Enantioselective synthesis of isoquinoline alkaloids: phenylethylisoquinoline and aporphine alkaloids[1]

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A new and improved procedure for the preparation of (*R*)-2-alkoxycarbonyl-1-formyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolines has been developed beginning from D-(−)-tartaric acid. The utility of these aldehydes in the asymmetric synthesis of isoquinoline alkaloids of high enantiomeric purity has been extended to the synthesis of phenylethylisoquinolines, which have been further transformed in straightforward steps into the homoprotoberberine and homoaporphine ring systems. In this manner, (*S*)-homolaudanosine, (*S*)-5′-methoxyhomolaudanosine, (*S*)-2,3,9,10,11-pentamethoxyhomoprotoberberine, and (*S*)-*O*-methylkreysigine have been synthesized. The conversion of (*S*)-laudanosine to (*S*)-glaucine, an aporphine alkaloid, has also been realized.

ZBIGNIEW CZARNOCKI, DAVID B. MACLEAN et WALTER A. SZAREK. Can. J. Chem. **65**, 2356 (1987).

Utilisant l'acide D-(−)-tartrique comme produit de départ, on a développé une nouvelle méthode améliorée pour la préparation des alkoxycarbonyl-2(*R*) formyl-1 tétrahydro-1,2,3,4 diméthoxy-6,7 isoquinoléines. L'utilité de ces aldéhydes dans les synthèses asymétriques de haute pureté énantiomérique des alcaloïdes de l'isoquinoléine a déjà été démontrée et on l'a étendue aux synthèses des phényléthylisoquinoléines qui ont été transformées par la suite, par des étapes ne créant pas d'ambiguités, en systèmes cycliques homoprotoberbérine et homoaporphine. De cette façon, on a synthétisé l'homolaudanosine-(*S*), la méthoxy-5′ homolaudanosine-(*S*), la pentaméthoxy-2,3,9,10,11 homoprotoberbérine-(*S*) et la *O*-méthylkreysigine-(*S*). On a aussi réalisé la transformation de la laudanosine-(*S*) en glaucine-(*S*), un alcaloïde aporphine.

[Traduit par la revue]

The asymmetric synthesis of several classes of isoquinoline alkaloids from (*R*)- and (*S*)-2-ethoxycarbonyl-1-formyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolines, (*R*)-**1** and (*S*)-**1**, has been reported by us in several publications (1*a*–*c*). These publications include a review of previous approaches to the asymmetric synthesis of isoquinoline alkaloids; in the interim, Noyori *et al.* (2) have described a new method, and Meyers and Bailey (3) have extended the chiral amidine approach to the synthesis of morphinans. Two methods were used by us to generate the enantiomeric aldehydes. The first was based upon the induction of asymmetry at C-1 of the tetrahydroisoquinoline system through a Pictet–Spengler reaction of dopamine hydrochloride with (*R*)-glyceraldehyde (1*a*,*b*) followed by subsequent transformation of the condensation product. In the second method, optically pure (*R*)- and (*S*)-calycotomine (see **2**) were prepared by resolution and converted to *N*-ethoxycarbonyl derivatives, which were then oxidized to the aldehydes (1*c*). In this article we report a third and improved procedure for the formation of the (*R*)-aldehyde, which is based upon the use of D-(−)-tartaric acid as a means of inducing asymmetry at C-1 of the isoquinoline system. The enantiomeric aldehyde would be equally accessible from L-(+)-tartaric acid. We also show that aldehydes (*R*)-**1** and the 2-methoxycarbonyl analogue (*R*)-**5** may be used as starting materials for the asymmetric synthesis of phenylethylisoquinolines and report the transformation of the latter into the homoprotoberberine (4) and the homoaporphine (4) ring systems. The conversion of the previously prepared (1*b*) (*S*)-laudanosine (**3**) into (*S*)-glaucine (**4**) (4) has also been achieved.

The new and improved procedure for the preparation of (*R*)-**1** and its *N*-methoxycarbonyl analogue (*R*)-**5** is partially outlined in Scheme 1. The starting material, methyl [(2*S*,3*R*)-dihydroxy-3-(6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinolin-1′ (*R*)-yl)] propanoate hydrochloride (**6**), was prepared by the method employed by Dörnyei and Szántay (5) for the preparation of the enantiomer. Treatment of **6** with an excess of ethyl chloroformate or an excess of methyl chloroformate provided the *N*,*O*-acylated compounds, **7** and **8**, respectively. The *O*-acyl groups were selectively removed from **7** and **8** by methanolysis affording the *N*-alkoxycarbonyldihydroxy compounds **9** and **10**, which, on periodate oxidation, yielded the aldehydes **1** and **5**, respectively. Both aldehydes are prone to racemization and should be used immediately in subsequent steps.

This method of preparation of (*R*)-**1** has several advantages over the preparation from glyceraldehyde (1*b*). Fewer steps are involved in formation of the immediate precursor to the aldehyde and the reaction leading to generation of asymmetry at C-1 is for all practical purposes stereospecific; none of the diastereomer of **6** was detected, confirming the previous report (5). The periodate cleavage of the glycol unit of **9** and **10** proceeds in nearly quantitative yield, as does glycol cleavage in the first method. However, the tartaric acid route has the potential advantage that it may be used to prepare 1-formylisoquinolines, with substituents other than *O*-methyl on the aromatic ring; such preparations are not practicable beginning from glyceraldehyde. In comparison with the route from (±)-calycotomine (1*c*), the present method is superior in terms of yield (33% from tartaric acid vs. 22% from (±)-calycotomine for (*R*)-**1**) and roughly similar in terms of convenience.

