J|A|C|S
COMMUNICATIONS

Published on Web 03/08/2002

Unexpected Role of O-2 "Protecting" Groups of Glycosyl Donors in Mediating Regioselective Glycosidation[1]

Bert Fraser-Reid,*,† J. Cristobal Lopez,‡ K. V. Radhakrishnan,† Mateusz Mach,† Urs Schlueter,† Ana M. Gomez,‡ and Clara Uriel‡

Natural Products and Glycotechnology Research Institute Inc. (NPG), 4118 Swarthmore Road, Durham, North Carolina 27706, and Instituto de Quimica Organica General (CSIC), Juan de la Cierva 3, Madrid 28006, Spain

Received October 18, 2001

Two decades ago in a seminal review article,[2] Paulsen observed that for optimal success in saccharide coupling, it is necessary that the glycosyl donor and acceptor should be "matched".[3−5] With respect to the former, the burgeoning array of new technologies to prepare glycosyl donors[6] testifies to the need to achieve greater efficiency and selectivity in saccharide coupling. The selectivity requirement usually refers to the outcome at the anomeric center, and in this context, the monumental insight of Isbell sixty years ago[7] inspired the rule-of-thumb that a participating group when present at O-2 of the glycosyl donor promotes 1,2-trans[8] selectivity and, by implication, its absence enhances the chances of 1,2-cis selectivity.[2,9] An ester or alkyl residue at O-2 is therefore seen as a stereocontrolling implement.[10] In this paper, we draw attention to the fact that the O-2 "protecting" group also exerts a powerful (frequently total) effect on **regio**control and, in addition, demonstrate that this regiopreference has important implications for efforts to "match" donors with acceptors.

This study emanated from the recent observations which showed that the 1,3-diol segment present in *myo*-inositol and mannopyranosides, summarized as **1** (Scheme 1), exhibited opposite regioselectivities toward acylating and alkylating reagents.[11]

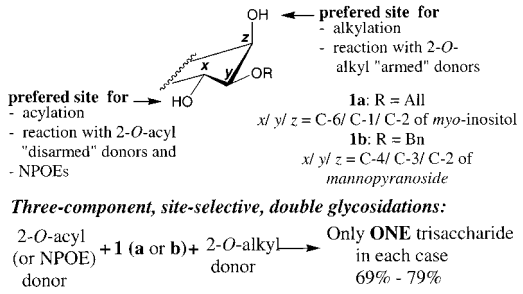
These surprising regioselectivities prompted us to undertake glycosidation studies, which showed that 2-*O*-acylated *n*-pentenyl donors (NPG_{AC}) displayed complete selectivity for the equatorial-OH.[12] Being functionally equivalent, *n*-pentenyl ortho esters (NPOEs)[13] gave the same exquisite regiopreference, but with higher yields. This result did not indicate that the equatorial-OH was "more reactive", since 2-*O*-alkylated *n*-pentenyl donors (NPG_{ALK}) showed preferences for the axial-OH, particularly so in the case of **1b**.[12]

These results indicate that a 2-*O*-acyl donor is very well "matched" with the equatorial-OH of **1**, and the critical importance of this observation for choice of O-2 "protecting" group is exemplified in the glycosidations in Scheme 2. Van Boom and coworkers[14] reported an 84% yield in mannosylation of pseudodisaccharide **2**, with the "disarmed" donor **3a**. By contrast, the yield with **3b** was only 17%,[15] *even though the latter is the "more reactive", "armed", donor.*[16]

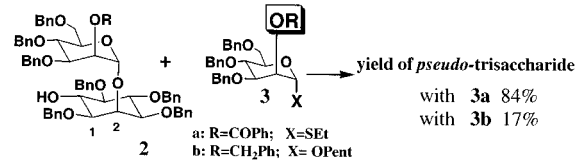
The regiocontrols described above are *unpromoted*, and therefore stand in contrast to popular tin-mediated protocols, introduced by Moffat,[18] where coordination confers enhanced nucleophilicity upon the chosen OH.[19]

We have therefore tested for *unpromoted* regioselective glycosidations in some polyol substrates. In view of the diverse spectrum of donors and reaction protocols available, we have confined our attention to *n*-pentenyl donors[20,21] to provide a level playing field.

