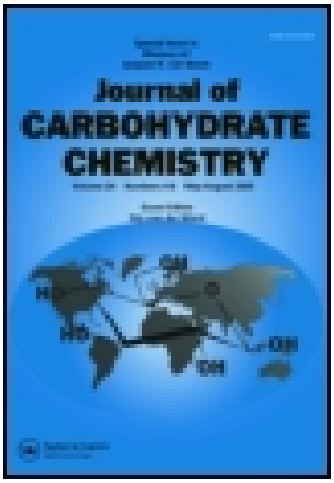

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Novel Selectivity in Carbohydrate Reactions III. Selective Deprotection of p-Methoxybenzyl (PMBn) Ethers of Carbohydrates by Tin(IV)Chloride

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COMMUNICATION

NOVEL SELECTIVITY IN CARBOHYDRATE REACTIONS III. SELECTIVE DEPROTECTION OF *p*-METHOXYBENZYL (PMBn) ETHERS OF CARBOHYDRATES BY TIN(IV)CHLORIDE[1]

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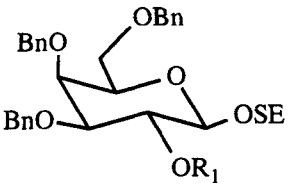
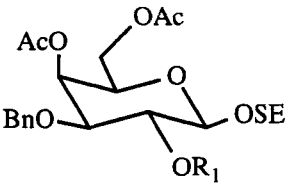
In multi-step syntheses involving polyhydroxylated natural products such as carbohydrates that are variously derivatized at different positions, orthogonal removal of one or another type of protecting group is of vital importance. Discrimination of different classes of protecting groups, such as ethers, esters, etc., is often possible with a great degree of success, as for example, selective removal of an *O*-acetyl by catalytic transesterification in the presence of an ether protecting group, or hydrogenolytic removal of a benzyl ether protection in the presence of ester groups such as acetates.[3] Differentiation of different types of protecting groups within a given class of protecting groups has also been similarly achieved with great success, as for example, hydrogenolytic removal of a benzyl ether group in the presence of a methyl ether.[3] However, the situation becomes more challenging when the same protecting group is used to mask more than one position in a polyfunctional molecule and their preferential partial deprotection is required. Selective unmasking of one or more of such protecting groups has been achieved in some cases.[4] Of particular interest to us was the regioselective deprotection of the 2-*O*-benzyl group of per-*O*-benzylated 1,6-anhydromannopyranose mediated by $SnCl_4$ (**1**) and $TiCl_4$ (**2**). Considering the greater susceptibility of *p*-methoxybenzyl (PMBn) ethers to Lewis acid catalysts[5] and the complexation of benzyl ethers with **1**[4b] and **2**[4b,6] we decided to

investigate the action of **1** on PMBn ethers of some carbohydrates. We expected the methoxy substituent on the phenyl group in the PMBn moiety to enhance complexation with **1**, possibly resulting in a facile reaction under mild conditions. Since **1** is a strong Lewis acid, the need to use chlorotrimethylsilane and anisole, as in the tin(II)chloride-chlorotrimethylsilane-anisole system for deprotection of PMBn ethers, can be eliminated. Moreover, the complex formation in the case of **1** presents possibilities for unusual regioselectivity in partial de-*O*-*p*-methoxybenzylation reactions, a problem that has not been addressed in reports on the oxidative cleavage of PMBn ethers by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[7] ceric ammonium nitrate (CAN),[8] *N*-bromosuccinimide (NBS)[8] or bromine.[8]

