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A study of *n*-pentenylorthoesters having *manno*, *gluco* and *galacto* configurations in regioselective glycosylations☆

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Dedicated to the memory of Professor Nikolay K. Kochetkov

Abstract—Kochetkov's extensive investigations of glycosyl orthoester and their analogs as glycosyl donors revealed that the alkyl derivatives were plagued by competition between the departing alcohol and the incoming acceptor. *n*-Pentenyl orthoesters (NPOEs) obviate competition by sequestering the departing pentenyl alcohol as a 2-halomethyl tetrahydrofuran. Exquisitely regioselective glycosidations of diol acceptors can be carried out with NPOEs triggered specifically with $Yb(OTf)_3$/NIS. However with $Sc(OTf)_3$, double glycosidation is the major reaction. *manno*, *gluco* and *galacto* NPOEs have been investigated. The latter two, which require a different experimental procedure for the *manno* counterpart, also give an excellent regioselectivity with $Yb(OTf)_3$, but the yields are much lower than with *manno*.

Keywords: *n*-Pentenylorthoesters; Regioselective glycosidation; Lanthanide triflates

1. Introduction

The prolonged impact of glycosyl orthoesters on carbohydrate chemistry may be judged by the fact that the very first (1945) issue of *Advances in Carbohydrate Chemistry* (later *Advances in Carbohydrate Chemistry and Biochemistry*) contained a 50-page review by Pacsu, one of the leading physical organic chemists of the day.[1] The first evidence of this structural type was Fischer's 'methyl L-rhamnoside triacetate', which contained an 'alkali-resistant acetate'.[2] Ten years elapsed before the anomaly was clarified by the assignment of glycosyl orthoester functionality **1** to the structure in question, by independent studies in the laboratories of Freudenberg[3] and Haworth.[4]

In the interim, the power of Koenigs–Knoor reaction[5] had been established as the preferred method of glycoside synthesis; but it would take a further 10 years for the attendant stereoselectivity to be rationalized by Frush and Isbell in a seminal paper entitled *sugar acetates, acetylglycosyl halides, and orthoacetates in relation to the Walden inversion*.[6] The paper recognized the advantage of orthoesters as isolable surrogates for the Koenigs–Knoor reaction via protic or Lewis acid-catalyzed rearrangement, **1**→**2**[7] (see Scheme 1). In a notable development Hanessian and Banoub extended the methodology to furanosyl systems in 1975[8].

Kochetkov and Backinowsky[9] extended the genre to 1,2-thioorthoesters, **3**, which then joined thioglycosides as emerging glycosyl donors,[10] and Kochetkov subsequently introduced the internal orthoester **4** as a substrate for a high-level cationic polymerization.[11] This activity led to the novel cyanoethylidene analogs which, upon careful study, were found to exhibit different responses to Lewis acid salts. For example, structure **5** upon treatment with trityl perchlorate ($TrClO_4$), underwent concatenation resulting in a linear polysaccharide

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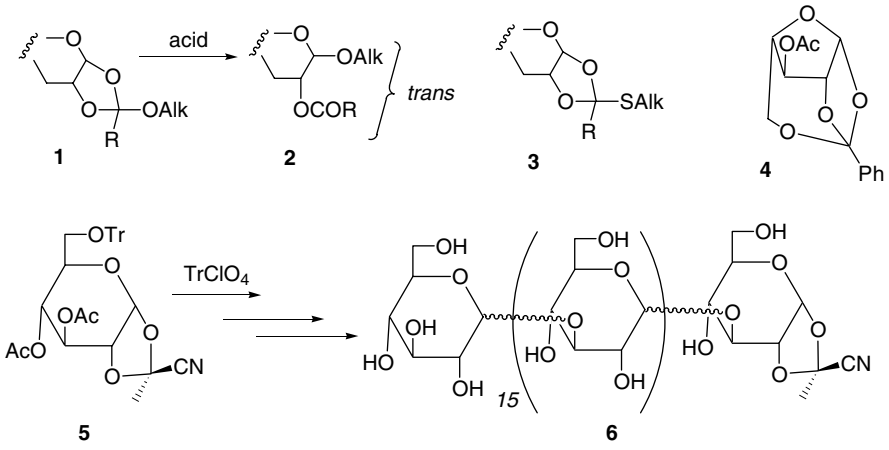
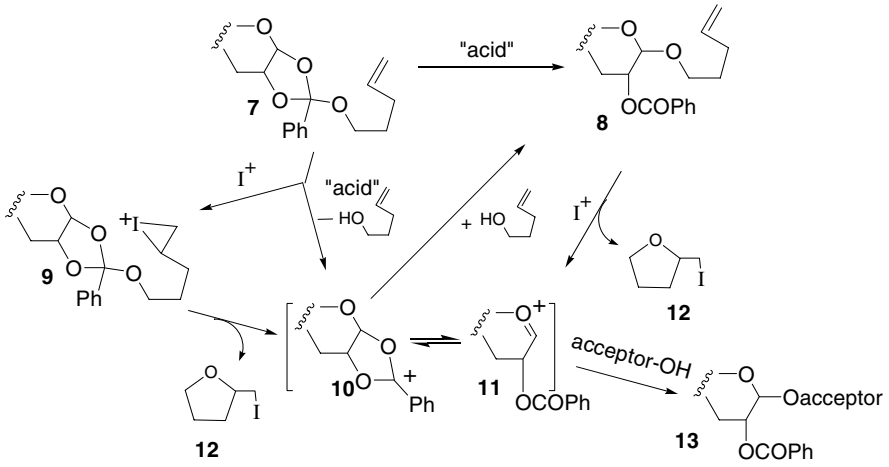


Scheme 1.



