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1-Naphthylpropargyl Ether Group: A Readily Cleaved and Sterically Minimal Protecting System for Stereoselective Glycosylation

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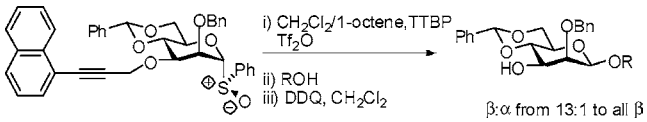
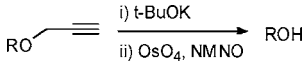
ABSTRACT



The (1-naphthyl)propargyl group is introduced as a sterically unobtrusive alcohol protecting group that is cleaved in a single step by exposure to dichlorodicyanoquinone in wet dichloromethane. In conjunction with the 4,6-*O*-benzylidene protecting group, and the use of the sulfoxide glycosylation method, 3-*O*-naphthylpropargyl-protected mannosyl donors are extremely *β*-selective.

The apposite use of protecting groups continues to be an essential element in preparative carbohydrate and oligosaccharide synthesis, with considerable effort devoted to their development in recent years.[1] This is due to the central role of protecting groups in modulating reactivity of both glycosyl donors and acceptors and, critically, in the control of regioselectivity[2] and stereoselectivity.[3] In response to a problem arising from the influence of protecting group size on the stereoselectivity of a glycosylation reaction,[4] we recently described the successful application of propargyl ethers as sterically unobtrusive donor protecting groups for *β*-mannosylation.[5] While, although the propargyl ethers were readily introduced and had the anticipated effect on stereoselectivity, they required a two-step deprotection protocol: an initial treatment with base followed by catalytic osmoylation of the resulting allenyl ether (Scheme 1).

Scheme 1. Deprotection of Propargyl Ethers



We considered that the advantages of the propargyl ether protecting system would be significantly enhanced if it could be modified in such a way as to be cleavable in a single step, orthogonal to the ubiquitous benzyl ethers. We report here on the successful accomplishment of this goal through the use of the naphthylpropargyl system.

The *p*-methoxybenzyl[6] and naphthylmethyl[7] ethers are widely employed as benzyl ether surrogates, cleavable under oxidative conditions. We reasoned that the insertion of an

(1) (a) Grindley, T. B. In *Modern Methods in Carbohydrate Chemistry*; Khan, S. H., O'Neill, R. A., Eds.; Harwood Academic: Amsterdam, 1996; p 225. (b) Green, L. G.; Ley, S. V. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, 2000; Vol. 1, p 427. (c) Fraser-Reid, B.; Lopez, J. C.; Gomez, A. M.; Uriel, C. *Eur. J. Org. Chem.* **2004**, 1387.

(2) Ley, S. V.; Baeschlin, D. K.; Dixon, D. J.; Foster, A. C.; Ince, S. J.; Priepke, H. W. M.; Reynolds, D. J. *Chem. Rev.* **2001**, *101*, 53.

(3) (a) Crich, D.; Vinod, A. U. *J. Org. Chem.* **2005**, *70*, 1291. (b) Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2001**, *123*, 6819. (c) Crich, D.; Jayalath, P. *J. Org. Chem.* **2005**, *70*, 7252. (d) Crich, D.; Yao, Q. *J. Am. Chem. Soc.* **2004**, *126*, 8232. (e) Crich, D.; Hutton, T. K.; Banerjee, A.; Jayalath, P.; Picione, J. *Tetrahedron*: *Asymmetry* **2005**, *16*, 105. (f) Crich, D.; Vinod, A. U.; Picione, J. *J. Org. Chem.* **2003**, *68*, 8453. (g) Crich, D.; Vinod, A. U.; Picione, J.; Wink, D. J. *ARKIVOC* **2005**, *vi*, 339. (h) Kim, J.-H.; Yang, H.; Boons, G.-J. *Angew. Chem., Int. Ed.* **2005**, *44*, 947. (i) Kim, J.-H.; Yang, H.; Park, J.; Boons, G.-J. *J. Am. Chem. Soc.* **2005**, *127*, 12090. (j) Smoot, J. T.; Pornsuriyasak, P.; Demchenko, A. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 7123. (k) Bowers, S. G.; Coe, D. M.; Boons, G.-J. *J. Org. Chem.* **1998**, *63*, 4570. (l) Jiao, H.; Hindsgaul, O. *Angew. Chem., Int. Ed.* **1999**, *38*, 346. (m) Crich, D.; Banerjee, A. *J. Am. Chem. Soc.* **2006**, *128*, 8078. (n) Crich, D.; Bowers, A. A. *J. Org. Chem.* **2006**, *71*, 3452.

