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Comparing *n*-pentenyl orthoesters and *n*-pentenyl glycosides as alternative glycosyl donors

Mateusz Mach,[a] Urs Schlueter,[a] Felix Mathew,[a] Bert Fraser-Reid[a,*] and Kevin C. Hazen[b]

[a]*Natural Products and Glycotechnology Research Institute, Inc., 4118 Swarthmore Road, Durham, NC 27707, USA*
[b]*Departments of Pathology and Microbiology, University of Virginia Health System, Charlottesville, VA 22908, USA*

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Abstract—As is well known, cyclic 1,2-glycosyl orthoesters undergo ready acid catalyzed rearrangement to 2-*O*-acyl glycosides in which the alkoxy group is transferred from the orthoester to the anomeric center in a highly stereocontrolled process. The related *n*-pentenyl derivatives are unique in that either the orthoester (NPOE) or its rearrangement product (NPG_{AC}) can function as a glycosyl donor, and mechanistic considerations indicate that both should (or could!) lead to the same product(s) arising from *trans*-orthoesterification, glycosidation, glycosyl esterification, etc. Experiments are described which show that the product obtained from a given reaction can be optimized by careful choice of the donor, NPOE or related NPG_{AC}, and careful attention to reaction conditions, electrophilic promoter, 'size' of the glycosyl acceptor, and experimental protocol.

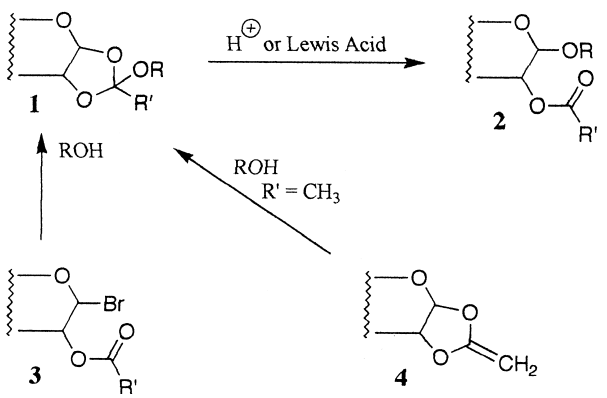
1. Introduction

Recent publications from several laboratories have focused attention on the value of glycosyl 1,2-orthoesters such as **1**, for oligosaccharide synthesis.[1–4] This interest grows out of the knowledge that orthoesters typically undergo facile acid catalyzed rearrangement, wherein the alkoxy group is transferred to the anomeric center resulting in the formation of glycosidic products such as **2**.[5–7] The process is highly stereoselective and, the OR group so transferred can be a simple alcohol or a complex sugar.[8] In this context, a recent study by Wang and Kong reported great improvements in the efficiency of the rearrangement for cases in which the migrating entity is an oligosaccharide.[1]

With regard to the orthoesters themselves, Allen and Fraser-Reid have reported that the classical procedure for their preparation from 2-*O*-acyl glycosyl bromides,[9,10] **3**, can be greatly improved by the addition of tetra *n*-butyl ammonium iodide.[4] A recent report from Hecht's laboratory on the use of ketene acetals, for example **4**, as precursors for **1** ($R{=}CH_3$) is an important new contribution (Scheme 1).[2]

Our interest centers upon the unique relationship between an *n*-pentenyl orthoester (NPOE) and the corresponding 2-*O*-acyl *n*-pentenyl glycoside (NPG_{AC}), such as **5** and **7**, respectively.[11] The standard acid catalyzed rearrangement presumably follows the pathway **5**→**6**→**7**,[12,13] in which the pentenyloxy group is transferred from the orthoester to the anomeric center. However, the susceptibility of the *n*-pentenyloxy residue to electrophilic attack provides alternative pathways from NPOE **5** and NPG_{AC} **7** to intermediate **6** via the furanylium ions **8** and **9**, respectively.[14] The advantage of the latter pathways is that the ejected species is the non-nucleophilic halomethylfuran **10**, which cannot compete with the added alcohol, SugOH, present in the medium to hamper formation of coupling product(s) e.g. **11**.

However, as indicated in Scheme 2, the crucial intermediate **6**, can also be captured by the alcohol at the site of highest electron deficiency, to give the *trans*-orthoesterification product, **12**.[13] The potential of this pathway needs to be examined since (a) it provides an alternative route to **11** via acid catalyzed rearrangement, and (b) it is usually the major reaction pathway for uronate glycosyl donors.[15] Notably, this trend is minimized with trichloroacetimidate donors.[16]



Scheme 1.

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* Corresponding author. Tel./fax: +1-919-493-6113;
e-mail: dglucose@aol.com

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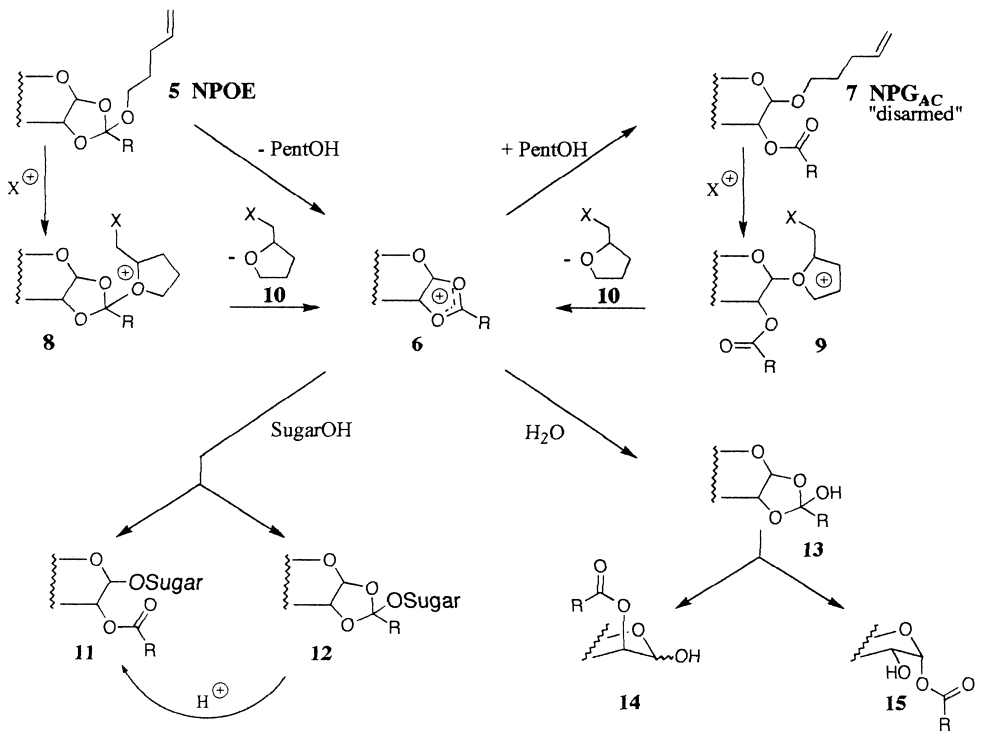
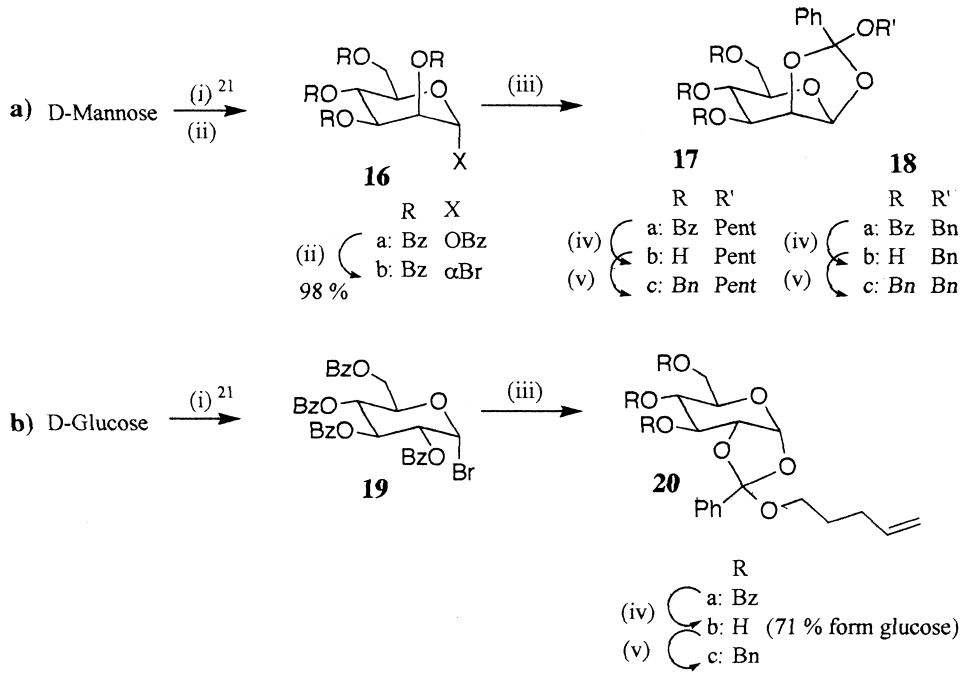


