Carbohydrate Research, 206 (1990) 361–366
Elsevier Science Publishers B.V., Amsterdam

Note

Displacement reactions of a 1,2-anhydro-α-D-hexopyranose: installation of useful functionality at the anomeric carbon

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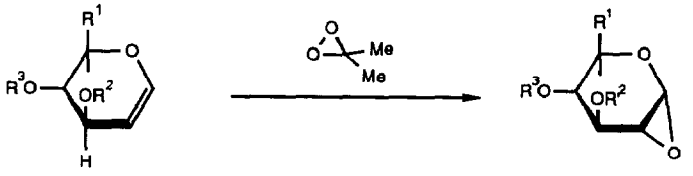
(Received January 25th, 1990; accepted, in revised form, April 19th, 1990)

Since the initial report of Brigl's anhydride (1,2-anhydro-3,4,6-tri-*O*-acetyl-α-D-glucopyranose) in 1922, 1,2-anhydro-α-D-hexopyranoses have received continuing attention in the carbohydrate community[1]. Recently we reported an important advance in the synthesis of 1,2-anhydro-α-D-hexopyranose derivatives **2** (Scheme 1). Our method involved direct epoxidation of the corresponding glycals **1** with 3,3-dimethyldioxirane[2a,b]. Hitherto, access to such oxiranes had involved more complicated sequences. Glycals are of particular interest to us since they can be generated in a few steps from the Lewis acid-catalyzed diene–aldehyde cyclocondensation (LACDAC) reaction[2c]. Glycals of non-natural sugars are also available by the same methodology. The ability to generate the epoxide in one step from glycals bearing a range of protecting groups is another important feature of this chemistry.



1 **2**

Scheme 1

It was demonstrated that epoxides of type **2** undergo displacement at C-1 (*via* catalysis by anhydrous zinc chloride) with a variety of secondary alcohols, including those derived from differentially protected sugars[2b]. If the resident protecting groups are of a non-participatory nature, the alcoholysis reactions occur with inversion of configuration at C-1. In this paper we describe other C-1 displacement reactions of the 1,2-anhydro-α-D-hexopyranose linkage. The substrate employed, **6**, was prepared by reaction of 3,3-dimethyldioxirane with the commercially available 3,4,6-tri-*O*-benzyl-

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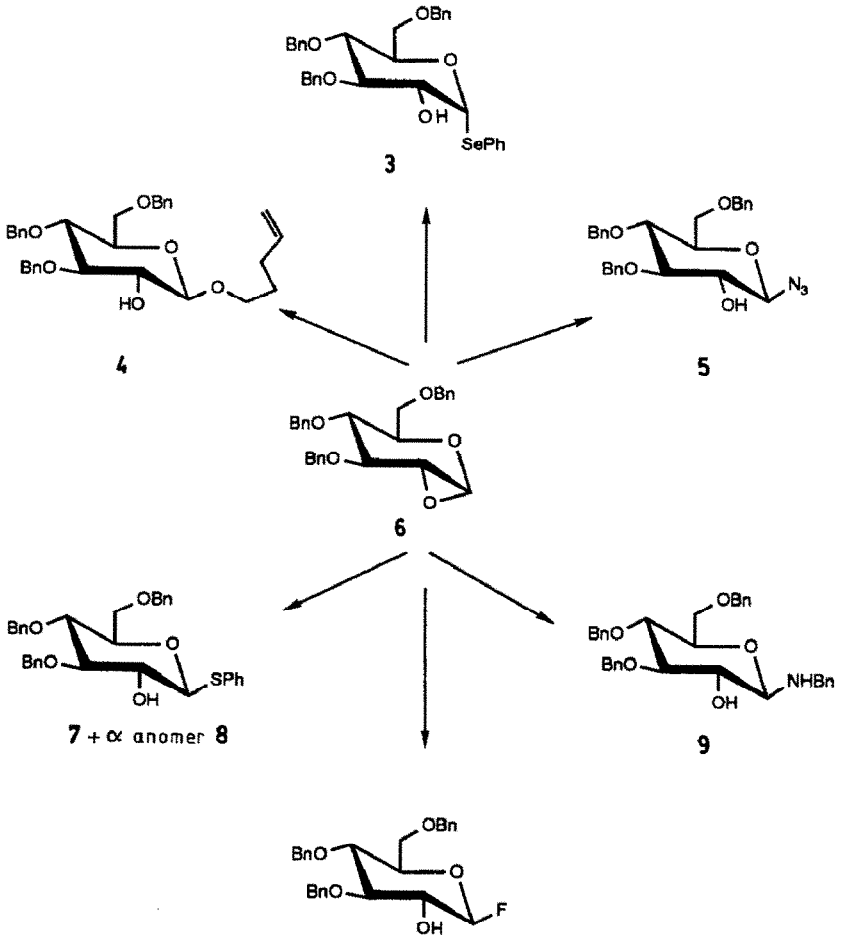
0008-6215/90/$ 03.50

D-glucal[3]. The physical and spectral properties of **6** were in agreement with those reported by Schuerch[1g].



