tate/hexane) provided 2.81 g (91%) of erythro dicarbamate **12** as white crystals: mp 168–169 °C (recrystallized from ethyl acetate–hexane); IR (film) 3325, 2960, 1690, 1540, 1320, 1300, 1255, 1230, 1195, 1025, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.30 (5 H, m), 5.66 (1 H, ddd, J = 17.3, 10.1, 6.0 Hz), 5.36 (1 H, NH), 5.23 (1 H, dd, J = 17.4, 1.2 Hz), 5.13 (1 H, dd, J = 10.2, 1.2 Hz), 4.82 (1 H, NH), 4.39 (1 H, m), 3.96 (1 H, m), 3.73 (2 H, s), 3.69 (3 H, s), 3.67 (3 H, s), 2.47 (2 H, m); CI mass spectrum, m/z (relative intensity) 339 (40, $M^+ + 1$), 307 (73, $M^+ + 1 - CH_3OH$), 264 (28), 149 (43), 91 (100).

Cyclization of Erythro Dicarbamate 12 to Urea 13. Sodium hydride (80% in mineral oil, 400 mg, 13.3 mmol) was added to an ice-cold solution of erythro-dicarbamate **12** (3.60 g, 10.7 mmol) in 250 mL of anhydrous THF. The ice bath was removed and the suspension was stirred for 3 h. Aqueous NaOH solution (15%, 3 mL) was added, and the mixture was stirred for an additional 4 h and was evaporated. The solid residue was partitioned between 50 mL of ethyl acetate and 50 mL of a 1:1 brine/H_2O mixture. The aqueous layer was extracted three times with 50-mL portions of ethyl acetate, the combined extracts were dried ($MgSO_4$), and the solution was evaporated. Purification of the residual yellow oil by flash chromatography (50 mm column, ethyl acetate) provided 2.34 g (89%) of cyclic urea **13** as a colorless oil: IR (film) 2960, 1720, 1440, 1320, 1265, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.26 (5 H, m), 5.72 (1 H, ddd, J = 17.0, 10.1, 7.0 Hz), 5.70 (1 H, NH), 5.25 (1 H, dd, J = 17.1, 0.9 Hz), 5.18 (1 H, dd, J = 9.6, 0.9 Hz), 4.23 (1 H, dd, J = 8.0, 7.2 Hz), 3.75 (1 H, dt, J = 8.4, 5.5 Hz), 3.69 (2 H, s), 2.44 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 163.35, 137.63, 133.07, 128.61, 128.36, 126.97, 118.27, 57.83, 54.91, 36.22, 32.57; EI mass spectrum, m/z (relative intensity) 248 (3), 111 (41), 91 (32), 84 (100); high-resolution mass spectrum calcd for $C_{13}H_{16}N_2OS$ 248.0983, found 248.0975.

Preparation of Tribenzyl Cyclic Urea 14. Sodium hydride (80% in mineral oil, 65 mg, 2.2 mmol) was added to an ice-cold solution of dicarbamate **12** (270 mg, 0.80 mmol) and benzyl bromide (0.25 mL, 2.1 mmol). The ice bath was removed and the mixture was stirred for 12 h. Saturated NH_4Cl solution (1 mL) was added to the mixture and the solvent was evaporated. The solid residue was partitioned between 50 mL of ethyl acetate and 50 mL of water. The aqueous layer was extracted three times with 25-mL portions of ethyl acetate, and the combined extracts were dried ($MgSO_4$) and evaporated. Purification of the residual oil by flash chromatography (20 mm column, 1:3 ethyl acetate/hexane) gave 329 mg (96%) of **14** as a colorless oil: IR (film) 1700, 1440, 1420, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.27 (10 H, m), 7.13 (5 H, m), 5.65 (1 H, ddd, J = 17.0, 10.1, 8.9 Hz), 5.31 (1 H, dd, J = 10.2, 1.5 Hz), 5.17 (1 H, dd, J = 16.9, 1.3 Hz), 4.90 (1 H, d, J = 15.1 Hz), 4.62 (1 H, d, J = 15.5 Hz), 4.06 (1 H, d, J = 15.5 Hz), 3.82 (1 H, d, J = 15.0 Hz), 3.80 (1 H, t, J = 8.4 Hz), 3.49 (2 H, s), 3.41 (1 H, ddd, J = 8.5, 8.4, 4.5 Hz), 2.43 (2 H, m); EI mass spectrum, m/z (relative intensity) 428 (2), 291 (79), 91 (100); high-resolution mass spectrum calcd for $C_{27}H_{28}N_2OS$ 428.1922, found 428.1908.

