Orthoesters versus 2-O-Acyl Glycosides as Glycosyl Donors: Theorectical and Experimental Studies

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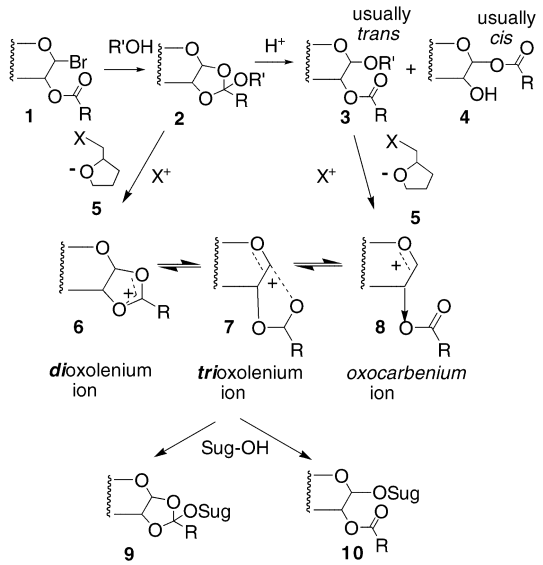
Abstract: *n*-Pentenyl orthoesters (NPOEs) undergo routine acid catalyzed rearrangement into 2-O-acyl *n*-pentenyl glycosides (NPGs). The reactant and product can both function as glycosyl donors affording 1,2-*trans* linked glycosides predominantly. However, both donors differ in their rates of reactions, the yields they produce, and the nature of their byproducts, indicating that the NPOE/NPG pair may not be reacting through the same intermediates. We have therefore applied quantum chemical calculations using DFT methods and MP second order perturbation theory to learn more about orthoesters and their 2-O-acyl glycosidic counterparts. The calculations show that in the case of a *manno* NPG and NPOE pair, each donor goes initially to a different cationic intermediate. Thus, the former goes to a high-energy oxocarbenium ion before descending to a trioxolenium ion in which the charge is distributed over the pyrano ring oxygen, as well as the carbonyl and ether oxygen atoms of the putative C2 ester. On the other hand, ionization of the NPOE produces a dioxolenium ion lying slightly above the more stable trioxolenium counterpart. For the *gluco* pair, the NPG also goes to a very high-energy oxocarbenium ion, which also descends to a trioxolenium ion. However, unlike the *manno* analogue, the *gluco* NPOE does not give a dioxolenium ion; indeed, the dioxolenium is not energetically distinguishable from the trioxolenium counterpart. The theoretical observations have been tested experimentally. Thus, it was found that with *manno* derivatives, the orthoester is a more reactive donor than the corresponding NPG donor, whereas, for *gluco* derivatives, there is no advantage to using one over the other, unless one resorts to carefully selected promoters.

Keywords: carbohydrates · density functional calculations · glycosides

Introduction

2-O-Acyl glycosyl bromides, **1**, are readily converted[1] into cyclic 1,2-orthoesters such as **2**, the OR′ unit of which may be a simple alkoxy residue, or a complex oligosaccharide.[2] Under acid catalysis, rearrangement of the latter to a 2-O-acyl glycoside, **3**, is the major reaction pathway,[3] although stereoelectronic controlled decomposition[4, 5] to give glycosyl esters such as **4** has been reported (Scheme 1).[6]

n-Pentenyl orthoesters (NPOEs) (i.e., **2**: R′ = pent-4-enyl) are unique in that either they or their *n*-pentenyl glycoside (NPG) rearrangement products (i.e., **3**: R′ = pent-4-enyl) can serve as glycosyl donors leading to the same glycosidation product for example **10**.[7] Thus, when treated with an halonium ion, both release a halomethyl furan **5**; this reaction results in the initial formation of cations **6** and **8**, respectively,



Scheme 1.

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which are interconvertible via a highly delocalized species symbolized by **7**. Thus, the charge can reside on one, two or three oxygen atoms in the oxocarbenium, dioxolenium and trioxolenium ions **8**, **6** and **7**, respectively.

