INTERMEDIATES IN THE SYNTHESIS OF DECUMBENSINE / OPHIOCARPINE

THE PREPARATION OF INTERMEDIATES IN THE SYNTHESIS OF (1R,7'R)-DECUMBENSINE AND (13R,14R)-OPHIOCARPINE

By

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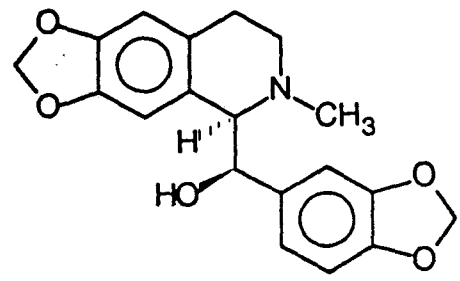
ABSTRACT

The synthesis of 2-ethoxycarbonyl-1-hydroxymethyl-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline **117** and 2-acetyl-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline-1-carboxaldehyde **126** are described. These compounds are potentially useful intermediates for the asymmetric synthesis of two tetrahydroisoquinoline alkaloids, (1R,7'R)-decumbensine and (13R,14R)-ophiocarpine. Decumbensine is a simple 1-benzyl-1,2,3,4-tetrahydroisoquinoline alkaloid having a hydroxyl group at the carbon atom adjacent to C-1 of the isoquinoline ring. Ophiocarpine belongs to the tetrahydroprotoberberine group of isoquinoline alkaloids and has a hydroxyl group in the same relative position in its ring system as that found in decumbensine.

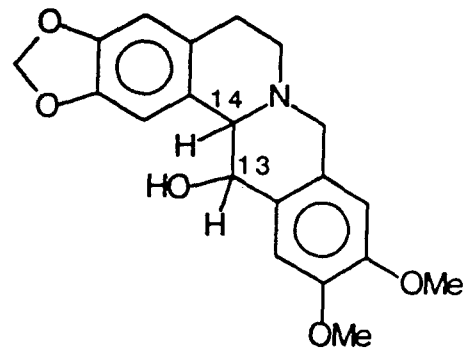
The first synthesis led to a racemic intermediate which would require resolution before proceeding with the asymmetric synthesis. The second synthesis led directly to an optically active aldehyde and would appear to be the more satisfactory route.

A procedure for the preparation of 3-benzyloxy-4-methoxy bromobenzene is also described. This compound, after halogen-metal exchange, would be used to introduce the second aromatic ring in the ophiocarpine synthesis.

The literature on asymmetric synthesis of tetrahydroisoquinoline alkaloids has been reviewed in the introduction.



Decumbensine



Ophiocarpine

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CHAPTER 1

INTRODUCTION

1.1 General Introduction

The purpose of this work was to investigate a pathway for the synthesis of (1R,7'R)-decumbensine and (13R,14R)-ophiocarpine, 1,2,3,4-tetrahydroisoquinoline alkaloids (THIQ), in their naturally occurring form. Although most of the alkaloids discussed in this report have been synthesized previously as racemates, only recently have asymmetric syntheses been effected to induce chirality at C-1 of the THIQ system. The asymmetric syntheses have been made possible through the development of methods to induce chirality at C-1 of the isoquinoline framework. In the following pages the author describes briefly the history of the discovery of molecular chirality and then provides a recent review of the various approaches taken to obtain asymmetric THIQ's in high optical yield. The synthetic plans for the synthesis of (1R,7'R)-decumbensine and (13R,14R)-ophiocarpine are outlined and the results discussed in chapter 2. The experimental procedures are described in chapter 3.

1.2 Discovery of Molecular Chirality

Early in the 19th century it was discovered that certain molecules have the ability to rotate plane polarized light. Biot was the first to observe this phenomenon and noted that it occurred in the solid state, in the liquid state or in solution. This was the first clue that the property might be attributed to the molecular structure. Biot continued his studies on tartaric acid obtained from wine lees and found it to be dextrorotatory. Racemic acid, known today as dl-tartaric acid, was found to be optically inactive. In 1831 Berzelius found that tartaric acid and racemic acid had the same molecular formula. Thus the term, isomerism, came into use to describe different substances having the same molecular formula. In 1844, Mitschelrich studied the ammonium salts of tartaric and racemic acid and reported that they were isomorphous and possessed the same physical properties.

Louis Pasteur in order to strengthen his knowledge of crystallography repeated a series of measurements made by de la Provostaye on the crystalline forms of various salts of tartaric acid. He achieved the same results as his predecessor but he noticed all the crystals displayed hemihedral faces. He observed in 1846 that all the crystals of d-tartaric acid were not symmetric but all had the same orientation and Biot had found that the d- and l-tartrates

were optically active in the same sense. Meanwhile, Herschel had demonstrated the relationship between the crystallographic and optical properties of quartz. Based on Herschel's findings, Pasteur assumed the structure of the tartaric acid salts must be related to their optical rotatory power. Mitschelrich made a crystallographic comparison of the sodium ammonium salts of tartaric and racemic acid. He reported that they differed only in that one is dextrorotatory and the other is optically inactive. Pasteur believed Mitschelrich may have overlooked the existence of hemihedry in the tartrate, so he repeated the experiment himself. He found sodium ammonium tartrate to be hemihedral (all faces turned in one direction) while sodium ammonium racemate also possessed hemihedral faces though some were turned to the right and some to the left. In 1848, using a microscope, Pasteur was successful in separating the two types of crystals, left- and right-handed, of sodium ammonium racemate. He referred to the isomers as real and mirror images. He found that one set of crystals was dextrorotatory while the other set of crystals rotated the plane of polarized light in an equal but opposite direction (levorotatory). Pasteur referred to an equal mixture of the two types as a racemate derived from the name racemic acid. It was determined later that the selective crystallization was dependent on temperature. If a hot solution were used then there was no evidence of hemihedral structure; the d and l salts were present in equal amounts in each crystal. The

molecular compound existed as the monohydrate, $Na(NH_4)C_4H_4O_6:H_2O$. When crystallization occurred below 28° a conglomerate of sodium ammonium d-tartrate and of sodium ammonium l-tartrate separated both of which were tetrahydrates, $Na(NH_4)C_4H_4O_6:4H_2O$.

As early as 1852, Pasteur found that racemic acid could be resolved using optically active natural bases such as brucine and quinine. His techniques established the foundation upon which all optical resolution is based today.

In 1873 Wislicenus is quoted, "If it is once granted that molecules can be structurally identical and yet possess dissimilar properties, this can only be explained on the grounds that the difference is due to a different arrangement of their atoms in space."(1) One year later van't Hoff and Le Bel separately but simultaneously proposed "the idea of the spatial arrangement of four substituents around a carbon atom."(1) Though scientists were beginning to understand the relationship between optical activity and molecular structure, the formation of optically active substances was still a mystery.

In 1894 Fischer reported the reaction of hydrogen cyanide with various sugars and observed epimers of the resulting cyanohydrin in varying proportions; this was one of the first successful records of an asymmetric synthesis. Many medicines isolated from plants or other living organisms were found to be optically active and thus the importance of asymmetric synthesis was recognized. A recent example is the

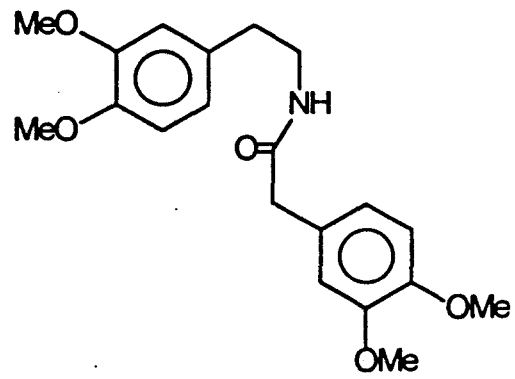
synthesis of L-DOPA (L-3,4-dihydroxyphenylalanine), a substance used to treat Parkinson's disease, by Knowles et al. (2) in 1968. They succeeded in synthesizing this compound in almost 100% optical purity using the Wilkinson catalyst.

1.3 Alkaloids

Alkaloids are a class of compounds that have interested chemists for many years. Long before any structural elucidation was complete and even before isolation of pure substances was achieved alkaloids were man's medicines as well as his poisons. The term alkaloid covers a broad spectrum of compounds. S.W.Pelletier provides the definition, "An alkaloid is a cyclic organic compound containing nitrogen in a negative oxidation state which is of limited distribution among living organisms."(3)

Perhaps the most common routes in the synthesis of tetrahydroisoquinoline alkaloids discussed in this thesis have been the Bischler-Napieralski and Pictet-Spengler ring closures. The initial Bischler-Napieralski reaction involved the conversion of N-acyl-2-arylethylamines 1 to the corresponding 3,4-dihydroisoquinolines 2 under the influence of P_2O_5, $POCl_3$, PCl_5 or $ZnCl_2$ (Scheme 1). The reaction, once thought to occur via carbonyl protonation, is now believed to proceed via a nitrilium cation 5 (4) (Scheme 2).
It has been shown (5,6) that 4 is an intermediate in the

SCHEME 1



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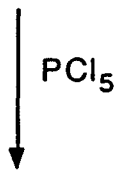
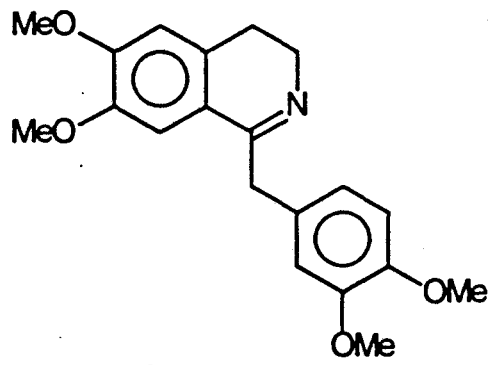
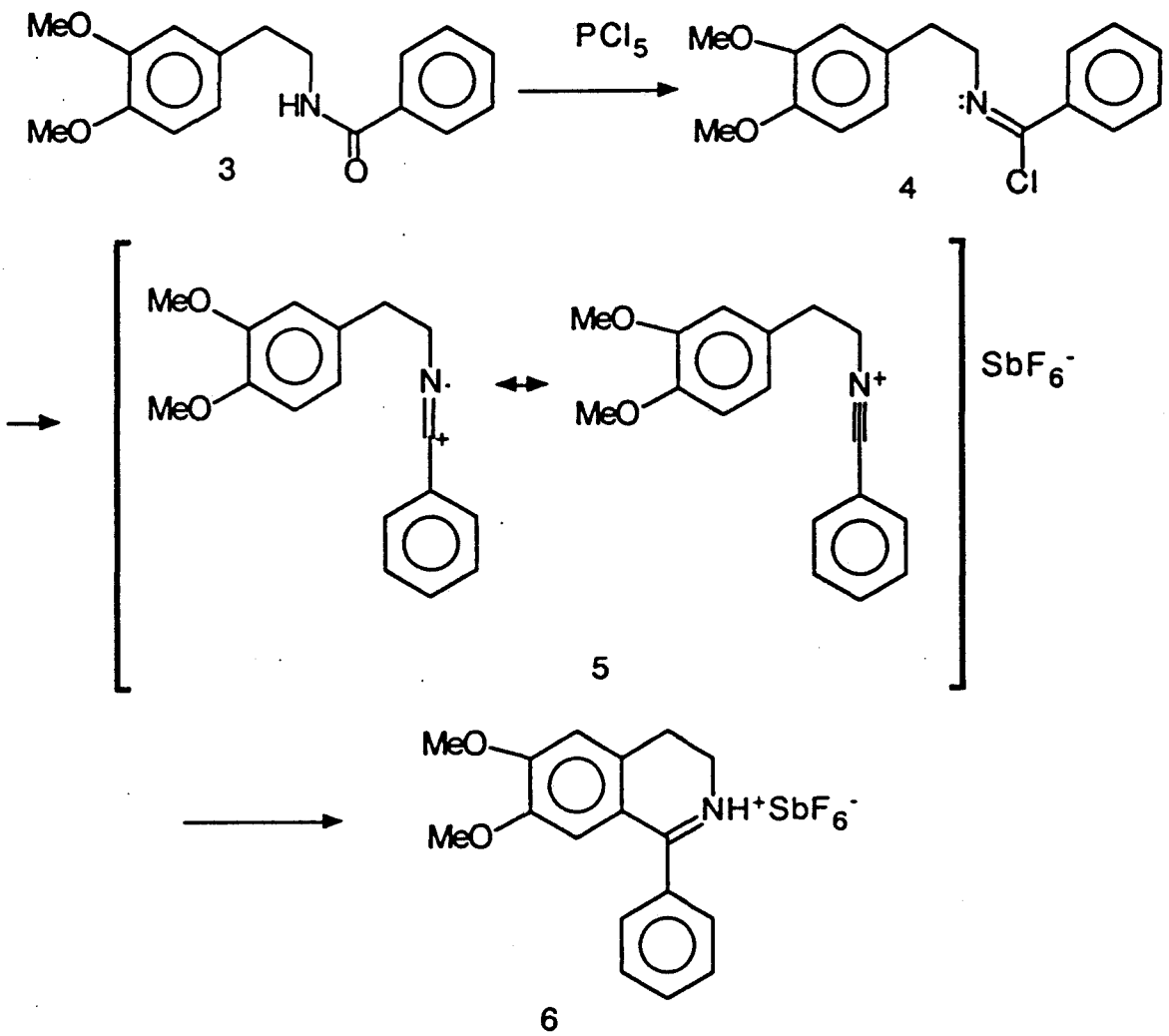




2

SCHEME 2


MeO
MeO
HN
O
3
PCl5
MeO
MeO
:N
Cl
4
MeO
MeO
N·
+
MeO
MeO
N+
SbF6-
5
MeO
MeO
NH+SbF6-
6

reaction of 3 with PCl_5. Compound 5 has been trapped as the SbF_6^- salt and subsequently was induced to undergo ring closure in solution to form the iminium salt 6.

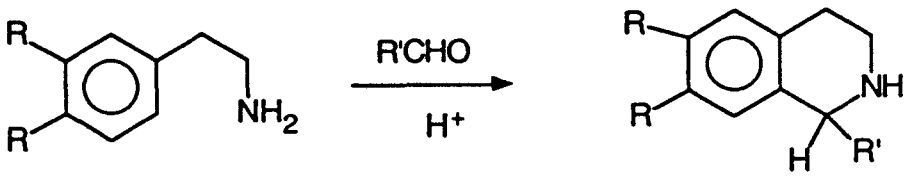
The Pictet-Spengler cyclization is a reaction between a β-arylethylamine 7 and a carbonyl compound to yield a tetrahydroisoquinoline 8 (7)(Scheme 3). The Pictet-Spengler reaction is believed to occur via a Schiff base intermediate. The intermediate has been isolated many times and cyclized using acid catalysts. Scheme 4 shows piperonal 9 undergoing a Pictet-Spengler condensation with formaldehyde to afford the Schiff base 10 and under acidic conditions, the tetrahydroisoquinoline 11 (8). It should be noted that the reaction proceeds more readily when a hydroxyl group is para to the site of ring closure (9).

1.3.1 Asymmetric Synthesis of Alkaloids

There are many different types of alkaloids but this report will deal solely with the asymmetric synthesis of those possessing the 1-substituted-1,2,3,4-tetrahydroisoquinoline framework (see Structure 8). These alkaloids comprise a large number of different structures (3,10,11). Here an attempt will be made to provide the reader with a review of recent advances in the asymmetric synthesis of 1-alkyl-1,2,3,4-tetrahydroisoquinolines and related structures.

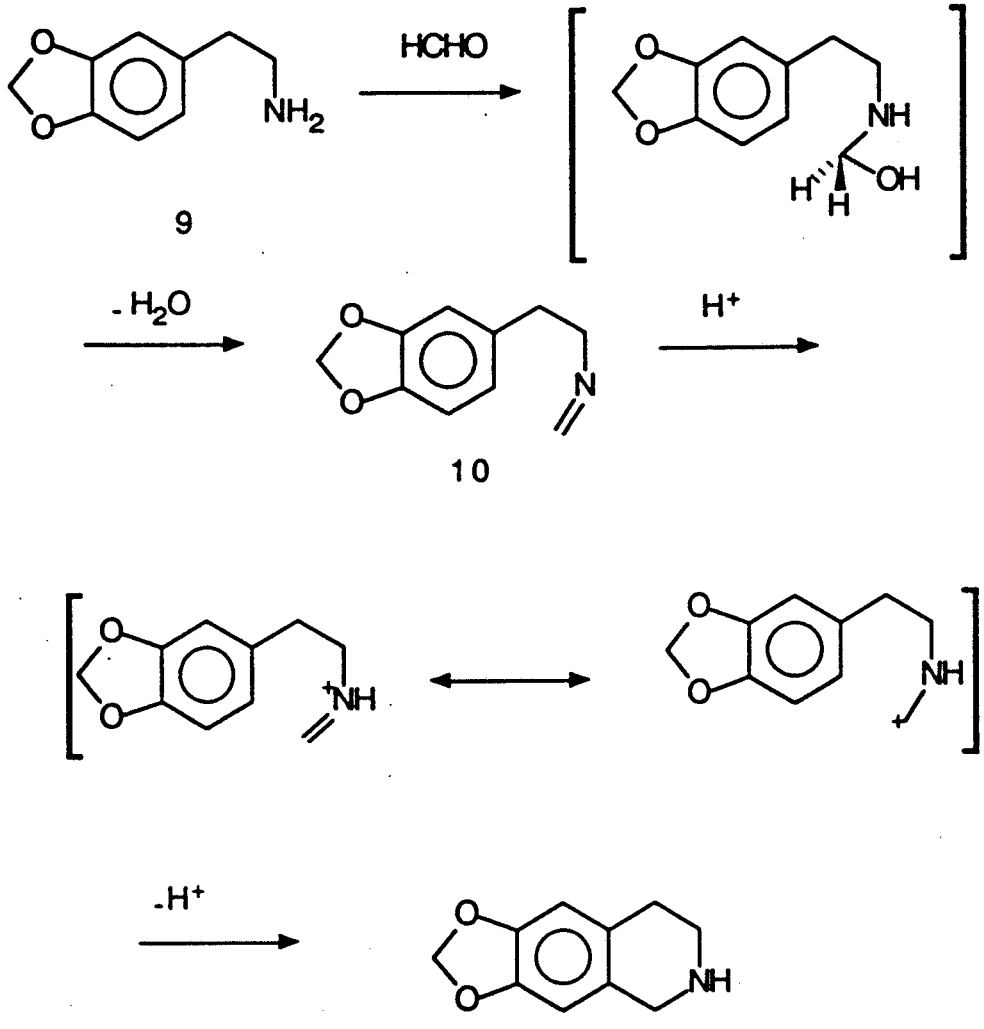
Various approaches have been taken to effect

SCHEME 3



7 8

SCHEME 4



enantioselective synthesis of tetrahydroisoquinolines substituted at C-1. Amongst them are metalation-alkylation reactions using chiral formamidines (12–14) and condensations such as the Pictet-Spengler ring closure (15–17) involving optically active components. Other methods include stereoselective photocyclization (18–20) , reductions of chiral 3,4-dihydroisoquinolines (21,22) and of chiral 3,4-dihydroisoquinolinium salts (23), and the use of chiral N-oxyacyliminium salts (24).

1.3.1.1 Metalation-Alkylation

Seebach and Enders published a review (25) on the umpolung of amine reactivity. They examined the concept of reversible umpolung in which an electrophilic site is changed into a nucleophilic site and back again or vice versa. The carbon atom alpha to an amine is normally electrophilic in character because of the adjacent electronegative nitrogen atom. In order to change the polarity at this site a modification at nitrogen is necessary. This objective was accomplished by attachment of a suitable substituent to the amino nitrogen.

One substituent found to fulfill these requirements was the nitroso group (Figure 1). Seebach et.al. (25) lithiated the nitroso derivative of 6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline, then alkylated the lithium derivative, thus providing a new synthetic route to 1-alkyl-1,2,3,4-tetra-hydroisoquinoline alkaloids. Nitroso compounds are extremely

toxic so alternative groups were sought. Among those found were $-PO(NMe_3)_2$, and hindered acyl ($-COCR_3$). Meyers (12) found that formamidines were sufficient activators.

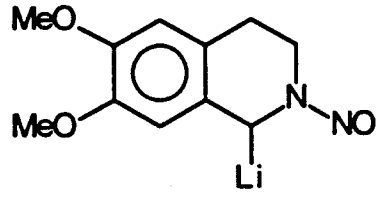


Figure 1: Lithiated nitroso derivative of THIQ

Meyers and coworkers (12–14,26–30) have made significant advances in the field of asymmetric synthesis pertaining to induced chirality at C-1 of 1,2,3,4-tetrahydroisoquinolines. They employed formamidines as the activating group on nitrogen to aid in the metallation at C-1 (12–14,26). The purpose was similar to that of the groups of Seebach (25) and Beak (31) who used hindered activating groups on nitrogen to enhance the acidity at C-1 in order to generate an anionic center (Figure 2).

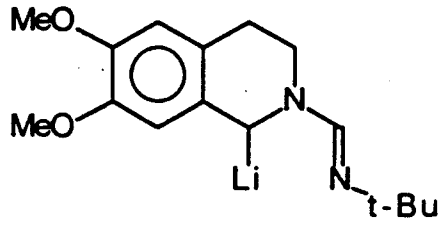


Figure 2: Lithiated formamidine derivative of a THIQ

The anion reacted with electrophiles creating a new C-C bond

and upon removal of the activating group, an alkylated tetrahydroisoquinoline was obtained (Figure 3).

