the final refinement and difference map. In the final refinement, the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in the structure-factor calculations but their parameters were not refined. The final discrepancy indices are $R = 0.044$ and $R_w = 0.055$ for the remaining 1328 observed reflections. The final difference map has no peaks greater than ± 0.2 e A^{-3}.

Acknowledgment. The encouragement and advice provided by Dr. Manfred Weigele is greatly appreciated.

Stereospecific Synthesis of (−)-Anisomycin from D-Galactose

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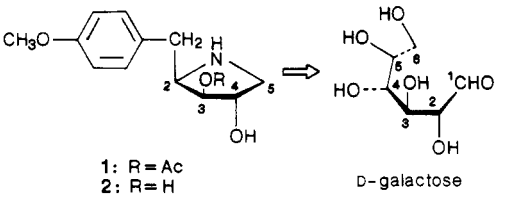
Received March 23, 1988

Synthesis starting from ethyl 2,3-di-*O*-benzyl-β-D-galactofuranoside (**3**), which is readily available from D-galactose, provided (2*R*,3*S*,4*S*)-2-(4-methoxybenzyl)pyrrolidine-3,4-diol (**2**, deacetylanisomycin) in eight steps with 18–20% overall yield. The sequence proceeded through the aldehyde **4** generated from **3** by periodate oxidation, conversion of **4** into ethyl 2,3-di-*O*-benzyl-5-deoxy-5-*C*-(4-methoxyphenyl)-α-L-arabinofuranoside (**6**) by Grignard reaction and subsequent ionic deoxygenation of the resulting alcohols **5**, and elaboration of the corresponding sugar oxime **8**. The latter was transformed by dehydrative mesylation into the L-arabinononitrile 4-mesylate **9**, which was reduced by diborane to the amine and cyclized by internal S_N2 reaction to give the dibenzyl ether **10** of **2**. Catalytic transfer hydrogenolysis then furnished **2**.

The streptomycetal antibiotic (−)-anisomycin (**1**) exhibits marked activity against some pathogenic protozoa and fungi.[1] The compound and its deacetyl derivative (**2**) have been used in the control of bean mildew and other fungal plant infections.[2] Early syntheses starting from L-tartaric acid,[3] diethyl L-tartrate,[4] or 2-(4-methoxybenzoyl)pyrrole[5] were nonstereoselective and gave low overall yields, but a highly selective synthesis from diethyl L-tartrate was recently accomplished by Iida et al.[6] who obtained **2** after 14, and **1** after 19 steps in yields of 5 and 2%, respectively. The racemic forms have been synthesized from D,L-tyrosine[7,8] and, most efficiently, from pyrrole-2-carboxaldehyde,[9] with the latter approach providing (±)-**2** and (±)-**1** in overall yields of 53 and 40% over 8 and 13 steps, respectively. Two chiral syntheses of **1** were based on the use of carbohydrates as starting materials. Thus, Verheyden et al.[10] described an 18-step sequence (8.5% yield) from 1,2;5,6-di-*O*-isopropylidene-D-glucose, and Buchanan et al.[11] reported a 13-step sequence (6% yield) from D-ribose. An alternative approach, comprising similar strategies but departing ultimately from (more economical) D-galactose, is disclosed in the present article. This sugar was considered particularly attractive from a viewpoint of stereochemical transformations required to reach the target: The C-2,3 moiety in D-galactose embodies the trans glycol grouping (C-4,3) of **2** with correct absolute configuration; conversion of OH-4 in the sugar into a leaving



group followed by its S_N2 displacement by amino nitrogen previously attached to C-1 was predicted to generate the pyrrolidine ring with its proper C-2 configuration; and the sugar C-5,6 terminal would serve to elaborate the benzylic substituent. Thus a single stereochemically significant and completely stereospecific transformation would be involved in the design that was realized as shown in Scheme I.