However, studies in our laboratory suggest that, in terms of rates, yields, and so on, donors such as NPOE **2** and NPG **3** are not "the same". Thus, there may be occasions when one serves better than the other. We are anxious to know whether this outcome is related to the cation **6** or **8** generated initially by the donor in question. We have therefore applied quantum chemical calculations, and provided experimental support, to learn more about orthoesters and their 2-O-acyl glycosidic counterparts, and to determine if there may be advantages to using one or other on occasion.

Computational Methods

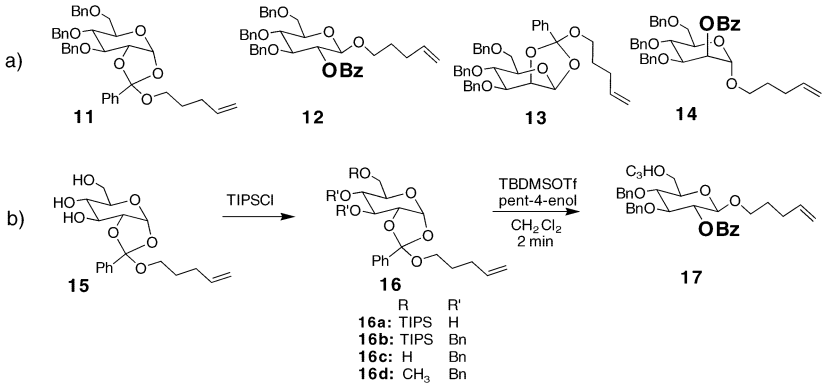
All calculations were performed on a 800 MHz LINUX-PC (2GB RAM) using the TURBOMOLE 5.3[8] program suite. Geometry optimizations were carried out using the BP[9, 10] and B3-LYP,[11, 12] density functional theory (DFT) methods, and a valence triple basis-set (TZVP).[13] B3-LYP optimizations for the very large 3,4,6-tri-*O*-benzyl-2-*O*-benzoyl-pyranosides were carried out using the smaller SV(P)[14] basis-set. For all optimized structures, Møller–Plesset second order pertubation theory[15] single-point calculations were performed using the RI-approximation (RIMP2)[16] and the TZVPP[13] basis set which includes additional polarization functions on all atoms. All calculations were performed without symmetry restrictions (C_1 point group) and all stationary points were verified as minima on the energetic potential surfaces by the absence of imaginary frequencies from vibrational normal mode calculations at the B3LYP/TZVP level of theory (**12** and **14**: BP/SV(P)). The relative energies are given with respect to the lowest lying donors (**14** and **19**). For the reaction energies from the neutral reactants to the cationic products, separate calculations for a free chloride anion were performed on the corresponding level of theory. The thus received energy was then substracted from the donor cation difference.

$E_{rx} = E_{donor} - E_{cation} - E_{Cl-}$

Results and Discussion

We have previously shown that competitive oxidative hydrolysis provides a ready procedure for evaluating the relative reactivity of a pair of NPG donors.[17] The success of the method relies on the competitive oxidative hydrolysis of one equivalent each of the two donors with one equivalent of *N*-bromosuccinimide (NBS). Upon complete disappearance of the NBS, the molar amounts of the *unreacted* donors are in direct proportion to their relative reactivity.[17]

The donors of interest are shown in Scheme 2a. We planned to use preparative thin-layer chromatography to isolate the *un*reacted donors, but the R_f values of the *gluco* pair, **11** and **12**, 0.48 and 0.43, respectively, were too close to permit convenient separation. It was therefore decided to use a "reporter" donor as a reference substrate. Compound **17**, the 6-*O*-methyl analogue of **12**, seemed an appropriate candidate,

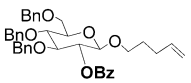
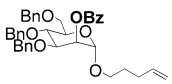
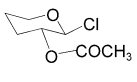
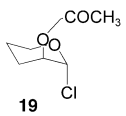


Scheme 2.

and the compound was readily prepared as shown in Scheme 2b. Thus, the *gluco* NPOE derivative **15**, prepared in the usual way,[7] was converted by routine transformations into **16a–d**, and rearrangement led to **17**, which was found to have a substantially different R_f value of 0.33, and was therefore an ideal "reporter"substrate.