Scheme 2.

6.[12] On the other hand, by the use of silver triflate, cyclic 1→6-oligosaccharides could also be prepared from these novel *pseudo*-orthoesters.[13]

Kochetkov's interest in compounds such as **5** arose initially from the challenges he faced by using normal orthoesters, for example, **1**, as the glycosyl donors. Thus, he found that the departed alcohol, AlkOH, competed with the acceptor-OH[12] for the donor.

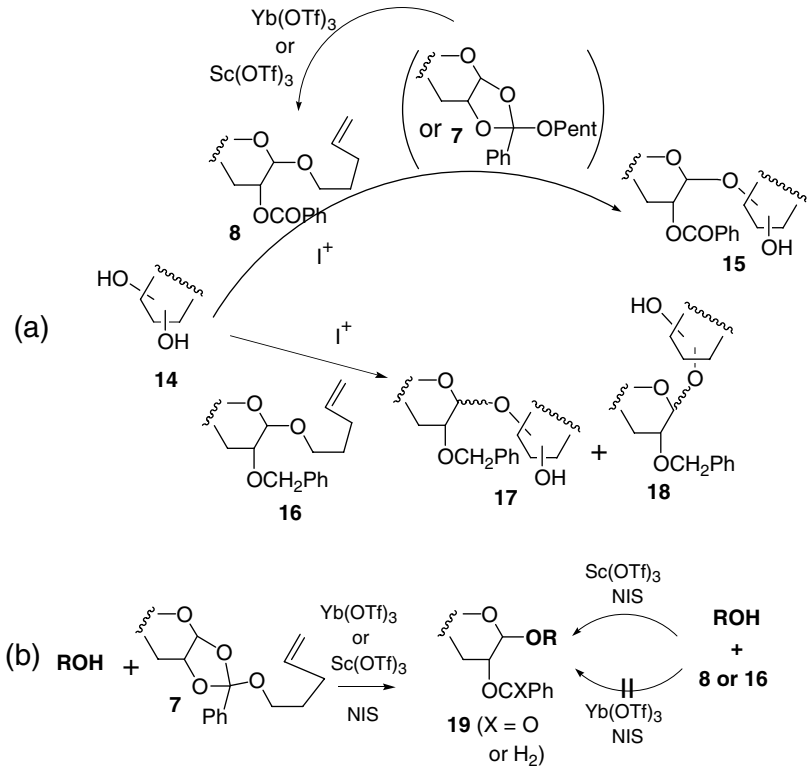
An *n*-pentenyl orthoester (NPOE) such as **7** (Scheme 2) obviates such competition by presenting optional pathways. Thus, the usual acid-catalyzed rearrangement gives the disarmed *n*-pentenyl glycoside (NPG), **8**. However, when presented with iodonium ion, I^+, cyclic iodonium ion, **9**, comes into play, so that the pentenyl-OH is removed as iodomethyl tetrahydrofuran **12**. The acceptor-OH therefore faces no competition from the departing alcohol with respect to the formation of glycoside **13**.

A further advantage is that NPOE can replace a disarmed *n*-pentenyl glycoside, **8**, which is much less reactive, and also prone to addition across the double bond, a problem never encountered with NPOEs.[14]

Recently, our focus has been on the issues of regioselectivity in the glycosidation of acceptor polyols[15] in the hope of reducing the number of protecting/deprotecting episodes that burdens the oligosaccharide assembly.[16] The burden is not only time consuming, but may be problematic because of the sometimes erratic behaviors of the protecting groups. In this manuscript, we report on some of our recent observations which support the view that excellent regioselective glycosidation of polyols can be achieved by the specific use of glycosyl orthoester donors promoted by ytterbium triflate/NIS.

2. Results and discussion

Isbell's seminal paper described above, established that a donor's O-2 protecting group can influence stereoselectivity in glycosidations.[6] That the same influence can be exerted by O-2 protecting groups on chemoselective couplings was demonstrated by the armed/disarmed strategy of saccharide coupling.[17] More recently, a third phenomenon, regioselectivity, has been demonstrated in



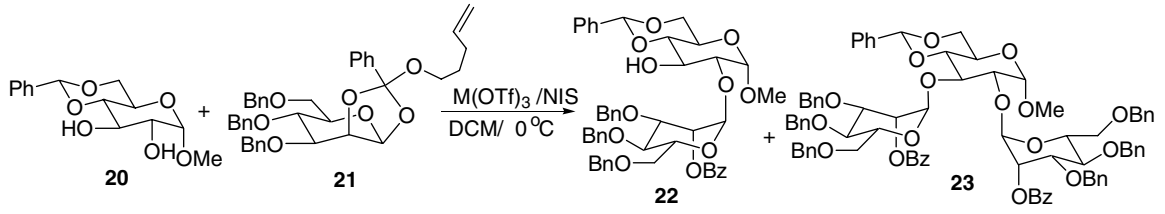
Scheme 3.

publications from our laboratory.[15,18] Thus, as illustrated with diol **14** (Scheme 3a) a disarmed *n*-pentenyl glycoside (NPG), for example, **8** may exhibit a highly regioselective glycosidation promoted by I^+ leading to a single product, for example, **15**. By contrast, an armed NPG, for example, **16**, is promiscuous, leading to mixtures, for example, **17** and **18**. These observations have been extended to thioglycosides, promoted by I^+, and trichloroacetimidates, promoted by Lewis acids,[19] and may therefore be general for all donors.

