THE TOTAL SYNTHESIS OF 3-HYDROXY-17-DEAZA-17-OXAISOMORPHINAN, A MORPHINAN ANALOGUE

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The Total Synthesis of 3-Hydroxy-17-Deaza-17-Oxaisomorphinan, a Morphinan Analogue

ABSTRACT

The synthesis of the analogue of 3-hydroxy-isomorphinan in which the nitrogen has been replaced with oxygen has been accomplished. The synthesis was approached by two different routes. One strategy attempted to cyclize 1-(4-methoxybenzyl)-isochroman analogues and failed due to the instability of the cyclic ether to acids. The second strategy, starting with 4a-(aminoethyl)-6-methoxy-1,2,3,4,4a,9-hexahydrophenanthrene, was ultimately successful. Hydroboration - oxidation of the 10,10a-double bond of the hexahydrophenanthrene was used to introduce the isomorphinan stereochemistry. Attempts to generate the morphinan isomer by means of isomerization of the 10,10a-double bond or by epoxidation of the olefin were unsuccessful.

Synthèse totale de l'hydroxy-3-déaza-17-oxa-17-isomorphinane, un analogue de la morphinane

RESUME

On a effectué la synthèse d'un analogue de l'hydroxy-3-isomorphinane dans lequel l'azote a été remplacé par un oxygène. Afin d'accomplir ceci, deux voies différentes de synthèse ont été explorées. Dans la première approche synthétique, les tentatives pour cycliser les analogues (méthoxy-4-benzyl)-1-isochromane ont échouées à cause de l'instabilité de l'éther cyclique aux conditions acides. La seconde voie de synthèse, utilisant le méthoxy-6-(aminoéthyl)-4a-hexahydrophénanthrène-1,2,3,4,4a,9 comme produit de départ, nous a permis d'effectuer avec succès la synthèse. La réaction d'hydroboration - oxydation de la double liaison-10,10a de l'hexahydrophénanthrène a été employée afin d'introduire la stéréochimie de l'isomorphinane. D'autre part les tentatives pour former l'isomère morphinane par l'isomérisation de la double liaison-10,10a ou par l'époxydation de l'oléfine ont échouées.

Acknowledgements

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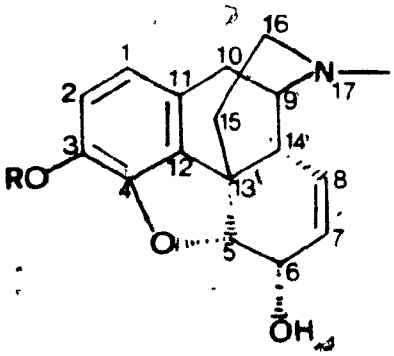
CHAPTER 1

INTRODUCTION

For centuries, extracts from the opium poppy, Papaver somniferum, have been used for medicinal and recreational purposes (1-3). In 1805, Sertürner was the first to isolate morphine in pure form from crude opium and recognize it as the agent responsible for the pharmacological properties of the opium poppy (3). There are 27 alkaloids in the crude extracts and morphine usually occurs as 10% of the dried opium powder (3). The correct structure for morphine was deduced by Gulland and Robipson in 1925 (3) and is shown in Figure 1 together with its derivative, codeine.



R=H morphine

$R=CH_3$ codeine

FIGURE 1: The structures of morphine and of codeine.

The use of morphine as an analgetic is ancient history, and the alkaloid is well-known to act primarily as a central nervous system depressant. Many morphine-like phenanthrene alkaloids cause sedation, euphoria, and alleviate anxiety. These effects are highly addictive and lead to tolerance which means that more and more drug is needed in order to achieve a constant effect. Morphine and analogous opiates also cause circulatory depression, nausea, vomiting, constipation,

hyperglycemia, suppression of the cough reflex, and respiratory depression leading to death in an overdose (3,4).

Hundreds of analogues and other compounds have been synthesized in an effort to minimize the undesirable effects of morphine and as a result many structures were found to behave as analgesics, emetics, antidiarrheals, and antitussives. Certain analogues can suppress the withdrawal symptoms associated with drug abstinence and are used for the treatment of addicts. Other modifications of the morphine structure led to compounds useful in the treatment of narcotic overdosing (1).

The general classes of analogues which are structurally related to morphine are assembled in Figure 2.

Morphine-like analgetic activity is characterized by the following general structural features: a tertiary nitrogen, a quaternary carbon atom separated from the nitrogen by a two carbon chain, and a phenyl group attached to the quaternary carbon (5). However, many exceptions to these generalizations are known (3-5).

In the morphine series of analogues, pharmacological action is associated with a single eantiomer, the levorotatory one. The dextrorotatory form of (+)-morphine is inactive (6). The simpler structure, such as the morphinan, levorphanol, is 6 to 8 times as potent as morphine (4) whereas its eantiomer, dextrorphan, is inactive (7) (Fig. 3). The O-methylated derivative of the (+)-isomer, dextromethorphan, displays some activity as an antitussive, yet shows none of the analgetic, constipative, central depressant, and addictive features of the opiates

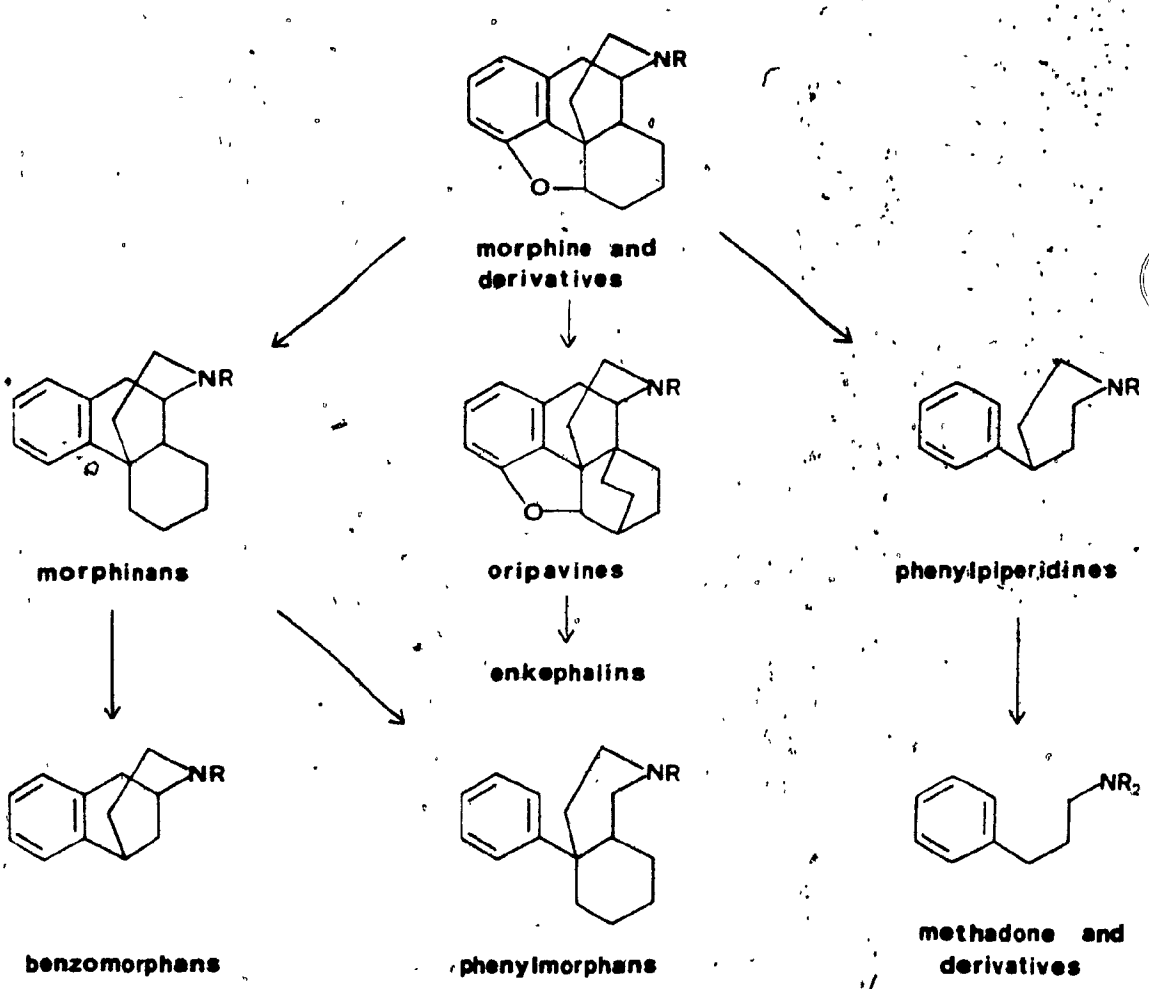
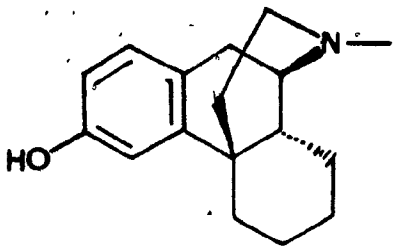
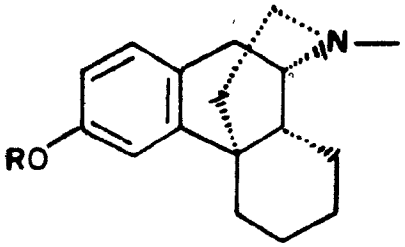


FIGURE 2: The general classes of compounds structurally related to morphine. Adapted from reference 3.



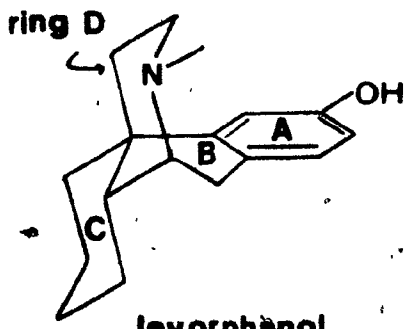
levorphanol



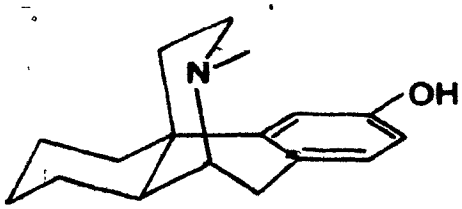
R=H dextrorphan
R=CH_3 dextromethorphan

FIGURE 3: The stereochemistry of the active analgesic, levorphanol, versus that of the inactive one, dextrorphan.

(4). Interestingly, the morphine receptor is hardly sensitive to changes in the B/C ring geometry. For instance, whereas levorphanol has the morphine stereochemistry at H-14, isolevorphanol where the B/C rings are trans-fused is even more potent (8); as with dextrorphan, the dextro-isomer of isolevorphanol is also inactive (8). The stereoselec-



levorphanol
B/C cis

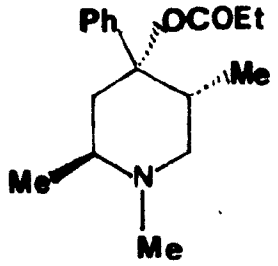


isolevorphanol
B/C trans

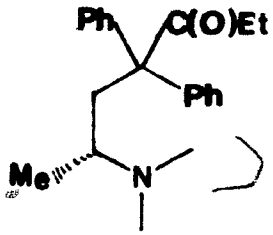
FIGURE 4

tivity of the receptor toward the less rigid analogues is not as clearly delineated: with α-trimeperidine, a phenylpiperidine analogue,

the two enatiomers are equipotent (9). For methadone, however, it is the levorotatory isomer which is active (3,4).



α-trimeperidine



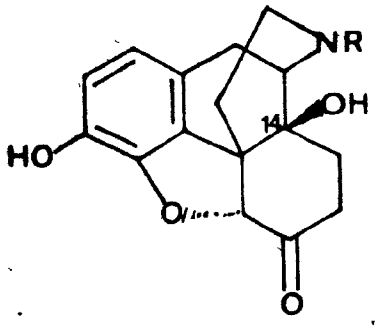
6R-methadone

FIGURE 5

The role of the N-substituent is generally important for opiates. Increasing its size usually leads to a decrease in agonist activity and an increase in antagonist effects. A narcotic antagonist is defined as a compound which inhibits all the effects of morphine. The first effective antagonist, nalorphine, was described in 1942; its structure was the N-allyl analogue of morphine. It effectively reverses the respiratory depression associated with overdoses of morphine (1). Remarkably, it was 10 years after this observation that nalorphine was found to possess analgetic activity in man (10). Although it appeared to have less addiction liability and to produce less respiratory depression than morphine, it could nevertheless not be used as an anti-nociceptive agent because of its severe psychomimetic side effects (10).

Subsequently, a prototype of so-called pure narcotic antagonists was discovered. Naloxone, the N-allyl analogue of the agonist oxymor-

phone, is highly effective in blocking all the narcotic-like effects of opioids yet it is devoid of any agonist activity (1,3). Unlike nalorphine, naloxone displays no psychomimetic side effects (1,3). The more recently developed analogue, naltrexone, appears to be more potent as an antagonist than naloxone (1). These "pure" narcotic antagonists incorporate in their structures a unique feature: a 14-β hydroxyl substituent (Fig. 6). Interestingly, the increased potency of the agonist oxymorphone also appears to be related to the presence of the 14-β OH function (11).



AGONIST

$R=CH_3$ **oxymorphone**

ANTAGONIST

$R=CH_2CH=CH$ **naloxone**

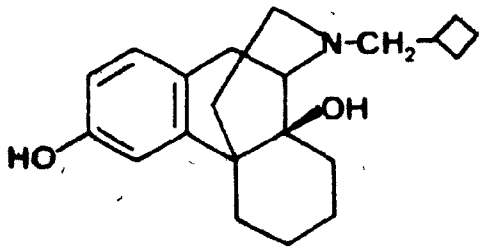
$R=CH_2$-cyclopropyl **naltrexone**

$R=CH_2$-cyclobutyl, $=O$, $-OH$ **nalbuphine**

FIGURE 6

Over the past fifteen years so-called second-generation narcotic antagonists, which display analgesic activity, have been developed. These act as relatively clean antagonists exhibiting weak respiratory depression, less dysphoria, and reduced dependence liability than the common opiates. Their general non-narcotic properties distinguish them from the so-called mixed agonist-antagonists typified by nalorphine. The expression metagonist has been suggested for this unusual class of drugs (12). Butorphanol (Fig. 7) and nalbuphine (Fig. 6) constitute

outstanding examples of this class; interestingly, both incorporate a 14-β OH function together with an N-cyclobutylmethyl substituent. Other classes of drugs falling in this general category are under active investigation (13).



butorphanol

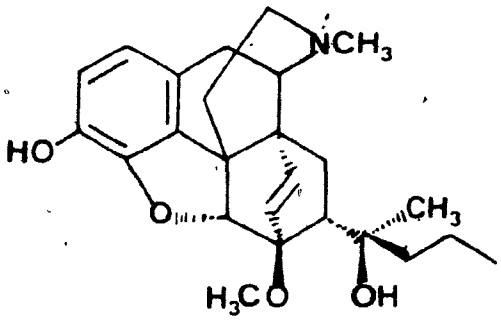
FIGURE 7

The role of the nitrogen substituent on the properties of the structurally less rigid classes is not as sharply defined. There are compounds of the phenylpiperidine class for example which behave as antagonists even though they carry an N-methyl group (14); furthermore, the presence of an N-allyl substituent in the non-rigid classes of drugs does not always antagonize activity (3).

In the rigid series, larger N-substituents than allyl or cyclobutylmethyl restore and enhance agonist activity. For example, N-cyclohexylethyl normorphine is 6 times as potent an agonist as morphine (3). The large N-phenylethyl group confers exceptional agonist activity to several members of many classes of narcotics (3).

There is much structure-activity relationship information available on opiates, and several theories of drug-opiate receptor interaction have been proposed in an attempt to reconcile the apparently con-

tradictory data. An early generalization of the receptor site(s) called for the presence of a flat lipophilic area in order to accomodate the aromatic ring, a cavity to hold the piperidine ring, and an anionic site to bind with the protonated basic nitrogen (7). Subsequently, an accessory lipophilic site for agonists was proposed (15) in order to explain the exceptional potency of the thebaine-derived oripavines (16). Etorphine (Fig. 8), for example, is at least 200 times as potent as morphine (17) thus suggesting the presence of a high affinity lipophilic site which may also accomodate the large phenyl groups of the potent N-phenylethyl analogues (15). Antagonists may interact with either the same set of sites or with a structurally closely related receptor (4) which would be selective for medium-sized substituents on the nitrogen (15).



etorphine

FIGURE 8

Evidence from animal models of behaviour, in vitro receptor affinities and cross-tolerance effects led to the conclusion that the opiate receptor exists in different forms with each sub-type responding

differently to certain prototypical agonists and antagonists (3,18). Morphine is the prototype for the μ-type of receptor subspecies (18).

The hypothesis of Beckett and Casy for the opiate receptor requires that the nitrogen atom be protonated at physiological pH in order for the drug to interact with a counter-anionic site (7). The pK_a of morphine is 7.91 (19), and reducing the basicity through the introduction of a double bond between C_{16} and C_{15} is detrimental to activity (20). Furthermore, the more potent analogue levorphanol is slightly more basic (pK_a = 8.18 (21)), and the incorporation of a 14-β OH (a substituent favorable to activity) tends to increase basicity (19). These trends have been interpreted to mean that ion pairing between the cationic nitrogen and the anionic binding site of the receptor triggers molecular events leading to the pharmacological response.

The lone pair electrons of the basic nitrogen of benzomorphans and morphinans are oriented away from the phenyl ring. In solution, 83% of the morphine and nalorphine molecules in the unprotonated form have the N-substituent equitorial relative to the piperidine ring (22,23). For the 14-β OH analogues, oxymorphone and naloxone, over 95% of the unprotonated molecules have their N-substituents equitorially oriented (23). Morphinan analogues having their N-lone pair oriented toward the phenyl ring have been shown to be inactive in vivo as μ-agonists or antagonists (12,24). The orientation of the N-lone pair appears crucial, and the lone pair may be involved in a stereoselective proton transfer process with a suitable acceptor site of the receptor

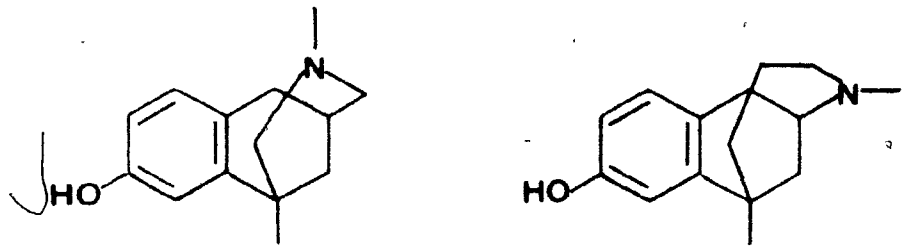
(12,25). It is clear that the lone pair, which would serve to either accept or donate a proton, has to be properly oriented in order for the transfer process to occur.

One of the arguments against the N-lone pair directionality theory centers on the weak, apparent activity of N-quaternary analogues of certain opiates. Since these structures are incapable of carrying a proton on their nitrogens this implies that only an ion-pairing mechanism would be necessary for the receptor complex to initiate an analgetic response. Thus, N-methyl morphine induced opiate-like analgesia and hypothermia after intracerebral administration in rats (26). However, the hypothermic response was not blocked by the antagonist, nalorphine, nor could cross-tolerance between N-methyl morphine and morphine be observed (26). Misra et al. found that the analgesic potency of N-methyl morphine was much lower than that of morphine and that the pharmacokinetic parameters differed markedly: the quaternary analogue has a much shorter duration of action (27). In vitro activity showed that N-methyl morphine was only 10% as active as morphine in blocking the electrically-induced contractions of guinea-pig ileal (GPI) tissue (26), and on occasion, the quaternary analogue appeared to reverse the blocking effects of morphine on the tissue (26).

The quaternary morphinan, N-methyl levorphanol, was shown to be active in the GPI test and its effects were reversed by naloxone (28). However, the activity was only 7% that of levorphanol and again the quaternary analogue had a much shorter duration of action (28).

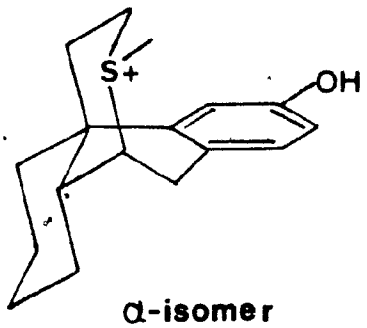
The effect of quaternization on antagonist activity was also investigated. For instance, N-methyl nalorphine with an equitorially oriented N-allyl group was 30% as active as nalorphine in the mouse vas deferens (MVD) assay (29).

Shiotani et al. showed that certain benzomorphans and ring C enlarged benzomorphans (homobenzomorphans) have their nitrogen lone-pair oriented toward the benzene ring, as determined by X-ray crystallographic analysis (Fig. 9) (30). The suggestion that these samples invalidate the nitrogen lone-pair directionality theory is however unjustified. The statement that the homobenzomorphan is as potent as morphine (30) is questionable, since in an earlier paper dealing with synthetic methods, the compound was reported to be too toxic to allow conclusions to be drawn about its analgesic activity (31). The benzomorphan analogue has an activity similar to codeine (32). This weak activity may be readily interpreted in terms of an interaction of the phenyl group with the second lipophilic site of the receptor (15), thus correctly orienting the nitrogen lone-pair toward the anionic site (33).



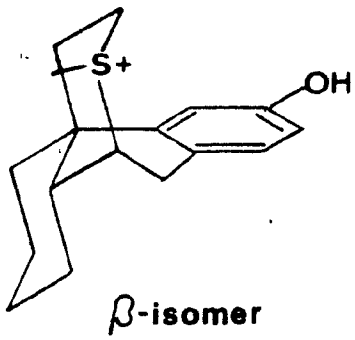
benzomorphan homobenzomorphan

FIGURE 9: Benzomorphans with the ntrogen lone-pair oriented toward the phenyl ring. From reference 30.

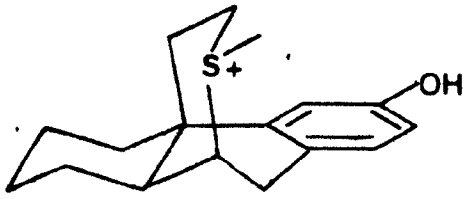


α-isomer

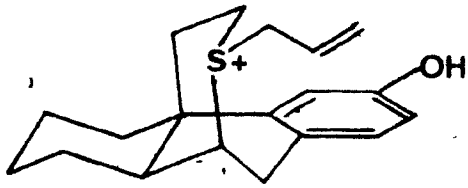
S-methyl sulforphanol



β-isomer



S-methyl
isosulforphanol



S-allyl

FIGURE 10: Sulfur analogues of levorphanol and isolevorphanol.

Recently, morphinans in which the nitrogen has been replaced by a sulfur atom have been synthesized in our laboratories (34-36). The S-methyl and S-allyl sulfonium cations which were generated (34,35) have substituents that usually confer agonist and antagonist activity, respectively, in the morphinan series. Since these sulfur analogues are permanently charged and cannot carry a proton, they can yield precise information about the role of ion-pairing in the absence of steric effects which are associated with the buried charge of quaternary nitrogen cations. These effects are not seen with sulfonium salts (33).

All of the S-methyl analogues behaved as antagonists in the GPI assay but as agonists when administered centrally in rats (33). Since levorphanol and isolevorphanol are potent agonists in both assays, it was concluded that ion-pairing alone can hardly be responsible for agonism in the GPI (33). On the other hand, the agonist activity of the sulfur analogues in the CNS implies that ion-pairing as such may be sufficient to produce analgesia (33).

The GPI results strongly suggest that a proton transfer process at the receptor level is necessary for agonism to be observed. Such a transfer would trigger a cascade leading to proton internalization. In other words, agonists would act as activators of a proton switch (33).