Calculations based on model donors: In order to calibrate our methodology, we carried out DFT calculations with two different basis sets to determine the relative energies of the anomeric *n*-pentenyl 3,4,6-tri-*O*-benzyl-2-*O*-benzoyl-*β-gluco*- and *α-manno*-pyranosides, **12** and **14** (Table 1). The pyranosyl donors were modeled by tetrahydropyrans having a C1 chloride as leaving group and a C2 acetoxy (sugar numbering) as illustrated for **18** and **19** (Table 1). The DFT energies (entries i and ii) refer to fully optimized calculations, whereas the MP2 energies (entry iii) are single-point calculations using the DFT geometries of the preceding row. Both methods show the *β*-glucoside **12** to be of higher energy than the

Table 1. Relative stabilities of experimental and model pyranosyl donors [kcal mol^{-1}].

	Calculation method	Experimental substrates		Model donors	
		β-gluco	*α-manno*	*β-gluco*	*α-manno*
					
		12	**14**	**18**	**19**
i	B3-LYP/SV(P)	2.7	0.0	–	–
ii	B3-LYP/TZVP	2.8	0.0	4.0	0.0
iii	MP2/TZVPP// B3-LYP/TZVP	–	–	3.5	0.0

α-mannoside **14** in keeping with established experimental observations and earlier theoretical calculations.[18–20]

Orthoester donors: The cyclic 1,2-orthoesters were modeled by tetrahydropyrans with a 1,3-dioxolane ring fused at C1 and C2, with geminal methyl and chloride groups in the *endo* or *exo* orientation at C3 of the dioxolane moiety as shown in Table 2.

With regard to the orthoesters, the energies for the *trans* series **22**/**23** (Table 2) are substantially higher than those for the *cis* analogues **20**/**21**, as is to be expected for such fused 6/5 bicyclic systems.[21] For the *cis-gluco* (**20a**, **b**) derivatives, the *exo* isomers are higher in energy than the *endo* (**20a** > **20b**), whereas for the *cis manno* (**21a**, **b**) derivatives, the situation is reversed, *endo* being higher in energy than *exo* (**21b** > **21a**). For the *trans* derivatives all *endo* isomers are slightly higher in energy, (i.e., **22b** > **22a** and **23b** > **23a**) in all calculations. Experimentally, the *n*-pentenyl analogues of the *exo* isomers are obtained as the major substrates.

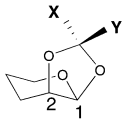
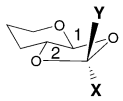
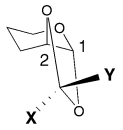
Calculation of the energy and structure of cationic products: The energies for the *manno* and *gluco* cationic intermediates in Table 3 are shown, which arise from the donor models shown in Tables 1 and 2. The DFT values refer to fully optimized calculations, whereas the MP2 values are single-point calculations using the DFT geometries of each preceding column. There are differences, albeit very small, between the *manno* and *gluco* oxocarbenium ions **24a** and **b**, with either calculation method. However, for the di- and trioxolenium ions, the DFT and MP2 energies are very similar owing, presumably, to the rigid geometry of the bicyclic structures.

The energy values in Table 3 show that the di- and trioxolenium ions **25a** and **26a**, were found as discrete structures in the case of the *manno* derivatives, whereas for the *gluco* derivatives, there was no energy difference between **25b** and **26b** by either MP2 or DFT calculation.

These energy data are supported by the MP2 derived geometries depicted in Table 4. Thus, in the *manno* derivative **25a**, both C–O bond lengths in the five-membered ring are the same (1.49 ± 0.01 Å) as expected for a pure dioxolenium ion, whereas in **26a** the bond to the anomeric center is much longer (1.57 versus 1.48 Å), as expected for the trioxolenium ion. However, the *gluco* analogues **25b** and **26b** show identical C–O bond lengths of 1.60 and 1.48 Å; this indicates that both structures are the same. Furthermore, the fact that the anomeric C–O bond is longer (1.60 versus 1.50 Å) assigns the structure as a tri- rather than a dioxolenium ion.

