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Note

Selective benzoylation of 2-deoxy-D-*arabino*-hexose: synthesis of 3,6-di-*O*-benzoyl-2,4-dideoxy-D-*threo*-hexopyranose

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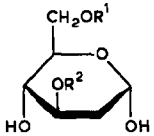
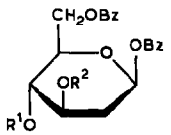
As a part of a search for antiviral agents acting by inhibition of protein glycosylation, we have reported[1] the synthesis and biological activity of several derivatives of UDPG. In order to study the influence of the sugar hydroxyl groups on the biological activity, several deoxy derivatives were needed, including 3,6-di-*O*-benzoyl-2,4-dideoxy-α-D-*threo*-hexopyranose (**10**). The reported[2–7] syntheses of 2,4-dideoxy-D-*threo*-hexopyranoses are long and low-yielding. We now report a facile, three-step synthesis of 1,3,6-tri-*O*-benzoyl-2,4-dideoxy-β-D-*threo*-hexopyranose (**9**) in 50% yield from 2-deoxy-D-*arabino*-hexopyranose (2-deoxy-D-glucose, **1**), and its regioselective 1-*O*-deacylation to give **10**.

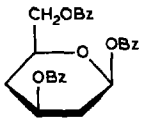
Reaction of **1** with 1 equiv. of benzoyl chloride in pyridine at −15° gave 79% of the 6-benzoate **2**, with 2 equiv. afforded the 1,6- (**3**, 40%) and 3,6-dibenzoate (**4**, 46%), with 3.2 equiv. gave **3** (8%), the 1,4,6-tribenzoate **6** (13%), and the 1,3,6-tribenzoate **5** (70%), and with an excess afforded the tetrabenzoate **7**, quantitatively. The benzoylation of **1** under different conditions afforded[8] a mixture of **7** and its α anomer in lower yield. The results of the above reactions indicate the order of reactivity to be HO-6 > HO-3 ≃ HO-1 > HO-4.



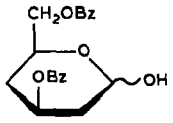
1 $R^1 = R^2 = H$
2 $R^1 = Bz, R^2 = H$
3 $R^1 = R^2 = Bz$



4 $R^1 = R^2 = H$
5 $R^1 = H, R^2 = Bz$
6 $R^1 = Bz, R^2 = H$
7 $R^1 = R^2 = Bz$
8 $R^1 = C(=S)-N$ (imidazolyl), $R^2 = Bz$



9



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0008-6215/86/$ 03.50

It has been found that HO-4 of D-glucose[9], 6-deoxy-D-glucose[10], and other pyranoses[9,11,12] is also benzoylated slowly. For **1**, however, probably due to steric reasons, the regioselectivity is higher. This fact allowed the preparation in one step of the 1,3,6-tribenzoate **5** in 70% yield from **1**. Selective deoxygenation[13] of **5** with thiocarbonyldi-imidazole gave 97% of the 4-(imidazolyl)thiocarbonyl derivative **8**. Reaction of **8** with tributyltin hydride and α,α'-azobisisobutyronitrile afforded 75% of **9**. Treatment[14] of **9** with ammonia in tetrahydrofuran–methanol removed BzO-1 and gave 75% of **10**.

The structures of **2–10** were readily determined by ^{1}H-n.m.r. spectroscopy, based on the strong deshielding (1–2 p.p.m.) produced by the benzoyl groups. Assignment of signals of the 2- and 4-methylene groups of **9** was accomplished by irradiation of H-1.

EXPERIMENTAL

General. — Melting points are uncorrected. ^{1}H-N.m.r. spectra (300 MHz, internal Me_4Si) were recorded with a Varian XL-300 spectrometer. Optical rotations were measured at 23 ±2° with a Perkin–Elmer 141 polarimeter. T.l.c. was performed on Silica Gel 60 F_{254} (Merck) and p.l.c. on Silica Gel PF_{254} (Merck). Compounds were detected, as appropriate, by u.v. light (254 nm) or by charring with sulfuric acid.

