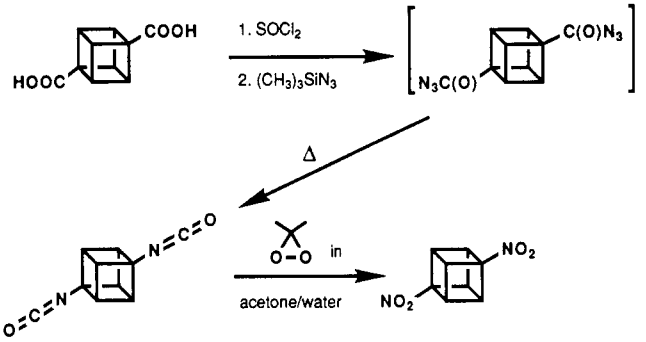
Scheme II



OV-225 on 80–100 mesh Chromosorb G-HP column at 100 °C. The concentration was usually between 0.07 and 0.12 M.

1,4-Diisocyanatocubane. *A heavy shield must be used. Solutions of cubane-1,4-bis(acyl azide) have not caused problems, but the crystalline compound detonates if touched. Great care should be exercised.* A mixture of 1,4-dicarboxycubane (2.30 g, 12.0 mmol) and 25 g of thionyl chloride (freshly distilled from triphenyl phosphite) was stirred at reflux under nitrogen for 3 h. Most of the excess thionyl chloride was recovered by distillation.[12] Approximately 15 mL of carbon tetrachloride (dried over 4A molecular sieves) was added and distilled; this operation was repeated. Azidotrimethylsilane (Aldrich, 6.50 mL, 49.0 mmol) was added, and the mixture was stirred at room temperature under nitrogen for 2 h (no longer!).[13] (The disappearance of the diacid chloride resonance at δ 4.45 and the appearance of the diacylazide peak at δ 4.27 ppm were followed by ^{1}H NMR analysis of diluted aliquots.) Approximately 80 mL of ethanol-free chloroform was added, and half of it was slowly distilled. Another 40 mL of the ethanol-free chloroform was added, and again half of the solution was distilled. The solvent and excess azidosilane were removed in vacuo. The residual yellow solid was sublimed (oil bath at 70–110 °C/0.3 Torr) to give 1.74 g (78%) of snow-white 1,4-diisocyanatocubane: mp 113–115 °C; ^{1}H NMR δ 3.98 (s, 6 H); ^{13}C NMR δ 124.1, 66.8, 49.7; IR (CCl_4) ν 3005, 2256, 1258, 1093 cm^{-1}. The material is sensitive to moisture but can be stored cold under nitrogen without deterioration for at least 1 month.

1,4-Dinitrocubane. 1,4-Diisocyanatocubane (1.30 g, 7.0 mmol) was added with stirring to a mixture of 1 L of 0.072 M dimethyldioxirane (72 mmol) in acetone and 175 mL of distilled water. The solution was stirred at room temperature in the dark under nitrogen for 1.5 h. (The progress of the reaction was followed by GC: $^1/_4$ in. × 6 ft glass column with 2% OV-225 on 80–100 mesh Chromosorb G-HP column; 23 mL/min flow; start at 140 °C, then 20 °C/min to 230 °C; retention times: diisocyanate, 2.4 min; dinitrocubane, 6.0 min.) The acetone was removed in vacuo (bath temperature 27 °C), leaving a white solid and some water. The solid was collected and crystallized from benzene (two crops) to give 1.15 g (85%) of snow-white 1,4-dinitrocubane: mp 260 °C dec; ^{1}H NMR δ 4.67 (s); ^{13}C NMR δ 86.3, 49.8; IR (KBr) ν 1510, 1372, 1358, 1194, 950, 811 cm^{-1}; MS (CI, isobutane), *m/e* (relative intensity) 195 (17), 118 (84), 102 (100), 90 (84).

Acknowledgment. This work was supported by the U.S. Army Research, Development and Engineering Center (via Geo-Centers, Inc.) and the Office of Naval Research. The National Science Foundation and the National Institutes of Health, the latter through The University of Chicago Cancer Research Center (CA 14599), contributed substantially to the departmental instrument facility. The principal investigator thanks the Alexander von Humboldt Foundation for a U.S. Senior Scientist Award during whose tenure this paper was drafted at Universität Köln, FRG, a very gracious host institution.

(12) A heating mantle should not be used; overheating and runaway reactions are possible. Use a temperature-controlled oil bath. The same recommendation applies to all work with the highly strained cubane system.

(13) If crystallization occurs, dilute immediately with chloroform.

Synthetic Approaches toward Mitomycins: Construction of *p*-Quinone Moiety on 1-Benzazocine Derivative

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Mitomycins[1] are an important class of antitumor antibiotics among which mitomycin C (MMC)[2] has been used in the treatment of various neoplastic diseases.[3] Although numerous synthetic studies[4] toward MMC have been carried out since its structural elucidation,[5] only Kishi[6] and Fukuyama[7] have achieved total syntheses of natural mitomycins.

In the course of our synthetic work related to MMC, a new reaction named criss-cross annulation was discovered[8] and applied to the synthesis of various natural products.[9] The reaction could be controlled to give benzazocine derivatives (**2**, **3**), which are key intermediates for our synthetic plan shown in Scheme I. In the present paper, we disclose the X-ray crystallographic analysis of the conformational isomers of **8A** and **8B** and an efficient synthesis of proposed MMC intermediate **12** by taking advantage of the reactivity difference of the conformers.

