A New, Efficient Glycosylation Method for Oligosaccharide Synthesis under Neutral Conditions: Preparation and Use of New DISAL Donors

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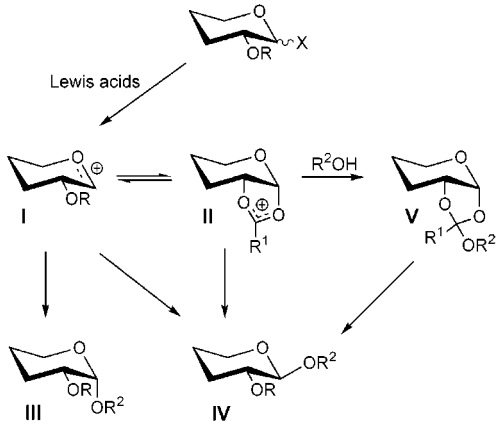
Efficient, stereoselective glycosylation methods are required for the synthesis of complex oligosaccharides as tools in glycobiology. All glycosylation methods, which have found wide acceptance, rely on Lewis acid activation of glycosyl donors prior to glycosylation. Here, we present a new and efficient method for glycosylation under neutral or mildly basic conditions. Glycosides of methyl 2-hydroxy-3,5-dinitrobenzoate (DISAL) and its para regioisomer, methyl 4-hydroxy-3,5-dinitrobenzoate, were prepared by nucleophilic aromatic substitution. In a first demonstration of their potential as glycosyl donors, stereospecific glycosylation of methanol was achieved. In the glycosylation of more hindered alcohols, the β-donor proved more reactive, and α-glucosides were predominantly formed. Glycosylation of protected monosaccharides, with free 6-OH or 3-OH, proceeded smoothly in 1-methyl-2-pyrrolidinone (NMP) at 40−60 °C in the absence of Lewis acids and bases in good to excellent yields. Glycosylation of 3-OH gave the α-linked disaccharide only.

Introduction

In recent years, a composite picture of the biological roles of oligosaccharides has emerged.[1] Cell surface oligosaccharides mediate cell−cell recognition through multiple simultaneous interactions with receptors on the cognate cell, but they also mediate the binding of bacterial and viral pathogens to target cells prior to infection. Cancer cells display an array of tumor-associated antigens, many of which are carbohydrate based. Glycans of glycopeptides and -proteins isolated from natural sources or after gene expression[2] are often heterogeneous. Easy access to pure and diverse oligosaccharides would hand the glycobiologists an important tool in the study of the biological roles of glycans, especially in glycoproteins. Furthermore, reagents that inhibit, modify, or mimic such specific carbohydrate−protein interactions are of great pharmaceutical importance and may lead to new pharmaceuticals for immunology, inflammation, and oncology.[3]

Numerous studies on the Lewis acid (electrophile)-promoted glycosylation of alcohols have been reported, and an ever increasing number of glycosylation procedures have been published.[4] In practically all cases, activation by a Lewis acid promoter gives rise to an oxocarbenium ion **I**, which in the case of a 2-*O*-acyl donor gives a dioxocarbenium ion **II** (Scheme 1), both as ion pairs. Nucleophilic attack by an alcohol on **I** can occur on either the α- or β-face to give the α- and β-glycosides

Scheme 1



III and **IV**, respectively. Attack on dioxocarbenium ion **II** by an alcohol gives β-glycoside **IV** or ortho ester **V**, which under acidic conditions can rearrange to the β-glycoside. Though many features of these reactions thus are well understood, the complex nature of the reactants often makes it difficult to predict the stereochemical outcome, and consequently, it may be difficult to predict which of the current glycosylation procedures is preferable for establishing a particular glycosidic linkage.

Glycosylation of *phenols* by glycosyl bromides,[5] chlorides,[6] and fluorides[7] under basic conditions, in which the phenoxide is formed, can proceed with a high degree of inversion at the anomeric center. However, this approach has generally not been successful for *aliphatic* alcohols,

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(1) (a) Varki, A. *Glycobiology* **1993**, *3*, 97−130. (b) *Molecular Glycobiology*; Fukuda, M., Hindsgaul, O., Eds.; IRL Press: Oxford, 1994. (c) Yarema, K. J., Bertozzi, C. R. *Curr. Opin. Chem. Biol.* **1998**, 49−61.

(2) Jenkins, N.; Parekh, R. B.; James, D. C. *Nature Biotechnol.* **1996**, *14*, 975−981.

(3) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2300−2324.

(4) (a) Paulsen, H. In *Modern Methods in Carbohydrate Synthesis*; Khan, S. H., O'Neill, R., Eds; Harwood Academic Publisher: Foster City, 1996; Vol. 1, pp 1−19. (b) Schmidt, R. R. *Angew. Chem.* **1986**, *98*, 213−236. (c) Sinay, P. *Pure Appl. Chem.* **1991**, *63*, 519−528. (d) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155−173. (e) Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137−2160.

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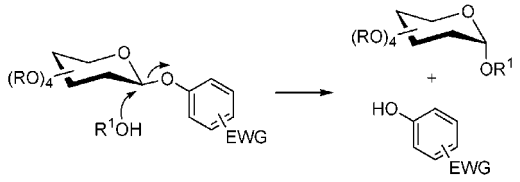
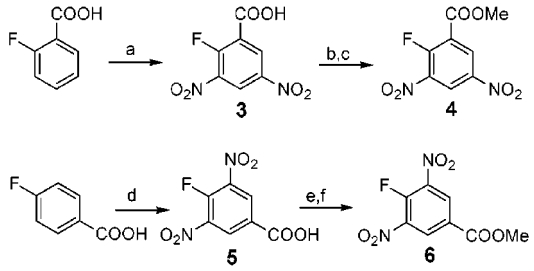
Scheme 2



especially if they are of the complexity of carbohydrate derivatives. On the other hand, glycosyl iodides have proven their value for the glycosylation of *aliphatic* alcohols in saccharides under mild, nonacidic conditions by an in situ anomerization mechanism.[8,4d] However, the main disadvantage of glycosyl iodides is their lack of stability and often the need to prepare them in situ.[8,9]

We are interested in developing new and efficient methods for glycosylation under nonacidic conditions[10] as this promises to simplify the reaction conditions and avoid at least some of the problems associated with Lewis acid promoted glycosylations. We reasoned that glycosides of phenols carrying sufficiently electron-withdrawing substituents[11] could possibly serve as glycosyl donors under neutral or mildly basic conditions (Scheme 2). Glycosides of 2,4-dinitrophenol, while labile to nucleophiles such as ammonia in methanol,[12] appeared not to be reactive enough in glycosylation reactions. To obtain more reactive glycosyl donors, we prepared glycosides of methyl 2-hydroxy-3,5-dinitrobenzoate[13] (DISAL) and methyl 4-hydroxy-3,5-dinitrobenzoate and applied them successfully to glycosylations. The name DISAL was derived from the former compound, a *di*nitro*sal*icylic acid derivative. For safety concerns, trinitrophenyl glycosides were not tested.

Scheme 3[a]



[a] Reagents and conditions: (a) fuming HNO_3 in fuming H_2SO_4 (65% oleum) (1:2), 1 h at 90 °C (84%); (b) $(COCl)_2$ (1.2 equiv), cat. DMF in CH_2Cl_2, 1 h at 25 °C; (c) MeOH (97%, two steps); (d) fuming HNO_3 in concentrated H_2SO_4 (1:2), 17 h at 90 °C (75%); (e) $(COCl)_2$ (1.2 equiv), cat. DMF in THF, 15 min at 25 °C; (f) MeOH in hexane (60%).

Results and Discussion

Synthesis of Precursors and Donors. Glycosides of 2,4-dinitrophenol are most conveniently prepared by nucleophilic aromatic substitution of 1-fluoro-2,4-dinitrobenzene with partially protected carbohydrate derivatives with a free 1-OH in DMF in the presence of DBU or DABCO.[14] Thus, Koeners et al. prepared 2,4-dinitrophenyl 2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranoside (**1**) from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**2**). To access glycosides of methyl 2-hydroxy-3,5-dinitrobenzoate and methyl 4-hydroxy-3,5-dinitrobenzoate, we required the corresponding fluoro precursors. Nitration of inexpensive 2-fluorobenzoic acid in a preformed mixture of 65% fuming sulfuric acid and fuming nitric acid (2:1)[15] gave the expected 2-fluoro-3,5-dinitrobenzoic acid (**3**) in a good yield of 84% (Scheme 3), which was an improvement over a previous report.[16] Reaction with oxalyl chloride in dichloromethane containing a catalytic amount of DMF converted the benzoic acid derivative **3** smoothly to the corresponding acid chloride, which was reacted immediately with excess methanol to give a high yield of methyl ester **4** after crystallization (Scheme 3). 4-Fluorobenzoic acid was dinitrated under somewhat milder conditions giving a slightly higher yield (75%) of 4-fluoro-3,5-dinitrobenzoic acid (**5**) than previously reported.[17] Benzoic acid derivative **5** was converted as before to the corresponding methyl ester **6** in 60% yield after crystallization. Higher lability of the aryl fluoride was observed in **6**, but it was successfully synthesized under mild reaction conditions. Even though **4** and **6** both are very good electrophiles, they store well as crystalline compounds.