Scheme 2.

Intermediate **6** is also a good scavenger for water with production of an orthoacid, e.g. **13**, an unstable compound that is prone to rearrangement to an hydroxy ester. The seminal investigations of King[17] established that the rearrangement is stereoelectronically driven[18] favoring the axially oriented ester on cyclohexyl scaffolds. On this basis, a *manno* orthoacid should give 2-*O*-acyl-mannose, such as **14**, where a *gluco* analog of **13** should give a glucosyl ester, such as **15**. Indeed, 2-hydroxy glucosyl acetates had been identified as early as 1930, as products from reactions of tetra-*O*-acetyl glucosyl bromide.[19,20]

From the network of intermediates shown in Scheme 2, it is seen that there are major opportunities for inter- or counterplay between various reacting species. Indeed, the annoying occurrence of unwanted side products in ortho-ester reactions,[12a] indicated the need for close scrutiny of



Scheme 3. (i) PhCOCl, pyridine, DMAP; CH_2Cl_2; (ii) Ac_2O, 30% HBr-AcOH(~85%); (iii) CH_2Cl_2, 2,6-lutidine, R′-OH or 4-pentenol, Bu_4NI; (iv) NaOMe, MeOH (89%); (v) NaH, $PhCH_2Br$, DMF (84%).

the presumed equivalence of donors such as **5** and **7**, and we report some of our results herein.

2. Results and discussion

2.1. Preparation of substrates

The substrates for these investigations were obtained as outlined in Scheme 3. Thus, 3,4,6-tri-*O*-benzyl-β-D-manno-pyranose 1,2-(pent-4-enyl orthobenzoate) **17c** was prepared by the more condensed route summarized in Scheme 3(a), which avoided excessive purification of intermediates as was done in the previously described procedure.[11] This updated protocol was utilized for the *manno* 1,2-(benzyl orthobenzoate) analogue, **18c**, as well as for the α-D-glucopyranose counterpart **20c** (Scheme 3(b)). In the latter case, the five step conversion of D-glucose into the NPOE triol **20b** could be accomplished in 71% overall yield.

2.2. Acid catalyzed rearrangement of glycosyl orthoesters

Rearrangement of the orthoesters to give the corresponding alkyl 2-*O*-benzoyl glycosides was studied carefully, beginning with the *manno* NPOE **17c**. Use of 'standard' conditions[11] (CH_2Cl_2/CAS/reflux) required 5 h whereas with TESOTf, the rearrangement was complete in ~5 min at room temperature to give **21a** in ~80% yield (Scheme 4(a), i). Significantly addition of 5–10 mol% of the appropriate alcohol raised the yield of the rearrangement product **21a** or **b** to 95% (Scheme 4(a), ii)).

With the *gluco* NPOE **20c**, a rapid reaction occurred (2 min) to give the desired *n*-pentenyl glycoside (NPG_{AC}) **24**, but contaminated with varying amounts of the glycosyl benzoate **22a** and the hydrolysis product **23a**. Compound **22a** was identified by the low field doublet at 6.48 ppm (J=3.0 Hz). Upon acetylation, the doublet shifted to 6.56 ppm (J=3.6 Hz), while a low field double doublet appeared at 5.16 ppm (J=3.6, 10.3 Hz), consistent with H-1 and H-2, respectively, of **22b**.

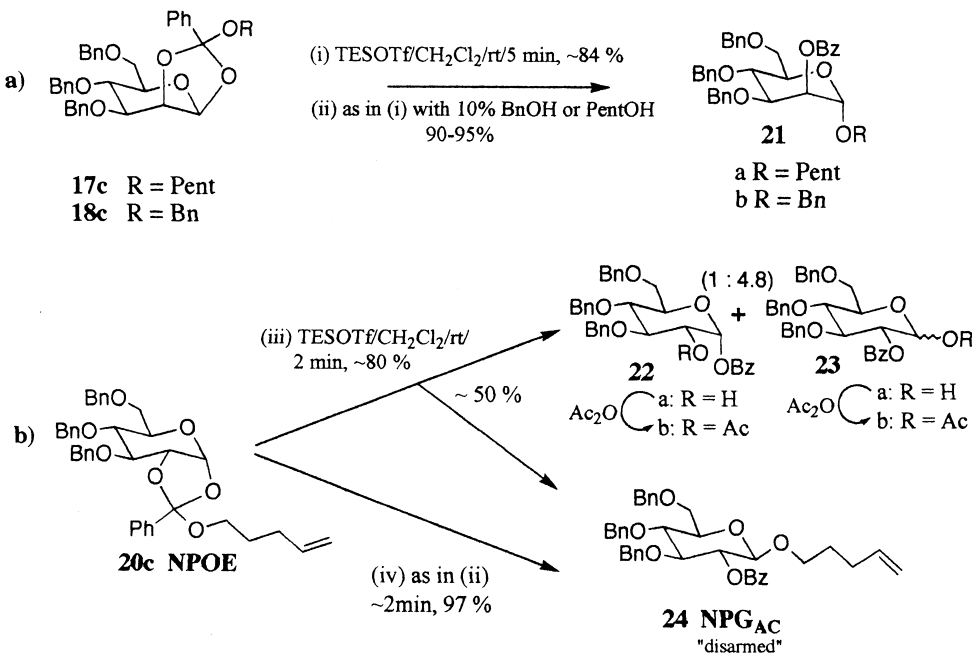
As with the *manno* analogue in Scheme 4(a), the rearrangement became virtually quantitative when a small amount of pent-4-enol was added, NPG_{AC} **24** being obtained in 97% yield (Scheme 4(b), iv)).

The conclusion from the studies in Scheme 4 is that *manno* NPOEs undergo acid catalyzed rearrangements in a straightforward way, while with *gluco* NPOEs, there can be problems depending on the conditions used.

