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ASYMMETRIC SYNTHESIS OF ISOQUINOLINE ALKALOIDS : (R)- AND (S)-2-ETHOXYCARBONYL-1-FORMYL-6,7-DIMETHOXY-1,2,3,4-TETRAHYDROISOQUINOLINE AS VERSATILE PRECURSORS

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ABSTRACT

A method is described for the preparation of (R)- and (S)-2-ethoxycarbonyl-1-formyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline involving a Swern-type oxidation of (R)- and (S)-2-ethoxycarbonyl-1-hydroxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline {(R)- and (S)-2-(ethoxycarbonyl)calycotomine}. The utility of these aldehydes in asymmetric synthesis of isoquinoline alkaloids has been demonstrated by their conversion into (S)- and (R)-xylopinine, respectively; also, the (R)-aldehyde has been employed for the synthesis of (8S,14S)-coralydine.

INTRODUCTION

The isoquinoline alkaloids are a large group of compounds found in a variety of plant families (1,2). Many of them are physiologically active and a large number are pharmacologically useful. The synthesis of the racemic alkaloids has been extensively investigated but it is only in the past two decades that serious effort has been applied to the asymmetric synthesis of the optically active alkaloids (3). Many of the alkaloids are 1,2,3,4-tetrahydroisoquinolines, or contain this unit within their structures, and carry a substituent at C-1 making this a chiral centre. The 1-benzyl-1,2,3,4-tetrahydroisoquinolines are widely distributed and serve as biosynthetic precursors of many of the other ring systems present in this family of alkaloids. It is not surprising therefore that much of the research on asymmetric synthesis of the isoquinolines has focused on the induction of asymmetry at C-1 of the tetrahydroisoquinoline system.

Three basic approaches have been applied in the enantioselective synthesis of the tetrahydroisoquinolines substituted at C-1. The first of these involved the reduction of 1-substituted 3,4-dihydroisoquinolines or the corresponding quaternary salts. Several examples of the reduction of 3,4-dihydroisoquinolines with chiral reducing agents have been reported (4-6); however, the optical yields were variable and the highest were of the order of 70% ee. 3,4-Dihydroisoquinolinium salts bearing a chiral alkyl group on nitrogen have

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been prepared and reduced catalytically with hydrogen (7), but again the optical yields were not high (15-44% ee).

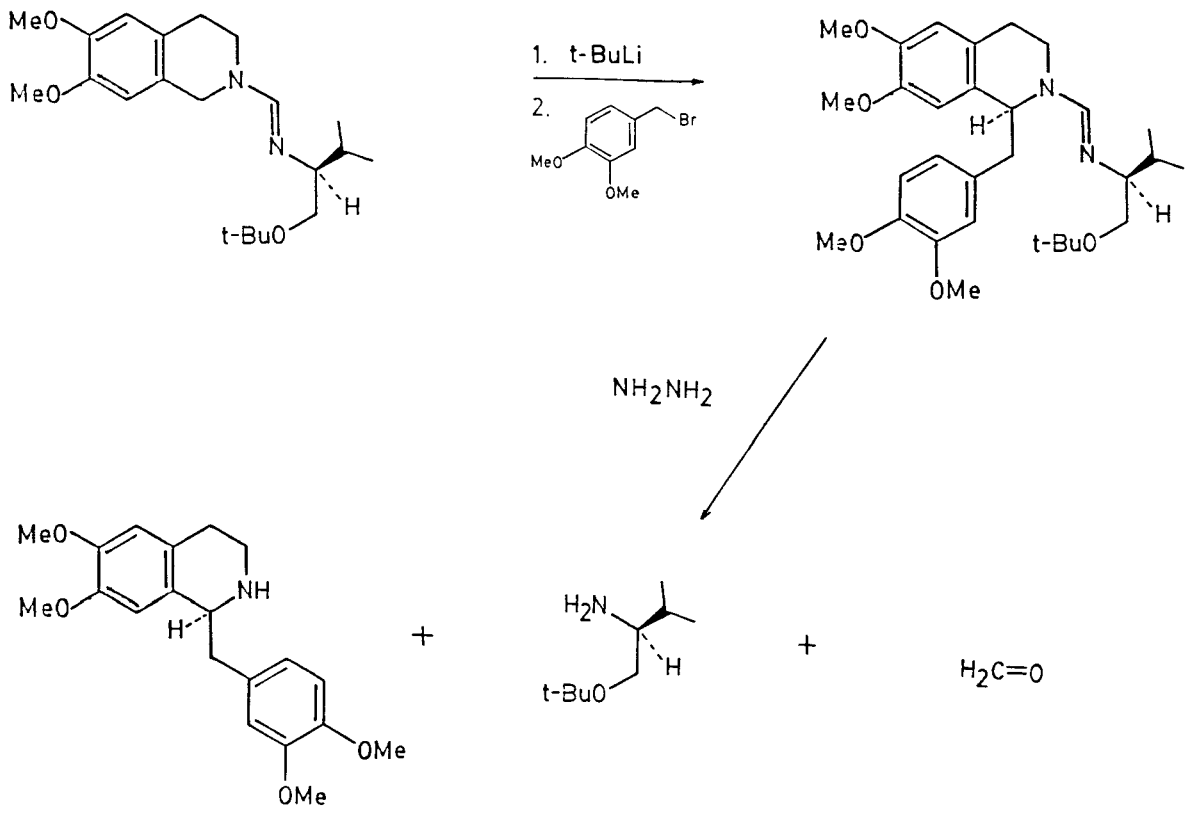
The second and most recent approach involves the alkylation of 1-metallo-1,2,3,4-tetrahydroisoquinolines in which the nitrogen atom of the isoquinoline has been incorporated into a chiral amidine function. This approach, illustrated in Scheme 1, has been developed by the group of A.I. Meyers (8a-f) and has been recently reviewed (8a,b). The alkylation proceeds with high enantioselectivity (>90%) and the chiral auxiliary is easily removed, and recovered, without loss of optical purity.

The third general method, and the one that has been studied most extensively, is the use of the Pictet-Spengler condensation or a related condensation. To induce asymmetry at C-1, an imine is used, or formed *in situ*, that contains a chiral centre either in the portion of the molecule derived from the amine or in the portion derived from the aldehyde.

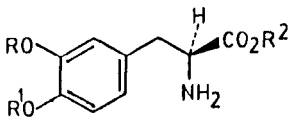
The use of enantiomerically pure amino acids as the amine component in the Pictet-Spengler synthesis of alkaloids has been investigated by S. Yamada and coworkers (9). In the case of the isoquinolines, (S)-(-)-(3,4-dihydroxyphenyl)alanine (L-dopa) (I) was used as starting material in the synthesis of (S)-(+)-(10) and (R)-(-)-laudanosine (11) (II and III, respectively) and of (S)-(+)-reticuline (3',7-des-O-methyl-(S)-laudanosine) (12) (IV). In practice, the methyl ester (V) of L-dopa as its hydrochloride was condensed with sodium (3,4-dimethoxyphenyl)glycidate (VI) (a (3,4-dimethoxyphenyl)acetaldehyde synthetic equivalent) to yield a separable mixture of diastereomeric products in which the (1S,3S) isomer (VII) was formed in preference to the (1R,3S) isomer (VIII) in a ratio of 2.3:1 (Scheme 2). Isomer VII, after O- and N-methylation to afford IX, was transformed into (S)-(+)-laudanosine. A key step in the synthesis was the development of a method for removal of the ester group at C-3. This operation was accomplished by way of conversion of the ester into the amide and then into the nitrile; treatment of the nitrile with sodium borohydride resulted in a clean replacement of the CN group by H (9a) to afford II. Compound X was converted similarly into III. Also, (S)-(+)-reticuline was prepared in an analogous fashion using suitably protected precursors. These syntheses provide examples of 1,3-transfer of asymmetry. The process may be referred to as a sacrifical asymmetric synthesis (13) in the sense that the chiral centre in the starting amine has been eliminated in proceeding to product.

Another example of the use of a chiral amine in a Pictet-Spengler condensation has been provided by Brossi and coworkers (14,15). It was found that the condensation of L-dopa (I) with acetaldehyde yielded the (1S,3S)-tetrahydroisoquinoline derivative (XI) (Scheme 3) in 90% ee. (This compound is a naturally-occurring substance (16)). Dean and Rapoport (17) used XI as an intermediate in a stereoselective synthesis of O-methylcorytenchirine (XV) as outlined in Scheme 3. Compound XI was converted in good yield and without loss of enantiomeric purity into XII. Alkylation of XII at nitrogen afforded XIII, which was converted into the unisolated intermediate iminium salt XIV; the salt cyclized stereospecifically to O-methylcorytenchirine (XV).

