# Monoalkylation of Tributyltin Activated Methyl 4,6-*O*-Benzylidene-α-D-gluco- and -galactopyranosides

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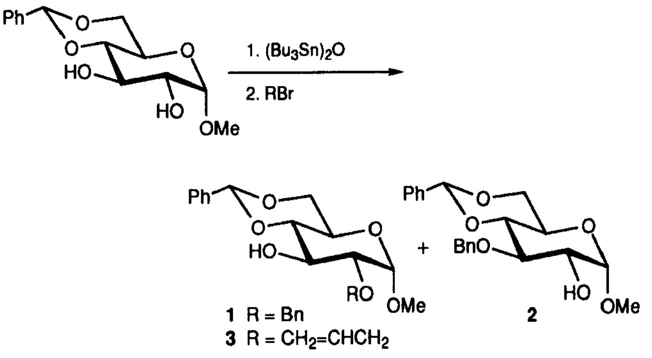
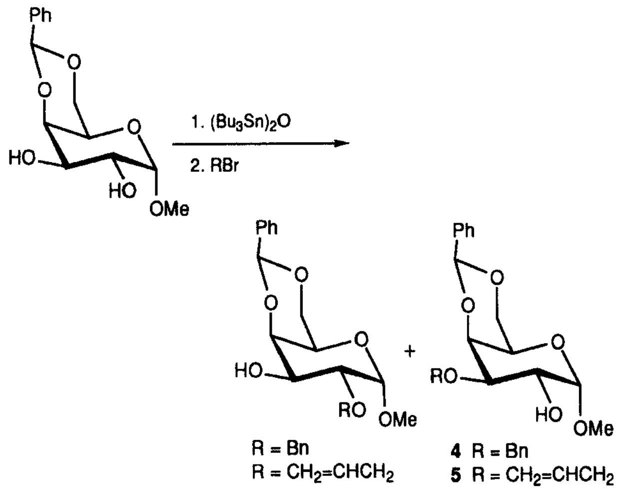
Monoalkylation of methyl 4,6-*O*-benzylidene-α-D-gluco- and galactopyranosides could be carried out in good yields using bis(tributyltin) oxide. Regioselectivity, giving predominant 2-substitution, was excellent in the case of D-glucopyranoside. The ratio of the tin reagent to that of the substrate seems to be critical in determining the yield and the extent of regioselectivity. Alkylation could also be carried out in solvents at a slower rate, using less reagent, but the regioselectivity was lower.





Partial substitution of hexopyranosides by way of activation with bis(tributyltin) oxide of hydroxyl groups to electrophilic attack has been shown useful in synthetic carbohydrate chemistry.[2,3] In partial substitution of 4,6-*O*-benzylidenehexopyranosides the relative reactivities of the 2-OH and the 3-OH groups follow the same general pattern as that observed in partial substitution by means of phase transfer catalysis (PTC). Thus, in the D-*gluco* and D-*manno* series, the 2-OH is substituted preferentially.[2-4] However, in the corresponding D-*galacto* compounds, the 3-OH is substituted preferentially upon partial substitution by means of PTC.[3,5,6]

Ogawa and Kaburagi reported that tributylstannylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside followed by alkylation with benzyl bromide in the absence of added solvent gave the 2-*O*- and 3-*O*-benzyl ethers in 59 and 40% yield, respectively.[7] We now report that the product composition in this reaction is highly dependent on reaction conditions. The corresponding tributyltin activated allylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside leading to the 2-*O*-allyl derivative (70%) is also described. Tributyltin activated benzylation and allylation of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside gave the 3-*O*-benzyl- and 3-*O*-allyl derivatives, respectively, by crystallization from the reaction mixtures.

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside was treated as described[8,9] with increasing amounts of bis(tributyltin) oxide in toluene. After removal of solvent, the tributyltin activated mixture was allowed to react with benzyl bromide. The ratio of 2-substituted (**1**) to 3-substituted (**2**) product, and also the yield of **1** (89%) reached a maximum at a molar ratio diol/bis(tributyltin) oxide of 1:1.5–2.2: The addition of toluene or dimethylformamide to the benzylation mixture substantially decreased the regioselectivity of the reaction (Table). Using the above optimum conditions for the allylation with allyl bromide of tin activated methyl 4,6-*O*-benzylidene-α-D-glucopyranoside similarly produced the 2-*O*-allyl ether **3** (75%).

