ORGANIC LETTERS

2008
Vol. 10, No. 11
2107−2110

Application of the Superarmed Glycosyl Donor to Chemoselective Oligosaccharide Synthesis

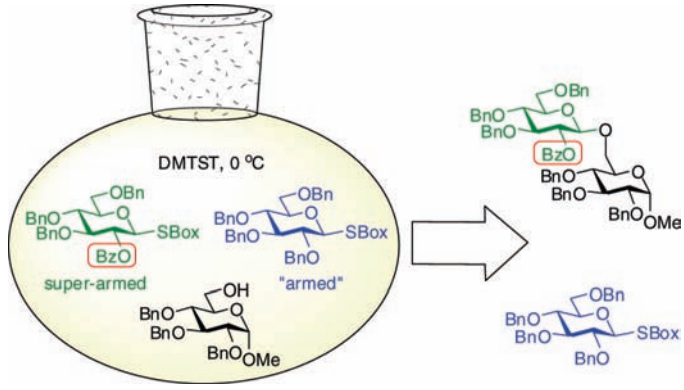
Laurel K. Mydock and Alexei V. Demchenko*

Department of Chemistry and Biochemistry, University of Missouri—St. Louis, One University Boulevard, St. Louis, Missouri 63121

demchenkoa@umsl.edu

Received March 20, 2008

ABSTRACT



Recently, we discovered a novel method for "superarming" glycosyl donors. Herein, this concept has been exemplified in one-pot oligosaccharide syntheses, whereby the superarmed glycosyl donor was chemoselectively activated over traditional "armed" and disarmed glycosyl acceptors. Direct side-by-side comparison of the reactivities of the classic armed and superarmed glycosyl donors further validates the credibility of the novel concept.

Thanks to the enormous progress that has been made in the area of synthetic and analytical chemistry, many classes of organic compounds are now accessible by widely applicable methods. Carbohydrates of even moderate complexity, however, still present a considerable challenge. Over the years, glycoscientists have learned to isolate certain classes of naturally occurring glycostructures. The availability of pure natural isolates, however, is still too inadequate to keep pace with the rapidly growing field of glycobiology.[1] Furthermore, along with the exigent problems associated with the isolation, purification, handling, and characterization of glycostructures, their considerable instability frequently results in erroneous structural assignments. Inevitably, these errors often lead to the misinterpretation of their functions. As a result, glycoscientists have turned to chemical and enzymatic synthesis as a means to access complex carbohydrates. Ideally, the efficient chemical synthesis of carbohydrates should yield significant quantities of pure natural analogues. Moreover, only the synthetic approach offers the means to access unnatural mimetics that are often needed for screening purposes. As such, the development of efficient methods for stereoselective glycosylation[2] and expeditious assembly of complex oligomers[3] remains an important area of research.

In the expansion of our studies on how protecting groups effect the reactivity of the anomeric leaving groups, we discovered that the strategic placement of common protecting groups leads to a new method for "super-arming" glycosyl donors.[4] Conceptualized from our studies on the O-2/O-5

(1) Prescher, J. A.; Bertozzi, C. R. *Nat. Chem. Biol.* **2005**, *1*, 13–21. Galonic, D. P.; Gin, D. Y. *Nature* **2007**, *446*, 1000–1007. Seeberger, P. H.; Werz, D. B. *Nature* **2007**, *446*, 1046–1051.

10.1021/ol800648d CCC: $40.75
Published on Web 05/01/2008

Cooperative Effect,[5] it was determined that *S*-benzoxazolyl (SBox) glycosides possessing both a participating moiety at C-2 (benzoyl) and remote benzyl substituents that electronically arm the lone pair at O-5 (e.g., glycosyl donors **1**−**3**, Figure 1) are exceptionally reactive.[4] Proving to be even

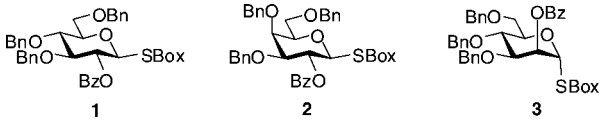


Figure 1. Superarmed glycosyl donors.

more reactive (superarmed)[6] than the traditional per-benzylated (armed) glycosyl donors, these building blocks possess the desirable quality of being both arming and participating glycosyl donors, traits not commonly found in other systems.[7]

