Novel Para-Substituted Benzyl Ethers for Hydroxyl Group Protection

Laurence Jobron and Ole Hindsgaul*

*Department of Chemistry, University of Alberta
Edmonton, Alberta T6G 2G2 Canada*

The observation that *p*-hydroxybenzyl ethers readily decompose under basic conditions to yield the free alcohol has allowed the development of novel solution-cleavable benzyl ethers as protecting groups in carbohydrate chemistry.

The *O*-benzyl group is the most commonly used "persistent" protecting group in carbohydrate chemistry, where it is almost always removed at the last step of multistep oligosaccharide synthesis by hydrogenolysis over insoluble catalysts such as Pd and PtO₂. Those cleavage procedures, besides being sensitive to catalyst poisoning by impurities, severely limit the use of the benzyl group in solid-phase oligosaccharide synthesis, where its removal on the resin would be desirable. We are therefore investigating the use of modified benzyl groups which are cleavable by soluble reagents. Here we describe the novel *p-acetoxybenzyl* (PAB) and 2-(trimethylsilyl)ethoxymethoxybenzyl (*p*-SEM-benzyl) groups.

The trichloracetimidate **3** and the bromide **4** were prepared as reagents for the introduction of the PAB group as shown in Scheme 1. The primary hydroxyl group of **1** was selectively

Scheme 1[a]
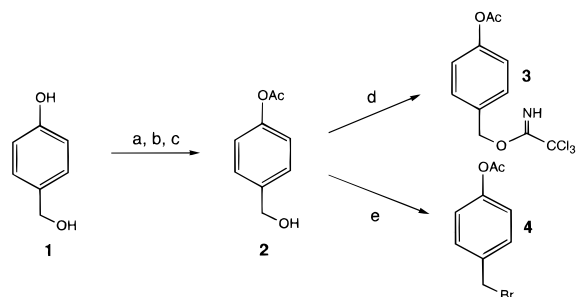
[a] Reagents and conditions: (a) TrCl, pyridine, 20 °C, 2 h, 96%; (b) Ac₂O, pyridine, 20 °C, 2 h, 97%; (c) 5% TFA, 5% TIS in CH₂Cl₂, 20 °C, 85%; (d) DBU, CCl₃CN, CH₂Cl₂, 20 °C, 5 min, 95%; (e) CBr₄, PPh₃, Et₂O, 20 °C, 15 min, 95%.

trR itylated followed by acetylation of the phenol and cleavage of the trityl group using a solution of 5% trifluoroacetic acid and 5% triisopropylsilane in CH₂Cl₂ at room temperature to give **2**. Treatment of **2** with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene gave the trichloroacetimidate **3** in 95% yield. The bromide **4** was obtained after treatment of **2** with carbon tetrabromide (2.2 equiv) and triphenylphosphine (4.4 equiv) in diethyl ether to give a 95% yield.

Reaction of the primary hydroxyl group of **5** with the trichloroacetimidate **3** employing trifluoromethanesulfonic acid (TfOH) or trifluoromethanesulfonic anhydride (Tf₂O)[1] as a catalyst in CH₂Cl₂ gave the protected compound **6** in 67% yield (Scheme 2). The same compound was produced in 78% yield on reaction of **5** with the bromide **4** by using silver trifluoromethanesulfonate (AgOTf) in hexane/CH₂Cl₂ (1/1). The PAB ether group can be selectively cleaved in quantitative yield in the presence of benzyl ethers as shown in Scheme 2. Treatment of **6** with NaOMe yields the phenoxide **7** which can be isolated by flash

(1) Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240.

Table 1. Mild Oxidation of *p*-Hydroxybenzyl Ethers[a]

reagent	solvent	time	temperature (°C)	yield (%)
NaOMe	MeOH	18 h	60	>95
DDQ (1 equiv)	CH₂Cl₂	30 min	0	>95
FeCl₃	Et₂O	5 min	20	>95
iodobenzene diacetate	CH₂Cl₂	2 h	20	90
Ag₂CO₃/Celite + Na₂SO₄	CH₂Cl₂	18 h	20	80

[a] The phenolic ethers were reacted with either NaOMe in MeOH or NaOMe in THF for 5 min at rt prior to the oxidation step.

