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Chemical Transformation of Protoberberines. VI.[1] Ring D Inversion of Protoberberine Alkaloids. Conversion of Berberine into Non-naturally Occurring 11,12-Oxygenated Protoberberines *via* Spirobenzylisoquinolines[2]

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Three methods were developed for the transformation of naturally occurring 9,10-oxygenated protoberberines into non-naturally occurring 11,12-oxygenated protoberberines through ring D inversion *via* spirobenzylisoquinolines. Berberine (**14**) was converted to the spirobenzylisoquinoline (**18**) through regioselective cleavage of the 8,14-cycloberbine (**17**). Alkaline hydrolysis of the oxazolidinone (**20**) derived from **18** efficiently afforded the 11,12-oxygenated protoberberine (**23**), which was also obtained from 8-methoxyberberinephenolbetaine (**24**) through treatment of the keto-hydroxy-spirobenzylisoquinoline (**25**) with alkali. The spirobenzylisoquinoline (**26**) derived from the 8,14-cycloberbine (**16**) was subjected to hydrogenolysis and subsequent hydrolysis to give the amino-ketone (**28**), photolysis of which furnished the 11,12-oxygenated protoberberine (**29**).

Keywords——11,12-oxygenated protoberberine; ring D inversion; retro-aldol reaction; protoberberine; spirobenzylisoquinoline; berberine; oxazolidinone ring

Ring D inversion seems to be a key step in the biogenetic transformation from protoberberine alkaloids to related alkaloids such as rhoeadine,[3] retroprotoberberine,[4] some spirobenzylisoquinoline,[5] and benzindenoazepine[6] alkaloids, as shown in Chart 1. On the basis of this biogenetic consideration we have synthesized the retroprotoberberine **3**[7] from tetrahydroberberine (**1**) *via* the C_8–N seco-product (**2**) through ring D inversion. A spirobenzylisoquinoline alkaloid, (±)-fumaricine (**4**),[8] and a rhoeadine alkaloid, (±)-*cis*-alpinigenine (**5**),[9] have been prepared from the non-natural 11,12-oxygenated protoberberines (**6** and **7**, respectively), which could be regarded as the ring D inverted products of the natural 9,10-oxygenated protoberberine alkaloids, sinactine (**8**) and tetrahydropalmatine (**9**), respectively.

This paper deals with a novel and efficient synthesis of non-natural 11,12-oxygenated protoberberines from a natural protoberberine alkaloid, berberine, *via* spirobenzylisoquinolines through ring D inversion, even though several conventional syntheses of 11,12-oxygenated protoberberines have already been reported.[10] The strategy for our transformation consists of two steps: the first step is to rearrange C_8 from the nitrogen to C_{14} of the starting protoberberine (**10**) to construct the spirobenzylisoquinoline (**11**), and the second step is to reconstruct the protoberberine (**12**) by rearrangement of the original C_{13} from C_{14} to the nitrogen, namely, the transposition of the a- and b-bonds in a protoberberine with each other *via* a spirobenzylisoquinoline (Chart 3).

In a previous paper,[1] we developed a novel and versatile synthetic method for spirobenzylisoquinolines from protoberberines *via* 8,14-cycloberbines. This method could be applied to the first step in the above strategy. In order to complete the second step, the intermediate spirobenzylisoquinoline should be modified with an appropriate functionality. The most promising one might be the amino-hydroxy-ketone (**13**), treatment of which with