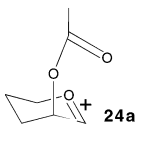
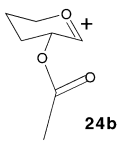
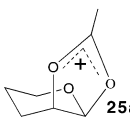
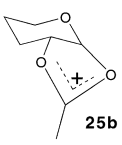
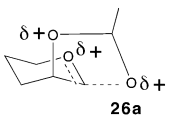
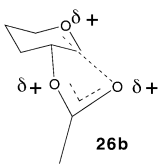
From donors to cations: The reaction energies for conversion of the donors into the cationic intermediates are shown over the arrows in Figure 1. In both the *manno* and *gluco* cases, the

Table 2. Relative energies[a] of model orthoester donors [kcal mol^{-1}].

Calculation method	*cis*				*trans*			
	α-gluco		*β-manno*		*β-gluco*		*α-manno*	
								
	20		**21**		**22**		**23**	
	20a	**20b**	**21a**	**21b**	**22a**	**22b**	**23a**	**23b**
	X = CH_3/Y = Cl	X = Cl/Y = CH_3	X = CH_3/Y = Cl	X = Cl/Y = CH_3	X = Cl/Y = CH_3	X = CH_3/Y = Cl	X = CH_3/Y = Cl	X = Cl/Y = CH_3
	exo	*endo*	*exo*	*endo*	*endo*	*exo*	*endo*	*exo*
i B3-LYP/TZVP	17.3 > 16.2		15.6 < 18.7		25.3 > 24.9		29.7 > 29.3	
ii MP2/TZVPP// B3-LYP/TZVP	13.4 > 12.5		11.0 < 13.4		19.7 > 19.0		24.4 > 23.8	

[a] With respect to derivative **19**.

Table 3. Relative energies[a] [kcal mol^{-1}] of model cationic substrates.

	Calculation method	**Oxo**carbenium ions		**Di**oxolenium ions		**Tri**oxolenium ions	
		 **24a**	 **24b**	 **25a**	 **25b**	 **26a**	 **26b**
		manno	*gluco*	*manno*	*gluco*	*manno*	*gluco*
i	B3-LYP/TZVPP	145.6	144.5	135.3	133.1	133.1	133.1
ii	MP2/TZVPP// 63-LYP/TZVP	159.9	158.7	142.9	142.1	141.9	142.1

[a] With respect to derivative **19** – Cl^{-1}.

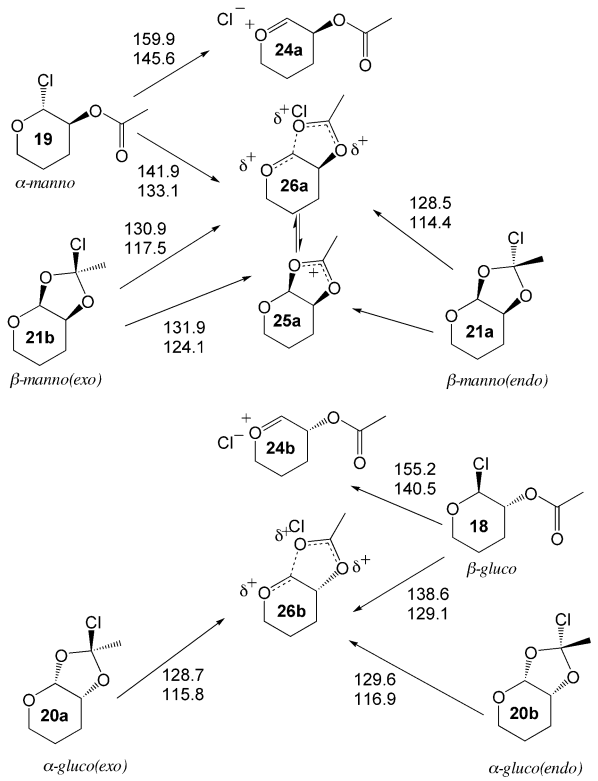


Figure 1. Calculated transition energies [kcal mol^{-1}] from donors to cationic intermediates (upper values from MP2, lower values from B3-LYP).

