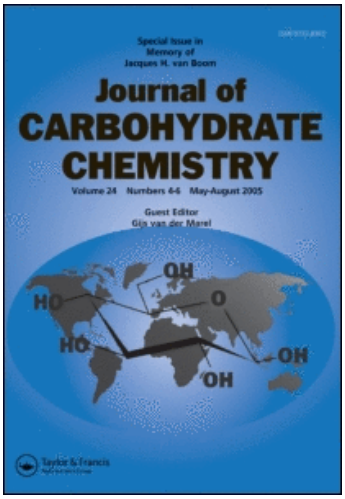

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NUCLEOPHILIC SUBSTITUTION VERSUS RADICAL REACTION FOR CARBOHYDRATES DEOXYGENATION : APPLICATION AT C-4 OF METHYL-α-D-GLUCOPYRANOSIDE DERIVATIVES

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ABSTRACT

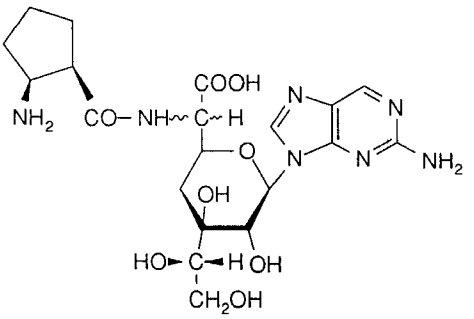
Two methods for deoxygenation at C-4 of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside are reported. The first one involves nucleophilic displacement of a secondary methane sulfonate by lithium triethylborohydride to afford methyl 2,3-di-*O*-benzyl-4-deoxy-α-D-*xylo*-hexopyranoside (**5**). Compound **5** was also obtained in similar yield (≈60%) by radical deoxygenation with tri-*n*-butyltin hydride of a thiocarbonylated derivative.

As part of an ongoing program directed towards the synthesis of Amipurimycin (**1**),[1] routine preparation of methyl 2,3-di-*O*-benzyl-4-deoxy-α-D-*xylo*-hexodialdo-1,5-pyranoside (**2**) was needed. Two routes to compound **2** from methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (**3**) have been reported.[2,3] In the first, **2** was formed together with its L-epimer.[2] In the second one, it was obtained by oxidation of **5**.[3] Although deoxygenation of glycopyranoside monotosylates with lithium aluminum hydride is usually accompanied with detosylation due to O-S bond cleavage,[4] we were able to obtain **5** from **3** in 42% yield.[3] In this case, intramolecular delivery of hydride from intermediate alkoxyaluminum hydride formed at C-6 was likely the reason for minimizing O-S cleavage. We now report more efficient preparations of **5** from readily available compound **3**.

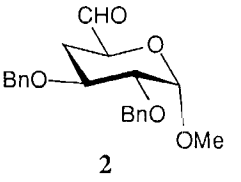
We assumed that using strongly nucleophilic lithium triethylborohydride reagent could allow clean displacement of a sulfonyl group without side reaction.[5,6]

Diol **3**[7] was converted *via* the 6-*O*-trityl derivative **6** into the known mesylate **7**[8] in 88% yield. Reaction between **7** and lithium triethylborohydride in THF solution was sluggish, presumably because of excessive steric hindrance due to the bulky protecting group at O-6. Actually, the mesylate **8** resulting from conventional detritylation (96% yield) was smoothly converted into the 4-deoxy derivative **5** in 74% yield.

