Ring C Homologation of Aporphines. A New Synthesis of Homoaporphines

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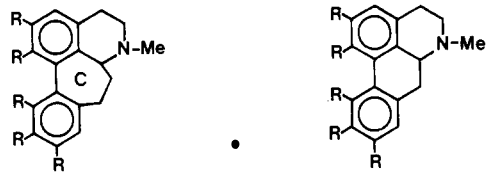
We describe an easy method for the ring C homologation of aporphines that is based on dichlorocarbene addition to dehydroaporphinoids and phenanthrene derivatives. **17a** and **17d**, however, gave the insertion products **23** and **21b**, respectively.

Homoaporphines constitute a small group of isoquinoline alkaloids closely related to aporphines. The main structural difference between them is the existence of a seven-membered ring C in homoaporphines.[2]



HOMOAPORPHINES APORPHINES

Up to the present, the preparation of homoaporphines has been performed by ab initio synthesis. All these methods invariably pass through the required tetrahydrophenethylisoquinoline, which by phenolic or nonphenolic coupling,[3] by photochemical cyclization,[4] or through quinol acetates[5] gives the desired homoaporphine. Curiously, although aporphines are the largest group of isoquinoline alkaloids, no efforts have been made toward their conversion into homoaporphines. We present here an easy and efficient strategy that covers this subject and that is based on dichlorocarbene addition to dehydroaporphinoids or phenanthrene derivatives.

Results and Discussion

Dehydroaporphine Approach. The enamine character of dehydroaporphines is well-known and explains their reactivity at C-7 toward acids[6] and dichlorocarbene.[7] We reasoned that by blocking the nitrogen lone electron pair the reactivity of the dehydroaporphine should be different, particularly the olefinic character of the C-6a–C-7 double bond. Thus, when the N-protected dehydroaporphine **1** was treated with dichlorocarbene generated by the phase-transfer method (PTM),[8] we obtained the adduct **2** in 86% yield after 20 min of stirring at room temperature. Extended reaction times and/or heating gave complex reaction mixtures without practical use. Reaction of **2** with $LiAlH_4$ in refluxing THF produced a mixture of 7-chloro-7,8-didehydrohomodicentrine (**6**) and 7,8-didehydrohomodicentrine (**5**) in 77% and 3% yields, respectively; this conversion involves the reduction of the carboxyethyl function of **2** to an *N*-methyl group, followed by ring expansion with the aid of the nitrogen lone pair and subsequent reduction of the iminium cation (Figure 1). Catalytic hydrogenation of **6** (10% Pd–C, NaOAc, EtOH) gave homodicentrine (**7**) in 63% overall yield with respect to **1**.

Phenanthrene Approach. The above ring C homologation of aporphines starts from an *N*-carbethoxy derivative, whose preparation from aporphines[9] or by total synthesis[10] requires several steps. To reduce this problem, we developed an alternative route based on the addition of dichlorocarbene to N-protected phenanthrene derivatives, which are easily available from aporphines (Figure 2). In this way, treatment of glaucine (**8**) with trifluoroacetic anhydride gave phenanthrene **9**, which upon dichlorocarbene addition (PTM) produced adduct **10**. This was easily N-deprotected (MeOH, Na_2CO_3) to amine **11**. Regeneration of ring B and homologation of ring C were achieved in one step by thermal electrocyclic ring opening of the dichlorocyclopropane ring of **11** and intramolecular trapping of the developing allylic cation by the nitrogen atom. The 7-chloro-7,8-didehydrohomoglaucine (**12**) thus obtained was converted into homoglaucine (**13**) by catalytic hydrogenation (43% overall yield from **8**).

The choice of the nitrogen-protecting group was of critical importance. Thus, while a trifluoroacetyl group was found to be ideal for our purposes because it resists Cl_2C: (PTM) and is easily removed, a carboxyethyl group (as in **16**) could not be hydrolyzed without the required dichlorocyclopropane being affected.

All our attempts to convert the chlorovinylic unit of **12** to a carbonyl group were unsuccessful. Thus, **12** was inert toward hydrolysis promoted by mercuric acetate,[11] palladium(II) chloride,[12] or sulfuric acid at 0 °C.[11] This lack of reactivity may be ascribed to the double bond not being activated because the nitrogen is protonated or coordinated to the metal. Under basic conditions (Me_2SO, KOH; 25 °C; 4 days), compound **12** reacted slowly, giving a complex mixture of products. Nevertheless, although **12** was recovered unchanged from its reaction with Zn(Ag),[13] the chlorovinyl compound **12** could be dehalogenated with

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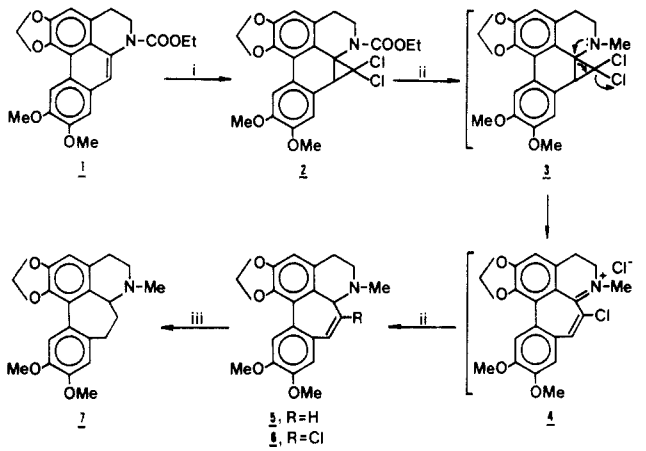

Figure 1. Reagents and conditions: (i) $CHCl_3$, 50% NaOH, TBAC, 86%; (ii) $LiAlH_4$, THF, 77%; (iii) H_2, 5% Pd–C, NaOAc, EtOH, 94%.

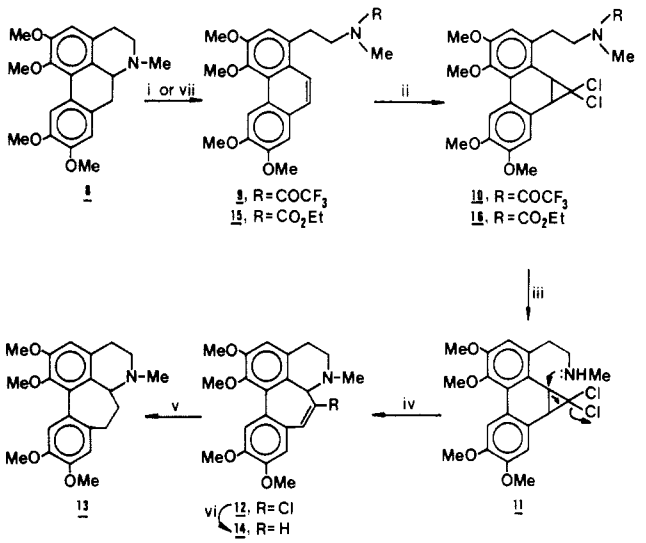

Figure 2. Reagents and conditions: (i) $(CF_3CO)_2O$, py, 86%; (ii) $CHCl_3$, 50% NaOH, TBAC, 69%; (iii) Na_2CO_3, MeOH, 25 °C; (iv) toluene, reflux, 78% from **10**; (v) H_2, 10% Pd–C, NaOAc, EtOH, 93%; (vi) $LiAlH_4$–$AlCl_3$, THF, 68%; (vii) $(EtOCO)_2O$, py, 98%.