In this laboratory (18,19) we have condensed (R)-(+)-glyceraldehyde of high enantiomeric purity with dopamine hydrochloride in a Pictet-Spengler reaction. The condensation product was a separable mixture of diastereomers, with


MeO
MeO
N
N
H
t-BuO
1. t-BuLi
2.
Br
MeO
OMe
MeO
MeO
H
N
N
H
MeO
OMe
t-BuO
NH2NH2
MeO
MeO
NH
H
OMe
OMe
+
H2N
H
t-BuO
+
H2C=O

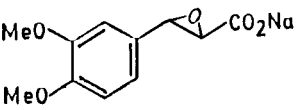
SCHEME 1



I $R = R^1 = R^2 = H$

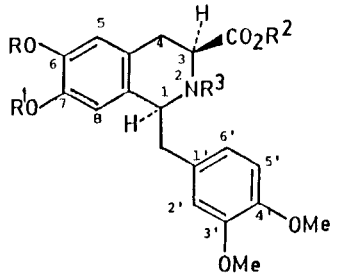
V $R = R^1 = H$, $R^2 = Me$

+



VI

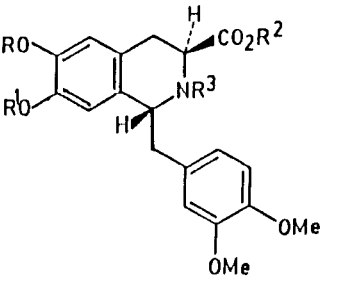
pH 4
35°C



VII $R = R^1 = R^3 = H$, $R^2 = Me$

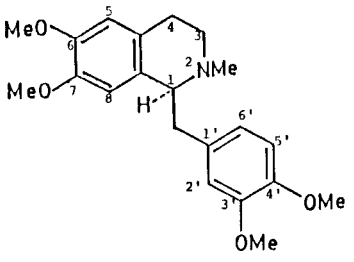
IX $R = R^1 = R^2 = R^3 = Me$

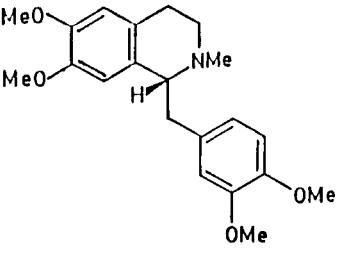
+



VIII $R = R^1 = R^3 = H$, $R^2 = Me$

X $R = R^1 = R^2 = R^3 = Me$



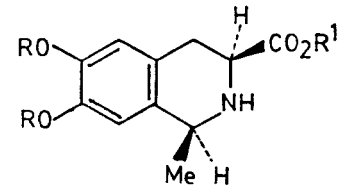


II (S)-(+)-Laudanosine

III (R)-(-)-Laudanosine

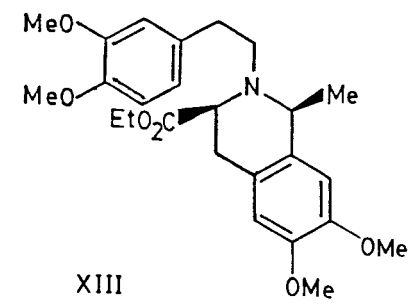
IV (S)-(+)-Reticuline {3',7-des-O-methyl-(S)-laudanosine}

SCHEME 2

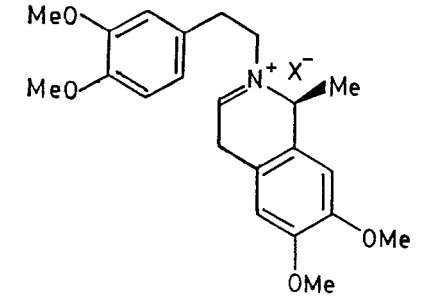


XI $R = R^1 = H$

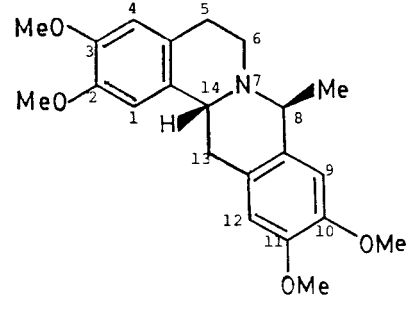
XII $R = Me$, $R^1 = Et$



XIII



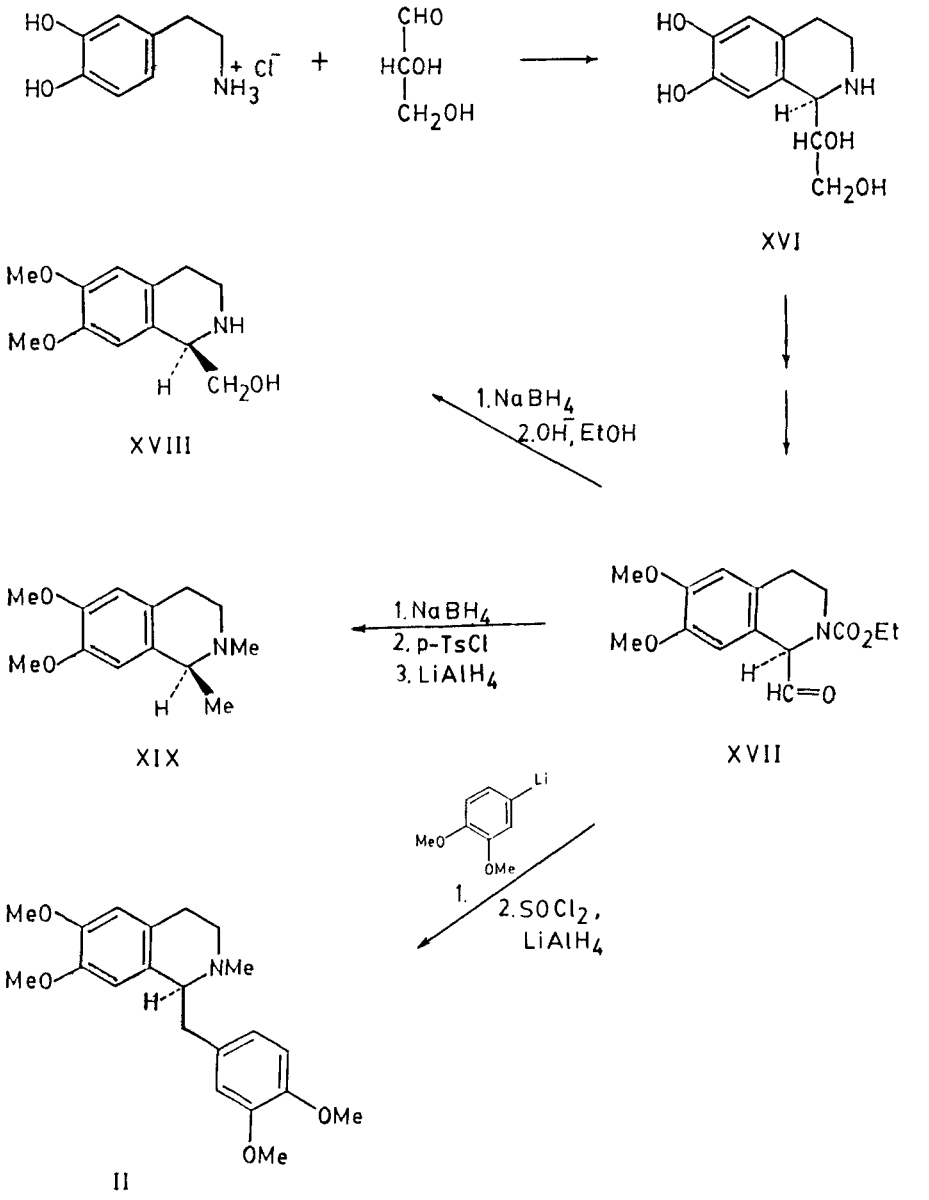
XIV



XV O-Methylcorytenchirine

SCHEME 3

the (R)-isomer at C-1 (XVI) being formed in preference to the (S)-isomer in a ratio of 9:1 (Scheme 4). In a series of steps, XVI was transformed into the aldehyde XVII that was converted as shown in Scheme 4 into (R)-(-)-calycotomine (XVIII), (S)-(-)-cargnegine (XIX) and (S)-(+)-laudanosine (II).



SCHEME 4

In a reaction related to the Pictet-Spengler condensation Kano et al. (20) have used enantiomerically pure N-acyliminium compounds to induce asymmetry at C-1. Several other approaches to asymmetric synthesis of the alkaloids have been described also. Kametani et al. (21) have synthesized (-)-xylopinine (XXV) of high enantiomeric purity using a photochemical cyclization of an enamide derived from L-dopa. In a related study Ninomiya and coworkers (22) prepared (-)-xylopinine by photocyclization of an achiral enamide in the presence of a chiral reducing agent.