Thus compound **5** was obtained from **3** in 62% yield compared to 42%.[3]



AMIPURIMYCINE



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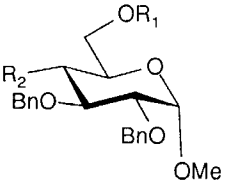

3 R_1 = H, R_2 = OH
4 R_1 = Bz, R_2 = TosO
5 R_1 = H, R_2 = H
6 R_1 = Tr, R_2 = OH
7 R_1 = Tr, R_2 = MesO
8 R_1 = H, R_2 = MesO
9a R_1 = Tr, R_2 = Ph-OC(S)O
9b R_1 = Tr, R_2 = 4-F-C_6H_4-OC(S)O
9c R_1 = Tr, R_2 = MeO-COCO-O

In an alternative approach we evaluated the radical deoxygenation of thiocarbonyl derivatives with tri-*n*-butyltin hydride (Barton-McCombie reaction[9]) which was claimed to afford good yields on carbohydrate substrates.[10] Furthermore recent work by Barton *et al.*[11] has proven the efficiency of phosphorus-centered radicals in radical chain deoxygenations, overcoming the problem of removing organotin by-products from the desired compounds.

We selected phenyl-[12] and 4-fluoro-phenyl-[13] chloro thionocarbonates together with methyl oxalyl chloride as derivatizing agents. Although not related to

thiocarbonyl series the latter reagent was successfully used for the deoxygenation of somewhat hindered tertiary alcohols.[14]

The above mentioned 6-*O*-trityl alcohol **6** was acylated with these reagents under standard conditions (4-*N*,*N*-dimethylaminopyridine as catalyst) to afford the derivatives **9a**,**b**,**c** which were subjected to radical chain deoxygenation leading to the 4-deoxy-6-*O*-trityl compound **10**.

As shown in the Table, the methyl oxalyl ester **9c** led to the desired compound with low yield together with a nearly equal amount of alcohol **6**. This behaviour - especially the amount of alcohol recovered- was rather unexpected owing to previously published results obtained from tertiary alcohols.[14] Although the derivatization step was slightly less efficient, thiocarbonyl derivatives **9a** and **9b** afforded better yields in radical chain deoxygenation. However tri-*n*-butyltin hydride as a hydrogen source proved to be superior to the phosphorus species both with respect to the yield and the reaction time.

Conventional detritylation of **10** was almost quantitative and the overall yield of **5** from **3** was very similar (64%) to that resulting from nucleophilic displacement of a tosylate by lithium triethylborohydride (*vide supra*).

On the examples studied, nucleophilic displacement of secondary methane sulfonate by lithium triethylborohydride and radical deoxygenation by tri-*n*-butyltin hydride give very similar results in terms of yield, number of steps and convenience.

EXPERIMENTAL

General methods. Melting points were determined on a Thomas-Hoover apparatus and are reported uncorrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. ^1H NMR spectra were recorded on a Bruker AC 200 spectrometer, using solutions in $CDCl_3$ (internal Me_4Si). Analytical TLC was performed on silica gel 60 F 254 followed by UV detection and by spraying with 1 M ethanolic H_2SO_4 followed by heating. For analytical TLC, the employed solvent systems were: eluent A (1:2.5 ethyl acetate - light petroleum), eluent B (1:2 chloroform - toluene), eluent C (1:4 ethyl acetate - light petroleum). Silica gel 60 (Merck, 230-400 mesh) was used for flash chromatography. Elemental analyses were performed at the "Service de Microanalyse" of the Pierre et Marie Curie University.

Methyl 2,3-di-*O*-benzyl-4-*O*-methanesulfonyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (7). Methanesulfonyl chloride (0.29 mL, 3.75 mmol) was added under stirring to a solution of **6** (1.54 g, 2.50 mmol) in dry pyridine (20 mL). After standing overnight at room temperature, the mesylation was complete. The excess of

Table. Radical deoxygenation of methyl 2,3-di-*O*-benzyl-6-*O*-triphenylmethyl-α-D-glucopyranoside derivatives.

