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PREPARATIVE SYNTHESES OF 2,6-DIDEOXY-α-L-*lyxo*-HEXOSE (2-DEOXY-α-L-FUCOSE) AND ITS D-*ribo* EPIMER (DIGITOXOSE)

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ABSTRACT

Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside (**1**) is converted into methyl 3,4-di-*O*-benzoyl-6-bromo-2,6-dideoxy-α-D-*ribo*-hexopyranoside (**3**) *via* the 3-*O*-benzoyl derivative (**2**) of **1** by subsequent treatment with *N*-bromosuccinimide. Compound **3** is the key intermediate in high-yielding, preparative syntheses of the title dideoxy sugars, which are constituents of many antibiotics. Dehydrohalogenation of **3** affords the 5,6-unsaturated glycoside **7**, which undergoes stereospecific reduction by hydrogen with net inversion at C-5 to give methyl 3,4-di-*O*-benzoyl-2,6-dideoxy-β-L-*lyxo*-hexopyranoside (**8**), whereas reductive dehalogenation of **3** provides the corresponding D-*ribo* derivative **4**. The unprotected glycosides **9** (L-*lyxo*) and **5** (D-*ribo*) are readily obtained by catalytic transesterification, and mild, acid hydrolysis gives the crystalline title sugars **10** (L-*lyxo*) and **6** (D-*ribo*) in 45 and 57% overall yield from **1** without the necessity of chromatographic purification at any of the steps.

INTRODUCTION

A program in this laboratory is concerned with the synthesis of analogs of the anthracycline antibiotics daunorubicin[1,2] and adriamycin[2,3] that are structurally and/or stereochemically modified[4] in the carbohydrate constituent. Both antibiotics are clinically effective against various forms of cancer, but their major drawback is a severe cardiotoxicity[5] manifested at the most effective dose-levels. Structurally related analogs, however, might display decreased toxicity and possibly exhibit an even broader spectrum of antitumor activity. Several semisynthetic anthracyclines[6] have already been prepared in which the original amino sugar, daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose), is replaced by its L-*arabino*[7], 6-hydroxy-L-*arabino*[8], and L-*ribo*[9] analogs, as well as coupled products[10] of daunomycinone with D-glucose and 2-amino-2-deoxy-D-glucose; some of these products appear to show significant activity and/or less toxicity than the parent drugs.

In order to study the effect of the amino group at C-3 in the sugar moiety upon the antibiotic activity of daunorubicin and adriamycin, the synthesis of 7-*O*-(2,6-dideoxy-L-*lyxo*-hexopyranosyl)-daunomycinone* and -adriamycinone was considered

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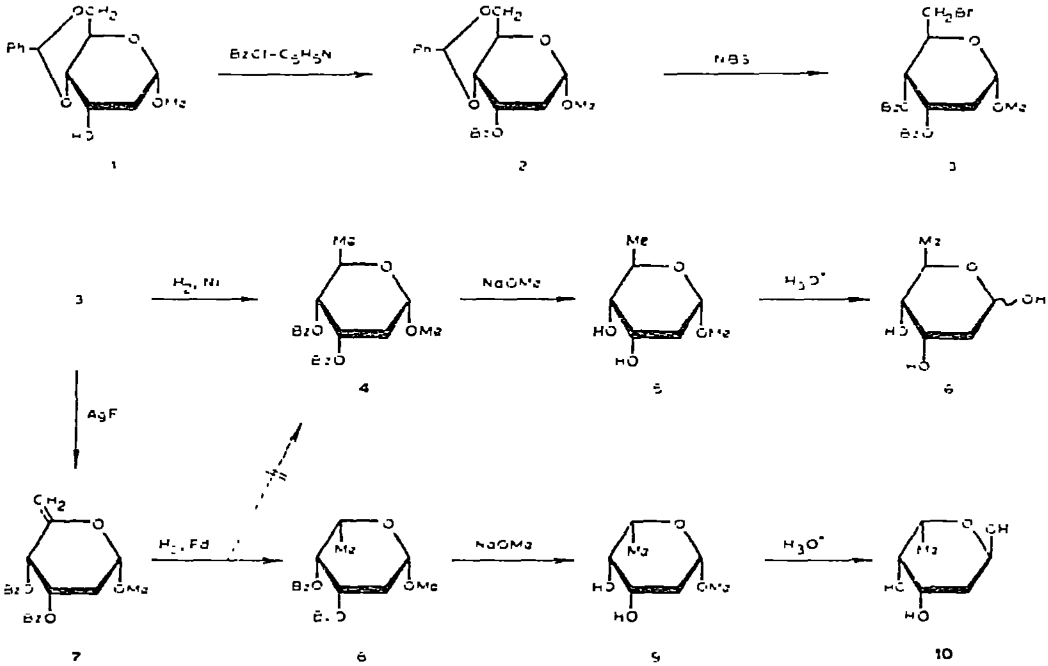
*Note added in proof: see E.-F. Fuchs, D. Horton, and W. Weckerle, *Carbohydr. Res.*, 57 (1977) C36–C39.

a desirable objective. The α anomers of these products would be identical to the parent antibiotics, except for exchange of the amino group by a hydroxyl function. With this in mind, a new synthesis of 2,6-dideoxy-L-*lyxo*-hexose (**10**; 2-deoxy-L-fucose) was designed, and is described in this paper together with the preparation of the closely related (5-epimeric) D-*ribo* analog **6** (digitoxose).

