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Note

Synthesis of benzyl 2,3-dideoxy-4-*O*-(3,4-di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentopyranosyl)-β-D-*glycero*-pentopyranoside, an anolog of anthracycline disaccharides

HASSAN S. EL KHADEM AND DAISABURO MATSUURA

Department of Chemistry and Chemical Engineering, Michigan Technological University, Houghton, Michigan 49931 (U.S.A.)

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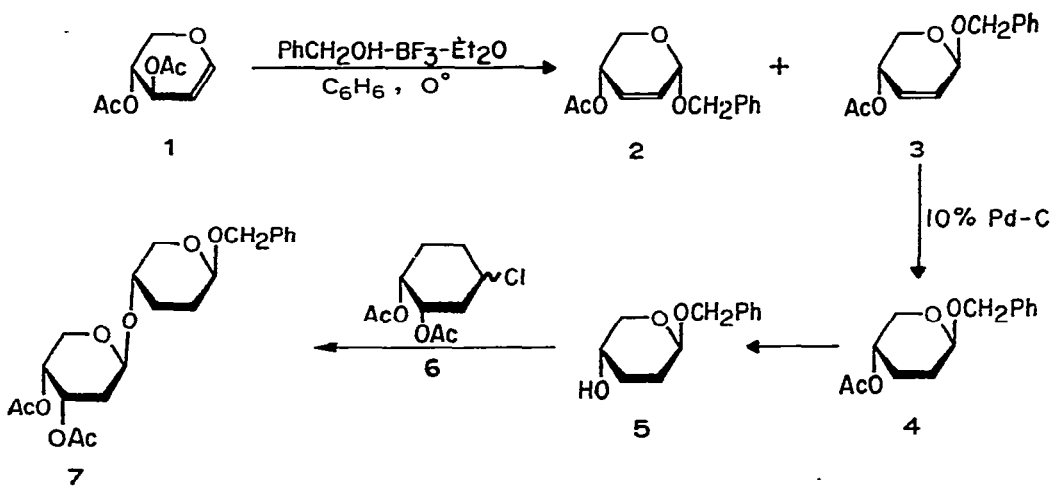
Several anthracycline antibiotics exist in the form of oligosaccharide glycosides. The most extensively studied of such oligosaccharides are present in rhodomycins[1] and cinerubin[2]. The monosaccharide components of these oligosaccharides include, in addition to rhodosamine [2,3,6-trideoxy-3-(dimethylamino)-L-*lyxo*-hexose], 2,6-dideoxy-L-*lyxo*-hexose and rhodinose (2,3,6-trideoxy-L-*threo*-hexose). Our work on synthetic anthracycline analogs has shown that the 5-*C*-methyl groups present in these monosaccharides might not be essential for antibiotic and antitumor activity[3], and we now describe the synthesis of a disaccharide similar to those found in anthracyclines, but lacking the 5-*C*-methyl groups. This compound is benzyl 2,3-dideoxy-4-*O*-(3,4-di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentopyranosyl)-β-D-*glycero*-pentopyranoside (7).

The synthesis started with di-*O*-acetyl-D-xylal[4] (**1**), which was treated with benzyl alcohol in the presence of BF_3-etherate[5] to give a mixture of the anomeric



benzyl 4-*O*-acetyl-2,3-dideoxy-α- and -β-D-*glycero*-pent-2-enopyranosides (**2** and **3**), which were separated by chromatography on silica gel. The β anomer (**3**) was then catalytically hydrogenated to benzyl 4-*O*-acetyl-2,3-dideoxy-β-D-*glycero*-pentopyranoside (**4**), and **4** was saponified to benzyl 2,3-dideoxy-β-D-*glycero*-pentopyranoside (**5**). Reaction of glycoside **5** with 3,4-di-*O*-acetyl-2-deoxy-D-*erythro*-pentopyranosyl chloride[6] under Koenigs–Knorr conditions[7] afforded mainly the desired β-disaccharide (**7**). Disaccharide **7** was separated from its α-linked isomer by chromatography on silica gel, and the β-anomeric configuration of its interglycosidic bond was determined by comparing the optical rotations of the two anomers.

