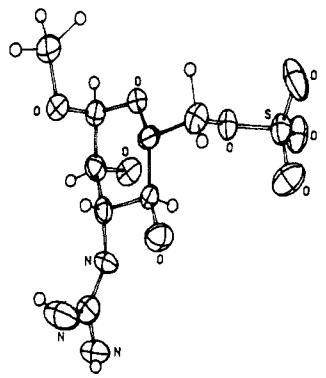

Figure 1. ORTEP diagram of IV.

two in general positions were found to have fractional occupancy factors (~30%). When the hydration was taken into account, reasonable agreement was found between observed and calculated density values.

Final anisotropic refinement of the nonhydrogen atoms to give $R = 0.071$ was made with 12 hydrogens (refined isotropically), and anomalous dispersion effects of sulfur were included.[16] All calculations were made by using the XRAY 76 progam system.[17]

An ORTEP diagram of the structure is shown in Figure 1. The hydrogen atoms depicted in this drawing correspond to those actually located in electron density difference maps; hydrogens of the two hydroxyl groups were not observed.

Acknowledgment. We thank Dr. J. Goodman and Mr. A. J. Shay and associates for large-scale fermentations and Mr. M. Dann and associates for large-scale recoveries. We also acknowledge Mr. L. Brancone and associates for microanalytical data and Dr. W. Gore, Mr. W. Fulmore and associates for spectral and rotational data. We especially thank Dr. J. C. French of the Parke Davis Co. for generously supplying us with several samples of myomycin. We are also obliged to Mr. Peter Demou of Yale University, who carried out the 270-MHz proton NMR spectroscopy.

Registry No. I, 87-89-8; II, 75919-38-9; III, 75919-39-0; IV, 75919-40-3; V·5H_2SO_4, 75919-42-5; VI·5H_2SO_4, 75947-46-5; VII·5H_2SO_4, 75919-44-7; VIII·5H_2SO_4, 75919-44-7; VIII, 75919-45-8; IX·2.5H_2SO_4, 75919-47-0; X·3H_2SO_4, 75933-28-7; XI·3.5H_2SO_4, 75933-30-1; XII·1.5H_2SO_4, 75919-49-2; XII methyl ester 2H_2SO_4, 75919-51-6; XII acetylated methyl ester, 75919-52-7; XIII·2H_2SO_4, 75919-54-9; XIII methyl ester 2.5H_2SO_4, 75919-56-1; XIII acetylated methyl ester, 75919-57-2; XIV, 75919-58-3; XIV methyl ester 3H_2SO_4, 75919-60-7; myomycin, 75919-61-8; L-β-lysine 2HCl, 35761-15-0; β-lysine methyl ester sulfate salt, 75919-63-0; β-lysine dipeptide methyl ester 1.5H_2SO_4, 75919-64-1.

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Synthesis of Substituted 2,6-Dioxabicyclo[3.1.1]heptanes. 1,3-Anhydro-2,4,6-tri-*O*-benzyl- and 1,3-Anhydro-2,4,6-tri-*O*-(*p*-bromobenzyl)-β-D-mannopyranose

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The title compounds 1,3-anhydro-2,4,6-tri-*O*-benzyl- and 1,3-anhydro-2,4,6-tri-*O*-(*p*-bromobenzyl)-β-D-mannopyranose were synthesized by a reaction sequence involving blocking the C-3 hydroxyl with an allyl group by first forming a dibutylstannylene complex between the C-2 and C-3 hydroxyls of methyl 6-*O*-trityl-α-D-mannopyranoside. The product was then detritylated, fully acetylated, carefully purified, and then benzylated. Acid hydrolysis removed the C-1 methoxy group, while the C-3 allyl was removed by conventional methods. Reaction with hydrogen chloride in ether led to the mannopyranosyl chlorides, which in the presence of strongs bases like NaH and *t*-BuOK yielded the desired anhydro sugars. These compounds are the required precursors for the synthesis of 1,3-mannopyranans by ring-opening polymerizations.

The preparation and polymerization of bicyclic acetals to produce stereoregular polysaccharides or related polyacetals is a goal of studies in a number of laboratories,[1-6] since the polymers obtained have proven to be useful model systems for immunological and other biochemical investigations.[7-9] Examples of stereoregular polymerization have been reported for a 1,2-anhydro-,[10] a 1,4-anhydro-,[11] and a number of 1,6-anhydroglycopyranose

