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Enhanced Diastereoselectivity in β-Mannopyranosylation through the Use of Sterically Minimal Propargyl Ether Protecting Groups

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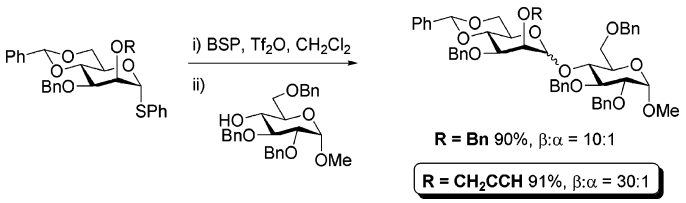

2-*O*-Propargyl ethers are shown to be advantageous in the 4,6-*O*-benzylidene acetal directed β-mannosylation reaction. The effect is most pronounced when the O3 protecting group is a bulky silyl ether or a glycosidic bond; however, even with a 3-*O*-benzyl ether, the use of a 2-*O*-propargyl ether results in a significant increase in diastereoselectivity. The beneficial effect of the propargyl ether is thought to be a combination of its minimal steric bulk, as determined by a measurement of the steric A-value and of its moderately disarming nature, as reflected in the pK_a of propargyl alcohol. Conversely, the application of a 3-*O*-propargyl ether in the benzylidene acetal directed mannosylation has a detrimental effect on stereoselectivity, for which no explanation is at present available. Deprotection is achieved by base-catalyzed isomerization of the propargyl ether group to the corresponding allenyl ether, followed by oxidative cleavage with *N*-methylmorpholine *N*-oxide and catalytic osmium tetroxide.

Introduction

Protecting groups play a central role in carbohydrate chemistry,[1] with applications extending beyond the simple blocking of hydroxyl groups to the modulation of reactivity of both glycosyl donors and acceptors and, critically, the control of anomeric stereochemistry. Indeed, the development of new protecting groups capable of rendering enhanced control of regioselectivity,[2] reactivity,[3] and stereoselectivity,[4] can be said to be one of the current frontiers of the discipline.

The influence of even remote protecting groups on the control of anomeric stereochemistry is illustrated by the 4,6-*O*-benzylidene protected β-mannosyl donors developed in this laboratory,[5] in which the benzylidene acetal, or its surrogate,[4d,6] is now understood to function by restricting the C5−C6 bond to the more disarming[7] *tg* conformer,[8,9] thereby limiting the lifetime of the transient contact ion pair[10] that is in equilibrium with the covalent glycosyl triflate intermediate.[5c,11]

However powerful this method may be in the synthesis of complex oligosaccharides containing the β-mannopyranoside and related linkages,[12,13] it is not without limitations. Thus, the use of donors bearing bulky groups on O3, either silyl ethers or glycosidic bonds, diminishes the selectivity of the mannosylation.[14]

Although the effect of the O3 protecting group on anomeric stereoselectivity is not yet fully understood, we introduced the use of 2-*O*-propargyl ether as a means of overcoming the loss of selectivity as a result of the use of bulky groups at O3.[15] In

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(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*, 53−80.

(3) (a) Glaudemans, C. P. J.; Fletcher, H. G. *J. Am. Chem. Soc.* **1965**, *87*, 4636−4641. (b) Ishikawa, T.; Fletcher, H. G. *J. Org. Chem.* **1969**, *34*, 563−571. (c) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583−5584. (d) Fraser-Reid, B.; Madsen, R. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Dekker: New York, 1997; pp 339−356. (e) Fraser-Reid, B.; Anilkumar, G.; Gilbert, M. R.; Joshi, S.; Kraehmer, R. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, 2000; Vol. 1, pp 135−154. (f) Douglas, N. L.; Ley, S. V.; Lucking, U.; Warriner, S. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 51−65. (g) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734−753.

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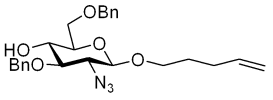
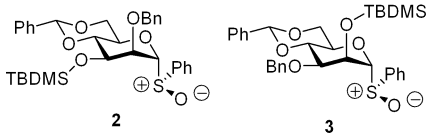
this article we examine in greater detail the potential of the readily cleavable, minimally sterically unintrusive propargyl ether protecting group and show how, in conjunction with the correct choice of other protecting groups, it can lead to considerable enhancements in the stereoselectivity of mannopyranosylation reactions and even the very challenging rhamnopyranosylations.

Results and Discussion

The problem of diminished selectivity caused by bulky groups on O3 was initially encountered in the synthesis of the common core pentasaccharide of the *N*-linked glycans,[13a] when coupling of the 2-*O*-benzyl-3-*O*-TBDMS mannosyl donor **2** with pentenyl glycoside acceptor **1** exhibited poor selectivity (77%, α/β = 1.8:1). In contrast, with the 2-*O*-TBDMS-3-*O*-benzyl donor **3**, the selectivity was significantly better (72%, α/β = 1:3), albeit still not at the high levels typically experienced with more standard 2,3-di-*O*-benzyl protected donors.[16]

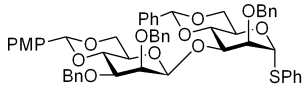


1



2 **3**

A more critical manifestation of this problem presented itself during the synthesis of the alternating β-(1 → 3)-β-(1 → 4)-mannan common to *Rhodotorula glutinis*, *Rhodotorula mucilaginosa*, and *Leptospira biflexa*.[14b] Donors **4** and **5**, both displaying very bulky glycosyl substituents on O3, showed unusually poor β selectivity in coupling reactions, thereby reducing the efficiency of the convergent synthesis of the target polysaccharide.



