USE OF IMINES AND IMINIUM SALTS IN ALKALOID SYNTHESIS

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by

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ABSTRACT

The usefulness of imines and iminium salts in the convergent synthesis of alkaloids and their synthetic analogues is described. Thus the anion derived from [3,4-*c*]pyridin-3[1*H*]-one, by treatment with LDA (lithium diisopropylamide) or LHS, (lithium bis-trimethylsilylamide) reacts with 2-methyl-3,4-dihydro-isoquinolinium salts yielding aza analogues of phthalideisoquinoline alkaloids. The condensation of the same anion with 3,4-dihydroisoquinolines has provided, in a single step, azaprotoberberines containing the benzo[*a*]pyrido[3,4-*g*]quinolizine structure found in a number of *Alangium* alkaloids.

The reaction of methyllithium with oxoberberine as a means of introducing a methyl group C-8 is described. The resulting iminium salt was reduced to a mixture of racemic α- and β-8-methylcanadines. This reaction has been applied to the synthesis of the *Alangium* alkaloid (±)-alamaridine.

Condensation of lithium salts of 3-cyano-4-methylpyridine and 3-cyano-4-methyl-5-vinylpyridine with a complex of 3,4-dihydroisoquinolines and trimethylsilyl trifluoromethanesulphonate has been studied. The amidines formed as condensation products were transformed by hydrolysis into 5,6,13,14-tetrahydro-8*H*-isoquino[2,1-*b*][2,7]-naphthyridin-8-ones, a ring system found in several alkaloids of *Alangium lamarckii*. These reactions have been employed in the synthesis of the

Alangium alkaloids, (±)-alangimaridine and alangimarine. The usefulness of this reaction has been further demonstrated in the synthesis of *N*-benzyl derivatives of 3,14-dihydronauclefine and 3,14-dihydroangustine containing 8,13,13b,14-tetrahydroindolo[2',3':3,4]pyrido[1,2-*b*][2,7]-naphthyridin-5[7*H*]-one.

Dedicated To

My Parents

and to

Those who taught me chemistry

Though analogy is often misleading,

it is the least misleading thing we have.

S. Butler, Notebooks (1912)

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CHAPTER 1

INTRODUCTION

1.1 HISTORY

Alkaloids are a diverse group of nitrogen containing natural products formed in nature by a variety of biosynthetic pathways and many of them are pharmacologically active. It has been estimated that the number of alkaloids now exceeds 5000.

The history of alkaloids is almost as old as human civilization. Archaeologists have recovered seeds and capsules of the opium poppy (*Papaver somniferum*) from neolithic sites, chiefly in western and central Europe dating its use to ca. 2500 BC. Mankind has long made use of plants containing alkaloids in potions, medicines, teas, poultices, and poisons.

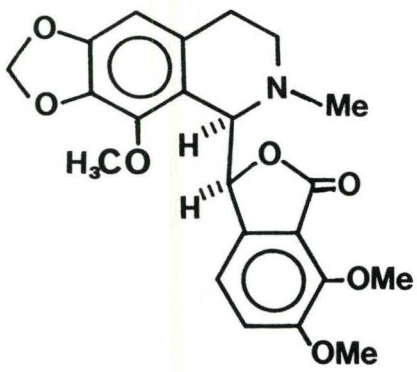
The dried latex of the poppy, "opium", was the first crude drug to be investigated chemically for its analgesic and narcotic properties. Derosine in 1803 isolated a semipure alkaloid from opium and named it narcotine 1. Two years later Serturner isolated morphine 2 and discovered its basic character. As a result of Serturner's extensive research work published in 1817 on the chemical and pharmacological investigation of morphine 2, he became famous not only as a discoverer of morphine, but also as the founder of the entire new field of plant

alkaloids and their chemistry. Pelletier and Caventou in a brief period (1807-1820) reported the isolation of a number of alkaloids many of them of great pharmacological importance, including strychnine 3, brucine 4, emetine 5, piperine 6, caffeine 7, cinchonine 8, quinine 9, and colchicine 10.(Figures 1 and 2). In 1826, Pelletier and Caventou also isolated coniine 11, an alkaloid responsible for the death of Socrates. Because of its simple molecular structure, coniine was the first alkaloid to be characterized (1870) and the first to be synthesized (1886).

With the introduction of sophisticated analytical and spectroscopic instruments, advances in the isolation and structural determination of new alkaloids have been dramatically rapid. Development of new synthetic methods and discovery of new synthetic reagents have contributed an enormous literature in the synthesis of alkaloids.

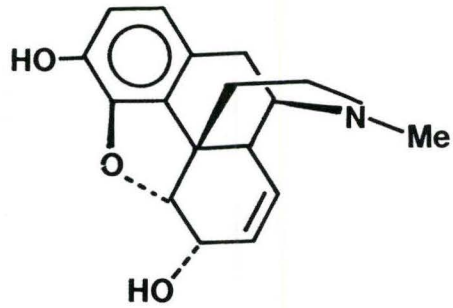
1.2 DEFINITION

The term "alkaloid" was introduced by a pharmacist W. Meissner in 1818 and implies a compound similar to an alkali but differing greatly in many of its properties from "true" alkalis. The following definition is given in Meyer's Konversations-Lexikon of 1896 "Alkaloids (plant bases) those substances that occur characteristically in plants and are frequently distinguished by their remarkable physiological activity; they contain carbon, hydrogen, and nitrogen and in most cases oxygen as well; in some respects they resemble alkalies (hence the name)". The first modern definition by Winterstien and Trier (1931) described these substances in a much broader sense as basic nitrogenous compounds of



1

Narcotine

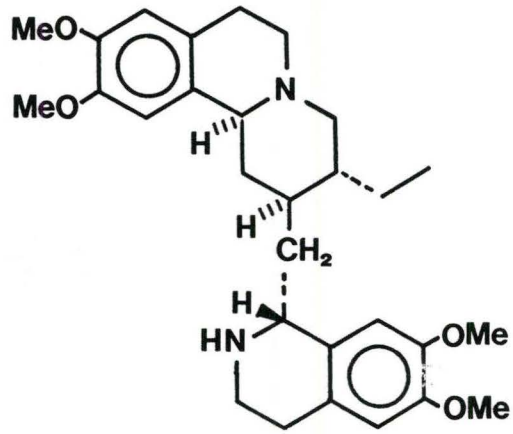


2

Morphine

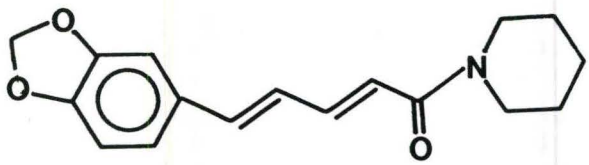
3 **R = H** *Strychnine*

4 **R = OCH_3** *Brucine*



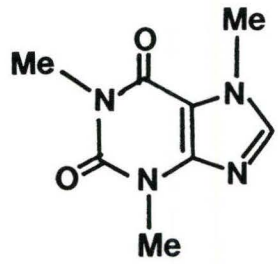
5

Emetine



6

Piperine

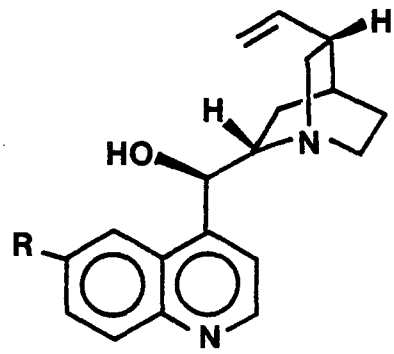


7

Caffeine

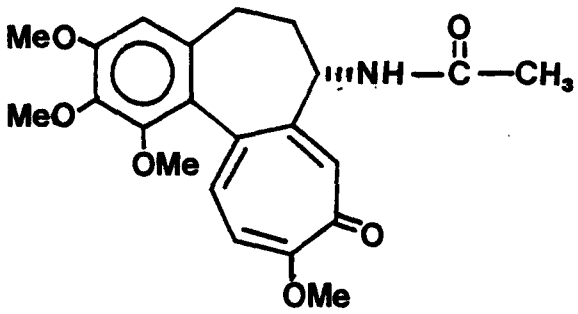
Some representive alkaloids

FIGURE 1



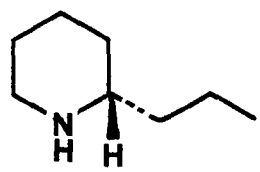
8 **R = H** *Cinchonine*

9 **R = OCH_3** *Quinine*



10

Colchicine



11

Coniine

Some representive alkaloids

FIGURE 2

either plant or animal origin. A recent and more satisfactory definition is given by S.W. Pelletier in his book, "Alkaloids, Chemical and Biological Perspectives", John Wiley and Sons, Inc., 1983; "An alkaloid is a cyclic organic compound containing nitrogen in a negative oxidation state which is of limited distribution among living organisms".

1.3 BIOGENESIS

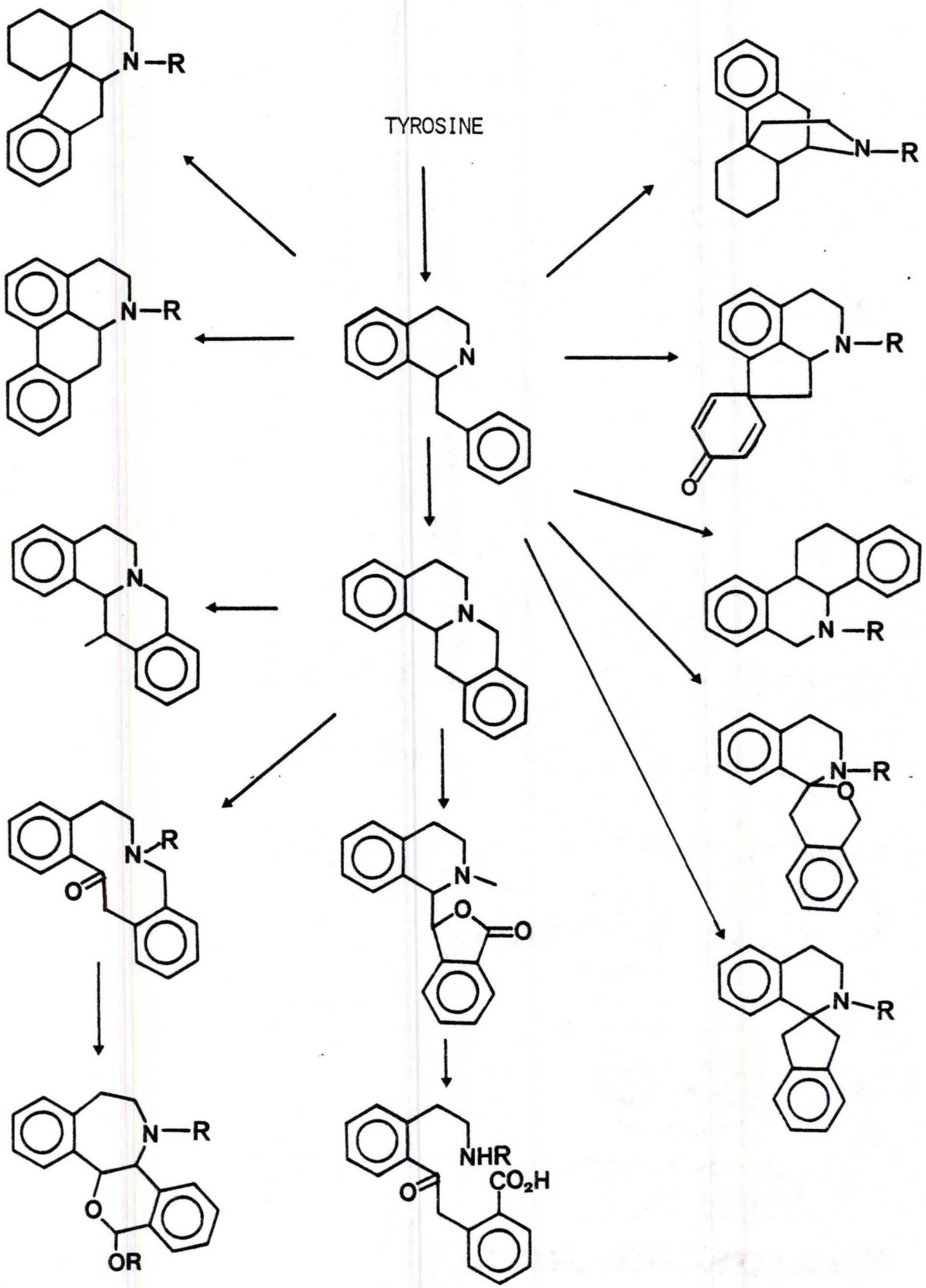
The term biogenesis refers to the manner in which naturally occurring organic compounds are synthesized, altered or degraded by living organisms, and alkaloid in this regard are also of interest. Although the same alkaloids may occur in various organisms, its biosynthetic formation may not necessarily be the same.

An example of the diverse alkaloids arising from the simple precursor, tyrosine 12, is shown in Scheme 1, and the manner in which tyrosine is converted to norlandanosoline 16, is depicted in Scheme 2.

For a detailed account on the history, occurrence, definition, classification, and biogenesis of alkaloids, readers are referred to these books (1-4).

1.4 ALKALOID SYNTHESIS WITH IMINES AND IMINIUM SALTS

Imines and iminium salts play an important role in the biosynthesis both of the α-amino acids and alkaloids. For instance, the formation of norlandanosoline 16 in nature proceeds via imine 15. Combination of 3,4-dihydroxyphenylethylamine 13 and 3,4-dihydroxyphenyl-acetaldehyde 14 generates the imine 15 which then undergoes cyclization



SCHEME 1

Biogenetic relationships among the isoquinoline alkaloids

to 16 (5) (Scheme 2). Bioformation of scoulerine 19 proceeds via iminium ion intermediate 18 (formed by oxidation of reticuline 17) as the key intermediate leading to the protoberberine system (6,7) (Scheme 3).

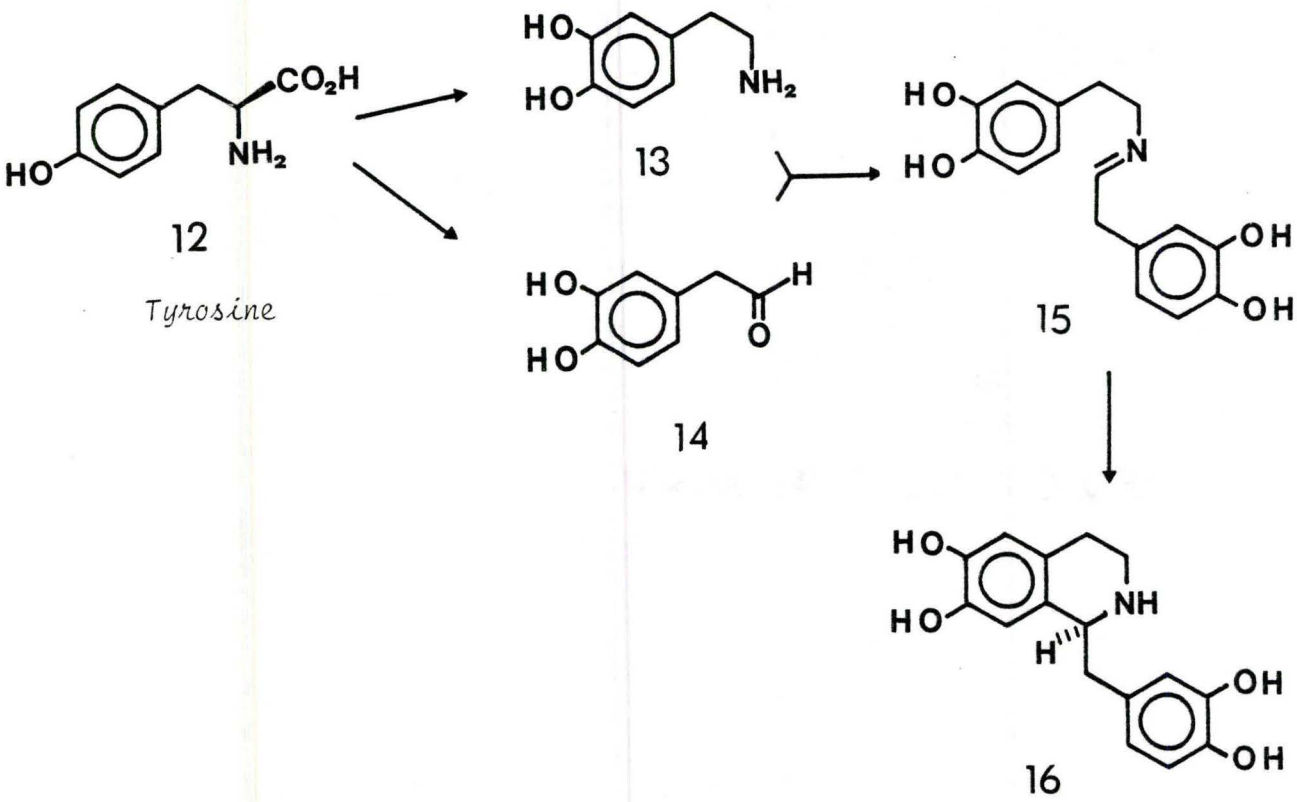
Since the first laboratory synthesis of coniine 11, a large number of alkaloids have been synthesized, many of them by several different synthetic strategies. These syntheses along with other aspects of alkaloid chemistry are reviewed in several series (8-10).

The present study deals with the development of new synthetic methods utilizing imines and iminium salts in the total synthesis of several alkaloids and their synthetic analogues. The alkaloidal skeletons which have been constructed in this study include benzo[2,1-*b*]-[2,7]naphthyridines, indolo[2',3';3,4]pyrido[1,2-*b*][2,7]naphthyridines and aza analogues of phthalideisoquinolines.

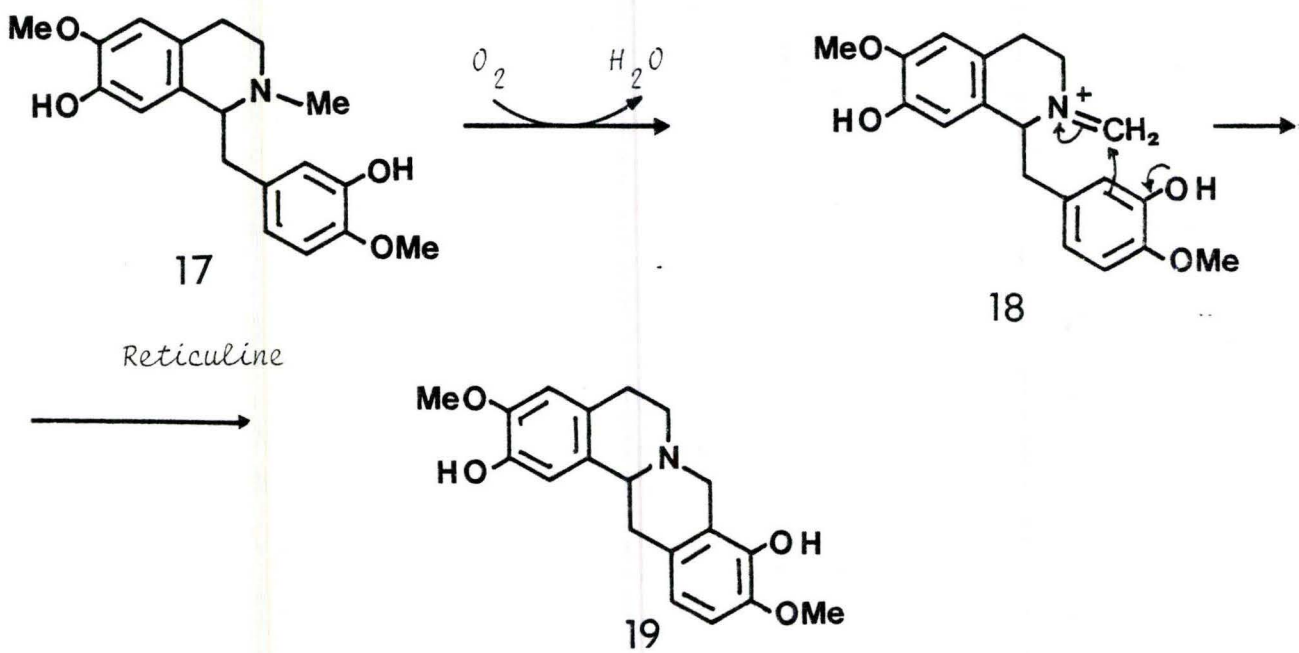
Several comprehensive reviews (11-14) have already appeared on the use of imines and iminium salts in heterocyclic chemistry. Nevertheless, it seems worthwhile to mention here some of the classical and modern approaches in alkaloid synthesis using these intermediates. Bischler-Napieralski, Pictet-Spengler, Pomeranz-Fritsch, and Mannich reactions are prominent in alkaloid syntheses, especially in isoquinoline chemistry. Other routes involving direct coupling, thermolytic, and Diels-Alder reactions have also contributed to this subject in recent years. Some of these approaches are briefly discussed here.

(i) Bischler-Napieralski Reaction

The most valuable and frequently used method in the synthesis of



SCHEME 2



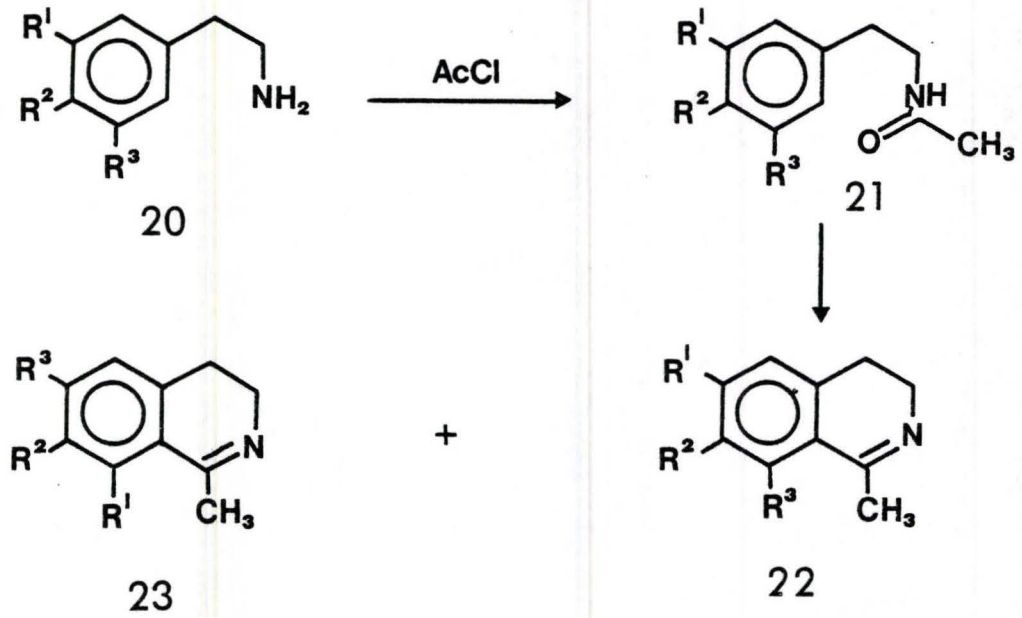
SCHEME 3

alkaloids, especially isoquinoline compounds, is the Bischler-Napieralski reaction (15-17). It involves cyclodehydration of an N-acyl derivative 21 of β-phenylethylamines 20 to a 3,4-dihydroisoquinoline in the presence of Lewis acids in a dry aprotic solvent. If the R^1 and R^3 groups are different, two products, are formed, 22 and 23, as shown in Scheme 4.

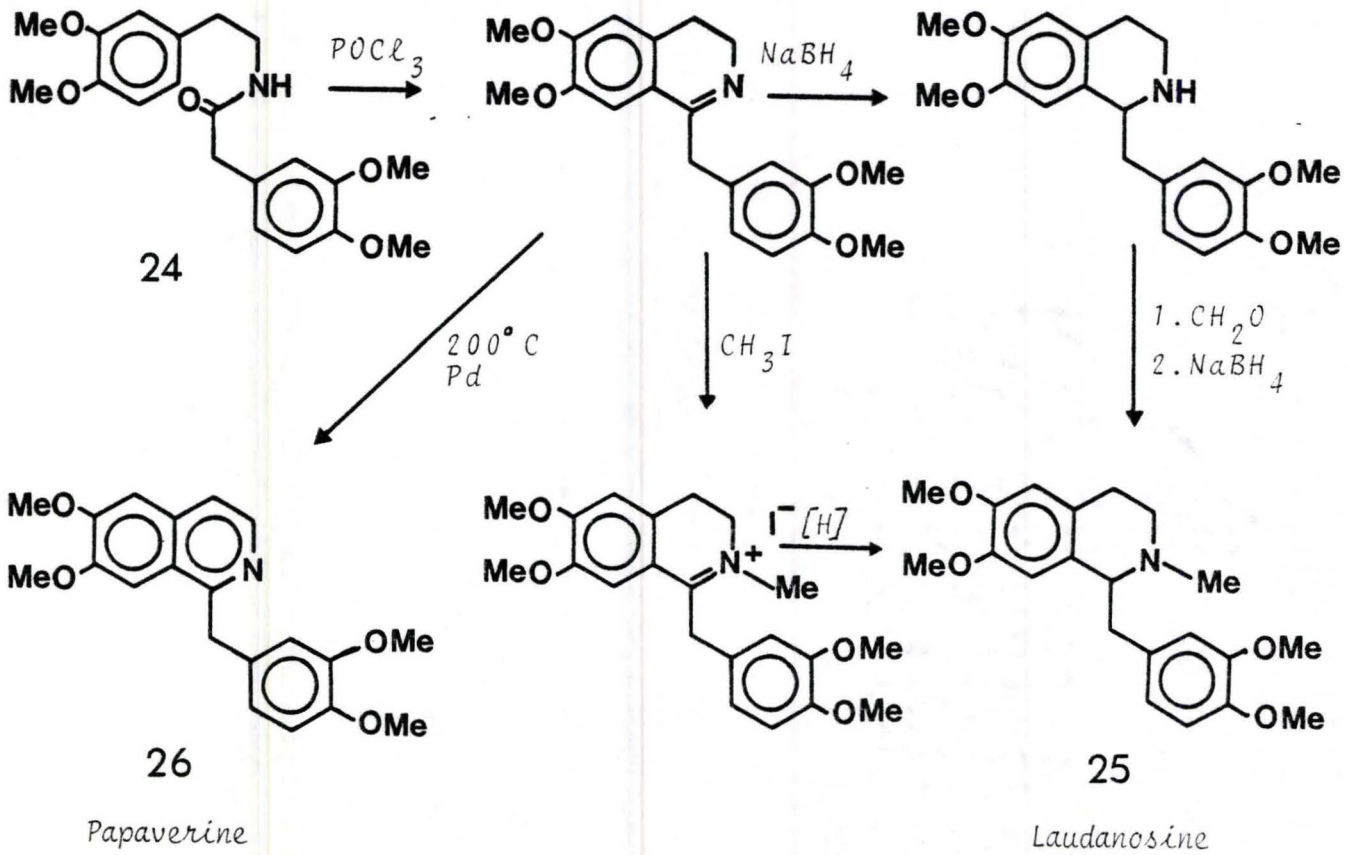
The reaction was discovered in 1893 by Bischler and Napieralski (18), who treated β-phenylethylformamide with phosphorus pentoxide or zinc chloride at high temperature. Investigation of a large number of Lewis acids (e.g. $POCl_3$, P_2O_5, $SbCl_6$, $SnCl_4$, $ZnCl_2$, $FeCl_3$, trifluoroacetic anhydride, trifluoromethylsulfonic acid etc.) and solvents, has shown that this reaction proceeds under various conditions usually milder than those used in the original procedure; therefore it is one of the most popular methods in isoquinoline synthesis. For example, the synthesis of laudanosine 25 (19,20) and papaverine 26 (21) from 24 using this reaction is depicted in Scheme 5. The commercial process for the manufacture of reserpine also involves this cyclization after the critical substitutions and stereochemistry have been established (22,23). Recently a comprehen-sive review by Fodor and Nagubundi (24) has covered the mechanistic details of this reaction.

(ii) Pictet-Spengler Reaction

The Pictet-Spengler reaction is the condensation of a phenylethylamine and an aldehyde under acidic conditions to give a tetrahydroisoquinoline directly and is a special case of the Mannich reaction. In 1911 Pictet and Spengler (25) reported the reaction of



SCHEME 4

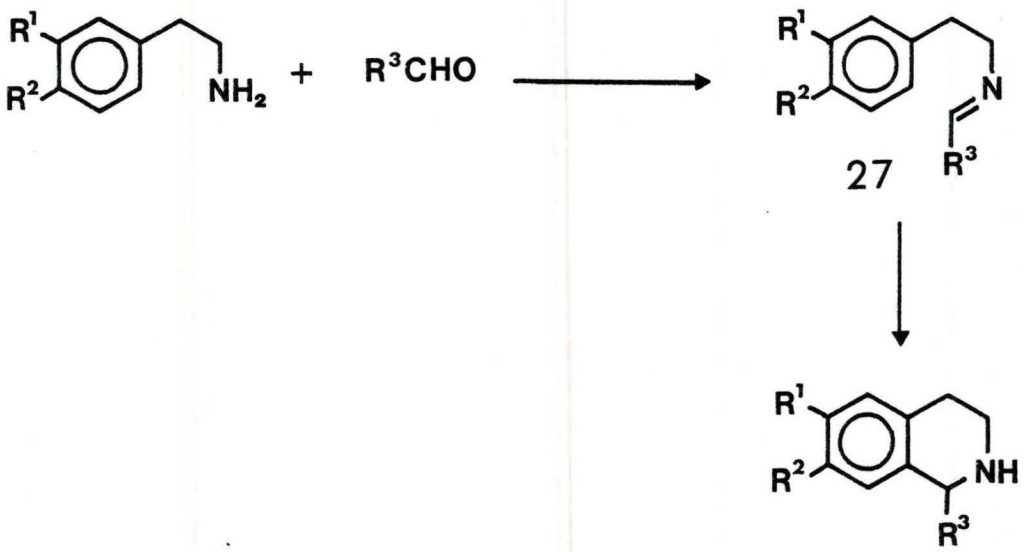


SCHEME 5

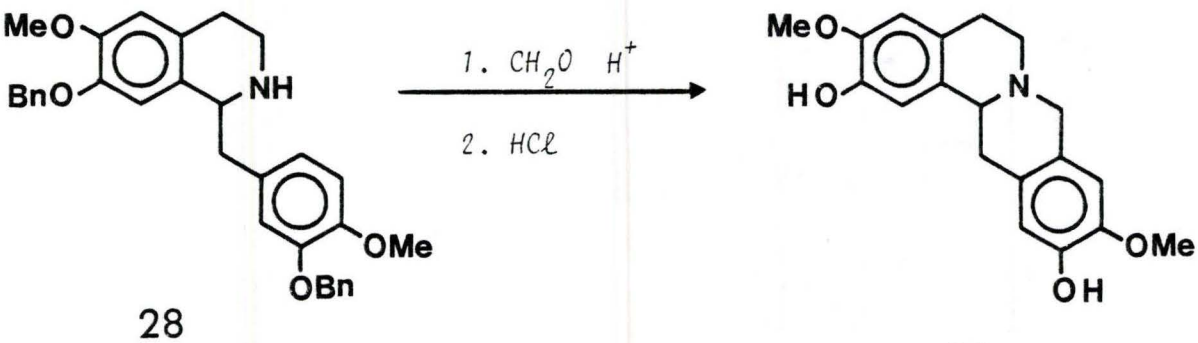
β-phenylethylamine with methylal in the presence of conc. hydrochloric acid to give tetrahydrosioquinoline. The reaction was extended immediately by Decker and Becker (26) to the condensation of substituted phenylethylamines with various aliphatic and aromatic aldehydes. The reactions were carried out in two steps as shown in Scheme 6, and the intermediate imine 27 was often isolated before the addition of the condensing agent. Whaley and Govindachari (27) have reviewed the literature on this reaction up to about 1950. More recent applications to alkaloid synthesis continue to appear in the literature and have been collectively discussed in several places (28-31). The reaction has been widely used in the synthesis of a number of alkaloids because it proceeds usually in good yield and under mild reaction conditions. A typical example of its use in the synthesis of berberine alkaloids (32) is exemplified by the conversion of (-)-*O*-*O*-dibenzyl-norreticuline 28 into (-)-coreximine 29 (Scheme 7).

The probable mechanism of this reaction involving an iminium ion intermediate is depicted in Scheme 8. The Shiff base 27 undergoes cyclization to the corresponding isoquinoline derivative 30 under acidic conditions. The electrophilic ring closure is facilitated by electron-donating groups in a suitable position and in many cases a free phenolic group ortho or para to the site of ring closure is required for a successful reaction.

The obvious extension of this reaction to the synthesis of tetrahydro-β-carbolines has provided one of the most versatile and general approaches to this system (27). The synthesis of 3-methyl



SCHEME 6

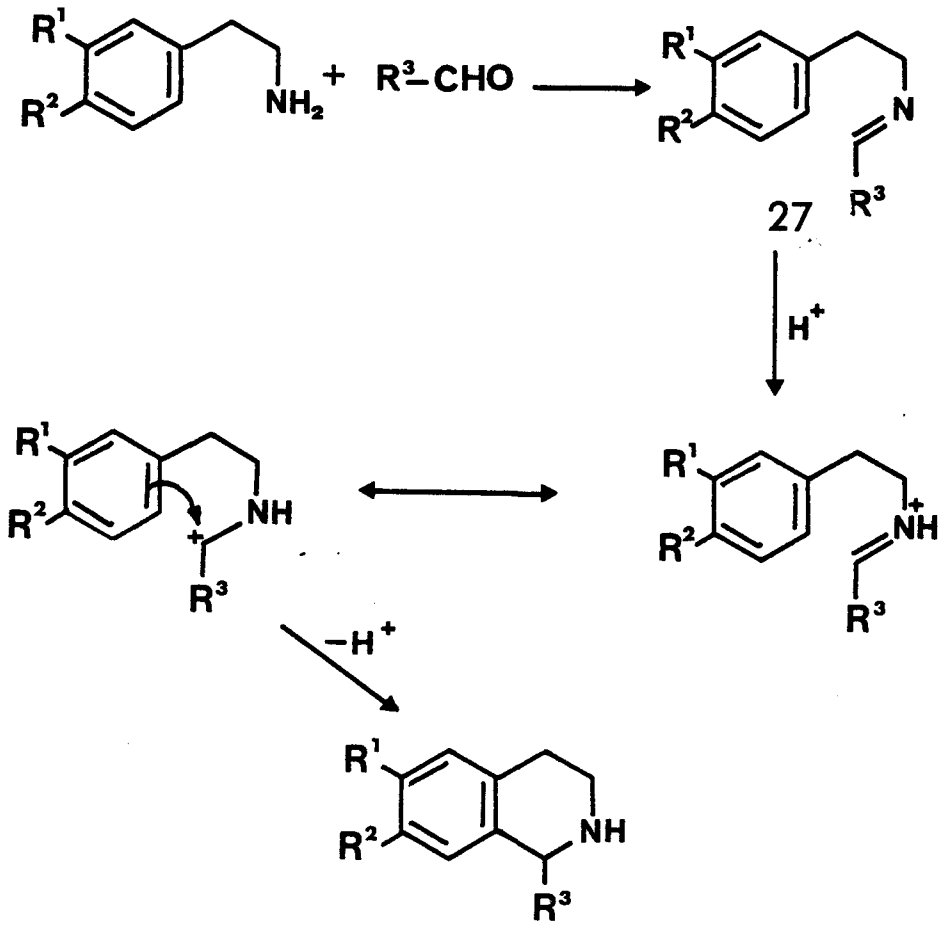


28

29

Coreximine

SCHEME 7



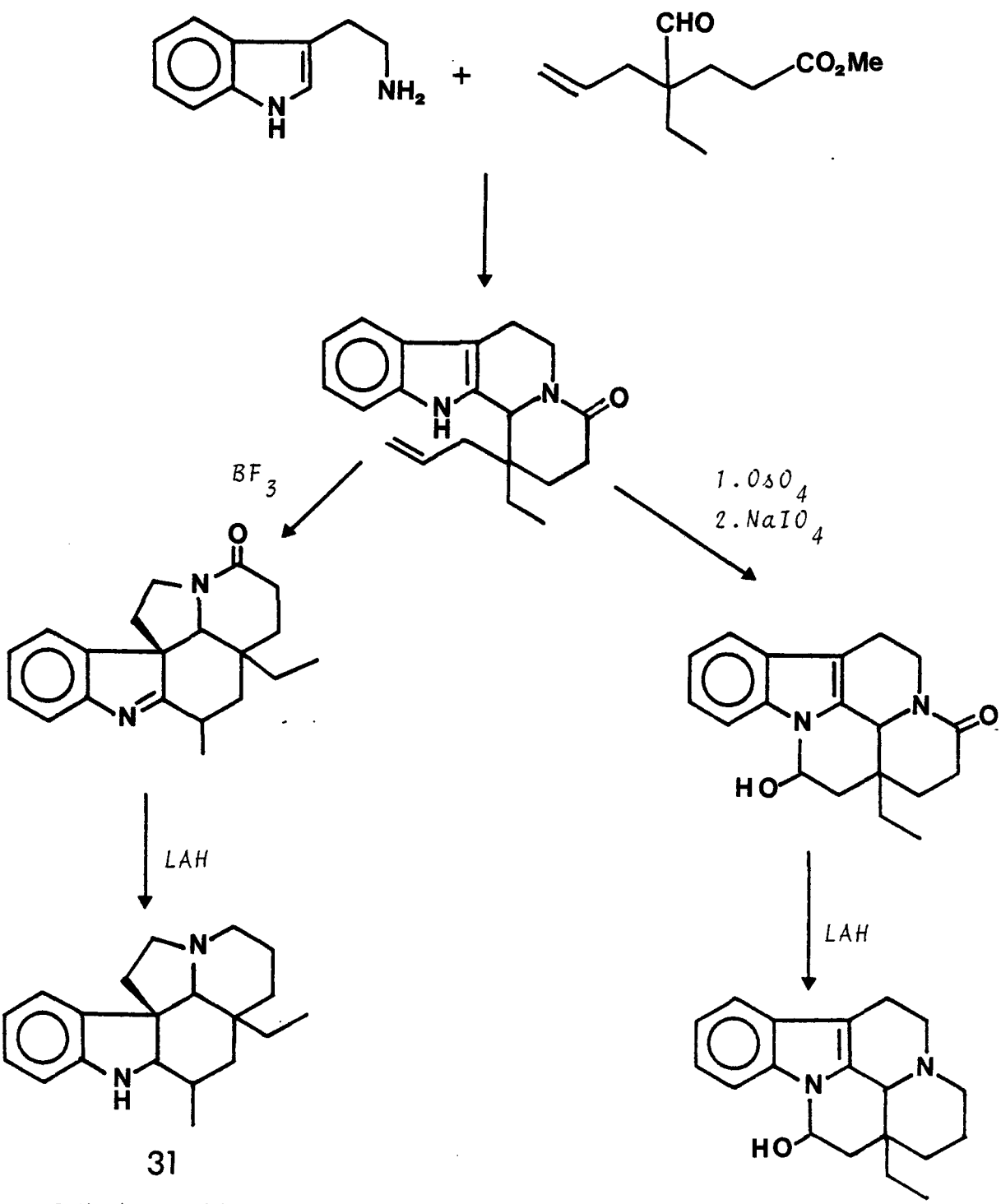
SCHEME 8

aspidospermidine 31 and eburnamine 32 exemplify the use of this reaction in the indole series (33) (Scheme 9).

Recently the Pictet-Spengler cyclization in aprotic media has also been realized, adding another important dimension to the use of this reaction (34). A number of modifications to the original Pictet-Spengler reaction, now available, generate the iminium ion intermediate under a variety of conditions for further ring closure. These include the Hoffmann modification (35), the Wenkert modification (36-42), and the Rapoport modification (43-45) and all have been used in constructing a variety of heterocyclic systems; the essential features are outlined in Scheme 10.

(iii) Kametani's Thermolytic Reactions

Benzocyclobutene derivatives, upon heating, undergo ring opening to give reactive o-quinodimethanes which can couple with imines and dienophiles (51,52). Kametani and co-workers (28,53-55) have extensively used this strategy in the synthesis of isoquinoline and indole alkaliods. For example, thermolysis of the hydrochloride salt of cyclobutene derivative 33 at 150-170°C for 20 min, gave the protoberberinium salt 35, *via* intermediates 34a and 34b, which on reduction gave xylopinine 36 in excellent yield (54) (Scheme 11). Similarly, thermolysis of 1-cyano-benzocyclobutenes 37 with 3,4-dihydro-6,7-dimethoxyisoquinoline gave the tetrahydroprotoberberines 38 in good yields (55). These reactions proceeded regioselectively as shown in Scheme 12. Other examples of this reaction applied to other ring systems are shown in Scheme 13.



31

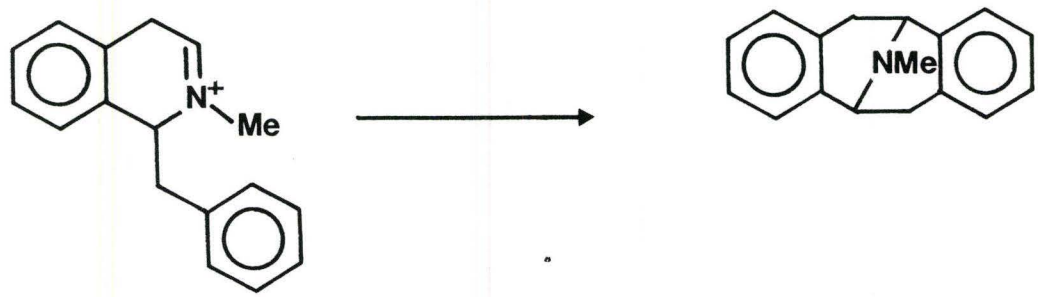
3-Methylaspidospermidine

32

Eburnamine

SCHEME 9

REFERENCE



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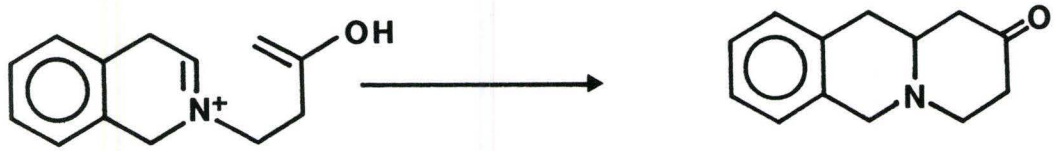
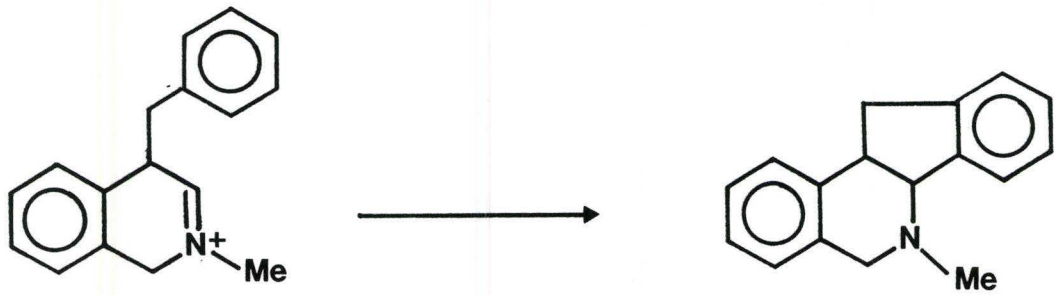


47



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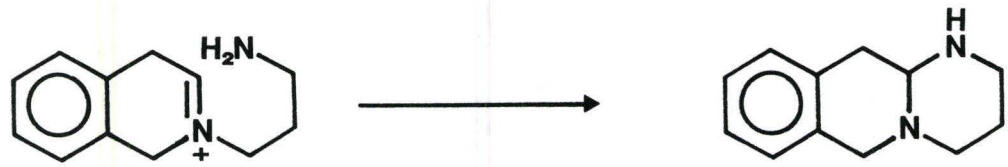
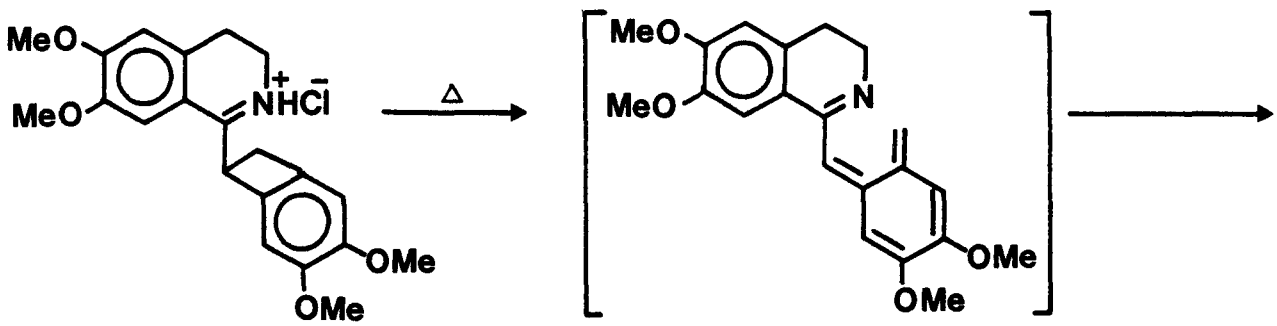
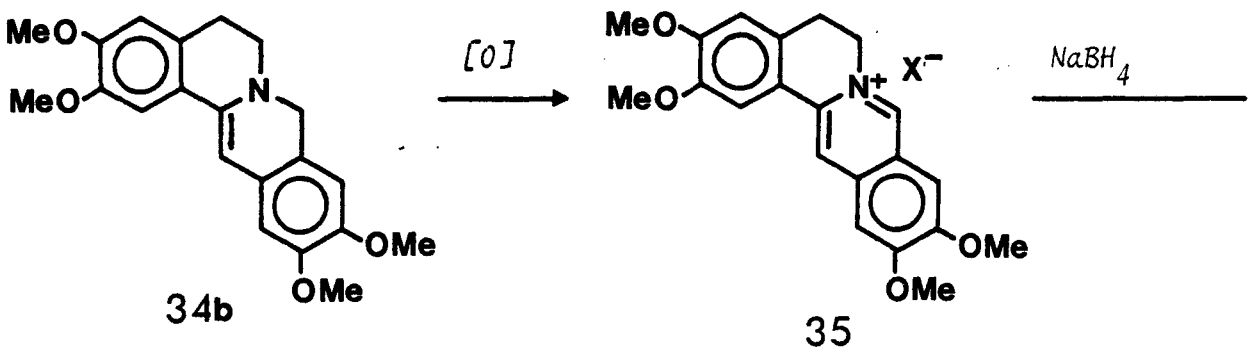


50

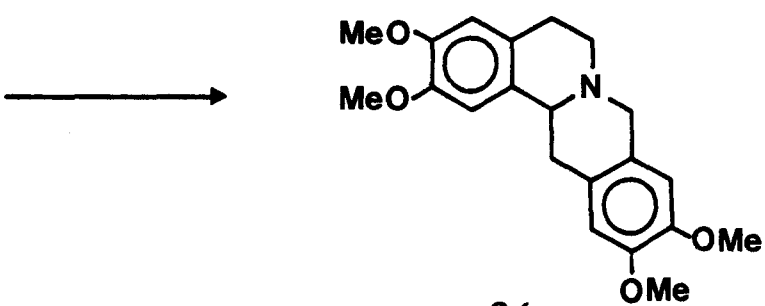
SCHEME 10



33 34a

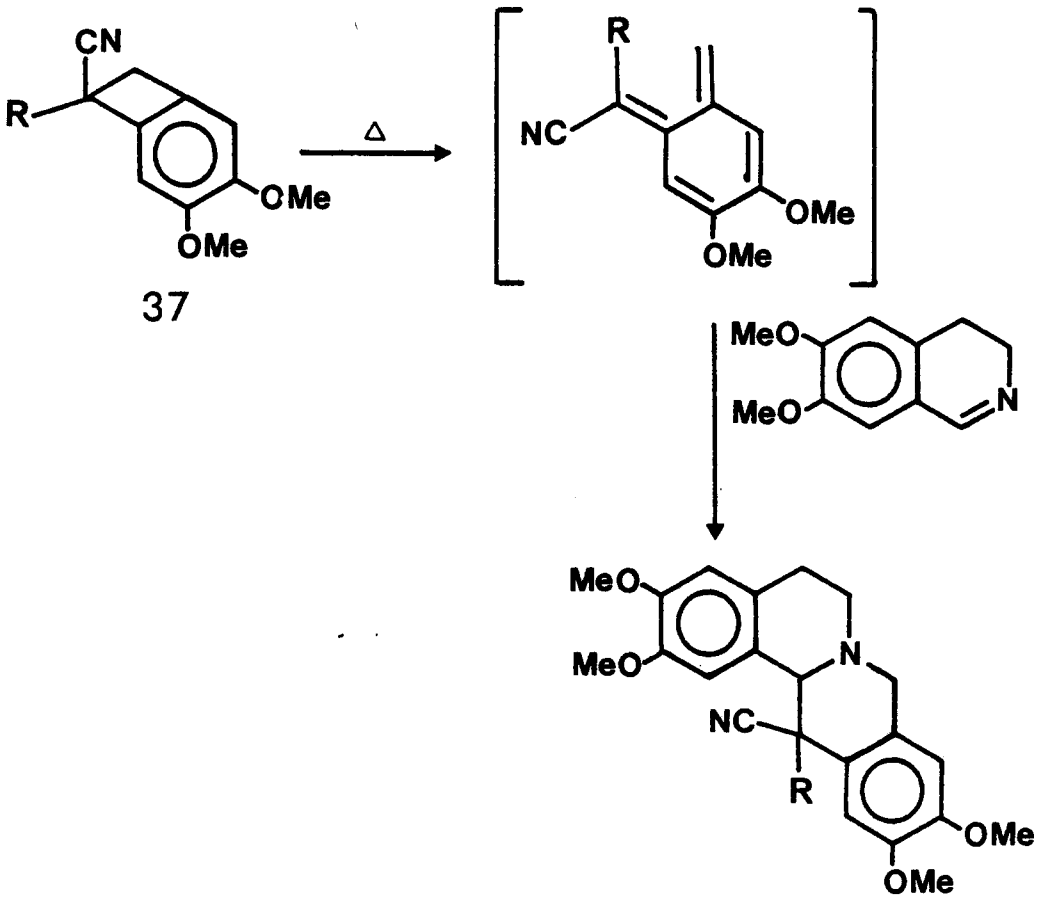


34b 35



36

SCHEME 11



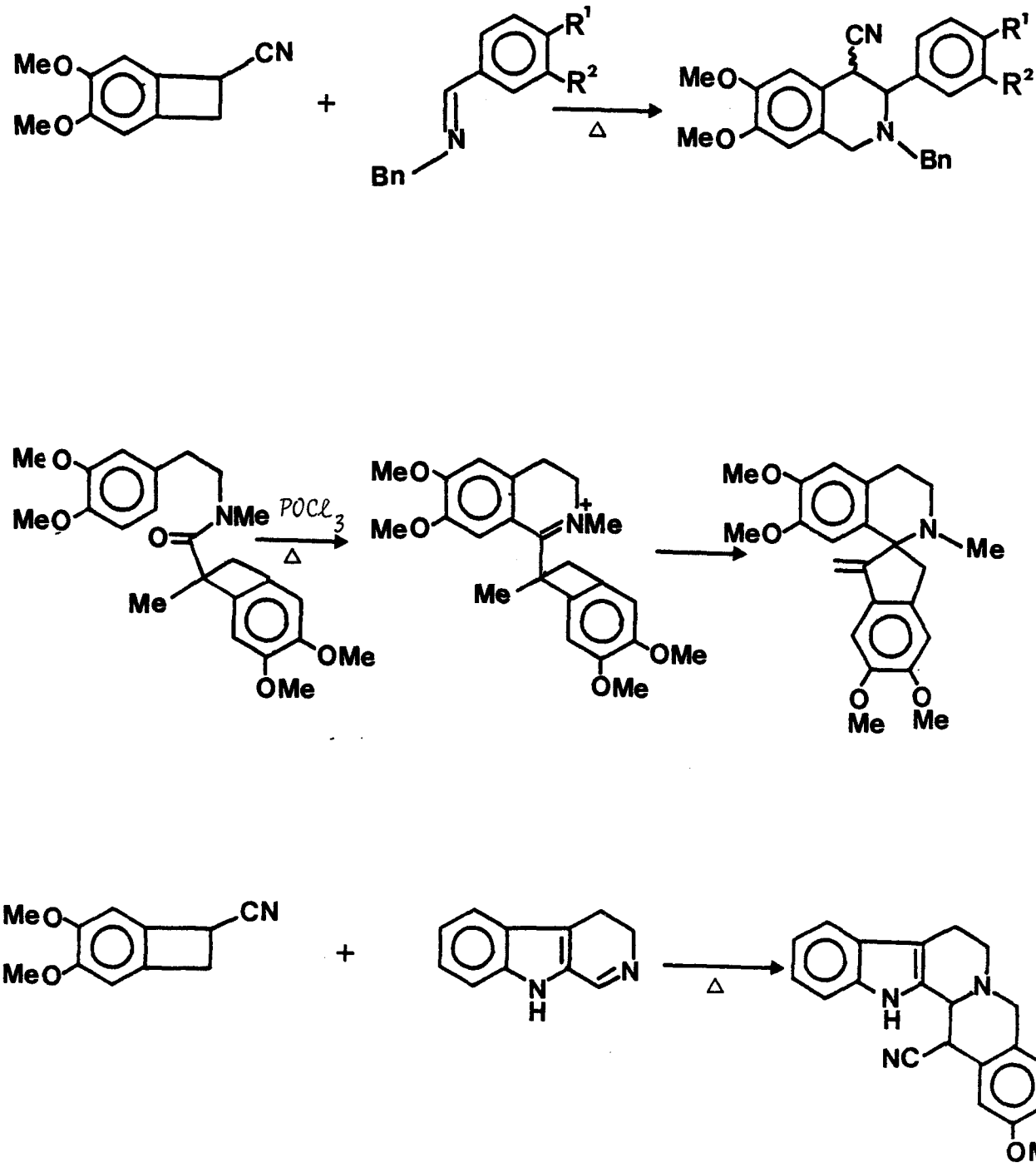
37

38

R = H , Me

(*cis* : *trans* = 1:1.5)

SCHEME 12


MeO
MeO
CN
+
R1
R2
N
Bn
Δ
CN
MeO
MeO
N
Bn
R1
R2
NMe
POCl3
Δ
Me
OMe
OMe
+NMe
N
Me
O
Me

SCHEME 13

(iv) Other Cycloaddition Reactions

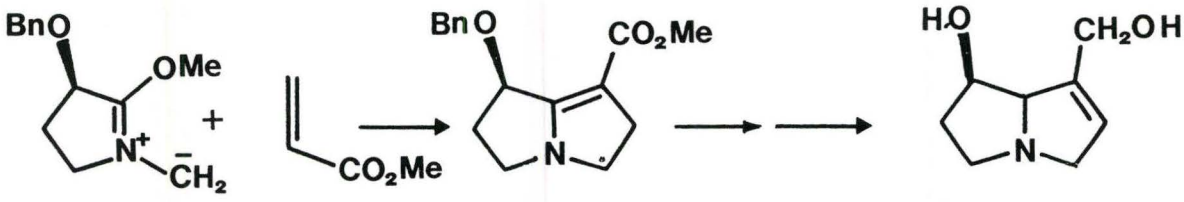
In the last decade 1,3-dipolar (both inter and intramolecular) cycloadditions have proved to be powerful methods in the synthesis of natural products. Imine or iminium ion equivalents may be used as synthons in these reactions. Their application in alkaloid synthesis has been reviewed by Tufariello (56) and Padwa (57) and therefore will not be discussed here. Synthesis of retronecine **39** (Scheme 14) and septicine **40** (Scheme 15) exemplify these 1,3-dipolar reactions.

Bohlmann and co-workers (58) have added thermally several imines to ethyl 2,4-pentadienoate **41** as shown in Scheme 16. Addition of **41** to 3,4-dihydroisoquinoline yielded the tricyclic compound **42** and addition to Δ^1-piperidine gave the bicyclic compound **43** which was converted to lupinine **44** (Scheme 16). Dannhardt and Wiegreb (59) have condensed several cyclic imines with dienes generated *in situ*, in alkaloid synthesis. For recent literature on Diels-Alder cycloaddition reactions of dienes and dienophiles containing heteroatoms in the synthesis of heterocycles and alkaloids, readers are referred to reviews by Weinreb and Staib (60), by Boger (61) and by Mariano and co-workers (62).

(v) Condensation of Imines with Homophthalic Anhydrides

(a) Haimova's Work

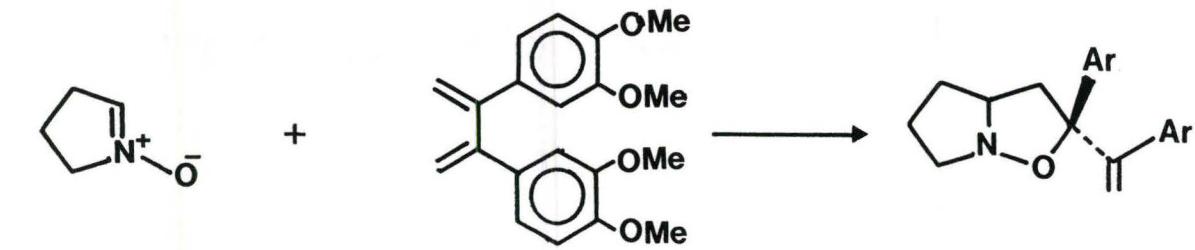
Haimova and co-workers (63) discovered a novel method for the stereoselective construction of 3,4-dihydro-1[2*H*]-isoquinolones **47** by condensing homophthalic anhydrides **45** with acyclic imines **46** (Scheme 17). These reactions proceeded in high yield on brief refluxing in

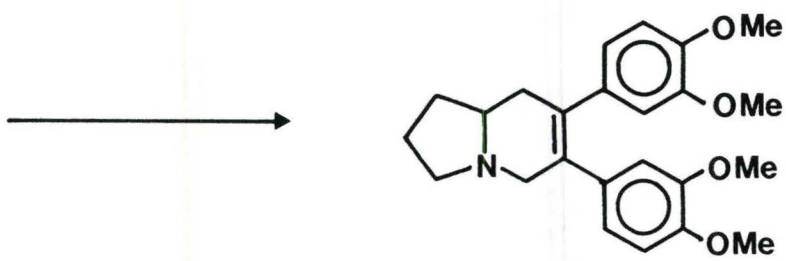


39

Retronecine

SCHEME 14

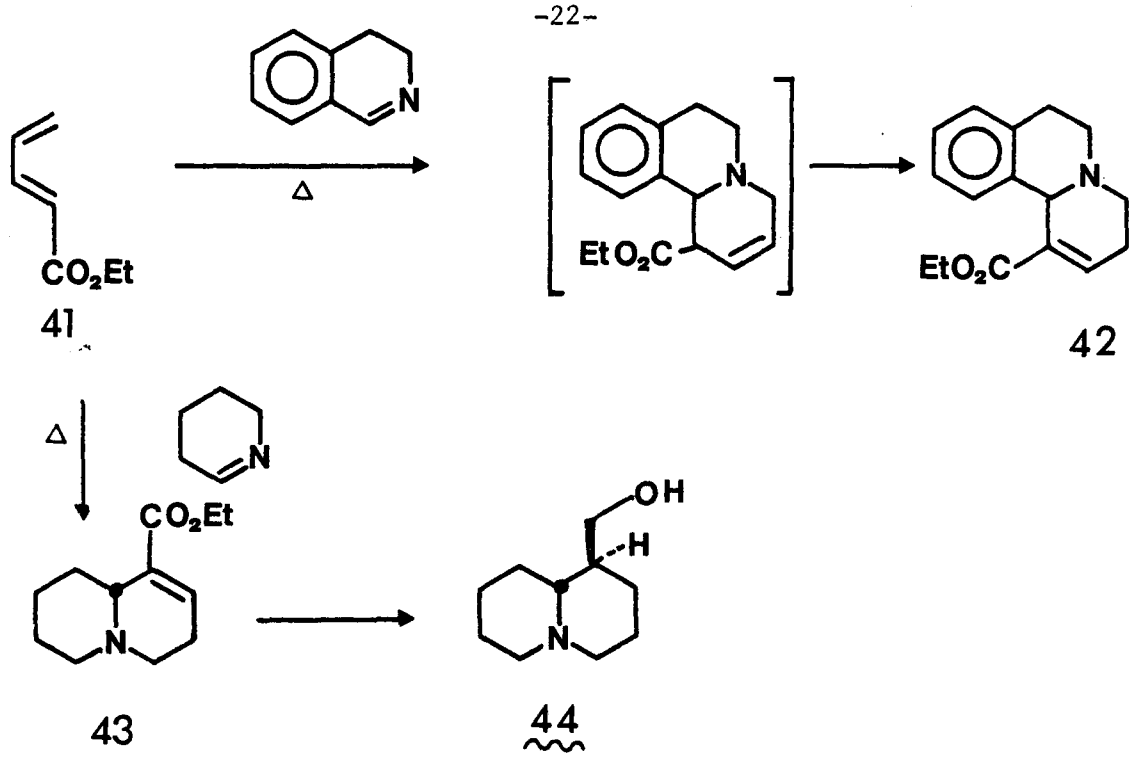




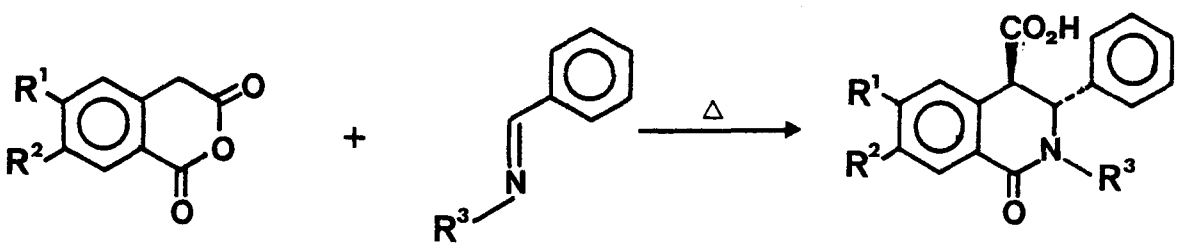
40

Septicine

SCHEME 15



SCHEME 16



SCHEME 17

dichloromethane. Based on these observations, the same group (64) successfully used this strategy in the stereoselective synthesis of protoberberine alkaloids 48 (Scheme 18). In an interesting variant to the above reaction, Haimova and co-workers (65) showed that lactims 49 could be condensed with homophthalic anhydrides (Scheme 19). In a similar manner, lactim 50 was converted into 51 and thence to xylopinine 36 (Scheme 19).

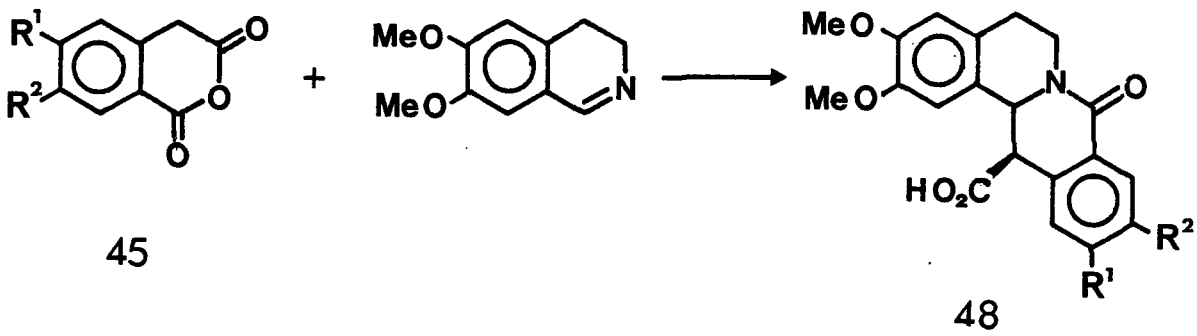
(b) Cushman's Work

Independently Cushman and co-workers (66) investigated the same reaction between imines and homophthalic anhydrides. Contrary to the report by Haimova and co-workers (63), Cushman's group (66) observed a mixture of 3,4-dihydro-1(2H)-isoquinolones in which *cis* 53 and *trans* 54 isomers were formed in the ratio of 1:2 (Scheme 20). Based on this elegant approach, Cushman and Cheng (67) have synthesized a number of benzophenanthridine alkaloids including a stereoselective synthesis of chelidonine. The same group have also synthesized a number of 13-methyl-protoberberines, for example (+)-thalictricavine, using this methodology (68-71). A recent review by Stanoeva and Khalimova (72) has covered the progress in this area.

(vi) Direct Condensation Approaches Using Iminium Salts and Anions

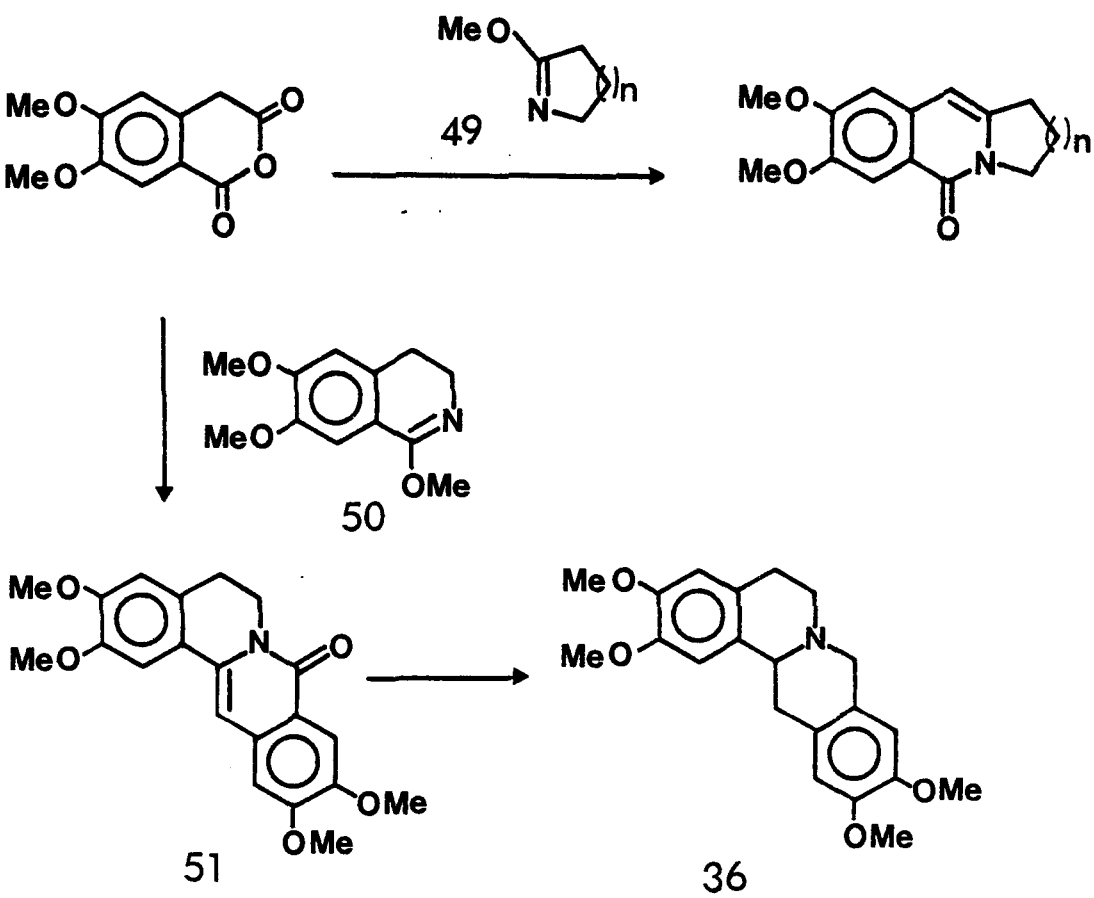
(a) Shono's Work

Shono and co-workers (73) have electroreductively added a variety of alkyl halides to iminium salts. By intramolecular annelation, a



45 48

SCHEME 18



Xylopinine

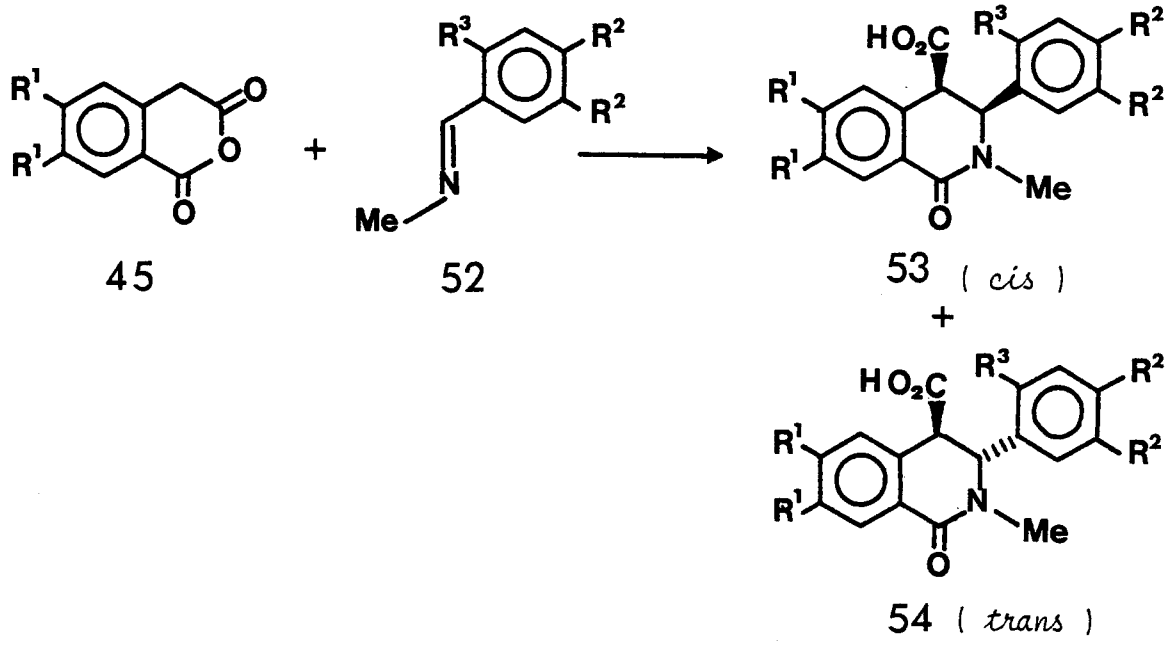
SCHEME 19

number of protoberberine and indole alkaloids were synthesized (Scheme 21, conditions shown in "a"). The usefulness of this reaction was extended to intermolecular condensations providing a convergent route to several benzylisoquinoline and phthalideisoquinoline alkaloids. In this way, the above investigators (74) have prepared laudanosine and several phthalideisoquinoline alkaloids including adlumine and corlumine (55 and 56), α- and β-hydrastine (57 and 58), and α- and β-narcotines (59 and 60) (Scheme 22, conditions shown in "a").

