

**SHORT CHIRAL SYNTHESSES  
OF MORPHINAN AND RELATED SYSTEMS**

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## **Abstract**

Morphine and its derivatives continue to challenge the creativity of synthetic chemists. The aim of this research is to execute a short chiral synthesis of the morphinan system. Chirality is introduced via asymmetric reduction; the key step is the formation of four rings- the tetracyclic phenanthrofurane by an intramolecular Diels-Alder cycloaddition. The fifth ring was completed by three different methods, and three different pentahydrophenanthrofurane systems were obtained.

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*To my mom, my husband Heng and my daughter Jessica*

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## List of Abbreviations

BTMAICl <sub>2</sub>	benzyltrimethylammonium iododichloride
CB	catecholborane
CDI	carbonyldiimidazole
COSY	correlation spectroscopy
DAIB	(diacetoxy)iodobenzene
DBS	dibenzosuberyl
DCC	N,N'-dicyclohexylcarbodiimide
DIBAL	diisobutylaluminumhydride
DMAP	4-(N,N-dimethylamino)pyridine
DMSO	dimethylsulfoxide
DPPB	1,4-Bis(diphenylphosphino)butane
EDG	electron donating group
ee	enantiomeric excess
EWG	electron withdrawing group
h	hour
HMDS	hexamethyldisilazane
HMQC	heteronuclear multiple quantum correlation
IMDA	intramolecular Diels-Alder
LAH	lithium aluminium hydride
PIFA	phenyliodonium (III) bis (trifluoroacetate)
rt	room temperature

RED-Al	sodium bis-(2-methoxyethoxy)aluminum hydride
TBDMS	tert-butyl dimethylsilyl
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
TLC	thin-layer chromatography
UHP	urea hydrogen peroxide

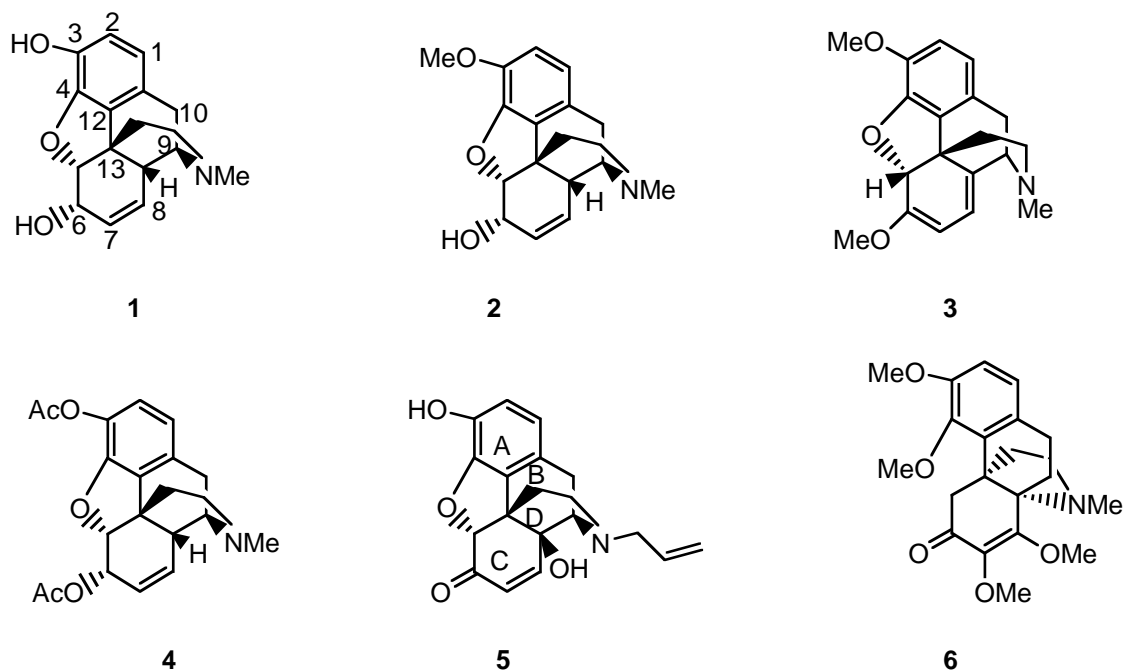
# CHAPTER 1

## INTRODUCTION

### 1.1 History of morphine and its derivatives

Morphine (**1**) is the active principal constituent of opium, which became well known as an analgesic in the fourth century BC.<sup>1</sup> Its pure form was isolated in 1806, and from then on, because of its medicinal value, people started to investigate its structure and synthesis.

All morphine used today is still obtained from poppy plants, which are mainly grown in India, Afghanistan, and Turkey, where poppies contain up to 20% of morphine in their latex.<sup>1</sup> Besides morphine, the latex contains approximately 3-4% codeine (**2**), 0.1-2% thebaine (**3**), 1-7% narcotine and 0.5%-1% papaverine as well.<sup>2</sup> Most of these opium alkaloids are used directly either in pain relief or for the production of synthetic opiates. Because of the highly addictive property of morphine, people tried to modify these alkaloids to produce less addictive drugs for medicinal purposes. Heroin (**4**), formed by simple acetylation of natural morphine, was an attempt to decrease addiction, but it has proved to be many times more addictive, and therefore more profitable on the illegal market. Naloxone (**5**), one antagonist (Figure 1.1), is effective in the treatment of accidental overdose of morphine, and has been shown to be useful in the treatment of alcohol abuse and eating disorders; it is manufactured from thebaine by synthetic modification in several steps.<sup>3</sup> Hasubanonine (**6**), is also an antagonist and represents the first example of a group of alkaloids related to the morphine structure. Since the nitrogen bridge in these compounds has the opposite configuration to that in the morphinan system, they are less active than morphine in their affinity for opiate receptors.<sup>4</sup>



**Figure 1.1** Morphine, congeners, and synthetic derivatives

To date, there are more than 20 total syntheses reported in addition to some other approaches to the morphine ring system, but a chiral synthesis at a cost competitive with that of isolation from natural opium has not been achieved yet. The search for a practical synthesis still continues.

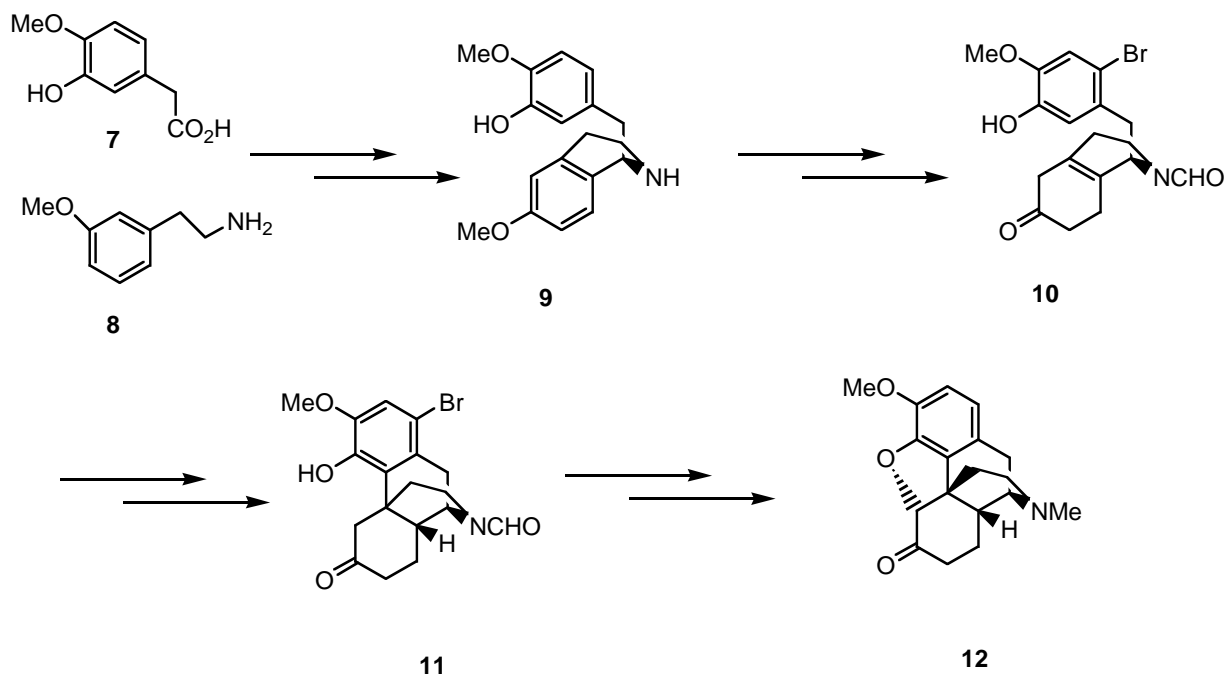
## 1.2 Literature review of total and formal syntheses

The total synthesis of the morphinan system has proven to be a difficult task, and has occupied the attention of several research groups for many years. The main difficulties remain the efficient formation of the C<sub>4</sub> secondary ether linkage and the C<sub>13</sub> quaternary center, with the correct absolute stereochemistry.<sup>3</sup>

Since Gates' landmark total synthesis of morphine in 1952, there have been 22 total syntheses of the morphinan system to date. Only four of the more important syntheses will be briefly summarized below, but recent reviews covering most of them and most recent synthetic studies since year of review are also available.<sup>1,5,6</sup>

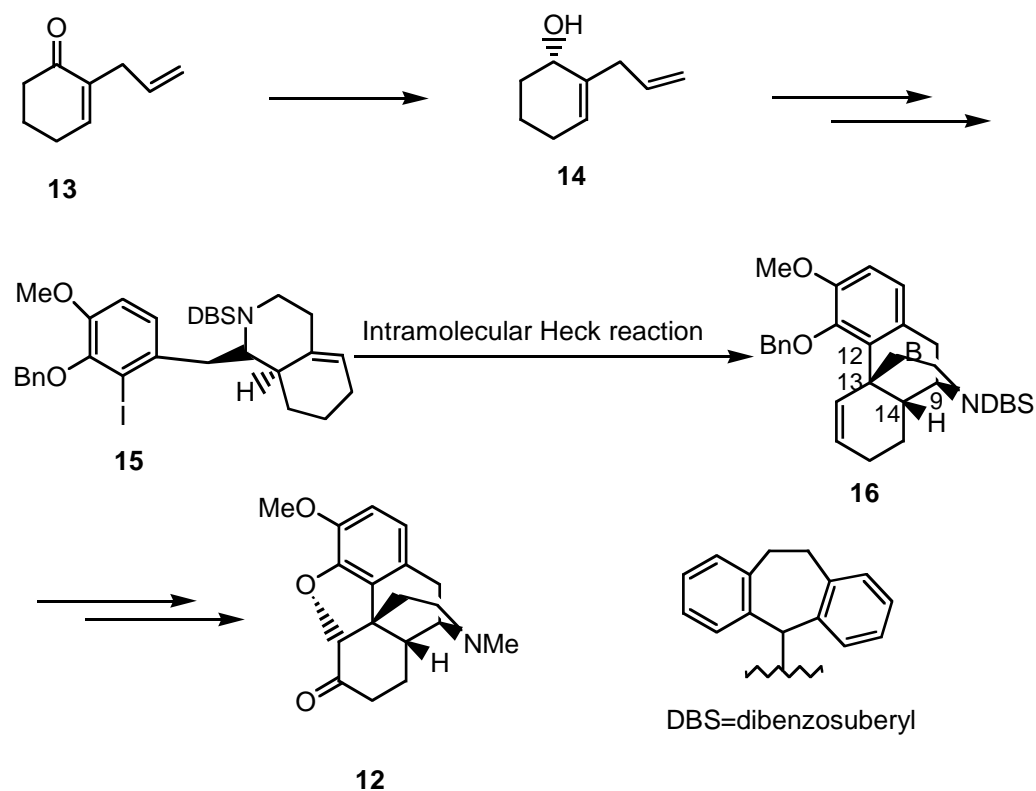
The most practical preparation of the morphinan system was achieved by Rice in 1980<sup>7</sup> (Scheme 1.1). This whole synthesis required isolation of only six intermediates, obtained sufficiently pure for immediate further use, and proceeded in 29% overall yield. The key feature is Rice's employment of bromo derivative **10** to avoid an undesired *para* coupling; the bromine atom could be easily removed by hydrogenolysis later. Resolution of ( $\pm$ )-**9** to separate the (R)-(-)-enantiomer afforded entry into the natural morphine series.

**Scheme 1.1** Rice's synthesis of (-)-dihydrocodeinone



Remarkably, all of the published syntheses of morphine until 1993 were either racemic or involved classical resolution. Overman changed this situation by reporting the first asymmetric route to the morphinan system.<sup>8</sup> An enantioselective reduction of 2-allylcyclohexenone (**13**) introduced chirality (Scheme 1.2), providing the corresponding (S)-(-)-cyclohexenol **14** in >96% ee. The crucial step involved an intramolecular Heck reaction to complete ring B, and afforded morphinan **16** with the correct stereochemistry at C<sub>9</sub>, C<sub>13</sub> and C<sub>14</sub>. Oxidation, followed by reductive cleavage of the DBS protecting group in the presence of formaldehyde yielded (-)-dihydrocodeinone (**12**) with 91% ee.

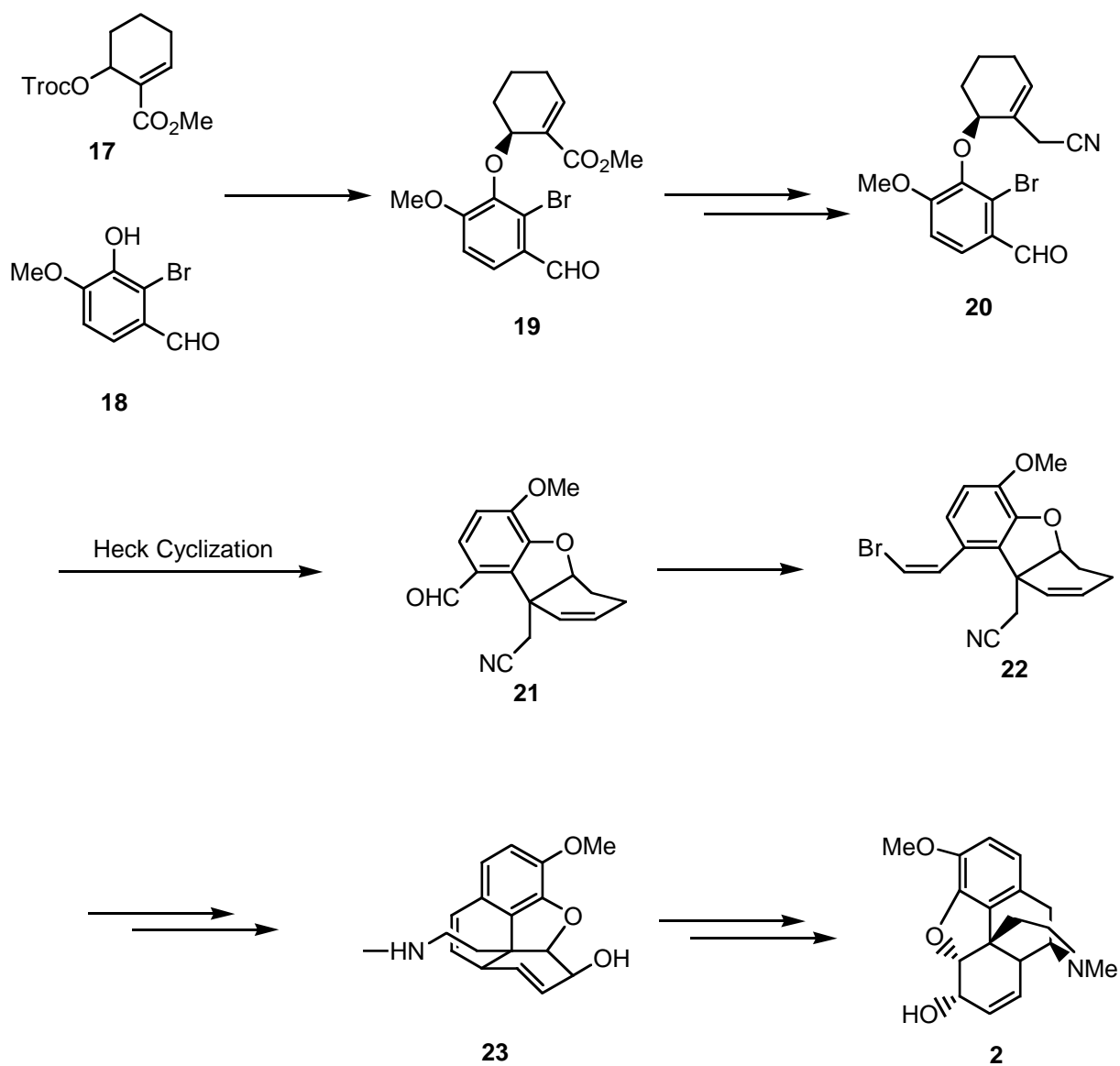
**Scheme 1.2** Overman's synthesis of (-)-dihydrocodeinone





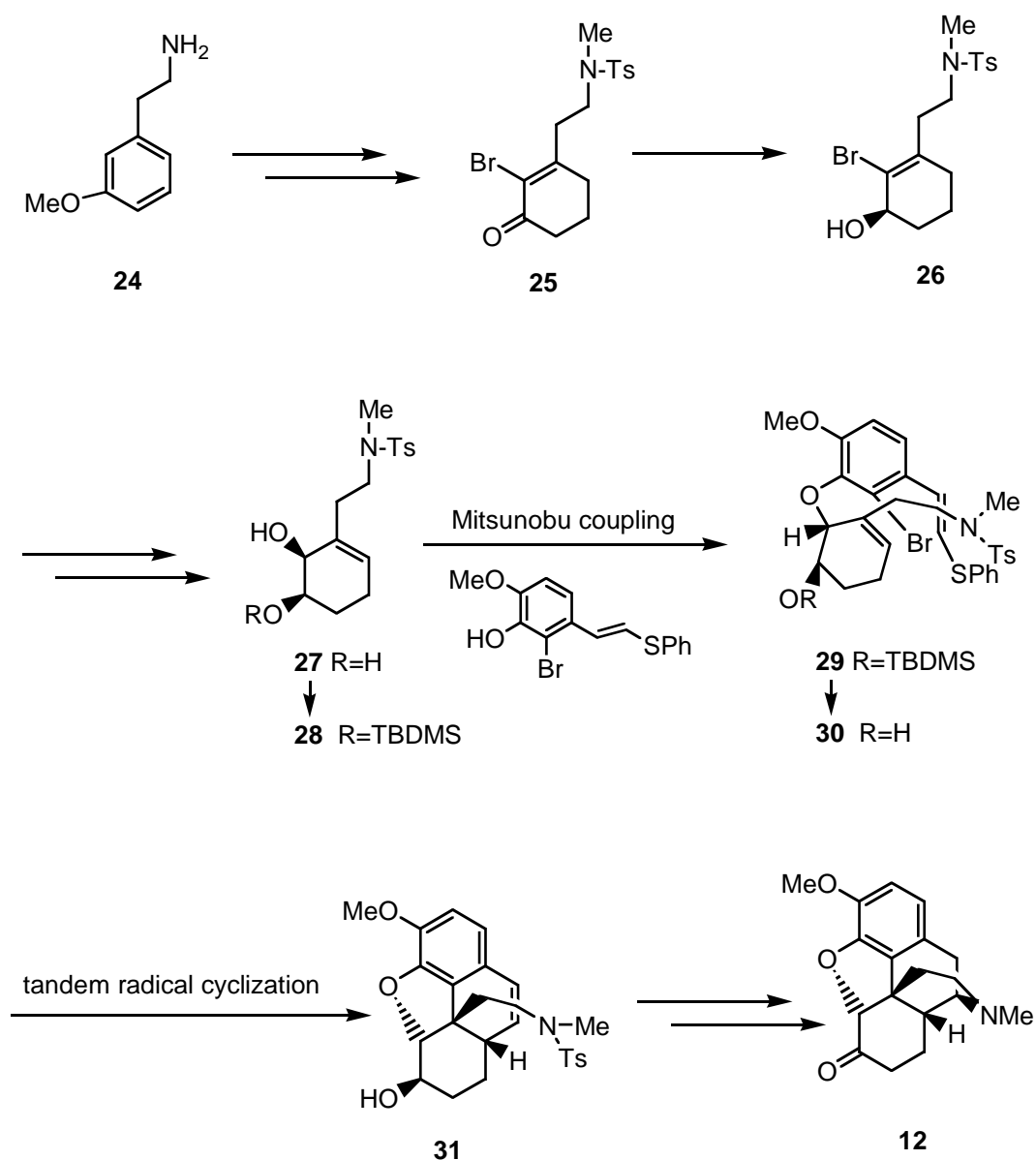
Trost's enantioselective total synthesis of (-)-codeine and (-)-morphine appeared in 2002.<sup>9</sup> Chirality was introduced via asymmetric allylic alkylation of phenol **18** (Scheme 1.3), with ester **17** to give **19** in good yield and ee (72% and 88%, respectively). The key features of Trost's synthesis are the Heck cyclization of nitrile **20**, establishing the C<sub>13</sub> quaternary center, Heck cyclization of **22** and an intramolecular hydroamination to produce (-)-codeine (**2**).

**Scheme 1.3** Trost's synthesis of (-)-codeine



Another noteworthy work is Parker's enantioselective synthesis of (-)-dihydrocodeinone (**12**), published in January 2006.<sup>5</sup> Cyclohexenol (R)-**26**, prepared by CBS reduction of enone **25**, is the source of chirality (Scheme 1.4). The key steps are accomplished by Mitsunobu coupling, affording aryl ether **29**, which undergoes tandem radical cyclization to produce a tetracyclic styrene **31**, then followed by reductive hydroamination to complete the synthesis of (-)-dihydrocodeinone (**12**) with 75% ee.

**Scheme 1.4** Parker's total synthesis of (-)-Dihydrocodeinone

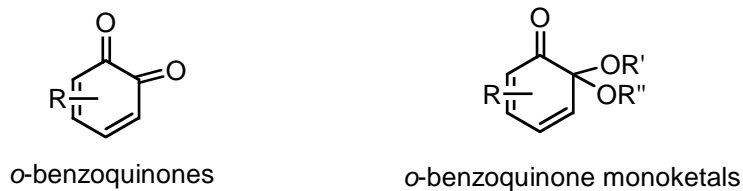


## 1.3 Previous work in our laboratory

### 1.3.1 *Ortho*-benzoquinone monoketals as synthetic intermediates

The pentacyclic morphine structure features three carbocycles and two heterocycles, which can be formed by different synthetic methods. Among these methods, the inter- and intramolecular Diels-Alder reaction has become one of the most useful reactions in our lab to synthesize several natural products since it provides easy access to a wide variety of cyclic compounds.

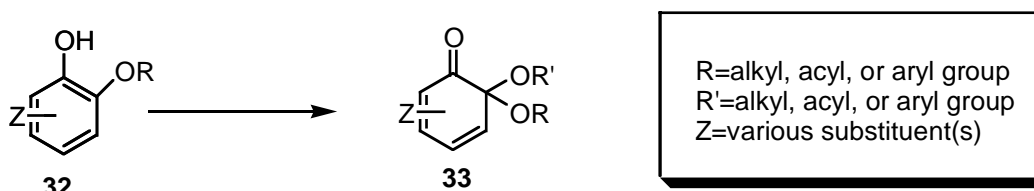
The use of *o*-benzoquinones and their monoketals (Figure 1.2) as dienes in Diels-Alder reactions has been well documented.<sup>10</sup> Their potential as intermediates in the synthesis of natural products has been restricted by their propensity for dimerization and rapid decomposition. However, their use as both dienes and dienophiles has been rapidly developed during the past 10 years.<sup>11,12,13</sup> These monoketals constitute valuable electrophilic intermediates because their electronically different double bonds have the potential of being regioselectively converted into various cyclic organic skeletons. Furthermore, the ketal group permits the differentiation of adjacent oxygen functionalities, and also provides monoprotection of the 1,2-dicarbonyl unit, therefore, *o*-benzoquinone monoketals sometimes are referred to as “masked” *ortho*-benzoquinones.<sup>10</sup> When they function as dienophiles in intermolecular Diels-Alder reactions, they are reacted in the presence of an excess amount of a diene (3 to 20 fold molar equivalents), thereby suppressing the dimerization and polymerization reactions to some extent.



**Figure 1.2** The structure of benzoquinones and monoketals

There are two methods most commonly used to generate *o*-benzoquinone monoketals: (1) chemical oxidative alkoxylation and (2) electrochemical anodic oxidation of phenols **32** (Scheme 1.5). Recent preparations have relied much more on chemical oxidation than anodic oxidation; non-toxic and easy-to-handle hypervalent iodine(III)-based reagents which effect chemical oxidation have been developed rapidly to make these quinonoid species.

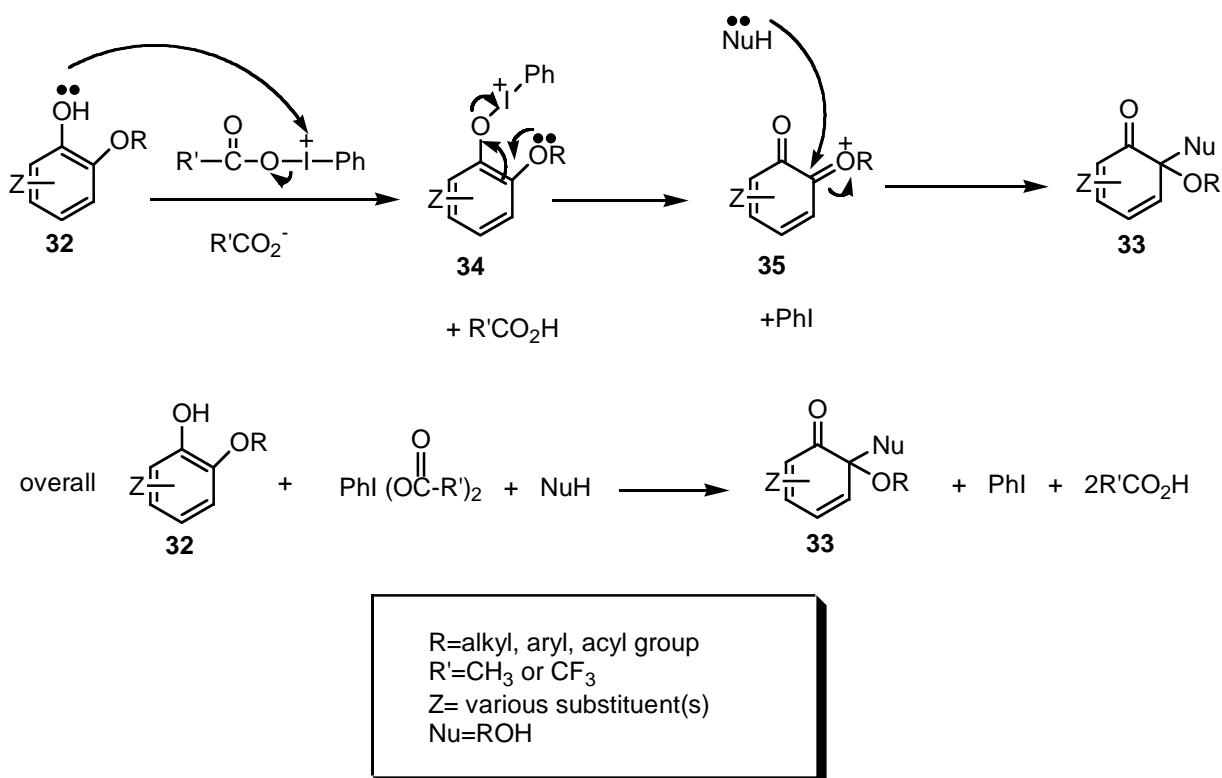
**Scheme 1.5** The generation of *o*-benzoquinone monoketals



The two hypervalent iodine reagents, diacetoxyiodobenzene  $\text{PhI}(\text{OAc})_2$ , also referred to as DAIB and phenyliodine(III) bis(trifluoroacetate), also referred to as PIFA, have been the most frequently used two-electron oxidants in recent preparations of *o*-benzoquinone monoketals from phenols. This popularity is due to their being good electrophiles as well as their possessing a good leaving group by releasing iodobenzene (PhI), and their lack of toxicity in comparison to traditional metallic oxidants. The oxidation process, (Scheme 1.6), has been postulated<sup>14</sup> to occur via **34** to give desired *o*-benzoquinone monoketals **33**. A small electron releasing *ortho*-substituent such as a methoxy group plays a significant role in both stabilizing

a cationic intermediate of type **35** and in orienting the nucleophilic attack preferentially at the corresponding substituted carbon center, even when this position is the most sterically hindered one.

**Scheme 1.6** The mechanism of formation of *o*-benzoquinone monoketals

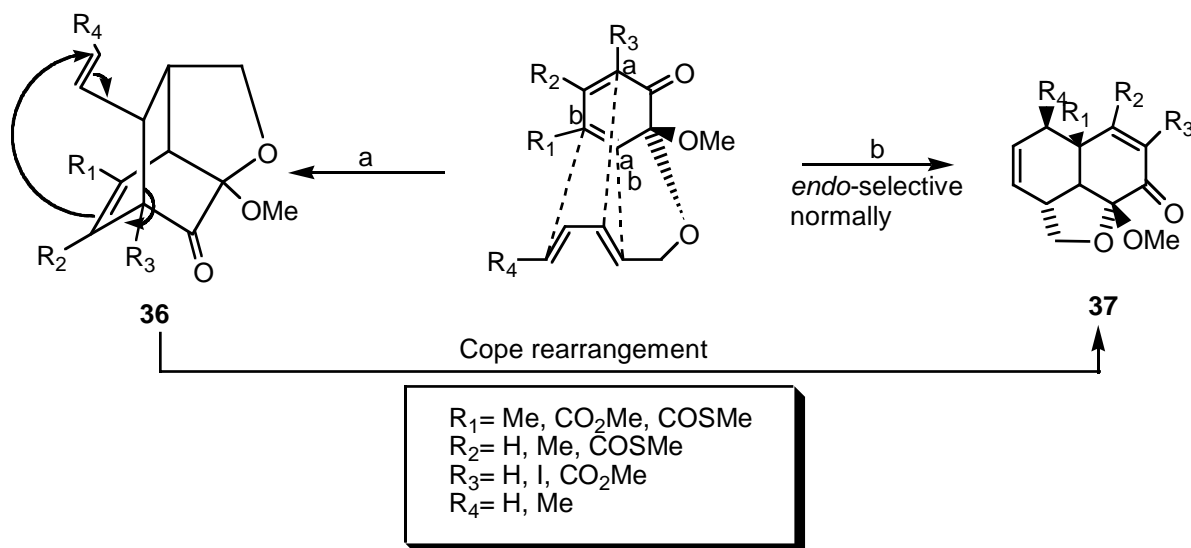


The capability of *o*-benzoquinone monoketals to react either as a diene or a dienophile component in  $[4\pi+2\pi]$  cycloadditions is their principal virtue in organic synthesis. Although most earlier utilizations<sup>15</sup> of *o*-benzoquinone monoketals in IMDA reactions have been as  $4\pi$  components, today an increasing number of reports describe<sup>12,13,16</sup> the use of the title ketals as  $2\pi$  dienones with electron-rich dienes. Normally, when *o*-benzoquinone monoketals react

intramolecularly with other  $4\pi$ - systems, they behave both as a diene and as a dienophile to give mixtures of *endo*- and bridged bicyclo[2.2.2]octenones. A typical example is the intramolecular reaction of dialkoxy- cyclohexa-2,4-dienone with a pendant diene: the moiety behaves both as a diene (path a) and as a dienophile (path b) to give mixtures of bicyclo[2,2,2]octenones of type **36** and *endo*-products of type **37** respectively. Furthermore, the bicyclo[2.2.2]octenones of type **36** undergo thermally-allowed [3,3]-sigmatropic Cope rearrangements to furnish compound **37**. (Scheme 1.7)

The tetracyclic phenanthrofurans system, which is related to morphine, is also readily accessible by application of the same chemistry.<sup>12</sup>

**Scheme 1.7**



### 1.3.2 Three step syntheses of phenanthrofurans related to (-)-morphine from *o*-benzoquinone monoketals

The reaction of methyl vanillate (**38**) with three equivalents of ( $\pm$ )-3-vinylcyclohex-2-enol (**39a**) in the presence of PIFA produced a mixture of *exo* **40** and *endo* **41** IMDA adducts, together with a small amount of the bridged adduct **42** (Scheme 1.8). During this reaction, the transitory monoketals were formed, it is believed, in two diastereomeric configurations (R\*S\* and S\*S\*), because the configuration at C<sub>4</sub> in the monoketal can not be controlled. The R\*S\* monoketal formed *exo* adducts **40** only, because intolerable steric interactions exist in the IMDA transition states leading to **41** and **42**. The S\*S\* monoketals formed *endo* and bridged adducts **41** and **42** respectively, since no such steric interactions exist in the transition states.