Compound **10** was prepared by Iselin and Reichstein[11] by the glycal method (the same synthesis with only minor modifications has been reported[12] quite recently) long before it was found in Nature[13] as a constituent of rhodomycins[14], cinerubin A (refs. 14 and 15) and B (refs. 14 and 16), the macrolide antibiotic azalomycin-B (ref. 17), and, apparently, as part of a cardiac glycoside[18] from *Pentopetia androsaemifolia*. The D enantiomorph of **10** is known as D-oliose[19]; the corresponding 3-methyl ethers (D- and L-diginose) frequently occur[13,20] in cardiac and pregnane glycosides, as do 2,6-dideoxy-D-*ribo*-hexose (**6**; digitoxose) and the enantiomeric 3-methyl ethers (D- and L-cymarose). Digitoxose[21] (**6**) was first synthesized by Iselin and Reichstein[22] through the glycal method, and, later, by Gut and Prins[23] and Bolliger and Ulrich[24] in moderate yields from a 2,3-anhydro-D-*allo* precursor through an epoxide ring-opening reaction and subsequent deoxygenation at C-6. In 1971, Haga and co-workers[25] described a route to compound **6** similar to the one presented here.



DISCUSSION

The reaction of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside (**1**) (prepared either by reductive cleavage[26] of the epoxide ring in the corresponding

TABLE I

100-MHz N.M.R. SPECTRAL DATA FOR COMPOUNDS **2**-**5** AND **7**-**9**

Compound[a]	*H-1* ($J_{1,2a}$)	*H-2e* ($J_{1,2e}$)	($J_{2e,2a}$)	*H-2a* ($J_{2a,3}$)	*H-3* ($J_{2e,3}$)	*H-4* ($J_{3,4}$)	*H-5* ($J_{4,5}$)	*H-6* ($J_{5,6}$)	*H-6'* ($J_{5,6'}$)	*Aryl*	*OMe-1*
	Chemical shifts (δ)[b] (first-order couplings, Hz, in parentheses)										
2[c]	4.74 dd (3.9)	2.38 ddd (1.0)	 (15.0)	2.05 dt (3.7)	5.56 m (3.0)	← 4.59-3.62 m → (4.0)				8.20-8.02 m 7.56-7.18 m	3.33 s
3[d]	4.87 dd (3.8)	← 2.43-1.96 m → (1.6)			5.76 m	5.21 dd (3.3)	4.62 ddd (9.8)	3.64 dd (3.0)	3.42 dd (6.4)	8.18-7.62 m	3.46 s
4	4.81 dd (3.9)	2.34 ddd (1.8)	 (15.0)	2.15 dt (3.9)	5.70 m (3.6)	5.05 dd (3.0)	4.53 dq (9.4)	1.27 d (6.2)	—	8.17-7.84 m 7.58-7.20 m	3.42 s
5[e]	4.76 dd (3.4)	2.18 ddd (1.2)	 (14.4)	1.87 dt (3.4)	3.93 m (3.2)	3.13 dd (3.5)	3.74 dq (9.8)	1.31 d (6.3)	—	—	3.37 s
7[f,g]	4.33 dd (6.2)	1.92 dt (3.5)	 (13.5)	2.32 ddd (8.9)	5.37 ddd (4.2)	5.96 d (3.2)	—	4.75 d	4.65 d	8.14-8.00 m 7.20-6.86 m	3.25 s
8[g]	4.11 dd (9.0)	2.14 ddd (3.2)	 (12.0)	2.32 ddd (12.0)	5.20 ddd (5.8)	5.49 dd (3.2)	3.24 dq (1.0)	1.15 d (6.5)	—	8.20-7.92 m 7.20-6.82 m	3.36 s
9[e]	4.60 dd (9.2)	1.96 ddd (2.3)	 (13.0)	1.68 dt (12.0)	← 3.85-3.35 m → (5.5)			1.30 d (6.2)	—	—	3.47 s

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[a] In chloroform-d, unless otherwise stated. [b] Signal multiplicities: d, doublet; m, multiplet; q, quartet; s, singlet; t, triplet. [c] Singlet at δ 5.58 (PhC-H). [d] $J_{6,6'}$ 10.7 Hz. [e] After exchange of the hydroxyl protons by deuterium. [f] $J_{6,6'}$ 1.0 Hz. [g] In benzene-d_6.

2,3-anhydro-D-*allo* derivative, or by reduction of the 3-keto analog of 1 with lithium aluminum hydride[4,27]) with benzoyl chloride proceeded readily to give the crystalline 3-*O*-benzoyl derivative **2**, that showed in its p.m.r. spectrum (see Table I), in particular, a 4-line pattern for H-3 at low field (δ 5.56). The i.r. spectrum displayed the anticipated ester C=O absorption at 1725 cm^{-1}, and mass-spectrometric data (intense molecular-ion at *m/e* 370; see Experimental section) further supported the structure assigned. The physical constants of **2** were in good agreement with those reported[25] in the literature for this compound.

