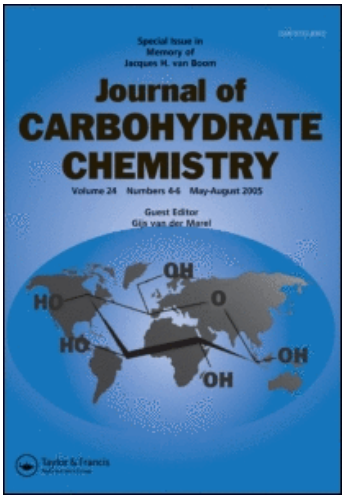

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ADDITION REACTIONS OF GLYCAL ESTERS: ACCESS TO GLYCOSYL DONORS OF Kdo, D-*glycero*-D-*talo*- AND D-*glycero*-D-*galacto*-2-OCTULOSONIC ACID RESIDUES

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ABSTRACT

Addition reactions of *O*-acetylated glycal esters of Kdo mono-, α-(2→8)- and α-(2→4)- linked Kdo disaccharide derivatives **1a - c** with NIS in acetic acid afforded good yields of *trans*-diaxial as well as minor amounts of *trans*-diequatorial and *cis*-configured 2-*O*-acetyl-3-deoxy-3-iodo derivatives, which were efficiently reduced with Bu_3SnH/AIBN to give the corresponding per-*O*-acetylated Kdo methyl ester derivatives. Similar reactions of **1a** with NBS or NCS furnished the *trans*-diaxial 2-*O*-acetyl-3-bromo-3-deoxy- as well as 3-chloro-3-deoxy derivatives as the main products. Reaction of **1a** with NBS in aqueous MeCN provided the 2,3-*trans*-bromohydrin derivative **11c**, which upon treatment with DBU in MeCN gave the elimination product **11** and the α-2,3-anhydro derivative **12** as a suitable donor of glycosides with D-*glycero*-D-*talo*- or D-*glycero*-D-*galacto* configuration, respectively.

INTRODUCTION

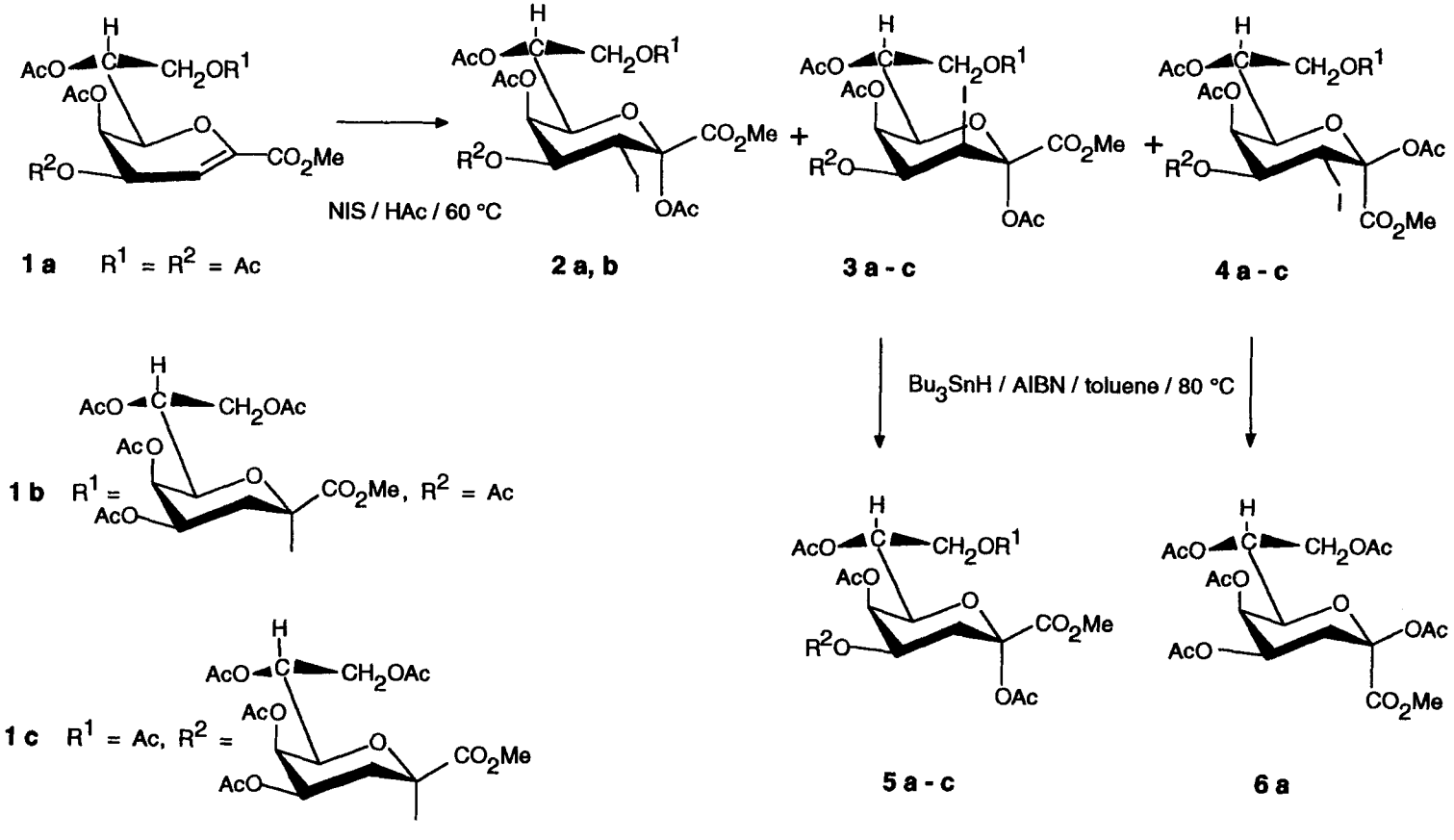
Functionalization of 2-deoxy-2,3-dehydro derivatives of *N*-acetylneuraminic acid methyl ester derivatives has been thoroughly studied in the context of developing novel stereospecific glycosyl donors.[1] Related reactions of 2-deoxy-2,3-dehydro compounds of

