The C-4 Configuration as a Probe for the Study of Glycosidation Reactions

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The difference in the electron-withdrawing powers of axial and equatorial OBn was used as a probe to investigate the glycosidation reaction. The reactivity of perbenzylated glucosyl and galactosyl donors were compared under a range of glycosidation conditions that involved variations in catalyst, solvent, and glycosyl acceptor. Generally, the galactosyl donor had a reactivity four to five times higher than the glucosyl donor, which is in accord with the transition state having positive character. In certain cases, however, particularly when triflate was present, equal reactivity of glucosyl and galactosyl donors were found. The results are explained in terms of changes in the rate-determining steps.

Introduction

Glycoside synthesis has been a central theme in carbohydrate chemistry for over 100 years. While much time has been, and is being, devoted to synthesis of specific oligosaccharides and new coupling procedures, relatively little attention has been devoted to systematic exploration of the general aspects of the reaction. Such investigations can, however, prove very valuable. As an example, the discovery and investigation of armed-disarmed effects[1−4] was to result in tuning of glycoside reactivity becoming a new tool with which to avoid functional group manipulations between glycoside coupling steps,[5,6] or to achieve one-pot glycosidations.[7] In this paper we report an investigation into the effect of stereochemistry on rates of glycosidation reactions.

The influence of stereochemistry on glycosyl donor reactivity has not received much attention in the literature. Wong and collaborators carried out a large study of thioglycoside reactivity towards methanol with NIS/TfOH activation and also compared several stereoisomeric donors.[4] They found that galactosyl donors were five to six times more reactive than glucosyl donors in this reaction, irrespective of the protection group. Lahmann and Oscarson have compared the relative rates of DMTST-promoted thioglycoside coupling to methyl 2,3,4-tri-*O*-benzylglucoside and similarly found that the galactosyl donors were three to seven times more reactive than the glucosyl donors.[6] Gervay and Hadd found that 2,3,4,6-tetra-*O*-benzylgalactosyl iodide was more reactive than the corresponding glucosyl iodide towards substitution with malonate ion.[8]

It was recently found that an axial polar group is less electron-withdrawing than the corresponding equatorial group (Figure 1).[9] For the axial hydroxy group, the σ_s values[9b] β or γ to the reference atom were 0.5 or 0.2, respectively, while the corresponding values for the equatorial hydroxy function was 1.3 and 0.6.[9b] Hammett plots using these σ_s values[10,11] show that the differing hydrolysis rates[12] of stereoisomeric methyl or aryl glycosides are due to this electronic effect. The effect is in all likelihood caused by differences in charge-dipole and electrostatic interactions between the polar substituent and a positive charge at the reference atom.

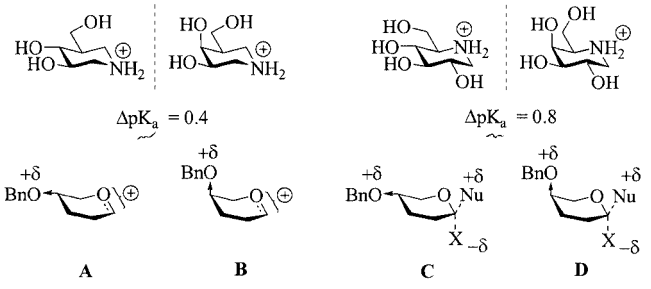

Figure 1. Axial polar groups show weaker electron-withdrawing effects than equatorial groups, as can be seen in the differences of the pK_as of piperidinium ions; the effect, presumably due to differences in charge-dipole and electrostatic interactions in the two cases, causes S_N1-like transition states **A** and **B** to differ in stability while S_N2-like transition states **C** and **D** will be less affected[9b]

The rate differences observed in the glycosidations described above[6−8] are encompassed by the electronic effect differences between the axial and equatorial oxygen functionalities when positive charge is generated in the glycon in the transition state. Assuming similar σ values for OBn and OH, one would expect that a perbenzylated galactosyl donor should be six to seven times more reactive than a perbenzylated glucosyl donor when fully charged at the ring oxygen in the transition state, while a rate difference of two to three times would be observed if the charge was at the anomeric carbon. The ratio between the rates of *galacto-*