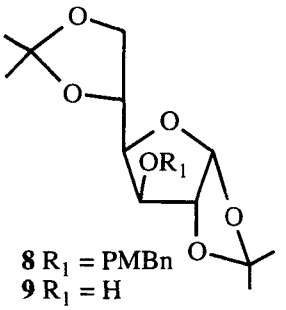
As benzyl ethers are shown to be susceptible to **1** from the work of Hori and coworkers,[4b] the first compound we examined was the mono-*O*-PMBn ether derivative **3** containing a Lewis/protic acid-sensitive group at the anomeric centre[9] and benzyl ether protection at the 3-*O*-, 4-*O*- and 6-*O*- positions. This compound, after deprotection of the PMBn group, served as a valuable intermediate in the synthesis of oligosaccharide fragments corresponding to the Type II Group B *Streptococcal* polysaccharide antigen.[10]



3 R_1 = PMBn
4 R_1 = H
5 R_1 = Ac



6 R_1 = PMBn
7 R_1 = H



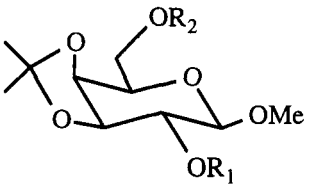
8 R_1 = PMBn
9 R_1 = H

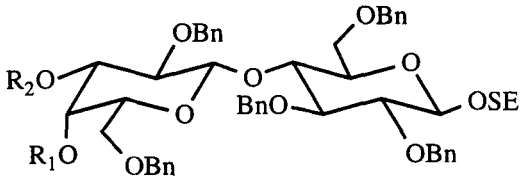
SE = 2-(trimethylsilyl)ethyl

Indeed, treatment of **3** with **1** (0.1 mol equiv) in dichloromethane (DCM) at 20 °C for 5-8 min followed by an aqueous work up and flash chromatography, gave a product **4** in 95% yield. The structure of **4** was confirmed by NMR. The signals corresponding to the PMBn group [cf. compound **3**, ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3H, OC*H*3); ^{13}C NMR ($CDCl_3$) δ 55.24, O*C*H3] were absent in the NMR spectrum of **4**. Importantly the benzyl groups [^{1}H NMR ($CDCl_3$) δ 4.40-5.00 (2d and 2q, 6H, C*H*2Ph)] and the 2-(trimethylsilyl)ethyl group [^{1}H NMR ($CDCl_3$) δ 0.02 (s, 9H, SiMe3), 1.02 (m, 2H, C*H*2SiMe3)] were unaffected. The structure of **4** was further confirmed by conversion to its crystalline mono-*O*-acetyl derivative **5** [mp 66-68 °C; ^{1}H NMR ($CDCl_3$) δ 5.42 (dd, 1H, $J_{1,2}$ = 8.1 Hz and $J_{2,3}$ = 9.8 Hz, H-2), 2.10 (s, 3H, OAc); Anal. Calcd for

$C_{34}H_{44}O_7Si$ (592.803): C, 68.89, H, 7.48; Found: C, 68.96, H, 7.52] by treatment with acetic anhydride in pyridine. When the reaction was extended to **6**,[11] which is also a valuable intermediate in the above oligosaccharide synthesis, **7**[10,11] could be isolated in 95% yield. Acetyl groups remained unaffected. Compound **8** bearing an extremely acid sensitive isopropylidene acetal function likewise gave **9**[12] in 90% yield when treated with **1** (0.1 mol equiv, 20 °C, 50 min), demonstrating the wider applicability of this method in multi-step oligosaccharide syntheses.

The possibility for regioselective de-*O*-*p*-methoxybenzylation was then explored using the di-*O*-PMBn derivative **10**[13] as a substrate. Thus when **10** (1 mmol) was treated with **1** (0.25 mmol) in DCM (10 mL) at -20 °C for 8 min the mono-*O*-PMBn ether **11**[13] (further characterised as its mono-*O*-acetyl derivative **12**[13]) was obtained in 70% yield after work up and purification by chromatography. Selective removal of the 2-*O*-PMBn group in





