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One-Pot Chemo-, Regio-, and Stereoselective Double-Differential Glycosidation Mediated by Lanthanide Triflates

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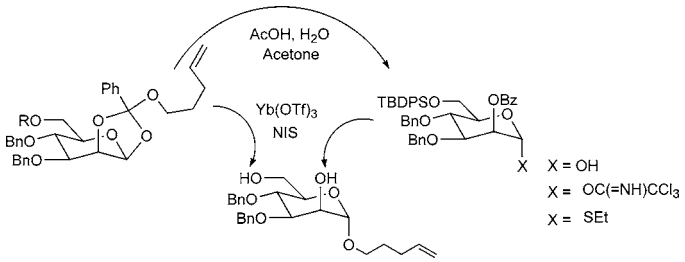
ABSTRACT



Nuanced activation of *n*-pentenyl, thioglycoside, and trichloroacetimidate donors by lanthanide salts coupled with donor/acceptor matching can simplify oligosaccharide assembly. Thus, a one-pot, double-differential glycosidation process can be designed, in which an *n*-pentenyl acceptor-diol is chemo- and regioselectively glycosidated by using an *n*-pentenyl ortho ester under the agency of $Yb(OTf)_3$/NIS followed by in situ addition of a 2-O-acylated trichloroacetimidate or ethyl thioglycoside to effect stereoselective glycosidation at the remaining OH.

Efficiency in organic synthesis relies on selectivities of four types: stereo-, chemo-, regio-, and enantioselectivity. In the case of saccharide coupling, the last is usually irrelevant unless issues of double stereodifferentiation[1] are of interest, as in the seminal studies of van Boeckel.[2] For the remaining three selectivities, the tools available for negotiating between them are virtually limited to protecting groups, and Isbell's 1939 recognition that O2 acylation promoted stereoselective trans coupling in glycosidation reactions[3] provided the first example of the nuanced effects that "protecting groups" can have.

The armed/disarmed strategy reported in 1988,[4] demonstrated that protecting groups could provide the basis for *chemo*selective activation for oligosaccharide assembly. Subsequently, several other devices for chemocontrolled coupling were applied, both to the donor's glycon[5,6] and aglycon.[7] With regard to regioselectivity, our laboratory has shown in several recent publications[8] that glycosidation of

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(2) Spijker, N. M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 180.

(3) Isbell, H. S. *Ann. Rev. Biochem.* **1940**, *9*, 65. Frush, H. L.; Isbell, H. S. *J. Res. Natl. Bur. Stand. (U.S.)* **1941**, *27*, 413.

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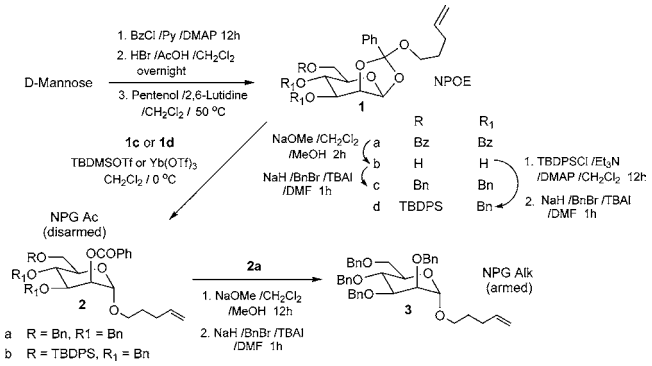
Scheme 1



acceptor polyols can be regulated by the donor's protecting group(s), observations that are reminiscent of Paulsen's concept of donor/acceptor "match".[9] That these observations are of general applicability is supported by the range of substrates that have been tested[8] and the agreement shared by *n*-pentenyl glycoside (NPG), thioglycoside, and trichloroacetimidate donors.[10] A recent publication by Moreau and co-workers[11] on regiocontrolled glycosidation of mannopyranoside 3,6-diols conforms to our precedents.[8]