The *n*-pentenyl orthoesters (NPOEs), for example, **7**, were found to display the same exclusive regioselectivity as their disarmed counterparts, for example, **8**, but afforded much higher yields of product **15**. NPOEs, therefore, have been adopted as the preferred tools for probing the regioselective reactions of polyols.[20]

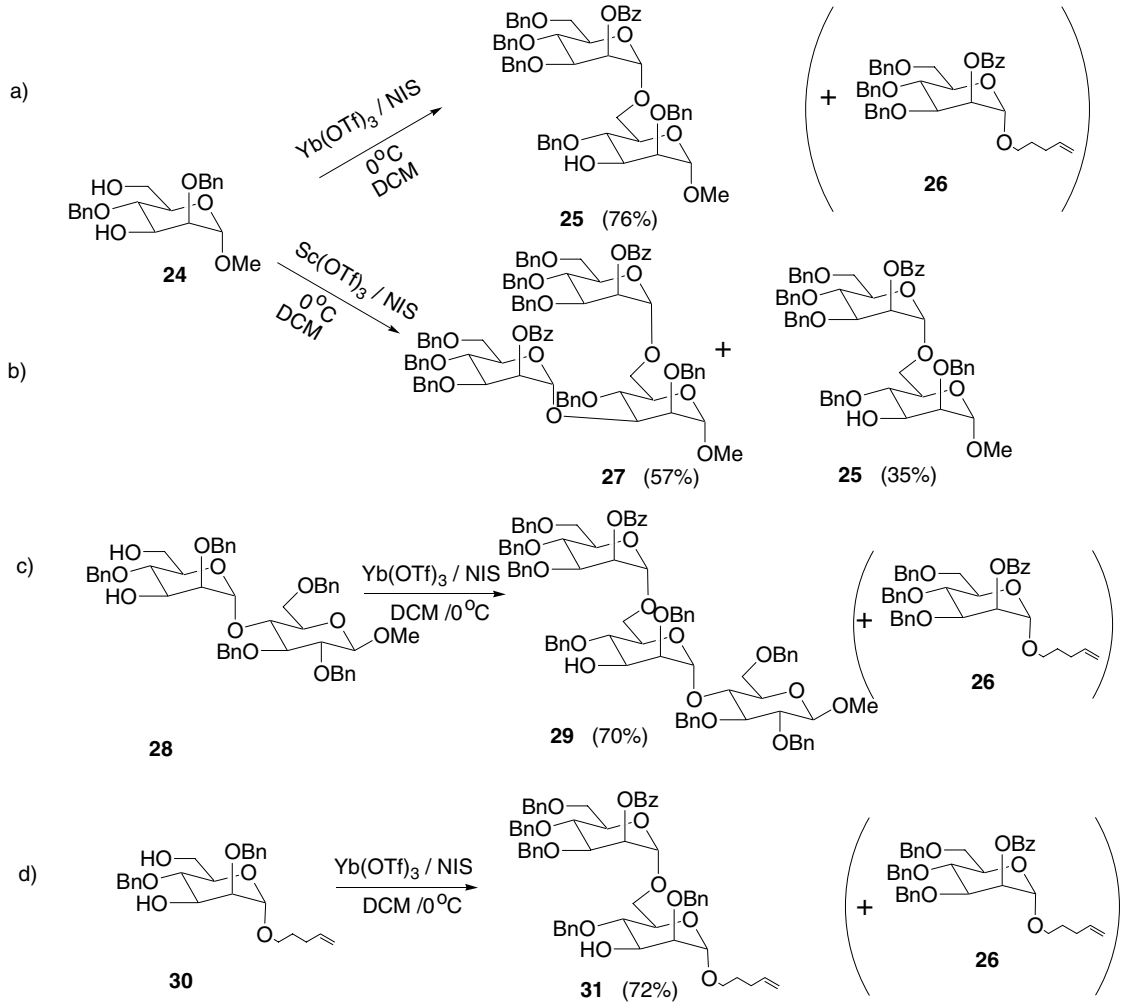
In this connection, we investigated the reactions of scandium ($Sc(OTf)_3$) and ytterbium ($Yb(OTf)_3$) triflates with *N*-iodosuccinimide to generate the iodonium ion needed to activate the *n*-pentenyl group.[21] First, both salts were found to induce the normal orthoester to glycoside rearrangement, for example, **7**→**8**. However, very nuanced differences were found with NIS-induced glycosidations.[22] Thus, as seen in Scheme 3b, the glycosidation of an alcohol, **ROH**, with an NPOE, **7**, can be induced by **either** salt reacting with NIS, affording glycoside **19** (X = O). However, disarmed and armed NPGs, for example, **8** and **16**, are triggered only by the stronger Lewis acid salt $Sc(OTf)_3$—not by $Yb(OTf)_3$.[20]

Scheme 4 provides a case in point. Diol **20** and NPOE **21** gave disaccharide **22** with a complete regioselectivity when $Yb(OTf)_3$/NIS was used. However, with $Sc(OTf)_3$/



$M(OTf)_3$			
Yb	only **17**	-	(62%)
Sc	1.15	1	(70%)

Scheme 4. See Ref. 20.



Scheme 5. Glycosidation of some 3,6-mannosidyl diols with *n*-pentenyl orthoester **21** (2 equiv) in the presence of a lanthanide triflate and NIS[‡].

NIS the double glycosidation product **23** was formed in substantial amount.

That this salt-induced chemoselectivity could be twinned with regioselective glycosylation was tested on the diols shown in Scheme 5. Branched 3,6-trimannans motifs occur in ubiquitous high-mannose glycoproteins[23] and hence regioselective preparation from the corresponding acceptor polyol precursors is of interest.[24,25] The treatment of known[26] diol **24** with 2 equiv of NPOE **21**, gave the monoglycosylated product **25** with exquisite regioselectivity (Scheme 5a), along with disarmed NPG **26** arising from the $Yb(OTf)_3$-catalyzed rearrangement of **21**. By contrast, the use of $Sc(OTf)_3$/NIS (Scheme 5b) gave trisaccharide **27** mainly, since this combination of reagents could also activate any **26** produced, to glycosylate (some of) disaccharide **25**.

