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## Note

# A new approach to the synthesis and selective hydrolysis of *tert*-butyl glycosides

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Recent developments in methods of glycosylation[1,2] have aroused interest in the use of the *tert*-butyl group for the temporary protection of the hemiacetal hydroxyl group. The *tert*-butyl group is cleaved under relatively mild acidic conditions which do not affect most hydroxyl-protecting groups utilized in oligosaccharide syntheses[3,4].

The inductive effect of the *tert*-butyl substituent activates the glycosidic oxygen and Derevitskaya *et al.*[5] have taken advantage of this property to achieve an improved synthesis of octa-*O*-acetyl-β,β-trehalose. Several syntheses of *tert*-butyl glycosides using Koenigs–Knorr or Helferich conditions have been proposed based on the reaction of acylglycosyl halides with *tert*-butyl alcohol in the presence of silver oxide[6], silver salicylate[4], mercuric succinate[3], and mercuric cyanide and mercuric bromide[7].

Risbood *et al.*[3] reported the glycosidation of β-D-galactose penta-acetate by *tert*-butyl alcohol in the presence of boron trifluoride etherate.

In the above-mentioned syntheses, the yields are moderate or low, and purification may be difficult due to the presence of orthoesters of similar polarity as by-products[4].

We now describe an improved synthesis of *tert*-butyl glycosides by a Koenigs–Knorr-type reaction, using mercuric oxide (HgO) and mercuric bromide ($HgBr_2$) as catalysts, in which *tert*-butyl alcohol is both solvent and glycosylating reagent. The reaction is performed at room temperature under nitrogen in the presence of Drierite. Thus, fully acetylated α-D-glucosyl, α-D-galactosyl, and α-D-xylosyl halides were converted into the corresponding *tert*-butyl β-glycosides in yields of 80–90%. With 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide, the

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TABLE I

SELECTED $^{13}$C-N.M.R. DATA[a] AND PHYSICAL CONSTANTS FOR *tert*-BUTYL HEPTA-*O*-ACETYL DISACCHARIDE β-GLYCOSIDES

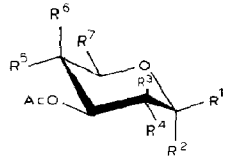
| *Compound* | *$^{13}$C-N.m.r. data[b]* | | | *M.p. (degrees)* | $[\alpha]_D^{20}$ (c *1, chloroform)* *(degrees)* | *Yield (%)* | *Elemental analysis[c]* |
|---|---|---|---|---|---|---|---|
| | *C-1β* | *C'-1* | *C-4* | | | | |
| **5** (maltose) | 95.6 | 95.1 | 75.9 | 134–135 (AcOEt–hexane) | +45 | 44 | C, 51.72; H, 6.42 |
| **6** (cellobiose) | 95.5 | 100.9 | 76.9 | 202–203 (AcOEt–hexane) | −21 | 50 | C, 51.68; H, 6.57 |
| **7** (lactose) | 95.5 | 101.2 | 77.1 | 147–149 (ether–hexane) | −10 | 48 | C, 51.84; H, 6.37 |

[a]Chemical shifts for solutions in $CHCl_3$ (internal $Me_4Si$); δ in p.p.m. [b]Primed numbers refer to the "non-reducing" carbohydrate moiety. [c]Calc. for $C_{30}H_{44}O_{18}$: C, 52.02; H, 6.35.

yield was lower (~20%).

The reaction was extended to the synthesis of disaccharide derivatives. From hepta-*O*-acetyl-α-cellobiosyl bromide, and the maltose and lactose analogues, with dichloromethane as the co-solvent, the corresponding *tert*-butyl β-glycosides (see Table I) were obtained in yields of ~50%. The products were purified easily by flash chromatography.

Analysis of the reaction of tetra-*O*-acetyl-D-galactopyranosyl bromide (acetobromogalactose) with *tert*-butyl alcohol as a model revealed ~1% each of *tert*-butyl 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranoside and octa-*O*-acetyl-β-β-*galacto*-trehalose. The latter compound resulted, presumably, from reaction of 2,3,4,6-tetra-*O*-acetyl-D-galactose with acetobromogalactose.




