Carbohydrate Research, 102 (1982) 298–301
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

Note

Synthesis of 4-deoxy-D-*erythro*-pentose ("4-deoxy-D-ribose")

TAKAMASA KINOSHITA, NOBUO NAKAMURA, AND TOSHIO MIWA
Department of Chemistry, Faculty of Science, Osaka City University, Sumiyoshiku, Osaka 558 (Japan)
(Received April 13th, 1981; accepted for publication in revised form, June 5th, 1981)

As a part of the program aimed at the total synthesis of deoxyriboflavins, this paper describes the synthesis of "4-deoxy-D-ribose" from D-glucose. Several groups have reported the synthesis of the D-[1,2], L-[1,3,4], or DL-forms[5] of 4-deoxyribose.

The known 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hex-5-enofuranose (**1**) appeared to be a suitable precursor of 4-deoxy-D-ribose derivatives, and its synthesis was achieved from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose *via* the five-step route previously described[6]. Selective hydroboration of (**1**) with bis(3-methyl-2-butyl)borane, prepared *in situ* by the hydroboration of 2-methyl-2-butene with diborane generated in the reaction of sodium borohydride with methyl iodide[7] in diglyme at 0°, followed by oxidation with 30% hydrogen peroxide, led to syrupy 3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**2**) as a single product in 93% yield. Compound **2** was converted into a mixture of methyl 4-deoxy-2-*O*-benzyl-β-D-*erythro*-pentopyranoside (**3a**) and its α anomer (**3b**) in a total yield of 63% *via* the following sequence of reactions: acid hydrolysis of the isopropylidene group, periodate oxidation of the C-1–C-2 bond, alkaline hydrolysis of the 3-formate, and glycosidation in methanol with 2% hydrogen chloride. The β-(**3a**) and α-(**3b**) glycosides were separated by chromatography and hydrogenated over 10% palladium-on-carbon catalyst to produce methyl 4-deoxy-β-D-*erythro*-pentopyranoside (**4a**) and the α anomer (**4b**) in quantitative yield, respectively. Acid hydrolysis of compound **4a** produced 4-deoxy-D-*erythro*-pentose (**5**). The β configuration for **4a** is confirmed by the large coupling constant (d, 3.8 Hz) of the anomeric proton and the negative optical rotation of −95.9° by comparison of those with **4b** (d, 2.0 Hz and +80.3°).

EXPERIMENTAL

General methods. — Melting points were determined on a micro hot stage and are uncorrected. T.l.c. was performed with 0.25-mm layers of Silica Gel 60 F_{254}, and indication was effected with sulfuric acid. Optical rotations were determined with a JASCO Model DIP-4 polarimeter. Elemental analyses were carried out on a Perkin–

0008-6215/82/0000–0000/S 02.75,

Elmer Model 240 elemental analyzer. Proton and carbon magnetic resonance spectra were recorded on JEOL PS-100, FX-60, and FX-100 spectrometers. Proton–proton spin-decoupling and proton–carbon selective decoupling experiments were performed with the FX-100 and the FX-60 instruments, respectively. Chemical shifts are given on the δ scale and spin couplings in Hz. Unless otherwise stated, n.m.r. spectra were measured at 25° in chloroform-*d*, with tetramethylsilane (δ 0.00) as the internal standard. Signals are described as s (singlet), d (doublet), t (triplet), q (quartet), o (octet), or m (complex multiplet). Spectra were analyzed on a first-order basis.

3-O-Benzyl-5,6-dideoxy-1,2-O-isopropylidene-α-D-ribo-hex-5-enofuranose (**1**).— This compound was prepared[6] from 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose. The distilled product had b.p. 115–120°/0.01 mmHg; $[\alpha]_D^{15}$ +60° (*c* 1.2, chloroform); [Lit.[6] b.p. 123–125°/0.1 Torr, $[\alpha]_D^{20}$ +64° (*c* 1.0, chloroform).]

