Chemical Transformation of Protoberberines. XVI.[1] Regioselective Introduction of an Oxy Functionality at the C_{12}-Position of the Benzo[*c*]phenanthridine Skeleton: A Convenient Synthesis of Macarpine from Oxychelirubine[2]

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A novel method for the introduction of an oxy functionality at the C_{12}-position of the benzo[*c*]phenanthridine skeleton was developed. This method was successfully applied to a biomimetic synthesis of macarpine (3) from oxychelirubine (15), which was easily derived from the corresponding protoberberine (9).

Keywords benzo[*c*]phenanthridine alkaloid; protoberberine; oxychelirubine; chelirubine; macarpine; dihydromacarpine; oxy functionality; biomimetic synthesis; *N*-iodosuccinimide

2,3,7,8- and 2,3,8,9-Tetraoxygenated benzo[*c*]phenanthridine alkaloids are well known to be biosynthesized from the corresponding protoberberine alkaloids[3,4] through oxidative C_6–N bond cleavage, followed by recombination between the C_6- and C_{13}-positions. Interestingly, a 2,3,7,8-tetraoxygenated benzo[*c*]phenanthridine alkaloid, sanguinarine (**1**), has recently been shown in biosynthetic studies with *Macleaya cordata* to be the biogenetic precursor of chelirubine (**2**), a 2,3,7,8,10-pentaoxygenated benzo[*c*]-phenanthridine alkaloid which is further transformed into a 2,3,7,8,10,12-hexaoxygenated one, macarpine (**3**), *via* consecutive methoxylation at the C_{10}- and C_{12}-position.[4]

In connection with our efforts to develop a convenient synthesis of fully aromatized benzo[*c*]phenanthridine alkaloids,[5,6] the above biogenetic route strongly suggested to us the possibility of developing a direct method for the introduction of an oxy functionality at the C_{12}-position of chelirubine (**2**). Since we had already completed an efficient and convenient procedure for a biomimetic conversion of protoberberine alkaloids into fully aromatized pentaoxygenated[6] as well as tetraoxygenated[5] benzo[*c*]phenanthridine alkaloids, the transformation of pentaoxygenated alkaloids into hexaoxygenated ones would enable us to synthesize all types of benzo[*c*]phenanthridine alkaloids according to a biogenetic-type route. We now describe a biomimetic synthesis of a 2,3,7,8,10,12-hexaoxygenated benzo[*c*]phenanthridine alkaloid, macarpine (**3**), as well as dihydromacarpine (**27**), from chelirubine (**2**), a representative 2,3,7,8,10-pentaoxygenated benzo[*c*]phenanthridine alkaloid.

Synthesis of Chelirubine (2) Chelirubine (**2**), an alkaloid from *Chelidonium majus*[7] and *Macleaya cordata*,[8] was synthesized by our biomimetic procedure from the corresponding protoberberine (**9**), although **2** has already been synthesized by conventional methods.[9] 3,4-Methylenedioxyphenethylamine (**4**) and 2-methoxy-4,5-methylenedioxyphenylacetic acid (**5**)[10] were heated at 190—200 °C for 3 h to give the amide (**6**) in 78% yield. The Bischler–Napieralski reaction of **6** with phosphorus oxychloride in refluxing toluene afforded the ring closed imine (**7**), which was subsequently treated with acetic formic anhydride to produce the stable enamide (**8**) in 80% overall yield as a single isomer. The signal of the formyl proton of **8** appeared at δ 8.08 ppm in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum. This high field shift[11] suggests that **8** is the thermodynamically more stable *Z*-isomer. Irradiation[11] of **8** with a 400 W high-pressure mercury lamp through a Pyrex filter effected photo-induced cyclization to give the protoberberine (**9**) in 71% yield. The protoberberine (**9**) was easily converted to the corresponding tetrahydro derivative (**10**) in 88% yield by sodium borohydride ($NaBH_4$) reduction in methanol. The structure of **10** was determined from the following spectral data: aromatic protons at δ 6.79 (1H, s), 6.58 (1H, s), and 6.42 (1H, s) in the ^{1}H-NMR spectrum, and a diagnostic fragment peak at *m/z* 178 due to the retro Diels–Alder fragmentation beside a parent peak at *m/z* 353 in the mass spectrum (MS). The protoberberine (**9**), a starting material for our synthesis of the benzo[*c*]phenanthridine alkaloid, was thus prepared in a usual manner.

The protoberberine (**9**) was reduced with lithium aluminum hydride (LAH) in dry tetrahydrofuran (THF) at room temperature to afford the dihydro derivative. This labile enamine was immediately methylated with dimethyl sulfate in refluxing benzene to give the methosulfate (**11**) in 81% overall yield. On exposure to 25% methanolic potassium hydroxide, the C_6–N bond fission of **11** was realized to furnish the dihydroisoquinoline derivative (**12**), which was oxidized with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in chloroform ($CHCl_3$) to give the stable enamide (**13**) in 50% overall yield. Treatment of **13** with thallium trinitrate (TTN) trihydrate[12] in methanol effected oxy functionalization at the styrene moiety in **13** to yield the dimethyl acetal (**14**), exposure of which to 10%

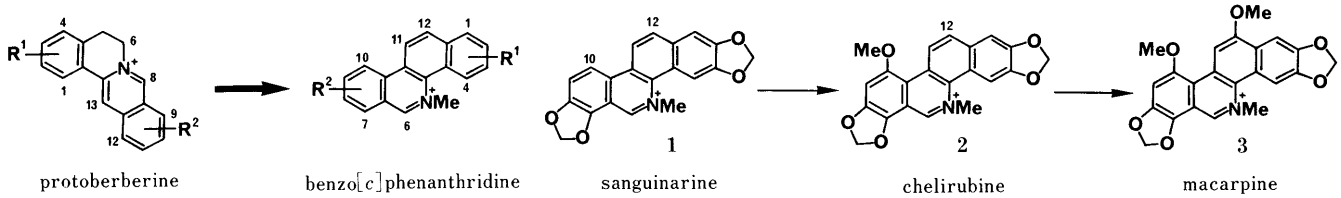

Chart 1

hydrochloric acid gave oxychelirubine (**15**) in 76% overall yield from **13**. Oxychelirubine (**15**) showed a parent peak at *m/z* 377 in the MS and an absorption band at 1650 cm^{-1} in the infrared (IR) spectrum. In particular, the benzo[*c*]phenanthridine skeleton of **15** was apparent from the aromatic proton signals at δ 9.00 and 7.48 (each 1H, AB-q, $J=9.0$ Hz) due to C_{11}- and C_{12}-H, respectively, in its ^{1}H-NMR spectrum.