Treatment of the benzoate **2** with *N*-bromosuccinimide in dry carbon tetrachloride, by the general procedure of Hanessian[28,29], led to opening of the 1,3-dioxane ring and formation of the 3,4-di-*O*-benzoyl-6-bromo-6-deoxy analog[25,29] **3**, isolated crystalline in 79% yield, and characterized by elemental analysis, and i.r., n.m.r. (see Table I), and mass spectrometry. Compound **3** constitutes the common precursor in the syntheses of the 5-epimeric title sugars, following procedures well-established in the preparation of the corresponding 3-amino-3-deoxy analogs having the D-*ribo*[30] (D-ristosamine) and L-*lyxo*[31] (daunosamine) configurations.

TABLE II

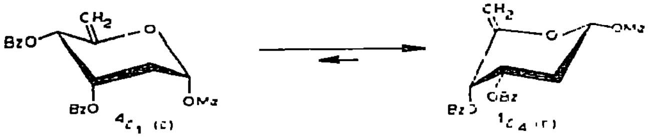
MAJOR FRAGMENT-IONS OBSERVED IN THE ELECTRON-IMPACT MASS SPECTRA OF COMPOUNDS **4**—**6** AND **8**—**10**

m/e of principal fragments[a] (*% of base peak*)						*Assignment*
Compound 4[b]	5	6	8[c]	9	10	
		149 (0.7)	371 (0.05)		149 (0.04)	M+1
370 (0.01)	162 (2.2)	148 (0.4)	370 (0.15)	162 (0.06)	148 (0.01)	$M^{+\cdot}$
369 (0.03)			369 (0.25)	161 (0.45)		M−1
338 (0.03)	130* (0.9)	130 (1.5)	338 (0.02)	130 (1)	130 (0.2)	A_1
216* (4.9)	112 (1.3)	112 (3)	216* (0.5)	112 (3)	112* (0.4)	A_2
201 (0.1)	97 (0.44)	97 (2.5)	201 (0.05)	97 (0.6)	97 (0.5)	A_3
—	68* (1.2)	68 (11)	—	68 (2.5)	68 (1.8)	A_4[d]
—	39 (8)	39 (32)	—	39 (13)	39 (5)	A_5[d]
—	94 (0.5)	94 (3.5)	—	94 (2)	94 (0.3)	A_3^1[d]
339 (0.1)	131 (7.5)	131 (0.8)	339 (0.03)	131 (0.4)	131 (1.2)	C_1
217* (1.6)	113* (3)	113 (1.1)	217* (0.2)	113* (1.3)	113 (1)	C_2
95* (5.5)	95 (1)	95 (2.5)	95* (1.3)	95 (1.4)	95 (0.3)	C_3
326 (0.1)	118 (6.2)	104 (6.5)	326 (0.4)	118 (4)	104 (8)	D_1
—	100 (1.1)	86 (75)	—	100 (0.9)	86 (41)	D_2^1
—	59* (100)	45 (70)	—	59* (90)	45 (50)	D_3^1
268 (1)	60* (94)	60* (100)	268 (1.1)	60* (100)	60* (100)	D_2^2
—	59 (100)	59 (4.5)	—	59 (90)	59 (2.5)	D_3^2
—	43 (25)	43 (89)	—	43 (24)	43 (37)	D_3^3
58 (0.9)	58 (55)	44 (70)	58 (0.9)	58 (50)	44 (15)	E_1^1
312 (0.03)	104 (27)	104 (6.5)	312 (0.08)	104* (20)	104 (8)	E_1^2

[a] Prominent metastable fragments observed in the spectra are indicated by an asterisk at the daughter ion of the process involved; deviations between observed and calculated values are less than ±0.1 mass units. [b] Additional fragment ions at *m/e* 248 (0.25, M − BzOH), 105 (100, $PhCO^+$), and 77 (20, Ph^+). [c] Additional fragment ions at *m/e* 248 (0.25, M − BzOH), 105 (100, $PhCO^+$), and 77 (25, Ph^+). [d] Adapted from the fragmentation pathways proposed by Takahashi *et al.* (ref. 17).

Reductive debromination of **3** was effected by Raney nickel in the presence of triethylamine to give the crystalline 6-deoxy derivative **4** in 94% yield. The well-resolved p.m.r. spectrum of **4** (see Table I) showed a doublet at high field (δ 1.27) indicative of the 5-*C*-methyl group coupled to H-5. The latter is represented by an 8-line signal (doubled quartet) at δ 4.53, as demonstrated by double-irradiation experiments; the remainder of the spectrum closely resembled that of the precursor **3** (see Table I). Mass-spectrometric data (see Table II) and elemental composition supported the structure indicated. as did the good correlation between the physical data of **4** with those given[25] for this product in the literature.

