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2-*O*-Propargyl Ethers: Readily Cleavable, Minimally Intrusive Protecting Groups for β-Mannosyl Donors

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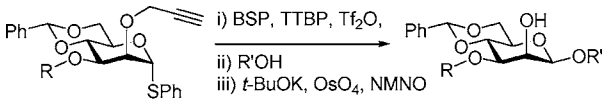
ABSTRACT



R = TBDMS or a glycoside, β;α from 5:1 to all β

The use of 2-*O*-propargyl ethers as protecting groups in 4,6-*O*-benzylidene-protected mannopyranosyl donors bearing either bulky silyl groups or glycosidic linkages on O3 overcomes the poor stereoselectivity achieved with the corresponding 2-*O*-benzyl ethers, due to a reduction of steric buttressing. Deprotection is conducted by treatment with potassium *tert*-butoxide followed by catalytic osmium tetroxide and *N*-methylmorpholine *N*-oxide.

Some time ago, we introduced 4,6-*O*-benzylidene-protected α-mannosyl triflates carrying non-participating, ether-type groups on O2 and O3 as highly stereoselective β-mannosyl donors,[1] thereby removing many of the barriers to the efficient solution of this classical problem in carbohydrate chemistry.[2] This protecting group array, whose effectiveness is now understood in terms of the locking of the mannose C5−C6 bond in the *tg*-conformation,[3] and which has subsequently been shown to be applicable to other rapid activation systems,[4] has permitted the synthesis of many β-mannopyranosidic linkages with a very broad range of acceptors.[5] Most recently, we have shown the same protecting group set also enables the direct synthesis of β-D- and -L-glycero-D-mannoheptopyranosides and,[6] with the help of a novel radical fragmentation,[7] β-D-rhamnopyranosides.[8] There remain, however, occasional linkage types that have not succumbed to this methodology and which continue to challenge our ingenuity. A case in point, and the focus of this paper, is the class of β-mannosides necessitating the use of a bulky protecting group, or a glycosidic bond, on O3 of the donor. We first became aware of this problem when attempting glycosylation of acceptor **1** with a view to the eventual synthesis of the common core pentasaccharide of the *N*-linked glycans.[9] With the donor **2** poor selectivity (77%, β/α = 1:1.8) was observed, in contrast to the coupling of **1** to **3** when results were much more favorable (72%, β/α = 3:1). Indeed, the poor selectivity observed with donor **2** caused us to modify our general strategy for the core pentasaccharide to one employing a 3-*O*-*p*-methoxybenzyl-

(1) (a) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321. (b) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217.

(2) (a) Barresi, F.; Hindsgaul, O. In *Modern Methods in Carbohydrate Synthesis*; Khan, S. H., O'Neill, R. A., Eds.; Harwood Academic Publishers: Amsterdam, 1996; p 251. (b) Demchenko, A. V. *Synlett* **2003**, 1225. (c) Pozsgay, V. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, 2000; Vol. 1, p 319. (d) Gridley, J. J.; Osborn, H. M. I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1471.

(3) Jensen, H. H.; Nordstrom, M.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 9205.

(4) (a) Weingart, R.; Schmidt, R. R. *Tetrahedron Lett.* **2000**, *41*, 8753. (b) Kim, K. S.; Kim, J. H.; Lee, Y. J.; Lee, Y. J.; Park, J. *J. Am. Chem. Soc.* **2001**, *123*, 8477. (c) Tsuda, T.; Sato, S.; Nakamura, S.; Hashimoto, S. *Hetereocycles* **2003**, *59*, 509.

(5) (a) Crich, D.; Lim, L. B. L. *Org. React.* **2004**, *64*, 115. (b) Dudkin, V. K.; Miller, J. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 736. (c) Wu, X.; Schmidt, R. R. *J. Org. Chem.* **2004**, *69*, 1853. (d) Crich, D.; Banerjee, A.; Yao, Q. *J. Am. Chem. Soc.* **2004**, *126*, 14930. (e) Crich, D.; Li, W.; Li, H. *J. Am. Chem. Soc.* **2004**, *126*, 15081. (f) Shao, N.; Guo, Z. *Pol. J. Chem.* **2005**, *79*, 297.