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derivatives,[12-15] and it, therefore, appears useful to investigate the synthesis of 1,3-anhydroglycopyranoses. The only report in the literature of a 1,3-anhydrosugar was that of 1,3-anhydro-β-D-galactopyranose,[16] but its structure was erroneously assigned on the basis that it failed to undergo periodate oxidation (implying lack of a 1,2-diol group). However, it is known that if the C-1 and C-2 hydroxyls are at an angle greater than 120°, then periodate oxidations are not feasible, and subsequent studies[18] conclusively proved that the compound was 1,6-anhydro-α-D-galactofuranose. Thus, it appears that the syntheses of 1,3-anhydro-2,4,6-tri-*O*-benzyl-β-D-mannopyranose (**11**) and 1,3-anhydro-2,4,6-tri-*O*-(*p*-bromobenzyl)-β-D-mannopyranose (**16**), which we are now reporting, and a glucose analogue which has recently been synthesized in our laboratory[19] give the first examples of this class of compounds. These monomers are of interest since their stereospecific polymerization would give an α-(1→3)-linked mannopyranan. A polysaccharide of this structure has once been reported as a component of the invertase molecule,[20] but the claim has been refuted.[21] However, terminal α-(1→3)-linked mannopyranose units are important immunodeterminants of yeast mannans,[22] and α-(1→3)-linked mannose units are found at branch points of glycosyl side chains of a number of glycoproteins.[23]

In previous syntheses of 1,2-anhydro- and 6-*O*-trityl a key intermediate has been a 1,2- or 1,3-diol, which dibutylstannylene oxide then been converted to the corresponding glycosyl chloride. In the present case, we attempted to use as starting material, both allyl and methyl α-D-mannopyranoside. Unfortunately, the intermediates allyl 3-*O*-allyl-α-D-mannopyranoside and its triacetate were not crystalline and were difficult to separate from isomeric impurities, so this route was abandoned.

Methyl α-D-mannopyranoside was converted to its 6-*O*-trityl derivative **2** by conventional methods[24] and allowed to react with dibutylstannylene oxide and allyl bromide according to a modification of Nashed's[25] method to form **3** and thence **4**. The use of **2** has been found to be preferable to Nashed's reaction with the 4,6-*O*-benzylidene derivative, since the latter compound in our hands is more difficult to prepare in high yield. Only very small quantities of isomeric byproducts appeared to be produced. Detritylation of **4** was effected with HBr in glacial acetic acid,[26] and the triol **5** thus obtained was acetylated with acetic anhydride in pyridine.[27] The triacetate **6** was carefully crystallized to remove traces of isomeric impurities, the presence of which was established by ^{13}C NMR spectroscopy of the mother liquors. Benzylation of **6** proceeded without rearrangement of the allyl group and the expected compound **7** was obtained as a syrup. Rearrangement of the allyl group to propenyl was achieved easily and quantitatively by refluxing with potassium *tert*-butoxide (*t*-BuOK) in tetrahydrofuran for a few hours. Hydrolysis of **8** proceeded cleanly in dioxane–water–HCl with no loss of methoxyl group. Acetolysis of the methoxyl group on **9** could not be achieved without debenzylation, but the methyl glycoside was converted to 2,4,6-tri-*O*-benzyl-α-D-mannopyranosyl chloride (**10**) by treatment with a saturated solution of hydrogen chloride in ether at room temperature for 72–96 h, under conditions devised by Micheel and Kreutzer[28] for displacing hydroxyl groups with chloride. This step proved satisfactory in small-scale experiments but was found difficult to scale up to larger quantities. Ring closure of **10** to the 1,3-anhydro derivative **11** was achieved by the use of potassium *tert*-butoxide or a slurry of sodium hydride in tetrahydrofuran.

The mass spectrum and ^1H NMR and ^{13}C NMR spectra of the product are consistent with a structure of 1,3-anhydro-2,4,6-tri-*O*-benzyl-β-D-mannopyranose. The mass spectrum, run at a chamber temperature of 200 °C, showed a parent peak of moderate intensity at 432, consistent with a molecular formula of $C_{27}H_{28}O_5$ (**11**).[29]

The anomeric peak position in the ^{13}C NMR spectrum is observed at 107.26 ppm, about 1.1 ppm lower field than its glucose analogue and about 7 ppm lower field than 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-mannopyranose (100.09 ppm).[30] The latter chemical-shift difference is in the direction expected from a comparison of oxetane (72.8 ppm) and tetrahydrofuran (68.6 ppm).[31,32] The anomeric peak position in the ^1H NMR spectrum appears as a doublet at 5.37 ppm with a coupling constant of 4 Hz. In the corresponding glucose analogue, the anomeric proton appeared as a triplet demonstrating both vicinal (1,2) and long-range coupling, with $^3J_{1,2} \simeq {}^4J_{1,3} \simeq 4$ Hz. In compound **11**, the dihedral angle between C-1–H-1 and C-2–H-2 bonds approaches 90° and therefore $^3J_{1,2}$ must be at a minimum and only $^4J_{1,3} \simeq 4$ Hz is observed. The steric requirements of C-6 assure that the preferred conformation of the fused six-membered rings in **11** will be chairlike for the 1,3-dioxane ring and boatlike for the pyranose ring. In this conformation the dihedral angle between C-1–H-1 and C-5–H-5 is such that long-range coupling in this sense can also be ignored.