The *endo* isomer **41a** was easily aromatized by treatment with TFA to eliminate MeOH and produce the dienone **43a**, followed by ester hydrolysis and decarboxylation to furnish **44a**. The *exo* isomer **40a** was stable to acid treatment at room temperature. Similarly, the 2-allylcyclohexenol **39b**, prepared from 2-allylcyclohexan-1,3-dione in a similar way to **39a**, reacted with methyl vanillate (**38**) and PIFA to provide a mixture of three adducts. The *endo* isomer **41b** was converted to dienone **43b** by brief exposure to TFA (trifluoroacetic acid) while *exo* adduct **40b** was stable to similar acid treatment. This was observed generally with many *exo* and *endo* adducts of this type and was attributed to an anomeric effect. Elimination of methanol can take place only when one lone pair of the endocyclic oxygen atom is anti and parallel with the C-OMe bond. This enables the lone pair to overlap with the antibonding orbital of the C-OMe bond thus weakening and lengthening it. Such differences in C-OMe bond lengths were confirmed by X-ray crystallography of several such examples.<sup>17</sup> The bridged adduct **42** was subjected to the thermal Cope rearrangement with elimination of MeOH

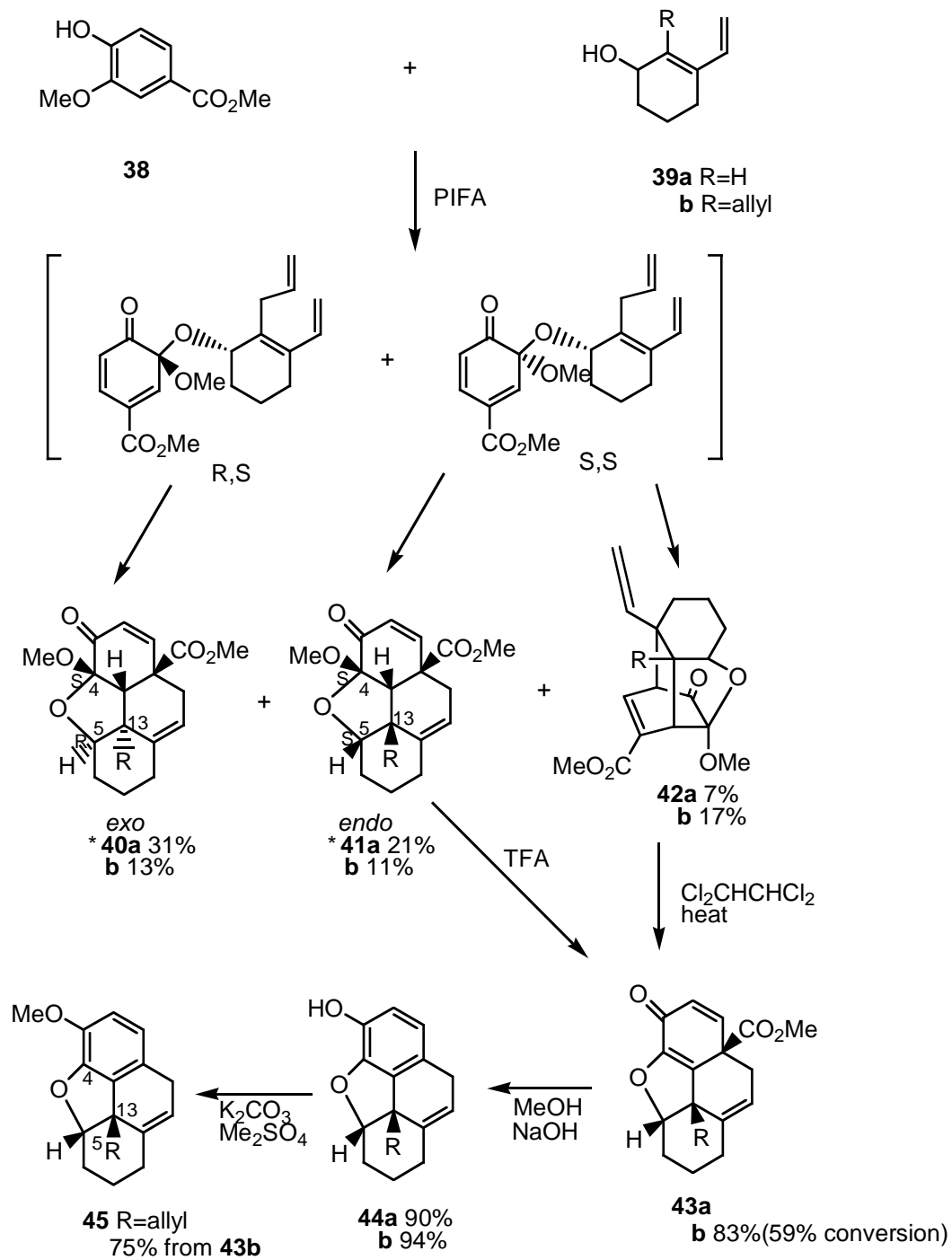
in refluxing 1,1,2,2-tetrachloroethane to produce **43b**, and saponification and decarboxylation resulted in **44b**.<sup>12</sup>

In this reaction, enantioselectivity was achieved by reduction of 2-allyl-3-vinylcyclohex-2-enone with borane and a (R)-oxazaborolidine ligand to provide the (S)-(-)-cyclohexenol **39b** in 50% yield and 91% ee.<sup>18</sup> Subsequent reaction with **38** then established the correct configurations at C<sub>5</sub> and C<sub>13</sub>.

The use of one step to deliver absolute stereocontrol at two of the five chiral centers of the molecule is very attractive, but some practical problems still remain, which include (1) the poor yield of the *endo-exo* mixture; (2) the inability to transform the *exo*-adduct to the next intermediate; (3) the necessity of using an excess of dienol and the difficulty of removing the high boiling dienol from the reaction after it is completed and (4) the incomplete conversion of **42** to **43** in the Cope reaction. Therefore, more work was needed to modify and improve this route.



**Scheme 1.8**



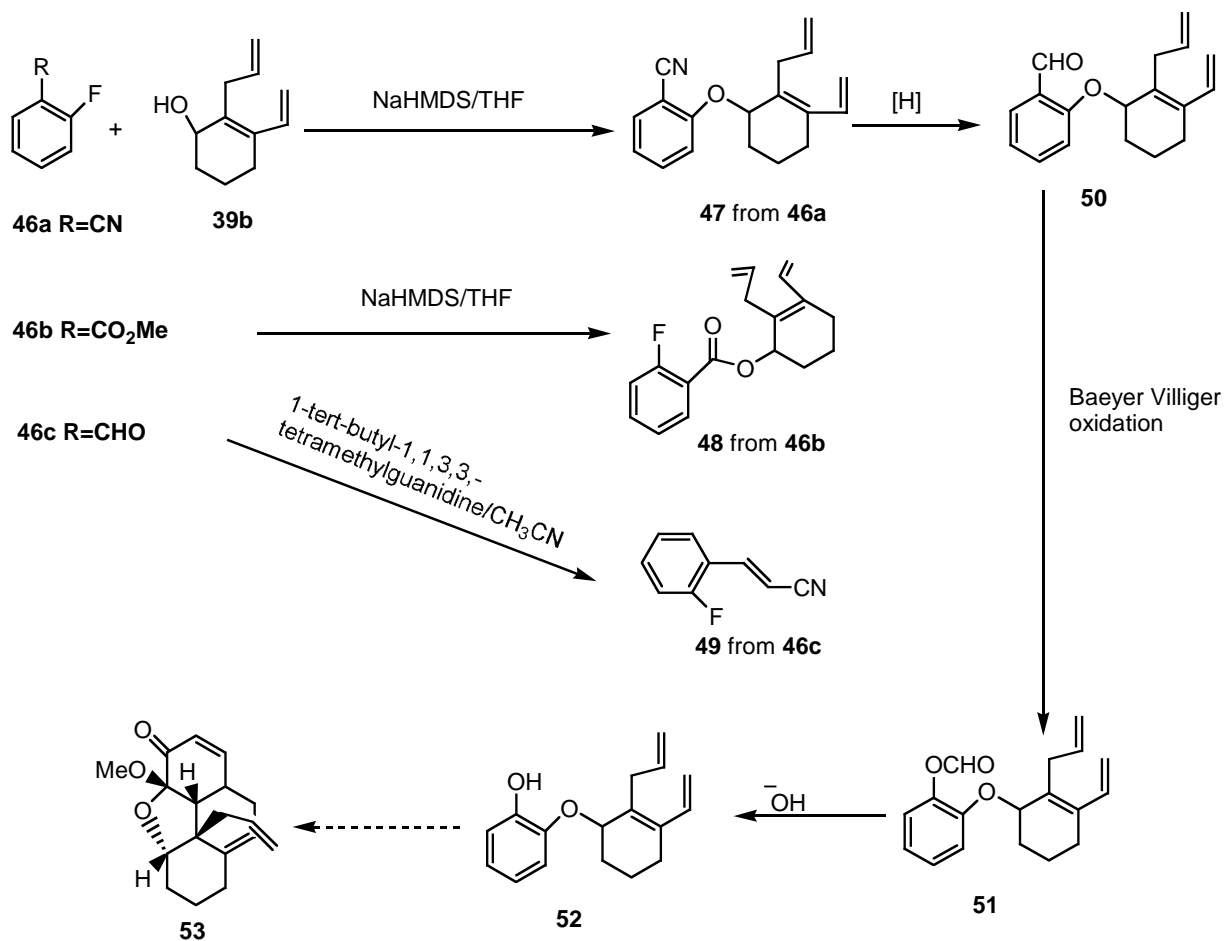
\* Relative configuration established by X-ray crystallography

### 1.3.3 Modification of IMDA reactants

Extensive studies have been performed in our laboratory on the design of a suitable diene and dienophile in order to solve the problems in the IMDA reaction,<sup>19</sup> and after evaluation of the results it was decided that prior attachment of the diene to the catechol (i.e. before oxidation) offers several advantages: (1) The use of excess of dienol in the IMDA reaction will be unnecessary; (2) Methanol can be used as solvent as well as nucleophile in the oxidation with PIFA. Recovery of the excess of the dienol is avoided and the excess methanol is easily removed; (3) The decarboxylation step is not required when a guaiacol is used without the C<sub>4</sub> ester, and the Cope rearrangement of any bridged adduct under mildly acidic conditions provides an aromatic compound directly, and might therefore be expected to go to completion. The desired catechol monoether **52** then becomes the key substrate for synthesis of the morphinan system by this route. (Scheme 1.9)

The synthesis of monoether **52** from catechol and **39b** proved to be challenging. The Mitsunobu reaction, palladium-catalyzed alkylation of allyl carbonates, and DCC coupling were performed<sup>18</sup> but with only marginal yields of the desired product **52**. Therefore nucleophilic aromatic substitutions of *ortho*- fluoro aromatic substrates such as **46a**, **46b**, **46c** were attempted, but only **46a** provided the desired substitution product **47**. Compound **47** undergoes a reduction to afford the corresponding aldehyde **50**, and although there are so many reports about this partial reduction of cyanides, only a complex formed from LAH and N,N'-dimethylethylenediamine<sup>20</sup> works in this case. Subsequently **50** was subjected to the Baeyer-Villiger oxidation with hydrogen peroxide and a catalytic amount of diphenyldiselenide<sup>21,22</sup> to give formate **51**; subsequent base hydrolysis generated target molecule **52**, initially as the racemate in 54% overall yield.

### Scheme 1.9



### 1.4 Synthetic strategy

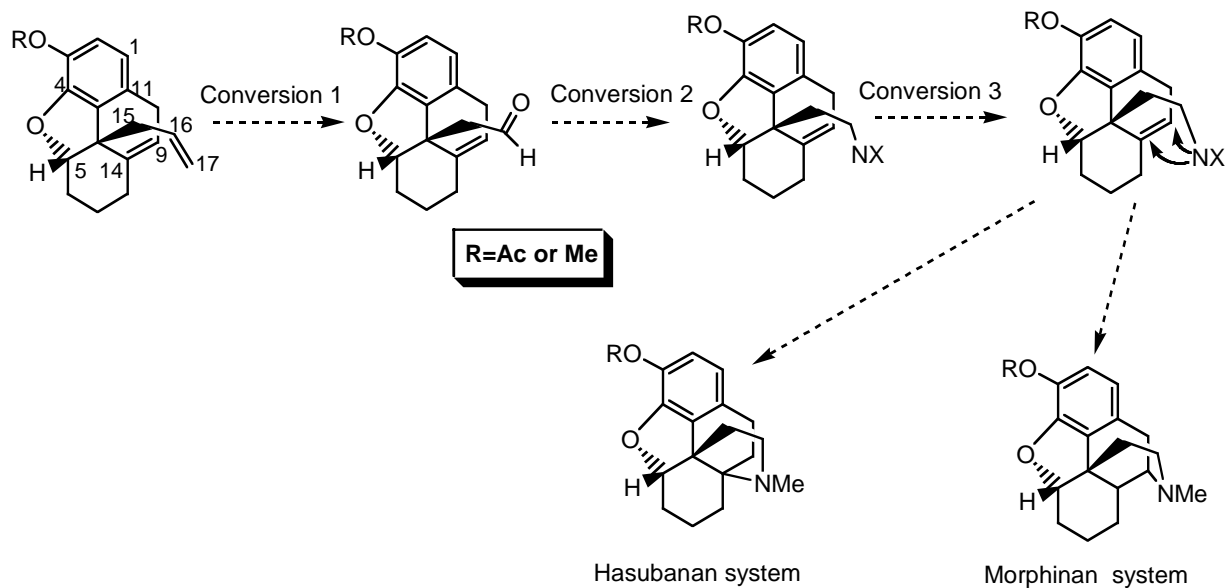
The previous outcome with the synthesis of monoether **52** was very promising. The following problems now remained to be addressed:

1. To prepare S-(-)-**52** with acceptable yield and enantiomeric excess;
2. To make tetracyclic system **44b** in better yield than before (Scheme 1.8); this would require significant improvement in the yield and experimental protocols of the IMDA-Cope sequence (Scheme 1.8);
3. To selectively oxidize the terminal C<sub>16</sub>-C<sub>17</sub> double bond of a tetracyclic system like **45** (Scheme 1.10, conversion 1);

4. Subsequently to incorporate the required nitrogen atom at C<sub>16</sub> (Scheme 1.10, conversion 2);
5. To complete the fifth ring by constructing the C<sub>9</sub>-N bond leading to morphinan system or constructing the C<sub>14</sub>-N bond resulting in a Hasubanan-like alkaloid system (Scheme 1.10, conversion3).

These efforts are summarized in the generalized Scheme 1.10 and described in the following sections.

**Scheme 1.10**



# CHAPTER 2

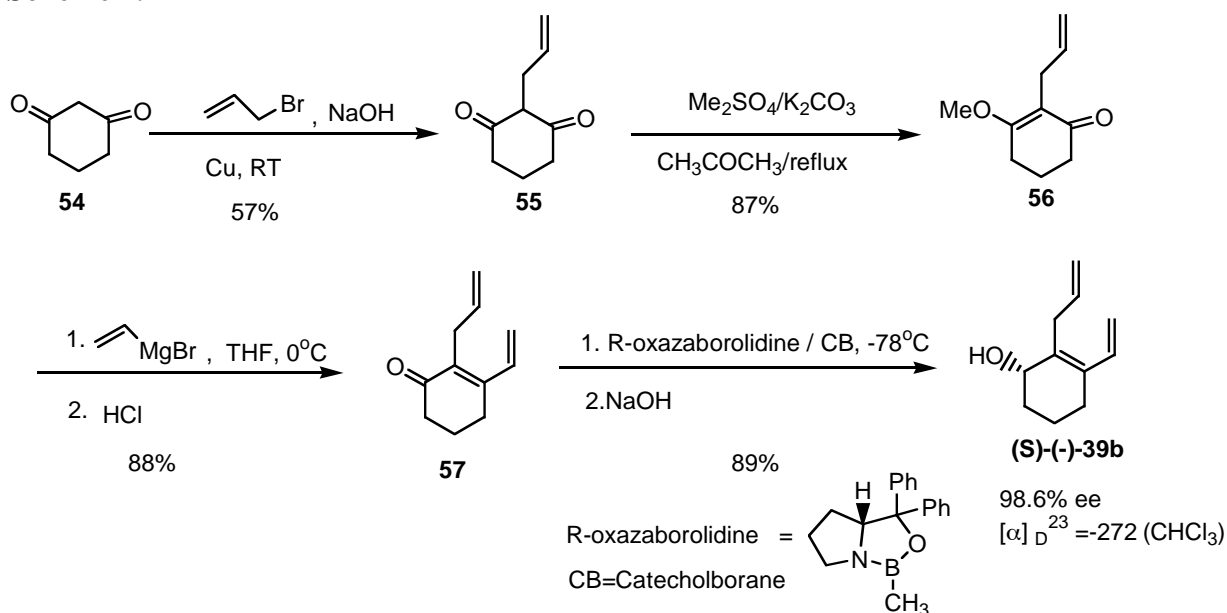
## Synthesis of homochiral tetracycles related to **45**

### 2.1 Synthesis of (S)-(-)-3-ethenyl-2-(2-propenyl)-2-cyclohexen-1-ol **39b**

This synthesis is mainly based on the previous preparation of racemic **52** (Scheme 1.9).<sup>19</sup> A few modifications have been incorporated to improve certain steps and a chiral reduction of the ketone **57** has been optimized.

The synthesis begins with the commercially available 1,3-cyclohexanedione (**54**) (Scheme 2.1), which is alkylated with allyl bromide. Instead of heating at reflux for 4 hours in dioxane and water as in the previous work, this experiment is performed with a metallic copper catalyst in water for 2 hours at room temperature.<sup>23</sup> The product 2-allyl-1,3-cyclohexanedione (**55**) was easily isolated by merely filtering and then separating the copper by dissolving **55** in CH<sub>2</sub>Cl<sub>2</sub> without the need for chromatographic purification. Several trial experiments showed that a reaction time of 2 h gives the best yield (57%) for this reaction compared to 1 hour or 3 hours' reaction yielding 33% and 38%, respectively. It is speculated that fewer hours result in incomplete reaction while more hours would lead to a double alkylation. Therefore, 2 hours reaction time, mild reaction conditions, and easier isolation of an intermediate pure enough for the next step make this method suitable for large-scale production, which is meaningful with respect to the entire synthetic route.

### Scheme 2.1



The allylation is followed by treatment of **55** with  $\text{Me}_2\text{SO}_4$ <sup>24</sup> to give O-methylated product **56**.  $\text{Me}_2\text{SO}_4$  is considerably cheaper than the  $\text{Et}_3\text{OBF}_4$  and  $\text{Me}_3\text{OBF}_4$  used previously; and also it is not sensitive to moisture, unlike  $\text{Et}_3\text{OBF}_4$  which must be from a freshly opened bottle and used at once to ensure that the reaction goes to completion. The product **56** is subsequently reacted with vinylmagnesium bromide to generate 3-ethenyl-2-(2-propenyl)-2-cyclohexen-1-one **57**, the precursor of (S)-(-)-3-ethenyl-2-(2-propenyl)-2-cyclohexen-1-ol **39b**. Since the concentration stated on the label of commercial vinylmagnesium bromide is always unreliable, freshly prepared vinyl magnesium bromide was used.

Chirality is introduced by reduction of enone **57** with 20mol% of R-oxazaborolidine as catalyst and catecholborane as reductant in toluene at  $-78^\circ\text{C}$  for 18 hours<sup>25</sup> to afford cyclohexenol (S)-(-)-**39b** 89% yield, 98.6% ee, and  $[\alpha]_{\text{D}}^{23} = -272$  ( $\text{CHCl}_3$ ). This is significant improvement when compared to using borane as reductant at  $35^\circ\text{C}$  as in the earlier work<sup>19</sup> providing the cyclohexenol (S)-(-)-**39b** 50% yield, 91% ee and  $[\alpha]_{\text{D}}^{23} = -235$  ( $\text{CHCl}_3$ ). This

difference is probably due to the fact that olefins are sensitive to borane at moderate temperatures and subject to hydroboration resulting in poorer yields, and the higher reaction temperature leads to poorer enantioselectivity.

## 2.2 Synthesis of (S)-(-)-2-[(2-allyl-3-vinylcyclohex-2-en-1-yl)oxy]phenol **52**

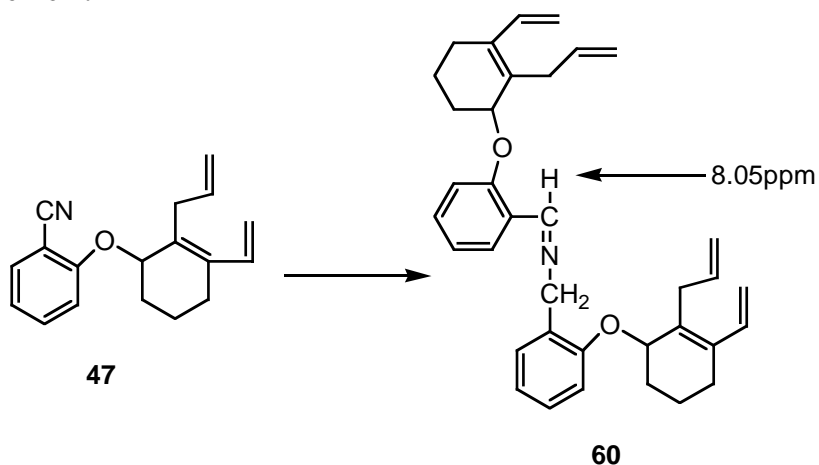
(S)-(-)-**39b** has the correct configuration needed for the morphinan system. Subsequent work follows the routes shown in Scheme 1.9 to furnish the key intermediate (S)-(-)-**52**. Some improvements are implemented at this stage and higher yields are realized as well.

*Ortho*-fluoro cyanide **46a** undergoes nucleophilic aromatic substitution with the anion of **39b** to generate chiral (S)-(-)-**47** with retention of configuration at C<sub>1</sub> of (S)-(-)-**39b**, ( $[\alpha]_{\text{D}}^{23} = -304.8$  (CHCl<sub>3</sub>)).

From (S)-(-)-benzonitrile **47** to (S)-(-)-phenol **52**, three steps are developed to be performed successively without any chromatographic purification between each step. The products in each step are pure enough for immediate use in the next. An overall three-step yield of 62% of (S)-(-)-phenol **52** is obtained after chromatographic purification.

(S)-(-)-benzonitrile **47** is reduced by the complex lithium N,N'-dimethylethylenediaminoaluminum hydride (LDMEDAH)<sup>20</sup> formed from LAH and N,N'-dimethylethylenediamine to generate (S)-(-)-benzaldehyde **50** (Scheme 1.9). The reaction is performed at 0°C and all the starting materials need to be pre-cooled; otherwise the aromatic imine **60** will be formed by overreduction of some of the nitrile to the benzyl amine. It displays a characteristic <sup>1</sup>H NMR peak at 8.05 ppm for the imine proton instead of the aldehyde <sup>1</sup>H NMR peak at 10.46 ppm (Scheme 2.2). This step proceeds with 100% conversion and furnishes a 84% yield of (S)-(-)-benzaldehyde **50** with optical rotation  $[\alpha]_{\text{D}}^{23} = -266$  (CHCl<sub>3</sub>).

**Scheme 2.2**



The product **50** undergoes a Baeyer-Villiger reaction with 30% aqueous hydrogen peroxide and 20 mol% of diphenyldiselenide which produces phenylseleninic acid to act as the oxidizing agent.<sup>21,22</sup> The reaction needs to be stirred vigorously due to the two phase conditions, and the benzaldehyde **50** is converted to (S)-(-)-formate **51** in 94% yield (Scheme 1.9). Without any purification, the formate **51** is dissolved in MeOH, treated with 4% aqueous  $K_2CO_3$ <sup>26</sup> instead of 4% aqueous KOH as the other option for this experiment which lead to variable yield ranging from 52% to 81%, and the formate **51** is completely converted to (S)-(-) **52** in a reproducible yield of 78%. It should be noted that **52** does not carry the ester group *para* to the hydroxyl group.

### 2.3 The intramolecular Diels-Alder reaction of (±)-**52** and (S)-(-)-**52**

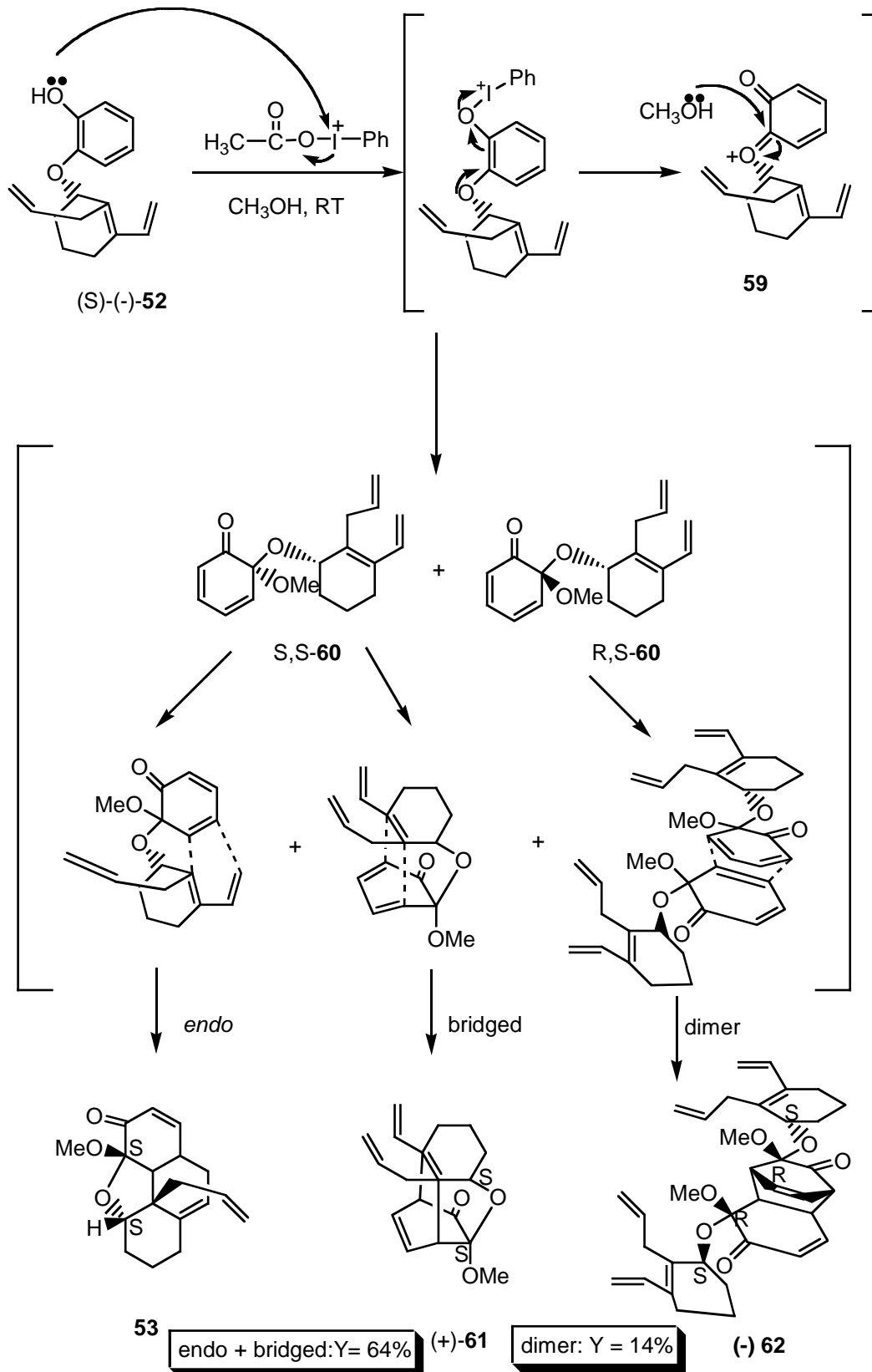
The IMDA cyclization is the key step that affords two more rings, one carbocyclic and one heterocyclic, of the morphinan system in one step with control of stereochemistry at C<sub>5</sub> and C<sub>13</sub>. Initially the key intermediate (±)-**52** was subjected to hypervalent iodine oxidation in methanol and IMDA cyclization to provide adducts *via* the *o*-benzoquinone monoketals **60** (Scheme 2.3).



As a result of nucleophilic attack of MeOH on oxonium ion **59** taking place without facial control, two diastereomeric pairs of ketals S\*S\* and R\*S\* will be formed.

As in the previous case of ketals generated in Scheme 1.8, it is proposed that the SS, RR pair **60** produces the *endo* and bridged IMDA adducts **53** and **61** corresponding to compound **41** and **42** of Scheme 1.8. The other RS, SR pair now lacking the C<sub>4</sub> ester group, is less activated to form IMDA *exo* adducts, (such an ester group was incorporated in the corresponding quinone monoketals of Scheme 1.8 to improve dienophilicity in the IMDA pathway); this diastereomer prefers to dimerise instead by an intermolecular Diels-Alder process. The dimer (±)-**62**, obtained from (±)-**52**, was separated and crystallized<sup>19</sup> and X-ray analysis was used to confirm its structure and RS, SR relative configuration at the ketal carbon atoms (Appendix 1).

Scheme 2.3



With (S)-(-)-**52**, the same reaction was performed. Thus (S)-(-)-**52** in methanol is added to a solution of DAIB in methanol over 1 h at room temperature. The resulting reaction mixture is stirred overnight at room temperature and monitored by TLC. The mixture of *endo* adduct **53**, bridged adduct **61** and dimer (-)-**62** is generated. The dimer **62** was again purified by chromatography and obtained in 14% yield. The *endo* product and bridged adducts can not be separated from each other in this step, as they overlap on TLC in several solvent systems; they are taken to the next step directly as a mixture. However, the <sup>1</sup>H NMR spectrum of the mixture clearly indicates the presence of both compounds **53** and **61** in a ratio of 1.2:1 as estimated by integration of the methoxyl signals of **53** (3.21ppm) and **61** (3.46ppm).

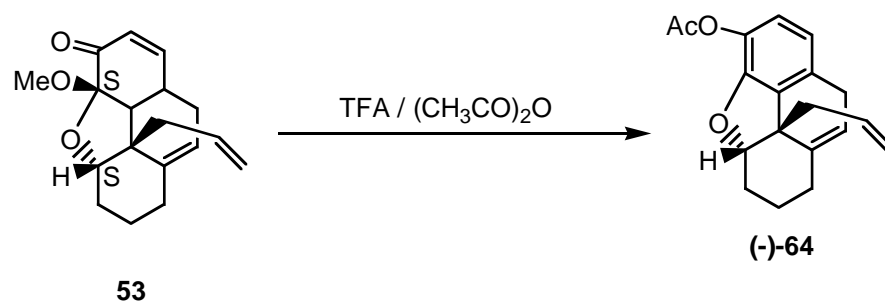
In an attempt to minimize the formation of the RS ketal, and thus to minimize the formation of dimer, one option explored was to vary the alkyl group of the solvent alcohol. Thus an experiment was performed by changing the solvent alcohol from methanol to isopropanol which has the more bulky alkyl group. From the ratio of dimer (18%), bridged and *endo* adducts (52%) obtained, it is inferred that the formation of the RS ketal increases when the size of alkyl group of the solvent alcohol does. Therefore methanol appears to be the most suitable solvent for this reaction.

The mixed *endo* and bridged adducts (-)-**53** and (+)-**61** both form aromatic compound (-)-**64**. When the mixture of (-)-**53** and (+)-**61** was treated with TFA and acetic anhydride for 15min, the *endo* adduct converts to the aromatic acetate leaving the bridged compound unchanged (Scheme 2.4). Pure (+)-**61** was thereby isolated  $[\alpha]_D^{23} = +299$  (CHCl<sub>3</sub>) by chromatography. Then (+)-**61** was heated in 1,1,2,2-tetrachloroethane with a few drops of acetic anhydride for 4 days at 140°C, and it undergoes the Cope arrangement to form aromatic compound (-)-**64** with complete conversion (Scheme 2.5). The solvent tetrachloroethane over

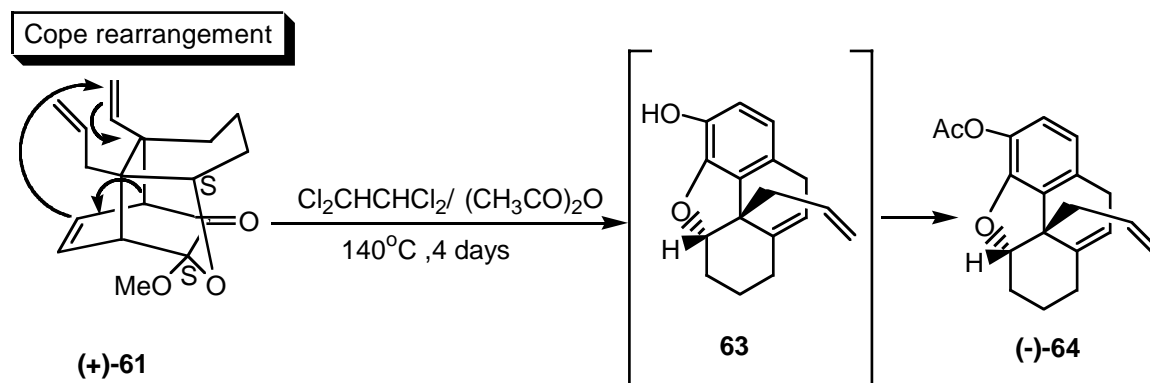
four days near its boiling point probably generates some acid which is responsible for the demethoxylation and aromatization of **53**. This aromatization also drives the Cope reaction to completion unlike in the previous case<sup>12</sup>, where only 59% conversion was realized. The acetic anhydride is used to directly transform the generated phenol **63** to acetate (-)-**64** since phenol **63** was previously found to be rather unstable. The whole reaction sequence results in a 42 % yield of the aromatic acetate (-)-**64** from (-)-**52**, it was purified by chromatography, providing  $[\alpha]_{\text{D}}^{23} = -208$  (CHCl<sub>3</sub>).

