Remote Participation-Assisted Synthesis of β-Mannosides

Cristina De Meo,[a] Medha N. Kamat,[a] and Alexei V. Demchenko*[a]

Keywords: Carbohydrates / Glycosylation / Remote participation / Stereoselective synthesis

The stereoselectivity of β-mannosylation can be improved with the use of a participating moiety at C-4 (*O*-anisoyl, *O*-thiocarbamoyl). This improvement was achieved in glycosidations of *S*-ethyl and, especially, *S*-benzoxazolyl (SBox) mannosides.

Introduction

The majority of carbohydrates found in nature exist as polysaccharides, glycoconjugates or glycosides in which monosaccharide units are connected by glycosidic bonds.[1–5] The necessity to form either a 1,2-*cis*- or 1,2-*trans*-glycosidic bond with complete stereoselectivity is the main reason chemical *O*-glycosylation is considered among the greatest challenges of modern synthetic chemistry. To address these issues, many new synthetic methodologies and strategies have been developed.[6–8] However, all of these developments are compromised when applied to the stereoselective synthesis of 1,2-*cis*-glycosides,[9–11] among which β-mannosides stand out as a particular challenge.[12–14] As a result, the synthesis of natural glycostructures containing one or more linkages of this type is problematic. Despite significant efforts and considerable progress made in the area of stereoselective β-mannosylation by Crich[15–20] and others,[21–41] each particular case still requires careful selection of techniques, protecting groups, promoters and synthetic strategies.

Results and Discussion

As a part of a program to develop novel methods for the synthesis of 1,2-*cis*-glycosides, we report here our attempt to address the synthetic challenges associated with stereoselective β-mannosylation. We decided to investigate whether a participating moiety (ester or thioester group) capable of-donation of a lone pair of electrons from the remote position of C-4 of the glycosyl donor would influence the stereochemical outcome of mannosylations.

[a] Department of Chemistry & Biochemistry,
University of Missouri – St. Louis,
One University Boulevard, St. Louis, Missouri 63121-4499, USA
Fax: (internat.) +1-314-516-5342
E-mail: demchenkoa@umsl.edu

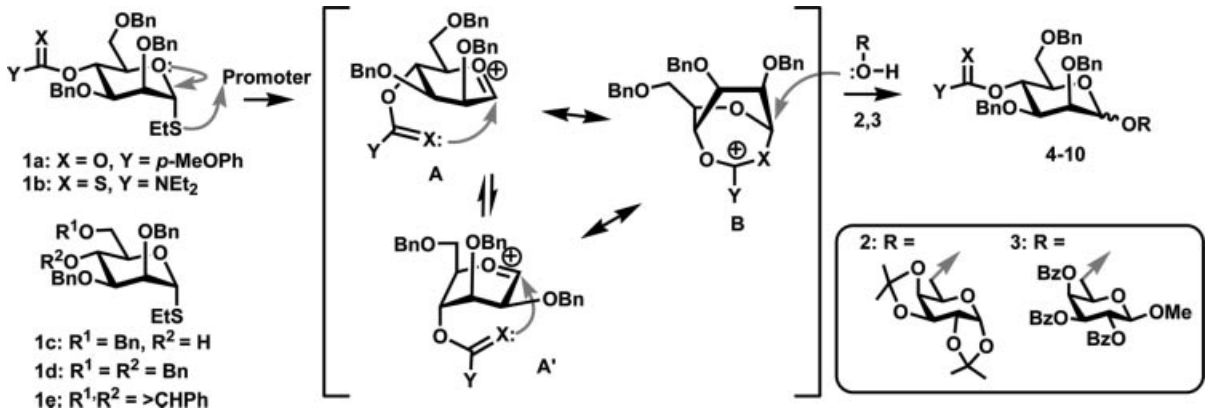
S-Ethyl glycosides, which have proven to be excellent glycosyl donors, were initially employed in our studies.[42,43] In order to investigate the remote effect on β-mannosylation, we obtained two thiomannosides modified at position C-4: **1a** (*p*-methoxybenzoyl, anisoyl) and **1b** (*N,N*-diethylthiocarbamoyl, Scheme 1). Their synthesis was accomplished by simple acylation (anisoyl chloride/pyridine or Et_2NCSCl/NaH/DMF, respectively) of the known 4-OH precursor **1c**.[44] It is noteworthy that both the anisoyl[45] and thiocarbamoyl[46,47] moieties have already been tested as remote participating groups on other sugar models.

For comparison, ethyl-2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-mannopyranoside (**1d**)[48] was used. Also, it has been previously documented that the 4,6-*O*-benzylidene acetal helps to improve the stereoselectivity of β-mannosylation by conformational modification of the transition state.[15,49] For this purpose we included ethyl-2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (**1e**)[44] in our comparative studies. On the other hand, compounds **2** and **3** [50] were selected as suitable glycosyl acceptors.

