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Note

Deprotection of *p*-methoxyphenyl pyranosides by anodic oxidation

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Chemical synthesis of oligosaccharides requires the selective protection and deprotection of various carbohydrate hydroxyl groups. To achieve selectivity in removal of protecting groups, a wide armamentarium of deprotection conditions has been developed. For example, those groups that may be oxidatively removed, such as *p*-methoxyphenyl (PMP) [1,2] and *p*-methoxybenzyl (PMB) [2], are frequently used in carbohydrate synthesis. Generally, chemical oxidation with ceric ammonium nitrate [1–4] is effective for their removal. However, there have been instances in which ceric ammonium nitrate, as well as other chemical oxidation methods, were ineffective in removing the PMP or PMB protecting group [5–7]. (Attempted removal of the PMP group from compounds **1**, **2**, **7** and **8** with CAN or by other chemical oxidations [7] were unsuccessful.) This note describes an electrochemical method [8] for the efficient removal of the PMP group from the anomeric position of various pyranoses. This method has been successful in several cases where chemical procedures have failed [6].

Removal of the PMP group of compounds **1–8** was accomplished by anodic oxidation of the PMP-glycosides at +1.55 V in aqueous acetonitrile to produce the reducing sugars in ≥ 74% yields (Table 1). Conversion of the resulting reducing sugar to the glycosyl fluoride may be accomplished without purification (Entry C). Thus, the crude product from compound **3** was readily converted, by treatment with DAST, into the corresponding glucosyl fluoride [9]. Entry H shows that this methodology can easily be used on > 0.100 mmol scale reactions.

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The requisite PMP-protected pyranoses, (*p*-methoxyphenyl) 2,3,4,6-tetra-*O*-acetyl-α-D-manno-, gluco-, or galacto-pyranosides (**1**,**3**,**5**) [1], were prepared by triflic acid-promoted glycosylation of *p*-methoxyphenol with the 1,2,3,4,6-penta-*O*-acetyl-α-D-manno-, gluco-, or galacto-pyranoses. The resulting acetylated pyranosides were either used directly or deacylated and benzylated to produce (*p*-methoxyphenyl) 2,3,4,6-tetra-*O*-benzyl-α-D-manno-, gluco-, or galacto-pyranosides (**2**,**4**,**6**). The synthesis of compounds **7** and **8** will be reported as part of a larger oligosaccharide synthesis [10].

1. Experimental

General methods.—All moisture-sensitive reactions were carried out under argon. Organic extracts were dried with anhydrous $MgSO_4$. Solvents were removed in vacuo on a Büchi rotary evaporator. Solvents and reagents obtained from commercial sources were used without further purification except the following were freshly distilled prior to

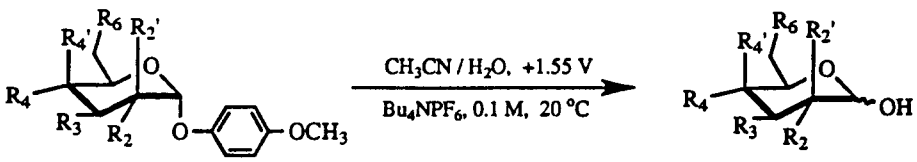
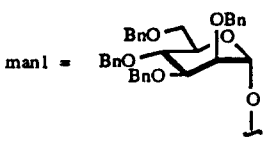
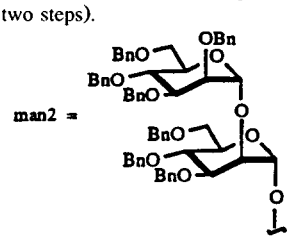