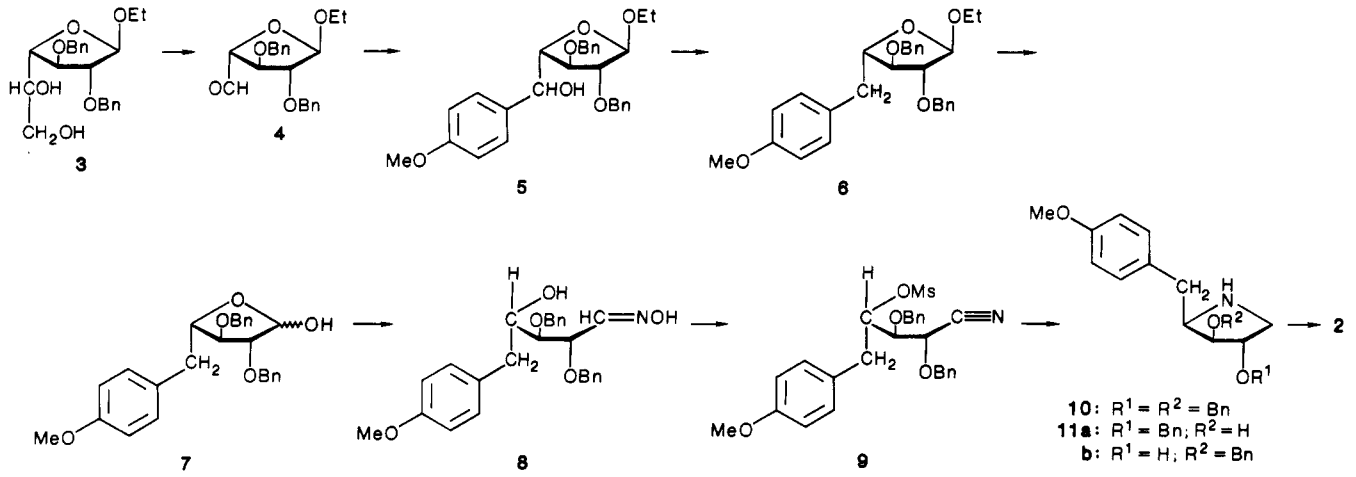
The known[12] ethyl 2,3-di-*O*-benzyl-β-D-galactofuranoside (**3**) served as the compound of departure. It is conveniently prepared from D-galactose via the diethyl dithioacetal[13] and ethyl β-D-galactofuranoside,[14] which is then protected as its 5,6-acetonide, benzylated, and deacetonated.[12] These five standard operations can be performed routinely on large scale, furnishing **3** in 30% yield.

Periodate oxidation of **3** gave the aldehyde **4** as an oil (ν_{max} 1730 cm^{-1}; ^1H NMR δ 9.63, d, J = 1.3 Hz), which, without further characterization, was allowed to react with (4-methoxyphenyl)magnesium bromide in ether. The resultant product was a mixture of epimeric alcohols (**5**), isolated in 87% yield after chromatography and fully characterized by ^1H NMR and analytical data. Epimer separation appeared possible but was difficult and was not pursued rigorously as the benzylic hydroxyl group was slated for removal in the next step. This was accomplished

(1) Jimenez, A.; Vazquez, D. In *Antibiotics*; Hahn, F. E., Ed.; Springer Verlag: Berlin, 1979; Vol. 5(2), pp 1–19.
(2) *The Merck Index*, 10th ed.; Rahway, NJ, 1983; p 691.
(3) Wong, C. M.; Buccini, J.; Te Raa, J. *Can. J. Chem.* **1968**, *46*, 3091.
(4) Felner, I.; Schenker, K. *Helv. Chim. Acta* **1970**, *53*, 754.
(5) Wong, C. M.; Buccini, J.; Chang, I.; Te Raa, J.; Schwenk, R. *Can. J. Chem.* **1969**, *47*, 2421.
(6) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 1069.
(7) Oida, S.; Ohki, E. *Chem. Pharm. Bull.* **1969**, *17*, 1405.
(8) In a brief communication a synthesis of optically active **2** from D-tyrosine has also been announced: Shono, T.; Kise, N. *Chem. Lett.* **1987**, 697.
(9) Schumacher, D. P.; Hall, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 6076.
(10) Verheyden, J. P. H.; Richardson, A. C.; Bhatt, R. S.; Grant, B. D.; Fitch, W. L.; Moffatt, J. G. *Pure Appl. Chem.* **1978**, *50*, 1363.
(11) Buchanan, J. G.; MacLean, K. A.; Wightman, R. H.; Paulsen, H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1463.
(12) Thiem, J.; Wessel, H.-P. *Justus Liebigs Ann. Chem.* **1983**, 2173.
(13) Green, J. W.; Pacsu, E. *J. Am. Chem. Soc.* **1937**, *59*, 1205.
(14) Pascu, E. *Methods Carbohydr. Chem.* **1963**, *2*, 354.

0022-3263/88/1953-4786$01.50/0

Scheme I



efficiently by ionic deoxygenation[10,15] with triethylsilane in the presence of trifluoroacetic acid, to produce ethyl 2,3-di-*O*-benzyl-5-deoxy-5-*C*-(4-methoxyphenyl)-α-L-arabinofuranoside (**6**). This furanoside proved remarkably resistant to acid hydrolysis under a variety of conditions; however, overnight boiling with 80% acetic acid did afford almost quantitatively the free sugar **7** as an anomeric mixture, which was not separable but obtained crystalline. Compounds **6** and **7** were chromatographically purified for determination of spectral and analytical data, although the crude materials were usable directly for the intended transformations. From **7** was then prepared the *E,Z* oxime **8**.