Having analysed possible mechanistic pathways, we assumed that upon promoter-assisted departure of the leaving group (*S*-ethyl), oxacarbenium ion **A** will be formed (Scheme 1). Subsequently, it is quite possible that participation would occur via acyloxonium ion **B**. It should be noted that in support of the feasibility of such a pathway, cyclic orthoesters (1,4- and 1,2,4-) of the D-*gluco* series have been isolated and characterised.[51–54] Presumably, in order to facilitate the remote participation, the oxacarbenium ion might have to first adopt a different pyranose ring conformation (such as **A′**).

Glycosidation of the perbenzylated **1d** was performed under standard reaction conditions for the thioglycoside activation[42,43] with the use of NIS/TMSOTf as a promoter and molecular sieves (4 Å) in DCM. As anticipated, coupling of **1d** with either **2** or **3** preferentially afforded the α-linked products **4** and **5**, respectively. These results are listed in Table 1 (entries 1 and 2). We found that this result could

  DOI: 10.1002/ejoc.200400616



Scheme 1.

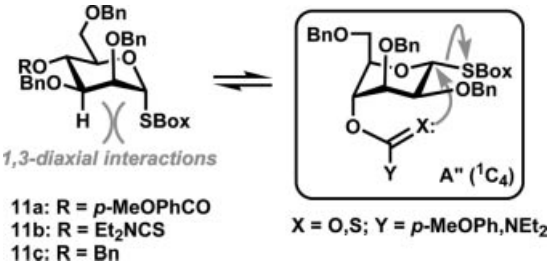
be slightly improved in terms of β-stereoselectivity by lowering the reaction temperature to –70 °C (entry 3). Varying other reaction conditions such as the promoter (MeOTf, DMTST, IDCP) and/or solvent (MeCN, DCM/ether, DCM/toluene) did not result in significant improvements in stereoselectivity. As initially anticipated, the glycosyl donor **1e** appeared to be more β-stereoselective. Thus, preferential formation of the β-linked disaccharides **6** and **7** was detected in these experiments (entries 4 and 6).

Table 1. NIS/TMSOTf-promoted glycosidations of the SEt mannosides **1a**, **b**, **e**, **d** in CH_2Cl_2.

Entry	Donor	Acc.	Temperature	Product	Yield, %	α/β ratio
1	**1d**	**2**	room temp.	**4**	86	2.7:1
2	**1d**	**3**	room temp.	**5**	98	1.6:1
3	**1d**	**3**	–70 → 0 °C	**5**	99	1.3:1
4	**1e**	**2**	room temp.	**6**	98	1:1.4
5	**1e**	**3**	room temp.	**7**	99	1.2:1
6	**1e**	**3**	–70 °C	**7**	99	1:2.1
7	**1a**	**2**	room temp.	**8**	99	1.6:1
8	**1a**	**3**	room temp.	**9**	63	1.2:1
9	**1a**	**3**	–70 °C → room temp.	**9**	90	1:1.5
10	**1b**	**3**	room temp.	**10**	63	1:1.1
11	**1b**	**3**	–70 °C → room temp.	**10**	64	1:1.5

Subsequently, we turned our attention to the glycosidation of mannosyl donors **1a** and **1b** bearing participating moieties at C-4. Unfortunately, the new mannosyl donors were only slightly β-stereoselective at low temperatures. In this respect, the thiocarbamoyl moiety allowed a marginally higher stereoselectivity at room temperature. Although some improvement was achieved in facilitating the acyloxonium ion **B** formation, the pyranose chair flip (**A** → **A′** , Scheme 1) does not seem to be a favoured pathway for the thioglycosides of the D-*manno* series.

We reasoned that if a sterically bulky leaving group were placed in the axial position at the anomeric centre, the 1,3-diaxial interactions would facilitate the chair in adopting a $^1C_4$ conformation and would therefore favour subsequent participation from the C-4 position. For these studies we selected a fairly bulky *S*-benzoxazolyl (SBox) anomeric moiety recently developed in our laboratory.[55,56] The adequately protected glycosyl donor **11a** (Scheme 2) was obtained from the corresponding *S*-ethyl glycoside **1a** via bromination with Br_2 followed by treatment with KSBox in the presence of 18-crown-6 in 58 % yield after two steps. This is a typical procedure for the synthesis of the SBox glycosides.[56] Similarly, the perbenzylated SBox mannoside **11c** was synthesised in 79% yield from **1d** to be used for comparison. Unfortunately, our efforts to obtain **11b** from **1b** according to this two-step pathway resulted in very low yields (15–20%). Therefore, we decided to explore the possibility of its direct synthesis from thioglycoside **11b** in the presence of a mild thiophilic promoter. This transformation was successfully achieved with HSBox in the presence of iodonium(dicollidine) perchlorate[57] and molecular sieves (4 Å). As a result, **11b** was obtained from **1b** in 49% yield.



Scheme 2.