Next, with these fluorobenzene derivatives synthesized, we turned to the formation of aryl glycosides as potential glycosyl donors. It was observed, as expected, that nucleophilic aromatic substitution was not feasible on **3**, which has a free carboxylic acid. However, formation of the aryl glycoside from the methyl esters **4** and **6** proceeded in high yields with short reaction times (Scheme 4). Initial experiments showed that high concentration of base, ions (even chloride ions), or weak nucleophiles were not well tolerated in the reaction mixture. Therefore, a double-base system was developed

(5) (a) Glaser, E.; Wulwek, W. *Biochem. Zeitschrift* **1924**, *145*, 514−534. (b) Abbas, S. A.; Matta, K. L *Carbohydr. Res.* **1983**, *124*, 115−121.

(6) (a) Ballardie, F.; Capon, B.; Sutherland, J. D. G.; Cocker, D.; Sinnott, M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2418−1429. (b) Courtin-Duchateau, M.-C.; Veyrières, A. *Carbohydr. Res.* **1978**, *65*, 23−33. (c) Delmotte, F. M.; Privat, J.-P. D. J.; Monsigny, M. L. P. *Carbohydr. Res.* **1975**, *40*, 353−364.

(7) (a) Voznyi, Y. V.; Kalicheva, I. S.; Galoyan, A. A. *Bioorg. Khim.* **1982**, *8*, 1388−1392. (b) Voznyi, Y. V.; Kalicheva, I. S.; Galoyan, A. A. *Bioorg. Khim.* **1985**, *11*, 970−972.

(8) Hadd, M. J.; Gervay, J. *Carbohydr. Res.* **1999**, *320*, 61−69.

(9) Caputo, R.; Kunz, H.; Mastroianni, D.; Palumbo, G.; Pedatella, S.; Solla, F. *Eur. J. Org. Chem.* **1999**, *11*, 3147−3150.

(10) Recent reports have described the use of lithium ions for the activation of glycosyl trichloroacetimidates, fluorides, and phosphites, as well as epoxides. However, the lithium salts still act as, albeit mild Lewis acids, hence the reaction conditions are not neutral in the strict sense used in this paper: (a) Lubineau, A.; Drouillat, B. *J. Carbohydr. Chem.* **1997**, *16*, 1179−1186. (b) Schene, H.; Waldmann, H. *Chem. Commun.* **1998**, 2759−2760. (c) Schmid, U.; Waldmann, H. *Chem. Eur. J.* **1998**, *4*, 494−501. (d) Schene, H.; Waldmann, H. *Synthesis* **1999**, 1411−1422.

(11) The synthesis of glycosyl donors by nucleophilic aromatic substitution is conceptually related to Mukaiyama's and Schmidt's preparation of hetaryl glycosides from electron-poor heterocycles. However, in contrast to the glycosylation method presented here, Mukaiyama's donors required activated, trimethylsilylated nucleoside bases and Schmidt's hetaryl glycosides required the presence of a Lewis acid (TMSOTf or BF_3·OEt_2) for efficient glycosylation of alcohols: (a) Mukaiyama, T.; Hashimoto, Y.; Hayashi, Y.; Shoda, S. *Chem. Lett.* **1984**, 557−560. (b) Huchel, U.; Schmidt, C.; Schmidt, R. R. *Tetrahedron Lett.* **1995**, *36*, 9457−9460. (c) Huchel, U.; Schmidt, C.; Schmidt, R. R. *Eur. J. Org. Chem.* **1998**, 1353−1360.

(12) (a) Glaser, E.; Thaler, A. C. *Arch. Pharm.* **1926**, 228−237. (b) Hengstenberg, W.; Wallenfels, K. *Carbohydr. Res.* **1969**, *11*, 85−91.

(13) Aryl glycosides of salicylic acid are significantly more labile to acid hydrolysis than the corresponding phenyl glycosides. This has been ascribed to acid catalysis by the free benzoic acid moiety; see: (a) Capon, B. *Tetrahedron Lett* **1963**, *14*, 9111−913. (b) Capon, B.; Smith, M. C.; Anderson, E.; Dahm, R. H.; Sankey, G. H. *J. Chem. Soc. B* **1969**, 1038−1047.

(14) Koeners, H. J.; de Kok, A. J.; Romers, C.; van Boom, J. H. *Recueil* **1980**, *99*, 355−362.

(15) The same yield was obtained in a mixture of concentrated sulfuric acid and fuming nitric acid, but longer reaction times were required.

Scheme 4

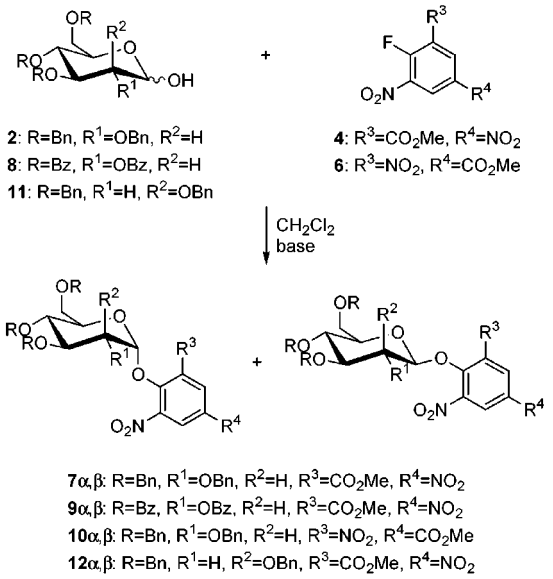


Table 1. Formation of Aryl Glycosides by Base-Catalyzed Nucleophilic Aromatic Substitution

entry	base	hemiacetal (α/β[a])	time (h)	DISAL glycoside	yield (%) (α/β[b])
1	DMAP	**2** (3:1)	0.5	**7α,*β***	89 (2.1:1)
2	DMAP	**2α**	0.5	**7α,*β***	89 (8.4:1)
3	DMAP	**8** (7:1)	0.5	**9α,*β***	92 (6.7:1)
4	DMAP	**2** (6:1)	0.5	**10α,*β***	65 (4.1:1)
5	DMAP	**11** (5:1)	0.5	**12α**	75
6	DMP	**2** (3:1)	2	**7α,*β***	89 (1:9)
7	DMP	**2** (4:1)	2 + 1[c]	**7α,*β***	78 (1:14.1)
8	DMP	**8** (4:1)	2	**9α,*β***	87 (1:8)

[a] Approximately anomeric distribution in starting material (^{13}C NMR). [b] Determined by RP-HPLC. [c] Aryl fluoride added over 2 h and then stirred for an additional 1 h.

where only a catalytic amount of the soluble base was used as a "shuttle" and a solid base (Li_2CO_3) acted as a drain for liberated HF from the reaction mixture. The solid base could then be used in excess without affecting the reaction. An extensive screening of potential soluble bases (see the Supporting Information) pointed to 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 0.3 equiv)[18] and 1,4-dimethylpiperazine (DMP, 0.5 equiv) as very effective.

The use of DMAP as base gave an α/β ratio similar to the starting 1-OH derivative (Table 1). Interestingly, formation of aryl β-glycoside **7***β* was favored using DMP as soluble base, and somewhat longer reaction times were required.[19] These two protocols were also applied to benzoyl-protected glucopyranose derivative **8** to give the benzoyl-protected glycoside **9**α,*β*.[20] Also, the benzyl-protected para donor **10** was synthesized from **2** and **6** in a DMAP-catalyzed reaction in 65% yield. The lower yield compared to ortho glycoside **7** was due to a higher lability of the para aryl glycoside.