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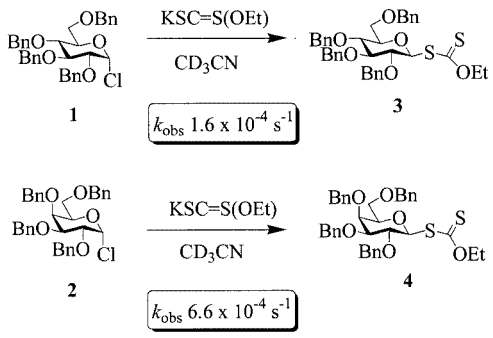
and *gluco*-configured donors in a glycosidation reaction therefore reveals the degree of charge in the transition state of the reaction and thereby also its degree of S_N1 or S_N2 character. Since an S_N2-like reaction mechanism is frequently desired or postulated in glycosidation reactions, it is valuable to be able to classify the S_N1/S_N2 character of various glycosidation reactions, and the purpose of this work was to attempt to do so on the basis of the relatively simple study of the influence of the 4-alkoxy group on the reaction rate. A ratio of reactivity between glucosyl and galactosyl donors of close to unity would indicate a charge-dispersed reaction ("S_N2-like"), while a ratio of 1 to 3−7 would indicate a high degree of positive charge at the ring oxygen or the anomeric carbon ("S_N1-like"). A low ratio may, however, also be caused by the rate-determining step being activation of the leaving group. It is noteworthy that the reactions discussed above[6−8] appear to belong to the S_N1 type, which is particularly remarkable for the substitution of the glycosyl iodides with carbanions.

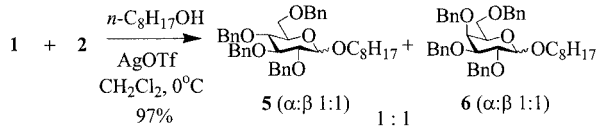
Results and Discussion

In order to investigate an S_N2-like reaction, glycosyl chlorides **1**[13] and **2**[14] were treated with potassium xanthogenate to obtain **3**[15] and **4**, respectively (Scheme 1). Both reactions gave inversion of configuration. By monitoring of the reaction by ^1H NMR in CD_3CN in the presence of excess KSCS(OEt) (5 equiv.) a pseudo-first-order reaction was deduced and rate constants for the two reactions were determined (Figure 2). The result show that the rate of conversion of the galactosyl chloride **2** is four times higher than that of the glucosyl chloride **1**. A similar set of experiments was also carried out with $NaSCH_2CH_2CH_2CH_3$ as nucleophile. In these experiments, **2** was also found to be more reactive than **1**, but elimination was a side-reaction that made it impossible to obtain rate constants. Nevertheless, both pairs of experiments show that substituent effects seriously affect the reaction, and there must be considerable S_N1 character in the transition state despite the clear Walden inversion indicating otherwise.



Scheme 1. Substitution of glycosyl chlorides with potassium xanthogenate

Glycosyl chlorides are classical glycosyl donors, often used to glycosidate alcohols. Silver triflate is a popular promoter in these reactions, and from the above result we expected donor **2** to be significantly more reactive than donor **1**. When a competition experiment was carried out with **1** and **2** (1.2 equivalents each) competing for 1-octanol (1 equivalent) in the presence of AgOTf (3.1 equivalents) in CH_2Cl_2 at 25 °C a 97% yield of glycosides **5**[16] and **6**[17] (α:β ratio 1:1) was obtained (Scheme 2). Surprisingly though, the ratio between **5** and **6** was 1:1, suggesting that the reaction is S_N2-like. We thus have a case in which the supposed S_N2-type reaction is sensitive to the electron-withdrawing effect of the 4-substituent, while the supposed S_N1 reaction is not!



