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Chemical Transformation of Protoberberines. VIII.[1] A Novel Synthesis of (±)-Fumaricine and a Formal Synthesis of (±)-Alpinigenine[2]

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Berberine (**1**) was transformed stereoselectively into either the *trans*- or *cis*-hydroxyspirobenzylisoquinoline (**9** or **10**) *via* the 8,14-cycloberbine (**3**). This method was applied to a first transformation of the protoberberine (**22**) into a spirobenzylisoquinoline alkaloid, (±)-fumaricine (**6**).

Irradiation of the phenolbetaine (**24**) derived from the protoberberine (**22**) afforded its valence isomer, the 8,14-cycloberbine (**25**), treatment of which with ethyl chloroformate gave the spirobenzylisoquinoline (**26**). Hydrogenolysis of **26** followed by lithium aluminum hydride reduction provided (±)-fumaricine (**6**). Similarly, palmatine (**31**) was converted *via* the 8,14-cycloberbine (**34**) and the keto-urethane (**35**) into the *trans*-hydroxyspirobenzylisoquinoline (**7**), the key intermediate in a synthesis of (±)-alpinigenine (**8**), a rhoeadine alkaloid.

Keywords——photochemical valence isomerization; regioselective ring cleavage; stereoselective reduction; protoberberine; palmatine; spirobenzylisoquinoline; fumaricine; alpinigenine; 8,14-cycloberbine; ethyl chloroformate

Spirobenzylisoquinoline alkaloids have been shown to be biosynthesized from the corresponding protoberberines.[3] Based on this biogenetic insight, several elegant rearrangements of protoberberine metho salts to a spirobenzylisoquinoline skeleton have been reported.[4-7] Recently we have also developed a novel transformation of berberine (**1**) to the spirobenzylisoquinoline (**4**) using photochemical valence isomerization of berberinephenolbetaine (**2**) followed by regioselective C_8–N bond cleavage of a valence isomer, the 8,14-cycloberbine (**3**).[8,9] However, synthesis of a spirobenzylisoquinoline alkaloid from a protoberberine has not so far been realized. We now describe the application of our methodology to achieving the first transformation of protoberberines into a spirobenzylisoquinoline alkaloid, (±)-fumaricine (**6**) and the spirobenzylisoquinoline (**7**),[10] the key intermediate in a synthesis of (±)-alpinigenine, a rhoeadine alkaloid.

Fumaricine (**6**),[11] an alkaloid from *Fumaria officinalis* L., was synthesized by the indandione method without stereoselectivity.[12] This alkaloid possesses a hydroxy group *trans* to the nitrogen on the five-membered ring (a *trans*-alcohol). In order to synthesize fumaricine stereoselectively, we first investigated the stereoselective synthesis of both the *trans*- and *cis*-alcohol (**9** and **10**) from **1** as a preliminary experiment.

Reduction of the 13-oxospirobenzylisoquinoline (**5**),[13] derived from **3**, with lithium aluminum hydride (LAH) in tetrahydrofuran (THF) afforded only the *trans*-alcohol (**9**) in 74% yield. The stereochemistry of this alcohol was anticipated on the basis of the similar result[10] obtained in the reduction of an analogous 13-oxospirobenzylisoquinoline and further supported by the presence of the band at 3565 cm^{-1} in the infrared (IR) spectrum due to a non-bonded alcohol. On the other hand, the oxazolidinone (**11**),[13] derived stereoselectively from **3** by sodium borohydride reduction and subsequent treatment with ethyl chloroformate,

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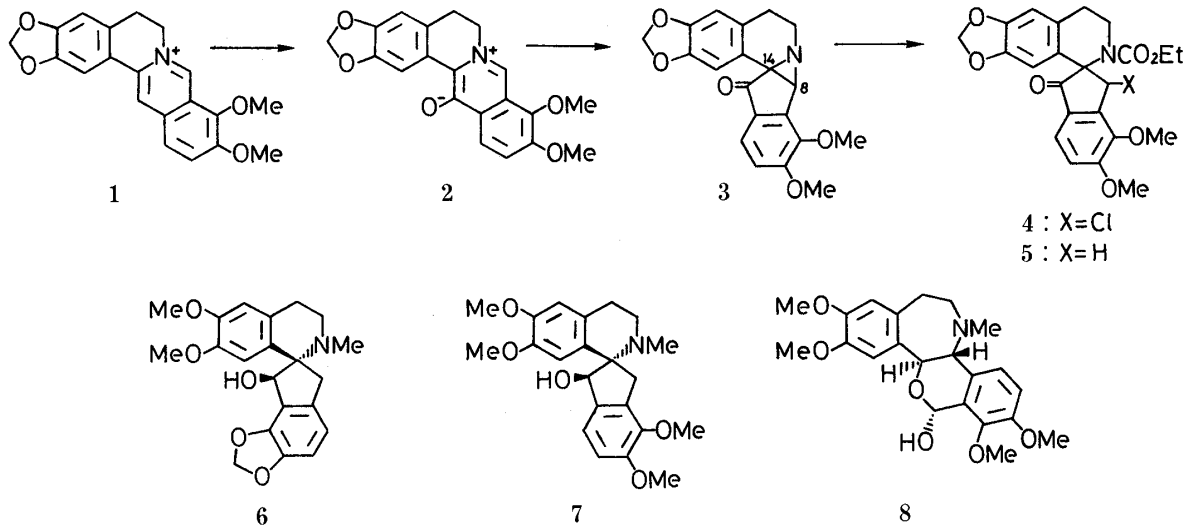

Chart 1

was hydrogenolyzed over 5% palladium on charcoal (Pd–C) to afford the dechlorinated oxazolidinone (**12**) in 97% yield. Reduction of **12** with LAH gave the *cis*-alcohol (**10**) in 62% yield. The stereochemistry of **9** and **10** was unambiguously established by comparison of the chemical shifts [5.24 (**9**) and 4.67 ppm (**10**)] due to H-13 in the proton nuclear magnetic resonance (^{1}H-NMR) spectra. The H-13 proton of **10** resonates at higher field because of the anisotropic effect of the aromatic ring A.[14] Thus, we have developed a procedure for the stereoselective synthesis of the *trans*- and *cis*-alcohol (**9** and **10**) from **1** *via* **3**. This procedure appeared to be promising for application to a total synthesis of fumaricine (**6**) as well as of dihydrofumariline-1 (**13**),[15] an alkaloid possessing a *cis*-alcohol moiety.