The assignments of the other carbon resonances in the ^{13}C NMR spectrum of the various compounds synthesized were based on comparison to the chemical shifts shown by methyl α-D-mannopyranoside[32] and of several partially benzylated and acetylated derivatives of D-mannopyranose.[33-37] In the methyl α-D-mannopyranoside the

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order of the C's going upfield is C-5, C-2, C-3, C-4, C-6, and the range is 62.1 to 73.6.[32] The C-6 resonance is readily identified (62.1 ppm) since in the off-resonance decoupled spectrum the hydroxymethyl carbon gives rise to a triplet, while the next highest field value (67.9 ppm) was assigned to C-4 since it is furthest away from the anomeric center. Identification of the C-2 signals was achieved by selective decoupling experiments.[32] Benzylation of an equatorial or primary hydroxyl is assumed to shift the attached carbon downfield ~7 ppm and adjacent carbons upfield ~1–2 ppm. Also, benzylation of an axial hydroxyl group (the one on C-2 in our case) would cause that particular carbon (C-2) to shift downfield by only ~3 ppm. No attempt was made to distinguish the benzylic methylene signals from those of C-2, C-3, C-4, and C-5 (though, in principle, this could be done by off-resonance spectroscopy); however, it would be safe to assume that etherified C-2 and C-3 would be further downfield as compared to etherified C-4, the benzylic methylenes, and C-5. Also, etherifed C-3 is expected to be slightly more downfield than etherified C-2, since the former is equatorial and the latter axial.

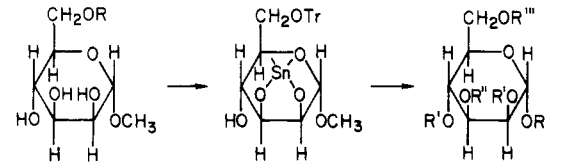
Although **11** was pure according to high-performance LC, and showed no evidence of impurities in the ^1H NMR, ^{13}C NMR, and mass spectra, the compound decomposed slightly with time at ordinary temperatures and there was difficulty in obtaining an accurate analysis. The synthesis was, therefore, repeated from compound **1** to **6**. Compound **6** was then converted to methyl 3-*O*-allyl-2,4,6-tri-*O*-(*p*-bromobenzyl)-α-D-mannopyranoside (**12**) in order to obtain analogous intermediates that were crystalline. Hydrolysis of the fully substituted glycoside was successfully carried out in a solution of hydrochloric acid in acetic acid to give **13**. Treatment of **13** with tris(triphenylphosphine)-chlororhodium in 90% ethanol gave directly 2,4,6-tri-*O*-(*p*-bromobenzyl)-D-mannopyranose (**14**). This crystalline compound **14** was converted to the corresponding crystalline glycosyl chloride **15** by the method of Micheel and Kreuzer.[28] Ring closure with sodium hydride in tetrahydrofuran gave a syrupy 1,3-anhydro-2,4,6-tri-*O*-(*p*-bromobenzyl)-β-D-mannopyranose (**16**) of correct analysis and with NMR spectral characteristics closely similar to those of **11** except in the aromatic region.

Experimental Section

General Methods. ^1H NMR spectra were determined with a Varian A-60-A spectrometer and ^{13}C NMR spectra were recorded with a Varian XL100-15 spectrometer, in the Fourier transform mode, for solutions in chloroform-*d* with Me_4Si as internal standard in 5-mm (o.d.) tubes. All values are in parts per million downfield of the Me_4Si signal. Peak assignments are based on comparison to the known chemical shifts of several derivatives of D-mannopyranose.[32-37] The compounds were purified on an analytical Waters Associates liquid chromatograph equipped with a differential refractomer R401, a differential U.V. detector, and a Glenco high-performance LC pumping system. Ethyl acetate–hexane mixtures were used on a silica gel column (Whatman, Partisil M9 10/25) at a flow rate of 8 mL/min. A stainless-steel column (2 ft × 0.75 in. (o.d.)) packed with polyvinyl acetate (Fractogel PVA 6000, EM Laboratories Inc., Elmsford, NY, 10523) was used at a toluene flow rate of 3 mL/min in the final purification of the anhydro monomer **11**. For large-scale separations a Waters Associates preparative HPLC 500 with a silica gel column was used. TLC was performed on Bakerflex silica gel 1B-F plates. The mass spectrum was obtained with a Hitachi Model RMU-6E mass spectrometer. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter in jacketed 1-dm cells at 25 °C.