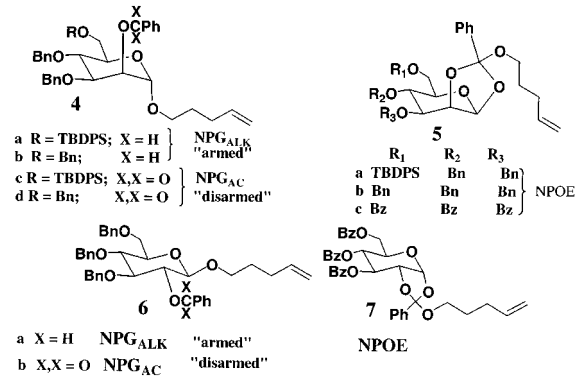
Scheme 1



Scheme 2



Scheme 3



Thus donors **4** to **7** (Scheme 3) were employed with methylene chloride as solvent, *N*-iodosuccinimide (NIS) as promoter, and Lewis acids (TBDMSOTf or $BF_3.OEt_2$).

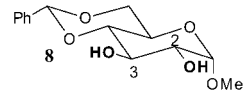
The methyl glucosides **8** and **9** (Scheme 4) were convenient starting points since their glycosidations under various conditions have been reported.[22,23] To leverage the slight differences between the contending hydroxyl groups of **8** or **9**, reactions were begun at −78 °C and allowed to gradually warm to room temperature. Under these conditions, substantial amounts of the acceptor diols were recovered; however, the regioselectivities were clearly discernible.

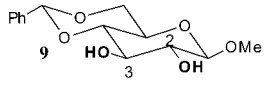
Thus, in reaction of the (NPG_{ALK}) donors **4a** and **6a** with substrate **8** there were mixed messages, since **4a** exhibited a preference for O-3, and **6a** for O-2[24] (Scheme 4, entries i and ii). By contrast, the NPOE/NPG_{AC} donors (entries iii−vi) were uniform in their choice for O-2 particularly to the extent of ∼7.5:1 in entries

* Address correspondence to this author. E-mail: dglucose@aol.com.
† Natural Products and Glycotechnology Research Institute Inc.
‡ Instituto de Quimica Organica General.

10.1021/ja012383m CCC: $22.00

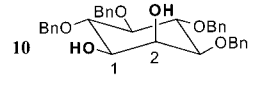
Scheme 4

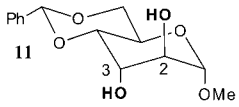




i	NPG_{ALK}	**4a** (36%)	3.0	:	1				
ii	NPG_{ALK}	**6a** (53%)	1	:	1.7				
iii	NPOE	**5b** (42%)	1	:	7.4				
iv	NPG_{AC}	**6b** (25%)	1	:	7.6	-78 °C			
v	NPG_{AC}	**6b** (42%)	1	:	3.0	0 °C			
vi	NPG_{AC}	**4b** (62%)	1	:	2.4				
vii	NPG_{ALK}	**4a** (35%)	2.9	:	1				
viii	NPG_{ALK}	**6a** (51%)	1	:	1.2				
ix	NPOE	**5b** (36%)	1	:	3.5				
x	NPG_{AC}	**4b** (46%)	1	:	2.3				
xi	NPG_{AC}	**6b** (11%)	1	:	1.8				

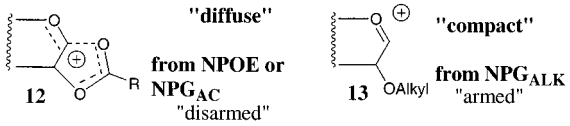
Scheme 5





i	NPG_{ALK}	**4a** (76%)	2.0	:	1	iii	NPG_{ALK}	**4a** (37%)	2.0 : 1
ii	NPOE	**5a** (70%)	6.0	:	1	iv	NPOE	**5a** (52%)	ONLY
						v	NPOE	**7** (61%)	ONLY
						vi	NPOE	**5b** (92%)	ONLY - 78 °C

Scheme 6



iii and iv. Notably, when the temperature was raised to 0 °C for donor **6b**, the yield improved, but the selectivity suffered (entries iv versus v).