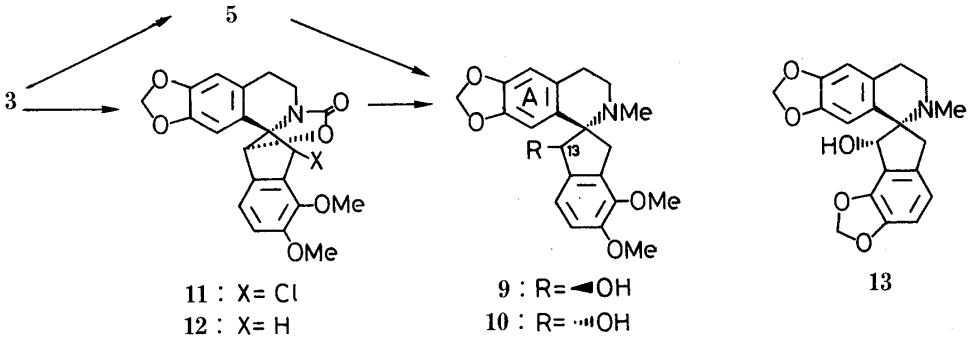

Chart 2

The required starting material for our strategy was the protoberberine (**22**), which was prepared through a conventional route as shown in Chart 3. Condensation of the amine (**14**) with the carboxylic acid (**16**) derived from the nitrile (**15**)[16] gave the amide (**17**) in 90% yield. The Bischler–Napieralski reaction of **17** followed by sodium borohydride reduction of the imine (**18**) afforded quantitatively the amine (**19**), which was treated with 37% formaldehyde in acetic acid to yield the tetrahydroprotoberberine (**20**)[17] along with the *N*-methyl derivative (**21**)[18] in 63 and 23% yields, respectively. Dehydrogenation of **20** with iodine gave quantitatively the desired **22**.

Reduction of **22** with LAH followed by oxidation of the resulting dihydro derivative (**23**) with *m*-chloroperbenzoic acid (*m*-CPBA) afforded the corresponding phenolbetaine (**24**) in 67% overall yield. Irradiation[8] of **24** in methanol effected valence isomerization to give the

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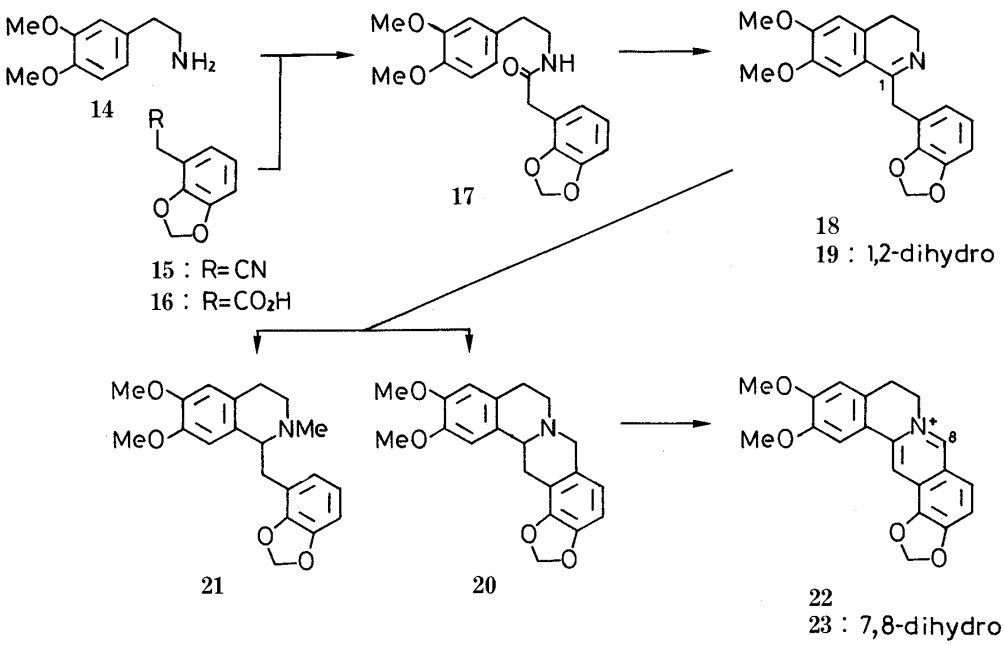

Chart 3

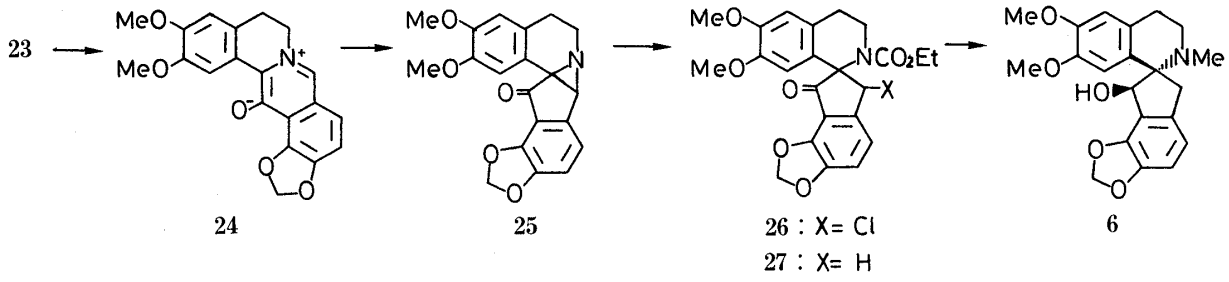

Chart 4

8,14-cycloberbine (**25**) in 45% yield. On treatment with ethyl chloroformate, **25** was subjected to regioselective cleavage of the C_8–N bond to produce the spiro compound (**26**) in 65% yield, and this was hydrogenolyzed over Pd–C to give the keto-urethane (**27**) in 90% yield. Reduction of **27** with LAH in THF afforded (±)-fumaricine (**6**), mp 148—150 °C (lit.[12] mp 147.5—149 °C) in 73% yield. The synthetic (±)-fumaricine was shown to be identical with an authentic sample in ^{1}H-NMR and IR spectral comparisons.

