A Comparative Study of the Influence of Protecting Groups on the Reactivity of *chiro*-Inositol Glycosyl Acceptors

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Abstract: The influence of protecting groups on the reactivity of glycosyl acceptors has been investigated through a series of competitive glycosylation experiments using differently substituted C2 symmetric D-*chiro*-inositol derivatives. It has been shown that, for a given glycosyl donor, the protective group pattern effectively modulates the reactivity of these derivatives in the glycosylation reaction.

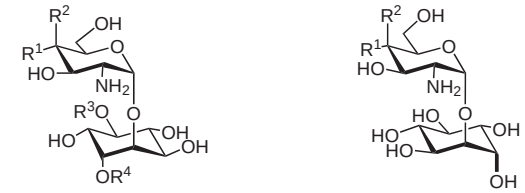
Key words: glycosylation, reactivity, stereoselectivity

Oligosaccharides play an important role in many biological processes.[2] In spite of recent progress in glycosylation methods and strategies, oligosaccharide synthesis still requires considerable effort. The preparation and the coupling of building blocks for oligosaccharide synthesis often involve extensive protecting group manipulation. The past two decades have witnessed an increasing understanding of protecting group effects on the anomeric reactivity of glycosyl donors.[3] As a consequence of the armed–disarmed concept, the possibility of tuning the reactivity of glycosyl donors through protecting group manipulation has culminated with the 'iterative one-pot synthesis of oligosaccharides'[4,5] which has greatly simplified the preparation of complex oligosaccharides.[6]

Nevertheless, much less attention has been paid to the reactivity of glycosyl acceptors. The nature of the protecting groups of glycosyl acceptors have been often proposed as a cause of glycosylation failure.[3a,7] However, the influence of protecting groups on acceptor reactivity has not been systematically evaluated. It is generally agreed[3] that the electron-donating or the electron-withdrawing effect of protecting groups may, respectively, activate or deactivate glycosyl acceptors. This effect has been long ago described[8] and more recently used to develop a chemoselective glycosylation strategy.[9] In spite of this, no attempt has been made to asses the effect of protecting groups on the relative reactivity of glycosyl acceptors through competitive experiments with the only exception of a recent study on the acceptor reactivity of the 4-hydroxy group of *N*-acetyl-, *N*-phthalimido-, and 2-azido-2-deoxy-D-glucosamine derivatives.[10]

In the frame of an ongoing program on the synthesis of inositolphosphoglycans as putative mediators in the insulin signalling process, we have prepared a variety of inositol containing oligosaccharides.[11–14] This work has involved extensive studies on the glycosylation of *myo*[11] and *chiro*[12–14] inositol derivatives with 2-azido-2-deoxy-D-gluco and D-galactopyranosyl trichloroacetimidates. This has offered a good opportunity to gain insight into the influence of the nature of glycosyl acceptors on the glycosylation reaction. We recently reported on the influence of steric and conformational features of the acceptor on the stereoselectivity of glycosylations.[14] We now present some observations on the influence of the protecting group pattern on the reactivity of glycosyl acceptors in the coupling reaction.

In the course of our studies on putative insulin mediators, the synthesis of molecules containing the structural motif 2-amino-2-deoxy-D-gluco and D-galactosaminyl-α(1→1) D- and L-*chiro*-inositols **I** and **II** (Figure 1) was carried out using a variety of D- and L-*chiro* inositol derivatives and D-gluco and galactopyranosyl trichloroacetimidates with different protecting group patterns.



R^1 = H, R^2 = OH or R^1 = OH, R^2 = H;
R^3 = H or Me, R^4 = H
R^1 = OH, R^2 = H; R^3 = H R^4 = PO_3H^-

R^1 = H, R^2 = OH
R^1 = OH, R^2 = H

Figure 1 2-Amino-2-deoxy-D-gluco and galactosaminyl-[α(1→1] D- and L-*chiro*-inositols **I** and **II**

It was found that small changes in the protecting group pattern of the glycosyl acceptor had a dramatic effect on the glycosylation yield under similar experimental conditions. While glycosylation of 6-*O*-allyl-2,3,4,5-tetra-*O*-benzyl-L-*chiro*-inositol (**1**) with 2-azido-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate (**2**)[15] afforded a mixture of α-(**3**) and β-(**4**) pseudodisaccharides in 80% overall yield,[11d] the reaction of **2** with 6-*O*-acetyl-2,3,4,5-tetra-*O*-benzyl-L-*chiro*-inositol (**5**)[16] gave a mixture of α-(**6**) and β-(**7**) anomers in 25% overall yield[17] (Scheme 1).