An excellent prospect for general regioselectivity is evident from the results in Scheme 5c and d, which show the formation of the monoglycosylated products **29** and **31** by the action of $Yb(OTf)_3$/NIS. The example in Scheme 5d is notable for combining regioselective glycosidation with chemoselective discriminations. Thus, while NPOE **21** reacts, both the armed acceptor **30** and the disarmed by-product **26** are not affected by the promoter in use, $Yb(OTf)_3$/NIS. The advantage of the chemoselectivity is that product **31** can serve as, either as a donor or an acceptor for future reactions in which $Sc(OTf)_3$/NIS would be the activator.

The studies in Schemes 4 and 5 utilized *manno* NPOE **21**. The corresponding *gluco* analog **32**, used recently in the synthesis of β-1→2-mannans,[27] displayed several differences with **21**, which prompted us to carry out theoretical studies[28] to seek clarification. These studies have revealed unexpected differences between diastereomeric

[‡] The diol and NPOE **21** (2 equiv) were dissolved in a small amount of toluene, the solution was evaporated to dryness, and kept overnight under vacuum. Methylene chloride (5 mL) was added, the solution cooled to 0 °C, NIS (3 equiv) was added and the resulting solution was stirred for several minutes. $Yb(OTf)_3$ or $Sc(OTf)_3$ (0.3 equiv) was then added, and stirring continued for 10 min. Standard processing followed.[15c]

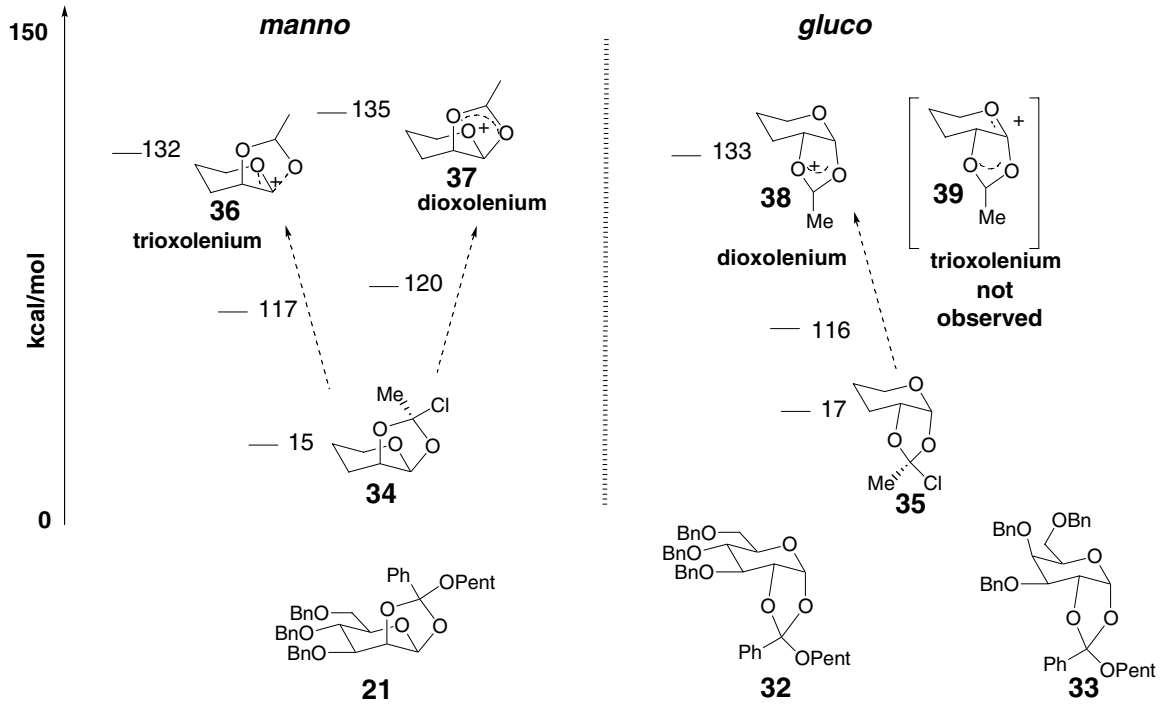


Chart 1. Conversion of model glycosyl orthoesters into di(tri)oxolenoum ions[¶] (B3-LYP/TZVP Transition Energies (non-bold) shown in kcal/mol).

glycosyl 1,2-orthoesters such as **21**, **32**, and **33**. Thus, chlorides **34** and **35** (Chart 1) were used as models for the diastereomeric orthoester donors having *manno* (**21**) and *gluco*/*galacto* (**32**/**35**) configurations respectively. The loss of chloride ion leads to the familiar dioxolenium ions **37** and **38**; however, in the *manno* case, a discrete trioxolenium ion **36** was also found which, interestingly, is of a lower energy than the dioxolenium counterpart **37**. Notably, a search for a similar trioxolenium ion (**39**) as a partner for **38** was unsuccessful.[28]

In Chart 1, the transition energies between the ground states and cationic intermediates are indicated. It is seen that *manno* model **34** is more stable than the *gluco*/*galacto* counterpart **35**, whereas the reverse is true for the corresponding dioxolenium intermediates **37** and **38**. Consequently, *gluco*/*galacto* NPOEs corresponding to **35** should be more reactive. Would they be also *less* regioselective?