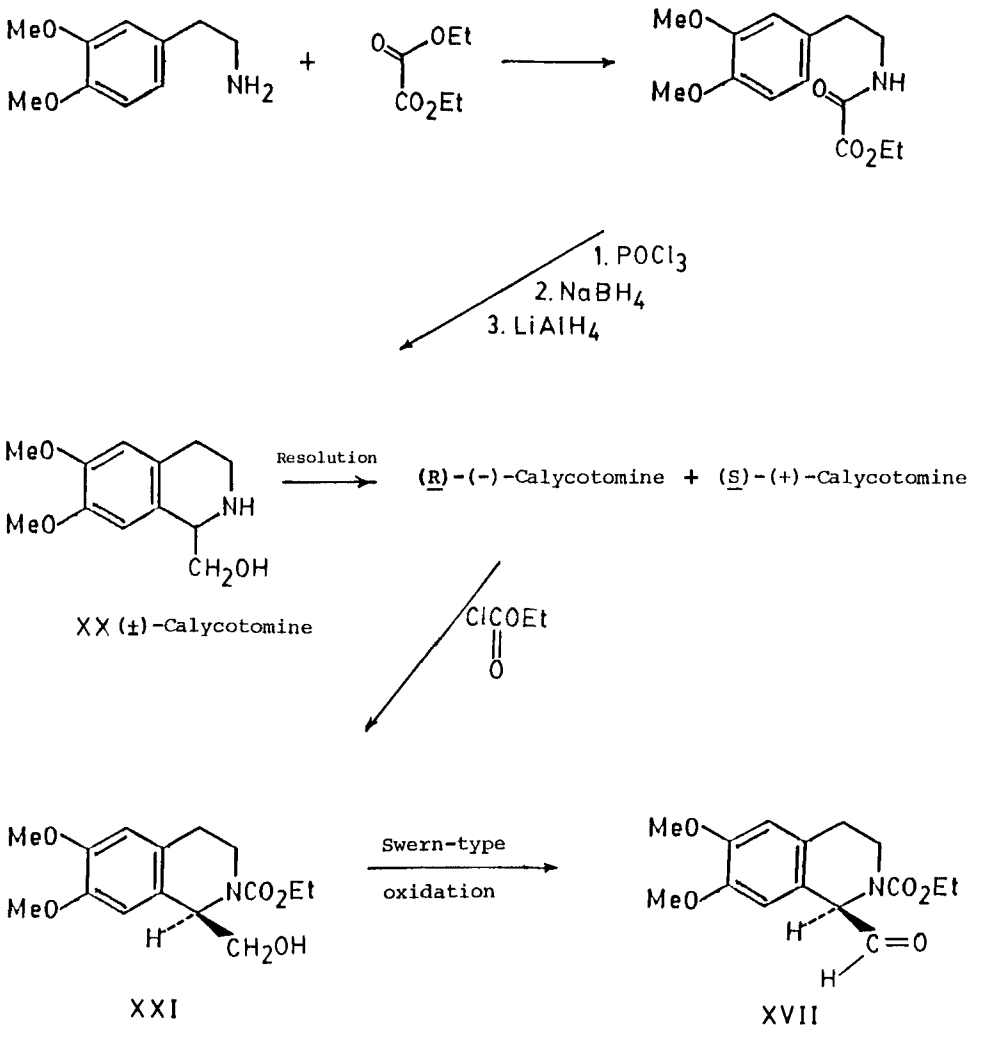
Other methods of induction of chirality at C-1 in isoquinoline systems have been reported by Dörnyei and Szántay (23) and from this laboratory (24).

Yamada and coworkers (25) have also studied asymmetric synthesis in the related Amaryllidaceae group of isoquinoline alkaloids, in particular, in the cases of maritidine and galanthamine. In that work they used L-tyrosine as starting material to induce asymmetry at another site in the final product; the original carboxyl group of tyrosine was removed in a later step.

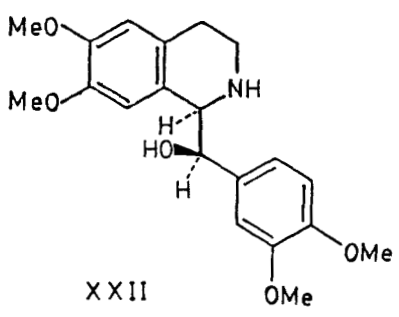
RESULTS AND DISCUSSION

As shown in Scheme 4, we have demonstrated that the aldehyde, (R)-2-ethoxycarbonyl-1-formyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XVII), is a versatile intermediate for the enantioselective synthesis of several isoquinoline alkaloids. In the present study a more convenient route to the key aldehyde XVII and its enantiomer has been developed. The method (see Scheme 5) involves the preparation of (±)-calycotomine (XX) essentially by the method of Grüssner et al. (26), and its resolution using (-)-tartaric acid as described by Brossi and Burkhardt (27) for (+)-tartaric acid, followed by conversion of the tartrate into the N-ethoxycarbonyl derivative XXI. A Swern-type oxidation (28) of XXI afforded the aldehyde XVII in ∿75% yield. The (S)-isomer of XVII was prepared analogously from (S)-(+)-calycotomine which had been obtained by resolution of (±)-calycotomine using (+)-tartaric acid. This improved route to XVII makes possible the undertaking of the synthesis of more-complicated ring systems in the isoquinoline family of alkaloids. In this article we describe the conversion of XVII and its enantiomer into (S)- and (R)-xylopinine, respectively, and of XVII into (8S,14S)-coralydine (XXXII). The aldehyde is prone to racemization, and should be used immediately upon isolation; qualitative studies have shown that 75% of its optical activity is lost upon chromatography on silica gel and ∿25% is lost during storage for 12 h in the cold.

In the previous study (19), we reported that treatment of XVII with 3,4-dimethoxyphenyllithium gave (+)-threo-N-(ethoxycarbonyl)hydroxynorlaudanosine in 64% yield. (We have now found, in an experiment performed with the racemic aldehyde, that at higher temperatures a small proportion of the erythro isomer is formed also.) Hydrolysis of this compound using sodium hydroxide in ethanol afforded (+)-threo-hydroxynorlaudanosine (XXII) in almost quantitative yield. Treatment of XXII with formaldehyde in ethanol in the presence of hydrochloric acid for 2 h at reflux temperature gave (1R,10bR)-1,5,6,10b-tetrahydro-8,9-dimethoxy-1-(3',4'-dimethoxyphenyl)-3H-oxazolo[4,3-a]isoquinoline (XXIII) (Scheme 6) in 84% yield. However, XXII was converted into the protoberberine XXIV in 89% yield by treatment with formaldehyde in water in the presence of hydrochloric acid for 3 h at reflux temperature; the progress of the reaction

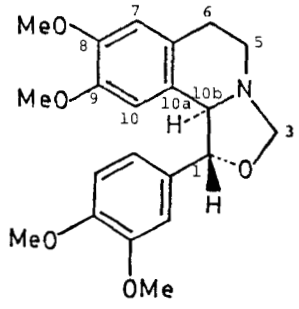

MeO
MeO
NH2
OEt
CO2Et
NH
CO2Et
1. POCl3
2. NaBH4
3. LiAlH4
Resolution
(R)-(-)-Calycotomine + (S)-(+)-Calycotomine
CH2OH
XX (±)-Calycotomine
ClCOEt
NCO2Et
H
CH2OH
XXI
Swern-type
oxidation
C=O
XVII