3-O-Benzyl-5-deoxy-1,2-O-isopropylidene-α-D-ribo-hexofuranose (**2**). — A solution of 2-methyl-2-butene (2.1 g, 30 mmol) and sodium borohydride (570 mg, 15 mmol) in dry diglyme (15 mL) was treated dropwise with a solution of methyl iodide (2.13 g, 15 mmol) in diglyme (3 mL) below 5° over a period of 30 min with magnetic stirring. Rapid evolution of gas (methane) was observed during the addition of methyl iodide. After stirring for 1.5 h at 0°, a solution of (**1**, 2.76 g, 10 mmol) in diglyme (10 mL) was added and the mixture stirred for 20 h at room temperature. The organoborane was oxidized by adding 4 mL of 3M sodium hydroxide at 10–15°, followed by dropwise addition of 4 mL of 30% hydrogen peroxide. The mixture was stirred for an additional 2 h at room temperature. Brine (30 mL) was added and the mixture extracted with three 50-mL portions of ether. The extracts were combined, washed once with water, and dried over anhydrous magnesium sulfate. After removal of the solvent, the product was chromatographed on silica gel (2:1 benzene–ethyl acetate), giving syrupy **2** (2.74 g, 93%); $[\alpha]_D^{15}$ +80.9° (*c* 1.24, methanol); ^{1}H-n.m.r. data ($CDCl_3$): δ 5.70 (d, $J_{1,2}$ 4.0 Hz, H-1), 4.56 (dd, $J_{2,3}$ 4.5 Hz, H-2), 3.50 (dd, $J_{3,4}$ 8.5 Hz, H-3), 4.15 (o, $J_{4,5}$ 4.8, $J_{4,5'}$ 7.0 Hz, H-4), 1.78–2.08 (m, $J_{5,6}$ 6.0 Hz, H-5), 3.75 (q, H-6), 4.65 (q, J_{benzylic} 11.3, OCH_2Ph), 1.37, 1.60 (s, CMe_2), 2.43 (t, OH), and 7.33 (s, arom).

Methyl 2-O-benzyl-4-deoxy-β- and -α-D-erythro-pentopyranosides (**3a** *and* **3b**). — A solution of **2** (8.7 g, 29.6 mmol) in 4% sulfuric acid (100 mL) was heated at 100° until the starting material was absent, as shown by t.l.c. (R_F 0.29; ethyl acetate). The solution was made neutral by addition of 3M aqueous sodium hydroxide and was concentrated to 10 mL. To the concentrate was added a solution of sodium periodate (11.2 g, 52.3 mmol) in 100 mL of water with stirring. After stirring for 30 min at room temperature (R_F 0.72; ethyl acetate), the mixture was extracted with chloroform (50 mL × 4). The extracts were combined, and evaporated to give 2-*O*-benzyl-4-deoxy-3-*O*-formyl-D-*erythro*-pentose as a syrup. The resultant formate was hydrolyzed with 0.1M sodium hydroxide (35 mL) in methanol (20 mL) at room temperature for 30 min (R_F 0.52; ethyl acetate). After being made neutral by addition of hydrochloric acid, the solution was evaporated to dryness, to give syrupy 2-*O*-benzyl-4-deoxy-D-*erythro*-pentose. The syrup was dissolved in the 2% methanolic hydrogen

