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Relevance of the Glycosyl Donor to the Regioselectivity of Glycosidation of Primary-Secondary Diol Acceptors and Application of These Ideas to in Situ Three-Component Double Differential Glycosidation§

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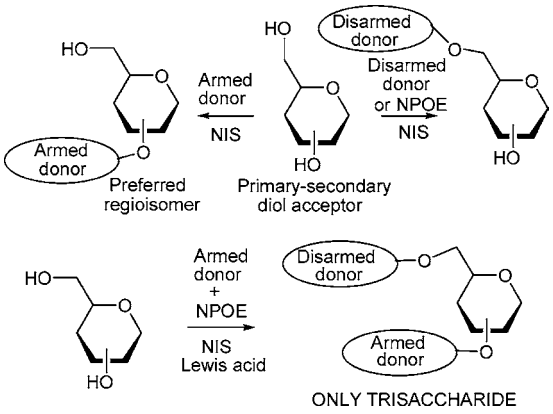
ABSTRACT



Three pairs of primary-secondary diol acceptors have been exposed to armed, disarmed, and *n*-pentenyl ortho ester glycosyl donors in glycosidation reactions. It is shown that the regioselectivity of those glycosylations is greatly influenced by the armed, disarmed, or ortho ester nature of the glycosyl donors. The selectivities observed have been used to devise efficient in situ three-component glycosylations involving two donors and one acceptor.

Conventional thinking in organic synthesis indicates that primary OHs are more reactive than secondary, and equatorial more than axial.[1] Such generalizations, however, if they could be extended to the glycosyl acceptors commonly used in modern carbohydrate chemistry, could greatly lessen the burdensome protection/deprotection episodes needed to ensure that a designated OH is selectively presented to partnering a glycosyl donor. However attempts to import such wisdom into donor/acceptor couplings have met with

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§ Dedicated to Prof. Joaquín Plumet on the occasion of his 60th birthday.

(1) Sugihara, J. M. *Adv. Carbohydr. Chem. Biochem.* **1953**, *8*, 1−44. Haines, A. H. *Adv. Carbohydr. Chem. Biochem.* **1976**, *33*, 11−109.

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limited success. Thus there may be hesitation to rely on reactivity, and thence regioselectivity, of a primary versus a secondary hydroxyl group. Accordingly, reactivity sequences have been advanced for different hydroxyl groups in a given monosaccharide.[2] In this communication we report some recent observations from our laboratories that clearly establish that primary hydroxyl groups can only be considered "more reactive" than secondary hydroxyl groups in reactions with disarmed glycosyl donors or ortho esters and that armed glycosyl donors can actually favor glycosylation at the secondary rather than the primary position. These observations have permitted us to elaborate a safe protocol for the glycosyl coupling of two donors and one acceptor-diol containing primary and secondary hydroxyl groups.[3]

Our studies were carried out with nonvicinal diol acceptors **1**−**3**. D-Gluco- and D-mannose derivatives **1** and **2** were selected because of the equatorial and axial nature of the (C2) OHs, respectively. D-Mannose derivative **3** was chosen as an example of a 3,6-diol, since 3,6-diglycosylated mannosides are ubiquitous in high-mannose glycoproteins.[4]

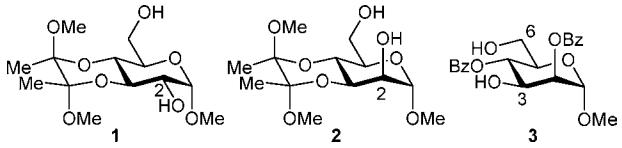


Figure 1. Primary-secondary nonvicinal diol acceptors.

As glycosyl donors in this study we selected the phenyl-1-thio-glycosides **4** and **5** and the *n*-pentenyl ortho ester **6**.

