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Chemical Transformation of Protoberberines. XII.[1] A Novel Synthesis of Rhoeadine Alkaloids. An Alternative Synthesis of a Key Intermediate, Benzindenoazepine, for a Synthesis of (±)-*cis*-Alpinigenine and (±)-*cis*-Alpinine from Palmatine[2]

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A formal synthesis of (±)-*cis*-alpinigenine (**3**) and (±)-*cis*-alpinine (**4**) was achieved by conversion of palmatine (**7**) into the key intermediate, benzindenoazepine (**16**), *via* the ring D-inverted 2,3,11,12-tetraoxygenated phenolbetaine (**14**) and the 8,14-cycloberbine (**15**) through photooxygenation, photochemical valence isomerization, and regioselective C–N bond cleavage of **15** as crucial reactions.

Keywords——rhoeadine alkaloid; protoberberine alkaloid; *cis*-alpinigenine; *cis*-alpinine; palmatine; benzindenoazepine framework; 8,14-cycloberbine; photooxygenation; photochemical isomerization; regioselective C–N bond cleavage

Rhoeadine alkaloids (**1**)[3] possess a unique framework having a benzazepine system fused with a six-membered hemiacetal or acetal. These alkaloids have been shown to be biosynthesized from the corresponding protoberberines (**2**).[4-6] Among several successful syntheses,[7-12] those through benzindenoazepines[9,10,12] such as **6** (R=Me)[10] are of great interest from the viewpoints of both biosynthesis and chemical transformation.

On the basis of biogenetic considerations, we planned a novel synthetic route to rhoeadine alkaloids (Chart 1). The protoberberine (**2**) is transformed to the ring D-inverted protoberberine (**5**) and then to the benzindenoazepine (**6**), which has already been converted to rhoeadine alkaloids (**1**).

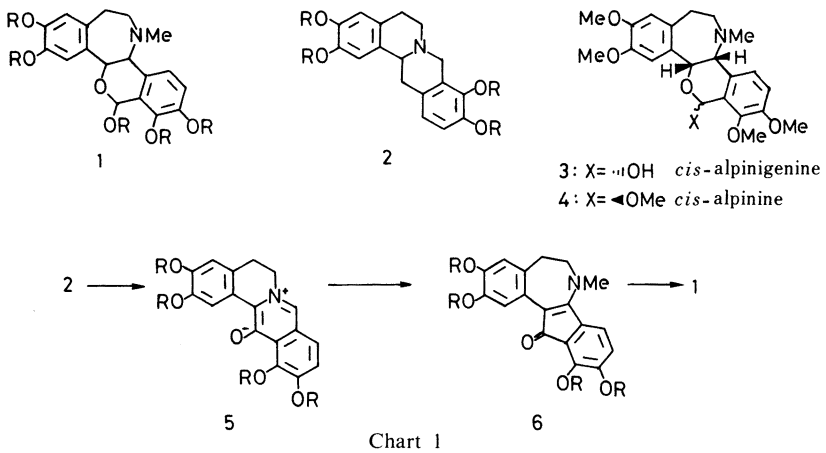

Chart 1

In the previous papers, we have demonstrated a convenient transformation of a natural 2,3,9,10-tetraoxygenated protoberberine (**2**) into a ring D-inverted unnatural 2,3,11,12-tetraoxygenated protoberberine (**5**) *via* a spirobenzylisoquinoline,[13] as well as an efficient synthesis of a benzindenoazepine system from a protoberberinephenolbetaine *via* an 8,14-cycloberbine.[2,14] Now we describe a novel and convenient synthesis of the key intermediate, benzindenoazepine (**6**), for total synthesis of (±)-*cis*-alpinigenine (**3**)[15] and (±)-*cis*-alpinine (**4**)[15] from a protoberberine alkaloid, palmatine (**7**) according to our novel pathway mentioned above.