Scheme 5

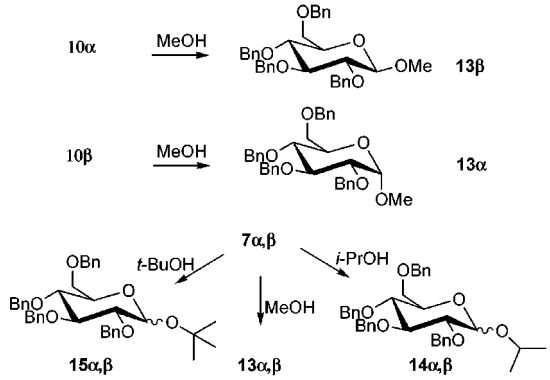


Table 2. Results from Solvolysis Experiments

entry	DISAL (α/β)	acceptor	product	yield[a] (%) (α/β)
1	**7α,*β*** (8.4:1)	MeOH[b]	**13α,*β***	98 (1:6.1)
2	**7α,*β*** (1:14.1)	MeOH[b]	**13α,*β***	98 (12.3:1)
3	**10α**	MeOH[c]	**13*β***	98
4	**10*β***	MeOH[c]	**13α**	98
5	**7α,*β*** (8.4:1)	*i*-PrOH[d]	**14α,*β***	97 (1.7:1)
6	**7α,*β*** (1:14.1)	*i*-PrOH[d]	**14α,*β***	98 (12.7:1)

[a] RP-HPLC (215 nm). [b] 30 °C for 6 h. [c] 25 °C for 2 h. [d] 30 °C for 16 h + 40 °C for 24 h.

Finally, the ortho donor derived from 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose[21] (**11**) was synthesized from **4** via the DMAP protocol and isolated in 75% yield as the pure α-anomer (**12**α).[22,23]

The selective synthesis of **7**α or **7***β* was also carried out. Tetrabenzylated glucose **2** was recrystallized twice form ethyl acetate to yield the pure α-anomer,[24] which was reacted with **4** under the DMAP protocol. This yielded donor **7**α (α/β 8.4:1) in the same yield as before (89%, entry 2); however, the presence of some β-glycoside indicated that even in fast reactions some anomerization of 1-OH occurred prior to formation of the aryl glycoside. To form **7***β* selectively, **4** was added slowly to a stirred solution of **2** (α/β 4:1) and DMP, in what amounts to a dynamic kinetic resolution. After isolation, 78% of donor **7***β* was obtained with only a minor amount of the α-anomer (α/β 1:14.1, entry 7). These results are summarized in Table 1. It should be emphasized that DISAL donors do *not* anomerize under the conditions used for their synthesis, i.e., in nonpolar solvents.

Solvolysis Experiments. In a first test of their potential as glycosyl donors, aryl glycoside **7**α,*β* was treated with simple alcohols under solvolytic conditions (Scheme 5, Table 2). Thus, treatment of **7**α (α/β 8.4:1) with methanol gave the methyl β-D-glucoside **13***β* (α/β 1:6.1). Similarly, **7***β* (α/β 1:14.1) with methanol gave the

(16) Goldstein, H.; Giddey, A. *Helv. Chim. Acta* **1954**, *37*, 1121−1125.

(17) Nielsen, A. T.; Chafin, A. P.; Christian, S. L. *J. Org. Chem.* **1984**, *49*, 4575−4580.

(18) This also removed the slight excess of aryl fluoride (1.2 equiv), presumably through formation of an ionic compound by substitution of the fluoride by the heterocyclic nitrogen of DMAP. This highly colored compound was *not* a reaction intermediate as addition of **2** to a preformed mixture of **4** and DMAP yielded no aryl glycoside.

(19) With respect to the carbohydrate, this reaction is an anomeric *O*-arylation in which the equatorial (β) anomeric oxide oxygen is likely to be more reactive than the axial (α) (see ref 4b). The DMP-promoted arylation of 1-OH derivative **2** thus seems to form the kinetic product by anomeric *O*-arylation of the more reactive equatorial (β) oxide oxygen.

(20) Whereas the anomers of benzyl-protected **7**α,*β* proved difficult to separate, the analogous benzoyl protected anomers **9**α,*β* were easily separated by chromatography on silica gel.

(21) Koto, S.; Morishima, N.; Miyata, Y.; Zen, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2639−2640

(22) Heteronuclear nondecoupled NMR showed $^1J_{C1,\,H1} = 178.1$ Hz indicating α-configuration.

(23) In the synthesis of a related aryl glycoside, the DMP promoted reaction between **11** and an aryl fluoride gave predominantly the β-mannoside, similar to the reaction of **2** to give β-glucoside **7***β*: Laursen, J. B.; Petersen, L.; Jensen, K. J. *Org. Lett.* **2001**, *2*, 687−690.

(24) Oscarson, S.; Sehgelmeble, F. W. *J. Am. Chem. Soc.* **2000**, *122*, 8869−8872.

Table 3. Model Glycosylation of Cyclohexanol, Solvent Evaluation[a]

entry	DISAL donor (α/β)	cyclohexanol (equiv)	additives (equiv)	solvent	yield[b] of **16** (%) (α/β)
1	**7** (2.1:1)	8	Et_3N (6)	DMA	41 (2.2:1)
2	**7** (2.1:1)	8	Et_3N (6)	NMP	71 (2.4:1)
3	**7** (2.1:1)	5	2,6-lutidine (5), 4 Å sieves	NMP	71 (2.4:1)
4	**7** (2.1:1)	5		NMP/CH_3CN	80 (2.1:1)
5	**7** (1:9)	5		NMP/CH_3CN	80 (2.1:1)
6	**7** (1.6:1)	5		CH_3NO_2[c]	81 (3.4:1)
7	**7** (1.6:1)	5	Et_3N (6)	NMP/ CH_3NO_2	84 (1.9:1)
8	**7** (2.1:1)	5		THF[c,d]	78[e] (8.1:1)
9	**7** (1.6:1)	5		NMP/THF	73 (2.0:1)
10	**10**α	5		NMP	86 (2.1:1)

[a] Temperature 40 °C, time 17 h. [b] RP-HPLC (215 nm). [c] 60 °C. [d] 40 h. [e] Isolated yield.

methyl α-D-glucoside **13**α (α/β 12.3:1).[25] That the glycosylation proceeded with *inversion* was further demonstrated by treating pure **10**α and **10**β with methanol, which gave **13**β and **13**α, respectively. From **10**α 93% of pure **13**β was isolated. It is thus a *stereospecific* glycosylation. Furthermore, sterically hindered alcohols also reacted with **7**α,β. The isopropyl glucoside **14**α,β was thus formed in high yields (Table 2, entries 5 and 6) and with a high degree of inversion for **7**β whereas **7**α was less reactive and gave an α/β ratio of 1.7:1. Similarly, reaction of **7**β with sterically hindered *tert*-butyl alcohol proceeded smoothly to give 89% of **15**α,β, whereas **7**α did not react. The lack of inversion for reaction of **7**α with 2-propanol can be explained by in situ anomerization of DISAL donor **7**α prior to the slow glycosylation (Table 2, entry 5).

Optimization of Glycosylation Conditions. Next, we turned our attention to the glycosylation of cyclohexanol as a model substrate. The anomers of cyclohexyl glucoside **16**α,β can readily be separated by RP-HPLC. In initial studies, DMF caused total breakdown of glycosyl donor **7**. This has also been observed for a glycosyl bromide under Koenigs−Knorr glycosylation conditions.[26] Other solvents such as DMSO, acetone, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU), or *N*,*N*-diethylformamide were also not compatible with **7**. Ethyl acetate, dioxane, dimethoxyethane, dichloromethane, 1,2-dichloroethane, or toluene were tolerated but gave sluggish reactions. The best solvents proved to be *N*,*N*-dimethylacetamide (DMA), 1-methyl-2-pyrrolidinone (NMP), or mixtures of the latter with acetonitrile or nitromethane. Nitromethane[27] and acetonitrile in themselves were good solvents, but required somewhat higher reaction temperatures.