In the case of substrate **9**, there was again a mixed message for armed donors **4a** and **6a**[24](entries vii and viii); but again, NPOE/NPG_{AC} donors **4a**, **5a**, and **6b** constantly favored O-2, albeit at modest levels.

Angyal and co-workers[25] had found that the *myo*-inositol derivative **10** underwent *unpromoted* regioselective acylation and alkylation at O-1 and O-2, respectively. Glycosidation of **10** was therefore examined. As shown in Scheme 5, the NPG_{ALK} **4a** showed slight discrimination for the equatorial-OH (entry i) whereas the NPOE **5a** showed overwhelming selectivity for the same center (entry ii).

Steric hindrance seemed to offer a convenient rationalization for the regiopreferences of the equatorial-OHs of **1** and **10** in reactions with the NPOEs. It was therefore appropriate to confront this facile explanation with the clear choice presented by the hydroxyl groups of the methyl altroside **11**. With the armed donors **4a** and **6a**, regioselectivity was poor or absent.[24] By contrast, NPOEs **5a** and **7** choose the more hindered O-3, with no evidence for reaction at the highly available O-2. Interestingly, with the more disarmed tri-*O*-benzoyl donor **5a**, yields of 92% were routine.

Our attempts to rationalize the above observations began with the contrasting results of NPOE/NPG_{AC} versus NPG_{ALK} donors, suggesting that the cationic species **12** and **13** (Scheme 6), which may be described as "diffuse" and "compact", respectively,[12] are somehow implicated. However, the (presumably) greater steric demands of the former cannot be the basis for its exquisite selectivity, as is apparent from Scheme 5 (entries iv, v, and vi). Our focus on the cationic intermediates ignores the proclivities of the glycosyl **acceptor,** a common and perilous shortcoming, as Vasella's work[22] shows. Thus, such donor-based rationalizations will have to be conflated with acceptor-based considerations such as hydrogen bonding[26] and relative nucleophilicity. Efforts to disentangle the multiple factors that are at play in these reactions are underway, and will be reported in due course.

In summary, we have shown that O-2 "protecting" groups (a) can profoundly control the direction and extent of regioselective glycosidations,and (b) can even affect the successful glycosidation of a **mono**hydroxylic acceptor as illustrated in Scheme 2. *Furthermore, it is clear that the designation "more reactive" is not absolute, and that "steric hindrance" may not ensure any predictive advantage.* These observations add a new dimension to the concept of "matching" donor and acceptor in saccharide coupling. In addition, the notably higher regioselectivity ratios of NPOEs versus their NPG_{ALK} counterparts are worth noting, as is the coincidental parallel preference between acylating agents and NPOE donors.

Supporting Information Available: Experimental procedures for the reactions of glycosol donors **4**, **5**, **6**, and **7** with the diol acceptors **8**−**11** andNMR and mass spectroscopic data for all regioisomeric coupling products obtained (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) B.F.R. is grateful to the Human Frontier Science Program Organization and Synthon Chiragenics of Monmouth Junction, NJ, for partial support of this work. C.U. thanks the Comunidad Autónoma de Madrid for a postdoctoral fellowship. Funding was from the *Dirección General de Investigación Científica y Técnica* (grant no. PPQ2000−1330).

(2) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 152−173.

(3) Paulsen, H.; Paal, M.; Hadamczyk, D.; Steiger, K−M. *Carbohydr. Res.* **1984**, *131*, C1−C5. Paulsen, H.; Lockhoff. *Chem. Ber.* **1981**, *114*, 3079−3101. Paulsen, H.; Hadamczyk, D.; Kutschker, W.; Bunsch, A. *Liebigs Ann. Chem.* **1985**, 129−141.

(4) The term "matching" in this context is not to be confused with the double asymmetric concept of Masamune. Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1−76. However, for an application of that concept in saccharide synthesis see ref 5b.

(5) For a powerful example of the value of donor/acceptor coordination see: (a) van Boeckel, C. A. A.; Petitou, M. *Angew Chem., Int. Ed. Engl.* **1993**, *32*, 1671−1690. (b) Spijker, N. M.; van Boeckel, C. A. A. *Angew Chem., Int. Ed. Engl.* **1991**, *30*, 180−183.