Accordingly, antagonism in the GPI can be viewed as a jamming of the proton switch, an effect clearly expected from a sulfonium analogue since ion-pairing with an external acceptor, A_1, would effectively exclude proton transfer (Fig. 12) (33). The tightness of a hydrogen

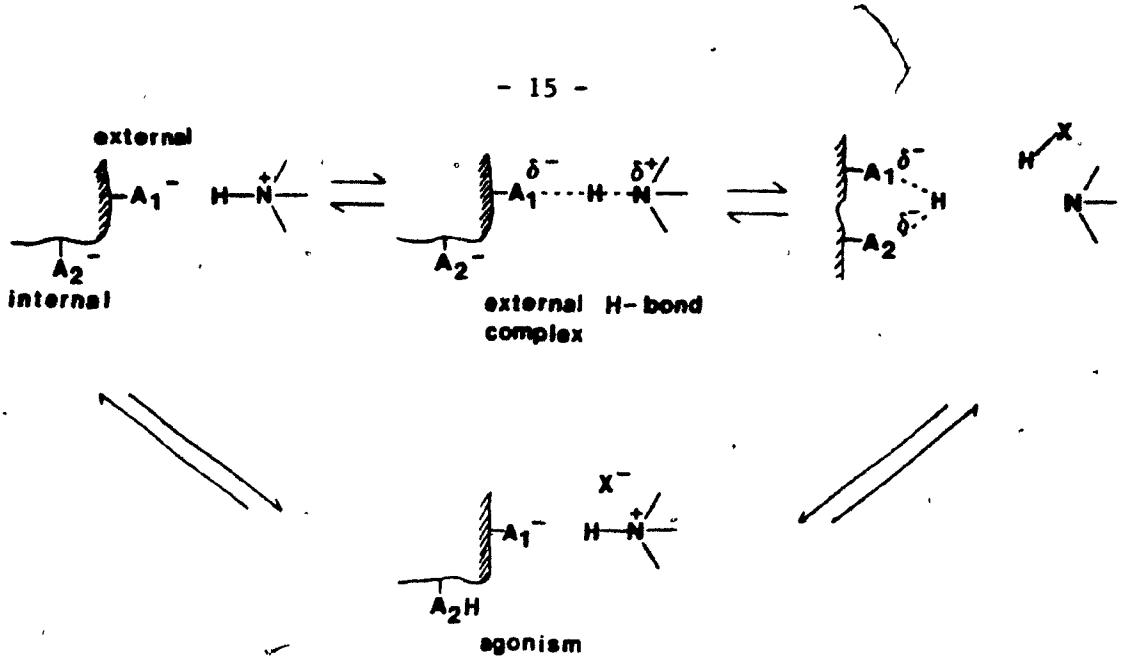
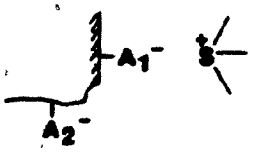


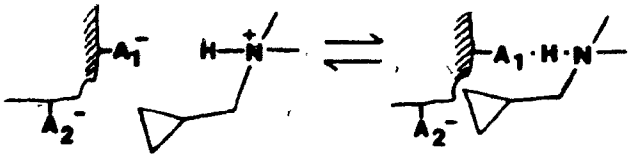
FIGURE 11: Agonism in the GPI may be the product of proton transfer from an external acceptor, A_1, to an internal one, A_2. From reference 33.

bonded proton transfer complex may be critically affected by the nature and size of the N-substituent of morphinans. An increase in binding forces may tighten the proton bridge to such an extent that the switch may be effectively jammed (Fig. 12) (33). This would account for antagonism as induced by specific types of N-substituents.

An interesting question arises as to what role a hydrogen bonded species such as -A-H•••B-, as opposed to a proton transfer complex such as $-A^-\cdots H-B^+-$, may play in the receptor chemistry. For transfer to take place the complex must eventually equilibrate with a hydrogen bonded species in order for the switch to be activated. The oxygen atom of cyclic ethers such as tetrahydrofuran (THF) and 2H-tetrahydropyran are strong hydrogen bond acceptors, which explains their miscibility with water as well as the strong interaction of THF with phenol



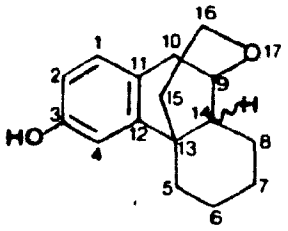
ion pair
no proton switch



tight H-complex
no proton switch

FIGURE 12: Antagonism in the GPI may be due to the blocking of proton transfer from an external acceptor, A_1, to an internal one, A_2. From reference 33.

($\Delta G^{\circ}_{H\text{-bond}}$ = -3 to -4 kcal mole^{-1}) (37). However, oxonium cations are not formed in the usual hydrolytic solvents. It was of interest therefore to generate 17-deaza-17-oxamorphinans as mechanistic probes of the receptor's primary response to a strong H-bond forming species (Fig. 13).



H 3-hydroxy-17-deaza-17-oxamorphinan

H 3-hydroxy-17-deaza-17-oxaisomorphinan

FIGURE 13: Target oxygen analogues of levorphanol and isolevorphanol.

In 1948, Grewe described an elegant, simple strategy, which has found widespread industrial applications, for the synthesis of the morphinan ring system (38). A retrosynthetic analysis of the ring system unravels three crucial disconnections as shown in Figure 14.

Grewe's synthesis involves construction of the carbon 12,13 bond from I, an approach forming the commercial synthesis of levorphanol (39,40) and several related benzomorphans (41). The process could even be adapted to the synthesis of 14-hydroxy morphinans (42). The sulfur analogue referred to above and possessing the isomorphinan geometry (trans-B/C junction) has been prepared by an adaptation of Grewe's strategy (35). Grewe's synthesis generally leads to the cis-B/C geometry (morphinan) although it is possible to obtain the isomorphinan stereochemistry depending on the choice of reagents and substrates (43,44).

Bond formation between the heteroatom at position 17 and C-9 forms the basis of both Gate's and Belleau's approach to morphinans. Gate's strategy using intermediate II was elegantly applied to the first total synthesis of morphine (45), and to synthesis of isomorphinans (46). Belleau's synthetic strategy utilizes the hexahydrophenanthrene intermediate III (47) which has been successfully exploited at Bristol Laboratories to produce morphinans, isomorphinans, and their 14-hydroxy analogues (47-49). This intermediate is also the industrial precursor of the analgesic butorphanol (Fig. 7). This approach offers the advantage of complete stereochemical control at position 14, and in

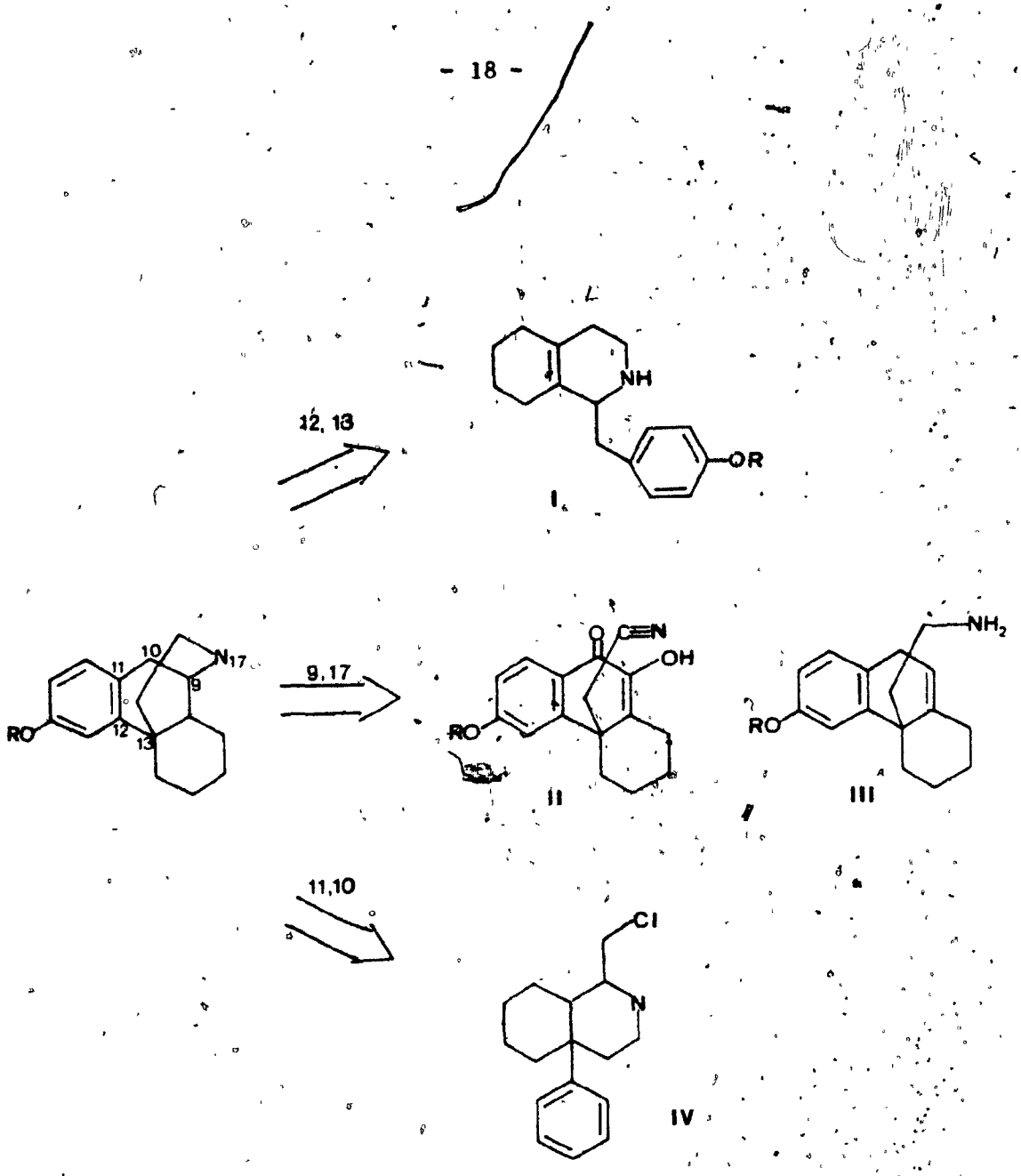


FIGURE 14: Retrosynthetic analysis of the morphinan molecule reveals three key disconnections.

the sulfur series of analogues both stereoisomers have been generated stereospecifically (34,36).

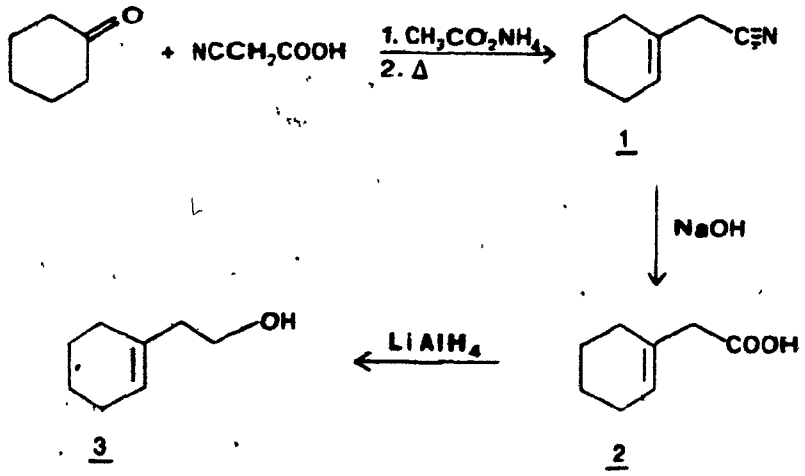
More recently, Evans has used bond formation between C-10 and C-11 in order to produce isomorphinans using intermediate IV (50). Morphinans can be obtained through isomerization of suitably functionalized isomorphinans (51).

Synthesis of the desired oxygen analogues was attempted using both the Grewe and the Belleau strategies. As it turned out, 3-hydroxy-17-deaza-17-oxaisomorphinan was successfully synthesized in 6% overall yield starting from intermediate III.

CHAPTER 2

2.1. Grewe-type Synthesis

The desired alcohol, 3, was made as outlined in Scheme I.



SCHEME I: Synthesis of 2-(1-cyclohexen-1-yl)-ethanol (3).

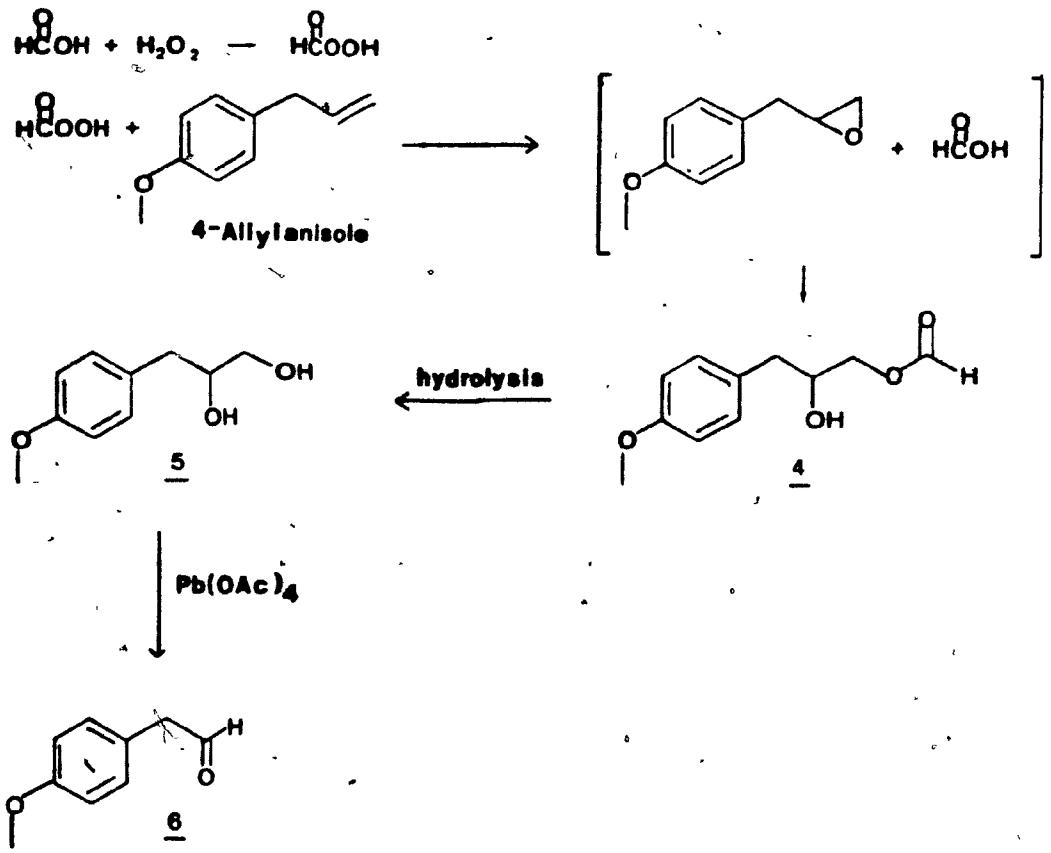
The nitrile, 1, was prepared according to the procedure of Cope et al. (35,52). Thus, cyclohexanone was condensed with cyanoacetic acid in the presence of ammonium acetate, and the resulting α,β-unsaturated-α-cyano carboxylic acid rearranged to the β, γ-unsaturated isomer (53). Thermal decarboxylation yielded the endocyclic double bond isomer through rearrangement of the intermediate exocyclic α,β-unsaturated nitrile. That the endocyclic olefinic structure was actually produced was established by NMR spectroscopy (60 MHz): the olefinic proton appeared as a multiplet centered at 5.8 ppm. If the exocyclic isomer had been produced, that resonance would have appeared further upfield as a singlet (54). The mass and IR spectra also confirmed the assignment: a C≡N stretching vibration at 2240 cm^{-1}, characteristic of aliphatic nitriles (55), was observed.

The nitrile was converted into the corresponding acid, 2, by base-catalyzed hydrolysis with 10% aqueous NaOH (35,56). The spectral properties of the product were consistent with the expected structure: its IR spectrum showed very broad OH stretching vibrations between 3500 and 3000 cm^{-1} as well as a carbonyl stretching mode at 1700 cm^{-1}.

The corresponding alcohol, 3, was then generated by $LiAlH_4$ reduction of the acid, 2, and was obtained in a 26% overall yield based on cyclohexanone. It showed a broad OH stretching vibration at 3420 cm^{-1} in the IR, and the carbonyl stretch of the acid was now absent.

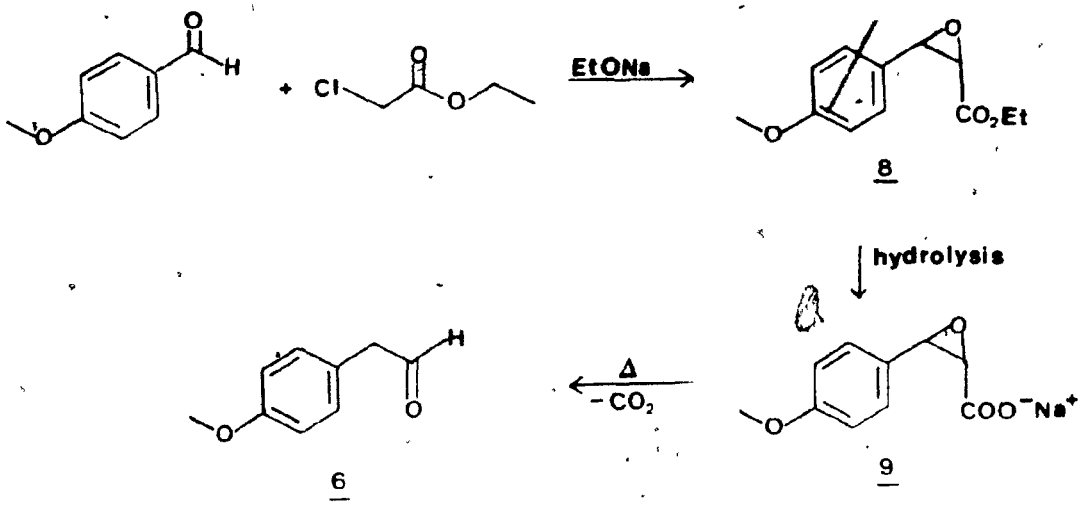
The key intermediate in our synthetic strategy, 4-methoxyphenylacetaldehyde (7), was synthesized by two different methods. The first one is outlined in Scheme II.

The starting material, 4-allylanisole (estragole) was hydroxylated with performic acid which, because of its instability, was generated *in situ* from formic acid and H_2O_2 (57). The intermediate oxirane is not isolatable under these conditions because the formic acid used as solvent opens the epoxide to produce the corresponding hydroxy formate, 4, which was not isolated but immediately hydrolyzed to the desired glycol, 1,2-dihydroxy-3-(4-methoxyphenyl)-propane (5) (57). After purification by vacuum distillation, the glycol's structure was confirmed by NMR, IR, and mass spectroscopy. Lead tetraacetate was then used in order to oxidatively cleave the glycol to the desired aldehyde, 6 (57). The aldehyde was generated in a 28% yield based on the starting alkene.



SCHEME II: Preparation of 4-methoxyphenylacetaldehye (6).

Preparation of this aldehyde was also approached through the glycidic ester intermediate, 9 (58). As outlined in Scheme III, Darzens condensation of 4-anisaldehyde with ethyl chloroacetate in the presence of sodium ethoxide afforded the glycidic ester, 8. The NMR spectrum of the product revealed that before recrystallization it was usually contaminated by the starting aldehyde, 7, and occasionally by the desired aldehyde, 6, itself. This conclusion was based on the observation of a singlet at 10 ppm and a triplet at 9.8 ppm, resonances attributable to the presence of 7 and 6, respectively.



8

9

6

SCHEME III: Alternative preparation of 4-methoxyphenylacetaldehyde (6).

The formation of aldehyde 6 may involve partial hydrolysis by NaOH, a contaminant of the NaOEt, to the sodium glycidate, 9, which then suffers decarboxylation during workup. Indeed, others have already generated the same sodium glycidate from the corresponding methyl ester and shown that the aldehvde, 6, is readily obtained by decarboxylation (59). Glycidic ester, 8, was purified by recrystallization from absolute ethanol to give a light yellow solid, mp 44 - 47° C, which appeared pure as judged by NMR spectroscopy. The pure white solid had mp 46 - 47° C.

Many years ago, Knorr et al. reported that the saponification of the ethyl glycidate leads directly to the aldehyde (60). An alternative synthesis of the aldehyde involves partial reduction followed by hydrolysis of 4-methoxybenzylacetonitrile (61).

In our hands, all attempts to clearly hydrolyse 8 using either aqueous acid or aqueous base, in the presence or absence of organic phases, failed. Many of the 60 MHz NMR spectra of the resulting mixtures showed the desired product to be contaminated with another aldehyde whose carbonyl proton appeared as a singlet in the 10 ppm region. This product may have arisen from the self-condensation of the initially generated aldehyde 6 to yield compound 10 (Fig. 15). Loss of water from aldol intermediate 10 would lead to the α,β-unsaturated aldehyde, but the expected olefinic proton was not seen in the NMR spectrum of the product(s). However, such a proton being β to a conjugated carbonyl should absorb in the 7 ppm region (62) where aromatic protons usually absorb. This may account for our failure to detect the olefinic proton.

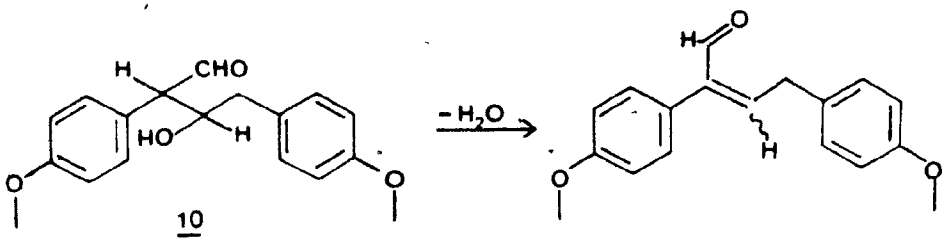
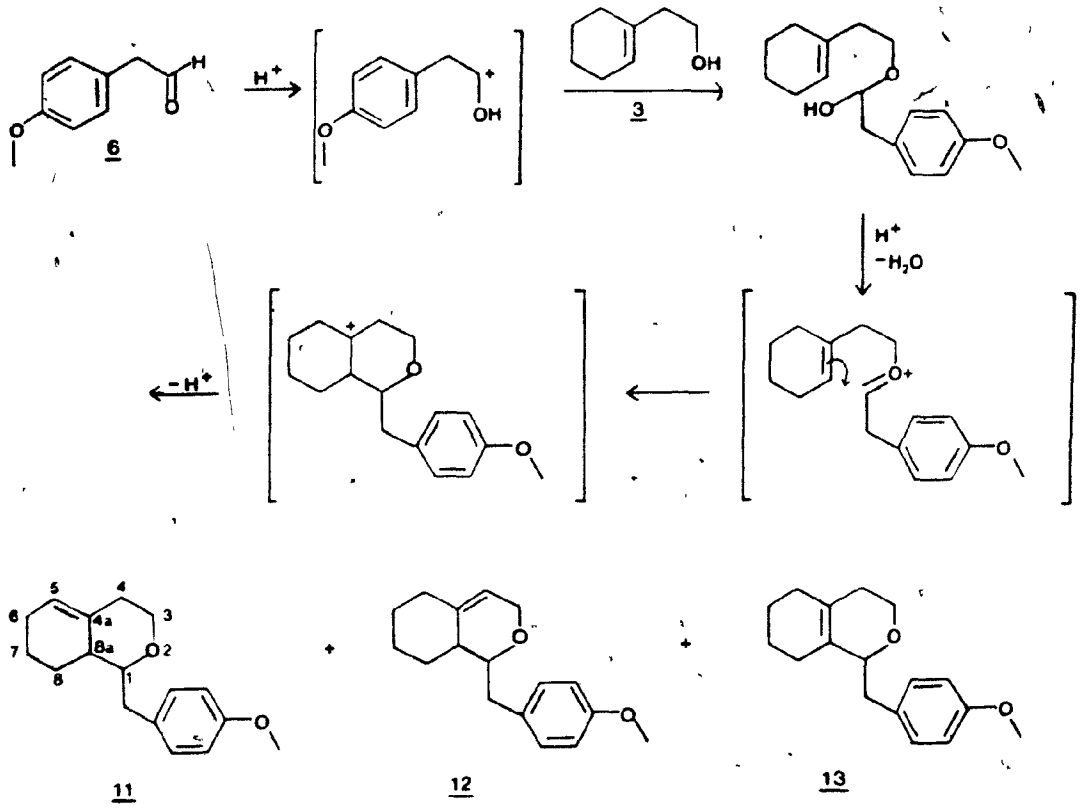


FIGURE 15: Possible side product from hydrolysis of ethyl-3-(4-methoxyphenyl)-2,3-epoxypropionate.

Attention was then turned to the possibility of condensing aldehyde 6 with the cyclohexenyl ethanol, 3, under Prins-like reaction conditions (63) with the hope of generating key intermediate 13. This strategy finds precedent in the work of Williams et al. who were able

to generate substituted dehydrotetrahydropyrans through the acid-catalysed condensation of 4-methyl-4-penten-2-ol with various aldehydes (64). Accordingly, a mixture of 6 and 3 was submitted to the action of trifluoroacetic acid in glacial acetic acid (Scheme IV). The reaction mechanism may be envisioned as involving attack by the alcohol on the carbenium ion resulting from protonation of the aldehyde. Under the influence of acid, the hemiacetal so created loses water, and the resulting oximinium cation suffers nucleophilic attack by the double bond, yielding an intermediate carbocation which may eliminate a proton in three different ways to generate the two tri-substituted olefins, 11 and 12, as well as the tetra-substituted one, 13. It has already been shown that Prins-like coupling of the same aldehyde with 2-(1-cyclohexen-1-yl)-ethane thiol afforded analogous cyclic olefins (35). With the alcohol, 3, mixtures of bicyclic olefins were produced which were separated by flash chromatography. In this manner, isomer 13 could be isolated and characterized by spectroscopic methods.

In the 200 MHz NMR spectrum of the tetrasubstituted olefin, the allylic proton on carbon-1 could be distinguished from the ring protons on carbon-3 by decoupling experiments. The allylic proton appeared as a broad doublet of doublets at 4.10 ppm, and its coupling constants with the benzylic protons at 2.94 and 2.65 ppm amounted to 4 and 8 Hz respectively. The methylene protons α to the ring oxygen appeared as multiplets centered at 4.0 and 3.6 ppm.



SCHEME IV: Coupling of aldehyde and alcohol in the Prins-type reaction.