In the glycosylation of cyclohexanol (Table 3), NMP proved superior to DMA in the presence of triethylamine (Table 3, entries 1 and 2), whereas substitution of the base with 2,6-lutidine, addition of 4 Å molecular sieves, and use of argon atmosphere did not improve the yield (Table 3, entry 3). However, a solvent mixture of NMP and acetonitrile gave a higher yield (Table 3, entry 4). Interestingly, the α/β ratio in glycosyl donor **7** did *not* affect the yield or α/β ratio of product cyclohexyl glycoside **16**. In all cases, the α/β ratio was about 2:1 (Table 3, entries 4 and 5). Similarly, in nitromethane a high amount of **16**α was obtained, though a higher temperature was needed to drive the reaction to completion (Table 3, entry 6). A mixture of NMP and nitromethane gave the cleanest reaction and highest yield, with an α/β ratio of 2.1:1 (Table 3, entry 7). Use of THF as solvent gave incomplete conversion using the standard protocol, but using more forcing conditions, the product was isolated in 78% yield with even higher α-selectivity (Table 3, entry 8) than in nitromethane. Changing the solvent to NMP−THF again gave complete conversion and an α/β ratio of 2.1:1 (Table 3, entry 9). The para donor **10** showed similar glycosyl donor properties as **7**. For the glycosylation of cyclohexanol, NMP again gave the best results (Table 3, entry 10). For ease of comparison, reaction times were kept constant; however, in neat NMP glycosylations of cyclohexanol (5 equiv) with **7** or **10** were complete within 2 h at 40 °C as observed by the disappearance of the donor.

It thus appears that the determining factor for the reaction rate was the solvent effect. If the solvent had a sufficiently high polarity, such as NMP, the glycosylations occurred smoothly.

These experiments clearly demonstrated that aryl glycosides **7** and **10** were indeed glycosyl donors under neutral conditions. Nonnucleophilic bases (triethylamine, Hünig's base, 2,6-lutidine, etc.) were also tolerated under these reaction conditions but were not required to promote the reaction. The fact that glycosylations also occurred in the presence of bases indicated that the glycosylations were not autocatalytical promoted by the released, acidic methyl 2-hydroxy-3,5-dinitrobenzoate.

In a control experiment, 2,4-dinitrophenyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside, **1**, gave *no* reaction or even breakdown when treated with cyclohexanol (5 equiv) and 2,6-lutidine in NMP for 4 days at 40 °C,[28] thus confirming our initial hypothesis that more electron withdrawing groups were required on the leaving group.

A general tendency in the glycosylation with DISAL donors was that more hindered alcohols gave increasing

(25) From **7** (α/β 1:9) in CD_3OD-CH_3CN (1:5) 75% yield of deuterated methyl glycoside (α/β 5:1) was obtained. ^1H and ^{13}C NMR showed no trace of a putative OCH_3 aglycon clearly indicating that formation of the methyl glycoside was not due to transfer of the ester methoxide but due to an intermolecular attack by CD_3OD.

(26) Lloyd, P. F.; Roberts, G. P. *J. Chem. Soc.* **1963**, 2962−2971.

(27) An important issue was the potential deprotonation of nitromethane by bases stronger than 2,6-lutidine (e.g., triethylamine) to give a stabilized anion. This anion appeared to be able to cleave the aryl glucoside as reactions under these conditions gave **2** and a new aromatic compound, indicative of cleavage by nucleophilic aromatic substitution at the aryl leaving group via a Meisenheimer complex (for a review of Meisenheimer complexes see: Terrier, F. *Chem. Rev.* **1982**, *82*, 77−152). Thus, when nitromethane was used, a judicious choice of base was required. These observations are in agreement with literature reports describing the attack of morpholine on a peracetylated 2,4-dinitrophenyl glycoside to give *N*-(2,4-dinitrophenyl)morpholine (see: Lindberg, B. *Acta Chem. Scand.* **1950**, *4*, 49−51).

(28) The stability of the 2,4-dinitrophenyl β-D-glucoside **1** to ethanol is implicit in the procedure by van Boom, as the final products were recrystallized from ethanol (see ref 14).

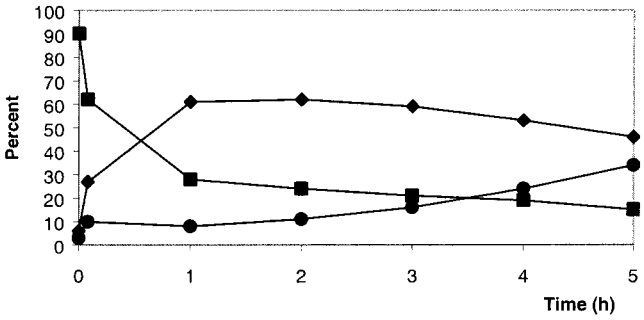


Figure 1. In situ anomerization experiment of **7***β* in NMP with methyl 2-hydroxy-3,5-dinitrobenzoate (1 equiv): **7**α (◆), **7***β* (■), hydrolysis (●).

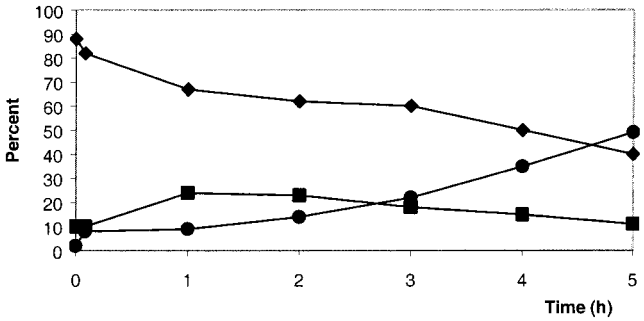
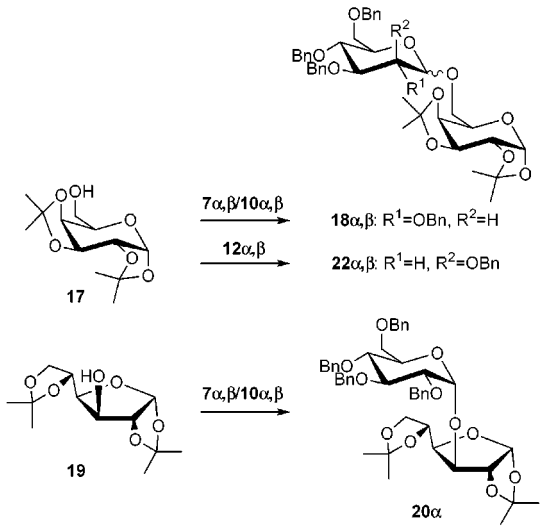


Figure 2. In situ anomerization experiment of **7**α in NMP with methyl 2-hydroxy-3,5-dinitrobenzoate (1 equiv): **7**α (◆), **7***β* (■), hydrolysis (●).

degrees of α-selectivity. We speculated that the lack of inversion in the glycosylation of alcohols other than methanol and the observed α-selectivity was due to in situ anomerization of the DISAL donor prior to slower reaction with the alcohol. To test this hypothesis, donor **7** was dissolved in NMP or CH_3NO_2 together with methyl 2-hydroxy-3,5-dinitrobenzoate[29] at 20 °C and the change in composition was monitored by HPLC. In NMP, donor **7***β* (α/*β* 1:14.1) anomerized within 2 h to give an α/*β* ratio of 3:1 (Figure 1). Similarly, donor **7***β* (α/*β* 8.4:1) anomerized within 1−2 h to give an α/*β* ratio of 3:1 (Figure 2). However, in CH_3NO_2 no anomerization was observed. Furthermore, *alkyl* glycosides were stable under these mild conditions and did not anomerize. It thus appears likely that the α-selectivity in the glycosylation of more hindered alcohols can be explained by an in situ anomerization of the DISAL donor prior to nucleophilic attack by the alcohol.

Disaccharide Synthesis. We then turned to the glycosylation of monosaccharide acceptors (Scheme 6). It was rewarding to observe that reaction of diisopropylidene protected galactose **17** carrying a *primary* hydroxy with glycosyl donor **7** gave the resultant disaccharide **18** in yields from 74 to 79% as α/*β* mixtures. Reactions were carried out as above in NMP either neat or in mixtures with acetonitrile or nitromethane (Table 4, entries 1−3) in the absence of added base and with an *excess of acceptor* (2 equiv). The yields could be further improved using an *excess of donor* (1.5 equiv) to 90% of disaccharide **18** after column chromatography (Table 4, entry 4). Turning to the diisopropylidene-protected glucose derivative **19**, which carries a free secondary hydroxy, disaccharide **20** was formed in somewhat lower yield (Table 4, entries 5−7). It proved advantageous to raise the reaction temperature to 60 °C as unreacted donor was still observed after 17 h at 40 °C. Interestingly, only the α-anomer of disaccharide **20** was obtained. The lower yield obtained when using DIEA as base (3 equiv) appeared to be due to increased formation of 2,3,4,6-tetra-*O*-benzyl-2-hydroxy-D-glucal, which was the major byproduct in all cases. The yield for the glycosylation of *sec*-alcohol **19** was improved to 74% by addition of a second 1.5 equiv of donor **7** after 6h (Table 4, entry 8). Tetrabenzyl glucose **2** which carries a free 1-OH was glycosylated to yield trehalose derivatives (Table 4, entry 9). By NMR, the products isolated were determined to be **21**α,α (18%) and **21**α,*β* (28%), but no *β*,*β* product could be observed.

