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Carbohydrate Research 342 (2007) 631–637
Carbohydrate RESEARCH

Note

Evaluation of thioglycosides of Kdo as glycosyl donors

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Received 17 July 2006; accepted 22 August 2006
Available online 9 October 2006

Dedicated to the memory of Professor Nikolay K. Kochetkov

Abstract—The use of Kdo thioglycosides as glycosyl donors using DMTST, IBr/AgOTf and NIS/AgOTf as promoters has been evaluated. Activation at low temperature allowed to escape the formation of 2,3-glycal byproducts to give glycosides in high yield and with good β-anomeric selectivity. The use of diethyl ether as solvent and (especially) isopropylidene acetals as protecting groups improved the α-anomeric selectivity. NIS/AgOTf as promoter surprisingly yielded the 3-iodo-product *via* the glycal intermediate.

Keywords: Thioglycoside donors; Kdo glycosides; Thiophilic promoters

3-Deoxy-D-*manno*-oct-2-ulosonic acid (Kdo) is a monosaccharide found in bacterial and plant polysaccharides. It is an important component of the inner core part of the lipopolysaccharide structure of Gram-negative bacteria, where it is found as the α-anomer.[1,2] In bacterial capsular polysaccharides, it is found both as the α- and the β-anomer. Glycosylations with Kdo-donors are often hampered by the concomitant formation of the α,β-unsaturated ester through an elimination reaction,[3] and, due to the 3-deoxy function, stereochemical control is a problem. So far, mainly halide donors (especially the bromide) have been utilized in Kdo glycosylation reactions.[4] Surprisingly, there is only one earlier report on the use of thioglycosides as Kdo glycosyl donors, then with NIS/TfOH as promoter.[5] In contrast, for sialylation reactions, plagued by the same problems due to the structural similarities between Kdo and sialic acids, thioglycosides have been used extensively,[6] for example, *O*-xanthates promoted by DMTST[7] or phenylsulfenyl triflate[8] and alkyl or aryl thioglycosides promoted by DMTST[9] or IBr.[10] Herein, we report our findings in glycosylation with various Kdo thioglycoside donors promoted with different promoter systems: DMTST,[11] IBr/AgOTf[10] and NIS/AgOTf.[12]

The thioglycoside **2** was prepared from the peracetylated Kdo methyl ester **1**[13] by treatment with EtSH/$ZnCl_2$ (Scheme 1). The use of BF_3-etherate as Lewis acid is reported to give exclusively the β-glycoside,[5] whereas $ZnCl_2$ gave an α/β-ratio of about 1:5, but the ratio is quite dependent on the reaction conditions, elevated temperature and prolonged reaction time giving not only increased amount of the α-anomer but also a decreased yield. The α/β-ratio can be changed to around 5:1 by following anomerization with $ZnCl_2$ in CH_3NO_2.[14] From compound **2**, the perbenzoylated analogue **4** as well as the di-*O*-isopropylidene derivative **5** were synthesized using known methodology. From **1**, the corresponding piperidine *N*-xanthate **7** was formed, via the bromo sugar **6**, according to the published procedure.[15]

The glycosylation reactions were performed with the spacer alcohol 2-(4-trifluoroacetamidophenyl)ethanol (**8**) as model acceptor and with different promoter systems, DMTST, IBr/AgOTf and NIS/AgOTf (Scheme 2), and the results are summarized in Table 1. To determine the anomeric configuration of compounds **10** and **11**, which is not trivial since Kdo lacks an anomeric proton, these derivatives were deprotected and acetylated, whereafter the NMR spectra of the obtained compounds were compared to the published spectra of **9α**.[16]

The use of DMTST and the peracetylated donor **2** (α/β 1:5) in CH_2Cl_2 at −15 °C (entry 1) gave similar

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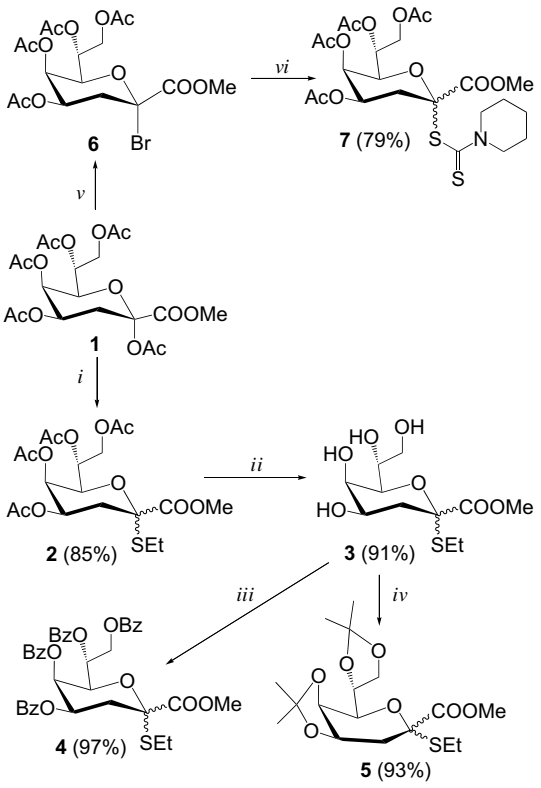
doi:10.1016/j.carres.2006.08.021