The ultimate objective of Meyer's research was to create a new C-C bond adjacent to nitrogen with simultaneous chiral induction (27). In Meyers' initial work (12–14,26) a t-butyl

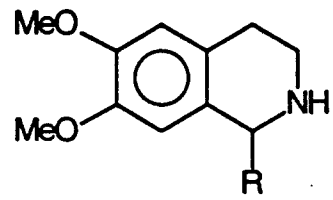
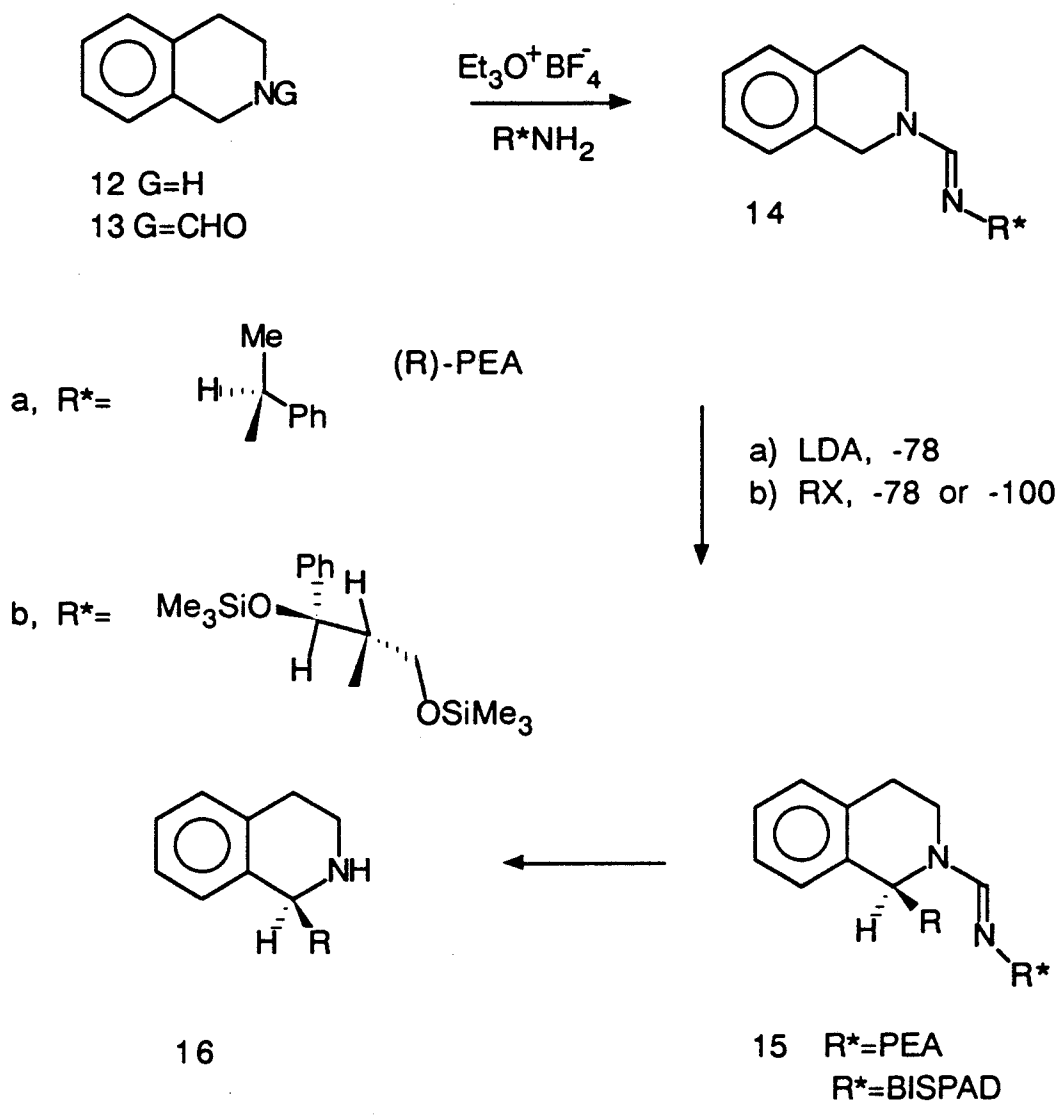


Figure 3: A tetrahydroisoquinoline alkylated at C-1

group was part of the formamidine but in his later work it was replaced with a chiral moiety. This chiral adduct was expected to promote stereoselective formation of the C-C bond at the anionic site (27–29). It was reasoned that a chiral auxiliary on the nitrogen might lead to stereoselective formation of the C-Li bond, or alternatively, that the angle of approach of the electrophile would be influenced by the relief features of the chiral portion of the molecule, an explanation based on Cram's rule. Meyers had proposed that, if either of these assumptions were true, a high degree of diastereoselection would be observed. The amine would be obtained by removal of the activating group.

In an initial investigation, (R)-(-)-α-phenethylamine (PEA) was chosen in place of the t-butyl group (27) (Scheme 5). Tetrahydroisoquinoline 12 was N-formylated affording 13

SCHEME 5


NG
12 G=H
13 G=CHO
$Et_3O^+BF_4^-$
R^*NH_2
N
N
R*
14
a, R*=
Me
H
Ph
(R)-PEA
a) LDA, -78
b) RX, -78 or -100
b, R*=
Ph
H
Me_3SiO
H
$OSiMe_3$
NH
H
R
16
N
H
R
N
R*
15 R*=PEA
R*=BISPAD

which was treated with Meerwein's reagent and then with PEA yielding the formamidine 14. Lithium diisopropylamide (LDA) was used to lithiate C-1 and a variety of alkyl halides were used as electrophiles. Hydrazinolysis of 15 yielded an excess of the enantiomer 16. Using PEA as the chiral adjuvant the enantiomeric excess (ee) fell in the range, 10-50%. When a bulkier R group was used, such as bis-silylphenylaminodiol (BISPAD), greater than 90% ee was obtained.

Meyers and coworkers (29) continued work with chiral formamidines and employed derivatives of natural amino acids as the chiral auxiliary. The amino acids are readily available and are easily converted to their corresponding alcohols without racemization.

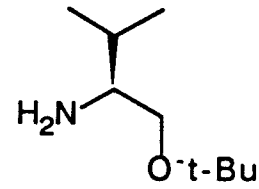
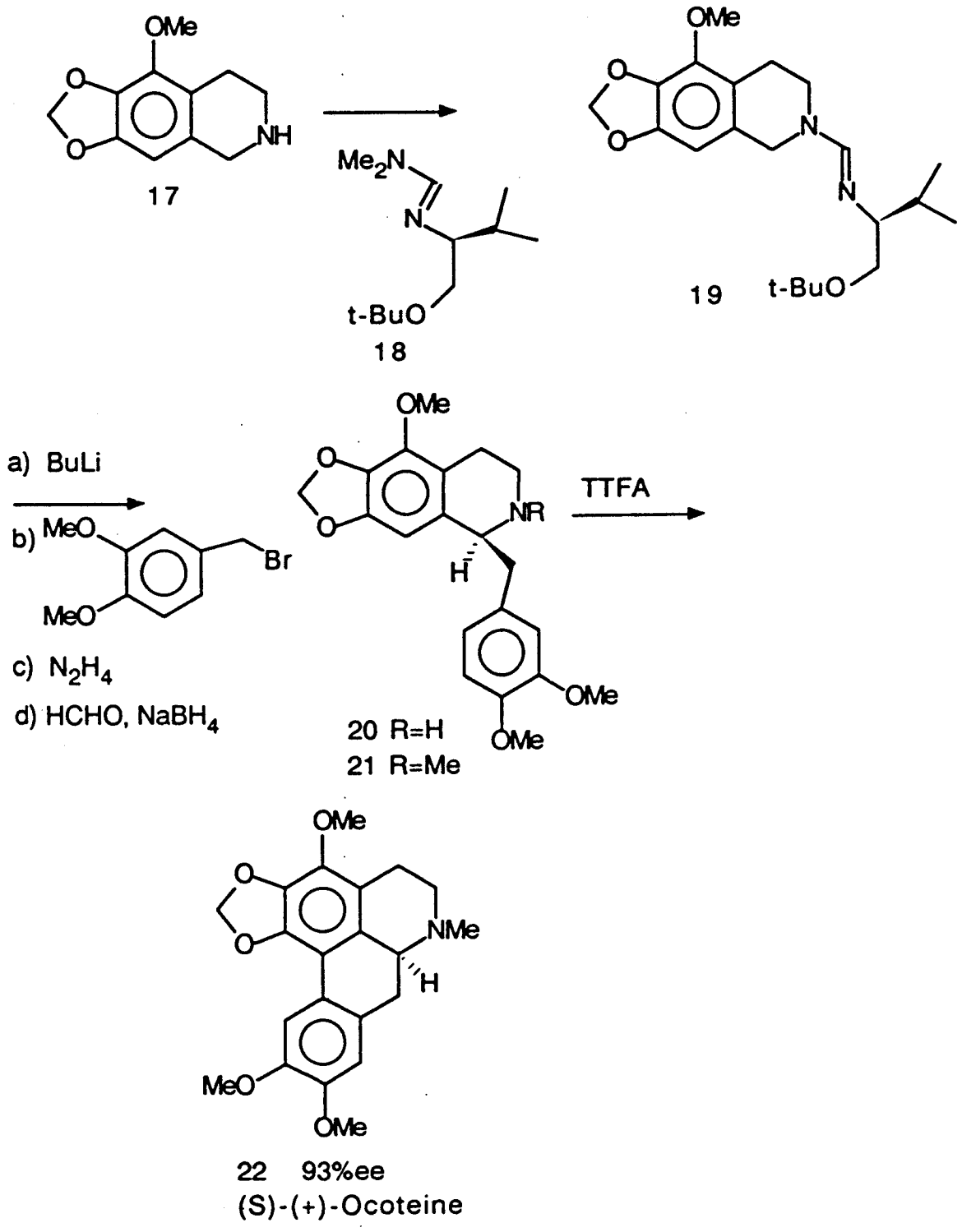


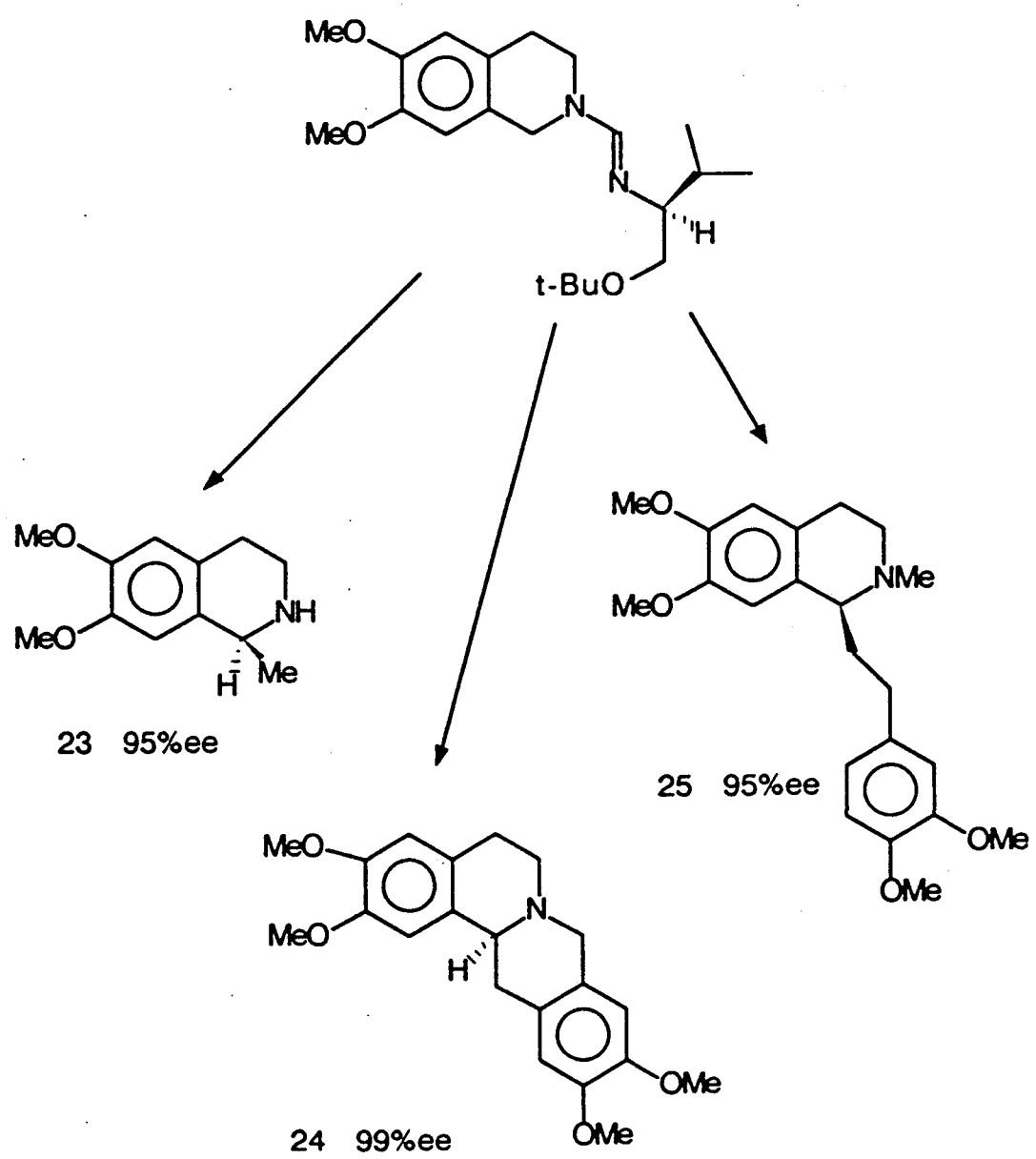
Figure 4: t-Butylether of valinol

The t-butylether of valinol (Figure 4) was prepared and used as a chiral auxiliary (29) and the asymmetric synthesis of (S)-1-alkyl-1,2,3,4-tetrahydroisoquinolines achieved in 93-99% ee (Scheme 6). In 1986 Dickman and Meyers (30) accomplished the asymmetric synthesis of (+)-ocoteine in 93% ee. The synthetic precursor was the known 2-methoxy-3,4-methylenedioxy-β-phenethylamine and the

SCHEME 6


OMe
O
O
NH
17
Me2N
N
t-BuO
18
OMe
O
O
N
N
19
t-BuO
a) BuLi
b)
MeO
MeO
Br
c) N2H4
d) HCHO, NaBH4
OMe
O
O
NR
H
20 R=H
21 R=Me
TTFA
OMe
OMe
OMe
O
O
NMe
H
MeO
OMe
22 93%ee
(S)-(+)-Ocoteine

SCHEME 7


MeO
MeO
N
N
H
t-BuO
MeO
MeO
NH
H
Me
23 95%ee
MeO
MeO
NMe
OMe
OMe
25 95%ee
MeO
MeO
N
H
OMe
OMe
24 99%ee

dihydroisoquinoline was obtained by Bischler-Napieralski ring closure. The desired amine 17 was obtained by reduction of the imine with $NaBH_4$. The formamidine 19 was prepared from the dimethylaminoformamidine of t-butylvalinol 18. Metalation of 19 was carried out with t-butyllithium and alkylation of the anion was achieved with 3,4-dimethoxybenzyl bromide. Hydrazinolysis afforded 20 which was N-methylated with formaldehyde-$NaBH_4$ to 21. The cyclization of 21 was effected with thallium(III) trifluoroacetate (TTFA) to afford (S)-(+)-ocoteine 22. The oxidative coupling proceeded without racemization.

In summary Meyers and coworkers have developed an efficient and useful pathway for the asymmetric synthesis of 1,2,3,4-tetrahydroisoquinoline alkaloids alkylated at C-1 by employing formamidines of high enantiomeric purity to induce asymmetry at C-1. The power of this technique was evident through the total synthesis of (-)-salsolidine 23, (-)-xylopinine 24, and (+)-homolaudanosine 25 among other 1,2,3,4-tetrahydroisoquinoline alkaloids (Scheme 7).

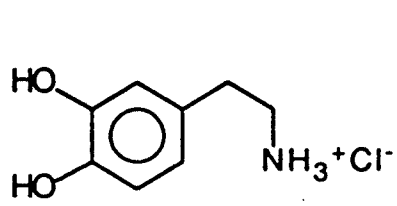
1.3.1.2 Condensations Using the Pictet-Spengler Reaction

MacLean, Szarek, and coworkers (15) in 1983 prepared tetrahydroisoquinolines using the Pictet-Spengler condensation between biogenic amines and aldoses. It was anticipated that the asymmetric sugar moiety would influence the stereoselectivity of the reaction forming the new chiral

center. The reaction of dopamine hydrochloride 26 with D-glucose 27 afforded the 6,7-dihydroxy-(1R)-and-(1S)-(D-glucopentitol-1'-yl)-1,2,3,4-tetrahydroisoquinoline hydrochlorides 28 in a diastereomeric ratio of 4:1 (Scheme 8). Dopamine hydrochloride 26 also reacted with 2,5-anhydro-D-mannose 29 to yield a 4:1 mixture of the (1R)- and (1S)-(α-D-arabinofuranosyl) 6,7-dihydroxy-1,2,3,4-tetrahydro-isoquinoline hydrochlorides 30 (Scheme 9). The resulting diastereomers were peracetylated using acetic anhydride and separated by column chromatography.

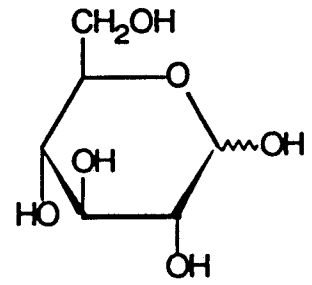
Further work related to that discussed above was reported by Z.Czarnocki et al. (16) in 1986. Using optically pure (R)-(+)-glyceraldehyde 31 and dopamine hydrochloride 26 as starting materials several 1-alkyl-1,2,3,4-tetrahydro-isoquinoline alkaloids were synthesized among which were (R)-(-)-calycotomine, (R)-(-)-N-methylcalycotomine and (S)-(-)-carnegine; all are cactus alkaloids (32). The Pictet-Spengler condensation of dopamine hydrochloride with (R)-(+)-glyceraldehyde gave a mixture of diastereomers 32a and 32b in approximately 9:1 ratio (Scheme 10). This high selectivity was explained on the basis of Cram's rule. Nucleophilic attack by the aromatic ring on the iminium salt was considered to be topographically influenced by the adjacent chiral center (Figure 5).

SCHEME 8



26

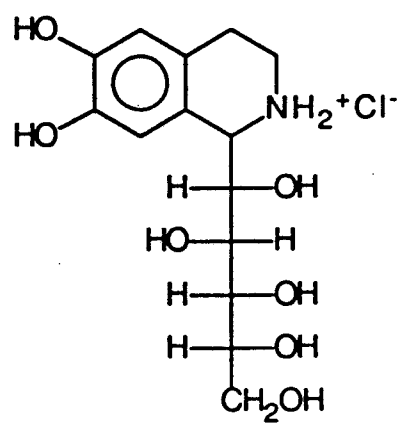
+



27

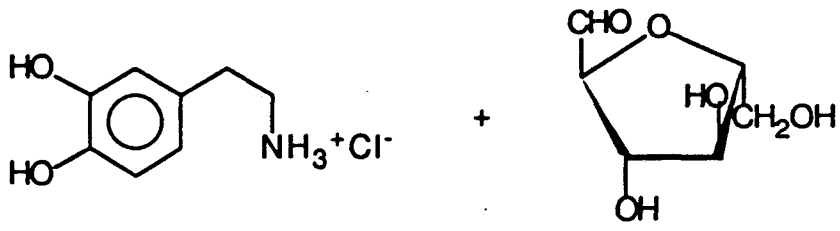
H_2O, Δ

48 h

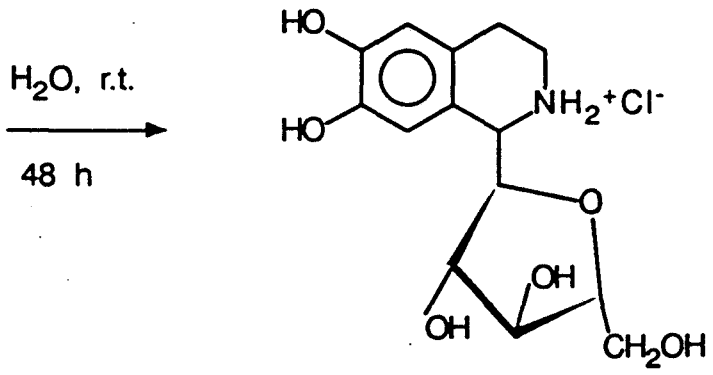


28 92%

SCHEME 9

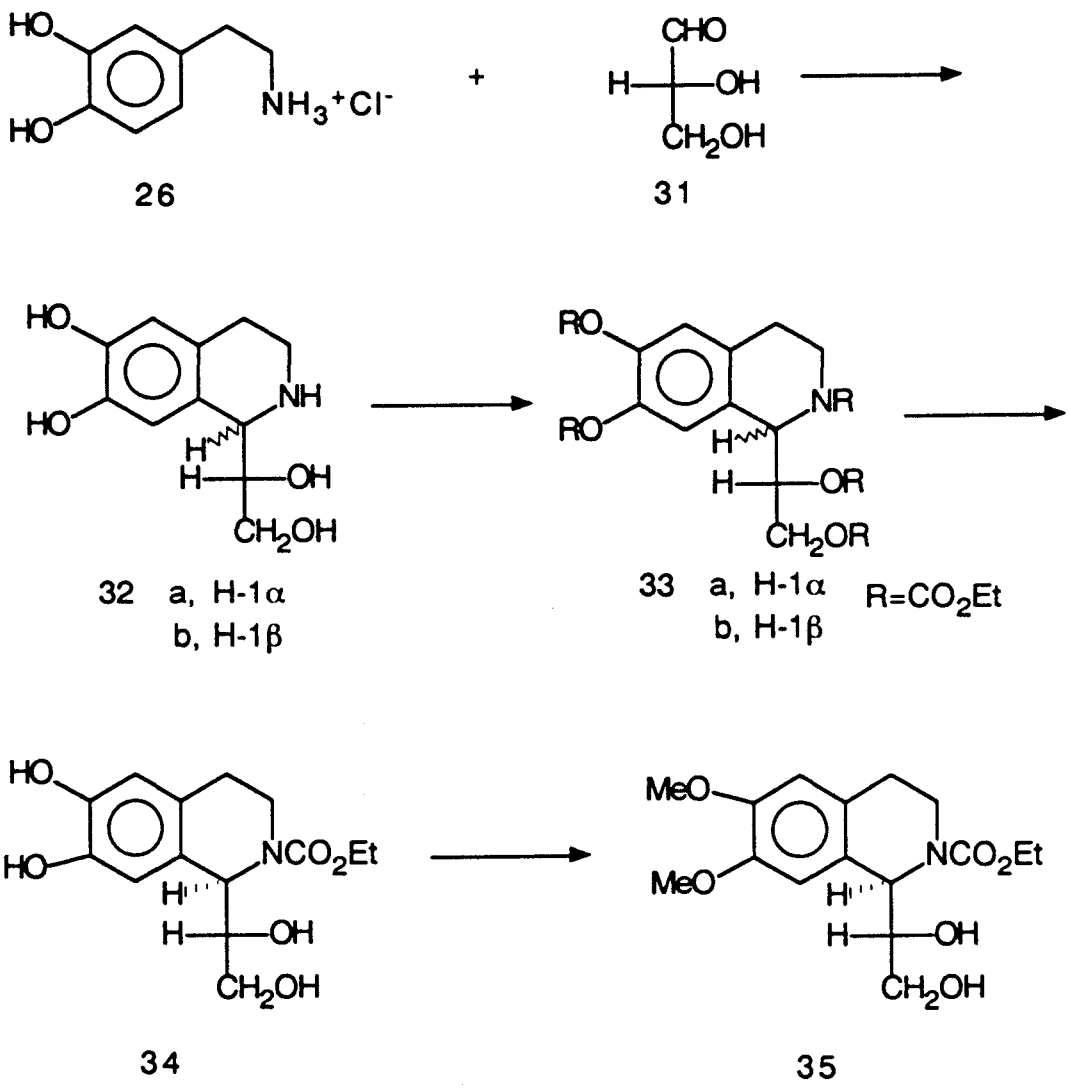


26 29



30 98%

SCHEME 10


HO
HO
NH3+Cl-
26
+
CHO
H
OH
CH2OH
31
HO
HO
NH
H
H
OH
CH2OH
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b, H-1β
RO
RO
NR
H
H
OR
CH2OR
33 a, H-1α
b, H-1β
R=CO2Et
HO
HO
NCO2Et
H
H
OH
CH2OH
34
MeO
MeO
NCO2Et
H
H
OH
CH2OH
35