Derivative yield (%) from **6**	Hydrogen atom source[a]	compound **10** (yield %) [c]	overall yield from **6** (%)
9a (74)	*n*-Bu_3SnH	95	70
9a (74)	H_3PO_2-Et_3N[b]	45	33
9b (79)	H_3PO_2-Et_3N[b]	84	66
9c (94)	*n*-Bu_3SnH	25[d]	23.5

a. AIBN was the initiator. b. see ref. 11. c. yield in pure **10** after column chromatography. d. alcohol **6** (20%) was also isolated.

reagent was hydrolyzed with water (1 mL, 30 min). After solvent evaporation and co-evaporation with toluene (4 x 20 mL) the residue was diluted with water (20 mL) and extracted with ether (20 mL). The organic layer was dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The crude product crystallized from ether-hexane to give **7** as white crystals (1.564 g, 90%), mp 142 °C; lit.[8] mp 143 - 144 °C.

Methyl 2,3-di-*O*-benzyl-4-*O*-methanesulfonyl-α-D-glucopyranoside (8). A solution of compound **7** (852 mg, 1.23 mmol) in acetic acid (20 mL) was diluted with water (5 mL) and heated at 70 °C for 1 h. After solvent evaporation under reduced pressure followed by co-evaporation with toluene (3 x 20 mL) the residue was purified by column chromatography (hexane/EtOAc 1:1) to give **8** as white crystals (538 mg, 96%), mp 80 °C; lit.[2] mp 83 °C.

Methyl 2,3-di-*O*-benzyl-4-deoxy-α-D-*xylo*-hexopyranoside (5). To a solution of mesylate **8** (505 mg, 1.12 mmol) in anhydrous THF (2 mL) was slowly added lithium triethylborohydride (4.5 mL of a 1 M solution in THF) under an argon atmosphere. After heating at reflux for 8 h the reaction mixture was stirred overnight at room temperature. Water (1 mL in 2 mL of THF) was carefully added with stirring. After 10 min, 12% aqueous NaOH (1.6 mL), and 30% aqueous H_2O_2 (1.6 mL) were successively added. After heating for 1 h at reflux, the mixture was allowed to cool down to room temperature and most of the THF was evaporated. The residue was diluted with water (20 mL) and extracted with diethyl ether (2 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by chromatography (1:1 hexane/EtOAc) yielded **5** as a syrup (296 mg, 74%); $[\alpha]_D$ + 78.4° (*c* 2.0, CH_2Cl_2) : lit.[3] $[\alpha]_D$ + 81.5° (*c* 2.0, CH_2Cl_2).

Methyl 2,3-di-*O*-benzyl-4-*O*-(phenoxy)-thionocarbonyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (9a). To a solution of **6** (614 mg, 0.99 mmol) and 4-*N*,*N*-dimethylaminopyridine (DMAP, 610 mg, 5 mmol) in dry acetonitrile (20 mL), phenyl-thionochlorocarbonate (0.410 mL, 3 mmol) was added with stirring. After stirring the reaction mixture overnight and heating at 50 °C for 8 h, the esterification was complete. The mixture was treated with 5% aqueous $NaHCO_3$ (10 mL) and stirred for 30 min. The solvent was evaporated, water (10 mL) was added and the mixture extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (3.5:1 toluene/$CHCl_3$) to give **9a** as crystals (556 mg, 74%) mp 158 °C; R_f 0.35 (eluent B); $[\alpha]_D$ + 21.1° (*c* 1.0, $CHCl_3$); ^1H NMR δ 7.22 - 7.49 (m, 30 H, 6 Ph), 5.47 (dd, 1 H, $J_{3,4}$ = 9.1 and $J_{4,5}$ = 10.3 Hz, H-4), 4.84 (AB, 2H, J_{AB} = 11.2 Hz, OCH_2Ph), 4.78 (AB, 1H, J_{AB} = 12.0 Hz, OCH_2Ph), 4.74 (d, 1 H, $J_{1,2}$ = 3.6 Hz, H-1), 4.13 (dd, 1 H, $J_{2,3}$ = 9.6 Hz, H-3), 4.09 (m, 1 H, H-5), 3.67 (dd, 1 H, H-2), 3.55 (s, 3 H, OCH_3), 3.24 (m, 2 H, H-6, H-6').