TABLE I

^{13}C-N.M.R. SPECTRA; CHEMICAL SHIFTS MEASURED AT 25 MHz

	Compound						
	1	**2**	**3a**	**3b**	**4a**	**4b**	**5**
Solvent	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	D_2O[a]	D_2O[c]	D_2O[a]
C-1	103.7 d	104.3 d	99.8 d	99.7 d	101.6 d	101.2 d	94.1 d (94.1)
C-2	79.1 d[b]	77.3 d	77.2 d	74.5 d	69.3 d	68.9 d	70.6 d (69.9)
C-3	81.8 d	82.1 d	65.7 d	65.2 d	65.8 d	67.8 d	66.2 d (68.2)
C-4	77.6 d[b]	77.1 d	30.4 t	31.8 t	28.7 t	28.7 t	29.5 t (27.6)
C-5	134.9 d	35.2 t	58.8 t	54.5 t	59.1 t	58.8 t	59.4 t (60.3)
C-6	118.8 t	60.4 t					
OCH_2Ph	72.2 t	72.4 t	72.7 t	70.4 t			
OMe			55.2 q	55.7 q	55.4 q	56.3 q	
Others[a]							

[a]With acetone (δ 30.30) as the internal standard. [b]Assignments may be interchanged. [c]Chemical shifts for compound **1**; 26.5, 26.8, 112.8, 127.9, 128.4, and 137.5: for **2**; 26.9, 113.1, 128.4, 128.7, and 137.5.

chloride (130 mL), and the solution kept overnight at room temperature (R_F 0.68 and 0.60; ethyl acetate). The acid was made neutral by addition of solid sodium carbonate, and the solution concentrated and extracted with chloroform (50 mL × 3). The combined extracts were dried (sodium sulfate) and evaporated to give an anomeric mixture of methyl 2-*O*-benzyl-4-deoxy-D-*erythro*-pentopyranoside (crude yield 6.17 g, 88%), which was chromatographed (R_F 0.45 for the β anomer (**3a**) and 0.35 for the α anomer (**3b**); 2:1 benzene–ethyl acetate) to give **3a** (3.61 g), **3b** (0.36 g), and a mixture (**3a** and **3b**) (0.50 g); total yield 64%. Compound **3a** had $[\alpha]_D^{15}$ −47.0° (*c* 1.6, methanol). ^{1}H-n.m.r. ($CDCl_3$): δ 4.65 (d, $J_{1,2}$ 4.0 Hz, H-1), 3.38 (m, H-2), 3.95 (m, H-3), 1.72 (m, $J_{4,5}$ 5.5 Hz, H-4), 3.68 (t, H-5), 3.38 (s, OMe), 4.63 (q, $J_{benzylic}$ 11.5, OCH_2Ph), 2.62 (d, OH), and 7.25 (s, arom).

Anal. Calc. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.23; H, 7.56.

Compound **3b** had $[\alpha]_D^{15}$ +65.8° (*c* 2.7, methanol); ^{1}H-n.m.r. ($CDCl_3$): δ 4.65 (d, $J_{1,2}$ 3.0 Hz, H-1), 3.50 (dd, $J_{2,3}$ 4.0 Hz, H-2), 4.15 (dd, $J_{3,4}$ 8.0 Hz, H-3), 1.84 (m, H-4), 3.30–3.55 (m, H-5), 3.90 (m, H-5′), 3.42 (s, OMe), 4.63 (q, $J_{benzylic}$ 12.0, OCH_2Ph), and 7.31 (s, arom).

Methyl 4-deoxy-β- and α-D-erythro-*pentopyranosides* (**4a** *and* **4b**). — Hydrogenation of the benzyl ether **3a** (420 mg) over 10% Pd–C (150 mg) in methanol (8 mL) for 3 h afforded syrupy **4a** (260 mg, 100%); $[\alpha]_D^{15}$ −95.9° (*c* 1.0, water) [lit.[3] $[\alpha]_D^{21}$ +39.2° (*c* 0.2, water) for the L enantiomer, and lit.[4] $[\alpha]_D^{21}$ +104° for ethyl 4-deoxy-β-L-*erythro*-pentopyranoside]; ^{1}H-n.m.r. (D_2O, with sodium 4,4-dimethyl-4-silapentane-1-sulfonate as the internal standard); δ 4.65 (d, $J_{1,2}$ 3.8 Hz, H-1), 3.64 (t, $J_{2,3}$ 3.2 Hz, H-2), 4.03 (o, $J_{3,4}$ 5.0, $J_{3,4'}$ 8.0 Hz, H-3), 1.80 (m, $J_{4,5}$ 5.0 Hz, H-4), 3.77 (dd, $J_{5,5'}$ 6.0 Hz, H-5), and 3.40 (s, OMe). The 2,3-Diacetate of **4a** had $[\alpha]_D^{15}$

