Total Synthesis of the Protoberberine Alkaloid (−)-Xylopinine by Photochemical 1,3-Asymmetric Induction

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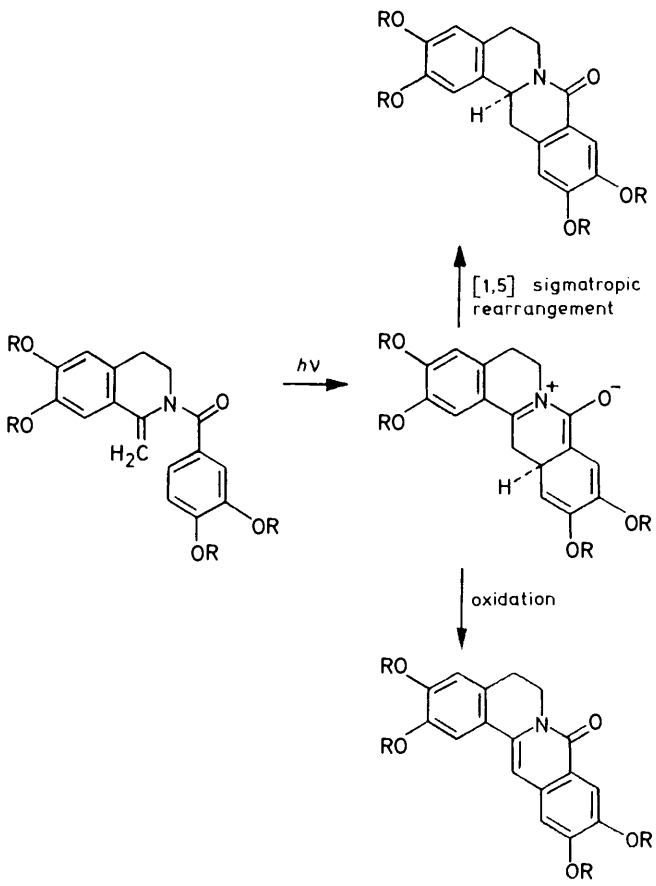
The protoberberine alkaloid, xylopinine (12), has been synthesised in an optically active form, a key reaction being the photochemical cyclisation of optically active 1,2,3,4-tetrahydro-6,7-dimethoxy-3-methoxycarbonyl-1-methylene-2-veratroylisoquinoline (4) with 1,3-asymmetric induction.

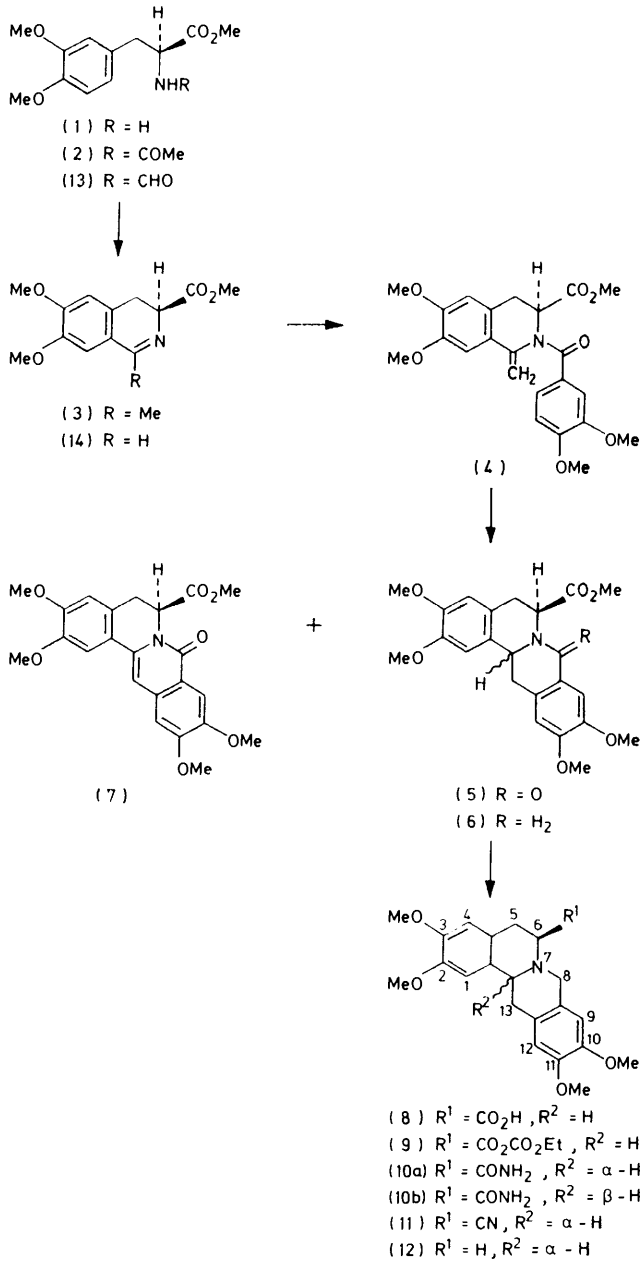
THE photoinduced cyclisation of the enamides, shown in the following Scheme, to give nitrogen-containing heterocycles has been well documented during the last ten years, and a wide range of alkaloids have been synthesised in this way.[1-9] In particular, in the synthesis of protoberberine alkaloids the photocyclisation of enamides has been regarded as a useful route, as has the thermolysis of benzocyclobutenes with 3,4-dihydroisoquinolines.[10-12]