The assignment of SS configurations to the *endo* and bridged adducts (-)-**53** and (+)-**61** is not simply based on a default argument. The relative configurations of the corresponding racemic *exo* and *endo* adducts (±)-**40a** and (±)-**41a** from the ketal of Scheme 1.8 was established by X-ray analysis as S\*R\* and S\*S\* respectively. There is little reason to doubt that the reaction follows a similar course with the ketals of Scheme 2.3. Furthermore the *endo* adduct (-)-**53** aromatises easily by elimination of methanol, a result entirely consistent with the behaviour of other SS adducts. The bridged adduct (+)-**61** undergoes a Cope rearrangement-acetylation sequence to afford (-)-**64** identical with the tetracyclic acetate obtained from (-)-**53** (Scheme 2.4). These facts serve to identify the absolute configurations of all three products (-)-**53**, (+)-**60** and (-)-**62** in Scheme 2.3 and support the proposal that relates configuration of the transitory *o*-quinone monoketals (SS and RS **60**) to the products of the reaction.

### Scheme 2.4



### Scheme 2.5



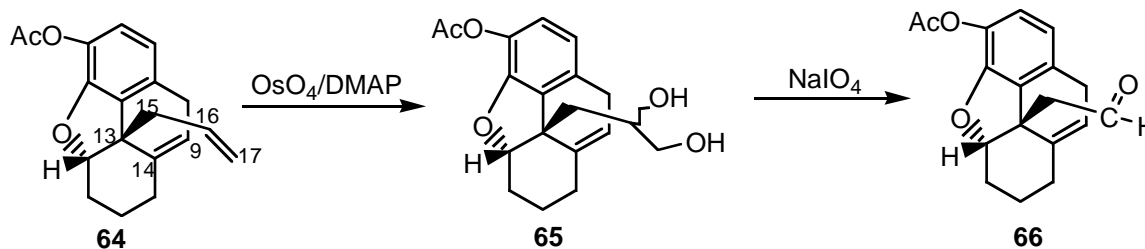
# CHAPTER 3

## INCORPORATION OF THE NITROGEN ATOM

### 3.1 Selective oxidation of double bond

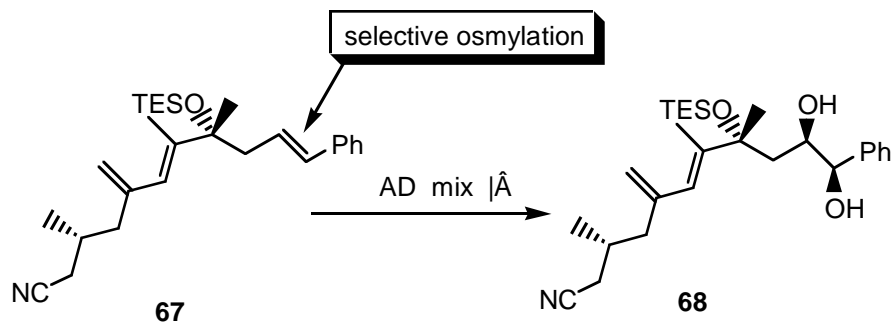
With the (-)-**64** in hand, a regioselective cleavage of the terminal double bond of the allyl group had to be attempted in order to generate a suitable substrate for incorporation of the nitrogen atom with loss of the terminal C<sub>17</sub> carbon. An appropriate target is the aldehyde **66** which might be accessed in two steps as shown in Scheme 3.1.

Scheme 3.1



Initial attempts at selective epoxidation resulted only in a mixture of  $\alpha$  and  $\beta$  9, 14 epoxides, leaving the allyl group unaffected<sup>12</sup>. Osmylation was therefore attempted with some hope of success since it had been reported<sup>27</sup> that regioselective osmylation of the only one double bond of three (Scheme 3.2), in a complex intermediate **67** was successfully achieved. That regioselectivity was attributed to a  $\pi$ -stacking interaction between the aromatic heterocyclic base used in the osmylation and a neighbouring benzene ring in the substrate<sup>27, 28</sup>.

### Scheme 3.2

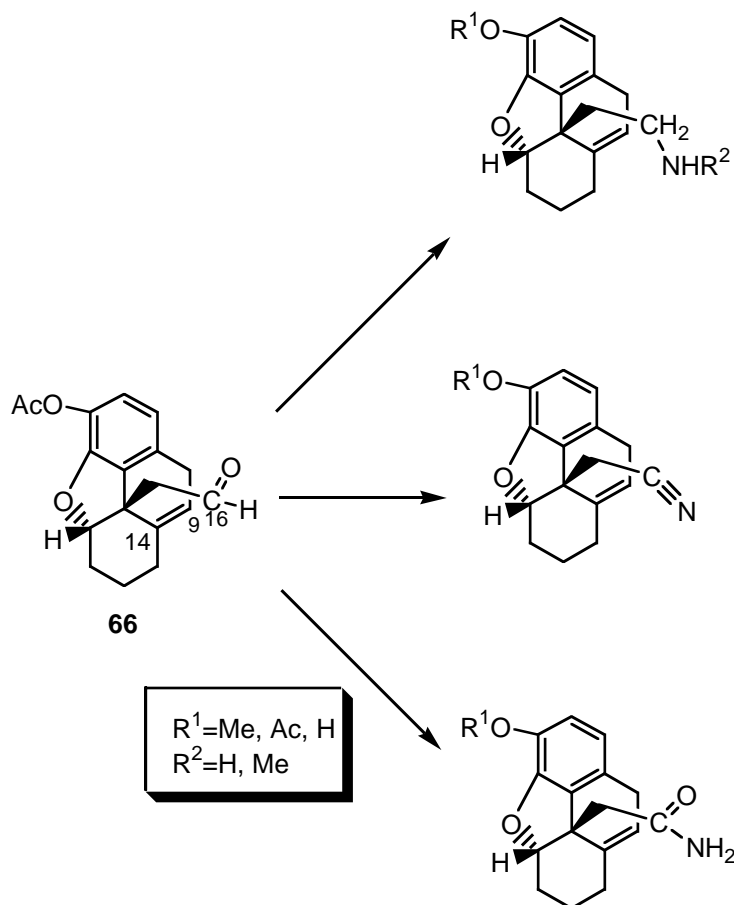


The structure of **64** offers the possibility that the C<sub>16</sub>-C<sub>17</sub> double bond, closer to the benzene ring, can adopt a position that permits such a  $\pi$ -stacking interaction by a mere rotation about the C<sub>13</sub>-C<sub>15</sub> single bond. This effect, as well as the greater accessibility of the C<sub>16</sub>-C<sub>17</sub> alkene to the OsO<sub>4</sub>-base complex in comparison with C<sub>9</sub>-C<sub>14</sub> bond augured well for the desired result. The experimental result of the osmylation, with DMAP as the heterocyclic base, was gratifying. The terminal double bond was indeed selectively hydroxylated in 91% yield and the mixture of diastereomeric diols produced was pure enough to be used directly for the subsequent cleavage. Oxidative cleavage of the diols **65** by NaIO<sub>4</sub> provided the aldehyde **66** in excellent yield (94%) and high purity. The two step process thus gives a pure product in 85% overall yield and was preferred to the one-pot osmylation-oxidation cleavage process (OsO<sub>4</sub>-NaIO<sub>4</sub>-2,6-lutidine) recently reported<sup>29</sup> because a trial experiment yielded the aldehyde in lower yield.

### 3.2 Conversion of aldehyde **66** to amine

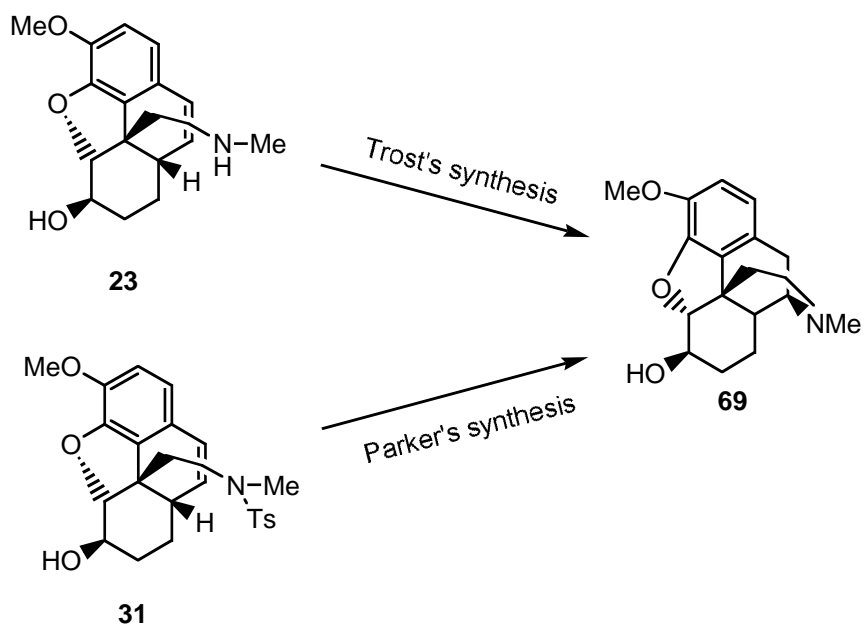
From the aldehyde **66**, the nitrogen atom can be introduced into a molecule in different ways (Scheme 3.3). Considerations leading to the choice of nitrogen functionality must include notions of subsequent cyclisation at C<sub>9</sub> or C<sub>14</sub> to form the fifth ring of the system. Parker's synthesis<sup>5</sup> and Trost's synthesis<sup>9</sup> of morphine employ a secondary amine function for ring closure by means of a reductive amination of a suitably placed double bond (Scheme 3.4). Formation of an amine at the C<sub>16</sub> carbon was therefore evaluated initially; two routes were attempted for this reaction as shown in Scheme 3.5.

**Scheme 3.3**

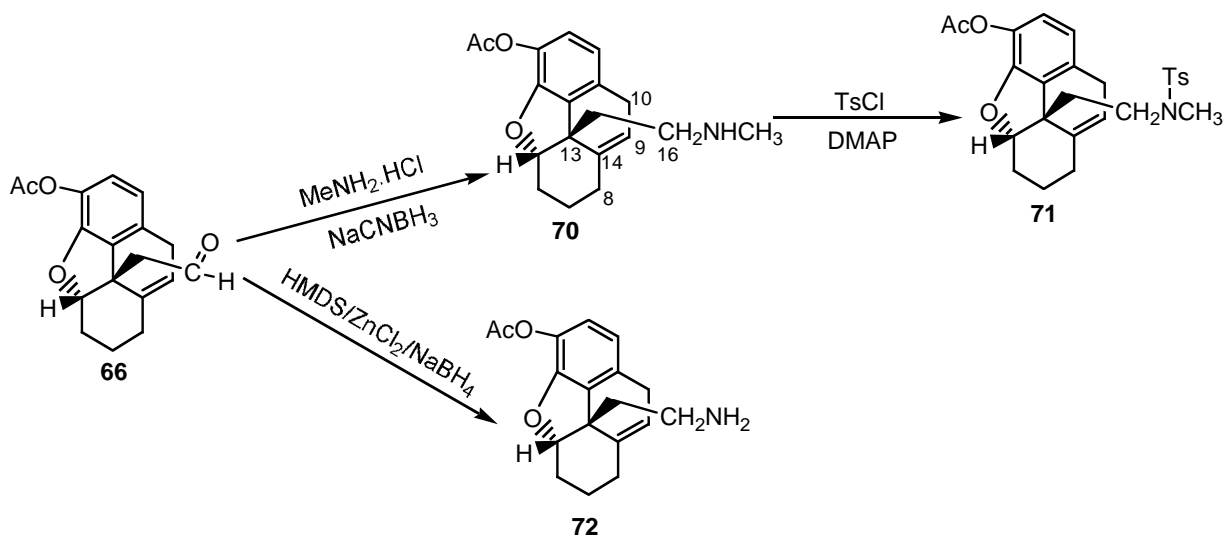




Scheme 3.4



Scheme 3.5



Reductive amination of aldehyde **66** was investigated with methylamine hydrochloride and sodium cyanoborohydride at pH 6-8<sup>30</sup>. However, only a modest yield of **70** was obtained (67%). Following a report that hexamethyldisilazane (HMDS) and ZnCl<sub>2</sub> can be used instead, to form a N-bisdimethylsilylaminal followed by NaBH<sub>4</sub> reduction to produce a primary amine<sup>31</sup> in high yield, the same procedure was attempted with **66**. A poor yield (ca. 40%) was obtained together with the C<sub>16</sub> alcohol from reduction of the aldehyde; therefore, the first route with methylamine hydrochloride and sodium cyanoborohydride was preferred.

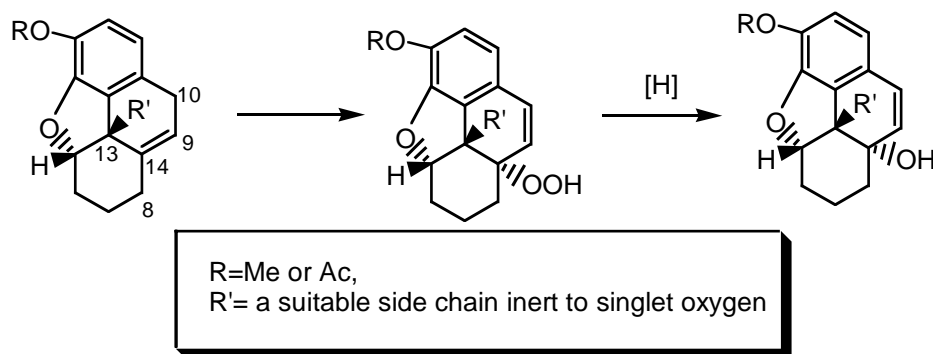
### 3.3 The position of the double bond

With compound **70** at hand, the regiochemistry of ring closure was considered. The double bond which can be used to construct the fifth ring is at C<sub>14</sub>-C<sub>9</sub>. However if the ring closure reaction is performed, it is likely that such a process will result in a 5-*exo*-trig cyclization at C<sub>14</sub> leading to the Hasubanan alkaloid skeleton rather the desired 6-*endo* cyclisation at C<sub>9</sub> to the mophinan ring system. The easiest way to solve this problem is to simply attempt a migration of the C<sub>9</sub>-C<sub>14</sub> bond to C<sub>9</sub>-C<sub>10</sub> bringing it into conjugation with the aromatic ring; cyclization will now become a 6-*exo*-trig process which is well precedented in morphine synthesis.

A particularly attractive possibility for this migration is a singlet oxygen ene reaction (Scheme 3.6). This reaction has been intensively studied and hydrogen abstraction in tri-substituted alkenes has been observed to occur on the more substituted side of the double bond<sup>32</sup>. Since there is no H atom at C<sub>13</sub>, the better possibility is H-abstraction at C<sub>10</sub> rather than at C<sub>8</sub> since the latter methylene group is on the less substituted side of the C<sub>9</sub>-C<sub>14</sub> double bond. The hydroxyl group then will end up at C<sub>14</sub> (perhaps in the  $\alpha$ -configuration) and the double

bond will relocate at C<sub>9</sub>-C<sub>10</sub>; more details for this singlet oxygen ene reaction will be discussed subsequently.

### Scheme 3.6



Amine **70** will probably not be stable to the singlet oxygen because it may be oxidized during the process, therefore it is better to convert the secondary amine to an amide which is more stable to singlet oxygen. TsCl and DMAP were used to convert **70** to **71** (scheme 3.5). This reaction proceeds in mild conditions and short time affording a 78% yield of the tosylamide **71**.

This compound is now ready for the singlet oxygen ene reaction. The reaction was performed with an oxygen bubbler and visible light irradiation in a polar solvent, with Rose Bengal as the sensitizer. After stirring for 7 h, the NMR spectrum showed no reaction at all, with the starting material left unchanged. The possible reason for the lack of reactivity was probably the steric hindrance from bulky group attached to nitrogen in the compound **71**, thus blocking access of oxygen from one side of the double bond. Therefore a smaller group may be

better, but such a group also needs to be unreactive to the oxygen. The cyanide group was chosen for these reasons.

### 3.4 Conversion of aldehyde **66** to a nitrile

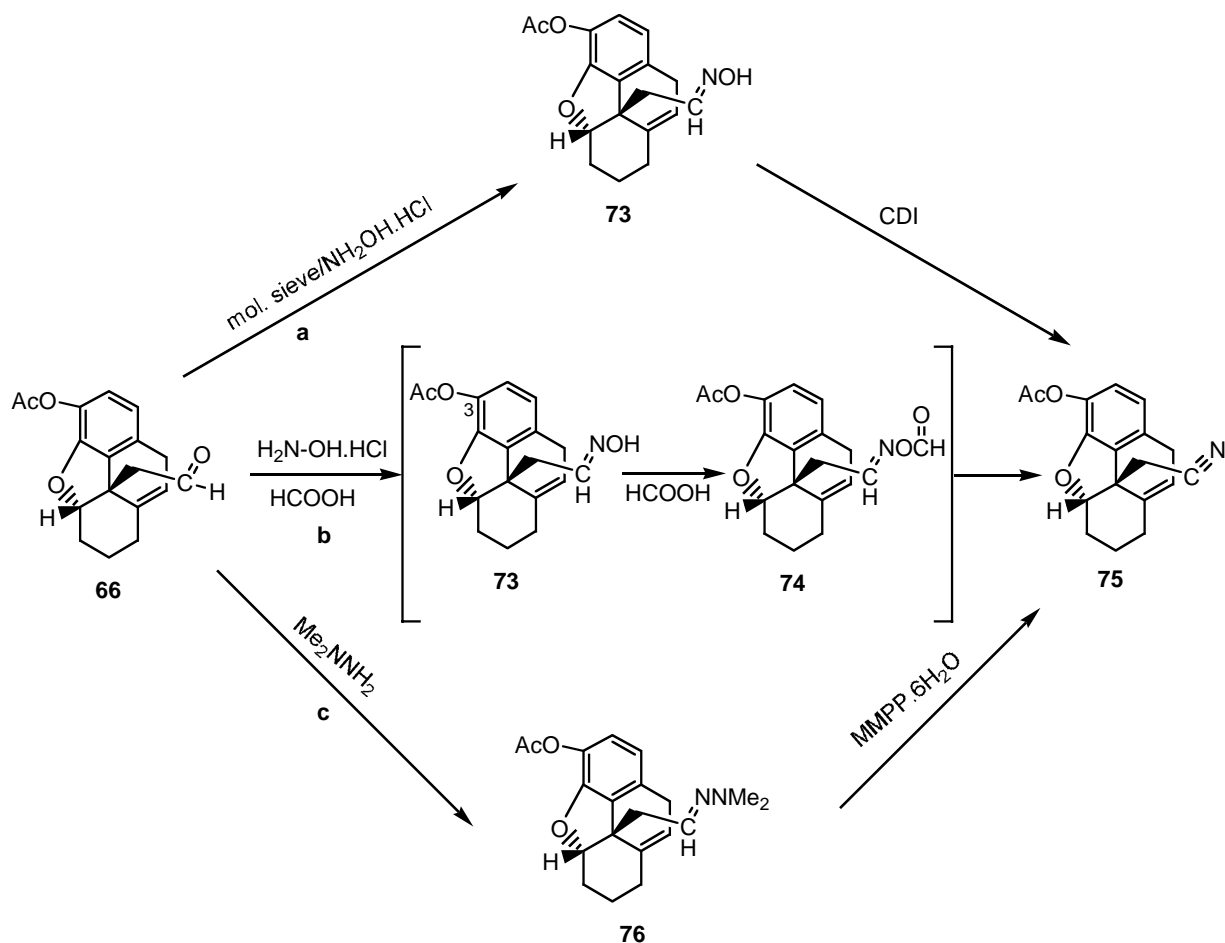
Three different methods were tried (Scheme 3.7) to convert aldehyde **66** to the corresponding cyanide.

In route **a** compound **66** is converted to aldoxime **73** in a reaction promoted by molecular sieves<sup>33</sup> and without the need for reflux or microwave heating. This is followed by dehydration with CDI<sup>34</sup> in refluxing CH<sub>2</sub>Cl<sub>2</sub>. Overall yield for the two steps is 34%. In route **b** compound **73** is simply refluxed in 95% formic acid with hydroxylamine for half an hour<sup>35</sup> (70-80°C), with a few drops of acetic anhydride to prevent the phenolic acetate at C<sub>3</sub> from hydrolyzing to a phenol under the conditions. The yield for this one step reaction was 63%.

Route **c** provides a new and easy “one-pot” route to nitriles from aldehydes via N,N-dialkylhydrazones and subsequent treatment of the reaction mixture with MMPP<sup>36</sup>. This new procedure for the conversion of an aldehyde to a nitrile via the hydrazone has some practical value compared with the previous synthesis of nitriles from aldehydes: 1) reagents (dimethylhydrazine and magnesium monoperoxyphthalate hexahydrate) are not expensive and very convenient to use; 2) short reaction times (5 minutes reaction from hydrazone to nitrile) and mild conditions (low temperature) are employed; 3) a simple work up and the nitriles are isolated without isomerization of any adjacent chiral centers. A Cope elimination of N,N-dimethylhydroxylamine is believed to produce the nitrile. This method gave the best overall yield (69%).

This route was therefore preferred for the conversion. After compound **75** was prepared, it was subjected to the singlet oxygen ene reaction, but again the reaction only returned the starting materials after 7 h of irradiation.

**Scheme 3.7**

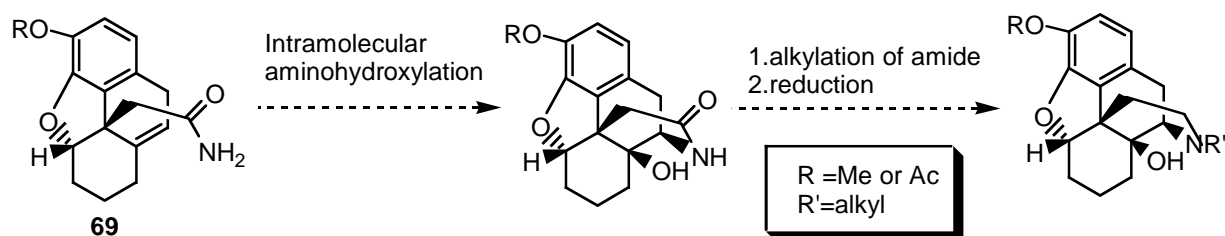


### 3.5 Conversion to an amide

Since the singlet oxygen ene reaction was unsuccessful, attention had to be turned to other routes. Amide formation was the next consideration, since intramolecular

aminohydroxylation<sup>37</sup> can only be attempted with the amide, perhaps with a favorable regiochemical outcome (Scheme 3.8).

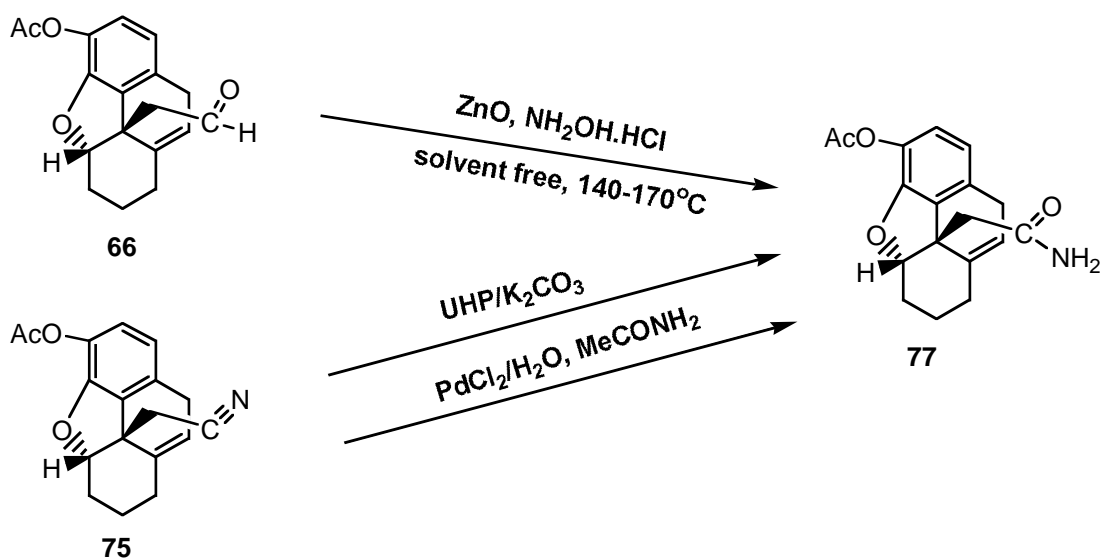
**Scheme 3.8**



Whether the intramolecular aminohydroxylation provides a 6-membered ring or a 5-membered one remains uncertain, however, since the preferred orientation of the Os (VIII) complex can't be predicted with certainty.

After a careful survey of the literature, three methods were evaluated for this amide preparation (Scheme 3.9).

**Scheme 3.9**

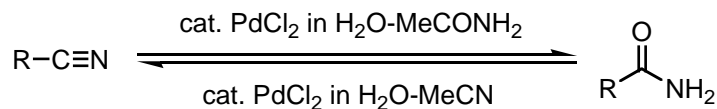


One of the methods reported<sup>38</sup> an efficient conversion of aldehydes into the corresponding amides via a Beckmann rearrangement. The catalyst ZnO is mixed with the aldehydes and hydroxylamine hydrochloride thoroughly. Then the mixture was heated at 140-170°C, without additional solvent. This method is unlike the normal Beckmann rearrangement requiring use of strong Bronsted or Lewis acids, which make sensitive starting materials unstable to the reaction conditions; in our case this experiment did not generate any product.

Another way to form amides is from nitriles. The partial hydrolysis of nitriles is a method frequently used for preparation of carboxylic acid amides. Traditional methods for the hydration of nitriles usually apply strongly acidic conditions, which precludes the use of sensitive substrates. One method reported<sup>39</sup> using an excess of UHP in the presence of a catalytic amount of potassium carbonate for the conversion of various nitrile to the respective amides without the use of strong acids. Our trial experiment resulted in no amide formation with only partially hydrolyzed byproduct (phenolic OAc hydrolyzed to OH and CN unchanged) formed. It appears that the K<sub>2</sub>CO<sub>3</sub> functioned as a reagent for phenyl acetate hydrolysis.

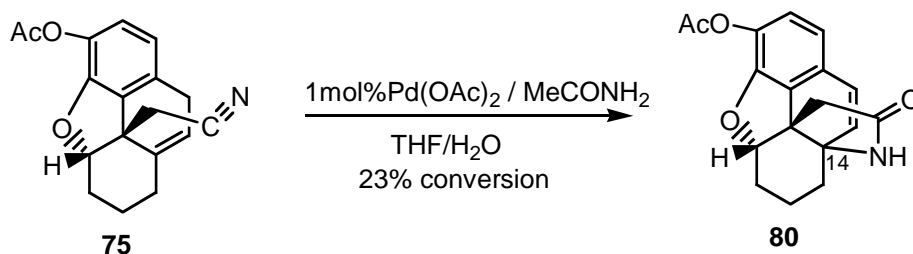
Another effective method<sup>40</sup> to convert nitrile to the amide is by application of a mild and reversible hydration of nitrile with PdCl<sub>2</sub> in aqueous acetamide (Scheme 3.10). It was found that primary amides were produced at room temperature from nitriles in THF/water by using acetamide to force the hydration process. This process was catalyzed by 0.1 equiv of PdCl<sub>2</sub> per mole of substrate. But Pd(OAc)<sub>2</sub> is better since it dissolves to give solutions with a pH in the range 4.7-5. Thus Pd(OAc)<sub>2</sub> would be preferred for substrates particularly sensitive to an strongly acidic environment.

### Scheme 3.10



When the reaction was performed with 1mol % Pd(OAc)<sub>2</sub> using **75**, it did not go to completion. After separation by chromatography, NMR analysis (Appendix 2) showed that the product has two alkene proton signals as clear doublets at  $\delta$  5.59 and 6.39 ( $J=9.6\text{Hz}$ ); the mass spectrum also showed that the molecular ion was at  $m/z$  311 suggesting the presence of one more unsaturated unit compared to the expected  $m/z$  313. From the COSY and HMQC spectra, it was deduced that the product is the result of a ring closure, with the amide nitrogen atom attached to C<sub>14</sub> to form the Hasubanan system (Scheme 3.11).

### Scheme 3.11



Even though the expected amide compound **77** was not produced, the process of five-membered ring closure is a promising result for further investigation. More details for this reaction and its mechanism will be discussed in the next section.



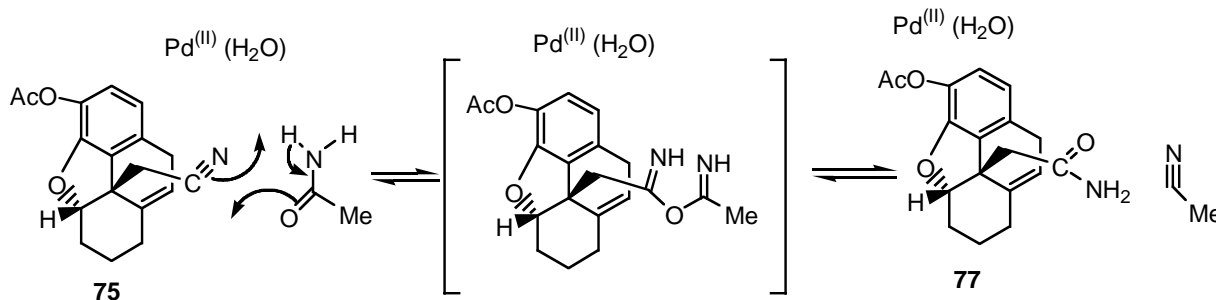
# CHAPTER 4

## CLOSURE OF THE FIFTH RING

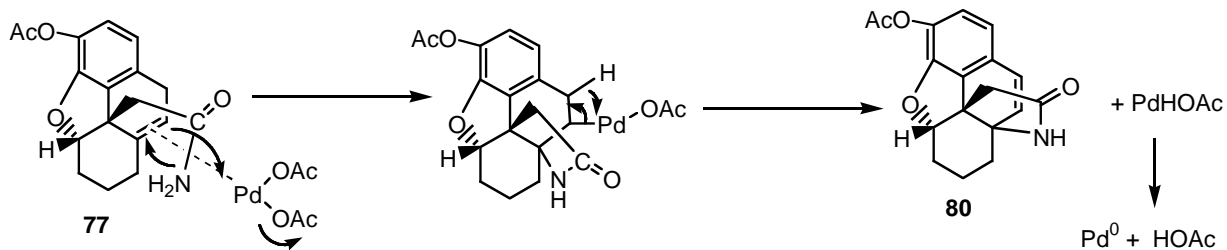
### 4.1 The ring closure to a five membered ring

As previously stated, nitrile **75** goes through a hydration-cyclisation process under the influence of  $\text{Pd}(\text{OAc})_2$  producing the five-membered ring by connecting the nitrogen atom with  $\text{C}_{14}$ . This interesting “one-pot” conversion probably proceeds in two separate steps. The hydration of the nitrile **75** by exchange of the elements of water between nitrile and acetamide produces the amide **77**. Even though water is not a participant in the proposed mechanism (Scheme 4.1) and no detailed information was provided about the role of water in this process, water is crucial for the reaction. Without water, no such conversion takes place<sup>40</sup>. Amide **77** then undergoes intramolecular cyclisation by nucleophilic attack of the nitrogen on the palladium (II) coordinated double bond, followed by the usual *syn* elimination of  $\text{PdHOAc}$ , which undergoes reductive elimination to  $\text{Pd}^0$  and acetic acid. (Schemes 4.1, 4.2)

**Scheme 4.1**



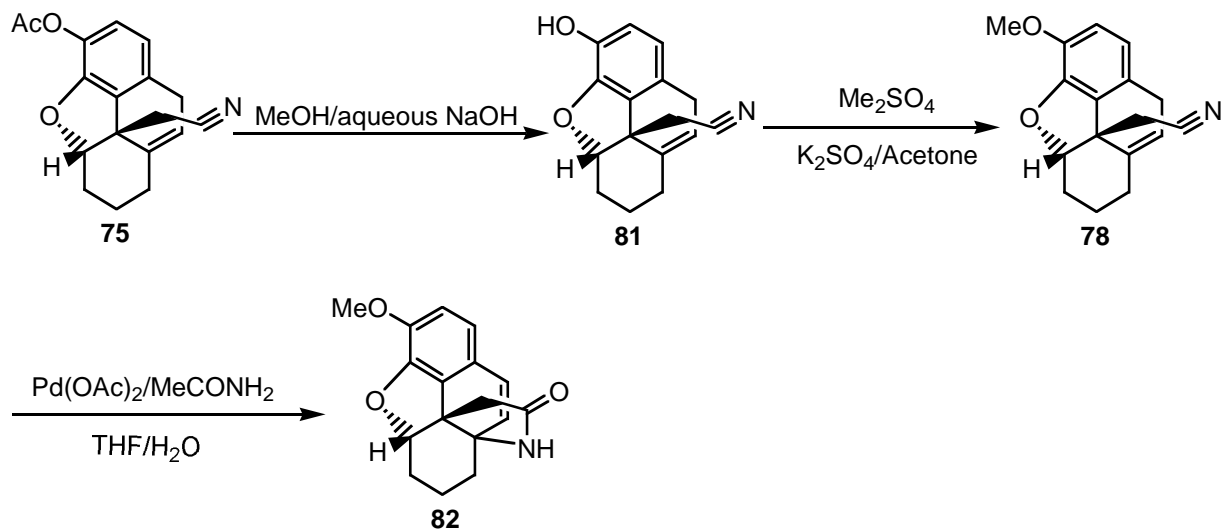
### Scheme 4.2



Since the two reactions in one pot both need Pd(II), making the reaction catalytic in Pd requires an oxidant to regenerate Pd(II). Initially, using a catalytic amount of  $\text{Pd}(\text{OAc})_2$  without an oxidant resulted in incomplete conversion of the starting material. Subsequently using a stoichiometric amount of  $\text{Pd}(\text{OAc})_2$ , and prolongation of the reaction time to 72 h made the reaction go to completion in 93% yield.