Among the most attractive strategies for oligosaccharide synthesis is Fraser-Reid's chemoselective (armed−disarmed) approach, which allows for the synthesis of a *cis*−*trans* patterned oligosaccharide sequence through the use of only one type of anomeric leaving group. The reactivities of the building blocks involved in such chemoselective activations are differentiated by the electronic characteristics of their protecting groups.[8] This strategy is based on the commonly accepted belief that benzylated derivatives are always significantly more reactive than their benzoylated counterparts,[9,10] and furthermore, it is thought that this effect predominates from the neighboring substituent at C-2.[10,11] Additionally, the overall glycosyl donor reactivity is presumed to be in direct correlation with the total number of benzyl substituents.[9,10]

In this context, the discovery of the superarmed SBox glycosides was somewhat surprising.[4] Previously, a number of glycosyl donors bearing the 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl protecting group pattern have been investigated, including thioglycosides,[12–17] *O*-pentenyl glycosides,[18,19] fluorides,[16,19,20] trichloroacetimidates,[21] hemiacetals,[22] and phosphates[23,24] to name a few. Although these building blocks have been probed in various expeditious[12,14,23] and one-pot[16,17,20] approaches for oligosaccharide synthesis, to the best of our knowledge no direct evidence of these glycosyl donors being more reactive than their benzylated counterparts has emerged. Therefore, numerous glycosyl donors bearing this protecting group pattern have been considered disarmed[14,17,18] or "partially disarmed".[19] On a few occasions, their reactivity has even been quantified and determined to be lower than that of the corresponding benzylated derivatives.[18,25] It should be noted, however, that this protecting group pattern is predominantly used due its relatively simple synthesis via common orthoesters or glycals, as well as for its flexibility in selectively liberating 2-OH by deacylation for subsequent glycosylations. Application to glycosyl donors of the D-manno series in the synthesis of (branched) polymannans is arguably the most representative.[13]

In an attempt to further broaden the scope and application of this novel superarmed concept, we proceeded to investigate whether the enhanced reactivity of our superarmed donors **1**−**3** was sufficient to allow for direct chemoselective couplings. For the purpose of this study, we chose disarmed glycosyl acceptors **5** and **6**, as well as armed benzylated building blocks **7**−**9**, all bearing the same leaving group (SBox). The key results of these preliminary studies are summarized in Table 1. We already demonstrated that armed glycosyl donor **4** can be activated over disarmed glycosyl acceptor **5** to afford disaccharide **10** in 65% yield (entry 1, Table 1).[5] Expectedly, the superarmed glycosyl donor **1** also smoothly reacted with acceptor **5** to afford the corresponding disaccharide **11** in 72% yield (entry 2). Ultimately, the superarmed concept was validated by the direct coupling of

(2) *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*; Demchenko, A. V., Ed.; Wiley-VCH: New York, 2008.

(3) Boons, G. J. *Tetrahedron* **1996**, *52*, 1095–1121. Demchenko, A. V. *Lett. Org. Chem.* **2005**, *2*, 580–589. Codee, J. D. C.; Litjens, R. E. J. N.; van den Bos, L. J.; Overkleeft, H. S.; van der Marel, G. A. *Chem. Soc. Rev.* **2005**, *34*, 769–782.

(4) Mydock, L. K.; Demchenko, A. V. *Org. Lett.* **2008**, *10*, 2103–2106.

(5) Kamat, M. N.; Demchenko, A. V. *Org. Lett.* **2005**, *7*, 3215–3218.

(6) Previously, the term "superarmed" was introduced by Bols and coworkers in their recent publications dedicated to conformationally modified glycosyl donors:Pedersen, C. M.; Nordstrom, L. U.; Bols, M *J. Am. Chem. Soc.* **2007**, *129*, 9222–9235. Jensen, H. H.; Pedersen, C. M.; Bols, M. *Chem.*−*Eur. J.* **2007**, *13*, 7576–7582.

(7) Smoot, J. T.; Pornsuriyasak, P.; Demchenko, A. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 7123–7126.

(8) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583–5584. Fraser-Reid, B.; Udodong, U. E.; Wu, Z. F.; Ottosson, H.; Merritt, J. R.; Rao, C. S.; Roberts, C.; Madsen, R. *Synlett* **1992**, *92*, 7–942.

(9) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155–173.

(10) Green, L. G.; Ley, S. V. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weinheim, NY, 2000; Vol. 1, pp 427−448..