Scheme 6



The para glycosyl donor **10** also proved effective in the glycosylation of monosaccharide **17** under the same conditions as for **7** to give the disaccharide **18** in 82% yield (Table 4, entry 10). Glycosylation of the secondary hydroxyl in **19** proceeded in 46% yield of the pure α-anomer **20**α (Table 4, entry 11). Mannose donor **12**α also proved to be an efficient donor under these conditions to produce the 1,6-linked disaccharide (**22**α,*β*) in good yields (Table 4, entries 12 and 13).

We also studied *benzoyl* protected aryl glycoside **9**α,*β* as a potential glycosyl donor, but in model studies this proved unsuccessful.[30]

The much increased reactivity of the DISAL glycosyl donors compared to the corresponding 2,4-dinitrophenyl glycosides can at least partially be attributed to the additional electron withdrawing substituent on the leaving group. Heterolysis of the glycosidic bond to form the oxonium phenoxide complex should be favored by polar

(29) Bartlett, P. D.; Trachtenberg, E. N. *J. Am. Chem. Soc.* **1958**, *80*, 5808−5810.

(30) The α-configured tetrabenzoate **9**α failed to react with neat methanol and application of more forcing conditions with cyclohexanol using the strong base 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (TBTMG) in neat NMP resulted only in breakdown of the donor and formation of 1,2,3,4,6-penta-*O*-benzoyl-*β*-D-glucopyranose. The aryl *β*-glycoside **9***β* gave the ortho ester when treated with cyclohexanol under basic conditions in THF. These results clearly show that *benzoyl* protection gives a significantly less reactive donor, with the α-anomer being practically unreactive and the *β*-anomer giving the ortho ester. This is due to intermolecular benzoyl transfer and the neighboring group participation from the 2-*O*-benzoyl moiety, respectively. Under the nonacidic conditions employed here the ortho ester cannot rearrange to the corresponding *β*-glycoside.

Table 4. Glycosylation of Monosaccharide Acceptors

entry	DISAL donor (α/β)	acceptor (equiv)	solvent	disaccharide	yield[a] (%) (α/β)
1	**7** (3.7:1)	**17** (2.0)	NMP/CH_3CN[b]	**18α,β**	74 (2.1:1)
2	**7** (3.7:1)	**17** (2.0)	NMP/CH_3NO_2[b]	**18α,β**	78 (2.1:1)
3	**7** (3.7:1)	**17** (2.0)	NMP[b]	**18α,β**	79 (2.3:1)
4	**7** (3.7:1)	**17** (0.67)	NMP[b]	**18α,β**	90 (2.4:1)
5	**7** (3.7:1)	**19** (0.67)	NMP[b]	**20α**	36
6	**7** (4.6:1)	**19** (0.67)	NMP[c]	**20α**	42
7	**7** (4.6:1)	**19** (0.67)	NMP[c,d]	**20α**	33
8	**7** (4.6:1)	**19** (0.33)	NMP[c]	**20α**	74
9	**7** (3.7:1)	**2** (0.67)	NMP[b]	**21**	18 (α,α), 28 (α,β)
10	**10** (4.1:1)	**17** (0.67)	NMP[b]	**18α,β**	82 (2.3:1)
11	**10** (4.1:1)	**19** (0.67)	NMP[b]	**20α**	46
12	**12α**	**17** (0.67)	NMP[b]	**22α,β**	78 (1.4:1)
13	**12α**	**17** (0.67)	NMP[c]	**22α,β**	84 (1.6:1)

[a] Isolated yields. [b] 40 °C for 17 h. [c] 60 °C for 17 h. [d] Et_3N was added (3 equiv).

solvents such as NMP, and this corresponds well with our findings. However, we speculated that an additional factor for the increased reactivity could be displacement of the phenoxide by nucleophilic attack of the aglycon carbonyl oxygen to form an oxonium ion. The reactive species thus formed could then react to form *O*-glycosides. However, as the glycosyl donor **10** with a para carboxy methyl moiety behaved much as the ortho analogue (**7**), this potential pathway seemed insignificant. Participation of the nucleophilic solvent by interception of reactive intermediates or attack by the solvent on the donor to form other reactive species is another potential pathway.

Conclusions

A new type of glycosyl donors was synthesized in high yields and with good control of the α/β ratio. Benzyl-protected (i.e., "armed") aryl glycosides **7**, **10**, and **12** were efficient glycosyl donors for *O*-glycosylation under neutral or mild basic conditions. Glycosylation of methanol under solvolytic conditions was stereospecific with inversion of anomeric configuration, whereas with sterically more demanding alcohols, α-selectivity was observed, most likely by in situ anomerization of the DISAL donor. DISAL donors were shown to undergo in situ anomerization under the reaction conditions. Glycosylations of monosaccharides and cyclohexanol proceeded in high yields and with α-selectivity in various solvents with NMP as the solvent of choice. The exclusive formation of α-linked disaccharides in glycosylation of *sec*-alcohol **19** amounts to a dynamic kinetic resolution. The 'normal' solvent effects used to direct the α/β ratio in Lewis acid promoted glycosylations, were not observed here. These donors are the first members in a new class of glycosyl donors, which are stable upon storage, yet do not require activation by a Lewis acid for efficient glycosylations. Compared to glycosyl iodides, the DISAL glycosyl donors have distinct advantages as they are stable on storage for a prolonged period, yet appear to be more reactive. Furthermore, the phenolic leaving group lends itself to further "fine-tuning" of reactivity of the glycosyl donor. Finally, aryl fluoride precursors were easily synthesized in large quantities from inexpensive starting materials.

Experimental Section

General Procedures. 2,3,4,6-Tetra-*O*-benzyl-D-glucose was purchased from Pfanstiehl (Cheshire, U.K.) and CMS Chemicals Ltd (Oxford, U.K.); the anomeric distribution was determined from the intensity of the anomeric carbons in ^{13}C NMR. 2-Fluorobenzoic acid and 4-fluorobenzoic acid were obtained from Fluka (Sigma-Aldrich Denmark). 1,4-Dimethylpiperazine was fractionally distilled and stored over 4 Å molecular sieves. Melting points were uncorrected. All solvents were distilled and/or stored over 3 or 4 Å molecular sieves as appropriate. ^1H NMR spectra were recorded on either a Varian Mercury 300 operating at 300.06 MHz equipped with a 4-nuclei probe or a Varian Unity Inova 500 operating at 499.87 MHz equipped with a *z*- (single axis) PFG inverse detection C-H-P probe. ^{13}C NMR were recorded on a Varian Mercury 300 operating at 75.46 MHz with relaxation delays of up to 30 s to detect all signals arising from quaternary carbons. Chemical shift (δ) values are in ppm, coupling constants (J) are in Hz. All assignments were supported by 2D homonuclear chemical-shift correlation spectroscopy (gCOSY) and heteronuclear single quantum correlated spectroscopy (gHSQC) experiments. Thin-layer chromatography was performed on Merck silica gel 60 F_{254} plates and spots were visualized by UV light at 254 nm and/or spraying with 10% aqueous H_2SO_4 followed by heating. Vacuum liquid chromatography was carried out on Merck silica gel 60H. HPLC analyses were carried out on a Waters system (600 control unit, 996 photodiode array (PDA) detector, 717 Plus autosampler, Millenium32 control software) on a Waters Nova-Pak C18 column (3.9 × 5.0 mm cartridge; 4 μm particle size) using a linear gradient of 0.1% aqueous TFA (A) and 0.1% TFA in CH_3CN (B): 0 min: 0% B, 2 min: 0% B, 5 min: 50% B, 12 min: 95% B, 13 min: 95% B, 13.5 min: 0% B, 20 min: 0% B. Monitoring was from 200 to 400 nm, integrations were performed at 215 and 265 nm, and individual peaks were analyzed by their UV spectra. The purity of compounds was determined from integrations at 215 nm. Prep. HPLC was performed on a Waters system with a Delta 600 pump and a 996 PDA detector using a stack of three 40 × 100 mm Prep Nova-Pak HR C18 6 μm 60 Å units eluting with gradients of H_2O-CH_3CN. MS analyses were performed on a Micromass LCT mass spectrometer.