Irradiation of palmatine (**7**) in methanol in the presence of sodium methoxide and rose bengal with a halogen lamp in a stream of oxygen at 0 °C followed by alumina column chromatography afforded 8-methoxypalmatinephenolbetaine (**8**)[16] in 60% yield. The structure of **8** was well established by the appearance of a low-field signal due to H-1 at δ 9.26 ppm as well as five methoxy signals in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum. Further irradiation[17] of **8** in methanol with a mercury lamp in a stream of nitrogen effected valence isomerization to give the presumed intermediate (**9**), which immediately decomposed to afford the spirobenzylisoquinoline (**10**) in 81% yield through solvolysis in methanol. The product showed a carbonyl band at 1710 cm^{-1} in the infrared (IR) spectrum and a high-field signal due to H-1 at δ 6.28 ppm (diagnostic of a spirobenzylisoquinoline skeleton)[18] and six methoxy signals in the ^{1}H-NMR spectrum. Sodium borohydride reduction of **10** afforded stereoselectively[17] the hydroxy-acetal (**11**) in a quantitative yield. The *trans* relationship between the nitrogen and the hydroxy group in **11** was supported by the H-13 signal at δ 4.92 ppm in the ^{1}H-NMR spectrum.[17] Deacetalization of **11** with 10% hydrochloric acid afforded quantitatively the hydroxy-ketone (**12**).

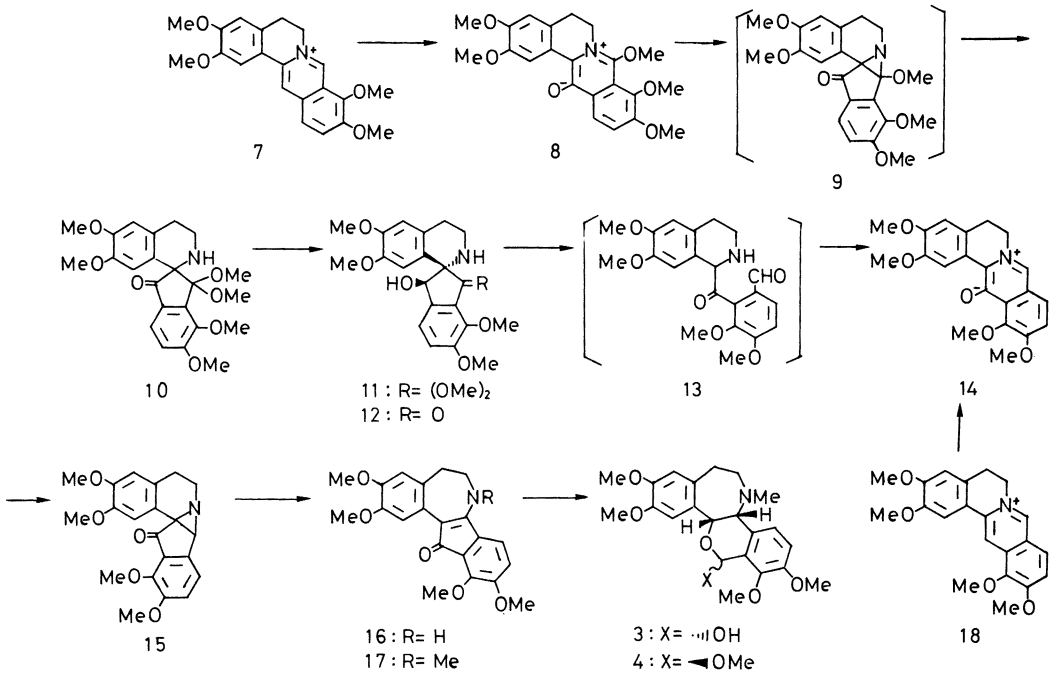

Chart 2

On exposure to 10% sodium hydroxide in ethanol,[13] **12** underwent retro-aldol reaction, recyclization, and dehydration successively to afford the expected ring D-inverted protoberberine (**14**) *via* the keto-aldehyde (**13**) in a quantitative yield. The structure of **14** was

supported by the chemical shift of an AB-quartet (7.38 and 7.25 ppm) due to the protons on ring D in comparison with that (8.52 and 7.43 ppm) of **8**.

The structure of **14** was fully confirmed by an alternative and conventional synthesis. The protoberberine (**18**)[19] was synthesized starting from 3,4-dimethoxyphenethylamine and 2,3-dimethoxyphenylacetic acid by a modification of the reported method.[20] Reduction of **18** with lithium aluminum hydride (LAH) in tetrahydrofuran (THF) followed by oxidation with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane afforded the betaine (**14**) in 63% yield. The product was identical with that obtained above.

Thus, we succeeded in the ring D inversion of palmatine (**7**) to the protoberberine (**14**), and therefore the next step is the transformation of **14** to the benzindenoazepine framework.

