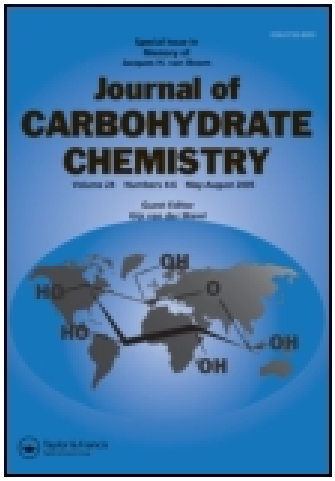

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Some Aspects of Selectivity in the Reaction of Glycosyl Donors

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Some Aspects of Selectivity in the Reaction of Glycosyl Donors

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Some advantages, disadvantages, and anomalies of various donors in glycosidations are discussed. By studying several two-component donor/acceptor-diol reactions, it is shown that regiopreferences are not very sensitive to the type of donor used. However, in competitive glycosidations within a given type of donor and between different types of donor, it is shown that regio- and chemoselectivities must be indexed to donor reactivity.

Keywords Chemo and regioselectivity in glycosylation, Donors in armed/disarmed competitive glycosylations

The data summarized in Schemes 1a,[1] 3b,[2] and 4a,[3] taken from the large body of van Boom's work, are symptomatic of the dilemma facing the seemingly simple task of coupling a glycosyl donor to an acceptor. Four types of selectivity—enantio, (dia)stereo, regio, and chemo—are suggested to be necessary for efficiency in organic synthesis by Trost.[4] In the case of oligosaccharide assembly, stereoselectivity was the first to be addressed in Isbell's historic rationalization[5] of the configurations of products formed in Koenigs Knorr reactions (see below). This rationalization inspired[6] what was later to become known as neighboring group participation,[7] whereby the O_2 acyl group would foster a trans-coupled product (see Sch. 5). Thus, Isbell,

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Dedicated to the memory of Professor Jacques van Boom.
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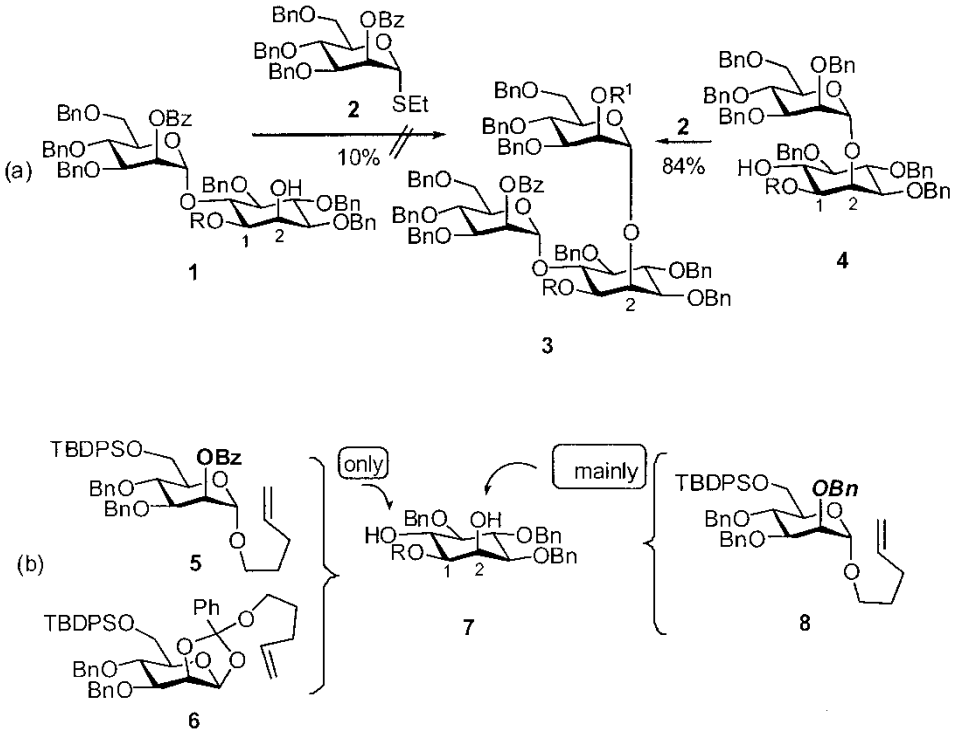