$LiAlH_4$–$AlCl_3$ (refluxing THF; 46 h), giving 7,8-dehydrohomoglaucine (**14**) in 63% yield (Figure 2).

Reaction of Dichlorocarbene with C-7-Substituted Dehydroaporphines. In order to extend the above approach to 7-substituted dehydroaporphines, we wanted to know the influence of the C-7 substituent on the enamine character of the dehydroaporphine and, thus, the feasibility of a Cl_2C: addition to that double bond.

The poor nucleophilic character of the enamine system of 7-methyl-6a,7-didehydrogluacine (**17b**) was clearly demonstrated by its slow reaction with methyl iodide and by its inertness toward formaldehyde/H_2 catalysis.[14] In accordance with this, when **17b** was treated with dichlorocarbene as above, the unstable adduct **18a** was obtained. Its reaction with $LiAlH_4$ (or $LiAlD_4$) in refluxing THF afforded **19** in about 60% yield. Catalytic hydrogenation of **19** (10% Pd–C, EtOH) gave a single diastereomer of 8-methylhomoglaucine (**20**) in 98% yield (Figure 3). The relative stereochemistry of H-6a and H-8 was deduced by measurement of nuclear Overhauser effects (NOE) and by selective ^1H–^1H decoupling experiments on **20a** and **20b**. The coupling constants for H-6a, H-7α, H-7β,

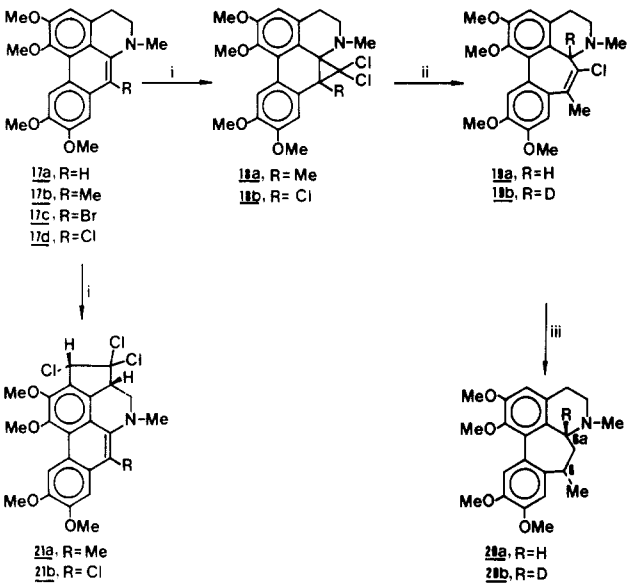

Figure 3. Reagents and conditions: (i) $CHCl_3$, 50% NaOH, TBAC; (ii) $LiAlH_4$ or $LiAlD_4$, THF; (iii) H_2, 10% Pd–C, EtOH.

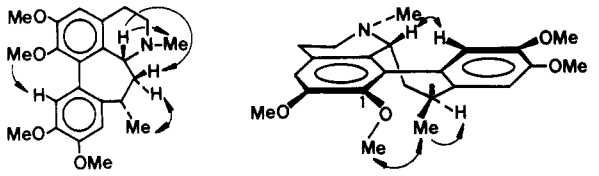

Figure 4. Results of NOE experiments on **20a**.

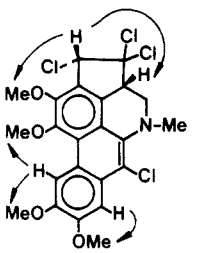

Figure 5. Results of NOE experiments on **21b**.

and H-8 were compatible with a cis relationship between H-6a and H-8, and in fact, only this stereochemical arrangement could explain the observed NOE between 8-Me and 1-OMe (Figure 4).

The reaction of **17b** with Cl_2C: also gave a small amount (about 3% yield) of a byproduct identified as the pentacyclic compound **21a** (see below).

The fact that dichlorocarbene adds to 7-methyl-6a,7-didehydroglaucine (**17b**) contrasts with the known C-7 formylation of dehydroaporphines[7] and suggested the possibility of preparing a simple homoaporphine by protecting the C-7 position of the dehydroaporphine. We reasoned that a chlorine or a bromine would be ideal for this purpose because it could be removed at a later stage together with the chlorine or the dichlorocyclopropane intermediate necessary for the ring C homologation. The required 7-halo-6a,7-didehydroaporphine was prepared from the corresponding 6a,7-didehydroaporphine by reaction with NCS or NBS.[15] Thus, when 6a,7-didehydroglaucine (**17a**) was treated with NBS (benzene; 25 °C; 20 min), we obtained a low yield (26%) of 7-bromo-6a,7-didehydroglaucine (**17c**)8, which rapidly decomposed upon manipulation. Nevertheless, 7-chloro-6a,7-didehydroglaucine (**17d**) could be prepared in 91% yield

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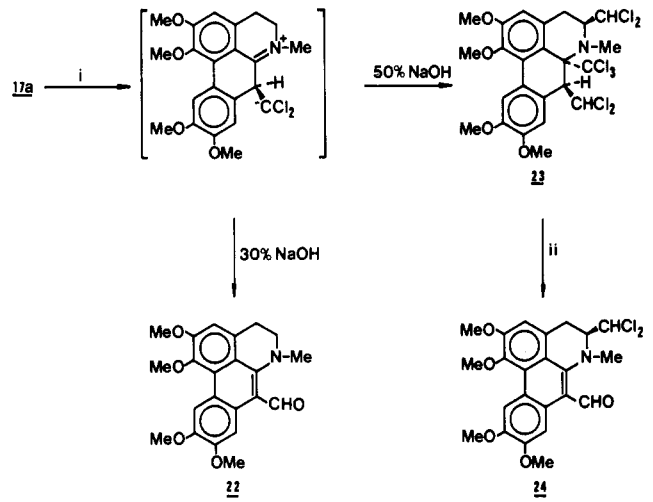
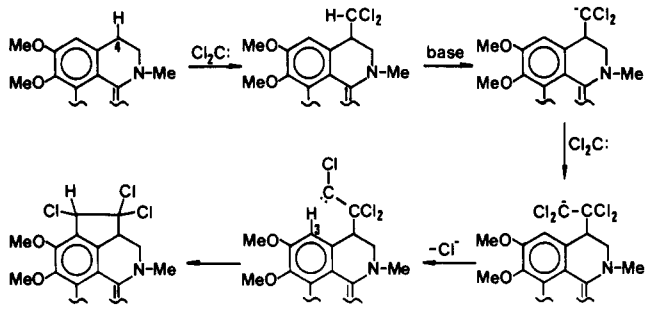


Figure 6. Reagents and conditions: (i) $CHCl_3$, 50% or 30% NaOH, TEBA; (ii) 90% EtOH, reflux.

Scheme I



when **17a** was reacted with NCS (benzene; 25 °C; 3.5 h), and this product can be stored for long periods of time without decomposition (Figure 3). Unexpectedly, when **17d** was reacted with dichlorocarbene (PTM), we did not obtain the desired adduct **18b**, but instead a 30% yield of the pentacyclic compound **21b**, whose structure was deduced from its ^1H NMR and MS spectra and NOE experiments (Figure 5). A similar product, **21a**, was obtained in very low yield from **17b** (Figure 3). The formation of **21a** and **21b** presumably starts with the insertion of dichlorocarbene into the benzylic C-4–H bond and proceeds as shown in Scheme I.

