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Targeted Glycosyl Donor Delivery for Site-Selective Glycosylation[†,1]

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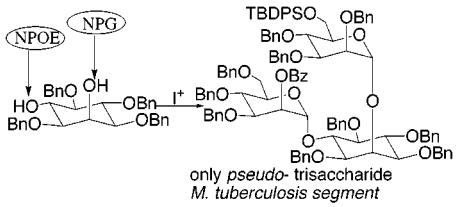
ABSTRACT



***n*-Pentenyl ortho esters (NPOEs) and *n*-pentenyl glycosides (NPGs) are interconvertible glycosyl donors which are activated by reaction with halonium ions. In a series of cyclic *syn*-1,3-diols, NPOEs have been found to specifically glycosylate the equatorial-OH while the NPG glycosylates predominantly, but not exclusively, the axial-OH. When the cyclic diol acceptor is presented with equivalent amounts of an NPOE and an NPG in a three-component-reaction, a single, double-glycosylation product is obtained, which conforms to the foregoing preferences, presenting evidence for site-selective glycosylation.**

The concept of armed/disarmed strategies for controlling oligosaccharide assembly, initially formulated in the context of *n*-pentenyl glycosides,[2] was rapidly extended to other glycosyl donors[3] and has become part of the fabric of synthetic carbohydrate chemistry.[4,5] The principle relies on the logistical deployment of "protecting groups" on the donor, and the effect can be engendered by electronic[6] or torsional[7] factors, the latter being elegantly demonstrated in recent reports from Crich and co-workers.[8] Glycosyl acceptors are the other partners in coupling reactions, and it is well-known that poly-hydroxyl substrates frequently display selectivity based on orientation,[9] hydrogen bonding,[10] etc. Both sets of selectivities are kinetically based. Thus, armed and disarmed donors can each react with a given acceptor, but the rates are sufficiently different that in a competitive setting one product is formed overwhelmingly. In this Letter, we describe a very different glycosidation phenomenon based on exquisite paring of donor and acceptor, which can be so selective that it constitutes evidence for "site-selective glycosidation".

n-Pentenyl donors[11] are unique among glycosylating agents currently in use[3,12] in that they may function in both 1,2-ortho ester (NPOE, **1**) and glycosidic (NPG, **2a**) modali-

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(2) Mootoo, D. R.; Konradson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583−5584.
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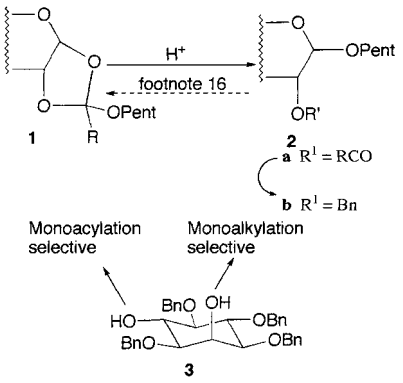
ties.[13,14] The latter are readily obtainable from the former by means of an efficient stereocontrolled, acid-catalyzed rearrangement.[15] The reverse process, **2a** → **1**, has not been formally reduced to practice, although it can be readily conceptualized.[16,17]

Our investigations were triggered by the recent observations that the partially protected *myo*-inositol **3** undergoes selective alkylation at C2-OH[18] but selective acylation at C6-OH (Scheme 1).[19] The possibility of comparable site-selective

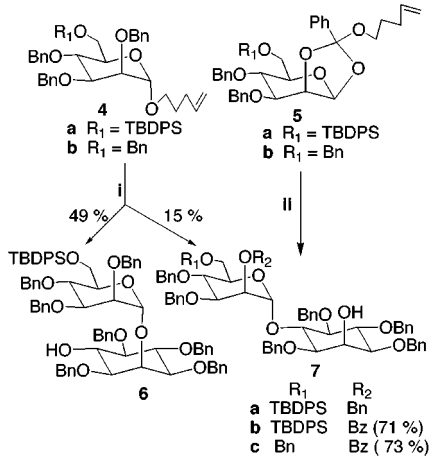
Scheme 1



glycosidation was of interest, since C2 and/or C6 mono- and diglycosylated inositols occur in inositides of glycosylphosphatidylinositols (GPIs)[20] and lipoarabinomannans (LAMs),[21] the biological "warheads" of malaria and tuberculosis cell-surface oligosaccharides, respectively.