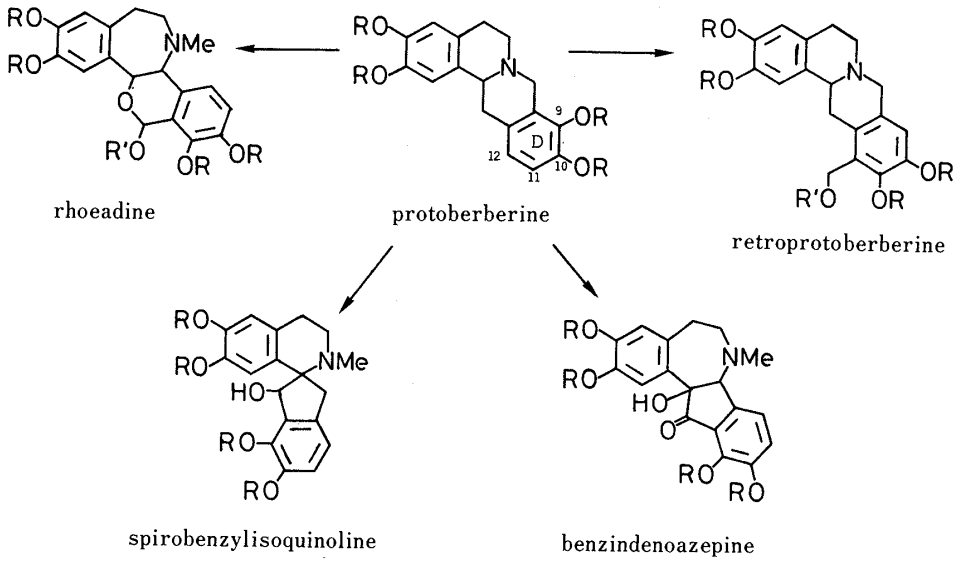

Chart 1

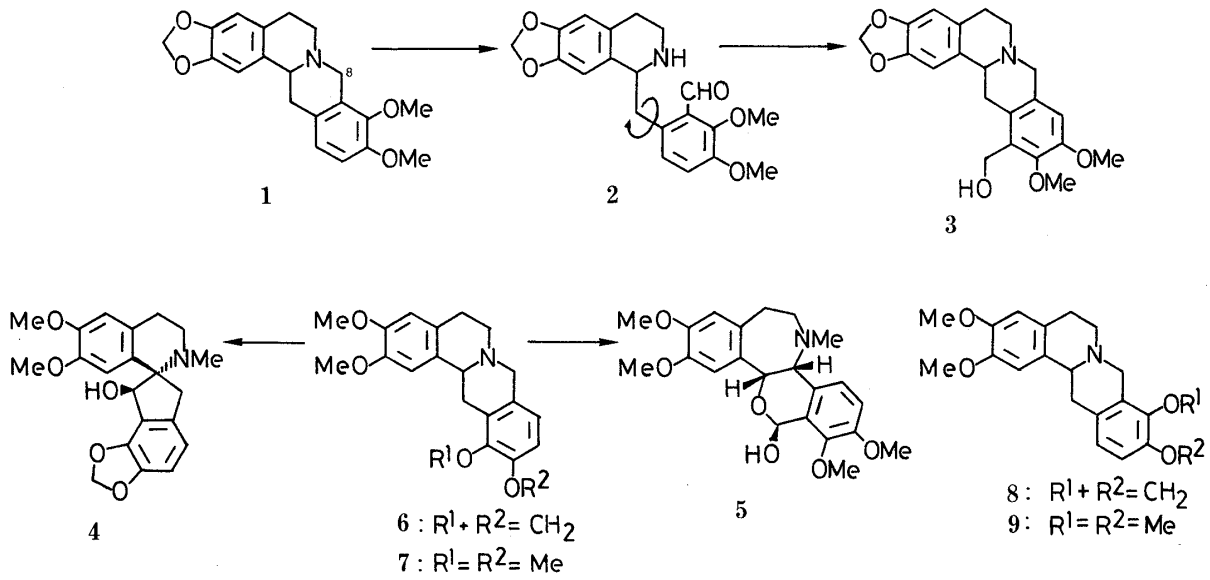

Chart 2

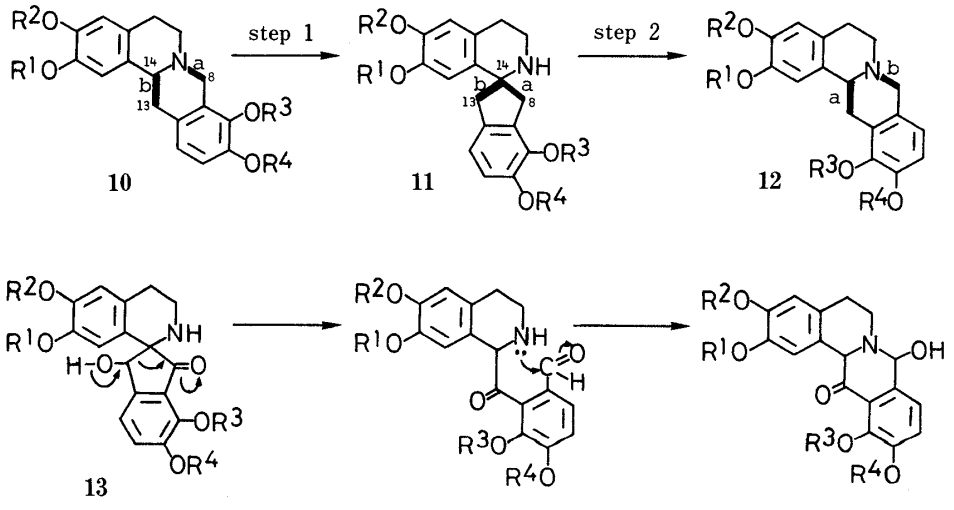

Chart 3

alkali would effect retro-aldol reaction with subsequent cyclization to afford the protoberberine with ring D inversion.

The 8,14-cycloberbine (**16**),[1,11] derived from berberine (**14**) *via* berberinephenolbetaine (**15**), was reduced with sodium borohydride in methanol–chloroform to afford stereoselectively the alcohol (**17**) in 95% yield. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of the product (**17**) exhibited a doublet at 5.63 ppm due to C_{13}–H. When the deshielding effect of the aromatic A ring is taken into account, the *cis*-relationship between C_{13}–H and ring A is suggested by the rather lower chemical shift of the C_{13}–H signal. The alcohol (**17**) was treated with ethyl chloroformate in benzene to give the oxazolidinone (**18**) in 60% yield through regioselective cleavage of the aziridine ring. The product showed a characteristic band due to an oxazolidinone at 1750 cm^{-1} in the infrared (IR) spectrum. The correct stereochemistry of the alcohol (**17**)[12] was thus established[13] by the formation of the oxazolidinone ring. On treatment with silver