Scheme 1

60 years ago, established that in the case of sugars, protecting groups do more than protect, an observation that was seminal in that substitutents at oxygen are, arguably, the only readily available tools to influence outcomes in synthetic carbohydrate chemistry.[8]

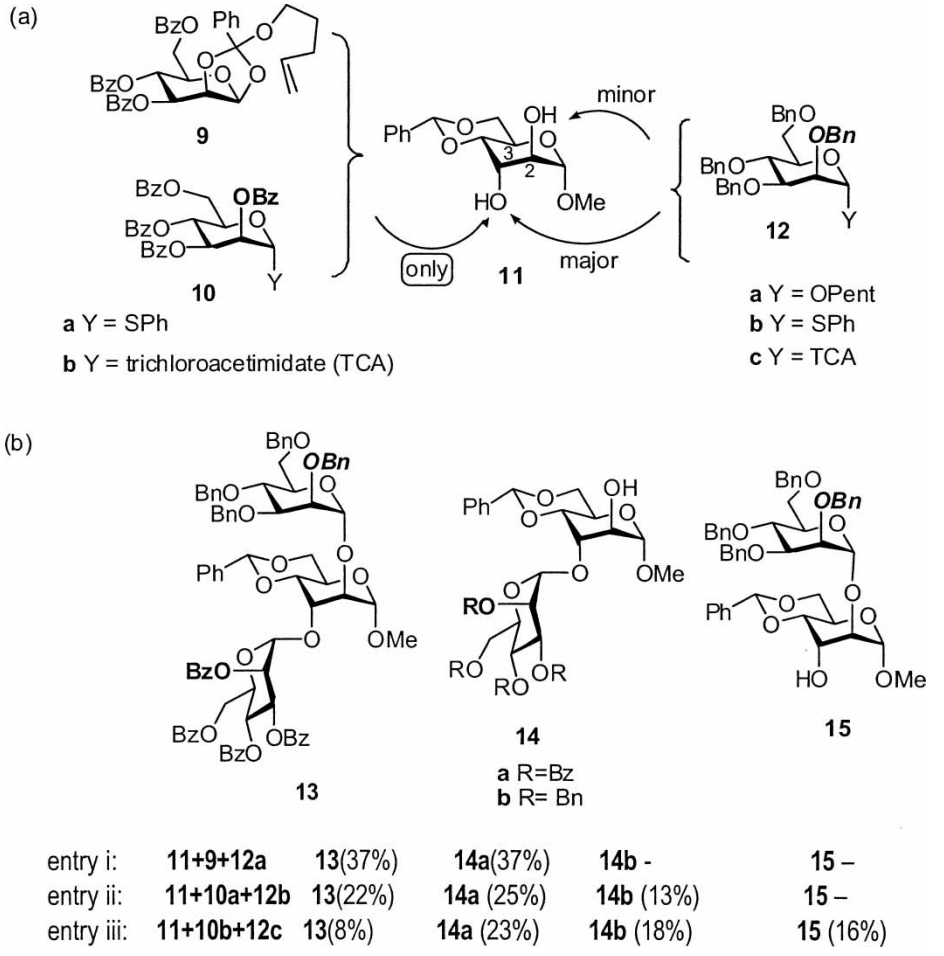
For the remaining three selectivities, enantioselectivity is usually irrelevant since for a given oligosaccharide target, nature specifies D and L options for the donor and acceptor. In this connection, van Boeckel's interesting study[9] showed that, in keeping with Masamune's principle of "double asymmetric synthesis",[10] such D and/or L partners may not be the best "match," even where that pairing occurs in nature.

The word "match," as used in Masamune's treatise,[10] differs from Paulsen's concept.[11] The latter was engendered by years of trial and error, which prompted Paulsen to conclude, in his historic 1982 review,[12] that "there are no universal reaction conditions for oligosaccharide synthesis," and so the "match" must be determined in each case. Although a crisp prescription for eliciting the best "match" was not offered, Paulsen's studies[13] implied that appropriate hallmarks are ready coupling and good yields.

Our appreciation of van Boom's experiments summarized in Scheme 1a emanated from 1999 observations with the diol **7**[14] (Sch. 1b). Glycosidation

with the 2-O-benzoylated donor **5** went only at O6, while the 2-O-benzyl counterpart **8** went mainly at O2.[15] The n-pentenyl orthoester (NPOE) **6** followed the same exclusive course as **5**. With the hindsight of our results, the 84% vs. 10% yields of **3** in Scheme 1a implied that the 2-O-benzoyl donors **2**, as in the case of **5**, is a good "match" for the O6-OH of inositol acceptors, but not O2-OH.