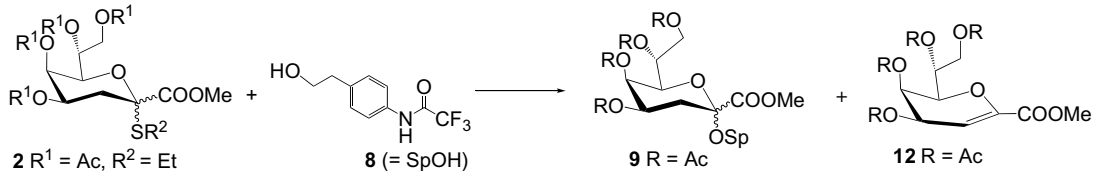
Scheme 1. Synthesis of the thioglycoside donors. Reagents and conditions: (i) EtSH, $ZnCl_2$, CH_2Cl_2; (ii) NaOMe, MeOH; (iii) BzCl, Pyridine; (iv) dimethoxypropane, *p*-TSOH, DMF; (v) HBr/HOAc; (vi) piperidine, NaH, CS_2.

results as those reported with NIS/TfOH as promoter,[5] that is, high yield of the spacer glycoside but with low stereoselectivity and with a preponderance for the β-anomer. Attempts to increase the amount of the α-anomer by performing the coupling reaction in diethyl ether[17] required a higher temperature with concomitant increase of elimination and other side products and severe decrease in yield and only minor increase in the α/β-ratio (entry 2).

In glycosylation reactions with neuraminic acid donors, good results have been obtained using *O*-xanthate donors at low temperature.[7,8,18] We have earlier synthesized anomeric piperidine *N*-xanthate derivatives of various hexoses and found that they functioned well as glycosyl donors.[15] With the Kdo *N*-xanthate **7** using DMTST as promoter, experiments proved −15 °C once more to be an optimal reaction temperature to avoid elimination, while still keeping the glycosylation reaction fast enough (entry 3). A high 84% yield of the Kdo-glycoside was obtained, mainly as the β-anomer (α/β 1:2.6). Again the use of diethyl ether as solvent not only marginally improved the α/β-ratio (α/β 1:1.5) but also lowered the yield due to competing elimination reaction at the higher temperature needed (entry 4).

Excellent results considering both the yields and stereoselectivity for the α-anomer have been reported using neuraminic thioglycoside donors in IBr/AgOTf promoted glycosylations.[10] Using this promoter system, it is possible to activate thioglycosides at very low temperature (−70 °C). This promoter was tried with the perbenzoylated donor **4**. To improve solubility at this low temperature, a 3:2 MeCN–CH_2Cl_2 solvent system was utilized. Glycosylation with donor **4** gave a one-spot TLC reaction, from which 81% of the spacer glycoside could be isolated (entry 5). The reaction proceeded with excellent stereoselectivity, giving exclusively the β-glycoside as the product. Thus, as with neuraminic acid donors, these coupling conditions preferentially yield the product with an axial carboxyl group and an equatorial aglycon (although the ring conformations are different: $^1C_4$ as compared to $^4C_1$). Performing this reaction at room temperature resulted in decreased stereocontrol and increased elimination as expected (entry 6).

Obviously, in these glycosylation reactions, the control of stereoselectivity is the major problem. To improve the α-selectivity it has been proposed by Imoto et al.[19] to use isopropylidene acetal protected Kdo donors. The 4,5-*O*-isopropylidene acetal force the ring to change from a chair to a boat conformation opening up the α-side for attack of an acceptor. In MeCN/CH_2Cl_2, glycosylation with donor **5** gave even at −70 °C, a considerable amount of the elimination product (**14**, 26%) together with the spacer glycoside product (**11**, 70%) but the α/β-ratio was much improved as compared to the perbenzoylated donor (entry 7). Surprisingly, the same yields were obtained at room temperature, but now with a 2:1 α/β-ratio (entry 8). With diethyl ether as solvent, the elimination reaction was once again more or less completely suppressed at low temperature. This also increased the α/β-ratio to



Scheme 2. Glycosylation reactions performed, for conditions, see Table 1.

