to afford 4-hydroxymorphinan (9) which can be converted to codeine (3) via dihydrothebainone (10) in 68% overall yield from (10)[23]. Scheme 1.3.



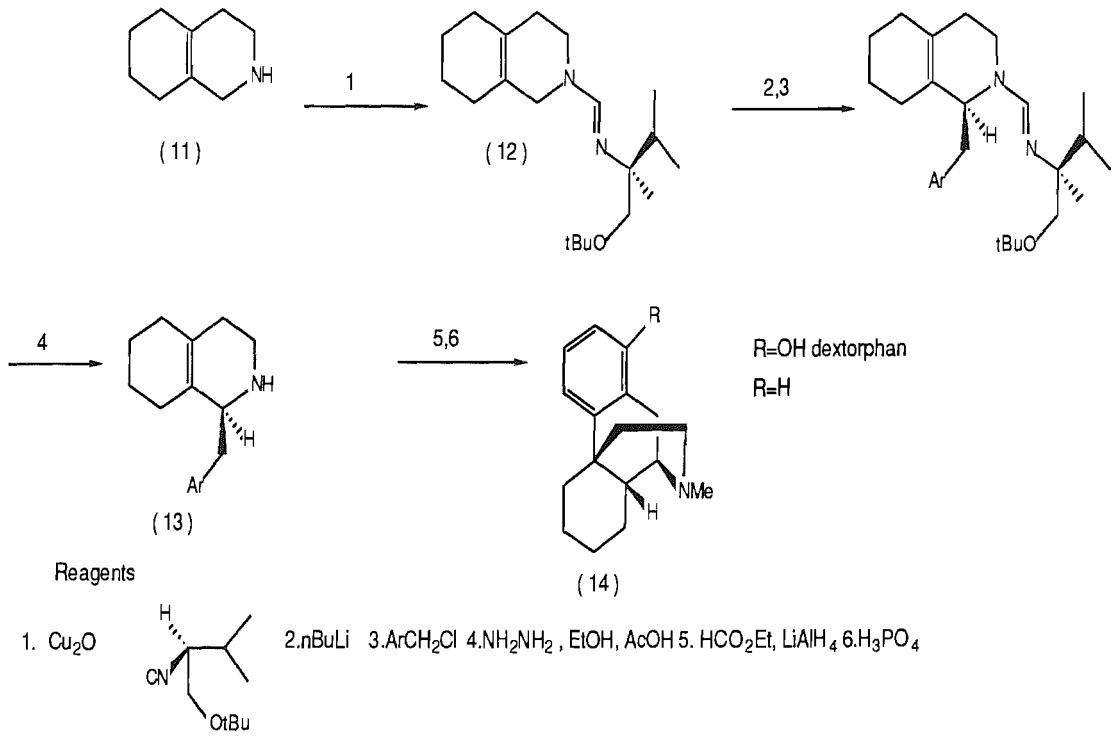
Reagents

1.200 °C 2. MeCN, $POCl_3$ 3. $NaCNBH_3$ 4. Li, NH_3 5. PhOCHO 6. ethylene glycol

7. NBA 8. HCO_2H, H_2O 9.14% $NH_4F.HF$, CF_3SO_3H, 0°C 10. 37% $HCl_{(aq)}$

Scheme 1.3

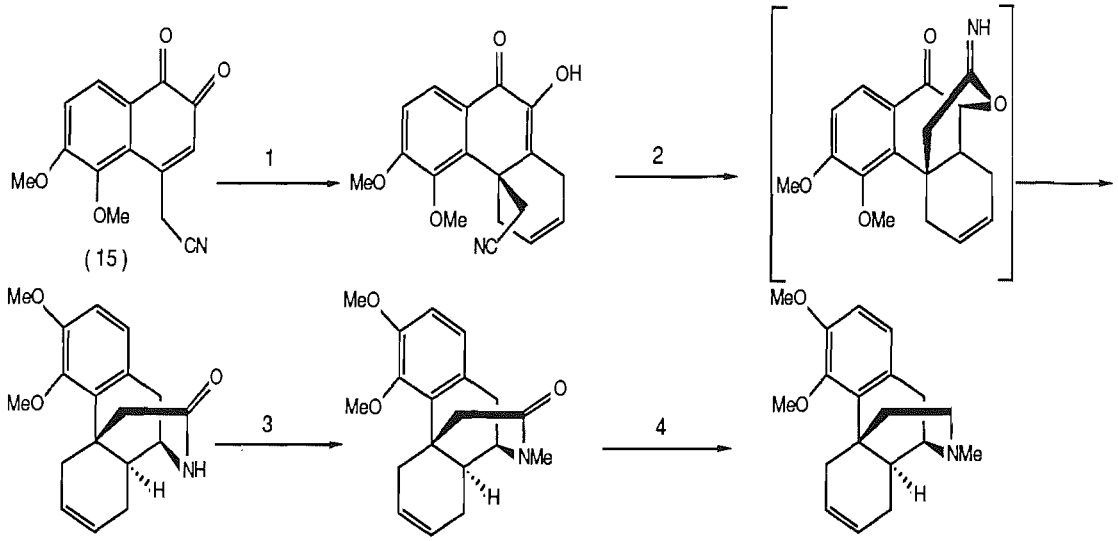
In concluding this short discussion on the electrophilic Grewe cyclisation a small note on Meyers contribution to this field is mentioned[24]. The synthesis of the narcotic analgesic dextorphan (14) and its desoxy derivative was accomplished by a highly selective asymmetric alkylation of octahydroisoquinoline (11). This was achieved by converting the latter to its chiral formadine (12) which upon treatment with n-BuLi formed an α-lithio anion which was subsequently quenched with benzyl chloride. Hydrazinolysis afforded the benzyl derivative (13) in >98% ee. Grewe cyclisation gave the chiral morphinan (14) as shown in Scheme 1.4.



Scheme 1.4

1.4 THE FIRST TOTAL SYNTHESIS OF MORPHINE[18]

Gates and Tshudi accomplished the first total synthesis of morphine using a Diels-Alder reaction to build the C ring. The dienophile (15) was obtained in 10 steps in an overall yield of 20% from 2,6-dihydroxynaphthalene and incorporated a cyano group to be used as a handle for the introduction of the ethanamine bridge. Scheme 1.5.

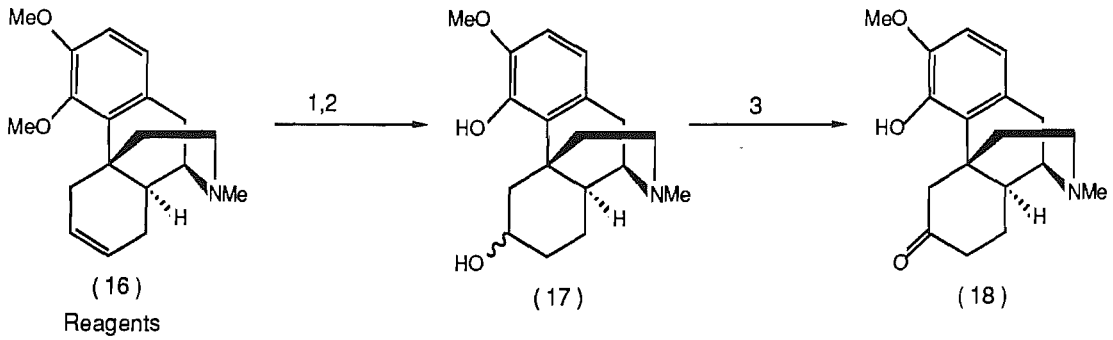


Reagents

1. Butadiene, Δ 2. Copper chromite, 27 bar, 130 °C 3. NaH, MeI 4. $LiAlH_4$

Scheme 1.5

Hydration of the double bond in (16) with aqueous sulphuric acid gave two products, one of which was partially demethylated with KOH in ethylene glycol to give phenol (17). Oxidation of this product with t-BuOK and benzophenone gave β-dihydrothebaine (18). Scheme 1.6.



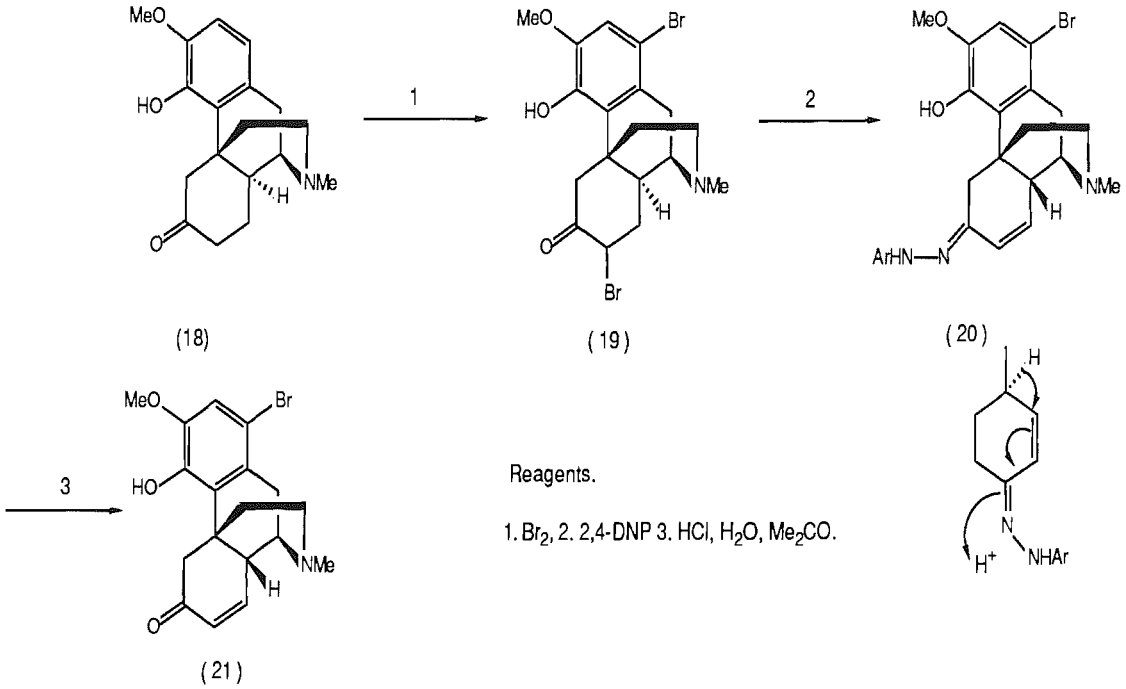
Reagents

1.H_2SO_4, H_2O 2. KOH, diethylene glycol 3. t-BuOK, benzophenone.

Scheme 1.6

β–Dihydrothebaine (18) was brominated to give the unstable morphinan (19) which was converted to the more stable compound (20) using 2,4-dinitrophenylhydrazine. As a result of this reaction

the desired inversion of the hydrogen at carbon (14) (Scheme 1.7 No.20) gave compound (21) whose stereochemistry was compatible with that of morphine (1). Scheme 1.7.



Scheme 1.7

A further five steps gave a synthetic sample of codeine (3) which was demethylated with pyridine hydrochloride to give morphine.

1.5 OTHER SYNTHETIC ROUTES TO MORPHINE

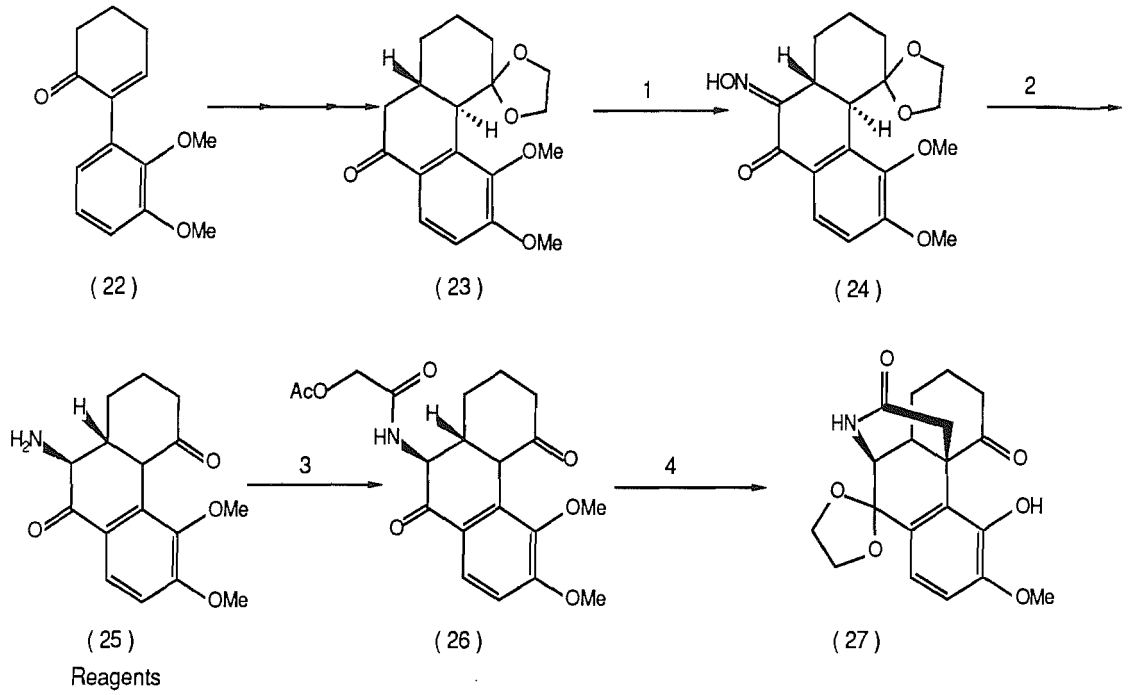
a) Elad and Ginsburg approach[25]

The second synthesis of morphine was successfully carried out by Elad and Ginsburg[25] who like Gates and Tschudi[18] used an unusual reaction to construct the ethanamine bridge. Their retro-synthetic analysis of morphine lead to a simple phenylcyclohexenone derivative (22) which was readily prepared from 1-(2,3-dimethoxyphenyl)-cyclohexanone[26]. Using seven more chemical transformations they arrived at ketal (23) which was

treated with amyl nitrate and sodium ethoxide to give the expected oximino derivative (24). The latter was reduced catalytically with palladium on charcoal in hydrochloric acid solution to furnish the corresponding aminodiketone (25) as its hydrochloride salt. Acylation of the nitrogen with acetylglycollyl chloride gave acetoxyacetamide (26). Heating this compound in a mixture of toluene and benzene for 8 hours in the presence of ethylene glycol and a catalytic amount of *p*TsOH afforded amide (27) and with it three interesting observations.

1. Cyclisation of the ethanamide chain.
2. Demethylation of the most hindered methoxy group.
3. Ketalisation of the carbonyl conjugated with the aromatic ring.

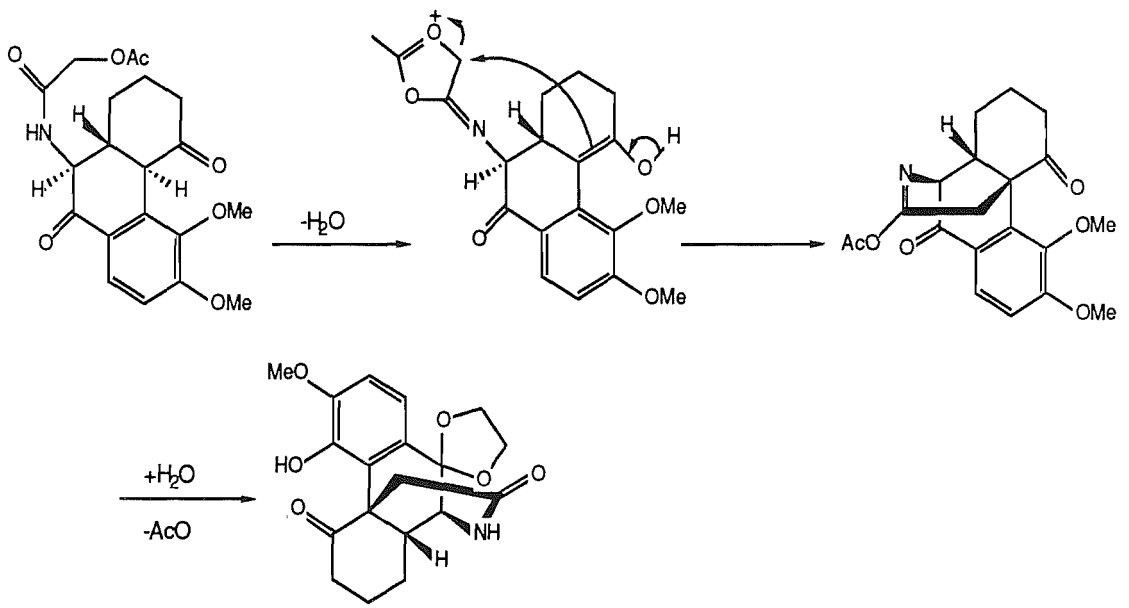
The latter reaction probably occurs after the formation of the amide ring as this makes the non conjugated carbonyl more sterically hindered. Scheme 1.8.



1. amyl nitrite, sodium ethoxide 2. Pd, C, HCl 3.acetoglycollyl chloride 4. TsOH, $(CH_2OH)_2$, Δ

Scheme 1.8

As regards the unusual formation of the amide ring a mechanism for its formation has been proposed by Stork[27]. Scheme 1.9.



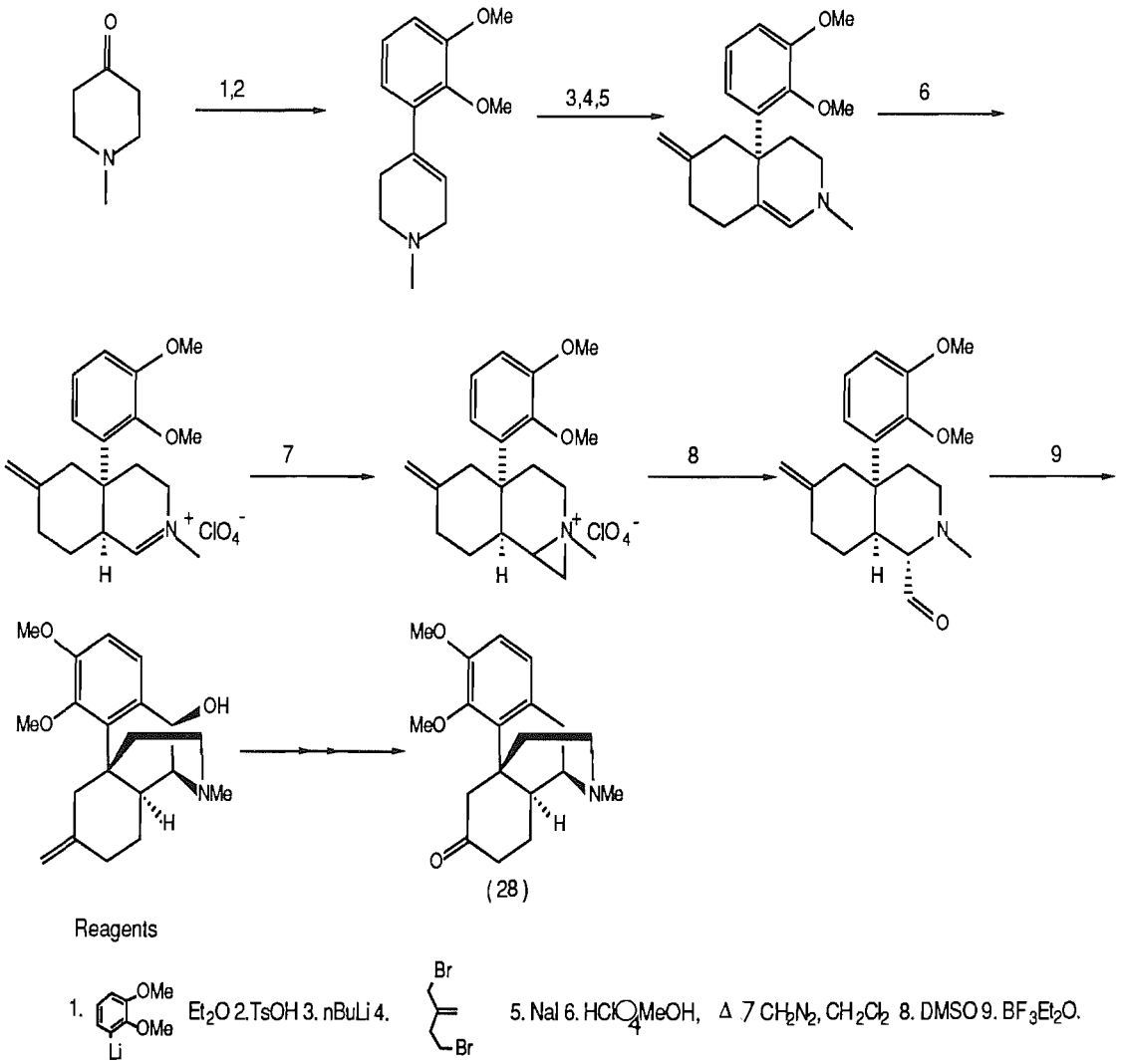
Scheme 1.9

The investigators then went on to make dihydrothebainone (10)

whose conversion to morphine has already been described by Gates and Tschudi[18].

b) Evans, Rapoport, and M^{c}Murray approach[28,29,30]

Evans, Rapoport and Evans and M^{c}Murray[28,29,30] have recognised that an aziridium ion, if manipulated correctly, could facilitate an intramolecular nucleophillic displacement by an appropriately positioned aromatic ring to form the basic morphinan framework. Using such an approach Evans[28] published the following synthesis of morphine via morphinan (28). Scheme 1.10.



Reagents

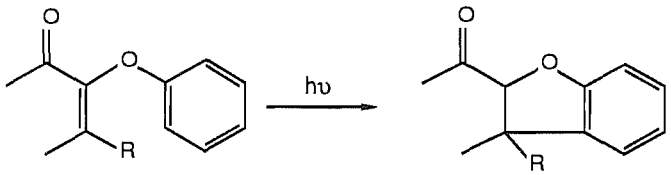
1. Et_2O 2.TsOH 3. nBuLi 4. 5. NaI 6. $HClO_4$/MeOH, Δ 7 CH_2N_2, CH_2Cl_2 8. DMSO 9. BF_3Et_2O.

Scheme 1.10

The next part of the discussion will consider other total synthesis and approaches to morphine which construct the benzodihydrofuran moiety at an early stage in the synthesis.

c) The Schultz approach[31]

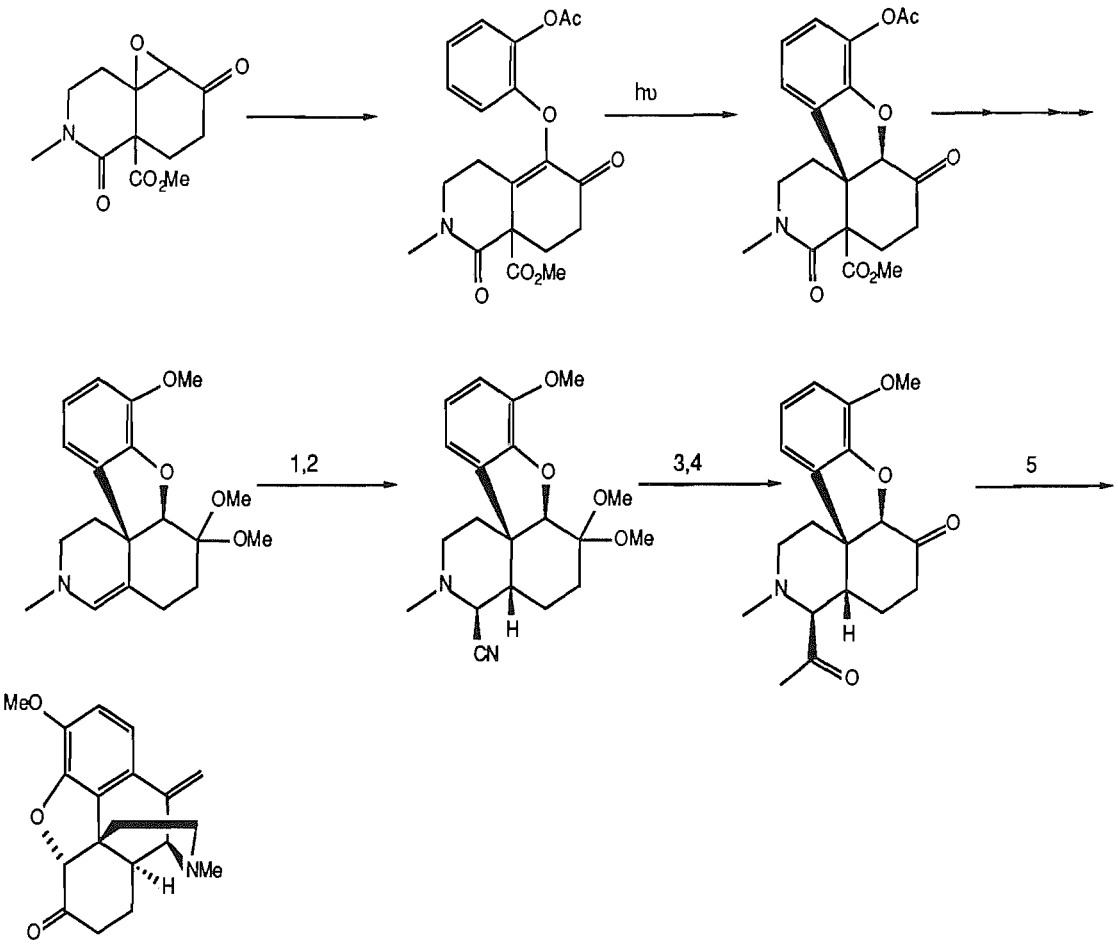
The first work to be published in this area was by Schultz *et al* and even though no total synthesis has yet been published to date by Schultz, his chemistry illustrates an early benzodihydrofuran ring construction by photocyclisation of an aryl vinyl ether e.g A to B. Scheme 1.11.



A B

Scheme 1.11

The conclusion to his work allowed the preparation of a B/C trans-fused morphine derivative using methodology developed by Rapoport and Gless[29]. Scheme1.12.



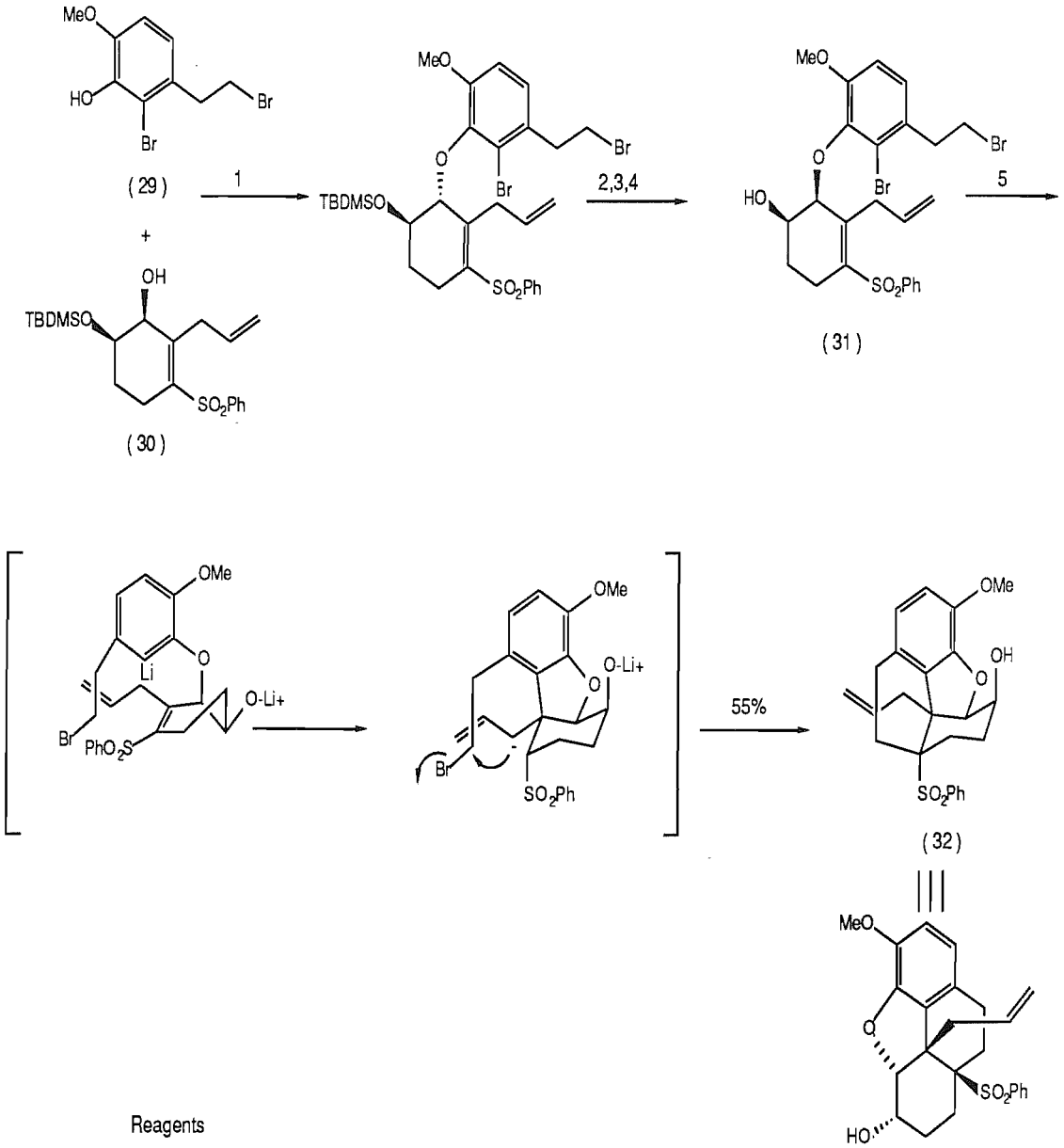
Reagents

1. $HClO_4$ 2. KCN 3. MeLi 4. H_3O^+ 5. CF_3SO_3H

Scheme 1.12

d) The Fuchs approach[32].

The Fuchs synthesis used an intramolecular cyclisation as the foundation strategy to secure the benzodihydrofuran moiety of morphine[32]. By treating precursor (31) with 2.2 equivalents of n-butyllithium, lithiation takes place on the aromatic ring which is followed by a Michael addition on to a vinyl sulphone. The resulting stabilised anion undergoes further alkylation by displacing the vicinal bromine in an S_N2 manner. Scheme 1.13.

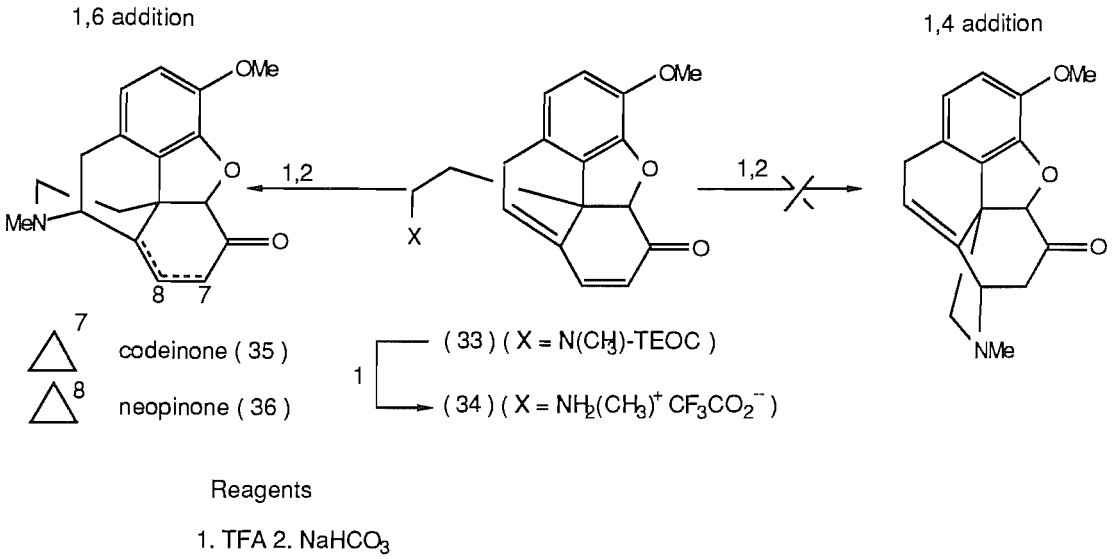


Reagents

1.PBu_3, DEAD 2. HF,3. Jones reagent 4. DIBAL 5. nBuLi.

Scheme 1.13

Elaboration of (32) by a further seven chemical steps gave Fuchs the opportunity to address the construction of the amine ring portion of morphine. A 1,6-intramolecular Michael addition was envisaged, which would hopefully take priority over the potentially competitive 1,4-addition. Scheme 1.14.

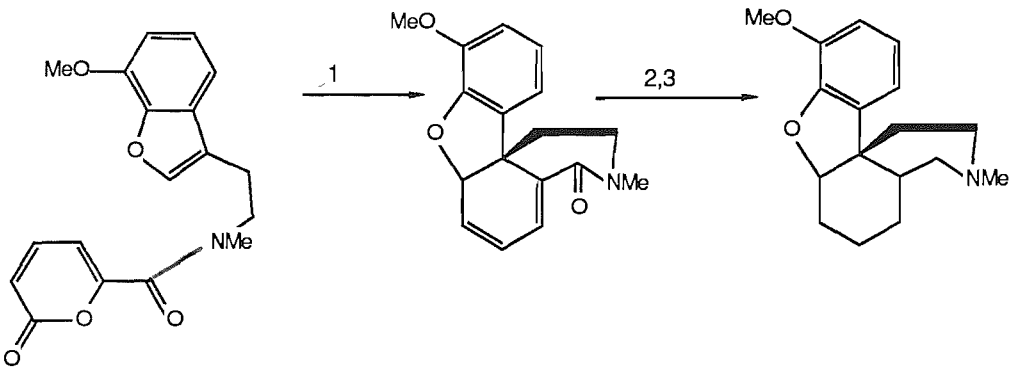


Scheme 1.14

Precursor (33) was treated with TFA, which resulted in rapid evolution of carbon dioxide and ethene to afford the dienone salt (34). Simple treatment of (34) with $NaHCO_3$ caused spontaneous cyclisation through a 1,6 Michael addition (Fuchs reported no 1,4 Michael addition). This gave a resultant mixture of codeinone (35) and neopinone (36) which were then used to provide racemic morphine in an overall yield of 1.1%.

e) The Ciganek approach.

Since Gates' first total synthesis of morphine[18] other groups[33,34] have shown an interest in using a Diels-Alder reaction to make this synthetically challenging molecule. The most notable of these is Ciganek's reported synthesis of a new morphinan fragment using the intramolecular Diels-Alder addition of a benzofuran[33]. Scheme 1.15.



Reagents

I. 215°C 2. H_2,Pd-C 3. BH_3SMe_2

Scheme 1.15

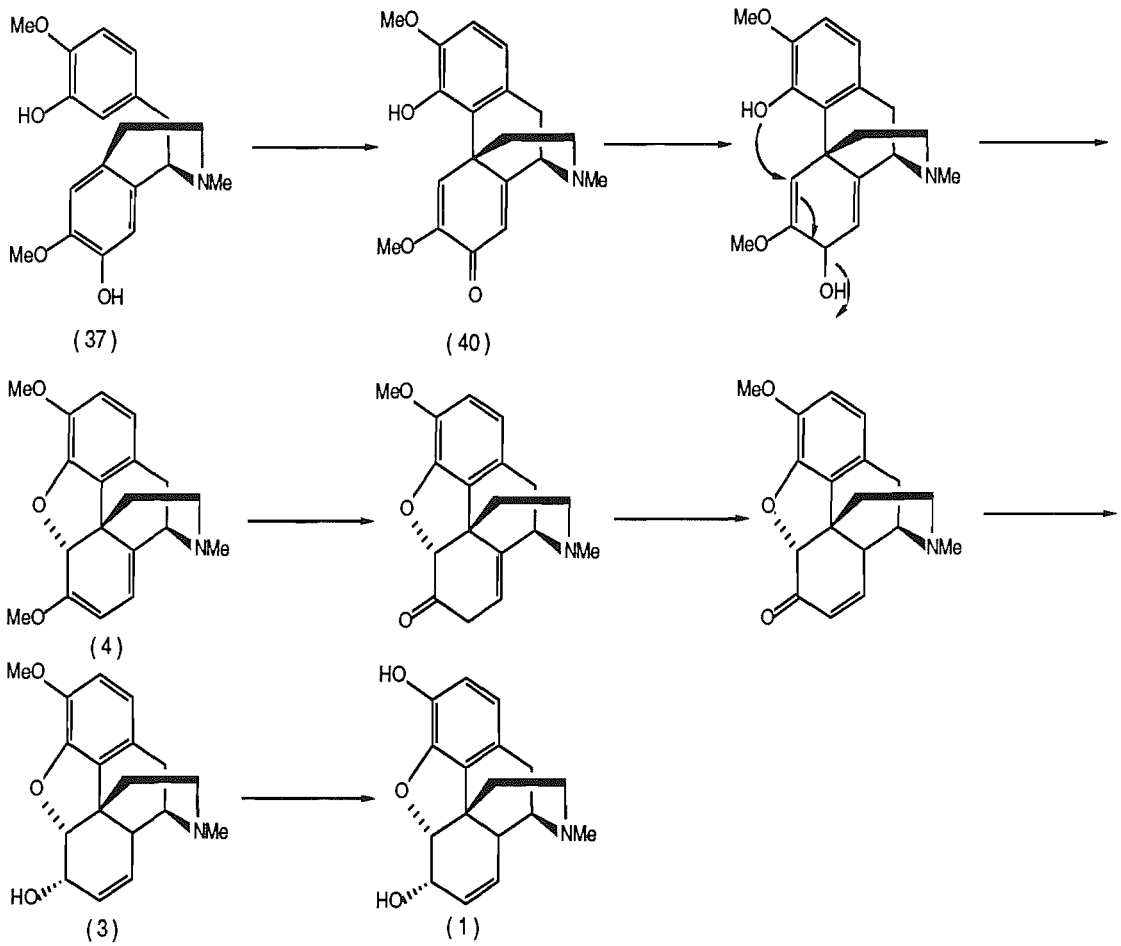
The structure of the product was close to that of morphine except for the omission of ring B, but is said to be biologically active.

In the next section three more synthesis of morphine will be discussed. The first of these demonstrates the biosynthesis of morphine itself whilst the last two illustrate how the biogenetic pathway has been duplicated in the laboratory.

1.6 BIOSYNTHESIS OF MORPHINE

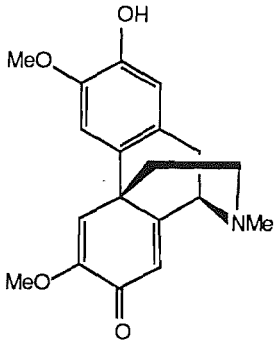
Since Robinson's original conception that the morphine alkaloids arise in the plant via an oxidative coupling of a phenolic benzylhydroisoquinoline[17], many workers have made much effort to elucidate the actual biogenetic pathway. Barton, Battersby and their co-workers[35] used ^{14}C and ^{3}H isotopic labelling techniques whilst later studies by Rapoport[36] confirmed that morphine was made via codeine (3) and thebaine (4). Scheme 1.16.

Biosynthesis of morphine.

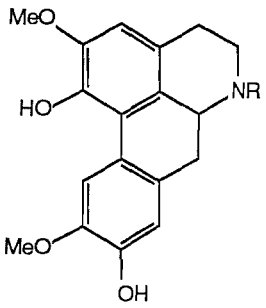


Scheme 1.16

However, attempts to mimic the plants biosynthetic pathway in the laboratory have met with the same problems encountered with the Grewe cyclisation. The many attempts to effect para-ortho coupling of (*dl*)-reticuline (37) using $K_3Fe(CN)_6$[35,37], MnO_2-silica gel[37], $AgCO_3$-celite and $VOCl_3$ have with two exceptions[35,38] yielded para-para coupling product (*dl*)-isosalutaridine (38) (0.3-4% yield) and/or the ortho-para coupling product (*dl*)-isoboldine (39) (0.4-53% yield).



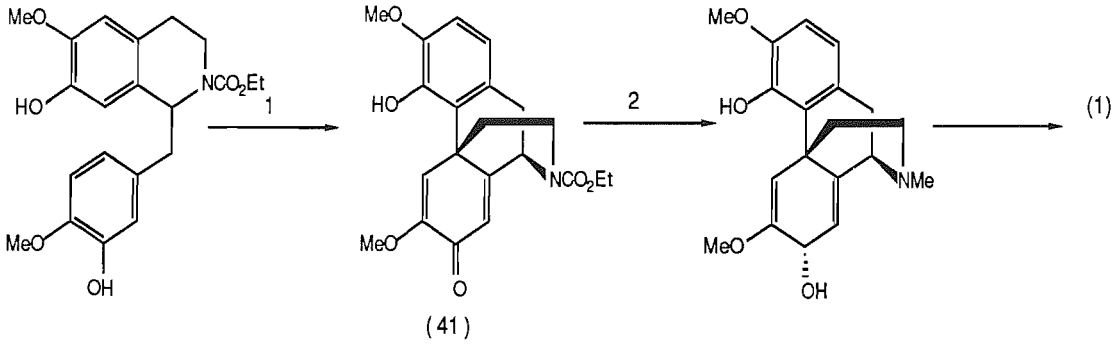
(38)



(39)

The first exception was reported by Barton and his co-workers[35] who after using ferricyanide oxidation, detected salutaridine (40) in a 0.03% yield after isotopic dilution techniques. Reduction with $NaBH_4$ followed by dehydration with acid gave thebaine. The conversion of thebaine to morphine has already been documented[36] so this work constitutes a formal synthesis.

A more significant contribution in this area was made by Schwartz *et al*[38] who used thallium tristrifluoroacetate (TTFA) to effect the oxidative coupling. This gave the salutaridine (41) in 23% yield. $LiAlH_4$ reduction followed by acid hydrolysis gave thebaine and therefore a total synthesis of morphine. Scheme 1.17.



(41)

Reagents

1. Thallium tristrifluroacetate 2. $LiAlH_4$

Scheme 1.17

This ends the first review on the first area of research on morphine and the next review concentrates on the research attempts to modify the pharmocological profile of morphine and its relatives.

1.7 PHYSIOLOGICAL EFFECTS OF MORPHINE

Primitive people have often used extracts of roots, bark, leaves, flowers, berries and seeds as drugs. This use of plants for medicinal purposes was not necessarily based on superstition or wishful thinking but was the result of mans first experiments into pharmacy. Ingestion of local vegetation to find out which plants gave therapeutic, pleasant or toxic effects would have enhanced mans medicinal culture or deepened his capacity for hunting and warfare.

The sensation of pain can be described as part of a mechanism warning the individual that there is a malfunction somewhere in their anatomy. Pain though can often persist past the point of casual stimulus to such an extent as to impair normal functions. Therefore the relief of pain has figured prominently in mans medicinal history.

It is widely accepted that when morphine is prescribed to a suffering individual, it does not interfere with the pain directly, but it enables the individual to gain a sense of detachment from that pain. Pain is not always physical but mental as well and the individual will subscribe to the drug in order to detach themselves from their mental trauma. Due to the euphoric qualities of the drug, the individual can develop a 'liking' for it and such enticement tends to lead to abuse. Repeated doses however produce a profound physiological effect. Frequently nausea, vomiting, sweating, dizziness and sluggishness occur with routine doses. If the dose is too great, the respiratory system may be suppressed enough to be considered life threatening. As frequent

exposure induces physical addiction and to complete the cycle abstinence by the user causes severe physical illness, morphine should be taken with care.

1.8 RESEARCH INTO CLEAN ANALGESICS

The question that arises now is how does morphine exert its biological effect?. The answer to this question is not known in detail but it basically involves a mechanism where morphine interacts with specific biopolymers known as receptors. These receptors are intended to operate with molecules (endogenious substances) produced by the organism as part of its natural function. Morphine acts as an agonist in the organism and is therefore only mimicking the role played by this endogenious substance. The mystery deepens when one considers that morphine is a natural product of vegetable origin and yet there are receptors to which it binds in *homo sapiens*. The question of which endogenious substances these receptors are intended for has now been documented[39]. A pair of pentapeptides which bind to the opiate receptors were isolated from mammalian brains and are called enkephalins (42,43).

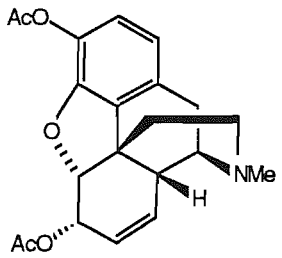
Htyr-Gly-Gly-Phe-MetOH = met-enkephalin (42)
Htyr-Gly-Gly-Phe-LeuOH = Leu-enkephalin (43)

These findings are too recent to have any impact on the design of analgesics but when folded properly, the enkephalins show a good topographical relationship to morphine.

As regards designing the 'ideal morphine', a drug which is a good analgesic but which does not inherit the addictive properties of

morphine would certainly be an achievement.

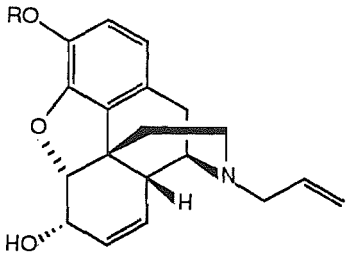
The first product which resulted from such a program was in 1874[40] when morphine was treated with acetic anhydride to form diacetylmorphine (44) which is now commonly known as heroin.



(44)

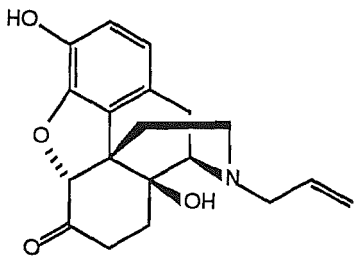
This was introduced into the medicinal world with claims of superiority over morphine because it did not cause respiratory depression or cause abstinence syndrome among chronic users when substituted for morphine. However, these claims were the result of poor interpretation of the observations being made. Heroin in fact causes a greater respiratory depression in the patient as well as physical addiction, these combined with the potent euphoric qualities of heroin have now lead to the drug being banned in the U.S.A.