*Benzoylation of 2-deoxy-*D-arabino-*hexopyranose* (**1**). — (*a*) *With 1 equiv. of benzoyl chloride.* To a solution of **1** (1 g, 6.1 mmol) in pyridine (25 mL) at −15° was slowly added a solution of benzoyl chloride (0.857 g, 6.1 mmol) in pyridine (5 mL). After stirring for 1 h at −15°, the solution was concentrated to dryness under reduced pressure, the residue was partitioned between chloroform and water, and the aqueous layer was concentrated to dryness under diminished pressure. The residue was extracted with acetone, and the extract was filtered and concentrated to dryness to give 6-*O*-benzoyl-2-deoxy-α-D-*arabino*-hexopyranose (**2**; 1.29 g, 79%), m.p. 116–117° (from acetone), $[\alpha]_D$ +60° (*c* 1, chloroform). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 1.49 (ddd, 1 H, $J_{1,2a}$ 3.4, $J_{2a,3}$ 11.9, $J_{2a,2e}$ 13.1 Hz, H-2*a*), 1.89 (ddd, 1 H, $J_{1,2e}$ 2.0, $J_{2e,3}$ 4.8 Hz, H-2*e*), 3.20 (dd, 1 H, $J_{3,4}$ 9.0, $J_{4,5}$ 9.3 Hz, H-4), 3.73 (ddd, 1 H, H-3), 3.93 (ddd, 1 H, H-5), 4.37 and 4.53 (2 dd, 2 H, H-6,6'), 5.16 (dd, 1 H, H-1).

Anal. Calc. for $C_{13}H_{16}O_6$: C, 58.21; H, 5.97. Found: C, 58.39; H, 5.71.

(*b*) *With 2 equiv.* To a solution of **1** (1 g, 6.1 mmol) in pyridine at −15° was slowly added a solution of benzoyl chloride (1.74 g, 12.2 mmol) in pyridine (10 mL). After stirring for 2 h at −15°, the solution was concentrated under reduced pressure, and the residue was washed with water and extracted with chloroform. The extract was dried (Na_2SO_4), filtered, and concentrated to dryness. P.l.c. (ethyl acetate–hexane, 2:5) of the product gave, in the fastest running band, 3,6-di-*O*-benzoyl-2-deoxy-D-*arabino*-hexopyranose (**3**; 1.1 g, 46%) as a 7:3 $\alpha\beta$-mixture, m.p. 138–139° (from ethyl acetate), $[\alpha]_D$ +73° (*c* 1, chloroform). ^{1}H-N.m.r. data

($CDCl_3$): α-**3**, δ 1.90 (ddd, 1 H, $J_{1,2a}$ 3.5, $J_{2a,2e}$ 12.8, $J_{2a,3}$ 11.7 Hz, H-2*a*), 2.37 (ddd, 1 H, $J_{1,2e}$ 1.1, $J_{2e,3}$ 5.1 Hz, H-2*e*), 3.74 (t, 1 H, *J* 9.2 Hz, H-4), 4.27 (ddd, 1 H, H-5), 4.61 and 4.75 (2 dd, 2 H, H-6,6'), 5.46 (dd, 1 H, H-1), 5.52 (ddd, 1 H, H-3); β-**3**, δ 1.77 (ddd, 1 H, $J_{1,2a}$ 9.5, $J_{2a,2e}$ 12.5, $J_{2a,3}$ 11.9 Hz, H-2*a*), 2.50 (ddd, 1 H, $J_{1,2a}$ 2.2, $J_{2e,3}$ 5.2 Hz, H-2*e*), 5.03 (dd, 1 H, H-1).

Anal. Calc. for $C_{20}H_{20}O_7$: C, 64.52; H, 5.32. Found: C, 64.67; H, 5.66.

The slowest running band afforded 1,6-di-*O*-benzoyl-2-deoxy-β-D-*arabino*-hexopyranose (**4**; 0.9 g, 40%), isolated as a foam, $[\alpha]_D$ −41° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 1.90 (ddd, 1 H, $J_{1,2a}$ 10.1, $J_{2a,2e}$ 12.3, $J_{2a,3}$ 11.3 Hz, H-2*a*), 2.37 (ddd, 1 H, $J_{1,2e}$ 2.2, $J_{2e,3}$ 5.0 Hz, H-2*e*), 3.36 (dd, 1 H, $J_{3,4}$ 9.1, $J_{4,5}$ 9.6 Hz, H-4), 3.65 (ddd, 1 H, H-5), 3.87 (ddd, 1 H, H-3), 4.45, 4.93 (2 dd, 2 H, H-6,6'), 6.02 (dd, 1 H, H-1).

