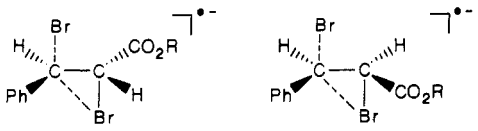
of the second bromine atom as depicted in **9**. On the other



9 **10**

hand, a transition state for threo isomer **3** should be unstable because of the two large eclipsed groups, as in **10**. Thus, the debromination from $\mathbf{3a}^{\bullet-}$ is slowed down considerably and the competing back-electron transfer to $ZnTPPS^{\bullet+}$ (eq 16) becomes predominant. The observed formation of a mixture of cis and trans olefin from **3a** suggests the radical nature of the debromination, i.e., the competitive C–C rotation and bromo radical elimination from α-bromo radical **5**. Similar cis/trans olefin ratios have been reported in the one-electron reductive radical debromination of 1,2-dibromostilbenes (**8**), i.e., *meso*-**8** gave 100% *trans*-stilbene, but *d,l*-**8** yielded a mixture of cis and trans olefin in a ratio of 0–0.04.[33]

Effect of Charges of Sensitizer and Substrates. Many reports have dealt with the retardation of a back electron transfer; i.e., migration toward the left side in eq 4 by invoking electrostatic repulsion of donor (D) and acceptor (A) of like charge. For the present case of anionic sensitizer ZnTPPS, electrostatic repulsion may be large with anionic substrate **1a**, but smaller with the undissociated acid **1b** and ester **1c**, and hence the forward electron transfer is more favorable with **1b** and **1c**. On the other hand, a backward transfer is expected to be slowed down in all of these cases. Thus the quantum efficiency of the debromination is expected to decrease in the order **1c** ~ **1b** > **1a**. However, the observed order of **1c** ~ **1a** > **1b** was quite different from the expected order. This fact suggests that the effect of charges of sensitizer and substrates is not so significant as to control the overall debromination efficiency.

In conclusion, the present studies have demonstrated that (i) the ZnTPPS-sensitized photodebromination of **1** is initiated by a one-electron transfer from $ZnTPPS^*$[3] to the dibromide and (ii) the quantum efficiency for the debromination is mainly controlled by the subsequent radical chain debromination.

Acknowledgment. We thank Takaya Yamanaka at IMS for his expert assistance in laser flash photolysis experiments. We thank Haruhiko Fukaya for helpful comments on the preparation of the software for the laser flash kinetics. This work was supported by a grant from the Ministry of Education of Japan (No. 61223012).

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Benzyne Cyclization Route to Benzo[*c*]phenanthridine Alkaloids. Synthesis of Chelerythrine, Decarine, and Nitidine

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The alkaloids chelerythrine (**8b**) and decarine (**7c**) have been synthesized through a benzyne-mediated cyclization of *N*-(2-halobenzyl)-1-naphthylamines **4** with KNH_2 in ammonia/ether. The 7-hydroxybenzo[*c*]phenanthridine structure **16a** proposed for the alkaloid fagaridine is questioned on the basis of comparison with a model compound (**16b**) synthesized by benzyne cyclization. For the 8,9-oxygenated alkaloids like nitidine (**8i**), this cyclization proceeded poorly, but a dramatic improvement occurred when LDA/THF at −78 °C was used instead of KNH_2/NH_3.

The search for new and more versatile synthetic routes to benzo[*c*]phenanthridine alkaloids continues,[1] primarily because of the cytotoxic activity[2] associated with this class of compounds. In a preliminary communication,[3] it was disclosed that benzyne-mediated cyclization[4] of anils derived from ortho-halogenated benzaldehydes can be used for the synthesis of 7,8-oxygenated benzo[*c*]-phenanthridines. We now report in full some applications of this route along with an important experimental modification, which enlarges its scope to the 8,9-oxygenated alkaloids.

For the synthesis of the alkaloid chelerythrine (**8b**), the bromo aldehyde **1b** was condensed with the naphthylamine **2b** (Schemes I and II). The obtained Schiff base **3b** was reduced with sodium borohydride to get **4b**. Reaction of this bromo amine with KNH_2 gave a mixture (**6b** and **7b**), which on treatment with manganese dioxide in chloroform furnished the benzo[*c*]phenanthridine **7b** in 80% yield. Its methylation[5] afforded a product (**8b**) identical with chelerythrine chloride.[6]

Structure **7c** has been assigned[7] to the alkaloid decarine. The position of the free phenolic group was confirmed by Ishii et al.[8] by synthesizing compound **7d**, which was shown

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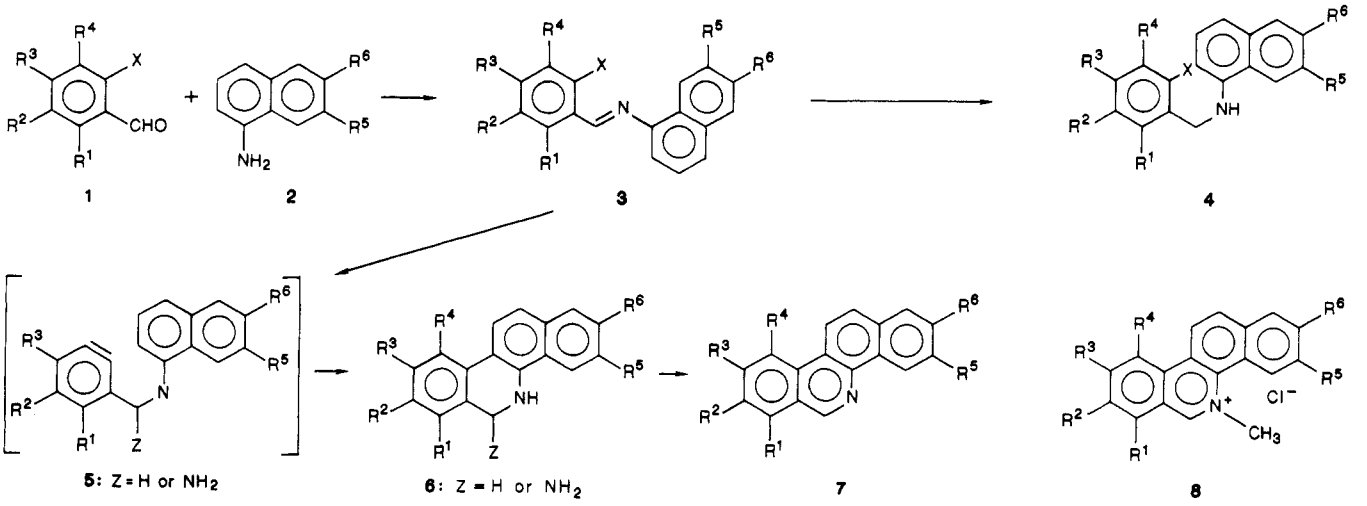
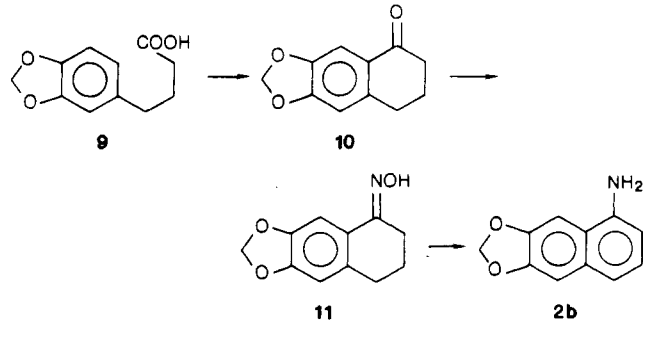
0022-3263/88/1953-1708$01.50/0