Treatment of **8** with methanesulfonyl chloride in pyridine caused dehydration and simultaneous *O*-mesylation, furnishing a good yield of the nitrile mesylate **9**. This reaction was precedented by an analogous one in the anisomycin synthesis of Buchanan et al.,[11] who proceeded to subject their particular nitrile mesylate to reductive cyclization (yield, 54%) with lithium aluminum hydride. Employing initially the same procedure we obtained the desired cyclization product **10** in similar yields. However, another method for nitrile reduction,[16] namely, with diborane in THF, proved to be preferable. Treatment of **9** with this reagent at the reflux temperature during 2–3 h led to complete reduction, and after processing and chromatography the main product **10** emerged pure in 65% yield, separate from 12% of less polar byproducts. The latter were partially debenzylated products; a small amount of one of them was obtained crystalline, and on the basis of spectral evidence it was tentatively assigned the structure **11a**, whereas a second byproduct seen in TLC presumably was the isomer **11b** (see also further below). The occurrence of benzyl ether cleavage as a significant side reaction appears noteworthy. Although full debenzylation of **10** was in fact required for completion of the synthesis, we did not investigate whether this could have been achieved by prolonging the diborane action under forcing conditions. Instead, conventional debenzylation by catalytic hydrogenolysis was chosen for that purpose. Hydrogenation over Pd/C was very sluggish, but transfer hydrogenolysis in the presence of formic acid[17] during 2 h at 45 °C proved satisfactory and led to crystalline (−)-deacetylanisomycin (**2**) in yields of 75–85%. Overall yields for the eight steps from readily accessible **3** were 18–20%. Conversion of **2** into **1** has been accomplished[4-6,9] quite efficiently,[18] so that the present work formally constitutes a new, and completely stereospecific, synthesis of the antibiotic.

The diol **2** obtained from **10** by transfer hydrogenolysis as just mentioned contained a small proportion of incompletely debenzylated material, which was removed during recrystallization and found to differ from **11a**. Spectroscopy suggested[19] that this contaminant was the regioisomeric benzyl ether **11b**.

Experimental Section

Column chromatography refers to flash chromatography on silica gel Merck 9385 (20–45 μm). Unless stated otherwise, the following solvent mixtures (v/v) were used: ethyl acetate–hexane, 1:1 (A), 1:2 (B), 1:3 (C), 1:5 (D), 1:10 (E), and 1:11.5 (F); and methanol–ethyl acetate, 1:4 (G). Optical rotations were measured at ~25 °C in a Perkin-Elmer 241 polarimeter. The IR data (ν_{max}) refer to spectra of thin films for syrups, and to Nujol mulls for solids. Mass spectral data (m/z) were obtained by the chemical ionization mode with ether. The NMR spectra were measured with a Varian XL 300 instrument; the ^1H data were obtained at 300 MHz, and the ^{13}C data at 75.43 MHz, both from $CDCl_3$ solutions unless othewise indicated.

Ethyl 2,3-Di-*O*-benzyl-β-D-galactofuranoside (3). This compound was obtained in 75% yield from ethyl β-D-galactofuranoside[14] by published procedures:[12] $[\alpha]_D$ −70.5° (*c* 1.3, $CHCl_3$) [lit.[12] $[\alpha]_D$ −71.7°]; m/z 389 ($M^+ + 1$), 343 ($M^+ - C_2H_5O$). The ^1H NMR data accorded fully with those reported.[12]

Ethyl (5*R*,*S*)-2,3-Di-*O*-benzyl-5-*C*-(4-methoxyphenyl)-α-L-arabinofuranoside (5). To a solution of **3** (5.6 g, 14.4 mmol) in 1:1 ethanol–water (60 mL) was added portionwise a solution of $NaIO_4$ (3.4 g, 15.9 mmol) in water (40 mL). The mixture was stirred at room temperature for 3 h, after which TLC (solvent A) indicated completion of the oxidation. The solvent was evaporated with several additions of toluene, and the aldehyde

(15) For a review, see: Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633.

(16) (a) Brown, H. C.; Korytnyk, W. *J. Am. Chem. Soc.* **1960**, *82*, 3866. (b) Brown, H. C.; Heim, P.; Yoon, N. M. *Ibid.* **1970**, *92*, 1637.

(17) Rao, V. S.; Perlin, A. S. *Carbohydr. Res.* **1980**, *83*, 175.

(18) Schumacher and Hall (ref 9) have performed this transformation on racemic **2**, achieving a 75% yield over five steps. Iida et al. (ref 6) employed a somewhat different five-step sequence and obtained a 45% yield of **1** from **2**.

(19) In their mass spectra, compounds **6–9** all exhibited prominent fragments at m/z 253, indicative of a structural moiety $MeOC_6H_4CH_2$-$(C_2H)OCH_2Ph$, and, although the pyrrolidine ring of **10** did not suffer fragmentation in this particular way, the monobenzyl ether **11b** did give a related fragment, m/z 252, which suggested that the *p*-methoxybenzyl and benzyloxy groups are situated on vicinal carbons. Such a peak was absent in the fragmentation patterns of **11a** and **2**. For **11b** the ^1H NMR signal H-4 ($J_{4,5} = 2$, $J_{4,5'} = 6$ Hz) showed coupling with a hydroxyl proton (removable by D_2O exchange), whereas the H-3 signal (d, $J_{2,3} = 4$, $J_{3,4} \sim 0$ Hz) did not. Although a similar, corroborating analysis for **11a** could not be made because of near coincidence of the H-3 and H-4 signals, the available evidence suppports a tentative attribution of the structures as shown.