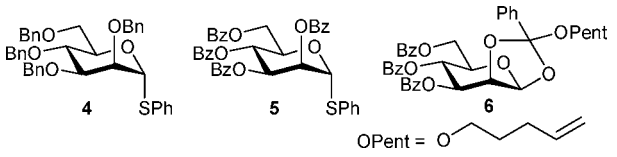
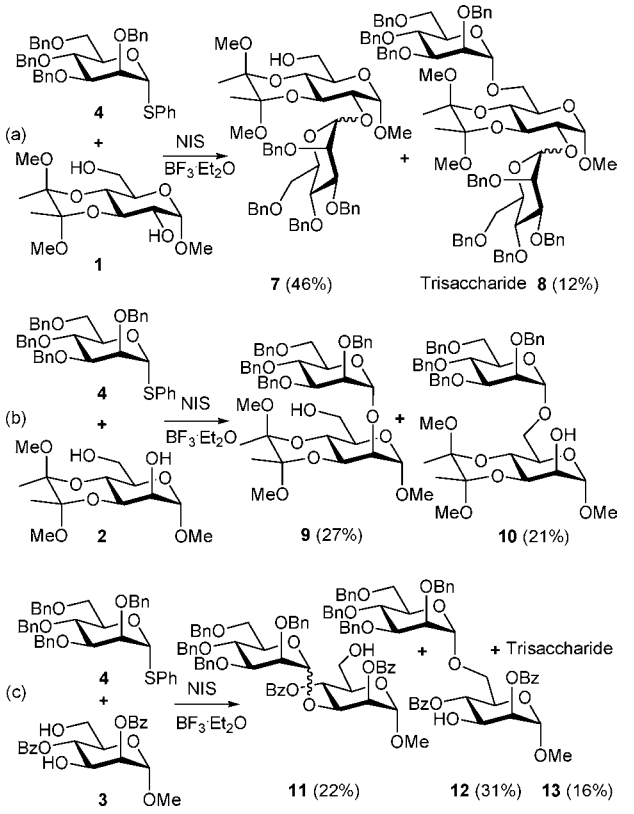


Figure 2. Glycosyl donors **4**−**6**.

Initial glycosylation experiments were carried out with armed glycosyl donor **4**, and the results are shown in Scheme 1. Glycosyl coupling of D-glucose acceptor **1** (1 equiv) with donor **4** (1 equiv), in the presence of NIS (2 equiv) and $BF_3 \cdot Et_2O$ at −30 °C in dichloromethane, led to a mixture of disaccharides **7** (α,β mixture) and trisaccharide **8**, thus showing the preference of donor **4** for the secondary (equatorial) C(2)OH versus the primary C(6)OH. Similarly, coupling of **2** (1 equiv) with donor **4** (1.2 equiv) led to a mixture of disaccharides **9** and **10**, also showing a greater

Scheme 1. Glycosylations of Diols **1**−**3** with Armed Glycosyl Donor **4**



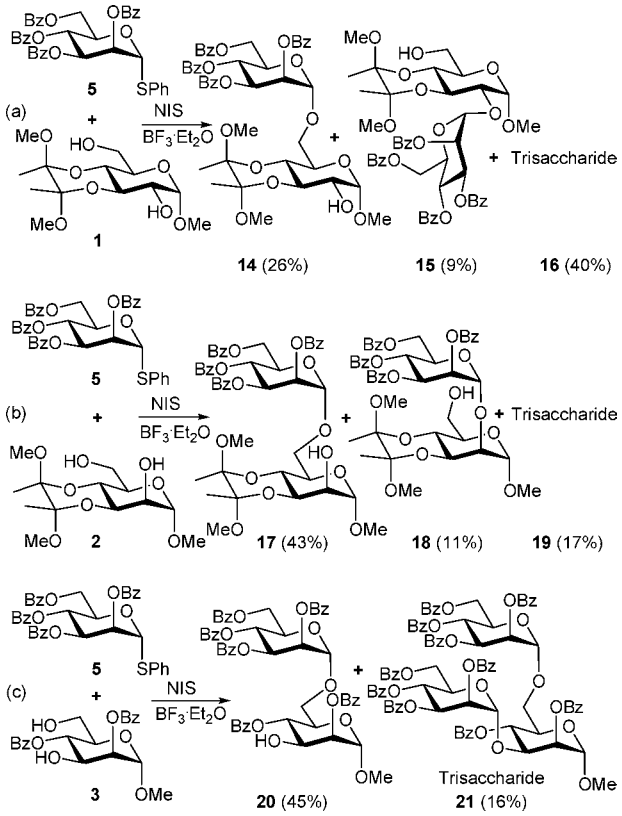
inclination for the secondary (axial) C(2)OH rather than C(6)OH (Scheme 1b).

Interestingly, no disaccharide resulting from glycosyl coupling at the C(6)OH was observed in the first case (Scheme 1a). The first examples of such couplings starting to become dominant were observed in the glycosylation of **2** and **3** (1 equiv) with donor **4** (1 equiv), which furnished **10**, albeit accompanied by disaccharide **9**, (Scheme 1b), and disaccharide **12** accompanied by **11** and trisaccharide **13** (Scheme 1c), respectively.