Scheme I

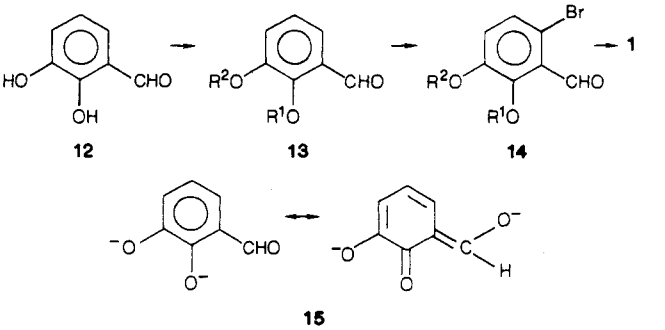


1a: $R^1 = R^2 = R^3 = R^4 = H$, X = Cl
1b: $R^1 = R^2 = MeO$, $R^3 = R^4 = H$, X = Br
1c: $R^1 = MeO$, $R^2 = PhCH_2O$, $R^3 = R^4 = H$, X = Br
1d: $R^1 = PhCH_2O$, $R^2 = MeO$, $R^3 = R^4 = H$, X = Br
1e: $R^1 = OH$, $R^2 = MeO$, $R^3 = R^4 = H$, X = Br
2a: $R^5 = R^6 = H$
2b: $R^5 = R^6 = OCH_2O$
3a, 4a: $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = H$, X = Cl
3b, 4b: $R^1 = R^2 = MeO$, $R^3 = R^4 = H$, $R^5 + R^6 = OCH_2O$, X = Br
3c, 4c: $R^1 = MeO$, $R^2 = PhCH_2O$, $R^3 = R^4 = H$, $R^5 + R^6 = OCH_2O$, X = Br
3d, 4d: $R^1 = PhCH_2O$, $R^2 = MeO$, $R^3 = R^4 = R^5 = R^6 = H$, X = Br
3e, 4e: $R^1 = R^4 = H$, $R^2 + R^3 = R^5 + R^6 = OCH_2O$, X = Cl
3f, 4f: $R^1 = R^4 = H$, $R^2 = R^3 = MeO$, $R^5 + R^6 = OCH_2O$, X = Cl
3g, 4g: $R^1 = R^4 = H$, $R^2 = R^3 = MeO$, $R^5 + R^6 = OCH_2O$, X = Br
3h, 4h: $R^1 = R^2 = R^4 = MeO$, $R^3 = R^5 = R^6 = H$, X = Br
3i, 4i: $R^1 = R^4 = R^5 = R^6 = H$, $R^2 = R^3 = MeO$, X = Br
4j: $R^1 = R^4 = R^5 = R^6 = H$, $R^2 + R^3 = OCH_2O$, X = I
6a, 7a, 8a: $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = H$
6b, 7b, 8b: $R^1 = R^2 = MeO$, $R^3 = R^4 = H$, $R^5 + R^6 = OCH_2O$
6c, 7c, 8c: $R^1 = MeO$, $R^2 = OH$, $R^3 = R^4 = H$, $R^5 + R^6 = OCH_2O$
6d, 7d, 8d: $R^1 = EtO$, $R^2 = MeO$, $R^3 = R^4 = H$, $R^5 + R^6 = OCH_2O$
6e, 7e, 8e: $R^1 = MeO$, $R^2 = PhCH_2O$, $R^3 = R^4 = H$, $R^5 + R^6 = OCH_2O$
6f, 7f, 8f: $R^1 = OH$, $R^2 = MeO$, $R^3 = R^4 = R^5 = R^6 = H$
6g, 7g, 8g: $R^1 = PhCH_2O$, $R^2 = MeO$, $R^3 = R^4 = R^5 = R^6 = H$
6h, 7h, 8h: $R^1 = R^4 = H$, $R^2 + R^3 = R^5 + R^6 = OCH_2O$
6i, 7i, 8i: $R^1 = R^4 = H$, $R^2 = R^3 = MeO$, $R^5 + R^6 = OCH_2O$
6j, 7j, 8j: $R^1 = R^4 = H$, $R^2 = R^3 = R^5 = MeO$, $R^6 = OH$
6k, 7k: $R^1 = R^4 = R^5 = R^6 = H$, $R^2 = R^3 = MeO$
6l, 7l: $R^1 = R^4 = R^5 = R^6 = H$, $R^2 + R^3 = OCH_2O$

Scheme II



Scheme III



13a: $R^1 = PhCH_2$, $R^2 = H$
13b: $R^1 = H$, $R^2 = PhCH_2$
13c: $R^1 = COOEt$, $R^2 = PhCH_2$
13d: $R^1 = COOEt$, $R^2 = Me$
14a: $R^1 = COEt$, $R^2 = PhCH_2$
14b: $R^1 = H$, $R^2 = PhCH_2$
14c: $R^1 = COOEt$, $R^2 = Me$

to be different from decarine ethyl ether. Synthesis of the alkaloid itself (**7c**) seemed easy by the benzyne route. The required aldehyde **1c** was obtained through a novel selective benzylation of the catechol **12** to **13a** (Scheme III), which exploits site selectivity reversal in catechoxide dianions.[9] Thus, in the dianion **15**, the negative charge of the ortho phenoxy group should be delocalized on the aldehydic function, rendering the other position more re-