The low yield in the reaction of acceptor **5** clearly seemed to be a consequence of a lower reactivity caused by the

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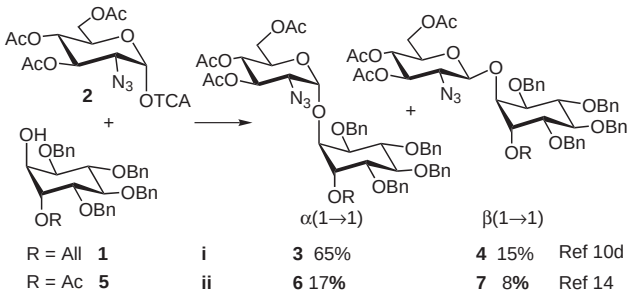
presence of an electron-withdrawing substituent at C6. In order to gain some further insight into the factors governing glycosyl acceptor reactivity, we now have performed a comparative study of the behavior of the C2 symmetric D-*chiro*-inositol acceptors **8**–**11** (Figure 2), with electron-donating and electron-withdrawing protecting groups in the glycosylation with 2-azido-2-deoxy-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate (**12**, Table 1).



Scheme 1 Glycosylation reactions of trichloroacetimidate **2** and L-*chiro*-inositols acceptors **1** and **5**. *Reagents and conditions*: i) **2** (3.0 equiv), **1** (1.0 equiv), TMSOTf (0.1 equiv), CH_2Cl_2, r.t.; ii) **2** (1.0 equiv), **5** (1.0 equiv), TMSOTf (0.04 equiv), CH_2Cl_2, r.t.

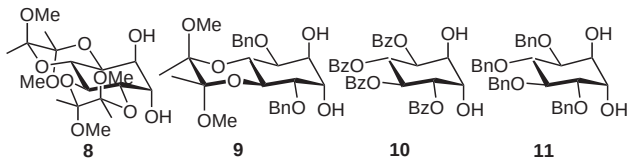
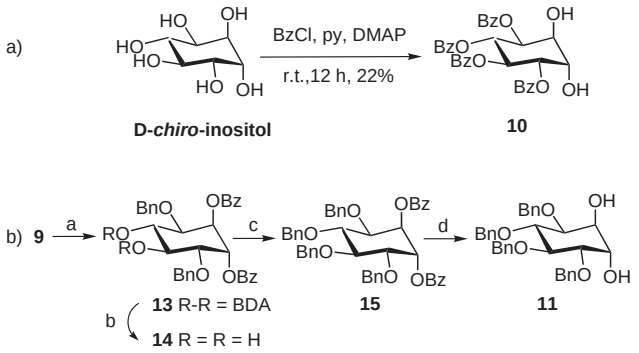


Figure 2 D-*Chiro*-inositols acceptors **8**–**11**

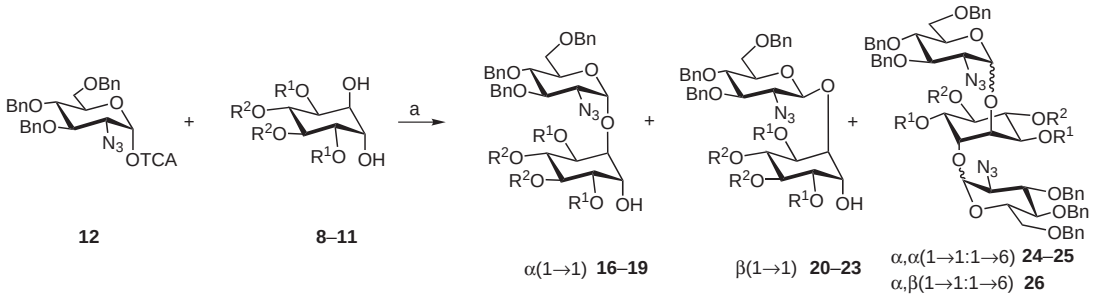
We had already prepared diols **8** and **9** and had investigated their glycosylation with **12**.[13a] Diol **10** was obtained by partial benzoylation of D-*chiro*-inositol in 22% yield (Scheme 2, a). By contrast, partial benzylation of D-*chiro*-inositol was not a practical route for the preparation of diol **11**. This diol was prepared from **9** through the sequence **13**→**14**→**15** (Scheme 2, b).[18]