Reagents. *N,N*-Dimethylformamide (DMF) was distilled from calcium hydride. All other solvents were spectral grade and used without further purification.

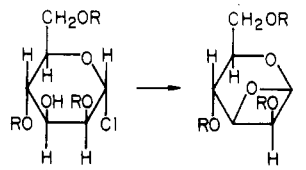
Scheme I



1, R = H
2, R = trityl (Tr)

3

4, R = CH_3; R′ = H; R″ = allyl; R‴ = trityl
5, R = CH_3; R′ = R‴ = H; R″ = allyl
6, R = CH_3; R′ = R‴ = acetyl; R″ = allyl
7, R = CH_3; R′ = R‴ = benzyl (Bzl); R″ = allyl
8, R = CH_3; R′ = R‴ = Bzl; R″ = prop-1-enyl
9, R = CH_3; R′ = R‴ = benzyl; R″ = H
12, R = CH_3; R′ = R‴ = *p*-bromobenzyl (Brbzl); R″ = allyl
13, R = H; R′ = R‴ = Brbzl; R″ = allyl
14, R = R″ = H; R′ = R‴ = Brbzl



10, R = Bzl
15, R = Brbzl

11, R = Bzl
16, R = Brbzl

Methyl 3-*O*-Allyl-α-D-mannopyranoside (5). Dibutyltin oxide (29 g, 0.116 mol) was added to a solution of **2** (50 g, 0.114 mol) in methanol (400 mL) and the mixture was refluxed for about 4 h until the solution became clear. The methanol was then stripped off to give a foamy white solid tin complex (presumably methyl 6-*O*-trityl-2,3-*O*-(dibutylstannylene)-α-D-mannopyranoside), which was dissolved in DMF (200 mL), and allyl bromide (30 mL, 0.35 mol) was added. The mixture was heated at 75–80 °C for 7 h after which the reaction was virtually complete, as indicated by TLC ($CHCl_3$–CH_3OH (4:1) or EtOAc–hexanes (1:1)). The excess allyl bromide and DMF were evaporated to leave a thick syrup. This crude reaction mixture was detritylated by dissolving it in glacial acetic acid (140 mL), cooling in an ice bath, and bubbling in HBr (9.5 g, 0.118 mol) with rapid stirring. Within 30 s the reaction was complete and trityl bromide precipitated out of solution. This mixture was filtered through sintered glass under vacuum into 1 L of ice–water. The ice–water mixture was partially neutralized with $NaHCO_3$ to destroy excess HBr and then extracted three times with 100 mL of $CHCl_3$. The 3-*O*-allyl derivative **5** remained in the water layer while the $CHCl_3$ layer contained traces of unreacted starting materials. The water layer was now evaporated at low temperature (~35 °C) to virtual dryness and extracted several times with $CHCl_3$, and the organic layer was dried with anhydrous Na_2SO_4 and evaporated to give a syrup of **5**. The physical constants and spectra obtained were the same as those obtained for the compound prepared by another route[38] (yield 75%).

Methyl 2,4,6-Tri-*O*-benzyl-3-*O*-α-D-mannopyranoside (7). Compound **5** was acetylated to give methyl 2,4,6-tri-*O*-acetyl-3-*O*-allyl-α-D-mannopyranoside (**6**) by the method reported previously.[38] It was found imperative to recrystallize **6** repeatedly to remove small quantities of isomeric compounds (presumably methyl 3,4,6-tri-*O*-acetyl-2-*O*-allyl- and/or 2,3,6-tri-*O*-acetyl-4-*O*-allyl-α-D-mannopyranoside), the presence of which was established from ^{13}C NMR. For example, the ^{13}C NMR of **6** showed single peaks at 55.25 ppm (OCH_3) and 99.16 (C-1) while the mother liquors also showed peaks of similar relative intensities