However, no synthesis of a protoberberine alkaloid in optically active form by these methods has been published to date. Here we report the first example of photoinduced asymmetric synthesis of the protoberberine alkaloid (−)-xylopinine.

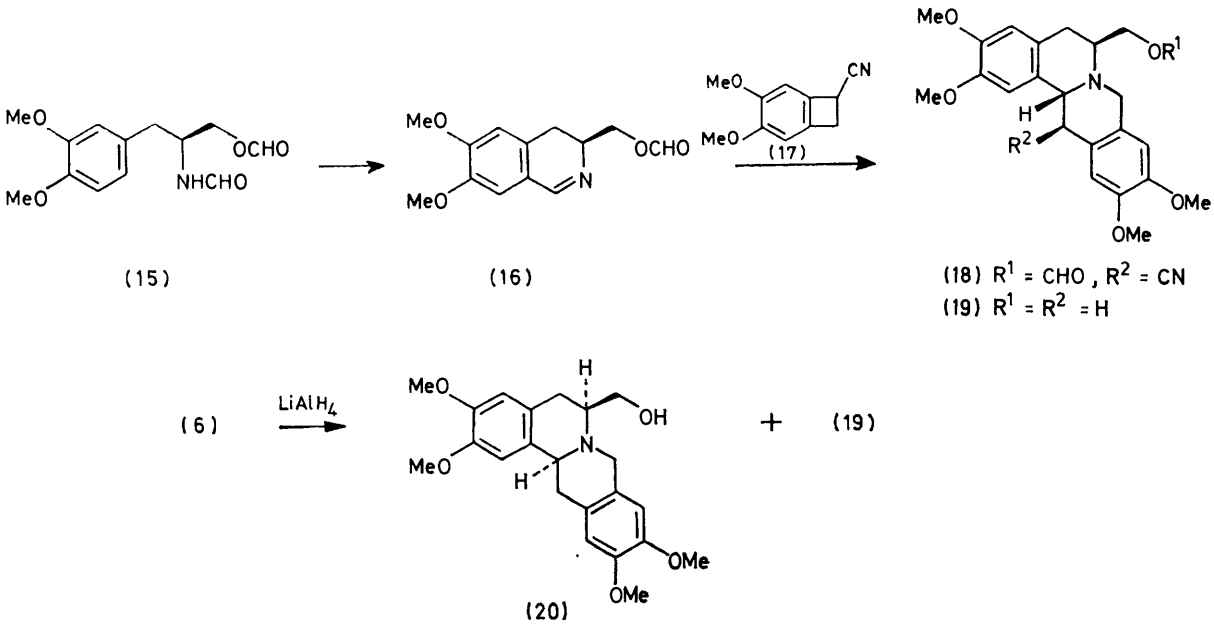
RESULTS AND DISCUSSION

Yamada [13] and his co-workers have reported the synthesis of the isoquinoline alkaloids (−)-laudanosine and (−)-reticuline by the asymmetric Pictet–Spengler reaction (1,3-asymmetric induction) involving (−)-phenylalanine derivatives and sodium glycidate. We therefore decided to exploit the enamide prepared from a (−)-