(6) Crich, D.; Banerjee, A. *Org. Lett.* **2005**, *7*, 1935.

(7) Crich, D.; Yao, Q. *Org. Lett.* **2003**, *5*, 2189.

(8) (a) Crich, D.; Yao, Q. *J. Am. Chem. Soc.* **2004**, *126*, 8232. (b) Kwon, Y. T.; Lee, Y. J.; Lee, K.; Kim, K. S. *Org. Lett.* **2004**, *6*, 3901.

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

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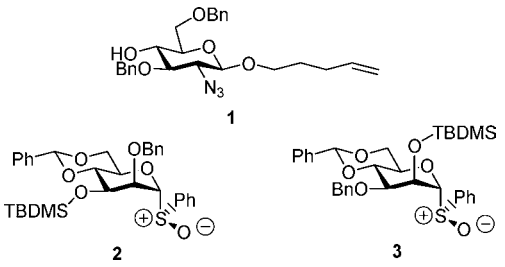
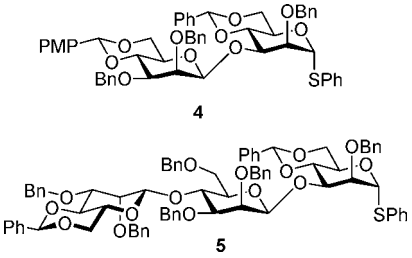
protected mannosyl donor in which the PMB group had to be exchanged for the desired silyl ether post-glycosylation.[10]



More recently, and even more problematic, we have found that disaccharide donors **4** and **5** gave very poor selectivities in coupling reactions, thereby significantly reducing the efficiency of our convergent synthesis of an alternating β-(1→3)−β-(1→4)-mannan common to *Rhodotorula glutinis*, *Rhodotorula mucilaginosa*, and *Leptospira biflexa*.[5e]



The common feature of donors **2**, **4**, and **5** is the presence of a bulky substituent on O3 which, in the absence of unusual ring conformations, reinforces our initial belief[9] that the problem is one of steric buttressing. Thus, as illustrated for the triflate derived from **2** (Figure 1), we reason that of the

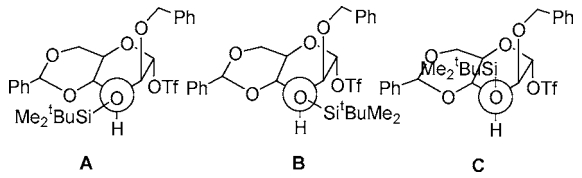


Figure 1. Staggered conformations about the O3 bond.

three possible staggered conformations around the O3-substituent bond, the first (**A**) is disfavored by the steric interaction with the rigid benzylidene ring. In the two remaining conformers, **B** and **C**, the steric interaction with the O2 benzyl group is minimized by rotating the benzyl ether over the anomeric center. In other words, viewed in terms of the conformation about the O2-substituent bond (Figure 2), the bulky group on O3 presumably destabilizes conformation **E** and leads to an increase in the population of **F**, if not of the highly congested **D**. This in turn leads to increased steric hindrance toward β-face attack on the

(10) Dudkin, V. Y.; Crich, D. *Tetrahedron Lett.* **2003**, *44*, 1787.

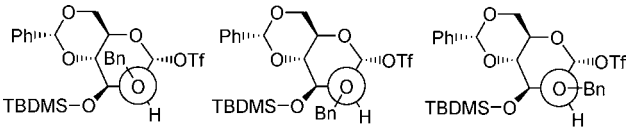
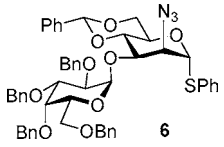


Figure 2. Staggered conformations about the O2 bond.