Hydrogenolysis of **2**[10] afforded primary amine **4** in 96% yield, which was oxidized with $Pb(OAc)_4$ (2.2 mol equiv) in CH_2Cl_2 to give *o*-quinone imide **5**. Hydrolysis of crude **5**, followed by hydrogenation gave catechol **7** in 48% overall yield. Direct ketalization[11] of **7** gave **8A** in up to 50% yield together with a significant amount of a byproduct. In an alternative preparation of **8**, catechol **7** was first converted to the corresponding benzyl ether. Under these conditions, the products were obtained as a 1:1 mixture of conformational isomers. Ketalization of this mixture under the same conditions as described above afforded smoothly the desired ketal **9** in 86% yield from **7** as a mixture of the conformers **9A** and **9B** (Scheme II). Since isomer **9A** slowly isomerized to **9B** even at room temperature, the ratio of **9A** and **9B** was different in every experiment (**9A**:**9B** = 1:3 ~1:10). Debenzylation of this mixture provided **8A** and **8B** in the same ratio as **9** in 85% yield. The conformational isomers (**8A** and **8B**) were easily separated by column chromatography.

In a previous paper,[12] the isolation of the conformational isomers of **3** (**3A**,**B**) was reported. Spectral data of **8A** and **8B** are parallel with those of **3A** and **3B**, respectively. Single X-ray crystallographic analysis[13] of **8A** and **8B** (Figure 1) showed that the conformation of both isomers is a twist-boat-chair form, in which the only difference between the structures is the stereochemistry of C-6 methyl group, which is pseudoequatorial in **8A** and pseudoaxial in **8B**. Isomerization of **8B** in benzene at reflux temperature for 42 h provided the thermodynamically more stable **8A** in 97% yield. The greater stability of **9B** is attributed to the severe steric interactions between C-7 benzyloxy and C-6 methyl groups in **9A**. Since **8A** and **8B** were not equilibrated at room temperature, debenzylation of a mixture of **9A** and **9B** afforded **8A** and **8B** in the same

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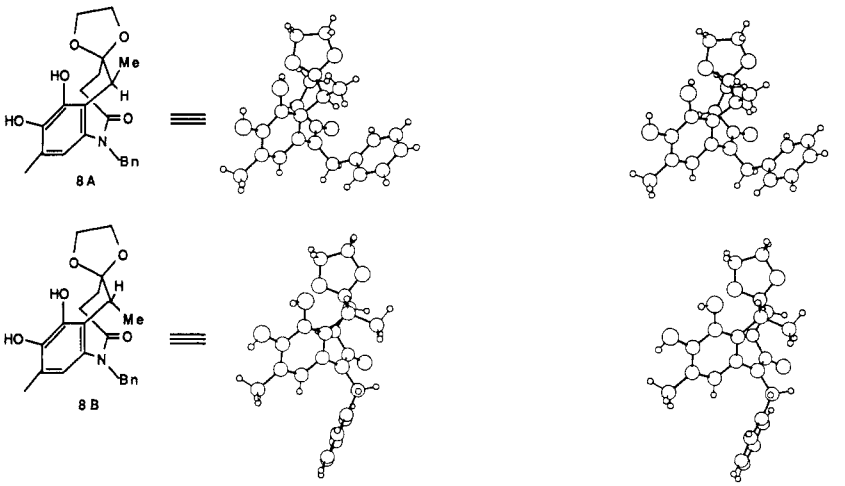
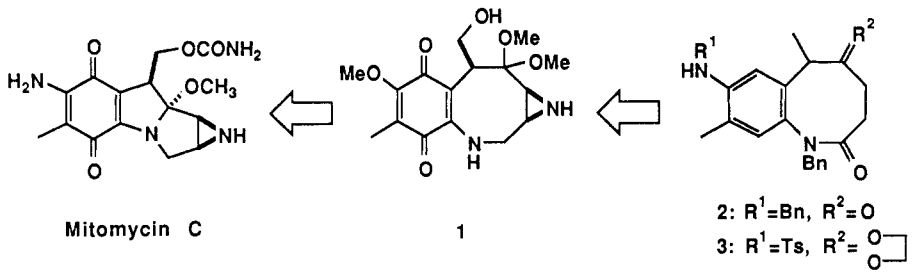


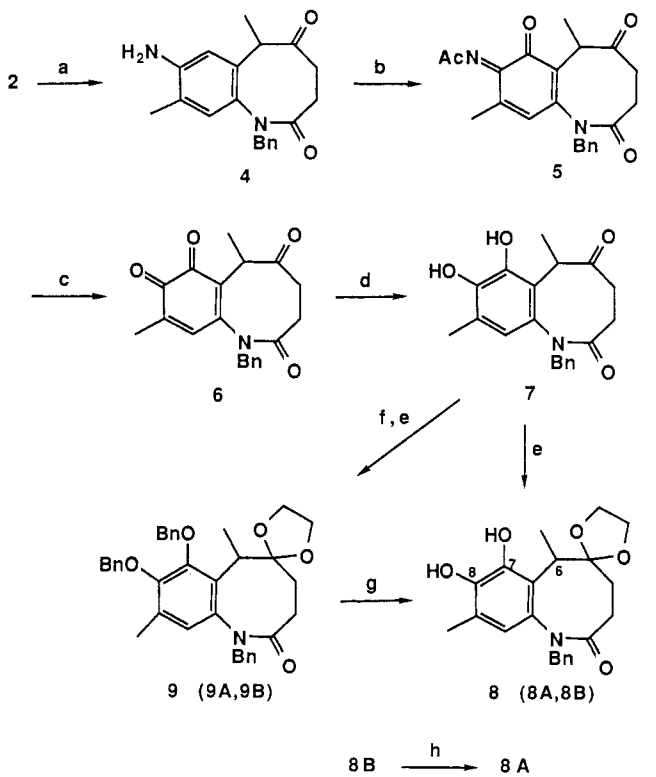
Figure 1.