SCHEME 5



XXII

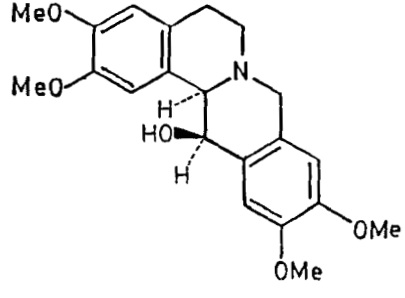
$H_2C{=}O$
EtOH
HCl
reflux
2 h



XXIII

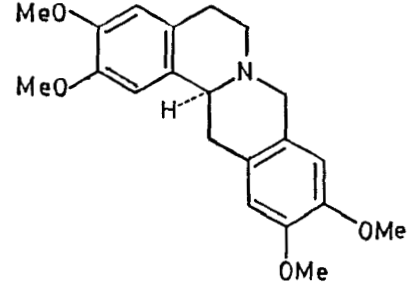
reflux
3 h

$H_2C{=}O$
H_2O
HCl



XXIV

$SOCl_2$,
$LiAlH_4$



XXV (S)-(-)-Xylopinine

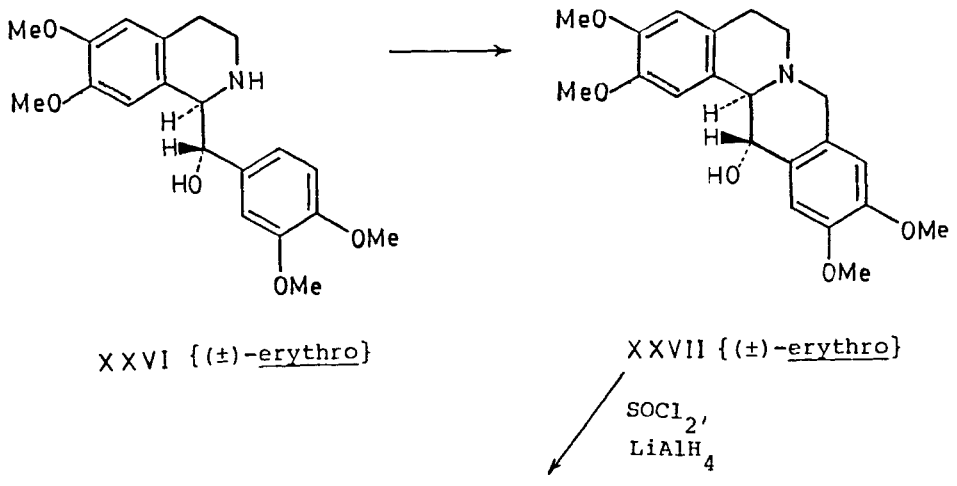
SCHEME 6

was monitored by thin-layer chromatography (5% methanol in chloroform), and, within the first 30-min interval, only the formation of an intermediate, presumably the oxazolo[4,3-a]isoquinoline XXIII, was observed. Deoxygenation of XXIV was effected by using a method developed in this laboratory (19) involving treatment with thionyl chloride and pyridine followed by the direct addition of lithium aluminum hydride; the target compound, (S)-xylopinine (XXV), was obtained in 75% yield and the ee was 92.3% {based on published data (29a)}.

The enantiomer of XXII was also prepared from the enantiomer of the aldehyde XVII and converted into (R)-xylopinine in an analogous manner. Also, (±)-erythro-hydroxynorlaudanosine (XXVI) and (±)-erythro-13-hydroxyxylopinine (XXVII) were obtained by the method of Kametani et al. (30), and the latter was converted into (±)-xylopinine (Scheme 7) using the deoxygenation procedure employed for the preparation of XXV from XXIV. {A sample of (±)-erythro-hydroxynorlaudanosine (XXVI) was prepared also by base-catalyzed hydrolysis of the sample of (±)-erythro-N-(ethoxycarbonyl)hydroxynorlaudanosine which had been obtained previously. The solvent employed for the conversion of XXVI into XXVII was ethanol; if methanol is employed, Kametani et al. (30) have reported that an oxazolo[4,3-a]isoquinoline is formed also.} This procedure was an improvement over that described by Kametani et al. (30).

Another example of the utility of the (R)-aldehyde (XVII) in asymmetric synthesis of isoquinoline alkaloids is provided by the preparation of (8S,14S)-coralydine (XXXII) (Scheme 8). A logical approach to XXXII (and to its epimer at C-8, namely the enantiomer of XV) appeared to be by way of a Pictet-Spengler condensation of XXII and acetaldehyde. However, in a model study, using (±)-erythro-hydroxynorlaudanosine (XXVI) and acetaldehyde under the conditions employed for the conversion of XXII into XXIV, none of the desired condensation product was obtained. {If (±)-erythro-hydroxynorlaudanosine (XXVI) were treated with acetaldehyde in water in the presence of hydrochloric acid, the product obtained was a 1:1 mixture of epimers at C-3 of (1R,10bR)-1,5,6,10b-tetrahydro-8,9-dimethoxy-3-methyl-1-(3',4'-dimethoxyphenyl)-3H-oxazolo[4,3-a]isoquinoline.} A successful cyclization was achieved by a Bischler-Napieralski reaction using (+)-threo-(O,N-diacetyl)hydroxynorlaudanosine (XXVIII) to afford the iminium salt (XXIX) (Scheme 8) in 68% yield. The formation of this salt proceeds satisfactorily only in the presence of a small proportion of pyridine; in the absence of pyridine, cyclization is accompanied by the elimination of acetic acid. Reduction of the iminium salt XXIX using sodium borohydride proceeds diastereoselectively to give crystalline (8S,13R,14R)-13-acetoxy-8-methyl-2,3,10,11-(tetramethoxy)tetrahydroprotoberberine (XXX) in 89% yield. Base-catalyzed hydrolysis of XXX afforded the 13-hydroxy compound XXXI in 85% yield. Deoxygenation of XXXI by the previously described method gave the target compound, namely (8S,14S)-coralydine (XXXII), which was isolated as the hydrochloride salt in 70% yield; the free base was liberated using aqueous ammonia. Brossi and coworkers (31) have reported the preparation of (+)- and (-)-coralydine and of (+)- and (-)-O-methylcorytenchirine and have established the absolute configuration of the four isomers by X-ray analysis.

(±)-erythro-Hydroxynorlaudanosine (XXVI) was converted into its O,N-diacetyl derivative {(±)-XXXIII} (30), which, when subjected to the analogous series of reactions that had been performed with (+)-threo-(O,N-diacetyl)hydroxynor-

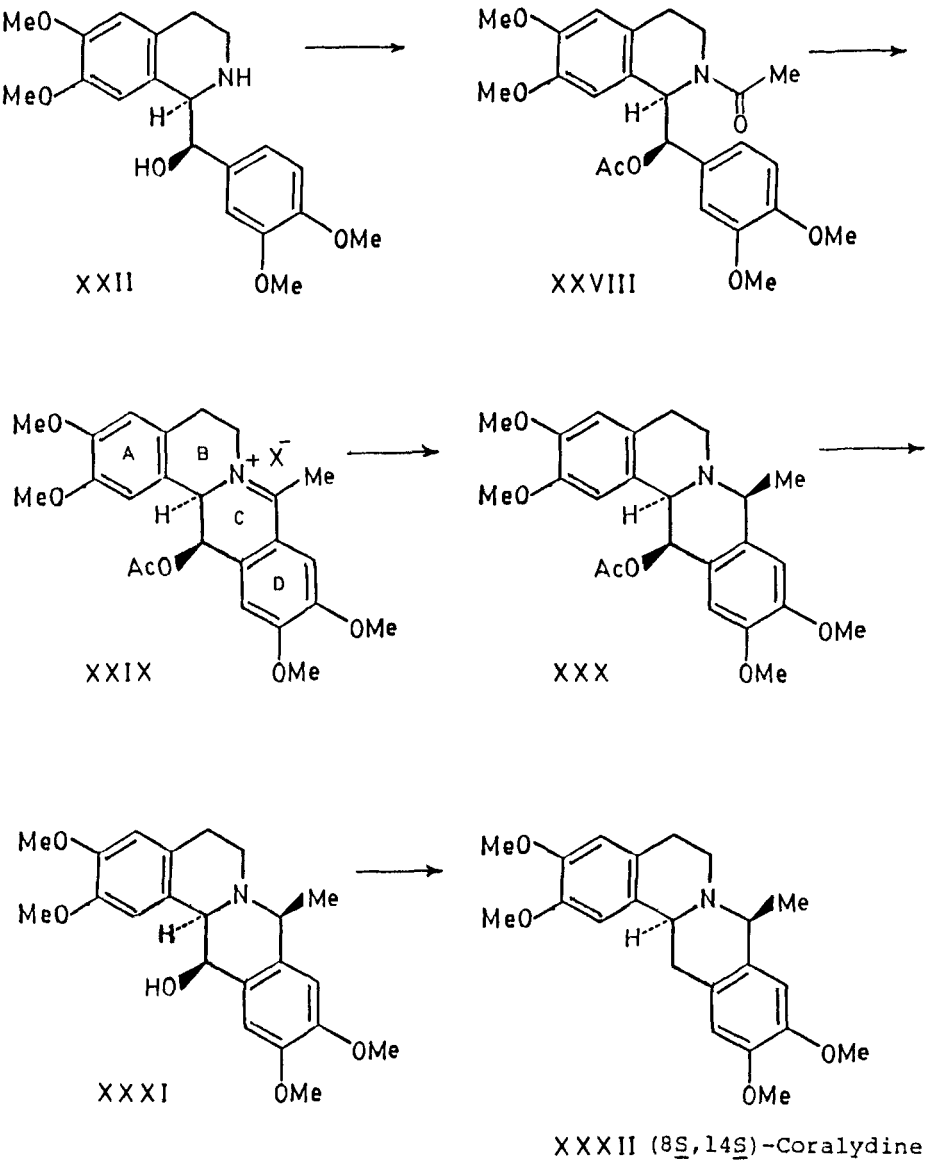


XXVI {(±)-erythro}

XXVII {(±)-erythro}

(±)-Xylopinine

SCHEME 7


MeO
MeO
NH
H
HO
OMe
OMe
XXII
MeO
MeO
N
Me
O
H
AcO
OMe
OMe
XXVIII
MeO
MeO
A
B
N+ X−
Me
H
C
AcO
D
OMe
OMe
XXIX
MeO
MeO
N
Me
H
AcO
OMe
OMe
XXX
MeO
MeO
N
Me
H
HO
OMe
OMe
XXXI
MeO
MeO
N
Me
H
OMe
OMe
XXXII (8S,14S)-Coralydine