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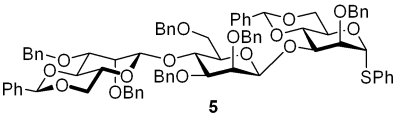
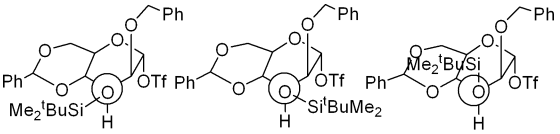


5

We hypothesized that the poor selectivity seen with donors **2**, **4**, and **5** was the result of steric buttressing between the O2 and O3 protecting groups, resulting in unusually high shielding of the β face of the glycosyl donor.[14a,15] Thus, as illustrated for the triflate derived from **2**, we reason that, of the three possible staggered conformations around the O3-substituent bond, **A** is disfavored by the steric interaction with the rigid benzylidene ring leading to the preferential population of conformers **B** and **C** in which the bulky silyl group is gauche to C2 and its substituent (Figure 1).



A **B** **C**

FIGURE 1. Staggered conformations about the C3−O3 bond.

Viewed from the perspective of the O2-substituent bond, the population of conformer **D** is likely extremely small due to high steric congestion. The bulky group on O3 presumably destabilizes conformation **E**, thus leaving **F** as the most populous state (Figure 2). In conformer **F** the 2-*O*-benzyl ether is in close

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(5) (a) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198−1199. (b) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321−8348. (c) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015−9020. (d) Crich, D. In *Glycochemistry: Principles, Synthesis, and Applications*; Wang, P. G., Bertozzi, C. R., Eds.; Dekker: New York, 2001; pp 53−75. (e) Crich, D. *J. Carbohydr. Chem.* **2002**, *21*, 663−686.

(6) (a) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2002**, *124*, 8867−8869. (b) Crich, D.; de la Mora, M.; Vinod, A. U. *J. Org. Chem.* **2003**, *68*, 8142−8148.

(7) In the terminology of Fraser-Reid, a disarming protecting group is one that deactivates a glycosyl donor, whereas an arming protecting group is one that activates a glycosyl donor.[1b,3c]

(8) Jensen, H. H.; Nordstrom, M.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 9205−9213.

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(10) Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5386−5389.

(11) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217−11223.

(12) For examples from this laboratory, see ref 4d and the following: (a) Crich, D.; Li, H.; Yao, Q.; Wink, D. J.; Sommer, R. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2001**, *121*, 5826−5828. (b) Crich, D.; Li, H. *J. Org. Chem.* **2002**, *67*, 4640−4646. (c) Crich, D.; Dai, Z. *Tetrahedron* **1999**, *55*, 1569−1580. (d) Crich, D.; Barba, G. R. *Tetrahedron Lett.* **1998**, *39*, 9339−9342. (e) Crich, D.; de la Mora, M. A.; Cruz, R. *Tetrahedron* **2002**, *58*, 35−44. (f) Crich, D.; Banerjee, A.; Yao, Q. *J. Am. Chem. Soc.* **2004**, *126*, 14930−14934. (g) Crich, D.; Banerjee, A. *Org. Lett.* **2005**, *7*, 1935−1938. (h) Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2002**, *124*, 2263−2266. (i) Dudkin, V. Y.; Crich, D. *Tetrahedron Lett.* **2003**, *44*, 1787−1789.

(13) For examples from other laboratories, see: (a) Dudkin, V. K.; Miller, J. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 736−738. (b) Miller, J. S.; Dudkin, V. Y.; Lyon, G. J.; Muir, T. W.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 431−434. (c) Nicolaou, K. C.; Mitchell, H. J.; Rodriguez, R. M.; Fylaktakidou, K. C.; Suzuki, H.; Conley, S. R. *Chem.—Eur. J.* **2000**, *6*, 3149−3165. (d) Kim, K. S.; Kang, S. S.; Seo, Y. S.; Kim, H. J.; Jeong, K.-S. *Synlett* **2003**, 1311−1314. (e) Wu, X.; Schmidt, R. R. *J. Org. Chem.* **2004**, *69*, 1853−1857. (f) Kwon, Y. T.; Lee, Y. J.; Lee, K.; Kim, K. S. *Org. Lett.* **2004**, *6*, 3901−3904. (g) Tanaka, S.-i.; Takashina, M.; Tokimoto, H.; Fujimoto, Y.; Tanaka, K.; Fukase, K. *Synlett* **2005**, 2325−2328.

(14) (a) Crich, D.; Dudkin, V. *Tetrahedron Lett.* **2000**, *41*, 5643−5646. (b) Crich, D.; Li, W.; Li, H. *J. Am. Chem. Soc.* **2004**, *126*, 15081−15086. (c) Codée, J. D. C.; Hossain, L. H.; Seeberger, P. H. *Org. Lett.* **2005**, *7*, 3251−3254.

(15) Crich, D.; Jayalath, P. *Org. Lett.* **2005**, *7*, 2277−2280.

(16) Crich, D.; Lim, L. B. L. *Org. React.* **2004**, *64*, 115−251.

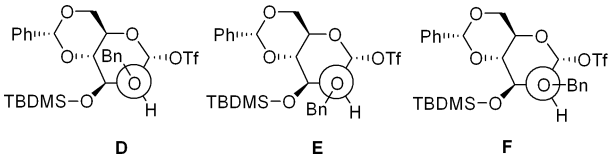
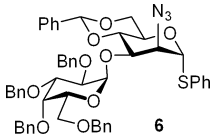


FIGURE 2. Staggered conformations about the C2−O2 bond.