Kdo, which are frequently formed in substantial amounts during glycosylation reactions with Kdo donors such as halides[2] or thioglycosides,[3] have received less attention. Addition of phenylsulfenyl chloride to glycal ester derivatives of Kdo[4] afforded 2α-chloro-3ß-phenylthio derivatives, which could be stereospecifically converted into glycosides of α-anomeric configuration due to the presence of a stereocontrolling auxiliary at C-3. In a similar fashion, phenylselenyl triflate or chloride was efficiently employed in glycosylation procedures.[5] Addition of bromine was reported to give a *trans*-diaxial 2,3-dibromo compound with excellent α-selectivity and sufficient reactivity towards primary alcohols.[6] In addition, reaction of **1a** with 3-chloroperbenzoic acid was reported to afford a 2,3-anhydro derivative, which was transformed into ketosides of D-*glycero*-D-*talo*- as well as D-*glycero*-D-*galacto* configuration,[7] respectively. The assignment of the configuration of the oxirane ring, however, was tentatively based on a comparison with NMR data of 1,2-anhydro derivatives of D-mannose and D-glucose, respectively.

For these reasons we have set out to investigate addition reactions of glycal esters of Kdo with the intention to reuse these compounds for subsequent glycosylation reactions and furthermore, to devise an unambiguous structural proof for the configurational assignment of 2,3-anhydro-Ko derivatives.

RESULTS AND DISCUSSION

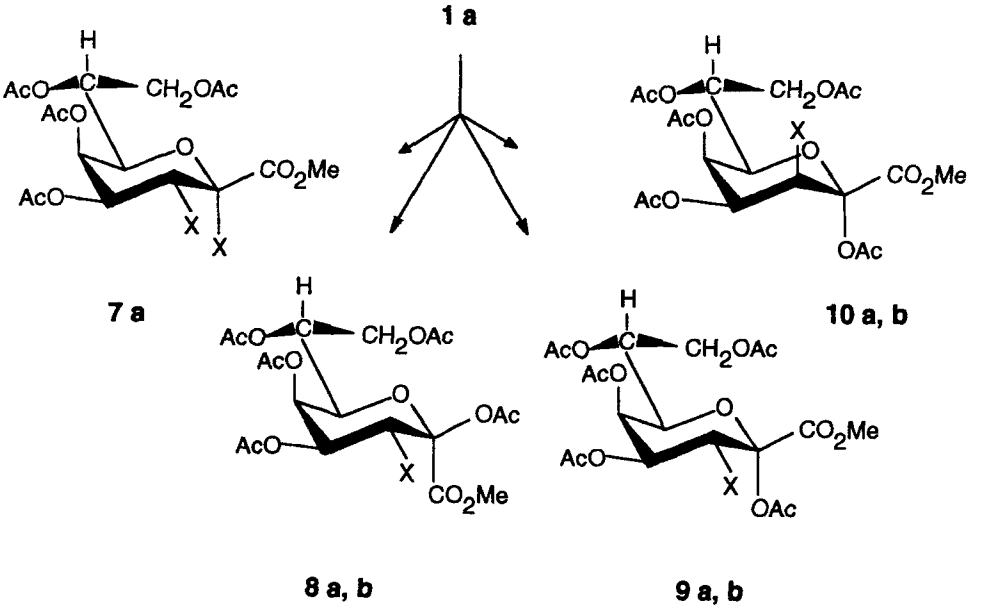
Acetoxyiodination[8] (NIS/acetic acid/60 °C) of the glycal methyl ester derivative **1a** afforded the 2,3-*trans*-diaxial addition product **3a** as the major isomer in 71% yield together with the 2,3-*trans*-diequatorial isomer **4a** (14%) and a small proportion of the 2,3-*cis* product **2a** (7%), which were all separated by silica gel chromatography (Scheme 1). The preferential formation of the thermodynamically favored diaxial isomer is consistent with previous findings on related reactions of *N*-acetylneuraminic acid derivatives.[1] The configuration of C-3 was readily deduced from the ^{1}H NMR data indicating a *trans*-arrangement of H-3 and H-4 for the D-*glycero*-D-*galacto*-derivatives ($J_{3,4}$= 11.6 and 11.9 Hz for **4a** and **2a**) and a *cis*-relationship for the D-*glycero*-D-*talo*-isomer ($J_{3,4}$= 5.0 Hz for **3a**). The anomeric configuration of the isomers was established following reduction of **3a** with AIBN/Bu_3SnH in toluene, which gave the known[9] α-linked 2-*O*-acetyl derivative **5a** in 76% yield. Similar treatment of compound **4a** provided the previously unknown ß-isomer **6a** in 90% yield.



Scheme 1

Similarly, the disaccharide derivatives **1b** and **1c**, originating as byproducts in the synthesis of *Chlamydia*-specific and enterobacterial Kdo antigens,[2b,10] were transformed without cleavage of the ketosidic bonds into the 3-deoxy-3-iodo compounds **2b** - **4b** and **3c** - **4c**, again with preferential formation of the 2,3-*trans*-diaxial isomers **3b** and **3c**. Reduction of **3b** and **3c** with AIBN/Bu_3SnH in toluene proceeded smoothly to give **5b** and **5c**, which may be further used in glycosylation reactions following conversion into the corresponding disaccharide bromide derivatives. Thus, the sequence of acetoxyiodination/reduction provides an efficient way to reuse these glycal esters and should also be applicable for NeuAc-2-en derivatives.

Addition reactions with NBS or NCS in neat acetic acid proved less advantageous, since they required higher temperatures and gave rise to smaller proportions of the 2,3-*trans*-diaxial adducts (Scheme 2). The assignment of the configuration of C-3 was again based on the large values of $J_{3,4}$ for the isomers **7a**, **8a,b** and **9a,b**, whereas the smaller values of $J_{3,4}$ for **10a,b** were consistent with the D-*glycero*-D-*talo*-configuration (Table).



