

p-Methoxybenzyl Ethers as Acid-Labile Protecting Groups in Oligosaccharide Synthesis

Lin Yan and Daniel Kahne*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544, USA

Received 24 February 1995

Dedicated to Professor Gilbert Stork in recognition of his outstanding achievements as a scientist and a human being.

Abstract: The p-methoxybenzyl (PMB) group can be removed selectively with trifluoroacetic acid (TFA) in the presence of multiple glycosidic linkages as well as other sensitive functionality used in oligosaccharide synthesis.

Successful strategies for oligosaccharide synthesis require methods for the selective differentiation of the various hydroxyl groups on the sugar rings. Many methods which permit the selective removal of different protecting groups have been developed over the years and it is generally possible to devise a series of compatible protecting group transformations for a desired synthetic approach.¹ For example, there are protecting groups that can be removed readily in the presence of base, of fluoride ion, or under reductive or oxidative conditions. However, there are few protecting groups for individual sugar alcohols that can be removed under acidic conditions. This is perhaps not surprising given the sensitivity of glycosidic linkages to acid. Recently, however, in the course of developing an approach to the synthesis of oligosaccharides on a solid support, we found ourselves in need of an acid-sensitive protecting group that can be removed without destroying existing glycosidic linkages.² We now report that the p-methoxybenzyl (PMB) group has the appropriate reactivity to be removed selectively with trifluoroacetic acid (TFA) in the presence of multiple glycosidic linkages as well as other functional groups commonly found during oligosaccharide synthesis.

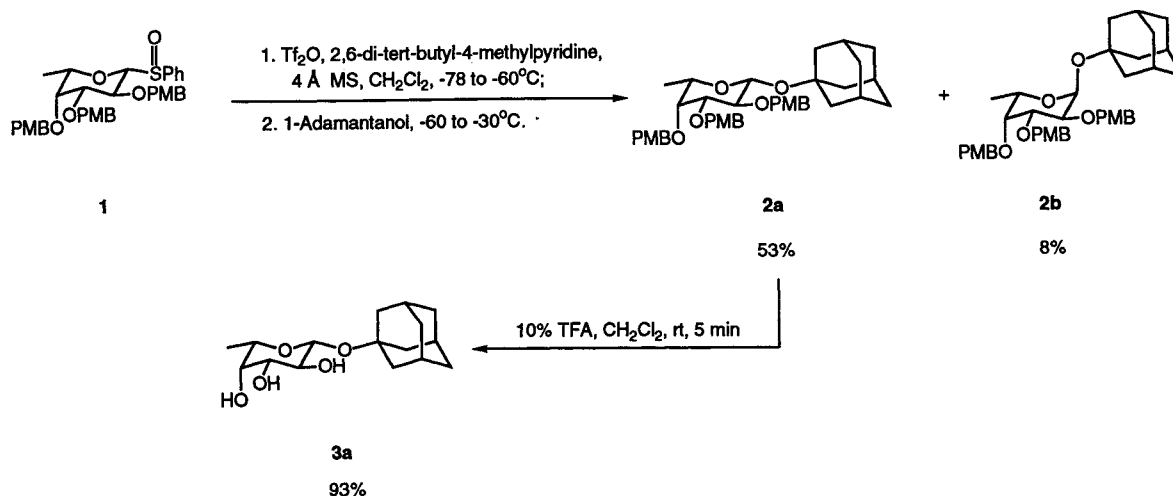
Scattered reports had suggested that it might be possible to remove PMB ethers under mildly acidic conditions. For example, it had been shown that the p-methoxybenzyl ethers of various phenols can be deprotected with mild acid.³ Moreover, PMB carbamates have been used as acid-labile protecting groups for amines in peptide synthesis, and PMB esters are sometimes used as protecting groups for carboxylic acids.⁴ However, these are all special cases. Removal of PMB ethers from simple alcohols was reported to require both strong acid and the presence of cation scavengers.⁵ Many substrates in oligosaccharide synthesis contain acid-labile glycosidic linkages as well as azides, thiophenyl glycosides, and other functional groups that might react with benzyl cations produced in the course of removing the PMB group. Nevertheless, we decided to investigate the potential utility of PMB ethers as acid-labile protecting groups for use in oligosaccharide synthesis.