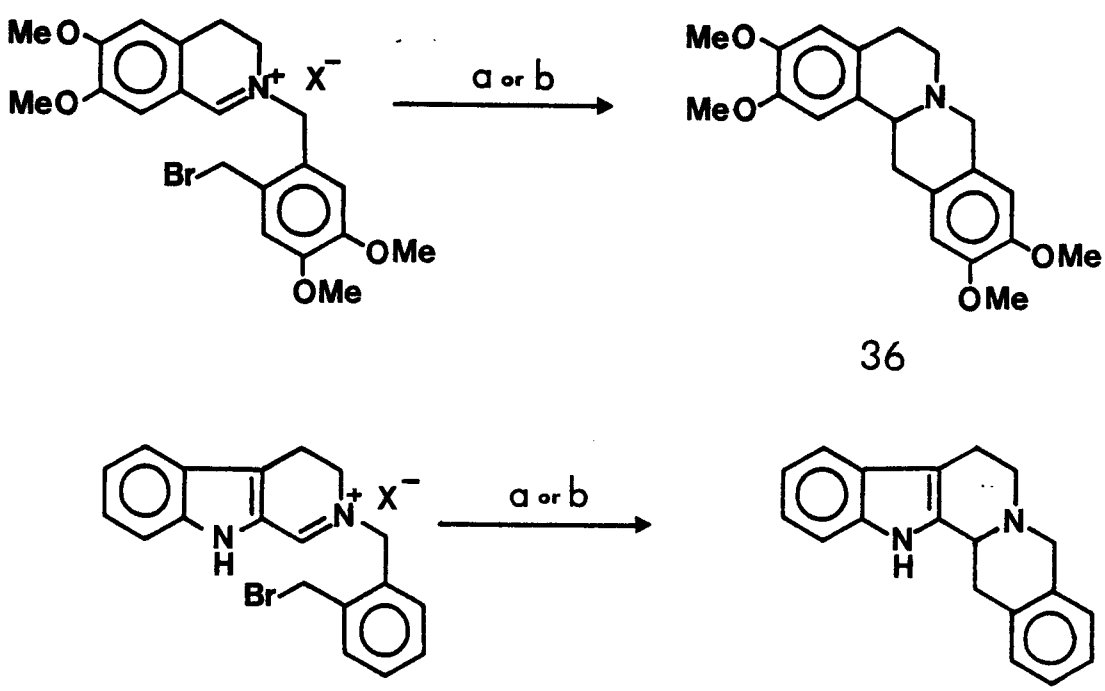
Shono and co-workers (75) in 1983 reported Zn-promoted coupling reactions of iminium salts with a number of alkyl halides. They applied this reaction both inter- and intramolecularly in the synthesis of several alkaloids as shown in Scheme 21 and Scheme 22 (conditions shown in "b").

(b) MacLean's Work

In the first contemporary convergent synthesis of the phthalide-isoquinoline alkaloids, MacLean and co-workers (76) reported the Zn and Zn-Cu couple promoted condensations of several halophthalides with the 2-methylisoquinolinium salts. A full account of this work, published in 1981 (77), reported the preparation of a number of phthalideisoquinoline alkaloids as shown in Scheme 22 (conditions shown in "c"). Both *threo* and *erythro* isomers were formed in equal amounts. Later on, MacLean's group (78,79) reported the first direct condensation of phthalide anions with 2-methyl-3,4-dihydroisoquinolium salts, and a number of phthalide-isoquinoline alkaloids were synthesized by this convergent approach (Scheme 22, conditions shown in "d").



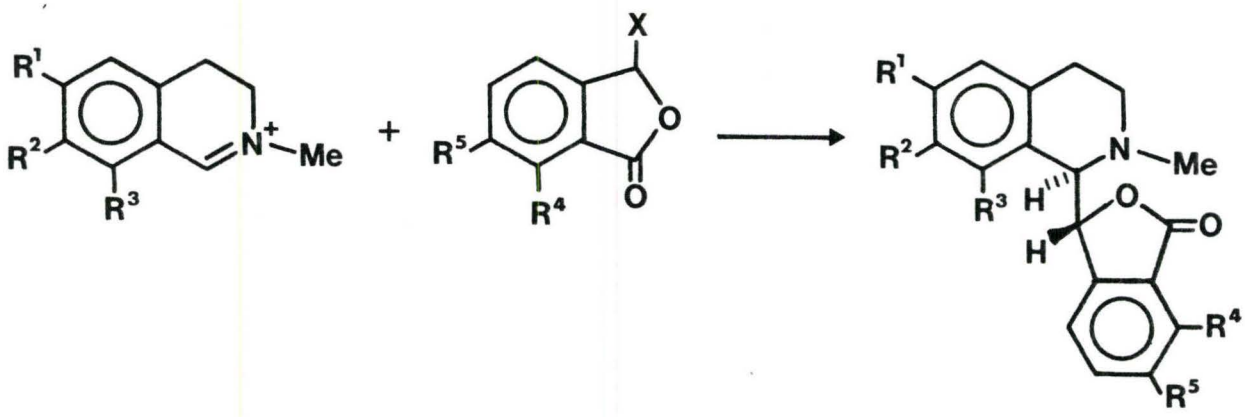
SCHEME 20



a; Electrochemical

b; Zn/CH_3CN

SCHEME 21



a; X= Br, electrochemical reduction

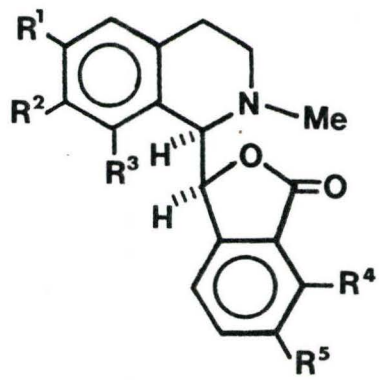
b; X= Br; Zn in CH_3CN

c; X= Cl or Br; Zn or Zn-Cu in DMF

d; X= Li, THF, -40° C

Threo

+



Erythro

		R^1	R^2	R^3	R^4	R^5
Adlumine and corlumine	55 and 56	OCH_3	OCH_3	H	OCH_2O	
α- and β-Hydrastines	57 and 58	OCH_2O		H	OCH_3	OCH_3
α- and β-Narcotines	59 and 60	OCH_2O		OCH_3	OCH_3	OCH_3

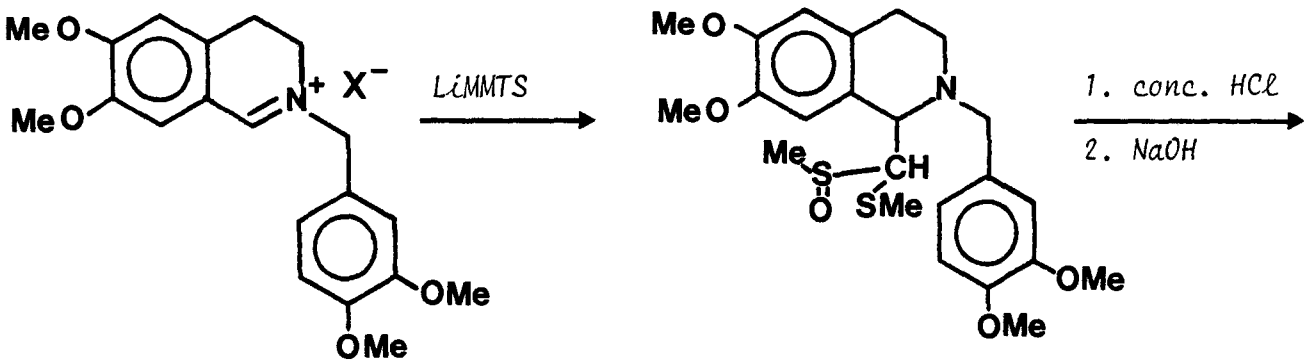
SCHEME 22

In an entirely different strategy adopted for constructing the protoberberine framework, MacLean and co-workers (80) added the lithium salt of methyl methylthiosulfoxide (LiMMTS) to the appropriately substituted N-benzyl-3,4-dihydroisoquinolium salts 61. The LiMMTS anion served as a C-1 synthon for the C-13 carbon of the protoberberine skeleton. The total synthesis of a variety of protoberberine alkaloids including xylopinine 36 (Scheme 23), tetrahydropalmatine, sinactine and corydaline was achieved.

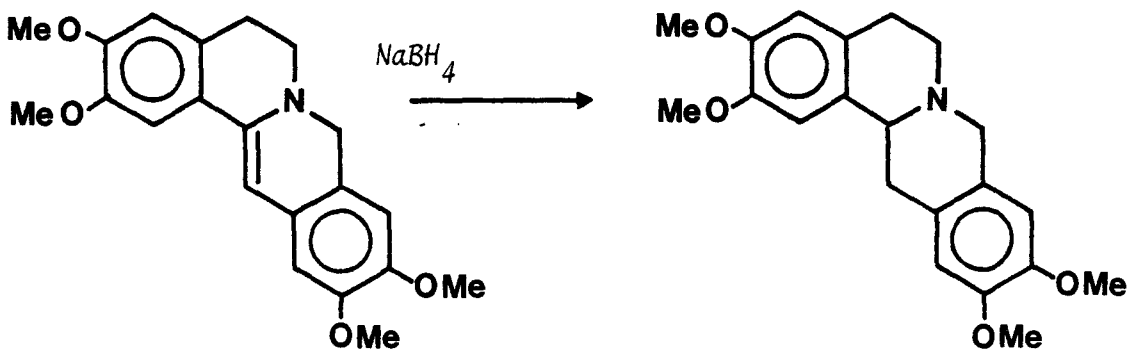
(c) Other Approaches

Takano and co-workers (81,82) recently reported silicon-mediated synthesis of isoquinoline alkaloids. Anions generated from the corresponding silyl derivatives (eg. 62 and 63) were condensed both inter and intramolecularly to an iminium function. Total syntheses of laudanosine 25 and xylopinine 36 have been achieved by this novel approach and are represented in Scheme 24.

In another approach Z-vinylsilane 64 was converted to dendrobatin toxin 251D 66 (83). The conversion was brought about by refluxing an ethanolic solution of 64 with paraformaldehyde in the presence of an acid. The main features of the total synthesis of 66 involving the hypothetical intermediate 65 is shown in Scheme 25. This method has also been successfully applied to the synthesis of indoloquinolizidines 69a and 69b, the latter being the indole alkaloid, deplanchaeine (84). The reactions of Z- and E-trisubstituted vinylsilanes 67a and 67b with paraformaldehyde and acid is thought to proceed *via* the hypothetical intermediate 68 with > 98% retention of configuration to give



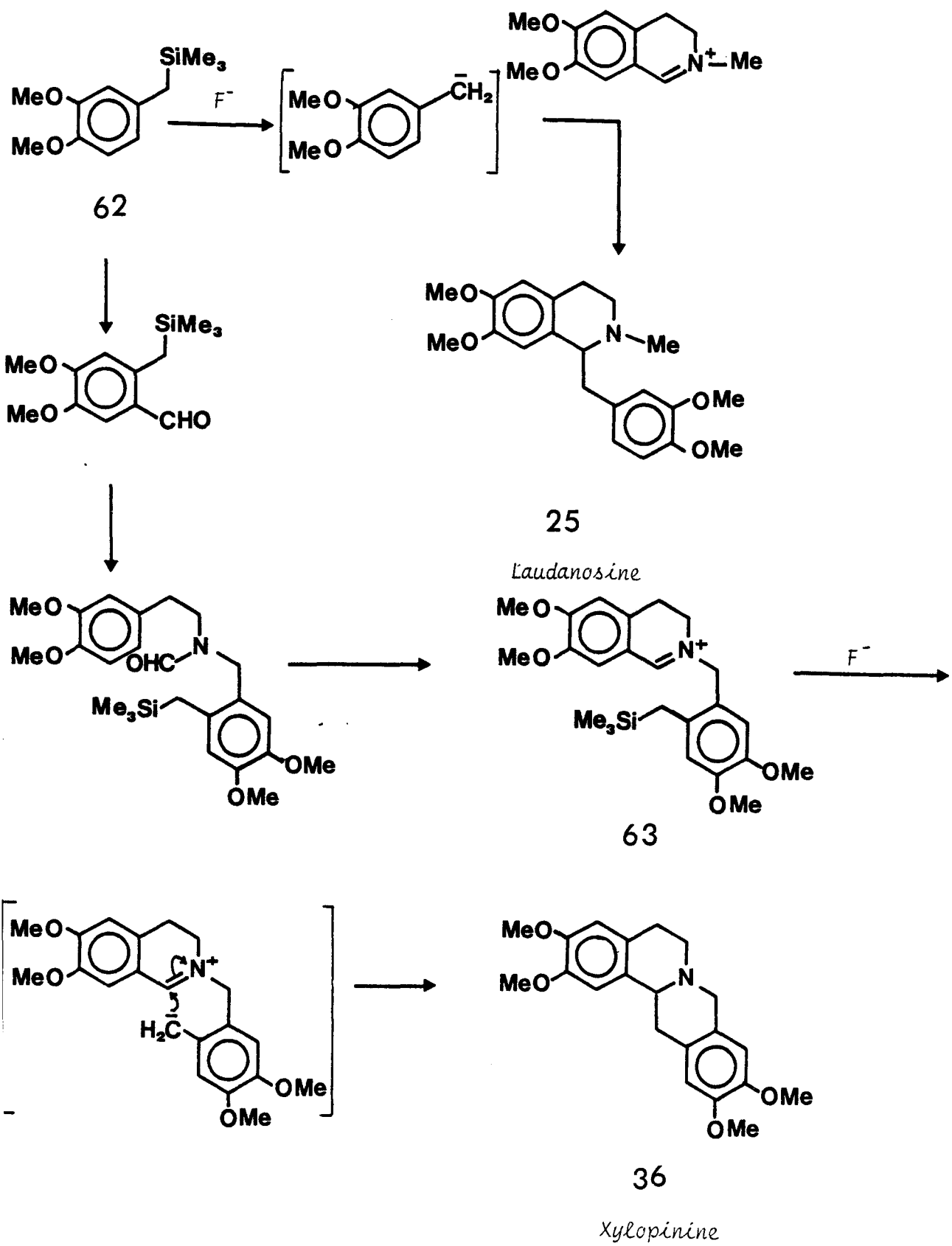
61



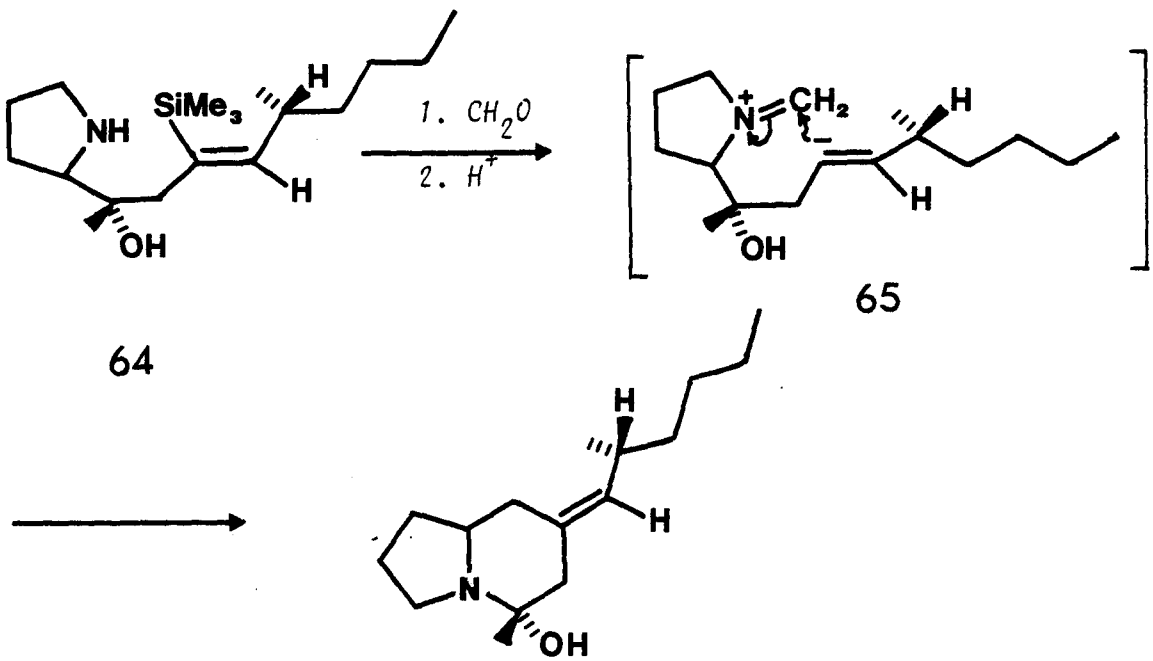
36

Xylopinine

SCHEME 23


SiMe3
MeO
MeO
F⁻
CH2
N+
Me
62
OMe
N
CHO
OHC
Me3Si
25
Laudanosine
63
H2C
36
Xylopinine

SCHEME 24



64

65

66

SCHEME 25

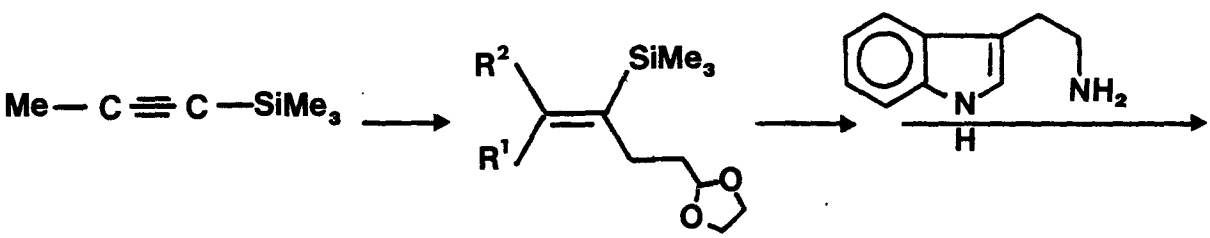
indoloquinolizidines 69a and 69b in excellent yields (Scheme 26). Since the iminium ion-vinylsilane cyclization of both Z- and E-isomers occurs with virtually complete retention of configuration, this method provides a convenient route to a number of alkaloids bearing an exocyclic substituted methylene group. An advantage of this approach lies in the accessibility of the vinylsilanes by short and stereoselective syntheses (85-88).

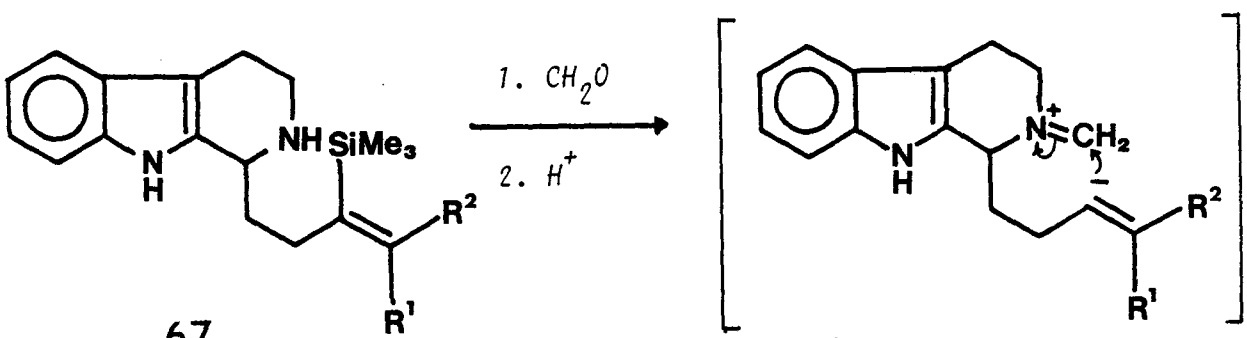
(vii) Condensation of Imines with Anions

Direct addition of anions to imines has been used only recently in alkaloid synthesis. Scully (89) prepared a tobacco alkaloid, anabasine 72, by 1,2-addition of 3-pyridyllithium 70 to the cyclic imine 71 (Scheme 27). Although proceeding in poor yield, this procedure gave a direct route to this alkaloid.

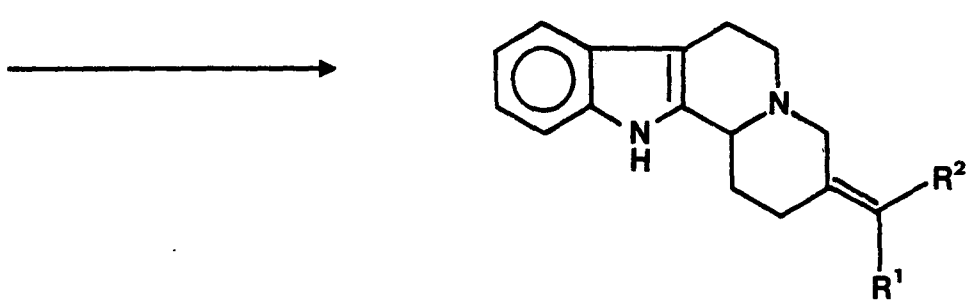
Several alkyllithiums have been reported to add across the C=N bond in lactims 49 (90). When only one equivalent of alkyllithium reagent was used, low yields of imines 73 were obtained. On the other hand, when a 5 fold excess of alkyllithium reagent was used, amines 74 were isolated in moderate yields (Scheme 28).

Volhardt and co-workers (91) added Grignard reagent 76 derived from 3-bromo-1-trimethylsilylpropyne to 3,4-dihydroisoquinolines 75. The alkylated amines 77 after several chemical transformations, were used in the synthesis of a number of protoberberine alkaloids (Scheme 29). In a related addition, Parham and co-workers (92) discovered that, at low temperatures, certain aryl halides bearing an electrophilic group(s) can





67 68

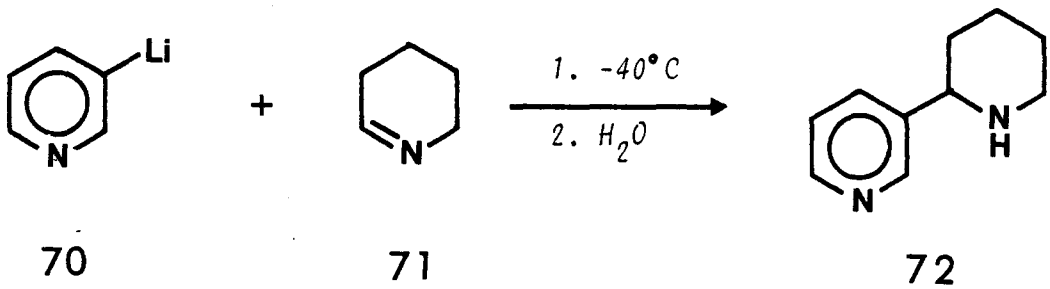


69

a $R^1 = H$ $R^2 = CH_3$

b $R^1 = CH_3$ $R^2 = H$

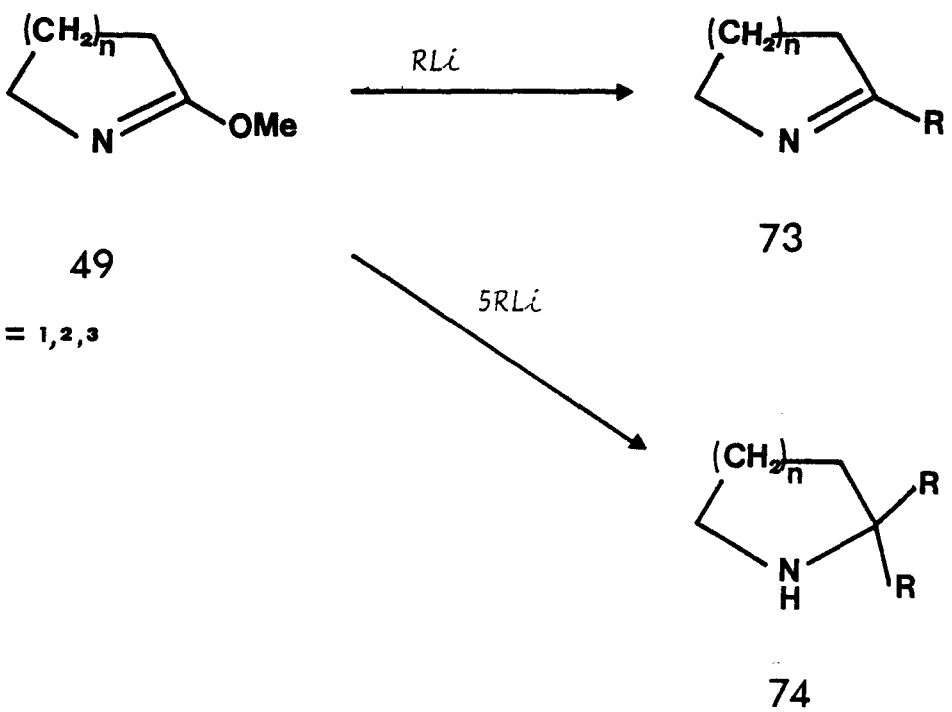
SCHEME 26



70 71 72

Anabasine

SCHEME 27



49

n = 1,2,3

73

74

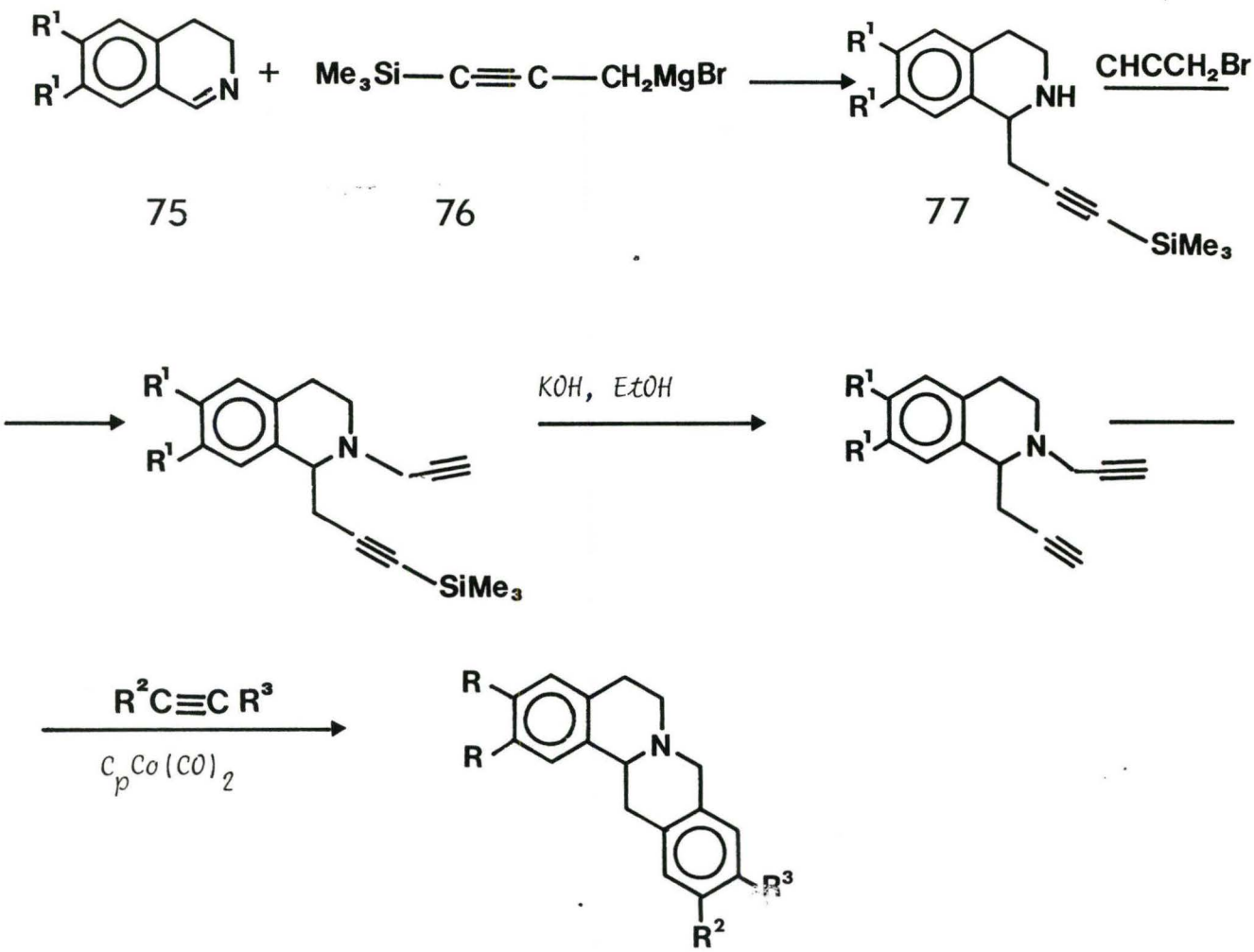
SCHEME 28

be selectively metalated affording synthetically useful bifunctionalized organolithium reagents. If the geometry of these bifunctional organolithium reagents is correct, direct cyclization may occur through the attack of the anionic center on the electrophilic group (93). A variety of 3,4-dihydroisoquinolines 80 have been prepared (92-94) in excellent yields from 78 by this method, through the addition of suitable nitriles to 79 as represented in Scheme 30.

In another investigation (95), when benzalanilines 82 were allowed to react with the organolithium reagent 81, dihydroisoindolines 83 were formed (Scheme 31). The effectiveness of this condensation reaction has also been explored intramolecularly. Thus, the organolithium reagent 85 derived from 84 by halogen-metal exchange, reacted with the built in imine forming 1-phenyltetrahydroisoquinolines 86 (Scheme 32).

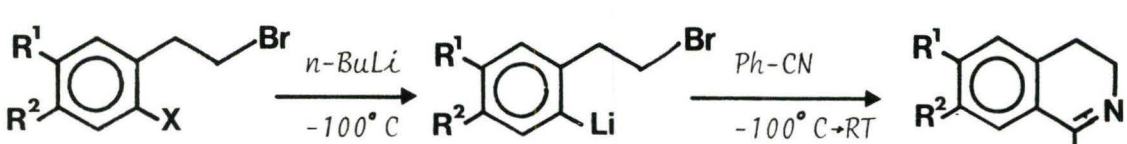
The intermolecular addition reactions of anions with imines have provided a new route to β-lactams. Barrett and Quayle (96) condensed lithium salts of several substituted ketenes 87 with acyclic imines 88. The cyclic enolates 89 formed in the reaction may be trapped with acetaldehyde thereby providing a direct route to a number of β-lactams 90 (Scheme 33).

In an interesting variation (97) of the above reaction, N-trimethylsilyl imines 91 were condensed with ester enolates 92 providing another application of imine-carbanion condensation reactions to the synthesis of β-lactams 93 (Scheme 34). Several other investigators have used similar reactions of anions with Schiff bases in



75 76 77

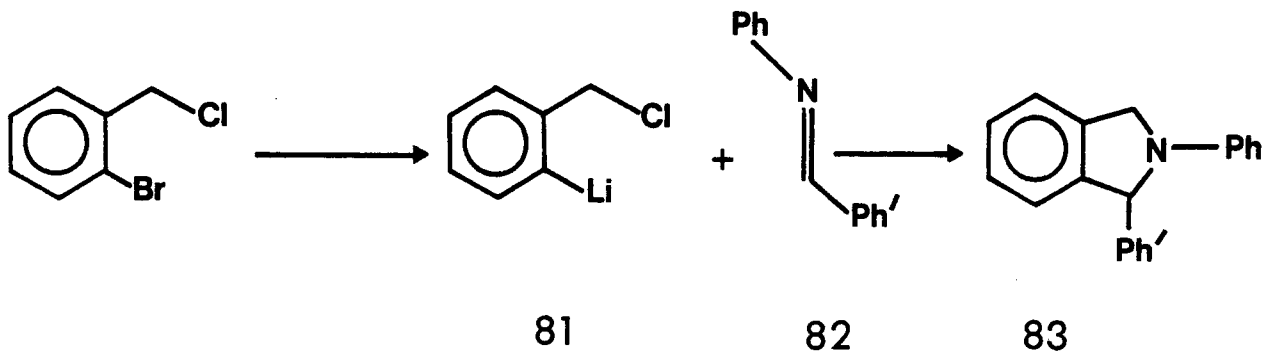
SCHEME 29



78
X = Br
= I

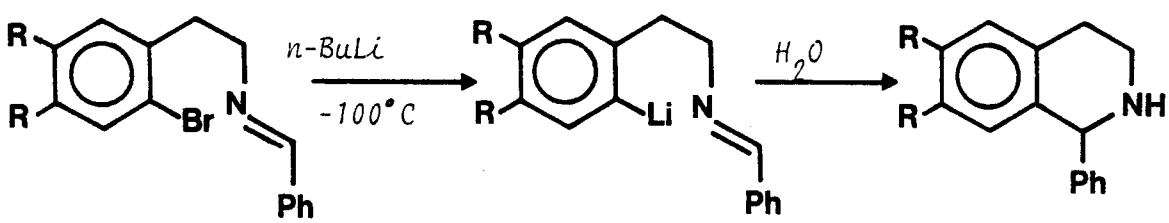
79 80

SCHEME 30



81 82 83

SCHEME 31



84 85 86

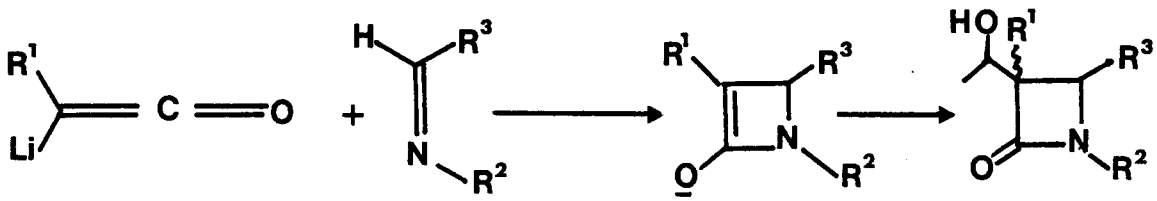
SCHEME 32

the synthesis of β-lactams (98), azetidines (99) and aziridines (100,101).

Clark (102) recently reported condensation of lithiated N,N-diethyl-*o*-toluamide 94 with benzaldimines 95. This convergent approach provided directly 3,4-dihydroisoquinolones 96 in 37-50% yields (Scheme 35). In another application of this method, when a cyclic imine 97a was reacted with 94, the protoberberine skeleton was formed in a single step. The synthesis of 2,3-dimethoxytetrahydro-8-oxoberberine 98 shown in Scheme 35 exemplifies this approach.

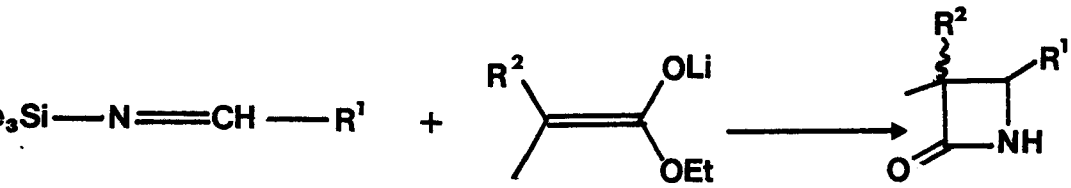
The synthetic applications of the reactive lithium salts derived from position 3 of phthalides, are well documented (103,104). Sammes' group utilized the reactivity of these compounds in the preparation of polycyclic systems (105,106). The same group also first explored the application of phthalide anions in heterocyclic chemistry (107,108). The reaction of acyclic imines 101 with phthalide anions 100, derived from the corresponding phthalides 99, on treatment with LDA, gave a mixture of *cis*- and *trans*-3,4-dihydroisoquinolones, 103 and 104 (Scheme 36). After the initial C-C bond forming reaction between phthalide anion and the electrophilic imine carbon, the imine nitrogen acquires a negative charge. This newly generated anion 102 reacts with the lactone carbonyl, forming a mixture of 3,4-dihydroisoquinolones (Scheme 36). The *cis*-isomer 103 was formed in preference to the *trans*-isomer 104.

Independently, Marsden and MacLean (109,110) studied the condensation of a variety of 3,4-dihydroisoquinolines 97 with phthalide anions 100. This reaction provided, stereoselectively *trans*-13-



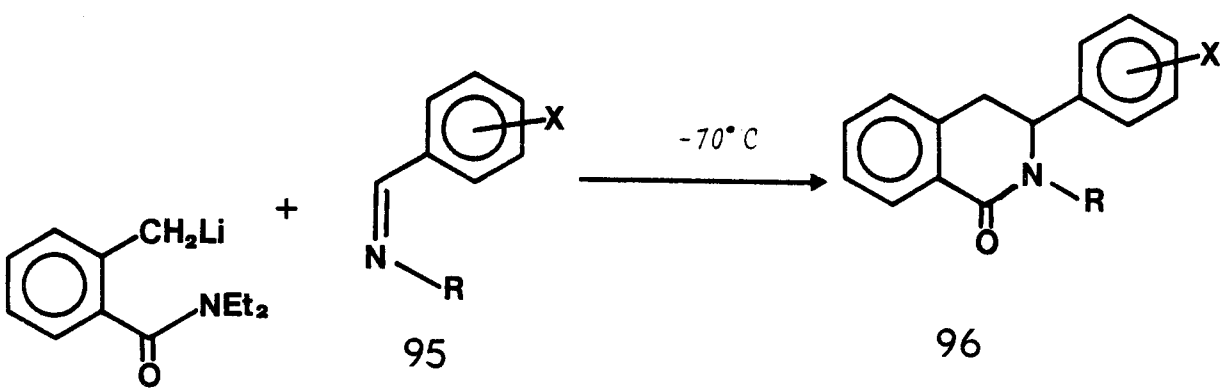
87 88 89 90

SCHEME 33

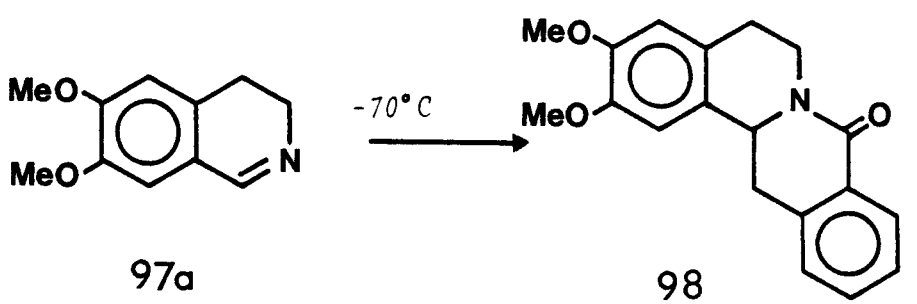


91 92 93

SCHEME 34

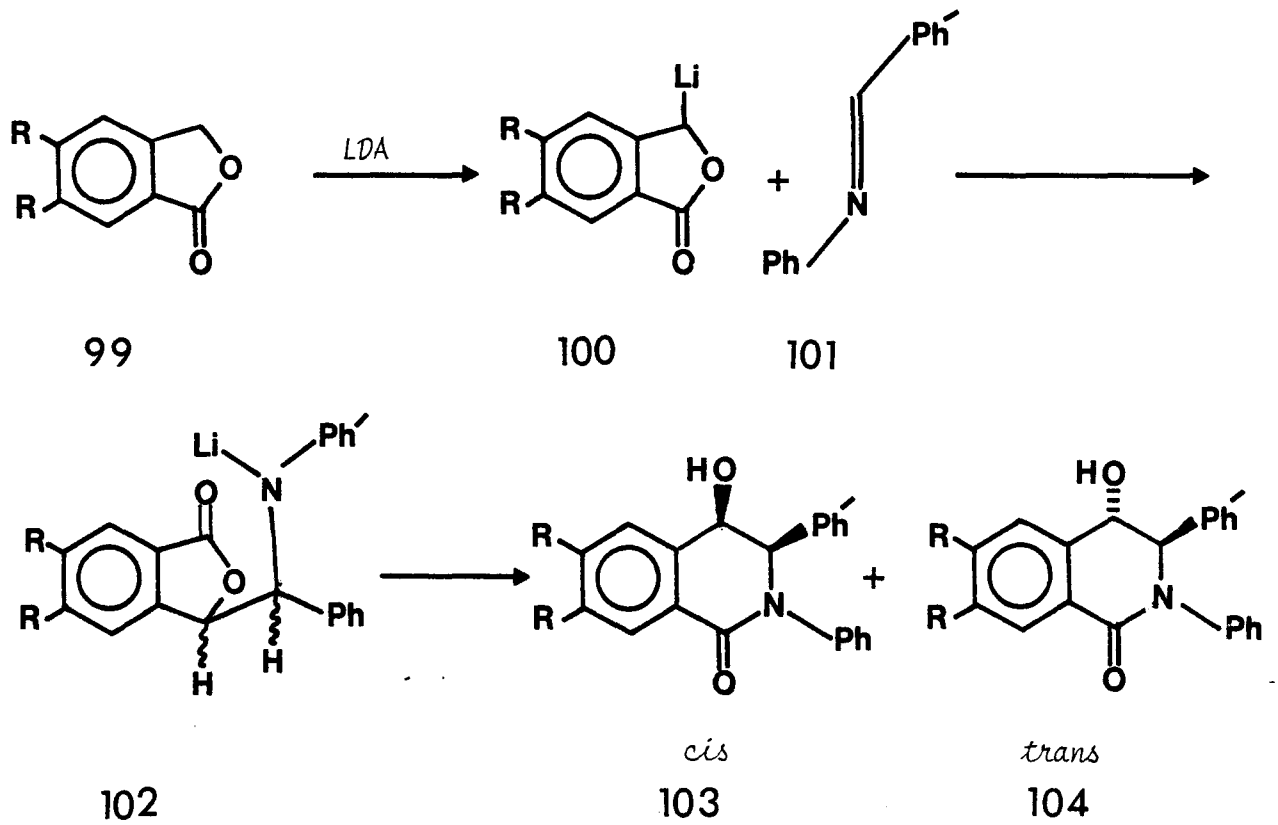


94 95 96



97a 98

SCHEME 35


R
R
O
O
LDA
Li
Ph
N
Ph
99
100
101
Li
N
Ph
Ph
H
H
102
HO
Ph
N
Ph
+
cis
103
HO
Ph
N
Ph
trans
104

SCHEME 36

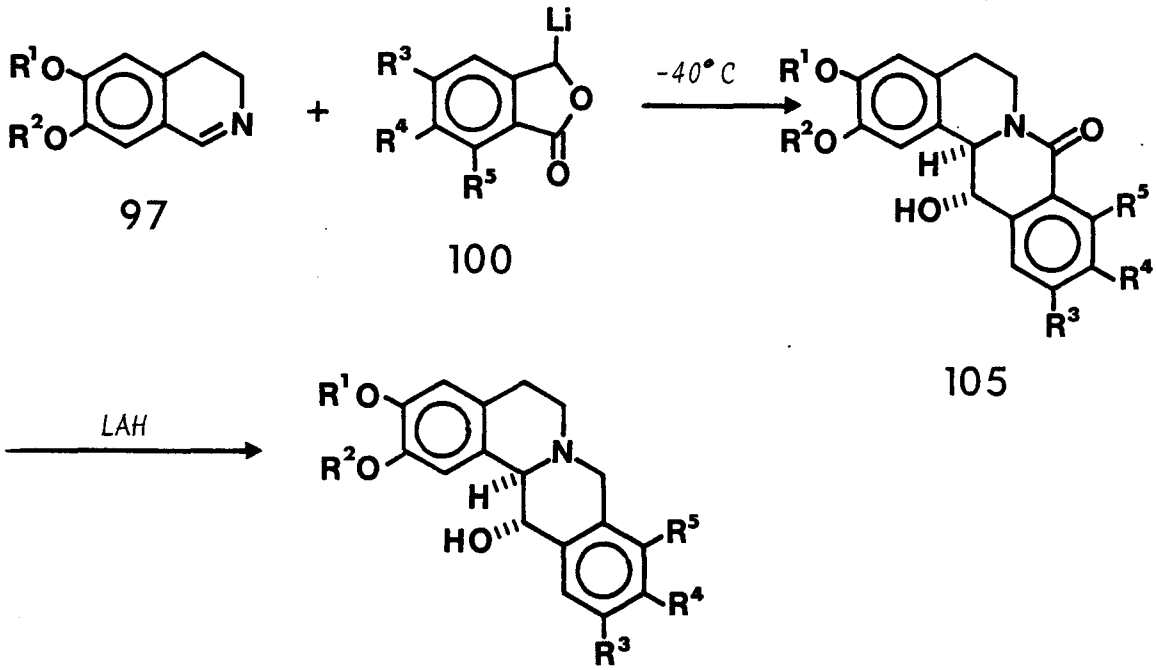
hydroxy-8-oxotetrahydroberberines **105** in good yields (Scheme 37). This method provided a novel and highly convergent route to protoberberine alkaloids. The high degree of stereoselectivity in this reaction implies that the two reactants must be interacting in an "endo" fashion with respect to each other (11).

The 13-methylprotoberberines have also been prepared (110) in a similar way using 3-methylphthalide anion **106** (Scheme 38). The condensation product **107** has been transformed to cavidine **108** and the 13-methyl compound **109**. Based on these findings, a number of thiaprotoberberines **110-112** have also been synthesized (111) and are shown in Scheme 39.

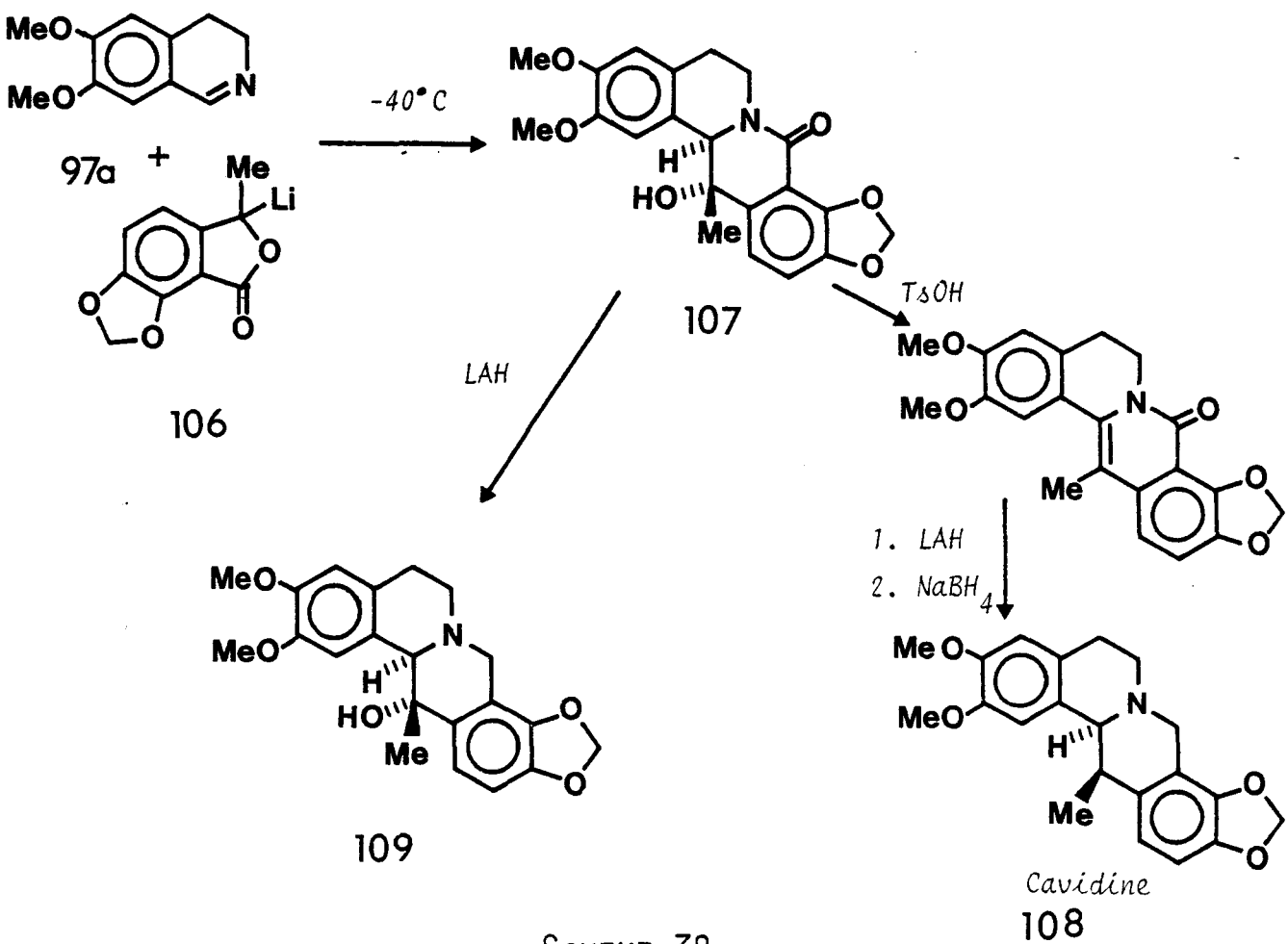
Marsden and MacLean (110) also studied the condensation of acyclic imines **52** with phthalide anions. In agreement with the observations of Dodsworth and co-workers (103), a mixture of *cis*- and *trans*-3,4-dihydroisoquinolones, **113** and **114**, with the *cis*-isomer predominating was obtained on reacting several lithium phthalides **100** with 3,4-dimethoxybenzylidene methylimine **52** as shown in Scheme 40.

(viii) Photochemical Reactions of Imines and Iminium Salts in Alkaloid Synthesis

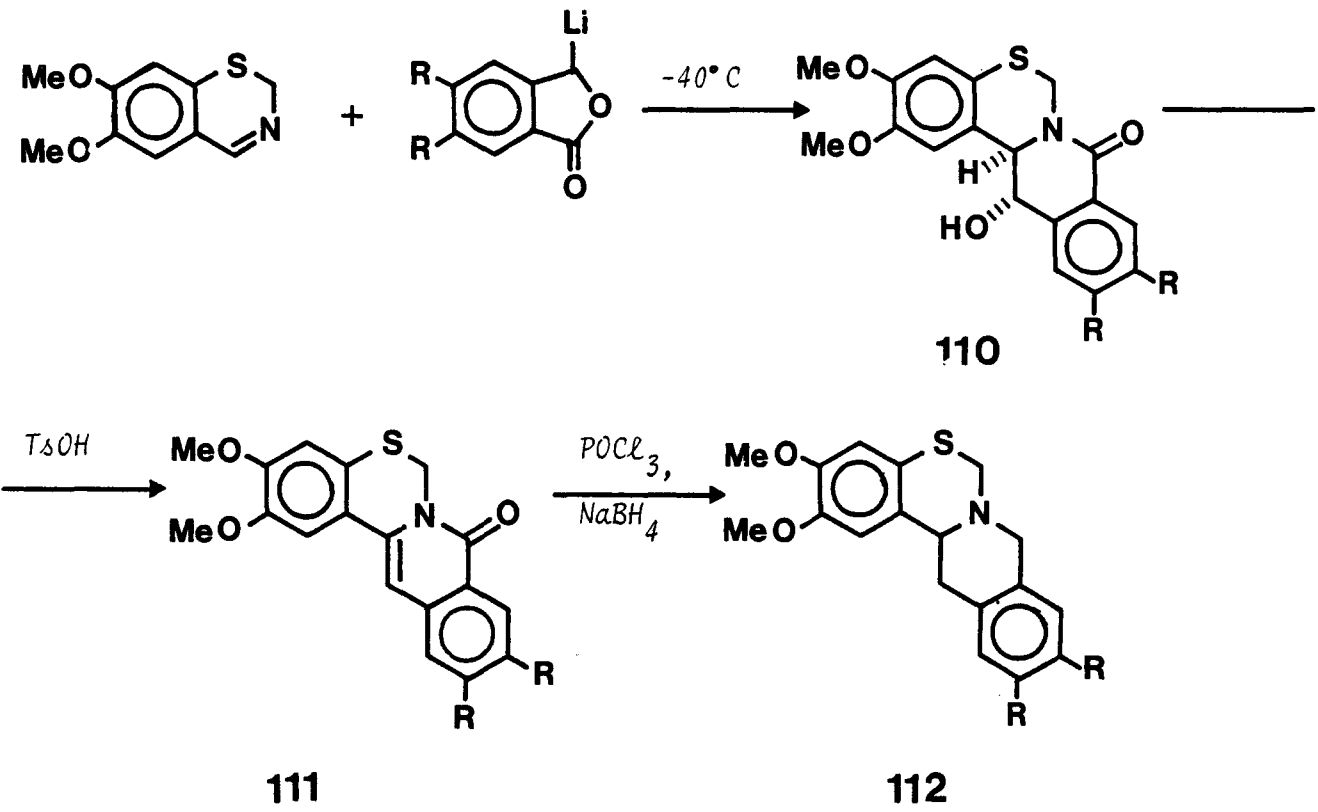
The increased interest in the synthetic applications of photochemical reactions of imines and iminium salts during the past decade has been stimulated by the successful application of the method to the synthesis of a number of natural products. Several reviews (12,112-114) have been either partially or completely devoted to the progress made in this field.



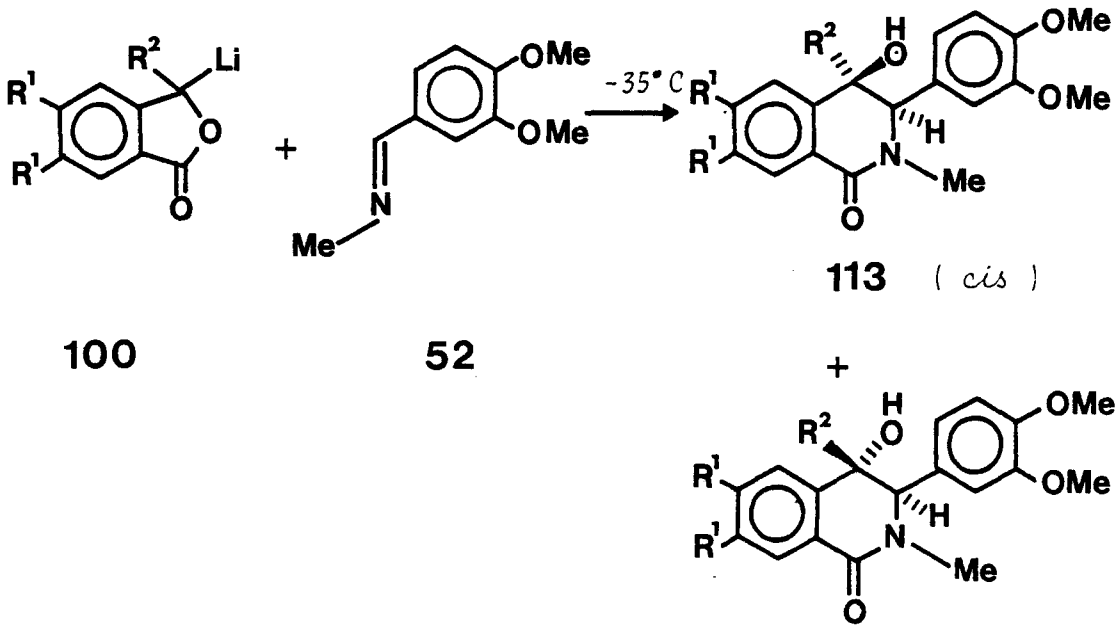
SCHEME 37



SCHEME 38



SCHEME 39



SCHEME 40

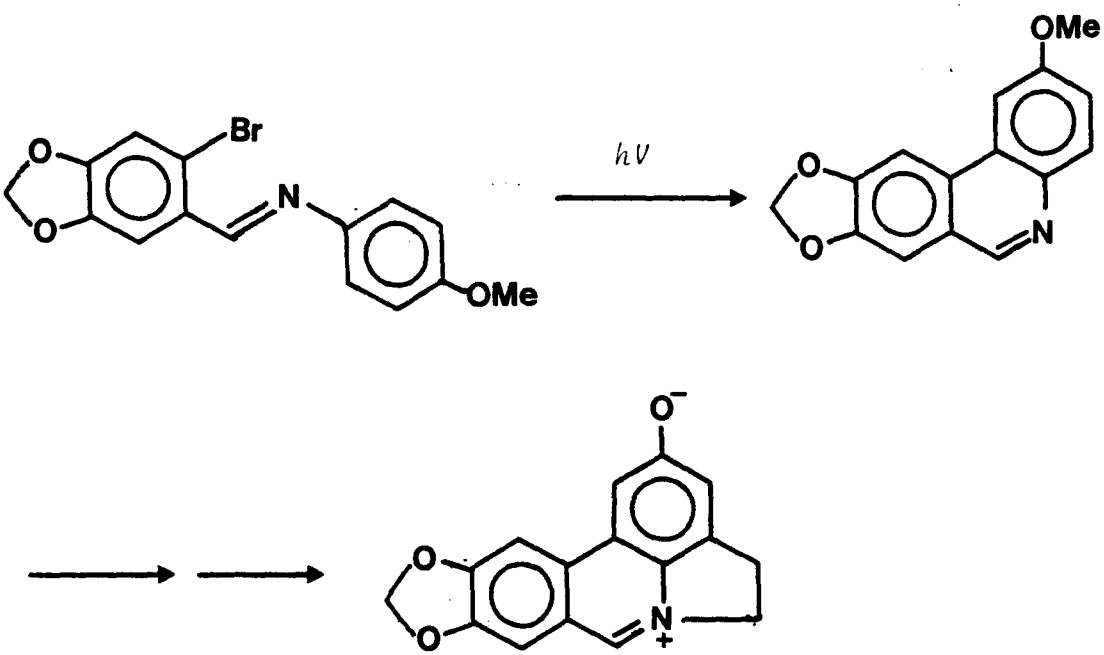
Onaka *et al.* (115) have used this aspect of imine chemistry in the synthesis of ungeramine 115, an antileukemic alkaloid (Scheme 41). The photochemistry of iminium salts has also been of considerable interest to chemists in recent years (116). Schofield and Mariano (117) have recently reported a novel photochemical synthesis of spiro compounds 117 from iminium salts 116 (Scheme 42). The possible application of this procedure in the synthesis of erythrina alkaloids is under investigation by the same group.

1.5 CONCLUSION

This survey has attempted to cover the recent developments in the synthesis of alkaloids using imines and iminium salts in a crucial step of their formation. Their usefulness in convergent syntheses has been emphasized. Because of space limitations some areas such as the use of N-acyl iminium intermediates (118) in alkaloid synthesis have not been included and photochemical methods have been mentioned only briefly. The present study, discussed in the subsequent chapters, will show further uses of imines and iminium salts in alkaloid synthesis.

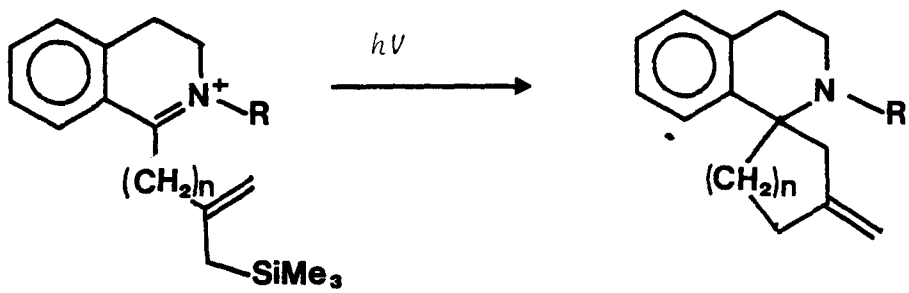
1.6 BENZOPYRIDOQUINOLIDINE AND INDOLOPYRIDOQUINOLIZIDINE ALKALOIDS: ISOLATION AND SYNTHESIS

A major portion of the synthetic work described in this investigation is devoted to the synthesis of compounds containing the two ring systems in the title above. This section of the introduction is therefore concerned with the isolation and synthesis of compounds with these ring systems.



115

SCHEME 41



116 **117**

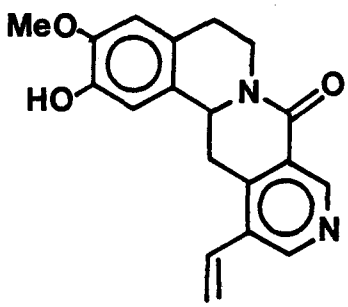
SCHEME 42

(i) Benzopyridoquinolizidines

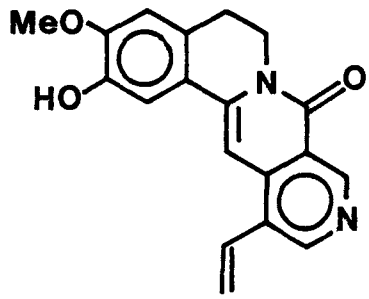
The various parts of *Alangium lamarckii* Thwaites (*Alangiaceae*) have been used in indigenous Indian medicines for a long time (119-121). It has been claimed that the extracts of this plant are useful in treatment of a large number of human disorders. Extensive investigation on this plant has resulted in the isolation of several biologically active alkaloids including emetine, cephaetine, and psychotrine (122).

Recently Pakrashi and co-workers (123-125) have isolated several new alkaloids from the seeds of *Alangium lamarckii*, namely, alangimaridine 118, alangimarine 119, isoalangimarine 120, alamarine 121, isoalamarine 122, dihydroalamarine 123, dihydroisoalamarine 124, alangimarinone 125, and alamaridine 126 (Figure 3). These alkaloids contain a pyridine ring instead of the benzenoid D ring found in the protoberberines and possess the novel isoquino[2,1-*b*][2,7]naphthyridine ring system (Figure 4).

Ninomiya and co-workers (126) reported the first total synthesis of alamarine 121 *via* a route involving enamide cyclization under both thermal and photochemical conditions. The enamide 127 when heated at 180-200°C for 20 min produced a mixture of two lactams 128 (43%) and 129 (10.0%). On the other hand, irradiation of the same enamide 127 with a low-pressure mercury lamp gave the lactams 128 and 129 in 25% and 13% yields, respectively, after 8h. Debenzylation and sodium borohydride reduction of the major product 128 gave alamarine 121 as shown in Scheme 43. Alamarine 121 had been dehydrated to alangimarine 119 (123).



118



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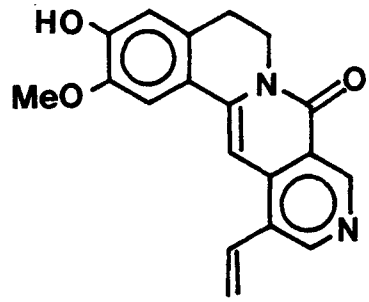

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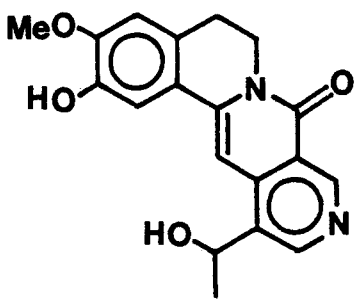

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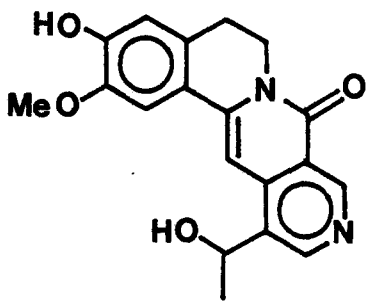

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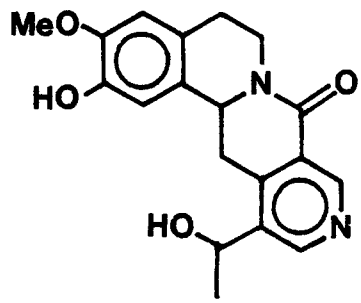
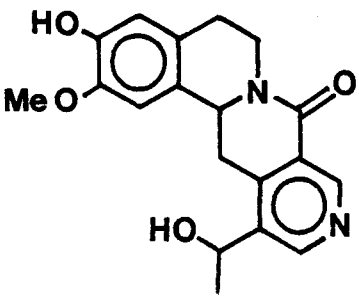


123



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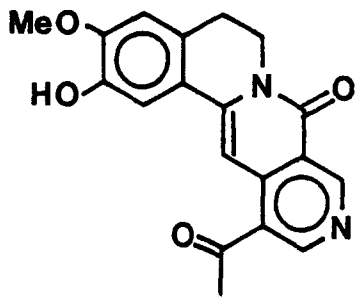

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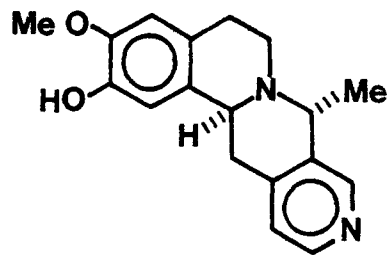
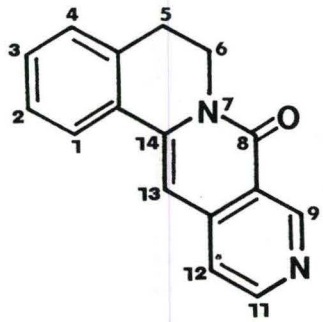


126

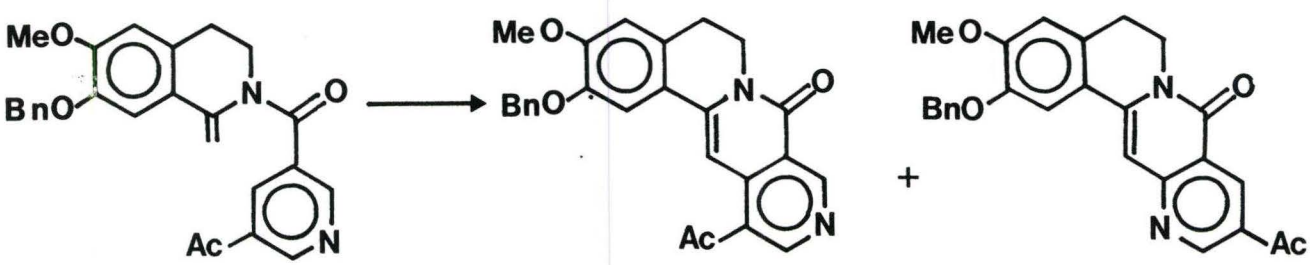
Benzopyridoquinolizidine alkaloids Alangium lamarckii

FIGURE 3



5,6-Dihydro-8H-isoquino[2,1-b][2,7]naphthyridin-8-one

FIGURE 4



127 **128** **129**

Δ 180-200°C	43 %	10%
hν	25 %	13%

1. H^+
2. $NaBH_4$

119 ← **121**

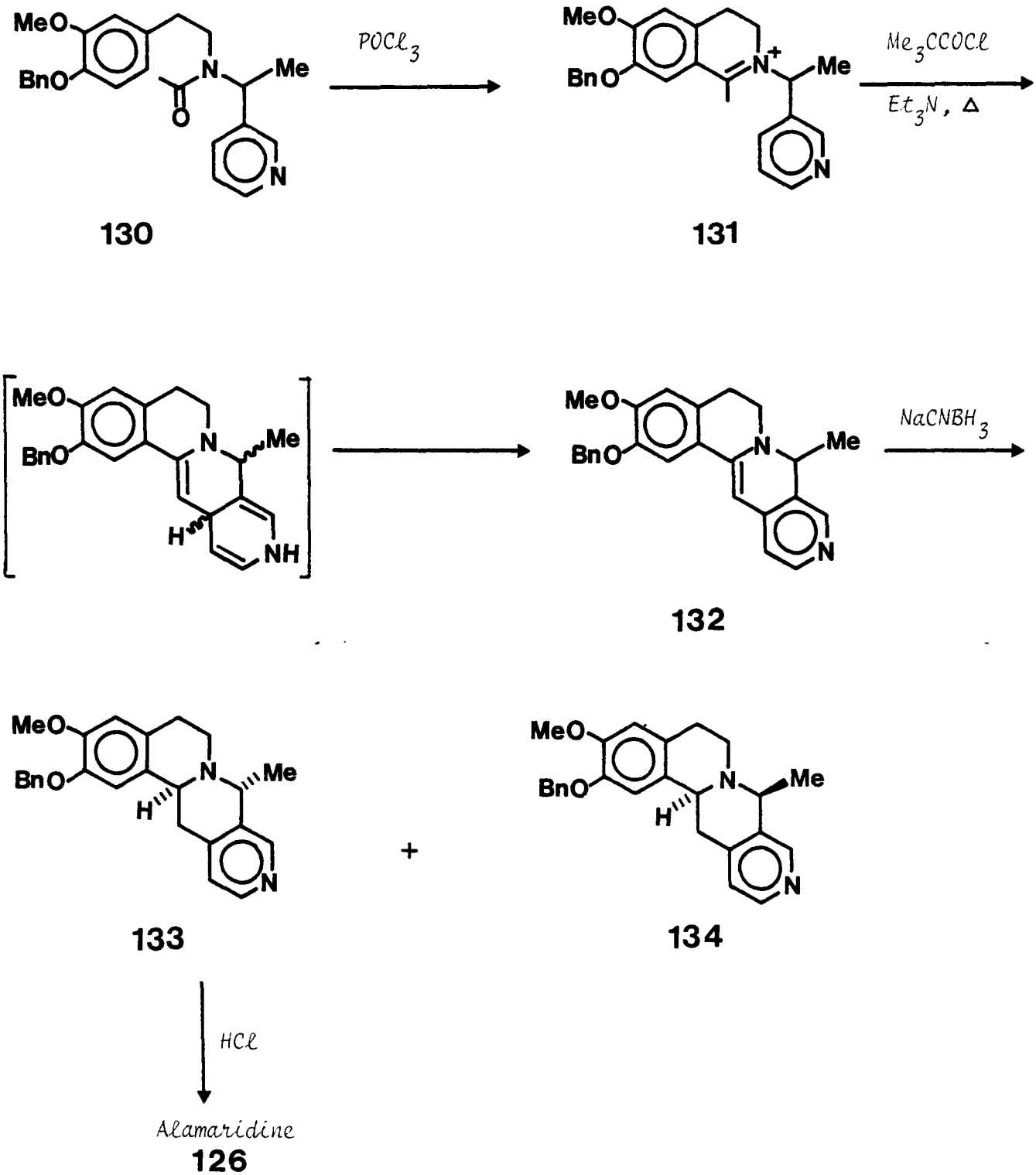
SCHEME 43

Recently, Pakrashi and co-workers (127) reported the first synthesis of alamaridine **126**, which also established the relative stereochemistry at the two chiral centers, C-8 and C-14, in the molecule. In this synthesis, amide **130** on Bischler-Napieralski cyclization with $POCl_3$ gave the isoquinolium salt **131** isolated as a bis-perchlorate. Treatment of the salt **131** with pivaloyl chloride and triethylamine gave the desired cyclized product **132**, which on subsequent reduction with sodium cyanoborohydride gave an isomeric mixture of 8-methyltetrahydroazaberberines **133** and **134**. The minor product **133** having the desired stereochemistry was then debenzylated to (±)-alamaridine **126** as shown in Scheme 44.