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Table I. Ultraviolet Absorption Maxima for 16b

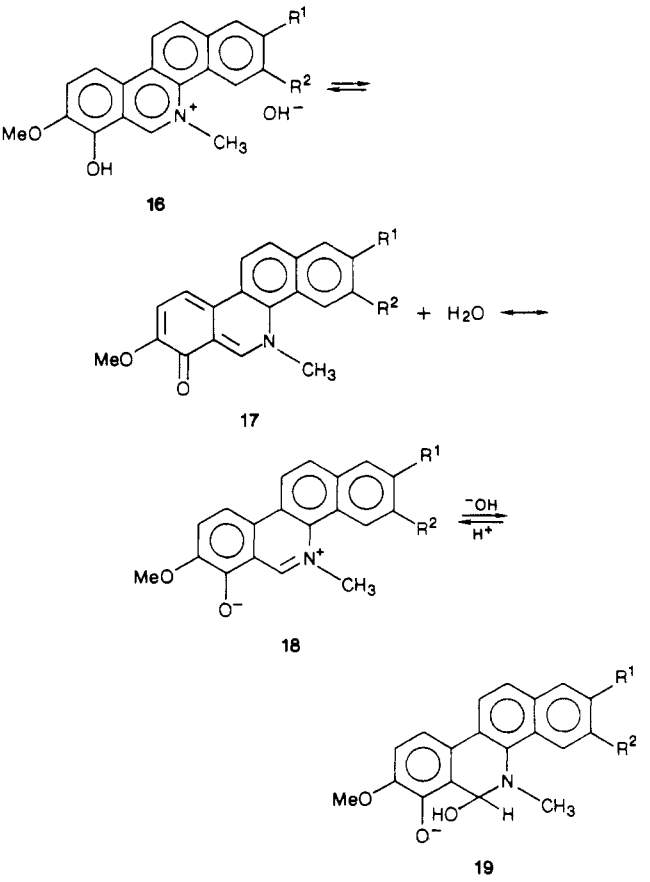
solvent	λ_{max}, nm
C_2H_5OH/HCl	231, 272, 321, 456
C_2H_5OH	226, 252 (sh), 265 (sh), 311 (sh), 395, 537
C_2H_5OH/NH_4OH	231, 224 (sh), 227, 252 (sh), 265 (sh), 311, 395, 537
C_2H_5OH/aqueous NaOH	223, 250

active. Benzylation of **12** using 1 molar equiv of sodium hydride in DMSO gave **13a**[10] while with 2 mol of sodium hydride the desired compound **13b** was obtained in 65% yield. The phenol **13b** was converted into a carbonate (**13c**),[11] which was elaborated to the bromo aldehyde **1c** through **14a** and **14b**. Condensation with the naphthylamine **2b** and sodium borohydride reduction followed by cyclization of the obtained amine **4c** with KNH_2/NH_3 furnished[12] **7e**. The compound formed on subsequent debenzylation was found to be identical with an authentic sample[13] of decarine (**7c**).

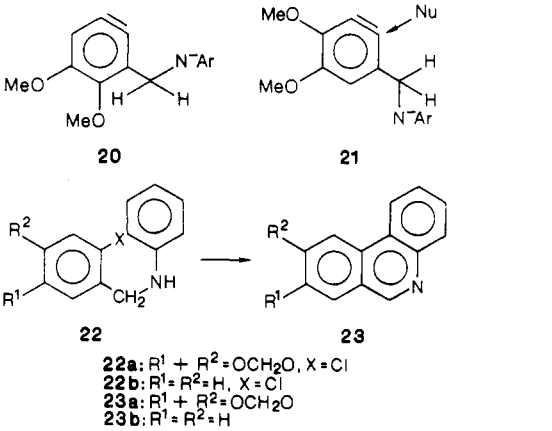
The phenolic alkaloid fagaridine isolated by Torto[14] and co-workers was assigned structure **16a** on the basis of NMR studies. From simple chemical considerations, the placement of the phenolic function at position 7 seems untenable. The positive charge on the nitrogen atom in **16a** should, through conjugation, greatly enhance the acidity of this phenolic group, leading to loss of a proton, especially in the presence of OH^- ions. The resulting zwitterion (**17a** ↔ **18a**) may remain hydrated, but it is expected to be highly colored (contribution from the extensively conjugated canonical structure **18a**). However, the alkaloid has been described[14] as a pale yellow solid. In this context, it was decided to synthesize the model compound **16b** and study its light-absorption characteristics. Cyclization of the bromo compound **4d** with KNH_2/NH_3 furnished the desired phenanthridine **7g** in good yield. If the reaction mixture was worked up after 3 h, instead of the usual 30 min, substantial debenzylation of **7g** also occurred. Considerable difficulty was experienced in the quaternization step,[15] but when the procedure detailed in the Experimental Section was followed, a TLC-pure purple compound with ^1H NMR and mass spectral data corresponding to **16b** was obtained. Its solution in 95% ethanol was deep violet and turned yellow on acidification. Subsequent addition of aqueous NH_4OH reversed the change. On addition of sodium hydroxide, the color started to fade again and ultimately the solution became colorless (Table I). These changes may be rationalized[16] as shown in Scheme IV. Anyway, **16a** seems to be an incorrect structure for fagaridine,[17] and a different placement of the hydroxy group is required.