Cyclization of Tribenzylurea 14 to Tetrahydrothiophene 15. Bromine–dioxane complex[7] was added in 20–30-mg portions to tribenzylurea **14** (55 mg, 0.13 mmol) in 15 mL of acetonitrile until starting material was consumed (TLC analysis). The yellow solution was stirred for 10 h, saturated sodium thiosulfate solution (5 mL) was added to the mixture, and the resulting solution was concentrated in vacuo. The residual material was partitioned between 20 mL of ethyl acetate and 20 mL of brine, and the aqueous layer was extracted three times with 20-mL portions of ethyl acetate. The combined extracts were dried ($MgSO_4$) and rotary evaporated to afford a yellow oil, which was purified by flash chromatography (10 mm column, 1:3 ethyl acetate/hexane) to give 47 mg (88%) of bromide **15** as a white solid: mp 128–129 °C (recrystallized from ethyl acetate–hexane); IR (film) 1695, 1455, 1450, 1240, 700 cm^{-1}; ^1H NMR (benzene-d_6, 360 MHz) δ 7.43 (2 H, m) 7.10 (8 H, m), 4.77 (1 H, d, J = 15.4 Hz), 4.75 (1 H, d, J = 15.4 Hz), 4.04 (1 H, d, J = 15.4 Hz), 3.79 (1 H, d, J = 15.4 Hz), 3.71 (1 H, d, J = 7.9 Hz), 3.34 (1 H, dd, J = 7.6, 4.4 Hz), 3.00 (1 H, dd, J = 11.9, 4.3 Hz), 2.88 (1 H, dd, J = 10.2, 4.3 Hz), 2.45 (1 H, dd, J = 11.9, 10.2 Hz), 2.27 (1 H, d, J = 12.9 Hz), 2.02 (1 H, dd, J = 13.0, 4.8 Hz); ^{13}C NMR ($CDCl_3$) δ 159.64, 137.50, 136.83, 128.71, 128.58, 128.23, 128.00, 127.64, 127.54, 65.45, 61.91, 53.84, 46.54, 46.27, 35.72, 34.26, 34.13; CI mass spectrum, m/z (relative intensity) 419 (93), 417 (100), 337 (68).

Preparation of Vinyl Sulfide 16. 1,8-Diazabicyclo[5.4.0]-undec-7-ene (DBU, 0.05 mL, 0.34 mmol) was added to a solution of bromide **15** (10 mg, 0.024 mmol) in 20 mL of a 2:1 mixture of benzene/CH_2Cl_2. The mixture was refluxed for 1 h and evaporated in vacuo to give an oil, which was purified by preparative TLC (1:2 ethyl acetate/hexane) to afford 6 mg (77%) of **16** as a colorless oil: IR (film) 2975, 2960, 1690, 1440, 1230, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.29 (10 H, m), 5.29 (1 H, s), 5.10 (1 H, s), 5.06 (1 H, d, J = 15.1 Hz), 4.81 (1 H, d, J = 15.3 Hz), 4.29–4.06 (2 H, m), 4.23 (1 H, d, J = 15.3 Hz), 4.02 (1 H, d, J = 15.6 Hz), 3.00 (2 H, m); CI mass spectrum, m/z (relative intensity) 337 (100).

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Supplementary Material Available: Tables of X-ray crystallographic data for tetrahydrothiophene **15** (9 pages). Ordering information is given on any current masthead page.

Syntheses of *ribo* and *arabino* Deoxy- and Deoxyaminoepoxybenzoxocin Sugar Analogues

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Previously, we have reported procedures to the epoxybenzoxocin ring system,[2,3] a structural fragment present in nogarol anthracyclines.[4] We have continued to explore the scope and limitations of various methods for functionalizing the pyranose ring in **1** and have now achieved brief, high-yield total syntheses of deoxy and deoxyamino sugar analogues with *ribo* and *arabino* configurations. Novel aspects of this work are our findings that the *erythro* acetamido ketobenzoxocin **7** can be equilibrated to the thermodynamically more stable *threo* isomer **8** and that the ketones **6** and **7** exist in the twist-boat conformation.

