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Note

β-Elimination in aldonolactones: synthesis of 2-O-benzoyl-3,5,6-trideoxy-α-DL-*threo*-hexofuranose

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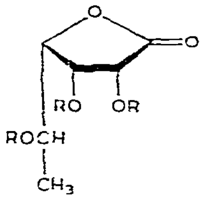
We have reported the synthesis of deoxy[1,2] and dideoxy[3,4] sugars *via* β-elimination reactions occurring on benzoylation of aldonolactones. Recently, we described the preparation of ascarylose[3] (3,6-dideoxy-L-*arabino*-hexose) and a crystalline, furanoid benzoate[4] of this sugar, starting from L-rhamnono-1,5-lactone. We now report that double elimination was observed when L-rhamnono-1,4-lactone was benzoylated under similar conditions. The unsaturated lactone derivative was used for the synthesis of 2-*O*-benzoyl-3,5,6-trideoxy-α-DL-*threo*-hexofuranose (**6**).



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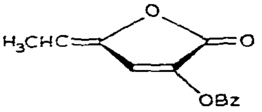
2 R = Bz



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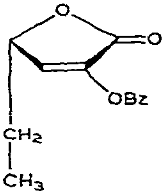
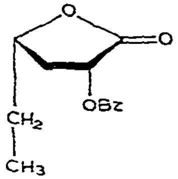
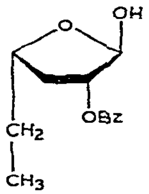


4 (DL)



5 (DL)



6 (DL)

Trideoxy sugars are not very common in Nature; 2,3,6-trideoxyhexoses have

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been found as components of antibiotics[5,6], but no 3,5,6-trideoxyaldoses, either natural or synthetic, have been reported.

Treatment of L-rhamnono-1,4-lactone (**1**) with a slight excess of benzoyl chloride and pyridine at room temperature for 90 min afforded crystalline 2,3,5-tri-*O*-benzoyl-L-rhamnono-1,4-lactone (**2**, 79% yield), which showed i.r. absorption characteristic of 1,4-lactones. The ^{1}H-n.m.r. data (Table I) were in accord with the structure; H-4 in the 1,4-lactone **2** resonates at higher field than H-5, and the opposite has been observed for the isomeric 1,5-lactone[7]. The smaller values observed for $J_{2,3}$ (5.2 Hz) and $J_{3,4}$ (3.0 Hz), as compared with those for 2,5-di-*O*-benzoyl-3,6-dideoxy-L-*arabino*-hexono-1,4-lactone[4] (**7**) and 2-*O*-benzoyl-3,5,6-trideoxy-DL-*threo*-hexono-1,4-lactone (**5**), are consistent[8] with the presence of an electronegative substituent on C-3.

Compound **2** underwent elimination on treatment with 20% triethylamine in chloroform for 6 h at room temperature and afforded crystalline 3-benzoyloxy-5-ethylidene-2(5*H*)-furanone (**3**). Preparation of **3** by benzoylation of L-rhamnono-1,4-lactone, without isolation of the intermediate, saturated benzoate **2**, gave poorer yields. Compound **3** was unstable at room temperature and the stereochemistry of the exocyclic double-bond was not determined. It was characterised by its spectroscopic data. The u.v. spectrum showed λ_{max} 280 nm (ε 5600), due to the furanone chromophore. The 1,4-lactone carbonyl absorption in the i.r. spectrum was shifted to 1770 cm^{-1} because of the conjugation. The signal for the vinylic H-4 of the furanone appeared at low field in the ^{1}H-n.m.r. spectrum, together with those of the aromatic protons, and the ethylidene proton gave a quartet at δ 5.83. The mass spectrum showed a molecular ion at *m/z* 230 and the fragmentation pattern was very simple; those ions corresponding to the aromatic series (105→77→51) being the most intense, as has been already observed for other benzoylated lactone derivatives[7]. Subsequent losses of benzoyl and a C_2O_2 fragment (probably 2 CO) from the molecular ion give rise to the ion at *m/z* 69, which undergoes elimination of carbon monoxide to give $C_3H_5^+$ (*m/z* 41). Analogous fragmentation has been observed in other α,β-unsaturated lactones[9].