2-Fluoro-3,5-dinitrobenzoic Acid (3). To 65% fuming sulfuric acid (160 mL) in a 500 mL conical flask cooled on an ice bath was slowly added fuming nitric acid (80 mL) over 15 min. The ice-cold and now clear mixture was stirred effectively while 2-fluorobenzoic acid (14.01 g, 0.10 mol) was suspended herein in small portions over 5 min. The temperature was slowly raised to 90 °C by means of an oil bath and the reaction mixture again became clear. The mixture was kept at 90 °C for 1 h, during which time the reaction mixture showed slight foaming and evolution of brown gas. When the reaction subsided, a drop was withdrawn and distributed between ethyl acetate and water. TLC of the organic phase showed only one compound (R_f 0.10−0.15; EtOAc−AcOH, 100:1). The reaction mixture was poured onto crushed ice (1 L), diluted to approximately 1.5 L with water, and extracted with ethyl acetate (4 × 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to yield slightly off-white crystals (19.22 g, 84%). Mp: 193−196 °C (lit.[16] mp 200 °C). Purity: >99%. Anal. Calcd for $C_7H_3FN_2O_6$: C, 36.54; H, 1.31; N, 12.17. Found: C, 36.64; H, 0.88; N, 12.18. ^1H NMR (500 MHz, acetone-d_6): δ = 12.3 (br s, 1H, COOH), 9.14 (dd, 1H, $^4J_{H,F}$ =

5.8 Hz, $^4J_{H,H}$ = 3.1 Hz), 9.05 (dd, 1H, $^4J_{H,F}$ = 5.5 Hz, $^4J_{H,H}$ = 3.1 Hz). ^{13}C NMR (75 MHz, acetone-d_6): δ = 161.5 (d, $^3J_{C,F}$ = 3.1 Hz, COOH), 158.1 (d, $^1J_{C,F}$ = 283.3 Hz), 143.2, 139.3, 131.9 (d, $^3J_{C,F}$ = 3.6 Hz), 125.5, 123.4 (d, $^2J_{C,F}$ = 12.5 Hz).

Methyl 2-Fluoro-3,5-dinitrobenzoate (4). Benzoic acid derivative **3** (6.90 g, 30 mmol) was suspended in CH_2Cl_2 (50 mL), and DMF (0.050 mL) and oxalyl chloride (2.83 mL, 33 mmol) were added. After being stirred at room temperature for 1 h, the reaction had become a clear solution and a small sample was withdrawn and diluted with dry methanol; TLC showed complete conversion to the methyl ester (R_f 0.84; EtOAc−AcOH, 100:1). Dry methanol (6 mL) was added, and the reaction mixture was stirred for 30 min. Elution through a VLC column (30 × 30 mm) with CH_2Cl_2 (100 mL) gave after evaporation of the relevant fractions an oil that was redissolved in pentane (50 mL) and CH_2Cl_2 (50 mL). The flask was placed in a freezer, and when the crystallization had set in, the solvent was partially evaporated, hexane (50 mL) was added, and the procedure was repeated twice. Filtration of the suspension gave a solid that after washing (hexane, 2 × 30 mL) and drying yielded crystals (7.10 g, 97%). Mp: 73−74 °C. Purity: >99%. Anal. Calcd for $C_8H_5FN_2O_6$: C, 39.36; H, 2.06; N, 11.47. Found: C, 39.53; H, 1.80; N, 11.47. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.05−9.00 (m, 2H), 4.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.3 (d, $^3J_{C,F}$ = 4.2 Hz, COOMe), 158.0 (d, $^1J_{C,F}$ = 287.4 Hz), 143.0, 139.1, 132.0 (d, $^3J_{C,F}$ = 6.3 Hz), 125.3, 123.3 (d, $^2J_{C,F}$ = 11.9 Hz), 54.0 (Me).

4-Fluoro-3,5-dinitrobenzoic Acid (5). Prepared from 4-fluorobenzoic acid by a literature procedure[17] (76% yield). Mp: 230−232 °C (lit.[17] mp 235−237 °C). Purity: 98%. ^{1}H NMR (300 MHz, acetone-d_6): δ = 11.0 (br. s., 1H, COOH), 8.97 (d, 2H, $^4J_{H,F}$ = 6.6 Hz). ^{13}C NMR (75 MHz, acetone-d_6): δ = 162.9 (d, $^5J_{C,F}$ = 1.3 Hz, COOH), 152.1 (d, $^1J_{C,F}$ = 283.9 Hz), 139.4, 131.7 (d, $^3J_{C,F}$ = 1.1 Hz), 127.5.

Methyl 4-Fluoro-3,5-dinitrobenzoate (6). Benzoic acid derivative **5** (1.15 g, 5 mmol) was dissolved in THF (5 mL), followed by addition of DMF (5 μL) and oxalyl chloride (0.52 mL, 6 mmol). After being stirred for 15 min, the mixture was added to a stirred solution of methanol (1.5 mL) in hexane (50 mL) cooled on an ice bath. After 5 min, the solid was collected by filtration, washed (hexane, 2 × 10 mL), and dried under vacuum (0.73 g; 60%). Mp: 96−97 °C (lit.[31] mp 93.5 °C). Purity: 98%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.93 (d, 2H, $^4J_{H,F}$ = 6.1 Hz), 4.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4 (d, $^5J_{C,F}$ = 1.1 Hz, COOMe), 151.9 (d, $^1J_{C,F}$ = 288.5 Hz), 139.2, 131.7 (d, $^3J_{C,F}$ = 1.1 Hz), 127.3 (d, $^2J_{C,F}$ = 5.7 Hz), 53.9 (Me).

2,3,4,6-Tetra-*O*-benzoyl-D-glucopyranose (8). 1,2,3,4,6-Penta-*O*-benzoyl-D-glucopyranoside[32] (2.80 g, 4.0 mmol; α/β = 1:6) was dissolved in DMF (25 mL), and upon cooling to 3 °C, hydrazinium acetate (1.11 g, 12.0 mmol; 3 equiv) was added. After being stirred for 17 h, the mixture was diluted with ethyl acetate (60 mL) and washed with brine (2 × 30 mL), aqueous HCl (1M, 2 × 30 mL), and brine (2 × 30 mL). The organic phase was dried ($MgSO_4$), concentrated, and dried under high vacuum to give a solid (2.39 g, 100%) containing the title compound (α/β = 4.1:1) in 97% purity. The purity was increased by dissolving the solid in diethyl ether (25 mL) and filtering through 5 mm of silica gel using additional diethyl ether (30 mL). Heptane (80 mL) was added to the filtrate, and the mixture was left in a beaker overnight allowing the diethyl ether to evaporate. The solid was collected by filtration, washed with heptane (2 × 15 mL), and air dried. This yielded a pure product (1.57 g; 82%) as an anomeric mixture (α/β 4:1). ^{1}H NMR data for the α-anomer was identical to literature values.[33]

General Method for Preparation of Glycosyl Donors. In a dried flask, protected carbohydrate derivatives **2**, **8**, or **11**, Li_2CO_3 (2 equiv), and aryl fluoride **4** or **6** (1.2 equiv) were suspended in CH_2Cl_2 (1−2 mL/mmol; dried over 4 Å molecular sieves). Reactions proceeded in the presence of either DMAP or DMP. (1) For reactions with DMAP catalysis, DMAP (0.3 equiv) was dissolved in CH_2Cl_2 (0.5 mL) and added to the suspension in five portions over 20 min. After addition of the first portion, the color changed from slightly discolored to strongly yellow/brown. After stirring for an additional 10 min, products were isolated by VLC chromatography (30 × 80 mm; CH_2Cl_2−Et_2O 1:0 → 19:1). Concentration of appropriate fractions gave the yields in Table 1. (2) For reactions with 1,4-dimethylpiperazine catalysis, DMP (distilled and stored over 4 Å molecular sieves; 0.5 equiv) was added and the mixture stirred for 2−3 h. Remaining aryl fluoride was then quenched by addition of DMAP[18] (0.3 equiv). After the mixture was stirred for an additional 15 min, isolation as above gave yields listed in Table 1.

General Method for Solvolysis, Model Glycosylations, and HPLC Analysis (Tables 2 and 3). The initial evaluation of solvents for the glycosylation was performed by reacting glycosyl donors **7**α,β or **10**α,β (typically 0.02 mmol) with cyclohexanol and either triethylamine, 2,6-lutidine, or in the absence of base in the solvent or neat alcohol as indicated (400−600 μL) on an Eppendorf Thermomixer 5436 (combined heater/shaker). After the mixture was shaken for the indicated period, a sample (10−40 μL) was diluted in acetonitrile (0.70−1.00 mL) and analyzed by analytical RP-HPLC. Reported yields are based on integrated areas.