Initial experiments with perbenzylated SBox glycoside **11c** were rather discouraging since no significant improvement was observed in comparison with that of *S*-ethyl mannoside **1d**. These results are presented in Table 2 (entries 1 and 2). Conversely, to our delight, SBox glycosyl donors bearing the anisoyl and thiocarbamoyl participating groups **11a** and **11b**, respectively, provided relatively high stereoselectivities, thus providing encouraging support for the remote participation concept. As listed in Table 2, these reactions were performed in CH_2Cl_2 at low temperature (–70 °C → room temp.). Interestingly, a number of promoters avail-

able for the activation of the SBox-functionality such as AgOTf, MeOTf or NIS/TMSOTf provided consistent β-stereoselectivity with a respectable ratio α/β = 1:3–5 (entries 3–7, Table 2).

Table 2. Glycosidation of the SBox mannosides **11a**–**c** with glycosyl acceptors **3, 12**–**14** in CH_2Cl_2.

Entry	Donor	Acc.	Promoter	Product	Yield, %	α/β ratio
1	**11c**	**3**	AgOTf	**5**	65	1:1.5
2	**11c**	**3**	MeOTf	**5**	72	1:2.2
3	**11a**	**3**	AgOTf	**9**	83	1:3.1
4	**11a**	**3**	MeOTf	**9**	96	1:3.5
5	**11a**	**3**	NIS/ TMSOTf	**9**	57	1:3.2
6	**11b**	**3**	AgOTf	**10**	82	1:4.9
7	**11b**	**3**	NIS/ TMSOTf	**10**	66	1:3.3
8	**11c**	**12**	MeOTf	**15**	83	1:5.9
9	**11a**	**12**	MeOTf	**16**	76	1:7.0
10	**11c**	**13**	MeOTf	**17**	83	1:2.5
11	**11a**	**13**	MeOTf	**18**	69	1:3.0
12	**11c**	**14**	MeOTf	**19**	72	1:2.3
13	**11a**	**14**	MeOTf	**20**	59	1:2.7

[a] AgOTf or NIS/TMSOTf-promoted glycosylations were initiated at –70 °C, whereas MeOTf-promoted reactions were initiated at –20 °C, the temperature was then allowed to gradually increase to room temperature.

Subsequently, we turned our attention to the glycosylation of a range of secondary glycosyl acceptors **12**–**14** (Figure 1).[58–60] These experiments were performed under standard reaction conditions in the presence of MeOTf. As a result, disaccharides **15**–**20** (Figure 1) were obtained with high stereoselectivities and yields (Table 2, entries 8–13).

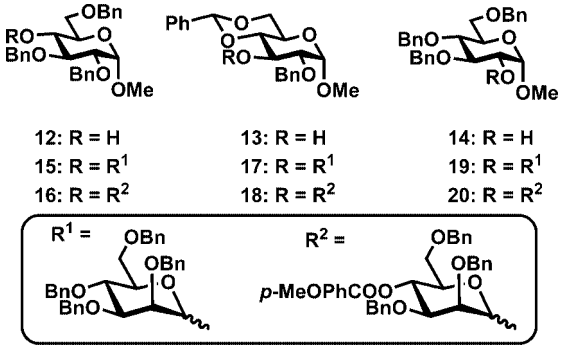


Figure 1. Structures of the glycosyl acceptors **12**–**14** and disaccharides **15**–**20**.

Conclusions

In conclusion, these results demonstrate that the stereoselectivity of β-mannosylation can be improved with the use of a participating moiety at C-4 for compounds of the D-*manno* series. Previously, similar long-range participation has been demonstrated for sugars of the D-galacto[45,47,61] and L-fuco[62,63] series. Initially, this influence was attributed to the electron-withdrawing effect of an ester group at a remote position.[64,65] As more experimental data has been acquired, the importance of remote participation has come to the foreground. For example, it has been previously demonstrated that for the glycosyl donors of the D-*galacto* series, an electron-withdrawing substituent at C-4 which is not capable of participation, such as 2,2,2-trifluoroethyl, does not affect the stereoselectivity. Conversely, remote groups capable of participation have a dramatic effect.[45] In the present work the improvement was especially notable when a bulky SBox substituent was used as the leaving group at the anomeric centre.

Experimental Section

General Remarks: Column chromatography was performed on silica gel 60 (EM Science, 70–230 mesh), reactions were monitored by TLC on Kieselgel 60 F_{254} (EM Science). The compounds were detected by examination under UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at <40 °C. DCM, $MeNO_2$ and MeCN were distilled from CaH_2 immediately prior to use. Anhydrous DMF (EM Science) was used as received. Methanol was dried by heating to reflux with magnesium methoxide, distilled and stored under argon. Pyridine was dried by heating to reflux with CaH_2 and then distilled and stored over molecular sieves (3 Å). Molecular sieves (3 Å), used for reactions, were crushed and activated in vacuo at 390 °C over 8 h in the first instance and then for 2–3 h at 390 °C directly before use. AgOTf (Acros) was coevaporated with toluene (3× 10 mL) and dried in vacuo for 2–3 h directly prior to application. Optical rotations were measured on a Jasco P-1020 polarimeter. ^{1}H NMR spectra were recorded at 300MHz and ^{13}C NMR spectra were recorded at 75MHz (Bruker Avance instrument). HRMS measurements were made with a JEOL MStation (JMS-700) Mass Spectrometer.