Scheme 2

Table 1. ^{1}H NMR chemical shifts (δ, ppm) and coupling constants (*J*, Hz) for NXS-adducts[a].

	X= I			X= Br		X= Cl		
	2a	**3a**	**4a**	**9b**	**10b**	**8a**	**9a**	**10a**
H-3	4.33	4.51	4.39	4.27	4.40	4.28	4.25	4.38
H-4	5.34	5.02	5.36	5.37	5.46	5.34	5.34	5.51
H-5	5.34	5.45	5.34	5.43	5.40	5.48	5.46	5.40
H-6	4.15	4.24	5.21	4.16	4.24	5.24	4.16	4.22
H-7	5.24	5.34	5.12	5.24	5.37	5.11	5.24	5.36
H-8a	4.41	4.52	4.39	4.42	4.52	4.39	4.43	4.53
H-8b	4.06	4.15	4.13	4.06	4.17	4.13	4.07	4.17
$J_{3,4}$	11.9	5.0	11.6	11.2	4.5	11.5	11.2	4.1
$J_{3,5}$	-	0.8	-	-	1.0	-	-	0.9
$J_{4,5}$	n.d.[b]	3.3	3.1	3.3	3.6	3.2	3.3	3.7
$J_{5,6}$	1.3	1.9	1.4	1.2	1.9	1.5	1.5	1.9
$J_{6,7}$	9.9	9.9	9.7	9.9	9.9	9.8	9.9	9.9
$J_{7,8a}$	2.3	2.2	2.1	2.2	2.4	2.2	2.3	2.3
$J_{7,8b}$	3.7	3.2	4.7	3.6	3.2	4.8	3.6	3.2
$J_{8a,8b}$	-12.5	-12.5	-12.3	-12.5	-12.5	-12.3	-12.5	-12.5

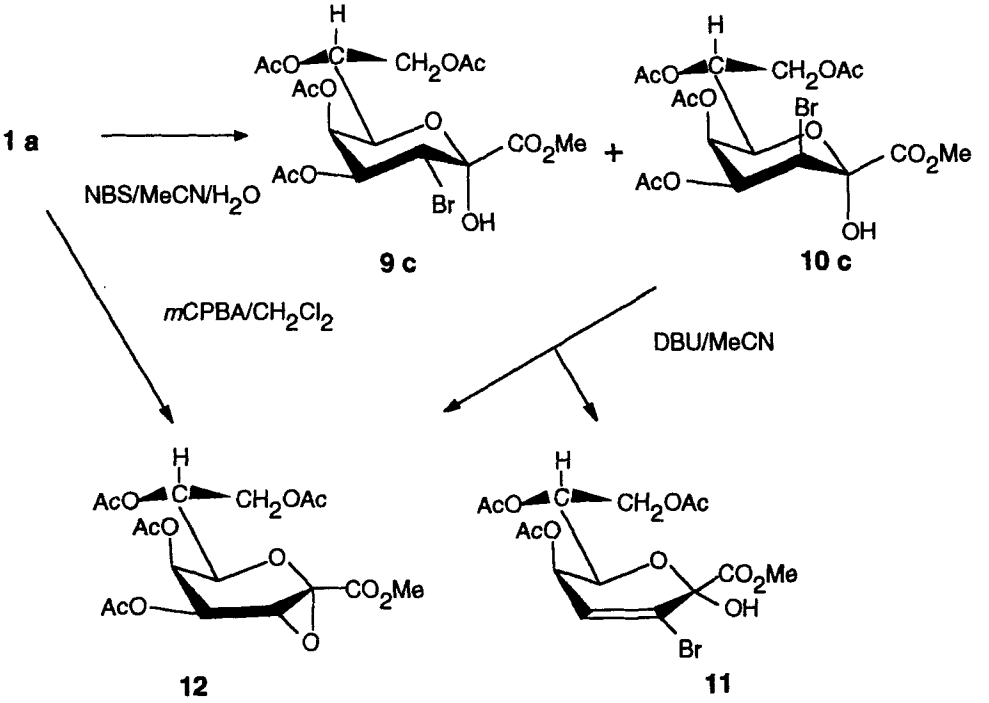
[a] Spectra were recorded in $CDCl_3$ at 295 K. [b] not determined.

Furthermore, in case of the NCS addition reaction, chloro-substitution at the anomeric center was observed. The α-anomeric configuration of the resulting 2,3-dichloro-derivative **7a** was determined using selective proton decoupled ^{13}C NMR measurements developed by Haverkamp *et al.* and Hori *et al.*[12] for derivatives of *N*-acetylneuraminic acid derivatives. Thus, selective decoupling of the ^{1}H NMR signal of the methyl ester group allowed the determination of long range coupling constants $J_{C1, H3ax}$. The ^{13}C NMR signals of C-1 at 166.5, 164.0 and 163.6 ppm (for compounds **8a, 9a** and **10a**) appeared as a doublet for **8a** (3.4 Hz) and singlets for **9a** and **10a**, respectively. Accordingly, the C-1 signal of **7a** was measured as a singlet at 163.6 ppm. Interestingly, H-6 of the ß-configured 2-*O*-acetyl derivatives **4a, 4b** and **8a** experienced a pronounced downfield shift in the ^{1}H NMR spectra (δ 5.00 - 5.44, Table 1); a similar effect may be noted in related 3-deoxy-3-halogeno derivatives of *N*-acetylneuraminic acid[9].