The major products from the reaction[22] of NPG **4a** with the diol acceptor **3** were the α-mannosides **6** and **7a**[23,24] in 3:1 ratio and ~65% combined yield (Scheme 2). In the hope

Scheme 2[a]

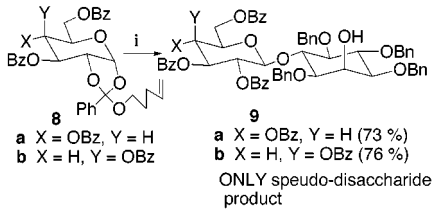


[a] Reaction conditions: (i) **3**, NIS (1.3 equiv), TBDMSOTf (cat.), CH_2Cl_2, rt, 10 min; (ii) **3**, NIS (1.3 equiv), TBDMSOTf (cat.), CH_2Cl_2, 0 °C, 20 min.

of improving the yield of **6**, we examined *n*-pentenyl ortho esters (NPOEs), since these donors have recently served us well.[17,25] Much to our surprise, NPOE glycosidation[22] with **5a** or **5b** displayed the completely alternative preference, giving **7b** or **7c**,[24] respectively, as the *only* coupling product in spot-to-spot conversion.

To determine whether α-face ortho esters would also exhibit similar preferences, the *gluco* and *galacto* NPOEs **8a** and **8b** were tested with diol **3** (Scheme 3). The products

Scheme 3[a]



[a] Reaction conditions: (i) **3**, NIS (1.3 equiv), TBDMSOTf (cat.), CH_2Cl_2, 0 °C, 20 min.

of C6-glycosidation, **9a** and **9b**, were the *only pseudo*-disaccharides obtained in 76 and 72% yields, respectively.

To demonstrate that these observations were not confined to inositols, we established that the mannoside diol **10** displayed comparable selectivities with both donors (Scheme 4). Thus, reaction with NPG **4b** gave **11** as the major product (69%) along with minor isomeric products, while with NPOE **5b** the *only isolable disaccharide* was **12**. Similar equatorial selectivities were also found for reaction of **10** with the *gluco* and *galacto* ortho esters **8a** and **8b**.

Rationalization of the results in Schemes 2, 3, and 4 must await further investigation, but the coincidence of the paired selectivities RCOX/NPOE versus $ArCH_2X$/NPG is an obvi-

(13) Thioortho esters undergo comparable rearrangement, e.g., **1** to **2**,[14a] but the former are not efficient glycosyl donors.[14b]

(14) (a) Krog-Jensen, C.; Oscarson, S. *Carbohydr. Res.* **1998**, *308* 287−296. (b) Bernlind, C.; Oscarson, S. *Carbohydr. Res.* **1997**, *297*, 251−260.

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

(16) By two steps involving conversion to the glycosyl bromide,[11] followed by treatment with lutidine[17] in the usual way.

(17) Roberts, C.; May, C. L.; Fraser-Reid, B. *Carbohydr. Lett.* **1994**, *1*, 89−93.

(18) Jia, Z. J.; Olsson, L.; Fraser-Reid, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 631−632.

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

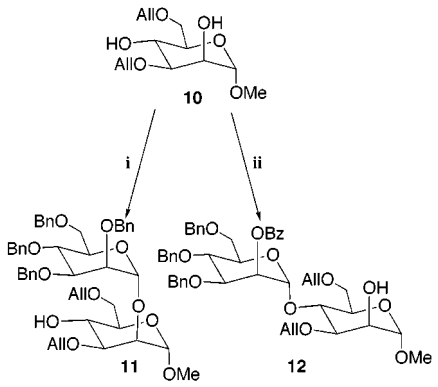
(20) Ferguson, M. A. J.; Brimacombe, J. S.; Brown, J. R.; Crossman, A.; Diz, A.; Field, R. A.; Guther, M. L. S.; Milne, K. G.; Sharma, D. K.; Smith, T. K. *Biochim. Biophys. Acta* **1999**, *1455*, 327−340. Gerold, P.; Eckert, V.; Schwarz, R. T. *Trends Glycosci. Glycotechnol.* **1996**, *8*, 265−277.

(21) Chatterjee, D.; Khoo, K.-H. *Glycobiology* **1998**, *8*, 113−120. Besra, G. S.; Morehouse, C. B.; Rittner, C. M.; Waechter, C. J.; Brennan, P. J. *J. Biol. Chem.* **1997**, *272*, 18460−18466. Nigou, J.; Gilleron, M.; Puzo.; G. *Biochem. J.* **1999**, *337*, 453−460.