When **3** was hydrogenated over palladium–barium sulfate until the hydrogen uptake corresponded to 1 mol. equiv., crystalline 2-*O*-benzoyl-3,5,6-trideoxy-DL-*glycero*-hex-2-enono-1,4-lactone (**4**) was obtained in 74% yield. As expected, the exocyclic double-bond of **3** was hydrogenated preferentially to the endocyclic, conjugated bond, resulting in a pair of enantiomers due to the planarity of the starting lactone. Compound **4** showed i.r. carbonyl absorptions corresponding to an unsaturated lactone (1770 cm^{-1}) and to a vinylic benzoate (1740 cm^{-1}). In the ^{1}H-n.m.r. spectrum, the methyl group gave a triplet at δ 1.04 coupled with H-5 and H-5'. The signal for the vinylic proton appeared at δ 7.30 together with those for the benzoate protons. The sextet shown at δ 4.98 was assigned to H-4. The ^{13}C-signal for C-1 appeared at 166.8 p.p.m., and was shifted upfield with respect to that of the lactone carbonyl in compound **2** due to α,β-unsaturation. The benzoate carbonyl also appeared at higher field because of the enolic structure. The partially coupled spectrum allowed the identification of the C-2 signal.

Complete hydrogenation of **3** gave 2-*O*-benzoyl-3,5,6-trideoxy-DL-*threo*-hexono-1,4-lactone (**5**). Compound **5** was homogeneous by t.l.c. and g.l.c. under different conditions; this fact, together with the ^{1}H-n.m.r. data, indicate that we are dealing with only one pair of enantiomers of the two theoretically possible from **4**. After hydrogenation of the exocyclic double-bond, the ethyl group attached to the ring would prevent attack from the same side, resulting in the formation of only one pair of enantiomers, in which the two chiral centers bear a *threo* relationship. We have already reported[2,10] stereoselectivity in the hydrogenation of enono-1,4-lactones over palladium. Furthermore, only one compound was detected by g.l.c. when **5** was analysed as the alditol acetate after debenzoylation and reduction.

The ^{1}H-n.m.r. spectrum of **5** showed a great resemblance, both in chemical shifts and coupling constants, to that of 2,5-di-*O*-benzoyl-3,6-dideoxy-L-*arabino*-hexono-1,4-lactone[4] (**7**, Table I), in accordance with the proposed configuration. The large values for $J_{2,3}$ (8.5 Hz), $J_{2,3'}$ (10.4 Hz), and $J_{3',4}$ (10.1 Hz) confirm the postulated *threo* relationship for the two chiral centers. In the *erythro* configuration, H-2 (or H-4) would lie outside the angle formed by H-3 and H-3′ and H-4 (or H-2) would bisect it, resulting in smaller coupling-constants.

Reduction of the trideoxy-lactone **5** with disiamylborane afforded 2-*O*-benzoyl-3,5,6-trideoxy-α-DL-*threo*-hexofuranose (**6**), which could not be crystallised. Debenzoylation of **6** with sodium methoxide gave 3,5,6-trideoxy-DL-*threo*-hexose (**8**), which was characterised as its 2,4-dinitrophenylhydrazone.

The i.r. spectrum of **6** showed absorptions at 3300 due to the anomeric hydroxyl group and at 1710 cm^{-1} assigned to the benzoate carbonyl group. The ^{1}H-n.m.r. data are shown in Table I. The hydroxyl group gave a broad singlet at δ 3.70, which

TABLE I

^{1}H-N.M.R. CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS (Hz)