4 was extracted from the residue by chloroform. Evaporation of the filtered extract gave 4 as an oil that was dried overnight in a high vacuum: yield 5.01 g (95%); IR 1730 cm^{-1}; ^1H NMR δ 9.63 (d, $J_{4,5}$ = 1.3 Hz). A Grignard reagent was prepared from 4-bromoanisole (10 g) in dry ether (30 mL), which was added dropwise during 1 h to a suspension of magnesium (1.22 g) in refluxing ether (70 mL), with addition of 3 droplets of Br_2 at the beginning. Refluxing was continued for 1.5 h, and aldehyde 4 (5.00 g) in dry ether (30 mL) was then added slowly during 40 min. The mixture was boiled for another 2 h, cooled, and processed by addition of ice water and NH_4Cl. Phase separation, extraction of the aqueous layer with fresh ether, washing of the combined organic phases with saturated $NaHCO_3$ solution followed by water, drying (Na_2SO_4), and evaporation of the solution gave crude 5 as an oil. In TLC the main products had R_f 0.15–0.2 (solvent D), but numerous faster spots were seen in addition.[20] The material was purified by chromatography (120 g of SiO_2), using as the eluant initially 1:7 ethyl acetate–hexane and changing the proportion gradually to 1:3. There was obtained a pure mixture of epimers 5 (5.49 g, 87% from 5 or 83% from 3): R_f 0.15 (preponderant) and 0.19, as a colorless oil; IR 3450, and strong bands at 1245 and 830 cm^{-1}; m/z 447 (M^+ – OH), 137 ($MeOC_6H_4CHOH$). Anal. Calcd for $C_{28}H_{32}O_6$ (464.5): C, 72.39; H, 6.94. Found: C, 72.24; H, 6.94.

Prior to pooling of the chromatographic fractions of 5, some of the slow-moving fractions that appeared to contain only the less polar epimer were collected separately. The syrup obtained therefrom had $[\alpha]_D$ –42° (c 0.8, $CHCl_3$): ^1H NMR δ 7.4–7.2 (m, 10 H, 2 Ph), 6.98 and 6.85 (m, 4 H, $MeOC_6H_4$), 5.09 (s, H-1), 4.61 (dd, and d after D_2O exchange, $J_{4,5}$ = 5.5 Hz, H-5), 4.50 (AB q, 2 H, $PhCH_2$), 4.26 (~t, J 5.5 Hz, 4-H), 4.22 (AB q, 2 H, $PhCH_2$), 3.97 (dd, $J_{1,2}$ = 1, $J_{2,3}$ = 2.2 Hz, H-2), 3.82 (dd, $J_{2,3}$ = 2.2, $J_{3,4}$ = 5.7 Hz, H-3), 3.79 (s, 3 H, OMe), 3.74 and 3.47 (2 dq, 1 H each, $MeCH_2$), 2.67 (d, exchangeable, OH), 1.19 (t, 3 H, J = 7 Hz, $MeCH_2$); ^{13}C NMR δ 159.2 and 132.1 (C-4, C-1 of $MeOC_6H_4$), 137.4 and 137.2 (C-1 of Ph and Ph'), 128.3–127.4 (arom), 133.7 (C-2,6 or -3,5 or $MeOC_6H_4$), 106.0 (C-1), 87.7, 85.8, 83.5 (C-2,3,4), 74.5 (C-5), 71.8 (2 CPh), 63.0 ($OCMe$), 55.2 ($MeOC_6H_4$), 15.1 (OCH_2Me).

Ethyl 2,3-Di-*O*-benzyl-5-deoxy-5-*C*-(4-methoxyphenyl)-α-L-arabinofuranoside (6). To a cooled (0–3 °C) solution of 5 (1.0 g) and triethylsilane (1 mL) in CH_2Cl_2 (100 mL) was added dropwise during 2 h a solution of trifluoroacetic acid (1 g) in CH_2Cl_2 (50 mL). The solution was stored at room temperature for 48 h, and then stirred with solid Na_2CO_3 until neutral, filtered, and evaporated to give crude 6, usable without purification for preparation of 7.

For analysis, crude 6 (from 1.0 g of 5) was purified by flash chromatography with solvent F as the eluant. The product was obtained as a colorless syrup (735 mg, 76%), showing no IR absorption in the 3000–3500-cm^{-1} region: m/z 447 (M^+ – 1, 15), 403 (M^+ – EtO, 20), 295 (55), 253 (100), 235 (32), 211 (41), 121 ($MeOC_7H_6$, 57); ^1H NMR δ 7.35–7.15 (m, 10 H, 2 Ph), 7.09 and 6.78 (AB q, 4 H, J = 8.6 Hz, p-$MeOC_6H_4$), 4.99 (d, $J_{1,2}$ = 1 Hz, H-1), 4.55–4.33 (2 partially overlapping AB q, 4 H, J_{gem} = 11.8 Hz, 2 $PhCH_2$), 4.22 (dt, $J_{3,4}$ = $J_{4,5}$ = $J_{4,5'}$ = 6.5 Hz, H-4), 3.97 (dd, $J_{1,2}$ = 1, $J_{2,3}$ = 3.5 Hz, H-2), 3.77 (s, 3 H, OMe), 3.7 (m, 2 H, H-3, $MeCHH_a$), 3.42 (dq, J = 7 and 11 Hz, $MeCHH_b$), 2.86 (d, 2 H, J = 6.5 Hz, H-5,5'), 1.17 (t, 3 H, J = 7 Hz, CH_2Me); ^{13}C NMR δ 158–113 region (as for 5), 105.5 (C-1), 88.7, 86.2, 81.3 (C-2,3,4), 72.0 (2 CPh), 62.8 ($OCMe$), 55.2 ($MeOC_6H_4$), 38.4 (C-5), 15.2 (OCH_2Me). Anal. Calcd for $C_{28}H_{32}O_5$ (448.5): C, 74.97; H, 7.19. Found: C 74.96; H, 7.31.