The asymmetric synthesis of a variety of alkaloids belonging to the 1-benzylisoquinoline family beginning from (*R*)-**1** has been reported previously by us (1*b*,*c*). We demonstrate here

[1]For a preliminary account of a part of this work, see ref. 15.
[2]Authors to whom correspondence may be addressed.

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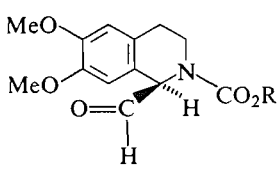
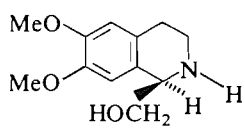
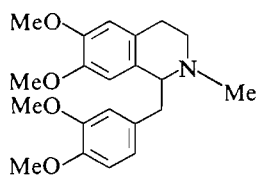


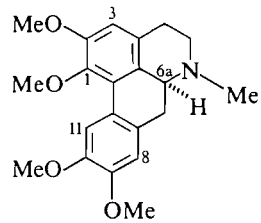
(*R*)-**1** R = Et
(*R*)-**5** R = Me



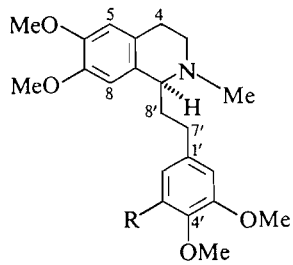
(*R*)-**2**



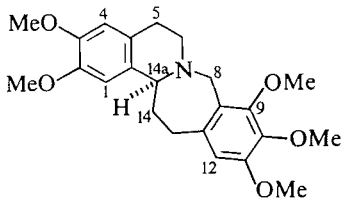
(*S*)-**3**



(*S*)-**4**



11 R = H
12 R = OMe



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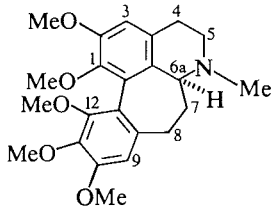


14

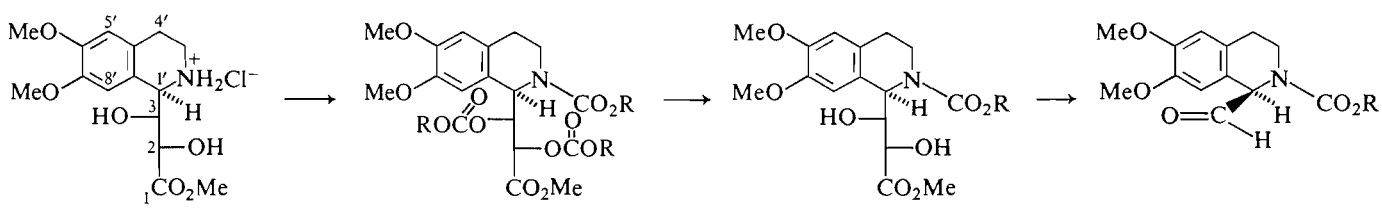
that (*R*)-**1** (or (*R*)-**5**) is an equally valuable starting material for the synthesis of several alkaloids and related compounds belonging to the 1-phenylethylisoquinoline group. Specifically, we have prepared (*S*)-homolaudanosine (**11**) (6, 7), (*S*)-5′-methoxyhomolaudanosine (**12**) (8, 9), (*S*)-2,3,9,10,11-pentamethoxyhomoprotoberberine (**13**) (10), and (*S*)-*O*-methylkreysigine (**14**) (8, 11).

The synthesis of (*S*)-homolaudanosine (**11**) is outlined in Scheme 2. The ylid **15** was prepared from 3,4-dimethoxybenzylphosphonium chloride by treatment with *n*-butyllithium in THF, first at −78°C and then at −20°C. The mixture was then cooled to −78°C and treated with a solution of **1** in THF. The product (**16**) was a *trans*-alkene as evidenced by ^{1}H nmr ($J_{7',8'} \approx 16$ Hz). Catalytic reduction of **16** afforded the carbamate **17**, which was reduced with lithium aluminium hydride (LAH) to (*S*)-homolaudanosine (**11**). The alkaloid was isolated as an oil in an overall chemical yield from (*R*)-**1** of 47% and in 78% ee (enantiomeric excess).

The synthesis of phenylethylisoquinoline **12**, homoprotoberberine **13**, and homoaporphine **14** is outlined in Scheme 3. Aldehyde **5** was used as starting material in these syntheses because the removal of the alkoxycarbonyl group is an essential step in the synthesis of **13** and it was thought that the methyl carbamate might be converted more readily into a secondary amine than the ethyl carbamate. Accordingly, aldehyde (*R*)-**5** was treated with 3,4,5-trimethoxybenzyltriphenylphosphonium ylid **18** under conditions similar to those used for the conversion of **1** to **16**. The product (**19**) of this reaction, also a *trans*-alkene ($J_{7',8'} \approx 15$ Hz), was reduced catalytically to the carbamate **20**. The conversion of **20** to the secondary amine proved to be difficult. Alkaline hydrolysis of the carbamate function of **20** proceeded slowly and was accompanied by racemization. Treatment with trimethylsilyl chloride and sodium iodide in refluxing acetonitrile yielded the secondary amine but there was extensive racemization and the reaction was therefore of little value in the context of this research. However, when **20** was treated with an excess of methyllithium in THF at room temperature, the reaction proceeded in acceptable chemical yield and without loss of optical purity. The conversion of **21** into homoprotoberberine **13** was accomplished by treatment of the hydrobromide of **21** with formaldehyde using a literature procedure (10). The spectroscopic properties of **13** were the same as those already reported (10) and the optical purity was 81.9% based on published data.