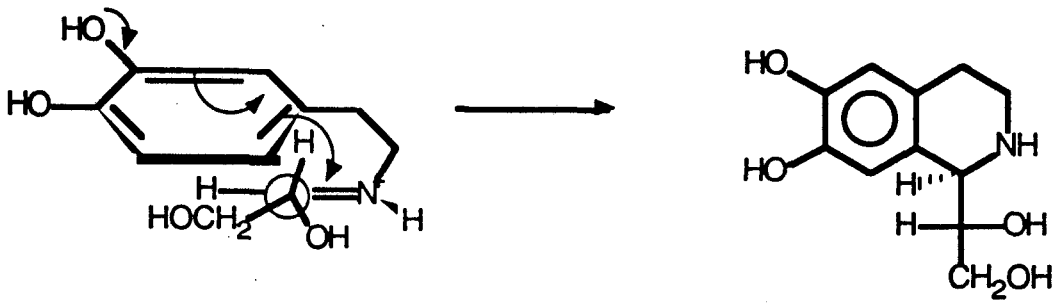
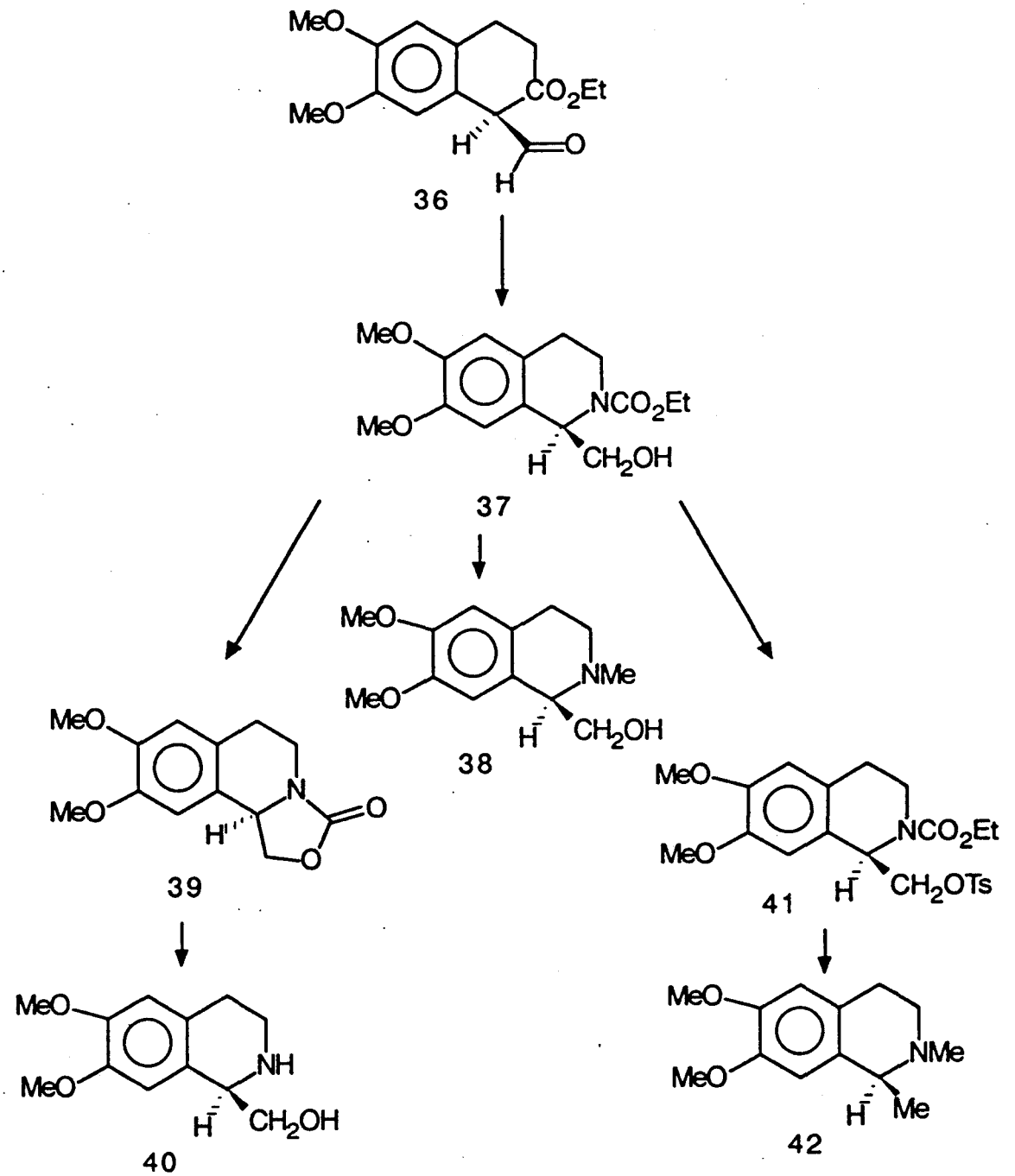


Figure 5: Nucleophilic attack on iminium salt

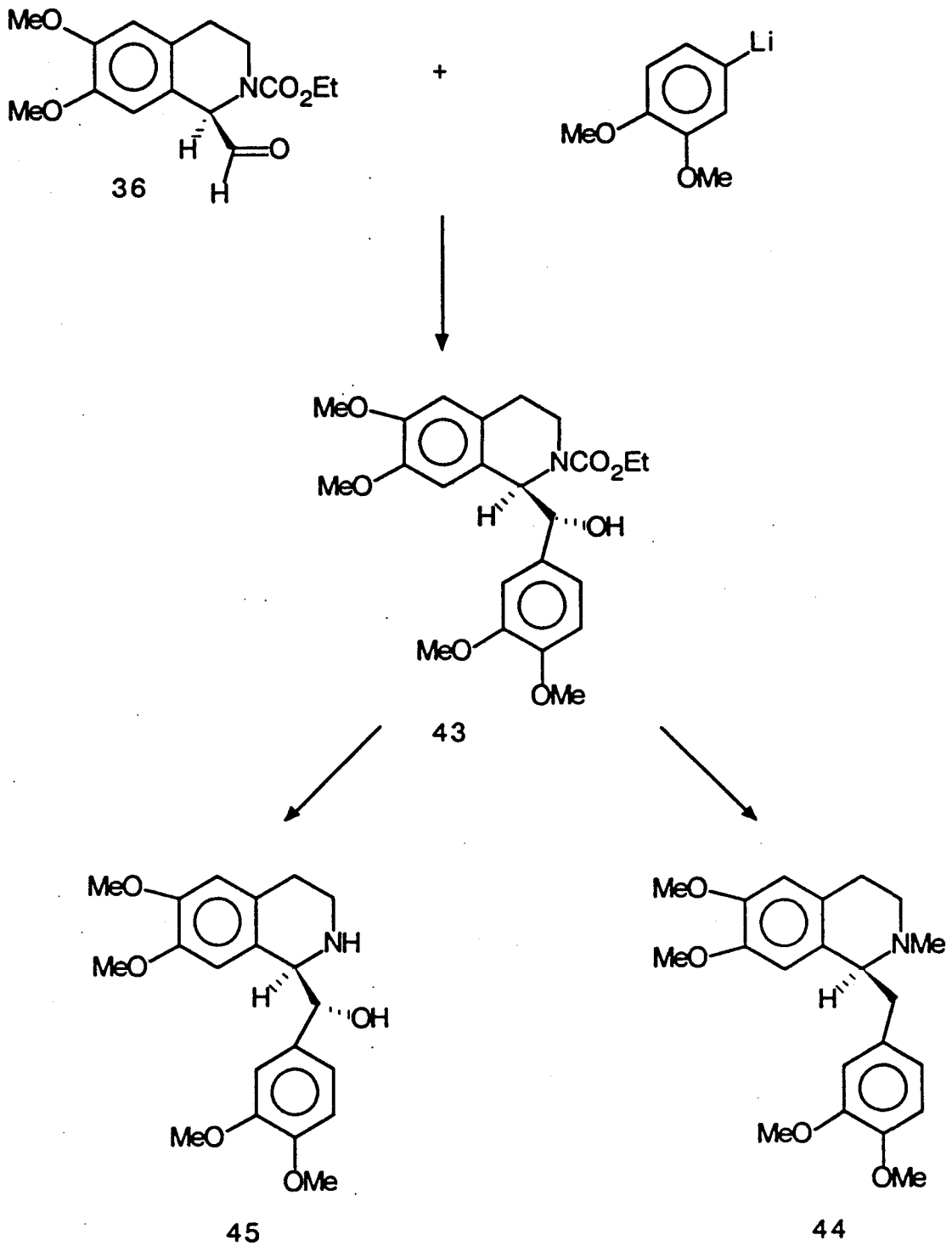
Treatment of 32a and b with ethyl chloroformate converted the amino group into a carbamate and the hydroxyl groups into carbonate esters. The major isomer 33a was separated by chromatography. The ester functions were removed using methanolic ammonia to give 34 and the phenolic hydroxyls were methylated using methyl iodide in the presence of potassium carbonate forming the optically active 6,7-dimethoxytetrahydroisoquinoline system 35. Periodate oxidation of 35 produced the aldehyde 36 which was reduced by $NaBH_4$ to 37. Treatment of 37 with lithium aluminum hydride afforded (R)-(-)-N-methylcalycotomine 38. (R)-(-)-Calycotomine 40 was prepared in 80% ee by treatment of 37 with 10% KOH in methanol to give the oxazolo[4,3-a]isoquinoline 39 which was hydrolysed in 10% NaOH in EtOH. Compound 37 was also used to synthesize (S)-(-)-carnegine 42 in 93% ee by reduction of the O-tosyl intermediate 41 using $LiAlH_4$. The procedure of sacrificing one chiral center for the induction of another is often referred to as sacrificial asymmetric synthesis (33) (Scheme 11).

SCHEME 11

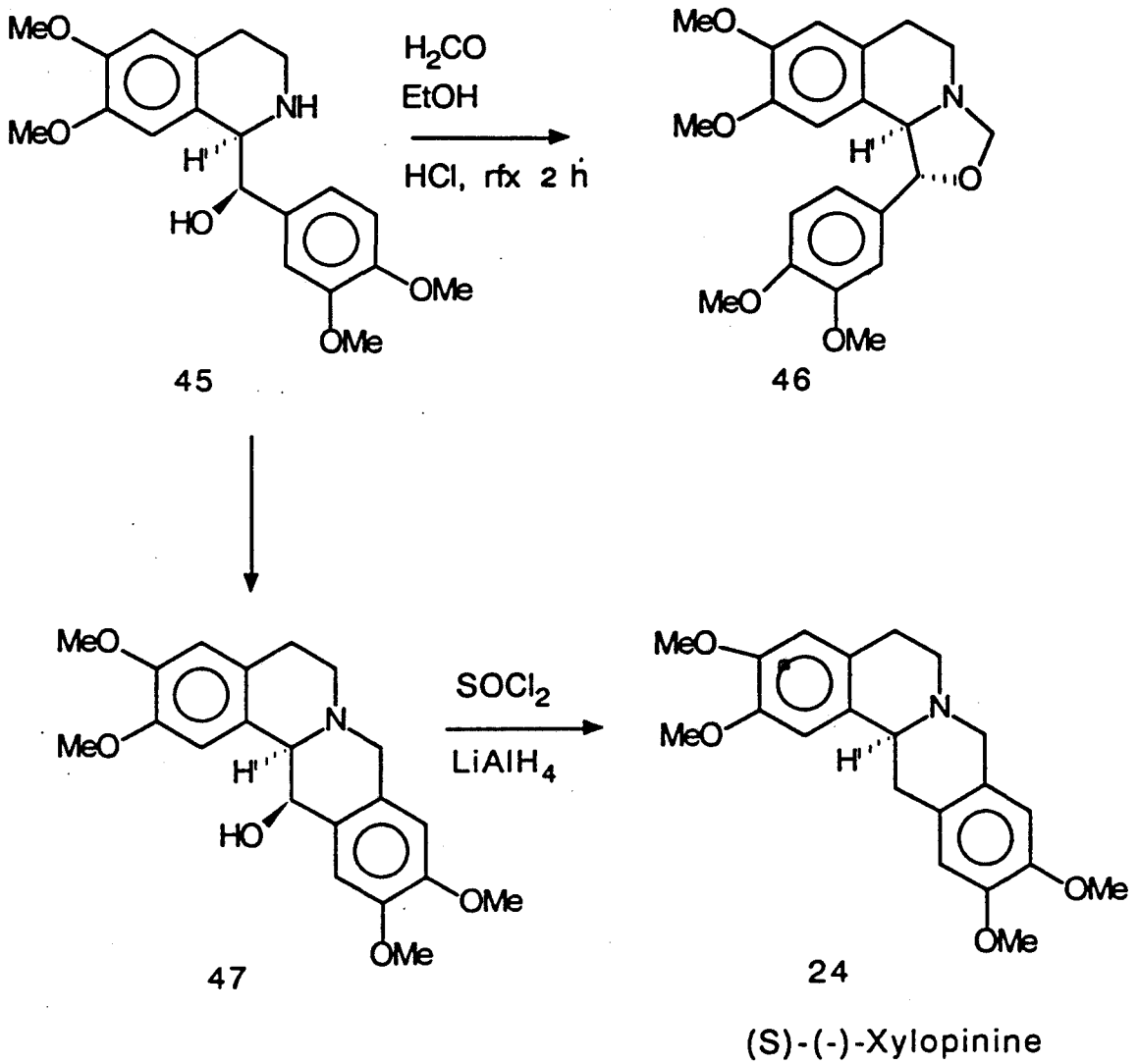

MeO
MeO
CO2Et
H
O
H
36
MeO
MeO
NCO2Et
H
CH2OH
37
MeO
MeO
NMe
H
CH2OH
38
MeO
MeO
N
O
H
O
39
MeO
MeO
NH
H
CH2OH
40
MeO
MeO
NCO2Et
H
CH2OTs
41
MeO
MeO
NMe
H
Me
42

The formation of the asymmetric aldehyde 36 is significant because it provides a methodology for obtaining 1-benzylisoquinolines (e.g. 43) with the generation of a second chiral center (Scheme 12).The isomer (R,R)-(+)-43 was obtained in 64% yield without a trace of the (R,S) isomer. The high diastereoselectivity may also be explained on the basis of Cram's rule. (S)-(+)-Laudanosine 44 in 79% ee was formed from (+)-43 by treatment with thionyl chloride and pyridine in THF at -10°C followed by reduction with lithium aluminum hydride. The method employed to remove the hydroxyl group did not cause racemization at C-1. Hydrolysis of the carbamate 43 with NaOH/EtOH gave the secondary amine, (R,R)-(+)-hydroxynorlaudanosine 45. The latter was used to form the protoberberine 24 via a Mannich reaction with formaldehyde. It is interesting to note that, using ethanol as the solvent, the oxazoloisoquinoline 46 was formed in good yield whereas, using water as the solvent, 47 was formed in good yield. The deoxygenation of 47 was completed (33) to yield the target compound (S)-(-)-xylopinine 24 in 92% ee (Scheme 13). (8S,14S)-Coralydine 52 was prepared by a Bischler-Napieralski cyclization of the O,N-diacetyl compound 48 to afford the iminium salt 49. The imine was reduced diastereoselectively by $NaBH_4$ to give (8S,13R,14R)-13-acetoxy-8-methyl-2,3,10,11-tetramethoxytetrahydroproto-berberine 50 in 89% yield. Hydrolysis with NaOH/MeOH to 51 followed by deoxygenation yielded the target molecule 52 (Scheme 14).

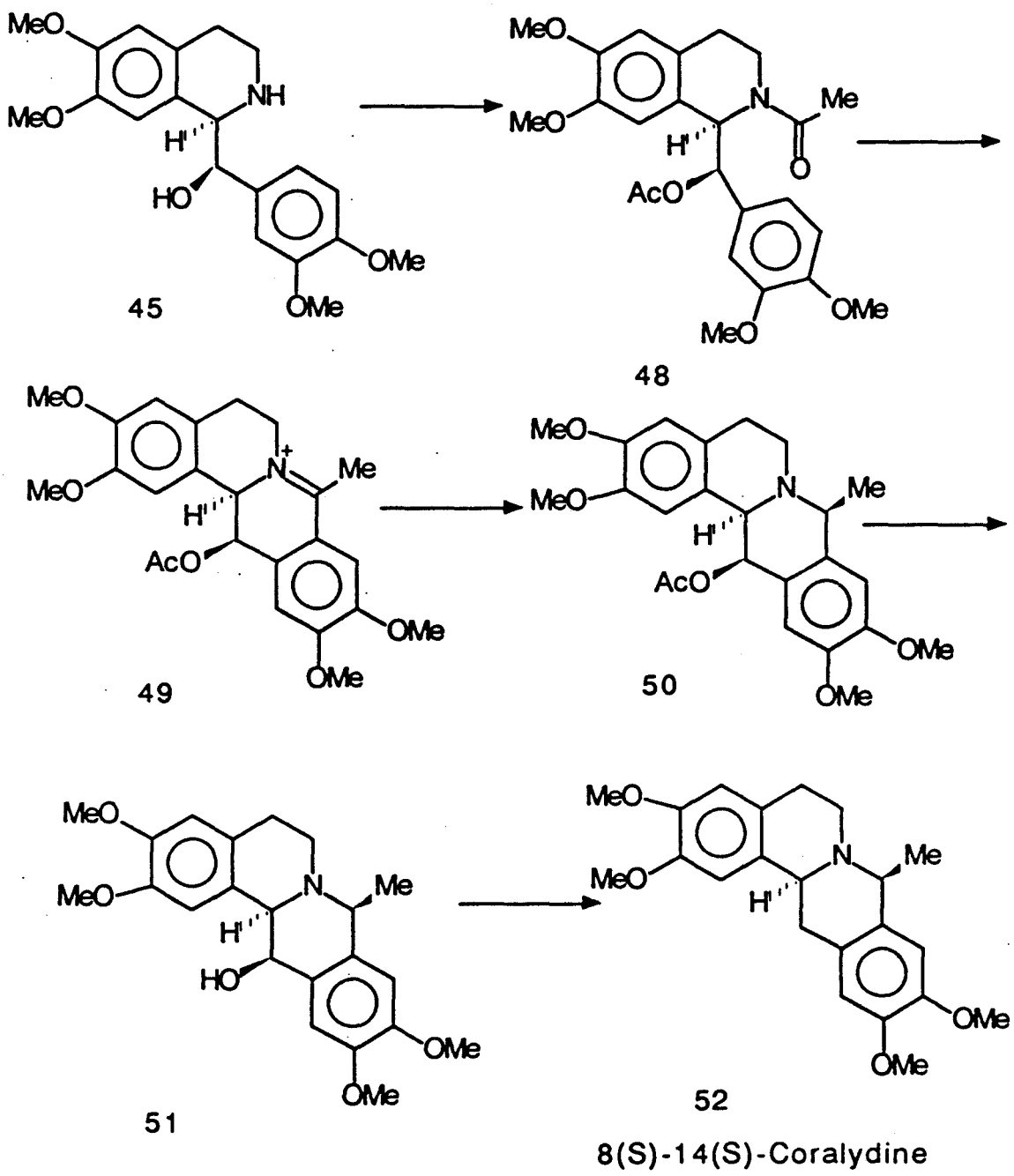
SCHEME 12


MeO
MeO
NCO2Et
H
O
H
36
+
Li
MeO
OMe
MeO
MeO
NCO2Et
H
OH
MeO
OMe
43
MeO
MeO
NH
H
OH
MeO
OMe
45
MeO
MeO
NMe
H
MeO
OMe
44

SCHEME 13


MeO
MeO
NH
H
HO
OMe
OMe
H_2CO
EtOH
HCl, rfx 2 h
45
MeO
MeO
N
H
O
MeO
OMe
46
MeO
MeO
N
H
HO
OMe
OMe
47
$SOCl_2$
$LiAlH_4$
MeO
MeO
N
H
OMe
OMe
24
(S)-(-)-Xylopinine

SCHEME 14


MeO
MeO
NH
H
HO
OMe
OMe
45
MeO
MeO
N
Me
O
H
AcO
OMe
MeO
OMe
48
MeO
MeO
N+
Me
H
AcO
OMe
OMe
49
MeO
MeO
N
Me
H
AcO
OMe
OMe
50
MeO
MeO
N
Me
H
HO
OMe
OMe
51
MeO
MeO
N
Me
H
OMe
OMe
52
8(S)-14(S)-Coralydine

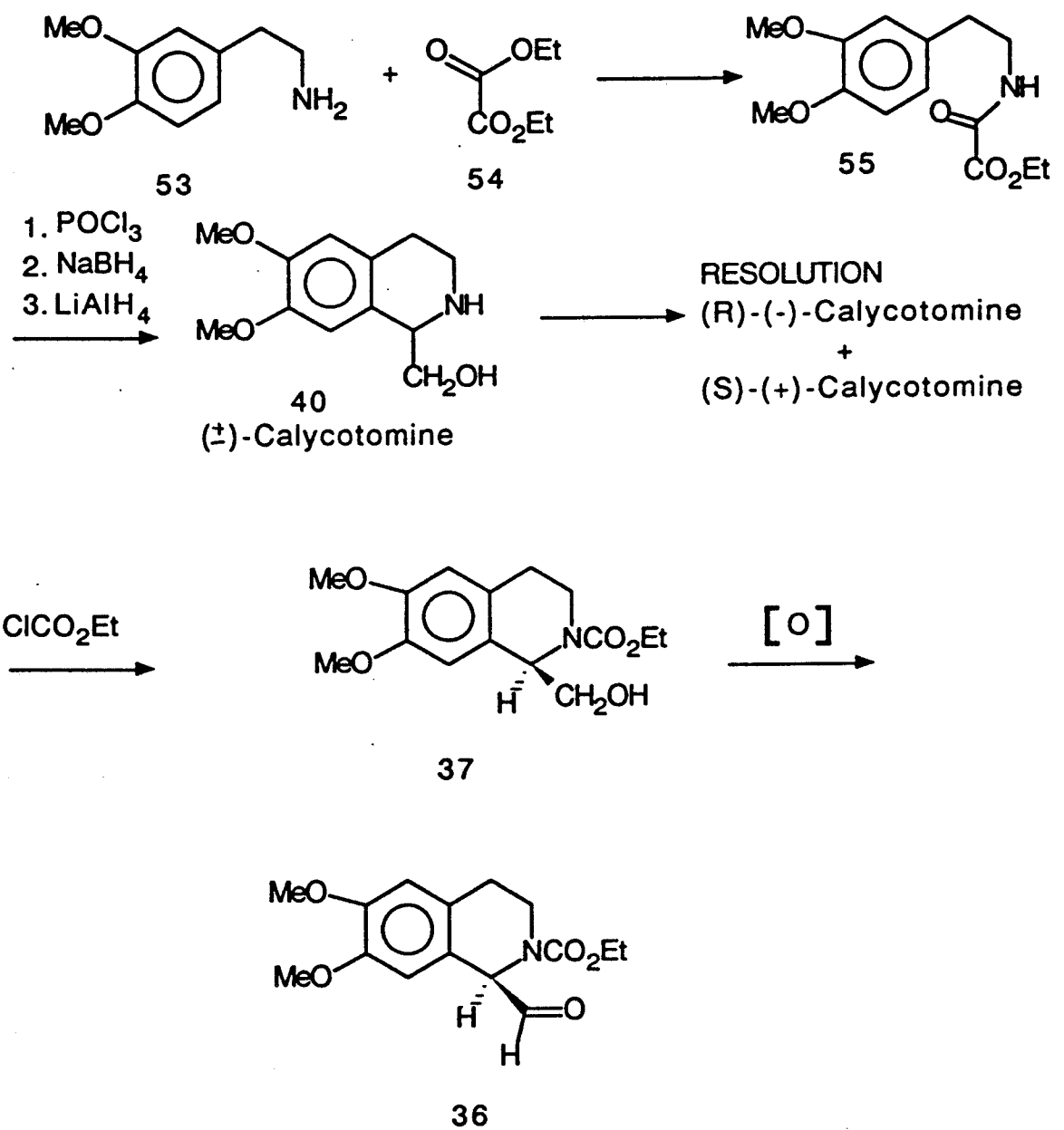
1.3.1.3 Condensations Using Bischler-Napieralski Cyclization

The importance of the aldehyde 36 was recognized for its potential use in the synthesis of benzylisoquinolines and related systems and also for effecting asymmetric synthesis of 1-hydroxyalkylisoquinolines. Because the former route to obtain the aldehyde was cumbersome, a new synthesis was devised by Z.Czarnocki et al. (17) to obtain the aldehyde more conveniently (Scheme 15).