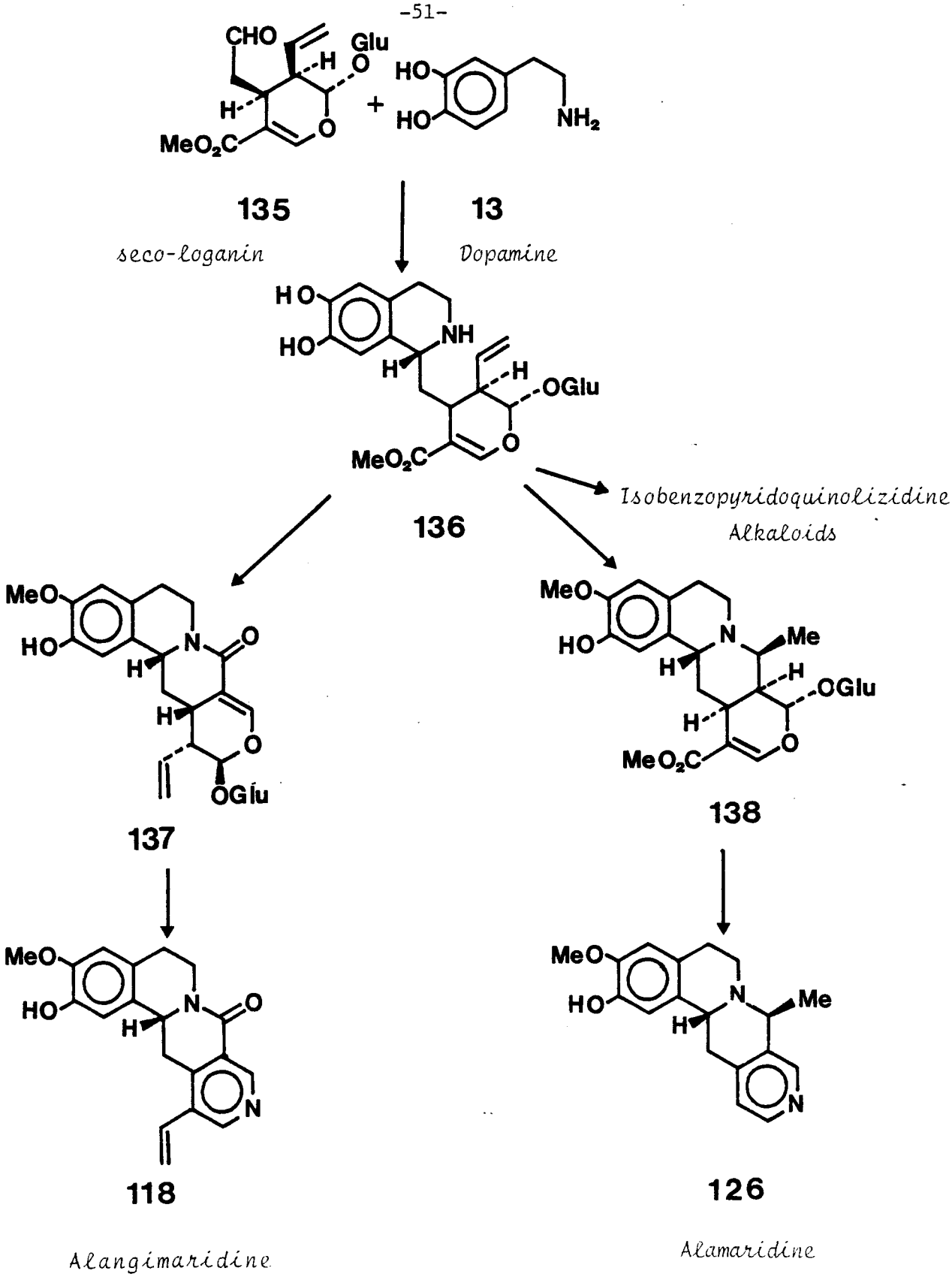
These alkaloids are considered to be related biogenetically to alangiside **137** which in turn is derived from seco-loganin **135** and dopamine **13** (128-132). Deacetylipecoside **136** through cyclization, hydrolysis, amination, and other unexceptional transformations could be imagined to produce these alkaloids as shown in Scheme 45. The R configuration is shown in the diagram but the absolute configuration of the alkaloids has not been established. It is also quite likely that alamaridine **126** is derived from deacetylipecoside **136** by ring closure between the isoquinoline nitrogen and the non terminal carbon of the vinyl group *via* **138**, followed by other transformations (Scheme 45). No biosynthetic studies have been reported on this new class of protoberberine analogues.

(ii) INDOLOPYRIDOQUINOLIZIDINES

During the last few years an increasing number of indole


MeO
BnO
N
Me
O
N
POCl3
MeO
BnO
N+
Me
N
Me3CCOCl
Et3N, Δ
130
131
MeO
BnO
N
Me
H
NH
MeO
BnO
N
Me
N
NaCNBH3
132
MeO
BnO
N
Me
H
N
MeO
BnO
N
Me
H
N
133
134
HCl
Alamaridine
126

SCHEME 44



SCHEME 45

Proposed biogenesis of benzopyridoquinolizidine alkaloids.

alkaloids containing the title ring system have been isolated (9,10,133). As in the case of the benzopyridoquinolizidine alkaloids, the pyridine part (E ring) of these alkaloids is considered to be derived from seco-loganin **135**, and in most cases they occur together with structurally related glycoalkaloids such as **140-143** (Scheme 46). The rings, A to C arise from tryptamine **139**. Representative alkaloids of this group are listed in Table 1. In some alkaloids, the C-10 unit of seco-loganin is present while in others it has been modified. The various structural types of this class of alkaloids are represented in Figure 5. The synthesis of these alkaloids is discussed below.

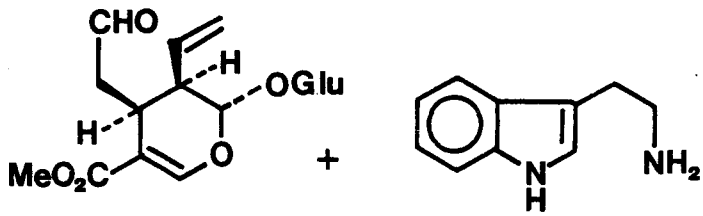
Hotellier *et al.* (135) obtained nauclefine **146**, in 6% yield by treating 3,4-dihydro-1-methyl-β-carboline **156** with an excess of nicotinoyl chloride (Scheme 47). Sainsbury and Webb (137) on photocyclization of the enamide **157**, derived from **156** and nicotinoyl chloride, obtained an isomeric mixture of two lactams **146** and **158** in a ratio of 100:9 in a total yield of 48% (Scheme 47). The major product **146** was identical with nauclefine (previously named parvine). Sainsbury and Uttley (142,143) have since reported its regioselective synthesis.

Ninomiya and co-workers (144) prepared the spirodihydropyridine derivative **159** by acylation of **156** with an excess of nicotinoyl chloride. Nauclefine **146** was then prepared from **159** by photorearrangement of the corresponding N-nor derivative **160** (Scheme 48). Ninomiya and co-workers (145-147) have also synthesised angustidine **152**, angustoline **145**, and nauclefine **147**. Irradiation of the enamide **161** gave a mixture of nauclefine **147** and an isomeric lactam **163** in 30 and 8% yields

Table 1

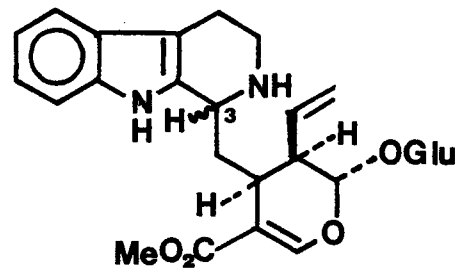
Indolo[2:3,3':4']pyrido[1,2-*b*][2,7]naphthyridine alkaloids

Name	Structure	Reference	Original Source
Angustine	144	134-137	*Stychnos angustifolia*
Angustoline	145	134,135	*S. Angustifolia*
Naucléfine	146	135,137,138	*Nauclea latifolia*
Nauclétine	147	135	*N. latifolia*
O-Acetylangustoline	148	138	*N. pobequinii*
3,14-Dihydroangustoline	149	138	*N. pobequinii*
Malindine	150	139	*S. decussata*
Isomalindine	151	140	*S. usambarensis*
Angustidine	152	135	*S. angustifolia*
Cadamine	153	141	*Anthocephalus cadamba*
Isocadamine	154	141	*A. Cadamba*
Naulafine	155	136	*N. latifolia*



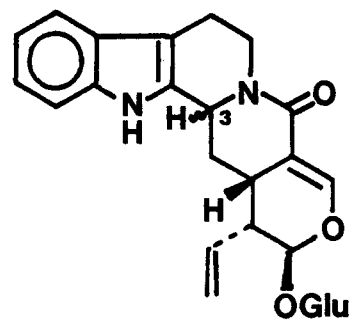
135 *seco-loganin*

139 *Tryptamine*



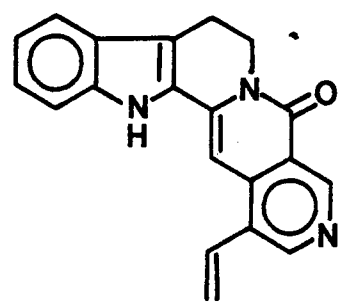
140 $\frac{\text{H-3}}{\alpha}$ *Strictosidine*

141 β *Vincoside*



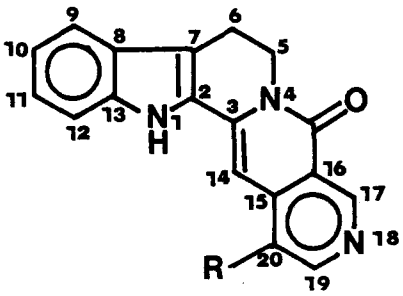
142 $\frac{\text{H-3}}{\alpha}$ *Strictosidine lactam*

143 β *Vincoside lactam*

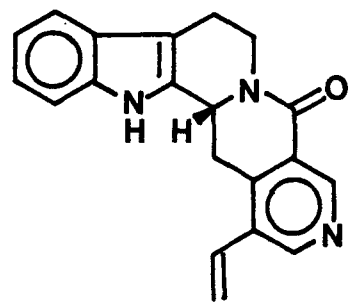


144 *Angustine*

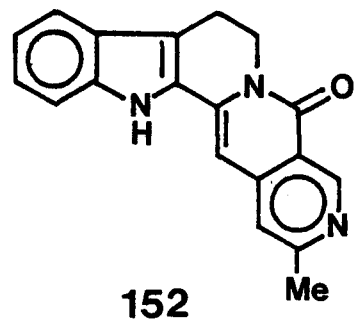
SCHEME 46



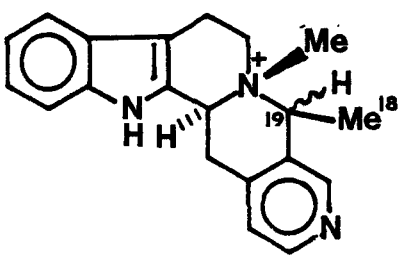
	R	
144	$CH=CH_2$	*Angustine*
145	$CH(OH)CH_3$	*Angustoline*
146	H	*Naucléfine*
147	$COCH_3$	*Nauclétine*
148	$CH(OAc)CH_3$	*O-Acetylangustoline*



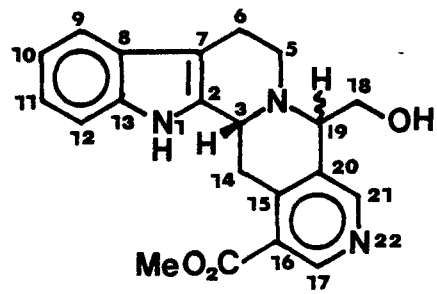
149 *3,14-Dihydroangustine*



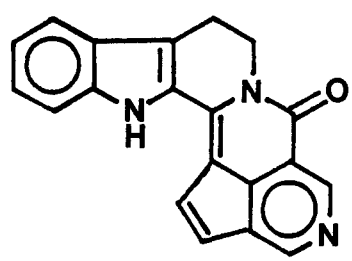
152 *Angustidine*



	H−19	
150	α	*Malindine*
151	β	*Isomalindine*



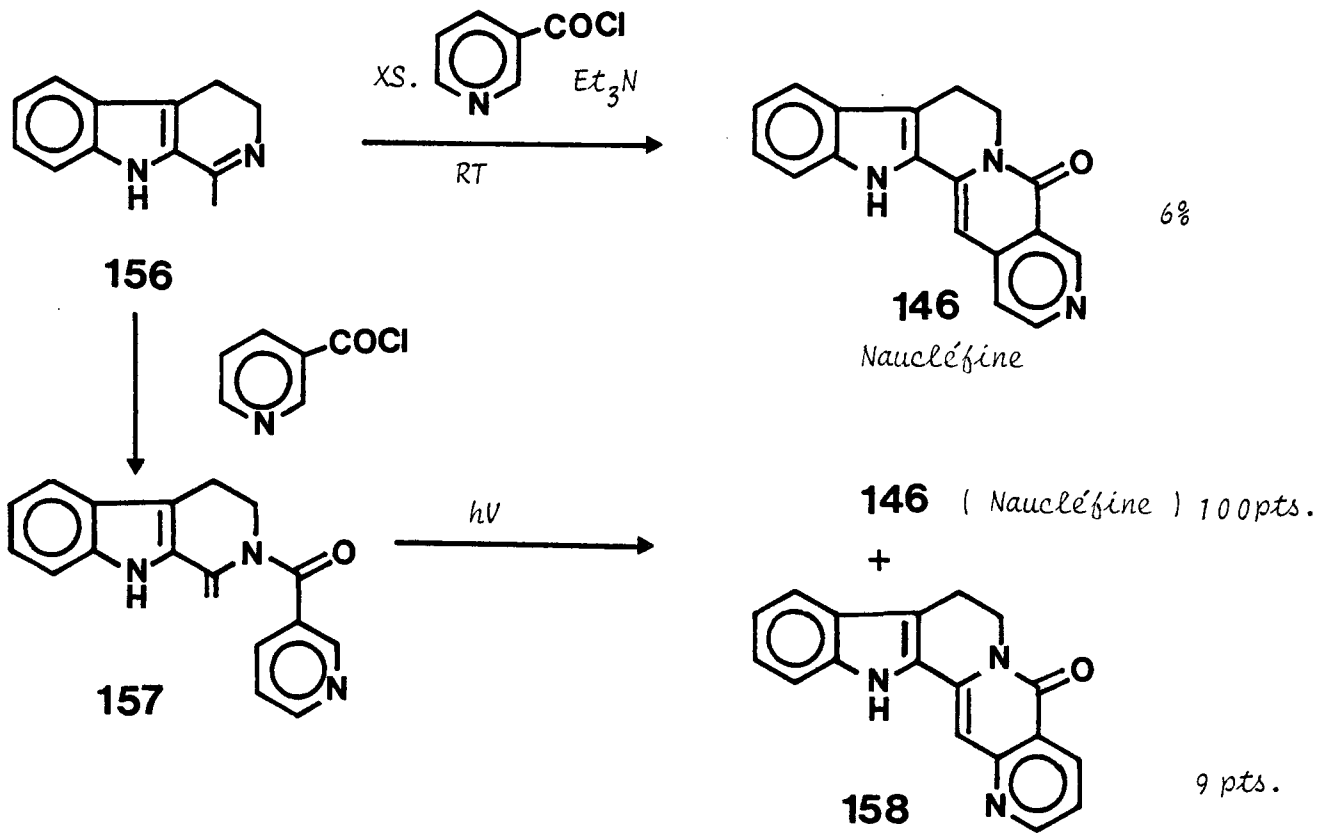
	H−19	
153	α	*Cadamine*
154	β	*Isocadamine*



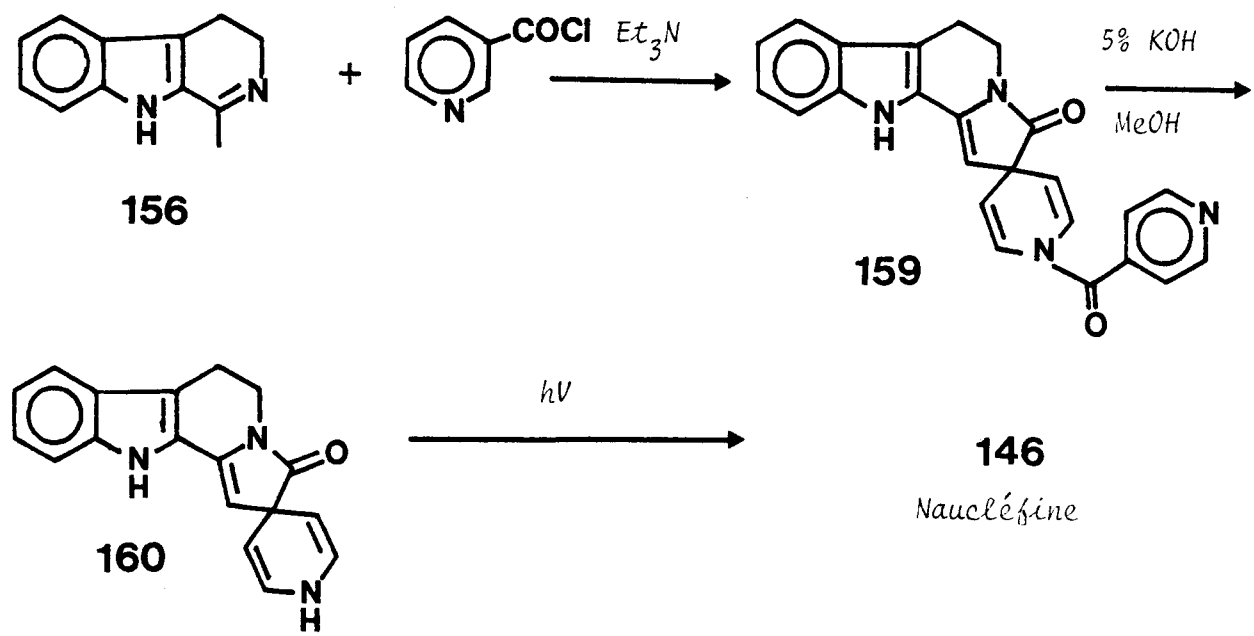
155 *Naulafine*

Indolopyridoquinolizidine alkalois

FIGURE 5



SCHEME 47



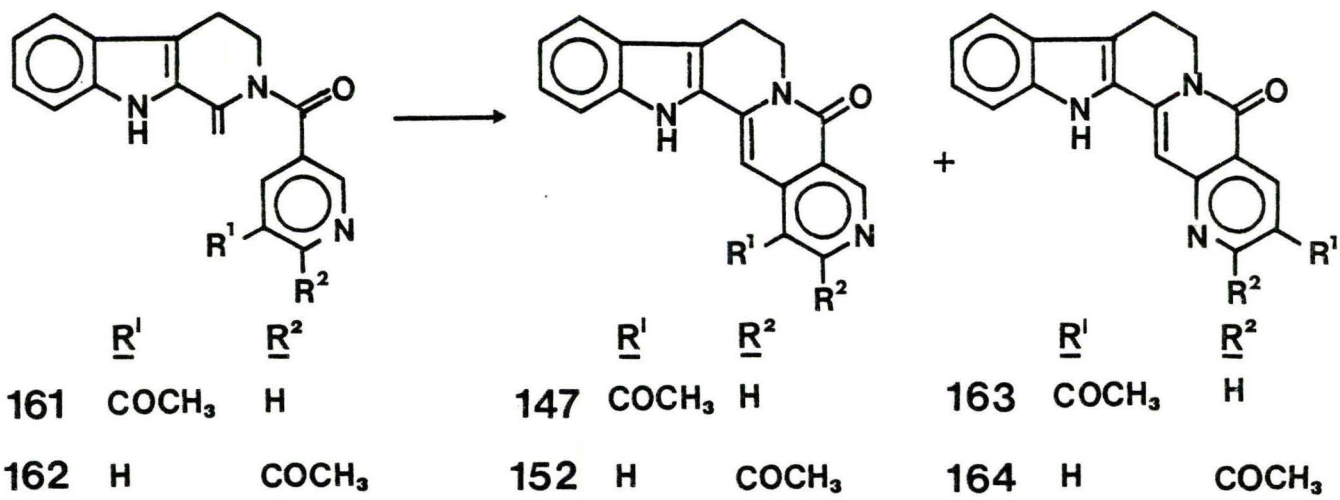
SCHEME 48

respectively (Scheme 49). Similarly, angustidine **152** was prepared in 21% yield along with 13% of the isomeric lactam **164** from enamide **162** (Scheme 49).

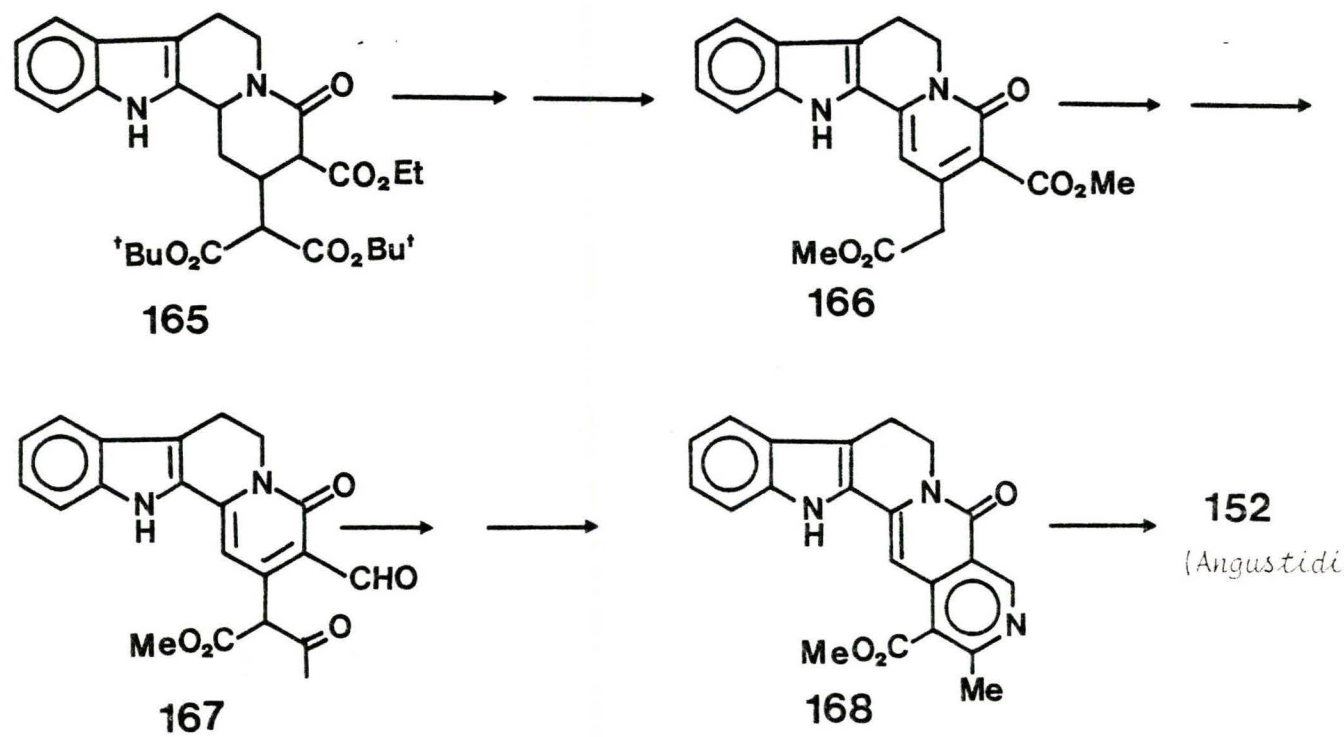
Shafiee and Winterfeldt (148), in a radically different approach synthesized angustidine **152** from the lactam **165**. The pyridine ring was formed by inserting ammonia into the β-dicarbonyl compound **167** (prepared from the intermediate **166**) as shown in Scheme 50.

Kametani *et al.* (149,150) developed another synthetic route to angustine **144** and nauclefine **146**. The condensation of **168** and **169** with tryptamine gave the azaisocarbostyrils **170** and **171** respectively, from which angustine **144** and nauclefine **146** were synthesized either by direct acid treatment or by basic hydrolysis followed by acidic cyclization (Scheme 51).

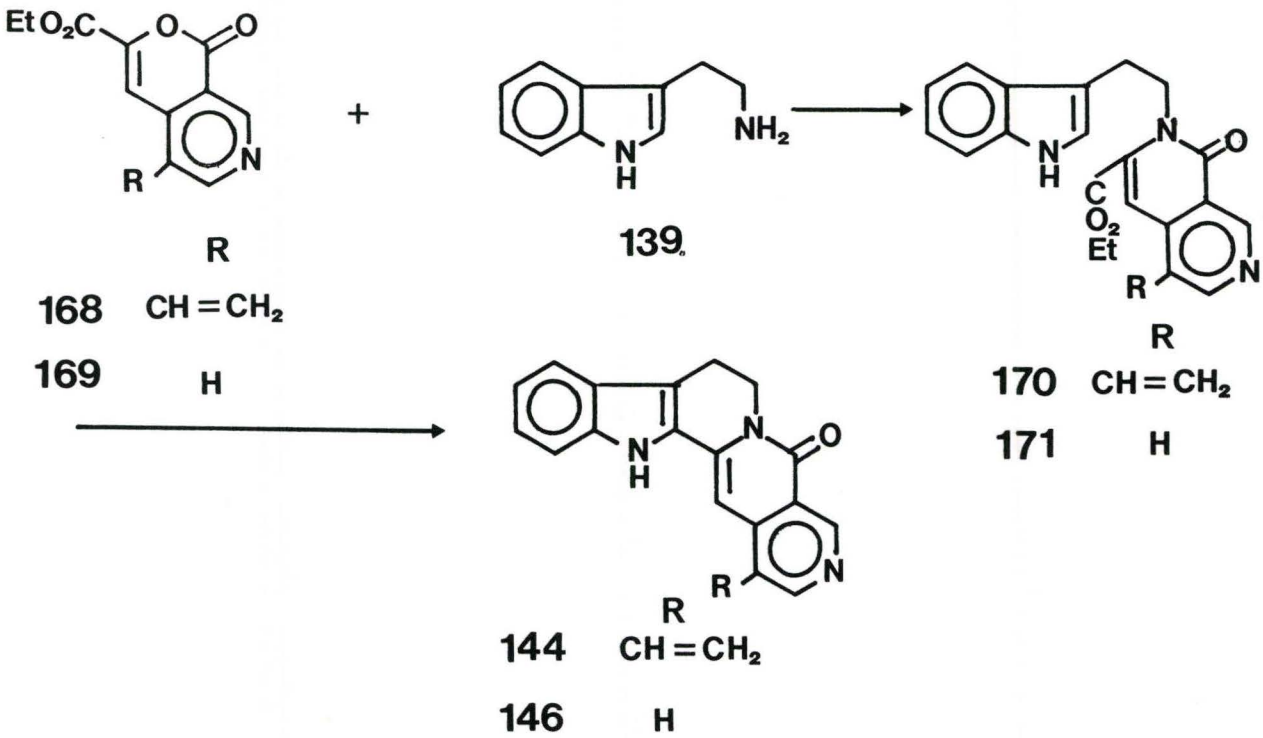
Pandit and co-workers (151) have synthesized nauclefine **146** by addition of the ester anion of 2-carboethoxy-1,3-dithiacyclopentane **173** to pyridinium salt **172** followed by desulfurization (Raney Ni) and cyclization as shown in Scheme 52. To the best of my knowledge, all the available syntheses of aza analogues of the protoberberine and the indole alkaloids have been discussed in this section. A new synthetic approach developed during the course of this study will be presented in the subsequent chapter.



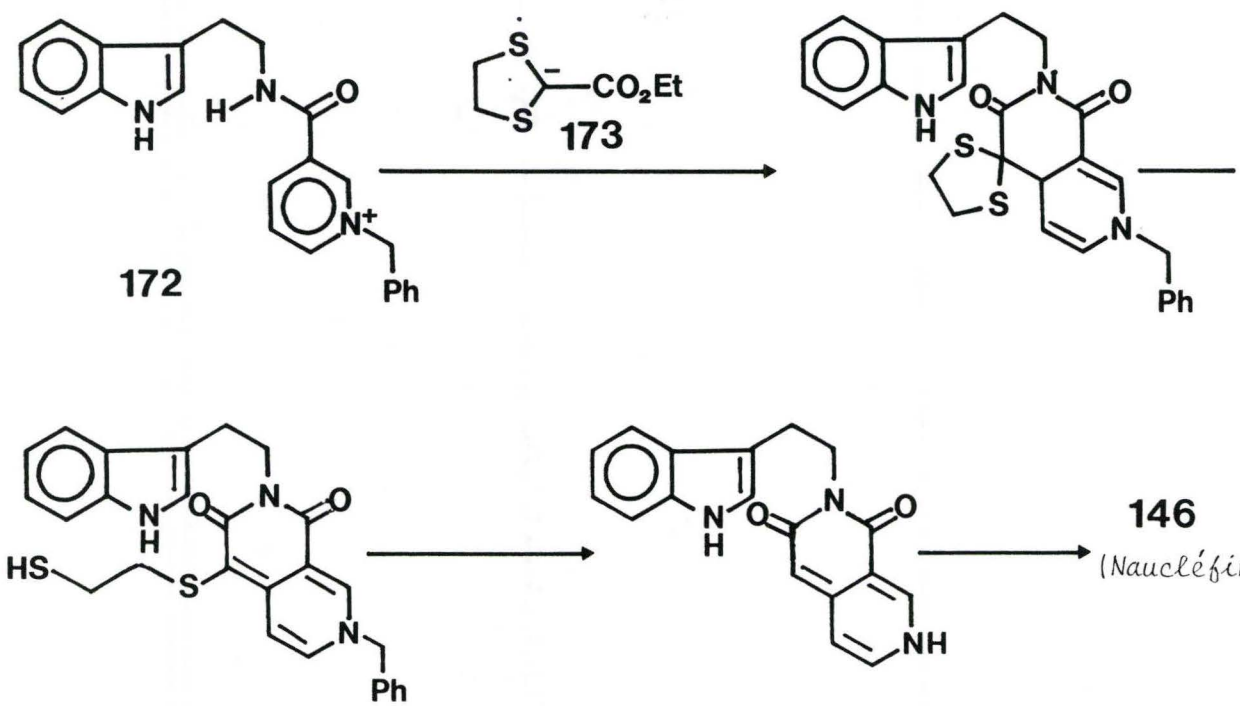
SCHEME 49



SCHEME 50



SCHEME 51



SCHEME 52

CHAPTER 2

RESULTS AND DISCUSSION

2.1 INTRODUCTION

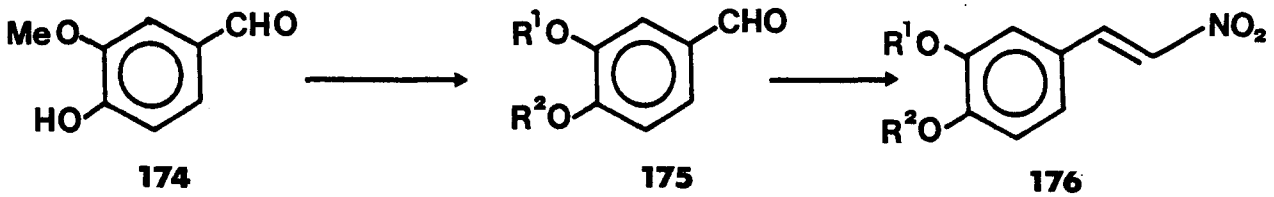
The condensation of imines and iminium salts with phthalide anions has provided convenient routes to protoberberine and phthalideisoquinoline alkaloids and their synthetic analogues. Several recent publications from this laboratory (78,79,109-111) have shown the usefulness of these convergent syntheses which were discussed in the previous chapter. Recently, the isolation of a number of pyridine analogues of the protoberberines such as **118**, **119**, and **126** (123-125) (Figure 3) and several pyridine containing indole alkaloids such as **144**, **146**, and **149** (134-141) (Figure 5) prompted us to investigate their syntheses, using a synthetic strategy similar to that employed for the synthesis of protoberberines (109,110). A number of aza analogues of phthalideisoquinoline alkaloids were also synthesized to investigate their pharmacological properties as GABA (γ-aminobutyric acid) antagonists. A convenient procedure for introducing a methyl group at C-8 of the protoberberine skeleton developed during the course of this study, has been used in the synthesis of 8-methylcanadines, ($\pm$)-alamaridine, and related compounds. Convergent syntheses of *Alangium* alkaloids and indole alkaloids developed in this study are discussed here. The imines, iminium salts, aza-

phthalides and other related compounds required in these syntheses were not commercially available and had to be prepared. These substrates were made mainly by using known reactions; problems encountered and modifications used in the course of their preparation are also discussed in this chapter.

2.2 PREPARATION OF IMINES AND IMINIUM SALTS

Except for the commercially available 3,4-dimethoxyphenylethylamine 177a, the related amines 177b and 177c were prepared by standard methods outlined in Scheme 53a. In the case of 177c, vanillin 174 was benzylated with benzyl chloride under mild conditions using potassium carbonate in dimethylformamide. This procedure (152) proved to be superior, in terms of yield, to that described by Buzas and Dufour (153) using potassium hydroxide in refluxing ethanol. The benzaldehydes, 175a and 175b, were converted to the corresponding β-nitrostyrenes 176a and 176b by reaction with nitromethane either in acidic medium in refluxing glacial acetic acid or under basic conditions using sodium carbonate in ethanol. The latter procedure (154) proved to be more effective for β-nitrostyrene 176b and proceeded at room temperature in 3-5 days. When the former procedure was used for the preparation of 176b, some debenzylation of the product was observed. The nitrostyrenes were reduced to the corresponding amines with lithium aluminum hydride (LAH) or by a modified Clemmensen reduction (155). The latter procedure proved to be more rapid and convenient at larger scale.

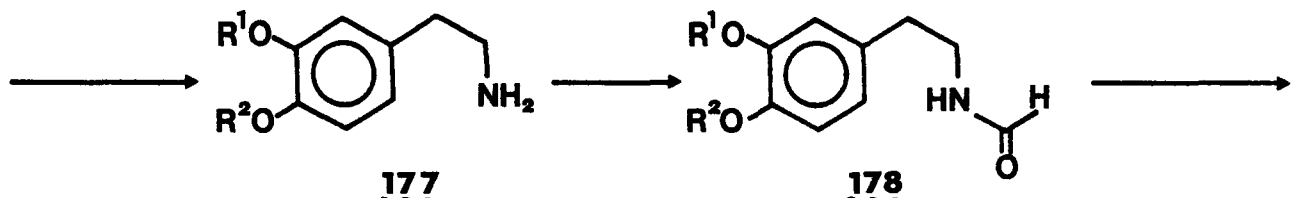
The phenylethylamines 177a, 177b, and 177c were formylated by



174 175 176

	R^1	R^2
a	$-CH_2-$	
b	Me	Bn

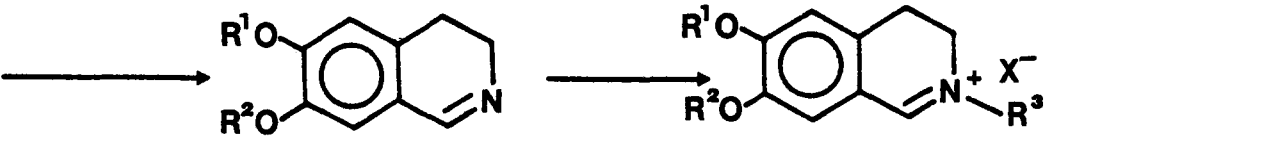
	R^1	R^2
a	$-CH_2-$	
b	Me	Bn



177 178

	R^1	R^2
a	Me	Me
b	$-CH_2-$	
c	Me	Bn

	R^1	R^2
a	Me	Me
b	$-CH_2-$	
c	Me	Bn

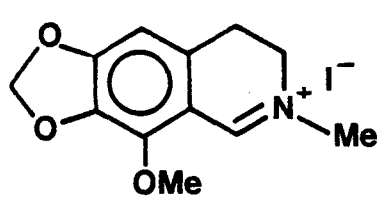


97 179

	R^1	R^2
a	Me	Me
b	$-CH_2-$	
c	Me	Bn
d	Bn	Me
e	Me	H

	R^1	R^2	R^3
a	Me	Me	Me
b	$-CH_2-$		Me
c	Me	Me	CH_2-Ph
d	Me	Me	$CH_2-CH=CH_2$
e	Me	Me	CH_2-(2-NO_2-Ph)

SCHEME 53A



179f

treatment with freshly distilled ethyl formate by stirring the solution for ca. 12 h at room temperature; the corresponding N-formyl derivatives, **178a**, **178b**, and **178c**, were isolated in nearly quantitative yield. The same reaction was also effected by heating the reaction mixture in a sealed tube at 120°C for 2 h. The imines, **97a**, **97b**, and **97c** were prepared by cyclization of the substituted N-formylphenethylamines **178a,b** and c with neat freshly distilled phosphoryl chloride ($POCl_3$) as the condensing agent. This procedure gave better yields than the usual method in which mixtures of $POCl_3$ and acetonitrile were employed.

McDonald and Suksamaru (156) have reported the preparation of 3,4-dihydroisoquinoline **97d** by treating an acetonitrile solution of formamide **178d** with $POCl_3$ at room temperature for 3 h (Scheme 53b). When this procedure was used for the preparation of **97c**, cyclization was accompanied by loss of the benzyl group as shown by the ^1H nmr spectrum and by a positive ferric chloride test. The imine isolated melted at 183°C and was identified as 7-hydroxy-6-methoxy-3,4-dihydroisoquinoline **97e** (157). Tomita and Watanabe (158) apparently obtained imine **97e** (mp 183°C) on cyclization of the formamide **178d** with $POCl_3$ in refluxing toluene, but reported they had obtained **178c**. Kametani and Ohkubo (159), following a similar procedure (158), obtained imine **97c** from the formamide **178c** but only in 28% yield. Their low yield was probably caused by the formation of **97e** as the major product.

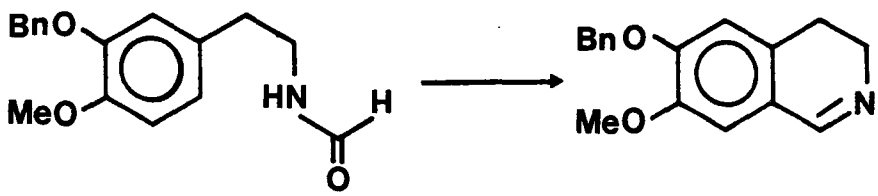
The imines **97a** and **97b**, were converted to their corresponding iminium salts, **179a-e**, by treatment with appropriate alkyl or benzyl halides, by standard procedures (Scheme 53a). Cotarnine iodide **179f** was

prepared by degradation of narcotine 1 (160).

9-Benzyl-3,4-dihydro-β-carboline 184 was prepared by the procedure shown in Scheme 54. Indole-3-acetonitrile 180 was converted to its N-benzyl derivative 181 in 78% yield by treatment of 180 with sodium hydride, followed by treatment with benzyl bromide. N-Benzyltryptamine 182 was prepared by the reduction of 181 in ethanolic ammonia with hydrogen (2.5 atm.) over rhodium on alumina at room temperature (161). The N-formylated tryptamine 183 prepared by treatment with ethyl formate at 120°C in a sealed tube, was subsequently cyclized to 184 with neat $POCl_3$.

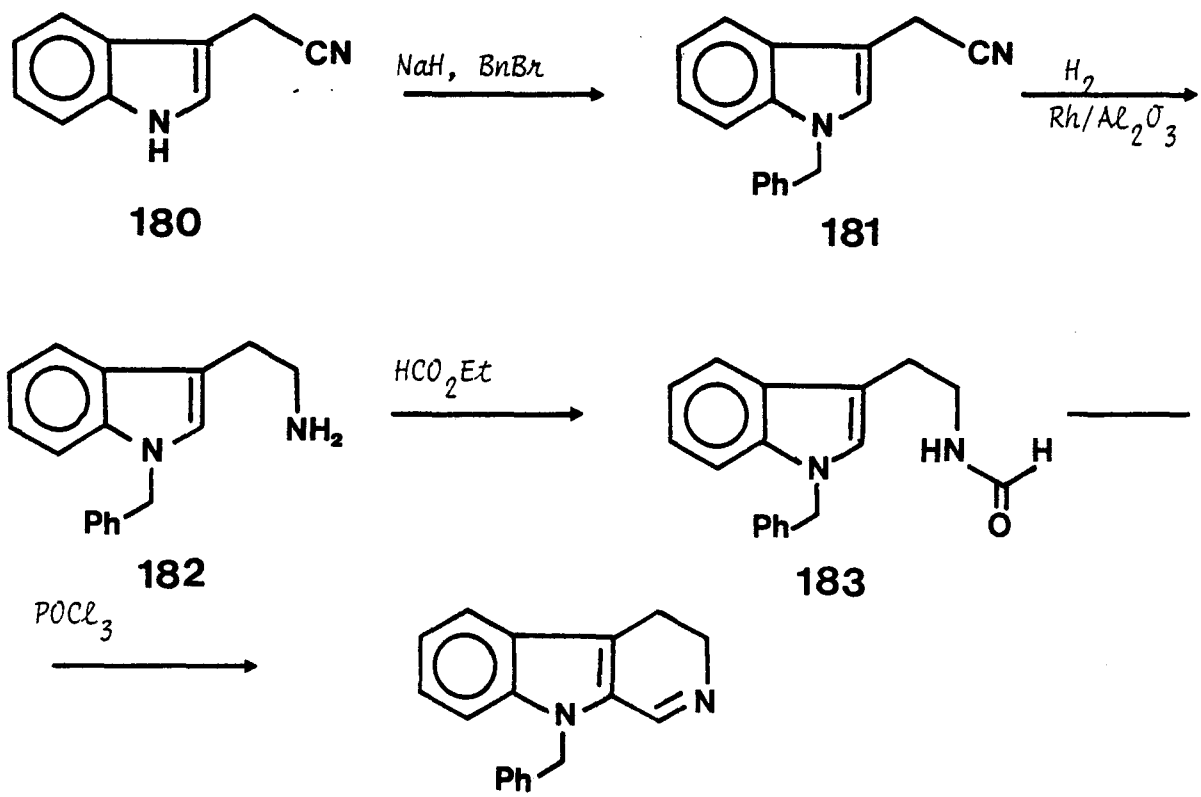
2.3 PREPARATION OF AZAPHTHALIDES AND RELATED COMPOUNDS

Ashcroft *et al.* (162) have reported the preparation of furo-[3,4-*c*]pyridin-3[1*H*]-one (azaphthalide) 188a in several steps from cinchomeronic acid 185 as shown in Scheme 55, but it was found that this route gave 188a in poor and variable yield. It was therefore necessary to investigate other procedures for its synthesis, because large quantities of 188a were required in the present study. It was discovered that 188a could be prepared satisfactorily by reduction of cinchomeronic anhydride 186 with sodium borohydride ($NaBH_4$) in dry tetrahydrofuran (THF) as outlined in Scheme 56. The desired azaphthalide was formed as the major product in the reduction and was readily separated by crystallization from the minor product (regioisomer) 189. This preparation was an adaptation of a method developed by Kayser and Morand (163) for reduction of other acid anhydrides and proved superior to the reduction



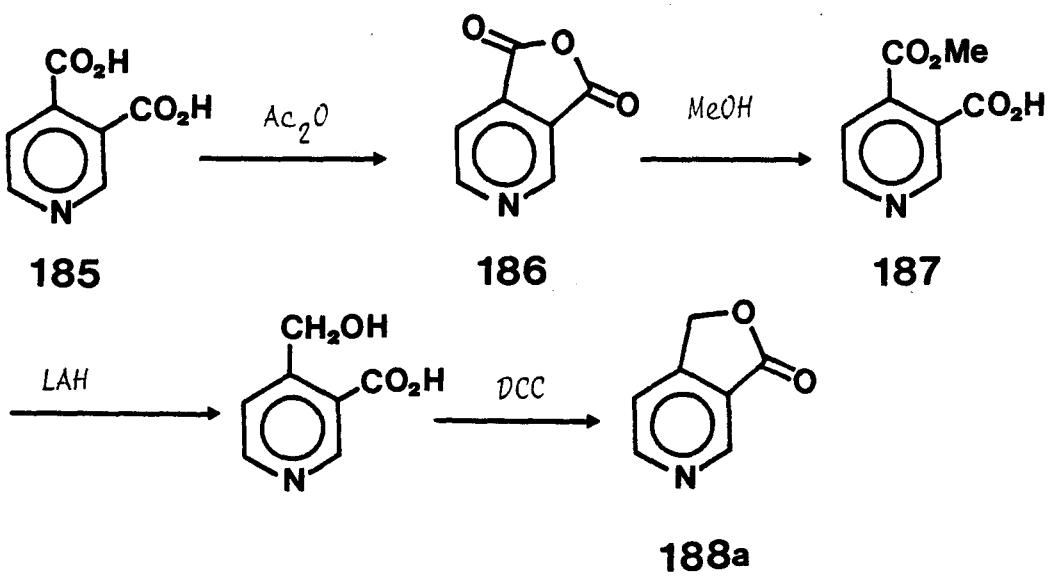
178d 97d

SCHEME 53B

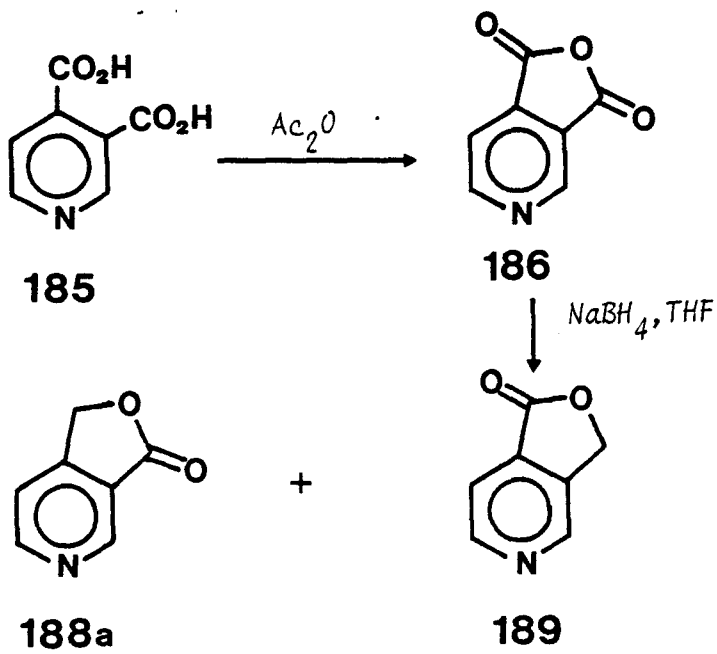


180 181 182 183 184

SCHEME 54



SCHEME 55

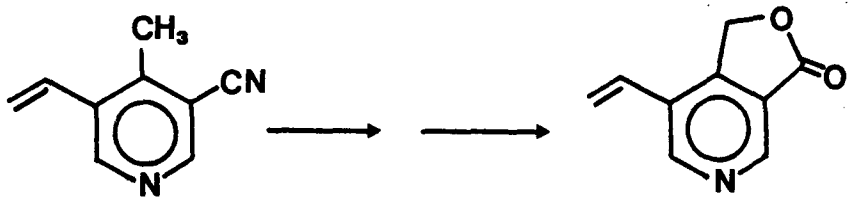


SCHEME 56

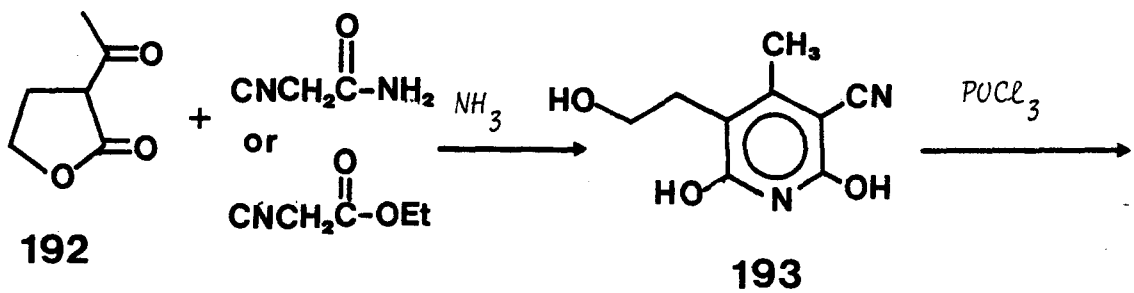
reduction of cinchomeronic anhydride with LAH (164) and of the half ester of cinchomeric acid 187 with LAH (162).

The convergent approach envisaged for the synthesis of pyridine-containing alkaloids uses an azaphthalide in the condensation step. As shown in Figures 3 and 5 a number of the pyridine-containing alkaloids have substituents at C-12 ($-CH=CH_2$, $-CHOHCH_3$, or $-COCH_3$). Therefore, an attempt was made to synthesize 7-vinyl-furo[3,4-*c*]pyridin- 3[1*H*]-one (azaphthalide) 191 with the expectation that the vinyl group could be modified to the other substituents at a later stage. 3-Cyano-4- methyl-5-vinylpyridine 190a is readily available by known synthetic procedures (165,166) and its transformation to azaphthalide 191a was investigated.

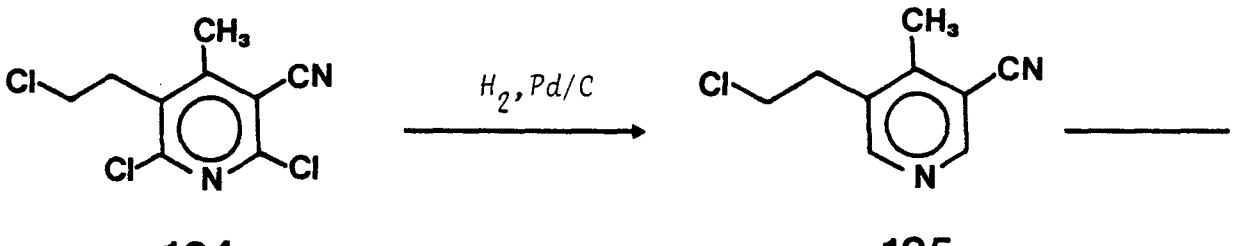
Condensation of α-acetylbutyrolactone 192 with either ethyl cyanoacetate or 2-cyanoacetamide and ammonia gave an ammonium salt in good yield that was transformed to 3-cyano-2,6-dihydroxy-5-(2'- hydroxy-ethyl)-4-methylpyridine 193 (167,168) (Scheme 57). Compound 193 was also obtained by reacting 192 with 2-cyanoacetamide using piperidine as catalyst (167) but there was little to be gained in terms of yield. The hydroxypyridine derivative 193 was converted to the chloro-derivative 194 on treatment with $POCl_3$ at elevated temperature (200-210°C) (166). Hydrogenation of compound 194 over 10% Pd-C gave 5-(2'-chloroethyl)-3-cyano-4-methylpyridine 195 in excellent yield. The modified Govindachari procedure (165) proved to be superior to the original procedure (166) in terms of yield. Dehydrohalogenation of 195 under alkaline conditions using potassium hydroxide in ethanol gave the desired compound 190a.



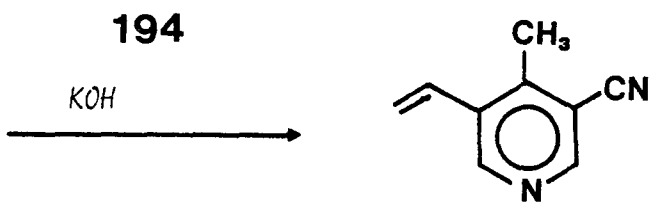
190a **191a**



192 **193**



194 **195**

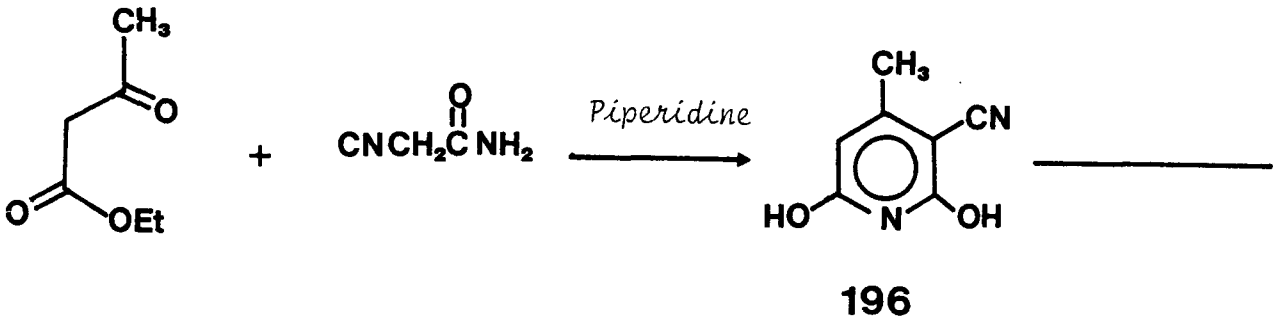


190a

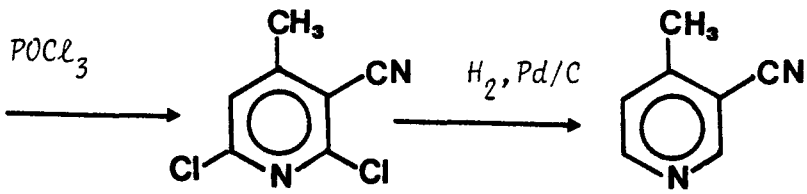
SCHEME 57

3-Cyano-4-methylpyridine 198a required in another experiment was prepared in a similar way as outlined in the synthetic Scheme 58. Thus, 3-cyano-2,6-dihydroxy-4-methylpyridine 196 was obtained by the condensation of ethylacetoacetate and 2-cyanoacetamide in the presence of piperidine (169). Treatment of 196 with an excess of $POCl_3$ at elevated temperature (200-220°C) gave 2,6-dichloro-3-cyano-4-methylpyridine 197, which was then transformed to 198a by treatment with hydrogen over 10% Pd-C.

Various attempts were made to transform the CH_3 group of 190a to CH_2OH so that azaphthalide 191a could be prepared. Initially an attempt was made to prepare the alcohol by way of a halide. However all attempts to brominate compound 190a with N-bromosuccinimide (NBS) under various conditions were unsuccessful. Similarly, halogenation of the lithium salt 190b either with bromine or chlorine gas failed to give the desired product. Next an attempt was made to convert the lithium salt 190b into a benzoate ester by treatment with dibenzoyl peroxide (DBP) (170-171). Hydrolysis of the ester would yield the alcohol, but only traces of the desired benzoate ester were formed as evidenced by ^1H nmr. Instead the major product was the dimer 199 identified by its ^1H nmr and mass spectra and elemental analysis (Scheme 59). Further investigation revealed that the lithium salts of α- and γ-picolines behaved similarly yielding 200 and 201, respectively. In another experiment it was found that reaction leading to the formation of dimer 199 required only one mole of DBP for each two moles of lithium salt 190b. The reaction probably proceeds by a

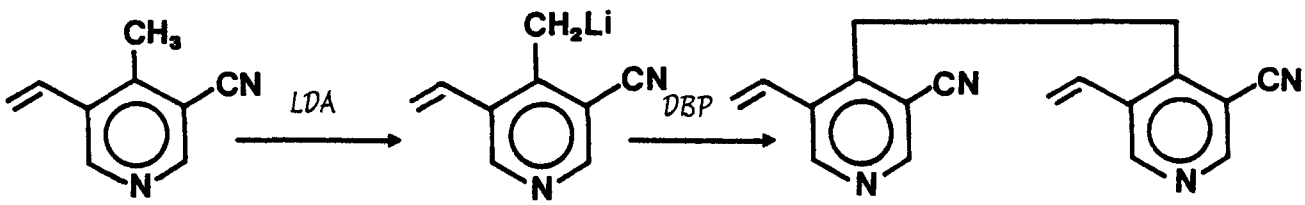


196



197 198a

SCHEME 58



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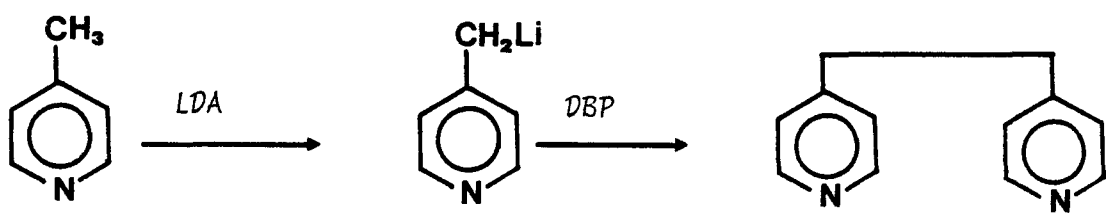
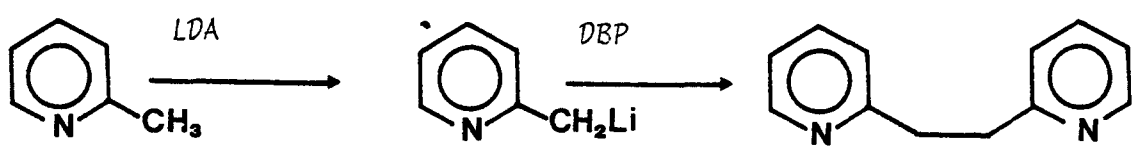


200



201

SCHEME 59

radical mechanism but investigation of the mechanism has not been undertaken because it lies outside the general area of this research.

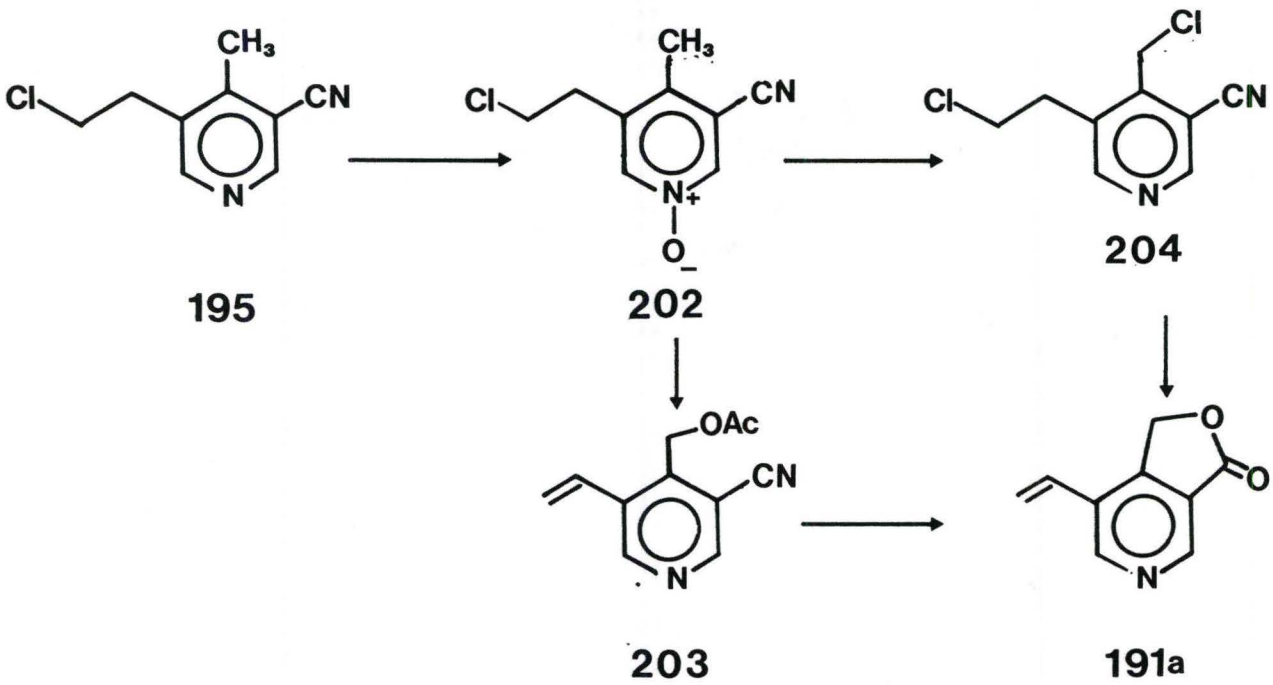
Attempts to convert the methyl group of 190a to -CHO were also unsuccessful. The procedure used was that of Godard *et al.* (172) who have converted 7-carbomethoxy-4-methylquinoline to the corresponding 7-carbomethoxy-4-formylquinoline with selenium dioxide.

Finally low yields of azaphthalide 191a were obtained beginning from the *N*-oxide 202. In one case, treatment of *N*-oxide 202 with acetic anhydride (173-177) yielded acetoxymethyl compound 203 which on alkaline hydrolysis and acid treatment gave azaphthalide 191a (Scheme 60). In another procedure the *N*-oxide 202 was treated with $POCl_3$ (178-180) yielding the chloromethyl compound 204 which was transformed to azaphthalide 191a (Scheme 60).

Any further investigation toward the practical synthesis of azaphthalide 191a was discontinued and 3-cyano-4-methyl-5-vinylpyridine 190a itself was used in the synthesis of pyridine-containing alkaloids.

2.4 SYNTHESIS OF AZA ANALOGUES OF PHTHALIDEISOQUINOLINE ALKALOIDS

The phthalideisoquinoline alkaloid, narcotine 1 has been found to possess antitussive property [its ability to allay or ameliorate coughing spasms (181a)] and to increase the amplitude of peristaltic pulses (181b). β-Hydrastine 58, another phthalideisoquinoline, produces convulsions in frog (182a) and inhibits the contraction of smooth muscle (182b). The most interesting action of the phthalideisoquinoline alkaloids is that exhibited by bicuculline 205. It was discovered by



SCHEME 60

Curtis *et al.* (183-185) that it has the ability to antagonize the effect of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA). Since this finding, several analogues of bicuculline have been investigated as GABA antogonists and as a result bicuculline methochloride was found to be the most effective (186,187). Kardos *et al.* (188) have recently examined a number of phthalideisoquinolines as GABA antagonists. The potential usefulness of phthalideisoquinolines in this area prompted us to synthesize a new class of compounds, which are aza analogues of phthalideisoquinoline alkaloids, and which were subsequently screened as GABA antagonists*1.

Based on the recent synthesis of phthalideisoquinolines reported from this laboratory (78), the desired azaphthalideisoquinolines might also be prepared by forming a C-C bond between an azaphthalide and a 2-methyl-3,4-dihydroisoquinolium moiety. A retrosynthetic analysis is depicted in Figure 6. The desired starting materials, iminium salts **179a,b,g**, and azaphthalide **188a**, are readily available as discussed previously.

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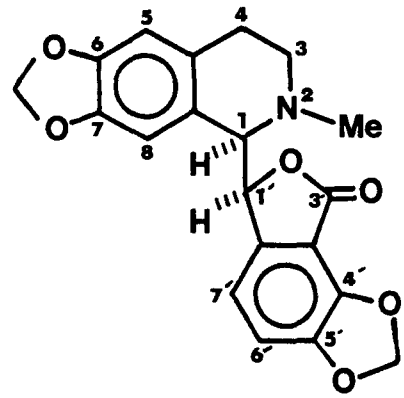
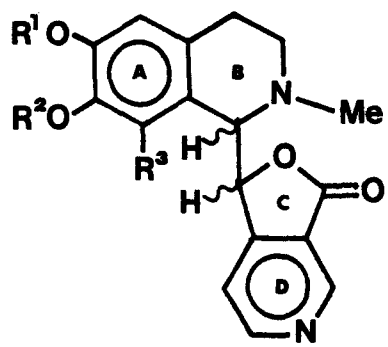
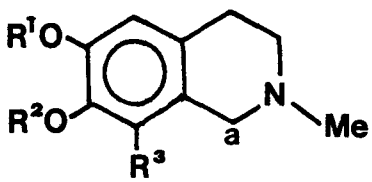
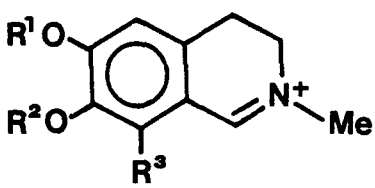
*1 The pyridine analogues of the phthalideisoquinoline alkaloids did not show significant activity on the GABA receptor even above 10 $^{-4}$M concentration in the ^{3}H-GABA binding assay. Private communication to Prof. D.B. MacLean from Prof. G. Blasko (Central Research Institute, Budapest) July 9, 1985.



205







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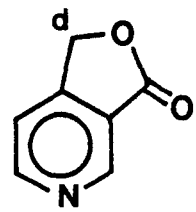
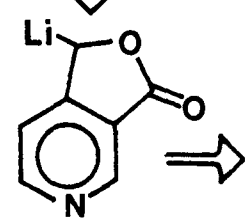




188b

a: Acceptor

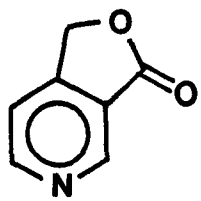
b: Donor

Retrosynthtic Analysis of Azaphthalideisoquinolines

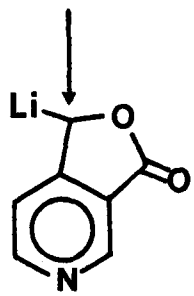
FIGURE 6

The one step synthesis of azaphthalideisoquinolines, 206a,b,c and 207a,b,c, from 188b and 179 is outlined in Scheme 61. The lithium salt 188b prepared by the treatment of the azaphthalide 188a with lithium di-isopropylamide (LDA) at -70°C, was added to a slurry of the iminium salt, 179a, 179b or 179f, in THF at -40°C. The reaction mixture was allowed to warm to room temperature and was worked up in the conventional manner yielding the expected mixtures of racemic *threo* 206a,b,c and *erythro* 207a,b,c diastereomers; the *erythro* isomers were difficult to crystallize. The yields reported for the two isomers refer to the crystalline products isolated from the reaction, and should not be used as a measure of the *threo*:*erythro* ratio present in the crude product mixtures and which was approximately 1:1 by ^{1}H nmr. The additional methoxy group at C-8 in cotarnine iodide 179f is probably causing steric crowding and consequently slowing the addition of azaphthalide anion to the iminium salt accounting for the low yield. Attempts were made to improve the yields of 206c and 207c by varying reaction conditions (temperature and time) but without success. Exchange of Li for Zn by treating the solution of Li-azaphthalide with freshly prepared anhydrous $ZnCl_2$ before the addition to cotarnine iodide was attempted but did not improve the yield.

The determination of the relative configuration of the phthalide-isoquinoline alkaloids has been the subject of numerous studies (189-196) and ^{1}H nmr spectroscopy has been reported to be a reliable method to establish their configurations. The chemical shift of protons, C-4' H and C-7' H and the coupling constant between C-1 H and C-1' H have been shown to be diagnostic of configuration for a given pair of

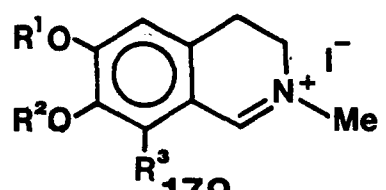


188a



188b

+



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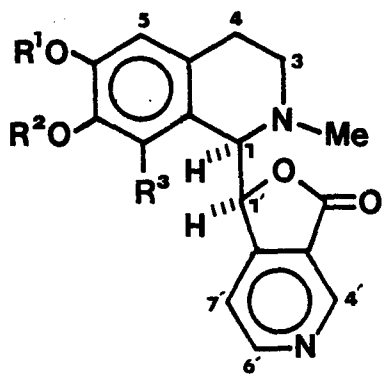
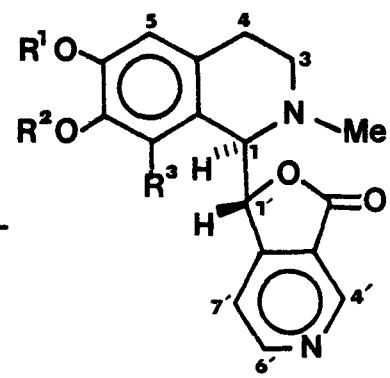


206 *Threo*

+



207 *Erythro*

	R¹	R²	R³		R¹	R²	R³
a	Me	Me	H	a	Me	Me	H
b	—CH_2—		H	b	—CH_2—		H
c	—CH_2—		MeO	c	—CH_2—		MeO

SCHEME 61

diastereomers. The assignment of configurations to the isomeric azaphthalideisoquinolines prepared in this investigation is based on comparison with those of the phthalideisoquinoline alkaloids where the conformational assignments are secure (189,194). In the *threo* isomers 206a and b examined in this work the protons at C-1' and C-7' are always deshielded and the proton at C-4' is shielded relative to the corresponding protons in the *erythro* series, 207a and b. This situation is similar to that observed for the phthalideisoquinolines themselves (190,191), indicating that the azaphthalideisoquinoline system in compounds 206a and b and 207a and b adopts the same preferred conformation as the corresponding rings in the alkaloids as represented for the *erythro* compounds by structure II and for the *threo* compounds by structure I (Figure 7) (190). In the *erythro* compounds, the preferred conformation places the hydrogen at C-7' in the shielding cone of the aromatic ring of the isoquinoline moiety, whereas in the favoured *threo* conformations this hydrogen is not in a position where it can be similarly affected. There is also consistency with respect to the coupling constants between hydrogens at C-1 and C-1'. In each series the *threo* isomer has a smaller coupling constant than the *erythro* isomer. The relevant ^{1}H nmr data are collated in Table 2.

MacLean and co-workers (197,198) have shown that ^{13}C nmr spectra are diagnostic of the relative configuration of the diastereomeric pair of the phthalideisoquinolines. In the *threo* compounds examined in this work C-3 and C-4 are deshielded and C-1' is shielded relative to the corresponding carbons in the *erythro* isomers, and this is consistent with

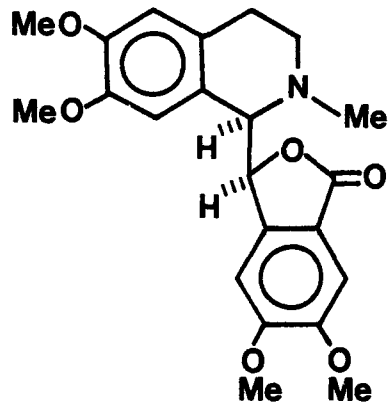
Table 2

^{1}H nmr Data of Phthalideisoquinolines and Azaphthalideisoquinolines

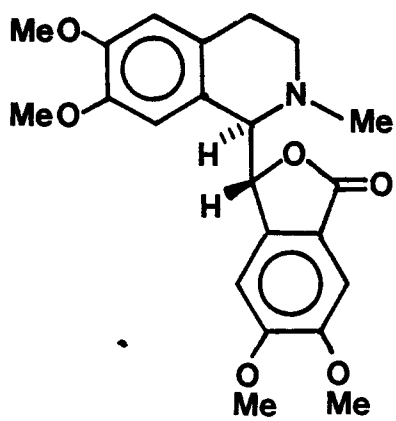
Compound	Chemical Shifts in ppm (δ)			Coupling Constant in Hz
	C-1' H	C-4' H	C-7' H	$J_{1H,1'H}$
208[a]	5.64	7.02	7.15	3.6
209[a]	5.59	7.25	6.22	3.8
57[b]	5.55	-	7.30	3.3
58[b]	5.48	-	6.52	4.0
206a	5.75	8.89	7.70	3.7
207a	5.66	9.12	6.65	4.5
206b	5.70	8.96	7.69	3.5
207b	5.57	9.13	6.65	4.8

[a] Data from Elango *et al.* (190).

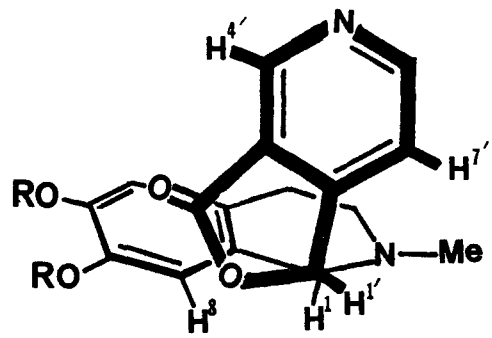
[b] The diastereomeric pair does not have C-4' H, but other proton signals are similar to those observed in other phthalideisoquinolines; more examples are given in reference (190).



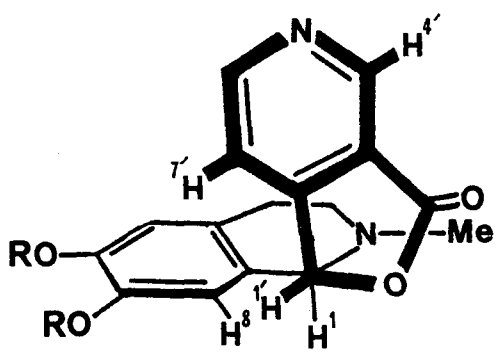
208 (*Threo*)



209 (*Erythro*)



Threo I



Erythro II

Perferred Cnformation of erythro- and threo- Azaphthalideisoquinolines

FIGURE 7

the previous studies (197,198). The relevant ^{13}C nmr data are collated in Table 3. The presence of a methoxyl substituent at C-8 in the phthalideisoquinolines alters the conformations of both the *threo* and *erythro* isomers and the relationships noted above do not apply (194).