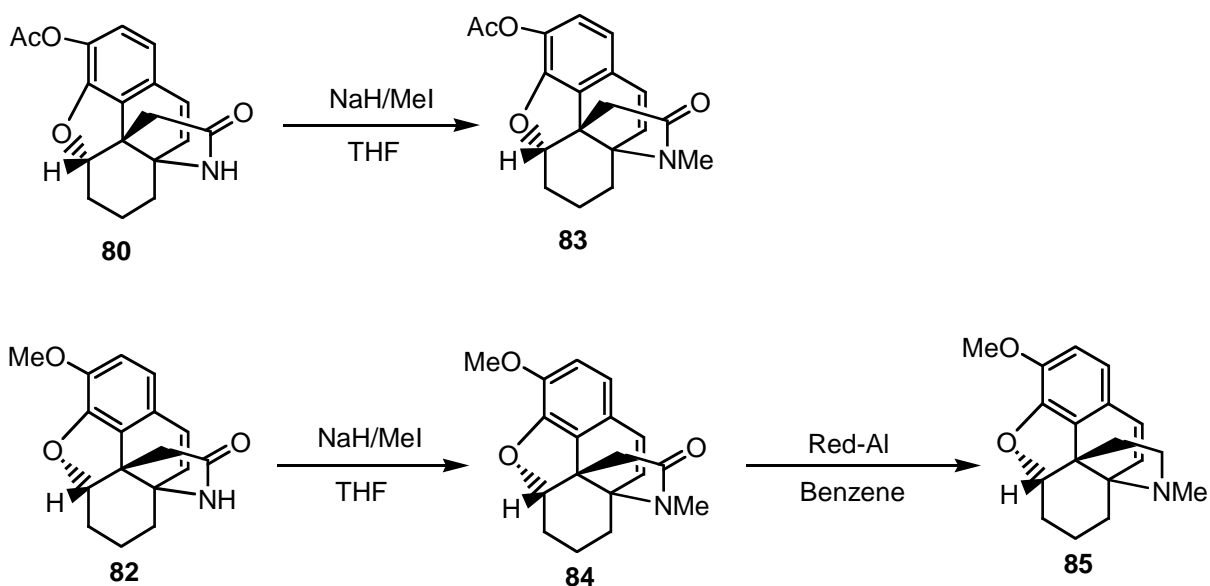
Compound **78**, produced by hydrolysis of **75** (Scheme 4.3) to **81**, and methylation with dimethyl sulfate, undergoes the same reaction to afford a 5-membered cyclised product **82** as well.

### Scheme 4.3



Both **80** and **82** undergo N-methylation by treatment with  $\text{NaH}^{41}$  in dry THF and iodomethane (Scheme 4.5) for 3 h at  $0^\circ\text{C}$  to afford **83** and **84**, respectively. Then reduction of **84** by Red-Al<sup>42</sup> provides the Hasubanonine like system **85** also known as the indolinocodeine system. Reduction of **83**, unlike **84**, gave a complex mixture of products probably due to reduction of the acetate as well as the amide.

**Scheme 4.4**



This intramolecular cyclization promoted by Pd(II) looks promising; therefore more investigations were conducted on this type of reaction hoping to make it catalytic and modify it for ring closure at C<sub>9</sub> and formation of the morphine system. Larock and co-workers have reported<sup>43</sup> a similar cyclization with the  $\text{Pd}(\text{OAc})_2/\text{O}_2/\text{DMSO}/\text{NaOAc}$  system. This catalytic system generally results in five- or six-membered ring products; some examples (Table 4.1)

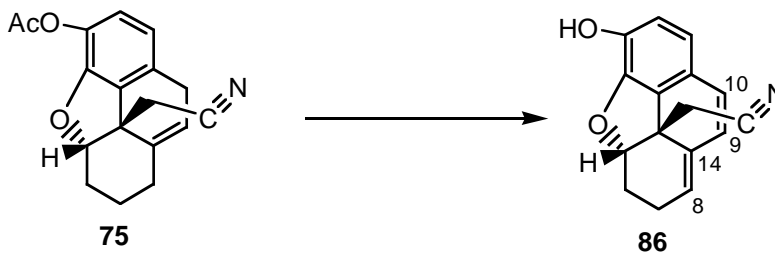
even show that this system is more prone to generate a 6-membered ring than other catalytic systems.

**Table 4.1 Cyclization with different catalytic system**<sup>43</sup>

entry	substrate	procedure	product
1		10mol% PdCl <sub>2</sub> (MeCN) <sub>2</sub> , Benzoquinone, LiCl, THF, reflux	
2		10mol%Pd(OAc) <sub>2</sub> , NaOAc, DMSO, O <sub>2</sub> 80°C, 72h	
3		10mol% PdCl <sub>2</sub> (MeCN) <sub>2</sub> , Benzoquinone, LiCl, THF, reflux	
4		10mol%Pd(OAc) <sub>2</sub> , NaOAc, DMSO, O <sub>2</sub> 80°C, 18h	

Based on this expectation, experiments were performed in an attempt to achieve a similar six-membered ring closure from the nitrile **75** via the amide **77** in one pot. Therefore using Larock's catalyst system for ring closure and combining it with the requirement of nitrile hydration to **77**, the following reaction conditions were tested: a catalytic amount of Pd(OAc)<sub>2</sub> in DMSO under an atmosphere of O<sub>2</sub> with NaOAc and acetamide were added to the nitrile, and the mixture was stirred at 80°C for 18 h. After purification, the NMR spectrum showed no OAc peak but one new signal appeared at  $\delta$  6-6.5 ppm. Based on COSY, HMQC and mass spectra (M<sup>+</sup> 251) data, the structure of this product is proposed to be **86** (Scheme 4.5). The NMR spectrum of compound **87** formed by methylation of **86**, is shown in Appendix 3.

### Scheme 4.5



This is a nice surprise because the reaction has generated the desired C<sub>9</sub>-C<sub>10</sub> double bond for subsequent 6-*exo*-trig ring closure at C<sub>9</sub>. In order to determine the role of the individual reactants and the best conditions for this reaction, a series of experiments were performed as outlined in Table 4.2.

**Table 4.2 The reaction conditions for compound 86**

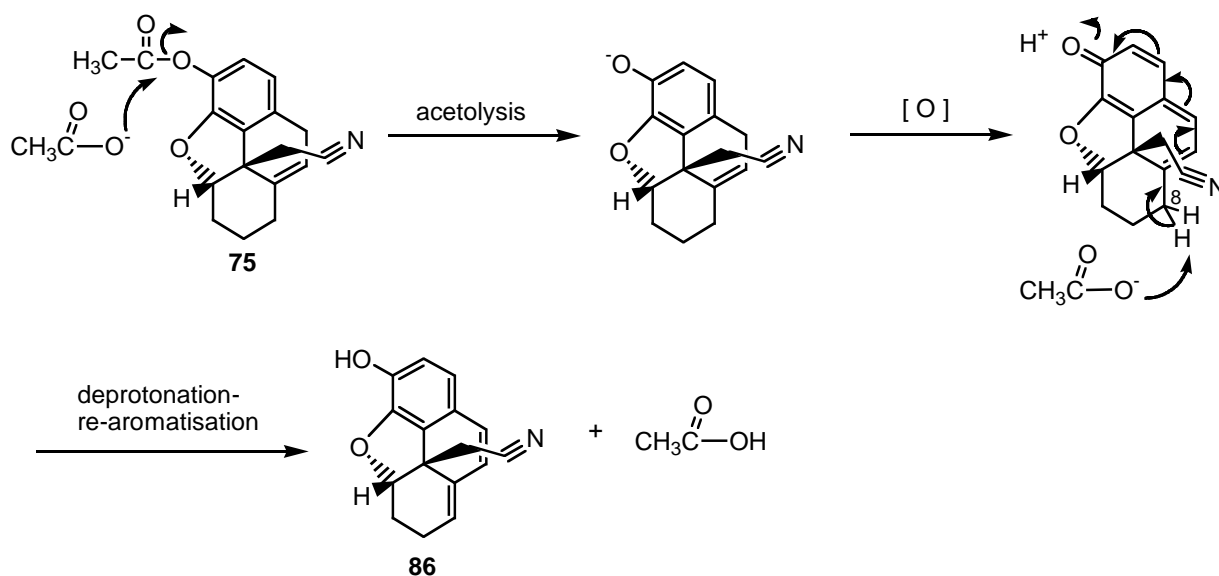
entry	Reagents and conditions	<b>86</b> yield %
1	Acetamide, 10mol% Pd(OAc) <sub>2</sub> , NaOAc, DMSO, O <sub>2</sub> , 80°C, 72h	56
2	Acetamide, 10mol% Pd(OAc) <sub>2</sub> , NaOAc, DMSO: H <sub>2</sub> O (3:1), O <sub>2</sub> , 80°C, 7days	No reaction
3	10mol% Pd(OAc) <sub>2</sub> , NaOAc, DMSO, O <sub>2</sub> , 80°C, 72h	64
4	NaOAc, DMSO, O <sub>2</sub> , 80°C, 72h	82

Entry **1** used the initial reaction conditions but longer reaction time in order to determine if the reaction is reproducible and whether the reaction will go to completion. The result shows it is reproducible with starting material completely consumed and a yield of 56%. However, one important reagent (water) is missing from the reactants in entry **1**. This is crucial in converting the nitrile to the amide as previously stated. Since water was missing in entry **1**

experiment causing the nitrile not to be converted to the amide, one more experiment (entry **2**) was performed with compound **75** using a catalytic amount of Pd(OAc)<sub>2</sub> in DMSO under an atmosphere of O<sub>2</sub> with NaOAc, acetamide, and water added to the nitrile and stirring continued at 80°C for 7days, but to our surprise no reaction occurred at all with the starting acetate being recovered.

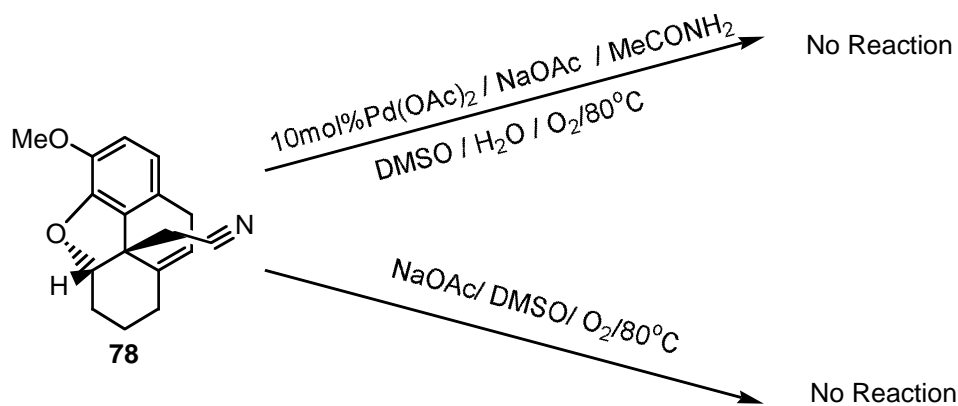
Since compound **75** was not converted to the amide under either set of conditions, acetamide might not be required in the reaction. Thus the conditions summarized in entry **3** were tested and the same product **86** was produced with a slightly better yield of 64%. Considering functions of the different reagents in entry **3**, the possibility that Pd(OAc)<sub>2</sub> might not be necessary at all since the nitrile was neither hydrated nor cyclised in the previous reactions, Pd(OAc)<sub>2</sub> was removed and the reaction performed under the conditions of entry **4**. A significant increase in yield (82%) of **86** was realized thereby. This reaction probably proceeds by acetolysis of the acetate, followed by oxidation of the resulting phenolate to form a transient, conjugated p-quinomethide which rearomatises by loss of proton from the C<sub>8</sub> methylene group (Scheme 4.6).

### Scheme 4.6



The requirement for initial formation of the phenolate from compound **75** was confirmed when the methyl ether **78** was found to be unaffected under the conditions of Entry **2** or **4** (Scheme 4.7).

### Scheme 4.7



The conditions in Entry **2**, include water, but the nitrile **75** was completely unaffected. This surprising stability can in fact be attributed to the presence of water as a large constituent of the solvent system (DMSO: H<sub>2</sub>O = 3:1). The nucleophilicity of the acetate (from anhydrous NaOAc), enhanced in dry DMSO, will be significantly reduced in water by solvation. Thus, the first step of the proposed mechanism (Scheme 4.6) is blocked, phenolate can not form and the subsequent reaction sequence can not ensue just like the case of methyl ether **78**.

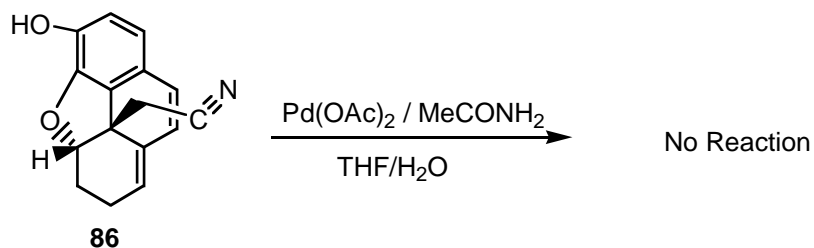
The attempts at cyclising **78** under palladium catalysis produced very different results which depended on the quantity of catalyst and the nature of the solvent. This is clear in Scheme 4.3 and 4.7. Therefore **78** was treated with a stoichiometric amount of catalyst (Table 4.3, Entry 4) under conditions of Entry 5 with no different result.

Then, the conditions in Scheme 4.4 were used on the phenolic nitrile **86** (Scheme 4.8), but no reaction occurred and **86** was returned unchanged. Suspecting that phenol **86** might not be compatible with the reaction conditions, it was methylated with dimethyl sulfate in acetone to convert it to methyl ether **87**. Treating **87** under the same conditions (Scheme 4.9) produced the same result. It would appear that the presence of the diene prevents the palladium-promoted hydration of the nitrile in some way.

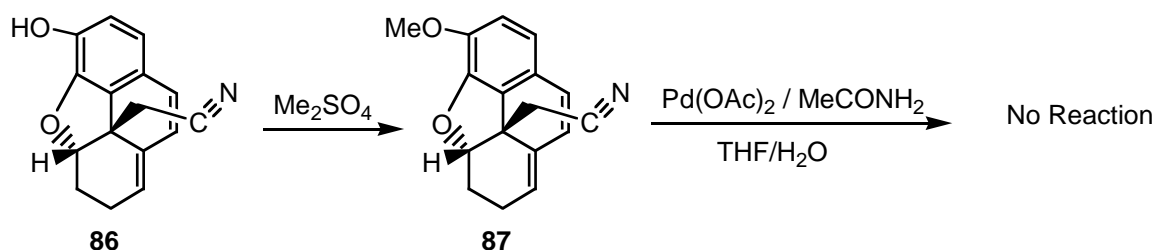
It was disappointing that the one-pot hydration-cyclisation reaction could not be performed with diene **86** or its methyl ether **87**, but other avenues have been opened up by these results for profitable processing of these dienes to the morphine system.



### Scheme 4.8

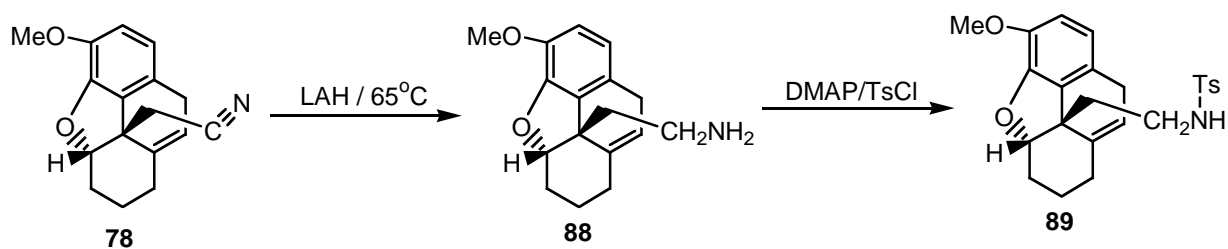


### Scheme 4.9



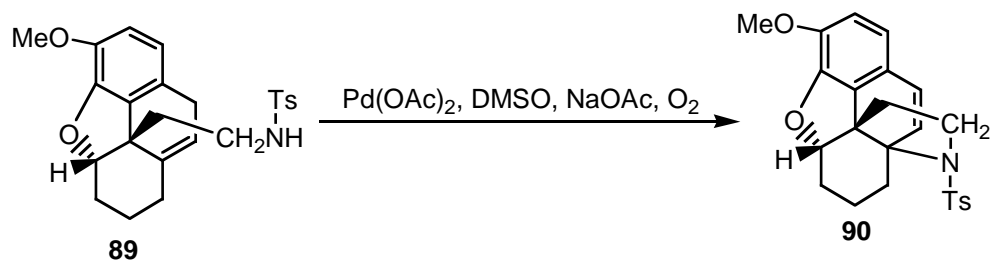
Larock and co-workers have reported that the cyclization of olefinic tosylamides with the  $\text{Pd}(\text{OAc})_2/\text{O}_2/\text{DMSO}/\text{NaOAc}$  system generally results in six-membered ring products. This possibility encouraged us to expect that the same result might occur in our system. Therefore compound **78** was converted to tosylamide by reduction with  $\text{LAH}^{44}$  to form amine **88** first, and then followed by tosylation<sup>5</sup> with DMAP, TsCl to obtain compound **89** (Scheme 4.10). This compound was the substrate for the “Larock cyclisation”.

### Scheme 4.10



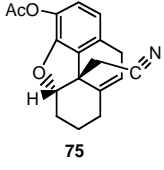
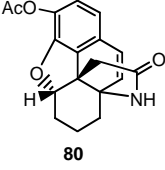
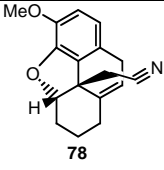
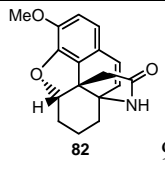
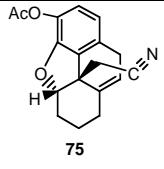
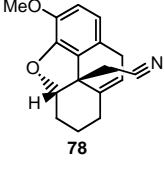
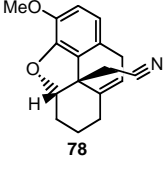
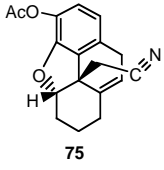
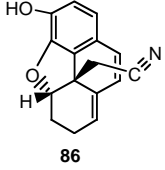
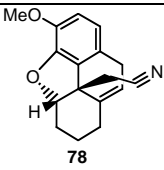
When the compound **89** was reacted under the Larock system, the product was still the 5-membered ring compound **90** based on <sup>1</sup>H NMR (Appendix 4), <sup>13</sup>C NMR, and MS. (Scheme 4.11)

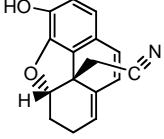
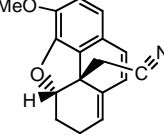
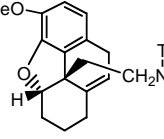
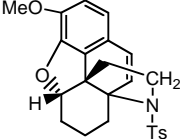
### Scheme 4.11



Other efforts to cyclise the various C<sub>9</sub>, C<sub>10</sub> unsaturated compounds at C<sub>9</sub> will be discussed later. For now, a brief summary of the results described in this section is provided in Table 4.3.

**Table 4.3 Results of attempts to cyclise various nitrile and amide substrates**

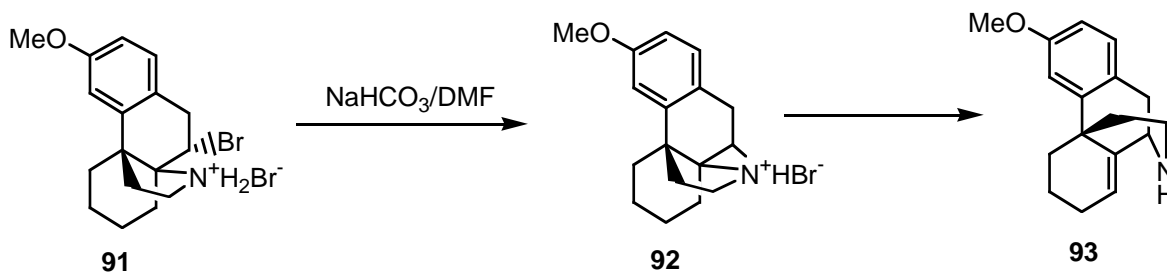
entry	substrate	reagents and conditions	results (yield%)
1	 <p>75</p>	$\xrightarrow[\text{THF/H}_2\text{O/RT}]{\text{Pd(OAc)}_2 / \text{MeCONH}_2}$	 <p>80 93%</p>
2	 <p>78</p>	$\xrightarrow[\text{THF/H}_2\text{O/RT}]{\text{Pd(OAc)}_2 / \text{MeCONH}_2}$	 <p>82 91%</p>
3	 <p>75</p>	$\xrightarrow[\text{DMSO/H}_2\text{O}/80^\circ\text{C}/7\text{days}]{\text{Cat. Pd(OAc)}_2/\text{NaOAc}/\text{O}_2/\text{Acetamide}}$	No Reaction
4	 <p>78</p>	$\xrightarrow[\text{DMSO/H}_2\text{O}/80^\circ\text{C}/3\text{days}]{\text{Pd(OAc)}_2/\text{NaOAc}/\text{Acetamide}}$	No Reaction
5	 <p>78</p>	$\xrightarrow[\text{DMSO/H}_2\text{O}/80^\circ\text{C}/7\text{days}]{\text{Cat. Pd(OAc)}_2/\text{NaOAc}/\text{O}_2/\text{Acetamide}}$	No Reaction
6	 <p>75</p>	$\xrightarrow{\text{NaOAc, DMSO, O}_2, 80^\circ\text{C}, 72\text{h}}$	 <p>86 82%</p>
7	 <p>78</p>	$\xrightarrow{\text{NaOAc, DMSO, O}_2, 80^\circ\text{C}, 72\text{h}}$	No Reaction

8	 <p>86</p>	$\xrightarrow[\text{THF/H}_2\text{O/RT}]{\text{Pd(OAc)}_2 / \text{MeCONH}_2}$	No Reaction
9	 <p>87</p>	$\xrightarrow[\text{THF/H}_2\text{O/RT}]{\text{Pd(OAc)}_2 / \text{MeCONH}_2}$	No Reaction
10	 <p>89</p>	$\xrightarrow{\text{Pd(OAc)}_2, \text{DMSO}, \text{NaOAc}, \text{O}_2}$	 <p>90 84%</p>

## 4.2 Rearrangement of the indolinocodeine to the mophinan system

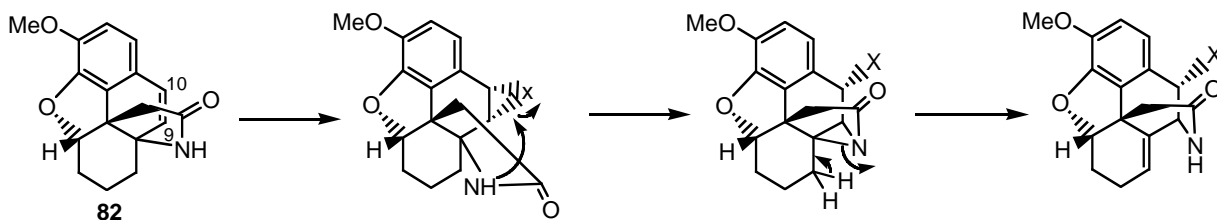
One of the efforts to achieve a six-membered ring was attempted from the five-membered ring products. An early report <sup>45</sup> that the hasubanan system **91** can be rearranged to the morphinan **93** via the aziridine intermediate **92** in good yield (Scheme 4.12), prompted us to attempt a similar transformation with our synthetic products containing a 9, 10 double bond and an ethanamine (or amide) at C<sub>15</sub> (eg. **85** and related compounds)

Scheme 4.12



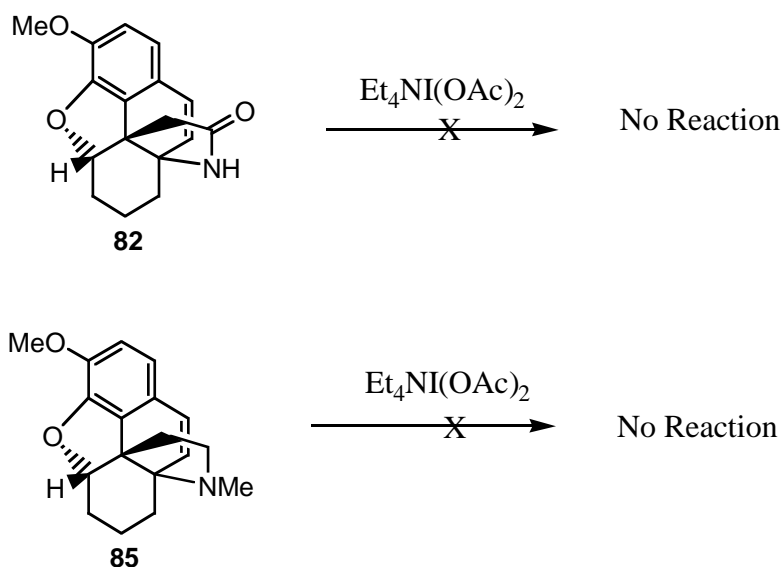
A leaving group at C<sub>9</sub> might be generated by functionalizing the double bond by electrophilic attack from its  $\alpha$ -face. (X=O, Br<sup>+</sup>, I<sup>+</sup>, or a leaving group as designated in Scheme 4.13).

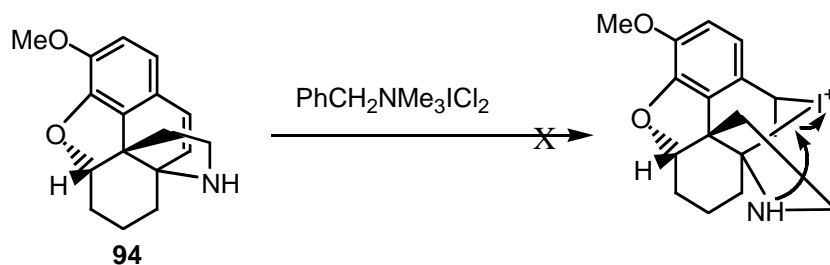
Scheme 4.13



First, formation of a 6-membered ring from the 5-membered ring amide **82** was attempted. It had been reported<sup>46</sup> that  $\text{Et}_4\text{NI}(\text{OAc})_2$  can be a source of acetyl hypoiodite (IOAc) which reacts with a cycloalkene such as cyclohexene to form a iodonium ion, followed by the nucleophilic attack of acetate to open the ring. With compound **82**, it was expected that the intermediate iodonium ion ( $\text{X}=\text{I}^+$ ) would be cleaved by nucleophilic attack of the amide nitrogen thus forming an aziridine similar to **92**. When the reaction was attempted with one equivalent of reagent  $\text{Et}_4\text{NI}(\text{OAc})_2$ , nothing happened. Therefore, a second equivalent was added, but still nothing happened. The lactam nitrogen might not be nucleophilic enough, so the more nucleophilic amine compound **85** was used, with two equivalent of  $\text{Et}_4\text{NI}(\text{OAc})_2$ , but still nothing happened. (Scheme 4.14); the alternative nucleophilic amine **94**, whose preparation will be discussed later, was reacted with  $\text{PhCH}_2\text{NMe}_3\text{ICl}_2$  (BTMAICl<sub>2</sub>) which is a source of  $\text{ICl}^{47}$ , hoping for the formation of a C<sub>9</sub>-C<sub>10</sub> iodonium species again, but no reaction occurred at all (Scheme 4.14).

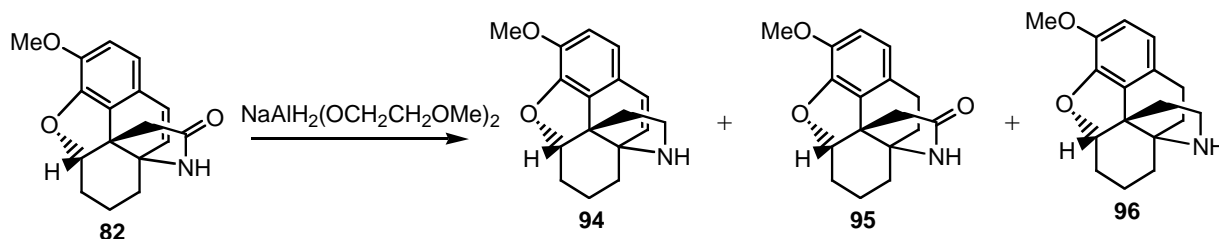
**Scheme 4.14**





Compound **94** was used because compound **85** is not a secondary amine like **88**. Therefore lactam **82** was reduced with 3 equivalents of Red-Al in order to obtain secondary amine **94**. After 2 h, the starting material was completely consumed, and three compounds formed were separated by column chromatography. After analyzing them by NMR, COSY, HMQC and mass spectrometry, their structures were assigned as shown in Scheme 4.15; the yield for these three compounds are 40% (compound **95**), 29% (compound **94**) and 11% (compound **96**).

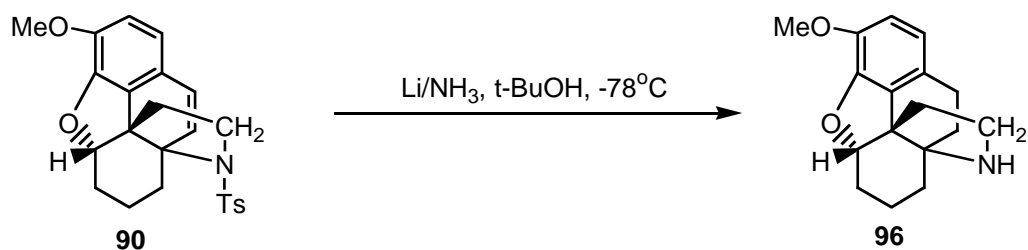
#### Scheme 4.15



One last effort was made to rearrange the 5-membered to the 6-membered ring employing  $\text{Li}/\text{NH}_3$ <sup>5</sup> with our 5-membered ring compound **90**. Since reductive detosylation will generate a nitrogen radical or radical anion based on Parker's synthesis of morphine, this intermediate might add to the C<sub>9</sub>-C<sub>10</sub> double bond with the possibility of rearrangement taking place. Treatment of tosylamide **90** with  $\text{Li}/\text{NH}_3$  in the presence of t-BuOH afforded one compound lacking a tosyl group (Scheme 4.16).

Based on  $^1\text{H}$ ,  $^{13}\text{C}$  NMR, COSY, HMQC and mass spectra, the product was assigned 5-membered ring structure **96**. The spectrum of the product was exactly the same as the compound **96** produced in Scheme 4.15.

#### Scheme 4.16



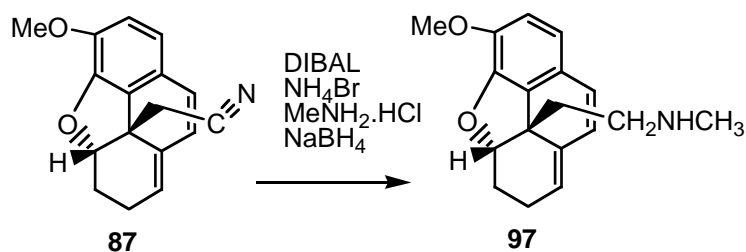
The five-membered ring substrates investigated so far had failed to rearrange like **91** did in the earlier work. However it should be noted that the successful ring expansion represented by the conversion of **91** to **93** was conducted in a substrate that did not contain a  $\text{C}_4\text{-C}_5$  oxygen bridge. The presence of this furanoid moiety in all our substrates presumably changes the shape of these molecules and denies easy access of the various electrophiles to the  $\text{C}_9\text{-C}_{10}$  double bond.



### 4.3 Attempts to cyclise N-methyl ethanamines

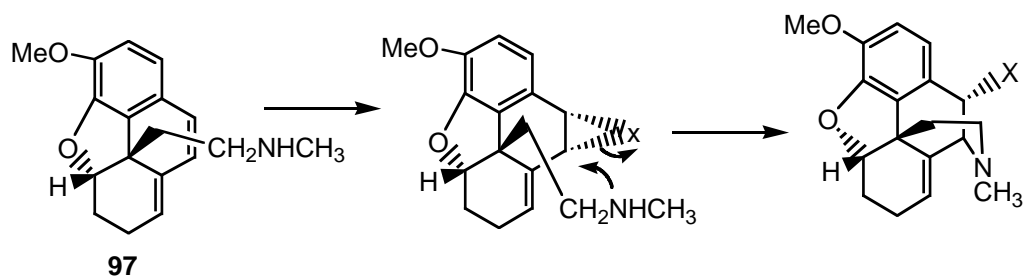
Since the nitrile group did not cyclise directly at C<sub>9</sub> under many conditions, in the next set of experiments, the compound **87** was converted to the amine **97** using a one pot reduction-transimination-reduction procedure<sup>9,48</sup> (Scheme 4.17). The cyano group was reduced by DIBAL at low temperature, when reduction was complete ammonium bromide in dry methanol was added to destroy excess DIBAL and to convert the imine-aluminium complex into the free N-H imine. Introduction of the N-methyl group was then achieved by conversion of the primary imine into the more stable secondary imine by addition of excess methyl amine hydrochloride. Sodium borohydride reduction overnight afforded the N-methyl β-ethanamine **97** in good overall yield (73%). The ring closure was then attempted with amine **97**.