Benzylation and allylation of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside gave in each instance a monoalkylated product mixture of **4** and **5** (70–80%), respectively. Careful TLC analysis using three consecutive elutions (see experimental part) of the benzoates of these showed that each reaction mixture contained ca. 1:1 mixtures of the 2- and 3-substituted ethers. Neither the monobenzyl ether mixture, nor the monoallyl mixture were amenable to preparative column separations.

The difference in the results obtained in the gluco and galacto series indicates the importance of the steric disposition of adjacent non-hydroxylic oxygens available for complex formation[8,9] in determining the site of activation in these tributyltin derivatives. Also the regioselectivity appears to depend on the ratio of the tin reagent to the substrate. (Table)

Melting points are corrected. Organic solutions, obtained after extraction and workup procedures, were dried ($MgSO_4$), and evaporated in vacuo. Optical rotations were measured in $CHCl_3$ solutions using a Perkin-Elmer model 141 polarimeter. $^1H$ and $^{13}C$NMR spectra were recorded with a JEOL GSX270 FTNMR (270 MHz) spectrometer. Decoupling was done as required to identify $^1H$ signals that could not be assigned unambiguously.

All reactions were carried out under $N_2$. Column chromatographic purifications were carried out on dry silica gel (Merck, 230–400 mesh; 75 g/g) columns. One or more of the solvent systems (v/v) toluene/EtOAc (I–V) and toluene/acetone (VI–XII) were used for chromatography purposes: I. 1:1; II. 2:1; III. 3:2; IV. 7:2; V. 9:2; VI. 3:1; VII. 8:1; VIII. 10:1; IX. 15:1; X. 20:1; XI. 30:1; XII. 40:1. Elemental analyses were carried out by Mikro Kemi AB (Uppsala, Sweden) and by Galbraith Laboratories, Knoxville, TN.

**Table.** Monoalkylation of Methyl 4,6-*O*-Benzylidene-α-D-glucopyranoside

| Entry | Mol Ratio Diol/$(Bu_3Sn)_2O$ | Solvent | T(°C)[a] | Reaction Time | Ratio[b] 2-*O*-Bn/3-*O*-Bn[c] | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | 1 : 0.5 | None | 90 | 2 d | 4 : 1 | 40 |
| 2 | 1 : 1.0 | None | 90 | 2 d | 7 : 1 | 40 |
| 3 | 1 : 1.5–2.2 | None | 90 | 2 d | 10 : 1 | > 90 |
| 4 | 1 : 1.5–2.2 | Toluene | 22–reflux | 5 d | 2–3 : 1 | 87 |
| 5 | 1 : 1.5–2.2 | DMF | 120–130 | 15–20 h | 1 : > 1[d,e] | 70 |

[a] Eight equivalents of benzyl bromide were added.

[b] After isolation of products.

[c] See experimental for physical constants.

[d] TLC observation.

[e] Two minor side products were also formed.

For new compounds satisfactory microanalyses obtained: C ± 0.3, H ± 0.09.

**Tributyltin Activated Monoalkylation of Methyl 4,6-*O*-Benzylidenehexopyranosides; General Procedure:**

The methyl 4,6-*O*-benzylidene derivative of the hexopyranoside to be reacted was dispersed in toluene (75 mL/g) contained in a suitable flask fitted with a Dean–Stark apparatus. One third of the toluene was distilled off and the required quantity of the $(Bu_3Sn)_2O$ was added (Table). More toluene (half of the remaining volume) was removed by distillation, the Dean–Stark assembly was replaced with a condenser, and the mixture was refluxed for 2–3 h. The mixture was concentrated, the syrupy residue was dried thoroughly and after the addition of the requisite quantity of the alkyl bromide, the mixture was stirred under $N_2$ at 90 °C. The syrupy product was transferred onto a dry silica gel column and eluted as noted under each individual compound.