Irradiation[17] of **14** in methanol with a mercury lamp in a stream of nitrogen afforded the 8,14-cycloberbine (**15**) in 78% yield; this product showed a singlet due to the proton on the aziridine ring at δ 3.79 ppm in the ^{1}H-NMR spectrum. Treatment of **15** with *p*-toluenesulfonic acid (*p*-TsOH)[14] effected regioselective C_{14}–N bond cleavage to afford the benzindenoazepine (**16**) in 58% yield. The product showed a band due to a vinylogous amide at 1655 cm^{-1} in the IR spectrum. On treatment with dimethyl sulfate in hexamethylphosphoric amide (HMPA) and benzene, **16** produced the *N*-methyl derivative (**17**) in 78% yield. The product was identical with an authentic sample[10] in IR and ^{1}H-NMR spectra and thin layer chromatographic behavior. Since **17** has already been converted to (±)-*cis*-alpinigenine (**3**) and (±)-*cis*-alpinine (**4**),[10] the present synthesis of **17** amounts to a formal synthesis of these alkaloids.

Thus, we have developed a novel synthesis of (±)-*cis*-alpinigenine and (±)-*cis*-alpinine and have provided a new general method for synthesis of rhoeadine 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 alumina (Aluminiumoxid 90, Aktivitätsstufe II—III, 70—230 mesh, Merck) and silica gel (Kieselgel 60, 70—230 mesh, Merck). Preparative thin-layer chromatography (pTLC) 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 spectrometer, and ^{1}H-NMR spectra with a JEOL FX-100 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard, unless otherwise stated. Irradiation was carried out with a 100W high-pressure mercury or halogen lamp with a Pyrex filter (Riko Kagaku Co.).

5,6-Dihydro-2,3,8,9,10-pentamethoxydibenzo[*a*,*g*]quinolizinium-13-olate (8-Methoxypalmatinephenolbetaine) (8)——Palmatinium chloride (**7**) (505 mg) and rose bengal (1% methanol solution, 0.1 ml) were dissolved in a solution of methanol (50 ml) containing sodium methoxide (prepared from Na, 100 mg), and the resulting solution was irradiated with a halogen lamp at 0 °C for 20 min in a stream of oxygen. The reaction solution was adjusted to pH 7—8 with conc. HCl and concentrated at 30—35 °C. Aqueous K_2CO_3 was added to the residue and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with sat. NaCl, dried, and concentrated. The residue was chromatographed on Al_2O_3 with CH_2Cl_2 and CH_2Cl_2–MeOH (99:1). The fraction eluted with CH_2Cl_2–MeOH was concentrated and the residue was washed with AcOEt to give the betaine (**8**) (310 mg, 60%) as an orange powder. MS *m/z* (%): 397 (M^+, 53), 382 (100). High-resolution MS *m/z*: Calcd for $C_{22}H_{23}NO_6$: 397.1523. Found: 397.1511. ^{1}H-NMR δ: 9.26 (1H, s, C_1-H), 8.52, 7.43 (2H, AB-q, J=9.5 Hz, C_{12}- and C_{11}-H), 6.70 (1H, s, C_4-H), 4.66 (2H, t, J=5.5 Hz, C_6-H), 4.03 (6H, s, $OCH_3 \times 2$), 4.00 (3H, s, OCH_3), 3.91 (6H, s, $OCH_3 \times 2$), 3.01 (2H, t, J=5.5 Hz, C_5-H).

2,3,8,8,9,10-Hexamethoxynorochotensan-13-one (10)[21]——A solution of the betaine (**8**) (309 mg) in MeOH (200 ml) was irradiated with an Hg lamp at 0 °C for 1 h in a stream of nitrogen. The solvent was evaporated off and the residue was chromatographed on Al_2O_3 with CH_2Cl_2 to give the spirobenzylisoquinoline (**10**) (272 mg, 81%) as colorless needles, mp 168—169 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (CO). MS *m/z* (%): 429 (M^+, 91), 414 (77), 398 (62), 382 (100). ^{1}H-NMR δ: 7.63, 7.22 (2H, AB-q, J=8.5 Hz, C_{12}- and C_{11}-H), 6.60 (1H, s, C_4-H), 6.28 (1H, s, C_1-H), 3.99, 3.90, 3.84, 3.46, 3.33, 3.21 (each 3H, s, $OCH_3 \times 6$). *Anal.* Calcd for $C_{23}H_{27}NO_7$: C, 64.32; H, 6.34, N, 3.26. Found: C, 64.12; H, 6.31; N, 3.34.