Recently, glycosides of an octulosonic acid (Ko) being isosteric to Kdo except for an additional, axially oriented OH-group at C-3 have been reported as constituents of the inner core in lipopolysaccharides of *Acinetobacter calcoaceticus* NCTC 10305 and *Pseudomonas cepacia*.[13] The configuration of this octulosonic acid was determined as D-*glycero*-D-*talo* by ^{1}H and ^{13}C NMR measurements and GC-MS comparison with synthetic model compounds of D-*glycero*-D-*talo* and D-*glycero*-D-*galacto* configuration, respectively. The synthetic derivatives were prepared from a 2,3-anhydro compound obtained *via* reaction of **1a** with 3-chloroperbenzoic acid. By comparison with NMR data from 1,2-anhydro derivatives of D-*mannose* and D-*glucose*, respectively, the anomeric configuration of the oxirane ring was deduced as β-D-*glycero*-D-*talo*.[7]

For the unambiguous configurational assignment of the 2,3-anhydro compound **12,** the glycal ester **1a** was transformed into the unstable bromohydrin derivatives **9c** and **10c** in 19% and 76% yield, respectively (Scheme 3). Whereas treatment of **10c** with *N,N*-ethyldiisopropylamine in either MeCN or CH_2Cl_2 did not give substantial amounts of the 2,3-anhydro derivative **12**, reaction with 1,8-diazabicyclo-[5.4.0.]-undec-7-ene (DBU) in MeCN at 0 °C afforded **12** in 30% yield together with the crystalline 3,4-unsaturated bromohydrin derivative **11** in 46% yield. The structure of **11** was deduced from the ^{1}H NMR data, which showed a singlet exchangeable with D_2O, a doublet at 6.55 ppm coupled to H-5, whereas H-6,7,8a and 8b were similar to *O*-acetylated Kdo derivatives. The spectroscopic and physical data of **12** were in full agreement with the previously re-

ported values of the 2,3-anhydro derivative obtained by direct epoxidation in the presence of *m*CPBA.[7] Therefore, the published configurational assignment of the oxirane ring has accordingly to be revised as α-D-*glycero*-D-*galacto*.



Scheme 3

EXPERIMENTAL

General methods. Melting points were determined with a Kofler hot stage and are uncorrected. Optical rotations were measured with a Perkin-Elmer 243 B polarimeter. ^{1}H NMR spectra were recorded with a Bruker AC 300F instrument and tetramethylsilane as the internal standard; coupling constants are first order. Homonuclear 2D NMR spectroscopy was performed with Bruker standard software. Thin-layer chromatography was performed on Merck precoated plates (5x10 cm, layer thickness 0.25 mm, Silica Gel $60F_{254}$); spots were detected by spraying with anisaldehyde-H_2SO_4 reagent. Column chromatography was performed on Merck Lichroprep columns (size *A*, 24x1; *B*, 31x2.5 and *C*, 44x3.7 cm; silica gel 40-63 μm) under pressure (0.2 MPa). Elemental analyses were performed by Dr. J. Theiner, Mikroanalytisches Laboratorium am Institut für Physikalische Chemie, Universität Wien.

Methyl 2,4,5,7,8-Penta-*O*-acetyl-3-deoxy-3-iodo-α-D-*glycero*-D-*galacto*-2-octulopyranosonate (2a), Methyl 2,4,5,7,8-Penta-*O*-acetyl-3-deoxy-3-iodo-α-D-*glycero*-D-*talo*-2-octulopyranosonate (3a), and **Methyl 2,4,5,7,8-Penta-*O*-acetyl-3-deoxy-3-iodo-ß-D-*glycero*-D-*galacto*-2-octulopyranosonate (4a).** A solution of **1a** (0.24 mmol, 100 mg) and *N*-iodosuccinimide (0.67 mmol, 150 mg) in acetic acid (20 mL) was heated at 60 °C for 15h. The reaction mixture was then poured into ice-cold saturated aq. $NaHCO_3$ (200 mL) and extracted with CH_2Cl_2 (100 mL). The organic layer was washed with 10% aq. $Na_2S_2O_3$ / water, dried (Na_2SO_4) and concentrated. Purification of the residue on a column of silica gel (*B*, 3:1 toluene-EtOAc) afforded first a mixture of **4a** and **2a**, then **3a** as the major product (100 mg, 71%), colorless crystals, mp 133-134 °C (EtOAc-hexane); $[\alpha]_D$ +52° (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.98, 2.03, 2.09, 2.14, 2.17 (5s, 15H, CH_3CO), 3.86 (s, 3H, CO_2CH_3).

Anal. Calcd for $C_{19}H_{25}IO_{13}$: C, 38.79; H, 4.28. Found: C, 38.59; H, 4.14.

The mixture of **4a** and **2a** was rechromatographed (*B*, 5:1 toluene-EtOAc), which furnished **4a** (21 mg, 14%) as a syrup, $[\alpha]_D$ +133° (*c* 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.00, 2.05, 2.02, 2.12, 2.16 (5s, 15H, CH_3CO), 3.82 (s, 3H, CO_2CH_3).

Anal. Calcd for $C_{19}H_{25}IO_{13}$: C, 38.79; H, 4.28. Found: C, 39.16; H, 4.23.

Further elution yielded **2a** as the slower migrating isomer (11 mg, 7%), colorless crystals, mp 165-168 °C (EtOAc-hexane), $[\alpha]_D$ +111° (*c* 0.6, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.98, 2.03, 2.05, 2.14, 2.23 (5s, 15H, CH_3CO), 3.86 (s, 3H, CO_2CH_3).

Anal. Calcd for $C_{19}H_{25}IO_{13}$: C, 38.79; H, 4.28. Found: C, 38.45; H, 4.22.

***O*-(Methyl 4,5,7,8-Tetra-*O*-acetyl-3-deoxy-α-D-*manno*-2-octulopyranosylonate)-(2→8)-(methyl 2,4,5,7-tetra-*O*-acetyl-3-deoxy-3-iodo-α-D-*glycero*-D-*galacto*-2-octulopyranosonate) (2b), O-(Methyl 4,5,7,8-Tetra-*O*-acetyl-3-deoxy-α-D-*manno*-2-octulopyranosylonate)-(2→8)-(methyl 2,4,5,7-tetra-*O*-acetyl-3-deoxy-3-iodo-α-D-*glycero*-D-*talo*-2-octulopyranosonate) (3b)** and ***O*-(Methyl 4,5,7,8-Tetra-*O*-acetyl-3-deoxy-α-D-*manno*-2-octulopyranosylonate)-(2→8)-(methyl 2,4,5,7-tetra-*O*-acetyl-3-deoxy-3-iodo-ß-D-*glycero*-D-*galacto*-2-octulopyranosonate) (4b).** Reaction conditions (**1b** : 0.54 mmol, 410 mg; NIS: 1.2 mmol, 0.27 g) and work-up were as described for **1a**. Column chromatography (*C*, 3:2 toluene-EtOAc) gave first a (1:1) mixture of **2b** and **4b** (55 mg, 11%) as a syrup. ^1H NMR ($CDCl_3$): δ 1.96, 2.00, 2.04, 2.05, 2.06, 2.08, 2.11, 2.15 (8s, 24H, CH_3CO), 2.07 (t, 1H, H-