Scheme 2 Preparation of D-*chiro*-inositol acceptors **10** and **11**. *Reagents and conditions*: a) BzCl, pyridine, DMAP, r.t.,12 h, 100%; b) TFA–H_2O 9:1, r.t., 86%; c) BnTCA, TfOH cat., C_6H_{12}–CH_2H_2 2:1; r.t., 87%; d) NaOMe–MeOH 1.0 M, MeOH–THF 5:1, r.t., 100%

Table 1 shows the results obtained in the glycosylation of **10** and **11** with trichloroacetimidate **12** and those previously reported by us for the glycosylation of **8** and **9**.[13a] Diols **8** and **9** showed similar reactivity towards donor **12** affording 2:1 α:β mixtures of the corresponding pseudodisaccharides (**16** and **20** from **8** and **17** and **21** from **9**) and a small amount of the αα-trisaccharides **24** (from **8**)

Table 1 Glycosylation Reactions[a]



Entry	Acceptor	Yield (%)			
		α(1→1)	β(1→1)	Trisaccharides	Overall
1	$R^1 = R^2$ = BDA (**8**)[11a,12]	43 (16)	20 (20)	7 (**24**) α,α	70
2	R^1 = Bn, R^2 = BDA (**9**)[11a,11]	42 (17)	18 (21)	7 (**25**) α,α	67
3	$R^1 = R^2$ = Bz (**10**)	18 (**18**)	7 (**22**)	–	25
4	$R^1 = R^2$ = Bn (**11**)	60 (**19**)	14 (**23**)	12 (**26**) α,β	86

[a] *Reagents and conditions*: a) **12** (1.6 equiv), **1Dc-f** (1.0 equiv), TMSOTf (0.1 equiv), CH_2Cl_2, –25 °C, 1 h.

and **25** (from **9**) in approximately 70% overall yield (Table 1, entries 1 and 2). Under the same experimental conditions, the glycosylation of **10** (entry 3) led to a mixture of α(1→1) and β(1→1) pseudodisaccharides (**18**:**22** = 72:28) in a poor 25% yield. On the other hand, the glycosylation of **11** (entry 4) afforded a 70:16:14 mixture of the α(1→1) (**19**) and the β(1→1) (**23**) pseudodisaccharides and the α,β-psedoditrisaccharide (**26**) in 60%, 14% and 12% yield, respectively.

A semi-quantitative evaluation of the difference of reactivity of these glycosyl acceptors was then attempted using a series of competitive glycosylation experiments. The results are summarized in Table 2. Equimolecular amounts of two glycosyl acceptors were reacted with glycosyl donor **12** and the ratio of reaction products determined after isolation from the reaction mixtures.

Competitive glycosylation of acceptors **8** and **10** (entry 1) gave a ratio of oligosaccharides from **10**:**8** = 1:3.7, compounds **8** and **9** displayed similar reactivity (entry 2) and compound **11** was almost 3 times more reactive than compound **9** (entry 3). Figure 3 illustrates the order of reactivity of acceptors **8**–**11**. It would be expected that **11** should be at least 10 times more reactive than **10**.

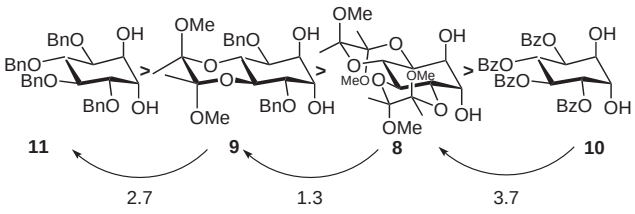


Figure 3 Order of reactivity of glycosyl acceptors **8**–**11**

These results constitute an experimental semi-quantitative evaluation of the influence of some of the protecting groups usually employed in carbohydrate chemistry (acyl, alkyl, acetal) on the reactivity of a given hydroxyl group as glycosyl acceptor. As previously shown for glycosyl donors, the above results indicate that the reactivity of a given glycosyl acceptor can also be tuned by a careful choice of protecting groups. In general terms, electron-withdrawing protecting groups clearly decrease the reactivity of the *chiro*-inositol diols as glycosyl acceptors, compound **10** being by far the less reactive derivative. The deactivating effect of benzoyl groups is much more pronounced than that observed for the bisacetal protected compound **8** or the monoacetal protected **9** with respect to the most reactive tetrabenzylated diol **11**. By contrast, it has been reported that bisacetal substituents such as BDA on L-rhamnose and D-mannose thioglycosides give rise to a greater deactivation of these derivatives as glycosyl donors than benzoyl groups on the same positions.[4b] This different effect of BDA on the reactivity of glycosyl donors and glycosyl acceptors could be attributed to the difficulty imposed by the bisacetalic substituent for the pyranoid ring of the glycosyl donor to flatten during oxonium ion formation. The relative reactivities observed for **8** and **9** indicate that these acetal systems may also be useful auxiliaries for the fine-tuning of the reactivity of glycosyl acceptors.