Scheme 4.17



Our attention was then turned to compound **97** and with the same idea of selectively functionalizing the C<sub>9</sub>-C<sub>10</sub> double bond (Scheme 4.18), the following experiments were attempted. (Table 4.4)

### Scheme 4.18



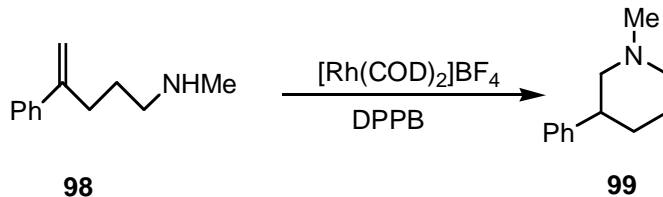
X=O, Br<sup>+</sup>, I<sup>+</sup>, or a metallic leaving group

**Table 4.4 Results of attempts to derivatize 97**

entry	procedure/reagents	result
1	Et <sub>3</sub> NIOAc	No reaction
2	BTMAICl <sub>2</sub>	No reaction
3	Red-Al/Cp <sub>2</sub> TiCl <sub>2</sub>	No reaction
4	OsO <sub>4</sub> /DMAP	Complex mixture of products
5	PIFA	Complex mixture of products
6	Rh(COD)BF <sub>4</sub> /DPPB	Complex mixture of products
7	BuLi	Complex mixture of products

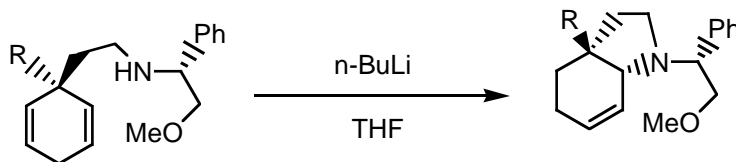
Entries 1-3 represent attempts similar to those made with the indolinocodeine substrates. The results were equally disappointing. Oxidative functionalisation (Entry 4,5) with osmium (VIII) and iodine(III) also failed presumably due to the presence of the basic nitrogen atom. The hydroamination represented by Entry 6 was based on the reported<sup>49</sup> anti-Markovnikov addition of amines to styrenes as in Scheme 4.19.

### Scheme 4.19



Entry 7 is based on intramolecular hydroamination of dienes<sup>50</sup> with high selectivity to the corresponding bicyclic allylic amines with catalytic amount of BuLi as a strong base (Scheme 4.20). Treatment of dienes with this strong base may provide a stabilized dienyl anion that would then be protonated intramolecularly by the secondary amine, but the reaction produced a complex mixture of products in our case.

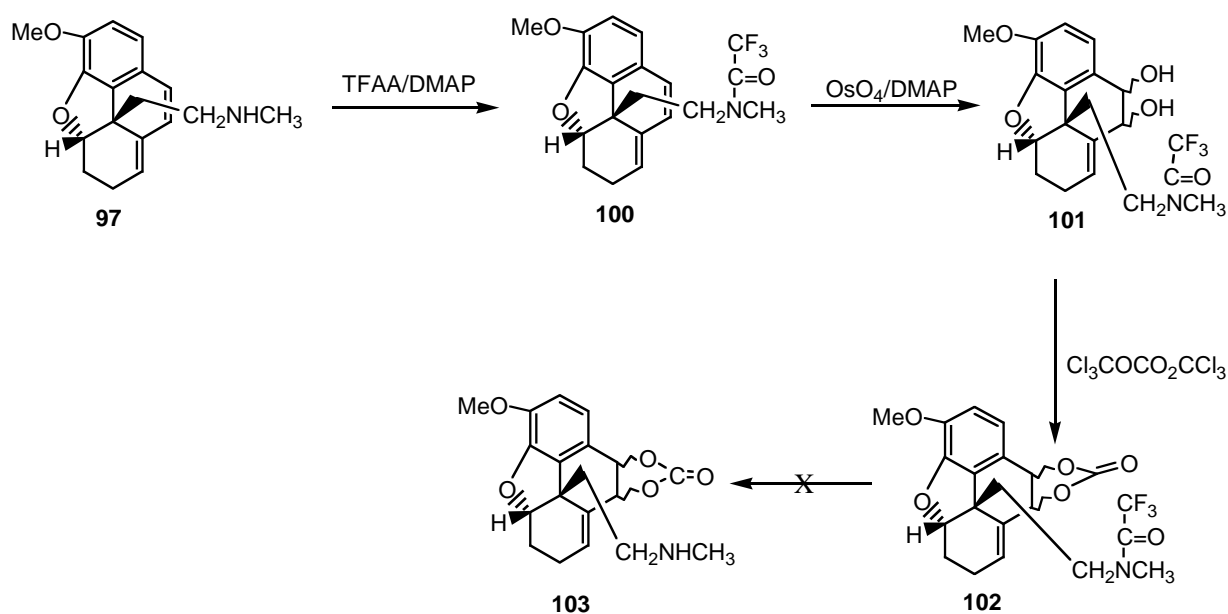
### Scheme 4.20



The presence of the basic nitrogen atom in **97** might have been responsible for the complex mixtures of products obtained in entries 4 and 5. The amine **97** was therefore acylated with TFAA<sup>51</sup> and the resulting amide **100** subjected to osmylation in the belief that  $\pi$ -stacking effects<sup>27,28</sup> would favor reaction at the C<sub>9</sub>-C<sub>10</sub> double bond (Scheme 4.21). The osmylation of the **100** produced the diol **101**, but its NMR spectrum was quite complex presumably because of the existence of amide tautomers. However, the cyclic carbonate **102** could be obtained by treatment with triphosgene<sup>52</sup> and although H<sub>9</sub> and H<sub>10</sub> signals could be seen, the spectrum was

still rather complex. A further problem was our inability to determine whether the carbonate was  $\alpha$  or  $\beta$  oriented with respect to the ethanamine. Attempts to hydrolyze the trifluoroacetamide led to complex mixtures of products, and lack of sufficient material led us abandon this multi-step ring closure in favour of more direct methods which are described next.

#### Scheme 4.21

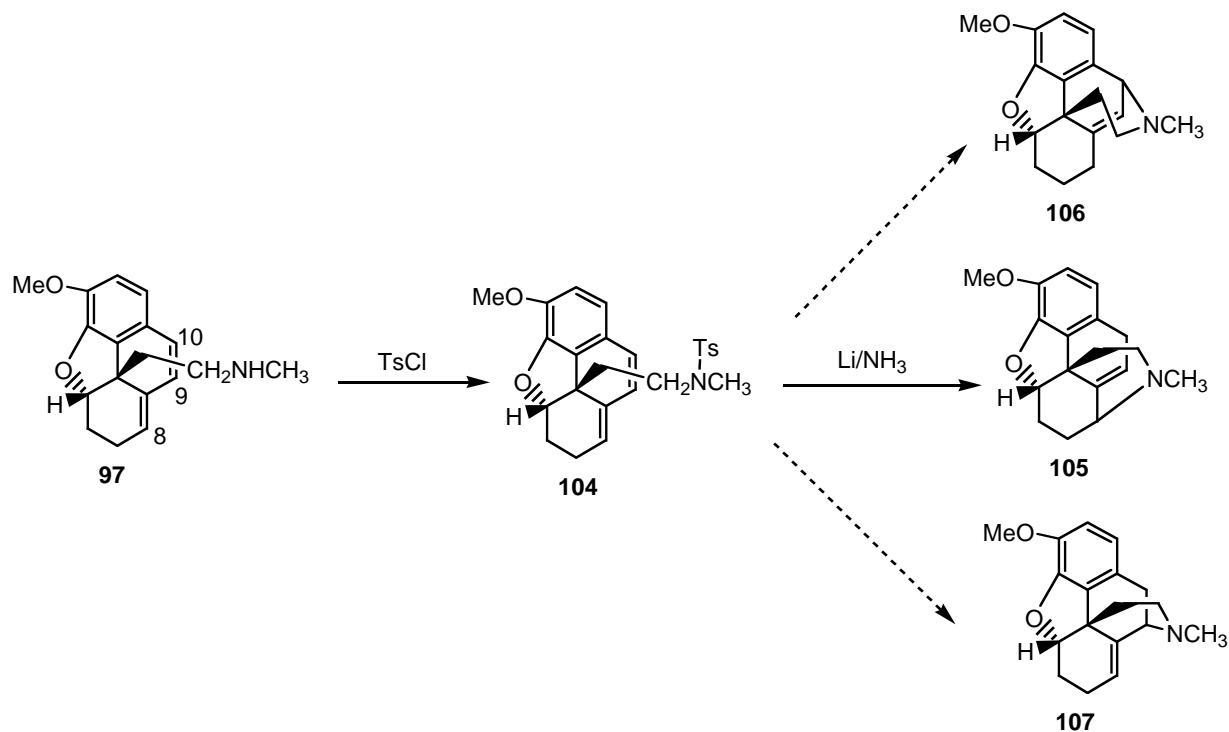


We decided to use our supplies of **97** instead to replicate ring closures achieved by Parker and Trost in their syntheses of the morphinan pentacycle. We were aware that those methods were applied to substrates containing only the one double bond at  $\text{C}_9\text{-C}_{10}$  rather than conjugated system of our substrate **97**.

Beginning with the Parker cyclisation<sup>5</sup>, the amine **97** was tosylated to afford the tosylamide **104** (Scheme 4.22) which was subjected to reduction with Li/liquid ammonia. A cyclized

product **105** lacking the tosyl group was obtained in 89% yield, but the regiochemistry of the cyclisation was questionable. Cyclization at the diene termini C<sub>8</sub>, C<sub>10</sub> or cyclization at C<sub>9</sub> are possible outcomes leading to structure **105**, **106**, **107**. The <sup>1</sup>H NMR spectrum (Appendix 5) of the product showed the presence of only one alkene proton ( $\delta=5.78-5.79\text{ppm}$ ) and the <sup>13</sup>C spectrum showed the presence of two alkene carbons: one quaternary, and the other bearing the single alkene proton. The mass spectrum ( $M^+$  283) at low and high resolution also indicated that cyclisation of the ethanamine had occurred.

#### Scheme 4.22

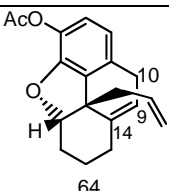
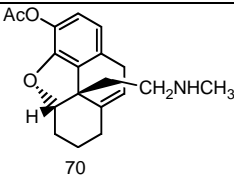
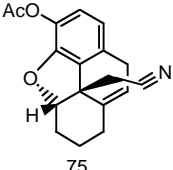


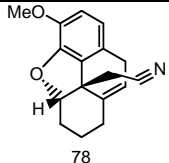
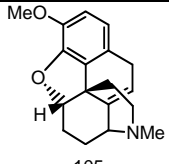
However, further examination of the NMR data clearly showed the presence of a two-proton signal centered at  $\delta 3.20$ . It was an ABX system ( $J_{\text{AB}} = 19 \text{ Hz}$ ) with each half further

coupled, but not identically, to a third proton. This signal was therefore assigned to the C<sub>10</sub> methylene group with the upfield part of quartet coupled ( $J=6\text{Hz}$ ) to the alkene proton H<sub>9</sub> at  $\delta$  5.78ppm. The downfield section of the AB quartet displayed a very small coupling to H<sub>9</sub> ( $J=3.6\text{Hz}$ ), which only produced a broadening of that part of the quartet. A similar H<sub>10</sub> proton pattern also appears for the several intermediates such as compounds **64**, **70**, **75**, **78** which have the same C<sub>9</sub>-C<sub>14</sub> alkene structure (Table 4.5). Further COSY and HMQC confirmed the <sup>1</sup>H assignments. Therefore structure **105** was assigned to the product.

The product **105** contains about 10% of an impurity whose structure could be the de-tosylated uncyclized amine, which we will attempt to separate from the product.

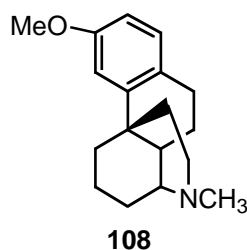
**Table 4.5 H<sub>10</sub> Comparison Among different compounds**

Compound	H <sub>10</sub> ( $\delta$ , $J$ )	H <sub>9</sub> ( $\delta$ )
 <p>64</p>	3.11-3.17, dd, $J=19.2, 6.0\text{Hz}$ 3.29-3.30, dd, $J=19.2, 3.5\text{Hz}$	5.70-5.86
 <p>70</p>	3.15-3.28, dd, $J=19.2, 6.0\text{Hz}$ 3.30-3.40, dd, $J=19.2, 3.5\text{Hz}$	5.80-5.85
 <p>75</p>	3.20-3.28, dd, $J=19.8, 6.0\text{Hz}$ 3.43-3.55, dd, $J=19.8, 3.5\text{Hz}$	5.99-6.01

 <p>78</p>	<p>3.11-3.20, dd, <math>J=19.8, 6.0\text{Hz}</math></p> <p>3.36-3.51, dd, <math>J=19.8, 3.5\text{Hz}</math></p>	<p>5.94-5.97</p>
 <p>105</p>	<p>3.11-3.17, dd, <math>J=19.1, 6.0\text{Hz}</math></p> <p>3.27-3.30, dd, <math>J=19.1, 3.6\text{Hz}</math></p>	<p>5.78-5.80</p>

This uncommon pentacyclic system (3-Methoxy-7, 9c-(methyliminoethano)-4a, 5, 6, 9, 9c-pentahydrophenanthro[4,5-*bcd*]furan) containing a ethanamine bridge has not been synthesized before. However, tetracycle **108** containing a similar ethanamine bridge had been prepared<sup>53</sup> much earlier in order that its analgesic properties could be evaluated. It may be worthwhile to determine the biological activity of this variant (**105**) of the morphinan pentacycle.

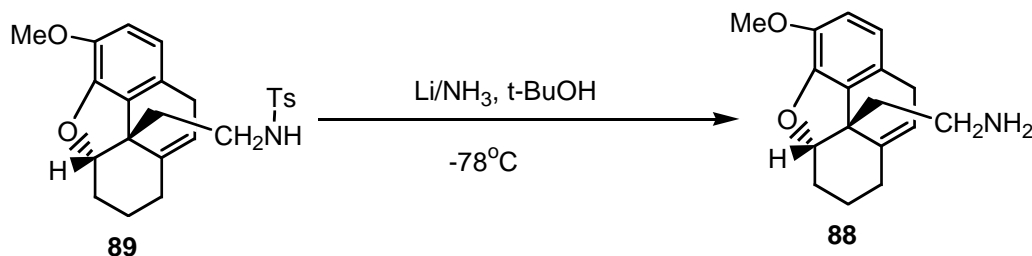
**Figure 4.1** The structure of compound **108**



One more experiment to apply the  $\text{Li}/\text{NH}_3$  reaction to compound **89** only caused de-tosylation without ring closure. The reason for attempting the same reaction on compound **89**

was that the nitrogen intermediate might add at C<sub>9</sub>, leaving a stable tertiary radical at C<sub>14</sub>, which may facilitate the reaction, but this was not the case unfortunately. (Scheme 4.23)

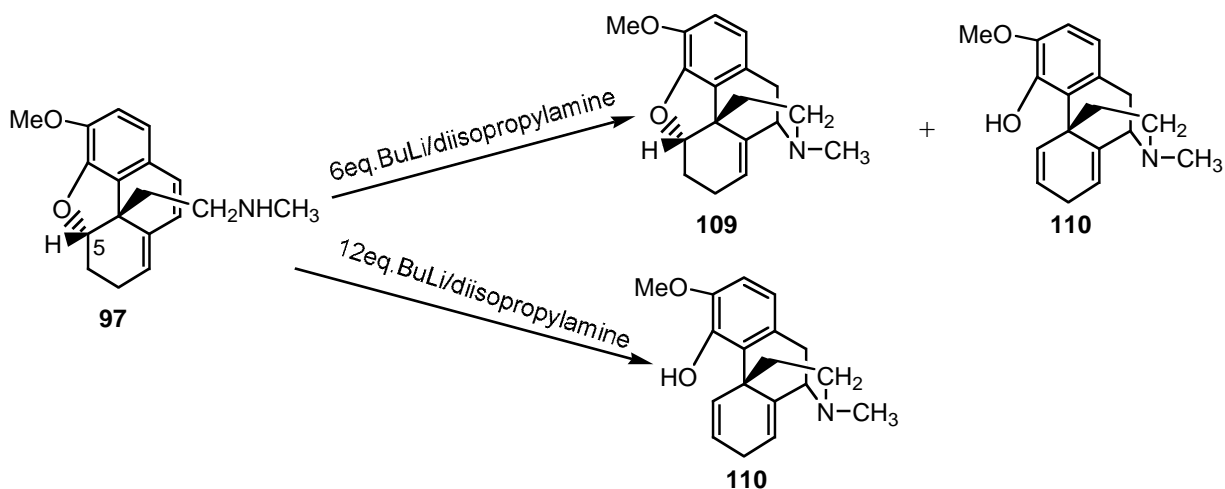
#### Scheme 4.23



A second experiment was tried based on Trost's synthesis<sup>9</sup> in which diisopropylamine was added to 6eq. of BuLi and **97** with irradiation by a visible light source. The experiment was attempted with our diene substrate under those conditions. The intramolecular hydroamination did not go to completion (55% conversion) and two compounds **109** and **110** were detected, in addition to unchanged starting material **97** (Scheme 4.24). Compound **109** and **110** can be separated by TLC, while compound **109** overlapped with starting material **97** in many solvent systems. The NMR spectrum of the mixture of **109** and **97** clearly showed the peaks attribute to **109** with one alkene proton signal. Believing that the ether linkage was opened by the strong base used, and that might have happened after the six-membered ring closure, more BuLi and diisopropylamine was added in order to convert compound **109** to compound **110** for easier separation. This was successful and it proved that more base cleaved the ether linkage completely, converting compound **109** to **110**. This also suggested that **109** has the same cyclic system as **110** but with the C<sub>4</sub>-C<sub>5</sub> ether linkage.



### Scheme 4.24



This reaction might be facilitated by single electron transfer process<sup>9</sup> initiated by irradiation with an ordinary tungsten light bulb. The suggested structure of **110** is based on its mass spectrum ( $M^+$  283),  $^1\text{H}$  NMR spectrum (Appendix 6) and COSY.  $M^+$ 283 implies same degree of unsaturation as the compound **105**. The  $^1\text{H}$  NMR spectrum showed the presence of three alkene protons ( $\delta=5.88\text{-}6.20\text{ppm}$ ), but with no  $\text{H}_5$  signal which usually appears at 4-5ppm. Although this reaction has been repeated with same outcome, we have been unable to purify the compound rigorously; it appears that the free phenol may be unstable, and can not easily be purified by the usual methods. Considerations will be given to acetylation of phenol **110** before attempting purification.

# CHAPTER 5

## SUMMARY AND FUTURE WORK

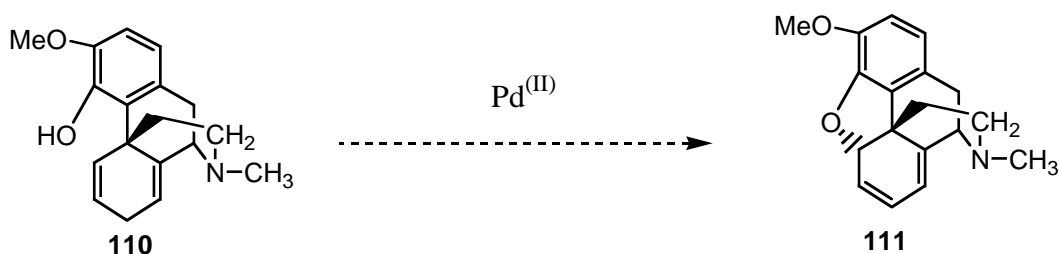
### 5.1 Summary

Short chiral syntheses of morphinan and two other related systems were completed in less than 20 steps. These three systems have the same tetracyclic intermediate **75**. Starting with **75**, one-pot hydration and cyclisation reaction by palladium furnished the hasubanan system; also starting with **75**, methylamine **97** was obtained and irradiated by a visible light source under LDA obtaining morphinan system; while Li/NH<sub>3</sub> reduction was applied on methylamine **97**, the third uncommon pentacyclic system was generated.

### 5.2 Future work

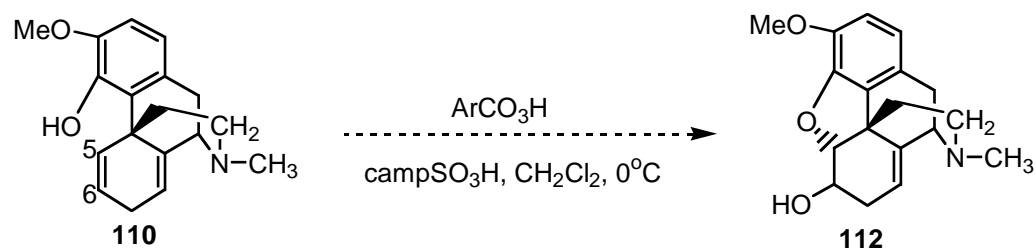
The structure **110** must be confirmed; if correct, it may undergo palladium(II)-catalyzed intramolecular cyclization<sup>56</sup> to generate 6-demethoxythebaine. (Scheme 5.1)

#### Scheme 5.1



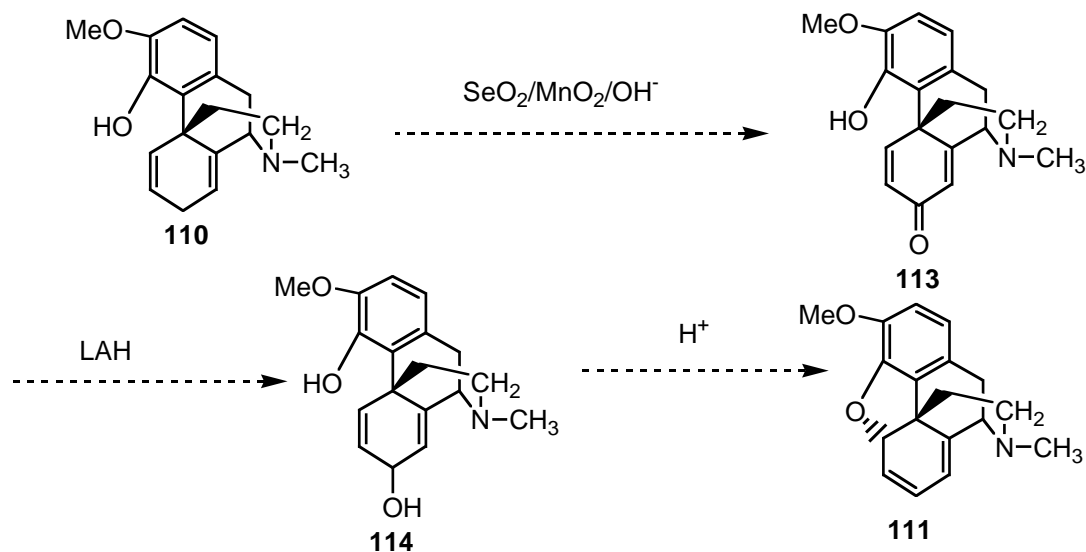
Other methods of oxygen ring closure are also possible such as selective epoxidation of the C<sub>5</sub>-C<sub>6</sub> double bond and intramolecular attack of the phenol to result in compound **112**.<sup>8</sup> (Scheme 5.2)

**Scheme 5.2**



Treatment of **110** with an oxidizing reagent<sup>57</sup> generates demethoxysalutaridine **113**, followed by reduction to form **114**, and ring closure to furnish demethoxythebaine **111**.<sup>58</sup> (Scheme 5.3)

**Scheme 5.3**



# CHAPTER 6

## EXPERIMENTAL PROCEDURES

### 6.1 General Conditions

All reactions involving air or moisture sensitive reagents were performed using oven dried glassware and under an inert atmosphere (Ar or N<sub>2</sub>). THF, ether, toluene and benzene were distilled from sodium using benzophenone ketyl as indicator. Dichloromethane was distilled from CaH<sub>2</sub>. Commercially available reagents were used without further purification.

For thin layer chromatography analysis, E. Merck 5554 pre-coated silica gel 60 F<sub>254</sub> aluminum sheets were used. The developed sheets were viewed under UV light or stained with an acidic oxidizing solution of NH<sub>4</sub>Ce(SO<sub>4</sub>)<sub>2</sub> & (NH<sub>4</sub>)<sub>6</sub>Mo<sub>7</sub>O<sub>24</sub>·H<sub>2</sub>O, or an acidic solution of vanillin. Flash chromatography was carried out using silica gel 60 (230-400 mesh), and the solvent mixtures used as eluent are indicated in each case.

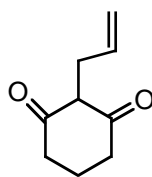
<sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained on Bruker AM-300 and AMX-500 instruments. Chemical shifts for NMR were determined relative to the internal standard tetramethylsilane (δ 0.00) or CDCl<sub>3</sub> (δ 7.26) for <sup>1</sup>H spectra, and CDCl<sub>3</sub> (δ 77.0) for <sup>13</sup>C spectra. Coupling constants were obtained directly from the spectra by first-order analysis. <sup>1</sup>H and <sup>13</sup>C NMR signals were assigned based on COSY and HMQC data. All NMR spectra were run in CDCl<sub>3</sub> unless otherwise specified. Mass spectra were run at the WATSPEC Mass Spectrometry Facility, Department of Chemistry, University of Waterloo. Specific rotations [α]<sub>D</sub> were measured on a Perkin-Elmer 241 Polarimeter instrument at ambient temperature. Chiral

separations were performed by HPLC using Chiralcel®-OD columns eluting with hexanes/isopropanol.

Regarding known compounds, only the reference to the reported preparation and characterization data is given; unless compounds have been prepared *via* a significantly modified or previously unreported route, in which case both experimental procedures and  $^1\text{H}$  NMR data have been included.

## 6.2 Reaction Conditions and Experimental Data

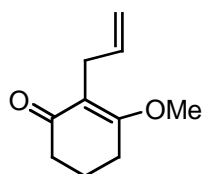
### 2-Allyl-1,3-cyclohexanedione 55



To a 5% aqueous KOH solution (250 mL, 0.223 mol) was added cyclohexanedione (25 g, 0.223 mol) and copper powder (14.2 g, 0.223 mol). While stirring, allyl bromide (26 mL, 0.307 mol) was added dropwise within 1h and the reaction mixture was stirred at room temperature for 2h more. After filtration, the residue was stirred in  $\text{CH}_2\text{Cl}_2$  (250 mL). The mixture was filtered again, and the filtrate was dried over  $\text{Na}_2\text{SO}_4$ , and evaporated to afford the solid. Washing with ether (2x50 mL) gave a white solid product (19.3 g, 57%) which was used without any purification in the next step.

$^1\text{H}$  NMR (300 MHz)  $\delta$  1.95 (2H, m), 2.43 (2H, t,  $J=6.4$  Hz), 2.55 (2H, t,  $J=6.4$  Hz), 3.05 (2H, d,  $J=6.4$  Hz, R- $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.01 (1H, d,  $J=10.2$  Hz, R- $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.10 (1H, d,  $J=17.3$  Hz, R- $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.82 (1H, m,  $J=17.3, 10.2, 7.2$  Hz, R- $\text{CH}_2\text{CH}=\text{CH}_2$ ). The  $^1\text{H}$  NMR spectrum recorded was in complete agreement with the data reported in the literature<sup>23</sup>

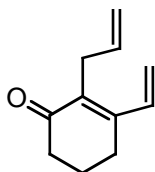
### 2-Allyl-3-methoxy-2-cyclohexenone 56



Cyclohexanedione **55** (20 g, 0.13 mol) was refluxed with  $\text{Me}_2\text{SO}_4$  (11.3 mL, 0.14 mol) and  $\text{K}_2\text{CO}_3$  (20.7 g, 0.15 mol) in acetone (300 mL) at  $80^\circ\text{C}$ . After 3h, acetone was removed *in vacuo*, and the residue was washed with water (250 mL), and extracted with EtOAc (2x300 mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. Purification by distillation (0.01 mm,  $82^\circ\text{C}$ ) gave the product (18.7 g, 87%) as a pale yellow liquid.

$^1\text{H}$  NMR (300 MHz) 1.96 (2H, m), 2.32 (2H, t,  $J=6.2$  Hz), 2.55 (2H, t,  $J=6.2$  Hz), 3.0 (2H, d,  $J=6.2$  Hz, R- $\text{CH}_2\text{CH}=\text{CH}_2$ ), 3.78 (3H, s), 4.85 (1H, dd,  $J=10.2, 1.8$  Hz, R- $\text{CH}_2\text{CH}=\text{CH}_2$ ), 4.95 (1H, dd,  $J=17.3, 1.8$  Hz, R- $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.75 (1H, m,  $J=17.3, 10.2, 6.2$  Hz, R- $\text{CH}_2\text{CH}=\text{CH}_2$ ). The  $^1\text{H}$  NMR spectrum recorded was in complete agreement with the data reported in the literature<sup>54</sup>.

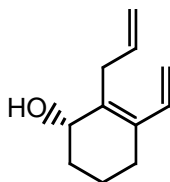
### 3-Ethenyl-2-(2-propenyl)-2-cyclohexen-1-one **57**



Vinylmagnesium bromide (1.0 M in THF, 80 mL, 79.5 mmol) was added dropwise over 1h to a solution of cyclohexenone **56** (8.8 g, 53 mmol) in dry THF (120 mL) at 0°C. The mixture was stirred for 5 h. A 3N aqueous HCl solution was added until pH 2-3 was reached and the resulting solution was stirred for 2 h more at room temperatures. The reaction was extracted with ether (2x150 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue was purified on a silica column (EtOAc: Hexanes 1:1) to give the product (7 g, 81%) as yellow oil.

<sup>1</sup>H NMR (300 MHz) δ 2.00 (2H, m), 2.43 (2H, t, *J*=6.6 Hz), 2.51 (2H, t, *J*=6.6 Hz), 3.19 (2H, d, *J*=6.0 Hz), 4.93 (2H, m), 5.45 (1H, d, *J*=11.0 Hz), 5.67 (1H, d, *J*=17.5 Hz), 5.78 (1H, m, *J*=17.8, 9.5, 6.0 Hz), 6.87 (1H, dd, *J*=17.5, 11.0 Hz). The <sup>1</sup>H NMR spectrum recorded was in complete agreement with the data reported in the literature<sup>12</sup>.

**(S)-3-Ethenyl-2-(2-propenyl)-2-cyclohexen-1-ol 39b**



To a solution of **57** (8 g, 0.049 mol) in dry toluene (200 mL) and Methyl Oxazaborolidine (1.0 M in toluene, 7.4 mL, 0.0074 mol) at  $-78^{\circ}\text{C}$  was added a solution of catecholborane (9.5 mL, 0.089 mol) in toluene (80 mL) via syringe pump over 1 h. After stirring for 18 h at  $-78^{\circ}\text{C}$ , NaOH solution (1N, 600 mL) was added; the resulting solution was stirred at room temperature for an additional 30 min. The organic phase was separated and the aqueous phase was extracted with diethyl ether (2x300 mL). The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (hexane:EtOAc=3:1) to give the product (7.2 g, 89%) as light yellow oil.

$^1\text{H}$  NMR (300 MHz)  $\delta$  1.56 (1H, d,  $J=6.9$  Hz), 1.65-1.85 (4H, m), 2.10-2.35 (2H, m), 3.10 (2H, d,  $J=6.0$  Hz), 4.15 (1H, br), 5.00-5.20 (3H, m), 5.30 (1H, d,  $J=17.2$  Hz), 5.84 (1H, m,  $J=17.2$ , 11.0, 6.0 Hz), 6.76 (1H, dd,  $J=17.2$ , 11.0 Hz).

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  17.5, 25.0, 31.8, 34.3, 68.2, 114.0, 115.4, 132.9, 134.6, 135.0, 136.7

LRMS(EI): 164 (6), 123 (100)

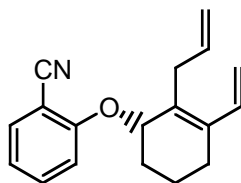
HRMS:  $m/z$  Calcd. For  $\text{C}_{11}\text{H}_{16}\text{O}$   $M^+$  164.1201, Found 164.1200

$[\alpha]_{\text{D}} = -271.5$  ( $c=0.73$ ,  $\text{CHCl}_3$ )

ee=98.66% (Appendix 7)



**(S)-2-[(2-Allyl-3-vinylcyclohex-2-en-1-yl)oxy]benzonitrile 47**



The general method of Wandless and coworkers<sup>55</sup> was employed. NaHMDS (1.0 M in THF, 60 mL, 60 mmol) was added dropwise over 1h to a solution of **(S)-39b** (7.5 g, 46 mmol) and 2-fluorobenzonitrile (7.2 g, 60 mmol) in dry THF (180 mL) at 0°C. The mixture was allowed to warm to room temperature and was stirred for 3 h. CH<sub>2</sub>Cl<sub>2</sub> (400 mL) was added and washed once with saturated aqueous NH<sub>4</sub>Cl (300 mL). The aqueous layer was back-extracted once with CH<sub>2</sub>Cl<sub>2</sub> (300 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue was purified on a silica column (EtOAc: hexanes 1:4) to give the product (10.8 g, 89%) as a yellow oil.