SCHEME 8

laudanosine (XXVIII), afforded (±)-coralydine (Scheme 9). It is noteworthy that reduction using sodium borohydride of the iminium salts in both of the cases of the (+)-threo and (±)-erythro compounds leads to the same relative configuration at C-8 and C-14. Reduction from the α-face would lead to a trans-quinolizidine (and hence to coralydine) whereas reduction from the β-face would lead to a cis-quinolizidine (and hence to O-methylcorytenchirine); however, examination of molecular models suggests that there is little difference in steric hindrance for attack from either face. It appears, then, that the course of the reaction is determined by product stability. In contrast, it has been reported (32) that reduction using sodium borohydride of a related system, in which ring C is aromatic and which lacks a substituent at C-13, leads to the formation of the stereoisomers having the hydrogens at C-8 and C-14 cis and trans in the ratio of 3:1, respectively.

The work described in this article provides a route to the asymmetric synthesis of the protoberberine alkaloids. The synthesis of (8S,14S)-coralydine complements the synthesis of (8S,14R)-O-methylcorytenchirine (XV) reported by Dean and Rapoport (17).

EXPERIMENTAL

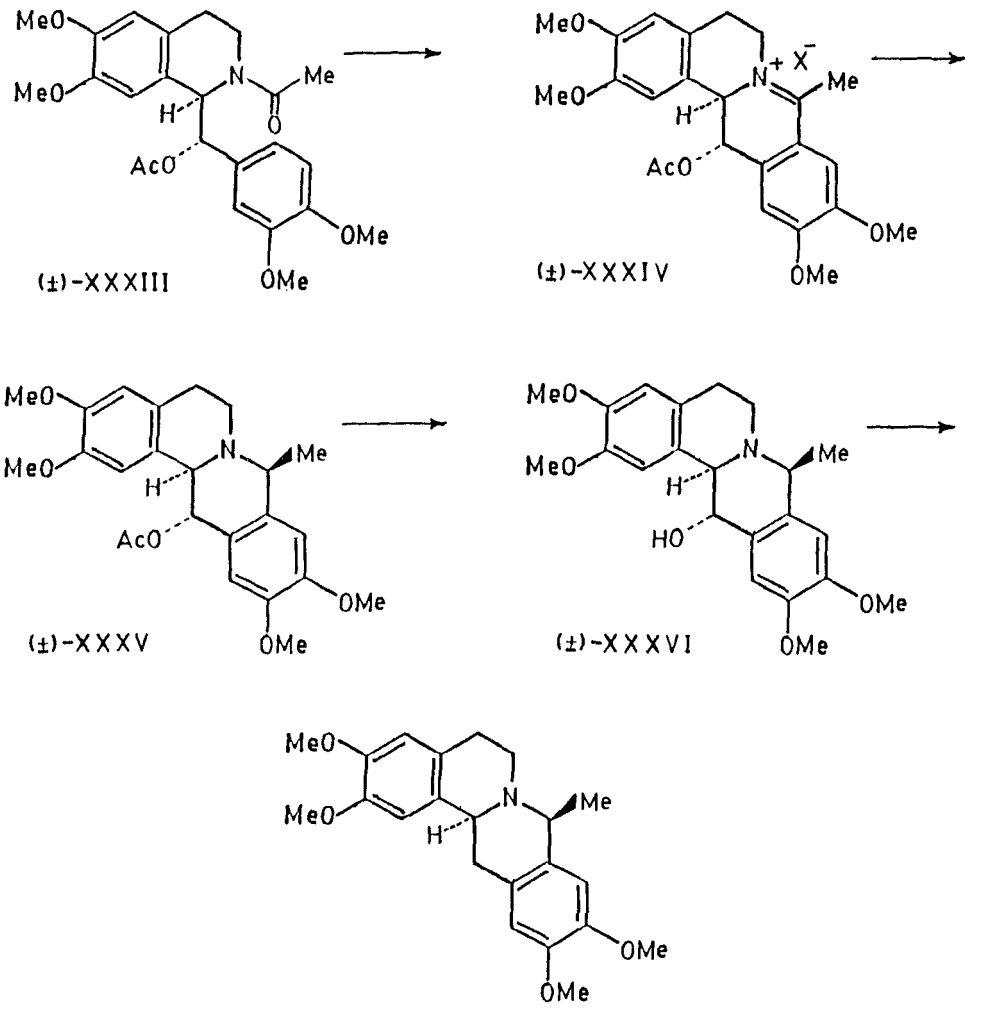
The ^{1}H NMR spectra were recorded on a Bruker AM500 spectrometer at 500 MHz or a Varian EM390 spectrometer at 90 MHz; $CDCl_3$ was the solvent, and, unless otherwise stated, tetramethylsilane (TMS) was used as the internal standard. Chemical shifts are reported in ppm (δ) downfield from the signal of TMS. The symbols, s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broadened), are used to report the multiplicity and shape of signals. EI mass spectra were recorded on a VG Micromass 7070F mass spectrometer at an ionizing voltage of 70 eV or on a VG Analytical ZAB-E mass spectrometer, and CI spectra were recorded using NH_3 at ~1 torr as reagent gas; data are given as m/z (% relative intensity). Infrared (ir) spectra were recorded on a Perkin-Elmer 283 spectrophotometer.

Melting points were determined using a Gallenkamp apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 247MC polarimeter in a 1-mL microcell that is 1 dm in length. The values for ee were calculated as described by Anderson et al. (33). Flash chromatography was performed on Kieselgel 60 (230-400 mesh).

The homogeneity of the products was established on the basis of chromatographic and spectroscopic (^{1}H NMR and mass spectral) examination.

Preparation of N-ethoxycarbonyl derivative XXI

A sample of (±)-calycotomine (XX) was prepared essentially by the method of Grüssner et al. (26) and resolved using (-)-tartaric acid, as described by Brossi and Burkhardt (27) for (+)-tartaric acid, to afford the tartrate of (-)-XX {31% based on (±)-XX}, mp 175-177°C, $[\alpha]_D^{23}$ -35.5° (c 1.19, H_2O) {lit. (27) for enantiomeric salt, mp 178-179°C, $[\alpha]_D$ +35° (H_2O)}. To a solution of (-)-XX (723 mg), which had been liberated from the tartrate, in water (30 mL) were added dichloromethane (50 mL) and a few drops of a 25% aqueous solution of sodium hydroxide. The mixture was stirred vigorously while ethyl chloroformate (3.5 mL) was added in small portions over a period of 30 min; the reaction mixture


MeO
MeO
N
Me
O
H
AcO
OMe
OMe
(±)-XXXIII
X⁻
(±)-XXXIV
(±)-XXXV
HO
(±)-XXXVI
(±)-Coralydine

SCHEME 9

was kept strongly alkaline. The mixture was then stirred for 30 min, and the organic phase was washed twice with a saturated aqueous solution of sodium chloride, dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel using 2% methanol in chloroform as the eluant afforded (+)-XXI as a colorless, viscous oil (95%), $[\alpha]_D^{23}$ +92.0° (c 1.77, $CHCl_3$) {lit. (19) $[\alpha]_D^{23}$ +88.8° (c 2.08, $CHCl_3$)}. The ^1H NMR and mass spectral data were identical with those reported previously (19).

Resolution of a sample of (±)-XX was effected also using (+)-tartaric acid to afford the tartrate of (+)-XX, mp 177-180°C, $[\alpha]_D^{23}$ +35° (c 1.27, H_2O); this salt was then converted, by the procedure described above, into the enantiomer of XXI, which was isolated as an oil, $[\alpha]_D^{23}$ -92.0° (c 1.77, $CHCl_3$).