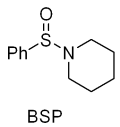
proximity to the β face of the α-mannosyl triflate. This enhanced steric shielding retards attack on the β face, either on the covalent triflate itself or on the transient contact ion pair arising from the covalent triflate, thereby resulting in the observed loss of β selectivity.

In systems such as **2** this problem can be circumvented by the simple ruse of switching to a less bulky O3 protecting group, however, in target-directed convergent oligosaccharide synthesis there is no way to avoid the use of donors such as **4** and **5**. We reasoned that the unfavorable steric interaction in conformer **E** could be reduced by minimizing the size of the O2 protecting group, which should have the effect of increasing the population of **E** at the expense of **F**. At the same time, the use of a protecting group with a low steric demand on O2, should serve to minimize the detrimental effect of any residual population of conformer **F**. We were encouraged in this line of thinking by the work of van Boom et al. on the successful β-glycosylation of several acceptors by donor **6** with the relatively small 2-azido group.[17] However, the size 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,[4e] and to focus instead on the allyl and propargyl ethers.



We began with the synthesis of the 3-*O*-silyl compounds **10** and **13** (Scheme 1) by standard means from the known thioglycoside **7**.[14b] In these syntheses, the 3-*O*-silyl group was introduced after the allyl or propargyl ethers to preempt problems of silyl migration that were anticipated in the reverse protocol.

Donors **10** and **13** were then coupled to the acceptor **14** by our standard BSP/TTBP/Tf_2O (BSP = 1-benzenesulfinyl piperidine, TTBP = 2,4,6-tri-*tert*-butylpyrimidine, and Tf_2O = trifluoromethanesulfonic anhydride) protocol[5c,16] leading to the yields and selectivities outlined in Table 1. Included in Table 1 for comparison is the previous coupling[14a] of donor **2** to acceptor **1** by the directly analogous sulfoxide method.[16]



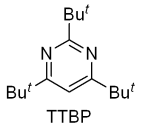
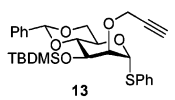
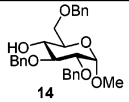
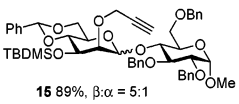
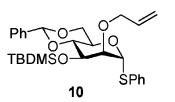
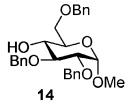
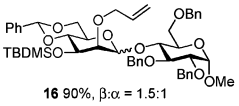
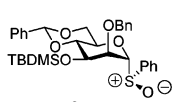
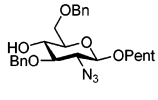
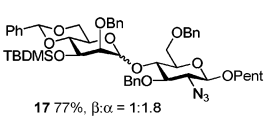
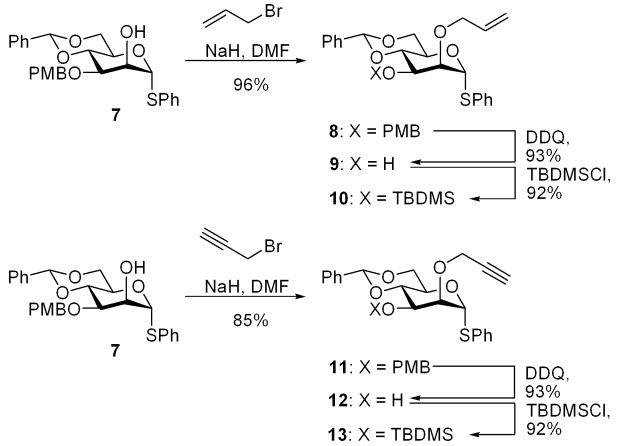


TABLE 1. Influence of the O2 Protecting Group on Selectivity

Donor	Acceptor	Product (yield, ratio)
 **13**	 **14**	 **15** 89%, β:α = 5:1
 **10**	 **14**	 **16** 90%, β:α = 1.5:1
 **2**	 **1**	 **17** 77%, β:α = 1:1.8

These results strongly support the hypothesis of the beneficial effect of reducing the bulk of the O2 protecting group on the stereochemical outcome of the reaction, with the best anomeric ratio obtained with the smallest O2 protecting group. To put the inverse relationship between the steric bulk of the O2 protecting group and the anomeric selectivity on a more secure footing, we measured steric A-values for the propargyloxy, allyloxy, benzyloxy, and *tert*-butyldimethylsiloxy groups by the classical ^{1}H VT-NMR method (Table 2).[18] The observed trend in A-values fully supports the initial hypothesis, with the propargyl ether being significantly smaller than the allyl ether, which in turn is smaller than the benzyl ether. The A-value for the *tert*-butyldimethylsiloxy group determined here, and included for comparison purposes, is significantly greater than that previously measured by Eliel for the same group using an alternative ^{13}C NMR method,[19] but is consistent with the general trend of coupling selectivities observed in this entire study.

SCHEME 1. Synthesis of Donors 10 and 13



In addition to the smaller size of the propargyl ether, we also considered the possibility that it might exhibit an electron-withdrawing effect. Indeed, the sp-hybridization of the alkyne carbon renders the propargyloxy group moderately electron-withdrawing with respect to the other ethers studied, as seen from the pK_a's of the corresponding alcohols (Table 2),[20] and

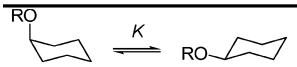
(17) (a) Codée, J. D. C.; Litjens, R. E. J. N.; den Heeten, R.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1519−1522. (b) Codée, J. D. C.; van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; van Boeckel, C. A. A.; van Boom, J. H.; van der Marel, G. A. *Tetrahedron* **2004**, *60*, 1057−1064.