(22) The diol (~0.092 mmol) and glycosyl donor (~0.119 mmol) were dissolved in a small quantity of toluene, azeotroped to dryness, and then dissolved in CH_2Cl_2 (2 mL) at 0 °C under an argon atmosphere. *N*-Iodosuccinimide (0.119 mmol) was added to the solution, and after stirring for 3 min, TDBMSOTf (0.027 mmol) was added. The reaction was quenched after 20 minutes with 10% aqueous sodium thiosulphate and saturated aqueous sodium bicarbonate, extracted with CH_2Cl_2, and worked up in the usual way.

(23) *β*-Anomers were detected in 5−10% yield with 2-O-benzylated NPGs.

Scheme 4[a]



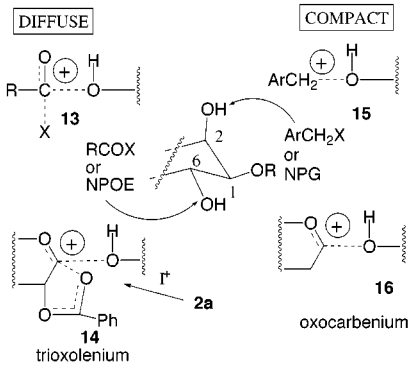
[a] Reaction conditions: (i) **4b** (1.3 equiv), NIS (1.3 equiv), TBDMSOTf (cat.), CH_2Cl_2, rt, 20 min, 66%; (ii) **5b** (1.3 equiv), NIS (1.3 equiv), TBDMSOTf (cat.), CH_2Cl_2, 0 °C, 20 min, 69%.

ous starting point. The corresponding key reacting entities are the tetrahedral intermediate **13**/trioxolenium ion **14** versus benzylic carbocation **15**/oxocarbenium ion **16.** In terms of charge delocalization, **13** and **14** may be considered *diffuse* and **15** and **16** *compact.*[26,27]

In this regard, **2a** is an NPG-but the C2−O-acyl group permits formation of the trioxolenium ion **14,** and it should show the same selectivity as the NPOE. Indeed, reaction of the C2−O-benzoyl NPG obtained from **5a,** led to the equatorial glycoside **7b** as the only product in somewhat lower yield (58%).

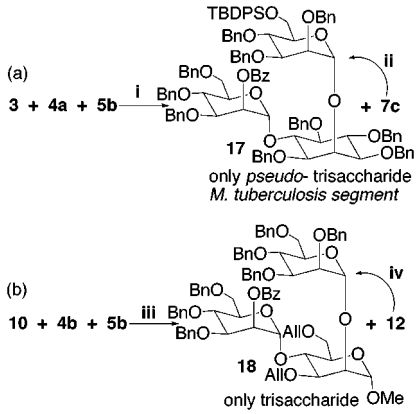
For challenging evaluations of the summary in Scheme 5, the diol acceptors, **3** or **10**, were separately presented with

Scheme 5



1.3 equiv of each type of donor. The results in Scheme 6 show that a single trisaccharide, **17** or **18**, was obtained as

Scheme 6[a]



[a] Reaction conditions: (i) NIS (2.6 equiv), TBDMSOTf (cat.), CH_2Cl_2, 0 °C to rt, 1 h, 79% (1:1), (ii) **4a** (1.3 equiv), NIS (1.3 equiv), TBDMSOTf (cat.), CH_2Cl_2, rt, 1 h, 14%; (iii) NIS (2.6 equiv), TBDMSOTf (cat.), CH_2Cl_2, 0 °C to rt, 1 h, 93% (∼1.5:1); (ii) **4b** (1.3 equiv), NIS (1.3 equiv), TBDMSOTf (cat.), CH_2Cl_2, rt, 1 h, 36%.

the major product in each case. Notably, the minor product was disaccharide **7c** or **12**, which arises from glycosylation with the NPOE rather than the NPG.

Thus, although rationalization for these *mutual* selectivities, and the implications of the *diffuse* versus *compact* concept, must await further experimentation, the advantage is apparent from the one-pot, site-selective, double-glycosidation leading to **17**, the core of the lipoarabinomannan antigen of *Mycobacterium tuberculosis.*[20]

Supporting Information Available: Experimental details. This information is available free of charge via the Internet at http://pubs.acs.org.

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(24) In a typical proof of regioselectivity, the product was acylated and the downshifted proton analyzed for two large (e.g., **6**) or two small (e.g., **7**) couplings.

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

(26) S_N2- and S_N1-like[27] are alternatives for *diffuse* and *compact*, but the former terms have other mechanistic connotations that may be inappropriate in the present context. HARD and SOFT are also possibilities, but which is which?

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