Next, we investigated a formal synthesis of alpinigenine (**8**),[19] a rhoeadine alkaloid from *Papaver alpinum* L., which has already been synthesized through the spirobenzylisoquinoline (**7**) as the key intermediate.[10] The stereochemistry of **7** is exactly the same as that of **6**, and therefore, the above synthetic method could be applied to a synthesis of this intermediate (**7**) from palmatine (**31**).

Palmatine (**31**) was prepared from tetrahydroberberine (**28**) through dihydroxyprotoberberine (**29**),[20] namely, sequential treatment of **28** with boron trichloride and diazomethane gave tetrahydropalmatine (**30**),[21] dehydrogenation of which with iodine[21a] produced **31** in 74% overall yield. Reduction of **31** with LAH followed by oxidation of the resulting dihydropalmatine (**32**) with *m*-CPBA afforded palmatinephenolbetaine (**33**) in 75% overall yield from **31**. Photochemical valence isomerization of **33** yielded the corresponding 8,14-cycloberbine (**34**) in 90% yield. Treatment of **34** with ethyl chloroformate afforded the spiroisoquinoline (**35**) in 70% yield, and this was hydrogenolyzed over Pd–C to produce the

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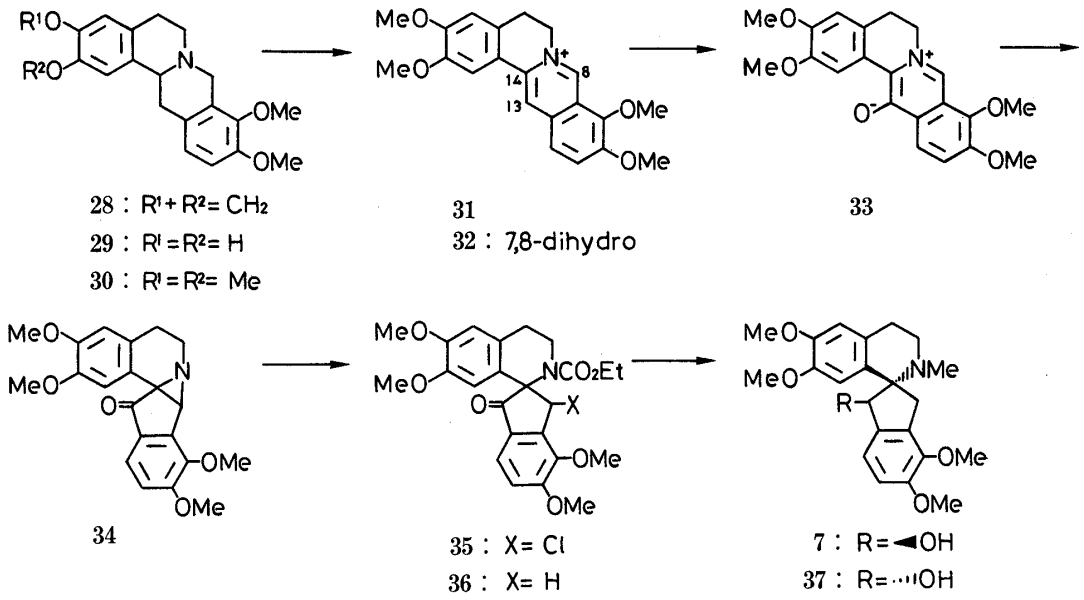

Chart 5

keto-urethane (**36**)[10,22] in 86% yield. Reduction of **36** with LAH in THF[10] provided the *trans*-alcohol (**7**), mp 171—172 °C (lit.[10] mp 173—174 °C), in 73% yield, whereas the same reduction in ether afforded two isomeric alcohols, the *trans*- and *cis*-alcohol (**7** and **37**) in 58 and 11% yields, respectively. Their stereochemistry was confirmed by the chemical shifts due to H-13 in the ^{1}H-NMR spectra [5.29 (**7**) and 4.69 ppm (**37**)]. The ^{1}H-NMR data of **7** were identical with those reported[10] for the key intermediate (**7**). As **7** has already been converted to (±)-alpinigenine (**8**),[10] the present synthesis of **7** amounts to a formal synthesis of this alkaloid.

Thus, we accomplished a stereoselective total synthesis of (±)-fumaricine and a formal synthesis of (±)-alpinigenine from the corresponding protoberberines by using our method[8] for the synthesis of spirobenzylisoquinolines *via* 8,14-cycloberbines. The present synthesis confirms the utility of our method as a general and efficient synthesis of spirobenzylisoquinoline alkaloids.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography was carried out with silica gel (Kieselgel 60, 70—230 mesh, Merck) and alumina (Aluminiumoxid 90, Aktivitätsstufe II—III, 70—230 mesh, Merck). Preparative thin-layer chromatography (p-TLC) was performed on alumina (Aluminiumoxid GF_{254} Typ 60/E, Merck). IR spectra were measured with a JASCO A-102 spectrometer, mass spectra (MS) with a Hitachi M-80 mass spectrometer, and ^{1}H-NMR spectra with a JEOL FX-100 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard at 25 °C unless otherwise stated. Irradiation was carried out with a 100 W high-pressure mercury lamp with a Pyrex filter (Riko Kagaku Co.).

