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Reductive Ring Opening of *o*-Nitrobenzylidene Acetals of Monosaccharides: Synthesis and Photolysis of Some Photolabile Sugars

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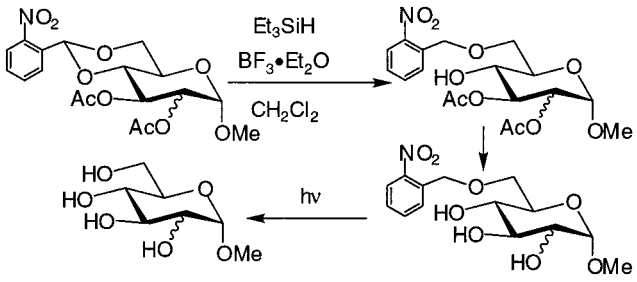
ABSTRACT



A 6-*O*-*o*-nitrobenzyl methylglucoside and methylmannoside were synthesized by reacting 4,6-*O*-*o*-nitrobenzylidene acetals with triethylsilane and boron trifluoride etherate. A 2,6-di-*O*-*o*-nitrobenzyl and a 3,6-di-*O*-*o*-nitrobenzyl methylmannoside were obtained from a 2,3:4,6-di-*O*-*o*-nitrobenzylidene methylmannoside by the same method. The photolabile sugars obtained were deprotected by irradiation at 350 nm to afford methylglycosides.

Recently, considerable attention has been paid to the biologically important functions of glycoconjugates.[1] The total synthesis of naturally occurring compounds containing sugar units is one of the most challenging areas in organic synthetic chemistry. Although many strategies have been developed for the synthesis of complex oligosaccharides, further useful protecting groups are required. Such protecting groups should be able to be selectively removed without affecting other protecting groups. Photolabile protecting groups are promising candidates as hydroxyl-protecting groups in sugars because they can be removed simply by irradiation in neutral media without any addition of chemical reagents.[2] Although several examples of sugar units protected by a photolabile substituent have been reported, almost all of them have an *o*-nitrobenzyl group at their anomeric position.[3] To use an *o*-nitrobenzyl group as a useful protecting group compared to other well-established protecting groups, new methods are needed to introduce an *o*-nitrobenzyl group into sugars at other than an anomeric position.[4] These photolabile sugars

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(2) Binkley, R. W.; Flechtner, T. W. *Synthetic Organic Photochemistry*; Horspool, W. M., Ed.; Plenum: New York, 1984; pp 375−423.

(3) (a) Zehavi, U.; Amit, B.; Patchornik, A. *J. Org. Chem.* **1972**, *37*, 2281−2285. (b) Zehavi, U.; Patchornik, A. *J. Org. Chem.* **1972**, *37*, 2285−2288. (c) Zehavi, U. *Adv. Carbohydr. Chem. Biochem.* **1988**, *46*, 179−204. (d) Nicolaou, K. C.; Hummel, C. W.; Nakada, M.; Shibayama, K.; Pitsinos, E. N.; Saimoto, H.; Mizuno, Y.; Baldenius, K.-U.; Smith, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 7625−7635. (e) Watanabe, S.; Hirokawa R.; Iwamura M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3375−3378.

(4) *o*-Nitrobenzyl derivatized methyl glucoside, see: Corrie, J. E. T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2161−2166.

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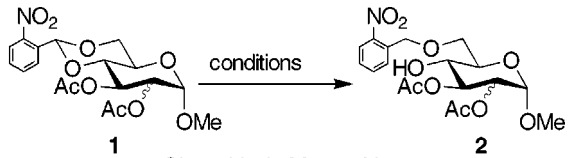
may also provide a new method for controlling the function of biologically important glycoconjugates by irradiation.[5] In this Letter, we report the synthesis and photoinduced deprotection of sugars with an *o*-nitrobenzyl group at a nonanomeric position.

We used a methylglucoside, a methylmannoside, and a methylgalactoside as model compounds. 4,6-*O*-*o*-Nitrobenzylidene acetals were prepared by a modified procedure reported previously.[6] An *o*-nitrobenzyl ether at C6 was obtained by the reductive ring-opening of 4,6-*O*-*o*-nitrobenzylidene acetals, as shown in Scheme 1 and Table 1.