(18) Jensen, F. R.; Bushweller, C. H.; Beck, B. H. *J. Am. Chem. Soc.* **1969**, *91*, 344−351.

(19) Eliel, E. L.; Satici, H. *J. Org. Chem.* **1994**, *59*, 688−689.

(20) *Dictionary of Organic Compounds*; Chapman and Hall: London, 1996.

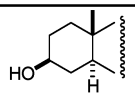
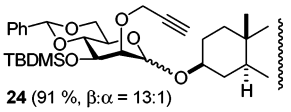
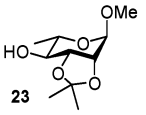
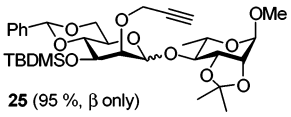
TABLE 2. Steric A-Values and pK_a's



A-Values, R' = C_6H_{11} (**18- 21**)				p*K*a (R' = H)
	Temp[a] (K)	*K*[b]	A[c]	
R'O	193	17.7	1.10	13.6
R'O	193	26.2	1.25	15.5
R'O	203	31.5	1.39	15.4
R'O−TBDMS	193	49.4	1.50	-

[a] Measurement temperature. [b] Equilbrium constant. [c] $A = RT\ln K$.

TABLE 3. Further Couplings to Donor 13

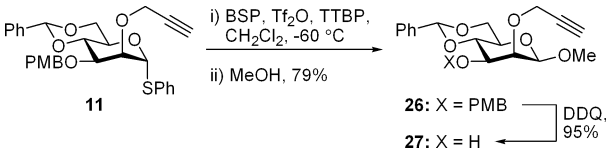
Acceptor	Coupled Product (yield, ratio)
 (3β-cholestanol) **22**	 **24** (91 %, β:α = 13:1)
 **23**	 **25** (95 %, β only)

it is likely that the beneficial effect of the 2-*O*-propargyl ethers arises from a combination of the minimal steric bulk and its moderately disarming property.

The coupling of donor **13** to two further substrates, again with excellent results (Table 3), confirmed the ability of the 2-*O*-propargyl ether protecting group to overcome the deleterious effects of a 3-*O*-silyl ether.

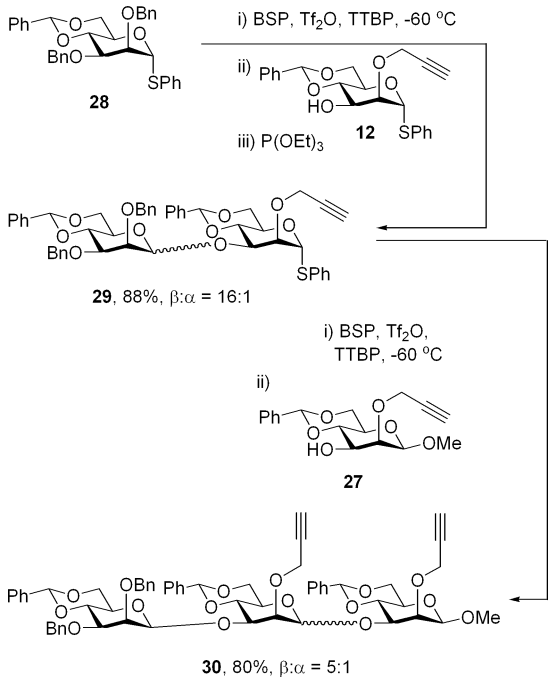
Attention was next focused on donors bearing a glycosidic bond at O3, analogous to the problematic **4** and **5**. Furthermore, bearing in mind the potential for the eventual use in mannan synthesis, a glycosyl acceptor carrying a 2-*O*-propargyl ether was also prepared (Scheme 2).

SCHEME 2. Synthesis of Acceptor 27



Acceptor **12** was successfully coupled to the known donor **28**[5c] with α/*β* selectivity of 1:16 in 88% yield (Scheme 3). Per the protocol of van Boom et al.,[14b,17,21] triethyl phosphite was added after the addition of the acceptor **12** to limit the premature activation of its thioglycoside functionality by any extraneous

SCHEME 3. Synthesis of a Mannotriose Using 2-*O*-Propargyl Ethers



thiophiles. The coupling of the disaccharide donor **29** to acceptor **27** then gave the mannotriose in 80% yield with an α/*β* ratio of 1:5, presenting a very significant improvement over the approximately 1:1 α/*β* ratio observed with donor **4** and a related acceptor.[14b] Additionally, the successful couplings employing compounds **12** and **27** illustrate that propargyl ethers are also suitable for the protection of acceptors.

With a means to overcome the unfavorable effect of a bulky O3 substituent in hand, we proceeded to undertake a broader investigation into the general effects of propargyl ethers on stereoselectivity in 4,6-*O*-benzylidene-directed *β*-mannosylation reactions. Specifically, we reasoned that while the steric buttressing effect discussed above and illustrated in Figures 1 and 2 will be maximized with a large group on O3, it will necessarily be present with more common protecting groups on O3, albeit to a lesser extent. Accordingly, the use of a 2-*O*-propargyl ether, even in conjunction with a 3-*O*-benzyl ether, should lead to enhanced selectivity over the more typical 2,3-di-*O*-benzyl-protected donors. To probe this idea, a series of four donors were prepared using standard techniques from diol **31**[14b] via the known monobenzyl ethers **32** and **34**[14b] (Scheme 4).