***rel*-(13*R*,14*S*)-9,10-Dimethoxy-2,3-methylenedioxyochotensan-13-ol (9)**[23]——A solution of the keto-urethane[13] (**5**) (196 mg) in anhyd. THF (5 ml) was added to a suspension of LAH (70 mg) in anhyd. THF (20 ml) and the resulting mixture was heated under reflux for 2 h with stirring. Excess LAH was decomposed with water. Inorganic precipitates were filtered off and washed with $CHCl_3$. The filtrate and washings were dried and concentrated. The residue was chromatographed on Al_2O_3 with $CHCl_3$ to give the *trans*-alcohol (**9**) (125 mg, 74%) as colorless needles, mp 188—190 °C (MeOH). IR $\nu_{max}^{CCl_4}$ cm^{-1} (0.015 mol solution): 3565 (OH). MS *m/e*: 369 (M^+). ^{1}H-NMR δ: 6.99 (1H, dd, J=8, 0.5 Hz, C_{12}-H), 6.83 (1H, d, J=8 Hz, C_{11}-H), 6.58 (1H, s, C_4-H), 6.21 (1H, s, C_1-H), 5.83, 5.80 (2H, AB-q, J=1 Hz, OCH_2O), 5.33—5.18 [1H, m, C_{13}-H; appeared at 5.24 as a doublet (J=0.5 Hz) on addition of D_2O], 3.90, 3.89 (each 3H, s, $OCH_3\times2$), 3.33, 3.28 (2H, AB-q, J=16.5 Hz, C_8-H), 2.42 (3H, s, NCH_3). *Anal.* Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.19; H, 6.13; N, 3.92.

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***rel*-(13*S*,14*S*)-9,10-Dimethoxy-2,3-methylenedioxynorochotensane-7,13-carbolactone (12)**——A solution of the oxazolidinone[13] (**11**) (130 mg) in AcOEt (25 ml) and EtOH (25 ml) was hydrogenated over 5% Pd–C (80 mg) at room temperature under atmospheric pressure of H_2 until no more hydrogen was absorbed. The catalyst was filtered off and the filtrate was concentrated. The residue was chromatographed on Al_2O_3 with $CHCl_3$ to afford the oxazolidinone (**12**) (115 mg, 97%) as colorless cubes, mp 234—237 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740 (OCO). MS *m/e*: 381 (M^+). ^{1}H-NMR δ: 7.22, 6.96 (2H, AB-q, J=8.5 Hz, C_{12}- and C_{11}-H), 6.57 (1H, s, C_4-H), 6.44 (1H, s, C_1-H), 5.92 (2H, s, OCH_2O), 5.67 (1H, s, C_{13}-H), 3.90, 3.86 (each 3H, s, $OCH_3 \times 2$), 3.55, 3.31 (2H, AB-q, J=17 Hz, C_8-H). *Anal.* Calcd for $C_{21}H_{19}NO_6$: C, 66.13; H, 5.02; N, 3.67. Found: C, 65.98; H, 4.86; N, 3.53.

***rel*-(13*S*,14*S*)-9,10-Dimethoxy-2,3-methylenedioxyochotensan-13-ol (10)**——A solution of the oxazolidinone (**12**) (86 mg) in anhyd. THF (5 ml) was added to a suspension of LAH (100 mg) in anhyd. THF (20 ml) and the resulting mixture was stirred for 8 h at room temperature. Work-up as usual gave the residue, which was chromatographed on Al_2O_3 with $CHCl_3$–MeOH (97:3) to afford the *cis*-alcohol (**10**) (52 mg, 62%) as colorless needles, mp 193—194 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3250 (OH). MS *m/e*: 369 (M^+). ^{1}H-NMR δ: 7.10, 6.82 (2H, AB-q, J=8 Hz, C_{12}- and C_{11}-H), 6.53 (1H, s, C_4-H), 6.18 (1H, s, C_1-H), 5.82, 5.79 (2H, AB-q, J=1.5 Hz, OCH_2O), 4.67 (1H, s, C_{13}-H), 3.89, 3.88 (each 3H, s, $OCH_3 \times 2$), 3.44, 3.15 (2H, AB-q, J=16 Hz, C_8-H), 2.42 (3H, s, NCH_3). *Anal.* Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 67.98; H, 6.26; N, 3.70.

2,3-Methylenedioxyphenylacetic Acid (16)——A solution of KOH (12.3 g) in water (80 ml) was added to a solution of the nitrile[16] (**15**) (14.5 g) in EtOH (80 ml) and the resulting solution was heated under reflux for 3 h with stirring. The organic solvent was evaporated off. The aqueous residue was washed with $CHCl_3$, acidified with conc. HCl, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried, and concentrated to leave the phenylacetic acid (**16**) (15.7 g, 97%) as colorless needles, mp 103—104 °C (iso-Pr_2O). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2500 (OH), 1715 (CO). MS *m/e*: 180 (M^+). ^{1}H-NMR δ: 6.76 (3H, s, Ar-H), 5.95 (2H, s, OCH_2O), 3.64 (2H, s, CH_2). *Anal.* Calcd for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 59.79; H, 4.51.

***N*-(3,4-Dimethoxyphenethyl)-2,3-methylenedioxyphenylacetamide (17)**——A mixture of the phenethylamine (**14**) (8.5 g) and the phenylacetic acid (**16**) (8.5 g) was heated at 180 °C for 3 h under an Ar atmosphere. The reaction mixture was chromatographed on Al_2O_3 with CH_2Cl_2 to afford the amide (**17**) (14.6 g, 90%) as colorless plates, mp 145—147 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH), 1660 (NCO). MS *m/e*: 343 (M^+). ^{1}H-NMR δ: 6.80—6.50 (6H, m, Ar-H), 5.83 (2H, s, OCH_2O), 5.60 (1H, br s, NH), 3.86, 3.83 (each 3H, s, $OCH_3 \times 2$), 3.48 (2H, s, $ArCH_2CO$), 3.44 (2H, t, J=6.5 Hz, $ArCH_2C\underline{H}_2$), 2.70 (2H, t, J=6.5 Hz, $ArC\underline{H}_2CH_2$). *Anal.* Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.24; H, 6.10; N, 4.12.