Synthesis of Glycosyl Donors

Ethyl 2,3,6-Tri-*O*-benzyl-4-*O*-(*p*-methoxybenzoyl)-1-thio-α-D-mannopyranoside (1a): Anisoyl chloride (2.03 mmol, 277 μL) was added dropwise to a stirred solution of ethyl-2,3,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (**1c**, 300 mg, 0.61 mmol) in pyridine (2.0 mL) under argon. The reaction mixture was kept for 16 h at room temperature, quenched with MeOH (5 mL) and concentrated in vacuo. The residue was coevaporated with toluene (3× 15 mL) and purified by silica gel column chromatography (ethyl acetate/hexane gradient elution) to afford **1a** as a colourless syrup (300 mg, 79%). R_f = 0.50 (ethyl acetate/toluene, 1:9, v/v). $[\alpha]_D^{22}$ = +44.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.89–7.96 (m, 19 H, aromatic), 5.62 (dd, $J_{4,5}$ = 9.7 Hz,1 H, H-4), 5.42 (br. s, 1 H, H-1), 4.72 (s, 2 H, CH_2Ph), 4.49 (s, 2 H, CH_2Ph), 4.46 (dd, ^2J = 12.2 Hz, 2 H, CH_2Ph), 4.32 (m, $J_{5,6a}$ = 6.2, $J_{5,6b}$ = 3.1 Hz, 1 H, H-5), 3.95 (m, 1 H, CH_2 ^{a}CH_3), 3.84–3.91 (m, $J_{3,4}$ = 8.7 Hz, 2 H, H-2,3), 3.86–3.91 (m, 5 H, H-2,3, OCH_3), 3.67 (dd, $J_{6a,6b}$ = 11.0 Hz, 1 H, H-6a), 3.62 (dd, 1 H, H-6b), 2.65 (m, 2 H, CH_2CH$_3$), 1.28 (t, 3 H, CH$_2$CH_3)ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.66, 138.37, 138.23, 137.99, 132.13, 128.56, 128.48, 128.35, 128.16, 128.06, 127.87, 127.81, 127.72, 127.52, 113.77, 82.32, 77.43, 76.03, 73.60, 72.57, 71.90, 71.17, 70.05, 69.40, 55.69, 25.46, 15.07 ppm. HR-FAB MS [M + H]$^+$ calcd. for $C_{37}H_{41}O_7S$ 629.2573, found 629.2571

Ethyl 2,3,6-Tri-*O*-benzyl-4-*O*-(*N*,*N*-diethylthiocarbamoyl)-1-thio-α-D-mannopyranoside (1b): NaH (60%, 32 mg, 0.40 mmol) was added

portionwise to a stirred solution of **1c** (200 mg, 0.80 mmol) and *N,N*-diethylthiocarbamoyl chloride (92 mg, 0.60 mmol) in DMF (2.0 mL) at 0 °C. The temperature was allowed to gradually rise to room temperature and the reaction mixture was stirred for 16 h. It wasthen poured into ice-water (50 mL) and stirred for an additional 30 min. The aqueous layer was extracted with ethyl acetate/Et_2O (1:1, v/v, 3× 15 mL). The organic layers were combined and washed with water (3× 20 mL), dried ($MgSO_4$) and concentrated in vacuo to dryness. The residue was purified by silica gel column chromatography (ethyl acetate/hexane gradient elution) to afford **1b** as a white foam (208 mg, 84%). R_f = 0.56 (ethyl acetate/toluene, 1:9, v/v). $[\alpha]_D^{22}$ = +48.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.40 (m, 18 H, aromatic), 6.17 (dd, $J_{4,5}$ = 8.7 Hz, 1 H, H-4), 5.39 (d, $J_{1,2}$ = 2.4 Hz, 1 H, H-1), 4.70 (dd, ^2J = 12.4 Hz, 2 H, CH_2Ph), 4.56 (dd, ^2J = 11.9 Hz, 2 H, CH_2Ph), 4.54 (dd, ^2J = 12.1 Hz, 2 H, CH_2Ph), 4.31 (m, 1 H, H-5), 3.95 (m, 1 H, CH_2 ^{a}CH$_3$), 3.84–3.91 (m, $J_{3,4}$ = 8.7 Hz, 2 H, H-2,3), 3.74–3.77 (m, 2 H, H-6a,6b), 3.66 (m, 1 H, CH_2 ^{b}CH$_3$), 3.18–3.42 (m, 2 H, CH_2CH$_3$), 2.70 (m, 1 H, CH_2CH$_3$), 1.31 (t, 3 H, CH$_2$CH_3), 1.23 (t, 3 H, CH$_2$CH_3), 1.02 (t, 3 H, CH$_2$CH_3)ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.92, 138.53, 138.24, 138.11, 128.48, 128.41, 128.35, 128.11, 127.80, 127.74, 127.67, 127.54, 81.71, 75.94, 75.37, 74.30, 73.47, 72.36, 71.83, 71.68, 70.10, 48.13, 43.34, 13.58, 12.03 ppm. HR-FAB MS [M + H]$^+$ calcd. for $C_{34}H_{44}NO_5S_2$ 610.2661, found 610.2670