Anal. Calcd for $C_{47}H_{44}O_7S$: C, 74.98; H, 5.89. Found: C, 74.68; H, 5.85.

Methyl 2,3-di-*O*-benzyl-4-deoxy-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranoside (10). Method A) A solution of **9a** (580 mg, 0.77 mmol), AIBN (25 mg, 0.15 mmol) and *n*-Bu_3SnH (350 mg, 1.20 mmol) in toluene (10 mL) was heated at 80 °C for 45 min under argon. After evaporation of the solvent the residue was purified by flash chromatography (hexane/EtOAc 7:1) to give **10** as a syrup (441 mg, 95 %): R_f 0.24 (eluent B); $[\alpha]_D$ +14,6° (*c* 1.0, $CHCl_3$); ^1H NMR δ 7.21-7.47 (m, 25 H, 5 Ph), 4.62-4.79 (m, 5 H, 2 OCH_2 Ph, H-1), 3.80-3.98 (m, 2 H, H-3, H-5), 3.46 (dd, 1 H, $J_{1,2}$ = 3.6 and $J_{2,3}$ = 9.4 Hz, H-2), 3.41 (s, 3 H, OCH_3) , 3.19 (dd, 1 H, $J_{5,6}$ = 6.1 and $J_{6,6'}$ = 9.6 Hz, H-6), 3.00 (dd, 1 H, $J_{5,6'}$ = 4.6 Hz, H-6'), 2.04 (ddd, 1 H, J = 1.8, 4.8 and $J_{4a,4e}$ = 12.4 Hz, H-4e), 1.40 (ddd, 1 H, H-4a).

Anal. Calcd for $C_{40}H_{40}O_5$: C, 79.97; H, 6.71. Found: C, 79.90; H, 6.81.

Method B) Hypophosphorous acid (0.22 mL of a 50 % by weight aqueous solution, 2.1 mmol) was dried upon azeotropic distillation with anhydrous dioxane (5 x 1 mL). Under argon the residue was diluted with dioxane (5 mL) and triethylamine (0.66 mL, 4.7 mmol) and **9a** (325 mg, 0.43 mmol) were added. The resulting solution was heated under reflux. Every 30 min 0.10 mL of a solution of AIBN (70 mg, 0.43 mmol) in dry dioxane (1.0 mL) was added (six additions were necessary). After concentration and dilution of the residue with water (10 mL) it was extracted with ether (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by column chromatography (hexane/EtOAc 7:1) yielded **10** (118 mg, 45 %).

Methyl 2,3-di-*O*-benzyl-4-*O*-(*p*-fluorophenoxy)-thionocarbonyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (9b). According to the procedure described for the preparation of **9a**, a solution of **6** (308 mg, 0,50 mmol) and DMAP (153 mg, 1.25 mmol) in dry acetonitrile (5 mL) was treated with *p*-fluorophenyl-thionochlorocarbonate (105 μL, 0.75 mmol). After stirring at 50 °C for 1 day and usual work-up, the crude product was purified by column chromatography (hexane/EtOAc 6:1) to give **9b** as crystals (303 mg, 79 %): mp 166 °C; R_f 0.33 (eluent C); $[\alpha]_D$ + 21,4° (*c* 1.0, $CHCl_3$); ^1H NMR δ 7.18 - 7.50 (m, 25 H, 5 Ph), 6.96-7.04 (m, 2 H, Ar-H), 6.54 - 6.61 (m, 2 H, Ar-H), 5.46 (dd, 1 H, $J_{3,4}$ = 9.3 and $J_{4,5}$ = 10.1 Hz, H-4), 4.84 (AB, 2H, J_{AB} = 11.0 Hz, OCH_2Ph), 4.78 (AB, 2H, J_{AB} = 12.4 Hz, OCH_2Ph), 4.74 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1), 4.13 (dd, 1 H, $J_{2,3}$ = 9.7 Hz, H-3), 4.07 (dd, 1 H, $J_{5,6}$ = 4.5 Hz, H-5), 3.68 (dd, 1 H, H-2), 3.55 (s, 3 H, OCH_3), 3.23 (m, 2 H, H-6, H-6').