3,4-Dihydro-6,7-dimethoxy-1-(2,3-methylenedioxyphenylmethyl)isoquinoline (18)——Phosphorus oxychloride (30 ml) was added to a solution of the amide (**17**) (11.6 g) in anhyd. C_6H_6 (200 ml) and the resulting mixture was heated under reflux for 3 h with stirring. C_6H_6 and excess $POCl_3$ were evaporated off. The residue was poured into ice-water, made alkaline with K_2CO_3, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water, dried, and concentrated to leave the oily imine (**18**) (11.2 g, quant.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640 (C=N). MS *m/e*: 325 (M^+). ^{1}H-NMR δ: 7.08 (1H, s, Ar-H), 6.85—6.60 (4H, m, Ar-H), 5.94 (2H, s, OCH_2O), 3.98 (2H, s, $ArCH_2$), 3.88, 3.81 (each 3H, s, $OCH_3 \times 2$), 3.72 (2H, t-like, $ArCH_2C\underline{H}_2$), 2.63 (2H, t-like, $ArC\underline{H}_2CH_2$).

Picrate: Yellow prisms, mp 182—184 °C ($CHCl_3$). *Anal.* Calcd for $C_{19}H_{19}NO_4 \cdot C_6H_3N_3O_7$: C, 54.16; H, 4.00; N, 10.10. Found: C, 54.27; H, 3.86; N, 9.95.

5,8,13,14-Tetrahydro-2,3-dimethoxy-11,12-methylenedioxy-6*H*-dibenzo[*a*,*g*]quinolizine (20) and 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methyl-1-(2,3-methylenedioxyphenylmethyl)isoquinoline (21)——Sodium borohydride (3 g) was added in portions to a solution of the imine (**18**) (11.1 g) in MeOH (300 ml) and stirring was continued for 2 h at room temperature. MeOH was evaporated off and the residue was taken up in CH_2Cl_2. The CH_2Cl_2 layer was washed with water, dried, and concentrated to leave the oily amine (**19**) (11.2 g). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (NH). MS *m/e*: 327 (M^+). ^{1}H-NMR δ: 6.80—6.65 (3H, m, Ar-H), 6.62, 6.58 (each 1H, s, Ar-H), 5.98 (2H, s, OCH_2O), 4.34—4.12 (1H, m, ArCHN), 3.85, 3.81 (each 3H, s, $OCH_3 \times 2$). A solution of the crude amine (**19**) (11.2 g) and 37% aqueous HCHO (110 ml) in AcOH (110 ml) was heated under reflux for 3.5 h with stirring. The solvents were evaporated off and the residue was taken up in $CHCl_3$. The $CHCl_3$ layer was washed with aqueous 10% K_2CO_3, then water, dried, and concentrated. The residue was chromatographed on SiO_2 with CH_2Cl_2–AcOEt (4:1) to afford two fractions. The less polar fraction gave the oily protoberberine (**20**) (7.4 g, 63%). MS *m/e*: 339 (M^+). ^{1}H-NMR δ: 6.74, 6.60 (each 1H, s, C_1- and C_4-H), 6.63, 6.58 (2H, AB-q, J=8 Hz, C_9- and C_{10}-H), 5.93 (2H, s, OCH_2O), 3.88, 3.86 (each 3H, s, $OCH_3 \times 2$).

Picrate: Yellow prisms, mp 190—193 °C (MeOH–$CHCl_3$). *Anal.* Calcd for $C_{20}H_{21}NO_4 \cdot C_6H_3N_3O_7$: C, 54.93; H, 4.26; N, 9.86. Found: C, 54.80; H, 4.20; N, 9.59.

The more polar fraction gave the oily *N*-methyl derivative (**21**) (2.6 g, 23%). MS *m/e*: 341 (M^+). ^{1}H-NMR δ: 6.76—6.52 (4H, m, Ar-H), 6.10 (1H, s, C_8-H), 5.89, 5.82 (2H, AB-q, J=1.5 Hz, OCH_2O), 3.87, 3.57 (each 3H, s, $OCH_3 \times 2$), 2.54 (3H, s, NCH_3).

5,6-Dihydro-2,3-dimethoxy-11,12-methylenedioxydibenzo[*a*,*g*]quinolizinium Iodide (22)——A solution of I_2 (15.4 g) in EtOH (460 ml) was added dropwise to a refluxed solution of the protoberberine (**20**) (7.05 g) and AcOK (9.3 g) in EtOH (230 ml) with stirring for 1 h, and stirring was continued for 2 h at the same temperature. After the

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reaction mixture had cooled to room temperature, the precipitates were collected by filtration. Sulfur dioxide gas was passed through a suspension of the precipitates in water (200 ml) for 2 h with stirring. The yellow precipitates were collected by filtration to give the quaternary iodide (**22**) (10.4 g, quant.) as yellow needles, mp 230 °C (dec.) (MeOH). MS *m/e*: 336 (M^+). ^{1}H-NMR δ (DMSO-d_6, 125 °C): 9.77 (1H, s, C_8-H), 8.50, 7.74, 7.05 (each 1H, s, C_1- C_{13}- and C_4-H), 8.16, 7.70 (2H, AB-q, J=9.5 Hz, C_9- and C_{10}-H), 6.50 (2H, s, OCH_2O), 4.79 (2H, t, J=7 Hz, C_6-H), 3.94, 3.89 (each 3H, s, $OCH_3 \times 2$), 3.23 (2H, t, J=7 Hz, C_5-H). *Anal.* Calcd for $C_{20}H_{18}INO_4 \cdot 2H_2O$: C, 48.11; H, 4.44; N, 2.81. Found: C, 47.99; H, 4.15; N, 2.87.

