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STUDIES RELATED TO THE USE OF FUSED BIPYRANOSES FOR SYNTHESIS OF POLYPROPIONATE ARRAYS*†

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ABSTRACT

A carbohydrate-based approach to the synthesis of polypropionate arrays (termed pyranosidic homologation) ultimately requires that the anomeric (*aldehydo*) group be liberated and then reduced to CH_3. The bipyranose **4a** has been examined in this context. Standard mercaptolysis reactions were ineffective due, in part, to the ease with which acid-catalyzed rearrangements occur. Even when the bicyclic system could be cleaved, hemiacetals [*e.g.*, 1,5-di-*O*-acetyl-3-*O*-benzyl-2-deoxy-4-*C*-methyl-2-*C*-(L-*lyxo*-2,3,4-triacetoxy-1-benzyloxybutyl)-α,β-L-arabinofuranose or 2-*C*-(D-*threo*-2-acetoxy-1-benzyloxybutyl)-3,4-di-*O*-benzyl-2-deoxy-4-*C*-methyl-L-xylopyranose (**10b**)] were resistant to mercaptolysis and were decomposed under the conditions for hydride reduction. The successful route developed in this report involved oxidation of **10b** to a pyranolactone [*e.g.*, 2-*C*-(D-*threo*-2-acetoxy-1-benzyloxybutyl)-3,4-di-*O*-benzyl-2-deoxy-4-*C*-methyl-L-xylono-1,5-lactone], which yielded the *N,N*-dimethylamide. The latter was then reduced to an aldehyde, which in turn was deoxygenated by the Wolff–Kishner reaction, in modest yield.

INTRODUCTION

Some of the most complex antibiotics, such as rifamycin[1], streptovaricin[2], and maytansine[3], are biosynthesized from propionate residues (**1**) and, hence, are characterized by an alternating array of methyl and oxygen functionalities, as exemplified in **2a**. The syntheses of such arrays present formidable challenges for stereocontrol[4] and we have described a carbohydrate-based approach, termed "pyranosidic homologation", in which a tripyranose (*e.g.*, **3**) was proposed[5] as an advanced precursor of **2**. This approach draws upon ample precedents in the carbohydrate literature in order to achieve the stereocontrolled creation and the

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1
2a X, Y = O
2b X = Y = SR
2c X = Y = H
3
4a R = H
4b R = Ac
Ac2O
BF3 • OEt2
10 min.
5
Ac2O
BF3 • OEt2
4h.
6
RSH
BF3 • OEt2
7
RSH
BF3 • OEt2
8a R = Et
8b R = (CH2)3SH

proof of all stereocenters by n.m.r. methods. Our plan calls for the subsequent unravelling of **3** in a manner that does not compromise the integrity of the preformed stereocenters.

However, there are two distinct phases to the successful realization of this concept. The first is to gain access to the anomeric center, preferably as the aldehyde, since cyclic hemiacetal forms can be resistant to reaction[6]. The second is to effect transformation of the aldehyde group so obtained (RCHO→RCH_3) without side reactions, such as epimerizations and β-elimination. These separate phases sometimes occur in tandem, as in the classical Fischer procedure[7], whereby a glycoside is converted directly into a dithioacetal[8]. We now report aspects of our work dealing with both problems.

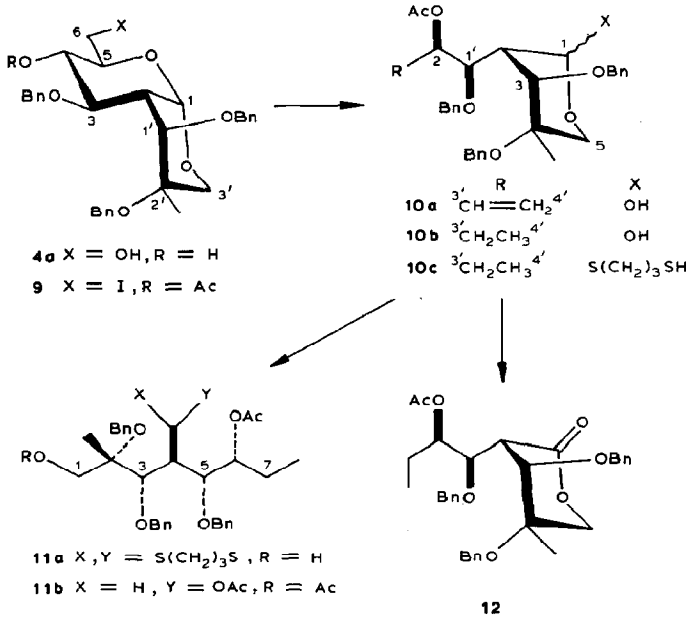
RESULTS AND DISCUSSION

Acid-catalyzed procedures. — One approach to the conversion of C-4a of **3** into a methyl group involves preparation of a dithioacetal (*e.g.*, **2b**) by Fischer procedures[8], and subsequently reduction with Raney nickel[9] (→**2c**). However, the applicability of this protocol to complex, polyfunctional systems, such as **3**, was a matter of concern and hence 3-*O*-benzyl-2-deoxy-2-*C*-(L-*threo*-1′,2′-dibenzyloxy-2′-methylpropane-1′,3′-diyl)-α-D-glucopyranoside[10] (**4a**) was chosen as a model compound for conversion into the dithioacetal **7**. However, **4a** was highly stable under standard mercaptolysis conditions and attempts to force the reaction led to decomposition.

The system was also highly prone to acid-catalyzed skeletal rearrangements. Thus, treatment of the diacetate **4b** with acetic anhydride and boron trifluoride etherate caused rapid ring contraction to give the pyranofuran **5**, followed by a slower acetolysis to give the furanose **6**. It was considered that **6** would provide easier access to the desired dithioacetal **7**. However, mercaptolysis of **6** stopped at the thioglycoside stage **8** (**a** and **b**) and these, after isolation and purification, could not be induced to give **7**.

The geminal C-4 substitution in **6** undoubtedly imposed a strong Thorpe–Ingold effect[11], which would stabilize the cyclic form *vis-a-vis* the acyclic counterpart. It was conceivable that a pyranose ring would undergo mercaptolysis more readily than the furanose **6** and, in order to explore this possibility, it was necessary to cleave the "upper" pyranoid ring of **3**. This was achieved *via* the iodide **9**, which was obtained from the diol **4a** under standard conditions. Compound **9** underwent reductive elimination[12,13] to yield 95% of the olefin **10a** which, upon hydrogenation, afforded the pyranose **10b**.

