ORGANIC LETTERS

2008
Vol. 10, No. 11
2103−2106

Superarming the *S*-Benzoxazolyl Glycosyl Donors by Simple 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl Protection

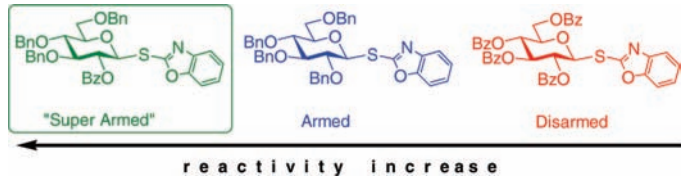
Laurel K. Mydock and Alexei V. Demchenko*

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

demchenkoa@umsl.edu

Received February 14, 2008

ABSTRACT



The strategic placement of common protecting groups led to the discovery of a new method for "superarming" glycosyl donors. Conceptualized from our previous studies on the O-2/O-5 Cooperative Effect, it was determined that *S*-benzoxazolyl glycosyl donors possessing both a participating moiety at C-2 and an electronically armed lone pair at O-5, such as the superarmed glycosyl donor shown above, were exceptionally reactive.

The availability of pure natural carbohydrate isolates is still far from being satisfactory. Hence, chemical and enzymatic methods for the synthesis of these natural products have become increasingly important. This has led to the development of many excellent new methods for glycoside synthesis,[1] from which a variety of expeditious strategies for oligosaccharide assembly have emerged.[2] Among these strategies, three major concepts could be identified: the chemoselective (protecting group based),[3,4] the selective (leaving group based),[5,6] and the preactivation-based approaches.[7] Of particular interest is the armed−disarmed strategy introduced by Fraser-Reid that allows for the synthesis of a *cis*−*trans* patterned oligosaccharide sequence with 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 the protecting groups.[3] This strategy is based on the commonly accepted belief that benzylated derivatives are always significantly more reactive than their

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

(2) 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.

(3) 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, and references therein.

(4) Douglas, N. L.; Ley, S. V.; Lucking, U.; Warriner, S. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, *5*, 1–65. Zhang, Z.; Ollmann, I. R.; Ye, X. S.; Wischnat, R.; Baasov, T.; Wong, C. H. *J. Am. Chem. Soc.* **1999**, *121*, 734–753. Ye, X. S.; Wong, C. H. *J. Org. Chem.* **2000**, *65*, 2410–2431.

(5) Koto, S.; Uchida, T.; Zen, S *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2520–2523. Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L *J. Am. Chem. Soc.* **1984**, *106*, 4189–4192. Randall, J. L.; Nicolaou, K. C. *ACS Symp. Ser.* **1988**, *374*, 13–28. Kanie, O.; Ito, Y.; Ogawa, T. *J. Am. Chem. Soc.* **1994**, *116*, 12073–12074. Kanie, O. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weinheim, NY, 2000; Vol. 1, pp 407−426. Demchenko, A. V.; De Meo, C. *Tetrahedron Lett.* **2002**, *43*, 8819–8822. Tanaka, H.; Adachi, M.; Tsukamoto, H.; Ikeda, T.; Yamada, H.; Takahashi, T. *Org. Lett.* **2002**, *4*, 4213–4216. Demchenko, A. V.; Kamat, M. N.; De Meo, C. *Synlett* **2003**, 1287–1290. Pornsuriyasak, P.; Demchenko, A. V. *Tetrahedron: Asymmetry* **2005**, *16*, 433–439.

(6) Baeschlin, D. K.; Chaperon, A. R.; Charbonneau, V.; Green, L. G.; Ley, S. V.; Lucking, U.; Walther, E. *Angew. Chem., Int. Ed.* **1998**, *37*, 3423–3428.

(7) Codee, J. D. C.; Litjens, R. E. J. N.; Heeten, R.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A *Org. Lett.* **2003**, *5*, 1519–1522. Huang, X.; Huang, L.; Wang, H.; Ye, X. S. *Angew Chem., Int. Ed.* **2004**, *43*, 5221–5224.