5,6-Dihydro-2,3-dimethoxy-11,12-methylenedioxydibenzo[*a*,*g*]quinolizinium-13-olate (24)——The quaternary salt (**22**) (8.00 g) was added in portions for 20 min to a stirred suspension of LAH (3.3 g) in anhyd. THF (200 ml) at 0 °C under an N_2 atmosphere, and stirring was continued for 2 h at room temperature. Excess LAH was decomposed with water and inorganic precipitates were removed by filtration through celite and washed with CH_2Cl_2. The filtrate and washings were concentrated to leave the residue, which was chromatographed on Al_2O_3 with CH_2Cl_2 to afford the dihydro derivative (**23**) (5.24 g, 97%) as a yellow solid. MS *m/e*: 337 (M^+). ^{1}H-NMR δ: 7.21 (1H, s, C_1-H), 6.60 (1H, s, C_4-H), 6.51 (2H, s, C_9- and C_{10}-H), 6.04 (1H, s, C_{13}-H), 5.95 (2H, s, OCH_2O), 4.18 (2H, s, C_8-H), 3.93, 3.89 (each 3H, s, $OCH_3 \times 2$). A solution of *m*-CPBA (4.5 g) in CH_2Cl_2 (100 ml) was added dropwise to a stirred solution of the dihydro derivative (**22**) (5.04 g) in CH_2Cl_2 (150 ml) at −30 °C under an N_2 atmosphere for 15 min and the mixture was stirred for a further 1 h at the same temperature. The reaction temperature was allowed to rise to 0 °C, and finely powdered Na_2SO_3 (5 g) was added to the reaction solution. The mixture was stirred vigorously at room temperature for 1 h. The inorganic precipitates were filtered off and the filtrate was concentrated to dryness. The residue was chromatographed on Al_2O_3 with CH_2Cl_2 and CH_2Cl_2–MeOH (49 : 1). The fraction eluted with CH_2Cl_2–MeOH gave the betaine (**24**) (3.62 g, 69%) as orange prisms, mp 142—143.5 °C (MeOH). MS *m/e*: 351 (M^+). High-resolution MS: Calcd for $C_{20}H_{17}NO_5$: 351.1106. Found: 351.1106. ^{1}H-NMR δ: 9.28 (1H, s, C_8-H), 7.51 (1H, s, C_1-H), 7.22, 7.18 (2H, AB-q, J=8.5 Hz, C_9- and C_{10}-H), 6.59 (1H, s, C_4-H), 6.28 (2H, s, OCH_2O), 4.41 (2H, t, J=6 Hz, C_6-H), 4.01, 3.88 (each 3H, s, $OCH_3 \times 2$), 3.01 (2H, t, J=6 Hz, C_5-H).

2,3-Dimethoxy-11,12-methylenedioxy-8,14-cycloberbin-13-one (25)——A solution of the betaine (**24**) (220 mg) in MeOH (250 ml) was irradiated for 50 min at room temperature under an N_2 atmosphere. The solvent was evaporated off. The residue was chromatographed on SiO_2 with C_6H_6–AcOEt (4 : 1) to afford the cycloberbine (**25**) (99 mg, 45%) as colorless cubes, mp 195—197 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (CO). MS *m/e*: 351 (M^+). ^{1}H-NMR δ: 7.38 (1H, s, C_1-H), 6.93 (2H, s, C_9- and C_{10}-H), 6.67 (1H, s, C_4-H), 6.13, 6.12 (2H, AB-q, J=1 Hz, OCH_2O), 3.90, 3.88 (each 3H, s, $OCH_3 \times 2$), 3.85 (1H, s, C_8-H). *Anal.* Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.20; H, 4.78; N, 4.12.

Ethyl 13-Chloro-2,3-dimethoxy-9,10-methylenedioxy-8-oxonorochotensane-7-carboxylate (26)——A solution of the cycloberbine (**25**) (30 mg) and ethyl chloroformate (0.1 g) in C_6H_6 (5 ml) was heated with stirring at 50 °C for 2 h. The solvent was evaporated off and the residue was chromatographed on p-TLC (Al_2O_3, $CHCl_3$) to afford the urethane (**26**) (26 mg, 65%) as pale pink prisms, mp 110—111 °C (isoPr$_2$O). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (CO), 1680 (NCO). MS *m/e*: 459, 461 (3 : 1, M^+). ^{1}H-NMR δ: 7.16 (2H, s, C_{11}- and C_{12}-H), 6.67 (1H, s, C_4-H), 6.20—6.10 (3H, OCH_2O, C_1- or C_{13}-H), 5.99 (1H, s, C_1- or C_{13}-H), 4.13 (2H, br q, J=7 Hz, $OC\underline{H}_2CH_3$), 3.84, 3.45 (each 3H, s, $OCH_3 \times 2$), 1.60—1.20 (3H, br t, J=7 Hz, $OCH_2C\underline{H}_3$). *Anal.* Calcd for $C_{23}H_{22}ClNO_7$: C, 60.07; H, 4.82; N, 3.05. Found: C, 59.83; H, 4.91; N, 3.31.

Ethyl 2,3-Dimethoxy-9,10-methylenedioxy-8-oxonorochotensane-7-carboxylate (27)—A solution of the urethane (**26**) (33 mg) in EtOH (20 ml) was hydrogenated over 5% Pd–C (150 mg) at room temperature under atmospheric pressure of H_2 until no more hydrogen was absorbed. The catalyst was filtered off and the filtrare was concentrated to dryness. The residue was chromatographed on Al_2O_3 with $CHCl_3$ to afford the dechlorinated urethane (**27**) (27 mg, 90%) as colorless needles, mp 192—193.5 °C (EtOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (CO), 1680 (NCO). MS *m/e*: 425 (M^+). ^{1}H-NMR δ: 7.10, 6.83 (2H, AB-q, J=8 Hz, C_9- and C_{10}-H), 6.64 (1H, s, C_4-H), 6.29 (1H, s, C_1-H), 6.12 (2H, s, OCH_2O), 4.26—3.93 (2H, br q, J=7 Hz, $OC\underline{H}_2CH_3$), 3.83, 3.51 (each 3H, s, $OCH_3 \times 2$), 1.39—1.14 (3H, br t, J=7 Hz, $OCH_2C\underline{H}_3$). *Anal.* Calcd for $C_{23}H_{23}NO_7$: C, 64.93; H, 5.45; N, 3.29. Found: C, 64.87; H, 5.46; N, 3.33.

