tosylhydrazine (1.73 g, 0.0093 mol) in methanol (8 mL) at room temperature for 2 h was concentrated, chromatographed on silica gel with 1:1 chloroform/hexane as the developer, and then recrystallized from methylene chloride/hexane to yield **6a** (2.21 g, 80%) as light yellow crystals: mp 114–116 °C; ^{1}H NMR (DMSO-d_6) δ 8.42 (s, 1 H, H at C-9), 7.13–7.94 (m, 5 H, aromatic *H* and N*H*), 6.10–5.64 (m, 7 H, cycloocta-*HC*=C*H*), and 2.40 (s, 3 H, CH_3). Anal. Calcd for $C_{16}H_{16}N_2SO_2$: C, 63.97; H, 5.37; N, 9.32. Found: C, 64.30; H, 5.46; N, 9.45.

1*H*-Cyclooctapyrazole (11a). Sodium hydride (0.127 g of 57% NaH in mineral oil, 0.0032 mol) was added slowly to **6a** (0.87 g, 0.0029 mol) in methylene chloride (20 mL) at 0 °C. After evolution of hydrogen ceased, the solvent was stripped at reduced pressure leaving sodium salt **7a** as a white powder coated on the flask wall. The flask was attached via an adapter (partially packed with glass wool to prevent spatter entrainment) to a vacuum system. Upon decomposing **7a** at 280 °C (0.3 Torr), a yellow liquid collected in the adapter and on the glass wool. The condensate solidified on cooling and was dissolved in methylene chloride. Concentration and recrystallization of the product from methylene chloride/hexane yielded yellow needles of **11a** (0.32 g, 76%): mp 103–105 °C; IR (KBr) 3270 cm^{-1} (N–H stretch); ^{1}H NMR ($CDCl_3$) δ 8.4 (s, 1 H, N*H*, the resonance is washed out by D_2O), 7.20 (s, 1 H, H at C-9) and 6.20–5.76 (m, 6 H, cycloocta-HC=C*H*); UV λ_{max} (95% C_2H_5OH) 209 (ϵ 6,040), 226 (9,760), 264 (14,180), 271 (13,960), and 283 (7,750); mass spectrum, *m/e* 144; exact mass calcd 144.0688, found 144.0687. Anal. Calcd for $C_9H_8N_2$: C, 74.97; H, 5.91. Found: C, 74.97; H, 5.80.

1,3,5,7-Cyclooctatetraen-1-yl Methyl Ketone *p*-Tosylhydrazone (6b). A solution of **5b** (2.08 g, 14.2 mmol) in absolute methanol (5 mL) was added to a warm mixture of *p*-tosylhydrazine (2.52 g, 14.2 mmol) in methanol (13 mL) containing concentrated hydrochloric acid (1 drop). After ~0.5 h, a yellow precipitate (2.36 g, 53%) of **6b** formed: mp 166–166.5 °C dec; ^{1}H NMR (DMSO-d_6) δ 7.28–7.92 (m, 4 H, aromatic *H*), 5.8 with shoulders at 6.08 and 6.2 (m, 7 H, HC=C*H*), 1.93 (s, 3 H, CH_3); mass spectrum, *m/e* 314.1. Anal. Calcd for $C_{17}H_{18}N_2SO_2$: C, 64.94; H, 5.77; N, 8.91. Found: C, 65.10; H, 5.76; N, 8.99.

3-Methyl-1*H*-cyclooctapyrazole (11b). A solution of **6b** (1.6 g, 5.1 mmol) in methylene chloride (20 mL) was added to a slurry of sodium hydride (57% NaH in mineral oil; 0.22 g, 5.1 mmol; washed well with pentane to remove the mineral oil) in methylene chloride (20 mL). Stirring the mixture at room temperature for 2.5 h and rotary evaporation gave **7b**, a yellow solid (dec ~100 °C). The reactor flask was attached to an adapter, a series of traps, and a vacuum system. Decomposition of **7b** was effected at 285 °C (0.2 Torr). The condensate in the adapter was dissolved in methylene chloride, filtered, concentrated, and recrystallized from hexane/methylene chloride to give **11c** (0.80 g, 99%), a yellow solid: mp 121 °C (from methylene chloride/hexane); IR (KBr) 3170 cm^{-1} (N–H stretch); ^{1}H NMR ($CDCl_3$) δ 12.04 (s, 1 H, N*H*, the absorption disappears in D_2O), 6.2–5.6 (m, 6 H, cycloocta-*HC*=C*H*), and 2.16 (s, 3 H, CH_3); mass spectrum, *m/e* 158.2. Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37. Found: C, 75.48; H, 6.37.

