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Formation of β-Mannopyranosides of Primary Alcohols Using the Sulfoxide Method

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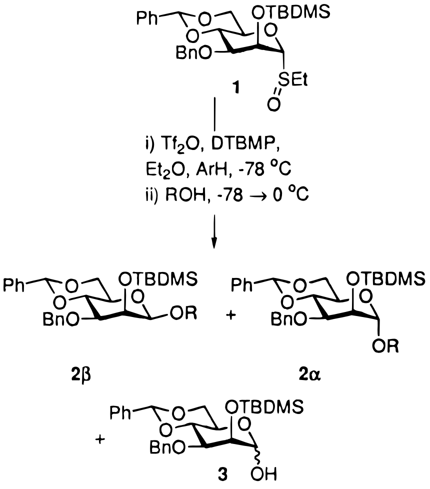
Introduction

The β-*O*-mannopyranosidic bond, as present in the common core pentasaccharide of the *N*-linked glycoproteins,[1] in various mannans and glycosphingolipids[2] and in lipopolysaccharides,[3] is arguably the most difficult type of glycosidic linkage with which nature has challenged the synthetic chemist.[4] The formidable combination of steric and stereoelectronic factors that weigh against formation of the β-mannoside in classical glycosidation protocols has prompted the development of less direct routes, principally reduction of 2-ulososes,[5] inversion of β-glucosides,[6] radical anomeric inversion of α-mannosides,[7] direct O-alkylation of pyranoses,[8] and, most successfully, preattachment of the aglycon by means of a suitable tether to the O-2 position of mannosyl donors.[9] While the successful synthesis of oligosaccharides has been achieved through several of these methods,[10] a protocol for the direct coupling of aglycons to simple mannopyranosyl donors with high β-selectivity[11] remains a very desirable goal. Here, we present such a method for primary glycosyl acceptors.

Results and Discussion

In the context of our studies into the radical inversion of α- to β-manno pyranosides, a variation of the Kahne sulfoxide glycosylation protocol[12] involving addition of triflic anhydride (Tf$_2$O) to a mixture of the glycosyl donor **1**, acceptor **4**, and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) in diethyl ether at −78 °C led to the isolation of the α- and β-mannosides **2**α and **2**β in yields of 59 and 6%, respectively, or a 10:1 α:β ratio. In subsequent work, **1** and Tf$_2$O were allowed to react in ether in the presence of DTBMP at −78 °C for 5 min before addition of a benzene solution of the acceptor **4** resulting in a striking reversal of selectivity (α:β = 1:10.5) and isolation of the α- and β-mannosides in 8 and 85% yields, respectively. Subsequent studies rapidly led to the conclusion that both the presence of benzene in the reaction mixture and the mode of addition impinge significantly on the coupling stereoselectivity.

Scheme 1



After some experimentation, a standard protocol (A) for the formation of β-mannosides was developed in which Tf$_2$O was added to 1:2 mixture of **1** and DTBMP in Et$_2$O/benzene (7/1) at −78 °C followed by addition of the glycosyl acceptor and slow warming to 0 °C (Scheme 1).[13] As indicated in Table 1, entry 1, this protocol enabled the formation of a 10.7:1 β:α ratio of mannosides when applied to acceptor **4** and the isolation of the pure β-mannoside in 86% yield. Repetition of the same protocol with the exclusion of benzene resulted in a lowering of the β:α ratio to 4.5:1 (Table 1, entry 2), so

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(13) Protocol A: Standard experimental part for the formation of β-mannosides: To a stirred solution of **1** (106.6 mg, 0.2 mmol) and DTBMP (82.2 mg, 0.4 mmol) in dry diethyl ether (7 mL) and benzene (1 mL) cooled to −78 °C under N$_2$ was added Tf$_2$O (37 μL, O.22 mmol) followed, after 2−5 min, by a solution of the acceptor (0.4 mmol) in diethyl ether (2 mL). The opaque reaction mixture was stirred at −78 °C for 1.5 h and then allowed to warm over 2 h to 0 °C and maintained there for a further 0.5 h before quenching with saturated aqueous NaHCO$_3$, washing with brine, drying (Na$_2$SO$_4$), concentration, and purification by chromatography on silica gel.

(14) The logical extrapolation to the use of neat benzene or toluene as solvent is not possible for reasons of solubility.

(15) Protocol B: Standard experimental part for the formation of α-mannosides: To a stirred solution of **1** (106.6 mg, 0.2 mmol), DTBMP (41.1 mg, 0.2 mmol), and the glycosyl acceptor (0.4 mmol) in dry diethyl ether (10 mL) at −78 °C was added dropwise Tf$_2$O (37 μL, 0.22 mmol) over 3−5 min. The turbid reaction mixture was stirred at −78 °C for 1.5 h and then allowed to warm over 2 h to 0 °C and maintained there for a further 0.5 h before quenching with saturated aqueous NaHCO$_3$, washing with brine, drying (Na$_2$SO$_4$), concentration, and purification by chromatography on silica gel.