In order to answer this question, we first tested diol **30**, which had been used in Scheme 5d. *It was immediately apparent that the experimental procedure, footnoted in Scheme 5 (where a solution containing manno NPOE 21 and acceptor was treated with NIS followed by Yb(OTf)$_3$) failed completely when applied to gluco or galacto analogs.* The inverse procedure, footnoted in Scheme 6, where the NPOE was the last ingredient added was required.

The results with acceptor **30**, in Schemes 5d and 6a,b show that *manno* NPOE **21** was best at 72%. With *gluco* NPOE **32**, regioselectivity was good, but the yield of product **40** was only 34%. On the other hand, with *galacto* counterpart **33**, the yield of the regioselective product **42** was greatly improved at 60%.

Notably, *galacto* NPOE **33** gave better results than *gluco* NPOE **32** (Scheme 6b vs a) and in order to see whether this finding was general, we tested two other acceptors, **44** and **47**. Indeed, the results in Scheme 6c–f show that the results for *gluco* NPOEs were not as good as for the *galacto*—although the high regioselectivity was maintained.

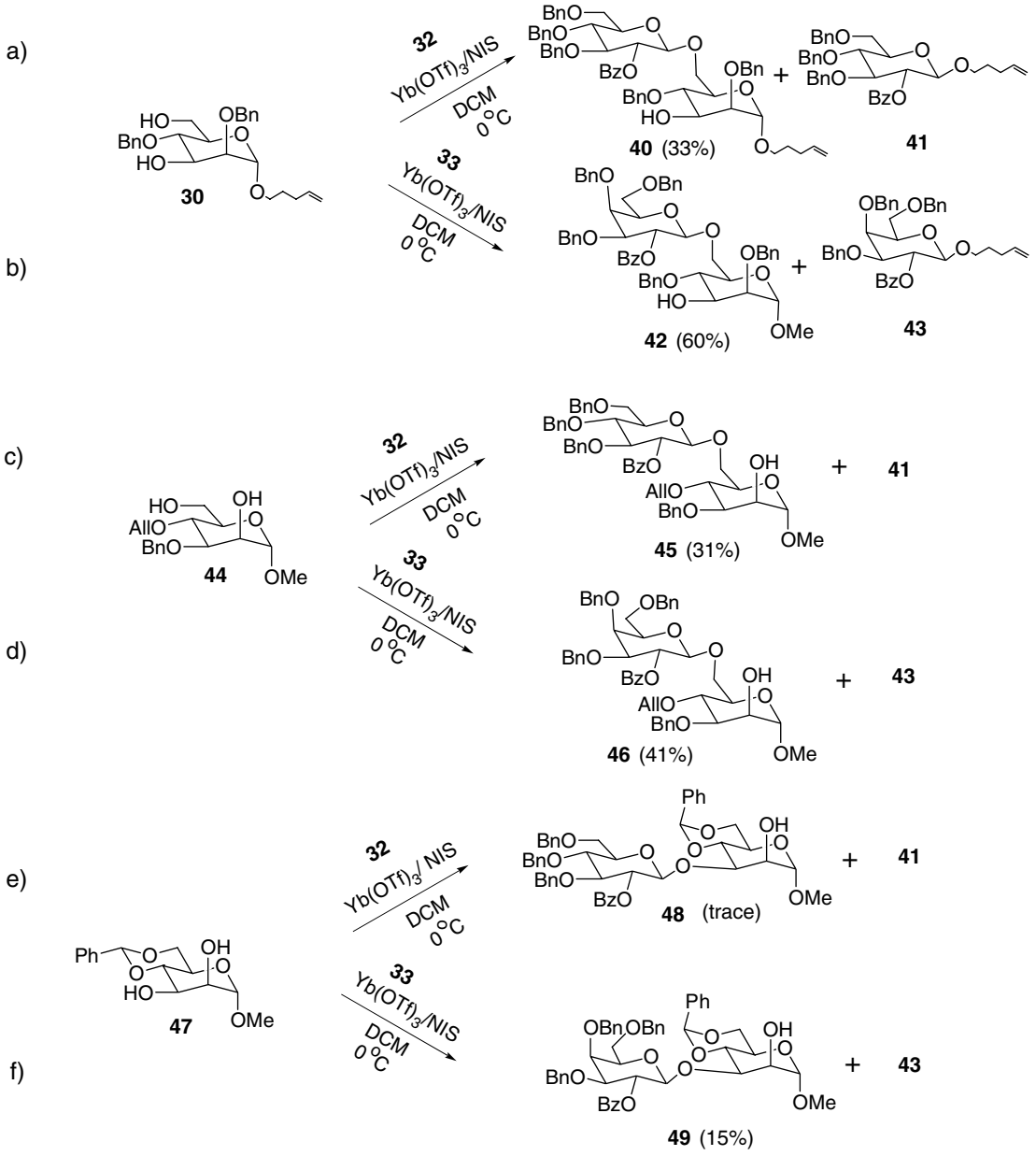
3. Conclusions

There are significant reactivity differences between diastereomeric *n*-pentenylorthoester glycosyl donors. As a consequence, experimental conditions for using *manno* donors, cannot be extended to *gluco* and *galacto* counterparts. Nevertheless, all three analogous donors are capable of regio and chemoselective reactions with diol acceptors, albeit to different degrees of efficiency.

4. Experimental

NMR spectra were recorded on a Varian 300 MHz spectrometer and chemical shifts are reported relative to internal TMS. Mass spectrometry was performed at the Duke University Department of Chemistry Mass

[¶] For a full account of related calculations see Ref. 28.



Scheme 6. Regioselective glycosidations with *gluco* and *galacto* *n*-pentenyl orthoesters **32** and **33**, respectively, with $Yb(OTf)_3$/NIS[§].