Good regioselectivity was observed with several diols,[16] a most impressive case being the altroside **11**.[17] As seen in Scheme 2a, the thioglycoside and trichloroacetimidate donors **10a** and **b** gave exclusive O3-OH regioselectivities, as did the NPOE **9**.[18] By contrast, the 2-O-benzyl donors **12a**, **b**, and **c** all



entry i:	**11+9+12a**	**13**(37%)	**14a**(37%)	**14b** -	**15** –
entry ii:	**11+10a+12b**	**13**(22%)	**14a** (25%)	**14b** (13%)	**15** –
entry iii:	**11+10b+12c**	**13**(8%)	**14a** (23%)	**14b** (18%)	**15** (16%)

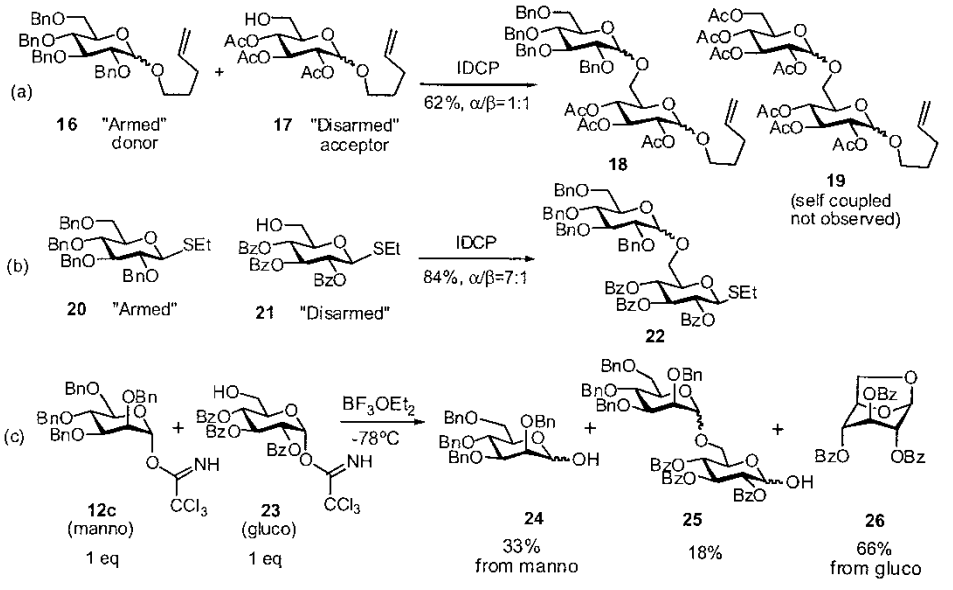
Scheme 2: (a) Regioseletivities in tow-component reactions of diol **11**. (b) Products from three-component reactions of diol **11** with pairs of donors.

displayed the same major and minor preferences for the O3-OH and O2-OH respectively.

Further, to the two-component reactions in Schemes 1b and 2a we have reported three-component reactions in which two different n-pentenyl donors are presented *simultaneously* to diol acceptors.[19] The results with a 1 : 1 : 1 mixture of diol **11** and n-pentenyl donors **9** and **12a** (Scheme 2b, entry i) typically gave only **13** (of four possible trisaccharides) and **14a** (of four possible disaccharides).[17]

We extended the three-component double glycosidation of diol **11** to the thioglycoside donors **10a** and **12b** (Scheme 2b, entry ii). Again the only trisaccharide was compound **13**, albeit formed in lesser amount. Compound **14b** was now added to the mix of products. With the trichloroacetimidates **10b** and **12c** (Sch. 2b, entry iii), **13** was again the only trisaccharide, although in almost negligible amounts. The yield of disaccharide **14a** was also lower. On the other hand, disaccharide **14b** was increased, and **15** was obtained for the first time in a three-component reaction.