Cyclization with KNH_2/NH_3 was also used for the synthesis of 8,9-oxygenated alkaloids avicine (**8h**) and nitidine (**8i**), but the yield was low (ca. 10%) compared to that of 7,8-oxygenated alkaloids (ca. 90%). In general,

Scheme IV



Scheme V



reactions of nucleophiles with dialkoxybenzyne intermediates have been found to proceed in poor yields.[18] Biehl[19] has suggested that polarization of the benzyne by the alkoxy groups increases its reactivity, resulting in indiscriminate reaction with more abundant solvent ammonia molecules. However, this alone does not explain why the benzyne intermediate **20** cyclizes well in contrast to **21**. We suggest that in **20** the ortho methoxy substituent forces the arylamino side chain into benzyne proximity, resulting

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(11) Kametani, T.; Honda, T.; Inous, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1221.
(12) Kessar, S. V.; Gupta, Y. P.; Mohammad, T.; Khurana, A.; Sawal, K. K. *Heterocycles* **1984**, *22*, 2723.
(13) Sample kindly provided by Prof. H. Ishii, Chiba University, Japan.
(14) Torto, F. G.; Mensah, I. A.; Baxter, I. *Phytochemistry* **1973**, *12*, 2315.
(15) Compare: Stermitz, F. R.; Gillespie, J. P.; Amoros, L. G.; Romero, R.; Stermitz, T. A. *J. Med. Chem.* **1975**, *18*, 708.
(16) Compare: Jonsson, G. *Acta Chem. Scand.* **1966**, *20*, 2755.
(17) Prof. H. Ishii has also questioned the structure **16a** for fagaridine (personal communication).
(18) Han, Y. X.; Jovanovic, M. V.; Biehl, E. R. *J. Org. Chem.* **1985**, *50*, 1334.
(19) Han, Y. X.; Biehl, E. R. *J. Org. Chem.* **1983**, *48*, 4397. Razzuk, A.; Biehl, E. R. *J. Org. Chem.* **1987**, *52*, 2619. Symmetrically placed dialkoxy substituents exert a less deleterious effect.

in an intramolecular reaction (Scheme V).

Even for the synthesis of 8,9-substituted alkaloids, the benzyne route is attractive, and Stermitz[15,20] used it for fagaronine (**8j**) and a number of related benzo[c]-phenanthridines of interest in cancer chemotherapy. Nevertheless, it was desirable to improve the cyclization yield. We argued that lowering the reaction temperature, decreasing the concentration, or increasing the size of the competing external nucleophile may favor cyclization. We were gratified to note that carrying out the reaction of **4f** with LDA/THF[21] at −78 °C dramatically improved the yield of **7i**.[22] The finding removes a major shortcoming of this route to benzophenanthridines, i.e., its inefficiency for 8,9-oxygenated alkaloids. The magnitude of yield improvement (10–70%) made us wonder if the change of conditions had led to a radical-mediated cyclization.[23] Recently, it has been observed that LDA in THF can react with certain aryl halides through a benzyne or an electron transfer radical mechanism.[24] In this context, the trimethoxy compound **4h**, in which benzyne formation is blocked and only a radical mechanism can operate, was synthesized and exposed to LDA/THF. The starting material was recovered unchanged, showing that in this case at least the radical cyclization does not occur. The increase in the cyclization yield of 8,9-oxygenated benzo[c]phenanthridines with LDA as compared to KNH_2 may be attributed to steric inhibition of competitive attack by the larger diisopropyl amide ion (structure **21**).

To test the applicability of LDA/THF to our benzyne phenanthridine synthesis in general, we reacted the dihydro anils **4i**, **4j**, and **22a** under these conditions. The cyclization yields were far superior to those obtained with KNH_2/NH_3. For substrates devoid of alkoxy substituents, like **22b**, longer reaction time was needed and the yield was inferior. Further, direct cyclization of Schiff bases, which presumably occurs through NH_2^- ion addition–expulsion across the azomethine bond,[4] fails with LDA/THF. Thus there is complementarity between KNH_2/NH_3 and LDA/THF conditions for the purpose of this cyclization.

Experimental Section

The melting points are uncorrected. The infrared spectra were run on a Perkin-Elmer 337 spectrometer. ^1H NMR spectra were obtained on a Varian 90-MHz EM-390 spectrometer with Me_4Si as an internal standard. Mass spectra were recorded on a VG Micromass 70-70F instrument. UV spectra were recorded on a Perkin-Elmer MPF-3 spectrophotometer equipped with a Hitachi 200 recorder. Elemental analyses (C, H, N) were carried out in the microanalytical section of this department.

6,7-(Methylenedioxy)-1-naphthylamine (2b). Ketone **10** was obtained from the carboxylic acid[25] **9** by treatment with phosphorus oxychloride at 140 °C for 4 min. A solution of its oxime **11** (0.5 g, 2.5 mmol) in acetic anhydride/acetic acid (1:5, 2.1 mL) was heated on a steam bath, and dry HCl gas was bubbled through it for 2 h. The precipitated amine hydrochloride was dissolved in hot water, treated with charcoal, and filtered. The filtrate was basified with 10% aqueous Na_2CO_3 (20 mL) and the obtained solid recrystallized from aqueous ethanol to yield the pure amine **2b** (0.13 g, 28%): mp 152–154 °C (lit.[3a] mp 152–154 °C).

2,3-Dimethoxy-6-bromobenzaldehyde (1b). 2-Hydroxy-3-methoxy-6-bromobenzaldehyde (**1e**) was prepared (40% overall yield) from *o*-vanillin, through **13d** and **14c** essentially by the procedure of Kametani et al.[11] It was methylated with DMS/NaH to yield **1b**: mp 76–77 °C (petroleum ether) (lit.[26] mp 77–78 °C).

2-(Benzyloxy)-3-hydroxybenzaldehyde (13a). Dimethyl sulfoxide (15 mL) and sodium hydride (from 0.096 g of 53% oil dispersion, 2.1 mmol) were heated (70 °C) with stirring under a nitrogen atmosphere for 1 h. A solution of 2,3-dihydroxybenzaldehyde[27] (**12**, 0.250 g, 1.81 mmol) in DMSO (1 mL) was injected dropwise. After 1 h, the mixture was cooled to room temperature, a solution of benzyl chloride (0.23 g, 1.81 mmol) in DMSO (1 mL) was injected slowly, the mixture was heated again at 70 °C for 1 h, water (15 mL) was added, and the reaction mixture was extracted with ether. The aqueous layer was acidified with 5% HCl and extracted with ether (3 × 15 mL). The organic layer was washed with water (3 × 15 mL) and dried. Evaporation of the solvent afforded a solid, which on recrystallization from benzene/petroleum ether (1:1) gave light yellow needles of the pure aldehyde **13a** (0.268 g, 44%): mp 84–85 °C; ^1H NMR ($CDCl_3$) δ 5.15 (s, 2 H), 6.90–7.50 (m, 8 H), 10.00 (s, 1 H), 11.15 (s, 1 H, exchangeable within D_2O). Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.68; H, 5.26. Found: C, 73.57; H, 5.24.