1,3,5,7-Cyclooctatetraen-1-yl Phenyl Ketone *p*-Tosylhydrazone (6c). Reaction of **5c** (1.85 g, 8.93 mmol) and *p*-tosylhydrazine (1.66 g, 8.93 mmole) in methanol (7 mL) containing hydrochloric acid (1 drop) yielded yellow crystals of **6c** (2.63 g, 78%): mp 175 °C (from EtOH, dec); ^{1}H NMR (DMSO-d_6) δ 7.8–6.9 (m, 10 H, aromatic H and NH), 5.82 (m, 7 H, cycloocta-*HC*=C*H*), and 2.45 (s, 3 H, CH_3). Anal. Calcd for $C_{22}H_{20}SO_2N_2$: C, 70.19; H, 5.36; N, 7.44; S, 8.52. Found: C, 70.01; H, 5.40; N, 7.44; S, 8.58.

3-Phenyl-1*H*-cyclooctapyrazole (11c) from 6c. To 6c (1.40 g, 3.72 mmol) in methylene chloride (20 mL) was added sodium hydride (0.16 g of 57% NaH in mineral oil, 3.72 mmol; washed with pentane). After gas evolution ceased, the solvent was rotary evaporated to give **7c**, a yellow solid, mp >265 °C dec. (Acidification of **7c** with hydrochloric acid yielded **6c** quantitatively.) Decomposition of **7c** [340 °C (0.1 Torr)] in the adapter–trap–vacuum system and crystallization of the volatilate from cyclohexane yielded **11c** (0.80 g, 95%): a yellow solid; mp 96–99 °C; IR (KBr) 3230 cm^{-1} (N–H stretch); ^{1}H NMR ($CDCl_3$) δ 10.8 (br s, 1 H, N*H*, there is no N*H* absorption in D_2O), 5.9–5.6 (m, 6 H, cycloocta-*HC*=C*H*), and 7.4–7.2 (m, 5 H, aromatic *H*); mass spectrum, *m/e* 220.1. Anal. Calcd for $C_{15}H_{12}N_2$: C, 81.78; H, 5.50; N, 12.71. Found: C, 81.61; H, 5.58; N, 12.55.

3-Phenyl-1*H*-cyclooctapyrazole (11c) from 14 and Phenyldiazomethane. *n*-Butyllithium (3.4 mL, 1.6 M in hexane, 5.4 mmol) was syringed into a solution of diisopropylamine (0.55 g, 0.54 mmol) and tetrahydrofuran (10 mL) at room temperature. The mixture was cooled to −78 °C and then added to a solution of 1-bromo-1,3,5,7-cyclooctatetraene (**13**; 1.00 g, 5.4 mmol) and phenyldiazomethane (1.0 g, 8.6 mmol) in tetrahydrofuran (25 mL) at −40 °C. The mixture was kept at −40 °C for 1 h, then allowed to warm slowly to room temperature, concentrated at reduced pressure, and diluted with ethyl ether. After the ether solution had been washed with water, dried (Na_2SO_4), and concentrated, the residue was crystallized from hexane to give **11c** (0.71 g, 60%, mp 97–99 °C) identical with that obtained by thermal decomposition of **7c**.

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Registry No. **5a**, 30844-12-3; **5a** (DNPH), 110661-69-3; **5b**, 6004-57-5; **5c**, 6004-58-6; **6a**, 110661-70-6; **6b**, 110661-72-8; **6c**, 110661-75-1; **7a**, 110661-71-7; **7b**, 110661-73-9; **7c**, 110661-76-2; **11a**, 16767-46-7; **11b**, 110661-74-0; **11c**, 110661-77-3; **13**, 7567-22-8; 1,3,5,7-cyclooctatetraene-1-carbonitrile, 37164-17-3; phenyldiazomethane, 766-91-6.