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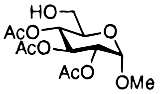
Table 1. Coupling of Aglycones with 1

entry	glycosyl acceptor	proto-col[a]	addi-tive	DTBMP equiv	**2**β % yield	**2**α % yield	3 % yield	β:α ratio
1	**4**	A	C_6H_6	2	86	8		10.7:1
2	**4**	A	none	2	69	15		4.5:1
3	**4**	A	none	1	75	15		5:1
4	**4**	B	none	1	9	71	7	0.12:1
5	**4**	B	none	2.3	65	22	7	3.0:1
6	**4**	C	DMB[b]	2	82	8		10.2:1
7	**5**	A	C_6H_6	2	84	10		8.6:1
8	**5**	C	DMB[b]	2	67	8	12	8.4:1
9	**6**	A	C_6H_6	2	50		15	>20:1
10	**6**	C	DMB[b]	2	51		30	>20:1
11	**7**	A	C_6H_6	2	64	10	23	6.4:1
12	**7**	C	DMB[b]	2	80		3	>20:1
13	**8**	A	C_6H_6	2	60	6	25	10.0:1
14	**8**	C	DMB[b]	2	70	7	17	10.0:1
15	**9**	A	C_6H_6	2	69	12	10	5.6:1
16	**9**	A	none	1	41	41	7	1.0:1
17	**9**	B	none	1	10	72	10	0.14:1
18	**9**	C	DMB[b]	2	61	14	15	4.3:1
19	**10**	A	C_6H_6	2	49	30	20	1.6:1
20	**10**	B	none	1	16	55	13	0.29:1
21	**10**	C	DMB[b]	2	50	33	10	1.5:1

[a] Protocol A: addition of ROH to premixed **1**, Tf_2O, and DTBMP in ether/benzene (footnote 13). Protocol B: addition of Tf_2O to premixed **1**, ROH and DTBMP in ether (footnote 15). Protocol C: as protocol A with DMB replacing benzene. [b] DMB: 1,4-dimethoxybenzene.

demonstrating the beneficial effect of the additive.[14] In the absence of benzene, the use of only a stoichiometric amount of DTBMP had little effect (contrast entries 2 and 3, Table 1). A second protocol (B),[15] involving addition of Tf_2O to a preformed mixture of the glycosyl donor and acceptor and DTBMP in the absence of benzene, enabled the formation of a mixture of glycosides highly enriched in the α-anomer (Table 1, entry 4). For protocol B, in the absence of benzene, the use of increased DTBMP led to a reversal in selectivity (Table 1, entry 5). A third protocol (C) was analogous to A except that benzene as a cosolvent was replaced by 4 molar equiv (with respect to **1**) of the electron-rich arene 1,4-dimethoxybenzene. It gave results mostly comparable to protocol A (Table 1, entry 6).

The extension of protocols A and C to the glycosyl acceptor **5** (Table 1, entries 7 and 8) resulted in good yields of β-mannoside, with the use of benzene as cosolvent proving marginally superior.[16] With aminoglucoside **6** both protocols A and C gave reaction mixtures devoid of α-mannoside as judged by ^{1}H-NMR spectroscopy, although the isolated yields of β-mannoside were only moderate (Table 1, entries 9 and 10). Use of racemic **7** as glycosyl acceptor resulted in good yields of the diastereomeric mixtures of β-mannoside, this time with C proving to be somewhat superior to A as protocol (Table 1, entries 11 and 12). The serine-derived glycosyl acceptor **8** was coupled to **1** in good yield and excellent β:α-ratios by either of protocols A or C, so demonstrating the potential of this coupling method for the formation of β-manno linked glycoproteins (Table 1, entries 13 and 14). With diisopropylidenegalactose (**9**) the best β:α ratio was obtained with protocol A (Table 1, entry 15). Application of protocol B to **9** permitted the isolation of the α-glycoside in good yield (Table 1, entry 17). Finally, attention was turned to the rhamnose derivative **10** as glycosyl acceptor. Unfortunately, by both protocols A and C disappointing β:α-ratios and yields not exceeding 50% were obtained (Table 1, entries 19 and 21). The use of protocol B enabled the isolation of the α-disaccharide in moderate yield (Table 1, entry 20). Inspection of Table 1 reveals that either of protocols A or C provide superior β:α ratios and permit the isolation of the pure β-mannosides in good to excellent yield when applied to a range of diverse primary glycosyl acceptors. Of these primary glycosyl acceptors **9** gave the lowest β:α ratio, but even in this case the β-mannoside could be isolated in 69% yield. Obviously, the lower ratio achieved with **9** is due to steric hindrance around the nucleophilic center, and this notion is strengthened by the poor selectivity observed with the secondary alcohol **10**.



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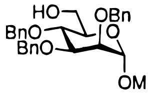

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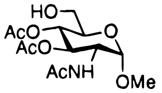

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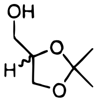

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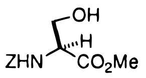

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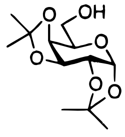

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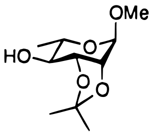

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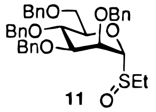

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The β-mannosylation appears to be limited to **1** as glycosyl donor, as application of either protocol A or C to the coupling of model alcohol **4** with the sulfoxide **11** gave disappointingly low β:α ratios (~1:2).

The precise mechanistic details underlying the reversal of selectivity brought about by the change in mixing sequence, as well as the role of the arenes including DTBMP, and of protecting groups in the donor are not yet apparent. However, it is clear that a rapid, efficient method is at hand for the formation of highly enriched β-mannopyranosides of primary glycosyl acceptors that is at least comparable in efficiency to other popular direct glycosylation methods,[11,17] as well as with recent indirect methods.[5−10] We are currently investigating the mechanism of the process as well as its extension to secondary glycosyl acceptors and further glycosyl donors and will report on these aspects in due course.

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Supporting Information Available: Listings of spectral data for **3** and all α- and β-mannosides reported (11 pages).

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[16] Anomeric configuration is readily assigned in each case by NOE difference spectroscopy and by inspection of the 1,2-coupling constant. It is confirmed, with the exception of **6**, which gave only the β-mannoside, in each case by simple application of Hudson's isorotation rule in which β-mannosides are predicted to have less positive/more negative specific rotations than their α-anomers.

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