Oxychelirubine (**15**) was successively reduced with LAH in dry THF and $NaBH_4$ in methanol to provide dihydrochelirubine (**16**) in 82% yield. Finally chelirubine (**2**) was obtained in 90% yield by DDQ oxidation of **16**, followed by treatment with hydrochloric acid. The synthetic chelirubine and dihydrochelirubine were shown to be identical with the natural products by comparison of their IR and ^{1}H-NMR spectra, and thin-layer chromatographic (TLC) behavior.

Conversion of Oxychelirubine (15) into Macarpine (3) Macarpine (**3**) has been isolated from *Macleaya cordata*[13,14] and several papaveraceous plants[15] and shown to have an unusual hexaoxygenated benzo[*c*]phenanthridine skeleton. The 2,3,7,8,10,12-hexasubstituted structure of macarpine (**3**) was unambiguously established by the synthesis[14] of its dihydro derivative, dihydromacarpine (**27**), which was isolated later from *Eschscholtzia californica cham.*[16] This unique hexaoxygenated substitution pattern can be found only in **3** and **27** among more than eighty of benzo[*c*]phenanthridine alkaloids[17] so far isolated. The biosynthetic route to macarpine (**3**)[4] mentioned earlier led us to investigate the introduction of an oxy functionality at the C_{12}-position of the benzo[*c*]phenanthridine skeleton.

During studies on a biomimetic synthesis of chelerythrine (**17**),[5a] we found that bromination occurred in a high yield at the C_4-position of the 1-isoquinolone derivative (**18**) to afford **19**, on treatment with *N*-bromosuccinimide (NBS) in refluxing carbon tetrachloride. With this result in mind, we predicted that the C_{12}-position of oxychelerythrine (**20**) would be halogenated by NBS or *N*-iodosuccinimide (NIS),[18] because **20** could be recognized to be a vinylogous homologue of **18**, as depicted. This expectation was strongly supported by PM3 calculations of frontier electron populations of **20** and **15** as shown in Table I. These calculations indicated that electrophilic and radical substitution would occur at the C_{12}-position rather than

Table I. Calculations of Frontier Electron Populations Calculated by PM3

	Electrophilic reaction		Radical reaction	
	Oxychelerythrine (**20**)	Oxychelirubine (**15**)	Oxychelerythrine (**20**)	Oxychelirubine (**15**)
C_1	0.087	0.084	0.088	0.075
C_2	0.048	0.053	0.119	0.103
C_3	0.028	0.023	0.016	0.013
C_4	0.082	0.080	0.108	0.092
C_{4a}	0.005	0.003	0.030	0.023
C_{4b}	0.221	0.235	0.269	0.264
N_5	0.336	0.291	0.200	0.178
C_6	0.010	0.011	0.008	0.010
C_{6a}	0.015	0.009	0.093	0.101
C_7	0.070	0.093	0.036	0.047
C_8	0.166	0.122	0.168	0.174
C_9	0.003	0.001	0.033	0.046
C_{10}	0.146	0.158	0.097	0.114
C_{10a}	0.060	0.089	0.127	0.164
C_{10b}	0.268	0.253	0.238	0.215
C_{11}	0.011	0.007	0.010	0.011
C_{12}	0.198	0.192	0.146	0.133
C_{12a}	0.018	0.025	0.067	0.066