Chemical research after the introduction of heroin followed in much the same vein. Pedestrian modification of the natural product by only a small degree produced varying degrees of analgesic potency but no real detachment from the side effects usually associated with morphine. The first real deviation in the biological activity of this family occurred with Pohl's synthesis of N-allylnarcodeine(45)[41]. This was followed up 30 years later with the morphine equivalent Nalorphine (46)[42].



(45) R = Me N - Allynarcodeine
(46) R = H Nalorphine

These molecules were found to be antagonistic towards morphine, that is they will prevent some of the side effects of morphine or its congeners such as respiratory depression, euphoria, nausea and drowsiness whilst still possessing some intrinsic analgesic activity. It is of interest that narcotic antagonists may in fact precipitate withdrawal symptoms on administration to addicts. Unfortunately, pychotomimetic side effects have rendered these compounds of little clinical use. However, because of this important discovery it lead to the design of new molecules which still retained the allyl group attached to nitrogen. The work on these molecules took advantage of the reactive diene system of thebaine and the most notable compound to be produced from this research was Naloxone (47)[43].

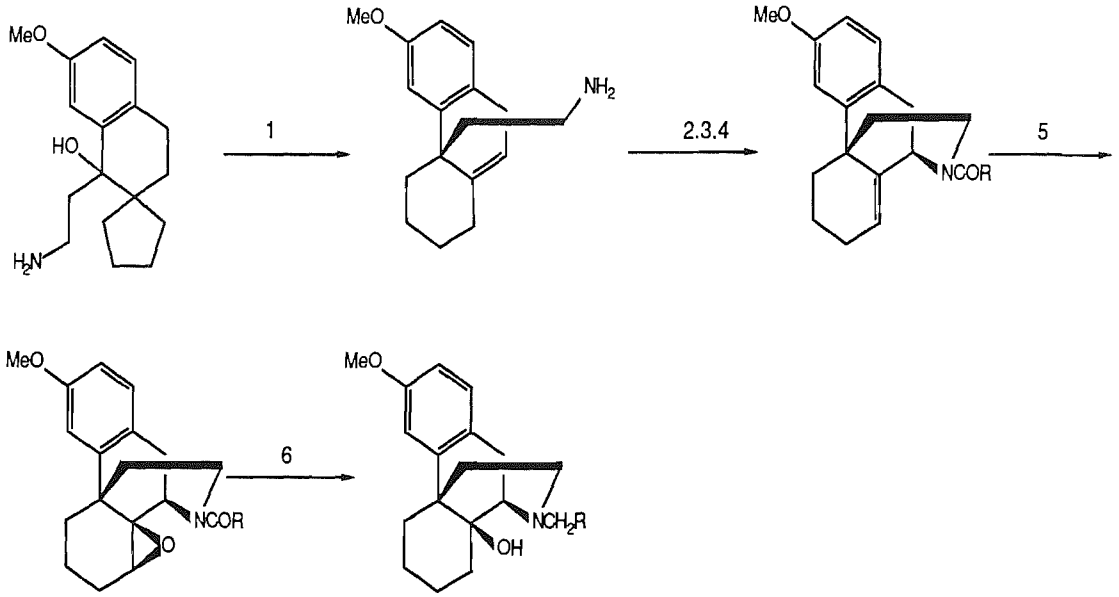


(47)

Naloxone has no agonist activity and is placed in a class of its own because it is a total or 'pure' antagonist. Pure antagonists such as naloxone find a very limited role in medicine but it should be noted that a mixture of naloxone and a narcotic has been used together to block the euphoriant effect of the narcotic. The reason

could be that the antagonist competes for the receptor site with the agonist. The research being undertaken today centres on building agonist properties into naloxone. On intravenous injection, the antagonist section will bind to the receptor site to block the euphoriant effect whilst at the same time, relay intrinsically its analgesic quality.

The pharmocological drawbacks of naloxone are that it is short acting and very poorly absorbed by the gut. Monkovic[44] has argued that since thebaine is a minor alkaloid of opium, routes to naloxone type structures have to be totally synthetic (this is not exactly true since thebaine is also derived from a related poppy *papaver bracteum* and constitutes 26% of the dried latex[45]). However, Monkovic morphinans have introduced deep seated changes to the morphine molecule by removing the furan ring altogether. There is much precedence in retaining analgesic activity when despatching with the ether linkage, one only has to refer back to Grewe's analogues which lack the furan ring by total synthesis but still possess agonistic activity. As other totally synthetic molecules such as cyclazocine (51) (see page 30) possess the qualities Monkovic wants to include in his naloxone analogues (i.e long acting and more orally effective), he set about synthesising 3,14-hydroxymorphinans which were representative of naloxone (47), cyclazocine (51) and Grewe's analogues. The benefits of these morphinans have yet to be described in the literature but an outline of his work is described in scheme 1.18.



Reagents

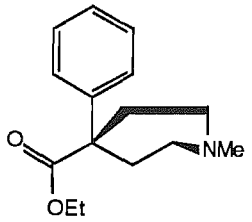
1. HCl, ether 2. Br_2, $CHCl_3$ 3. $NaHCO_3$, DMF 4. $(C_3H_5CO)_2O$ 5. mCPBA 6. $LiAlH_4$

Scheme 1.18

In a further simplification of the morphine skeleton two other classes of analgesics, the benzomorphans (page 29) and the 4-phenylpiperidines illustrate that even with radical dissection of the morphine framework potent analgesic activity can still exist.

4-phenyl piperidines

It became known as early as the late 1930's that the complete morphine framework was not necessary for analgesic activity. A German research team whilst pursuing other medicinal goals made pethidine (48), which after routine screening showed morphine-like characteristics[46].



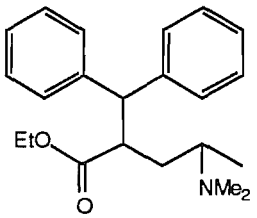
(48)

This was introduced into the medicinal world billed as a better type of morphine for much the same reasons as heroin was but a thorough examination revealed that pethidine needs the same precautions as morphine. It is interesting to point out why some analgesics don't live up to expectation whilst others tend to surpass theirs. The root cause to these faulty interpretations and sometimes big disappointments lies in the validity of animal experiments in determining the analgesic or physical dependence properties of a certain compound. Narlorphine (46) was one of those compounds which did not give a positive test in the laboratory but was incidently shown to be analgesic in man. Likewise some benzomorphans (a class that will be mentioned later) did not support a physical dependence in the rhesus monkey but did in man. Whilst with the phenyl piperidines a reversal of the situation is observed. Such confusing data is attributed to the different ways a species will metabolise a certain compound. Newer methods for screening analgesics are now being used, which are by no means perfect, but do reduce the chances of a false negative result occurring in the laboratory[47].

Many phenylpiperidines have been synthesised and some possess very potent analgesic activity , but a separation of analgesia from physical dependence has never been realised from this family of compounds. One of the common side effects of morphine is constipation, due to decreased mortality of the gastrointestinal

tract. Chemical modification of pethidine has produced compounds which retain this side effect whilst losing the analgesic activity and have therefore found a role in the treatment of diarrhoea[48].

Due to the chemical features common to pethidine and morphine a class of analgesics called methadone (49)[49] and its congeners was synthesised.

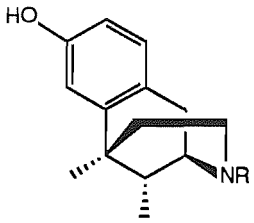


(49)

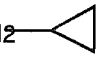
When taken orally methadone parallels the analgesic qualities of morphine. Methadone causes tolerance and dependence of the morphine type and therefore can be substituted for other narcotics. Compared with morphine or heroin the methadone abstinence syndrome is much slower in onset, longer in duration and much less intense. It is the drug of choice used to ameliorate the distress of withdrawal from narcotics and because of its prolonged oral effect, is used for maintenence of dependence of the morphine type when such is judged advisable.

The Benzomorphans

The benzomorphans are a class of compounds which illustrate that by dispensing with one of the carbocyclic rings, retention of analgesia persists. Even more interesting is the fact that they seem to exhibit an analgesic activity but reduced addictiveness as well as antagonistic activity.

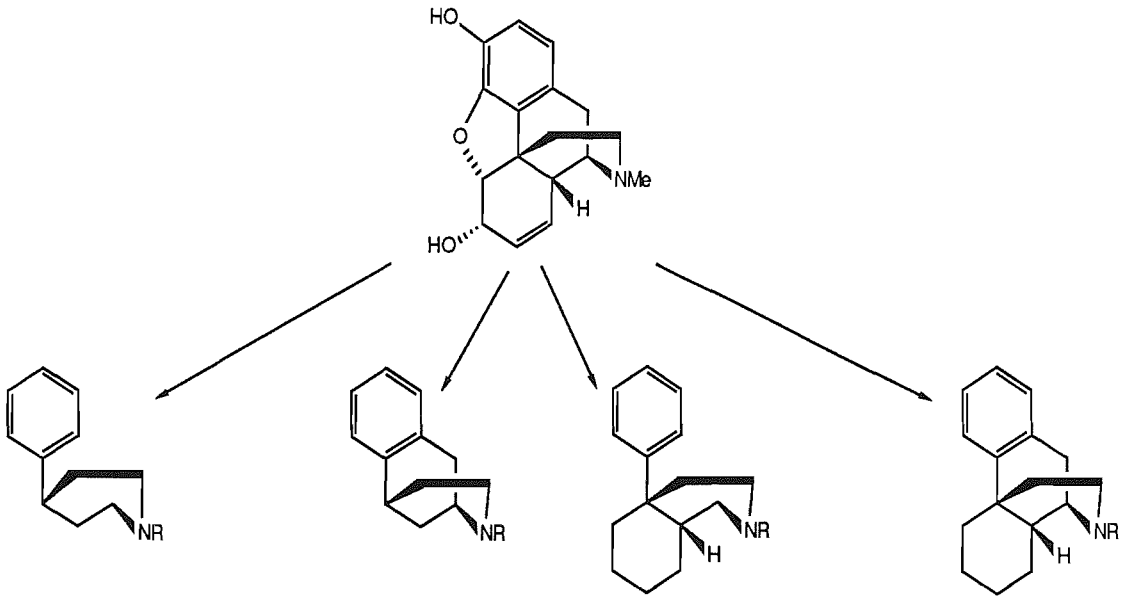


(50) R = CH_2CHCMe_2 pentazocine

(51) R = CH_2  cyclazocine

One such compound pentazocine (50), has found considerable use in the clinic. As regards its agonistic properties it is one fiftieth the strength of morphine on a milligram per milligram basis. In addition there is considerable evidence that this drug has a lesser addiction potential than morphine[50]. Another family in this group is cyclazocine (51), this is many times more potent as an analgesic and antagonist than morphine and nalorphine (46) respectivly. However its analgesic properties are insidious in nature as by the time the analgesic dose is reached, pyschomimetic effects have already started to take place in the individual. Nevertheless, it has still found a role in the clinic.

Medicinal chemists looked for the common denominator in the compounds described in order to rationalise what caused analgesic activity. The so called "Morphine rule"[51] evolved; a generalised rule exposing the common formulation feature to all these classes of compounds. Like all generalisations it has its exceptions but an aromatic moiety attached to a quarternary centre which is two carbons away from a tertiary nitrogen serves as a useful "rule of thumb". Scheme 1.19.



Scheme 1.19

Why molecules obeying the "morphine rule" show such varied activity is beyond the scope of this thesis. However, a simple overview is offered to the reader. For a long time it had been assumed that only one receptor was responsible for the effects of morphine and its derivatives. Recent evidence points to the existence of different opiate receptors that are responsible for the wide ranging psychotropic activity of morphine analogues[50]. The receptors in question are designated μ,δ,κ and σ. The μ receptor is defined as a high affinity site at which morphine like drugs produce pain killing and other opiate effects. The σ receptor produces stimulant and psychomimetic responses when bound to benzomorphan opiates. The δ receptor is found in the CNS and exhibits a higher affinity for the natural enkephalins than for morphine derived analgesics. The κ receptor binds cyclazocine like opiates producing analgesic and sedative effects. In conclusion it appears that the effects of opiates on nervous tissue occurs by interaction with at least four different sites. The question

remains as to whether the μ, δ, σ and κ opiate receptors are different or interconvertable forms of the same receptor.

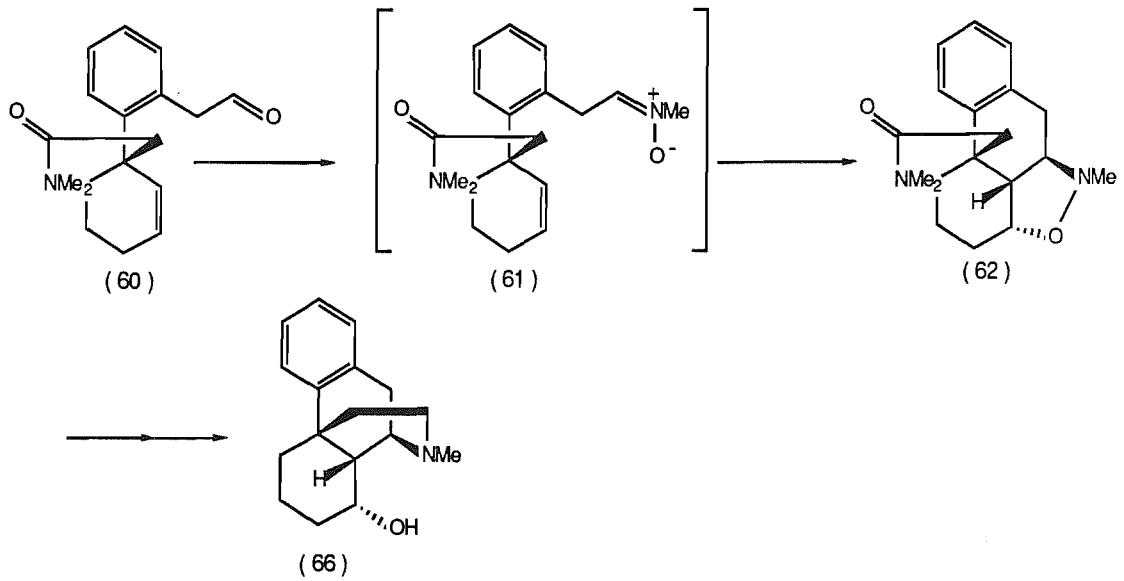
CHAPTER TWO

2.1 MODEL STUDIES CONDUCTED BY CHANDLER

One of the many ideas from our laboratory which can be utilised in a total synthesis of morphine, concerns the possibility of a nitrone under going an intramolecular (3+2) cycloaddition reaction. A number of methods are avalaible for the formation of nitrones[52]. Two of the most commonly used are:

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

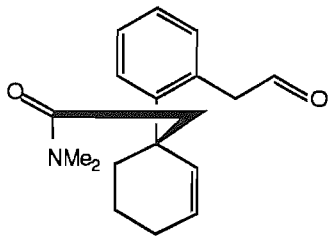
Our key nitrone (61) would be made by reacting N-methylhydroxylamine with the aldehyde (60). The nitrone (61) would undergo an intramolecular concerted dipolar cycloaddition reaction onto a double bond resulting in a rapid entry into the morphine framework. Scheme 2.1.



Scheme 2.1

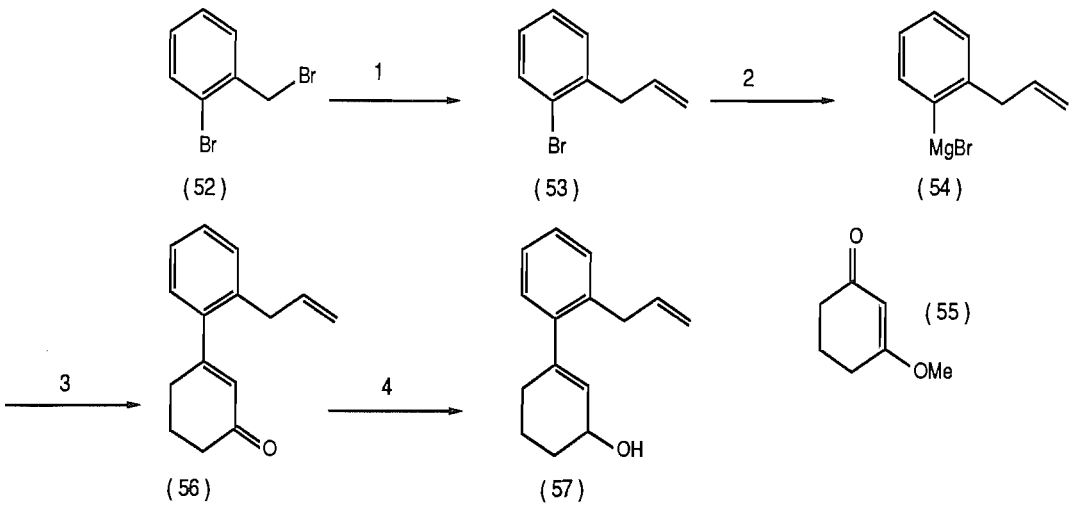
A model study was conducted by Parsons and Chandler[53] to determine the feasibility of this approach and to discover and

solve the problems likely to occur if the route was developed into a total synthesis. The first target molecule in the strategy was



(60)

the aldehyde (60) which incorporates the A and C rings of the morphine framework. This transformation was accomplished by coupling the Grignard reagent (54) with 3-methoxy-2-cyclohexen-1-one (55). Subsequent acid hydrolysis of the product gave the enone (56). The bromide (53) required for formation of Grignard reagent (54) was made in one step by treating o-bromobenzyl bromide with vinylmagnesium bromide in the presence of equimolar quantities of copper (I) iodide and 2,2-dipyridyl. Reduction of enone (56) with sodium borohydride in THF/H_2O (1:1) was performed in the presence of cerium (III) chloride to prevent 1,4 reduction[54] and gave the allylic alcohol (57) in quantitative yield. Scheme 2.2.

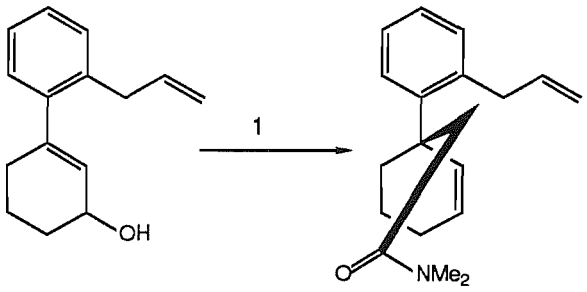


Reagents

1. Vinylmagnesium bromide, CuI, 2,2-dipyridyl, THF 2. Mg, ether 3. 3-methoxy-2-cyclohexen-1-one (55) . H_3O^+ 4. $NaBH_4$, $CeCl_3$, THF / H_2O

Scheme 2.2

Attempts to effect the Claisen rearrangement with ethyl vinyl ether failed completely under a variety of conditions. A large mixture of unidentified products were reported when an Ireland-Claisen[55] rearrangement was conducted and a similar result was observed when a Johnson-Claisen rearrangement[56] was attempted. Fortunately the Eshenmoser-Claisen rearrangement[57] was successful. This involved heating the allylic alcohol (57) in toluene under reflux with N,N-dimethylacetamide dimethylacetal to give the required amide (58) in 60% yield. Scheme 2.3.



(57) (58)

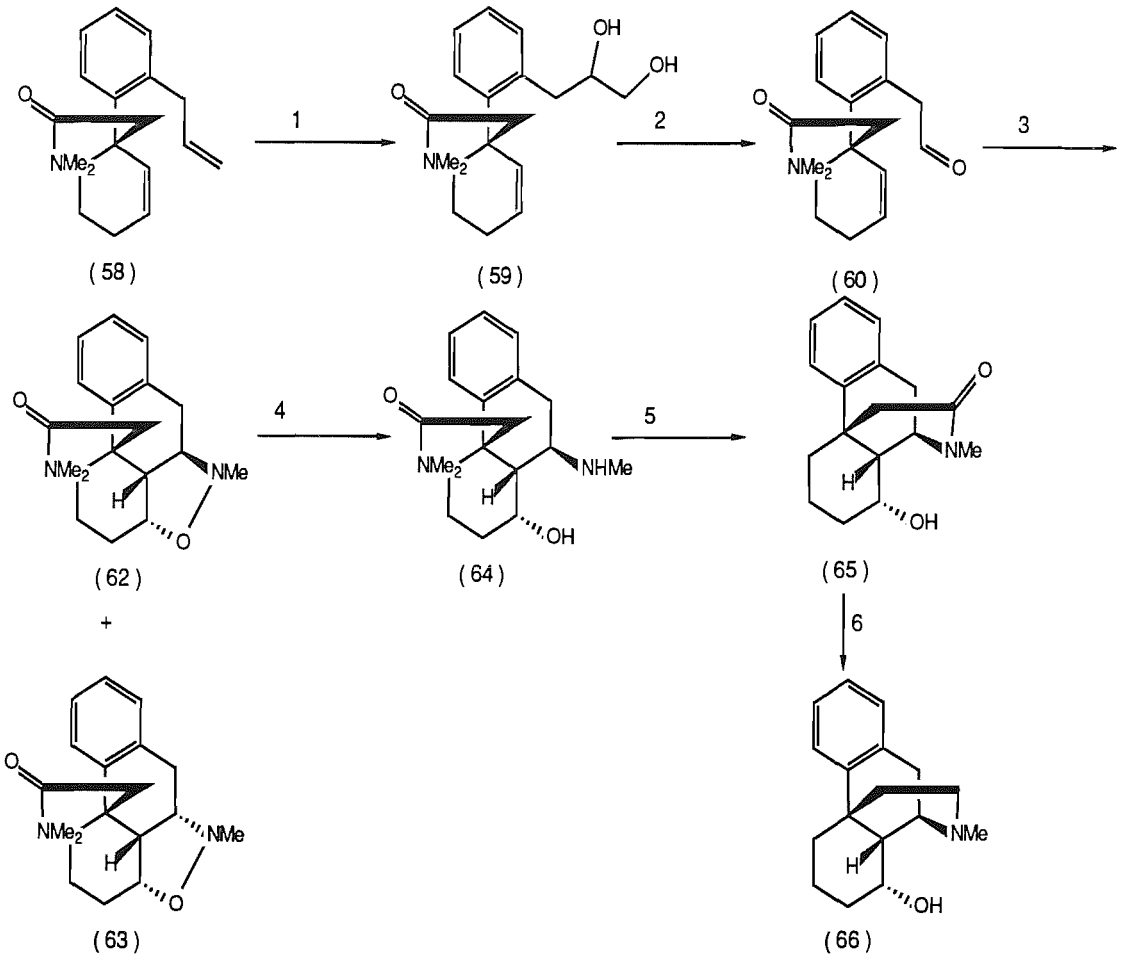
Reagents

1. **N,N**-Dimethylacetamide dimethylacetal, toluene , Δ

Scheme 2.3

Treatment of the amide (58) with osmium tetroxide and trimethylamine-N-oxide followed by cleavage of the resulting diol (59) with sodium periodate in acetic acid, gave the aldehyde (60) in quantitative yield.

With the aldehyde (60) in hand, Parsons and Chandler turned their attention to the crucial nitrone cycloaddition. This was carried out by simply adding excess N-methylhydroxylamine to a refluxing solution of the aldehyde (60) in benzene, in the presence of 4A molecular sieves. Two compounds were isolated in 1:1 ratio corresponding to the two possible adducts formed through *exo* (62) and *endo* (63) addition. Hydrogenation of (62) in acetic acid using Raney nickel as a catalyst, followed by basification, gave the amine (64). Treatment of (64) with hydrogen chloride gas followed by fusion of the resulting salt gave morphinan (65). Lithium aluminium hydride reduction of the lactam (65) gave the simple 8-hydroxymorphinan (66). Scheme 2.4.



Reagents

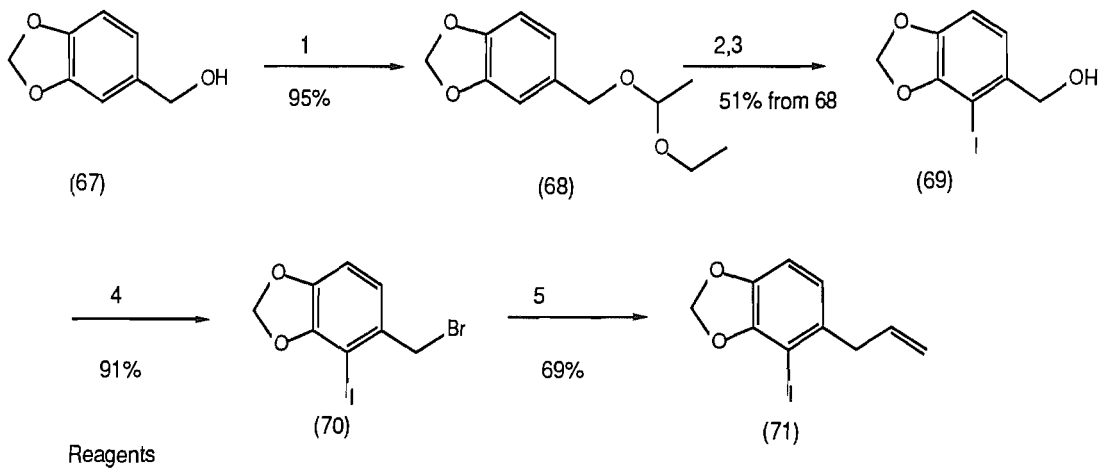
1.OsO_4, trimethylamine-N-oxide 2. $NaIO_4$ 3. MeNHOH, heat 4. Raney Ni-H_2 5. HCl 6. $LiAlH_4$

Scheme 2.4

2.2 THE MATTHEWS APPROACH

The first stage in Matthews' work centred around the efficient construction of the aromatic moiety (71), which was suitably substituted in two respects. Firstly, as in Chandlers case, iodine was to be incorporated in the ring in order to form an organometallic reagent to couple with 3-methoxy-2-cyclohexen-1-one (55). Secondly a methylenedioxy group would also be attached to that aromatic moiety to be used to

form the furan ring in the final stages of the synthesis. Scheme 2.5 illustrates how this was achieved.

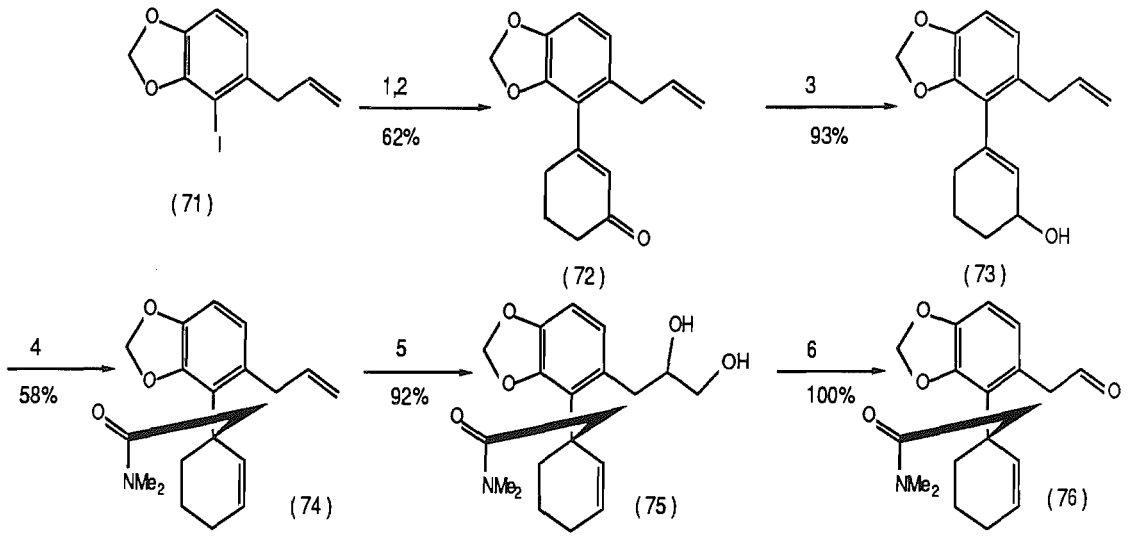


Reagents

1. Ethyl vinyl ether, TFA 2. n-butyllithium, I_2 3. H_3O^+, MeOH 4. PBr_3 5. vinylmagnesium bromide , CuI, 2,2-dipyridyl

Scheme 2.5

All that now remained was to make aldehyde (76), the precursor for the nitrone addition. Aldehyde (76) was made according to scheme 2.6.

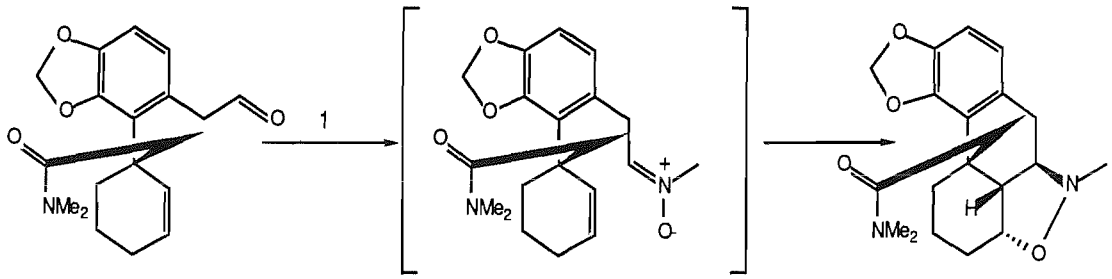


Reagents

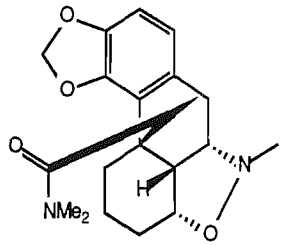
1. Mg, (55) 2. H_3O^+ 3. $NaBH_4$, $CeCl_3$ 4. N,N-dimethylacetamide dimethylacetal, toluene , reflux 5. OsO_4, trimethylamine-N-oxide THF, H_20, t-BuOH 6. $NaIO_4$

Scheme 2.6

The aldehyde (76) was treated with freshly prepared N-methylhydroxylamine in boiling benzene in the presence of 4A molecular sieves. This gave rise to two products (78) and (79) in almost equal ratio. Scheme 2.7.



(76) (77) (78)



(79)

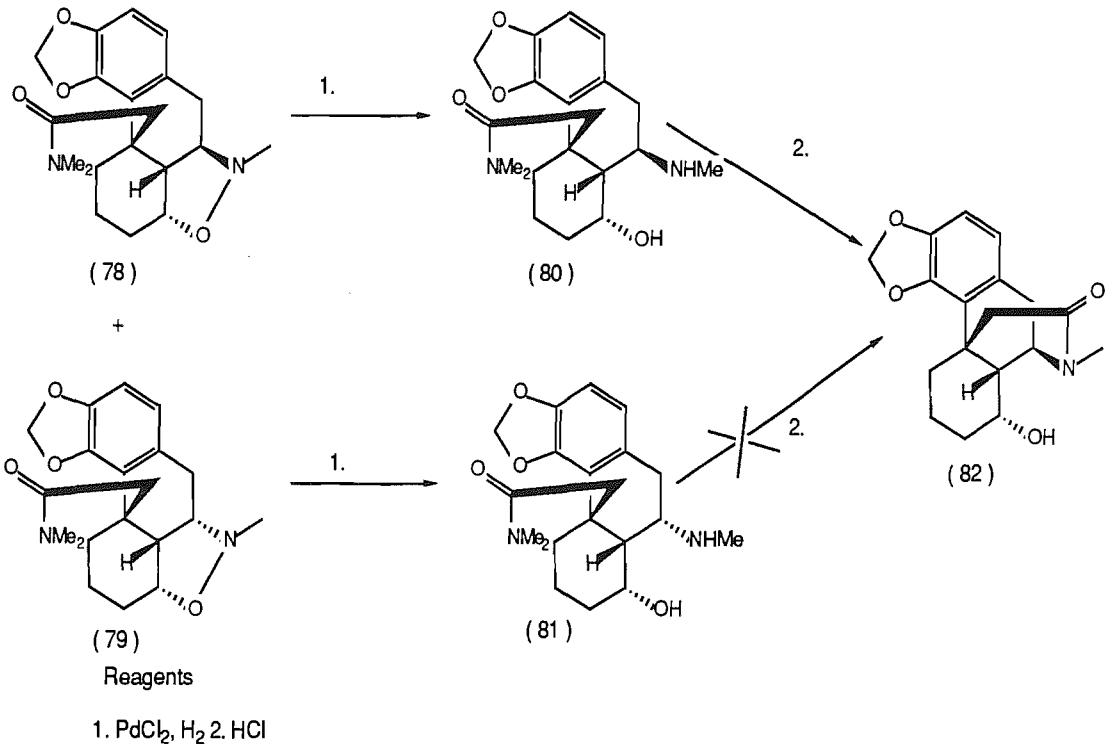
Reagents

1. MeNHOH, benzene, Δ

Scheme 2.7

To determine which was the desired *exo* cyclisation product, each isomer was taken in turn and reduced with palladium (II) chloride in methanol under an atmosphere of hydrogen. This gave the corresponding amino alcohols (80) and (81). The reduced products were converted into their hydrochloride salts and heated to180^{o}C under vacuum. As expected this caused the salt derived from (80) to cyclise whereas the salt derived from (81), the *endo*

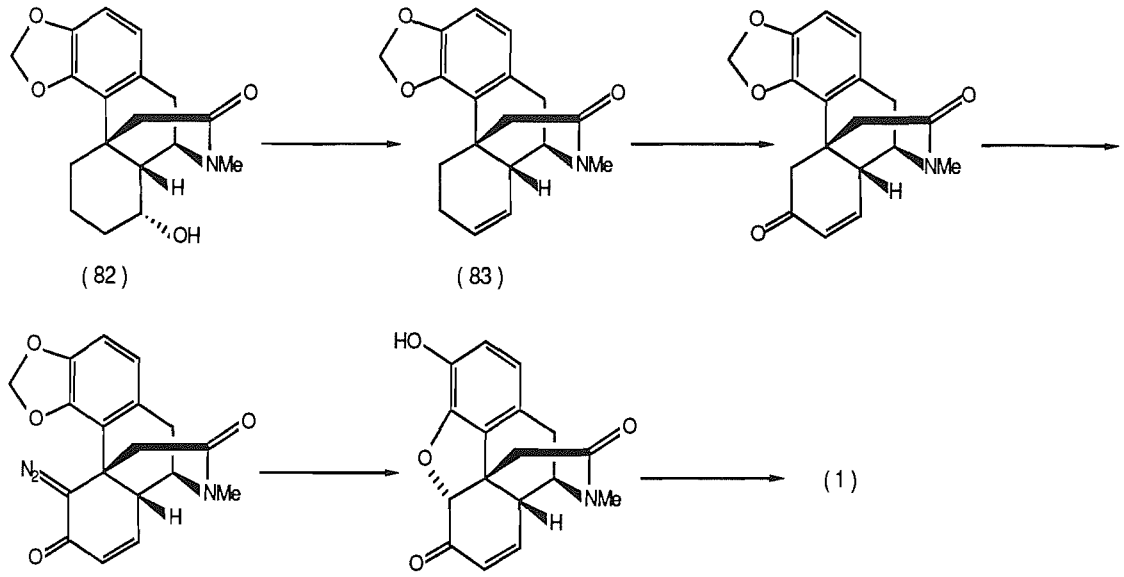
adduct, decomposed under these experimental conditions Scheme 2.8.



Scheme 2.8

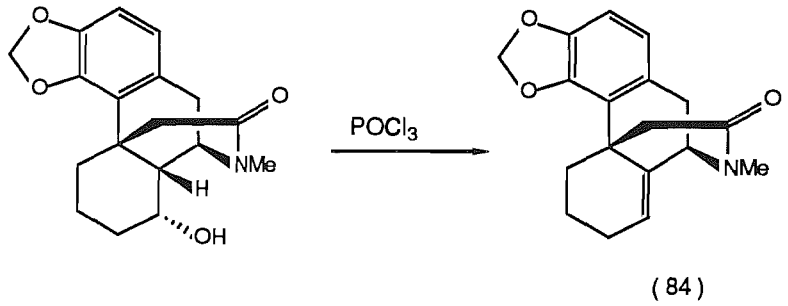
After Matthews had elegantly determined the desired *exo* adduct isomer, he embarked on a course to complete the synthesis of morphine.

The first task was to dehydrate the alcohol (82) in order to give the less substituted alkene (83), and if this was successful the final stages in the synthesis of morphine would be carried out as outlined in scheme 2.9.



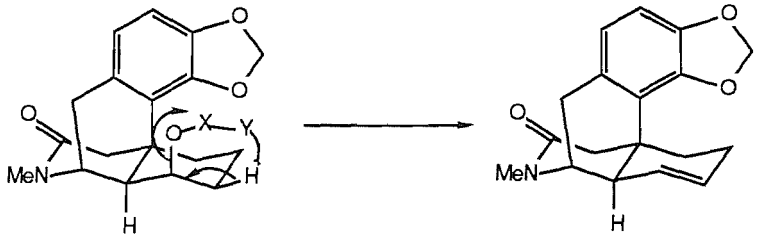
Scheme 2.9

However, the manipulation of the axial hydroxyl group in (82) presented serious problems in the synthesis. Elimination of the alcohol group with phosphorus oxychloride gave the more highly substituted alkene (84). Scheme 2.10.



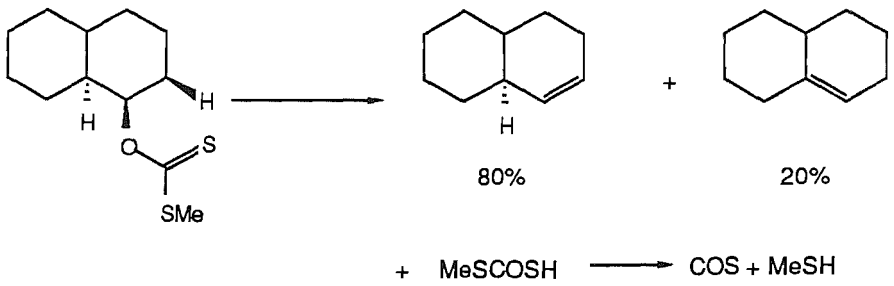
Scheme 2.10.

However, scheme 2.11 illustrates that a simple *syn* elimination procedure would give the correct olefin because the proton at the ring junction is in no way embraced by the six membered transition state that preceeds the concerted mechanism of elimination.



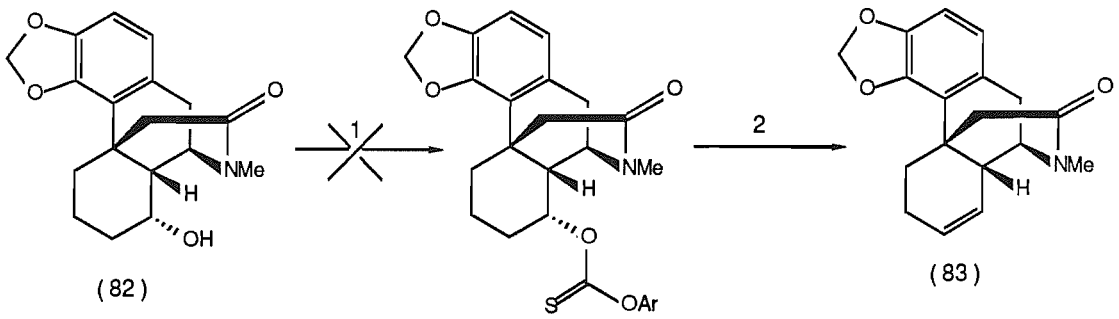
Scheme 2.11

The first reaction studied for the desired transformation was a Chugaev reaction[58]. This relies on the formation of a xanthate ester which undergoes *syn* elimination on heating to give an alkene. Scheme 2.12.



Scheme 2.12

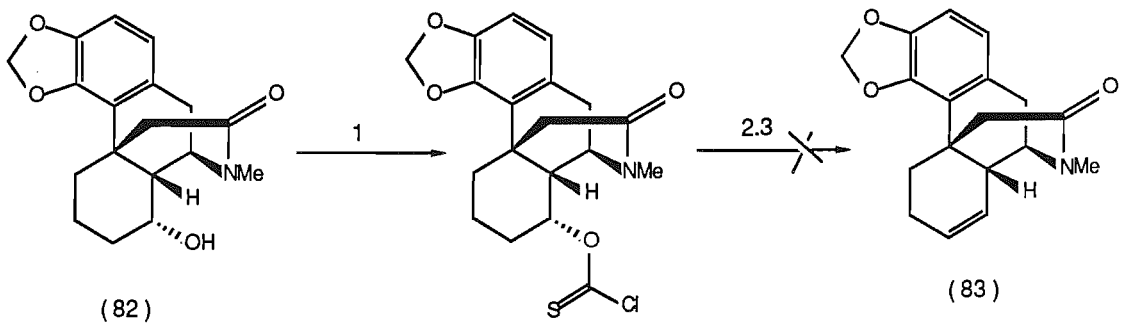
Unfortunately, Matthews reported a large number of unidentified products and the idea was revised according to the method of Gerlach[59]. By treating an alcohol with *o*-4-methylphenyl chlorothioformate a thiocarbonate is produced, which on heating results in the formation of an alkene. Unfortunately, this procedure was unsuccessful when applied to the key alcohol (82) despite a variety of solvent conditions. When the reaction was conducted in DMF only the undesired more substituted olefin (84) was obtained. Scheme 2.13



Reagents
1. ArOCSCl 2. Δ

Scheme 2.13

Next Matthews' attention was attracted to the idea that the alcohol (82) could be treated firstly with thiophosgene to give the xanthate (86) followed by ethanethiol. Heating the resulting ester should give olefin (83). Scheme 2.14.



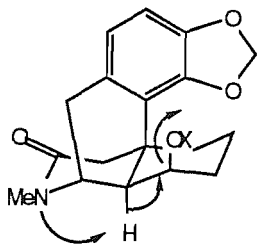
Reagents
1. ClCSCl 2. EtSH 3. Δ

Scheme 2.14

When the procedure was attempted in boiling acetonitrile a mixture of the more substituted olefin (84) and starting material were isolated. Repeating the experiment in dichloromethane containing triethylamine gave the same result.

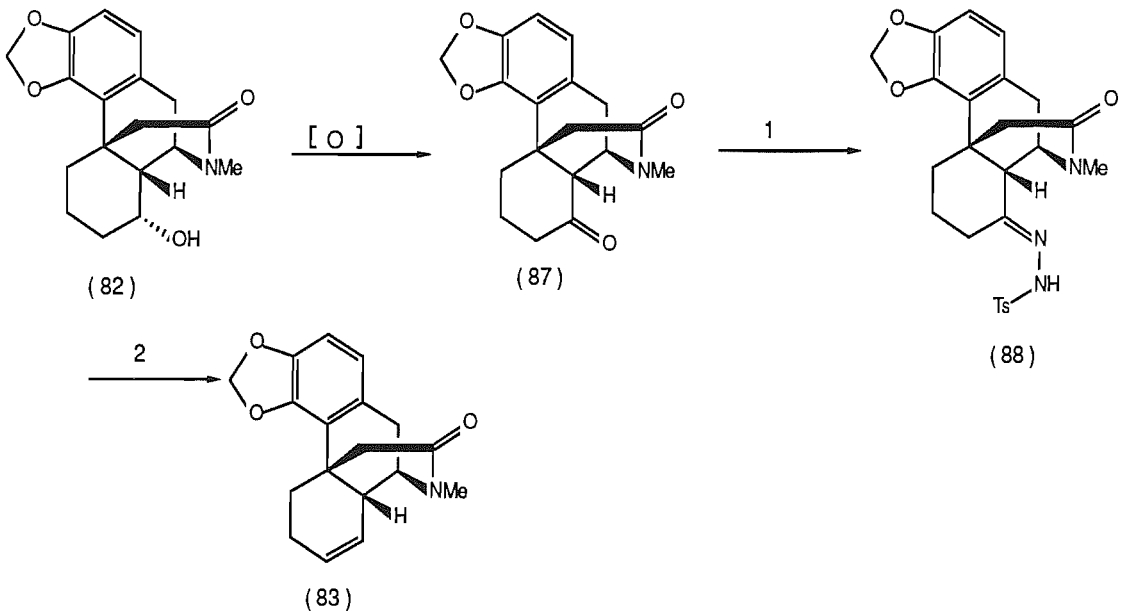
The dehydration was also attempted using Burgess' salt[60]. This

salt is readily made by the action of methanol on chlorosulphonyl isocyanate followed by treating the resulting crystals with triethylamine in toluene. However, under these conditions only the undesired Saytzeff olefin (84) was obtained. Matthews rationalised these disappointing results by postulating neighbouring group participation from the lone pair on the amide nitrogen which, by virtue of its close proximity, assisted a *trans, anti* elimination of the alkylated oxygen. Scheme 2.15.



Scheme 2.15

In an final attempt to obtain the elusive alkene (83), Matthews and Parsons considered oxidising the alcohol (82) to a ketone and converting it to the tosyl hydrazone derivative (88) such that a Shapiro reaction[61] could be attempted. Scheme 2.16.