As indicated in Scheme I, catalytic hydrogenation of **1a**[2] gave the saturated ketone compound **1b** quantitatively. Addition of a solution of the ketone **1b** and isoamyl nitrite to a solution of sodium methoxide routinely furnished the α-oximino ketone **2** in 88% yield. These conditions were established only after considerable study; the use of other reagents or protocols gave little or no product. Sodium borohydride reduction of **2** to the alcohol **3a**, followed by catalytic reduction of the oxime functionality in **3a** and acetylation of the amino alcohol intermediate, furnished the diacetate **4a**. Ammonolysis of **4a** selectively cleaved the *O*-acetyl functionality and gave the acetamido hydroxyepoxybenzoxocin **4b** with the *ribo* configuration. The overall preparation of **4b** was stereospecific since both reduction steps occurred exclusively from the exo face due

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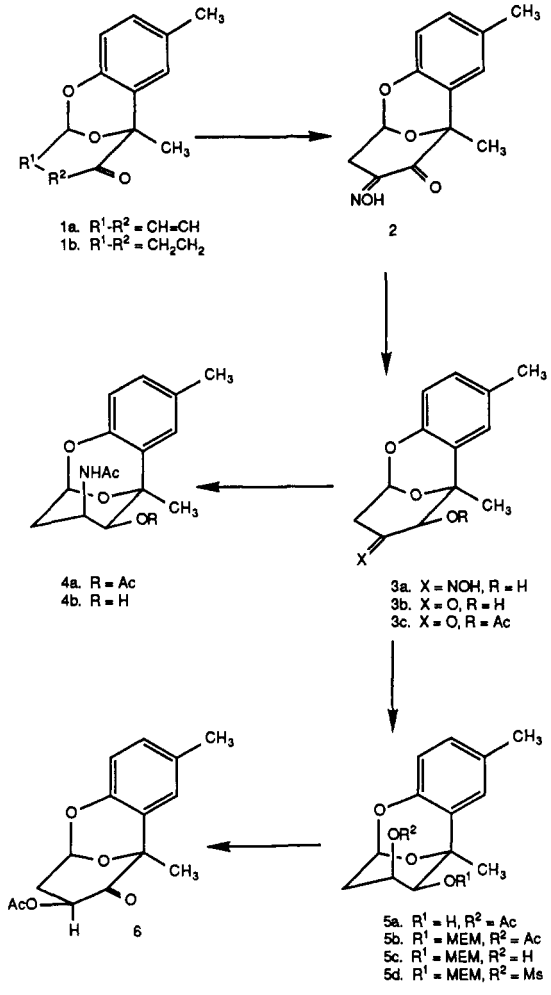
(2) Hauser, F. M.; Ellenberger, W. P.; Adams, T. C., Jr *J. Org. Chem.* **1984**, *49*, 1169.

(3) Hauser, F. M.; Adams, T. C., Jr. *J. Org. Chem.* **1984**, *49*, 2296.

(4) Wiley, P. F. *J. Nat. Prod.* **1979**, *42*, 569. Wiley, P. F.; *Anthracycline Antibiotics*; El Khadem, H. S., Ed., Academic: New York, NY 1982; pp 98–117. Wiley, P. F.; Elrod, D. W.; Houser, D. J.; Richard, F. A. *J. Med. Chem.* **1982**, *25*, 560. Wiley, P. F.; Elrod, D. W.; Houser, D. J.; Johnson, J. L.; Pschigoda, L. M.; Krueger, W. C.; Moscowitz, A. *J. Org. Chem.* **1979**, *44*, 4030. Eckle, E.; Stezowski, J.; Wiley, P. F. *Tetrahedron Lett.* **1980**, *21*, 507. Arora, S. K. *J. Am. Chem. Soc.* **1983**, *105*, 1328.

0022-3263/88/1953-1118$01.50/0

Scheme I



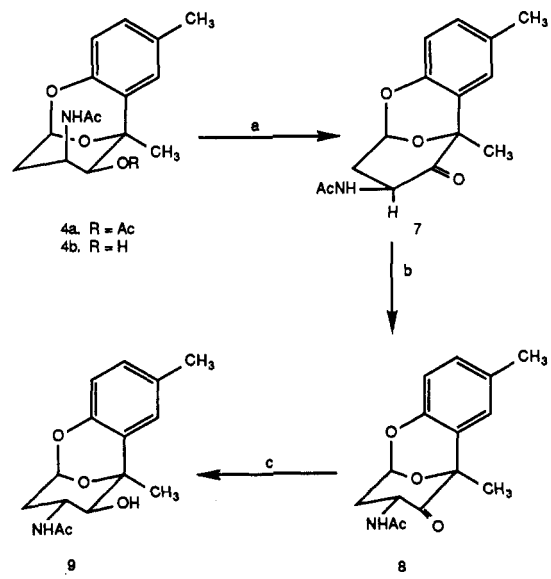
1a → 1b: H_2, Pd/C, EtOAc; 99%. 1b → 2: NaOMe, MeOH, isoamylnitrite; 88%. 2 → 3a: $NaBH_4$, IPA; 96%. 3a → 4a: H_2, Pd/C, HOAc; Ac_2O, Py; 69%. 4a → 4b: NH_3, MeOH; 100%. 3a → 3b: CH_3COCO_2H, HCl, THF; 96%. 3b → 3c: Ac_2O, Py; 96%. 3c → 5a: $NaBH_4$, IPA; 94%. 5a → 5b: MEMCl, diisopropylethylamine, CH_2Cl_2; 92%. 5b → 5c: LAH, Et_2O; 85%. 5c → 5d: MsCl, Py; 85%. 5a → 6: CrO_3·2Py, CH_2Cl_2; 68%.

to the diastereofacial bias of the ring system.