Inversion of the configuration at C-5, in order to prepare the L-*lyxo* derivative **8**, was achieved by exploiting the elimination-reduction sequence successfully used[31] in the analogous synthesis of daunosamine. Treatment of the bromide **3** with silver fluoride[23] furnished the 5,6-unsaturated derivative **7** as a homogeneous (by t.l.c.) syrup in high yield. The structure assigned this product was confirmed by its i.r. spectrum (vinyl-stretching absorption at 1660 cm^{-1}) as well as by p.m.r. data (see Table I). In addition to the anticipated methoxyl and aryl proton signals, the spectrum of **7** in benzene-d_6 showed two narrow, one-proton doublets for H-6 (δ 4.75) and H-6′ (δ 4.65), each displaying a small geminal coupling ($J_{6,6'}$ 1 Hz). The large values for $J_{1,2a}$ and $J_{2a,3}$ (6.2 and 8.9 Hz, respectively) indicated the presence of three consecutive, preponderantly *trans*-diaxially disposed protons (at C-1-C-3), suggesting that the $^1C_4$(D) conformation is strongly favored, despite the anomeric effect, which generally operates to favor the axial orientation of the 1-methoxyl group[33]. This predisposition could be the result of a strong interaction[34] between the 1-methoxyl and the 3-benzoyloxy group in the $^4C_1$(D) conformation, as the methylene substituent at C-5 presumably exhibits little significant interaction favoring either the one conformation or the other. The close resemblance of this spectrum to that of compound **8** (see Table I; see next paragraph), including the fact that H-2*e* and H-3 resonate at higher field than H-2*a* and H-4, respectively, and, that the values for $J_{1,2e}$ and $J_{2e,3}$ (3.5 and 4.2 Hz) are relatively large, provides further indication of the preponderance of the $^1C_4$(D) conformation for compound **7** in solution. In addition there is the "negative evidence" that* no long-range coupling between H-1 and H-3 was observed; such coupling would have been expected for the $^4C_1$(D) conformation (as was verified in the spectrum of the related compound **4**, where $^4J_{1,3}$ is ~1 Hz), but not for the $^1C_4$(D) conformation.



Compound **7** in the $^4C_1$ (D) and $^1C_4$ (D) conformations

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*We are indebted to a referee for this argument.

Catalytic hydrogenation of **7** in the presence of palladium on barium sulfate led to a single, crystalline product (**8**) that was different from the D-*ribo* compound **4** (by g.l.c.), although it gave a mass spectrum (see Table II) identical to that of **4**, except for the intensities of the fragment ions. The 100-MHz, p.m.r. spectrum in benzene-d_6 (see Table I) was essentially first-order, displaying, in particular, a 3-proton doublet at high field (δ 1.15, C-Me) and well-resolved, one-proton signals for H-1 (δ 4.11), H-3 (δ 5.20), and H-4 (δ 5.49); these data establish unequivocally the L-*lyxo* stereochemistry of the product obtained. The assignment of the higher- (and lower-) field signals (δ 2.14 and 2.32) of the geminal protons at C-2 to the equatorially (and axially) disposed hydrogen atoms is based on the observed coupling-constants, and is consistent with data for other 2-deoxyhexopyranoses that have been thoroughly studied[35] by n.m.r. spectroscopy. Although this interpretation contrasts with the conventional view, this assignment is considered correct, and is ascribed to the deshielding (or shielding) effect of the neighboring *O*-benzoyl group upon the axial (or equatorial) hydrogen atom at C-2. Indeed, the frequently used generalization that equatorial-proton signals lie downfield from those of axial protons in pyranose systems has been shown before to be reversed in such compounds as methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose[27,36], its oxime[27], and[35,37] methyl 3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (methyl di-acetylristosaminide), although these have been said[38] to be exceptional.

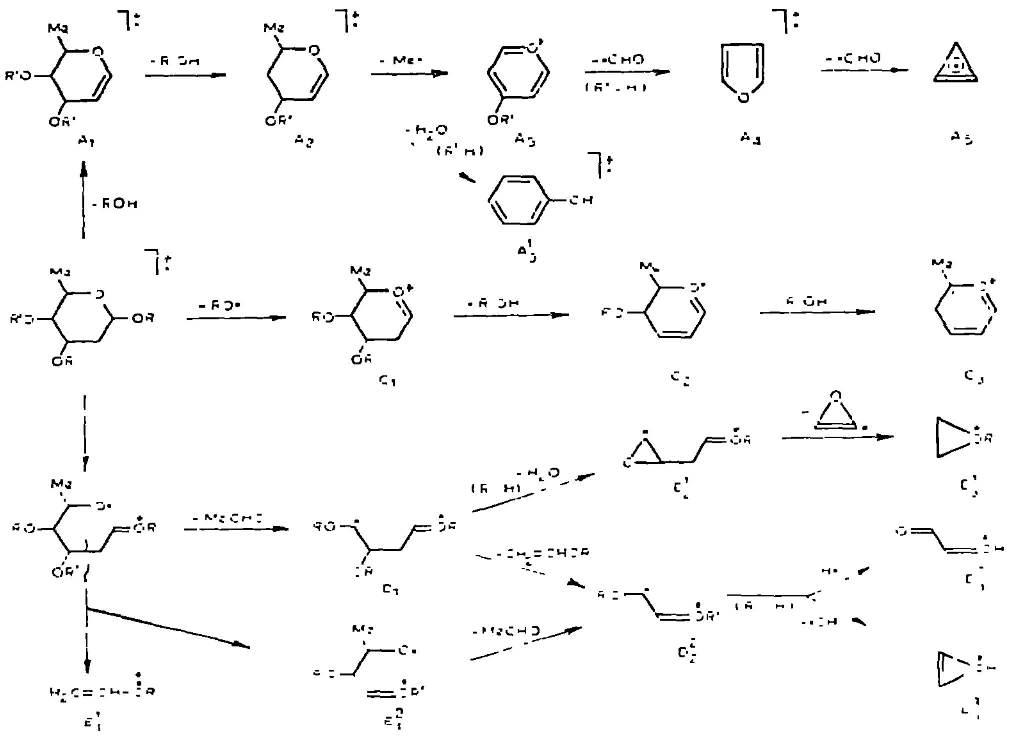
O-Deacylation of **4** and **8** was effected by catalytic transesterification to give the syrupy D-*ribo* (**5**) and crystalline L-*lyxo* (**9**) methyl glycosides in good yields; their physical constants were consistent with those recorded for[24,25,39] **5** and[12] **9** in the literature.