Total Synthesis of 4-Demethoxy-13-dihydro-8-nordaunomycin

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Anthracycline antitumor antibiotics have received considerable attention in recent years.[2] During the course of our work in this area, we desired a synthetic method for the construction of 8-nor analogues. While this work was in progress, alternative syntheses for the 8-nor aglycon were reported.[3,4] Our approach provides a direct and efficient entry into functionalized cyclopent[*b*]anthracenedione ring systems via geminal dialkylation of ethyl acetoacetate with bis(bromomethyl)anthraquinone. Subsequent functional group manipulation and osmium tetraoxide hydroxylation resulted in the desired protected *cis*-diol aglycon. Glycosidation followed by deprotection afforded the target compound.

Dimethylquinizarin **1**[5] served as starting material and was converted to dibromide **3** according to modified literature procedures[5,6] (Scheme I). Geminal dialkylation of ethyl acetoacetate with dibromide **3** (LDA, THF, room temperature) afforded the key intermediate cyclopent[*b*]anthracenedione **4** (40–45%) accompanied by bis-alkylated diketo diester **15** (10–15%). Saponification fol-

(1) Analytical Bio-Chemistry Laboratories, P. O. Box 1097, Columbia, MO 65205.

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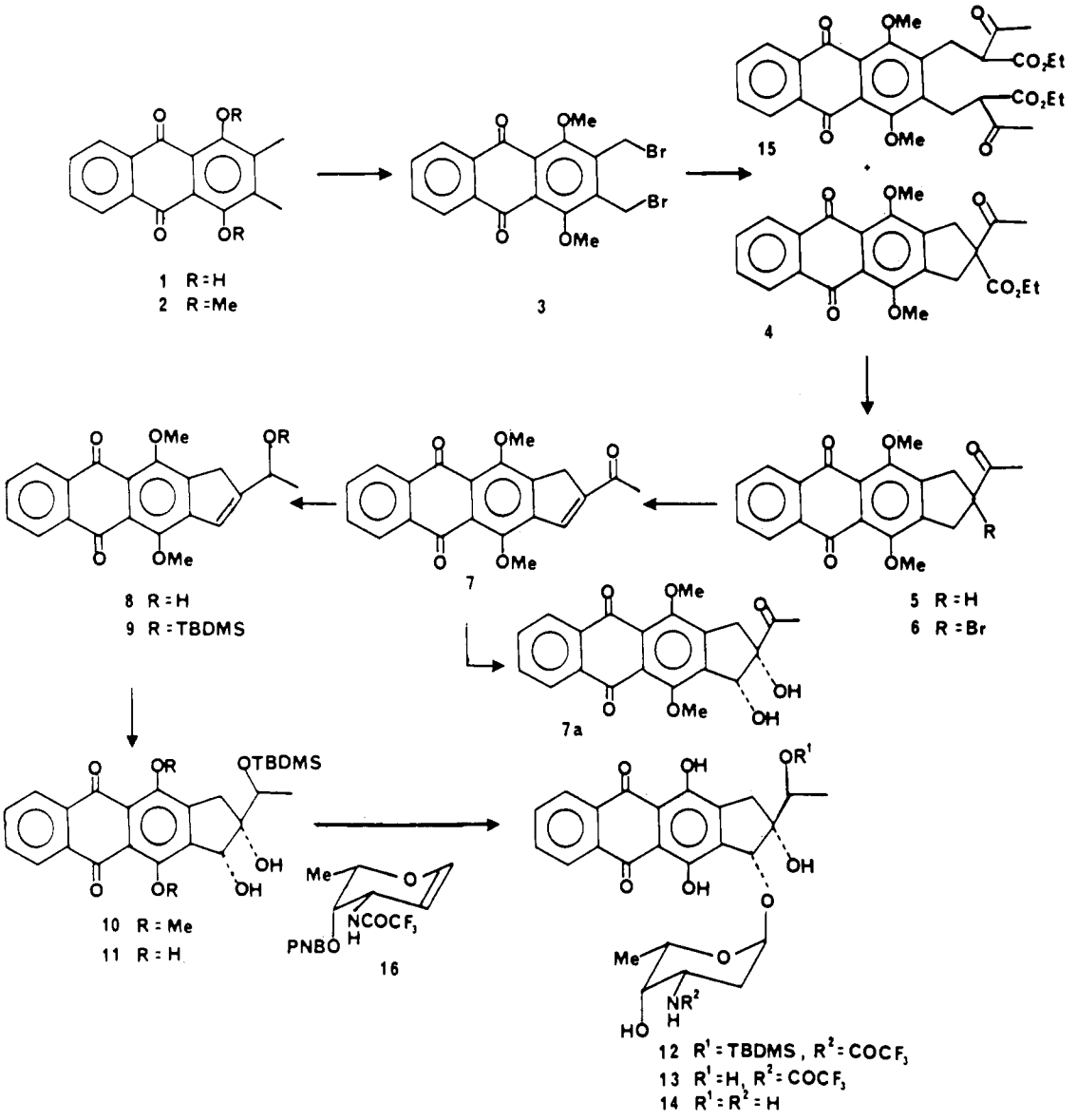
0022-3263/87/1952-5624$01.50/0