Anal. Calc. for $C_{20}H_{20}O_7$: C, 64.52; H, 5.32. Found: C, 64.28; H, 5.60.

(*c*) *With 3 equiv.* A solution of **1** (1 g, 6.1 mmol) in pyridine (25 mL) was treated for 3 h with a solution of benzoyl chloride (2.74 g, 19.5 mmol) in pyridine (10 mL) as in (*b*). P.l.c. of the product gave, in the fastest running band, 1,3,6-tri-*O*-benzoyl-2-deoxy-β-D-*arabino*-hexopyranose (**5**; 2.025 g, 70%), isolated as a foam, $[\alpha]_D$ +2° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 2.12 (ddd, 1 H, $J_{1,2a}$ 9.4, $J_{2a,2e}$ 12.6, $J_{2a,3}$ 11.1 Hz, H-2*a*), 2.61 (ddd, 1 H, $J_{1,2e}$ 2.2, $J_{2e,3}$ 5.5 Hz, H-2*e*), 3.84 (m, 2 H, H-4,5), 4.59 and 4.84 (2 dd, 2 H, H-6,6'), 5.31 (m, 1 H, H-3), 6.17 (dd, 1 H, H-1).

Anal. Calc. for $C_{27}H_{24}O_8$: C, 68.07; H, 5.04. Found: C, 67.99; H, 5.18.

The second band gave 1,4,6-tri-*O*-benzoyl-2-deoxy-β-D-*arabino*-hexopyranose (**6**; 0.38 g, 13%), m.p. 136° (from ethyl acetate–hexane), $[\alpha]_D$ +70° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 2.12 (ddd, 1 H, $J_{1,2a}$ 9.7, $J_{2a,2e}$ 12.8, $J_{2a,3}$ 11.3 Hz, H-2*a*), 2.54 (ddd, 1 H, $J_{1,2e}$ 2.4, $J_{2e,3}$ 5.1 Hz, H-2*e*), 4.13 (m, 2 H, H-3,5), 4.43 and 4.63 (2 dd, 2 H, H-6,6'), 5.19 (t, 1 H, *J* 9.1 Hz, H-4), 6.13 (dd, 1 H, H-1).

Anal. Calc. for $C_{27}H_{24}O_8$: C, 68.07; H, 5.04. Found: C, 68.04; H, 5.18.

The slowest running band afforded **3** (0.18 g, 8%).

1,3,4,6-Tetra-O-*benzoyl*-β-D-arabino-*hexopyranose* (**7**). — A solution of **1** (1 g, 6.1 mmol), benzoyl chloride (4.29 g, 31 mmol), and pyridine (35 mL) was stirred at −15° for 24 h and then concentrated under reduced pressure. A solution of the residue in chloroform was washed with water, dried (Na_2SO_4), filtered, and concentrated. The residue was crystallised from ether to give **7** (3.53 g, 100%), m.p. 145°, $[\alpha]_D$ +12° (*c* 1, chloroform); lit.[8] m.p. 145°. ^{1}H-N.m.r. data ($CDCl_3$): δ 2.28 (ddd, 1 H, $J_{1,2a}$ 9.4, $J_{2a,2e}$ 12.8, $J_{2a,3}$ 10.7 Hz, H-2*a*), 2.78 (ddd, 1 H, $J_{1,2e}$ 2.5, $J_{2e,3}$ 5.1 Hz, H-2*e*), 4.26 (ddd, 1 H, H-5), 4.51 and 4.66 (2 dd, 2 H, H-6,6'), 5.56 (ddd, 1 H, $J_{3,4}$ 9.0 Hz, H-3), 5.70 (dd, 1 H, $J_{4,5}$ 9.2 Hz, H-4), 6.29 (dd, 1 H, H-1).