The above results clearly show that the presence of a substituent on the C-7 carbon of the dehydroaporphine substantially modifies the reactivity of the double bond toward dichlorocarbene. Thus, enamine **17b** reacts as an olefin to produce adduct **18a**, whereas no such adduct is obtained from **17d**, which gives instead the insertion product **21b**. Surprisingly, when 6a,7-didehydroglaucine (**17a**) was treated as above ($CHCl_3$, 50% NaOH, TEBA), no 7-formyl derivative **22** was obtained in spite of a published report,[7] but instead, a 34% yield of **23** was obtained. The formation of **23** can be easily explained as the result of the trapping of the intermediate iminium ion by Cl_3C^- followed by dichlorocarbene insertion (Figure 6). In fact, when the trichloromethyl anion concentration is lowered (30% NaOH instead of 50%), no such trapping occurs and the dehydroaporphine **17a** is converted into the aldehyde **22**.[16] Further treatment of **22** with $CHCl_3$/50% NaOH/TEBA gave a complex mixture of compounds. The highly chlorinated product **23** could be smoothly transformed into the aldehyde **24** by hydrolysis. NOE experiments on **23** point to the stereochemistry shown in Figure 7 and, in particular, demonstrate a cis relationship between the two dichloromethyl groups.

(16) Guitián, E., personal communication.

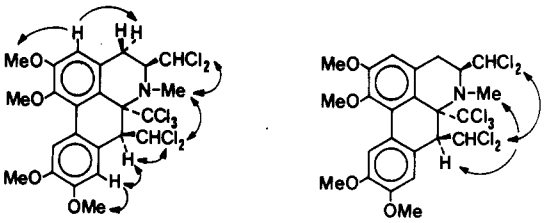


Figure 7. Results of NOE experiments on **23**.

Experimental Section

General Procedures. Melting points are uncorrected. NMR spectra were recorded in a Bruker WM 250 spectrometer (250.13 MHz for ^1H, 62.83 MHz for ^{13}C). Chemical shifts are reported in δ with tetramethylsilane as internal reference. Nuclear Overhauser effect difference spectroscopy (NOEDS) experiments were run with standard Bruker microprograms. THF and toluene were dried from sodium benzophenone ketyl prior to use. Pyridine was distilled from potassium hydroxide and stored over solid KOH. Ethanol-free chloroform was obtained by filtration through neutral alumina (activity I) and stored in the dark under argon. Preparative thick-layer chromatography (preparative TLC) was performed on 20 × 20 cm plates coated with a 1–2-mm layer of Merck silica gel 60 GF 254. Merck silica gel 60 (70–230 mesh) and Woelm neutral alumina (activity III) were used for column chromatography.

Reaction of *N*-Carbethoxy-6a,7-didehydronordicentrine (1) with Dichlorocarbene. A solution of **1**[10] (100 mg) in chloroform (30 mL) was vigorously stirred with 50% aqueous NaOH (10 mL). After 15 min, tetrabutylammonium chloride (TBAC, 10 mg) was added, and the stirring was continued for 20 min. The organic phase was decanted off and the aqueous layer extracted with chloroform (2 × 15 mL). The combined organic extracts were washed with water (2 × 10 mL) and dried over Na_2SO_4, and the solvent was removed. The remaining material was purified by preparative TLC (silica gel, CH_2Cl_2–2% 2-propanol), giving 103 mg (86%) of adduct **2**, which crystallized from absolute ethanol: mp 160–162 °C; ^1H NMR (80 MHz) δ 8.11 (s, 1 H, Ar), 6.98 (s, 1 H, Ar), 6.60 (s, 1 H, Ar), 6.05 (br s, 2 H, OCH_2O), 3.93 (s, 3 H, CH_3O), 3.87 (s, 3 H, CH_3O), 4.65–2.60 (m, 7 H, CH_2), 1.13 (t, 3 H, J = 6.3 Hz, CH_3); ^{13}C NMR δ 156.05, 148.81, 148.75, 147.80, 142.09, 128.92, 122.24, 120.63, 119.04, 116.09, 112.66, 110.89, 107.82, 100.75, 77.20, 64.08, 61.65, 55.93, 55.89, 49.52, 43.35, 27.37, 14.34; IR (KBr) 1700, 1605, 1130, 1100, 1050 cm^{-1}; MS, m/e 479 (M^+ + 2, 2.9), 477 (M^+, 4.3), 444 (37), 442 (100), 408 (16), 395 (11), 378 (20). Anal. Calcd for $C_{23}H_{21}Cl_2NO_6$: C, 57.75; H, 4.43; N, 2.93. Found: C, 57.69; H, 4.47; N, 2.63.

Reduction of Adduct 2 with $LiAlH_4$. A solution of adduct **2** (80 mg, 0.17 mmol) in dried THF (5 mL) was added to a stirred suspension of $LiAlH_4$ (120 mg, 4.28 mmol) in dried THF (15 mL). The reaction mixture was refluxed under an argon atmosphere for 3.5 h before excess hydride was destroyed by dropwise addition of the minimal amount of water. The organic phase was decanted by centrifugation, and the remaining solid was washed with chloroform (4 × 15 mL). The organic extracts were dried over Na_2SO_4, and the solvent was evaporated. The remaining solid was purified by preparative TLC (silica gel, CH_2Cl_2–2% 2-propanol) to yield 50 mg (77%) of **6** and 2 mg (3%) of **5**.

5: ^1H NMR δ 7.33 (s, 1 H, H-12), 6.83 (s, 1 H, H-9), 6.68 (s, 1 H, H-3), 6.51 (dd, 1 H, J = 10.3, 2.0 Hz, H-8), 6.13 (dd, 1 H, J = 10.3, 5.1 Hz, H-7), 6.05 (d, 1 H, J = 1.4 Hz, OCH_2O), 5.78 (d, 1 H, J = 1.4 Hz, OCH_2O), 3.94 (s, 6 H, 2 CH_3O), 3.58 (dd, 1 H, J = 5.1, 1.9 Hz, H-6a), 3.20–2.70 (m, 4 H, H-4, H-5), 2.53 (s, 3 H, NCH_3); MS, m/e 351 (M^+, 82), 350 (100), 336 (35), 322 (12), 320 (12), 308 (53), 393 (18), 277 (15), 235 (35).

6: mp 191–192 °C (absolute ethanol); ^1H NMR δ 7.27 (s, 1 H, H-12), 6.80 (s, 1 H, H-9), 6.71 (br s, 2 H, H-3, H-8), 6.08 (d, 1 H, J = 1.4 Hz, OCH_2O), 5.80 (d, 1 H, J = 1.4 Hz, OCH_2O), 3.94 (s, 3 H, CH_3O), 3.93 (s, 3 H, CH_3O), 3.68 (br s, 1 H, H-6a) 3.35 (m, 1 H, H-5), 3.01 (m, 1 H, H-5), 2.69 (m, 2 H, H-4), 2.50 (s, 3 H, NCH_3); ^{13}C NMR δ 148.40, 147.14, 145.66, 143.50, 136.66, 131.77, 128.24, 127.20, 126.08, 124.62, 118.95, 113.24, 110.73, 107.88, 100.51,

62.11, 55.96, 55.85, 49.54, 44.05, 29.27; IR (KBr) 2980, 2910, 2820, 1600, 1515, 1250, 1100, 1040, 1020, 930, 860 cm^{-1}; MS, *m/e* 387 ($M^+ + 2$, 6), 385 (M^+, 20), 384 (11), 370 (3), 357 (6), 355 (13), 350 (100), 349 (41), 334 (26), 322 (11), 318 (13), 306 (15), 391 (7), 277 (9). Anal. Calcd for $C_{21}H_{20}ClNO_4$: C, 65.37; H, 5.23; N, 3.63. Found: C, 65.44; H, 5.12; N, 3.68.