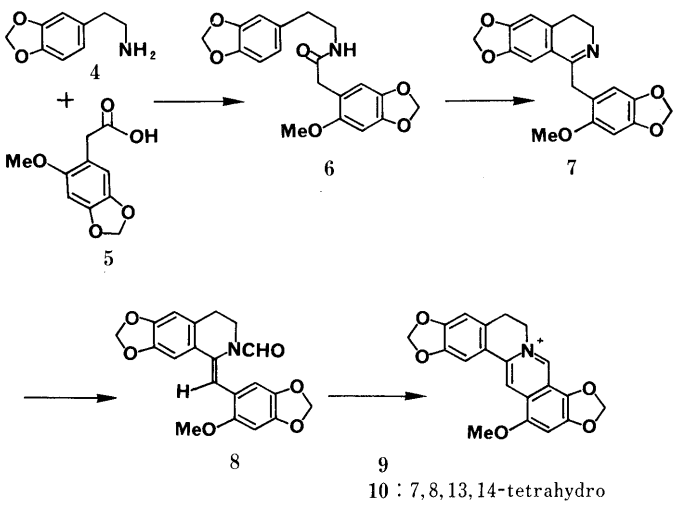

Chart 2

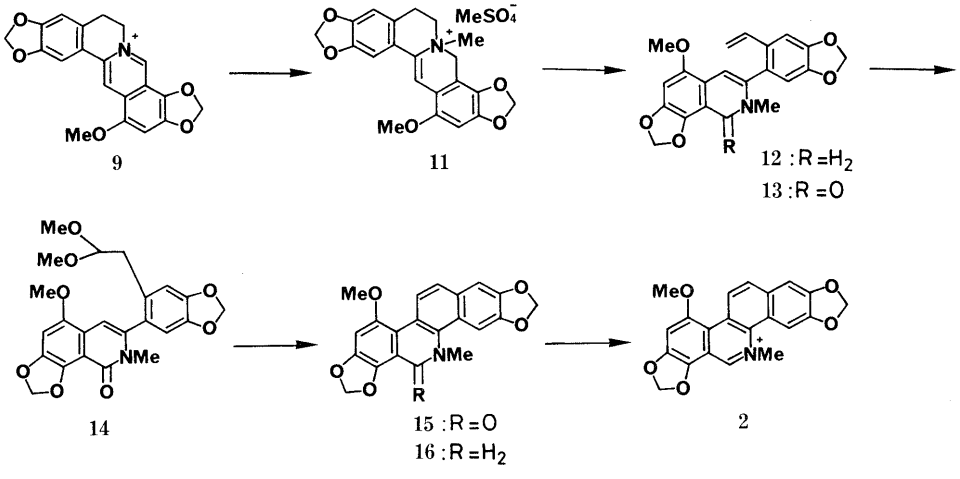

Chart 3

other unsubstituted positions of 2,3,7,8- and 2,3,7,8,10-oxygenated-6-oxobenzo[*c*]phenanthridines (**20** and **15**). Therefore, we first examined the introduction of a halogen atom, a latent oxygen functionality, into oxychelerythrine (**20**). Oxychelerythrine (**20**) was heated with 1.2 eq of NBS in carbon tetrachloride under reflux for 18 h to provide **21** in 93% yield as a sole product. Upon similar treatment with NIS in $CHCl_3$, **20** produced the corresponding iodo derivative (**22**) in 83% yield. ^{1}H-NMR spectral data of these compounds in the aromatic region summarized in Table II. A diagnostic down-field shift[19] of the signals of C_1- and C_{11}-H in the halogenated products (**21** and **22**) compared to those in the starting material (**20**) strongly indicated that substitution had occurred at the C_{12}-position and not at the C_9-, C_{10}-, or C_{11}-position, as expected. Other halogenating reagents such as iodine and iodine monochloride were ineffective in this conversion. It is noteworthy that no reaction took place and the starting material was recovered after $NaBH_4$ reduction when dihydrochelerythrine was employed instead of oxychelerythrine (**20**) as a substrate for halogenation.

TABLE II. ^{1}H-NMR Spectral Data for Benzo[*c*]phenanthridines

Compd.	Chemical shift (ppm, *J* in Hz in $CDCl_3$)					
	H-1	H-4	H-9	H-10	H-11	H-12
20	7.14 (s)	7.53 (s)	7.37 (d) (J=8.0)	7.97 (d)	7.97 (d) (J=8.0)	7.51 (d)
21	7.46 (s)	7.58 (s)	7.36 (d) (J=9.0)	7.86 (d)	8.21 (s)	—
22	7.43 (s)	7.52 (s)	7.36 (d) (J=9.0)	7.88 (d)	8.51 (s)	—
23	7.28 (s)	7.49 (s)	7.36 (d) (J=9.0)	7.91 (d)	7.61 (s)	—
24	7.29 (s)	7.49 (s)	7.35 (d) (J=9.0)	7.89 (d)	7.65 (s)	—
15	7.13 (s)	7.47 (s)	6.96 (s)	—	9.00 (d) (J=9.0)	7.48 (d)
25	7.39 (s)	7.53 (s)	6.96 (s)	—	9.61 (s)	—
26	7.46 (s)	7.59 (s)	6.96 (s)	—	8.57 (s)	—

The regioselective introduction of a halogen atom at the C_{12}-position of the benzo[*c*]phenanthridine skeleton was thus achieved. Our next effort was then focused on an efficient conversion of the aromatic halogen atom into a methoxy group. First of all, the bromo derivative (**21**) was refluxed with sodium methoxide in methanol–pyridine in the presence of cuprous iodide (CuI) and cupric oxide (CuO).[20] However, no characteristic product was isolated from the reaction mixture. Changing the catalyst (*e.g.* cuprous bromide), solvent, and/or reaction temperature did not work. The more reactive iodo derivative (**22**) was found to be a suitable substrate for our purpose. On exposure to conditions similar to those[20] described for **21**, **22** underwent substitution at the C_{12}-position with the methoxide to afford the 12-methoxyoxychelerythrine (**23**) in a satisfactory yield (82%) along with the dehalogenated product, oxychelerythrine (**20**, 10%). Introduction of an ethoxy group was also realized by using sodium ethoxide/ethanol instead of sodium methoxide/methanol to give 12-ethoxyoxychelerythrine (**24**) in a rather low yield (58%).

A characteristic feature of **23** and **24** in their ^{1}H-NMR spectra was the significant high-field shift of the C_{11}-H signal. Furthermore, no such shift of the C_9- or C_{10}-H signal was observed. These ^{1}H-NMR spectral analyses strongly indicated that the substitution has occurred at the C_{12}-position without any migration. Since we had developed an efficient methoxylation (and also ethoxylation) at the C_{12}-position of a benzo[*c*]phenanthridine alkaloid, oxychelerythrine (**20**), we next turned to a biomimetic synthesis