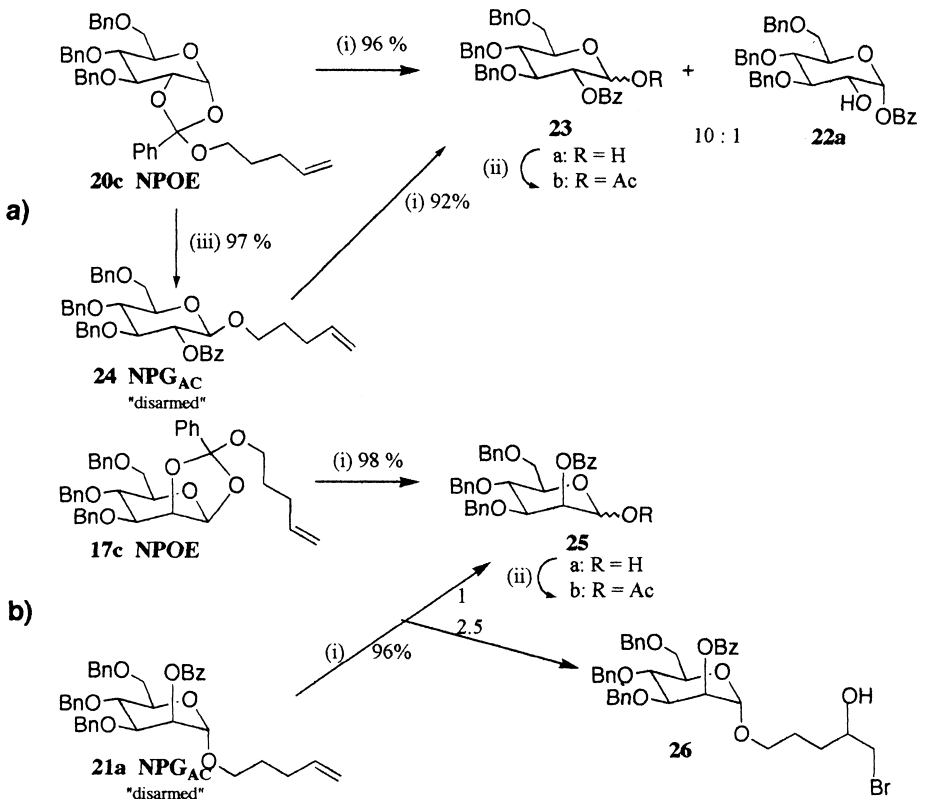
2.3. Oxidative hydrolysis of NPOE and NPG_{AC}: donors

According to Scheme 2, key intermediate **6**, can be obtained either from **5** or **7**. An NPOE and its *trans* NPG_{AC} counterpart should therefore give the same hydrolysis product(s). That they do not is evident from the studies summarized in Scheme 5a. Thus, oxidative hydrolysis of the disarmed NPG_{AC} **24**, gave ONLY the 2-*O*-benzoyl glucose **23a** as a (4:1) α/β mixture in 92% yield. The material was directly acetylated, and although the mixture of anomeric acetates, **23b**, could not be separated by chromatography, the α and β anomers could be assigned on the basis of characteristic ^{1}H NMR signals for H-1 and H-2. Thus, the ^{1}H NMR spectrum showed a doublet at 6.44 ppm (J=3.6 Hz) along with a higher-field double-doublet at 5.32 ppm (J=3.6, 10.2 Hz) consistent with H-1 and H-2 of **23bα**. The corresponding signals for **23bβ** appeared at 5.79 ppm (J=8.1 Hz) and 5.40 ppm (J=8.1, 8.7 Hz).

In the case of the *gluco* NPOE **20c**, oxidative hydrolysis gave a 10:1 mixture of **23a** and the already described glucosyl benzoate, **22a**, in 96% overall yield.



Scheme 4.



Scheme 5. (i) CH_3CN, H_2O, NBS; (ii) Ac_2O, pyridine, DMAP; (iii) CH_2Cl_2, TBDMSOTf, 2 min.

The *manno* NPOE **17c** gave rise to the 2-*O*-benzoyl mannose **25a** in 98% yield (Scheme 5(b)) with no evidence for the mannosyl benzoate (corresponding to **22a**) in keeping with King's stereoelectronic principle.[17] Under the hydrolysis conditions used, disarmed donor **21a** gave the hydrolysis products **25a**, along with bromohydrin **26**.[14]

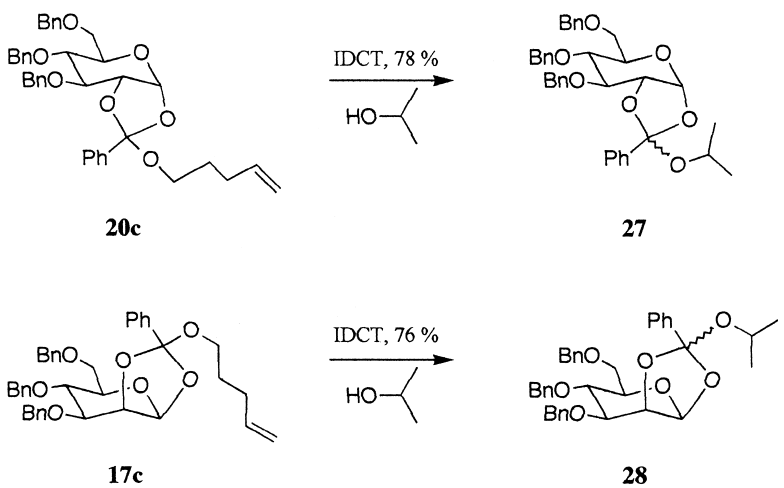
As was the case with the acid-catalyzed hydrolyses in Scheme 4, the oxidative alternative in Scheme 5 is (can be!) more problematic for *gluco* NPOEs than for *manno*. However, for the NPG_{AC} counterparts, oxidative hydrolysis of the *gluco* derivative is more straightforward. The formation of some bromohydrin **26** is undoubtedly a reflection of the great stability of mannoside **21a**.[22]

2.4. Transorthoesterification versus glycosidation

It is evident from Scheme 2 that either of the *n*-pentenyl donors (**5** or **7**) can give rise to an orthoester such as **12**, as well as the desired glycosidic product **11**.

Can one or other product be optimized?

It is well-known that glycosyl orthoesters are best prepared under non-acidic conditions, and this is in keeping with their acid lability.[12] In this regard, *n*-pentenyl donors can be activated under a variety of conditions, acidic (NBS/Lewis acid), neutral (NBS), or slightly basic[3,4] e.g. iodonium sym-dicollidinium perchlorate (IDCP)[23] and



Scheme 6.

trichoromethanesulfonate (IDCT[24]) promoters. We were therefore interested to see how NPOEs behaved under these different conditions.