The *erythro* and *threo* isomers also exhibit a similar chromatographic behaviour in each series. The *threo* isomer is less polar than the *erythro* on silica columns and shows a higher R_f value on tlc plates.

Cleavage of the doubly benzylic bond, C(1)-C(1'), constitutes the major mass spectral fragmentation in the azaphthalideisoquinolines and in each case, the base peak arises from the isoquinoline moiety.

2.5 AZA ANALOGUES OF PROTOBERBERINE ALKALOIDS: A CONVERGENT SYNTHESIS OF THE ISOQUINO[2,1-*b*][2,7]NAPHTHYRIDINE RING SYSTEM

Recently, Pakrashi *et al.* (123-125) isolated a number of alkaloids from the seeds of *Alangium lawarckii* containing the isoquino-[2,1-*b*][2,7]naphthyridine ring system (Figure 3). The discovery of this new class of alkaloids prompted us to investigate their synthesis by a route similar to that used for the synthesis of the protoberberines (109,110). A retrosynthetic analysis using imines and phthalide precursor is depicted in Figure 8. As discussed earlier, the desired azaphthalide **188a** and various 3,4-dihydroisoquinolines **97a,b**, and **c** are readily available.

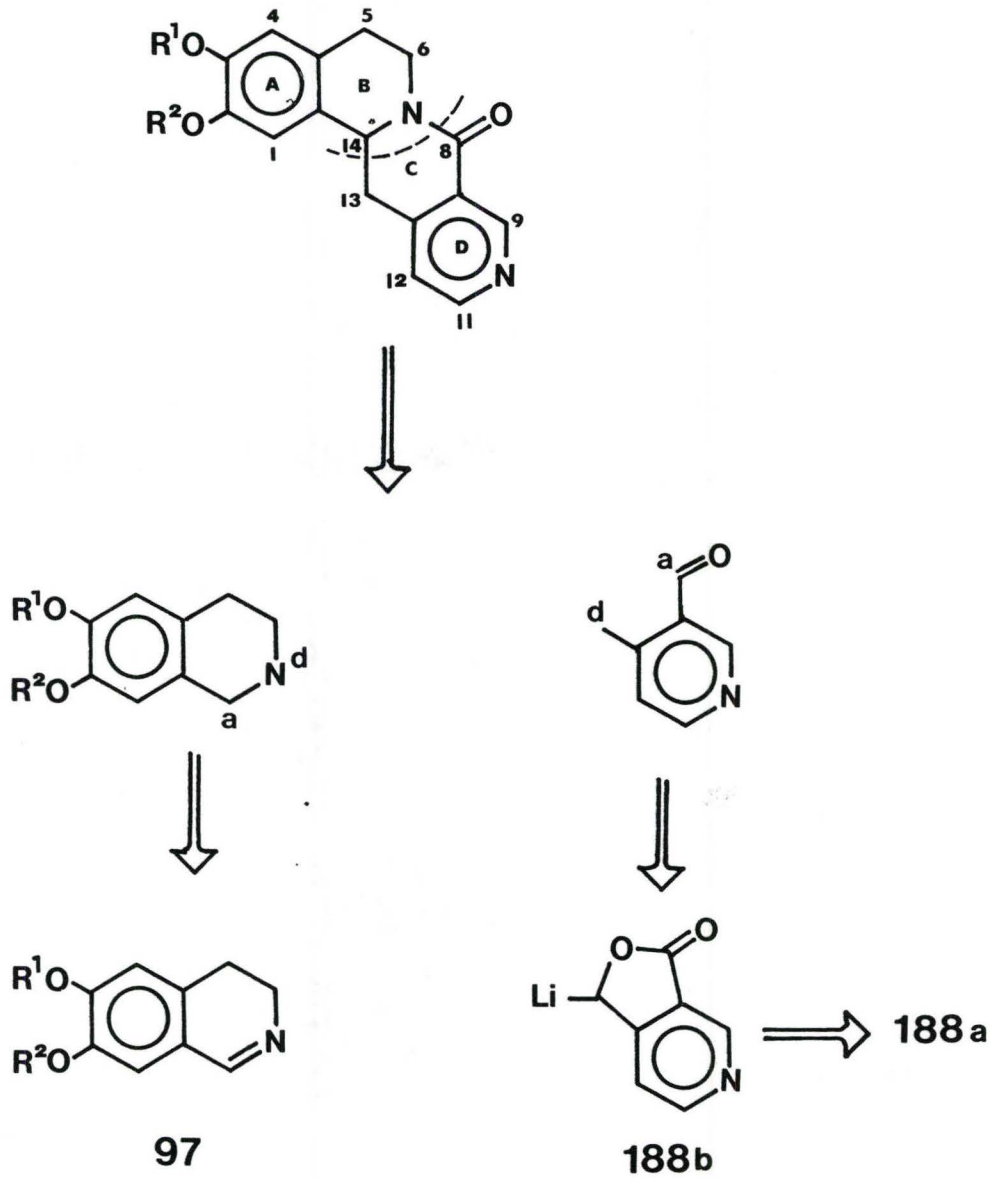
Reaction of the lithium salt **188b**, derived from the azaphthalide **188a** with the 3,4-dihydroisoquinolines, **97a**, **97b** and **97c**, is outlined in

Table 3

^{13}C nmr Data of Phthalideisoquinolines and Azaphthalideisoquinolines

Compound	Chemical Shifts in ppm (δ)		
	C-3	C-4	C-1'
57[a]	51.3	29.2	81.8
58[a]	49.0	26.7	82.7
55[a]	51.7	29.1	82.1
56[a]	49.5	26.5	84.9
206a	50.8	29.5	81.4
207b	50.0	27.0	84.7
206b	51.5	29.6	82.0
207b	50.1	27.6	84.8

[a] Data of MacLean and co-workers (197,198).



a: Acceptor
d: Donor

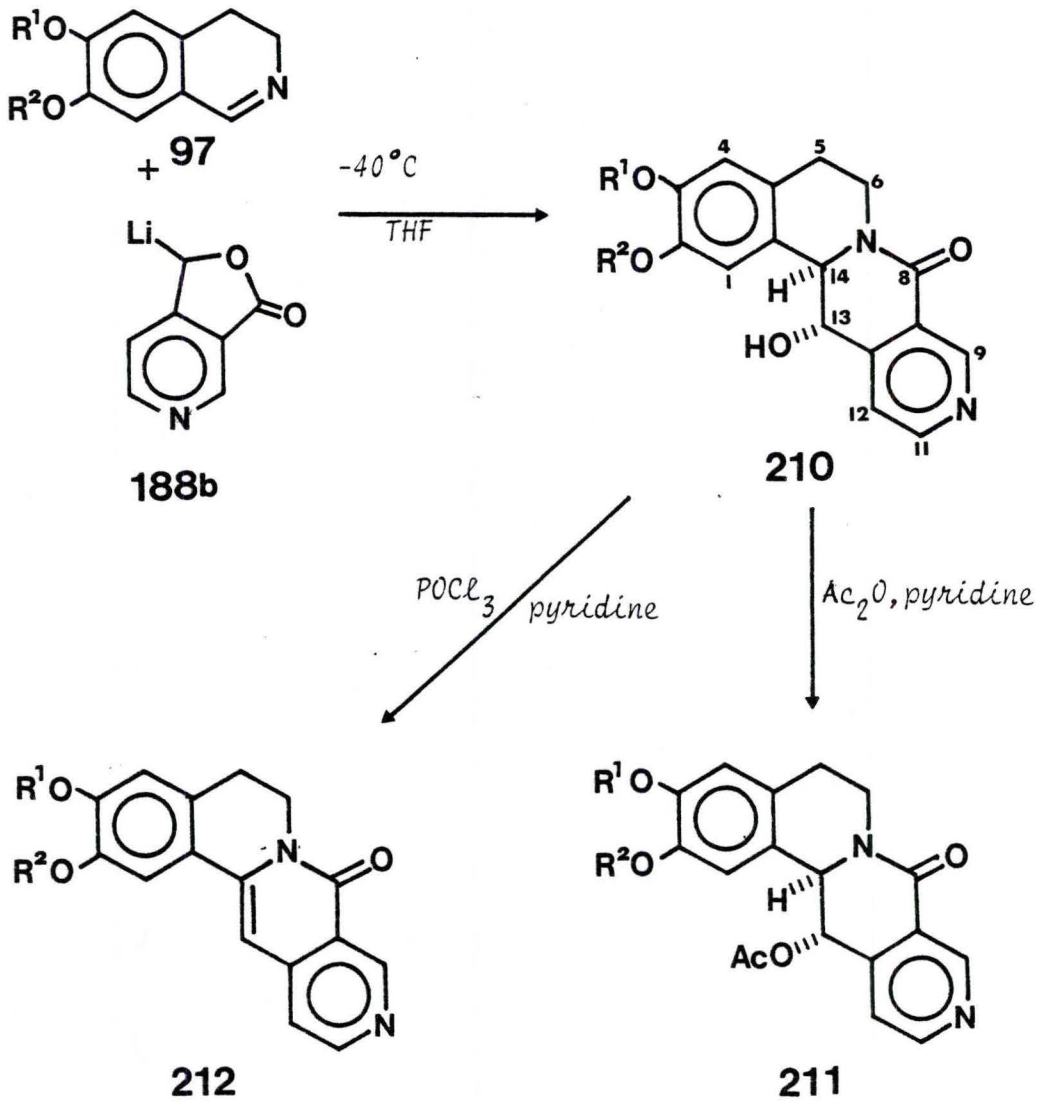
FIGURE 8

Retrosynthetic Analysis of Azaberberines

Scheme 62. The lithium salt **188b** was treated with the imines **97a,b** and **c** at -40°C for ca. 2 h, and then the reaction mixture was warmed slowly to room temperature. In accord with the earlier observations (109,110) 13-hydroxy-5,6,13,14-tetrahydro-8H-isoquino[2,1-*b*][2,7]naphthyridin-8-one derivatives **210a**, **210b** and **210c** were formed in a single step. The structures of the products **210a,b,c** (only one diastereomer was formed) were assigned on the basis of spectroscopic examination of these compounds and of their *O*-acetyl derivatives **211a,b,c** and also by comparison with previously studied products of similar reactions (109,110).

The infrared spectra of **210a**, **210b** and **210c** displayed, in addition to OH absorption, absorption in the carbonyl region at ca. 1645 cm^{-1} attributed to the conjugated six-membered lactam function. The infrared spectra of *O*-acetates **211a**, **211b**, and **211c** in each case showed two absorption bands in the carbonyl region at ca. 1760 and 1650 cm^{-1}, the former absorption assigned to the ester function and the latter to the lactam.

The relative configuration at C-13 and C-14 could not be established with certainty by examination of the ^{1}H nmr spectra of alcohols **210a,b**, and **c**, but that of their *O*-acetyl derivatives **211a,b**, and **c** clearly showed that C-13 H and C-14 H were *trans* to each other. The hydrogens at C-13 and C-14 in alcohols **210a,b**, and **c** had very similar chemical shifts and signals were centered at δ 4.63. On the other hand, in the *O*-acetyl compounds **211a,b**, and **c**, signals for C-13 H and C-14 H were well separated and the C-13 H signal was shifted downfield by ca.



	R¹	R²
a	Me	Me
b	—CH₂—	
c	Me	Bn

SCHEME 62

1.1 ppm. The large coupling constant (J=10.7 Hz) between the hydrogens at C-13 and C-14 in the *O*-acetyl derivatives **211a,b**, and **c** is compatible with a *trans* diaxial arrangement of the two hydrogens (110,199).

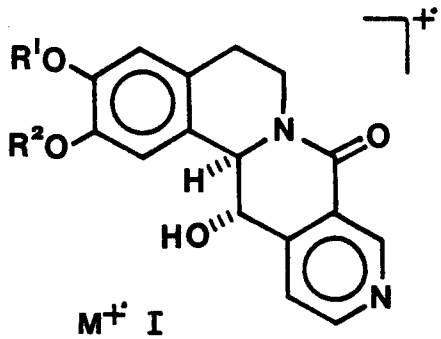
Attempted dehydration of the alcohols **210a,b**, and **c** under a variety of acidic conditions resulted in the exclusive recovery of starting material. However dehydration was effected at room temperature by treatment with $POCl_3$ in pyridine, affording in excellent yields, the isocarbostyril compounds **212a**, **212b**, and **212c**. These compounds exhibited the anticipated spectroscopic behaviour. Compound **212a** had been prepared previously (200) and the physical properties reported in the literature were in agreement with those measured here. The infrared spectra of the dehydrolactams **212a**, **212b**, and **212c**, displayed the expected absorption band at ca. 1650 cm^{-1}. In their ^1H nmr spectra, the signal associated with the vinylic proton at C-13 appeared at ca. δ 7.20. Thus, the condensation of lithium salt **188b** with the 3,4-dihydroisoquinolines provided a convenient route to the ring system found in the *Alangium* alkaloids.

Alternative routes to this ring system, which are non- regiospecific and which involve photochemical (201) or thermal (202) cyclization of tricyclic enamides, have been discussed in the previous chapter (section 1.6,i).

The mass spectral fragmentation of compounds **210a,b**, and **c**, prepared in this study, is analogous to that of the corresponding protoberberines (109,110). The major fragmentation involves a *retro*-Diels-Alder opening of ring C of the azaberberine system of the $M^{+\bullet}$

ions (I) as shown in Scheme 63. Ions corresponding to the isoquinoline moiety plus a hydrogen (II) are observed in all three compounds at m/z 192, 176 and 268, respectively and an ion derived from rings C and D (III) is present in all three compounds at m/z 135. Fragment ion (III) loses -CHO to give ion IV at m/z 106 in all three cases. The mass spectra of the *O*-acetyl derivatives **211a, 211b** and **211c** showed the loss of CH_3CO and an intense fragment ion at M-60 arising from the loss of CH_3COOH from the molecular ions. The compositions of some fragment ions were established by accurate mass measurements. The dehydrolactams, **212a, 212b** and **212c**, displayed strong molecular ions in their mass spectra and fragment ions arising mainly by loss of substituents from ring A of the molecular ions.

The above condensation reaction between the cyclic imines and azaphthalide anion was highly stereoselective yielding only one of the two possible racemic diastereomers. This stereoselectivity has been observed previously in the synthesis of protoberberines (109,110). The high degree of stereoselectivity in these condensations may be explained if the reactants interact in an "endo relationship" with respect to each other in a manner shown in Figure 9. This preference for an endo relationship may be a result of co-ordination of the Li ion with the electron lone pairs on the isoquinoline nitrogen atom and the two oxygen atoms of the phthalide ring. The fourth ligand involved in the co-ordination may be the carbon atom at C-1 of another lithium azaphthalide or a THF molecule. This model is illustrated in Figure 10. It is assumed that the C(13)-C(14) bond forms initially and that the

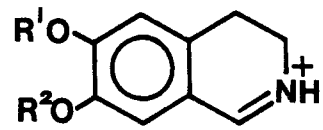


$M^{+\cdot}$ I

210a m/z 326(27)

210b m/z 310(23)

210c m/z 402(24)

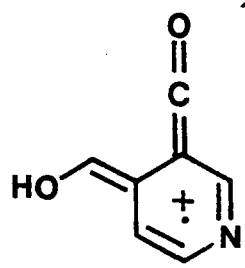


II

210a m/z *192(100)

210b m/z *176(97)

210c m/z *268(12)



III

m/z *135(10)

m/z *135(21)

m/z *135(100)

$-\dot{C}HO$

IV

$C_6H_4NO^+$

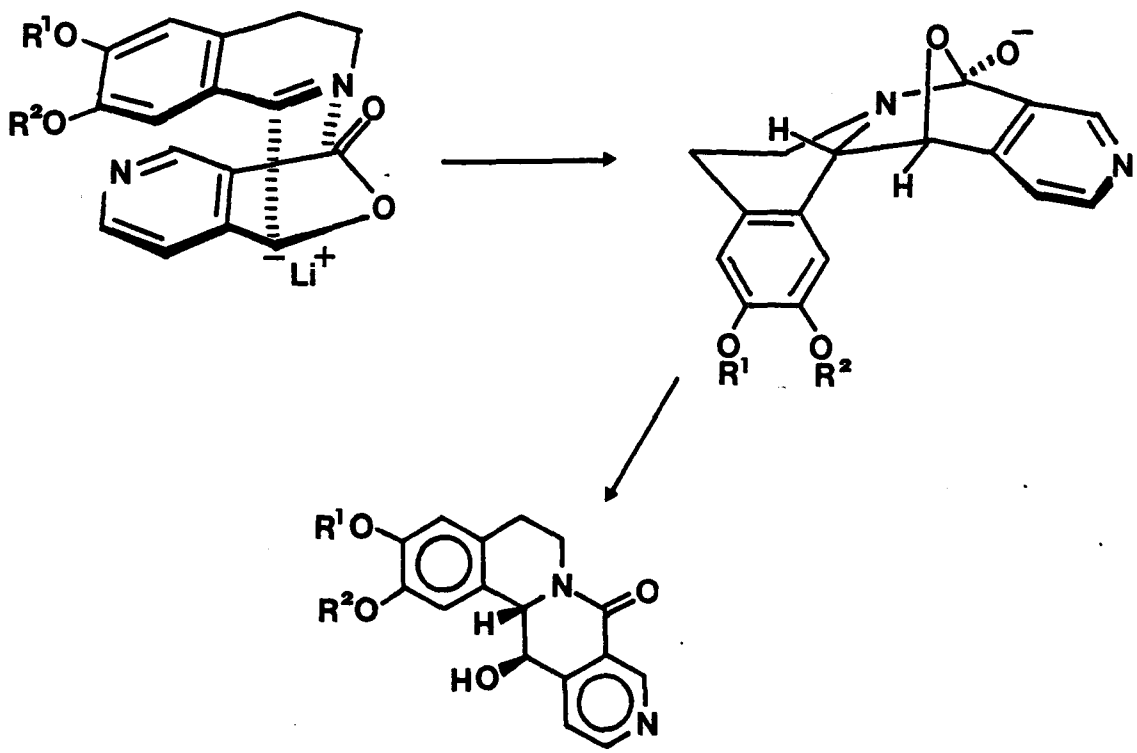
210a m/z *106(18)

210b m/z *106(100)

210c m/z *106(75)

SCHEME 63

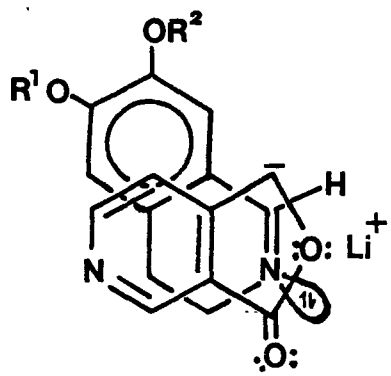
*compositions verified with hrms.



210

Postulated Mechanism for the formation of 13-hydroxy-8-oxoazaberberines

FIGURE 9



Postulated endo-interaction between azaphthalide anion and 3,4-dihydro-isoquinolines

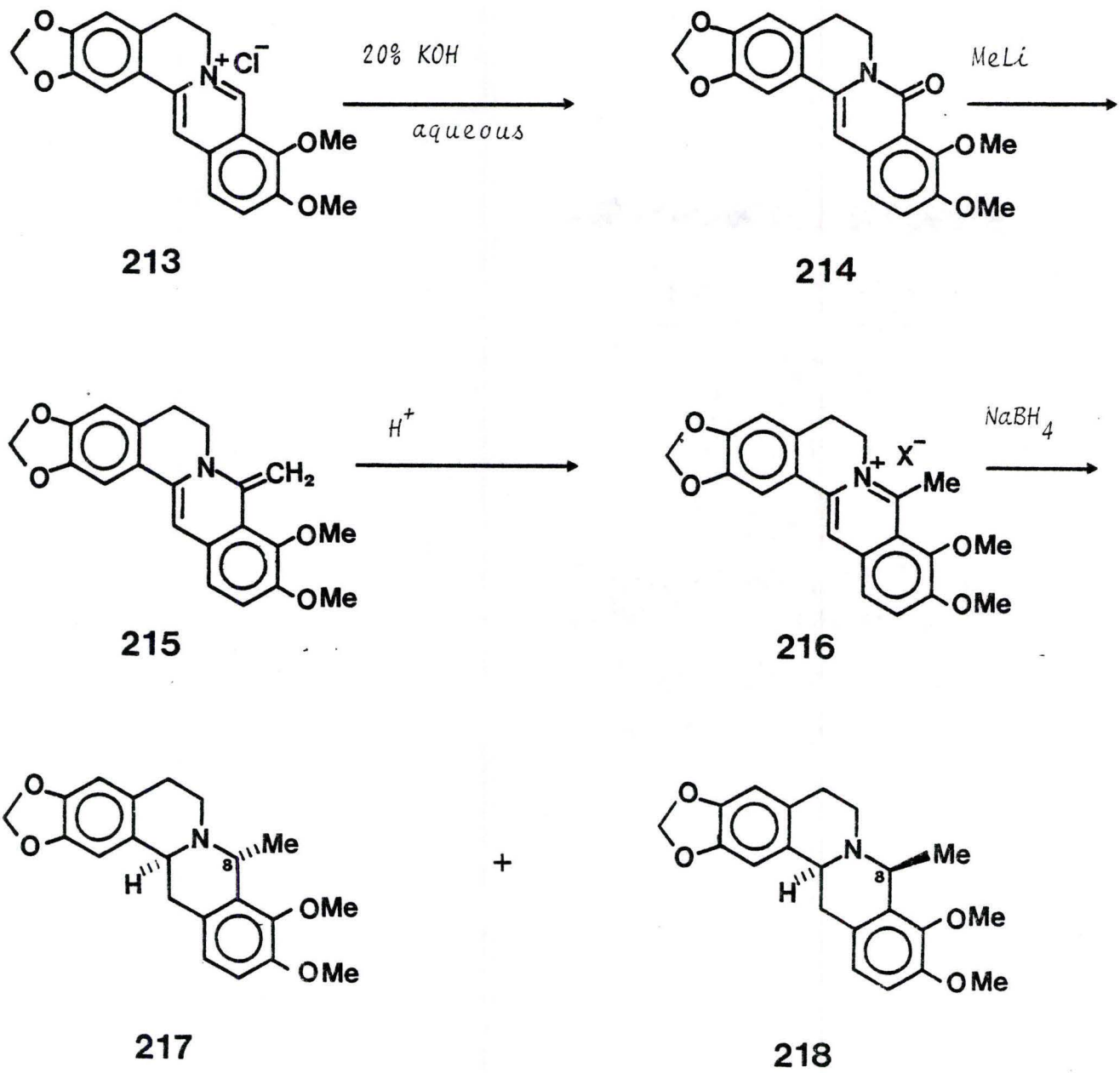
FIGURE 10

resulting anionic nitrogen attacks the lactone ring to give the pentacyclic intermediate which then collapses to product. The net result of this series of reactions is a *trans* relationship between the hydrogens at C-13 and C-14 in the product.

2.6 PREPARATION OF 8-METHYLBERBERINES AND THEIR AZA ANALOGUES: TOTAL SYNTHESIS OF (±)-ALAMARIDINE

In 1984 Pakrashi and co-workers (125) reported the isolation of alamaridine 126 as a minor constituent (0.0001%) of the seeds of *Alangium lamarckeii* Thw. and more recently its first synthesis (127). Their synthesis also clarified the relative stereochemistry at the two chiral centers, C-8 and C-14, in the previously proposed structure. In this section a second synthesis of (±)-alamaridine 126 is reported which is based on the addition of MeLi to lactams such as 212c whose preparation was described in the previous section.

Although uncommon, the addition of organolithium reagents to lactams are documented in the literature (203-207). 8-Oxoberberine 214, because of its availability, was used as a model compound to investigate the reaction of methylithium with a lactam function at C-8 as a means for the introduction of a methyl group at this site. 8-Oxoberberine 214 was prepared from berberine chloride 213 following the procedure of Perkin Jr. (208) and its physical data were in agreement with those reported in the literature (209,210). The route outlined in Scheme 64 was used for the synthesis of the 8-methylberberines. Treatment of lactam 214 with methyllithium at -40°C followed by work-up of the reaction mixture under



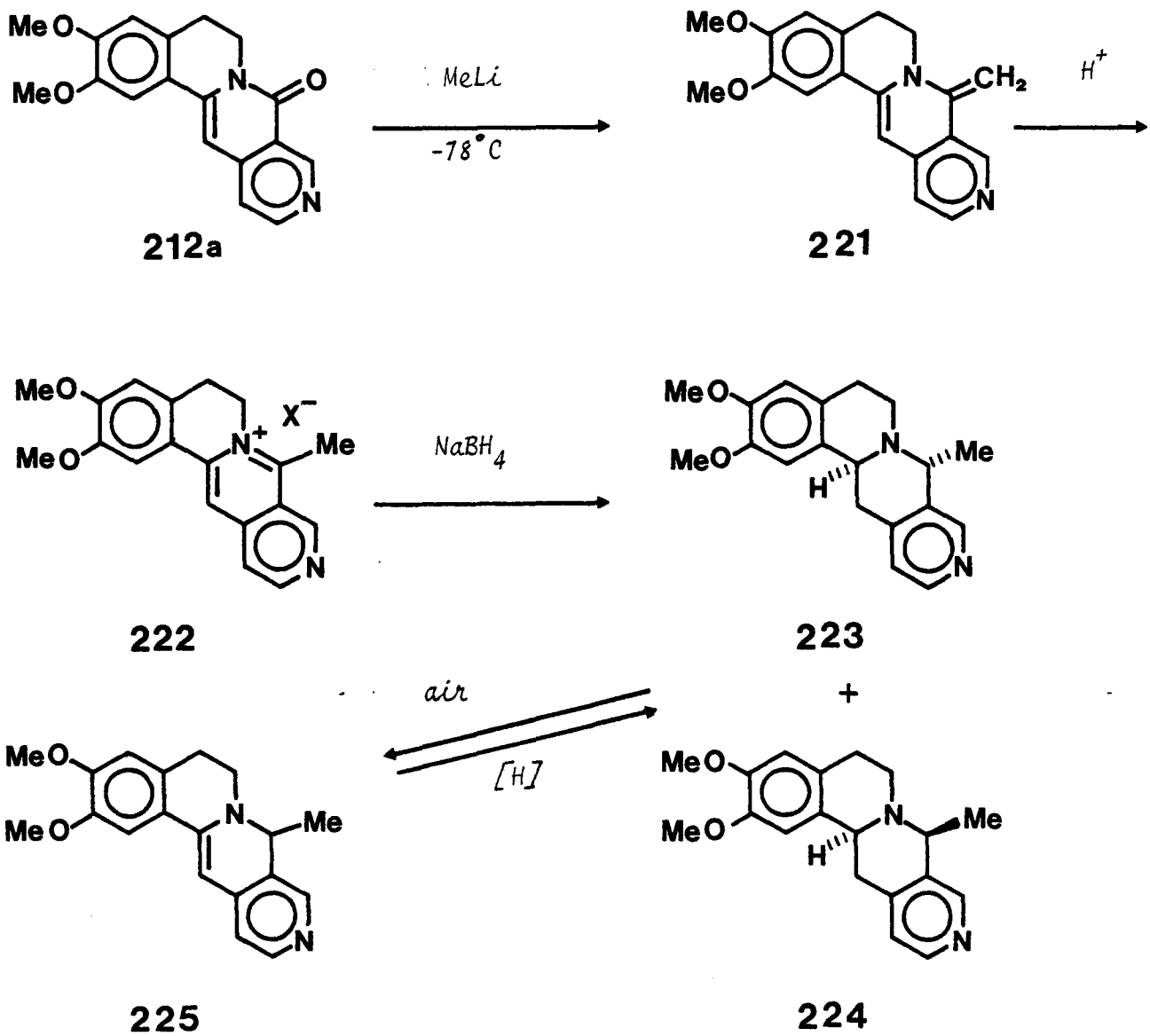
SCHEME 64

alkaline conditions afforded the exo-methylene compound 215. The presence of two singlets in the ^{1}H nmr spectrum of 215 at δ 4.20 and 5.35 was indicative of the presence of a >C=CH_2 group. Compound 215 in acidic media was transformed (as expected) into the corresponding iminium salt 216. The formation of 216 was evident from its ^{1}H nmr spectrum which showed a signal (3H) at δ3.60 in the region expected of a methyl group α to a quaternary nitrogen atom in an iminium system (211). Reduction of 216 with sodium borohydride in ethanol afforded a separable mixture of (8R*, 14S*) and (8S*, 14S*)-8-methylcanadines, 217 and 218, respectively in a ratio of ca. 1:3. The ratio is similar to that observed in the borohydride reduction of 8-methylberberium salts which have oxygen substituents at C-10 and C-11 (212-215). 8-Oxoberberine 214 could also be converted into a mixture of 217 and 218 in 25 and 69% yield respectively, as pure crystalline products, without isolation of intermediates, in a "one-pot" synthesis.

The assignment of the relative stereochemistry of 217 and 218 is based upon spectroscopic examination of the two isomers and a comparison of their ir and nmr spectra with those of *O*-methylcorytenchirine 219 and coralydine 220 (213,216) whose relative stereochemistries have been established by X-ray analysis (217). The infrared spectrum of 8-β-methylcanadine 218 like that of coralydine 220, displays Bohlmann bands at 2820-2470 cm^{-1} but these are absent in the spectra of 8-α-methylcanadine 217 and *O*-methylcorytenchirine 219. Thus 218 like coralydine 220, has a *trans*-quinolizidine ring fusion and 217 like *O*-methylcorytenchirine 219, a *cis* fusion at the N-C(14) bond. ^{1}H and ^{13}C

nmr data in support of these assignments will be discussed later collectively with other similar compounds prepared in this study.

Addition of alkyl and aryllithiums to carbon atoms α to nitrogen of the pyridine ring has been reported by Hauck and Giam (218) and also by Meyers *et al.* (219). Therefore another model synthesis was undertaken using the lactam **212a** to investigate whether MeLi adds to the C-8 lactam function in preference to the α-positions (C-9 and C-11) of the pyridine nucleus (ring D). The result of this investigation was gratifying. The reaction of the lactam **212a** with MeLi at -78°C proceeded analogously to that of 8-oxoberberine **214**. The exo-methylene compound **221** isolated on alkaline work-up, was readily converted in acidic media into the corresponding iminium salt **222** (Scheme 65). The presence of two singlets at δ 4.65 and 5.95 in the ^{1}H nmr spectrum of **221** was indicative of the $>C=CH_2$ group and was similar to that observed previously. Reduction of **222** with sodium borohydride in ethanol afforded a separable 1:3 mixture of the $(8R^*,14S^*)$- and $(8S^*,14S^*)$-8-methyl compounds, **223** and **224**, respectively; the former corresponding in structure to (±)-*O*-methylalamaridine. Compounds **223** and **224** may also be prepared without isolation of the intermediates in a "one-pot" reaction. The assignment of relative stereochemistry to **223** and **224** is based on their spectroscopic properties. Of special importance is the fact that **224** shows Bohlmann bands (2820-2740 cm^{-1}) in its ir spectrum. The infrared spectrum of *O*-methylalamaridine **223**, on the other hand, does not show these Bohlmann bands and therefore has a *cis*-conformation at the N-C(14) bond. Other spectral data (^{1}H, ^{13}C nmr and ms) will be discussed later.

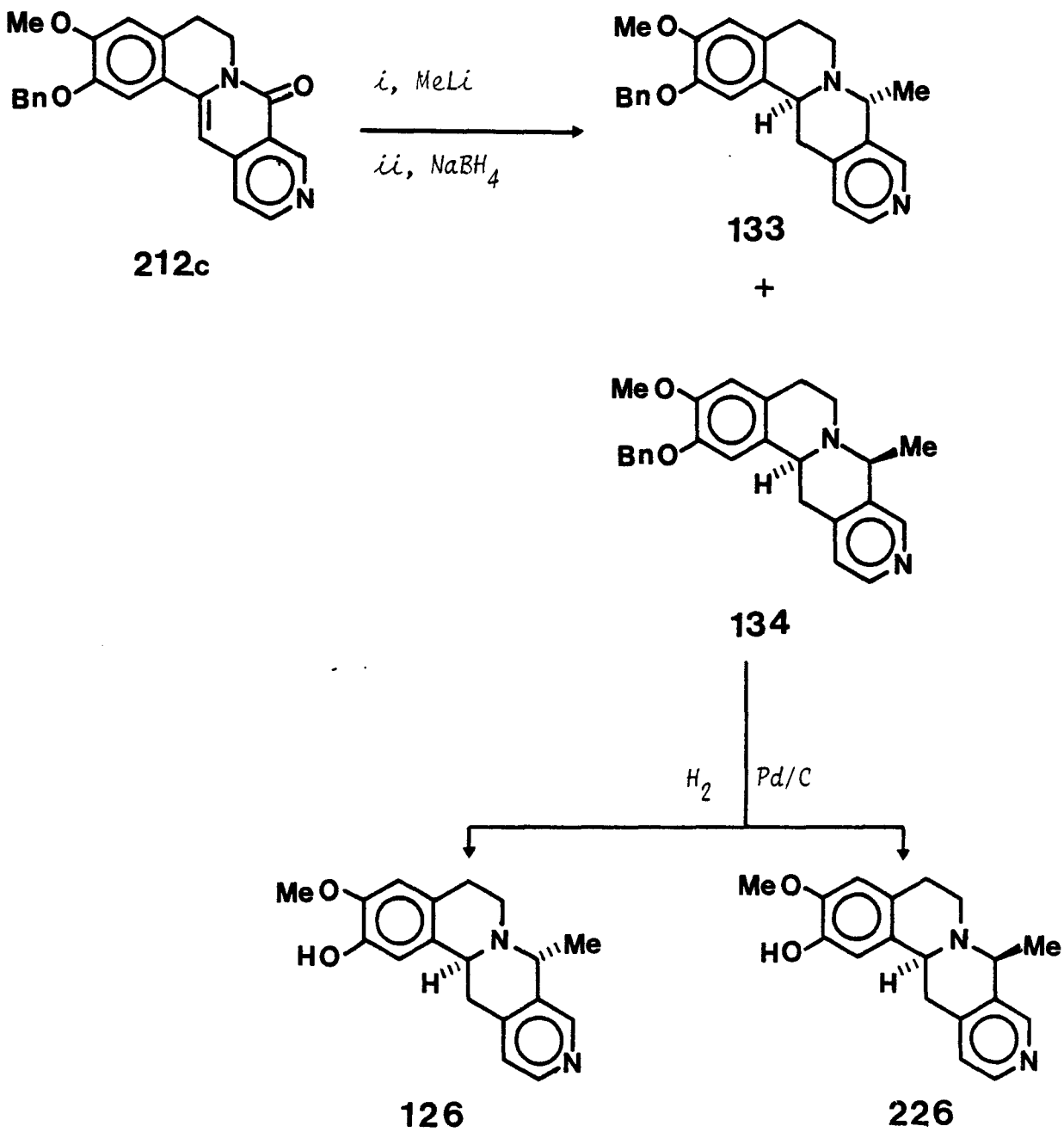

MeO
MeO
N
O
N
212a
MeLi
-78°C
MeO
MeO
N
CH2
N
221
H+
MeO
MeO
N+
X−
Me
N
222
NaBH4
MeO
MeO
N
Me
H
N
223
air
[H]
+
MeO
MeO
N
Me
N
225
MeO
MeO
N
Me
H
N
224

SCHEME 65

The tetrahydro compounds 223 and 224 were highly susceptible to aerial oxidation yielding strongly fluorescent solutions, which was a complicating factor in their isolation and purification. The spectral data of the product 225 of aerial oxidations suggested that it was a 13,14-dehydro compound. Dihydro-2,7-naphthyridines have been reported to exhibit similar strong green fluorescence as one of their characteristics (220). It should be noted that (±)-alamaridine (*vide infra*) does not undergo a similar facile oxidation.

The treatment of 225 with sodium borohydride in ethanol afforded, as expected, the same ratio of products as that obtained in the reduction of 222.

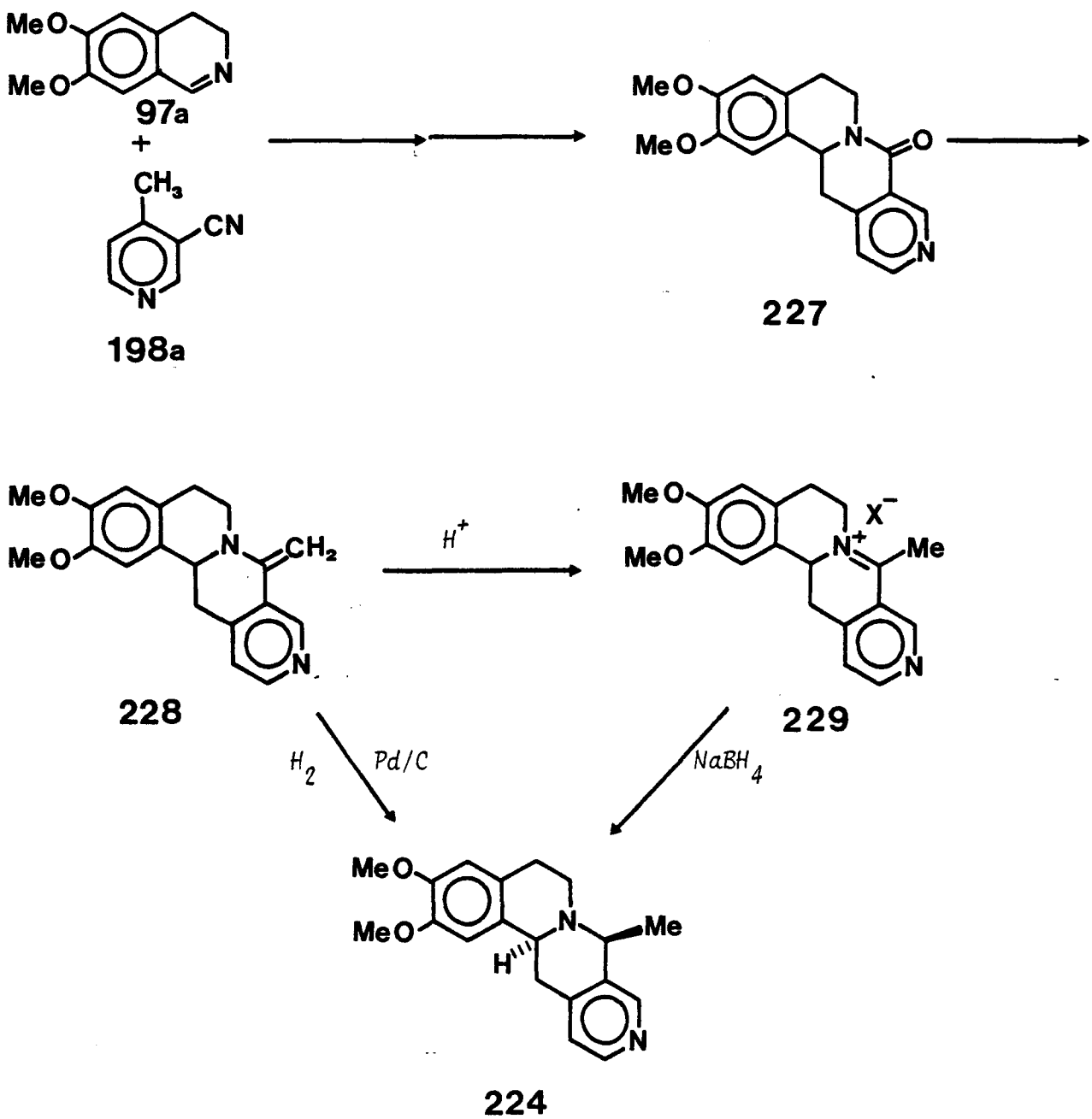
The synthesis of (±)-alamaridine was now undertaken. The *O*-benzyllactam 212c was converted without isolation of intermediates into a mixture of 133 and 134 in a ratio of 1:3 (Scheme 66). Only the 8-β-isomer 134 was isolated in pure form. The mixture of 133 and 134, like the mixture of compounds 223 and 224 was also highly susceptible to aerial oxidation. As a result, the separation and purification of the isomers was only partially successful. Debenzylation of the mixture of 133 and 134 was effected by hydrogenolysis, affording a separable mixture of (±)-8-epialamaridine 226 and (±)-alamaridine 126. The infrared and ^{1}H nmr spectra of (±)-alamaridine prepared in this study corresponded closely with those reported for the natural alamaridine. The infrared spectrum of 226 displayed Bohlmann bands (2820-2740 cm^{-1}) typical of a *trans* quinolizidine system but these bands were absent in the spectrum of alamaridine.


MeO
BnO
N
O
N
212c
i, MeLi
ii, NaBH4
MeO
BnO
N
Me
H
N
133
+
MeO
BnO
N
Me
H
N
134
H2
Pd/C
MeO
HO
N
Me
H
N
126
MeO
HO
N
Me
H
N
226

SCHEME 66

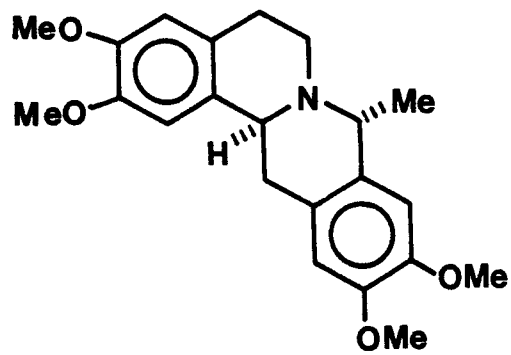
We also examined the reaction of lactam 227 with MeLi, and the subsequent treatment of the addition product with borohydride and with hydrogen to determine the isomer ratio (8α to 8β) of the reduction products (Scheme 67). Compound 227 was prepared in two steps from 3,4-dihydro-6,7-dimethoxyisoquinoline 97a and 3-cyano-4-methylpyridine 198a and its synthesis along with other related syntheses will be discussed in the subsequent section. Treatment of the lactam 227 with methyllithium afforded a product on alkaline work-up presumably 228, that was hydrogenated over 10% Pd-C catalyst. The reduction product, homogenous on tlc, was identical with the 8-β-methyl isomer 224 (^{1}H nmr). In another experiment, the crude product from the methyllithium reaction was taken up in glacial acetic acid, in which 228 would be expected to be converted into 229, and then treated with sodium cyanoborohydride. Again, only the 8-β-methyl isomer 224 was isolated, and the crude reaction product did not show any evidence of the 8-α-methyl isomer 223 by ^{1}H nmr. In the sodium cyanoborohydride reduction of 229, the iminium bond undergoing reduction is the N-C(8) double bond. In the other cases examined involving reduction of berberinium salts, and in the case of 222, the last bond to be reduced would be an iminium bond between C-14 and N. It is apparent that the reduction of the two bonds are subject to different steric constraints. The stereospecific reduction of the N-C(8) double bond has also been observed in a recently reported asymmetric synthesis of coralydine (211).

Tourwe *et al.* (216) have used ^{1}H nmr spectroscopy effectively to ascertain the conformation of dibenzo[a,g]quinolizidines. In an

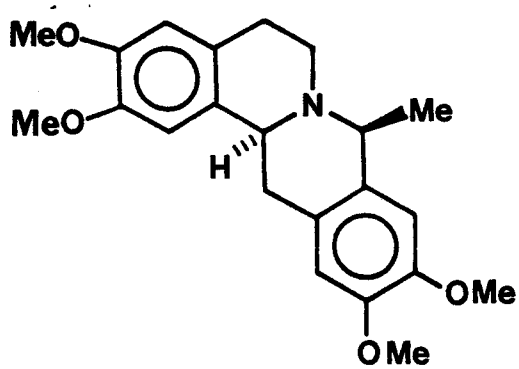


SCHEME 67

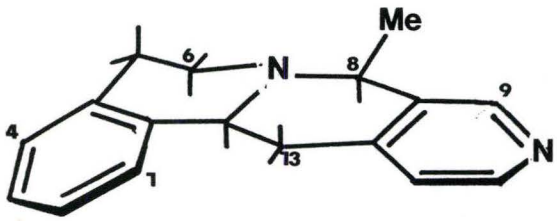
examination of the 270 MHz ^{1}H nmr spectra of coralydine 220 and *O*-methylcorytenchirine 219 they have concluded that the chemical shift of the protons, C-8 H, C-8 CH_3 and C-14 H, and the coupling constant between C-8 H and C-8 CH_3 are diagnostic of the conformation and configuration of the molecules. In the *trans*-quinolizidine, coralydine 220, the methyl group at C-8 is deshielded and the protons at C-8 and C-14 are shielded relative to the corresponding signals in *O*-methylcorytenchirine 219 which has been assigned a *cis* quinolizidine conformation, and which is a diastereomer of coralydine. Coralydine 220 has been assigned the conformation shown in structure I and *O*-methylcorytenchirine 219 has been represented by the *cis* conformational structure II (Figure 11). The coupling constant between C-8 H and C-8 CH_3 also differs in the two systems as shown in Table 4. In the same Table the relevant data for the isomeric pairs of 8-methyl compounds prepared in this investigation are collated. It is evident that there is an excellent correlation between the conformation (as ascertained by IR examination) and the ^{1}H nmr of the signals examined. The large coupling constant between C-14 H and C-13 H_{ax} ($J \simeq 11.0$ Hz) in the 8-α-methyl compounds favours the *cis* structure II (in which C-14 H is axial in ring C and has a *trans* relationship with C-13 H_{ax}) over the *cis* conformational structure III (in which C-14 H is equatorial in ring C and where the dihedral angle to C-13 hydrogens is ca. 55°. It may be inferred therefore that the conclusions drawn by Tourwe *et al.* (216) regarding the use of ^{1}H nmr spectroscopy is assigning the conformation of the quinolizidine ring in 8-methylberberines substituted at C-10 and C-11 are generally valid for other berberines and



219

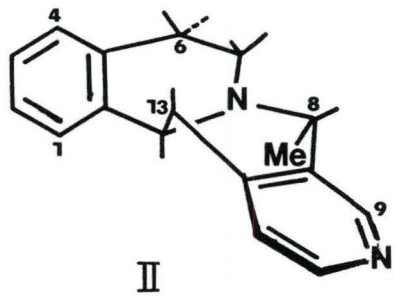


220



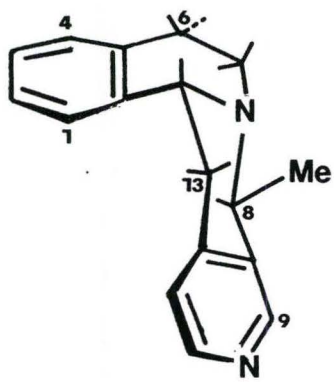
I

TRANS



II

CIS



III

CIS

Preferred Conformatios of cis- and trans- 5,6,13,14-tetrahydro--8-methylazaberberines

FIGURE 11

Table 4

Correlation Between Stereochemistry and ^{1}H nmr of 8-methylberberines and 8-methylazaberberines

8-α Compounds	Chemical Shift in ppm (δ)			Coupling Constants Hz	8-β Compounds	Chemical Shift in ppm (δ)			Coupling Constants Hz
	8β Me	8α H	14 H	$J_{8H,Me}$		8β Me	8α H	14 H	$J_{8H,Me}$
[a]Coralydine 220	1.54	3.72	3.71	6.2	[a]*O*-Methylcory-tenchirine 219	1.40	4.10	4.24	6.6
8-β-Methyl-canadine 218	1.50	3.81	3.53	6.1	8-α-Methyl-canadine 217	1.37	4.30	4.19	6.7
8-epi-*O*-Methyl-alamaridine 224	1.60	3.83	3.75	6.4	*O*-Methyl-alamaridine 223	1.42	4.23	4.27	6.9
(±)-8-epi-Alamaridine 226	1.60	3.79	3.71	6.4	(±)-Alamaridine 126	1.41	4.24	4.21	6.9

[a] Data of Tourwe' et al. (216).

apply equally well to the related systems prepared in this investigation. Therefore, the 8-β-methyl compounds prepared in this study can be represented by the *trans* structure I and the 8-α-methyl compounds by the *cis* structure II (Figure 11).

An examination of the ^{13}C nmr spectra of the 8-methylberberines and 8-methylazaberberines has revealed a correlation between the chemical shifts of selected carbon atoms and the stereochemistry. These data, collated in Table 5 show that the signals at C-8, C-8 CH_3 and C-14 are diagnostic of the stereochemistry. Signals at C-6 which have been used in assigning conformations in other protoberberines (221-224), are not appreciably different in the isomeric pairs examined in this study and the signals have not been tabulated. In the case of the 8-β- methyl compounds prepared in this thesis, signals at C-8, C-13, C-14 and C-8 CH_3 are deshielded relative to the corresponding signals in the 8-α-methyl compounds. The previously assigned (213) signals for C-8 (58.8) and C-14 (50.0) in *O*-methylcorytenchirine are probably incorrect and should be reversed in the view of our observations. The assignment of signals to C-8 and C-14 in 8-α-methylcanadine **217** and 8-β-methylcanadine **218** was made on the basis of a hetero-COSY experiment; in both compounds the protons at C-8 and C-14 were well separated in their 500 MHz ^1H nmr spectra. The assign-ment of signals to C-8 and C-14 in **219** and **220** was made prior to the development of 2D nmr techniques (213).

The mass spectra of **217** and **218** showed a fragmentation pattern (Scheme 68) characteristic of the tetrahydroprotoberberines (225-230). Both isomers had intense molecular ions (I) and M-1 ions (II) at m/z 353

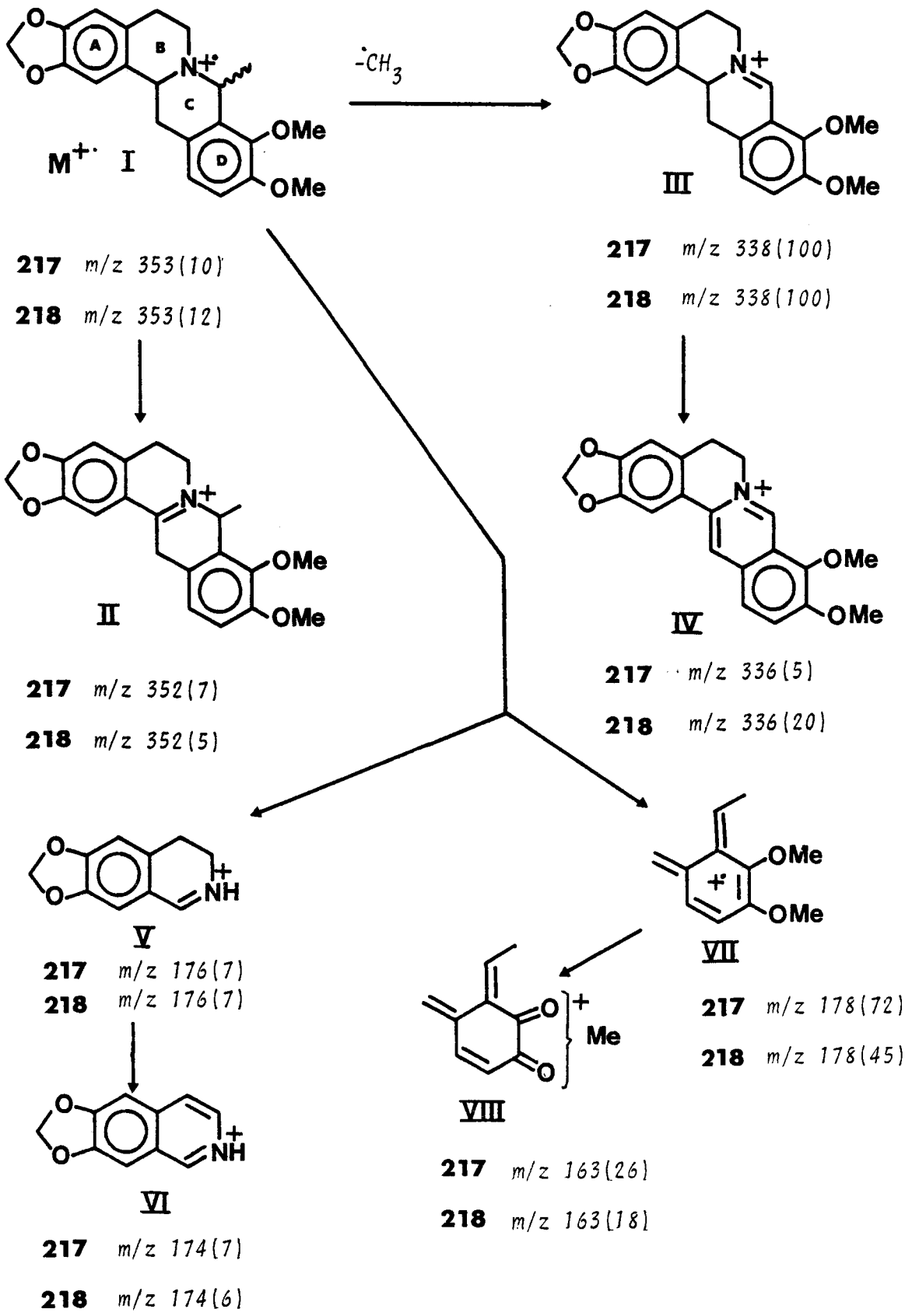
Table 5

Correlation Between Stereochemistry and ^{13}C nmr Signals of 8-Methylberberines and 8-Methylazaberberines

8-β Compounds	Chemical Shifts in ppm (δ) C-8	C-14	C-8 Me	8-α Compounds	Chemical Shifts in ppm (δ) C-8	C-14	C-8 Me
[a]Coralydine 220	58.9	58.6	21.3	[a]*O*-Methylcory-tenchirine 219	58.8	50.0	17.1
8-β-Methyl-canadine 218	57.3	59.1	23.0	[b]8-α-Methyl-canadine 217	50.7	55.6	15.9
8-epi-*O*-Methyl-alamaridine 224	57.6	58.3	21.2	8-*O*-Methyl-alamaridine 223	49.9	56.7	17.7
(±)-epi-Alamaridine 226	57.8	58.4	21.4	(±)-Alamaridine 126	49.7	57.0	17.3

[a] Data of Kametani et al. (213); the assignment of signals to C-8 and C-14 in 219 should be reversed.

[b] Assignment of signals to C-8 and C-14 in 217 and 218 was made on the basis of a hetero-COSY experiment.

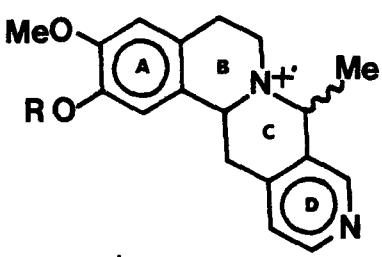

M+· I
-·CH3
III
217 m/z 353(10)
218 m/z 353(12)
217 m/z 338(100)
218 m/z 338(100)
II
IV
217 m/z 352(7)
218 m/z 352(5)
217 m/z 336(5)
218 m/z 336(20)
V
217 m/z 176(7)
218 m/z 176(7)
VII
217 m/z 178(72)
218 m/z 178(45)
VI
217 m/z 174(7)
218 m/z 174(6)
VIII
217 m/z 163(26)
218 m/z 163(18)

SCHEME 68

and 352, respectively. The base peak (III) at m/z 338 corresponds to loss of a methyl group from C-8 in both compounds and ions (IV) at m/z 336 were also present in both compounds. The other major fragmentation involves the *retro*-Diels-Alder opening of ring C. Ions V and VI arising from the isoquinoline moeity are observed in both compounds at m/z 176 and 174, respectively. The non-nitrogenous fragment ion VII at m/z 178, derived from rings C and D, which loses a methyl group forming another daughter ion (VIII) of significant intensity at m/z 163 in both cases. The mass spectra of the isomeric pairs (223 and 224; 126 and 226) of 8-methylazaberberines, prepared in this study, also exhibited a fragmentation pattern analogous to that observed in 8-methylcanadines and is represented in Scheme 69.

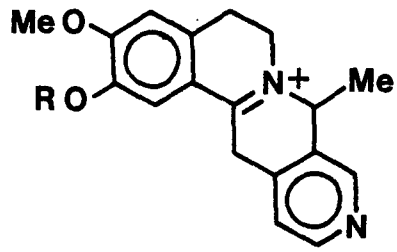
2.7 SYNTHETIC INVESTIGATIONS ON BENZOPYRIDOQUINOLIZIDINE ALKALOIDS OF *Alangium lamarckii*; A CONVERGENT SYNTHESIS OF ALANGIMARIDINE AND ALANGIMARINE

Pakrashi *et al.* (123,124) have reported the isolation (from the seeds of *Alangium lamarckii* Thw) of a number of benzopyridoquinolizidine alkaloids possessing the novel isoquino[2,1-*b*][2,7]naphthyridin-8-one ring system.[c] This group of eight alkaloids includes 118, 119, 120, 121, 122, 123, 124 and 125, all have a two carbon unit at C-12. Recently alamarine 121 has been synthesized in a non-regiospecific synthesis *via* a route involving enamide cyclization (126) as described in the previous chapter (Sect. 1.6,i). Aside from its lack of regiospecificity, the disadvantage of the reported synthesis lies in its inability to provide



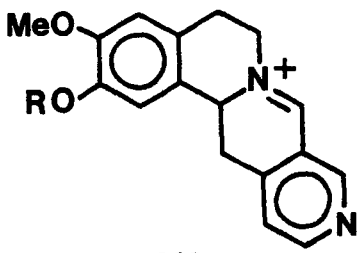
$M^{+\cdot}$ I

223 m/z 310(45)
224 m/z 310(41)
126 m/z 296(36)
226 m/z 296(33)



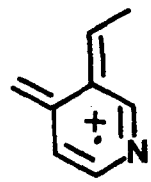
II

223 m/z 309(40)
224 m/z 309(43)
126 m/z 295(29)
226 m/z 295(36)



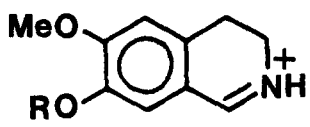
III

223 m/z 295(100)
224 m/z 295(100)
126 m/z 281(100)
226 m/z 281(100)



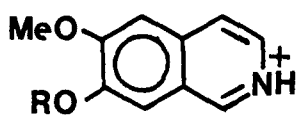
VI

223 m/z 119(10)
224 m/z 119(9)
126 m/z 119(11)
226 m/z 119(11)



IV

223 m/z 192(13)
224 m/z 192(12)
126 m/z 178(38)
226 m/z 178(18)



V

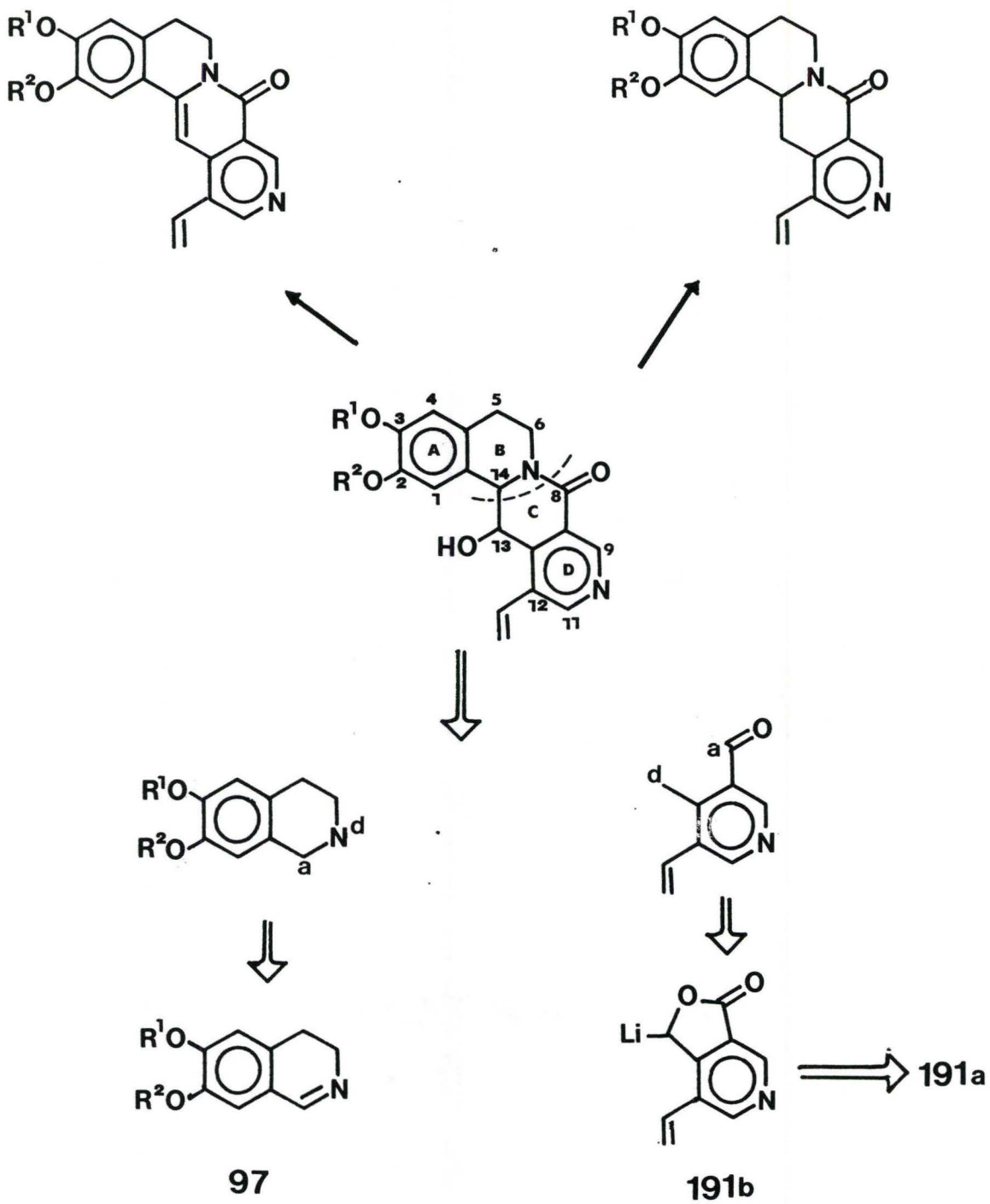
223 m/z 190(49)
224 m/z 190(39)
126 m/z 176(29)
226 m/z 176(32)

SCHEME 69

the 13,14-dihydro compounds that are present in many *Alangium* alkaloids. The 13,14-dihydro compounds are not easily accessible from the corresponding 13,14-dehydro compounds, although the reverse reaction may be achieved by simple oxidation.

The present study was undertaken to develop a convergent synthesis leading to the *Alangium* alkaloids and other related systems as shown in the *retro*-synthetic analysis (Figure 12). A synthesis involving condensation of the lithium salt of the azaphthalide **191a** and 3,4-dihydroisoquinoline **97c** was an obvious choice and was based on similar reactions described in Section 2.5. The vinyl side chain already built into the azaphthalide **191a** might be modified later to provide the side chains present in the other alkaloids. The initial products of condensation, the 13-hydroxy compounds, could be either dehydrated to give 13,14-dehydro compounds or deoxygenated to give the corresponding tetrahydro compounds. Unfortunately, the synthesis of the azaphthalide **191a** proved to be laborious and of little practical use. Therefore, the approach requiring the use of **191a** had to be abandoned, and other routes were investigated.

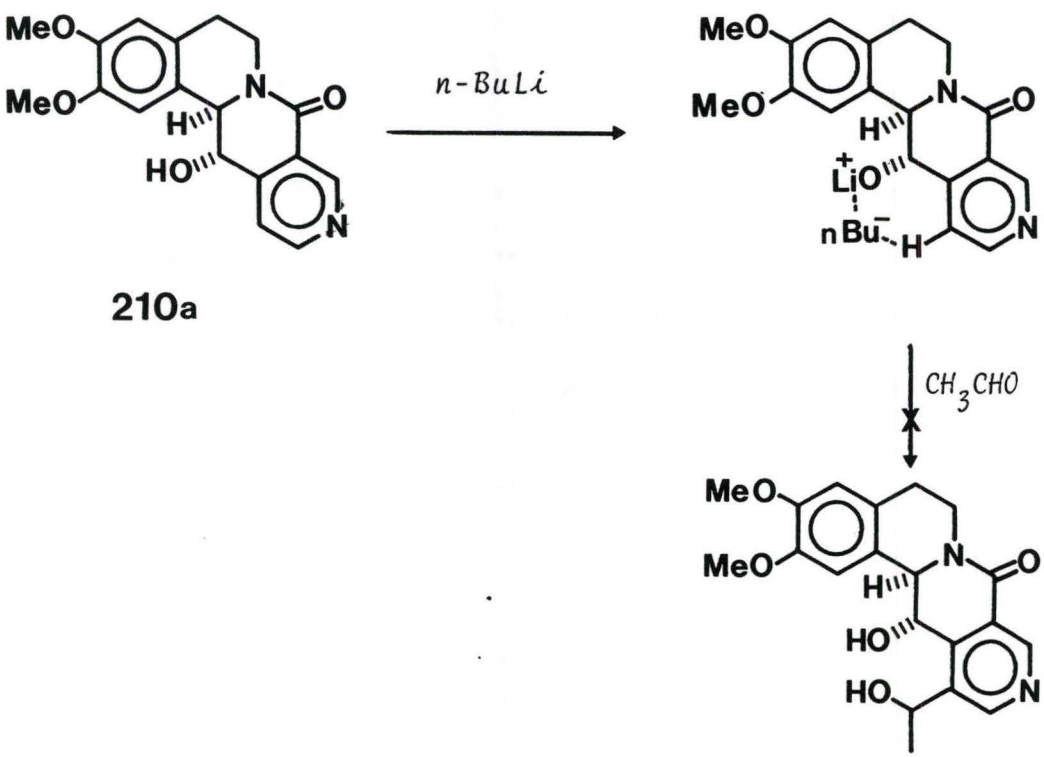
It is known that benzyl alcohols can be readily *ortho* lithiated (231,232). It was hoped that the 13-hydroxy group in compounds such as **210a** might be used similarly, as a handle for directing lithiation at the C-12 position of ring D and therefore serve as a means of introducing a two carbon side chain. Accordingly the 13-hydroxy compound **210a** was treated with 2.2 equivalents of n-butyllithium and the resulting solution was treated with an excess of freshly dried acetaldehyde (Scheme 70).



Retrosynthetic Analysis of Some Alangium Alkaloids

a: acceotor
d: Donor

FIGURE 12



210a

SCHEME 70

The resulting product was a complex mixture probably because of competing reactions and was not further investigated.

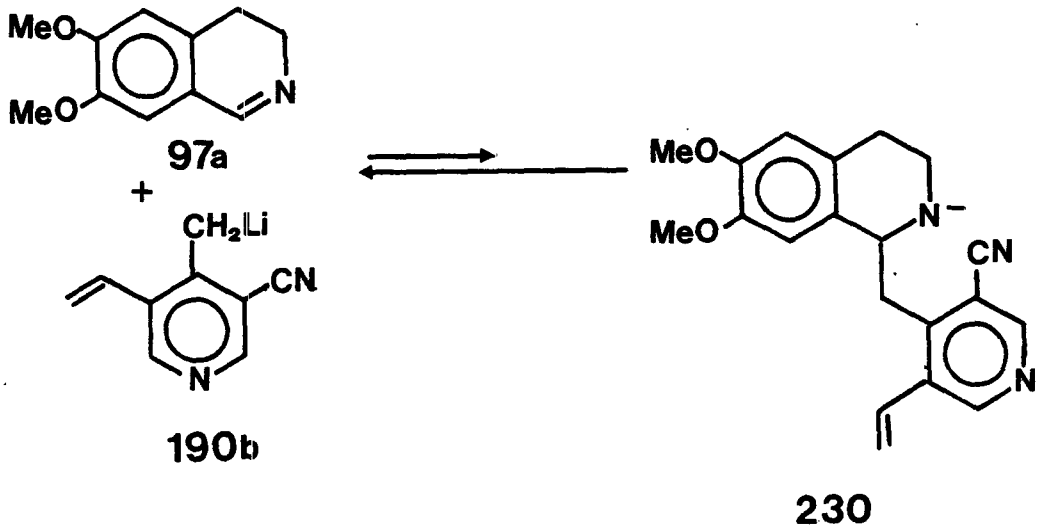
Because of the difficulties in the preparation of **191a**, the readily available 3-cyano-4-methyl-5-vinylpyridine **190a** was assessed as a starting material. In principle, compound **190a** should serve as a synthetically equivalent reagent to the azaphthalide **191a**, in which the anion generated at the methyl group would be a donor site and the 3-cyano group an acceptor site. However when the lithium salt **190b** was treated with **97a** reaction failed to occur and only starting materials were recovered. Compound **190a** was treated with either LDA or lithium hexamethyldisilazideamide (LHS) at -78°C yielding a red lithium salt solution to which 3,4-dihydroisoquinoline **97a** was added (Scheme 71). The reaction was repeated under various conditions of bath temperature and reaction time but without success.

Kametani *et al.* (165) have reported the condensation of **190a** with ethyl oxalate using sodium hydride as base in the synthesis of gentianine. However the use of NaH on our system under their conditions failed to yield the desired product.

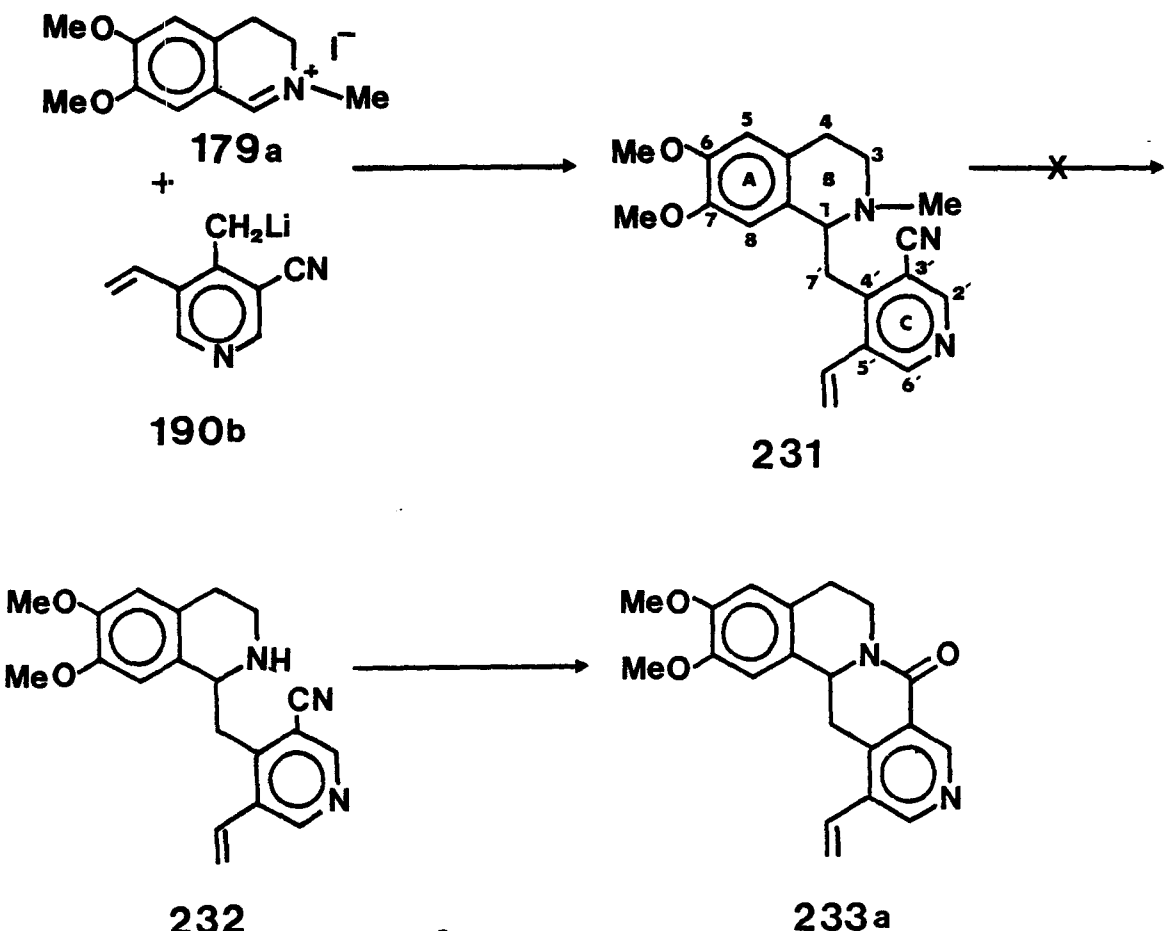
The unfavourable equilibrium (Scheme 71) may be the reason for the failure of the condensation of the lithium salt **190b** with cyclic imine **97a**. The amide anion **230** if generated would be a stronger base than **190b**. It seemed likely, therefore, that the reaction could be brought about by quaternizing the isoquinoline nitrogen or by complexing with an appropriate Lewis acid.