phenylalanine derivative which would induce 1,3-asymmetric transfer during the photolysis followed by [1,5] sigmatropic rearrangement. Thus, the requisite enamide was synthesised from (−)-3,4-dimethoxyphenylalanine (1) by three steps as follows. Acetylation of the amino-acid (1) [14] with acetic anhydride–pyridine gave the amide (2), which was cyclized with phosphoryl chloride in acetonitrile at 60 °C to afford the 3,4-dihydro-1-methylisoquinoline (3). The enamide (4) was prepared by treatment of (3) with 3,4-dimethoxybenzoyl chloride in the presence of triethylamine in benzene. Irradiation * of a solution of the enamide (4) in dry benzene with a high-pressure mercury lamp equipped with a Pyrex filter at 20—30 °C for 5 h furnished the 8-oxoprotoberberine (5) and the oxidised product (7) in 64.1 and 9.1% yield, respectively. Treatment of compound (5) with phosphoryl chloride gave the quaternary chloride, which without isolation was reduced with sodium borohydride in methanol to afford the amide (6) as an inseparable diastereoisomeric mixture in 88.8% yield. Removal of carboxylate ester unit at the C-6 position from (6) was then carried out to complete the synthesis of the optically active xylopinine. Although difficulties were initially encountered in the conversion of (6) to (12) [*e.g.* attempted decarboxylation by treatment of the acid (8) with phosphoryl chloride [15] or oxalyl chloride,[16] followed by sodium borohydride reduction], adoption of Yamada's procedure [13] with slight modification afforded the desired product. Thus, the ester (6) was hydrolysed with potassium hydroxide in ethanol to the carboxylic acid (8), which was then converted to a separable diastereoisomeric mixture of the primary amides (10a, b) *via* the corresponding mixed anhydride (9) in 45.1% overall yield from (6). Separation of the amides by silica gel column chromatography gave the desired amide (10a) and its isomer (10b) in a ratio of 3.7 : 1. Dehydration of the former amide (10a) with phosphorus pentaoxide and Celite in pyridine afforded the nitrile (11), whose decyanation with sodium borohydride in pyridine and ethanol furnished (−)-xylopinine (12), m.p. 160—163 °C (EtOH), $[\alpha]_D^{20}$ −281° (*c* 0.19, $CHCl_3$) [lit.,[17] $[\alpha]_D$ −297° ($CHCl_3$)] in 66.1% yield. Thus, the synthesis of (−)-xylopinine (optical purity 94.7%) was achieved by photoinduced 1,3-asymmetric induction, and this method is expected to provide a useful route to synthesise various types of alkaloids in an optically active form.

Since it is well known [18,19] that the thermolysis of benzocyclobutenes with optically active dienophiles gives adducts with high optical purity, we investigated the intermolecular cycloaddition of the benzocyclobutene [10] (17) with the (+)-3,4-dihydroisoquinoline (14). However, only the aromatised isoquinoline and the dimer of benzocyclobutene were isolated from the reaction mixture, because of the instability of (14). The benzocyclobutene (17) was then heated with the 3-formyloxy-

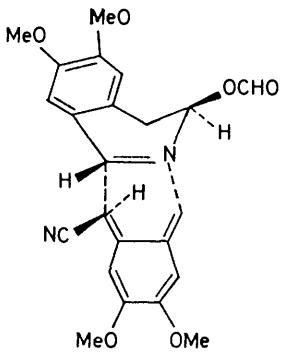


methyl-3,4-dihydroisoquinoline derivative (16) in *o*-dichlorobenzene to afford the adduct (18) in 40% yield. Reductive decyanation of (18) with sodium in liquid ammonia gave the alcohol (19), which showed no Bohlmann bands in the i.r. spectrum. The stereochemistry of the B/C ring junction of (19) was therefore assigned to be *cis*; presumably the *o*-quinodimethane, generated *in situ* by thermolysis of the benzocyclobutene (17), reacted with the 3,4-dihydroisoquinoline (16) from the less hindered side as shown.