(11) Lemieux, R. U. *Adv. Carbohydr. Chem. Biochem.* **1954**, *9*, 1–57. Lemieux, R. *Pure Appl. Chem.* **1971**, *25*, 527–548. Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056–4062.

(12) Geurtsen, R.; Cote, F.; Hahn, M. G.; Boons, G. J. *J. Org. Chem.* **1999**, *64*, 7828–7835.

(13) Geng, X.; Dudkin, V. Y.; Mandal, M.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2562–2565.

(14) Hederos, M.; Konradsson, P. *J. Org. Chem.* **2005**, *70*, 7196–7207.

(15) Sato, K.; Akai, K. S.; Kojima, M.; Murakami, H.; Idoji, T. *Tetrahedron Lett.* **2005**, *46*, 7411–7414.

(16) Tanaka, H.; Adachi, M.; Takahashi, T. *Chem.*−*Eur. J.* **2005**, *11*, 849–862.

(17) Wang, C.; Wang, H.; Huang, X.; Zhang, L. H.; Ye, X. S. *Synlett* **2006**, 2846–2850.

(18) Fraser-Reid, B.; Lopez, J. C.; Radhakrishnan, K. V.; Nandakumar, M. V.; Gomez, A. M.; Uriel, C. *Chem. Commun.* **2002**, 2104–2105.

(19) Lopez, J. C.; Uriel, C.; Guillamon-Martin, A.; Valverde, S.; Gomez, A. M. *Org. Lett.* **2007**, *9*, 2759–2762.

(20) Hashihayata, T.; Ikegai, K.; Takeuchi, K.; Jona, H.; Mukaiyama, T *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1829–1848. Tanaka, H.; Adachi, M.; Takahashi, T. *Tetrahedron Lett.* **2004**, *45*, 1433–1436.

(21) Okada, Y.; Nagata, O.; Taira, M.; Yamada, H. *Org. Lett.* **2007**, *9*, 2755–2758. Jayaprakash, K. N.; Chaudhuri, S. R.; Murty, C. V. S. R.; Fraser-Reid, B. *J. Org. Chem.* **2007**, *72*, 5534–5545. Rising, T. W. D. F.; Heidecke, C. D.; Fairbanks, A. J. *Synlett* **2007**, 1421–1425.

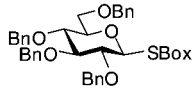
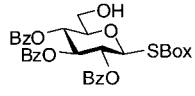
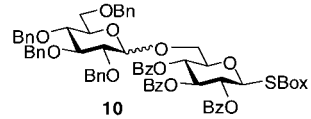
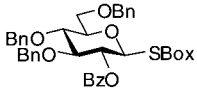
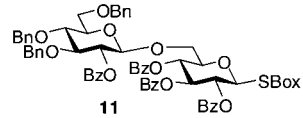
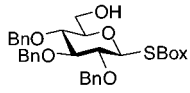
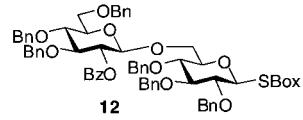
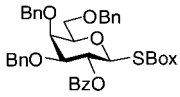
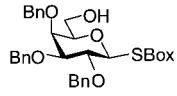
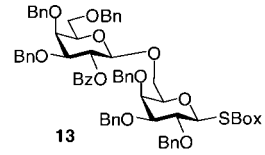
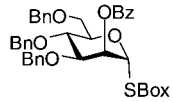
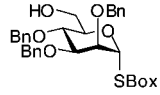
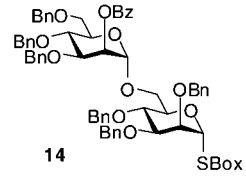
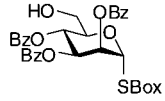
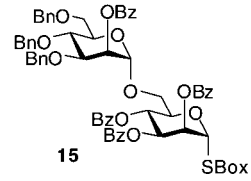
(22) Nguyen, H. M.; Chen, Y. N.; Duron, S. G.; Gin, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 8766–8772.

(23) Plante, O. J.; Palmacci, E. R.; Andrade, R. B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545–9554.

(24) Ravidà, A.; Liu, X.; Kovacs, L.; Seeberger, P. H *Org. Lett.* **2006**, *8*, 1815–1818.