Scheme 2

Treatment of **6** with either an azide salt or a silyl azide was expected to provide an entry into the glucosyl azide series[4]. Indeed, reaction of **6** with tetrabutylammonium azide in tetrahydrofuran (THF) afforded a 47% yield of the β-azide **5** ($J_{1,2}$ 8.20 Hz). Likewise the anomeric glucosyl amine substructure[5] can be generated by the zinc chloride catalyzed solvolysis of the 1,2-anhydro-α-D-hexopyranose. Thus, reaction of **6** with benzylamine in the presence of anhydrous zinc chloride produced a 71% yield of the pure β-D-glucosylamine **9** ($J_{1,2}$ 9.70 Hz).

It was also of interest to evaluate the usefulness of the 1,2-anhydro-α-D-hexopyranoses for the installation of functional groups already known for their ability to impart glycosyl donor character to the anomeric carbon atom[6,7]. In particular we sought to correlate with the large body of work detailing the preparation and exploitation of

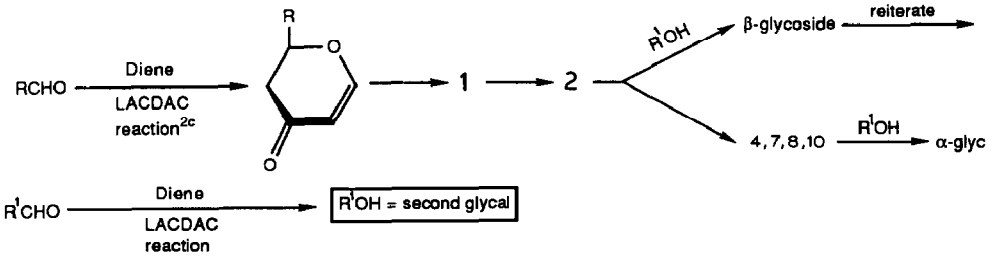
glycosyl fluorides[4a,8,9] and phenyl thioglycosides[10,11]. Toward that goal, reaction of **6** with tetrabutylammonium fluoride was studied. There was obtained a 53% yield of **10** ($J_{1,2}$ 6.40 Hz). Similar reaction of **6** with tetrabutylammonium thiophenolate provided a 50% yield of a 6:1 ratio of phenyl β,α-thioglycosides **7** and **8** ($J_{1,2}$ 9.62 and 5.36 Hz, respectively).

Recently Fraser-Reid and colleagues have demonstrated the power of 4-pentenyl glycosides (NPGs) as glycosyl donors. These workers have published detailed accounts of the scope of the NPG methodology[12], the effects of protecting groups on the susceptibility of NPGs to electrophilic attack[13], and the application of the NPG approach to the preparation of a complex oligosaccharide[14]. Reaction of **6** with 4-penten-1-ol, catalyzed by zinc chloride, afforded a 63% yield of the pentenyl glycoside **4** as the pure β-anomer ($J_{1,2}$ 7.15 Hz). Finally in this connection we note that reaction of **6** with benzeneselenol provides an 86% yield of the phenyl α-selenoglycoside **3** ($J_{1,2}$ 5.12 Hz) (ref. 10a).

It will be noted that all of these reactions give rise to products where a differentiated alcohol is produced at C-2. After suitable protection of this alcohol (with a non-participating function), essentially known methodology can be exploited to obtain α-D-glycosides from C-1 fluoro (*cf.* **10**), C-1 phenyl thio (*cf.* **7**) or C-1 NPG (*cf.* **4**) derivatives. Thus, a pathway to pure α-D-glycosides from glycals can be charted.

In multistep ventures, there could well be an advantage in working with stereochemically homogeneous systems (*cf.* **4** and **10**). Also, the possibility that the ratio of α:β-glycoside might be at least somewhat improved by starting with pure β-leaving groups in worthy of future exploration. Such matters will be evaluated as part of our general program addressed to the conversion of glycals to various glycoconjugates.

