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Can preferential β-mannopyranoside formation with 4,6-*O*-benzylidene protected mannopyranosyl sulfoxides be reached with trichloroacetimidates?

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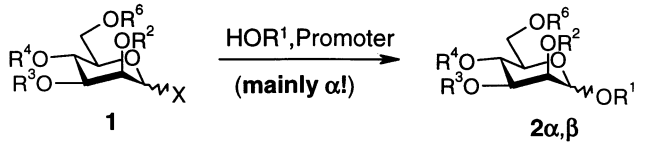
Abstract

Studies with 3-*O*-allyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosyl sulfoxide (**3d**) and the corresponding trichloroacetimidate (**4**) as glycosyl donors and various acceptors (**A**–**F**) led under similar reaction conditions to similar glycosylation results, i.e. mainly or exclusively the β-anomers of glycosides **5dA**–**5dF** could be obtained. Thus, the versatile building block **5dA** for *N*-glycan synthesis is readily available. For the activation of the sulfoxide leaving group, one equivalent of Tf_2O and two equivalents of DTBMP are required, whereas for trichloroacetimidate activation catalytic amounts of TMSOTf are sufficient; hence, the trichloroacetimidate based procedure is very convenient. Various parameters were modified in the reaction of **4** with **A** (catalyst concentration, configuration of **4**, size of the 2-*O*-protective group, solvent), thus, a proposal for the reaction course was derived. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: glycosidation; glycosyl donors; sulfoxides; trichloroacetimidates; β-mannopyranosides; *N*-glycans.

Mannopyranosyl donors **1**, having nonparticipating protective groups and different leaving groups X, were investigated for their β-selectivity; however, in general α-products **2** were obtained[1–3] (Scheme 1). Activation of mannopyranosyl halides with silver salts in a two phase



Scheme 1.

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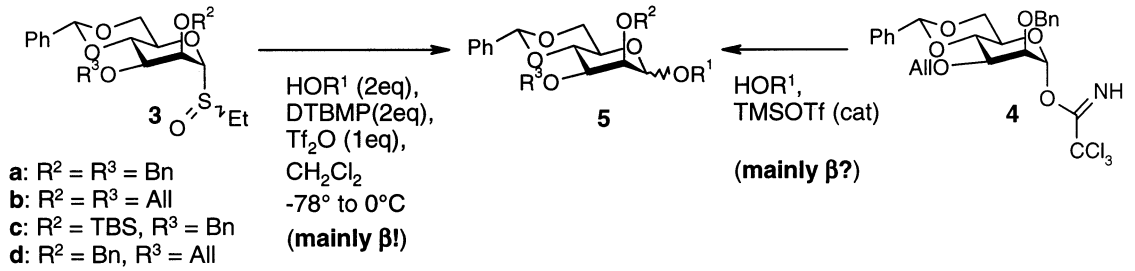
system,[4,5] application of the nitrile effect,[6] and anomeric *O*-alkylation[7,8] led to some success in this endeavour. Yet, intramolecular aglycon delivery from the β-side[9–11] and epimerisation of β-glucopyranosides to β-mannopyranosides[12–16] became the methods of choice.

Also, mannopyranosyl donors with bifunctional *O*-protection, thus having rings attached, had already been investigated for β-mannopyranoside formation, yet with limited success.[17] Therefore, the observation of Crich et al.[18] was a big surprise that 2,3-di-*O*-alkyl-4,6-*O*-benzylidene-protected mannopyranosyl sulfoxides (for instance **3a–c**, Scheme 2) furnished with various acceptors in excess in dichloromethane as solvent and at low temperatures high β/α-ratios of **5**; in this useful method, generally one equivalent of trifluoromethanesulfonic anhydride (Tf_2O) and two equivalents of di-*tert*-butyl-methylpyridine (DTBMP) are employed for donor activation.[18,19] Further investigations showed that this method is limited to compounds of type **3**.[20] An important question, giving further insight into the stereocontrol mechanism and also being of practical importance, concerns the possible limitation of preferential β-mannopyranoside formation to sulfoxide leaving groups. The ease of *O*-glycosyl trichloroacetimidate formation, their high reactivity under simple acid catalysis in different solvents and also at low temperatures[2] were reasons for performing a comparative study. Based on previous experience it was expected that reactive intermediates proposed for sulfoxide activation should likewise be accessible from trichloroacetimidates under similar reaction conditions.