By 200 MHz NMR spectroscopy, the olefinic protons of the major tri-substituted isomer 11 and the minor isomer 12 could be distinguished: they appeared at 5.54 and 5.44 ppm, respectively. Decoupling experiments proved that the major isomer was 11: irradiation of the olefinic proton had no effect on the signals due to the protons α to the oxygen. Decoupling of these (at 3.28 and 3.99 ppm) unmasked one of the H-4 protons of 11 which absorbed in the alkyl region between 2.45 and 2.17 ppm but the other which also absorbed in the alkyl region was

obscured by other signals. The ratio of 11 to 12 was greater than 85:15.

The same hexahydro-isochromans 11, 12, and 13 could also be prepared using *in situ* generated aldehyde from glycidic ester 8 in 10% aqueous HCl containing some ethanol as a solubilizing cosolvent. Similar condensations have been accomplished using the ethyl or methyl glycidate but in the prsence of γ,δ-unsaturated amines (58,65) or substituted amines (66). This methodology avoided the problem of aldehyde self-condensation to 10 which happened when the glycidic esters were submitted to degradation in a separate step. No products of hydrogen chloride addition were detected. It has already been reported by Hanschke (67) that the HCl- or H_2SO_4-catalyzed Prins reaction of allyl carbinol with various aldehydes leads to 2,4-disubstituted-tetrahydropyrans where the 2-substituent is supplied by the R group of the aldehyde and the 4-substituent is either Cl or OH depending on whether HCl or H_2SO_4 is used as catalyst. The corresponding 2-substituted-3,4- or 4,5-dihydropyrans could be generated from the disubstituted intermediates in a separate step (67). In contrast, the reaction of glycidic ester 8 with aldehyde 6 gave only the unsaturated products 11, 12, and 13. The overall yield was almost double that obtained when TFA was used as the catalyst. In the TFA/acetic acid medium, much of the aldehyde suffered polymerization rather than reacting in a productive manner. In aqueous HCl, the aldehyde intermediate could not accumulate as it was productively consumed once generated from the glycidic ester.

The next problem involved a Grewe-like ring closure to the desired 17-deaza-17-oxamorphinan through a Friedel-Craft type of intramolecular alkylation. A valid precedent for this strategy is found in the HF-catalyzed ring closure of the sulfur analogue of 11 (35) which leads to the isosulforphan stereochemistry (B/C rings trans-fused; 14-β H) rather than the morphinan stereochemistry (cis-B/C rings) seen in the nitrogen series of analogues, a process catalyzed by acids such as H_3PO_4 (39,58) or HBr (58).

As mentioned, the Grewe process with an N-methyl tetra-substituted intermediate leads predominantly to the morphinan ring system in the presence of a Brönsted acid whereas the isomorphinan geometry can be produced when a Lewis acid such as $AlBr_3$ is used (43). Gates postulated that the proton lost at C-12 of the arenium ion intermediate displaces the coordinated Lewis acid at C-14 with inversion of configuration (43); with a Brönsted acid, however, direct protonation at C-14 occurs (Fig. 16).

The geometry at position-1 of the tri-substituted alkene intermediates 11 and 12 is imposed during the Prins-type cyclization process. The planar carbocation intermediate in the reaction may approach the double bond so as to minimize eclipsing effects with the cyclohexene ring. The methoxybenzyl group will adopt an orientation disfavoring such eclipsing effects, and thus yield a transoid product such as 11 rather than the cisoid arrangement as shown in Figure 17.

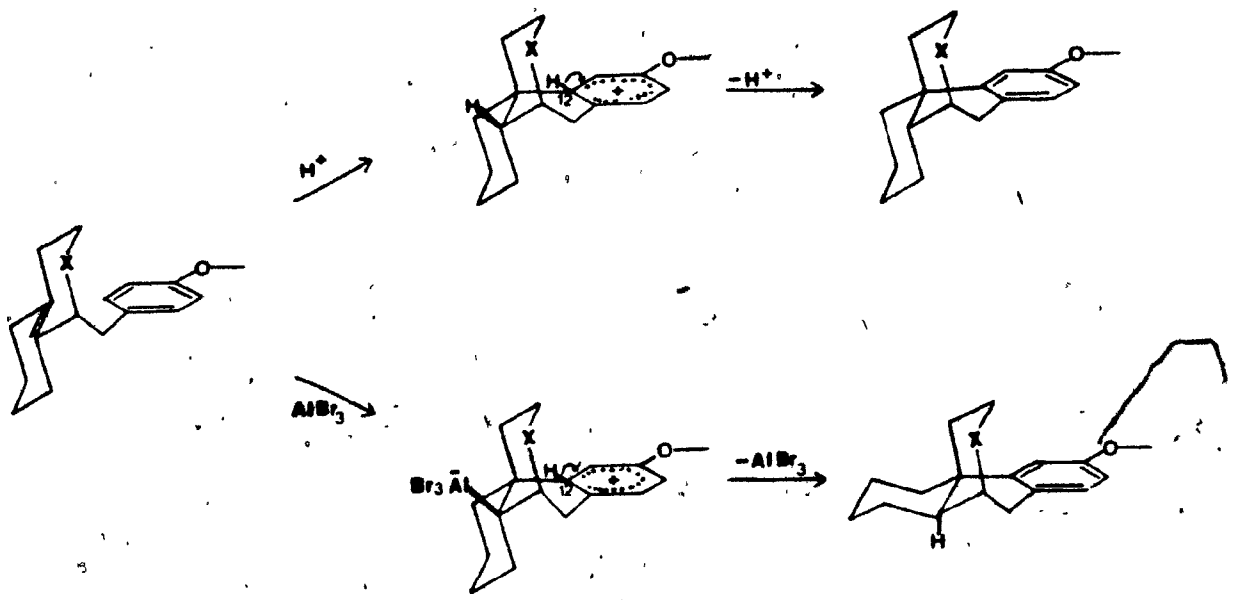


FIGURE 16: Stereochemical outcome of cyclization of the tetra-substituted isomer with H^+ or Lewis acids where X = NCH_3, S, or O (13). Adapted from reference 43.

The stereochemical outcome of a Grewe-like ring closure of trisubstituted olefins 11 and 12 is predetermined by the relative configuration of carbon-8a (43,68). The hydrogen at carbon-8a is found at position 14 after ring closure and will be either cis or trans to the hydrogen initially at position 1 of 11 and 12. Accordingly, their cyclization will lead either to the morphinan or isomorphinan geometries (Fig. 17). In the sulfur series of analogues (35), the exclusive generation of the isomorphinan geometry suggests that isomerization at position 8a (or 14 in the product) does not occur during the process of cyclization.

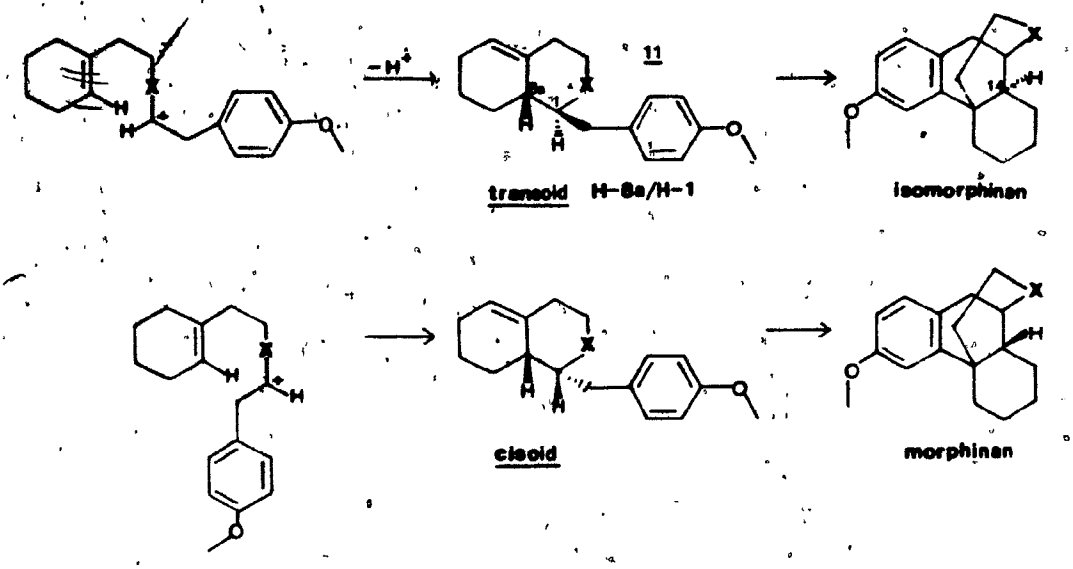


FIGURE 17: Stereochemical consequences of the Prins-type cyclization and subsequent Friedel-Crafts alkylation where X = NCH_3, S, or O.

Unfortunately, all attempts at ring closing 11, 12, and 13 under a variety of conditions failed. Some explanation for these negative results was sought using mechanistic considerations. In order for cyclization to take place the 4-methoxybenzyl group must assume a pseudo-axial orientation since a pseudo-equatorial conformation of the aromatic ring would not allow the carbocation to attack the π-electrons of the olefin. Spectroscopic evidence relating to this point was sought. In the 200 MHz NMR spectra of 11 and 12, the benzyl protons appeared as an AB quartet and the pattern of H-1 was a broad triplet of doublets (1:1:2:2:1:1) (Fig. 18). Since the A and B protons were coupled to H-1 with coupling constants of 9 and 3 Hz, respectively, the H-1 proton must also be coupled to H-8a with a coupling constant of approximately 9 Hz. This value of 9 Hz suggests a trans- or cis-copla-

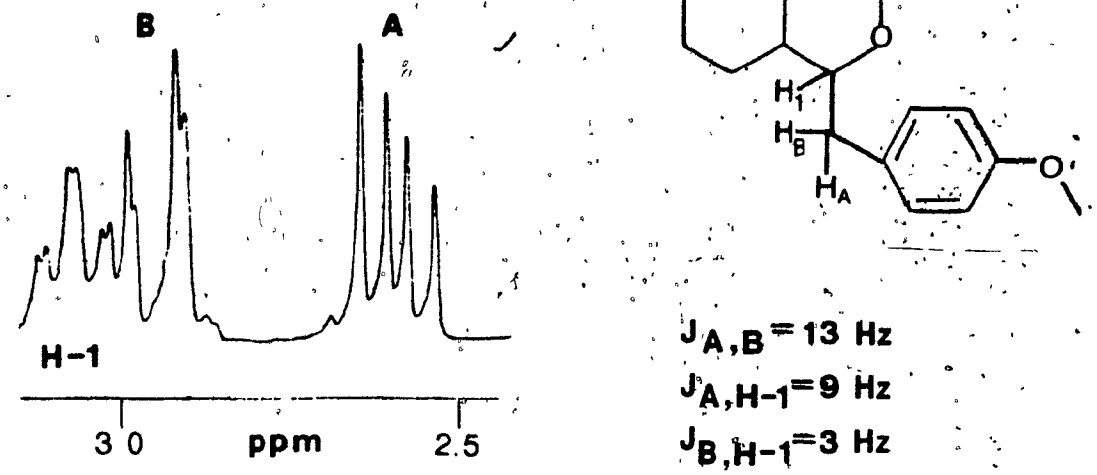
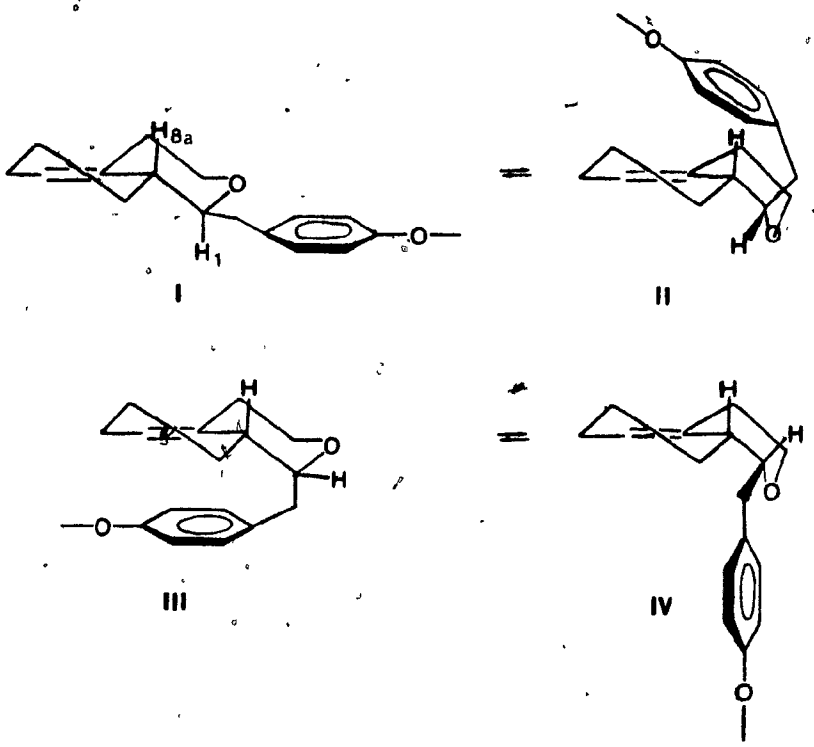


FIGURE 18: A portion of the 200 MHz NMR spectrum of 1-(4-methoxybenzyl)-6,7,8-trihydroisochroman (11).

nar arrangement between H-1 and H-8a as predicted by the Karplus equation (54). This conformation is most closely approached when the benzyl substituent is pseudo-equitorially oriented in the transoid trisubstituted isomer I (Fig. 19). Whether the required pseudo-axial conformer II might be enforced under the cyclization conditions cannot be predicted. For the other isomers, 12 and 13, the benzyl group must also assume a pseudo-axial orientation in order for smooth cyclization to occur.

The failure to cyclize these isomeric olefins to morphinan analogues may be more readily explained on the basis of the instability of the ether function in strong acids. In fact, polymeric material was isolated when cyclization was attempted in HF. As outlined in Figure 20, one reaction pathway may involve fluoride ion attack of the protonated ether followed by loss of water to form a phenyl-1,3-butadiene species which would readily polymerize.



H-8a/H-1		ϕ°	J (Hz)
transoid	I	170	9
	II	60	2
cisoid	III	60	2
	IV	10	8

FIGURE 19: Possible isomers of 1-(4-methoxybenzyl)-6,7,8,8a-tetrahydroisochroman (11) showing the approximate angles, ϕ, between H-8a and H-1 as well as their expected coupling constants.

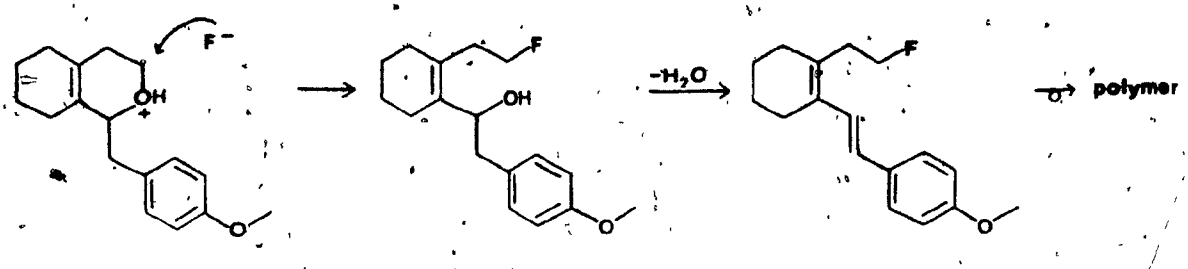


FIGURE 20: One possible pathway for the reaction of 1-(4-methoxybenzyl)-5,6,7,8-tetrahydroisochroman (14) with HF.

One product could have arisen as in Figure 21. Some NMR spectroscopic evidence (60 MHz) was obtained which supports this product. A similar mechanism can obviously be written for the tri-substituted isomers through initial prototropic shifts.

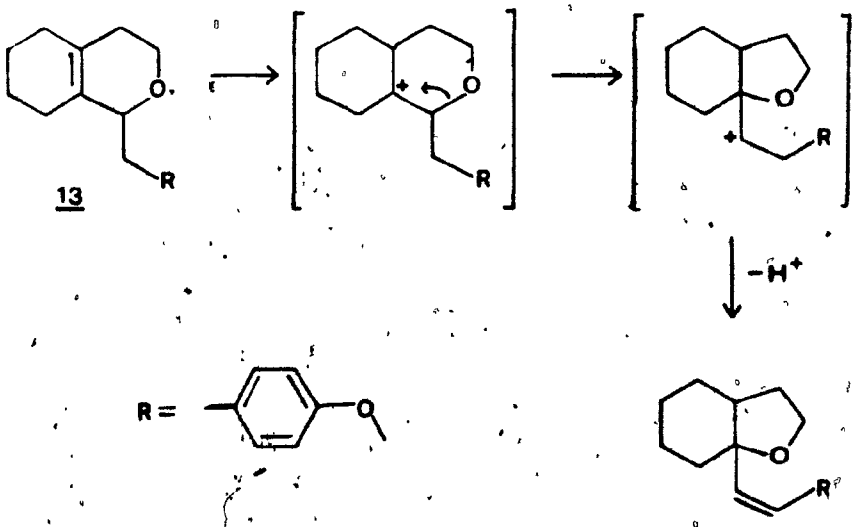


FIGURE 21: Acid catalyzed rearrangement of 1-(4-methoxybenzyl)-5,6,7,8-tetrahydroisochroman (13).

Interestingly, when tin (IV) chloride was used as the Friedel-Craft catalyst, the major product that could be isolated was a conjugated diene whose probable structure is shown in Figure 22. It is to be

expected that the allylic ether oxygens of isomers 12 and 13 will be quite reactive since allyl groups are well-known to stabilize electron deficient carbons.

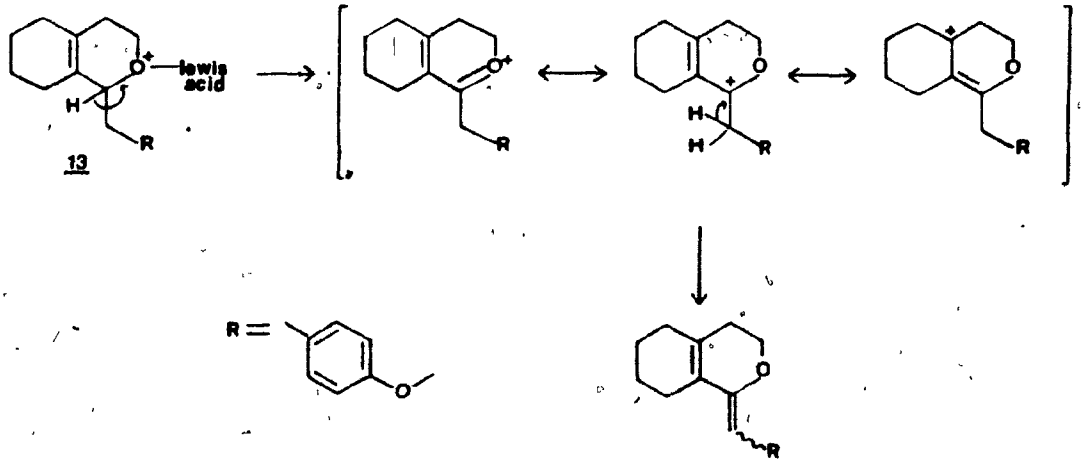


FIGURE 22: Allylic stabiilzation of a positive charge α to an ether oxygen.

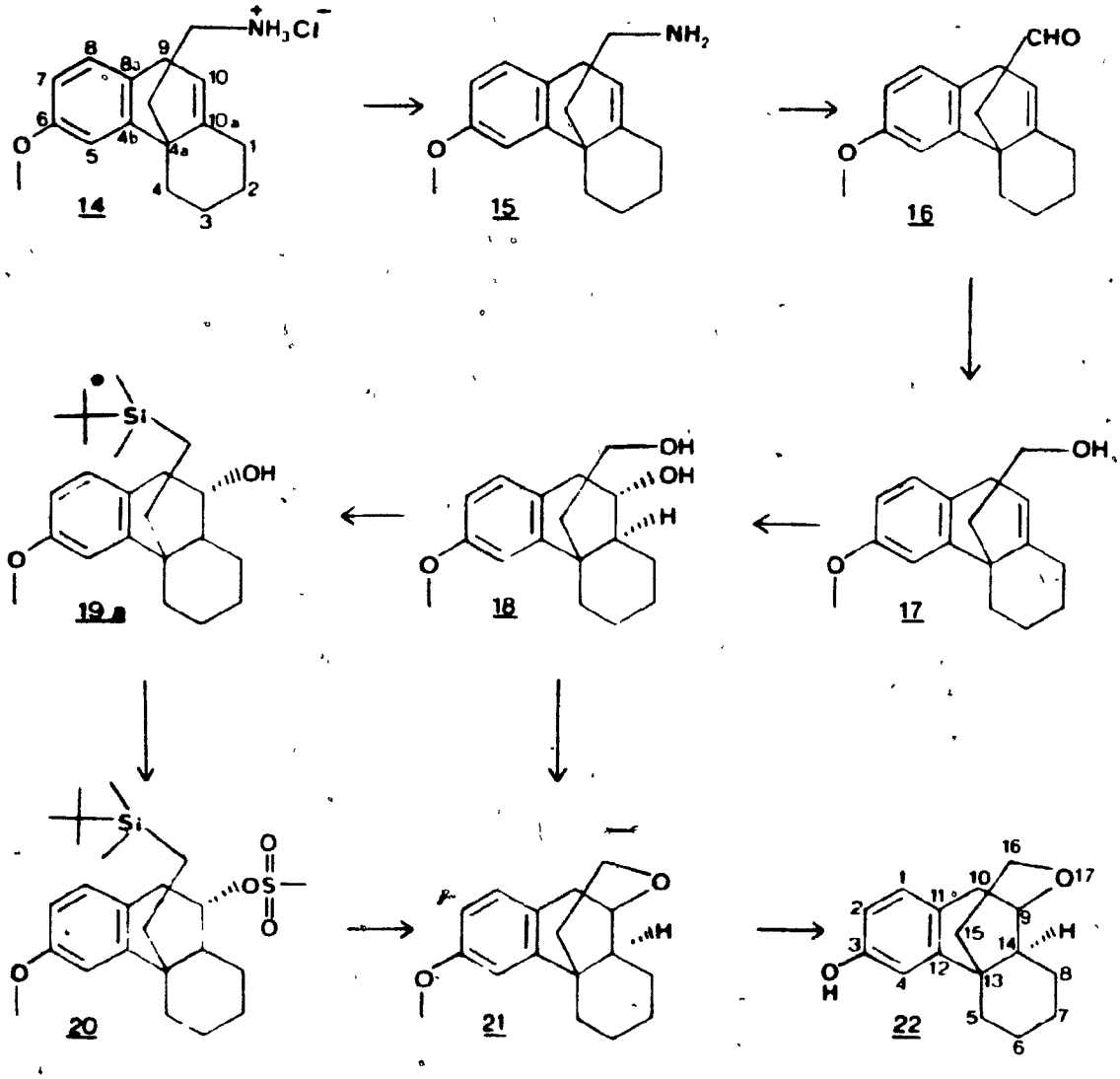
Having failed to generate 17-deaza-17-oxamorphinans by cationic cyclization of 11, 12, and 13, we turned our attention to the possibility of achieving ring closure through radical intermediates using the purified tri- and tetra-substituted isomers as intermediates. These were heated under reflux in benzene for 48 h in the presence of dibenzoyl peroxide as the radical initiator (69). The reaction mixtures were then saponified according to the method of Mashimo and Sato (70) in order to cleave the intermediate benzoates derivable from 11, 12, or 13, and thus liberate hydroxyl groups at the 5, 15, or 14 position (morphinan numbering), respectively. However with the tri-substituted isomers as substrates, only the starting materials were recovered

whereas the tetra-substituted isomer led, as judged by 200 MHz NMR spectroscopy, to 5 compounds, none of which corresponded to the desired product.

2.2. Alternative Strategy

In light of the above negative results, a completely different approach was designed as outlined in Scheme V.

It had already been shown that aldehyde intermediate 16 was obtainable in acceptable yields from the aminoethyl phenanthrene derivative, 14 (34,36). The free base 15 suffers ready transamination when reacted with ninhydrin, a process involving an imine intermediate which undergoes a prototropic shift upon treatment with a suitable base as illustrated in Figure 23 (71,72). As the reaction progresses, a dark purple color develops due to the formation of the diketohydrindylidine - diketohydrinamine anion known as Ruhemann's purple. The yield of 16 was found to depend critically on the purity of the starting material 14. After chromatography of the ninhydrin reaction mixture, aldehyde 16 was obtained in 39% yield as pure white crystals, mp 72 - 74° C. Its mass spectrum showed a weak parent ion at 256 accompanied by a base peak at 212, which is accounted for by the loss of $H_2C{=}C{=}O$. In the 200 MHz NMR spectrum of the product, the protons α to the aldehyde appeared at 3.15 and 2.55 ppm, the latter can be assumed to lie over the aromatic ring. Each of these protons appeared as doublet of doublets and were coupled differently to the aldehydic proton: the downfield one



SCHEME V: Synthesis of 3-hydroxy-17-deaza-17-oxaisomorphinan (22) from 4a-aminoethyl-1,2,3,4,4a,9-hexahydro-6-methoxyphenanthrene hydrochloride (14).

had J = 3.5 Hz and the upfield one had J = 2.0 Hz. The large geminal coupling constant of 15.3 Hz for the methylene protons indicates a contribution from the π-system (54) leading to the conclusion that these hydrogens are oriented toward the π-bonds. The aldehydic proton gave rise to a very closely spaced doublet of doublets at 9.26 ppm. In the IR, the aldehyde carbonyl absorbed at 1715 cm^{-1} as expected.