Scheme I



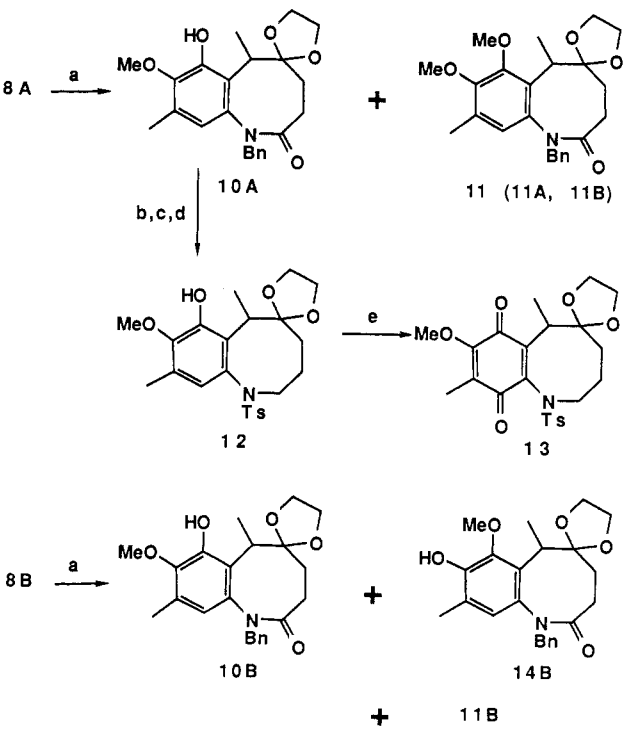
Mitomycin C 1 2: R^1=Bn, R^2=O 3: R^1=Ts, R^2=O,O

Scheme II[a]



[a] (a) 20% $Pd(OH)_2$-C/H_2, AcOEt; (b) $Pb(OAc)_4$ (2.2 equiv), CH_2Cl_2, 0 °C, 20 min; (c) 60% $HClO_4$:THF:CH_2Cl_2 = 1:6:6, 0 °C, 5 min; (d) 10% Pd-C/H_2, AcOEt; (e) TMSCl, $HOCH_2CH_2OH$, MeOH, CH_2Cl_2; (f) BnBr, K_2CO_3, acetone, 18-crown-6, reflux, 2.5 h; (g) 10% Pd-C/H_2, THF; (h) C_6H_6, reflux.

Scheme III[a]



[a] (a) Me_2SO_4, K_2CO_3, $CHCl_3$, room temperature; (b) $LiAlH_4$, THF, room temperature, 1 h; (c) 20% $Pd(OH)_2$-C/H_2, MeOH, 5 h; (d) TsCl, Py, CH_2Cl_2; (e) salcomine/O_2, DMF, room temperature, 3 h.

ratio. These results are quite interesting from the viewpoint of the synthetic studies of mitomycins.

It is expected that the regioselective methylation of phenol group at C-8 position of conformer **8A** would be

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possible because the methyl group at C-6 position blocks the phenol hydroxyl group at C-7. On the other hand, no selectivity would be expected with conformer **8B**. In fact, methylation of **8A** afforded **10A**, **11A**, and **11B** in 70%, 3%, and 8% yields, respectively (Scheme III). The dimethylated minor product **11A** isomerized partially to **11B** under the reaction conditions as a consequence of the steric repulsion between C-6 methyl and C-7 methoxy groups. On the other hand, methylation of **8B** under the same conditions as described above afforded **10B**, **14B**, and **11B** in 40%, 28%, and 7% yields, respectively. Under these conditions, the conformation of the products remained unchanged.

Lithium aluminun hydride reduction of lactam **10A** followed by hydrogenolysis[14] provided an unstable amino phenol, which was directly tosylated to give **12** in 75% overall yield. Bis(salicylidene)ethylenediiminocobalt(II) (salcomine)[15] oxidation of **12** in DMF smoothly provided *p*-quinone **13** as yellow crystals in 94% yield.

In summary, the structure of the conformational isomers **8A** and **8B** was elucidated. An efficient synthesis of **13**, a potential intermediate for mitomycin synthesis, has been accomplished from **2** by exploiting the reactivity difference between the conformational isomers **8A** and **8B**. Further studies aimed at attaching the aziridine ring and other functionality of **1** are in progress.

Experimental Section

Melting points are uncorrected. ^1H NMR spectra were determined (100 or 270 MHz). $CDCl_3$ was used as solvent for NMR spectra unless noted otherwise. All solvents were reagent grade unless otherwise stated. Dry solvents were dried immediately before use. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Methylene chloride was distilled from potassium hydride. Thin-layer chromatography (TLC) was carried out on Merck glass plates precoated with silica gel 60 PF_{254}. Column chromatographic separations were performed on silica gel (Merck silica gel 60, 70–325 mesh ASTM).