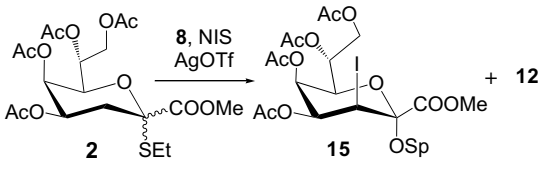
Table 1.

Entry	Donor	Promoter	Temp (°C)	Solvent	Yield (%)	Product/α:β ratio	Elimination (%)
1	**2**	DMTST	−15	CH_2Cl_2	81	**9**/1:3	—
2	**2**	DMTST	0	Et_2O	29	**9**/1:2	15 (**12**)
3	**7**	DMTST	−15	CH_2Cl_2	84	**9**/1:2.6	—
4	**7**	DMTST	0	Et_2O	51	**9**/1:1.5	24 (**12**)
5	**4**	IBr/AgOTf	−70	3:2 MeCN–CH_2Cl_2	81	**10**/0:1	—
6	**4**	IBr/AgOTf	rt	3:2 MeCN–CH_2Cl_2	34	**10**/1:2	44 (**13**)
7	**5**	IBr/AgOTf	−70	3:2 MeCN–CH_2Cl_2	70	**11**/1:1	26 (**14**)
8	**5**	IBr/AgOTf	rt	3:2 MeCN–CH_2Cl_2	70	**11**/2:1	26 (**14**)
9	**5**	IBr/AgOTf	−70	Et_2O	60	**11**/3:1	—
10	**5**	IBr/AgOTf	rt	Et_2O	32	**11**/3.5:1	56 (**14**)
11	**5**	IBr/AgOTf	−30	Et_2O	78	**11**/3:1	—
12	**2**	NIS/AgOTf	−30	CH_2Cl_2	54	**15**/1:0	45 (**12**)

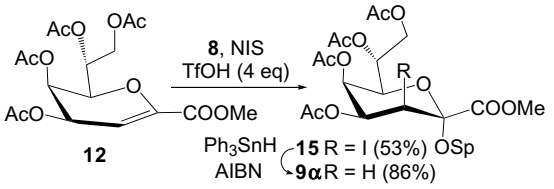
Since the mixture of anomers was not separable, the α/β-ratio was determined by integration of the equatorial H-3 in the ^{1}H NMR spectra.

3:1, but slowed down the reaction to yield 60% of product **11** together with still unreacted starting material (entry 9). At room temperature the effect on the α/β-ratio was small, and elimination was the major reaction (entry 10). With the encouraging results obtained with donor **5** in Et_2O at −70 °C, we reasoned that the amount of starting material left was due mainly to solubility problems and, thus, tried the reaction at −30 °C. Elimination was still avoided and the α/β-ratio was the same, but the yield of spacer glycoside was improved to 78% (entry 11).

The use of NIS/AgOTf as promoter together with donor **2** gave results (Scheme 3, entry 12), which were quite different from those of van Boom et al. using NIS/TfOH.[5] TLC-monitoring of the reaction showed that at first (after 1 h) the only product formed in almost quantitative yield was the elimination product **12**. If the reaction was allowed to continue, a new product increasingly started to appear. When no more of this new product was formed (18 h), the reaction was worked up and the new product was identified as the 3-iodo α-linked spacer glycoside **15** (54%). This was unexpected, since normally the double bond in **12** is resistant to the commonly used iodonium electrophiles due to the stabilization by the ester function. We tried NIS, NIS/AgOTf, iodonium dicollidinium perchlorate (IDCP) and the corresponding triflate (IDCT) to activate the glycal **12**[20] in the presence of the spacer alcohol to obtain **15**, but found, as Brenken[21] also reports, no addition to the double bond. In the above reaction, however, some iodonium species obviously form in situ, which is active enough to activate the double bond. Interestingly, activation of **12** with NIS/TfOH was found to work and gave **15** in 53% (Scheme 4).[22]



Scheme 3. Glycosylation with NIS/AgOTf as promoter.



Scheme 4. Activation of the Kdo glycal with NIS/TfOH.

However, in contrast to glycosylation reactions with thioglycoside donors, where only a catalytic amount of TfOH is used, the glycal activation required excess of TfOH (4 equiv). Very recently, Tanaka et al. published similar findings.[23] They used the more activated 4,5,7,8-tetra-O-benzylated Kdo glycal derivative, but still stoichiometric amounts of TfOH were needed to afford 3-iodo-α-Kdo glycosides in high yields. The iodo function in **15** could efficiently be reduced by triphenyltin hydride to give **9α** in 86% yield.