nitrate in aqueous tetrahydrofuran (THF), the chloride (**18**) gave the hydroxy-oxazolidinone (**19**) in 58% yield. Oxidation of **19** with pyridinium dichromate[14] in dimethylformamide (DMF) provided the keto-oxazolidinone (**20**) in 85% yield, though the oxidation with the Jones reagent or pyridinium chlorochromate was unsuccessful. The product (**20**) has appropriate functionality, properly situated, for rearrangement to a protoberberine with ring D inversion to be effected. Heating of **20** with 10% aqueous sodium hydroxide in ethanol effected hydrolysis of the oxazolidinone, retro-aldol reaction, cyclization, and subsequent dehydration to provide successfully the 11,12-oxygenated phenolbetaine (**23**) in a quantitative yield *via* the hydroxy-ketone (**21**) and the keto-aldehyde (**22**). The 11,12-oxygenated structure of the betaine (**23**) was well established by comparison of the AB-quartet (7.40 and 7.29 ppm) due to two aromatic protons at ring D of **23** with that (8.18 and 7.24 ppm) of berberinephenolbetaine (**15**) having the 9,10-oxygenated structure. The ring D inversion was thus achieved by conversion of berberine (**14**) to the 11,12-oxygenated protoberberine (**23**) according to our initial strategy described above.

