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Note

Synthesis of substituted 2,6-dioxabicyclo[3.1.1]heptanes: 1,3-anhydro-2,4-di-*O*-benzyl-6-deoxy-β-L-talopyranose

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As a part of our program on the synthesis of the 2,6-dioxabicyclo[3.1.1]heptane ring system occurring in thromboxane A_2 (TXA_2) [1,2], a compound of substantial importance in biological chemistry, we have investigated 1,3-anhydro-L- and -D-rhamno- [3,4], -D-galacto- [5], -6-deoxy-D-gluco- [6], and -L-fuco-pyranose [7]. Earlier, 1,3-anhydro-D-gluco- [8,9], and -D-manno-pyranose [10,11] derivatives had been prepared by Schuerch's group. We now report the synthesis of 1,3-anhydro-2,4-di-*O*-benzyl-6-deoxy-β-L-talopyranose, whose stereoregular polymerization and subsequent deprotection could afford α,1 → 3-linked 6-deoxy-L-talopyranan, a useful model compound for polysaccharide research.

Methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-talopyranoside (**1**), obtained by a reported method [12,13], was benzylated to afford methyl 4-*O*-benzyl-6-deoxy-2,3-*O*-isopropylidene-α-L-talopyranoside (**2**). Removal of the isopropylidene group under mild acidic conditions gave methyl 4-*O*-benzyl-6-deoxy-α-L-talopyranoside (**3**). Treatment of the dibutylstannylene derivative of compound **3** with benzyl bromide (2 equiv) and tetrabutylammonium bromide (1 equiv) in toluene afforded the 2-*O*-benzyl derivative **4** in 30% yield, together with methyl 3,4-di-*O*-benzyl-6-deoxy-α-L-talopyranoside (**9**). Aspinall and Takeo [14] reported a similar method for the preparation of benzyl 2,4-di-*O*-

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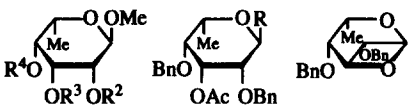

	R^2	R^3	R^4		R	
1	L Ipd J		H	6	OAc	8
2	L Ipd J		Bn	7	Cl	
3	H	H	Bn			
4	Bn	H	Bn			
5	Bn	Ac	Bn			
9	H	Bn	Bn			

Formule 1

benzyl-6-deoxy-α-L-talopyranoside, and obtained an almost identical result. Lipták et al. [15] obtained the 2,4-di-*O*-benzyl ether in 83% yield by reductive cleavage of the 2,3-*endo*-benzylidene acetal. Other methods that we tried, such as phase transfer conditions or direct monobenzylation with benzyl bromide (1 equiv) and sodium hydride (1 equiv) gave poorer yields of **4**. The R_f value of **9** (0.38) was larger than that of **4** (0.30) on TLC (3:1 petroleum ether–ethyl acetate), while just the opposite was observed for the mannopyranoside analogues. Acetylation of compound **4** with acetic anhydride in pyridine gave the 3-acetate **5** quantitatively, and acetolysis of **5** with acetic anhydride–acetic acid under catalysis by sulfuric acid furnished 1,3-diacetate **6**. The conversion of compound **6** into 3-*O*-acetyl-2,4-di-*O*-benzyl-6-deoxy-α-L-talopyranosyl chloride (**7**) was effected with hydrogen chloride in ether solution according to the method of Micheel and Kreutzer [16]. The key intermediate **7** was not stable — it decomposed when subjected to TLC. It was therefore committed to further reaction immediately after purification by analytical LC. The ring closure of **7** with potassium *tert*-butoxide in oxolane at room temperature afforded 1,3-anhydro-2,4-di-*O*-benzyl-6-deoxy-β-L-talopyranose (**8**) in good yield. The target compound **8** was acid labile, decomposing on silica gel plates, but relatively stable under basic conditions. Purification of **8** was carried out by analytical LC, using a column packed with Lichrosorb-NH_2. Methanolysis of the 1,3-anhydropyranose **8** was conducted to investigate its reactivity [17]. Reaction occurred immediately when boron trifloride etherate was added to a solution of **8** in methanol, giving a single product identified by TLC and ^{1}H NMR as compound **4**. This indicated that the ring opening was stereospecific.