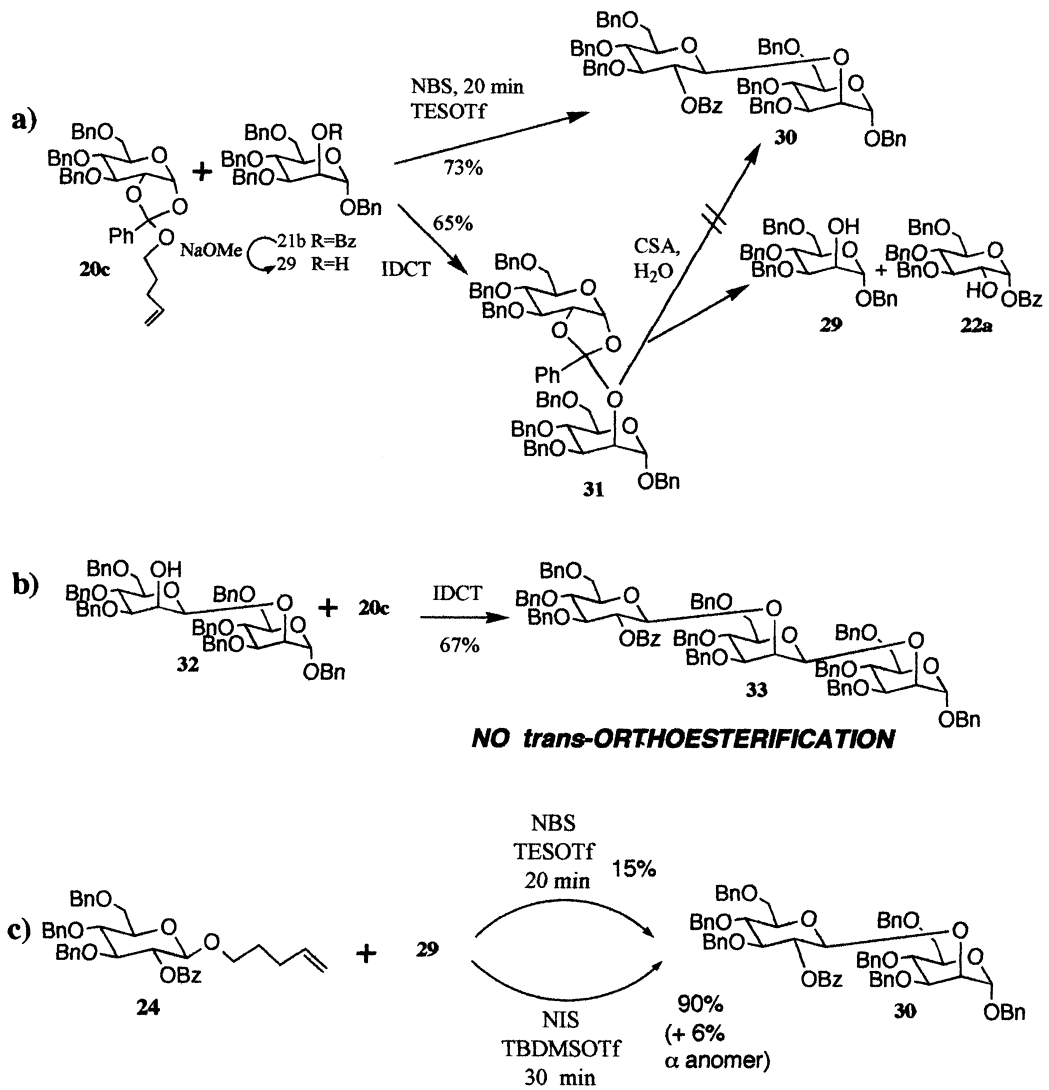
Isopropyl alcohol was chosen as a model acceptor for IDCT promoted reactions. As indicated in Scheme 6, the *gluco* and *manno* NPOEs **20c** and **17c** both underwent *trans*-orthoesterification to the same extents. That the products were mixtures of *exo* and *endo* isomers of **27** and **28** was evident from the presence of two CMR signals around 120 ppm in each case.

It was important to determine if the product(s) from NPOE donors are dependent upon the promoter used, and so we decided to probe this issue as shown in Scheme 7. In order to avoid premature reaction of the acid-labile NPOEs, the protocol was changed from the usual practice[3,4] of adding the promoter to a solution containing the donor and acceptor, to one in which the acceptor and promoter were dissolved in methylene chloride, and then the NPOE was added dropwise as a solution in toluene. In this way, the concentration of the oxolenium intermediate(s) was kept low, and the chances of scavenging by traces of adventitious water were reduced.

Thus, the *gluco* NPOE donor **20c** and the benzyl mannoside acceptor **29**, (which was obtained by desterification of benzoate **21b**), were dissolved in methylene chloride. Portions of the solution were treated with the slightly acidic and slightly basic reagents, NBS/TESOTf and IDCT, respectively. The effect of the promoter was clearly demonstrated since both experiments led to different coupling products exclusively in virtually the same yields (Scheme 7(a)), the 'acidic' promoter giving disaccharide, **30**, and the 'basic' promoter the *trans*-orthoesterification product **31**.

Notably, attempts to rearrange orthoester **31** into disaccharide **30** with camphorsulfonic acid were not successful, the products being the starting benzyl glycoside **29** and the glycosyl benzoate **22a**.

The facile *trans*-orthoesterification in Scheme 7(a) does not hold for all glycosyl acceptors as is evident by comparison



Scheme 7.

with the results in Scheme 7(b). Thus, changing the acceptor from the monosaccharide **29** to the disaccharide **32**, produced the trisaccharide **33** in 67% yield with no evidence for the *trans*-orthoesterification product. The conflicting results in Schemes 6 and 7 with respect to IDCT as promoter, make it clear that the 'size' of the acceptor may influence the occurrence of *trans*-orthoesterification.

The effects of matching donor with promoter is evident in Scheme 7(c). When NBS/TESOTf was used as promoter for coupling the disarmed donor **24** to acceptor **29**, the yield of disaccharide **30** was only 15%. Replacing NBS with NIS increased the yield to 90%.

In summary, an *n*-pentenylorthoester (NPOE) and its acid-catalyzed rearrangement product (NPG_{AC}) can both function as a glycosyl donor. Although on mechanistic grounds both should lead to the same product(s), our experiments have shown that this is frequently not the case. We have shown that the product(s), whether arising from *trans*-orthoesterification, glycosidation, glycosyl esterification, etc. is dependent on careful choice of the donor, NPOE or related NPG_{AC}, and also on the reaction conditions, electrophilic promoter, size of the glycosyl acceptor, and experimental protocol. The situation is further complicated by the fact that *manno* orthoesters are much more robust than the *gluco* counterparts. It is therefore recommended that the latter be stored as a solution in rigorously dry toluene, and used under the experimental conditions described for preparation of **30**.

Efforts are underway to develop conditions in which an NPOE donor will react, but not its NPG_{AC} rearranged counterpart. These results will be described in due course.

3. Experimental

All NMR spectra were recorded on GE 300 or Varian 400 MHz NMR spectrometers and chemical shifts are reported relative to internal TMS. Mass spectrometry was performed at the Duke University Department of Chemistry Mass Spectrometry Facility. Chemical Ionization (CI) was done on a Hewlett–Packard 5988A GC/MS using 1% ammonia in methane as the reagent gas, with a source temperature of 100°C, at 1 Torr. High resolution mass spectra (HRMS) and fast atom bombardment (FAB) analyses were recorded with a JEOL JMS-SX102A mass spectrometer operating at 10 K resolution, using a dithiothreitol/dithioerythritol or *m*-nitrobenzyl alcohol as the matrix with xenon as the fast atom. Elemental analyses were conducted at Atlantic Microlab, Norcross, GA. All reactions were conducted under argon atmosphere. Thin layer Chromatography (TLC): Riedel–de Haen, coated with silicagel 60F 254 and were detected by UV or by 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. NBS was crystallized from hot water and dried on high-vac.

3.1. General procedures

Oxidative hydrolysis. The NPOE or corresponding NPG_{AC} (30 mg, 0.04817 mmol) was dissolved in 5 ml of acetonitrile. Water (0.5 ml) and NBS (26 mg, 1.461 mmol) were added and the reaction mixture was kept at room temperature in darkness until TLC (hexanes/ethyl acetate 4:1) indicated the full disappearance of starting material. The reaction mixture was diluted with ethyl acetate, and washed with 10% $Na_2S_2O_3$, water, brine and dried over sodium sulphate. The products of the reaction were separated by column chromatography or by preparative TLC.

Acetylation. This was done using Ac_2O, DMAP, pyridine in dry dichloromethane at room temperature. After completion (TLC) the reaction mixture was diluted with ethyl acetate and washed with water, then saturated aqueous sodium bicarbonate solution and dried. The crude acetate(s) was (were) purified by column chromatography or by preparative TLC. Average yield: 80–90%.

Deesterifcation. To a flask containing methanol, sodium metal was added in small portions (ca. 2 g per 100 ml). When sodium was fully reacted, the substrate was added as a solution in dry THF. After completion (TLC, 0.5–1 h) the reaction mixture was concentrated to dryness, water and ethyl acetate were added, and the organic layer was washed with water, brine, dried and concentrated. The final product was purified by column chromatography.