General Method for Glycosylations and Isolation (Tables 4). The glycosyl donor (**7**α,β, **9**α,β, **10**α,β, or **12**α,β) and acceptor (cyclohexanol, **17**, or **19**) were placed in a 1.5 mL Eppendorf tube, the indicated solvent (1 mL) added, and the mixture shaken on an Eppendorf Thermomixer 5436 for the time and temperature stated. After the indicated reaction time, reaction mixtures with volatile solvents were concentrated and products isolated by VLC chromatography, whereas NMP-containing reactions were extracted prior to chromatography. Reaction mixtures were diluted with ethyl acetate (30 mL) and washed with brine (2 × 20 mL), aqueous NaOH (0.5 M; 2 × 20 mL), and brine (2 × 20 mL). The organic phases were dried (Na_2SO_4) and concentrated, the residues were dissolved in a small volume of CH_2Cl_2, and products were isolated by VLC chromatography (20 × 80 mm, gradient of toluene, 20 mL, ethyl acetate−toluene 1:60, 20 mL, 1:20, 40 mL, and 1:10, 100 mL). Reactions in NMP were injected directly into the preparative HPLC. Appropriate fractions were concentrated in vacuo at 30 °C, traces of toluene were removed by coevaporation twice with CH_2Cl_2, and the product was dried under high vacuum to give the isolated yields in Table 4.

Physical Data for Glycosyl Donors 7α,β, 9α,β, 10α,β, and 12α. 2,4-Dinitro-6-(methoxy carbonyl)phenyl 2,3,4,6,-tetra-*O*-benzyl-α-D-glucopyranoside (**7**α). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.66 (d, 1H, $^4J_{H,H}$ = 2.9 Hz), 8.54 (d, 1H, $^4J_{H,H}$ = 2.9 Hz), 7.40−6.96 (m, 20H), 5.42 (d, 1H, $^3J_{1,2}$ = 3.4 Hz, H-1α), 4.91 (dd, 2H, $^2J_{gem}$ = 16.2 and 10.7 Hz, Bn), 4.86 (d, 1H, $^2J_{gem}$ = 11.1 Hz, Bn), 4.64 (d, 1H, $^2J_{gem}$ = 11.5 Hz, Bn), 4.55 (dd, 2H, $^2J_{gem}$ = 11.1 and 3.4 Hz, Bn), 4.47 (d, 1H, $^2J_{gem}$ = 12.0 Hz, Bn), 4.34 (d, 1H, $^2J_{gem}$ = 11.5 Hz, Bn), 4.11 (t, 1H, ^3J = 9.4 Hz, H-3), 3.99 (ddd, 1H, $^3J_{4,5}$ = 9.4, $^3J_{5,6}$ = 3.4, $^3J_{5,6'}$ = 2.1 Hz, H-5), 3.90 (s, 3H, OMe), 3.74 (dd, 1H, $^2J_{gem}$ = 11.1 Hz, and $^3J_{5,6}$ = 3.4 Hz, H-6), 3.73 (t, 1H, ^3J = 9.4 Hz, H-4), 3.64 (dd, 1H, $^2J_{gem}$ = 11.1 Hz, $^3J_{5,6'}$ = 2.1 Hz, H-6′), 3.62 (dd, 1H, $^3J_{2,3}$ = 9.4, $^3J_{1,2}$ = 3.4 Hz, H-2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.9 (carbonyl), 154.4, 144.9, 141.9, 138.6, 138.3, 137.9, 137.1, 129.8, 128.8−127.6 (m; benzyl), 123.5, 104.4 (C-1α), 81.6, 81.1, 76.7, 76.1, 75.2, 74.5, 74.1, 73.7, 68.2, 53.6 (OMe); ESI (positive mode) of an anomeric mixture: *m*/*z* calcd for $C_{42}H_{42}N_2O_{13}$ (M + NH_4)$^+$ 782.3; found 782.3, 800.1 (M + H_2O + NH_4)$^+$. The title compound was stored as a foam at −10 °C.

2,4-Dinitro-6-(methoxycarbonyl)phenyl 2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranoside (7β). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.81 (d, 1H, ^4J = 2.7 Hz), 8.71 (d, 1H, ^4J = 2.7 Hz), 7.45−7.13 (m, 20H), 5.18 (d, 1H, $^3J_{1,2}$ = 7.0 Hz, H-1β), 5.03 (d, 1H, $^2J_{gem}$ =10.9 Hz), 4.96 (d, 1H, $^2J_{gem}$ = 11.1 Hz), 4.84−4.77 (m, 3H), 4.56 (d, 1H, $^2J_{gem}$ = 10.9 Hz), 4.50 (d, 1H,

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(32) Ness, R. K.; Hewitt, G.; Hudson, C. S. *J. Am. Chem. Soc.* **1950**, *72*, 2200−2205.
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$^2J_{gem}$ = 11.8 Hz), 4.39 (d, 1H, $^2J_{gem}$ = 11.9 Hz), 3.85 (s, 3H; OMe), 3.76 (dd, 1H, $^3J_{2,3}$ = 8.5, $^3J_{1,2}$ = 7.0 Hz, H-2), 3.71 (dd, 1H, ^3J = 8.8 Hz, H-3), 3.63 (dd, 1H, ^3J = 9.1 Hz, H-4), 3.56 (br. d, 2H, $^2J_{gem}$ = 4.5 Hz, 2 × H-6), 3.36 (dt, 1H, $^3J_{4,5}$ = 9.2, $^3J_{4,5}$ = 3.3 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.5 (carbonyl), 151.6, 146.7, 145.8, 143.2, 138.6, 138.2, 138.1, 138.1, 130.6, 129.3, 128.7−127.9 (m; benzyl), 123.0, 104.8 (C-1β), 84.5, 82.5, 77.5, 76.2, 75.9, 75.5, 75.4, 73.8, 69.0, 53.7 (OMe). The title compound was stored as a foam at −10 °C.

2,4-Dinitro-6-(methoxycarbonyl)phenyl 2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranoside (9α). Mp: 91−92 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.59 (d, 1H, ^4J = 2.8 Hz), 8.57 (d, 1H, ^4J = 2.8 Hz), 8.00−7.85 (m, 8H), 7.60−7.30 (m, 12H), 6.35 (t, 1H, ^3J = 9.8 Hz, H-3), 6.32 (d, 1H, $^3J_{1,2}$ = 3.7 Hz, H-1α), 5.73 (t, 1H, ^3J = 9.8 Hz, H-4), 5.55 (dd, 1H, $^3J_{2,3}$ = 9.8 Hz, $^3J_{1,2}$ = 3.7 Hz, H-2), 4.58−4.39 (m, 3H; H-5, 6, and 6′), 4.00 (s, 3H; OMe). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9, 165.8, 165.6, 165.4, 163.5, 151.4, 144.0, 141.7, 137.0, 134.0, 133.9, 133.6, 133.5, 130.3−128.6 (m), 127.4, 123.5, 99.0 (C-1α), 71.7, 71.3, 69.5, 68.6, 62.5, 54.1 (OMe). ESI (positive mode) of an anomeric mixture: *m*/*z* calcd for $C_{42}H_{34}N_2O_{17}$ $(M + NH_4)^+$ 838.2; found 837.8. The title compound was stored as an off-white solid at 5 °C.

2,4-Dinitro-6-(methoxycarbonyl)phenyl 2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranoside (9β). Mp: 97.5−100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.70 (d, 1H, ^4J = 2.9 Hz), 8.63 (d, 1H, ^4J = 2.9 Hz), 8.10−8.03 (m, 2H), 7.95−7.82 (m, 6H), 7.60−7.30 (m, 12H), 5.99 (t, 1H, ^3J = 9.6 Hz, H-3), 5.86 (dd, 1H, $^3J_{2,3}$ = 9.7 Hz, $^3J_{1,2}$ = 7.7 Hz, H-2), 5.67 (t, 1H, ^3J = 9.7 Hz, H-4), 5.66 (d, 1H, $^3J_{1,2}$ = 7.7 Hz, H-1β), 4.50−4.38 (m, 2H; H-6 and 6′), 4.15−4.07 (m, 1H; H-5), 3.80 (s, 3H; OMe). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9, 165.8, 165.2, 165.2, 162.9 (carbonyl), 150.8, 146.6, 143.7, 133.8, 133.6, 133.5, 130.9, 130.3−128.5 (m), 123.1, 102.4 (C-1β), 73.3, 72.6, 72.0, 69.5, 62.7, 53.5 (OMe). The title compound was stored as an off-white solid at 5 °C.