Initially, we attempted to prepare the *arabino* aminobenzoxocin **9** through the intermediacy of *ribo* alcohol precursors **5**. Cleavage of the oxime group in **3a** by pyruvic acid exchange furnished the keto alcohol **3b**, which was acetylated to give **3c**. Reduction of the ketone moiety in **3c** with a variety of agents proceeded stereospecifically, but always produced the acetoxy alcohol **5a** resulting from migration of the acetate group to the newly formed axial hydroxyl group. The structural assignment was based on the ^1H NMR spectrum, which showed a resonance for the acetate methyl at 1.5 ppm compared with 2.2 ppm in **3c**. This shift is a consequence of the proximity of the acetate methyl in **5a** to the shielding cone of the aromatic ring. In order to chemically verify the structural assignment, **5a** was oxidized with Collins reagent[5] (CrO_3·2Py) to the *erythro* ketone **6**, the physical properties of which differed from **3c**. The occurrence of the acetate methyl absorption at 2.1 ppm in the ^1H NMR spectrum of **6** indicated that the acetate functionality was no longer proximate to the shielding cone of the aromatic ring. The observation and the presence of the C-4 proton as a doublet of doublets with J = 13.1 and 7.6 Hz indicated that the pyranose ring

(5) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.

Scheme II



a. ClCOCOCl, DMSO, Et_3N; 87%. b. Et_3N, CH_2Cl_2. c. $NaBH_4$, IPA; 95%.

in **6** had undergone conformational inversion to a twist-boat.

The acetate migration, initially viewed as a problem, was used advantageously for selective protection of the C-5 alcohol group. Thus, reaction of **5a** with (methoxyethoxy)methyl chloride and diisopropylamine gave the MEM ether derivative **5b** in 81% yield. Reductive cleavage (LAH/ether) of the acetate group furnished the protected *ribo* alcohol **5c** in 85% yield. Repeated attempts to prepare a nitrogen containing *arabino* intermediate through nucleophilic displacement of the C-4 oxygen functionality with azide in the 4-*O*-mesyl derivative **5d** or through Mitsunobu reaction[6] of **5c** were unsuccessful.

As indicated in Scheme II, epimerization of the *erythro* ketone **7** to the *threo* ketone **8** was used to prepare the *ribo* aminoepoxybenzoxocin **9**. Swern oxidation[7] of **4b** furnished the ketone **7** in 87% yield. The acetamido methyl was at 1.99 ppm, downfield relative to its position at 1.49 ppm in the ^1H NMR spectrum of **4b**. This result paralleled that obtained with the acetoxy ketone **6**, and similarly, analysis of the ^1H NMR spectrum of **7** led to the conclusion that the pyranose ring had undergone inversion from a chair to a twist-boat. Sodium borohydride reduction of the ketone from the oxidation gave predominantly the starting *arabino* alcohol **4b**, thereby establishing that epimerization of **7** to **8** had not occurred under the basic conditions of the Swern reaction.[7] Purification of the reduction product led to the isolation of a small amount (5%) of a second component. The ^1H NMR spectrum of this material was consistent with the *arabino* product **9**, indicating that epimerization had occurred to a small extent.

The isomerization of **7** to **8** proved to be sensitive to the reaction conditions. Treatment of **7** with DBU or triethylamine in THF led to destruction of the starting material. With additional study, it was found that quantitative epimerization of **7** to **8** could be accomplished with triethylamine in methylene chloride, the base and solvent used in the Swern reaction. Reduction of **8** with sodium borohydride furnished the objective *arabino* epoxybenz-

(6) Mitsunobu, O. *Synthesis*, **1981**, 1.
(7) Mancuso, A.; Swern, D. J. *Synthesis* **1981**, 165.

oxocin **9** in 95% overall yield from **7**.

In summary, these studies show that although the manipulation of stereocenters on the pyranose ring of the epoxybenzoxocin ring system through nucleophilic substitution is not viable, epimerization of functionality is synthetically useful. The synthetic work presented herein should be useful for establishing structure–activity relationships in nogarol anthracyclines.

Experimental Section

General Procedures. Melting points were taken on a Kofler hot-stage microscope and are uncorrected. Proton and carbon magnetic resonance spectra were obtained with a JEOL FX-90Q spectrometer. Chemical shifts are expressed in δ units. Mass spectra were obtained with VG 7070E, Du Pont CEC 21-110B, Du Pont 21-491B, or Finnigan 40-21 mass spectrometers. Carbon, hydrogen, and nitrogen analyses were performed by Gailbraith Laboratories, Knoxville, TN.