Benzoxazolyl 2,3,6-Tri-*O*-benzyl-4-*O*-(*p*-methoxybenzoyl)-1-thio-α-D-mannopyranoside (11a): A solution of **1a** (300 mg, 0.477 mmol) in CH_2Cl_2 (7.0 mL) together with activated molecular sieves (3 Å, 240 mg) was stirred under argon for 1 h. A freshly prepared solution of Br_2 in CH_2Cl_2 (4.5 mL, 1:165, v/v) was then added and the reaction mixture was kept for 5 min at room temp. After this, the solid was removed by filtration and the filtrate was concentrated in vacuo at room temp. The crude residue was then treated with KSBox (0.57 mmol) and 18-crown-6 (0.04 mmol) in dry acetone (5.0 mL) under argon for 2 h at room temp. Upon completion the mixture was diluted with toluene, the solid removed by filtration and the residuewashed with toluene. Thefiltrates(30 mL) were combined and washed with 1% aq. NaOH (15 mL) and water (3× 10 mL). The organic layer was separated, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/toluene gradient elution) to afford **11a** as a colourless syrup (200 mg, 58%). R_f = 0.50 (ethyl acetate/toluene, 1:9, v/v). $[\alpha]_D^{22}$–12.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.91–7.96 (m, 23 H, aromatic), 5.90 (d, $J_{1,2}$ = 1.3 Hz, 1 H, H-1), 5.69 (dd, $J_{4,5}$ = 9.5 Hz, 1 H, H-4), 4.96 (dd, ^2J = 11.5 Hz, 2 H, CH_2Ph), 4.65 (dd, ^2J = 12.2 Hz, 2 H, CH_2Ph), 4.44 (dd, ^2J = 11.7 Hz, 2 H, CH_2Ph), 4.25 (br. d, H-2), 3.83–4.00 (m, $J_{3,4}$ = 9.5 Hz, 2 H, H-3,5), 3.89 (s, 3 H, OCH$_3$), 3.71 (d, $J_{5,6a}$ = $J_{5,.6b}$ = $J_{6a,6b}$ = 4.8 Hz, 2 H, H-6a,6b)ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.77, 152.06, 141.85, 138.11, 137.62, 137.47, 132.08, 128.81, 128.64, 128.51, 128.24, 128.12, 128.07, 127.84, 127.46, 124.59, 124.35, 122.23, 118.81, 113.84, 110.26, 84.76, 80.38, 79.48, 75.80, 74.97, 73.66, 72.67, 70.05, 68.89, 55.67 ppm. HR-FAB MS [M + H]$^+$ calcd. for $C_{42}H_{40}NO_8S$ 718.2475, found 718.2480

Benzoxazolyl 2,3,6-Tri-*O*-benzyl-4-*O*-(*N,N*-diethylthiocarbamoyl)-1-thio-α-D-mannopyranoside (11b): A mixture of **1b** (44.3 mg, 0.073 mmol), HSBox (21 mg, 0.145 mmol) and freshly activated molecular sieves (4 Å, 120 mg) in CH_2Cl_2 (2 mL) was stirred under argon for 1.5 h. The reaction mixture was then cooled to 0 °C and iodonium(dicollidine)perchlorate (102 mg, 0.20 mmol) was added. The temperature was then allowed to gradually increase to room temperature and the reaction mixture was stirred for 24 h. Upon completion, the reaction mixture was diluted with CH_2Cl_2, the solid removed by filtration and the residue washed with CH_2Cl_2. Thefiltrates were combined (30 mL) and washed with 20% aq. $NaHCO_3$ (15 mL) and water (3× 10 mL). The organic phase was separated, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/toluene gradient elution) to afford **11b** as a clear syrup in 49% yield. R_f = 0.60 (ethyl acetate/toluene, 1:9, v/v). $[\alpha]_D^{22}$ –5.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.66–7.70 (m, 19 H, aromatic), 6.37 (dd, $J_{4,5}$ = 9.8 Hz, 1 H, H-4), 6.04 (d, $J_{1,2}$ = 1.2 Hz, 1 H, H-1), 4.65 (dd, ^2J = 11.9 Hz, 2 H, CH_2Ph), 4.53 (dd, ^2J = 12.2 Hz, 2 H, CH_2Ph), 4.46 (m, 1 H, H-5), 4.44 (dd, ^2J = 11.5 Hz, 2 H, CH_2Ph), 4.00 (m, 1 H, CH_2 ^{a}CH$_3$), 3.82–3.94 (m, $J_{3,4}$ = 9.8 Hz, 2 H, H-2,3), 3.74 (d, $J_{5,6a}$ = $J_{5,.6b}$ = $J_{6a,6b}$ = 4.7 Hz, 2 H, H-6a,6b), 3.63 (m, 1 H, CH_2 ^{b}CH$_3$), 3.38 (m, 1 H, CH_2 ^{a}CH$_3$), 3.18 (m, 1 H, CH_2 ^{b}CH$_3$), 1.24 (m, 3 H, CH$_2$CH_3), 1.01 (t, 3 H, CH$_2$CH_3)ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.02, 177.00, 147.21, 138.10, 137.80, 131.47, 128.70, 128.63, 128.54, 128.27, 128.04, 127.88, 127.79, 127.72, 124.81, 124.03, 115.96, 109.70, 87.20, 80.65, 78.18, 74.97, 74.21, 73.61, 72.57, 72.37, 69.72, 48.48, 43.53, 13.66, 12.09 ppm. HR-FAB MS [M + H]$^+$ calcd. for $C_{39}H_{43}N_2O_6S_2$ 699.2563, found 699.2567