2,6-Dinitro-4-(methoxycarbonyl)phenyl 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranoside (10α). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.49 (s, 2H), 7.40−7.00 (m, 20H; benzyl), 5.28 (d, 1H, $^3J_{1,2}$ = 3.0 Hz, H-1α), 4.90 (2 × d, 2H, $^2J_{gem}$ = 11.1 Hz), 4.83 (d, 1H, $^2J_{gem}$ = 11.1 Hz), 4.65 (d, 1H, $^2J_{gem}$ = 11.9 Hz), 4.55 (2×d, 2H, $^2J_{gem}$ =11.1 Hz), 4.43 (2×d, 2H, $^2J_{gem}$ = 11.9 Hz), 4.09 (t, 1H, ^3J = 9.4 Hz, H-3), 4.01 (s, 3H; OMe), 3.93 (ddd, 1H, $^3J_{4,5}$ = 9.4 Hz, $^3J_{5,6}$ = 3.0 Hz, $^3J_{5,6'}$ = 1.7 Hz, H-5), 3.75 (dd, 1H, $^2J_{gem}$ =11.1 Hz, $^3J_{5,6'}$ = 1.7 Hz, H-6′), 3.73 (t, 1H, ^3J = 9.4 Hz, H-4), 3.63 (dd, 1H, $^2J_{gem}$ = 11.1 Hz, $^3J_{5,6}$ = 3.0 Hz, H-6), 3.60 (dd, 1H, $^3J_{2,3}$ = 9.4 Hz, $^3J_{1,2}$ = 3.0 Hz, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.1 (carbonyl), 147.3, 145.1, 138.7, 138.3, 138.0, 137.3, 129.5, 129.0−127.0 (m; benzyl), 125.5, 104.8 (C-1α), 81.5, 80.2, 76.6, 76.0, 75.2, 74.5, 74.4, 73.7, 68.1, 53.4 (OMe). ESI (positive mode) of an anomeric mixture: *m*/*z* calcd for $C_{42}H_{42}N_2O_{13}$ $(M + NH_4)^+$ 782.3, found 782.0, 787.0 $(M + Na)^+$. The title compound was stored as a foam at −10 °C.

2,6-Dinitro-4-(methoxycarbonyl)phenyl 2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranoside (10β). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.60 (s, 2H), 7.45−7.10 (m, 20H; benzyl), 5.18 (d, 1H, $^3J_{1,2}$ = 7.7 Hz, H-1β), 5.00 (d, 1H, $^2J_{gem}$ = 10.7 Hz), 4.93 (d, 1H, $^2J_{gem}$ = 11.1 Hz), 4.79 (dd, 2H, $^2J_{gem}$ = 10.7 Hz, $^2J_{gem}$ = 2.1 Hz), 4.77 (d, 1H, $^2J_{gem}$ = 10.7 Hz), 4.54 (d, 1H, $^2J_{gem}$ = 11.1 Hz), 4.47 (d, 1H, $^2J_{gem}$ = 11.9 Hz), 4.41 (d, 1H, $^2J_{gem}$ = 11.9 Hz), 4.02 (s, 3H; OMe), 3.78 (dd, 1H, $^3J_{2,3}$ = 9.0 Hz, $^3J_{1,2}$ = 7.7 Hz, H-2), 3.70 (t, 1H, ^3J = 9.0 Hz, H-3), 3.62 (dd, 1H, $^3J_{4,5}$ = 9.8 Hz, $^3J_{3,4}$ = 9.0 Hz, H-4), 3.57 (br. d, 2H, ^3J = 3.4 Hz, 2×H-6), 3.40 (dt, 1H, $^3J_{4,5}$ = 9.8 Hz, $^3J_{5,6}$ = 3.4 Hz, H-5). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.1 (carbonyl), 146.4, 144.6, 138.6, 138.2, 138.1, 138.0, 129.1, 128.7−127.7 (m; benzyl), 127.2, 104.6 (C-1β), 84.3, 82.3, 77.3, 76.1, 75.9, 75.5, 75.3, 73.7, 68.9, 53.5 (OMe). The title compound was stored as a foam at −10 °C.

2,4-Dinitro-6-(methoxy arbonyl)phenyl 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranoside (12α). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.80 (d, 1H, ^3J = 2.9 Hz, Ar-H), 8.68 (d, 1H, ^3J = 2.9 Hz, Ar-H), 7.44−7.15 (m, 20H, benzyl), 5.63 (d, 1H, $^3J_{1,2}$ = 2.0 Hz, H-1), 4.86−4.36 (m, 8H, benzyl methylene), 4.32 (dd, 1H, $^3J_{2,3}$ = 3.0 Hz, $^3J_{2,1}$ = 2.0 Hz, H-2), 4.13 (dd, 1H, $^3J_{3,4}$ = 9.2 Hz, $^3J_{4,5}$ = 9.4 Hz, H-4), 4.00 (dd, 1H, $^3J_{2,3}$ = 3.0 Hz, $^3J_{3,4}$ = 9.2 Hz, H-3), 3.90 (s, 3H, OMe), 3.72 (dd, 1H, $^3J_{gem}$ = 10.8 Hz, $^3J_{5,6}$ = 4.0 Hz, H-6), 3.63 (ddd, 1H, $^3J_{4,5}$ = 9.4 Hz, $^3J_{5,6}$ = 4.0 Hz, $^3J_{5,6'}$ = 1.7 Hz, H-5), 3.53 (dd, 1H, $^3J_{gem}$ = 10.8 Hz, $^3J_{5,6'}$ = 1.7 Hz, H-6′). Heteronuclear coupling constant: $^2J_{C1,H1}$ = 178.1 (α). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.1 (carbonyl), 153.7, 145.5, 142.1, 138.5, 138.5, 138.3, 129.8, 128.6−127.7 (m; benzyl), 123.5, 104.9 (C-1), 79.2, 75.6, 75.2, 75.1, 73.9, 73.6, 73.3, 72.8, 68.8, 53.7. ESI (positive mode) *m*/*z* calcd for $C_{42}H_{42}N_2O_{13}$ $(M + NH_4)^+$ 782.2687; found 782.0, 800.1 $(M + H_2O + NH_4)^+$. The title compound was stored as a foam at −10 °C.

Physical Data for Glycosides 13α,β, 14α,β, 15α,β, 16α,β, 18α,β, 20α, and 22α,β: Methyl 2,3,4,6-Tetra-*O*-benzyl-α,β-D-glucopyranoside (13 α,β). Observed data were identical to literature values.[34]

Isopropyl 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranoside (14α,β). Observed data were identical to literature values.[35]

***tert*-Butyl 2,3,4,6-Tetra-*O*-benzyl-α,β-D-glucopyranoside (15 α,β).** Observed data were identical to literature values.[36]

Cyclohexyl 2,3,4,6-Tetra-*O*-benzyl-α,β-D-glucopyranoside (16α,β). Observed data were identical to literature values.[37]

Disaccharides 18α,β, 20α, and 22α,β. Observed data were identical to literature values.[38]

Octa-*O*-benzyl-α,α-trehalose 21α,α. Selected data. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.28 (d, 1H, $^3J_{1,2}$ = 3.7 Hz, H-1α). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 94.6 ppm. HSQC showed strong coupling between these signals. ESI (positive mode): *m*/*z* calcd for $C_{68}H_{71}O_{11}$ $(M + H)^+$ 1063.5, found 1063.4; *m*/*z* calcd for $C_{68}H_{72}O_{12}$ $(M + NH_4)^+$ 1080.5, found 1080.5.

Octa-*O*-benzyl-α,β-trehalose 21α,β. Selected data. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.17 (d, 1H, $^3J_{1,2}$ = 3.4 Hz, H-1α), 4.59 (d, 1H, $^3J_{1,2}$ = 7.7 Hz, H-1′β). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 104.4 (C-1′β), 99.7 (C-1α). ESI (positive mode): *m*/*z* calcd for $C_{68}H_{71}O_{11}$ $(M + H)^+$ 1063.5, found 1063.4; *m*/*z* calcd for $C_{68}H_{72}O_{12}$ $(M + NH_4)^+$ 1080.5, found 1080.5.

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Supporting Information Available: Detailed discussion of the choice of bases and reaction kinetics for the formation of glycosyl donors. This material is available free of charge via the Internet at http://pubs.acs.org.

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