The synthesis of (*S*)-*O*-methylkreysigine (**14**) (11) was achieved by oxidative cyclization of **12** using the procedure of Taylor *et al.* (8). Compound **12**, prepared by reduction of **20** with LAH, was treated with thallium(III) trifluoroacetate. *O*-Methylkreysigine was isolated as an oil in 27% chemical yield based on **12** and in 84% ee. The spectroscopic properties of **12** and **14** were in accord with those reported (8, 11).

Finally, the procedure of Taylor *et al.* (8) was applied to the synthesis of (*S*)-glaucine (**4**). To this end, (*S*)-laudanosine (**3**) in 82% ee, prepared in the manner previously described (1*b*), was treated with thallium(III) trifluoroacetate. Oxidative coupling occurred in the expected fashion affording (+)-



6

7 R = Et
8 R = Me

9 R = Et
10 R = Me

1 R = Et
5 R = Me

SCHEME 1

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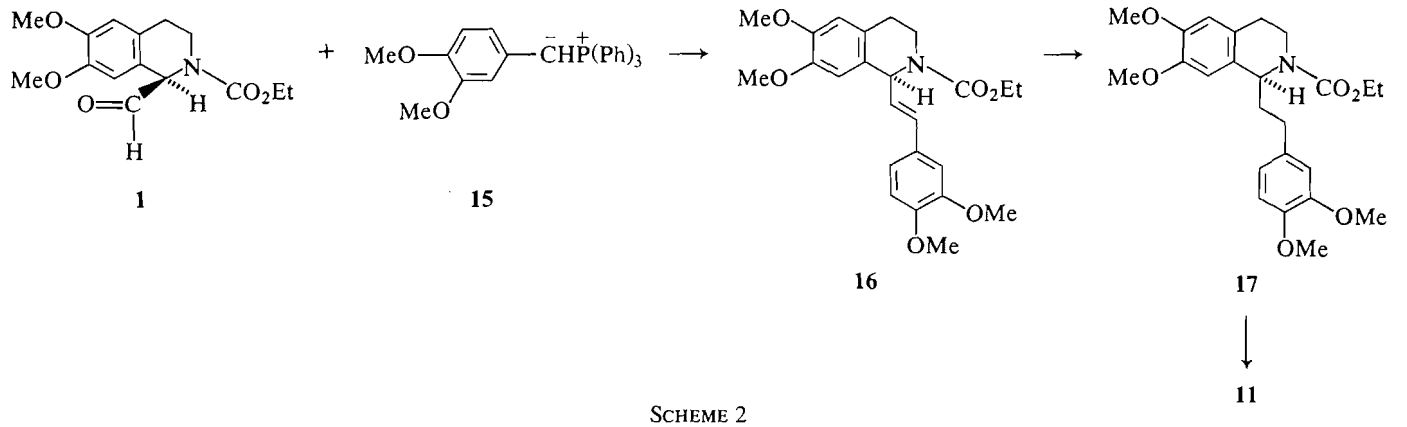
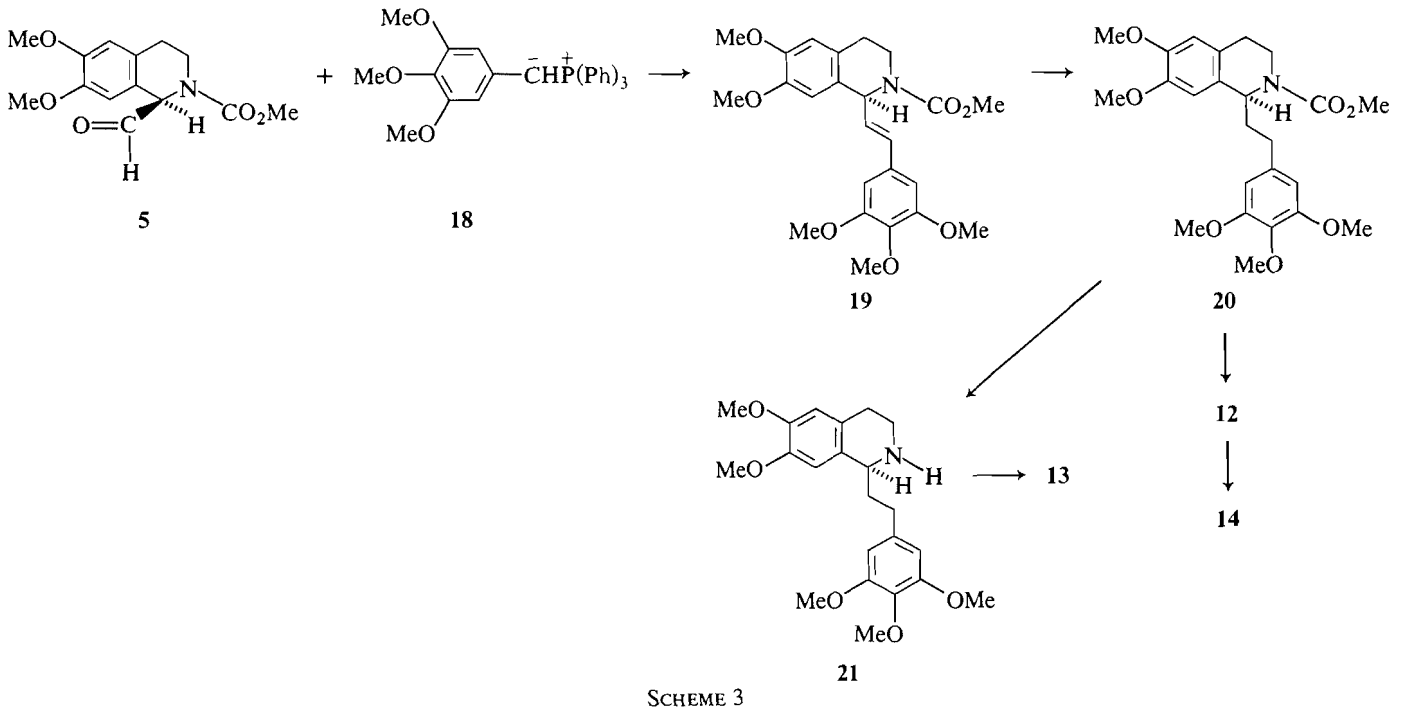


SCHEME 2



SCHEME 3

glaucine in 47% chemical yield and in 83% ee. Thus, the coupling reaction proceeded without racemization at the asymmetric centre.