***rel*-(13*R*,14*S*)-2,3,8,8,9,10-Hexamethoxynorochotensan-13-ol (11)**——Sodium borohydride (100 mg) was added portionwise to a stirred solution of the ketone (**10**) (134 mg) in MeOH (10 ml)–$CHCl_3$ (3 ml) under ice cooling, and the mixture was stirred at the same temperature for 2 h. The solvents were evaporated off and the residue was taken

up in $CHCl_3$. The $CHCl_3$ layer was washed with sat. NaCl, dried, and concentrated. The residue was chromatographed on Al_2O_3 with CH_2Cl_2 to afford the alcohol (**11**) (131 mg, 98%) as colorless plates, mp 147—148 °C (iso-Pr_2O). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH). MS *m/z* (%): 416 ($M^+ - 15$, 46), 399 (32), 368 (100). ^{1}H-NMR δ: 7.11 (1H, dd, J= 8.5, 1 Hz, C_{12}-H), 7.00 (1H, d, J=8.5 Hz, C_{11}-H), 6.62 (1H, s, C_4-H), 6.13 (1H, s, C_1-H), 4.92 [1H, dd, J=10, 1 Hz, C_{13}-H (→d, J=1 Hz, by addition of D_2O)], 3.89, 3.86, 3.84, 3.36, 3.35, 3.20 (each 3H, s, $OCH_3 \times 6$). *Anal.* Calcd for $C_{23}H_{29}NO_7$: C, 64.02; H, 6.77; N, 3.25. Found: C, 63.84; H, 6.83; N, 3.30.

***rel*-(13*R*,14*S*)-13-Hydroxy-2,3,9,10-tetramethoxynorochotensan-8-one (12)**——Hydrochloric acid (10%, 6 ml) was added to a solution of the acetal (**11**) (110 mg) in MeOH (6 ml) and the reaction mixture was heated under reflux for 1 h. After evaporation of the MeOH, the residue was made alkaline with aqueous K_2CO_3 and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with sat. NaCl, dried, and concentrated. The crude hydroxy-ketone (**12**) (98 mg, 100%) was recrystallized from iso-Pr_2O to give colorless plates, mp 127.5—129.5 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1710 (CO). MS *m/z* (%): 385 (M^+, 100), 326 (45), 192 (47). ^{1}H-NMR δ: 7.38 (1H, dd, J=8, 0.7 Hz, C_{12}-H), 7.30 (1H, d, J=8 Hz, C_{11}-H), 6.66 (1H, s, C_4-H), 5.96 (1H, s, C_1-H), 5.16 (1H, d, J=0.7 Hz, C_{13}-H), 4.03, 3.94, 3.84, 3.47 (each 3H, s, $OCH_3 \times 4$). *Anal.* Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.41; H, 5.98; N, 3.52.

5,6-Dihydro-2,3,11,12-tetramethoxydibenzo[*a*,*g*]quinolizinium-13-olate (14)——1) A solution of the hydroxy-ketone (**12**) (116 mg) and 10% aqueous NaOH (2 ml) in EtOH (6 ml) was heated under reflux with stirring for 40 min. The EtOH was evaporated off and the residue was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with sat. NaCl, dried, and concentrated. The residue was chromatographed on Al_2O_3 with CH_2Cl_2–MeOH (49:1) to afford the betaine (**14**) (110 mg, 100%) as yellow needles, mp 162—164 °C (MeOH). MS *m/z* (%): 367 (M^+, 85), 352 (100), 334 (33). High-resolution MS *m/z*: Calcd for $C_{21}H_{21}NO_5$: 367.1417. Found: 367.1413. ^{1}H-NMR δ: 9.15 (1H, s, C_1-H), 7.40 (1H, s, C_8-H), 7.38, 7.25 (2H, AB-q, J=8 Hz, C_9- and C_{10}-H), 6.64 (1H, s, C_4-H), 4.36 (2H, t, J=5.5 Hz, C_6-H), 4.02, 3.97, 3.88, 3.47 (each 3H, s, $OCH_3 \times 4$), 2.30 (2H, t, J=5.5 Hz, C_5-H).