To test the validity of the above argument, a suspension of 2-methyl-3,4-dihydroisoquinolium iodide **179a** was treated with a solution of the lithium salt **190b** at -78°C. The anticipated addition product was obtained in excellent yield (98%) (Scheme 72). The spectral and analytical data were in agreement with the structure **231**. The infrared spectrum showed an absorption band at 2225 cm^{-1} for the nitrile function. The ^{1}H nmr spectrum had a singlet at δ 2.41 typical of an *N*-methyl group, and two aromatic singlets at δ 6.16 and 6.60 for the C-8 and C-5 hydrogens, respectively. Two aromatic singlets at δ 8.71 and 8.75 were assigned to the two hydrogens of the pyridine moeity. The ^{1}H and mass spectral data of this compound along with those of related compounds will be discussed later.

The ring system of the *Alangium* alkaloids could now in principle be obtained, first by *N*-demethylation of **231** to yield secondary amine **232**, and then by hydrolysis and intramolecular ring closure to lactam **233a** (Scheme 72). Several chloroformate reagents have been reported to effect *N*-dealkylations (233-237) and ethyl chloroformate was investigated. The *N*-methyl compound **231** in dry benzene was treated under reflux with ethylchloroformate for 2h under argon, yielding a complex mixture which was not further investigated. Kometani *et al.* (237) have reported that the order of reactivity in C-N bond cleavage in simple amines with ethyl chloroformate is: benzyl > allyl > methyl > ethyl > other alkyl groups. In protopines preferential cleavage of the N-C benzylic bonds in the presence of an *N*-methyl group has been reported (238) with ethyl chloroformate. Therefore, the cleavage of the C-1-N benzylic bond could



SCHEME 71

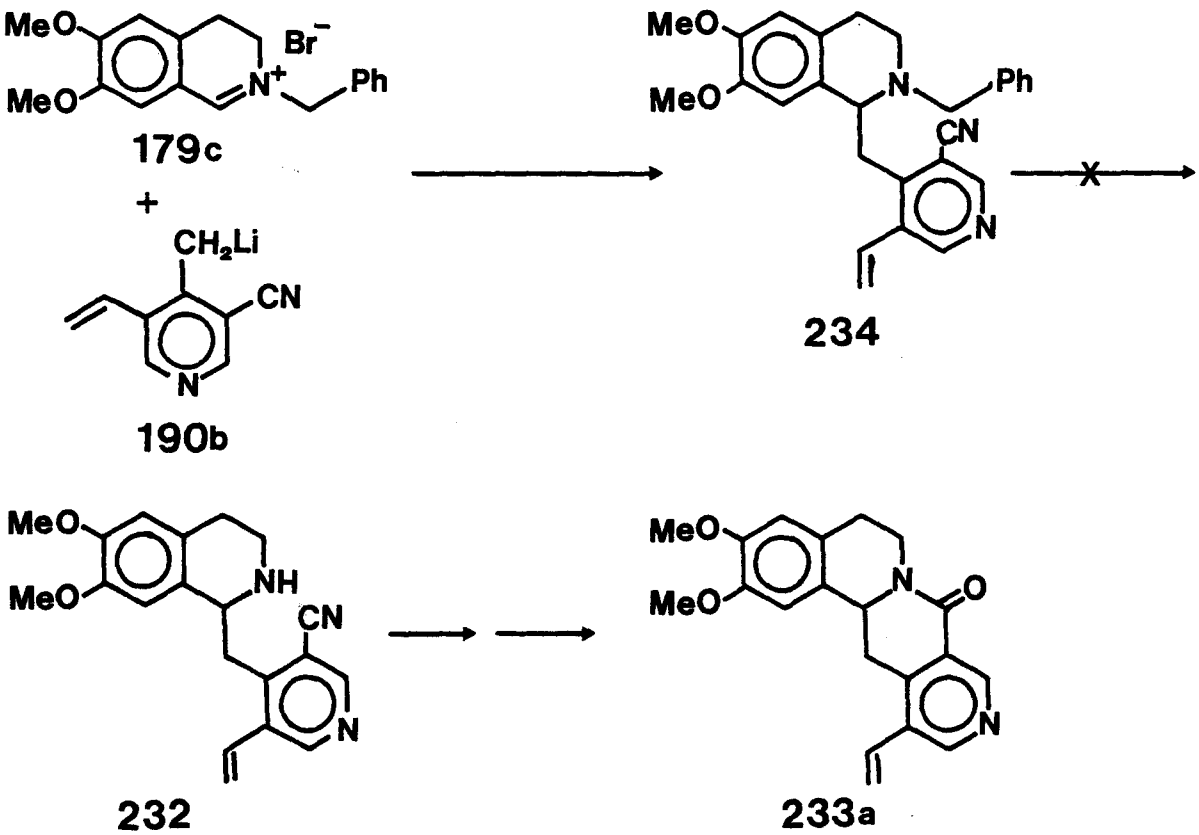


SCHEME 72

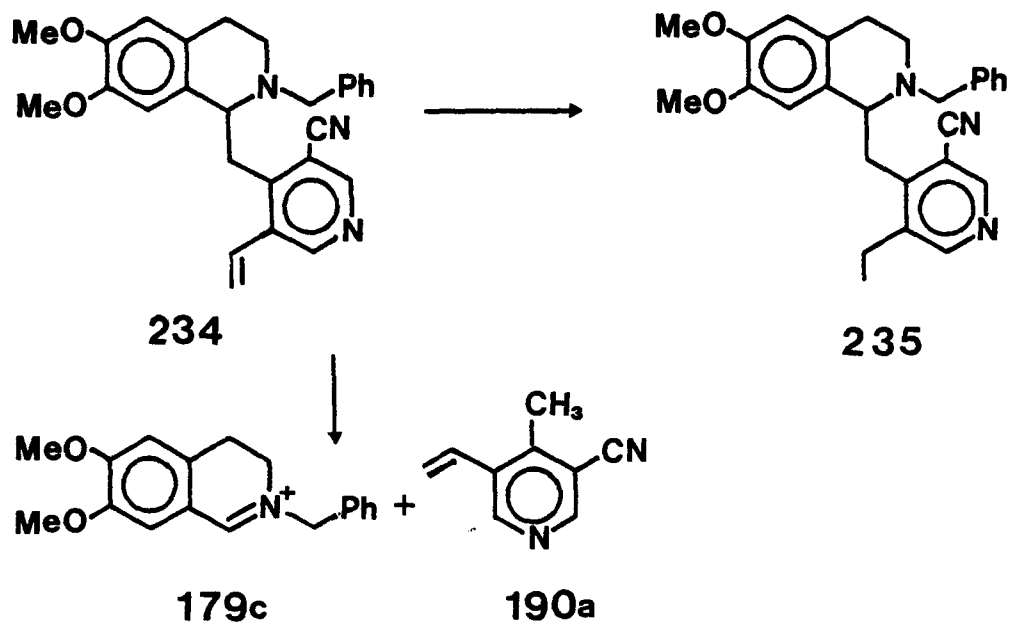
be the complicating factors in the attempted demethylation of 231.

Recently, Monkovic *et al.* (239) have reported procedures for dealkylations which they successfully applied to a number of tertiary amines. Following their procedure, the *N*-methyl compound 231 was first treated with m-chloroperbenzoic acid in dichloromethane followed by treatment with a catalytic amount of iron (II) chloride solution. Unfortunately, the reaction did not yield 232; a polar compound isolated from the reaction mixture was not further investigated.

A tertiary amine containing an *N*-benzyl group is known to lose its benzyl preferentially over other alkyl groups on treatment with ethyl chloroformate (237). Therefore, the *N*-benzyl analogue of 231, compound 234, was prepared and examined. The addition of the lithium salt 190b to a suspension of 2-benzyl-3,4-dihydroisoquinolium bromide 179c in THF, proceeded smoothly at -78°C and the desired addition product 234 was isolated as a crystalline solid in 97% yield (Scheme 73). The infrared spectrum of 234 displayed an absorption band at 2220 cm^{-1} for the nitrile function and other spectral and analytical data were also in agreement with the structure 234. The ^{1}H and mass spectral data will be discussed later collectively with other compounds of similar skeleton. When the N-benzyl compound 234 was treated with ethyl chloroformate under a variety of conditions only complex mixtures were formed. An attempted N-debenzylation by catalytic hydrogenolysis (240) of 234 over 10% Pd-C at 25°C for 30 min yielded the dihydro compound 235 quantitatively (Scheme 74). The ^{1}H nmr spectrum of 235 had no signals for vinylic hydrogens but



SCHEME 73



SCHEME 74

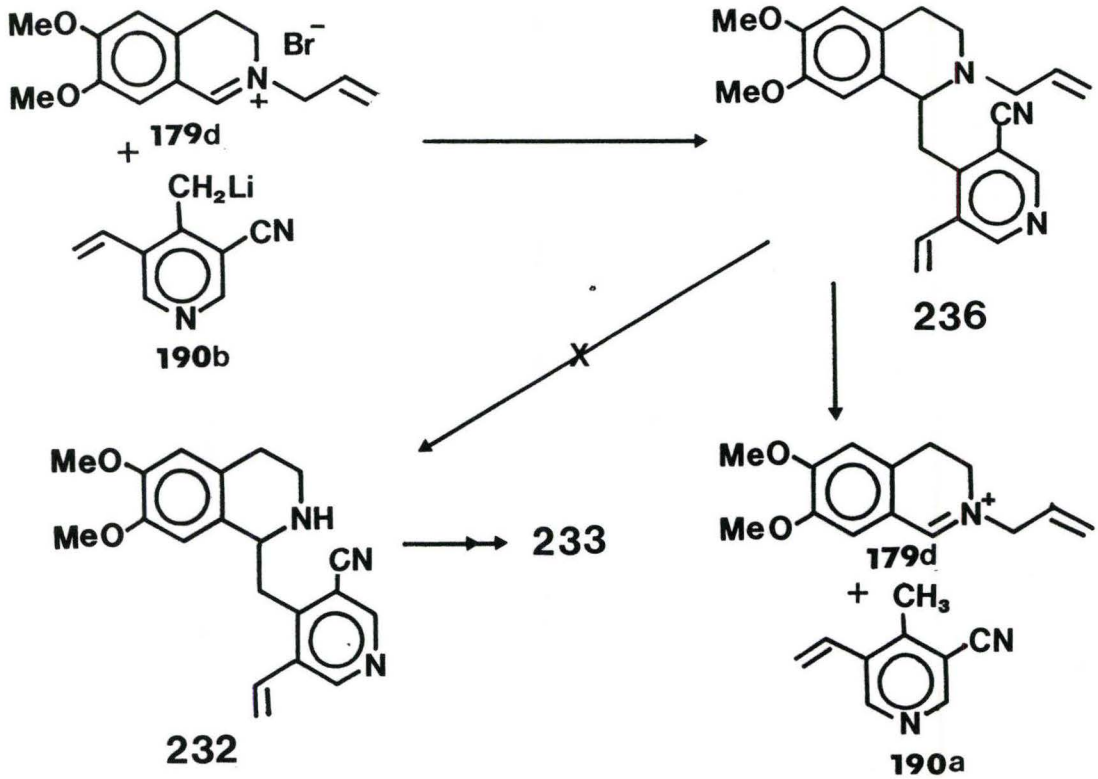
instead signals for an ethyl group and the *N*-benzyl group was not affected. In another experiment, when the treatment of **234** with hydrogen was prolonged, a complex mixture was formed. Attempted hydrogenolysis under acidic conditions also did not give satisfactory results.

El-Amin *et al.* (241) have shown that *O*- and *N*-benzyl protecting groups in peptides may be removed by "catalytic transfer hydrogenation" with formic acid. Picq *et al.* (242) have *N*-dealkylated amino sugars by a modified catalytic transfer hydrogenation using 10% Pd-C and methanesulphonic acid in ethanol. Based on these observations, an ethanolic solution of *N*-benzyl compound **234** was heated under reflux with 10% Pd-C and methanesulphonic acid for 12h. The ^{1}H nmr spectrum of the crude product showed the formation of 3-cyano-4-methyl-5-vinylpyridine **190a** and a highly polar compound with an ^{1}H nmr spectrum similar to that of 2-benzyl-3,4-dihydroisoquinolium bromide **179c** Scheme 74. The two compounds were recovered pure by column chromatography and their structures verified by comparison with authentic samples. The course of this unusual fragmentation was not further investigated.

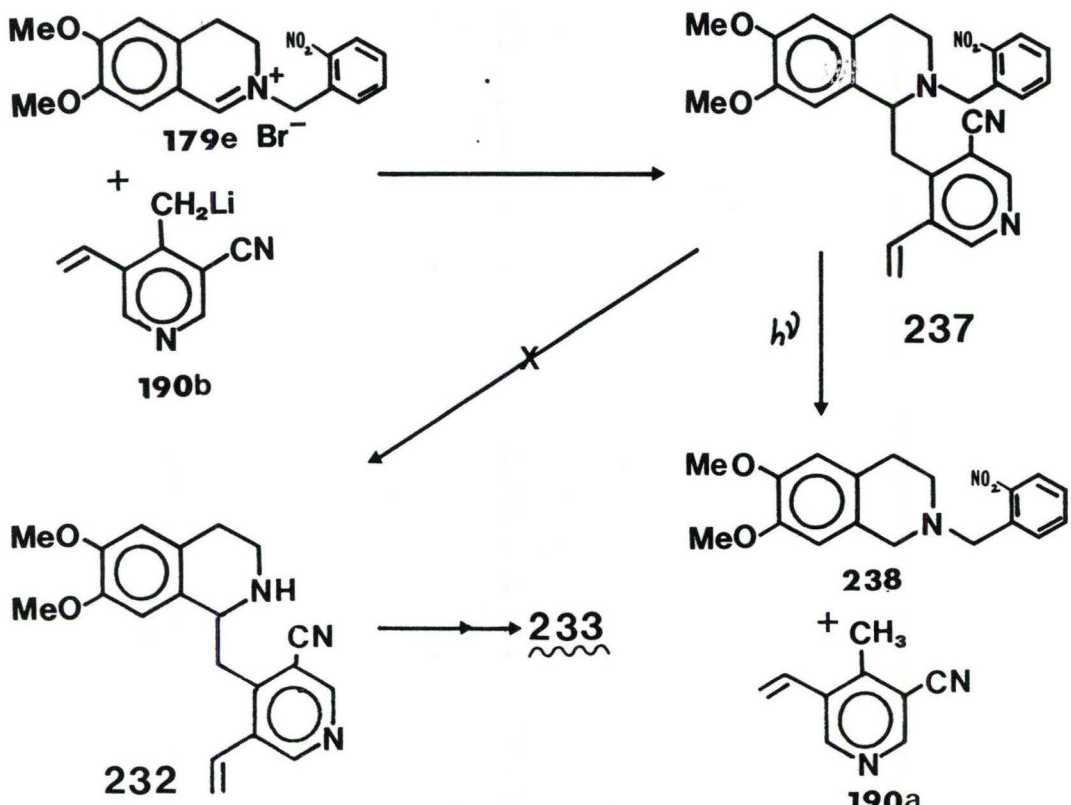
The use of allyl as a protecting group on amines has advantages over other blocking groups in certain cases. It may be removed under a variety of conditions (242-246) including metal catalysed dealkylations (242,247), and by base or metal promoted isomerization to the corresponding enamines. The enamines may then be hydrolysed (243,248) or oxidized (249) to obtain the secondary amine. Accordingly, the *N*-allyl analogue of **231**, compound **236**, was prepared in the usual manner by condensation of lithium salt **190b** with 2-allyl-3,4-dihydroisoquinolium

bromide 179d in 94% yield (Scheme 75). The spectral data (ir, ^{1}H nmr and mass) were in agreement with the structure 236. In an effort to remove the *N*-allyl group by base catalysed isomerization, compound 236 was heated under reflux with potassium tert-butoxide in dimethylsulphoxide for 1h and then acidified with 1N HCl solution. A complex mixture was formed and was not investigated further. The procedure of Picq *et al.* (242) used unsuccessfully for the *N*-benzyl compound, was also tried on 236. An ethanolic solution of 236 was heated under reflux with 10% Pd-C and a few drops of methanesulphonic acid, but only fragmentation products, 190a and a polar compound similar to 179d were formed as indicated by examination of an ^{1}H nmr spectrum of the crude product (Scheme 75). The compounds were separated by column chromatography and were identified by comparison with authentic samples.

The photolabile *o*-nitrobenzyl group and other similar groups have been successfully used as blocking groups for carboxylic acid functions in peptides, and for OH groups in carbohydrates (250-255). Kalbag and Roeska (256) have used the *o*-nitrobenzyl group for the protection of the imidazole side chain in the amino acid, histidine. It was hoped that this protecting group might be similarly used in this study. The *N*-*o*-nitrobenzyl compound 237 was prepared from the lithium salt 190b and 2-*o*-nitrobenzyl-3,4-dihydroisoquinolium bromide 179e in the manner described previously in 93% yield (Scheme 76). The structure 237 was in agreement with spectral and analytical data. To remove the *N*-*o*-nitrobenzyl group, a methanolic solution of 237 (0.5%) was subjected to photolysis with a 450 Watt medium pressure mercury lamp for 6h. The



SCHEME 75



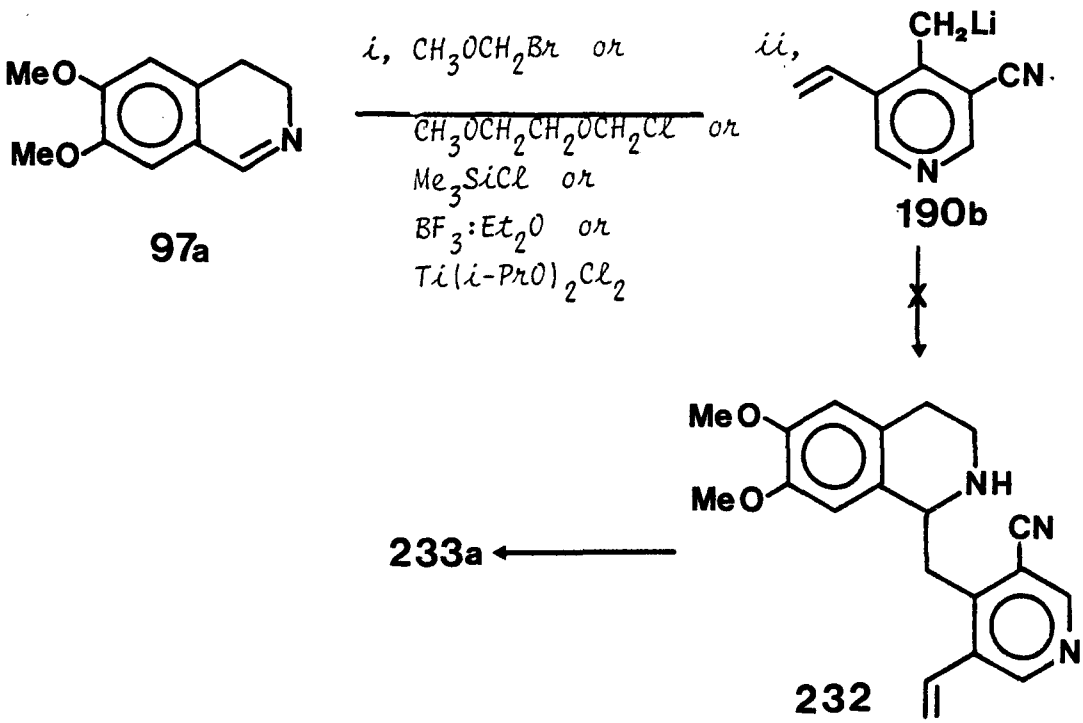
SCHEME 76

reaction mixture showed a complete disappearance of 237 and the presence of a new single spot in several tlc systems, but the ^{1}H nmr spectrum of the crude product revealed the presence of two compounds. The mixture was separated by careful removal of **190a** by sublimation and the fragmentation products 190a and 238 were identified by direct comparison with authentic samples (Scheme 76). The tetrahydroisoquinoline derivative 238, for comparison purpose was prepared by the sodium borohydride reduction of 179e. Why this unusual cleavage is preferred over the documented *N-o*-nitrobenzyl cleavage is not clear and should be investigated further.

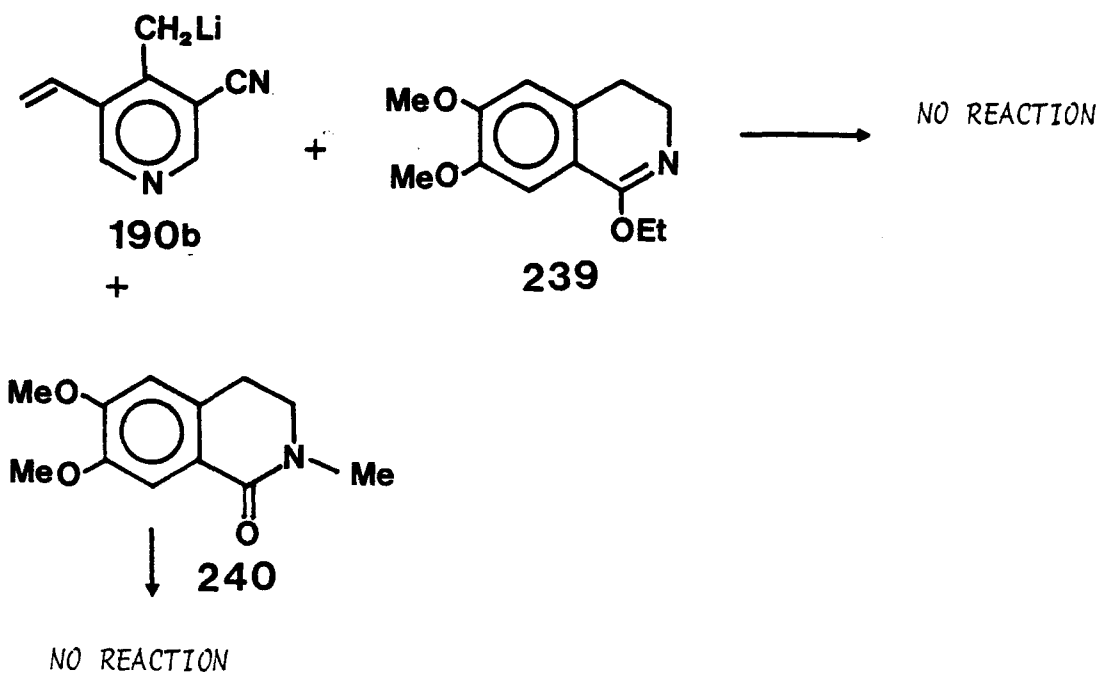
The use of methoxymethyl (MOM), methoxyethoxymethyl (MEM) and trimethylsilyl (TMS) groups as possible protecting groups for the isoquin oline nitrogen was also investigated. A cloudy suspension was formed when imine **97a** was allowed to react with methoxymethyl bromide (MOMBr) in THF for ca. 12h. However addition did not occur when a solution of the lithium salt **190b** was added to the above cloudy suspension; only starting materials, **97a** and **190a**, were recovered (Scheme 77). Similar results were obtained when methoxyethoxymethyl chloride (MEMCl) was used for the protection of imine **97a** (Scheme 77). Experiments with trimethylsilyl chloride (TMSCl) were similarly unrewarding.

The lithium salt **190b** also failed to react with lactim 239 or lactam 240 (Scheme 78).

An examination of the ^{1}H nmr spectra of the 2-alkyl-1-picolyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline derivatives 231, 234, 235,



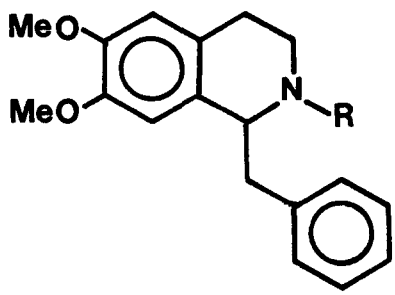
SCHEME 77



SCHEME 78

236 and 237, revealed that in some compounds the protons at C-8 and C-7 OCH_3 were shielded. These data along with relevant data on 1-benzyltetrahydroisoquinolines are collated in Table 6. Dalton and co-workers (257,258) have examined a number of 1-benzyltetrahydroisoquinolines and observed that the protons, C-8 H and C-7 OCH_3, were shielded in the *N*-methyl compound 242 and *N*-ethyl compound 243 relative to the corresponding signals in the nor-compound 241. They found that the extent of shielding was a function of the size of the *N*-alkyl group and have suggested that, for *N*-alkyl-1-benzyltetrahydroisoquinolines in their favoured conformations, ring C lies underneath ring A causing the shielding of the C-8 and C-7 OCH_3 protons (Figure 13). The ^1H nmr data of the *N*-methyl compound 231 conforms with the observations of Dalton and co-workers (257,258), while the other compounds examined in the investigation, showed either a less pronounced shielding effect on the protons, C-8 H and C-7 OCH_3, or it was absent (Table 6). The presence of substituents at C-3 and C-5 on the pyridine moiety (ring C) probably causes a conformational change in ring B as the substituents on the nitrogen atom of the isoquinoline nitrogen becomes bulkier, thus, their conformations will differ from that represented in Figure 13.

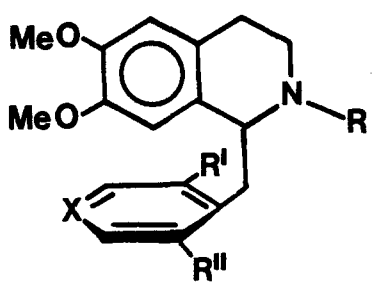
The mass spectra of the 1-picolyltetrahydroisoquinoline derivatives 231, 234, 235, 236 and 237 exhibited a fragmentation pattern analogous to that observed for 1-benzyltetrahydroisoquinolines (228). In the EI mass spectra of these compounds, molecular ions were either weak or absent. However their DCI spectra showed M+1 ions (I) of significant intensities and major fragment ions, II and III, were formed by the



241, R = H

242, R = Me

243, R = Et



X = CH, N

Preferred conformation of 1-Aryl-1,2,3,4-tetrahydroisoquinolines

FIGURE 13

Table 6

^{1}H nmr Parameters of 1-Benzyl- and 1-Picolyl-1,2,3,4-tetrahydroisoquinolines

Compound	Chemical Shifts in ppm (δ)			
	H-5	H-8	C-6 Me	C-7 OMe
241[a]	6.59	6.59	3.82	3.77
242[a]	6.56	6.26	3.81	3.65
243[a]	6.54	5.93	3.82	3.50
231	6.60	6.16	3.85	3.62
236	6.60	6.42	3.82	3.73
234	6.64	6.60	3.88	3.80
235	6.66	6.64	3.89	3.79
237	6.65	6.64	3.80	3.89

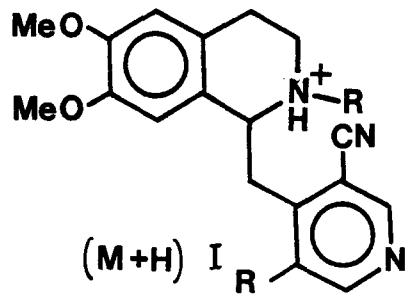
[a] Data of Dalton and co-workers (257,258).

fission of the doubly benzylic bond, C(1)-C(7'). Ions corresponding to the isoquinoline moiety were observed in the five compounds, **231**, **234**, **235**, **236** and **237**, at m/z 206, 282, 282, 232, and 327, respectively, and an ion (III), derived from ring C plus two hydrogens, is present at m/z 145 in **231**, **234**, **236**, and **237**, and at 147 in **235** (Scheme 79). Ions II appeared at the expected mass units but ions III appeared at two mass units higher than expected for reasons which were not apparent.

Our observations on the addition of picolyl anion to imines and iminium salts lead us to believe that addition is practicable only when the imine nitrogen is quaternized. However, iminium salts did not prove to be useful in this investigation because the products of addition could not be converted to the secondary amines required for cyclization. A reagent that would activate the imine by quaternization and would subsequently be readily removable, would therefore be highly desirable.

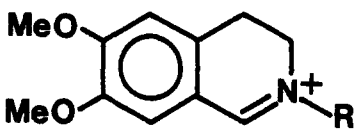
A literature search revealed that Volkmann *et al.* (259) had reported the activation of an imine with boron trifluoride (BF_3) in a reaction with the lithium salt of isothiocyanatoacetate ester in the synthesis of d-biotin. Accordingly, two Lewis acids, boron trifluoride and titanium di-isopropyloxydichloride ($Ti(OCHMe_2)_2Cl_2$), were examined as activating and readily removable agents for 3,4-dihydroisoquinoline **97a** (Scheme 77), but without success.

However trimethylsilyl trifluoromethanesulphonate (triflate) **244** proved to be an effective reagent and its use in the synthesis of several alkaloids is discussed below. Trimethylsilyl triflate (TMSOTf) has been used previously as a powerful silylating agent for a wide range of active



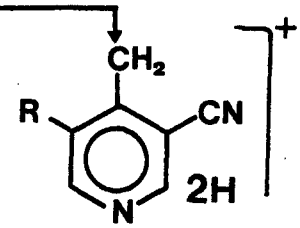
(M+H) I

231	*m/z 350(51)*
234	*m/z 426(38)*
235	*m/z 428(20)*
236	*m/z 376(38)*
237	*m/z 471(100)*



II

231	*m/z 206(100)*
234	*m/z 282(100)*
235	*m/z 282(100)*
236	*m/z 232(100)*
237	*m/z 327(88)*



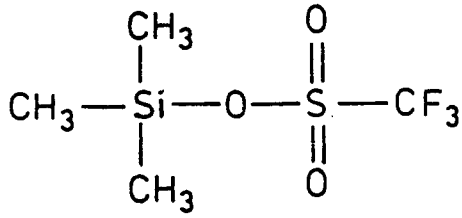
III

231	*m/z 145(19)*
234	*m/z 145(27)*
235	*m/z 147(58)*
236	*m/z 145(38)*
237	*m/z 145(49)*

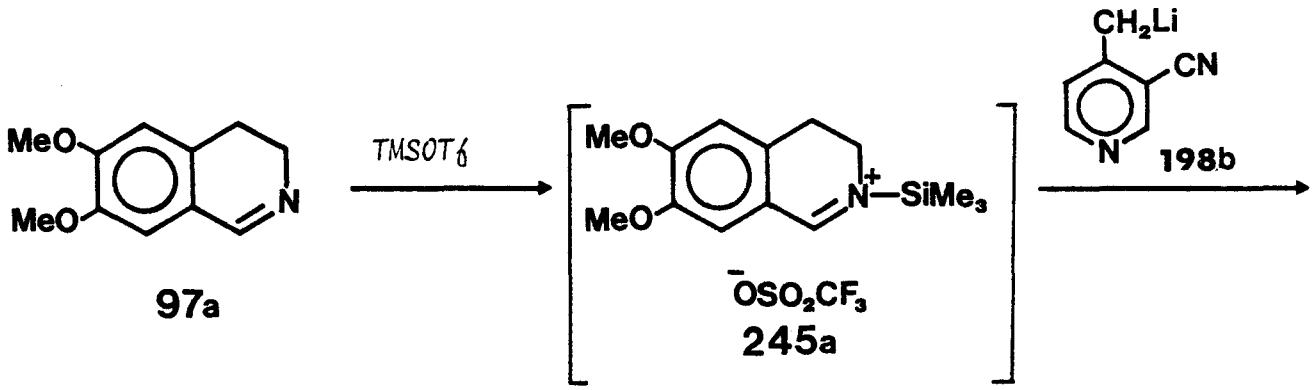
SCHEME 79

hydrogen compounds (260) and also for converting imines to the corresponding enamines (261,262) in the presence of alkylamine bases. To our knowledge its use to activate an imine toward nucleophilic reaction has not been reported.

Treatment of 3,4-dihydroisoquinoline 97a with trimethylsilyl triflate formed a complex formulated as 245a (Scheme 80). In a model study, the lithio derivative 198b of 3-cyano-4-methylpyridine 198a was treated with the complex 245a. The product of the reaction was a polar crystalline compound isolated in 97% yield. Its infrared spectrum displayed an absorption band at 1615 cm^{-1} indicative of an amidine function (>N-C=NH). The EI mass spectrum showed a molecular ion at m/z 309 of composition, $C_{18}H_{19}N_3O_2$, as determined by high resolution mass spectroscopy. The ^1H nmr spectrum showed signals for pyridine protons which resembled, in their chemical shifts, those of the synthetic 8-oxo-azaberberines 210a,b, and c. All the spectral evidence indicated that the product isolated was a tetracyclic amidine of structure 246 (Scheme 80). The mode of cyclization is probably similar to that described earlier for the reactions between Li azaphthalide 188b and imines 97a-c, except that here the isoquinoline nitrogen reacts with the suitably disposed nitrile function. The exact role of the trimethylsilyl group in this reaction, except for activating the imine, has not been clarified but the reaction reported here did not proceed in the absence of this reagent. However, it seems likely that the trimethylsilyl group resides eventually on the amidine nitrogen atom and is lost on work-up. Hydrolysis of the amidine 246 with 20% KOH solution (aq.) in dioxane



244

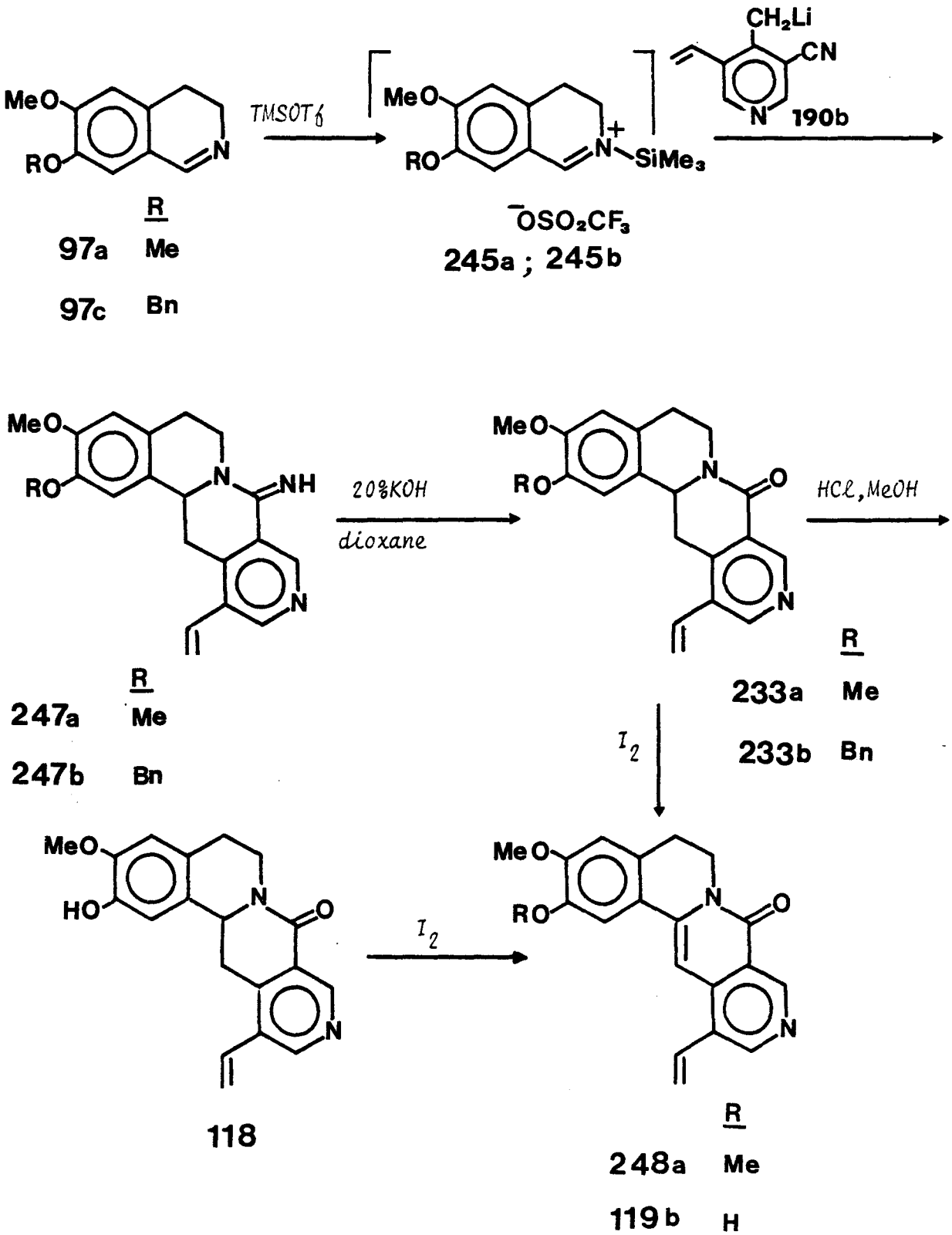


SCHEME 80

in 92% yield the expected lactam **227**, an analogue of the alkaloid alangimaridine. The infrared spectrum showed an absorption band at 1655 cm^{-1} attributed to the lactam function and the mass spectrum a base peak at m/z 310 of composition, $C_{18}H_{18}N_2O_3$. The ^1H nmr spectrum of this lactam **227** was similar to that of amidine **246**. The lactam **227** was converted in 94% yield to the previously synthesized 13,14-dehydro lactam **212a** by oxidation with iodine in refluxing methanol thereby confirming its structure.

With these results in hand the synthesis of the OMe derivative of the *Alangium* alkaloids, **233a** and **248** was undertaken (Scheme 81). The lithium salt **190b** was treated with the complex **245a** at -40°C. Amidine **247a**, highly polar in nature, was isolated as a crystalline solid in 87% yield and was characterized by spectral means. The infrared spectrum displayed an absorption band at 1610 cm^{-1} characteristic of an amidine function, and the mass spectrum showed a molecular ion at m/z 335 of composition, $C_{20}H_{21}N_3O_2$ as the base peak. The ^1H nmr and mass spectral data were in agreement with the structure **247a**. Hydrolysis of the amidine **247a** with 20% KOH solution (aq.) in dioxane afforded (±)-*O*-methylalangimaridine **233a** in 99% yield. The ^1H nmr spectrum of lactam **233a**, except for the extra methoxyl signal, closely resembled that reported for alangimaridine **118** (124). Oxidation of **233a** with iodine in refluxing methanol gave *O*-methylalangimarine **248** in 81% yield and its spectral data were consistent with the structure.

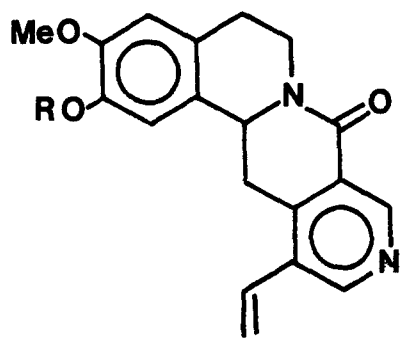
The synthesis of the *Alangium* alkaloids themselves was accomplished using imine **97c**, in which C-7 carried an *O*-benzyl group, and


MeO
RO
N
TMSOTf
SiMe3
OSO2CF3
245a ; 245b
CH2Li
CN
190b
R
97a Me
97c Bn
NH
20%KOH
dioxane
HCl, MeOH
247a Me
247b Bn
233a Me
233b Bn
I2
HO
118
248a Me
119b H

SCHEME 81

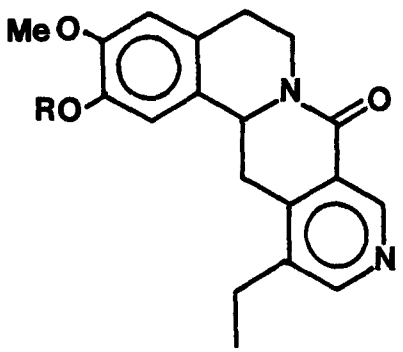
3-cyano-4-methyl-5-vinylpyridine 190a. Condensation of the lithium salt 190b with the complex 245b afforded in 98% yield amidine 247b, which was then hydrolysed to the lactam 233b in 98% yield. Debenzylation of the protected phenol in 233b was readily achieved by heating in ethanolic hydrochloric acid; racemic alangimaridine 118 was obtained in 97% yield (Scheme 81). The spectroscopic properties in solution of (±)-alangimaridine, prepared in this study, agree with those reported (124) for the natural product. The chemical shifts of the aliphatic protons in the ^{1}H nmr spectrum of 118, assigned previously (124) in analogy with the ^{1}H nmr data reported for 8-oxotetrahydroberberines (263), were reconfirmed by high field (500 MHz) 2D-^{1}H nmr (COSY) spectroscopy. Dehydrogenation of 118 with iodine in refluxing methanol afforded alangimarine 119 in 86% yield. The ^{1}H nmr and infrared spectral data of the synthetic alangimarine were in agreement with those reported (124) for the natural alkaloid. (±)-*O*-Methylalangimaridine 233a and (±)-alangimaridine 118 on catalytic hydrogenation over 10% Pd-C afforded the corresponding 12-ethyl derivatives, 249a and 249b, respectively, in almost quantitative yields. Compound 249b has been prepared previously (124) and was used for comparison.

Examination of the ^{1}H nmr spectra of lactams 227, 233a, 118, 249a, and 249b revealed that the angular proton at C-14 was deshielded and appeared below δ 4.80 in comparison to the amidines 246, 247a, and 247b in which the chemical shift was between δ 4.49 and 4.56. Both in the lactams and amidines the C-6 axial proton was the most shielded among the aliphatic protons of the ring system. The large coupling constant



	R
233a	Me
118	H

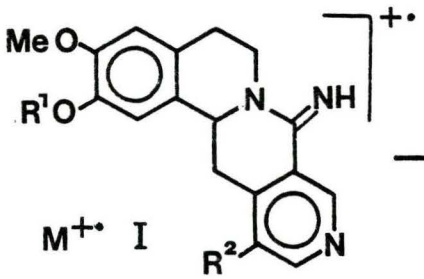
H_2, Pd/C



	R
249a	Me
249b	H

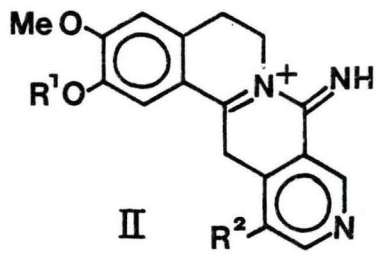
3-cyano-4-methyl-5-vinylpyridine **190a**. Condensation of the lithium salt **190b** with the complex **245b** afforded in 98% yield amidine **247b**, which was then hydrolysed to the lactam **233b** in 98% yield. Debenzylation of the protected phenol in **233b** was readily achieved by heating in ethanolic hydrochloric acid; racemic alangimaridine **118** was obtained in 97% yield (Scheme 81). The spectroscopic properties in solution of (±)-alangimaridine, prepared in this study, agree with those reported (124) for the natural product. The chemical shifts of the aliphatic protons in the ^{1}H nmr spectrum of **118**, assigned previously (124) in analogy with the ^{1}H nmr data reported for 8-oxotetrahydroberberines (263), were reconfirmed by high field (500 MHz) 2D-^{1}H nmr (COSY) spectroscopy. Dehydrogenation of **118** with iodine in refluxing methanol afforded alangimarine **119** in 86% yield. The ^{1}H nmr and infrared spectral data of the synthetic alangimarine were in agreement with those reported (124) for the natural alkaloid. (±)-*O*-Methylalangimaridine **233a** and (±)-alangimaridine **118** on catalytic hydrogenation over 10% Pd-C afforded the corresponding 12-ethyl derivatives, **249a** and **249b**, respectively, in almost quantitative yields. Compound **249b** has been prepared previously (124) and was used for comparison.

Examination of the ^{1}H nmr spectra of lactams **227**, **233a**, **118**, **249a**, and **249b** revealed that the angular proton at C-14 was deshielded and appeared below δ 4.80 in comparison to the amidines **246**, **247a**, and **247b** in which the chemical shift was between δ 4.49 and 4.56. Both in the lactams and amidines the C-6 axial proton was the most shielded among the aliphatic protons of the ring system. The large coupling constant



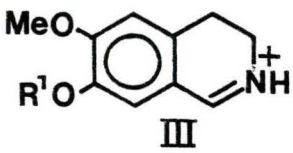
$M^{+\cdot}$ I

246 m/z 309(100)
247a m/z 335(100)
247b m/z 411(7)



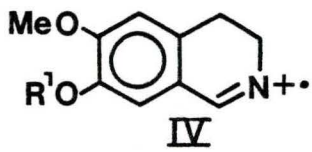
II

246 m/z 308(29)
247a m/z 334(24)
247b m/z 410(2)



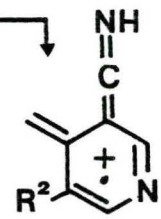
III

246 m/z 192( )
247a m/z 192( )
247b m/z 268(1), m/z 178(3)



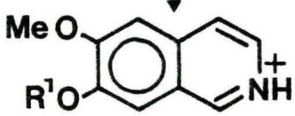
IV

246 m/z 191(17)
247a m/z 191(13)
247b m/z 177(4)



VI

246 m/z 118(35)
247a m/z 144(10)
247b m/z 144(2)



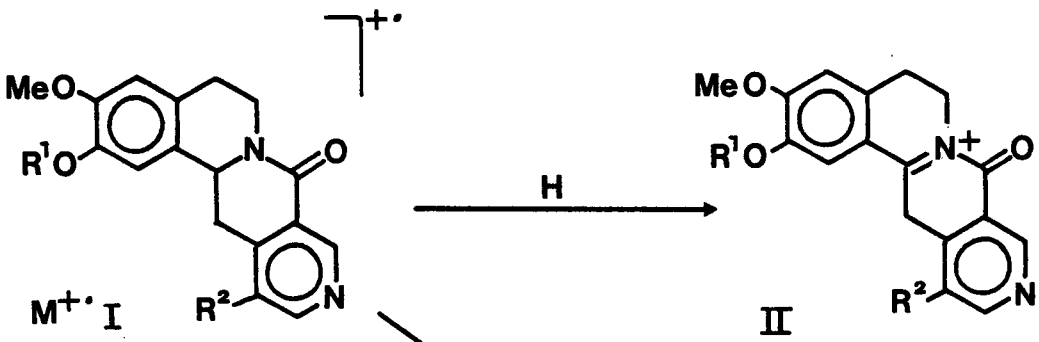
V

246 m/z 190(15)
247a m/z 190(14)
247b m/z 176(6)

VII

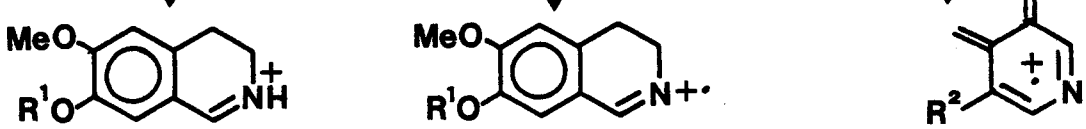
246 m/z 91(22)
247a m/z 117(13)
247b m/z 117(3)

SCHEME 82



227 m/z 310(100)
233a m/z 336(100)
233b m/z 412(33)
118 m/z 322(100)
249a m/z 338(100)
249b m/z 324(100)

227 m/z 309(66)
233a m/z 335(52)
233b m/z 411(6)
118 m/z 321(53)
249a m/z 337(76)
249b m/z 323(68)



III

227 m/z 192(9)
233a m/z 192(9)
233b m/z 178(1)
118 m/z 178(7)
249a m/z 192(3)
249b m/z 178(3)

IV

227 m/z 191(22)
233a m/z 191(14)
233b m/z 177(3)
118 m/z 177(13)
249a m/z 191(27)
249b m/z 177(11)

V

227 m/z 119(51)
233a m/z 145(19)
233b m/z 145(2)
118 m/z 145(18)
249a m/z 147(34)
249b m/z 147(23)

VI

227 m/z 91(61)
233a m/z 117(57)
233b m/z 117(7)
118 m/z 117(46)
249a m/z 119(63)
249b m/z 119(30)

SCHEME 83

for the C-14 proton ($J_{14,13ax} \simeq 13.0$ Hz) in the lactams and the amidines, clearly indicated that this proton has a diaxial relationship with the C-13 axial proton. A comparison of the chemical shift of C-9 H in the tetrahydrolactams with those in the corresponding 13,14-dehydrolactams showed that C-9 H underwent deshielding by ca. 0.3 ppm with the oxidation of C(13)-C(14) bond.

Under electron-impact conditions the molecular ions of amidines **246** and **247a** were the base peaks in their respective mass spectra, while the amidine **247b** with an *O*-benzyl group exhibited the ion at m/z 91 as the base peak. The fragmentation pattern of the amidines is shown in Scheme 82. The compounds also showed strong M-1 peaks arising by loss of the C-14 hydrogen atom. Other major ions in the spectra were the result of the *retro*-Diels-Alder opening of ring C. Ions corresponding to the isoquinoline moiety and ions derived from ring C and D were also observed in all three compounds. The latter appear at m/z 144 in **247a** and **247b** and at m/z 118 in **246** and undergo further fragmentation by losing HCN to give ions at m/z 117 in **247a** and **247b**, and at m/z 91 in **246**.

The mass spectral fragmentation of the lactams **227**, **233a**, **233b**, **118**, **249a** and **249b**, prepared in this study, is analogous to that of 8-oxytetrahydroberberines. All lactams, except **233b** with an O-benzyl group, had the molecular ions as the base peak and strong corresponding M-1 ions as shown in Scheme 83. Other important fragment ions in the mass spectra were due to the *retro*-Diels-Alder opening of ring C. Ions corresponding to the isoquinoline moiety and fragment ions derived from ring C and D were present in all five compounds. The latter fragment

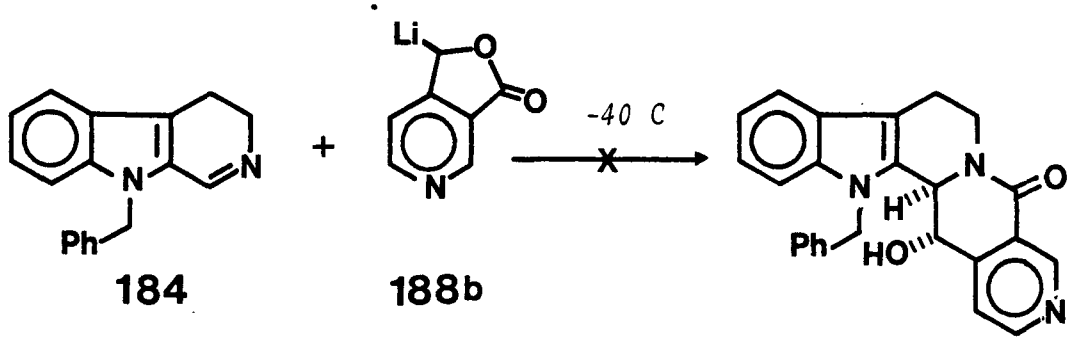
ions lose the elements of carbon monoxide to give further daughter ions. The mass spectra of the 13,14-dehydrolactams **212a**, **119**, **248** did not exhibit significant fragmentation as expected of these aromatic compounds.

2.8 INDOLOPYRIDOQUINOLIZINE ALKALOIDS: SYNTHESIS OF *N*-BENZYL DERIVATIVES OF 3,14-DIHYDRONAUCLEFINE AND 3,14-DIHYDROANGUSTINE

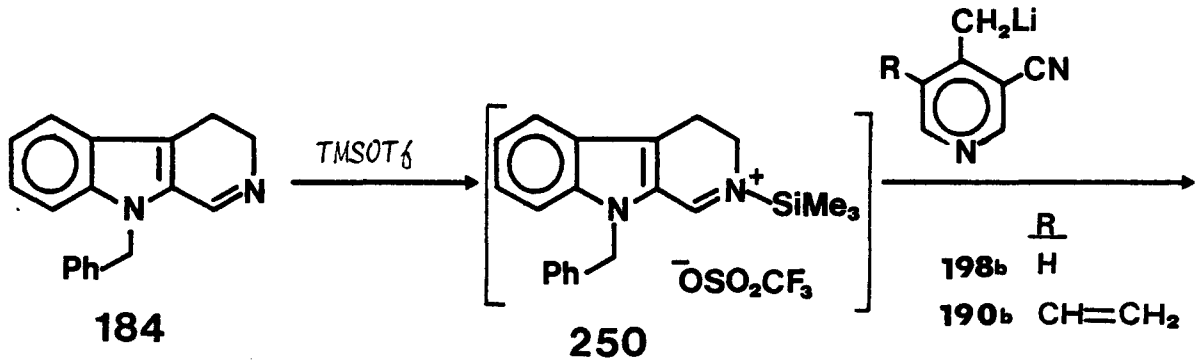
In recent years a number of indole alkaloids possessing the indolo[2',3';3,4]pyrido[1,2-*b*][2,7]naphthyridin-5[7*H*]-one ring system such as angustine **144**, nauclefine **146**, angustidine **152**, and dihydroangustine **149** (Figure 5) have been isolated. As discussed in the previous chapter (Sect. 1.6,ii), none of the reported syntheses of these indole alkaloids gave the tetrahydro compounds. In this section the synthesis of some indolopyridoquinolizines is described using a procedure analogous to that for *Alangium* alkaloids.

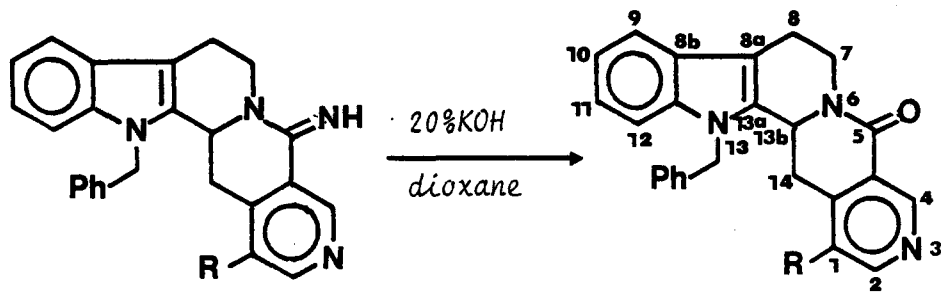
Initially the reaction between the lithium salt **188b** and 9-benzyl-3,4-dihydro-β-carboline **184** at -40°C was examined (Scheme 84) but condensation did not occur. The failure of this condensation may be attributed to the diminished electrophilic nature (because of resonance) of the imine carbon in the 3,4-dihydro-β-carboline **184** relative to that in the 3,4-dihydroisoquinolines. Magnus *et al.* (264) also encountered a similar problem when using benzyl as an *N*- protecting group; it was overcome by using an arylsulphonyl group in its place.

However the complex of TMSOTf with the imine **184**, formulated as **250**, upon treatment with the lithium salt **198b** of 3-cyano-4-methylpyridine **198a** at -40°C, afforded amidine **251a** in 89% yield. The mode of



SCHEME 84





	R
251a	H
251b	CH=CH2

	R
252a	H
252b	CH=CH2

SCHEME 85

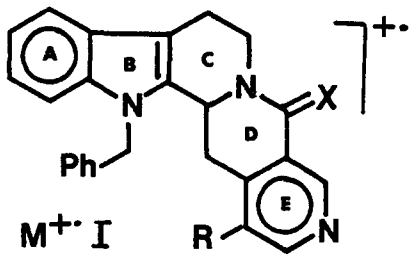
252a and **252b**, respectively. Ions VIII are derived from ions VII in the case of amidines, **251a** and **251b**, by the loss of HCN at m/z 91 of 117 respectively, and in the case of lactams, **252a** and **252b**, by the loss of CO at m/z 91 and 117, respectively. The fragmentation of these indole compounds is represented in Scheme 86.

2.9 CONCLUSION

In conclusion the present study has demonstrated new applications of imines and iminium salts in alkaloid synthesis. Condensation of azaphthalide anions with 2-methyl-3,4-dihydroisoquinolium salts has provided a direct route to a number of aza analogues of phthalideisoquinoline alkaloids and the condensation with 3,4-dihydroisoquinolines gave aza analogues of protoberberine alkaloids, a ring system found in some *Alangium* alkaloids.

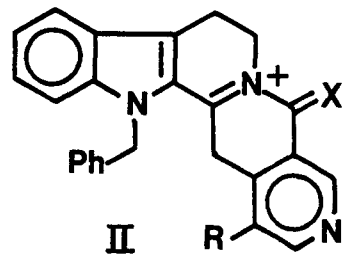
The addition of methyllithium to oxoberberine and its aza analogues has provided a convenient route to the corresponding C-8 methyl compounds. This reaction was used in the total synthesis of (±)-alamaridine.

It should be emphasized that the cyclization reaction of the resonance stabilized carbanions with imines occurred only when a suitably disposed electrophilic centre was present in the molecule containing the anionic centre. In instances where no addition took place because of the diminished reactivity of imines, activation of the imine moiety was achieved by the formation of the corresponding iminium salts. The use of trimethylsilyl trifluoromethanesulphonate as a reagent to activate imines



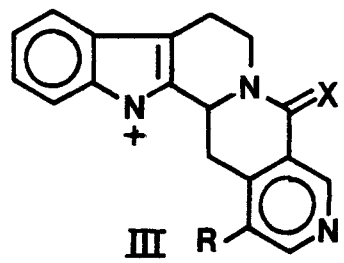
$M^{+\cdot}$ I

251a *m/z 378(57)*
251b *m/z 404(15)*
252a *m/z 379(63)*
252b *m/z 405(61)*



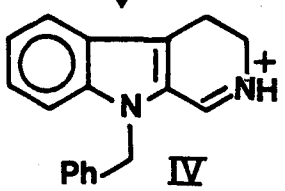
II

251a *m/z 377(25)*
251b *m/z 403(6)*
252a *m/z 378(10)*
252b *m/z 404(9)*



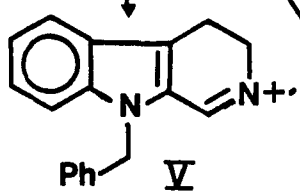
III

251a *m/z 287(100)*
251b *m/z 313(30)*
252a *m/z 288(35)*
252b *m/z 314(32)*



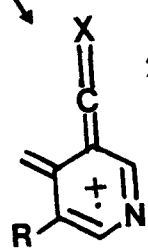
IV

251a *m/z 261(5)*
251b *m/z 261(3)*
252a *m/z 261(2)*
252b *m/z 261(4)*



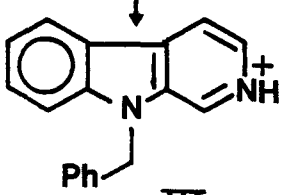
V

251a *m/z 260(7)*
251b *m/z 260(6)*
252a *m/z 260(7)*
252b *m/z 260(11)*



VII

251a *m/z 118(7)*
251b *m/z 144(5)*
252a *m/z 119(14)*
252b *m/z 145(3)*



VI

251a *m/z 259(7)*
251b *m/z 259(3)*
252a *m/z 259(13)*
252b *m/z 259(8)*

VIII

251a *m/z 91(67)*
251b *m/z 117(3)*
252a *m/z 91(100)*
252b *m/z 117(13)*

SCHEME 36

toward nucleophilic reagents has been discovered particularly useful. The usefulness of the reagent as a removable protective group for imines has been demonstrated in the synthesis of ring systems found among the isoquinoline and indole alkaloids. The generality of the reagent was also investigated by the examination of addition reactions (not reported here) of imines with carbanions that failed to react in the absence of the reagent. This method in principle should be applic-able to the synthesis of other heterocyclic systems thereby providing ready access to a number of biologically active substances.

CHAPTER 3

EXPERIMENTAL

Apparatus, Materials and Methods

The continuous wave ^{1}H nmr spectra were recorded on a Varian EM 390 spectrometer and the Fourier transform spectra on either a Bruker WP 80 (80 MHz), WM 250 (250 MHz) or WM 500 (500 MHz) spectrometer. Unless otherwise specified, the samples were dissolved in chloroform-d using tetramethylsilane (TMS) as internal standard. Chemical shifts, quoted as δ values, were measured in relation to TMS. The symbols, s, singlet, d, doublet, t, triplet, q, quartet, br, broad, and m, multiplet are used in reporting spectra. The ^{13}C spectra were recorded at 62.9 MHz on a Bruker WM 250 FT or at 125.76 MHz on a WM 500 FT spectrometer at ambient temperature.

EI mass spectra were recorded at 70 eV with a source temperature of ca 200°C either on a VG Micromass 7070 F mass spectrometer equipped with a data system comprised of a PDP 8A with VG 2000 software or a VG analytical ZAB E mass spectrometer equipped with a VG 11-250 data system. High resolution mass spectra (hrms) were recorded on either of the above instruments. CI mass spectra were recorded on a VG Micromass 7070 F mass spectrometer using NH_3 at ca. 1 Torr, as reagent gas and DCI mass spectra were recorded under similar conditions on a VG analytical ZAB E mass

spectrometer. Infrared spectra were run on a Perkin-Elmer 283 spectrometer in $CHCl_3$ solution or $CHCl_3$ film. Melting points were determined using a Gallenkamp apparatus and are uncorrected. The microanalyses were performed by the Guelph Chemical Laboratories Ltd., Guelph, Ontario.

Thin layer chromatography (tlc) was performed using Polygram Sil G/UV_{254} and Polygram Aloxn/UV_{254} plates. For flash column chromatography (266) Kieselgel 60 (230-400 mesh) was used.

All reactions involving lithiation steps were carried out in flame dried apparatus under a blanket of argon, using septa and syringes for transfer of reagents. Diisopropylamine and 1,1,1,3,3,3-hexamethyldisilazane were heated under reflux over calcium hydride and distilled onto activated molecular sieves (4A) for storage. THF was dried by distillation from Na/benzophenone under a nitrogen atmosphere just prior to use.

Preparation of 3,4-Methylenedioxyphenylethylamine (Homopiperonylamine) 177b:

(a) 3,4-Methylenedioxy-β-nitrostyrene 176a:

To a solution of piperonal 175a (15 g, 0.1 mol) in glacial acetic acid (150 mL) were added nitromethane (10.2 g, 0.17 mol) and ammonium acetate (20 g), and the mixture heated on a steam bath for 6h. The resulting dark red solution was poured onto crushed ice (350 g) and allowed to stand for 2h. The yellow precipitate was filtered, washed with water, and crystallized from ethanol as yellow needles (14.7 g, 76%), mp. 159-160°C (lit. (110) mp. 159-160°C, lit. (267,268) mp. 161°C); ^1H nmr (90 MHz), δ: 6.10 (2H, s, $-OCH_2O-$), 6.91(1H, d, J=8.0 Hz, C-5 H),

7.04(1H, d, J=2.0 Hz, C-2 H), 7.13 (1H, dd, J=8.0 Hz and 2.0 Hz, C-6 H), 7.51(1H, d, J=13.5 Hz, vinyl-H), and 7.99(1H, d, J=13.5 Hz, vinyl-H).

(b) $LiAlH_4$ Reduction of 3,4-methylenedioxy-β-nitrostyrene 176a:

A solution of 3,4-methylenedioxy-β-nitrostyrene (9.6 g, 50 mmol) in dry THF (200 mL) was added dropwise to a stirred slurry of $LiAlH_4$ (6 g, 150 mmol) in refluxing THF (300 mL) over a period of 3h; heating under reflux was continued for another 5h. The mixture was cooled in an ice bath and excess $LiAlH_4$ decomposed by careful addition of water (6 mL), 15% NaOH (6 mL), and water (18 mL), in that order. Ether (500 mL) was added and the inorganic material removed by filtration. Evaporation of the filtrate to dryness *in vacuo* gave a brown oil which was distilled under vacuum to give 177b as colourless oil (5.9 g, 72%), bp. 75--80°C/0.05 Torr, hydrochloride mp. 206-207°C (lit. (269) mp. 208-210°C); ^1H nmr (90 MHz) free base, δ: 1.15(2H, br s, exchanges with D_2O, $-NH_2$), 2.55-3.05 (4H, m, $-CH_2CH_2-$), 5.90 (2H, s, $-OCH_2O-$), and 6.50-6.80 (3H, m, aromatic H's); ms(EI), m/z(%): 165(31)$M^{+\cdot}$, 149(31), 148(64), 136(91), 135(100), 105(11), and 77(34).

Preparation of 4-Benzyloxy-3-methoxyphenylethylamine 177c:

(a) 4-Benzyloxy-3-methoxybenzaldehyde 175b:

To a mixture of 4-hydroxy-3-methoxybenzaldehyde (Vanillin) 174 (80g, 0.53 mol), K_2CO_3 (35 g, anhyd.) and DMF (300 mL) was added benzyl chloride (75 g, 0.6 mol) dropwise during 30 min at reflux temperature, and refluxing continued for a further 2h. The mixture was poured onto

ice-water, extracted with CH_2Cl_2, the CH_2Cl_2 extract washed with 0.3 N NaOH solution (aq.) and dried over K_2CO_3 (anhyd.). Evaporation of the solvent and crystallization from ethanol afforded 4-benzyloxy-3-methoxy-benzaldehyde 175b (111.1 g, 87%), mp. 63-64°C (lit. (155) mp. 60-62°C); ^1H nmr (90 MHz), δ: 3.95(3H, s, $-OCH_3$), 5.22(2H, s, $-OCH_2Ar$), 7.02(1H, d, J=9.0 Hz, aromatic H), 7.25-7.55 (7H, m, aromatic H's), and 9.90(1H, s, -CHO); ms(EI), m/z (%): 242(24)M^+, 214(3), 152(27), 151(20), 91(100), and 65(35).

(b) 4-Benzyloxy-3-methoxy-β-nitrostyrene 176b:

A mixture of 4-benzyloxy-3-methoxybenzaldehyde 175b (25 g), nitromethane (7 g), methylamine hydrochloride (1 g), and Na_2CO_3 (1 g) in EtOH (50 mL) was warmed on steam bath until a clear solution was obtrained. The reaction mixture was then left at room temperature in a stoppered flask for 5 days. The β-nitrostyrene 176b that separated as yellow needles was collected by filtration (54.3 g, 92%), mp. 128-130°C (EtOH) [lit. (154) mp. 120-121°C (acetone)]; ^1H nmr (90 MHz), δ: 3.95 (3H, s, $-OCH_3$), 5.23 (2H, s, $-OCH_2Ar$), 6.85-7.22 (2H, m, aromatic H's), 7.30-7.65 (7H, m, aromatic H's and vinyl-H), and 8.0 (1H, d, J=13.0 Hz, vinyl-H); ms(EI), m/z(%): 285(45)$M^{+\cdot}$, 242(9), 147(5), 92(88), 91(100), and 65(59).

(c) 4-Benzyloxy-3-methoxyphenylethyl amine 177c:

This compound was prepared by the procedure of Inubushi *et al* (152) using a modified Clemmensen reduction as follows. To a suspension

of zinc amalgam [from mercuric chloride (10 g) and Zn powder (100 g) in MeOH (100 mL)] in an ice-water bath, conc. HCl (140 mL) and a solution of β-nitrostyrene 176b (20 g) in THF (200 mL) were alternately added, with vigorous mechanical stirring. During the addition the temperature was kept below 20°C and maintained at this temperature for a further 30 min. The mixture was filtered, and the filtrate neutralized with solid Na_2CO_3 while vigorously stirring. The solution was concentrated to ca. 150 mL *in vacuo*, made basic with conc. NH_3 solution (aq.) and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with 2% NaOH solution (aq.) and dried over K_2CO_3 (anhyd.). Evaporation of the solvent gave the desired amine 177c as an oil (17.42 g, 97%), which crystallized from benzene-pet. ether (30-60) affording white needles; mp. 61-62°C (lit. (152,155) mp. 59-62°C); ^1H nmr (90 MHz), δ: 1.30(2H, br s, exchanges with D_2O, $-NH_2$), 2.70(2H, m, benzylic H's), 2.92(2H, m, $-NCH_2$), 3.86(3H, s, $-OCH_3$), 5.10(2H, s, $-OCH_2Ar$), 6.55-6.95(3H, m, aromatic H's), and 7.25-7.55(5H, m, aromatic H's); ms(EI), m/z(%): 257(7) $M^{+\cdot}$, 228(25), 137(48), 91(100), and 84(49).

General Methods for the Preparation of N-Formyl-β-phenylethylamines:

Method A:

A solution of the β-phenylethylamine 177 (10g) and freshly distilled ethyl formate (40 g) was stirred at room temperature for ca. 12h. Removal of EtOH and excess ethyl formate by vacuum distillation gave the formamide 178 quantitatively. Bulb to bulb distillation under vacuum gave an analytical sample.

Method B:

A mixture of β-phenylethylamine 177 (10 g) and ethyl formate (100 mL) was heated in a sealed tube at 120°C for 2h. The reaction mixture was cooled and the removal of EtOH and the excess ethyl formate *in vacuo* gave the N-formyl derivative 178 almost quantitatively, which was purified by bulb to bulb distillation.

(a) N-Formyl-3,4-dimethoxyphenylethylamine 178a:

mp. 133°C/0.1 Torr (lit. (270) bp. 208-210°C/2-3 Torr); ^{1}H nmr (90 MHz), δ: 2.75(2H, t, J=7.5 Hz, benzylic H's), 3.33-3.71(2H, m, $-NCH_2$), 3.86(6H, s, 2 x OCH_3), 6.35(1H, br, s, -NH), 6.65-6.87(3H, m, aromatic H's), and 8.15(1H, br s, -CHO); ms(EI), m/z(%): 209(15)$M^{+\cdot}$, 164(100), 151(66), 149(12), and 107(11).

(b) N-Formyl-3,4-methylenedioxyphenylethylamine 178b:

mp. 59-61°C (Et_2O-acetone) (lit. (77) mp. 60-62°C); ^{1}H nmr (90 MHz), δ: 2.70(2H, t, J=7.5 Hz, benzylic H's), 3.30-3.70(2H, m, $-NCH_2$), 5.91(2H, s, $-OCH_2O-$), 6.50-6.90(3H, m, aromatic H's), and 8.19(1H, br s, -CHO); ms(EI), m/z(%): 193(13)$M^{+\cdot}$, 148(100), 135(62), 105(6), and 77(14).