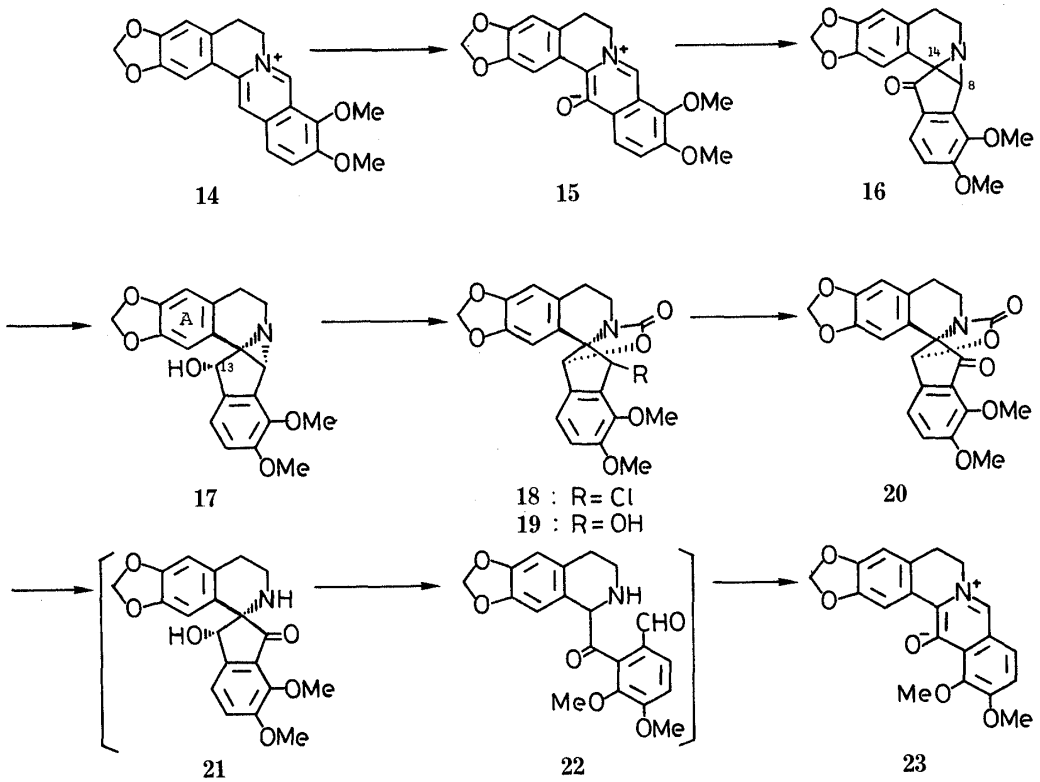

Chart 4

An alternative and more convenient ring D inversion was accomplished starting from the spirobenzylisoquinoline (**25**),[1] which was obtained in 73% overall yield from 8-methoxyberberinephenolbetaine (**24**)[15,16] derived from berberine (**14**). The compound (**25**) has exactly the same functionality as the key compound (**13**) in our strategy. Treatment of the spirobenzylisoquinoline (**25**) with 10% aqueous sodium hydroxide in ethanol furnished the expected phenolbetaine (**23**) in 95% yield; it was identical with the authentic specimen obtained above.

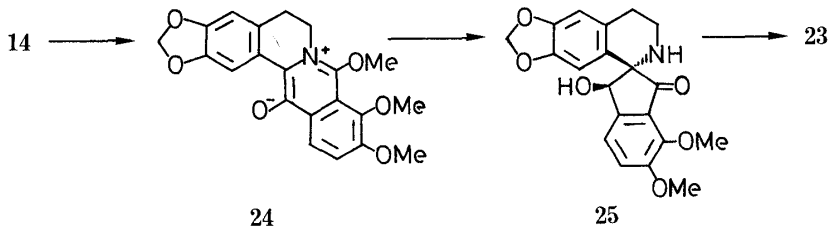

Chart 5

The third conversion was achieved by the application of photochemical transformation of a spirobenzylisoquinoline to a protoberberine.[17] Hydrogenolysis of the spirobenzylisoquinoline (**26**),[1] derived from the 8,14-cycloberbine (**16**), over 5% palladium–charcoal afforded the dehalogenated ketone (**27**) in 88% yield, and this was hydrolyzed with 20% aqueous potassium hydroxide to give the amino-ketone (**28**) in 73% yield. Irradiation of **28** in THF provided the 11,12-oxygenated protoberberine (**29**) in 43% yield. The structure was confirmed by the appearance of the C_9–H signal as a half of an AB-quartet (8.10 and 6.95 ppm) at very low field in comparison with an AB-quartet (7.30 and 7.27 ppm) due to C_{11}– and C_{12}–H of the corresponding 9,10-oxygenated protoberberine, oxyberberine (**30**).