2) The quaternary base (**18**) (2.216 g) was added portionwise to an ice-cooled suspension of LAH (1.0 g) in THF (50 ml), and the reaction mixture was stirred at room temperature for 3 h in a stream of nitrogen. Excess LAH was decomposed with water and inorganic precipitates were filtered off through a filter cell and washed with CH_2Cl_2. The filtrate and washings were concentrated and the residue was chromatographed on Al_2O_3 with CH_2Cl_2 to afford the dihydro base (1.529 g). A solution of *m*-CPBA (1.32 g) in CH_2Cl_2 (20 ml) was added dropwise to a stirred solution of the above dihydro base in CH_2Cl_2 (50 ml) at −20 °C for 15 min in a stream of nitrogen, and the mixture was stirred for a further 1 h at the same temperature. The reaction temperature was allowed to rise to 0 °C, finely powdered Na_2SO_3 (2 g) was added to the reaction solution and 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 treated as described in 1) to afford the betaine (**14**) (1.064 g, 63%) which was identical with that obtained in 1).

2,3,11,12-Tetramethoxy-8,14-cycloberbin-13-one (15)——A solution of the betaine (**14**) (110 mg) in MeOH (150 ml) was irradiated with an Hg lamp at room temperature for 1 h in a stream of nitrogen. The solvent was evaporated off and the residue was chromatographed on SiO_2 with C_6H_6–AcOEt (4:1) to afford the cycloberbine (**15**) (85.4 mg, 78%) as pale yellow prisms, mp 157.5—158.5 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (CO). MS *m/z*: 367 (M^+). ^{1}H-NMR δ: 7.40 (1H, s, C_1-H), 7.17, 7.02 (2H, AB-q, J=8 Hz, C_9- and C_{10}-H), 6.67 (1H, s, C_4-H), 4.04, 3.91 (each 3H, s, $OCH_3 \times 2$), 3.87 (6H, s, $OCH_3 \times 2$), 3.79 (1H, s, C_8-H). *Anal.* Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.42; H, 5.77; N, 3.52.

5,6,7,13-Tetrahydro-2,3,11,12-tetramethoxybenz[*d*]indeno[1,2-*b*]azepin-13-one (16)[22]——A solution of the cycloberbine (**15**) (105.7 mg) and *p*-TsOH (71 mg) in anhyd. C_6H_6 (10 ml) was heated under reflux for 1.5 h with stirring. The C_6H_6 was evaporated off and the residue was taken up in $CHCl_3$. The $CHCl_3$ layer was washed with aqueous K_2CO_3, water, dried, and concentrated. The residue was chromatographed on pTLC (Al_2O_3, $CHCl_3$) to afford the azepine (**16**) (61 mg, 58%) as red prisms, mp 234—237 °C (MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425 (NH), 1655 (CO). MS *m/z* (%): 367 (M^+, 100), 352 (45). ^{1}H-NMR δ: 8.06 (1H, s, C_1-H), 6.76, 6.68 (2H, AB-q, J=8 Hz, C_9- and C_{10}-H), 6.53 (1H, s, C_4-H), 4.03, 3.92, 3.87, 3.83 (each 3H, s, $OCH_3 \times 4$), 3.90—3.60 (2H, m, C_6-H), 3.05—2.95 (2H, m, C_5-H), *Anal.* Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.40; H, 5.82; N, 3.81.

5,6,7,13-Tetrahydro-2,3,11,12-tetramethoxy-7-methylbenz[*d*]indeno[1,2-*b*]azepin-13-one (17)——Sodium hydride (40 mg, 50% mineral oil dispersion) was added to a solution of the azepine (**16**) (59 mg) in HMPA (0.5 ml) and anhyd. C_6H_6 (2 ml). The resulting solution was stirred at room temperature for 15 min. Dimethyl sulfate (3 drops) was added to the stirred solution and stirring was continued at room temperature for 1 h. Aqueous NH_3 (28%, 1 ml) was added to the reaction mixture and stirring was continued at room temperature for 30 min. The reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and evaporated to dryness. The residue was subjected to pTLC [Al_2O_3, C_6H_6–AcOEt (4:1)] to afford the *N*-methyl derivative (**17**) (48 mg, 78%) as reddish purple prisms, mp 164—166 °C (MeOH) (lit.[10] mp 159—161 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650 (CO). MS *m/z* (%): 381 (M^+, 100), 366 (53). ^{1}H-NMR δ: 7.81 (1H, s, C_1-H), 7.01, 6.66 (2H, AB-q, J=8 Hz, C_9- and C_{10}-H), 6.54 (1H, s, C_4-H), 4.01, 3.94, 3.87, 3.85 (each 3H, s, $OCH_3 \times 4$), 3.95—3.60 (2H, m, C_6-H), 3.40 (3H, s, NCH_3), 3.00—2.80 (2H, m, C_5-H). *Anal.* Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.18; H, 6.13; N, 3.39. The product was identical with an authentic specimen[10] (IR and ^{1}H-NMR spectra, and mixed melting point).