The final step in the two sequences was accomplished by hydrolysis of the methyl glycosides **5** and **9** with aqueous acetic acid, to yield crystalline 2,6-dideoxy-D-*ribo*-hexose (digitoxose, **6**) and the slightly hygroscopic, crystalline, 5-epimeric, L-*lyxo* compound **10** (2-deoxy-L-fucose). The physical data (m.p., specific rotation in methanol and in water at equilibrium) of compound **6** were in general accord with those recorded for digitoxose obtained[21] from natural sources and[22-25] for synthetic products. Because of the complex mutarotation, no assignment of the anomeric form in the crystalline state was made, although Bolliger and Ulrich claimed[24] that it is the β anomer.

The L-*lyxo* analog **10**, which is the enantiomorph of the naturally occurring dideoxy sugar oliose[19], crystallized in the α-L form, as evidenced by its upward mutarotation in water and acetone; the final specific rotations showed good correlation with those recorded for the synthetic[11] and[17] natural product.

The foregoing syntheses afford the title sugars **6** and **10** from **1** in 57 and 45% net yield, based on intermediates isolated directly, with no chromatographic purification involved at any of the steps; all of the reactions are readily amenable to scaled-up operations.

Mass-spectrometric data for the derivatives **2**, **3**, and **7** are given in the Experimental section. For the other compounds described in this paper, the principal fragments, together with their relative intensities, are summarized in Table II. The pathways deduced for the fragmentation, as detailed in Scheme 1, are based on plausible mechanistic steps and accord, in part, with those proposed[17] by Takahashi and co-workers.



Scheme 1

Cleavage of the glycosidic bond leads to ions of the A and C series: A_1 and C_1 undergo successive loss of two more ring-substituents, affording the substituted pyrylium ions A_3 and C_3. The former loses[17] two formyl radicals to furnish A_4 and A_5. Alternatively, A_2 may rearrange[17] and give, through elimination of water, the odd-electron ion A_3^1. Through C-1–O-5 rupture of the pyranose ring, ions of the D and E series arise by subsequent cleavage of a second ring-bond between C-2 and C-3 (E series) or C-4 and C-5 (D series). Fragmentation of D_1 may proceed either by loss of water and an oxiranyl radical to form D_3^1 as one of the most abundant ions in the spectra of the unsubstituted compounds (**5**, **6**, **9**, and **10**), or D_1 may decompose, with loss of a C_2-fragment, into D_2^2. This odd-electron ion may alternatively arise from fragment E_1^2 through elimination of acetaldehyde; it decays further by expulsion of a proton or a hydroxyl radical, to form an open-chain (D_3^2) or cyclic (D_3^3) cation, respectively.

The aforementioned assignments are in many instances supported by metastable fragments observed in the spectra (as indicated in Table II), but the possibility of isomeric structures is not precluded.

EXPERIMENTAL

General methods. — Evaporations were performed under diminished pressure at a bath temperature below 50°. Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. A Perkin–Elmer Model 141 polarimeter and 1-dm tubes were used for measurement of specific rotations. I.r spectra were recorded with a Perkin–Elmer Model 457 grating i.r. spectrophotometer, with solids dispersed in potassium bromide and syrups as films on sodium chloride discs. ^{1}H-N.m.r. spectra were recorded at 100 MHz with a Varian HA-100 spectrometer; chemical shifts refer to an internal standard of tetramethylsilane ($\delta = 0.00$), and are listed, together with spin-coupling values (Hz, measured at a sweep width of 250 Hz) in Table I. The assignments were confirmed in most instances by decoupling experiments. Integrations were consistent with the peak assignments in all instances. T.l.c. was performed on precoated plates of Silica Gel 60 (E. Merck, Darmstadt); zones were detected by u.v. light, and by spraying with sulfuric acid and subsequent heating. Solvent volumes are v/v; petroleum ether refers to the fraction boiling at 65–110°. Column filtration was performed with silica gel (Merck No. 7734; 63–200 μm). Microanalyses were performed by W. N. Rond of this Department. Mass spectra were recorded by C. R. Weisenberger with an AEI MS-9 double-focusing, high-resolution spectrometer operating at an ionizing potential of 70 eV and an accelerating potential of 8 kV; the source temperature (direct-inlet system) was 120°. Data and probable assignments for compounds **4–6** and **8–10** are summarized in Table II and Scheme 1. The notations h_1 and h_2 in the assignment of compound **2** refer to the α-rupture proposed by Chizhov *et al* [40]. X-Ray powder diffraction data give interplanar spacings, Å, for CuKα radiation. The camera diameter was 114.59 mm. Relative intensities were estimated visually: m, moderate, s, strong; v, very; w, weak. The strongest lines are numbered (1, strongest); double numbers indicate approximately equal intensities.

