

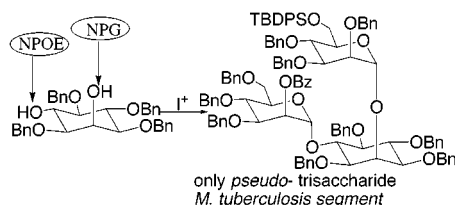
Targeted Glycosyl Donor Delivery for
Site-Selective Glycosylation^{†,1}

G. Anilkumar, Latha G. Nair, and Bert Fraser-Reid*

*Natural Products and Glycotechnology Research Institute, Inc.,[‡]
4118 Swarthmore Road, Durham, North Carolina 27707**npgresearch@hotmail.com*

Received May 4, 2000

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 donors³ 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 electronic⁶ or torsional⁷ 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 pairing of donor and acceptor, which can be so selective that it constitutes evidence for “site-selective glycosidation”.

n-Pentenyl donors¹¹ 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**) modalities.

[†] Dedicated to Professor R. U. Lemieux in honor of his 80th birthday.

[‡] A nonprofit organization at Centennial Campus (North Carolina State University), Raleigh, NC.

(1) Financial support from the Research in Tropical Diseases (TDR) program of the World Health Organization and the NIH (GM40171) is gratefully acknowledged.

(2) Mootoo, D. R.; Konradson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583–5584.

(3) Boons, G. J. *Tetrahedron* **1996**, *52*, 1095–1121.

(4) Collins, P. M.; Ferrier, R. J. *Monosaccharides—Their Chemistry and Their Roles in Natural Products*; Wiley & Sons: New York, 1995.

(5) Boons, G.-J. *Carbohydrate Chemistry*; Blackie Academic and Professional, Chapman and Hall: London, 1999.

(6) Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H. *J. Org. Chem.* **1990**, *55*, 6068–6070.

(7) Fraser-Reid, B.; Wu, Z.; Andrews, C. W.; Skowronski, E.; Bowen, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 1434–1435. Andrews, C. W.; Rodebaugh, R.; Fraser-Reid, B. *J. Org. Chem.* **1996**, *61*, 5280–5289.

(8) Crich, D.; Cai, W.; Dai, Z.; *J. Org. Chem.* **2000**, *65*, 1291–1297. Crich, D.; Sun, S.; *J. Am. Chem. Soc.* **1998**, *120*, 435–436.

(9) Jacquinot, J. C.; Duchet, D.; Milat, M. L.; Sinay, P. *J. Chem. Soc., Perkin Trans. 1* **1981**, 326–330. Jacquinot, J. C.; Paulsen, H. *Tetrahedron Lett.* **1981**, *22*, 1387–1390.

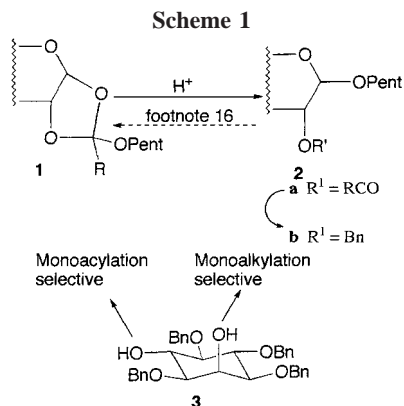
(10) Vasella, A. In *Bioorganic Chemistry Carbohydrates*; Hecht, S. M., Ed.; Oxford University Press: New York, 1999; pp 56–88.

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

(12) *Bioorganic Chemistry: Carbohydrates*; Hecht, S. M., Ed.; Oxford University Press: 1999. *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker, 1997. *Modern Methods in Carbohydrate Synthesis*; Khan, S. H., O'Neill, R. A., Eds.; Harwood Academic Publishers: 1996.

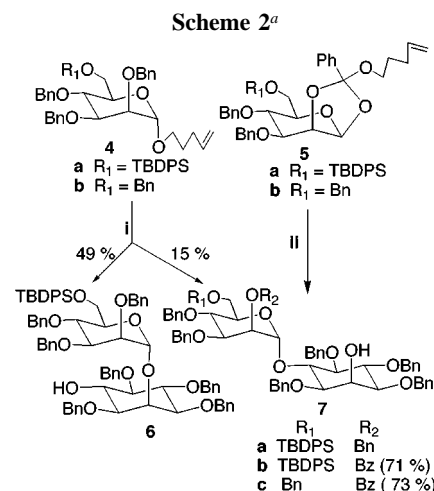
ties.^{13,14} The latter are readily obtainable from the former by means of an efficient stereocontrolled, acid-catalyzed rearrangement.¹⁵ The reverse process, **2a** \rightarrow **1**, has not been formally reduced to practice, although it can be readily conceptualized.^{16,17}

Our investigations were triggered by the recent observations that the partially protected *myo*-inositol **3** undergoes selective alkylation at C2-OH¹⁸ but selective acylation at C6-OH (Scheme 1).¹⁹ The possibility of comparable site-selective



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.