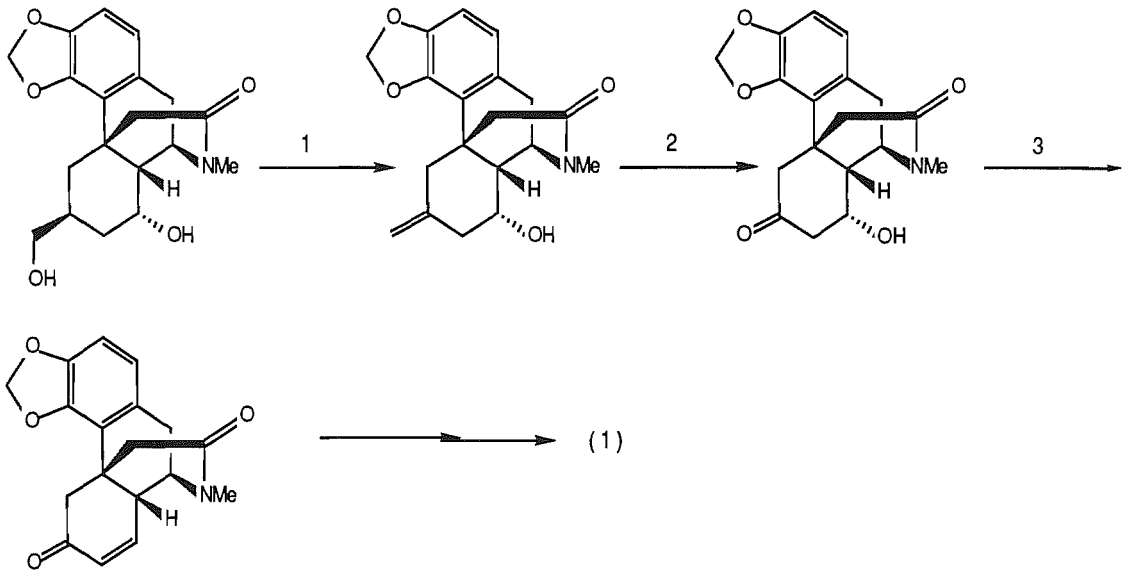
(82) (87) (88) (83)

Reagents

1. Tosyl hydrazine 2. n-butyllithium

Scheme 2.16

Attempts to oxidise the alcohol functionality in (82) by Jones reagent or PCC proved difficult due to competing degradation of the reactant. The synthesis was revised in an effort to overcome the difficult transformation. In the new approach Matthews incorporated an extra substituent on the C ring in order to circumvent the problems being encountered with (82). Scheme 2.17.

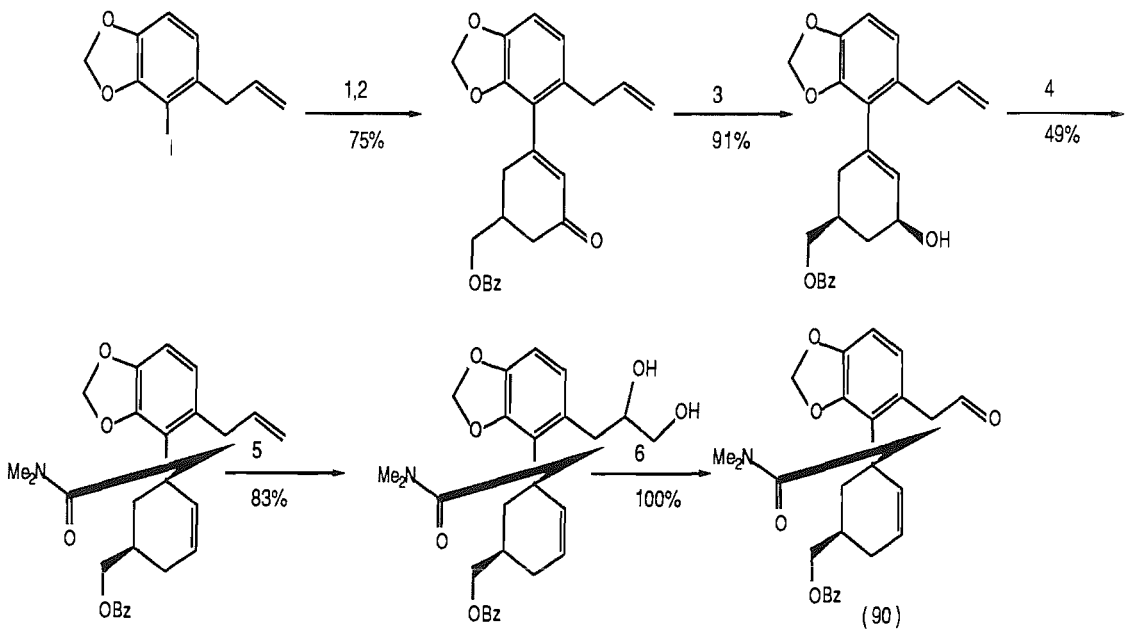


Reagents

1. MsCl, Et_3N 2. O_3, Me_2S 3. $POCl_3$

Scheme 2.17

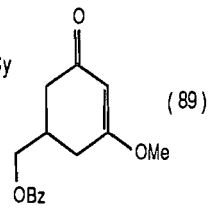
Repeating the same series of chemical transformations for this series, afforded the key aldehyde (90). Scheme 2.18.



Reagents

1. Mg, (89) 2. H_3O^+ 3. $NaBH_4$, $CeCl_3$ 4. N,N-dimethylaetamide dimethylacetal, MeCy, EtCy

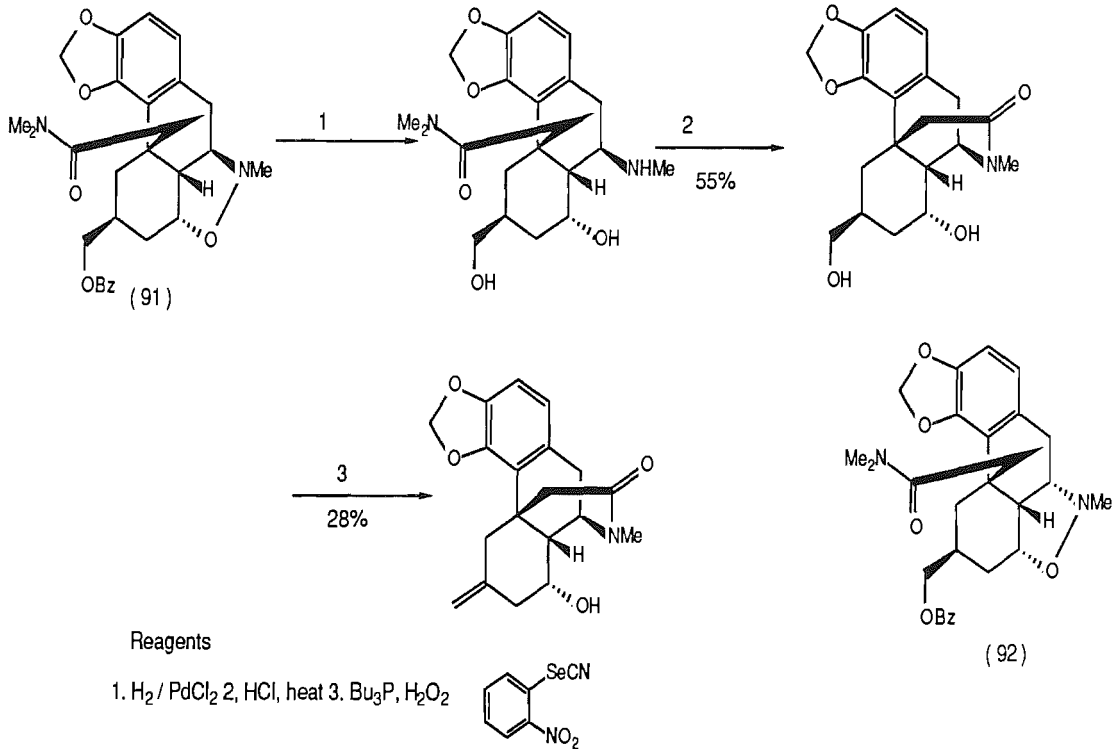
5. OsO_4, trimethylamine-N-oxide 6. $NaIO_4$, TFA



(89)

Scheme 2.18

The nitrone addition on this substrate proved to be even more of a disappointment compared to the first case. A mixture of isomers (91) and (92) in a ratio of 8:1 in favour of the endo product (92) was obtained. Matthews however managed to complete a few more steps in the synthesis before time ran out. Scheme 2.19.



Scheme 2.19

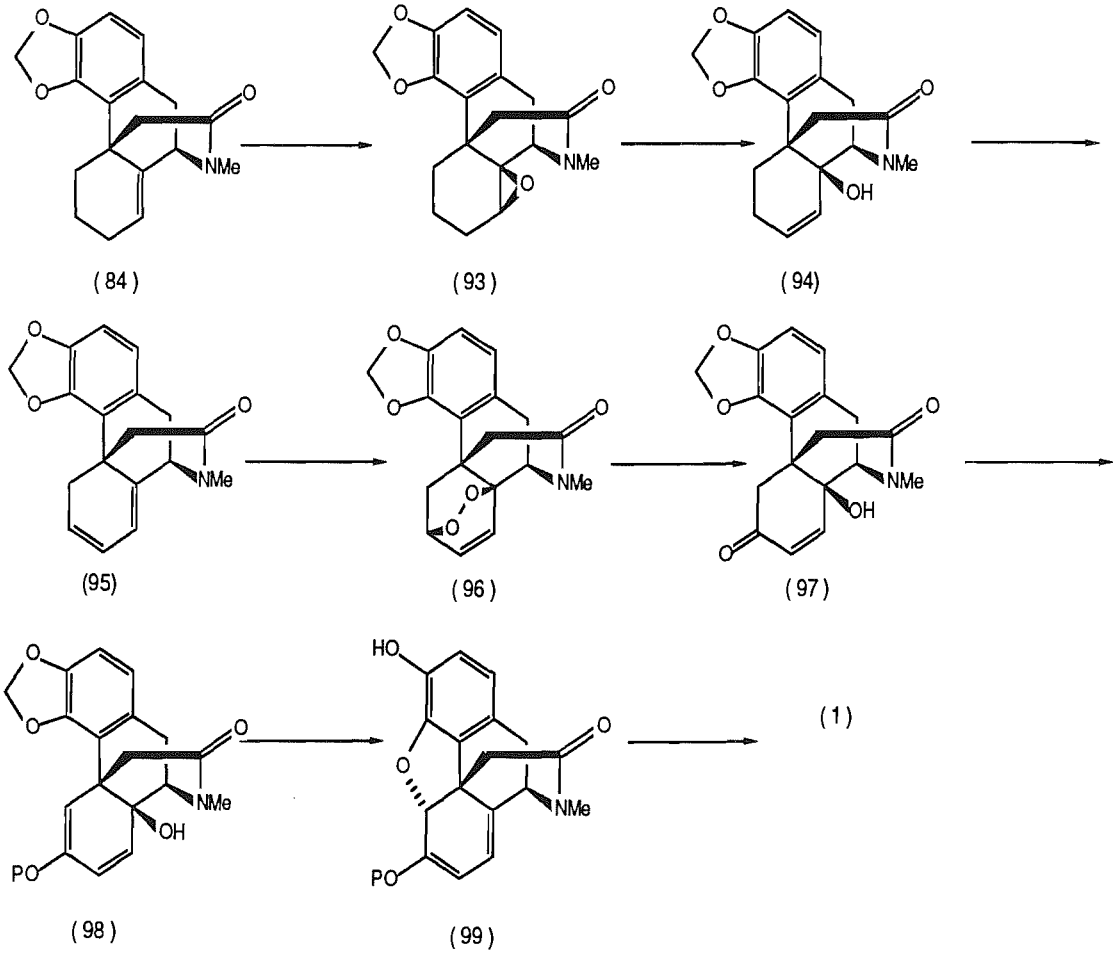
2.3 CONTINUATION OF MATHEWS WORK

Since Matthews had made such deep inroads into the morphine synthesis we decided to continue his work to completion. Before a new synthetic plan could be devised one had to consider the problem which had been beset by Matthews.

The stumbling block in the synthesis was the attempted dehydration of the axial hydroxyl group in (82) to furnish the less substituted double bond. Unfortunately all attempts to achieve this transformation gave the more highly substituted olefin (84). Since the production of the olefin was a facile and clean process we reasoned that such an olefin could be used to our advantage.

As illustrated earlier (see page 27) Monkovic had epoxidised olefins in the same position. Thus epoxidation of the olefin (84)

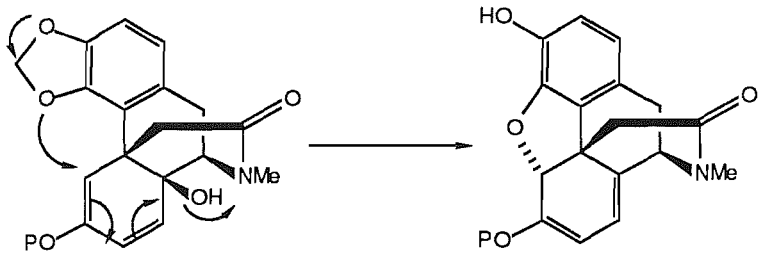
and treatment of the resulting epoxide (93) with sodium phenyl selenide followed by oxidation of the resulting selenide with H_2O_2 would afford (94). The final series of chemical reactions is outlined in scheme 2.20.



Scheme 2.20

Modification of the allylic alcohol (94) should give the diene (95) which would hopefully undergo a singlet oxygen Diels-Alder reaction to give peroxide (96). Treatment of the peroxide (96) with triethylamine would give the oxymorphine analogue (97) which by further elaboration would furnish diene (98). The diene (98) would be the key precursor for the synthesis of morphine, since deprotection of the catechol functionality would hopefully result

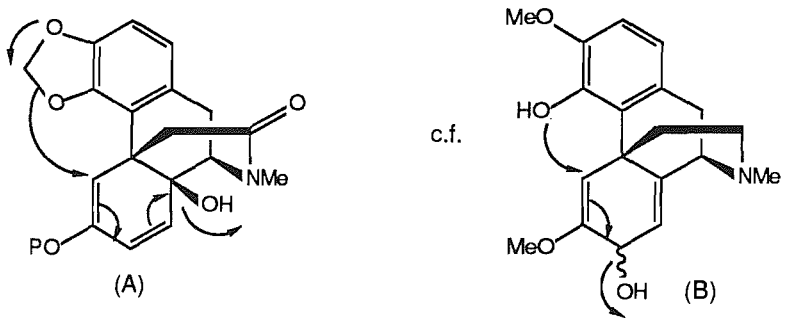
in concommitant cyclisation to give the thebaine related morphinan (99). Scheme 2.21.



(98) (99)

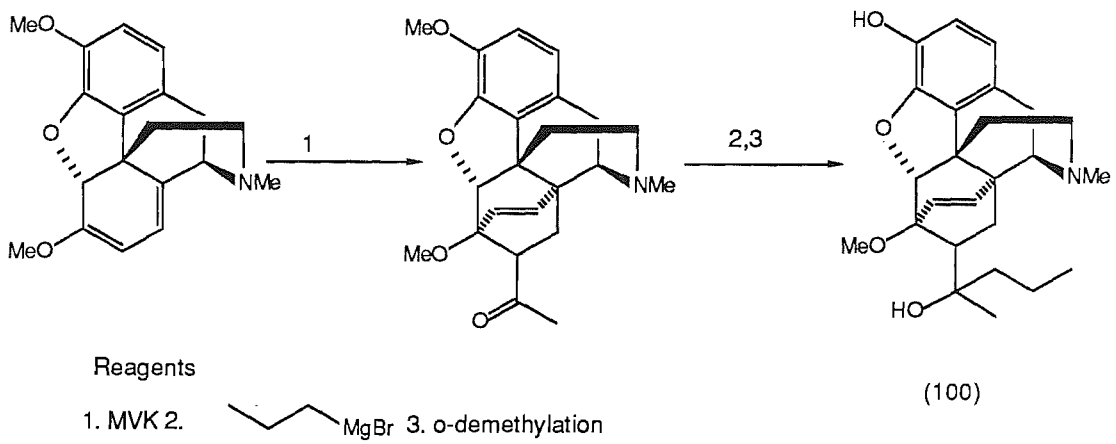
Scheme 2.21

Cyclisations of this nature to form the furan ring and thus complete the morphine synthesis is employed by the plant itself (see page 19), differing only in ejection of the ε-hydroxyl group (A) instead of the γ-hydroxyl group (B). Scheme 2.22.



Scheme 2.22

The other key reaction in the proposed route is in the hetero Diels-Alder reaction. Diels-Alder reactions involving the reactive diene system of thebaine have been employed by Bentley *et al*[62]. His work produced entorphan (100), a highly addictive analgesic 2000 times more powerful than morphine. Scheme 2.23.



Reagents

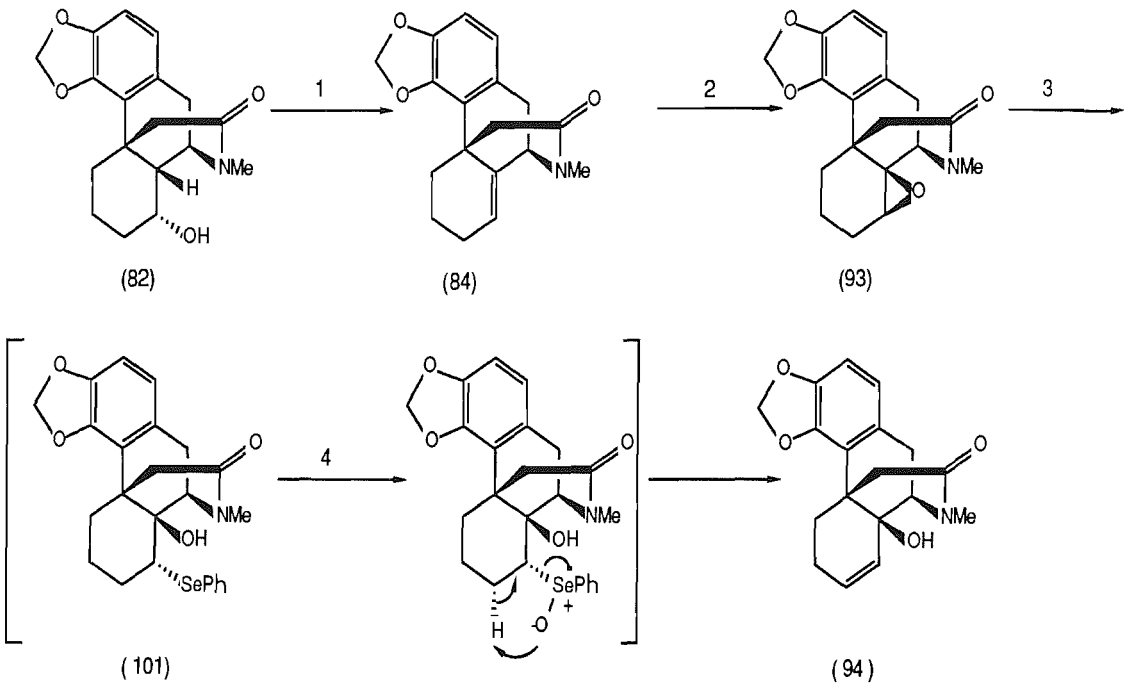
1. MVK 2. MgBr 3. o-demethylation

(100)

Scheme 2.23

2.4 STUDIES TO COMPLETE THE MORPHINE SYNTHESIS

The key lactam (82) was efficiently produced using the Matthews methodology and attempts were made to convert it to the key diene (95). This was done in the following way. The lactam (82) was stirred in pyridine and phosphorus oxychloride to give the olefin (84) in 68% yield. Epoxidation of (84) with *m*CPBA in dichloromethane gave the epoxide (93) in 58% yield. The epoxide (93) was then opened up regioselectivly with sodium selenide in boiling n-propanol to give the selenide (101) which was not isolated but was oxidised *in situ* to give allylic alcohol (94) in 53% yield. Scheme 2.24.



(82) (84) (93)

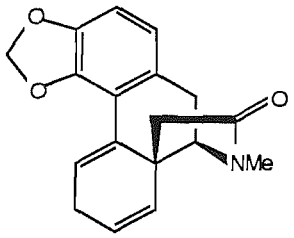
(101) (94)

Reagents

1. $POCl_3$ 2. *m*CPBA 3. NaSePh 4. H_2O_2

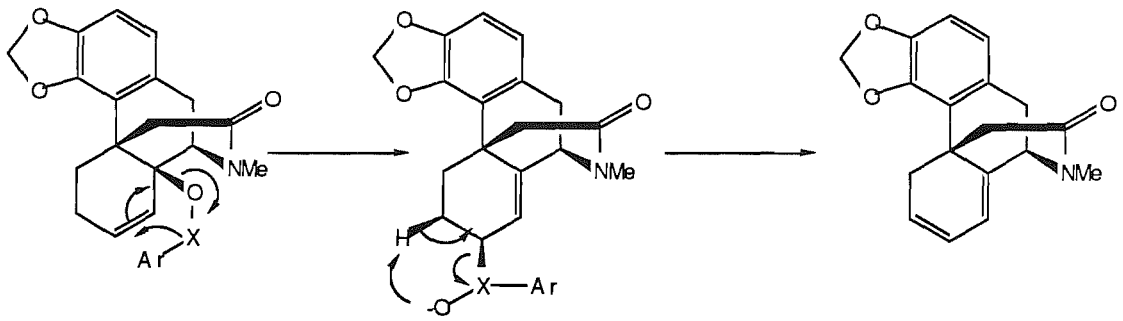
Scheme 2.24

To obtain the required diene (95) a simple dehydrating procedure involving $POCl_3$ was attempted on the understanding that only one product could be obtained since the hydrogen next to nitrogen would give rise to an '*anti* -Bredt' alkene. A less polar product on TLC was isolated. However, the nmr and ir spectral characteristics of this new product were not compatible with the required diene; for example, the amide stretch had shifted to 1680 cm^{-1} (indicative of a five membered ring lactam). Examination of the ^{13}C nmr spectrum showed the loss of the benzylic quaternary carbon and therefore the product was assigned the structure (102).



(102)

On the basis of this result it was reasoned that any chemical reaction employed to form diene (95) would have to be concerted in nature. Scheme 2.25.



Scheme 2.25.

Addition of PhSCl (prepared by the method of Mueller *et al* [63]) to the allylic alcohol (94) resulted in the isolation of starting material on workup. Presumably the sulphoxide-sulphenate rearrangement equilibrium lies to the side of the sulphenate which is hydrolised on workup. As by this time so little of our material remained it was decided to embark on a new and totally different approach to morphine which will be discussed in chapter 3.

CHAPTER THREE

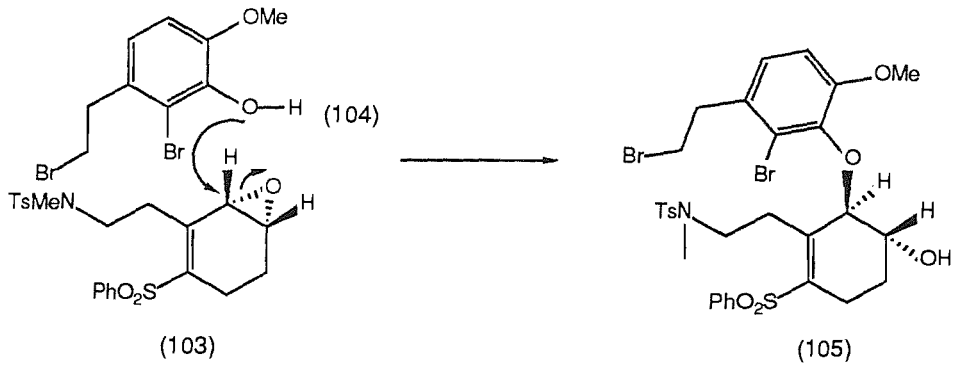
3.1 INTRODUCTION; THE EPOXIDE APPROACH.

Even though our nitrone methodology offers a viable and efficient entry into the morphine framework, it seemed evident from our present studies that the formation of the furan ring would prove to be a difficult problem. It was reasoned that a possible solution to this problem was to construct the ether linkage at an early stage in the synthesis. The aim of this project was to explore the possibility of effecting construction of the furan ring system by opening an epoxide, which in turn would provide the functionality with which to strategically place a double bond for the key nitrone cycloaddition. Clearly, the main issue regarding this approach is that the epoxide must be of the correct stereochemistry with respect to the amide group.

Fuchs[32] and Moskowitz[64] have published approaches which have employed or attempted to employ such a methodology for constructing the furan junction of morphine.

a) FUCHS' INTERMOLECULAR APPROACH[32]

Fuchs' synthetic plan involved the acid, or base catalysed opening of epoxide (103), at the activated allylic position by a substituted phenol (104), to produce the *trans*-(aryloxy)hydroxy ether (105). Scheme 3.1.



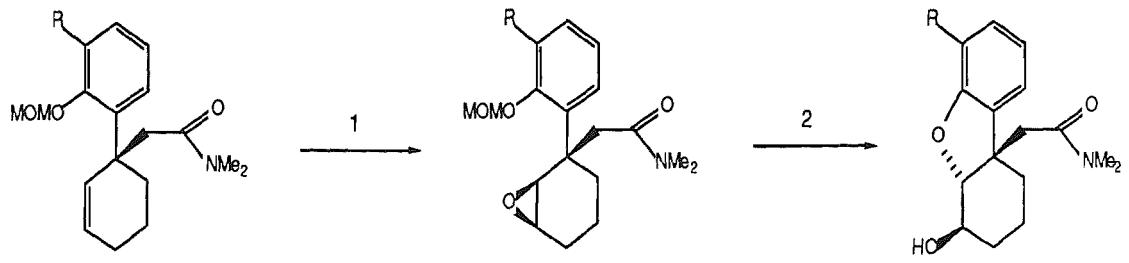
(103) (105)

Scheme 3.1

However, all attempts to effect this transformation were totally unsuccessful.

b) MOSKOWITZ 'S INTRAMOLECULAR APPROACH [64]

Moskowitz published a highly selective epoxidation of 1-aryl-2-cyclohexene (106). The cyclohexene (106) was synthesised by an Eschenmoser-Claisen rearrangement reaction[57]. By heating epoxide (107) under reflux in dichloromethane Moskowitz obtained the tricyclic system (108) in 70% yield. Scheme 3.2.



(106) (107) (108)

Reagents R = F, Cl

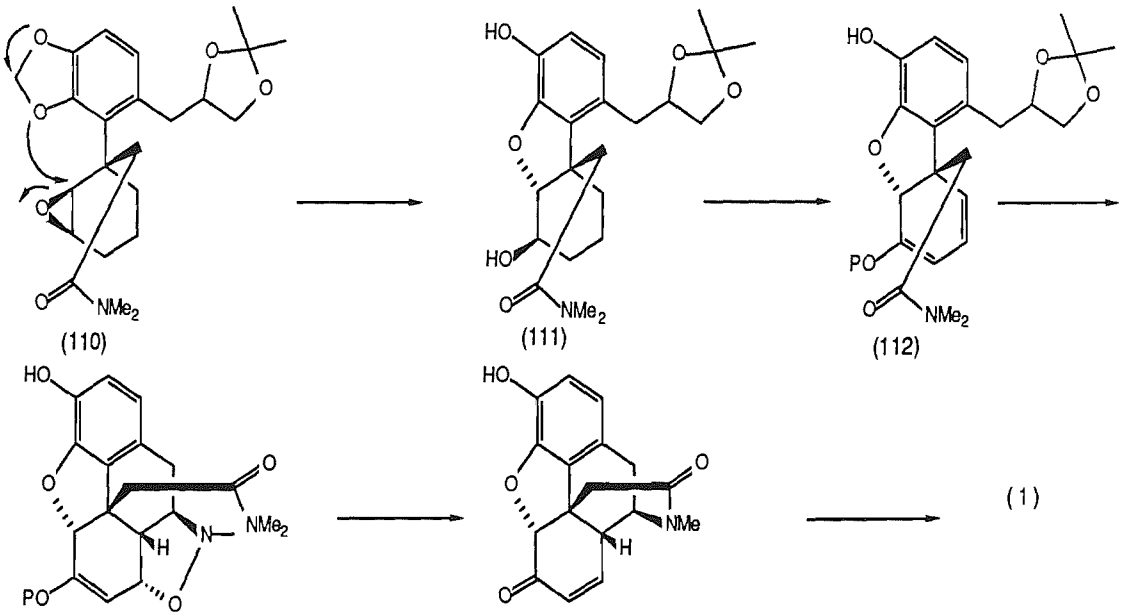
1. Cl_3CCN, H_2O_2, CH_2Cl_2, K_2CO_3 2. Δ

Scheme 3.2

3.2 AIM OF PROJECT.

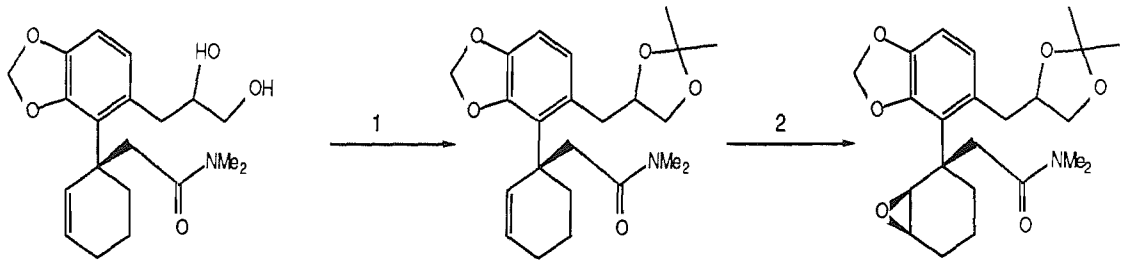
To overcome the difficulty of ether formation an extension of

Moskowitz's methodology was adopted. The obvious difference in our system is in the extra functionality in the precursor (110). An acetal is strategically placed in the aromatic portion of the cyclohexene (110) to allow the formation of a nitrone at a later stage. The alcohol functionality resulting from the newly formed tricyclic system would then be manipulated correctly to establish a dipolarphilic double bond in the molecule in the correct position. Scheme 3.3.



Scheme 3.3

The first task was to construct the epoxide (110) which was achieved in two steps as shown in scheme 3.4.



(75) (109) (110)

Reagents

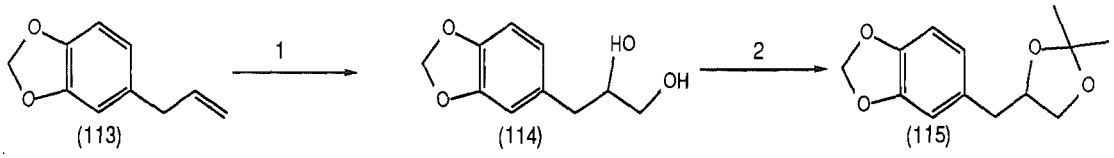
1. 2,2-dimethoxypropane, pyTs, CH_2Cl_2 2. pNPBA, CH_2Cl_2

Scheme 3.4

Acetal (109) was obtained in >76% yield by stirring diol (75) with 2,2-dimethoxypropane and a catalytic amount of pyridinium tosylate in dichloromethane. Acetal (109) was then treated with *para*nitroperbenzoic acid to give epoxide (110) in 58% yield. The attempts to achieve the intramolecular epoxide opening were unsuccessful. These included heating the pure epoxide in dichloromethane or acetonitrile under reflux, or by generating the epoxide *in situ* and heating in dichloromethane. In all cases none of the desired tricyclic product (111) was obtained.

a). Attempts to cleave the methylenedioxy protecting group.

Although we were unable to open the epoxide (110) in a manner which paralleled Moskowitz's work it was nevertheless decided to pursue this approach but with a different strategy. By conducting experiments on a suitably chosen model it was hoped to selectively deprotect the catechol moiety in the presence of the acetal group in (110). The model chosen was acetal (115), made in two steps from safrole (113) as shown in scheme 3.5.



Reagents

1.OsO_4, trimethylamine-N-oxide 2. pyTs,CH_2Cl_2,2,2-dimethoxypropane

Scheme 3.5

Safrole (113) was converted into the diol (114) using osmium tetroxide catalysed hydroxylation. Protection of diol (114) with 2,2-dimethoxypropane proceeded in 97% yield.

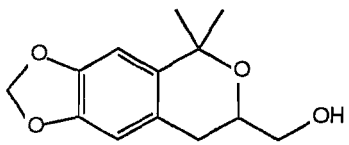
Aluminium triiodide[65] was selected from the list of reagents commonly utilised for ether cleavage[66]. This is prepared by heating equimolar amounts of aluminium foil and iodine in acetonitrile. Substrate (115) was added to the aluminium triiodide in acetonitrile and heated under reflux for thirty minutes. This resulted in the loss of the starting material. The major product was assigned as diol (114) whilst nmr spectral analysis of the crude reaction mixture showed the protected catechol intact. A number of other experiments were tried in order to facilitate ring cleavage and the results of these studies are shown in table 3.1.

table 3.1

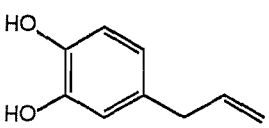
Entry	Substrate	Reaction conditions	Result
1.	(115)	$MgBr_2$, THF	product(116)
2.	(115)	$Cu(OTf)_2$,MeCN 5 minutes	diol (114)

3.	(115)	DDQ	no reaction
4.	(115)	PCC	no reaction
5.	(115)	$(Ph_3)C^+BF_3^-$	complex mixture*
6.	(114)	$Cu(OTf)_2$, RT MeCN	no reaction
7.	(114)	$Cu(OTf)_2$, 80°C MeCN	no reaction.
8.	(114)	$MgBr_2$	no reaction
9.	(114)	$MgBr_2$/NaI	no reaction
10.	(113)	BBr_3/RT CH_2Cl_2	product (117)
11.	(113)	(AlI_3) 80°C MeCN	products (117) and (118) (2:1)
12.	(114)	$AlBr_3$, EtSH	complex mixture*
13.	(114)	AlI_3, RT, MeCN	no reaction
14.	(114)	AlI_3, 80°C MeCN	one new spot*
15.	(114)	BBr_3, CH_2Cl_2	complex mixture*
16.	(113)	1. PCl_5. 2. H_2O	complex mixture*

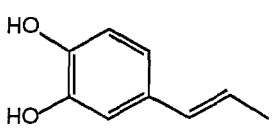
* These reactions were washed with 20% NaOH to extract any catechol.



(116)



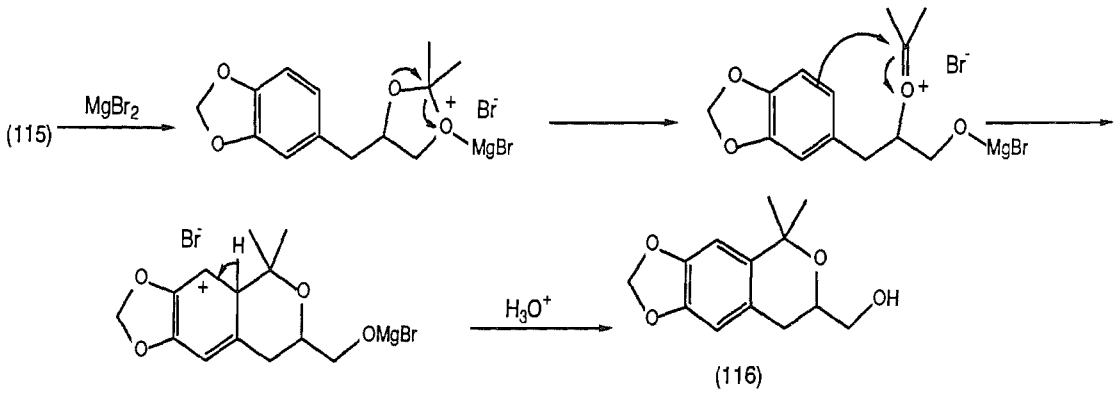
(117)



(118)

Conclusion from reaction table.

Although we were unable to find a reagent that would selectively cleave the methylenedioxy protecting group in the presence of the acetal, boron tribromide[67] and aluminium triiodide[65] cleaved the methylene dioxy protecting group quite effectively. It is nevertheless interesting to consider entries 1 and 2. Ultrasonication of acetal (115) with $MgBr_2$ (20 equivalents) caused cyclisation of the acetal moiety on to the aromatic ring. Ultrasonicating acetal (115) for 12 minutes with $MgBr_2$ (20 equivalents) caused approximately 50% conversion. Further stirring at room temperature without ultrasonication saw the reaction go to completion after 10 hours. The proposed mechanism for the cyclisation of (115) to (116) is shown in scheme 3.6.

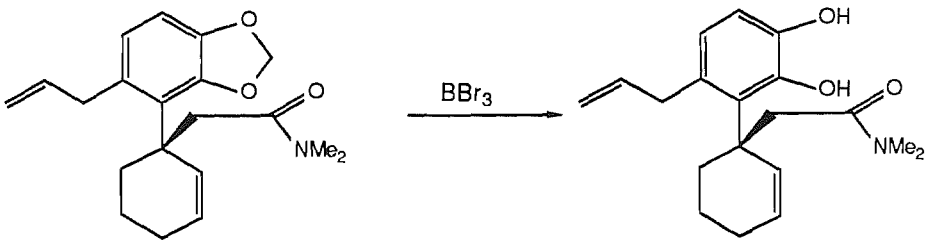


Scheme 3.6

When acetal (115) was stirred with 1 equivalent of copper (II) triflate[68] in acetonitrile, deprotection of the acetal occurred within five minutes. The mechanistic explanation for this transformation remains an enigma.

As boron tribromide emerged as the only real candidate for our purposes, a suitable candidate in our series of morphine substrates had to be chosen. Amide (74) was chosen as this

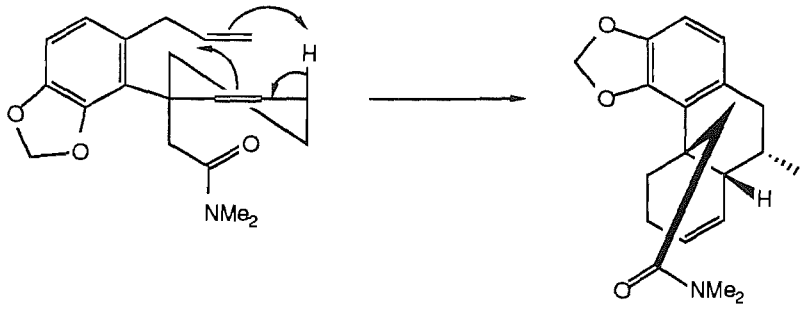
seemed to pattern safrole (113). Scheme 3.7.



(74) (119)

Scheme 3.7

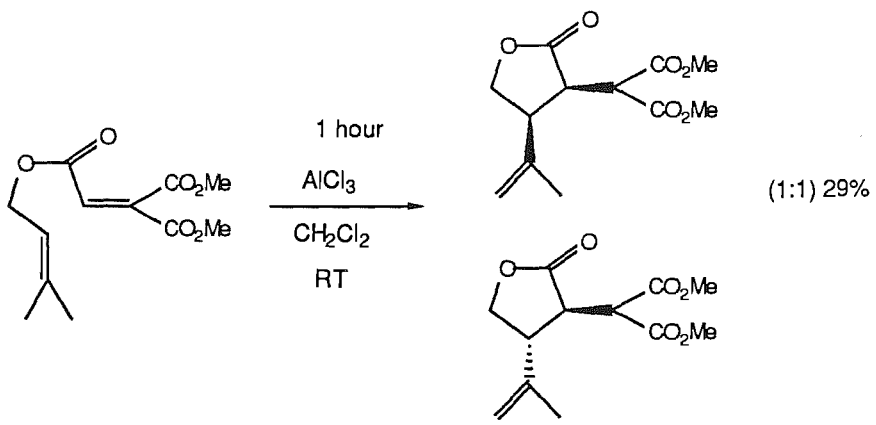
Treating amide (74) at -78°C with1 equivalent of BBr_3, gave only recovered starting material. When amide (74) was treated with 2 equivalents of BBr_3 at room temperature starting material was also obtained. In the light of these results, the amide (74) was heated in acetonitrile with three equivalents of freshly prepared aluminium triiodide under reflux. Even though from the results shown in table 3.1 this was an inferior reagent to BBr_3 the reaction was still attempted. After 5 hours at reflux, TLC analysis showed some starting material and a new product. It was felt prudent at this point to halt the reaction and extract this new compound. A white crystalline compound was obtained in 37% yield (uncorrected for starting material) which was assigned the structure (120) on the strength of ir, nmr (proton, carbon, COSY and decoupling experiments) and mass spectroscopy analysis. Compound (120) was formed via an intramolecular Alder-ene reaction[69] as shown in scheme 3.8.



(120)

Scheme 3.8

This is quite plausible in view of the fact that aluminium trichloride has been shown to catalyse ene reactions on highly activated olefins[70]. Scheme 3.9.

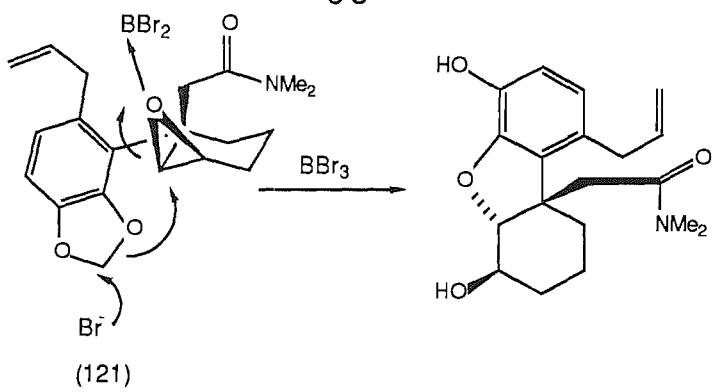


(1:1) 29%

Scheme 3.9

This example seems to be the first of its kind which illustrates the aluminium trihalide catalysed ene reaction of a non activated olefin.

It became clear from the experiments that the methylenedioxy group is very resistant to cleavage. One final approach was to selectively epoxidise the endocyclic double bond and then to add a Lewis acid in order to facilitate opening of the epoxide by the neighbouring methylenedioxy oxygen. Scheme 3.10.



(121)

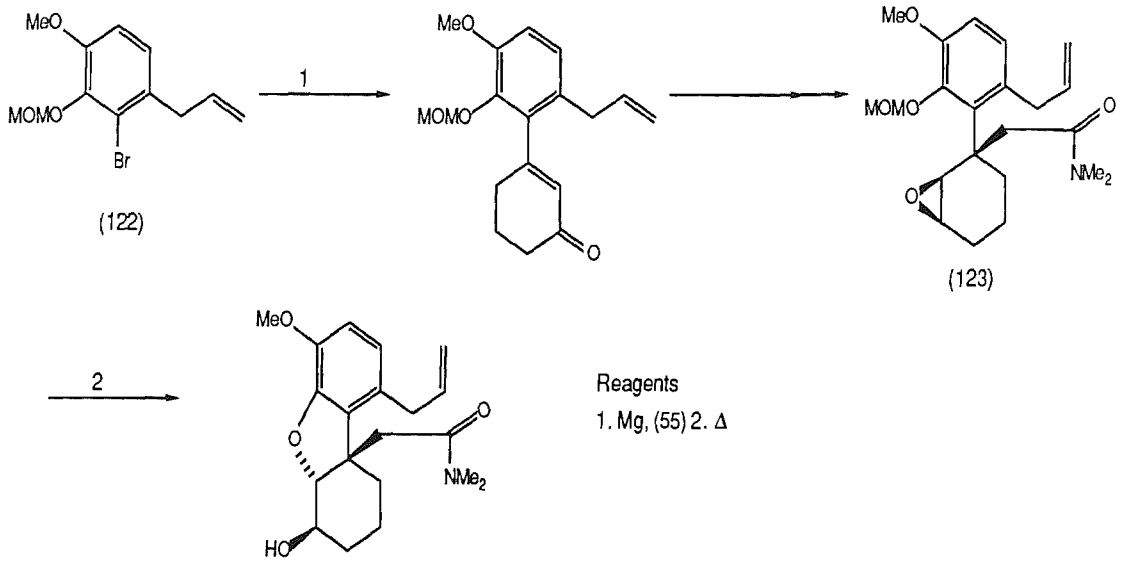
Scheme 3.10

Selective epoxidation with *p*-nitroperbenzoic acid of the endocyclic double bond gave compound (121) in 78% yield. When (121) was treated with four equivalents of BBr_3 at 0^oC three new spots on TLC were observed.

Nmr spectral analysis of the crude reaction mixture showed a broadened triplet at δ 4.62 which is characteristic of a furan ring. Chromatography of the crude reaction mixture led to extensive decomposition and no products could be isolated. It was at this point in time that our energies were already being channelled into a parallel study.

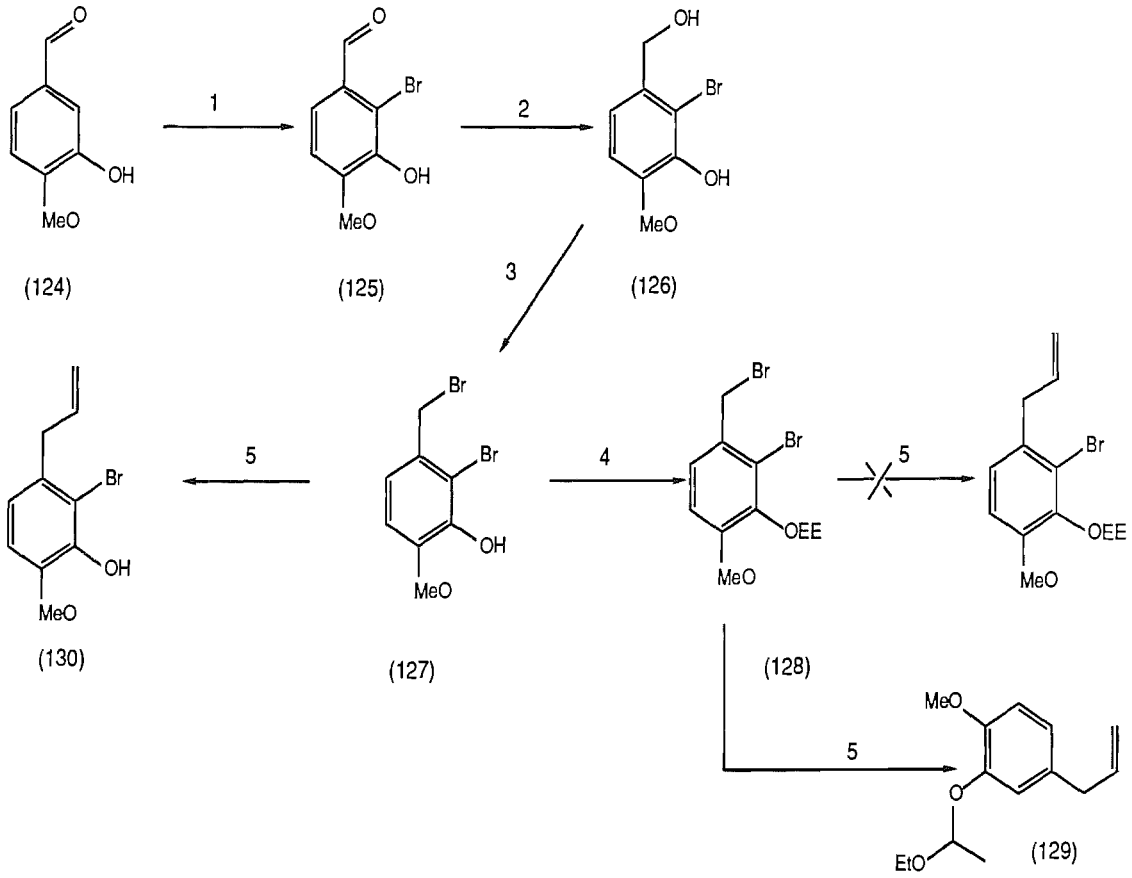
b). The isovanillin route.