$-88.8°$ (*c* 0.93, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 4.62 (d, $J_{1,2}$ 2.5 Hz, H-1), 5.02 (t, $J_{2,3}$ 3.0 Hz, H-2), 5.21 (o, $J_{3,4}$ 5.0 Hz, H-3), 1.82 (m, H-4), 3.70–3.95 (m, H-5), 3.37 (s, OMe), and 2.02, 2.11 (s, $OCOCH_3$).

Anal. Calc. for the 2,3-diacetate $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.51; H, 6.93.

The α anomer (**3b**) gave **4b** (98%); $[\alpha]_D^{15}$ $+80.3°$ (*c* 1.1, water); ^{1}H-n.m.r.: (D_2O, with sodium 4,4-dimethyl-4-silapentane-1-sulfonate as the internal standard): δ 4.48 (d, $J_{1,2}$ 2.0 Hz, H-1), 3.80 (t, H-2), 3.30–4.05 (m, H-3, H-5), 1.78 (q, H-4), and 3.45 (s, OMe). The bis(*p*-nitrobenzoate) of **4b** had m.p. 184–185°; ^{1}H-n.m.r. data ($CDCl_3$): δ 4.80 (d, $J_{1,2}$ 2.8 Hz, H-1), 5.42 (t, $J_{2,3}$ 2.8 Hz, H-2), 5.55 (m, H-3), 2.18 (q, $J_{4,5}$ 4.5, H-4), 3.50–4.20 (m, H-5), and 3.50 (s, OMe).

Anal. Calc. for the bis(*p*-nitrobenzoate) $C_{20}H_{18}N_2O_{10}$: C, 53.81; H, 4.06; N, 6.28. Found: C, 53.93; H, 4.11; N, 6.23.

4-Deoxy-D-erythro-*pentose* (**5**). — Compound **4a** (209 mg) was hydrolyzed at 100° with M sulfuric acid (20 mL). During 4 h the optical rotation changed from -93.4 to $-20.1°$ (const). The solution was made neutral with sodium carbonate and then evaporated to dryness, and the residue extracted with hot ethyl acetate. Evaporation of the extract gave 4-deoxy-D-*erythro*-pentose (**5**) (160 mg, 85%) as a colorless syrup; $[\alpha]_D^{15}$ $-25.0°$ (*c* 1.1, water) [Lit.[1] $[\alpha]_D^{23}$ $-27.6°$ (*c* 0.5, water)].

ACKNOWLEDGMENTS

The authors are greatly indebted to Dr. Sabu Kasai for the measurement of the ^{13}C-n.m.r. spectra and to Mr. Junichi Goda for the elemental analyses.

REFERENCES

1 F. W. Lichtenthaler, T. Sakakibara, and E. Egert, *Chem. Ber.*, 113 (1980) 471–488.
2 G. W. E. Plaut and R. L. Beach, *Proc. Int. Symp. Chem. Biol. Pteridines, 5th* (1975) 101–24 [*Chem. Abstr.*, 84 (1976) 131916k].
3 P. W. Kent and P. F. V. Ward, *J. Chem. Soc.*, (1953) 416–418.
4 J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, 34 (1969) 2643–2645.
5 R. M. Srivastava and R. K. Brown, *Can. J. Chem.*, 49 (1971) 1339–1342.
6 D. Horton and C. G. Tindall, Jr., *Carbohydr. Res.*, 15 (1970) 215–232.
7 H. M. Bell, C. W. Vanderslice, and A. Spehar, *J. Org. Chem.*, 34 (1969) 3923–3926.