Benzoxazolyl 2,3,4,6-Tetra-O-benzyl-1-thio-α-D-mannopyranoside (11c): This was obtained from **1d**, as described for the synthesis of **11a**, as a colourless syrup in 79% yield. R_f = 0.60 (ethyl acetate/toluene, 1:9, v/v). $[\alpha]_D^{22}$ –12.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.05–7.53 (m, 24 H, aromatic), 5.72 (d, $J_{1,2}$ = 0.8 Hz, 1 H, H-1), 4.86 (dd, ^2J = 11.4 Hz, 2 H, CH_2Ph), 4.71 (s, 2 H, CH_2Ph), 4.65 (dd, ^2J = 10.9 Hz, 2 H, CH_2Ph), 4.47 (dd, ^2J = 11.9 Hz, 2 H, CH_2Ph), 4.12 (br. d, $J_{2,3}$ = 1.2 Hz, 1 H, H-2), 3.97 (dd, $J_{4,5}$ = 9.7 Hz, 1 H, H-4), 3.58–3.76 (m, 4 H, H-3,5,6a,6b)ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.27, 151.82, 141.71, 138.28, 138.16, 137.90, 137.81,128.52, 128.32, 128.27, 128.25, 128.17, 127.94, 127.88, 127.77, 127.64, 127.37, 124.33, 124.07, 118.61, 110.01, 84.65, 83.64, 80.52, 76.76, 76.58, 75.07, 74.92, 74.43, 73.44, 72.98, 69.07 ppm. HR-FAB MS [M + H]$^+$ calcd. for $C_{41}H_{40}NO_6S$ 674.2576, found 674.2574.

Synthesis of Disaccharides

Typical AgOTf-Promoted Glycosylation Procedure (Activation of the SBox Glycosides 11a–c): A mixture the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol) and freshly activated molecular sieves (3 Å, 200 mg) in CH_2Cl_2 (2 mL) was stirred under argon for 1.5 h. The reaction mixture was cooled to –70 °C and freshly conditioned AgOTf (0.22 mmol) was added. The temperature was then allowed to gradually increase to room temperature and the reaction mixture was stirred for 1–16 h. Upon completion, the reaction mixture was diluted with CH_2Cl_2, the solid removed by filtration and the residue washed with CH_2Cl_2. The filtrates were combined (30 mL) and washed with 20% aq. $NaHCO_3$ (15 mL) and water (3× 10 mL). The organic phase was then separated, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane gradient elution).

Typical MeOTf-Promoted Glycosylation Procedure (Activation of the SBox Glycosides 11a–c): A mixture the glycosyl donor (0.11 mmol), glycosyl acceptor (0.10 mmol) and freshly activated molecular sieves (3 Å, 200 mg) in CH_2Cl_2 (2 mL) was stirred under argon for 1.5 h. The reaction mixture was cooled to –20 °C and MeOTf (0.33 mmol) was added. The temperature was then allowed to gradually increase to room temperature and the reaction mixture was stirred for 1–16 h. Upon completion, the reaction mixture was diluted with CH_2Cl_2, the solid removed by filtration and the residue washed with CH_2Cl_2. The filtrates were combined (30 mL) and

washed with 20% aq. $NaHCO_3$ (15 mL) and water (3× 10 mL). The organic phase was separated, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane gradient elution).

Typical NIS/TMSOTf-Promoted Glycosylation Procedure (Activation of the S-ethyl Glycosides 1a–c): A mixture the glycosyl donor (0.125 mmol), glycosyl acceptor (0.10 mmol) and freshly activated molecular sieves (4 Å, 200 mg) in CH_2Cl_2 (2 mL) was stirred for 1 h under an atmosphere of argon. NIS (0.25 mmol) and TMSOTf (0.025 mmol) were then added and the reaction mixture was stirred for 2–24 h at room temp. Upon completion, the solid was removed by filtration and the residue washed with CH_2Cl_2. The filtrates were combined (30 mL) and washed with 20% aq. $Na_2S_2O_3$ (15 mL) and water (3× 10 mL). The organic phase was separated, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane gradient elution).