2,3,4,5-Tetra-*O*-benzoyl-D-*chiro*-inositol (10)
$[\alpha]_D^{20}$ +32.0 (*c* 0.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.96 (2 H_{ortho}, 4 H), 7.85 (2 H_{ortho}, 4 H), 7.50–7.20 (m, 12 H, 4 Bz), 6.21 (m, 2 H, H_3 and H_4), 5.84 (m, 2 H, H_2 and H_5), 4.58 (s, 2 H, H_1 and H_6). Anal. Calcd for $C_{34}H_{28}O_{10}$ (%): C, 68.45; H, 4.73%. Found: C, 68.05; H, 4.63. FAB-HRMS: *m*/*z* calcd for $C_{34}H_{28}O_{10}$: 596.1682; found: 596.1686.

2,3,4,5-Tetra-*O*-benzyl-D-*chiro*-inositol (11)
$[\alpha]_D^{20}$ +17.5 (*c* 0.6, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.20 (m, 20 H, 4 Bn), 4.85–4.65 (4 AB syst, 8 H), 4.17 (s, 2 H, H_1 and H_6), 3.85 (m, 2 H, H_2 and H_5), 3.80 (m, 2 H, H_3 and H_4), 2.50 (s, 2 H, OH). Anal. Calcd for $C_{48}H_{44}O_8$ + 2 H_2O (%): C, 70.81; H, 6.90. Found: C, 70.54; H, 6.50. FAB-HRMS: *m*/*z* calcd for $C_{34}H_{36}O_6$: 540.6525; found: 540.6529.

3,4,6-Tri-*O*-benzyl-2-azido-2-deoxy-D-glucopyranosyl-α(1→1)-2,3,4,5-tetra-*O*-benzoyl-D-*chiro*-inositol (18) and 3,4,6-Tri-*O*-benzyl-2-azido-2-deoxy-D-glucopyranosyl-β(1→1)-2,3,4,5-tetra-*O*-benzoyl-D-*chiro*-inositol (22)
A mixture of **12** (66 mg, 0.107 mmol) and **10** (40 mg, 0.067 mmol) was co-evaporated 3 times with toluene, 4 Å MS was added and the residue dried under vacuum overnight. The mixture was dissolved

Table 2 Competitive Experiments with Acceptors **8**–**11**

Entry	Donor **12**	Glycosylation products (%)				Ratio[a]
	Acceptors	α(1→1)	β(1→1)	Trisaccharides	Overall	
1	**10**	**18** 8	**22** 4	–	12	**10**:**8**
	8	**16** 29	**20** 14	**24** 2	45	1:3.7
2	**8**	**16** 16	**20** 9	**24** 3	28	**8**:**9**
	9	**17** 22	**21** 13	**25** 2	37	1:1.3
3	**9**	**17** 10	**21** 4	**25** 2	16	**9**:**11**
	11	**19** 23	**23** 13	**26** 8	44	1:2.7

[a] Relative reactivity of acceptors **8**–**11**.

in 2 mL of CH_2Cl_2 under argon and stirred at r.t. for 30 min, then 0.1 equiv (60 μL of a 0.1 M solution) of TMSOTf were added at –25 °C. After stirring the reaction mixture for 1 h, it was quenched with Et_3N, concentrated and purified by flash chromatography (hexane–EtOAc, 4:1 to 2:1) to yield 13 mg (18%) of **18** and 5 mg (7%) of **22**.