Homodicentrine (7). To a solution of 7-chloro-7,8-didehydrohomodicentrine (**6**; 35 mg, 0.09 mmol) in absolute ethanol (25 mL) was added anhydrous sodium acetate (45 mg), and the resulting mixture was hydrogenated at atmospheric pressure and room temperature on 5% Pd–C (10 mg). After 16 h, the catalyst was filtered off and the solvent was removed. The residue was dissolved in water (10 mL) and extracted with chloroform (4 × 20 mL). The solvent was dried (Na_2SO_4) and evaporated to give 30 mg (94%) of homodicentrine (**7**) as an amorphous solid: ^1H NMR δ 7.05 (s, 1 H, Ar), 6.79 (s, 1 H, Ar), 6.59 (s, 1 H, Ar), 6.01 (d, 1 H, J = 1.4 Hz, OCH_2O), 5.85 (d, 1 H, J = 1.4 Hz, OCH_2O), 3.92 and 3.89 (s, 6 H, 2 CH_3O), 3.36 (dd, 1 H, J = 11.3, 6.9 Hz, H-6a), 3.25–2.93 (m, 2 H, CH_2), 2.77 (dd, 1 H, J = 11.9, 5.3 Hz, CH_2), 2.61–2.10 (m, 5 H, CH_2), 2.37 (s, 3 H, NCH_3); ^{13}C NMR δ 148.53, 147.14, 145.97, 142.16, 132.52, 128.17, 126.83, 124.60, 120.74, 112.91, 111.76, 107.37, 100.47, 58.34, 56.16, 55.91, 44.86, 41.71, 35.53, 30.32, 25.81; MS, *m/e* 353 (M^+, 45), 352 (26), 338 (13), 323 (61), 322 (100), 310(24), 308 (27), 306 (11), 294 (8), 280 (10), 216 (27), 190 (37).

Methiodide of **7**: mp 257–259 °C (acetone); IR (KBr) 1610, 1515, 1465, 1250, 1205, 1100 cm^{-1}. Anal. Calcd for $C_{22}H_{26}INO_4$: C, 53.34; H, 5.29; N, 2.83. Found: C, 53.57; H, 5.06; N, 2.71.

1-[2-[*N*-Methyl-*N*-(trifluoroacetyl)amino]ethyl]-3,4,6,7-tetramethoxyphenanthrene (9). To an ice-cold solution of glaucine (**8**; 1.05 g, 2.96 mmol) in pyridine (30 mL), was slowly added trifluoroacetic anhydride (1 mL), and the resulting mixture was heated at 100 °C for 1 h 20 min under an argon atmosphere. The solvent was removed, and the residue was dissolved in CH_2Cl_2 (50 mL), washed with 10% HCl (4 × 15 mL), and dried (Na_2SO_4). Evaporation of the solvent gave a solid, which was purified by column chromatography (silica gel, CH_2Cl_2) and crystallized (ether–10% CH_2Cl_2) to give 1.15 g (86%) of **9** as needles: mp 144–146 °C; ^1H NMR δ 9.28 (s, 1 H, H-5), 7.86 and 7.67 (d, 1 H, J = 9.1 Hz, H-10, two rotamers, ratio 3:1), 7.60 (d, 1 H, J = 9.1 Hz, H-9), 7.23 (s, 1 H, H-8), 7.15 and 7.13 (s, 1 H, H-2, two rotamers), 4.08, 4.06, 4.02, and 3.93 (s, 12 H, 4 CH_3O), 3.76 (t, 2 H, J = 7.9 Hz, NCH_2), 3.39 (t, 2 H, J = 7.9 Hz, CH_2), 3.12 and 2.92 (s, 3 H, NCH_3, two rotamers, ratio 1:3); IR (KBr) 3000, 1700, 1595, 1255, 1240, 1110, 990, 870, 845 cm^{-1}; MS, *m/e* 451 (M^+, 52), 324 (8), 312 (23), 311 (100), 281 (6), 277 (9), 265 (17), 140 (23). Anal. Calcd for $C_{23}H_{24}F_3NO_5$: C, 61.19; H, 5.36; N, 3.10. Found: C, 61.16; H, 5.35; N, 3.34.

Reaction of 9 with Dichlorocarbene. Preparation of 10. A solution of **9** (500 mg, 1.11 mmol) in chloroform (50 mL) was vigorously stirred at 55 °C with 50% aqueous NaOH (15 mL) and TBAC (20 mg). After 2.5 h, water was added (30 mL) and the organic phase was decanted. The organic layer was extracted twice with CH_2Cl_2 (25 mL), and the combined organic phases were washed once with 10% HCl (15 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (silica gel, CH_2Cl_2) to give 410 mg (69%) of adduct **10**, which was crystallized from ether–20% CH_2Cl_2: mp 145–146 °C; ^1H NMR δ 8.76 (s, 1 H, H-5), 6.94 (s, 1 H, H-8), 6.76 and 6.72 (s, 1 H, H-2, two rotamers), 3.99, 3.93, 3.91, and 3.74 (s, 12 H, 4 CH_3O), 3.69 (m, 2 H, NCH_2), 3.36 (m, 2 H, H-9, H-10), 3.19 and 3.11 (s, 3 H, NCH_3, two rotamers), 3.07 (m, 2 H, CH_2); IR (KBr) 3140, 3100, 3020, 2980, 1700, 1570, 1470, 1255, 1180, 1140, 1110, 1090, 1045, 990 cm^{-1}; MS, *m/e* 535 ($M^+ + 2$, 7), 533 (M^+, 11), 501 (32), 500 (54), 499 (92), 498 (100), 468 (8), 464 (10), 451 (39), 372 (28), 359 (93), 301 (87), 140 (76). Anal. Calcd for $C_{24}H_{24}Cl_2F_3NO_5$: C, 53.94; H, 4.53; N, 2.62. Found: C, 53.96; H, 4.33; N, 2.51.

1-[2-(Methylamino)ethyl]-9,10-(dichloromethano)-3,4,6,7-tetramethoxy-9,10-dihydrophenanthrene (11). To a solution of **10** (270 mg, 0.51 mmol) in methanol (30 mL) and CH_2Cl_2 (5 mL) was added a saturated aqueous solution of Na_2CO_3 (2 mL), and the resulting mixture was stirred at room temperature for 7.5 h. Water (15 mL) was added, and the methanol was removed under reduced pressure (bath temperature 35–40 °C). The aqueous layer was extracted with chloroform (4 × 15 mL), and the organic extracts were dried (Na_2SO_4) and carefully concentrated (35–40 °C) to give the amine **11**, which was used without further purification: ^1H NMR δ 8.76 (s, 1 H, H-5), 6.93 (s, 1 H, H-8), 6.81 (s, 1 H, H-2), 3.98 (s, 3 H, CH_3O), 3.92 (s, 6 H, 2 CH_3O), 3.73 (s, 3 H, CH_3O), 3.36 and 3.29 (AB system, 2 H, J = 10.9 Hz, H-9, H-10), 3.00 (m, 4 H, CH_2), 2.53 (s, 3 H, NCH_3).