3'*a*), 2.20 (dd, 1H, $J_{3'e,3'a}$ =-12.5, $J_{3'e,4'}$ =5.0 Hz, H-3'*e*), 3.58 (dd, 1H, $J_{8a,8b}$ =-11.2, $J_{8b,7}$ =3.7 Hz, H-8b), 3.65 (dd, 1H, $J_{8a,7}$ =2.3 Hz, H-8a), 3.77 (s, 3H, CO_2CH_3), 3.90 (s, 3H, CO_2CH_3), 4.09 (dd, 1H, $J_{6',5'}$ =1.4, $J_{6',7'}$ =9.5 Hz, H-6'), 4.24 (dd, 1H, $J_{8'b,8'a}$ =-12.1, $J_{8'b,7'}$ =6.2 Hz, H-8'b), 4.28 (dd, 1H, H-6 of **2b**), 4.34 (d, 1H, $J_{3,4}$ =11.9 Hz, H-3), 4.49 (dd, 1H, $J_{8'a,7'}$ =2.4 Hz, H-8'a), 4.97 (ddd, 1H, H-7), 5.26 -5.40 (m, 5H, H-4,5,4',5',7'), 5.44 (dd, 1H, $J_{6,5}$ =1.3, $J_{6,7}$ =9.9 Hz, H-6 of **4b**).

Further elution of the column gave **3b** (355 mg, 66%) as a syrup.$[\alpha]_D$ +45° (*c* 0.9, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.99 (t, 1H, $J_{3'a,3'e}$ =-12.6 Hz, H-3'*a*), 1.96, 2.02, 2.04, 2.09, 2.12, 2.13, 2.24 (7s, 24H, CH_3CO), 2.23 (dd, 1H, H-3'*e*), 3.66 (dd, 1H, $J_{8a,8b}$ =-11.8, $J_{8b,7}$ =2.7 Hz, H-8b), 3.77 (s, 3H, CO_2CH_3), 3.77 (dd, 1H, $J_{8a,7}$ =2.5 Hz, H-8a), 3.83 (s, 3H, CO_2CH_3), 4.05 (dd, 1H, $J_{6',5'}$ =1.4, $J_{6',7'}$ =9.5 Hz, H-6'), 4.15 (dd, 1H, $J_{7,8'b}$ =5.1, $J_{8'a,8'b}$ =-12.2 Hz, H-8'b), 4.34 (dd, 1H, $J_{6,5}$ =2.0, $J_{6,7}$ =9.9 Hz, H-6), 4.51 (dd, 1H, $^4J_{3,5}$ =0.8, $J_{3,4}$ =4.9 Hz, H-3), 4.55 (dd, 1H, $J_{7,8'a}$ =2.4 Hz, H-8'a), 5.04 (dd, 1H, $J_{4,5}$ =3.6 Hz, H-4), 5.12 (ddd, 1H, $J_{4',5'}$ =3.0, $J_{4',3'e}$ =5.0, $J_{4',3'a}$ =12.3 Hz, H-4'), 5.15 (dt, 1H, H-7), 5.24 (ddd, 1H, H-7'), 5.34 (br. d, 1H, H-5'), 5.55 (ddd, 1H, H-5).

Anal. Calcd for $C_{34}H_{45}IO_{23}$: C, 43.05; H, 4.78. Found: C, 42.83; H, 4.65.

O-(Methyl 4,5,7,8-Tetra-*O*-acetyl-3-deoxy-α-D-*manno*-2-octulopyranosylonate)-(2→4)-(methyl 2,5,7,8-tetra-*O*-acetyl-3-deoxy-3-iodo-α-D-*glycero*-D-*talo*-2-octulopyranosonate) (3c) and ***O*-(Methyl 4,5,7,8-Tetra-*O*-acetyl-3-deoxy-α-D-*manno*-2-octulopyranosylonate)-(2→4)-(methyl 2,5,7,8-tetra-*O*-acetyl-3-deoxy-3-iodo-ß-D-*glycero*-D-*galacto*-2-octulopyranosonate) (4c).** Reaction conditions (**1c** : 0.09 mmol, 70 mg NIS : 0.44 mmol, 0.1 g) and work-up were as described for **1a**. Column chromatography (*B*, 1 : 1 toluene-EtOAc) gave first the faster migrating isomer **4c**, then **3c**. Yield for **4c**: 4.9 mg (5%), colorless syrup; ^1H NMR ($CDCl_3$): δ 1.98, 2.00, 2.04, 2.05, 2.07 (double intensity), 2.11, 2.15 (7s, 24H, CH_3CO), 2.10 - 2.19 (m, 2H, H-3'*a*, H-3'*e*), 3.58 and 3.84 (2s, 6H, CO_2CH_3), 4.09 (dd, 1H, $J_{8a,8b}$ =-12.1, $J_{8b,7}$ =3.7 Hz, H-8b), 4.17 (dd, 1H, $J_{8'b,7'}$ =7.2, $J_{8'b,8'a}$ =-11.9 Hz, H-8'b), 4.39 (dd, 1H, $J_{8a,7}$ =1.8 Hz, H-8a), 4.56 (dd, 1H, $J_{4,3}$ =11.6, $J_{4,5}$ =2.5 Hz, H-4), 4.60 (dd, 1H, $J_{7,8'a}$ =2.9 Hz, H-8'a), 4.67 (d, 1H, H-3), 4.85 - 4.90 (m, 2H, H-6,7), 5.01 (dd, 1H, $J_{6',7'}$ =9.3, $J_{6',5'}$ =1.8 Hz, H-6'), 5.25 (dd, 1H, $J_{5,6}$ =1.0 Hz, H-5), 5.28 (ddd, 1H, H-7'), 5.40 (ddd, 1H, H-5'), 5.50 (ddd, 1H, $J_{4',5'}$ =2.8, $J_{4',3'e}$ =6.0, $J_{4',3'a}$ =11.5 Hz, H-4'). Yield for **3c** : 68 mg (78 %), colorless syrup. $[\alpha]_D$ +84° (*c* 1.1, $CHCl_3$). ^1H NMR