Preparation of aldehyde XVII

Oxalyl chloride (0.3 mL) was added to dry dichloromethane (15 mL) under nitrogen at -70°C; a solution of dimethyl sulfoxide (0.53 mL) in dichloromethane (7 mL) was added slowly while the temperature was maintained below -50°C. After 20 min, a solution of (+)-XXI (1.02 g) in dichloromethane (5 mL) was added with stirring at -60°C, and then after 15 min, triethylamine (2.35 mL) was slowly added. The reaction mixture was stirred for 10 min at -60°C, warmed to room temperature, and evaporated under reduced pressure at a bath temperature of <35°C. To the residue were added benzene (30 mL) and water (20 mL), and the organic phase was washed with a saturated aqueous solution of sodium chloride, with 1% hydrochloric acid, and then successively with saturated aqueous solutions of sodium chloride, sodium hydrogen carbonate, and sodium chloride. The organic solution was dried ($MgSO_4$) and evaporated almost to dryness; the residue, which contained traces of benzene, was utilized without further purification. The product aldehyde XVII (~75%), $[\alpha]_D^{23} \simeq -10°$ ($CHCl_3$), exhibited ^1H NMR and mass spectra identical with those of the material prepared previously (19).

Conversion of (+)-threo-N-(ethoxycarbonyl)hydroxynorlaudanosine into (+)-threo-hydroxynorlaudanosine (XXII)

A solution of (+)-threo-N-(ethoxycarbonyl)hydroxynorlaudanosine (19) (250 mg) in dry ethanol (15 mL) containing sodium hydroxide (140 mg) was heated at reflux temperature under nitrogen for 3 h. The solvent was evaporated, and the residue in water (50 mL) was extracted three times with dichloromethane. The organic solution was washed twice with a saturated aqueous solution of sodium chloride, dried ($MgSO_4$), and evaporated to give a crystalline residue, which was recrystallized from methanol to give (+)-threo-hydroxynorlaudanosine (XXII) (95%), mp 187-189°C, $[\alpha]_D^{23}$ +82.5° (c 2.48, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ : 6.95, 6.82 and 6.55 (1H, 2H and 1H s's, aromatic H's), 5.26 (1H, s, H-8), 4.60 (1H, d, J=7.5 Hz, CHOH), 3.86 (7H, br s, H-1, $2OCH_3$), 3.83 (3H, s, OCH_3), 3.42 (3H, s, OCH_3 at C-7), 3.23-2.93 (3H, m, 2H-3, OH), 2.83-2.60 (2H, m, 2H-4); ms (CI) : 360 $(M+1)^+$ (25), 342(18), 194(10), 192(100).

A sample of (±)-threo-hydroxynorlaudanosine was prepared by an analogous procedure and had mp 168-171°C.

Conversion of (+)-threo-hydroxynorlaudanosine (XXII) into (1R,10bR)-1,5,6,10b-tetrahydro-8,9-dimethoxy-1-(3',4'-dimethoxyphenyl)-3H-oxazolo[4,3-a]isoquinoline (XXIII)

A solution of XXII (128 mg) in ethanol (20 mL) was treated with a 37% solution of formaldehyde (0.5 mL) and concentrated hydrochloric acid (1 drop) at reflux temperature for 2 h. The solution was evaporated, and the residue was dissolved in chloroform. The chloroform solution was washed successively with saturated aqueous solutions of sodium hydrogen carbonate and sodium chloride, dried ($MgSO_4$), and evaporated to a brown gum, which was chromatographed on silica gel using 2% methanol in chloroform to afford XXIII as a colorless oil (108 mg, 84%), $[\alpha]_D^{23}$ +33.3° (c 2.77, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ : 6.92 and 6.66 (3H and 1H s's, aromatic H's), 5.93 (1H, s, H-10), 5.10 and 4.80 (two 1H d's, J = 7 Hz, 2H-3), 4.50 (1H, d, J=9 Hz, H-1), 4.05 (1H, d, J=9 Hz, H-10b), 3.83 (9H, s, $3OCH_3$), 3.47 (3H, s, OCH_3 at C-9), 3.17-2.56 (4H, m, 2H-5, 2H-6); ms (CI) : 372 $(M+1)^+$ (100), 205(75), 167(25).

Conversion of (+)-threo-hydroxynorlaudanosine (XXII) into protoberberine XXIV

A mixture of XXII (243 mg) in water (30 mL) was treated with a 37% solution of formaldehyde (1 mL) and concentrated hydrochloric acid (0.35 mL) at reflux temperature under nitrogen for 3 h. The solution was cooled and made basic by the addition of sodium carbonate, and the mixture was extracted three times with chloroform. The organic solution was washed twice with a saturated aqueous solution of sodium chloride, dried ($MgSO_4$), and evaporated. The residue was recrystallized from methanol-diethyl ether to give XXIV (223 mg, 89%), mp 150-152°C, $[\alpha]_D^{23}$ -298.2° (c 2.72, $CHCl_3$); ν_{max} ($CHCl_3$) : 3400-3200, 2830, 2810, 2750 cm^{-1}, ^1H NMR (90 MHz, $CDCl_3$) δ : 7.07, 6.87, 6.68 and 6.63 (four 1H s's, aromatic H's), 4.82 (1H, br m, d after addition of D_2O, J=1.5 Hz, H-13), 3.93 (13H, br s, H-14, $4OCH_3$), 3.72 (2H, br s, 2H-8), 3.33-2.93 (2H, m, 2H-6), 2.90-2.47 (2H, m, 2H-5), 2.66 (1H, br s, exchanged with D_2O, OH); ms (CI) : 372 $(M+1)^+$ (10), 355(5), 354(15), 193(5), 192(100), 180(20), 179(7), 151(3).

A sample of the (±)-modification of XXIV was prepared by an analogous procedure and had mp 199-201°C [lit. (34) mp 198-200°C].

(S)-(-)Xylopinine (XXV)

To a solution of compound XXIV (165 mg) in dry tetrahydrofuran (50 mL) were added, under nitrogen and at <-10°C, dry pyridine (0.04 mL) and then thionyl chloride (0.035 mL), and the reaction mixture was stirred at -10 to -20°C for 30 min. Solid lithium aluminium hydride (150 mg) was then added in small portions, and the mixture was heated at reflux temperature for 15 min. To the mixture were added successively water (0.15 mL), a 15% aqueous solution of sodium hydroxide (0.15 mL), and water (0.45 mL); the mixture was filtered, the residue was washed three times with hot chloroform, and the combined filtrate and washings were evaporated. Chromatography of the residue on silica gel using 2% methanol in chloroform as the eluant gave a viscous oil which crystallized from ethanol-diethyl ether to afford XXV (75%), mp 178-180°C, $[\alpha]_D^{23}$ -274° (c 2.11, $CHCl_3$) [lit. (29a) mp 182°C, $[\alpha]_D$ -297° ($CHCl_3$)]; ms (EI) : 355 $(M)^+$ (100), 190(17), 164(60). The ^1H NMR data are in agreement with those reported by Tourwé et al. (29b).

(R)-(+)-Xylopinine

The enantiomer of the N-ethoxycarbonyl derivative XXI, namely (S)-2-(ethoxycarbonyl)calycotomine, was converted into the enantiomer of the aldehyde XVII, namely (S)-2-ethoxycarbonyl-1-formyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, by a Swern-type oxidation as described for the conversion of XXI into XVII. Treatment of the enantiomer of the aldehyde XVII with 3,4-dimethoxyphenyllithium (see ref. 19) afforded (-)-threo-N-(ethoxycarbonyl)hydroxynorlaudanosine as an oil, $[\alpha]_D^{23}$ -29.2° (c 2.36, $CHCl_3$); base-catalyzed hydrolysis of this compound, as described for the preparation of XXII, gave (-)-threo-hydroxynorlaudanosine, which was crystallized from methanol and had mp 186-188°C, $[\alpha]_D^{23}$ -78.9° (c 3.49, $CHCl_3$). (-)-threo-Hydroxynorlaudanosine was converted into the enantiomer of protoberberine XXIV as described for the preparation of XXIV; the product was crystallized from methanol-diethyl ether and had mp 150-152°C, $[\alpha]_D^{23}$ +296.5° (c 2.67, $CHCl_3$). Deoxygenation of the enantiomer of protoberberine XXIV, as described for the preparation of XXV, afforded a sample of (R)-(+)-xylopinine, which crystallized from ethanol and had mp 178-180°C, $[\alpha]_D^{23}$ +271° (c 2.25, $CHCl_3$). All of the compounds prepared by this sequence of reactions exhibited ^1H NMR and mass spectra identical with those of the corresponding enantiomers.