8-Amino-1-benzyl-6,9-dimethyl-2,5-dioxo-1,2,3,4,5,6-hexahydro-1-benzazocine (4). A solution of **2** (5.00 g, 12.1 mmol) in 170 mL of ethyl acetate was hydrogenated over 20% $Pd(OH)_2$–C (500 mg) at atmospheric pressure for 24 h. The catalyst was removed by filtration through Celite. Evaporation of the solvent in vacuo gave a caramel residue, which was crystallized from ether to afford 3.74 g (96%) of colorless prisms: mp 189–190 °C; IR (Nujol) 3430, 3350, 1705, 1695, 1625 cm^{-1}; 100-MHz NMR δ 0.80 (d, 3 H, J = 6.8 Hz), 2.20 (s, 3 H), 2.2–2.9 (m, 4 H), 3.27 (q, 1 H, J = 6.8 Hz), 3.7–4.7 (br m, 2 H), 4.96 (AB q, 2 H, J = 13.4 Hz), 6.51 (s, 1 H), 6.98 (s, 1 H), 7.22 (s, 5 H). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.59; H, 6.98; N, 8.60.

8-(Acetylimino)-1-benzyl-6,9-dimethyl-2,5,7-trioxo-1,2,3,4,5,6,7,8-octahydro-1-benzazocine (5). To a suspension of $Pb(OAc)_4$ (1.08 g, 2.2 mmol) in 5 mL of dry CH_2Cl_2 was added dropwise a solution of **4** (322 mg, 1.00 mmol) in 10 mL of dry CH_2Cl_2 at 0 °C. After being stirred for 15 min at 0 °C, the reaction was quenched by the addition of 0.5 mL of ethylene glycol. The reaction mixture was successively washed with water and saturated $NaHCO_3$ and dried over anhydrous Na_2SO_4. After removal of the solvent, the orange residue was purified by chromatography. Elution with a 2:1 mixture of ethyl acetate and hexane gave 150 mg (40%) of orange crystals: mp 177–179 °C; IR (Nujol) 1710, 1670 cm^{-1}; 100-MHz NMR δ 0.75 (d, 3 H, J = 5.6 Hz), 2.18 (d, 3 H, J = 0.8 Hz), 2.27 (s, 3 H), 2.4–2.8 (m, 4 H), 2.98 (q, 1 H, J = 5.6 Hz), 4.89 (AB q, 2 H, J = 13.9 Hz), 6.72 (br s, 1 H), 7.33 (s, 5 H). Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.83; H, 5.94; N, 7.15.

1-Benzyl-6,9-dimethyl-2,5,7,8-tetraoxo-1,2,3,4,5,6,7,8-octahydro-1-benzazocine (6). A solution of **5** (916 mg, 0.423 mmol) in 4 mL of THF and 0.2 mL of 60% perchloric acid was stirred at 0 °C for 10 min. The reaction mixture was diluted with ethyl acetate and successively washed with water, saturated $NaHCO_3$, and brine. The extract was dried over anhydrous Na_2SO_4. After removal of the solvent, 136 mg (95%) of pure *o*-quinone **6** was obtained as orange crystals: mp 165–170 °C; IR (Nujol) 1710, 1680, 1660 cm^{-1}; 100-MHz NMR δ 0.81 (d, 3 H, J = 6.6 Hz), 2.08 (d, 3 H, J = 1.7 Hz), 2.4-2.8 (m, 4 H), 2.98 (q, 1 H, J = 6.6 Hz), 4.95 (AB q, 2 H, J = 14.4 Hz), 6.93 (q, 1 H, J = 1.7 Hz), 7.34 (s, 5 H). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.36; H, 5.63; N, 4.00.

1-Benzyl-7,8-dihydroxy-6,9-dimethyl-2,5-dioxo-1,2,3,4,5,6-hexahydro-1-benzazocine (7). A solution of **6** (130 mg, 0.385 mmol) in 4 mL of ethyl acetate was hydrogenated over 10% Pd–C (5 mg) for 0.5 h. The catalyst was removed by filtration. The filtrate was concentrated to give a pale yellowish oil, which was crystallized from ethyl acetate to give 129 mg (98%) of catechol **7** as colorless prisms: mp 232–234 °C; IR (Nujol) 3450, 1710, 1610 cm^{-1}; 270-MHz NMR δ 0.82 (d, 3 H, J = 7.0 Hz), 2.27 (d, 3 H, J = 0.7 Hz), 2.0–2.5 (m, 3 H), 2.7–2.9 (m, 1 H), 3.47 (q, 1 H, J = 7.0 Hz), 5.00 (AB q, 2 H, J = 13.4 Hz), 5.73 (br s, 1 H), 6.78 (q, 1 H, J = 0.7 Hz), 7.25 (s, 5 H). Anal. Calcd for $C_{22}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.80; H, 6.31; N, 4.02.