Aromatic bromide (122) was chosen as the substrate to undergo Grignard addition to enone (55). This could then be converted to the amide (123) by reduction followed by an Echenmoser-Claisen rearrangement reaction[57]. Hopefully this would enable us to pattern Moskowitz' work more effectively. Scheme 3.11.



Scheme 3.11

The starting material for the new approach was isovanillin (124) which was brominated to give (125)[71] and reduced to the benzyl alcohol (126)[72]. Bromination of the alcohol (126) in the usual manner with PBr_3 in dichloromethane gave the bromide (127) in 88% yield. The phenol (127) was protected as its ethoxyethyl ether (128) and then treated with 1 equivalent of vinylmagnesium bromide (in the presence of catalytic quantities of CuI and 2,2-dipyridyl). This gave a new spot on TLC slightly more polar than the starting material. This observation was uncharacteristic with our experience with this type of reaction and a second equivalent of the Grignard reagent was added. This produced a new spot on TLC which was less polar than the starting material. Nmr spectral analysis of the isolated product confirmed this compound to be acetal (129) as shown in Scheme 3.12 (page 67). Attempted formation of the TBDMS ether of phenol (127) also failed. Bromide (127) was treated with three equivalents of vinylmagnesium bromide under the usual conditions giving the aromatic bromide (130) in 49% yield. Scheme 3.12.



Reagents

1.Br_2, AcOH, NaOAc, Fe 2. $NaBH_4$, NaOH, H_2O, 3. PBr_3, CH_2Cl_2 4. Ethyl vinyl ether , TFA
5. Vinylmagnesium bromide, CuI, 2,2-dipyridyl THF.

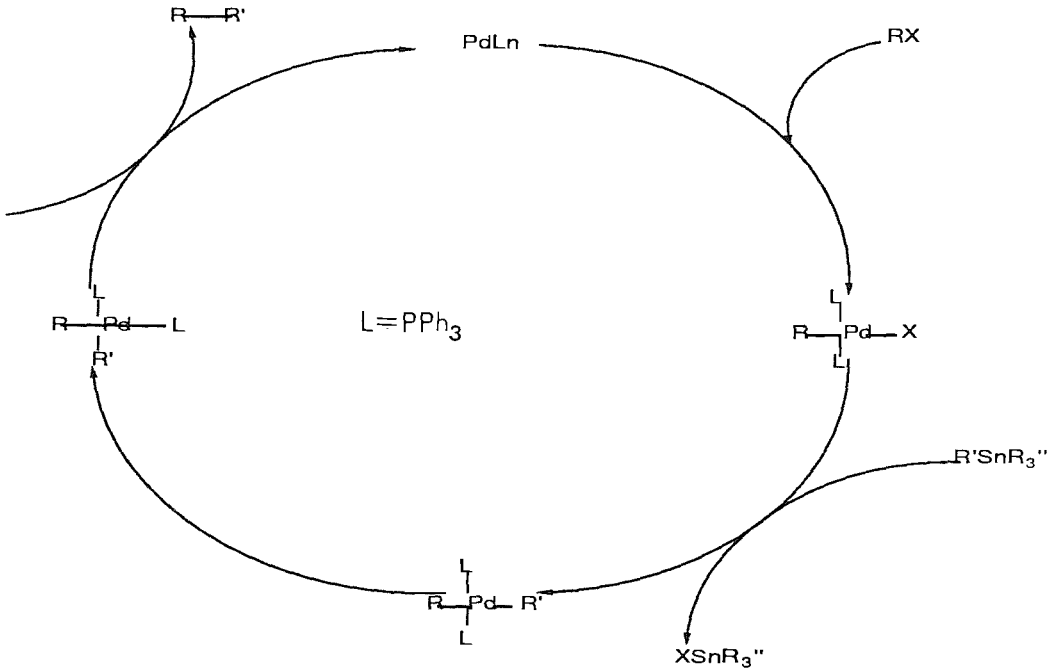
Scheme 3.12

c). The intermolecular palladium approach.

Since the phenol (130) was produced in a modest yield, an alternative strategy was considered to make it. J.K.Stille has published an excellent review on the palladium catalysed cross coupling reactions of organo-tin reagents with organic electrophiles[73]. This mild versatile reaction is tolerant to a wide variety of functional groups on either coupling partner so that the tedious protection and deprotection steps are avoided.

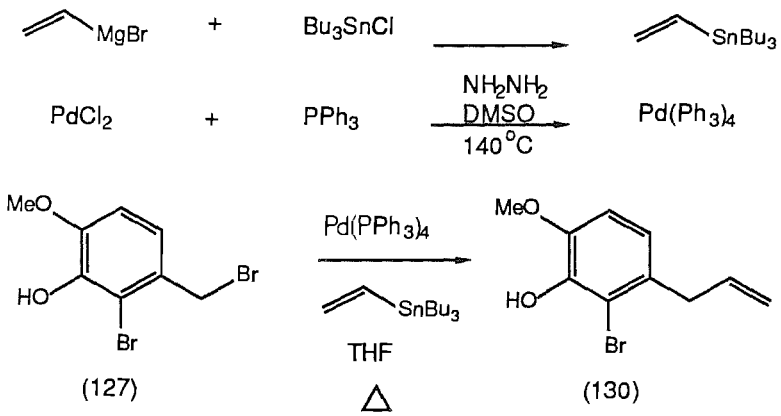
$$RX + R'SnR^{II}_3 \xrightarrow{(PdL_4)} R{-}R' + XSnR^{II}_3$$

The catalytic cycle in scheme 3.13 serves as a working model for the directed coupling reaction.



Scheme 3.13

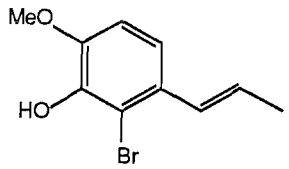
Although this cycle has yet to be established for the coupling, many of the individual steps have been documented[74]. It was decided to take advantage of this novel reaction to make phenol (130). Scheme (3.14).



Scheme 3.14

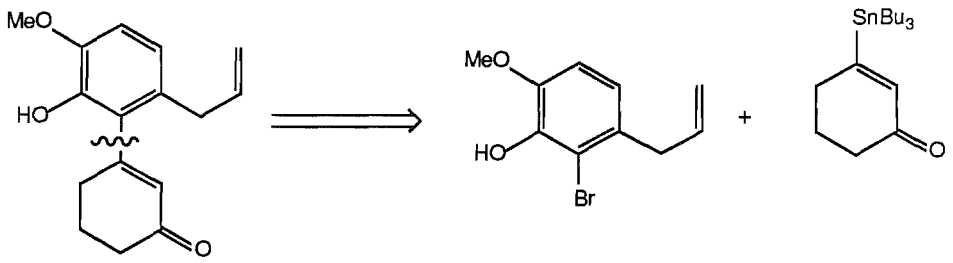
Vinyltributyltin was made according to the method of Seyferth[75]

and $Pd(Ph_3)_4$ was prepared as described by Coulson[76]. The reaction was initially successful and the aromatic phenol (130) was produced in 65% yield when equimolar amounts of the bromide (127) and vinyltributyltin were heated in boiling THF with the palladium catalyst (10 mol%). However, on scale up, the reaction became quite capricious giving some of the corresponding styrene (131) which was almost inseparable from the desired alkene (130).



(131)

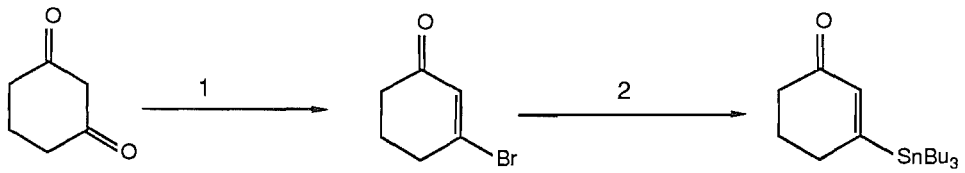
Influenced by the initial success in this area it was decided to take further advantage of this methodology to assemble the carbon skeleton of the enone (132). The retrosynthetic analysis for enone (132) produced two fragments, (130) and (133). Scheme 3.15.



(132) (130) (133)

Scheme 3.15

The tin enone (133) was prepared in 65% yield by a modification of Piers method[77]. Scheme 3.16.



(134) (133)

Reagents

1. PBr_3 2. $[Bu_3SnCuSPh]Li$, -78°C → 0°C, THF

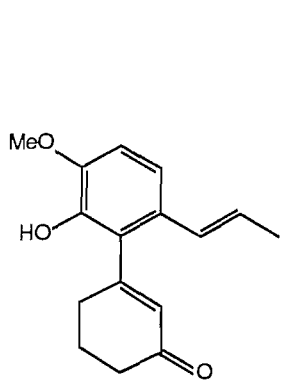
Scheme 3.16

The bromoenone (134) was made by the method of Crossley[78] and the cuprate reagent was made by mixing Bu_3SnLi and PhSCu[79]. Tributyltin lithium was initially made by treating tributyltin chloride with lithium metal but it was found to be more expedient to treat hexabutylditin with 1 equivalent of n-butyllithium[77]. As previously demonstrated, the tin enone (133) was mixed with the aromatic bromide and heated under reflux in THF. Table 3.2 summarises the conditions and substrates tried in order to effect the desired coupling.

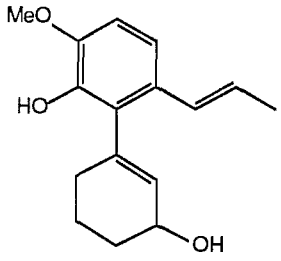
Table 3.2

Entry	Substrate	Solvent	Time	Result
1.	(133)	THF	24 hours	no reaction
2.	(133)	Toluene	6 days	complex mixture with (135) as major product*
3.	vinyltributyl--tin	Toluene	24 hours	mixture of (136) and (137)
4.	(138)	toluene	5 days	complex mixture with (139) as major product*

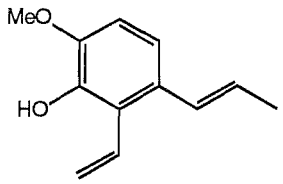
* very low yield



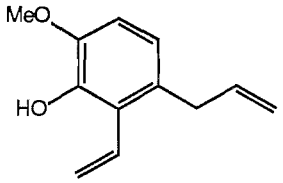
(135)



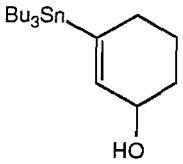
(139)



(136)

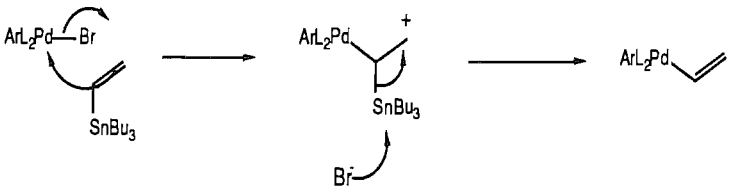


(137)

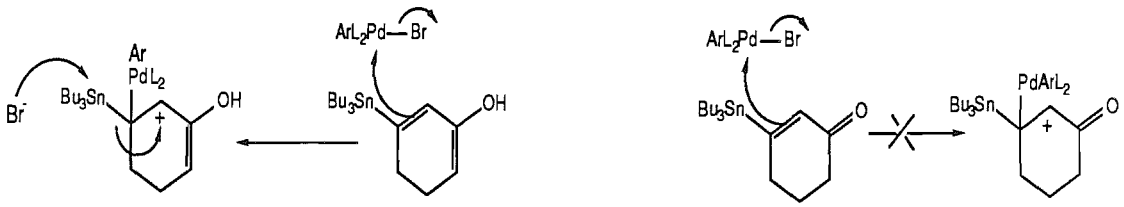


(138)

As entry 3 exhibits a reaction which is fairly fast in relative terms with respect to the other entries. It was felt that the slow reaction exhibited by enone (133) was caused by electronic factors. Scheme (3.17).



Where as

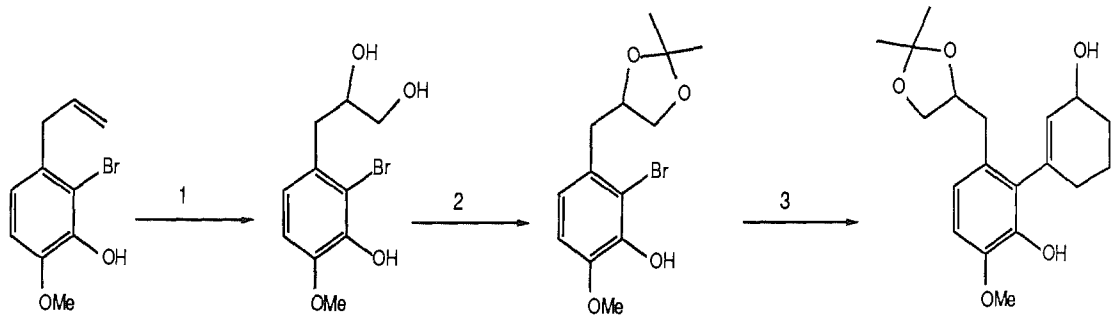


(140)

Scheme 3.17

The tin enone (133) could be coupling through its enol form (140) as it is unlikely that a carbocation will reside next to the carbonyl group; this explains its slow reactivity. With this hypothesis in mind the enone was reduced to the allylic alcohol (138) in 90% yield using sodium borohydride. However entry 4 in the table suggests other factors are slowing down the reaction. The first

conclusion drawn was that the allylic double bond ought to be protected in order to circumvent the formation of the styrene (131). Scheme 3.18.



(130) (141) (142) (143)

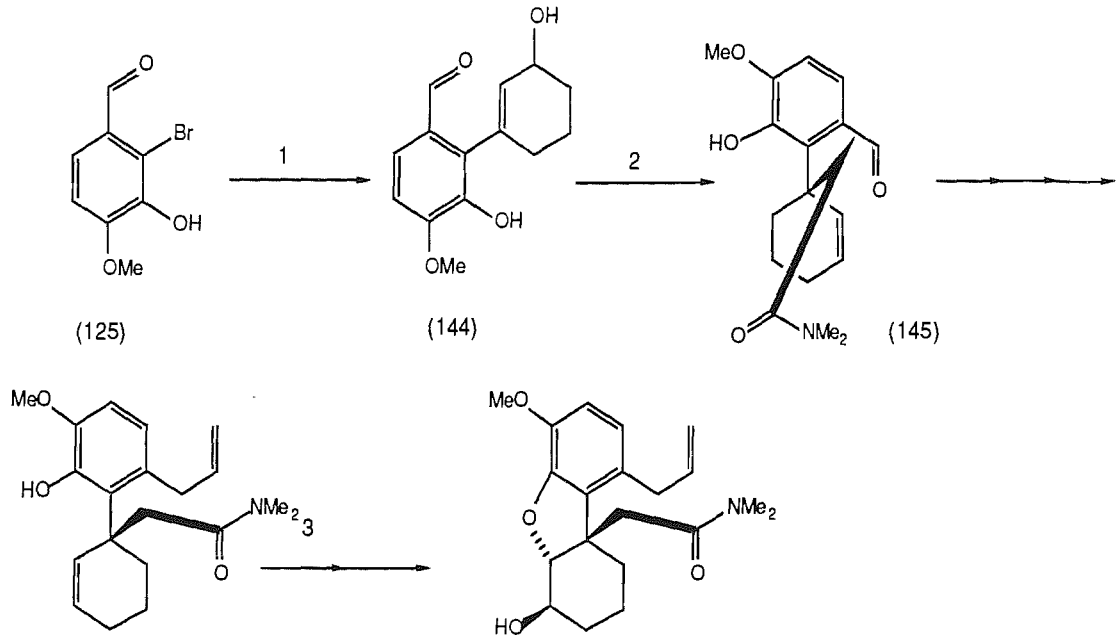
Reagents

1. OsO_4, trimethylamine-N-oxide, THF,t-BuOH 2. 2,2-dimethoxypropane pyTs
3. $Pd(Ph_3)_4$, toluene, (138) Δ.

Scheme 3.18

The diol (141) was routinely formed from aromatic bromide (130) using catalytic osmium tetroxide hydroxylation and was never isolated but used crude to form acetal (142) in 87% yield (2 steps). Attempted coupling of the acetal (142) with (138) under normal experimental conditions afforded a complex mixture of products.

Scott has stated that oxidative addition into carbon bromine bonds is akin in many ways to nucleophilic substition reactions[80]. Functional groups which reduce the π–electron density of the arene act to facilitate oxidative addition. Since bromoisovanillin (125) possesses an electron withdrawing group in the form of an aldehyde, it was hoped this would facilitate the coupling reaction being pursued. The new route in the synthesis is outlined in scheme 3.19.

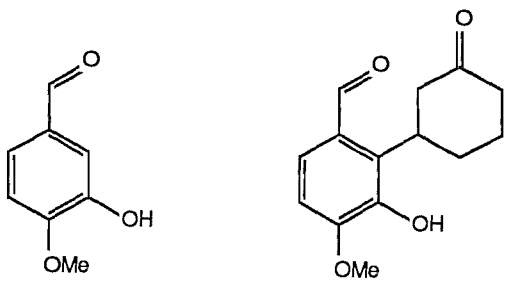


(125) (144) (145)

Reagents
1.Pd(Ph $_3$)$_4$, toluene, (138) 2. N,N-Dimethylacetamide dimethylacetal, toluene, heat

Scheme 3.19

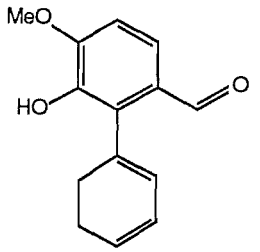
Heating bromoisovanillin (125) with allylic alcohol (138) in toluene and $Pd(Ph_3)_4$ gave four products. The desired product (144) was formed in 20% yield along with isovanillin (124) and a product which was tentatively assigned to ketone (146).



(124) (146)

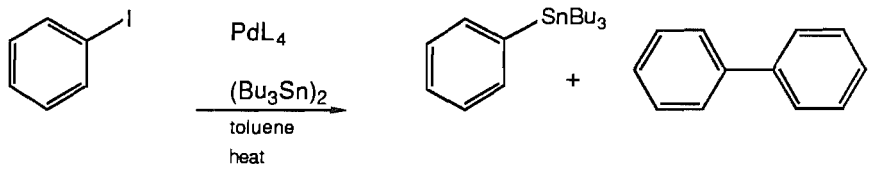
The excitement caused by the attainment of this long pursued goal was diminished by the result of the Eschenmoser-Claisen rearrangement reaction[57]. Heating allylic alcohol (144) with

N,N-dimethylacetamide dimethylacetal gave one product which was instantly recognised as diene (147).



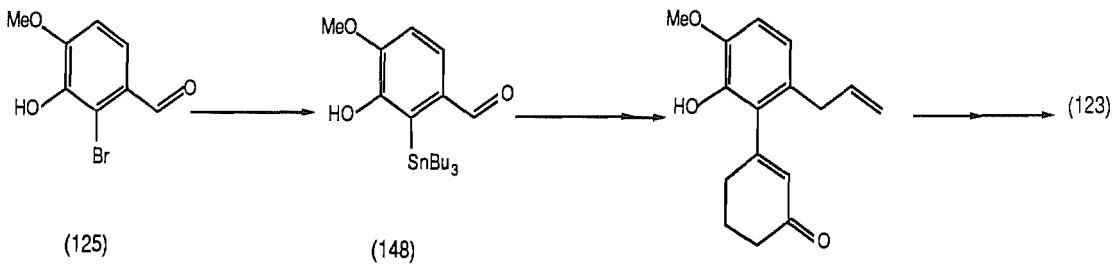
(147)

Eaborn *et al* [81] have reported the mild, palladium-catalysed coupling of hexaalkyldistannanes with aryl, benzyl or alkylhalides to provide a unique method of synthesis of trialkyltin reagents. Scheme 3.20.



Scheme 3.20

The scheme to make aromatic amide (145) was revised to accommodate such a literature precedent. Scheme 3.21.

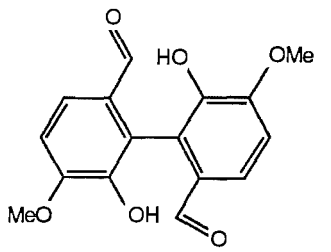


(125) (148)

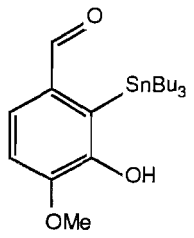
Scheme 3.21

Bromoisovanillin (125) was heated at reflux for 6 hours with hexabutylditin (1 equivalent) and $Pd(Ph_3)_4$ (10 mol%). As expected this gave two products which were initially assigned the

structures (149) and (148).

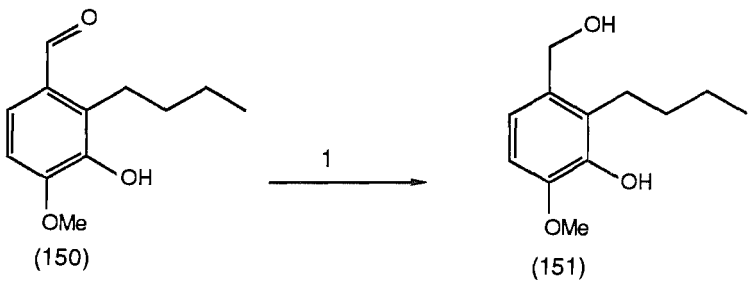


(149)



(148)

However, full spectroscopic examination revealed that (149) was not the dimer but isovanillin (124). As regards the trialkyl aromatic tin compound (148), the nmr spectrum gave rise to serious doubts about its authenticity. Reduction of the aldehyde (148) with sodium borohydride effectively removed all the tin bromide residues confirming structure (148) to be (150). Scheme 3.22.



(150) (151)

Reagents
1. $NaBH_4$, THF, H_2O

Scheme 3.22

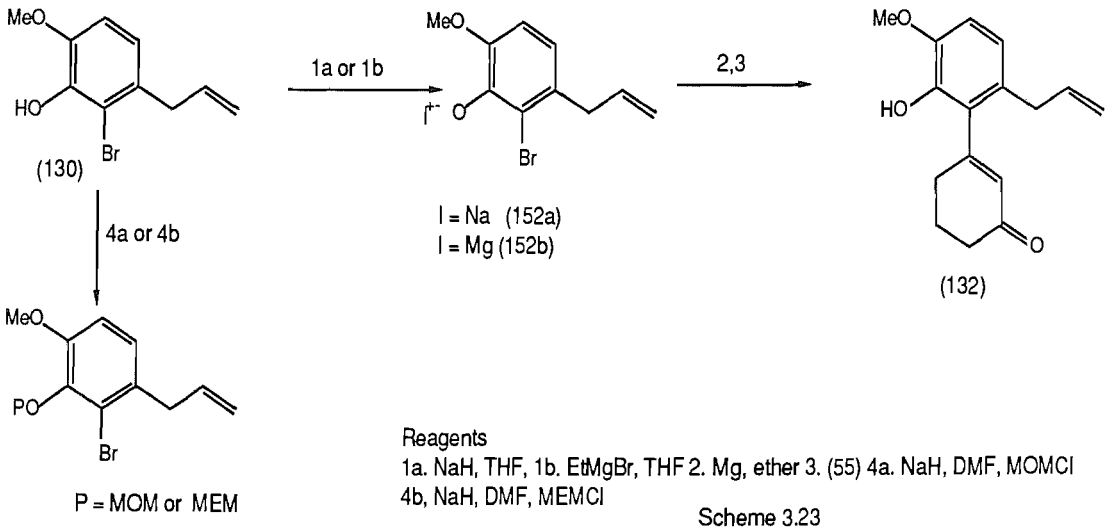
The butyl group was transferred in preference to the tributyltin moiety.

Concluding remarks.

The excursion into palladium chemistry revealed some interesting results, however, taken in the context of what was intended to be achieved, this route was dismissed since no deep inroads were made into the morphine skeleton.

d). Grignards revisited.

Initial attempts to assemble the carbon skeleton of aromatic enone (132) via a Grignard route centred around the possibility of forming an aromatic dianion (152) which would hopefully undergo nucleophilic addition to enone (55). Scheme 3.23.



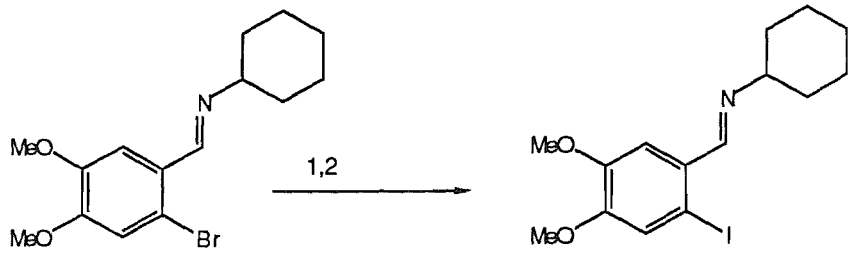
Reagents
1a. NaH, THF, 1b. EtMgBr, THF 2. Mg, ether 3. (55) 4a. NaH, DMF, MOMCl 4b, NaH, DMF, MEMCl

Scheme 3.23

The sodium salt of phenol (130) was prepared by adding a THF solution of (130) to NaH. By means of a solid side arm, magnesium metal was dropped into the reaction vessel and the mixture was heated in an ultrasonicator. The required Grignard reagent was not formed and therefore the counter ion was changed to magnesium. This was achieved by treating phenol (130) with 1.1 equivalents of ethylmagnesium bromide. Once again this brought very little success and no Grignard reagent was formed even with classical initiators such as iodine, mercuric chloride and ethyl bromide. With this disappointing result it was decided to protect the phenol (130) with a group which could easily be removed later on in the synthesis. MEM and MOM were the two groups chosen, which could be attached to the phenol (130) using NaH/toluene or Et_3N/CH_2Cl_2,

however, the best yields were achieved with NaH in DMF. Scheme 3.23 (page 76). In short, none of the required Grignard reagent could be formed. The only interesting result to emerge from these studies is that $MgBr_2$ cleaved the MOM protecting group in yields greater than 90% to give phenol (130). These reaction conditions were not employed with the MEM protecting group but Kim[82] has documented that $MgBr_2$ cleaves THP ethers in the presence of MOM groups and he also stipulates that MOM groups are resistant to such conditions. In spite of the lack of success in this area we nevertheless pursued the Grignard approach. Our experience in this area has shown that aromatic iodides form Grignard reagents with great facility.

Ziegler et al[83] converted aromatic bromide (153) to aromatic iodide (154) by treating the bromide with one equivalent of n-butylithium at -78°C and quenching the resulting anion with iodine. Scheme 3.24.

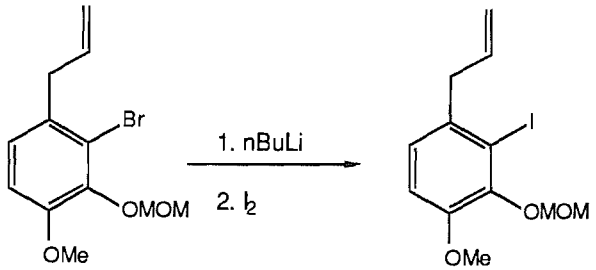


(153) (154)

Reagents
1. nBuLi, THF, -78°C 2. I_2

Scheme 3.24

It was intended to conduct an analogous reaction with the aromatic bromide (155). Scheme 3.25.



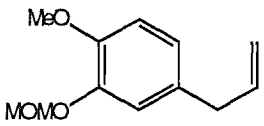
(155) (156)

Scheme 3.25

No reaction was observed under Zieglers conditions. Variation of the temperature of the reaction revealed that the substrate (155) did not transmetalate until -60°C (glc analysis). Table 3.3 summarises the attempts to furnish (156).

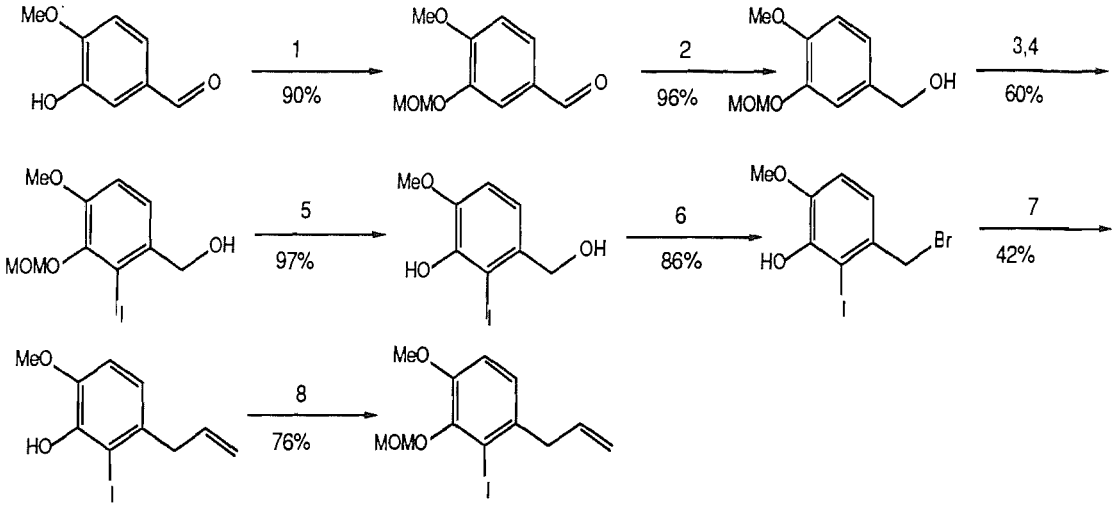
Table 3.3

Entry	Reaction conditions	Electrophile	Result
1.	1 eq nBuLi, THF, -78°C	I_2	SM
2.	2 eq nBuLi, THF, 0°C	I_2	(157)
3.	2 eq nBuLi, THF, -60°C	I_2	(157)
4.	2 eq nBuLi, THF, 0°C	MeI	(157)
5.	2 eq nBuLi, THF, 0°C, TMEDA	MeI	(157)



(157)

Due to the lack of success with this approach a new scheme was devised to make the required aromatic iodide (156). Scheme 3.26.



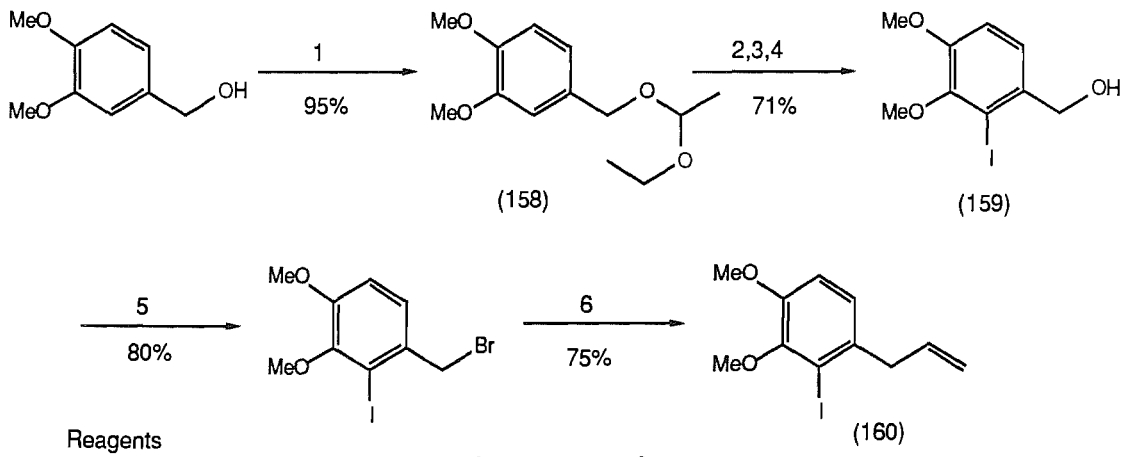
(156)

Reagents

1. NaOH, $Bu_4N^+HSO_4^-$, MOMCl , CH_2Cl_2 2. $NaBH_4$, THF, H_2O 3. n-BuLi, THF, 0°C 4. I_2, THF, -60°C
5.TsOH, MeOH 6. PBr_3 , CH_2Cl_2 7. vinylmagnesium bromide CuI, 2,2-dipyridyl, THF
8. NaH, DMF, MOMCl 0°C.

Scheme 3.26

All attempts to form a Grignard reagent from aromatic iodide (156) were once again unsuccessful. Assuming that the Grignard reagent did not form on steric grounds, the dimethoxy analogue (160) was constructed. Grignard formation from this substrate was a facile process. The dimethoxy analogue (160) was routinely made according to scheme 3.27.



(158) (159) (160)

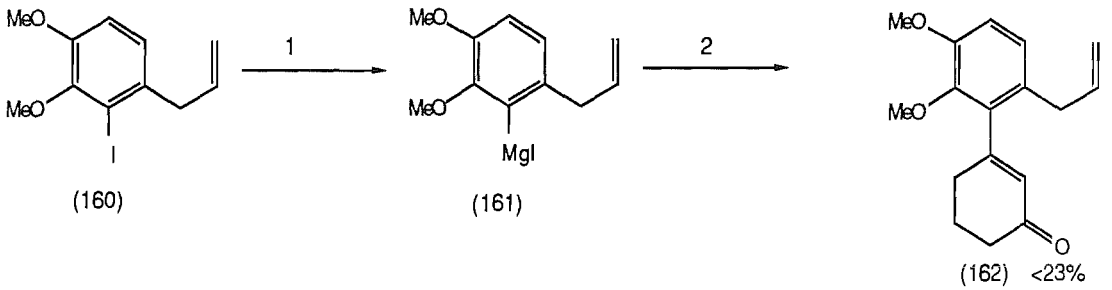
Reagents

1. ethyl vinyl ether, TFA 2. n-BuLi, THF, 0 °C 3. I_2, THF, -60°C, 4. MeOH , H_2SO_4
5. PBr_3, CH_2Cl_2 6. vinylmagnesium bromide, CuI, 2,2-dipyridyl, THF.

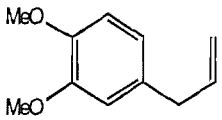
Scheme 3.27

Although formation of the Grignard reagent (161) occurred

readily when the iodide (160) was heated in an ultrasonicator, the addition to the electrophile (55) was low yielding (23% maximum); eugenol methyl ether (163) was formed in yields greater than 60%. Scheme 3.28.



(160) (161) (162) <23%



(163) > 60%

Reagents
1. Mg, ether / cyclohexane 2. (55), cyclohexane

Scheme 3.28

A number of experiments were conducted to try and increase the yield of the coupling step and they are summarised in table 3.4.

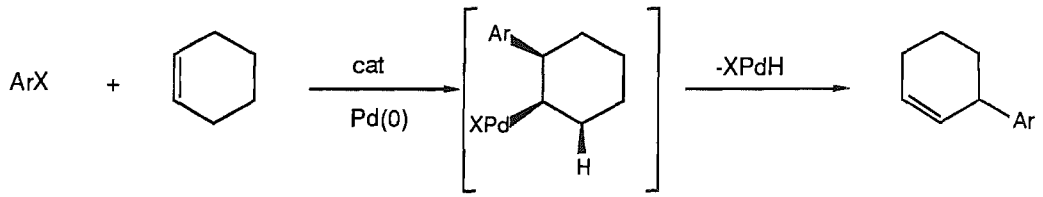
Table 3.4

Solvent system Grignard formed in:	1. Additional solvent or reagents. 2. electrophile.	Temp.	Result.
ether	1. cyclohexane 2. (55)	reflux	<23% (162) >61% (163)
DME	1. cyclohexane 2. (55)	reflux	complex mixture
DME	1. THF	reflux	>80% (163)

	2. (55)		No (162)
ether/ THF	1. CuI added at 0°C	-78°C	>80% (163)
	2. (134)		No (162)
ether/THF	PhSCu added at 0°C	-78°C	> 80% (163)
	2. (134)		No (162)

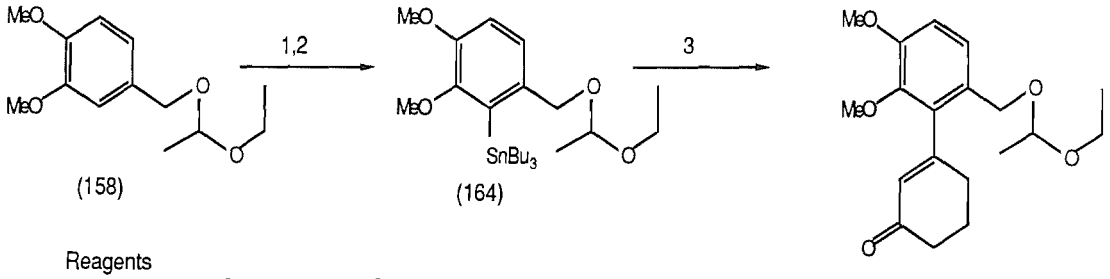
In all cases the Grignard reagent (161) formed quite readily. However, as Matthews had worked hard to establish the best conditions for this reaction, the Grignard approach was shelved in favour of an intermolecular Heck reaction[84].

Aryl halides are known to undergo palladium catalysed cross coupling with cyclic alkenes[84].



Scheme 3.28

A brief survey of the literature revealed no cross coupling reactions between 2-cyclohexene-1-one and aromatic halides. However, aromatic iodide (160), potassium carbonate (2 equivalents), 2-cyclohexene-1-one and palladium acetate (10 mol%) were all heated in DMF at 120°C. These conditions resulted in the formation of a complex mixture. Two other approaches were attempted to obtain the would be A and C rings of morphine in good yield. The first involved another palladium *tetrakis*triphenylphosphine catalysed coupling reaction. Scheme 3.29.

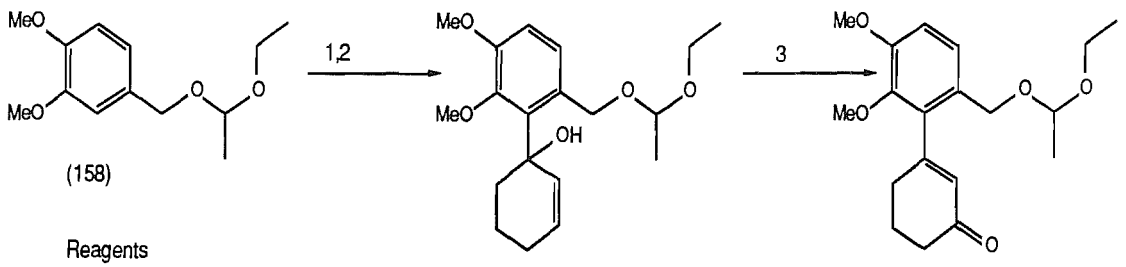


Reagents
1. nBuLi, ether, 0 °C 2. Bu_3SnCl, 0 °C 3. $Pd(Ph_3)_4$ toluene (134)

Scheme 3.29

The organostannane (164) was made quite easily and in good yield by treating acetal (158) with n-butyllithium folowed by quenching the resulting anion with tributyltin chloride. Heating (164) at reflux in toluene with bromoenone (134) and $Pd(Ph_3)_4$ (10 mol%) resulted in a complex mixture of products. Nmr spectral analysis of the crude reaction mixture showed no olefinic protons in the desired region of 5.8 to 6.2.

Another approach attempted was to quench the anion of acetal (158) with 2-cyclohexene-1-one and then perform a 1,3-sigmatropic shift with concominant oxidation with PCC. Scheme 3.30.

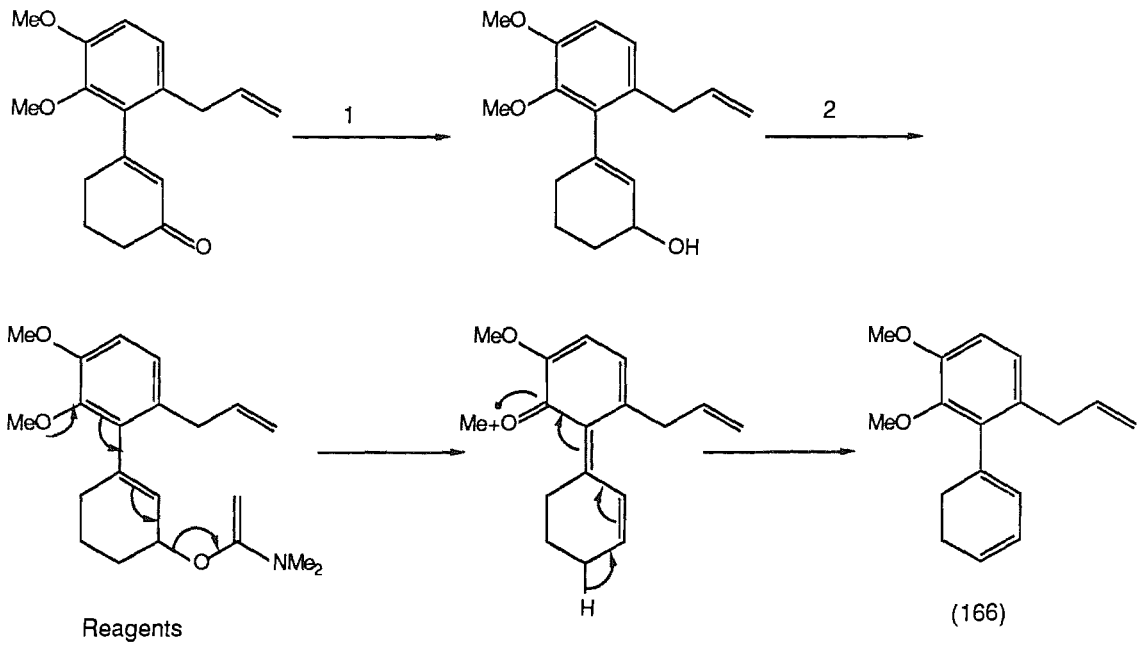


Reagents
1. n-BuLi, ether 2. 2-cyclohexene-1-one 3. PCC

Scheme 3.30

However, treating acetal (158) with n-butyllithium followed by 2-cyclohexene-1-one gave only starting material. It was felt prudent to work with the yields obtained with the Grignard approach to carry out epoxide opening. Enone (162) was reduced

with sodium borohydride in the presence of cerium (III) chloride to give allylic alcohol (165). Eschenmoser-Claisen rearrangement[57] under routine conditions furnished one product in good yield which was the unwanted diene (166). None of the required amide was detected at all (TLC and nmr spectral analysis of the crude reaction mixture). The reason why the original route furnishes amide (74) whilst the dimethoxy analogue (165) does not, has been attributed to the influence of the lone pairs of electrons on the methoxy group promoting elimination of the Eschenmoser-Claisen intermediate. Scheme 3.31.



Reagents

1. $NaBH_4$, $CeCl_3$ 2. N,N-Dimethylacetamide dimethylacetal, toluene, Δ

Scheme 3.31

e). Concluding remarks.

It has been demonstrated that the dimethoxy and isovanillin series of analogues have no contribution to make in our projected synthesis of morphine. The isovanillin series did not form a Grignard reagent and in the light of the fact that the dimethoxy

analogue failed at the Eschenmoser-Claisen step, it probably would not form the amide. The methylenedioxy series shows the most promise, however, this protecting group is highly resistant to cleavage.

CHAPTER FOUR

4.1 INTRODUCTION

The use of radical reactions as a general methodology for the synthetic organic chemist has increased dramatically over the last ten years. Its origins by no means begin there; Gomberg[85] investigated the formation and reaction of triphenylmethyl radical in 1900 whilst Paneth showed that less stabilised alkyl radicals also exist[86]. Organic synthesis with radicals began in 1937 when Hey and Waters described the phenylation of aromatic compounds by benzoyl peroxides as a radical reaction[87]. Radical processes were established in the polymer industry well before the synthetic organic chemist exploited the synthetic usefulness of these species.