Subsequent coupling of this series of donors to a standard acceptor **14** gave the results presented in Table 4. A comparison of entries 1 and 2 in Table 4 clearly demonstrates that a 2-*O*-propargyl ether leads to enhanced *β* selectivity even with the 3-*O*-benzyl-protected system, in accordance with the above stated hypothesis. The 3-*O*-propargyl donor **35** (Table 4, entry 3) gave surprisingly poor but reproducible results for which we have no satisfactory explanation at the present time. It is clear, however, that the O3 group plays a major role in these 4,6-*O*-benzylidene protected *β*-mannosylation reactions and that the issue of steric bulk and buttressing discussed here is only one facet of the problem.[22] Taking into account the selectivities obtained with donors **33** and **35**, it is clear that the modest 10:1 *β*/α selectivity obtained with the 2,3-di-*O*-propargyl-protected

(21) (a) 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*, 1947−1950. (b) Sliedregt, L. A. J. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1994**, *35*, 4015−4018. (c) Alonso, I.; Khiar, N.; Martin-Lomas, M. *Tetrahedron Lett.* **1996**, *37*, 1477−1480.

SCHEME 4. Synthesis of Donors 33, 35, and 36

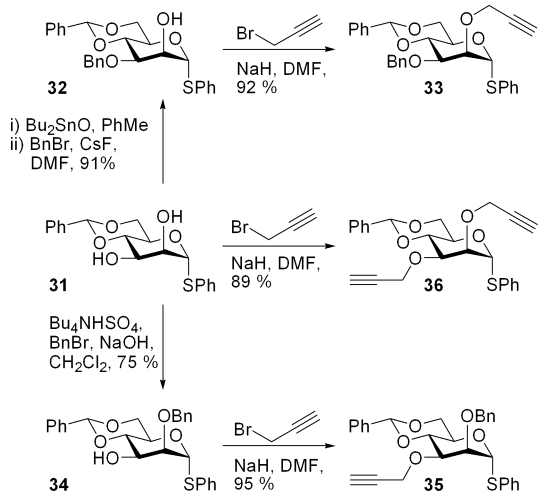
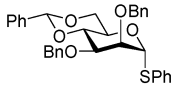
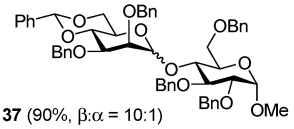
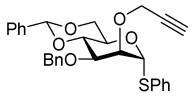
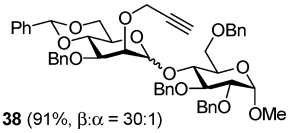
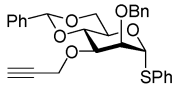
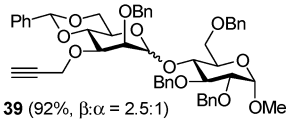
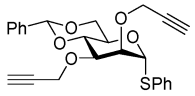
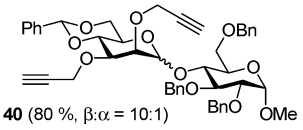


TABLE 4. Coupling of Mono- and Di-*O*-proparyl Protected Donors to 14

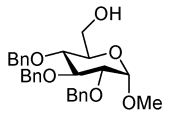
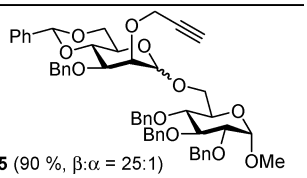
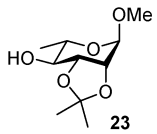
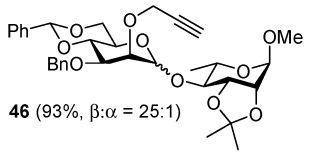
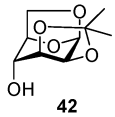
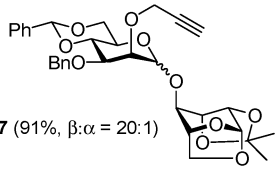
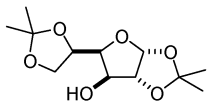
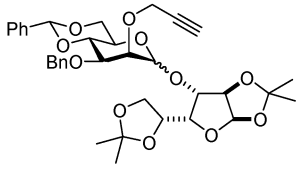
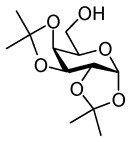
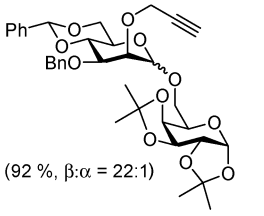
Donor	Product (yield, ratio)
 **28**	 **37** (90%, β:α = 10:1)
 **33**	 **38** (91%, β:α = 30:1)
 **35**	 **39** (92%, β:α = 2.5:1)
 **36**	 **40** (80 %, β:α = 10:1)

donor **36** (Table 4, entry 4) is a compromise between the excellent selectivity obtained with a 2-*O*-propargyl group alone and the obviously harmful effect of the 3-*O*-propargyl ether.

The very encouraging results obtained with donor **33**, featuring the combination of the 2-*O*-propargyl and 3-*O*-benzyl ether protecting groups, were then extended to encompass a broader range of typical acceptor alcohols (Table 5). In each case, excellent yields and β/α selectivies surpassing 20:1 were obtained.