α-mannosyl triflate, or the transient contact ion pair derived from it,[11] resulting in the observed loss of β-selectivity.

For donor **2** the problem may be circumvented by avoiding the use of the bulky O3 silyl protecting group but in target-directed convergent oligosaccharide synthesis there is no way around the use of donors such as **4** and **5**. This led us to reason that the steric congestion between the substituents on O2 and O3, which disfavors conformation **E**, and the detrimental effects of conformation **F** on stereoselectivity might both be reduced by the use of a much less sterically demanding protecting group for O2. We were encouraged in this line of thinking by the successful β-glycosylation of several acceptors by donor **6** reported by the van Boom laboratory,[12] but obviously the minimal steric bulk of the azido group cannot be viewed independently of its strongly disarming properties, thereby complicating the interpretation of this precedent. For similar reasons, we decided not to pursue the very small but also moderately disarming cyanate esters[13] and focused instead on the arming allyl and propargyl ethers.



Thus, we began with the preparation of donors **10** and **13** by standard means from the known[5e] thiomannoside **7** (Scheme 1). A series of coupling reactions were then carried

Scheme 1. Preparation of 2-*O*-Allyl and 2-*O*-Propargyl Donors

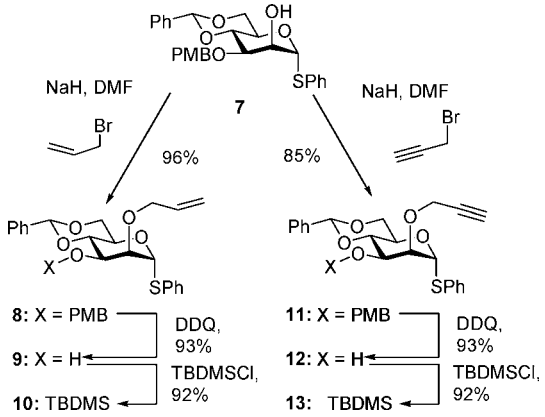
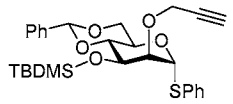
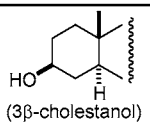
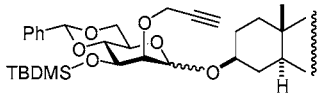
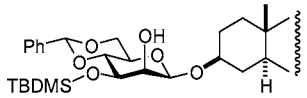
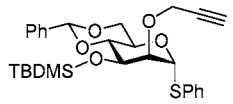
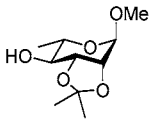
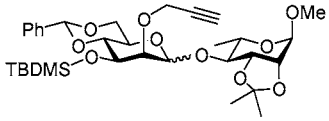
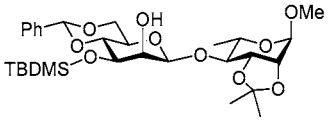
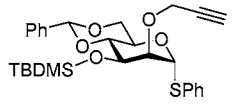
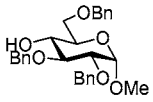
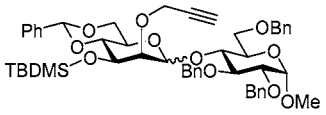
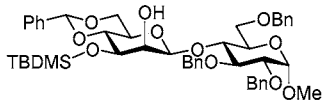
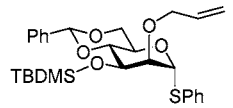
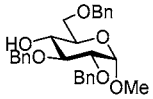
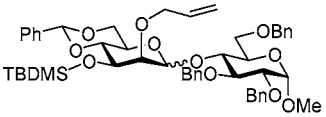


Table 1. Coupling Reactions with Donors **10** and **13** and Deprotection of the Products