Scheme 2. Competition experiments performed with glycosyl chlorides

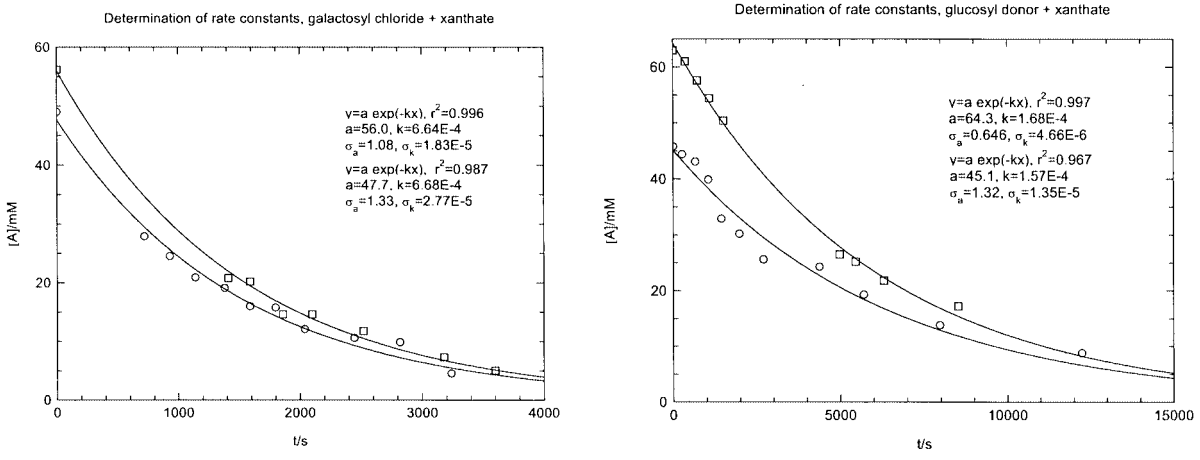


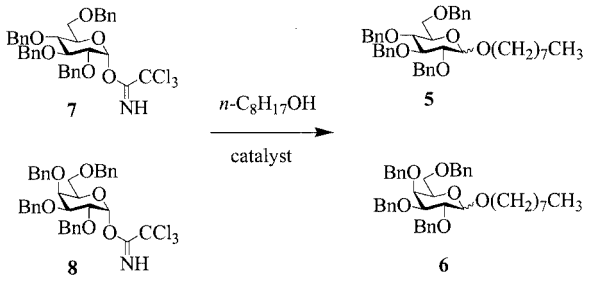
Figure 2. Determination of rate constants for the reactions of **1** and **2** with excess potassium xanthogenate (4−5 equivalents); each diagram show two determinations for each reaction

Table 1. Results of competition experiments between glucosyl and galactosyl imidates, **7** and **8**, with 1-octanol; unless otherwise noted, the experiment was with 1 equivalent of **7**, **8** and alcohol, 0.10−0.17 equivalent catalyst at 0 °C

Entry	Catalyst/promoter	Solvent	Equivalent catalyst	Yield	Gal(6):Glc(5)	α:β
1	$BF_3{\cdot}OEt_2$	CH_2Cl_2	0.14	97%	2:1	1:5
2[a]	$BF_3{\cdot}OEt_2$	CH_2Cl_2	0.14	100%	5:1	0:1
3	$BF_3{\cdot}OEt_2$	MeCN	0.14	37%	5:1	0:1
4	$BF_3{\cdot}OEt_2$	Et_2O	0.14	100%	3:1	0:1
5	TfOH	CH_2Cl_2	0.1	82%	1:1	1:4
6	TfOH	MeCN	0.1	71%	1:1	0:1
7	TMSOTf	CH_2Cl_2	0.17	45%	1:1	1:5
8	TMSOTf	MeCN	0.17	76%	1:1	1:3
9	AgOTf	MeCN	2.9	60%	1:1	1:4
10	$BF_3{\cdot}OEt_2$/AgOTf	MeCN	0.14 +0.4[b]	50%	2:1	0:1
11	$BF_3{\cdot}OEt_2$/CsOTf	MeCN	0.14 +2[c]	37%	3:2	0:1
12[d]	TfOH	CH_2Cl_2	0.1	87%	5:1	0:1

[a] 2 equivalents of **7** and **8** used. [b] 0.4 equivalents of AgOTf. [c] 2 equivalents of CsOTf. [d] At −78 °C.

More insight into this apparent inconsistency was obtained from the study of glycosidation with trichloroacetimidates.[18] Table 1 shows a series of competition experiments performed between the α-trichloroacetimidate donors **7**[19] and **8**[20] competing for 1-octanol as acceptor (Scheme 3). These experiments, unless otherwise specified, were carried out by having 1 equivalent of each donor and the acceptor present at 0 °C and adding the catalyst.



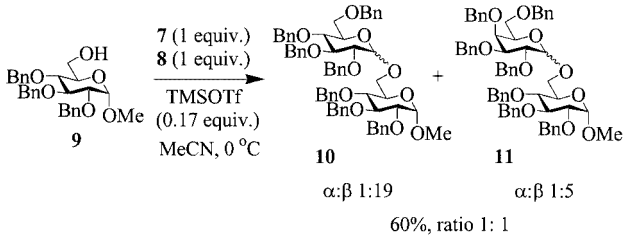
Scheme 3. Competition experiments performed as specified in Table 1

First of all, it can be seen that octyl glycosides **5** and **6** were obtained predominantly or exclusively with β configurations on use of a variety of catalysts and solvents. This could misleadingly suggest that these reactions proceed through an S_N2 mechanism. From Entry 1, in which BF_3 was catalyst in CH_2Cl_2, however, it can be seen that a 2:1 ratio in favor of the galactoside **6** was obtained in high yield (Entry 1). This means that the ratio between the rates of **7** and **8** must be higher than 2:1, because only one equivalent of each donor is used and **8** becomes depleted. A product ratio closer to the ratio of rates is obtained when 2 equivalents of each of the donors are used. This gave a 5:1 ratio (Entry 2). Changes in the solvent to MeCN or ether similarly gave high *galacto*/*gluco* ratios (Entries 3−4). These results are as expected and clearly show that the reaction has, as predicted, a highly charged transition state. When, however, trifluoromethanesulfonic acid (TfOH) was used as catalyst a crucial and surprising effect was observed (Entry 5−6). Regardless of the polarity of the solvent, the *gluco*/*galacto* product ratio became 1:1. Remarkably, the stereoselectivity was unchanged. The 1:1 ratio was also obtained when TMSOTf or AgOTf were used to catalyze the reaction (Entry 7−9). The effect therefore appears to be associated with the presence of triflate. To check that, two experiments in which triflate ions in the form of AgOTf (Entry 10) or CsOTf (Entry 11) were added to the BF_3-catalyzed reaction mixture were carried out (CsOTf alone does not catalyze the reaction.). Both reactions produced a decrease in *gal*/*glc* ratio in relation to BF_3 alone (Entry 3).