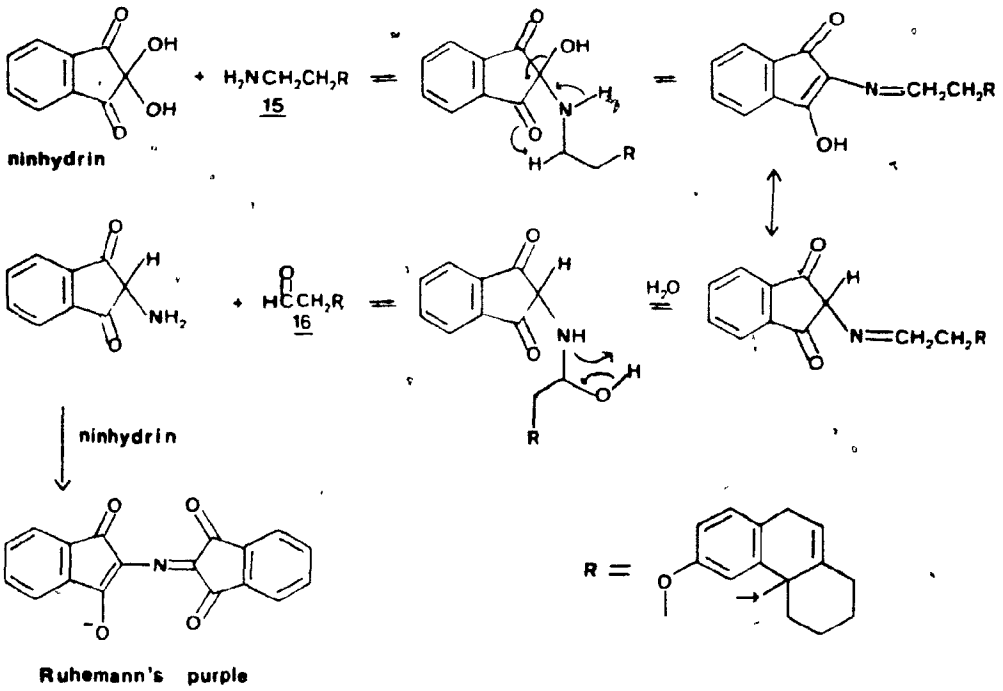


FIGURE 23: Transformation of a primary amine to an aldehyde using ninhydrin. Adapted from references 71 and 72.

The aldehyde function was then reduced in the conventional manner with $NaBH_4$ in ethanol (34,36) to afford the alcohol, 17, (93% yield) which after recrystallization gave a fluffy white solid, mp 69 - 70° C. It is well known that $NaBH_4$ reacts quickly with carbonyl groups but

that it neither reduces isolated olefins nor benzene rings (73-75). The mechanism of reduction is believed to be a stepwise one in which the solvent is involved (76). The IR spectrum of the product was devoid of carbonyl absorbtion but included an OH band centered at 3300 cm^{-1}. The mass spectrum of the alcohol displayed the parent ion at 258, and loss of the ethanol side chain accounts for the base peak at 213. The 200 MHz NMR spectrum of the product was in agreement with the structure but was complicated by an overlap of the resonances due to the benzyl protons and those α to the hydroxyl group.

The stage was now set to attempt the establishment of a bond between the oxygen atom and the double bond of ring B so as to generate the six-membered ether ring. Cyclic ether formation from olefinic alcohols is a well-known process and generally involves electrophilic attack on the olefin followed by nucleophilic attack leading to ether bridge formations. It can be safely predicted that an initial electrophilic attack on the olefin will generate a carbon cation at the more substituted carbon so that ether formation will preferentially involve this carbon atom. A number of literature examples of cyclic ether formation are available and involve base catalysed addition (77), phenylselenoetherification (78), or acetoxymercuration followed by reduction (79). However, it is clear in our case, that the olefinic alcohol, 17, will preferentially lead to five-membered oxa-analogues of hasubanan rather than 17-deaza-17-oxamorphinan. Accordingly, a method imposing six-membered ring formation had to be developed and to this end the generation of diol 18 (34,36) as an intermediate was undertaken by

capitalizing on the stereochemical course of olefin hydroboration as promulgated by H.C. Brown et al.

The expected stereochemical outcome of this reaction at position 10a demands that the final product adopt exclusively the isomorphinan geometry at position 14, as shown in Scheme V. Indeed, it is well known that diborane adds in a syn fashion to the less hindered face of olefins and that the subsequent boron oxidation step proceeds with retention of configuration (80). In addition, with unsymmetrical olefins the reaction is regioselective: the more electro-positive boron atom adds to the least substituted carbon (80). In the case of our 4a-substituted-1,2,3,4,4a,9-hexahydrophenanthrene system, the α-face is clearly less hindered, so that the boron will attach itself in the α-orientation at C-10 and the hydrogen will also be in the α-orientation at C-10a. Subsequent oxidation of the intermediate should then yield the desired diol, 18, with stereochemistry ideal for six-membered ring formation. A valid precedent for these expectations is found in the reaction of the amine analogues of 15 with B_2H_6 in THF which was shown to proceed in the anticipated manner (81).

Alcohol intermediate 17 was therefore treated with a 10-fold excess of the borane - methylsulfide complex in methylene chloride, a modified reagent which shows the same regio- and stereo-selectivity as other borane reagents (82). After the addition, the intermediate was oxidized with H_2O_2 to give diol 18 in a 63% overall yield after purification by chromatography. The hydroxyl protons were identified by the upfield shift of their 200 MHz NMR resonances when the temperature was

increased (a): at 21.4° C, the secondary hydroxyl appeared as a doublet centered at 4.60 ppm, and the primary one, as a triplet at 4.17 ppm. The mass spectrum of the diol showed a very weak molecular ion, and its IR spectrum was insufficiently resolved to be of much value although the hydroxyl stretching mode was seen at 3320 cm^{-1}.

We were now ready to attempt ring closure of the product. Many methods are available for the synthesis of tetrahydropyran rings from 1,5-diols. Cyclodehydration using acid catalysts such as HCl (83) or acidic ion exchange resins (84) will induce cyclic ether formation (85). Alternatively, transformation of one of the hydroxyls into a better leaving group, such as a sulfonate ester, is frequently employed in order to facilitate ring closure by way of alkoxide attack on the carbon bearing the leaving group (86,87). This may be accomplished in a one-pot process by treating the diol with tosyl chloride in pyridine, a procedure previously used for the preparation of various steroid oxa-analogues (88). Ring C oxa-analogues of the morphinans were generated by treatment of diol-monomesylates with potassium t-butoxide (89) or sodium hydride (90) in DMF. It has also been shown that the reaction of certain 1,5-diols with cyanuric chloride leads to tetrahydropyrans (91). Other reagents which will effect ring closure of appropriate diols include Me_2SO (92,93), the sulfurane $Ph_2S(OC(CF_3)_2Ph)_2$ (94), N,N,N'-trialkylcarbodiimidium ion (95), and diethyl azodicarboxylate in the presence of triphenylphosphine (96).

(a) Obtained by F. Sauriol

Tetrahydropyrans have also been obtained through cyclization of 1,5-diol bis-tosylates instead of mono-tosylates. Treatment of a bis-tosylate in hot HMPA promotes attack by water on the di-tosylate to give a mono-tosylate which then suffers cyclization as shown in Figure 24 (87).

In the case of our 1,5-diol, 18, the secondary α-hydroxyl function on ring B is incorrectly oriented for attack on the carbon bearing the primary alcohol group so that monotosylation of the primary OH would not be productive. Unfortunately, selective monotosylation of

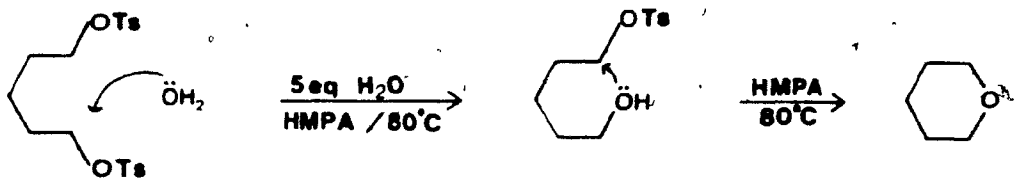


FIGURE 24: Tetrahydropyran formation by intramolecular cyclization of ditosylate. Adapted from reference 27.

the secondary OH is not feasible directly but the bis-tosylate could be readily obtained by treatment of the diol with p-toluenesulfonyl chloride in pyridine for two days at 4° C (97). The product was shown by NMR spectroscopy to have both its OH groups in the form of tosylates. The aromatic region of the spectrum integrated for 11 protons: 3 from the aromatic ring of the phenanthrene system and 8 from the two tolyl residues. The two para-methyl groups appeared at 2.48 and 2.45 ppm as expected.

The ditosylate 23 was heated with 5 equivalents of H_2O in HMPA at 80° C for 6 h, which led to a mixture of 8 products as judged by TLC.

The major product isolated constituted over 50% by weight of the mixture. It was identified by 200 MHz NMR spectroscopy as the tosyloxy-olefin 24a (Fig. 25). Its spectrum showed only one tosyl group at 2.42 ppm and one olefinic proton at 5.60 ppm. This structural assignment was confirmed by direct comparison with an authentic sample obtained by tosylation of alcohol 17 (a,36).

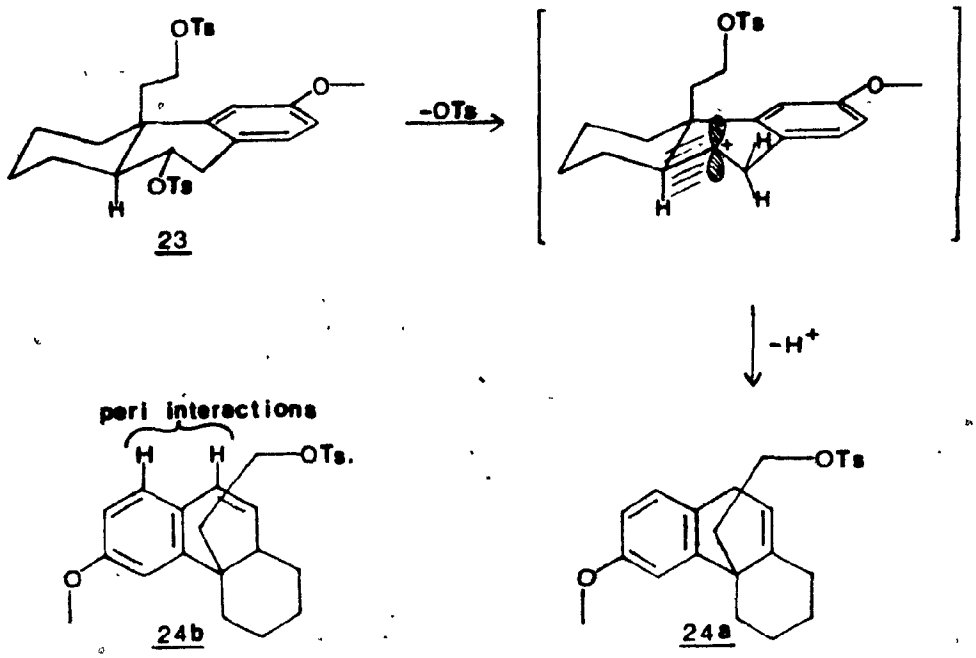


FIGURE 25: Dehydrosulfonation of the ditosylate 23.

This outcome can be explained on the basis that secondary tosylates are known to generate olefins upon solvolysis, a pathway promoted by heating in HMPA or Me_2SO (98). It is interesting to note that the solvolysis did not yield the conjugated styrene 24b but the more sub-

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a. Prepared by R. Camicioli

stituted, albeit unconjugated, olefin 24a where peri-interactions are minimized relative to the styrene isomer.

Since the primary tosylate did not generate the OH group, which would otherwise have displaced the secondary tosyl groups under the reaction conditions, a different strategy had to be developed. The relatively bulky tert-butyldimethylsilyl group should be attachable selectively to the unhindered primary OH group and should be subsequently removable under conditions affecting O-silyl bonds. This strategy would allow for selective mesylation of the secondary hydroxyl. Accordingly, the diol, 18, was reacted with tert-butyldimethylchlorosilane under the conditions of Corey and Venkateswarlu (99). Surprisingly, a significant amount of di-silylated derivative, 19b, was obtained even though only 1.2 equivalents of the reagent was used. The mono- and di-silylated products were obtained, after separation by flash chromatography, in yields of 72 and 14% respectively. The monosilylated diol, 19a, was then mesylated (97) to afford the doubly derivatized intermediate 20. The structure was readily confirmed by ^{1}H NMR spectroscopy (60 MHz): both the silyl ether and the sulfonate ester functions displayed the expected resonances at 3.1 ppm for the mesyloxy methyl and at 0.9 and 0.0 ppm for the tert-butyl group and methyl groups, respectively, attached to the silicon atom.

The O-tert-butyldimethylsilyl protecting group is commonly removed with fluoride ion in DMF at 25° C (99). A modification of this procedure which avoids the use of the troublesome anhydrous tetra-n-butylammonium fluoride involves the application of phase transfer cata-

lysis in the presence of tetra-n-butylammonium chloride and potassium fluoride dihydrate in acetonitrile at 25° C (100). The exchange between $KF \cdot 2H_2O$ and the insoluble $(n\text{-}Bu)_4N^+Cl^-$ generates $(n\text{-}Bu)_4N^+F^-$ *in situ* which is soluble in acetonitrile. Under these conditions derivative 20 was heated overnight in refluxing acetonitrile whereupon the desired cyclic ether, 21, was obtained in a 26% overall yield based on the diol, 18. No products of elimination reactions were observed even though mesylates are known to solvolyse in polar solvents (98). Obviously, deprotection of the silyl group by the fluoride ion created the corresponding alkoxide ion which then attacked the secondary mesylate group. Thus, it was unnecessary to generate the free primary alcohol function in a separate step prior to cyclization. When the recommended reaction time and temperature (4 h, 25° C) (100) were used for O-desilylation, no deprotection was observed as judged by TLC and by NMR spectroscopy. The di-silylated by-product, 19b, was also left unchanged under the same recommended reaction conditions.

Although the above strategy for the synthesis of 21 proved adequate, it was eventually found that the same product could be obtained simply by heating the diol, 18, in Me_2SO at 150° C for 20 h. This method has been used previously to generate 5-, 6-, and 7-membered cyclic ethers from the appropriate diols (92). It is relevant to note that tertiary and secondary alcohols can be dehydrated by heating in Me_2SO (37); however, in our case, cyclization occurred without evidence of dehydration of the secondary alcohol function.

Two mechanisms have been postulated for this cycic ether-forming reaction. The first postulates the formation of a six-membred transition state (TS I, Fig. 26) (93); the other would involve Me_2SO association with one of the hydroxyls to form a four-membered transition state (TS II, Fig. 26) (101). When diastereomeric disecondary 1,4-diols are cyclized under these conditions, the stereochemistry of the product 2,5-dialkyl-tetrahydrofurans can only be explained by an SN_2-type mechanism. Mihailovic et al. argue that the hydroxyl groups of 1,4-diols are too far apart to interact <u>simultaneously</u> with Me_2SO, thus disfavoring the formation of a 6-membered TS (101).

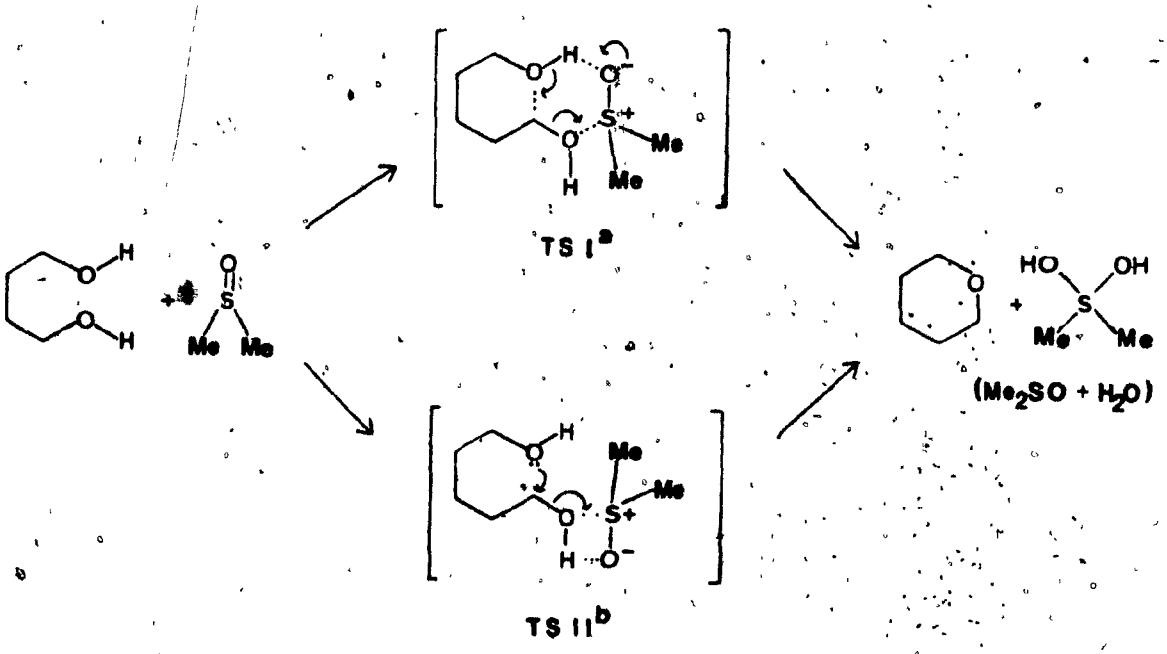


FIGURE 26: - Proposed transition states, TS, for reaction of Me_2SO with 1,5-diols.

a. Adapted from reference 93.

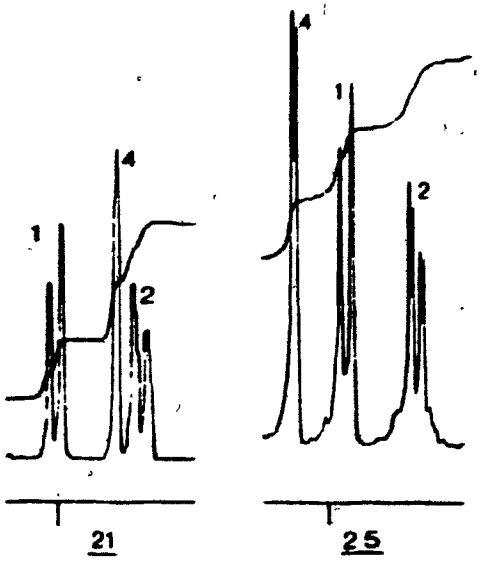
b. Adapted from reference 101.

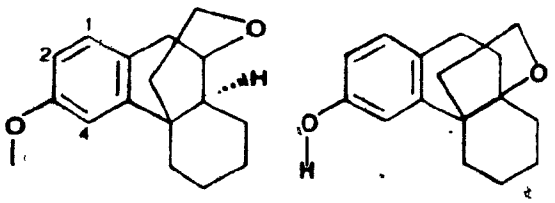
Apart from establishing the identity of the cyclic ether, 21, spectroscopic analysis (200 MHz NMR, IR, and MS) also established that no isomerization of the proton at position 14 could have occurred: the spectra of 21 synthesized by the O-silyl-O'-mesylate route and those of the Me_2SO route were identical.

It remained to deprotect the phenolic hydroxy group of the product. This function has been generally masked as a methyl ether in the field of morphinan synthesis because of its stability to a wide range of experimental conditions and ready removal under selective, non-destructive conditions (102). In some Grewe-type syntheses of morphinans, O-demethylation and cyclization are accomplished in a single step (40,58,66).

The reagent of choice to cleave ethers is BBr_3 which gives good results in both the nitrogen and sulfur series analogues (34-36). Accordingly, the 3-methoxyoxaisomorphinan, 21, was treated with BBr_3 in CH_2Cl_2 at -78° C, then stirred at room temperature for 1 h. After workup, a complex mixture of products was obtained, the major one surprisingly being 3-hydroxy-17-deaza-17-oxahasubanan (25). The structure was assigned on the basis of NMR, IR, and mass spectral characteristics. There are interesting differences in the aromatic region in the NMR spectrum of this ring system relative to that of the starting material 21 (Fig. 27). In 25, the H-4 proton was shifted downfield, possibly due to greater crowding by the protons at positions 5 and 15 of the hasubanan analogue. A plausible mechanism for this unexpected rearrangement of 21 to 25 is shown in Figure 28.

We then exposed 21 to BBr_3 under a variety of different experimental conditions by changing the reagent concentration, the reaction time and temperature but to no avail. Attention was then turned to iodotrimethylsilane, a reagent known to be effective in causing O-alkyl fissions. It is also known, however, to cleave aliphatic ethers including cyclic ones, but it is not clear whether aromatic ethers are more susceptible to its action than aliphatic ones. Whereas Jung and Lyster found that dialkyl ethers are cleaved faster than aryl methyl ethers (103), Olah et al. found the reverse to be true (104). The mechanism of aromatic methyl ether cleavage involves attack by the





21 25

δ (ppm)	21	25
H-1	7.06	6.93
H-2	6.75	6.70
H-4	6.83	7.14

FIGURE 27: Aromatic region of the 200 MHz NMR spectrum of the oxaisomorphinan 21 and of the oxahasubanan 25.

silicon on the oxygen atom to give an intermediate complex of structure $H_3C(R)O^+$-Si(Me)$_3$. This reacts with iodide to give methyl iodide and the O-silyl intermediate which is eventually decomposed by methanolysis (102). The reaction proceeds well when quinoline is used as the solvent (105), the actual reactant being a 1:1 complex between iodotrimethylsilane and quinoline. In order to account for the enhanced silylating ability of tert-butylchlorodimethylsilane in the presence of imidazole, Corey et al. have proposed the formation of an analogous complex (99).

The methoxyphenol 21 was heated at 130° C with Me_3SiI in quinoline for 2.5 h under N_2 to yield a mixture of products as judged by TLC. After chromatography compound 26 was isolated and characterized

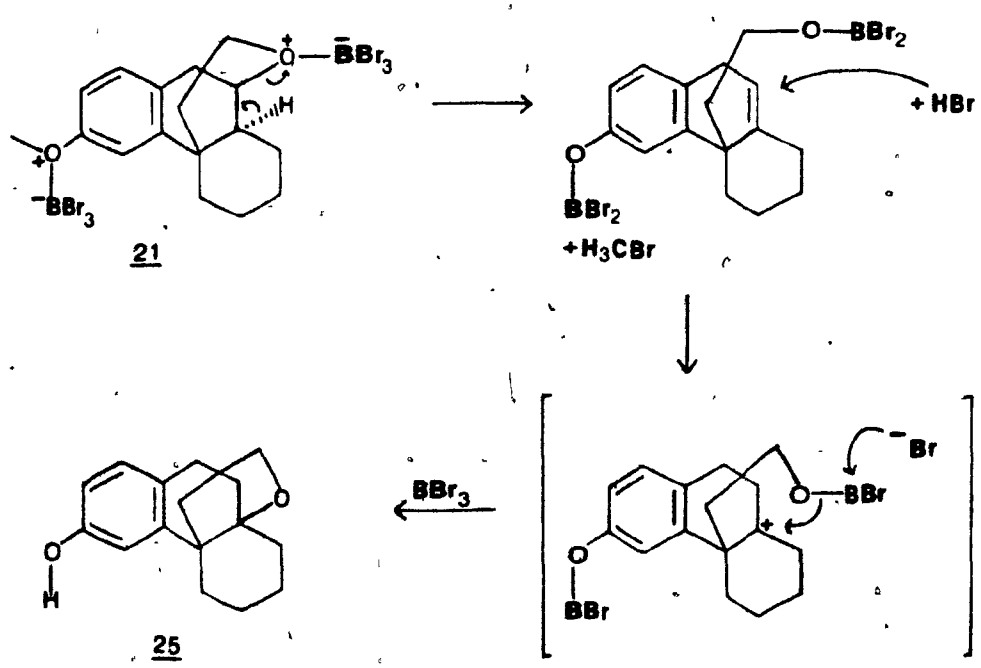


FIGURE 28: Possible mechanism for the rearrangement of the oxaisomorphinan 21 to the oxahasubanan 25.

by 200 MHz NMR, IR, and mass spectroscopy. The mechanism of this reaction would appear to involve a quinoline-promoted proton elimination from a silyloxonium ion intermediate as shown in Figure 29. The NMR spectrum of that product showed resonances characteristic of a styrene double bond: two doublet of doublets at 6.45 and 5.56 ppm arising from H-9 and H-10, respectively (37). The coupling constant for the cis-olefinic protons amounted to 9.5 Hz. The vicinal constant for H-10 and H-10a was 2.4 Hz, and a transoid allylic coupling of 3.4 Hz for H-9 and H-10a was observed.