While the use of allyl ethers as protecting groups is extremely widespread,[1a,23] that of propargyl ethers is novel and requires

TABLE 5. Coupling of 33 to Further Acceptors

Acceptor	Product (yield, ratio)
 **41**	 **45** (90 %, β:α = 25:1)
 **23**	 **46** (93%, β:α = 25:1)
 **42**	 **47** (91%, β:α = 20:1)
 **43**	 **48** (90%, β:α = 23:1)
 **44**	 **49** (92 %, β:α = 22:1)

the investigation of suitable deprotection conditions. It has been reported that propargyl ethers may be cleaved with benzyltriethylammonium tetrathiomolybdate,[24] with low-valent titanium in hot THF,[25] and by a nickel-catalyzed electrochemical protocol.[26] However, on the basis of experience in our laboratory with allyl ethers in oligosaccharide synthesis,[12c,d,27] we have preferred a method involving base-catalyzed isomerization to the corresponding allenyl ether, followed by an oxidative cleavage with catalytic osmium tetroxide in the presence of *N*-methyl morpholine *N*-oxide (NMNO), as reported by Mereyala and co-workers,[28] albeit under somewhat milder conditions. Thus, a representative series of propargyl ether-protected saccharides was treated with potassium *tert*-butoxide in THF at room temperature, followed by exposure to catalytic OsO_4 in the presence of NMNO, also at room temperature, resulting in a hydrolysis to the corresponding alcohols (Table 6).

Finally, we have briefly investigated the potential of the 2-*O*-propargyl ether protecting group in the synthesis of β-L-

(22) For example, we have previously discussed the highly α-selective couplings obtained in the presence of a 3-*O*-carboxylate ester. The origin of these effects is currently under active investigation in our laboratory. See ref 4d and Crich, D.; Cai, W.; Dai, Z. *J. Org. Chem.* **2000**, *65*, 1291−1297.

(23) (a) Guibé, F. *Tetrahedron* **1997**, *53*, 13509−13556. (b) Guibé, F. *Tetrahedron* **1998**, *54*, 2967−3042. (c) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Thieme: Stuttgart, 2005. (d) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.

(24) Swamy, V. M.; Ilankumaran, P.; Chandrasekaran, S. *Synlett* **1997**, 513−514.

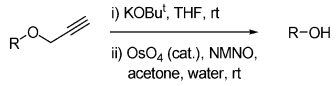
(25) Nayak, S. K.; Kadam, S. M.; Banerji, A. *Synlett* **1993**, 581−582.

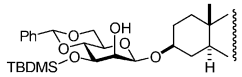
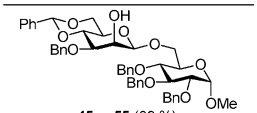
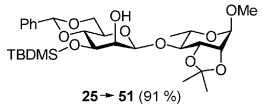
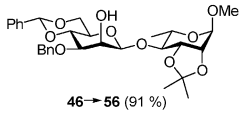
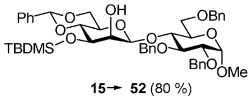
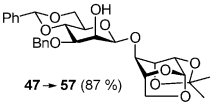
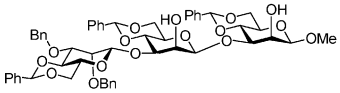
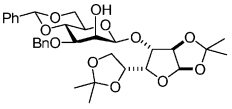
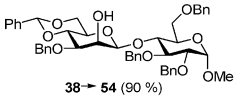
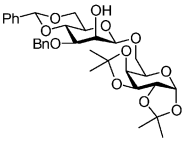
(26) Olivero, S.; Dunach, E. *Tetrahedron Lett.* **1997**, *38*, 6193−6196.

(27) Crich, D.; Hwang, J.-T.; Yuan, H. *J. Org. Chem.* **1996**, *61*, 6189−6198.

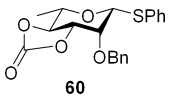
(28) Mereyala, H. B.; Gurrala, S. R.; Mohan, S. K. *Tetrahedron* **1999**, *55*, 11331−11342.

TABLE 6. Cleavage of Propargyl Ethers



Deprotected Product (yield)	Deprotected Product (yield)
 **24** → **50** (85 %)	 **45** → **55** (89 %)
 **25** → **51** (91 %)	 **46** → **56** (91 %)
 **15** → **52** (80 %)	 **47** → **57** (87 %)
 **30** → **53** (82 %)	 **48** → **58** (88 %)
 **38** → **54** (90 %)	 **49** → **59** (90 %)

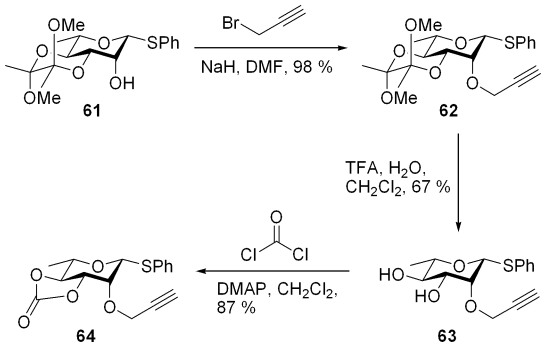
rhamnopyranosides, a cognate problem to that of the β-D-mannopyranosides but one which does not allow the use of the stereo-directing 4,6-*O*-benzylidene acetal function in the donor. As part of our ongoing effort in this area,[4e,29] we reported that the 3,4-*O*-carbonate-protected rhamnosyl donor **60** gave moderate to good β/α selectivity (1.5:1 to β only) on coupling to various acceptors under the standard BSP/Tf_2O/TTBP conditions, depending on the reactivity of the acceptor.[4f]


60

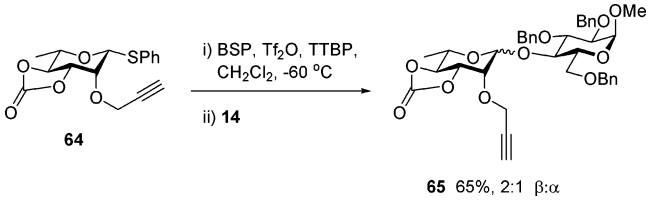
It was reasonable, therefore, to investigate the analogous 2,3-*O*-carbonate **64**, which was prepared as set out in Scheme 5 from the known[4f] bisacetal **61**.