<sup>1</sup>H NMR (300 MHz) δ 1.63-1.71 (2H, m), 1.85-2.17 (3H, m), 2.37-2.44 (1H, m), 2.87-2.95 (1H, dd, *J*=15.7, 7.6 Hz), 3.19-3.25 (1H, dd, *J*=15.7, 4.8 Hz), 4.82 (1H, br), 4.90-5.00 (2H, m), 5.16 (1H, d, *J*=11.0 Hz), 5.34 (1H, d, *J*=17.4 Hz), 5.79 (1H, m, R-CH<sub>2</sub>CH=CH<sub>2</sub>), 6.78 (1H, dd, *J*=17.4, 11.0 Hz, R-CH=CH<sub>2</sub>), 6.93-7.03 (2H, m), 7.45-7.56 (2H, m)

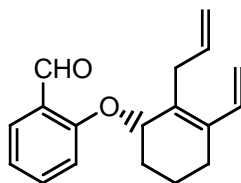
<sup>13</sup>C NMR (75 MHz) δ 17.5, 25.0, 27.5, 34.2, 75.1, 103.4, 113.8, 114.9, 115.7, 116.6, 120.7, 130.9, 134.0, 134.1, 134.3, 135.4, 136.0, 160.4

LRMS(EI): 265(2.2), 147(100), 105(35), 91(35)

HRMS: *m/z* Calcd. For C<sub>18</sub>H<sub>19</sub>ON M<sup>+</sup> 265.1467 Found 265.1465.

[α]<sub>D</sub> = -304.8 (c=1.3, CHCl<sub>3</sub>)

**(S)-2-[(2-Allyl-3-vinylcyclohex-2-en-1-yl)oxy]benzaldehyde 50**



Ice cold N,N'-dimethylethylenediamine (1.5 mL, 0.0139 mol) was added *via* cannula to a suspension of LAH (0.53 g, 0.0139 mol) in dry THF (30 mL) at -78°C under argon. The suspension was stirred for 1 h and hydrogen was released through a bubbler. Then the mixture was diluted with dry THF (24 mL) and allowed to warm to 0°C.

To the above mixture was added a cooled solution of benzonitrile **47** (2.45 g, 0.0093mol) in THF (20 mL) and the mixture was stirred at 0°C for 1.5 h. Cold 3N HCl (30 mL) was added until the pH reached 2-3 and stirring continued for 10min. The mixture was extracted with EtOAc (3x50 mL), the combined organic layer was washed successively with saturated aqueous NaHCO<sub>3</sub> (30 mL), brine (20 mL), dried and concentrated to give the product used directly without purification for the next step. For the purpose of accurate rotation measurement, the residue was purified on a silica column (EtOAc: hexanes = 1:2) to give the product (2.1 g, 84%) as a yellow oil.

<sup>1</sup>H NMR (300 MHz) δ 1.72-1.82 (3H, m), 2.08-2.21 (2H, m), 2.42 (1H, m), 2.87-2.95 (1H,dd, *J*=15.7, 7.0 Hz), 3.19-3.25 (1H,dd, *J*=15.7, 4.8 Hz), 4.91 (1H,br), 4.94-5.06 (2H, m), 5.22 (1H, d, *J*=11.0 Hz), 5.39 (1H, d, *J*=17.4 Hz), 5.81 (1H, m, R-CH<sub>2</sub>CH=CH<sub>2</sub>), 6.83 (1H, dd, *J*=17.4, 11.0 Hz, R-CH=CH<sub>2</sub>), 6.96-7.24 (2H, m), 7.49 (1H, m), 7.82 (1H,m), 10.50 (1H,s)

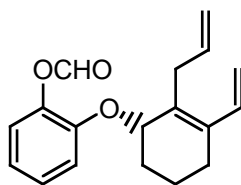
$^{13}\text{C}$  NMR (75 MHz)  $\delta$  17.7, 25.0, 27.5, 34.3, 74.3, 113.7, 114.9, 115.7, 120.5, 125.9, 128.3, 131.2, 134.2, 135.2, 135.8, 135.9, 161.1, 190.1

LRMS(EI): 268(2), 147(100), 105(35), 91(35)

HRMS: m/z Calcd. For  $\text{C}_{18}\text{H}_{20}\text{O}_2$   $\text{M}^+$  268.1463. Found 268.1465

$[\alpha]_{\text{D}} = -265.7$  (c=1.8,  $\text{CHCl}_3$ )

**(S)-2-[(2-Allyl-3-vinylcyclohex-2-en-1-yl)oxy] phenylformate 51**



To a solution of PhSeSePh (230 mg, 0.74 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 mL) was added  $\text{H}_2\text{O}_2$  (1.7 g, 15 mmol, 30% w/w). The yellow solution was stirred until colorless, and a solution of benzaldehyde **50** (1 g, 3.7 mmol) in  $\text{CH}_2\text{Cl}_2$  (30 mL) was added. The reaction was stirred vigorously at rt overnight. Water (50 mL) was added, and the reaction mixture was separated. The organic layer was washed successively with 10% aqueous  $\text{NaHSO}_3$  (20 mL), sat. aqueous  $\text{NaHCO}_3$  (20 mL), brine (30 mL), dried and concentrated. The resulting yellow oil (1.0 g, 94%) was directly used for the next step without further purification.

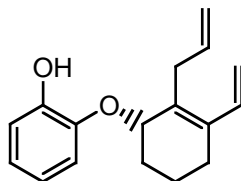
$^1\text{H}$  NMR (300 MHz)  $\delta$  1.57-1.69 (3H, m), 1.98-2.04 (2H, m), 2.34 (1H, m), 2.89-2.93 (1H, dd,  $J=15.7, 7.2$  Hz), 3.14-3.17 (1H, dd,  $J=15.7, 4.6$  Hz), 4.74 (1H, br), 4.92-5.01 (2H, m), 5.15 (1H, d,  $J=11.0$  Hz), 5.33 (1H, d,  $J=17.4$  Hz), 5.78 (1H, m), 6.78 (1H, dd,  $J=17.4, 11.0$  Hz), 6.91-6.97 (1H, m), 7.03-7.11 (2H, m), 7.17-7.20 (1H, m), 8.23 (1H, s)

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  17.5, 25.0, 27.3, 34.0, 74.4, 114.5, 115.0, 115.5, 120.9, 122.9, 127.2, 131.6, 134.4, 135.0, 135.8, 136.1, 149.6, 159.3

LRMS(EI): 147 (100), 105(35), 91(30)

LRMS(CI):  $[\text{M}+\text{NH}_4]^+$  302.2

**(S)-2-[(2-Allyl-3-vinylcyclohex-2-en-1-yl)oxy]phenol 52**



Ice cold aqueous  $\text{K}_2\text{CO}_3$  solution (12.2 mL, 3.52 mmol, 4%v/v) was added dropwise over 30min. to the solution of phenyl formate **51** (1 g, 3.52 mmol) in methanol (20 mL) at  $0^\circ\text{C}$ . The reaction mixture was stirred at  $0^\circ\text{C}$  for 1h. After evaporating the methanol, the mixture was neutralized with dry ice to pH=7, then extracted with EtOAc (2x30 mL). The combined organic layer was dried and concentrated. The residue was purified on a silica column (EtOAc: hexanes = 1:4) to give the product (0.7 g, 78%) as a yellow oil.

$^1\text{H}$  NMR (300 MHz)  $\delta$  1.56-1.75 (3H, m), 2.01-2.07 (2H, m), 2.37 (1H, m), 2.97-3.00 (1H,dd,  $J=15.7, 7.0$  Hz), 3.08-3.10 (1H,dd,  $J=15.7, 5.0$  Hz), 4.75 (1H,br), 4.96-5.05 (2H, m), 5.18 (1H, d,  $J=11.0$  Hz), 5.35 (1H, d,  $J=17.2$  Hz), 5.75-5.95 (2H, m), 6.78-6.94 (5H, m)

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  17.7, 24.9, 27.5, 34.3, 75.2, 112.8, 114.7, 114.8, 115.6, 120.0, 121.4, 131.5, 134.3, 135.2, 136.3, 145.1, 146.7

LRMS(EI): 256 (2), 147 (100), 105(40), 91(35)

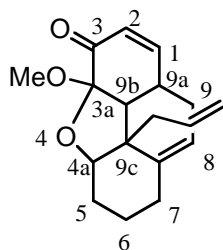
HRMS: m/z Calcd. For  $\text{C}_{17}\text{H}_{20}\text{O}_2$   $\text{M}^+$  256.1461. Found 256.1463

$[\alpha]_{\text{D}} = -247$  (c=1.2,  $\text{CHCl}_3$ )

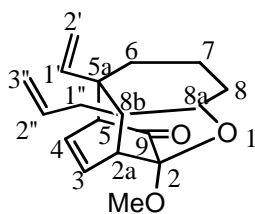
### **Oxidation and intramolecular Diels Alder reaction of (-)-2-[(2-allyl-3-vinylcyclohex-2-en-1-yl)oxy]phenol **52****

To a solution of phenol **52** (1 g, 3.9 mmol) in methanol (50 mL) was added a solution of DAIB (1.50 g, 4.66 mmol) in methanol (70 mL) *via* syringe pump over 1h. The reaction mixture was stirred overnight,  $\text{NaHCO}_3$  (1.25 g) was added and the mixture stirred for 20 min. After the methanol was removed *in vacuo*, the residue was extracted with EtOAc (2x40 mL), washed with water (50 mL), brine (40 mL), dried and evaporated. The residue was purified on a silica column ( $\text{CH}_2\text{Cl}_2$ : hexane:  $\text{CH}_3\text{OH}$ =5:1:0.1) to give the *endo* **53** and bridged compound **61** mixture (714 mg, 64%, *endo*: bridged = 1.2:1) as a yellow oil, and the dimer **62** (312 mg, 14%) as a yellow solid. The *endo* **53** and bridged compound **61** mixture could not be separated in any solvent system, therefore it was used directly for the next reaction.

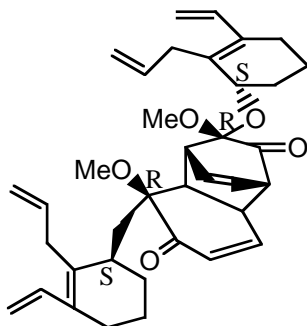
### **3a-methoxy-9c-(2'-propenyl)-3,3a,4a,5,6,7,9,9a,9b,9c-decahydrophenanthro[4,5-*bcd*]furan-3-one **53****



**8b-(2''-propenyl)-2-methoxy-9-oxo-5a-ethenyl-2,5-methano-2a,5,5a,6,7,8,8a,8b-octahydro[2H]naphtha[1,8-*bc*]furan 61**



**Dimer compound (-)62**



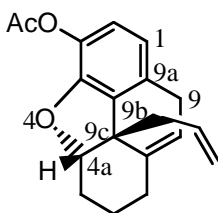
$^1\text{H NMR}$  (300 MHz)  $\delta$  1.15-1.75 (4H, m), 1.85-2.15 (5H, m), 2.16-2.30 (2H, m), 2.65-2.85 (2H, m), 2.86-3.05 (2H,m), 3.15-3.25 (3H,m), 3.30 (1H,s), 3.42 (4H, br), 3.49 (3H, s), 3.79 (1H, br), 4.24 (1H, br), 4.87-4.97 (4H, m), 5.02-5.09 (2H, m), 5.21-5.27(2H, dd,  $J=17.3$  Hz,

$J=10.0$  Hz), 5.50-5.72 (2H, m), 5.75-5.82 (1H, t,  $J=7$  Hz), 6.05-6.13 (1H, d,  $J=10$  Hz), 6.27-6.35 (1H, t,  $J=7$  Hz), 6.45-6.55 (1H, dd,  $J=10$  Hz,  $J=4$  Hz), 6.58-6.75 (2H, m)

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  17.5, 17.7, 24.9, 24.9, 28.4, 29.3, 30.8, 31.8, 32.9, 40.0, 41.1, 42.4, 49.7, 50.6, 53.0, 72.1, 72.3, 96.9, 100.2, 114.4, 114.8, 115.3, 115.5, 127.3, 129.4, 133.1, 133.4, 134.4, 134.4, 134.4, 134.6, 135.2, 136.1, 146.8, 193.8, 202.5

$[\alpha]_{\text{D}} = -118.6$  ( $c=0.57$ ,  $\text{CHCl}_3$ )

### 3-Acetoxy -9c-(2'-propenyl)-4a, 5, 6, 7, 9, 9c-pentahydrophenanthro[4,5-*bcd*]furan 64



TFA (3.0 mL) and acetic anhydride (3.0 mL) were added to a solution of mixture of *endo* **53** and bridged compound **61** (500 mg, 1.75 mmol) in  $\text{CH}_2\text{Cl}_2$  (80 mL), and stirred at rt for 15 min.  $\text{NaHCO}_3$  was added in small portions until the pH reached 7, then washed with water (2x30 mL). The layers were partitioned and organic layer was dried and concentrated to give an oil that was further purified by column chromatography (hexane:ether = 6:1) to give the product (214 mg, 76%) as a light yellow oil ( $R_f=0.33$ ) and the unchanged bridged adduct (225 mg) as a light yellow oil ( $R_f=0.2$ ).

To a solution of bridged compound **61** (225 mg, 0.79 mmol) in tetrachloroethane (20 mL) was added acetic anhydride (3 mL). The reaction mixture was stirred at  $140^\circ\text{C}$  for four days. After

the tetrachloroethane was removed by vacuum distillation, the residue was extracted with EtOAc(50 mL) and washed with water (2x20 mL). The organic layer was dried and concentrated. The residue was purified by column chromatography (hexane: ether=6:1) to give the product (147 mg, 63%) as a light yellow oil.

**Bridged compound 61:**

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.45 (1H, m), 1.57-1.60 (2H, m), 1.75-1.95 (3H, m), 2.10 (1H, dd,  $J=14.3, 7.0$  Hz), 2.17 (1H, dd,  $J=14.3, 7.8$  Hz), 2.88-2.90 (1H, dd,  $J=6.5, 1.1$  Hz), 3.20-3.22 (1H, dd,  $J=6.4, 1.7$  Hz), 3.49 (3H, s), 4.28 (1H, t), 5.04-5.12 (4H, m), 5.75-5.85 (1H, m), 5.97-6.03 (1H, dd,  $J=17.5, 11.1$  Hz), 6.18-6.28 (2H, m)

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  16.0, 25.6, 32.2, 38.3, 44.3, 48.4, 48.5, 48.9, 60.0, 80.0, 99.5, 113.4, 118.7, 128.3, 131.8, 134.2, 141.7, 201.8

LRMS(EI): 258(50), 217(100), 157(45), 131(52)

LRMS(CI):  $[\text{M}+\text{NH}_4]^+$  304.2 (100)

HRMS:  $m/z$  Calcd. For  $\text{C}_{18}\text{H}_{22}\text{O}_3$   $[\text{M}-\text{CO}]^+$  258.1620 Found 258.1621

$[\alpha]_{\text{D}} = +299$  ( $c=0.34$ ,  $\text{CHCl}_3$ )

**3-Acetoxy -9c-(2'-propenyl)-4a, 5, 6, 7, 9, 9c-pentahydrophenanthro[4,5-*bcd*]furan 64**

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.10-1.24 (1H, m), 1.45-1.60 (1H, m), 1.70-1.78 (2H, m), 2.29-2.37 (7H, m), 3.11-3.17 (1H, dd,  $J=19.2, 6.0$  Hz), 3.29-3.30 (1H, dd,  $J=19.2, 3.5$  Hz), 4.74-4.78 (1H, dd,  $J=12.2, 4.2$  Hz), 5.05-5.09 (2H, m), 5.72-5.80 (2H, m), 6.70 (1H, d,  $J=8.0$  Hz), 6.80 (1H, d,  $J=8.0$  Hz)



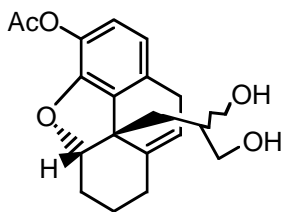
$^{13}\text{C}$  NMR (75 MHz)  $\delta$  17.5, 20.8, 25.3, 25.7, 29.7, 42.0, 50.1, 90.2, 118.4, 118.9, 121.1, 123.3, 132.5, 133.7, 134.0, 134.2, 140.5, 147.0, 168.7

LRMS(EI): 296(6), 255(87), 213(75), 195(100), 167(45)

HRMS: m/z Calcd. For  $\text{C}_{19}\text{H}_{20}\text{O}_3$   $\text{M}^+$  296.1412 Found 296.1411

$[\alpha]_{\text{D}} = -208$  (c=0.19,  $\text{CHCl}_3$ )

### 3-Acetoxy -9c-(2', 3'-hydroxy)-4a, 5, 6, 7, 9, 9c-pentahydrophenanthro[4,5-*bcd*]furan 65



To a solution of DMAP (644 mg, 5.28 mmol) and phenanthrofuran **64** (650 mg, 2.20 mmol) in THF (150 mL) was added  $\text{OsO}_4$  (676 mg, 2.64 mmol) at  $0^\circ\text{C}$ . The reaction mixture was allowed to stir at  $0^\circ\text{C}$  for 12 h, then 10%  $\text{NaHSO}_3$  solution (30 mL) was added and stirring continued for another hour. The mixture was extracted with EtOAc (2x40 mL), and the organic layer separated washed with brine (80 mL), then dried and concentrated to give the product (661 mg, 91%), a colorless oil, as a diastereomeric mixture which was used directly without further purification for the next step.

$^1\text{H}$  NMR (500 MHz) mixture of diastereomers  $\delta$  1.10-1.75 (4H, m), 1.85-1.95 (1H, m), 2.17 (1H, m), 2.30-2.50 (7H, m), 3.19-3.55 (4H, m), 3.65 (0.55H, m), 4.00 (0.45H, m), 4.86-4.88

(0.45H, dd,  $J=12.5, 4.5$  Hz), 5.00-5.04 (0.55H, dd,  $J=12.5, 4.5$  Hz), 5.79-5.81(0.45H, m), 5.73-5.75(0.55H, m), 6.73-6.82 (2H, m)

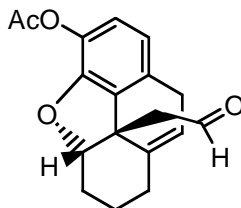
$^{13}\text{C}$  NMR (75 MHz)  $\delta$  19.0,19.1 (1C) 20.7, 24.9, 25.5, 29.3,29.4 (1C) 39.9, 40.1 (1C), 48.6, 48.8 (1C), 67.1, 67.2 (1C), 69.6, 69.9 (1C), 90.9, 91.0(1C) 119.2, 119.3 (1C) 120.7, 122.4, 123.4 (2C), 132.2, 133.3, 133.8, 134.3, (2C), 141.4, 141.6 (1C), 146.7, 147.1 (1C), 168.8, 169.1(1C)

LRMS(EI): 330 (25), 288(40), 255(55), 213(100), 195(60)

HRMS:  $m/z$  Calcd. For  $\text{C}_{19}\text{H}_{22}\text{O}_5$   $M^+$  330.1467. Found 330.1462

$[\alpha]_{\text{D}} = -29.2$  ( $c=0.76$ ,  $\text{CHCl}_3$ )

### 3-Acetoxy -9c-(2'-oxo-ethyl)-4a, 5, 6, 7, 9, 9c-pentahydrophenanthro[4,5-*bcd*]furan 66



$\text{NaIO}_4$  (1.52 g, 7.1 mmol) was added to a solution of diol **65** (650 mg, 1.97 mmol) in water and  $t\text{-BuOH}$  (25 mL:25 mL), and stirred at rt for 1.5 h. The reaction mixture was extracted with  $\text{EtOAc}$  (80 mL), the organic layer was washed with water (2x30 mL), dried and concentrated to give a colorless oil (552 mg, 94%) directly used for the next reaction without further purification.

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.17-1.79 (3H, m), 2.29-2.50 (6H, m), 2.59-2.65 (1H, dd,  $J=14.9$ , 3.0 Hz), 2.68-2.73 (1H, dd,  $J=14.9$ , 2.6 Hz), 3.23-3.26 (2H, m), 4.82-4.86 (1H, dd,  $J=12.2$ , 4.6 Hz), 5.83-5.86 (1H, m), 6.75-6.77 (1H, d,  $J=8.0$ ), 6.83-6.86 (1H, d,  $J=8.0$ ), 9.65 (1H, t,  $J=2.8$  Hz)

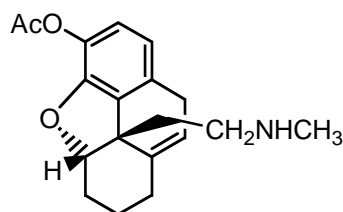
$^{13}\text{C}$  NMR (75 MHz)  $\delta$  17.5, 20.7, 25.0, 25.4, 29.6, 47.5, 50.2, 90.7, 119.5, 121.9, 124.5, 132.7, 132.8, 133.9, 139.7, 147.1, 168.5, 200.9

LRMS(EI): 298(20), 256(65), 212(100), 195(35)

HRMS:  $m/z$  Calcd. For  $\text{C}_{18}\text{H}_{18}\text{O}_4$   $\text{M}^+$  298.1211. Found 298.1205

$[\alpha]_{\text{D}} = -51.8$  ( $c=0.95$ ,  $\text{CHCl}_3$ )

**3-Acetoxy -9c-(2'-methylaminoethyl)-4a, 5, 6, 7, 9, 9c-pentahydrophenanthro[4,5-*bcd*]furan 70**



To a solution of aldehyde **66** (43 mg, 0.144 mmol) in methanol (10 mL) was added  $\text{MeNH}_2 \cdot \text{HCl}$  (58.4 mg, 0.864 mmol), and the mixture was stirred for 6 h at rt. Then  $\text{NaCNBH}_3$  (18 mg, 0.288 mmol) was added and stirred overnight. After methanol was evaporated, the residue was extracted with EtOAc (2x15 mL); the organic layer was washed with water (2x10 mL), dried, and evaporated. The residue was purified by column chromatography (hexane: ether=6:1) to give the product (30 mg, 67%) as a yellowish oil.

$^1\text{H}$  NMR (300 MHz)  $\delta$  1.05-1.85 (5H, m), 2.00 (3H, s), 2.20-2.50 (7H, m), 2.75-3.10 (2H, m), 3.15-3.28 (1H, dd,  $J=19.2, 6.0$  Hz), 3.30-3.40 (1H, dd,  $J=19.2, 3.5$  Hz), 4.80-4.87 (1H, dd,  $J=12.2, 4.5$  Hz), 5.80-5.85(1H, m), 6.80 (1H, d,  $J=8.0$  Hz), 6.85(1H, d,  $J=8.0$  Hz)

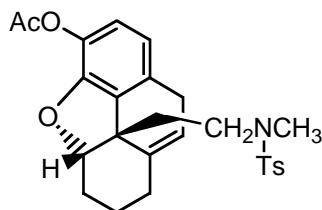
$^{13}\text{C}$  NMR (75 MHz)  $\delta$  17.5, 20.7, 25.0, 25.5, 25.8, 30.1, 34.6, 48.6, 52.5, 90.6, 119.6, 121.9, 125.5, 132.7, 132.9, 134.1, 138.9, 147.0, 168.5

LRMS(EI): 313(15), 254(25), 212(100), 195(30)

HRMS:  $m/z$  Calcd. For  $\text{C}_{19}\text{H}_{23}\text{NO}_3$   $M^+$  313.1678. Found 313.1674

$[\alpha]_{\text{D}} = -62.6$  ( $c=0.51, \text{CHCl}_3$ )

**3-Acetoxy -9c-(2'-methyltosylaminoethyl)-4a, 5, 6, 7, 9, 9c-pentahydrophenanthro[4,5-*bcd*]furan 71**



To a solution of methylamine **70** (30 mg, 0.095 mmol) in methanol (10 mL) were added DMAP (23.2 mg, 0.19 mmol) and TsCl (27.2 mg, 0.14 mmol), the mixture was stirred for 6 h at rt. The methanol was evaporated, the residue was extracted with EtOAc (2x10 mL); the organic layer was washed with water (2x10 mL), dried, and evaporated. The residue was purified by column chromatography (hexane: ether=1:1) to give the product (35 mg, 78%) as a yellowish oil.

$^1\text{H}$  NMR (300 MHz)  $\delta$  1.15-1.78 (4H, m), 1.90-2.03 (2H, m), 2.32(3H, s), 2.45 (5H, br), 2.63(3H, s), 2.90-2.99 (1H, m), 3.19-3.23 (2H,m), 3.24-3.6 (1H, m), 4.73-4.76 (1H, dd,  $J=12$  Hz,  $J=5$  Hz), 5.80-5.81 (1H, m), 6.72-6.73 (1H, d,  $J=8$  Hz), 6.81-6.82 (1H, d,  $J=8$  Hz), 7.28-7.35 (2H, BB'), 7.62-7.64 (2H, AA')

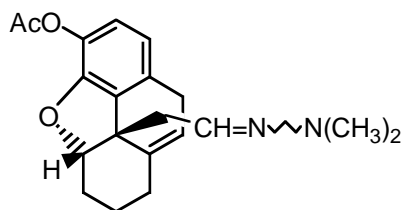
$^{13}\text{C}$  NMR (75 MHz)  $\delta$  17.5, 20.7, 20.8, 25.2, 29.7, 35.3, 35.7, 40.1, 47.0, 48.6, 91.1, 119.1, 121.9, 123.1, 127.5, 128.3, 129.6, 129.8, 132.7, 132.9, 133.9, 134.4, 140.2, 143.2, 147.2, 168.4

LRMS(EI): 467(22), 425(29), 312(58), 270(100), 213(88), 185(46)

HRMS:  $m/z$  Calcd. For  $\text{C}_{26}\text{H}_{29}\text{NO}_5\text{S}$   $M^+$  467.1770. Found 467.1776

$[\alpha]_D = -43.2$  ( $c=0.36$ ,  $\text{CHCl}_3$ )

**3-Acetoxy -9c-(2'-oxoethyl-N,N-dimethylhydrazone)-4a, 5, 6, 7, 9, 9c-pentahydrophenanthro[4,5-*bcd*]furan 76**



N, N-Dimethylhydrazine (0.12 mL, 1.57 mmol) was added to a solution of aldehyde **66** (334 mg, 1.12 mmol) in methanol (60 mL). The mixture was stirred for 2hrs at rt., and methanol was removed *in vacuo*. The residue was extracted with EtOAc (70 mL), washed with water (50 mL) and separated. The organic layer was dried and concentrated to give a colorless oil (339 mg, 89%) used directly for the next reaction without further purification.

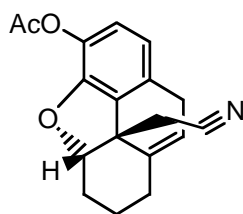
$^1\text{H}$  NMR (300 MHz) mixture of diastereomers  $\delta$  1.11-1.72 (4H, m), 2.25-2.39 (6H, m), 2.48-2.52 (1H, m), 2.68-2.71 (6H, m), 3.08-3.35 (2H, dd,  $J=19.1, 5.7$  Hz), 4.78-4.84 (1H, m), 5.73-5.76 (1H, m), 6.35-6.40 (1H, m), 6.60-6.79 (2H, d,  $J=8.0$  Hz)

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  17.4, 17.6 (1C), 20.7, 25.1, 25.4(1C), 29.3, 29.5, 29.7(2C), 39.9, 40.1(1C), 43.0, 43.2, 49.7, 49.9(1C), 89.4, 89.9 (1C), 115.5, 119.0, 119.2(1C), 121.2, 123.0, 132.4, 133.5, 133.9, 140.4, 140.6(1C), 147.5, 168.5

LRMS(EI): 340(30), 255(80), 213(100), 195(90), 86(45)

HRMS:  $m/z$  Calcd. For  $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_3$   $\text{M}^+$  340.1787. Found 340.1794

### 3-Acetoxy -9c-(2'-cyanoethyl)-4a, 5, 6, 7, 9, 9c-pentahydrophenanthro[4,5-*bcd*]furan 75



To a solution of MMPP.6H<sub>2</sub>O (890 mg, 1.8 mmol) in methanol (10 mL) was added a solution of dimethylhydrazone **76** (259 mg, 0.76 mmol) in methanol (30 mL) at 0°C. The mixture was allowed to stir for 5 min., and H<sub>2</sub>O (180 mL) was added. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (60 mL) and the aqueous layer was extracted again with CH<sub>2</sub>Cl<sub>2</sub> (2x50 mL), and the combined organic extracts were dried and concentrated. The residue was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>) to give a white solid product (173 mg, 77%).

$^1\text{H}$  NMR (300 MHz)  $\delta$  1.18-1.86 (4H, m), 2.31-2.50 (4H, m), 2.54-2.73 (3H, m), 3.20-3.28 (1H, dd,  $J=19.8, 6.0$  Hz), 3.43-3.55 (1H, dd,  $J=19.8$  Hz, 3.5 Hz), 4.80-4.87 (1H, dd,  $J=12.1, 4.4$  Hz), 5.99-6.01 (1H, m), 6.77-6.84 (1H, d,  $J=8.1$  Hz), 6.87-6.91 (1H, d,  $J=8.1$  Hz)

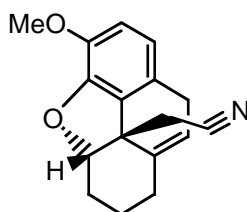
$^{13}\text{C}$  NMR (75 MHz)  $\delta$  17.2, 20.7, 25.0, 25.3, 25.6, 29.7, 47.5, 90.5, 117.5, 119.7, 122.5, 126.3, 131.3, 132.9, 134.3, 137.9, 147.0, 168.5

LRMS(EI): 295(25), 253(85), 213(100), 195(57), 167(25)

HRMS:  $m/z$  Calcd. For  $\text{C}_{18}\text{H}_{17}\text{N O}_3$   $\text{M}^+$  295.1208. Found 295.1214

$[\alpha]_{\text{D}} = -89.8$  ( $c=1.1, \text{CHCl}_3$ )

### 3-Methoxy -9c-(2'-cyanoethyl)-4a, 5, 6, 7, 9, 9c-pentahydrophenanthro[4,5-*bcd*]furan 78



NaOH (5 mL, 1N) was added to a solution of acetoxy nitrile **75** (50 mg, 0.17 mmol) in MeOH (15 mL). The reaction mixture was stirred at rt overnight. Methanol was removed *in vacuo*, and dry ice was added to reach a pH of 6-7. The resulting mixture was extracted with EtOAc (2x10 mL). The organic layer was dried, concentrated to obtain crude 3-hydroxy -9c-(2'-cyanoethyl)-4a, 5, 6, 7, 9, 9c-pentahydrophenanthro[4,5-*bcd*]furan. To the solution of above product and dimethylsulfate (74.8 mg, 0.68 mmol) in acetone (10 mL) was added  $\text{K}_2\text{CO}_3$  (234.6 mg, 1.7 mmol) The mixture was stirred at rt for 16 h, and acetone removed *in vacuo*. The residue was extracted with  $\text{CH}_2\text{Cl}_2$  (20 mL), and washed with water (15 mL). The aqueous layer was

extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x10 mL), and the combined organic extracts were dried, concentrated and purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>) to give a white solid (41 mg, 91%).

<sup>1</sup>H NMR (300 MHz) δ 1.13-1.86 (4H, m), 2.38-2.65 (4H, m), 3.11-3.20 (1H, dd, *J*=19.8, 6.0 Hz), 3.36-3.51 (1H, dd, *J*=19.8, 3.5 Hz), 3.85 (3H, s), 4.76-4.82 (1H, dd, *J*=12.1, 4.4 Hz), 5.94-5.97 (1H, m), 6.71 (2H, s)

<sup>13</sup>C NMR (75 MHz) 17.3, 25.1, 25.4, 25.6, 29.3, 47.5, 56.5, 89.7, 113.2, 117.6, 119.5, 126.6, 128.5, 130.3, 137.9, 143.3, 145.3

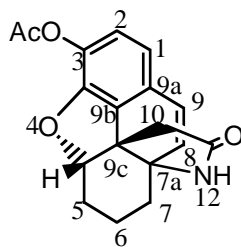
LRMS(EI): 267(85), 227(58), 195(100)

HRMS: *m/z* Calcd. For C<sub>17</sub>H<sub>17</sub>NO<sub>2</sub> M<sup>+</sup> 267.1257 Found 267.1259

[α]<sub>D</sub> = -108.3 (c=0.45, CHCl<sub>3</sub>)

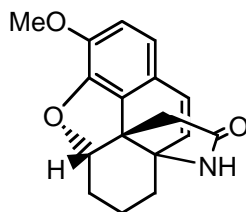
### Palladium catalyzed cyclization of tetracyclic nitriles

#### 3-Acetoxy-7a, 9c-(aminoethano)-4a, 5, 6, 7, 9c-pentahydrophenanthro[4,5-*bcd*]furan 80



#### 3-Methoxy-7a, 9c-(aminoethano)-4a, 5, 6, 7, 9c-pentahydrophenanthro[4,5-*bcd*]furan 82





The nitrile **75** or **78** (0.15 mmol) was dissolved in a mixture of H<sub>2</sub>O: THF = 1:3 (12 mL). Acetamide (0.60 mmol) and Pd(OAc)<sub>2</sub> (0.16 mmol) were added and the mixture was stirred at rt for 3 days. THF was removed in *vacuo*, and resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x20 mL). The organic layer was washed with water (20 mL), dried and concentrated. The residue was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>: CH<sub>3</sub>OH=99:1) to give the product.

**3-Acetoxy –7a, 9c-(aminoethano)-4a, 5, 6, 7, 9c-pentahydrophenanthro[4,5-*bcd*]furan** was obtained in 93% yield as a light yellow solid by the above procedure.