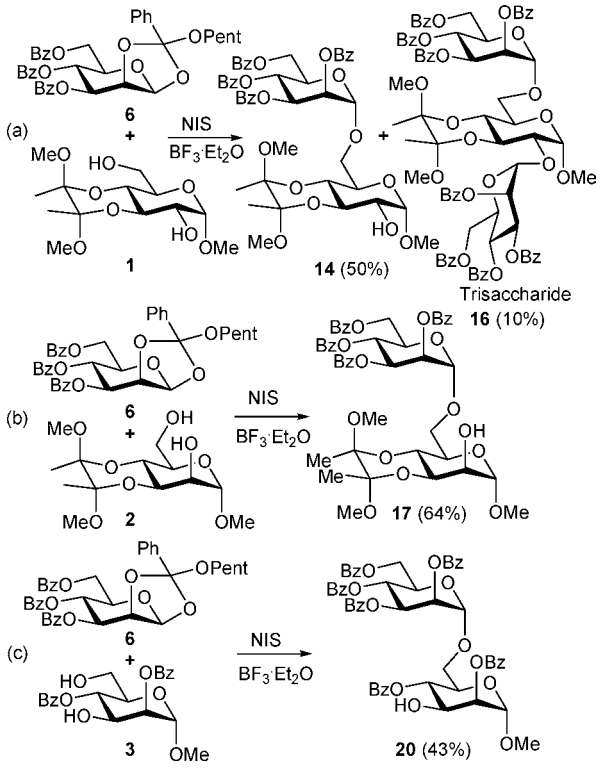
The glycosylation of diol acceptors **1**−**3** with disarmed donor **5** resulted in qualitatively the opposite results (Scheme 2). Thus coupling of diol **1** (1 equiv) with **5** (1.25 equiv) resulted in the formation of disaccharide **14** (26%), from coupling at the C(6)OH, as the major regioisomer compared to **15** (9%) arising from coupling at OH-2. A considerable amount of trisaccharide **16** was also observed (40%). Likewise, reaction of diol **2** (1 equiv) with disarmed donor **5** (1 equiv) took place regioselectively at OH-6 rather than at OH-2 to give disaccharides **17** (43%) and **18** (11%),

(2) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155−173.
(3) Fraser-Reid, B.; López, J. C.; Radhakrishnan, K. V.; Nandakumar M. V.; Gómez, A. M.; Uriel, C. *Chem. Commun*. **2002**, 2104−2105.
(4) Geng, X.; Dudkin, V. Y.; Mandal, M.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2562−2565. Mandal, M.; Dudkin, V. Y.; Geng, X.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2557−2561. Dudkin, V. Y.; Orlova, M.; Geng, X.; Mandal, M.; W. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 9560−9562. Lee, H.-K.; Scanlan, C. N.; Huang, C.-Y.; Chang, A. Y.; Calarese, D. A.; Dwek, R. A.; Rudd, P. M.; Burton, D. R.; Wilson, I. A.; Wong, C.-H., *Angew. Chem., Int. Ed.* **2004**, *43*, 1000−1003. Ratner, D. M.; Plante, O. J.; Seeberger, P. H. *Eur. J. Org. Chem.* **2002**, 826−833.

Scheme 2. Glycosylations of Diol Acceptors **1**−**3** with Disarmed Glycosyl Donor **5**



Scheme 3. Glycosylations of Diol Acceptors **1**−**3** with *n*-Pentenyl Ortho Ester (NPOE) Glycosyl Donor **6**



respectively. Along these lines, the coupling of diol **3** (1 equiv) with donor **5** (1 equiv) resulted in the formation of compound **20** (45%) as the sole observed disaccharide, although it was accompanied by trisaccharide **21**.