3.1.1. 3,4,6-Tri-*O*-benzyl-β-D-mannopyranose 1,2-(pent-4-enyl orthobenzoate) (17c). α-D-Mannose (20.5 g, 0.114 mol) and DMAP (0.1 g, 0.8 mmol) were dissolved in pyridine (250 ml) and benzoyl chloride (100 ml, 0.862 mol) was slowly added with cooling and stirring. The resulting reaction mixture was stirred for 24 h at room temperature and then evaporated to dryness. The solid residue was dissolved in CH_2Cl_2, and water was carefully added with cooling and vigorous stirring to decompose the excess of benzoyl chloride. The product (R_f=0.45 in Hex/AcOEt 2:1) was extracted with CH_2Cl_2, processed in the usual way, and dried to provide the crude pentabenzoate **16a**, in approximately 85% yield. The crude material (**16a**, 85.0 g, 0.121 mol) was dissolved in CH_2Cl_2 (300 ml) and acetic anhydride (30.0 ml, 0.318 mol) was added to ensure anhydrous conditions. The reaction mixture was cooled to 0°C, 30% HBr/AcOH solution (250 ml) was slowly added and the reaction mixture was stirred at 0°C for 1 h. The temperature of the reaction mixture was then raised up to ~10°C, the flask was sealed and stored in the refrigerator (+5°C) overnight. The reaction mixture was then diluted with cold (−78°C) CH_2Cl_2 and cold water (0°C) was added. The organic layer was washed with cold water, cold saturated $NaHCO_3$ and dried. After evaporation of solvent the crude glycosyl bromide 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl bromide, **16b**,[21] (R_f=0.59 in Hex/EtOAc 2:1) was obtained in approximate yield 98% (78.6 g). The crude glycosyl bromide **16b** (73.0 g, 0.111 mol) was dissolved in dry CH_2Cl_2 (250 ml), and 2,6-lutidine (20 ml, 0.172 mmol), 4-pentenyl alcohol (14 ml, 0.14 mol), tetra-*n*-butylammonium iodide (2.0 g, 5.4 mmol) were added. The resulting mixture was refluxed under argon for 24 h, when

TLC (R_f=0.59 in Hex/EtOAc 3:1) showed complete disappearance of **16b**. After cooling to room temperature, water and diethyl ether were added, and the organic layer was washed with water, brine and dried. After evaporation the residue was filtered through silica gel using hexanes/ethyl acetate (from 9:1 to 4:1) to effect partial purification from polar impurities. The following spectroscopic data for **17a** were completely consistent with the literature values.[11] For **17a**: R_f=0.3, Hex/EtOac 4:1, ^{1}H NMR δ: 8.10–7.23 (m, 20H, Ph), 5.97 (t, 1H, H-4), 5.81 (d, 1H, H-1), 5.78–5.63 (m, 2H, H-3, CH=CH_2), 5.12 (t, 1H, H-2) 4.99–4.85 (m, 2H, CH=CH_2), 4.57 (dd, 1H, CH_2), 4.39 (dd, 1H, CH_2), 4.13 (m, 1H, H-5), 3.42 (t, 2H, CH_2), 2.15–2.03 (m, 2H, CH_2), 1.73–1.61 (m, 2H, CH_2); ^{13}C NMR δ 166.1, 166.0, 165.2 (3Bz), 122.9 (PhC–$(OR)_3$), 114.9 (=CH_2), 97.9 (C-1), 30.1, 28.7 (2CH_2).

The benzoyl groups of compound **17a** were removed under the general deesterifation conditions. Column chromatography {(Hex/EtOAc (4:1)→ethyl acetate→EtOAc/Hex (9:1)} afforded the triol **17b** as a colorless syrup, 29.0 g, (68% total yield from α-D-mannose). The resulting triol **17b** (14.0 g, 37.4 mmol) and imidazole (0.25 g, 3.67 mmol) were dissolved in dry DMF (100 ml). Sodium hydride (11.0 g of 60% dispersion in mineral oil, 0.764 mol) was slowly added and the reaction mixture was stirred at room temperature for 20 min. Benzyl bromide (20 ml, 0.17 mmol) was added in portions, in such a way that the temperature of the reaction mixture (both during generation of anion and addition of benzyl bromide) did not exceed 70°C. The reaction mixture was stirred for 2 h and then diethyl ether was added. Excess of sodium hydride was decomposed by careful addition of water, and the organic layer was washed with water, brine and dried. After evaporation and purification by column chromatography (Hex/EtOAc 9:1→3:1) product **17c** was obtained as an oil (23 g, 95%). The following data for **17c** was in complete agreement with the literature data.[11] For **17c**: R_f=0.49, Hex/EtOAc 4:1, ^{1}H NMR δ: 7.78–7.21 (m 20H, Ph), 5.87 (m, 1H, CH=CH_2), 5.52 (d, 1H, H-1), 5.13–4.85 (m, H), 4.51–4.41 (m, H), 4.09–3.41 (m, H), 2.27–2.18 (m, 2H, CH_2), 1.82–1.70 (m, 2H, CH_2); ^{13}C NMR δ 122.2 (PhC$(OR)_3$) 114.9 (=CH_2), 97.8 (C-1), 30.3, 28.8 (2CH_2).

3.1.2. 3,4,6-Tri-*O*-benzyl-β-D-mannopyranose 1,2-(benzyl orthobenzoate) (18c). The mannosyl bromide **16b** was converted into compound **18a** as described above for the NPOE **17a**, replacing 4-pentenol with benzyl alcohol to give the benzyl analogue **18a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.10–7.18 (m, 25H, arom.), 5.96 (t, 1H, *J*=9.5 Hz), 5.78 (d, 1H, *J*=2.9 Hz), 5.68 (dd, 1H, *J*=3.9, 10.1 Hz), 5.40 (dd, 1H, *J*=3.1, 3.6 Hz), 4.58 (dd, 1H, *J*=3.3, 12.0 Hz, H-6a), 4.45 (s, 2H), 4.38 (dd, 1H, *J*=4.7, 12.0 Hz, H-6b), 4.15–4.06 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 165.8, 165.6, 164.9 (3×*C*(O)Ph), 137.3–120.4 (arom.), 122.8 ((–O–)$_2$-*C*(Ph)OBn), 97.8, 76.1, 72.0, 70.8 (4×CH), 66.4 (CH and *C*H_2Ph), 63.0 (CH_2). Debenzoylation and benzylation, as used above, then led to the compound **18c** in 85% yield. For **18c** ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.76–7.23 (m, 25H, arom.), 5.49 (d, 1H, *J*=3.9 Hz, H-1), 4.90 (d, 1H, *J*=11.1 Hz), 4.75–4.62 (m, 4H), 4.50 (AB signal, 2H, *J*=11.7, 15.3 Hz), 4.42 (AB signal 2H, *J*=12.3, 15.9 Hz), 3.98 (dd, 1H, *J*=8.7, 9.6 Hz), 3.82 (dd, 1H, *J*=3.6, 8.7 Hz), 3.68 (dd, 1H, *J*=5.4, 11.1 Hz, H-6a), 3.57 (dd, 1H, *J*=2.1, 11.1 Hz, H-6b), 3.53–3.47 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 138.2, 138.1, 137.1, 136.7 (4×OCH_2*Ph*, quaternary), 129.0–126.7 (arom.), 122.3 ((–O–)$_2$-*C*(Ph)OBn), 97.8, 78.3, 76.1 (3×CH), 75.0 (CH and CH_2), 74.3 (CH), 73.2, 71.7, 69.1, 66.1 (4×CH_2).