Mercaptolysis of **10b**, using propane-1,3-dithiol and boron trifluoride etherate in dichloromethane at room temperature, gave the thioglycoside **10c**. Prolonged reaction in the hope of obtaining the dithioacetal **11a** gave a mixture of two compounds in low yield, the ^{1}H-n.m.r. spectra of which indicated the presence of 1,3-dithianyl residues. However, the loss of acetyl and/or benzyl groups was



inconsistent with the desired structure (**11a**) and, hence, this study was not pursued.

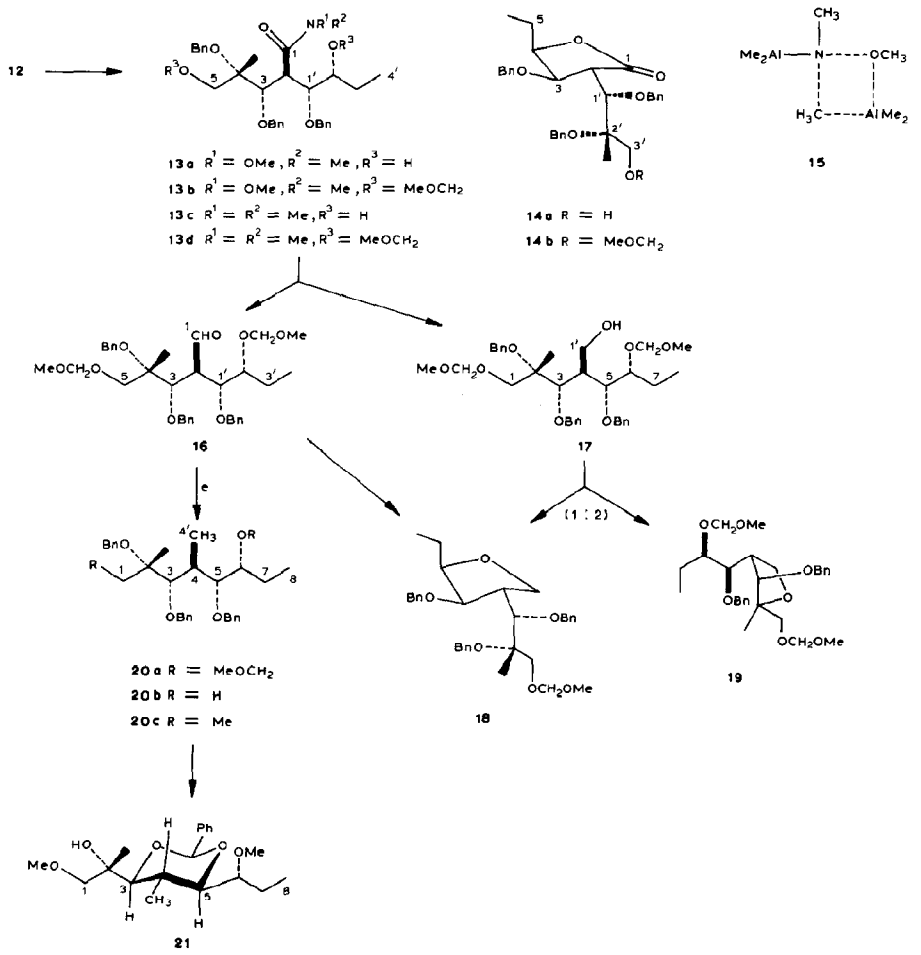
Reductive procedures. — The foregoing results showed that acid-catalyzed procedures were untenable for **10b**. Reductive conditions were therefore investigated. However, the lactol functionality was resistant to lithium aluminum hydride, but reaction was achieved with sodium borohydride in aqueous 1,4-dioxane at reflux to give **11b** after acetylation. The yield of the material was only 36% and this was traced to the fact that substantial β-elimination had occurred during the reduction. Reductive cleavage of **10b** was therefore another unpromising route.

Oxidative/reductive procedures. — Attention was turned next to an oxidative approach in the expectation that lactone **12** could be converted into an amide, which could subsequently be reduced to an aldehyde and thence to the desired methyl group. This approach required the peparation of an *N,O*-dimethylhydroxyl-amide, which can be reduced to an aldehyde with lithium aluminum hydride[14].

Treatment of lactone **12** with $Me_2AlNMe(OMe)$ gave the desired amide **13a** which, in contrast to the systems studied by Weinreb[14], was unstable, cyclizing readily to give the γ-lactone **14a** at room temperature. However, the corresponding *N,N*-dimethylamide **13c**, obtainable in 81% yield, was completely stable and showed no tendency to lactonize.

Me_2AlNMe_2 was prepared by a procedure different to that reported[14] by reaction of *N,O*-dimethylhydroxylamine with two equivalents of trimethyl-aluminum, presumably *via* the intermediate **15**.

Reduction of the bis-methoxymethyl ether **13d** by the Mukaiyama protocol[15] afforded a mixture of the aldehyde **16** and the corresponding alcohol **17**. In view of the difficulties experienced in the use of acid-catalyzed transformations, C-1′



deoxygenation of **17** was investigated next. However, attempts to prepare the primary iodide or methanesulfonate of **17** resulted in a 1:2 mixture of two compounds, the ^{1}H-n.m.r. spectra of which showed the loss of one methoxymethyl and one benzyl group, respectively, and were consistent with the furans **18** and **19**, respectively. Their occurrence indicated that participation by RO-5 was favored strongly in these systems and, thus, furan formation would be inevitable once the primary center was activated by a good leaving group. Therefore, these approaches were abandoned.

The sequence RCHO→RCH=NHTs→R–CH_3 was investigated next. Treatment of the aldehyde **16** with toluene-*p*-sulfonylhydrazine in ethanol at room temperature and reduction of the resulting hydrazone, with either sodium borohydride[17] in ethanol at reflux or cathecolborane[18] in tetrahydrofuran, afforded the previously obtained furan **18**, but none of the desired C–CH_3 product (*e.g.*, **20**) was detected. We are not aware of any precedents for this aberrant reaction course.

Participation by RO-5 seems to be implicated, but a full rationalization awaits further experimentation.

The desired methyl derivative **20a** was finally obtained, albeit in only 30% yield, *via* the Wolff–Kishner reduction of aldehyde **16** using the Huang–Minlon modification[19]. Thus, the hydrazone was first formed at room temperature and then treated with base at 200° to give **20a**. Optimization of this reaction is under investigation.

The configuration at C-4 was a matter of concern because of the nature of the reactions which had been utilized for the functionalization of C-4′. Thus, in each of the intermediates **10b, 12, 13d**, and **16**, C-4 is an epimerizable center and loss of stereochemical integrity was a possibility. In order to gain information on this aspect, **20a** was converted by standard procedures into a benzylidene derivative. That the structure of this material was **21** was apparent from the ^{1}H-n.m.r. parameters, $J_{3,4} = J_{4,5} = 10.2$ Hz, thereby verifying that the configuration at C-4 had been preserved.