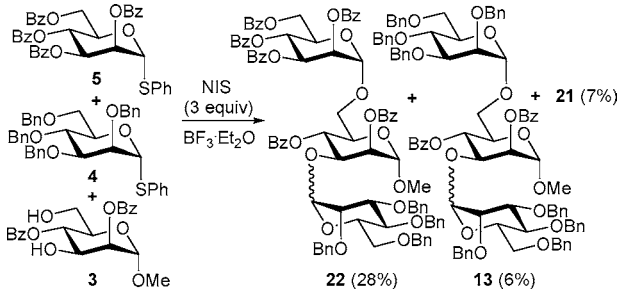
Finally, ortho ester **6** proved to be the most regioselective donor in all of the glycosyl couplings we studied with diols **1**−**3**. In all three glycosylations shown in Scheme 3, only one disaccharide, resulting from coupling at 6-OH, was observed, albeit with some trisaccharide (**16**) in the reaction of **1** with **6**.

The trisaccharides obtained in Schemes 1−3 all arose from double glycosidation of the diol acceptor by the **same** donor.

These observations are especially pertinent since the successful implementation of our recently described protocol for the coupling of one diol acceptor to two glycosyl donors[3] requires prior knowledge of *reciprocal donor acceptor selectivities* (*RDAS*)[5] of the given donors and acceptors. Accordingly, the in situ three-component glycosylation of diol **3** (1 equiv) with armed glycosyl donor **4** (1 equiv) and disarmed donor **5** (1 equiv) furnished **22** as the major product (Scheme 4) conforming to the RDAS superiority of the disarmed versus armed for the primary OH (Schemes 2c versus 1c).

In view of the fact than *n*-pentenyl ortho ester (NPOE) **6** gave a 2-fold higher yield of **14** than did the disarmed donor **5**, it was logical to experiment with **6**. In the event, diol **3** was presented with 1:1 amounts of NPOE **6** and the armed donor **4** along with 3 equiv of NIS (Scheme 5a). The sought compound **22** was obtained as the sole trisaccharide, albeit in only 10% yield.

Scheme 4. Three-Component Glycosylation of Diol **3** with Donors **4** and **5**

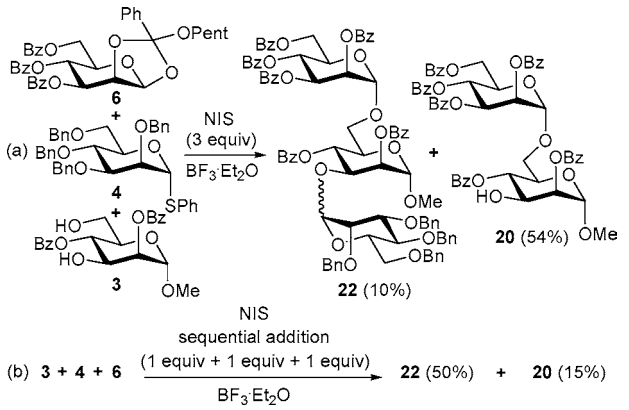


However, this defect could be simply overcome by adding the 3 equiv of NIS portionwise. Indeed, when equimolar amounts of **3**, **4**, and **6** were submitted to the sequential NIS addition protocol, the yield of trisaccharide **22** increased to 50% (Scheme 5b) with concomitant diminution in disaccharide **20** to 15%.

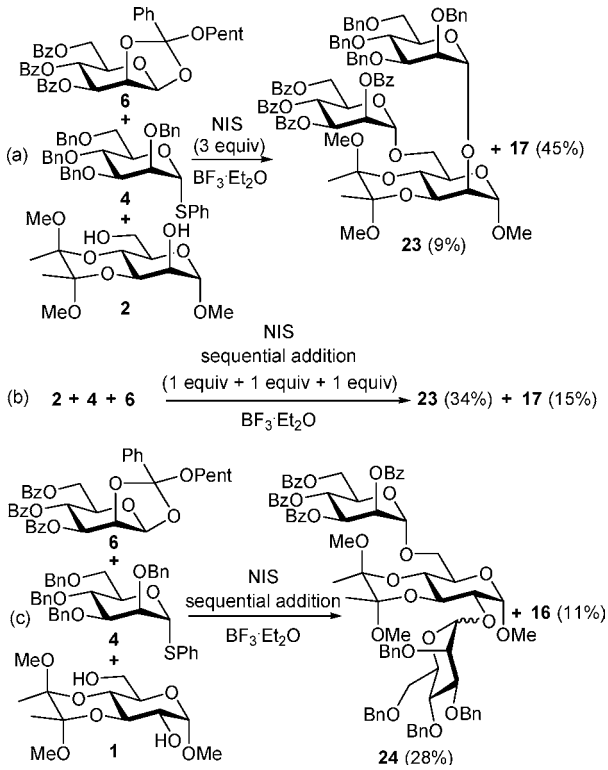
We suggest that the rationale behind this improvement came from the combination of two factors: (1) the iodonium transfer[6] between *n*-pentenyl and phenyl-1-thio-glycosyl