7-Chloro-7,8-didehydrohomoglaucine (12). A solution of the amine **11** (200 mg) in dried toluene (30 mL) was refluxed under an argon atmosphere for 2 h. The solvent was removed in a rotary evaporater, and the residue was dissolved in chloroform (30 mL), washed with 10% NaOH (1 × 15 mL), and dried (Na_2SO_4). Evaporation of the solvent followed by preparative TLC purification (silica gel, CH_2Cl_2–3% EtOH) gave 160 mg (78% yield from **10**) of **12** as a crystalline compound: mp 188–189 °C (absolute ethanol); ^1H NMR δ 7.34 (s, 1 H, H-12), 6.77 (s, 1 H, Ar), 6.74 (s, 1 H, Ar), 6.68 (d, 1 H, J = 1.4 Hz, H-8), 3.94, 3.89, and 3.88 (s, 9 H, 3 CH_3O), 3.63 (d, 1 H, J = 1.4 Hz, H-6a), 3.29 (s, 3 H, 1-CH_3O), 3.37–3.25 (m, 1 H, CH_2), 3.13–3.00 (m, 1 H, CH_2), 2.78–2.64 (m, 2 H, CH_2), 2.48 (s, 3 H, NCH_3); ^{13}C NMR δ 151.00 (s), 148.04 (s), 146.57 (s), 145.11 (s), 137.39 (s), 132.45 (s), 129.77 (s), 129.00 (s), 128.17 (s), 127.11 (s), 124.45 (d), 114.44 (d), 111.04 (d), 109.69 (d), 62.06 (d), 60.17 (q), 55.78 (q), 55.74 (q),, 55.61 (q), 49.51 (t), 44.10 (q), 29.29 (t); IR (KBr) 2980, 2920, 2830, 2790, 1590, 1515, 1250, 1115, 1020; MS, *m/e* 403 ($M^+ + 2$, 10), 401 (M^+, 30), 388 (8), 386 (19), 372 (15), 370 (44), 366 (100), 365 (67), 350 (51), 336 (13), 334 (18), 308 (15), 185 (23), 183 (18). Anal. Calcd for $C_{22}H_{24}ClNO_4$: C, 65.75; H, 6.02; N, 3.49. Found: C, 65.99; H, 5.97; N, 3.31.

Homoglaucine (13). Homoglaucine (**13**) was obtained in 93% yield by catalytic hydrogenation of **12** as in the case of homodicentrine (**7**): ^1H NMR δ 7.10 (s, 1 H, Ar), 6.77 (s, 1 H, Ar), 6.68 (s, 1 H, Ar), 3.94, 3.90, 3.87, and 3.42 (s, 12 H, 4 CH_3O), 3.32–2.96 (m, 3 H, H-6a, CH_2), 2.84–2.74 (m, 1 H, CH_2), 2.68–2.02 (m, 5 H, CH_2), 2.39 (s, 3 H, NCH_3); ^{13}C NMR δ 151.57, 148.28, 146.94, 144.12, 132.46, 131.87, 128.56, 127.00, 126.86, 113.90, 111.20, 110.81, 60.17, 58.32, 55.92, 55.76, 55.71, 45.00, 41.61, 34.90, 29.97, 25.45; MS, *m/e* 369 (M^+, 28), 368 (13), 354 (18), 338 (100), 33.6 (5), 322 (10), 232 (9).

Methiodide of **13**: mp 234–236 °C (acetone; IR (KBr) 1590, 1515, 1475, 1330, 1250, 1110, 1095, 1030, 995, 915, 860 cm^{-1}. Anal. Calcd for $C_{23}H_{30}INO_4$: C, 54.01; H, 5.91; N, 2.74. Found: C, 53.84; H, 5.84; N, 2.76.

7,8-Didehydrohomoglaucine (14). To an ice-cold solution of 7-chloro-7,8-didehydrohomoglaucine (**12**; 100 mg, 0.25 mmol) and $AlCl_3$ (170 mg, 1.20 mmol) in dried THF (40 mL) was added $LiAlH_4$ (200 mg, 5.27 mmol). The mixture was refluxed under an argon atmosphere for 36 h before excess hydride was destroyed by dropwise addition of the minimal amount of a saturated aqueous solution of Na_2SO_4. The resulting suspension was centrifuged and the pellet washed with chloroform (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness. The residue was purified by preparative TLC (silica gel, CH_2Cl_2–3.5% EtOH), giving 62 mg (68%) of **14** as an amorphous solid: ^1H NMR δ 7.42 (s, 1 H, H-12), 6.81 (s, 1 H, Ar), 6.74 (s, 1 H, Ar), 6.50 (dd, 1 H, J = 10.3, 2.0 Hz, H-8), 6.16 (dd, 1 H, J = 10.3, 5.0 Hz, H-7), 3.95, 3.92, and 3.87 (s, 9 H, 3 CH_3O), 3.51 (dd, 1 H, J = 5.0, 1.9 Hz, H-6a), 3.26 (s, 3 H, 1-CH_3O), 3.17–2.74 (m, 4 H, CH_2), 2.51 (s, 3 H, NCH_3); ^{13}C NMR δ 150.74 (s), 147.83 (s), 146.26 (s), 145.13 (s), 134.73 (s), 133.32 (s), 129.90 (s), 129.44 (s), 127.27 (s), 126.90 (s), 126.65 (d), 114.69 (d), 111.26 (d), 109.91 (d), 59.94 (q), 59.80 (d), 55.81 (q), 55.74 (q), 55.60 (q), 47.89 (t), 42.62 (q), 28.07 (t); MS, *m/e* 367 (M^+, 100), 366 (74), 352 (33), 337 (17), 336 (26), 324 (21), 322 (11), 320 (9), 309 (36), 294 (10), 278 (10), 266 (11), 250 (9).

Methiodide of **14**: mp 246–248 °C dec (acetone); IR (KBr) 1605, 1590, 1515, 1330, 1250, 1120, 1100, 1035, 1005, 990, 920, 870, 810, 780, 760, 750 cm^{-1}. Anal. Calcd for $C_{23}H_{28}INO_4$: C, 54.23; H, 5.54; N, 2.75. Found: C, 54.62; H, 5.67; N, 2.43.

1-[2-[*N*-Methyl-*N*-(ethoxycarbonyl)amino]ethyl]-3,4,6,7-tetramethoxyphenanthrene (15). To an ice-cold solution of glaucine (**8**; 330 mg, 0.93 mmol) in pyridine (10 mL) was added dropwise ethyl chloroformate (0.7 mL), and the mixture was heated at 100 °C for 1.5 h under an argon atmosphere. The reaction mixture was acidified with 10% HCl and extracted with ether (4 × 25 mL). The ether extracts were dried (Na_2SO_4) and evaporated to give 390 mg (98%) of **15**, which was crystallized from absolute ethanol: mp 109–110 °C; ^1H NMR (80 MHz) δ 9.28

(s, 1 H, H-5), 7.85 and 7.86 (AB system, 2 H, J = 9 Hz, H-9, H-10), 7.21 (s, 1 H, H-8), 7.15 (br s, 1 H, H-2), 4.07, 4.04, 4.02, and 3.92 (s, 12 H, 4 CH_3O), 3.68–3.19 (m, 4 H, CH_2), 2.89 (br s, 3 H, NCH_3), 1.25 (t, 3 H, J = 7.0 Hz, CH_3); IR (KBr) 3150, 2930, 1685, 1590 1470, 1305, 1270, 1240, 1120, 890, 865, 845, 770 cm^{-1}; MS, m/e 427 (M^+, 40), 324 (8), 311 (100), 265 (12), 116 (30). Anal. Calcd for $C_{24}H_{29}NO_6$: C, 67.43; H, 6.84; N, 3.28. Found: C, 67.86; H, 6.57; N, 3.34.