(Compound **18c** was characterizad by rearrangement to **29**—see below).

3.1.3. 3,4,6-Tri-*O*-benzyl-α-D-glucopyranose 1,2-(pent-4-enyl orthobenzoate) (20c). α-D-Glucose (20.5 g) was converted into the glucosyl bromide **19** and thence into compound **20c** using similar steps as described above for the *manno* analogue **17c**. For **20a**: ^{1}H NMR 200 MHz, $CDCl_3$) δ: 8.12–7.20 (m, 20H, arom.), 6.06 (d, 1H, *J*=5.2 Hz, H-1), 5.83–5.63 (m, 1H, H-4 from pent.), 5.78 (dd, 1H, *J*=1.2, 3.1 Hz), 5.52 (d, broad, 1H, *J*=8.8 Hz), 5.01–4.87 (m, 2H), 4.79 (ddd, 1H, *J*=1.1, 3.1, 5.1 Hz), 4.53 (dd, 1H, *J*=2.9, 12.0 Hz, H-6a), 4.38 (dd, 1H, *J*=4.8, 12.0 Hz, H-6b), 4.20–4.11 (m, 1H), 3.43–3.25 (m, 2H), 2.15–2.01 (m, 2H), 1.68–1.54 (m, 2H). ^{13}C NMR 50 MHz, $CDCl_3$) δ: 165.8, 165.0, 164.4 (3×*C*(O)Ph), 137.7 (C-4 from pent.), 133.5–126.1 (arom.), 121.1 (quaternary from orthoester), 114.8 (CH_2 from pent.), 97.4, 72.0, 69.1, 68.4, 67.4 (5×CH), 63.9, 63.4. 30.1, 28.6 (4×CH_2). For **20b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.68–7.28 (m, 5H, arom.), 5.86 (d, 1H, *J*=5.1 Hz, H-1), 5.83–5.64 (m, 1H, H-4 from pent.), 5.01–4.98 (m, 2H), 4.41–4.26 (m, 2H), 3.81 (dd, 1H, *J*=4.8, 5.0 Hz), 3.66 (s, broad, 2H), 3.50–3.45 (m, 1H), 3.35–3.28 (m, 2H), 2.10–2.00 (m, 2H), 1.67–1.53 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 137.7 (C-4 from pent.), 136.5 (arom. quaternary), 129.1, 128.2, 125.0 (3×CH arom.), 119.7 (quaternary from orthoester), 114.7 (CH_2 from pent.), 97.9, 76.7, 73.0, 72.6, 68.1 (5×CH), 63.0, 61.2. 30.1, 28.6 (4×CH_2). The title compound **20c** was prepared from **20b** as described above (for **17c**) in 84% yield. For **20c**: ^{1}H NMR 300 MHz, $CDCl_3$) δ: 7.66–7.14 (m, 20H, arom.), 5.95 (d, 1H, *J*=5.1 Hz, H-1), 5.83–5.70 (m, 1H, H-4 from pent.), 5.02–4.93 (m, 2H), 4.74–4.33 (m, 7H), 3.90 (t, 1H, *J*=3.7 Hz), 3.78–3.68 (m, 2H), 3.60 (d, broad, 2H, *J*=2.9 Hz), 3.35–3.27 (m, 2H), 2.11–2.04 (m, 2H), 1.67–1.57 (m, 2H). ^{13}C NMR 50 MHz, $CDCl_3$) δ: 137.9 (quaternary benzyl), 137.8 (C-4 from pent.), 137.5, 136.1 (2×quaternary benzyl), 128.8–126.1 (arom.), 120.0 (quaternary from orthoester), 114.7 (CH_2 from pent.), 98.0, 77.8, 75.3, 74.9 (4×CH), 73.0, 72.5, 71.9 (3×CH_2OPh), 70.2 (CH), 68.9, 63.0, 30.2, 28.7 (4×CH_2).

(HR, LSIMS) Calcd for $C_{39}H_{42}O_7Na$: 645.2828; found: 645.2843 ($M+Na^+$).

3.1.4. Acid catalyzed rearrangement of *gluco n*-pentenylorthoester (NPOE) 20c. *(i) With added n-pentenyl alcohol*. The NPOE **20c** (0.5 g, 0.803 mmol) and 4-pentenol (20 μl, 0.044 mmol) were dissolved under argon in dry CH_2Cl_2 (10 ml) and TBDMSOTf (10 μl, 0.044 mmol) was added. The reaction mixture was stirred at room temperature for 2 min and then diluted with diethyl ether. Water was added and the organic layer was washed with saturated $NaHCO_3$, water, brine then dried and concentrated. Column chromatography (hexanes/ethyl acetate from 9:1 to 3:1) provided 0.470 g of 4-pentenyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (**24**) in 97% yield. For **24**:

([α]$_D$=25.9° *c*=1.4, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.02–8.00 (m, 2H, *ortho* protons from benzoate), 7.57–7.12 (m, 18H, arom.), 5.68–5.60 (m, 1H, H-4 from pent.), 5.26 (dd, 1H, *J*=8.0, 9.3 Hz, H-2), 4.83–4.56 (m, 8H), 4.50 (d, 1H, *J*=7.9 Hz, H-1), 3.90–3.71 (m, 5H), 3.55 (ddd, 1H, *J*=2.0, 4.8, 9.7 Hz), 3.48–3.44 (m, 1H), 2.01–1.89 (m, 2H), 1.66–1.56 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 165.0 (C=O), 138.0 (quaternary benzyl), 137.8 (double intensity: C-4 from pent. and quaternary benzyl), 137.6 (quaternary benzyl), 132.9–127.5 (arom.), 114.6 (CH_2 from pent.), 101.0, 82.7, 78.0, 75.2 (4×CH), 74.9 (double intensity: 2×CH_2OPh), 73.8 (CH), 73.4 (OCH_2Ph), 68.8, 68.7, 29.8, 28.6 (4×CH_2).

(ii) Without added n-pentenyl alcohol. When the reaction in part (i) was done without addition of pent-4-enol, a rapid rearrangement (~2 min) gave compound **24** along with 1-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranose (**22a**) as a 4.8:1 mixture. For **22a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.02 (d, 2H, *J*=7.2 Hz, *ortho* protons from benzoate), 7.61–7.15 (m, 18H, arom.), 6.48 (d, 1H, *J*=3.0 Hz, H-1), 5.00–4.82 (m, 3H), 4.67–4.48 (m, 3H), 3.98–3.78 (m, 5H), 3.68 (dd, 1H, *J*=2.1, 10.8 Hz), 2.11 (s, broad, 1H, –OH). Acetylated under the standard conditions gave **22b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.05 (d, 2H, *J*=7.3 Hz, *ortho* protons from benzoate), 7.52–7.13 (m, 18H, arom.), 6.56 (d, 1H, *J*=3.6 Hz, H-1), 5.16 (dd, 1H, *J*=3.6, 10.3 Hz, H-2), 4.90–4.77 (m, 3H), 4.67–4.51 (m, 3H), 4.12 (dd, 1H, *J*=8.8, 10.3 Hz), 4.04 (d, broad, *J*=10.3 Hz), 3.92 (t, 1H, *J*=9.5 Hz), 3.82 (dd, 1H, *J*=3.7, 11.0 Hz, H-6a), 3.70 (dd, 1H, *J*=1.5, 11.0 Hz, H-6b), 1.94 (s, 3H, C(O)CH_3).

Low. resolution mass (FAB) $C_{35}H_{36}O$ Calcd 552.67; Found 551.7 (M^+-1).