The 1,3-anhydropyranose **8** was characterized by its mass spectrum and by ^{1}H NMR. The mass spectrum showed a molecular ion of low intensity at m/z 326, and a relatively strong peak at m/z 253 that is characteristic for 1,3-anhydro glycopyranoses [18] and attributable to the ion BnOCH=CHCH=O$^+$Bn. Peaks of moderate intensity at m/z 181, 161, 149, and 107 were also observed.

In the ^{1}H NMR spectrum of **8** the anomeric proton, H-1, appeared as a characteristic doublet at δ 5.38 with a spacing of 4.4 Hz, caused by coupling with H-3. Such a large value of $^4J_{1,3}$ probably reflects coupling through two W paths, as found in cyclobutane

derivatives [19]. The H-2 of **8** appeared as a singlet, indicative of a dihedral angle $\phi_{1,2}$ close to 90° [3].

1. Experimental

General methods.—Instrumental and chromatographic procedures were carried out as previously described [7].

Methyl 4-O-benzyl-6-deoxy-2,3-O-isopropylidene-α-L-talopyranoside (**2**).—To a solution of **1** (3.25 g, 15 mmol) in dry oxolane (50 mL) in an ice bath was added sodium hydride (80% in oil, 1.35 g, 45 mmol) with stirring. The mixture was boiled under reflux, and benzyl bromide (1.90 mL, 16 mmol) was added dropwise. Stirring under reflux was continued for 4 h, when TLC (3 : 1 petroleum ether–ethyl acetate) indicated that the reaction was complete. The solution was cooled, filtered, and washed with dicloromethane. The organic phase was concentrated to a syrup, which on purification by column chromatography (3 : 1 petroleum ether–ethyl acetate) yielded white crystals of **2** (3.80 g, 83%), mp 67–68°C; $[\alpha]_D^{23}$ − 0.3° (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.40–7.25 (m, 5 H, aromatic H), 4.87 and 4.56 (ABq, 2 H, *J* 12.2 Hz, CH_2Ph), 4.84 (d, 1 H, $J_{1,2}$ 2.0 Hz, H-1), 4.38 (dd, 1 H, $J_{2,3}$ 6.8, $J_{3,4}$ 4.5 Hz, H-3), 4.02 (dd, 1 H, H-2), 3.86 (m, 1 H, $J_{4,5}$ 3.2, $J_{5,6}$ 6.6 Hz, H-5), 3.57 (dd, 1 H, H-4), 3.39 (s, 3 H, OCH_3), 1.58, 1.37 [2 s, 6 H, C(CH_3)$_2$], and 1.21 (d, 3 H, H-6). Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.23; H, 7.79. Found: C, 66.21; H, 7.91.

Methyl 4-O-benzyl-6-deoxy-α-L-talopyranoside (**3**).—To a solution of compound **2** (3.36 g, 11 mmol) in methanol (30 mL) was added HCl (4 mL, 0.5 N), and the mixture was boiled under reflux for 1 h. TLC showed that all of the starting material had disappeared. The solution was concentrated, the residue was dissolved in dichloromethane, and this solution was washed sequentially with saturated $NaHCO_3$ and water, then dried (Na_2SO_4). Evaporation of the solvent afforded a residue of **3**. Recrystallization from ethyl acetate–petroleum ether furnished pure **3** as white needles (2.69 g, 92%), mp 61–62°C; $[\alpha]_D^{23}$ − 89° (*c* 0.5, $CHCl_3$); ^{1}H NMR: δ 7.38–7.30 (m, 5 H, aromatic H), 4.79 and 4.70 (ABq, 2 H, *J* 11.5 Hz, CH_2Ph), 4.76 (s, 1 H, H-1), 3.87 (m, 1 H, $J_{4,5}$ 0.5, $J_{5,6}$ 6.6 Hz, H-5), 3.83 (t, 1 H, $J_{2,3} = J_{3,4}$ 3.3 Hz, H-3), 3.69–3.61 (m, 2 H, H-2, H-4), 3.36 (s, 3 H, OCH_3), 3.10–2.40 (br s, 2 H, OH), and 1.28 (d, 3 H, H-6). Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.69; H, 7.46. Found: C, 62.41; H, 7.23.