All synthesised disaccharides have appropriate ^1H, ^{13}C NMR and HRMS data. Anomeric ratios were determined by comparing the integral intensities of relevant signals in the ^1H NMR spectra.

Acknowledgments

This work was supported by "The Foundation BLANCEFLOR Boncompagni-Ludovisi, née Bildt" and the University of Missouri Research Board. The authors also thank the NSF for grants to purchase the NMR spectrometer (CHE-9974801) and the mass spectrometer (CHE-9708640).

[1] A. Varki, *Glycobiology* **1993**, *3*, 97–130.
[2] R. A. Dwek, *Chem. Rev.* **1996**, *96*, 683–720.
[3] A. Varki, R. Cummings, J. Esko, H. Freeze, G. Hart, J. Marth, *Essentials of Glycobiology*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N. Y., **1999**.
[4] C. R. Bertozzi, L. L. Kiessling, *Science* **2001**, *291*, 2357–2364.
[5] G. E. Ritchie, B. E. Moffatt, R. B. Sim, B. P. Morgan, R. A. Dwek, P. M. Rudd, *Chem. Rev.* **2002**, *102*, 305–319.
[6] K. Toshima, K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503–1531.
[7] B. G. Davis, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2137–2160.
[8] K. C. Nicolaou, H. J. Mitchell, *Angew. Chem. Int. Ed.* **2001**, *40*, 1576–1624.
[9] A. V. Demchenko, *Curr. Org. Chem.* **2003**, *7*, 35–79.
[10] A. V. Demchenko, *Synlett* **2003**, 1225–1240.
[11] A. J. Fairbanks, *Synlett* **2003**, 1945–1958.
[12] J. J. Gridley, H. M. I. Osborn, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1471–1491.
[13] V. Pozsgay in *Carbohydrates in Chemistry and Biology*, vol. 1 (Eds.: B. Ernst, G. W. Hart, P. Sinaÿ), Wiley-VCH, Weinheim, New York, **2000**, pp. 319–343.
[14] D. Crich, *J. Carbohydr. Chem.* **2002**, *21*, 667–690.
[15] D. Crich, S. Sun, *J. Org. Chem.* **1996**, *61*, 4506–4507.
[16] D. Crich, S. Sun, *J. Org. Chem.* **1997**, *62*, 1198–1199.
[17] D. Crich, S. Sun, *J. Am. Chem. Soc.* **1998**, *120*, 435–436.
[18] D. Crich, M. Smith, *Org. Lett.* **2000**, *2*, 4067–4069.
[19] D. Crich, H. Li, *J. Org. Chem.* **2002**, *67*, 4640–4646.
[20] D. Crich, M. Smith, *J. Am. Chem. Soc.* **2002**, *124*, 8867–8869.
[21] H. Paulsen, O. Lockhoff, *Chem. Ber.* **1981**, *114*, 3102–3114.
[22] F. Barresi, O. Hindsgaul, *J. Am. Chem. Soc.* **1991**, *113*, 9376–9377.
[23] E. M. Klimov, A. V. Demchenko, N. N. Malysheva, N. K. Kochetkov, *Bioorg. Khim.* **1991**, *17*, 1660–1664.
[24] G. Stork, G. Kim, *J. Am. Chem. Soc.* **1992**, *114*, 1087–1088.
[25] V. K. Srivastava, C. Schuerch, *J. Org. Chem.* **1981**, *46*, 1121–1126.
[26] J. Tamura, R. R. Schmidt, *J. Carbohydr. Chem.* **1995**, *14*, 895–911.
[27] G. Hodosi, P. Kovac, *J. Am. Chem. Soc.* **1997**, *119*, 2335–2336.
[28] A. Dan, M. Lergenmuller, M. Amano, Y. Nakahara, T. Ogawa, Y. Ito, *Chem. Eur. J.* **1998**, *4*, 2182–2190.
[29] T. Ziegler, G. Lemanski, *Eur. J. Org. Chem.* **1998**, 163–170.
[30] S. K. Chung, K. H. Park, *Tetrahedron Lett.* **2001**, *42*, 4005–4007.
[31] I. Cumpstey, A. J. Fairbanks, A. J. Redgrave, *Org. Lett.* **2001**, *3*, 2371–2374.
[32] S. C. Ennis, A. J. Fairbanks, C. A. Slinn, R. J. Tennant-Eyles, H. S. Yeates, *Tetrahedron* **2001**, *57*, 4221–4230.
[33] K. S. Kim, J. H. Kim, Y. J. Lee, Y. J. Lee, J. Park, *J. Am. Chem. Soc.* **2001**, *123*, 8477–8481.