Spectrometry Facility. MALDI was measured on an Applied Biosystems Voyager DE-Pro Workstation. The reactions were usually conducted under an argon atmosphere. Thin layer chromatography (TLC) was done on plates (Riedel-de Haen) coated with Silica Gel 60F 254, detection was by UV, spraying or dipping in a solution of ammonium molybdate (6.25 g) and cerium(IV) sulfate (25 g) in 10% aqueous sulfuric acid (250 mL) and subsequent heating. Flash column chromatography was performed on silica gel (spectrum SIL 58, 230–400 mesh, grade 60) using mixtures of hexane and ethyl acetate as eluants. Dichloromethane and toluene were distilled from CaH_2. *N*-Iodosuccinimide (NIS) was crystallized from hot methylene chloride/hexane, dried, and kept under high-vacuum. The β-D-mannopyranose 1,2-pent-4-enyl orthobenzoates {*n*-pentenylorthoesters (NPOEs)} **21**,[15c] **32**,[27a] *n*-pentenyl glycosides (NPGs) **26**,[28] **41**,[27a] **43**[30] and diols **24**,[15b] **30**,[29] **44**,[15a] **47**[15a] were prepared as described previously.

[§]The diol and NPOE (2.2 equiv) were dissolved separately in small amounts of toluene, the solutions were evaporated to dryness, and kept overnight under vacuum. The diol was dissolved in methylene chloride (5 mL), the solution cooled to 0 °C, NIS (2.5 equiv) was added, followed by $Yb(OTf)_3$ (0.3 equiv). After stirring for a few minutes, methylene chloride solution of the NPOE was then added dropwise over ~15 min. Standard processing[15c] followed.

4.1. Glycosidation conditions (A) using *manno* NPOE 21

The acceptor (1 equiv) and NPOE **21** (2 equiv) were dissolved together in a small quantity of toluene, azeotroped to dryness and kept overnight under vacuum. The acceptor was dissolved in dry CH_2Cl_2 (5 mL) cooled to 0 °C under an argon atmosphere, NIS (3 equiv) was added, and after stirring for 5 min, the lanthanide salt (0.3 equiv) was added. The reaction was monitored by TLC, and when complete, the reaction was quenched with 10% aqueous sodium thiosulfate and saturated sodium bicarbonate solutions, extracted with CH_2Cl_2, and purified by chromatography.

4.2. Glycosidation conditions (B) using *gluco* and *galacto* NPOEs 27 and 28

The diol (1 equiv) and NPOE **32** or **33** (2.2 equiv) were dissolved *separately* in small quantities of toluene, azeotroped to dryness, and kept overnight under vacuum. The diol was dissolved in dry CH_2Cl_2 (5 mL) cooled to 0 °C under an argon atmosphere, NIS (2.5 equiv) was added, and after stirring for 5 min, the $Yb(OTf)_3$ (0.3 equiv) was added and stirred for a few minutes. To the above mixture, a dichloromethane solution of the donor was added dropwise over a period of 15 min. TLC was checked and quenched the reaction mixture with satd $NaHCO_3$ and 10% sodium thiosulfate solutions, which was extracted with CH_2Cl_2 and dried over Na_2SO_4. Solvents were removed under diminished pressure and the residue was purified by chromatography to give the desired compound.

4.3. Preparation of galactose orthoester 33

Galactose NPOE **33** was made according the general procedure reported earlier.[25] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.58 (m, 2H), 7.20–7.40 (m, 18H), 5.94 (d, *J* 4.8 Hz, 1H), 5.64–5.83 (m, 1H), 3.33–5.02 (m, 14H), 2.13–2.06 (m, 2H), 1.70–1.59 (m, 2H). MS for $C_{39}H_{42}O_7$ Calcd 622.29. Found 645.4 [M+Na].

4.4. Methyl 2,4-di-*O*-benzyl-6-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-α-D-mannopyranoside 25

Diol **24** (0.031 g, 0.084 mmol) was treated with NPOE **21** under glycosidation condition (A) using $Yb(OTf)_3$ to give title compound **25** (0.056 g, 76%). For **25**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.09 (d, *J* 7.5 Hz, 2H), 7.55 (t, *J* 7.5 Hz, 1H), 7.16–7.38 (m, 27H), 5.72 (dd, *J* 1.6, 3.2 Hz, 1H), 5.11 (d, *J* 1.6 Hz, 1H), 3.57–4.92 (m, 22H), 3.28 (s, 3H), 2.40 (d, *J* 10 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.72, 138.75, 138.69, 138.13, 137.87, 133.31, 130.23, 129.12, 128.86, 128.58, 128.56, 128.36, 128.28, 128.14, 127.85, 127.80, 127.76, 127.68, 98.29, 97.92, 78.81, 77.84, 75.55, 75.00, 74.56, 73.29, 72.24, 71.98, 71.40, 70.68, 69.72, 69.08, 66.81, 55.13. MS for $C_{55}H_{58}O_{12}$ Calcd 910.39. Found 933.4 [M+Na].