(c) 4-Benzyloxy-N-formyl-3-methoxyphenylethylamine 178c:

^{1}H nmr (90 MHz), δ: 2.67-2.90(2H, m, benzylic H's), 3.45-3.67(2H, m, $-NCH_2$), 3.90(3H, s, $-OCH_3$), 5.13(2H, s, $-OCH_2Ar$), 5.82(1H, br s, -NH), 6.68-6.95(3H, m, Aromatic H's), 7.30-7.60(5H, m,

Aromatic H's), 8.15(1H, br s, -CHO); ms(EI), m/z(%): 285(3)$M^{+\cdot}$, 240(15), 149(22), 137(10) and 91(100).

Preparation of 3,4-dihydroisoquinolines:

The appropriate formamides, N-formyl-3,4-dimethoxyphenylethyl amine **178a**, N-formyl-3,4-methylenedioxyphenylethylamine **178b** and 4-benzyloxy-N-formyl-3-methoxyphenylethylamine **178c** (25.0 g) were treated slowly and carefully at ice bath temperature with freshly distilled $POCl_3$ (60 mL) in a flask protected with a $CaCl_2$ tube. When the vigorous initial reaction subsided, the mixture was warmed to room temperature over a period of 10-20 min, then heated to 40°C for 5 min, and finally kept at room temperature for 2h. The excess $POCl_3$ was destroyed carefully by addition of the reaction mixture to crushed ice and the resulting solution made basic with conc. aqueous NH_3. The mixture was extracted with $CHCl_3$, the $CHCl_3$ extract dried (Na_2SO_4 anhyd.) and evaporated, and the residue purified by bulb to bulb distillation. The products **97a,b**, and c were obtained in 80-90% yield.

(a) 3,4-Dihydro-6,7-dimethoxyisoquinoline **97a**:

bp. 100-105°/0.5 Torr (lit. (270) bp 150-156°C/2-3 Torr); ^1H nmr (90 MHz), δ: 2.53-2.78(2H, t, J=7.5 Hz, benzylic H's), 3.60-3.80(2H, m, $-CH_2N-$), 3.90(3H, s, $-OCH_3$), 3.94(3H, s, $-OCH_3$), 6.70(1H, s, C-5 H), 6.70(1H, s, C-8 H), and 8.23(1H, br s, C-1 H); ms(EI), m/z(%): 191(100)$M^{+\cdot}$, 190(27), 176(71), 164(23), and 152(17).

(b) 3,4-Dihydro-6,7-methylenedioxyisoquinoline (norhydrastinine) 97b:

As beige solid (77) ^{1}H nmr (90 MHz), δ: 2.62(2H, t, J=7.5 Hz, benzylic H's), 3.71(2H, dt, J=7.5 and 2.0 Hz, $-CH_2N-$), 6.02(2H, s, $-OCH_2O-$), 6.70(1H, s, C-5 H), 6.87(1H, s, C-8 H), and 8.15(1H, t, J=2.0 Hz, C-1 H); ms(EI), m/z(%): 175(100)$M^{+\cdot}$, 174(73), 148(23), 147(18), 118(14), 117(22), 116(22), 89(44), and 63(37).

(c) 7-Benzyloxy-3,4-dihydro-6-methoxyisoquinoline 97c:

mp. 100-101°C (hexane) (lit. (159) mp. 101-101.5°C, lit. (271) 95-96°C); ^{1}H nmr (90 MHz), δ: 2.60(2H, t, J=8.0 Hz, benzylic H's), 3.68(2H, m, $-CH_2N-$), 3.90(3H, s, $-OCH_3$), 5.10(2H, s, $-OCH_2Ar$), 6.67(1H, s, C-5 H), 6.82(1H, s, C-8 H), 7.17-7.55(5H, m, aromatic H's), and 8.15(1H, br s, C-1 H); ms(EI), m/z(%): 267(15)$M^{+\cdot}$, 176(18), and 91(100).

Preparation of 9-benzyl-3,4-dihydro-β-carboline 184

(a) 1-Benzyl-3-indoleacetonitrile 181:

To a stirred solution of 3-indoleacetonitrile 180 (25 g, 0.16 mol) in dry benzene (300 mL) was added NaH (9.2 g, 50% suspension in oil, 1.2 equiv.) and the reaction mixture was heated under reflux for 15 min. Benzyl chloride (20 mL) was then added dropwise at room temperature with stirring, the mixture heated under reflux for 20 min, and then left at room temperature for ca. 12 h. The mixture was poured onto ice-water (200 mL), the benzene layer was separated and the aqueous phase extracted with CH_2Cl_2. The combined organic extract was combined with the afore mentioned organic layer, dried (Na_2SO_4 anhyd.), and evaporated yielding

the crude product which crystallized from EtOH, 181 (30.5 g, 78%); mp. 95-96°C (lit. (272) mp. 95-96°C). ^{1}H nmr (90 MHz), δ: 3.38 (2H, s, $-CH_2-CN$), 5.28 (2H, s, $-NCH_2-Ar$), 7.05-7.43(9H, m, aromatic H's), 7.54-7.70(1H, m, aromatic H); ms(EI), m/z(%): 246(35)$M^{+\cdot}$, 156(14), 155(19), 130(10), and 91(100).

(b) 1-Benzyltryptamine 182:

A mixture containing 1-benzyl-3-indoleacetonitrile 181 (10 g, 40.65 mmol), THF (50 mL), 10% ethanolic-ammonia (150 mL) and 5% Rh-Al_2O_3 (2 g) was treated with H_2 at 40 psi for 2 days. The catalyst was removed by filtration and the evaporation of the filtrate *in vacuo* afforded the desired 1-benzyltryptamine 182 (9.7 g, 95%), bp. 193-198°C/0.1 Torr (lit. (273) bp. 148-200°C/0.5 Torr); ^{1}H nmr (90 MHz), δ: 1.15(2H, br s, $-NH_2$ exchanges with D_2O), 2.75-3.20(4H, m, $-CH_2-CH_2-$), 5.23(2H, s, $-NCH_2Ar$), 6.96(1H, s, C-2 H), 7.03-7.50(7H, m, aromatic H's), 7.55-7.85(2H, m, aromatic H's); ms(EI), m/z(%): 250(9)$M^{+\cdot}$, 221(25), 220(42), and 91(100).

(c) 1-Benzyl-N-formyltryptamine 183 :

A mixture of 1-benzyltryptamine 182 (15 g) and ethyl formate (100 mL) was treated in a sealed tube at 120°C for 2 h. The removal of excess ethyl formate and EtOH *in vacuo* gave 1-benzyl-N-formyltryptamine 183 (16.05 g, 96%) as an oil; ^{1}H (90 MHz), δ: 2.85-3.05 (2H, m, $-\underline{CH_2}CH_2-N-$), 3.37-3.75(2H, m, $-CH_2\underline{CH_2}-N-$), 5.02(2H, s, $-NCH_2Ar$), 5.70(1H, br s, -NH), 6.95(1H, s, C-2 H), 7.0-7.30(8H, m, aromatic H's), 7.60-7.80(1H, m, aromatic H), and 8.05(1H, br s, -CHO); ms(EI), m/z(%): 278(15)$M^{+\cdot}$, 233(27), 220(71), 129(9), and 91(100).

(d) 9-Benzyl-3,4-dihydro-β-carboline 184:

This compound was prepared from 1-benzyl-N-formyltryplamine 183 (5 g) and $POCl_3$ (20 mL) under the same conditions that were used to prepare 3,4-dihydro-6,7-dimethoxyisoquinoline 97a. The product crystallized from ethanol or ethyl acetate (3.58 g, 77%); mp. 148-149°C (EtOAc), and 140-141°C (EtOH) (lit. (274) mp. 138°C (EtOH)); R_f. 0.76 (alumina, EtOAc); ^1H nmr (90 MHz), δ: 2.95(2H, t, J=8.0 Hz, C-4 H's), 3.94(2H, dt, J=8.0 and 2.0 Hz, C-3 H's), 5.42(2H, s, benzylic H's), 6.95-7.45(8H, m, aromatic H's), 7.55-7.73(1H, m, aromatic H), and 8.50(1H, m, C-1 H); ms(EI), m/z(%): 260(100)$M^{+\cdot}$, 169(36), 156(16), 142(34), 140(15), 116(21), 115(41), 91(87), and 65(26).

Preparation of iminium salts:

The iminium salts 179a, 179b, 179c, 179d and 179e were prepared from the corresponding imines and alkyl halides as described below. To a solution of an imine (5 mmol) in THF (10 mL) was added an alkyl halide (6 mmol) at room tempertaure and the mixture was stirred for ca. 12h. The precipitated iminium salt was collected by filtration, washed successively with THF and ether and dried over P_2O_5 under reduced pressure.

(a) 3,4-Dihydro-6,7-dimethoxy-2-methylisoquinolium iodide 179a:

86%, mp. 198-200°C (EtOH) (lit. (270) mp. 201-202°C).

(b) 3,4-Dihydro-2-methyl-6,7-methylenedioxyisoquinolium iodide 179b:

91%, mp. 232-235°C (lit. (275) mp. 235°C).

(c) 2-Benzyl-3,4-dihydro-6,7-dimethoxyisoquinolium bromide 179c:

94%, mp. 194-195°C (EtOH) (lit. (276) mp 192-195°C); ^{1}H nmr (90 MHz), δ: 3.20 (2H, t, J=7.5 Hz, C-4 H's), 3.80-4.13(2H, m, C-3 H's), 3.93(3H, s, $-OCH_3$), 4.0(3H, s, $-OCH_3$), 5.52(2H, s, $-NCH_2Ar$), 6.87(1H, s, C-5 H), 7.34-7.50(3H, m, aromatic H's), 7.50-7.80(3H, m, aromatic H's), and 10.45(1H, s, C-1 H); ms(EI), m/z(%): 282(21)M^+, 192(10), 164(31) and 91(100).

(d) 2-Allyl-3,4-dihydro-6,7-dimethoxyisoquinolium bromide 179d:

mp. 118-123°C. ^{1}H nmr (90 MHz), TFA, δ: 3.33(2H, t, J=8.0 Hz, C-4 H's), 3.90-4,30(2H, m, C-3 H's), 4.08(3H, s, $-OCH_3$), 4.12(3H, s, $-OCH_3$), 4.61(2H, d, J=5.7 Hz, $-\underline{CH_2}-CH=CH_2$), 5.50-6.02(3H, m, vinylic H's), 7.10(1H, s, C-5 H), 7.45(1H, s, C-8 H), 8.79(1H, s, C-1 H); ms(EI), m/z(%): 232(22)M^+, 191(14), 189(100), and 164(52).

(e) 3,4-Dihydro-6,7-dimethoxy-2-(*o*-nitrobenzyl)isoquinolium bromide 179e:

93%; mp. 200-201°C dec. (EtOH); ^{1}H nmr (90 MHz), $CDCl_3$ + CF_3COOH, δ: 3.25 (2H, t, J=6.9 Hz, C-4 H), 3.92 (3H, s, $-OCH_3$), 4.03 (3H, s, $-OCH_3$), 4.10 (3H, t, J=6.9 Hz, overlapped with $-OCH_3$ signal, C-3 H's), 5.52 (2H, s, $-CH_2Ar$), 6.90 (1H, s, C-5 H), 7.31 (1H, s, C-8 H), 7.70-8.10 (3H, complex m, aromatic H's), 8.27-8.41 (1H, m, aromatic H), 8.80 (1H, s, C-1 H); Anal. calcd. for $C_{18}H_{19}BrN_2O_4$, C 53.07, H 4.67, N 6.88%; found: C 53.45, H 5.05 and N 6.71%.

(f) Cotarnine iodide 179f:

Compound 179f was prepared from narcotine 1 by its oxidative cleavage according to Rakshit's procedure (160); mp. (cotarnine) 134°C (lit. (160) mp. 132-133°C); mp. (cotarnine iodide) 187-189°C (MeOH); ^{1}H nmr (90 MHz) TFA, δ: 3.30(2H, t, J=7.5 Hz, C-4 H's), 3.82(3H, s, $-NCH_3$), 4.03(2H, t, J=7.5 Hz, C-3 H's), 4.37(3H, s, $-OCH_3$), 6.25(2H, s, $-OCH_2O-$), 6.70(1H, s, C-5 H), and 8.90(1H, s, C-1 H); ms(EI), m/z(%): 220(19)$M^{+\cdot}$, 205(56), 148(20), 147(29), and 142(100).

Reduction of iminium salt 179e

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-(*o*-nitrobenzyl)isoquinoline 238

The iminium salt was reduced with $NaBH_4$ by a standard procedure as described below. A mixture of the iminium salt 179e (100 mg) and $NaBH_4$ (50 mg) in EtOH (3 mL) was stirred at room temperature for 30 min., the solvent evaporated and the excess $NaBH_4$ destroyed with glacial acetic acid. The mixture was treated with water (10 mL) and basified with saturated Na_2CO_3 solution (aq.). Standard extraction procedures using $CHCl_3$ gave the coresponding amine 238, (98%), mp. 138-140°C (hexane), R_f. 0.36 (silica, $CHCl_3$), ir($CHCl_3$, film), ν_{max}: 1520 cm^{-1}; ^{1}H nmr (90 MHz), δ: 2.78(4H, m, C-3 and C-4 H's), 3.60(2H, s, C-1 or C-1' H's), 3.80(3H, s, $-OCH_3$), 3.85(3H, s, $-OCH_3$), 3.97(2H, s, C-1' or C-1 H's), 6.47(1H, s, C-5 H), 6.70(1H, s, C-8 H), 7.25-8.0(4H, m, aromatic H's); ms(EI), m/z(%): 328(15)$M^{+\cdot}$, 327(22), 311(20), 293(15), 280(33), 192(45), and 164(100); Exact mass (hrms): calcd. for $C_{18}H_{20}N_2O_4$: 328.143, found: 328.146; calcd. for fragment ion $C_{18}H_{19}N_2O_3$: 311.140, found: 311.142; calcd. for fragment ion $C_{18}H_{18}NO_2$: 280.134, found: 280.130.

Preparation of azaphthalides and 3-cyano-4-methylpyridines:

(i) Preparation of azaphthalide 188a:

(a) Pyridine-3,4-dicarboxylic acid anhydride (Cinchomeronic anhydride) 186:

A solution of pyridine-3,4-dicarboxylic acid 185 (25 g) in acetic anhydride (100 mL) was heated under reflux gently in a dry atmosphere for ca. 1 h. The reaction mixture turned purple in ca. 15 min. The excess of the acetic anhydride was removed *in vacuo* and bulb to bulb distillation of the crude product under vacuum afforded cinchomeronic anhydride 186 (20.3 g, 91%). Crystallization from $CHCl_3$ afforded colourless crystals, mp. 76-78°C (lit. (277), mp. 76-77°C); ^1H nmr (90 MHz) δ: 7.96 (1H, d, J=5.5 Hz, C-5 H), 9.30 (1H, d, J=5.5 Hz, C-6 H), 9.43 (1H, s, C-2 H); ms(EI), m/z(%): 149(50) $M^{+\cdot}$; 105(100), 78(20), 77(51), and 51(10).

(b) Reduction of pyridine-3,4-dicarboxylic anhydride 186:

A suspension of $NaBH_4$ (1.9 g, 0.05 mol) in freshly distilled THF (100 mL) and dry DMF (10 mL) was heated under reflux in a 2-necked, flame-dried, round bottom flask under an argon atmosphere for 20 min. The reaction mixture was then cooled to 0°C in an ice bath and finely powdered pyridine-3,4-dicarboxylic anhydride 186 (7.48 g, 0.05 mol) was added in one portion. The mixture, which turned faintly pink, was stirred for 1h at 0°C, the ice bath was removed, and stirring continued for a further 3h. Excess $NaBH_4$ was destroyed by careful addition of a few drops of conc. aqueous HCl at 0°C. The solvent was then evaporated,

the residue taken up in 30 mL 10M HCl (aq) and the mixture heated under reflux for 1h. The solution was then cooled and carefully neutralized to pH 8-9 with solid K_2CO_3. The neutral solution was extracted with $CHCl_3$, the extract washed with brine, then dried over Na_2SO_4 (anhyd.). The residue obtained on evaporation of the dried $CHCl_3$ extract was a mixture of azaphthalides 188a and 189 in a ratio of ca. 4:1 as determined by ^1H nmr. The crude yields in a number of reactions ranged from 40-50%. The azaphthalides 188a and 189 were purified by fractional sublimation and by fractional crystallization from chloroform-ether.

(i) Furo[3,4-c]pyridin-3[1*H*]-one 188a: mp. 142-143°C (lit. (162) mp. 130-135°C; lit. (278) mp. 145°C); ^1H nmr (90 MHz), δ: 5.40 (2H, s, C-1 H's), 7.55 (1H, d, J=5.5 Hz, C-7 H), 8.95 (1H, d, J=5.5 Hz, C-6 H), and 9.30 (1H, s, C-4 H); ms (EI), m/z (%): 135(100) $M^{+\cdot}$, 106(65), 78(48), and 51(24).

(ii) Furo[3,4-c]pyridine-1[3*H*]-one 189: mp. 116-118°C (lit. (162,278) mp. 118°C); ^1H nmr (90 MHz), δ: 5.45 (2H, s, C-3 H's), 7.85 (1H, d, J=5.5 Hz, C-7 H), 8.87 (1H, d, J=5.5 Hz, C-6 H), and 9.00 (1H, s, C-4 H); ms (EI), m/z (%): 135 (85) $M^{+\cdot}$, 106(100), 78(39), and 51(21).

(ii) Preparation of 3-cyano-4-methyl-5-vinylpyridine 190a:

(a) 3-Cyano-2,6-dihydroxy-5-(2'-hydroxyethyl)-4-methylpyridine 190a:

Compound 193 was prepared by the following methods:

Method A:

To a mixture of acetyl 2-butyrolactone 192 (65 g, 0.5 mol), and ethyl cyanoacetate (56.5 g, 0.5 mol), conc. NH_3 solution (150 mL, aq.)

was gradually added with shaking yielding a voluminous white mixture that dissolved on continued shaking. The mixture was kept at room temperature for 5 days, and the ammonium salt that separated was collected by filtration, washed with EtOH and dried over P_2O_5 under vacuum, mp. darkens at 250°C and decomposes at 280-290°C (lit. (167) mp darkens at 250°C and decomposes at 290°C). The ammonium salt was converted to free base **193** as described in the following method.

Method B:

A mixture of 2-cyanoacetamide (42 g, 0.5 mol), acetylbutyrolactone **192** (64 g, 0.5 mol) and conc. NH_3 solution (170 mL, aq.) was shaken until all the initially formed solid had dissolved. The mixture was left at room temperature for 5 days. The ammonium salt that precipitated was collected by filtration, washed with absolute ethanol and dried; yield (78.3 g, 74%).

The ammonium salt of **193** (50 g) was dissolved in hot water (500 mL) and the solution was cooled and made acidic to "congo red" with 3N HCl solution (aq.). The crystalline precipitate that separated was collected by filtration and washed with a small amount of cold water to afford the free base **193**, mp. darkens at 208°C and decomposes at 315-316° (lit. (167) mp darkens at 200°C and effervesces at 315°C); ms(EI), m/z(%): 194(1)$M^{+\cdot}$, 176(100), 175(64), 163(9), and 147(10).

(b) 2,6-Dichloro-5-(2'-chloroethyl)-3-cyano-4-methylpyridine **194**:

The ammonium salt of **193** (40 g, 0.19 mol) was added to cold $POCl_3$

(100 mL) and the reaction mixture was heated in a glass-lined autoclave at 200-210°C for 4 h. The excess $POCl_3$ was destroyed by cautious addition of the reaction mixture to crushed-ice. The resulting mixture was basified to pH 8-9 with conc. NH_3 solution (aq.) and extracted with Et_2O, the ether extract was washed with water and dried over Na_2SO_4 (anhyd.). Removal of the solvent *in vacuo* afforded 194 (45.98 g, 95%) as an oil which solidified on standing. Trituration with hexane gave white needle-like crystals, mp. 59-60°C; ^1H nmr (90 MHz), δ: 2.70(3H, s, C-4 CH_3), 3.30(2H, t, J=7.0 Hz, C-1' H's), and 3.78(2H, t, J=7.0 Hz, C-2' H's); ms(EI), m/z(%): 252(5)$(M+4)^{+\cdot}$, 250(16)$(M+2)^{+\cdot}$, 248(17)$M^{+\cdot}$, 203(10), 201(59), and 199(100).

(c) 5-(2'-Chloroethyl)-3-cyano-4-methylpyridine 195:

A solution of 2,6-dichloro-5-(2'-chloroethyl)-3-cyano-4- methyl-pyridine 194 (48 g, 0.194 mol) in MeOH (150 mL) containing NaOAc (anhyd. 41 g) and 10% Pd-C (9.5 g) was treated with H_2 at room temperature until no more H_2 had been absorbed. The catalyst was removed by filtration through Celite and the filtrate evaporated *in vacuo* to an oil. The oily residue was treated with water (100 mL) and saturated Na_2CO_3 solution (100 mL aq.), and then thoroughly extracted with $CHCl_3$. The combined $CHCl_3$ extracts were decolourized with charcoal, dried over Na_2SO_4 (anhyd.) and evaporated *in vacuo* to an oil. Bulb to bulb distillation at 100°/0.08 Torr afforded 195 (33.97 g, 97%) which solidified on standing (lit. (166) bp. 144-145°C/3 Torr); R_f. 0.47 [alumina; pet. ether-ether, (1:1)]; ^1H nmr (90 MHz), δ: 2.55(3H, s, C-4 CH_3), 3.17(2H, t, J=7.0 Hz,

C-1' H's), 3.75(2H, t, J=7.0 Hz, C-2' H's), 8.62 and 8.77 (each 1H, s's, C-2 and C-6 H's); ms(EI), m/z(%): 182(9)$(M+2)^{+\cdot}$, 180(23)$M^{+\cdot}$, 131(100), 164(15), and 77(19).

(d) 3-Cyano-4-methyl-5-vinylpyridine 190a:

A mixture of compound 195 (29 g) and KOH (10 g) in EtOH (100 mL) was stirred at room temperaure for ca. 12h and the reaction progress was monitored by tlc. When reaction was complete the mixture was first heated with water (50 mL) and then concentrated to ca. 50 mL *in vacuo*, and thoroughly extracted with CH_2Cl_2. The CH_2Cl_2 extract was decolourized with charcoal, and dried over Na_2SO_4 (anhyd.). Removal of the solvent *in vacuo* followed by bulb to bulb distillation at 65°C/0.1 Torr afforded 3-cyano-4-methyl-5-vinylpyridine 190a (22.3 g, 97%), which solidified on standing (lit. (166) bp. 135-145°C/10 Torr); ^1H nmr (90 MHz), δ: 2.55(3H, s, C-4 CH_3), 5.50(1H, d, J=11.0 Hz, -CH=$\underline{CH_2}$), 5.74(1H, d, J=18.0 Hz, -CH=$\underline{CH_2}$), 6.85(1H, dd, J=18.0 and 11.0 Hz, -$\underline{CH}$=CH_2), 8.70 and 8.80 (each 1H, s's, C-2 and C-6 H's); ms(EI), m/z(%): 144(100)$M^{+\cdot}$, 143(89), 142(11), 129(15), 117(11), 116(24), 90(14), 89(15), 64(10), and 63(16).

(iii) Preparation of 3-cyano-4-methylpyridine 198a

(a) 3-Cyano-2,6-dihydroxy-4-methylpyridine 196:

Compound 196 was prepared from 2-cyanoacetamide (84 g, 1 mol), ethyl acetoacetate (126.4 mL, 1 mol), and piperidine (100 mL, 1 mol) in MeOH (320 mL) according to Bobbitt and Scola's procedure (169), yield (138.2 g, 92%), piperidinium salt of 196 mp. 228-235° dec. (lit. (169) mp. 229-235°C; free base 196 mp. 316-319°C (lit. (169) mp. 315-320°C).

(b) 2,6-Dichloro-3-cyano-4-methylpyridine 197:

Compound 197 was prepared from 3-cyano-2,6-dihydroxy-4-methylpyridine 196 (50 g, 0.33 mol) and freshly distilled $POCl_3$ (120 mL, 1.3 mol) according to Bobbitt and Scala's procedure (169); yield (56.1 g, 91%); mp. 108-110°C (EtOH), (lit. (169) mp. 109-110°C); ^1H nmr (90 MHz), δ: 2.58(3H, s, C-4 CH_3), 7.33(1H, s, C-5 H); ms(EI), m/z(%): 190(10)$(M+4)^{+\cdot}$, 188(63)$(M+2)^{+\cdot}$, 186(100)$M^{+\cdot}$, 153(12), 152(11), 151(38), 150(25), and 115(15).

(c) 3-Cyano-4-methylpyridine 198a:

Compound 198a was prepared from 3-cyano-2,6-dichloro-4-methylpyridine 197 (40 g, 0.24 mol), NaOAc anhyd. (35 g, 0.43 mol), and $PdCl_2$ (0.75 g) in methanol (300 mL) by reductive hydrogenation using Bobitt and Scola's procedure (169), yield (21.3 g, 84%); mp. 46°C (lit. (169) mp. 45-46°C; lit (279) mp. 41-43°C); ^1H nmr (90 MHz), δ: 2.56(3H, C-4 CH_3), 7.33(1H, d, J=5.5 Hz, C-5 H), 8.70(1H, d, J=5.5 Hz, C-6 H), and 8.82(1H, s, C-2 H); ms(EI), m/z(%): 118(100)$M^{+\cdot}$, 91(28), 64(21), and 61(14).

(iv) Reaction of lithium salt of methylpyridines with dibenzoyl peroxide (DBP):

(a) 1,2-Bis(3'-cyano-5'-vinyl-4'-pyridyl)ethane 199:

To a stirred solution of diisopropylamine (0.31 mL, 2.2 mmol) in dry THF (2 mL) at -20°C was added a solution of n-BuLi (1.37 mL, 1.6 M in hexane, 2.2 mmol) and the resulting LDA solution was stirred at this

temperture for a further 10 min. The LDA solution was cooled to -78°C (Dry Ice-acetone bath) and treated dropwise with a solution of compound **190a** (288 mg, 2 mmol) in dry THF (3 mL), producing a red solution. After stirring the mixture at -78°C for 20 min, it was treated dropwise with a solution of dibenzoyl peroxide (484 mg, 2 mmol) in dry THF (3 mL). The red colour of the solution was completely discharged at the end of the addition, and stirring of the mixture was continued at -78°C for a further 2h, and it was then allowed to warm to room temperature and stirred over night. The reaction mixture was then treated with 10% sodium sulphite solution (aq. 1 mL) and concentrated to a thick paste *in vacuo*. The residue was basified with saturated Na_2CO_3 solution (aq.) and thoroughly extracted with chloroform. The combined chloroform extracts were washed with brine, dried over Na_2SO_4 anhyd. and evaporated to dryness *in vacuo*. The crude product obtained, was purified by column chromatography on silica gel and eluting with hexane-CH_2Cl_2, gave the dimeric compound **199** (220 mg, 77%) which was crystallized from acetone; mp 189-191°C; R_f. 0.33 (alumina, $CHCl_3$); ^1H nmr (90 MHz), δ: 3.22 (4H, s, $-CH_2CH_2-$), 5.60 (1H, d, J=11.5 Hz, $-CH=\underline{CH_2}$), 5.80 (1H, d, J=18.0 Hz, $-CH=\underline{CH_2}$), 7.05 (1H, dd, J=18.0 and 11.5 Hz, $-\underline{CH}=CH_2$), 8.80 (1H, s, C-6' or C-2' H), and 8.90 (1H, s, C-2' or C-6' H); ms (EI), m/z (%): 286 (81)$M^{+\cdot}$, 285 (76), 272 (22), 271 (100), 258 (14), 253 (13), 149 (16), 143 (46), 142 (38) and 116 (18); Exact mass (hrms), calcd. for fragment ions $C_{17}H_{11}N_4$: 271.098; found: 271.098; Anal. calc. for $C_{18}H_{14}N_4$: C 75.52, H 4.90, N 19.58%; found: C 75.10, H 5.24, N 19.63%.

(b) 1,2-Bis(4'-pyridyl)ethane 200:

An LDA solution (4.4 mmol), prepared as described above, was treated with a solution of 4-methylpyridine (0.39 mL, 4 mmol) in dry THF (2 mL) at -78°C. The resulting yellowish solution was stirred at -78°C for 20 min, and then treated dropwise with a solution of dibenzoyl peroxide (989 mg, 4 mmol) in dry THF (5 mL). The reaction mixture was first stirred at -78°C for 2 h then slowly raised to room temperature and stirred over night. The work up of the reaction mixture in the usual manner gave an oil which was distilled under vacuum (bp 120°C/0.1 Torr) to give a colourless oil 200 (265 mg, 72%). Crystallization from ethyl-acetate-hexane afforded needle shape crystals, mp. 109-110°C (lit. (280) mp 106-109°C); ^{1}H nmr (90 MHz), δ: 2.95 (4H, s, $-CH_2CH_2-$), 7.03-7.20 (4H, m, C-3' H's), and 8.50-8.64 (4H, m, C-2' H's); ms (EI), m/z (%): 184 (100)$M^{+\cdot}$, 92 (69), 65 (33), and 57 (14).

(c) 1,2-Bis(2-pyridyl)ethane 201:

An LDA solution, prepared as described previously, was treated dropwise with a solution of 2-methylpyridine (0.4 mL, 4 mmol) in dry THF (2 mL) at -78°C. The resulting orange coloured solution was stirred for 20 min at -78°C and then was treated with a solution of dibenzoyl peroxide (968 mg, 4 mmol) in dry THF (5 mL) in the manner described above. The work up as usual and bulb to bulb distillation gave 201 as an oil (140 mg, 38%) which was crystallized from ethyl acetate-hexane, mp 47-49° (lit (281) mp 48-49°C (EtOAc-Pet. ether).

(v) Preparation of 7-vinylfuro[3,4-*c*]pyridin-3[1*H*]-one 191a:

(a) 5-(2'-Chloroethyl)-3-cyano-4-methylpyridine-N-oxide 202.

To a solution of 5-(2'-chloroethyl)-3-cyano-4-methylpyridine 195 (4 g) in chloroform (50 mL) was added dropwise a solution of m-chloroperbenzoic acid (10% excess, 5.25 g) in chloroform (50 mL) over a period of 1 h. The reaction mixture was stirred at room temperature for 48 h. At the end of the reaction, excess of the reagent was destroyed with 10% Na_2SO_3 solution (aq.) until it gave negative test with starch-iodide paper. The reaction mixture was basified with 80% $NaHCO_3$ solution (aq.) and thoroughly extracted with chloroform. The combined $CHCl_3$ extracts were washed with brine and dried over Na_2SO_4 (anhyd.); removal of the solvent *in vacuo* and crystallization from benzene afforded the N-oxide 202 (3.9 g, 90%), mp 132-134°C; ^1H (90 MHz), δ: 2.51 (3H, s, C-4 CH_3), 3.10 (2H, t, J=6.9 Hz, $-CH_2Ar$), 3.75 (2H, t, J=6.9 Hz, $-CH_2Cl$), 8.30 (1H, s, C-6 or C-2 H), and 8.37 (1H, s, C-2 or C-6 H); ms (EI), m/z (%): 198 (22)(M+2), 196 (65)$M^{+\cdot}$, 182 (9), 180 (28), 131 (100), 120 (24), and 77 (26); Anal. calc. for $C_9H_9Cl_2N_2O$: C 54.96, H 4.58, Cl 18.07, N 14.25; found: C 55.51, H 4.94, Cl 18.16, N 14.00%.

(b) Reaction of the N-oxide 202 with acetic anhydride:

A mixture of the N-oxide 202 (2.5 g) in acetic anhydride (10 mL) and acetic acid (2 mL) was heated under reflux at 130-140°C under argon for 3h. The colour of the reaction mixture changed to red in 10 min and at the completion of the reaction excess of the reagent was evaporated *in vacuo*. The residue was diluted with water (20 mL), basified with $NaHCO_3$

solution (aq.) and thoroughly extracted with chloroform, the combined extracts were washed with brine and dried over Na_2SO_4 anhyd. Removal of the solvent *in vacuo* afforded crude 4-acetoxy derivative 203 (2.2 g, 76%) and was used without further purification in the following reaction. ^1H nmr (90 MHz), δ: 2.15 (3H, s, $OCOCH_3$), 3.05-3.30 (2H, m, $ClCH_2\underline{CH_2}Ar$), 3.60-3.90 (2H, m, $Cl\underline{CH_2}CH_2Ar$), 5.32 (2H, s, $-OCH_2Ar$), 8.73 (1H, s, C-6 or C-2 H), and 8.83 (1H, s, C-2 or C-6 H).

(c) Azaphthalide 191a:

A solution of the compound 203 (2.2 g), obtained above, in methanol (20 mL) and 20% KOH solution (aq. 10 mL) was gently heated under reflux for 1 h, then stirred at room temperature for 24 h. The reaction mixture was carefully acidified with conc. HCl solution and then heated under reflux for 2 h. The solution was concentrated *in vacuo* and the residue neutralized with Na_2CO_3 solution (aq.) and the resulting mixture thoroughly extracted with chloroform. The combined chloroform extracts were washed with brine, dried (Na_2SO_4 anhyd.) and the solvent removed *in vacuo* to give azaphthalide 191a (130 mg, 8.3%); mp. 153-154°C R_f 0.4 (alumina, $CHCl_3$); ^1H nmr (90 MHz), δ: 5.40 (2H, s, C-1 H's), 5.50 (1H, d, J=11.5 Hz, $-CH=\underline{CH_2}$), 5.60 (1H, d, J=17.5 Hz, $-CH=\underline{CH_2}$), 6.86 (1H, dd, J=17.5 and 11.5 Hz, $-\underline{CH}=CH_2$), 8.74 (1H, s, C-6 H), and 9.03 (1H, s, C-4 H): ms (EI), m/z (%): 161 (100)$M^{+\cdot}$, 132 (90), 104 (73), 78 (23), and 77 (35); Exact mass (hrms), calcd. for $C_9H_7NO_2$: 161.048; found: 161.047; calcd. for fragment ion C_8H_6NO: 132.045; found: 132.045; calcd. for fragment ion C_7H_6N: 104.050; found: 104.049.

(d) Preparation of azaphthalide 191a via 4-chloromethylpyridine 204.

To a stirred solution of N-oxide 202 (19.13 mmol) in dry CH_2Cl_2 (20 mL) was added a solution of $POCl_3$ (2.15 mL, 2.3 mmol) in CH_2Cl_2 (10 mL) under N_2 atmosphere. After one-tenth of the $POCl_3$ solution had been added, simultaneously the addition of a solution of triethylamine (3.2 mL, 2.3 mmol) in CH_2Cl_2 (10 mL) was begun. The rate of the addition of the $POCl_3$ solution and triethylamine solution was same and such that the heat of the reaction maintained the reaction at reflux. After the addition of the $POCl_3$ solution has been completed, the remaining 1/10 of the triethylamine solution was added and the reaction mixture was first stirred for a further 10 min then gently heated under reflux for 30 min. The reaction mixture was cooled and the excess of $POCl_3$ was carefully destroyed with ice; the mixture was then basified with solid sat. Na_2CO_3 solution (aq.) and thoroughly extracted with chloroform. The combined chloroform extracts were treated with charcoal, filtered, and dried over Na_2SO_4 anhyd. Removal of the solvent *in vacuo* afforded a reddish brown oil (3.34 g) which was chromatographed on neutral alumina, elution with CH_2Cl_2 gave 204 as yellow oil (1 g); ^1H nmr (90 MHz) δ: 3.30 (2H, t, J=6.9 Hz, $ClCH_2\underline{CH_2}Ar$), 3.87 (2H, t, J=6.9 Hz, $Cl\underline{CH_2}CH_2Ar$), 4.80 (2H, s, $Cl\underline{CH_2}Ar$), 8.82 (1H, s, C-6 or C-2 H), and 8.90 (1H, s, C-2 or C-6 H).

To a solution of compound 204 (700 mg), obtained above, was added Amberlyst A26 resin in carbonate form (3 g) and the reaction mixture was stirred vigorously and heated under reflux for 4 h under N_2 atmosphere. The resin was then filtered off and washed with CH_2Cl_2 and methanol. The filtrate was concentrated *in vacuo* and the residue diluted with methanol

(10 mL) and acidified with conc. HCl solution and the mixture stirred for 3 h at room temperature. Work up in the usual manner afforded the azaphthalide 191a (85 mg, 17%) identical with the sample prepared previously.

Preparation of azaphthalideisoquinolines:

(a) Reaction of iminium salt 179a with the anion of azaphthalide 188a:

n-BuLi (2.56 mmol) in hexane (1.6 M) was added to a stirred solution of diisopropylamine (2.56 mmol) in dry THF (5 mL) at -78°C under an argon atmosphere. The temperature of the LDA solution was raised to 0°C for 10-15 min and then cooled again to -78°C before proceeding with the dropwise addition of a solution of the azaphthalide 188a (2.2 mmol in THF, 3 mL). Towards the end of the addition the initially formed red solution became turbid but became homogeneous again on raising the temperature to -40°C. The temperature was kept at -40°C during the remainder of the addition and for an additional 20 min. The solution was then transferred through a syringe tube into a flask fitted with a magnetic stirrer containing a suspension of 3,4-dihydro-6,7-dimethoxy-2-methylisoquinolinium iodide 179a (740 mg, 2.2 mmol) in dry THF (3 mL). The mixture was stirred at -40°C for 3-4 h and then at ambient temperature overnight. The solvent was evaporated from the reaction mixture and the crude residue passed through a column of neutral alumina (activity I) using EtOAc as eluant. The residue obtained upon evaporation of the EtOAc was taken up in EtOH and from this solution the crystalline *threo* isomer 206a obtained. The mother liquors were taken to dryness and the

residue, dissolved in EtOAc, was separated into *threo* and *erythro* components by flash chromatography.

Threo: **206a** (213 mg, 25.6%); mp 198°C (from EtOH); R_f 0.48 (silica, EtOAc); ir ($CHCl_3$) ν_{max}; 1762 cm^{-1}; ^1H nmr (250 MHz) δ: 2.40-3.20 (4H, m, C-3 H's, and C-4 H's), 2.71 (3H, s, $-NCH_3$), 3.71 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.19 (1H, d, J=3.7 Hz, C-1 H), 5.75 (1H, d, J=3.7 Hz, C-1' H), 6.31 (1H, s, C-5 H), 6.66 (1H, s, C-8 H), 7.70 (1H, d, J=5.1 Hz, C-7'H), 8.63 (1H, d, J=5.1 Hz, C-6' H), and 8.89 (1H, s, C-4' H); ^{13}C nmr (62.9 MHz) δ: 29.5 (C-4); 45.1 ($-NCH_3$), 51.7 (C-3); 55.8, 56.1 (2 x OCH_3), 65.5 (C-1), 81.4 (C-1'), 110.1, 111.2, 118.8, 152.4, and 156.7, (5 x ArCH), 123.0, 123.5, 128.1, 147.3, 147.5, and 148.0, (6 x ArC); 169.1, (C=O); ms(CI), m/z(%): 341(16)(M^++1), 207(14), 206(100), 136(44). Anal. calcd. for $C_{19}H_{20}N_2O_4$: C 67.06, H 5.88, N 8.24%; found: C 66.92, H 5.62, N 8.32%.

Erythro: **207a** (65.8 mg, 9%); mp 108-110°C (from EtOH); R_f 0.22 (silica, EtOAc); ir ($CHCl_3$) ν_{max}: 1768 cm^{-1}; ^1H nmr (250 MHz) δ: 2.17-2.90 (4H, m, C-3 H's, C-4 H's), 2.57 (3H, s, $-NCH_3$), 3.80 (3H, s, $-OCH_3$), 3.91 (3H, s, $-OCH_3$), 4.16 (1H, d, J=4.5 Hz, C-1 H), 5.66 (1H, d, J=4.5 Hz, C-1' H); 6.50 (1H, s, C-5 H); 6.64 (1H, s, C-8 H), 6.65 (1H, d, J=5.1 Hz, C-7' H); 8.66 (1H, d, J=5.1 Hz, C-6' H), and 9.12 (1H, s, C-4' H); ^{13}C nmr (62.9 MHz) δ: 27.0 (C-4), 45.6, ($-NCH_3$), 50.0, (C-3), 56.3 (2 x OCH_3), 65.30 (C-1); 84.7 (C-1'); 111.1, 111.8, 118.5, 147.7, and 152.6 (5 x ArCH); 123.5, 124.1, 129.5, 147.9, 148.9, and 156.3 (6 x ArC), 168.5 (C=O); ms(CI), m/z(%): 341(23)$(M+1)^+$, 206(100); Anal. calcd. for $C_{19}H_{20}N_2O_4$; C 67.06, H 5.88, N 8.24%; found: C 66.83, H 6.20, N 7.90%.

(b) Reaction of iminium salt 179b with the anion of azaphthalide 188a:

This reaction was carried out in the same manner as that decsribed in the previous section except that 3,4-dihydro-6,7- methylene-dioxy-2-methylisoquinolinium iodide 179b was used. The reaction mixture was worked up similarly and the mixture of isomeric products separated by flash chromatography using 1% MeOH in EtOAc as eluant.

Threo: 206b (212 mg, 30%); mp 151-153°C dec. (from EtOH-Et_2O); R_f 0.66 (silica, EtOAc); ir ($CHCl_3$) ν_{max}; 1765 cm^{-1}; ^1H nmr (250 MHz) δ: 2.43-3.17 (4H, m, C-3 and C-4 H's), 2.62 (3H, s, $-NCH_3$), 4.14 (1H, d, J=3.5 Hz, C-1 H), 5.70 (1H, d, J=3.5 Hz, C-1'H), 5.82 (2H, d, J=4.9 Hz, $-OCH_2O-$), 6.34 (1H, s, C-5 H), 6.63 (1H, s, C-8 H), 7.39 (1H, d, J=5.1 Hz, C-7' H), 8.67 (1H, d, J=5.1 Hz, C-6' H), and 8.96 (1H, s, C-4' H); ^{13}C nmr (62.9 MHz) δ: 29.6 (C-4), 45.2 ($-NCH_3$), 51.5 (C-3), 66.0 (C-1), 82.0 (C-1'), 101.1 ($-OCH_2O-$), 107.4, 108.5, 118.7, 147.6, and 152.5 (5 x ArCH), 123.7, 124.3, 129.8, 146.3, 146.9, and 156.6 (6 x ArC); 168.7 (C=O); ms(CI), m/z(%): 325(5)$(M+1)^+$, 191(28.2), and 190(100); Anal. calc. for $C_{18}H_{16}N_2O_4$: C 66.66, H 4.94, N 8.64; found: C 66.32, H 5.31, N 8.28%.

Erythro: 207b (180 mg, 25%); mp 144-146°C dec. (from EtOH-Et_2O) R_f 0.38 (silica, EtOAc); ir ($CHCl_3$) ν_{max}: 1760 cm^{-1}; ^1H nmr (250 MHz) δ: 2.10-2.90 (4H, m, C-3 and C-4 H's), 2.54 (3H, s, $-NCH_3$); 4.11 (1H, d, J=4.8 Hz, C-1 H), 5.57 (1H, d, J=4.8 Hz, C-1' H), 5.98 (2H, s, $-OCH_2O-$), 6.62 (1H, s, C-5 or C-8 H), 6.65 (1H, d, J=5.1 Hz, C-7' H), 6.66 (1H, s, C-8 or C-5 H), 8.66 (1H, d, J=5.1 Hz, C-6' H), and 9.13 (1H, s, C-4' H); ^{13}C nmr (62.9 MHz) δ: 27.6 (C-4), 45.8 ($-NCH_3$), 50.1 (C-3), 65.6 (C-1),

84.8 (C-1'), 101.3 ($-OCH_2O-$), 108.0, 108.8, 118.6, 147.8, and 152.7 (5 x ArCH), 124.1, 124.7, 130.8, 146.6, 147.4, and 156.1 (6 x ArC), 168.6 (C=O); ms(CI), m/z(%): 325(35)$(M+1)^+$, 191(38), and 190(100); Anal. calcd. for $C_{18}H_{16}N_2O_4$: C 66.66, H 4.94, N 8.64%; found: C 66.26, H 5.15, N 8.33%.

(c) Reaction of iminium salt **179f** with the anion of azaphthalide **188a**:

This reaction was carried out in the similar manner as that described in the previously except that 3,4-dihydro-8-methoxy-6,7-methylenedioxy-2-methylisoquinolinium iodide **179f** was used. The reaction was worked up similarly and the mixture of isomeric products (total yield ≃ 10%) were separated by flash chromatography (silica) using 1% MeOH in EtOAc as eluent.

Threo: 206c (17 mg), mp 155-157°C (MeOH); ^1H nmr (90 MHz), δ: 2.20(3H, s, $-NCH_3$), 2.45-3.20(4H, m, C-3 and C-4 H's), 3.90(3H, s, $-OCH_3$), 4.30(1H, d, J=3.5 Hz, C-1 H), 5.72 (1H, d, J=3.5 Hz, C-1' H), 5.87 (2H, s, $-OCH_2O-$), 6.38 (1H, s, C-5 H), 7.30 (1H, d, J=5.1 Hz, C-7' H), 8.83 (1H, d, J=5.1 Hz, C-6' H) and 9.20 (1H, s, C-4' H).

Erythro: 207c (13 mg), oil, (was not obtained analytically pure); ^1H nmr (90 MHz), δ: 2.60(3H, s, $-NCH_3$), 2.30-2.85(4H, m, C-3 and C-4 H's), 4.10 (3H, s, $-OCH_3$), 4.55 (1H, d, J=4.8 Hz, C-1 H), 5.77 (1H, d, J=4.8 Hz, C-1' H), 6.00 (2H, s, $-OCH_2O-$), 6.40 (1H, s, C-5 H), 6.46 (1H, d, J=5.1 Hz, C-7' H), 8.66 (1H, d, J=5.1 Hz, C-6' H), and 9.22 (1H, s, C-4' H).

Reaction of the lithium salt of azaphthalide 188a with 3,4-dihydroisoquinolines:

(a) *trans*-13-Hydroxy-2,3-dimethoxy-5,6,13,14-tetrahydro-8*H*-isoquino-[2,1-*b*][2,7]naphthyridin-8-one 210a:

A solution of n-BuLi (2.44 mmol) in hexane 1.6M was added dropwise with stirring to a solution of diisopropylamine (2.44 mmol) in THF at -20° under an argon atmosphere. The LDA solution was stirred for an additional 5 min at the same temperature. After the addition was complete, the temperature of the reaction mixture was then lowered to -60°C and a solution of azaphthalide 188a (300 mg, 2.22 mmol) in THF (2 mL) was added dropwise to the LDA solution. The solution of the red anion so generated was stirred for a further 15 min. at -60°. Imine 97a (439 mg, 2.22 mmol) in 3 mL THF was then added dropwise and, when addition was complete, stirring of the solution was continued another 2 h. The temperature was raised to 20°C and the reaction mixture kept at this temperature for ca. 12 h. The mixture was worked up in the usual manner (110,111) affording the condensation product 210a (590 mg, 81%), mp 230-235°C dec. ($CHCl_3$-acetone); R_f 0.22 (alumina, EtOAc); ir ($CHCl_3$), ν_{max}, 1645 cm^{-1}; ^1H nmr (90 MHz) δ: 2.80-3.00 (3H, m, C-5 H's and C-6 H_{ax}), 3.87 (3H, s, $-OCH_3$), 3.90 (3H, s, $-OCH_3$), 4.57-4.75 (2H, m, C-13 H and C-14 H), 4.85-5.05 (1H, m, C-6 Heq.), 6.75 (1H, s, C-4 H), 7.03 (1H, s, C-1 H), 7.70 (1H, d, J=5.5 Hz, C-12 H), 8.74 (1H, d, J=5.5 Hz, C-11 H), 9.13 (1H, s, C-9 H); ^{13}C nmr (62.9 MHz), δ: 30.3 (C-5), 39.3 (C-6), 56.3, 56.5, (2 x OCH_3), 61.4 (C-14), 71.3 (C-13), 112.4, 118.5, 123.3, 123.9, 129.2, 147.9, 149.1, 149.6, 149.7, 153.0, (aromatic carbon

atoms)[2], 162.8 (C=O); ms(EI), m/z (%): 326 (26.5) $M^{+\cdot}$, 309(5), 192(100), 135(10), 134(7), and 106(18); Exact mass (hrms), calcd for $C_{18}H_{18}N_2O_4$: 326.127; found: 326.127; calcd. for $C_{11}H_{14}NO_2$: 192.102, found: 192.095; calcd. for fragment ion $C_7H_5NO_2$: 135.032; found: 135.030, calcd. for fragment ion C_6H_4NO: 106.029, found: 106.027; Anal. calcd. for $C_{18}H_{18}N_2O_4$: C 66.26, H 5.52, N 8.59%; found: C 66.11, H 5.59, N 8.58%.

(b) *trans*-13-Hydroxy-2,3-methylenedioxy-5,6,13,14-tetrahydro-8*H*-isoquino-[2,1-*b*][2,7]naphthyridin-8-one **210b**:

This reaction was carried out in exactly the same manner as that described above. The condensation product **210b** was separated as an oil but crystallzied from ethylacetate (420 mg, 61%); mp 230-231°C; R_f 0.46 (alumina, EtOAc); ir ($CHCl_3$), ν_{max}: 1640 cm^{-1}; ^1H nmr (90 MHz), δ: 2.80-3.13 (3H, m, C-5 H's and C-6 H_{ax}), 4.53-4.73 (2H, m, C-13 H and C-14 H), 4.83-5.03 (1H, m, C-6 H_{eq}), 5.97 (2H, s, $-OCH_2O-$), 6.73 (1H, s, C-4 H), 6.97 (1H, s, C-1 H), 7.67 (1H, d, J=5.5 Hz, C-12 H), 8.77 (1H, d, J=5.5 Hz, C-11 H), and 9.20 (1H, s, C-9 H); ^{13}C nmr (62.9 MHz), $CDCl_3$ + DMSO-d_6: 30.0 (C-5), 38.9 (C-6), 60.7 (C-14), 69.8 (C-13), 100.8 ($-OCH_2O-$), 108.1, 109.9, 119.0, 122.8, 125.4, 129.5, 145.4, 146.5, 148.6, 151.2, and 152.4 (11 x aromatic carbons), 162.0 (C=O); ms (EI), m/z (%): 310(23)$M^{+\cdot}$, 176(96), 135(21), and 106(100); Exact mass (hrms): calcd. for $C_{17}H_{14}N_2O_4$: 310.095, found: 310.094; calcd. for fragment ion

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[2]Ten signals were observed for 11 carbon atoms.

$C_{10}H_{10}NO_2$: 176.071, found: 176.068; calcd. for fragment ion $C_7H_5NO_2$: 135.032, found: 135.029; calcd. for fragment ion C_6H_4NO: 106.029, found: 106.026; Anal. calcd. for $C_{17}H_{14}N_2O_4$: C 65.80, H 4.52, N 9.03 %; found: C 65.70, H 4.71, N 9.23%.

(c) *trans*-2-Benzyloxy-13-hydroxy-3-methoxy-5,6,13,14-tetrahydro-8*H*-isoquino[2,1-*b*][2,7]naphthyridin-8-one 210*c*:

The reaction was carried out in the manner described for the reaction between 97a and 188b except that 1.85 mmol of 97c was used and other quantities adjusted accordingly. The product 210c was recrystallized from $CHCl_3$-acetone (317 mg, 43%); mp 222-223°C; R_f 0.56 (alumina, EtOAc); ir ($CHCl_3$), ν_{max}: 1650 cm^{-1}; ^1H nmr (90 MHz), δ: 2.67-3.00 (3H, m, C-5 H's and C-6 H_{ax}), 3.97 (3H, s, $-OCH_3$), 4.47-4.67 (2H, m, C-13 H and C-14 H), 4.87-5.03 (1H, m, C-6 H_{eq}), 6.70 (1H, s, C-4 H), 6.95 (1H, s, C-1 H), 7.30-7.53 (5H, m, C_6H_5); 7.60 (1H, d, J=5.5 Hz, C-12 H), 8.75 (1H, d, J=5.5 Hz, C-11 H), and 9.20 (1H, s, C-9 H), ^{13}C nmr (62.9 MHz): 29.8 (C-5), 39.0 (C-6), 55.9 (OCH_3), 60.6 (C-14), 70.2 (C-13 or OCH_2Ar), 71.0 (C-13 or OCH_2Ar), 111.7, 115.7, 119.0, 123.0, 124.4, 127.4, 127.5, 127.8, 128.4, 129.0, 137.0, 146.1, 148.8, 148.9, 151.1, and 152.6, (aromatic carbons)[3] and 162.5 (C=O); ms(EI), m/z (%): 402(24)$M^{+\cdot}$, 268(12), 177(10), 135(100), 134(26), 106(75), and 91(68); Exact mass (hrms), calcd. for fragment ion $C_{17}H_{18}NO_2$: 268.134, found: 268.132; calcd. for fragment ion $C_7H_5NO_2$: 135.032, found: 135.004; calcd. for

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[3] 16 signals observed for 17 aromatic carbon atoms.

fragment ion C_6H_4NO: 106.029, found: 106.028; Anal. calcd. for $C_{24}H_{22}N_2O_4$: C 71.64, H 5.47, N 6.97%; found: C 71.98, H 5.76, N 7.14%.

Acetylation of Alcohols 210a, 210b and 210c.

(a) O-Acetyl derivative of 210a:

Compound **210a** (50 mg) was dissolved in pyridine (0.5 mL) and treated with an excess of acetic anhydride (1.5 mL). The mixture was kept in a stoppered flask for ca. 12 h, the excess reagent removed under vacuum, and water (5 mL) added to the residue. The aqueous suspension was extracted with chloroform, the chloroform extract washed with brine, dried over $NaSO_4$, and evaporated to dryness. The *O*-acetate **211a** crystallized from methanol (47 mg, 83%); mp 249-250°C (dec.) (MeOH); R_f 0.36 (alumina, EtOAc); ir ($CHCl_3$), ν_{max}: 1645, 1745 cm^{-1}; ^1H nmr (250 MHz), δ: 2.23 (3H, s, $-OCOCH_3$), 2.78-3.10(3H, m, C-5 H's and C-6 H_{ax}), 3.88 (3H, s, $-OCH_3$), 3.90 (3H, s, $-OCH_3$), 4.92 (1H, d, J=10.7 Hz, C-14 H), 4.90-5.00 (1H, m, C-6 H_{eq}), 6.05 (1H, d, J=10.7 Hz, C-13 H), 6.72 (1H, s, C-4 H), 6.76 (1H, s, C-1 H), 7.15 (1H, d, J=5.2 Hz, C-12 H), 8.76 (1H, d, J=6.2 Hz; C-11 H), and 9.27 (1H, s, C-9 H); ^{13}C nmr (62.9 MHz) δ: 21.0 (CH_3CO), 30.0 (C-5), 39.8 (C-6), 56.0, 56.4 (2 x OCH_3), 59.1 (C-14), 71.3 (C-13), 111.7, 111.8, 118.0, 120.8, 122.3, 125.5, 129.5, 146.2, 150.2, and 153.0, (aromatic carbon atoms)[4], 160.57 (lactam C=O), and 172.9 ($CH_3\underline{CO}$); ms(EI), m/z (%): 368(1)$M^{+\cdot}$, 325(23), 308(100), 293(39), 135(19), and 134(66); Exact mass (hrms): calcd. for fragment ion

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[4] 10 signals observed for 11 aromatic carbon atoms.

$C_{18}H_{17}N_2O_4$ ($M-C_2H_3O$): 325.119; found: 325.121; calcd. for fragment ion $C_{18}H_{16}N_2O_3$($M-C_2H_4O_2$): 308.116; found: 308.121.

(b) O-Acetyl derivative of 210b:

This compound was prepared from 50 mg of 210b under the conditions used to prepare 211a. The product 211b crystallized from methanol, (55 mg, 97%); mp 232-233°C (MeOH); R_f 0.63 (Al_2O_3, EtOAc); ir ($CHCl_3$) ν_{max}: 1650, 1750 cm^{-1}; ^1H nmr (250 MHz), δ: 2.23 (3H, s, CH_3CO), 2.76-3.05 (3H, m, C-5 H's and C-6 H_{ax}), 4.87 (1H, d, J=10.7 Hz, C-14 H), 4.90-4.96 (1H, m, C-6 H_{eq}), 5.96 (2H, s, $-OCH_2O-$), 5.97 (1H, d, J=10.7 Hz, C-13 H), 6.69 (1H, s, C-4 or C-1 H), 6.71 (1H, s, C-1 or C-4 H), 7.16 (1H, d, J=5.2 Hz, C-12 H), 8.76 (1H, d, J=5.2 Hz, C-11 H), and 9.26 (1H, s, C-9 H); ms(EI), m/z(%): 352(1)$M^{+\cdot}$, 309(8), 292(57), 277(30), 176(14), 135(11), and 134(33); Exact mass (hrms): calcd. for fragment ion $C_{17}H_{13}N_2O_4$ ($M-C_2H_3O$): 309.088; found: 309.082; calcd. for fragment ion $C_{17}H_{12}N_2O_3$ ($M-C_2H_4O_2$): 292.085, found: 292.083; Anal. calcd. for $C_{19}H_{16}N_2O_5$: C 64.77, H 4.55, N 7.95%; found: C 64.42, H 4.62, N 7.86%.

(c) O-Acetyl derivative of 210c:

This compound was prepared from 25 mg of 210c under the conditions used to prepare 211a. The product 211c crystallized from chloroform- ether (23 mg, 83%); mp 182-185°C; R_f 0.80 (alumina, EtOAc), 0.52 (silica, EtOAc); ir ($CHCl_3$), ν_{max}: 1655, 1760 cm^{-1}; ^1H nmr (250 MHz) δ: 2.08 (3H, s, CH_3CO), 2.80-3.10 (3H, m, C-6 H's and C-5 H_{ax}), 3.88 (3H, s,

$-OCH_3$), 4.80-5.00 (2H, m, C-14 H and C-5 H_{eq}), 5.08 (2H, s, $-CH_2Ar$), 5.95 (1H, d, J=10.3 Hz C-13 H), 6.72 (1H, s, C-1 or C-4 H), 6.80 (1H, s, C-1 or C-4 H), 7.09 (1H, d, J=5.0 Hz, C-12 H), 7.30-7.50 (5H, m, aromatic H's), 8.72 (1H, d, J=5.0 Hz, C-11 H), and 9.24 (1H, s, C-9 H); ms (EI), m/z(%): 444(3)$M^{+\cdot}$, 401(5), 384(44), 293(20), 134(20), and 91(100); Exact mass (hrms): calcd. for fragment ion $C_{24}H_{21}N_2O_4$: 401.150, found: 401.142; calcd. for fragment ion $C_{24}H_{20}N_2O_3$ ($M-C_2H_4O_2$): 384.147; found: 384.147.

Dehydration of Alcohols 210a, 210b and 210c:

(a) 5,6-Dihydro-2,3-dimethoxy-8*H*-isoquino[2,1-*b*][2,7]naphthyridin-8-one 212a

To a solution of alcohol 210a (100 mg) in dry pyridine (5 mL) was added freshly distilled $POCl_3$ (1 mL) and the reaction mixture was left at ca. 20°C for 3 hrs. The excess of the reagent was evaporated *in vacuo* and the residue dissolved in water (10 mL), made basic with conc. aqueous NH_3 and thoroughly extracted into chloroform. The combined chloroform extracts were washed with brine, dried over anhyd. Na_2SO_4, and evaporated *in vacuo*. The last traces of pyridine were removed by co-distillation using benzene. The crude material on crystallization from MeOH gave product 212a (62 mg, 65.6%); mp 185-186°C (MeOH) [(lit. (200) mp. 169--172°C)]; R_f. 0.37 (alumina, EtOAc); ir ($CHCl_3$), ν_{max}: 1650 cm^{-1}; ^1H nmr (250 MHz), δ: 2.97 (3H, t, J=6.1 Hz, C-5 H's), 3.96 (3H, s, $-OCH_3$), 4.00 (3H, s, $-OCH_3$), 4.33 (2H, t, J=6.1 Hz, C-6 H's), 6.72 (1H, s, C-4 H), 6.77 (1H, s, C-1 H), 7.27 (1H, s, C-13 H), 7.37 (1H, d, J=5.5 Hz, C-12

H), 8.67 (1H, d, J=5.5 Hz, C-11 H), and 9.58 (1H, s, C-9 H); ^{13}C nmr (62.9 MHz) δ: 27.7 (C-5), 39.4 (C-6), 56.0, 56.3 (2 x OCH_3), 99.1, 108.5, 110.6, 118.9, 120.2, 129.5, 141.7, 142.9, 148.6, 150.4, 151.1, and 151.2 (vinylic and aromatic carbons),[5] and 161.6 (C=O); ms(EI), m/z(%): 308(100)$M^{+\cdot}$, 307(17), 294(13), 293(68), 291(5), 277(4), and 265(5); Exact mass (hrms): calcd. for $C_{18}H_{16}N_2O_3$: 308.117; found: 308.116.

(b) 5,6-Dihydro-2,3-methylenedioxy-8*H*-isoquino[2,1-*b*][2,7]-naphthyridin-8-one 212b:

This reaction was carried out under the same conditions used for the preparation of 212a. The product was obtained in 77% yield, mp 288-290°C (dec.); R_f. 0.58 (alumina, EtOAc); ir ($CHCl_3$), ν_{max}: 1650 cm^{-1}; ^1H nmr (250 MHz) δ: 2.94 (2H, t, J=6.2 Hz, C-5 H's), 4.33 (2H, t, J=6.2 Hz, C-6 H's), 6.05 (2H, s, $-OCH_2O-$), 6.75 (2H, s, C-1 and C-4 H's), 7.26 (1H, s, C-13 H), 7.34 (1H, d, J=5.3 Hz, C-12 H), 8.67 (1H, d, J=5.3 Hz, C-11 H), and 9.58 (1H, s, C-9 H); ms (EI), m/z (%): 292(97)$M^{+\cdot}$, 291(34), 277(100), 233(26), and 205(24); Exact mass (hrms): calcd. for $C_{17}H_{12}N_2O_3$: 292.085; Found: 292.082.

(c) 2-Benzyloxy-5,6-dihydro-3-methoxy-8*H*-isoquino[2,1-*b*][2,7]-naphthyridin-8-one 212c:

This reaction was carried out in the same manner used for the dehydration of 210a. The product 212c was obtained in 95% yield. mp

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[5] 12 signals observed for 13 carbon atoms.

180-182°C (EtOAc-hexane); R_f 0.68 (alumina, EtOAc); ir ($CHCl_3$), ν_{max}; 1655 cm^{-1}; ^1H nmr (90 MHz), δ: 3.05 (2H, t, J=6.2 Hz, C-5 H's), 4.05 (3H, s, OCH_3), 4.40 (2H, t, J=6.2 Hz, C-6 H's), 5.34 (2H, s, $-OCH_2Ar$), 6.73 (1H, s, C-1 H or C-4 H), 6.90 (1H, s, C-4 H or C-1 H), 7.30-7.67 (7H, m, C_6H_5, C-12 H and C-13 H), 8.87 (1H, d, J=5.5 Hz, C-11 H), and 9.58 (1H, s, C-9 H); ^{13}C nmr (62.9 MHz), δ: 29.9 (C-5), 41.5 (C-6), 58.1 (OCH_3), 74.0 (OCH_2Ar), 101.1, 113.1, 114.1, 120.7, 123.5, 129.6, 130.2, 130.7, 132.4, 138.9, 143.9, 149.8, 152.6, 153.6, and 154.4 (vinylic and aromatic carbons)[6], 163.1 (C=O); ms(EI), m/z(%): 384(74)$M^{+\cdot}$, 383(9), 293(9), 265(7), and 91(100); Exact mass (hrms): calcd. for $C_{24}H_{20}N_2O_3$: 384.147; Found: 384.148.

Preparation of C-8 methylberberines and their aza analogues:

5,6-Dihydro-9,10-dimethoxy-2,3-methylenedioxy-8*H*-dibenzo[a,g]quinolizin-8-one (Oxyberberine) 214

Oxyberberine 214 was prepared by the procedure of Perkin (208) from berberine chloride by refluxing with 30% NaOH solution (aq) for 3 h; mp 204°C (EtOAc) (lit. 209) mp 200°C; lit. (210) mp 192-195°C); ^1H nmr (90 MHz), δ: 2.85 (2H, t, J=6.0 Hz, C-5 H's), 3.95 (3H, s, $-OCH_3$), 4.00 (3H, s, $-OCH_3$), 4.25 (2H, t, J=6.0 Hz, C-6 H's), 5.97 (2H, s, $-OCH_2O-$), 6.70 (2H, s, C-1 and C-4 H's), 7.20 (1H, apparent s, C-13 H), 7.30 (2H, apparent s, C-11 and C-12 H's); ms (EI), m/z (%): 351 (100)$M^{+\cdot}$, 336 (84), 321 (33), 308 (28), 291 (25), and 83 (14).

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[6] 15 signals observed for the carbon atoms.

(8α)- and (8β)-8-Methylcanadine, 217 and 218, respectively, from 214,

(a) Without isolation of intermediates

To a stirred solution of oxyberberine 214 (0.526 g, 1.5 mmol) in dry THF (100 mL) at -40°C was added a solution of MeLi (5 mL, 1.5 M in hexane, 7.5 mmol) under an argon atmosphere. The reaction mixture was stirred at -40°C for 3 h and then the temperature was raised slowly to ca. 20°C and stirring was continued for a further 2-3 h. The excess of MeLi was destroyed by adding water (1 mL) at 0°C and a few drops of conc. HCl solution (aq). The reaction mixture was then stirred for another 15 min at room temperature. Sodium borohydride (0.57 g, 15 mmol) was added in portions to the above stirred reaction mixture and stirring continued for 1 h. At this point the solution became clear and the solvent was evaporated *in vacuo* affording in nearly quantitative yield a mixture of isomeric 8-methylcanadines in a ratio (8α:8β = 1:3) as estimated by ^{1}H nmr. The crude product on crystallization from EtOH (95%) gave the 8β-isomer 218 (0.2 g). The ethanolic mother liquor was evaporated and the residue subjected to flash chromatography on silica gel (eluting with cyclohexane and EtOH in a ratio of 10:3) affording an additional 0.163 g of the 8β-isomer, (8S*, 13aS*) 218 and the 8α-isomer, (8R*, 13aS*) 217 (0.13 g).

8-β-isomer 218: (0.363 g, 69%); R_f 0.70 (silica, EtOAc cyclohexane-(1:1)]; mp 166-167°C (EtOH); ir ($CHCl_3$), ν_{max}: 2820-2740 cm^{-1} (Bohlmann bands); ^{1}H nmr (500 MHz), δ: 1.50 (3H, d, J=6.1 Hz, C-8 CH_3), 2.52 (1H, m, C-6 H_{ax}), 2.65 (1H, apparent d, J=16.0 Hz, C-5 H_{ax}), 2.80 (1H, m, C-13

H_{ax}), 3.10 (2H, m, C-5 H_{eq} and C-13 H_{aq}), 3.30 (1H, m, C-6 H_{eq}), 3.53 (1H, d, J=10.8 Hz, C-14 H), 3.81 (1H, q, J=6.1 Hz, partially overlapped by OCH_3 signals, C-8 H), 3.85 (3H, s, $-OCH_3$), 3.86 (3H, s, $-OCH_3$), 5.88 (2H, m, $-OCH_2O-$), 6.58 (1H, s, C-4 H), 6.75 (1H, s, C-1 H), 6.78 (1H, A part of AB, J=8.3 Hz, C-11 H), 6.86 (1H, B part of AB, J=8.3 Hz, C-12 H); ^{13}C nmr (125.76 MHz), δ: 23.0 (q, C-8 CH_3), 30.8 (t, C-5), 37.8 (t, C-13), 49.3 (t, C-6), 56.0 (q, $-OCH_3$), 57.3 (d, C-8), 59.1 (d, C-14), 60.4 (q, OCH_3), 100.8 (t, $-OCH_2O-$), 105.8 (d, C-4), 108.6 (d, C-1), 110.8 (d, C-12), 123.6 (d, C-11), 128.5, 129.1, 131.6, 134.0, 146.0, 146.1, 146.2, 151.1 (s's, Ar C's); ms(EI), m/z (%): 353 (10)$M^{+\cdot}$, 338 (100), 336 (20), 178 (45) and 163 (18); Exact mass (hrms): calcd. for: $C_{21}H_{23}NO_4$, 353.163; found: 353.163.

<u>8α-Isomer 217</u>: (0.13 g, 25%), R_f 0.52 [silica, EtOAc - cyclohexane, (1:1]; mp 138°C (EtOAc-hexane); ir ($CHCl_3$), ν_{max}: no Bohlmann bands; ^1H nmr (500 MHz), δ: 1.37 (3H, d, J=6.7 Hz, C-8 CH_3), 2.71-3.10 (6H, complex m, C-5, C-6 and C-13 H's), 3.83 (3H, s, $-OCH_3$), 3.85 (3H, s, $-OCH_3$), 4.19 (1H, dd, J=11.3 and 4.2 Hz, C-14 H), 4.30 (1H, q, J=6.7 Hz, C-8 H), 5.88 (2H, s, $-OCH_2O-$), 6.57 (1H, s, C-4 H), 6.67 (1H, s, C-1 H), 6.76 (1H, A part of AB, J=8.4 Hz, C-11 H), 6.80 (1H, B part of AB, J=8.4 Hz, C-12 H); ^{13}C nmr (125.76 MHz), δ: 15.9 (q, C-8 CH_3), 30.0 (t, C-5), 35.2 (t, C-13), 47.2 (t, C-6), 50.7 (d, C-8), 55.6 (d, C-14), 55.9 (q, $-OCH_3$), 60.6 (q, $-OCH_3$), 100.8 (t, $-OCH_2O-$), 106.3 (d, C-1), 108.7 (d, C-4), 111.3 (d, C-11), 124.1 (d, C-12), 126.6, 127.6, 132.2, 133.7, 145.4, 146.0, 146.1, and 150.5 (s's, Ar C's); ms (EI), m/z (%): 353 (12)$M^{+\cdot}$, 338 (100)8, 178 (72), 163 (26), and 135 (10); Exact mass (hrms): calcd. for $C_{21}H_{23}NO_4$: 353.163; found: 353.160.

(b) With isolation of intermediates:

8-Methylene-5,6-dihydro-9,10-dimethoxy-2,3-methylenedioxy-8*H*-dibenzo-[a,g]quinolizine 215

The reaction was carried out using oxyberberine 214 (1.5 mmol) as described previously. After an appropriate reaction time, the excess MeLi was destroyed by adding a saturated solution of Na_2SO_4 (2 mL aq). The reaction mixture was diluted with $CHCl_3$ (100 mL), dried over Na_2SO_4 (anhyd.) and filtered. The residue was washed several times with $CHCl_3$ and the combined $CHCl_3$ filtrates were evaporated *in vacuo* to give the exo-methylene compound as an oil in almost quantitative yield. ^1H nmr (90 MHz), δ: 2.87 (2H, t, J=6.0 Hz, C-5 H's), 3.48 (2H, q, J=6.0 Hz, C-6 H's), 3.80 (3H, s, $-OCH_3$), 3.86 (3H, s, $-OCH_3$), 4.20 and 5.35 (1H each, s's, methylene protons), 5.90 (2H, s, $-OCH_2O-$), 6.00 (1H, s, C-13 H), 6.63 (1H, s, C-4 H), 6.87 (2H, s, C-11 and C-12 H's), 7.10 (1H, s, C-1 H).