In conclusion, Kdo thioglycosides are good glycosyl donors. The competing elimination reaction can efficiently be suppressed by using low temperature in combination with most promoters and solvents. Good to excellent β-selectivity is obtained with peracylated donors. To achieve high stereoselectivity for the often desired α-linkage is a more difficult problem. Diethyl ether as solvent and/or higher temperature only slightly increase α/β-ratio and the latter cause severe elimination to occur, but isopropylidene protecting groups considerably increase the amount of α-anomer. The use of donor **5** promoted by IBr/AgOTf in diethyl ether at low temperature (entry 11) shows promising results, especially since it can be expected that more hindered saccharide acceptors will improve the α-selectivity even more.

1. Experimental

1.1. General

Organic solvents were dried over $MgSO_4$ before concentration, which was performed under diminished pressure

at <40 °C (bath temperature). TLC was carried out on E. Merck precoated 60 F_{254} plates with detection by UV-light and/or 8% sulfuric acid. Column chromatography was performed on silica gel (0.040–0.063 mm, Amicom). NMR spectra were recorded in $CDCl_3$ at 25 °C on a Varian 300 or 400 MHz instrument. MALDI-TOF spectra were recorded on a Bruker Biflex III instrument using 2′,4′,6′-trihydroxyacetophenone trihydrate (THAP) as matrix.

1.2. Methyl (ethyl 4,5,7,8-tetra-*O*-acetyl-3-deoxy-2-thio-D-*manno*-oct-2-ulopyranosid)onate (2)

Zinc chloride (1.3 g, 9.5 mmol) was added at 0 °C to a stirred solution of **1**[13] (2.7 g, 5.8 mmol) and ethanethiol (0.87 mL, 12 mmol) in CH_2Cl_2 (25 mL). After 18 h, the solution was diluted with CH_2Cl_2, washed with water and satd aq $NaHCO_3$, filtered and evaporated. The residue was purified by silica gel chromatography (4:1 light petroleum bp 40–60 °C–EtOAc) to give **2** (2.3 g, 8.1 mmol, 85%) as an α/β-mixture 1:5; $[\alpha]_D$ +49 (*c* 1.5, $CHCl_3$); NMR data: α-anomer: ^{13}C, δ 13.7 (SCH_2CH_3), 20.5, 20.6 (CH_3CO), 22.3 (SCH_2CH_3), 31.5 (C-3), 52.6 (OCH_3), 61.7, 64.2, 66.8, 67.4, 68.2, (C-4, 5, 6, 7, 8), 84.6 (C-2), 168.4–170.5 (C-1, C═OAc); β-anomer: ^{13}C, δ 14.0 (SCH_2CH_3), 20.5, 20.6 (CH_3CO), 23.2 (SCH_2CH_3), 32.3 (C-3), 52.6 (OCH_3), 62.1, 63.8, 67.0, 67.6, 71.7 (C-4, 5, 6, 7, 8), 83.9 (C-2), 168.4, 169.5, 169.6, 170.3, 170.5 (C-1, C═OAc). Anal. Calcd for $C_{19}H_{28}O_{11}S$: C, 49.13; H, 6.08. Found: C, 49.55; H, 5.99.

1.3. Methyl (ethyl 3-deoxy-2-thio-D-*manno*-oct-2-ulopyranosid)onate (3)

Compound **2** (65 mg, 0.14 mmol) was dissolved in MeOH (3 mL) and the pH was adjusted to 11 by treatment with 1 M NaOMe (in MeOH). The mixture was stirred for 2 h, neutralized with Dowex 50 (H^+) ion exchange resin, filtered and concentrated. Purification by silica gel chromatography (10:1 CH_2Cl_2–MeOH) gave **3** (38 mg, 0.13 mmol, 91%); ^{13}C NMR (α-anomer) δ 14.2 (SCH_2CH_3), 23.3 (SCH_2CH_3), 35.6 (C-3), 53.1 (OCH_3), 64.4, 65.8, 67.3, 69.5, 76.5 (C-4, 5, 6, 7, 8), 84.0 (C-2), 170.7 (C-1).

1.4. Methyl (ethyl 4,5,7,8-tetra-*O*-benzoyl-3-deoxy-2-thio-D-*manno*-oct-2-ulopyranosid)onate (4)

Benzoyl chloride (59 μL, 0.51 mmol) was added to a stirred solution of **3** (15 mg, 0.051 mmol) in pyridine. The reaction mixture was stirred at room temperature overnight, quenched by addition of MeOH and concentrated. Purification by silica gel chromatography (10:1 toluene–EtOAc) gave **4** (35 mg, 0.049 mmol, 97%); ^{13}C NMR (β-anomer) δ 14.4 (SCH_2CH_3), 23.7 (SCH_2CH_3), 33.2 (C-3), 53.1 (OCH_3), 63.3, 65.0, 68.2, 68.7, 73.0 (C-4, 5, 6, 7, 8), 84.6 (C-2), 128.3–133.7 (aromatic C), 165.2, 165.4, 165.5, 166.2, 169.1 (C-1, C═OBz). Anal. Calcd for $C_{39}H_{36}O_{11}S$: C, 65.72; H, 5.09. Found: C, 65.08; H, 5.08.