10.1021/ol800345j CCC: $40.75
Published on Web 05/01/2008

benzoylated counterparts,[8] and furthermore, it is thought that this effect predominates from the neighboring substituent at C-2.[9] In addition, the overall glycosyl donor reactivity is presumed to be in direct correlation with the total number of benzyl substituents.[8]

Although first discovered with *O*-pentenyl glycosides, the armed−disarmed concept has been proven with many other classes of compounds, including thioglycosides,[10] selenoglycosides,[6] fluorides,[11] phosphoroamidates,[12] substituted thioformimidates,[13] and glycals.[14] The *S*-benzoxazolyl (SBox) and *S*-thiazolinyl (STaz) glycosyl donors developed in our laboratory were also found to react accordingly.[15,16] For instance, we have confirmed that the armed per-benzylated SBox glycoside **1** (Figure 1) is significantly more reactive

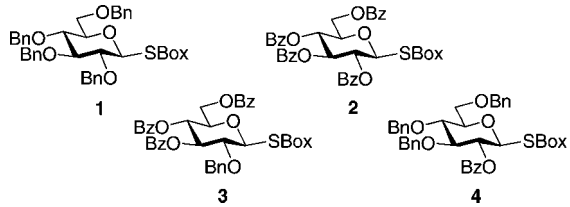
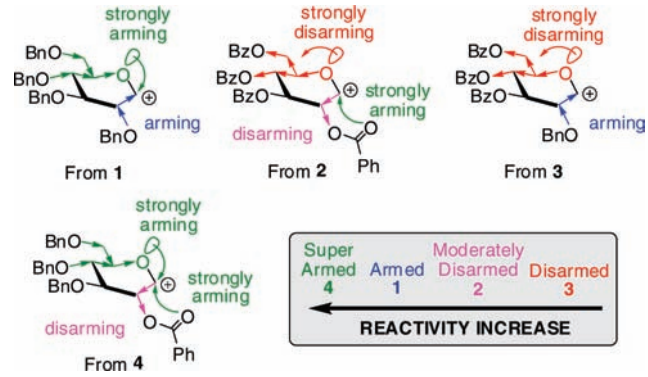


Figure 1. SBox glucosyl donors with varying protecting group arrangements.

than its disarmed benzoylated counterpart **2**.[15] Therefore, when glycosyl donors with the mixed protecting group pattern, such as 2-*O*-benzyl-3,4,6-tri-*O*-acyl derivative **3**, were considered, it was believed that their reactivity would lie between that of the armed and disarmed glycosyl donors **1** and **2**, respectively. Unexpectedly, glycosyl donor **3** was determined to be less reactive than either **1** or **2**.[15]

This was the first indication that the reactivity of the glycosyl donor was not limited to the electron-withdrawing/-donating properties of its protecting groups. This finding ultimately gave rise to the theory that we call "The O-2/O-5 Cooperative Effect,"[15] wherein we experimentally determined that glycosyl donor reactivity was also dependent on the stability of the glycosyl cation that is formed upon leaving group departure. In the case of the armed, benzylated glycosyl donor **1**, stabilization can be efficiently achieved through resonance with the electronically "armed" lone pair electrons of O-5, via the oxocarbenium intermediate (Scheme

Scheme 1. Cooperative Arming and Disarming Effects in Glycosyl Donors of the D-Gluco Series