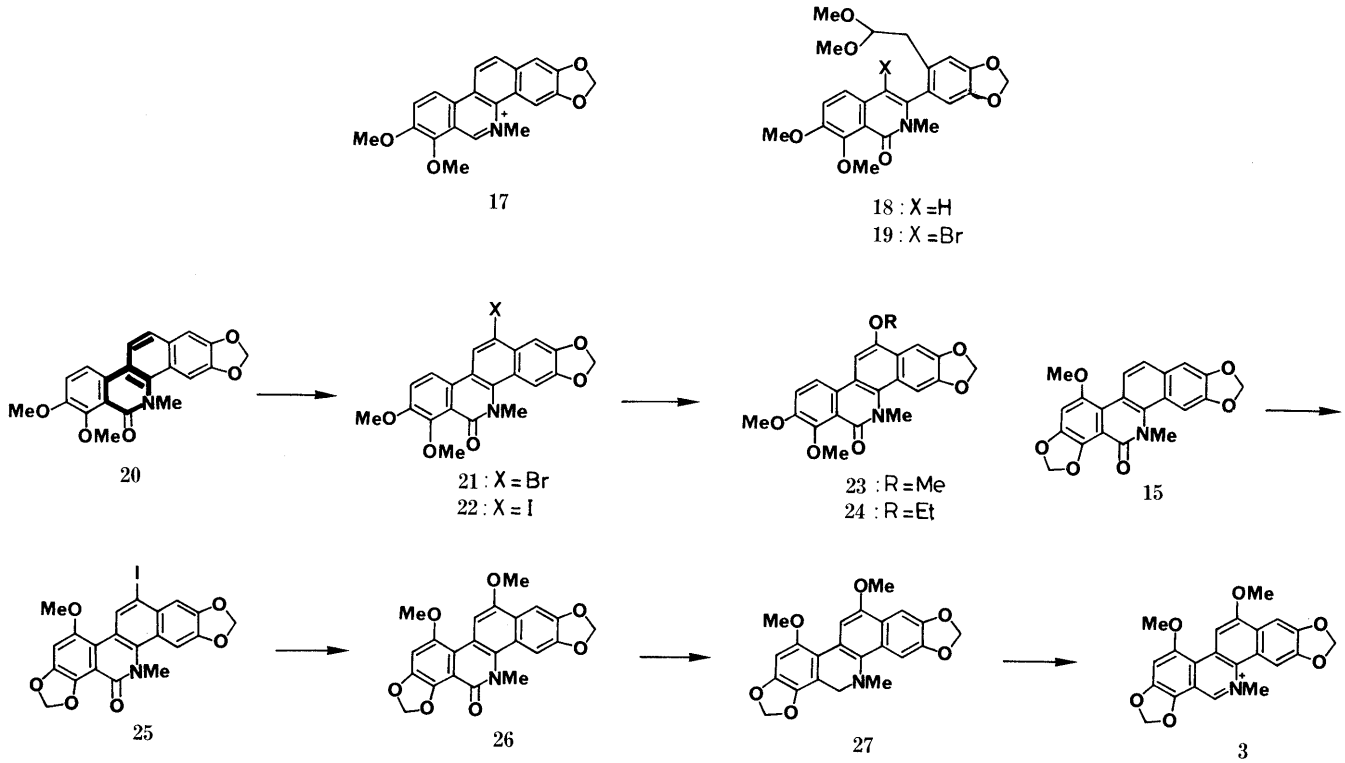

Chart 4

of macarpine (**3**) from oxychelirubine (**15**) by applying the above novel method.

Oxychelirubine (**15**) was iodinated with NIS[18] under the similar conditions to those described for **22** to give the C_{12}-iodo derivative (**25**) in 79% yield, as expected. The structure of **25** was manifest from the spectral data (see Table II). The down-field-shifted C_1- and C_{11}-H signals appeared at δ 7.46 and 9.61 ppm, respectively, each as a singlet. This down-field shift is in accordance with the observations in the ^{1}H-NMR spectra of **21** and **22**. Oxymacarpine (**26**), in 70% yield, was obtained by displacement of the iodine atom in **25** with sodium methoxide. Finally dihydromacarpine (**27**), obtained by the usual reduction of **26** in 92% yield, was converted into macarpine (**3**) by DDQ oxidation, followed by treatment with concentrated hydrochloric acid, in 91% yield. Synthetic macarpine and dihydromacarpine were shown to be identical with natural macarpine and dihydromacarpine, respectively, by comparison of their spectra and TLC behavior.

Thus, we have developed a new method for the introduction of an oxy functionality at the C_{12}-position of the benzo[*c*]phenanthridine skeleton. This efficient and convenient method could be successfully applied for the biomimetic conversion of a 2,3,7,8,10-pentaoxygenated benzo[*c*]phenanthridine alkaloid, oxychelirubine, into macarpine and dihydromacarpine, 2,3,7,8,10,12-hexaoxygenated benzo[*c*]phenanthridine alkaloids.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Alumina (Aluminiumoxid 90, Aktivitätsstufe II—III, 70—230 mesh, Merck) and silica gel (Kieselgel 60, 70—230 mesh, Merck) were used for column chromatography. Organic extracts were dried over anhydrous Na_2SO_4. IR spectra were measured with a JASCO A-102 spectrometer in $CHCl_3$, MS with a Hitachi M-80 mass spectrometer, ultraviolet (UV) spectra with a Hitachi U-3200 spectrophotometer, 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 400 W high-pressure mercury lamp equipped with a Pyrex filter (Riko Kagaku Co.).

***N*-(3,4-Methylenedioxyphenethyl)-2-methoxy-4,5-methylenedioxyphenylacetamide (6)** A mixture of the phenethylamine (**4**) (1.10 g, 6.67 mmol) and the phenylacetic acid (**5**) (1.00 g, 4.78 mmol) was heated at 190—200 °C for 3 h in a stream of nitrogen. The reaction mixture was dissolved in CH_2Cl_2 and the solution was washed successively with 10% hydrochloric acid, 10% sodium hydroxide, and brine, then dried and evaporated to give a residue, which was chromatographed on silica gel with $CHCl_3$ to afford the amide (**6**) (1.33 g, 78%), colorless needles, mp 147—148 °C (AcOEt). IR ν_{max} cm^{-1}: 1650 (amide). UV λ_{max}^{MeOH} nm (log ε): 292 (3.88), 236 (3.92). ^{1}H-NMR δ: 6.68, 6.54 (each 1H, AB-q, J=8.0 Hz, aromatic H), 6.65, 6.52, 6.50 (each 1H, each s, aromatic H), 5.92 (4H, s, $OCH_2O\times2$), 5.67 (1H, s, NH), 3.70 (3H, s, OMe), 3.48 (2H, s, $C\underline{H}_2CONH$), 3.36 (2H, t, J=6.5 Hz, $CH_2C\underline{H}_2N$), 2.63 (2H, t, J=6.5 Hz, $C\underline{H}_2CH_2N$). MS *m/z* (%): 357 (M^+, 41), 165 (100). *Anal.* Calcd for $C_{19}H_{19}NO_6$: C, 64.04; H, 5.09; N, 3.93. Found: C, 63.87; H, 5.34; N, 3.88.

(*Z*)-2-Formyl-1,2,3,4-tetrahydro-1-(2-methoxy-4,5-methylenedioxyphenylethylidene)-6,7-methylenedioxyisoquinoline (8) $POCl_3$ (14 ml, 154 mmol) was added to a solution of the amide (**6**) (5.50 g, 15 mmol) in toluene (80 ml). The mixture was heated under reflux for 30 min, then allowed to cool. *n*-Hexane (20 ml) was added, and the whole was allowed to stand for 30 min. The organic solvents were removed by decantation. This procedure was repeated again. The residue was made alkaline with 28% aqueous ammonia and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water and brine, dried, and evaporated. The residue was dissolved in acetic formic anhydride (45 ml). AcONa (9.60 g, 117 mmol) was added to the anhydride solution and the reaction mixture was stirred for 1 h at room temperature, then MeOH (20 ml) was added to remove excess anhydride. The whole was stirred for 30 min, then the solvent was evaporated off. The residue was taken up in CH_2Cl_2. The organic solution was washed with saturated $NaHCO_3$ solution, water, and brine, dried, and concentrated to dryness. Chromatography of the residue on silica gel with $CHCl_3$ gave the isoquinoline (**8**) (4.52 g, 80%), pale yellow needles, mp 197—199 °C (MeOH). IR ν_{max} cm^{-1}: 1660 (amide). UV λ_{max}^{MeOH} nm (log ε): 218 (4.56), 231 sh (4.41), 278 (4.05), 348 (4.25). ^{1}H-NMR δ: 8.08 (1H, s, CHO), 7.24 (1H, s, C=CH), 6.83 6.76, 6.58, 6.52 (each 1H, each s, aromatic H), 5.96, 5.91 (each 2H, each s, $OCH_2O\times2$), 3.92 (2H, t, J=6.0 Hz, $CH_2C\underline{H}_2N$), 3.81 (3H, s, OMe), 2.84 (2H, t, J=6.0 Hz, $C\underline{H}_2CH_2N$). MS *m/z* (%): 367 (M^+, 55), 308 (100). *Anal.* Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.22; H, 4.63; N, 3.71.