1.5. Methyl (ethyl 4,5;7,8-di-*O*-isopropylidene-3-deoxy-2-thio-D-*manno*-oct-2-ulopyranosid)onate (5)

Dimethoxypropane (88 μL, 0.72 mmol) and *p*-TsOH (cat.) were added to a stirred solution of **3** (53 mg, 0.18 mmol) in DMF. After 2 h, the reaction mixture was quenched by addition of Et_3N, concentrated and purified by silica gel chromatography (5:1 toluene–EtOAc) to give **5** (59 mg, 0.16 mmol, 93%); ^{13}C NMR (α-anomer) δ 14.4 (SCH_2CH_3), 22.7, 25.2, 25.3, 25.7, 27.1 (SCH_2CH_3, $C(CH_3)_2$), 32.8 (C-3), 52.7 (OCH_3), 67.4, 70.5, 71.8, 72.6, 73.5 (C-4, 5, 6, 7, 8), 88.6 (C-2), 109.6, 109.9 ($C(CH_3)_2$), 170.5 (C-1); (β-anomer) δ 14.6 (SCH_2CH_3), 23.7, 25.4, 26.1, 27.1, 27.6 (SCH_2CH_3, $C(CH_3)_2$), 34.6 (C-3), 52.7 (OCH_3), 67.2, 70.3, 70.8, 73.9, 74.7 (C-4, 5, 6, 7, 8), 82.8 (C-2), 109.5, 109.8 ($C(CH_3)_2$), 170.1 (C-1). Anal. Calcd for $C_{17}H_{28}O_7S$: C, 54.24; H, 7.50. Found: C, 53.63; H, 7.59.

1.6. Methyl (4,5,7,8-tetra-*O*-acetyl-3-deoxy-2-D-*manno*-oct-2-ulopyranosyl bromide)onate (6)[3]

Compound **1** (200 mg, 0.43 mmol) was dissolved in a saturated solution of hydrogen bromide in glacial acetic acid (10 mL). After stirring for 30 min, the solution was diluted with toluene, concentrated and coevaporated three times with dry toluene. The glycosyl bromide **6** was used without further purification. ^{13}C NMR: δ 20.4, 20.5, 20.6, (CH_3CO), 36.6 (C-3), 53.6 (OCH_3), 61.9, 63.5, 66.6, 67.1, 72.8, (C-4, 5, 6, 7, 8), 92.6 (C-2), 165.9 (C-1), 169.4, 169.6, 169.9, 170.5 (C═OAc).

1.7. Methyl [(4,5,7,8-tetra-*O*-acetyl-3-deoxy-D-*manno*-oct-2-ulopyranosyl) 2-piperidinecarbodithioate]onate (7)

Piperidine (43 μL, 0.43 mmol) was added at 0 °C to a stirred mixture of NaH (60%, 16 mg, 0.39 mmol) in DMF (2 mL). After 10 min, CS_2 (31 μL, 0.51 mmol) was added and the mixture was stirred for another 30 min. The temperature was decreased to −25 °C and a solution of **6** (200 mg, 0.41 mmol) in DMF (10 mL) was added dropwise. After 1 h, the mixture was poured onto ice and the organic phase was separated, dried and concentrated. The residue was purified by silica gel chromatography (6:1 toluene–EtOAc) to give **7** (185 mg, 0.34 mmol, 79%); ^{13}C NMR (α-anomer): δ 20.6, 20.7 (CH_3CO), 24.0, 25.6 (piperidine), 32.2 (C-3), 52.5 (CH_2N piperidine), 53.3 (OCH_3), 62.7, 64.2, 66.6, 67.9, 72.4 (C-4, 5, 6, 7, 8), 88.8 (C-2), 169.5, 169.6, 169.7, 170.3, 170.5 (C-1, C═OAc), 188.2 (CS_2). Anal. Calcd

for $C_{23}H_{33}O_{11}NS_2$: C, 49.01; H, 5.90; N, 2.48. Found: C, 48.94; H, 5.78; N, 2.38.

1.8. Glycosylation with DMTST as promoter

1.8.1. Thioglycoside 2 as donor. DMTST (209 mg, 0.81 mmol) was added at −15 °C to a solution of **2** (94 mg, 0.20 mmol) and 2-(4-trifluoroacetamidophenyl)ethanol (**8**, 60 mg, 0.30 mmol) in CH_2Cl_2 (5 mL) containing molecular sieves (4 Å). The mixture was stirred at −15 °C for 4 h and then left to attain room temperature. After 2 h, Et_3N (1 mL) was added and the stirring was continued for 20 min. The mixture was filtered, concentrated and the residue was purified by silica gel chromatography (4:1 toluene–EtOAc) to give a mixture of **9α** and **9β** (1:3, 105 mg, 82%).