To confirm the stereochemistry of (19), the diastereoisomeric mixture of the ester (6) was reduced with lithium aluminium hydride in tetrahydrofuran to give the alcohols (20) and (19) in a ratio of 4 : 1, which is consistent with

* When the irradiation was carried out with a newly purchased u.v. lamp, the lactam (5) was isolated in only 73.3% yield.

that of the primary amides (11a) and (11b). The major alcohol (20), which has been deduced to have a *trans*-B/C ring junction by its conversion to (−)-xylopinine, exhibits characteristic Bohlmann bands at 2 700—2 800 cm^{-1}, whereas the minor one, identical with the specimen (19) obtained from thermolysis of the benzocyclobutene, has no Bohlmann bands in its i.r. spectrum.



The above results show that enantioselective synthesis of protoberberine alkaloids is possible by thermolysis or photolysis.

EXPERIMENTAL

M.p.s were taken with a Yanagimoto micro-melting point apparatus (MP-S2). I.r. spectra were measured with a Hitachi 260-10 recording spectrophotometer, n.m.r. spectra with a JEOL JNM-PMX 60 spectrometer, and mass spectra with a Hitachi M-52G.

N-*Acetyl*-L-3,4-*dimethoxyphenylalanine Methyl Ester* (2).—To a stirred solution of the amine (1) (3.83 g) in pyridine (7.6 ml) was added acetic anhydride (2.3 ml) at ambient temperature. After being stirred for 8 h, the mixture was diluted with water (100 ml), and basified with sodium hydrogencarbonate solution. The basic solution was extracted with chloroform and the extract was washed with water, dried (Na_2SO_4), and evaporated to give the *amide* (2) (3.91 g, 86.9%) as needles (from methanol–ether), m.p. 116 °C (Found: C, 59.65; H, 6.8; N, 4.85. $C_{14}H_{19}NO_5$ requires C, 59.75; H, 6.80; N, 5.00%); $\nu_{max.}$ ($CHCl_3$) 3 450 (NH), 1 740 (C=O), and 1 680 cm^{-1} (C=O); δ($CDCl_3$) 1.99 (3 H, s, COMe), 3.11 (2 H, d, *J* 5.8 Hz, CH_2), 3.75 (3 H, s, CO_2Me), 3.97 (6 H, s, 2 × OMe), 4.93 (1 H, m, CHCO), and 5.85 (1 H, s, NH); $[\alpha]_D^{28}$ +19.9° (*c* 1.30, methanol).

Methyl 3,4-*Dihydro*-6,7-*dimethoxy*-1-*methylisoquinoline*-3-*carboxylate* (3).—A solution of the amide (2) (3.0 g) and phosphoryl chloride (1 ml) in dry acetonitrile (15 ml) was warmed at 60 °C for 2 h. After evaporation of the solvent the residue was basified with 10% ammonium hydroxide solution, and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give the 3,4-dihydroisoquinoline (3) (2.7 g, 99%) as a powder, $\nu_{max.}$ ($CHCl_3$) 1 720 (C=O) and 1 660 cm^{-1} (C=N), which without further purification was used in the following reaction.