Scheme I



lowed by decarboxylation (H_2SO_4, THF, reflux) afforded methyl ketone **5** (92%). Enone **7** was prepared in 64% overall yield by regioselective bromination of **5** (pyrrolidone hydrotribromide, THF, room temperature) and subsequent dehydrobromination (DBN, CH_2Cl_2, −78 °C).

Diol **7a** was unstable and could only be generated in 40% yield by using catalytic amounts of osmium tetraoxide and barium perchlorate. Alternatively, enone **7** was reduced ($NaBH_4$, $CeCl_3$, CH_2Cl_2, −78 °C), affording allylic alcohol **8** (91%) serving as precursor to the potent 13-dihydrodaunorubicin system. Hydroxy group protection (81%) followed by osmium tetraoxide oxidation (OsO_4, *N*-methylmorpholine *N*-oxide, dioxane, room temperature) afforded *cis*-diol **10** (76%). Deprotection (BCl_3, CH_2Cl_2, −78 °C) afforded aglycon **11** (74%). Glycosidation of **11** with glycal **16**[7] (benzene, *p*-TsOH, room temperature) provided desired but inseparable diastereoisomeric glycosides **12** (55%). Desilylation (Bu_4NF, THF, room temperature, 85%) and hydrolysis (0.05 N NaOH, THF, room temperature, 50%) gave diastereoisomeric target **14** whose MS, NMR, and elemental analyses were consistent with the assigned structures. Further work with this mixture is not planned since no advantages over doxorubicin were observed in experimental tumor systems.

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Experimental Section

General. All starting materials were reagent grade, were obtained from commercial suppliers, and were used without further purification. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All reactions involving organometallic reagents, boron trichloride, and DBN were executed under 1 atm of dry argon using oven-dried glassware. IR spectra were determined in Nujol on a Perkin-Elmer 137 or Perkin-Elmer 399 infrared recording spectrophotomer. ^1H NMR spectra were determined in $CDCl_3$ using either a Varian T-60 (60 MHz), a Brucker WM-300 (300 MHz), or a Nicolet NTC-500 (500 MHz) spectrophotometer. Chemical shifts are expressed in parts per million (δ) downfield from internal tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Coupling constants are given in hertz (Hz). Preparative high-performance liquid chromatography (HPLC) was carried out on a Waters Prep LC 500 instrument using two Prep Pak columns. Elemental analyses were performed by Galbraith Laboratories, Inc.

1,4-Dimethoxy-2,3-dimethylanthraquinone (2). To a solution of 2,3-dimethylquinizarin (20.0 g, 0.075 mol) in diglyme (400 mL) were added methyl *p*-toluenesulfonate (41.0 g, 0.22 mol)

and potassium carbonate (51.0 g, 0.37 mol). The solution was heated to reflux, and additional methyl *p*-toluenesulfonate (14.0 g, 0.075 mol) and potassium carbonate (10.3 g, 0.075 mol) were added every 2 h over a 4-h period. The reaction mixture was heated for another 18 h and cooled to room temperature. Water was added and the precipitate was washed with water (100 mL) and ethanol (95%, 3 × 75 mL) affording 18.3 g (83%) of **2** as light yellow needles: mp 158–160 °C dec (lit.[5] mp 159–160 °C).