The product thus characterized was not entirely homogeneous: there was a minor spot (R_f 0.65) besides the main spot (R_f 0.75) in TLC (solvent B), and the NMR spectra contained additional, small signals. Upon isolation by repeated chromatography, the minor component was revealed by its NMR spectra to be the β-*anomer* of 6, which had evidently arisen by a slow anomerization under the influence of trifluoroacetic acid: essential differences in the ^1H NMR spectrum δ 4.82 (d, $J_{1,2}$ = 4.2 Hz, H-1), 4.60 and 4.40 (2 AB q, 4 H, 2 $PhCH_2$), 4.05 (m, 3 H, H-2,3,4), 3.80 and 3.43 (2 dq, 1 H each, J = 7 and 11 Hz, $MeCH_aH_b$), 2.92 (dd, $J_{4,5}$ = 7.4, J_{gem} = 13.9 Hz, H-5), 2.81 (dd, $J_{4,5'}$ = 6.4, J_{gem} = 13.9 Hz, H-5'); essential differences in the ^{13}C NMR spectrum δ 100.1 (C-1), 85.4, 84.5, 82.0 (C-2,3,4), 72.5 and 72.2 (CPh), 63.2 ($OCMe$), 55.3 ($MeOC_6H_4$), 41.7 (C-5), 15.3 (OCH_2Me). The presence of the anomer was of no consequence for the subsequent step.

2,3-Di-*O*-benzyl-5-deoxy-5-*C*-(4-methoxyphenyl)-α,β-L-arabinose (7). Crude 5-deoxyglycoside 6, obtained from 1.0 g of 5 (and shown to contain at least 735 mg of 6), was boiled overnight under reflux in 80% acetic acid (50 mL). The acid was evaporated at reduced pressure, with several additions of toluene, to give 7 as a partially crystallizing syrup: R_f 0.4 (solvent B); IR 3400 cm^{-1} (br). Chromatographic purification on SiO_2 by sequential elution with solvents E, D, C, and B furnished pure 7 (666 mg, 97%): m/z 420 (M^+, 1.5), 403 (M^+ – OH, 13), 295 (32), 253 (34), 235 (30), 211 (24), 191 (24), 181 (21), 163 (18), 121 ($MeOC_7H_6$, 100); ^1H NMR (for *major anomer*) δ 7.3 (m, 10 H, 2 Ph), 7.07 and 6.80 (AB q, 4 H, p-$MeOC_6H_4$), 5.39 (d, $J_{1,2}$ = 7.8 Hz; s after D_2O exchange, H-1), 4.58 and 4.30 (2 AB q, 2 × 2 H, 2 $PhCH_2$), 4.43 (sx, J = 3.5 and 7.0 Hz, H-4), 3.95 (nm, 1 H), 3.78 (s, 3 H, OMe), 3.75 (nm, 1 H), 3.10 (d, J = 8.1 Hz, exchangeable, OH), 2.93 (dd, J = 6.5 and 14 Hz, H-5), 2.78 (dd, J = 7.5 and 14 Hz, H-5'). The *minor anomer* gave at δ 5.35 a dd (collapsing to d with D_2O) with $J_{1,2}$ = 4 Hz for H-1, and at δ 3.51 a d (exchangeable) with J = 9 Hz for OH; multiplets for H-2,3,4 were in the δ 4.0–3.8 region. Anal. Calcd for $C_{26}H_{28}O_5$ (420.5): C, 74.26; H, 6.71. Found: C, 74.13; H, 6.55.

When the product was crystallized and recrystallized from ethyl acetate–hexane it showed mp 114–116 °C, $[\alpha]_D$ +6° (c 0.8, $CHCl_3$) but was essentially unchanged with respect to anomeric composition (NMR).

Preliminary studies of hydrolysis of 6 with HCl or H_2SO_4 in aqueous dioxane at the reflux temperature showed that 7 was produced slowly in the course of several hours, but considerable amounts of decomposition products were also formed (TLC).