As in the D-hexose series[5], the α anomer (**2**) of the pent-2-enopyranoside had a less positive optical rotation than the β anomer **3**. However, upon hydrogenation, the saturated β anomer **4** showed, as expected, an optical rotation (−119°) less positive than that of the α anomer (+92.6°).

EXPERIMENTAL

General. — Melting points were determined with a Kofler block and are uncorrected. Optical rotations were measured with a Bendix series 1100 polarimeter. N.m.r. spectra were recorded with a Varian EM-360 spectrometer, using tetramethylsilane as the internal standard and CCl_4 as the solvent. Thin-layer chromatography was conducted on Eastman Kodak 13181 silica gel plates. Chromatographic columns were packed with Sargent–Welch SC 14608 silica gel (60–200 mesh). Microanalyses were performed by Mrs. S. Brotherton in the Department of Chemistry and Chemical Engineering Microanalysis Laboratory.

Benzyl 4-O-acetyl-2,3-dideoxy-α- and -β-D-glycero-pent-2-enopyranoside (**2** *and* **3**). — Di-*O*-acetyl-D-xylal[4] (**1**; 14.3 g) was dissolved in a mixture of benzyl alcohol (14.3 g) and benzene (57 mL). The solution was then cooled in ice–water, and stirred for 2 h at 1° with boron trifluoride etherate ($BF_3 \cdot Et_2O$; 1.4 mL). Anhydrous sodium carbonate (25 g) was added to the mixture (to neutralize the acid); it was filtered, and the precipitate was washed with three 15-mL portions of benzene. The filtrate and washings were combined, and evaporated under diminished pressure, to give a syrup which was distilled at 125–131°/0.65–0.75 torr. A mixture of the anomers **2** and **3** distilled, to give a colorless, viscous oil (yield 16.3 g, 92%).

To separate the mixture, a solution of the distillate in absolute ether was treated with petroleum ether (b.p. 30–60°) to incipient turbidity. The β anomer **3** crystallized in needles (yield 10.7 g), m.p. 57°, $[\alpha]_D^{20}$ +127° (*c* 1.04, chloroform).

Anal. Calc. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 68.13; H, 6.41.

The mother liquor was chromatographed on silica gel, to give the pure α anomer **2**, isolated as a syrup; $[\alpha]_D^{20}$ +87.2° (*c* 1.40, chloroform).

Anal. Calc. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 68.00; H, 6.41.

Benzyl 4-O-acetyl-2,3-dideoxy-β-D-glycero-pentopyranoside (**4**). — A solution of **3** (10.7 g) in ethyl acetate (25 mL) was treated with 10% Pd–C catalyst (0.626 g) and hydrogen at 54 lb.in.$^{-2}$ for 2 h. The catalyst was then filtered off, and washed

TABLE I

N.M.R. DATA[a] FOR THE MONOSACCHARIDES PREPARED

Compound No.	*δ (p.p.m.)*						
	H-1	*H-2,3*	*H-4*	*H-5,5'*	*CH_2*	*Ph*	*Ac*
2	5.00 (d), $J_{1,2}$ 2	5.95 (m)	5.32 (m)	3.80 (d)	4.70 (q)	7.35	2.00
3	5.02 (d), $J_{1,2}$ 2	6.05 (m)	4.88 (m)	3.74 (q), $J_{5,5'}$ 13, $J_{4,5}$ 3.0 4.18 (q), $J_{4,5'}$ 1	4.66 (q)	7.34	2.02
4	4.92 (m)	1.91 (m)	4.92 (m)	3.56 (q), $J_{5,5'}$ 13, $J_{4,5}$ 2 4.07 (q), $J_{4,5'}$ 1.5	4.70 (q)	7.42	2.08
5	4.74 (m)	1.76 (m)	3.51 (m)	3.48–4.05 (m)	4.60 (q)	7.34	—

[a]Key: d, doublet; m, multiplet; and q, quartet.

twice with ethyl acetate (15 mL). The filtrate and washings were combined, and evaporated under diminished pressure, to give **4** as a syrup (10 g); $[\alpha]_D^{20}$ −119° (*c* 1.18, chloroform).

Anal. Calc. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.84; H, 7.25.