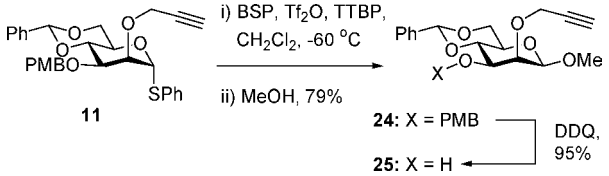
donor	acceptor	coupled product (yield, ratio)	deprotected product[a] (yield)
 **13**	 (3β-cholestanol) **14**	 **15** (91%, β:α = 13:1)	 **16** (85%)
 **13**	 **17**	 **18** (95%, β-only)	 **19** (91%)
 **13**	 **20**	 **21** (89%, β:α = 5:1)	 **22** (80%)
 **10**	 **20**	 **23** (90%, β:α = 1.5:1)	– -

[a] Only the β-isomer was deprotected.

out with activation by the 1-benzenesulfinyl piperidine (BSP)/triflic anhydride couple[14] in the presence of 2,4,6-tri-*tert*-butylpyrimidine (TTBP)[15] at −60 °C in CH_2Cl_2 before addition of the acceptor alcohol. On the basis of these couplings (Table 1),[16] it is clear that the use of the 2-*O*-propargyl ether **13** successfully overcomes the effect of the bulky silyl ether at O3, thereby vindicating our buttressing hypothesis. The allyl protected donor **10**, on the other hand, was only moderately successful in this respect and was not pursued further. Removal of the propargyl ether was achieved in a one pot protocol by isomerization to the corresponding allene with potassium *tert*-butoxide in THF, followed by cleavage with catalytic osmium tetroxide and *N*-methylmorpholine *N*-oxide (Table 1).[17] Direct exposure of the propargyl ethers to the OsO_4/NMNO conditions, without prior isomerization, also successfully brought about cleavage although in lower yields (70−80%).[18]

We next turned to the investigation of the potential use of the 2-*O*-propargyl ether in overcoming the effect of bulky glycosidic linkages at O3 of mannosyl donors. Thus, activation of **11** with BSP/Tf_2O/TTBP followed by addition of methanol gave the β-mannoside **24** in 79% yield, as a single anomer, from which removal of the PMB group afforded acceptor **25** in 95% yield (Scheme 2).

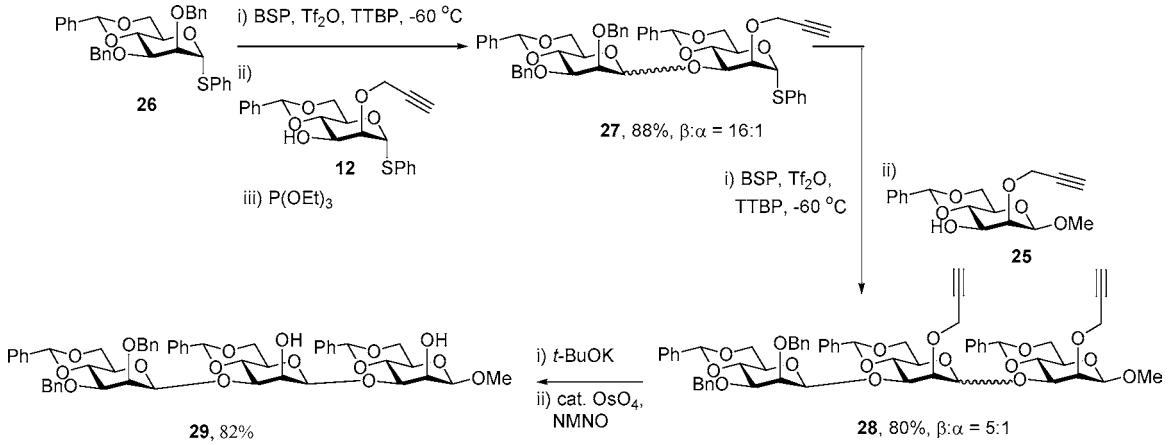
Scheme 2. Preparation of Acceptor **25**