A possible explanation of why the BF_3- and the triflate-catalyzed reactions differ could be that glycosyl triflates are intermediates in the latter case. These results could be explained by the triflate increasing the reaction rate, giving a diffusion-controlled rate. The rate difference becomes hidden as the reaction of both donors reaches the upper limit of diffusion, and the inherently greater reactivity of the galactosyl donor **8** cannot be seen. The TfOH-catalyzed reaction was therefore performed at −78 °C (Entry 12) and indeed a 1:5 ratio of products **5** and **6** was obtained. This shows that a positively charged intermediate is also formed in the TfOH-catalyzed reaction when the reaction is slowed sufficiently that rate differences are possible. The most likely explanation for the observed triflate effect is therefore that triflate increases the rate of the reaction so that by room temperature it reaches the diffusion-controlled limit. The most likely intermediacy of triflate could be through the formation of a glycosyl triflate, as has been suggested in related reactions.[21]

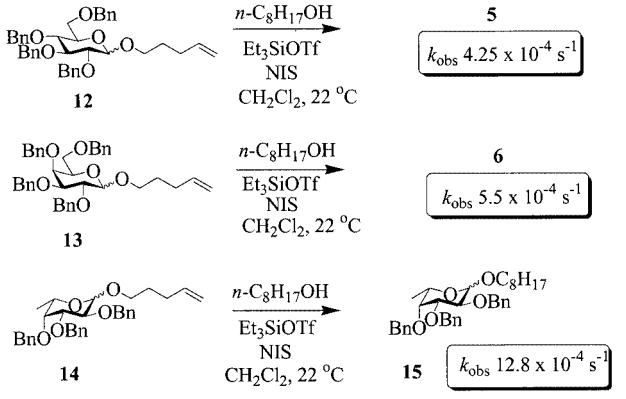
The reaction was also performed with a carbohydrate alcohol. Allowing the imidates **7** and **8** to compete for methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**9**)[22] catalyzed by TMSOTf at 0 °C gave a 1:1 ratio of the glucoside **10**[23,24] and galactoside **11**[25,26] (Scheme 4) predominantly as β-glycosides. The triflate effect is thus also observed in disaccharide synthesis.

Glycosidation with *n*-pentenyl glycosides was also investigated. Competition experiments such as those performed in Table 1 were difficult with these donors, due to the similarit-



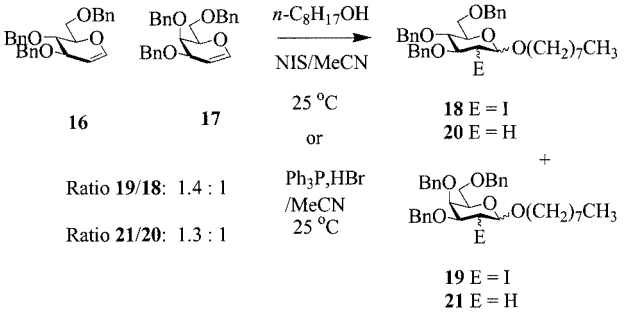
Scheme 4. Competition experiment with trichloroacetimidates and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside

ies of the ^{13}C NMR spectra of donors and products. These reactions are relatively slow at room temperature, though, so the rates of reaction of three pentenyl glycosides with 1-octanol in the presence of NIS/Et_3SiOTf were monitored directly. The reactions were carried out under pseudo-first-order conditions and samples were taken at different time intervals to determine the degree of conversion by ^1H NMR spectroscopy. This gave observed rate constants as outlined in Scheme 5. The pentenyl fucoside **14**[27] has been included in the comparison. This donor would be expected to be more reactive than **13** since it is lacking the electron-withdrawing 6-substituent. The results show relatively small reactivity differences between the three donors: the galactosyl donor **13**[27] is 1.3 times more reactive than **12**,[28] **14** reacts three times more quickly than **12**. These rate differences are relatively small compared to rate differences found for acidic hydrolysis of methyl glycosides, for which the *glc*:*gal*:*fuc* relative rate ratio is 1:5:30[12a] or for NIS/TfOH activation of thioglycosides, for which Wong et al. found the ratio to be 1:6:27.[4] This, however, is in accord with the observation by Fraser-Reid et al. that armed-disarmed effects are smaller in pentenyl glycosides when activated by NIS/Et_3SiOTf.[29] These workers thus found that the difference in reactivity between benzyl- and benzoyl-protected pentenyl glucosides was only 5:1 with this activation, while Wong has found that the comparable ratio for thioglucosides activated by NIS/TfOH is a staggering 2000:1.