Scheme 2
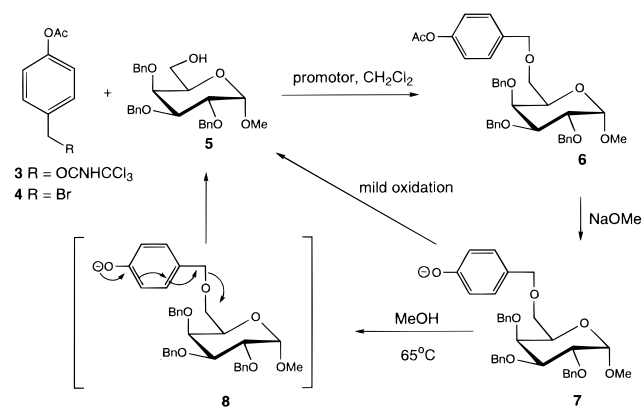
Scheme 3[a]
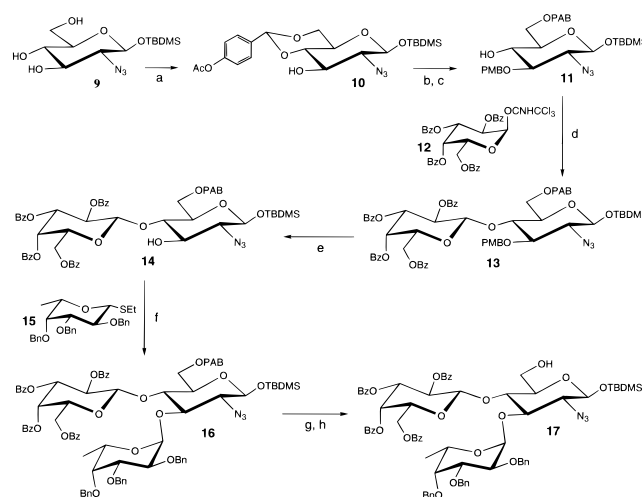
[a] Reagents and conditions: (a) *p*-acetoxybenzaldehyde, ZnCl₂, CH₂Cl₂, 20 °C, 18 h, 85%; (b) PMBOCNHCCl₃, BF₃·Et₂O, CH₂Cl₂, −78 °C, 5 min, 65%; (c) HCl/Et₂O, NaBH₃CN, THF, 20 °C, 74%; (d) BF₃·Et₂O, CH₂Cl₂, 20 °C, 1 h, 80%; (e) DDQ, CH₂Cl₂, 20 °C, 30 min, 90%; (f) DMTST, CH₂Cl₂, MS 4 Å, 20 °C, 52%; (g) NaOMe, MeOH, 0 °C, 5 min (quant); (h) FeCl₃, Et₂O, 20 °C, 15 min, 95% (two steps).
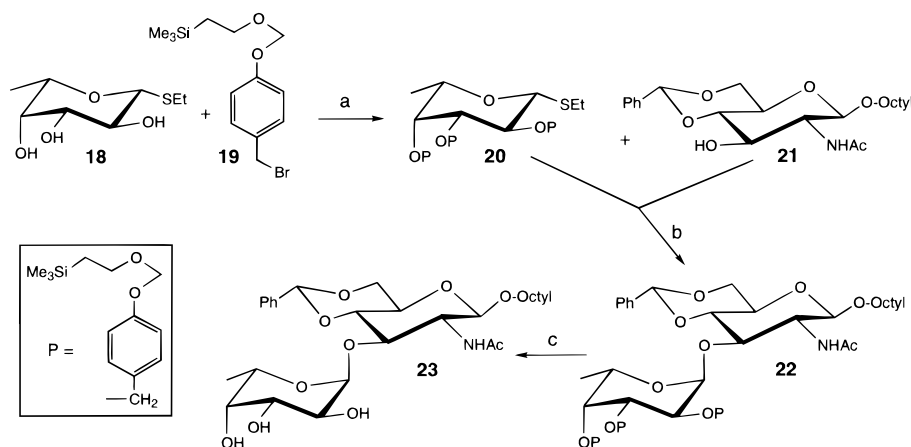
chromatography if desired. Heating of **7** to 65 °C, however, results in the loss of the PAB group, presumably by formation of a methylene quinone as shown in **8**. Alternatively, the phenoxide **7** can be removed by mild oxidizing agents such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[2] FeCl₃,[3] iodobenzene diacetate,[4] and silver carbonate on Celite[5] (for conditions and yields, see Table 1).

(2) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1967; Vol. 1, p 215.
(3) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1967; Vol. 1, p 390.
(4) Fieser, M.; Fieser, L. F. *Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1974; Vol. 4, p 266.

Scheme 4[a]

[a] Reagents and conditions: (a) NaH, DMF, 0 °C, 90 min, 75%; (b) DMTST, CH$_2$Cl$_2$, MS 4 Å, 20 °C, 1 h, 52%; (c) Bu$_4$NF, DMF, 80 °C, 48 h, 90%.