Following the same procedure as above, but starting at 0 °C instead of −15 °C and using diethyl ether as solvent instead of CH_2Cl_2 gave a mixture of **9α** and **9β** (1:2, 29%) and elimination product **12** (15%).

1.8.2. *N*-Xanthate 7 as donor. DMTST (185 mg, 0.72 mmol) was added at −15 °C to a solution of **7** (103 mg, 0.18 mmol) and 2-(4-trifluoroacetamidophenyl)ethanol (**8**, 52 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) containing molecular sieves (4 Å). The mixture was left to attain room temperature. After 2 h Et_3N (1 mL) was added and the stirring was continued for 20 min. The mixture was filtered, concentrated and the residue was purified by silica gel chromatography (4:1 toluene–EtOAc) to give a mixture of **9α** and **9β** (2:5, 98 mg, 0.15 mmol, 84%).

Following the same procedure as above, but starting at 0 °C instead of −15 °C and using Et_2O as solvent instead of CH_2Cl_2 gave a mixture of **9α** and **9β** (2:3, 51%) and elimination product **12** (24%) was obtained.

1.9. Methyl [2-(4-trifluoroacetamidophenyl)ethyl 4,5,7,8-tetra-*O*-acetyl-3-deoxy-D-*manno*-oct-2-ulopyranosid]-onate (9α,β)

1.9.1. Compound 9α. NMR data were in agreement with those already published:[16] ^{13}C, δ 20.5, 20.7, 20.7, 20.8, 20.9 (CH_3CO), 32.0 (C-3), 35.3 ($ArCH_2CH_2O$), 52.8 (OCH_3), 62.4, 64.2, 64.5, 66.4, 67.4, 68.4 (C-4, 5, 6, 7, 8, $ArCH_2CH_2O$), 98.7 (C-2), 113.7, 118.0 (CF_3) 120.9, 129.8, 134.2, 136.5 (aromatic C), 154.7, 155.2 (amide C═O), 167.1, 169.8, 170.2, 170.6, 170.7 (C-1, C═OAc); ^{1}H NMR: δ 1.96–2.10 (m, 1H, H-3a), 2.16 (dd, 1H, H-3e), 3.57 (dd, 1H, H-6), 4.00 (dd, 1H, H-8), 4.51 (dd, 1H, H-8′), 5.15–5.29 (m, 3H, H-4, 5, 7).

1.9.2. Compound 9β. ($CDCl_3$): ^{13}C, δ 20.7, 20.8 (CH_3CO), 32.3 (C-3), 35.7 ($ArCH_2CH_2O$), 52.7 (OCH_3), 62.4, 64.0, 65.2, 67.1, 68.0, 70.6 (C-4, 5, 6, 7, 8, $ArCH_2CH_2O$), 99.3 (C-2), 120.8, 129.9, 133.6, 136.9 (aromatic C), 168.3, 169.9, 170.0, 170.5, 170.9 (C-1, C═OAc); ^{1}H NMR: δ 1.95–2.13 (m, 1H, H-3a), 2.32 (dd, 1H, H-3e), 4.12 (dd, 1H, H-6), 4.25 (d, 2H, H-8, 8′), 4.86 (ddd, 1H, H-4), 5.00 (dt, 1H, H-7), 5.26 (m, 1H, H-5).

1.10. Glycosylations with IBr/AgOTf as promoter

1.10.1. General procedure. AgOTf (3.0 equiv) in MeCN (3.0 mL) was added to a stirred solution of **4** or **5** (1.0 equiv), 2-(4-trifluoroacetamidophenyl)ethanol (**8**, 1.5 equiv) and 3 Å molecular sieves in CH_2Cl_2 (2.0 mL). The solution was cooled to −70 °C and IBr (1 M in CH_2Cl_2, 2.0 equiv) was added dropwise. The reaction mixture was stirred at −70 °C and after 2 h Et_3N (10 equiv) was added, followed by stirring for another 20 min before filtration and concentration.

