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Regioselective Deprotection of *p*-Methoxybenzyl Ethers of Furanose Derivatives

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Abstract: *Reaction of per-p-methoxybenzylated hexofuranoses and pentofuranoses with either a catalytic amount of tin chloride dihydrate ($SnCl_2 \bullet 2H_2O$) or 0.5-10% solution of trifluoroacetic acid in dichloromethane afforded regioselectively the corresponding monosaccharide derivatives having a single free hydroxyl group at C(5) in good yields.* © 1999 Elsevier Science Ltd. All rights reserved.

In carbohydrate chemistry, multistep protection and deprotection strategies are often required to furnish monosaccharide derivatives having only one free hydroxyl group.[2] Regioselective deprotection of pyranose derivatives has been extensively studied.[3] For example, selective de-*O*-benzylation has been achieved using both protic[4] or Lewis acids.[5] In addition, reductive cleavage of acetals and ketals with hydrides[6] or Lewis acids[7] furnishes hydroxy alkyl ethers. On the other hand, few examples have described the regioselective deprotection of furanose derivatives. These include de-*O*-benzylation[8] and deacylation[9] of the hydroxyl group on C(2).

We recently reported that the use of EtSH and catalytic amounts of Lewis acids, such as $AlCl_3$ and $SnCl_2 \bullet 2H_2O$, cleaves efficiently and selectively the *p*-methoxybenzyl (PMB) ether in the presence of other protecting groups including benzyl ether.[10] We now report that the application of these mild conditions to per-*p*-methoxybenzylated sugars having furanose skeletons can regioselectively afford the corresponding monosaccharides with free 5-OH in high yields. For example, treatment of 3-*O*-benzyl-1,2-*O*-isopropylidene-5,6-di-*O*-*p*-methoxybenzyl-α-D-glucofuranose (**1**)[11] with EtSH (4 equiv) and catalytic $SnCl_2 \bullet 2H_2O$ (0.2 equiv) in dichloromethane at room temperature for 2 hours gave secondary alcohol **2**[12,13] in 70% yield contaminated with small amounts of primary alcohol **3** (7%) and vicinal diol **4** (5%, Scheme 1). Similarly, we found that the PMB ether at C(5) could be selectively cleaved with a 0.5% solution of TFA in CH_2Cl_2 to afford alcohol **2** in 75% yield.[14] On the contrary, selective deprotection of PMB ether was not observed when **1** was treated with ceric ammonium nitrate (CAN) [15] or 1,2-dichloro-4,5-dicyanoquinone (DDQ)[16] and equal mixtures of **2** and **3** were accompanied by substantial amounts of diol.

The presence of an alkoxy group at C(3) was not essential for regioselective deprotection of 5-OH and treatment of 3-*O*-deoxyfuranose **5**[17] with $SnCl_2 \bullet 2H_2O$-EtSH or with a 0.5% solution of TFA in CH_2Cl_2 gave respectively secondary alcohol **6** in 72% yield and 81% yield. Primary alcohol **7** and diol **8** were obtained in less than 10% total yield. Regioselective deprotection of 5-OH was also observed when furanose **9**,[18] bearing two PMB ether groups at C(5) and C(3) on treatement with $SnCl_2 \bullet 2H_2O$-EtSH or a 0.5% solution of TFA, alcohol **10** was isolated in 81% and 88% yield, respectively, accompanied by 3-7% of 3-OH derivative **11** and diol **12**. Interestingly, treatment of the tri-*p*-methoxybenzylated hexofuranose **13**[11] under the same conditions (0.5% TFA) led selectively to the 5-OH derivative **14** in 80% yield accompanied by 5% of primary alcohol **15**.

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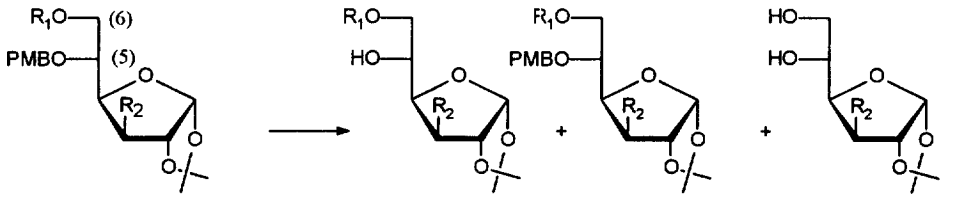
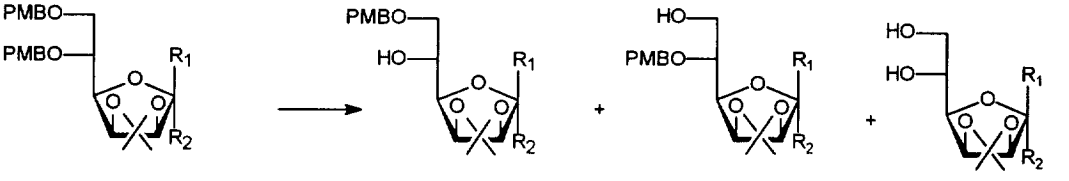
Scheme 1