The study reported here shows that, for complex polyoxygenated fused systems, such as **3**, accessibility to the *aldehydo* group is plagued by multiple side-reactions and, even after the aldehyde is exposed (as in **16**), derivatization or reduction can be a problem. The solution achieved (**12**→**13**→**16**) provides a viable alternative for converting "stable" hemiacetals into their acyclic counterparts. However, further work is needed to discover how to effect high-yielding transformations in sensitive, highly functionalized aldehydes, such as **16**. Such studies are in progress.

EXPERIMENTAL

General procedures. — Melting points were determined in capillary tubes, using a Buchi Model 510 melting-point apparatus, and are uncorrected. Elemental analyses were performed by M-H-W Laboratories (P.O. Box 15149, Phoenix, AZ). I.r. spectra were recorded with a Perkin–Elmer 298 spectrometer using sodium chloride plates for thin films of liquids, syrups, or solids in Nujol mulls. Optical rotations were determined at the sodium D line, using a Perkin–Elmer 241 polarimeter. ^{1}H-N.m.r. spectra were recorded with a Varian XL-300 spectrometer for solutions in $CDCl_3$ (internal Me_4Si). The coupling constants were verified by homonuclear decoupling experiments. The progress of all reactions was monitored by t.l.c. on Silica Gel HF-254 (0.2-mm layers) (Merck, 5539), using EtOAc–light petroleum mixtures *A*, 1:9; *B*, 1:4; *C*, 3:7; *D*, 1:1; and *E*, Et_2O–CH_2Cl_2 (1:9). Detection was first by u.v. light (254 nm) and then charring with sulfuric acid or with a solution of ammonium molybdate(VI) tetrahydrate (12.5 g) and cerium(IV) sulfate tetrahydrate (5.0 g) in aqueous 10% sulfuric acid (500 mL). Flash chromatography was performed using Kieselgel 60 (230–400 mesh, Merck).

Standard procedure for acetylation. — A solution of the alcohol and 4-dimethylaminopyridine (1.5 mmol/mmol of alcohol) in dry ethyl acetate (5 mL/mmol

of alcohol) was treated with acetic anhydride (91.5 mmol/mmol of alcohol) at room temperature. The reaction was monitored by t.l.c. and, upon completion, was quenched with methanol. The volatiles were removed *in vacuo* and the residue was purified by flash chromatography.

*2-C-(*L-threo-*3'-Acetoxy-1'-benzyloxy-2'-methylpropane-1',2'-diyl)-4,6-di-*O-*acetyl-3-*O-*benzyl-2-deoxy-α-*D-*glucopyranoside* (**5**). — 3-*O*-Benzyl-2-deoxy-2-*C*-(L-*threo*-1',2'-dibenzyloxy-2'-methylpropane-1',3'-diyl)-α-D-glucopyranoside (**4a**) was converted into the diacetate **4b** (230 mg, 0.38 mmol), a solution of which in acetic anhydride (3 mL) at 0° was treated with boron trifluoride etherate (0.05 mL, 0.4 mmol). After 10 min, the mixture was diluted with dichloromethane and washed successively with saturated aqueous solutions of sodium hydrogencarbonate and sodium chloride. The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Flash chromatography of the crude product afforded **5** as a clear gum (150 mg, 70%), R_F 0.32 (solvent *E*, double development), $[\alpha]_D^{25}$ +92° (*c* 1.1, chloroform). ^{1}H-N.m.r. data: δ 1.24 (s, 3 H, Me-2'), 1.99, 2.06, 2.09 (3 s, each 3 H, 3 Ac), 2.53 (m, 1 H, H-2), 3.56 (t, 1 H, *J* 6.3 Hz, H-3), 3.67 (d, 1 H, *J* 4.8 Hz, H-1'), 4.00 (m, 1 H, H-5), 4.09 (dd, 1 H, $J_{5,6a}$ 2.7, J_{gem} 12.0 Hz, H-6a), 4.17 (ABq, 2 H, *J* 11.7 Hz, Δδ = 0.16, CH_2-3'), 4.33 (dd, 1 H, $J_{5,6b}$ 5.4, J_{gem} 12.0 Hz, H-6b), 4.41 (ABq, 2 H, *J* 12.0 Hz, Δδ = 0.08, PhCH_2), 4.63 (ABq, 2 H, *J* 12.0 Hz, Δδ = 0.17, PhCH_2), 5.08 (dd, 1 H, $J_{3,4}$ 6.3, $J_{4,5}$ 8.7 Hz, H-4), 5.60 (d, 1 H, *J* 5.4 Hz, H-1), 7.30 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{30}H_{36}O_{10}$: C, 64.74; H, 6.52;. Found: C, 64.83; H, 6.64.

*1,5-Di-*O*-acetyl-3-*O*-benzyl-2-deoxy-4-*C*-methyl-2-*C*-(*L*-lyxo-2',3',4'-tri-acetoxy-1'-benzyloxybutyl)-α,β-*L*-arabinofuranose* (**6**). — The diacetate **4b** (230 mg, 0.38 mmol) was treated, as described in the preceding experiment, but for 4 h. Similar work-up gave a 3:1 α,β-mixture (219 mg, 89%). Compound **6α** had R_F 0.30 (solvent *E*, double development), $[\alpha]_D^{25}$ +3.4° (*c* 1.3, chloroform). ^{1}H-N.m.r. data: δ 1.23 (s, 3 H, Me-4), 1.86, 1.93, 1.96, 1.98, and 1.99 (5 s, 15 H, 5 Ac), 2.85 (m, 1 H, H-2), 3.80 (t, 1 H, *J* 6.5 Hz, H-1'), 4.01 (dd, 1 H, $J_{3',4a'}$ 7.2, J_{gem} 12.0 Hz, H-4'a), 4.03 (d, 1 H, *J* 7.5 Hz, H-3), 4.25 (ABq, 1 H, *J* 12.3 Hz, Δδ = 0.10, CH_2-5), 4.28 (dd, 1 H, $J_{3',4'b}$ 2.3, J_{gem} 12.0 Hz, H-4'b), 4.55 (m, 4 H, 2 PhCH_2), 5.21 (m, 1 H, H-3'), 5.35 (t, 1 H, *J* 6.5 Hz, H-2'), 6.01 (d, 1 H, *J* 3.3 Hz, H-1), 7.23 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{34}H_{42}O_{13}$: C, 62.00; H, 6.43. Found: C, 62.20; H, 6.29.