*Methyl 3-O-benzoyl-4,6-O-benzylidene-2-deoxy-α-*D*-*ribo*-hexopyranoside* (**2**). — To a solution of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside[4,26,27] (**1**; 12.38 g, 46.5 mmol) in dry pyridine (200 ml), cooled in an ice–water bath, was added benzoyl chloride (5.6 ml, 48 mmol). The mixture was kept for 12 h at ~25°, after which time t.l.c. (4:1 ether–petroleum ether) indicated the reaction to be complete. The mixture was then poured into ice-water (600 ml), and the product was extracted with dichloromethane (two 120-ml portions). The extracts were combined, washed successively with aqueous sodium hydrogencarbonate and water, dried (magnesium sulfate), and evaporated. Toluene (two 20-ml portions) was added to and evaporated from the residue, and the crystalline material was recrystallized from ethanol, to give pure **2**; yield 15.31 g (89%), m.p. 94–95°, $[\alpha]_D^{22}$ +185° (*c* 1, chloroform) (lit.[25] m.p. 95–97°, $[\alpha]_D$ +192.1° in chloroform); ν_{max}^{KBr} 1725 (ester C=O), 750 and 695 cm^{-1} (aryl); *m/e* (rel. intensity): 370 (17.2, M$^{+\cdot}$), 369 (5, M − H·), 339 (0.16, M − MeO·), 293 (0.4, M − Ph·), 264 (0.5, M − PhCHO), 247 (0.1, M − BzOH), 221 (50, h_1; m* at 132.0, calc. 132.00), 149 (5, h_2), 99 (100, h_1 − BzOH; m* at 44.3, calc. 44.35), 105 (85), 91 (9.5), and 77 (27); X-ray powder diffraction data: 11.47 w, 8.62 w, 7.72 s (3,3), 7.31 vw, 6.70 w, 8.84 s (3,3), 5.45 m, 6.60 s (1,1), 4.51 s (1,1), 5.64 w, 4.12 s (2,2), and 3.98 s (2,2).

Anal. Calc. for $C_{21}H_{22}O_6$ (370.40): C, 68.10; H, 5.98. Found: C, 68.26; H, 5.85.

*Methyl 3,4-di-O-benzoyl-6-bromo-2,6-dideoxy-α-D-*ribo*-hexopyranoside* (3). — A mixture of the benzylidene acetal 2 (25.7 g, 69.4 mmol), *N*-bromosuccinimide (13.35 g, 75 mmol), and barium carbonate (20 g) in dry carbon tetrachloride (500 ml) was boiled for 5 h with stirring under reflux, during which time the color of the solution, originally colorless, became successively yellow, red, and finally pale-yellow. The solvent was distilled off, and the residue extracted with dichloromethane (three 150-ml portions). The extracts were combined, washed successively with aqueous solutions of sodium hydrogensulfite and sodium hydrogencarbonate, dried (magnesium sulfate), and evaporated to dryness. The resulting, crystalline residue was recrystallized from ethanol to give analytically pure **3**: yield 24.7 g (79%), m.p. 96–98°, $[\alpha]_D^{22}$ +192.5° (*c* 0.6, chloroform) (lit.[25] m.p. 100–102°, $[\alpha]_D$ +172.6° in chloroform, and[29] m.p. 95–96°); ν_{max}^{KBr} 1725 (ester C=O), 1600 and 1580 cm^{-1} (monosubstituted phenyl); *m/e* (rel. intensity): 449 (0.2, M$^{+\cdot}$), 418 (0.05, M − MeO·), 417 (0.1, M − MeOH), 369 (1.7, M − Br·), 327 (0.25, M − BzOH), 105 (100), and 77 (18). X-ray powder diffraction data: 10.71 vw, 9.66 s (3), 8.62 w, 6.68 w, 6.10 m, 5.43 w, 5.17 vw, 4.91 vw, 4.75 s (2,2), 4.34 s (2,2), and 3.82 vs (1).

Anal. Calc. for $C_{21}H_{21}BrO_6$ (449.30): C, 56.13; H, 4.71; Br, 17.78. Found: C, 55.91; H, 4.69; Br, 17.97.

*Methyl 3,4-di-O-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranoside* (4). — A mixture of the bromide **3** (10.2 g, 22.7 mmol), Raney nickel (~8 g), and triethylamine (9 ml) in methanol (200 ml) was shaken under hydrogen at 4.2 kg.cm^{-2} for 18 h at ~25°, whereupon t.l.c. (9:1 benzene–ether) indicated the reaction to be complete. The catalyst was removed by filtration, the filtrate evaporated, and the residue dissolved in chloroform (150 ml). The solution was washed twice with water to remove triethylammonium bromide, dried (magnesium sulfate), and evaporated to give crystals that were recrystallized from hexane to afford pure **4**; yield 7.9 g (94%), m.p. 80–82°, $[\alpha]_D^{23}$ +227.9° (*c* 1, chloroform) (lit.[25] m.p. 83–85°, $[\alpha]_D$ +214.6° in chloroform); ν_{max}^{KBr} 1720 cm^{-1} (ester C=O); X-ray powder diffraction data: 10.21 s, 9.40 m, 6.23 m, 5.15 vs (1), 4.91 s (2), 4.65 s, 4.44 s (3,3), 3.97 s (3,3), 3.77 w, 3.48 m, 3.35 m, and 3.19 m.

Anal. Calc. for $C_{21}H_{22}O_6$ (370.40): C, 68.10; H, 5.98. Found: C, 67.94; H, 6.36.