Methyl 1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-1-*methylene*-2-*veratroylisoquinoline*-3-*carboxylate* (4).—To a stirred solution of the 3,4-dihydroisoquinoline (3) (2.79 g) and triethylamine (1.60 g) in dry benzene (30 ml) was added a solution of veratroyl chloride (2.13 g) in benzene (10 ml) at room temperature in a current of nitrogen and the resulting mixture was then refluxed for 3 h. After insoluble material had been filtered off the filtrate was concentrated to afford the unstable enamide (4) (4.53 g, 100%); $\nu_{max.}$ ($CHCl_3$) 1 730 (C=O), 1 630 (C=O), and 1 590 cm^{-1} (C=C); δ($CDCl_3$) 4.51 (1 H, s, C=CH*H*) and 5.28 (1 H, s, C=C*H*H).

Photolysis of the Enamide (4).—A solution of the enamide (4) (4.53 g) in dry benzene (700 ml) was irradiated at 20—30 °C with a Riko 400-W high-pressure mercury lamp equipped with a Pyrex filter for 5 h. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel and eluted with chloroform to give the *lactam* (6) (2.90 g, 64.1%) as needles (from methanol), m.p. 157—158 °C (Found: C, 64.05; H, 5.85; N, 2.95. $C_{23}H_{25}NO_2 \cdot 0.25H_2O$ requires C, 63.95; H, 5.95; N, 3.25%); $\nu_{max.}$ ($CHCl_3$) 1 730 (C=O) and 1 640 cm^{-1} (C=O); δ($CDCl_3$), 3.33 (2 H, m, 5-H_2), 3.55 (3 H, s, CO_2Me), 3.75—3.93 (12 H, 4 × OMe), 5.77 (1 H, t, *J* 8 Hz, 13a-H), 5.55 (1 H, m, 6-H), 6.69 (1 H, s, Ar-H), 6.73 (1 H, s, Ar-H), 6.85 (1 H, s, Ar-H), and 7.60 (1 H, s, 9-H), $[\alpha]_D^{22}$ +1.60° (*c* 0.66, chloroform) (Found: M^+, 427.1596. $C_{23}H_{25}NO_4$ requires *M*, 427.1629): and the *dehydro-lactam* (7) (0.41 g, 9.1%) as needles (from methanol), m.p. 158 °C (Found: C, 62.8; H, 5.65; N, 2.95. $C_{23}H_{23}NO_3 \cdot 0.25H_2O$ requires C, 62.95; H, 5.65; N, 3.20%); $\nu_{max.}$ ($CHCl_3$) 1 730 (C=O), 1 630 (C=O), and 1 590 cm^{-1} (C=C); δ($CDCl_3$) 3.16—3.63 (2 H, m, 5-H_2), 3.55 (3 H, s, CO_2Me), 3.92—3.99 (12 H, 4 × OMe), 6.03—6.26 (1 H, m, 6-H), 6.69 (1 H, s, Ar-H), 6.81 (1 H, s, Ar-H), 6.91 (1 H, s, Ar-H), 7.20 (1 H, s, Ar-H), and 7.75 (1 H, s, 9-*H*); $[\alpha]_D^{22}$ −0.94° (*c* 0.64, chloroform) (Found: M^+, 425.1494. $C_{23}H_{23}NO_7$ requires *M*, 425.1747).

Methyl 7,8,13,13a-*Tetrahydro*-2,3,10,11-*tetramethoxyprotoberberine*-6-*carboxylate* (6).—A mixture of the lactam (5) (1.21 g) and phosphoryl chloride (32.9 ml) was refluxed for 2 h and then evaporated. The residue was dissolved in methanol (50 ml) under nitrogen and sodium borohydride (0.33 g) was added in small portions with stirring at 0 °C. After being stirred at the same temperature for 30 min, the solution was evaporated and the residue was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give the *ester* (6) (1.03 g, 88.8%) as needles (from ether–n-hexane), m.p. 101—103 °C (Found: C, 66.5; H, 6.5; N, 3.25. $C_{23}H_{27}NO_6$ requires C, 66.80; H, 6.60; N, 3.40%); $\nu_{max.}$ ($CHCl_3$) 2 750—2 800 cm^{-1} (Bohlmann bands); δ($CDCl_3$) 3.90—3.94 (15 H, 5 × OMe), 6.53 (1 H, s, Ar-H), 6.56 (1 H, s, Ar-H), 6.65 (1 H, s, Ar-H), and 6.73 (1 H, s, Ar-H); $[\alpha]_D^{20}$ −110.82° (*c* 0.39, chloroform); *m/e* 413 (M^+).