The amide 55 was formed by the condensation of 3,4-dimethoxyphenethylamine 53 with diethyl oxalate, 54. The Bischler-Napieralski cyclization was carried out using $POCl_3$ (34) and $NaBH_4$ was used to reduce the resulting imine. $LiAlH_4$ reduced the ester to the alcohol affording (+)-calycotomine 40. Calycotomine was resolved by the method of Brossi and Burkhardt (35) using optically pure D-tartaric acid. Protection of the amine by treatment with ethyl chloroformate afforded the carbamate 37 which underwent a Swern-type oxidation to the aldehyde 36.

Dornyei and Szantay (36) established a method for obtaining 1-substituted-1,2,3,4-tetrahydroisoquinolines with three chiral centers. Starting with derivatized D-tartaric acid 56 and the appropriate phenethylamine 53, the amide 57 was formed which could then undergo a Bischler-Napieralski ring closure 58. Removal of the acetyl groups by methanolysis left the imine 59 which underwent stereoselective reduction

SCHEME 15


MeO
MeO
NH2
53
+
O
OEt
CO2Et
54
MeO
MeO
NH
O
CO2Et
55
1. POCl3
2. NaBH4
3. LiAlH4
MeO
MeO
NH
CH2OH
40
(±)-Calycotomine
RESOLUTION
(R)-(-)-Calycotomine
+
(S)-(+)-Calycotomine
ClCO2Et
MeO
MeO
NCO2Et
H
CH2OH
37
[O]
MeO
MeO
NCO2Et
H
O
H
36

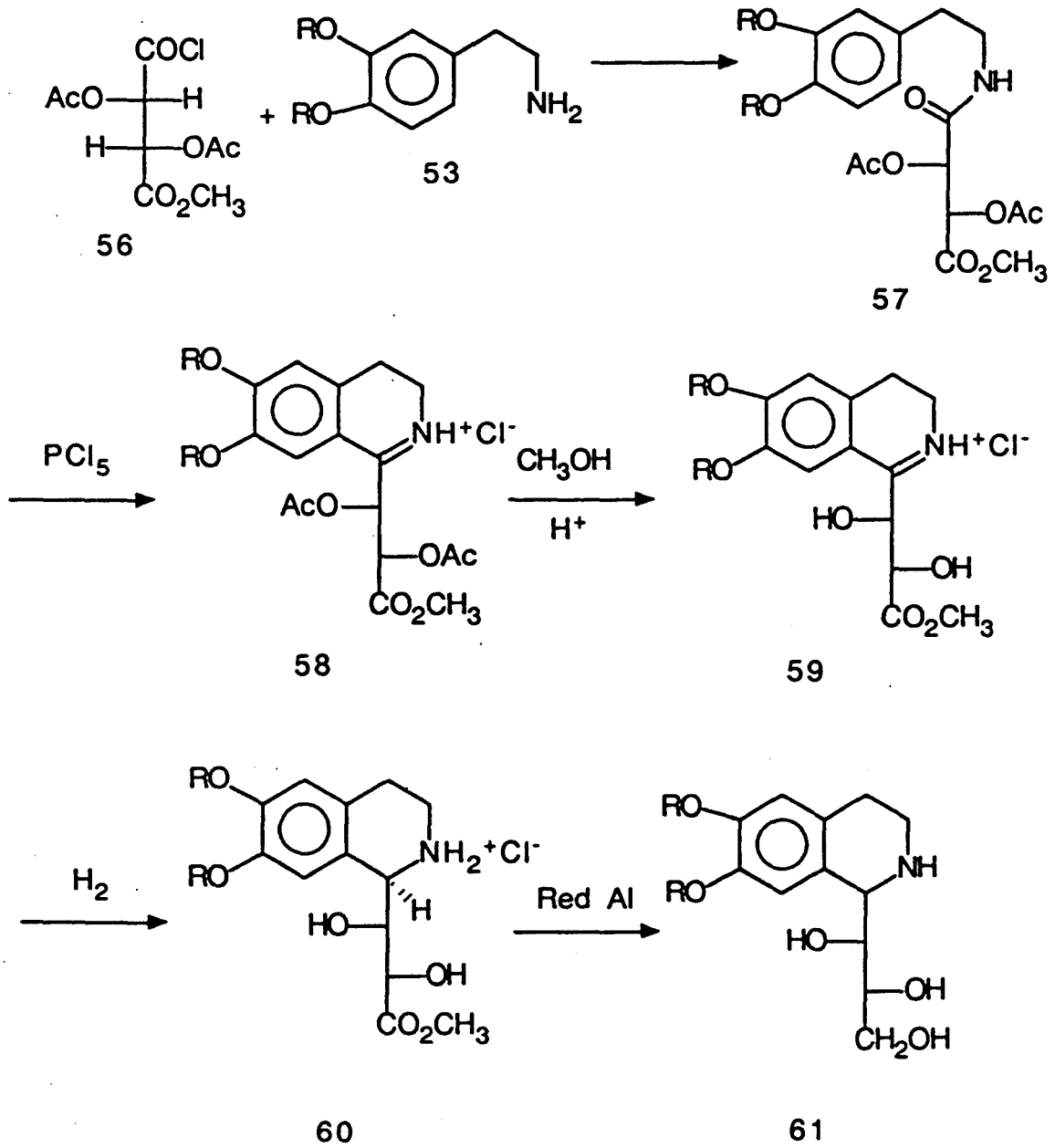
to 60. Reaction of the hydrochloride with sodium bis-(2-methoxyethoxy) aluminum hydride (Red-Al) afforded 61 (scheme 16). Compound 61 could also be obtained directly from 59 using Red-Al. The (1S,1'S,2'S) isomer could be selectively crystallized over the (1R,1'S,2'S) isomer.

MacLean and coworkers (37) recognized the importance of this method for obtaining the aldehyde 36 in good optical yield from the diol 60 by protecting the nitrogen as a carbamate. The hydroxyl groups were simultaneously esterified to carbonates but methanolysis produced the diol substituted at nitrogen. Sodium periodate oxidation afforded the aldehyde 36.

1.3.1.4 Cyclization of Optically Active N-Oxyacyliminium salts

Kano et.al. (24) prepared optically active 1-(α -hydroxyalkyl)-1,2,3,4-tetrahydroisoquinolines by generating optically active N-oxaacyliminium ion intermediates. The azide 62 when treated with methyl (S)-(+)-lactate, methyl (S)-(+)-mandelate or methyl (R)-(-)-mandelate gave the corresponding carbamates 63a-c. Reduction of 63a-c using diisobutylaluminum hydride afforded 64a-c. Treatment with formic acid generated the acyliminium ion 65 which underwent cyclization to the 1-substituted oxazolo[4,3-a]isoquinolines 66a-c. Lithium aluminum hydride reduction of 66a-c yielded the 1-(-hydroxyalkyl)-1,2,3,4-tetrahydroisoquinolines 67a-c.

SCHEME 16


COCl
AcO
H
H
OAc
CO2CH3
56
RO
RO
NH2
53
NH
O
AcO
OAc
CO2CH3
57
PCl5
NH+Cl-
AcO
OAc
CO2CH3
58
CH3OH
H+
HO
OH
59
H2
NH2+Cl-
HO
H
OH
60
Red Al
NH
HO
OH
CH2OH
61

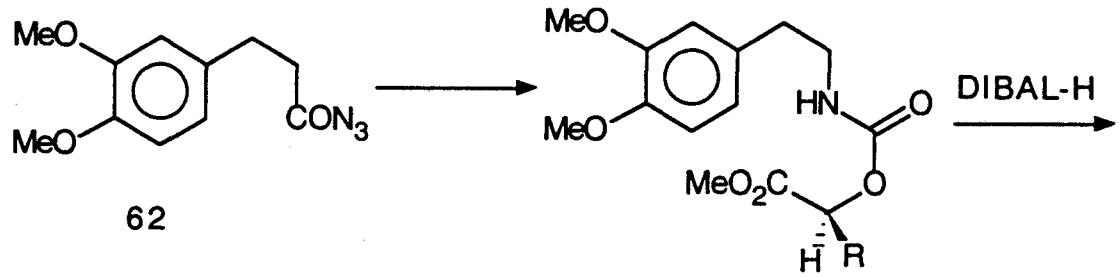
The authors do not report enantiomeric excess values; however, they showed that the configuration of the starting material influenced the stereochemistry in the ring closure reaction (Scheme 17).

1.3.1.5 Reduction of Imines and Enamides Using Chiral Complexes

T.Iwakuma and coworkers (21) studied the reduction of 3,4-dihydropapaverine 68 with a chiral sodium acyloxyborohydride 69 prepared from N-acyl prolines (Scheme 18). The acyloxy borohydrides were prepared using one equivalent of $NaBH_4$ and three equivalents of the (S)-N-acylproline, where $R^1=R^2=-(CH_2)_3-$ and $R^3=-OCH_2Ph$, Me, Ph or -O-t-Bu (Scheme 19). These reductions provided (S)-norlaudanosine hydrochloride 70 in 55-60% ee. Triacyloxyborohydrides formed from other α-amino acids, where R^1= Me, $CHMe_2$ or CH_2Ph, R^2= H and $R^3=-CH_2Ph$, were less effective affording products in 8-16% ee.

Using the (S)-N-acylproline oxyborohydride derivative where $R^3=-OCH_2Ph$ and by using a halogenated alkane as the solvent (ie. CH_2Cl_2 or $CHCl_2CH_3$) optical yields of 70-86% were obtained in the synthesis of (S)-salsolidine 23, (S)-norcryptostyline I and (S)-norcryptostyline II from their corresponding cyclic imines; the latter were obtained via the Bischler-Napieralski reaction (Figure 6). The reduction proceeds in good chemical yield (85-90%).

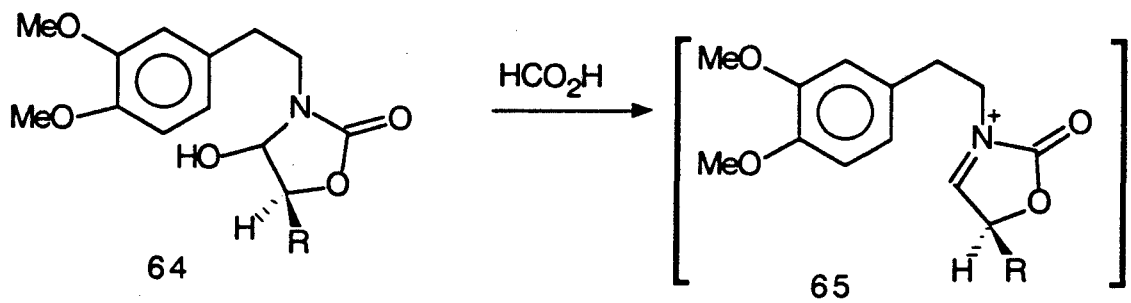
SCHEME 17



62

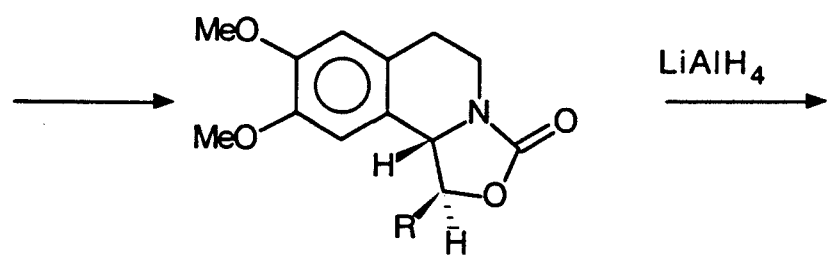
63 a, R=CH_3
b, R=C_6H_5

c, enantiomer of b



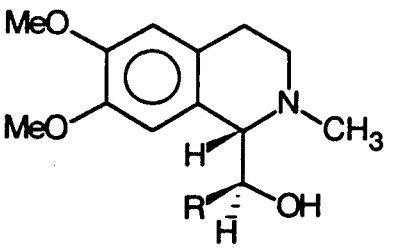
64

65

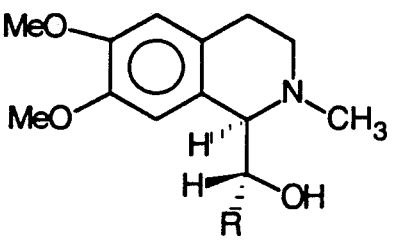


66 a, R = CH_3
b, R = C_6H_5
c, enantiomer of b

SCHEME 17 (continued)

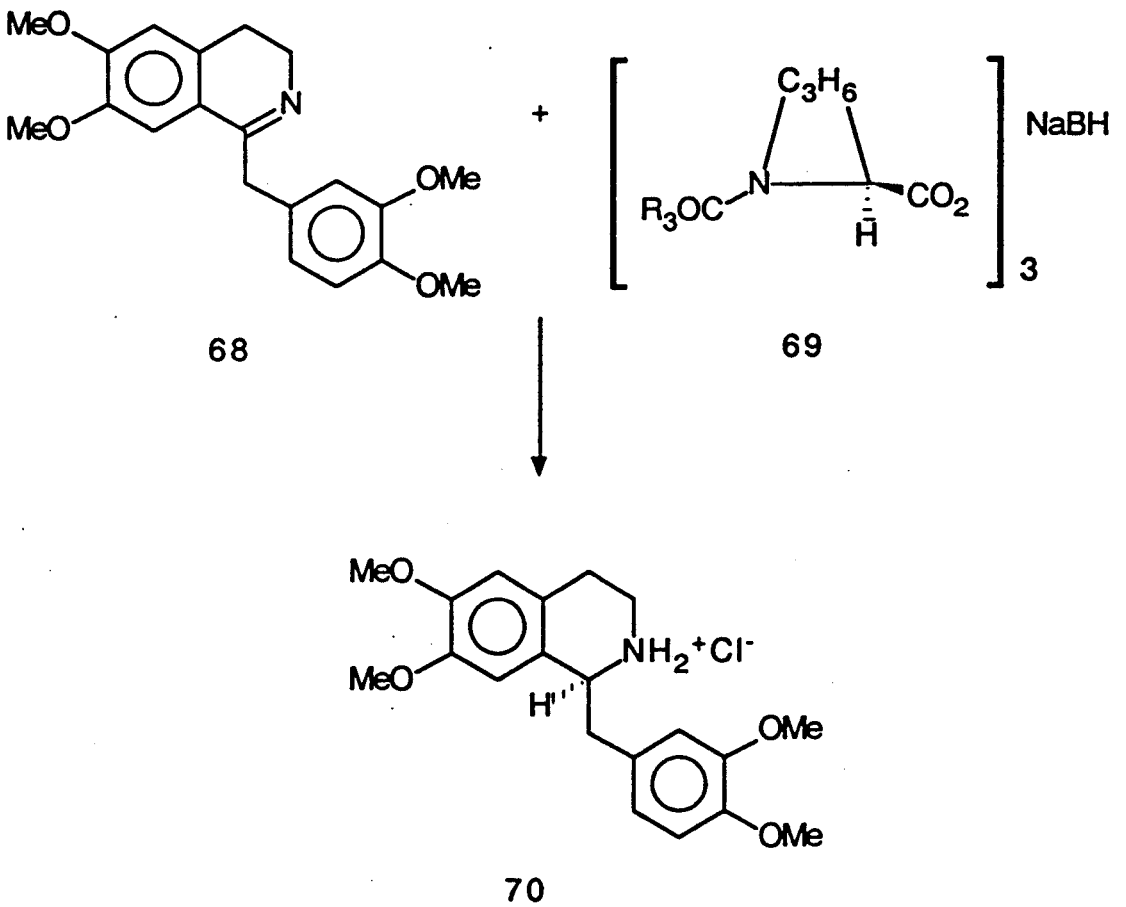


67 a, R = CH_3
b, R = C_6H_5

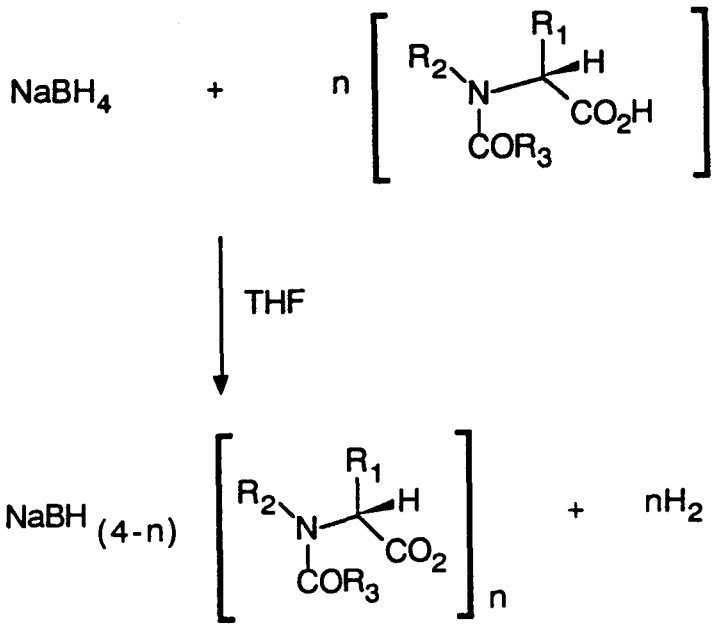


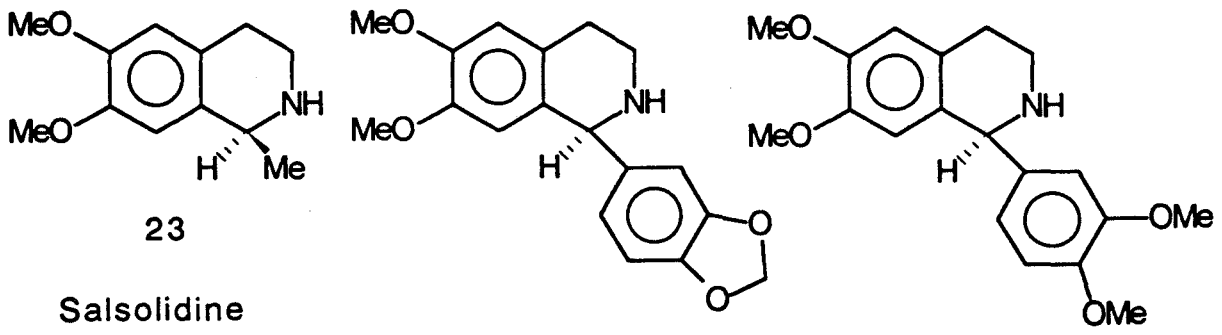
67 c, R = C_6H_5

SCHEME 18


MeO
MeO
N
OMe
OMe
68
+
C3H6
N
R3OC
CO2
H
NaBH
3
69
MeO
MeO
NH2+Cl-
H
OMe
OMe
70

SCHEME 19





23

Salsolidine

Norcryptostyline I

Norcryptostyline II

Figure 6: Tetrahydroisoquinoline reduction products using a chiral complex

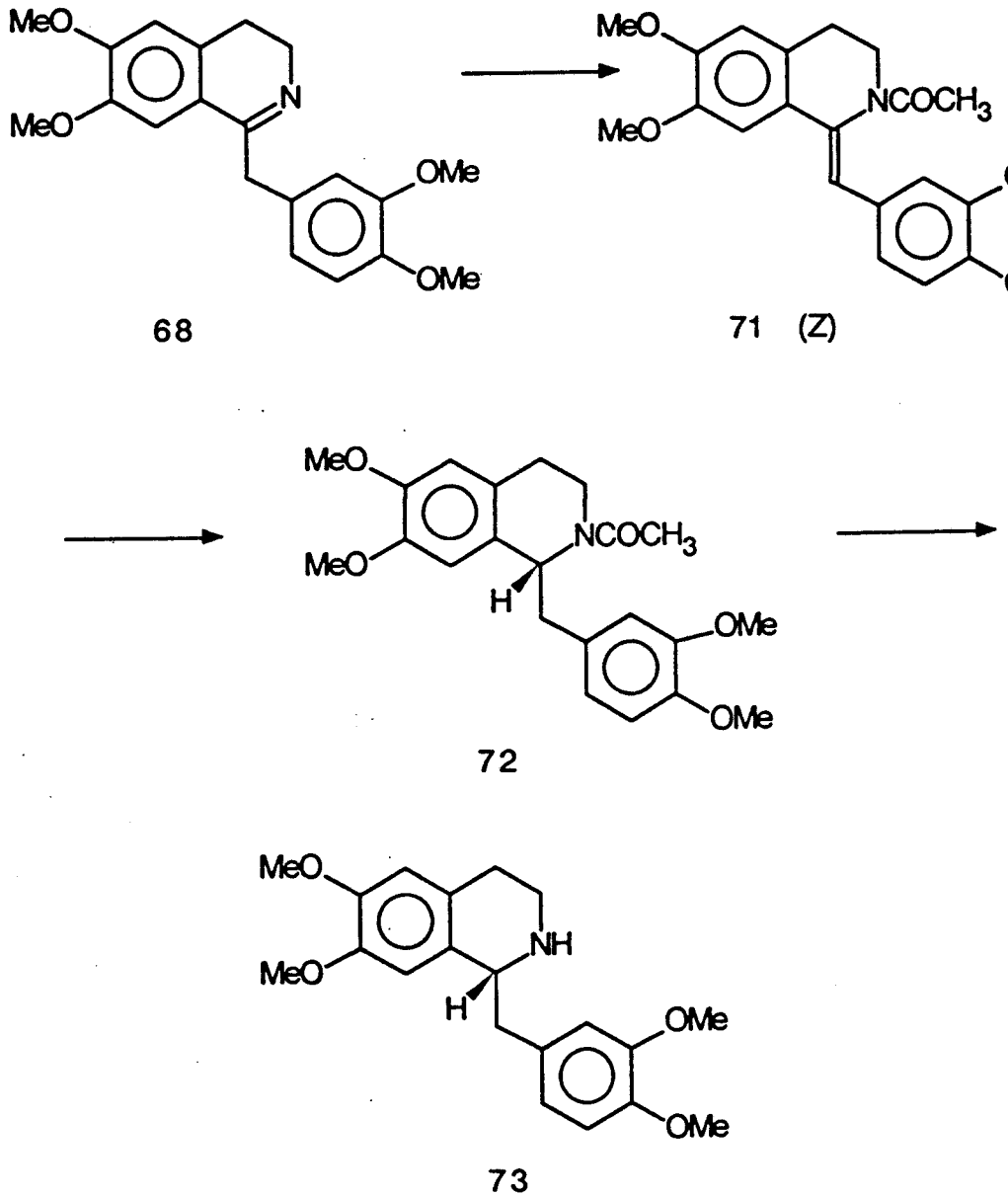
Kagan et al. (22) have reduced the imine 68 using a chiral rhodium complex obtaining 1,2,3,4-tetrahydropapaverine 73 (Scheme 20) in an enantiomeric excess of 38%.