4.2 METHODS OF RADICAL FORMATION

The work described in this chapter will focus on carbon centred radicals generated by cleavage of a carbon-halogen bond, which can then undergo intramolecular cyclisation. The most common ways of forming these are described below[88]:

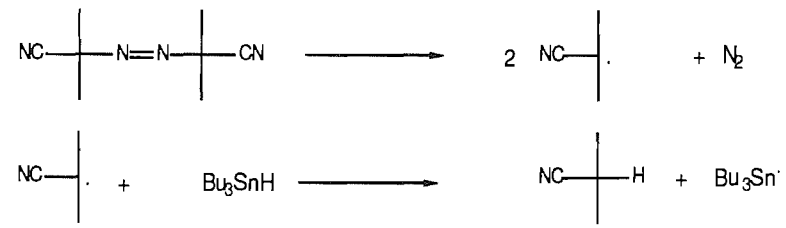
1. Bu_3SnH, AIBN (azoisobutyronitrile) or hυ
2. $(Bu_3Sn)_2$, hυ
3. Bu_3GeH, AIBN
4. hυ or AIBN
5. + others

4.3 MECHANISTIC PATHWAY OF RADICALS

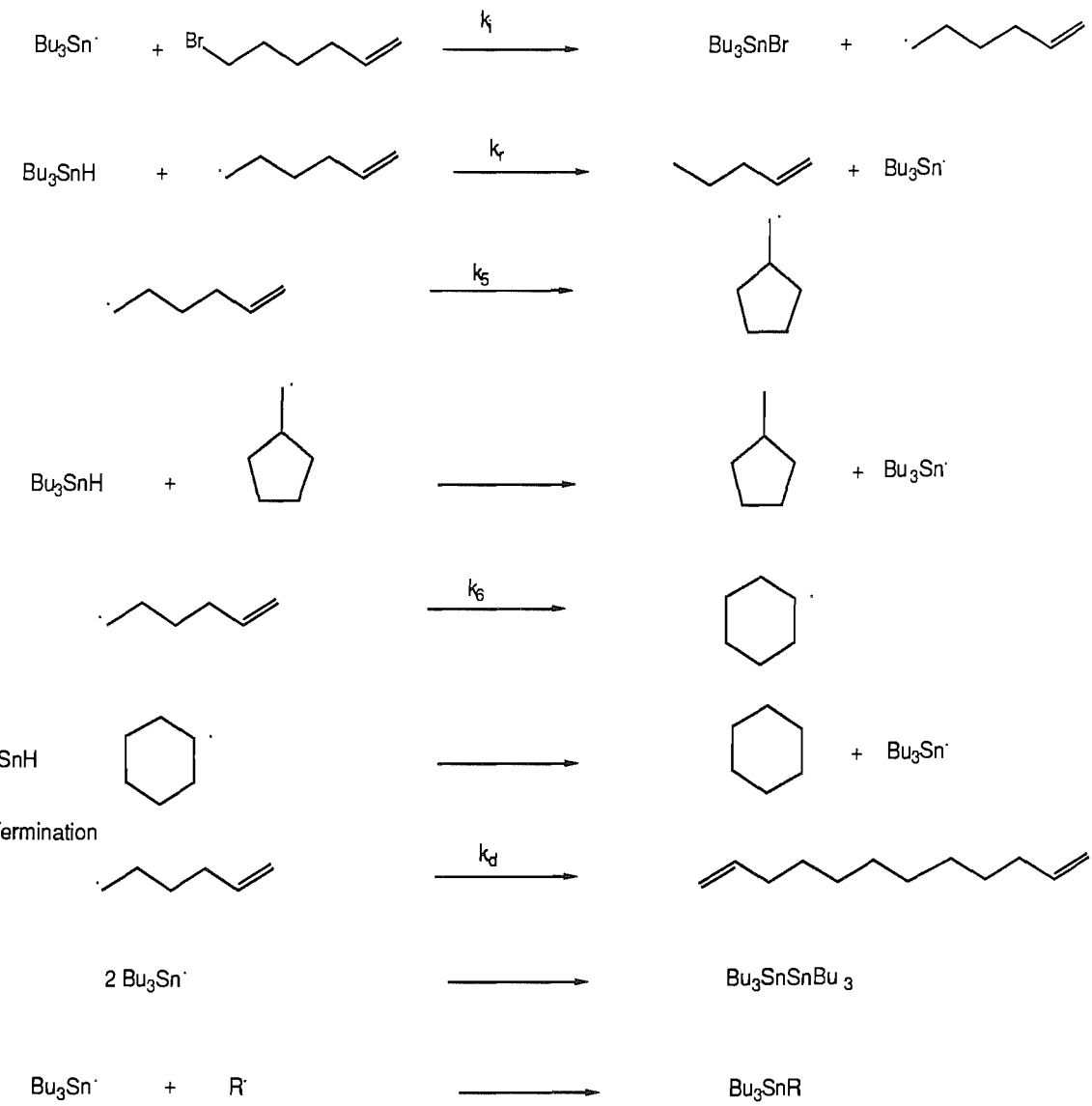
Radical reactions are normally chain processes and the mechanistic details are illustrated in Scheme 4.1[89]. The reaction between

tributyltin hydride and 6-bromo-1-hexene in the presence of a radical initiator (In) such as azoisobutyronitrile (AIBN) can be used as a example.

Initiation



Propogation

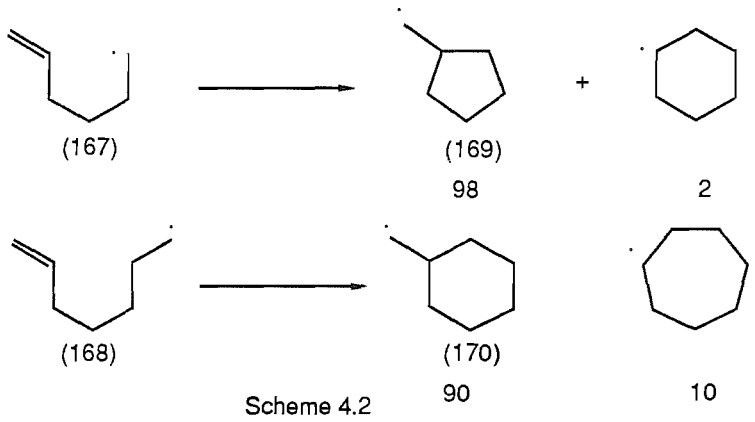


Termination

Scheme 4.1

4.4 REGIOSELECTIVITY

5-Hexenyl and 6-heptenyl radicals (167) and (168) cyclise predominently to give the smaller rings (169) and (170)[90]. Scheme 4.2.



Scheme 4.2

Beckwith explains these regioselectivities in terms of stereoelectronic effects[90]. The addition of alkyl radicals to olefins proceeds through a transition state structure in which the three reactive centres are situated at the vertices of a slightly obtuse triangle lying within a plane orthogonal to the nodal plane of the π–system. Fig 4.1.

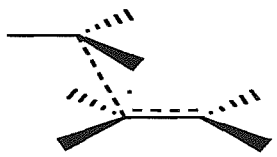


Fig 4.1

By the same token a radical cyclisation will proceed through a transition state which is best able to accommodate the above stereoelectronic criteria. For the 6-hex-1-enyl radical the *exo* and *endo* transition states are depicted in Fig 4.2[90].

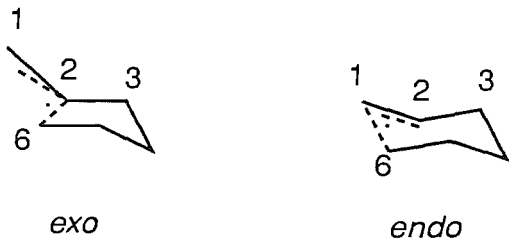
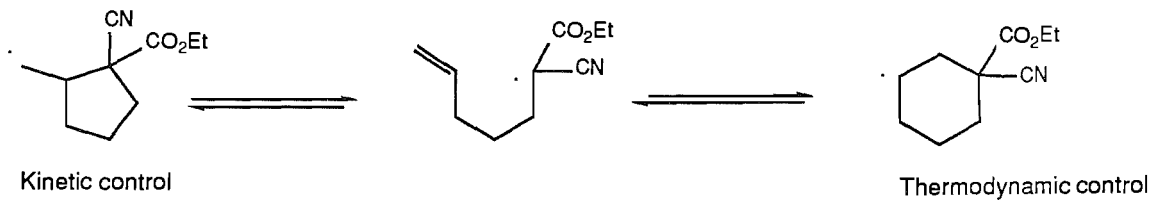


Fig 4.2

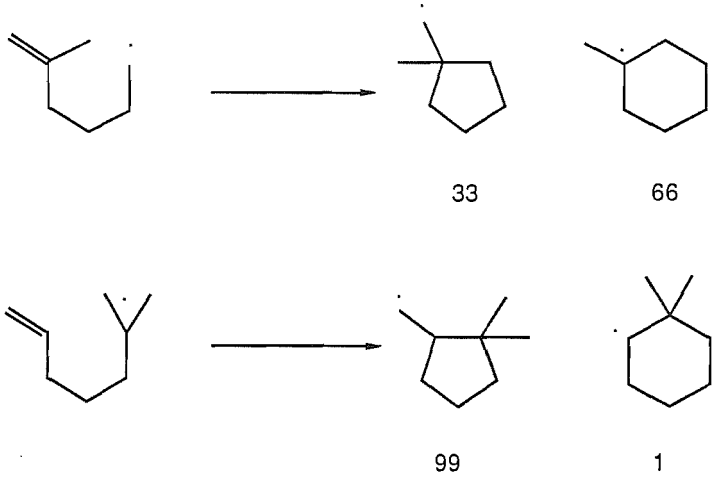
The above transition structures were obtained using force field calculations to optimise the relative positions of carbons 1,2 and 6 in order to obtain maximum overlap of the singly occupied molecular orbital (SOMO) and the π-cloud.

The whole scenario is summarised by saying smaller rings are formed due to less strained transition states. Stereoelectronic predictions concerning regiochemistry of radical cyclisations changes when the reactions become reversible. Julia has shown that under thermodynamic conditions, six membered rings are predominently formed[91]. Scheme 4.3.



Scheme 4.3

The ratio of five to six membered rings can be altered depending on the degree of substitution on the radical or olefin[90]. Scheme 4.4.



Scheme 4.4

4.5 STEREOSELECTIVITY

Beckwith proposed the following guidelines for predicting ring closure of substituted hexenyl radicals[92].

a) 1 or 3 substituted radicals preferentially give *cis* - disubstituted cyclopentyl products.

b) 2 or 4 substituted radicals give mainly *trans* -disubstituted cyclopentyl products.

These rules are based on steric effects resulting from 1,3-diaxial interactions in the transition state. Fig 4.3.

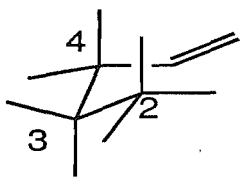
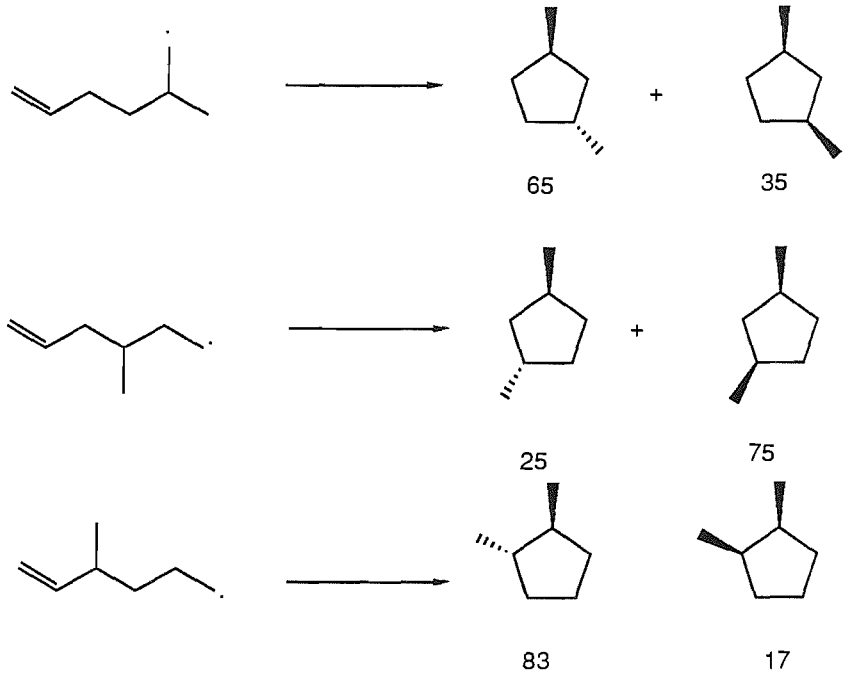


Fig 4.3

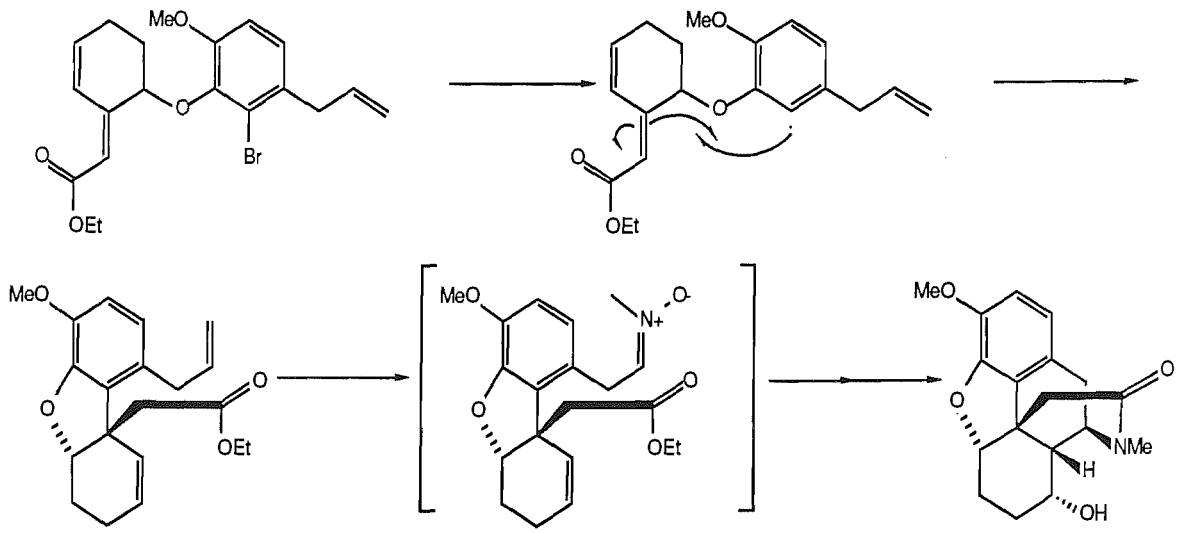
Therefore the more favourable conformer contains substituents on C-2, C-3, and C-4 in the equatorial position. This effect is illustrated by the following cyclisations[90]. Scheme 4.5.



Scheme 4.5

4.6 AIM OF PROJECT

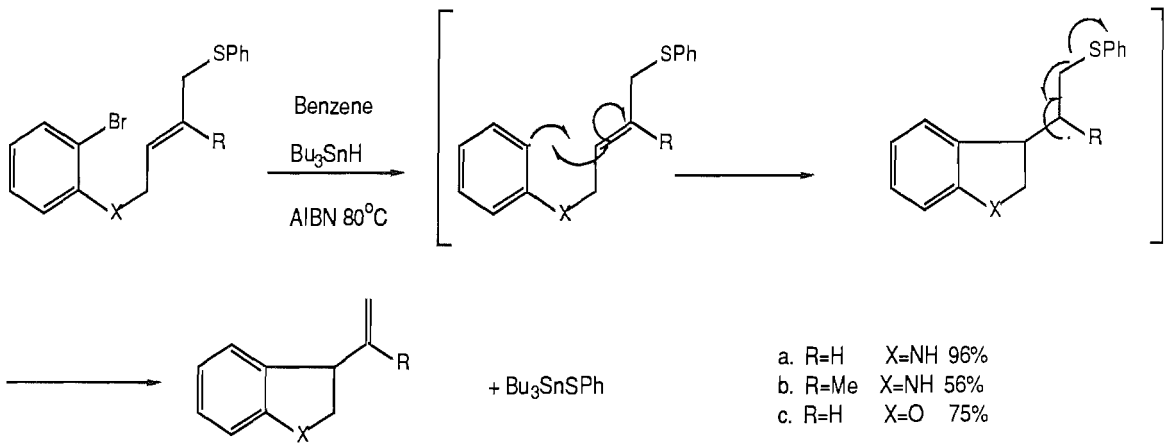
An aryl radical cyclisation can be employed to assemble the furan ring of morphine. Scheme 4.6.



Scheme 4.6

Studies of cyclisations initiated by aryl radicals are fairly scarce

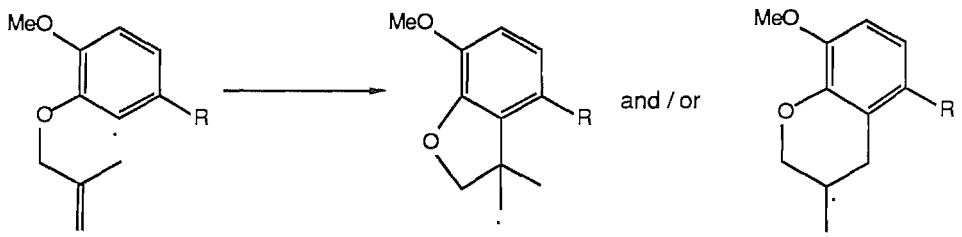
compared to vinyl or alkyl radicals; however, interesting chemistry is emerging in this area. For example Ueno published a very useful methodology for making dihydroindoles and dihydrobenzofurans[93]. Scheme 4.7.



Scheme 4.7

The aryl radical formed undergoes an intramolecular cyclisation which is followed by ejection of a thiophenyl radical.

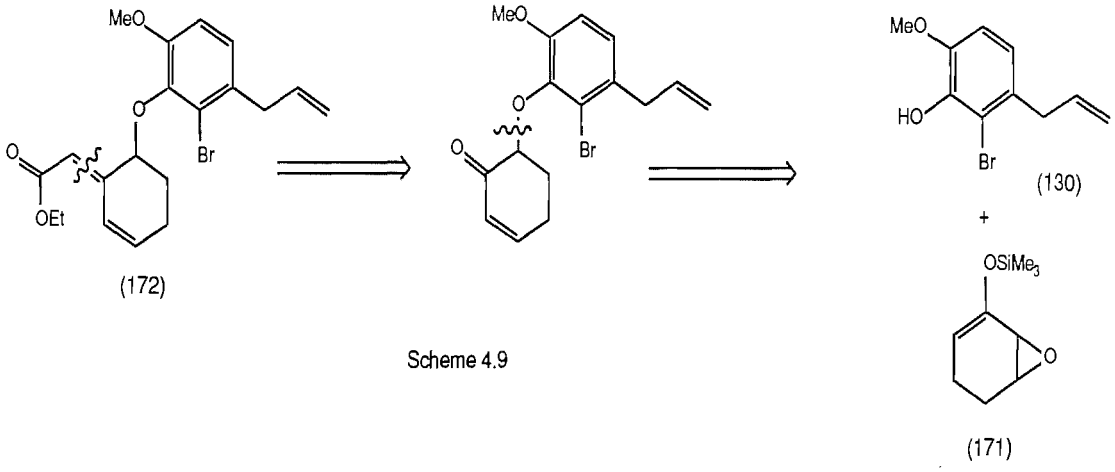
Parker[94] observed that aryl substituents have an effect on the ring size of aryl radical initiated cyclisations. Scheme 4.8.



Scheme 4.8

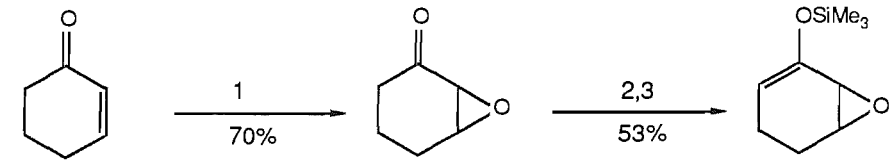
a). Results and discussion.

The retrosynthetic analysis for the synthesis of the precursor (172) is shown in scheme 4.9.



Scheme 4.9

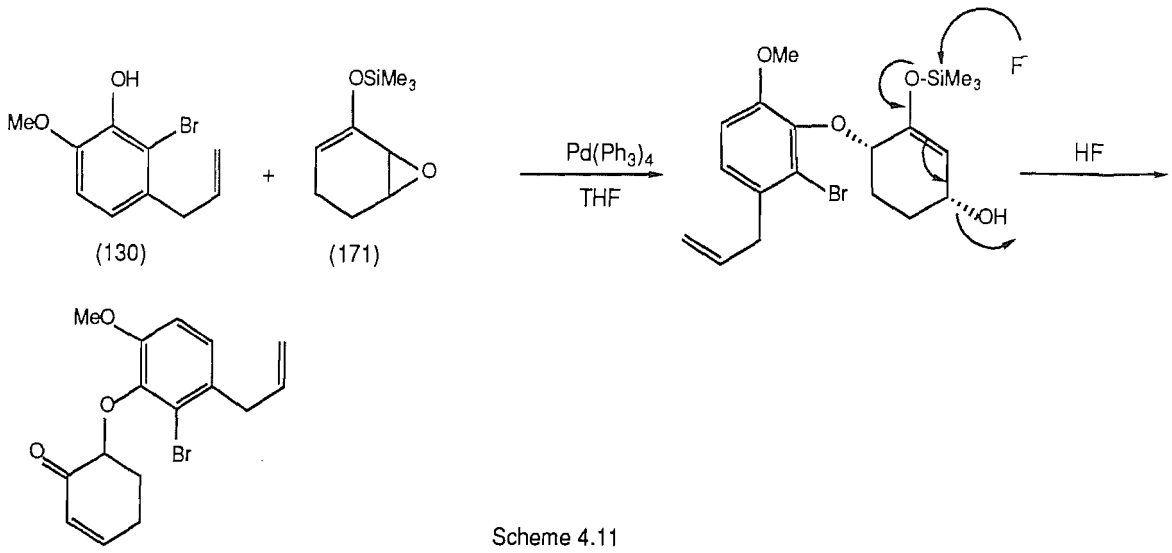
Epoxide (171) was made according to scheme 4.10.



Reagents
1. 30% H_2O_2, catalytic NaOH 2. HMDSLi, THF, - 78°C 3. Et_3N,TMSCl, THF -78°C⟶ 0°C.

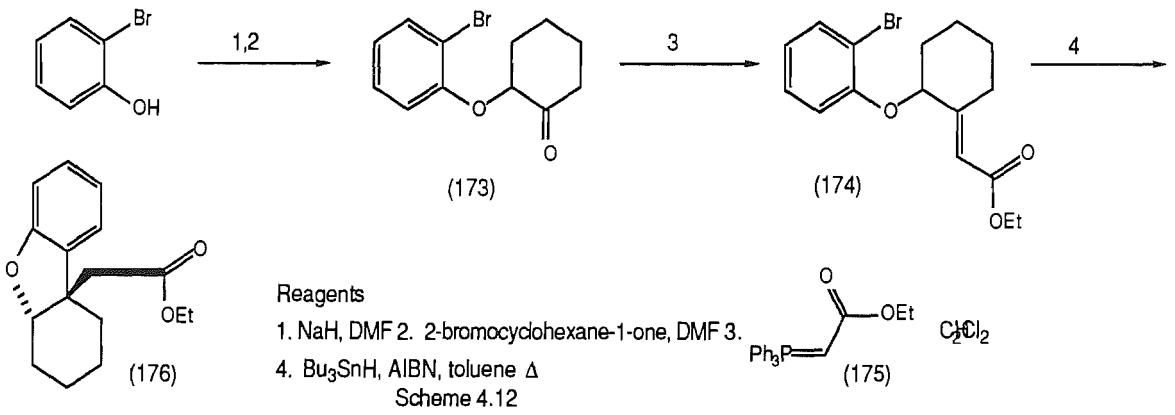
Scheme 4.10

Cyclohexenone oxide was made in 70% yield as described by Eschenmoser[95] and the silyl enol ether (171) was formed in 53% yield. It was thought that the coupling of the silyl enol ether (171) with phenol (130) could occur by a 1,4-nucleophilic addition in the presence of catalytic *tetrakis* palladiumtriphenylphosphine[96]. Scheme 4.11.



Scheme 4.11

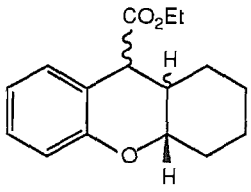
In addition we investigated the key radical cyclisation reaction on a simple substrate to assess the feasibility of the process. The substrate chosen was ester (174) which was made according to scheme 4.12.



Scheme 4.12

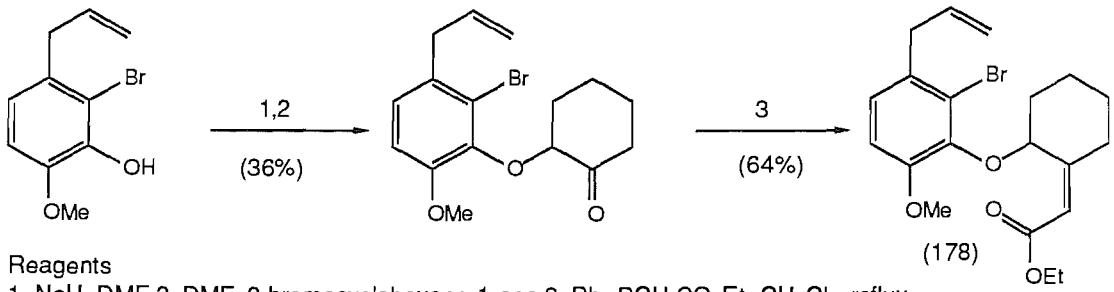
o-Bromophenol was treated with sodium hydride in DMF and the resulting anion alkylated with 2-bromocyclohexane-1-one to furnish the aromatic bromide (173) in 44% yield. Stirring the bromide (173) with the phosphorane (175) in dichloromethane for 48 hours yielded the unsaturated ester (174) in 82% yield. The unsaturated ester was heated in toluene under reflux with 1.3 equivalents of tributyltin hydride and a catalytic quantity of AIBN (10 mol%). This furnished

ester (176) in 45% yield and ester (177) in 30% yield.



(177)

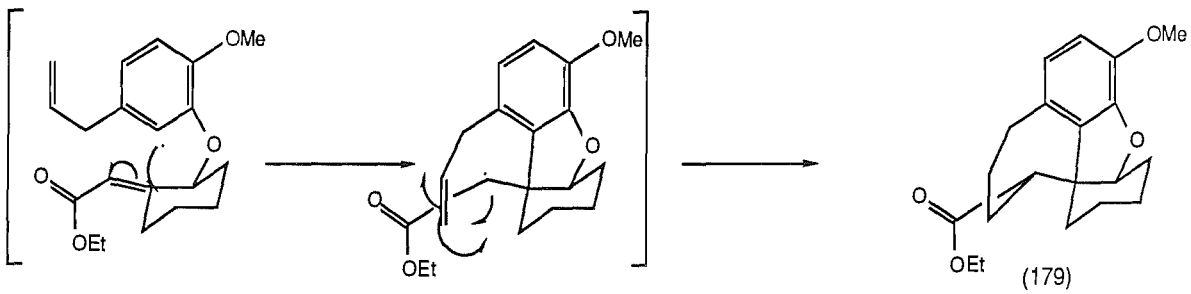
With this success, a more advanced precursor, ester (178), was made according to scheme 4.13.



Reagents
1. NaH, DMF 2. DMF, 2-bromocyclohexane-1-one 3. $Ph_3PCH\ CO_2Et$, CH_2Cl_2, reflux

Scheme 4.13

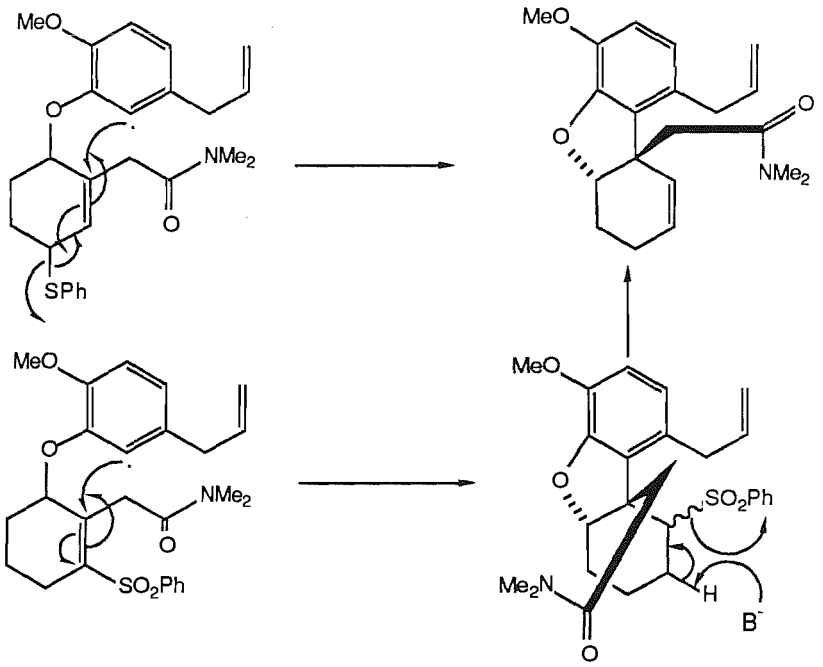
Treating ester (178) with 1.3 equivalents of tributyltin hydride in refluxing toluene gave a complex mixture of products; however, a white crystalline solid (179) was isolated in 37% yield. Scheme 4.14.



Scheme 4.14

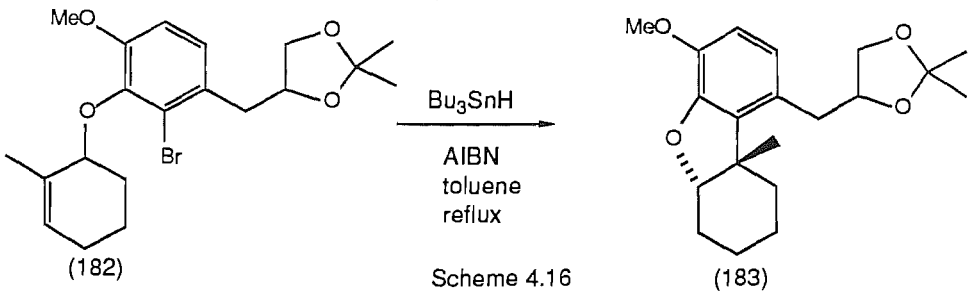
Even though the aryl radical had undergone a tandem cyclisation, this was not felt to pose a problem as the double bond could be suitably protected to prevent this from occurring. Having established the methodology as being feasible for construction of the furan ring, the

palladium catalysed coupling of the phenol (130) to silyl enol ether (171) was investigated. A model investigation was pursued which involved phenol being stirred with 1 equivalent of the silyl enol ether (171) in THF in the presence of a catalytic quantity of $Pd(Ph_3)_4$. One new product formed which was isolated and characterised as cyclohexenone oxide . With this failure in mind the scheme was revised such that the double bond required to undergo cyclisation was inside the cyclohexane ring. Scheme 4.15.



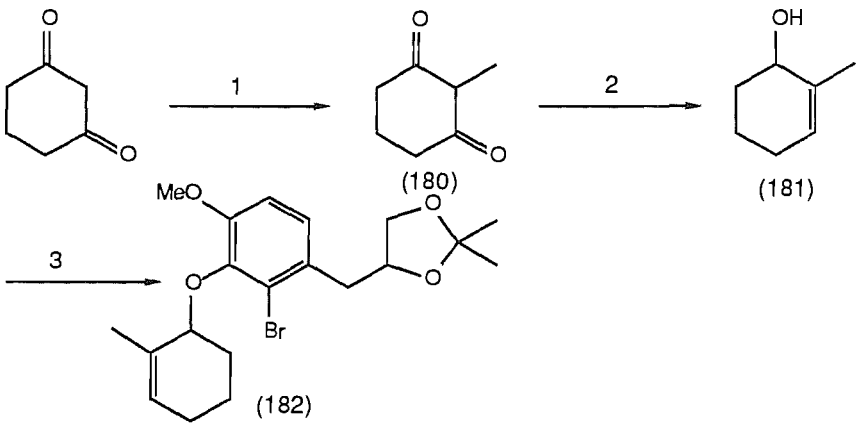
Scheme 4.15

Before either route could be explored it seemed prudent to investigate the simple aryl closure as shown in scheme 4.16. The acetal was incorporated into the molecule (182) because molecular models suggested that a tandem cyclisation would be inevitable.



(182) Scheme 4.16 (183)

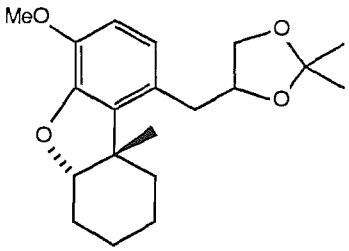
Substrate (182) was made according to scheme 4.17.



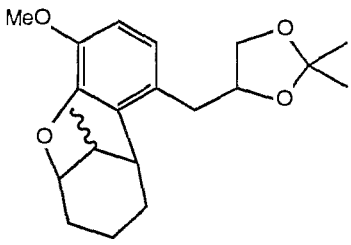
Reagents
1. KOH, Cu, MeI 2. $LiAlH_4$. THF 3. DEAD, PBu_3, THF, (142)

Scheme 4.17

1,3-Cyclohexadione was methylated using KOH, copper powder and MeI to give (180) in 35% yield. Lithium aluminium hydride reduction furnished allylic alcohol (181) in 50% yield. Mitsunobu conditions[97] were employed to assemble acetal (182). Tributylphosphine was used to help mediate the coupling reaction which was achieved in 57% yield because triphenylphosphine gave a disappointing yield of 37%. Treating precursor (182) with 2 equivalents of tributyltin hydride gave a 1:1 mixture of two products (183) and (184).

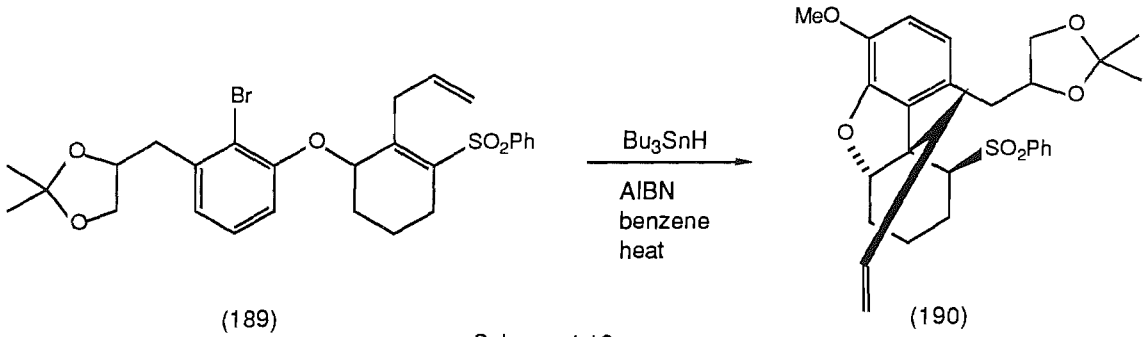


(183)



(184)

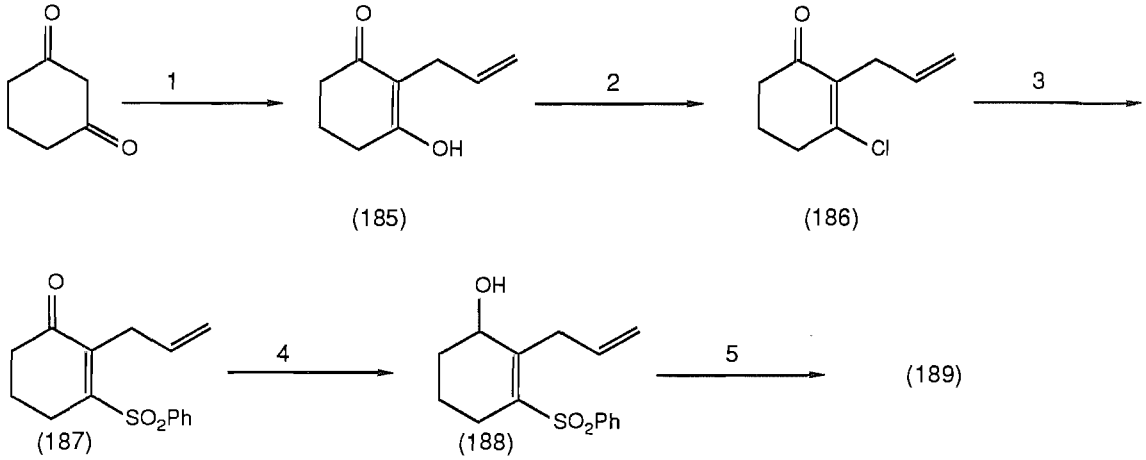
Having established that protection of the allylic double bond had encouraged no unforseen side reactions, substrate (189) was chosen as the target molecule to build. The sulphonate was incorporated into substrate (189) in order to facilitate exclusive 5 membered ring formation. Scheme 4.18.



(189) (190)

Scheme 4.18

Substrate (189) was made according to scheme 4.19

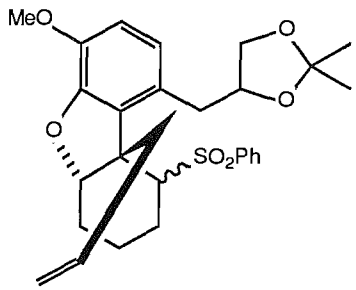


Reagents
1. KOH, Cu, allyl bromide 2. CH_2Cl_2 / $CHCl_3$ oxalyl chloride 3. $Na^{+-}SO_2Ph$, benzene,60 °C, $Bu_4N^+HSO_4^-$4. $NaBH_4$, $CeCl_3$, MeOH, 5. PBu_3, DEAD, THF, (142)

Scheme 4.19

1,3-Cyclohexadione was alkylated in 70% yield according to the method of Stetter[98]. Treating (185) with oxalyl chloride furnished the chloroenone (186) in 82% yield. The addition elimination reaction of sodium benzenesulphinate and chloroenone (186) was achieved in warm benzene (60°C) which contained a catalytic quantity of *tetra*-n-butyl ammonium hydrogen sulphate to give enone (187) in 92% yield. Cerium (III) chloride mediated sodium borohydride reduction of enone (187) gave allylic alcohol (188) in 87%. Coupling of the acetal (142) with the alcohol (188) was achieved by using a modified Mitsunobu procedure. Freshly distilled PBu_3 was added to DEAD in THF at 0°C. The resulting solution was stirred for 15 minutes and then transferred via syringe to a flask containing the phenol (142) and alcohol (188), this gave our required adduct in 78% yield. This substrate (189) was treated with 2 equivalents of tributyltin hydride to give the required cyclised product (190) in 23% yield.

100



(190)

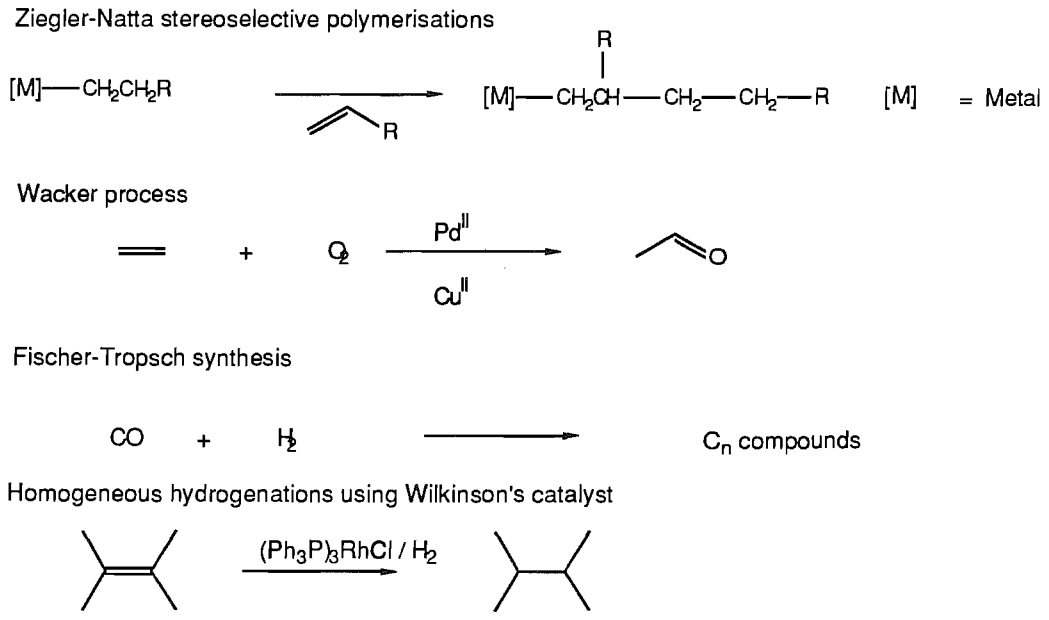
b) Conclusion.

The radical reactions were not clean reactions and gave a mixture of 5 and 6 ring cyclised products which were difficult to purify. Coupled with the low yield obtained in the key step we diverted our attentions to a different approach to the problem which is described in chapter 5.

CHAPTER FIVE

5.1 INTRODUCTION

The last two decades has seen the development and understanding of structure and reactivity of transition metal complexes. It is only in recent years however, that transition metal chemistry has been exploited by organic chemists for the construction of organic molecules. The fact that many transition metal reagents can be used catalytically has made their use in synthesis more acceptable. A certain number of remarkable organic reactions only take place in the presence of transition metal complexes. Scheme 5.1.



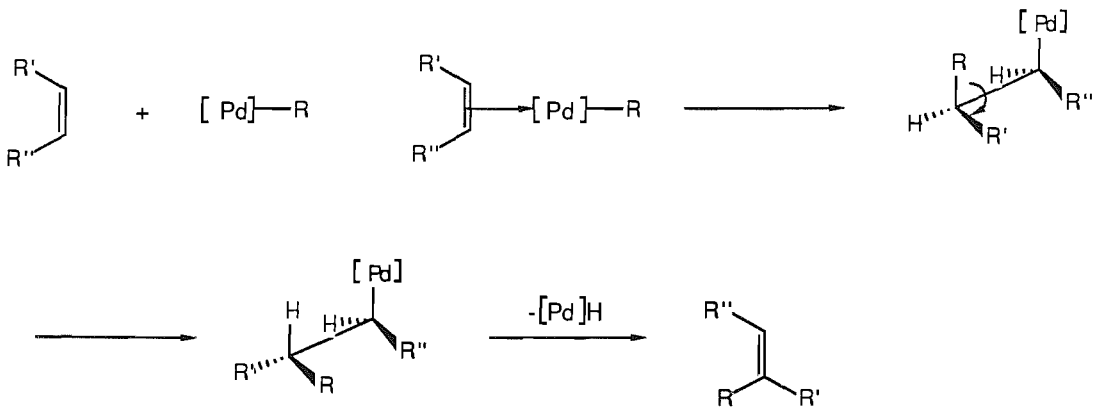
Scheme 5.1

A transition metal species will influence the reactivity of organic compounds by interacting with them and forming stable (or unstable) organometallic intermediates which then react further. Utilisation of this property and adapting it has proven highly valuable for the cyclisation of nitrogen (carbon and oxygen) containing ortho-haloaryl

alkenes to heterocycles[99]. Palladium catalysts have been most useful for such cyclisations.

5.2 THE HECK REACTION.

The *cis* addition of a R[Pd] species across a double bond is called the Heck reaction[84]. In cases where this generates a β-hydrogen *syn* to the [Pd] , elimination of the [Pd] and formation of a double bond takes place. Scheme 5.2.



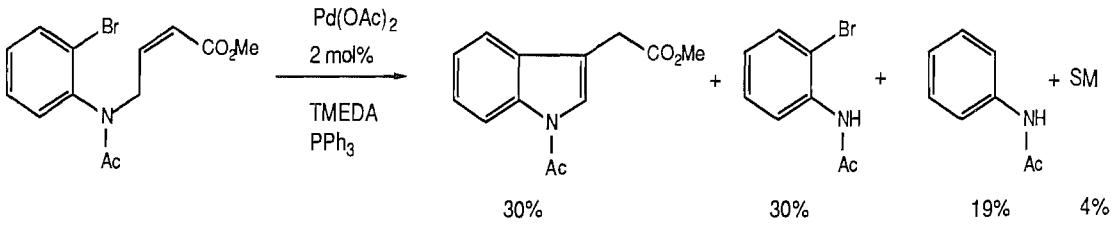
Scheme 5.2

5.3 THE INTRAMOLECULAR HECK REACTION.

The intramolecular version of the Heck reaction has been applied to the synthesis of indoles, quinolines, oxindoles, bezofurans and aromatic carbocycles[99].

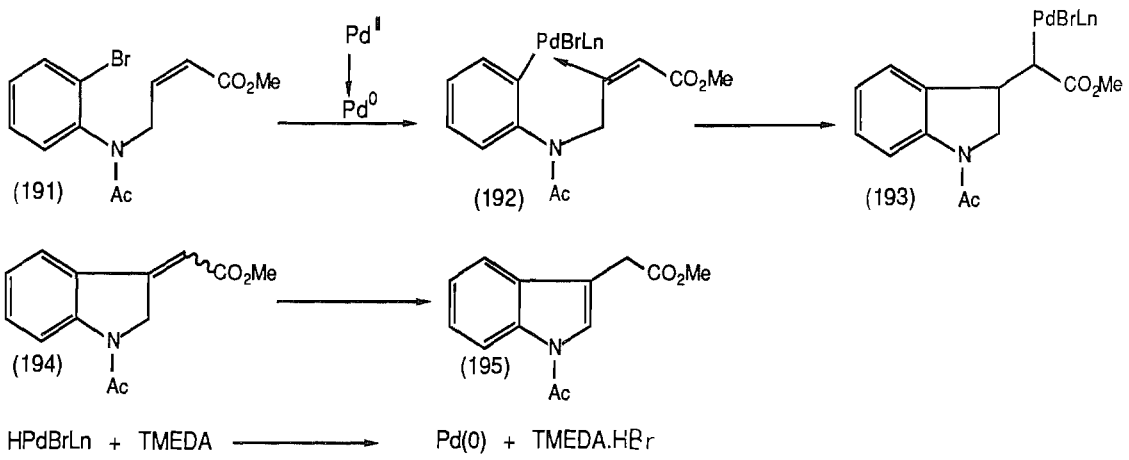
a). Nitrogen containing ortho-haloaryl alkenes

Mori *et al* have made indoles and isoquinolines from ortho-haloaryl alkenes using palladium catalysed cyclisations[100]. Scheme 5.3.