**1α** $R^1 = R^3 = R^5 = H, R^2 = O^tBu, R^4 = R^6 = OAc, R^7 = CH_2OAc$

**1β** $R^2 = R^3 = R^5 = H, R^1 = O^tBu, R^4 = R^6 = OAc, R^7 = CH_2OAc$

**2** $R^1 = O^tBu, R^2 = R^3 = R^6 = H, R^4 = R^5 = OAc, R^7 = CH_2OAc$

**3** $R^1 = O^tBu, R^2 = R^3 = R^6 = R^7 = H, R^4 = R^5 = OAc$

**4** $R^2 = O^tBu, R^1 = R^4 = R^6 = H, R^3 = R^5 = OAc, R^7 = CH_2OAc$

**5** $R^1 = O^tBu, R^2 = R^3 = R^6 = H, R^4 = OAc, R^7 = CH_2OAc, R^5 = \alpha\text{-D-Glc}p$

**6** $R^1 = O^tBu, R^2 = R^3 = R^6 = H, R^4 = OAc, R^7 = CH_2OAc, R^5 = \beta\text{-D-Glc}p$

**7** $R^1 = O^tBu, R^2 = R^3 = R^6 = H, R^4 = OAc, R^7 = CH_2OAc, R^5 = \beta\text{-D-Gal}p$

Confirmation of structures was based conventionally on $^1$H- and $^{13}$C-n.m.r. data. The resonances for C-1α and C-1β in the *tert*-butyl glycosides are shifted (~5 p.p.m.) as compared to the corresponding carbon atoms in methyl glycosides[8] (Table II), due to the γ-shielding effect of the three methyl groups. A similar effect was observed for the anomeric carbon of the "reducing" carbohydrate moiety of disaccharide derivatives (see Table I).

The $^1$H-n.m.r. data for the acetylated *tert*-butyl glycosides of α- and β-D-galactopyranose (**1**), α-D-mannopyranose (**4**), β-maltose (**5**), β-cellobiose (**6**), and β-lactose (**7**) derivatives, reported in Table III, accord with expectations. Particularly noteworthy is the strong deshielding effect observed in compound **1** for H-3 (+0.28 p.p.m.) and H-5 (+0.48 p.p.m.) when going from the β to the α anomer, presumably due to 1,3-syn-diaxial interactions of H-3,5 and the axial anomeric *tert*-butyl group. In addition, H-1 was deshielded by 0.76 p.p.m. with $J_{1,2}$ 3.9 and 8.3 Hz, respectively, in **1**α and **1**β.

Preliminary results showed that the *tert*-butyl group can be removed select-

TABLE II

$^{13}$C-N.M.R. DATA[a] AND PHYSICAL CONSTANTS FOR ACETYLATED *tert*-BUTYL MONOSACCHARIDE GLYCOSIDES

| *Compound* | *$^{13}$C-N.m.r. data (δ)* | | | | | | *M.p. (degrees)* | $[\alpha]_D^{20}$ (c *1, chloroform) (degrees)* | *Yield (%)* |
|---|---|---|---|---|---|---|---|---|---|
| | *C-1* | *C-2* | *C-3* | *C-4* | *C-5* | *C-6* | | | |
| Gal **1**α | 90.8 | 68.6[b] | 68.5[b] | 67.9 | 66.0 | 62.0 | 99–100 (éther–hexane)<br>lit.[3] 134 | +137<br>lit.[3] +141.4 | <1 |
| **1**β | 96.1 | 69.4 | 70.7 | 67.5 | 71.4 | 61.8 | 79–80 (éther–hexane)<br>lit.[3] 70 | −1.7<br>lit.[3] −20.8 | 82 |
| Glc **2** | 95.6 | 71.8 | 73.2 | 69.0 | 71.7 | 62.6 | 143–144 (AcOEt–ether)<br>lit.[4] 143–144 | −10.3<br>lit.[4] −13 | 85 |
| Xyl **3** | 95.8 | 71.7 | 72.3 | 69.2 | 62.2 | | 128–129 (AcOEt–ether)<br>lit.[7] 131–133 | −38.3<br>lit.[7] −43.1 | 80 |
| Man **4** | 92.4 | 71.4 | 69.3 | 66.8 | 68.2 | 62.8 | oil[c] | +35 | 20 |

[a]For solutions in $CHCl_3$ (internal $Me_4Si$); δ in p.p.m. [b]Assigments may have to be interchanged. [c]Calc. for $C_{18}H_{28}O_{10}$: C, 53.47; H, 6.93. Found: C, 53.45; H, 7.12.