Reaction of the racemic modification of aldehyde XVII with 3,4-dimethoxyphenyllithium

A solution of bromoveratrole (2.13 g) in dry tetrahydrofuran (50 mL) was treated with a 2.4 M solution of n-butyllithium in n-hexane (4.5 mL) at -78°C (Dry Ice-methanol) for 15 min. A solution of the racemic modification of aldehyde XVII (720 mg) in tetrahydrofuran (15 mL) was added at a rate such that the temperature rose to -50°C; the reaction mixture was then stirred at -78°C for 10 min. Methanol (2 mL) was added, and the mixture was warmed to room temperature and processed, as described previously (19) for a reaction with XVII, to afford an oil, which was chromatographed on silica gel using 1% methanol in chloroform as the eluant to give (±)-threo-N-(ethoxycarbonyl)hydroxynorlaudanosine (see ref. 19) (520 mg, 49.1%) and a lesspolar component, namely (±)-erythro-N-(ethoxycarbonyl)hydroxynorlaudanosine, as a colorless oil (84 mg, 7.9%); ^1H NMR (90 MHz, C_6D_6) δ : 6.97-6.37 (5H, m, aromatic H's), 5.67 (1H, br s, d after addition of D_2O, J=3 Hz, CHOH), 5.35 (1H, br s, $w_{1/2}$=12 Hz, H-1), 4.50 (1H, br s, exchanged with D_2O, OH), 4.10 (2H, q, J=6 Hz, CH_2CH_3), 3.43 (10H, s, H-3_{eq}, $3OCH_3$), 3.40 (3H, s, OCH_3), 2.70-2.43 (1H, m, H-3_{ax}), 2.40-2.07 (2H, m, 2H-4), 1.05 (3H, t, J=6 Hz, CH_2CH_3).

Conversion of (±)-erythro-N-(ethoxycarbonyl)hydroxynorlaudanosine into (±)-erythro-hydroxynorlaudanosine (XXVI)

A solution of (±)-erythro-N-(ethoxycarbonyl)hydroxynorlaudanosine (72 mg) in 3% sodium hydroxide in ethanol (20 mL) was heated at reflux temperature for 3 h. The solvent was evaporated, and the residue in an aqueous solution of sodium chloride was extracted with chloroform. The crystalline product was recrystallized from methanol to afford (±)-erythro-hydroxynorlaudanosine (XXVI) as colorless crystals (55 mg, 92%), mp 137-140°C; ^1H NMR (500 MHz, $CDCl_3$) δ : 6.85-6.54 (5H, m, aromatic H's), 4.96 (1H, d, J=4.8 Hz, CHOH), 4.27 (1H, d, J

= 4.8 Hz, H-1), 3.85, 3.83, 3.73 and 3.72 (four 3H s's, $4OCH_3$), 2.90-2.79 (2H, m, 2H-3), 2.59-2.49 (2H, m, 2H-4), 1.90-1.50 (2H, br s, exchanged with D_2O, OH, NH); ms (CI) : 360 $(M+1)^+$ (100), 342(10), 192(80), 167(17). The ^1H NMR data are in agreement with those reported by Kametani et al. (30).

(±)-Xylopinine

Samples of (±)-erythro-hydroxynorlaudanosine (XXVI) and (±)-erythro-13-hydroxyxylopinine (XXVII) were prepared by the method of Kametani et al. (30); the latter had mp 158-160°C (from benzene {lit. (30) mp 158-160°C (from benzene)}. To a solution of XXVII (91 mg) in dry tetrahydrofuran (30 mL) were added, at -25°C, dry pyridine (0.022 mL) and then thionyl chloride (0.018 mL), and the reaction mixture was stirred at this temperature for 20 min. Solid lithium aluminum hydride (300 mg) was then added in small portions, and the mixture was heated at reflux temperature for 30 min and then processed in the usual manner. Chromatography of the product on silica gel using 2% methanol in chloroform as the eluant afforded (±)-xylopinine as a yellow oil (73 mg, 84% based on XXVII). The ^1H NMR and mass spectra were identical with those exhibited by (+)- and (-)-xylopinine.

Preparation of (+)-threo-(O,N-diacetyl)hydroxynorlaudanosine (XXVIII)

A solution of (+)-threo-hydroxynorlaudanosine (XXII) (420 mg) in a mixture of pyridine (5 mL) and acetic anhydride (4 mL) was kept overnight in a refrigerator and then evaporated at 30°C under the influence of a stream of nitrogen. A solution of the residue in benzene was washed three times with a saturated aqueous solution of sodium chloride, dried ($MgSO_4$), and evaporated to afford a pale-yellow oil which crystallized from methanol to give the diacetyl compound XXVIII as white crystals (472 mg, 91%), mp 161-163°C, $[\alpha]_D^{23}$ +21.8° (c 1.55, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ : 6.87-6.51 (4H, m, H-5, H-2', H-5', H-6'), 5.95-5.67 ($2^1/_3$H, m), 4.90 ($^1/_3$H, d, J=11.4 Hz) and 4.58-4.52 ($^1/_3$H, m) (H-8, CHOAc and H-1), 3.83, 3.82, 3.81, 3.80, 3.79 and 3.78 (9H, six s's, OCH_3 group at C-6, C-3' and C-4), 3.72-3.66 (1H, m, $H\text{-}3_{eq}$), 3.44 and 3.42 (3H, two s's, OCH_3 at C-7), 2.93-2.71 (3H, m, $H\text{-}3_{ax}$, 2H-4), 2.27 ($1\frac{1}{2}$H, s), 2.16 ($1\frac{1}{2}$H, s) and 2.05 (3H, s) (OAc and NAc); ms (CI) : 444 $(M+1)^+$ (30), 384(100), 234(75), 192 (38).

A sample of (±)-threo-(O,N-diacetyl)hydroxynorlaudanosine was prepared from (±)-threo-hydroxynorlaudanosine by an analogous procedure in 95% yield and had mp 143-145°C (from methanol).

Preparation of iminium salt XXIX

To a solution of the diacetyl compound XXVIII (384 mg) in acetonitrile (20 mL) were added pyridine (0.1 mL) and then phosphorus oxychloride (1 mL), and the reaction mixture was heated at reflux temperature on a steam bath for 2 min and then kept at room temperature for 15 min. The mixture was evaporated under reduced pressure, toluene (10 mL) was added, and the evaporation process was repeated. Crystallization of the residue from methanol-diethyl ether afforded the iminium salt as a yellow powder (271 mg, 68%), mp >250°C (dec.), $[\alpha]_D^{23}$ -10.0° (c 0.77, CH_3OH); ^1H NMR (90 MHz, CD_3OD) δ : 7.74, 7.35, 7.20 and 6.97 (four 1H s's, aromatic H's), 6.41 (1H, d, J=3 Hz, H-13), 5.57 (1H, br s,

$w_{1/2}$=6 Hz, H-14), 4.03 (6H, s, $2OCH_3$), 3.87 (6H, s, $2OCH_3$), 3.37 (3H, s, CH_3 at C-8), 3.42-2.97 (4H, m, 2H-5, 2H-6), 1.72 (3H, s, OAc).

A sample of the racemic modification of XXIX was prepared by an analogous procedure in 72% yield and had mp ∿255°C (dec.).

Preparation of (8S,13R,14R)-13-acetoxy-8-methyl-2,3,10,11-(tetramethoxy)tetrahydroprotoberberine (XXX)

To a solution of the iminium salt XXIX (350 mg) in methanol (40 mL) was added sodium borohydride (0.75 g), slowly with stirring, with the temperature being maintained below 5°C using an ice bath. The reaction mixture was stirred for a further period of 15 min, and then warmed to room temperature and evaporated under reduced pressure; chloroform was added to the residue, and the solution was washed twice with a saturated aqueous solution of sodium chloride, dried ($MgSO_4$), and evaporated to leave an oil. Addition of warm diethyl ether afforded crystals of compound XXX (287 mg, 89%), mp 159-163°C (dec.); ν_{max} ($CHCl_3$) : 2830-2800, 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ : 6.98, 6.74, 6.72 and 6.61 (four 1H s's, aromatic H's), 6.51 (1H, d, J=2.4 Hz, H-13), 3.91 (1H, d, J=2.4 Hz, H-14), 3.89, 3.86 and 3.85 (3H, 6H and 3H s's, $4OCH_3$), 3.60 (1H, q, J=6.2 Hz, H-8), 3.55-3.48 (1H, m, $H\text{-}6_{eq}$), 3.14-3.09 (1H, m, $H\text{-}5_{ax}$), 2.68 (1H, br d, J=15.9 Hz, $H\text{-}5_{eq}$), 2.45-2.40 (1H, m, $H\text{-}6_{ax}$), 1.77 (3H, s, OAc), 1.63 (3H, d, J=6.2 Hz, CMe); ms (CI) : 428 $(M+1)^+$ (25), 368(100), 192(7).