5,6-Dihydro-9,10-dimethoxy-2,3-methylenedioxydibenzo[a,g]quinolizinium bromide 216

To a methanolic solution of the crude exo-methylene compound 215 was added 48% HBr solution (1 mL, aq). The reaction mixture was stirred for 5 min. at room temperature and then evaporated to dryness *in vacuo* to give the quaternary bromide (0.6 g), which was crystallized from MeOH (0.405 g, 63%), mp 220-223°C (dec.); ^1H nmr (90 MHz), TFA, δ: 3.25 (2H, t, J=6.0 Hz, C-5 H's), 3.60 (3H, s, C-8 CH_3), 4.20 (6H, s, 2 x OCH_3), 4.88 (2H, t, J=6.0 Hz, C-6 H's), 6.12 (2H, s, $-OCH_2O-$), 6.95 (1H, s, C-4

H), 7.48 (1H, s, C-1 H), 8.04 (2H, s, C-11 and C-12 H's), 8.37 (1H, s, C-13 H); ms (EI), m/z (%): 350 (19)M^+, 349 (35), 334 (100), 318 (25), 290 (34), 167 (24), 148 (36), and 135 (32).

Sodium borohydride reduction of the iminium salt 216

To a stirred solution of the salt 216 (0.3 g) in EtOH (50 mL) was added $NaBH_4$ (0.3 g) in small portions with cooling and the reaction mixture was stirred for 1 h at room temperature. The excess $NaBH_4$ was carefully destroyed with glacial acetic acid at 0°C and the solution was made basic by conc. NH_3 solution (aq) and then the product was thoroughly extracted into $CHCl_3$. The combined $CHCl_3$ extracts were washed with brine, and evaporated *in vacuo*. The crude product containing an isomeric mixture of 8-methylcanadines 217 and 218 was subjected to flash chromatography on silica gel eluting with EtOAc-cyclohexane (3:10) to give the 8-β-isomer (0.17 g, 73%) and the 8-α-isomer (0.056 g, 23%), identical with the samples described above (mp, tlc, ^1H nmr, and mass spec.).

(8S*, 14S*)-5,6-13,14-Tetrahydro-2,3-dimethoxy-8-methyl-8*H*-isoquino-[2,1-*c*][2,7]naphthyridine 224 and its epimer at C-8 223

(a) Without isolation of intermediates

To a solution of the lactam 212a (0.39 g, 1.27 mmol) in dry THF (25 mL) was added a solution of MeLi (6 mL, 1.5 M in hexane) dropwise at -78°C and the mixture was then stirred for ca. 3 h. The excess MeLi was destroyed with saturated Na_2SO_4 solution (2 mL), a few drops of 48% HBr (aq) were added, and the solution stirred for 10 min. Excess $NaBH_4$ (0.4

g) was added to the reaction mixture which was stirred for a further 3 h, and then the solvent was removed *in vacuo*. The excess $NaBH_4$ was destroyed with glacial acetic acid, the resulting solution basified with conc. NH_3 (aq), and the solution thoroughly extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed successively with water and brine, and then dried over Na_2SO_4 (anhyd.). Evaporation of the solvent *in vacuo* gave the crude product (0.378 g) which was approximately a 3:1 mixture of 224 and 223 as estimated ^1H nmr of the crude product. The reduced product undergoes rapid aerial oxidation giving a highly fluorescent green coloured solution and therefore it must be immediately chromatographed after work-up. Flash chromatography on silica gel using 1 to 5% MeOH in $CHCl_3$ enabled the two isomers to be separated.

<u>8-β-isomer 224</u>: 213 mg (54%); mp 158-159°C (EtOAc); R_f 0.30[alumina; EtOAc-hexane (1:1)]; ir ($CHCl_3$ film), ν_{max}: 2820-2740 cm^{-1} (Bohlmann bands); ^1H nmr (500 MHz), δ: 1.60 (3H, d, J=6.4 Hz, C-8 CH_3), 2.48 (1H, dt, J=11.2 and 3.5 Hz, C-6 H_{ax}), 2.73 (1H, br d, J=16.0 Hz, C-5 H_{eq}), 2.91 (1H, dd, J=16.5 and 11.2 Hz, C-13 H_{ax}), 3.06 (1H, m, C-5 H_{ax}), 3.18 (1H, dd, J=16.5 and 3.1 Hz, C-13 H_{eq}), 3.39 (1H, complex m, C-6 H_{eq}), 3.75 (1H, apparent d, J=10.0 Hz, C-14 H), 3.83 (1H, q, J=6.4 Hz, C-8 H), 3.87 (3H, s, $-OCH_3$), 3.89 (3H, s, $-OCH_3$), 6.63 (1H, s, C-4 H), 6.71 (1H, s, C-1 H), 7.07 (1H, d, J=5.0 Hz, C-12 H), 8.35 (1H, d, J=5.0 Hz, C-11 H), 8.49 (1H, s, C-9 H); ^{13}C nmr (125.76 MHz), δ: 21.2 (C-8 CH_3), 29.6 (C-5), 36.6 (C-13), 46.5 (C-6), 55.9 ($-OCH_3$), 56.2 ($-OCH_3$), 57.6 and 58.3 (C-8 and C-14), 109.01, 111.5, 123.0, 127.1, 129.7, 135.6, 143.6, 146.7,

147.8 and 148.4 (aromatic carbons); ms (EI), m/z (%): 310 (41)$M^{+\cdot}$, 309 (43), 295 (100), 191 (25), 190 (39), 176 (17), and 118 (11); Exact mass (hrms): calcd. for $C_{19}H_{22}N_2O_2$: 310.168; found: 310.168.

8-α-isomer 223: 97 mg (25%); glossy solid; R_f.0.23 [alumina, EtOAc--hexane, (1:1)]; ir ($CHCl_3$), ν_{max}: no Bohlmann bands; ^1H nmr (500 MHz), δ: 1.42 (3H, d, J=6.9 Hz, C-8 CH_3), 2.90-3.10 (5H, complex m, C-5 H, C-6 H and C-13 H_{ax}), 3.13 (1H, dd, J=17.2 and 4.2 Hz, C-13 H_{eq}), 3.87 (3H, s, $-OCH_3$), 3.89 (3H, s, $-OCH_3$), 4.23-4.27 (2H, m, C-8 and C-14 H's), 6.63 (1H, s, C-4 H), 6.69 (1H, s, C-1 H), 7.03 (1H, d, J=5.0 Hz, C-12 H), 8.33 (1H, d, J=5.0 Hz, C-11 H), and 8.35 (1H, s, C-9 H); ^{13}C nmr (125.76 MHz), δ: 17.70 (C-8 CH_3), 29.7 (C-5), 35.9 (C-13), 47.5 (C-6), 49.9 (C-8), 56.1 (C-14), 56.3 ($-OCH_3$), 57.2 ($-OCH_3$), 109.4, 111.8, 123.8, 126.9, 130.2, 136.4, 143.1, 147.1, 147.7, 147.8, and 148.9 (aromatic carbons); ms (EI), m/z (%): 310 (45)$M^{+\cdot}$, 309 (40), 295 (100), 192 (13), 191 (35), 190 (49), 176 (20), 120 (8), 119 (9) and 118 (12); Exact mass (hrms): calcd. for $C_{19}H_{22}N_2O_2$: 310.168; found: 310.167.

(b) With isolation of intermediates

(i) 8-Methylene-5,6-dihydro-2,3-dimethoxy-8*H*-isoquino[2,1-*b*][2,7]-naphthyridine 221

To a solution of lactam 212a (0.2 g) in dry THF (12 mL) was added a solution of MeLi (5 mL, 1.5 M in hexane) dropwise at -78°C as described previously. The reaction mixture was stirred under argon at -78°C for 3-4 hr (reaction monitored by tlc). The excess MeLi was destroyed with

saturated Na_2SO_4 (2 mL, aq). The reaction mixture was diluted with $CHCl_3$, filtered through a pad of Na_2SO_4 (anhyd.), and the residue washed several times with $CHCl_3$. Evaporation of the $CHCl_3$ filtrate *in vacuo* afforded an oil (0.187 g, 94%); ^1H nmr (90 MHz), δ: 2.90 (2H, t, J=6.0 Hz, C-5 H's), 3.45 (2H, t, J=6.0 Hz, C-6 H's), 3.90 (3H, s, $-OCH_3$), 3.93 (3H, s, $-OCH_3$), 4.65 and 5.95 (1H each, s's, methylene protons), 6.68 (1H, s, C-4 H), 6.93 (1H, d, J=5.5 Hz, C-12 H), 7.00 (1H, s, C-1 H), 7.17 (1H, s, C-13 H), 8.35 (1H, d, J=5.5 Hz, C-11 H), and 8.83 (1H, s, C-9 H).

(ii) 5,6-Dihydro-2,3-dimethoxy-8-methylisoquino[2,1-*b*][2,7]-naphthyridinium bromide 222:

The crude product 221 obtained above was taken into EtOH (5 mL, 48%) HBr solution (1 mL aq.) added, and the reaction mixture was stirred for 15 min. The solvent was evaporated *in vacuo* and the last traces of water were removed by co-distillation with benzene. The crude product 222 was crystallized from EtOH-EtOAc (0.12 g, 51%), mp 190-198°C dec., ^1H nmr (90 MHz), δ: 2.95 (2H, t, J=6.0 Hz, C-5 H's), 3.95 (6H, s, $-OCH_3$ and $-NCH_3$), 4.00 (3H, s, OCH_3), 4.34 (2H, t, J=6.0 Hz, C-6 H's), 6.76 (2H, s, C-1 and C-4 H's), 7.30 (1H, s, C-13 H), 7.39 (1H, d, J=5.4 Hz, C-12 H), 8.68 (1H, d, J=5.4 Hz, C-11 H), 9.61 (1H, s, C-9 H); ms (EI), m/z (%): 307 (23)M^+, 306 (100), 305 (75), 291 (68), and 289 (30).

(+)-5,6-Dihydro-2,3-dimethoxy-8-methyl-8*H*-isoquino[2,1-*b*][2,7]-naphthyridine 225:

A chloroform solution of a mixture of 223 and 224 undergoes rapid

aerial oxidation producing a highly fluorescent green solution. A sample of the mixture when left open to air for ca. 48 h at room temperature was found completely oxidized to **225**. The crude product was purified on neutral alumina (EtOAc) yielding a glassy solid; ^{1}H nmr (90 MHz), δ: 1.28 (3H, d, J=6.5 Hz, C-8 CH_3), 2.80-3.05 (2H, m, C-5 H's), 3.30-3.63 (2H, m, C-6 H's), 3.90 (3H, s, $-OCH_3$), 3.95 (3H, s, $-OCH_3$), 4.65 (1H, q, J=6.5 Hz, C-8 H), 5.76 (1H, s, C-13 H), 6.76 (1H, s, C-4 H), 6.88 (1H, d, J=5.2 Hz, C-12 H), 7.25 (1H, s, C-1 H), 8.18 (1H, s, C-9 H), 8.30 (1H, J=5.2 Hz, C-11 H); ms (EI), m/z (%): 308 (14)$M^{+\cdot}$, 293 (100), and 277 (20). This compound was reduced with $NaBH_4$ to give an isomeric mixture of **223** and **224** in a ratio of ca. 1:3.

(8S*,14S*)-2-Benzyloxy-5,6,13,14-tetrahydro-3-methoxy-8-methyl-8*H*-isoquino[2,1-*b*][2,7]naphthyridine **134**:

To a solution of lactam **212c** (0.3 g, 0.78 mmol) in dry THF (20 mL) was added a solution of MeLi (4 mL, 1.5 M in hexane) dropwise and the resulting solution was stirred for 3.5 h at -78°C. The excess MeLi was then decomposed with a saturated Na_2SO_4 solution (2 mL aq.). The resulting mixture was treated with an excess of $NaBH_4$ (0.4 g) and stirred for ca. 3 h at room temperature. After removal of the solvent *in vacuo*, the excess $NaBH_4$ was carefully destroyed with glacial acetic acid. The mixture was basified with conc. NH_3 solution and thoroughly extracted with $CHCl_3$. The $CHCl_3$ extract was washed with brine, dried over Na_2SO_4 (anhyd.) and the solvent recovered *in vacuo* affording a crude product (0.293 g, 97%) which was a mixture of (8S*, 14S*)-isomer **134** and (8R*,

14S*)-isomer 133 as shown by ^{1}H nmr of the crude product.

The reduced product in solution oxidizes rapidly in air forming a highly fluorescent-green coloured mixture and must be chromatographed immediately.

The reduced product was separated into two fractions by flash chromatography on silica gel ($CHCl_3^*$-EtOAc, 8:1) but only the (8S*, 14S*)-isomer 134 was obtained in pure form, (167 mg, 55%); mp 137-141° (EtOAc-hexane), R_f 0.65 [silica, $CHCl_3$-EtOAc (2:1)]; ir ($CHCl_3$) ν_{max}: 2840-2740 cm^{-1} (Bohlmann bands); ^{1}H nmr (500 MHz), δ: 1.59 (3H, d, J=6.4 Hz, C-8 CH_3), 2.47 (1H, d of t, J=11.0 and 3.6 Hz, C-6 H_{ax}), 2.71-3.01 (3H, complex m, C-5 and C-13 H_{ax} H's), 3.05 (1H, dd, J=17.3 and 3.1 Hz, C-13 H_{eq}), 3.31 (1H, complex m, C-6 H_{eq}), 3.71 (1H, m, C-14 H), 3.79 (1H, q, J=6.4 Hz, C-8 H), 3.88 (3H, s, OCH_3), 5.13 (2H, m, $O\underline{CH_2}Ar$), 6.66 and 6.67 (1H each, s's, C-1 and C-4 H's), 7.18 (1H, d, J=5.8 Hz, C-12 H), 7.32-7.44 (5H, complex m, aromatic H's), 8.31 (1H, d, J=5.8 Hz, C-11 H), and 8.44 (1H, s, C-9 H), ms (EI), m/z (%): 386 (53)$M^{+\cdot}$, 385 (38), 371 (95), 295 (33), 280 (21), 279 (27), 267 (14), 266 (25), 120 (21), 119 (12), 118 (16), and 91 (100); Exact mass (hrms): calcd. for $C_{25}H_{26}N_2O_2$: 386.199; found 386.199.

<u>(+)-8-epi-Alamaridine 226 and (+)-alamaridine 126</u>

The crude mixture of 133 and 134 obtained from the reaction of 300 mg of lactam 212c and excess MeLi under conditions described above, was dissolved in MeOH (15 mL) and glacial acetic acid (1 mL), 10% Pd-C (0.1 g) was added, and the reaction mixture was treated with H_2 for ca.

12 h at 30 psi. The catalyst was removed by filtration through Celite and the residue washed with $CHCl_3$. The filtrate was diluted with water (25 mL), basified with 20% Na_2CO_3 solution (aq.) and thoroughly extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with brine, dried over Na_2SO_4 (anhyd.) and evaporated *in vacuo* to give a mixture (0.167 g, 72%) containing **126** and **226** which was subjected to flash chromatography (silica gel, eluting with 5 to 10% MeOH in $CHCl_3$), yielding two components.

(a) (±)-8-epi-Alamaridine **226**: 93 mg (40%), mp 197-200°C dec. (EtOAc--hexane); R_f. 0.26 [silica, $CHCl_3$-MeOH, (10:1)]; ir ($CHCl_3$), ν_{max}: 3550 cm^{-1}, 2820-2740 cm^{-1} (Bohlmann bands); ^1H nmr (500 MHz), δ: 1.60 (3H, d, J=6.4 Hz, C-8, CH_3), 2.46 (1H, d of t, J=11.3 and 3.5 Hz, C-6 H_{ax}), 2.71 (1H, apparent d, J=15.8 Hz, C-5 H_{ax}), 2.89 (1H, dd, J=16.5 and 11.2 Hz, C-13 H_{ax}), 3.05 (1H, m, C-5 H_{eq}), 3.13 (1H, dd, J=16.5 and 2.8 Hz, C-13 H_{eq}), 3.39 (1H, m, C-6 H_{eq}), 3.71 (1H, d, J=10.9 Hz, C-14 H), 3.79 (1H, q, J=6.4 Hz, C-8 H), 3.87 (3H, s, $-OCH_3$), 5.55 (1H, brs, phenolic -OH), 6.61 (1H, s, C-4 H), 6.80 (1H, s, C-1 H), 7.05 (1H, d, J=4.9 Hz, C-12 H), 8.34 (1H, d, J=4.9 Hz, C-11 H), and 8.48 (1H, s, C-9 H); ^{13}C nmr (125.76 MHz), δ: 21.4 (C-8, CH_3), 29.8 (C-5), 36.7 (C-13), 47.0 (C-6), 56.1 ($-OCH_3$), 57.8 (C-8), 58.4 (C-14), 110.8 (C-1), 111.7 (C-4), 123.4, 126.4, 130.6, 135.8, 144.0, 144.2, 145.5, 146.8, and 148.4 (aromatic carbons); ms (EI), m/z (%): 296 (33)$M^{+\cdot}$, 295 (36), 281 (100), 279 (25), 178 (18), 177 (20), 176 (32), 162 (13), 120 (18), 119 (11), and 118 (12); Exact mass (hrms): calcd. for $C_{18}H_{20}N_2O_2$: 296.152; found: 296.152.

(b) (+)-Alamaridine 126:

46 mg (20%); mp 178-182°C; R_f 0.20 [silica, $CHCl_3$-MeOH (10:1)]; ^1H nmr (500 MHz), δ: 1.41 (3H, d, J=6.9 Hz, C-8 CH_3), 2.76-3.14 (5H, complex m, C-5, C-6 and C-13 H_{ax} H's), 3.12 (1H, dd, J=17.5 and 4.5 Hz, C-13 H_{eq}), 3.88 (3H, s, $-OCH_3$), 4.21 (1H, dd, J=11.0 and 4.5 Hz, C-14 H, partially overlapped with q of C-8 H), 4.24 (1H, q, J=6.9 Hz, C-8 H), 5.20 (1H, br s, phenolic OH), 6.60 (1H, s, C-4 H), 6.77 (1H, s, C-1 H), 7.02 (1H, d, J=4.9 Hz, C-12 H), 8.32 (1H, d, J=4.9 Hz, C-11 H), and 8.37 (1H, s, C-9 H); ^{13}C nmr (125.76 MHz), δ: 17.3 (C-8 CH_3), 29.7 (C-5), 35.8 (C-13), 47.4 (C-6), 49.7 (C-8), 56.0 ($-OCH_3$), 57.0 (C-14), 110.9 (C-1), 111.9 (C-4), 123.7, 126.0, 130.9, 136.2, 143.0, 144.1, 145.2, 146.9, and 148.6 (aromatic carbons); ms (EI), m/z (%): 296 (36)$M^{+\cdot}$, 295 (29), 281 (100), 237 (4), 178 (38), 177 (19), 176 (29), 163 (11), 162 (16), 120 (18), 119 (11), and 118 (5); Exact mass (hrms): calcd. for $C_{18}H_{20}N_2O_2$: 296.153; found: 296.150. The ir spectrum of the synthetic sample was identical with that of natural alamaridine. The ^1H nmr (500 MHz) spectrum of our synthetic sample and the ^1H nmr (100 MHz, $CDCl_3$) spectra of natural alamaridine (125) and synthetic alamaridine (127) of Pakrashi had chemical shifts for C-methyl, O-methyl and aromatic protons that agreed within experimetnal error. Other signals that appeared as multiplets fell within the same range of δ values.

(+)-5,6,13,14-Tetrahydro-2,3-dimethoxy-8*H*-isoquino[2,1-*b*][2,7]naphthyridin-8-imine 246

A solution of imine 97a (0.6 g, 3.15 mmol) in dry THF (4 mL) was

treated dropwise with trimethylsilyl triflate (0.75 mL, 3.83 mmol) at -78°C under an argon atmosphere. The resulting cloudy suspension was stirred first at -78°C for 1 h then at 0°C for an additional 1 h. Meanwhile a solution of n-BuLi (2.33 mL, 1.55 M in hexane, 3.6 mmol) was added dropwise to a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (0.76 mL, 3.6 mmol) in dry THF (3 mL) at -78°C. The lithium bis-trimethylsilylamide (LHS) solution so generated was stirred for an additional 10 min. at -20°C and then cooled to -78°C. A solution of 3-cyano-4--methylpyridine 198a (0.354 g, 3 mmol) in dry THF (2 mL) was added dropwise to the above LHS solution at -78°C and the golden anion solution generated was stirred for a further 15 in. at -78°C. The anion solution was then added dropwise to the imine-TMS triflate complex at -78°C and when the addition was complete, the mixture was stirred for a further 4 h at -40°C. The reaction mixture was allowed to warm slowly to room temperature and stirred for ca. 12 h. The mixture was quenched with saturated NH_4Cl solution (1 mL aq.) and the resulting mixture was evaporated to dryness, water added and the contents extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 (anhyd.) and the solvent evaporated *in vacuo*. The crude product was filtered through a short neutral alumina column, eluting first with $CHCl_3$ and then with $CHCl_3$-MeOH (3:1) affording the amidine 246 (0.904 g, 97.5%); mp 160-163°C (EtOAc); ir ($CHCl_3$ film), ν_{max}: 1615 cm^{-1}; ^1H nmr (500 MHz), δ: 2.79-2.82 (1H, m, C-6 H_{ax}), 2.92-3.05 (3H, complex m, C-5, and C-13 H_{ax} H's), 3.16 (1H, dd, J=16.0 Hz, and 2.6 Hz, C-13 H_{eq}), 3.90 (6H, s, 2 x OCH_3), 4.63 (1H, dd, J=12.4 and 2.6 Hz, C-14 H), 4.85 (1H, m, C-6 H_{eq}), 6.68 (1H, s, C-4 H), 6.71

(1H, s, C-1 H), 7.20 (1H, d, J=4.9 Hz, C-12 H), 8.60 (1H, d, J=4.9 Hz, C-11 H), and 9.13 (1H, s, C-9 H); ^{13}C nmr (125.76 MHz), δ: 29.2 (C-5), 38.3 (C-13), 39.9 (C-6), 54.5 (C-14), 56.1 ($-OCH_3$), 56.4 ($-OCH_3$), 109.1, 111.6, 122.5, 147.8, and 150.8 (15 x Ar CH's), 125.5, 144.9, 148.2, 148.3 and 150.8 (Ar C's)[7], and 159.6 (>C=NH); ms (EI), m/z (%): 309 (100)$M^{+\cdot}$, 294 (58), 255 (18), 192 (40), 190 (24), 176 (59), 149 (40), and 118 (47), Exact mass (hrms): calcd. for $C_{18}H_{19}N_2O_3$: 309.148; found: 309.146.

(±)-5,6,13,14-Tetrahydro-2,3-dimethoxy-8*H*-isoquino[2,1-*b*][2,7]naphthyridin-8-one 227

Amidine 246 (250 mg) was dissolved in a mixture of dioxane (15 mL) and 20% KOH solution (10 mL, aq.) and the mixture was gently heated under reflux for 2 days. The solution was then evaporated to dryness *in vacuo*, acidified with conc. HCl (aq.) and heated under reflux for an additional 30 min. Evaporation of the acidified solution was followed by basification with saturated Na_2CO_3 solution (aq.) and extraction with $CHCl_3$. The combined $CHCl_3$ extracts were washed with brine and dried over $MgSO_4$ (anhyd.). Removal of the solvent *in vacuo* and crystallization from EtOAc gave lactam 227 (231 mg, 92%); mp 173-175°C (EtOAc); R_f. 0.34 (alumina, EtOAc); ir ($CHCl_3$, film), ν_{max}: 1655 cm^{-1}; ^1H nmr (500 MHz), δ: 2.78-2.80 (1H, C-6 H_{ax}), 2.93-3.00 (3H, complex m, C-5 and C-13 H_{ax} H's), 3.24 (1H, dd, J=16.2 and 3.3 Hz, C-13 H_{eq}), 3.90 (3H, s, $-OCH_3$), 3.91 (3H, s, $-OCH_3$), 4.85 (1H, dd, J=13.3 and 3.3 Hz, C-14 H), 4.98-5.00

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[7]Five signals were observed for the six aromatic quaternary C-atoms.

(1H, m, C-6 H_{eq}), 6.70 and 6.72 (1H each, s's, C-1 and C-4 H's), 7.21 (1H, d, J=4.7 Hz, C-12 H), 8.66 (1H, d, J=4.7 Hz, C-11 H), and 9.27 (1H, s, C-9 H); ^{13}C nmr (125.76 MHz), δ: 29.1 (C-5), 37.4 (C-13), 38.8 (C-6), 54.5 (C-14), 56.1 ($-OCH_3$), 56.4 ($-OCH_3$), 108.9, 111.8, 121.7, 150.3 and 152.3 (5 x Ar CH's), 124.9, 126.9, 127.4, 145.8, 148.4 and 148.4 (6 x Ar C's) and 163.3 (>C=O); ms (EI), m/z (%): 310 (100)$M^{+\cdot}$, 295 (46), 279 (42), 190 (48), 176 (20), 149 (21), and 119 (51); Exact mass (hrms): calcd. for $C_{18}H_{18}N_2O_3$: 310.132, found: 310.130.

Reaction of lactam 227 with MeLi followed by Reduction with $NaCNBH_3$ in glacial acetic acid.

To a solution of lactam 227 (0.1 g, 0.323 mmol), in dry THF (10 mL) was added dropwise with stirring a solution of MeLi (1.5 mL, 1.5 M in hexane, 2.26 mmol) at -78°C under an argon atmosphere. The stirrring was continued for ca. 4 h after which the excess MeLi was decomposed at -78°C with saturated Na_2CO_3 solution (1 mL aq.). The reaction mixture was diluted with $CHCl_3$ (50 mL), filtered, and the residue washed several times with $CHCl_3$. The combined $CHCl_3$ extracts were washed with brine and then dried over Na_2SO_4 (anhyd). Removal of the solvent *in vacuo* provided a crude product which was a mixture of mainly 8-exo-methylene compound 228 and some iminium salt 229 (by ^1H nmr).

The crude material obtained above was dissolved in glacial acetic (3 mL), an excess of $NaCNBH_3$ was added and the reaction mixture was stirred for ca. 30 min. at 5-10°C. The mixture was then evaporated to dryness *in vacuo*, basified with conc. NH_3 solution (aq.), and thoroughly

extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with brine, dried over Na_2SO_4 (anhyd.) and evaporated to dryness yielding 85 mg of product homogeneous on tlc. It proved to be identical with the ($8S^*$, $13aS^*$)-- isomer 224 (tlc., ^1H nmr, and mass spec.).

Reaction of lactam 227 with MeLi followed by catalytic reduction of the 8-exo-methylene compound 228.

Lactam 227 (100 mg) was heated with excess of MeLi in the manner already described. The reaction mixture was treated with a sat. Na_2CO_3 solution (1 mL) at -78°C, and extracted with $CHCl_3$ as in the previous experiment. The crude exo-methylene compound so obtained was dissolved in EtOH (10 mL) and a few drops of conc. NH_3 solution. It was then treated with H_2 over 10% Pd-C (50 mg) at room temperature for ca. 12 h. The catalyst was removed and the residue was washed with $CHCl_3$. Evaporation of the filtrate and washings *in vacuo* gave a compound (88 mg, 88%) homogeneous by tlc. that proved to be identical with the ($8S^*$,$14S^*$)-- isomer 224 (tlc., ^1H nmr and mass spec.).

Condensation of iminium salts 179a, 179c, 179d and 179e with the lithium salt of 3-cyano-4-methyl-5-vinylpyridine 190a:

(a) 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methyl-1-(3'-cyano-5'-vinyl-4'-picolyl)isoquinoline 231

To a stirred solution of diisopropylamine (0.55 ml, 3.89 mmol) in dry THF (5 ml) at -20°C was added n-Buli (2.44 mL, 1.6M solution in hexane, 3.9 mmol). After 5 min, the LDA solution was cooled to -78°C

(dry ice-acetone bath) and treated dropwise with a solution of 3-cyano-4-methyl-5-vinylpyridine **190a** (0.51 g, 3.54 mmol) in dry THF (8 mL), producing a red solution. After stirring the mixture at -78°C for 20 min, the solution was added to a suspension of 3,4-dihydro-6,7-dimethoxy-2-methylisoquinolinium iodide **179a** (1.18 g, 3.54 mmol) in dry THF (8 mL). The mixture was stirred at -78°C for 2 h, then allowed slowly to warm to room temperature and stirred for ca. 12 h. The THF was evaporated, water (25 mL) added, the solution basified with conc. NH_3 solution (aq.) and the solution extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with water and dried over Na_2SO_4 (anhyd.). Removal of the solvent *in vacuo* afforded **231** (1.21 g, 98%), mp 87-88°C (EtOH); R_f. 0.82 (alumina, EtOAc), 0.39 (silica, EtOAc); ir ($CHCl_3$, film), ν_{max}: 2225 cm^{-1}; ^1H nmr (250 MHz), δ: 2.41 (3H, s, $-NCH_3$), 2.44-3.60 (7H, complex m, C-1, C-3, C-4 and C-7' H's), 3.62 (3H, s, $-OCH_3$), 3.85 (3H, s, $-OCH_3$), 5.47 (1H, d, J=11.0 Hz, $-CH=\underline{CH}_2$), 5.69 (1H, d, J=17.4 Hz, $-CH=\underline{CH}_2$), 6.16 (1H, s, C-8 H), 6.60 (1H, s, C-5 H), 6.74 (1H, dd, J=17.4 and 11.0 Hz, $-\underline{CH}=CH_2$), 8.71 (1H, s, C-6' or C-2' H), and 8.75 (1H, s, C-2' or C-6' H); ^{13}C nmr (125.76 MHz), δ: 24.0 (C-4), 36.8 (C-7'), 42.4 ($-NCH_3$), 45.5 (C-3), 55.7 ($-OCH_3$), 55.8 ($-OCH_3$), 63.1 (C-1), 120.0 ($-\underline{CH}=CH_2$), 130.7 ($-CH=\underline{CH}_2$), 110.5, 111.6, 150.2 and 151.5 (4 x ArCH), 126.4, 127.5, 134.5, 147.0, 148.0 and 149.8 (ArC's)[8], and 116.4 (-CN); ms (DCI), m/z (%): 350 (51)$(M+1)^+$, 206 (100), and 145 (19); Anal. calcd. for $C_{21}H_{23}N_3O_2$: C 72.21, H 6.59, N 12.03%; found: C 72.06, H 7.00, N 12.35%.

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[8] 6 signals observed for 7 aromatic carbons (ArC).

(b) 2-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3'-cyano-5'-vinyl-4'-picolyl) isoquinoline 234

An LDA solution (4.4 mmol) prepared as described above, was treated with a solution of 3-cyano-4-methyl-5-vinylpyridine **190a** (0.576 g, 4 mmol) in dry THF. The resulting red solution was stirred for 20 min at -20°C and was added dropwise to suspension of 2-benzyl-3,4-dihydro-6,7-dimethoxyisoquinolinium bromide **179c** (1.448 g, 4 mmol) in dry THF at -78°C. The mixture was kept at -78°C for 2 h, then allowed to warm to room temperature and stirred for ca. 12 h. The usual work-up and chromatography on neutral alumina eluting with CH_2Cl_2, gave **234** (1.65 g, 97%); mp. 134-135°C (EtOH); R_f. 0.74 (alumina, EtOAc); ir ($CHCl_3$ film) ν_{max}: 2220 cm^{-1}; ^1H nmr (250 MHz), δ: 2.46-3.74 (9H, complex m, C-1, C-3, C-4, C-7' and $-NCH_2Ph$ H's), 3.80 (3H, s, $-OCH_3$), 3.88 (3H, s, $-OCH_3$), 5.46 (2H, dd, J=17.0 and 10.6 Hz, $-CH=\underline{CH}_2$), 6.60 (1H, s, C-8 H), 6.64 (1H, s, C-5 H), 6.73-7.12 (8H, complex m, $-\underline{CH}=CH_2$ and aromatic H's), 8.59 (1H, s, C-6' or C-2' H), and 8.61 (1H, s, C-2' or C-6' H); ^{13}C nmr (125.76 MHz), δ: 22.8 (C-4), 38.0 (C-7'), 44.4 (C-3), 55.9 ($-OCH_3$), 56.0 ($-OCH_3$), 57.3 ($-NCH_2Ph$), 59.0 (C-1), 120.1 ($-CH=\underline{CH}_2$), 130.9 ($-\underline{CH}=CH_2$), 110.8, 111.6, 126.7, 128.0, 128.0, 128.6, 128.6, 150.2, and 151.3 (9 x ArCH), 111.4, 126.6, 127.8, 134.4, 138.6, 147.6, 148.0 and 150.0 (8 x ArC), and 116.7 (-CN); ms (DCI), m/z (%): 426 (38)$(M+1)^+$, 283 (63), 282 (100), 192 (15), 190 (25), and 145 (27); Anal. calcd. for $C_{27}H_{27}N_3O_2$: C 76.24, H 6.35, N 9.88%; found: C 75.91, H 6.66, N 9.24%.

(c) 2-Allyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3'-cyano-5'-vinyl-4'-picolyl) isoquinoline 236

An LDA solution (4.4 mmol) in dry THF (5 mL) prepared from diisopropylamine (0.616 mL) and n-BuLi (2.98 mL of 1.48 M solution in hexane) was treated dropwise with a solution of 3-cyano-4-methyl-5-vinylpyridine 190a (0.576 g, 4 mmol) as described previously in the preparation of 231. The red coloured solution of the anion so generated was treated with a suspension of 2-allyl-3,4-dihydro-6,7-dimethoxyisoquinolium bromide 179d (1.248 g, 4 mmol) in dry THF (10 mL) at -78°C as described previously. The work-up as usual and chromatography on neutral alumina eluting with CH_2Cl_2, gave 236 as an oil (1.41 g, 94%); R_f. 0.88 (alumina, EtOAc), 0.76 (silica, EtOAc); ir ($CHCl_3$, film), ν_{max}: 2220 cm^{-1}; ^1H nmr (250 MHz), δ: 2.30-3.84 (9H, complex m, C-1, C-3, C-4, C-7' and $-\underline{CH_2}-CH=CH_2$ H's), 3.73 (3H, s, $-OCH_3$), 3.86 (3H, s, $-OCH_3$), 4.05 (2H, dd, J=16.7 and 8.5 Hz, $-CH_2-CH=\underline{CH_2}$), 5.25-5.41 (1H, complex m, $-CH_2-\underline{CH}=CH_2$), 5.53 (1H, d, J=10.9 Hz, $-CH=\underline{CH_2}$), 5.72 (1H, d, J=17.5 Hz, $-CH=\underline{CH_2}$), 6.42 (1H, s, C-8 H), 6.60 (1H, s, C-5 H), 6.88 (1H, dd, J=17.5 and 10.9 Hz, $-\underline{CH}=CH_2$), 8.72 (1H, s, C-6' or C-2' H), and 8.76 (1H, s, C-2' or C-6' H); ms (CI), m/z (%): 376 (38)$(M+1)^+$, 248 (10), 232 (100), 208 (7), 190 (12), and 145 (38). Exact mass (hrms): calcd. for fragment ion $C_{14}H_{18}NO_2$: 232.134; found: 232.134; calcd for fragment ion $C_9H_7N_2$: 143.061, found: 143.060.

(d) 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-*o*-nitrobenzyl-1-(3'-cyano-5'-vinyl-4'-picolyl) isoquinoline 237

An LDA solution (1.47 mmol) as described previously, was treated

dropwise with a solution of 3-cyano-4-methyl-5-vinylpyridine 190a (0.187 g, 1.3 mmol) in dry THF. Treatment of the red solution with a suspension of 3,4-dihydro-6,7-dimethoxy-2-(o-nitrobenzyl)isoquinolium bromide 179e (0.510 g, 1.3 mmol) in dry THF and work-up as described above, after crystallization from EtOAc gave the product 237 (0.534 g, 93%); mp. 144-145°C (EtOAc),; R_f. 0.86 (alumina, EtOAc); 0.71 (silica, EtOAc); ir ($CHCl_3$, film), ν_{max}: 2220, 1520 cm^{-1}; ^1H nmr (500 MHz), δ: 2.50-4.31 (9H, complex m, C-1, C-3, C-4, $-NCH_2Ar$, and C-7' H's), 3.80 (3H, s, $-OCH_3$), 3.89 (3H, s, $-OCH_3$), 5.47 (1H, d, J=11.2 Hz, $-CH=\underline{CH_2}$), 5.60 (1H, d, J=17.5 Hz, $-CH=\underline{CH_2}$), 6.64 (1H, s, C-8 or C-5' H), 6.65 (1H, s, C-5 or C-8 H), 6.73 (1H, dd, J=17.5 and 11.2 Hz, $-\underline{CH}=CH_2$), 7.11-7.63 (4H, complex m, aromatic H's), 8.50 (1H, s, C-6' H), and 8.65 (1H, s, C-2' H); ^{13}C nmr (125.76 MHz), δ: 22.8 (C-4), 37.9 (C-7'), 44.7 (C-3), 54.3 ($-NCH_2Ar$), 55.8 ($-OCH_3$), 55.9 ($-OCH_3$), 59.9 (C-1), 120.4 ($-CH=\underline{CH_2}$), 130.7 ($-\underline{CH}=CH_2$), 110.7, 111.6, 124.9, 128.0, 131.5, 132.3, 150.7 and 151.4 (8 x ArCH's), 110.3, 126.3, 127.2, 134.2, 134.3, 147.4, 148.1, 149.0, and 149.4 (9 x ArC's), and 116.5 (-CN). ms (DCI), m/z (%): 471 (100)$(M+1)^+$, 441 (14), 327 (88), 297 (27), 192(37), 190 (29), and 145 (49); Anal. calcd. for $C_{27}H_{26}N_4O_4$: C 68.94, H 5.53, N 11.91%; found: C 69.04, H 5.83, N 11.65%.

Attempted N-Debenzylation of 234

(a) By hydrogenolysis:

A solution of compound 234 (100 mg) in EtOH (5 mL), containing 10% Pd-C (40 mg) was treated with H_2 at room temperature for ca. 12 h.

The reaction mixture was diluted with $CHCl_3$ (20 mL) and the catalyst was removed by filtration through Celite. Removal of the solvent *in vacuo* afforded 235 (100 mg, 100%) as the only product, which crystallized from benzene-pet. ether (65-110); mp 108-110°C; ^1H nmr (250 MHz), δ: 1.18 (3H, t, J=7.7 Hz, $-CH_2\underline{CH}_3$), 2.63 (2H, q, J=7.7 Hz, $-\underline{CH}_2CH_3$), 2.45-3.70 (9H, complex m, C-1, C-3, C-4, $-NC\underline{H}_2Ph$ and C-7' H's), 3.79 (3H, s, $-OCH_3$), 3.89 (3H, s, $-OCH_3$), 6.64 (1H, s, C-8 H), 6.66 (1H, s, C-5 H), 6.83 (2H, m, aromatic H's), 7.01-7.12 (3H, m, aromatic H's), 8.47 (1H, s, C-6' or C-2' H), and 8.50 (1H, s, C-2' or C-6' H); ^{13}C nmr (125.76 MHz), δ: 14.5 ($-CH_2\underline{CH}_3$), 22.8 ($-\underline{CH}_2CH_3$), 23.0 (C-4), 37.7 (C-7'), 44.3 (C-3), 55.8 ($-OCH_3$), 55.9 ($-OCH_3$), 57.4 ($-NCH_2Ph$), 59.5 (C-1), 110.8, 111.5, 126.8, 128.0, 128.0, 128.6, 128.6, 150.4 and 152.4 (9 x ArCH's), 111.2, 126.5, 127.9, 138.6, 138.9, 147.6, 147.9, and 150.8 (8 x ArC's), and 117.1 (-CN); ms (DCI), m/z (%): 428 (20)$(M+1)^+$, 282 (100), 192 (18), and 147 (58); Anal. calcd. for $C_{27}H_{29}N_3O_2$: C 75.52, H 6.76, N 9.79%; found: C 75.35, H 7.07, N 9.26%. Prolonged treatment of 234 with H_2 gave a complex mixture.

(b) <u>By a hydrogen transfer procedure</u>:

A solution of the compound 234 (50 mg) in absolute EtOH (4 mL) containing 10% Pd-C (30 mg) and five drops of methane sulphonic acid was gently heated under reflux for ca. 12 h under a N_2 atmosphere. The mixture was diluted with $CHCl_3$ (25 mL) and the catalyst was removed by filtration through Celite. The filtrate was basified with conc. NH_3 solution (aq.), dried over Na_2SO_4 (anhyd.) and evaporated *in vacuo*. The

column chromatographic purification followed by the ^1H nmr of the reaction product showed the formation of 3-cyano-4-methyl-5-vinylpyridine 190a (tlc ^1H nmr and mass spec.) and a highly polar component with ^1H nmr similar to that of 2-benzyl-3,4-dihydro-6,7-dimethoxyisoquinolinium bromide 179c.

Attempted N-Deallylation of 236:

A mixture of the N-allylamine 236 (100 mg), methane sulphonic acid (2 drops) and a catalytic amount of 10% Pd-C in EtOH (4 mL), was gently heated under reflux on a steam bath for ca. 12 h. The reaction mixture was diluted with $CHCl_3$ (20 mL) and work-up as usual gave a mixture which was separated by chromatography into 3-cyano-4-methyl-5-vinylpyridine 190a (by tlc, ^1H nmr and mass spec.) and a highly polar component with a ^1H nmr similar to that of 2-allyl-3,4-dihydro-6,7-dimethoxyisoquinolium bromide 179d.

Attempted Photochemical N-*o*-nitrodebenylation of 237:

A solution of compound 237 (200 mg) in MeOH (40 mL) was irridiated with $\geq$ 300 nm using 450 watt medium pressure mercury lamp in a pyrex apparatus for 6 h. Evaporation of the solvent *in vacuo* and chromatographic purification of the residue on neutral alumina, eluting with CH_2Cl_2, gave a mixture of 3-cyano-4-methyl-5-vinylpyridine 190a and 1,2,3,4-tetrahydro-6,7-dimethoxy-2-(*o*-nitrobenzyl)isoquinoline 238. The mixture was separated and compounds 190a and 238 were characterized by comparison with authentic samples (tlc, ^1H nmr and mass spec.).

Trimethylsilyl Triflate Activated Cyclization of 3,4-dihydroisoquinolines with the Lithium Salt of 3-Cyano-4-Methyl-5-Vinylpyridine 190a:

(a) 12-Ethenyl-5,6,13,14-tetrahydro-2,3-dimethoxy-8*H*-isoquino[2,1-*b*]-[2,7]naphthyridin-8-imine 247:

A solution of 3,4-dihydro-6,7-dimethoxyisoquinoline 97a (0.61 g, 3.19 mmol) in dry THF (4 mL) was treated dropwise with TMSOTf (0.75 mL, 3.83 mmol), at -78°C under an argon atmosphere. The resulting cloudy suspension was stirred first at -78°C for 1 h then at 0°C for an additional 2 h. Meanwhile a solution of n-BuLi (2.33 mL of a 1.55 M in hexane, 3.6 mmol) was added dropwise to a stirred solution of 1,1,1,3,3,3-hexamethyl disilazane (0.76 mL, 3.6 mmol) in THF (3 mL) at -78°C. The lithium bis-trimethylsilylamide (LHS) solution so generated was stirred for an additional 10 min at -20°C and then cooled to -78°C. A solution of 3-cyano-4-methyl-5-vinylpyridine 190a (0.432 g, 3 mmol) in THF (2 mL) was added dropwise to the above LHS solution at -78°C, and the red solution so generated was stirred for a further 20 min at -78°C.

The red anion solution was then added dropwise at -78°C to the imine-TMS-triflate complex and when the addition was complete, the mixture was stirred at -40°C for 4 h. The mixture was allowed to warm to room temperature and stirred for ca. 12 h. The reaction mixture was quenched with saturated NH_4Cl solution (1 mL aq.) and the resulting mixture was evaporated, water added, and the contents extracted with $CHCl_3$, the $CHCl_3$ extract was dried (Na_2SO_4 anhyd.) and evaporated to dryness *in vacuo*. The crude product was filtered through a short neutral

alumina column eluting with CH_2Cl_2 to remove any starting materials, then with $CHCl_3$-MeOH (3:1) yielding **247a** (0.87 g, 87%); mp 189-191°C (EtOAc); ir ($CHCl_3$, film), ν_{max}: 1610 cm^{-1}; ^1H nmr (500 MHz), δ: 2.76-2.82 (2H, complex m, C-6 H_{ax} and C-13 H_{ax} H's), 2.99-3.04 (2H, complex m, C-5 H's), 3.29 (1H, dd, J=16.4 and 3.0 Hz, C-13 H_{eq}), 3.89 (3H, s, $-OCH_3$), 3.90 (3H, s, $-OCH_3$), 4.56 (1H, dd, J=12.2 and 3.0 Hz, C-14 H), 4.81 (1H, m, C-6 H_{eq}), 5.54 (1H, d, J=11.2 Hz, $-CH=\underline{CH_2}$), 5.77 (1H, dd, J=17.6 Hz, $-CH=\underline{CH_2}$), 6.66 (1H, s, C-4 H), 6.70 (1H, s, C-1 H), 6.83 (1H, dd, J=17.6 and 11.2 Hz, $-\underline{CH}=CH_2$), 8.71 (1H, s, C-11 H), and 9.03 (1H, s, C-9 H); ^{13}C nmr (125.76 MHz), δ: 29.2 (C-5), 35.9 (C-13), 39.8 (C-6), 54.1 (C-14), 56.1 ($-OCH_3$), 56.5 ($-OCH_3$), 119.8 ($-CH=\underline{CH_2}$), 130.7 ($-\underline{CH}=CH_2$), 109.4, 111.7, 147.0, and 148.6 (4 x ArCH's), 125.2, 127.5, 127.6, 131.2, 141.8, 148.2 and 148.3 (7 x ArC's), and 159.6 (>C=NH); ms(EI), m/z (%): 335 (100) $M^{+\cdot}$, 334 (24), 320 (41), 318 (5), 192 (24), 191 (13), 190 (14), 176 (37), 144 (10), 143 (39), 117 (13), 90 (11). Exact mass (hrms): calcd. for $C_{20}H_{21}N_3O_2$: 335.163; found: 335.163; calcd. for fragment ion $C_{19}H_{18}N_3O_2$ ($M-CH_3$): 320.140; found: 320.140; calcd. for fragment ion $C_9H_7N_2$: 143.061; found: 143.061.

(b) <u>2-Benzyloxy-12-ethenyl-5,6,13,14-tetrahydro-3-methoxy-8*H*-isoquino-[2,1-*b*][2,7]naphthyridin-8-imine **247b**</u>

This condensation was carried out in a similar manner as that described previously for the conversion of **97a** to **247**, using imine **97c** (0.804 g, 3 mmol), and LHS (3.3 mmol). The reaction mixture was worked-up in the usual manner and the crude product chromatographed on neutral

alumina eluting first with CH_2Cl_2 and then with increasing concentrations of MeOH, affording the amidine 247b (1.023 g, 83%); mp 218-221° C dec. (EtOH-EtOAc); ir ($CHCl_3$), ν_{max}: 1615 cm^{-1}; ^1H nmr (500 MHz), MeOH-d_4, δ: 2.90-3.04 (1H, m, C-6 H_{ax}), 3.17-3.44 (3H, complex m, C-5 and C-13 H_{ax} H's), 3.65-3.67 (1H, m, C-13 H_{eq}), 4.06 (3H, s, $-OCH_3$), 4.49 (1H, m, C-14 H), 4.96 (1H, m, C-6 H_{eq}), 5.31 (2H, ABq, J=21.6 and 12.3 Hz, $-OCH_2Ar$), 5.37 (1H, d, J=11.1 Hz, $-CH=\underline{CH_2}$), 5.55 (1H, d, J=17.3 Hz, $-CH=\underline{CH_2}$), 6.90 (1H, s, C-4 H), 6.97 (1H, dd, J=17.3 and 11.1 Hz, $-\underline{CH}=CH_2$), 7.04 (1H, s, C-1 H), 7.45-7.72 (5H, complex m, aromatic H's), 9.06 (1H, s, C-11 H), and 9.18 (1H, s, C-9 H); ms (EI), m/z (%): 411 (7) $M^{+\cdot}$, 410 (2), 320 (95), 268 (1), 178(2), 177(4), 176 (6), 144 (2), 143 (5), 117 (3), 91 (100), and 90 (4); Exact mass calcd. for $C_{26}H_{25}N_3O_2$: 411.195; found: 411.194.

Hydrolysis of Amidines 247a and 247b to Lactams 233a and 233b:

(a) 12-Ethenyl-5,6,13,14-tetrahydro-2,3-dimethoxy-8*H*-isoquino[2,1-*b*]-[2,7]naphthyridin-8-one 233a

Amidine 233a (250 mg) was dissolved in a mixture of dioxane (15 mL) and 20% KOH solution (10 mL, aq.) and the mixture was gently heated under reflux for 2 days. The solution was then evaporated to dryness *in vacuo*, acidified wtih conc. HCl (aq.) and heated under reflux for an additional 30 min. Evaporation of the acidified solution was followed by basification with saturated Na_2CO_3 solution (aq.), and extraction with $CHCl_3$. The combined $CHCl_3$ extracts were washed with brine and dried over $MgSO_4$ (anhyd.). Removal of the solvent *in vacuo* and crystallization from

EtOAc gave lactam **247a** (249 mg, 99.3%) as cubic crystals; mp 181-182°C; R_f. 0.46 (alumina, 2% MeOH in $CHCl_3$), 0.14 (silica, 5% MeOH in $CHCl_3$); ir ($CHCl_3$, film), ν_{max}: 1650 cm^{-1}; ^1H nmr (500 MHz), δ: 2.76-2.82 (2H, complex m, C-6 H_{ax} and C-13 H_{ax} H's), 2.84-2.99 (2H, complex m, C-5 H's), 3.40 (1H, dd, J=16.5 and 3.6 Hz, C-13 H_{eq}), 3.90 (3H, s, $-OCH_3$), 3.91 (3H, s, $-OCH_3$), 4.84 (1H, dd, J=13.1 and 3.6 Hz, C-14 H), 4.97 (1H, m, C-6 H_{eq}), 5.56 (1H, d, J=11.2 Hz, $-CH=\underline{CH_2}$), 5.79 (1H, d, J=17.6 Hz, $-CH=\underline{CH_2}$), 6.71 (1H, s, C-4 or C-1 H), 6.72 (1H, s, C-1 or C-4 H), 6.86 (1H, dd, J=17.6 and 11.2 Hz, $-\underline{CH}=CH_2$), 8.77 (1H, s, C-11 H), and 9.19 (1H, s, C-9 H); ^{13}C nmr (125.76 MHz), δ: 29.1 (C-5), 34.5 (C-13), 38.7 (C-6), 54.2 (C-14), 56.1 ($-OCH_3$), 56.5 ($-OCH_3$), 119.8 ($-CH=\underline{CH_2}$), 130.5 ($-\underline{CH}=CH_2$), 109.1, 111.8, 149.3 and 150.1 (4 x ArCH's), 124.4, 126.9, 127.5, 130.5, 142.4, 148.3 and 148.4 (7 x ArC's), and 165.6 (>C=O); ms (EI), m/z (%): 336 (100)$M^{+\cdot}$, 335 (52), 321 (30), 307 (11), 305 (23), 192 (9), 191 (14), 190 (21), 176 (20), 145 (19), 117 (57), and 90 (22); Exact mass (hrms): calcd. for $C_{20}H_{20}N_2O_3$: 336.147; found: 336.149; calcd. for fragment ion $C_{11}H_{12}NO_2$: 190.087; found: 190.087; calcd. for fragment ion C_9H_7NO: 145.053; found: 145.052.

(b) <u>2-Benzyloxy-12-ethenyl-5,6,13,14-tetrahydro-3-methoxy-8*H*-isoquino-[2,1-*b*][2,7]naphthyridin-8-one **233b**.</u>

Hydrolysis of the amidine **247b** (250 mg) was achieved with 20% KOH solution (15 mL, aq.) in dioxane (25 mL) under the conditions described previously for the preparation of **233a** from **247a** with slight modification. The reaction mixture was heated under reflux for 2 days, the

dioxane removed *in vacuo* and the mixture diluted with water (50 mL). The product was extracted thoroughly with CH_2Cl_2 and after successively washing the extract with water and brine, it was dried over $MgSO_4$ (anhyd.). Evaporation of the solvent *in vacuo* gave the lactam **233** (246 mg, 98%); mp 175-177°C (EtOAc); R_f. 0.53 (alumina, EtOAc); ir ($CHCl_3$, film), ν_{max}: 1655 cm^{-1}, ^1H nmr (500 MHz), $CDCl_3$ + MeOH-d_4, δ: 2.65-2.71 (1H, m, C-6 H_{ax}), 2.81-3.00 (3H, complex m, C-5 and C-13 H_{ax} H's), 3.17 (1H, dd, J=16.7 and 3.8 Hz, C-13 H_{eq}), 3.93 (3H, s, $-OCH_3$), 4.80 (1H, dd, J=13.1 and 3.8 Hz, C-14 H), 4.86-4.90 (1H, m, C-6 H_{eq}), 5.22 (2H, AB q, J=43.9 and 12.6 Hz, $-OCH_2Ar$), 5.61 (1H, d, J=11.7 Hz, $-CH=\underline{CH_2}$), 5.81 (1H, d, J=17.0 Hz, $-CH=\underline{CH_2}$), 6.69 (1H, s, C-4 or C-1 H), 6.77 (1H, dd, J=17.0 and 11.7 Hz, $-\underline{CH}=CH_2$), 7.26 (1H, s, C-1 or C-4 H), 7.34-7.47 (5H, complex m, aromatic H's), 8.72 (1H, s, C-11 H), and 9.06 (1H, s, C-9 H); ms (EI), m/z (%): 412 (33)$M^{+\cdot}$, 411 (6), 321 (12), 176 (3), 145 (2), 117 (7), 91 (100) and 90 (6); Exact mass (hrms); calcd. for $C_{26}H_{24}N_2O_3$: 412.179; found: 412.178.

<u>(+)-Alangimaridine(12-Ethenyl-5,6,13,14-tetrahydro-2-hydroxy-3-methoxy-8*H*-isoquino[2,1-*b*][2,7]naphthyridin-8-one **118**</u>.

A solution of *O*-benzyl lactam **233b** (50 mg) in EtOH (5 mL) and conc. HCl solution (5 mL) was heated under reflux gently for 3 h under a nitrogen atmosphere. The solvent was removed *in vacuo*, the residue treated with water (10 mL) and the mixture basified with saturated $NaHCO_3$ solution (aq.). The resulting mixture was extracted with $CHCl_3$, the $CHCl_3$ extract washed with brine and dried over Na_2SO_4 (anhyd.). Removal of the solvent and crystallization from MeOH-$CHCl_3$ gave colourless

crystals of (±)alangimaridine 118 (38 mg, 97.2%), mp 242-245°C, R_f. 0.20 (silica, 10% MeOH in $CHCl_3$); ir ($CHCl_3$, film), ν_{max}: 1650 cm^{-1}; ^1H nmr (500 MHz), δ: 2.76-2.82 (2H, complex m, C-6 H_{ax} and C-13 H_{ax} H's), 2.94-3.00 (2H, complex m, C-5 H's), 3.40 (1H, dd, J=16.5 and 3.8 Hz, C-13 H_{eq}), 3.92 (3H, s, $-OCH_3$), 4.81 (1H, dd, J=13.1 and 3.8 Hz, C-14 H), 4.95 (1H, m, C-6 H_{eq}), 5.55 (1H, d, J=11.1 Hz, $-CH=\underline{CH_2}$), 5.73 (1H, s, exchanges with D_2O, phenolic OH), 5.77 (1H, d, J=17.5 Hz, $-CH=\underline{CH_2}$), 6.69 (1H, s, C-4 H), 6.81 (1H, s, C-1 H), 6.85 (1H, dd, J=17.5 and 11.1 Hz, $-\underline{CH}=CH_2$), 8.77 (1H, s, C-11 H), and 9.20 (1H, s, C-9 H); ^{13}C nmr (125.76 MHz), δ: 29.0 (C-5), 34.1 (C-13), 38.8 (C-6), 53.8 (C-14), 56.0 ($-OCH_3$), 119.8 ($-CH=\underline{CH_2}$), 130.6 ($-\underline{CH}=CH_2$), 111.0, 111.7, 149.1 and 149.9 (4 x ArCH's), 124.3, 126.6, 127.6, 130.3, 142.7, 144.8 and 145.8 (7 x ArC's), and 163.5 (>C=O); ms (EI), m/z (%): 322 (100) $M^{+\cdot}$, 321 (53), 307 (23), 305 (12), 291 (7), 293 (12), 178 (7), 177 (7), 176 (13), 162 (16), 145 (18), 117 (46), and 90 (28); Exact mass (hrms): calcd. for $C_{19}H_{18}N_2O_3$: 322.132; found: 322.131.

Oxidation of Lactams 227, 233a and 118 to dehydro lactams 212a, 248 and 119:

(a) 5,6-Dihydro-2,3-dimethoxy-8*H*-isoquino[2,1-*b*][2,7]naphthyridin-8-one 212a.

A solution of lactam 227 (30 mg) and iodine (100 mg) in EtOH (10 mL) was gently heated under reflux on a steam bath for 6h. The progress of the reaction was monitored by tlc. When the reaction was complete, the solvent was evaporated *in vacuo* and 10% $Na_2S_2O_3$ solution (5 mL, aq.)

was added to decompose excess iodine. The mixture was basified with saturated Na_2CO_3 solution (aq) and the product was thoroughly extracted into $CHCl_3$. The combined $CHCl_3$ extracts were washed successively with 10% $Na_2S_2O_3$ solution, and brine, and dried over Na_2SO_4 (anhyd.). Evaporation of the solvent and crystallization of the residue from EtOAc gave **212a** (28 mg, 94%), mp 185-186°C; spectral data were identical with the sample of lactam **212a** prepared previously.

(b) 5,6-Dihydro-12-ethenyl-2,3-dimethoxy-8*H*-isoquino[2,1-*b*][2,7]-naphthyridin-8-one **248**.

Oxidation of the lactam **233a** (50 mg) with iodine (100 mg) by the method described previously for the oxidation of **227** to **212a**, gave dehydrolactam **248** (41 mg, 81%) as an amorphous solid, mp 145-150°C dec. ($CHCl_3$-MeOH); R_f. 0.26 (alumina, 5% MeOH in $CHCl_3$); 0.60 (alumina, EtOAc); ir ($CHCl_3$, film), ν_{max}: 1650 cm^{-1}, ^1H nmr (500 MHz) δ: 2.97 (2H, t, J=5.9 Hz, C-5 H's), 3.96 (3H, s, $-OCH_3$), 4.01 (3H, s, $-OCH_3$), 4.35 (2H, t, J=5.9 Hz, C-6 H's), 5.59 (1H, d, J=11.9 Hz, $-CH=\underline{CH_2}$), 5.87 (1H, d, J=17.5 Hz, $-CH=\underline{CH_2}$), 6.77 (1H, s, C-4 H), 6.94 (1H, s, C-1 H), 7.15 (1H, dd, J=17.5 and 11.9 Hz, $-\underline{CH}=CH_2$), 7.27 (1H, s, C-13 H), 8.98 (1H, s, C-11 H) and 9.52 (1H, s, C-9 H); ms (EI), m/z (%): 334 (100) $M^{+\cdot}$, and 319 (55); Exact mass (hrms) calcd. for $C_{20}H_{18}N_2O_3$: 334.132; found: 334.132.

(c) Alangimarine (12-Ethenyl-5,6-dihydro-2-hydroxy-3-methoxy-8*H*-isoquino[2,1-*b*]-[2,7]naphthyridin-8-one) **119**

Oxidation of the lactam **118** (20 mg) with iodine (50 mg) in EtOH

(20 mL) by the method described previously for the oxidation of 227 to 212a gave the crude product which was purified by flash column chromatography or silica gel eluting with 5% MeOH in $CHCl_3$. Crystallization from MeOH afforded yellow needles of 119 (17 mg, 86%): mp 245-247°C dec. (lit (124) mp 247°C ($CHCl_3$-MeOH); R_f. 0.35 (silica, 10% MeOH in $CHCl_3$); ^1H nmr (500 MHz), δ: 2.96 (2H, t, J=6.3 Hz, C-5 H's), 3.98 (3H, s, $-OCH_3$), 4.35 (2H, t, J=6.3 Hz, C-6 H's), 5.58 (1H, d, J=11.1 Hz, $-CH=\underline{CH}_2$), 5.84 (1H, d, J=17.4, $-CH=\underline{CH}_2$), 5.84 (1H, s, exchanges with D_2O, phenolic OH), 6.75 (1H, s, C-4 H), 6.98 (1H, s, C-1 H), 7.12 (1H, dd, J=17.1 and 11.1 Hz, $-\underline{CH}=CH_2$), 7.42 (1H, s, C-13 H), 8.76 (1H, s, C-11 H) and 9.50 (1H, s, C-9 H); ^{13}C nmr (125.76 MHz), δ: 28.1 (C-5), 39.8 (C-6), 56.3 ($-OCH_3$), 96.4, 110.1, 111.7, 119.1, 119.6, 122.6, 127.9, 129.0, 130.7, 139.5, 145.4, 148.2, 148.9, 150.9, and 150.9 (vinylic and aromatic carbons), 162.0 (>C=O); ms (EI), m/z (%): 320 (100) $M^{+\cdot}$, and 305 (66); Exact mass calcd. for $C_{19}H_{16}N_2O_3$: 320.116; found: 320.115.

Hydrogenation of Lactams 233a and 118 to Dihydro compounds 249a and 249b:

(a) 12-Ethyl-5,6,13,14-tetrahydro-2,3-dimethoxy-8*H*-isoquino[2,1-*b*][2,7]naphthyridin-8-one 249a

A solution of lactam 233a (100 mg) in EtOH (15 mL) containing 10% Pd-C (50 mg) was treated with H_2 at room temperature for 3h. The reaction mixture was filtered through Celite to remove catalyst and the Celite thoroughly washed with $CHCl_3$. The filtrate and washings were evaporated to dryness *in vacuo* and the residue crystallized from EtOH yielding white cubic crystals of 249a (100 mg, 99%); mp 185-187°C; R_f. 0.45 (alumina, EtOAc), 0.26 (silica, EtOAc); ir ($CHCl_3$, film), ν_{max}:

1650 cm^{-1}; ^1H nmr (500 MHz), δ: 1.26 (3H, t, J=7.6 Hz, $-CH_2\underline{CH_3}$), 2.73-2.81 (4H, complex m, C-6 H_{ax}, $-\underline{CH_2}-CH_3$, and C-5 H_{ax} H's), 2.93-2.97 (2H, m, C-5 H_{ax} and C-13 H_{ax}), 3.31 (1H, dd, J=16.4 and 3.5 Hz, C-13 H_{eq}), 3.91 (3H, s, $-OCH_3$), 3.92 (3H, s, $-OCH_3$), 4.84 (1H, dd, J=13.1 and 3.5 Hz, C-14 H), 4.98 (1H, m, C-6 H_{eq}), 6.69 (1H, s, C-4 H), 6.72 (1H, s, C-1 H), 8.54 (1H, s, C-11 H), and 9.16 (1H, s, C-9 H); ^{13}C nmr (125.76 MHz), δ: 14.6 ($-CH_2\underline{CH_3}$), 23.1 ($-\underline{CH_2}CH_3$), 29.1 (C-5), 34.0 (C-13), 38.6 (C-6), 54.2 (C-14), 56.0 (2 x OCH_3), 109.2, 111.8, 148.2, and 152.1 (4 x ArCH's), 124.4, 126.9, 127.6, 135.0, 143.6 and 148.4 (ArC's)[9] and 163.6 (>C=O); ms (EI), m/z (%): 338 (100) $M^{+\cdot}$, 337 (76), 323 (61), 309 (37), 307 (50), 192 (8), 191 (27), 190 (37), 147 (34), 119 (63), 92 (24), 91 (82); Exact mass (hrms); calcd. for $C_{20}H_{22}N_2O_3$, 338.163; found: 338.161.

(b) <u>12-Ethyl-5,6,13,14-tetrahydro-2-hydroxy-3-methoxy-8*H*-isoquino [2,1-*b*][2,7]naphthyridin-8-one 249b</u>

Hydrogenation of lactam 118 (10 mg) with 10% Pd-C (10 mg) in EtOH (15 mL) by the method described above for the hydrogenation of 233a gave compound 249b (10 mg, 99%) which crystallized as colorless crystals from MeOH; mp 228°C (lit. (124) mp 232°C (EtOH)); R_f. 0.44 (silica, 10% MeOH in $CHCl_3$); ir ($CHCl_3$, film), ν_{max}: 1655 cm^{-1}; ^1H nmr (500 MHz) δ: 1.24 (3H, t, J=7.7 Hz, $-CH_2-\underline{CH_3}$), 2.71-2.79 (4H, complex m, $-\underline{CH_2}CH_3$, C-5 H_{ax} and C-6 H_{ax} H's), 2.94-2.98 (2H, m, C-5 H_{eq} and C-13 H_{ax} H's), 3.33 (1H,

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[9] 6 signals observed for 7 aromatic carbons (ArC).

dd, J=16.4 and 3.6 Hz, C-13 H_{eq}), 3.92 (3H, s, $-OCH_3$), 4.80 (1H, dd, J=13.3 and 3.6 Hz, C-14 H), 4.95-4.98 (1H, m, C-6 H_{aq}), 5.75 (1H, s, exchanges with D_2O, phenolic OH), 6.69 (1H, s, C-4 H), 6.81 (1H, s, C-1 H), 8.54 (1H, s, C-11 H), and 9.15 (1H, s, C-9 H); ^{13}C nmr (125.76 MHz), δ: 14.9 ($-CH_2\underline{C}H_3$), 23.3 ($-\underline{C}H_2CH_3$), 29.3 (C-5), 34.0 (C-13), 38.9 (C-6), 54.2 (C-14), 56.2 ($-OCH_3$), 111.1, 111.8, 126.7, 127.8, 130.6, 135.3, 142.8, 143.8, 148.4, 150.2, and 152.3 (aromatic carbons), and 163.5 (>C=O); ms (EI), m/z (%): 324 (100) $M^{+\cdot}$, 323 (68), 309 (31), 307 (14), 295 (19), 178 (3), 177 (11), 176 (15), 162 (26), 147 (23), 119 (30), 92 (8) and 91 (32); Exact mass (hrms): calcd. for $C_{19}H_{20}N_2O_3$: 324.147; found: 324.147.

Trimethylsilyl Triflate Activated Condensation of 9-benzyl-3,4-dihydro-β-carboline 184 with Lithium salts of 3-cyano-4-methylpyridines:

(a) 13-Benzyl-8,13,13b,14-tetrahydroindolo[2',3':3:4]pyrido[1,2-*b*][2,7]-naphthyridin-5(7*H*)-imine 251a:

The trimethylsilyl triflate β-carboline complex was prepared in the usual manner as described for 246, from 9-benzyl-3,4-dihydro-β-carboline 184 (0.542 mg, 2 mmol) in dry THF (8 mL) and TMS-triflate (0.45 mL, 2.2 mmol). The lithium salt of 3-cyano-4-methylpyridine 198a (0.248 g, 2 mmol) was made as previously described using LHS (2.2 mmol) in THF (3 mL). The anion of 198a was added to the above complex at -78°C, then stirred first at -40°C for 4 h and then at 20°C for ca. 12 h; work-up as usual gave the crude amidine 251a. The crude product was purified by column chromatography on neutral alumina, eluting first with $CHCl_3$ then

with the increasing concentrations of MeOH (5-25%) in $CHCl_3$. The product 251a after the removal of the solvent was crystallized from ethylacetate (0.669 g, 89%); mp. 190-192°C; ir ($CHCl_3$, film), ν_{max}: 1615 cm^{-1}; ^1H nmr (500 MHz), δ: 2.84-3.08 (5H, complex m, C-7 H_{ax}, C-8, and C-14 H's), 4.71 (1H, apparent d, J=11.6 Hz, C-13b H), 5.08 (1H, m, C-7 H_{eq}), 5.11 (1H, br s, -NH), 5.32 (2H, s, $-NCH_2Ar$), 6.91 (1H, d, J=4.9 Hz, C-1 H), 6.99 (2H, m, aromatic H's), 7.18 - 7.32 (6H, complex m, aromatic H's), 7.62 - 7.64 (1H, apparent d, J=7.1 Hz, aromatic H's), 8.54 (1H, d, J=4.9 Hz, C-2 H), and 9.11 (1H, s, C-4 H); ^{13}C nmr (125.76 MHz), δ: 21.5 (C-8), 37.2 (C-14), 40.5 (C-7), 47.4 ($-NCH_2Ar$), 51.4 (C-13b), 110.0, 118.7, 120.1, 122.2, 122.5, 125.9, 125.9, 127.8, 129.1, 129.1, 147.9, and 150.8 (12 x ArCH's), 110.9, 125.3, 126.5, 133.6, 137.3, 138.2 and 144.0 (7 x ArC's), and 159.7 (>C=NH); ms (EI), m/z (%): 378 (57)$M^{+\cdot}$, 377 (25), 361 (23), 287 (100), 286 (5), 285 (10), 261 (5), 260 (7), 259 (7), 170 (10), 169 (23), 168 (9), 118 (7), and 91 (67); Exact mass (hrms): calcd. for $C_{25}H_{22}N_4$: 378.184; found: 378.181; calcd. for fragment ion $C_{18}H_{15}N_4$ ($M-CH_2C_6H_5$): 287.130; found: 287.128.

(b) <u>13-Benzyl-1-ethenyl-8,13,13b,14-tetrahydroindolo[2',3':3,4]pyrido-[2,1-*b*][2,7]-naphthyridin-5[7*H*]-imine 251b</u>

Addition of the red anion of 3-cyano-4-methyl-5-vinylpyridine 190a (288 mg, 2 mmol) to the complex of 9-benzyl-3,4-dihydro-β-carboline 184 (542 mg, 2 mmol) with TMS-triflate (0.45 mL, 2.2 mmol) and work-up as described for the preparation of 251a gave a residue which furnished amidine 251b (458 mg), crystallization from MeOH. The mother liquor was

chromatographed on neutral alumina, first eluting with $CHCl_3$, then with increasing concentrations of MeOH in $CHCl_3$. In this way another 234 mg of 251b was obtained, combined yield (86%); mp. 276-278°C (MeOH); ir (nujol), ν_{max}: 1620 cm^{-1}; ^1H nmr (500 MHz), $CDCl_3$ + MeOH-d_4, δ: 2.69 (1H, dd, J=17.0 and 13.4 Hz, C-7 H_{ax}), 3.13-3.54 (4H, complex m, C-8, C-14 H's), 4.65 (1H, dd, J=13.0 and 3.5 Hz, C-13b H), 5.06 (1H, m, C-7 H_{eq}), 5.28 (1H, d, J=17.9 Hz, $-NCH_2Ar$), 5.32 (1H, d, J=11.2 Hz, $-CH=\underline{CH_2}$), 5.46 (1H, d, J=17.9 Hz, $-NCH_2Ar$), 5.62 (1H, d, J=17.5 Hz, $-CH=\underline{CH_2}$), 5.99 (1H, dd, J=17.5 and 11.2 Hz, $-\underline{CH}=CH_2$), 7.03-7.04 (2H, m, aromatic H's), 7.24-7.41 (6H, complex m, aromatic H's), 7.66-7.67 (1H, m, aromatic H), 8.80 (1H, s, C-2 H), and 9.03 (1H, s, C-4 H); ^{13}C nmr (125.76 MHz), $CDCl_3$ + MeOH-d_4, δ: 20.9 (C-8), 32.6 (C-14), 44.5 (C-7), 47.0 ($-NCH_2Ar$), 52.5 (C-13b), 110.0, 119.2, 120.7, 123.5, 125.8, 125.8, 127.9, 128.4, 129.4, 129.4, 146.7 and 151.7 (11 x ArCH's + $-\underline{CH}=CH_2$), 109.5, 120.1, 121.8, 125.7, 130.3, 131.8, 137.0, 138.5 and 143.2 (8 x ArC's + $-CH=\underline{CH_2}$), and 158.9 (>C=NH); ms (EI), m/z (%): 404 (15) $M^{+\cdot}$, 403 (6), 387 (3), 386 (2), 313 (30), 287 (17), 286 (3), 285 (5), 261 (3), 260 (6), 259 (3), 169 (18), 168 (7), 144 (5), 143 (12), 117 (4) and 91 (100); Exact mass (hrms): calcd. for $C_{27}H_{24}N_4$: 404.200; found: 404.192; calcd. for fragment ion $C_{20}H_{17}N_4$ ($M-CH_2C_6H_5$): 313.145, found: 313.142; calcd. for fragment ion $C_{18}H_{16}N_2$: 260.131, found: 260.129.