Noyori et.al. (38) reduced enamides using a chiral ruthenium complex and, depending on the ligands, they were able to predict the formation of (1R) or (1S) products. The enamide substrates were prepared from 3,4-dihydropapaverine 68 by treatment with acyl chlorides and triethylamine. Introduction of a catalytic amount of the chiral ruthenium complex under H_2 induced the asymmetric reduction of 71 (Z) to 72. (R)-Tetrahydropapaverine 73 was obtained by deacetylation of 72 in 95% ee (Scheme 20).

1.3.1.6 Photochemical Enamide Cyclization

Kametani et al. (18) in 1981 reported the synthesis of

SCHEME 20



68 71 (Z) 72 73

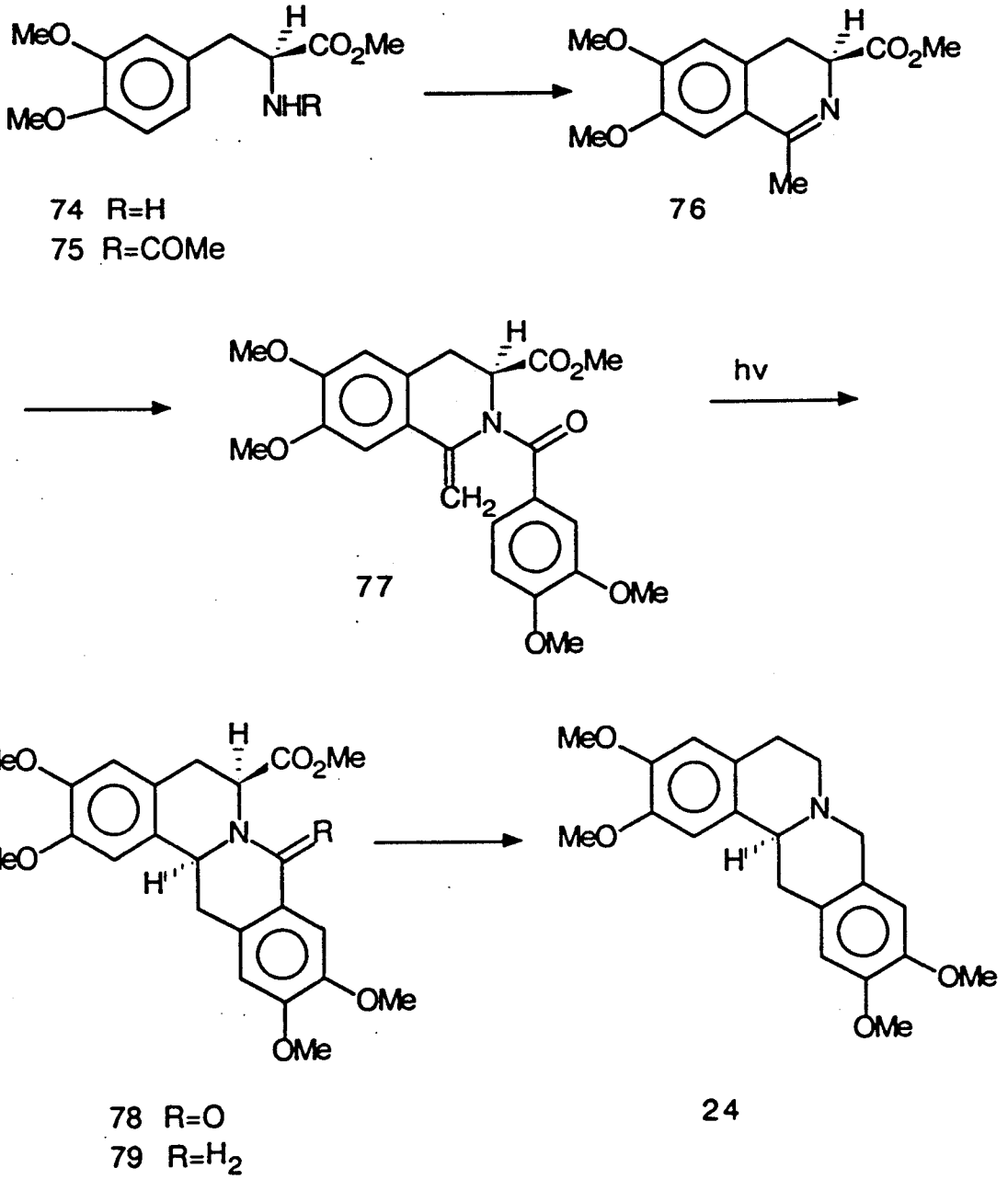
optically active xylopinine 24 in 95% ee by irradiation of enamide 77. The enantiomerically pure amino acid, 74 was converted into 75 using acetic anhydride in pyridine and cyclized with $POCl_3$ in acetonitrile to afford the 3,4-dihydro-1-methylisoquinoline 76. Treatment of 76 with 3,4-dimethoxybenzoyl chloride gave the enamide 77 which was irradiated using a high pressure mercury lamp fitted with a pyrex filter. The photolysis was allowed to proceed for 5 h at room temperature affording the lactam 78 in 73% yield. Compound 78 was converted to 24 using conventional methods. The above mentioned appears to be the first application of 1,3-asymmetric induction by photolysis in isoquinoline alkaloid synthesis (Scheme 21).

Ninomiya and coworkers (19), have also reported the enantioselective synthesis of xylopinine 24 under reductive conditions by employing a chiral metal hydride prepared from lithium aluminum hydride and quinine in the solution undergoing photolysis.

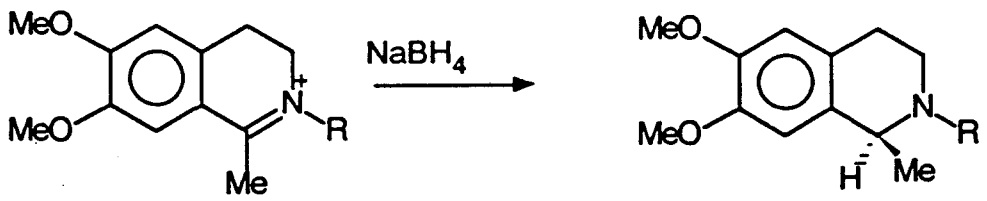
1.3.1.7 Reduction of Chiral 3,4-Dihydroisoquinolinium Salts

Kametani and Okawara (23) studied the reduction with $NaBH_4$ of a series of chiral imines 80 to 81. Hydrogenolysis of the product amines 81 over 10% palladium/charcoal yielded optically active salsolidine 23 in enantiomeric excesses of 15-44% (Scheme 22). When the R groups were derived from the (R)-(+)-amines (R)-(+)-salsolidine was obtained and when the

SCHEME 21

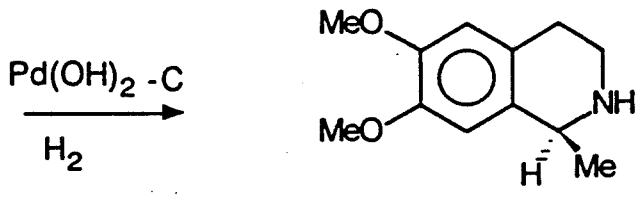


SCHEME 22



80 R=(R)-(+)-PhCHMe
R=(S)-(-)-PhCHMe
R=(S)-(-)-PhCHEt
R=(S)-(-)-$C_{10}H_7$CHMe

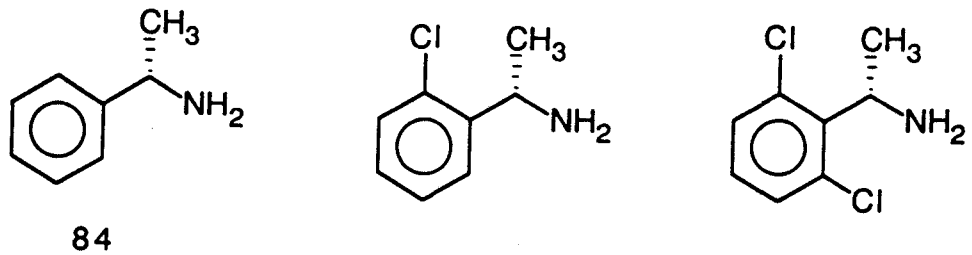
81



23 %ee
39-41
36-44
15-21
28-31

R group was derived from a (S)-(-)-amine (S)-(-)-salsolidine was obtained.

Polniaszek and Kaufman (39) recently reported the synthesis of (S)-(-)-salsolidine in 98% ee by reducing with sodium borohydride the corresponding chiral iminium salt of type 82 affording 83 (Scheme 23). The chiral adjuvant was removed from 83 to afford 23. The chiral moieties on nitrogen were chlorinated derivatives of 84 (Figure 7).
The stereoselectivity was shown to increase with an increase relative to 84 with introduction of chlorine at the o-positions.



84

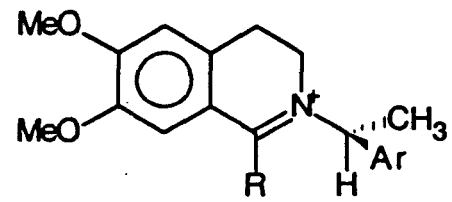
Figure 7: (S)-(-)-α -Phenethylamine and chlorinated derivatives

1.4 Ophiocarpine

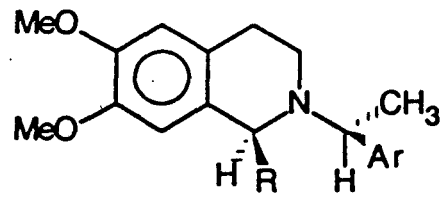
One of the initial objectives of this work was to synthesize ophiocarpine 85 in its naturally occurring form, (-)-ophiocarpine. Ophiocarpine was first isolated in 1939 by Manske (40) from Corydalis ophiocarpa (0.25% abundance), a plant native to China.

Ophiocarpine is one of two protoberberines containing a

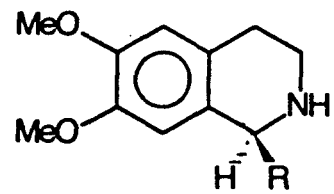
SCHEME 23



82



83



23

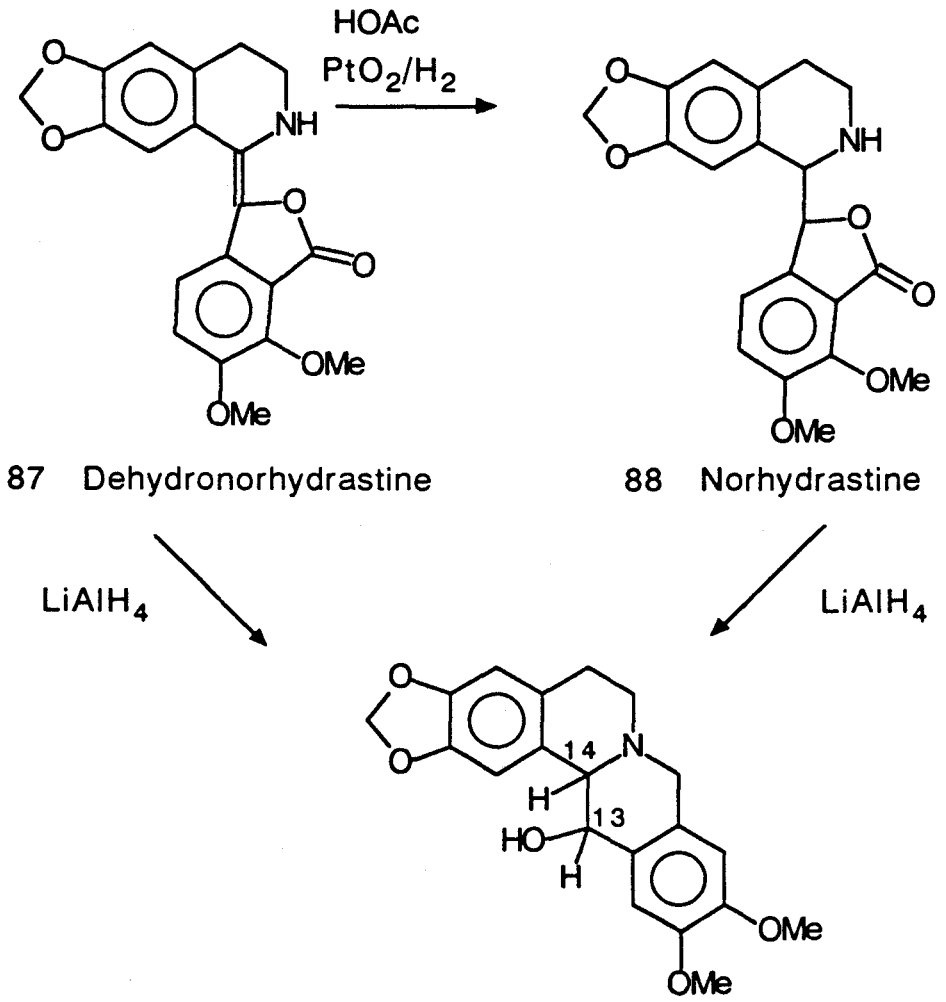
hydroxyl group at C-13 (41) and it is interesting to note that the hydroxyl is in the same position that it occupies in the phthalideisoquinolines and as that in decumbensine, a 1-benzyl-1,2,3,4-tetrahydroisoquinoline.

1.4.1 Synthesis of Ophiocarpine

The first synthesis of ophiocarpine was reported by Govindachari and Rajadurai (42) in 1957 (Scheme 24). They were interested in ophiocarpine because it was a possible link between the protoberberine and the protopine alkaloids. N-(3,4-Methylenedioxyphenethyl)-meconine-β-carboxyamide was prepared and cyclized by the method of Perkin et al. (43) to yield dehydronorhydrastine 87. Reduction of the enamine with acetic acid and Adams' catalyst in hydrogen produced norhydrastine, 88. Lithium aluminum hydride reduction of 88 afforded (±)-ophiocarpine 85 (C-13 H and C-14 H are cis) and (±)-epiophiocarpine 86, its epimer (C-13 H and C-14 H are trans)(Scheme 24). Govindachari and co-workers (44) found later that 87 could be converted directly to 85. In 1967, Elliot (45) prepared both (±)-ophiocarpine and (±)-epiophiocarpine starting from berberinium chloride 89 which was reduced in pyridine with sodium borohydride to afford the dihydroberberine 90. Compound 90 was hydrated by the hydroboration-oxidation method producing (±)-ophiocarpine 85 and (±)-epiophiocarpine 86 (Scheme 25).

In 1977 Kametani and co-workers (46) reported the

SCHEME 24



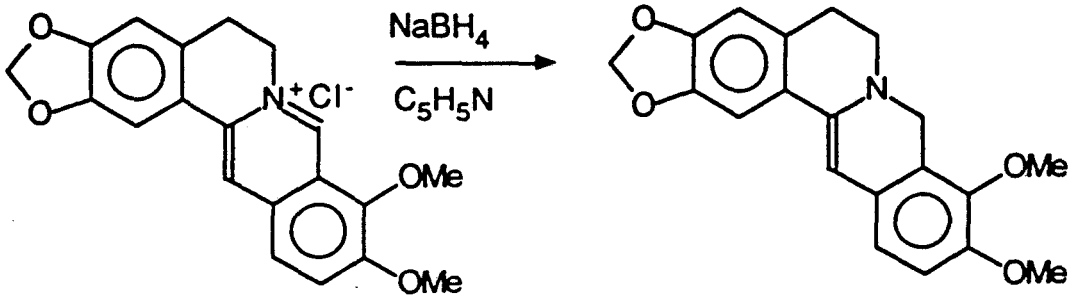
87 Dehydronorhydrastine

88 Norhydrastine

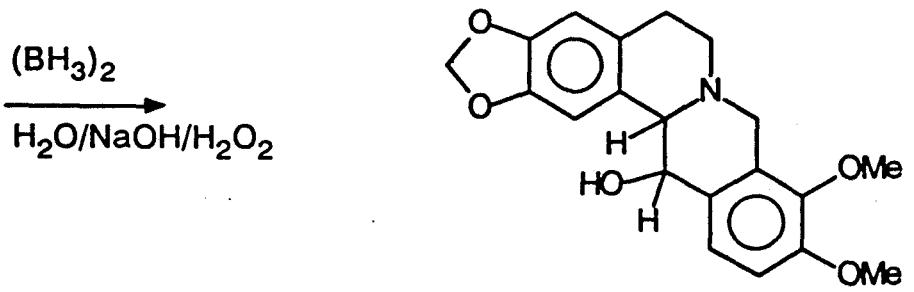
85 (±) -Ophiocarpine (C-13 OH and C-14 H are trans)

86 (±) -Epiophiocarpine (C-13 OH and C-14 H are cis)

SCHEME 25



89 90 Dihydroberberine



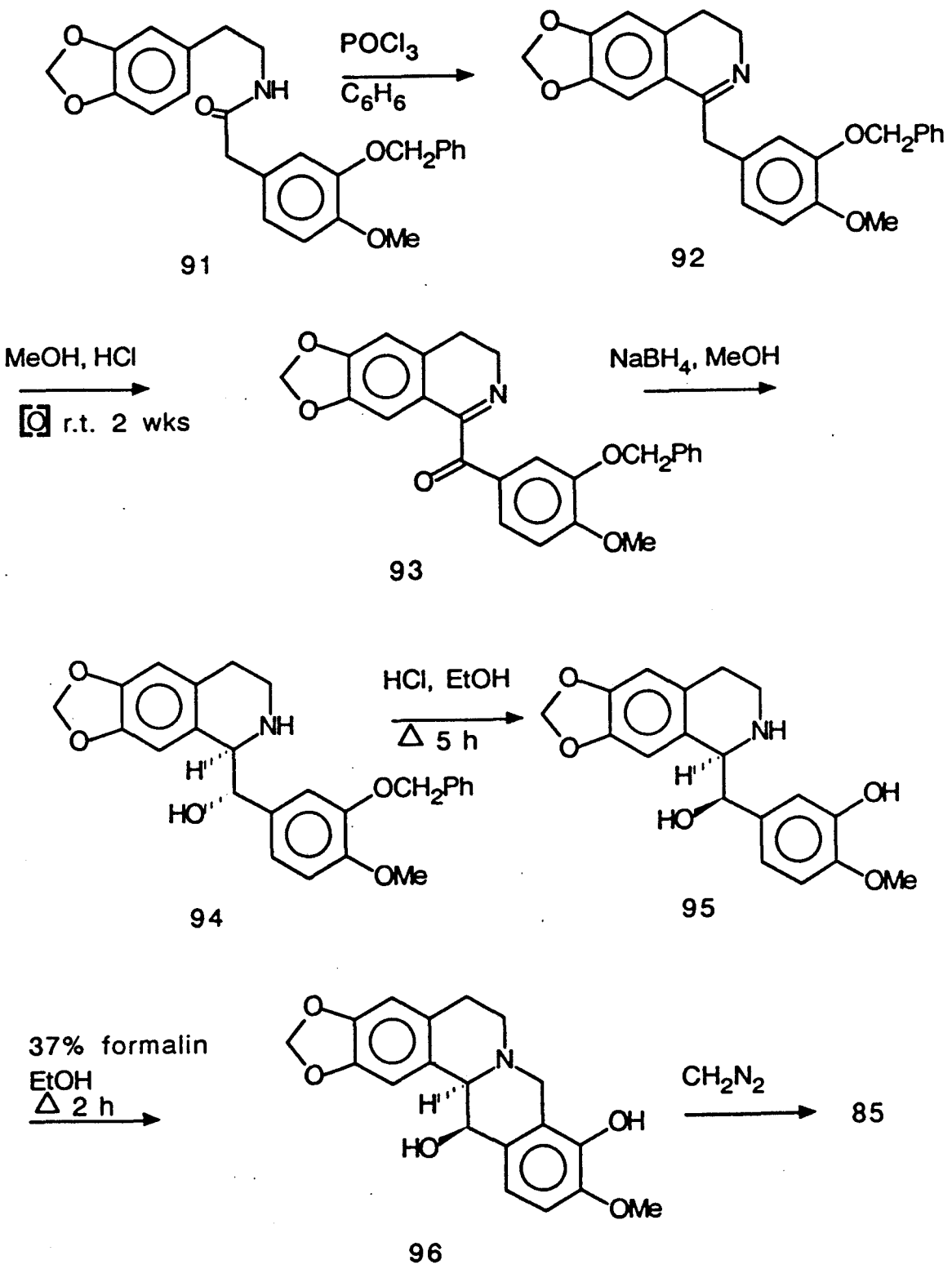
85 (±)-Ophiocarpine
86 (±)-Epiophiocarpine

synthesis of (±)-ophiocarpine as well as a similar synthesis for (±)-epiophiocarpine. They were interested in ophiocarpine because of the structural similarities with adrenalin. They prepared 1-benzyl-3,4-dihydroisoquinoline 92 (47) via the Bischler-Napieralski condensation of the corresponding amide 91 (Scheme 26). Aerial oxidation under acidic conditions in methanol for 2 weeks afforded the ketone 93 which was reduced to (1R*)-1-[(7'R*)-3'-benzyloxy-7'-hydroxy-4'-methoxybenzyl]-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline 94. Debenzylation in acidic ethanol caused epimerization of the alcohol to afford (1R*)-1-[(7'S*)-3',7'-dihydroxy-4-methoxy benzyl]-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline 95. The phenolic cyclization was carried out using 37% formalin in ethanol resulting in the methylenedioxyprotoberberine 96. Treatment with diazomethane methylated the phenolic hydroxyl yielding ophiocarpine 85. (±)-Epiophiocarpine 86 was prepared using the phenolic 1-benzyl-isoquinoline 97. The phenolic cyclization was carried out using 37% formalin in ethanol resulting in the methylenedioxyprotoberberine 98. Treatment with diazomethane methylated the phenolic hydroxyl yielding (±)-epiophiocarpine 86 (Scheme 27).