A sample of the racemic modification of XXX was prepared by an analogous procedure in 94% yield and had mp 162-165°C (from diethyl ether).

Preparation of 13-hydroxy compound XXXI

Compound XXX (225 mg) was treated with sodium hydroxide (250 mg) in methanol (30 mL) with stirring overnight. The solvent was evaporated, a saturated aqueous solution of sodium chloride (20 mL) was added to the residue, and the mixture was extracted three times with chloroform. The organic solution was dried ($MgSO_4$) and evaporated to leave an oil. Addition of methanol (0.5 mL) and diethyl ether (∿3 mL) afforded crystals of compound XXXI (174 mg, 85%), mp 178-181°C, $[\alpha]_D^{23}$ -243.5° (c 0.94, $CHCl_3$); ν_{max} ($CHCl_3$) : 3600-3500, 2810-2750 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ : 6.95, 6.89, 6.75 and 6.68 (four 1H s's, aromatic H's), 4.75 (1H, br d, J≃9 Hz, br s after addition of D_2O, $w_{1/2}$=3.5 Hz, H-13), 3.93 (12H, br s, $4OCH_3$), 3.77 (1H, q, J=7.5 Hz, H-8), 3.56-2.33 (6H, m, D_2O exchange caused disappearance of a signal at δ 3.10 corresponding to 1H), 1.58 (3H, d, J=7.5 Hz, CMe); ms (CI) : 386 $(M+1)^+$ (100), 368(40), 192 (40).

A sample of the racemic modification of XXXI was prepared by an analogous procedure in 95% yield and had mp 165-166°C.

(8S,14S)-Coralydine (XXXII)

To a solution of compound XXXI (182 mg) in dry tetrahydrofuran (35 mL) were added, under nitrogen and at -78°C, dry pyridine (0.05 mL) and then thionyl chloride (0.045 mL), and the mixture was stirred at this temperature for 30 min. Solid lithium aluminium hydride (0.25 g) was then added in small portions, and the mixture was heated at reflux temperature for 20 h and then processed in the usual manner. The product, compound XXXII, formed a hydrochlo-

ride salt (135 mg, 70.3%), which crystallized from acetone-diethyl ether and had mp 246-250°C (dec.), $[\alpha]_D^{23}$ -130.4° (c 1.27, $CHCl_3$) {lit. (31) mp 256-258°C, $[\alpha]_D$ -138° ($CHCl_3$)}. The free base was liberated using aqueous ammonia and recrystallized from ethanol-diethyl ether-hexanes; mp 124-127°C, $[\alpha]_D^{23}$ -219.3° (c 0.88, $CHCl_3$) {lit. (31) mp 129-130°C (from methanol), $[\alpha]_D$ -226° ($CHCl_3$)}. The ^1H NMR spectrum of XXXII was identical with that of (±)-coralydine reported below.

Preparation of iminium salt (±)-XXXIV

To a solution of (±)-erythro-(O,N-diacetyl)hydroxynorlaudanosine {(±)-XXXIII} (787 mg), which had been prepared from (±)-erythro-hydroxynorlaudanosine (XXVI) by the method of Kametani et al. (30), in dry acetonitrile (30 mL) was added phosphorus oxychloride (4 mL), and the reaction mixture was heated on a steam bath for 5 min and kept at room temperature for 30 min. The mixture was evaporated on a steam bath under reduced pressure, toluene was added, and the evaporation process was repeated. To a solution of the crystalline residue in methanol (4 mL) was added gradually diethyl ether (~20 mL); the iminium salt (±)-XXXIV was obtained as a yellow powder (541 mg, 70%), mp >250°C (dec.); ^1H NMR (90 MHz, CD_3OD) δ : 7.68, 7.34, 6.98 and 6.95 (four 1H s's, aromatic H's), 6.58 (1H, d, J=8 Hz, H-13), 5.43 (1H, d, J=8 Hz, H-14), 4.05, 3.98, 3.85 and 3.82 (four 3H s's, $4OCH_3$), 4.23-3.80 (m, overlapped by methoxyl signals, 2H-6), 3.50-3.20 (m, 2H-5), 3.03 (3H, s, CH_3 at C-8), 2.15 (3H, s, OAc).

Preparation of protoberberine (±)-XXXV

To a solution of the iminium salt (±)-XXXIV (474 mg) in methanol (50 mL) was added sodium borohydride (1.0 g) in small portions over a 10-min period at 0 to 5°C. The reaction mixture was stirred for a further period of 10 min at 5°C and evaporated; chloroform was added to the residue, and the solution was washed twice with a saturated aqueous solution of sodium chloride, dried ($MgSO_4$), and evaporated to leave a crystalline residue. Recrystallization from methanol afforded protoberberine (±)-XXXV (420 mg, 95%), mp 181-183°C; ν_{max} (KBr) : 2830-2800, 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ : 6.74, 6.72, 6.71 and 6.63 (four 1H s's, aromatic H's), 6.17 (1H, d, J=8.4 Hz, H-13), 4.23 (1H, q, J=6.8 Hz, H-8), 4.13 (1H, d, J=8.4 Hz, H-14), 3.89, 3.85, 3.84 and 3.81 (four 3H s's, $4OCH_3$), 2.88-2.82 (1H, m, H-6_{eq}), 2.80-2.77 (3H, m, 2H-5, H-6_{ax}), 2.20 (3H, s, OAc), 1.60 (3H, d, J=6.8 Hz, CH_3 at C-8); ms (CI) : 428 $(M+1)^+$ (55), 391(7), 368(100), 352(30), 236(12), 194(20).

Preparation of 13-hydroxy compound (±)-XXXVI

To a solution of compound (±)-XXXV (400 mg) in methanol (50 mL) was added sodium hydroxide (500 mg), and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated, the residue was dissolved in water (20 mL), and the solution was extracted three times with chloroform. The extracts were washed with a saturated aqueous solution of sodium chloride, dried ($MgSO_4$), and evaporated to afford the 13-hydroxy compound (±)-XXXVI as needles (88%), mp 187-189°C (dec.) (from methanol); ν_{max} ($CHCl_3$) : 3600, 2850-2800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ : 7.18, 7.06, 6.69 and 6.45 (four 1H s's, aromatic H's), 4.69 (1H, m, d after addition of D_2O, J=8.6 Hz, H-13), 4.06 (1H, q, J=6.6 Hz, H-8), 3.89, 3.88, 3.87 and 3.86 (four 3H s's, $4OCH_3$), 3.73 (1H, d, J=8.6 Hz, H-14), 3.11 (1H, m, H-6_{eq}), 2.90 (1H, m, H-5_{ax}), 2.82 (1H, m,

$H\text{-}5_{eq}$), 2.64 (1H, m, $H\text{-}6_{ax}$), 2.10 (1H, br m, exchanged with D_2O, OH), 1.56 (3H, d, J=6.6 Hz, CH_3 at C-8); ms (CI) : 386 $(M+1)^+$ (30), 368(50), 192(60), 190(100).

(±)-Coralydine

To a solution of the 13-hydroxy compound (±)-XXXVI (220 mg) in dry tetrahydrofuran (30 mL) were added, at -15 to -20°C, dry pyridine (0.05 mL) and then thionyl chloride (0.045 mL), and the mixture was stirred in this temperature range for 30 min. Solid lithium aluminum hydride (250 mg) was then added in small portions, and the mixture was heated at reflux temperature for 20 min and then processed in the usual manner. Chromatography of the residue on silica gel using 2% methanol in chloroform as the eluant gave a product, which was recrystallized from methanol-diethyl ether to afford (±)-coralydine as yellow crystals (81%), mp 114-115°C (lit. (29a) mp 115°C); ^1H NMR (500 MHz, $CDCl_3$) δ : 6.74, 6.67, 6.64 and 6.61 (four 1H s's, aromatic H's), 3.87, 3.86 and 3.85 (3H, 6H and 3H s's, $4OCH_3$), 3.72-3.66 (2H, m, $H\text{-}8_{ax}$, H-14), 3.38-3.34 (1H, m, $H\text{-}6_{eq}$), 3.14-2.02 (2H, m, $H\text{-}5_{ax}$, $H\text{-}13_{eq}$), 2.88-2.82 (1H, m, $H\text{-}13_{ax}$), 2.73-2.66 (1H, m, $H\text{-}5_{eq}$), 2.49-2.41 (1H, m, $H\text{-}6_{ax}$), 1.53 (3H, d, J=6.4 Hz, CH_3 at C-8); ms (EI) : 368 $(M-1)^+$ (8), 354(30), 338(5), 192(5), 178(100), 163(10). The ^1H NMR data are in agreement with those reported by Brossi and coworkers (31).

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