1-Benzyl-7,8-dihydroxy-6,9-dimethyl-5,5-(ethylenedioxy)-2-oxo-1,2,3,4,5,6-hexahydro-1-benzazocine (8A). To a solution of **7** (500 mg, 1.47 mmol) in 2 mL of dry CH_2Cl_2, 2 mL of methanol, and ethylene glycol (822 μL, 14.7 mmol) was added dropwise chlorotrimethylsilane (746 μL, 5.88 mmol) at 0 °C. After the addition was complete, the solution was warmed to room temperature and stirred for 20 h. The solution was diluted with

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(13) Crystal data for **8A**: $C_{22}H_{25}NO_5$; M_r 383.45; a = 11.239 (2), b = 17.932 (3), and c = 9.424 (1) Å; U = 1899.4 (5) Å^3; $P2_12_12_1$; Z = 4; D_m = 1.341 g cm^{-3}; λ (Cu Kα) = 1.5418 Å. A total of 1861 unique reflections (2θ < 130) were measured, of which 1734 with $|F| \geq 2.67\sigma(F)$ were observed. No absorption corrections applied (μ = 17.8 cm^{-1}, crystal size 0.2 × 0.4 × 0.4 mm). Direct method with MULTAN80, block-diagonal-matrix least-squares method on F heavy atoms anisotropic, H atoms isotropic, seven refrections omitted in last cycles, final R = 0.048, $1/\sqrt{w} = \sigma(F)$, w_R = 0.059, $(\Delta\rho)_{max}$ = 0.05. Crystal data for **8B**: $C_{22}H_{25}NO_5$; M_r = 383.45; a = 14.804 (2), b = 9.566 (2), and c = 14.233 (2) Å; β = 103.33 (1)°; U = 1961.2 (5) Å^3; $P2_1/n$; Z = 4; D_m = 1.299 g cm^{-3}; λ (Cu Kα) = 1.5418 Å. A total of 3336 unique reflections (2θ < 130) were measured, of which 2848 with $|F| \geq 2.67\sigma(F)$ were observed. No absorption corrections applied (μ = 17.2 cm^{-1}, crystal size 0.2 × 0.2 × 0.4 mm). Direct method with MULTAN80, block-diagonal-matrix least-squares method on F heavy atoms anisotropic, H atoms isotropic, 36 refrections omitted in last cycles, final R = 0.087, $1/\sqrt{w} = \sigma(F)$, w_R = 0.097, $(\Delta\rho)_{max}$ = 0.12.
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ethyl acetate and successively washed with water, saturated $NaHCO_3$, and brine before being dried over anhydrous Na_2SO_4. The crude product was purified by chromatography with a 1:1 mixture of ethyl acetate and hexane as eluent afforded 280 mg (50%) of **8A** as colorless crystals, which was recrystallized from ethanol–CH_2Cl_2: mp 151–153 °C; IR ($CHCl_3$) 3550, 3300, 1640 cm^{-1}; 270-MHz NMR δ 0.79 (d, 3 H, J = 7.3 Hz), 1.6–2.4 (m, 4 h), 2.26 (d, 3 H, J = 0.7 Hz), 2.62 (q, 1 H, J = 7.3 Hz), 3.8–4.2 (m, 4 H), 4.99 (AB q, 2 H, J = 13.7 Hz), 5.86 (br, 1 H), 6.69 (br, 1 H), 7.21 (s, 5 H), 7.66 (s, 1 H). Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.79; H, 6.53; N, 3.59.

1-Benzyl-7,8-bis(benzyloxy)-6,9-dimethyl-5,5-(ethylenedioxy)-2-oxo-1,2,3,4,5,6-hexahydro-1-benzazocine (9A and 9B). To a solution of **7** (7.88 g, 23.0 mmol) in 120 mL of acetone was added anhydrous K_2CO_3 (9.50 g, 69 mmol), benzyl bromide (13.6 mL, 115 mmol), and 18-crown-6 (100 mg). The mixture was refluxed under argon for 2.5 h. After being cooled, the reaction mixture was concentrated in vacuo and the product was extracted with ethyl acetate. The extracts were washed with water and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by chromatography. Elution with a 1:2 mixture of ethyl acetate and hexane provided 11.1 g (92%) of the product as a mixture of the conformational isomers (1:1). This material was dissolved in 100 mL of dry CH_2Cl_2, 50 mL of methanol, and ethylene glycol (24 mL, 0.426 mol). To this solution was added dropwise chlorotrimethylsilane (27.0 mL, 0.213 mol) at 0 °C. This mixture was stirred at room temperature for 4 h and was diluted with CH_2Cl_2. The organic layer was successively washed with water, saturated $NaHCO_3$, and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified chormatography with 1:2 mixture of ethyl acetate and hexane as eluent, affording 11.1 g (93%) of **9** as a mixture of the conformational isomers (**9A**:**9B** = 1:3). Analytically pure samples of the isomers were obtained by rechromatography with the same solvent system. **9A**: colorless oil; IR ($CHCl_3$) 1640 cm^{-1}; 270-MHz NMR δ 0.93 (d, 3 H, J = 7.7 Hz), 1.7–2.5 (m, 4 H), 2.09 (s, 3 H), 2.69 (q, 1 H, J =7.7 Hz), 3.5-4.2 (m, 4 H), 4.93 (AB q, 2 H, J = 13.6 Hz), 4.96 (s, 2 H), 5.15 (AB q, 2 H, J = 11.7 Hz), 6.77 (s, 1 H), 7.0–7.5 (m, 15 H); high-resolution mass spectrum calcd for $C_{36}H_{37}NO_5$ 563.2672, found 563.2683. **9B**: colorless crystals; mp 122–123 °C (from ether); IR ($CHCl_3$) 1640 cm^{-1}; 270-MHz NMR δ 1.01 (d, 3 H, J = 7.7 Hz), 1.98 (s, 3 H), 2.1–2.4 (m, 4 H), 3.6–4.1 (m, 5 H), 4.74 (AB q, 2 H, J = 14.7 Hz), 5.04 (AB q, 2 H, J = 11.4 Hz), 5.04 (AB q, 2 H, J = 11.0 Hz), 6.37 (s, 1 H), 7.2–7.5 (m, 15 H). Anal. Calcd for $C_{36}H_{37}NO_5$: C, 76.71; H, 6.62; N, 2.48. Found: C, 76.70; H, 6.59; N, 2.45.