1,4-Dimethoxy-2,3-bis(bromomethyl)anthraquinone (3). To a solution of anthraquinone **2** (30.0 g, 0.1 mol) in carbon tetrachloride (1.5 L) were added *N*-bromosuccinimide (39.7 g, 0.22 mol) and benzoyl peroxide (1.0 g, 4.1 mmol). The mixture was heated to reflux for 4 h and another portion of benzoyl peroxide (0.9 g, 3.7 mmol) was added. The mixture was heated for an additional 18 h and cooled to 10 °C. The solid was filtered and washed with carbon tetrachloride (3 × 100 mL). The filtrate was concentrated and the residue was washed with carbon tetrachloride/hexane (1:1, 3 × 100 mL), affording 45.0 g (97%) of **3** as bright yellow needles: mp 173–174 °C dec (lit.[5] mp 174–176 °C).

2-Acetyl-2-(ethoxycarbonyl)-4,11-dimethoxy-2,3-dihydro-1*H*-cyclopent[*b*]anthracene-5,10-dione (4). The enolate of ethyl acetoacetate (16.0 g, 0.123 mol) [generated at −20 to −30 °C with LDA (0.136 mol) in THF (150 mL)] was transferred via a double-ended needle to a solution of the dibromide **3** (14.0 g, 0.031 mol) in THF (800 mL) held at room temperature. The mixture was stirred at room temperature for 42 h, diluted with ether (500 mL), and washed with aqueous saturated sodium chloride solution (2 × 500 mL). The aqueous layer was back-washed with methylene chloride (4 × 200 mL) and the combined organic layer was dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude residue was purified by HPLC eluted with hexane/ethyl acetate (3:1), affording 5.6 g (43%) of **4** as a light yellow solid: mp 163–164 °C; IR 1725, 1665, 1575 cm^{-1}; NMR δ 8.0–8.2 (m, 2 H, Ar H), 7.5–7.7 (m, 2 H, Ar H), 4.22 (q, 2 H, J = 6 Hz, CH_2CH_3), 3.93 (s, 6 H, OCH_3), 3.63 (s, 4 H, benzylic), 2.27 (s, 3 H, $COCH_3$), 1.26 (t, 3 H, J = 6 Hz, CH_2CH_3).

Anal. Calcd for $C_{24}H_{22}O_7$: C, 68.24; H, 5.25. Found: C, 68.12; H, 5.25.

2-Acetyl-4,11-dimethoxy-2,3-dihydro-1*H*-cyclopent[*b*]anthracene-5,10-dione (5). To a solution of keto ester **4** (6.0 g, 14.2 mmol) in THF (650 mL) was added 40% sulfuric acid (250 mL). The mixture was heated at reflux for 72 h, cooled, and diluted with ether (500 mL). The mixture was washed with aqueous saturated sodium chloride solution (2 × 250 mL) and the aqueous layer was back-washed with methylene chloride. The combined organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude material was purified by gravity column (SiO_2) eluted with hexane/ethyl acetate (3:1) to give 4.6 g (92%) of **5** as a light yellow solid: mp 170–171 °C; IR 1700, 1660, 1565 cm^{-1}; NMR (300 MHz) δ 8.17 (dd, 2 H, Ar H, J = 3.32 and 5.83 Hz), 7.73 (dd, 2 H, Ar H, J = 3.32 and 5.83 Hz), 3.94 (s, 6 H, OCH_3), 3.48–3.58 (m, 1 H, CH), 3.27–3.42 (m, 4 H, benzylic), 2.31 (s, 3 H, $COCH_3$).

Anal. Calcd for $C_{21}H_{18}O_5$: C, 71.98; H, 5.19. Found: C, 72.14; H, 5.29.