direct reaction from pyranosyl donor to trioxolenium ions is favored over proceeding to the corresponding oxocarbenium ions. For example in the *manno* case, transition **19** → **26a** is more energetically favorable than the alternative **19** → **24a**. Similarly in the *gluco* case, transition **18** → **26b** is preferred to **18**σ → **24b**. These DFT calculations (lower values over the arrows in Figure 1) give a difference of ~12 kcal mol^{-1} for both *manno* and *gluco* cases in favor of the trioxolenium ions. (Notably the energy differences, according to MP2 calculations, are slightly higher, between 16–18 kcal mol^{-1}.)

Comparison of theoretical and experimental results

Figure 2 gives another representation of the data in Figure 1 with the following simplifying modifications:

i) The *trans* orthoesters have been ignored, because the *manno* derivatives **23a** and **b** are impossible, and the *gluco* analogues, **22a** and **b** are so highly strained as to be uselessly unstable.

ii) As indicated in Scheme 1, the rearrangement product of orthoesters, for example **3**, is (usually) 1,2-*trans*, and so we need to be concerned ONLY with β glucosides, (e.g. **18**) and α mannosides (e.g. **19**). (However, this is not a major issue since the reaction energies for the unrepresented anomers are virtually the same.)

iii) Only the DFT energies in Figure 1 (lower values over the arrows) are shown for the transitions in Figure 2.

The oxocarbenium ions **24a** and **b** are very high in energy—as is to be expected in view of the absence of charge delocalization. The relative energies in Table 4 show that the trioxolenium ion **26a** is 1.5–3.4 kcal mol^{-1} more stable than the corresponding dioxolenium derivative **25a**, the DFT results being higher than the MP2.

For experimental verification, the "reporter" **17**, was first tested against its 6-*O*-benzyl analogue **12**. In a typical experiment, 1:1:1 molar amounts of **12**, **17**, and NBS were allowed to react for at least 10 h; this is the length of time which had previously been shown to be adequate for complete hydrolysis of reporter **17**. Unreacted **17** and **12** were isolated by preparative thin-layer chromatography. On the basis of the recovered amounts, their relative reactivity, $k_{12/17}$, was found to be 0.93 (Table 5, entry i). Thus, compounds **17** and **12** have virtually the same reactivity, which confirms that for our purposes, 6-*O*-methyl and 6-*O*-benzyl protecting groups were equivalent for our measurements.

The same procedure was applied to determine the relative reactivity of other pairs of donors: **17** and **11**, **17** and **13**, and **17** and **14**, which were found to be 0.99, 1.15 and 3.19, respectively (Table 5, entries ii–iv). The results, presented in Table 5, are consistent with the theoretical findings:

1) first, the ratios in entries iii) and iv) indicate that the mannosides are "more stable" than the glucosides, as suggested by the energies in Table 1;

2) second, the experimental value of 0.99 for the NPOE and NPG, **11** and **17**, confirms the theoretical finding that these *gluco* counterparts have the same reactivities, whereas,