Analytical thin-layer chromatograms (TLC) were conducted on 5 × 10 cm precoated plates (silica gel 60, F 254, 0.25-mm thickness) manufactured by E. Merck and Co. Radial preparative thick-layer chromatography was performed on a Chromatotron (Harrison Research) with rotors coated to 2- and 4-mm thickness (Merck silica gel 60, PF 254). Column chromatograpy was performed with silica gel 60, 70–230 mesh ASTM. All other solvents were reagent grade and were not further purified.

(±)-*cis*-3,4-Dihydro-6,8-dimethyl-2,6-epoxy-2*H*-1-benzoxocin-5(6*H*)-one (1b). A mixture of **1a** (2.68 g, 12.2 mmol), 5% palladium on carbon (250 mg), and ethyl acetate (100 mL) was shaken under hydrogen at 40 psi for 12 h. The mixture was filtered and evaporated at reduced pressure to give 2.67 g (99%) of **1b** as a colorless solid with mp 75–77 °C: ^{1}H NMR ($CDCl_3$) δ 1.65 (s, 3 H), 2.25 (s, 3 H), 2.39 (m, 4 H), 5.82 (m, 1 H), 6.80 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 208.2, 148.0, 130.7, 130.2, 125.8, 122.1, 116.8, 92.8, 79.0, 31.1, 29.5, 20.9, 20.6.

(±)-*cis*-2,3-Dihydro-6,8-dimethyl-4-oximino-2,6-epoxy-2*H*-1-benzoxocin-5(6*H*)-one (2). To a cold (0 °C) stirred solution of sodium methoxide (3.7 mL of a 2.6 M solution in methanol) in methanol (25 mL) was added rapidly a solution of **1b** (2.11 g, 9.5 mmol) and isoamyl nitrite (4 mL, 30 mmol) in methanol (10 mL). The reaction was stirred overnight at room temperature, then quenched with hydrochloric acid (50 mL, 1 N), and extracted with methylene chloride (3 × 100 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was purified by column chromatography (silica gel, 100 g, 8:2 hexanes/ethyl acetate) to give 2.07 g (88%) of **2** as light yellow crystals with mp 167–169 °C: ^{1}H NMR ($CDCl_3$) δ 1.77 (s, 3 H), 2.23 (s, 3 H), 2.95 (dd, J = 20.1 Hz, J = 1.0 Hz, 1 H), 3.54 (dd, J = 20.2 Hz, J = 7.0 Hz, 1 H), 5.87 (dd, J = 7.0 Hz, J = 1.1 Hz, 1 H), 6.89 (m, 3 H); mass spectrum, m/z 247 ($M^{\bullet+}$), 202.

(±)-*cis*-2,3-Dihydro-6,8-dimethyl-4-oximino-2,6-epoxy-2*H*-1-benzoxocin-5β(6*H*)-ol (3a). To a solution of **2** in isopropyl alcohol (50 mL) was added sodium borohydride (0.3 g, 7.9 mmol), and the mixture was stirred for 1 h at room temperature. The solvent was evaporated at reduced pressure, and the residue was taken up in water (50 mL) and extracted with methylene chloride (3 × 50 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was purified by column chromatography (silica gel, 50 g, 8:2 hexanes/ethyl acetate) to give 1.83 g (96%) of **3a** as a white solid with mp 101–104 °C. ^{1}H NMR ($CDCl_3$) δ 1.74 (s, 3 H), 2.27 (s, 3 H), 2.43 (dd, J = 15.6 Hz, J = 4.8 Hz, 2 H), 3.22 (br s, 1 H), 3.59 (dd, J = 15.8 Hz, 1 H), 4.30 (d, J = 5.5 Hz, 1 H), 5.73 (d, J = 4.4 Hz, 1 H), 6.92 (m, 3 H); mass spectrum, m/z 249 ($M^{\bullet+}$), 232.