TABLE III

$^1$H-N.M.R. DATA[a] ($\delta$ IN P.P.M., $J$ IN Hz) FOR *tert*-BUTYL GLYCOSIDES **1** AND **4–7**

| *Compound* | *H-1* | *H-2* | *H-3* | *H-4* | *H-5* | *H-6,6'* | *O$^t$Bu* |
|---|---|---|---|---|---|---|---|
| **1**$\alpha$ | 5.38 (d, 3.9) | 5.03 (dd, 11.2) | 5.33 (dd, 3.5) | 5.42 (dd, 1.2) | 4.38 (dd, 6.7) | 4.07,4.03 (um)[c] | 1.21 |
| **1**$\beta$ | 4.62 (d, 8.3) | 5.20 (dd, 10.9) | 5.05 (dd, 3.9) | 5.40 (dd, 1.0) | 3.9 (dd, 6.8) | 4.12 (2 H, um)[c] | 1.25 |
| **4** | 5.1 (d, 1.9) | 5.03 (dd, 3.3) | 5.37 (dd, 10.0) | 5.23 (t, 10.0) | 4.14 (m, 6.0, 2.2) | 4.26 (dd, 11.85) | 1.24 |
| | | | | | | 4.03 (dd, 11.85) | |
| ring A[b] | 4.65 (d, 8.0) | 4.75 (dd, 8.7) | 5.33 (t, 9.0) | 3.93 (t, 9.2) | 3.68 (m, 2.8) | 4.39 (dd, 12.2) | 1.20 |
| **5** | | | | | | 4.22 (2 H, um)[c] | |
| ring B[b] | 5.39 (d, 4.0) | 4.8 (dd, 10.4) | 5.26 (dd, 9.6) | 5.0 (t, 9.6) | 3.97 (um)[c] | 4.01 (1 H, um)[c] | |
| ring A | 4.57 (d, 8.0) | 4.81 (dd, 9.5) | 5.15 (dd, 9.2) | 3.67 (t, 9.2) | 3.6 (um)[c] | 4.42 (1.5, 12.4) | 1.17 |
| **6** | | | | | | 4.32 (4.4, 12.4) | |
| ring B | 4.48 (d, 7.8) | 4.92 (dd, 8.1) | 5.02 (t, 9.1) | 5.10 (t, 9.1) | 3.6 (um)[c] | 4.03 (2 H, um)[c] | |
| ring A | 4.6 (d, 8.0) | 4.82 (dd, 9.5) | 5.19 (dd, 8.9) | 3.70 (t, 9.0) | 3.6 (um)[c] | 4.40 (dd, 2.8, 11.5) | 1.19 |
| **7** | | | | | | | |
| ring B | 4.45 (d, 7.8) | 5.09 (dd, 10.4) | 4.93 (dd, 3.4) | 5.33 (dd, 1.1) | 3.86 (dt, 7.5) | 4.1 (3 H, um)[c] | |

[a]For solutions in $CHCl_3$ (internal $Me_4Si$). [b]A and B stand for reducing and non-reducing units, respectively. [c]Unresolved multiplet.

ively without extensive hydrolysis of the interglycosidic linkage. Treatment of *tert*-butyl β-lactoside hepta-acetate (**7**) with either trifluoracetic acid in $CH_2Cl_2$ at −10° or titanium tetrabromide at room temperature under nitrogen gave 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-lactose in yields (not optimized) of 68 and 75%, respectively. Likewise, the hepta-*O*-benzyl analogue of **7** could be converted into hepta-*O*-benzyl-lactose in 65% yield.