Data of α(1→1) pseudodisaccharide **18**: $[\alpha]_D^{20}$ +70.6 (*c* 0.6, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.96 (d, 2 H, *J* = 8.0 Hz, H_{ortho}), 7.91 (d, 2 H, *J* = 8.0 Hz, H_{ortho}), 7.87 (d, 2 H, *J* = 8.0 Hz, H_{ortho}), 7.85 (d, 2 H, *J* = 8.0 Hz, H_{ortho}), 7.50–7.00 (m, 15 H, 3 Bn and 12 H, 4 Bz), 6.23 (t, 1 H, *J* = 9.9 Hz, H_4), 6.16 (t, 1 H, *J* = 9.9 Hz, H_3), 5.90–5.85 (m, 2 H, H_5 and H_2), 5.05 (d, 1 H, *J* = 3.6 Hz, $H_{1'}$), 5.00–4.07 (3 AB syst., 6 H), 4.63 (br s, 1 H, H_6), 4.57 (t, 1 H, *J* = 3.8 Hz, H_1), 4.13 (t, 1 H, *J* = 9.6 Hz, $H_{3'}$), 3.91 (m, 1 H, $H_{5'}$), 3.69 (t, 1 H, *J* = 9.6 Hz, $H_{4'}$), 3.53 (dd, 1 H, *J* = 9.6, 3.6 Hz, $H_{2'}$), 2.96 (br d, 1 H, *J* = 10.8 Hz, $H_{6a'}$), 2.82 (br d, 1 H, *J* = 10.7 Hz, $H_{6b'}$), 2.67 (br s, 1 H, C_6OH). Anal. Calcd for $C_{61}H_{55}O_{14}N_3$ + 3 H_2O (%): C, 66.11; H, 5.50; N, 3.79. Found: C, 66.22; H, 5.30; N, 3.57

Data of β(1→1) pseudodisaccharide **22**: $[\alpha]_D^{20}$ +14.0 (*c* 0.2, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.02 (d, 2 H, *J* = 8.0 Hz, H_{ortho}), 7.93 (d, 2 H, *J* = 8.0 Hz, H_{ortho}), 7.87 (d, 2 H, *J* = 8.0 Hz, H_{ortho}), 7.85 (d, 2 H, *J* = 8.0 Hz, H_{ortho}), 7.50–7.00 (m, 15 H, 3 Bn and 12 H, 4 Bz), 6.24 (t, 1 H, *J* = 9.7 Hz, H_3), 6.17 (t, 1 H, *J* = 9.7 Hz, H_4), 5.87 (dd, 1 H, *J* = 9.7, 3.1 Hz, H_2), 5.80 (dd, 1 H, *J* = 9.7, 2.9 Hz, H_5), 4.87–4.42 (m, 6 H, 3 AB syst.), 4.68 (br s, 1 H, H_6), 4.56 (s, 1 H, H_1), 4.38 (d, 1 H, *J* = 8.2 Hz, $H_{1'}$), 3.65–3.57 (m, 4 H, $2H_{6'}$, $H_{3'}$, $H_{2'}$), 3.34–3.28 (m, 2 H, $H_{4'}$, $H_{5'}$), 2.47 (br s, 1 H, C_6OH). Anal. Calcd for $C_{61}H_{55}O_{14}N_3$ + 3 H_2O (%): C, 66.11; H, 5.50; N, 3.7. Found: C, 66.34; H, 5.58; N, 3.38.

3,4,6-Tri-*O*-benzyl-2-azido-2-deoxy-D-glucopyranosyl-α(1→1)-2,3,4,5-tetra-*O*-benzyl-D-*chiro*-inositol (19), 3,4,6-Tri-*O*-benzyl-2-azido-2-deoxy-D-glucopyranosyl-β(1→1)-2,3,4,5-tetra-*O*-benzyl-D-*chiro*-inositol (23) and Di(3,4,6-tri-*O*-benzyl-2-azido-2-deoxy-D-glucopyranosyl)-α,α-(1→1:1→6)-2,3,4,5-tetra-*O*-benzyl-D-*chiro*-inositol (26)

These compounds were prepared from **12** (55 mg, 0.088 mmol) and **11** (30 mg, 0.055 mmol) as described in the preparation of **18** and **22**, adding 0.1 equiv (55 μL of a 0.1 M solution) of TMSOTf at –25 °C, in CH_2Cl_2 (2 mL) and stirring the reaction mixture for 1 h, yielding after flash chromatography (hexane–EtOAc, 6:1 to 2:1), 33 mg (60%) of **19**, 8 mg (14%) of **23**, and 10 mg (12%) of the pseudotrisaccharide αβ **26**.