2-Acetyl-2-bromo-4,11-dimethoxy-2,3-dihydro-1*H*-cyclopent[*b*]anthracene-5,10-dione (6). To a solution of methyl ketone **5** (4.0 g, 11.4 mmol) in THF (400 mL) were added pyrrolidone hydrotribromide (7.9 g, 16 mmol) and sodium bicarbonate (288 mg, 3.4 mmol). The mixture was stirred at room temperature for 3.5 h, diluted with ether (200 mL), and washed with aqueous saturated sodium chloride solution (2 × 150 mL). The aqueous layer was back-washed with methylene chloride (200 mL), and the combined organic layer was dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was washed with ether to give 4.3 g (88%) of **6** as a light yellow solid: mp 181–182 °C dec; IR 1710, 1660, 1575 cm^{-1}; NMR δ 8.0–8.2 (m, 2 H, Ar H), 7.5–7.8 (m, 2 H, Ar H), 3.93 (s, 6 H, OCH_3), 3.73 (s, 4 H, benzylic), 2.57 (s, 3 H, $COCH_3$).

Anal. Calcd for $C_{21}H_{17}O_5Br$: C, 58.75; H, 3.99. Found: C, 58.33; H, 4.10.

2-Acetyl-4,11-dimethoxy-1*H*-cyclopent[*b*]anthracene-5,10-dione (7). To a solution of bromo ketone **6** (1.0 g, 2.33 mmol) in dichloromethane (20 mL) was added 1,5-diazabicyclo[4.3.0]-non-5-ene (578 mg, 4.66 mmol) at −78 °C. The mixture was stirred at −78 °C for 2 h and passed through a gravity column (SiO_2) eluted with dichloromethane/ethyl acetate (20:1). The eluate was concentrated and washed with ethyl acetate to give 580 mg (72%) of **7** as a pale yellow solid: mp 228–230 °C dec; IR 1650, 1620, 1570 cm^{-1}; NMR δ 8.0–8.2 (m, 2 H, Ar H), 7.5–7.8 (m, 3 H, 2 Ar H and 1 vinyl H), 4.03 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 3.83 (d, 2 H, J = 2 Hz, benzylic), 2.53 (s, 3 H, $COCH_3$).

Anal. Calcd for $C_{21}H_{16}O_5$: C, 72.40; H, 4.63. Found: C, 72.04; H, 4.76.

2-(1-Hydroxyethyl)-4,11-dimethoxy-1*H*-cyclopent[*b*]anthracene-5,10-dione (8). To a solution of enone **7** (2.5 g, 7.2 mmol) in dichloromethane (225 mL) and methanol (75 mL) were added cerium trichloride heptahydrate (2.67 g, 7.2 mmol) and sodium borohydride (300 mg, 7.9 mmol) at −78 °C. The mixture was stirred at −78 °C for 2 h. Another portion of sodium borohydride (60 mg, 1.6 mmol) was added, and the mixture was stirred at −78 °C for an additional hour. The excess sodium borohydride was quenched with 1 N HCl (6 mL), the resulting solution was washed with water (2 × 200 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was washed with ether to give 2.3 g (91%) of **8** as a light yellow solid: mp 191–192 °C dec; IR 1660, 1570 cm^{-1}; NMR δ 8.0–8.2 (m, 2 H, Ar H), 7.5–7.8 (m, 2 H, Ar H), 6.90 (d, 1 H, J = 1 Hz, vinyl), 4.77 (q, 1 H, J = 7 Hz, CH), 3.97 (s, 6 H, OCH_3), 3.63 (d, 2 H, J = 1 Hz, benzylic), 1.52 (d, 3 H, J = 7 Hz, CH_3).

Anal. Calcd for $C_{21}H_{18}O_5$: C, 71.99; H, 5.18. Found: C, 72.27; H, 5.25.

2-[1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4,11-dimethoxy-1*H*-cyclopent[*b*]anthracene-5,10-dione (9). To a solution of allylic alcohol **8** (2.1 g, 6 mmol) in DMF (100 mL) were added *tert*-butyldimethylsilyl chloride (2.7 g, 18 mmol) and imidazole (4.08 g, 60 mmol) at room temperature. The mixture was stirred at room temperature for 5 h. Ethyl acetate (150 mL) was added, and the solution was washed with saturated aqueous sodium chloride solution (2 × 100 mL). The aqueous layer was back-washed with ethyl acetate (2 × 100 mL), the combined organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by a gravity column (SiO_2) eluted with hexane/ethyl acetate (7:1) to give 2.25 g of **9** (81%) as a yellow solid: mp 126–127 °C dec; IR 1660, 1575 cm^{-1}; NMR δ 8.0–8.3 (m, 2 H, Ar H), 7.5–7.8 (m, 2 H, Ar H), 6.87 (b s, 1 H, vinyl), 4.83 (q, 1 H, J = 6 Hz, CH), 4.00 (s, 6 H, OCH_3), 3.63 (b s, 2 H, benzylic), 1.45 (d, 3 H, J = 6 Hz, CH_3), 0.93 (s, 9 H, *t*-Bu), 0.13 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$).