1.10.2. Methyl [2-(4-trifluoroacetamidophenyl)ethyl 4,5,7,8-tetra-*O*-benzoyl-3-deoxy-D-*manno*-oct-2-ulopyranosid]-onate (10) and methyl 4,5,7,8-tetra-*O*-benzoyl-2,6-anhydro-3-deoxy-D-*manno*-oct-2-enonate (13). The compound was prepared according to the general method, using **4** (100 mg, 0.140 mmol), **8** (50 mg, 0.21 mmol), AgOTf (110 mg, 0.113 mmol), IBr (1 M in CH_2Cl_2 0.280 mL, 0.288 mmol) and Et_3N (0.195 mL, 1.40 mmol). Purification by silica gel chromatography (5:1 toluene–EtOAc) gave **10β** (100 mg, 0.113 mmol, 81%); $[\alpha]_D$ −37 (*c* 1, $CHCl_3$); NMR data ($CDCl_3$): ^{1}H, δ 2.36 (m, 1H, $J_{3a,4}$ 12.9 Hz, H-3a), 2.62 (dd, 1H, $J_{3e,3a}$ 12.6 Hz, $J_{3e,4}$ 4.6 Hz, H-3e), 2.94, (t, 2H, $ArCH_2CH_2O$), 3.70 (s, 3H, OCH_3), 3.82–3.74 (m, 1H, $ArCH_2CH_2O$), 4.13–4.05 (m, 1H, $ArCH_2CH_2O$), 4.71–4.54 (m, 3H, $J_{8,8'}$ 12.4 Hz, $J_{8',7}$ 2.3 Hz, H-6, 8, 8′), 5.35 (br d, 1H, H-4), 5.45 (m, 1H, H-7), 5.79 (s, 1H, H-5), 8.24–7.16 (m, 24H, Ar–H); ^{13}C, δ 32.9 (C-3), 36.0 ($ArCH_2CH_2O$), 52.9 (OCH_3), 63.4, 65.1, 65.5, 68.1, 68.9, 71.6 (C-4, 5, 6, 7, 8, $ArCH_2CH_2O$), 99.4 (C-2), 121.4, 128.3–133.5, 137.5 (aromatic C), 165.4, 165.4, 165.5, 166.3, 168.7 (C-1, C═OBz). Anal. Calcd for $C_{47}H_{40}F_3NO_{13}$: C, 63.87; H, 4.56. Found: C, 63.68; H, 4.67.

Following the same procedure using **4** (50 mg, 0.070 mmol), 2-(4-trifluoroacetamido-phenyl)ethanol (**7**, 30 mg, 0.14 mmol), AgOTf (36 mg, 0.21 mmol), IBr (1 M in CH_2Cl_2 0.11 mL, 0.11 mmol) and Et_3N (0.098 mL, 0.70 mmol), but stirring at room temperature instead of −70 °C gave a mixture of **10** (α/β 1:2, 21 mg, 0.24 mmol, 34%) and elimination product **13** (20 mg, 0.031 mmol, 44%); $[\alpha]_D$ −103 (*c* 1, $CHCl_3$); ^{1}H NMR: δ 3.86 (s, 3H, OCH_3), 4.77 (m, 2H, $J_{6,7}$ 8.5 Hz, $J_{8,7}$ 4.7 Hz, H-6, 8), 4.98 (dd, 1H, $J_{8',7}$ 2.7 Hz, $J_{8',8}$ 12.4 Hz, H-8′), 5.83 (m, 1H, H-7), 6.00 (m, 1H, H-5), 6.14–6.13 (m, 3H, H-3, 4), 8.02–7.22 (m, 20H, Ar–H); ^{13}C, δ 52.8 (OCH_3), 61.9, 63.0, 65.8, 68.4, 74.5 (C-4, 5, 6, 7, 8), 108.2 (C-3), 120.8, 128.4–133.6 (aromatic C), 145.2 (C-2), 161.8, 165.2, 165.6, 165.7, 166.2

(C-1, C=OBz). Anal. Calcd for $C_{37}H_{30}O_{11}$: C, 68.30; H, 4.65. Found: C, 68.12; H, 4.62.

Compound **10α**: ^{13}C NMR: δ 32.8 (C-3), 35.5 (Ar*C*H$_2$CH$_2$O), 52.9 (O*C*H$_3$), 63.5, 64.8, 65.4, 67.5, 68.5, 69.6 (C-4, 5, 6, 7, 8, ArCH$_2$*C*H$_2$O), 99.1 (C-1), 121.0, 128.4–133.8, 137.0 (aromatic C), 165.2, 165.5, 165.5, 167.8, 168.7 (C-1, C=OBz).

1.10.3. Methyl [2-(4-trifluoroacetamidophenyl)ethyl 3-deoxy-4,5;7,8-di-*O*-isopropylidene-D-*manno*-oct-2-ulopyranosid]onate (11). Compound **11** was prepared according to the general method using **5** (175 mg, 0.465 mmol), 2-(4-trifluoroacetamidophenyl)ethanol (**8**, 169 mg, 0.725 mol), AgOTf (369 mg, 1.45 mmol), IBr (1M in CH_2Cl_2 0.966 mL, 0.966 mmol), and triethylamine (0.679 mL, 4.83 mmol) to give a mixture of **11** (α/β 2:1, 162 mg, 0.325 mmol, 70%) and elimination product **14**[24] (38 mg, 0.121 mmol, 26%).