1-[2-[*N*-Methyl-*N*-(ethoxycarbonyl)amino]ethyl]-9,10-(dichloromethano)-3,4,6,7-tetramethoxy-9,10-dihydrophenanthrene (16). The reaction of **15** (200 mg, 0.47 mmol) with dichlorocarbene (PTM; 25 °C; 2 h of stirring) gave, after the usual workup and preparative TLC purification (silica gel, CH_2Cl_2–2% EtOH), 115 mg (48%) of adduct **16**, which was crystallized from hexane–ether: mp 143–145 °C; ^1H NMR (80 MHz) δ 8.75 (s, 1 H, H-5), 6.92 (s, 1 H, H-8), 6.77 (br s, 1 H, H-2), 4.17 (q, 2 H, J = 7.2 Hz, CH_2O), 3.97 (s, 3 H, CH_3O), 3.92 (s, 6 H, 2 CH_3O), 3.73 (s, 3 H, CH_3O), 2.96 (s, 3 H, NCH_3), 1.28 (t, 3 H, J = 7.2 Hz, CH_3); IR (KBr) 3180, 3020, 2930, 1685, 1605, 1590, 1570, 1520, 1470, 1260, 1110, 1050, 1030, 990, 825, 775, 765 cm^{-1}; MS m/e 511 (M^+ + 2, 5), 509 (M^+, 7), 487 (13), 486 (29), 485 (34), 484 (63), 427 (7), 359 (23), 343 (13), 323 (16), 311 (21), 115 (100). Anal. Calcd for $C_{25}H_{29}Cl_2NO_6$: C, 58.83; H, 5.73; N, 2.74. Found: C, 58.77; H, 5.65; N, 2.70.

Reaction of 7-Methyl-6a,7-didehydroglaucine (17b) with Dichlorocarbene. The reaction of **17b**[17] (50 mg, 0.14 mmol with dichlorocarbene as above (30 min of stirring) gave, after careful solvent evaporation (bath temperature below 40 °C), the unstable adduct **18a** as a yellow amorphous solid, which was used without further purification: ^1H NMR δ 8.85 (s, 1 H, H-11), 7.06 (s, 1 H, Ar), 6.71 (s, 1 H, Ar), 3.98, 3.94, 3.93, and 3.74 (s, 12 H, 4 CH_3O), 3.61 (m, 1 H, CH_2), 3.14 (m, 2 H, CH_2), 2.72 (m, 1 H, CH_2), 2.29 (s, 3 H, NCH_3), 1.91 (s, 3 H, CH_3).

Reduction of Adduct 18a with $LiAlH_4$. Treatment of adduct **18a** with $LiAlH_4$ (60 mg, 0.58 mmol; 3 h of reflux) gave, after the usual workup and preparative TLC purification (silica gel, CH_2Cl_2–1.5% EtOH), 36 mg (63% from **17b**; R_f 0.4) of **19a** and 2 mg (R_f 0.6) of **21a**.

19a: ^1H NMR δ 7.25 (s, 1 H, H-12), 6.94 (s, 1 H, H-9), 6.71 (s, 1 H, H-3), 3.97 (s, 3 H, CH_3O), 3.89 (s, 6 H, 2 CH_3O), 3.63 (s, 1 H, H-6a), 3.40 (s, 3 H, 1-CH_3O), 3.27–3.06 (m, 2 H, CH_2), 2.72–2.62 (m, 2 H, CH_2), 2.45 (s, 3 H, NCH_3), 2.20 (s, 3 H, 8-CH_3); MS, m/e 417 (M^+ + 2, 15), 415 (M^+, 41), 402 (10), 400 (27), 386 (18), 384 (45), 380 (65), 379 (88), 364 (100), 350 (12), 348 (20), 336 (35), 322 (14), 320 (13), 306 (17), 278 (10), 192 (27).

Methiodide of **19**: mp 204–206 °C (acetone); IR (KBr) 1600, 1590, 1510, 1245, 1115, 1055, 995, 855, 760 cm^{-1}. Anal. Calcd for $C_{24}H_{29}ClINO_4$: C, 51.67; H, 5.24; N, 2.51. Found: C, 51.43; H, 5.48; N, 2.65.

21a: ^1H NMR δ 7.67 (s, 1 H, Ar), 7.18 (s, 1 H, Ar), 4.80 (s, 1 H, ArC*H*Cl), 4.01 and 3.98 (s, 6 H, 2 CH_3O), 3.76 (dd, 1 H, J = 15.1, 8.6 Hz, NCH_2), 3.61 and 3.57 (s, 6 H, 2 CH_3O), 3.24 (dd, 1 H, J = 15.1, 7.2 Hz, NCH_2), 2.77 (s, 3 H, NCH_3), 2.62 (s, 3 H, CH_3), 2.30 (dd, 1 H, J = 8.6, 7.2 Hz, ArC*H*); MS, m/e 499, 497, and 495 (M^+ + 4, M^+ + 2, and M^+; relative intensity 33:88:100).

Reduction of Adduct 18a with $LiAlD_4$. Treatment of **18a** with $LiAlD_4$ (99% deuteriation) as above produced **19b** in 67% isolated yield with respect to **17b**: ^1H NMR (80 MHz) δ 7.24 (s, 1 H, H-12), 6.94 (s, 1 H, H-9), 6.70 (s, 1 H, H-3), 3.96 (s, 3 H, CH_3O), 3.88 (s, 6 H, 2 CH_3O), 3.40 (s, 3 H, 1-CH_3O), 3.40–2.50 (m, 4 H, CH_2), 2.46 (s, 3 H, NCH_3), 2.19 (s, 3 H, 8-CH_3); MS, m/e 418 (M^+ + 2, 19), 416 (M^+, 53), 403 (13), 401 (31), 387 (19), 385 (53), 381 (63), 380 (88), 365 (100), 337 (44), 323 (19), 321 (19), 307 (21).