Compound **6β** had R_F 0.25 (solvent *E*, double development), $[\alpha]_D^{25}$ −3.7° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 1.03 (s, 3 H, Me-4), 1.95, 1.96, 1.99 (3 s, 15 H, 5 Ac), 2.90 (m, 1 H, H-2), 3.81 (t, 1 H, *J* 4.2 Hz, H-1'), 3.99 (ABq, 2 H, *J* 18.0 Hz, Δδ = 0.15, CH_2-5), 4.08 (m, 1 H, H-4'a), 4.19 (d, 1 H, *J* 9.0 Hz, H-3), 4.34 (m, 2 H, H-8b, PhC*H*), 4.58 (m, 3 H, 3 PhC*H*), 5.30 (m, 2 H, H-2',3'), 6.21 (d, 1 H, *J* 4.8 Hz, H-1), 7.24 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{34}H_{42}O_{13}$: C, 62.00; H, 6.43. Found: C, 62.02; H, 6.38.

Mercaptolysis of **6αβ**. — (*a*) A solution of **6αβ** (15 mg, 0.023 mmol) and ethanethiol (0.1 mL, 1.9 mmol) in dichloromethane (1 mL) was treated with boron

trifluoride etherate (0.01 mL, 0.08 mmol) for 10 min at 0°. Ethyl 5-*O*-acetyl-3-*O*-benzyl-2-deoxy-4-*C*-methyl-1-thio-2-*C*-(L-*lyxo*-2′,3′,4′-triacetoxy-1′-benzyloxybutyl)-α,β-L-arabinofuranoside (**8a**, 9 mg, 60%) was obtained as a clear gum (after flash chromatography), R_F 0.13 (solvent *B*), $[\alpha]_D^{25}$ +35° (*c* 1, chloroform). ^{1}H-N.m.r. data: δ 2.00 (t, 3 H, *J* 6.3 Hz, CH_3CH_2S), 1.22 (s, 3 H, Me-4), 1.82, 1.97, 1.99, 2.04 (4 s, each 3 H, 4 Ac), 2.54 (q, 2 H, *J* 6.3 Hz, CH_3CH_2S), 2.60 (m, 1 H, H-2), 3.76 (dd, 1 H, $J_{1',2}$ 1.5, $J_{1'2'}$ 5.1 Hz, H-1′), 4.07 (dd, 1 H, $J_{3',4'a}$ 6.6, J_{gem} 11.4 Hz, H-4′a), 4.17 (d, 1 H, *J* 8.7 Hz, H-3), 4.21 (ABq, 2 H, *J* 11.7 Hz, Δδ = 0.10, CH_2-5), 4.29 (dd, 1 H, $J_{3',4'b}$ 3.9, J_{gem} 11.4 Hz, H-4′b), 4.60 (ABq, 2 H, *J* 11.7 Hz, Δδ = 0.15, PhCH_2), 4.66 (ABq, 2 H, *J* 10.8 Hz, Δδ = 0.11, PhCH_2), 4.76 (d, 1 H, *J* 10.2 Hz, H-1), 5.27 (m, 1 H, H-3′), 5.55 (dd, 1 H, $J_{1',2'}$ 5.1, $J_{2',3'}$ 8.7 Hz, H-2′), 7.28 (m, 10 H, 2 Ph).

(*b*) Treatment of **6αβ** (30 mg, 0.046 mmol) with 1,3-propanedithiol, as described in (*a*), gave 3-thiopropyl 5-*O*-acetyl-3-*O*-benzyl-2-deoxy-4-*C*-methyl-1-thio-2-*C*-(L-*lyxo*-2′,3′,4′-triacetoxy-1′-benzyloxybutyl)-α,β-L-arabinofuranoside (**8b**) as a colorless gum (21 mg, 65%) after flash chromatography, R_F 0.13 (solvent *B*), $[\alpha]_D^{25}$ +44° (*c* 1.1, chloroform). ^{1}H-N.m.r. data: δ 1.23 (s, 3 H, Me-4), 1.82 (m, 2 H, SCH_2CH_2SH), 1.86, 1.99, 2.02, 2.07 (4 s, each 3 H, 4 Ac), 2.62 (m, 5 H, H-2, $SCH_2CH_2CH_2SH$), 3.76 (dd, 1 H, $J_{4,5}$ 1.5, $J_{1',2'}$ 5.1 Hz, H-1′), 4.09 (dd, 1 H, $J_{3',4'a}$ 8.4, J_{gem} 11.4 Hz, H-4′a), 4.18 (d, 1 H, *J* 7.2 Hz, H-3), 4.24 (ABq, 2 H, *J* 11.4 Hz, Δδ = 0.10, CH_2-5), 4.32 (dd, 1 H, $J_{3',4'b}$ 5.0, J_{gem} 11.4 Hz, H-4′b), 4.62 (ABq, 2 H, *J* 11.7 Hz, Δδ = 0.15, PhCH_2), 4.69 (ABq, 2 H, *J* 10.5 Hz, Δδ = 0.12, PhCH_2), 4.73 (d, 1 H, *J* 8.1 Hz, H-1), 5.30 (m, 1 H, H-3), 5.56 (dd, H-1, $J_{1',2'}$ 5.1, $J_{2',3'}$ 8.7 Hz, H-2′), 7.32 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{35}H_{46}O_{11}S_2$: C, 59.47; H, 6.46. Found: C, 59.30; H, 6.65.