2-Hydroxy-3-(benzyloxy)benzaldehyde (13b). When the above experiment was repeated with double the amount of sodium hydride (from 0.192 g of 53% oil dispersion), the aldehyde **13b** was obtained in 65% yield: mp 90–91 °C (lit.[10] mp 90–91 °C); ^1H NMR ($CDCl_3$) δ 5.13 (s, 2 H), 5.21 (s, 1 H, exchangeable with D_2O), 7.43 (m, 8 H), 10.25 (s, 1 H).

6-(Benzyloxy)-2-formylphenyl Ethyl Carbonate (13c). To a solution of **13b** (0.5 g, 2.192 mmol) and triethylamine (0.4 mL) in dry benzene (15 mL) was added ethyl chloroformate (0.5 mL) in benzene (5 mL) in 20 min. After the mixture was stirred for 2 h, the workup gave **13c** (0.65 g, 98.8%): mp 58–59 °C; IR (Nujol) 1670, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3 H), 4.35 (q, 2 H), 5.15 (s, 2 H), 7.20–7.60 (m, 8 H), 10.30 (s, 1 H). Anal. Calcd for $C_{17}H_{16}O_5$: C, 68.00; H, 5.30. Found: C, 67.52; H, 5.29.

2-Hydroxy-3-(benzyloxy)-6-bromobenzaldehyde (14b). To a suspension of **13c** (1.4 g, 4.67 mmol) in water (40 mL) containing KBr (3.0 g) was added bromine (0.4 mL) with stirring. Workup gave the crude **14a** as an oil, which was dissolved in methanol (30 mL) and treated with 10% NaOH (5 mL). The separated solid was filtered, acidified with 10% HCl (10 mL), and extracted with chloroform (93 × 10 mL). Evaporation of the solvent furnished a viscous oil (0.5 g, 55.5%): ^1H NMR ($CDCl_3$) δ 3.60 (s, 6 H), 5.15 (s, 2 H), 5.85 (s, 1 H), 6.80 (d, 1 H), 7.05 (d, 1 H), 7.38–7.63 (m, 5 H), 8.90 (br s, 1 H, exchangeable with D_2O). Absence of the low-field aldehydic signal and the presence of singlets at δ 5.85 and 3.60 suggested acetal formation. A solution of this oil (0.25 g), acetone (20 mL), and 33% HCl (9 mL) was refluxed for 10 h, the solvent was evaporated, and the residue was chromatographed over silica gel to yield the bromo compound **14b** (0.22 g, 62%): mp 61–62 °C; ^1H NMR ($CDCl_3$) δ 5.20 (s, 2 H), 6.95 (d, 1 H), 7.10 (d, 1 H), 7.30–7.65 (m, 5 H), 10.40 (s, 1 H), 12.40 (s, 1 H). Anal. Calcd for $C_{14}H_{11}BrO_3$: C, 54.72; H, 3.58. Found: C, 54.61; H, 3.55.

2-Methoxy-3-(benzyloxy)-6-bromobenzaldehyde (1c). A mixture of **14b** (0.850 g, 2.76 mmol), methyl iodide (2 mL), dry acetone (40 mL), and anhydrous potassium carbonate was refluxed for 5 h. The residue obtained on workup was recrystallized from aqueous methanol to give **1c** (0.808 g, 91%): mp 74–75 °C; ^1H NMR ($CDCl_3$) δ 4.00 (s, 3 H), 5.15 (s, 2 H), 7.05 (d, 1 H), 7.45 (m, 6 H), 10.40 (s, 1 H); MS, *m/e* 322, 320 (M^+), 321, 231, 230, 229, 228. Anal. Calcd for $C_{15}H_{13}BrO_3$: C, 56.07; H, 4.05. Found C, 56.03; H, 4.03.

2-Formyl-6-methoxyphenyl ethyl carbonate (13d): obtained from *o*-vanillin (5.0 g, 32.8 mmol), triethylamine (3.5 g, 34.6 mmol), and ethyl chloroformate (4.3 g, 39.8 mmol) as an oil (6 g, 81.9); bp 152–155 °C (4–5 mmHg); ^1H NMR (CCl_4) δ 1.45 (t, 3 H, J = 7 Hz), 4.00 (s, 3 H), 4.35 (q, 2 H, J = 7 Hz), 7.20–7.60 (m, 3 H), 10.30 (s, 1 H). Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.35. Found: C, 58.65; H, 5.32.

2-Formyl-3-bromo-6-methoxyphenyl Ethyl Carbonate (14c). To a stirred solution of **13d** (5.5 g, 24.5 mmol) in glacial

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acetic acid (75 mL) containing a small amount of iron powder (0.25 g) was added bromine (2.5 mL) in glacial acetic acid (25 mL) dropwise. It was stirred further for 5 h at room temperature, allowed to stand overnight, diluted with water (100 mL), and extracted with chloroform. The chloroform layer was washed with 5% sodium thiosulfate. Workup followed by recrystallization from isopropyl alcohol furnished **1c** (2.9 g, 35.3%): mp 82–84 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3 H, J = 7 Hz), 3.90 (s, 3 H), 4.45 (q, 2 H, J = 7 Hz), 7.15 (d, 1 H, J = 9 Hz), 7.65 (d, 1 H, J = 9 Hz), 10.55 (s, 1 H). Anal. Calcd for $C_{11}H_{11}BrO_5$: C, 43.56; H, 3.63. Found: C, 43.71; H, 3.64.

2-(Benzyloxy)-3-methoxy-6-bromobenzaldehyde (1d). A mixture of 1e[11] (2.2 g, 9.5 mmol), methanol (25 mL), benzyl chloride (1.4 mL), and anhydrous potassium carbonate (1.0 g) was refluxed for 5 h, filtered while hot, and the residue washed with methanol. Distillation of the solvent followed by steam distillation to remove unreacted benzyl chloride provided, on workup, a yellow viscous liquid (2.568 g, 72.2%): ^{1}H NMR (CCl_4) δ 3.85 (s, 3 H), 5.05 (s, 2 H), 6.90 (d, 1 H, J = 9 Hz), 7.25 (d, 1 H, J = 9 Hz), 7.30–7.50 (m, 5 H), 10.25 (s, 1 H); IR (Nujol) 1695 cm^{-1}.

Preparation of *N*-Benzylidene-1-naphthylamines 3. General Procedure. A solution of equimolar quantities of the halo aldehyde and the amine in ethanol was refluxed for 2 h. It was concentrated and cooled to furnish the pure Schiff bases.