Although in the classic morphinan series, O-demethylation by BBr_3 is straightforward, our difficulties with BBr_3 as an O-demethylating reagent for cyclic ether 21 are not entirely unprecedented. In fact,

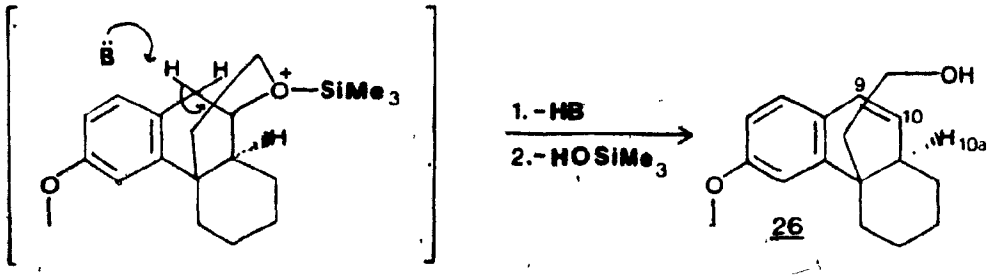


FIGURE 29: Formation of 4a-(2-ethanol)-6-methoxy-1,2,3,4,4a,10a-hexahydrophenanthrene (26).

some ring C oxamorphinan analogues such as I and IV (Fig. 30) appeared to suffer some ring cleavage upon attempted O-demethylation with BBr_3 (89,90). Intriguing substituent effects on the relative stability of the ether rings have been noted.

The desired O-methyl fission can fortunately be accomplished by different methods not relying on the Lewis acid properties of the reagent. Nucleophilic attack of the methyl group by suitable reagents can effect O-demethylation since the phenoxide anion is a good leaving group in such displacement reactions. For instance, both the morphinans and isomorphinans of general formula I and IV (Fig. 30) are O-demethylated by the nucleophilic ethylthiolate anion in DMF, or by the diphenylphosphide anion in THF (89,90). We were therefore encouraged to apply such an apparoach to our problem of selective O-demethylation of 21, keeping in mind that reagents with strong Lewis acid properties attack the ring oxygen very readily. Most nucleophilic reagents are reputed to be selective for aryl alkyl ethers (106). A few, such as sodium or lithium in liquid ammonia with a suitable co-solvent, sodium in piperidine, or sodium N-methylanalide in HMPA, also cleave diaryl ethers (106).

It has been reported that lithium iodide in 2,4,6-collidine will O-demethylate a phenol of the steroid series upon heating under reflux for 48 h (107). In our hands, when 21 was subjected to the same conditions for 72 h, only starting material was recovered. Similarly, when 21 was treated with NaCN in hot Me_2SO for 72 h, only starting material was again recovered even though McCarthy et al. could deprotect all but the most electron-rich by this method (108).

More encouraging were the reports that the thioethoxide ion will effectively O-demethylate morphinan analogues incorporating heterocyclic oxygen rings (89,90), a finding based on the general method of

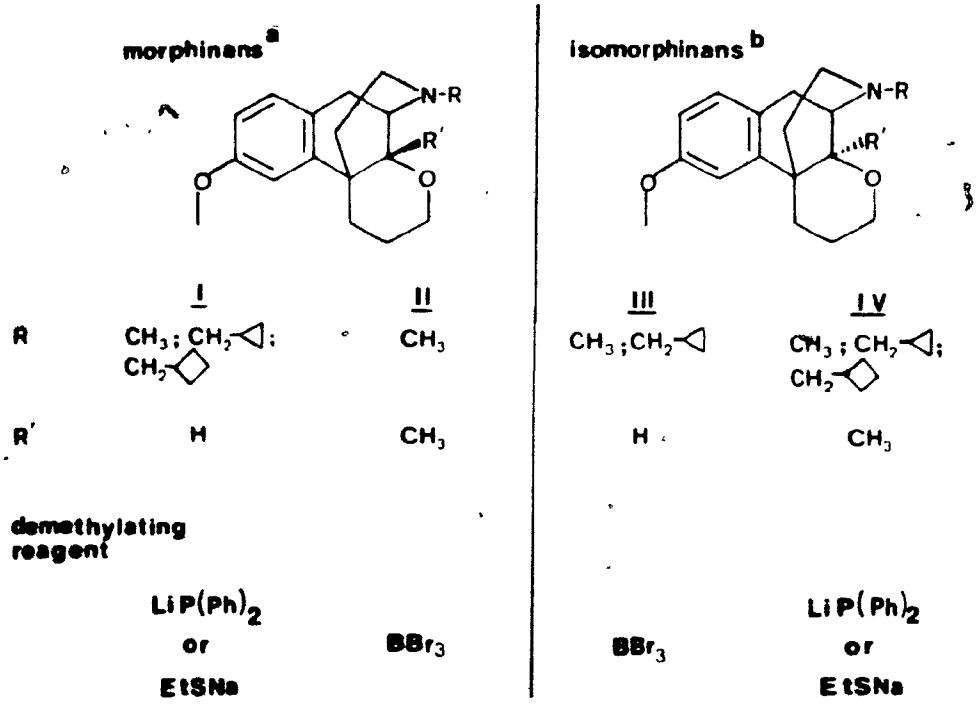


FIGURE 30: Demethylation of 3-methoxymorphinans containing an oxygen heterocycle.

a. Adapted from reference 90.

b. Adapted from reference 89.

Feutrill and Mirrington (109). Accordingly, ethane thiol was added to sodium hydride in DMF at 0° under nitrogen, and to the resulting solution of sodium thioethoxide, the oxaisomorphinan, 21, was added, and the reaction was heated to reflux for 5 h. The desired phenol, 22, was isolated from the resulting mixture in 37% yield after chromatography. Recrystallization from absolute ether afforded white crystals, mp 158.5 - 160° C. The starting material was recovered in 31% yield.

The identity of 22 was established by ^{1}H- and ^{13}C-NMR (see Appendix), IR, and mass spectroscopy. In the mass spectrum of the product the molecular ion of mass 244 was also the base peak.

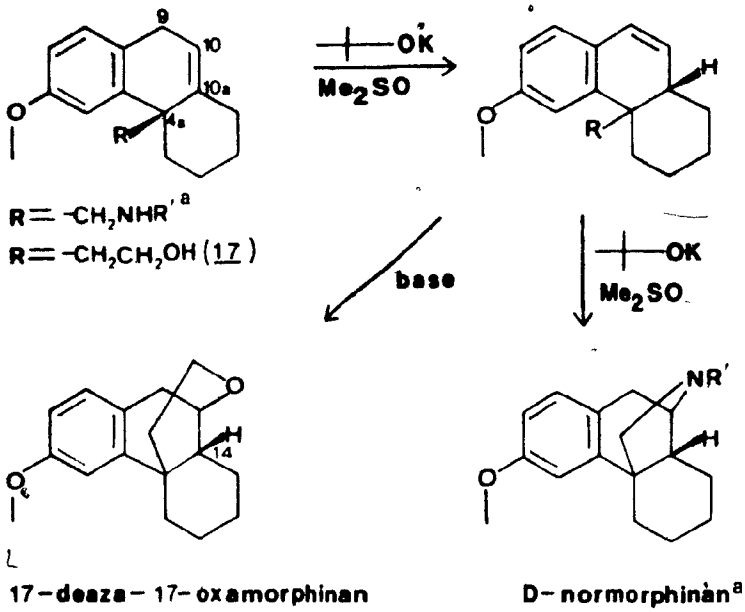
The overall yield of 22 from diol 18 was 28% by the direct Me_2SO cyclization route and 10% by the O-silyl-O'-mesylate route. The total yields from the ammonium salt, 14, were 6 and 2%, respectively.

CHAPTER 3

3.1. Approaches to the Synthesis of Oxamorphinans

It was envisioned that the morphinan isomer of 22, where the B/C ring junction is cis, might be obtainable from the olefin intermediate 17 already described. The rationale is based on the finding of Conway et al. that potassium tert-butoxide smoothly catalyzes double bond migration from the 10,10a-position of N-alkyl-4a-aminomethyl-hexahydrophenanthrene systems to the conjugated isomers as shown in Scheme VI (48). This proton transfer process is stereospecific and leads exclusively to the morphinan geometry through β-face protonation at C-10a by a thermodynamically controlled mechanism. This ready access to the styrene analogue was taken advantage of by capitalizing on the ability of the styrene double bond to act as an electrophile in a ring closure reaction leading to D-normorphinans as shown. Under similar conditions olefinic alcohol 17 could be induced to isomerize stereospecifically to 27 (34,36). It was anticipated that 27 might also be induced to undergo ring closure to 17-oxamorphinan upon further treatment with a strong base since the addition of alkoxide to a styrene system is known (77).

Accordingly, the isomerization of 17 to 27 was attempted using potassium tert-butoxide in Me_2SO under N_2. After 4 days (34,36), analysis of the mixture by TLC revealed the presence of two products, neither corresponding to the starting alcohol. The NMR spectrum of the crude product showed unaccountable resonances, and the hydroxyl absorbtion in the IR was absent. Chromatographic separation was not attempted because alcohol 27 is known to be unstable in air or in the



SCHEME VI: The use of base to produce morphinans. a. Adapted from reference 48.

adsorbed state. However, authentic alcohol 27 was available from previous work (a), and attempts to cyclize it to the oxamorphinan were undertaken.

The alcohol 27 was heated to 100° C with 1.6 equivalents of potassium tert-butoxide in dry DMF under N_2, according to the conditions of Giles et al. (77). After 12 h, no evidence that the substrate had been consumed was obtained (TLC; NMR and IR spectroscopy). Attention was then turned to the possibility of using the epoxide corresponding to 27. Epoxidation of the substrate followed by reduction might provide a diol intermediate such as shown in Scheme VII which

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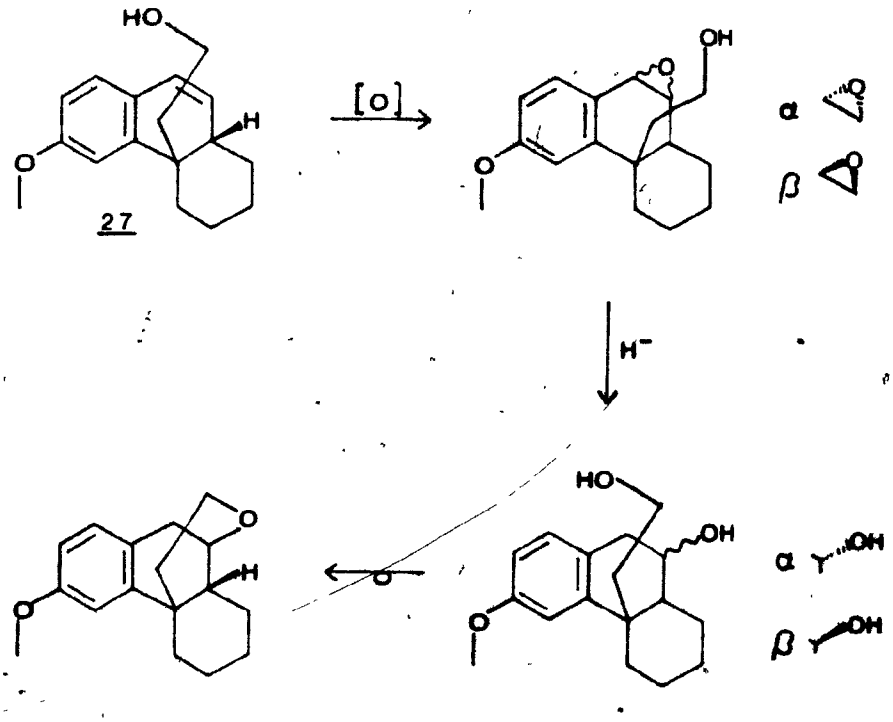
a. Prepared by R. Camicioli

should be readily cyclizable in a manner similar to that already used successfully in the oxaisomorphinan series (Scheme V).

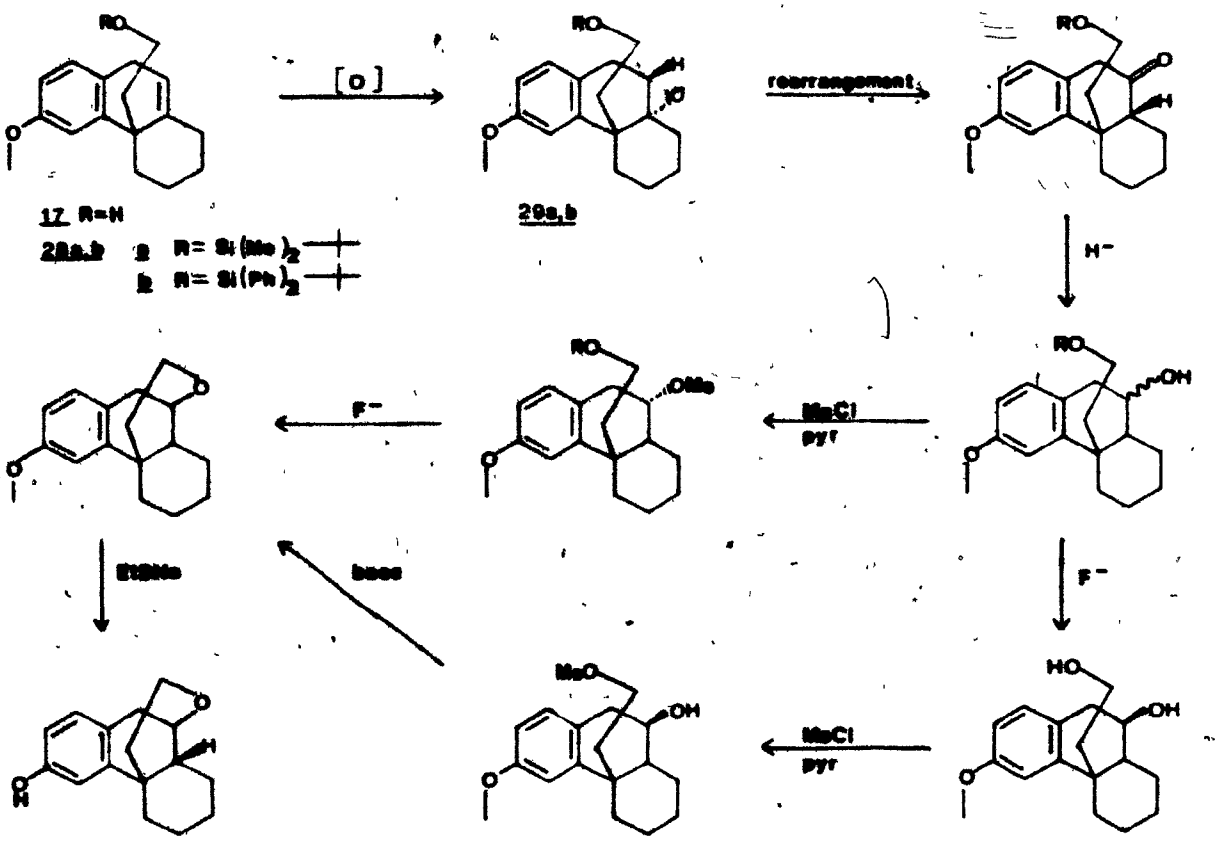


SCHEME VII: Synthesis of oxamorphinan from the isomerized alcohol 27.

Meta-chloroperbenzoic acid was chosen as the epoxidation reagent for 27. It is known that epoxidizing reagents usually proceed by attack of the least hindered face of the olefin (110), which in the case of 27 coincides with the α-face of the molecule. Approach from the β-face is hindered by the angular substituent, but this effect may be offset by the possibility of H-bonding between the free OH group and

the reagent (110). In such a case, the β-epoxide would be formed predominantly. As it turned out, reaction of 27 with MCPBA (111) led to a complex mixture of products as judged by TLC, and little if any of the desired intermediate appeared to be formed.

Not only were these hypothetical routes fruitless, the difficulties associated with the preparation of consistently pure 27 induced us to explore other strategies. One such strategy is outlined in Scheme VIII.



SCHEME VIII: Synthetic route toward 6-hydroxy-17-deaza-17-oxamorphinan.

The rearrangement of epoxides into carbonyl compounds is well known and occurs upon heating or through the influence of protons, Lewis acids, or bases (112,113). With an unsymmetrical epoxide there are two main factors which determine the nature of the product (112,114): the C-O bond breaks preferentially at the more substituted carbon atom, and the substituent which preferentially migrates is, in order of probabilities, aryl > acyl > H > ethyl > methyl. The incipient tertiary carbocation of the α-epoxides, 29a and 29b, is a factor which should favor opening of the epoxide at position 10a, thus inducing stereospecific migration of the antiperiplanar β-H at position 10 to position 10a as shown in Figure 31. This process leads to the desired cis-B/C ring fusion.

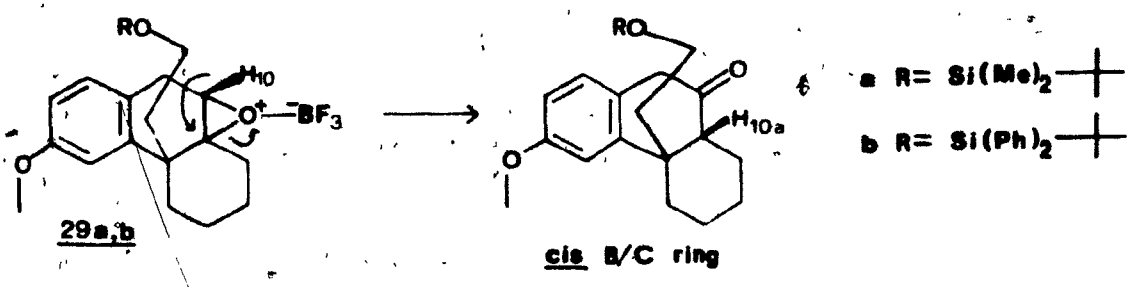


FIGURE 31: Boron trifluoride catalyzed epoxide rearrangement.

The newly generated carbonyl group might then be reduced stereospecifically to yield either the α- or β-alcohol, either of which could ultimately be cyclizable to the oxamorphinan.

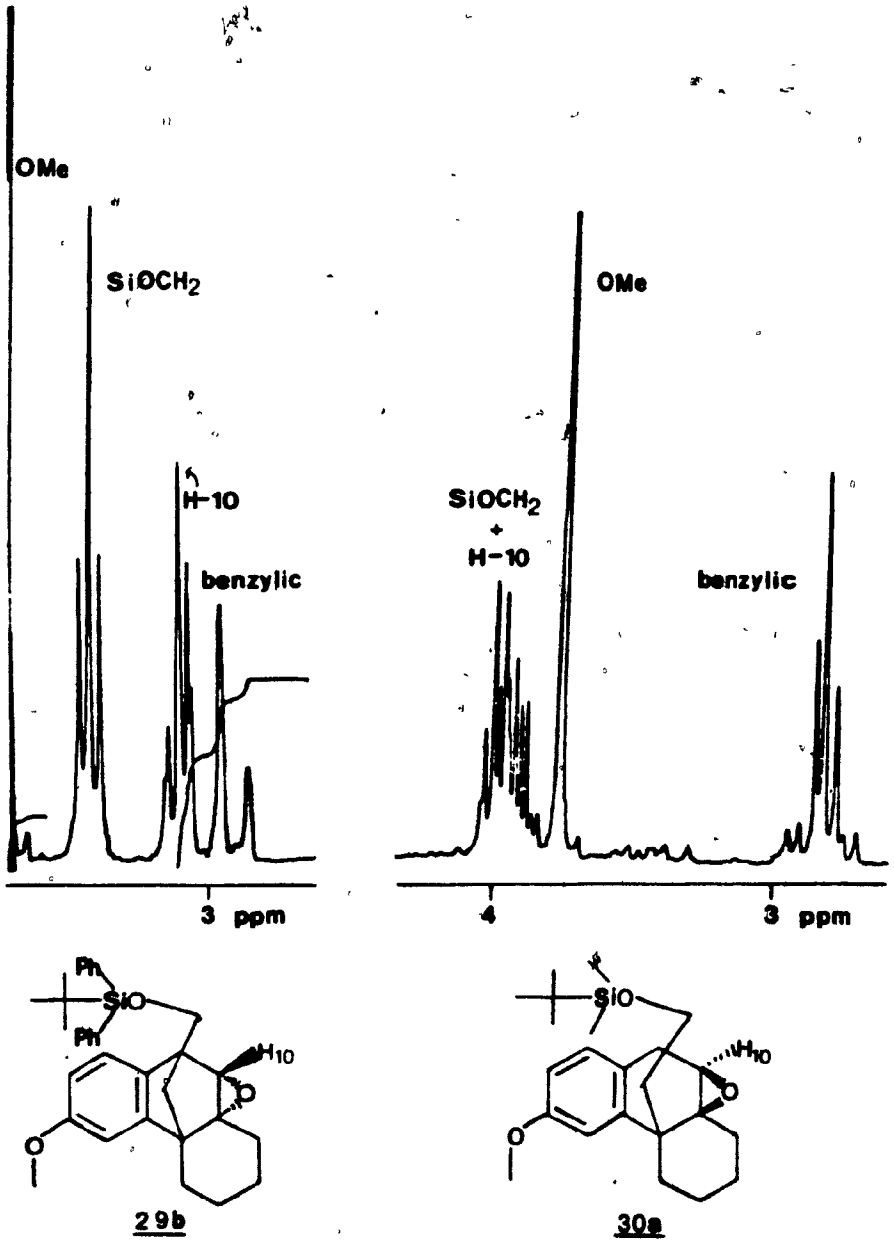
The hydroxyl function of 17 was first protected as the tert-butyldimethylsilyl ether (99). Subsequent oxidation of the olefin with MCPBA (111) afforded a mixture of α- and β-epoxides which were separa-

ted by flash chromatography. The desired α-isomer was isolated in 92% yield; the balance consisted of the β-isomer. The mass spectrum of both epoxides showed a weak molecular ion and a relatively strong M-57 peak corresponding to the loss of the t-butyl group.

In the 200 MHz spectrum of the α-epoxide an AB quartet at 3.20 and 3.11 ppm was observed for the benzylic protons. The geminal coupling constant was 17 Hz. The C-H proton of the epoxide appeared within the pattern and was centered at 3.21 ppm. The methylene group alpha to the silyl ether appeared as a triplet centered at 3.35 ppm and the vicinal coupling constant of these protons amounted to 7.5 Hz.

For the β-epoxide, the benzylic protons gave rise to an AB system at 2.88 and 2.78 ppm. Both protons were coupled to the proton of the epoxide and characterized by J values of 6 and 10 Hz respectively. The geminal coupling constant was 16.5 Hz and the center peaks were coincident, so that seven instead of eight lines were seen (Fig. 32). The epoxide proton was identified by decoupling of the benzylic ones to reveal characteristic resonances between 4.1 and 3.8 ppm. The $SiOCH_2$ protons also absorbed in this region, suggesting that interaction with the electronegative oxygen of the epoxide might account for these protons appearing downfield relative to those of the α-epoxide.

The next step involved BF_3-catalyzed rearrangement of the epoxide 29a. The question of the stability of the tert-butyldimethylsilyl protecting group to the catalyst should depend on the reaction conditions (102). When the protected alcohol 28a was reacted with $BF_3 \cdot OEt_2$ in dry benzene at room temperature under nitrogen, O-deprotection



29b 30a

FIGURE 32: 200 MHz NMR spectra of α-epoxide 29b and β-epoxide 30a.

occurred and reached completion after 10 minutes. After one minute, the recommended time of exposure for epoxide rearrangement (115,116), a significant amount of starting material remained unchanged. Under these conditions, the α-epoxide 29a led, after one minute, to a mixture of products as judged by TLC and which showed OH absorbtion in the IR.

Therefore, we elected to protect alcohol 17 as the more stable tert-butyldiphenylsilyl ether derivative (117). This function is known to be stable toward $BF_3 \cdot OEt_2$ (102) while being easily removable by exposure to fluoride ion. Derivative 28b was characterized in the usual manner by NMR, IR, and mass spectroscopy. As anticipated, in the mass spectrum the parent ion was absent because of the ready loss of the t-butyl group. The derivative was then epoxidized with MCPBA (111) to give exclusively the α-epoxide, 29b; a result reflecting the greater bulk of the tert-butyldiphenylsilyl group relative to that of the tert-butyldimethylsilyl group. The epoxide was characterized as before by NMR, IR, and mass spectroscopy. Here again, the parent ion was not observed in the mass spectrum because of the ready loss of the t-butyl group.

The relevant NMR characteristics of this α-epoxide are shown in Figure 32 where it can be seen that the benzylic protons appeared as an AB quartet, one of them, probably the α-proton, is at 3.10 ppm and shows coupling to the epoxide proton with a constant of 4 Hz. Since the β-benzylic proton is trans-co-planar to the electronegative epoxide, its vicinal coupling constant with H-10 should be reduced (54), and, indeed, the resonance at 2.92 ppm is broadened, indicating little

coupling if any. The epoxide proton appeared at 3.11 ppm and the $SiOCH_2$ protons showed a triplet at 3.43 ppm (J = 7.0 Hz).

The α-epoxide, 29b, thus obtained was exposed to $BF_3 \cdot OEt_2$, and after one minute, the starting material had remained unchanged. Longer reaction times led to decomposition.

We then turned our attention to another type of catalyst. It is known that lithium perchlorate catalyses the rearrangement of tertiary epoxides without inducing side reactions such as polymerization or halohydrin formation which occur with BF_3 (118). Catalysis by BF_3 involves a concerted mechanism (Fig. 31) (114,116) whereas catalysis with $LiClO_4$ proceeds through a carbenium ion intermediate (Fig. 33) (118,119). The salt is slightly soluble in solvents such as benzene (118) or toluene (120), and the Li^+ complexes with the epoxide oxygen to promote opening of the tertiary C-O bond. For 1-methyl-1-cyclohexene oxide as an example, the ketone is favoured to the extent of 80% over the aldehyde (118), reflecting the migratory aptitudes of H over $-CH_2-$.