*4-O-Acetyl-3-O-benzyl-2-C-(*L-threo-*1′,2′-dibenzyloxy-2′-methylpropane-1′,3′-diyl)-2,6-dideoxy-6-iodo-α-*D-*glucopyranoside* (**9**). — A solution of triphenylphosphine (524 mg, 2.0 mmol) in dry benzene (10 mL) was added to a solution of iodine (540 mg, 2.12 mmol) in benzene (10 mL) at room temperature under argon. After 5 min, a solution of **3a** (650 mg, 1.25 mmol) and imidazole (145 mg, 2.13 mmol) in dry benzene (10 mL) was added to the brown suspension, and the mixture was stirred for 0.5 h at room temperature, then diluted with ether (50 mL), and washed with aqueous 10% sodium thiosulfate. The organic phase was concentrated *in vacuo* and a solution of the crude residue in ethyl acetate (10 mL) was treated with acetic anhydride (1 mL) and 4-dimethylaminopyridine (120 mg, 10 mmol). Flash chromatography of the crude reaction mixture gave **9** (800 mg, 95%) as prisms (from ethanol), m.p. 109–110°, R_F 0.40 (solvent *A*), $[\alpha]_D^{25}$ +89° (*c* 0.9, chloroform); ν_{max} 1750 cm^{-1}. ^{1}H-N.m.r. data: δ 1.17 (s, 3 H, CH_3-2′), 1.85 (s, 3 H, Ac), 2.19 (dt, 1 H, $J_{1,2} = J_{1',2'} = 4.2$, $J_{2,3}$ 9.0 Hz, H-2), 3.12 (dd, 1 H, $J_{5,6a}$ 6.9, J_{gem} 10.5 Hz, H-6a), 3.31 (dd, 1 H, $J_{5,6b}$ 3.0, J_{gem} 10.5 Hz, H-6b), 3.67 (m, 1 H, H-1′), 3.69 (d, 1 H, J_{gem} 14.0 Hz, H-3′*a*), 3.90 (m, 1 H, H-5), 4.15 (ABq, 2 H, *J* 11.7 Hz, Δδ = 0.15, PhCH_2), 4.21 (dd, 1 H, $J_{3'e,1'}$ 1.0, J_{gem} 14.0 Hz, H-3′*e*), 4.45 (t, 1 H, *J* 9.0 Hz, H-3), 4.49 (ABq, 2 H, *J* 11.7 Hz, Δδ = 0.20, PhCH_2), 4.52 (ABq, 2 H, *J*

10.8 Hz, $\Delta\delta$ = 0.07, PhCH_2), 4.77 (t, 1 H, *J* 9.0 Hz, H-4), 5.15 (d, 1 H, *J* 4.2 Hz, H-1), 7.31 (m, 15 H, 3 Ph).

Anal. Calc. for $C_{33}H_{36}IO_7$: C, 58.93; H, 5.55. Found: C, 59.00; H, 5.67.

*2-C-(*D-threo-*2'-Acetoxy-1'-benzyloxy-but-3'-enyl)-3,4-di-*O*-benzyl-2-deoxy-4-C-methyl-*L-*xylopyranose* (**10a**). — A mixture of **9** (800 mg, 1.19 mmol), freshly activated zinc[13] (650 mg, 10 mmol), and ammonium chloride (105 mg, 3 mmol) in aqueous 95% ethanol (30 mL) was boiled under reflux for 0.5 h, then filtered through a short column of florisil, and concentrated *in vacuo*. Flash chromatography of the yellow oil gave **10a** (617 mg, 95%) as a clear syrup, R_F 0.30 (solvent *A*); ν_{max} 3425, 1730, 1600 w, 930 w cm^{-1}. ^{1}H-N.m.r. data: δ 1.34 and 1.43 (2 s, ratio 6:1, 3 H, Me-4), 1.96 and 2.06 (2 s, ratio 6:1, 3 H, Ac), 2.04, 2.15 (2 m, H-1'), 4.85 (m, 1 H, H-5), 5.20 (m, 3 H, CH_2-4', OH), 5.62–5.88 (m, 2 H, H-2',3'), 7.28 (m, 15 H, 3 Ph).

Anal. Calc. for $C_{33}H_{38}O_7$: C, 72.51; H, 7.01. Found: C, 72.58; H, 7.01.

*2-C-(*D-threo-*2'-Acetoxy-1'-benzyloxybutyl)-3,4-di-*O*-benzyl-2-deoxy-4-C-methyl-*L-*xylono-1,5-lactone* (**12**). — A mixture of **10a** (182 mg, 0.33 mmol) and 10% Pd/C (36 mg) in ethyl acetate (20 mL) was stirred for 2 h at room temperature under hydrogen, then filtered through Celite, and concentrated *in vacuo* to give the crude lactol **10b**, R_F 0.30 (solvent *A*). ^{1}H-N.m.r. data: *inter alia* δ 0.72 (t, *J* 7.5 Hz, CH_3CH$_2$), 1.30, 1.36 (2 s, Me-4), 1.58 (m, CH$_3$CH_2), 1.90 and 1.98 (2 s, Ac), 5.10 and 5.35 (2 m, H-1,1'). The crude material was oxidized using pyridinium chlorochromate (1.2 g, 6.0 mmol), anhydrous sodium acetate (0.5 g, 6.0 mmol), and florisil (120 mg) in dichloromethane (10 mL), and **12** (155 mg, 85%) was obtained by flash chromatography, R_F 0.50 (solvent *A*), $[\alpha]_D^{25}$ −21° (*c* 2, chloroform); ν_{max} 1740 br cm^{-1}. ^{1}H-N.m.r. data: δ 0.72 (t, 3 H, *J* 6.0 Hz, H-4'), 1.46 (s, 3 H, Me-4), 1.55 (m, 2 H, CH_2-3'), 1.99 (s, 3 H, Ac), 2.73 (dd, 1 H, $J_{2,3}$ 6.0, $J_{1',2'}$ 3.9 Hz, H-2), 4.19 (d, 1 H, *J* 6.0 Hz, H-3), 4.20 (ABq, 2 H, *J* 12.6 Hz, $\Delta\delta$ = 0.10, CH_2-5), 4.25 (dd, 1 H, $J_{1',2'}$ 3.9, $J_{1',2'}$ 8.7 Hz, H-1'), 4.50 (ABq, 2 H, *J* 11.7 Hz, $\Delta\delta$ = 0.09, PhCH_2), 4.57 (b s, 2 H, PhCH_2), 4.81 (ABq, 2 H, *J* 12.0 Hz, $\Delta\delta$ = 0.06, PhCH_2), 5.22 (dt, 1 H, $J_{1',2'} = J_{2',3'a}$ 8.7, $J_{2',3'b}$ 2.1 Hz, H-2'), 7.26 (m, 15 H, 3 Ph).

Anal. Calc. for $C_{33}H_{38}O_7$: C, 72.51; H, 7.01. Found: C, 72.71; H, 6.94.