[34] H. Nagai, K. Kawahara, S. Matsumura, K. Toshima, *Tetrahedron Lett.* **2001**, *42*, 4159–4162.
[35] O. Nashiru, D. L. Zechel, D. Stoll, T. Mohammadzadeh, R. A. J. Warren, S. G. Withers, *Angew. Chem. Int. Ed.* **2001**, *40*, 417–420.
[36] A. A. H. Abdel-Rahman, E. Jonke, E. S. H. El Ashry, R. R. Schmidt, *Angew. Chem. Int. Ed.* **2002**, *41*, 2972–2974.
[37] T. Tsuda, S. Sato, S. Nakamura, S. Hashimoto, *Heterocycles* **2003**, *59*, 509–515.
[38] T. Mukaiyama, T. Hashihayata, H. Mandai, *Chem. Lett.* **2003**, *32*, 340–341.
[39] S. J. Marsh, K. P. R. Kartha, R. A. Field, *Synlett* **2003**, 1376–1378.
[40] H. Nagai, S. Matsumura, K. Toshima, *Carbohydr. Res.* **2003**, *338*, 1531–1534.
[41] E. Kaji, Y. Hosokawa, Y. Watanabe, M. Kobayashi, M. Yamakawa, *Heterocycles* **2003**, *61*, 459–470.
[42] P. J. Garegg, *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179–205.
[43] S. Oscarson in *Carbohydrates in Chemistry and Biology, Vol. 1* (Eds.: B. Ernst, G. W. Hart, P. Sinaÿ), Wiley-VCH, Weinheim, New York, **2000**, pp. 93–116.
[44] P. J. Garegg, I. Kvarnstrom, A. Niklasson, G. Niklasson, S. C. T. Svensson, *J. Carbohydr. Chem.* **1993**, *12*, 933–953.
[45] A. V. Demchenko, E. Rousson, G. J. Boons, *Tetrahedron Lett.* **1999**, *40*, 6523–6526.
[46] T. Mukaiyama, T. Ishikawa, H. Uchiro, *Chem. Lett.* **1997**, 389–390.
[47] T. Mukaiyama, M. Suenaga, H. Chiba, H. Jona, *Chem. Lett.* **2002**, 56–57.
[48] F. Dasgupta, P. J. Garegg, *Acta Chem. Scand.* **1989**, *43*, 471–475.
[49] M. Yun, Y. Shin, K. H. Chun, J. E. N. Shin, *Bull. Korean Chem. Soc.* **2000**, *21*, 562–566.
[50] I. E. Valashek, M. K. Shakhova, V. A. Minaev, G. I. Samokhvalov, *Zh. Obshch. Khim.* **1974**, *44*, 1161–1164.
[51] A. F. Bochkov, Y. V. Voznyi, V. M. Kalinevich, A. S. Shashkov, N. K. Kochetkov, *Izv. Akad. Nauk Ser. Khim.* **1975**, 415–420.
[52] C. A. A. van Boeckel, L. P. C. Delbressine, F. M. Kaspersen, *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 259–265.
[53] K. Katano, P. I. Chang, A. Millar, V. Pozsgay, D. K. Minster, T. Ohgi, S. M. Hecht, *J. Org. Chem.* **1985**, *50*, 5807–5815.
[54] N. K. Kochetkov, N. N. Malysheva, A. V. Demchenko, N. G. Kolotyrkina, E. M. Klimov, *Bioorg. Khim.* **1991**, *17*, 1655–1659.
[55] A. V. Demchenko, N. N. Malysheva, C. De Meo, *Org. Lett.* **2003**, *5*, 455–458.
[56] A. V. Demchenko, M. N. Kamat, C. De Meo, *Synlett* **2003**, 1287–1290.
[57] R. U. Lemieux, A. R. Morgan, *Can. J. Chem.* **1965**, *43*, 2190–2198.
[58] P. J. Garegg, H. Hultberg, *Carbohydr. Res.* **1981**, *93*, C10–C11.
[59] Y. Kondo, *Agric. Biol. Chem.* **1975**, *39*, 1879–1881.

[60] A. J. Pearce, P. Sinaÿ, *Angew. Chem. Int. Ed.* **2000**, *39*, 3610–3612.
[61] Y. P. Cheng, H. T. Chen, C. C. Lin, *Tetrahedron Lett.* **2002**, *43*, 7721–7723.
[62] E. J. Corey, P. Carpino, *J. Am. Chem. Soc.* **1989**, *111*, 5472–5473.
[63] A. G. Gerbst, N. E. Ustuzhanina, A. A. Grachev, D. E. Tsvetkov, E. A. Khatuntseva, N. E. Nifant′ev, *Mendeleev Commun.* **1999**, 114–116.
[64] C. A. A. van Boeckel, T. Beetz, S. F. van Aelst, *Tetrahedron* **1984**, *40*, 4097–4107 and references cited therein.
[65] C. A. A. van Boeckel, T. Beetz, *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 171–173.

Received: September 1, 2004