*Methyl 2-O-Benzyl-4,6-O-benzylidene-α-D-glucopyranoside* (**1**): Method A (*Benzylation Without Solvent*): Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (0.45 g, 1.59 mmol) was dispersed in toluene (30 mL) and treated with $(Bu_3Sn)_2O$ (1.8 mL, 3.53 mmol) and benzyl bromide (4 mL, 33.6 mmol) in the manner described above. After 2 d, TLC (solvent IV) indicated the formation of a major ($R_f$ 0.43) and a minor product ($R_f$ 0.27). These were isolated by column chromatography (silica gel, 60 g) using solvent VI (60 mL) and VII as eluents. Product **1** was eluted first (0.52 g, 89 %); mp 133–134 °C ($CH_2Cl_2$/hexane); $[\alpha]_D^{22}$ + 33° (*c* = 1.4, $CHCl_3$) [Lit.[10,11] mp 131–132 °C; $[\alpha]_D$ + 35° ($CHCl_3$)].

Further elution provided methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**2**) as a syrup (0.06 g, 10 %); mp 176–177 °C ($CH_2Cl_2$/hexane); $[\alpha]_D^{22}$ + 79° (*c* = 1.2, $CHCl_3$) [Lit.[11,12] mp 187–188 °C; $[\alpha]_D$ + 78° ($CHCl_3$)].

The reaction was scaled up using methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (14 g, 49.59 mmol), $(Bu_3Sn)_2O$ (55 mL, 107.9 mmol) and benzyl bromide (35 mL, 294.35 mmol) to afford, after chromatographic purification, compound **1** (14.4 g, 78 %).

Method B (*Benzylation in Toluene*): Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (0.3 g, 1.06 mmol) was treated with $(Bu_3Sn)_2O$ (1.0 mL, 1.96 mmol) in toluene (65 mL) as described in the general procedure. After activation, benzyl bromide (0.8 mL, 6.72 mmol) was added and refluxing was continued for 5 d, at the end of which TLC (solvent IV) indicated almost complete conversion to products. Evaporation of the solvent and usual purification afforded compounds **1** (0.24 g, 60 %) and **2** (0.08 g, 27 %).

*Methyl 2-O-Allyl-4,6-O-benzylidene-α-D-glucopyranoside* (**3**): Tin activation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (2 g, 7.02 mmol) was carried out in toluene (70 mL) using $(Bu_3Sn)_2O$ (5.4 mL, 10.59 mmol) and then the mixture was treated with allyl bromide (5 mL) at 100 °C (12–16 h). The crude mixture of products, obtained in the manner described earlier, was purified by column chromatography (silica gel, 150 g) using solvents VIII (200 mL) and X (800 mL) successively as the eluents to give pure **3** (1.72 g, 75 %); mp 114–115 °C ($CH_2Cl_2$/hexane); $[\alpha]_D^{20}$ + 81° (*c* = 1.4, $CHCl_3$).

$^1$H NMR ($CDCl_3$/TMS): $\delta = 7.60–7.30$ (m, 5 $H_{arom}$), 5.95 (m, 1 H, $C\underline{H}=CH_2$), 5.55 (s, 1 H, PhCH=), 5.30 (m, 2 H, $CH=C\underline{H}_2$), 4.80 (d, 1 H, $J_{1,2} = 3.6$ Hz, H-1), 4.22 (m, 2 H, $OCH_2CH=$), 4.30 (q, 1 H, $J = 4.3$ Hz, 10 Hz, H-6), 4.11 (d of t, 1 H, $J_{2,3} = J_{3,4} = 9.3$ Hz, $J_{H,OH} = 1.7$ Hz, $D_2O$ exchange afforded a triplet $J = 9.5$ Hz, H-3), 3.85 (m, 1 H, H-5), 3.75 (t, 1 H, $J_{5,6} = J_{6,6'} = 10$ Hz, H-6'), 3.55 (t, 1 H, $J = 9.3$ Hz, H-4), 3.50–3.30 (s superimposed on a d, $J_{1,2} = 3.6$ Hz, H-2, $OCH_3$), 2.62 (d, 1 H, $J_{H,OH} = 1.8$ Hz, 3-OH, $D_2O$ exchanged).

Compound **3** (0.5 g, 1.55 mmol) was benzoylated using benzoyl chloride (excess) in pyridine. Washing the $CHCl_3$ solution of the mixture with $H_2O$, aq $NaHCO_3$ and $H_2O$ followed by multiple coevaporation of the organic layer with toluene gave a solid which was recrystallized from $CH_2Cl_2$/hexane, to afford methyl 2-*O*-allyl-3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (0.6 g, 90 %); mp 131–133 °C, $[\alpha]_D^{20}$ + 11° (*c* = 1, $CHCl_3$).