Scheme 5.3

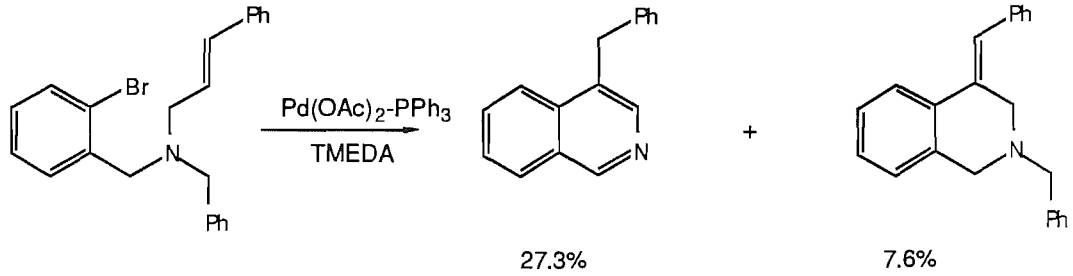
Mori suggested that the mechanism of the above reaction may be regarded as follows. The palladium (II)-complex $[Pd(OAc)_2(PPh_3)_2]$ was first converted to palladium (0) by reductive action of the olefinic moiety of (191). This was associated with the attack of a nucleophile, (AcO^-) followed by oxidative insertion of Pd (0) into the carbon-bromine bond, forming the palladium (II)-complex (192). The internal rearrangement of palladium from the aromatic ring to the olefinic carbon occurs to generate the σ–complex (193). The hydridopalladium halide moiety then eliminates to form (194), which was easily isomerised to the final product (195). The hydridopalladium halide finally generated palladium (0) by action of TMEDA to prevent accumulation of HBr. Scheme 5.4.



Scheme 5.4

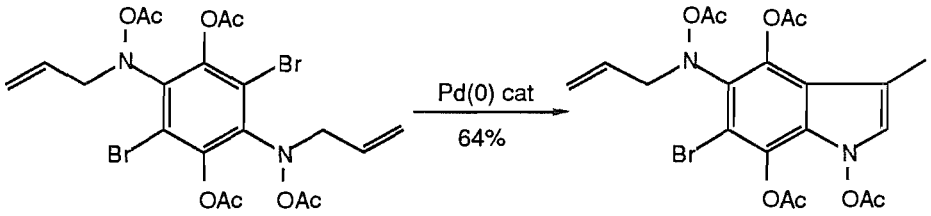
Mori produced isoquinolines by further exploitation of this

methodology[100]. Scheme 5.5.



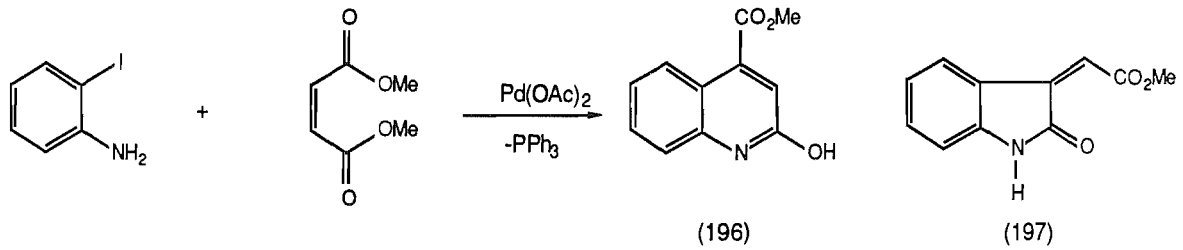
Scheme 5.5

Hegedus adopted palladium mediated cyclisations as part of his overall program to develop synthetic routes to the indoloquinone nucleus common to the mitosenes[101]. Scheme 5.6.



Scheme 5.6

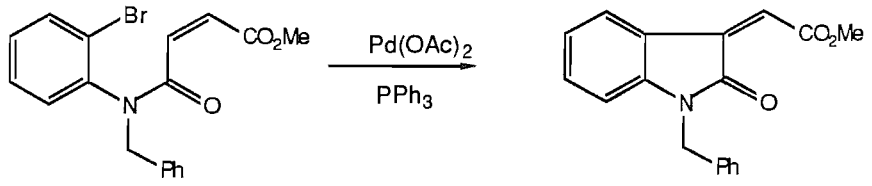
Heck reported that the reaction of o-iodoaniline with dimethylmaleate and a catalytic amount of $Pd(OAc)_2$ in the presence of a base gave exclusively the quinoline derivative (196) in excellent yield without generation of the oxindole (197)[102]. Scheme 5.7.



(196) (197)

Scheme 5.7

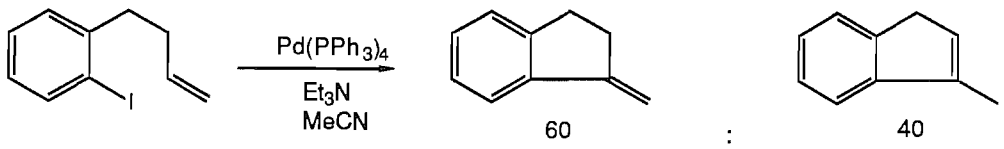
This result was in stark contrast to Mori's results in this area[103]. Scheme 5.8.



Scheme 5.8

b) Carbon containing ortho-haloaryl alkenes.

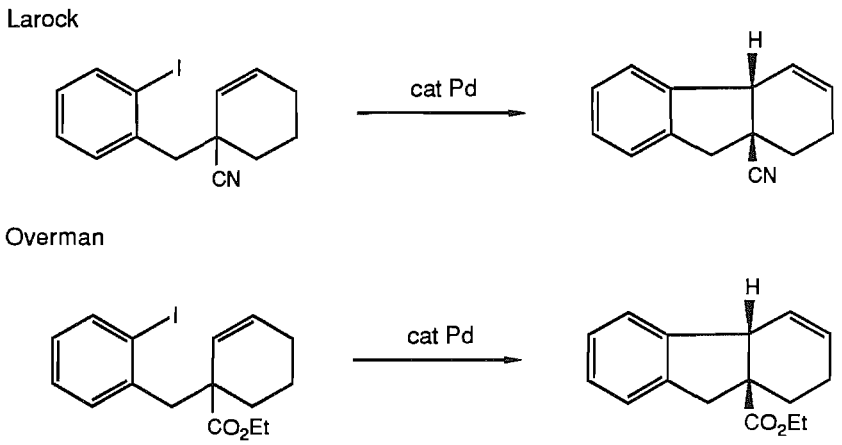
Negishi during his course of study of cyclic acylpalladation found that aryl iodide (198) was converted into a 60:40 mixture of (199) and (200) in 90% yield[104]. Scheme 5.9.



(198) (199) (200)

Scheme 5.9

Similar results to Negishi were documented by Larock[105], Overman[106], and Grigg[107]. The only difference being the extra degree of functionality. Scheme 5.10.

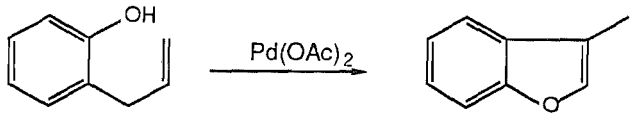


Scheme 5.10

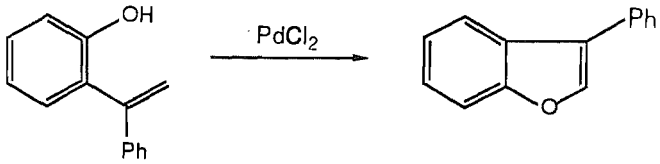
c). *Oxygen containing ortho-haloaryl alkenes*.

While the palladium promoted cyclisation of o-allylic[108] or vinylic

phenols[109] to 2 and 3 substituted benzofurans respectively (equations 1 and 2) have proven quite successful, the cyclisation of

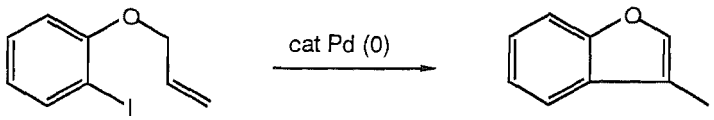


Equation 1



Equation 2

o-iodoaryl allyl ethers to benzofurans (equation 3) is much more

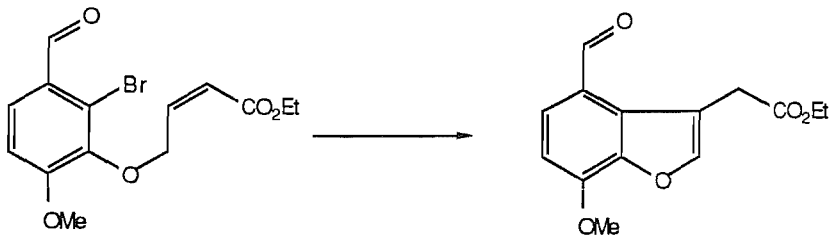


Equation 3

problematical as a route to benzofurans in view of the known ability of palladium (0) to react with aryl allyl ethers to form π-allylpalladium compounds[110] (equation 4).

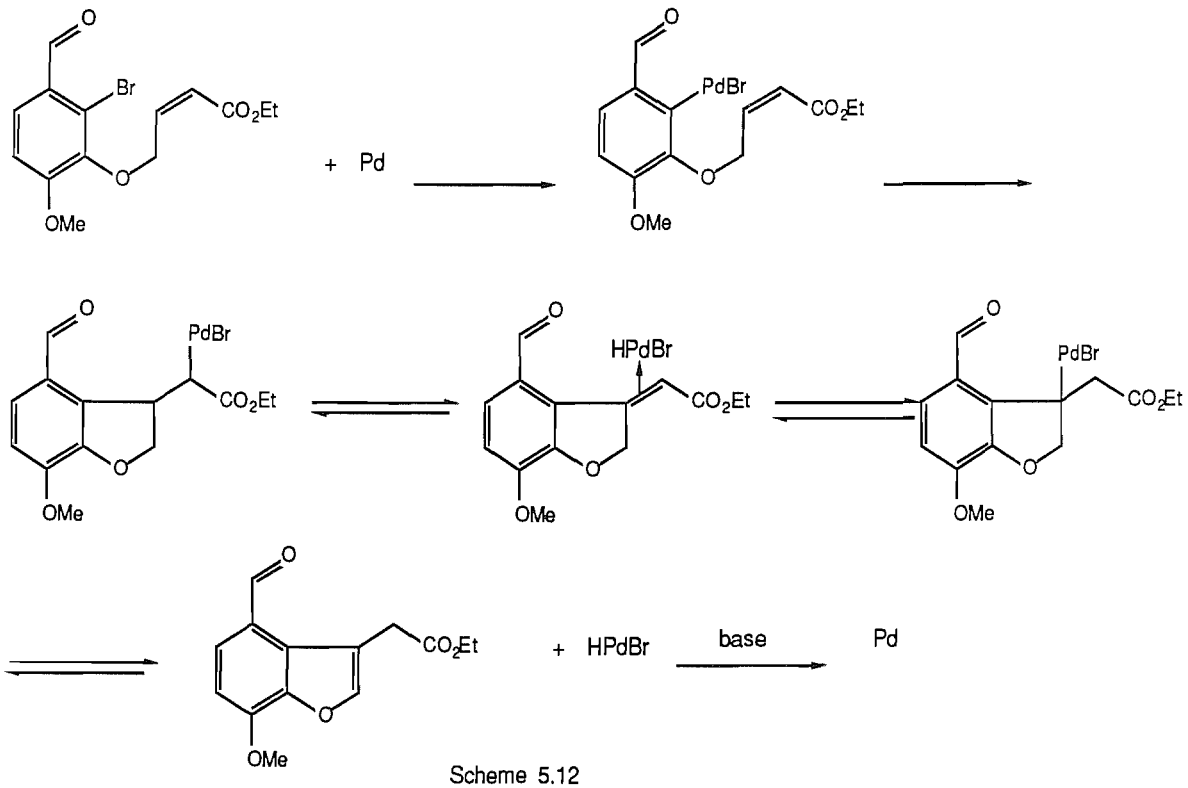
$H_2C{=}CH{-}CH_2OAr + \text{cat Pd} \longrightarrow \pi{-}C_3H_7PdOAr$ Equation 4

After considerable experimentation Parsons and Ellwood[111] in their pursuit of highly functionalised benzofurans have found reaction conditions which effect the cyclisation described in equation 3. Under mild conditions good isolated yields are obtained without the formation of any products arising from palladium insertion into the carbon oxygen bond. Scheme 5.11.



Scheme 5.11

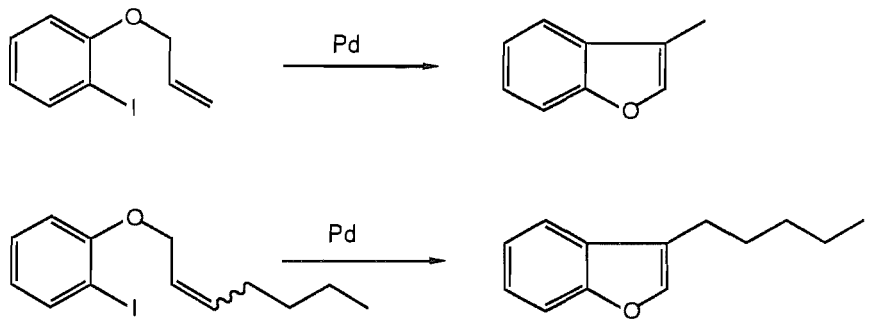
Mechanistically the reaction is thought to proceed as shown in scheme 5.12.



Scheme 5.12

N.B. *Additional ligands on palladium have been omitted for clarity.*

Larock recently published similar conditions with much simpler substrates[112]. Scheme 5.13.

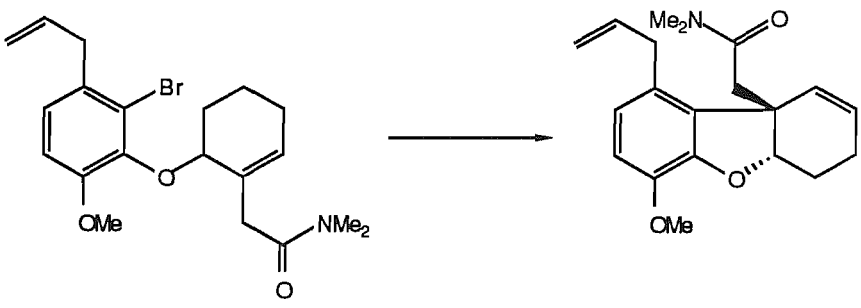


Scheme 5.13

The optimum conditions for the palladium promoted cyclisations involve a catalytic quantity of palladium acetate (usually 5-10 mol%) and two equivalents of potassium carbonate. The reaction mixture is heated in acetonitrile or DMF.

5.4. AIM OF PROJECT.

It was envisaged that an intramolecular Heck reaction could compliment our radical cyclisation approach and furthermore could incorporate an extra degree of unsaturation into the new product. Scheme 5.14.



Scheme 5.14

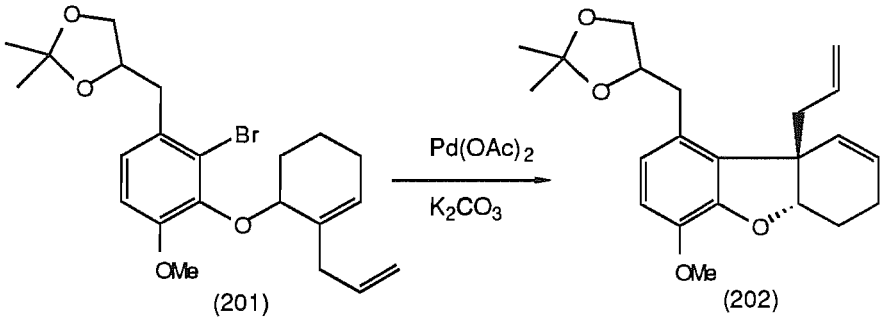
The problems likely to be encountered are twofold:

1. The double bond in the substrate is trisubstituted and therefore could slow the rate of reaction to such an extent that decomposition

of the catalyst could occur[112].

2. The known lability of Pd(0) to form π-allylpalladium compounds might become the dominent side reaction with this class of compounds[110].

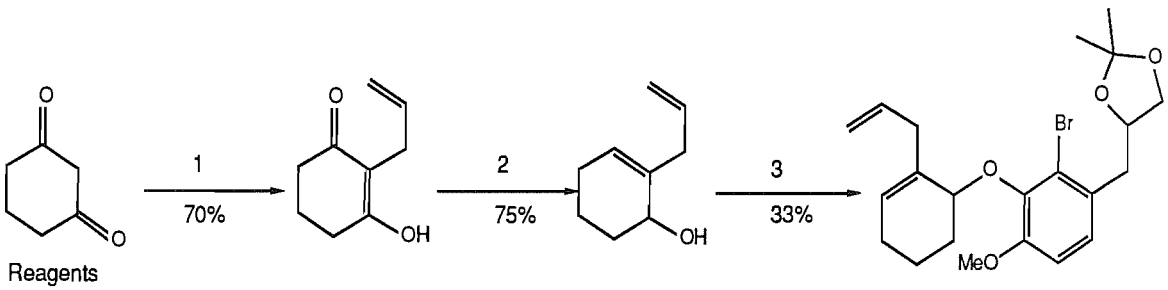
Because of these potential problems it was felt prudent to conduct the study on a suitable model, which was acetal (201). Scheme 5.15.



(201) (202)

Scheme 5.15

Acetal (201) was made according to scheme 5.16.

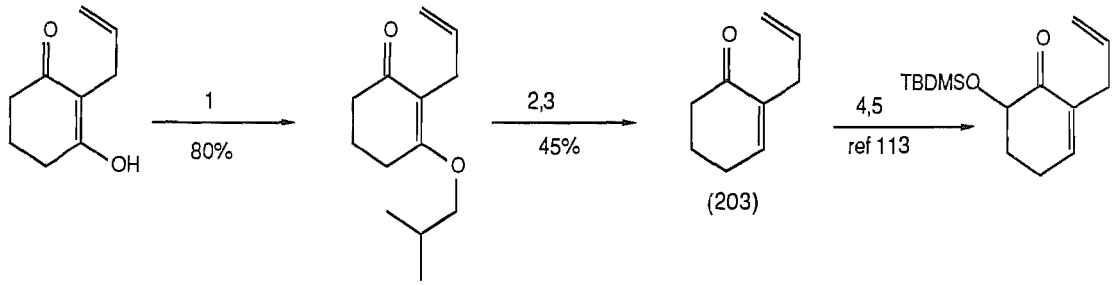


Reagents
1. KOH, Cu, allylbromide 2. $LiAlH_4$ 3. PBu_3, DEAD, THF (142)

(201)

Scheme 5.16

As for the real system, ketone (203) seemed a very attractive target. This ketone (203) would be used to incorporate a protected hydroxyl functionality which would be released when required to form the alcohol functionality of the C ring of morphine. Scheme 5.17.



Reagents
1. *iso*-butanol, benzene, CSA 2. $NaBH_4$, THF, H_20 3. Silica gel 4. TBDMSOTf, Et_3N, 5. *m*CPBA

Scheme 5.17

Heating acetal (201) in acetonitrile under reflux resulted in the formation of acetal (141) as the major product and the desired cycloadduct (202) was formed as the minor adduct. A number of substrates were reacted under these cyclisation conditions and the results of these studies are shown in table 5.1.

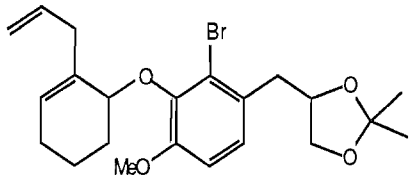
table 5.1

Substrate	Solvent	Time	Products	Yield
$(201)^+$	MeCN/Δ	4 days	(141)	21%
$(204)^+$	MeCN	12 hours	(205)	32%
	pyrolysis		(206), (207)	minor quantities
			(208)	20%
(204)	MeCN/Δ	6 days	(209)	
			(210)	
			(211)	
$(212)^+$	MeCN/Δ	3 days	complex	
			mixture	
$(213)^+$	MeCN/Δ	2 days	(214)	66% ratio 3
			(215)	3
			(216)	1
(213)	DMF/120°C	2 days	(214)	48% ratio 3

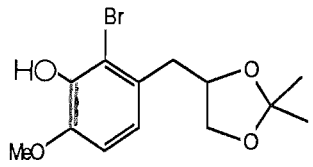
(215)	3
(216)	1

* Note all reactions needed incremental amounts of catalyst to be added every day.

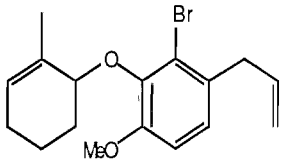
+ These substrates were made by coupling the corresponding alcohol and phenol under Mitsunobu conditions (PBu_3, THF, and DEAD at room temperature).



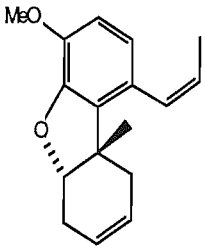
(201)



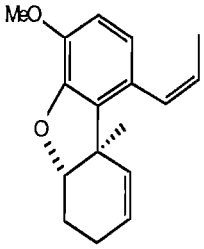
(141)



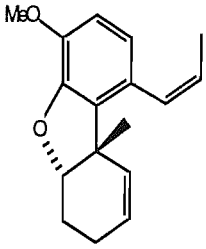
(204)



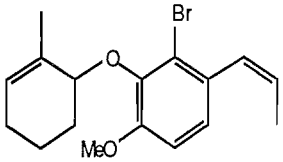
(205)



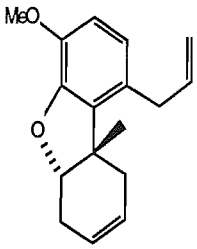
(206)



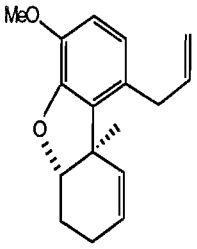
(207)



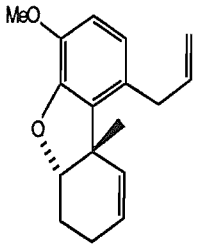
(208)



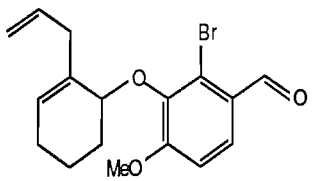
(209)



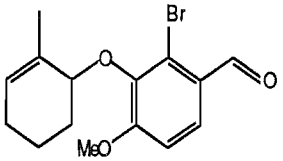
(210)



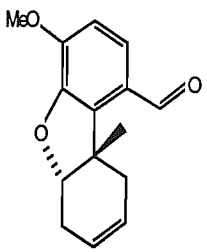
(211)



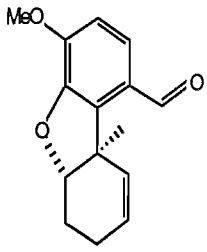
(212)



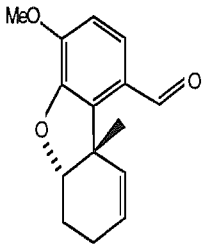
(213)



(214)



(215)

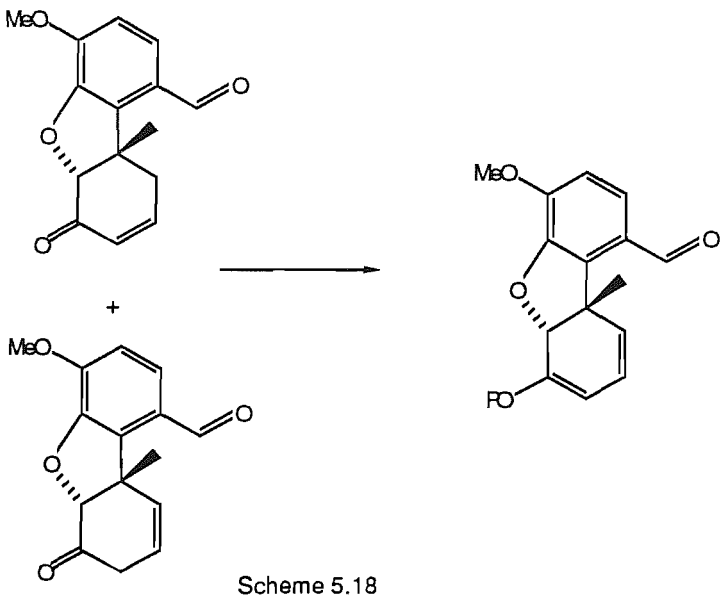


(216)

The problems arising from these cyclisations reactions were:

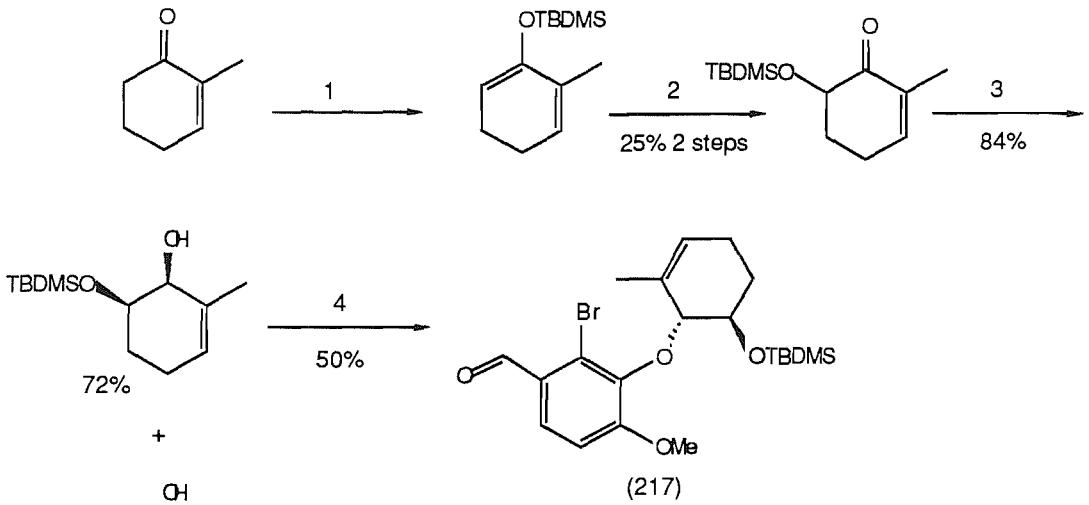
1. Formation of the unwanted *trans* compound
2. The isomerisation of the double bond in the cyclohexene ring.

To circumvent this problem, it was envisaged that a carbonyl group residing α to the ether linkage could be used as a handle to relocate the double bond into the correct position for the nitrone cycloaddition. Scheme 5.18.



Scheme 5.18

The precursor chosen for the cyclisation was aldehyde (217) which was made according to scheme 5.19.



Reagents
1. TBDMSOTf, Et_3N, 0°C 2, mCPBA, CH_2Cl_2, -78°C
3. $NaBH_4$, $CeCl_3$, MeOH 4. PBu_3, DEAD, THF, bromoisovanillin.

Scheme 5.19

Heating aldehyde (217) in DMF at 25°C with $Pd(OAc)_2$ (50 mol%) gave the products shown below.

(218) Major product

(219) (220) minor qantities

5.5. CONCLUSION TO THE PALLADIUM STUDY.

The model study conducted illustrates that this is a useful methodolgy for making highly functionalised benzofurans If the quarternary methyl group was replaced with an amide group then the methodogy could be developed into a total synthesis of morphine as well as producing potentially active compounds *en route*.

CHAPTER SIX

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

I.r. spectra were recorded in cm^{-1} on a Perkin Elmer 298 spectrometer and calibrated using the $1603cm^{-1}$ peak of a polystyrene film as reference. The following standard conventions have been adopted when quoting physical data:

s-strong, m-medium, w-weak and br-broad.

Proton nmr spectra were recorded on the following machines:

Bruker AM 360.

Joel JMM GX 270.

Bruker AM 250.

Varian Associates XL100/12.

Perkin Elmer R24B 60.

Tetramethylsilane (TMS) was used as an internal standard. Chemical shifts are quoted as δ values and the following descriptions are used for peak description: br-broad, s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet.

Carbon nmr spectra were recorded on the following machines:

Bruker AM 360 at 90.6 MHz.

Joel GX 270 at 67.5 MHz

Varian Associates XL100/12 at 25.2 MHz.

Mass spectra were taken on a Kratos MS30 spectrometer using a DS 55S data system or on a V.G 70-250-S.E. double focussing spectrometer. The ionisation mode was Electron Impact (EI) at 70 eV unless otherwise stated.

Thin layer chromatography (TLC) was carried out using Merk Kieselgel 60H glass coated plates (0.25 mm thickness) and visualised by U.V., vanillin or potassium permanganate. Two methods of

quantitative chromatographic separations were used.

a) Suction flash chromatography using Merck Kieselgel 60H (art 7736)[114].

b) Flash column chromatography using Silica Gel 60 (230-400 mesh)[115].

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

THF	sodium in the presence of benzophenone.
Ether	as above.
Methanol	magnesium methoxide.
Chloroform	phosphorus pentoxide.
Carbon tetrachloride	as above.
All other solvents	calcium hydride.

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

n-Butyllithium	2.5 M in hexanes and 1.7 M in hexanes.

4-(1-Ethoxyethoxymethyl)-1,2-(1,3-benzodioxole) (68). Piperonyl alcohol (67) (90 g, 0.59 mol) and TFA (1 ml) were dissolved in ethyl vinyl ether (500 ml) and stirred at ambient temperature until none of the alcohol remained by TLC analysis (approximately 48 h). The reaction mixture was diluted with ether (500 ml) and then poured into a saturated solution of sodium bicarbonate. The organic layer was separated from the aqueous layer, dried ($MgSO_4$) and then concentrated *in vacuo* to give a colourless oil. Distillation gave the title compound as a colourless oil (126 g, 95%). Physical properties

and spectroscopic data were in agreement with the literature[116].

[1,2-Dimethoxy-4-(1-ethoxyethoxymethyl)]benzene (158).

Acetal (158) was prepared by the same procedure as for (68) from 3,4-dimethoxy benylalcohol in 95% yield.

$\upsilon_{max.}$(film): 2950s, 1610m, 1600s and 1520s.

δ_H (270 MHz): 1.12 (3H, t, **J** 8.1 Hz, $OCH_2C\underline{H}_3$), 1.25 (3H, d, **J** 5.2 Hz, $O_2CHC\underline{H}_3$), 3.38-3.60 (2H, m, $ArC\underline{H}_2$), 3.73 (3H, s, $OC\underline{H}_3$), 3.76 (3H, s, $OC\underline{H}_3$), 4.41 (2H, ABX, **J** 11 Hz, $OC\underline{H}_2CH_3$), 4.68 (1H, q, **J** 5.2 Hz, $OC\underline{H}O$), 6.71 (1H, d, **J** 8 Hz, aryl proton) and 6.76 (2H, m, aryl protons).

δ_C (67.5 MHz): 15.02 (CH_3), 19.59 (CH_3), 55.40 (CH_3), 55.50 (CH_3), 60.27 (CH_2), 66.66 (CH_2), 98.63 (CH), 110.68 (CH), 110.82 (CH), 119.88 (CH), 130.71 (C), 148.19 (C) and 148.66 (C).

3-Iodo-1,2-(1,3-benzodioxole)-4-methanol (69).

To a vigorously stirred cold solution (-5^{o}C) of acetal (68) (70 g, 0.313 mol) in dry ether (1.5 l) was added a solution of n-butyllithium (0.344 mol) such that the reaction mixture did not exceed 0^{o}C. The reaction mixture was maintained at this temperature for 2 hours and then cooled to -78^{o}C. Iodine (90 g, 0.345 mol) in THF (220 ml) was added dropwise in such a way that the temperature did not exceed -60^{o}C. The external cooling source was removed and the reaction mixture was allowed to warm to room temperature. Sodium thiosulphate solution (500 ml) was added to the mixture and then the aqueous phase was separated

from the organic phase and poured into ether. The organic phases were combined, dried ($MgSO_4$) and the solvent volume was removed *in vacuo* to give a brown oil. The crude brown oil was diluted with methanol (50 ml) followed by concentrated HCl (10 ml). Three hours after the addition of the HCl, the reaction mixture was cooled to 0°C and the pH was adjusted to 6 with aqueous NaOH, this was followed by further addition of sodium bicarbonate solution. The resulting white solid was filtered off and dissolved in dichloromethane. Drying ($MgSO_4$) followed by the solvent volume being concentrated *in vacuo* gave a white solid which was recrystallised from cyclohexane to give the title compound as white needles (51.3 g, 59%). M.p. 93-95°C. (Found: C, 34.5% H, 2.4%. $C_8H_7IO_3$ requires C, 34.6%, H, 2.5%.)

υ_{max} (CH_2Cl_2): 3450m, 1460s and 1050s.

δ_H (250 MHz): 2.16 (1H, t, **J** 5 Hz, O<u>H</u>), 4.6 (2H, d, **J** 5 Hz, C<u>H</u>$_2$OH), 6.04 (2H, s, OC<u>H</u>$_2$O), 6.74 (1H, d, **J** 8 Hz, aryl proton) and 6.92 (1H, d, **J** 8 Hz, aryl proton).

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

2-Iodo-3,4-dimethoxybenzylalcohol (159).

Iodo alcohol (159) was produced by the same procedure as for acetal (69) to give a white crystalline solid in 71% yield. M.p. 88-90°C.

υ_{max} (CH_2Cl_2): 3450, 2950s, 1590m and1470s.

δ_H (270 MHz): 2.4 (1H, bs, O<u>H</u>), 3.82 (3H, s, OC<u>H</u>$_3$), 3.85 (3H, s, OC<u>H</u>$_3$), 4.61 (2H, s, C<u>H</u>$_2$OH), 6.86 (1H, d, **J** 8.5 Hz, aryl proton) and 7.14 (1H, d, **J** 8.5 Hz, aryl

proton).

δ_C (67.5 MHz): 56.10 (CH_3), 60.36 (CH_3), 69.08 (CH_2), 96.58 (Cl), 112.25 (CH), 124.34 (CH), 135.75 (C), 148.68 (C) and 151.96 (C).

m/z (%): 294 (M^+, 100).

2-Iodo-3-methoxymethoxy-4-methoxybenzylalcohol.

This was produced using the same procedure except 2.2 equivalents of n-BuLi were added. This gave the title compound in 60% yield as a colourless oil which solidified in the fridge.

υ_{max} (CH_2Cl_2): 3600br and 1590m.

δ_H (270 MHz): 3.56 (3H, s, C<u>H</u>$_3$), 3.71 (3H, s, C<u>H</u>$_3$), 4.44 (2H, C<u>H</u>$_2$OH), 5.02 (2H, s, OC<u>H</u>$_2$O), 6.73 (1H, d, **J** 8.5 Hz, aryl proton) and 7.01 (1H, d, **J** 8.5 Hz, aryl proton). O<u>H</u> proton not observed.

δ_C (67.5 MHz): 55.85 (CH_3), 58.27 (CH_3), 68.62 (CH_2), 94.46 (C), 98.80 (CH_2), 112.03 (CH), 123.65 (CH), 135.79 (C), 145.08 (C) and 150.98 (C).

3-Iodo-4-(2-propenyl)-1,2-(1,3)-benzodioxole (71) .

To a well stirred solution of the benzyl bromide (70) (20 g, 58.6 mmol), copper (I) iodide (1.12 g, 5.88 mmol) and 2,2-dipyridyl (0.92 g, 5.89 mmol) in THF (120 ml) at 0^oC was added vinylmagnesium bromide solution (59 ml of a 1 M solution in THF, 59 mmol). After stirring for 2 hours at ambient temperature, saturated ammonium chloride solution was added followed by wet ether (150 ml) and concentrated ammonia solution (300 ml). The mixture was stirred vigorously until a deep blue phase was

produced. The organic layer was separated and washed with dilute HCl (250 ml) followed by sodium bicarbonate solution (200 ml). After drying ($MgSO_4$) 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^oC, 0.035 mmHg) to give the title compound as a colourless oil (11.64 g, 69%).

υ_{max} (film): 2900s, 1638m and 1410s.

δ_H (100 MHz): 3.24-3.6 (2H, m, benzylic protons), 4.91-5.25 (2H, m, CHC$\underline{H}_2$), 5.73-6.20 (1H, m, C$\underline{H}$CH_2), 6.02 (2H, s, OC$\underline{H}_2$O) and 6.72 (2H, s, aryl protons).

δ_C (90.6 MHz): 43.3 (CH_2), 77.9 (CI), 100.8 (CH_2), 108.2 (CH), 116.7 (CH_2), 122.3 (CH), 135.7 (C), 136.5 (CH), 144.7 (C) and 149.9 (C).

High resolution: 287.9628; $C_{10}H_9IO_2$ requires 287.9648.

m/z (%): 288 (M^+, 100), 261 (9), 131 (26) and103 (34).

2-Iodo-3,4-dimethoxy-1-(2'-propenyl) benzene (160).

This was prepared according to the previous procedure in 70% yield.

υ_{max} (film): 2950s, 1642m and 1590s.

δ_H (270 MHz): 3.47 (2H, d, **J** 5.5 Hz, benzylic protons), 3.82 (3H, s, OC$\underline{H}_3$), 3.82 (3H, s, OC$\underline{H}_3$), 5.02-5.12 (2H, m, CHC$\underline{H}_2$), 5.85-5.98 (1H, m, C$\underline{H}$CH_2), 6.82 (1H, d, **J** 8.5 Hz, aryl proton) and 6.92 (1H, d, **J** 8.5 Hz, aryl proton).

δ_H (67.5 MHz): 44.35 (CH_2), 55.95 (CH_3), 60.07 (CH_3), 99.58 (C), 112.28 (CH), 116.27 (CH_2), 124.60 (CH), 135.57 (C), 136.15 (CH), 148.71 (C) and 150.69 (C).

m/z (%): 304 (58) and 84 (100).

2-Hydroxy-3-iodo-1-methoxy-4-(2-propenyl) benzene .

This was prepared according to the previous procedure except 2 equivalents of vinylmagnesium bromide were added and the reaction mixture was worked up with saturated ammonium chloride solution and ether to give a white solid in 42% yield. M.p. 58-60^{o}C.

υ_{max} (CH_2Cl_2): 3500br, 2850s, 1640w, 1600w and 1490s.

δ_H (270 MHz): 3.46-3.49 (2H, m, $C\underline{H}_2CHCH_2$), 3.88 (3H, s, $OC\underline{H}_3$), 5.04-5.14 (2H, m, $CH_2CHC\underline{H}_2$), 5.88-6.03 (1H, m, $CH_2C\underline{H}CH_2$), 6.21 (1H, s, O<u>H</u>) and 6.78 (2H, s, aryl protons).

δ_C (67.5 MHz): 44.16 (CH_2), 56.43 (CH_3), 116.40 (CH_2), 88.56 (C), 110.45 (CH), 116.40 (CH_2), 120.43 (CH), 135.73 (C), 136.35 (CH), 144.28 (C) and 145.65 (C).

m/z (%): 290 (M^+, 100), 275 (15), 263 (12) 131 (28) and 103 (31).

3-Bromo-2-hydroxy-1-methoxy-4-(2-propenyl) benzene (130).

This was prepared according to the previous procedure except 3 equivalents of vinylmagnesium bromide were used and the reaction mixture worked up with saturated ammonium chloride solution and ether to give the title compound as a white solid in 49% yield. M.p.

51-53°C.

υ_{max} (CH_2Cl_2): 3500br, 1642m and 1612m.

δ_H (270 MHz): 3.48 (2H, d, **J** 1.35 Hz, C<u>H</u>$_2$Ar), 3.90 (3H, s, OC<u>H</u>$_3$), 5.02-5.12 (2H, m, CHC<u>H</u>$_2$), 5.89-6.03 (2H, m, C<u>H</u>CH$_2$ and O<u>H</u>), 6.75 (1H, d, **J** 8.3 Hz, aryl proton) and 6.79 (1H, d, **J** 8.3 Hz, aryl proton).

δ_C (67.5 MHz): 39.71 (CH_2), 56.50 (CH_3), 109.77 (CH), 113.13 (CBr), 116.32 (CH_2), 120.61 (CH), 132.62 (C), 136.12 (CH), 143.26 (C) and 145.61 (C).

High resolution: 241.9950; $C_{10}H_{11}O_2Br$ requires 241.9942.

m/z (%): 242 (M^+, 100), 227 (32), 215 (26), 148 (23), 131 (63) and 103 (47).

Alternative procedure for (130).

A suspension of aromatic bromide (127) (1 g, 5.1 mmol), tri-n-butylvinyltin (1.3 g, 5.1 mmol), and palladium *tetrakis*triphenylphosphine (50 mg, 0.046 mmol) in THF (50 ml) was heated to 50°C for thirty hours. The mixture was allowed to cool and then the solvent was removed *in vacuo* to give the crude product. Suction flash chromatography gave the title compound with physical and spectral properties identical to that documented previously.

2-Bromo-3-hydroxy-4-methoxy-1-(1-propenyl) (131).

When the preceeding method is scaled up to the 20 g level, mixtures of aromatic bromide (130) and the corresponding styrene

(131) are obtained. On one occasion the above procedure furnished exclusively (131).

$\upsilon_{max}(CH_2Cl_2)$: 3500br and 1610m.

δ_H (270 MHz): 1.90 (2H, d, **J** 5.1 Hz, $C\underline{H}_3CH$), 3.88 (3H, s, $OC\underline{H}_3$), 5.96 (1H, s, $O\underline{H}$), 6.03-6.19 (1H, dq, **J** 16 Hz and 6.5 Hz, $CHC\underline{H}CH_3$), 6.67 (1H, d, **J** 16 Hz, $ArC\underline{H}$), 6.77 (1H, d, **J** 9.7 Hz, aryl proton) and 7.02 (1H, d, **J** 9.7 Hz, aryl proton).

δ_C (65.7 MHz): 18.63 (CH_3), 56.43 (OCH_3), 109.73 (C), 109.90 (CH), 117.48 (CH), 127.35 (CH), 129.51 (CH), 131.48 (C), 142.90 (C) and 145.88 (C).

m/z (%): 242 (M^+, 100), 227 (47) and 91 (44).

4-Bromomethyl-3-iodo-1,2-(1,3)-benzodioxole (70).

Freshly distilled phosphorus tribromide (16 ml, 0.17 mol) was added to a stirred solution of the benzyl alcohol (69) (30 g, 0.11 mol) in dichloromethane (800 ml) at 0°C. The reaction mixture was allowed to attain room temperature over 1 hour with stirring before being poured into a large vessel containing sodium bicarbonate solution. The organic layer was separated and the aqueous layer washed with dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude solid product. Recrystallisation from cyclohexane gave the title compound as white needles (33.6 g, 91%). M.p. 122-125°C. (Found: C, 28.2%, H,1.8%. $C_8H_6BrIO_2$ requires C, 28.2%, H, 1.8%).

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

δ_H (250 MHz): 4.60 (2H, s, $C\underline{H}_2Br$), 6.05 (2H, s, $OC\underline{H}_2O$), 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_2), 76.9 (Cl), 101.0 (CH_2), 108.2 (CH), 124.1 (CH), 133.0 (C), 146.2 (C) and150.3 (C).

m/z (%): 341 (M^+, 6) and 261 (100).

2-Bromo-3-hydroxy-4-methoxy-benzylbromide (127).

This was prepared using the same procedure as before to give the title compound as white needles in 77% yield. M.p. 93-94°C.

υ_{max} (CH_2Cl_2): 3400br, 1605m and 1490s.

δ_H (360 MHz): 3.88 (3H, s, $OC\underline{H}_3$), 4.61 (2H, s, $C\underline{H}_2Br$), 6.1 (1H, s, O<u>H</u>), 6.75 (1H, d, J 8.5 Hz, aryl proton) and 7.05 (1H, d, J 8.5 Hz, aryl proton).

δ_C (90.6 MHz): 34.11 (CH_2), 56.52 (OCH_3), 109.78 (CH), 110.82 (C), 122.13 (CH), 130.08 (C) 143.82 (C) and 147.34 (C).

3-Methoxy-2-cyclohex-1-one (55).

1,3-Cyclohexadione (31 g, 0.28 mol), methanol (75 ml), concentrated sulphuric acid (1 ml) magnesium sulphate (55 g) 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 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 the title compound as a colourless oil which solidified in the fridge to a low melting white solid (31.5 g, 90%).

υ_{max} (film): 2960s, 1660s and1610s.

δ_H (360 MHz): 1.97 (2H, quintet, J 6 Hz, C$\underline{H}_2$), 2.29 (2H, t, J 6 Hz, C$\underline{H}_2$), 2.42 (2H, t, J 6 Hz, C$\underline{H}_2$), 3.71 (3H, s, OC$\underline{H}_3$) and 5.33 (1H, s, C$\underline{H}$).

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 (CH_3) and198.6 (CO).

3-[4-(2-propenyl)-1,2-(1,3)-benzodioxol-3-yl]-2-cyclohexen-1-one (72).

A flask charged with a mixture of the aromatic iodide (71) (10.1 g, 35 mmol) and magnesium turnings (0.84 g, 35 mmol) in ether (30 ml) was heated in a ultrasonic cleaning bath to boiling for 24 minutes. Cyclohexane (30 ml) was added to give a two phase solution which was stirred vigorously and then brought to reflux. 3-methoxy-2-cyclohexen-1-one (55) (6.1 g, 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 mixture was allowed to cool. Dilute hydrochloric acid (50 ml) was added and the reaction mixture stirred until all the gummy residue had dissolved. The aqueous layer was separated from the organic phase and washed with ether. The combined organic extracts were then washed with sodium bicarbonate solution, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Chromatography (petrol:ether, 1:1) gave the title compound as an almost colourless viscous oil (5.53 g, 62%). (Found: C, 74.7%, H, 6.4%. $C_{16}H_{16}O_3$ requires C,74.4% H, 6.3%).

λ_{max}: 235 nm (ε 14,000 dm^3 mol^{-1} cm^{-1}) and 268nm

(ε 7920).

υ_{max} (film): 2890m, 1669s, 1640m and 1450s.

δ_H (100 MHz): 1.96-2.70 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 3.21-3.38 (2H, m, benzylic protons), 4.92-5.17 (2H, m, $CHC\underline{H}_2$), 5.60-6.08 (2H, m, $C\underline{H}CH_2$ and $COC\underline{H}C$), 5.96 (2H, s, $OC\underline{H}_2O$) 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 (CH_3), 108.1 (CH), 116.0 (C), 122.7 (CH), 123.0 (CH), 129.9 (CH_2), 130.0 (CH), 137.6 (C), 144.3 (C),145.9 (C), 157.5 (C) and199.0 (CO).