***N*-(6-Bromo-2,3-dimethoxybenzylidene)-6,7-(methylenedioxy)-1-naphthylamine (3b)**: yield 74%; mp 93–95 °C. Anal. Calcd for $C_{20}H_{16}BrNO_4$: N, 3.40. Found: N, 3.44.

***N*-(6-Bromo-2-(benzyloxy)-3-methoxybenzylidene)-1-naphthylamine (3d)**: yield 73.7%; mp 103–104 °C (ethanol); ^{1}H NMR (CCl_4) δ 4.00 (s, 3 H), 5.20 (s, 2 H), 6.85 (d, 1 H, J = 9 Hz), 7.35 (d, 1 H, J = 9 Hz), 7.30–8.35 (m, 12 H), 9.35 (s, 1 H). Anal. Calcd for $C_{25}H_{20}BrNO_2$: C, 67.26; H, 4.48; N, 3.14. Found: C, 66.95; H, 4.43; N, 3.12.

***N*-(2-Chloro-4,5-(methylenedioxy)benzylidene)-6,7-(methylenedioxy)-1-naphthylamine (3e)**: yield 78%; mp 186–188 °C (ethanol). Anal. Calcd for $C_{19}H_{12}NO_4Cl$: C, 64.75; H, 3.40; N, 3.97. Found: C, 64.68; H, 3.48; N, 4.09.

***N*-(2-Chloro-4,5-dimethoxybenzylidene)-6,7-(methylenedioxy)-1-naphthylamine (3f)**: yield 75%; mp 197–199 °C (ethanol). Anal. Calcd for $C_{20}H_{16}NO_4Cl$: C, 65.04; H, 4.32; N, 3.80. Found: C, 65.45; H, 4.38; N, 3.71.

***N*-(6-Bromo-2-methoxy-3-(benzyloxy)benzylidene)-6,7-(methylenedioxy)-1-naphthylamine (3c).** A mixture of **1c** (0.160 g, 0.5 mmol) and **2b** (0.0935 g, 0.5 mmol) was heated in a test tube at 160–170 °C for 2 h to furnish **3c** (0.24 g, 98%) as a viscous liquid: ^{1}H NMR ($CDCl_3$) δ 4.05 (s, 3 H), 5.15 (s, 2 H), 6.05 (s, 2 H), 6.80–7.70 (m, 11 H), 7.80 (s, 1 H), 8.80 (s, 1 H).

***N*-(2-Bromo-4,5-dimethoxybenzylidene)-6,7-(methylenedioxy)-1-naphthylamine (3g)**: yield 72%; mp 232–234 °C. Anal. Calcd for $C_{20}H_{16}BrNO_4$: C, 57.97; H, 3.86; N, 3.38. Found: C, 57.82; H, 3.90; N, 3.34.

***N*-(2-Bromo-3,5,6-trimethoxybenzylidene)-1-naphthylamine (3h)**: from 2,3,5-trimethoxy-6-bromobenzaldehyde[28] and 1-naphthylamine in 72% yield; mp 131–132 °C. Anal. Calcd for $C_{20}H_{18}BrNO_3$: N, 3.50. Found: N, 3.52.

***N*-(2-Bromo-4,5-dimethoxybenzylidene)-1-naphthylamine (3i)**: yield 86%; mp 162–163 °C (ethanol); ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3 H), 3.98 (s, 3 H), 7.00–8.50 (m, 9 H), 8.85 (s, 1 H). Anal. Calcd for $C_{19}H_{16}BrNO_2$: N, 3.77. Found: N, 3.96.

Sodium Borohydride Reduction of *N*-Benzylidene-1-naphthylamines to *N*-Benzyl-1-naphthylamines (4). General Procedure. A solution of the anil **3** (1.0 g) in ethanol (50 mL) was refluxed with sodium borohydride (2 g) for 3 h. The solvent was distilled off and the residue decomposed with water, extracted with chloroform, and dried. The solvent was evaporated and the residue crystallized to yield the pure benzylamine.

***N*-(*o*-Chlorobenzyl)-1-naphthylamine (4a)**: yield 79%; mp 109–111 °C (ethanol) (lit.[29] mp 110–112 °C).

***N*-(6-Bromo-2,3-dimethoxybenzyl)-6,7-(methylenedioxy)-1-naphthylamine (4b)**: yield 64%; mp 121–122 °C (ethanol). Anal. Calcd for $C_{20}H_{18}BrNO_4$: C, 57.69; H, 4.32; N, 3.36. Found: C, 57.00; H, 4.21; N, 3.53.

***N*-(6-Bromo-2-methoxy-3-(benzyloxy)benzyl)-6,7-(methylenedioxy)-1-naphthylamine (4c)**: yield 62%; mp 141–143 °C (ethanol); ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3 H), 4.35 (br s, 1 H), 4.60 (s, 2 H), 5.15 (s, 2 H), 6.05 (s, 2 H), 6.80–7.60 (m, 12 H). Anal. Calcd for $C_{26}H_{22}BrNO_4$: C, 63.41; H, 4.47; N, 2.84. Found: C, 63.17; H, 4.45; N, 2.83.

***N*-(6-Bromo-2-(benzyloxy)-3-methoxybenzyl)-1-naphthylamine (4d)**: yield 39%; mp 133–134 °C (ethanol); ^{1}H NMR (CCl_4) δ 3.90 (s, 3 H), 4.55 (m, 3 H), 5.10 (s, 2 H), 6.85–7.80 (m, 14 H). Anal. Calcd for $C_{25}H_{22}BrNO_2$: C, 66.96; H, 4.91; N, 3.12. Found: C, 66.64; H, 4.89; N, 3.10.

***N*-(2-Chloro-4,5-(methylenedioxy)benzyl)-6,7-(methylenedioxy)-1-naphthylamine (4e)**: yield 70%; mp 167–169 °C (ethanol). Anal. Calcd for $C_{19}H_{14}ClNO_4$: C, 64.40; H, 3.96; N, 3.96. Found: C, 64.10; H, 3.99; N, 3.87.

***N*-(2-Chloro-4,5-dimethoxybenzyl)-6,7-(methylenedioxy)-1-naphthylamine (4f)**: yield 85%; mp 187–189 °C (ethanol). Anal. Calcd for $C_{20}H_{18}ClNO_4$: C, 64.50; H, 4.84; N, 3.76. Found: C, 64.50; H, 5.03; N, 3.80.