Methyl 2,4-di-O-benzyl-6-deoxy-α-L-talopyranoside (**4**) *and its 3-acetate* **5**.—A mixture of **3** (2.54 g, 9.5 mmol) and dibutyltin oxide (2.38 g, 9.6 mmol) in methanol (60 mL) was stirred and boiled. After the mixture became transparent heating was continued for 1 h, then the solution was concentrated to give a white foamy residue. To the residue was added toluene (100 mL), tetrabutylammonium bromide (3.06 g, 9.5 mmol), and benzyl bromide (2.37 mL, 20 mmol), and the mixture was boiled under reflux for 24 h. TLC (3 : 1 petroleum ether–ethyl acetate) showed the presence of methyl 3,4-di-*O*-benzyl-6-deoxy-α-L-talopyranoside (**9**, R_f 0.38) and **4** (R_f 0.30), together with a small amount of the starting marterial. After evaporation of the solvent, the brownish residue was purified by column chromatography (3 : 1 petroleum ether–ethyl acetate). Pure compound **4** (1.01 g, 30%), together with **9** (1.74 g, 51%), and the starting material **3**

(0.36 g), was obtained, $[\alpha]_D^{23} - 18.2°$ (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.40–7.24 (m, 10 H, aromatic H), 4.83 and 4.48 (ABq, 2 H, *J* 12.0 Hz, CH_2Ph), 4.80 and 4.63 (ABq, 2 H, *J* 11.7 Hz, CH_2Ph), 4.82 (d, 1 H, $J_{1,2}$ 1.2 Hz, H-1), 3.86 (m, 1 H, $J_{4,5}$ 1.7, $J_{5,6}$ 6.6 Hz, H-5), 3.81 (t, 1 H, $J_{2,3} = J_{3,4}$ 4.5 Hz, H-3), 3.53–3.47 (m, 2 H, H-2, H-4), 3.36 (s, 3 H, OCH_3), and 1.32 (d, 3 H, H-6). Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.39; H, 7.26. Found: C, 70.51; H, 7.30.

Compound **4** (210 mg, 0.59 mmol) was acetylated with acetic anhydride in pyridine at room temperature, and **5** was obtained in quantitative yield, $[\alpha]_D^{23} - 40°$ (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.42–7.24 (m, 10 H, aromatic H), 5.09 (t, $J_{2,3} = J_{3,4}$ 3.5 Hz, H-3), 4.81 and 4.57 (ABq, 2 H, *J* 12.5 Hz, CH_2Ph), 4.83 (d, 1 H, $J_{1,2}$ 2.0 Hz, H-1), 4.70 (s, 2 H, CH_2Ph), 3.95 (m, 1 H, $J_{4,5}$ 1.9, $J_{5,6}$ 6.6 Hz, H-5), 3.62–3.56 (m, 2 H, H-2, H-4), 3.35 (s, 3 H, OCH_3), 1.90 (s, 3 H, CH_3CO), and 1.32 (d, 3 H, H-6).

*1,3-Di-*O*-acetyl-2,4-di-*O*-benzyl-6-deoxy-α-*L*-talopyranose* (**6**).—Compound **5** (215 mg, 0.54 mmol) was dissolved in a mixture of 50:20:0.1 acetic anhydride–acetic acid–H_2SO_4 (3 mL), the solution was stirred for 5 h at room temperature, and then poured into ice–aq Na_2CO_3. The product was extracted with dichloromethane, and the extract was dried (Na_2SO_4), concentrated, and purified by column chromatography (3:1 petroleum ether–ethyl acetate) to give **6** as a syrup (170 mg, 74%), $[\alpha]_D^{23} - 22.0°$ (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.44–7.23 (m, 10 H, aromatic H), 6.25 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 5.14 (t, 1 H, $J_{2,3} = J_{3,4}$ 3.5 Hz, H-3), 4.86 and 4.58 (ABq, 2 H, *J* 12.5 Hz, CH_2Ph), 4.76 and 4.69 (ABq, 2 H, *J* 12.0 Hz, CH_2Ph), 4.10 (m, 1 H, $J_{4,5}$ 2.2, $J_{5,6}$ 6.6 Hz, H-5), 3.66–3.57 (m, 2 H, H-2, H-4), 2.08, 1.91 (2 s, 6 H, 2 CH_3CO), and 1.33 (d, 3 H, H-6). Anal. Calcd for $C_{24}H_{28}O_7$: C, 67.29; H, 6.54. Found: C, 67.45; H, 6.67.