Compound	*H-1* ($J_{1,2}$)	*H-2* ($J_{2,3}$)	*H-3* ($J_{2,3'}$)	*H-3′* ($J_{3',4}$)	($\lvert J_{3,3'}\rvert$)	*H-4* ($J_{3,4}$)	*H-5*[a] ($J_{4,5}$)	*H-6* ($J_{5,6}$)	*Bz*
2	—	6.03 (d) (5.2)		6.16 (q)		4.81 (q) (3.0)	5.52 (m) (8.0)	1.61 (d) (6.1)	7.1–7.9 (m)
5	—	5.66 (q) (8.5)	2.87 (m) (10.4)	2.05 (m) (10.1)	(12.5)	4.41 (m) (6.2)	1.80 (m) (5.5)	1.08 (t) (6.8)	7.2–8.1 (m)
7	—	5.68 (q) (8.4)	2.96 (m) (10.2)	2.34 (m) (10.0)	(12.5)	4.63 (m) (6.5)	5.37 (m) (5.0)	1.49 (d) (6.4)	7.3–8.2 (m)
6	5.50 (d) (<0.5)	5.27 (q) (6.4)	2.60 (m) (2.4)	1.80 (m) (6.2)	(14.2)	4.26 (m) (6.8)	1.56 (m) (7.0)	1.00 (t) (7.0)	7.2–8.2 (m)
9	5.57 (d) (<0.5)	5.25 (q) (6.7)	2.72 (m) (1.8)	2.05 (m) (6.2)	(14.2)	4.46 (m) (7.0)	5.32 (m) (6.5)	1.42 (d) (6.5)	7.2–8.2 (m)

[a] For **5** and **6**, the signals of H-5 and H-5′ have coincident chemical shifts

TABLE II

DAERM ANALYSIS[a] OF COUPLINGS FOR COMPOUND **6**

Protons coupled	*Case*	J_1[b]	J_2	θ_1[b]	θ_2	k_1	k_2
H-2; H-3,3′	i	6.4	2.4	3	127	6.68	7.40
	ii	6.4	2.4	55	69	20.30	20.86
	iii	2.4	6.4	48	172	5.98	6.81
	iv	2.4	6.4	68	56	19.10	21.36
H-4; H-3,3′	v	6.8	6.2	23	147	8.36	9.21
	vi	6.8	6.2	61	63	30.12	31.43
	vii	6.2	6.8	27	151	8.16	9.25
	viii	6.2	6.8	62	62	29.40	32.12

[a] $\omega = 124°$ and $k_1/k_2 = 0.9$ are typical values for a furanoid system[11]. [b] J_1 *cis*-coupling; θ_1 is the corresponding angle.

TABLE III

ANGLE ESTIMATIONS FOR COMPOUND **2**

$J_{2,3}$	$J_{3,4}$	$\theta_{2,3}$	$\theta_{3,4}$	*Relationship used*
5.2	3.0	36	51	Karplus[12]
5.2	3.0	34	56	Durette and Horton[13]
5.2	3.0	47	56	Karplus and DAERM parameters

disappeared on deuteration. The anomeric proton gave a doublet at δ 5.50 ($J_{1,2}$ <0.5 Hz), and the small value of the coupling constant is consistent[12] with the α configuration. As expected, there is a great similarity, both in chemical shifts and coupling constants, between the ^{1}H-n.m.r. spectra of **6** and 2-*O*-benzoyl-3,6-dideoxy-α-L-*arabino*-hexofuranose[4] (**9**, Table I).

The conformational properties of **5** and **6** were analysed on the basis of their ^{1}H-n.m.r. spectra (Table I). The dihedral angles between H-2, H-3, and H-3′ were estimated by DAERM (dihedral angle estimation by the ratio method)[4,11]. The results obtained (Table II) accord with those found[4] for **7** and **9**, respectively, which also indicate a *threo* relationship between the substituents at C-2 and C-4.

The ^{1}H-n.m.r. spectrum of **2** could not be analysed by DAERM, because there is no methylene group in the ring. The estimation of the dihedral angles was made by use of the Karplus relationship[12], and by a modification introduced by Durette and Horton[13] which accounts for the electronegativities of the substituents. The angles were also estimated by introducing in the Karplus equation the values found for the Karplus constants by DAERM calculations for the deoxy-lactones (Table III). These results indicate a conformation in which the substituents on C-2 and C-4 are *quasi*-equatorial and BzO-3 is *quasi*-axial.