3.1.5. Pentenyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (21a). 3,4,6-Tri-*O*-benzyl-β-D-mannopyranose 1,2-(pentenyl orthobenzoate) **17c** (23 g, 36.933 mmol) was azeotroped on rotavap with toluene, then dried under high-vacuum. Rearrangement in the presence of pent-4-enol, conducted as described above for **20c→24**, required ~5 min to provide 19.4 g of product **21a** (84% yield). The physical constant agreed completely with the material previously prepared by a more lengthy route.[11]

3.1.6. Oxidative hydrolysis of *n*-pentenylorthoesters (NPOEs) and NPGs$_{AC}$. *(a) Gluco donors*. (i) The *gluco* NPG$_{AC}$ (**24**) upon being subjected to the general conditions for oxidative hydrolysis gave only a mixture of the anomeric glucoses, **23a** in 92% yield (α/β=4:1). The material was identified by acetylation. Selected signals for the resulting anomeric acetates: For **23bα**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.44 (d, 1H, *J*=3.6 Hz, H-1), 5.32 (dd, 1H, *J*=3.6, 10.2 Hz, H-2), 2.09 (s, 3H, C(O)CH_3). For **23bβ** δ: 5.79 (d, 1H, *J*=8.1 Hz, H-1), 5.40 (dd, 1H, *J*=8.1, 8.7 Hz, H-2), 2.00 (s, 3H, C(O)CH_3).

(ii) When the *gluco* NPOE (**20c**), was subjected to similar hydrolysis, the above described glucopyranose (**23a**) and benzoyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranose (**22a**) were obtained as a 10:1 mixture in 96% yield.

(b) Manno donors. (i) When the *manno* NPOE (**17c**), was treated as in part a (i), the reaction gave the anomeric mixture **25a** (α and β) exclusively in 98% yield. The anomers were partially separated by preparative TLC and acetylated. For 1-*O*-acetyl-2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranose (**23bα**): ^{1}H NMR δ: 8.06 (d, 2H, *J*=7.2 Hz, *ortho* protons from benzoate), 7.58–7.18 (m, 18H, arom), 6.24 (d, 1H, *J*=2.1 Hz, H-1), 5.61 (t, 1H, *J*=3.0 Hz, H-2), 4.89–4.72 (m, 3H), 4.61–4.52 (m, 3H), 4.18 (dd, 1H, *J*=8.7, 9.6 Hz), 4.09 (dd, 1H, *J*=2.7, 9.3 Hz), 3.93–3.89 (m, 2H), 3.79–3.74 (m, 1H), 2.10 (s, 3H, C(O)CH_3). For 1-*O*-acetyl-2-*O*-acetyl-2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-mannopyranose (**23bβ**) ^{1}H NMR δ: 8.11 (d, 2H, *J*=7.2 Hz, arom. *ortho* protons from benzoate), 7.60–7.16 (m, 18H, arom), 5.84–5.83 (m, 2H, H-1 and H-2), 4.89–4.72 (m, 3H), 4.58–4.53 (m, 3H), 4.10 (t, 1H, *J*=9.6 Hz), 3.91–3.80 (m, 3H), 3.68–3.63 (m, 1H), 2.05 (s, 3H, C(O)CH_3).

For **23bα**: low resolution mass (FAB) $C_{35}H_{36}O_6$ calcd 552.67; Found 551.6 (M^+-1).

(ii) Hydrolysis of the *manno* NPG$_{AC}$ **21a** provided a mixture of **25a** (α and β) see above part b (i), and a trace of bromohydrin 26.[14]

3.1.7. 3,4,6-Tri-*O*-benzyl-α-D-glucopyranose 1,2-(isopropyl orthobenzoate) (27). 3,4,6-Tri-*O*-benzyl-α-D-glucopyranose 1,2-(pent-4-enyl orthobenzoate), **20c** (0.250 g, 0.401 mmol) and freshly distilled isopropanol (middle fraction, 0.4 ml, 5.2 mmol) were dissolved in dry dichloromethane (6 ml) under argon. Iodonium dicollidine triflate (IDCT)[24] (0.420 g, 0.810 mmol) was added and the reaction mixture was stirred for 30 min at room temperature, at which time TLC (Hex/EtOAc 4:1) showed disappearance of the starting material and formation of a new product. To the reaction mixture was then added 10% aqueous $Na_2S_2O_3$ and ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulfate and concentrated. Column chromatography of the residue with (Hex/EtOAc 9:1→4:1) provided an exo/endo mixture of the epimeric transortho-esterification products **27** in 78% yield. For **27**: ^{1}H NMR (300 MHz, $CDCl_3$, selected signals) δ: 5.95–5.93 (m, both H-1 protons in ca. 1:4 ratio and *J*=ca. 5.0 Hz), 1.18–1.04 (m, 6H, C(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, selected signals) δ: 120.4, 120.1 (both quaternary carbons), 98.0, 97.9 (both C-1), 23.3, 22.1 (both C(*C*H_3)$_2$).

Low resolution mass (FAB) $C_{37}H_{40}O_7$ Calcd 596.71; Found 595.7 (M^+-1), 597.1 (M^++1).

3.1.8. Benzyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranose 1,2-(isopropyl orthobenzoate) (28). 3,4,6-Tri-*O*-benzyl-β-D-mannopyranose 1,2-(pent-4-enyl orthobenzoate), **17c**, was treated as described above for **20c**, leading to **28** in 76% as the only product. For **28**: ^{1}H NMR (300 MHz, $CDCl_3$, selected signals) δ: 5.49–5.47 (m, both H-1 protons in ca 1:4 ratio and *J*=ca. 3.0 Hz), 1.52–1.09 (m, 6H, C(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, selected signals) δ: 122.5, 122.1 (both quaternary carbons), 97.7, 97.5 (both C-1), 23.6, 23.3 (both C(*C*H_3)$_2$).

Low resolution mass (FAB) $C_{37}H_{40}O_7$ Calcd 596.71; found 595.7 (M^+-1), 598.7 (M^++2).

3.1.9. Benzyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (29). The benzyl orthobenzoate **18c** was rearranged to benzyl mannoside **21b** as described above for **17c→21a**. The benzoyl group of compound **21b** (19.2 g, 29.779 mmol) was removed under the general deesterification conditions. Product **29** (R_f=0.4, Hex/EtOAc 3:2) was obtained as a colorless syrup, 14.8 g (92% yield) after column chromatography (Hex/EtOAc 4:1→1:1). For **29**: ($[\alpha]_D$=57.8° *c*=1.36, $CHCl_3$).

Literature:[25] 48.0° (*c*=1.85, $CHCl_3$),[26] 48.0° (*c*=0.6, $CHCl_3$).[27] ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.38–7.15 (m, 20H, arom.), 4.99 (d, 1H, *J*=1.6 Hz, H-1), 4.84–4.45 (m, 8H), 4.06 (s, broad, 1H), 3.91–3.66 (m, 5H), 2.61 (d, 1H, *J*=2.6 Hz, OH). ^{13}C NMR 50 MHz, $CDCl_3$) δ: 138.09, 138.05, 137.8, 137.0 (4×OCH_2*Ph*, quaternary), 128.5.0–127.3 (arom.), 98.4, 80.2 (2×CH), 75.1 (CH_2), 74.2 (CH), 73.4, 71.9 (2×CH_2), 71.2 (CH), 69.0, 68.8 (2×CH_2), 68.3 (CH).

(HR, LSIMS) Calcd for $C_{34}H_{36}O_6Na$: 563.2410; found: 563.2410 (M+Na^+).