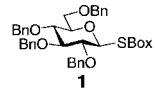
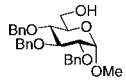
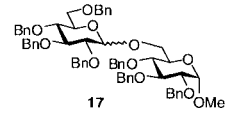
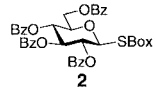
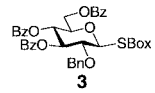
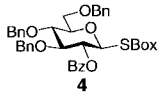
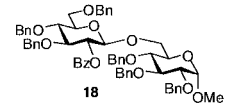
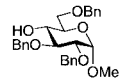
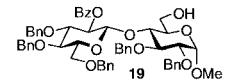
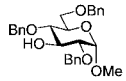
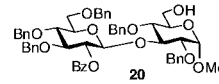
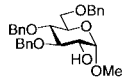
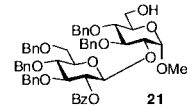
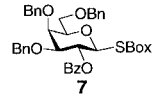
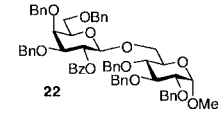
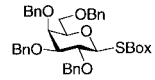
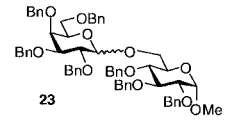
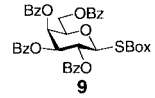
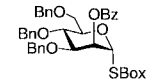
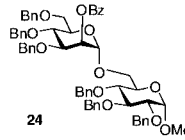
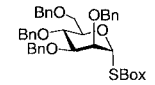
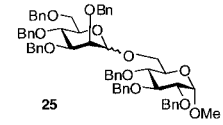
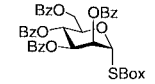
1). However, in the case of the per-benzoylated derivative **2**, this type of stabilization is less likely due to the electron-withdrawing substituents at C-4 and C-6. Instead, the acyl substituent at C-2 allows for stabilization via the acyloxonium intermediate. In combination, these two competing effects result in an overall moderate disarming of glycosyl donor **2**. Additionally, Crich and Li recently suggested the importance of the 1,2-*trans* anomeric configuration for the SBox glycosyl donors of the D-gluco series, in order for this stabilizing participation to occur.[17] In the case of glycosyl donor **3**, the O-5 disarming effect is only slightly compensated by the electron-donating 2-*O*-benzyl moiety, whose arming effect is mild. This anticipated "lack of cooperation" is in agreement with experimental results, which indicate an overall strong disarming effect for compound **3**.[15]

The studies presented herein are based on the postulate that glycosyl donors with a participating moiety at C-2 and electronically armed lone pair at O-5, such as **4** (Figure 1), would have exceptionally high reactivity. In comparison to the application of the traditional per-benzylated armed glycosyl donor **1**, the "superarmed"[18] glycosyl donor **4** would offer advantages that could significantly enhance the way we currently obtain oligosaccharide sequences. To explore this concept, we obtained benzoxazolyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (**4**) as shown in Scheme 2. In addition, we generated a series of glycosyl donors of the D-galacto and D-manno series that would further allow us to investigate comparative superarming (**7** and **10**), arming (**8** and **11**[19]), and disarming effects (**9**[19] and **12**,[19] Scheme 2). These relatively simple building blocks were generated from known advanced precursors[20,21] by known or slightly modified experimental procedures.[16,21,22]

Having synthesized a variety of glycosyl donors, we turned our attention to their comparative glycosidations. It is

(8) Paulsen, H. *Angew. Chem. Int. Edit. Engl.* **1982**, *21*, 155–173.
(9) Lemieux, R. U *Adv. Carbohydr. Chem. Biochem.* **1954**, *9*, 1–57. Lemieux, R. U. *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.
(10) Veeneman, G. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275–278.
(11) Barrena, M. I.; Echarri, R.; Castillon, S. *Synlett* **1996**, 675–676.
(12) Hashimoto, S. I.; Sakamoto, H.; Honda, T.; Abe, H.; Nakamura, S. I.; Ikegami, S. *Tetrahedron Lett.* **1997**, *38*, 8969–8972.
(13) Chiba, H.; Funasaka, S.; Kiyota, K.; Mukaiyama, T. *Chem. Lett.* **2002**, 746–747.
(14) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656–6660.
(15) Kamat, M. N.; Demchenko, A. V. *Org. Lett.* **2005**, *7*, 3215–3218.
(16) Smoot, J. T.; Pornsuriyasak, P.; Demchenko, A. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 7123–7126.
(17) Crich, D.; Li, M. *Org. Lett.* **2007**, *9*, 4115–4118.
(18) Previously, the term "superarmed" was coined 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.
(19) Kamat, M. N.; Rath, N. P.; Demchenko, A. V. *J. Org. Chem.* **2007**, *72*, 6938–6946. Kamat, M. N.; De Meo, C.; Demchenko, A. V. *J. Org. Chem.* **2007**, *72*, 6947–6955.