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at 55.66, 55.31, and 55.19 (OCH_3) and at 99.46, 99.10, and 98.82 ppm (C-1). To a solution of **6** (12 g, 0.037 mol) in toluene (150 mL) was added finely powdered KOH (46 g). Benzyl chloride (94 g, 0.74 mol) was then slowly added and the mixture refluxed under vigorous agitation with a mechanical stirrer for 5–6 h. The reaction mixture was extracted with water to remove most of the KOH, but the solution was left slightly basic. The excess benzyl chloride was removed by steam distillation. The mixture was extracted repeatedly with CH_2Cl_2, the organic layer dried with anhydrous Na_2SO_4, and the CH_2Cl_2 stripped off. After compound **7** thus obtained was purified by high-performance LC (EtOAc–hexanes, 1:4), both the ^1H NMR and ^{13}C NMR showed that **7** was pure; however, it failed to crystallize: yield 85%; $[\alpha]_D^{23}$ +33.3° (*c* 0.4, chloroform); ^1H NMR ($CDCl_3$) δ 7.25–7.18 (15 H, m, aromatic H), 6.17–5.62 (1 H, m, CH_2=$CHCH_2O$), 5.45–4.98 (2 H, m, CH_2=$CHCH_2O$), 4.80–4.30 (7 H, m, H-1, 3 CH_2Ph), 4.10–3.75 (8 H, m, H-2, H-3, H-4 H-5, 2 H-6, OCH_2CH=CH_2), 3.27 (3 H, s, OCH_3); ^{13}C NMR ($CDCl_3$) 139.09, 138.87 (aromatic C-1), 135.40 (H_2C=$CHCH_2O$), 128.54, 128.13, 127.95, 127.77 (aromatic C), 116.69 (H_2C=$CHCH_2O$), 99.41 (C-1), 80.22 (C-3), 75.16 (C-2), 73.54, 72.88, 72.11 (C-4, C-5, OCH_2), 71.15 (H_2C=$CHCH_2O$), 69.68 (C-6), 54.77 (OCH_3).

Anal. Calcd for $C_{31}H_{36}O_6$: C, 73.79; H, 7.19. Found: C, 72.85; H, 6.33.

Methyl 2,4,6-Tri-*O*-benzyl-3-*O*-propenyl-α-D-mannopyranoside (8). To a solution of **7** (7 g, 0.014 mol) in toluene (40 mL) was added *t*-BuOK (6 g, 0.053 mol) and the mixture refluxed for 6 h. The toluene was extracted with water to remove the excess *t*-BuOK, and the solution concentrated on a rotary evaporator to give a syrup which could not be crystallized. While the ^1H NMR showed that the reaction was quantitative, the yield of the isolated pure compound was 90%: $[\alpha]^{23}_D$ +45.6° (*c* 0.5, chloroform); ^1H NMR ($CDCl_3$) δ 7.27–7.20 (15 H, m, aromatic H), 6.18–6.08 (1 H, m, OCH=$CHCH_3$), 5.00–4.32 (8 H, m, H-1, CH_2Ph, OCH=$CHCH_3$), 4.08–3.75 (6 H, m, H-2, H-3, H-4, H-5, 2 H-6), 3.32 (3 H, s, OCH_3), 1.73–1.60 (3 H, J_{H,CH_3}(trans) = 1.5, J_{H,CH_3}(cis) = 7 Hz, CH_3CH=CHO); ^{13}C NMR ($CDCl_3$) 145.77 (CH_3CH=CHO), 138.73 (aromatic C-1), 128.48, 127.90, 127.79 (aromatic C), 100.77 (CH_3CH=CHO), 99.69 (C-1), 82.84 (C-3), 76.44 (C-2), 75.01, 74.81, 73.57, 73.32, 71.88 (C-4, C-5, OCH_2Ph), 69.41 (C-6), 9.42 (CH_3CH=CHO).

Methyl 2,4,6-Tri-*O*-benzyl-α-D-mannopyranoside (9). To a solution of **8** (5.4 g, 0.011 mol) in 50 mL of dioxane was added 1 N HCl (4 mL) in water and the mixture refluxed for 1 h. Most of the dioxane was evaporated, and the product was extracted into $CHCl_3$, dried with anhydrous Na_2SO_4, and cleaned by preparative high-performance LC (EtOAc–hexanes, 1:2): yield 95%; $[\alpha]^{23}_D$ +16.9° (*c* 1.5, chloroform); ^1H NMR ($CDCl_3$) δ 7.26–7.20 (15 H, m, aromatic H), 4.85–3.67 (13 H, m, H-1, H-2, H-3, H-4, H-5, 2 H-6, 3 CH_2Ph), 3.30 (3 H, s, OCH_3), 2.25 (1 H, s, OH); ^{13}C NMR ($CDCl_3$) 138.79, 138.61, 138.12 (aromatic C-1), 128.59, 128.42, 127.95, 127.64 (aromatic C), 98.20 (C-1), 78.54 (C-2), 76.64, 74.67, 73.42, 72.87, 71.86, 71.08 (C-3, C-4, C-5, OCH_2), 69.41 (C-6), 54.76 (OCH_3).