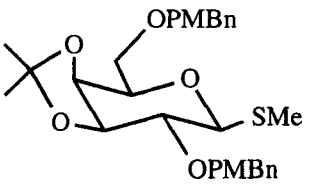
SE=2-(trimethylsilyl)ethyl

10 $R_1 = R_2 =$ PMBn
11 $R_1 =$ H, $R_2 =$ PMBn
12 $R_1 =$ Ac, $R_2 =$ PMBn
13 $R_1 = R_2 =$ H

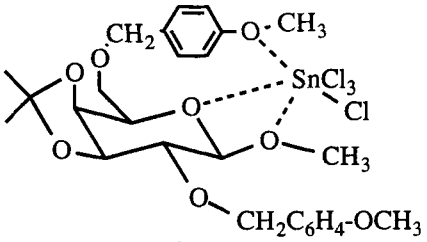
14 $R_1 = R_2 =$ PMBn
15 $R_1 =$ H, $R_2 =$ PMBn
16 $R_1 =$ Ac, $R_2 =$ PMBn
17 $R_1 = R_2 =$ H

10 is contrary to the selectivity observed in acetolysis of benzyl ethers catalyzed by Lewis acids[4c] in that the rate of acetolysis of a primary benzyl ether is significantly greater than that of a secondary benzyl ether. When the same reaction was carried out using 0.1 mmol of $SnCl_4$ at 20 °C for 4.5 h an 85% yield of the diol **13**[14] was obtained. Encouraged by this reverse order of reactivity for the selective removal of *O*-PMBn group in **10**, we extended the reaction to **14**,[16] which is easily accessible from its diol precursor **17**,[15] to examine the possibility for the preparation of the valuable disaccharide acceptor **15**. Indeed, reaction of **14** (0.25 mmol) with **1** (0.25 mmol) in DCM (10 mL) at 0 °C for 3 min gave **15**[16] (further characterized as the mono-*O*-acetyl drivative **16**[16]) in 73% yield after chromatography. Optimisation of the reaction conditions for the complete deprotection of the PMBn groups showed that by using 0.2 mol equiv of **1** and allowing the reaction mixture to slowly warm to 10 °C, and continuing the reaction for 5 h, (or, alternatively, 0.5 mol equiv of **1**, 20 °C, 1 h) the parent diol **17** could be recovered in 90% yield.

Addition of **1** to a solution of **10** in DCM resulted (as did **3**, **6**, **8** and **14**) in the formation of a purple coloured complex with absorption maxima in the region of 443 and 523 nm. Increasing the quantity of **1** was accompanied by an increase in the colour-intensity of the complex, and an exponential increase in the reaction rate. Thus at 20 °C while formation of **13** took 4.5 h at a concentration of 0.1 mol of **1**/mol of **10** for completion of the reaction (see above), it was complete in a few seconds (with the concomitant separation of **13** as crystals) when the reaction was carried out in the presence of 1 mol of **1**/mol of **10**. Continued reaction resulted in the partial hydrolysis of the isopropylidene acetal. Interestingly, the 1-thio- analogue of **10**, namely **18**, failed to react with $SnCl_4$ under the above conditions.



18



19

The above observations strongly indicate that the reaction is not a simple Lewis acid catalyzed hydrolysis. When **1** (0.1-1.0 mol equiv) was added to a solution of PMBn chloride (PMBnCl) in DCM (1 mL/mmol) a coloured complex with several absorption maxima in the range 420-570 nm was instantly formed. The intensity of the coloured complex thus formed increased rapidly with time, the rate of increase being higher in the initial stages of addition. This process was also accompanied by variations in the absorption maxima, indicating a state of flux. A λ_{max} of 524 nm was obtained in an hour. Further, the coloured complex gave bright blue fluorescence on TLC and had slightly lower mobility (ethyl acetate-hexane, 1:8) than PMBnCl. Benzyl chloride on the other hand did not produce a coloured complex with **1**. These observations indicate the possibility of a charge transfer complex in the **1**-PMBnCl system. The initial preferential removal of the 2-*O*-PMBn group in **10** can be rationalised if a complex of structure **19** is assumed to be formed initially. However, with the release of PMBnCl into the solution formation of a new complex (cf. **1**-PMBnCl complex) with it becomes possible, thereby freeing the 6-*O*-PMBn group for further reaction. It is noteworthy that fluorescence as noted for the **1**-PMBnCl system is obtained in all the de-*O*-*p*-methoxybenzylation reactions described here with the release of some PMBnCl into the reaction mixture. Inability of **1** to react with **18** confirms the involvement of the anomeric oxygen atom in the complex. In the case of