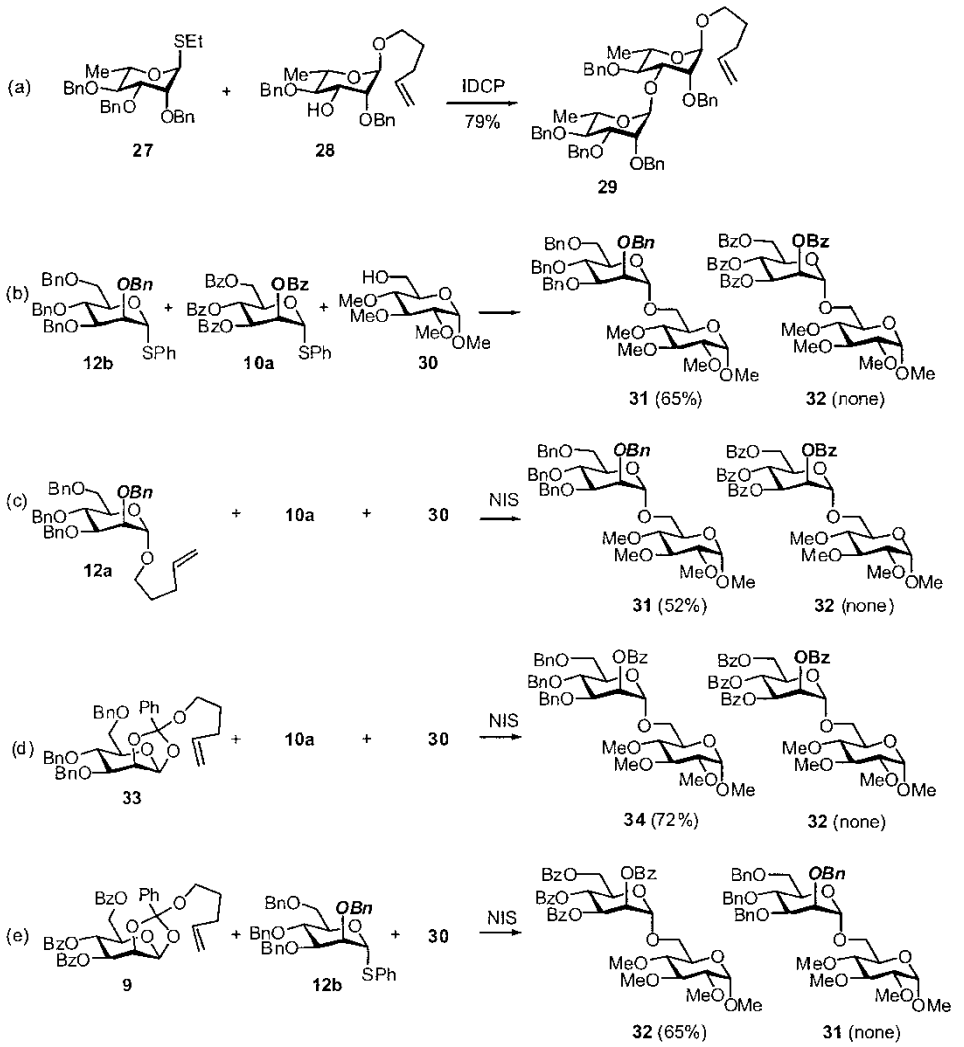
The fact that all three types of donors exhibited the same trends in the two-component (Sch. 2a) but not in the three-component (Sch. 2b) reactions was curious, and caused us to reflect on the 1988 armed/disarmed experiments (Sch. 3a), which showed that an O2-protecting group could be used to control chemoselective acceptor/donor choices in NPG couplings.[20] This phenomenon was soon extended to thioglycosides by van Boom (Sch. 3b).[2]



Scheme 3

However, to our knowledge, the armed/disarmed protocol had not been reported for trichloroacetimidates. Accordingly, the experiments in Scheme 3c were undertaken. It is seen that **12c** and **23** do not exhibit the armed/disarmed behavior (even at −78°C) as do NPG and thioglycoside analogs. Thus, formation of the 1,6-anhydrosugar **26**, which was not seen in Schemes 3a and b, suggests that the condition for chemocontrol is not met.