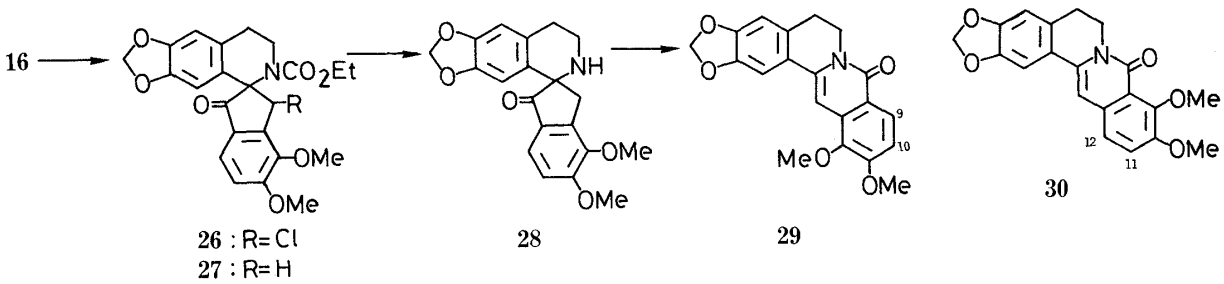

Chart 6

Thus, three methods were developed for the conversion of the naturally occurring 9,10-oxygenated protoberberine to the non-naturally occurring 11,12-oxygenated protoberberine by ring D inversion. These results provide new routes for the transformation of protoberberines into related alkaloids and suggest an important role of spirobenzylisoquinolines in the bio-transformations of these 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). IR spectra were measured with a JASCO A-102 spectrometer, mass spectra (MS) with a Hitachi M-80 mass spectrometer, ultraviolet (UV) spectra with a Hitachi 323 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* (8*R*,13*S*,14*R*)-9,10-Dimethoxy-2,3-methylenedioxy-8,14-cycloberbin-13-ol (17)**——$NaBH_4$ (240 mg) was added in portions to a solution of the cycloberbine (**16**, 1.11 g) in $CHCl_3$ (20 ml) and MeOH (40 ml) at 0—5 °C with stirring, and stirring was continued at 0—5 °C for 1 h then at room temperature for 2 h. Organic solvents were evaporated off. Water was added to the residue and the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and concentrated to dryness. The residue was purified by chromatography on a short column of Al_2O_3 with $CHCl_3$ to give the alcohol (**17**, 1.06 g, 95%) as colorless prisms, mp 168.5—169.5 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (OH). MS *m/e*: 353 (M^+). ^{1}H-NMR δ: 7.14 (1H, s, C_1–H), 7.11, 6.83 (2H, AB-q, J=8.5 Hz, C_{11}– and C_{12}–H), 6.63 (1H, s, C_4–H), 5.94 (2H, s, OCH_2O), 5.63 (1H, d, J=10.5 Hz, C_{13}–H), 3.88, 3.76 (each 3H, s, $OCH_3 \times 2$), 3.72 (1H, s, C_8–H). *Anal.* Calcd for $C_{20}H_{19}NO_5$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.20; H, 5.85; N, 3.78.

8-Chloro-9,10-dimethoxy-2,3-methylenedioxynorochotensane-7,13-carbolactone (18)[18]——A solution of the alcohol (**17**, 1.18 g) and ethyl chloroformate (2.0 g) in C_6H_6 (40 ml) was heated under reflux with stirring for 3 h and then concentrated to dryness. The residue was taken up in $CHCl_3$, washed with aqueous K_2CO_3 and water, then dried, and concentrated. The residue was chromatographed on SiO_2 with AcOEt–C_6H_6 (1 : 1) to afford the oxazolidinone (**18**, 831 mg, 60%) as colorless needles, mp 180—182.5 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750 (CO). MS *m/e*: 417, 415 (1 : 3, M^+). ^{1}H-NMR δ: 7.10, 6.98 (2H, AB-q, J=8 Hz, C_{11}– and C_{12}–H), 6.65, 6.54 (each 1H, s, C_4– and C_1–H), 5.87 (2H, s, OCH_2O), 5.78 (1H, s, C_8–H), 5.48 (1H, s, C_{13}–H), 3.93, 3.85 (each 3H, s, $OCH_3 \times 2$). *Anal.* Calcd for $C_{21}H_{18}ClNO_6$: C, 60.66; H, 4.36; N, 3.37. Found: C, 60.61; H, 4.23; N, 3.66.