formation of **15** from **14** it appears that the complexation of **1** involves the benzyl groups on the galactose residue and the interglycosidic oxygen in **14**. Proximity of the axial PMBn group along with the steric factor may be responsible for its preferential removal. Although the tin complex formed in some of the reactions described above has been isolated at the end of the reaction and obtained as a solid, preliminary X-ray crystallography showed it to be an amorphous compound. Elucidation of the precise nature of the complexes in these and other situations[17] and the reaction mechanism, therefore, must await further studies.

In conclusion, tin(IV)chloride has been found to be an extremely efficient reagent for the selective deprotection of PMBn ethers of carbohydrates.[19] The reactions described in this paper unravel possibilities for selectivities that are otherwise unusual in Lewis acid catalyzed acetolysis and that haven't been achieved in other methods for the deprotection of PMBn ethers.

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11. Selected NMR data: Compound **6**, ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 9H, $SiMe_3$), 1.05 (q, 2H, CH_2SiMe_3), 2.04 and 2.11 (2s, 6H, OAc), 3.77 (s, 3H, OMe), 4.15 (dd, 2H, H-6a and H-6b), 4.35 (d, 1H, $J_{1,2}$ = 7.4 Hz, H-1), 4.45-4.85 (2d and q, 4H, CH_2Ph and CH_2Ph-*p*-OMe), 5.46 (near d, 1H, H-4) and 6.75-7.35 (d and m, 9H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ -1.53 ($SiMe_3$), 20.71 and 20.84 ($OCOCH_3$), 55.20 (Ph-*p*-OCH_3) and 103.21 (C-1); Compound **7**, ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 9H, $SiMe_3$), 1.05 (m, 2H, CH_2SiMe_3), 2.05 and 2.10 (2s, 6H, OAc),3.45 (dd, 1H, $J_{3,4}$ = 3.3 Hz, $J_{2,3}$ = 9.8 Hz, H-3),3.58 and 3.96 (2m, 2H, $CH_2CH_2SiMe_3$), 4.12 (m, 2H, H-6a and H-6b), 4.29 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), 4.48 and 4.77 (2d, 2H, CH_2Ph), 5.47 (d, 1H, H-4) and 7.21-7.36 (m, 5H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ -1.46 ($SiMe_3$), 20.78 ($OCOCH_3$), and 102.46 (C-1)
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13. Analytical data: Compound **10**, $[\alpha]_D$ +19.1° (*c* 1.41, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.29, 7.27, 6.89, 6.86 (4d, 8H, H_{Ar}), 4.75, 4.70, 4.58, 4.49 (4d, 4H, 11.2-11.5 Hz, CH_2Ph), 4.22 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1), 4.11-4.15 (m, 2H, H-3 and H-4), 3.88 (m, 1H, H-5), 3.80, 3.79 (2s, 6H, PhOMe), 3.56 (s, 3H, OMe), 1.35, 1.32 (2s, 6H, Me); Anal. Calcd for $C_{26}H_{34}O_8$ (474.550): C, 65.81, H, 7.22; Found: C, 65.90, H, 7.23; Compound **11**, $[\alpha]_D$ -1.33° (*c* 1.