2,4,6-Tri-*O*-benzyl-α-D-mannopyranosyl Chloride (10). Compound **9** (2 g, 0.0043 mol) was dissolved in dry ethyl ether (200 mL) and HCl gas bubbled in to saturation under a N_2 atmosphere and in an ice bath. After 3 days, the reaction was ~85% complete as indicted by NMR. Ether was evaporated and the product then purified by analytical LC (EtOAc–hexanes, 1:2), using a silica gel column: $[\alpha]^{23}_D$ +51.3° (*c* 1.2, chloroform); ^1H NMR ($CDCl_3$) δ 7.25–7.21 (15 H, m, aromatic H), 6.13 (1 H, d, *J* = 1 Hz, H-1), 4.92–4.20 (8 H, m, 3 CH_2Ph, 2 H-6), 3.92–3.72 (4 H, m, H-2, H-3, H-4, H-5), 2.45 (1 H, s, OH); ^{13}C NMR ($CDCl_3$) 138.44, 138.26, 137.42 (aromatic C-1), 128.72, 128.46, 127.88, 127.72, 127.08 (aromatic C), 91.11 (C-1), 81.11 (C-2), 75.68, 74.90, 74.07, 73.41, 73.12 (C-3, C-4, C-5, OCH_2), 70.43 (C-6).

Anal. Calcd for $C_{27}H_{29}ClO_5$ (**10**): C, 69.15; H, 6.23. Found: C, 68.38; H, 5.53.

1,3-Anhydro-2,4,6-tri-*O*-benzyl-β-D-mannopyranose (11). Compound **10** (1.1 g, 0.0023 mol) was dissolved in freshly distilled tetrahydrofuran (50 mL) and *t*-BuOK (2.5 g, 0.022 mol) was added. The mixture was refluxed for 18 h, after which most of the solvent was evaporated and excess *t*-BuOK was destroyed by adding water. The product was extracted with CH_2Cl_2, and the solution was dried with anhydrous Na_2SO_4 and evaporated to a syrup which was then purified by analytical LC (EtOAc–hexanes, 1:2), using a silica gel column: yield 95%; $[\alpha]^{23}_D$ +53.0 (*c* 1.8, chloroform); ^1H NMR ($CDCl_3$) δ 7.25–7.20 (15 H, m, aromatic H), 5.36 (1 H, d, $^4J_{1,3}$ = 4 Hz, H-1), 3.55–4.55 (12 H, m, H-2, H-3, H-4, H-5, 2 H-6, 3 CH_2Ph); ^{13}C NMR ($CDCl_3$) 138.30, 137.94, 137.47 (aromatic C-1), 128.77, 128.64, 128.29, 128.05, 127.94 (aromatic C), 107.26 (C-1), 81.97, 80.20 (C-2, C-3), 76.42, 74.90, 73.60, 72.33, 72.15 (C-4, C-5, OCH_2), 71.68 (C-6); mass spectrum, *m/e* 432 (M^+).

Anal. Calcd for $C_{27}H_{28}O_5$ (**11**): C, 74.97; H, 6.52. Found: C, 74.39, H, 6.58.

2,4,6-Tri-*O*-(*p*-bromobenzyl)-D-mannopyranose (14). Compound **6** (6.5 g, 0.020 mol) was dissolved in toluene (50 mL) and finely powdered KOH (11.2 g) and *p*-bromobenzyl bromide (50 g) in toluene (100 mL) was added. This heterogeneous mixture was refluxed overnight under vigorous stirring to virtual completion of the reaction. Some of the bis(*p*-bromobenzyl) ether generated was removed by steam distillation, the rest was separated by means of a prep-500 HPLC system using CH_2Cl_2–hexanes (2:3) as a solvent. Only the bis(*p*-bromobenzyl) ether could be removed by this solvent system, and the target compound methyl 3-*O*-allyl-2,4,6-tri-*O*-(*p*-bromobenzyl)-α-D-mannopyranoside (**12**) was washed off the column with pure ethyl acetate. The yield after complete workup was 72%, mp 76–77 °C. Compound **12** was analyzed by ^1H NMR before going on to the next step: ^1H NMR ($CDCl_3$) δ 7.63–7.28 (12 H, m, aromatic H), 6.32–5.87 (1 H, m, CH_2=$CHCH_2O$), 5.53–5.05 (2 H, m, CH_2=$CHCH_2O$), 4.88–3.70 (15 H, m, H-1, H-2, H-3, H-4, H-5, CH_2O, CH_2=$CHCH_2O$), $CH_2C_6H_4Br$), 3.40 (3 H, s, OCH_3).