The work described in this article is a further demonstration of the utility of 2-alkoxycarbonyl-1-formyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolines in the synthesis of a wide variety of isoquinoline alkaloids of high enantiomeric purity. Of the three routes developed by us for the preparation of the (*R*)-aldehydes, the one described in this article, namely that from D-(−)-tartaric acid, is the method of choice.

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 (1 Torr = 133.3 Pa) as reagent gas; data are given as *m*/*z* (% relative intensity).

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 Andersen *et al.* (12). 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.

*Methyl [(2S,3R)-dihydroxy-3-(6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinolin-1′(R)-yl)]propanoate hydrochloride (**6**)*

The compound was prepared by the procedure of Dörnyei and Szántay (5) except that D-tartaric acid (2*S*,3*S*) was used in place of the enantiomer employed in the earlier study.[3] The hydrochloride was obtained as colorless crystals from methanol in 57% overall yield from D-tartaric acid; mp 184–186°C (lit. (5) mp 186–187°C for the enantiomer); $[\alpha]_D^{25}$ −82.2° (*c* 1.31, H_2O); ^{1}H nmr (500 MHz, DMSO-d_6) δ: 2.84 (1H, m, C-3′ H_{ax}), 2.99 (2H, m, C-4′ H's), 3.05 (2H, m, disappeared in D_2O, 2 × OH), 3.33 (2H, br s, disappeared in D_2O, NH_2), 3.54 (1H, m, C-3′ H_{eq}), 3.67 (3H, s, CO_2CH_3), 3.75 and

[3]The previous authors have inadvertently designated the acid employed by them as D-tartaric acid; however, their stereostructures clearly show that the L-isomer, (2*R*,3*R*), was used.

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3.76 (3H each, s's, 2 × OCH_3), 3.98 (1H, d, J = 1.1 Hz, C-1′ H), 4.45–4.65 (2H, br m, C-2 H and C-3′ H, collapses to br s at 4.64 on addition of D_2O), 6.85 and 6.89 (1H each, s's, C-5′ and C-8′ H's).

Preparation of carbamate 7 by treatment of 6 with ethyl chloroformate

Ethyl chloroformate (12 mL) was added dropwise over a period of 30 min to a vigorously stirred solution of **6** (10.77 g) in pyridine (100 mL). The temperature was maintained in the range 5–10°C during the addition and the mixture was stirred an additional 45 min at 5°C. The pyridine was then removed under reduced pressure and the residue taken up in $CHCl_3$. The $CHCl_3$ solution was washed first with water, then with 2% HCl(aq), and again with water before drying over $MgSO_4$. Evaporation of the solvent yielded a residue that crystallized from CH_3OH–Et_2O. The product **7** (13.99 g, 86% based on **1**) melted at 159–161°C; $[\alpha]_D^{25}$ +112.8° (*c* 1.66, $CHCl_3$); ^1H nmr (90 MHz, $CDCl_3$) δ: 1.11, 1.23, 1.38 (3H each, t's, J = 7.1, 7.3 and 6.7 Hz, resp., 3 × CH_2CH_3), 2.73–2.95 (2H, m, C-4′ H's), 3.30–3.57 (2H, m, C-3′ H's), 3.78 (3H, s, CO_2CH_3), 3.87 (6H, s, 2 × OCH_3), 3.93–4.37 (6H, m, 3 × CH_2CH_3), 5.27–5.40 (3H, m, C-1′ H, C-3 H, and C-2 H), 6.65 and 6.83 (1H each, s's, C-5′ H and C-8′ H); ms (CI, NH_3) *m/z* (%): 528 (M + 1, 100), 264 (85), 192 (10). *Anal.* calcd. for $C_{24}H_{33}NO_{12}$: C 54.64, H 6.31, N 2.65; found: C 54.83, H 6.63, N 2.40.

Preparation of carbamate 8 by treatment of 6 with methyl chloroformate

Methyl chloroformate (17.8 mL) was added to a solution of **6** (14.4 g) in pyridine (150 mL) under conditions identical with those described for the preparation of **7**. The reaction mixture was processed similarly affording **8** (17.7 g, 88% from **1**) as white crystals from $CHCl_3$–MeOH–Et_2O; mp 178–180°C; $[\alpha]_D^{25}$ +114.8° (*c* 1.97, $CHCl_3$); ^1H nmr (90 MHz, $CDCl_3$) δ: 2.73–2.97 (2H, m, C-4′ H's), 3.26–3.50 (2H, m, C-3′ H's), 3.57 (3H, s, CO_2CH_3), 3.70, 3.85, 3.88, 3.89, 3.90 (3H each, 5s, 5 × OCH_3), 5.27–5.38 (3H, m, C-1′ H, C-2 H, C-3 H), 6.65 and 6.95 (1H each, s's, C-5′ and C-8′ H's); ms (CI, NH_3) *m/z* (%): 486 (M + 1, 50), 250 (100).