($CDCl_3$): δ 1.97, 1.99, 2.01, 2.05, 2.08, 2.13, 2.15, 2.17 (8s, 24H, CH_3CO), 2.00 - 2.17 (m, 1H, H-3'*e*), 2.24 (t, 1H, $J_{3'a,3'e} = J_{3'a,4'}$ =11.6 Hz, H-3'*a*), 3.86 and 3.89 (2s, 6H, CO_2CH_3), 3.99 (dd, 1H, $J_{8'a,8'b}$ =-12.2, $J_{8'b,7'}$ =3.5 Hz, H-8'b), 4.08 (dd, 1H, $J_{6',5'}$ =1.2 Hz, H-6'), 4.13 (dd, 1H, H-8b), 4.15 (dd, 1H, H-6), 4.38 (dd, 1H, $^4J_{3,5}$ =0.5, $J_{3,4}$ =5.2 Hz, H-3), 4.44 (dd, 1H, $J_{4,5}$ =3.6 Hz, H-4), 4.50 (dd, 1H, $J_{8a,8b}$ =-12.5, $J_{8a,7}$ =2.2 Hz, H-8a), 4.82 (dd, 1H, $J_{8'a,7'}$ =2.8 Hz, H-8'a), 5.16 (ddd, 1H, $J_{6',7'}$ =9.2 Hz, H-7'), 5.25 (ddd, 1H, $J_{7,8b}$ =3.0, $J_{7,6}$ =10.0 Hz, H-7), 5.30 (ddd, 1H, H-5), 5.41 (ddd, 1H, $J_{4',5'}$ =2.5, $J_{4',3'e}$ =4.7 Hz, H-4'), 5.43 (dd, 1H, H-5').

Anal. Calcd for $C_{34}H_{45}IO_{23}$: C, 43.05; H, 4.78. Found: C, 42.64; H, 4.56.

Methyl 2,4,5,7,8-Penta-*O*-acetyl-3-deoxy-α-D-*manno*-2-octulopyranosonate (5a). A solution of **3a** (0.09 mmol, 51 mg), azabisisobutyronitrile (AIBN, 20 mg) and tributyltin hydride (0.93 mmol, 250 μL) in dry toluene (40 mL) was stirred at 80 °C for 4h under N_2. The solution was concentrated and purified by flash chromatography on silica gel (*B*, 1:1 toluene-EtOAc) giving **5a** (30 mg, 76%) as colorless crystals, mp 155-157 °C, $[\alpha]_D$ +95°(*c* 1.2 $CHCl_3$); (lit:[10] mp 155-158 °C, $[\alpha]_D$+87.1°). ^1H NMR ($CDCl_3$): δ 1.99, 2.00, 2.05, 2.11, 2.14 (5s, 15H, CH_3CO), 2.23 (m, 2H, H-3*a*, 3*e*), 3.81 (s, 3H, CO_2CH_3), 4.11 (dd, 1H, $J_{8b,7}$ =4.0, $J_{8b,8a}$ =-12.5 Hz, H-8b), 4.18 (dd, 1H, $J_{6,7}$ =9.5 Hz, H-6), 4.48 (dd, 1H, $J_{8a,7}$ =2.5 Hz, H-8a), 5.22 (ddd, 1H, H-7), 5.33 (ddd, 1H, $J_{4,5}$ =3.0 Hz, H-4), 5.39 (br. d, 1H, H-5).

Methyl 2,4,5,7,8-Penta-*O*-acetyl-3-deoxy-ß-D-*manno*-2-octulopyranosonate (6a). A solution of **4a** (0.05 mmol, 30.9 mg) in toluene (25 mL) was treated with AIBN (20 mg) and Bu_3SnH (0.1 mL) as described for **5a**. Column chromatography (*A*, 1:1 toluene-EtOAc) afforded **6a** as a syrup (22 mg, 90 %), $[\alpha]_D$+39° (*c* 0.7, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.99, 2.00, 2.08, 2.11, 2.12 (5s, 15H, CH_3CO), 2.20 (t, 1H, $J_{3e,3a} = J_{3a,4}$ =12.7 Hz, H-3*a*), 2.41 (dd, 1H, $J_{3e,4}$ =4.7 Hz, H-3*e*), 3.79 (s, 3H, CO_2CH_3), 4.20 (dd, 1H, $J_{8b,7}$ =4.9, $J_{8b,8a}$ =-12.2 Hz, H-8b), 4.43 (dd, 1H, $J_{8a,7}$ =2.5 Hz, H-8a), 4.63 (dd, 1H, $J_{6,5}$ =1.2, $J_{6,7}$ =9.7 Hz, H-6), 5.16 (ddd, 1H, $J_{4,5}$ =2.3 Hz, H-4), 5.17 (ddd, 1H, H-7), 5.35 (br. d, 1H, H-5).

Anal. Calcd for $C_{19}H_{26}O_{13}$: C, 49.35; H, 5.67. Found: C, 49.13; H, 5.73.