(4) Crich, D.; Dudkin, V. *Tetrahedron Lett.* **2000**, *41*, 5643.

(5) (a) Crich, D.; Jayalath, P. *Org. Lett.* **2005**, *7*, 2277. (b) Crich, D.; Jayalath, P.; Hutton, T. K. *J. Org. Chem.* **2006**, *71*, 3064.

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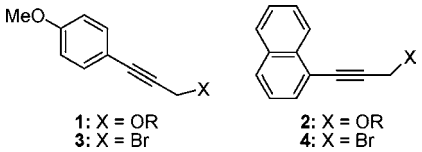
acetylenic group into the aryl−methylene bond of either the PMB or naphthylmethyl system would afford a system combining the steric advantages of the propargyl ether with the facile oxidative cleavage of the PMB and naphthylmethyl ethers. This line of thought led us to the ethers **1** and **2**, which we assumed could be assembled from the known bromides **3** and **4**.[8,9]

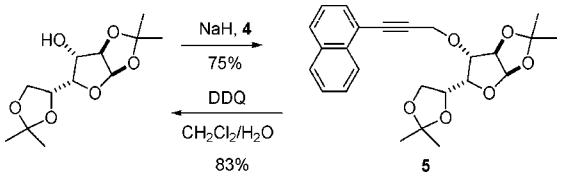


1: X = OR
3: X = Br

2: X = OR
4: X = Br

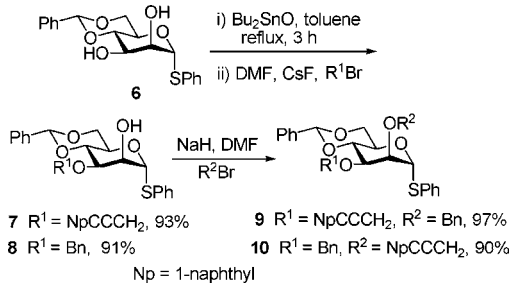
Alkylation of 1,2;5,6-diacetone-D-glucofuranose with sodium hydride and bromide **4** gave the model ether **5** (Scheme 2). Treatment of this compound with DDQ in wet dichloromethane, typical conditions for the removal of PMB and naphthylmethyl ethers, returned the alcohol in 83% yield, thereby establishing proof of principle. Directly analogous transformations with the *p*-methoxyphenylpropargyl-protected system were also successful. However, it subsequently became clear that the more electron-rich *p*-methoxyphenylpropargyl group **1** was incompatible with various glycosylation conditions leading to our subsequent preference for system **2**.

Scheme 2. Deprotection of a Naphthylpropargyl Ether

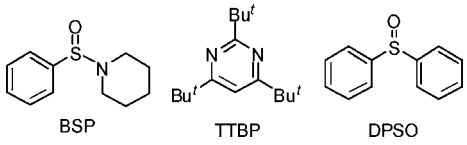


To examine the effect of the new protecting group **2** on the stereoselectivity of glycosylation reactions, when located at both O2 and O3, we prepared donors **9** and **10** from known diol **6**[10] by standard means as set out in Scheme 3.

Scheme 3. Preparation of Donors **9** and **10**

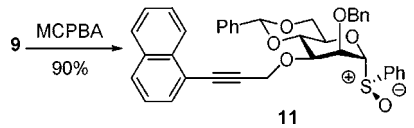


Attempted activation of donors **9** and **10** by our standard treatment with 1-benzenesulfinyl piperidine (BSP) and trifluoromethanesulfonic anhydride[11] in the presence of the hindered base tri-*tert*-butylpyrimidine (TTBP)[12] was unproductive, resulting in either no reaction or complex mixtures. We turned, therefore, to the more potent combination of diphenyl sulfoxide (DPSO) and triflic anhydride[13] when consumption of the donors was observed, but complex reaction mixtures were obtained. Study of the byproducts indicated that electrophilic attack on the arylpropargyl system was the root of the problem.



Precedent suggested, however, the activation of glycosyl sulfoxides with Tf_2O to be compatible with electron-rich aromatic systems, especially when used in conjunction with an electrophile scavenger.[14] Accordingly, donor **9** was oxidized to the sulfoxide **11** (Scheme 4), which was formed as a single diastereomer whose configuration rests on analogy.[15]

Scheme 4. Preparation of Sulfoxide **11**



Treatment of **11** with triflic anhydride in the presence of TTBP at −78 °C in a 3:1 mixture of CH_2Cl_2 and 1-octene, to give an intermediate glycosyl triflate,[16] followed by addition of 1-adamantanol, finally resulted in the formation

(6) (a) Bhattacharyya, S.; Magnusson, B.; Wellmar, U. *J. Chem. Soc., Perkin Trans. 1* **2000**, *8*, 886. (b) Maruyama, M.; Takeda, T.; Shimizu, N. *Carbohydr. Res.* **2000**, *325*, 83. (c) Yan, L.; Kahne, D. *Synlett* **1995**, 523. (d) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: Hoboken, 1991; p 86. (e) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Thieme: Stuttgart, Germany, 2005; Chapter 4, p 257. (f) Wuts, P. G. M. In *Handbook of Reagents for Organic Synthesis*; Crich, D., Ed.; Wiley: Chichester, 2005; p 425.