(±)-Fumaricine (6)——A solution of the urethane (**27**), (82.3 mg) in anhyd. THF (2 ml) was added to a suspension of LAH (90 mg) in anhyd. THF (10 ml), and the resulting mixture was heated under reflux for 2.5 h with stirring. Work-up as usual gave the residue, which was chromatographed on Al_2O_3 with $CHCl_3$–MeOH (99 : 1) to afford (±)-fumaricine (**6**) (52.1 mg, 73%) as colorless prisms, mp 148—150 °C (EtOH–isoPr$_2$O) (lit.[12] mp 147.5—149 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), MS *m/e*: 369 (M^+). ^{1}H-NMR δ: 6.74, 6.73 (2H, AB-q, J=9 Hz, C_{11}- and C_{12}-H), 6.60 (1H, s, C_4-H), 6.41 (1H, s, C_1-H), 5.96, 5.94 (2H, AB-q, J=1.5 Hz, OCH_2O), 5.47 (1H, br d, J=6 Hz, C_8-H), 3.84, 3.51 (each 3H, s, $OCH_3 \times 2$), 3.30 (2H, s, C_{13}-H), 2.40 (3H, s, NCH_3). *Anal.* Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.01; H, 6.32; N, 3.72.

Tetrahydropalmatine (30)——A solution of BCl_3 (1.2 g) in CH_2Cl_2 (10 ml) was added dropwise for 10 min to an ice-cooled solution of tetrahydroberberine (**28**) (1.7 g) in CH_2Cl_2 (50 ml) with stirring. The reaction solution was kept standing overnight at room temperature. MeOH (15 ml) was added to the reaction solution and the solvents were evaporated off. The residual precipitates were collected by filtration and washed with ice-cooled MeOH to give the dihydroxyprotoberberine (**29**).[20] A solution of a large excess of CH_2N_2 in Et_2O was added to a solution of the crude

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product (**29**) in MeOH (250 ml) and the reaction solution was evaporated off and the residue was taken up in $CHCl_3$. The $CHCl_3$ layer was washed with 10% aqueous K_2CO_3 then water, dried, and concentrated. The residue was chromatographed on SiO_2 with $CHCl_3$ to afford tetrahydropalmatine (**30**) (1.32 g, 74%) as colorless plates, mp 146—148 °C (AcOEt) (lit.[21a] mp 147 °C). MS *m/e*: 355 (M^+). ^{1}H-NMR δ: 6.85, 6.82 (2H, AB-q, J=8.5 Hz, C_{12}- and C_{11}-H), 6.73, 6.62 (each 1H, s, C_1- and C_4-H), 4.24, 3.55 (2H, AB-q, J=15 Hz, C_8-H), 3.89, 3.87 (each 3H, s, $OCH_3\times2$), 3.86 (6H, s, $OCH_3\times2$). *Anal.* Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09, N, 3.94. Found: C, 70.63; H, 7.06; N, 3.82.

Palmatinium Iodide (31)——According to the method of Kiparissides *et al.*,[21a] **30** was oxidized with I_2 to give quantitatively palmatinium iodide (**31**) as yellow needles, mp 237—238 °C (MeOH) (lit.[21a] mp 237—238 °C). MS *m/e*: 351 (M^+). ^{1}H-NMR δ (DMSO-d_6): 9.88 (1H, s, C_8-H), 9.04 (1H, s, C_{13}-H), 8.20, 8.05 (2H, AB-q, J=9 Hz, C_{12}- and C_{11}-H), 7.71 (1H, s, C_1-H), 7.10 (1H, s, C_4-H), 4.96 (2H, br t, J=5 Hz, C_6-H), 4.11, 4.08, 3.95, 3.88 (each 3H, s, $OCH_3\times4$). *Anal.* Calcd for $C_{21}H_{22}INO_4$: C, 52.62; H, 4.63; N, 2.92. Found: C, 52.43; H, 4.58; N, 2.72.

5,6-Dihydro-2,3,9,10-tetramethoxydibenzo[*a*,*g*]quinolizinium-13-olate [Palmatinephenolbetaine (33)]——Palmatinium iodide (**31**) (1.71 g) was added in portions for 10 min to a suspension of LAH (0.75 g) in anhyd. THF (45 ml) at 0 °C with stirring under an N_2 atmosphere and stirring was continued for a further 3 h at room temperature. Work-up as usual gave dihydropalmatine (**32**) (1.18 g, 94%). MS *m/e*: 353 (M^+), ^{1}H-NMR δ: 7.12 (1H, s, C_1-H), 6.66 (2H, s, C_{12}- and C_{11}-H), 6.53 (1H, s, C_4-H), 5.91 (1H, s, C_{13}-H), 4.27 (2H, s, C_8-H), 3.90, 3.83 (each 3H, s, $OCH_3\times2$), 3.81 (6H, s, $OCH_3\times2$). 3.13 (2H, t, J=5 Hz, C_6-H), 2.86 (2H, t, J=5 Hz, C_5-H). A solution of *m*-CPBA (1.1 g) in CH_2Cl_2 (30 ml) was added dropwise for 15 min to a stirred solution of dihydropalmatine (**32**) (1.18 g) in CH_2Cl_2 (50 ml) at −40 °C under an N_2 atmosphere and the mixture was stirred for a further 1 h at the same temperature. Work-up as usual gave the residue, which was chromatographed on Al_2O_3 with CH_2Cl_2 and CH_2Cl_2–MeOH (50 : 1). The fraction eluted with CH_2Cl_2–MeOH gave the betaine (**33**) (948 mg, 80%) as orange plates, mp 192—193 °C (AcOEt). MS *m/e*: 367 (M^+). ^{1}H-NMR δ: 9.00 (1H, s, C_8-H), 8.10, 7.20 (2H, AB-q, J=9 Hz, C_{12}- and C_{11}-H), 7.57 (1H, s, C_1-H), 6.52 (1H, s, C_4-H), 4.36 (2H, br t, J=7 Hz, C_6-H), 3.95, 3.93, 3.90, 3.78 (each 3H, s, $OCH_3\times4$), 3.03 (2H, br t, J=7 Hz, C_5-H). *Anal.* Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.61; H, 5.66; N, 4.06.