1-Benzyl-7,8-dihydroxy-6,9-dimethyl-5,5-(ethylenedioxy)-2-oxo-1,2,3,4,5,6-hexahydro-1-benzazocine (8A and 8B). A mixture of **9A** and **9B** (1:3) (124 mg, 0.22 mmol) was dissolved in 2 mL of dry THF and hydrogenated over 10% Pd–C (57 mg) for 14 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to give white solid, which was purified by chromatography. Elution with a 1:5 mixture of ethyl acetate and CH_2Cl_2 gave 18 mg (21%) of **8A** and 61 mg (73%) of **8B**. Recrystallization of the latter from acetone–hexane gave the analytical sample. **8B**: mp 236–238 °C; IR ($CHCl_3$) 3550, 3350, 1640 cm^{-1}; 270-MHz NMR δ 1.19 (d, 3 H, J = 7.6 Hz), 1.8–2.4 (m, 4 H), 2.10 (d, 3 H, J = 0.7 Hz), 3.55 (q, 1 H, J = 7.6 Hz), 3.8–4.2 (m, 4 H), 4.85 (AB q, 2 H, J = 14.9 Hz), 5.77 (br, 1 H), 6.39 (br, 1 H), 6.71 (s, 1 H), 7.34 (s, 5 H). Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.78, H, 6.68; N, 3.73.

Thermal Isomerization of 8B to 8A. A sample of **8B** (19.4 g, 50.7 mmol) was dissolved in 700 mL of dry benzene, and the solution was heated at reflux temperature for 42 h. The less soluble isomer **8A** gradually precipitated. After being cooled, the precipitate was collected by filtration to give 18.9 g (97%) of pure **8A**, which was identical with an authentic specimen.

Methylation of 8A. To a solution of **8A** (500 mg, 1.31 mmol) in 15 mL of chloroform was added dimethyl sulfate (127 μL, 1.34 mmol), anhydrous K_2CO_3 (360 mg, 2.62 mmol), and 18-crown-6 (10 mg, 0.038 mmol). After being stirred at room temperature for 96 h, the reaction mixture was acidified by 10% HCl and diluted with CH_2Cl_2. The organic layer was successively washed with water, saturated $NaHCO_3$, and brine. The extract was dried over anhydrous Na_2SO_4 and evaporated. Purification of the residue by chromatography with ether–hexane (1:1) as eluent gave 361 mg (70%) of **10A** as colorless crystals [mp 167–169 °C; IR ($CHCl_3$) 3270, 1640 cm^{-1}; 270-MHz NMR δ 0.85 (d, 3 H, J = 7.1 Hz), 1.8–2.4 (m, 4 H), 2.27 (d, 3 H, J = 0.7 Hz), 2.66 (q, 1 H, J = 7.1 Hz), 3.6–4.4 (m, 4 H), 3.83 (s, 3 H), 4.98 (AB q, 2 H, J = 14.0 Hz), 6.64 (q, 1 H, J = 0.7 Hz), 7.22 (s, 5 H), 7.64 (s, 1 H). Anal. Calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.54; H, 6.88; H, 3.61] and and unseparable mixture of **11A** and **11B** (61 mg, 11%). The ratio of the isomers (**11A**:**11B** = 1:2.7) was determined by NMR analysis. An aliquot of this mixture was separated by Lobar prepacked column [size A (240-10) LiChroprep Si 60 (40–63 μm)] with hexane–ether (1:2) to give **11A** [IR ($CHCl_3$) 1640 cm^{-1}; 100-MHz NMR δ 0.88 (d, 3 H, J = 7.3 Hz), 1.8–2.4 (m, 4 H), 2.24 (d, 3 H, J = 0.7 Hz), 2.67 (q, 1 H, J = 7.3 Hz), 3.77 (s, 3 H), 3.77 (s, 3 H), 3.6–4.2 (m, 4 H), 4.91 (AB q, 2 H, J = 13.4 Hz), 6.75 (q, 1 H, J = 0.7 Hz), 7.17 (s, 2 H), 7.19 (s, 3 H); high-resolution mass spectrum calcd for $C_{24}H_{29}NO_5$ 411.2046, found 411.2075] and **11B**, which was recrystallized from CH_2Cl_2–ether to give colorless plates: mp 142–143 °C; IR ($CHCl_3$) 1635 cm^{-1}; 100-MHz NMR δ 1.16 (d, 3 H, J = 7.8 Hz), 2.0–2.4 (m, 4 H), 2.06 (d, 3 H, J = 0.7 Hz), 3.81 (s, 3 H), 3.84 (s, 3 H), 3.6–4.2 (m, 6 H), 5.52 (d, 1 H, J = 14.4 Hz), 6.36 (q, 1 H, J = 0.7 Hz), 7.32 (s, 5 H). Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.01; N, 3.40. Found: C, 69.84; H, 7.09; N, 3.44.