<sup>1</sup>H NMR (300 MHz) δ 1.20-1.59 (4H, m), 1.78-1.83 (1H, m), 2.05-2.15 (1H, m), 2.29 (3H, s), 2.52-2.59 (1H, d, *J*=16.9 Hz), 2.61-2.67 (1H, d, *J*=16.9 Hz), 4.74-4.81 (1H, dd, *J*=10.3, 7.0 Hz), 5.59 (1H, d, *J*=9.6 Hz), 5.91 (1H, br), 6.39 (1H, d, *J*=9.6 Hz), 6.78-6.81 (1H, d, *J*=8.0 Hz), 6.85-6.88 (1H, d, *J*=8.0 Hz)

<sup>13</sup>C NMR (75 MHz) δ 15.2, 20.7, 28.1, 31.8, 42.8, 47.7, 62.9, 92.3, 118.4, 122.6, 123.2, 126.8, 127.3, 133.7, 134.7, 147.7, 168.4, 176.6

LRMS(EI): 311(19), 269(100)

HRMS: *m/z* Calcd. For C<sub>18</sub>H<sub>17</sub>NO<sub>4</sub> M<sup>+</sup>311.1158. Found 311.1157

[α]<sub>D</sub>=-158.5 (c=1.1, CHCl<sub>3</sub>)

**3-Methoxy-7a, 9c-(aminoethano)-4a, 5, 6, 7, 9c-pentahydrophenanthro[4,5-*bcd*]furan** was obtained in 91% yield as a light yellow solid by the above procedure.

$^1\text{H NMR}$  (300 MHz)  $\delta$  1.19-1.52 (4H, m), 1.80-1.85 (1H, m), 2.05-2.15 (1H, m), 2.50-2.56 (1H, d,  $J=16.8$  Hz), 2.57-2.64 (1H, d,  $J=16.8$  Hz), 3.86 (3H, s), 4.73-4.80 (1H, dd,  $J=10.3, 7.0$  Hz), 5.59 (1H, d,  $J=9.6$  Hz), 6.34 (1H, d,  $J=9.6$  Hz), 6.57 (1H, br), 6.65-6.68 (1H, d,  $J=8.0$  Hz), 6.69-6.72 (1H, d,  $J=8.0$  Hz)

$^{13}\text{C NMR}$  (75 MHz)  $\delta$  14.1, 28.3, 31.9, 43.0, 48.1, 56.3, 62.8, 91.4, 113.1, 118.6, 121.9, 122.8, 126.4, 131.8, 144.8, 145.3, 176.6

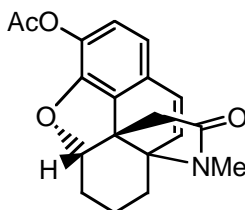
LRMS(EI): 283(100), 240(10)

HRMS:  $m/z$  Calcd. For  $\text{C}_{17}\text{H}_{17}\text{NO}_3$   $M^+$ 283.1206. Found 283.1208

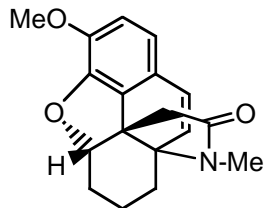
$[\alpha]_{\text{D}}=-172.3$  ( $c=1.3$ ,  $\text{CHCl}_3$ )

### N-methylation of pentacyclic lactams

**3-Acetoxy -7a, 9c-(methylaminoethano)-4a, 5, 6, 7, 9c-pentahydrophenanthro[4,5-*bcd*]furan 83**



**3-Methoxy-7a, 9c-(methylaminoethano)-4a, 5, 6, 7, 9c-pentahydrophenanthro[4,5-*bcd*]furan 84**



NaH (0.14 mmol, 60% in mineral oil) was added to a solution of amide **80** or **82** (0.096 mmol) and MeI (6.6 mL) in THF (20 mL) at 0°C. The reaction mixture was continued to stir at 0°C for 3 h and warmed to rt. After adding Sat. NH<sub>4</sub>Cl (15 mL), the aqueous layer was extracted with diethyl ether (2x15 mL). The combined organic layers were washed with brine (10 mL), separated and dried. The residue was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>: CH<sub>3</sub>OH=99:1) to give the product.

**3-Acetoxy -7a, 9c-(methylaminoethano)-4a, 5, 6, 7, 9c-pentahydrophenanthro[4,5-*bcd*]furan** was obtained in 87% yield as a light yellow solid.

<sup>1</sup>H NMR (300 MHz) δ 0.99-1.29 (4H, m), 1.99-2.23 (2H, m), 2.29 (3H, s), 2.58 (2H, s), 2.84 (3H, s), 4.68-4.75 (1H, dd, *J*=10.3, 7.0 Hz), 5.67 (1H, d, *J*=9.6 Hz), 6.41 (1H, d, *J*=9.6 Hz), 6.69-6.72 (1H, d, *J*=8.0 Hz), 6.86-6.89 (1H, d, *J*=8.0 Hz)

<sup>13</sup>C NMR (75 MHz) δ 16.0, 20.3, 28.1, 30.2, 31.8, 40.8, 44.7, 62.9, 92.3, 118.4, 122.8, 123.6, 127.1, 127.3, 133.7, 134.7, 147.7, 168.4, 174.8

LRMS(EI): 325(25), 283(100)

HRMS: *m/z* Calcd. For C<sub>19</sub>H<sub>19</sub>NO<sub>4</sub> M<sup>+</sup> 325.1314 Found 325.1315

[α]<sub>D</sub> = -153.1 (c=0.89, CHCl<sub>3</sub>)

**3-Methoxy-7a, 9c-(methylaminoethano)-4a, 5, 6, 7, 9c-pentahydrophenanthro[4,5-*bcd*]furan** was obtained (89%) as a light yellow solid.

$^1\text{H NMR}$  (300 MHz)  $\delta$  1.03-1.33 (2H, m), 1.44-1.56 (2H, m), 1.99-2.17 (2H, m), 2.49-2.54 (1H, d,  $J=16.5$  Hz), 2.56-2.63 (1H, d,  $J=16.5$  Hz), 2.83 (3H, s), 3.87 (3H, s), 4.67-4.74 (1H, dd,  $J=10.3, 7.0$  Hz), 5.56 (1H, d,  $J=9.6$  Hz), 6.38 (1H, d,  $J=9.6$  Hz), 6.65-6.68 (1H, d,  $J=8.0$  Hz), 6.69-6.73 (1H, d,  $J=8.0$  Hz)

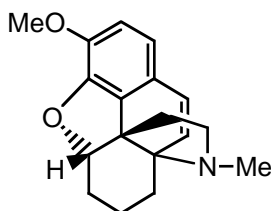
$^{13}\text{C NMR}$  (75MHz)  $\delta$  15.1, 24.6, 28.2, 29.9, 42.5, 46.7, 56.3, 66.1, 91.4, 113.1, 118.6, 122.1, 123.3, 126.8, 126.9, 144.8, 145.3, 174.3

LRMS(EI): 297(100), 283(10)

HRMS:  $m/z$  Calcd. For  $\text{C}_{18}\text{H}_{19}\text{NO}_3$   $\text{M}^+$  297.1360 Found 297.1365

$[\alpha]_{\text{D}} = -166.7$  ( $c=0.67$ ,  $\text{CHCl}_3$ )

**3-Methoxy-7a, 9c-(methyliminoethano)-4a, 5, 6, 7, 9c-pentahydrophenanthro[4,5-*bcd*]furan **85****



Compound **84** (10 mg, 0.034 mmol) in benzene (3 mL) was added to a solution of Red-Al (15  $\mu\text{L}$ , 0.051 mmol, 65% w/w) in benzene (0.5 mL). The reaction mixture heated spontaneously and the apparatus was connected with a condenser. The mixture was stirred at rt for 1.5 h.

Water (6 mL) was added until precipitation occurred and the mixture was extracted with EtOAc (2x10 mL). The combined organic layers were dried, concentrated, purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH: =95:5) to give a white solid (7.4 mg, 77 %).

<sup>1</sup>H NMR (300 MHz) δ 1.03-1.87 (6H, m), 2.11-2.25 (2H, m), 2.37 (3H, s), 2.40-2.44 (1H, m), 3.17-3.20 (1H, m), 3.86 (3H, s), 4.73-4.80 (1H, dd, *J*=10.3, 7.0Hz), 5.79 (1H, d, *J*=9.6 Hz), 6.40 (1H, d, *J*=9.6 Hz), 6.61-6.64 (1H, d, *J*=8.0 Hz), 6.65-6.68 (1H, d, *J*=8.0 Hz)

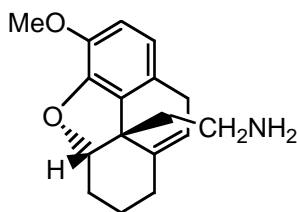
<sup>13</sup>C NMR (75 MHz) δ 15.1, 20.4, 24.6, 28.2, 42.5, 46.7, 48.0, 56.7, 66.1, 92.4, 112.3, 117.4, 122.1, 123.3, 125.8, 126.1, 144.5, 145.1

LRMS(EI): 283 (100), 268(50), 149( 50), 57(48)

HRMS: *m/z* Calcd. For C<sub>18</sub>H<sub>21</sub>NO<sub>2</sub> M<sup>+</sup> 283.1568 Found 283.1572

[α]<sub>D</sub> = -169.1(c=0.15, CHCl<sub>3</sub>)

### 3-Methoxy -9c-(2'-aminoethyl)-4a, 5, 6, 7, 9c-pentahydrophenanthro[4,5-*bcd*]furan 88



To a solution of LAH (5.5 mg, 0.144 mmol) in ether (5 mL) was added nitrile **78** (8.5 mg, 0.032 mmol) at rt. The reaction mixture was refluxed for 5 h, and water (8 mL) was added. The mixture was separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x5 mL). The

combined organic layer was dried and concentrated. Flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>: CH<sub>3</sub>OH: NH<sub>4</sub>OH = 90:10:10) provided the amine (5.9 mg, 69%) as a light yellow oil.

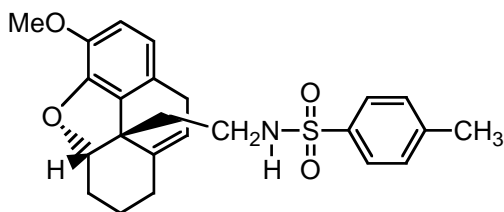
<sup>1</sup>H NMR (300 MHz) δ 1.05-1.40 (4H, m), 1.60-1.95 (4H, m), 2.25-2.45 (2H, m), 2.58-2.81 (2H, m), 3.03-3.15 (1H, dd, *J*=19.3, 6.0 Hz), 3.18-3.35 (1H, dd, *J*=19.3, 3.5 Hz), 3.83 (3H, s), 4.67-4.73 (1H, dd, *J*=12.1, 4.4 Hz), 5.70-5.78 (1H, m), 6.67 (2H, s)

<sup>13</sup>C NMR (75 MHz) δ 17.5, 25.4, 25.8, 29.3, 34.1, 42.4, 47.5, 56.5, 90.5, 113.2, 119.5, 126.6, 128.5, 130.3, 137.9, 143.3, 145.3

LRMS(EI): 271(22), 228( 100), 195(30)

HRMS: *m/z* Calcd. For C<sub>17</sub>H<sub>21</sub>NO<sub>2</sub> M<sup>+</sup> 271.1563. Found 271.1572

### 3-Methoxy -9c-(2'-tosylaminoethyl)-4a, 5, 6, 7, 9, 9c-pentahydrophenanthro[4,5-*bcd*]furan 89



A solution of methoxy ethylamine **88** (5.9 mg, 0.022 mmol) and DMAP (4 mg, 0.033 mmol) in THF (10 ml) at 0°C was treated with TsCl (5.5 mg, 0.029 mmol). The reaction was stirred 3 h at rt, and acidified with HCl (1N) to pH=1-2, and after stirring at rt for 6 h, two layers in the reaction mixture was separated. The aqueous layer was extracted with ether (2x25 mL). The

combined organic layer was dried and concentrated. Flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH:NH<sub>4</sub>OH = 90:5:5) provided amine tosylate (8.0 mg, 85.5%) as a white solid.

<sup>1</sup>H NMR (300 MHz) δ 1.05-1.17 (1H, m), 1.50-1.60 (2H, m), 1.69-1.76 (2H, m), 1.9-1.94 (1H, m), 2.30-2.34 (2H, m), 2.44-2.49 (4H, br), 2.96-3.00 (2H, m), 3.10-3.11(1H, br), 3.87 (3H, s), 4.29 (1H, tr, *J*=6.1 Hz), 4.63-4.67 (1H, dd, *J*=12.1, 4.4 Hz), 5.76-5.78 (1H, br), 6.63-6.69(2H, ABq, *J*=8.0 Hz), 7.23-7.27(2H, BB'), 7.64-7.77 (2H, AA')

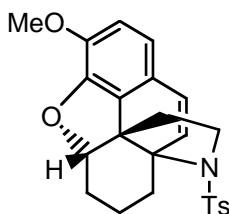
<sup>13</sup>C NMR (75MHz) δ 17.5, 20.8, 25.0, 25.1, 28.7, 36.9, 39.7, 48.8, 55.3, 74.3, 89.8, 113.0, 118.9, 122.8, 126.5, 126.6, 128.1, 128.5, 131.7, 136.9, 140.4, 143.2, 143.3, 144.3

LRMS(EI): 425(28), 270( 40), 227 (75), 71(100)

HRMS: *m/z* Calcd. For C<sub>24</sub>H<sub>27</sub>NO<sub>4</sub>S M<sup>+</sup> 425.1658 Found 425.1661

### 3-Methoxy-7a, 9c-(tosyliminoethano)-4a, 5, 6, 7, 9c-pentahydrophenanthro[4,5-*bcd*]furan

90



NaOAc (3.1 mg, 0.038 mmol) and PdOAc (0.3 mg, 0.0019 mmol) were added to a solution of amine tosylate **89** (8.0 mg, 0.019 mmol) in DMSO (10 mL) under an atmosphere of O<sub>2</sub>. The mixture was allowed to stir at 80°C for 3days, and then cooled to rt, diluted with THF and ether (10 mL+20 mL). The mixture was washed with brine and then the aqueous layer was extracted

with ether (2x15 mL). The combined organic layers were washed with 10% NaCl solution (10 mL), dried and concentrated. Flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH:NH<sub>4</sub>OH = 90:5:5) gave the product as a yellow solid (6.7 mg, 84%).

<sup>1</sup>H NMR (300 MHz) δ 0.95-1.45 (4H, m), 1.90-2.10 (3H, m), 2.45 (3H, s), 2.83-2.90 (1H, m), 3.16-3.25 (1H, m), 3.73-3.77 (1H, m), 3.89 (3H, s), 4.51-4.54 (1H, dd, *J*=10.2, 6.5 Hz), 6.26-6.34 (2H, ABq, *J*=9.7 Hz), 6.70-6.75(2H, ABq, *J*=8.0 Hz), 7.32-7.35(2H, BB'), 7.78-7.80 (2H, AA')

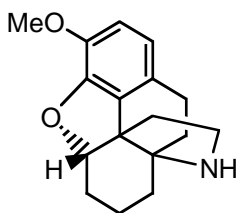
<sup>13</sup>C NMR (75 MHz) δ 22.7, 28.7, 28.9, 29.2, 29.6, 45.9, 52.4, 56.2, 72.0, 89.6, 116.5, 118.3, 122.4, 125.0, 127.2, 127.4, 127.5, 128.1, 130.2, 138.6, 140.7, 143.0, 144.4, 144.9

LRMS(EI): 423(100), 268(60), 225(18)

HRMS: *m/z* Calcd. For C<sub>24</sub>H<sub>25</sub>NO<sub>4</sub>S M<sup>+</sup> 423.1496 Found 423.1504

### 3-Methoxy-7a, 9c-(iminoethano)-4a, 5, 6, 7, 8, 9, 9c-heptahydrophenanthro[4,5-*bcd*]furan

96



To a two-necked round bottom flask (50 mL) containing dry THF (10 mL) fitted with a dry ice condenser, was added NH<sub>3</sub> (40 mL) and t-BuOH (0.05 mL) at -78°C. With stirring, Li (20 mg) was added. After the solution turned blue, a solution of amine tosylate (6.5 mg, 0.015 mmol) in



THF (5 mL) was added. The reaction mixture stirred for 15 min at  $-78^{\circ}\text{C}$ , then the dry ice bath was removed, and the  $\text{NH}_3$  allowed to evaporate.  $\text{NH}_4\text{Cl}$  (10 mg) in  $\text{CH}_3\text{OH}$  (3 mL) solution was added dropwise, and reaction mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3x15 mL). The organic layer was dried, evaporated and purified by column chromatography ( $\text{CH}_2\text{Cl}_2$ :  $\text{CH}_3\text{OH}$ :  $\text{NH}_4\text{OH}$ =90:5:5) to give product (3.4 mg, 80%) as a yellow solid.

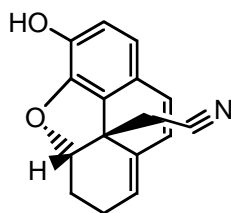
$^1\text{H}$  NMR (300 MHz)  $\delta$  1.03-1.40 (2H, m), 1.42-1.56 (3H, m), 1.58-1.65 (1H, m), 1.95-2.08 (3H, m), 2.25-2.36 (1H, m), 2.61-2.70 (1H, m), 2.81-2.92 (2H, m), 3.15-3.28(2H, m), 3.89 (3H, s), 4.62-4.66 (1H, dd,  $J=10.3, 6.8$  Hz), 6.65-6.68 (1H, d,  $J=8.1$  Hz), 6.74-6.76(1H, d,  $J=8.1$  Hz)

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  17.4, 25.1, 28.2, 29.7, 35.5, 38.9, 43.7, 51.2, 56.5, 61.7, 91.3, 113.2, 119.8, 125.8, 131.0, 143.3, 145.7

LRMS(EI): 271(100), 228( 50), 120(15)

HRMS:  $m/z$  Calcd. For  $\text{C}_{17}\text{H}_{21}\text{NO}_2$   $M^+$  271.1578 Found 271.1572

### 3-Hydroxy -9c-(2'-cyanoethyl)-4a, 5, 6, 9c-tetrahydrophenanthro[4,5-*bcd*]furan 86



$\text{NaOAc}$  (51 mg, 0.62 mmol) was added to a solution of acetoxy nitrile **75** (91 mg, 0.31 mmol) in  $\text{DMSO}$  (25 mL) under an atmosphere of  $\text{O}_2$ . The mixture was allowed to stir at  $80^{\circ}\text{C}$  for 3 days, and then cooled to rt, diluted with THF and ether (20 mL+40 mL). The mixture was

washed with brine and two layers was separated. The aqueous layer was extracted with ether (2x30 mL). The combined organic layers were washed with 10% NaCl solution (20 mL), dried and concentrated to give a white solid (64 mg, 82%) directly used for the next reaction without further purification.

$^1\text{H NMR}$  (300 MHz)  $\delta$  1.27-1.42 (2H, m), 2.21-2.32 (2H, m), 2.55-2.74 (2H, ABq,  $J=16.6$  Hz), 4.85 (1H, br), 5.21-5.25 (1H, m), 6.21(2H, m), 6.44 (1H, d,  $J=9.7$  Hz), 6.66-6.74 (2H, ABq,  $J=8.0$  Hz)

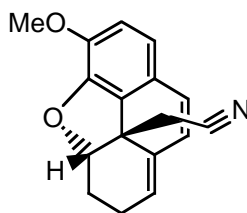
$^{13}\text{C NMR}$  (75 MHz)  $\delta$  21.1, 26.2, 28.9, 46.3, 90.4, 117.1, 117.2, 118.7, 123.8, 124.1, 124.5, 126.9, 131.9, 136.6, 140.5, 142.6

LRMS(EI): 251(35), 211(100), 165(27)

HRMS:  $m/z$  Calcd. For  $\text{C}_{16}\text{H}_{13}\text{NO}_2$   $M^+$  251.0942 Found 251.0946

$[\alpha]_{\text{D}} = +110.3$  ( $c=0.36$ ,  $\text{CHCl}_3$ )

### 3-Methoxy -9c-(2'-cyanoethyl)-4a, 5, 6, 9c-tetrahydrophenanthro[4,5-*bcd*]furan **87**



$\text{K}_2\text{CO}_3$  (303.6 mg, 2.2 mmol) was added to a solution of hydroxy nitrile **86** (55 mg, 0.22 mmol) and dimethylsulfate (0.084 mL, 0.88 mmol) in acetone (30 mL). The mixture was stirred at rt for 16 h, and acetone removed in *vacuo*. The residue was extracted with  $\text{CH}_2\text{Cl}_2$  (40 mL), and

washed with water (30 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x20 mL), and the combined organic extracts were dried, concentrated and purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>) to give a white solid (56 mg, 96%)

<sup>1</sup>H NMR (500 MHz) δ 1.25-1.35 (2H, m), 2.21-2.24 (2H, m), 2.53-2.74 (2H, ABq, *J*=16.5 Hz), 3.87 (3H, s), 5.19-5.23 (1H, m), 6.20-6.24 (2H, m), 6.45 (1H, d, *J*=9.7 Hz), 6.72 (2H, s)

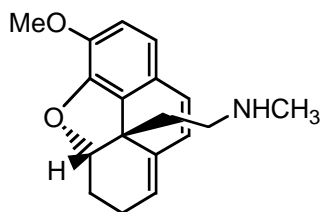
<sup>13</sup>C NMR (75 MHz) δ 21.2, 26.3, 28.9, 46.3, 56.3, 90.0, 113.2, 117.2, 118.4, 123.8, 124.1, 124.9, 126.9, 130.9, 132.4, 136.6, 142.6

LRMS(EI): 265(35), 225(100), 165(15)

HRMS: *m/z* Calcd. For C<sub>17</sub>H<sub>15</sub>NO<sub>2</sub> M<sup>+</sup> 265.1103. Found 265.1096

[α]<sub>D</sub> = +136.7 (c=0.29, CHCl<sub>3</sub>)

### 3-Methoxy -9c-(2'-methylaminoethyl)-4a, 5, 6, 9c-tetrahydrophenanthro[4,5-*bcd*]furan 97



To a solution of methoxy diene nitrile **87** (45 mg, 0.17 mmol) in a mixed solvent of Et<sub>2</sub>O and CH<sub>2</sub>Cl<sub>2</sub> (2 mL+2 mL) was added DIBAL (0.59 mL, 1 M in hexane) at -78°C. After stirring at -78°C for 2 h, the reaction mixture was warmed to 0°C and stirred for an additional 1 h. To the reaction mixture was added a solution of NH<sub>4</sub>Br (46 mg, 0.47 mmol) in dry methanol (1 mL) followed by a MeNH<sub>2</sub> (1.4 mL, 2 M) solution in methanol. The cooling bath was removed and

the stirring was continued for 2h at room temperature. The mixture was cooled in an ice bath and NaBH<sub>4</sub> (114 mg, 3 mmol) was added in three portions. The reaction mixture was stirred overnight at rt. The excess NaBH<sub>4</sub> was destroyed by addition of HCl (2 M). The pH was adjusted to >12 using 3N NaOH. The resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4x25 mL). The combined organic layer was dried and concentrated. Flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>: CH<sub>3</sub>OH: NH<sub>4</sub>OH=90:5:5) provided amine (35 mg, 73%) as a white solid.

<sup>1</sup>H NMR (300 MHz) δ 1.23-1.94 (5H, m), 2.09-2.20 (2H, m), 2.33 (3H, s), 2.57-2.80(2H, m), 3.85 (3H, s), 5.03-5.11 (1H, m), 5.93(1H, m) 6.12 (1H, d, *J*=9.6 Hz), 6.36 (1H, d, *J*=9.6 Hz), 6.90 (2H, s)

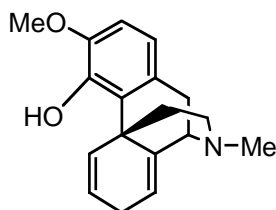
<sup>13</sup>C NMR (300 MHz) δ 21.5, 29.2, 36.5, 37.4, 46.7, 47.6, 56.2, 90.3, 111.8, 117.8, 123.9, 124.6, 125.6, 128.3, 130.4, 135.2, 139.9, 144.3

LRMS(EI): 283(40), 226(100)

HRMS: *m/z* Calcd. For C<sub>18</sub>H<sub>21</sub>NO<sub>2</sub> M<sup>+</sup> 283.1572. Found 283.1573

[α]<sub>D</sub> = +103.2 (c=0.49, CHCl<sub>3</sub>)

### 6-demethoxy-7-deoxysalutaridine 110



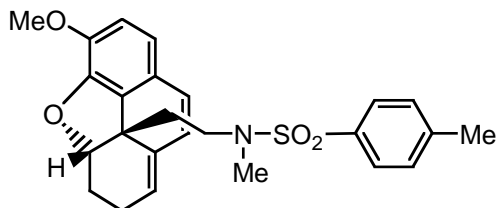
To a solution of methylamine **97** (6 mg, 0.021 mmol) in a mixed solvent of THF (1 mL) and diisopropylamine (0.36 mL) was added *n*-BuLi (174  $\mu$ L, 0.252 mmol, 1.45 M in hexane) at -78°C. The reaction mixture was warmed to rt and stirred for 7 h under argon with irradiation from a 600 W tungsten lamp at a distance of 0.7 m. The solution was quenched with aqueous NaHCO<sub>3</sub> (5 mL), and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x6 mL). The organic layer was dried, concentrated and purified by column chromatography to give the product as a white solid (2.6 mg, 61%) and recovered starting material (1.7 mg).

<sup>1</sup>H NMR (300 MHz)  $\delta$  1.23-1.55 (3H, m), 1.73-1.83 (2H, m), 2.03-2.20 (2H, m), 2.37 (3H, s), 2.61-2.64 (1H, m), 2.72-2.79 (1H, m), 3.86 (3H, s), 5.88 (1H, br), 6.09-6.19 (2H, m) 6.55 (1H, d, *J*=8.1 Hz), 6.65(1H, d, *J*=8.1 Hz)

LRMS(EI): 283(47), 240(45), 226(63), 193(100), 165(55)

HRMS: *m/z* Calcd. For C<sub>18</sub>H<sub>21</sub>NO<sub>2</sub> M<sup>+</sup> 283.1572. Found 283.1573

**3-Methoxy -9c-(2'-methyltosylaminoethyl)-4a, 5, 6, 9c-tetrahydrophenanthro[4,5-*bcd*]furan **104****



To a solution of methyl amine **97** (5 mg, 0.018 mmol) in a CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added TsCl (4.5 mg, 0.023 mmol) and DMAP (4.4 mg, 0.036 mmol). The reaction mixture was stirred at rt for

5 h, and water (5 mL) was added. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x5 mL). The combined organic layer was dried and concentrated. Flash column chromatography (hexane: ether: CH<sub>3</sub>OH: NH<sub>4</sub>OH = 90:90:10:10) provided amine tosylate (6.3 mg, 82%) as a white solid.

<sup>1</sup>H NMR (300 MHz) δ 1.23-1.94 (4H, m), 2.11-2.20 (2H, m), 2.39 (3H, s), 2.60 (3H, s), 2.57-2.80(2H, m), 3.85 (3H, s), 5.00-5.06 (1H, m), 5.97(1H, m) 6.13 (1H, d, *J*=9.6 Hz), 6.36 (1H, d, *J*=9.6 Hz), 6.67 (2H, s), 7.25 (2H, BB'), 7.58 (2H, AA')

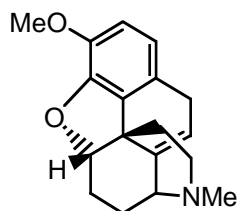
<sup>13</sup>C NMR (75 MHz) δ 21.5, 21.5, 29.1, 34.5, 34.7, 46.2, 56.2, 89.8, 112.1, 118.0, 124.0, 124.4, 125.4, 126.4, 127.0, 127.3, 128.0, 129.4, 129.8, 132.3, 134.5, 138.8, 140.1, 143.2, 144.4

LRMS(EI): 421(27), 266(45), 225(100)

HRMS: *m/z* Calcd. For C<sub>25</sub>H<sub>27</sub>NO<sub>3</sub>S M<sup>+</sup> 421.1710. Found 421.1712

[α]<sub>D</sub> = +89.2 (c=0.12, CHCl<sub>3</sub>)

### **3-Methoxy-7, 9c-(methyliminoethano)-4a, 5, 6, 9, 9c-pentahydrophenanthro[4,5-*bcd*]furan 105**



To a two-necked round bottom flask (50 mL) containing dry THF (10 mL) cooled to -78°C and fitted with a dry ice condenser was added NH<sub>3</sub> (40 mL) and t-BuOH (0.05 mL). With stirring, Li (20 mg) was added. After the solution turned blue, a solution of methyl amine

tosylate **104** (6.3 mg, 0.015 mmol) in THF (5 mL) was added. The reaction mixture stirred for 15min at  $-78^{\circ}\text{C}$ , then the dry ice bath was removed, and the  $\text{NH}_3$  allowed to evaporate.  $\text{NH}_4\text{Cl}$  (10 mg) in  $\text{CH}_3\text{OH}$  (3 mL) solution was added dropwise, and reaction mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3x15 mL). The organic layer was dried, evaporated and purified by column chromatography ( $\text{CH}_2\text{Cl}_2$ :  $\text{CH}_3\text{OH}$ :  $\text{NH}_4\text{OH}$ =90:5:5) to give product (3.8 mg, 89%) as a yellow solid.