Scheme 5. Reactions between pentenyl glycosides and excess 1-octanol (5 equivalents) promoted by NIS/Et_3SiOTf in CH_2Cl_2; rate constants for the pseudo first-order reaction

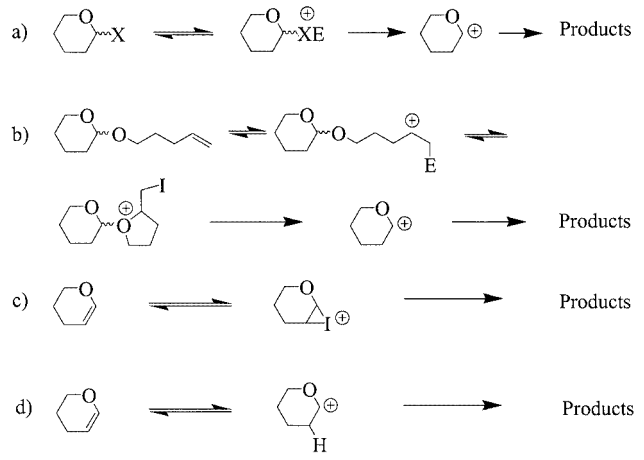
Two competition experiments with glucal **16** and the galactal **17** were also made (Scheme 6). Both activation with NIS in MeCN[30] at 25 °C to give 2-iodoglycosides **18** and **19** and activation with $Ph_3P{\cdot}HBr$ in MeCN[31] at 25 °C to give 2-deoxyglycosides **20**[32] and **21** gave slightly better conversion (1.4 to 1 or 1.3 to 1) of galactal donor than of glucal donor.



Scheme 6. Competition experiments between glycals **16** and **17** under two sets of conditions

The above results can be understood in the light of the reaction mechanisms outlined in Scheme 7 (adapted from ref.[29]). From the substitution experiments with potassium xanthogenate (Scheme 1) it is clear that even a relatively straightforward S_N2 process is heavily affected by electronic effects from the 4-alkoxy group (i.e., the transition state is late and has considerable carbocation character). So, why do other conditions give 1:1 or low *gal*/*glc* ratios? The reactions with halide, imidate and thioglycoside follow the mechanism shown in Scheme 7 (a), which involves initial activation of the leaving group, formation of the oxocarbenium ion, and reaction between the alcohol and the oxocarbenium ion. A low *gal*/*glc* ratio can occur if either the first or the third steps are rate-determining. In the reaction of the very reactive glycosyl chlorides **1** and **2** with AgOTf it is quite likely that the first step would become rate-determining. When glycosyl imidates are activated by BF_3 the rate-determining step must be the second step involving formation of a glycosyl cation (Scheme 7, a). The same must be the case when thioglycosides are activated by NIS/TfOH.[4] The first step, however, becomes rate-determining when TfOH is used to activate imidates, presumably because the rate of step 2 is increased, possibly to a diffusion-controlled rate. On reducing the temperature the second step becomes slower and this now become rate-determining. Pentenyl glycosides differ from other glycosyl donors[29] in that two preequilibration steps are involved in their activation, as outlined in Scheme 7 (b). The first step is a remote activation of the pentenyl double bond, while the second is the formation of a tetrahydrofuranyl oxonium ion. The very small electronic effects observed on Et_3SiOTf/NIS activation of pentenyl glycosides are probably because one of these preequilibration steps is rate-determining. Since a small effect is seen, it is suggested that the second preequilibration step, which involves exocyclic oxygen, is the rate-

determining step in this reaction. Glycals, on the other hand, are not activated through a preequilibration step and the oxocarbenium ion is presumably formed directly. In the NIS reaction the low electronic effect can easily be explained through the formation of an iodonium ion, which has the positive charge further separated from the substituents (Scheme 7, c). The similarly small effect in the reaction activated by $Ph_3P{\cdot}HBr$, however, suggests a more complex mechanism in that case (Scheme 7, d).



