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SYNTHESIS OF β-D-MANNOPYRANOSIDES AND REGIOSELECTIVE O-ALKYLATION OF DIBUTYLSTANNYLENE COMPLEXES

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Abstract: Alkylation of dibutylstannylene complexes of 3,4,6-tri-O-benzyl-D-mannopyranose, methyl 6-O-trityl-α-D-mannopyranoside and methyl α-D-mannopyranoside gives respectively β-D-mannopyranoside and 3-O-alkyl derivatives with high selectivity.

We have been engaged in an investigation of the synthesis of glycopyranosides of high stereoselectivity and yield. The least readily available glycosides are those with a 1 equatorial, 2 axial relationship like the β-D-mannopyranosides, which have been prepared by Koenigs-Knorr reaction using 4,6-di-O-acetyl-α-D-mannopyranosyl bromide 2,3-carbonate[1,2] and by stereoselective reduction of glycosides such as methyl β-D-arabino-hexopyranosidulose.[3-5] An important demonstration has been published by Nashed and Anderson[6] showing that a cyclic dibutylstannylene derivative of vicinal equatorial and axial hydroxyl groups selectively activates the equatorial oxygen for O-alkylation or acylation. Similar observations have been made by other workers.[7-9] This observation suggested to us an alternative synthesis for β-D-mannopyranosides. Since mannose derivatives maintain a $^4C_1$ conformation, the only probable dibutyltin complex with oxygen on C-1 and C-2 would involve a 1 eq., 2 ax. relationship. The expected product of O-alkylation would then be a β-D-mannopyranoside.

We now find that dibutyltin oxide forms a complex with 3,4,6-tri-O-benzyl-D-mannopyranose (1) as indicated by solution of the tin compound and an ^{1}H NMR spectrum with no peaks for OH groups. Reaction of this 1,2-O-dibutylstannylene complex (2) with methyl iodide (1.5 mole) at 45° in N,N-dimethylformamide followed by chromatography on silica gel with $CHCl_3$:MeOH (9:1) yields 94% of methyl 3,4,6-tri-O-benzyl-β-D-mannopyranoside (3); $[\alpha]_D^{20}$ -10.2° (c 0.45, $CHCl_3$), ^{1}H NMR data ($CDCl_3$): β-anomer, singlet for H-1 at δ 4.35, singlet for OCH_3 at δ 3.55, in agreement with the data reported by Lemieux and Fraser-Reid[10] for methyl 2-bromo-2-deoxy-3,4,6-tri-O-acetyl-β-D-mannopyranoside. Debenzylation of 3 with Pd-C gave methyl β-D-mannopyranoside (4), $[\alpha]_D^{20}$ -67° (c 1.2, EtOH), -67.6° (c 1.2, H_2O). [Lit.[11] $[\alpha]_D^{21}$ -66° (c 1.05, H_2O)]. Acetylation with acetic anhydride in pyridine gave methyl tetra-O-acetyl-β-D-mannopyranoside (5), mp 158-159°, $[\alpha]_D^{20}$ -45.2° (c 0.7, $CHCl_3$). [Lit.,[4] mp 161-163°, $[\alpha]_D^{22}$ -47° (c 0.8, $CHCl_3$)].

Reaction of complex 2 with allyl bromide (1.5 mole) at 75° C in N,N-dimethylformamide gave a quantitative yield of allyl 3,4,6-tri-O-benzyl-β-D-mannopyranoside (6), mp 48-49° (ether-n-hexane); $[\alpha]_D^{23}$ +5.9° (c 0.72, $CHCl_3$). ^{1}H NMR ($CDCl_3$):

δ 6.30-5.67 (m, 1H, -CH=CH_2), 5.40-5.10 (m, 2H, -CH=CH_2), 5.02-4.59 (m, 6H, $3CH_2$, benzyl), 4.46 (s, 1H, H-1_β): Anal. Calcd for $C_{30}H_{34}O_6$: C, 73.45; H, 6.98. Found: C, 73.50; H, 6.99.

Reaction of dibutyltin complex 2 with methyl p-toluenesulfonate did not proceed at 45°, but gave a mixture of methyl 3,4,6-tri-O-benzyl-α- and β-D-mannopyranosides (7) and (3) at 75°. ^{1}H NMR data ($CDCl_3$): β-anomer, OCH_3 at δ 3.56; α-anomer, OCH_3 at δ 3.35 (β:α = 63:37). Reaction of 2 with dimethylsulfate in DMF at 80° gave a mixture of 3,4,6-tri-O-benzyl-α- (7) and -β-D-mannopyranoside (3) in a ratio of 7:3. Dibutyltin complex is involved in these nonselective alkylations also, for free diol 1 did not react with dimethylsulfate in DMF at 80°.

The complex of 3,4,6-tri-O-benzyl-D-glucose (8) and dibutyltin oxide with methyl iodide in DMF at 45° gave a mixture of two products, namely 3,4,6-tri-O-benzyl-2-O-methyl-D-glucopyranose (9, 70%) and methyl 3,4,6-tri-O-benzyl-α-D-glucopyranoside (10, 30%). Compound 9 was crystallized (ethyl ether-n-hexane) from the mixture and was obtained pure after three crystallizations, mp 111-112°; $[\alpha]_D^{20}$ +38.2° (c 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$); singlet at δ 3.46 for OMe at C-2. Compound 9 gave a positive Fehlings test and showed two anomeric peaks in the ^{13}C NMR spectrum (Table 1). Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C 72.78; H, 6.94.

Table 1. ^{13}C NMR ($CDCl_3$) spectra (proton decoupled).