*1,3-Anhydro-2,4-di-*O*-benzyl-6-deoxy-β-*L*-talopyranose* (**8**).—Compound **6** (120 mg, 0.28 mmol) was dissolved in dry diethyl ether (5 mL), and HCl was bubbled in to saturation at 0°C under nitrogen protection. The solution was kept at room temperature in a sealed bottle for 2 h. TLC (3:1 petroleum ether–ethyl acetate) indicated that the reaction was complete. The solution was concentrated to a syrup, which was dissolved in dichloromethane (2 mL), and the solution was evaporated. This procedure was repeated 7 or 8 times to reduce residual hydrogen chloride to the minimum. The product was then purified by analytical LC (3:1 petroleum ether–ethyl acetate) to give **7** as a syrup (89 mg, 79%), $[\alpha]_D^{23} - 107°$ (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.42–7.24 (m, 10 H, aromatic H), 6.19 (s, 1 H, H-1), 5.29 (t, 1 H, $J_{2,3} = J_{3,4}$ 3.5 Hz, H-3), 4.85 and 4.55 (ABq, 2 H, *J* 12.5 Hz, CH_2Ph), 4.66 and 4.64 (2 s, 2 H, CH_2Ph), 4.25 (m, 1 H, $J_{5,6}$ 6.4 Hz, H-5), 3.85 (m, 1 H, H-4), 3.70 (m, 1 H, H-2), 1.89 (s, 3 H, CH_3CO), and 1.32 (d, 3 H, H-6); MS: *m/z* 369 ($M^+ - Cl$), 326 ($M^+ - Cl - CH_3CO$), and 313 ($M^+ - CH_2Ph$).

To a solution of compound **7** (84 mg, 0.21 mmol) in dry oxolane (4 mL) was added potassium *tert*-butoxide (94 mg, 0.84 mmol). The mixture was stirred at room temperature. After 2 h the reaction was complete as indicated by TLC (3:1 petroleum ether–ethyl acetate). The solvent was evaporated, the residue was extracted with 3:1 petroleum ether–ethyl acetate, and the extracts were combined and concentrated. Purification of the syrup by analytical LC (on Lichrosorb-NH_2, 3:1 petroleum ether–ethyl acetate) afforded **8** (58 mg, 86%), $[\alpha]_D^{23} - 2.9°$ (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.42–7.25 (m, 10 H, aromatic H), 5.38 (d, 1 H, $J_{1,3}$ 4.4 Hz, H-1), 4.73–4.46 (m, 4 H,

2 CH_2Ph), 4.65 (m, 1 H, H-3), 4.53 (m, 1 H, H-5), 4.41 (s, 1 H, H-2), 3.65 (dd, 1 H, $J_{3,4}$ 2.4, $J_{4,5}$ 4.9 Hz, H-4), and 1.38 (d, 1 H, $J_{5,6}$ 6.4 Hz, H-6); MS: m/z 326 (M^+), 253 (BnO^+=CH–CH=CHOBn), 181 ($C_6H_5-^+CH-CH_2-C_6H_5$), 161 (BnO^+=CH–CH=C=O), 149 (BnO=CH–CH=O^+), 107 ($C_7H_7O^+$), and 91 ($C_7H_7^+$). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.62; H, 6.75. Found: C, 73.78; H, 6.75.

Methanolysis of compound **8**.—Compound **8** (5 mg, 0.02 mmol) was dissolved in absolute methanol (1 mL), and boron trifluoride etherate (4 μL) was added to the solution. The mixture was stirred at room temperature for 0.5 h, when TLC (3:1 petroleum ether–ethyl acetate) showed the reaction was complete. The solution was evaporated to afford the methanolysis product, the ^{1}H NMR spectrum of which was identical to that of compound **4**.

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