Table 1
Anodic oxidation of PMP glycosides

Entry	Compound	Pyranose	ROPMP (mmol)	R_2	$R_{2'}$	R_3	R_4	$R_{4'}$	R_6	Time (h)	Yield (%)
A	**1**	mannose	0.009	H	OAc	OAc	OAc	H	OAc	4	87
B	**2**	mannose	0.006	H	OBn	OBn	OBn	H	OBn	4	92
C	**3**	glucose	0.009	OAc	H	OAc	OAc	H	OAc	4	[a]
D	**4**	glucose	0.009	OBn	H	OBn	OBn	H	OBn	4	74
E	**5**	galactose	0.009	OAc	H	OAc	H	OAc	OAc	8	78
F	**6**	galactose	0.011	OBn	H	OBn	H	OBn	OBn	4	74
G	**7**	mannose	0.003	H	OBn	OBn	OBn	H	man1	3	100
H	**7**	mannose	0.139	H	OBn	OBn	OBn	H	man1	72	74
I	**8**	mannose	0.003	H	OBn	OBn	OBn	H	man2	3	78
J	**8**	mannose	0.015	H	OBn	OBn	OBn	H	man2	12	76

[a] The reducing sugar was fluorinated directly using DAST–THF, −30 to 22°C, to produce 2,3,4,6-tetra-*O*-acetyl-α,β-D-glucopyranosyl fluoride [9] (61% yield over two steps).





use: benzyl bromide, *N*,*N*-dimethylformamide, MeCN (from CaH_2) and tetrahydrofuran (from sodium–benzophenone). Reactions were monitored by TLC on Baker glass-backed silica gel plates (0.25 μm thickness) with a 254-nm fluorescent indicator. The chromatograms were visualized by dipping in an ethanolic solution of 2.5% *p*-anisaldehyde, 3.5% H_2SO_4, and 1% HOAc followed by heating. Purifications were performed either by flash chromatography on Baker silica gel (40 μm), or by preparative TLC. NMR data were obtained on a Bruker AM-300 FT NMR spectrometer and Me_4Si (0.03%) was used as an internal standard for all ^1H NMR spectra ($CDCl_3$). An EG&G Model 174A polarographic analyzer was used as the potentiostat and the Pt (98 cm^2) electrodes were rinsed with concd HNO_3 followed by H_2O prior to use.

p-*Methoxyphenyl 2,3,4,6-tetra*-O-*benzyl*-α-D-*mannopyranoside* (**2**).—*p*-Methoxyphenyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**1**, 100 mg, 0.22 mmol) [1] was dissolved in 20 mL of 10:1 MeOH–H_2O and Dowex 1-X2 resin in the hydroxide form (2 g) was added. The suspension was stirred for 24 h at 22°C. When TLC (7:1 $CHCl_3$–MeOH, $R_f = 0.32$) showed that the reaction was complete, the resin was removed by filtration and washed with MeOH (5 × 10 mL). The filtrate was concentrated and the white powder, crude *p*-methoxyphenyl D-mannopyranoside [1] (45 mg, 0.156 mmol, 71% yield) was azeotropically dried by evaporation of toluene from it and then dissolved in DMF (1 mL). The suspension was cooled to 0°C and NaH (100 mg, 50% dispersion in mineral oil, 1.25 mmol) was added. After 25 min of stirring at 22°C, the suspension was again cooled to 0°C and benzyl bromide (214 mg, 0.148 mL, 1.25 mmol) was added. The reaction was monitored by TLC (1:1 hexane–ether, $R_{f\,(product)} = 0.80$) while stirring for 2 h at 22°C (protected from light by aluminum wrap). When the reaction was complete, $NaHCO_3$ (1 M, 1 mL) was added and the mixture was extracted with ether (4 × 1 mL). The combined ether layers were washed with $NaHCO_3$ (1 M, 4 × 1 mL), dried, and concentrated. Flash silica-gel chromatography using step-gradient elution was used to obtain pure product. The step-gradient procedure was as follows. The column was equilibrated with hexane; the crude sample was dissolved in 1% CH_2Cl_2–hexane and applied to the column; hexane was used to remove the unreacted benzyl bromide followed by 2:1 hexane–ether to obtain the desired product (84 mg, 0.129 mmol, 83% yield). ^1H NMR ($CDCl_3$) δ 3.78 (s, 3 H, OCH_3), 3.68–4.18 (m, 6 H), 4.48 (d, 1 H, *J* 12 Hz, CH_2Ph), 4.55 (d, 1 H, *J* 12 Hz, CH_2Ph), 4.65 (d, 1 H, *J* 12 Hz, CH_2Ph), 4.70 (Ψ, 1 H, *J* 12 Hz, CH_2Ph), 4.80 (Ψ, 1 H, *J* 12 Hz, CH_2Ph), 4.93 (d, 1 H, *J* 12 Hz, CH_2Ph), 5.50 (d, 1 H, *H*-1), 6.79 (d, 2 H, *J* 9 Hz, PMP), 6.98 (d, 2 H, *J* 9 Hz, PMP), 7.18–7.42 (m, 20 H).