Compound **12** (2 g, 0.0027 mol) was taken in 80% acetic acid (50 mL) to which was added dioxane (~15 mL) to cause dissolution, then concentrated HCl (2.8 mL, 36%) was added and the mixture heated over a steam bath for 5 h. TLC (EtOAc–hexanes, 1:2) indicated completion of the reaction. The solvent was evaporated, the syrup dissolved in $CHCl_3$, and the solution washed with sodium bicarbonate and water several times, dried over anhydrous Na_2SO_4, and evaporated to give the product, 3-*O*-allyl-2,4,6-tri-*O*-(*p*-bromobenzyl)-D-mannopyranose (**13**), in >90% yield. Compound **13** failed to crystallize and was analyzed by ^1H NMR: ^1H NMR ($CDCl_3$) δ 7.63–7.28 (12 H, m, aromatic H), 6.40–5.79 (1 H, m, CH_2=$CHCH_2O$), 5.60–3.78 (17 H, m, H-1, H-2, H-3, H-4, H-5, CH_2O, OCH_2CH=CH_2), 2.65 (1 H, s, OH). Compound **13** (1.7 g, 0.0023 mol) was dissolved in 90% ethanol (30 mL) and the solution refluxed. To this was added tris(triphenylphosphine)chlororhodium (0.144 g, 0.000 16 mol) and the refluxing continued for 5 h. The solvent was evaporated, the product taken up in CH_2Cl_2, and the solution washed with brine, dried over anhydrous Na_2SO_4, and evaporated. After being cleaned by analytical LC, the syrup crystallized into sperulite-like white crystals of 2,4,6-tri-*O*-(*p*-bromobenzyl)-D-mannopyranose (**14**). **14** was recrystallized, using $CHCl_3$–hexanes as the solvent. The yield was about 60%: mp 125.5–126.5 °C; $[\alpha]^{25}_D$ –7.7° (*c* 0.87, chloroform); ^1H NMR ($CDCl_3$) δ 7.65–7.28 (12 H, m, aromatic H), 5.38 (1 H, d, $^3J_{1,2}$ = 1 Hz, H-1), 4.90–3.63 (12 H, m, H-2, H-3, H-4, H-5, CH_2O, $CH_2C_6H_4Br$), 2.47 (1 H, s, OH), 2.30 (1 H, s, OH).

Anal. Calcd for $C_{27}H_{27}Br_3O_6$ (**14**): C, 47.19; H, 3.95. Found: C, 47.65; H, 4.04.

2,4,6-Tri-*O*-(*p*-bromobenzyl)-α-D-mannopyranosyl Chloride (15). A solution of compound **14** (1 g, 0.0015 mol) in ether (100 mL) was cooled in an ice bath, and dry HCl gas was bubbled in under a N_2 atmosphere until saturation. The flask was stoppered securely and the solution left stirring at room temperature. After 7 h TLC indicated completion of the reaction. The ether was blown off with a stream of N_2 gas to yield a whitish solid: mp 77.5–78.5 °C; $[\alpha]^{25}_D$ +42.2° (*c* 0.91, chloroform); ^1H NMR ($CDCl_3$) δ 7.39–6.93 (12 H, m, aromatic H), 6.01 (1 H, s, H-1), 4.60–3.17 (12 H, m, H-2, H-3, H-4, H-5, CH_2O, $CH_2C_6H_4Br$); ^{13}C NMR ($CDCl_3$) 137.42, 137.30, 136.39 (aromatic C-1), 132.09, 131.77, 129.62 (aromatic C), 122.52, 121.91 (aromatic CBr), 90.76 (C-1), 81.42, 75.81, 74.18, 74.08, 72.87, 72.62, 70.56, (C-2, C-3, C-4, C-5, OCH_2), 68.53 (C-6).

Anal. Calcd for $C_{27}H_{28}Br_3ClO_5$ (**15**); C, 45.95; H, 3.71. Found: C, 45.68; H, 3.69.

1,3-Anhydro-2,4,6-tri-*O*-(*p*-bromobenzyl)-β-D-mannopyranose (16). Sodium hydride (0.5 g, 0.02 mol) was washed with dry hexane to remove the mineral oil coating and was added to a solution of compound **15** (0.65 g, 0.0009 mol) in dry tetra-

hydrofuran (50 mL). The mixture was refluxed for 1 h, the solution cooled, excess NaH filtered off, solvent evaporated at low temperature (~35 °C), and the resulting syrup cleaned by analytical LC (EtOAc–hexanes, 1:2), using a silica gel column, to give **16** in 90% yield: $[\alpha]^{25}_D$ +31.2° (*c* 0.52, chloroform); ^{1}H NMR ($CDCl_3$) δ 7.55–7.02 (12 H, m, aromatic H), 5.42 (1 H, d, $^4J_{1,3}$ = 4 Hz, H-1), 4.58–3.57 (12 H, m, H-2, H-3, H-4, H-5, CH_2O, $CH_2C_6H_4Br$); ^{13}C NMR ($CDCl_3$) 137.59, 137.30, 136.88 (aromatic C-1), 131.92, 131.80 (aromatic C), 107.15 (C-1), 81.88, 80.33 (C-2, C-3), 76.36, 74.97, 73.96, 72.87, 71.75 (C-4, C-5, OCH_2), 71.40 (C-6).