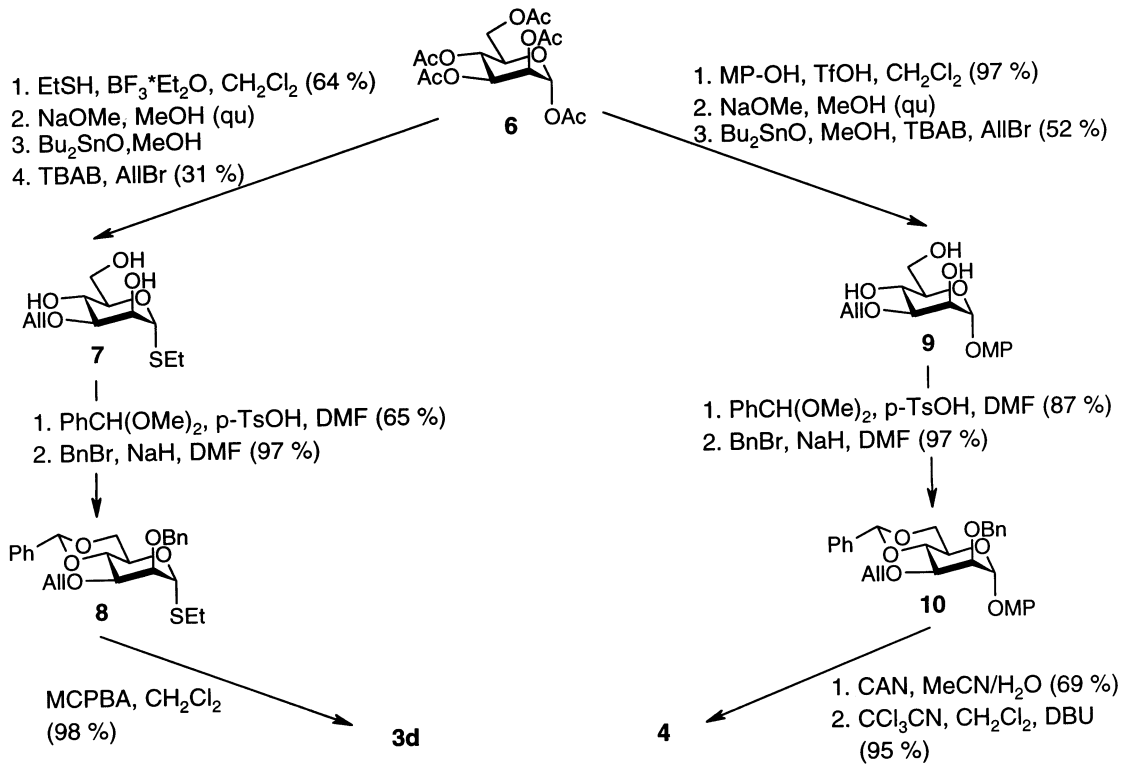


Scheme 2.

For our study, 3-*O*-allyl-2-*O*-benzyl-4,6-*O*-benzylidene-mannopyranosyl donors **3d** and **4** were selected, because their β-(1→4)-linkage to a GlcNAc (or a chitobiose) derivative will provide a properly protected building block for glycopeptide *N*-glycan synthesis.[14] Thus, the required regioselective access to the 3-*O*, 6-*O*, and 4-*O*, respectively, of the mannosyl residue is available.

The synthesis of **3d** and **4** could be readily performed starting from per-*O*-acetyl mannopyranose **6** (Scheme 3). Reaction of **6** with ethyl mercaptan in the presence of $BF_3{\cdot}OEt_2$ as catalyst afforded ethyl α-thiomannoside;[21] ensuing de-*O*-acetylation and then regioselective 3-*O*-allylation by treatment with dibutyltin oxide and then with allyl bromide in the presence of tetrabutylammonium bromide (TBAB) gave **7**. 4,6-*O*-Benzylidenation of **7** with benzaldehyde dimethylacetal in the presence of *p*-toluenesulfonic acid (*p*-TsOH) and then treatment with benzyl bromide in the presence of sodium hydride furnished fully *O*-protected **8**, which gave on oxidation with *m*-chloroperbenzoic acid (MCPBA) a diastereomeric mixture of **3d** (overall yield from **6**: 12%). Similarly, from **6** and *p*-methoxyphenol (MP-OH) in the presence of TfOH as catalyst, the methoxyphenyl α-mannopyranoside was obtained, which was transformed into **9** and **10** as described above. Oxidation of **10** with ceric(III) ammonium nitrate (CAN) in $MeCN/H_2O$ (4:1) as solvent liberated the anomeric hydroxy group; ensuing treatment with