2,3-Di-*O*-benzyl-5-deoxy-5-*C*-(4-methoxyphenyl)-L-arabinose (*E*,*Z*)-Oxime (8). A mixture of 7 (650 mg), hydroxylamine hydrochloride (200 mg), pyridine (5 mL), and absolute ethanol (25 mL) was gently heated under reflux for 5 h, concentrated in vacuo, and poured into ice water. The product was extracted into chloroform, and the extract dried (Na_2SO_4) and evaporated with several portions of added toluene. The semicrystalline residue was chromatographed on SiO_2 (20 g) with solvent E followed by solvent D, to give 8 (578 mg, 86%): R_f 0.2 and 0.15 (TLC, solvent B); $[\alpha]_D$ +15.6° (c 1.4, $CHCl_3$); m/z 436 (M^+ + 1, 7), 418 (M^+ – OH, 26), 253 (23), 211 (22), 163 (12), 121 ($MeOC_6H_4CH_2$, 100); ^1H NMR δ 7.53 (d, 0.7 H, $J_{1,2}$ = 7.8 Hz, H-1_E), 6.99 (d, 0.3 H, $J_{1,2}$ = 6.4 Hz, H-1_Z), 7.3 (m, 10 H, 2 Ph), 7.06 and 6.80 (AB q, 4 H, $MeOC_6H_4$), 5.12 (dd, 0.3 H, J = 3.6 and 6.4 Hz, H-2_Z), 4.6 (m, 3 H, benzylic), 4.4 (2 d, 0.7 and 0.3 H, benzylic), 4.32 (dd, 0.7 H, J = 4.5 and 7.7 Hz, H-2_E), 3.98 (m, 1 H, H-4), 3.76 (s, 3 H, OMe), 3.65 (dd, 0.3 H, J = 3.6 and 6.0 Hz, H-3_Z), 3.52 (dd, 0.7 H, J = 4.5 and 6.0 Hz, H-3_E), 2.86 (dd, 1 H, J = 3.4 and 13.9 Hz, H-5), 2.54 (m, H-5'), 2.48 and 2.38 (2 d, 0.7 and 0.3 H, exchangeable, OH). The assignments were derived from a COSY spectrum. Anal. Calcd for $C_{26}H_{29}NO_5$ (435.5): C, 71.70; H, 6.71; N, 3.22. Found: C, 71.44; H, 6.68; N, 3.38.

2,3-Di-*O*-benzyl-5-deoxy-5-*C*-(4-methoxyphenyl)-4-*O*-(methylsulfonyl)-L-arabinononitrile (9). A solution of oxime 8 (930 mg) in pyridine (45 mL) was added dropwise in the course of 1 h to a solution of mesyl chloride (6 mL) in pyridine (30 mL), stirred at room temperature. The mixture was then heated in a bath (60–70 °C) for 2 h, cooled, treated with a little water for 15 min, and stirred into ice water. Ether extraction, drying and evaporation of the extract, and repeated evaporation of added toluene from the residue gave crude 9 as a reddish-brown oil. Chromatography on SiO_2 (25 g), using first hexane and then solvent E as irrigants, gave 9 (750 mg, 71%) as a syrup, homogeneous in TLC (R_f 0.6, solvent B): $[\alpha]_D$ +19° (c 0.6, $CHCl_3$); IR 1355, 1170 cm^{-1} (MsO; a CN band was not discernible, as is not uncommon for highly oxygenated nitriles); m/z 496 (M^+ + 1, 16), 400 (M^+ – CH_3SO_3, 89), 253 (58), 232 (42), 211 (24), 149 (33), 121 (100); ^1H NMR δ 7.3 (m, 10 H, 2 Ph), 7.11 and 6.82 (AB q, 4 H, $MeOC_6H_4$), 4.98 (ddd, J = 3.2, 3.8 and 10 Hz, H-4), 4.8–4.5 (2 overlapping AB q, 4 H, 2 $PhCH_2$), 4.27 (d, $J_{2,3}$ = 5.5 Hz, H-2), 4.03 (dd, $J_{3,4}$ = 3.2, $J_{2,3}$ = 5.4 Hz, H-3), 3.77 (s, 3 H, Me), 3.18 (dd, $J_{4,5}$ = 3.7, J_{gem} = 14.5 Hz, H-5), 2.98 (dd, $J_{4,5'}$ = 10 Hz, J_{gem} = 14.5

(20) The same observation was reported in ref 10 for a similar reaction with the same Grignard reagent.

Hz, H-5′), 2.35 (s, 3 H, Me-SO_3). Anal. Calcd for $C_{27}H_{29}NO_6S$ (495.6): C, 65.44; H, 5.90; N, 2.83; S, 6.47. Found: C, 65.22; H, 5.78; N, 2.74; S, 6.61.

(2*R*,3*S*,4*S*)-3,4-Bis(benzyloxy)-2-(4-methoxybenzyl)-pyrrolidine (10) and Monobenzyloxy Hydroxy Analogue 11a. To ice-cooled 1 M BH_3 in THF (17 mL) was added slowly a solution of **9** (1.55 g) in dry THF (50 mL, freshly distilled from $LiAlH_4$). The solution was then boiled under reflux for 3 h (under N_2). After cooling and addition of 2 M HCl, the refluxing was resumed, and, after 20 min, most of the THF was distilled off at ordinary pressure.[21] The remaining, largely aqueous solution was evaporated in vacuo, and six portions of added methanol were sequentially evaporated from the residue, which was then triturated with water and basified with KOH pellets. The organic product was extracted into ether, and the extract was washed once with 1 M KOH and twice with water, dried ($MgSO_4$), and evaporated to give a colorless syrup (1.09 g after thorough drying in a desiccator; crude yield, 86.4%). The TLC (solvent G) showed a very strong spot for **10** (R_f 0.5), a weak double spot for **11** (R_f 0.3–0.15), and a minor contaminant at R_f 0.95. The strong IR band for CH_3SO_2O at 1355 cm^{-1} seen in **9** had disappeared.