Methylation of 8B. To a solution of catechol **8B** (500 mg, 1.31 mmol) in 15 mL of chloroform was added dimethyl sulfate (127 μL, 1.34 mmol), anhydrous K_2CO_3 (360 mg, 2.62 mmol), and 18-crown-6 (10 mg, 0.038 mmol). After the mixture was stirred at room temperature for 45 h, the reaction was stopped and the product was isolated as described above for **8A**. The residue was purified by chromatography with a 1:1 mixture of ether and hexane as eluent, providing an unseparable mixture of **10B** and **14B** (352 mg, 68%, **10B**:**14B** = 7:5) and **11B** (36 mg, 7%), the last of which was identified by comparison with an authentic sample. Separation of **10B** and **14B** was performed on Lobar prepacked column [size A (240-10) LiChroprep Si 60 (40–63 μm)] with hexane–acetone (4:1). **10B**: colorless oil; IR ($CHCl_3$) 3370, 1640 cm^{-1}; 100-MHz NMR δ 1.16 (d, 3 H, J = 7.6 Hz), 1.8–2.5 (m, 4 H), 2.11 (d, 3 H, J = 0.7 Hz), 3.76 (q, 1 H, J = 7.6 Hz), 3.7–4.3 (m, 4 H), 3.80 (s, 3 H), 4.77 (AB q, 2 H, J = 14.7 Hz), 6.22 (q, 1 H, J = 0.7 Hz), 6.27 (s, 1 H), 7.32 (s, 5 H); high-resolution mass spectrum calcd for $C_{23}H_{27}NO_5$ 397.1889, found 397.1894. **14B**: colorless oil; IR ($CHCl_3$) 3350, 1640 cm^{-1}; 100-MHz NMR δ 1.18 (d, 3 H, J = 7.8 Hz), 1.8–2.3 (m, 4 H), 2.07 (d, 3 H, J = 0.7 Hz), 3.52 (q, 1 H, J = 7.8 Hz), 3.7–4.2 (m, 5 H), 5.49 (d, 1 H, J = 14.4 Hz), 5.65 (br, 1 H), 6.37 (q, 1 H, J = 0.7 Hz), 7.31 (s, 5 H); high-resolution mass spectrum calcd for $C_{23}H_{27}NO_5$ 397.1889, found 397.1867.

6,9-Dimethyl-5,5-(ethylenedioxy)-7-hydroxy-8-methoxy-1-(*p*-tolylsulfonyl)-1,2,3,4,5,6-hexahydro-1-benzazocine (12). To a suspension of lithium aluminum hydride (1.25 g, 33.0 mmol) in 20 mL of dry THF was added dropwise a solution of **10A** (3.97 g, 10.0 mmol) in 50 mL of THF at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The excess hydride was carefully decomposed by $Na_2SO_4 \cdot 10H_2O$ at 0 °C, and the mixture was stirred at room temperature for 2 h to complete the reaction. The precipitate was removed by filtration and washed with ethyl acetate. The filtrate and washings were combined and concentrated in vacuo to give a colorless oil. The crude amine was dissolved in 200 mL of methanol and hydrogenated over 20% $Pd(OH)_2$–C (400 mg) at room temperature and ordinary pressure for 5 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give 2.76 g of an air-sensitive aminophenol as a light violet oil. To a solution of the crude material in 50 mL of CH_2Cl_2 and 4 mL of pyridine was added by portions *p*-toluenesulfonyl chloride (1.90 g, 10.0 mmol). The mixture was stirred at room temperature for 40 h. The reaction mixture was neutralized by adding 10% hydrochloric acid at 0 °C. The organic layer was successively washed with water, saturated $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by chromatography with ether–hexane (2:1) as eluent to give 3.37 g (75% overall yield) of **12** as colorless prisms: mp 207–208 °C; IR ($CHCl_3$) 3300, 1340, 1160 cm^{-1}; 270-MHz NMR δ 1.25 (d, 3 H, J = 7.1 Hz), 2.12 (d, 3 H, J = 0.7 Hz), 2.44 (s, 3 H), 1.6–2.5 (m, 4 H), 2.5–3.0 (m, 1 H), 3.84 (s, 3 H), 3.7–4.5 (m, 6 H), 6.33 (q, 1 H, J = 0.7 Hz),

7.72 (s, 1 H), 7.30 (d, 2 H, J = 8.3 Hz), 7.72 (d, 2 H, J = 8.3 Hz). Anal. Calcd for $C_{23}H_{29}NO_6S$: C, 61.73; H, 6.53; N, 3.13. Found: C, 61.81; H, 6.46; N, 2.93.