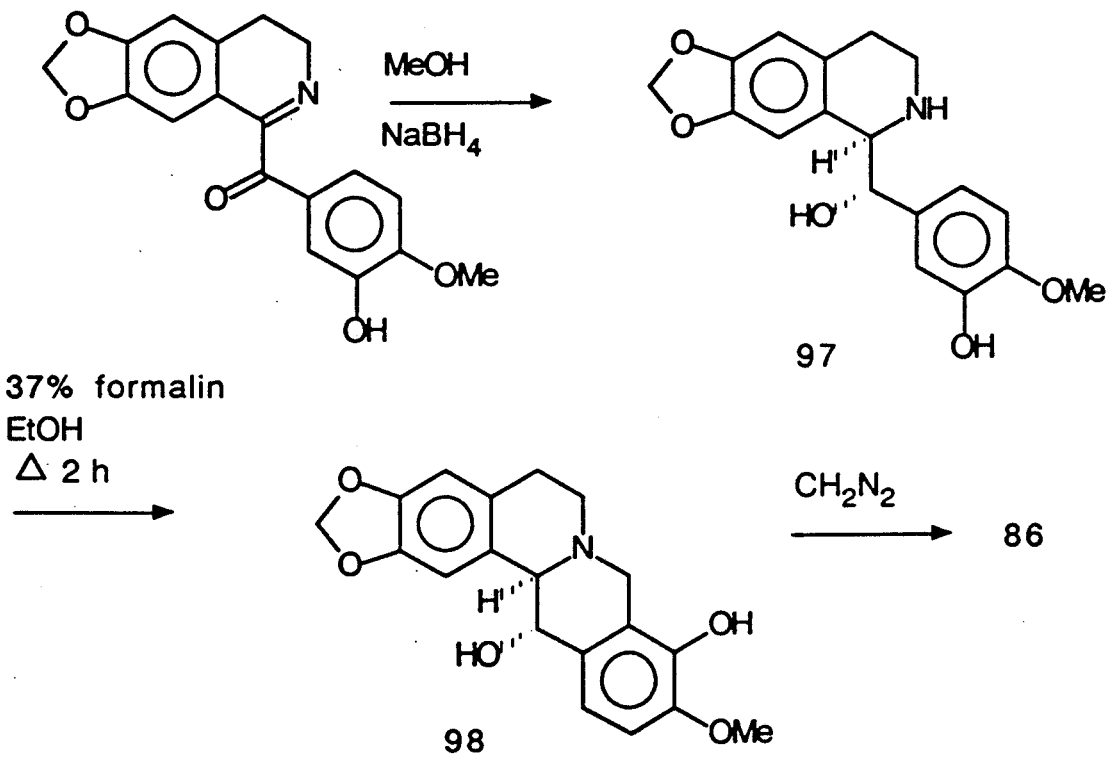
1.5 Decumbensine

(1R,7'S)-Decumbensine 99 and (1R,7'R)-decumbensine 100 were isolated in 1988 by Zhang and Xu (48) from the Chinese

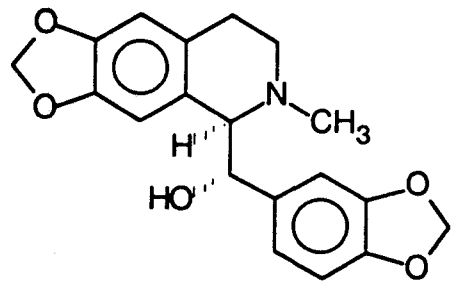
SCHEME 26


POCl3
C6H6
91
92
MeOH, HCl
[O] r.t. 2 wks
NaBH4, MeOH
93
HCl, EtOH
Δ 5 h
94
95
37% formalin
EtOH
Δ 2 h
CH2N2
85
96

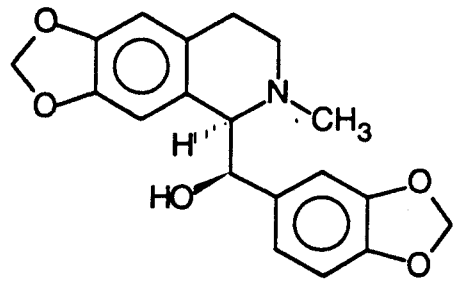
SCHEME 27



medicinal plant, Corydalis decumbens. This plant was used in folk medicine to treat central nervous system diseases. The structure of decumbensine (Figure 8) is similar to the intermediate used by Kametani and coworkers (45) in the synthesis of ophiocarpine.



99



100

Figure 8: (1R,7'S)-Decumbensine and (1R,7'R)-Decumbensine

In the following chapters, the preparation of potential intermediates for the synthesis of (-)-ophiocarpine and (1R,7'R)-decumbensine will be described.

CHAPTER 2

RESULTS AND DISCUSSION

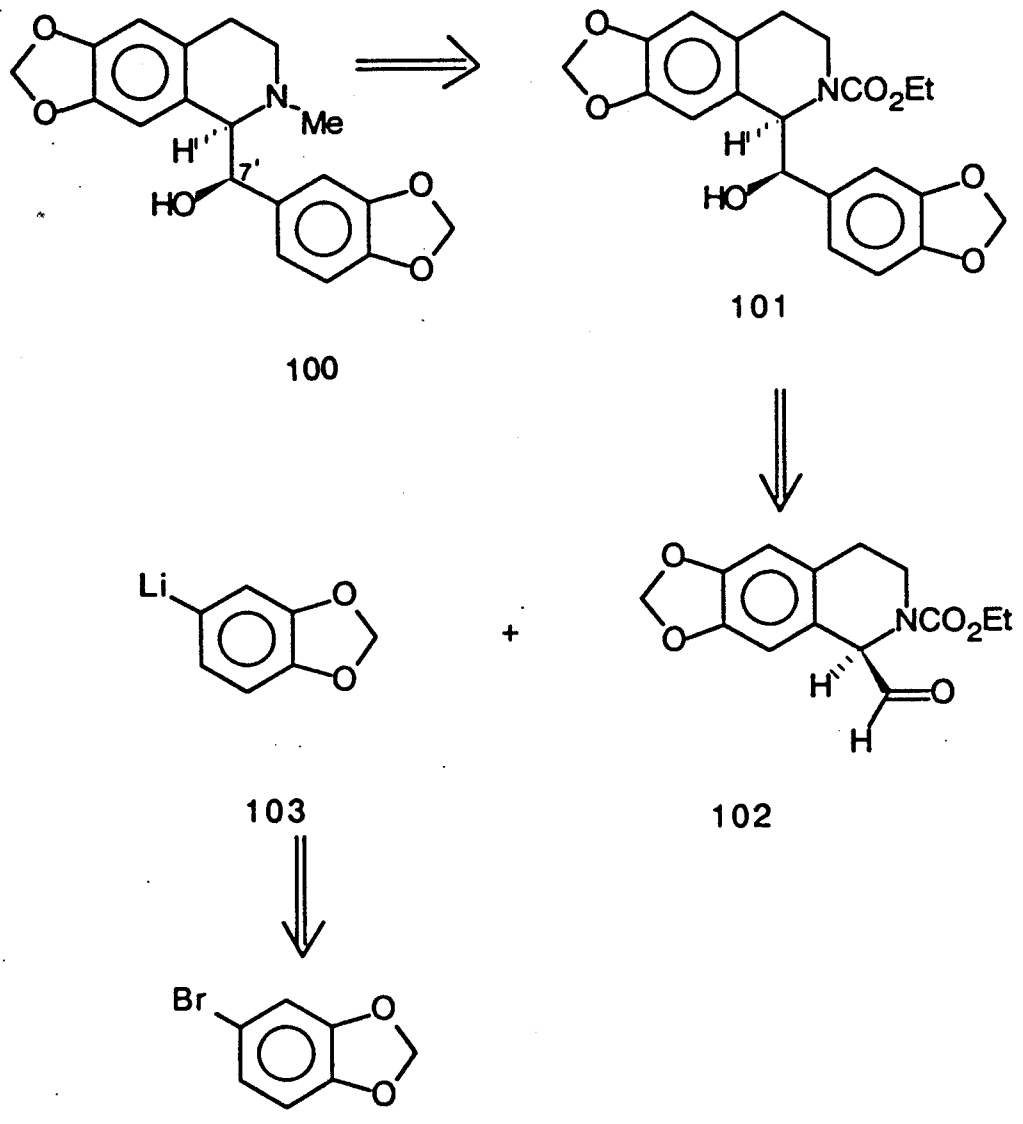
2.1 Retrosynthetic Analysis of (1R,7'R)-Decumbensine and (13R,14R)-Ophiocarpine

Decumbensine and ophiocarpine are related in the sense that they carry a hydroxyl substituent on the carbon atom alpha to C-1 of the THIQ system. A retrosynthetic analysis to afford decumbensine is outlined in Scheme 28 and a similar analysis for ophiocarpine in Scheme 29. It is evident from an examination of the Schemes that the aldehyde **102** is involved in both synthesis.

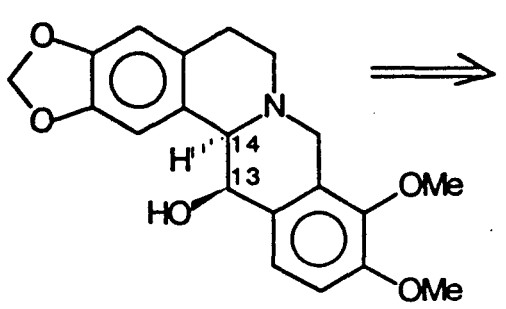
In Scheme 28 the precursor of decumbensine is the carbamate **101** from which decumbensine could be derived by hydride reduction. The carbamate in turn could be derived by reaction between the aldehyde **102** and the lithiated compound **103** obtained from 1-bromo-3,4-methylenedioxybenzene. The latter compound is commercially available. The aldehyde **102** has not been described in the literature but the preparation of the (1R)-dimethoxy analogue has been reported. In the reaction of the (1R)-dimethoxy analogue with 3,4-dimethoxyphenyllithium only the (7'R) isomer was obtained.

In Scheme 29 the precursor to ophiocarpine is the phenolic compound **104** in which the phenolic hydroxyl group is ortho to

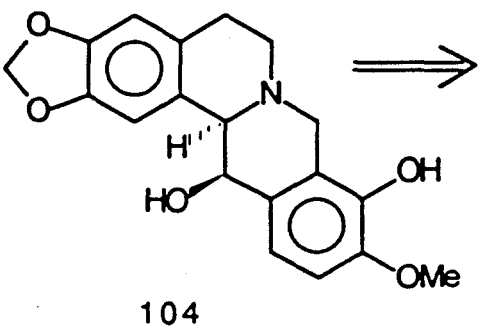
SCHEME 28


N
Me
H
7'
HO
O
O
O
O
100
NCO2Et
H
HO
O
O
101
Li
O
O
+
NCO2Et
H
O
H
103
102
Br
O
O

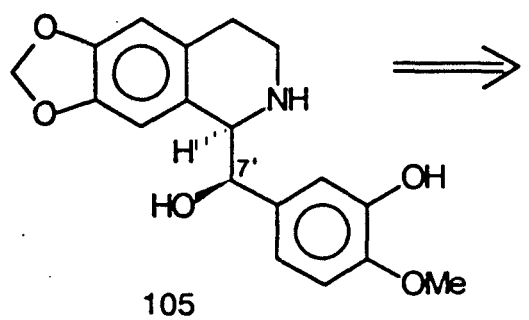
SCHEME 29



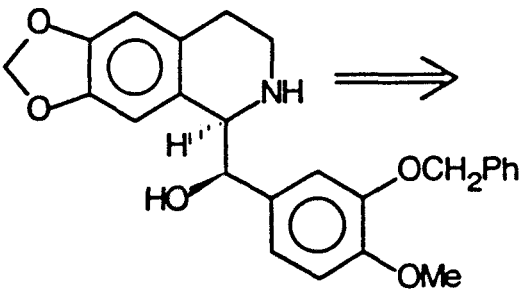
85



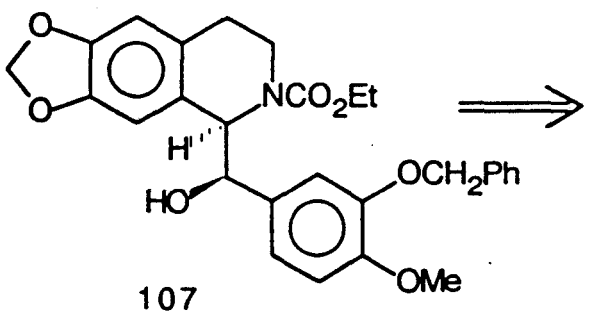
104



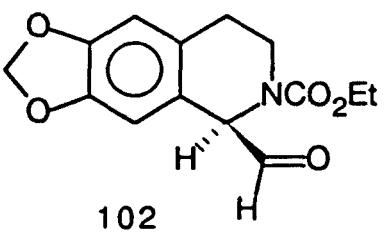
105



106

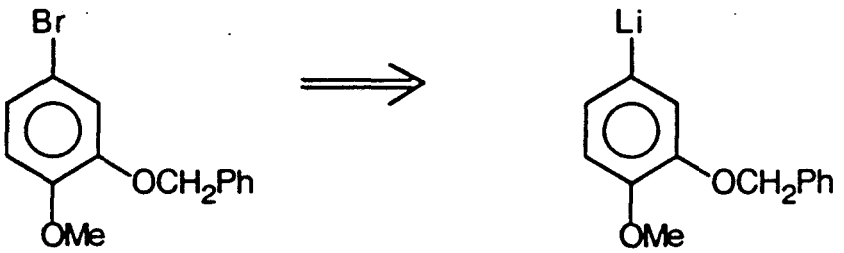


107



102

+



111

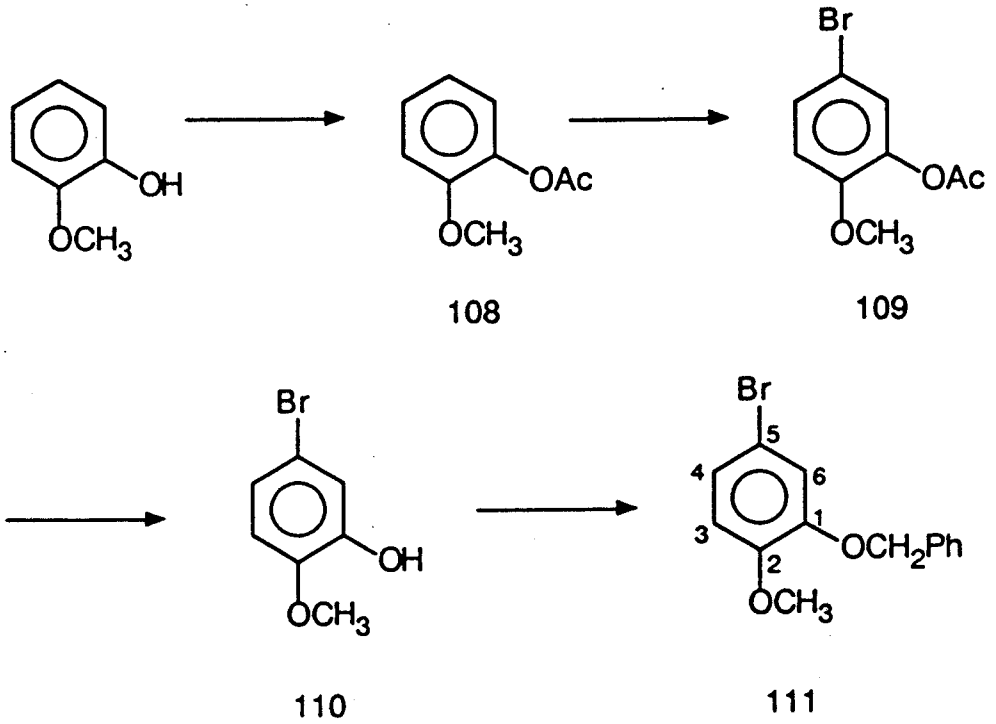
the site of ring closure. Ophiocarpine may be obtained from **104** by methylation using diazomethane. Compound **104** could be prepared from the 1-substituted THIQ **105** via a Mannich reaction. This reaction has been shown (17), for the racemic system, to proceed in acceptable yield using formaldehyde under acidic conditions. A side reaction producing the compound where ring closure occurred para to the hydroxyl group also occurred but the two compounds were separated by chromatography. Debenzylation of **106** under acidic conditions would afford **105**. Compound **106** could be prepared from **107** which is analogous to compound **101** in the synthesis of decumbensine. Again, the (R) isomer at the carbon atom alpha to C-1 would be expected to be formed preferentially when the resulting configuration at C-1 is (S). The aldehyde would be coupled to the lithiated compound derived from 5-bromoguaiacol-O-benzyl ether **111**.

The success of these reaction Schemes is dependent on obtaining the aldehyde in high enantiomeric excess.

2.2 Synthesis of 5-Bromoguaiacol-O-benzyl ether

5-Bromoguaiacol-O-benzyl ether **111** was prepared from guaiacol (Scheme 30). Acetylation of guaiacol followed by bromination led to the introduction of bromine para to the methoxy group (53). This structure was confirmed through examination of the ^{1}H nmr spectrum of **109**. The acetyl group appeared at 2.28 ppm and the methoxy group at 3.79 ppm. The

SCHEME 30



108 109

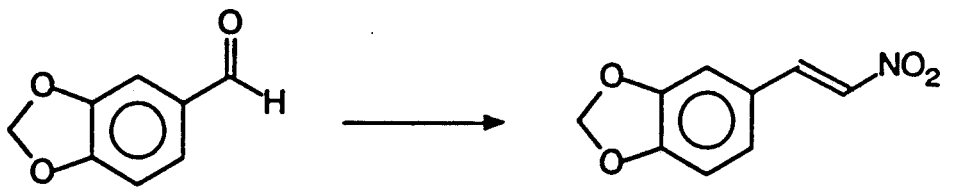
110 111

protons at C-3 and C-4 were present in an AB quartet and C-4 displayed meta coupling to C-6. To ensure that bromination had occurred at C-5 and not at C-3 a nuclear Overhauser effect difference experiment was done. The signal for H-3 was enhanced by saturating the methoxy group. Deacetylation followed by benzylation afforded 5-bromoguaiacol-O-benzyl ether. The spectroscopic properties of **110** and **111** were in agreement with the assigned structures.

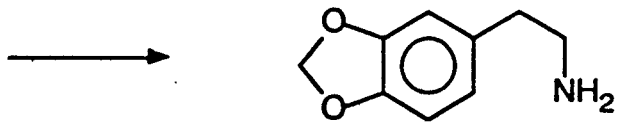
2.3 Synthesis of the Alcohol 117 and the N-Acetyl Analogue 127 and the Aldehyde 126

Two different methods were investigated to obtain the aldehydes (**102** and **126**). Both were based on those used in the synthesis of N-ethoxycarbonyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline-1-carboxaldehyde and were adapted to the synthesis of the methylenedioxy analogue. The first involved the preparation of a racemate and a resolution would be necessary to obtain the enantiomeric aldehydes. In the second, an optically active reactant was used in the synthesis so that a resolution step would not be necessary. In both cases the synthesis began by condensing piperonal with nitromethane to afford 3,4-methylenedioxy-β-nitrostyrene **112**. Compound **112** was reduced with lithium aluminum hydride or with zinc-mercury amalgam to obtain homopiperonyl amine **9** as in Scheme 31. Higher yields were obtained using the hydride method but it was necessary to limit the scale for

SCHEME 31



112



9

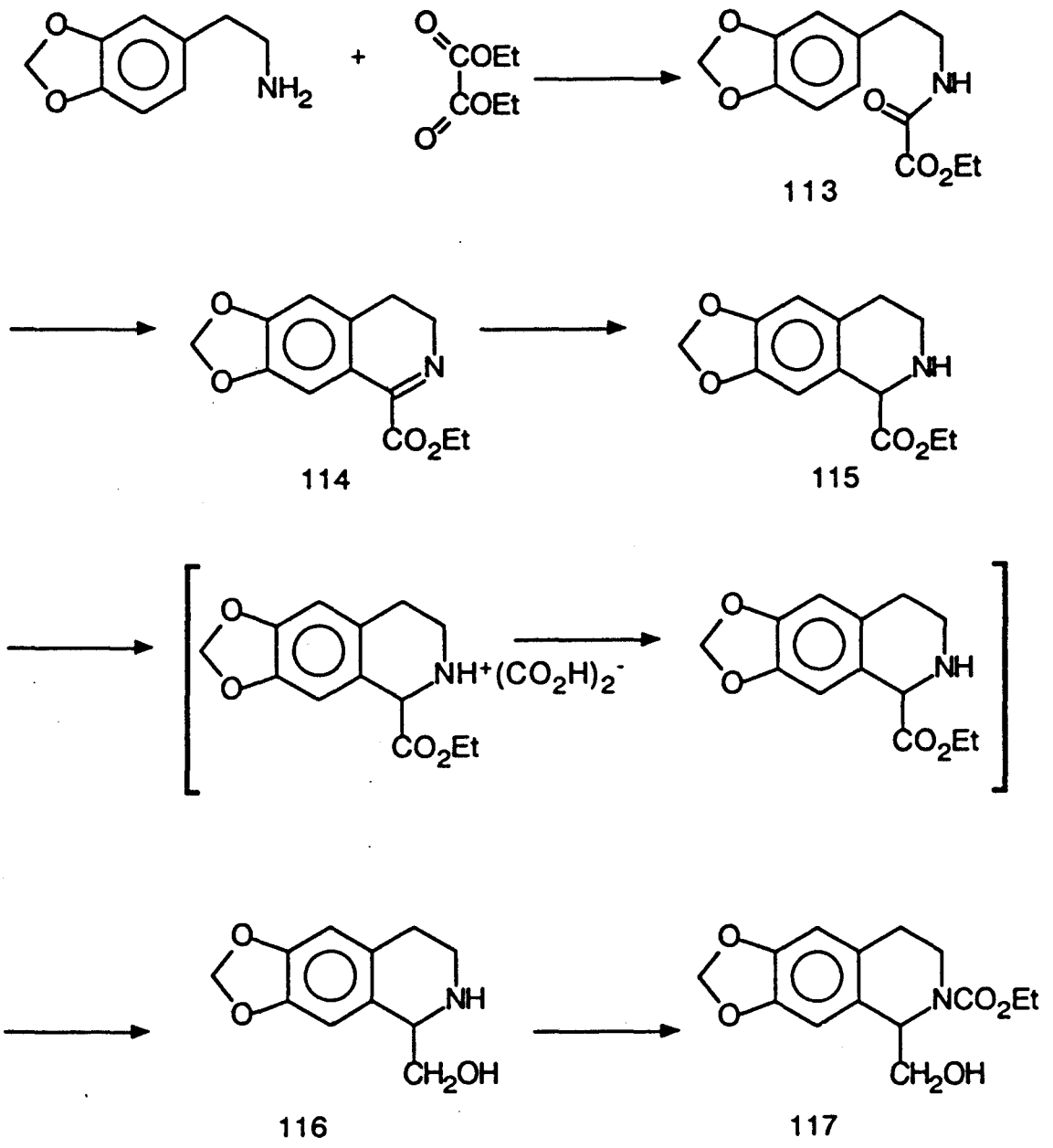
safety reasons. The amalgam method was more convenient in that a large amount of material could be reduced at one time even though the yield was inferior.

2.3.1 Preparation of Alcohol 117, Method 1

A synthetic approach for obtaining the racemic aldehyde 102 is outlined in Scheme 32. Homopiperonylamine was treated with diethyl oxalate to afford the amide 113. The proton nmr spectrum showed the amide proton at 7.11 ppm as a broad peak. The methylene group adjacent to the nitrogen appeared at 3.50 ppm as a broad triplet. The methylene group adjacent to the ring also appeared as a triplet at 2.72 ppm. The EI mass spectrum revealed the molecular ion at m/z 265. A 4.5 fold excess of diethyl oxalate was necessary to prevent the diamide from forming.

Cyclization of 113 to the dihydroisoquinoline 114 was effected using phosphoryl chloride in toluene. The reaction product was not purified but the EI mass spectrum of the crude product showed a molecular ion at m/z 247 indicating that the reaction had proceeded in the expected manner. Reduction of 114 was carried out on the crude material using sodium borohydride to obtain the secondary amine 115. Compound 115 was purified by dissolving in acetone and adding oxalic acid to afford the salt which crystallized from the solution. The salt, once collected was easily converted to the free amine by treatment with an aqueous potassium

SCHEME 32


NH2
COEt
COEt
NH
CO2Et
113
N
114
115
NH+(CO2H)2-
116
CH2OH
NCO2Et
117

carbonate solution and the amine recovered by extraction with chloroform. In the ^1H nmr spectrum of 115 a broad singlet appeared at 4.68 ppm which was assigned to the proton at C-1. The methylene group adjacent to the aromatic ring appeared as a triplet at 2.62 ppm and the neighbouring methylene group as a multiplet at 3.05-3.27 ppm. Two singlets in the aromatic region at 6.49 ppm and 6.79 ppm represent the protons at C-8 and C-5 indicating that cyclization had taken place. The CI mass spectrum had an M+1 ion at m/z 250 and a fragment ion at m/z 176 which is attributed to a protonated 3,4-dihydro-6,7-methylenedioxyisoquinoline.