With regard to NPGs and thioglycosides, van Boom's experiment in Scheme 4a represented a case of chemoselectivity, as well as the first example of a reaction between orthogonal donors.[3] The selectivity was

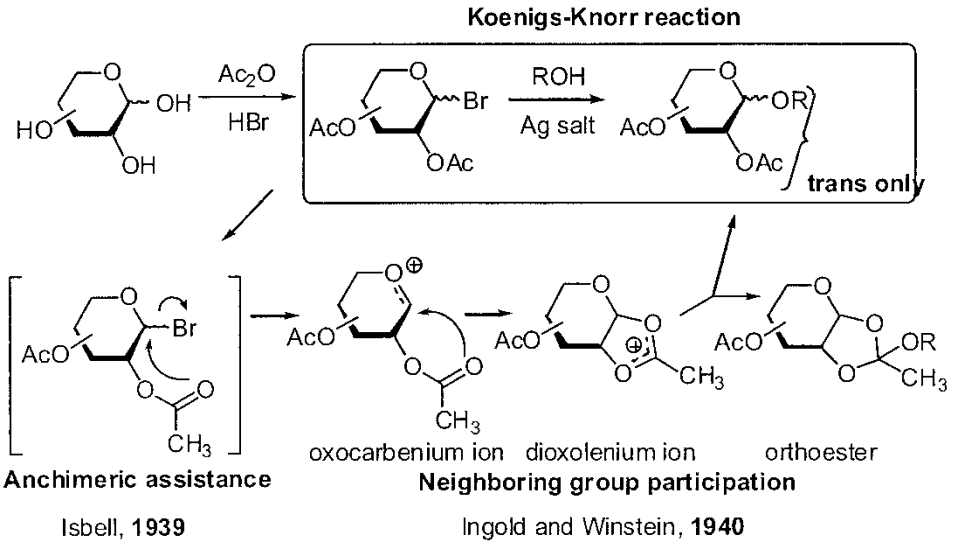


Scheme 4

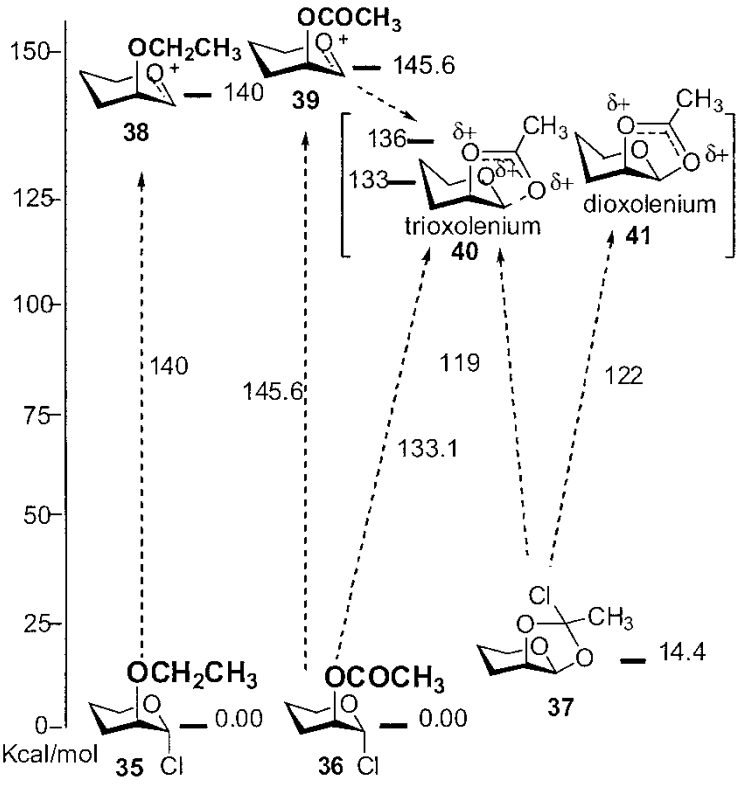
conceivably based on the preference of iodonium ion (I^+) to react with sulfur rather than an alkene. However, recent experiments in our laboratory indicate that the O2-protecting group profoundly affects orthogonal preference.[17] Thus, in Schemes 4b and c the armed donors **12a** and **12b** completely shut out the disarmed competitor **10a** to give disaccharide **31** as the main product.[17] On the other hand, Schemes 4d and 4e illustrate the preference of iodonium ion (I^+) to react with an alkene rather than sulfur when NPOEs **33** and **9** react instead of either disarmed or armed thioglycosides **10a** and **12b**, to yield disaccharides **34** and **32**, respectively.