1,3,6-Tri-O-*benzoyl-2-deoxy-4*-O-[*(imidazol-1-yl)thiocarbonyl*]-β-D-arabino-*hexopyranose* (**8**). — A solution of **5** (1.45 g, 3.05 mmol) and thiocarbonyldiimidazole (2.17 g, 12.19 mmol) in 1,2-dimethoxyethane (50 mL) was boiled under reflux for 7 h, and then concentrated under reduced pressure. Chromatography (ether) of the residue gave **8** (1.73 g, 97%) as a chromatographically homogeneous

syrup, $[\alpha]_D$ +7° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 2.35 (ddd, 1 H, $J_{1,2a}$ 9.0, $J_{2a,2e}$ 12.7, $J_{2a,3}$ 10.7 Hz, H-2*a*), 2.76 (ddd, 1 H, $J_{1,2e}$ 2.4, $J_{2e,3}$ 5.3 Hz, H-2*e*), 4.35 (ddd, 1 H, H-5), 4.51 and 4.67 (2 dd, 2 H, H-6,6'), 5.68 (ddd, 1 H, $J_{3,4}$ 8.74 Hz, H-3), 6.28 (ddd, 1 H, $J_{4,5}$ 9.0 Hz, H-4), 6.30 (dd, 1 H, H-1), 6.96 (dd, 1 H, H-5 imidazole), 8.24 (s, 1 H, H-2 imidazole).

Anal. Calc. for $C_{31}H_{25}N_2O_8S$: C, 63.59; H, 4.27; N, 4.79; S, 5.47. Found: C, 63.36; H, 4.29; N, 4.95; S, 5.21.

*1,3,6-Tri-*O*-benzoyl-2,4-dideoxy-*β*-*D*-threo-hexopyranose* (**9**). — A solution of **8** (1.52 g, 5.59 mmol), *n*-Bu_3SnH (3.04 g, 15 mmol), and α,α'-azobisisobutyronitrile (0.73 g, 4.45 mmol) in benzene (40 mL) was boiled under reflux for 2 h and then concentrated. Chromatography (ethyl acetate–hexane, 1:2) gave **9** (0.91 g, 76%) as a chromatographically homogeneous syrup, $[\alpha]_D$ +8° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 1.75 (ddd, 1 H, $J_{3,4a}$ 10.8, $J_{4a,5}$ 11.0, $J_{4a,4e}$ 12.6 Hz, H-4*a*), 2.02 (ddd, 1 H, $J_{1,2a}$ 9.5, $J_{2a,2e}$ 12.0 $J_{2a,3}$ 11.0 Hz, H-2*a*), 2.33 (dddd, 1 H, $J_{2e,4e}$ 1.4, $J_{3,4e}$ 4.8, $J_{4e,5}$ 4.8 Hz, H-4*e*), 2.53 (dddd, 1 H, $J_{1,2e}$ 2.5, $J_{2e,3}$ 4.9 Hz, H-2*e*), 4.12 (m, 1 H, H-5), 4.48 (m, 2 H, H-6,6'), 5.37 (dddd, 1 H, H-3), 6.12 (dd, 1 H, H-1).

Anal. Calc. for $C_{27}H_{24}O_7$: C, 70.43; H, 5.22. Found: C, 70.28; H, 5.39.

*3,6-Di-*O*-benzoyl-2,4-dideoxy-*D*-threo-hexopyranose* (**10**). — Ammonia was bubbled through a cooled solution (ice-bath) of **9** (0.7 g, 1.52 mmol) in tetrahydrofuran–methanol (7:3, 20 mL) for 10 min, and the mixture was stirred at 0° for 2 days and then concentrated to dryness under reduced pressure. Chromatography (ethyl acetate–hexane, 2:5) of the residue gave **10** (0.4 g, 74%) as a 2:1 $\alpha\beta$-mixture, m.p. 116–117° (from ether), $[\alpha]_D$ +37° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): **α-10**, δ 1.64 (m, 3 H, H-4*a*, and H-2*a*,4*a* of **β-10**), 1.82 (ddd, 1 H, $J_{1,2a}$ 3.9, $J_{2a,2e}$ 12.4, $J_{2a,3}$ 11.6 Hz, H-2*a*), 2.30 (m, 2 H, H-2*e*,4*e*), 4.39–4.52 (m, 3 H, H-5,6,6'), 5.53 (dd, 1 H, $J_{1,2e}$ 1.2 Hz, H-1), 5.56 (m, 1 H, H-3); **β-10**, δ 2.21 (m, 1 H, H-4*e*), 2.43 (m, 1 H, H-2*e*), 3.93 (m, 1 H, H-5), 4.42 (m, 2 H, H-6,6'), 4.92 (dd, 1 H, $J_{1,2a}$ 9.7, $J_{1,2e}$ 2.0 Hz, H-1), 5.24 (m, 1 H, H-3).

Anal. Calc. for $C_{20}H_{20}O_6$: C, 67.42; H, 5.62. Found: C, 67.58; H, 5.75.

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