3.1.10. Benzyl 3,4,6-tri-*O*-benzyl-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-(1→2)-α-D-mannopyranoside (30). (i) The acceptor, **29** (2.36 g, 4.37 mmol) and an excess of 3,4,6-Tri-*O*-benzyl-α-D-glucopyranose 1,2-(pent-4-enyl orthobenzoate) **20c** (8.16 g, 13.10 mmol) were azeotroped separately with toluene and dried in vacuo. Acceptor **29** was dissolved in dry dichloromethane (120 ml), and molecular sieves and NBS (3.11 g, 17.47 mmol) were added. The reaction mixture was stirred under argon for 5 min to dissolve NBS, and then TESOTf (0.300 ml, 1.327 mmol) was added. The reaction mixture was stirred for further 5 min, and then donor **20c**, dissolved in dry toluene (20 ml), was added dropwise over ~10 min via a syringe at room temperature. Stirring was continued for an additional 20 min at which time the reaction was quenched with 10% $Na_2S_2O_3$ and saturated $NaHCO_3$ aqueous solutions. The molecular sieves were filtered and washed with Et_2O, and the organic layer was washed with water, brine and dried. Column chromatography (Hex/EtOAc 9:1→3:1) provided the title compound **30** in 73% (3.43 g).

(ii) Pent-4-enyl 3,4,6-tri-*O*-benzyl-2-*O*-benzoyl-β-D-glucopyranoside, **24** (2.21 g, 3.54 mmol) and acceptor **29** (0.96 g, 1.77 mmol) were azeotroped together with toluene. The resulting dry syrup was redissolved in dry CH_2Cl_2 (25 ml) at 0°C. Molecular seives and NIS (1.2 g, 5.51 mmol) were stirred for 3 min and then TBDMSOTf (0.117, 0.44 mmol) was added. The reaction mixture was kept at room temperature for 30 min, and then the reaction was quenched with 10% $Na_2S_2O_3$ and saturated $NaHCO_3$ aqueous solutions. The molecular sieves were filtered and washed with Et_2O and the organic layer was washed with water, brine and dried. Column chromatography (Hex/EtOAc 4:1) provided compound **30** in 89% along with 6% of the corresponding α-anomer.

For **30**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.94 (d, 2H, *J*=7.2 Hz, *ortho* protons from benzoate), 7.39–7.13 (m, 38H, arom.), 5.38 (dd, 1H, *J*=8.1, 8.7 Hz, H-2_{gluco}), 4.83–4.48 (m, 11H), 4.38–4.15 (m, 5H), 3.89 (dd, 1H, *J*=3.0, 8.1 Hz), 3.82–3.53 (m, 9H), 3.26 (dd, 1H, *J*=6.6, 10.8 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 164.8 (C=O), 138.5, 138.4, 138.3, 137.8, 137.7 (double intensity), 137.1 (7×OCH_2Ph, quaternary), 132.8–127.5 (arom.), 99.9, 96.4, 82.6, 77.9, 77.8, 75.3 (6×CH), 75.0 (CH_2), 74.9 (CH), 74.80, 74.75 (2×CH_2), 74.1, 73.6 (2×CH), 73.5, 73.0 (2×CH_2), 72.2 (CH), 70.9, 70.0, 69.2, 68.7 (4×CH_2).

Low resolution mass (FAB) $C_{68}H_{68}O_{12}$ Calcd 1077.29; Found 1076.12 (M^+−1), 1079.01 (M^++2).

3.1.11. 3,4,6-Tri-*O*-benzyl-α-D-glucopyranose 1,2-(benzyl 3,4,6-tri-*O*-benzyl)-α-D-mannopyranosyl orthobenzoate) (31). (The experiment was carried out as in the preceding case, except that the promoter was now IDCT).[24] The mannopyranoside acceptor **29** (0.250 g, 0.462 mmol) which had been previously azeotroped with toluene and dried on high-vaccuum was dissolved in dry dichloromethane (25 ml) under argon. Molecular sieves were added followed by the NPOE **20c** (0.750 g, 1.204 mmol), as a solution in dry toluene. Iodonium dicollidine triflate (IDCT)[24] (1.0 g, 1.929 mmol) was added and the reaction mixture was stirred for 30 min at room temperature, at which time the reaction mixture was quenched with 10% aqueous $Na_2S_2O_3$, and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated. Column chromatography (Hex/EtOAc 9:1→4:1) provided the title compound **31** in 65% yield. It was found that product **31** did not respond to treatment with sodium methoxide.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.65–7.11 (m, 40H, arom.), 5.92 (d, 1H, *J*=5.7 Hz, H-1_{gluco}), 4.88 (d, 1H, *J*=10.5 Hz), 4.74–4.38 (m, 15H), 4.31 (dd, 1H, *J*=5.7, 11.7 Hz, H-2_{gluco}), 3.92–3.71 (m, 6H), 3.66 (s, 2H), 3.56 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.3 (double intensity), 138.1, 137.9, 137.6, 137.2, 135.8 (7×OCH_2Ph, quaternary), 129.2–126.5 (arom), 120.3, (quaternary), 98.0, 97.3 (both C-1), 78.7, 77.6, 75.1 (double intensity), 74.7, 74.6, 73.2, 73.0, 72.5, 71.9, 71.7, 71.6, 70.0 (double intensity), 69.3, 68.9, 68.7 (17 signals from benzyl groups and carbohydrate carbon atoms). The ^{13}C NMR data showed that compound **32** was obtained as a single diastereoisomer.

3.1.12. Attempted conversion of orthoester 31 into disaccharide 30. Compound **31** (200 mg) was dissolved in dry dichloromethane, a catalytic amount of camphorsulfonic acid (CSA) was added and the reaction mixture was stirred at room temperature for 30 min. At this time the starting material (R_f=0.42 Hex/EtOAc 4:1) had disappeared completely, and two polar products (R_f=0.19 (**29**) and 0.27 (**22a**) Hex/EtOAc 4:1) were formed quantitatively.

3.1.13. Benzyl 3,4,6-tri-*O*-benzyl-*O*-(2-*O*-beznoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-(1→2)-*O*-(3,4,6-tri-*O*-benzyl-β-D-mannopyranosyl)-(1→2)-α-D-mannopyranoside (33). The disaccharide[29] benzyl 3,4,6-tri-*O*-benzyl-*O*-(3,4,6-tri-*O*-benzyl-β-D-mannopyranosyl)-(1→2)-α-D-mannopyranoside, **32**, (4.0 g, 4.11 mmol) and **20c** (8.5 g, 13.65 mmol) were azeotroped together with toluene, dried in vacuo and dissolved under argon in dry dichloromethane (60 ml). Molecular sieves were added and after the reaction

mixture had beeen stirred at room temperature for 15 min, IDCT (8.5 g, 16.40 mmol) was added. The stirring was prolonged for another 30 min before the reaction was quenched with 10% $Na_2S_2O_3$. Molecular sieves were filtered off and washed with diethyl ether, and the filtrate extracted with diethyl ether. The organic layer was washed with 2% aqueous H_2SO_4 to remove any collidine and to decompose transorthoesterification products, and then with water, saturated $NaHCO_3$, brine, before being dried and concentrated. The resulting dark syrup was filtered through a thin layer of silica gel. The filtrate was concentrated and subjected to column chromatography (Hex/EtOAc 9:1→3:2), which provided trisaccharide **34** (2.86 g) in 67% yield based on recovered acceptor **32**(1.26 g). NMR data for **34**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.0 (d, 2H, J=7.2 Hz, *ortho* protons from benzoate), 7.39–7.06 (m, 53H, arom.), 5.59 (d, 1H, J=7.8 Hz, H-1$_{gluco}$), 5.38 (dd, 1H, J=7.8, 8.1 Hz, H-2$_{gluco}$), 4.98–4.16 (m, 22H), 4.04–3.44 (m, 15H), 3.34 (t, 1H, J=8.1 Hz), 2.94 (dd, 1H, J=7.5, 10.5 Hz).

(HR, LSIMS) Calcd for $C_{95}H_{96}O_{17}$: 1509.81; found: 1511. 56 (M+^{1}).

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