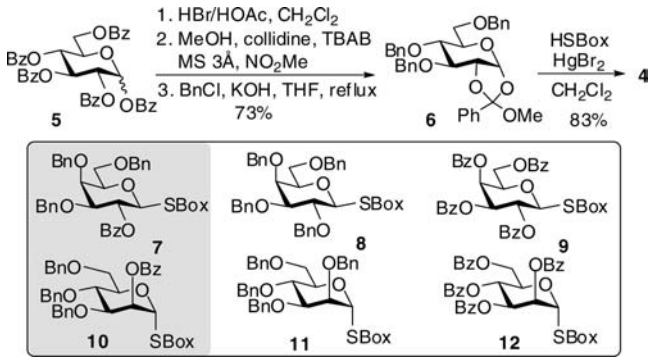
Table 1. Comparative Glycosidations of Glycosyl Donors **1**−**4** and **7**−**12** in the Presence of DMTST

entry	donor	acceptor	temperature[a]	time	product	yield	α:β ratio
1	 **1**	 **13**	0 → 25 °C	2 h	 **17**	91%	1.2:1
2	 **2**	**13**	0 → 25 °C	16 h	no reaction	-	-
3	 **3**	**13**	0 → 25 °C	16 h	no reaction	-	-
4	 **4**	**13**	0 °C	< 5 min	 **18**	90%	β only
5	**4**	 **14**	0 °C	< 5 min	 **19**	92%	β only
6	**4**	 **15**	0 °C	< 5 min	 **20**	97%	β only
7	**4**	 **16**	0 °C	< 5 min	 **21**	88%	β only
8	 **7**	**13**	0 °C	< 5 min	 **22**	92%	β only
9	 **8**	**13**	0 → 13 °C	40 min	 **23**	85%	2:1
10	 **9**	**13**	0 → 25 °C	16 h	no reaction	-	-
11	 **10**	**13**	0 → 18 °C	50 min	 **24**	79%	α only
12	 **11**	**13**	0 → 22 °C	1.5 h	 **25**	79%	1.1:1
13	 **12**	**13**	0 → 25 °C	16 h	no reaction	-	-

[a] All glycosylations were started at 0 °C, and then the temperature was allowed to gradually increase.

important to note that the key feature of the armed−disarmed glycosylation is the availability of a suitable activator (promoter) that allows for differentiation among the reactivity levels of the various (dis)armed substrates. Upon investigating a range of activators, including mildly electrophilic copper(II) triflate, methyl triflate, and iodonium(di-γ-collidine)perchlorate (IDCP), we chose dimethyl(methylthio) sulfonium triflate (DMTST)[23] as the appropriate promoter. The results of the DMTST (3 equiv) mediated glycosylations in 1,2-dichloroethane are summarized in Table 1. Glycosidation of the benzylated glycosyl donor **1** with glycosyl acceptor **13**[24] proceeded smoothly and was completed in 2 h

Scheme 2. Synthesis of the SBox Glycoside **4** and its Analogues



affording the corresponding disaccharide **17**[25] in 91% yield (entry 1, Table 1). When reactions between moderately disarmed and disarmed glycosyl donors **2** and **3**, respectively, and glycosyl acceptor **13** were set up under essentially the same reaction conditions, no formation of the corresponding coupling products was detected (entries 2 and 3). Encouragingly, the anticipated superarmed glycosyl donor **4** reacted nearly instantaneously, under the same reaction conditions, to provide disaccharide **18**[25] in 90% yield (entry 4). The reactivity of the superarmed glycosyl donor **4** was then tested in reactions with less reactive secondary glycosyl acceptors **14**−**16**.[26] These couplings were also efficient, resulting in the formation of the respective disaccharides **19**,[25] **20**,[27] and **21** in high yields (88−97%, entries 5−7, Table 1).