Scheme 7. Mechanisms for activation of various glycosyl donors

From the results in this paper is apparent that even seemingly clear-cut S_N2 reactions at the anomeric center, such as substitution of halide with a strong nucleophile, are affected by the stereochemistry at C-4 and thus have some S_N1 character. It is not therefore likely that substitution with an alcohol nucleophile can occur purely by S_N2, and these reactions are also likely to be associated with a high degree of positive charge being formed in the ring. It is also seen that the presence of triflate causes a change in the rate-determining step in glycoside couplings. It is not clear what the effect of the triflate is, but its influence could be through the formation of a stable glycosyl triflate ion pair and increasing the rate of leaving group departure. Finally, it is clear that the reaction conditions are crucial for the success of armed-disarmed strategies as it is necessary to employ activating conditions under which the formation of the oxocarbenium ion is rate-determining.

Experimental Section

General: ^{13}C NMR, ^1H NMR, and COSY spectra were recorded with Varian Gemini 200 or Varian 400 instruments with $CDCl_3$ (δ = 7.26 ppm and 77.16 ppm) or TMS (δ = 0.00 ppm) as references. Mass spectra were obtained with a Micromass LC-TOF mass spectrometer. Merck silica gel 60 (230−400 mesh) was used as stationary phase for flash chromatography. TLC (Merck, Kieselgel 60, F_{254}) plates were viewed by use of a "Ce-Mol" solution [Ce(IV)sulfate (10 g) and ammonium molybdate (15 g) dissolved in 10% H_2SO_4 (1 L), a ninhydrin solution (0.20 g in 100 mL 1-butanol and 5 mL 10% AcOH] or UV light. HPLC was carried with a Hewlett−Packard 1100 instrument with a silica gel column (Nucleosil 50−5) and *i*PrOH/hexane (3:97) as eluent. The flow rate was 0.8 mL/min.

Glycosyl donors **1**,[13] **2**,[14] **7**,[19] **8**,[20] **12**,[28] **13**,[27] and **14**[27] were prepared as described in the literature, while **16** and **17** where obtained commercially (Aldrich). Products **3**,[15] **4**, **5**,[16] **6**,[17] **10**,[23,24] **11**,[25,26] **15**,[33] and **20**[32] were made as reference compounds by known methods. Reference compounds **18**, **19**, and **21** were made as described below.

Determination of Substitution Rates of Glycosyl Chlorides with Potassium Ethylxanthogenate: The glycosyl chloride (**1** or **2**, ca. 15 mg) was dissolved in CD_3CN (0.5 mL) in an NMR tube and a spectrum was recorded (i.e., t = 0 s). Excess KSCSOEt (15−20 mg, 4−5 equiv.) was then added and ^1H NMR spectra were recorded at regular time intervals. In this way, the degree of conversion of the glycosyl chloride was measured and by assuming a pseudo-first-order reaction the recorded data were fitted to the general relationship $[A] = [A]^0 \times e^{-kt}$. From logarithmic plots of concentration versus time, the rate constants were determined to 1.63×10^{-4} s^{-1} for the reaction of **1** and 6.66×10^{-4} s^{-1} for the reaction of **2**.

Competition Reactions with Trichloroacetimidates as Donors: Trichloroacetimidates **7** and **8** (40 mg, 0.0584 mmol of each) were dissolved in 2 mL of solvent (see Table 1). 1-Octanol (9.2 μL, 0.0583 mmol) was added, and the resulting mixture was cooled to 0 °C. An activating agent was added and the reaction mixture was stirred for 1 h before being quenched with $NaHCO_3$(s)/H_2O and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was filtered on silica gel (EtOAc/pentane, 1:20) and the resulting mixture of glycosides **5** and **6** was analyzed by ^{13}C NMR spectroscopy. The ratio was determined from the peak heights of the anomeric ^{13}C NMR signals and by comparison with those of reference compounds of **5α** (δ = 96.95 ppm), **5β** (δ = 103.80 ppm), **6α** (δ = 97.58 ppm) and **6β** (δ = 104.13 ppm).

The competition reaction with **9** as glycosyl acceptor was carried out as above with the following changes. Trichloroacetimidates **7** and **8** (300 mg, 0.439 mmol of each) were used, with acetonitrile (12 mL), **9** (204 mg, 0.439 mmol), and trimethylsilyl triflate (13.6 μL, 0.075 mmol). Reaction time was 2 h at 0 °C before quenching with ice water and workup as above. The products, **10** and **11**, were analyzed by ^1H NMR and HPLC. The ratio of **10** to **11** was determined from peak areas of the HPLC signals and comparison with those of reference compounds. Retention times were: **10β** (3.602 min), **11α** (5.173 min), and **11β** (3.815 min) in *i*PrOH/hexane, 3:97 (0.800 mL/min).