Activation of **64**, which proceeded smoothly under the standard conditions, was followed by the addition of methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **14**, a member of the glucose 4-OH derivatives that are known to be relatively difficult to glycosylate,[30] giving the disaccharide **65** in 65% yield in the form of a 2:1 β/α mixture (Scheme 6). This represents only a modest improvement of selectivity over the 1.5:1 β/α ratio obtained on the coupling of **60** with **14**,[4f] and this discouraged us from further work with this donor. Presumably, there is very little buttressing interaction between the tied back carbonate and the protecting group on O2. As such, the effect on stereoselectivity from changing the O2 protecting from the benzyl ether to the propargyl ether is very small.

SCHEME 5. Preparation of Rhamnosyl Donor 64



SCHEME 6. Glycosylation in the Rhamnopyranose Series



Overall, propargyl ethers are readily introduced and cleaved protecting groups for alcohols that bring about significant improvements in the diastereoselectivity of many mannosylation reactions, which we attribute to the combination of their minimal steric bulk and their modest disarming power. While we have focused on the application of this protecting group to the solution of current problems in our laboratory, we anticipate that it will find a broader application in organic synthesis, especially in situations in which the steric bulk of a protecting group is a factor.

Experimental Section

Phenyl 4,6-*O*-Benzylidene-2-*O*-(prop-2-ynyl)-3-*O*-*p*-methoxybenzyl-1-thio-α-D-mannopyranoside (11). To a stirred solution of phenyl 4,6-*O*-benzylidene-3-*O*-*p*-methoxybenzyl-1-thio-α-D-mannopyranoside (2.5 g, 5.5 mmol) in dry dimethylformamide (15 mL) at 0 °C was added 60% NaH in oil (0.33 g, 8.3 mmol). The mixture was stirred for 15 min. Propargyl bromide (0.93 mL, 8.3 mmol) was added dropwise to the above reaction mixture, and stirring was continued for 3 h. The reaction mixture was quenched by the addition of methanol, diluted with CH_2Cl_2 (25 mL), and washed with saturated $NaHCO_3$. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel (hexane/ethyl acetate, 8:1) to give **11** (2.46 g, 85%): $[\alpha]^{24.5}_D$ +155.8 (*c* 2.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.4 (t, *J* = 2.4 Hz, 1H), 3.82 (s, 3H), 3.87 (t, *J* = 11.0 Hz, 1H), 3.98 (dd, *J* = 3.0, 10.0 Hz, 1H), 4.19−4.24 (m, 3H), 4.26−4.31 (m, 1H), 4.4 (dd, *J* = 0.5, 2.0 Hz, 2H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 5.61 (d, *J* = 1.5 Hz, 1H), 5.63 (s, 1H), 6.9 (d, *J* = 8.6 Hz, 2H), 7.3−7.45 (m, 10H), 7.5−7.56 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.3, 58.8, 65.4, 68.5, 72.9, 75.2, 75.7, 77.6, 79.0, 79.4, 87.4, 101.5, 113.8, 126.1, 127.6, 128.2, 128.8, 129.1, 129.2, 129.4, 130.2, 131.6, 133.7, 134.5, 137.5, 159.3. ESI-HRMS calcd for $C_{30}H_{30}O_6S$ $[M + Na]^+$, 541.1661; found, 541.1658.

Phenyl 4,6-*O*-Benzylidene-2-*O*-(prop-2-ynyl)-1-thio-α-D-mannopyranoside (12). To a stirred solution of **11** (0.47 g, 0.91 mmol) in CH_2Cl_2 (8 mL) and water (0.4 mL) was added DDQ (0.3 g, 1.3 mmol) at room temperature. After 3 h, saturated $NaHCO_3$ was

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added, and the mixture was extracted with CH_2Cl_2. The extract was washed several times with saturated $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave an oil, which was chromatographed on a flash silica gel column (hexane/ethyl acetate, 4:1) to give **12** (0.34 g, 93%) as a white solid: mp 128 °C; $[\alpha]^{27}_D$ +119 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.49 (t, J = 2.4 Hz, 1H), 2.5 (br s, 1H), 3.84 (t, J = 10.2 Hz, 1H), 3.9 (t, J = 9.6 Hz, 1H), 4.16 (dd, J = 3.6, 10.0 Hz, 1H), 4.21−4.24 (m, 2H), 4.27−4.32 (m, 1H), 4.34 (dd, J = 2.4, 16.1 Hz, 1H), 4.42 (dd, J = 2.4, 16.1 Hz, 1H), 5.59 (s, 1H), 5.68 (s, 1H), 7.32−7.53 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 58.6, 64.7, 68.4, 68.9, 75.7, 78.9, 79.3, 79.4, 86.4, 102.2, 126.3, 127.7, 128.3, 129.2, 131.7, 133.8, 137.2. ESI-HRMS calcd for $C_{22}H_{22}O_5S$ [M + Na]$^+$, 421.1086; found, 421.1095.