Activation of the known donor **26**[14] with BSP/Tf_2O/TTBP followed by the addition of **12** gave the disaccharide donor **27** in 88% yield with anomeric selectivity of 16:1 in favor of the β-anomer. In this type of coupling, in which the acceptor alcohol is also a thioglycoside, the reaction mixture is treated with triethyl phosphite after the addition of the

(11) Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5386.
(12) Codée, J. D. C.; van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; van Boeckel, C. A. A.; van Boom, J. H.; van der Marel, G. A. *Tetrahedron* **2004**, *60*, 1057.
(13) Crich, D.; Hutton, T. K.; Banerjee, A.; Jayalath, P.; Picione, J. *Tetrahedron: Asymmetry* **2005**, *16*, 105.
(14) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015.
(15) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323.
(16) The anomeric configuration at the newly formed glycosidic bonds of all couplings described here was assigned on the basis of the diagnostic chemical shift of the mannose H5 as discussed previously[1] and was confirmed by the measurement of $^1J_{C,H}$ coupling constants for the anomeric carbon: Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293.
(17) Cleavage with tetrabutylammonium tetrathiomolybdate, as recommended for the removal of propargyl oxycarbonyl groups, was not successful: Ramesh, R.; Ramakrishna, G. B.; Chandrasekarahan, S. *J. Org. Chem.* **2005**, *70*, 837.
(18) Presumably, this chemistry results from β-elimination at the level of the intermediate 1,2-dihydroxyalkene.

Scheme 3. Stereoselective Synthesis of a β-(1→3)-Mannan



acceptor and before it is allowed to warm to room temperature. This protocol, introduced by van Boom,[12a,19,20] is designed to quench any thiophilic species in the reaction mixture before they are able to activate the thioglycoside in the product, reduce yields and complicate isolation.[21,22] Coupling of disaccharide donor **27** to acceptor **25** was achieved by the standard BSP/Tf_2O/TTBP preactivation protocol, yielding the trisaccharide **28** in 80% yield as a 5:1 separable β/α mixture. Finally, the two propargyl ether protecting groups were cleaved from **28** in 82% yield by the isomerization/catalytic osmoylation protocol (Scheme 3).

The 5:1 β/α ratio obtained in the coupling of **27** to **25** represents a very significant improvement over the ratios obtained previously[5e] in couplings to the related disaccharide donors **4** and **5** and, together with the facile removal of the propargyl ether group, suggests that a means to the convergent, stereoselective assembly of β-mannans linked via O3 is at hand.

We conclude that 2-*O*-propargyl ether protected mannosyl donors provide a means of overcoming the poor stereoselectivity previously observed with donors bearing bulky groups, silyl ethers or glycosidic bonds, on O-3. We hypothesize that the increased selectivity arises because of a minimization of a buttressing effect between the O2 and O3 protecting groups, which generally results in a more open β-face in the glycosyl donor.

Acknowledgment. We thank the NIGMHS for financial support (GM 57335).

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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(19) (a) 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. (b) Codée, J. D. C.; van den Bos, J.; Litjens, R. E. J. N.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1947.

(20) The use of phosphites to clean up extraneous thiophiles in sulfoxide glycosylations has also been described by van Boom and others: (a) Sliedregt, L. A. J. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1994**, *35*, 4015. (b) Alonso, I.; Khiar, N.; Martin-Lomas, M. *Tetrahedron Lett.* **1996**, *37*, 1477.

(21) For a recent synthesis of a small oligosaccharide library using the thioglycoside/BSP method and involving the use of thioglycoside alcohols as acceptors, see: Yamago, S.; Yamada, H.; Maruyama, T.; Yoshida, J.-i. *Angew. Chem., Int. Ed.* **2004**, *43*, 2145.

(22) Other traps for thiophilic agents previously employed in the sulfoxide method include alkenes and alkynes: (a) Yan, L.; Kahne, D. *J. Am. Chem. Soc.* **1996**, *118*, 9239. (b) Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580.