*4-C-(Acetoxymethyl)-1,6-di-*O*-acetyl-2,3,5-tri-*O*-benzyl-4,7,8-trideoxy-2-C-methyl-*D-glycero-D-talo-*octitol* (**11b**). — Sodium borohydride (5 mg, 0.14 mmol) was added to a solution of **10b** (18 mg, 0.033) in 1,4-dioxane (4 mL) and water (2 mL), and the mixture was boiled under reflux for 1 h, then cooled to 0°, and neutralized with acetic acid. After stirring at room temperature for an additional 0.5 h, the volatiles were removed *in vacuo* and the crude product was acetylated, as described above for **9**, to give **11b** (8 mg, 36%), isolated as a colorless gum, R_F 0.27 (solvent *A*), $[\alpha]_D^{25}$ −6.25° (*c* 1.3, chloroform). ^{1}H-N.m.r. data: δ 0.65 (t, 3 H, *J* 7.2 Hz, CH_3CH$_2$), 1.25, 1.52 (2 m, each 1 H, CH$_3$CH_2), 1.32 (s, 3 H, Me-2), 1.98, 2.01, 2.02 (3 s, 9 H, 3 Ac), 2.58 (m, 1 H, H-4), 3.71 (d, 1 H, *J* 4.3 Hz, H-3), 3.91 (t, 1 H, *J* 4.3 Hz, H-5), 4.24 (dd, 1 H, $J_{4,4'}$ 8.0, J_{gem} 10.3 Hz, H-4'), 4.36 (m, 4 H, CH_2-1, H-4'b, PhC*H*), 4.55 (m, 4 H, 4 PhC*H*), 4.83 (d of ABq, 1 H, *J* 10.4 Hz, PhC*H*), 5.20 (m, 1 H, H-6), 7.30 (m, 15 H, 3 Ph).

Anal. Calc. for $C_{37}H_{46}O_9$: C, 70.01; H, 7.31. Found: C, 69.99; H, 7.48.

$Me_2AlNMe(OMe)$ and the N,N-*dimethyl analogue.* — *N,O*-Dimethylhydroxylamine (b.p. 42–43°) was distilled from a solution of the corresponding hydrochloride in aqueous 50% potassium hydroxide[14]. The distillate was redistilled twice after stirring with potassium hydroxide and calcium hydride, respectively. To a portion (630 mg, 10.33 mmol) of this material in dry CH_2Cl_2 (5 mL) was added 5 mL of 2.0M trimethylaluminum in hexane (10 mmol) at 0° under argon. The mixture was stirred for 0.5 h at 0° before the $Me_2AlNMe(OMe)$ was used. The stock solution could be stored for months in the refrigerator.

Stock solutions of Me_2AlNMe_2 were prepared similarly, using 2 mol of Me_3Al per mol of *N,O*-dimethylhydroxylamine.

Reaction of the δ-lactone **12** *with $Me_2AlNMe(OMe)$.* — $Me_2AlNMe(OMe)$ (5.1 mL of 1.0M solution, 5.1 mmol) was added to a solution of **12** (350 mg, 0.64 mmol) in dry dichloromethane (5 mL) at room temperature under argon. After stirring for 16 h, the solution was added slowly to M hydrochloric acid (15 mL) at 0° and the mixture was extracted with dichloromethane. The combined extracts were washed with saturated aqueous sodium hydrogencarbonate, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue (230 mg) was a mixture of the amide **13a** and the corresponding γ-lactone **14a**, the former being converted into the latter on storage. The mixture was treated with chloromethyl methyl ether (0.38 mL, 5 mmol) and ethyl di-isopropylamine (1.24 mL, 7 mmol) in dichloromethane (5 mL) for 16 h at room temperature. The mixture was washed successively with saturated aqueous solutions of sodium hydrogencarbonate and sodium chloride, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Flash chromatography of the crude residue afforded 3-*O*-benzyl-2,5,6-trideoxy-2-*C*-(L-*erythro*-1′,2′-dibenzyloxy-3′-methoxymethyloxy-2′-methylpropyl)-D-*xylo*-hexono-1,4-lactone (**14b**), R_F 0.46 (solvent *B*), $[\alpha]_D^{25}$ +49° (*c* 1.2, chloroform); ν_{max} 1755 cm^{-1}. ^{1}H-N.m.r. data: δ 0.95 (t, 3 H, *J* 7.0 Hz, CH_3CH_2), 1.42 (s, 3 H, Me-2′), 1.75 (m, 2 H, CH_3CH_2), 3.08 (dd, $J_{1',2'}$ 1.0, $J_{2,3}$ 3.0 Hz, H-2), 3.32 (s, 3 H, CH_2OMe), 3.78 (ABq, 2 H, *J* 14.0 Hz, Δδ = 0.03, CH_2-3′), 4.24 (ABq, 2 H, *J* 10.0 Hz, Δδ = 0.18, $PhCH_2$), 4.30 (d, 1 H, *J* 1.0 Hz, H-1′), 4.40 (m, overlapped by ABq, 1 H, H-3), 4.65 (m, 7 H, 2 $PhCH_2$, CH_2OCH_3, H-4), 7.30 (m, 15 H, 3 Ph).

Anal. Calc. for $C_{33}H_{40}O_7$: C, 72.24; H, 7.35. Found: C, 72.38; H, 7.29.

3,4-Di-*O*-benzyl-2-*C*-(D-*threo*-1′-benzyloxy-2′-methoxymethoxybutyl)-2-deoxy-*N*-methoxy-5-*O*-methoxymethyl-4-*C*-methyl-*N*-methyl-L-xylonamide (**13b**) had R_F 0.36 (solvent *B*), $[\alpha]_D^{25}$ −9° (*c* 1, chloroform); ν_{max} 1630 br cm^{-1}. ^{1}H-N.m.r. data: δ 0.85 (t, 3 H, *J* 6.6 Hz, CH_3CH_2), 1.33 (s, 3 H, Me-4), 1.41, 1.70 (2 m, each, 1 H, CH_3CH_2), 2.89 (s, 3 H, NMe), 3.18, 3.32 (2 s, 9 H, 3 OMe), 3.33 (m, overlapped by s, 2 H, CH_2-5), 3.78 (m, 4 H, H-2,3,1′,2′), 4.52 (m, 9 H, 5 PhC*H*, 2 CH_2OMe), 4.99 (d of ABq, 1 H, *J* 12.0 Hz, PhC*H*), 7.28 (m, 15 H, 3 Ph).

Anal. Calc. for $C_{37}H_{51}NO_9$: C, 67.97; H, 7.86. Found: C, 68.13; H, 8.12.