5,6-Dihydro-12-methoxy-2,3,9,10-bismethylenedioxydibenzo[*a*,*g*]quinolizinium Iodide (9) A solution of **8** (500 mg, 1.36 mmol) in CH_2Cl_2 and EtOH (20 and 400 ml, respectively) was irradiated in a stream of nitrogen for 2 h, then concentrated to *ca.* 50 ml. Hydroiodic acid (57%, 1 ml) was added to the above solution and the resulting precipitates were collected by filtration. Recrystallization of the crude product from MeOH afforded the protoberberine (**9**) (461 mg, 71%), reddish brown crystals, mp 270—273 °C (dec.). UV λ_{max}^{MeOH} nm (log ε): 224 (4.69), 241 sh (4.54), 282 (4.40). ^{1}H-NMR [$(CD_3)_2SO$] δ: 9.85 (1H, s, H-8), 8.68, 7.88, 7.73, 7.05 (each 1H, each s, aromatic H), 6.46, 6.15 (each 2H, each s, $OCH_2O\times2$), 4.86—4.83 (2H, m, H-6), 4.07 (3H, s, OMe), 3.25—3.20 (2H, m, H-5). *Anal.* Calcd for $C_{20}H_{16}NO_5\cdot I$: C, 50.33; H, 3.38; N, 2.93. Found: C, 50.27; H, 3.22; N, 2.57.

5,8,13,14-Tetrahydro-12-methoxy-2,3,9,10-bismethylenedioxy-6*H*-dibenzo[*a*,*g*]quinolizine (10) $NaBH_4$ (24 mg, 0.63 mmol) was added to a solution of the protoberberine (**9**) (30 mg, 0.063 mmol) in MeOH (15 ml). The mixture was stirred for 2 h at room temperature, then MeOH was evaporated off and the residue was taken up in CH_2Cl_2. This solution was washed with water and brine, dried, and concentrated to dryness. Recrystallization of the residue from MeOH furnished **10** (20 mg, 88%), colorless needles, mp 218—220 °C. ^{1}H-NMR δ: 6.79, 6.58, 6.42 (each 1H, each s, aromatic H), 5.91, 5.89 (each 2H, each s, $OCH_2O\times2$), 3.76 (3H, s, OMe). MS *m/z* (%): 353 (M^+, 15), 163 (100), 178 (26). *Anal.* Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.75; H, 5.39; N, 3.94.

5,6,7,8-Tetrahydro-12-methoxy-7-methyl-2,3,9,10-bismethylenedioxydibenzo[*a*,*g*]quinolizinium Monomethylsulfate (11) The protoberberine (**9**) (1.90 g, 3.98 mmol) was added portionwise to a stirred suspension of LAH (454 mg, 12.0 mmol) in dry THF (50 ml) over a period of 10 min in a stream of nitrogen at 0 °C. The suspension was stirred for 2 h at room temperature, then water was added and the whole was filtered. The filtrate was concentrated to leave the crude 7,8-dihydro derivative, which was dissolved in dry benzene (50 ml). Dimethyl sulfate (1.13 ml, 12.0 mmol) was added dropwise to the refluxing benzene solution over a period of 5 min. Reflux was continued for 2 h. After cooling of the reaction mixture to room temperature, the resulting precipitates were collected by filtration and dried to provide **11** (1.54 g, 81%), brownish yellow crystals, mp 240—241 °C (EtOH). UV λ_{max}^{MeOH} nm (log ε): 231 (4.15), 260 (4.03), 307 (3.99). ^{1}H-NMR [$(CD_3)_2SO$] δ: 7.57, 7.51, 6.98, 6.92 (each 1H, each s, aromatic H and olefinic H), 6.20—6.00 (4H, m, $OCH_2O\times2$), 4.96 (2H, s, H-8), 3.88 (3H, s, OMe), 3.10 (3H, s, NMe). *Anal.* Calcd for $C_{21}H_{20}NO_5\cdot CH_3SO_4$: C, 55.34; H, 4.86; N, 2.93. Found: C, 55.04; H, 4.70; N, 2.90.

5-Methoxy-2-methyl-7,8-methylenedioxy-3-(4,5-methylenedioxy-2-vinylphenyl)isoquinolin-1(2*H*)-one (13) The methosulfate (**11**) (500 mg, 1.05 mmol) was added at once to refluxing 25% methanolic potassium hydroxide (12 ml) and the mixture was heated under reflux for 10 min. The reaction mixture was poured into ice-water (20 ml) and extracted with $CHCl_3$. The extract was washed with water and brine, and dried. DDQ (286 mg, 1.26 mmol) was added portionwise to the stirred $CHCl_3$ solution and stirring was continued for 17 h at room temperature. The $CHCl_3$ solution was then washed with saturated $NaHCO_3$ solution, water, and brine, dried, and concentrated to dryness. Chromatography of the residue on silica gel with CH_2Cl_2–MeOH (100 : 2) furnished the enamide (**13**) (200 mg, 50%), pale yellow needles, mp 242—244 °C (MeOH). IR ν_{max} cm^{-1}: 1660 (amide). UV λ_{max}^{MeOH} nm (log ε): 226 (4.46), 240 sh (4.29), 288 (3.78), 341 (3.90). ^{1}H-NMR δ: 7.12, 6.81, 6.73, 6.66 (each 1H, each s, aromatic H and H-4), 6.43 (1H, dd, J=17.3, 10.7 Hz, $CH_2=C\underline{H}Ar$), 6.17, 6.03 (each 2H, each s, $OCH_2O\times2$), 5.58 (1H, dd, J=17.3, 1.0 Hz, $C\underline{H}_2=CHAr$), 5.12 (1H, dd, J=10.7, 1.0 Hz, $C\underline{H}_2=CHAr$), 3.86 (3H, s, OMe), 3.22 (3H, s, NMe). MS *m/z* (%): 379 (M^+, 100), 335 (28). *Anal.* Calcd for $C_{21}H_{17}NO_6$: C, 66.48; H, 4.52; N, 3.69. Found: C, 66.14; H, 4.39; N, 3.78.