(7) (a) Wright, J. A.; Yu, J.; Spencer, J. B. *Tetrahedron Lett.* **2001**, *42*, 4033. (b) Csávás, M.; Szabó, Z. B.; Borbás, A.; Lipták, A. In *Handbook of Reagents for Organic Synthesis*; Crich, D., Ed.; Wiley: Chichester, 2005; p 459. (c) Szabo, Z. B.; Borbas, A.; Bajza, I.; Liptak, A. *Tetrahedron: Asymmetry* **2005**, *16*, 83. (d) Csavas, M.; Borbas, A.; Szilagyi, L.; Liptak, A. *Synlett* **2002**, *6*, 887.

(8) Bromide **3** was prepared according to: Batey, R. A.; Shen, M.; Lough, A. J. *Org. Lett.* **2002**, *4*, 1411.

(9) Bromide **4** was prepared according to: Banerjee, M.; Roy, S. *Org. Lett.* **2004**, *6*, 2137.

(10) Crich, D.; Li, W.; Li, H. *J. Am. Chem. Soc.* **2004**, *126*, 15081.

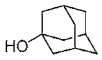
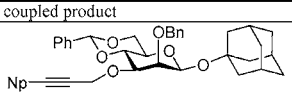
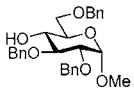
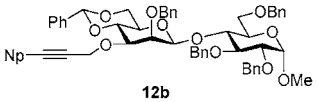
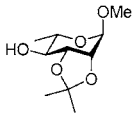
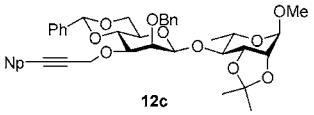
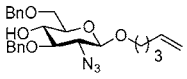
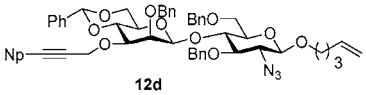
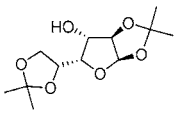
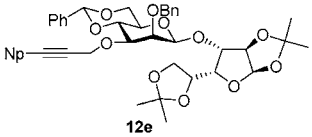
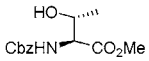
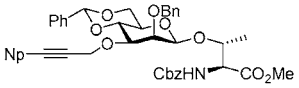
(11) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015.

(12) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, *2*, 323.

(13) Codée, J. D. C.; Litjens, R. E. J. N.; Den Heeten, R.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1519.

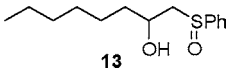
(14) (a) Yan, L.; Kahne, D. *J. Am. Chem. Soc.* **1996**, *118*, 9239. (b) Gildersleeve, J.; Smith, A.; Sakurai, k.; Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1999**, *121*, 6176.

Table 1. Coupling Reactions of Donor **11**

entry	acceptor	coupled product	yield[a]	α:β ratio[b]
1		 **12a**	77%	β-only
2		 **12b**	46%	β-only
3		 **12c**	87%	1:13
4		 **12d**	43%	β-only
5		 **12e**	74%	β-only
6		 **12f**	85%	β-only

[a] Isolated yields after column chromatography. [b] Ratio was determined by ^{1}H NMR of crude reaction mixtures.

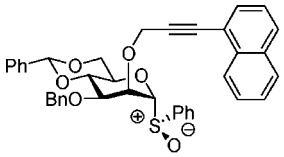
of the β-mannoside **12a** with impeccable selectivity (Table 1, entry 1). That 1-octene fulfilled its role of trapping extraneous thiophilic species was established by isolation of **13** from the reaction mixture.