During storage of the syrup for a few days, a small quantity of colorless needles of the monobenzyl ether **11a** crystallized and remained partly undissolved when the material was taken up in a small volume of cold ethyl acetate for column chromatography. Isolated **11a** (16 mg) had mp 157 °C: R_f 0.15; IR 3270 cm^{-1} (sharp, medium strong); *m/z* 314 (M^+ + 1, 100), 192 (M^+ − $MeOC_6H_4CH_2$, 73), 122 (8), 121 (31); ^1H NMR (DMSO-d_6) δ 7.3 (m, 5 H, Ph), 7.16 and 6.81 (AB q, 4 H, $MeOC_6H_4$), 4.44 (narrow AB signal, 2 H, *Ph*CH_2), 3.76 (nm, 2 H, H-3,4), 3.70 (s, 3 H, OMe), 2.8–2.5 (m, 5 H, H-2,5,5′ and CH_2 *Ar*). Anal. Calcd for $C_{19}H_{23}NO_3$ (313.5): C, 72.79; H, 7.40; N, 4.47. Found: C, 72.78; H, 7.31; N, 4.36.

Chromatography of the bulk of the product mixture on SiO_2 (15 g) with 1:4 ethanol–ethyl acetate gave the fast-running, unidentified impurity as a yellow oil (45 mg), followed by homogeneous **10** (R_f 0.5, solvent G) as a colorless syrup (820 mg, 65%) and by inhomogeneous end fractions, giving syrupy (52 mg) and solid (50 mg) materials, judged on the basis of IR and mass spectra to consist chiefly of **11a** and small proportions of **10** and possibly **11b**.

Compound **10** had $[\alpha]_D$ −62° (*c* 1.4, EtOH): IR 3330 (w, NH), 3050 region (4 bands, arom CH), 2900 (aliph, CH), 1607 (s), 1580 (w), 1507 (s), 1490 (w), 1450 (triplet), 1390, 1355, 1297, 1240 (s), 1200, 1175, 1130–1070 (s, br), 1030 (doublet), 950, 910, 820 (br), 730 (s, shoulder at 750), 695 (s) cm^{-1}; *m/z* 404 (M^+ + 1, 100), 312 (M^+ − C_7H_7, 4), 282 (M^+ − $MeOC_6H_4CH_2$, 31), 149 (15), 121 ($MeOC_7H_6$, 8); ^1H NMR δ 7.3 (m, 10 H, 2 *Ph*), 7.12 and 6.79 (AB q, 4 H, $MeOC_6H_4$), 4.54–4.42 (2 superposed AB q, 4 H, 2 *Ph*CH_2), 4.01 (ddd, $J_{3,4} < 1$, $J_{4,5} = 3.5$, $J_{4,5'} = 6$ Hz, H-4), 3.77 (s, 3 H, OMe), 3.69 (dd, $J_{3,4} < 1$, $J_{2,3} = 3.9$ Hz, H-3), 3.46 (dd, J = 6.0 and 12.4 Hz, H-5′), 3.37 (dt, $J_{2,3} = 4$, $J_{2,6} = J_{2,6'} = 7.5$ Hz, H-2), 2.88 (m, 3 H, H-5,6,6′) (assignments verified by COSY method). Anal. Calcd for $C_{26}H_{29}NO_3$ (403.5): C, 77.39; H, 7.24; N, 3.47. Found: C, 77.37; H, 7.30; N, 3.53.

