Direct Synthesis of β-Mannopyranosides by the Sulfoxide Method

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In a recent extension of Kahne's[1,2] sulfoxide glycosylation method, we reported that activation of the glycosyl donor **1** with triflic anhydride (Tf_2O) and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) at −78 °C in ether/arene mixtures followed by addition of a primary glycosyl acceptor resulted in the formation of mannopyranosides in high yield and high β:α-ratios (protocol A).[3] Coupling of **1** with secondary glycosyl acceptors under these conditions, however, resulted in significantly reduced β:α ratios. Premixing of **1**, a primary acceptor, and DTBMP before addition of Tf_2O under otherwise identical conditions also provided mainly the α-anomer of the product (protocol B). A working hypothesis that attempts to rationalize these observations and that provides the basis for the experiments outlined in this paper is given in Scheme 1.

According to this rationale, Tf_2O serves to activate **1** in the form of **2**, which rapidly expels a sulfinate ester to give the oxycarbenium cation **3**. In protocol A, in the absence of other nucleophiles, **3** is trapped axially by triflate anion to give the glycosyl triflate **4**. On addition of the acceptor ROH, an S_N2-like reaction then occurs to give the β-mannoside **5**. Under the conditions of protocol B, the oxycarbenium cation **3** is simply trapped preferentially by ROH along the axial direction to give the α-mannoside **6**. When ROH is a secondary alcohol, the direct displacement of TfO^- from **4** is retarded for steric reasons and leads to the formation of **6**, via **3**, even with protocol A. The sulfoxide **1** therefore merely serves as a convenient precursor for the in situ generation of the glycosyl triflate **4**.[4] Other unstable mannosyl sulfonate esters have previously been explored successfully for the generation of β-mannopyranosides by Schuerch[5,6] although their use has not been widely explored, presumably for reasons of instability.

On the basis of this hypothesis, it can be predicted that reducing the bulk of the *O*-2 protecting group will lead to greater β:α-ratios for secondary glycosyl acceptors. Therefore, glycosyl donors **7** and **8** were prepared and reacted with the L-rhamnose derivative **9** under the conditions of protocol A in ether, giving rise to the formation of the corresponding β- and α-mannopyranoside in the yields and ratios indicated in Table 1, entries 1 and 2.[7] Contrasting these results with those previously obtained[3] with **1** and **9** under the same conditions (Table 1, entry 3) very clearly atests to the correctness of the prediction. We also investigated coupling of the 2-*O*-benzyl phenyl sulfoxide **10** with **9**. It was somewhat insoluble in pure ether at −78 °C; however, in 1:1 ether/CH_2Cl_2 an excellent β:α ratio of 21:1 was obtained (Table 1, entry 4). The high yield and ratio obtained in this experiment prompted us to explore neat CH_2Cl_2 as solvent when we were unable to detect the α-anomer of the product (Table 1, entry 5). A similar improvement was seen with donor **7** (Table 1, entry 6), and even the more hindered donor **1** gave a respectable yield and β:α-ratio in this solvent (Table 1, entry 7). Dichloromethane therefore became the solvent of choice for future reactions.

Scheme 1

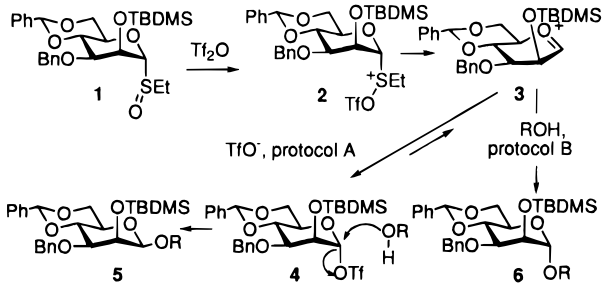


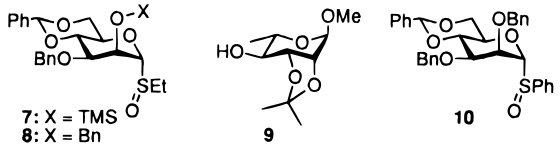
Table 1. Reaction of Glycosyl Donors with 9

entry	donor	solvent	% yield β-mannoside	% yield α-mannoside	β:α ratio
1	**7**	Et_2O	76	15	5.1:1
2	**8**	Et_2O	74	11	6.7:1
3	**1**	Et_2O	49	30	1.6:1
4	**10**	Et_2O:CH_2Cl_2 1:1	85	4	21.3:1
5	**10**	CH_2Cl_2	90	0	>25:1
6	**7**	CH_2Cl_2	82	11	7.5:1
7	**1**	Ch_2Cl_2	82	11	7.5:1

Table 2. Glycosylation of Secondary Acceptors in CH_2Cl_2

entry	donor	acceptor	% yield β-mannoside	% yield α-mannoside	β:α ratio
1	**10**	**12**	93	5	18.6:1
2	**10**	**13**	90	6	15.0:1
3	**10**	**14**	94	5	18.8:1
4	**10**	**15**	31	8	3.8:1[a]
5	**10**	**16**	94	3	31.3:1
6	**8**	**14**	90	7	12.9:1
7	**11**	**14**	90	7	12.9:1

[a] The reaction mixture was allowed to come to rt and stirred there for 24 h before workup.