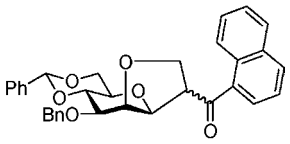
13

A number of couplings were then conducted with more standard glycosyl acceptors, leading to the yields and selectivities collected in Table 1. The influence of the 3-*O*-naphthylpropargyl group on selectivity is best illustrated in entry 4 (Table 1): previously, coupling of the identical acceptor to the 3-*O*-*tert*-butyldimethylsilyl analogue of **11** resulted in the formation of a 1.8:1 mixture of glycosides favoring the α-anomer.[4]

Oxidation of thioglycoside **10** afforded the sulfoxide **14**, as a single diastereomer, in 94% yield. Activation of **14** under the conditions employed for **11** afforded β-mannosides with excellent selectivity (Table 2). Unfortunately, the reaction mixtures were relatively complex and included a significant byproduct, ketone **15**, resulting from cyclization of the protecting group onto the activated glycosyl donor. In the face of this problem, couplings to donor **14** were not pursued further.

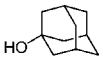
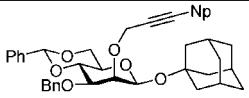
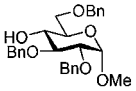
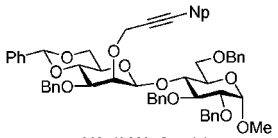
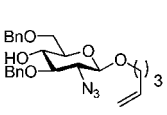
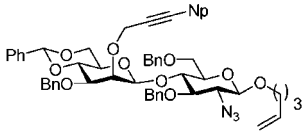


14



15

Table 2. Coupling Reactions of Donor **14**

acceptor	coupled product (yield[a], α:β ratio[b])
	 **16a** (67%, β-only)
	 **16b** (38%, β-only)
	 **16c** (13%, β-only)

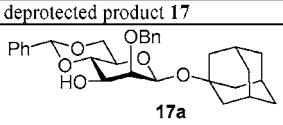
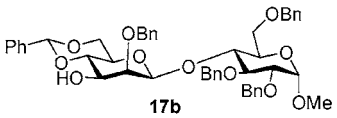
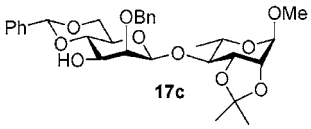
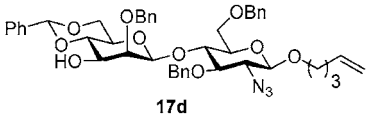
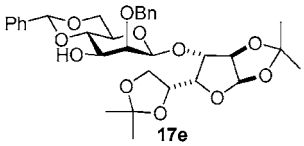
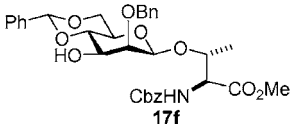
[a] Isolated yields after column chromatography. [b] Ratio was determined by ^{1}H NMR of crude reaction mixtures.

The excellent stereoselectivity obtained with the 3-*O*-naphthylpropargyl-protected donor **11** contrasts with the poor selectivity delivered by the corresponding 3-*O*-propargyl

(15) (a) Crich, D.; Mataka, J.; Zakharov, L. *J. Am. Chem. Soc.* **2002**, *124*, 6028. (b) Crich, D.; Mataka, J.; Sun, S.; Lam, K. C.; Rheingold, A. R.; Wink, D. J. *J. Chem. Soc., Chem. Commun.* **1998**, *24*, 2763.

(16) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217.

Table 3. Cleavage of Naphthylpropargyl Ethers

entry	deprotected product **17**	yield[a]
1	 **17a**	86%
2	 **17b**	80%
3	 **17c**	89%
4	 **17d**	90%
5	 **17e**	84%
6	 **17f**	86%

[a] Isolated yields after column chromatography.

donor.[5b] On the other hand, 4,6-*O*-benzylidene mannosyl donors carrying a 2-*O*-propargyl group were previously found to be highly efficient, in contrast to the 2-*O*-naphthylpropargyl system **14**, and highly β-selective.[5] Thus, in addition to their different requirements for deprotection, the propargyl and naphthylpropargyl systems are highly complementary.

In accordance with the model experiments (Scheme 2), selective deprotection of the glycosides **12** was accomplished with DDQ in CH_2Cl_2/H_2O (20:1) over a period of 2−3 h at room temperature in excellent yield as reported in Table 3. The employment of other solvent systems recommended for the cleavage of 2-naphthylmethyl ethers, such as CH_2Cl_2/CH_3OH,[17] $CHCl_3/H_2O$, and CH_2Cl_2 alone,[18] was less satisfactory.

To conclude, we report the development of the naphthylpropargyl ether system. In conjunction with the sulfoxide glycosylation method, when introduced on the 3-position of 4,6-*O*-benzylidene-protected mannosyl donors, this system affords extremely β-selective coupling reactions and the possibility of orthogonal cleavage in a single step with DDQ. We anticipate that this group will find application in oligosaccharide synthesis and, because of its minimal steric character and ease of deprotection, beyond the confines of carbohydrate chemistry.

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Supporting Information Available: Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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