Anal. Calcd for $C_{27}H_{32}O_5Si$: C, 69.79; H, 6.94. Found: C, 69.89; H, 7.15.

2-[1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2,3-*cis*-dihydroxy-4,11-dimethoxy-1*H*-cyclopent[*b*]anthracene-5,10-dione (10). To a stirred solution of **9** (1.74 g, 3.75 mmol) in dioxane (120 mL) was added a solution of osmium tetraoxide (1.0 g, 3.94 mmol) in *tert*-butyl alcohol (40 mL) at room temperature. *N*-Methylmorpholine *N*-oxide in three portions (607 mg, 200 mg, 500 mg) was added after stirring 6, 24, and 31 h. The mixture was stirred at room temperature for another 18 h and a solution of sodium bisulfite (7.48 g, 39 mmol) in water (50 mL) was added. The mixture was stirred for 1 h, diluted with dichloromethane (100 mL), and washed with saturated aqueous sodium chloride solution (2 × 125 mL). The aqueous layer was back-washed with dichloromethane (50 mL) and the combined organic layer was dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by a gravity column (SiO_2) eluted with hexane/ethyl acetate (3:1) to give 1.47 g (76%) of **10** as a yellow viscous oil: IR 3440, 1660, 1570 cm^{-1}; NMR δ 8.0–8.3 (m, 2 H, Ar H), 7.5–7.8 (m, 2 H, Ar H), 5.36 (d, 1 H, J = 4.0 Hz, benzylic C*H*-OH), 4.03 (b s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 3.87 (m, 1 H, CH), 3.13 (b s, 2 H, benzylic), 1.33 (d, 3 H, J = 6 Hz, CH_3), 0.93 (s, 9 H, *t*-Bu), 0.20 (s, 6 H, 2 $SiCH_3$).

Anal. Calcd for $C_{27}H_{34}O_7Si$: C, 65.03; H, 6.87. Found: C, 65.10; H, 6.97.

4-Demethoxy-13-dihydro-13-*O*-(*tert*-butyldimethylsilyl)-8-nordaunomycinone (11). To a solution of diol **10** (1.58 g, 3.17 mmol) in dichloromethane (100 mL) was added a solution of boron trichloride (19.0 mmol, 1 M solution in dichloromethane) at −78 °C. The mixture was stirred at −78 °C for 0.25 h, and water (10 mL) was added. The solution was washed with saturated aqueous sodium chloride solution (2 × 100 mL) and the aqueous

layer was back-washed with dichloromethane (2 × 50 mL). The combined organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude material was purified by a gravity column (SiO_2) eluted with hexane/ethyl acetate (3:1) to give 1.1 g (74%) of **11** as a red solid: mp 198–199 °C dec; IR 3230, 1590, 1555 cm^{-1}; NMR (500 MHz) δ 13.26 (s, 1 H, phenolic OH), 12.99 (s, 1 H, phenolic OH), 8.33–8.35 (m, 2 H, Ar H), 7.82–7.84 (m, 2 H, Ar H), 5.41 (s, 1 H, benzylic C*H*-OH), 4.00 (q, 1 H, J = 6.2 Hz, CH), 3.09 (s, 2 H, benzylic), 1.31 (d, 3 H, J = 6.2 Hz, CH_3), 0.88 (s, 9 H, *t*-Bu), 0.13 (s, 6 H, 2 $SiCH_3$).

Anal. Calcd for $C_{25}H_{30}O_7Si$: C, 63.81; H, 6.43. Found: C, 64.19; H, 6.44.