The carboethoxy group of compound 115 was reduced using sodium borohydride and a Lewis acid, calcium chloride, to afford the alcohol 116. The reduction product showed a broad peak of area 2 at 2.80 ppm attributed to the protons at C-1'. The CI mass spectrum showed an M+1 ion at m/z 208 and an ion at m/z 190 attributed to the loss of water from $(M+H)^+$. The ion corresponding to a protonated dihydroisoquinoline, m/z 176, was present as well. Conversion of the secondary amine into a carbamate via treatment of 116 with ethyl chloroformate afforded 117. The CI mass spectrum of 117 had a pseudo- molecular ion $(M+H)^+$ at m/z 280. A dihydroisoquinolinium ion was also present at m/z 176. The ^1H nmr showed the methyl triplet at 1.28 ppm which integrated for area 3 (J=7.5 Hz) and the methylene group at 4.21 ppm as a quartet with area 2 (J=7.5 Hz). This,

accompanied with the other data confirmed that the carbamate had formed. The yield of 117 was unsatisfactory; therefore, an alternative method was sought in order to continue with the synthesis of decumbensine and ophiocarpine.

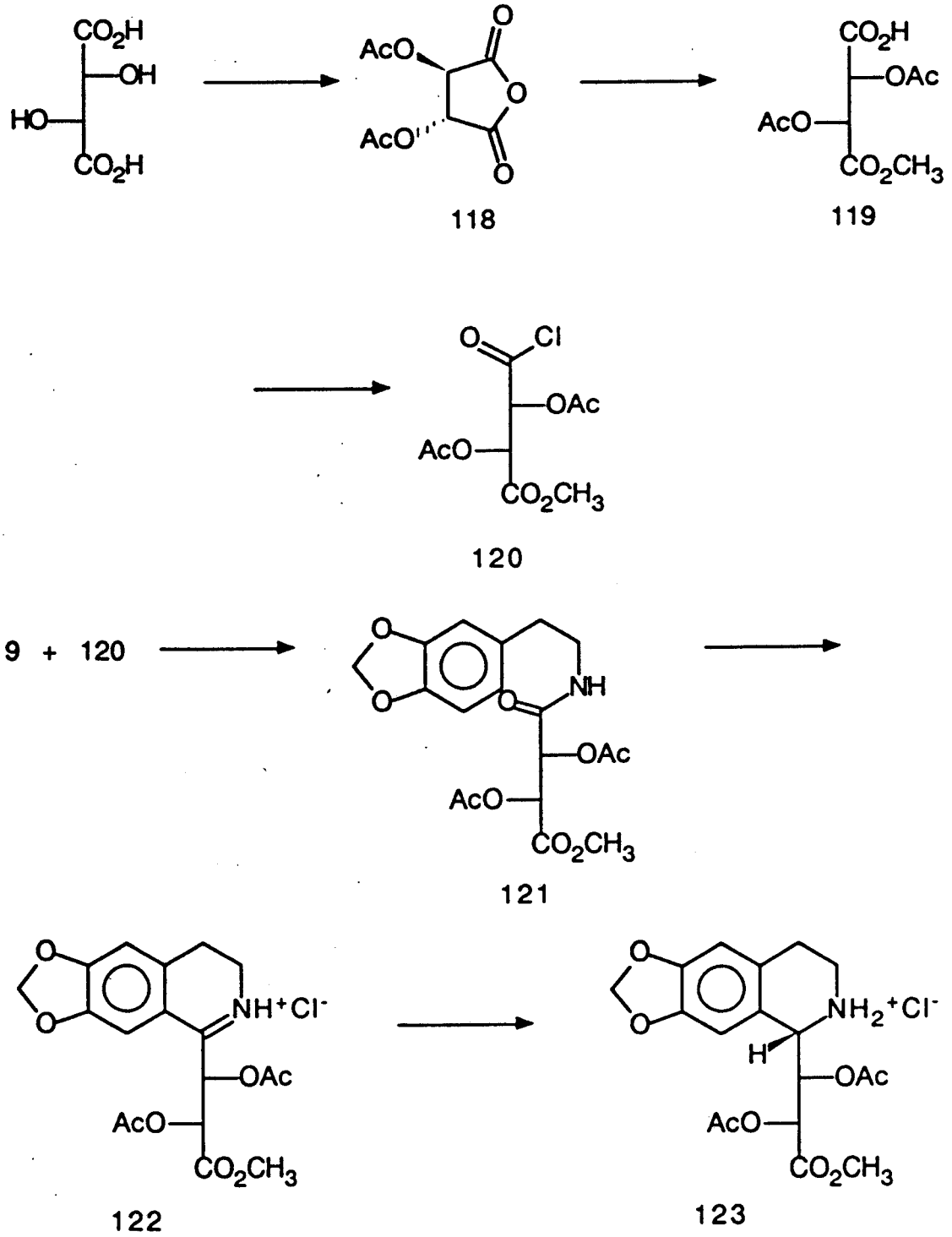
Resolution of the alcohol 116 was not carried out because the yield of 116 was too low to continue with the intended synthetic strategy.

2.3.2 Preparation of Aldehyde 126, Method 2

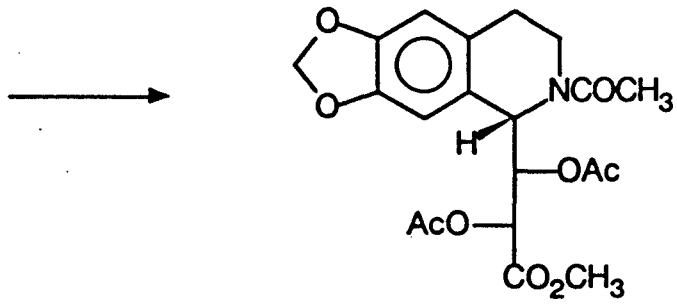
The second approach to the synthesis of the aldehyde was designed to avoid a resolution step. The reaction pathway is outlined in Scheme 33. L-Tartaric acid[1] was treated with acetic anhydride to afford the anhydride 118 which gave the half acid ester 119 on addition of methanol. The acid chloride was prepared by reaction of 119 with thionyl chloride. All three reactions were carried out by established procedures (36). Treatment of homopiperonylamine with the acid chloride afforded the amide 121. The infrared spectrum of this compound showed a band at 1650 cm^{-1} which is indicative of the carbonyl stretching of the amide. In the ^1H nmr spectrum of 121 the NH proton is observed as a broad triplet at 6.26 ppm. The proton at C-6 appeared as a doublet

[1]L-Tartaric acid was used in these preliminary experiments because it was less expensive than D-tartaric acid. D-Tartaric acid would be required as starting material in order to synthesize the target molecules.

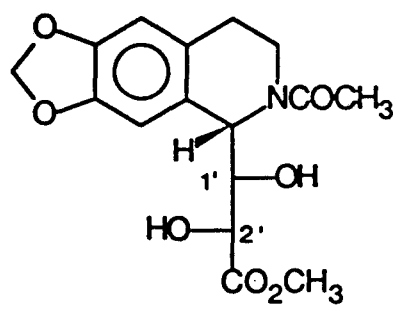
SCHEME 33


CO2H
OH
HO
CO2H
AcO
AcO
O
O
O
O
118
CO2H
OAc
AcO
CO2CH3
119
O
Cl
OAc
AcO
CO2CH3
120
9 + 120
O
O
NH
O
OAc
AcO
CO2CH3
121
O
O
NH+Cl-
OAc
AcO
CO2CH3
122
O
O
NH2+Cl-
H
OAc
AcO
CO2CH3
123

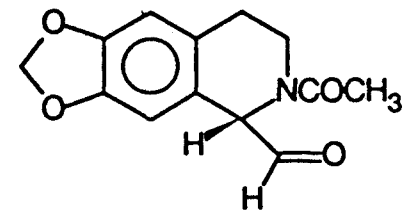
SCHEME 33 (continued)



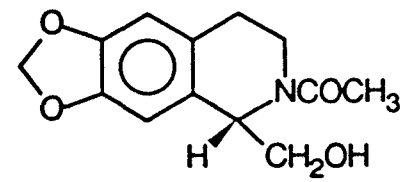
124



125



126



127

of doublets at 6.59 ppm. It is part of an AB quartet and also displays meta coupling to the C-2 H. The coupling constants are 7.8 Hz and 1.4 Hz, respectively. The proton at C-2 appeared at 6.64 ppm (J=1.4 Hz) and that at C-5 as a doublet at 6.72 ppm (J=7.8 Hz). Another AB quartet centered at 5.61 ppm was observed for the protons at C-1' and C-2' (J=2.3 Hz). The DCI mass spectrum showed a pseudomolecular ion $(M+H)^+$ at m/z 396 and an ion at m/z 148 which was also present in the EI mass spectrum of compound **113**. The fragment ion at m/z 148 may be formulated as a 3,4-methylenedioxystyrene ion.

Compound **121** underwent Bischler-Napieralski cyclization under mild conditions affording the imine hydrochloride **122**. It was intended to remove the acetyl groups in order to obtain the deacetylated iminium salt, a procedure used successfully in the preparation of the dimethoxy analogue. However, the salt failed to crystallize from the methanolysis solution and attempts to isolate it were unsuccessful so an alternative procedure was followed. The free imine was isolated from the reaction medium by basification with sodium bicarbonate followed by extraction into methylene chloride. The methylene chloride solution was poured immediately into an acidic solution of methanol. The mixture was then evaporated to dryness, taken up in methanol and reduced over Adam's catalyst at atmospheric pressure. (In the process of extraction the free imine may have racemized and as a result the product obtained from the reduction reaction is unlikely

to be diastereomerically pure.) The reduction product 123 was not isolated but was converted directly to the acetamide 124 which was isolated and examined spectroscopicly. The infrared spectrum of 124 had an absorption band at 1660 cm^{-1} indicating the presence of an amide function. The ^1H nmr spectrum had a singlet at 1.92 ppm and another singlet at 2.11 ppm corresponding to the protons of the O-acetyl groups. The N-acetyl group appeared at 2.27 ppm. The methoxyl protons appeared as a singlet at 3.68 ppm. Both methane and ammonia CI mass spectra showed an M+1 ion at m/z 422 along with the dihydroisoquinolinium ion at m/z 176. Other signals in the nmr spectrum were in agreement with the structure assigned.

The acetamide 124 was converted to the diol 125 by treatment with sodium methoxide in methanol. The proton spectrum of 125 gave a singlet at 2.17 ppm attributed to the N-acetyl group but signals that might be attributed to O-acetyl groups were absent. The protons at C-1' and C-2' formed an AB quartet with signals appearing at 3.91 and 5.21 ppm, respectively. The methylenedioxy signal was present as an AB quartet centered at 5.91 ppm.

The aldehyde 126 was obtained by sodium periodate oxidation of 125. The aldehyde proton of 126 was observed at 9.45 ppm and the proton at C-1 at 5.73 ppm in the ^1H nmr spectrum. The aromatic protons were present as two singlets at 6.64 ppm and 6.84 ppm. The methylenedioxy protons appeared as a singlet at 5.95 ppm which integrated for area 2. The EI and

CI mass spectra both showed the dihydroisoquinolinium ion at m/z 176. The EI showed the molecular ion at m/z 247 while the CI spectrum showed the pseudomolecular ion $(M+H)^+$ at m/z 248. The specific rotation was +95.91° (c 1.76, $CHCl_3$).

The aldehyde **126** is prone to racemization at C-1 so it must be used immediately. In order to store the compound and avoid racemization, procedures were followed that have been developed to reduce the aldehyde to the more stable alcohol **127**. The aldehyde **126** was reduced to **127** via a borohydride reduction. The spectral data of **127** coincided with the assigned structure. The nmr spectrum showed a triplet at 5.03 ppm which was indicative of the C-1 proton. The DCI mass spectrum revealed the pseudomolecular ion at m/z 250 and the fragment ion at m/z 176. The compound had a specific rotation of -29.95° (c 1.85, $CHCl_3$).

Several attempts were made to determine the enantiomeric excess of the alcohol **127**, using an HPLC Pirkle Covalent Phenylglycine column from Regis Chemical Company (25 cm x 4.6 mm ID). Preliminary experiments were carried out with the racemic alcohol **117** which has an N-ethoxycarbonyl group. The racemic alcohol **117** was separated into its components using 10% propanol in hexane as eluant. The first enantiomer eluted after 20 min and the second after 21.5 min. Injections of 20 μL of a 1 gL^{-1} solution were made. A UV detector set at 254 nm was used to detect the sample; a flow rate of 1 $mLmin^{-1}$ was used.

However, the alcohol **127**, which has an N-acetyl group, but

is otherwise the same as 117, could not be separated under these conditions. The sample eluted with a retention time of 60 min under conditions that were effective for 117 but there was no separation of the racemic material. Other solvent systems were investigated without success. Further attempts at separation of the enantiomers of 127 using this column were abandoned.

2.4 Conclusion

The alcohol 117 and the aldehyde 126 were synthesized using different approaches. The method used to obtain 126 proved to be the more desirable approach because of a higher yield of product and because an optically active product was obtained. Unfortunately the enantiomeric purity was not established. In future preparations involving method 2 it is recommended that the nitrogen atom be protected as the carbamate. This will enable the enantiomeric excess to be determined at the stage of the alcohol. Although decumbensine and ophiocarpine were not synthesized due to time restrictions, methods had been developed for the synthesis of key intermediates. Future work should be directed to the synthesis of aldehyde 102 of proper configuration at C-1. In the light of the successful treatment of the dimethoxy analogue of 102 with lithium reagents it should then be possible to proceed with the synthesis of decumbensine and ophiocarpine.

CHAPTER 3

EXPERIMENTAL

3.1 Apparatus and Methods

^{1}H nmr spectra were recorded at 90 MHz on a Varian EM390 spectrometer and at 200 MHz on a Bruker AC200 spectrometer unless otherwise specified. Chemical shifts are reported as ppm(δ) and are relative to tetramethylsilane (TMS). In reporting the nature of the signals, s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet, and br, broad are used. CI mass spectra were recorded on a VG ZAB-E mass spectrometer equipped with a VG11/250J data system and on a VG Micromass 7070 F mass spectrometer equipped with a VG11/250 data system using NH_3 or CH_4 as the reagent gas. EI (70 eV) mass spectra were recorded on the 7070 F, VG11/250 system. Mass spectral results are reported as m/z (rel. int. %). Infrared spectra were recorded on a Perkin-Elmer Infrared Spectrophotometer 283. Optical rotations were measured on a Perkin-Elmer 241 MC Polarimeter. Thin layer chromatographs were run on POLYGRAM SIL G/UV254 silica sheets (Brinkman Instruments). Melting points are uncorrected and were done on a Gallenkamp melting point apparatus. HPLC experiments were performed on a DuPont Instruments 870 Pump Module using a UV Spectrometer for detection.

3.2 Preparation of 2-methoxyphenyl acetate, 108

Guaiacol (6.2g, $5.0x10^{-2}$ mol) was mixed with acetic anhydride (5.6g, $5.5x10^{-2}$ mol) and sulfuric acid (2 drops) and stirred for 3 h. at 100° (53) in an oil bath. The acidic mixture was carefully neutralized using Na_2CO_3 and extracted with $CHCl_3$. The organic layer was dried with $CaCl_2$ and chromatographed on a silica column using $CHCl_3$ as the eluent. A clear liquid was obtained. (4.85g, $3.0x10^{-2}$ mol, 60%)
^1H nmr (90 MHz), $CDCl_3$, δ: 2.29 (3H, s, $-OCOCH_3$), 3.80 (3H, s, $-OCH_3$), 6.90-7.32 (4H, m, aromatic H's).
MS (CI, NH_3): 350 (2M+18)(20), 184 (M+18)(100), 166 (M)(15), 124 (35).

3.3 Monobromination of 2-methoxyphenyl acetate, 109

2-Methoxyphenyl acetate (1.0g, $6.02x10^{-3}$ mol) was dissolved in $CHCl_3$ and bromine (1.0g, $6.02x10^{-3}$ mol), also dissolved in $CHCl_3$, was added dropwise. HBr was liberated and detected using moist pH paper. The $CHCl_3$ was evaporated once decolorization was complete and the yellow liquid redissolved in toluene. The sample was applied to a column packed with alumina (neutral) Typ T (one inch in diameter and approximately two inches in length) and eluted with toluene only. The fractions were collected and the toluene evaporated. Colorless leaf-like crystals of 5-bromo-2-methoxyphenyl acetate resulted, m.p.58-59° [lit.

62-63° (54)], (1.06g, 4.3×10^{-3} mol, 72%).

^{1}H nmr (500 MHz), $CDCl_3$, δ: 2.28 (3H, s, CH_3CO_2-), 3.79 (3H, s, $-OCH_3$), 6.81-6.83 (1H, d, J=8.7 Hz, C-3 H), 7.16-7.17 (1H, d, J=2.4, C-6 H), 7.28-7.30 (1H, dd, J=8.7 Hz and J=2.4 Hz, C-4 H). C-3 H and C-4 H form an AB quartet.

MS (EI): 244 and 246 ($M^{+\cdot}$)(20), 202 and 204 (100), 187 and 189 (45), 159 and 161 (10).

An nOe difference experiment showed enhancement of C-3 H by saturating the methoxy group at C-2.

3.4 Preparation of 5-bromoguaiacol, 110

5-Bromo-2-methoxyphenyl acetate 109, (1.043g, 4.26×10^{-3} mol) was dissolved in ethanol (95%, 14mL) and made basic with NaOH (1.933g dissolved in a small amount of water). The mixture was stirred and refluxed for 30 min (54). The ethanol was evaporated and the residue taken up in ether and acidified using 1 N HCl. The ether layer was collected. To purify, the ether extract was made alkaline using 15% NaOH and the aqueous fraction collected. This was acidified and extracted with ether once more. Evaporation of the ether resulted in a clear oil (0.734g, 3.62×10^{-3} mol, 85%).

^{1}H nmr (90 MHz), $CDCl_3$, δ: 3.88 (3H, s, $-OCH_3$), 5.50 (1H, s, -OH), 6.58-6.66 (1H, d, J=9.0 Hz, C-3 H), 6.83-6.85 (1H, d, J=2.5 Hz, C-6 H), 6.98-7.13 (1H, dd, J=9.0 Hz and J=2.5 Hz, C-4 H)

MS (EI): 202 and 204 ($M^{+\cdot}$)(100), 187 and 189 (80), 159 and

161 (40).

3.5 5-Bromoguaiacol benzylether, 111

5-Bromoguaiacol 110, (0.734g, 3.62×10^{-3} mol) was dissolved in 95% EtOH (3 mL) and refluxed. KOH (0.6 g in 0.6 mL) was added and the refluxing continued. Benzyl chloride (0.61 mL, 5.32×10^{-3} mol) was added slowly and the mixture refluxed for an additional 1.5 h. The reaction mixture was filtered hot to remove the KCl and the benzylated species was crystallized from 95% EtOH to afford fluffy white crystals. (0.623g, 2.13×10^{-3} mol, 40%). m.p. 74-76°.

^{1}H nmr (500 MHz), $CDCl_3$, δ: 3.83 (3H, s, $-CH_3$), 5.09 (2H, s, CH_2), 6.73-6.75 (1H, d, J=8.2 Hz, C-3 H), 7.01-7.03 (1H, q, J=8.2 Hz and J=2.2 Hz, C-4 H), 7.01 (1H, br s, C-6 H), 7.30 (1H, t, J=7.1 Hz, C-4' H), 7.36 (2H, t, J=7.1 Hz, C-3' H and C-5' H), 7.41 (2H, d, J=7.1 Hz, C-2' H and C-6' H).

MS (EI): 292 and 294 ($M^{+\cdot}$)(100).

MS (CI,NH_3): 310 and 312 (M+18)(100), 292 and 294 (M^+)(10).

3.6 3,4-Methylenedioxy-β-nitrostyrene, 112. (49)

Nitromethane (9.0 mL, 1.67×10^{-1} mol) and ammonium acetate (20g) were added to a solution of piperonal (9g, 6.00×10^{-2} mol, in glacial acetic acid (150 mL). The mixture was heated on a steam bath for 5-6 h. The dark colored solution was poured onto crushed ice and allowed to stand for

approximately 2 h. The yellow precipitate was collected, washed with water and crystallized from absolute ethanol. The pure product was in the form of yellow needles. (9.2g, 4.77×10^{-2} mol, 79%), m.p. 157-158°, [lit. 159-160° (49), lit. 161° (50)].

^{1}H nmr (90 MHz), $CDCl_3$, δ: 6.10 (2H, s, $-OCH_2O-$), 6.89 (1H, d, J=7.5 Hz, C-5 H), 7.06 (1H, d, J=2.0 Hz, C-2 H), 7.12 (1H, dd, J=7.5 Hz and J=2.0 Hz, C-6 H), 7.49 (1H, d, J=13.8 Hz, vinyl H), 7.98 (1H, d, J=13.8 Hz, vinyl H).

MS (CI, NH_3): 193 ($M^{+\cdot}$)(100), 146 (80), 117 (20).

3.7.1 3,4-Methylenedioxyphenylethylamine (Homopiperonylamine), 9. (50)

METHOD 1

A solution of nitrostyrene, 112, (9.2g, 4.77×10^{-2} mol) in dry tetrahydrofuran (THF), (200 mL, dried by refluxing over $LiAlH_4$) was added dropwise to a refluxing solution of $LiAlH_4$ (6g) in dry THF (300 mL) over a period of 2.5 h. The mixture was left to cool in an ice bath and the excess $LiAlH_4$ was decomposed by the careful addition of H_2O (6 mL), NaOH (15%, 6 mL), and H_2O (18 mL) (51). Ether (500 mL) was added to the solution and the inorganic material was filtered off and washed with ether. The solvent was evaporated to yield a dark colored oil which was distilled at 120°/0.3 torr resulting in a clear oil (6.1g, 3.70×10^{-2} mol, 78%).

^{1}H nmr (90 MHz), $CDCl_3$, δ: 1.15 (2H, br s, $-NH_2$), 2.57-3.01 (4H, m, $-CH_2CH_2-$), 5.90 (2H, s, $-OCH_2O-$), 6.52-6.78 (3H, m, aromatic H's).

MS (CI, NH_3): 166 (M+1)(100), 136 (10).

3.7.2 METHOD 2

A zinc amalgam was prepared by a method reported by Vogel (52), in which zinc powder (200g) was combined with mercuric chloride (15g), conc. HCl (10 mL) and H_2O (250 mL). The mixture was stirred for approximately 5 min. CAUTION! The initial reaction is quite vigorous. The aqueous portion was decanted and MeOH (200 mL) was added. While stirring vigorously in an ice water bath, conc. HCl (280 mL) and 3,4-methylenedioxy-β-nitrostyrene (40g) in THF (400 mL) were added slowly in order to maintain the temperature below 20°C. Once the additions were complete and after a further 30 min., the solution was filtered and the filtrate neutralized using Na_2CO_3. The volume was reduced to approximately 500 mL and made alkaline with an ammonia solution and extracted with $CHCl_3$. The organic phase was washed with a 2% NaOH solution and dried over K_2CO_3. Evaporation of the solvent afforded the amine and, upon vacuum distillation, a clear oil was obtained (18g, 1.095×10^{-1} mol, 53%). The proton and mass spectra were identical with that reported above.