Methyl [(2S,3R)-dihydroxy-3-(N-ethoxycarbonyl-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinolin-1′-(R)-yl)]propanoate (9): methanolysis of 7

A solution of **7** (1.095 g) and NaOMe (200 mg) in dry MeOH (100 mL) was stirred at room temperature under nitrogen for 4 h or until the reaction was complete. The reaction was monitored by tlc (solvent system, 5% MeOH in $CHCl_3$). The solution was neutralized with acetic acid and evaporated to dryness. The residue was treated with H_2O (50 mL) and $CHCl_3$ (50 mL), the $CHCl_3$ layer separated and washed with saturated $NaHCO_3$(aq). The $CHCl_3$ solution was dried over $MgSO_4$ and evaporated, and the residue was taken up in $CHCl_3$ and chromatographed on a column of silica gel. The nonpolar impurities were eluted with $CHCl_3$ and compound **9** with 5% MeOH in $CHCl_3$. The product (640 mg, 80.4%) was obtained as an unstable oil; $[\alpha]_D^{25}$ +29.3° (*c* 1.28, $CHCl_3$); ^1H nmr (90 MHz, $CDCl_3$) δ: 1.27 (3H, t, J = 7.5 Hz, CH_2CH_3), 2.83 (2H, apparent t, J = 6.4 Hz, C-4′ H's), 3.30–3.67 (2H, m, C-3′ H's), 3.20 (2H, m, disappeared in D_2O, 2 × OH), 3.75 (3H, s, CO_2CH_3), 3.85 (6H, s, 2 × OCH_3), 4.02 (1H, m, sharpens on addition of D_2O to a broad doublet, J = 9.0 Hz, C-3 H), 4.20 (2H, q, J = 7.5 Hz, CH_2CH_3), 4.38 (1H, m, sharpens on addition of D_2O to doublet, J = 1.5 Hz, C-2 H), 4.98 (1H, d, J = 9.0 Hz, C-1′ H), 6.66 and 6.97 (1H each, s's, C-5′ H and C-8′ H); ms (CI, NH_3) *m/z* (%): 384 (M + 1, 25), 338 (28), 294 (85), 264 (80), 236 (60), 192 (100), 176 (40).

Methyl [(2S,3R)-dihydroxy-3-(N-methoxycarbonyl-6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinolin-1′-(R)-yl)]propanoate (10): methanolysis of 8

A solution of **8** (1.148 g) and NaOMe (238 mg) in dry MeOH (100 mL) was treated under the same conditions as those described above for the methanolysis of **7**. Compound **10** was isolated as an unstable oil (609 mg, 69.8%); $[\alpha]_D^{25}$ +27.3° (*c* 1.63, $CHCl_3$); ^1H nmr (90 MHz, $CDCl_3$) δ: 2.83 (2H apparent t, J = 7.5 Hz, C-4′ H's), 3.40–3.61 (2H, m, C-3′ H's), 3.50 (2H, m, disappeared in D_2O, 2 × OH), 3.78 and 3.88 (6H each, s's, 4 × OCH_3), 4.05 (1H, m, on addition of D_2O becomes dd, J = 1.5 and 9.0 Hz, C-3 H), 4.43 (1H, d, J = 1.5 Hz, C-2 H), 5.12 (1H, d, J = 9.0 Hz, C-1′ H); 6.68 and 7.00 (1H each, s's, C-5′ and C-8′ H); ms (CI, NH_3) *m/z* (%): 370 (M + 1, 100), 250 (100).

(R)-2-Ethoxycarbonyl-1-formyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (1)

A solution of $NaIO_4$ (852 mg) in H_2O (30 mL) was added over a period of 5 min to a stirred solution of **9** (762 mg) in MeOH (100 mL) at 5°C. The resulting mixture was stirred at the same temperature for 1 h and then filtered to remove inorganic precipitates. The methanol was then evaporated, benzene (100 mL) was added to the residue, and the organic layer was washed three times with water (50 mL each) before drying over $MgSO_4$. Evaporation of the solvent yielded **1** as a colorless oil (554 mg, 95%), which was used immediately. The analytical properties of **1** were identical with those already described (*1b,c*).

(R)-2-Methoxycarbonyl-1-formyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5)

Compound **5** was prepared from **10** using a procedure identical with that described for the conversion of **9** to **1**. Thus, **10** (2.435 g) in MeOH (220 mL) was treated with $NaIO_4$ (2.72 g) in H_2O (50 mL). The product **5** isolated in similar fashion to **1** was an oil (1.84 g, 90%), which rapidly racemizes and must be used immediately in subsequent steps; ^1H nmr (90 MHz, $CDCl_3$) δ: 2.76–2.87 (2H, m, C-4 H's), 3.23–3.57 (2H, m, C-3 H's), 3.82 (3H, s, CO_2CH_3), 3.90 and 3.93 (3H each, s's, 2 × OCH_3), 5.36 (1H, br s, C-1 H), 6.72 and 6.88 (1H each, s's, C-5 H and C-8 H), 9.60 (1H, s, CH=O); ms (CI, NH_3) *m/z* (%): 280 (M + 1, 100), 250 (14). *Mol. Wt.* calcd. for $C_{14}H_{17}NO_5$: 279.1107; found (hrms): 279.1111.

Preparation of homolaudanosine (11)

(a) Preparation of the Wittig reagent 15

3,4-Dimethoxybenzyltriphenylphosphonium chloride was prepared by heating on the steam bath for 1 h a mixture of 3,4-dimethoxybenzyl chloride (2.98 g) and triphenylphosphine (4.21 g). The crystalline product (6.33 g, 88%) obtained from EtOH melted at 235–237°C. A suspension of the salt (908 mg) in dry THF (50 mL) was treated under nitrogen at −78°C over a 5-min period with *n*-butyllithium (0.93 mL of 2.4 *M* *n*-BuLi in hexane). The orange-colored mixture was stirred for another 0.5 h at the same temperature and then slowly warmed to −20°C at which temperature it was maintained for another 0.5 h. The solution containing the ylid **15** was cooled to −78°C before proceeding to the next step.