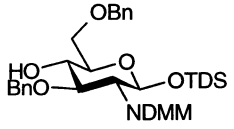
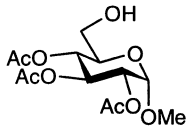
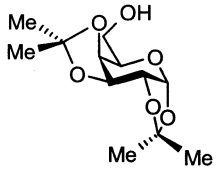
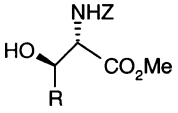
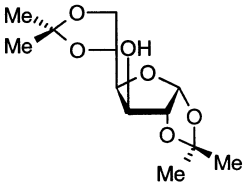
trichloroacetonitrile in the presence of DBU afforded at 0°C within 15 min almost exclusively the α-anomer **4** (overall yield from **6**: 28%); higher temperatures and/or longer reaction times led to some β-anomer **4β**, which could be separated.



Scheme 3.

The reaction of **3d** or **4** with 4-*O*-unprotected glucosamine derivative **A**[14,22] as acceptor was particularly well investigated, because the β-linked disaccharide product **5dA** constitutes an ideal building block for *N*-glycan synthesis.[14] For **3d** activation, the standard promoter system and reaction conditions were employed (Scheme 2). The reactions with **4** were carried out with 0.15 equivalents of TMSOTf as catalyst in dichloromethane at −50°C under inverse conditions,[23] i.e. **4** was added to a solution of **A** and TMSOTf. The results, also with acceptors **B**–**F**[24] providing **5dB**–**5dF**, are compiled in Table 1.[25,26] Obviously, compared with sulfoxide **3d** the experimental procedure for the reaction with trichloroacetimidate **4** is much simpler, because just catalytic amounts of TMSOTf have to be added for activation of the donor. This may be the reason why it was easier to obtain good results with **4**. For comparison, literature results with structurally related sulfoxide donors **3a**,**b**[18] are also included in Table 1. In these experiments the α/β-ratio was determined by integration of the ^{1}H NMR spectra of crude reaction mixtures.[18] Therefore, within experimental error, the results with **3a**,**b** and **4** are practically the same, thus supporting the view that activation of **3** or **4** leads to (a) common intermediate(s) which favour(s) β-product formation; this is particularly true for less reactive acceptors.

Table 1
Mannopyranoside formation with 4,6-*O*-benzylidene protected donors

Acceptor HOR[1]		Results with **4** and **3d**				Lit. Results with **3a**,**b** (Ref 18)			
		Donor	Product	Yield[a] [%]	α / β - Ratio[a]	Donor	Product	Yield [%]	α/ β - Ratio[b]
	**A**	**4** **3d**	**5dA** **5dA**	71 18	1:3.6 1:2.7	**3a**[c]	**5aA**[d]	39	1:3.8
	**B**	**4**	**5dB**	72	only β	**3a** **3b**	**5aB** **5aB**	95 95	only β 1:22.8
	**C**	**4** **3d**	**5dC** **5dC**	88 36	1:2.1 1:3.6	**3a**[c]	**5aC**	86	1:5.6
	**D (R = Me)** **E (R = H)**	**4** **4**	**5dD** **5dE**	71 86	1:8 1:2.6	**3a** **3a**	**5aD** **5aE**	97 n.d.	1:31.3 n.d.
	**F**	**4** **3d**	**5dF** **5dF**	59 59	only β only β	**3a** **3b**	**5aF** **5bF**	98 97	1:13.0 1:12.9

a)Yield and α/β-ratios were assigned after separation of the α– and β-isomer.
b)The α/β -ratios were assigned on integration of ^{1}H NMR spectra of crude reaction mixtures.
c)The leaving group is phenylsulfoxide.
d)The acceptor is benzyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy- α-D-glucopyranoside.