*3,4-Di-*O*-benzyl-2-*C*-(*D-threo-*1′-benzyloxy-2′-methoxymethoxybutyl)-2-*

*deoxy-5-*O*-methoxymethyl-4-*C*-methyl-*N,N*-dimethyl-*L*-xylonamide* (**13d**). — The lactone **12** (190 mg, 0.35 mmol) was treated with Me_2AlNMe_2 (6 mL of a 0.6M solution, 3.6 mmol), following the procedure in the preceding experiment. After storage for 16 h at room temperature, the mixture was processed. Flash chromatography of the crude product afforded the *N,N*-dimethylamide **13c** (155 mg, 81%) as a colorless gum, R_F 0.05 (solvent *C*), $[\alpha]_D^{25}$ +10° (*c* 1.71, chloroform); ν_{max} 3435, 1630 br cm^{-1}. ^{1}H-N.m.r. data: δ 0.95 (t, 3 H, *J* 7.2 Hz, CH_3CH_2), 1.25 (s, 3 H, Me-4), 1.52 (m, 2 H, CH_3CH_2), 2.11 (d, 1 H, *J* 9.1 Hz, HO-2), 2.71 and 2.80 (2 s, each 3 H, NMe_2), 3.37 (m, 1 H, H-2'), 3.55 (dd, 1 H, $J_{5a,OH}$ 8.7, J_{gem} 13.2 Hz, H-5a), 3.67 (dd, 1 H, $J_{5b,OH}$ 5.4, J_{gem} 13.2 Hz, H-5b), 3.86 (dd, 1 H, HO-5), 3.88 (d, 1 H, $J_{2,3}$ 3.9 Hz, H-3), 3.98 (dd, 1 H, $J_{1',2'}$ 8.7, $J_{1',2'}$ 1.8 Hz, H-1'), 4.15 (dd, 1 H, H-2), 4.50 (ABq, 2 H, *J* 10.2 Hz, $\Delta\delta$ = 0.13, $PhCH_2$), 4.51 (ABq, 2 H, *J* 10.8 Hz, $\Delta\delta$ = 0.32, $PhCH_2$), 4.95 (ABq, 2 H, *J* 11.0 Hz, $\Delta\delta$ = 0.39, $PhCH_2$), 7.32 (m, 15 H, 3 Ph).

The compound was characterized as **13d** (which was prepared as described above for **13b**).

Anal. Calc. for $C_{37}H_{51}NO_8$: C, 69.68; H, 8.06. Found: C, 69.86; H, 7.97.

*3,4-Di-*O*-benzyl-2-*C*-(*D*-threo-1'-benzyloxy-2'-methoxymethoxybutyl)-2-deoxy-5-*O*-methoxymethyl-4-*C*-methyl-*L*-xylose* (**16**). — *N*-Methylpiperazine (0.35 mL, 3.16 mmol) was added to a suspension of lithium aluminum hydride (62 mg, 1.56 mmol) in dry tetrahydrofuran (2 mL) under argon[15]. The mixture was stirred at room temperature for 1.5 h, then a solution of **13d** (160 mg, 0.25 mmol) in tetrahydrofuran (2 mL) was added, the mixture was boiled under reflux for 3.5 h and cooled to 0°, and anhydrous sodium sulfate and sodium sulfate hydrated with saturated aqueous ammonium chloride were added successively. The suspension was diluted with wet ether, stirred at room temperature for 0.5 h, and filtered. The residue was washed with ethyl acetate, and the filtrate was concentrated *in vacuo*. The crude product was subjected to flash chromatography and gave **16** (94 mg, 63%), contaminated with the corresponding xylitol **17** (30 mg, 20%). Compound **16** was isolated as a clear syrup, R_F 0.50 (solvent *D*), $[\alpha]_D^{25}$ −25° (*c* 1.7, chloroform); ν_{max} 1718 cm^{-1}. ^{1}H-N.m.r. data: δ 0.64 (t, 3 H, *J* 8.1 Hz, CH_3CH_2), 1.33 (s, 3 H, Me-4), 1.60 (m, 2 H, CH_3CH_2), 3.13 (m, 1 H, H-2), 3.26, 3.33 (2 s, each 3 H, 2 OCH_2OMe), 3.74 (s, 2 H, CH_2-5), 3.75 (m, 1 H, overlapped by s, H-2'), 4.05 (t, 1 H, *J* 4.5 Hz, H-1'), 4.33 (d, 1 H, *J* 5.7 Hz, H-3), 4.46 (ABq, 2 H, *J* 7.0 Hz, $\Delta\delta$ = 0.19, $-OCH_2OMe$), 4.55 (m, 6 H, 2 $PhCH_2$, OCH_2OMe), 4.75 (ABq, 2 H, *J* 11.0 Hz, $\Delta\delta$ = 0.12, $PhCH_2$), 7.30 (m, 15 H, 3 Ph), 9.90 (d, 1 H, *J* 1.0 Hz, H-1).

Anal. Calc. for $C_{35}H_{46}O_8$: C, 70.68; H, 7.80. Found: C, 70.50; H, 7.85.

*1,4-Anhydro-3-*O*-benzyl-2,5,6-trideoxy-2-*C*-(*L*-erythro-1',2'-dibenzyloxy-3'-methoxymethoxy-2'-methylpropyl)-*D*-xylitol* (**18**). — Toluene-*p*-sulfonylhydrazine (10 mg, 0.054 mmol) was added to a solution of **16** (28 mg, 0.047 mmol) in ethanol (2 mL) at room temperature. A less polar compound was formed within 5 min (R_F 0.27, solvent *C*). Sodium borohydride (10 mg, 0.27 mmol) was then added to the

mixture which was boiled under reflux for 4 h, cooled to 0°, and neutralized with acetic acid, and the volatiles were evaporated *in vacuo*. The crude product was purified by flash chromatography to give **18** as a clear gum, R_F 0.42 (solvent *D*), $[\alpha]_D^{25}$ +82° (*c* 1.2, chloroform). ^{1}H-N.m.r. data: δ 0.92 (t, 3 H, *J* 7.5 Hz, CH_3CH_2), 1.35 (s, 3 H, Me-2'), 1.68 (m, 2 H, CH_3CH_2), 2.74 (m, 1 H, H-2), 3.34 (s, 3 H, OCH_2Me), 3.53 (m, 3 H, H-1a,3,4), 3.72 (ABq, 2 H, *J* 10.5 Hz, $\Delta\delta$ = 0.10, CH_2-5), 4.14 (m, 2 H, H-1b,1'), 4.41 (ABq, 2 H, *J* 11.4 Hz, $\Delta\delta$ = 0.13, PhCH_2), 4.58 (m, 5 H, 3 PhC*H*, OCH_2OMe), 4.84 (d of ABq, *J* 10.8 Hz, PhC*H*), 7.23 (m, 15 H, 3 Ph).

Anal. Calc. for $C_{33}H_{42}O_6$: C, 74.13; H, 7.92. Found: C, 73.92; H, 7.96.