8-Methylhomoglaucine (20a). A solution of **19a** (100 mg, 0.24 mmol) in absolute ethanol (25 mL) was hydrogenated at 1 atm on 10% Pd–C for 4.5 h. The usual workup gave 90 mg (98%) of **20a** as an amorphous solid: ^1H NMR δ 7.11 (s, 1 H, Ar), 6.71 (s, 1 H, Ar), 6.65 (s, 1 H, Ar), 3.94, 3.89, and 3.86 (s, 9 H, 3 CH_3O), 3.44 (s, 3 H, 1-CH_3O), 3.35 (dd, 1 H, J = 11.8, 5.9 Hz, H-6a), 3.17 (dt, 1 H, J = 11.6, 4.2 Hz, H-5), 3.08–2.90 (m, 2 H, H-5, H-8), 2.83–2.73 (m, 1 H, H-4), 2.69–2.56 (m, 2 H, H-4, H-7β), 2.40 (s, 3 H, NCH_3), 1.87 (t, 1 H, J = 12.6 Hz, H-7α), 0.83 (d, 3 H, J = 7.5 Hz, 8-CH_3); ^{13}C NMR δ 151.36 (s), 147.75 (s), 146.60 (s), 143.65 (s), 136.57 (s), 132.77 (s), 128.66 (s), 128.19 (s), 125.78 (s), 115.14 (d), 111.90 (d), 111.00 (d), 59.46 (q), 58.01 (d), 55.74 (q), 55.55 (q), 55.50 (q), 45.19 (t), 41.77 (t), 41.74 (q), 36.73 (d), 25.73 (t), 22.24 (q); MS, m/e 383 (M^+, 22), 382 (12), 268 (24), 352 (100), 340 (12), 336 (8), 246 (22).

Methiodide of **20a**: mp 196–198 °C (ethyl acetate); IR (KBr) 1600, 1520, 1470, 1250, 1110, 1070, 1050, 1025, 1010, 970 cm^{-1}. Anal. Calcd for $C_{24}H_{32}INO_4$: C, 54.86; H, 6.14; N, 2.67. Found: C, 54.98; H, 5.80; N, 2.47.

6a-Deuterio-8-methylhomoglaucine (20b). Catalytic hydrogenation of **19b** (40 mg) as above (5 h) gave 35 mg (94%) of the deuteriated homoaporphine **20b** as an amorphous solid: ^1H NMR δ 7.11 (s, 1 H, Ar), 6.71 (s, 1 H, Ar), 6.65 (s, 1 H, Ar), 3.94, 3.89, and 3.86 (s, 9 H, 3 CH_3O), 3.44 (s, 3 H, 1-CH_3O), 3.16 (dt, 1 H, J = 11.5, 4.5 Hz, H-5), 3.05–2.93 (m, 2 H, H-5, H-8), 2.82–2.72 (m, 1 H, H-4), 2.65 (m, 1 H, H-4), 2.58 (dd, 1 H, J = 12.9, 9.0 Hz, H-7β), 2.38 (s, 3 H, NCH_3), 1.87 (d, 1 H, J = 12.9 Hz, H-7α), 0.82 (d, 3 H, J = 7.5 Hz, 8-CH_3); MS, m/e 384 (M^+, 31), 369 (25), 353 (100), 341 (11), 337 (7), 246 (22).

7-Bromo-6a,7-didehydroglaucine (17c). To a solution of **17a**[18] (50 mg, 0.14 mmol) in dried benzene (15 mL) was added NBS (30 mg, 0.17 mmol), and the resulting mixture was stirred at room temperature and under an argon atmosphere for 15 min. The resulting brown reaction mixture was filtered, and the solvent was removed. The remaining material was purified by preparative TLC (silica gel, CH_2Cl_2–3% EtOH, R_f 0.8), giving 16 mg (26%) of **17c** as an unstable solid, which rapidly decomposed on the silica gel plate: ^1H NMR δ 9.31 (s, 1 H, H-11), 7.85 (s, 1 H, H-8), 7.10 (s, 1 H, H-3), 4.10, 4.06, 4.04, and 3.88 (s, 12 H, 4 CH_3O), 3.43 (t, 2 H, J = 5.7 Hz, H-5), 3.19 (t, 2 H, J = 5.7 Hz, H-4), 2.97 (s, 3 H, NCH_3); MS, m/e 433 (M^+ + 2, 98), 431 (M^+, 100), 417 (31), 415 (33), 386 (20), 352 (41), 337 (22), 321 (18), 96 (50), 94 (51), 81 (20), 79 (20).

7-Chloro-6a,7-didehydroglaucine (17d). To a stirred solution of **17a** (200 mg, 0.57 mmol) in dried benzene (20 mL) was added NCS (84 mg, 0.63 mmol), and stirring was continued under an argon atmosphere for 3.5 h. The solvent was removed, and the resulting solid was purified by column chromatography (aluminum oxide activity III, benzene) to give 200 mg (91%) of **17d**, which was crystallized from absolute ethanol: mp 142–143 °C; ^1H NMR δ 9.30 (s, 1 H, H-11), 7.78 (s, 1 H, H-8), 7.10 (s, 1 H, H-3), 4.10, 4.06, 4.04, and 3.89 (s, 12 H, 4 CH_3O), 3.44 (t, 2 H, J = 5.6 Hz, H-5), 3.19 (t, 2 H, J = 5.6 Hz, H-4), 2.99 (s, 3 H, NCH_3); ^{13}C NMR δ 150.66 (s), 149.40 (s), 147.76 (s), 144.51 (s), 139.66 (s), 129.95 (s), 126.63 (s), 124.00 (s), 122.12 (s), 120.70 (s), 119.52 (s), 111.93 (d), 108.86 (d), 104.75 (d), 60.02 (q), 56.33 (q), 55.72 (q), 55.72 (q), 49.63 (t), 41.38 (q), 24.98 (t); IR (KBr) 3140, 2995, 2940, 2845, 1600, 1505, 1250, 1120, 1070, 1010, 840 cm^{-1}; MS, m/e 389 (M^+ + 2, 37), 387 (M^+, 100), 374 (13), 372 (37), 356 (7), 353 (12), 314 (13); HR-MS calcd for $C_{21}H_{22}ClNO_4$ 387.1237, found 387.1235.

Reaction of 7-Chloro-6a,7-didehydroglaucine (17d) with Dichlorocarbene. To a solution of **17d** (50 mg) in chloroform (ethanol free, 20 mL) were added 50% aqueous NaOH (5 mL) and TBAC (5 mg). The two-phase system was stirred at room temperature for 1.5 h. The usual workup followed by column chromatography purification (aluminum oxide activity III, benzene) gave 20 mg (30%) of the pentacyclic compound **21b**, which crystallized from methanol–ether: mp 235–238 °C dec; ^1H NMR δ 7.67 (s, 1 H, H-11), 7.55 (s, 1 H, H-8), 4.78 (s, 1 H, ArC*H*Cl), 4.05 (s, 3 H, 9-CH_3O), 3.99 (s, 3 H, 10-CH_3O), 3.81 (dd, 1 H, J = 15.2, 8.6 Hz, H-5), 3.62 (s, 3 H, 2-CH_3O), 3.59 (s, 3 H, 1-CH_3O), 3.29 (dd, 1 H, J = 15.2, 7.3 Hz, H-5), 2.92 (s, 3 H, NCH_3), 2.35 (dd, 1 H, J = 8.6, 7.3 Hz, H-4); IR (KBr) 1620, 1570, 1565, 1510, 1260, 1250, 1110, 1095, 1050, 1020, 795, 780, 760, 750 cm^{-1}; MS, m/e 521, 519, 517, 515 (M^+ + 6, M^+ + 4, M^+ + 2, and M^+ relative intensity 15:50:100:78); HR-MS calcd for $C_{23}H_{21}Cl_4NO_4$ 515.0221, found 515.0239.