$^1\text{H}$  NMR (500 MHz)  $\delta$  1.03-1.87 (6H, m), 1.92-1.95 (1H, m), 2.36 (3H, s), 2.54-2.57 (1H, m), 2.66-2.70 (1H, m), 3.15 (1H, dd,  $J$ =19.1, 6.0 Hz), 3.27 (1H, dd,  $J$ =19.1, 3.6 Hz), 3.89 (3H, s), 4.75-4.79 (1H, dd,  $J$ =12.1, 4.6 Hz), 5.78 (1H, m), 6.70 (2H, s)

$^{13}\text{C}$  NMR (75 MHz)  $\delta$  17.7, 25.4, 29.4, 36.5, 37.9, 47.8, 56.4, 61.6, 66.8, 90.5, 111.9, 119.0, 123.4, 128.7, 132.9, 141.0, 143.0, 144.4

LRMS(EI): 283(50), 228(100), 211(40), 195(35)

HRMS:  $m/z$  Calcd. For  $\text{C}_{18}\text{H}_{21}\text{NO}_2$   $M^+$  283.1569. Found 283.1572

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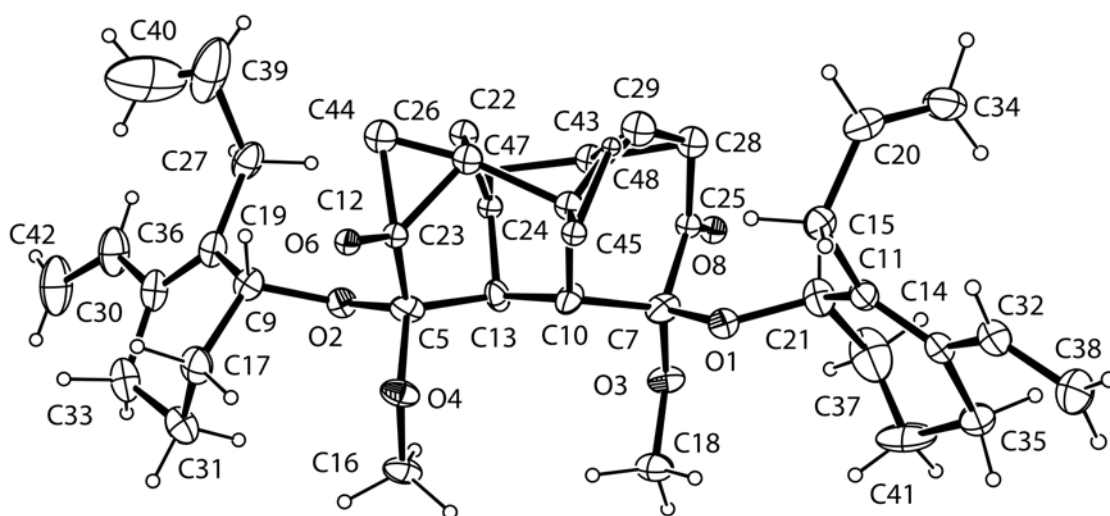
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## APPENDIX

### 1. X-ray structure of dimer compound 62<sup>19</sup>



**Table 1. Crystal data and structure refinement for dimer compound 62**

Empirical formula	C <sub>36</sub> H <sub>44</sub> O <sub>6</sub>
Formula weight	572.71
Temperature	150(1) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, Pbca
Unit cell dimensions	a = 8.9733(18) Å, b = 19.948(4) Å, c = 34.123(7) Å
Volume	6108(2) Å <sup>3</sup>
Z, Calculated density	8, 1.246 mg/m <sup>3</sup>
Absorption coefficient	0.083 mm <sup>-1</sup>
F(000)	2464
Crystal size	0.40 x 0.38 x 0.11 mm
Theta range for data collection	2.04 to 26.02 deg.
Limiting indices	-10<h<11, -24<k<24, -40<l<42
Reflections collected / unique	35634 / 6003 [R(int) = 0.0432]

Completeness to $\theta = 26.02$	100.0 %
Absorption correction	None
Refinement method	Full-matrix least-squares on $F^2$
Data / restraints / parameters	6003 / 0 / 380
Goodness-of-fit on $F^2$	3.149
Final R indices [ $I > 2\sigma(I)$ ]	R1 = 0.0670, wR2 = 0.1212
R indices (all data)	R1 = 0.0824, wR2 = 0.1227
Extinction coefficient	0.0010(2)
Largest diff. peak and hole	0.688 and -0.508 e. $\text{\AA}^{-3}$

**Table 2. Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ )**

	x	y	z	U(eq)
C(1)	766(2)	3954(1)	-207(1)	43(1)
C(2)	1985(3)	4346(1)	-420(1)	38(1)
C(3)	3497(2)	3982(1)	-402(1)	32(1)
C(4)	3327(2)	3443(1)	-74(1)	33(1)
C(4A)	2798(2)	3822(1)	301(1)	32(1)
C(5)	3026(2)	3434(1)	683(1)	33(1)
C(6)	1938(3)	2832(1)	697(1)	40(1)
C(7)	372(3)	3032(1)	654(1)	47(1)
C(8)	42(3)	3599(1)	456(1)	43(1)
C(8A)	1127(2)	4026(1)	249(1)	37(1)
C(9)	2171(3)	2954(1)	-218(1)	39(1)
C(10)	887(3)	3222(1)	-310(1)	43(1)
O(11)	1819(2)	4905(1)	-556(1)	45(1)
O(12)	3855(2)	3625(1)	-749(1)	32(1)
C(13)	3583(3)	3932(1)	-1132(1)	38(1)
C(14)	3522(3)	3353(1)	-1416(1)	44(1)
C(15)	4557(3)	3264(1)	-1697(1)	55(1)
C(16)	5932(3)	3682(1)	-1715(1)	65(1)
C(17)	6174(3)	4110(1)	-1350(1)	55(1)

C(18)	4733(3)	4453(1)	-1239(1)	47(1)
C(19)	2151(3)	2924(1)	-1374(1)	52(1)
C(20)	562(9)	3194(3)	-1538(2)	54(2)
C(21)	521(7)	3564(3)	-1831(2)	71(2)
C(20A)	1061(7)	3233(3)	-1630(2)	52(2)
C(21A)	-229(7)	3442(3)	-1474(2)	72(2)
C(22)	4379(4)	2763(1)	-2008(1)	79(1)
C(23)	5320(5)	2664(2)	-2304(1)	114(2)
O(24)	4545(2)	4486(1)	-314(1)	38(1)
C(25)	6074(2)	4273(1)	-300(1)	42(1)
O(26)	2723(2)	3909(1)	983(1)	32(1)
C(27)	2173(3)	3666(1)	1362(1)	46(1)
C(28)	1572(2)	4276(1)	1572(1)	35(1)
C(29)	2067(2)	4465(1)	1925(1)	41(1)
C(30)	3376(3)	4127(2)	2120(1)	65(1)
C(31)	4234(3)	3691(2)	1821(1)	87(1)
C(32)	3269(4)	3262(2)	1599(1)	80(1)
C(33)	305(2)	4616(1)	1358(1)	36(1)
C(34)	-1209(3)	4351(1)	1457(1)	45(1)
C(35)	-1535(3)	3950(1)	1746(1)	58(1)
C(36)	1351(3)	5009(1)	2144(1)	54(1)
C(37)	1772(3)	5253(2)	2491(1)	80(1)
O(38)	4462(2)	3157(1)	716(1)	36(1)
C(39)	5645(2)	3628(1)	749(1)	45(1)
O(40)	2324(2)	2264(1)	754(1)	52(1)

—



**Table 3. Bond lengths [ $\text{\AA}$ ] and angles [ $^\circ$ ]**

C(1)-C(10)	1.505(3)
C(1)-C(2)	1.528(3)
C(1)-C(8A)	1.595(3)
C(2)-O(11)	1.218(2)
C(2)-C(3)	1.540(3)
C(3)-O(24)	1.408(2)
C(3)-O(12)	1.419(2)
C(3)-C(4)	1.560(3)
C(4)-C(9)	1.507(3)
C(4)-C(4A)	1.559(3)
C(4A)-C(5)	1.529(3)
C(4A)-C(8A)	1.564(3)
C(5)-O(38)	1.406(2)
C(5)-O(26)	1.420(2)
C(5)-C(6)	1.549(3)
C(6)-O(40)	1.201(3)
C(6)-C(7)	1.468(3)
C(7)-C(8)	1.351(3)
C(8)-C(8A)	1.474(3)
C(9)-C(10)	1.307(3)
O(12)-C(13)	1.464(2)
C(13)-C(18)	1.510(3)
C(13)-C(14)	1.510(3)
C(14)-C(15)	1.347(3)
C(14)-C(19)	1.506(3)

C(15)-C(22)	1.467(4)
C(15)-C(16)	1.490(4)
C(16)-C(17)	1.526(3)
C(17)-C(18)	1.511(3)
C(19)-C(20A)	1.450(7)
C(19)-C(20)	1.624(8)
C(20)-C(21)	1.243(9)
C(20A)-C(21A)	1.340(9)
C(22)-C(23)	1.330(4)
O(24)-C(25)	1.437(2)
O(26)-C(27)	1.469(3)
C(27)-C(32)	1.507(3)
C(27)-C(28)	1.510(3)
C(28)-C(29)	1.339(3)
C(28)-C(33)	1.511(3)
C(29)-C(36)	1.467(3)
C(29)-C(30)	1.510(3)
C(30)-C(31)	1.547(4)
C(31)-C(32)	1.434(4)
C(33)-C(34)	1.496(3)
C(34)-C(35)	1.302(3)
C(36)-C(37)	1.334(3)
O(38)-C(39)	1.421(2)
C(10)-C(1)-C(2)	109.48(19)
C(10)-C(1)-C(8A)	107.42(19)
C(2)-C(1)-C(8A)	105.79(18)

O(11)-C(2)-C(1)	124.2(2)
O(11)-C(2)-C(3)	123.7(2)
C(1)-C(2)-C(3)	111.78(19)
O(24)-C(3)-O(12)	112.58(16)
O(24)-C(3)-C(2)	105.13(16)
O(12)-C(3)-C(2)	113.68(17)
O(24)-C(3)-C(4)	113.91(17)
O(12)-C(3)-C(4)	106.00(15)
C(2)-C(3)-C(4)	105.50(17)
C(9)-C(4)-C(4A)	111.89(17)
C(9)-C(4)-C(3)	106.16(17)
C(4A)-C(4)-C(3)	106.47(16)
C(5)-C(4A)-C(4)	114.31(17)
C(5)-C(4A)-C(8A)	110.92(16)
C(4)-C(4A)-C(8A)	108.95(17)
O(38)-C(5)-O(26)	112.25(16)
O(38)-C(5)-C(4A)	113.01(17)
O(26)-C(5)-C(4A)	104.48(16)
O(38)-C(5)-C(6)	105.71(17)
O(26)-C(5)-C(6)	111.93(17)
C(4A)-C(5)-C(6)	109.58(17)
O(40)-C(6)-C(7)	123.3(2)
O(40)-C(6)-C(5)	123.7(2)
C(7)-C(6)-C(5)	112.95(19)
C(8)-C(7)-C(6)	119.1(2)
C(7)-C(8)-C(8A)	125.4(2)
C(8)-C(8A)-C(4A)	115.38(18)

C(8)-C(8A)-C(1)	106.37(18)
C(4A)-C(8A)-C(1)	106.39(16)
C(10)-C(9)-C(4)	114.9(2)
C(9)-C(10)-C(1)	113.9(2)
C(3)-O(12)-C(13)	119.91(15)
O(12)-C(13)-C(18)	112.96(18)
O(12)-C(13)-C(14)	105.09(16)
C(18)-C(13)-C(14)	113.35(19)
C(15)-C(14)-C(19)	123.9(2)
C(15)-C(14)-C(13)	122.2(2)
C(19)-C(14)-C(13)	113.7(2)
C(14)-C(15)-C(22)	122.0(3)
C(14)-C(15)-C(16)	121.7(2)
C(22)-C(15)-C(16)	116.3(3)
C(15)-C(16)-C(17)	113.5(2)
C(18)-C(17)-C(16)	109.6(2)
C(13)-C(18)-C(17)	109.46(19)
C(20A)-C(19)-C(14)	104.5(3)
C(20A)-C(19)-C(20)	19.6(3)
C(14)-C(19)-C(20)	119.7(3)
C(21)-C(20)-C(19)	120.1(7)
C(21A)-C(20A)-C(19)	118.4(6)
C(23)-C(22)-C(15)	125.5(3)
C(3)-O(24)-C(25)	115.71(15)
C(5)-O(26)-C(27)	118.64(16)
O(26)-C(27)-C(32)	115.5(2)
O(26)-C(27)-C(28)	105.73(17)

C(32)-C(27)-C(28)	114.3(2)
C(29)-C(28)-C(27)	122.3(2)
C(29)-C(28)-C(33)	123.8(2)
C(27)-C(28)-C(33)	113.76(19)
C(28)-C(29)-C(36)	121.5(2)
C(28)-C(29)-C(30)	122.0(2)
C(36)-C(29)-C(30)	116.5(2)
C(29)-C(30)-C(31)	110.2(2)
C(32)-C(31)-C(30)	112.6(2)
C(31)-C(32)-C(27)	110.9(3)
C(34)-C(33)-C(28)	114.56(19)
C(35)-C(34)-C(33)	126.3(2)
C(37)-C(36)-C(29)	126.8(3)
C(5)-O(38)-C(39)	115.55(16)

**Table 4. Hydrogen coordinates ( $\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ )**

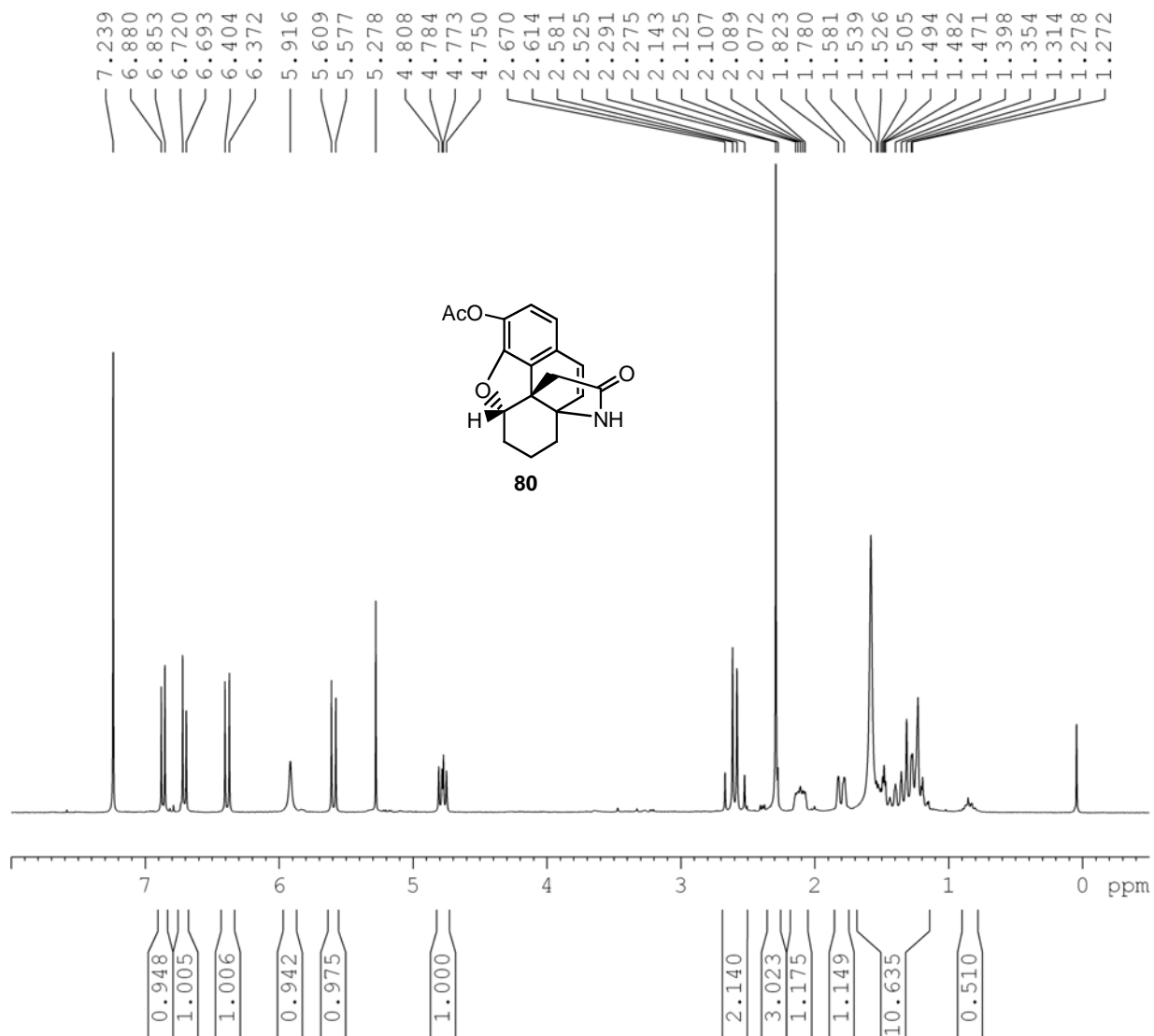
	x	y	z	U(eq)
H(1)	-246	4134	-271	51
H(4)	4296	3210	-25	40
H(4A)	3392	4245	320	38
H(7)	-399	2766	765	56
H(8)	-973	3734	450	52
H(8A)	989	4503	331	45
H(9)	2360	2488	-241	47
H(10)	103	2977	-430	51
H(13)	2582	4152	-1126	46
H(16X)	5873	3979	-1946	78
H(16Y)	6804	3384	-1750	78
H(17X)	6515	3823	-1130	66
H(17Y)	6953	4450	-1402	66
H(18X)	4904	4756	-1014	56
H(18Y)	4370	4725	-1462	56
H(19U)	2006	2823	-1087	62
H(19V)	2344	2479	-1499	62
H(20)	-341	3113	-1411	57
H(21U)	1453	3648	-1968	100
H(21V)	-370	3717	-1934	100

H(19X)	2352	2447	-1451	62
H(19Y)	1793	2913	-1094	62
H(20A)	1228	3302	-1904	57
H(21X)	-406	3353	-1205	100
H(21Y)	-975	3631	-1634	100
H(22)	3520	2485	-1998	95
H(23X)	6194	2931	-2326	171
H(23Y)	5119	2327	-2493	171
H(25X)	6123	3784	-328	63
H(25Y)	6510	4403	-47	63
H(25Z)	6631	4485	-513	63
H(27)	1304	3367	1307	55
H(30X)	3017	3841	2338	78
H(30Y)	4052	4470	2231	78
H(31X)	4784	3988	1638	105
H(31Y)	4975	3413	1962	105
H(32X)	2721	2961	1780	95
H(32Y)	3873	2979	1421	95
H(33X)	331	5101	1419	43
H(33Y)	466	4567	1073	43
H(34)	-2009	4488	1293	54
H(35X)	-773	3799	1917	86
H(35Y)	-2535	3809	1784	86
H(36)	499	5209	2027	64
H(37X)	2617	5071	2621	120
H(37Y)	1227	5608	2608	120
H(39X)	5734	3880	503	67

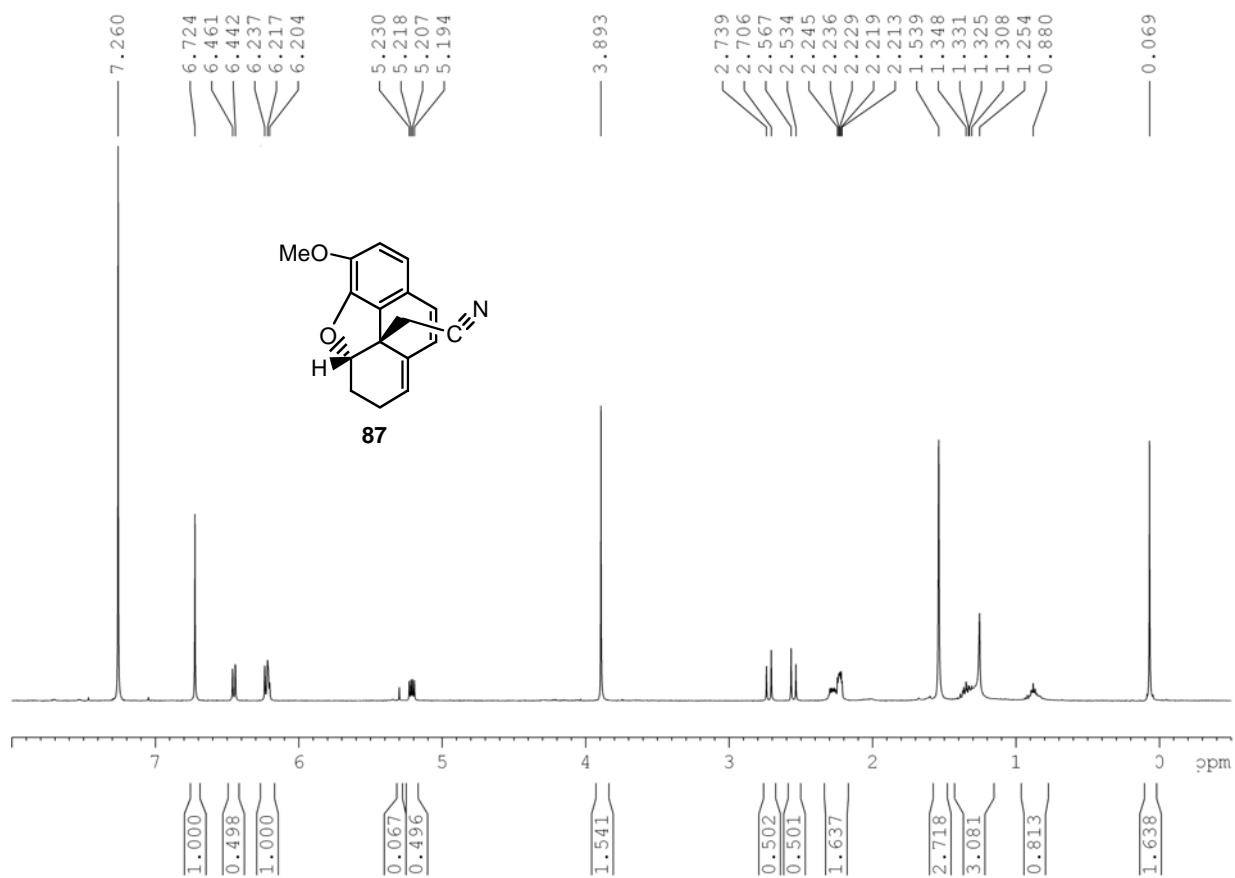
H(39Y)	6580	3390	801	67
H(39Z)	5437	3939	964	67



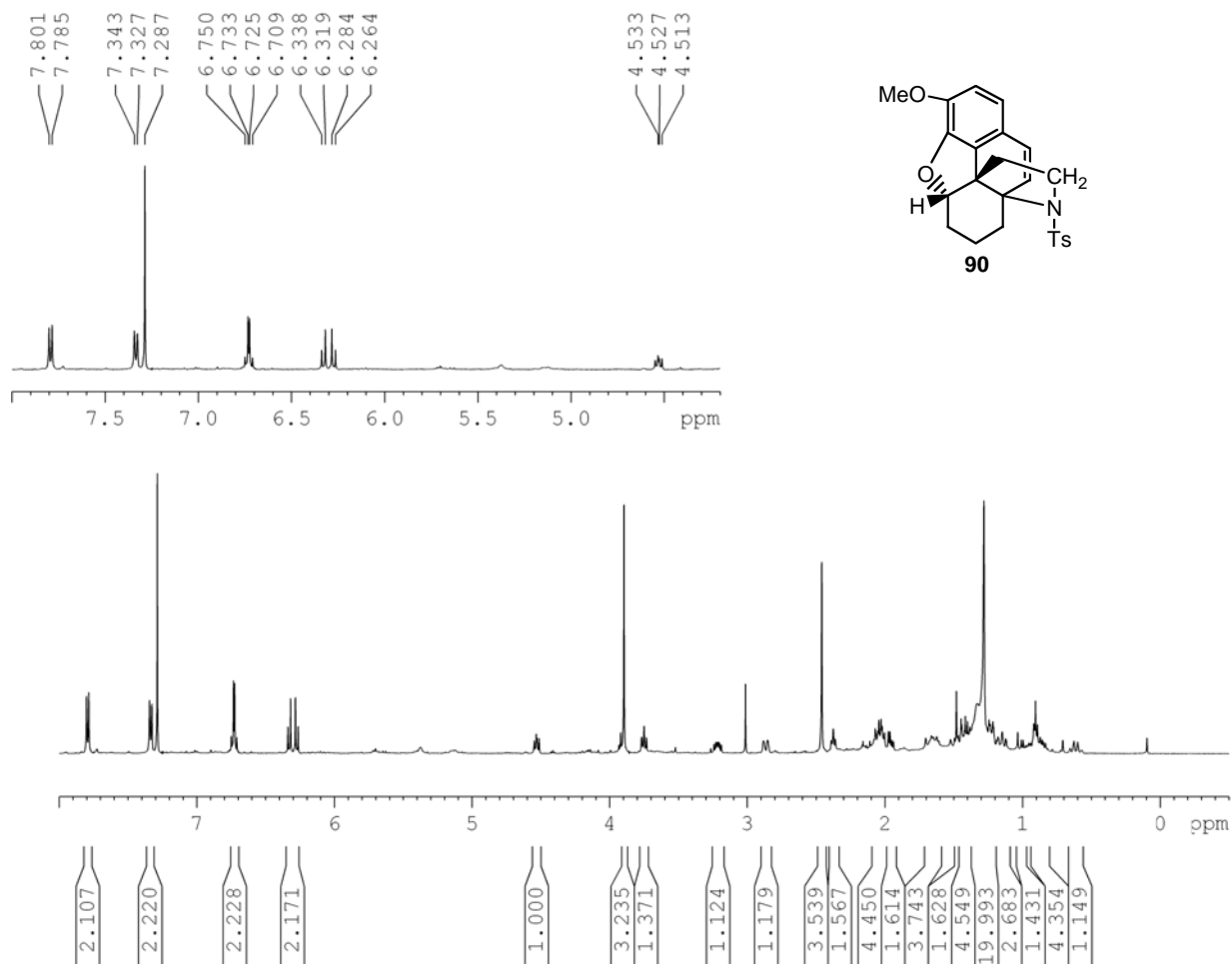
## 2. NMR spectrum of 80



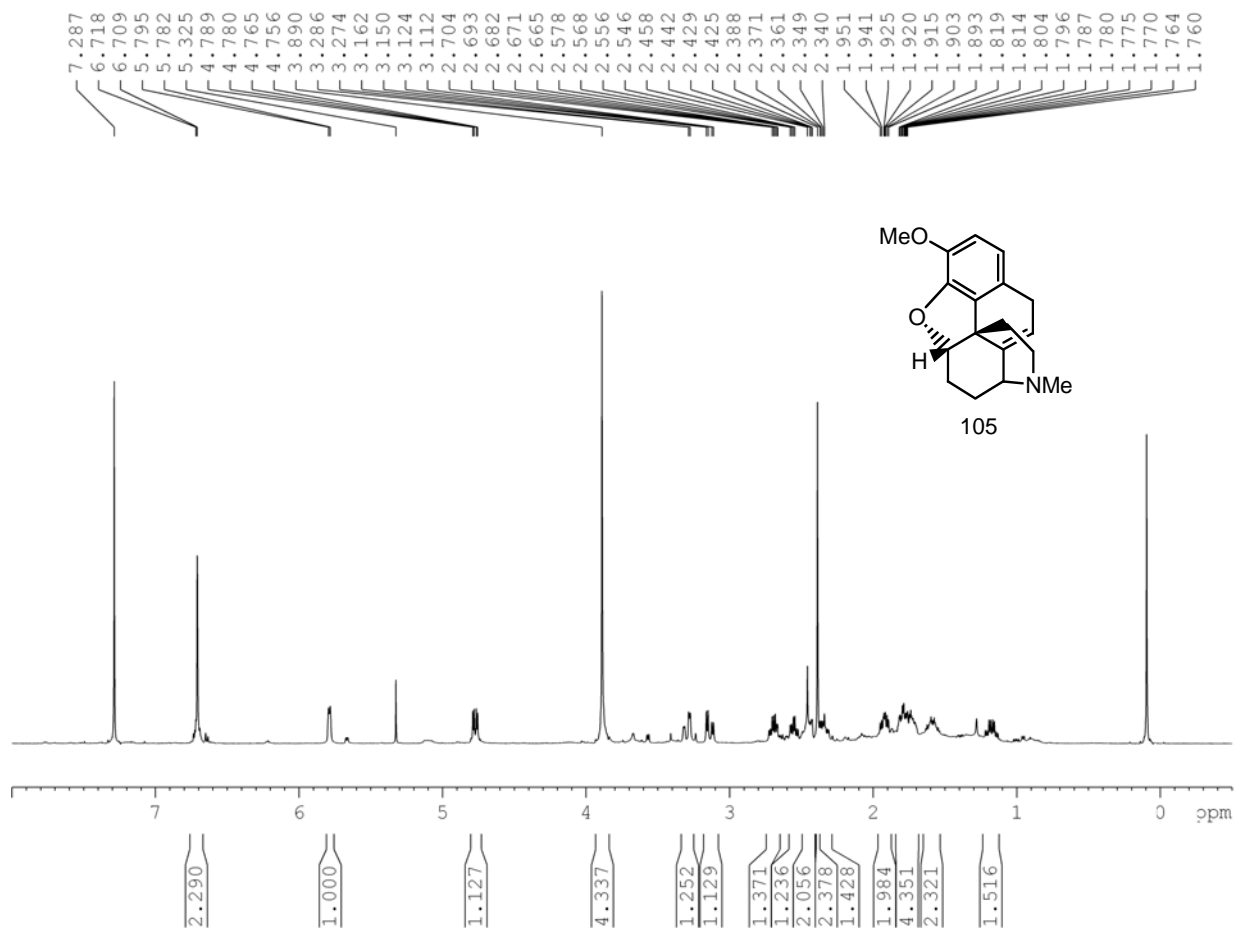
### 3. NMR spectrum of 87



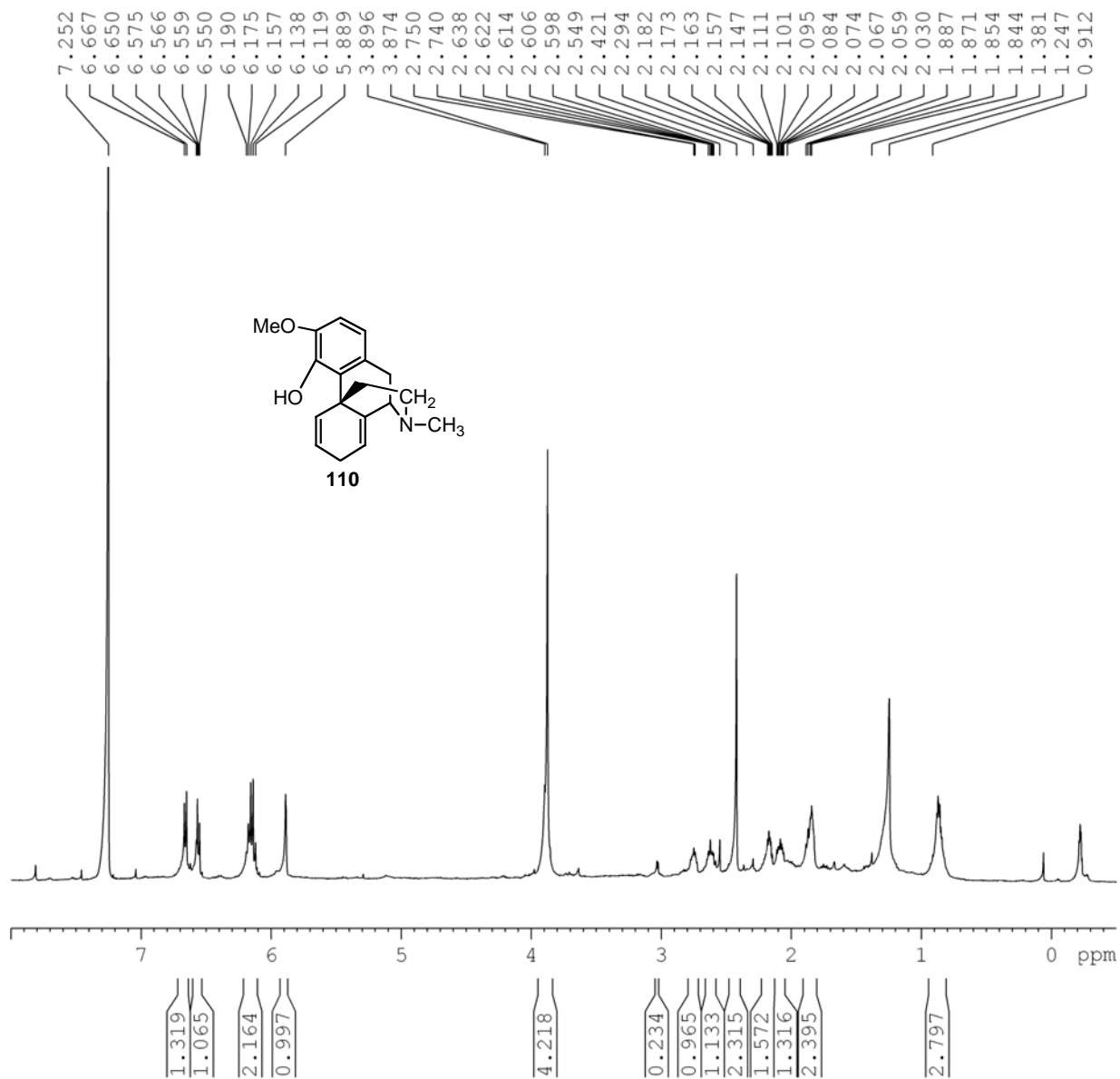
#### 4. NMR spectrum of 90



## 5. NMR spectrum of 105



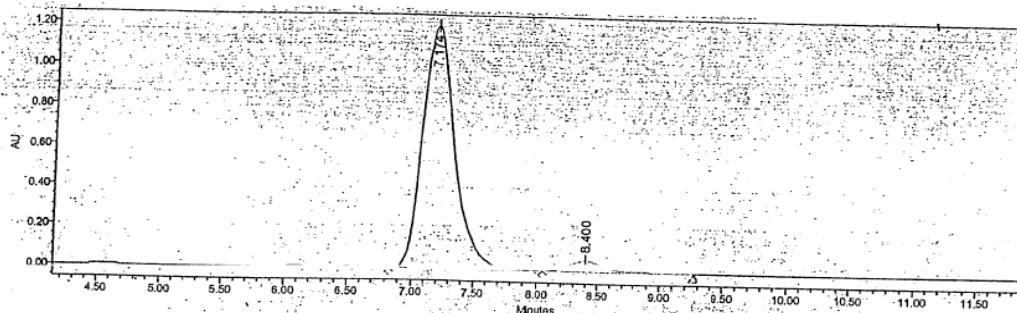
## 6. NMR spectrum of 110



## 7. HPLC Chromatogram of (S)-(-)-39b

Conditions: OD-H column  
Flow rate 1.5ml  
Solvent: 1% iPrOH, 99% Hexanes, 0.1% TFA  
 $\lambda=254\text{nm}$

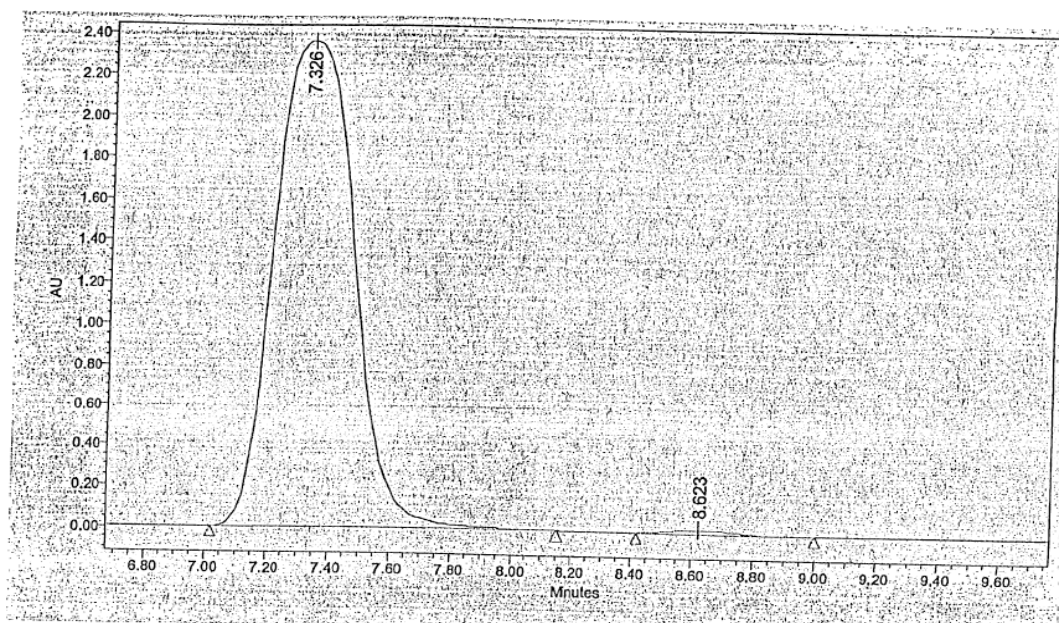
Chiral reduction with  $\text{BH}_3\text{-THF}$  complex



	Retention Time	Area	% Area	Height
1	7.174	21362705	95.37	1197538
2	8.400	1036996	4.63	52016

ee% = 90.7%

Reduction with Catachol Borane



	Retention Time	Area	% Area
1	7.326	42501557	99.33
2	8.623	285296	0.67

ee% = 98.6%