1 R_1 = PMB, R_2 = OBn	**2** R_1 = PMB, R_2 = OBn	**3** R_1 = H, R_2 = OBn	**4** R_2 = OBn
$SnCl_2 \cdot 2H_2O$ (0.2 equiv), EtSH, CH_2Cl_2	70%	7%	5%
CF_3COOH (0.5%), CH_2Cl_2	75%	6%	5%
5 R_1 = PMB, R_2 = H	**6** R_1 = PMB, R_2 = H	**7** R_1 = H, R_2 = H	**8** R_2 = H
$SnCl_2 \cdot 2H_2O$ (0.2 equiv), EtSH, CH_2Cl_2	72%	5%	3%
CF_3COOH (0.5%), CH_2Cl_2	81%	7%	3%
9 R_1 = Bn, R_2 = OPMB	**10** R_1 = Bn, R_2 = OPMB	**11** R_1 = Bn, R_2 = OH	**12** R_1 = H, R_2 = OH
$SnCl_2 \cdot 2H_2O$ (0.2 equiv), EtSH, CH_2Cl_2	81%	3%	7%
CF_3COOH (0.5%), CH_2Cl_2	88%	5%	3%
13 R_1 = PMB, R_2 = OPMB	**14** R_1 = PMB, R_2 = OPMB	**15** R_1 = H, R_2 = OPMB	-
CF_3COOH (0.5%), CH_2Cl_2	80%	5%	

Regioselective PMB ether cleavage with TFA was also accomplished with mannose derivatives and both anomeric allyloxy furanosides **16**[19] and **20**[19] gave the same cleavage pattern, liberating the 5-hydroxy derivatives **17** and **21** in 75% and 71% yield, respectively (Scheme 2). The 6-OH derivatives **18** and **22** were isolated in less than 7-10% yield and diols **19** and **23** in 5-8% yield.

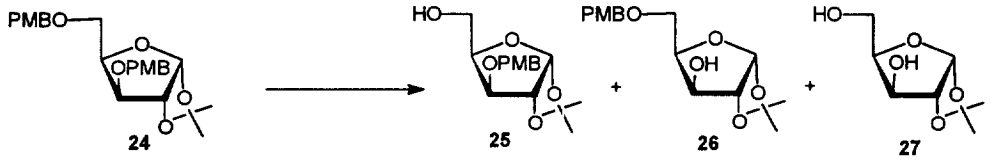
Scheme 2



16 R_1 = H, R_2 = OAll	**17** R_1 = H, R_2 = OAll	**18** R_1 = H, R_2 = OAll	**19** R_1 = H, R_2 = OAll
CF_3COOH (0.5%), CH_2Cl_2	75%	7%	5%
20 R_1 = OAll, R_2 = H	**21** R_1 = OAll, R_2 = H	**22** R_1 = OAll, R_2 = H	**23** R_1 = OAll, R_2 = H
CF_3COOH (0.5%), CH_2Cl_2	71%	10%	8%

Pentofuranoses were also regioselectively deprotected by using larger amounts of acid. For example, treatment of 1,2-isopropylidene-3,5-di-*O*-*p*-methoxybenzyl-D-xylofuranose **24**[11] with 0.2 equiv of $SnCl_2 \cdot 2H_2O$ or with 0.5% of TFA gave mostly recoverred starting material after 3 h (Scheme 3). Alcohols **25** and **26** were produced with moderate selectivity and good conversion using 0.8 equiv of $SnCl_2 \cdot 2H_2O$ or 4% of TFA in CH_2Cl_2. Diol **27** could not be isolated due to its high solubility in water during the work up.