As the first test case, we chose to investigate the acidic hydrolysis of the three PMB ethers of per-p-methoxy benzylated

adamantyl fucoside **2a**. Both the glycosidic linkage and the t-butyl ether linkage to adamantane in **2a** are acid sensitive. In fact, it is well-known that t-butyl ethers can be readily cleaved with TFA.⁶ We felt that the sensitivity of this adamantyl glycoside to acid made it an ideal model system to evaluate the potential utility of PMB ethers as acid-labile protecting groups for oligosaccharide synthesis. Accordingly, the protected sulfoxide **1** was synthesized from the corresponding L-fucose.⁷ Sulfoxide **1** was then treated with triflic anhydride and 2,6-di-*tert*-butyl-4-methyl pyridine in the presence of 4 Å molecular sieves and then 1-adamantanol was added to produce **2** in 61% yield.⁸ We should note that this is the first report of the use of a glycosyl sulfoxide to glycosylate a tertiary alcohol; the yield compares favorably with the best reported methods for glycosylation of closely related systems.⁹ The stereoselectivity is approximately 6.5:1 favoring the β anomer (**2a**). Although we typically obtain high α selectivity for glycosylation of hindered alcohols in the absence of neighboring group participation, the adamantyl group is so large that steric hindrance evidently prevents approach from the α face.

2a was treated with 10% TFA in methylene chloride at room temperature for 5 minutes. Following an aqueous workup the fully deprotected product was isolated in 93% yield after flash chromatography on silica gel. Not surprisingly, we found that extensive decomposition of **2a** occurred under exposure to 10% TFA in CH₂Cl₂ for longer times. Similarly, more concentrated TFA solutions also caused decomposition. Nevertheless, the reactivity of the PMB groups was sufficiently different from the other acid-labile groups that it was possible to remove them all with essentially no cleavage of either the glycosidic linkage or the adamantyl ether linkage. The success of this case prompted us to investigate other examples more closely related to the systems with which we were working.

Entries 1 and 2 in Table 1 show that PMB group can be removed under mildly acidic conditions in almost quantitative yield from both primary and secondary hydroxyl groups on sugar substrates. Entry 3 shows that the PMB group can be removed almost quantitatively in the presence of other sensitive functionality, including a secondary glycosidic linkage, an azide, and a thiophenyl glycoside. Finally, entry 4 shows the removal of multiple PMB groups in a trisaccharide related to Le^a. The reaction proceeded rapidly and gave a high yield. In contrast to **2a**, this trisaccharide did not decompose even when exposed to the deprotection conditions as long as overnight at room temperature. The overall yields for deprotection of **2a** and the



Scheme 1

Table 1^a

Entry	Substrate	Product	Time	Yield
1			15 min	97%
2			20 min	99%
3			30 min	97%
4			15 min	84%

^a All the reactions are carried out in 10% TFA in CH₂Cl₂ at room temperature.

trisaccharide in Table 1 (entry 4) suggest that the yield for removal of each individual PMB group is between 94-97%. No ester group migration or PMB group scrambling have been observed in our studies.

In conclusion, we have found that the PMB group has the appropriate reactivity to be used as an acid-sensitive protecting group for oligosaccharide synthesis. One of the most important uses for this protecting group strategy will likely be in solid phase oligosaccharide synthesis, where protecting group strategies that work well in solution frequently fail. For example, it is problematic to remove benzyl ethers from glycosides attached to a solid support because hydrogenation is difficult to carry out on the solid phase.¹⁰ Similarly, it is extremely difficult to remove PMB ethers under oxidative conditions (DDQ) on the solid phase. Furthermore, DDQ changes the physical properties of polystyrene-based resins.¹¹ Acid-labile PMB ethers may provide a solution to protecting group problems encountered in solid phase oligosaccharide synthesis.