***O*-(Methyl 4,5,7,8-Tetra-*O*-acetyl-3-deoxy-α-D-*manno*-2-octulopyranosylonate)-(2→8)-(methyl 2,4,5,7-tetra-*O*-acetyl-3-deoxy-α-D-*manno*-2-octulopyranosonate) (5b).** A solution of **3b** (0.328 mmol, 310 mg), AIBN (20 mg) and Bu_3SnH (1.66 mmol, 0.44 mL) in toluene

(50 mL) was heated at 80 °C for 4h under N_2. The solution was concentrated, diluted with CH_2Cl_2 (50 mL), washed with saturated aq $NaHCO_3$, dried (Na_2SO_4) and evaporated. Chromatography of the residue on silica gel (*B*, 1:1 toluene-EtOAc) gave **5b** as a syrup (240 mg, 89%). $[\alpha]_D$ +83° (*c* 1.1, $CHCl_3$); (lit:[14] $[\alpha]_D$+90°). ^1H NMR data were identical to literature values.[14]

***O*-(Methyl 4,5,7,8-Tetra-*O*-acetyl-3-deoxy-α-D-*manno*-2-octulopyranosylonate)-(2→4)-(methyl 2,5,7,8-tetra-*O*-acetyl-3-deoxy-α-D-*manno*-2-octulopyranosonate) (5c).** A solution of **3c** (0.06 mmol, 58 mg), AIBN (15 mg) and Bu_3SnH (0.16 mmol, 0.04 mL) in toluene (20 mL) was heated at 80 °C for 6h. Work-up as described for **5b** gave **5c** (43 mg, 85% yield) as colorless crystals, mp 177-179 °C (EtOAc-hexane), lit:[11a] mp 178-179 °C. ^1H NMR data were identical to literature values.[11a]

Methyl (4,5,7,8-Tetra-*O*-acetyl-3-chloro-3-deoxy-α-D-*glycero*-D-*galacto*-2-octulopyranosyl chloride) onate (7a), Methyl 2,4,5,7,8-Penta-*O*-acetyl-3-chloro-3-deoxy-ß-D-*glycero*-D-*galacto*-2-octulopyranosonate (8a), Methyl 2,4,5,7,8-Penta-*O*-acetyl-3-chloro-3-deoxy-α-D-*glycero*-D-*galacto*-2-octulopyranosonate (9a) and **Methyl 2,4,5,7,8-Penta-*O*-acetyl-3-chloro-3-deoxy-α-D-*glycero*-D-*talo*-2-octulopyranosonate (10a).** A solution of **1a** (0.66 mmol, 290 mg) and *N*-chlorosuccinimide (3 mmol, 400 mg) in glacial acetic acid (50 mL) was stirred overnight at 120 °C. The solution was cooled to room temperature and evaporated. The residue was diluted with water and dichloromethane (50 mL each) and washed with saturated aq. $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated. Purification of the residue by column chromatography (*C*, 2:1 toluene-EtOAc) afforded **7a** as the higher migrating compound. Yield: 76 mg (16%), colorless syrup, $[\alpha]_D$ +141° (*c* 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.01, 2.05, 2.09 and 2.12 (4s, 12 H, CH_3CO), 3.93 (s, 3H, CO_2Me), 4.09 (dd, 1H, $J_{8b,8a}$ =-12.2, $J_{8b,7}$ =4.3 Hz, H-8b), 4.39 (dd, 1H, $J_{8a,7}$ =2.2 Hz, H-8a), 4.62 (dd, 1H, $J_{6,7}$ =9.7, $J_{6,5}$ =1.2 Hz, H-6), 4.71 (d, 1H, $J_{3,4}$ =11.1 Hz, H-3), 5.21 (ddd, 1H, H-7), 5.36 (dd, 1H, $J_{4,5}$ =3.3 Hz, H-4), 5.49 (dd, 1H, H-5).

Anal. Calcd for $C_{17}H_{22}Cl_2O_{11}$: C, 43.14; H, 4.69. Found: C, 43.51; H, 4.58.

Further elution of the column afforded **8a** as a syrup. Yield: 38 mg (8%), $[\alpha]_D$ +63° (*c* 1.4, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.00, 2.04, 2.06, 2.12 and 2.17 (5s, 15H, CH_3CO), 3.81 (s, 3H, CO_2Me). Elution of the column with 1:1 toluene-EtOAc gave **9a** as colorless crystals, mp 164-166 °C (EtOAc-hexane). Yield : 166 mg (33%), $[\alpha]_D$ +120° (*c* 1.0,

$CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.98, 2.04, 2.05, 2.13 and 2.23 (5s, 15H, CH_3CO), 3.86 (s, 3H, CO_2Me). Finally, **10a** was obtained as the slowest migrating isomer. Yield: 146 mg (29%) of **10a** as syrup; $[\alpha]_D$ +61° (*c* 1.3, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.97, 2.03, 2.09 (double intensity) and 2.17 (4s, 15H, CH_3CO), 3.85 (s, CO_2Me).

Anal. Calcd for $C_{19}H_{25}ClO_{13}$: C, 45.93; H, 5.07. Found: C, 46.17; H, 5.10.

Methyl 2,4,5,7,8-Penta-*O*-acetyl-3-bromo-3-deoxy-α-D-*glycero*-D-*galacto*-2-octulopyranosonate (9b) and **Methyl 2,4,5,7,8-Penta-*O*-acetyl-3-bromo-3-deoxy-α-D-*glycero*-D-*talo*-2-octulopyranosonate (10b)**. A solution of **1a** (0.83 mmol, 332 mg) and *N*-bromosuccinimide (2.16 mmol, 386 mg) in acetic acid (30 mL) was stirred for 15h at 70 °C. Work-up as described for **7a** and purification of the residue by column chromatography (*C*, 3:1 → 1:1 toluene-EtOAc) afforded **9b** as the higher migrating compound, which was chromatographed a second time using 5:1 toluene-EtOAc. Yield: 181 mg (17%), colorless crystals; mp 173-175 °C (EtOAc-hexane), $[\alpha]_D$ +114° (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.98, 2.04, 2.06, 2.14 and 2.24 (5s, 15H, CH_3O), 3.86 (s, 3H, CO_2Me).

Anal. Calcd for $C_{19}H_{25}BrO_{13}$: C, 42.16; H, 4.66. Found: C, 42.05; H, 4.58.