EXPERIMENTAL

General methods. — Melting points were determined with a Fischer–Johns apparatus and are uncorrected. Optical rotations were recorded with a Perkin–Elmer 141 polarimeter, i.r. spectra with a Perkin–Elmer Model 421 spectrophotometer, and u.v. spectra with a Beckman DK-2A spectrophotometer. ^{1}H-N.m.r. spectra were recorded with a Varian XL-100-15 spectrometer for solutions in chloroform-*d* with tetramethylsilane as internal reference; the apparent coupling constants (Hz) reported are the directly observed line-spacings. ^{13}C-N.m.r. spectra were recorded at 20 MHz with a Bruker HX-90 spectrometer. Mass spectra were obtained with a Varian MAT CH 7 spectrometer coupled to Varian MAT data system 166. T.l.c. was performed on silica gel G (Merck) with *A*, benzene–ethyl acetate (19:1); *B*, benzene–ethyl acetate (9:1); and *C*, chloroform–methanol (6:1). Detection was effected with iodine vapor, or with 5% ethanolic sulfuric acid and heating at 100°. G.l.c. was performed with a Hewlett-Packard 5830 A gas chromatograph equipped with glass columns (180 × 0.2 cm) packed with *D*, 3% of SE-30 on Chrom W (AW/DMCS) (80–100 mesh), T_i 270°, T_d 300°, T_c 240°, with nitrogen at a flow rate of 23 ml/min; and *E*, 3% of ECNSS-M on Gas Chrom Q (100–120 mesh), T_i 250°, T_d 250°, T_c 170°, with nitrogen at a flow rate of 31 ml/min. L-Rhamnono-1,4-lactone was obtained[14,15] by bromine oxidation of L-rhamnose.

*2,3,5-Tri-O-benzoyl-*L*-rhamnono-1,4-lactone* (**2**). — L-Rhamnono-1,4-lactone (**1**, 2 g) was suspended in anhydrous pyridine (10 ml), and benzoyl chloride (9 ml) was slowly added. The mixture was shaken for 90 min at room temperature, poured with stirring into 100 ml of ice–water, and treated as already described[7]. The product crystallised upon addition of ethanol (yield: 4.64 g; 79%) and was recrystallised from the same solvent, to give **2**, m.p. 103°, $[\alpha]_D^{20}$ +55° (*c* 0.9, chloroform); R_F 0.50 (solvent *A*) and 0.56 (solvent *B*); ν_{max}^{Nujol} 1800 (1,4-lactone C=O), 1710 (benzoate C=O), and 1600 cm^{-1} (aromatic C=C). The ^{1}H-n.m.r. data are shown in Table I; ^{13}C-n.m.r. ($CDCl_3$): 169.5 (C-1), 164.9 (COPh), 164.7 (2 COPh), 133.8, 133.3, 130.1, 129.9, 129.6, 128.6, 128.4, 128.0 (aromatic carbons), 79.8 (C-2), 69.6 (C-3 or C-4), 68.8 (C-3 or C-4), 67.3 (C-5), and 17.5 p.p.m. (C-6).

Anal. Calc. for $C_{27}H_{22}O_8$: C, 68.35; H, 4.64. Found: C, 68.39; H, 4.90.

3-Benzoyloxy-5-ethylidene-2-(5H)-furanone (**3**). — To a solution of **2** (1.02 g) in chloroform (24 ml) was added triethylamine (6 ml). After stirring for 8 h at room temperature in the dark, no starting material could be detected by t.l.c. The mixture was concentrated *in vacuo* with repeated additions of toluene in order to eliminate triethylamine. The syrupy residue crystallised from methanol–water (6:4), and the product (0.37 g, 75%) was recrystallised from the same solvent mixture, to give **3**, m.p. 93–95°, R_F 0.67 (solvent *A*); $\lambda_{max}^{CH_3OH}$ 228 (ε 12600) and 280 nm (ε 5600) (furanone); ν_{max}^{Nujol} 1770 (α,β-unsaturated-1,4-lactone C=O), 1740 (vinyl benzoate C=O), 1650 (conjugated C=C), and 1600 cm^{-1} (aromatic C=C); ^{1}H-n.m.r.: δ 8.2–7.3 (m, 6 H, H-4 and Bz), 5.83 (q, $J_{5,6}$ 7.8 Hz, =CH-CH$_3$), and 1.95 (d, 3 H, CH$_3$);

m/z 230 ($M^{+\cdot}$, 2.7%), 105 (100), 77 (34), 69 (0.9), 53 (0.7), 51 (7.5), 50 (1.3), and 41 (0.5).