The issue of reactivity requires that the role of the O2-protecting group be examined more closely. Isbell's landmark insight[5] was aimed at rationalizing the stereochemical outcome of the Koenigs-Knorr reaction (Sch. 5), and the concept of neighboring group participation met this need. However, subsequent examination of the phenomenon revealed a kinetic aspect, which came to be known as "anchimeric assistance".[7] It therefore seemed anomalous that the trans-2-O-acyl donors, for example, **17** and **21** (Sch. 3), be "disarmed" with respect to the 2-O-alkyl counterparts **16** and **20**, respectively.

We have probed the matter theoretically using the tetrahydropyranyl chlorides **35** and **36** to represent the armed and disarmed donors and **38** and **39** as the carbocations derived from them, respectively.[21] The transition energy is seen to be higher for the disarmed species by approximately 5.6 kcal (Scheme 6). The dioxolenium ion **41** was found, but calculations also revealed a trioxolenium counterpart **40** with charge being distributed to each of the three oxygens.



Scheme 5



Scheme 6

These same ions would also be generated from the bicyclic precursor **37** at much less energetic cost, as is clear from the results in Scheme 4d and 4e.

The formation of cross-coupled products **18** and **22** (Sch. 3) is consistent with **16** and **20** being the donors; otherwise, self-coupled products would have been formed. By corollary, **17** and **21** could not have benefitted from anchimeric assistance leading to di/trioxolenium ions, or they would not have behaved as acceptors.

The contrasting results between pentenyl glycosides/thioglycosides (**9**/**10a**) on the one hand and trichloroacetimidate **10b** on the other (Sch. 2) could imply that in the case of the latter, reaction proceeds directly through the di/trioxolenium ion (**40**/**41**), whereas the former follows the more energetic pathway, going first to **39** before plunging to **40**/**41**.

SUMMARY

The results above draw attention to advantages and disadvantages, as well as the anomalies, of donor reactivity in glycosidation. Chemoselective coupling

within a given type (e.g., armed/disarmed in Sch. 3a and 3b) and between different types (i.e., orthogonal, Sch. 4a, 4d) can be advantageous. On the other hand, the failure to observe armed/disarmed coupling for trichloroacetimidates, even at $-78^{\circ}C$ (Sch. 3c) can be considered a disadvantage. This is evident in the results in Scheme 2. All three types of armed and disarmed donors showed the same regiopreferences in the two-component reactions (Sch. 2a). However, when these donors were made to compete in three-component reactions, the success of regioselective, double differential glycosidations to give **13** was best with NPGs, the least reactive of the three sets of donors examined in Scheme 2.

The results in Schemes 2 and 3 indicate that regio- and chemoselectivities must be indexed to donor reactivities. Thus, the transition energy gaps in Scheme 6 could be increased or decreased depending on the models chosen. This should be amenable to theoretical analysis, and appropriate studies are currently underway.

EXPERIMENTAL

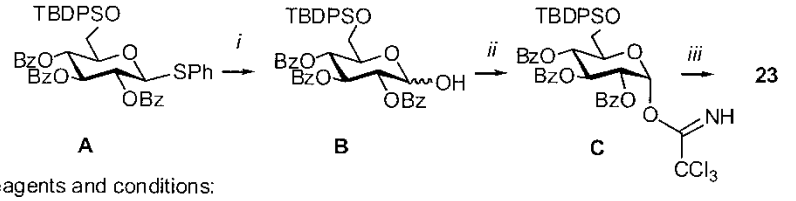
General Methods

Optical rotations were determined at the sodium D line. ^{1}H NMR spectra were recorded at 200, 300, or 500 MHz; chemical shifts (δ) are relative to residual nondeuterated solvent as internal reference. TLC was conducted in precoated Kieselgel 60 F_{254}. Detection was first by UV (254 nm), then charring with a solution of ammonium molybdate (VI) tetrahydrate (12.5 g) and cerium (IV) sulfate tetrahydrate (5.0 g) in 10% aqueous sulfuric acid (500 mL). Column chromatography was carried out on Kieselgel (230–400 mesh) and, unless otherwise noted, mixtures of hexane-EtOAc were used as eluant. All reactions were conducted under atmosphere of argon. Anhydrous $MgSO_4$ or Na_2SO_4 were used to dry the organic solutions during work-ups and the removal of the solvents was done under vacuum with a rotavapor. Unless otherwise noted, materials were obtained from commercially available sources and used without further purification. Solvents were dried and purified using standard methods.