(5) Fraser-Reid, B.; López, J. C.; Radhakrishnan, K. V.; Mach, M.; Gómez, A. M., Uriel, C. *J. Am. Chem. Soc.* **2002**, *124*, 3198−3199. Fraser-Reid, B.; López, J. C.; Radhakrishnan, K. V.; Mach, M.; Schlueter, U.; Gómez, A. M.; Uriel, C. *Can. J. Chem.* **2002**, *80*, 1075−1087.

Scheme 5. Three-Component Glycosylations of Diol **3** with Donors **4** and **6**, with and without NIS Sequential Addition



Scheme 6. Three-Component Reactions of Diols with Donors **4** and **6** with NIS Sequential Addition



donors[7] and (2) the higher reactivity of ortho esters when compared to other armed or disarmed *n*-pentenyl or phenyl-1-thio glycosyl donors.[8]

The implementation of this protocol was further demonstrated with the successful in situ assembly of glycosyl acceptors **1** or **2**, presented simultaneously to a mixture of armed donor **4** and ortho ester **6**. Thus, reaction of diol **2** (1 equiv) with donors **4** (1 equiv) and **6** (1 equiv) in the presence of NIS (3 equiv) and $BF_3{\cdot}Et_2O$ resulted in the formation of disaccharide **17**[9] (45%) and trisaccharide **23**[9] (9%) (Scheme 6a), whereas similar reaction of diol **2** (1 equiv) with donor **4** (1.5 equiv) and ortho ester **6** (1 equiv) under sequential NIS addition (3 equiv, one at a time) yielded trisaccharide **23** in 34% yield accompanied by **17** (15%) (Scheme 6b).

Similarly, sequential NIS addition to a mixture of diol **1** (1 equiv) and donors **4** (1.2 equiv) and **6** (1 equiv) resulted in the formation of trisaccharide **24** in 28% yield (Scheme 6c).

Several conclusions can be drawn from these results: (1) the nature of the glycosyl donor plays a prominent role in eliciting regioselective glycosyl coupling of primary versus secondary diols, (2) NPOEs, the most reactive of the glycosyl donors employed, are the most selective toward C(6)OH groups, and (3) the most efficient implementation of the RDAS protocol for in situ three-component differential double glycosidation of primary-secondary diol acceptors requires the use of NPOE donors.

The NPOE's preference for the primary C(6)OH group can, in our opinion, be rationalized by assuming a sterically demanding trioxolenium ion intermediate.[10] This steric demand, which will decrease for bicyclic dioxolenium ions arising from disarmed donors[10] and, even more so, for "open" oxocarbenium ions (from armed donors), accounts for the observed regiopreferences.

In summary, we have shown that pairs of primary-secondary diol acceptors can be successfully submitted to our recently described in situ, two-donor, one-acceptor methodology for glycosyl assembly. However, along the RDAS lines we have shown that primary hydroxyl groups "match" better with NPOEs, making the latter the preferred choice as one of the donor partners.

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Supporting Information Available: Experimental procedures and characterization data and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via Internet at http://pubs.acs.org.

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(6) Rodebaugh, R.; Fraser-Reid, B. *J. Am. Chem. Soc*. **1994**, *116*, 3155−3156. Fraser-Reid, B.; Merritt, J. R.; Handlon, A. L.; Andrews, C. W. *Pure Appl. Chem*. **1993**, *65*, 779−786. Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottoson, H. *J. Org. Chem.* **1990**, *55*, 6068−6070.

(7) Veeneman, G. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275−278.

(8) For the procedure for determining the relative reactivities of two pentenyl glycosides by competitive oxidative hydrolysis, see: Wilson, B. G.; Fraser-Reid, B. *J. Org. Chem.* **1995**, *60*, 317−320.

(9) The structure of the regioisomeric disaccharides was determined by acylation and ^1H NMR analysis of the newly downshifted proton, whereas the structure of the trisaccharides was confirmed by unequivocal glycosylation of the corresponding disaccharides.

(10) Fraser-Reid, B.; Grimme, S.; Piacenza, M.; Mach, M.; Schlueter, U. *Chem. Eur. J.* **2003**, *9*, 4687−4692.