1,2′-Anhydro-2,3,6-trideoxy-3-acetamido-4-acetoxy-5-*C*-(2-hydroxy-5-methylphenyl)-α-DL-*ribo*-hexopyranose (4a). A mixture of **3a** (0.50 g, 2.0 mmol), 5% palladium on carbon (0.10 g), and acetic acid (30 mL) was shaken under hydrogen at 40 psi for 12 h. The reaction was filtered, and the solvent was evaporated at reduced pressure. The residue was taken up in methylene chloride (50 mL), and acetic anhydride (2 mL) and pyridine (5 mL) were added. The mixture was stirred at room temperature for 4 h and then quenched with saturated sodium bicarbonate. The layers were separated, and the aqueous phase was further extracted with methylene chloride (2 × 50 mL). The combined organic solutions were dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was purified by radial chromatography (silica gel, 6:4 hexanes/ethyl acetate) to give 0.44 g (69%) of **4a** as a white solid with mp 121–122 °C: ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 3 H), 1.56 (s, 3 H), 2.08 (s, 3 H), 2.27 (m, 2 H), 2.33 (s, 3 H), 4.61 (m, 1 H), 4.75 (br s, 1 H), 5.09 (d, J = 5.0 Hz, 1 H), 5.65 (dd, J = 3.5 Hz, J = 2.0 Hz, 1 H), 6.97 (m, 3 H); mass spectrum, m/z 319 ($M^{\bullet+}$), 276. Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.71; H, 6.93; N, 4.11.

1,2′-Anhydro-2,3,6-trideoxy-3-acetamido-5-*C*-(2-hydroxy-5-methylphenyl)-α-DL-*ribo*-hexopyranose (4b). A solution of **4a** (0.10 g, 0.31 mmol) in cold (0 °C) methanol was saturated with ammonia and then stirred for 1 h. The solvent was removed at reduced pressure, and the residue was purified by radial chromatography (silica gel, ethyl acetate) to give 0.09 g (100%) of **4b** as a colorless solid with mp 180–184 °C: ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 3 H), 1.63 (s, 3 H), 2.19 (t, J = 2.0 Hz, 1 H), 2.29 (s, 3 H), 2.31 (m, 1 H), 3.50 (br s, 1 H), 3.91 (d, J = 5.1 Hz, 1 H), 4.47 (m, 1 H), 5.05 (br s, 1 H), 5.64 (dd, J = 3.6 Hz, J = 1.4 Hz, 1 H), 6.91 (m, 3 H).

1,2′-Anhydro-2,6-dideoxy-5-*C*-(2-hydroxy-5-methylphenyl)-α-DL-*erythro*-hex-3-ulose (3b). A mixture of **3a** (0.92 g, 3.8 mmol), pyruvic acid (3.5 g, 40 mmol), tetrahydrofuran (25 mL), and 1.5 N hydrochloric acid (25 mL) was stirred for 16 h at room temperature. The reaction mixture was extracted with methylene chloride (4 × 50 mL), and the combined extracts were dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was purified by radial chromatography (silica gel, 6:4 hexanes/ethyl acetate) to give 0.85 g (96%) of **3b** as a white solid with mp 151–152 °C: ^{1}H NMR ($CDCl_3$) δ 1.76 (s, 3 H), 2.24 (s, 3 H), 2.86 (d, J = 1.4 Hz, 1 H), 2.95 (dd, J = 4.8 Hz, J = 1.2 Hz, 1 H), 3.47 (d, J = 5.0 Hz, 1 H), 4.30 (dd, J = 5.0 Hz, J = 1.2 Hz, 1 H), 5.97 (dd, J = 4.8 Hz, J = 1.4 Hz, 1 H), 6.91 (m, 3H); mass spectrum, m/z 234 ($M^{\bullet+}$).

1,2′-Anhydro-2,6-dideoxy-5-*C*-(2-hydroxy-5-methylphenyl)-α-DL-*erythro*-hex-3-ulose 5-Acetate (3c). Acetylation of **3b** (1.50 g, 6.4 mmol) with acetic anhydride (0.5 mL) and pyridine (0.7 mL) in methylene chloride (50 mL) furnished 1.69 g (96%) of **3c** with mp 179–182 °C after chromatography (silica gel, 75g, 6:4 hexanes/ethyl acetate): ^{1}H NMR ($CDCl_3$) δ 1.69 (s, 3 H), 2.20 (s, 3 H), 2.25 (s, 3 H), 2.84 (d, J = 1.4 Hz, 1 H), 2.94 (dd, J = 5.1 Hz, J = 1.3 Hz, 1 H), 5.32 (d, J = 1.3 Hz, 1 H), 5.95 (dd, J = 5.1 Hz, J = 1.4 Hz, 1 H), 6.93 (m, 3 H); mass spectrum, m/z 276 ($M^{\bullet+}$), 234.