Further elution gave **10b** as a syrup. Yield: 217 mg (49%); $[\alpha]_D$ +51° (*c* 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.98, 2.04, 2.10, 2.11 and 2.17 (5s, 15H, CH_3CO), 3.86 (s, 3H, CO_2Me).

Anal. Calcd for $C_{19}H_{25}BrO_{13}$: C, 42.16; H, 4.66. Found: C, 42.71; H, 4.60.

Methyl 4,5,7,8-Tetra-*O*-acetyl-3-bromo-3-deoxy-α-D-*glycero*-D-*galacto*-2-octulopyranosonate (9c) and **Methyl 4,5,7,8-Tetra-*O*-acetyl-3-bromo-3-deoxy-α-D-*glycero*-D-*talo*-2-octulopyranosonate (10c).** A solution of **1a** (0.447 mmol, 180 mg) and *N*-bromosuccinimide (0.49 mmol, 110 mg) in 5:1 MeCN-H_2O (6 mL) was stirred at 85 °C for 30 min. The solution was concentrated and subjected to silica gel chromatography (*B*, 1:1 toluene-EtOAc). Pooling of the fractions containing the faster migrating compound gave **9c** as a syrup. Yield: 42 mg (19%), $[\alpha]_D$ +75° (*c* 0.9, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.00, 2.04, 2.08, 2.13 (4s, 12H, CH_3CO), 3.95 (s, 3H, CO_2CH_3), 4.09 (dd, 1H, $J_{8b,8a}$=-12.3, $J_{8b,7}$ =4.5 Hz, H-8b), 4.38 (dd, 1H, $J_{8a,7}$=2.5 Hz, H-8a), 4.48 (dd, 1H, $J_{6,5}$ =1.3, $J_{6,7}$ = 9.9 Hz, H-6), 4.55 (m, 1H, H-3), 4.59 (br s, 1H, OH), 5.16 (ddd, 1H, H-7), 5.40 (dd, 1H, $J_{4,3}$ =9.7, $J_{4,5}$ =3.3 Hz, H-4), 5.43 (m, 1H, H-5).

Anal. Calcd for $C_{17}H_{23}BrO_{12}$: C, 40.90; H, 4.64. Found: C, 41.23; H, 4.59.

Further elution of the column furnished **10c** (170 mg, 76%) as a syrup, $[\alpha]_D$ +11° (*c* 0.9, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.00, 2.08, 2.09, (3s, 12H, CH_3CO), 3.87 (s, 3H,

CO_2CH_3), 4.37 (dd, 1H, $J_{8a,8b}$=-12.4, $J_{8b,7}$ =3.1 Hz, H-8b), 4.40 (dd, 1H, $^4J_{3,5}$ =0.9, $J_{3,4}$ =4.3 Hz, H-3), 4.44 (dd, 1H, $J_{6,7}$ =10.0, $J_{6,5}$ =1.9 Hz, H-6), 4.45 (dd, 1H, $J_{8a,7}$ =3.5 Hz, H-8a), 4.58 (s, 1H, OH), 5.36 (dt, 1H, H-7), 5.38 (m, 1H, H-5), 5.51 (dd, 1H, $J_{4,5}$ =3.6 Hz, H-4).

Methyl 5,7,8-Tri-*O*-acetyl-3-bromo-3,4-dideoxy-D-*arabino*-oct-3-en-2-ulopyranosonate (11) and **Methyl 4,5,7,8-Tetra-*O*-acetyl-2,3-anhydro-α-D-*glycero*-D-*galacto*-2-octulopyranosonate (12).** A solution of **10c** (0.09 mmol, 45 mg) in dry MeCN (6 mL) was cooled to 0 °C. DBU (5 μL) was added, the solution was stirred for 2 min and immediately applied to column of silica gel (*A*, 2:1 toluene-EtOAc). Pooling of the faster migrating compound afforded **11** (18 mg, 46%) as colorless prisms, mp 154-155 °C (pentane-EtOAc), $[\alpha]_D$ -59° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.03, 2.07, 2.08, (3s, 9H, CH_3CO), 3.93 (s, 3H, CO_2CH_3), 4.25 (dd, 1H, $J_{8b,7}$ =4.4, $J_{8b,8a}$ =-12.4 Hz, H-8b), 4.42 (dd, 1H, $J_{8a,7}$ =2.3 Hz, H-8a), 4.46 (dd, 1H, $J_{6,5}$ =2.4, $J_{6,7}$ =9.8 Hz, H-6), 4.55 (s, 1H, OH), 5.16 (dd, 1H, $J_{5,4}$ =6.2 Hz, H-5), 5.27 (ddd, 1H, H-7), 6.55 (d, 1H, H-4).

Anal. Calcd for $C_{15}H_{19}BrO_{10}$: C, 41.02; H, 4.36. Found: C, 41.26; H, 4.37.

Further elution gave **12** (12.5 mg, 30%) as a syrup, $[\alpha]_D$ +41° (*c* 0.7, $CHCl_3$), lit:[7] +37° (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.02, 2.06, 2.07, 2.10, (4s, 12H, CH_3CO), 3.48 (d, 1H, $J_{3,4}$ =1.5 Hz, H-3), 3.86 (s, 3H, CO_2CH_3), 4.05 (dd, 1H, $^4J_{6,4}$ =0.8, $J_{6,7}$=9.6 Hz, H-6), 4.21 (dd, 1H, $J_{8b,8a}$= -12.4, $J_{8b,7}$ =4.2 Hz, H-8b), 4.56 (dd, 1H, $J_{8a,7}$ =2.4 Hz, H-8a), 5.20 (dd, 1H, H-7), 5.21 (d, 1H, $J_{5,4}$ =4.3 Hz, H-5), 5.26 (ddd, 1H, H-4). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 53.39 (OCH_3), 54.70 (C-3), 59.93 (C-4), 61.84 (C-8), 66.44 (C-5), 67.49 (C-7), 68.57 (C-6).

Anal. Calcd for $C_{17}H_{22}O_{12}$: C, 48.81; H, 5.30. Found: C, 48.98; H, 5.24.

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