*Methyl 2,6-dideoxy-α-D-*ribo*-hexopyranoside* (5). — To a solution of compound **4** (1.37 g, 3.7 mmol) in abs. methanol (30 ml) was added M sodium methoxide (0.4 ml), and the mixture was kept for 12 h at 25°, at which point t.l.c. (19:1 ethyl acetate–methanol) indicated that transesterification was complete. The solution was evaporated, and the residue placed on a small column (250 × 20 mm) of silica gel. Chloroform was used first as eluant to remove methyl benzoate. The product was then washed off the column with acetone, and the effluent was evaporated, to give **5** as a colorless syrup: yield 560 mg (93%). To secure an analytical sample, a portion of the syrup was distilled at 40 mtorr (bath temperature 60–80°). $[\alpha]_D^{21}$ +192.4° (*c* 1.45, methanol) and +169.1 (*c* 2.3, chloroform) (lit.[24] $[\alpha]_D$ +192.0 ± 1° in methanol: $[\alpha]_D$ +178.4° in chloroform[25]; and[39] $[\alpha]_D$ +174° in chloroform).

Anal. Calc. for $C_7H_{14}O_4$ (162.18): C, 51.84; H, 8.70. Found: C, 51.80; H, 9.00.

*2,6-Dideoxy-*D-ribo-*hexose* (D-*digitoxose*, **6**). — A solution of the glycoside **5** (356 mg, 2.2 mmol) in acetic acid (3 ml) and water (7 ml) was boiled under reflux for 45 min, after which time t.l.c. (19.1 ethyl acetate–methanol) indicated that hydrolysis was complete. Evaporation gave a residue that readily crystallized upon addition of a little acetone. The crystals were filtered off, and recrystallized from acetone to give pure **6**; yield 303 mg (93%), m.p. 105–108°, $[\alpha]_D^{22}$ + 42.5 (5.20 min) → +51.7 (7.50 min) → +47.5 (20 min) → +47.8° (1 h, equil.; *c* 1.06, water) and +36.5° (*c* 0.74, methanol); X-ray powder diffraction data: 8.22 vw, 7.31 vw, 6.63 vs (2), 5.66 m, 5.01 w, 4.74 vw, 4.33 s (3), 4.10 vs (1), 3.88 vw, 3.65 m, 3.50 m, and 3.39 m.

Anal. Calc. for $C_6H_{12}O_4$ (148.16): C, 48.64; H, 8.16. Found: C, 48.79; H, 8.08.

For this compound, the following constants have been reported: m.p. 108–110°, $[\alpha]_D$ +37.1 ±2° in methanol[22]; m.p. 108–111°, $[\alpha]_D$ +38.1 ±2° in methanol[23]; m.p. 110–112°, $[\alpha]_D$ +43.6 ±2 (7 min) → +50.2 ±2 (1 h, equil.) in water[24]; and[25] m.p. 109–111°, $[\alpha]_D$ +51.3° (equil.) in water. For digitoxose isolated from a natural source, Micheel gave[21] m.p. 105–107°, $[\alpha]_D$ +46.3° in water and +38.1° in methanol.

*Methyl 3,4-di-O-benzoyl-2,6-dideoxy-α-*D-erythro-*hex-5-enopyranoside* (**7**). — A mixture of the bromide **3** (9.1 g, 20.25 mmol) and dry, technical-grade silver fluoride[32] (8 g) in dry pyridine (100 ml) was thoroughly stirred for 40 h at 25°, whereupon t.l.c. (chloroform) revealed that all of the **3** had reacted. The dark solution was poured into ether (500 ml), and the resultant mixture was filtered. The filtrate was evaporated, and toluene (three 30-ml portions) was added to and distilled from the residue to remove all of the pyridine. The remaining, dark syrup was filtered through a small column (400 × 20 mm) of silica gel with acetone as eluant, to remove residual silver salts. Evaporation of the effluent afforded syrupy **7**, sufficiently pure for the following step: yield 6.86 g (92%), $[\alpha]_D^{23}$ +123° (*c* 2.9, chloroform); ν_{max}^{film} 1730 (ester C=O), 1660 (C=C), 1600 and 1580 cm^{-1} (monosubstituted phenyl); *m/e* (rel. intensity): 369 (0.07, M+1), 368 (0.02, $M^{+\cdot}$), 337 (0.13, M−MeO·), 215 (1.2, 337−BzOH), 336 (0.5, M−MeOH), 214 (1.7, 336−BzOH), 246 (4, M−BzOH), 122 (7, $BzOH^{+\cdot}$), 105 (100, $PhCO^+$; m* at 90.4, calc. for 122 → 105: 90.37), and 77 (20).

Although the product migrated as a single zone in t.l.c. (R_F 0.83 in 9:1 benzene–ether), and no signals due to impurities were detected in its n.m.r. spectrum, an elemental analysis lying within acceptable limits could not be obtained.