The chemistry described herein, in conjunction with known methodology[9,11–14], provides a route to generate artificial oligosaccharides *via* the protocol shown in Scheme 3. Examples of this capability will be described in due course.



Scheme 3

EXPERIMENTAL

General procedure for compounds **5**, **7** *and* **10**. — To a solution of 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose **6** (52 mg, 120 mmol) in anhydrous THF (2 mL) was added a solution of the appropriate tetrabutylammonium salt (600 μmol) in THF (600 μL). The reaction was followed by thin-layer chromatography, and when consumption of anhydro sugar was indicated, the mixture was diluted with H_2O (5 mL) and washed with ethyl acetate (4 × 5 mL). The combined ethyl acetate extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified by SiO_2 chromatography (15–20% ethyl acetate in hexane).

*3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl azide* (**5**). — 1,2-Anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose **6** and tetrabutylammonium azide gave **5** (26.8 mg, 56 μmol, 47%): $[\alpha]_D^{25}$ −4.2° (*c* 1.15, $CHCl_3$); m.p. 65–67°; i.r. ($CHCl_3$) 3400. 3045, 3010, 2900, 2850, 2110, 1490, 1445, 1355, 1245, 1080, and 1060 cm^{-1}; ^{1}H-n.m.r. (250 MHz, $CDCl_3$) δ 7.35–7.14 (m, 15 H), 4.90–4.78 (m, 3 H), 4.65–4.49 (m, 3 H), 4.52 (d, 1 H, *J* 8.2 Hz), 3.73–3.43 (m, 6 H), 2.25 (d, 1 H, *J* 2.64 Hz).

Anal. Calc. for $C_{27}H_{29}N_3O_5$: C, 68.21; H, 6.10. Found: C, 68.06; H, 6.03.

*Phenyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside* (**7**). — 1,2-Anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose **6** and tetrabutylammonium thiophenolate gave **7** (27.9 mg, 51 μmol, 43%): $[\alpha]_D^{25}$ −11.89° (*c* 2.7, $CHCl_3$); m.p. 71–73°; i.r. ($CHCl_3$) 3540, 3050, 3020, 2980, 2900, 2850, 1570, 1490, 1450, 1110, and 1070 cm^{-1}; ^{1}H-n.m.r. (250 MHz, $CDCl_3$) δ 7.62–7.56 (m, 2 H), 7.40–7.18 (m, 18 H), 4.96–4.82 (m, 3 H), 4.72–4.55 (m, 3 H), 4.51 (d, 1 H, *J* 9.62 Hz), 3.87–3.73 (m, 2 H), 3.68–3.49 (m, 4 H), 2.45 (bs, 1 H).

Anal. Calc. for $C_{33}H_{34}O_5S$: C, 73.06; H, 6.27. Found: C, 73.22; H, 6.55.

*3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl fluoride* (**10**). — 1,2-Anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose (**6**) and tetrabutylammonium fluoride gave **10** (29 mg, 64 μmol, 53%): $[\alpha]_D^{25}$ +25.2° (*c* 1.5, $CHCl_3$); m.p. 80–82°; i.r. ($CHCl_3$) 3400, 3045, 3015, 2900, 2860, 1490, and 1095 cm^{-1}; ^{1}H-n.m.r. (250 MHz, $CDCl_3$) δ 7.32–7.15 (m, 15 H), 5.15 (dd, 1 H, *J* 53.15, 6.40 Hz), 4.81–4.74 (m, 3 H), 4.63–4.50 (m, 3 H), 3.74–3.55 (m, 6 H), 2.51 (bs, 1 H).

Anal. Calc. for $C_{27}H_{29}FO_5$: C, 71.68; H, 6.42. Found: C, 71.45; H, 6.67.

*Phenyl 3,4,6-tri-*O*-benzyl-1-seleno-α-D-glucopyranoside* (**3**). To a solution of 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose **6** (52 mg, 120 μmol) in anhydrous THF (2 mL) was added benzeneselenol (64 μL, 600 μmol). The reaction was followed by thin-layer chromatography, and, when consumption of anhydro sugar was indicated, the mixture was concentrated *in vacuo*, and the residue was purified by SiO_2 chromatography (5:95 ethyl acetate–toluene) to give **3** (60.6 mg, 103 μmol, 86%): $[\alpha]_D^{25}$ +234.4° (*c* 2.25, $CHCl_3$); m.p. 114–116°; i.r. ($CHCl_3$) 3600, 3070, 3040, 2930, 2880, 1610, 1580, 1505, 1480, 1460, and 1080 cm^{-1}; ^{1}H-n.m.r. (250 MHz, $CDCl_3$) δ 7.63–7.59 (m, 2 H), 7.39–7.17 (m, 18 H), 5.95 (d, 1 H, *J* 5.12 Hz), 4.95–4.81 (m, 3 H), 4.66–4.45 (m, 3 H), 3.90–3.57 (m, 6 H), 2.39 (d, 1 H, *J* 5.94 Hz).