(−)-Deacetylanisomycin (2). A 200-mL flask containing **10** (790 mg) and 10% Pd/C (1.5 g) in a mixture of 99% ethanol (50 mL) and 99% formic acid (12 mL) under an N_2 atmosphere was immersed in an ultrasonic bath at 45 °C. After sonication for 90 min (or more, vide infra), only slow-moving product (R_f 0.1, solvent G) was seen in TLC. The catalyst was filtered off and washed exhaustively with methanol, and the filtrate was evaporated to dryness with several additions of toluene followed by a portion of water. The partly crystalline residue was dissolved in a minimum amount of warm water; addition of 1 M NaOH (4 mL) produced a copious white precipitate of microscopic needles (**2**) that were washed with cold water. Further crops were obtained by concentrating the mother liquor, for a total of 337 mg (77%). All crops gave identical IR spectra and melted within ~2 °C in the range of 167–173 °C. Combined and recrystallized, the product showed mp 172–173 °C (needles precipitating from water), 173–175 °C (stout prisms from slowly evaporating mother liquor), or 176–177 °C (needles from 95% EtOH), and $[\alpha]_D$ −22.7° (*c* 1, MeOH) (lit.[4,6,22] mp 173–174 °C, 176–177 °C, 176–178 °C, and lit.[4,22] $[\alpha]_D$ −24 ± 1 and −20°); *m/z* 224 (M^+ + 1, 93), 122 (19), 121 (34), 102 (M^+ − $MeOC_7H_6$); IR 3450–3300 (br), 3260 (sharp) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.16 and 6.81 (AB q, 4 H, $MeOC_6H_4$), 4.63 (d, J = 3.2 Hz, exchangeable, OH), 4.57 (d, J = 4.8 Hz, exchangeable, OH), 3.83 (m; dd after exchange, J ~ 2, 5.5 Hz, H-4), 3.70 (s, 3 H, OMe), 3.47 (nt, d after exchange, J = 3.5 Hz, H-3), 3.17 (dd, J = 5.6 and 11.9 Hz, H-5′), 2.98 (ddd, J = 3.5, 6.8, 7.6 Hz, H-2), 2.74 (dd, J = 7.6 and 13.4 Hz, H-6), 2.53 (dd, partly obscured by DMSO signals, J = 6.8 Hz, H-6′), 2.38 (dd, J = 2.1 and 11.8 Hz, H-5), in good agreement with reported[8] data.

The *hydrochloride*[22] of **2** had mp 227–229 °C dec; $[\alpha]_D$ +6° (*c* 0.7, MeOH) (lit.[3,22] mp 224–226 °C, lit.[3] $[\alpha]_D$ +7°).

The rate of the heterogeneous transfer hydrogenolysis of **10** just described probably depends on the efficiency of agitation. Therefore it is important to monitor the reaction by TLC and, if necessary, prolong sonication accordingly. In one 90-min run, a small proportion of incompletely hydrogenolyzed material (R_f ~0.3) had persisted, and the **2** obtained in several crystalline fractions showed elevated $[\alpha]_D$ values (e.g., −28°, −32°), due evidently to the presence of some strongly levorotatory impurity. During recrystallization of such fractions from hot water, a small proportion of sparingly soluble material, $[\alpha]_D$ −84° (*c* 1, MeOH), could be separated. It was not crystallizable from ethyl acetate by seeding with **11a** and also differed from the latter in its mass and ^1H NMR spectra, which indicated, however, that some **2** (~30%) was present. The main component in the material was designated **11b**. The mass spectrum showed the following peaks (in addition to those attributable in part to **2**): *m/z* 314 (M^+ + 1, 100), 252 (3.2), 192 (46), 149 (11); ^1H NMR (DMSO-d_6) for **11b** δ 7.3 (m, 5 H, Ph), 7.10 and 6.80 (AB q, 4 H, $MeOC_6H_4$), 4.61 and 4.37 (AB q, 2 H, *PH*CH_2), 4.16 (ddd, $J_{3,4} < 1$, $J_{4,5'} = 6$, $J_{4,5} = 2$ Hz, H-4), 3.71 (s, 3 H, OMe), 3.40 (dd, $J_{3,4} < 1$, $J_{2,3} = 3.5$ Hz, H-3), 3.25–3.15 (m, 2 H, $J_{4,5'} = 6$, $J_{5,5'} = 12$ Hz, H-2 and -5′), 2.75 (dd, j = 8 and 14 Hz, H-6), 2.64 (dd, J = 6.5 and 14 Hz, H-6′), 2.49 (dd, downfield part obscured by DMSO signals, $J_{4,5} = 2$ Hz, H-5). The assignments were derived from a COSY plot.

Acknowledgment. This work was supported by Grant GM-35244 from the National Institutes of Health, U.S. Public Health Service.

Registry No. **1**, 22862-76-6; **2**, 27958-06-1; **2**·HCl, 1963-47-9; **3**, 76696-18-9; **4**, 115828-68-7; **5** (epimer 1), 115828-69-8; **5** (epimer 2), 115828-70-1; **6**, 115828-71-2; α-**7**, 115828-72-3; β-**7**, 115828-73-4; (*E*)-**8**, 115828-74-5; (*Z*)-**8**, 115828-75-6; **9**, 115828-76-7; **10**, 115828-77-8; **11a**, 115828-78-9; **11b**, 115828-79-0; 4-BrC_6H_4OMe, 104-92-7; ethyl β-D-galactofuranoside, 13403-13-9; D-galactose, 59-23-4.

(21) The procedure described (ref 16) for nitrile reduction was followed. The acid treatment is said to be necessary for hydrolytic liberation of the amine from a trialkylborazole that arises from the nitrile on reduction. It was not investigated whether such a trimer does in fact form in the present case where the primary amine has an opportunity to react immediately by intramolecular S_N2 displacement. If a borazole was first formed, cyclization of the liberated amino mesylate must have taken place rapidly during the subsequent, alkaline processing.

(22) Beereboom, J. J.; Butler, K.; Pennington, F. C.; Solomons, I. A. *J. Org. Chem.* **1965**, *30*, 2334.