7,8,13,13a-*Tetrahydro*-2,3,10,11-*tetramethoxyprotoberberine*-6-*carboxamide* (10a *and* b).—A solution of the ester (6) (573 mg) in 20% ethanolic potassium hydroxide (20 ml) was heated at 80 °C for 20 h. After evaporation of the solvent, the residue was acidified with 10% hydrochloric acid solution and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give the residue, which was re-dissolved in benzene (20 ml), and re-extracted with saturated sodium hydrogencarbonate solution. The aqueous layer was acidified with 10% hydrochloric acid solution and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give the acid (8) (444 mg, 80.1%), which without purification was used directly in the following reaction.

To a solution of the acid (8) (444 mg) and triethylamine (17 mg) in methylene chloride (20 ml) was added ethyl chloroformate (17 mg) at ambient temperature under nitrogen. After being stirred for 3 h, the solution was washed

with water, dried (Na_2SO_4), and evaporated to give the mixed anhydride (9); $\nu_{max.}$ ($CHCl_3$), 1 820 and 1 760 cm^{-1} (C=O); $\delta(CDCl_3)$ 1.23 (3 H, t, *J* 7 Hz, CH_2Me) and 4.23 (2 H, q, *J* 7 Hz, CH_2Me). Through a stirred solution of (9) in chloroform (20 ml) was bubbled dry ammonia gas at room temperature. After being stirred for 3 h, the solution was washed with water, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with chloroform afforded the amide (10a) [195 mg, 53.6% from (6)] (Found: M^+, 398.1819. $C_{22}H_{26}N_2O_6$ requires *M*, 398.1840); $\nu_{max.}$ ($CHCl_3$) 1 675 cm^{-1} (C=O); $\delta(CDCl_3)$ 3.90 (12 H, 4 × OMe), 6.60 (1 H, s, Ar-H), 6.69 (1 H, s, Ar-H), 6.78 (1 H, s, Ar-H), and 6.82 (1 H, s, Ar-H); $[\alpha]_D^{20}$ −55.1° (*c* 0.49, methanol): and the isomer (10b) [54 mg, 14.9% from (6)] (Found: M^+, 398.1821. $C_{22}H_{26}N_2O_5$ requires *M*, 398.1840); $\nu_{max.}$ ($CHCl_3$) 1 675 cm^{-1} (C=O); $\delta(CDCl_3)$ 3.86 (12 H, 4 × OMe), 6.53 (1 H, s, Ar-H), 6.66 (2 H, s, 2 × Ar-H), and 6.68 (1 H, s, Ar-H); $[\alpha]_D^{20}$ −20.3° (*c* 0.14, methanol).

(−)-*Xylopinine* (12).—To a stirred suspension of phosphorus pentaoxide (1.10 g) and Celite (1.95 g) in pyridine (19.5 ml) was added a solution of the amide (10a) (207 mg) in pyridine at 80 °C in a current of nitrogen. After being stirred at 100 °C for 20 min, the insoluble materials were filtered off and the filtrate was concentrated to give the residue, which was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give the nitrile (11), $\nu_{max.}$ ($CHCl_3$) 2 220 cm^{-1} (C≡N), which was directly used in the following reaction. To a stirred solution of the nitrile (11) in pyridine (1.46 ml) and ethanol (3.04 ml) was added sodium borohydride (73 mg) at room temperature, and the mixture was stirred at ambient temperature for 3 days under nitrogen. After evaporation of the solvent, the residue was extracted with chloroform and the extract was washed with water and dried (Na_2SO_4). Evaporation of the solvent afforded a yellow gum, which was subjected to silica gel column chromatography. Elution with chloroform–methanol (99 : 1 v/v) gave (−)-xylopinine (12) (122 mg, 66.1%) as needles, m.p. 160—163 °C (from ethanol) [lit.,[17] 157—158 °C (ethanol)], $[\alpha]_D^{20}$ −281° (*c* 0.19, chloroform) [lit.,[17] −297° (chloroform)] (optical purity 94.7%), identical with an authentic specimen.[19]