Having investigated the glucosyl donor **4**, we then refocused our investigation to superarmed galactosyl donor **7**. Similar to our previous observations, compound **7** was found to be significantly more reactive than the armed per-benzylated derivative **8**. Thus, disaccharides **22**[27] and **23**[25] were formed in 5 min (92%) and 40 min (85%), respectively (entries 8 and 9). As in the previous case, no reaction took place with the per-benzoylated galactoside **9** (entry 10). Similar observations were also made with mannosides **10**−**12**: the disaccharides **24**[28] and **25**[29] were formed in 50 min (79%) and 90 min (79%), respectively (entries 11 and 12), whereas no glycosidation of the disarmed acceptor took place (entry 13). To this end, we determined that not only did the 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl donors **4**, **7**, and **10** readily react, while the disarmed glycosyl donors (**2**, **3**, **9**, **12**) did not, but also, as postulated, they proved to be more reactive than their armed counterparts (**1**, **8**, **11**).

In conclusion, we have devised a novel method for "superarming" glycosyl donors, through the strategic placement of common protecting groups. Furthermore, these superarmed glycosyl donors are easily obtained, through either an orthoester or a glycal route. Complementary to the anomeric mixture often obtained with the common per-benzylated analogues, the superarmed glycosyl donor offers an entirely 1,2-*trans* stereoselective glycosidation. This can be achieved at ambient or slightly reduced temperatures. Although not covered by the scope of these preliminary studies, it is expected that these super-reactive glycosyl donors can be useful in cases of difficult glycosylations, wherein classic per-acylated glycosyl donors fail. Further expansion and application of this concept to chemoselective oligosaccharide synthesis will be discussed in the following manuscript.[30]

Acknowledgment. The authors thank NIGMS (GM077170) for financial support of this research program 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, UM—St. Louis) are thanked for HRMS determinations.

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

OL800345J

(20) Lemieux, R. U. In *Methods in carbohydrate chemistry*; Whistler, R. L., Wolform, M. L., Eds.; Academic Press Inc.: New York and London, 1963; Vol. 2, pp 226−228. Ekborg, G.; Glaudemans, C. P. J. *Carbohydr. Res.* **1984**, *129*, 287–292. Dasgupta, F.; Garegg, P. J *Acta Chem. Scand.* **1989**, *43*, 471–475. Ottosson, H. *Carbohydr. Res.* **1990**, *197*, 101–107. Kong, F.; Du, J.; Shang, H. *Carbohydr. Res.* **1987**, *162*, 217–225. Kihlberg, J. O.; Leigh, D. A.; Bundle, D. R. *J. Org. Chem.* **1990**, *55*, 2860–2863. 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.

(21) Abdel-Rahman, A. A. H.; El Ashry, E. S. H.; Schmidt, R. R. *Carbohydr. Res.* **2002**, *337*, 195–206.

(22) Franks, N. E.; Montgomery, R. *Carbohydr. Res.* **1968**, *6*, 286–298. Kochetkov, N. K.; Backinowsky, L. V.; Tsvetkov, Y. E. *Tetrahedron Lett.* **1977**, *41*, 3681–3684. Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661–6666. Beignet, J.; Tiernan, J.; Woo, C. H.; Benson, M. K.; Cox, L. R. *J. Org. Chem.* **2004**, *69*, 6341–6356.

(23) Ravenscroft, M.; Roberts, R. M. G.; Tillett, J. G. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1569–1972.

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

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

(26) Garegg, P. J.; Hultberg, H. *Carbohydr. Res.* **1981**, *93*, C10–C11. Koto, S.; Takebe, Y.; Zen, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 291–293. Pearce, A. J.; Sinay, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3610–3612.

(27) Mukaiyama, T.; Takeuchi, K.; Jona, H.; Maeshima, H.; Saitoh, T. *Helv. Chim. Acta* **2000**, *83*, 1901–1918.

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

(29) Hotha, S.; Kashyap, S. *J. Am. Chem. Soc.* **2006**, *128*, 9620–9621.

(30) Mydock, L. K.; Demchenko, A. V. *Org. Lett.* **2008**, *10*, 2107–2110.