p-*Methoxyphenyl 2,3,4,6-tetra*-O-*benzyl*-α-D-*glucopyranoside* (**4**).—Following the same procedure: *p*-methoxyphenyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**4**, 54 mg, 0.084 mmol, 52% yield) was produced from the *p*-methoxyphenyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside (**3**, 73 mg, 0.161 mmol). The ^1H NMR spectrum was identical to that in the literature [11].

p-*Methoxyphenyl 2,3,4,6-tetra*-O-*benzyl*-α-D-*galactopyranoside* (**6**).—Compound **6** (48 mg, 0.075 mmol, 31% yield) was produced from *p*-methoxyphenyl 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranoside (**5**, 110 mg, 0.242 mmol). ^1H NMR ($CDCl_3$) δ 3.55 (m, 2 H), 3.76 (s, 3 H, OCH_3), 4.05 (m, 1 H), 4.15 (m, 3 H), 4.34 (d, 1 H, *J* 11.65 Hz, CH_2Ph), 4.40 (d, 1 H, *J* 11.70 Hz, CH_2Ph), 4.59 (d, 1 H, *J* 11.40 Hz, CH_2Ph), 4.71

(d, 1 H, *J* 11.90 Hz, CH_2Ph), 4.79 (d, 1 H, *J* 11.65 Hz, CH_2Ph), 4.84 (d, 1 H, *J* 11.90 Hz, CH_2Ph), 4.90 (d, 1 H, *J* 11.70 Hz, CH_2Ph), 4.98 (d, 1 H, *J* 11.40 Hz, CH_2Ph), 5.38 (d, 1 H, *J* 3.13 Hz, *H*-1), 6.75 (d, 2 H, *J* 9 Hz, PMP), 7.03 (d, 2 H, *J* 9 Hz, PMP), 7.19–7.44 (m, 20 H).

Electrochemical oxidation procedure.—The reaction vessel used for this system was simply a beaker equipped with a Ag/AgCl reference electrode and two Pt electrodes separated by a porous glass plate. In a typical procedure, the PMP-protected pyranose **2** (4 mg, 0.006 mmol) was dissolved in 19:1 MeCN–H_2O (60 mL) with tetrabutylammonium hexafluorophosphate (Bu_4NPF_6, 0.1 M, 2.3 g) as the electrolyte. The solution was stirred at 20°C as a voltage of +1.55 V was applied. The progress of the reaction was monitored by TLC (1:1 hexane–ether, $R_{f(\text{product})} = 0.29$). (The time required for complete reaction varied according to several factors, including amount of substrate, electrolyte concentration, and electrode surface area. The reaction times necessary under the conditions described here are presented in Table 1. In principle, the reaction times for larger samples could be decreased by utilizing larger electrodes.) When the reaction was complete, the solution was transferred to a round-bottomed flask, concentrated by rotary evaporation, $NaHCO_3$ (1 M, ~ 50 mL) then added, and the mixture was extracted with ether (3 × 50 mL). The white precipitate, Bu_4NPF_6, was recollected by filtration for future use. The combined ether layers were dried, filtered, and concentrated. The reducing sugar was purified by preparative TLC {1:1 hexane–ether, 92% yield [where the yields in the table are lower (e.g. Entries D, F, and H; 74% each), the remaining mass balance was made up of some unreacted starting material as well as traces of other unidentified oxidation products]}. The same procedure was followed for the deprotection of compounds **1** and **3–8**. The ^{1}H NMR spectra for the products from compounds **1**, **4** and **5** were identical to literature spectra [12,13]. The ^{1}H NMR spectra for the deprotected pyranose derived from compounds **2** and **6** were identical to those of authentic samples (Toronto Research Chemicals, Inc., Ontario, Canada).

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