Data of α(1→1) pseudodisaccharide **19**: $[\alpha]_D^{20}$ +37.3 (*c* 1.6, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6): δ = 7.50–7.10 (m, 35 H, 7 Bn), 5.10–4.32 (7 AB syst., 14 H), 4.56 (d, 1 H, *J* = 3.5 Hz, $H_{1'}$), 4.49 (m, 1 H, $H_{5'}$), 4.31 (br t, 1 H, *J* = 3.3 Hz, H_1), 4.25–4.03 (m, 5 H, H_2, H_3, H_4, H_5, $H_{3'}$), 3.99 (br t, 1 H, H_6), 3.95 (t, 1 H, *J* = 9.6 Hz, $H_{4'}$), 3.58 (dd, 1 H, *J* = 10.1, 2.8 Hz, $H_{6'a}$), 3.39 (d, 1 H, *J* = 10.0 Hz $H_{6'b}$), 3.22 (dd, 1 H, *J* = 10.1, 3.5 Hz, $H_{2'}$), 2.55 (br s, 1 H, C_6OH). Anal. Calcd for $C_{61}H_{63}O_{10}N_3$ + H_2O (%): C, 72.74; H, 6.40; N, 4.17. Found: C, 72.81; H, 6.45; N, 4.50.

Data of β(1→1) pseudodisaccharide **23**: $[\alpha]_D^{20}$ +2.0 (*c* 0.6, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6): δ = 7.50–7.10 (m, 35 H, 7 Bn), 5.28–4.55 (7 AB syst, 14 H), 4.66 (d, 1 H, *J* = 8.0 Hz, $H_{1'}$), 4.53–4.40 (m, 3 H, H_6, H_1, H_4 or H_3), 4.25 (dd, 1 H, *J* = 9.5, 2.6 Hz, H_5 or H_2), 4.14 (dd, 1 H, *J* = 9.5, 2.6 Hz, H_2 or H_5), 4.09 (t, 1 H, *J* = 9.5 Hz, H_3 or H_4), 3.65 (m, 3 H, $H_{4'}$, 2 $H_{6'}$), 3.44 (dd, 1 H, *J* = 9.0, 8.0 Hz, $H_{2'}$), 3.35 (t, 1 H, *J* = 9.0 Hz $H_{3'}$), 3.28 (m, 1 H, $H_{5'}$), 2.45 (br s, 1 H, OH). Anal. Calcd for $C_{61}H_{63}O_{10}N_3$ (%): C, 73.40; H, 6.36; N, 4.21. Found: C, 73.73; H, 6.69; N, 4.13.

Data of αβ pseudotrisaccharide **26**: ^1H NMR (500 MHz, C_6D_6): δ = 7.60–7.10 (m, 50 H, 10 Bn), 5.30–4.40 (10 AB syst., 20 H), 4.86 (d, 1 H, *J* = 3.5 Hz, $H_{1\alpha'}$), 4.73 (d, 1 H, *J* = 8.7 Hz, $H_{1\beta''}$), 4.63 (br t, 1 H, H_1 or H_6), 4.42 (m, 1 H, $H_{5\alpha'}$), 4.43 (m, 2 H, H_4 or H_3, H_1 or H_6), 4.30–4.20 (m, 3 H, H_4 or H_3, H_2, H_5), 4.18 (t, 1 H, *J* = 9.9 Hz, $H_{3\alpha'}$), 3.97 (t, 1 H, *J* = 9.9 Hz $H_{4\alpha'}$), 3.73–3.38 (m, 8 H, 2 $H_{6\alpha'}$, 2 $H_{6\beta''}$, $H_{4\beta''}$, $H_{2\beta''}$, $H_{3\beta''}$, $H_{5\beta''}$), 3.17 (dd, 1 H, *J* = 10.0, 3.5 Hz, $H_{2\alpha'}$).

Competitive experiments of aceptors **8**–**11** with trichloroacetimidate donor **10** were carried out from a equimolecular mixture of trichloroacetimidate (0.024 mmol) and acceptors (0.024 mmol) as described in the preparation of **18** and **22**, adding 0.1 equiv of TMSOTf at –25 °C, in CH_2Cl_2 (1 mL) and stirring the reaction mixture for 1 h.

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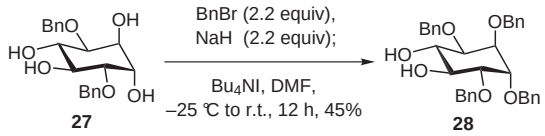
(18) When D-*chiro*-inositol was submitted to standard basic benzylation conditions a complex mixture of products, from which **11** could not been isolated, was obtained. When the tetraol **27** precursor of **9** was treated with BnBr compound **28**, resulting from benzylation of the axially oriented hydroxyl groups, was observed (Scheme 3).



27 **28**

Scheme 3