*Benzyl 2,3-dideoxy-β-*D-glycero-*pentopyranoside* (**5**). — A mixture of **4** (10 g), methanol (125 mL), water (67 mL), and triethylamine (17 mL) was stirred overnight at room temperature and then evaporated under diminished pressure to a syrup to which toluene was added and evaporated until the triethylamine had been completely removed. The resulting liquid was distilled at 115–120°/0.07–0.08 torr, to give pure compound **5** (7.31 g), which slowly solidified; m.p. 34°, $[\alpha]_D^{20}$ −149° (*c* 1.03, chloroform).

Anal. Calc. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.86; H, 7.96.

*Benzyl 2,3-dideoxy-4-*O-(*3,4-di-*O-*acetyl-2-deoxy-β-*D-erythro-*pentopyranosyl*)-*β-*D-glycero-*pentopyranoside* (**7**). — A mixture of mercuric bromide (517 mg), yellow mercuric oxide (519 mg), finely powdered, 4A molecular sieves (5 g) in dry dichloromethane (25 mL), **5** (675 mg) and **6** (618 mg, prepared by the action of HCl on di-*O*-acetyl-D-arabinal[6]) was stirred for 12 h at room temperature. The solids were then filtered off and washed with chloroform several times, and the filtrate and washings were combined, successively washed with M potassium iodide solution (25 mL) and water, dried (anhydrous sodium sulfate), and evaporated under diminished pressure to yield a syrup which was chromatographed on a column of silica gel, eluted with 3:7 ethyl acetate–hexane, to give, first, the α-linked isomer (91 mg); $[\alpha]_D^{20}$ −116° (*c* 1.18, chloroform). This was followed by the β-linked isomer **7** (693 mg); $[\alpha]_D^{20}$ −193° (*c* 1.00, chloroform).

The n.m.r. spectra of the disaccharides showed the characteristic peaks from both sugar components. The two acetyl groups of the glycosyl group appeared at δ 2.00 and 2.25, respectively, and the 1-benzyl group of the glycoside residue showed

a phenyl peak at δ 4.70, and the methylene group at δ 5.33. The remaining protons integrated correctly.

Anal. Calc. for $C_{21}H_{28}O_8$: C, 61.75; H, 6.91. Found: C, 61.66; H, 7.18.

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REFERENCES

1 H. Brockmann and H. Greve, *Tetrahedron Lett.*, (1975) 831–834.
2 L. Ettlinger, E. Garrmann, R. Hütter, W. Keller-Schlierlein, F. Kradolter, L. Neipp, V. Prelog, P. Reusser, and H. Zähner, *Chem. Ber.*, 92 (1959) 1867–1879; W. Richle, E. K. Winkler, D. M. Hawley, M. Dobler, and W. Keller-Schlierlein, *Helv. Chim. Acta*, 55 (1972) 467–480.
3 H. S. El Khadem, D. L. Swartz, and R. C. Cermak, *J. Med. Chem.*, 20 (1977) 957–960; H. S. El Khadem and D. L. Swartz, *Carbohydr. Res.*, 65 (1978) c1–c2.
4 P. A. Levene and T. Mori, *J. Biol. Chem.*, 83 (1929) 803–816. See also, F. Weygand, *Methods Carbohydr. Chem.*, 1 (1962) 182–185.
5 R. J. Ferrier and N. Prasad, *J. Chem. Soc., C*, (1969) 570–575; B. Fraser-Reid, A. McLean, E. W. Usherwood, and M. Yunker, *Can. J. Chem.*, 48 (1970) 2877–2884.
6 L. Vargha and J. Kuszmann, *Chem. Ber.*, 96 (1963) 411–419. See also, G. Etzold and P. Langen, in W. W. Zorbach and R. S. Tipson (Eds.), *Synthetic Procedures in Nucleic Acid Chemistry*, Vol. 1, Interscience, New York, 1968, pp. 335–338.
7 L. R. Schroeder and J. W. Green, *J. Chem. Soc., C*, (1966) 530–531; E. F. Fuchs, D. Horton, and W. Weckerle, *Carbohydr. Res.*, 57 (1977) c36–c39.