General glycosidation procedure for thioglycoside and *n*-pentenyl donors. To a solution containing the glycosyl acceptor (42.3 mg, 0.15 mmol) and the glycosyl donor (0.15 mmol) in anhydrous CH_2Cl_2 (3 mL) were added molecular sieves 5Å (1 mg/mg donor) and *N*-iodosuccinimide (1 eq.) at $-30^{\circ}C$. After stirring the mixture for 5 min BF_3OEt_2 (0.045 mmol) was added. The reaction was monitored by TLC and, after disappearance of the acceptor, solutions of saturated $NaHCO_3$ and $Na_2S_2O_3$ were added. The reaction mixture was extracted with methylene chloride and dried over

anhydrous sodium sulfate. Solvents were removed and the residue was purified by flash chromatography.

Preparation of trichloroacetimidates 23 and 12c. The "disarmed" trichloroacetimidate **23** [^{1}H NMR (300 MHz) δ: 8.53 (s, 1H) 7.90–7.79 (m, 5H), 7.75–7.15 (m, 10H), 6.73 (d, 1H), 6.22 (t, 1H, $J = 9.8$ Hz), 5.54 (t, 1H, $J = 9.8$ Hz), 5.48 (dd, 1H, $J = 10.2$, 3.5 Hz), 4.16 (m, 1H), 3.71 (m, 2H)] was prepared from the known[22] phenyl 2,3,4-tri-*O*-benzoyl-6-*O*–(*t*-butyldiphenylsilyl)-1-thio-β-D-glucopyranoside (**A**) by oxidative hydrolysis with NBS in aqueous acetone, and standard[23] reaction with DBU and $CNCCl_3$, followed by desilylation with HF/pyridine complex. The "armed" counterpart **12c** was prepared likewise from thioglycoside **12b**.



Reagents and conditions:
(i) NBS (3eq), acetone (20mL/mmol) , H_2O (40µ l/mmol), 1.5h, rt, 95%
(ii) CH_2Cl_2, DBU (1eq), $CNCCl_3$ (2eq), 0 °C, 1h, 85%
(iii) Excess of a solution of HF/pyridine; (THF: pyr: HF/pyr) (4: 2 :1), 0 °C to rt, 1h, 80%.

Glycosidation procedure for trichloroacetimidate donors. To a solution of glycosyl trichloroacetimidates **12c** and **23** (0.09 mmol each) in anhydrous CH_2Cl_2 (3 mL) were added molecular sieves 5Å (1 mg/mg donor) and BF_3OEt_2 (0.3 eq.) at -78°C for **23**: The reaction was quenched after 10 min with saturated aqueous sodium bicarbonate, extracted with dichloromethane, dried over Na_2SO_4, and concentrated. The mixture was purified by flash chromatography (hexane: EtOAc, 9 : 1 to 7 : 3) to give known monosaccharides **24** (16 mg, 33%) and **26** (28 mg, 66%) and disaccharide **25** (18 mg, 18%).

Data for compound 34. ^{1}H NMR (300 MHz) δ: 3.02 (dd, 1H, $J = 9.98$, 8.85 Hz, H-4), 3.14 (dd, 1H, $J = 9.61$, 3.58 Hz, H-2), 3.40 (s, 3H, OMe), 3.43 (s, 3H, OMe), 3.27–3.54 (m, 2H), 3.56 (s, 3H, OMe), 3.63 (dd, 1H, $J = 11.30$, 1.70 Hz), 3.69–4.02 (m, 7H), 4.43–4.53 (m, 4H), 4.63–4.74 (m, 5H), 4.81 (d, 1H, $J = 10.9$ Hz), 4.99 (d, 1H, $J = 1.88$ Hz, H-1′), 5.58 (m, 1H, H-2′), 7.09–7.31 (m, 18H, Ar) 7.98–8.01(m, 2H, Ar). ^{13}C NMR (75 MHz) δ: 55.4, 59.4, 60.9, 61.2 (4 × OMe), 66.4, 69.4, 71.8, 73.8, 75.6 (5 × CH_2), 69.2, 70.1, 72.1, 74.6 (C-2, C-3, C-4, C-5), 78.2, 79.9, 82.2, 84.0 (C-2′, C-3′, C-4′, C-5′) 97.6, 98.5 (C-1, C-1′), 127.8, 127.9, 128.0, 128.3, 128.5, 128.6, 128.7, 128.8, 130.3, 130.4, 133.5, 138.9 (Ar) 166.1 (C = O).

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