Anal. Calcd for $C_{27}H_{25}Br_3O_5$ (**16**): C, 48.46; H, 3.77. Found: C, 48.30; H, 3.66.

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16β-Alkoxy-17aα-hydroxy-*D*-homo-17-oxapregnan-20-ones: Preparation, Chemistry, and X-ray Crystallographic Analysis

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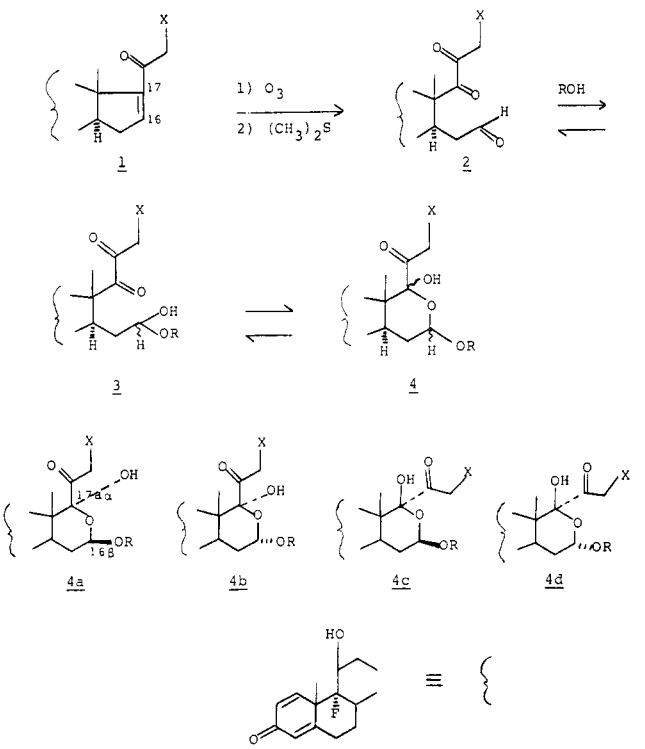
Ozonolysis of certain Δ^{16}-20-oxopregnanes in mixtures of dichloromethane–lower alkanol leads, after reductive workup with dimethyl sulfide, to novel derivatives of the 16β-alkoxy-17aα-hydroxy-*D*-homo-17-oxapregnane system. Under appropriate acidic conditions both the 16β-alkoxyl and 17aα-hydroxyl groups of these compounds can be replaced by alkoxyl groups derived from the solvent. The results of X-ray analysis of the 21-bromo derivative **4a** (X = Br, R = Me) define the stereochemistry as 16β-methoxy-17aα-hydroxy. Comparison of the spectroscopic and physical properties of **4a** (X = Br, R = Me) and the rest of the compounds prepared strongly supports an analogous assignment. X-ray analysis also reveals an unprecedented (solid state) conformation for the C-17a side chain when compared to those of normal pregnan-20-ones.

Our interest in the chemistry of Δ^{16}-20-oxo steroids[1] led us to examine the ozonolysis of triene **1**. After reductive workup, a single product was obtained that we have characterized as a *D*-homo-17-oxapregnane by chemical and spectroscopic means. Confirmation of this assignment, definition of the 17a stereochemistry, and demonstration of an unprecedented C-17a side chain conformation have been provided by X-ray analysis of a 21-bromo derivative. At this time we detail these studies.

Results and Discussion

Preparation and Chemistry. Treatment of **1** (X = AcO) in dichloromethane–methanol (2:1) at −78 °C with 1.1 equiv of ozone, followed by immediate reductive workup[2] with a large excess of dimethyl sulfide, gave a single product (75%) after chromatography on silica gel. Elemental analysis indicated that the elements of O_2 and MeOH had been incorporated. Cursory examination of the ^{1}H NMR spectrum confirmed the addition of methanol (singlet at 3.23 ppm) to the functionality resulting from oxidation of the Δ^{16}-olefin (since the signals attributable to the $\Delta^{1,4}$-3-ketone moiety were present). At this point we reasoned that a sequence of reactions similar to those of Scheme I had occurred to produce **4** from **1**. Further examination of the ^{1}H NMR spectrum of **4** strongly suggested that the C16 hydrogen was axial (4.80 ppm, broadened d, $J_{15,16}$ = 10 Hz), eliminating structures **4b** and **4d** from consideration and narrowing the possibilities to **4a** or **4c**. Consideration of the "anomeric effect"[3] led us

Scheme I



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