Phenyl 4,6-*O*-Benzylidene-2-*O*-(prop-2-ynyl)-3-*O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-*β*-D-mannopyranosyl)-1-thio-α-D-mannopyranoside 29*β* and the α-Anomer 29α. To a stirred solution of donor **28** (480 mg, 0.88 mmol), BSP (223 mg 1.06 mmol), TTBP (331 mg, 1.33 mmol), and 4-Å molecular sieves in CH_2Cl_2 (5 mL), at −60 °C under an Ar atmosphere, was added Tf_2O (195 μL 1.15 mmol). After 30 min, the temperature was brought down to −78 °C, and then acceptor **12** (424 mg 1.06 mmol) in CH_2Cl_2 (3 mL) was slowly added. The reaction mixture was stirred for 2 h at −78 °C and quenched by the addition of triethyl phosphite (435 μL, 2.7 mmol). The mixture continued stirring for 1 h at −78 °C and was then allowed to reach room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL), the molecular sieves were filtered off, and the mixture was washed with saturated $NaHCO_3$. The organic layer was separated, dried, and concentrated. The crude was purified by radial chromatography (hexane/ethyl acetate, 8:1) to give **29*β*** and **29α** in 83 and 5% yield, respectively. **29*β***: $[\alpha]^{24}_D$ + 26.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.23 (t, J = 2.4 Hz, 1H), 3.29−3.34 (m, 1H), 3.6 (dd, J = 3.2, 9.7 Hz, 1H), 3.86 (t, J = 10.3 Hz, 1H), 3.93 (t, J = 10.3 Hz, 1H), 4.0 (d, J = 3.0 Hz, 1H), 4.13 (t, J = 9.7 Hz, 1H), 4.25−4.40 (m, 8H), 4.65 (d, J = 12.5 Hz, 1H), 4.76 (d, J = 12.5 Hz, 1H), 4.84 (s, 1H), 4.86 (d, J = 11.9 Hz, 1H), 4.98 (d, J = 11.8 Hz, 1H), 5.58 (s, 1H), 5.62 (s, 1H), 5.64 (s, 1H), 7.24−7.49 (m, 25H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 57.5, 65.3, 67.8, 68.5, 68.6, 72.3, 73.4, 74.8, 75.6, 75.7, 76.5, 77.5, 77.6, 78.6, 79.0, 86.0, 98.9, 101.3, 101.9, 126.0, 126.2, 127.4, 127.6, 127.7, 127.8, 128.0, 128.1, 128.2, 128.3, 128.4, 128.8, 129.0, 129.2, 131.6, 133.6, 137.3, 137.6, 138.4, 138.7. ESI-HRMS calcd for $C_{49}H_{48}O_{10}S$ [M + Na]$^+$, 851.2866; found, 851.2875. **29α**: $[\alpha]^{24}_D$ +76.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.4 (t, J = 2.4 Hz, 1H), 3.8 (t, J = 10.5 Hz, 1H), 3.92−3.96 (m, 2H), 3.99−4.04 (m, 2H), 4.15 (t, J = 9.5 Hz, 1H), 4.2 (dd, J = 2.5, 16.1 Hz, 1H), 4.25−4.38 (m, 7H), 4.5 (d, J = 12.4 Hz, 1H), 4.62 (d, J = 12.4 Hz, 1H), 4.63 (d, J = 12.2 Hz, 1H), 4.7 (d, J = 12.2 Hz, 1H), 5.4 (d, J = 1.2 Hz, 1H), 5.57 (s, 1H), 5.59 (s, 1H), 5.67 (s, 1H), 7.15−7.52 (m, 25H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 58.3, 64.7, 65.1, 68.5, 68.8, 72.1, 72.7, 72.8, 75.3, 75.7, 78.5, 79.0, 79.2, 86.9, 99.6, 101.4, 101.9, 125.9, 126.1, 127.5, 127.6, 127.7, 127.8, 128.2, 128.4, 128.8, 129.2, 129.3, 131.6, 133.5, 137.3, 137.7, 137.8, 138.5. ESI-HRMS calcd for $C_{49}H_{48}O_{10}S$ [M + Na]$^+$, 851.2866; found, 851.2874.

General Procedure for the Deprotection of Propargyl Ethers. To a stirred solution of propargyl ether (1 mmol) in dry THF (5 mL) was added KO*t*-Bu (1.1 mmol), and stirring was continued at room temperature for 3−12 h until the TLC indicated completion. The reaction mixture was diluted with CH_2Cl_2 (10 mL). The organic phase was separated, washed with water, dried (Na_2SO_4), and concentrated on a rotary evaporator to give the allenyl ethers in quantitative yields. A homogeneous solution of allenyl ethers (1 mmol) in acetone/water (4:1, 5 mL) was treated with OsO_4 (0.1 mmol) and *N*-methyl morpholine *N*-oxide (2 mmol), and the mixture was stirred for 3 h at room temperature. After the completion of the reaction, acetone was removed under vacuum, and the residue was dissolved in CH_2Cl_2 (10 mL) and washed with saturated $NaHSO_3$. The organic phase was separated, dried (Na_2SO_4), and concentrated on a rotary evaporator. The residues were purified by flash or radial chromatography on silica gel to yield deprotected di- and trisaccharides in 80−91%.

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Supporting Information Available: Full experimental details and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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