Scheme 1. Synthesis of 6-*O*-*o*-Nitrobenzyl Methylglycosides **2**



1 **2**

a: Glucoside, b: Mannoside

Reductive single-bond cleavage of the benzylidene acetal moiety of methylglucoside **1a** and methylmannoside **1b** proceeded smoothly by the treatment of acetal with triethylsilane (12 equiv) and boron trifluoride etherate (6 equiv).[7] A 4,6-*O*-*o*-nitrobenzylidene methylgalactoside gave a complex mixture under the same conditions. When we used $NaBH_4CN/TiCl_4$ or $NaBH_4CN/TMSCl$ instead of $Et_3SiH/BF_3{\cdot}Et_2O$, the yield of the target material was lower.

Table 1. Yields of 6-*O*-*o*-Nitrobenzyl Methylglycosides **2**

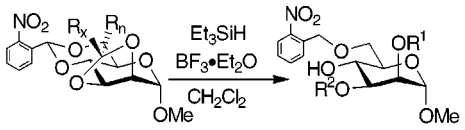
1	conditions[b]	**2**	recovery of **1**
1a[a]	A	17%	29%
1a	B	47%	43%
1a	C	88%	
1b	C	73%	

[a] *o*-Nitrobenzyl alcohol was also obtained in 39% yield. [b] Condition A: $NaBH_4CN/TiCl_4/CH_3CN$, −30 to 10 °C, 5 h. Condition B: $NaBH_4CN/TMSCl/CH_3CN$, rt, 3 d. Condition C: $Et_3SiH/BF_3{\cdot}Et_2O/CH_2Cl_2$, rt, 3 h.

In the case of a 4,6-*O*-benzylidene acetal of sugar derivatives, a 6-*O*-benzyl and a 4-*O*-benzyl derivative were generated in a selective manner by the careful selection of reagents.[8] In the present case, 6-*O*-*o*-nitrobenzyl derivatives with a free hydroxyl group at the C4 were exclusively obtained, and their structures were confirmed by NMR spectroscopy. A doublet at 5.57 and 5.42 ppm in the ^1H NMR spectra of **2a** and **2b** (DMSO-d_6) suggested that there were free secondary alcohols at C4 in both compounds.[9] These compounds were deacetylated using sodium methoxide in methanol to afford 6-*O*-*o*-nitrobenzyl derivatives **3a** and **3b**.[10]

Both *endo*- and *exo*-2,3:4,6-di-*O*-*o*-nitrobenzylidene methylmannoside, **4** and **5**,[6] were treated with $Et_3SiH/BF_3{\cdot}Et_2O$ to afford two products with two *o*-nitrobenzyl groups per molecule, 2,6-di-*O*-*o*-nitrobenzyl and 3,6-di-*O*-*o*-nitrobenzyl methylmannoside, **6** and **7** (Scheme 2). The structures of

Scheme 2. Synthesis of Di-*O*-*o*-nitrobenzyl Derivatives **6** and **7**



	6	**7**
4	36%	30%
5[a]	6%	46%

4: R_x=H, R_n=*o*-nitrophenyl
5: R_x=*o*-nitrophenyl, R_n=H

6: R^1=*o*-nitrobenzyl, R^2=H
7: R^1=H, R^2=*o*-nitrobenzyl

[a] The exo-isomer **5** contains 17% of the endo-isomer **4**.

these products were determined by H−H COSY, C−H COSY, and differential NOE spectra after the acetylation of free hydroxyl groups.[11]

The *exo*-2,3:4,6-di-*O*-*o*-nitrobenzylidene methylmannoside **5** used here contained about 17% of the endo-isomer **4** due to the difficulty of separation. Therefore, the 2,6-di-*O*-*o*-nitrobenzyl methylmannoside **6** obtained in the present experiment was considered to have been derived exclusively from **4**. This result means that *exo*-2,3:4,6-di-*O*-*o*-nitrobenzylidene methylmannoside **5** gives 3,6-di-*O*-*o*-nitrobenzyl methylmannoside **7** selectively in about 50% yield.

Although the origin of the regioselectivity of the ring opening has not yet been fully explained, steric congestion may affect this reaction. A nitro group also plays a role in this reaction, since the selectivity is somewhat different from that for other *O*-benzylidene acetals.[8]

To examine their availability as photolabile synthetic building units as well as caged sugars, solutions of **3a**, **3b**,

(5) Caged glycosphingolipids with an *o*-nitrobenzyl group at their aglycone moiety were reported, see: (a) Zehavi, U. *Chem. Phys. Lipids* **1997**, *90*, 55−61. (b) Tuchinsky, A.; Zehavi, U. *Chem. Phys. Lipids* **1998**, *92*, 91−97.