(25) Wilson, B. G.; Fraser-Reid, B. *J. Org. Chem.* **1995**, *60*, 317–320. Zhang, Z.; Ollmann, I. R.; Ye, X. S.; Wischnat, R.; Baasov, T.; Wong, C. H. *J. Am. Chem. Soc.* **1999**, *121*, 734–753. Douglas, N. L.; Ley, S. V.; Lucking, U.; Warriner, S. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 51–65.

Table 1. Chemoselective Activation of Superarmed Donors **1**−**3** over Glycosyl Acceptors **4**−**8**[27]

entry	donor	acceptor	temperature[a]	time	product	yield	α:β ratio
1	 **4**	 **5**			 **10**	65%[5]	3/1[5]
2	 **1**	**5**	0 °C	15 min	 **11**	72%	β only
3	**1**	 **7**	0 °C	12 min	 **12**	70%	β only
4	 **2**	 **8**	-20 °C	45 min	 **13**	80%	β only
5	 **3**	 **9**	0 °C	2 h	 **14**	51%	α only
6	**3**	 **6**	10 → 25 °C	1 h	 **15**	90%	α only

the superarmed glycosyl donor **1** and benzylated ("armed") acceptor **7**. As in the previous coupling, no self-condensation products were detected, and disaccharide **12** was isolated in 70% yield (entry 3).

The superarmed galactosyl donor **2** corroborated the previous result: its coupling with benzylated galactosyl acceptor **8** afforded the corresponding disaccharide **13** in 80% yield (entry 4). To ensure successful coupling, the reaction temperature was lowered to −20 °C, so as to minimize the competing side reaction of the isomerization of galactosyl donor **2** into its corresponding unreactive N-linked (NBox) counterpart.[5] Coupling between the superarmed mannosyl donor **3** and benzylated mannosyl acceptor **9** was somewhat less efficient. Although no self-condensation products were observed, the disaccharide **14** could only be isolated in 51% yield (entry 5). The only additional compound recovered after 2 h was the unreacted glycosyl acceptor **9** (30%). We believe that this complication derives from the less significant difference of the reactivity between mannosyl donor **3** and its per-benzylated counterpart.[4] In lieu of this result, the additional glycosylation of the disarmed mannosyl acceptor **6** with the superarmed mannosyl donor **3** was performed. This reaction was straightforward and afforded the anticipated disaccharide **15** in 90% yield.

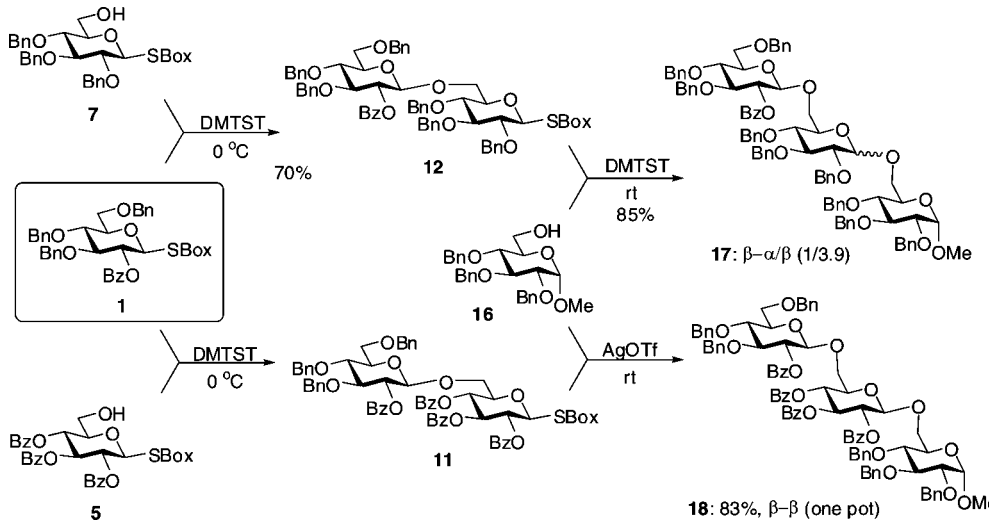
Additionally, sequential trisaccharide syntheses were carried out with the use of the superarmed glycosyl donor **1**, thus allowing us to introduce a 1,2-*trans* linkage prior to other linkages. This is not possible in the classic armed−disarmed approach. In the first sequence, we performed a stepwise coupling of building blocks **1** and **7**, and the isolated disaccharide **12** was reacted with glycosyl acceptor **16**[26] at room temperature, to afford trisaccharide **17** in 60% overall yield (Scheme 1). The same sequencing could also be performed in a one-pot fashion without isolating the intermediate. In this case, trisaccharide **17** was isolated in a 74% yield. Similarly, a one-pot synthesis of the *trans*−*trans*-linked trisaccharide **18**, from building blocks **1**, **5**, and **16**, was accomplished in 83% overall yield.