Anal. Calcd for $C_{47}H_{43}FO_7S$: C, 73.24; H, 5.62. Found: C, 73.59; H, 5.60.

Methyl 2,3-di-*O*-benzyl-4-deoxy-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranoside (10) from 9b. According to the procedure described for the deoxygenation of compound **9a** (method B), **9b** (278 mg, 0.36 mmol) was reacted with H_3PO_2 (1.75 mmol) and triethylamine (0.55 mL, 3.9 mmol) in dioxane (5 mL) in the presence of AIBN. Work-up and usual purification yielded **10** (182 mg, 84 %).

Methyl 2,3-di-*O*-benzyl-4-*O*-methyloxalyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (9c). To a solution of **6** (1.54 g, 2.50 mmol) in dry pyridine (25 mL), oxalyl chloride-methyl ester (0.35 mL, 3.75 mmol) and DMAP (15 mg, 0.12 mmol) were added with stirring. The reaction was complete after 15 h at room temperature. After solvent evaporation followed by co-evaporation with toluene (3 x 30 mL), the mixture was diluted with water (20 mL) and extracted with ether (2 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give **9c** as a syrup (1.647 g, 94 %): R_f 0.26 (eluent A); $[\alpha]_D$ + 26° (*c* 1.05, $CHCl_3$); ^1H NMR δ 7.19-7.45 (m, 25 H, 5 Ph), 5.20 (dd, 1 H, $J_{3,4}$ = 9.4 and $J_{4,5}$ = 10.1 Hz, H-4), 4.80 (AB, 2H, J_{AB} = 12.0 Hz, OCH_2Ph), 4.78 (AB, 2H, J_{AB} = 11.4 Hz, OCH_2Ph), 4.71 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1) 4.02 (dd, 1 H, $J_{2,3}$ = 9.5 Hz, H-3), 3.92 (ddd, 1 H, $J_{5,6}$ = 2.6 and $J_{5,6'}$ = 4.5 Hz, H-5), 3.76 (s, 3 H, OCH_3), 3.69 (dd, 1 H, H-2), 3.46 (s, 3 H, OCH_3), 3.24 (dd, 1 H, $J_{6,6'}$ = 10.4 Hz, H-6), 3.08 (dd, 1 H, H-6').

Anal. Calcd for $C_{43}H_{42}O_9$: C, 73.49; H, 6.02. Found: C, 73.40; H, 6.07.

Radical chain deoxygenation of compound (9c). A solution of **9c** (703 mg, 1.00 mmol), *n*-Bu_3SnH (580 mg, 2.00 mmol) and AIBN (100 mg, 0.60 mmol) in toluene (7 mL) was heated at reflux under an argon atmosphere. After 5 h no starting material was detected, TLC showing the formation of **10** accompanied by side-products. After concentration *in vacuo* the mixture was separated by column chromatography. Elution

with hexane/EtOAc (7:1) afforded **10** as a syrup (153 mg, 25 %). Further elution with hexane/EtOAc (5:1) afforded **6** (122 mg, 20%) which was identified by comparison with an authentic sample.

Methyl 2,3 di-*O*-benzyl-4-deoxy-α-D-*xylo*-hexopyranoside (5). A solution of **10** (435 mg, 0.72 mmol) in acetic acid (16 mL) was diluted with water (4 mL) with stirring and then heated at 70 °C for 30 min. After evaporation of the solvent and co-evaporation with toluene (4 x 20 mL), the residue was chromatographed on silica gel (1:1.5 hexane/EtOAc) to give **5** as a syrup (242 mg, 93 %); $[\alpha]_D$ +83.8° (*c* 2.0, CH_2Cl_2); lit.[3] $[\alpha]_D$ +81.5° (*c* 2.0, CH_2Cl_2).

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