Anal. Calc. for $C_{33}H_{34}O_5Se$: C, 67.23; H, 5.81. Found: C, 66.99; H, 5.81.

4-Pentenyl 3,4,6-tri-O-benzyl-β-D-glucopyranoside (**4**). — To a solution of 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose **6** (52 mg, 120 mmol) in anhydrous THF (3 mL) was added 4-penten-1-ol (62 μL, 600 μmol). The mixture was cooled to 0° and M $ZnCl_2$ in Et_2O (120 mL) was added in one portion. The reaction mixture was allowed to warm to ambient temperature over the course of 2 h, and it was then stirred for an additional 10 h. The mixture was diluted with H_2O (10 mL) and washed with ethyl acetate (3 × 10 mL). The combined ethyl acetate extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was purified by SiO_2 chromatography (14:86 ethyl acetate–hexane) to give **4** (39.3 mg, 76 μmol, 63%): $[\alpha]_D^{25}$ −5.39° (*c* 1.95, $CHCl_3$); m.p. 57–58°; i.r. ($CHCl_3$) 3550, 3030, 3000, 2980, 2880, 2840, 1645, 1580, 1480, 1440, 1345, 1100, 1050, and 900 cm^{-1}; ^{1}H-n.m.r. (250 MHz, $CDCl_3$) δ 7.39–7.21 (m, 13 H), 7.18–7.15 (m, 2 H), 5.90–5.74 (m, 1 H), 5.07–4.81 (m, 5 H), 4.64–4.51 (m, 3 H), 4.23 (d, 1 H, *J* 7.15 Hz), 3.98–3.89 (m, 1 H), 3.77–3.44 (m, 7 H), 2.31 (bs, 1 H), 2.18–2.10 (m, 2 H), 1.79–1.68 (m, 2 H).

Anal. Calc. for $C_{32}H_{38}O_6$: C, 74.11; H, 7.39. Found: C, 73.92; H, 7.45.

Benzyl 3,4,6-tri-O-benzyl-β-D-glucopyranosylamine (**9**). — To a solution of 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose **6** (52 mg, 120 μmol) in anhydrous THF (2 mL) was added benzylamine (66 μL, 600 μmol). The mixture was cooled to 0°, and M $ZnCl_2$ in Et_2O (120 μL) was added in one portion. The reaction mixture was allowed to warm to ambient temperature over the course of 2 h, and it was then stirred for an additional 10 h. The mixture was diluted with 5% aqueous sodium bicarbonate (10 mL) and washed with methylene chloride (3 × 10 mL). The combined methylene chloride extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was purified by SiO_2 chromatography (1:9 ethyl acetate–methylene chloride) to give **9** (46.1 mg, 85 μmol, 71%): $[\alpha]_D^{25}$ −7.13° (*c* 2.3, $CHCl_3$); m.p. 117–119°; i.r. ($CHCl_3$) 3530, 3330, 3085, 3060, 3015, 3005, 2870, 1600, 1570, 1495, 1455, 1360, 1290, 1100, 1055, and 1030 cm^{-1}; ^{1}H-n.m.r. (250 MHz, $CDCl_3$) δ 7.41–7.13 (m, 20 H), 5.01–4.49 (m, 5 H), 4.51 (d, 1 H, *J* 9.70 Hz), 4.13 (d, 1 H, *J* 13.13 Hz, 1/2 AB q), 3.89–3.55 (m, 6 H), 3.45–3.33 (m, 2 H), 2.68 (bs, 1 H), 1.97 (bs, 1 H).

Anal. Calc. for $C_{34}H_{37}NO_5$: C, 75.66; H, 6.91. Found: C, 75.36; H, 6.99.

ACKNOWLEDGMENTS

We thank the NIH (Grant AI-16943) for financial support in this work. An NSF Predoctoral Fellowship to D.M.G. is gratefully acknowledged. N.m.r. spectra were obtained through the auspices of the Northeast Regional NSF/NMR facility at Yale University, which was supported by NSF Chemistry Division Grant CHE-7916210.

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