A typical experimental procedure follows: **2a** (60 mg, 0.0912 mmol) dissolved in 5 mL 10% trifluoroacetic acid in CH₂Cl₂ was stirred at room temperature and the reaction was followed by TLC (5% MeOH in EtOAc). After five minutes the reaction was quenched by pouring into 100 mL saturated NaHCO₃. The aqueous layer was extracted thirty times¹² with ethyl acetate and the combined organic layers were concentrated and purified by flash chromatography (5% MeOH in EtOAc) to give **3a** (25.2 mg, 93%) as white solid.¹³

Acknowledgement This work was supported by the Office of Naval Research.

References and Notes

- Binkley, R. W. In *Modern Carbohydrate Chemistry*, Marcel Dekker, Inc., 1988, Chapter 8.
- Yan, L.; Taylor, C. M.; Goodnow, R.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 6953.
- White, J. D.; Amedio, J. C. *J. Org. Chem.* **1989**, *54*, 736.
- Chen, S.-T.; Wang, K.-T. *Synthesis*, **1989**, 36; Stewart, F. H. *Aust. J. Chem.* **1968**, *21*, 2543.

5. Losse, G.; Pechstein, B. *J. prakt. Chemie.* **1989**, *331*, 46.

6. Beyerman, H. C.; Helszwofl, G. *J. Chem. Soc.* **1963**, 755.

7. 1) Ac₂O, pyridine, rt; 2) PhSH, BF₃·Et₂O, CH₂Cl₂, rt (2 steps, 94%); 3) NaOMe, MeOH, rt; 4) PMBCl, NaH, DMF, rt (2 steps, 78%); 5) mCPBA, CH₂Cl₂, -78°C (77%).

8. Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.

9. a) Corey, E. J.; Wu, Y.-J. *J. Am. Chem. Soc.* **1993**, *115*, 8871; b) Hatakeyama, S.; Kawamura, M.; Takano, S. *J. Am. Chem. Soc.* **1994**, *116*, 4081.

10. Schlatter, J. M.; Mazur, R. H.; Goodmonson, O. *Tetrahedron Lett.* **1977**, *33*, 2851.

11. Goodnow, R.; Kahne, D. unpublished results.

12. The extensive extraction required for **3a** reflects the amphiphilic nature of this particular compound.

13. Data: **2a**: R_f=0.28 (4% Et₂O in CH₂Cl₂); ¹HNMR (270MHz, CDCl₃) δ: 7.3-6.8 (m, 12H, ArH), 4.9-4.6 (m, 6H, ArCH₂), 4.56 (d, J=7.59Hz, 1H, H-1), 3.81, 3.80, 3.79 (3s, 3x3H, OCH₃), 3.71 (dd, J=8.90, 7.59Hz, 1H, H-2), 3.46-3.41 (m, 2H, H-3 and H-4), 3.37 (br. q, J=6.27Hz, 1H, H-5), 2.1-1.6 (m, adamantyl-H), 1.09 (d, J=6.27Hz, 3H, 5-CH₃); ¹³CNMR (68MHz, CDCl₃) δ: 159.03, 131.33, 131.07, 131.01, 130.13, 129.83, 129.11, 113.69, 113.63, 113.39, 96.32, 82.81, 79.25, 75.84, 74.76, 74.57, 73.84, 72.92, 69.86, 55.26, 45.35, 42.70, 36.39, 36.07, 30.72, 30.67, 17.17. **3a**: R_f=0.33 (10% MeOH in EtOAc); ¹HNMR (270MHz, CD₃OD) δ: 4.90 (d, J=6.92Hz, 1H, H-1), 3.6-3.5 (m, 2H, H-5 and H-4), 3.47 (dd, J=3.30, 9.57Hz, 1H, H-3), 3.40 (dd, J=7.26, 9.90Hz, 1H, H-2), 2.1-2.6 (m, 15H, adamantyl-H), 1.24 (d, J=6.60Hz, 3H, 5-CH₃); ¹³CNMR (68MHz, CDCl₃) δ: 95.77, 75.23, 74.09, 71.70, 71.24, 70.25, 42.53, 36.19, 30.64, 16.61.