5,7-Bis(dichloromethyl)-6a-(trichloromethyl)glaucine (23). A solution of dehydroglaucine (**17a**; 60 mg) in chloroform (ethanol free, 30 mL) was vigorously stirred with 50% NaOH (10 mL) and triethylbenzylammonium chloride (TEB, 10 mg) at room temperature for 30 min. The usual workup followed by preparative

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TLC purification (silica gel, chloroform) gave 36 mg (34%) of **23** as an unstable solid, which decomposed on heating: ^{1}H NMR δ 8.17 (s, 1 H, H-11), 6.93 (s, 1 H, H-8), 6.63 (s, 1 H, H-3), 6.49 (d, 1 H, J = 1.9 Hz, 7-$CHCl_2$), 5.77 (d, 1 H, J = 5.1 Hz, 5-$CHCl_2$), 4.64 (d, 1 H, J = 1.9 Hz, H-7α), 3.97 (s, 3 H, 9-CH_3O), 3.94 (s, 3 H, 2-CH_3O), 3.91 (s, 3 H, 10-CH_3O), 3.91 (dd, 1 H, J = 16.0, 8.0 Hz, H-4β), 3.81 (dd, 1 H, J = 8.0, 5.1 Hz, H-5α), 3.66 (s, 3 H, 1-CH_3O), 3.20 (d, 1 H, J = 16.0 Hz, H-4α), 3.11 (s, 3 H, NCH_3); ^{13}C NMR δ 154.61 (s), 149.84 (s), 148.33 (s), 144.31 (s), 131.93 (s), 129.65 (s), 129.01 (s), 121.77 (s), 120.40 (s), 114.83 (d), 111.78 (s), 111.02 (d), 110.51 (d), 77.44 (s), 75.52 (d), 75.32 (d), 67.63 (d) 59.89 (q), 55.97 (q), 55.86 (q), 55.76 (q), 55.40 (d), 39.37 (q), 29.49 (t); IR (KBr) 2940, 2820, 1600, 1575, 1515, 1460, 1395, 1320, 1255, 1215, 1110, 1080, 1025, 980, 880, 870, 800, 780, 770, 735 cm^{-1}.

5-(Dichloromethyl)-7-formyl-6a,7-didehydroglaucine (24). A solution of **23** (15 mg) in absolute ethanol (6 mL) and water (0.1 mL) was refluxed for 30 min. The solvent was removed, and the residue was purified by preparative TLC (silica gel, chloroform) to give the aldehyde **24** (10 mg, 69%), which crystallized from absolute ethanol: mp 192-194 °C; ^{1}H NMR δ 10.48 (s, 1 H, CHO), 9.15 (s, 1 H, H-11), 8.95 (s, 1 H, H-8), 7.03 (s, 1 H, H-3), 5.49 (d, 1 H, J = 9.2 Hz, 5-$CHCl_2$), 4.10 (s, 3 H, 9-CH_3O), 4.07 (s, 3 H, 2-CH_3O), 4.04 (s, 3 H, 10-CH_3O)8 3.87 (s, 3 H, 1-CH_3O)8 3.76-3.62 (m, 2 H, H-4β, H-5α), 3.50 (d, 1 H, J = 15.5 Hz, H-4α), 3.49 (s, 3 H, NCH_3); IR (KBr) 2920, 1660, 1590, 1580, 1500, 1460, 1390, 1240, 1120, 1050, 990, 775, 755 cm^{-1}; MS, m/e 465 (M^+ + 2, 23), 463 (M^+ 35), 437 (8), 435 (13), 381 (26), 380 (100), 364 (20), 352 (60), 336 (17), 334 (10), 322 (12), 306 (9); HR-MS calcd for $C_{23}H_{23}Cl_2NO_5$ 463.0948, found 463.0952.

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Registry No. **1**, 49715-56-2; **2**, 96839-01-9; **4**, 96839-04-2; **5**, 108510-88-9; **6**, 96838-54-9; **7**, 96838-53-8; **7**·MeI, 96838-55-0; **8**, 475-81-0; **9**, 103769-56-8; **10**, 96839-03-1; **12**, 96838-49-2; **13**, 96838-45-8; **13**·MeI, 96838-52-7; **14**, 108510-92-5; **14**·MeI, 108511-06-4; **15**, 103769-55-7; **16**, 108510-93-6; **17a**, 22212-26-6; **17b**, 72498-26-1; **17c**, 98931-17-0; **17d**, 108510-97-0; **18a**, 96839-02-0; **19a**, 96838-46-9; **19a**·MeI, 108511-03-1; **19b**, 96838-47-0; **20a**, 96838-50-5; **20a**·MeI, 96838-51-6; **20b**, 96838-48-1; **21b**, 108510-98-1; **23**, 108510-99-2; **24**, 108511-00-8.

Brominated Tyrosine Metabolites from an Unidentified Sponge

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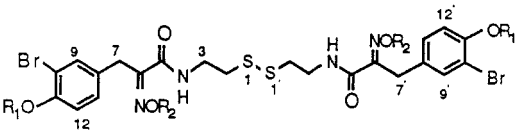
Two new isomeric brominated tyrosine metabolites containing disulfide linkages have been isolated from an unidentified sponge from Guam. Their structures were determined primarily from ^{1}H and ^{13}C NMR data. (3-Bromo-4-hydroxyphenyl)acetonitrile was also isolated.

Bromotyrosine-derived metabolites are typical of the sponge family Verongidae.[2] Especially novel among these are the bastadins, some of which are macrocycles comprised of several bromotyrosine units.[3] We wish to report novel additions to the bromotyrosine metabolite group, namely, symmetrical compounds with cystamine as the central unit. Among the many brominated tyrosine derivatives, the new compounds **1** and **5** are the first to contain a disulfide moiety. Although the sponge from which these compounds were isolated is unidentified, it is probably of the Verongidae family judging from the nature of its metabolites. Examination of this sponge was prompted by the fact that its extracts showed cytotoxicity, but the compounds described herein are not the cytotoxic components.

The metabolites were obtained from methanol and methanol/chloroform extracts and are quite polar but could be purified by silica gel chromatography followed by reverse-phase HPLC. For the predominant metabolite **1** the molecular formula $C_{22}H_{24}Br_2N_4O_6S_2$, implying 12 degrees of unsaturation, was established by combustion analysis, high-resolution fast atom bombardment (FAB) mass spectrometry, and ^{1}H and ^{13}C NMR (Table I). Since



	R_1	R_2
1 (E,E)	H	H
2 (E,E)	Ac	Ac
3 (E,E)	Me	Me
5 (E,Z)	H	H

only 11 carbon resonances were observed in the ^{13}C NMR spectrum, it could be concluded that **1** was symmetrically dimeric. The presence of amide and possibly oxime or imine groups was indicated by distinct infrared absorptions at 1636 and 1657 cm^{-1}, respectively. ^{13}C NMR signals at 167.5 and 154.7 ppm provided further evidence for these functionalities. Exchangeable proton signals were observed in the ^{1}H NMR spectrum in pyridine-d_5 at 14 (s), 12 (s), and 8.56 (t) ppm, consistent with the presence of oxime and phenolic protons and the proton of an amide flanked by a methylene group. The amide proton (8.56 ppm) was identified as part of the limited spin system shown in partial structure A by decoupling and deuterium exchange (3.48 ppm, q → t). Decoupling confirmed that the three aromatic proton signals were part of a 1,2,4-trisubstituted benzene unit and NOE difference data confirmed that the two-proton singlet at 4.01 ppm was due to a benzylic methylene group situated as shown in partial structure B.

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