Competition Reaction with Glycosyl Chlorides as Donors: AgOTf (47 mg, 0.183 mmol), molecular sieves (3Å), collidine (15 mL, 0.113 mmol), and 1-octanol were mixed in CH_2Cl_2 (0.5 mL). A solution of glycosyl chlorides **1** and **2** (40 mg, 0.0584 mmol each) in CH_2Cl_2 (0.5 mL) was added, and the reaction mixture was stirred for 1.5 h at 25 °C. The reaction mixture was washed with H_2O and aqueous $Na_2S_2O_3$ (10%) and dried over $MgSO_4$. After evaporation the resulting syrup was filtered through silica gel (1:20, EtOAc/pentane) to give a mixture of the glycosides **5** and **6**, which was analyzed by ^{13}C NMR and compared with reference compounds as above.

Competition Reactions with Glycals as Donors: Glycals **16** and **17** (100 mg, 0.240 mmol each) were dissolved in CH_2Cl_2 (2 mL). 1-

Octanol (37 μL, 0.234 mmol) was added followed by the activating agent [NIS (150 mg, 0.667 mmol) or Ph_3P·HBr (5 mg, 0.015 mmol)]. Reaction times varied from 5 min with NIS to 2.5 h with Ph_3P·HBr. After workup the resulting syrups were filtered through silica gel (EtOAc/pentane, 1:20) and analyzed by ^{13}C NMR spectroscopy.

Determination of Reaction Rates for Pentenyl Glycosides 12−14: The pentenyl glycoside (**12** or **13**, 200 mg, 0.33 mmol) and 1-octanol (0.26 mL, 1.65 mmol, 5 equivalents) were dissolved in dry CH_2Cl_2 (2.5 mL) together with crushed molecular sieves (4Å) under an atmosphere of nitrogen. *N*-Iodosuccinimide (111 mg, 0.495 mmol, 1.5 equiv.) was then added, followed by triethylsilyl triflate (0.2 equiv., 15 μL, 0.066 mmol). For **14** the amounts were: pentenyl fucopyranoside (200 mg, 0.4 mmol), 1-octanol (0.31 mL, 2.0 mmol), NIS (130 mg, 0.6 mmol), and TESOTf (18 μL, 0.08 mmol). The reaction mixture was kept at 22 °C for 90 min. Every 15 min a 0.5 mL sample was withdrawn, immediately diluted with CH_2Cl_2 (5 mL) and quenched by washing with $Na_2S_2O_3$ solution (10%, 3 × 10 mL) and $NaHCO_3$ (5%, 3 × 10 mL). The dried and concentrated sample was analyzed by ^1H NMR spectroscopy. In this way, the decay of pentenyl glycoside could be followed and by assuming a pseudo-first-order reaction the recorded data were fitted to the general relationship $[A] = [A]^0 \times e^{-kt}$. From logarithmic plots of concentration versus time, the rate constants were determined to 4.25×10^{-4} s^{-1} for the reaction of **12**, 5.5×10^{-4} s^{-1} for the reaction of **13** and 1.275×10^{-3} s^{-1} for the reaction of **14**.

Octyl 3,4,6-Tri-*O*-benzyl-2-deoxy-2-iodo-α-D-mannopyranoside (18a)/Octyl 3,4,6-Tri-*O*-benzyl-2-deoxy-2-iodo-β-D-glucopyranoside (18b): 3,4,6-Tri-*O*-benzyl-D-glucal (**16**, 207 mg, 0.497 mmol), 1-octanol (170 μL, 1.077 mmol), and molecular sieves (3Å) were stirred in dry MeCN (5 mL) for 30 min at room temperature. The mixture was cooled to 0 °C and *N*-iodosuccinimide (344 mg, 1.53 mmol) was added. The temperature was raised to 25 °C, and the reaction mixture was stirred for 15 min. It was diluted with CH_2Cl_2 (5 mL) and washed with $Na_2S_2O_3$ (10%, 5 mL) and water (5 mL). The organic phase was dried with $MgSO_4$ and the solvents were evaporated to a syrup, which was purified by flash chromatography [pentane/EtOAc, 20:1, R_f(**18a**) 0.66, R_f(**18b**) 0.57] to give **18a** (208 mg, 62%) and **18b** (36 mg, 11%) as colorless syrups. ^{13}C NMR (50 MHz, $CDCl_3$), **18a**: δ = 138.49, 138.32, 137.86, 128.48−127.54, 101.46 (C1), 77.16, 76.07, 75.37, 73.47, 72.19, 71.01, 69.03, 68.25, 33.93, 31.93, 29.55, 29.45, 29.32, 26.21, 22.78, 14.24. **18b:** δ = 138.16, 137.88, 128.60−127.77, 103.31 (C1), 86.09, 79.81, 75.65, 75.36, 75.10, 73.67, 70.55, 68.75, 33.38, 32.00, 29.53, 29.49, 29.41, 26.13, 22.83, 14.29. HRMS (ES): *m*/*z* calcd. for $C_{35}H_{45}O_5I$ + Na: 695.2211, Found: **18a**: 695.2209, **18b**: 695.2213