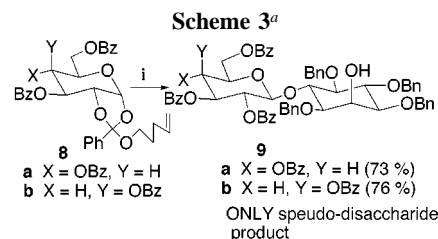
The major products from the reaction²² of NPG **4a** with the diol acceptor **3** were the α -mannosides **6** and **7a**^{23,24} in 3:1 ratio and ~65% combined yield (Scheme 2). In the hope



^a Reaction conditions: (i) **3**, NIS (1.3 equiv), TBDMSOTf (cat.), CH₂Cl₂, rt, 10 min; (ii) **3**, NIS (1.3 equiv), TBDMSOTf (cat.), CH₂Cl₂, 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 glycosidation²² 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



^a Reaction conditions: (i) **3**, NIS (1.3 equiv), TBDMSOTf (cat.), CH₂Cl₂, 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 $\text{ArCH}_2\text{X/NPG}$ 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.; Zaiikov, 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 lutidine¹⁷ 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. I* **1998**, 631–632.

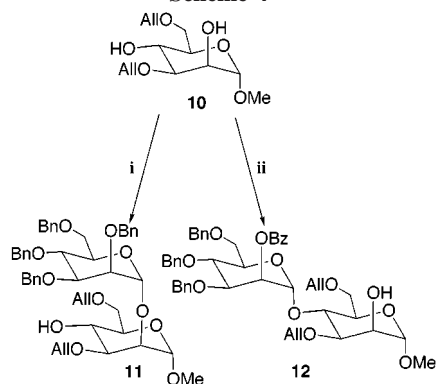
(19) Anilkumar, G.; Jia, Z. J.; Kraehmer, R.; Fraser-Reid, B. *J. Chem. Soc., Perkin Trans. I* **1999**, 3591–3596.

(20) Ferguson, M. A. J.; Brimacombe, J. S.; Brown, J. R.; Crossman, A.; Diz, A.; Field, R. A.; Guthrie, 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

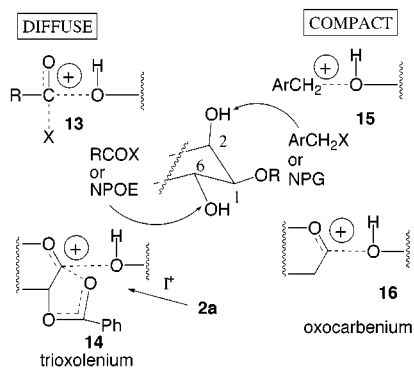
^a Reaction conditions: (i) **4b** (1.3 equiv), NIS (1.3 equiv), TBDMSOTf (cat.), CH₂Cl₂, rt, 20 min, 66%; (ii) **5b** (1.3 equiv), NIS (1.3 equiv), TBDMSOTf (cat.), CH₂Cl₂, 0 °C, 20 min, 69%.

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}

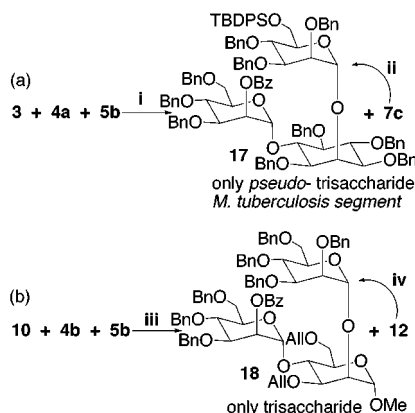
In this regard, **2a** is an NPG-but the C2–O-acyl group permits formation of the trioxolenium ion **14**, and it should show the same selectivity as the NPOE. Indeed, reaction of the C2–O-benzoyl NPG obtained from **5a**, led to the equatorial glycoside **7b** as the only product in somewhat lower yield (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.), CH₂Cl₂, 0 °C to rt, 1 h, 79% (1:1); (ii) **4a** (1.3 equiv), NIS (1.3 equiv), TBDMSOTf (cat.), CH₂Cl₂, rt, 1 h, 14%; (iii) NIS (2.6 equiv), TBDMSOTf (cat.), CH₂Cl₂, 0 °C to rt, 1 h, 93% (~1.5:1); (ii) **4b** (1.3 equiv), NIS (1.3 equiv), TBDMSOTf (cat.), CH₂Cl₂, 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-glycosylation 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>.

OL0001214

(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-like²⁷ 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?

(27) Angyal, S. J.; Tate, M. E. *J. Chem. Soc.* **1965**, 6964–6951.