	C-1	C-2	C-3	C-4	C-5	C-6	Alkoxyl
Compound 6	98.8	69.5	81.8	75.5	74.46	68.4	134, 117.8
Compound 9 α-anomer	90.7 (90.7)[a]	81.8 (81.9)	82.6	77.8	73.5	68.9	59.0 (59.3)
Compound 9 β-anomer	97.3 (97.1)[a]	85.3 (85.2)	84.8	77.8	74.7	69.0	60.6 (61.7)
Compound 10	99.8 (100.5)[b]	73.0 (73.1)	83.4	77.8	70.6	69.1	55.3 (56.8)
Compound 12 in D_2O	101.9 (102.0)	67.4 (66.9)	81.8 (81.3)	66.2 (66.9)	73.38 (73.78)	61.8 (62.2)	57.6, 56.0 (57.5, 55.9)
Compound 13	(101.9)[c]	(71.7)	(71.0)	(67.9)	(73.60)	(62.1)	(56.2)
Compound 14	101.2	68.3	79.5	65.6	72.5	61.7	135,118,71.7,55.0
Compound 15[d]	99.2	68.9	74.7	68.7	67.9	63.1	134.6,117.3,70.8, 55.3

[a] Lit.[14] values for 2-O-methyl-α,β-D-glucoses in parentheses.
[b] Lit.[14] values for methyl α-D-glucopyranoside in parentheses.
[c] Lit.[15] values for compound 13 in parentheses.
[d] Acetyl 170.9, 170.5, 170.0, 20.9 ($2CH_3$), 20.8.

In the case of glucose, it appears that O-alkylation takes place by two routes on a single 1 ax., 2 eq. complex. Attack to form the 2-O-methyl derivative is favored by a steric factor and attack on O-1 to form axial glycoside presumably by an electronic factor.

It was of interest to see if substitution would be regioselective in the presence of two equatorial hydroxyl groups and one axial hydroxyl group. Thus, methyl 6-O-trityl-α-D-mannopyranoside[12] (11) was treated with dibutyltin oxide (1.1 mole) followed by reaction with methyl iodide (1.5 mole) as described above. Detritylation with acetic acid gave methyl 3-O-methyl α-D-mannopyranoside (12) in 75% yield after silica gel column chromatography ($CHCl_3$:MeOH 4:1) along with small amounts of other unidentified products. Compound 12 had $[\alpha]_D^{22}$ +57.2° (c 1.08, EtOH), +59.8° (c 0.8, $CHCl_3$). [Lit[8] $[\alpha]_D^{25}$ +59.6° (c 1.8, $CHCl_3$)]. ^1H NMR ($CDCl_3$) δ 4.77 (d, 1H, $J_{1,2}$, 1.2 Hz, H-1), 3.47, 3.35 (s, 3H each, OMe). The pronounced downfield shift of 10.3 ppm[13] exhibited by C-3 upon methylation of its hydroxyl function, and upfield shifts of C-2 (4.8 ppm) and C-4 (1.0 ppm) confirm the position of substitution on 12. (Cf. Table 1. Data for methyl α-D-mannopyranoside (13) from ref. 15).

Substitution was less complete but still regioselective in the presence of four hydroxyl groups, only one of which was axial. Thus methyl α-D-mannopyranoside (13) was treated with dibutyltin oxide (1.1 mole) followed by reaction with allyl bromide (1.5 mole) as described above. Methyl 3-O-allyl-α-D-mannopyranoside (14) was isolated in 42% yield after silica gel column chromatography ($CHCl_3$:MeOH, 4:1) together with 30% of starting material (13) and small amounts of unidentified products. Compound 14 was further purified by liquid chromatography on a silica gel column (ethyl acetate:acetone, 4:1) to afford pure 14 (37%), $[\alpha]_D^{21}$ +55.2°, (c 2.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.36-5.74 (m, 1H, $-CH=CH_2$), 5.47-5.15 (m, 2H, $-CH=CH_2$), 4.78 (s, 1H, H-1). The pronounced downfield shift of 9.5 ppm exhibited by C-3 on allylation of its hydroxyl function and upfield shifts of C-2 (3.5 ppm) and C-4 (2.3 ppm) confirm the position of substitution in compound 14. It appears that the dibutylstannylene complex of 13 is somewhat unstable and dissociates during reaction. Similar results have been reported for the dibutylstannylene complex of methyl α-D-glucopyranoside.[16] Acetylation of 14 with acetic anhydride in pyridine gave methyl 2,4,6-tri-O-acetyl-3-O-allyl-α-D-mannopyranoside (15), mp 63-64° (from ether-n-hexane), $[\alpha]_D^{23}$ +20.2° (c 0.8, $CHCl_3$), ^1H NMR ($CDCl_3$): δ 6.19-5.57 (m, 1H, $-CH=CH_2$), 5.37-5.03 (4H, H-2, H-4, $-CH=CH_2$), 4.71 (d, $J_{1,2}$, 1.2 Hz, H-1), 4.26-4.08 (3H, H-3, H-6, H-6'), 4.02 (m, 2H, $-OCH_2-CH=CH_2$), 3.80 (q, 1H, H-5), 3.36 (s, 3H, OMe), 2.10, 2.05 (s, 3H, 6H, 3OAc). Anal. Calcd for $C_{16}H_{24}O_9$: C 53.33; H, 6.71. Found: C 53.53; H 6.66.

In conclusion, the use of dibutyltin complex appears to have substantial experimental advantages over methods previously available for the synthesis of β-D-mannopyranosides and in some cases provides a method for alkylation in the presence of unprotected OH groups. (Cf. ref. 16.) The obvious extension of this reaction to more complex glycosides is under investigation.

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