Reduction of the Ester (6) *with* $LiAlH_4$.—A mixture of the ester (6) (326 mg), lithium aluminium hydride (60 mg), and dry tetrahydrofuran (20 ml) was refluxed for 5 h in a current of nitrogen. After the addition of a small amount of water, the mixture was filtered through Celite, and the filtrate was concentrated to give the alcohol, which was subjected to silica gel column chromatography. Elution with chloroform–methanol (97.3 v/v) afforded the *alcohol* (20) (132 mg, 43.4%) as needles, m.p. 170—173 °C (from methylene chloride–n-hexane) (Found: C, 68.25; H, 7.0; N, 3.4%; M^+, 385.1915. $C_{22}H_{27}NO_5$ requires C, 68.55; H, 7.05; N, 3.65%; *M*, 385.1890); $\nu_{max.}$ ($CHCl_3$) 3 350 (OH), 2 700—2 800 cm^{-1} (Bohlmann bands); $\delta(CDCl_3)$ 3.80 (12 H, s, 4 × OMe), 6.53 (2 H, s, 2 × Ar-H), 6.58 (1 H, s, Ar-H), and 6.66 (1 H, s, Ar-H); $[\alpha]_D^{20}$ −66.9° (*c* 2.64, chloroform) (Found: M^+, 385.1915. $C_{22}H_{27}NO_5$ requires *M*, 385.1890); and the isomer (11b) (33 mg, 10.9%) as needles, identical with the sample obtained from the thermolysis of the benzocyclobutene (17).

N-*Formyl*-3,4-*dimethoxyphenylalanine Methyl Ester* (15).—A mixture of the amine (1) (10 g), 99% formic acid (90 ml), and acetic anhydride (30 ml) was stirred at room temperature for 30 min. Evaporation of the solvent gave the amide[21] (15) (10.63 g, 96%), m.p. 209—210 °C (from methanol).

Methyl 3,4-*Dihydro*-6,7-*dimethoxyisoquinoline*-3-*carboxylate* (16).—A mixture of the amide (15) (1 g), phosphoryl chloride (1 g), and acetonitrile (20 ml) was stirred at ambient temperature for 30 min, then poured into an excess of n-hexane. The precipitated powder was separated and washed with n-hexane several times to give the *isoquinoline hydrochloride* (16) (0.86 g, 80%), m.p. 173—175 °C (from methanol–n-hexane) (Found: C, 54.75; H, 5.8; N, 4.95. $C_{13}H_{16}ClNO_4$ requires C, 54.65; H, 5.65; N, 4.9%); $\nu_{max.}$ ($CHCl_3$) 1 740 (C=O) and 1 610 cm^{-1} (C=N); $\delta(CDCl_3)$ 3.60 (2 H, d, *J* 6 Hz, Ar-CH_2), 3.80 (3 H, s, OMe), 4.00 (6 H, s, 2 × OMe), and 7.00—7.50 (3 H, m, 3 × Ar-H); $[\alpha]_D^{19}$ +249° (*c* 1.26, chloroform); *m/e* 249 (M^+).

NO-*Diformyl*-L-3,4-*dimethoxyphenylalaninol* (15).—A mixture of L-3,4-dimethoxyphenylalaninol[14] (120 mg), formic acid (4.4 ml), and acetic anhydride (2.0 ml) was stirred at ambient temperature for 30 min, and extracted with methylene chloride. The extract was washed with sodium hydrogencarbonate and water, and dried (Na_2SO_4). Evaporation of the solvent afforded the *amide* (15) (115 mg, 95%) as needles (from benzene–n-hexane), m.p. 73—74 °C (Found: C, 58 35; H, 6.3; N, 5.05. $C_{13}H_{17}NO_5$ requires C, 58.40; H, 6.40; N, 5.25%); $\nu_{max.}$ ($CHCl_3$) 1 720 (C=O) and 1 680 cm^{-1} (C=O); $\delta(CDCl_3)$ 2.70—2.90 (2 H, d, *J* 7 Hz, Ar-CH_2), 3.85 (6 H, s, 2 × OMe), 4.17 (2 H, d, *J* 5 Hz, CH_2OCHO), 6.70 (3 H, s, 3 × Ar-H), 8.05 (2 H, s, NCHO and OCHO); $[\alpha]_D^{20}$ −19.7° (*c* 1.57, chloroform); *m/e* 267 (M^+).