5-Methoxy-3-[2-(2,2-dimethoxyethyl)-4,5-methylenedioxyphenyl]-2-methyl-7,8-methylenedioxyisoquinolin-1(2*H*)-one (14) A solution of TTN trihydrate (165 mg, 0.37 mmol) in MeOH (30 ml) was added dropwise to a solution of **13** (80 mg, 0.21 mmol) in MeOH (30 ml) at −10 °C and the

reaction mixture was stirred for 10 min. Saturated $NaHCO_3$ solution was then added and the whole was extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue on silica gel with CH_2Cl_2–MeOH (100 : 2) afforded **14** (74.5 mg, 80%), colorless amorphous solid. IR ν_{max} cm^{-1}: 1650 (amide). UV λ_{max}^{MeOH} nm (log ε): 241 sh (4.28), 317 (4.12). ^{1}H-NMR δ: 6.92, 6.81, 6.69, 6.64 (each 1H, each s, aromatic H and H-4), 6.17, 6.10 (each 2H, each s, $OCH_2O \times 2$), 4.38 [1H, dd, J=6.1, 4.6 Hz, C<u>H</u>$(OMe)_2$], 3.85, 3.25, 3.24 (each 3H, each s, OMe × 3), 3.18 (3H, s, NMe), 2.95—2.50 [2H, m, C<u>H</u>$_2$CH$(OMe)_2$]. MS m/z (%): 441 (M^+, 55), 75 (100). High-resolution mass Calcd for $C_{23}H_{23}NO_8$: 441.1422. Found: 441.1423.

10-Methoxy-5-methyl-2,3,7,8-bismethylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (Oxychelirubine) (15) A solution of **14** (50 mg, 0.113 mmol) and 10% hydrochloric acid (2 ml) in MeOH (10 ml) was heated at 50—60 °C for 1.5 h. MeOH was evaporated off and the residue was taken up in CH_2Cl_2. The solution was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue on silica gel with CH_2Cl_2–MeOH (100 : 2) provided **15** (35 mg, 82%), pale yellow needles, mp >300°C (CH_2Cl_2) (lit.[20] 307—308 °C). IR ν_{max} cm^{-1}: 1645. UV λ_{max}^{MeOH} nm (log ε): 241 (4.68), 249 sh (4.52). ^{1}H-NMR δ: 9.00, 7.48 (each 1H, AB-q, J=9.0 Hz, H-11 and H-12), 7.47, 7.13, 6.96 (each 1H, each s, aromatic H), 6.21, 6.07 (each 2H, each s, OCH_2O), 4.00 (3H, s, OMe), 3.84 (3H, s, OMe). MS m/z (%): 377 (M^+, 100), 362 (81), 304 (26). *Anal.* Calcd for $C_{21}H_{15}NO_6$: C, 66.84; H, 4.01; N, 3.71. Found: C, 66.53; H, 3.83; N, 3.98.

Oxychelirubine (**15**) (31 mg, 76%) was directly obtained from **13** (40 mg, 0.11 mmol) by the above method without isolation of **14**.

5,6-Dihydro-10-methoxy-5-methyl-2,3,7,8-bismethylenedioxybenzo-[*c*]phenanthridine (Dihydrochelirubine) (16) LAH (19 mg, 0.53 mmol) was added portionwise to a stirred solution of **15** (20 mg, 0.053 mmol) in dry THF (10 ml) in a stream of nitrogen at 0 °C and stirring was continued for 1 h at room temperature, then the reaction mixture was diluted with water and filtered. The filtrate was concentrated and the residue was dissolved in MeOH (10 ml). $NaBH_4$ (19 mg, 0.50 mmol) was added to the MeOH solution and the mixture was kept for 30 min at room temperature. MeOH was evaporated off and the residue was taken up in CH_2Cl_2. This solution was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue on alumina with $CHCl_3$ afforded **16** (16 mg, 82%), colorless plates, mp 202—204 °C (MeOH) (lit.[9] 205—207 °C). λ_{max}^{MeOH} nm (log ε): 235 (4.60), 251 (4.45), 257 (4.46), 264 (4.46), 280 (4.50), 290 sh (4.30), 337 (4.28). ^{1}H-NMR δ: 8.31, 7.46 (each 1H, AB-q, J=8.8 Hz, H-11 and H-12), 7.70, 7.10, 6.60 (each 1H, each s, aromatic H), 6.03, 6.00 (each 2H, each s, $OCH_2O \times 2$), 4.11 (2H, s, H-6), 3.87 (3H, s, OMe), 2.59 (3H, s, NMe). *Anal.* Calcd for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.72; N, 3.86. Found: C, 69.11; H, 4.62; N, 3.92.

10-Methoxy-5-methyl-2,3,7,8-bismethylenedioxybenzo[*c*]phenanthridinium Chloride (Chelirubine Chloride) (2) DDQ (17 mg, 0.075 mmol) was added to a vigorously stirred solution of **16** (12 mg, 0.033 mmol) and 5% aqueous sodium hydroxide (1 ml) in benzene (10 ml). The mixture was stirred for 2 h at room temperature, then the benzene layer was separated and the water layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried, and concentrated to dryness. Concentrated hydrochloric acid (0.5 ml) was added to the above residue, and the resulting precipitates were collected by filtration. The solid was recrystallized from EtOH to give **2** (12 mg, 90%), reddish brown crystals, mp 280—283 °C (dec.) (lit.[7c] 282—283°C). UV λ_{max}^{MeOH} nm (log ε): 232 (4.40), 283 (4.38), 353 (4.19). ^{1}H-NMR (CD_3OD) δ: 9.82 (1H, s, H-6), 9.42, 8.11 (each 1H, AB-q, J=9.3 Hz, H-11 and H-12), 8.02, 7.76, 7.50 (each 1H, each s, aromatic H), 6.47, 6.26 (each 2H, each s, $OCH_2O \times 2$), 4.88 (3H, s, NMe), 4.21 (3H, s, OMe).