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

m/z (%): 256 (M^+, 61), 228 (100), 200 (46) and185 (44).

3-[4-(2-Propenyl)-1,2-dimethoxy-3-phenyl]-2-cyclohexen-1-one (162).

This was prepared according to the previous procedure in 23% yield to give a pale yellow oil.

υ_{max} (film): 2950s, 1665s, 1640m and 1630m.

δ_H (270 MHz): 2.11-2.80 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 3.21-3.40 (2H, m, $C\underline{H}_2CHCH_2$), 3.74 (3H, s, $OC\underline{H}_3$), 3.85 (3H, s, $OC\underline{H}_3$), 4.84-5.03 (2H, m, $CHC\underline{H}_2$), 5.59-5.95 (2H, m, $C\underline{H}CH_2$ and $C\underline{H}CO$), 6.85 (1H, d, **J** 9.5 Hz, aryl proton) and 6.93 (1H, d, **J** 9.5 Hz, aryl proton).

3-[4-(2-propenyl)-1,2-(1,3-benzodioxol)-3-yl]-2-cyclohexen-1-ol (73).

Sodium borohydride (2.5 g, 66 mmol) was added in portions over 10 mins to a stirred solution of the enone (72) (16.7 g, 65 mmol) and cerium (III) chloride (24.1 g, 65 mmol) in methanol (100 ml). After stirring for 1.5 hours, dilute hydrochloric acid was added slowly. When the effervescence had ceased, the solvent was removed *in vacuo* . The residue was partitioned between sodium bicarbonate solution (100 ml) and ether (200 ml) and the organic phase was separated. The aqueous phase was washed with ether and the combined organic layers were dried ($MgSO_4$) and removed *in vacuo* to give the crude product. Suction flash chromatography followed by distillation (b.p. 166-170^{o}C, 0.06 mmHg) gave the title compound as a colourless viscous oil (15.58 g, 93%). (Found: C, 74.2%, H, 7.2%. $C_{16}H_{18}O_3$ requires C, 74.4%, H, 7.0%).

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

υ_{max} (CCl_4): 3400br, 2940s and1640m.

δ_H (100 MHz): 1.37-2.60 (7H, m, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$, and O<u>H</u>), 3.08-3.34 (2H, m, benzylic protons), 4.32 (1H, m, C<u>H</u>OH), 4.70-5.10 (2H, m, CHC<u>H</u>$_2$), 5.33-6.08 (2H, m, C<u>H</u>CH$_2$ and C<u>H</u>CAr), 5.87 (2H, s, OC<u>H</u>$_2$O) 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 (CH), 100.7 (CH_2), 107.0 (CH), 115.5 (CH_2), 122.4 (CH), 124.8 (C), 130.5 (CH), 131.1 (C), 135.9 (C), 138.3 (CH), 144.7 (C) and145.4 (C).

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

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

3-[4-(2-Propenyl)-1,2-dimethoxy-3-phenyl]-2-cyclohexen-1-ol (165).

This was produced using the same procedure as before to give the title compound as a colourless oil in 90%.

υ_{max} (film): 3450 br, 2950s and 1645m.

δ_H (270 MHz): 1.67-2.40 (7H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$ and O$\underline{H}$), 3.18-3.44 (2H, m, $C\underline{H}_2CHCH_2$), 3.77 (3H, s, $OC\underline{H}_3$), 3.85 (3H, s, $OC\underline{H}_3$), 4.32 (1H, bs, C$\underline{H}$OH), 4.95-5.10 (2H, m, $CHC\underline{H}_2$), 5.61 (1H, bs, C$\underline{H}$CHOH), 5.8-6.0 (1H, m, C$\underline{H}CH_2$), 6.80 (1H, d, **J** 8.5 Hz, aryl proton), 6.90 (1H, d, **J** 8.5 Hz, aryl proton).

δ_C (67.5 MHz): 19.45 (CH_2), 30.25 (CH_2), 31.69 (CH_2), 36.83 (CH_2), 55.99 (CH_3), 61.29 (CH_3), 65.91 (CH), 111.07 (CH), 115.52 (CH_2), 124.82 (CH), 128.59 (CH), 128.89 (CH), 130.19 (C), 130.62 (C), 138.42 (C), 138.68 (CH) and 146.10 (C).

N,N-Dimethyl-1-[4-(2-propenyl),-1,2-(1,3-benzodioxol)-3-yl]-2-cyclohexen-1-acetamide (74).

Freshly distilled N,N-dimethylacetamide dimethylacetal (21.2 ml, 145 mmol) was added to a solution of the allylic alcohol (73) (10.3 g, 40 mmol), in toluene (300 ml) at reflux. Heating was continued for a further 16 hours (during this time methanol was removed from the system by passing the distillate through a pressure equalising dropping funnel charged with 4A molecular

sieves). The reaction mixture was allowed to cool and was washed with dilute hydrochloric acid (100 ml) followed by sodium bicarbonate solution (100 ml) and then dried ($MgSO_4$). The solvent volume was concentrated *in vacuo* to give a brown oil which solidified on standing. Suction flash chromatography gave a white solid which was recrystallised from petrol (boiling range 80-100°C) to give the title compound as white needles (7.57 g, 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%).

υ_{max} (CCl_4): 2930m, 1662s and1430m.

δ_H (100 MHz): 1.32-2.04 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 2.61 (1H, d, **J** 17 Hz, C<u>H</u>HCON), 2.85 (3H, s, $NC\underline{H}_3CH_3$), 2.97 (3H, s, $NCH_3C\underline{H}_3$), 3.51 (1H, d, **J** 17 Hz, CH<u>H</u>CON), 3.57-3.76 (2H, m, benzylic protons), 4.80-5.10 (2H, m, $CHC\underline{H}_2$), 5.55-6.17 (2H, m, C<u>H</u>CH_2 and C<u>H</u>$CHCH_2$), 5.74 (1H, d, **J** 1.5 Hz, OC<u>H</u>HO), 5.85 (1H, d, **J** 1.5 Hz, OCH<u>H</u>O), 6.53 (1H, t, **J** 2 Hz, $CHC\underline{H}CH_2$) 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 (CH_2), 106.5 (CH), 114.7 (CH_2), 125.1 (CH), 125.6 (CH), 129.4 (C), 133.1 (C), 136.5 (CH), 139.7 (CH), 144.7 (C),145.3 (C) and171.2 (CO).

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

N,N-Dimethyl-1-[4-(propan-2,3-diol)-1,2-(1,3-benzodioxol)-3-yl]-2-cyclohexene-1-acetamide (75).

A solution of the amide (74) (4.52 g, 13.8 mmol) in THF/H_2O/t-BuOH (30:4:1) was stirred for 25 hours with osmium tetroxide (4 ml of a 0.5 w/v solution in t-butanol) and trimethylamine-N-oxide dihydrate (3.07 g, 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 with dichloromethane, dried ($MgSO_4$) and the solvent removed *in vacuo* to give the crude product. Suction flash chromatography (ethyl acetate) gave the title compound as a gum. (4.59 g, 92%).

υ_{max} (CH_2Cl_2): 3400br, 2940m and1636s.

δ_H (360 MHz): 1.3-3.2 (10H, m, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$, C<u>H</u>$_2$CO, O<u>H</u> and O<u>H</u>), 2.82 (3H, s, NC<u>H</u>$_3$CH$_3$), 2.97 (3H, s, NCH$_3$C<u>H</u>$_3$), 3.4-4.1 (5H, m, C<u>H</u>$_2$OH, C<u>H</u>OH and benzylic protons), 5.7-5.9 (3H, m, OC<u>H</u>$_2$O and C<u>H</u>CHCH$_2$) and 6.4-6.8 (3H, m, CHC<u>H</u>CH$_2$ and aryl protons).

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

m/z (%): 361 (M^+, 3), 301 (10), 214 (85) and 87(100).

N,N-Dimethyl-1-(4-(2-formaldehyde)-1,2-(1,3)-benzodioxol-3-yl)-2-cyclohexene-1-acetamide (76).

The diol (75) (7.31 g, 20.2 mmol) and sodium periodate (7.5 g, 35.1 mmol) were dissolved in THF/H_2O (2:1, 210 ml) at ambient temperature and trifluoroacetic acid (1 ml) was added. The

reaction mixture was stirred for 30 min during which a white precipitate formed. Sodium bicarbonate solution (50 ml) was added and the product extracted into ether. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give the the title compound as a gum (6.67 g, 100%).

υ_{max} ($CHCl_3$): 2940s, 1718s and1639s.

δ_H (360 MHz): 1.2-3.0 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 2.49 (1H, d, **J** 17 Hz, C<u>H</u>HCON), 2.83 (3H, s, $NC\underline{H}_3CH_3$), 2.97 (3H, s, $NCH_3C\underline{H}_3$), 3.59 (1H, d, C<u>H</u>HCON), 3.80 (1H, d, **J** 18 Hz, CH<u>H</u>CHO), 4.27 (1H, d, **J** 18 Hz, C<u>H</u>HCHO), 5.73 (1H, dt, **J** 10.3 and 3.5 Hz, $CHC\underline{H}CH_2$), 5.82 (1H, s, OC<u>H</u>HO), 5.89 (1H, s, OCH<u>H</u>O), 6.46 (1H, d, **J** 10.3 Hz, $C\underline{H}CHCH_2$), 6.52 (1H, d, **J** 8 Hz, aryl proton), 6.65 (1H, d, **J** 8 Hz, aryl proton) and 9.68 (1H, s, C<u>H</u>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 (C), 44.0 (CH_2), 49.7 (CH_2), 99.7 (CH_2), 106.6 (CH), 126.6 (C), 127.0 (CH), 127.3 (CH), 130.0 (C), 136.3 (CH), 145.0 (C), 146.6 (C), 171.0 (C) and 200.9 (C).

High resolution: 329.1574; $C_{19}H_{23}NO_4$ requires 329.1627.

m/z (%): 329 (M^+, 3), 301 (15), 242 (9), 214 (34), 214 (34) and 87 (100).

(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 (78).

To the aldehyde (76) (1 g, 3.0 mmol) in benzene (35 ml) at reflux was added N-methylhydroxylamine (300 mg, 6.4 mmol). The water was removed from the reaction mixture with a Dean and Stark apparatus. The reaction mixture was heated under reflux for two hours and then allowed to cool. The solvent was removed *in vacuo* to give the crude product as a brown solid. Suction flash chromatography (petrol/acetone eluent) gave the title compound as a fawn coloured solid (250 mg, 23%).

υ_{max} (CH_2Cl_2): 2930s, 1640s, 1441m and 1049m.

δ_H (270 MHz): 1.2-2.3 (7H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$ and $C\underline{H}$), 2.7-3.3 (5H, m, $C\underline{H}_2CO$, $ArC\underline{H}_2$ and $NC\underline{H}$), 2.80 (3H, s, $NC\underline{H}_3$), 2.86 (3H, s, $NC\underline{H}_3$), 2.99 (3H, s, $NC\underline{H}_3$), 3.24 (1H, m, $C\underline{H}O$), 5.86 (1H, d, **J** 1.5 Hz, $OC\underline{H}HO$), 5.87 (1H, d, **J** 1.5 Hz, $OC\underline{H}HO$) and 7.26 (2H, s, aryl protons).

δ_C (67.5 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_2), 106 .6 (CH), 122.8 (CH), 127.7 (C), 128.8 (C), 144.3 (C), 145.9 (C) and 170.7 (C).

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).

(7α,8β,11aα)-6,7,8,9,10,11-Hexahydro-8-hydroxy-N,N-dimethyl-7-(methylamino)phenenthro[3,4-d]-1,3-dioxole-11a(7aH)-acetamide (80).

The isoxazolidine (78) (240 mg, 0.7 mmol) in methanol (10 ml) was stirred overnight with a catalytic amount of palladium (II) chloride (10 mol%) under an atmosphere of nitrogen (3.1 bar). The reaction mixture was filtered through celite and the solvent volume concentrated *in vacuo* to give a brown oil. The oil was diluted with dichloromethane (25 ml) and washed with sodium hydroxide solution. The organic layer was separated from the aqueous layer and dried ($MgSO_4$) and the solvent removed *in vacuo* to give the title compound as a brown oil (193 mg, 80%).

υ_{max} (CH_2Cl_2): 2940s, 1643s and 1444s.

δ_H (270 MHz): 1.2-2.0 (9H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$, C<u>H</u> and O<u>H</u>), 2.6-3.2 (5H, m, $ArC\underline{H}_2$, C<u>H</u>N and $C\underline{H}_2$), 2.55 (3H, s, $NC\underline{H}_3$), 2.82 (3H, s, $NC\underline{H}_3$), 3.02 (3H, s, $NC\underline{H}_3$), 4.0-4.2 (1H, m, C<u>H</u>OH), 5.82 (1H, d, **J** 1.5 Hz, OC<u>H</u>HO), 5.86 (1H, d, **J** 1.5 Hz, OCH<u>H</u>O), 6.55 (1H, d, **J** 8 Hz, aryl proton) and 6.61 (1H, d, **J** 8 Hz, aryl proton).

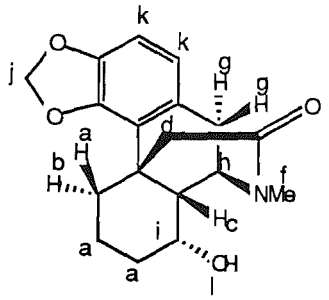
High resolution: 360.2046; $C_{20}H_{28}N_2O_4$ requires 360.2049.

m/z (%): 360 (M^+, 3), 242 (100) and 87 (69).

dl-8-Hydroxy-17-methyl-3,4-methylenedioxy-morphinan-16-one (82).

To a solution of the amino alcohol (80) (0.5 g, 1.39 mmol) in

dichloromethane (3 ml) was added a solution of anhydrous hydrogen chloride in ether (2.2 ml, 0.95 mol). 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 a 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 (0.38 g, 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%).



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

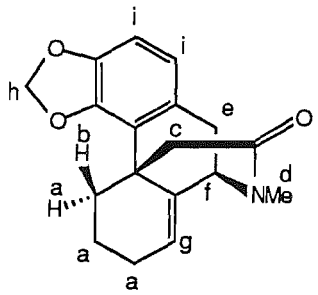
δ_H (360 MHz): 0.9-1.9 (6H, m, a and l), 2.02 (1H, t, **J** 3 Hz, c), 2.34 (1H, d, **J** 17.5 Hz, d), 2.58 (1H, d, **J** 17.5 Hz, d), 2.80 (1H, d, **J** 17 Hz, e), 2.98 (3H, s, f), 3.2-3.3 (1H, m, b), 3.63 (2H, dd, **J** 17 Hz and 5Hz, g), 3.75 (1H, t, **J** 3.8 Hz, h), 4.1-4.2 (1H, m, i), 5.85 (1H,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

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

m/z (%): 315 (M^+, 59), 297 (10), 254 (35) and 42 (100).

8,14-Didehydro-17-methyl-3,4-methylenedioxy-morphinan-16-one (84).

Phosphorus oxychloride (4 ml) was added to a stirred solution of the alcohol (82) (0.5 g, 1.59 mmol) in pyridine (15 ml) at 5°C. The reaction was stirred overnight and then poured on to crushed ice (20 g). (care!). The aqueous phase was extracted with ether (5x10 ml) and the ether layer then washed with sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and then concentrated *in vacuo*. Flash chromatography (ethyl acetate) gave the title compound as a foam (0.32 g, 68%). (Found C, 72.5%, H, 6.5%, N, 4.7%. $C_{22}H_{19}NO_3$ requires C, 72.7%, H, 6.4%, N, 4.7%).



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

δ_H (360 MHz): 1.5-2.2 (5H, m, a) 2.50 (1H, dt, **J** 14 Hz and 3 Hz, b), 2.68 (2H, s, c), 2.90 (3H, s, d), 2.94 (1H, dd, **J** 16.3 Hz and 2.5 Hz, e), 3.11 (1H, dd, **J** 16 Hz and 2.5 Hz, e), 3.98 (1H, t, **J** 2.6 Hz, f), 5.82 (1H, dd, **J** 5.3 Hz and 2.2 Hz, g), 5.89 (1H, d, **J** 7.9 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 (C), 61.3

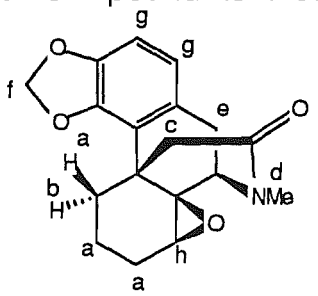
(CH), 100.6 (CH_2), 107.4 (CH), 121.8 (CH), 122.2 (CH), 126.0 (C), 126.3 (C), 135.2 (C), 144.8 (C), 146.7 (C) and 169.9 (C).

High resolution: 297.1335; $C_{16}H_{19}NO_3$ requires 297.1365.

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

dl-(8β,14β),-8,14-Epoxy-17-methyl-3,4-methylenedioxy-morphinan-16-one (93).

The alkene (84) (0.3 g, 1.01 mmol) was stirred in dichloromethane (10 ml) for 48 hours at ambient temperature with *m*CPBA (350 mg, 1.01 mmol). The reaction mixture was then diluted with sodium bisulphite solution (5 ml) and then poured into sodium bicarbonate solution (5 ml). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Flash chromatography gave the title compound as a foam (0.184 g, 58%).



υ_{max} (CH_2Cl_2): 2950m, 1643s, 1448s and1243m.

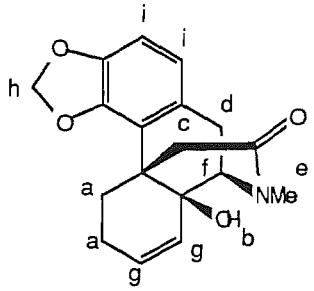
δ_H (360 MHz): 0.9-1.6 (3H, m, a), 1.7-2.2 (2H, m, a), 2.5-2.6 (1H, m, b), 2.65 (1H, d, J 16.8 Hz, c), 2.78 (1H, d, J 16.8 Hz, c), 2.89 (3H, s, d), 2.9-3.4 (4H, m, e, h), 5.87 (1H, d, J 1.5 Hz, f), 5.95 (1H, d, J 1.5 Hz, f), 6.58 (1H, d, J 8 Hz, g) and 6.70 (1H, d, J 8 Hz, g).

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 (CH), 60.9 (CH), 61.3 (C), 100.6 (CH_2), 108.0 (CH), 123.0 (CH), 126.6 (C), 129.8 (C), 144.7 (C), 146.6 (C) and 168.9 (C).
High resolution:	313.1316; $C_{18}H_{19}NO_4$ requires 313.1314.
m/z (%):	313 (M^+, 31), 242 (34), 205 (18), and 83 (100).

dl(14β)-7,8-Didehydro-14-hydroxy-17-methyl-3,4-methylenedio xy-morphinan-16-one (94).

To the epoxide (93) (166 mg, 0.53 mmol), in n-propanol (4 ml) was added a solution of phenyl selenide (prepared by the addition of sodium borohydride on diphenyldiselenide) in n-propanol. The reaction mixture was brought to reflux and heating continued for 1.5 hours before cooling to 0°C. The reaction mixture was diluted with THF (1 ml) followed by dropwise addition of hydrogen peroxide solution (30%, 0.65 ml). The reaction mixture was stirred at less than 20°C for 1.5 hours and then poured into water (2 ml). The reaction mixture was then diluted with ethyl acetate and the ethyl acetate phase was washed with sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and the solvent volume removed *in vacuo* to give the crude product. Flash chromatography (acetone:petrol, 2:1) gave the title compound as a white solid (88 mg, 53%).

139



υ_{max} (CH_2Cl_2): 3680w, 2920m, 1633s and 1447s.

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** 8Hz, i).

δ_C (90 MHz): 22.3 (CH_2), 23.5 (CH_2), 30.8 (CH_2), 32.8 (CH_3),

$(CD_3)_2SO$) 39.6 (C), 41.4 (CH_2), 62.4 (CH), 65.7 (C), 100.2 (CH_2), 107.1 (CH), 122.0 (CH),122.8 (C), 123.3 (C), 128.6 (CH), 130.1 (CH), 144.6 (C), 145.2 (C) and 168.1 (C).

m/z (%): 313 (M^+, 100), 242 (16) and 212 (15).

2-Allyl-3-iso-butoxy-2-cyclohexenone.

A solution of 2-allyl-1,3-cyclohexanedione (4.95 g, 32.5 mmol), *iso*-butanol (80 ml) and CSA (10 mg) in dry benzene (250 ml) was heated to reflux for six hours. The water produced was collected by a Dean and Stark separator. The solution was allowed to cool and was then concentrated *in vacuo* to give a red/brown oil which was purified by suction flash chromatography to yield the title compound (5.41 g, 80%).

υ_{max} (CCl_4): 3090w, 2850s, 1665s, 1625s, 1360s and1240s.

δ_H (60 MHz): 0.99 (6H, d, **J** 7 Hz, $HCC\underline{H}_3C\underline{H}_3$), 1.5-2.3 (5H, m, $C\underline{H}_2C\underline{H}_2$ and $C\underline{H}Me_2$), 2.4-2.7 (2H, m, $C\underline{H}_2CO$), 2.9 (2H, bd, **J** 7 Hz, $C\underline{H}_2CHCH_2$), 3.75 (2H, d, **J** 7 Hz, $OC\underline{H}_2$), 4.7-5.1 (2H, m, $CH_2CHC\underline{H}_2$) and 5.3-6.0 (1H, m, $CH_2C\underline{H}CH_2$).

1,1-Dimethyl-6,7-(1,3-methylenedioxy)-3-isochromanylmethanol (116).

A suspension of acetal (115) (1 g, 4.25 mmol), magnesium (1.2 g, 0.05 mol), and 1,2-dibromoethane (4 ml, 0.044 mol), in ether (20 ml) was heated in an ultrasonicator for 24 minutes. The ultrasonicator was then removed and the reaction mixture was allowed to stir at room temperature for a further 10 hours. The reaction mixture was then diluted with wet ether (50 ml) and then poured into water (50 ml). The organic phase was separated from the aqueous phase and the aqueous phase was diluted with ether again. The organic extracts were combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to give a white solid. Suction flash chromatography yielded the title compound as a white solid (900 mg, 90%). M.p. 88-90^{o}C.

υ_{max} (CH_2Cl_2): 3600br, 1510s and 1490s.

δ_H (270 MHz): 1.48 (3H, s, $C\underline{H}_3$), 1.49 (3H, s, $C\underline{H}_3$), 2.44 (1H, dd, **J** 16 Hz and 3 Hz, $ArC\underline{H}H$), 2.49 (1H, bs, $O\underline{H}$), 5.89 (2H, s, $OC\underline{H}_2O$), 6.52 (1H, s, aryl

proton) and 6.58 (1H, s, aryl proton).

δ_C (67.5 MHz): 28.68 (CH_3), 31.00 (CH_2), 31.50 (CH_3), 65.79 (CH_2), 69.41 (CH), 75.58 (C), 100.85 (CH_2), 105.38 (CH), 108.51 (CH), 125.35 (C), 135.78 (C), 145.90 (C) and 146.17 (C).

m/z (%): 236 (M^+, 24), 221 (100), 135 (36), 117 (33) and 43 (23).

3-Hydroxy-4-methoxy-2-butyl-1-benzaldehyde (150).

A suspension of bromoisovanillin (250 mg, 1.08 mmol), $Pd(PPh_3)_4$ (30 mg, 0.00026 mmol), and freshly distilled hexabutylditin (660 mg, 1.29 mmol), in toluene was heated under reflux for 6 hours. The reaction mixture was allowed to cool and then the solvent was removed *in vacuo* to give the crude product. Suction flash chromatography yielded two products, isovanillin and the title compound.

υ_{max} (film): 2850s,1700s and 1610s.

δ_H (270 MHz): 0.77-1.75 (32H, m, $\underline{Bu}_3SnBr$ and $C\underline{H}_2C\underline{H}_2C\underline{H}_3$), 3.08 (2H, t, **J** 8.1 Hz, $ArC\underline{H}_2$), 3.98 (3H, s, $OC\underline{H}_3$), 5.82 (1H, s, O<u>H</u>), 6.85 (1H, d, **J** 8.2 Hz, aryl proton), 7.42 (1H, d, **J** 8.2 Hz, aryl proton) and 10.11 (1H, s, C<u>H</u>O).

3-Hydroxy-4-methoxy-2-butyl-1-benzylalcohol (151).

To a vigorously stirred solution of $NaBH_4$ (115 mg, 3.06 mmol) in THF/H_2O (10 ml, 1:1) at 0^oC was added a solution of the crude aldehyde (150) (450 mg combined weight containing Bu_3SnBr) in THF (5 ml). Thirty minutes after the completion of the addition,

the solvent in the reaction mixture was concentrated to half its volume and then diluted with ethyl acetate. The aqueous phase was separated from the organic phase and rewashed with ethyl acetate. The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Suction flash chromatography yielded the title compound as a white crystalline solid. (140 mg, 61% yield from bromoisovanillin (125) and homogenous by glc (OV-101)). M.p. 86-87°C.

υ_{max} (CH_2Cl_2): 3500br and 2950s.

δ_H (270 MHz): 0.95 (3H, t, **J** 7.3 Hz, $C\underline{H}_3$), 1.39-1.61 (5H, m, $C\underline{H}_2C\underline{H}_2$ and O<u>H</u>), 2.73 (2H, t, **J** 8.1 Hz, $ArC\underline{H}_2$), 3.88 (3H, s, $OC\underline{H}_3$), 4.64 (2H, s, $C\underline{H}_2OH$), 5.75 (1H, s, Ar<u>O</u>H), 6.71 (1H, d, **J** 8.3 Hz, aryl proton) and 6.87 (1H, d, **J** 8.3 Hz, aryl proton).

δ_C (67.5 MHz): 14.12 (CH_3), 23.21 (CH_2), 25.87 (CH_2), 32.40 (CH_2), 56.04 (CH_3), 63.34 (CH_2), 107.86 (CH), 119.75 (CH), 127.63 (C), 132.20 (C), 143.82 (C) and 146.17 (C).

m/z (%): 210 (M^+, 100), 192 (28), 149 (82) and 137 (32).

2-(2-Bromo-6-phenoxy)-cyclohexane-1-one (173).

To a stirred solution of NaH (690 mg, 0.173 mmol, 60% dispersion in mineral oil) in DMF (15 ml) was added a solution of o-bromophenol (3 g, 0.173 mmol), in DMF (5 ml). The reaction mixture was then stirred efficiently for 10 minutes. A solution of 2-bromocyclohexanone (3.06 g, 0.173 mmol) in DMF (10 ml) was

added dropwise to the reaction mixture. Thirty minutes after the completion of the addition the reaction mixture was diluted with ether (200 ml) and then poured into water (100 ml). The aqueous phase was separated from the organic phase and the organic phase was washed with water again. The ethereal layer was separated from the aqueous layer, dried ($MgSO_4$), and the solvent removed *in vacuo* to give the crude product. Suction flash chromatography gave the title compound as a white solid (1.8 g, 44%).

υ_{max} (CH_2Cl_2): 2955s and 1720s.

δ_H (270 MHz): 1.59-2.54 (8H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 4.54 (1H, dd, J 9 and 4.9 Hz, OC<u>H</u>) and 6.6-7.43 (4H, m, aryl protons).

δ_C (67.5 MHz): 22.32 (CH_2), 27.80 (CH_2), 34.34 (CH_2), 40.16 (CH_2), 81.80 (CH), 112.87 (C), 115.59 (CH), 122.80 (CH), 128.32 (CH), 133.41 (CH), 154.09 (C) and 208.07 (C).

2-[2-Bromo-3-(2-propenyl)-6-methoxyphenoxy]-cyclohexane-1-one.

This was obtained by the same procedure as above in 36% yield.

υ_{max}: (CH_2Cl_2): 1720s and 1640m.

δ_H (60 MHz): 1.2-3.3 (8H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 3.45 (2H, d, J 6 Hz, Ar$C\underline{H}_2$), 3.80 (3H, s, $OC\underline{H}_3$), 4.6 (1H, m, C<u>H</u>OAr), 4.8-5.2 (2H, m, $CHC\underline{H}_2$), 5.5-6.2 (1H, m, $C\underline{H}CH_2$), 6.8 (1H, s, aryl proton) and 6.9 (1H, s, aryl proton).

N,N-Dimethyl-1-[4-(2,3-isopropylenedioxypropyl)-1,2-(1,3)-ben zodioxol-3-yl]-2-cyclohexene-1-acetamide (109).

To a suspension of the diol (1.36 g, 3.76 mmol) in dry CH_2Cl_2 (50 ml) at room temperature was added 2,2-dimethoxypropane (50 ml) and pyridinium tosylate (10 mg). The reaction mixture was stirred for 3 hours and then diluted with dichloromethane. The mixture was poured into sodium bicarbonate solution and the organic phase was separated from the aqueous phase. The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo.* Suction flash chromatography yielded the title compound as a white solid (1.1 g, 73%). M.p. 105-107°C.

υ_{max} (CH_2Cl_2): 2850m and 1640s.

δ_H (270 MHz): 1.33 (3H, s, C$\underline{H}_3$), 1.44 (3H, s, C$\underline{H}_3$), 1.23-2.32 (6H, m, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$), 2.54 (1H, d, **J** 16.2 Hz, C$\underline{H}$CO), 2.83 (3H, s, NC$\underline{H}_3$), 2.96 (3H, s, NC$\underline{H}_3$), 3.12-3.29 (2H, m, ArC$\underline{H}_2$), 3.57 (1H, d, **J** 16.2 Hz, C$\underline{H}$CO), 3.57-3.99 (2H, m, CHC$\underline{H}_2$), 4.22-4.37 (1H, m, ArCH$_2$C$\underline{H}$O), 5.72 (1H, d, **J** 1.5 Hz, OC$\underline{H}$HO), 5.85 (1H, d, **J** 1.5 Hz, OCH$\underline{H}$O), 6.60 (1H, t, **J** 5 Hz, CHC$\underline{H}$CH$_2$), 6.65 (1H, d, **J** 8.5 Hz, aryl proton) and 6.71 (1H, d, **J** 8.5 Hz, aryl proton).

δ_C (67.5 MHz): 19.43 (CH_2), 25.23 (CH_2), 26.00 (CH_3), 27.22 (CH_3), 35.43 (CH_3), 35.90 (CH_2), 37.56

(CH_3), 38.13 (C), 43.11 (C), 44.51 (CH_2), 69.12 (CH_2), 77.53 (CH), 99.44 (CH_2), 106.61(CH), 108.81(C), 125.92 (CH), 126.21 (CH), 129.66 (C), 131.65 (C), 136.52 (CH), 144.68 (C), 145.72 (C) and 171.25 (C).

m/z (%): 401 (M^+, 23), 314 (16), 238 (100), 214 (95) and 87 (92).

1-(2-Bromophenoxy)-2-ethoxycarbonylethylidene-cyclohexane (174).

A solution of aromatic bromide (173) (0.5 g, 1.47 mmol) and phosphorane (175) (2.56 g, 7.38 mmol) was stirred at ambient temperature for 36 hours. The reaction mixture was then concentrated *in vacuo* to give the crude product. Suction flash chromatography gave the title compound as a colourless oil (516 mg, 82%).

υ_{max} (film): 1720s and 1660m.

δ_H (270 MHz): 1.17 (3H, t, J 7.2 Hz, $OCH_2C\underline{H}_3$), 1.20-2.46 (7H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}H$), 3.39-3.62 (1H, m, $CH\underline{H}$), 4.06 (2H, q, J 7.2 Hz, $OC\underline{H}_2CH_3$), 4.51-4.55 (1H, m, $C\underline{H}O$), 5.87 (1H, s, $C\underline{H}CO_2Et$), 6.70-7.46 (4H, m, aryl protons).

δ_C (67.5 MHz): 14.30 (CH_3), 23.32 (CH_2), 27.77 (CH_2), 27.82 (CH_2), 34.87 (CH_2), 59.90 (CH_2), 80.43 (CH), 113.21 (C), 113.43 (CH), 115.37 (CH), 122.41 (CH), 128.33 (CH),133.57 (CH), 154.03 (C), 158.91 (C) and 166.62 (C).

m/z (%): 340 (M^+, 2), 293 (8), 167 (100), 139 (52), 121 (62), 93 (42) and 77 (18).

1-(3-Bromo-4-(2-propenyl)-1-methoxy-2-phenoxy)-2-ethoxycar bonylethylidene-cyclohexane (178).

This was prepared according to the previous procedure except the reaction mixture was refluxed for 36 hours to give the title compound as a colourless oil in 64% yield.

υ_{max} (film): 1720s,1660m and 1600w.

δ_H (270 MHz): 1.16 (3H, t, **J** 7.1 Hz, $OCH_2C\underline{H}_3$), 1.12-2.58 (8H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 3.37 (2H, d, **J** 6.3 Hz, $ArC\underline{H}_2$), 3.67 (3H, s, $OC\underline{H}_3$), 4.06 (2H, q, **J** 7.1 Hz, $OC\underline{H}_2CH_3$), 4.51-4.60 (1H, m, $C\underline{H}OAr$), 4.91-5.00 (2H, m, $CHC\underline{H}_2$), 5.78-5.93 (1H, m, $C\underline{H}CH_2$), 5.93 (1H, s, $C\underline{H}CO_2Et$), 6.69 (1H, d, **J** 8.5 Hz, aryl proton) and 6.81 (1H, d, **J** 8.5 Hz, aryl proton).

δ_C (67.5 MHz): 14.30 (CH_3), 22.89 (CH_2), 27.40 (CH_2), 27.54 (CH_2), 34.34 (CH_2), 40.00 (CH_2), 56.82 (OCH_3), 59.61 (CH_2), 83.09 (CH), 114.43 (CH), 113.30 (CH), 116.16 (CH_2), 120.76 (C), 124.62 (CH) 132.75 (C) and 136.03 (C).

m/z (%): 408 (M^+, 1), 365 (8), 242 (100), 167 (23), 131 (32), 121 (33) and 91 (25).

3,4-Epoxy-2-trimethylsilyloxycyclohex-1,3-diene (171).

A solution of LHMDSA, prepared from HMDSA (25 ml, 120 mmol),

and n-BuLi (47 ml, 120 mmol) in THF (200 ml) at -78°C, was charged slowly with a solution of cyclohexenone oxide in THF (30 ml). The reaction mixture was stirred at -78°C for 45 minutes. Et_3N (25 ml) and TMSCl (25 ml) were added and the reaction mixture was allowed to stir at -78°C for a further 4 hours and then at ambient temperature. The reaction mixture was then diluted with pentane (500 ml) and then poured over ice (1000 g). The reaction mixture was washed with chilled 4% HCl (300 ml) followed by chilled $NaHCO_3$ (300 ml). The organic phase was dried ($MgSO_4$) and the solvent volume was concentrated *in vacuo* to give a yellow residue. Distillation gave the title compound as a clear oil (10.6 g, 53%). B.p. 80°C at 2 mmHg.

υ_{max} (film): 1660s and 1600s.

δ_H (60 MHz): 0.2 (9H, s, $Si(C\underline{H}_3)_3$), 0.5-2.2 (4H, m, $C\underline{H}_2C\underline{H}_2$), 2.8 (1H, d, J 6 Hz, $CC\underline{H}O$), 3.4-3.6 (1H, m, $CH_2C\underline{H}O$) and 4.8-5.0 (1H, m, $C\underline{H}$).

3-(Tri-n-butylstannyl)-2-cyclohexen-1-one (133).

To a well stirred solution of tri-n-butylstannyllithium (47.5 mmol) prepared from hexabutylditin (24 ml, 47.5 mmol) and n-butyllithium (31.5 ml, 1.6 M solution, 47.5 mmol) in THF (225 ml) at 0°C, was added in one portion solid phenylthiocopper (7.47 g, 47.5 mmol). The reaction mixture was stirred at 0°C for 15 minutes and became dark red in colour. The reaction mixture was cooled to -78°C and was then slowly charged with a solution of the bromoenone (134) (8.3 g, 47.4 mmol) in THF (225 ml). The reaction mixture was stirred at -78°C for 1 hour, at -20°C for 1

hour and then warmed to room temperature at which it was stirred for a further 1 hour. The reaction mixture was then diluted with ether (500 ml) followed by methanol (5 ml) and the resulting slurry was filtered through a column of florisil (50 g). The florisil column was washed twice with ether (400 ml total) and the combined organic washings were dried ($MgSO_4$) and the solvent removed *in vacuo* to give the crude product. Suction flash chromatography gave the title compound as a clear oil (11.9 g, 65%). The spectroscopic and physical data were in agreement with the literature[77].

3-(Tri-n-butylstannyl)-2-cyclohexen-1-ol (138).

To a well stirred solution of $NaBH_4$ (1.5 g, 39.7 mmol) in THF/H_2O (140 ml, 1:1) at 0^oC was added dropwise a solution of the tin-enone (133) (8 g, 20.8 mmol) in THF (30 ml). The cooling vessel was removed and the reaction mixture was stirred at ambient temperature. Eight hours after completion of the addition the reaction mixture was poured into ether (220 ml) and the organic phase was separated from the aqueous phase. The aqueous phase was washed with ether and the combined organic extracts dried ($MgSO_4$). The solvent was removed *in vacuo* to give a colourless oil (7 g, 87%).

υ_{max} (film): 3350br and 1660m.

δ_H (270 MHz): 0.75-2.16 (35H, m, <u>Bu</u>Sn, O<u>H</u> and C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$), 4.13 (1H, bs, C<u>H</u>OH) and 5.85 (1H, m, C<u>H</u>CHOH).

δ_C (67.5 MHz): 0.9 (CH_2), 13.50 (CH_3), 20.05 (CH_2), 27.80 (CH_2), 29.48 (CH_2), 32.79 (CH_2), 32.83 (CH_2), 66.80

(CH), 139.50 (CH) and 144.56 (C).

3-Methoxymethoxy-4-methoxy-benzaldehyde. To a suspension of isovanillin (124) (22 g, 0.145 mol) in CH_2Cl_2 (200 ml) at room temperature was added a solution of NaOH (6.07 g, 0.15 mol) in H_2O (24 ml). When the isovanillin had completely dissolved, *tetra*-butylammonium hydrogen sulphate (4.95 g, 10 mol%) was added in one portion. Fifteen minutes after the addition of the catalyst, a solution of chloromethyl methyl ether (14.34 g, 0.152 mol) in CH_2Cl_2 (25 ml) was injected into the reaction mixture in 2 ml portions. Eighteen hours after the completion of the addition the dichloromethane phase was separated from the aqueous phase and dried ($MgSO_4$). The solvent volume was concentrated *in vacuo* to give the crude product which was purified by suction flash chromatography to give the title compound as a clear oil (26.1 g, 90%).

υ_{max} (CH_2Cl_2): 3500br, 1605m, 1592m and1510s.

δ_H (270 MHz): 3.12 (3H, s, C$\underline{H}_3$), 3.5-3.6 (3H, s, C$\underline{H}_3$), 4.88 (2H, s, OC$\underline{H}_2$O), 6.63 (1H, d, J 8.3 Hz, aryl proton), 7.14 (1H, dd, J 8.3 and 1.9 Hz, aryl proton), 7.26 (1H, d, J 1.9 Hz, aryl proton) and 9.44 (1H, s, C$\underline{H}$O).

δ_C (67.5 MHz): 55.97 (CH_3), 56.15 (CH_3), 95.13 (CH_2), 110.98 (CH), 114.93 (CH), 126.72 (CH), 129.89 (C), 146.72 (C), 154.88 (C) and 190.56 (CH).

m/z (%): 196 (M^+, 49), 166 (19) and 45 (100).

2- Iodo-3-(methoxymethoxy)-4-methoxy-1-(2-propenyl)benzene.

A suspension of unwashed 60% NaH (44 mg, 1.2 mmol) in DMF (2 ml) at 0°C was treated dropwise with a solution of 2-iodo-3-phenoxy-4-methoxy-1-(2-propenyl)benzene (320 mg, 1.1 mmol) in DMF (4 ml). Thirty minutes after the completion of the addition, chloromethyl methyl ether (96 mg, 1.2 mmol) was injected dropwise into the reaction mixture. The external cooling source was removed and the reaction mixture allowed to stir at ambient temperature for 18 hours. The reaction mixture was diluted with ether and poured into water. The organic phase was separated from the aqueous phase and the aqueous phase was diluted with ether again. The organic layers were combined, dried ($MgSO_4$) and the solvent was removed *in vacuo* to give the crude product. Purification by suction flash chromatography gave the title compound as a colourless oil (280 mg, 76%).

υ_{max} (film): 2950s, 1645m,1597s and 1395s.

δ_H (270 MHz): 3.38 (2H, d, **J** 6.2 Hz, $ArC\underline{H}_2$), 3.58 (3H, s, $OCH_2OC\underline{H}_3$), 3.70 (3H, s, $C\underline{H}_3$), 4.93 (1H, dq, **J** 17 and 1.6 Hz, $CHC\underline{H}_2$), 5.03 (1H, dq, **J** 10.4 and 1.6 Hz, $CHC\underline{H}_2$), 5.06 (2H, s, $OC\underline{H}_2O$), 5.79-5.89 (1H, m, $C\underline{H}CH_2$), 6.74 (1H, d, **J** 6.5 Hz, aryl proton) and 6.84 (1H, d, **J** 6.5 Hz, aryl proton).

δ_C (67.5 MHz): 44.61 (CH_2), 56.05 (CH_3), 58.41 (CH_3), 92.65 (CI), 98.63 (CH_2), 112.42 (CH), 116.34

(CH_2), 124.69 (CH), 135.92 (C), 136.19 (CH), 145.65 (C) and 150.30 (C).

3-Methoxymethoxy-4-methoxy-benzaldehyde .

This was also prepared by the same procedure in 80% yield showing the same physical and spectral properties as stated previously.

2-Bromo-3-methoxymethoxy-4-methoxy-1-(2-propenyl)benzene.

This was prepared by the same procedure in 79% yield.

υ_{max} (film): 2950s, 1640m,1610m and1590m.

δ_H (270 MHz): 3.55 (2H, d, **J** 6 Hz, Ar$C\underline{H}_2$), 3.72 (3H, s, $C\underline{H}_3$), 3.91 (3H, s, $C\underline{H}_3$), 5.10-5.25 (2H, m, $CHC\underline{H}_2$), 5.25 (2H, s, $OC\underline{H}_2O$), 5.95-6.15 (1H, m, $C\underline{H}CH_2$), 6.95 (1H, d, **J** 7.7 Hz, aryl proton) and 7.03 (1H, d, **J** 7.7 Hz, aryl proton).

δ_C (67.5 MHz): 39.8 (CH_2) 55.8 (CH_3), 56.6 (CH_3), 98.3 (CH_2), 112.1 (CH), 114.3 (C), 118.2 (CH_2), 125.6 (CH), 133.4 (C), 136.3 (CH), 143.2 (C) and 152.1 (C).

3-Methoxymethoxy-4-methoxy-1-benzylalcohol.

To a stirred solution of $NaBH_4$ (5.2 g, 0.137 mol) in THF (100 ml) and H_20 (100 ml) at 0^oC was added a solution of 3-methoxymethoxy-4-methoxy-1-benzaldehyde (8.5 g, 0.043 mol) in THF (100 ml) dropwise. The external cooling source was removed and the reaction mixture was stirred at ambient temperature for 2 hours. The solvent was removed *in vacuo* to a volume of 100 ml and then diluted with ether (300 ml). The

organic phase was separated from the aqueous phase and the aqueous phase was washed with ether. The ethereal layers were combined, dried ($MgSO_4$) and the solvent was removed *in vacuo* to give the title compound as a colourless oil (8.3 g, 96%).

υ_{max} (film): 3500br, 1612m and 1592m.

δ_H (270 MHz): 2.85 (1H, bs, O<u>H</u>), 3.38 (1H, s, C<u>H</u>$_3$), 3.75 (3H, s, C<u>H</u>$_3$), 4.43 (2H, s, C<u>H</u>$_2$OH), 5.09 (2H, s, OC<u>H</u>$_2$O), 6.75 (1H, d, **J** 8.3 Hz, aryl proton), 6.84 (1H, dd, **J** 8.3 and 1.92 Hz, aryl proton) and 7.03 (1H, d, **J** 1.92 Hz, aryl proton).

δ_C (67.5 MHz): 55.86 (CH_3), 56.13 (CH_3), 64.60 (CH_2), 95.25 (CH_2), 111.56 (CH), 115.39 (CH), 121.11 (CH), 133.82 (C), 146.19 (C) and 149.03 (C).

m/z (%): 198 (M^+, 70), 168 (37), 108 (38) and 45 (100).

2-Bromo-3-hydroxy-4-methoxyphenyl-1-(propan-2,3-diol) (141).

A solution of the aromatic bromide (130) (3 g, 12.3 mmol) in THF/H_2O/t-BuOH (30:4:1, 175 ml) was stirred for 48 hours with osmium tetroxide (4 ml of a 0.5 w/v solution in t-butanol) and triethylamine-N-oxide dihydrate (2.75 g, 24.6 mmol). The reaction mixture was diluted with sodium metabisulphite and stirred for 30 minutes. The solvent volume was concentrated *in vacuo* to 50 ml and then diluted with ethyl acetate (100 ml). The resulting mixture was poured into water and the organic phase decanted off. The aqueous phase was washed again with ethyl acetate (100 ml) then the organic phases were combined, dried ($MgSO_4$) and

concentrated *in vacuo* to give the crude product which was then used in crude form for the next step. However, a small aliquot was purified (flash column using ethyl acetate as a eluent) to give the title compound.

υ_{max} (CH_2Cl_2): 3600br and 2950s.

δ_H (60 MHz): 2.1- 3.3 (3H, m, ArC<u>H</u>$_2$CO, O<u>H</u> and O<u>H</u>), 3.4-4.2 (6H, m, OC<u>H</u>$_3$,C<u>H</u>$_2$O and C<u>H</u>O), 5.3 (1H, s, ArO<u>H</u>) and 6.8 (2H, bs, aryl protons).