The α-epoxide, 29a, which carries an O-tert-butyldimethylsilyl protecting group was therefore heated with $LiClO_4$ in toluene at 85° C under nitrogen for 76 h. The reaction was monitored by TLC and after 75 min, the starting material was still present as the major constituent but accompanied by at least seven other compounds, the major one of these having an R_f value greater than that of the α-epoxide. This product was isolated by preparative thick layer chromatography, and when examined by 200 MHz NMR and IR spectroscopy was found surprisingly

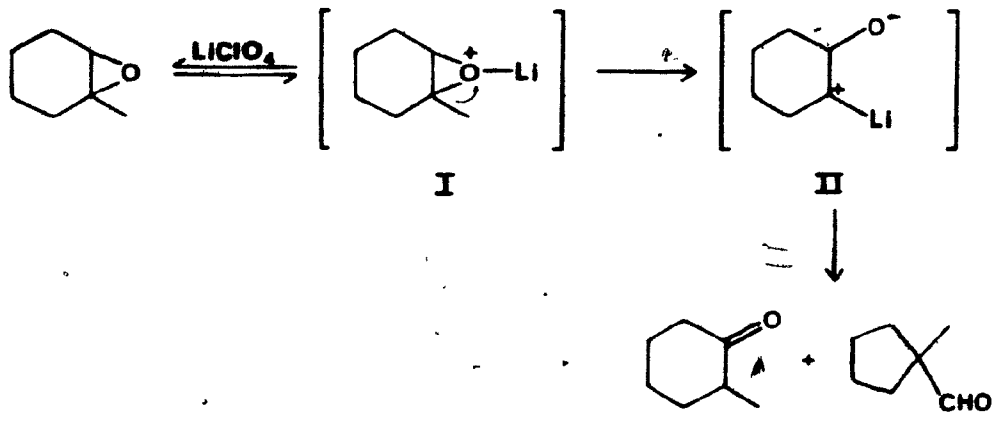


FIGURE 33: Epoxide rearrangemeat using $LiClO_4$. Adapted from references 118 and 120.

to be the β-epoxide, 30a. The NMR spectrum of this was compared with that of authentic β-epoxide prepared by epoxidation of the alcohol, 17, with purified (121) MCPBA followed by tert-butyldimethylsilylation. With 17, β-face epoxidation is favored by the interaction of the peracid through hydrogen bonding with the free hydroxyl (110). In order to maximize this interaction the MCPBA was purified so as to avoid interference by impurities with H-bonding. After purification by preparative thick layer chromatography, the O-protected β-epoxide 30a was isolated in 47% overall yield based on alcohol 17. However, the product was impure as judged by TLC and contained a contaminant displaying the same R_f as the α-epoxide 29a but differing in its NMR characteristics about the benzylic and $SiOCH_2$ protons. It also showed a small absorbtion in the carbonyl region of the IR.

A plausible mechanism for the rearrangement of the α-epoxide to the β-isomer is shown in Figure 34. Ring C of the key spiro intermedi-

ate I may add to the planar carbenium ion from either the α- or β-face to afford ultimately the α- or β-epoxides. The spiro intermediate is similar to that arising from the Wagner-Meerwein rearrangement of 1-(aminoethyl)-1-hydroxy-2,2-tetramethylene-7-methoxy-1,2,3,4-tetrahydronapthalene to form the starting amine, 15 (47) (Fig. 35).

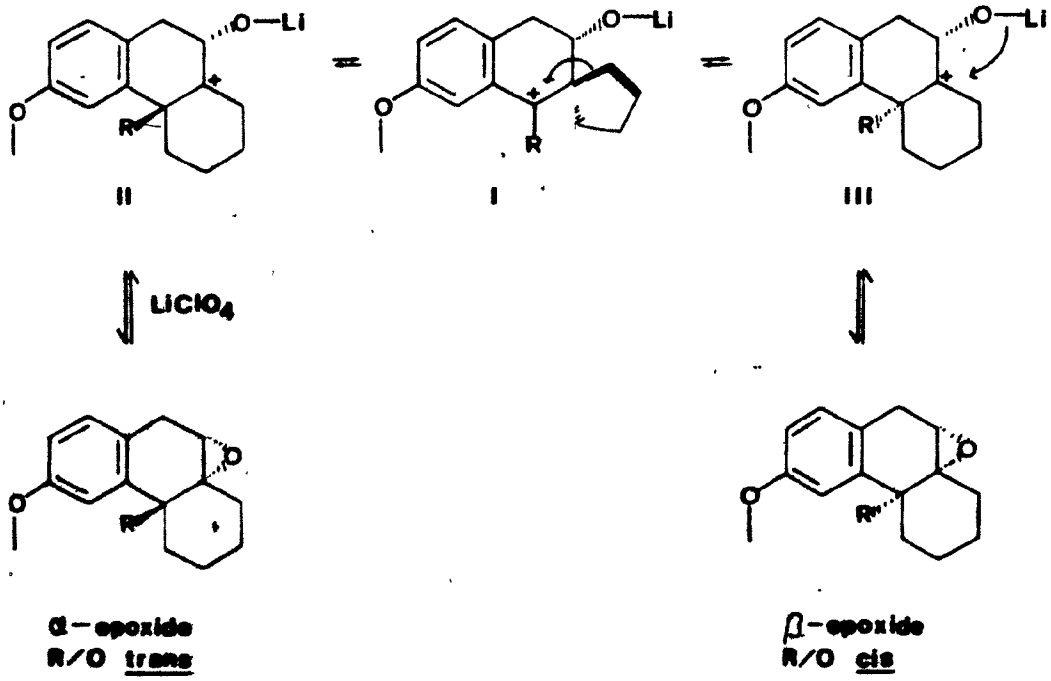


FIGURE 34: Possible rearrangement of α-epoxide to β-epoxide through spiro intermediate I where R = $-CH_2CH_2Si(Me)_2$-t-Bu.

It is known that epoxide rearrangements are disfavored in the cis-decalin series or when large syn-diaxial interactions are introduced (114). For instance, the rearrangement of steroid B-ring epoxides into cis-decalin geometry proceeds slower and in lower yields than with A-ring epoxides (114). The transition state for the B-ring epox-

ide necessitates the simultaneous distortion of both the A- and B-rings from their chair conformations whereas only ring A need be distorted for ring A epoxide rearrangements (114). On that basis our attempted rearrangement of the B-ring epoxides, 29a and 29b, to form the desired morphinan-like geometry may not have occurred, especially if one takes into account that ring B is critically distorted by its fusion to an aromatic ring.

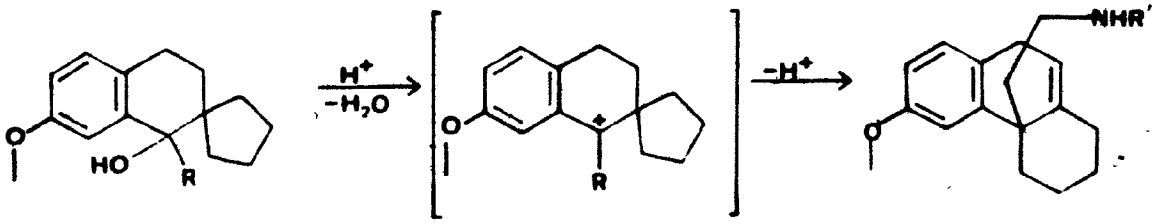


FIGURE 35: Formation of key hexahydrophenanthrene starting material from Wagner - Meerwein rearrangement of spiro alcohols. From reference 47.

Despite our failure to effect rearrangement of these epoxides, the approach may nevertheless be applicable through the use of different reagents. Epoxide rearrangements involving enolate ions as intermediates can be base-promoted (113) or induced by treatment with Me_2SO, n-propyliodide and sodium iodide (121). Attack by hydrogen on the planar intermediate can give either a cis- or a trans-decalin arrangement which offers the possibility of generating the morphinan as well as the isomorphinan geometries.

CHAPTER 4

EXPERIMENTAL

4.1 General Experimental

Reagent grade solvents were used unless otherwise specified. Solvents were dried when necessary by the use of molecular sieves (H_3CCN, benzene, DMF, Me_2SO, and toluene), by reflux and distillation over P_2O_5 (CH_2Cl_2), or by the use of commercially available dry solvents (anhyd diethylether from Malinckrodt Canada, Ltd., Toronto, and abs EtOH from Consolidated Alcohols, Ltd., Toronto). Solvents were dried during workup with sodium sulfate or magnesium sulfate.

The hexahydrophenanthrene intermediate, 14, was provided by Bristol Laboratories.

Aluminum backed sheets pre-coated with Kieselgel 60 F_{254}, 0.2 mm thick (Merck Co. Ltd., Darmstadt) were used for thin layer chromatography. The compounds were visualized with ceric dip (10.0 g ceric sulfate, 25.0 g ammonium molybdate, 100 mL conc H_2SO_4, and 900 mL H_2O) or with UV lamps (long wave model SL 3660 and short wave model SL 2537 by Ultra-violet Products, Inc., South Pasadena, California).

Flash chromatography was done according to the method of Still et al. (127) using 230 - 400 mesh silica gel (British Drug Houses, Toronto). The crude mixtures were evaporated onto a minimum amount of silica gel before being applied to the column.

Preparative layer chromatography was done on 20 cm x 20 cm plates coated with a 2 mm thick layer of Kieselgel 60 F_{254} (Merck). These were provided by Dr. Ogilvie's laboratory in the Chemistry Department. The compounds were visualized by UV, and the products were obtained by elution with CH_2Cl_2 or ethyl acetate.

Melting points were recorded in open capillary tubes using a Buchi SMP-20 apparatus, and are uncorrected.

Infrared (IR) spectra were recorded on a Perkin-Elmer 257 spectrometer calibrated with polystyrene. The samples were handled either as dilute solutions with $CHCl_3$ in NaCl cells, neat films between NaCl plates, or as KBr disks. The absorbtions are given in cm^{-1}.

Proton nuclear magnetic resonance (NMR) spectra were recorded on Varian F-60, T-60A, XL-200, or XL-300 spectrophotometers in $CDCl_3$ or Me_2SO-d_6 (both from MSD Isotopes, Merck Frost Canada, Inc., Montreal), using Me_4Si as a standard. The chemical shifts are reported in parts per million on the δ scale. The peaks are described as singlets (s), doublets (d), triplets (t), quartets (q), doublet of doublets (dd), triplet of doublets (td, 1:1:2:2:1:1 pattern), multiplets (m), or broad (br).

Mass spectra were recorded on a Hewlett-Packard 5980A or a Dupont 21-492B spectrophotometer by O. Mamer of the Biomedical Mass Spectrometry Unit of McGill University or J. Finkenbine of the Chemistry Department, respectively. Unless otherwise specified, all spectra were at 70 eV electron impact mode with the ion source at 250° C. The spectra are reported as m/z, assignment, relative intensity, and the probe temperature for direct inlet is given.

4.2 Procedures

Synthesis of Nitrile: 1-Cyclohexen-1-yl-acetonitrile (1)

The nitrile was prepared according to the method of Cope et al. (52). Cyclohexanone (216 g, 2.2 mol), cyanoacetic acid (170 g, 2 mol), and ammonium acetate (6 g, 0.08 mol) were refluxed in benzene (300 mL) for 20 h, and the water (36 mL, 2 mol) was removed with a Dean-Stark trap. The solvent was evaporated in vacuo to afford a light yellow solid. Decarboxylation was achieved by distillation through a short Vigreaux column under reduced pressure. The nitrile (156 g, 65% yield) came over at 135 - 145° C, ca. 3 kPa (lit. (52) bp 110 - 112° C, 3.3 kPa).

IR ($CHCl_3$) 3010 (olefinic CH stretching); 2940, 2860, 2840 (aliphatic CH stretching); 2240 (C≡N), 1630 (C=C), 1445, 1435, 1410 (CH deformations) cm^{-1}.

NMR ($CDCl_3$, 60 MHz) δ 5.6 - 5.9 (m, 1, olefinic), 3.0 (br, s, 1, CH_2CN), 1.8 - 2.3 (m, 4, $H_2C-C=C-CH_2$), 1.5 - 1.8 (m, 4, CH_2CH_2).

Mass spectrum, GC inlet, 6% OV101, 2 m × 6 mm, 100° C + 16° C min^{-1}, 4.5 min estimated retention time: 121 ($M^{+\cdot}$, 14), 81 ($M^{+\cdot}-CH_2CN$, 100).

Synthesis of Acid (35): 2-(1-cyclohexen-1-yl)-acetic acid (2)

The nitrile (50 g, 0.41 mol) was refluxed overnight in 10% aqueous NaOH (300 mL). Any side products were removed by extracting the reaction mixture with $CHCl_3$ (3x). The aqueous layer was then acidified with HCl to approximately pH 1, and this was extracted with $CHCl_3$ (3x).

The organic extracts were combined, dried, filtered, and evaporated in vacuo to give 56 g of light green oil. The above was repeated twice, and all the crude product was combined. Distillation under reduced pressure (bp 150° C, ca. 3 kPa) afforded the acid as colorless waxy crystals (119 g, mp ca. 26° C) in 69% yield.

IR ($CHCl_3$) 3500 - 2500 (OH, strongly H-bonded); 2910 (aliphatic CH stretching); 1700 (C=O); 1435, 1404 (CH deformations) cm^{-1}.

NMR ($CDCl_3$, 60 MHz) δ 10.4 (br, s, 1, CO_2H), 5.6 (m, 1, olefinic), 3.0 (br, s, 2, CH_2CO_2H), 1.8 - 2.3 (m, 4, $H_2C-C=C-CH_2$), 1.2 -1.8 (m, 4, CH_2CH_2).

Mass spectrum, Me_3Si ester made for GC inlet, 6% OV101, 2 m × 6 mm, 80° C + 16° C min^{-1}, 5.8 min estimated retention time: 212 ($M^{+\cdot}$, 3), 197 ($M^{+\cdot}-CH_3^{\cdot}$, 2), 73 (100).

Synthesis of Alcohol (35): 2-(1-Cyclohexen-1-yl)-ethanol (3)

A solution of 2-(1-cyclohexen-1-yl)-acetic acid (10 g, 0.071 mol) in anhyd ether (30 mL) was added dropwise with stirring to a suspension of 95% $LiAlH_4$ (2.8 g, 0.074 mol) in anhyd ether (20 mL) under N_2. The reaction was stirred for 1 h, then the excess $LiAlH_4$ was destroyed by the dropwise addition of H_2O (10 mL). The mixture was added with stirring to 10% aqueous HCl (200 mL), followed by conc HCl until the solid was gone. The ether layer was removed, and the aqueous layer was extracted with ether (3x). The organics were combined, dried, filtered, and evaporated in vacuo. The residue was purified by distilla-

tion (bp 100° C, ca. 3 kPa) to give a 57% yield of the alcohol (5 g, 0.04 mol).

IR ($CHCl_3$) 3420 (br, OH); 3000 (olefinic CH stretching); 2930, 2850, 2830 (aliphatic CH stretching); 1630 (C=C), 1445, 1435 (CH_2 deformations); 1040 (C-O stretching) cm^{-1}.

NMR ($CDCl_3$, 60 MHz) δ 5.5 (m, 1, olefinic), 3.9 (m, 1, OH), 3.6 (t, 2, J = 7 Hz, $-CH_2O$), 2.2 (br t, 2, J = 7 Hz, $\underline{CH_2}CH_2O$), 1.8 - 2.2 (m, 4, $H_2C-C=C-CH_2$), 1.4 - 1.8 (m, 4, CH_2CH_2).

Mass spectrum, 210° C ion source: 126 ($M^{+\cdot}$, 16), 108 ($M^{+\cdot}-H_2O$, 20), 79 (100).

Synthesis of Glycol: 1,2-Dihydroxy-3-(4-methoxyphenyl)-propane (5)

The glycol was made according to the method of Bruba (57). Performic acid was prepared by adding 30% aqueous H_2O_2 (37 mL, 1.2 mol) to 3.5 equiv of 90% aqueous formic acid (160 mL), and vigorously stirring for 15 min. 4-Allylanisole (5 mL) was added and the reaction was heated to 40° C. The temperature was maintained between 40 - 45° C by heating or cooling as necessary while a further 35 mL of 4-allylanisole (0.26 mol total) was carefully added dropwise. The reaction mixture was stirred at room temperature overnight; then evaporated in vacuo to give a red residue. To this was added 37% aqueous NaOH (45 mL) at 45° C, and H_2O (65 mL). The solution was heated to 50° C for 1 h, then cooled. Concentrated HCl (33 mL) was added and the mixture was extracted with $CHCl_3$ (3x). The combined organic extracts were dried, filtered, and evaporated. The residue was distilled using an air-cooled

condenser to afford 29.8 g (0.16 mol, 63% yield) of the glycol: bp 150 - 152° C, 0.3 kPa (lit. (57) bp 158° C, 0.3 kPa).

IR ($CHCl_3$) 3400 (br, OH stretching); 3000, 2950, 2930, 2910 (CH stretching); 2830 ($OC-H_3$ stretching); 1610, 1580, 1505 (C=C stretching) cm^{-1}.

NMR ($CDCl_3$, 200 MHz) δ 6.82 - 7.14 (m, AA'XX', 4, aromatic), 4.13 (br s, 2, OH), 3.81 (m, 1, CH), 3.74 (s, 3, OCH_3), 3.54 (d, 1, J_{gem} = 10 Hz, benzylic), 3.38 (dd, 1, J_{gem} = 10 Hz, J_{vic} = 8 Hz, benzylic), 2.62 (d, 2, J = 6 Hz, $C\underline{H}_2OH$).

Mass spectrum, 45° C probe temperature: 182 ($M^{+\cdot}$, 31), 164 ($M^{+\cdot}-H_2O$, 11), 151 ($M^{+\cdot}-CH_2OH^{\cdot}$, 11), 149 (19), 148 (58), 133 (24), 121 (100).

Synthesis of Aldehyde: 4-Methoxyphenylacetaldehyde (6)

The aldehyde was made by the procedure of Bruba (57). The glycol (22.3 g, 0.12 mol) was dissolved in benzene (1250 mL) which had been dried over 4 Å sieves. Ten percent of the solvent (125 mL) was distilled off under N_2 to assure dryness. After cooling, one equiv of lead tetraacetate (55.4 g) was added, and the reaction was stirred overnight. The reaction mixture was poured into H_2O (1000 mL), and the lead oxides produced were removed by filtration through celite. The aqueous layer was removed, and the benzene was washed with H_2O (2 × 500 mL) and aqueous saturated $NaHCO_3$ (1 × 500 mL). The organic layer was dried, filtered, and concentrated in vacuo. The residue was distilled through a Vigreaux column under reduced pressure (bp 76 - 77° C, 0.03

kPa; lit. (57) 78 - 79° C, 0.013 kPa and lit. (60) 120° C, 1.3 kPa) to afford the aldehyde (8.3 g, 0.06 mol) in 45% yield as a pale yellow liquid.

IR (neat) 3420 (C=O overtone), 3030 (aromatic CH stretching); 3000, 2950, 2930, 2900 (CH_2 stretching); 2830 ($OC-H_3$ stretching); 2820, 2720 (aldehyde CH); 1720 (C=O); 1607, 1580, 1510 (aromatic C=C); 1455, 1440 (CH deformations) cm^{-1}.

NMR ($CDCl_3$, 60 MHz) δ 9.7 (m, 1, CHO), 6.8 - 7.2 (m, AA'BB', 4, aromatic), 3.8 (s, 3, OCH_3).

Mass spectrum, 35° C probe temperature: 150 ($M^{+\cdot}$, 38), 121 (100).

Synthesis of Glycidic Ester: Ethyl-3-(4-methoxyphenyl)-2,3-epoxypropionate (8)

The glycidic ester was prepared according to the method of Douglas and Meunier (58). Sodium ethoxide (40 g, 0.59 mol) was mixed with a mechanical stirrer in toluene (200 mL) at 0° C under N_2. A solution of 4-anisaldehyde (50 g, 0.37 mol) and ethyl chloroacetate (45.3 g, 0.37 mol) in toluene (200 mL) was carefully added dropwise, maintaining the temperature below 10° C. Toluene (100 mL) was added and the reaction was then stirred at room temperature for ca. 20 h. The toluene was washed with H_2O (3x), then dried, filtered, and evaporated in vacuo to afford a yellow oil. Light yellow crystals, mp 44 - 47° C, were obtained by crystallization from absolute anhydrous ethanol at -78° C in 31% yield (25.2 g, 0.11 mol). Recrystallization from absolute anhy-

drous ethanol afforded pure white crystals: mp 46 - 47° C (lit. (58) mp 40 - 43° C).

IR ($CHCl_3$) 3015, 3010, 2980, 2960, 2940 (aromatic and aliphatic CH stretchings); 1740 (C=O); 1615, 1515 (aryl C=C); 1250, 1195, 1175, 1030 (C–O stretches) cm^{-1}.

NMR ($CDCl_3$, 60 MHz) δ 6.8 - 7.3 (m, AA'BB', 4, aromatic), 4.3 (q, 2, J = 7 Hz, $CO_2\underline{CH_2}CH_3$), 4.1 (d, 1, J = 2 Hz, epoxide), 3.8 (s, 3, OCH_3), 3.6 (d, 1, J = 2 Hz, epoxide), 1.3 (t, 3, J = 7 Hz, $CO_2CH_2\underline{CH_3}$).

Mass spectrum, 210° C ion source, 80° C probe temperature: 222 ($M^{+\cdot}$, 18), 165 (77), 148 (38), 137 (66), 135 (18), 121 (100).

Prins Method Synthesis of 1-(4-Methoxybenzyl)-isochromans: 11, 12, 13

A solution of alcohol 3 (1.01 g, 0.008 mol) in glacial acetic acid (2.5 mL) was slowly added dropwise to a mixture of aldehyde (4.33 g, 0.029 mol), glacial acid (2 mL), and trifluoroacetic acid (3 mL) under N_2. The reaction was stirred overnight at room temperature. The mixture was poured into ice water, and neutralized with $NaHCO_3$. This was extracted with ether (3x) to afford, after drying, filtration, and evaporation, a yellow oil. The tetra-substituted isomer, 13, could be separated from the tri-substituted ones, 11 and 12, by flash chromatography (3 × 20 cm, 25:1 petroleum ether/ethyl acetate). The total yield was 38%, corresponding to a total 0.79 g of purified material.

Glycidic Ester Method Synthesis of 1-(4-Methoxybenzyl)-isochromans: 11, 12, 13.

The alcohol 3 (2.0 g, 0.016 mol) was heated with 10% aqueous HCl (100 mL), and ethanol (20 mL) to near reflux. Glycidic ester 8 (10 g, 0.045 mol) was added. The reaction mixture was refluxed overnight; then cooled, and poured into cold H_2O (100 mL). After neutralization with Na_2CO_3, the H_2O was extracted with Et_2O until the organic layer was clear. The combined organic extracts were dried, filtered, and evaporated to afford a yellow residue. The tetra-isomer, 13, could be separated from the tri-isomers, 11 and 12, by flash chromatography (3 x 24 cm, 25:1 petroleum ether/ethyl acetate). The total yield was 68% (2.8 g).

Tetra-isomer, 13:

IR (neat) 2930, 2850 (C-H stretching); 2830 ($OC-H_3$); 1610, 1580, 1510 (C=C); 1440, 1460 (C-H deformations); 1245, 1175, 1105, 1030 (asymmetrical and symmetrical stretching of aliphatic and aryl aliphatic ethers) cm^{-1}.

NMR ($CDCl_3$, 200 MHz) δ 6.8 - 7.3 (m, AA'XX', 4, aromatic), 4.10 (dd, 1, J = 8 Hz, 6 Hz, vinylic), 3.9 - 4.1 (m, 1, CH_2O), 3.79 (s, 3, OCH_3), 3.5 - 3.7 (m, 1, CH_2O), 2.94 (dd, 1, J_{gem} = 15 Hz, J_{vic} = 4 Hz, benzylic), 2.65 (dd, 1, J_{gem} = 15 Hz, J_{vic} = 8 Hz, benzylic), 0.8 - 2.2 (10, aliphatic).

Mass spectrum, 50° C probe temperature: 258 ($M^{+\bullet}$, 38), 137 ($M^{+\bullet}$-4-methoxybenzyl$^+$, 100), 121 (4-methoxybenzyl$^+$, 65).

Tri-isomers, 11 and 12:

IR (KBr) 2950, 2910, 2850, 2830 (CH stretching); 1610, 1510 (C=C); 1295, 1240, 1165, 1095, 1020 (asymmetrical and symmetrical stretching of aliphatic and aryl aliphatic ethers) cm^{-1}.

NMR ($CDCl_3$, 200 MHz), δ 6.84 - 7.24 (m, AA'XX', 4, aromatic), 5.54 (br s, 1, olefinic major isomer, 11), 5.44 (br s, 1, olefinic minor isomer, 12), 3.99 (dd at 4.02, dd at 3.96, 1, J_{gem} = 9 Hz, $J_{3e,4a}$ = 4 Hz, $J_{3e,4e}$ = 0.5 Hz, H-3e: $CH_2\underline{CH}_2O$), 3.31 (s, 1, OCH_3), 3.28 (td, 1, J_{gem} = 9 Hz, $J_{3a,4a}$ = 9 Hz, $J_{3a,4e}$ = 3 Hz, H-3a: $CH_2\underline{CH}_2O$), 3.11 (td, 1, $J_{1,9a}$ = 9 Hz, J_{vic} = 9 Hz, J_{vic} = 3 Hz, H-1a: CH-O), 2.99 (dd, 1, J_{gem} = 13 Hz, J_{vic} = 3 Hz, benzylic), 2.63 (dd, 1, J_{gem} = 13 Hz, J_{vic} = 9 Hz, benzylic), 0.83 - 2.13 (8, aliphatic).