4-Bromo-7,8-dimethoxy-3-[2-(2,2-dimethoxyethyl)-4,5-methylenedioxy]-2-methylisoquinolin-1(2*H*)-one (19) A solution of the isoquinoline (**18**)[5a] (75 mg, 0.18 mmol) and NBS (43 mg, 0.24 mmol) in carbon tetrachloride (30 ml) was refluxed for 30 min. The solvent was evaporated off and the residue was taken up in CH_2Cl_2. The solution was washed with saturated $NaHCO_3$ solution, water, and brine, dried, and concentrated to dryness. Chromatography of the residue on alumina with $CHCl_3$ afforded **19** (81 mg, 91%) as an oil. IR ν_{max} cm^{-1}: 1640. UV λ_{max}^{MeOH} nm (log ε): 228 (4.64), 296 (4.28), 306 (4.27), 355 (3.88). ^{1}H-NMR δ: 7.75, 7.40 (each 1H, AB-q, J=9.0 Hz, H-5 and H-6), 6.98, 6.63 (each 1H, each s, aromatic H), 6.04 (2H, s, OCH_2O), 4.46 [1H, dd, J=6.0, 5.0 Hz, C<u>H</u>$(OMe)_2$], 4.02, 3.98 (each 3H, each s, OMe × 2), 3.26 (6H, s, OMe × 2), 3.20 (3H, s, NMe), 2.73 [1H, dd, J=15, 6.0 Hz, C<u>H</u>$_2$CH$(OMe)_2$], 2.60 [1H, dd, J=15, 5.0 Hz, C<u>H</u>$_2$CH$(OMe)_2$]. MS m/z (%): 505 (M^+, 100), 507 (M^+, 100). High resolution mass Calcd for $C_{23}H_{24}BrNO_7$: 505.0735. Found: 505.0758.

12-Bromo-7,8-dimethoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (12-Bromo-oxychelerythrine) (21) A solution of oxychelerythrine (**20**) (200 mg, 0.55 mmol) and NBS (118 mg, 0.66 mmol) in carbon tetrachloride (30 ml) was heated under reflux for 18 h, then allowed to cool. $CHCl_3$ (30 ml) was added to the reaction mixture. The organic solution was washed with saturated $NaHCO_3$ solution, water, and brine, dried, and concentrated to leave the crude product, which was recrystallized from MeOH to give **21** (224 mg, 93%), colorless needles, mp 216—218 °C. IR ν_{max} cm^{-1}: 1650 (amide). UV λ_{max}^{MeOH} nm (log ε): 244 (4.56), 283 (4.70), 293 (4.82), 329 (4.23). ^{1}H-NMR δ: 8.21 (1H, s, H-11), 7.86, 7.36 (each 1H, AB-q, J=9.0 Hz, H-10 and H-9), 7.58, 7.46 (each 1H, each s, H-4 and H-1), 6.12 (2H, s, OCH_2O), 4.07, 3.98 (each 3H, each s, OMe × 2), 3.83 (3H, s, NMe). MS m/z (%): 443 (M^+, 98), 441 (M^+, 100), 428 (49), 426 (42). *Anal.* Calcd for $C_{21}H_{16}BrNO_5$: C, 57.03; H, 3.65; N, 3.17. Found: C, 57.04; H, 3.39; N, 2.89.

12-Iodo-7,8-dimethoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (12-Iodo-oxychelerythrine) (22) NCS (221 mg, 1.65 mmol) was dissolved in dry acetone (2 ml), and then NaI (248 mg, 1.65 mmol) was added. The mixture was stirred for 15 min at room temperature, and the resulting NaCl was removed by filtration. The filtrate was concentrated to dryness. A solution of oxychelerythrine (**20**) (200 mg, 0.551 mmol) in $CHCl_3$ (40 ml) was added to the above residue and the reaction mixture was heated under reflux for 18 h. The solution was washed successively with saturated sodium thiosulfate and $NaHCO_3$ solution, water, and brine, then dried and evaporated to provide the crude product, which was recrystallized from MeOH to leave **22** (223 mg, 83%), pale yellow needles, mp 223—224 °C. IR ν_{max} cm^{-1}: 1650 (amide). UV λ_{max}^{MeOH} nm (log ε): 212 (4.00), 245 (4.40), 294 (4.49), 340 (4.01). ^{1}H-NMR δ: 8.51 (1H, s, H-11), 7.88, 7.36 (each 1H, AB-q, J=9.0 Hz, H-10 and H-9), 7.52, 7.43 (each 1H, each s, H-4, H-1), 6.12 (2H, s, OCH_2O), 4.07, 3.98 (each 3H, each s, OMe × 2), 3.83 (3H, s, NMe). MS m/z (%): 489 (M^+, 100). *Anal.* Calcd for $C_{21}H_{16}INO_5$: C, 51.55; H, 3.30; N, 2.86. Found: C, 51.75; H, 3.20; N, 2.72.

7,8,12-Trimethoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (12-Methoxyoxychelerythrine) (23) CuO (26 mg, 0.33 mmol) and a solution of sodium methoxide (89 mg, 1.64 mmol) in dry MeOH (5 ml) (prepared from 38 mg of sodium and 5 ml of MeOH) were successively added to a solution of CuI (31 mg, 0.165 mmol) in dry pyridine (8 ml) at room temperature. The reaction mixture was heated under reflux for 8 h, then allowed to cool to room temperature. Water (10 ml) was added to the reaction mixture, and the whole was stirred for 15 min. Inorganic materials were filtered off and the filtrate was extracted with $CHCl_3$. The extract was washed with 10% hydrochloric acid, water, and brine, dried, and concentrated to dryness. Chromatography of the residue on silica gel with CH_2Cl_2–MeOH (100 : 2) gave **23** and oxychelerythrine (**20**) (6 mg, 10%). **23**: (53 mg, 82%), pale yellow needles, mp 163.5—164.5 °C (MeOH). IR ν_{max} cm^{-1}: 1645 (amide). UV λ_{max}^{MeOH} nm (log ε): 237 (4.54), 292 (4.55), 330 (4.33), 341 (4.08). ^{1}H-NMR δ: 7.91, 7.36 (each 1H, AB-q, J=9.0 Hz, H-10 and H-9), 7.61, 7.49, 7.28 (each 1H, each s, aromatic H), 6.08 (2H, s, OCH_2O), 4.08, 4.07, 3.98 (each 3H, each s, OMe × 3), 3.85 (3H, s, NMe). MS m/z (%): 393 (M^+, 100), 378 (51). *Anal.* Calcd for $C_{22}H_{19}NO_6$: C, 67.17; H, 4.87; N, 3.56. Found: C, 67.11; H, 4.82; N, 3.53.