Anal. Calc. for $C_{13}H_{10}O_4$: C, 67.83; H, 4.35. Found: C, 67.92; H, 4.42.

*2-O-Benzoyl-3,5,6-trideoxy-*DL-glycero-*hex-2-enono-1,4-lactone* (**4**). — A solution of **3** (0.32 g) in ethyl acetate (50 ml) was hydrogenated at 0° and atmospheric pressure over 10% palladium–barium sulfate (0.06 g) until the hydrogen consumption corresponded to 1 mol/mol of **3**. The mixture was filtered, the solution was concentrated, and the residue crystallised on addition of ethanol–water. Recrystallisation of the product (0.24 g, 74%) gave **4**, m.p. 54–56°, $[\alpha]_D^{20}$ 0° (*c* 1, chloroform), R_F 0.53 (solvent *A*); ν_{max}^{Nujol} 1770 (α,β-unsaturated-1,4-lactone C=O), 1740 (vinyl benzoate C=O), and 1670 cm^{-1} (conjugated C=C); ^1H-n.m.r.: δ 8.2–7.3 (m, 5 H, Bz), 7.30 (d, $J_{3,4}$ 1.8 Hz, H-3), 4.98 (m, $J_{4,5}$ 6.0 Hz, H-4), 1.83 (m, 2 H, $J_{5,6}$ 7.2 Hz, H-5,5′), and 1.04 (t, 3 H, CH_3); ^{13}C-n.m.r. ($CDCl_3$): 166.8 (C-1), 162.9 (COPh), 137.9 (C-2), 134.3, 133.3, 130.4, 128.7, 127.9 (aromatic C and C-3), 80.2 (C-4), 26.8 (C-5), and 8.7 p.p.m. (C-6).

Anal. Calc. for $C_{13}H_{12}O_4$: C, 67.24; H, 5.17. Found: C, 67.19; H, 5.15.

*2-O-Benzoyl-3,5,6-trideoxy-*DL-threo-*hexono-1,4-lactone* (**5**). — A solution of **3** (0.37 g) in ethyl acetate was hydrogenated over 10% palladium–charcoal until no **3** remained (t.l.c.). The catalyst was removed by filtration and the solution evaporated to a syrup which crystallised from ethanol–water. Recrystallisation of the product (0.322 g, 86%) gave **5**, m.p. 36–38°, $[\alpha]_D^{20}$ 0° (*c* 1.1, chloroform), R_F 0.52 (solvent *A*); ν_{max}^{Nujol} 1800 (1,4-lactone C=O) and 1720 cm^{-1} (benzoate C=O). G.l.c. (column *D*) showed only one peak with *T* 2.14, relative to 1,2,3,4-tetra-*O*-acetylerythritol. The ^1H-n.m.r. data are shown in Table I.

Anal. Calc. for $C_{13}H_{14}O_4$: C, 66.67; H, 5.98. Found: C, 66.68; H, 6.04.

Treatment of **5** with 0.1M methanolic sodium methoxide for 3 h at room temperature gave 3,5,6-trideoxy-DL-*threo*-hexono-1,4-lactone (**10**) as a syrup, which was chromatographically homogeneous, R_F 0.67 (solvent *C*).

Anal. Calc. for $C_6H_{10}O_3$: C, 55.38; H, 7.69. Found: C, 55.13; H, 7.76.