Mass spectrum, 50° C probe temperature: 258 ($M^{+\bullet}$, 36), 137 ($M^{+\bullet}$-4-methoxybenzyl$^+$, 100), 121 (4-methoxybenzyl$^+$, 50).

Synthesis of Aldehyde (34,36): 16

The amine salt (5 g, 0.017 mol) was taken up in 5% aqueous $NaHCO_3$ (250 mL), and the free base was extracted with $CHCl_3$ (4 x 150 mL). The combined $CHCl_3$ layers were dried, filtered, and evaporated to give 4.6 g of the amine. The residue was taken up in 1:1 $EtOH/H_2O$ (100 mL). A 2-fold excess of ninhydrin (6 g) in 1:1 $EtOH/H_2O$ (100 mL) was added to the amine solution in a light-protected flask under N_2. Ethanol (100 mL) was added, and after 0.5 h $NaHCO_3$ (7.5 g) was added. The mixture was stirred overnight. The EtOH was removed in vacuo, and the aqueous remainder was poured into aqueous saturated NaCl solution (200 mL).

This was extracted with ethyl acetate (8 × 100 mL). The organics were dried, filtered, and evaporated to yield 6 g of crude material. Flash chromatography (3 × 24 cm, 9:1 hexanes/ethyl acetate) afforded the aldehyde (3.3 g) as a yellow oil. Trituration with a small amount of hexanes gave 1.7 g of white crystals, mp 72 - 74° C (lit (34) mp 72 - 74° C). The total yield from the amine salt was 39%.

IR (KBr) 2920, 2850, 2820, 2720 (CH stretchings); 1715 (C=O); 1605, 1570, 1495 (C=C), 1235, 1035 (C-O stretching) cm^{-1}.

NMR ($CDCl_3$, 200 MHz) δ 9.21 (dd, 1, J = 3.5 Hz, 2 Hz, CHO), 6.97 (d, 1, J = 8.5 Hz, H-8), 6.81 (d, 1, J = 3 Hz, H-5), 6.71 (dd, 1, J = 8.5 Hz, 3 Hz, H-7), 5.69 (m, 1, olefinic), 3.76 (s, 3, OCH_3), 3.32 (m, 2, benzylic), 3.15 (dd, 1, J = 15.3 Hz, 3.5 Hz, CHCHO), 2.55 (dd, 1, J = 15.3 Hz, 2 Hz, CHCHO), 1.2 - 2.5 (8, aliphatic).

Mass spectrum, 210° C ion source, 80° C probe temperature: 256 ($M^{+\cdot}$, 0.4), 214 (6), 213 ($M^{+\cdot}$-ketene, 36), 212 (100), 184 (19).

Synthesis of 4a-(1-Hydroxyethyl)-6-methoxy-1,2,3,4,4a,9-hexahydrophenanthrene (34,36): 17

A slurry of $NaBH_4$ (0.16 g, 4.2 mmol) in abs ethanol (10 mL) was added to a 0° C solution of the aldehyde (1.1 g, 4.3 mmol) in $CHCl_3$ (40 mL) under N_2. After 0.5 h of mixing at 0° C the reaction was poured into H_2O (80 mL). The excess reagent was destroyed by the addition of 10% (v/v) aqueous HCl until the aqueous layer was clear. The organic layer was separated, and the aqueous fraction was extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were washed with saturated

aqueous NaCl (1 × 50 mL). The $CHCl_3$ was dried, filtered, and evaporated to afford 1.2 g of light yellow oil. Crystallization from hexanes gave 1.0 g (4.0 mmol, 93% yield) of fluffy white crystals, mp 69 - 70° C (lit (34) mp 71 - 73° C).

IR (KBr) 3300 (br, OH stretching); 2920, 2840 (CH stretching); 1605, 1570, 1490 (C=C); 1220, 1035, 1020 (C-O-C and C-OH stretching) cm^{-1}.

NMR ($CDCl_3$, 200 MHz) δ 7.00 (d, 1, J = 8.4 Hz, H-8), 6.83 (d, 1, J = 2.6 Hz, H-5), 6.73 (dd, 1, J = 8.4 Hz, 2.6 Hz, H-7), 5.66 (m, 1, olefinic), 3.78 (s, 3, OCH_3), 3.16 - 3.52 (m, 4, benzylic and $\underline{CH_2}OH$), 0.81 -2.68 (11, OH, $\underline{CH_2}CH_2OH$, and aliphatic).

Mass spectrum, 45° C probe temperature: 258 ($M^{+\cdot}$, 7), 257 (32), 256 (73), 214 (50), 213 ($M^{+\cdot}-CH_2CH_2OH^{\cdot}$, 100), 212 (75), 184 (40).

Synthesis of 4a-(1-Hydroxyethyl)-10-hydroxy-6-methoxy-1,2,3,4,4a,9,10,-10a-octahydrophenanthrene (34,36): 18

Borane-methyl sulfide complex (4 mL, 10 M, 5% excess $(H_3C)_2S$) was added to a 0° C solution of the alcohol (0.91 g, 3.5 mmol) in dry CH_2Cl_2 (40 mL) under N_2. The reaction was stirred at room temperature for 24 h. The excess reagent was destroyed by the slow dropwise addition of 10% (v/v) aqueous H_2SO_4 (30 mL), and the N_2 was turned off. This was stirred for 0.5 h; then 15% (w/v) aqueous NaOH (80 mL) was added dropwise, followed by 30% (v/v) aqueous H_2O_2 (80 mL). The reaction was stirred at room temperature for 24 h. The CH_2Cl_2 fraction was removed and the aqueous layer was extracted with CH_2Cl_2 (3 × 75 mL).

The combined organics were washed with 15% (w/v) aqueous sodium potassium tartrate (3 × 100 mL), and with H_2O (3 × 100 mL). The CH_2Cl_2 was dried, filtered, and evaporated to 1.0 g of white foam. Flash chromatography (3 × 23 cm, 2:1 ethyl acetate/hexanes) afforded 0.91 g of white solid which could be recrystallized from ethyl acetate to give 0.61 g (2.2 mmol, 63% yield) of the diol: mp 138 - 139° C (lit. (34) mp 138 - 139° C).

IR (KBr) 3320 (OH); 3010, 2950, 2940, 2920, 2900, 2860, 2840 (CH stretching); 1610, 1570, 1490 (C=C); 1040 (C-OH stretching) cm^{-1}.

NMR (Me_2SO-d_6, 200 MHz) δ 6.67 - 6.97 (m, 3, aromatic), 4.60 (d, 1, J = 6 Hz, secondary OH), 4.17 (t, 1, J = 5 Hz, primary OH), 3.72 (s, 3, OCH_3), 1.0 - 3.7 (16, aliphatic).

Mass spectrum, 60° C probe temperature: 276 ($M^{+\bullet}$, 0.3), 258 ($M^{+\bullet}-H_2O$, 2), 214 (4), 213 (20), 212 (16), 184 (6), 83 (100).

Synthesis of t-Butyldimethylsilyl-protected Diol: 19a

The diol was protected at the primary hydroxyl function by the method of Corey and Venkateswarlu (99). The diol (0.250 g, 0.90 mmol), 1.2 equiv of tert-butyldimethylchlorosilane (0.163 g, 1.1 mmol), and 2.5 equiv of imidazole (0.153 g, 2.2 mmol) were stirred, under N_2, in dry DMF (5 mL) at 40° C for 6 h; then at room temperature for 24 h. The solvent was evaporated under reduced pressure, with toluene occasionally added to form an azeotrope with DMF. The residue was taken up in petroleum ether, and this was washed with H_2O (3x). The combined aqueous layers were back extracted once with petroleum ether. After

drying, filtration, and evaporation of the organics, there remained 0.315 g of a colorless oil. Separation of the mono- and di-protected products was achieved by flash chromatography (3 × 14 cm, 17:1 hexanes/ethyl acetate) to yield 0.255 g (0.65 mmol, 72% yield) and 0.063 g (0.12 mmol, 14% yield), respectively.

Mono-silated product, 19a:

IR (neat) 3380 (br, OH stretching); 2980, 2960, 2860 (CH stretching); 1610, 1575, 1490 (C=C) cm^{-1}.

NMR ($CDCl_3$, 60 MHz) δ 6.6 - 7.1 (m, 3, aromatic), 3.8 (s, 3, OCH_3), 1.1 - 4.3 (17, aliphatic and OH), 0.9 (s, 9, $SiC(CH_3)_3$), 0 (s, 6, $Si(CH_3)_2$).

Mass spectrum, 70° C probe temperature: 390 ($M^{+\cdot}$, 3), 388 ($M^{+\cdot}-H_2$, 4), 333 ($M^{+\cdot}$-t-Bu$^{\cdot}$, 71), 214 (61), 213 (80), 212 (22), 75 (100).

Di-silated product, 19b:

IR (neat) no OH stretching seen.

NMR ($CDCl_3$, 60 MHz) δ 6.6 - 7.1 (m, 3, aromatic), 1.1 - 4.2 (16, aliphatic), 3.8 (s, 3, OCH_3), 1.0 (s, 9, secondary $SiC(CH_3)_3$), 0.9 (s, 9, primary $SiC(CH_3)_3$), 0.1 (s, 6, secondary $Si(CH_3)_2$), 0.0 (s, 6, primary $Si(CH_3)_2$).

Mass spectrum, 40° C probe temperature: 71 (100), no parent ion seen.

Synthesis of di-Functionalized Diol: 20

The mono-silyl-protected diol, 19a (0.255 g, 0.65 mmol) and 2 equiv of mesyl chloride (0.1 mL, 1.3 mmol) were combined in dry pyridine (6.5 mL) under N_2 at 0° C for 0.5 h; then at 4° C overnight. Then a further 2 equiv of reagent was added, followed by another 2 equiv 5 h later. After 36 h the reaction mixture was poured into petroleum ether (20 mL). The solvent was extracted with H_2O (10 × 10 mL) to get rid of the pyridine. The combined H_2O washings were back extracted with petroleum ether (1 × 50 mL). The organic layers were combined, dried, filtered, and evaporated under reduced pressure to afford 0.235 g (0.50 mmol, 77% crude yield) of a yellow oil, which was used without purification.

IR (neat) 2950, 2930, 2825 (CH stretching); 1610, 1575, 1495 (C=C) cm^{-1}.

NMR ($CDCl_3$, 60 MHz) δ 6.6 - 7.1 (m, 3, aromatic), 4.8 - 5.3 (m, 1, CHOMs), 3.8 (s, 3, OCH_3), 1.0 - 3.8 (15, aliphatic), 3.1 (s, 3, SCH_3), 0.9 (s, 9, $SiC(CH_3)_3$), 0.0 (s, 6, $Si(CH_3)_2$).

Di-functionalized Diol Synthesis of 3-Methoxy-17-deaza-17-oxaisomorphinan: (21)

The di-functionalized diol, 20 (0.193 g, 0.41 mmol), 3.2 equiv of tetra-n-butylammonium chloride (0.363 g, 1.3 mmol), and 3.4 equiv of potassium fluoride dihydrate (0.132 g, 1.4 mmol) were heated at 55° C for 9 h in dry acetonitrile (6 mL) under N_2. More solvent (7 mL) was added, and the reaction was refluxed overnight; then it was stirred at

room temperature for 5 h. The mixture was poured into petroleum ether (20 mL), and washed with H_2O (3 × 10 mL). Drying, filtration, and evaporation in vacuo gave 0.052 g of yellow oil. Flash chromatography (2 × 15 cm, 3:1 hexanes/ethyl acetate) afforded 0.050 (0.19 mmol, 47% yield) of the cyclized product.

Me$_2$SO-promoted Synthesis of 3-Methoxy-17-deaza-17-oxaisomorphinan: (21)

The diol, 18 (0.200 g, 0.72 mmol) was dissolved in dry Me$_2$SO (20 mL) and heated to 150° C for 20 h. The mixture was cooled and poured into H_2O (55 mL). The H_2O was extracted with hexanes (4 × 35 mL), and the combined organic layers were washed with H_2O (3 × 70 mL) to get rid of any Me$_2$SO. The hexanes were dried, filtered, and evaporated to yield a yellow residue. Purification by flash chromatography (2 × 15 cm, 3:1 hexanes/ethyl acetate) afforded the cyclized product in 76% yield (0.142 g, 0.55 mmol).

IR (neat) 2910, 2850, 2810 (CH stretching); 1605, 1565, 1490 (C=C) cm^{-1}.

NMR ($CDCl_3$, 200 MHz) δ 7.06 (d, 1, J = 8.5 Hz, H-1), 6.83 (d, 1, J = 3 Hz, H-4), 6.75 (dd, 1, J = 8.5 Hz, 3 Hz, H-2), 3.94 (br d, X of ABX, 1, $J_{9,10}$ = 6 Hz, H-9), 3.80 (s, 3, OCH_3), 3.70 (br dd, A of AB, 1, J_{gem} = 12 Hz, $J_{16e,15a}$ = 6 Hz, H-16e), 3.51 (td, B of AB, 1, J_{gem} = 12 Hz, $J_{16a,15a}$ = 12 Hz, $J_{16a,15e}$ = 3 Hz, H-16a), 3.17 (dd, A of ABX, 1, J_{gem} = 20 Hz, $J_{9,10}$ = 6 Hz, α-benzylic), 3.06 (br d, B of ABX, J_{gem} = 20 Hz, β-benzylic), 2.49 (td, 1, J_{gem} = 13 Hz, $J_{15a,16a}$ = 12 Hz, $J_{15a,16e}$

= 6 Hz, H-15a), 1.1 - 2.4 (9, aliphatic), 0.82 (dd, 1, J_{gem} = 13 Hz, $J_{15e,16a}$ = 3 Hz, H-15e).

Mass spectrum, 40° C probe temperature: 259 ($M^{+\cdot}$ + $H^{\cdot}$, 57), 258 ($M^{+\cdot}$, 100), 215 (44), 214 (46), 213 (56), 212 (30).

Synthesis of Isomorphinan: 3-Hydroxy-17-deaza-17-oxaisomorphinan (22)

Sodium hydride (0.673 g of a 50% dispersion in oil, washed with hexanes 2x, 0.014 mol) was stirred in dry DMF (15 mL) at 0° C under N_2. Ethane thiol (1.4 mL, 0.019 mol) was slowly added with a syringe; then the methoxy-isomorphinan, 21 (0.355 g, 1.4 mmol) in DMF (5 mL) was added. The reaction was heated to reflux for 5 h. The mixture was cooled, poured into H_2O (100 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with H_2O (3 × 75 mL). Drying, filtration, and evaporation with toluene (5x) to form an azeotrope with any remaining DMF, afforded 0.340 g of yellow oil. Preparative layer chromatography (4:1 hexanes/ethyl acetate, both spectrograde) was used to isolate the 3-hydroxy isomorphinan (0.124 g, 0.51 mmol, 37% yield): mp 151 - 153° C. Recrystallization from anhyd ether gave a white solid: mp 158.5 - 160° C.

IR (KBr) 3240 (OH stretching); 2960, 2930, 2890, 2870 (CH stretching); 1615, 1570, 1495 (C=C) cm^{-1}.

NMR ($CDCl_3$, 300 MHz) δ 6.98 (d, 1, J = 8.2 Hz, H-1), 6.75 (d, 1, J = 2 Hz, H-4), 6.65 (dd, 1, J = 8.2 Hz, 2.6 Hz, H-2), 5.72 (s, 1, OH), 3.96 (d, 1, J = 5.6 Hz, H-9), 3.68 (dd, A of AB, 1, J = 5.6 Hz, 12.5 Hz, H-16e), 3.51 (td, B of AB, 1, J = 3.0 Hz, 12.5 Hz, 12.5 Hz, H-16a),

3.14 (dd, A of AB, 1, J = 5.6 Hz, 18.4 Hz, α-benzylic), 3.02 (d, B of AB, 1, J = 18.4 Hz, β-benzylic), 2.48 (td, 1, J = 5.6 Hz, 12.5 Hz, 12.5 Hz, H-15a), 2.1 - 2.2 (m, 1, H-5e), 2.02 (qd, 1, J = 14 Hz, 14 Hz, 14 Hz, 3.8 Hz, H-8a), 1.75 - 1.9 (m, 1, H-7e), 1.6 - 1.75 (m, 2, H-6a and H-6e), 1.43 - 1.6 (m, 3, H-8e, H-14 and H-5a), 1.15 - 1.35 (qt, 1, H-7a), 0.81 (dd, 1, J = 12.5 Hz, 3.0 Hz, H-15e).

Mass spectrum, 210° C ion source, 200° C probe temperature: 255 ($M^{+\cdot} + H^{\cdot}$, 18), 254 ($M^{+\cdot}$, 100), 201 (27), 200 (27) 199 (39).

Protection of Alcohol as t-Butyldimethyl Silyl Ether: 28a

The alcohol was protected as a silyl ether by the method of Corey and Venkateswarlu (99). The alcohol (0.247 g, 0.96 mmol), 2.2 equiv of imidazole (0.144 g, 2.2 mmol) and 1.4 equiv of tert-butyldimethylsilyl chloride (0.202 g, 1.3 mmol) were combined in dry DMF (5 mL) under N_2 for 5.5 h at 40° C. The DMF was removed under reduced pressure as an azeotrope with toluene (3 × 20 mL). The residue was taken up in CH_2Cl_2 (30 mL) and H_2O (15 mL). The organic layer was separated and washed with H_2O (2 × 15 mL). The aqueous fractions were combined and back extracted with CH_2Cl_2 (1 × 22 mL). All the CH_2Cl_2 was dried, filtered, and evaporated to yield 0.321 g (0.86 mmol, 90% crude yield) of a clear solid: mp 47 - 53° C.

IR (KBr) 2950, 2930, 2880, 2850 (CH stretching); 1605, 1570, 1495 (C=C) cm^{-1}.

NMR ($CDCl_3$, 60 MHz) δ 6.7 - 7.2 (m, 3, aromatic), 5.8 (m, 1, olefinic), 3.9 (s, 3, OCH_3), 1.1 - 3.8 (14, aliphatic), 0.9 (s, 9, $SiC(CH_3)_3$), 0.0 (s, 6, $Si(CH_3)_2$).

Mass spectrum, 50° C probe temperature: 372 ($M^{+\cdot}$, 2), 315 ($M^{+\cdot}$ - t-Bu$^{\cdot}$, 100), 214 (99), 213 (96), 212 (96), 184 (22).

Epoxidation of tert-Butyldimethylsilyl Protected Alcohol: 29a and 30a

The silyl-protected alcohol (0.129 g, 0.35 mmol) was dissolved in dry CH_2Cl_2 (4 mL) under N_2 at 0° C and 1.3 equiv MCPBA (0.090 g, 85%, 0.44 mmol) were added. After 6 h the reaction was poured into CH_2Cl_2 (25 mL). The organics were washed with 10% (w/v) aqueous NaS_2O_3 (1 × 15 mL), 5% (w/v) aqueous $NaHCO_3$ (1 × 15 mL), and H_2O (3 × 15 mL). After drying, filtration, and evaporation, there remained 0.136 g of white solid. The isomers were separated by flash chromatography (2 × 15 cm, 4:1 hexanes/ethyl acetate) to afford 0.011 g (28 μmol, 8% yield) of the β-epoxide 30a and 0.124 g (0.32 mmol, 92% yield) of the desired α-epoxide 29a as a colorless oil.

Synthesis of β-Epoxide and Protection: 30a

Purified (121) MCPBA (0.104 g, 0.6 mmol) was added to the alcohol (0.097 g, 0.4 mmol) in dry CH_2Cl_2 (6 mL) at 0° C under Ar. The reaction was stirred at 4° C for 24 h; then poured into CH_2Cl_2 (25 mL). The organics were washed with 10% (w/v) aqueous $Na_2S_2O_5$ (1 × 15 mL) and with water (2 × 15 mL). Drying, filtration, and evaporation afforded a yellow solid (0.088 g, 85% crude yield) which was used without further purification.

The β-epoxide alcohol was protected as the tert-butyldimethylsilyl ether by the method of Corey and Venkateswarlu (99) in 47% yield

after purification by preparative layer chromatography (7:1 hexanes/-ethyl acetate, both spectrograde).

α-epoxide, 29a:

IR (neat) 2950, 2930, 2850 (CH stretching); 1605, 1575, 1495 (C=C) cm^{-1}.

NMR ($CDCl_3$, 200 MHz) δ 6.6 - 6.9 (m, 3, aromatic), 3.74 (s, 3, OCH_3), 3.35 (t, 2, J = 7.5 Hz, $-CH_2OSi$), 3.0 - 3.2 (m, 3, benzylic and epoxide-H), 1.0 - 2.4 (10, aliphatic), 0.8 (s, 9, $SiC(CH_3)_3$), 0.0 (s, 6, $Si(CH_3)_2$).

Mass spectrum, 50° C probe temperature: 388 ($M^{+\bullet}$, 1), 331 ($M^{+\bullet}$-t-$Bu^{\bullet}$, 41), 213 (56), 71 (100).

β-epoxide, 30a:

IR (neat) 2950, 2930, 2880, 2850 (CH stretching); 1610, 1575, 1495 (C=C) cm^{-1}.

NMR ($CDCl_3$, 200 MHz) δ 6.99 (d, 1, J = 9.2 Hz, H-8), 6.85 (d, 1, J = 3.2 Hz, H-5), 6.70 (dd, 1, J = 9.2 Hz, 3.2 Hz, H-7), 3.8 - 4.1 (m, 3, $-CH_2OSi$ and epoxide-H), 3.8 (s, 3, OCH_3), 2.84 (dd, A of ABX, 1, J_{gem} = 16.8 Hz, J_{vic} = 7.4 Hz, β-benzylic), 2.74 (dd, B of ABX, 1, J_{gem} = 16.8 Hz, J_{vic} = 8.6 Hz, α-benzylic), 0.8 - 2.2 (10, aliphatic), 0.9 (s, 9, $SiC(CH_3)_3$), 0.1 (s, 3, $SiCH_3$), 0.0 (s, 3, $SiCH_3$).

Mass spectrum, 45° C probe temperature: 388 ($M^{+\bullet}$, 0.4), 331 ($M^{+\bullet}$-t-$Bu^{\bullet}$, 52), 213 (100).

Protection of Alcohol as tert-Butyldiphenylsilyl Ether: 28b

The alcohol was protected as a tert-butyldiphenylsilyl ether by the method of Hanessian and Lavallee (117). The alcohol (0.203 g, 0.79 mmol), 2.2 equiv of imidazole (0.117 g, 1.7 mmol), and 1.1 equiv of tert-butylchlorodiphenylsilane (0.23 mL, 0.88 mmol) were combined under nitrogen in dry DMF (4 mL) for 4.5 h at room temperature. The solvent was removed under reduced pressure as an azeotrope with toluene (3x). The residue was taken up in CH_2Cl_2 (60 mL) and H_2O (30 mL). The H_2O was separated, and the organic layer was washed with water (2 x 30 mL). After drying, filtration, and evaporation, there remained 0.505 g of yellow oil. Flash chromatography (3 x 14 cm, 9:1 hexanes/ethyl acetate) afforded 0.291 g (0.58 mmol, 75% yield) of the silyl ether.

IR (neat) 3080, 3060, 3020, 3005, 2970, 2935, 2860 (aromatic and aliphatic CH stretchings); 1615, 1590, 1505 (C=C); 1428 (Si-Ph) cm^{-1}.

NMR ($CDCl_3$, 60 MHz) δ 7.1 - 7.8 (m, 10, $SiPh_2$), 6.5 - 6.8 (m, 3, aromatic), 5.5 (m, 1, olefinic), 3.7 (s, 3, OCH_3), 1.1 - 3.5 (14, benzylic and aliphatic), 1.0 (s, 3, $SiCCH_3$), 0.9 (s, 6, $SiC(CH_3)_2$).

Mass spectrum, 210° C ion source, 260° C probe temperature: 439 ($M^{+\cdot}$-t-$Bu^{\cdot}$, 100).

Epoxidation of tert-Butyldiphenylsilyl Ether: 30b

Meta-chloroperbenzoic acid (0.198 g, 85%, 0.97 mmol) was added to the protected alcohol, 28b (0.297 g, 0.60 mmol) in dry CH_2Cl_2 (5 mL) at 0° C under Ar; then stirred at 4° C under Ar overnight. The mixture was poured into CH_2Cl_2 (25 mL) and washed with 10% (w/v) aqueous

$Na_2S_2O_3$ (2 × 15 mL); then with H_2O (3 × 15 mL). The organic layer was dried, filtered, and evaporated to yield 0.340 g of solid. Preparative layer chromatography (7:1 hexanes/ethyl acetate, 2 elutions) was used to isolate the product (0.036 g, 0.070 mmol, 12% yield).

IR (neat) 3080, 3060, 3005, 2970, 2945, 2870, 2840 (aromatic and aliphatic CH stretchings); 1615, 1593, 1583 (C=C) cm^{-1}.