3-*Formyloxymethyl*-3,4-*dihydro*-6,7-*dimethoxyisoquinoline* (16).—A mixture of the amide (15) (500 mg), phosphoryl chloride (0.5 ml), and dry acetonitrile (10 ml) was refluxed for 30 min in a current of nitrogen. After evaporation of the solvent, the residue was basified with 10% ammonium hydroxide solution and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give the 3,4-dihydroisoquinoline (16) (340 mg, 73%) as an amorphous powder; $\nu_{max.}$ ($CHCl_3$) 1 720 (C=O) and 1 630 cm^{-1} (C=N); $\delta(CDCl_3)$ 2.50—2.80 (2 H, m, Ar-CH_2), 3.90 (6 H, s, 2 × OMe), 4.45 (2 H, d, *J* 6 Hz, CH_2OCHO), and 6.75 (2 H, d, *J* 6 Hz, CH=N); *m/e* 249 (M^+): this was converted into the *picrate*, m.p. 168—169 °C (from ethanol) (Found: C, 47.7; H, 3.75; N, 11.55. $C_{19}H_{18}N_4O_{11}$ requires C, 47.70; H, 3.80; N, 11.70%).

13β-*Cyano*-6-*formyloxymethyl*-7,8,13,13a-*tetrahydro*-2,3,10,11-*tetramethoxyprotoberberine* (18).—A solution of benzocyclobutene (17) (190 mg) and 3,4-dihydroisoquinoline (16) (258 mg) in *o*-dichlorobenzene (6 ml) was heated at 180 °C in a current of nitrogen for 3 h. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel and eluted with benzene–acetone (100 : 1 v/v) to give the *protoberberine derivative* (18) (182 mg, 40%) as needles, m.p. 133—134 °C (from benzene–n-hexane) (Found: C, 65.6; H, 5.7; N, 6.25. $C_{24}H_{26}N_2O_6$ requires C, 65.75; H, 6.00; N, 6.40%); $\nu_{max.}$ ($CHCl_3$) 2 225 (C≡N), 1 720 cm^{-1} (C=O); $\delta(CDCl_3)$ 3.90 (12 H, s, 4 × OMe), 6.60—7.20 (4 H, m, 4 × Ar-H), and 8.05 (1 H, s, OCHO); $[\alpha]_D^{20}$ +136.3° (*c* 0.32, chloroform); *m/e* 438 (M^+).

7,8,13,13a-*Tetrahydro*-6-*hydroxymethyl*-2,3,10,11-*tetramethoxyprotoberberine* (19).—To a stirred solution of the cyano-compound (18) (691 mg) in liquid ammonia (100 ml), tetrahydrofuran (10 ml), and propan-2-ol (700 mg) was added lithium metal (22 mg) in a current of nitrogen. After stirring for a further 2 h, the solvent was evaporated to give

the residue, which was extracted with ether. The ethereal layer was washed with water, dried (Na_2SO_4), and evaporated to give the alcohol (19) (533 mg, 88%) as needles (from methylene chloride), m.p. 169—170 °C; $\nu_{max.}$ ($CHCl_3$) 3 550 cm^{-1} (OH); δ($CDCl_3$) 3.90 (12 H, s, 4 × OMe), 6.50—6.70 (4 H, 4 × Ar-H); $[\alpha]_D^{20}$ +97.1° (*c* 0.315, chloroform) (Found: M^+, 385.1925. $C_{22}H_{27}NO_5$ requires *M*, 385.1890).

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