1,2′-Anhydro-2,6-dideoxy-5-*C*-(2-hydroxy-5-methylphenyl)-α-DL-*ribo*-hexopyranose 3-Acetate (5a). Sodium borohydride (0.36 g, 9.5 mmol) was added to a stirred solution of **3c** (1.73 g, 6.3 mmol) in 2-propanol (75 mL), and the mixture was stirred at room temperature for 2 h. The solvent was removed at reduced pressure, and the residue was dissolved in water (50 mL). The aqueous layer was extracted with methylene chloride (3 × 50 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was purified by column chromatography (silica gel, 80 g, 7:3 hexanes/ethyl acetate) to give 1.65 g (94%) of **5a** as a white solid with mp 161–163 °C: ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 3 H), 1.64 (s, 3 H), 2.18 (t, J = 2.0 Hz, 1 H), 2.26 (s, 3 H), 2.31 (m, 1 H), 3.80 (dd, J = 10.0 Hz, J = 4.0 Hz, 1 H), 5.08 (m, 1 H), 5.60 (dd, J = 4.0 Hz, J = 2.0 Hz, 1 H), 6.80 (m, 3 H); mass spectrum, m/z 278 ($M^{\bullet+}$).

1,2′-Anhydro-2,6-dideoxy-3β-acetoxy-5-*C*-(2-hydroxy-5-methylphenyl)-α-DL-hex-4-ulose (6). Chromium trioxide (650 mg, 6.5 mmol) was added to a solution of pyridine (1.1 mL) in methylene chloride, and the resulting mixture was stirred for 15 min. A solution of **5a** (60 mg, 0.22 mmol) in methylene chloride (10 mL) was added rapidly, and the resulting mixture was stirred for 30 min. The reaction was diluted with ether (100 mL), and the mixture was filtered through a bed of Celite. The ether was evaporated at reduced pressure, and the residue was purified by radial chromatography (4:1; hexanes/ethyl acetate) to furnish 40 mg (68%) of **6** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 3 H), 2.10 (s, 3 H), 2.12 (m, 1 H), 2.25 (s, 3 H), 2.84 (dt, J = 13.1 Hz, J = 8.8 Hz, 1 H), 5.65 (dd, J = 13.1 Hz, J = 7.6 Hz, 1 H), 5.96 (dd, J = 8.8 Hz, J = 4.8 Hz, 1 H), 6.87 (m, 3 H).

1,2′-Anhydro-2,3,6-trideoxy-3-acetamido-5-*C*-(2-hydroxy-5-methylphenyl)-α-DL-*erythro*-hex-4-ulose (7). A stirred

mixture of oxalyl chloride (0.44 mL, 5.0 mmol) in methylene chloride (30 mL) under nitrogen was cooled to −78 °C. Dimethyl sulfoxide was added, and the reaction was stirred for 10 min. A solution of **4b** in methylene chloride (10 mL) was added slowly, and the reaction was stirred for 30 min. Triethylamine (4.2 mL, 30.1 mmol) was added dropwise, and after 15 min, the cooling bath was removed, and the reaction was allowed to come to room temperature for 1 h. The reaction was quenched with saturated sodium bicarbonate (30 mL), and the phases were separated. The aqueous phase was extracted with methylene chloride (3 × 40 mL). The combined organic phases were washed with 2% hydrochloric acid (2 × 40 mL), dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue, purified by radial chromatography (silica gel, ethyl acetate), furnished 0.70 g (88%) of **7** as a colorless solid, which sublimes at 160 °C: ^1H NMR ($CDCl_3$) δ 1.62 (m, 1 H), 1.69 (s, 3 H), 1.99 (s, 3 H), 2.29 (s, 3 H), 3.26 (ddd, J = 14.5 Hz, J = 8.6 Hz, J = 7.2 Hz, 1 H), 4.86 (dd, J = 13.1 Hz, J = 7.2 Hz, 1 H), 5.95 (br s, 1 H), 5.98 (dd, J = 8.6 Hz, J = 5.1 Hz, 1 H), 6.93 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 209.3, 170.2, 146.1, 131.4, 130.6, 126.0, 122.2, 117.5, 92.3, 79.3, 49.2, 31.7, 23.0, 22.0, 20.7; mass spectrum, m/z 275 ($M^{\cdot+}$), 232.

1,2′-Anhydro-2,3,6-trideoxy-3-acetamido-5-*C*-(2-hydroxy-5-methylphenyl)-α-DL-*threo*-hex-4-ulose (8). A solution of **7** (0.45 g, 1.6 mmol) and triethylamine (2 mL) in methylene chloride (30 mL) was stirred overnight at room temperature. The solvent was removed at reduced pressure, and the residue was purified by radial chromatography (silica gel, ethyl acetate) to give 0.45 g (100%) of **8** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.64 (s, 3 H), 1.96 (s, 3 H), 2.27 (s, 3 H), 2.35 (m, 1 H), 3.57 (m, 2 H), 5.40 (br s, 1 H), 5.61 (dd, J = 5.1 Hz, J = 2.6 Hz, 1 H), 6.84 (m, 3 H); mass spectrum, m/z 275 ($M^{\cdot+}$), 232.