6,9-Dimethyl-7,10-dioxo-5,5-(ethylenedioxy)-8-methoxy-1-(*p*-tolylsulfonyl)-1,2,3,4,5,6,7,10-octahydro-1-benzazocine (13). To a solution of **12** (31 mg, 0.069 mmol) in 2 mL of dry DMF was added bis(salicylidene)ethylenediiminocobalt(II) (11 mg, 0.035 mmol). The dark suspension was stirred under an oxygen atmosphere for 3 h. The mixture was filtered through Celite to remove the catalyst, and the catalyst was washed with ethyl acetate. The filtrate and washings were combined, washed with water, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by chromatography with a 1:2 mixture of ethyl acetate and hexane as eluent to provide 30 mg (94%) of **13** as bright yellow crystals: mp 175–177 °C; IR ($CHCl_3$) 1660 cm^{-1}; 270-MHz NMR δ 1.60 (d, 3 H, J = 7.7 Hz), 1.6–1.8 (m, 1 H), 1.87 (s, 3 H), 2.1–2.3 (m, 1 H), 2.46 (s, 3 H), 3.12 (ddd, 1 H, J = 10.6, 4.4, 1.5 Hz), 3.6–4.2 (m, 8 H), 4.01 (s, 3 H), 7.33 (d, 2 H, J = 8.4 Hz), 7.64 (d, 2 H, J = 8.4 Hz). Anal. Calcd for $C_{23}H_{27}NO_7S$: C, 59.86; H, 5.90; N, 3.03. Found: C, 59.87; H, 5.95; N, 2.83.

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Registry No. **2**, 88609-66-9; **4**, 116437-99-1; **5**, 116438-00-7; **6**, 116438-01-8; **7**, 116438-02-9; **7** dibenzyl ether, 116438-04-1; **8**, 116438-03-0; **9**, 116438-05-2; **10**, 116438-06-3; **10** (debenzyl derivative), 116438-08-5; **10** (debenzyl deoxo derivative), 116438-09-6; **11**, 116438-07-4; **12**, 116438-10-9; **13**, 116438-11-0; **14**, 116438-12-1; mitomycin, 1404-00-8.

Supplementary Material Available: Crystal data for **8A,B**, the atomic numbering system used in the X-ray analysis, and tables of fractional coordinates, isotropic temperature factors, bond lengths, and bond angles for **8A,B** (6 pages). Ordering information is given on any current masthead page.

8-Ethyl-1-methoxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one *C*-Glycosides by Acid-Catalyzed Glycosylation

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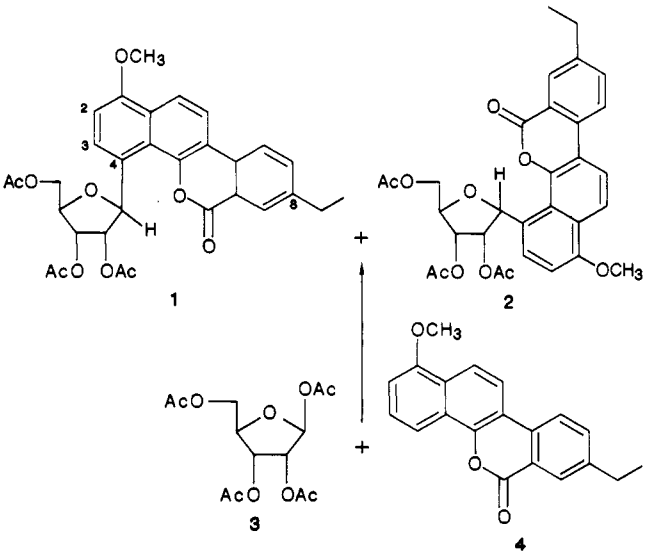
We recently reported[1,2] the first synthesis of *C*-glycosides[3] structurally related to the benzo[*d*]naphtho-[1,2-*b*]pyran-6-one *C*-glycoside antibiotics ravidomycin,[4] the gilvocarcins[5] (toromycin[6]), and the chrysomycins[7] (virenomycin,[8] the albacarcins[9]). The key reaction in these syntheses[1,2] was a palladium-mediated coupling[10] of a glycal (1,2-unsaturated carbohydrate) with a tri-*n*-butylstannyl derivative of the tetracyclic aglycone, which gives rise to 2′-deoxyfuranosyl or 2′-deoxypyranosyl *C*-glycosides. We now report a new, complementary procedure, which was used for preparation of 8-ethyl-1-methoxybenzo[*d*]-naphtho[1,2-*b*]pyran-6-one ribofuranosyl *C*-glycosides **1** and **2**. This procedure involves the direct formation of the *C*-glycosides by Lewis acid-catalyzed condensation of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose[11] (**3**) with aglycon **4**.[12]



The aglycon 8-ethyl-1-methoxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one[12] (**4**) was prepared by a sequence developed by Chebaane et al.[13] involving acid-catalyzed condensation of 1,5-naphthalenediol (**5**) with 2-carbethoxy-4-ethylcyclohexanone[14] (**6**) to yield 8-ethyl-1-hydroxy-7,8,9,10-tetrahydrobenzo[*d*]naphtho[1,2-*b*]pyran-6-one (**7**). Methylation of the phenolic hydroxyl of **7** (dimethyl sulfate, potassium carbonate) produced **8**; the tetrahydro ring of this intermediate was aromatized with palladium on carbon to yield aglycon **4**.[12]

Treatment of equimolar portions of **4** and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose[11] (**3**) in dry dichloroethane solution with stannic chloride at room temperature effected condensation with elimination of acetic acid to produce a 1:1 mixture of β- and α-*C*-glycosides **1** and **2** in 60% isolated yield. The *C*-glycoside anomers were separated by chromatography (silica gel) and characterized spectroscopically. Mass spectra of each isolated compound exhibited a molecular ion at m/z 562, establishing their isomeric nature and compositions.

The critical structural assignments of (a) the site of

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