***N*-(2-Bromo-4,5-dimethoxybenzyl)-6,7-(methylenedioxy)-1-naphthylamine (4g)**: yield 83%; mp 203–204 °C (ethanol); ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3 H), 3.98 (s, 3 H), 4.52 (s, 2 H), 6.12 (s, 2 H), 7.05–7.52 (m, 7 H). Anal. Calcd for $C_{20}H_{18}BrNO_4$: N, 3.36. Found: N, 3.40.

***N*-(2-Bromo-3,5,6-trimethoxybenzyl)-1-naphthylamine (4h)**: yield 85%; mp 117–118 °C (CH_2Cl_2/hexane). Anal. Calcd for $C_{20}H_{20}BrNO_3$: N, 3.48. Found: N, 3.51.

***N*-(2-Bromo-4,5-dimethoxybenzyl)-1-naphthylamine (4i)**: yield 85%; mp 148–149 °C (ethanol); ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3 H), 3.97 (s, 3 H), 4.56 (s, 2 H), 6.90–8.14 (m, 9 H). Anal. Calcd for $C_{19}H_{18}BrNO_2$: N, 3.76. Found: N, 3.84.

***N*-(2-Iodo-4,5-(methylenedioxy)benzyl)-1-naphthylamine (4j)**: yield 65%; mp 108–110 °C (ethanol). Anal. Calcd for $C_{18}H_{14}INO_2$: C, 53.60; H, 3.47; N, 3.47. Found: C, 53.95; H, 3.64; N, 3.72.

KNH_2 Cyclization of 4a and 3a to 6a and 7a. Under the earlier described conditions,[4a] potassium amide (from 0.73 g, 18.7 mmol, of the metal) was prepared in 300 mL of liquid ammonia and anhydrous ether (150 mL) was added to it. Then the amine **4a** (0.50 g, 1.87 mmol) was introduced and the reaction mixture worked up after 3 h of stirring to yield **6a** (0.275 g, 64%), mp 199–202 °C. Oxidation[4a] by stirring with manganese dioxide (1.5 g) in chloroform (10 mL) afforded **7a** (0.116 g, 78%), mp 136 °C (ethanol) (lit.[30] mp 135–135.5 °C). Cyclization of **3a** under identical conditions gave **7a** (63%) directly.

2,3-(Methylenedioxy)-7,8-dimethoxybenzo[*c*]phenanthridine (7b): from reaction of **4b** with potassium amide in liquid ammonia/ethyl ether followed by MnO_2 oxidation; 80% yield; mp 210–212 °C (lit.[5] mp 213 °C).

Chelerythrine Chloride (8b): prepared from **7b** according to the method of Bailey et al.;[5] mp 199–200 °C (lit.[5] mp 201–202 °C). Its identity was confirmed by admixture melting point (198–199 °C) and TLC comparison with an authentic sample of **8b**.[6]

Benzyldecarine (7e): obtained in 62% yield from KNH_2 cyclization of **4c**; mp 210–211 °C; ^{1}H NMR ($CDCl_3$) δ 4.15 (s, 3 H), 5.35 (s, 2 H), 6.15 (s, 2 H), 7.30–8.00 (m, 8 H), 8.35–8.45 (d, 2 H), 8.80 (s, 1 H), 8.85 (s, 1 H); MS, m/e (relative intensity) 409 (M^+, 100), 318 (90), 290 (82), 275 (35). Anal. Calcd for $C_{26}H_{19}NO_4$: C, 76.28; H, 4.64; N, 3.42. Found: C, 75.96; H, 4.62; N, 3.40.

Decarine (7c). The crude product from KNH_2 cyclization of **4c** (0.125 g, 0.254 mmol) was refluxed for 1 h with a mixture of hydrochloric acid (0.75 mL) and acetic acid (0.75 mL). The acids were distilled off under reduced pressure, and the residue was basified with a saturated solution of sodium bicarbonate. The organic material was extracted with chloroform, washed with water, and dried. Evaporation of the solvent and recrystallization from methanol/chloroform furnished pure decarine (**7c**, 0.030 g, 37%), identified by TLC comparison and admixture melting point (230–231 °C) with an authentic sample[13] (mp 231–232 °C); ^{1}H NMR (deuteriated DMSO) δ 4.05 (s, 3 H), 6.30 (s, 2 H), 7.50 (s, 1 H), 8.62 (s, 1 H), 9.65 (s, 1 H), 8.05 (d, 1 H), 8.55 (d, 1 H), 7.65

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7-(Benzyloxy)-8-methoxybenzo[*c*]phenanthridine (7g). Amine **4d** (0.45 g, 1.04 mmol) was treated with potassium amide (from 0.273 g, 7.00 mmol, of potassium metal) in liquid ammonia/ethyl ether for 25 min. The solid obtained on workup was recrystallized from methanol to give **7g** (0.180 g, 49%): mp 138–139 °C; 1H NMR (CCl_4) δ 4.00 (s, 3 H), 5.30 (s, 2 H), 7.30–8.00 (m, 10 H), 8.25 (d, 1 H), 8.40 (d, 1 H), 9.40 (d, 1 H), 9.85 (s, 1 H); MS, m/e (relative intensity) 365 (M^+, 100), 274 (96), 246 (80). Anal. Calcd for $C_{25}H_{19}NO_2$: C, 82.19; H, 5.20; N, 3.83. Found: C, 82.60; H, 5.23; N, 3.85.

An identical reaction quenched after 3 h furnished a mixture of **7g** and **7f**. Recrystallization from methanol gave pure **7f**: MS, m/e 275 (M^+), 260, 232. Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.54; H, 4.72; N, 5.09. Found: C, 78.32; H, 4.70; N, 5.06.

***N*-Methylation of 7-(Benzyloxy)-8-methoxybenzo[*c*]phenanthridine (7g).** A solution of **7g** (0.080 g, 0.22 mmol) in xylene (2 mL) containing freshly neutralized[31] dimethyl sulfate (0.6 mL) was refluxed for 45 min. The mixture was cooled, and the yellow solid thus formed was centrifuged and washed with benzene (3 × 1 mL) and petroleum ether (40–60 °C, 3 × 2 mL). The solid was warmed with water and the insoluble part centrifuged out. The clear aqueous solution was basified with a few drops of ammonia and extracted with chloroform (2 × 5 mL). The solvent was evaporated to yield **17b** (single spot on TLC) as a dark violet solid (0.015 g, 23.6%): mp >310 °C; 1H NMR (CF_3COOH) δ 3.80 (s, 3 H), 4.70 (s, 3 H), 9.5 (s, 1 H); MS, m/e (relative intensity) 289 (M^+, 39), 274 (100), 259 (56), 231 (31).