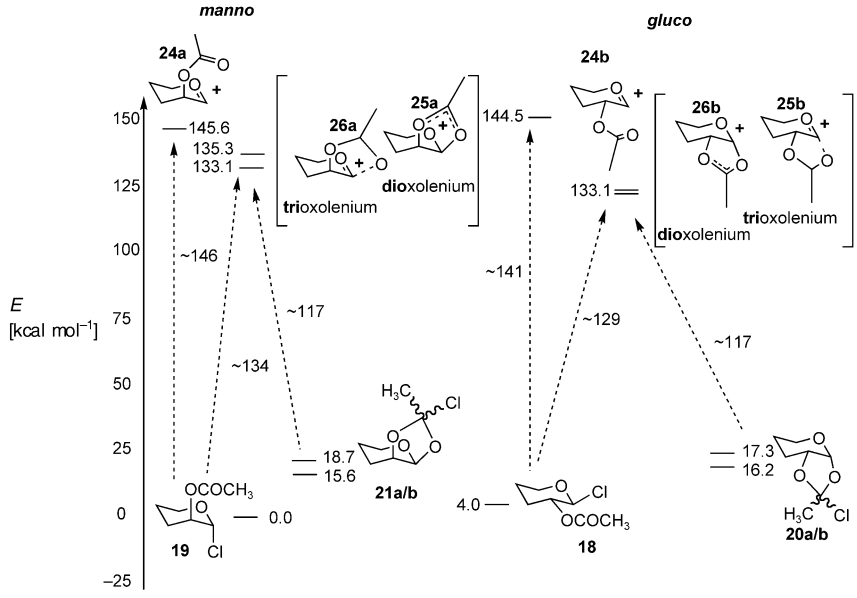
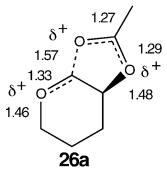
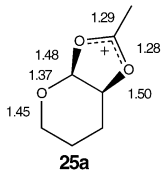
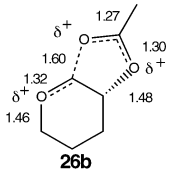
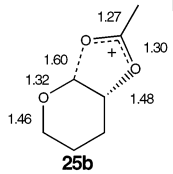


Figure 2. B3-LYP/TZVP Transition energies [kcal mol^{-1}] from donors to cations.

Table 4. Relative energies[a] [kcal mol^{-1}] and optimized geometries of dioxolenium and trioxolenium ions.

	Structure	MP2 TZVP	BP TZVP	B3-LYP TZVP	B3-LYP TZVPP
manno					
i	 **26a**	0.0	0.0	0.0	0.0
ii	 **25a**	1.5	3.4	2.2	2.2
gluco					
iii	 **26b**	0.5	−0.1	0.0	−0.0(1)
iv	 [b] **25b**	0.5	−0.1	−0.0(4)	−0.0(4)

[a] With respect to derivative **19** − Cl^{-1}. [b] Not stable.

Table 5. Competitive oxidative hydrolysis between "reporter" **17** and other donors.

	Competitors	Before reaction [mol × 10^{-4}]		Unreacted amounts [mol × 10^{-4}]		Relative ratio
		17	other donor	**17**	other donor	other donor/**17**
gluco						
i	**17** vs **12*β***	1.6061	1.6058	0.9723	0.9025	**12*β*/17** = 0.93
ii	**17** vs **11**	1.6061	1.6058	0.8067	0.7985	**11/17** = 0.99
manno						
iii	**17** vs **13**	1.6061	1.6058	0.8086	0.9266[a]	**13/17** = 1.15
iv	**17** vs **14*α***	1.6061	1.6058	0.4336	1.3626	**14*α*/17** = 3.14

[a] On the basis of ^{1}H NMR analysis of the reaction mixture containing **17** and **13**.

3) third, the *manno* NPG and NPOE donors display very different relative reactivities (entries iii and iv), the ratios of 1.15 and 3.14 indicating that orthoester **13** is 2.73 times more reactive than the NPG counterpart **14**.

In summary, the experimental results support the theoretical findings, that the *manno* NPOE and NPG pair initially go to different intermediates while the *gluco* counterparts go to the same intermediate. In other words, the *manno* derivatives, the orthoester is a better or more reactive donor than the corresponding glycoside, whereas for *gluco* derivatives, there is no advantage to using one or the other.

Experimental Section

General: 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. All reactions were conducted under argon atmosphere. Thin-layer chromatography(TLC): Riedel-de Haen, coated with silica gel 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. *N*-Bromosuccinimide was purchased from Aldrich and recrystallized from hot water and dried on vacuum.