$^1$H NMR ($CDCl_3$, TMS): $\delta = 8.10–7.20$ (m, 10 $H_{arom}$), 5.89–5.21 (t superimposed on a m, 2 H, $J = 9.3$ Hz, H-3, $C\underline{H}=CH_2$), 5.50 (s, 1 H, $PhC\underline{H}=$), 5.22 (m, 2 H, $CH=C\underline{H}_2$), 4.90 (d, 1 H, $J_{1,2} = 3.6$ Hz, H-1), 3.85–3.60 (m, 4 H, signals due to H-4 and H-2 are shifted upfield and overlaps those of H-5 and H-6').

*Methyl 3-O-Benzyl-4,6-O-benzylidene-α-D-galactopyranoside* (**4**): Methyl 4,6-*O*-benzylidene-α-D-galactopyranoside (3.9 g, 13.81 mmol) in toluene (130 mL) was treated with $(Bu_3Sn)_2O$ (10.3 mL, 20.22 mmol) and benzyl bromide (13 mL, 109.33 mmol) as described in the general procedure. Column chromatography of the crude product (silica gel, 280 g) using solvent III (450 mL), solvent IV (600 mL) and then solvent II afforded a monoalkylated product mixture (4.0 g, 78 %). Two successive recrystallizations from $CH_2Cl_2$/hexane gave pure **4**, (~20 %) mp 185–186 °C, $[\alpha]_D^{20}$ + 192° (*c* = 1.28, $CHCl_3$) [Lit.[13] mp 194 °C; $[\alpha]_D^{20}$ + 186° ($CHCl_3$)].

$^1$H NMR ($CDCl_3$/TMS): $\delta = 7.60–7.25$ (m, 10 $H_{arom}$), 5.51 (s, 1 H, $PhC\underline{H}=$), 5.00 (d, 1 H, $J_{1,2} = 3.6$ Hz, H-1), 4.72 (s, 2 H, $PhC\underline{H}_2$), 4.31–4.11 (m, 3 H, H-2,5,6), 4.00 (dd, 1 H, $J = 1.9$, 12 Hz, H-6'), 3.81 (dd, 1 H, $J = 3.2$, 10 Hz, H-3), 3.62 (d, 1 H, $J = 1.1$ Hz, H-4), 3.42 (s, 3 H, $OCH_3$), 2.25 (d, $D_2O$ exchanged, 2-OH).

*Methyl 3-O-Allyl-4,6-O-benzylidene-α-D-galactopyranoside* (**5**): Monoallylation of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside (3.0 g, 10.62 mmol) was carried out in toluene (125 mL), in the manner described, using $(Bu_3Sn)_2O$ (8.1 mL, 15.89 mmol) and allyl bromide (7.3 mL 84.36 mmol). After the usual workup and column chromatography (silica gel, 200 g) and elution with solvent X (120 mL) and solvent XII the monoalkylated product mixture was obtained (1.6 g, ~ 70 %). Two recrystallizations from $CH_2Cl_2$/hexane afforded **5** (0.57 g, 25 %) mp 160–161 °C; $[\alpha]_D^{20}$ + 216° (*c* = 1.3, $CHCl_3$).

$^1$H NMR ($CDCl_3$/TMS): $\delta = 7.55–7.30$ (2 m, 5 $H_{arom}$), 5.95 (m, 1 H, $C\underline{H}=CH_2$), 5.55 (s, 1 H, $PhC\underline{H}$), 5.35–5.15 (4 m, 2 H, $CH=C\underline{H}_2$), 4.95 (d, 1 H, $J_{1,2} = 4.96$ Hz, H-1), 4.35–4.05 [m with two superimposed dd ($J = 1.7$ Hz, 12.4 Hz), 6 H, H-2,5,6,6′ and $OC\underline{H}_2CH{=}CH_2$], 3.74 (dd, 1 H, $J = 3.5$, 10 Hz, H-3), 3.66 (br d, 1 H, H-4), 3.45 (s, 3 H, $OCH_3$), 2.25 (d, 1 H, $D_2O$ exchanged, OH).

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