(6) For some very recent examples, see: Kim, K.; Kim, J. H.; Lee, Y. J.; Lee, Y. J.; Park, J. J. *J. Am. Chem. Soc.* **2001**, *122*, 8477−8481. Hinklin, R. J.; Kiessling, L. L. *J. Am. Chem. Soc.* **2001**, *123*, 3379−3380. Davis, B. G.; Ward, S. J.; Rendle, P. M. *Chem. Commun.* **2001**, 189−190.

(7) Isbell, H. S. *Annu. Rev. Biochem.* **1940**, *9*, 65−92.

(8) See, for example: R. U. Lemieux. *Adv. Carbohydr. Chem.* **1954**, *9*, 1−57.

(9) Paulsen, H. *Modern Methods in Carbohydrate Synthesis*; Khan, S. H., O'Neill, R. A., Eds.; Barwood Academic Publishers: London, UK, 1996.

(10) See for example.: Pigman, W. W.; Goepp, R. M., Jr. *Carbohydrate Chemistry*; Academic Press: London, UK, 1948; p 159 et seq. Collins, P.; Ferrier, R. *Monosaccharides: Their Chemistry and Their Roles in Natural Products*; John Wiley and Sons: England, 1995; Chapter 3.

(11) Anilkumar, G.; Jia, Z. J.; Kraehmer, R.; Fraser-Reid, B. *J. Chem. Soc., Perkin 1* **1999**, 3591−3596.

(12) Anilkumar, G.; Nair, L. G.; Fraser-Reid, B. B. *Org. Lett.* **2000**, *2*, 2587−2589

(13) Allen, J. G.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1999**, *121*, 468−469.

(14) Veeneman, G. H.; Van Leeuwen, S. H.; Zurmond, H.; van Boom, J. H. *J. Carbohydr. Chem.* **1990**, *9*, 783−796. Elie, C. J. J.; Verduyn, R.; Dreef, C. E.; Brounts, D. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1990**, *46*, 8243−8254.

(15) Anilkumar, G.; Gilbert, M. R.; Fraser-Reid, B. *Tetrahedron* **2000**, *56*, 1993−1997.

(16) The reactivities of the armed and disarmed donors **5b** and **4d** have been compared by the competition protocol described previously by one of us.[17] Unpublished work of MM.

(17) Wilson, B. G.; Fraser-Reid, B. *J. Org. Chem.* **1995**, *60*, 317−320.

(18) Wagner, D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 1.

(19) Grindley T. B. *Adv. Carbohydr. Chem. Biochem.* **1998,** *53*, 17−142.

(20) Fraser-Reid, B.; Udodong, U. R.; Wu, Z.; Ottosson, H.; Merritt, R.; Rao, C. S.; Roberts, C.; Madsen, R. *Synlett* **1992**, 927−942.

(21) However, this technology should be applicable to a wide range of donors as is the "armed/disarmed" protocol which was also observed first with NPGs.[20]

(22) (a) Muddasani, P. R.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1994**, *77*, 334−350. (b) Muddasani, P. R.; Bozo, E.; Bernet, B.; Vasella, A. *Helv. Chim Acta* **1994**, *77*, 257−290.

(23) (a) Takeo, K. *Carbohydr. Res.* **1979**, *77*, 131−135. (b) Hanessian, S.; Banoub, J. *Carbohydr. Res.* **1977**, *53*, C13−C16. (c) Coxon, B.; Fletcher, H. G. *J. Org. Chem.* **1961**, *26*, 2892−2899.

(24) The products from glycosidating **2** and **3** with **4b** and **6b** gave ^{1}H NMR spectra that agreed completely with those reported by Vasella in ref 22b.

(25) Angyal, S. J.; Tate, M. E. *J. Chem. Soc.* **1965**, 6949−6955. Angyal, S. J.; Gero, S. D. *J. Chem. Soc.* **1965**, 5255−5258.

(26) Bernet, B.; Vasella A. *Helv. Chim. Acta* **2000**, *83*, 2053−2071 and references therein.

JA012383M