As a verification of these results, we also deemed it necessary to carry out a series of competitive glycosylations, wherein both the armed and superarmed donor, **4** and **1**, respectively, would be placed in the same reaction vessel

(26) Kuester, J. M.; Dyong, I. *Justus Liebigs Ann. Chem.* **1975**, 2179−2189.

(27) Glycosyl acceptors **7**−**9** have been obtained from known corresponding 6-*O*-trityl thioglycosides:Ottosson, H *Carbohydr. Res.* **1990**, *197*, 101–107. Houdier, S.; Vottero, P. J. A. *Carbohydr. Res.* **1993**, *248*, 377–384. Ruda, K.; Lindberg, J.; Garegg, P. J.; Oscarson, S.; Konradsson, P. *J. Am. Chem. Soc.* **2000**, *122*, 11067–11072.

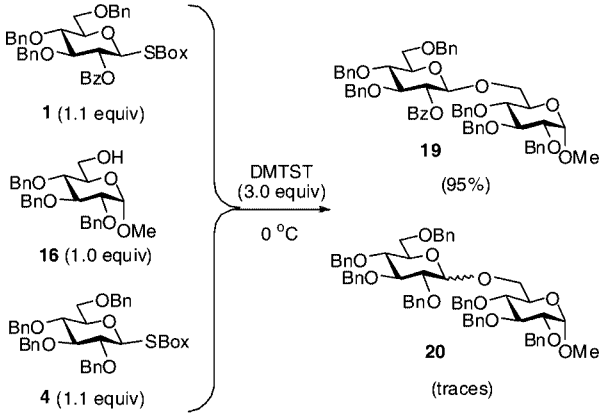
Scheme 1. Chemoselective Sequential Synthesis of Trisaccharides **17** and **18**



with the glycosyl acceptor **16**. Upon addition of the promoter (DMTST), the two glycosyl donors would then compete to react with the glycosyl acceptor **16**. As depicted in Scheme 2, the superarmed glycosyl donor **1** was clearly significantly more reactive than its per-benzylated analogue **4** and led to the formation of the corresponding disaccharide **19** which contained only trace (<5%) amounts of disaccharide **20** for a combined yield of 95%. In addition, the unreacted glycosyl donor **4** was recovered in 87% yield.

In conclusion, we have discovered that this new concept for superarming glycosyl donors through the use of common protecting groups allows for the expansion of the classic armed−disarmed strategy. These easily accessible superarmed glycosyl donors offer an entirely 1,2-*trans* stereoselective glycosidation. Consequently, the novelty of having *both* an armed *and* a 1,2-*trans* directing glycosyl donor makes this approach a very useful concept in many practical applications. Although not covered by the scope of these preliminary studies, it is expected that these super-reactive glycosyl donors can be applied in cases of difficult glycosylations, wherein classic per-acylated glycosyl donors fail. In combination with our previous studies on the O-2/O-5 cooperative effect, this superarmed glycosyl donor offers further significance, as it has allowed for the development of a versatile tool kit, consisting of both α- and *β*-directing armed glycosyl donors, as well as both α- and *β*-directing disarmed glycosyl donors, respectively. Future studies on the superarmed glycosyl donor concept are currently underway in our laboratory.

Scheme 2. Competitive Glycosidations of Glycosyl Donors **1** and **4** with Glycosyl Acceptor **16** in the Presence of DMTST



Acknowledgment. The authors thank NIGMS (GM077170) for financial support of this research and NSF for grants to purchase the NMR spectrometer (CHE-9974801) and the mass spectrometer (CHE-9708640) used in this work. Dr. R. E. K. Winter and Mr. J. Kramer (Department of Chemistry and Biochemistry, University of Missouri—St. Louis) are thanked for HRMS determinations.

Supporting Information Available: Experimental procedures for the synthesis of all new compounds and their ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800648D