5,6-Dihydro-2,3,11,12-Tetramethoxydibenzo[*a*,*g*]quinolizinium Iodide (18)——A mixture of 3,4-dimethoxyphenethylamine (8.00 g) and 2,3-dimethoxyphenylacetic acid (7.50 g) was heated at 190 °C for 5 h under an Ar atmosphere. The reaction mixture was recrystallized from MeOH to afford *N*-(3,4-dimethoxyphenethyl)-2,3-dimethoxyphenylacetamide (11.5 g, 83%) as colorless needles, mp 138—138.5 °C (lit.[20a] mp 130—130.5 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650 (CO). MS *m/z*: 359 (M^+). ^{1}H-NMR δ: 7.11—6.53 (6H, m, Ar-H), 5.88 (1H, br s, NH), 3.87, 3.85, 3.83, 3.78 (each 3H, s, $OCH_3 \times 4$), 3.53 (2H, s, $COCH_2$), 3.39 (2H, t, J=6.5 Hz, $NHCH_2$), 2.67 (2H, t, J=6.5 Hz, $ArCH_2CH_2$). *Anal.* Calcd for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.90. Found: C, 66.83; H, 7.08; N, 3.92.

Phosphorus oxychloride (47 g) was added to a solution of the amide (9.3 g) in anhyd. C_6H_6 (140 ml), and the resulting mixture was heated under reflux for 6 h with stirring. The 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 $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and concentrated to leave the oily imine (8.5 g, 96%). Sodium borohydride (1.2 g) was added portionwise to a solution of the imine (8.5 g) in MeOH (130 ml) and stirring was continued at room temperature for 6 h. The MeOH was evaporated off and the residue was taken up in $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and concentrated to leave the oily amine (8.5 g, quant.). A solution of the crude amine (8.5 g) and 37% HCHO (105 ml) in AcOH (105 ml) was heated under reflux for 6 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 K_2CO_3, water, dried, and concentrated to leave the tetrahydroprotoberberine (8.2 g, 97%) which was recrystallized from MeOH to afford pale yellow plates, mp 167—167.5 °C (lit.[19a] mp 162—163 °C). MS *m/z*: 355 (M^+). ^{1}H-NMR δ: 6.81 (1H, s, C_1-H), 6.79 (2H, s, C_9- and C_{10}-H), 6.62 (1H, s, C_4-H), 3.92, 3.87, 3.85, 3.81 (each 3H, s, $OCH_3 \times 4$). *Anal.* Calcd for $C_{21}H_{25}NO_4$: C, 70.96, H, 7.09; N, 3.94. Found: C, 70.95; H, 7.10; N, 4.03.

A solution of I_2 (7.3 g) in EtOH (40 ml) was added dropwise to a refluxing solution of the tetrahydroprotoberberine (3.0 g) and AcOK (4.7 g) in EtOH (200 ml) with stirring for 1 h, and stirring was continued at the same temperature for 1.5 h. After the 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 (20 ml) for 2 h with stirring. The yellow precipitates were collected by filtration to give the quaternary base (**18**) (3.9 g, quant.) as yellow needles, mp 201—202 °C (MeOH). ^{1}H-NMR (DMSO-d_6) δ: 9.88 (1H, s, C_8-H), 8.65 (1H, s, C_{13}-H), 8.28, 7.95 (2H, AB-q, J= 9.3 Hz, C_9- and C_{10}-H), 7.74 (1H, s, C_1-H), 7.12 (1H, s, C_4-H), 4.80 (2H, t, J=5.5 Hz, C_6-H), 4.14, 4.02, 3.97, 3.89 (each 3H, s, $OCH_3 \times 4$), 3.24 (2H, t, J=5.5 Hz, C_5-H).

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