4.5. Methyl 2,4-di-*O*-benzyl-6-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-α-D-mannopyranoside 25 and methyl 2,4-di-*O*-benzyl-3,6-di-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-α-D-mannopyranoside 27

Diol **24** (0.021 g, 0.056 mmol) glycosidated with NPOE **21** using $Sc(OTf)_3$ in procedure (A) gave trisaccharide **27** (0.060 g) and the above described disaccharide **25** (0.016) in an overall yield (92%). For **27**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.09 (d, 7.5 Hz, 2H), 8.02 (d, 7.8 Hz, 2H), 7.52 (m, 2H), 7.01–7.38 (m, 42H), 5.77 (dd, *J* 1.6, 3.00 Hz, 1H), 5.74 (dd, *J* 1.8, 3.2 Hz), 5.34 (d, *J* 1.8 Hz, 1H), 5.11 (d, *J* 1.6 Hz, 1H), 3.68–4.93 (m, 33H), 3.25 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.68, 165.62, 138.88, 138.79, 138.72, 138.39, 138.11, 133.29, 130.24, 130.19, 129.12, 128.70, 128.60, 128.56, 128.52, 128.24, 128.15, 127.98, 127.91, 127.83, 127.76, 127.74, 127.67, 99.99, 98.48, 78.98, 78.53, 75.53, 75.36, 74.74, 74.55, 74.36, 73.82, 73.71, 72.77, 72.72, 72.08, 71.91, 71.48, 71.35, 69.73, 69.43, 69.31, 69.05, 66.84, 55.13. MS for $C_{89}H_{90}O_{18}$ Calcd 1446.61. Found 1469.6 [M+Na].

4.6. Methyl (2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→6)-2,4-di-*O*-benzyl-3-α-D-mannopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-mannopyranoside 29

Diol **28** (0.024 g, 0.030 mmol) was treated with NPOE **21** and $Yb(OTf)_3$ using procedure (A) to give **29** (0.028 g, 70%). For **29**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.05 (d, *J* 2.5 Hz, 2H), 7.56 (d, *J* 7.5 Hz, 1H), 7.02–7.34 (m, 42H), 5.69 (dd, *J* 1.8, 3.00 Hz, 1H), 5.25 (s, 1H), 5.14 (d, *J* 11.00 Hz, 1H), 5.01 (d, *J* 1.8 Hz, 1H), 3.49–4.89 (m, 33H), 3.39 (s, 3H), 2.23 (d, *J* 9.00 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.54, 138.89, 138.73, 138.64, 138.24, 138.03, 133.98, 130.17, 129.08, 128.66, 128.60, 128.53, 128.48, 128.38, 128.34, 128.28, 128.16, 128.04, 127.88, 127.67, 127.28, 99.27, 98.47, 97.95, 81.65, 80.43, 79.44, 78.13, 76.32, 75.49, 79.99, 74.48, 73.62, 73.44, 72.50, 72.00, 71.66, 71.39, 70.03, 69.55, 69.15, 68.88, 66.61, 55.62. MS for $C_{82}H_{86}O_{17}$ Calcd 1342.59. Found 1365.7 [M+Na].

4.7. Pent-4-enyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→6)-2,4-di-*O*-benzyl-3-α-D-mannopyranoside 31

Diol **30** (0.090 g, 0.210 mmol) and NPOE donor **21** were treated with $Yb(OTf)_3$ under condition (A) to give compound **31** (0.145 g, 72%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.10 (d, *J* 7.2 Hz, 2H), 7.56 (t, *J* 7.5 Hz, 1H), 7.12–7.39

(m, 27H), 5.72–5.86 (m, 1H), 5.76 (dd, *J* 1.6, 3.00 Hz) 5.13 (d, *J* 1.5 Hz, 1H), 4.48–5.05 (m, 10H), 3.59–4.17 (m, 11H), 3.37–3.42 (m, 1H), 2.43 (d, *J* 10.2 Hz, 1H), 2.06–2.14 (m, 2H), 1.60–1.70 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.66, 138.74, 138.67, 138.63, 138.16, 137.89, 133.28, 130.21, 128.59, 128.54, 128.49, 128.47, 128.33, 128.30, 128.12, 127.90, 127.79, 127.74, 127.67, 115.24, 98.29, 96.82, 78.99, 78.14, 76.74, 75.56, 75.56, 75.08, 74.53, 73.68, 73.26, 72.31, 71.97, 71.47, 70.49, 69.20, 69.01, 67.27, 66.77. MS for $C_{59}H_{64}O_{12}$ Calcd 964.44. Found 987.4 [M+Na].

4.8. Pent-4-enyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,4-di-*O*-benzyl-3-α-D-mannopyranoside 40

Diol **30** (0.050 g, 0.117 mmol), donor **32** (0.160 g, 2.2 equiv), NIS (0.066 g, 2.5 equiv) were treated with $Yb(OTf)_3$ (0.022 g, 0.3 equiv) by using procedure (B) described above to give compound **40** (0.037 g, 33%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.94 (d, *J* 7.00 Hz, 2H), 7.08–7.57 (m, 28H), 5.68–5.80 (m, 1H), 5.37 (t, *J* 8.1 Hz, 1H), 3.37–4.99 (m, 24H), 3.00–3.07 (m, 1H), 2.17 (d, *J* 9.6 Hz, 1H), 2.00–2.10 (m, 2H), 1.44–1.49 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.01, 138.63, 138.32, 138.10, 137.98, 137.89, 133.25, 133.09, 133.30, 133.02, 129.93, 129.07, 128.77, 128.696, 128.61, 128.56, 128.49, 128.42, 128.19, 128.16, 128.11, 128.03, 127.97, 127.92, 127.81, 127.78, 127.74, 114.92, 101.84, 96.54, 83.07, 78.57, 78.38, 75.65, 75.33, 74.74, 74.64, 74.33, 74.03, 73.80, 72.94, 72.00, 70.39, 69.22, 69.14, 66.86, 30.63, 28.81. MS for $C_{59}H_{64}O_{12}$ Calcd 964.44. Found 987.2 [M+Na].