2-Bromo-3-hydroxy-4-methoxy-phenyl-1-(2,3-iso-propylenedio xypropyl) (142).

To a suspension of the crude diol (141) in dichloromethane (50 ml) at room temperature was added 2,2-dimethoxypropane (30 ml) and 3 crystals of pyridinium tosylate (3 mg). The mixture was stirred for 2 hours then diluted with dichloromethane, washed with sodium bicarbonate solution and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a brown oil. Suction flash chromatography yielded the title compound as a white solid (3.4 g, 87%). M.p. 103-105^{o}C.

υ_{max} (CH_2Cl_2): 3600m and 1610m.

δ_H (270 MHz): 1.34 (3H, s, C<u>H</u>$_3$), 1.44 (3H, s, C<u>H</u>$_3$), 3.41 (2H, m, ArC<u>H</u>$_2$), 3.69 (1H, dd, J 8 and 6.6 Hz, C<u>H</u>HO), 3.87 (3H, s, OC<u>H</u>$_3$), 3.98 (1H, dd, J 8 and 6.6 Hz, CH<u>H</u>O), 4.40 (1H, m, CH$_2$C<u>H</u>O), 6.08 (1H, s, ArO<u>H</u>), 6.76 (1H, d, J 8.5 Hz, aryl proton) and 6.81 (1H, d, J 8.5 Hz, aryl proton).

δ_C (67.5 MHz): 25.75 (CH_3), 27.11 (CH_3), 39.62 (CH_2), 56.37 (CH_3), 68.81 (CH_2), 75.27 (CH), 109.21 (C), 109.61 (CH),111.11 (C), 121.62 (CH), 130.07 (C), 143.26 (C) and 145.87 (C).

High resolution: 316.0321; $C_{13}H_{17}BrO_4$ requires 316.0310.

m/z (%): 316 (M^+, 18), 162 (24), 101 (100) and 43 (39).

4-(2,3-Isoproylenedioxypropyl) -1,2-(1,3-Benzodioxole).

This was prepared according to the previous procedure to give the title compound as a colourless oil in 97% yield.

υ_{max} (film): 3000s, 1520s, 1500s and 1260s.

δ_H (270 MHz): 1.28 (3H, s, C$\underline{H}_3$), 1.37 (3H, s, C$\underline{H}_3$), 2.46-2.86 (2H, qd, **J** 6.8 Hz, C$\underline{H}_2$CHO), 3.50-3.56 (1H, m, C$\underline{H}$HO), 3.84-3.90 (1H, m, CH$\underline{H}$O), 4.15-4.20 (1H, m, C$\underline{H}$O), 5.80 (2H, s, OC$\underline{H}_2$O), 6.57 (1H, d, **J** 8 Hz, aryl proton) and 6.64-6.67 (2H, m, aryl protons).

δ_C (67.5 MHz): 25.37 (CH_3), 26.68 (CH_3), 39.47 (CH_2), 68.52 (CH_2), 76.47 (CH), 100.56 (CH_2), 107.87 (CH), 108.72 (C), 109.25 (CH), 121.69 (CH), 131.08 (C), 145.94 (C) and 147.39 (C).

m/z (%): 236 (M^+, 46), 135 (35), 101 (100) and 43 (54).

N,N-Dimethyl-1-[4-(2-propenyl)-1,2-(1,3-benzodioxol)-3-yl]-2, 3-epoxy-cyclohexene-1-acetamide.

To a stirred solution of amide (74) (243 mg, 0.71 mmol) in dichloromethane (4 ml) was added *p*NPBA (200 mg, 1.09 mmol) in one portion. The reaction mixture was stirred for 1 hour where

upon a further 50 mg of *p*NPBA was added. The reaction mixture was stirred for a further 1 hour and was then diluted with saturated sodium bicarbonate solution. The organic phase was decanted off and the aqueous phase was poured into dichloromethane. The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Suction flash chromatography gave the title compound as a white gum (260 mg, 78%).

υ_{max} (CH_2Cl_2): 2850s, 1650s and 1610m.

δ_H (270 MHz): 1.15-2.17 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 2.89 (3H, s, $NC\underline{H}_3CH_3$), 3.03 (3H, s, $NCH_3C\underline{H}_3$), 2.62-3.76 (5H, m, $C\underline{H}_2CO$, benzylic and $C\underline{H}O$), 3.98 (1H, d, **J** 3.7 Hz, $C\underline{H}O$), 5.07-5.39 (2H, m, $CHC\underline{H}_2$), 5.67 (1H, d, **J** 1.5 Hz, $OC\underline{H}HO$), 5.85 (1H, d, **J** 1.5 Hz, $OC\underline{H}HO$), 5.84-6.02 (1H, m, $C\underline{H}CH_2$), 6.65 (1H, d, **J** 8.1 Hz, aryl proton) and 6.71 (1H, d, **J** 8.1 Hz, aryl proton).

δ_C (67.5 MHz): 16.07 (CH_2), 23.84 (CH_2), 34.41 (CH_2), 35.20 (CH_3), 37.26 (CH_3), 37.59 (CH_2), 40.27 (CH_2), 40.40 (C), 99.26 (CH_2), 106.68 (CH), 115.76 (CH_2), 125.57 (CH), 128.17 (C), 131.04 (C), 138.40 (CH), 144.98 (C), 145.26 (C) and 171.76 (C).

m/z (%): 343 (M^+, 4), 276 (25), 256 (20), 238 (100), 87 (75), 77 (74) and 39 (60).

N,N-Dimethyl-1-[4-(2,3-isopropylenedioxypropyl)-1,2-(1,3-benz odioxol)-3-yl]-2,3-epoxy-1-acetamide.

This was prepared using the previous procedure to give the title compound as a white solid (58%). M.p. 120-122°C.

υ_{max} (CH_2Cl_2): 2900s and 1650s.

δ_H (270 MHz): 1.30 (3H, s, C<u>H</u>$_3$), 1.41 (3H, s, C<u>H</u>$_3$), 1.24-2.12 (6H, m, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$), 2.87 (3H, s, NC<u>H</u>$_3$), 3.01 (3H, s, NC<u>H</u>$_3$), 3.04 (1H, d, **J** 18.5 Hz, CH<u>H</u>CO), 2.81-4.06 (5H, m, C<u>H</u>HO, ArC<u>H</u>$_2$ and CHOC<u>H</u>), 3.27 (1H, d, **J** 18.5 Hz, C<u>H</u>HCO), 4.01 (1H, d, **J** 3.1 Hz, C<u>H</u>OCH), 4.02 (1H, m, CH<u>H</u>O), 4.39-4.42 (1H, m, CH_2C<u>H</u>OCH_2), 5.64 (1H, d, **J** 1.5 Hz, OC<u>H</u>HO), 5.82 (1H, d, **J** 1.5 Hz, OCH<u>H</u>O), 6.61 (1H, d, **J** 8 Hz, aryl proton) and 6.68 (1H, d, **J** 8 Hz, aryl proton).

δ_C (67.5 MHz): 16.31 (CH_2), 23.99 (CH_2), 25.89 (CH_3), 27.24 (CH_3), 34.80 (CH_2), 35.42 (CH_3), 37.48 (CH_3), 37.54 (CH_2), 40.54 (CH_2), 40.96 (C), 56.70 (CH), 59.61 (CH), 69.69 (CH_2), 77.15 (CH), 99.51 (CH_2), 106.95 (C), 108.89 (CH), 124.75 (CH), 128.82 (C), 129.77 (C), 145.39 (C), 145.85 (C) and 171.89 (C).

m/z (%): 417 (M^+, 8), 402 (18), 299 (64), 254 (42),

212 (72), 101 (44),87 (77), 72 (100) and 43 (55).

General procedure for the radical cyclisations.

A solution of the substrate in toluene (20 mmol) was heated under reflux for 3 days with 1-2 equivalents of tributyltin hydride and a catalytic quantity of AIBN (5-12%). The reaction mixture was allowed to cool and was then concentrated *in vacuo* to give the crude product. Suction flash chromatography was performed several times in order to obtain a pure product. The Rf values of the products were usually the same (if not similiar) compared to the starting material.

Ethyl (5,6,7,8, 8ab-tetrahydro-dibenzofuran-4b-yl) acetate (176).

υ_{max} (film): 2950s, 1732s and 1600s.

δ_H (270 MHz): 1.10 (3H, t, **J** 7 Hz, $OCH_2C\underline{H}_3$), 1.10-1.84 (8H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 2.51 (2H, s, $C\underline{H}_2CO$), 3.99 (2H, q, **J** 7 Hz, $OC\underline{H}_2CH_3$), 4.64 (1H,dd, **J** 5.1 Hz, $OC\underline{H}$) and 6.70-7.17 (4H, m ,aryl protons).

δ_C (67.5 MHz): 14.27 (CH_3), 19.88 (CH_2), 20.56 (CH_2), 26.85 (CH_2), 32.31 (CH_2), 43.23 (CH_2), 46.22 (C), 60.44 (CH_2), 86.03 (CH), 110.37 (CH), 120.60 (CH), 123.20 (CH), 128.43 (CH), 134.22 (C), 158.81 (C) and 171.15 (C).

m/z (%): 260 (M^+, 44), 173 (100) and 145 (30).

1-Methoxy-9,10,11,12,12ab-hexhydrobenzofuran-8-ethoxycarbon ylspiro[4,8a] heptanyl (179).

υ_{max} (CH_2Cl_2): 2950s, 1742s, 1630w, 1599w and 1510s.

δ_H (360 MHz): 1.16 (3H, t, J 7.1 Hz, $OCH_2C\underline{H}_3$), 1.2-2.6 (14H, m, $7xC\underline{H}_2$), 2.95 (1H, t, J 3.9 Hz, $C\underline{H}CO$), 3.84 (3H, s, $OC\underline{H}_3$), 4.04 (3H, q, J 7.1 Hz, $OC\underline{H}_2CH_3$), 4.51 (1H, t, J 3.2 Hz, $OC\underline{H}$), 6.52 (1H, d, J 8.1 Hz, aryl proton) and 6.61 (1H, d, J 8.1 Hz, aryl proton).

δ_C (90.6 MHz): 14.19 (CH_3), 18.69 (CH_2), 24.30 (CH_2), 24.44 (CH_2), 28.98 (CH_2), 30.13 (CH_2), 32.81 (CH_2), 34.52 (CH_2), 40.14 (C), 47.23 (CH), 55.92 (CH_3), 60.12 (CH_2), 86.09 (CH), 110.43 (CH), 120.43 (C), 120.96 (CH), 131.19 (C), 134.82 (C), 144.61 (C) and 173.29 (C).

m/z (%): 330 (M^+, 100), 257 (46) and 215 (72).

N,N-dimethyl-10α-methyl-5,6-(1,3-methylenedioxy)-3,4,9,10,10 aβ,-tetrahydrophenanthryl-acetamide (120).

A suspension of aluminium foil (8 mg, 0.3 mmol) and iodine (61 mg, 0.3 mmol) was heated in MeCN (2 ml) under reflux for 3 hours. The reaction mixture was then allowed to cool and became quite thick. A solution of amide (74) (100 mg, 0.3 mmol) in MeCN (2 ml) was added dropwise to the vigorously stirred mixture. The reaction mixture was then brought to reflux and maintained in that state for 5 hours. The reaction mixture was allowed to cool and then diluted with ether (30 ml) and water (30 ml). The mixture was washed with saturated sodium bicarbonate solution, then the organic phase was decanted off and dried ($MgSO_4$). Concentration

of the organic phase *in vacuo* gave the crude product. Suction flash chromatography gave the title compound as a white solid (36 mg, 37% uncorrected for recovered starting material).

υ_{max} (CH_2Cl_2): 2850s, 1682s and 1630s.

δ_H (360 MHz): 1.12 (3H, d, **J** 1.8 Hz, $CHC\underline{H}_3$), 1.21-2.52 (8H, m, $ArC\underline{H}_2$, $C\underline{H}CH_3$, $C\underline{H}_2$, $C\underline{H}_2$ and $C\underline{H}CHCH_3$), 2.61 (1H, d, **J** 14 Hz, $C\underline{H}HCO$), 2.94 (3H, s, $NC\underline{H}_3CH_3$), 3.01 (3H, s, $NCH_3C\underline{H}_3$), 2.98 (1H, d, **J** 14 Hz, $CH\underline{H}CO$), 5.59-5.72 (2H, m, $C\underline{H}C\underline{H}$), 5.88 (1H, d, **J** 1.5 Hz, $OC\underline{H}HO$), 5.91 (1H, d, **J** 1.5 Hz, $OCH\underline{H}O$), 6.56 (1H, d, **J** 8 Hz, aryl proton) and 6.66 (1H, d, **J** 8 Hz, aryl proton).

δ_C (67.5 MHz): 18.66 (CH_3), 21.55 (CH), 22.99 (CH_2), 27.86 (CH), 29.53 (CH_2), 34.14 (CH_2), 35.69 (CH), 38.40 (CH_3), 40.29 (CH_2), 41.44 (C), 42.39 (CH_3), 100.18 (CH_2), 106.79 (CH), 121.95 (CH), 124.62 (C), 125.81 (CH), 128.78 (CH), 132.55 (C), 145.78 (C), 145.26 (C) and 171.50 (C).

m/z (%): 327 (M^+, 14), 240 (100), 167 (140) and 121 (24).

6-[(tert-Butyldimethylsilyl)oxy]-2-methyl-2-cyclohexene.

A solution of 2-methyl-2-cyclohexen-1-one (1 g, 8.9 mmol) and triethylamine (3.8 ml, 26.7 mmol) in dichloromethane (20 ml) was

cooled to -20°C and treated dropwise over 30 minutes with *tert*-butyldimethylsilyltrifloromethanesulphonate (2.4 ml, 8.9 mmol). After the addition was complete, the external cooling source was removed and the reaction mixture was stirred at ambient temperature for 1 hour. The reaction mixture was diluted with dichloromethane and then poured into a ice cold solution of 2% HCl (100 ml). The aqueous phase was separated from the organic phase and the organic phase was washed with a solution of saturated sodium bicarbonate. The organic phase was dried (Na_2SO_4) and the solvent volume was concentrated *in vacuo* to 50 ml. The dichloromethane solution was cooled to -78°C and treated with *m*CPBA (3.13 g, 8.9 mmol, 50-55%) in one portion. The reaction mixture was stirred for 10 minutes at -78°C and then allowed to warm to 0°C over 15 minutes. At this point TLC analysis indicated incomplete conversion and the reaction mixture was recooled to -78°C and treated with *m*CPBA (600 mg, 3.4 mmol). The warming cycle was repeated again and at 0°C TLC analysis showed complete conversion. The reaction mixture was poured into a vigorously stirred solution of sodium bicarbonate (100 ml) and dichloromethane (100 ml). The organic phase was separated from the aqueous phase, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Suction flash chromatography gave the title compound as a amber oil (880 mg, 25%).

υ_{max} (film): 1700s and 1660w.

δ_H (270 MHz): 0.01 (3H, s, SiC<u>H</u>$_3$), 0.10 (3H, s, SiC<u>H</u>$_3$), 0.84 (9H, s, t-<u>Bu</u>Si), 1.71 (3H, s, C<u>H</u>$_3$), 1.72-2.36 (4H,

m, $C\underline{H}_2C\underline{H}_2$), 4.09 (1H, dd, **J** 11.5 and 5 Hz, C<u>H</u>OSi) and 6.60 (1H, bs, C<u>H</u>CCH_3).

δ_C (67.5 MHz): -5.4 (CH_3), -4.5 (CH_3), 15.79 (CH_3), 24.58 (CH_2), 25.79 (CH_3), 32.78 (CH_2), 74.29 (CH),134.45 (C), 144.37 (CH) and 199.13 (C).

1-[2-Bromo-3-(2-propenyl)-5-methoxyphenoxy]-2-methyl-2-cyc lohexene.

To a vigorously stirred solution of PBu_3 (116 mg, 0.82 mmol) was added a solution of freshly distilled DEAD (143 mg, 0.82 mmol) in THF (1 ml) at 0°C. Five minutes after the completion of the addition a solution of the allylic alcohol (181) (92 mg, 0.82 mmol) and aromatic bromide (130) (200 mg, 0.82 mmol) in THF (2 ml) was added dropwise. The external cooling source was removed and the reaction mixture stirred for 12 hours at ambient temperature. The solvent removed *in vacuo* to give a brown gum. Suction flash chromatography yielded the title compound as a colourless oil (160 mg, 57%).

υ_{max} (CH_2Cl_2): 2850s, 1660w and 1610w.

δ_H (270 MHz): 1.22-2.25 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 1.95 (3H, s, $C\underline{H}_3$), 3.48 (2H, d, **J** 6.5 Hz, $ArC\underline{H}_2$), 3.81 (3H, s, $OC\underline{H}_3$), 4.70 (1H, bs, C<u>H</u>OAr), 4.91-5.11 (2H, m, $CHC\underline{H}_2$), 5.61 (1H, bs, C<u>H</u>CH_3), 5.81-6.01 (1H, m, C<u>H</u>CH_2), 6.70 (1H, d, **J** 8.5 Hz, aryl proton) and 6.81 (1H, d, **J** 8.5 Hz, aryl proton).

δ_C (67.5 MHz): 18.31 (CH_2), 21.29 (CH_3), 25.54 (CH_2), 28.29 (CH_2), 40.06 (CH_2), 55.75 (CH_3), 78.35 (CH), 111.15 (CH), 116.04 (CH_2), 120.97 (C), 124.21 (CH), 127.42 (CH), 132.46 (C), 133.40 (C), 136.12 (CH), 144.79 (C) and 151.97 (C).

m/z (%): 242 (100) and 95 (87).

1-[2-Bromo-4-methoxy-1-benzaldehyde]-2-(2-propenyl)-2-cyclo hexene (212).

This was prepared using the same procedure as above.

υ_{max} (CH_2Cl_2): 1700s, 1650w and 1600s.

δ_H (270 MHz): 1.44-2.20 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 3.04 (2H, **J** 6 and 1.2 Hz, $C\underline{H}_2CHCH_2$), 3.91 (3H, s, $OC\underline{H}_3$), 4.81 (1H, bs, C<u>H</u>OAr), 4.96-5.05 (2H, m, $CHC\underline{H}_2$), 5.76 (1H, bs, $C\underline{H}CCH_3$), 5.84-5.99 (1H, m, $C\underline{H}CH_2$), 6.94 (1H, d, **J** 8.7 Hz, aryl proton), 7.70 (1H, d, **J** 8.7 Hz, aryl proton) and 10.27 (1H, s, C<u>H</u>O).

δ_C (67.5 MHz): 12.93 (CH_2), 20.42 (CH_2), 23.90 (CH_2), 33.28 (CH_2), 50.92 (CH_3), 71.92 (CH), 105.69 (CH), 110.50 (CH_2), 118.63 (C), 120.66 (CH), 122.40 (C), 123.40 (C), 123.63 (CH), 130.15 (C), 131.94 (CH), 139.48 (C), 153.46 (C) and 186.29 (CH).

1-[2-Bromo-1-(2,3-isopropylenedioxypropan)-4-methoxybenzene]-2-methyl-2-cyclohexene.

This was prepared using the previous method.

υ_{max} (film): 2850s and1600s.

δ_H (270 MHz): 1.35-2.10 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 1.35 (3H, s, $C\underline{H}_3$), 1.44 (3H, s, $C\underline{H}_3$), 2.91-3.11 (2H, m, $ArC\underline{H}_2$), 3.64-3.72 (1H, m, $C\underline{H}HO$), 3.82 (3H, s, $OC\underline{H}_3$), 3.94-4.01 (1H, m, $CH\underline{H}O$), 4.38-4.42 (1H, m, $ArCH_2C\underline{H}O$), 4.72 (1H, bs, $C\underline{H}O$), 5.70 (1H, bs, $CH_3C\underline{H}$), 6.80 (1H, d, **J** 8.5 Hz, aryl proton) and 6.98 (1H, d, **J** 8.5 Hz, aryl proton).

δ_C (67.5 MHz): 18.43 (CH_2), 21.35 (CH_3), 25.64 (CH_2), 25.82 (CH_3), 27.14 (CH_3), 28.45 (CH_2) 40.01 (CH_2), 55.81 (CH_3), 68.79 (CH_2), 75.30 (CH), 78.46 (CH), 109.17 (C), 111.21 (CH), 121.32 (C), 125.35 (CH), 127.55 (CH), 130.16 (C), 133.49 (C), 144.96 (C) and 152.42 (C).

trans-1-[2-Bromo-3-formyl-6-methoxyphenoxy]-6-[(tert-butyld imethylsilyl)oxy]-2-methyl-2-cyclohexene.

This was prepared using the previous procedure.

υ_{max} (film): 2850s, 1690s and 1600s.

δ_H (270 MHz): -0.26 (3H, s, $C\underline{H}_3$), -0.21 (3H, s, $C\underline{H}_3$), 0.66 (9H, s, t-Bu), 0.91-2.21 (4H, m, $C\underline{H}_2C\underline{H}_2$), 1.80 (3H, s, $CC\underline{H}_3$), 3.86 (3H, s, $OC\underline{H}_3$), 3.92 (1H, bs, $C\underline{H}OSi$), 4.37 (1H, bs, $C\underline{H}OAr$), 5.71 (1H, bs, $C\underline{H}CCH_3$), 6.88 (1H, d, **J** 8.8 Hz, aryl proton), 7.64 (1H, d, **J** 8.8 Hz, aryl proton) and 10.20 (1H, s, $C\underline{H}O$).

General procedure for a palladium cyclisation reaction.

A solution of the substrate in DMF (127 mmol) was heated at

120°C in the presence of $Pd(OAc)_2$ (10 mol%) and potassium carbonate (200 mol%) until the starting material had completely disappeared. The reaction mixture was allowed to cool, diluted with 5 volumes of ether and then poured into 5 volumes of water. The mixture was filtered through celite and the ethereal phase was separated from aqueous phase. Drying ($MgSO_4$) followed by concentration *in vacuo* gave the crude product. Chromatography yielded an inseparable mixtures of isomers.

4-Formyl-1-methoxy-4bb-methyl-7,8,8ab-tetrahydrobenzofuran (216).

υ_{max} (CH_2Cl_2): 1700bs and 1620bm. (for all three components combined).

Proton data for

4-Formyl-1-methoxy-4bβ-methyl-5,8,8aβ-tetrahydrobenzofuran (214)..

δ_H (260 MHz): 1.60 (3H, s, $C\underline{H}_3$), 1.8-2.7 (4H, m, $C\underline{H}_2C\underline{H}_2$), 3.95 (3H, s, $OC\underline{H}_3$), 4.65 (1H, t, **J** 4.9 Hz, $OC\underline{H}$), 5.81-5.92 (2H, m, $C\underline{H}CH$), 6.86 (1H, d, **J** 8.5 Hz, aryl proton), 7.35 (1H, d, **J** 8.5 Hz, aryl proton) and (1H, s, CHO).

δ_H (90.6 MHz): 27.12 (CH_3), 28.39 (CH_2), 34.27 (CH_2), 47.57 (C), 56.09 (CH), 90.89 (CH), 110.30 (CH), 190.51 (CH) and the aromatic and olefin signals are difficult to assign.

Proton data for

4-Formyl-1-methoxy-4bα-methyl-7,8,8aβ-tetrahydrobenzofuran

(215).

δ_H (360 MHz): 1.55 (3H, s, OC<u>H</u>$_3$), 1.8-2.7 (4H, m, C<u>H</u>$_2$C<u>H</u>$_2$), 3.93 (3H, s, OC<u>H</u>$_3$), 4.65 (1H, t, **J** 4.9 Hz, OC<u>H</u>), 5.74-5.79 (1H, m, C<u>H</u>CH), 6.02-6.56 (1H, m, CHC<u>H</u>), 6.84 (1H, d, **J** 8.5 Hz, aryl proton), 7.35 (1H, d, **J** 8.5 Hz, aryl proton) and 9.96 (1H, s, C<u>H</u>O).

δ_H (90.6 MHz): 19.19 (CH_2), 23.29 (CH_2), 25.71 (CH_3), 47.00 (C), 56.09 (CH), 88.80 (CH), 110.29 (CH), 190.51 (CH) and the olefinic and aromatic signals difficult to assign.

m/z (%): 244 (M^+, 100), 229 (35) and 190 (100).

proton data for

4-Formyl-1-methoxy-4bβ-methyl-t-butyldimethylsilyoxy-5,8α,8aβ-tetrahydrofuran (218).

δ_H (270 MHz): 0.05 (3H, s, SiC<u>H</u>$_3$), 0.13 (3H, s, C<u>H</u>$_3$Si), 0.91 (9H, s, t<u>Bu</u>), 1.21-2.29 (2H, m, C<u>H</u>$_2$), 3.94 (3H, s, OC<u>H</u>$_3$), 4.10 (1H, m, OC<u>H</u>OSi), 4.48 (1H, d, **J** 5.1 Hz, C<u>H</u>O), 5.62 (1H, dt, **J** 10.1 Hz, C<u>H</u>CH), 6.32 (1H, d, **J** 10.1 Hz, CHC<u>H</u>), 6.88 (1H, d, **J** 8.5 Hz, aryl proton), 7.39 (1H, d, **J** 8.5 Hz, aryl proton) and 9.97(1H, s, C<u>H</u>O).

δ_C (67.5 MHz): -4.97 (CH_3), -4.67 (CH_3), 25.83 (CH_3), 25.93 (CH_3), 27.17 (C), 29.83 (CH_2), 48.51 (C), 56.10

(CH_3), 67.63 (CH), 92.49 (CH), 110.43 (CH), 122.62 (CH), 129.01 (CH), 130.55 (CH), 131.23 (C), 135.61 (C), 150.09 (C) and 190.43 (C).

m/z (%): 317 (100), 235 (46), 220 (95) and 73 (58).

2-Phenylsulphonyl-2-(2-propenyl)-2-cyclohexene-1-ol.

To a stirred solution of the *3-phenylsulphonyl-2-(2-propenyl)-2-cyclohexene-1-one* (5 g, 18.1 mmol), $CeCl_3$ (6.74 g, 18.1 mmol) in MeOH (70 ml) and CH_2Cl_2 (70 ml) was added portions of $NaBH_4$ (685 mg, 18.1 mmol). One hour after the completion of the addition, the solvent was removed *in vacuo* to a white solid. The white solid was suspended in CH_2Cl_2 and then vigorously stirred with 2% aq HCl. The organic phase was separated from the aqueous phase and the aqueous phase was washed twice with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo*. Suction flash chromatography gave the title compound as a clear viscous oil (4.4 g, 87%).

υ_{max} (film): 3500br, 2950s and 1630s.

δ_H (270 MHz): 1.17-2.42 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 3.80 (1H, m, $C\underline{H}CHCH_2$), 3.80-3.92 (1H, m, $CHC\underline{H}CH_2$), 4.18 (1H, bs, $C\underline{H}O$), 5.01-5.10 (2H, m, $CHC\underline{H}_2$), 5.71-5.84 (1H, m, $C\underline{H}CH_2$) and 7.48-7.87 (5H, m, aryl protons).

δ_C (67.5 MHz): 17.74 (CH_2), 26.97 (CH_2), 30.52 (CH_2), 34.86 (CH_2), 67.14 (CH), 117.43 (CH_2), 127.40 (CH),

129.22 (CH), 133.36 (CH), 135.49 (CH), 137.49 (C), 140.92 (C) and 148.10 (C).

m/z (%): 278 (M^+, 3), 260 (47), 125 (62) and 91 (100).

2-Iodo-3-hydroxy-4-methoxybenzylalcohol. To a suspension of 2-Iodo-3-methoxymethoxy-4-methoxybenzylalcohol (6.41 g, 22.9 mmol) and MeOH (50 ml) was added *p*TSA (250 mg, 5 mol%). Eighteen hours after the completion of the addition, solid sodium bicarbonate was added and then the reaction mixture was filtered. The filtrate was concentrated *in vacuo* to give a white solid. Recrystallisation (water) gave the title compound as white crystals (5.4 g, 97%). M.p. 127-128°C.

υ_{max} (CH_2Cl_2): 3500br and 2850s.

δ_H (360 MHz): 3.51 (1H, s, O<u>H</u>), 3.89 (3H, s, OC<u>H</u>$_3$), 4.47 (2H, s, C<u>H</u>$_2$OH), 5.31 (1H, s, O<u>H</u>), 7.01 (1H, d, **J** 8.3 Hz, aryl proton) and 7.06 (1H, d, **J** 8.3 Hz, aryl proton).

δ_C (90.6 MHz): 56.11 (CH_3), 67.28 (CH_2OH), 87.14 (C), 111.13 (CH), 117.97 (CH), 136.16 (C), 145.51 (C) and 145.75 (C).

m/z (%): 280 (M^+, 87), 263 (36), 198 (11), 167 (7), 151 (12), 93 (34) and 45 (100).

REFERENCES

1. F. W. A. Serturner, *J. Pharmazie.*, 1805, **13**, 229.

2. P. J. Robiquet, *Ann. Chim. Phys.*, 1817, **5**, 275.

3. P. J. Robiquet, *Ann. Chim. Phys.*, 1832, **51**, 225.

4. J. Pelletier, *J. Pharmacol.*, 1835, **21**, 555.

5. G. Merck, *Justus Liebig's Ann. Chem.*, 1848, **66**, 125.

6. A. Jermstadt, *Das Opium.*, (Verlag Hartleben, Wien, 1921).

7. N. N. Vorozhtzof and A. T. Troschenko, *Compt. Rend. Acad. Sci. U.S.S.R.*, 1935, **2**, 555.

8. L. Gregory, *Annelen. der Chemie.*, 1833, **7**, 261.

9. W. L. Dean and E. S. Brady, *J. Chem. Soc.*, 1865, 34.

10. G. Fouquet, *Bull. Soc. Chim.*, 1882, **37**, 472.

11. S. I. Kanewskaja, *J. Prakt. Chem.*, 1924, **108**, 247.

12. M. J. Liebig, *Ann. Chim et Phys.*, 1831, **47**, 147.

13. F. Raoult, *ibid.*, 1884, **2**, 66.

14. M. A. Laurent, *ibid.*, 1847, **19**, 359.

15. G. Bertrand and L. Meyer, *ibid.*, 1909, **17**, 501.

16. K. W. Bentley, 'The Chemistry of the Morphine Alkaloids', Oxford 1954. Chapter 1 and references cited therein.

17. J. M. Gullard and R. Robinson, *Memoirs of the proceedings of the Manchester Literary and Philisophical Society.*, 1925, **69**, 79.

18. M. Gates and G. Tschudi, *J. Am. Chem. Soc.*, 1952, **74**, 1109; M. Gates and G. Tschudi, *J. Am. Chem. Soc.*,1955, **78**, 1380.

19. R. Grewe and A. Mondon, *Chem. Ber.*, 1948, **81**, 279; R. Grewe, A. Mondon and E. Nolte., *Annalen.*, 1949, **32**, 821.

20. G. C. Morrison, R. O. Waite and J. Shavel, Jr., *Tetrahedron Lett.*, 1967, 4055; R. Grewe, H. Fischer and W. Friedrichsen, *Chem Ber.*, 1967, **100**, 1.

21. A. Manmade, J. L. Marshall, R. Minns, M. Dalzell and R. K. Razdan, *J. Org. Chem.*, 1982, **47**, 1717 and references cited therein.

22. K. C. Rice, *J. Org. Chem.*, 1980, **45**, 3135; F. L. Hsu, K. C. Rice and A. Brossi, *Helv. Chim. Acta.*, 1980, **63**, 2042.

23. D. D. Weller, H. Rapoport, *J. Med. Chem.*, 1976, **19**, 1171.

24. A. I. Meyers and T. R. Bailey, *J. Org. Chem.*, 1986, **51**, 872.

25. D. Elad and D. Ginsburg, *J. Am. Chem. Soc.*, 1954, **76**, 312.

26. D. Ginsburg and R. Pappo, *J. Chem. Soc.*, 1951, 516.

27. G. Stork in " The Alkaloids, " Vol VI. ed. R. H. F. Manske, Academic Press, New York (1960) p. 235.

28. D. A. Evans, C. H. Mitch, R. C. Thomas, D. M. Zimmerman and R. L. Robey, *J. Am. Chem. Soc.*, 1980, **102**, 5956; D. A. Evans and C. H. Mitch, *Tetrahedron Lett.*, 1982, **23**, 285.

29. W. H. Moos, R. D. Gless and H. Rapoport, *J. Org. Chem.*, 1983, **48**, 227.

30. J. E. M^{c}Murray and V. Farina, *Tetrahedron Lett.*, 1983, **24**, 4653; J. E. M^{c}Murray, V. Farina, W. J. Scott, A. H. Davidson, D. R. Summers and A. Shenvi, *J. Org. Chem.*, 1984, **49**, 3803.

31. A. G. Shultz, R. D. Lucci, J. J. Napier, H. Kinoshita, R. Ravishandra, P. Shannon and Y. K. Yee, *J. Org. Chem.*, 1985, **50**, 217.

32. J. E. Toth, P. R. Hammann and P.L. Fuchs, *J. Org. Chem.*, 1988, **53**, 4694.

33. E. Ciganek, *J. Am. Chem. Soc.*, 1981, **103**, 6261.

34. S. Handa, K. Jones, C. G. Newton and D. J. Williams, *J. Chem Soc., Chem. Commun.*, 1985, 1362.

35. A. R. Battersby and R. Binks, *Proc. Chem. Soc.*, 1960, 360; A. R.

Battersby and R. Binks, *Quart. Rev.*, 1961, **15**, 277; A. R. Battersby, R. Binks, D. M. Foulkes, R. J. Francis, D. J. Macaldin and H. Ramuz, *Proc. Chem.Soc.*, 1963, 203; A. R. Battersby, R. Binks, D. M. Foulkes, *J. Chem. Soc.*, 1965, 3323; D. H. R. Barton, G. W. Kirby, W. Steglich, G. M. Thomas, A. R. Battersby, T. A. Dobson and H. Ramuz, *J. Chem. Soc.*, 1965, 2423; D. H. R. Barton, D. S. Bhakumi, R. James and G. W. Kirby, *J. Chem. Soc., Chem. Commun.*, 1967, 128.

36. H. I. Parker, G. Blaschke and H. Rapoport, *J. Am. Chem. Soc.*, 1972, **94**, 1276; J. S. Horn, A. G. Paul and H. Rapoport, *J. Am. Chem. Soc.*, 1978, **100**, 276; P. R. Borkowski, J. S. Horn and H. Rapoport, *J. Am. Chem. Soc.*, 1978, **100**, 276.

37. W. W. C. Chang and P. Maitland, *J. Chem. Soc., Chem. Commun.*, 1966, 753; A. H. Jackson and J. A. Martin, *ibid.*, 1966, 2061; T. Kamentani, K. Fuchomoto, A. Kozuka, H. Yagi and M. Koizumi, *ibid.*, 1969, 2034; T. Kamentani, A. Kozuka and K. Fukumoto, *ibid.*, 1971, 1021.

38. M. A. Schwartz and I. S. Mami, *J. Am. Chem. Soc.*, 1975, **97**, 1239.

39. J. Hughes, T. W. Smith, H. W. Kosterlitz, L. A. Fothergill, B. A. Morgan and H. R. Morris, *Nature.*, 1975, **258**, 577.

40. C. R. A. Wright, *J. Chem. Soc.*, 1874, **27**, 1031.

41. J. Pohl, *Z. Exp. Pathol. Ther.*, 1915, **17**, 370.

42. J. Weijlard and A. E, Erickson, *J. Am. Chem. Soc.*, 1942, **64**, 869.

43. M. J. Lewenstein and J. Fishman, U.S. patent 3,254,088, (1966).

44. I. Monkovic, H. Wong, A. W. Pircio, Y. S. Perron, I. J. Pachter and B. Belleau, *Can. J. Chem.*, 1975, **53**, 3094.

45. N. Sharghi and L. Lalezari, *Nature.*, 1967, **213**, 1244.

46. O. Eisleb and O. Schaumann, *Deut. Med. Wochenschr.*, 1939, **65**, 967.

47. J. Pearl, H. Stander, D. Mckean, *J. Pharmacol. Exp. Ther.*, 1969, **167**, 9; P. L. Nilsen, *Acta Pharmacol. Toxicol.*, 1961, **18**, 10; T. D. Perrine, L. Atwell, I. B. Tice, A. E. Jacobson and E. L. May, *J. Pharm. Sci.*, 1972, **61**, 86.

48. D. Lednicer and L. A. Mitscher, ' The Organic Chemistry of Drug Synthesis Volume 2," J. Wiley and sons 1980, page 329.

49. M. Bockmuhl and G. Ehrhart, *Justus Liebig's Ann. Chem.*, 1949, **561**, 52.

50. S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson and J. G. Bird, *J. Med. Chem.*, 1964, **7**, 123.

51. A. H. Beckett and A. F. Casey, *J. Pharm. Pharmacol.*, 1954, **6**, 986.

52. J. Hamer and A. Macaluso, *Chem. Rev.*, 1964, **64**, 473.

53. M. Chandler and P. J. Parsons, *J. Chem. Soc., Chem. Commun.*, 1984, 322.

54. A. L. Gemal and J. L. Lucke, *J. Am. Chem. Soc.*, 1981, **103**, 5454.

55. R. E. Ireland, R. H. Mueller and A. K. Willard, *J. Am. Chem. Soc.*, 1976, **98**, 2868.

56. W. S. Johnson, L. Werthmann, W. R. Bartlett, T. J. Brocksom, T. T. Li, D. J. Faulkner and M. R. Peterson, *J. Am. Chem. Soc.*, 1970, **92**, 741.

57. D. Felix, K. Gschwend-Steen, A. E. Wick and A. Eschenmoser, *Helv. Chim. Acta.*, 1969, **52**, 1030.

58. For reviews see:

C. H. De Puy and R. W. King, *Chem. Rev.*, 1960, **60**, 431-435;
H. R. Nace, *Org. React.*, 1962, **12**, 57.

59. H. Gerlach, T. T. Huong and W. Muller, *J. Chem. Soc., Chem. Commun.*, 1972, 1215; H. Gerlach and W. Muller, *Helv. Chim. Acta.*, 1972, **55**, 2277.

60. E. M. Burgess, H. R. Penton, Jr., and E. A. Taylor, *J. Org. Chem.*, 1973, **38**, 26.

61. R. H. Shapiro and M. J. Heath, *J. Am. Chem. Soc.*, 1967, **89**, 5734.

62. K. W. Bentley, D. G. Hardy and B. Meek, *J. Am. Chem. Soc.*, 1967, **89**, 3267.

63. W. H. Mueller and P. E. Butler, *J. Am. Chem. Soc.*, 1968, **90**, 2075.

64. S. Labidalle, Z. Y. Min, A. Reynet, H. Moskowitz, J. M. Vierford and M. Miocque, *Tetrahedron.*, 1988, **44**, 1171.

65. M. V. Bhatt and J. Ramesh Babu, *Tetrahedron Lett.*, 1984, 3497.

66. M. V. Bhatt and S. U. Kulkarni, *Synthesis.*, 1983, 249.

67. F. L. Fenton and T. E. Dillon, *J. Am. Chem. Soc.*, 1942, **64**, 1128.

68. C. L. Jenkins and J. K. Kochi, *J. Am. Chem. Soc.*,1972, **94**, 843.

69. G. Desimoni, G. Tacconi, A. Barco and G. P. Pollini, "Natural Products Synthesis Through Pericyclic Reactions," ACS Monograph; 1980 page 339.

70. B. B. Snider and D. M. Roush, *J. Org. Chem.*, 1979, **44**, 4229.

71. S. E. Haglet and R. J. Brotherton, *J. Org. Chem.*, 1962, **27**, 3253.

72. M. Brink, *Acta. Chem. Scand.*, 1965, **19**, 255.

73. J. K. Stille, *New Synthetic Methods.*, 1986, **58**, 508.

74. A. Moravskiy and J. K. Stille, *J. Am. Chem. Soc.*,1981, **103**, 4182; J. K. Stille and K. S. Y. Lau, *Acc. Chem. Res.*, 1977, **10**, 434; A. Gillie and J. K. Stille, *J. Am. Chem. Soc.*, 1980, **102**, 4933; M. K. Loar and J. K. Stille, *J. Am. Chem. Soc.*, 1981, **103**, 4174; K. Tatsumi, R. Hoffmann, Y. Yamamoto and J. K. Stille, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 1857.

75. D. Seyferth and M. A. Weiner, *J. Am. Chem. Soc.*, 1961, **83**, 3583.

76. D. R. Coulson, *Inorg. Synth.*, 1972, **13**, 121.

77. E. Piers, Howard E. Morton and J. M. Chong, *Can. J. Chem.*, 1987, **65**, 78.

78. A. W. Crossley, *J. Am. Chem. Soc.*, 1903, **83**, 494.

79. G. H. Posner, *Org. React.*, 1972, **19**, 1; J. F. Normant, *Synthesis.*, 1972, 63.

80. William. J. Scott, *J. Chem. Soc., Chem. Commun.*, 1987, 1755.

81. H. Azizian, C. E. Eaborn and A. Pidcock, *J. Organomet. Chem.*, 1981, **49**, 215.

82. S. Kim and J. H. Park, *Tetrahedron Lett.*, 1987, **28**, 439.

83. F. E. Ziegler, K. W. Fowler, W. B. Rodgers and R. T. Wester, *Org. Synth.*, 1987, **65**, 108.

84. R. F. Heck, *Acc. Chem. Res.*, 1979, **12**, 146.

85. M. Gomberg, *J. Am. Chem. Soc.*, 1900, **22**, 757; M. Gomberg *Chem. Ber.* 1900, **33**, 3150.

86. F. Paneth and W. Hofeditz, *Chem. Ber.*, 1929, **62**, 1335.

87. D. H. Hey and W. A. Waters, *Chem. Rev.*, 1937, **21**, 169.

88. B. Giese, " Radicals in organic synthesis: Formation of carbon-carbon bonds," Pergamon Press 1986. Page 268 and references cited therein.

89. C. Walling, *Tetrahedron.*, 1981, **37**, 3073.

90. A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron.*, 1985, **41**, 3925; A. L. J. Beckwith and G. F. Meijs, *J. Chem. Soc., Perkin. Trans. II.*, 1979, 1535; A. L. J. Beckwith, G. Phillipou and A. K. Serelis, *Tetrahedron Lett.*, 1981, **22**, 2811.

91. M. Julia, *Acc. Chem. Res.*, 1971, **4**, 386; M. Julia, *Pure Appl. Chem.* 1974, **40**, 553.

92. A. L. J. Beckwith, C. J. Easton and A. K. Serelis, *J. Chem. Soc., Chem. Commun.*, 1980, 482.

93. Y. Ueno, K. Chino, M. Okawara, *Tetrahedron Lett.*, 1982, **23**, 2575.

94. K. A. Parker, D. M. Spero and K. C. Inman, *Tetrahedron Lett.*, 1986, **27**, 2833.

95. D. Felix, C. Winter and A. Eshenmoser, *Org. Synth.*, Vol 6 page 679.

96. J. K. Stille and R. Divakaruna, *J. Org. Chem.*, 1979, **44**, 3474.

97. O. Mitsunobu, *Synthesis.*, 1981, 1.

98. H. Stetter and W. Diericks, *Chem. Ber.*, 1952, **85**, 1061.

99. R. C. Larock and S. Babu, *Tetrahedron Lett.*, 1987, **28**, 5291 and references therein.

100. M. Mori, K. Chiba and Y. Ban, *Tetrahedron Lett.*, 1977, **12**, 1037.

101. L. S. Hegedus, T. A. Mulhern and A. Mori, *J. Org. Chem.*, 1985, **50**, 4282.

102. N. A. Cortese, C. B. Ziegler, Jr., B. J. Hrnjez and R. F. Heck, *J. Org. Chem.*, 1978, **43**, 2952.

103. M. Mori and Y. Ban, *Tetrahedron Lett.*, 1979, **13**, 1133.

104. E. Negishi, Y. Zhang and B. O'Connor, *Tetrahedron Lett.*, 1988,

24, 2915.

105. R. C. Larock, H. Song, B. E. Baker and W. H. Gong, *Tetrahedron Lett.*, 1988, **24**, 2919.

106. M. M. Abelman, T. Oh and L. E. Overman, *J. Org. Chem.*, 1987, **52**, 4130.

107. R. Grigg, V. Sridharan, P. Stevenson and T. Worakun, *J. Chem. Soc., Chem. Commun.*, 1986, 1697.

108. T. Hosokawa, K. Maeda, K. Koga and I. Moritani, *Tetrahedron Lett.*, 1973, **46**, 739; T. Hosokawa, H. Ohkata and I. Moritani, *Bull. Chem. Soc. Jpn.*, 1975,**48**, 1533; T. Hosokawa, S. Yamashita, S. Murahashi and A. Snoda, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 3662; T. Hosokawa, S. Miyagi, S. Murahashi and A. Snoda, *J. Chem. Soc., Chem Commun.*, 1978, 687; T. Hosokawa, T. Uno, S. Inui and S. Murahashi, *J. Am. Chem. Soc.*, 1981, **103**, 2318.

109. B. Cardillo, M. Cornia and L. Merlini, *Gazz. Chim. Ital.*, 1975, **105**, 1151; G. Casiraghi, G. Casnati, G. Puglia, G. Sartori and C. Terenghi, *Synthesis.*, 1977, 122.

110. J. Tsuji, Y. Kobayashi, H. Kataoka and T. Takahashi, *Tetrahedron Lett.*, 1980, **21**, 1475.

111. P. J. Parsons and C. E. Ellwood, unpublished results, Southampton University.

112, R. C. Larock and Dean E. Stinn, *Tetrahedron Lett.*, 1988, **29**, 4687.

113. G. M. Rubottom, M. A. Vaszquez and D. R. Pelegrina, *Tetrahedron Lett.*, 1974, 4319.

114. L. M. Harwood, *Aldrichchemica Acta.*, 1985, **18**, 25.

115. W. C. Still, M. Kaln and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

116. E. Napolitano, E. Giannone, R. Fiaschi and A. Marsili, *J. Org. Chem.*, 1983, **48**, 3653.