(b) Preparation of 16 by treatment of 1 with the Wittig reagent 15

To the solution prepared in (*a*) above was added all at once a solution of freshly prepared **1** (590 mg) in THF (10 mL). The reaction mixture was stirred vigorously during the addition and for another 2 h at −78 to −60°C. The mixture was stored in a freezer overnight at −30°C before removing the solvent. The residue was thoroughly extracted with dry Et_2O (6 × 30 mL each), and the extract dried and evaporated. The residue was taken up in 5% EtOAc in C_6H_6 and chromatographed on a column of silica gel with the same solvent system. Compound **16** was isolated as a colorless oil (596 mg, 69%); $[\alpha]_D^{25}$ +135.5° (*c* 0.90, $CHCl_3$); ^1H nmr (90 MHz, $CDCl_3$) δ: 1.32 (3H, t, J = 7.5 Hz, CH_2CH_3), 2.66–2.93 (2H, m, C-4 H's), 3.10–3.50 (2H, m, C-3 H's), 3.85 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.92 (6H, s, 2 × OCH_3), 4.23 (2H, q, J = 7.5 Hz, CH_2CH_3), 5.73 (1H, d, J = 4.5 Hz, C-1 H), 6.06–6.51 (2H, m, $J \approx$ 16.0 Hz, C-7′ H and C-8′ H),[4] 6.72 (2H, apparent s, C-5 and C-8 H's), 6.86 (1H, br s, C-2′ H), 6.93 (2H, m, C-5′ and C-6′ H's); ms (CI, NH_3) *m/z* (%): 428 (M + 1, 60), 354 (15), 264 (100).

(c) Preparation of 17 by catalytic reduction of 16

Compound **16** (224 mg) prepared above was dissolved in EtOH (50 mL) and treated with H_2 over Adams' catalyst for 4 h at 1 atm (1 atm = 101.3 kPa). The catalyst was separated by filtration and the solvent evaporated, affording **17** as a colorless oil (218 mg, 97%);

[4]The C-8′ proton is coupled to the C-1 proton but the signal is poorly resolved even at 50°C presumably because of restricted rotation of the carbamate function.

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$[\alpha]_D^{25}$ +64.9° (*c* 1.68, $CHCl_3$); ^1H nmr (90 MHz, $CDCl_3$) δ: 1.30 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 1.92–2.25 (2H, m, C-8′ H's), 2.55–2.93 (4H, m, C-4 H's and C-7′ H's), 3.05–3.48 (2H, m, C-3 H's), 3.85 (9H, apparent s, 3 × OCH_3), 3.88 (3H, s, OCH_3), 4.22 (2H, q, *J* = 7.2 Hz, CH_2CH_3), 5.17 (1H, apparent t, *J* = 7.5 Hz, C-1 H), 6.60 and 6.63 (1H each, s's, C-5 and C-8 H's), 6.82 (3H, br s, C-2′, C-5′, and C-6′ H's); ms (CI, NH_3) *m/z* (%): 430 (M + 1, 20), 358 (10), 328 (5), 296 (11), 264 (100). *Mol. Wt.* calcd. for $C_{24}H_{31}NO_6$: 429.2151; found (hrms): 429.2149.

(d) Preparation of ***11*** *by reduction of* ***17*** *with lithium aluminium hydride*

Compound **17** (417 mg), dissolved in THF (75 mL), was treated with LAH (400 mg). The mixture was then heated under reflux for 1.5 h, cooled, and the excess of hydride decomposed by addition of saturated NaCl(aq). Chloroform (30 mL) and $MgSO_4$ (ca. 2 g) were added and the mixture was heated under reflux for 15 min. The cooled mixture was filtered free of inorganic salts, the solids were washed twice with boiling $CHCl_3$, and the combined filtrate evaporated to dryness. The residue was taken up in $CHCl_3$, adsorbed on a column of silica gel, and eluted with 2% MeOH in $CHCl_3$. Homolaudanosine (**11**) was obtained as a colorless oil (254 mg, 70.1%); $[\alpha]_D^{25}$ +8.61° (*c* 0.85, EtOH) (lit. (6) $[\alpha]_D^{25}$ +11.0° (*c* 0.21, EtOH)]; ^1H nmr (500 MHz, $CDCl_3$) δ: 2.02 (2H, m, C-8′ H's), 2.45 (3H, s, NCH_3), 2.51 (1H, m, C-3 H_{ax}), 2.70 (4H, m, C-4 H's and C-7′ H's), 3.13 (1H, m, C-3 H_{eq}), 3.40 (1H, t, *J* = 5.4 Hz, C-1 H), 3.78, 3.79, 3.80, 3.82 (3H each, s's, 4 × OCH_3), 6.51 and 6.54 (1H each, s's, C-5 and C-8 H's), 6.69 (1H, d, *J* = 1.8 Hz, C-2′ H), 6.70 (1H, dd, *J* = 1.8 and 8.4 Hz, C-6′ H), 6.75 (1H, d, *J* = 8.4 Hz, C-5′ H) (lit. spectrum (6)); ms (CI, NH_3) *m/z* (%): 372 (M + 1, 100), 342 (7). *Mol. Wt.* calcd. for $C_{22}H_{29}NO_4$: 371.2097; found (hrms): 371.2099.