The promising results outlined in Table 1 prompted us to investigate the coupling of donors **8**, **10**, and the di-*O*-allyl protected analog **11**, with a range of secondary glycosyl acceptors (**12**−**16**) by protocol A in dichloromethane. The results of these couplings, given in Table 2, clearly illustrate that a very effective new method for the rapid, one-pot synthesis of mannopyranosides rich in the β-anomer is at hand. Only in the notoriously unreactive glucosamine 4-OH series was a low yield of β-mannoside obtained (Table 2, entry 4), yet, even here,

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(4) Low-temperature ^1H- and ^{19}F-NMR studies in CD_2Cl_2 are in full agreement with the postulate that triflate **4** is the true glycosyl donor. Crich, D.; Sun, S. Unpublished results.
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(7) The anomeric configuration is assigned in each case with the aid of NOE measurements on the β-anomer.

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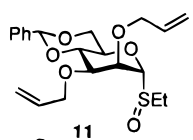
Table 3. Glycosylation of Primary Acceptors

entry	donor	acceptor	% yield β-mannoside	% yield α-mannoside	β:α ratio
1[a]	**8**	**17**	95	0	>25:1
2[a]	**10**	**17**	95	0	>25:1
3[a]	**11**	**17**	91	4	22.8:1
4[a]	**1**	**17**	95	4	23.8:1
5[b]	**1**	**17**	86	8	10.7:1
6[a]	**10**	**18**	73	13	5.6:1
7[b]	**1**	**18**	69	12	5.6:1

[a] Reaction in pure CH_2Cl_2. [b] Taken from ref 3, reaction in Et_2O: benzene.

the anomeric ratio was adequate with the mass balance made up of other as yet undetermined products.



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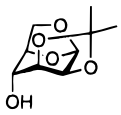

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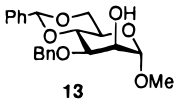

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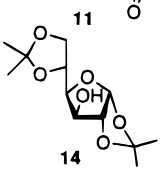

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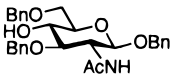

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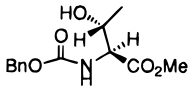

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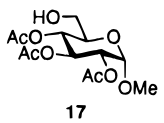
A final series of experiments involved coupling the primary glycosyl acceptor **17** with donors **1**, **8**, **10**, and **11** by protocol A in dichloromethane. As seen from Table 3 (entries 1−4), very high yields and β:α ratios were obtained whatever the nature of the *O*-2 protecting group. These results, contrasted with the previous best (Table 3, entry 5) for the reaction of donor **1** with **17** in ether doped with benzene, again atest to the superiority of dichloromethane as a solvent for this reaction. Curiously, therefore, the coupling of **18** with **10** in dichloromethane (Table 3, entry 6) did not give a better ratio than observed previously for its reaction with **1** in ether (Table 3, entry 7). The poor ratios obtained with **18**, worse than with the secondary alcohols, must be a function of some as yet undetermined factor over and above simple steric hindrance.



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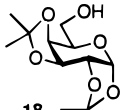

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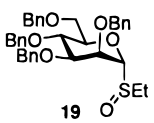

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Finally, we note that as previously[3] very poor β:α-ratios were observed using the more conformationally mobile donor **19** in whatever solvent. This observation is also encompassed by the general mechanistic hypothesis of Scheme 1. Thus, as Fraser-Reid has shown,[8] 4,6-benzylidene-protected pyranosyl systems resist formation of oxycarbenium cations more than do their 4,6-di-*O*-benzyl congeners. This is due to the greater strain such a conformational deformation imposes on the trans-fused bicyclic nucleus. The difference between **1**, **7**, **8**, **10**, and **11** on the one hand, and **19** on the other, therefore most likely simply reflects a shift in the α-glycosyl triflate: oxycarbenium cation equilibrium. The ultimate prediction of Scheme 1, that authentic 4,6-benzylidene-α-mannosyl triflates will give β:α-ratios comparable to those observed here, has yet to be tested owing to our inability to prepare and characterize such unstable species[9] at present.

In conclusion, we have presented a general strategy for the direct synthesis of β-mannopyranosides applicable to a wide variety of primary and secondary glycosyl acceptors. The simple protocol, high yields, and excellent β:α-ratios suggest that this method will be at least comparable in efficiency to other methods developed recently[10−22] and so will find a place in oligosaccharide synthesis.

General experimental protocol for the preparation of β-mannopyranosides: to a stirred solution of the glycosyl sulfoxide (0.2 mmol) and DTBMP (0.4 mmol) in dichloromethane (8 mL) at −78 °C under an inert atmosphere was added Tf_2O (0.22 mol) and, after 2−5 min, a solution of the glycosyl acceptor (0.4 mmol) in dichloromethane (2 mL) dropwise. The reaction mixture was stirred at −78 °C for 1 h and then allowed to warm to 0 °C before it was quenched with saturated aqueous $NaHCO_3$, washed with brine, dried (Na_2SO_4), concentrated in vacuo, and purified by chromatography on silica gel.

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Supporting Information Available: Listings of spectral data for **7**, **8**, **10**, and **11** and all α- and β-mannosides prepared (20 pages).

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