In order to gain more insight into the reaction course some parameters were varied. The reaction of **4β** with **A** was investigated, yet, under the same reaction conditions practically the same result was obtained as observed for the α-isomer **4**. When, for the reaction of **4** with **A**, the solvent was changed to less polar toluene the yield of **5dA** and the β-content decreased. Also, the relative amount of catalyst had an effect on the reaction of **4** with **A** (0.03 equiv. TMSOTf: 48% yield, α/β = 1:2.5; 1.5 equiv. TMSOTf: 43% yield, α/β = 1:6.2); thus, compared with the results obtained with 0.15 equivalents of TMSOTf (Table 1) the yields dropped, whereas the β/α-ratio slightly increased with the amount of catalyst. Also, the influence of the size of the 2-*O*-protective group was investigated; to this end the 2-*O*-benzyl group in **4** was replaced by the

mesitylmethyl and the *tert*-butyldimethylsilyl (TBS) group; yet, in reactions with **A** under standard conditions the yields and β/α-ratios decreased for both cases. Under the reaction conditions for activation of **4**, product anomerisation and decomposition were not observed, therefore, the α/β-ratios are directly correlated with the rate of α- versus β-product formation. However, the results described above are not compatible with the reaction mechanism proposed for sulfoxides **3**, where α-triflate intermediates are thought to play a decisive role in β-product formation.[18,20] For instance, the amount of catalyst had only a minor effect on β-selectivity (50-fold increase of TMSOTf led only to a twofold increase in β-selectivity). The less polar solvent toluene which should favour α-triflate formation led to an even lower β/α-ratio. Rather, the unique effect of the 4,6-*O*-benzylidene group on the anomeric stereocontrol is due to a conformational effect exerted on the pyranosyl ring, thus favouring a twist-boat type intermediate. For stereoelectronic and steric reasons, this intermediate will be preferentially attacked from the β-side, thus providing a twist-boat product which equilibrates to the $^4C_1$-conformer **5**. This proposal could reconcile all results thus far found with different mannopyranosyl donors.

In conclusion, preferential β-glycoside formation with 4,6-*O*-benzylidene-protected mannopyranosyl sulfoxides is conveniently achieved with trichloroacetimidate leaving groups because they are accessible to activation with catalytic amounts of TMSOTf. Thus, for instance with a glucosamine derived acceptor a versatile β-(1→4)-linked disaccharide building block for *N*-glycan synthesis could be obtained. For the reaction course the intermediacy of a twist-boat type structure is proposed.

Acknowledgements

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24. Acceptors **B**–**F** were either readily available following standard literature procedures (**B**, **C**, **F**) or they were commercially available (**D**, **E**).
25. Heteronuclear one-bond coupling constants of α- and β-glycosyl imidates: ^{1}H NMR (600 MHz, $CDCl_3$): **4**α: $^1J_{1C,1H}=179.1$ Hz, **4**β: $^1J_{1C,1H}=163.2$ Hz; α- and β-linked glycosides: ^{1}H NMR (600 MHz, $CDCl_3$): **5dA**α: $^1J_{1C,1H}=174.6$ Hz, **5dA**β: $^1J_{1C,1H}=158.2$ Hz, **5dB**β: $^1J_{1C,1H}=157.4$ Hz, **5dC**α: $^1J_{1C,1H}=171.8$ Hz, **5dC**β: $^1J_{1C,1H}=156.2$ Hz, **5dD**α: $^1J_{1C,1H}=170.8$ Hz, **5dD**β: $^1J_{1C,1H}=156$ Hz, **5dE**α: $^1J_{1C,1H}=170.8$ Hz, **5dE**β: $^1J_{1C,1H}=156.1$ Hz, **5dF**β: $^1J_{1C,1H}=156.2$ Hz.
26. The reactions with **3d** were carried out following the standard protocol D in Ref. 18e. For the reactions with **4** the following procedure was employed: acceptor (0.167 mmol) was dissolved in dry dichloromethane (0.5 ml) and cooled to −50°C. TMSOTf (3.6 μl, 25 μmol) was added and a solution of donor **4** (109 mg, 0.25 mmol) in dry dichloromethane (1 ml) was injected directly (the needle dipped into the solution) over 25 min using a syringe pump. 20 min later, the mixture was neutralised with triethylamine. The solvent was evaporated and after a short column (Tol/EE) a mixture of the crude α- and β-compound was obtained. The α- and β-compounds were separated by medium pressure chromatography (PE/EE) and then structurally assigned.