The suitability of the PAB ether in oligosaccharide synthesis is demonstrated by the synthesis of the Le^x trisaccharide derivative **13** (Scheme 3). This scheme employs many of the reagents, protecting-group manipulations, and glycosylation conditions that are standard in the field. Treatment of **9**[6] with *p*-acetoxybenzaldehyde and zinc chloride in CH$_2$Cl$_2$ at room temperature gave the 4,6-*O*-*p*-acetoxybenzylidene derivative **10** in 85% yield. The protection of the remaining hydroxyl group with *p*-methoxybenzyl trichloroacetimidate (PMBOCNHCCl$_3$),[7] followed by reductive opening of the benzylidene group with HCl/Et$_2$O and sodium cyanoborohydride in THF[8] gave exclusively **11**, protected at the 6-position by the PAB group. Glycosylation of **11** with **12**[9] by using BF$_3$·Et$_2$O as the catalyst in CH$_2$Cl$_2$ in the presence of 4 Å molecular sieves gave the desired lactosamine derivative **13**. The *p*-methoxybenzyl ether could be cleaved from **13** by treatment with DDQ without affecting the PAB group. Glycosylation of **14** with **15**[10] by using dimethyl(methylthio)sulfonium triflate (DMTST)[11] as promoter and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as base in CH$_2$Cl$_2$ in the presence of 4 Å molecular sieves gave exclusively the α-fucosylated product **16** (52%). The PAB group could be selectively removed from **16** by treatment with sodium methoxide in methanol at 0 °C followed by anhydrous ferric chloride in Et$_2$O to give the desired Le^x trisaccharide **17** (95% yield over 2 steps) with OH-6 free. Scheme 3 also demonstrates that PAB group removal is compatible with benzoate-protecting groups.

The phenoxide (as in **8**) is the key intermediate in both the thermal and oxidative cleavage of the PAB group and was generated by nucleophilic removal of the acetate in **6**. In principle, any phenolic-protecting group could be removed for the generation of this key intermediate, suggesting a potential series of orthogonally protected *p*-hydroxylbenzyl ethers. To demonstrate this principle, we developed the *p*-SEM-benzyl group as an alternative to the PAB group. The hydroxyl groups of ethyl 1-thio-α-L-

fucopyranoside[9] were protected by *p*-SEM-benzyl ethers using the bromide **19** (readily prepared in four steps from 4-hydroxybenzaldehyde) and NaH in DMF in 75% yield. Glycosylation of **20** with **21**,[12] employing DMTST and DTBMP in CH$_2$Cl$_2$ in the presence of 4 Å molecular sieves, gave exclusively the β-disaccharide **22** in 52% yield. The *p*-SEM-benzyl ethers were selectively cleaved by using Bu$_4$NF in DMF at 80 °C over 48 h to give **23** in 90% yield (Scheme 4). We have therefore demonstrated that the two new *p*-substituted benzyl-protecting groups are cleavable by soluble reagents and compatible with benzyl- and *p*-methoxybenzyl-protecting groups. As expected, the *p*-substituted benzyl groups are also cleavable under the standard conditions of hydrogenolysis (Pd/C, MeOH) used for benzyl group removal.

In summary, *p*-hydroxybenzyl-derived protecting groups presented here can be removed in near quantitative yield either thermally or by mild oxidation. When the phenoxy oxygen is protected as its acetate ester or SEM acetal, the resulting *p*-substituted benzyl ethers are compatible with many of the standard manipulations of oligosaccharide synthesis. Additionally, these groups are orthogonal to both benzyl and *p*-methoxybenzyl ethers. Clearly, additional protecting groups for the phenolic OH are required that can be specifically removed under mild conditions, and more rapidly than the SEM acetal, for such solution-cleavable benzyl ethers to be generally applicable in oligosaccharide synthesis. Work is also in progress to assess the removal of para-substituted benzyl ethers in the course of solid-phase oligosaccharide synthesis. The report of Fukase et al.[13] on the oxidative removal of aminated benzyl ethers on the solid phase suggests that deprotection of the oxy-benzyl ethers reported in the present work will not be problematic on the solid phase.

(5) Balogh, V.; Fétizon, M.; Golfier, M. *J. Org. Chem.* **1971**, *36*, 1339.
(6) Kinzy, W.; Schmidt, R. R. *Liebigs Ann. Chem.* **1985**, 1537.
(7) Patil, V. J. *Tetrahedron Lett.* **1996**, *37*, 1481.
(8) Garegg, P. J.; Hultberg, H. *Carbohydr. Res.* **1981**, *93*, 123.
(9) Rio, S.; Beau, J. M.; Jacquinet, J.-C. *Carbohydr. Res.* **1991**, *219*, 71.
(10) Lönn, H. *Carbohydr. Res.* **1985**, *139*, 105.

(11) Nilsson, M.; Norberg, T. *Carbohydr. Res.* **1988**, *183*, 71.
(12) Malet, C.; Hindsgaul, O. *Carbohydr. Res.* **1997**, *303*, 51.
(13) Fukase, K.; Egusa, K.; Nakai, Y.; Kusukoto, S. *Mol. Diversity* **1996**, *2*, 182.