12-Ethoxy-7,8-dimethoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (12-Ethoxyoxychelerythrine) (24) The iodo compound (**22**) (50 mg, 0.102 mmol) was treated with CuO (8 mg, 0.102 mmol) and CuI (19.5 mg, 0.102 mmol) in the presence of sodium ethoxide (69.5 mg, 1.02 mmol) in dry EtOH (5 ml) and dry pyridine (8 ml). Work-up and chromatography of the residue on silica gel with CH_2Cl_2–MeOH (100 : 2) gave **24** (24 mg, 58%), pale yellow needles, mp 202—203 °C (MeOH). IR ν_{max} cm^{-1}: 1640 (amide). UV λ_{max}^{MeOH} nm (log ε): 236 (4.62), 292 (4.72), 335 (4.15), 373 (4.00). ^{1}H-NMR δ: 7.89, 7.35 (each 1H, AB-q, J=9.0 Hz, H-10 and H-9), 7.65, 7.49, 7.29 (each 1H, each s, aromatic H), 6.09 (2H, s, OCH_2O), 4.29 (2H, q, J=7.0 Hz, C<u>H</u>$_2$CH$_3$), 4.08, 3.98 (each 3H, each s, OMe × 2), 3.86 (3H, s, NMe), 1.58 (3H, t, J=7.0 Hz, CH$_2$C<u>H</u>$_3$). MS m/z (%): 407 (M^+, 100). *Anal.* Calcd for $C_{23}H_{21}NO_6 \cdot 1/3MeOH$: C, 67.04; H, 5.38; N, 3.35. Found: C, 67.12; H, 5.23; N, 3.15.

12-Iodo-10-methoxy-5-methyl-2,3,7,8-bismethylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (12-Iodo-oxychelirubine) (25) According to the procedure described for the synthesis of **22**, **15** (116 mg, 0.31 mmol) was treated with NIS (208 mg, 0.92 mmol) (prepared from NCS and NaI) in refluxing $CHCl_3$ (20 ml) for 4 h. Work-up and chromatography of the residue on silica gel with CH_2Cl_2–MeOH (100 : 2) gave **25** (122 mg, 79%), pale yellow needles, mp 298—300 °C ($CHCl_3$–MeOH). IR ν_{max} cm^{-1}: 1635 (amide). UV λ_{max}^{MeOH} nm (log ε): 247 (4.40), 292 (4.44), 345 (4.03). ^{1}H-NMR

δ: 9.61 (1H, s, H-11), 7.53, 7.39, 6.96 (each 1H, each s, aromatic H), 6.22, 6.12 (each 2H, each s, $OCH_2O \times 2$), 4.03 (3H, s, OMe), 3.80 (3H, s, NMe). MS *m/z* (%): 503 (M^+, 100), 411 (33), 361 (88). *Anal.* Calcd for $C_{21}H_{14}INO_6$: C, 50.12; H, 2.80; N, 2.78. Found: C, 50.32; H, 2.91; N, 2.91.

10,12-Dimethoxy-5-methyl-2,3,7,8-bismethylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (Oxymacarpine) (26) 12-Iodo-oxychelirubine (**25**) (70 mg, 0.14 mmol) was treated with CuI (27 mg, 0.14 mmol), CuO (22 mg, 0.28 mmol), and sodium methoxide (80 mg, 1.48 mmol) in MeOH–pyridine (5 ml–8 ml) as described for **23** to yield **26** (40 mg, 70%), pale yellow needles, mp >300 °C (CH_2Cl_2–EtOH) and oxychelirubine (**15**) (14 mg, 26%). **26**: IR ν_{max} cm^{-1}: 1630 (amide). UV λ_{max}^{MeOH} nm (log ε): 240 (4.53), 267 (4.42), 292 (4.55), 298 sh (4.33), 351 (4.09). ^{1}H-NMR δ: 8.57 (1H, s, H-11), 7.59, 7.46, 6.96 (each 1H, each s, aromatic H), 6.21, 6.08 (each 2H, each s, $OCH_2O \times 2$), 4.04, 4.01 (each 3H, each s, OMe × 2), 3.82 (3H, s, NMe). *Anal.* Calcd for $C_{22}H_{17}NO_7$: C, 64.87; H, 4.20; N, 3.44. Found: C, 64.76; H, 3.99; N, 3.36.

5,6-Dihydro-10,12-dimethoxy-5-methyl-2,3,7,8-bismethylenedioxybenzo[*c*]phenanthridine (Dihydromacarpine) (27) Oxymacarpine (**26**) (18.5 mg, 0.045 mmol) was successively reduced with LAH (30 mg, 0.79 mmol) in dry THF (10 ml) and $NaBH_4$ (30 mg, 0.79 mmol) in MeOH (10 ml) as described for **16** to afford **27** (16.5 mg, 92%), colorless needles, mp 177—178 °C (Et_2O) (lit.[14] 178—179 °C). UV λ_{max}^{MeOH} nm (log ε): 219 (4.61), 284 (4.53), 314 (4.13), 339 (4.22). ^{1}H-NMR δ: 7.82 (1H, s, H-11), 7.67, 7.53, 6.61 (each 1H, each s, aromatic H), 6.03, 6.00 (each 2H, each s, $OCH_2O \times 2$), 4.09 (2H, s, H-6), 4.00, 3.88 (each 3H, each s, OMe × 2), 2.53 (3H, s, NMe). MS *m/z* (%): 393 (M^+, 100), 378 (85). *Anal.* Calcd for $C_{22}H_{19}NO_6$: C, 65.03; H, 5.19; N, 3.79. Found: C, 65.21; H, 5.20; N, 3.72.

10,12-Dimethoxy-5-methyl-2,3,7,8-bismethylenedioxybenzo[*c*]phenanthridinium Chloride (Macarpine Chloride) (3) Dihydromacarpine (16.5 mg, 0.047 mmol) was oxidized with DDQ (16 mg, 0.07 mmol) and treated with concentrated hydrochloric acid as described for **2** to give **3** (16 mg, 91%), reddish brown crystals, mp 275—278 °C (lit.[14] 283—285 °C). UV λ_{max}^{MeOH} nm (log ε): 220 (4.52), 238 sh (4.35), 286 (4.44), 293 sh (4.25), 315 (4.03), 343 (4.15). ^{1}H-NMR [$(CD_3)_2SO$] δ: 9.79 (1H, s, H-6), 8.77 (1H, s, H-11), 8.12, 7.88, 7.66 (each 1H, each s, aromatic H), 6.53, 6.34 (each 2H, each s, $OCH_2O \times 2$), 4.81 (3H, s, NMe), 4.18, 4.14 (each 3H, each s, OMe × 2).

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