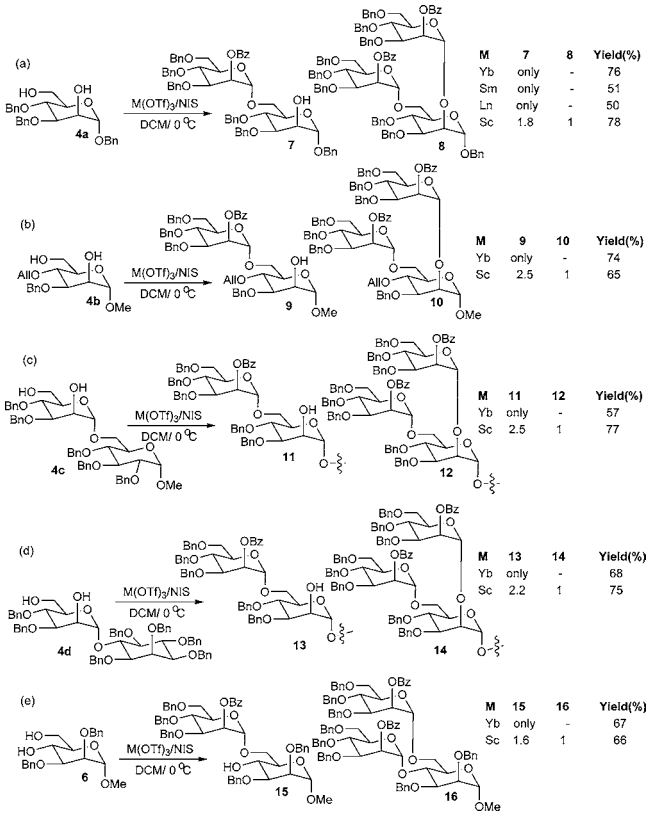
The foregoing successes notwithstanding, protecting groups present their own problems for installation and/or removal. We are therefore interested in regiocontrol protocols that do not rely on protecting groups, and in this manuscript we report upon a study that achieves this objective.

As illustrated for mannose in Scheme 1, *n*-pentenyl ortho esters (NPOEs), **1**, readily prepared from the parent aldose in three easy steps,[12] undergo standard acid-catalyzed rearrangement[13] to give a disarmed *n*-pentenyl glycoside (NPG$_{Ac}$), e.g., **2**, from which the corresponding armed counterpart (NPG$_{Alk}$), e.g., **3**, is readily obtained (Scheme 1).

We have recently investigated the use of Lewis acid salts to generate iodonium ion (I^+), needed to activate *n*-pentenyl donors, from *N*-iodosuccinimide (NIS) and found that ytterbium triflate (Yb(OTf)$_3$)/NIS activates NPOEs but not the armed (NPG$_{Alk}$) or disarmed (NPG$_{Ac}$) counterparts.[14] We were interested to see whether these lanthanide triflate-based chemoselectivities could be combined with the regioselectivities described above[8] in the glycosidation of polyols.

The diol **4a** was chosen as the initial test candidate in view of its potential as starting material for the highlighted trimannan repeating unit of lipomannan, **5**, from *Mycobacterium tuberculosis* glycolipids.[15] Upon treatment with 2 equiv of NPOE **1c** and NIS activated by Yb(OTf)$_3$, the only product formed was disaccharide **7** in 76% yield, Scheme 2a. The location of the free OH in **7** was readily identified by acetylation and examining the parameters of the downfield-shifted proton in the ^{1}H NMR spectrum ($\delta = 5.44$; dd $J = 1.8$ & 3.0 Hz). Two other salts, samarium triflate (Sm(OTf)$_3$) and lanthanum triflate (Ln(OTf)$_3$), tried under similar conditions, also gave **7** only but in somewhat lower yields (51 and 50%, respectively).

Scheme 2. Glycosidation of Primary/Secondary Diols with NPOE **1c** (2 equiv) Using Lanthanide Triflates (M(OTf)$_3$) (0.3 equiv) and NIS (2.5 equiv) in CH_2Cl_2 at 0 °C



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(13) For a convenient summary, see: Bochkov, A. F.; Zaikov, G. E. *Chemistry of the O-Glycosidic Bond*; Pergamon Press: Oxford, UK, 1979, Chapter 2.

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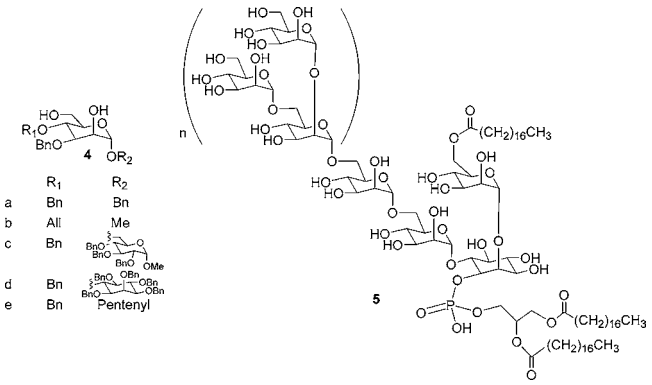