The *n*-pentenyl orthoeters, NPOEs **11**, **13** and **15**, and 2-*O*-benzoyl *n*-pentenyl glycosides NPG **12** and **14** were prepared as previously described.[22]

Pent-4-enyl 3,4-di-*O*-benzyl-6-*O*-methyl-*β*-D-glucopyranose (17): α-D-Glucopyranose 1,2-(pent-4-enyl orthobenzoate), **15**,[22] (2.2 g, 6.2 mmol), diisopropylethylamine, (2.2 mL, 12.7 mmol), 90% triisopropylsilyl chloride (2 mL, 8.4 mmol) and DMAP (50 mg, 0.4 mmol) were dissolved in dry dichloromethane (20 mL) and stirred overnight at room temperature. Water was added and the product was extracted into ethyl acetate. The organic layer was washed with water, brine, dried and chromatography on silica (hexanes/ethyl acetate 6:1 → 1:1) provided the syrupy diol **16a** (2.67 g, 84%). The compound was dissolved in dimethylformamide (50 mL). Sodium hydride (50% suspension in mineral oil, 2.0 g, 41.2 mmol) was added and the reaction mixture was stirred at 0 °C for 30 min. Benzyl bromide (2.0 mL, 16.8 mmol) was then added dropwise, the temperature of the reaction being maintained below 10 °C. Then, cooling bath was removed and the reaction mixture was stirred at room temperature until TLC (hexanes/ethyl acetate 4:1) showed full disappearance of the starting material and formation of a new, less polar product (ca. 1 h). The reaction mixture was diluted with diethyl ether, cooled to 0 °C, and water was carefully added to decompose the excess sodium hydride. The product was extracted into diethyl ether, the organic layer was washed with water, brine, dried over sodium sulfate and concentrated. Column chromatography (hexanes/ethyl acetate 9:1 → 5:1) provided product **16b** (3.29 g, 91%). The material was dissolved in THF (10 mL), and added to a mixture of 2,6-lutidine (0.2 mL, 1.7 mmol) and TBAF (1M in THF, 10 mL). The reaction mixture was stirred at room temperature overnight. Water was added and the product was extracted into ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulfate and concentrated. The crude product, **16d**, was treated with methyl iodide under the same conditions as used for the above-described benzylation, except that cooling was omitted. After column chromatography the product **16d** was obtained (3.29 g, 91%). Compound **16c** was directly dissolved in dry dichloromethane (10 mL) under argon, 4-pentenol (50 μL, 0.49 mmol) and TBDMSOTf (10 μL, 0.044 mmol) were added. The reaction mixture was stirred at room temperature for 2 min and then diluted with diethyl ether. Water was added and the product was extracted with diethyl ether. The organic layer was washed with 2% sulfuric acid, water, saturated $NaHCO_3$, water, brine, dried over sodium sulfate and concentrated. Column chromatography (hexanes/ethyl acetate 9:1 → 3:1) provided provided NPG **17** (1.83 g, 70%) as a syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, 2H, J = 7.2 Hz, *ortho* protons from benzoate), 7.59–7.33 (m, 13H, arom.), 5.69–5.55 (m, 1H, H-4 from pent.), 5.26 (dd, 1H, J = 8.1, 8.7 Hz, H-2), 4.88–4.62 (m, 6H), 4.48 (d, 1H, J = 7.2 Hz, H-1), 3.91–3.60 (m, 5H), 3.52–3.39 (m, 2H), 3.40 (s, 3H, OCH_3), 2.00–1.86 (m, 2H), 1.64–1.48 (m, 2H); HR-LSIMS: m/z: calcd for $C_{33}H_{38}O_7Na$: 569.2515; found: 569.2523 [M^++Na].

Conditions for competition reactions: Our recently described procedure for determining the relative reactivity of two NPGs[17] was used. Thus, the hydrolysis solution was prepared from acetonitroile (49.5 mL), NBS

(0.143 g, 0.8038 mmol) and water (0.5 mL). The "reporter donor" **17** (87.8 mg, 1.606 mmol) and the substrate donor (1.605 mmol) were dissolved in acetonitrile (2 mL), and the hydrolysis solution (10 mL) was added. The reaction mixture was left for 10 h, previous tests having shown that this time is sufficient to hydrolyse the "reporter donor" **17** completely. Diethyl ether was then added and the reaction mixture was quenched with 10% $Na_2S_2O_3$, washed with water, brine, dried, concentrated and subjected to a silica gel column to clean up the material. A portion of the product was then separated by preparative layer chromatography, the zones of interest being detected by UV light, scraped off, extracted with purified ethyl acetate and weighed.

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