Preparation of homoprotoberberine ***13***

(a) Preparation of the Wittig reagent ***18***

3,4,5-Trimethoxybenzyltriphenylphosphonium chloride was prepared by heating on the steam bath for 1 h a mixture of triphenylphosphine (1.65 g) and 3,4,5-trimethoxybenzyl chloride (1.37 g). The product was recrystallized from EtOH, affording colorless crystals (2.53 g, 84%), mp 234–236°C. A suspension of the product chloride (1.42 g) in THF (200 mL) was treated under nitrogen at −78°C over a period of 5 min with *n*-butyllithium (1.38 mL of 2.4 *M* *n*-BuLi in hexane). The orange solution containing the ylid **18** was kept at this temperature for 0.5 h and then warmed to −20°C for another 0.5 h.

(b) Preparation of ***19*** *by treatment of* ***5*** *with the Wittig reagent* ***18***

The Wittig reagent prepared above was cooled to −78°C and treated all at once with a solution of freshly prepared **5** (820 mg) in THF (10 mL). The reaction mixture was processed in the same manner as that described above for the preparation of **16**, affording **19** as a colorless oil (865 mg, 66%); $[\alpha]_D^{25}$ +129.4° (*c* 0.935, $CHCl_3$); ^1H nmr (90 MHz, $CDCl_3$) δ: 2.68–2.93 (2H, m, C-4 H's), 3.10–3.48 (2H, m, C-3 H's), 3.80 (3H, s, CO_2Me), 3.88 (15H, br s, 5 × OCH_3), 5.77 (1H, d, *J* ≈ 1.0 Hz, C-1 H), 5.97–6.40 (2H, AB m, *J* ≈ 15 Hz, C-7′ and C-8′ H's), 6.65 and 6.73 (2H each, apparent s's, C-2′ H, C-6′ H, C-5 H, and C-8 H); ms (CI, NH_3) *m/z* (%): 444 (M + 1, 45), 250 (100). *Mol. Wt.* calcd. for $C_{24}H_{29}NO_7$: 443.1944; found (hrms): 443.1955.

(c) Preparation of ***20*** *by catalytic reduction of* ***19***

Compound **19** (758 mg) was treated with H_2 over Adams' catalyst (140 mg) in methanol in the manner described for the conversion of **16** to **17**. The product **20** was obtained as a colorless oil (746 mg, 98%); $[\alpha]_D^{25}$ +66.2° (*c* 1.12, $CHCl_3$); ^1H nmr (90 MHz, $CDCl_3$) δ: 1.97–2.23 (2H, m, C-8′ H's), 2.58–2.88 (4H, m, C-4 H's and C-7′ H's), 3.05–3.47 (2H, m, C-3 H's), 3.78 (3H, s, CO_2CH_3), 3.88 (15H, apparent s, 5 × OCH_3), 5.18 (1H, br s, C-1 H), 6.48 (2H, apparent s, C-2′ and C-6′ H's), 6.62 and 6.65 (1H each, s's, C-5 and C-8 H's); ms (CI, NH_3) *m/z* (%): 446 (M + 1, 7), 392 (10), 362 (15), 280 (10), 250 (100). *Mol. Wt.* calcd. for $C_{24}H_{31}NO_7$: 445.2101; found (hrms): 445.2115.

(d) Preparation of ***21*** *by treatment of* ***20*** *with methyllithium*

A solution of **20** (255 mg) in THF (5 mL) was added dropwise to a vigorously stirred solution of methyllithium (2.67 mL of 1.5 *M* MeLi in Et_2O) in THF (25 mL) at room temperature. The mixture was stirred for a further 1 h and then the excess of methyllithium was decomposed by the addition of MeOH (1 mL). The solvents were evaporated and a saturated solution of NaCl and enough NH_3(aq) to make the solution strongly basic were added to the residue before extraction with benzene (4 × 20 mL). Evaporation of the dried extract yielded a residue from which compound **21** was obtained as a colorless oil (117 mg, 53%) after purification by column chromatography on silica gel; $[\alpha]_D^{25}$ −12.3° (*c* 1.71, $CHCl_3$); ^1H nmr (90 MHz, $CDCl_3$) δ: 1.83 (1H, br s, disappeared in D_2O, NH), 2.00–2.33 (2H, m, C-8′ H's), 2.60–2.86 (4H, m, C-4 H's and C-7′ H's), 2.98–3.40 (3H, C-1 H and C-3 H's), 3.87 (15H, br s, 5 × OCH_3), 6.48 (2H, apparent s, H-2′ and H-6′), 6.61 and 6.63 (1H each, s's, C-5 and C-8 H's); ms (CI, NH_3) *m/z* (%): 388 (M + 1, 100), 192 (10).

(e) Preparation of ***13*** *by treatment of* ***21*** *with formaldehyde*

A solution of the hydrobromide of **21** (109.0 mg) in H_2O (8 mL) and formaldehyde (5 mL, 37%) was heated under reflux in a nitrogen atmosphere for 3 h. The mixture was cooled, made strongly alkaline by addition of solid NaOH, and extracted 4 times with benzene (15 mL each). The extract was washed with saturated NaCl, dried, and evaporated. The residue was purified by chromatography on silica gel, eluting with 1% MeOH in $CHCl_3$. Compound **13** (54 mg, 58%) was obtained as a glass. The base was converted to the hydrochloride (for measurement of optical rotation), which was isolated also as a glassy solid; $[\alpha]_D^{25}$ −97.8° (*c* 1.07, MeOH) (lit. (10) $[\alpha]_D$ −112.5° (MeOH)); ^1H nmr (90 MHz, $CDCl_3$), free base, δ: 1.80–2.00 (2H, m, C-14 H's), 2.57–2.83 (4H, m, C-5 H's and C-13 H's), 2.97–3.40 (3H, m, C-14a H and C-6 H's), 3.79, 3.81, 3.82, 3.83, 3.84 (3H each, s's, 5 × OCH_3), 3.89 and 3.46 (1H each, ABq, *J* = 17 Hz, C-8 H's), 6.50, 6.57, 6.59 (1H each, s's, C-1 H, C-4 H, and C-12 H) (lit. spectrum (10)); ms (CI, NH_3) *m/z* (%): 400 (M + 1, 100), 208 (52). *Mol. Wt.* calcd. for $C_{23}H_{29}NO_5$: 399.2019; found (hrms): 399.2045.