## EXPERIMENTAL

*General.* — Organic solutions were concentrated *in vacuo* at ≦40°. $^{13}$C-N.m.r. spectra were recorded at 25.2 MHz with a Bruker WP-80 spectrometer on solutions in $CHCl_3$ (internal $Me_4Si$). $^1$H-N.m.r. spectra were recorded at 250 MHz with a Bruker AC-250 spectrometer. Optical rotations were measured at 20° with a Perkin-Elmer MC-241 polarimeter. Flash chromatography was performed on Matrix Silica 35–70 NY (Amicon) and t.l.c. on Silica Gel F254 (Merck) with detection by charring with 10% sulfuric acid in ethanol. Melting points were determined on a Buchi apparatus and are not corrected. Monosaccharide glycosyl halides were prepared by a standard procedure[9]. Disaccharide glycosyl halides were obtained by reaction of peracetylated derivatives with hydrogen bromide in glacial acetic acid[10].

Elemental analyses were performed at the Service Central de Microanalyse du Centre National de la Recherche Scientifique E.N.S.C.M. (Montpellier).

*Acetylated* tert-*butyl monosaccharide glycosides* (**1–4**). — A mixture of mercuric oxide (0.508 g), mercuric bromide (0.034 g), Drierite (0.4 g), and *tert*-butyl alcohol (5 mL) was stirred for 15 min under nitrogen at 25°. The acetylated glycosyl bromide (2.5 mmol) was then added, and the suspension was stirred for 30 min until t.l.c. monitoring showed complete disappearance of the glycosyl bromide.

The mixture was diluted with $CH_2Cl_2$ and filtered through Celite, which was then washed with $CH_2Cl_2$. The combined filtrate and washings were concentrated *in vacuo* to remove *tert*-butyl alcohol, and a solution of the residue in $CH_2Cl_2$ was washed with aqueous 10% KI, water, saturated aqueous sodium thiosulfate, and water, dried ($Na_2SO_4$), and concentrated. Flash chromatography (EtOAc–hexane) of the residue afforded analytically pure *tert*-butyl glycosides. See Tables I and III for physical constants and n.m.r. data.

*Acetylated* tert-*butyl disaccharide glycosides* (**5–7**). — The above procedure was used except that dichloromethane (5 mL) was added to the initial mixture in order to dissolve the starting materials. See Tables II and III for physical constants and n.m.r. data.

*Selective removal of the* tert-*butyl group.* — *(a)* To a solution of *tert*-butyl β-lactoside hepta-acetate (**7**) (70 mg, 0.1 mmol) in $CH_2Cl_2$ (3 mL) at −10° was added trifluoroacetic acid (3 mL). When t.l.c. showed that no **7** remained, the mixture was diluted with $CH_2Cl_2$ (50 mL), washed with saturated aqueous hydrogencarbonate and water, then dried ($Na_2SO_4$), and concentrated. Column chromatography (hex-

ane–ethyl acetate) of the residue gave lactose hepta-acetate as an oil (46 mg, 65%), $[\alpha]_D^{20}$ +30.5° (*c* 1, pyridine). $^{13}$C-N.m.r. data: δ 101.1 (Gal C-1), 90.1 (Glc C-1α), and 95.2 (Glc C-1β).

The hepta-*O*-benzyl analogue of **7** was treated as above to afford the corresponding reducing sugar, $[\alpha]_D^{20}$ +15° (*c* 1, chloroform). $^{13}$C-N.m.r. data: δ 103 (Gal C-1), 91.5 (Glc C-1α), and 97.6 (Glc C-1β).

(*b*) To a solution of **7** (692 mg, 1 mmol) in $CH_2Cl_2$–EtOAc (3.3 mL, 1:0.1) at 0° under nitrogen was added titanium tetrabromide (877 mg, 2.4 mmol). The mixture was stirred for 45 min, then diluted with toluene (11 mL), acetonitrile (1.5 mL), and sodium acetate (2.6 g), stirred vigorously until clear, then filtered, and concentrated. Column chromatography (hexane–ethyl acetate) afforded lactose hepta-acetate (426 mg, 75%).

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