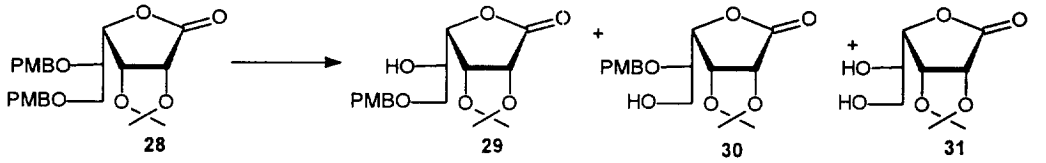
Scheme 3



$SnCl_2 \cdot 2H_2O$ (0.8 equiv), EtSH, CH_2Cl_2	56%	15%	-
TFA (4%), CH_2Cl_2	61%	17%	-

In light of these results, the selective cleavage of PMB ether at O(5) could be explained by a chelation of Sn^{2+} or H^+ by the basic oxygen atom on the furanic ring and the PMB ether oxygen followed by the cleavage of the O(5)-PMB bond to give the 5-OH derivative.[20] This hypothesis was supported by the lack of regioselectivity observed in the case the L-mannonic-γ-lactone **28** (Scheme 4) where the furanic oxygen atom is much less basic. The treatment of the hexonolactone **28** with 1 equiv of $SnCl_2 \cdot 2H_2O$ or with 10% of TFA led to an equal mixture of **29** and **30** accompanied with the diol **31**.

Scheme 4



$SnCl_2 \cdot 2H_2O$ (1 equiv), EtSH, CH_2Cl_2	17%	22%	19%
TFA (10%), CH_2Cl_2	26%	25%	22%

In conclusion, full *p*-methoxybenzylation regioselective de-*O*-*p*-methoxybenzylation sequence[21] is an efficient method to access the free 5-OH derivatives of furanoside systems.

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11. The PMB ethers **1, 5, 13, 16, 20** and **24** were prepared by treatment of the parent diols and triol with NaH and PMBCl in DMF. PMB ether **28** was prepared by treatment of the parent diol with Ag_2O and PMBCl in toluene at a reflux.
12. The structures of **2** and **3** were identified by ^{13}C-NMR and 2D-COSY. For **2**, the signals of C(5) and C(6) were respectively found at 68.0 and 72.4 ppm, whereas for **3**, C(5) and C(6) were found at 75.5 and 62.2 ppm. The 5-OH hexofuranose derivatives **2, 6, 10, 14, 17** and **21**, all were oxidized with pyridinium chlorochromate in dichloromethane to their corresponding ketones and no aldehyde proton was detected in the ^{1}H NMR spectra. Oxidation of the 5-OH pentofuranose derivative **25** under the same conditions gave the corresponding aldehyde (δ 9.5 ppm).
13. $[\alpha]_D^{23}$ values of the 5-OH derivatives: **2** $[\alpha]_D^{23}$ -30.2 (*c* = 1, $CHCl_3$), **6** $[\alpha]_D^{23}$ - 6.5 (*c* = 1, $CHCl_3$), **10** $[\alpha]_D^{23}$ -30.6 (*c* = 2, $CHCl_3$), **14** $[\alpha]_D^{23}$ -15.8 (*c* = 5, $CHCl_3$), **17** $[\alpha]_D^{23}$ + 48.8 (*c* = 1.5, $CHCl_3$), **21** $[\alpha]_D^{23}$ - 31.0 (*c* = 0.1, $CHCl_3$), **25** $[\alpha]_D^{23}$ -58.0 (*c* = 2, $CHCl_3$).
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18. Compound **9** was prepared in three steps from diacetone-D-glucose 1) 70% AcOH, 91% 2) i) Bu_2SnO, toluene, ii) BnBr, CsF, DMF, 78% 3) NaH, PMBCl, DMF, 92%.
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20. The demonstration that the configuration at C5 of **2** was maintained is clearly established by the fact that product **2** was converted to 1,2-*O*-isopropylidene-α-D-glucofuranose by hydrogenation using 5% Pd/C and comparison with an authentic sample and its commercial epimer.
21. Typical procedure: To a solution of **1** (155 mg, 0.28 mmol) in CH_2Cl_2 (10 mL) was added TFA (0.05 mL, 0.5 mmol) or $SnCl_2 \cdot 2H_2O$ (12.6 mg, 0.05 mmol) and EtSH (74.0 μL, 1.0 mmol). The reaction was stirred at room temperature for 1-2 h then quenched with saturated aqueous $NaHCO_3$ solution. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash chromatography with EtOAc/Hexanes (20/80) as eluent afforded **2**, **3** and **4** in 75%, 6% and 5% yield (or 70%, 7% and 5% yield). All compounds were characterized by ^{1}H, ^{13}C, 2D-NMR, IR and HRMS.