2,3-(Methylenedioxy)-8,9-dimethoxybenzo[*c*]phenanthridine (7i). Treatment of **4f** (0.5 g, 1.2 mmol) with potassium amide (from 0.4 g, 12 mmol, of potassium metal) in liquid ammonia/ethyl ether for 3 h, followed by MnO_2 oxidation, gave a dark solid (0.4 g). It was repeatedly recrystallized from ethanol to yield pure **7i** (0.04 g, 10%), mp 274–276 °C (lit.[32] mp 277–279 °C). Its identity was confirmed by admixture melting point (274–276 °C) and TLC comparison with an authentic sample.[32] Similar cyclization of **4e** gave **7h** in a comparable yield.

2,3:8,9-Bis(methylenedioxy)benzo[*c*]phenanthridine (7h). Reduction of **17** (0.1 g, 0.3 mmol) with $LiAlH_4$ (0.15 g) in refluxing dioxane (100 mL) afforded **7h** (0.07 g, 73%) identical with the earlier prepared sample.

LDA/THF Cyclization of 4g. Reaction of **4g** (0.083 g, 0.2 mmol) with LDA (0.6 mmol) in THF at −78 °C for 3 h and then at 40 °C for 18 h, followed by MnO_2 oxidation, gave a light brown solid (0.055 g). It was recrystallized from ethanol to yield pure **7i** in 75% yield.

8,9-Dimethoxybenzo[*c*]phenanthridine (7h): from LDA/THF cyclization of **4h** in 83% (14%)[33] yield; mp 225–226 °C.

8,9-(Methylenedioxy)benzo[*c*]phenanthridine (7l): from LDA/THF cyclization of **4i** in 91% (11%) yield; mp 227–228 °C (lit.[34] mp 223–225 °C).

8,9-(Methylenedioxy)phenanthridine (23a): from LDA/THF cyclization of **22a**[4b] in 80.7% (13%) yield; mp 137–138 °C (lit.[4b] mp 138–139 °C).

Phenanthridine (23b): from **22b**[4a] by treatment with LDA/THF at 25 °C for 48 h in 75% (>90%) yield; mp 104–105 °C (lit.[4a] mp 103–105 °C).

Registry No. **1a**, 89-98-5; **1b**, 53811-50-0; **1c**, 95712-55-3; **1d**, 113250-72-9; **1e**, 20035-41-0; **1** ($R^1 = R^4 = H$, $R^2 + R^3 = OCH_2O$, X = Cl), 15952-61-1; **1** ($R^1 = R^4 = H$, $R^2 = R^3 = OMe$, X = Cl), 18093-05-5; **1** ($R^1 = R^4 = H$, $R^2 = R^3 = OMe$, X = Br), 5392-10-9; **1** ($R^1 = R^2 = R^4 = OMe$, $R^3 = H$, X = Br), 64108-61-8; **1** ($R^1 = R^4 = H$, $R^2 + R^3 = OCH_2O$, X = I), 58343-53-6; **2a**, 134-32-7; **2b**, 53811-49-7; **3a**, 113250-73-0; **3b**, 53811-51-1; **3c**, 113250-74-1; **3d**, 113250-75-2; **3e**, 113250-76-3; **3f**, 113250-77-4; **3g**, 113250-78-5; **3h**, 113250-79-6; **3i**, 56516-98-4; **3j**, 113250-94-5; **4a**, 113250-80-9; **4b**, 53811-52-2; **4c**, 95712-58-6; **4d**, 113250-81-0; **4e**, 113250-82-1; **4f**, 113250-83-2; **4g**, 113250-84-3; **4h**, 113250-85-4; **4i**, 113250-86-5; **4j**, 113250-93-4; **6a**, 113250-95-6; **7a**, 218-38-2; **7b**, 6900-99-8; **7c**, 54354-62-0; **7e**, 3895-92-9; **7f**, 113250-91-2; **7g**, 113250-90-1; **7h**, 217-52-7; **7i**, 18034-03-2; **7l**, 214-06-2; **8b**, 3895-92-9; **9**, 41303-44-0; **10**, 41303-45-1; **11**, 53811-53-3; **12**, 24677-78-9; **13a**, 86734-60-3; **13b**, 86734-59-0; **13c**, 95712-56-4; **13d**, 113250-88-7; **13** ($R^1 = H$, $R^2 = Me$), 148-53-8; **14a**, 95712-57-5; **14b**, 95712-54-2; **14b** (dimethyl acetal), 113250-87-6; **14c**, 113250-89-8; **16a**, 51059-64-4; **17b**, 113250-92-3; **17h**, 113250-96-7; **22a**, 41001-82-5; **22b**, 41001-24-5; **23a**, 224-11-3; **23b**, 229-87-8.

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Acid-Catalyzed Isomerization of 7-Dehydrocholesterol Benzoate. A Revised Mechanism and an Improved Synthetic Procedure

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A revised mechanism has been proposed for the low-temperature HCl-catalyzed isomerization of 3β-(benzoyloxy)cholesta-5,7-diene to 3β-(benzoyloxy)-5α-cholesta-7,14-diene. Two byproducts, 3β-(benzoyloxy)-5β-cholesta-7,14-diene and 3β-(benzoyloxy)-5β-cholesta-8,14-diene, and a new intermediate, 3β-(benzoyloxy)-6α-chloro-5α-cholest-7-ene, were isolated from this reaction. An improved procedure for the synthesis of 3β-(benzoyloxy)-5α-cholesta-7,14-diene minimizes the levels of these and other contaminants in the reaction product. All new sterols were characterized by 1H and 13C NMR.

3β-Hydroxy-5α-cholest-8(14)-en-15-one (1) is a potent inhibitor of sterol synthesis in cultured mammalian cells.[1] Oral administration of 1 to Rhesus monkys resulted in marked decreases in serum low density lipoprotein cholesterol levels and substantial increases in high density lipoprotein cholesterol levels.[2] These changes are generally considered to be beneficial for the treatment and/or prevention of atherosclerosis. For the completion of investigations concerning the effects of 1 in primates, several kilograms of 1 were required. A critical step in the most attractive route[1,3] for the large-scale preparation of 1 is the

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