1,2′-Anhydro-2,3,6-trideoxy-3-acetamido-4-hydroxy-5-*C*-(2-hydroxy-5-methylphenyl)-α-DL-*arabino*-hexopyranose (9). To a stirred, cold (0 °C) solution of sodium borohydride (0.10 g, 2.6 mmol) in 2-propanol (20 mL) was added a solution of **8** (0.38 g, 1.4 mmol) in 2-propanol (10 mL), and the mixture was stirred at room temperature for 2 h. The solvent was removed at reduced pressure, the residue was dissolved in water (30 mL), and the aqueous phase was extracted with methylene chloride (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated at reduced pressure. The residue was purified by radial chromatography (silica gel, ethyl acetate) to give 0.37 g (95%) of **9** as a colorless solid with mp 193–198 °C: ^1H NMR ($CDCl_3$) δ 1.65 (s, 3 H), 1.87 (m, 1 H), 1.98 (s, 3 H), 2.28 (s, 3 H), 2.31 (m, 1 H), 3.46 (d, J = 10.1 Hz, 1 H), 3.75 (m, 1 H), 5.44 (br s, 1 H), 5.62 (d, J = 2.2 Hz, 1 H), 6.85 (m, 3 H); mass spectrum, m/z 277 ($M^{\cdot+}$). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.31; H, 6.88; N, 4.74.

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Assignment of Absolute Configurations for 4-Methylcarnitine Stereoisomers by Proton Nuclear Magnetic Resonance

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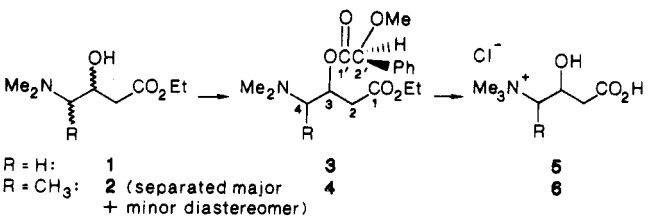
We recently reported[1] a chromatographic resolution for synthetic precursors of carnitine (**5**) and 4-methylcarnitine (**6**), although at that time the absolute configurations of **6** were not assigned. NMR has been increasingly used for such assignments (see ref 2 for a review), and it became apparent that the NMR method of Trost[3] for determining the absolute configuration of secondary alcohols as their *O*-methylmandelate esters might be applicable in these systems. Here we report the success of Trost's model for predicting the known configurations of carnitine enantiomers and describe a simple ^1H NMR method for establishing the absolute configurations for the two asymmetric centers in the four stereoisomers of 4-methylcarnitine.

Scheme I[a]



[a] See ref 1 for experimental details.

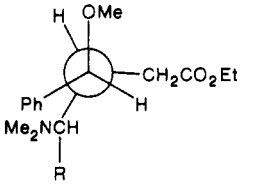
Table I. Summary of ^1H NMR Data for the Configurational Assignments of 5 and 6

configuration	chemical shift (δ) of NMe_2 resonance in precursor **3** or **4** ($CDCl_3$)	$J_{3,4}$ (Hz) for **5** or **6** (D_2O)
(+)-(*S*)-**5**[a]	2.13	1.87 (gauche)[b] 9.83 (anti)
(−)-(*R*)-**5**[a]	2.27	1.87 (gauche)[b] 9.83 (anti)
(−)-(3*S*,4*S*)-**6**[c]	2.07	7.1
(+)-(3*R*,4*R*)-**6**[c]	2.22	7.1
(+)-(3*S*,4*R*)-**6**[d]	2.09	1.0
(−)-(3*R*,4*S*)-**6**[d]	2.22	1.0

[a] Configuration known (ref 4). [b] Values taken from ref 6. [c] From major diastereomer of **2**. [d] From minor diastereomer of **2**.

Results and Discussion

Scheme I summarizes the method that was previously employed[1] for the resolutions of synthetic precursors to carnitine (**5**) and 4-methylcarnitine (**6**). As shown, the resolutions were achieved via chromatographic separation of the *O*-methylmandelate esters of hydroxy ester precursors **1** and **2**, and Trost[3] recently proposed a model that uses such esters for establishing the absolute configuration of secondary alcohols. As illustrated by the extended Newman projections (ester linkage omitted) for **3** and **4**,



(3*S*, 2′*S*)-**3**, R = H
(3*S*, 2′*S*)-**4**, R = CH_3

this model places the ester in a "Mosher-type" conformation. The substituent on the secondary alcohol which is closest to the phenyl group is always shielded in the ^1H NMR spectrum relative to the other secondary alcohol substituent. Thus by using (*S*)-*O*-methylmandelic acid and

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