Preparation of ***12*** *by treatment of* ***20*** *with lithium aluminium hydride*

To a solution of **20** (120 mg) in THF (50 mL) was added LAH (150 mg). The mixture was heated under reflux in a nitrogen atmosphere for 2 h, cooled, and the excess of hydride decomposed by careful addition of a saturated solution of sodium sulfate. Solid $MgSO_4$ and $CHCl_3$ were added to the system, which was then heated under reflux for 5 min. The suspension was filtered, the solid residue washed three times with boiling chloroform, and the combined filtrates evaporated to dryness. The residue was taken up in $CHCl_3$ and adsorbed on a column of silica gel. Elution of the column with 2% MeOH in $CHCl_3$ yielded **12** (78 mg, 72%) as a colorless oil, as the main fraction; $[\alpha]_D^{25}$ +4.51° (*c* 0.96, MeOH) (lit. (9) $[\alpha]_D^{25}$ 4.8° (MeOH)); ^1H nmr (90 MHz, $CDCl_3$) δ: 1.95–2.23 (2H, m, C-8′ H's), 2.50 (3H, s, NCH_3), 2.58–2.83 (4H, m, C-4 H's and C-7′ H's), 3.08–3.53 (3H, m, C-1 H and C-3 H's), 3.87 (15H, br s, 5 × OCH_3), 6.45 (2H, apparent s, H-2′ and H-6′), 6.60 and 6.62 (1H each, s, C-5 H and C-8 H) (lit. spectrum (8, 9)); ms (CI, NH_3) *m/z* (%): 402 (M + 1, 100), 318 (17), 206 (16). *Mol. Wt.* calcd. for $C_{23}H_{31}NO_5$: 401.2202; found (hrms): 401.2204.

*(S)-O-Methylkreysigine (****14****)*

A solution of **12** (150 mg) in freshly distilled and deoxygenated trifluoroacetic acid (100 mL) was treated at 0°C under a nitrogen atmosphere, first with thallium(III) trifluoroacetate (260 mg) and then with boron trifluoride etherate (1 mL). The mixture was stirred for 8 h at 0°C and for an additional 20 h at room temperature. The mixture was then taken to dryness under reduced pressure and the residue treated with H_2O (30 mL). The resulting solution was made strongly alkaline with NH_3 and extracted with $CHCl_3$ (4 × 20 mL). The combined extract was dried over K_2CO_3 and then evaporated. The residual brown oil was purified by preparative layer chromatography on silica plates; 10% MeOH in $CHCl_3$ was used as developing agent. The main fraction eluted from the plates was **14**, obtained as a yellow oil (41 mg, 27%); $[\alpha]_D^{25}$ +68.1° (*c* 0.84, $CHCl_3$) (lit. (11) $[\alpha]_D^{21}$ +81° (*c* 0.43, $CHCl_3$)); ^1H nmr (90 MHz, $CDCl_3$) δ: 1.97–2.33 (2H, m, C-7 H's), 2.43 (3H, s, NCH_3), 2.60–3.40 (7H, m, C-4 H's, C-5 H's, C-6a H, C-8 H's), 3.55, 3.65, 3.84, 3.88, 3.92 (15H, 5s, 5 × OMe), 6.57, 6.70 (each 1H, s, C-3 H and C-9 H) (lit. spectrum (8, 11));

ms (EI) m/z (%): 399 (30), 384 (20), 368 (100). *Mol. Wt.* calcd. for $C_{23}H_{29}NO_5$: 399.2045; found (hrms): 399.2019.

(S)-Glaucine (4)

A solution of (*S*)-laudanosine (1*b*) (76 mg) (82% ee) in freshly distilled and deoxygenated trifluoroacetic acid (70 mL) was treated at 0°C under a nitrogen atmosphere with thallium(III) trifluoroacetate (117 mg) followed by $BF_3 \cdot Et_2O$ (0.6 mL). The temperature was maintained at 0°C for 3 h and the mixture, which was stirred throughout, was allowed to warm slowly to room temperature. The mixture was taken to dryness, the residue taken up in water (30 mL), the resulting solution made strongly alkaline with ammonia and then extracted with $CHCl_3$ (4 × 20 mL). The combined extract was dried over K_2CO_3, evaporated to dryness, and the residual oil chromatographed on a column of silica gel using 2% MeOH in $CHCl_3$. The oily residue (35.4 mg, 47%), obtained on evaporation of the eluant, crystallized on addition of ethyl acetate yielding (+)-glaucine as a colorless crystalline solid; mp 117–118°C; $[\alpha]_D^{25}$ +99.6° (*c* 0.89, $CHCl_3$) (lit. (13) mp 119–120°C (EtOAc); $[\alpha]_D$ +120° ($CHCl_3$)); ^1H nmr (90 MHz, $CDCl_3$) δ: 2.37–3.12 (7H, m, C-4 H's, C-5 H's, C-7 H's, C-6a H), 2.57 (3H, s, N—CH_3), 3.68, 3.90, 3.90, 3.98 (12H each, s's, 4 × OCH_3), 6.63, 6.81 (1H each, s's, C-3 H and C-8 H), 8.16 (1H, s, C-11 H) (lit. spectrum (14)); ms (EI) m/z (%): 355 (80), 354 (100), 340 (50), 324 (23), 206 (34). *Mol. Wt.* calcd. for $C_{21}H_{23}NO_4$: 355.1772; found (hrms): 355.1773.

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