*1,4-Anhydro-3-*O*-benzyl-2-*C*-(*D*-threo-1'-benzyloxy-2'-methoxymethoxybutyl)-2-deoxy-5-*O*-methoxymethyl-4-*C*-methyl-*L*-xylitol* (**19**). — Methanesulfonyl chloride (0.01 mL, 0.13 mmol) was added to a solution of triethylamine (0.025 mL, 0.18 mmol), 2,4-dimethylaminopyridine (1 mg, 0.008 mmol), and **17** (18 mg, 0.036 mmol) in dry dichloromethane (2 mL) at 0°. After 5 min, the mixture was diluted with ether, washed with saturated aqueous sodium hydrogencarbonate, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Flash chromatography of the residue gave **19** (7 mg, 40%) and **18** (4 mg, 21%). Compound **16** had R_F 0.34 (solvent *D*), $[\alpha]_D^{25}$ +21° (*c* 1.25, chloroform). ^{1}H-N.m.r. data: δ 0.97 (t, 3 H, *J* 7.2 Hz, CH_3CH_2), 1.18 (s, 3 H, Me-4), 1.49, 1.72 (2 m, each 1 H, CH_3CH_2), 2.58 (m, 1 H, H-2), 3.34, 3.40 (2 s, each 3 H, 2 OCH_2OMe), 3.46 (dd, 1 H, $J_{1',2'}$ 7.5, $J_{1',2'}$ 3.9 Hz, H-1'), 3.64 (ABq, 2 H, *J* 10.0 Hz, $\Delta\delta$ = 0.18, CH_2-5), 3.68 (m, 1 H, H-2'), 3.80 (dd, 1 H, $J_{1a,2}$ 6.3, J_{gem} 10.8 Hz, H-1a), 3.81 (d, 1 H, *J* 4.2 Hz, H-3), 4.00 (dd, 1 H, $J_{1b,2}$ 10.0, J_{gem} 10.8 Hz, H1b), 4.50 (ABq, 2 H, *J* 11.4 Hz, $\Delta\delta$ = 0.08, PhCH_2), 4.65 (ABq, 2 H, *J* 10.8 Hz, $\Delta\delta$ = 0.21, PhCH_2), 4.66 (s, 2 H, OCH_2OMe), 4.69 (ABq, 2 H, *J* 7.2 Hz, $\Delta\delta$ = 0.04, OCH_2OMe), 7.24 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{28}H_{40}O_7$: C, 68.83; H, 8.25. Found: C, 68.68; H, 7.72.

*2,3,5-Tri-*O*-benzyl-4,7,8-trideoxy-1,6-di-*O*-methoxymethyl-2,4-di-*C*-methyl-*D*-glycero-*D*-talo-octitol* (**20a**). — A solution of **16** (48 mg, 0.081 mmol) and hydrazine hydrate (0.1 mL, 2.06 mmol) in ethanol (0.5 mL) and ethylene glycol (2 mL) was stirred for 0.5 h at room temperature. The temperature was raised to 150° and aqueous 50% potassium hydroxide (0.2 mL) was added slowly. The mixture was maintained for 1 h at 200°, most of the solvent was then removed *in vacuo*, and the residue was diluted with water (10 mL) and extracted with ether. The combined organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Flash chromatography of the crude product gave **20a** (14 mg, 30%), isolated as a clear syrup, R_F 0.53 (solvent *A*), $[\alpha]_D^{25}$ +18° (*c* 0.6, chloroform). ^{1}H-N.m.r. data: δ 0.72 (t, 3 H, *J* 6.3 Hz, CH_3CH_2), 1.11 (d, 3 H, *J* 6.6 Hz, Me-4), 1.33 (s, 3 H, Me-2), 1.52 (m, 2 H, CH_3CH_2), 2.26 (m, 1 H, H-4), 3.24, 3.30 (2 s, each 3 H, 2 OCH_2OMe), 3.55 (dt, 1 H, $J_{4,5}$ 6.6, $J_{5,6}$ 2.3 Hz, H-5), 3.61 (m, 1 H, H-6), 3.72 (d, 1 H, *J* 5.4 Hz, H-3), 3.79 (bs, 2 H, CH_2-1), 4.55 (m, 10 H, 3 PhCH_2, 2 OCH_2OMe), 7.28 (m, 15 H, 3 Ph).

Anal. Calc. for $C_{35}H_{48}O_7$: C, 72.39; H, 8.33. Found: C, 72.49; H, 8.10.

3,5-O-Benzylidene-4,7,8-trideoxy-2,4-di-C-methyl-1,6-di-O-methyl-D-glycero-D-talo-*octitol* (**21**). — (±)-Camphorsulfonic acid was added to a solution of **20a** (17 mg, 0.029 mmol) in dry methanol (2 mL) so as to achieve a pH of 3. The mixture was stirred at room temperature for 4 days, then neutralized with sodium hydrogencarbonate, and concentrated *in vacuo*. Flash chromatography of the residue gave the diol **20b** as a clear gum (8 mg, 56%), R_F 0.15 (solvent *B*). The material was dissolved in *N,N*-dimethylformamide and treated[20] with sodium hydride, methyl iodide, and tetrabutylammonium bromide. The resulting 1,6-di-*O*-methyl derivative **20c** was dried in a high vacuum and dissolved in dry tetrahydrofuran (2 mL), and liquid ammonia (2 mL) was condensed into the solution at −78°. The mixture was warmed to −33° and sodium (10 mg, 0.44 mmol) was added until the bright blue color persisted for 10 min. The reaction was quenched with ammonium chloride, the ammonia allowed to evaporate, and the residual solvent removed *in vacuo*. The crude solid was triturated with dichloromethane, filtered, and concentrated *in vacuo*. The resulting gum was dried under high vacuum and dissolved in dry dichloromethane (2 mL), and excess of benzaldehyde dimethyl acetal (0.5 mL, 3.29 mmol) and (±)-camphorsulfonic acid (2 mg, 0.01 mmol) were added. After storage for 10 min at room temperature, the mixture was diluted with dichloromethane, washed with saturated aqueous sodium hydrogencarbonate, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Flash chromatography of the residue afforded **21** (2 mg, 37%), isolated as a clear gum, R_F 0.25 (solvent *B*), $[\alpha]_D^{25}$ +23° (*c* 0.9, chloroform). ^{1}H-N.m.r. data: δ 0.97 (t, 3 H, *J* 8.1 Hz, 3 H-8), 1.02 (d, 3 H, *J* 6.0 Hz, Me-4), 1.29 (s, 3 H, Me-2), 1.75 (m, 2 H, CH_2CH_3), 2.24 (m, 1 H, H-4), 2.95 (s, 1 H, OH), 3.97, 3.43 (2 s, each 3 H, 2 OMe), 3.42 (m, overlapped by singlets, 3 H, CH_2-1, H-6), 3.51 (dd, 1 H, overlapped by m, $J_{4,5}$ 10.2, $J_{5,6}$ 4.0 Hz, H-5), 3.72 (d, 1 H, *J* 10.2 Hz, H-3), 5.50 (s, 1 H, PhC*H*), 7.40 (m, 5 H, Ph).

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