NMR ($CDCl_3$, 200 MHz) δ 7.30 - 7.59 (m, 10, $SiPh_2$), 6.62 - 6.87 (m, 3, aromatic), 3.72 (s, 3, OCH_3), 3.43 (t, 2, J = 7.0 Hz, $-CH_2O$), 3.11 (br s, 1, epoxide CH), 3.10 (dd, A of ABX, 1, J_{gem} = 18 Hz, J_{vic} = 4 Hz, α-benzylic), 2.92 (br d, B of ABX, 1, J = 18 Hz, β-benzylic), 1.55 - 2.35 (10, aliphatic), 1.00 (s, 9, $SiC(CH_3)_3$).

Mass spectrum, 210° C ion source, 220° C probe temperature: 455 ($M^{+\cdot}$-t-$Bu^{\cdot}$, 100).

Synthesis of Ditosylate: 23

The ditosylate was made according to the general method outlined by Fieser and Fieser (97). The diol, 18 (0.20 g, 0.72 mmol) was dissolved in dry pyridine (15 mL) at 0° C, and 3.6 equiv para-toluenesulfonyl chloride (0.5 g, 2.6 mmol) was added. The reaction was stirred at 0° C for 3 h; then held at 4° C for 48 h. When complete, the solution was poured into H_2O (15 mL). This was extracted with CH_2Cl_2 (3 × 20 mL), and the organic extracts were washed several times with 20% (v/v) aqueous HCl to get rid of the pyridine. The organic layer was dried, filtered, and evaporated to afford 0.41 g (0.70 mmol, 97% crude yield) of brown residue which was used without further purification.

IR (neat) 3060, 2950, 2930, 2860, 2830 (aromatic and aliphatic CH stretchings); 1610, 1595, 1575, 1500, 1490 (C=C); 1170, 1185 (tosylate) cm^{-1}.

NMR ($CDCl_3$, 60 MHz) δ 7.2 - 8.1 (m, 8, $S(C_6\underline{H}_4-CH_3)_2$), 6.6 - 7.2 (m, 3, aromatic), 0.7 - 5.0 (14, aliphatic), 3.8 (s, 3, OCH_3), 2.48 (s, 3, $SC_6H_4-C\underline{H}_3$), 2.45 (s, 3, $SC_6H_4-C\underline{H}_3$).

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APPENDIX

The ^{13}C chemical shifts (Table 1) in the NMR spectrum of 17-deaza-17-oxaisomorphinan were assigned unambiguously from heteroscalar and homoscalar 2-D spectra (a.) (Figures 36 - 40) after determination of the number of attached H atoms by DEPT (b) experiments and by consideration of peak heights. The shifts for levorphanol (c) and isolevorphanol (d) (X = NCH_3, R = H) were determined from heteroscalar correlated spectra in the 20 to 60 ppm region, by analogy to known spectral analyses (121,122), and by calculation of the expected shifts in the aromatic region (124). The peak assignments for levorphanol were complicated by the conformational flexibility of ring C: thus carbons 7 and 8 could not be assigned unambiguously because the ring C protons did not show absorptions in the homoscalar correlated 2-D ^1H-NMR spectrum. The assignments for levorphanol agreed with those reported for O-methyl levorphanol (123). The assignments for isolevorphanol were made difficult owing to insufficient amounts of compound: many of the expected absorbtions in the correlated spectra were weak or absent so that small amounts of impurities obscured the results. The assignments for the sulfur analogues were obtained from reference 34.

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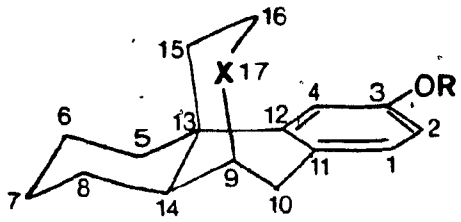
a. All spectra were obtained by F. Sauriol on a Varian XL-300 spectrometer.

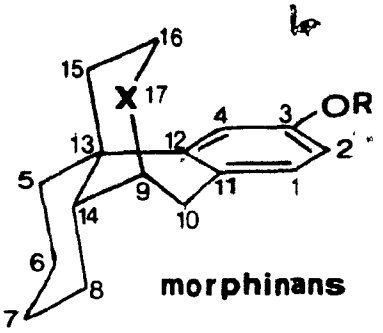
b. Distortionless enhancement by polarization transfer.

c. As free base from levorphanol tartrate (gift from Bristol Laboratories).

d. As HI salt (gift from M. Gates, Rochester, NY).



isomorphinans



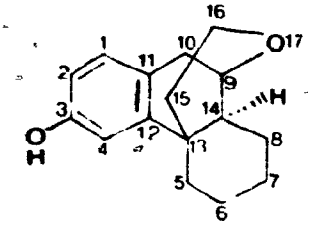
morphinans

Table 1: 75.4 MHz ^{13}C Chemical Shifts
ppm from Me_4Si

	isomorphinans			morphinans	
X	O	N-CH_3	S (1)	N-CH_3	S (1)
R	H	H	H	H	CH_3
1	128.59	128.59	129.25	128.67 (a)	129.30
2	113.25	113.01 (a)	111.13 (a)	113.65 (b)	111.18 (a)
3	154.27	153.92	158.30	155.72	158.65
4	110.79	110.88 (a)	110.19 (a)	112.47 (b)	110.87 (a)
5	36.00	35.94	37.94	36.46	38.05
6	22.14	23.35	22.12	22.20	22.31
7	25.79	26.58 (b)	25.82	26.40 (c)	26.94
8	26.00	27.21 (b)	27.52	26.76 (c)	29.60
9	72.56	59.02	39.55	58.14	37.17
10	35.42	26.12	40.82	23.62	35.62
11	128.21	128.59	129.25	127.88 (a)	129.51
12	146.91	147.51	145.66	141.22	140.60
13	33.99	34.50	35.64	37.00	38.40
14	40.63	42.01	41.15	44.37	46.17
15	30.60	31.27	31.52	42.43	44.41
16	59.81	47.71	22.97	47.29	22.67
OCH_3					55.24
NCH_3		42.97		41.35	

(1) Data from reference 34.

(a, b, c) - These assignments may be interchanged.



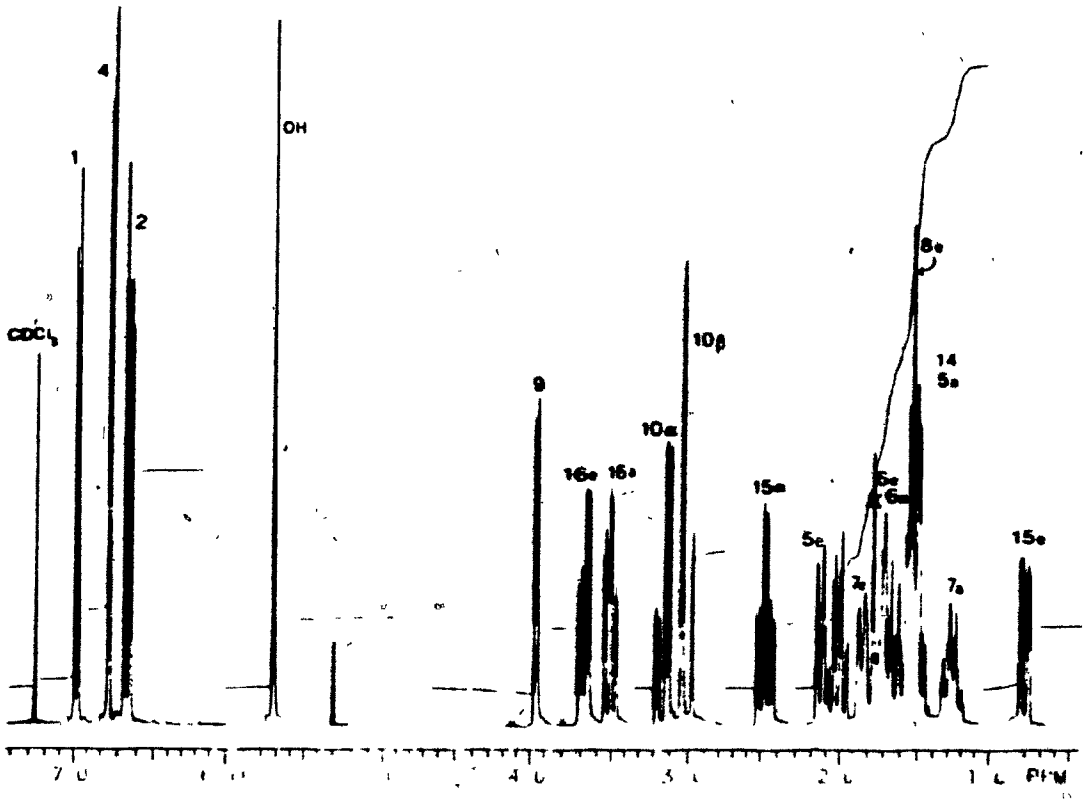


FIGURE 36: Complete ^{1}H-NMR spectrum of 3-hydroxy-17-deaza-17-oxaisomorphinan.

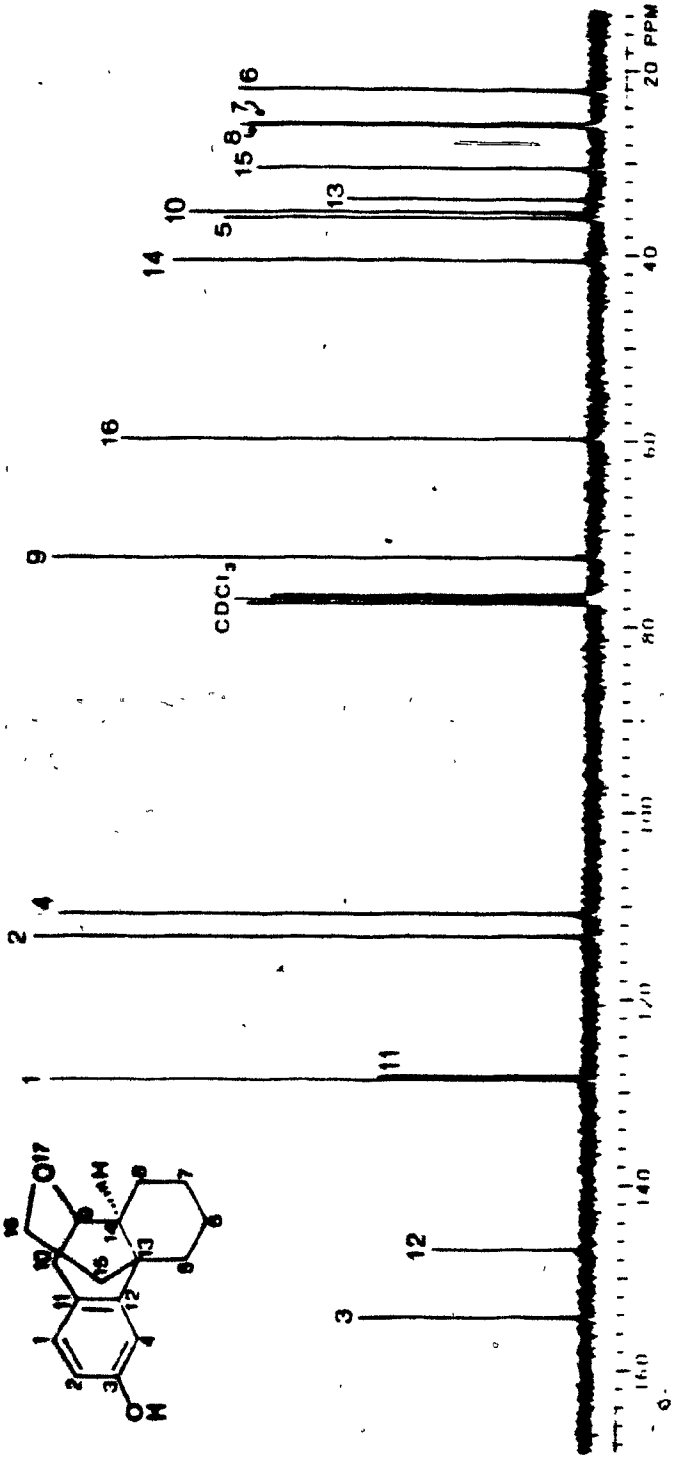


FIGURE 37: Complete ^{13}C-NMR spectrum of 3-hydroxy-17-deaza-17-oxaisomorphinan.

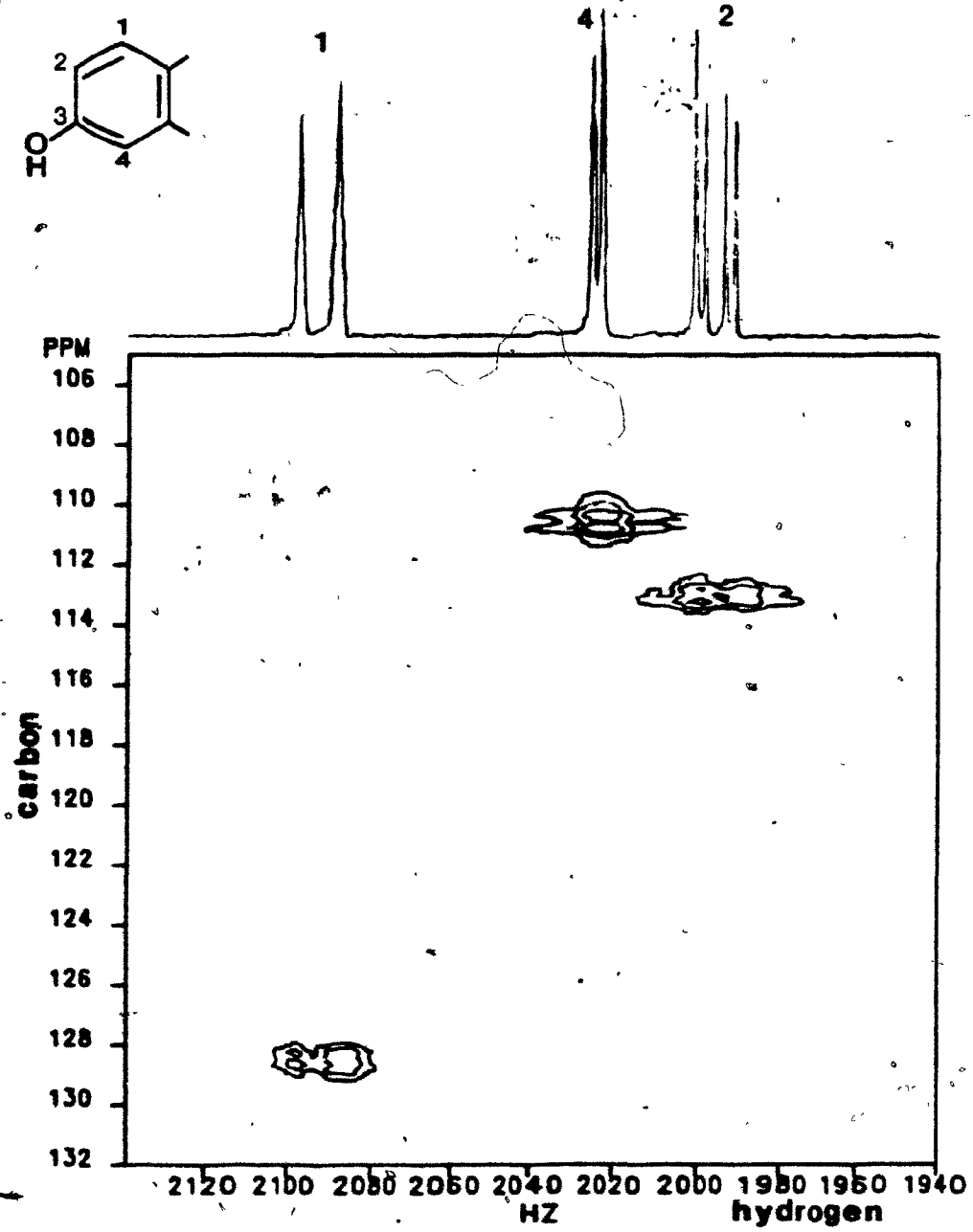


FIGURE 38: Heteroscalar correlated 2D-NMR spectrum of aromatic region.

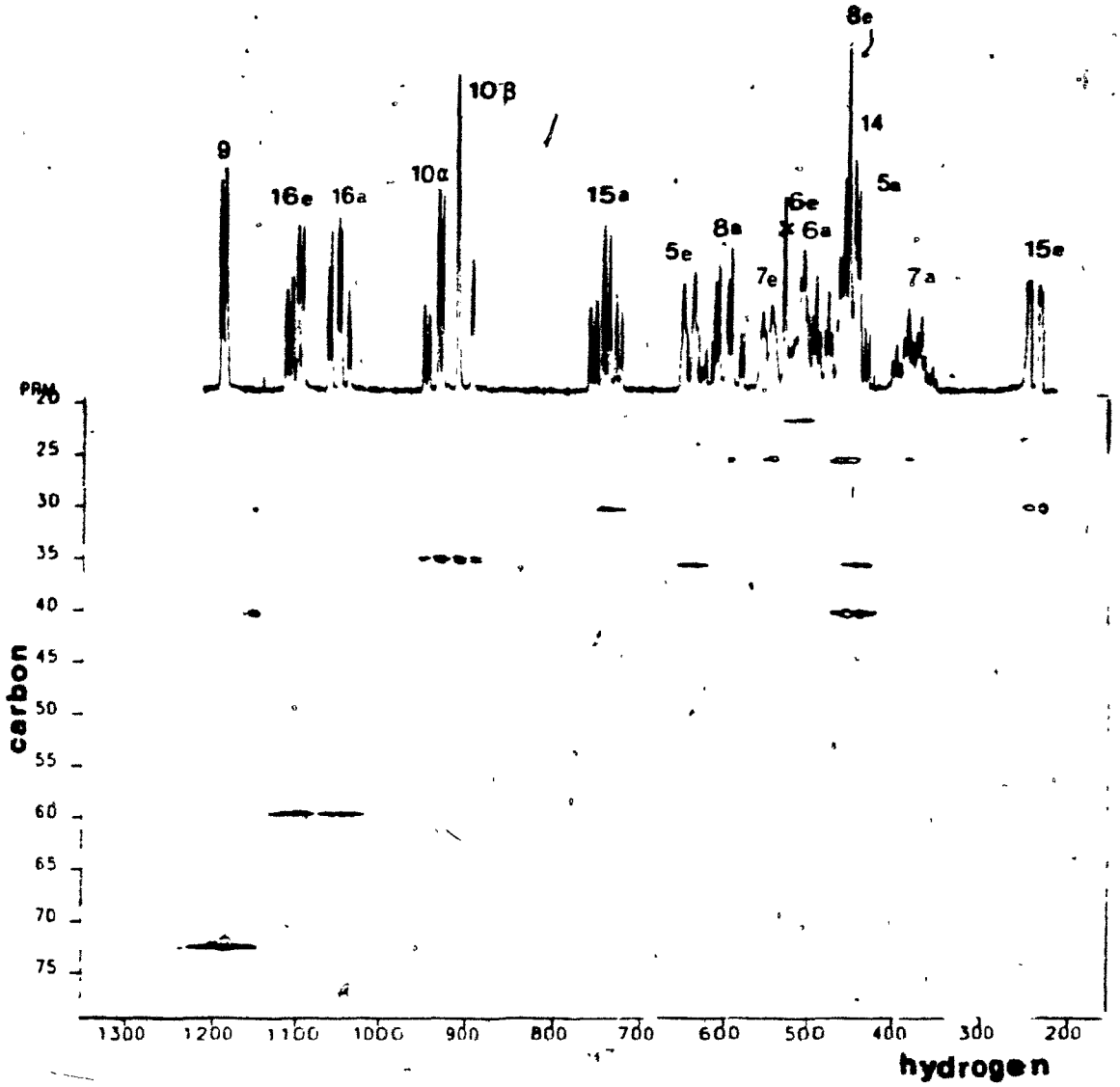


FIGURE 39: Heteroscalar correlated 2D-NMR spectrum of aliphatic region.

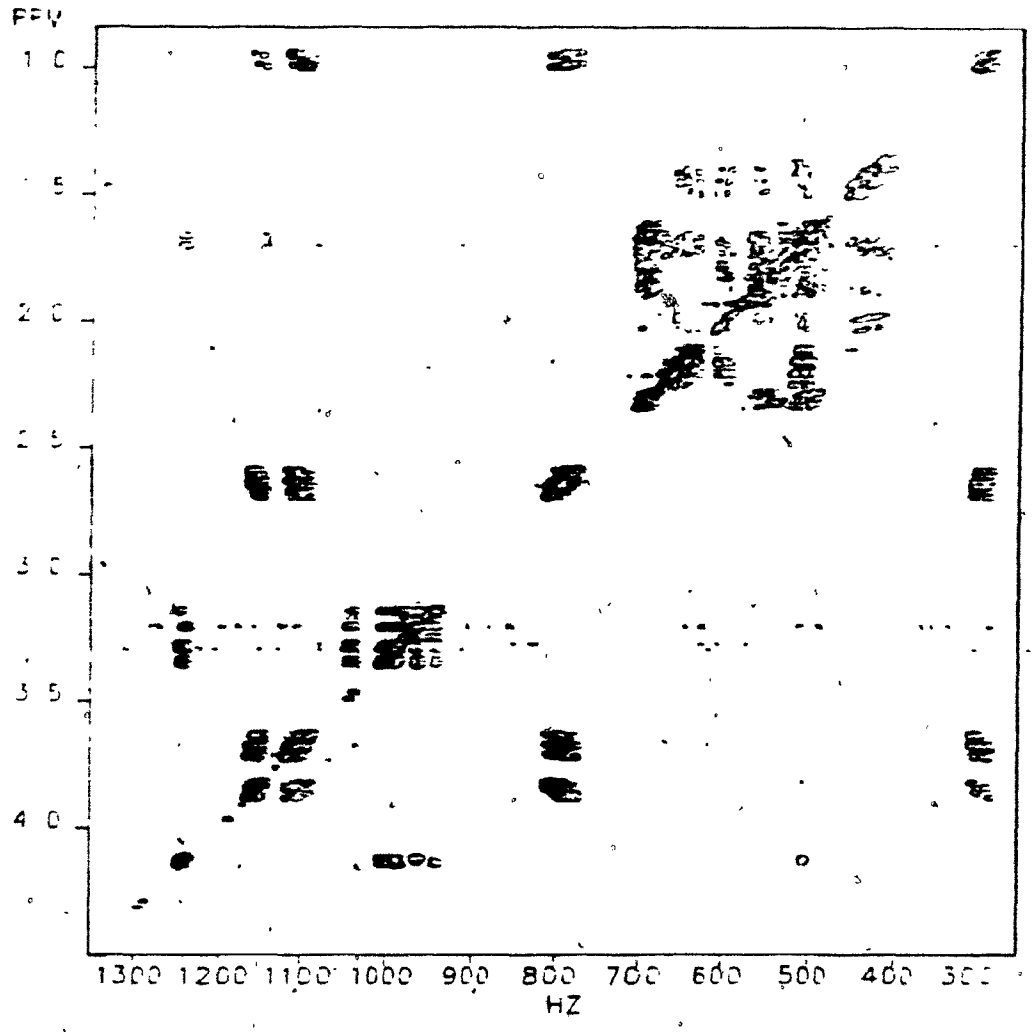


FIGURE 40: Homoscalar correlated 2D-NMR spectrum of aliphatic region.

The carbons α to the heteroatom at 17, C-9 and C-16, appeared furthest downfield in the iso-oxa analogue, had an intermediate value in the nitrogen series, and were furthest upfield in the sulfur analogues, the trend reflects the Pauling electronegativity order of the respective heteroatoms: O (3.5) > N (3.0) > S (2.5) (125). Upon N-alkylation, the carbons α to the nitrogen of morphinans (123) and benzomorphans (126) appear further downfield relative to the corresponding secondary amines. In N-norlevorphanol carbon 10 appears at 33.8 ppm (123) but appeared at 26.12 and 23.62 ppm in isolevorphanol and levorphanol, respectively, due to the γ-gauche shielding (124) of C-10 by the equitorial methyl group on the nitrogen.

The carbon-13 NMR spectra served to characterize the stereochemical differences between the isomorphinan and morphinan ring systems. Thus, carbon-10 appeared further upfield in the morphinan series due to the γ-shielding of C-8. Whereas carbon-15 appeared at 31 ppm in the isomorphinans, it was shifted downfield by 10 ppm in the morphinan series. This carbon (C-15) is γ-shielded by C-6, C-8, and C-9 in the isomorphinans but γ-shielded only by C-9 in the morphinan analogues. These shielding effects account neatly for the observed spectral characteristics of the B/C isomers. Since the 17-oxa analogue also showed a C-15 resonance near 31 ppm, the trans-B/C geometry is accordingly confirmed.

The ^{1}H-resonances (Fig. 36) of 17-deaza-17-oxaisomorphinan were assigned through decoupling experiments (e) and by 2D-NMR experiments. Space-filling CPK models showed that the equitorial proton on C-15 lies

over the aromatic ring, so that the anisotropy strongly shields that proton accounting for its upfield shift to 0.81 ppm; in contrast the axial proton on C-15 appeared at 2.48 ppm. The equitorial ring-C protons are all downfield relative to the respective axial ones owing to the anisotropy of the sigma bonds (62), with the exception of the C-8 protons where the axial one appeared at 2.02 ppm and the equitorial one at 1.43 - 1.60 ppm. This different behaviour of the C-8 protons may be due to deshielding of the axial one by the electronegative heteroatom.