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.28, 6.88 (2d, 4H, H_{Ar}), 4.53 (2d, 2H, CH_2Ph), 4.16 (dd, 1H, $J_{3,4}$ = 5.3 Hz, $J_{4,5}$ = 2.0 Hz, H-4), 4.09 (d, 1H, $J_{1,2}$ = 8.2 Hz, H-1), 4.04 (dd, 1H, H-3), 3.95 (m, 1H, H-5), 3.80, s, 3H, PhOMe), 3.55 (s, 3H, OMe), 1.51, 1.34 (2S, 6H, Me); IR (film) 3300-3600 (OH) cm^{-1}; Anal. Calcd for $C_{18}H_{26}O_7$ (354.399): C, 61.00, H, 7.39; Found: C, 61.05, H, 7.42; Compound **12**, $[\alpha]_D$ +2.56° (*c* 2.73, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.28, 6.89 (2d, 4H, H_{Ar}), 4.96 (dd, 1H, $J_{1,2}$ = 8.1 Hz, $J_{2,3}$ = 7.0 Hz, H-2), 4.54 (dd, 1H, 11.5 Hz, CH_2Ph), 4.25 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1), 4.12-4.21 (m, 2H, H-3 and H-4),3.95 (m, 1H, H-5), 3.80 (s, 3H, PhOMe), 3.48 (s. 3H, OMe), 2.09 (s, 3H, OAc), 155, 1.33 (2s, 6H, Me); Anal. Calcd for $C_{20}H_{28}O_8$ (396.436): C, 60.60, H, 7.12; Found: C, 60.64, H, 7.14.
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16. Analytical data: Compound **14**, mp 42 °C; $[\alpha]_D$ = +11.6° (*c* 0.61, CH_2Cl_2); Anal. Calcd for $C_{68}H_{80}O_{13}Si$ (1133.458): C, 72.06, H, 7.11; Found: C, 72.18, H, 7.15; Compound **15**, $[\alpha]_D$ +16.27° (*c* 1.29, CH_2Cl_2); ^{1}H NMR δ 7.25 (m, 27H, H_{Ar}), 6.85 (d, 2H, the remaining H_{Ar}), 3.78 (s, 3H, OMe); IR 3300-3600 (OH) cm^{-1}; Anal. Calcd for $C_{60}H_{72}O_{12}Si$ (1013.308): C, 71.12, H, 7.16; Found: C, 71.08, H, 7.19; Compound **16**, $[\alpha]_D$ +17.44° (*c* 1.55, CH_2Cl_2); ^{1}H NMR δ: 7.25 (m, 27H, H_{Ar}), 6.80 (d, 2H, the remaining H_{Ar}), 5.55 (d, 1H, $J_{3',4'}$ = 2.4 Hz, H-4'), 3.78 (s, 3H, OMe), 2.03 (s, 3 H, OAc); IR 1750 (C=O) cm^{-1}; Anal. Calcd for $C_{62}H_{74}O_{13}Si$ (1055.345): C, 70.56, H, 7.08; Found: C, 70.65, H, 7.10.
17. When 2-(trimethylsilyl)ethyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-methoxybenzyl-β-D-galacto-pyranoside (**20**) was treated with **1** (0.25 mol equiv, 0 °C, 30 min) the de-*O*-*p*-methoxybenzylated product, 2-(trimethylsilyl)ethyl 2,3,4-tri-*O*-acetyl-β-D-galacto-pyranoside[18] was obtained in 70% yield after chromatographic purification. The poorer yield obtained in this reaction is due to the fact that a portion of **20** remained unchanged even on prolonged exposure to **1**.
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19. **Typical Procedure:** *Preparation of Compound 11 from 10:* A soln of **1** (250 μL, 1.0M in DCM) was added, during stirring, to a soln of **10** (474.5 mg, 1 mmol) in anhyd DCM (10 mL) cooled to -20 °C. After 8 min of stirring, aq Na_2CO_3 soln was added to it to quench the reaction. The mixture was then transferred to a separatory funnel and extracted with DCM (3 x 30 mL). The organic layer was then washed successively with aq Na_2CO_3 soln and water, dried (Na_2SO_4), concd to a syrup and chromatographed on a column of silica gel (200 mL) using EtOAc-hexane, 1:3 and 1:1 successively, as eluent to give **11** as a clear syrup (248 mg, 70%).