4-Demethoxy-13-dihydro-13-*O*-(*tert*-butyldimethylsilyl)-3′-*N*-(trifluoroacetyl)-8-nordaunomycin (12). To a solution of glycal **16** (190 mg, 0.51 mmol) in dry benzene (10 mL) were added aglycon **11** (200 mg, 0.43 mmol) and *p*-toluenesulfonic acid (5–7 mg). The solution was stirred at room temperature for 3 h, and another portion of **16** (100 mg, 0.27 mmol) was added. Stirring was continued for 18 h. The mixture was diluted with dichloromethane (30 mL) and washed with saturated aqueous sodium bicarbonate solution (2 × 30 mL). The aqueous layer was back-washed with dichloromethane (2 × 20 mL). The combined organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was redissolved in triethylamine/methanol (1:9, 15 mL) and stirred at room temperature for 1 h. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (20 mL). The organic solution was washed with saturated aqueous sodium bicarbonate solution (2 × 10 mL), and the aqueous layer was back-washed with dichloromethane (1 × 10 mL). The combined organic solution was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude material was passed through a gravity column (SiO_2) eluted with hexane/ethyl acetate (3:1) to give 30 mg of starting material **11** (higher R_f fraction) and 140 mg (55% based on recovered starting material) of **12** (lower R_f fraction) as an inseparable mixture of 4 diasteromers: IR 3175, 1680, 1590, 1560 cm^{-1}.

Anal. Calcd for $C_{33}H_{40}O_{10}SiF_3N$: C, 56.96; H, 5.79; N, 2.01. Found: C, 57.00; H, 6.13; N, 2.01.

4-Demethoxy-13-dihydro-8-nordaunomycin (14). To a solution of glycoside **12** (140 mg, 0.2 mmol) in THF (10 mL) was added a solution of tetrabutylammonium fluoride (0.98 mmol, 1 M solution in THF). The solution was stirred at room temperature for 6 h, diluted with dichloromethane (20 mL), and washed with saturated aqueous sodium chloride solution (2 × 20 mL). The aqueous layer was back-washed with dichloromethane (2 × 10 mL) and the combined organic solution was dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude material was purified by a gravity column (SiO_2) eluted with hexane/ethyl acetate (1:2) followed by ethyl acetate and 5% methanol in ethyl acetate to give 100 mg (85%) of **13** as a red solid.

To a solution of diol **13** (100 mg, 0.17 mmol) in THF (10 mL) was added a 0.05 N NaOH solution (19 mL, 0.95 mmol). The solution was stirred at room temperature for 18 h and solid CO_2 was added until the color of the solution changed from purple to red. The solvent was removed under reduced pressure. The residue was dissolved in methanol, and the white precipitate was filtered. The filtrate was concentrated and the residue was purified by a gravity column (SiO_2) eluted with methanol/dichloromethane (1:2) followed by methanol to give 41 mg (50%) of **14** as a dark red solid.

Anal. Calcd for $C_{25}H_{27}O_9N\cdot 2H_2O$: C, 57.57; H, 5.99; N, 2.68. Found: C, 57.70; H, 5.91; N, 2.70.

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Stereoselective Access to α- and β-D-Fructofuranosyl C-Glycosides

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C-Glycosides have gained interest as potential inhibitors of metabolic processes[1] and as chiral intermediates in organic syntheses.[2] Although many examples of syntheses of these compounds have recently been described, in only few cases has the formation of a tri-C-substituted carbon center been reported.[3] In particular, in spite of the biological importance of D-fructose, the synthesis of C-fructosides has received little attention.[4,5]

In connection with a project directed toward the synthesis of potential inhibitors of carbohydrate metabolism, we were interested in developing an efficient method to obtain α- and/or β-C-D-fructofuranosides.

In principle both α- and β-C-D-fructofuranosides can be derived from a common precursor such as A (Scheme I) which, through differential manipulation of the groups C_x and C_y, leads to synthons such as B and C. B and C, besides being α- and β-C-D-fructofuranosides, contain an unprotected hydroxymethyl group that may be elaborated.

Results and Discussion

The Lewis acid catalyzed formation of an oxonium ion, and the subsequent addition of a proper C-nucleophile,[6] seemed the most suitable route to a C-fructoside. The stereochemistry of this reaction was not predictable. In fact whereas in glycopyranosides (in $^4C_1$ conformation) the anomeric effect leads the nucleophile to attack the oxonium ion from the α face,[6a] in glycofuranosides the anom-

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