Reduction of **10** with sodium borohydride afforded a trideoxyalditol, R_F 0.38 (solvent *C*). G.l.c. (column *E*) of the alditol acetate showed only one peak, *T* 0.32 relative to 1,2,3,4-tetra-*O*-acetylerythritol.

*2-O-Benzoyl-3,5,6-trideoxy-α-*DL-threo-*hexofuranose* (**6**). — Reduction of the trideoxy-lactone **5** (0.28 g) with disiamylborane was effected as described previously[3,4], to give a main product (R_F 0.25, t.l.c., solvent *B*) together with **5**. The mixture was subjected to dry-column chromatography on silica gel (Davison), using benzene with increasing concentrations of ethyl acetate, to give **6** as a homogeneous syrup (0.21 g, 75%); ν_{max}^{film} 3300 (OH), 1700 (benzoate C=O), 1580 and 1600 cm^{-1} (aromatic C=C). The ^1H-n.m.r. data are given in Table I.

Anal. Calc. for $C_{13}H_{16}O_4$: C, 66.10; H, 6.78. Found: C, 66.18; H, 6.93.

*3,5,6-Trideoxy-*DL-threo-*hexose* (**8**). — Compound **6** (0.11 g) was dissolved in chloroform (3 ml), and 0.5M sodium methoxide in methanol (2 ml) was added with stirring at 0°. After 0.5 h, no **6** could be detected by t.l.c. Extraction with water and decationisation with Dowex 50 (H^+) resin gave **8** as a chromatographically homogeneous syrup that was characterised as its crystalline 2,4-dinitrophenylhydrazone.

A solution of **8** (0.05 g) in water (0.5 ml) was added to a solution of 2,4-dinitrophenylhydrazine (0.07 g) in 2M hydrochloric acid (3.5 ml). The mixture was heated for 10 min in a water bath to give the 2,4-dinitrophenylhydrazone, m.p. 117–120° (from benzene–ethyl acetate), ν_{max}^{Nujol} 1610 cm^{-1} (C=N).

Anal. Calc. for $C_{12}H_{16}N_4O_6$: C, 46.15; H, 5.13; N, 17.95. Found: C, 46.03; H, 4.81; N, 18.11.

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REFERENCES

1 R. M. De Lederkremer and L. F. Sala, *Carbohydr. Res.*, 40 (1975) 385–386.
2 L. F. Sala, A. Fernández Cirelli, and R. M. De Lederkremer, *Carbohydr. Res.*, 78 (1980) 61–66.
3 O. J. Varela, A. Fernández Cirelli, and R. M. De Lederkremer, *Carbohydr. Res.*, 70 (1979) 27–35.
4 O. J. Varela, A. Fernández Cirelli, and R. M. De Lederkremer, *Carbohydr. Res.*, 85 (1980) 130–135.
5 C. L. Stevens, K. Nagarajan, and T. H. Haskell, *J. Org. Chem.*, 27 (1962) 2991–3005.
6 S. Hanessian, *Adv. Carbohydr. Chem.*, 21 (1966) 143–207.
7 O. J. Varela, A. Fernández Cirelli, and R. M. De Lederkremer, *Carbohydr. Res.*, 79 (1980) 219–224.
8 H. Booth, *Tetrahedron Lett.*, (1965) 411–416.
9 G. S. King and E. S. Waight, *J. Chem. Soc., Perkin Trans. 1*, (1974) 1499–1504.
10 M. I. Litter and R. M. De Lederkremer, *Carbohydr. Res.*, 26 (1973) 431–434.
11 L. D. Hall, S. A. Black, K. N. Slessor, and A. S. Tracey, *Can. J. Chem.*, 50 (1972) 1912–1924.
12 M. K. Karplus, *J. Chem. Phys.*, 30 (1959) 11–15.
13 P. L. Durette and D. Horton, *Adv. Carbohydr. Chem. Biochem.*, 26 (1971) 49–122.
14 C. S. Hudson and H. S. Isbell, *J. Am. Chem. Soc.*, 51 (1929) 2225–2229.
15 H. S. Isbell and H. L. Frush, *Bur. Stand. J. Res.*, 11 (1933) 649–664.