8-Hydroxy-9,10-dimethoxy-2,3-methylenedioxynorochotensane-7,13-carbolactone (19)——A solution of $AgNO_3$ (170 mg) in distilled water (5 ml) was added to a solution of the chloride (**18**, 62 mg) in THF (10 ml) and the resulting mixture was stirred for 72 h at room temperature. The THF was evaporated off and the aqueous layer was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and concentrated to dryness. The residue was chromatographed on SiO_2 with AcOEt–C_6H_6 (1 : 1) to afford the alcohol (**19**, 34.3 mg, 58%) as colorless prisms, mp 258—260 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH), 1735 (CO). MS *m/e*: 397 (M^+). ^{1}H-NMR δ: 7.23, 7.07 (2H, AB-q, J=8.5 Hz, C_{11}– and C_{12}–H), 6.61 (1H, s, C_4–H), 6.24 (1H, s, C_1–H), 5.91 (2H, s, OCH_2O), 5.39 (1H, s, C_{13}–H), 5.36 (1H, d, J=7.5 Hz, C_8–H), 3.96, 3.91 (each 3H, s, $OCH_3 \times 2$). *Anal.* Calcd for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.82; N, 3.53. Found: C, 63.25; H, 4.83; N, 3.53.

9,10-Dimethoxy-2,3-methylenedioxy-8-oxonorochotensane-7,13-carbolactone (20)——Pyridinium dichromate (121 mg) was added to a solution of the alcohol (**19**, 41.3 mg) in DMF (3 ml) with stirring, and stirring was continued for 5 h at room temperature. The DMF was evaporated off and the residue was taken up in $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and concentrated. The residue was chromatographed on Al_2O_3 with $CHCl_3$ to give the ketone (**20**, 34.9 mg, 85%) as colorless prisms, mp 274—275 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750 (CO), 1715 (CO). MS *m/e*: 395 (M^+). ^{1}H-NMR δ: 7.29 (2H, s, C_{11}– and C_{12}–H), 6.56 (1H, s, C_4–H), 6.09 (1H, s, C_1–H), 5.53 (1H, s, C_{13}–H), 3.97, 3.89 (each 3H, s, $OCH_3 \times 2$). *Anal.* Calcd for $C_{21}H_{17}NO_7$: C, 63.79; H, 4.33; N, 3.54. Found: C, 63.55; H, 4.06; N, 3.76.

5,6-Dihydro-11,12-dimethoxy-2,3-methylenedioxydibenzo[*a*,*g*]quinolizinium-13-olate (23)——1) A solution of the oxazolidinone (**20**, 48.8 mg) and 10% aqueous NaOH (4 ml) in EtOH (10 ml) was heated under reflux with stirring for 1 h. The EtOH was evaporated off and the aqueous layer was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water, dried, and concentrated. The residue was chromatographed on Al_2O_3 with CH_2Cl_2–MeOH (50 : 1) to afford the betaine (**23**, 44.4 mg, quant.) as orange prisms, mp 181—182 °C (MeOH). UV λ_{max}^{MeOH} nm (log ε): 222 (4.51), 246 (4.32), 289 (4.00), 384 (3.72), 430 (3.82). MS *m/e*: 351 (M^+). ^{1}H-NMR δ: 8.93 (1H, s, C_8–H), 7.40, 7.29 (2H, AB-q, J=8 Hz, C_9– and C_{10}–H), 7.37 (1H, s, C_1–H), 6.62 (1H, s, C_4–H), 5.94 (2H, s, OCH_2O), 4.37 (2H, t, J=6 Hz, C_6–H), 4.03, 3.98 (each 3H, s, $OCH_3 \times 2$), 2.99 (2H, t, J=6 Hz, C_5–H). *Anal.* Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.07; H, 4.90; N, 3.92.

2) A solution of the hydroxy-ketone (**25**, 469.6 mg) and 10% aqueous NaOH (10 ml) in EtOH (20 ml) was heated under reflux with stirring for 45 min. Work-up as mentioned in 1) gave the betaine (**23**, 424.4 mg, 95%), which was identical with the authentic specimen obtained in 1) on the basis of IR, ^{1}H-NMR, and thin layer chromatography (TLC) behavior.