2,3,9,10-Tetramethoxy-8,14-cycloberbin-13-one (34)——A solution of the betaine (**33**) (185 mg) in MeOH (250 ml) was irradiated at room temperature for 1 h under an N_2 atmosphere. The solvent was evaporated off and the residue was chromatographed on Al_2O_3 with C_6H_6–AcOEt (4 : 1) to afford the cycloberbine (**34**) (161 mg, 90%) as colorless scales, mp 165—166 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (CO). MS *m/e*: 367 (M^+). ^{1}H-NMR δ: 7.59, 6.93 (2H, AB-q, J=8.5 Hz, C_{12}- and C_{11}-H), 7.39 (1H, s, C_1-H), 6.69 (1H, s, C_4-H), 4.06 (1H, s, C_8-H), 3.98, 3.94, 3.92, 3.89 (each 3H, s, $OCH_3\times4$). *Anal.* Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.67; H, 5.66; N, 3.59.

Ethyl 8-Chloro-2,3,9,10-tetramethoxy-13-oxonorochotensane-7-carboxylate (35)——A solution of the cycloberbine (**34**) (137 mg) and ethyl chloroformate (0.9 g) in THF (20 ml) was kept standing for 24 h at room temperature. The solvent was evaporated off and the residue was chromatographed on Al_2O_3 with C_6H_6–AcOEt (4 : 1) to afford the urethane (**35**) (126 mg, 70%) as colorless cubes, mp 116—118 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (CO), 1680 (NCO). MS *m/e*: 475, 477 (3 : 1, M^+). ^{1}H-NMR δ: 7.66, 7.12 (2H, AB-q, J=8 Hz, C_{12}- and C_{11}-H), 6.66 (1H, s, C_4-H), 6.12, 5.97 (each 1H, s, C_1- and C_8-H), 3.99, 3.95, 3.85, 3.43 (each 3H, s, $OCH_3\times4$), 1.28 (3H, t, J=6 Hz, $OCH_2C\underline{H}_3$). *Anal.* Calcd for $C_{24}H_{26}ClNO_7$: C, 60.57; H, 5.51; N, 2.94. Found: C, 60.85; H, 5.74; N, 2.91.

Ethyl 2,3,9,10-Tetramethoxy-13-oxonorochotensane-7-carboxylate (36)——A solution of the urethane (**35**) (80 mg) in MeOH (80 ml) was hydrogenated over 5% Pd–C (126 mg) at room temperature under atmospheric pressure of H_2 until no more hydrogen was absorbed. Work-up as usual gave the residue, which was chromatographed on Al_2O_3 with C_6H_6–AcOEt (4 : 1) to afford the dechlorinated urethane (**36**) (63 mg, 86%) as colorless crystals, mp 84—86 °C (Et_2O). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (CO), 1680 (NCO). MS *m/e*: 441 (M^+). High-resolution MS: Calcd for $C_{24}H_{27}NO_7$: 441.1786. Found: 441.1810. ^{1}H-NMR δ: 7.59, 7.02 (2H, AB-q, J=9 Hz, C_{12}- and C_{11}-H), 6.63 (1H, s, C_4-H), 6.16 (1H, s, C_1-H), 3.98, 3.92, 3.82, 3.45 (each 3H, s, $OCH_3\times4$). 3.60 (2H, s, C_8-H), 1.40—1.25 (3H, m, $OCH_2C\underline{H}_3$). ^{1}H-NMR δ (70 °C): 7.52, 7.02 (2H, AB-q, J=9 Hz, C_{12}- and C_{11}-H), 6.63 (1H, s, C_4-H), 6.19 (1H, s, C_1-H), 4.04 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 3.96, 3.91, 3.80, 3.46 (each 3H, s, $OCH_3\times4$), 3.58 (2H, s, C_8-H), 1.04 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$).

***rel*-(13*R*,14*S*)- and *rel*-(13*S*,14*S*)-2,3,9,10-Tetramethoxyochotensan-13-ol (7 and 37)**——1) A solution of the urethane (**36**) (86.7 mg) in anhyd. THF (5 ml) was added to a suspension of LAH (0.1 g) in anhyd. THF (10 ml) and the resulting mixture was heated under reflux for 2.5 h with stirring. Work-up as usual gave the residue which was chromatographed on Al_2O_3 with $CHCl_3$–MeOH (99 : 1) to afford the *trans*-alcohol (**7**) (55.3 mg, 73%) as colorless needles, mp 171—172 °C (EtOH) (lit.[10] mp 173—174 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH). MS *m/e*: 385 (M^+). ^{1}H-NMR δ: 6.98, 6.84 (2H, AB-q, J=8 Hz, C_{12}- and C_{11}-H), 6.60 (1H, s, C_4-H), 6.20 (1H, s, C_1-H), 5.29 (1H, s, C_{13}-H), 3.90, 3.88, 3.83, 3.45 (each 3H, s, $OCH_3\times4$), 3.39, 3.32 (2H, AB-q, J=12 Hz, C_8-H), 2.45 (3H, s, NCH_3). *Anal.* Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.23; H, 7.07; N, 3.53.

2) A solution of the urethane (**36**) (40 mg) in anhyd. Et_2O (3 ml) was added to a suspension of LAH (0.1 g) in anhyd. Et_2O (20 ml) and the resulting mixture was heated under reflux for 10 h with stirring. Work-up as usual gave the residue, which was chromatographed on Al_2O_3 with C_6H_6–AcOEt (4 : 1) to afford two fractions. The less polar fraction gave the *cis*-alcohol (**37**) (4 mg, 11%). MS *m/e*: 385 (M^+). ^{1}H-NMR δ: 7.10, 6.83 (2H, AB-q, J=8 Hz, C_{12}-

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and C_{11}-H), 6.34 (1H, s, C_4-H), 6.16 (1H, s, C_1-H), 4.69 (1H, s, C_{13}-H), 3.90, 3.88, 3.82, 3.43 (each 3H, s, $OCH_3 \times 4$), 2.50 (3H, s, NCH_3). The more polar fraction gave the *trans*-alcohol (7) (20 mg, 58%), which was identical with that obtained in 1).

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