Hydrolysis of Amidines 251a and 251b to Lactams 252a and 252b:

(a) 1-Benzyl-3,14-dihydronauclefine[13-Benzyl-8,13,13b,14-tetrahydro-indolo[2',3':3,4]pyrido[1,2-*b*][2,7]naphthyridin-5[7*H*]one] 252a

A solution of amidine 251a (250 mg) in dioxane (30 mL) and 20%

KOH solution (aq., 10 mL) was gently heated under reflux for 48 h and the progress of the reaction was monitored by tlc. The mixture was then evaporated *in vacuo*, the residue treated with water (50 mL) and the solution thoroughly extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with brine, dried ($MagSO_4$ anhyd.) and solvent removed *in vacuo* affording lactam **252a** (223 mg, 89%); mp 125-127°C (EtOAc); R_f. 0.52 (alumina, EtOAc); ir ($CHCl_3$, film), ν_{max}: 1655 cm^{-1}; ^1H nmr (500 MHz), δ: 2.86-3.07 (5H, complex m, C-7 H_{ax}, C-8, and C-14 H's), 4.97 (1H, apparent d, J=12.5 Hz, C-13b H), 5.21-5.23 (1H, m, C-7 H_{eq}), 5.35 (2H, s, $-NCH_2Ar$), 6.94 (1H, d, J=4.9 Hz, C-1 H), 7.00-7.02 (2H, d, J=6.9 Hz, aromatic H's), 7.18-7.33 (6H, complex m, aromatic H's), 7.62 (1H, m, aromatic H), 8.60 (1H, d, J=4.9 Hz, C-2 H), and 9.26 (1H, s, C-4 H); ^{13}C nmr (125.76 MHz), δ: 21.6 (C-8), 36.0 (C-14), 39.6 (C-7), 47.6 ($-NCH_2Ar$), 51.8 (C-13b), 111.3, 118.9, 120.3, 121.5, 122.8, 126.0, 126.0, 128.0, 129.3, 129.3, 150.4 and 152.3 (12 x ArCH's), 110.1, 124.9, 126.9, 133.1, 137.2, 138.2 and 145.1 (7 x ArC's), and 163.6 (>C=O); ms (EI), m/z (%): 379 (63), 378 (10), 288 (35), 287 (9), 261 (2), 260 (7), 259 (13), 169 (5), 168 (5), 119 (14), and 91 (100); Exact mass (hrms): calcd. for $C_{25}H_{21}N_3O$: 379.168, found: 379.165; calcd. for fragment ion $C_{18}H_{14}N_3O$ ($M-CH_2C_6H_5$): 288.114; found: 288.112.

(b) 1-Benzyl-3,14-dihydroangustine[13-Benzyl-1-ethenyl-8,13,13b,14-tetrahydroindolo[2',3':3,4]pyrido[2,1-*b*][2,7]naphthyridin-5[7*H*]-one **252b**

The hydrolysis of amidine **251b** (300 mg) was carried out in a similar manner to that described above for amidine **251a** yielding lactam

252b (283 mg, 94%); mp 226-230°C (EtOH); R_f. 0.35 (alumina, EtOAc); ir ($CHCl_3$, film), ν_{max}: 1650 cm^{-1}; ^1H nmr (500 MHz), δ: 2.60 (1H, dd, J=16.6 and 13.0 Hz, C-7 (H_{ax}), 2.93-3.06 (3H, complex m, C-8 and C-14 H's), 3.25 (1H, dd, J=16.6 and 3.4 Hz, C-14 H), 4.95 (1H, d, J=11.8 Hz, C-13b H), 5.19 (1H, d, partially overlapped by C-7 H_{eq} signal, J=11.2 Hz, $-CH=\underline{CH_2}$), 5.27 (1H, m, C-7 H_{eq}), 5.27 (1H, d, J=17.6 Hz, $-CH=\underline{CH_2}$), 5.46-5.52 (2H, m, four lines, $-NCH_2Ar$), 6.02 (1H, dd, J=17.6 and 11.2 Hz, $-\underline{CH}=CH_2$), 7.04 (2H, d, J=6.6 Hz, aromatic H's), 7.06-7.35 (6H, complex m, aromatic H's), 7.63-7.65 (1H, m, aromatic H), 8.67 (1H, s, C-2 H), and 9.17 (1H, s, C-4 H); ^{13}C nmr (125.76 MHz), δ: 21.6 (C-8), 32.9 (C-14), 39.6 (C-7), 47.5 ($-NCH_2Ar$), 51.4 (C-13b), 109.9, 118.9, 120.4, 123.0, 125.9, 125.9, 127.8, 129.3, 129.3, 149.4, and 150.1 (11 x ArCH's and $-\underline{CH}=CH_2$), 111.1, 119.7, 124.5, 126.4, 130.4, 133.1, 137.4, 138.5, and 142.0 (8 x ArC's and $-CH=\underline{CH_2}$), and 163.8 (>C=O); ms (EI), m/z (%): 405 (61)$M^{+\cdot}$, 404 (9), 314 (32), 313 (7), 261 (4), 260 (11), 259 (8), 169 (6), 168 (5), 145 (3), 117 (13), and 91 (100); Exact mass (hrms): calcd. for $C_{27}H_{23}N_3O$: 405.184, found: 405.183, calcd. for fragment ion $C_{20}H_{16}N_3O$ ($M-CH_2C_6H_5$): 314.129, found: 314.123.

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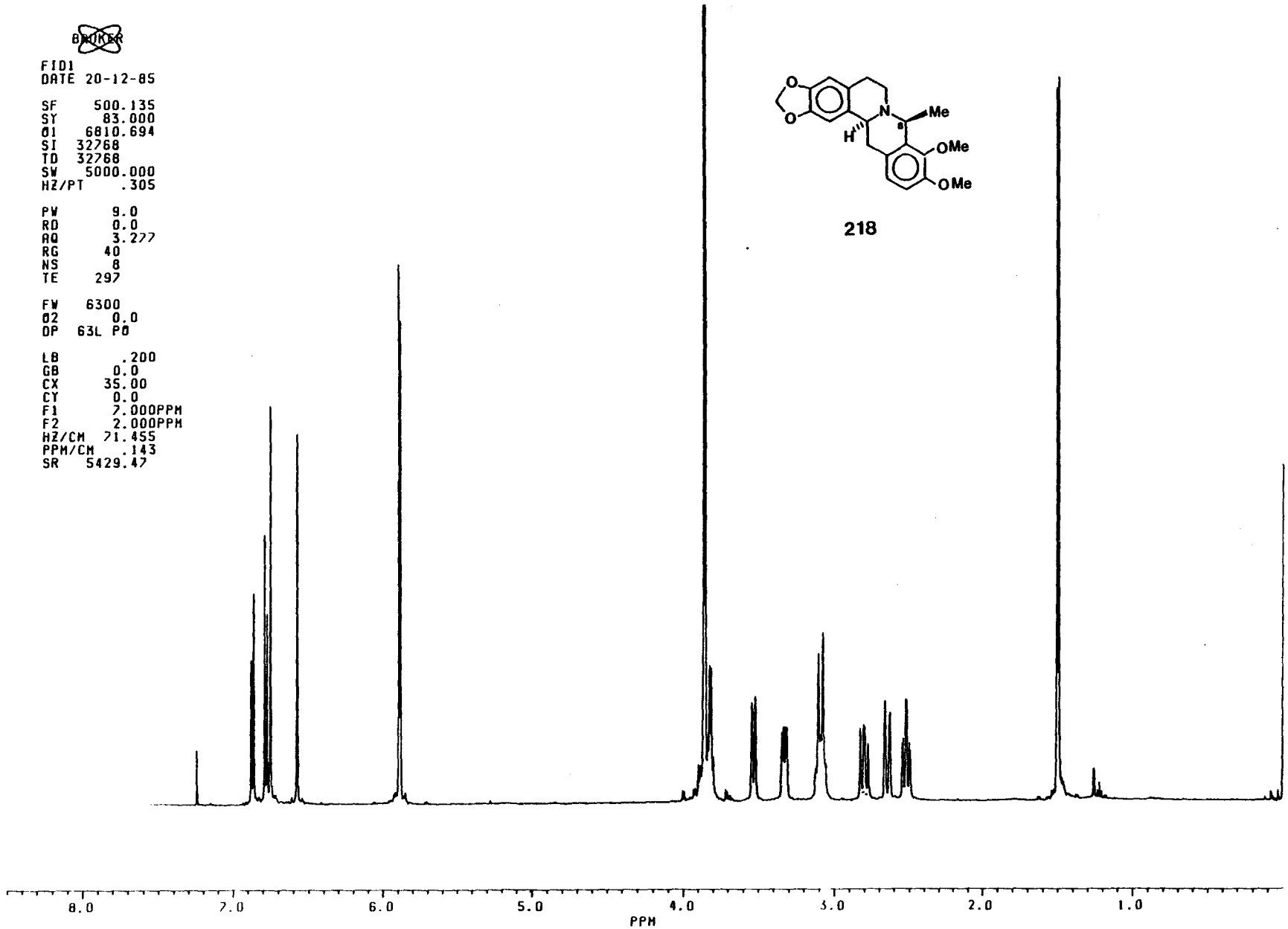
APPENDIX

LIST OF SPECTRA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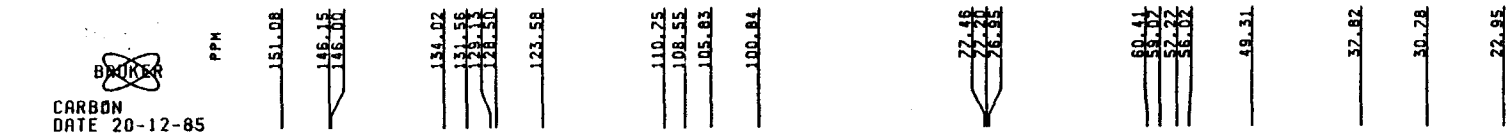

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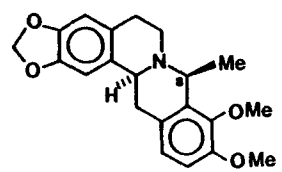

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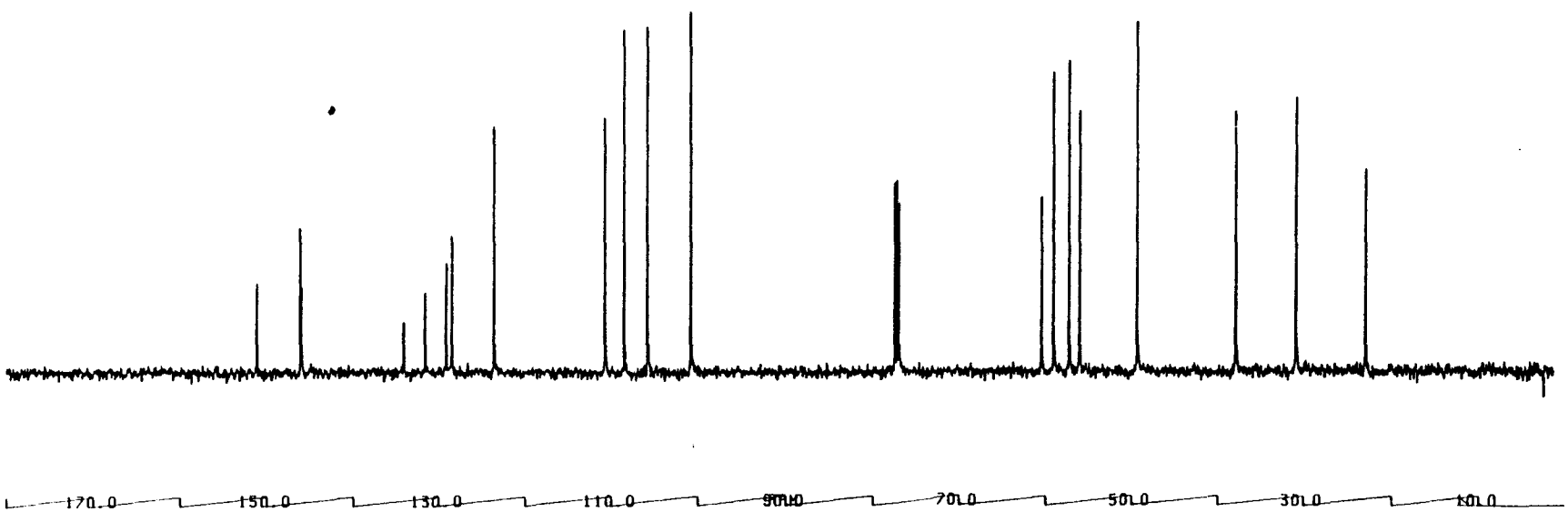

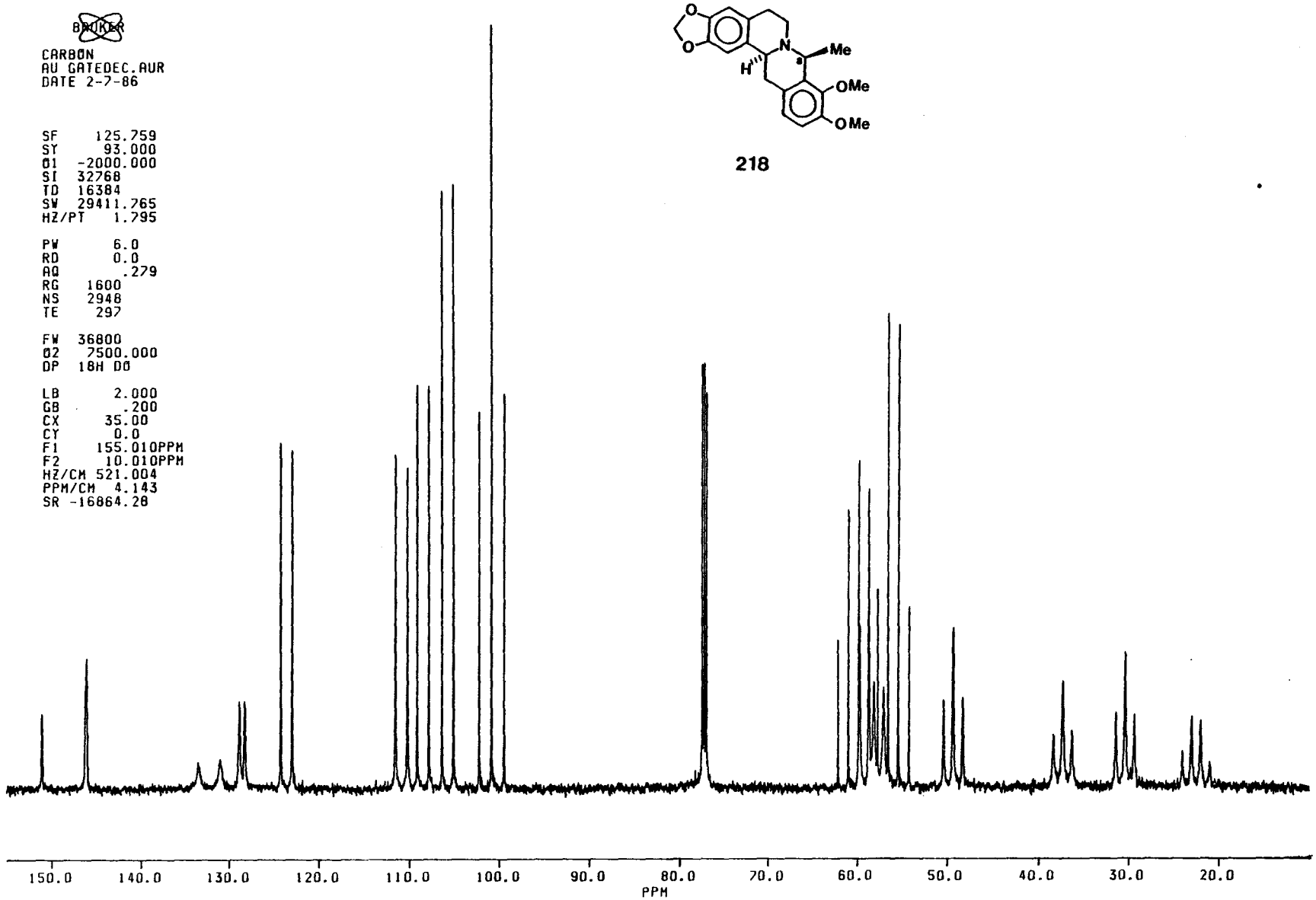
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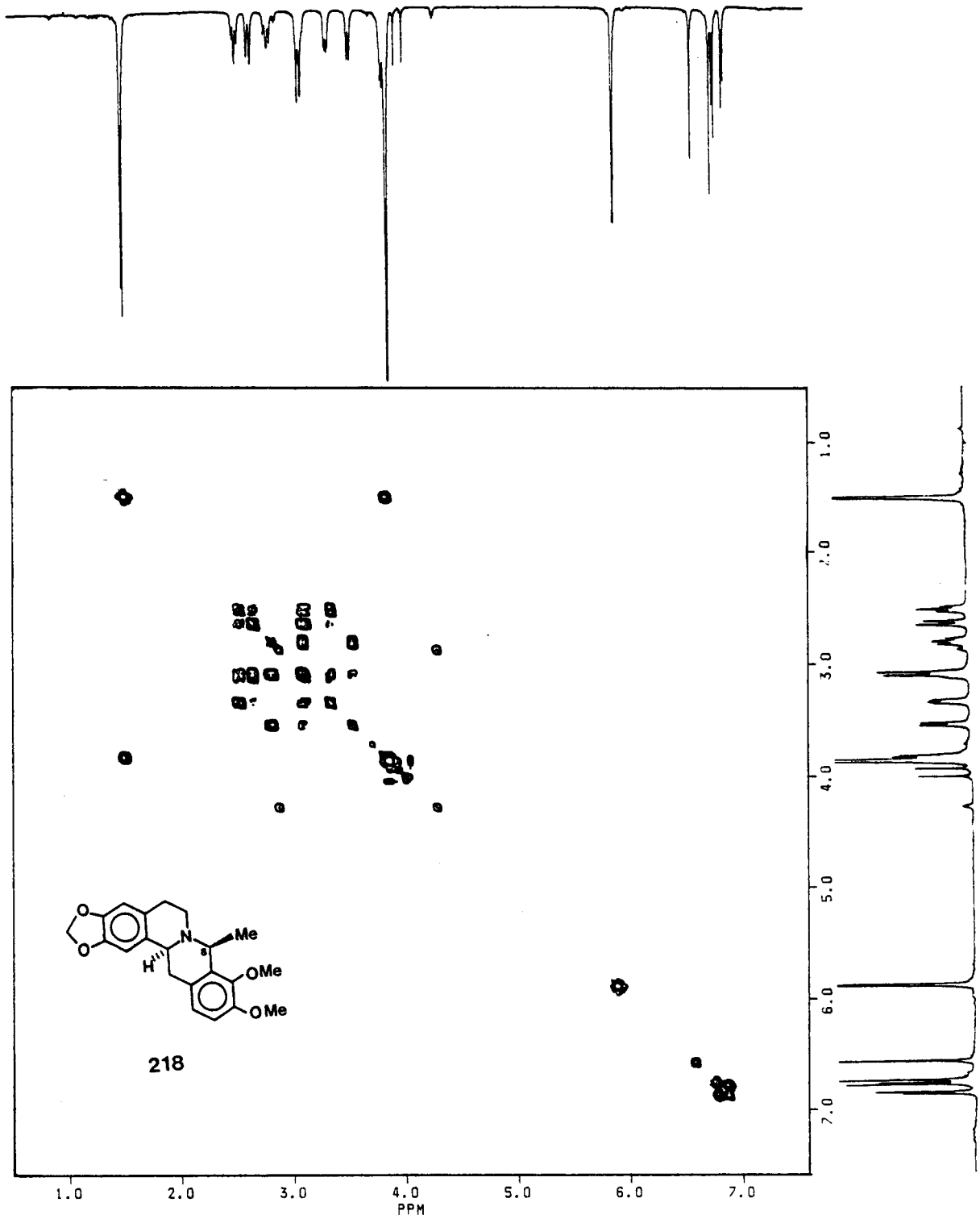

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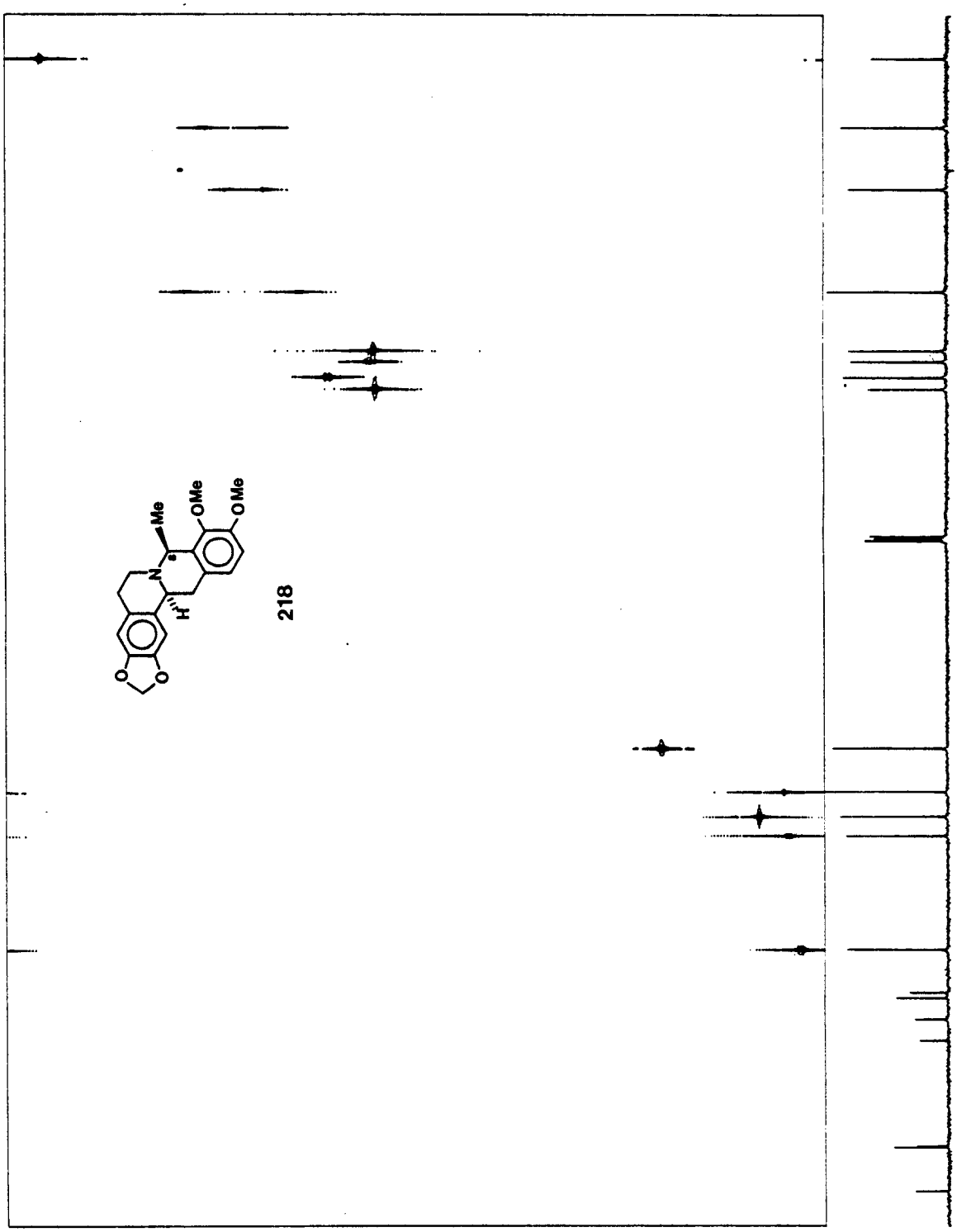
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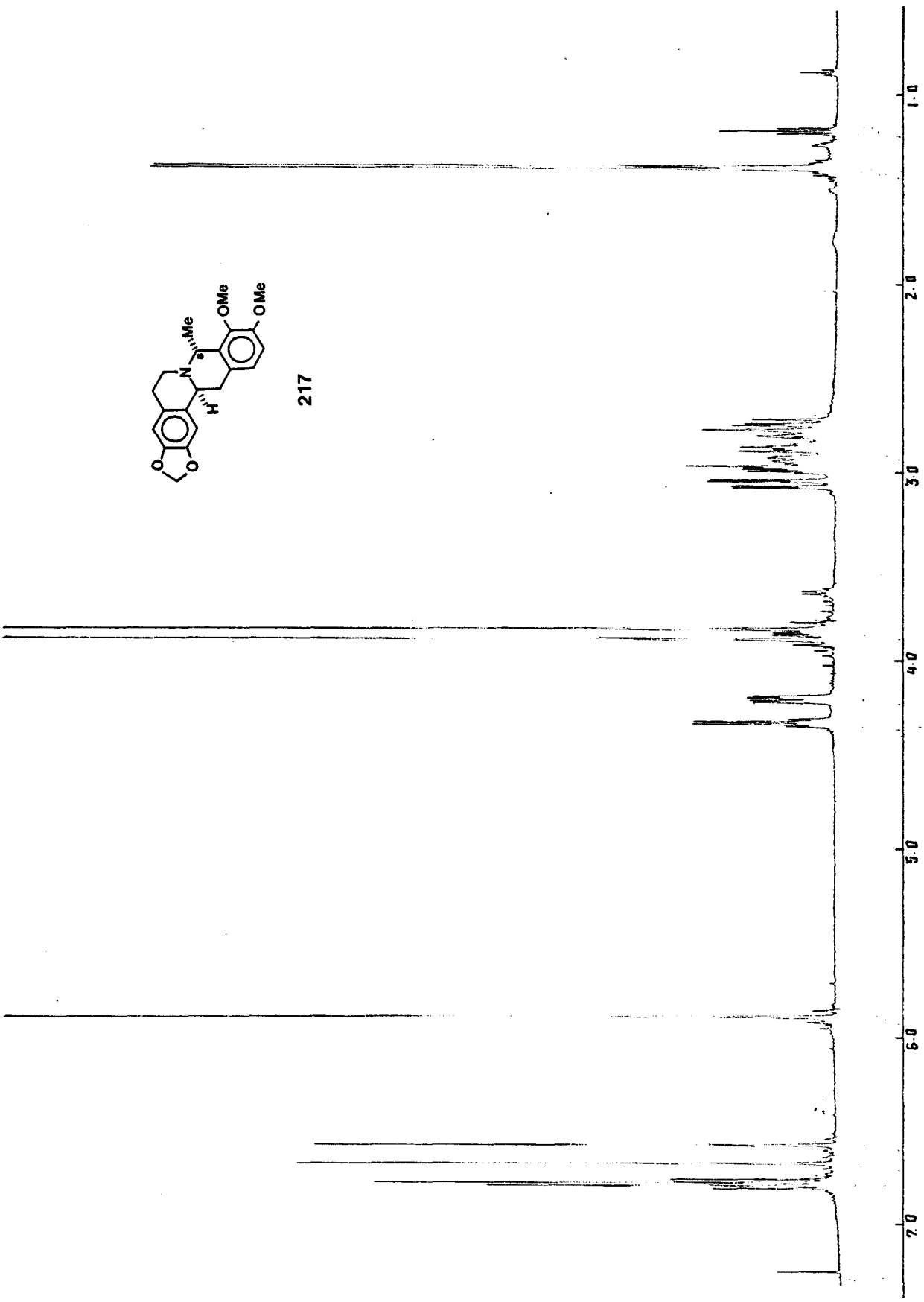
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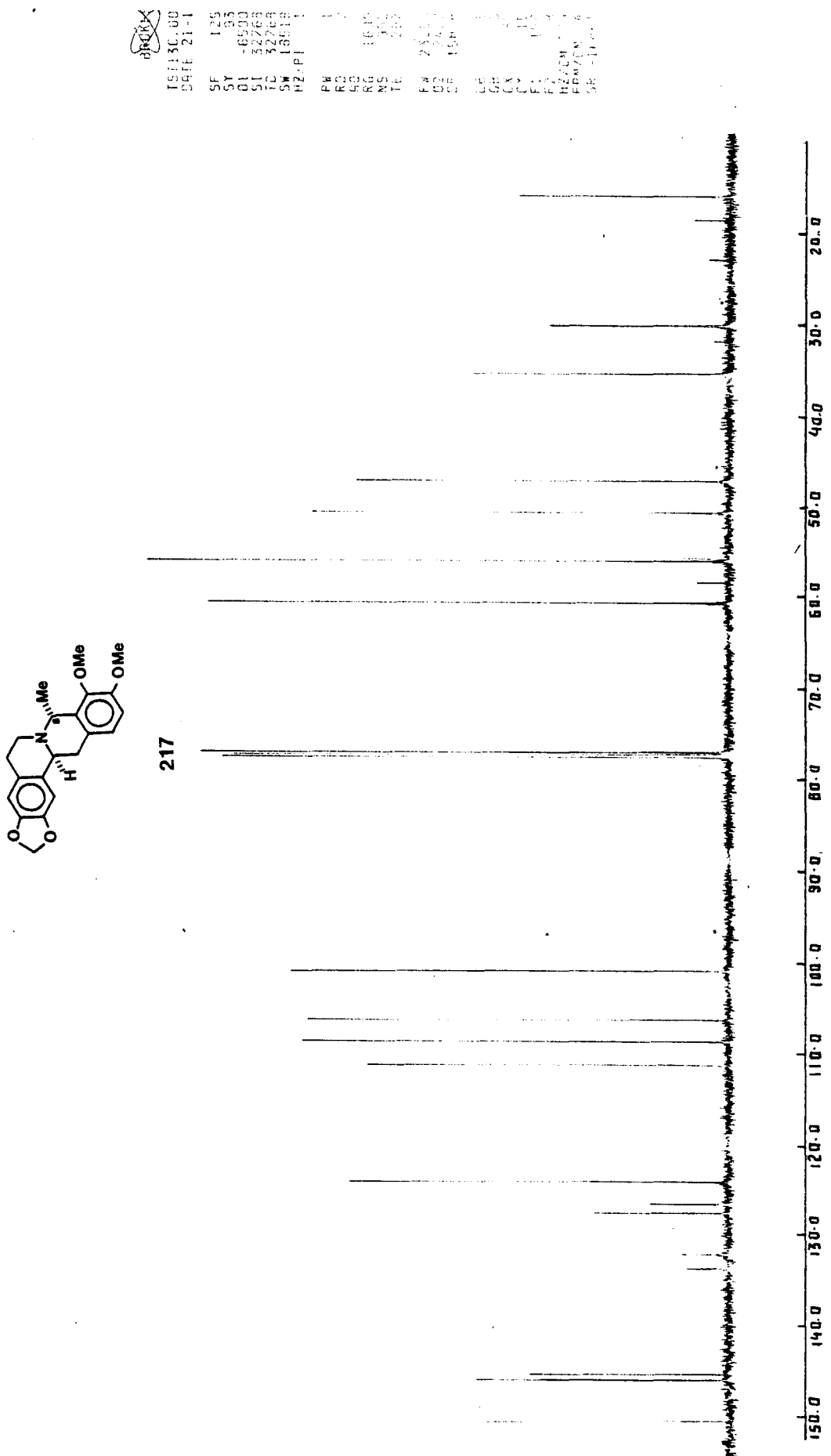
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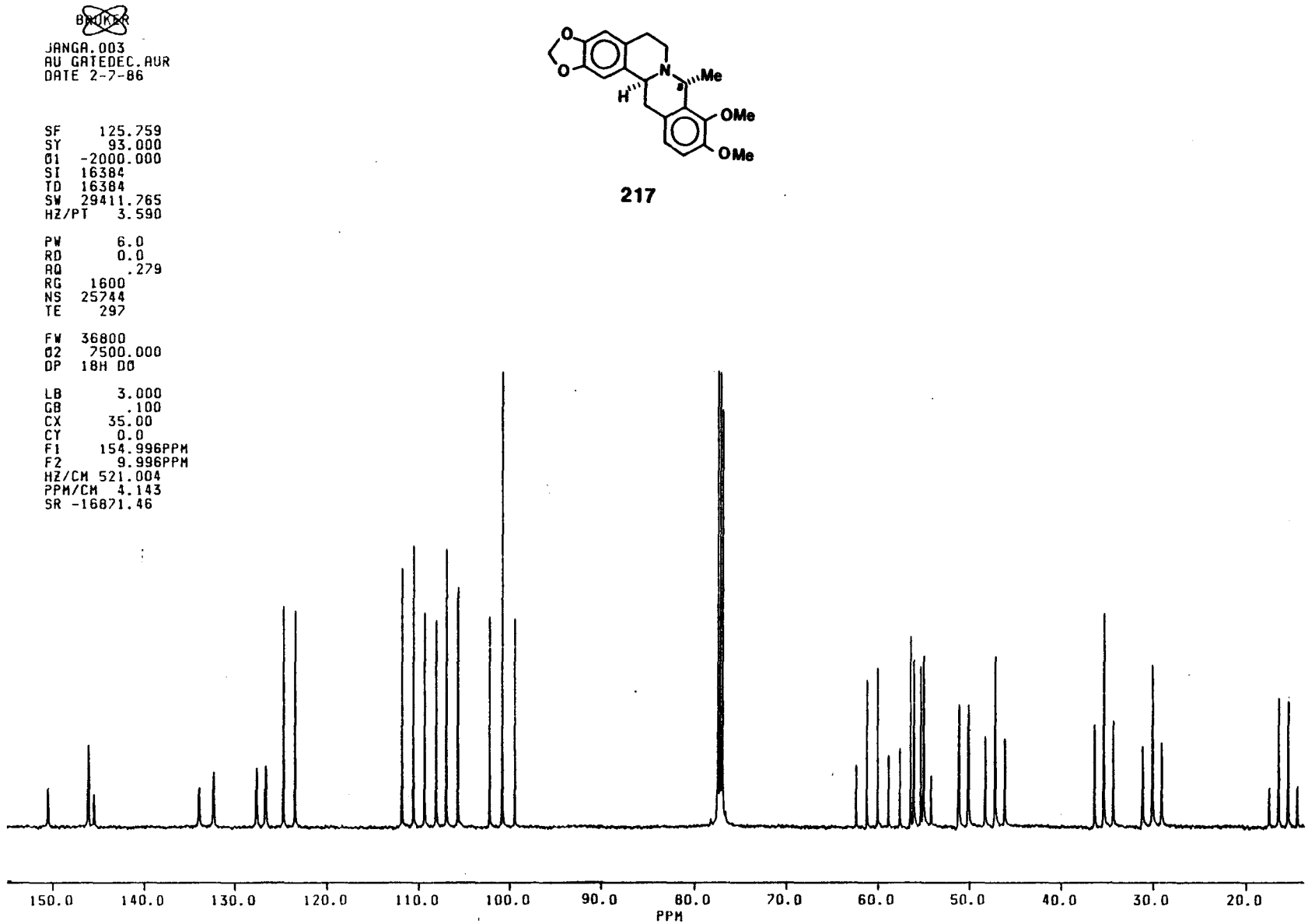
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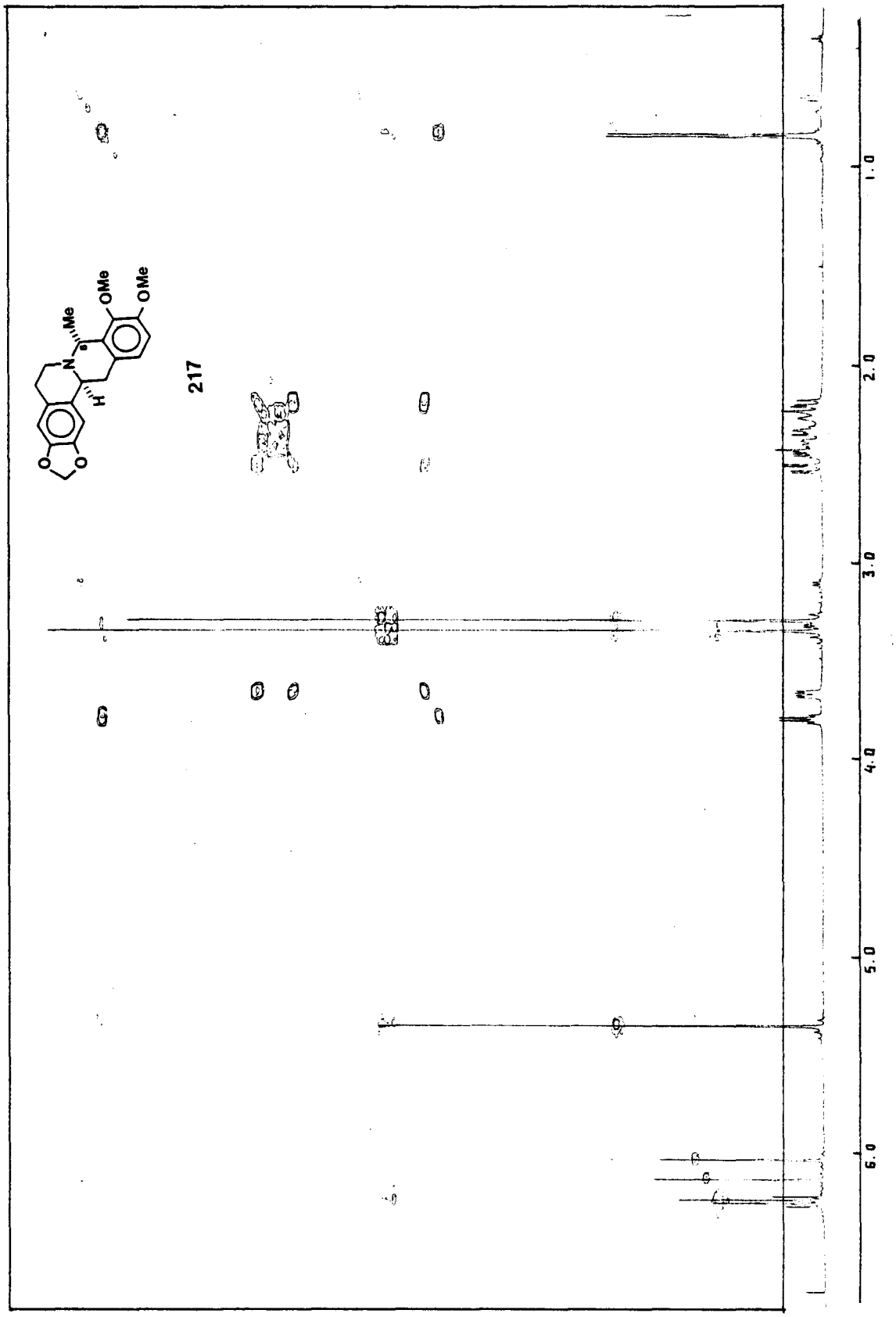
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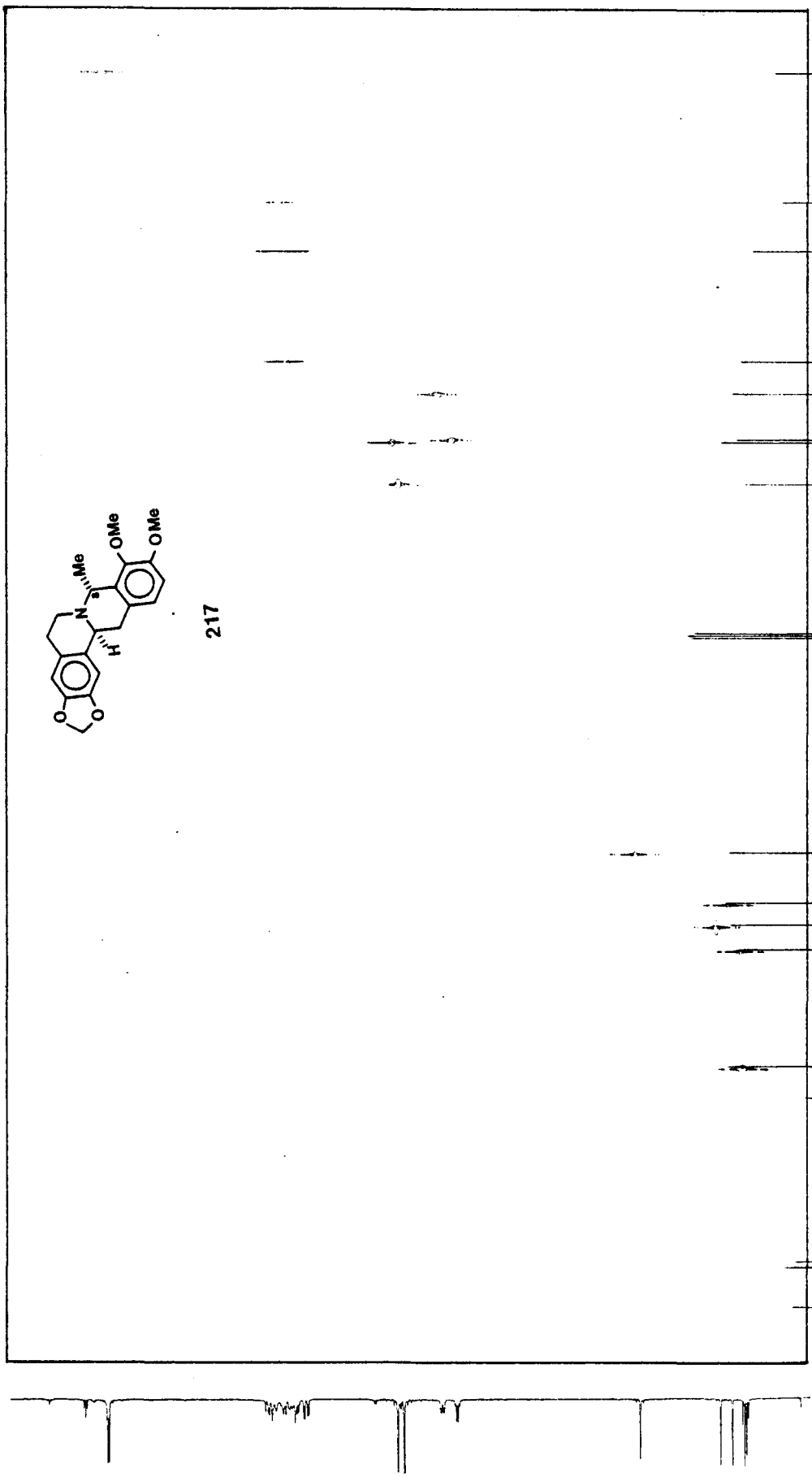
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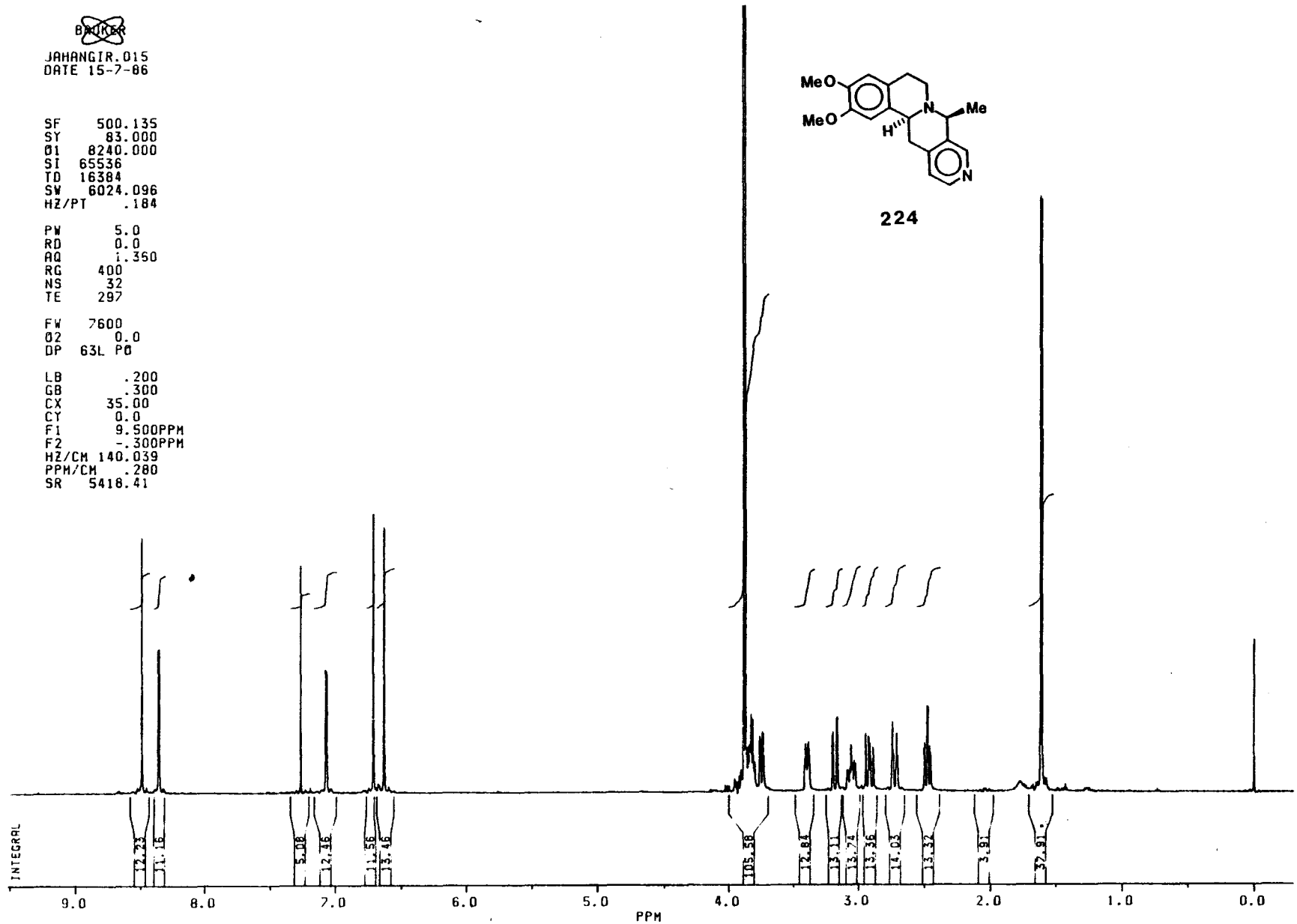
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SI 65536
TD 16384
SW 6024.096
HZ/PT .184
PW 5.0
RD 0.0
AQ 1.350
RG 400
NS 32
TE 297
FW 7600
02 0.0
DP 63L PO
LB .200
GB .300
CX 35.00
CY 0.0
F1 9.500PPM
F2 -.300PPM
HZ/CM 140.039
PPM/CM .280
SR 5418.41
MeO
MeO
N
Me
H
N
224
INTEGRAL
12.23
11.16
5.08
12.46
11.56
13.46
105.58
12.84
13.11
13.74
13.36
14.03
13.32
3.91
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5.0
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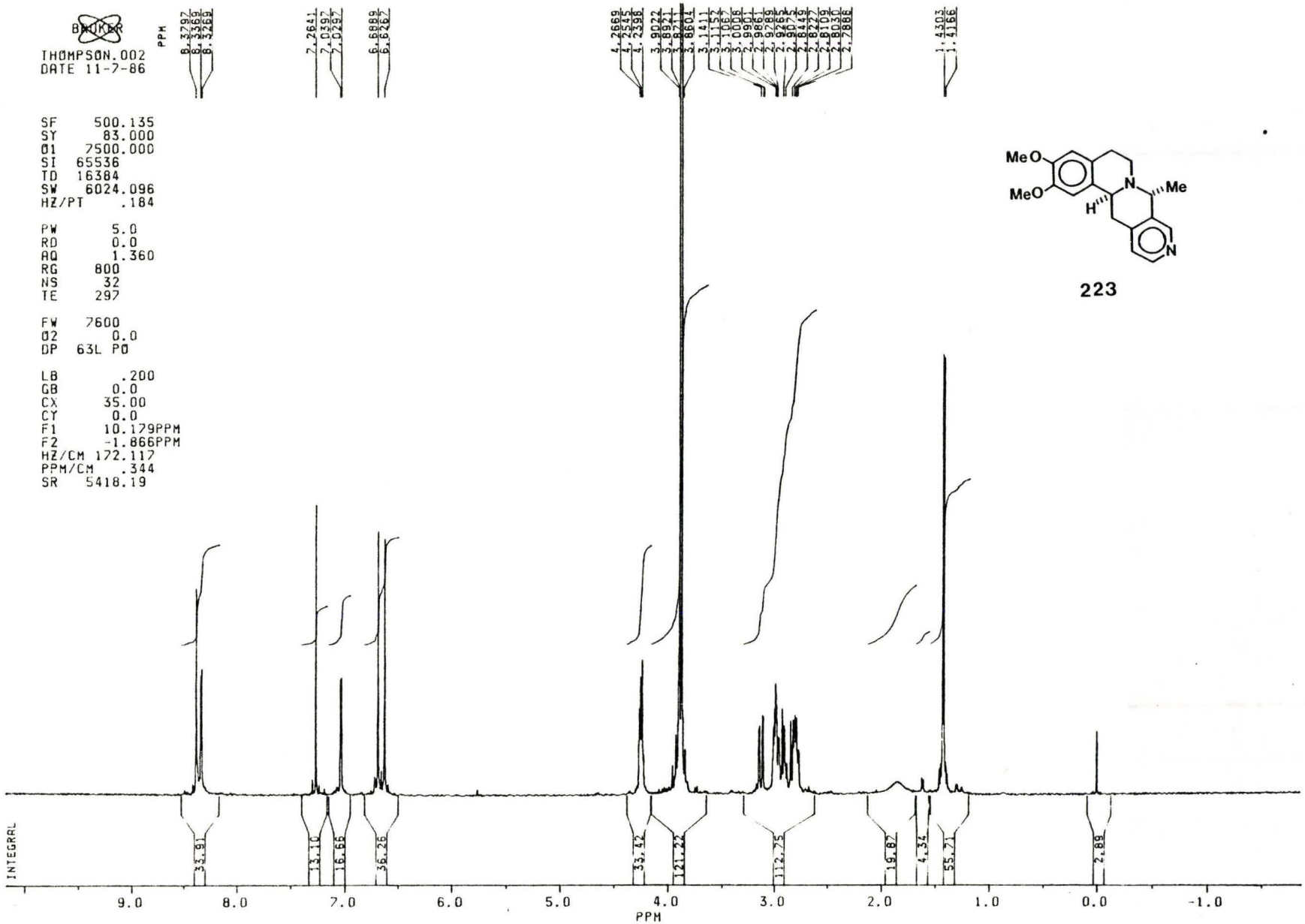
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THOMPSON.002
DATE 11-7-86
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SY 83.000
01 7500.000
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TD 16384
SW 6024.096
HZ/PT .184
PW 5.0
RD 0.0
AQ 1.360
RG 800
NS 32
TE 297
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PPM/CM .344
SR 5418.19
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16.66
36.26
33.42
121.22
112.75
19.87
4.34
55.71
2.89
9.0
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7.0
6.0
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PPM

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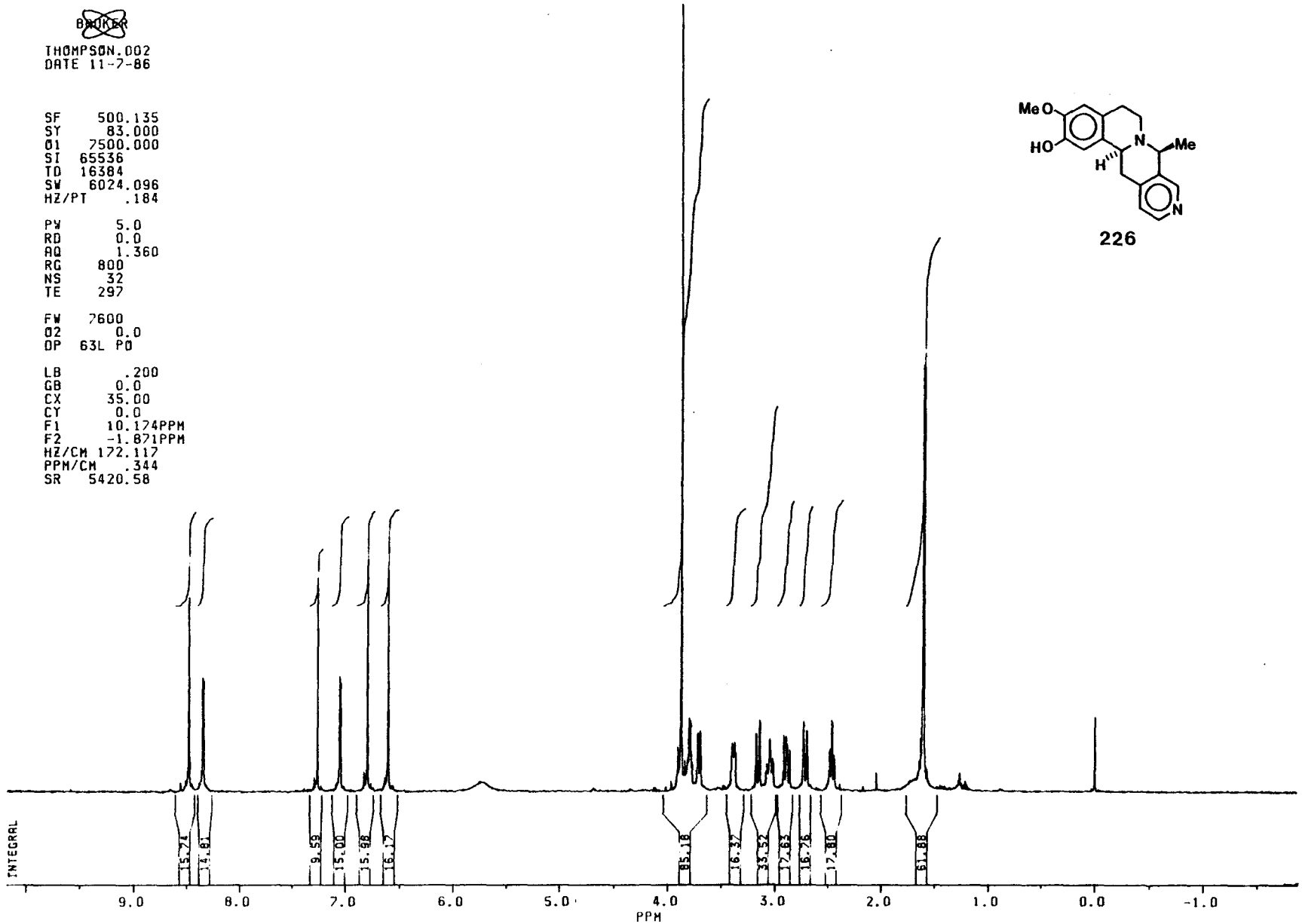
N

223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DATE 11-7-86
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PW 5.0
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AQ 1.360
RG 800
NS 32
TE 297
FW 7600
02 0.0
OP 63L PO
LB .200
GB 0.0
CX 35.00
CY 0.0
F1 10.174PPM
F2 -1.871PPM
HZ/CM 172.117
PPM/CM .344
SR 5420.58
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HO
N
Me
H
N
226
INTEGRAL
15.74
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15.00
15.98
16.17
85.18
16.32
33.52
17.63
16.76
17.80
61.88
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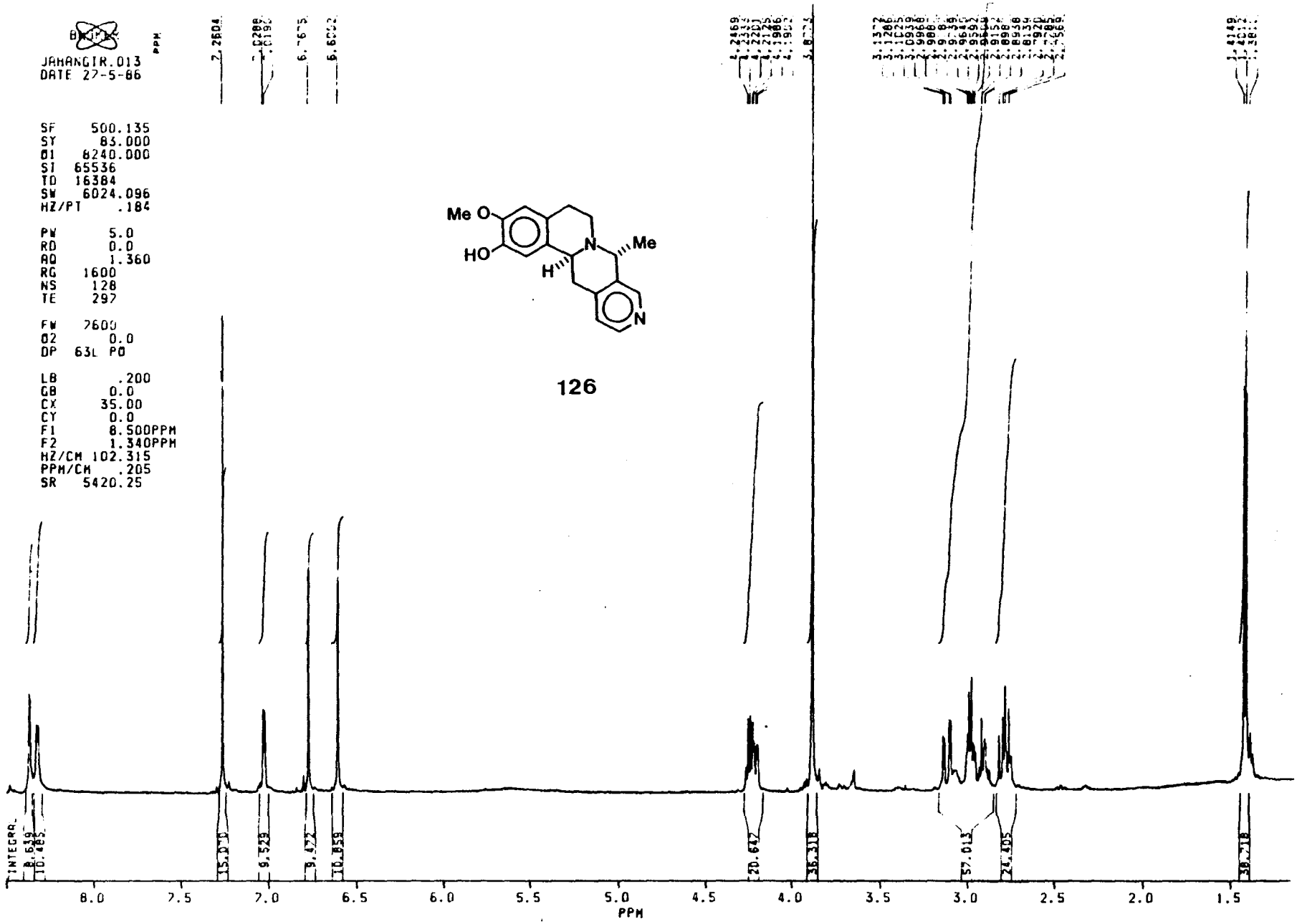
-1.0
PPM


JAHANGIR.013
DATE 27-5-86
SF 500.135
SY 85.000
01 8240.000
SI 65536
TD 16384
SW 6024.096
HZ/PT .184
PW 5.0
RD 0.0
AQ 1.360
RG 1600
NS 128
TE 297
FW 7600
02 0.0
DP 63L PD
LB .200
GB 0.0
CX 35.00
CY 0.0
F1 8.500PPM
F2 1.340PPM
HZ/CM 102.315
PPM/CM .205
SR 5420.25
Me O
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N
Me
H
N
126
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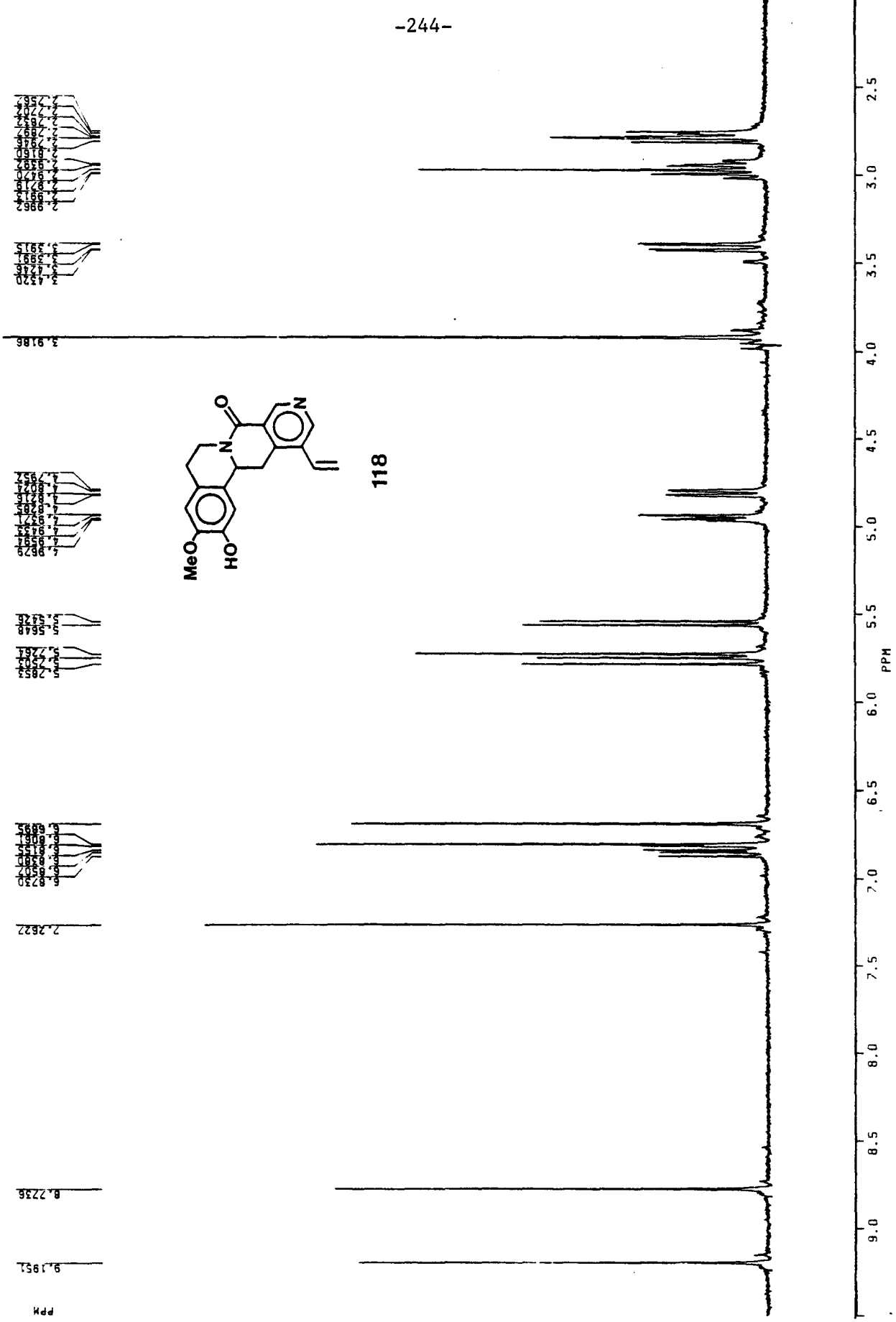
PPM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118
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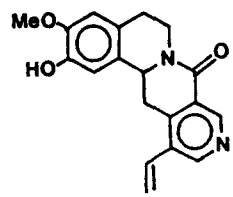
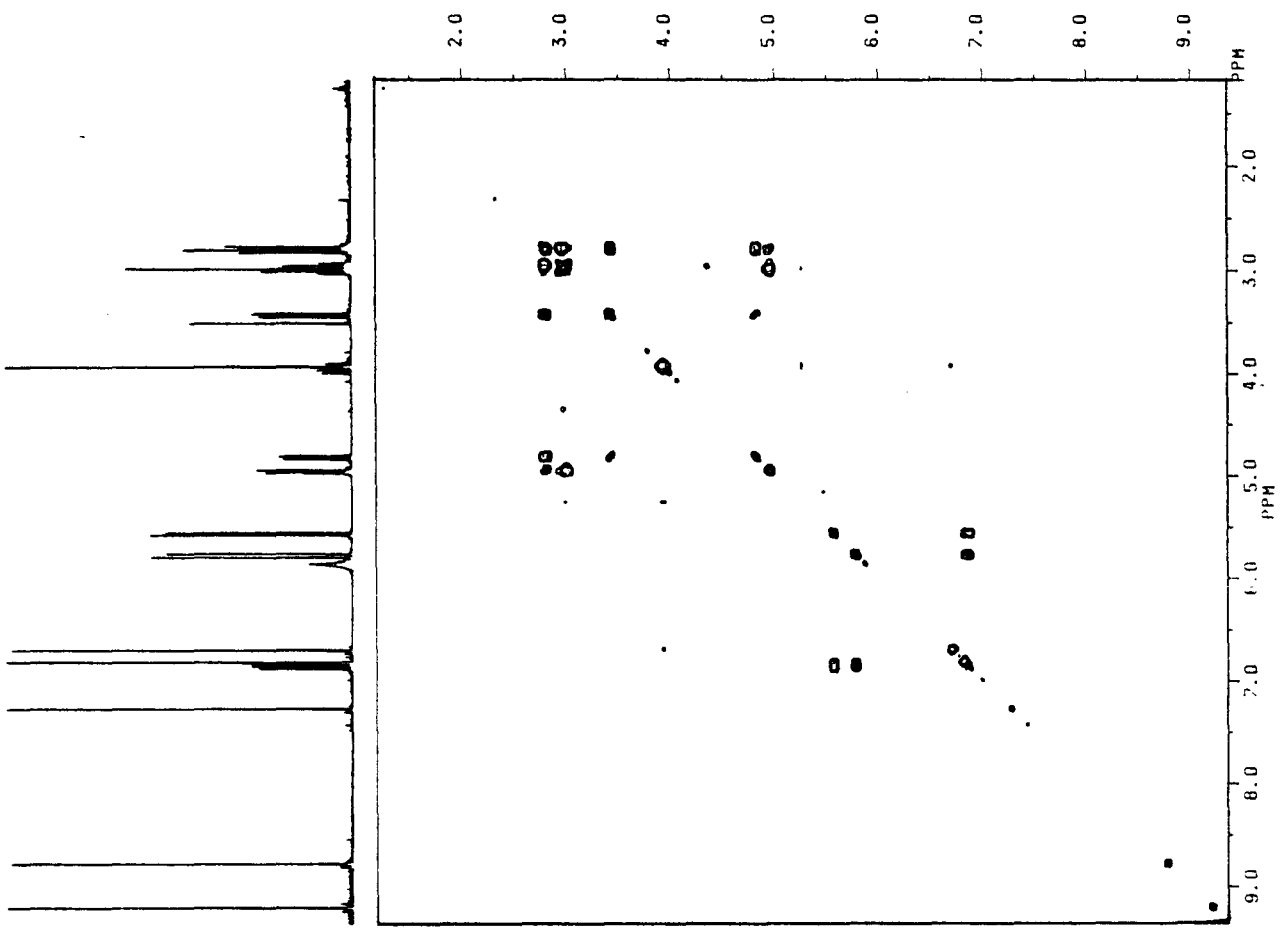
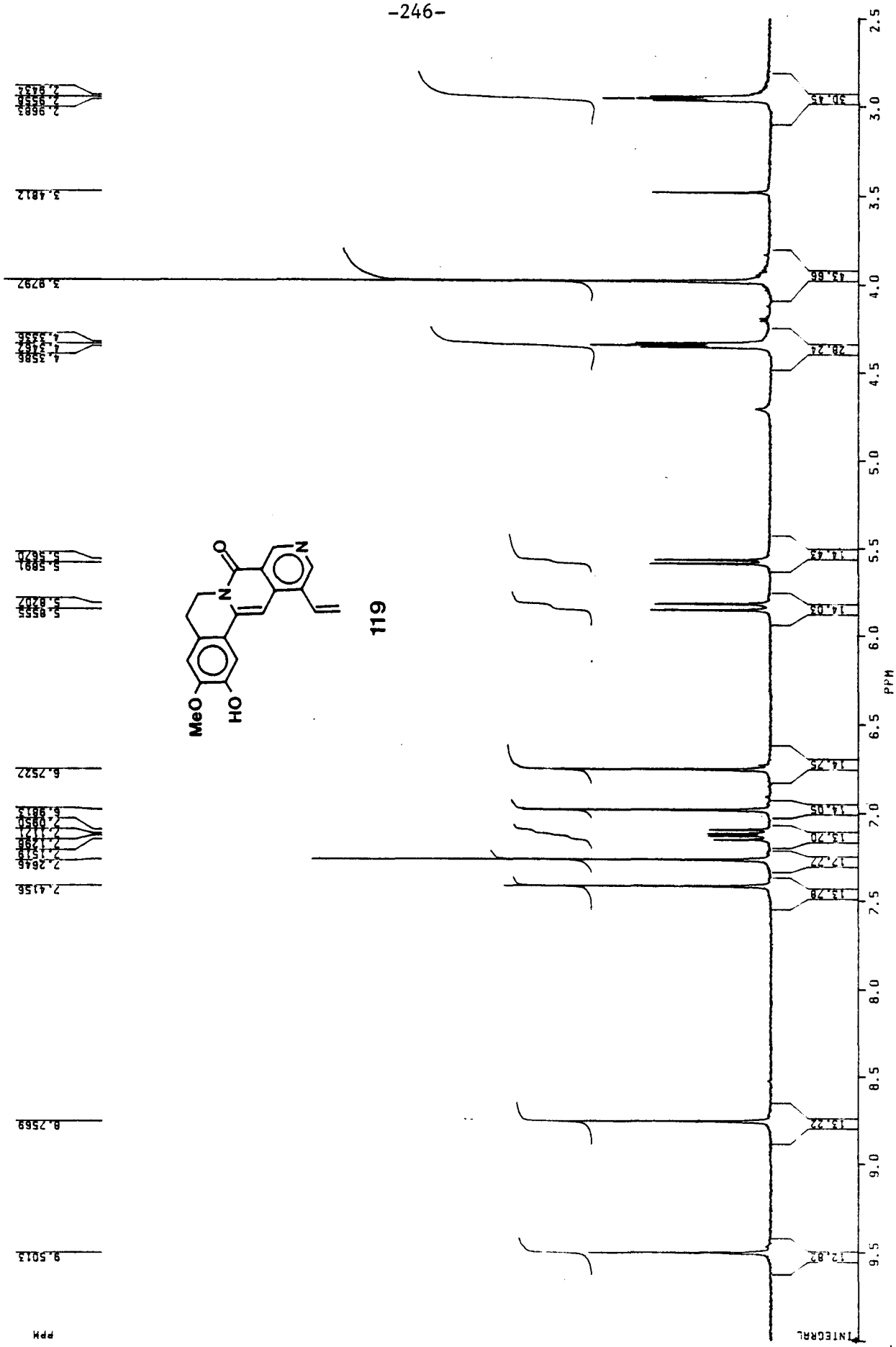


118




MeO
HO
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O
119
PPM
INTEGRAL