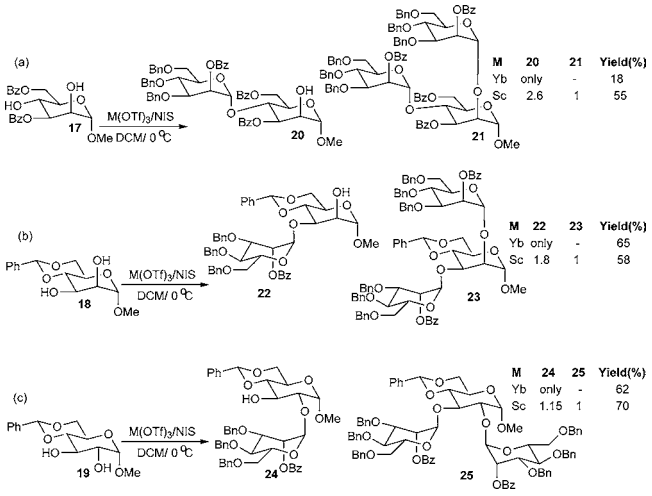
The foregoing results were remarkable in that **7** was the only product, even though 2 equiv of the donor **1c** had been used. However, when scandium triflate ($Sc(OTf)_3$) was used as the Lewis salt for activating NIS, trisaccharide **8** was formed in a substantial amount along with disaccharide **7**.

The results with diol **4a** suggested that the best salts for activating NIS, in terms of overall yields, were $Yb(OTf)_3$ and $Sc(OTf)_3$, and so these salts were applied to the analogous 2,6-diol **4b** as well as disaccharides **4c** and **4d**. The results in Schemes 2b−d show that $Yb(OTf)_3$ was exquisitely selective in each case, giving a single product, **9**, **11**, and **13**, respectively, whereas with $Sc(OTf)_3$ these products were accompanied by appreciable amounts of doubly mannosylated materials, **10**, **12**, and **14** respectively.

The 4,6-diol acceptor, **6**, also followed the same trend in $Yb(OTf)_3$/NIS and gave complete regioselectivity with formation of **15** only, while with $Sc(OTf)_3$/NIS, double-glycosidation counterpart **16** was also obtained (Scheme 2e).

Regioselective glycosidation of the primary hydroxyl groups in diols **4a**−**d** and **6** might seem to be the obvious outcome of simple steric preferences. We therefore tested diols **17**−**19** (Scheme 3) in which the choice was between two secondary hydroxyl groups. The pattern of results was again similar, $Yb(OTf)_3$/NIS being regioselective for one of

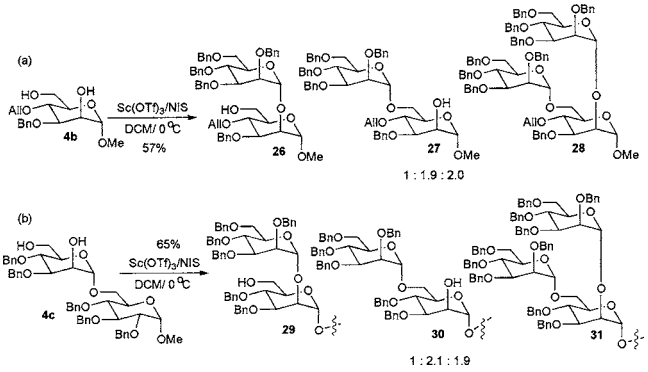
Scheme 3. Glycosidation of Secondary/Secondary Diols with NPOE **1c** (2 equiv) Using Lanthanide Triflates ($M(OTf)_3$) (0.3 equiv) and NIS (2.5 equiv) in CH_2Cl_2 at 0 °C



the two secondary hydroxyl groups, affording one disaccharide **20**, **22**, and **24**, respectively, and $Sc(OTf)_3$/NIS giving these products along with appreciable amounts of trisaccharides **21**, **23**, and **25** respectively.