*Methyl 3,4-di-O-benzoyl-2,6-dideoxy-β-*L-lyxo-*hexopyranoside* (**8**). — The unsaturated sugar **7** (4.45 g, 12.1 mmol) in dry methanol (100 ml) was hydrogenated at 25° under atmospheric pressure in the presence of 10% palladium on barium sulfate (450 mg). After 30 min, the theoretical amount of hydrogen had been taken up, and t.l.c. (9:1 benzene–ether) verified that the reaction was complete. As shown by g.l.c. [Hewlett-Packard gas chromatograph Series 5720A, equipped with a flame-ionization detector and a glass column (1.83 m × 3 mm) packed with 2% of OV-1 on Chromosorb, at 260° (isothermal), with helium as the carrier gas at a flow-rate of 25 ml min^{-1}], the mixture contained only a single product (retention time ~4 min) that was different from methyl 3,4-di-*O*-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranoside (**4**; retention time ~3 min) by comparison of the retention times, as well as by the mixed-injection technique. The catalyst was filtered off, and the filtrate was evaporated to give a crystalline, chromatographically homogeneous (R_F 0.75) residue that was recrystallized from ethanol to furnish **8** as fine needles; yield 3.92 g (88%), m.p. 122–123°, $[\alpha]_D^{22}$ −63.4° (*c* 0.9, chloroform); ν_{max}^{KBr} 1725 (ester C=O), 1600 and 1585 cm^{-1} (monosubstituted phenyl); X-ray powder diffraction data: 12.90 m, 8.00 s, 7.31 s, 6.83 w, 6.37 w, 5.43 m, 5.11 s (3), 4.80 w, 4.53 s (1,1), 4.16 s (1,1), 3.81 vw, and 3.65 s (2).

Anal. Calc. for $C_{21}H_{22}O_6$ (370.40): C, 68.10; H, 5.98. Found: C, 68.13; H, 6.02.

*Methyl 2,6-dideoxy-β-*L*-*lyxo*-hexopyranoside* (**9**). — To a solution of the fully protected glycoside **8** (5.3 g, 17 mmol) in abs. methanol (50 ml) was added M sodium methoxide (0.75 ml), and the mixture was kept for 12 h at 25°, after which time t.l.c. (19:1 ethyl acetate–methanol) indicated that transesterification was complete. The solvent was distilled off, and a chloroform solution of the residue was placed on a small column (450 × 20 mm) of silica gel. Chloroform was used as the eluant first, to remove methyl benzoate, and the product was then eluted with acetone, the effluent evaporated, and the crystalline product recrystallized from ether to give pure **9**: yield 2.2 g (80%), m.p. 110°, $[\alpha]_D^{22}$ +44° (*c* 0.8, methanol) and +50.3 (*c* 1.2, chloroform); X-ray powder diffraction data: 11.89 m, 10.51 w, 9.45 m, 7.53 w, 6.73 m, 6.00 vs (1), 5.45 s, 4.48 s (3,3), 4.16 s (3,3), 4.00 m, 3.82 m, and 3.50 s (2).

Anal. Calc. for $C_7H_{14}O_4$ (162.18): C, 51.84; H, 8.70. Found: C, 51.80; H, 9.00.

For this compound, prepared by the glycal method, Garegg and Norberg reported[12] m.p. 108–109°, $[\alpha]_D$ +48° in chloroform.

*2,6-Dideoxy-α-*L*-*lyxo*-hexose* (*2-deoxy-α-*L*-fucose, α-*L*-oliose*, **10**). — A solution of the methyl glycoside **9** (990 mg, 6.10 mmol) in acetic acid (3 ml) and water (12 ml) was boiled for 30 min under reflux, at which time t.l.c. (19:1 ethyl acetate–methanol) indicated that hydrolysis of the glycoside was complete. The solvent was evaporated off, and water (three successive 10-ml portions) was added to the concentrated solution (~2 ml) and evaporated after each addition to remove all of the acetic acid. Finally, the solution was evaporated to dryness, to afford a colorless, hygroscopic syrup (**10**; R_F 0.29) that was dried over phosphorus pentaoxide and potassium hydroxide for several days; yield 890 mg (98%). Addition of a little acetone effected crystallization, and the crystals (**10**) were filtered off in an inert atmosphere (nitrogen), and dried; yield 630 mg, m.p. 102–105°, $[\alpha]_D^{23}$ −97 (initial, extrapolated) → −81.2 (4 min) → −73.8 (6 min) → −64.8 (10 min) → −51.5° (2 h, equil.; *c* 1.04, water) and

-134 (initial, extrapolated) $\rightarrow -131.1$ (7.50 min) $\rightarrow -128.3$ (15 min) $\rightarrow -122.7$ (30 min) $\rightarrow -75.6°$ (10 h, equil.; *c* 0.99, acetone); X-ray powder diffraction data: 7.93 s (3), 6.78 w, 6.12 vs (2), 5.37 m, 4.82 w, 4.31 vs (1), 4.12 m, 3.94 m, 3.72 w, and 3.48 m.

Anal. Calc. for $C_6H_{12}O_4$ (148.16): C, 48.64; H, 8.16. Found: C, 48.65; H, 8.37.

Iselin and Reichstein reported[11] for this product m.p. 103–106°, $[\alpha]_D$ $-136.2 \pm 3°$ in acetone and -90.4 ± 2 (5 min) $\rightarrow -61.6 \pm 2°$ (90 min, equil.) in water. For a compound isolated from a macrolide antibiotic, Takahashi and co-workers gave[17] m.p. 92–94°, $[\alpha]_D$ -134 (7 min) $\rightarrow -87°$ (3 h) in acetone and -75 (5 min) $\rightarrow -57°$ (90 min) in water.

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