(6) Collins, P. M.; Oparaeche, N. N. *Carbohydr. Res.* **1974**, *33*, 35−46.

(7) Debenham, S. D.; Toone, E. J. *Tetrahedron: Asymmetry* **2000**, *11*, 385−387.

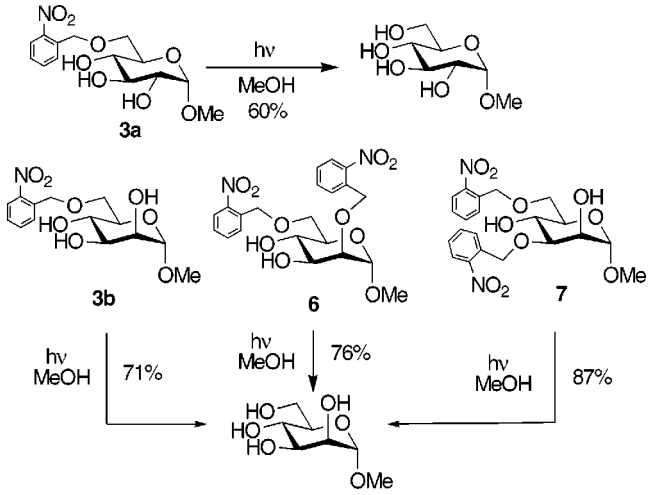
(8) Garegg, P. J. *Preparative carbohydrate chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; pp 53−67.

(9) The intensity of these signals was weakened by adding D_2O to the NMR sample, see: Chapman, O. L.; King, R. W. *J. Am. Chem. Soc.* **1964**, *86*, 1256−1258.

(10) Methyl 6-*O*-(2-nitrobenzyl)-α-D-glucopyranoside **3a**: ^1H NMR (CD_3OD) δ 3.25−3.33 (m, 2H), 3.45 (s, 3H), 3.58−3.85 (m, 4H), 4.69 (d, J = 4.0 Hz, 1H), 4.98 (s, 2H), 7.50 (t, J = 7.6 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H); ^{13}C NMR (CD_3OD) δ 55.6 (q), 70.9 (t), 71.4 (t), 71.6 (d), 72.5 (d), 73.4 (d), 75.1 (d), 101.1 (d), 125.5 (d), 129.2 (d), 129.9 (d), 134.6 (d), 135.9 (s), 148.8 (s). Methyl 6-*O*-(2-nitrobenzyl)-α-D-mannopyranoside **3b**: ^1H NMR ($CDCl_3$) δ 3.29 (s, 3H), 3.35−3.84 (m, 5H), 4.66 (s, 2H), 4.88 (s, 2H), 7.36 (dd, J = 7.3, 7.8 Hz, 1H), 7.56 (dd, J = 7.3, 7.6 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.1 (q), 68.3 (d), 70.4 (t), 70.6 (t), 70.7 (d), 71.8 (d), 77.0 (d), 100.8 (d), 124.6 (d), 128.1 (d), 128.9 (d), 133.5 (d), 134.3 (s), 147.4 (s).

(11) See Supporting Information.

Scheme 3. Deprotection of *o*-Nitrobenzyl Groups by Irradiation (350 nm) of Photolabile Sugars **3a**, **3b**, **6**, and **7**



6, and **7** in methanol were irradiated by a Rayonet photochemical reactor (3500 Å × 12) with light at 350 nm. After exhaustive irradiation (15 h), methylglycosides were obtained in 60−87% isolated yield, indicating that these photolabile sugars are useful building blocks for oligosaccharide synthesis (Scheme 3).

In this Letter, we report a new method for preparing photolabile monosaccharides with *o*-nitrobenzyl groups at nonanomeric positions. While the photolabile protecting group tolerates reaction conditions that would remove other well-known protecting groups, it can be readily removed under mild conditions such as irradiation. The present facile synthetic method may provide a new tool for the synthesis of complex oligosaccharides.

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Supporting Information Available: Experimental procedures for the synthesis of photolabile sugars and their spectral data. This material is available free of charge via the Internet at http://www.pubs.acs.org.

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