Carbohydrate Research, 79 (1980) C13–C16

Preliminary communication

A synthesis of β-D-mannopyranosides by glycosidation at C-1

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(Received September 4th, 1979; accepted for publication, November 3rd, 1979)

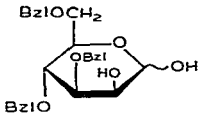
The direct stereoselective synthesis of β-D-mannopyranosides continues to remain a challenge in spite of the contributions of Gorin and Perlin[1], and Garegg and Iversen[2]. We previously reported the stereospecific synthesis of simple β-D-mannopyranosides by O-1 alkylation of a dibutylstannylene complex of 3,4,6-tri-*O*-benzyl-D-mannopyranose[3]. We now report a more general synthesis of β-D-mannopyranosides, by glycosidation of C-1, based on the following rationale:

cis-Glycosides of the 1-axial, 2-equatorial class (*gluco* and *galacto*) frequently may be prepared with high stereoselectivity from derivatives having a C-1 electronegative leaving-group and a nonparticipating ether-substituent at C-2. β-D-Mannosides, however, are not formed with high selectivity from simple derivatives of this type. We, therefore, sought some structural modification that would enhance β-selectivity. It is known that the configuration at C-2 has a substantial influence on the thermodynamic stability of the anomeric forms of free sugars. Aqueous solutions of D-glucose contain, at equilibrium, 36% of the α-pyranose form, whereas D-mannose solutions contain 67%. The higher preference of D-mannose for the α form is ascribed primarily to a favorable relationship between the dipoles of the C-1– and C-2–OH bonds[4]. It appeared, therefore, that if a D-mannopyranosyl derivative having a C-1α electronegative substituent and a nonparticipating C-2 substituent were chosen to enhance the C-2–O dipole, differences would also be observed in the rate and stereoselectivity of subsequent glycosidation reactions.

The thermodynamic factors might be unfavorable for β-D anomer formation, for the potential energy difference between α and β forms would be greater with enhanced preference for the α form. Since the enhanced C-2–O dipole should shorten and strengthen the C-1–X bond, the activation energy of glycosidation might also be higher, and the rate of reaction lower. However, since these glycosidation reactions are kinetically controlled, the influence of the structural difference on the reaction mechanism and transition state, or ion-pair intermediate, should be of more significance and favorable. Considering the reaction course on the shielded carbo-cation of an ion-pair as of SN1 type, one might expect the stronger C-2–O dipole to influence the ion-pair intermediate to retain its α configuration. This would require an approach of the nucleophilic alcohol group from the back, and would result in the formation of a C-1β–O bonded glycoside. Furthermore, the en-

hanced strength of the C-1—X bond, caused by the greater C-2—O dipole, might require the nucleophilic oxygen atom to approach C-1 more closely in the transition state, thus in effect enhancing the SN2 character of the reaction and improving its β stereoselectivity. The reactions described in the following paragraphs confirmed our expectations regarding rate and stereoselectivity, and provide a highly stereoselective route.

3,4,6-Tri-*O*-benzyl-2-*O*-methylsulfonyl-α-D-mannopyranosyl chloride (**2**) was prepared by treatment of 3,4,6-tri-*O*-benzyl-D-mannose (**1**, 1 mol) with methanesulfonyl chloride (2.5 mol) in 2,6-dimethylpyridine for 20 min at 0—5° (presumably *via* the 1,2-di-*O*-mesyl derivative as intermediate). The reaction mixture was purified by silica gel chromatography to afford pure **2** (54% yield), syrup, $[\alpha]_D^{22}$ +55.4° (*c* 0.93, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.35—7.29 (15 H, aromatic), 6.25 (d, 1 H, $J_{1,2} \sim 1.8$ Hz, H-1), 5.15 (t, 1 H, $J_{2,3} \sim 3.0$ Hz, H-2), 4.80—4.58 (6 H, $CH_2C_6H_5$), 4.50—3.93 (3 H, H-3, -4, -5), 3.78 (m, 2 H, H-6, -6′), and 2.99 (s, 3 H, CH_3).



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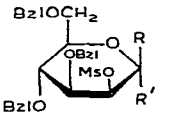
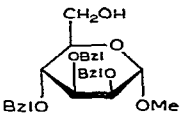


2 R = H, R′ = Cl
3 R = H, R′ = Ts
4 R = OMe, R′ = H



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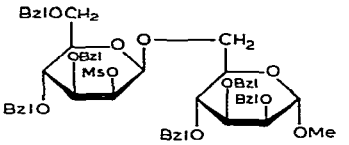