4.9. Pent-4-enyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→6)-2,4-di-*O*-benzyl-3-α-D-mannopyranoside 42

Diol **30** (0.055 g, 0.128 mmol), donor **33** (0.159 g, 2 equiv), and NIS (0.072 g, 2.5 equiv) were treated with $Yb(OTf)_3$ (0.024 g, 0.3 equiv) using procedure (B) to give compound **42** (0.073 g, 60%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.96 (d, *J* 7.2 Hz, 2H), 7.55 (t, *J* 7.2 Hz, 1H), 7.11–7.37 (m, 22H), 5.68–5.80 (m, 1H), 5.73 (dd, *J* 9.9, 7.7 Hz, 1H), 5.01 (d, *J* 11.5 Hz, 1H), 4.92–4.96 (m, 2H), 3.37–4.72 (m, 21H), 2.98–3.03 (m, 1H), 2.21 (d, 9.6 Hz, 1H), 1.95–2.04 (m, 2H), 1.40–1.47 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.18, 138.65, 138.41, 138.03, 137.93, 137.87, 132.96, 130.57, 130.10, 128.75, 128.66, 128.47, 128.41, 128.36, 128.14, 128.11, 128.06, 127.85, 127.75, 127.70, 114.87, 102.27, 96.45, 80.20, 78.54, 77.03, 74.81, 74.71, 73.94, 73.88, 72.90, 72.80, 71.16, 72.00, 71.97, 70.36, 69.12, 68.85, 68.811. MS for $C_{59}H_{64}O_{12}$ Calcd 964.44. Found 987.3 [M+Na].

4.10. Methyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,4-di-*O*-benzyl-3-α-D-mannopyranoside 45

Diol **44** (0.046 g, 0.148 mmol) and donor **32** (0.202 g, 2.2 equiv), NIS (0.083 g, 2.5 equiv) were treated with $Yb(OTf)_3$ under conditions (B) to give compound **45** (0.038 g, 31%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.99 (d, *J* 8.00 Hz, 2H), 7.50 (t, *J* 8.00 Hz, 1H), 7.10–7.37 (m, 22H), 5.68–5.81 (m, 1H), 5.32 (t, *J* 8.5 Hz, 1H), 5.03–5.15 (m, 2H), 4.51–4.83 (m, 9H), 3.37–4.20 (m, 14H), 3.02 (s, 3H), 2.41 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.28, 138.30, 138.14, 138.08, 137.96, 134.89, 133.16, 130.16, 129.99, 128.60, 128.56, 128.47, 128.44, 128.19, 128.15, 128.03, 127.96, 127.79, 116.64, 101.82, 100.06, 83.08, 80.07, 78.29, 75.53, 75.36, 75.31, 74.50, 29.19, 73.95, 73.76, 72.10, 70.71, 69.20, 69.02, 68.43, 54.79. MS for $C_{51}H_{56}O_{12}$ Calcd 860.38. Found 883.3 [M+Na].

4.11. Methyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→6)-2,4-di-*O*-benzyl-3-α-D-mannopyranoside 46

Diol **44** (0.094 g, 0.29 mmol), donor **33** (0.361 g, 2 equiv), NIS (0.165 g, 2.5 equiv) were treated with $Yb(OTf)_3$ under conditions (B) to give compound **46** (0.103 g, 41%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.01 (d, *J* 7.00 Hz, 2H), 7.53 (t, *J* 7.5 Hz, 1H), 7.14–7.41 (m, 22H), 5.68–5.80 (m, 1H), 5.70 (dd, *J* 9.9, 7.8 Hz, 1H), 5.03–5.17 (m, 2H), 5.01 (d, *J* 11.5 Hz, 1H), 3.37–4.69 (m, 2H), 3.01 (s, 3H), 2.48 (d, *J* 3.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.43, 138.62, 138.19, 138.05, 137.87, 134.92, 133.04, 130.45, 130.07, 128.66, 128.62, 128.51, 128.49, 128.42, 128.15, 128.06, 127.99, 127.95, 127.85, 127.78, 116.64, 102.30, 99.99, 80.17, 80.10, 74.81, 74.63, 73.95, 73.89, 72.81, 72.32, 72.16, 72.03, 70.75, 69.12, 68.88, 68.48, 54.77. MS for $C_{51}H_{56}O_{12}$ Calcd 860.38. Found 883.3 [M+Na].

4.12. Methyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→3)-4,6-*O*-benzylidene-α-D-mannopyranoside 48

Diol **47** (0.040 g, 0.140 mmol), donor **33** (0.174 g, 2 equiv), NIS (0.080 g, 2.5 equiv) were treated with $Yb(OTf)_3$ under conditions (B) to give compound **48** (0.017 g, 15%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.05 (d, *J* 7.5 Hz, 2H), 7.04–7.58 (m, 23H), 5.59 (s, 1H), 5.56 (dd, *J* 9.5, 7.8 Hz, 1H), 4.94 (d, *J* 11.4 Hz, 1H), 3.98–4.70 (m, 20H), 3.67 (s, 3H), 2.87 (d, *J* 1.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.09, 138.47, 138.37, 138.22, 137.94, 137.83, 137.75, 133.50, 133.27, 130.13, 130.09, 129.99, 129.79, 129.54, 128.65, 128.61, 128.56, 128.52, 128.45, 128.21, 128.16, 128.09, 128.00,

127.92, 127.86, 127.83, 127.75, 127.72, 127.64, 100.12, 96.70, 91.25, 77.48, 76.47, 75.08, 75.02, 74.96, 74.86, 74.72, 74.04, 73.91, 73.87, 73.67, 73.51, 73.11, 72.90, 72.44, 71.87, 69.83, 69.51, 68.60. MS for $C_{48}H_{50}O_{12}$ Calcd 818.33. Found 841.3 [M+Na].

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