Ethyl 9,10-Dimethoxy-2,3-methylenedioxy-13-oxonorochotensane-7-carboxylate (27)——A solution of the urethane (**26**, 822 mg) in THF (30 ml) and MeOH (30 ml) was hydrogenated over 5% Pd–C (0.5 g) 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 to dryness. The residue was chromatographed on Al_2O_3 with $CHCl_3$ to afford a colorless oil (**27**, 670 mg, 88%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1717 (CO), 1680 (CO). MS *m/e*: 425 (M^+). High resolution MS *m/e*: Calcd for $C_{23}H_{23}NO_7$: 425.1473. Found: 425.1473. ^{1}H-NMR δ: 7.53, 6.94 (2H, AB-q, J=8.5 Hz, C_{12}– and C_{11}–H), 6.54 (1H, s, C_4–H), 6.08 (1H, s, C_1–H), 5.78, 5.73 (2H, AB-q, J=1.5 Hz, OCH_2O), 3.95, 3.89 (each 3H, s, $OCH_3 \times 2$), 3.53 (2H, s, C_8–H). ^{1}H-NMR (90 °C) δ: 7.52, 6.98 (2H, AB-q, J=8.5 Hz, C_{12}– and C_{11}–H), 6.58 (1H, s, C_4–H), 6.15 (1H, s, C_1–H), 5.80, 5.76 (2H, AB-q, J=1.5 Hz, OCH_2O), 4.40—4.26 (1H, m, C_6–H), 4.02 (2H, q, J=7 Hz, OCH_2CH_3), 3.95, 3.91 (each 3H, s, $OCH_3 \times 2$), 3.53 (2H, s, C_8–H), 3.40—3.19 (1H, m, C_6–H), 3.10—2.55 (2H, m, C_5–H), 1.01 (3H, t, J=7 Hz, OCH_2CH_3).

9,10-Dimethoxy-2,3-methylenedioxynorochotensan-13-one (28)——A solution of the urethane (**27**, 341 mg) and 20% aqueous KOH (5 ml) in EtOH (25 ml) was heated under reflux with stirring for 41 h. The EtOH was evaporated off and the aqueous layer was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and concentrated. The residue was chromatographed on Al_2O_3 with $CHCl_3$ to afford two fractions. The first fraction gave the amine [**28**, 206.5 mg, 73% (83% based on consumed starting material)] as colorless needles, mp 150—152 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700 (CO). MS *m/e*: 353 (M^+). ^{1}H-NMR δ: 7.47, 6.87 (2H, AB-q, J=8.5 Hz, C_{12}– and C_{11}–H), 6.43 (1H, s, C_4–H), 5.99 (1H, s, C_1–H), 5.70 (2H, s, OCH_2O), 3.89, 3.82 (each 3H, s, $OCH_3 \times 2$), 3.35 (2H, s, C_8–H). *Anal.* Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.80; H, 5.25; N, 3.72. The second fraction gave the starting urethane (**27**, 37 mg, 11%), which was identical with an authentic specimen.

5,6-Dihydro-11,12-dimethoxy-2,3-methylenedioxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-one (29)——A solution of the amine (**28**, 161.4 mg) in THF was irradiated under an Ar atmosphere for 1 h at room temperature and the THF was evaporated off. The residue was chromatographed on Al_2O_3 with AcOEt–C_6H_6 (1 : 4) to afford the protoberberine (**29**, 69.1 mg, 43%), as yellow needles, mp 236—237 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640 (CO). MS *m/e*: 351 (M^+). ^{1}H-NMR δ: 8.10, 6.95 (2H, AB-q, J=8.5 Hz, C_9– and C_{10}–H), 7.18 (1H, s, C_{13}–H), 6.97 (1H, s, C_1–H), 6.57 (1H, s, C_4–H), 5.89 (2H, s, OCH_2O), 4.23 (2H, t, J=6.5 Hz, C_6–H), 3.90, 3.88 (each 3H, s, $OCH_3 \times 2$), 2.83 (2H, t, J=6.5 Hz, C_5–H). *Anal.* Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.32; H, 4.84; N, 3.80.

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