3.8 Ethyl N-(-3,4-methylenedioxyphenylethyl)-oxamate, 113.

The following method is analogous to that of Grùssner et. al. (34). Diethyl oxalate (7.5g, 5.14×10^{-2} mol) was heated to 100° in an oil bath and 3,4-methylenedioxyphenylethylamine (2g, 1.21×10^{-2} mol) was added dropwise. Once all the ethanol that was formed in the reaction was released to the atmosphere, the excess oxalate was evaporated. The white crystals that remained were recrystallized from benzene (2.57g, 9.70×10^{-3} mol, 80%) m.p. 122-123°C.

ν_{max} (nujol), 1210 cm^{-1} (C-O, ester), 1240 cm^{-1} (C-O, ester), 1660 cm^{-1} (C=O, amide), 1750 cm^{-1} (C=O, ester), 1775 cm^{-1} (C=O, ester).

^1H nmr (90 MHz), $CDCl_3$, δ: 1.32 (3H, t, J=7.8 Hz, $-CH_3$), 2.72 (2H, t, J=7.5 Hz, $Ar-CH_2-$), 3.50 (2H, apparent q, J=7.5 Hz, $-CH_2NH-$), 4.28 (2H, q, J=7.8, $-C\underline{H}_2CH_3$), 5.89 (2H, s,$-OCH_2O-$), 6.50-6.79 (3H, m, aromatic H's), 7.11 (1H, br, -NH-).

^{13}C nmr (50.32 MHz), $CDCl_3$, δ: 121.8 (C-1), 109.2[a] (C-2), 146.7[b] (C-3), 148.2[b] (C-4), 108.7[a] (C-5), 132.0 (C-6), 101.2 ($-OCH_2O-$), 35.2 ($ArCH_2-$), 41.4 ($-CH_2NH-$), 156.7 (-NCO-),160.9 ($-\underline{C}O_2Et$), 63.3 ($-OC\underline{H}_2CH_3$), 14.2 ($-CH_3$)

[a,b]Assignments may be interchanged.

MS (EI): 265 (10)($M^{+\cdot}$), 148 (100), 135 (40).

Formula weight: calculated for $C_{13}H_{15}NO_5$ (M): 265.0951

Found: 265.0959

3.9 Ethyl 3,4-dihydro-6,7-methylenedioxyisoquinoline 1-carboxylate, 114.

The dihydroisoquinoline was prepared similarly to that of Grùssner et. al.(34). The amide 113, (10.24g, 3.86×10^{-3} mol) was dissolved with heating in toluene (80 mL dried over Na_2SO_4) and absolute ethanol (7.3 mL). Once the amide was dissolved, $POCl_3$ (18 mL) was added dropwise. The mixture was then heated to 120°C over a period of 3.5 h at which point two layers appeared. The residual toluene was evaporated and the residue was taken up in absolute ethanol. The resulting solution was poured onto a mixture of ice, K_2CO_3 (50% aqueous, 100 mL) , and ether:benzene=2:1 (250 mL). The aqueous layer was extracted several times with the ether:benzene solution and dried over $MgSO_4$. The organic phase was then evaporated and a brown oil was obtained. This oil was not purified, TLC (EtOAc:CH_2Cl_2, 1:5), amide R_f=0.52, imine Rf=0.35. (9.993g).
MS (EI): 247 (20)($M^{+\cdot}$), 175 (100).

3.10 Reduction of 114 to (±)ethyl 1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline 1-carboxylate, 115.

The mixture prepared above was dissolved with stirring in absolute ethanol (85 mL). The reaction vessel was placed in

an ice bath and $NaBH_4$ (2.0 g) was added slowly. The mixture was allowed to stir for an additional 2 h. The solution was evaporated to dryness, treated with 10% NaCl (150 mL) and the solution extracted with chloroform several times. The dried chloroform extract was evaporated affording a light colored oil. The compound was isolated in the form of its oxalate by first dissolving the oil in acetone and adding dropwise to the solution one equivalent of oxalic acid in acetone. The salt was then filtered and triturated with absolute ethanol to remove soluble impurities. The salt was dried in a desiccator over P_2O_5. (4.72g, 1.39×10^{-2} mol, 36% from amide), mp. 200°C(d).

To liberate the free amine, the salt was dissolved in H_2O, made basic with a 50% K_2CO_3 solution and then the mixture extracted with chloroform many times. The chloroform extract was evaporated and a clear oil was obtained. (1.80g, 7.23×10^{-3} mol, 98%).

^1H nmr (90 MHz), $CDCl_3$, δ: 1.24 (3H, t, J=7.5 Hz, $-CH_3$), 2.62 (2H, t, J=6.5 Hz, $Ar-CH_2$), 3.05-3.27 (2H, m, CH_2-N), 4.16 (2H, q, J=7.5 Hz, $-C\underline{H}_2CH_3$), 4.68 (1H, broad s, C-1 H), 5.84 (2H, s, $-OCH_2O-$), 6.49 (1H, s, C-8 H), 6.79 (1H, s, C-5 H).

MS (CI, NH_3): 250(100)(M+1), 208(20), 176(30)

3.11 Reduction of 115 to (±)1,2,3,4-tetrahydro-1-hydroxymethyl-6,7-methylenedioxyisoquinoline, 116

The ester 115 (0.82g, 3.31×10^{-3} mol) was dissolved in absolute ethanol (75 mL) and treated with two equivalents of $NaBH_4$ and two equivalents of $CaCl_2$. The reaction mixture was stirred overnight at room temperature. More $NaBH_4$ was added and the mixture left overnight again. The ethanol was removed by evaporation, $CHCl_3$ was added and the suspension was filtered through Celite. The Celite was washed many times with hot $CHCl_3$. The $CHCl_3$ was evaporated and the isoquinoline was recrystallized from ethanol, m.p. 145-147°. (0.589g, 2.84×10^{-3} mol, 86%)

^1H nmr (500 MHz), CD_3OD, δ: 2.80 (2H, br m, C-1' H's), 3.04-3.29 (2H, m, C-4 H's), 3.71-3.83 (2H, m, C-3 H's), 4.05 (1H, m, C-1 H), 5.85 (2H, s, $-OCH_2O-$), 6.61 (1H, s, C-8 H), 6.68 (1H, s, C-5 H)

MS (CI, NH_3): 208 (90)(M+1), 190 (50), 176 (100)

Formula weight: calculated for $C_{11}H_{14}NO_3$ (M+H): 208.0974

Found: 208.0977

3.12 Preparation of the carbamate, 117.

This procedure is similar to that used by Czarnocki et al. (17). The amine 116, (0.930g, 4.49×10^{-3} mol) was added to a mixture of H_2O (30 mL) and CH_2Cl_2 (50 mL) containing

several drops of 25% aqueous NaOH and the suspension vigorously stirred. Ethyl chloroformate (3.0 mL, 3.14×10^{-2} mol) was added dropwise over a 30 min. period. The mixture was then stirred for an additional 30 min. The organic phase was separated and washed twice with a saturated NaCl solution and dried over $MgSO_4$. The CH_2Cl_2 was evaporated and the residue chromatographed on a silica column using $CHCl_3$ followed by 2% methanol in $CHCl_3$ as eluants. White crystals were obtained on elution with EtOAc:CH_2Cl_2=1:5. m.p. 55-57°
^{1}H nmr (90 MHz), $CDCl_3$, δ: 1.28 (3H, t, J=7.5 Hz, $-CH_2\underline{CH_3}$), 1.65 (1H, br m, -OH), 2.75 (2H, m, C-4 H's), 3.46 (2H, m, C-3 H's), 3.80 (2H, d, J=6.0 Hz, C-1'H), 4.21 (2H, q, J=7.5 Hz, $-\underline{CH_2}CH_3$), 5.13 (1H, t, J=6.0 Hz, C-1 H), 5.93 (2H, s, $-OCH_2O-$), 6.62 (1H, s, aromatic H), 6.68 (1H, s, aromatic H).
MS (CI,NH_3): 280 (100)(M+1), 251 (20), 234 (30), 176 (10).
Formula weight: calculated for $C_{14}H_{18}NO_5$ (M+H): 280.1185
Found: 280.1182

3.13 Preparation of O,O-diacetyltartaric anhydride, 118

L-Tartaric acid (20g, 1.33×10^{-1} mol) was dissolved in acetic anhydride (100 mL) and refluxed for 2 h. The mixture was cooled in an ice bath and allowed to sit overnight. The resulting white solid was collected. (16.2g, 7.57×10^{-2} mol, 57%), m.p. 130-131°, (lit. 134° (36)).
^{1}H nmr (90 MHz), $CDCl_3$, : 2.25 (6H, s, CH_3CO_2), 5.68

(2H, s, 2x C-H).

3.14 Preparation of (2R,3R)-diacetyl monomethyltartrate, 119

O,O-Diacetyltartaric anhydride (16.2g, $7.57x10^{-2}$ mol) was dissolved in methanol (32 mL) by warming slightly. The excess methanol was removed immediately by evaporation to afford a white powder, monomethyl diacetyltartrate. ((18.1g, $7.3x10^{-2}$ mol, 97%), m.p. 122-124°, (lit. 124.7° (36)).

^{1}H nmr (90 MHz), $CDCl_3$, δ: 2.20 (6H, s, 2x CH_3CO_2), 3.81 (3H, s, $-OCH_3$), 5.78 (2H, s, 2x -CHOAc), 8.58-8.82 (1H, br, s, $-CO_2H$).

MS (EI): 189 (M-59)(17), 161 (20), 147 (15), 132 (30), 129 (100), 103 (15).

3.15 Preparation of (2R,3R)-diacetoxy-3-carbomethoxy propionyl chloride, 120

The half acid ester (18.1g, $7.30x10^{-2}$ mol) was dissolved in $SOCl_2$ (18 mL) and heated for 3 h at 60°C. The excess $SOCl_2$ was removed under vacuum. The acid chloride was recrystallized from diisopropyl ether. (9.1g, $3.44x10^{-2}$ mol, 47%), m.p. 102°, (lit. 108.5° (36)).

^{1}H nmr (90 MHz), $CDCl_3$, δ: 2.22 (6H, s, 2x CH_3CO_2), 3.82 (3H, s, $-OCH_3$), 5.90 (2H, J=4.0 Hz, 2x C-H, AB q).

MS (EI): 203 (M-COCl)(20), 161 (100), 129 (30), 119 (15).

MS (CI): shows formation of amide

3.16 Methyl [(2R,3R)-diacetoxy-3-(N-3,4-methylenedioxy phenylethylcarbamoyl)]propionate, 121

The amine 9, (18.95g, $1.15x10^{-1}$ mol) was dissolved in dioxane (400 mL) at room temperature and triethylamine (1.05 equivalents) was added. The mixture was stirred vigorously while the acid chloride 120 (30.59g, $1.15x10^{-1}$ mol) in dioxane (300 mL) was added dropwise. The solution was allowed to stir for an additional 3 h. The precipitate was removed by filtration and washed with dioxane. The filtrate was evaporated and the residue taken up in toluene. The organic phase was washed twice with 1% HCl, and then with brine, a saturated solution of $NaHCO_3$, and once again with brine. After drying over $MgSO_4$, the toluene was evaporated to yield a residue that could be recrystallized from benzene. (23.94g, $6.06x10^{-2}$ mol, 53%), mp.104-105° C, $[\alpha]_D$ -19.08° (c 2.165, $CHCl_3$).

ν_{max} (nujol), 1210 cm^{-1} with shoulder (C-O, ester), 1240 cm^{-1} (C-O, ester), 1650 cm^{-1} (C=O, amide), 1740 cm^{-1} (C=O, ester), 1760 cm^{-1} (C=O, ester), 3280 cm^{-1} (N-H, amide).

^1H nmr (200 MHz), $CDCl_3$, δ: 2.07 (3H, s, $C\underline{H}_3CO_2$), 2.08 (3H, s, $C\underline{H}_3CO_2$), 2.53 (2H, t, J=6.8 Hz, Ar-$C\underline{H}_2$-), 3.46 (2H, m, -$C\underline{H}_2NH$-), 3.69 (3H, s, -$OC\underline{H}_3$), 5.61 (2H, AB q, J=2.3 Hz, -$C\underline{H}CONH$-, and, -$C\underline{H}CO_2Me$), 5.90 (2H, s, -OCH_2O-), 6.26 (1H, t, NH), 6.59 (1H, dd, J=7.8 Hz and J=1.4 Hz, C-6 H), 6.64

(1H, d, J=1.4 Hz, C-2 H), 6.72 (1H, d, J=7.8 Hz, C-5 H). ^{13}C nmr (62.89 MHz), $CDCl_3$, δ: 121.7 (C-1), 109.1[c] (C-2), 146.5[d] (C-3), 148.1[d] (C-4), 108.5[c] (C-5), 132.2 (C-6), 101.1 ($-OCH_2O-$), 35.4 ($ArCH_2$), 40.7 ($-CH_2NH-$), 165.5[a] (-NCO-), 72.0[b] (C-1'), 71.5[b] (C-2'), 167.4[e] (C-3'), 168.7[e] (1'-$CH_3\underline{C}O_2$), 20.5[a] (1'- $\underline{C}H_3CO_2$), 169.4[a] (2'- $CH_3\underline{C}O_2$), 20.4[a] (2'- $\underline{C}H_3CO_2$), 52.8 (3'-OCH_3).

[a,b,c,d,e]Assignments may be interchanged.

MS (DCI, NH_3): 396 (M+1)(100), 354 (40), 148 (20).

3.17 Bischler-Napieralski cyclization of the amide, 121

Phosphorus pentachloride (2g, $9.59x10^{-3}$ mol) was dissolved in CH_2Cl_2 (20 mL) at 0-5° C. The amide 121, (2.011g, $5.09x10^{-3}$ mol) dissolved in CH_2Cl_2 (20 mL) was added to the PCl_5 and stirred at 0-5° C for 5 h. The mixture was poured into $NaHCO_3$ solution (6 equivalents) and the organic phase extracted. The aqueous layer was washed with CH_2Cl_2 and the organic fractions combined and washed once with brine. The solution was dried quickly with $MgSO_4$ and filtered. An acidic methanolic solution (2 mL acetyl chloride in 50 mL MeOH) was poured into the CH_2Cl_2 solution and evaporated. This product 122, was not purified further.

3.18 Reduction of the imine hydrochloride to 122 and N-acetylation

The crude iminium salt 122, prepared above was dissolved in MeOH (50 mL) and a catalytic amount of PtO_2 was added and a balloon filled with H_2 was attached. The reaction was allowed to proceed for approximately 1.5 h. It appeared from the TLC (10% MeOH in $CHCl_3$) that partial deacetylation may have occurred. The residue was dissolved in pyridine and 3 mL acetic anhydride were added and the mixture stirred at 0° for 2 h. A small volume of MeOH was added and the solvent evaporated. The residue was evaporated once again from toluene to remove unwanted MeOH. The residue was taken up in toluene and extracted with 1% HCl until all traces of pyridine were gone. The toluene solution was then washed with $NaHCO_3$, dried over $MgSO_4$, filtered and taken to dryness. Compound 124 was purified on a Chromatotron using diethyl ether as the eluant. mp. 86°C, $[\alpha]_D^{25}$ -59.25° (c 2.135, $CHCl_3$).

ν_{max} (nujol), 1210 cm^{-1} (C-O, ester), 1240 cm^{-1} (C-O, ester), 1660 cm^{-1} (C=O, amide), 1750 cm^{-1} (C=O, ester), 1775 cm^{-1} (C=O, ester).

^1H nmr (200 MHz), $CDCl_3$, δ: 1.92 (3H, s, $C\underline{H}_3CO_2$), 2.11 (3H, s, $C\underline{H}_3CO_2$), 2.27 (3H, s, $-NCOCH_3$), 2.83-2.90 (2H, m, $Ar-CH_2$), 3.68 (3H, s, $-OCH_3$), 3.68-3.74 (2H, m, $-C\underline{H}_2NH-$), 5.19 (1H, d, J=1.7 Hz, C-1 H), 5.48 (1H, dd, J=1.7 Hz and J=9.1 Hz, C-1'

H), 5.89 (1H, d, J=9.1 Hz, C-2' H), 5.92 (2H, s, -OC$\underline{H}_2$O-), 6.56 (1H, s, C-5 H), 6.67 (1H, s, C-8 H).

^{13}C nmr (62.89 MHz), $CDCl_3$, δ: 52.7[b] (C-1), 42.0 (C-3), 28.5 (C-4), 126.1[e] (C-4a), 109.1[d] (C-5), 147.8[f] (C-6), 146.0[f] (C-7), 108.6[d] (C-8), 127.7[e] (C-8a), 101.1 (-OCH_2O-), 21.7 (NCO$\underline{C}H_3$), 72.3[c] (C-1'), 70.4[c] (C-2'), 169.4[g] (C-3'), 170.6[g] (1'- $CH_3\underline{C}O_2$), 20.9[a] (1'- $\underline{C}H_3CO_2$), 170.3[g] (2'- $CH_3\underline{C}O_2$), 20.9[a] (2'- $\underline{C}H_3CO_2$), 50.7[b] (3'-OCH_3)

A signal has not been assigned to the amide carbonyl. It may coincide with an ester carbonyl.

[a,b,c,d,e,f,g]Assignments may be interchanged.

MS (EI): 230 (30), 218 (100), 176 (85).

MS (CI, NH_3): 422 (M+1)(100), 176 (20).

MS (CI, CH_4): 422 (M+1)(37), 380 (38), 362 (40), 320 (15), 230 (30), 218 (100), 176 (60), 149 (20), 103 (25).

Formula weight: calculated for $C_{20}H_{24}NO_9$ (M+H): 422.1451

Found: 422.1443

3.19 Methanolysis of 124 to methyl[(2R,3R)-dihydroxy-3-(N-acetyl-6',7'-methylenedioxy-1',2',3',4'-tetrahydroisoquinolin-(1'S)-yl)] propanoate, 125

The N-acetyl compound 124, (0.462 g, 1.097 x 10^{-3} mol) was dissolved in MeOH (40 mL) and NaOMe (85 mg) was added. After 3 hours of stirring at room temperature, 1 drop of acetic acid was added to quench the reaction. The mixture was

evaporated, the residue taken up in CH_2Cl_2 and extracted first with $NaHCO_3$ and then with brine. After drying over $MgSO_4$, the CH_2Cl_2 was evaporated to yield a light green oil. The product (94mg, 2.789×10^{-4} mol, 25% yield) appeared pure on TLC (5% MeOH in $CHCl_3$). $[\alpha]_D^{25}$ +6.54° (c 2.40, $CHCl_3$)

^1H nmr (200MHz), $CDCl_3$, δ: 2.17 (3H, s, $-NCOCH_3$), 2.82-2.96 (2H, m, C-4 H), 3.67-3.71 (2H, m, C-3 H), 3.48-3.65 (2H, m, -OH), 3.74 (3H, s, $-OCH_3$), 3.91 (1H, d, J=8.9 Hz, C-1' H), 4.21 (1H, s, C-1 H), 5.21 (1H, d, J=8.9 Hz, C-2' H), 5.90 (1H, d, J=1.4 Hz, $-OCH_2O-$), 5.92 (1H, d, J=1.4 Hz, $-OCH_2O-$), 6.63 (1H, s, aromatic H), 6.79 (1H, s, aromatic H)

^{13}C nmr (50.32 MHz), $CDCl_3$, δ: 22.3 ($-NCOCH_3$), 28.5 (C-4), 44.1 (C-3), 52.6* (C-3' $-OCH_3$), 56.3* (C-1), 70.9 (C-2'), 75.1 (C-1'), 101.3 ($-OCH_2O-$), 108.2 (C-8), 110.0 (C-5), 127.0 (C-4a), 127.8 (C-8a), 146.5 (C-7), 147.5 (C-6), 172.2 (C-3'), 173.2 ($-NCOCH_3$)

MS (EI): 218 (80), 176 (100).

MS (CI, NH_3): 338 (M+1)(15), 248 (100), 220 (25), 176 (60), 126 (30), 124 (30), 77 (15).

Formula weight: calculated for $C_{16}H_{20}NO_7$ (M+H): 338.1240

Found: 338.1251

3.20 Oxidation of 125 to N-acetyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (1R)-carboxaldehyde 126

The diol 125 (120 mg) was dissolved in methanol (10 mL) at 0°C. Sodium periodate (90 mg) was dissolved in water (1 mL) and added to the diol and stirred for 1.5 h. The reaction mixture was filtered and the residue was washed with cold methanol and the combined filtrates were evaporated below 30°C. The residue was taken up in dichloromethane, dried over $MgSO_4$ and evaporated. Evaporation from dry benzene was necessary to remove traces of water. The aldehyde 126, obtained as an oil, was used in further operations without additional purification. (84 mg, 3.401×10^{-4} mol, 96%) $[\alpha]_D^{25}$ +95.91° (c 1.76, $CHCl_3$)

^1H nmr (200 MHz), $CDCl_3$, δ: 2.23 (3H, s, $-NCOCH_3$), 2.77 (2H, apparent t, J=5.8 Hz, C-4 H's), 3.64 (2H, apparent q, J=5.8 Hz, C-3 H's), 5.73 (1H, s, C-1 H), 5.95 (2H, s, $-OCH_2O-$), 6.64 (1H, s, aromatic H), 6.84 (1H, s, aromatic H), 9.45 (1H, s, C-1' H)

^{13}C nmr (50.32 MHz), $CDCl_3$, δ: 21.8 ($-NCOCH_3$), 29.3 (C-4), 43.4 (C-3), 63.5 (C-1), 101.5 ($-OCH_2O-$), 108.3[a] (C-8), 108.8[a] (C-5), 121.1[b] (C-4a), 128.9[b] (C-8a), 147.1[c] (C-7), 147.8[c] (C-6), 170.7 ($-NCOCH_3$), 195.7 (C-1')

MS (EI): 247 ($M^{+\cdot}$) (5), 230 (15), 218 (60), 204 (20), 176 (100)

Formula weight: calculated for $C_{13}H_{13}NO_4$ (M): 247.0857

Found: 247.0857

3.21 Reduction of 126 to the Alcohol 127

The aldehyde 126 (120 mg, 3.56×10^{-4} mol) was dissolved in methanol at 0-5°C and sodium borohydride (80 mg) was added slowly over 1 h. The reaction was allowed to continue for 45 min. The reaction mixture was evaporated and chromatography on silica gel using 5% methanol in chloroform afforded 127 as a clear oil. (37 mg, 1.49×10^{-4} mol, 42%)

$[\alpha]_D^{25}$ -29.95° (c 1.85, $CHCl_3$)

^1H nmr (200 MHz), CD_3OD, δ:2.16 (3H, s, $-NCOCH_3$), 2.40-2.86 (2H, m, C-4 H's), 3.16-3.62 (4H, m, C-3 H's and C-1' H's), 5.03 (1H, t, J=6.0 Hz, C-1 H), 6.06 (2H, s, $-OCH_2O-$), 6.80 (1H, s, aromatic H), 6.89 (1H, s, aromatic H)

MS (DCI, NH_3): 250 (M+1) (100), 218 (20), 176 (20)

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