Octyl 3,4,6-Tri-*O*-benzyl-2-deoxy-2-iodo-α-D-talopyranoside (19a), Octyl 3,4,6-Tri-*O*-benzyl-2-deoxy-2-iodo-α-D-galactopyranoside (19b), and Octyl 3,4,6-Tri-*O*-benzyl-2-deoxy-2-iodo-β-D-galactopyranoside (19c): 3,4,6-Tri-*O*-benzyl-D-galactal (**17**, 212 mg, 0.509 mmol), 1-octanol (170 μL, 1.077 mmol), and molecular sieves (3 Å) were stirred in dry MeCN (5 mL) for 30 min at 25 °C. The mixture was cooled to 0 °C and *N*-iodosuccinimide (357 mg, 1.59 mmol) was added. The temperature was raised to 25 °C, and the reaction mixture was stirred for 15 min, diluted with CH_2Cl_2 (5 mL), and washed with $Na_2S_2O_3$ (10%, 5 mL) and water (5 mL). The organic phase was dried over $MgSO_4$ and the solvents were evaporated to give a yellow syrup, which was purified by flash chromatography [pentane/EtOAc, 20:1, R_f(**19a/19b**) 0.53, R_f(**19c**) 0.42] to give a mixture of **19a** and **19b** (72 mg, 21%), **19c** (39 mg, 11%) and a mixture fraction (183 mg, 53%) all as colorless syrups. ^{13}C NMR (50 MHz, $CDCl_3$): **19a/19b:** δ = 138.86, 138.46, 138.27, 137.90, 128.51−127.45, 102.27(α-talo-C1), 99.91(α-gal-C1), 79.53, 74.97, 74.69, 74.15, 73.57, 73.44, 72.89, 70.82, 70.67, 69.76, 69.35, 69.04, 68.92, 68.40, 31.96, 30.70, 29.85, 29.58, 29.50, 29.38, 26.25, 25.07, 22.81, 14.27 ppm; **19c:** δ = 138.4, 137.9, 137.4, 128.6−127.8, 103.9 (C1), 84.0, 74.6, 74.1, 73.7, 73.1, 72.9, 70.3, 68.7, 33.8, 31.9, 29.8, 29.5, 29.4, 26.1, 22.8, 14.3 ppm. HRMS (**19c**, ES): *m*/*z* calcd. for $C_{35}H_{45}O_5I$ + Na: 695.2211, found 695.2202.

Octyl 3,4,6-Tri-*O*-benzyl-2-deoxy-α-D-galactopyranoside (21): Ph_3P·HBr (5 mg, 0.015 mmol) was added to a solution of tri-*O*-benzyl-D-galactal (**17**, 109 mg, 0.262 mmol) and 1-octanol (50 μL; 0.317 mmol) in dry CH_2Cl_2 (1.5 mL), and the mixture was left stirring for 3 h at 25 °C. The mixture was then washed with $NaHCO_3$ (satd., 1 mL) and NaCl (satd., 1 mL) and dried over Na_2SO_4. After evaporation, the resulting syrup was chromatographed (EtOAc/pentane, 1:20, R_f = 0.34) to give 113 mg of octyl 3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranoside (**21**, 79%) and trace amounts of the β-anomer **21β**. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.40−7.06 (m, 15 H, ArH), 4.89 (s, 1 H, 1-H), 4.85 (d, *J* = 10.8 Hz, 1 H, $PhCH_2$), 4.59−4.27 (m, 5 H, 5 $PhCH_2$), 3.93−3.18 (m, 7 H, 3-H, 4-H, 5-H, 2 × 6-H, $-OCH_2-$), 2.15 (dt, 1 H, *J* = 3.6 Hz, *J* = 12.4 Hz, 2-$H_{eq.}$), 1.94 (dt, 1 H, *J* = 12.4 Hz, *J* = 4.4 Hz, 2-$H_{ax.}$), 1.55−1.38 [m, 2 H, $-OCH_2CH_2(CH_2)_5CH_3$], 1.28−1.09 (m, 10 H, $-O(CH_2)_2(CH_2)_5CH_3$], 0.80 (t, *J* = 6.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.99, 138.64, 138.21, 97.79 (C1), 75.01, 74.33, 73.52, 73.12, 70.51, 69.85, 69.69, 67.57, 31.93, 31.39, 29.65, 29.50, 29.36, 26.34, 22.77, 14.23 ppm. The minor anomer **21β** was seen in the ^{13}C NMR spectra with a peak at δ = 100.51 (C1) ppm. HRMS (**21**, ES): *m*/*z* calcd. for $C_{35}H_{46}O_5$ + Na: 569.3243, found 569.3248.

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