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Treatment of chloride **2** on a high-vacuum rack with silver *p*-toluenesulfonate in acetonitrile afforded the 1-*O*-tosyl derivative **3**, as described for the D-galactopyranosyl and D-glucopyranosyl derivatives[5—7]. Compound **3** was not isolated, but was treated directly with 1 equiv. of methanol for 36 h at room temperature in the dark. The reaction afforded methyl 3,4,6-tri-*O*-benzyl-2-*O*-methylsulfonyl-β-D-mannopyranoside (**4**) in 90% yield after chromatography on silica gel (1 : 2, v/v, ethyl acetate—hexane), $[\alpha]_D^{22}$ −39.4° (*c* 0.89, chloroform); no α anomer could be detected; ^{1}H-n.m.r. ($CDCl_3$): δ 5.15 (d, 1 H, H-2), 5.02—4.45 (6 H, $CH_2C_6H_5$), 4.42 (s, 1 H, H-1β), 3.84—3.69 (5 H, H-3, -4, -5, -6, -6′), 3.55 (s, 3 H, OMe-β), and 3.12 (s, 3 H, Ms); ^{13}C-n.m.r. ($CDCl_3$): 99.6 (C-1β), 79.8 (C-3), 77.2 (C-4), 76.0 (C-5), 74.4 (C-2), 69.3 (C-6), 57.15 (OMe-β), and 39.3 (Ms). Singlet for H-1 at δ 4.42 and singlet for OCH_3 at δ 3.55 are in agreement with the data reported[3,8] in the literature for β-D-mannopyranoside derivatives. For glycosides of 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-pyranoside, H-1α has been observed[9] in the range of δ 4.99—4.92 and for 2-acyl derivatives[9], OCH_3-α in the range of δ 3.42—3.31. ^{13}C-n.m.r. data for OCH_3 (57.15 p.p.m.) and a negative value of optical rotation also supported a β-anomer assignment to **4**.

Anal. Calc. for $C_{29}H_{35}O_8S$: C, 64.07; H, 6.49; S, 5.90. Found: C, 63.97; H, 6.20; S, 5.72.

It was of interest to see whether reaction with a sugar alcohol also would be stereoselective and afford a β-linked disaccharide. Therefore, methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (**5**) was prepared in pure form by acetylation followed by deacetylation[10]

of crude **5**, syrup, $[\alpha]_D^{24}$ +24.8° (*c* 1.7, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.26 (15 H, aromatic), 4.86–4.63 (7 H, H-1 and $CH_2C_6H_5$), 4.07–3.77 (6 H, ring), 3.32 (s, 3 H, OCH_3), and 2.12 (bs, 1 H, OH). Reaction of **3** with **5** was carried out in acetonitrile for 48 h. Chromatography on silica gel (1 : 2, v/v, ethyl acetate–hexane) separated about 10% of unreacted **5** and a mixture of two additional compounds. ^{1}H-n.m.r. ($CDCl_3$) of the mixture gave two peaks for mesyl protons at δ 3.02 (s, 0.5 H, Ms-α) and 2.99 (s, 2.5 H, Ms-β) in a ratio of 1 : 5 (≃ 17% of α-D anomer). The earlier-eluted compound (containing some of the later-eluted compound) was purified by a second chromatography and showed $[\alpha]_D^{25}$ +11.2° (*c* 0.58, chloroform). The later-eluted compound, obtained in larger proportion, was also isolated as a syrup of lower optical rotation {$[\alpha]_D^{25}$ +8.18° (*c* 0.66, chloroform)}, which showed a single mesyl peak in the ^{1}H-n.m.r. ($CDCl_3$) spectrum: δ 7.45–7.35 (30 H, aromatic), 5.05 (1 H, H-2′), 4.97–4.58 (13 H, H-1α, $CH_2C_6H_5$), 4.42 (1 H, H-1′β), 4.07–3.55 (11 H, ring), 3.33 (s, 3 H, OCH_3), and 2.99 (s, 3 H, CH_3); the peak at δ 4.42 was absent in the spectrum of **5**, and its position corresponds to that of H-1β in **4**. In the ^{13}C-n.m.r. spectrum ($CDCl_3$), two anomeric peaks were found, the chemical shift of one corresponding to C-1β in **4**: δ 99.76 (C-1′β), 98.88 (C-1α), 69.39 (C-6′), 68.43 (C-6), 54.94 (OCH_3), and 39.43 (Ms).

The reaction was more stereoselective, and also faster, when the 1-*O*-(2,2,2-trifluoroethylsulfonyl) was used in place of the 1-*O*-tosyl derivative. Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-methylsulfonyl-(β-D-mannopyranosyl)-α-D-mannopyranoside (**6**) was formed after 18 h in over 90% yield, $[\alpha]_D^{25}$ +7.3° (*c* 1, chloroform). Its ^{1}H-n.m.r. spectrum was identical to that of the previous preparation. The α-linked disaccharide was not formed in detectable amount.

Anal. Calc. for $C_{56}H_{62}O_{13}S$: C, 68.98; H, 6.40; S, 3.29. Found: C, 68.64; H, 6.11; S, 3.04.

In summary, the nature of the leaving group at C-1 and the nonparticipating group at C-2 of D-mannopyranosyl derivatives alters both the rate and stereoselectivity of reactions at C-1. Appropriate choices of substituents should give practical synthetic routes for a variety of β-D-mannopyranosides. The obvious extension of this class of reactions to more complex glycosides is under investigation.

ACKNOWLEDGMENT

This research was supported by a grant (CHE 78-07141) from the National Science Foundation.

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