A striking feature of the results in Schemes 2 and 3 is the formation of only one of two possible disaccharides. That the absence of the "other" disaccharide was tied to the donor was demonstrated by presenting the armed NPG **3** to diols **4b** and **4c** under the agency of $Sc(OTf)_3$/NIS. The results in Scheme 4 show formation of appreciable amounts of the

Scheme 4. Glycosidation of Primary/Secondary Diols with NPG_{Alk} **3** (2 equiv) Using $Sc(OTf)_3$ (0.3 equiv) and NIS (2.5 equiv) in CH_2Cl_2 at 0 °C



"other" disaccharides, **26** and **29**, that had been missing in Schemes 2b and 2d. These results are in keeping with our observations on the "match" between mannoside 2-OH acceptors and armed *n*-pentenyl donors.[8]

The differences in results with $Yb(OTf)_3$ and $Sc(OTf)_3$ in Schemes 2 and 3 can be rationalized as follows. Both salts are able to induce rearrangement of NPOE to NPG_{Ac}, **1**→**2**, and this occurs, to some extent, in the presence of an acceptor and NIS. With $Yb(OTf)_3$, glycosidation occurs by NPOE **1** *only*, and in these reactions **2** was indeed recovered. By contrast, the stronger salt, $Sc(OTf)_3$, is able to induce glycosidation by both **1** and **2**.

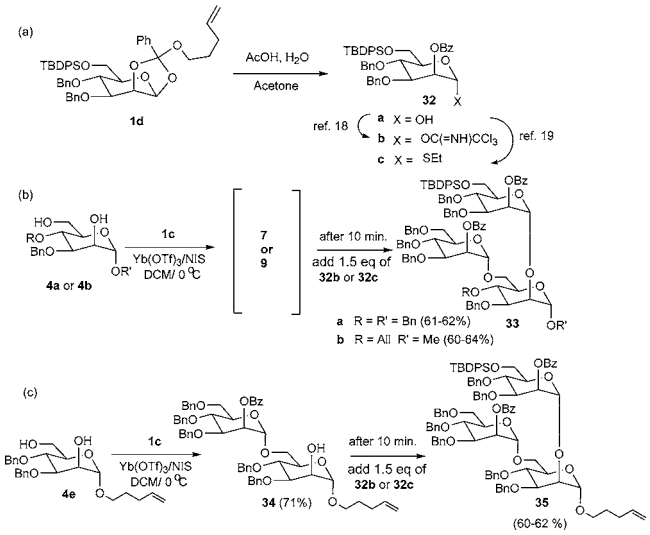
The utilitarian aspect of this postulate invited immediate evaluation. Since reaction of the diols with an NPOE is complete within the time required to take a TLC sample, addition of a second donor should enable a one-pot synthesis[16] of a trisaccharide. It would be best that the second donor also be activated by $Yb(OTf)_3$, since, as noted in the preceding paragraph, $Sc(OTf)_3$ would induce reaction with any disarmed NPG that had been produced by rearrangement of the NPOE.

Investigation of several donors showed that trichloroacetimidates[17] and ethyl thioglycosides are activated by

(16) See for example: Fraser-Reid, B.; Udodong, U. E.; Wu, Z.; Ottosson, H.; Merritt, J. R.; Rao. C. S.; Roberts, C. *Synlett* **1992**, 927. Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580. Yamada, H.; Harada, T.; Miyazaki, H.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 3979. Grice, P.; Ley, S. V.; Pietruszka, J.; Osborn, M.; Henning, W. M.; Priepke, H. W. M.; Warriner, S. L. *Chem. Eur. J.* **1997**, 431.

(17) For reaction of trifluroacetimides, see: Adinolfi, M.; Iadonisi, A.; Schiattarella, M. *Tetrahedron Lett.* **2003**, *44*, 6479.

Scheme 5



$Yb(OTf)_3$. Accordingly, NPOE **1d** was hydrolyzed with acetic acid and water, and the resulting glycose, **32a**, was converted into the trichloroacetimidate **32b** and ethyl thioglycoside **32c** using standard procedures[18,19] (Scheme 5a).

In the event, diol **4a** or **4b** was treated with 2 equiv of NPOE **1c** and $Yb(OTf)_3$/NIS, and after 10 min, **32b** or **32c** was added and the reaction was allowed to continue for 15 min. Trisaccharide **33a** or **33b** was isolated in ~62% yield from either reaction.

The formation of **33a** and **33b** represented regio- and stereoselective processes. The possibility of adding chemoselectivity to the process became feasible when the NPG **4e**, obtained readily from **2b**, was found to react with NPOE **1c** to give a 71% yield of disaccharide **34**. In a one-pot operation, the process was repeated except that trichloroacetimidate **32b** or thioglycoside **32c** was added after 10 min. Trisaccharide **35** was thereby obtained in ~61% overall yield.

These observations hold out great promise to combine the nuanced effects of various donors, the donor's protecting groups, and lanthanide salt activation for selective glycosidations. Further examples are being investigated and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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