Following the same procedure using **5** (50 mg, 0.14 mmol), **8** (64 mg, 0.28 mmol), AgOTf (108 mg, 0.42 mmol), IBr (1M in CH_2Cl_2 0.21 mL, 0.21 mmol), and triethylamine (0.2 mL, 1.4 mmol), but with Et_2O as solvent instead of MeCN/CH_2Cl_2 gave, after purification by silica gel chromatography (10:1 toluene–EtOAc), **11** (α/β 3:1, 44 mg, 0.082 mmol, 60%). Compound **11α**: ^{13}C NMR: δ 25.0, 25.3, 25.5, 26.9, (C(*C*H$_3$)$_2$), 32.9 (C-3), 35.6 (Ar*C*H$_2$CH$_2$O), 52.5 (O*C*H$_3$), 63.7, 67.2, 70.0, 72.0, 72.1, 73.7 (C-4, 5, 6, 7, 8, ArCH$_2$*C*H$_2$O), 97.5 (C-2), 109.3, 109.6 (*C*(CH$_3$)$_2$), 120.7–137.2 (aromatic C), 169.4 (C-1). Compound **11β**: ^{13}C NMR: δ 25.1, 25.3, 26.6, 27.1 (*C*(CH$_3$)$_2$), 36.0 (C-3), 38.7 (Ar*C*H$_2$CH$_2$O), 52.5 (O*C*H$_3$), 63.5, 65.2, 70.1, 71.3, 73.7, 73.9 (C-4, 5, 6, 7, 8, ArCH$_2$*C*H$_2$O), 98.6 (C-2), 109.4, 109.5, (*C*(CH$_3$)$_2$), 120.7–137.2 (aromatic C), 170.4 (C-1). Anal. Calcd for $C_{25}H_{32}F_3NO_9$: C, 54.84; H, 5.89. Found: C, 54.62; H, 5.94.

1.11. Glycosylations with NIS as promoter

1.11.1. NIS/AgOTf. NIS (486 mg, 2.2 mmol) and AgOTf (554 mg, 2.2 mmol) were added at −30 °C to a mixture of **2** (250 mg, 0.54 mmol) and **8** (189 mg 0.81 mmol) in CH_2Cl_2 (15 mL) containing molecular sieves (4 Å). The mixture was stirred for 3 h, left to attain room temperature and then stirred for another 20 h. Et_3N (1 mL) was added, and the stirring was continued for 20 min. The mixture was filtered, concentrated and the residue was purified by silica gel chromatography (30:1 $CHCl_3$–acetone) to give one pure fraction of **12** (81 mg, 0.81 mmol, 37%), one mixed fraction of **12** and **15** (83 mg, 1:2) and one pure fraction of methyl [2-(4-trifluoroacetamidophenyl)ethyl 4,5,7,8-tetra-*O*-acetyl-3-deoxy-3-iodo-D-*glycero*-α-D-*talo*-oct-2-ulopyranoside]onate (**15**, 155 mg, 0.84 mmol, 38%). ^{13}C NMR ($CDCl_3$): δ 20.5, 20.8, 20.8, 20.9 (*C*H$_3$CO), 22.0 (C-3), 34.6 (Ar*C*H$_2$CH$_2$O), 53.1 (O*C*H$_3$), 62.0, 63.1, 65.3, 66.0, 67.3, 68.2 (C-4, 5, 6, 7, 8, ArCH$_2$-*C*H$_2$O), 101.8 (C-2), 113.9, 117.7 (CF_3), 122.6–139.5 (aromatic C), 165.9, 169.4, 169.6, 170.2, 170.5 (C-1, C=OAc).

1.11.2. NIS/TfOH (Glycal activation). TfOH (1.33 mL, 1.99 mmol) was added dropwise to a stirred solution of methyl 4,5,7,8,-tetra-*O*-acetyl-2,6-anhydro-3-deoxy-D-*manno*-oct-2-enonate[20] (**12**, 200 mg, 0.497 mmol), 2-(4-trifluoroacetamidophenyl)ethanol (**8**, 174 mg, 0.746 mmol), NIS (487 mg, 1.99 mmol) and 4 Å molecular sieves in CH_2Cl_2. The reaction mixture was stirred at room temperature overnight. Et_3N was added and the reaction mixture was filtered and concentrated. Purification by silica gel chromatography (5:1 toluene–EtOAc) gave **15** (200 mg, 0.263 mmol, 53%).

AIBN (4.3 mg, 0.02 mmol) and Ph_3SnH (37 mg, 0.10 mmol) were added to a solution of **15** (35 mg, 0.05 mmol) in toluene (10 mL). The solution was refluxed for 1 h and then concentrated. The residue was purified by silica gel chromatography (4:1 toluene–EtOAc) to give **9α** (25 mg, 86%).

Acknowledgements

We thank the Swedish Research Council for financial support.

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