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Synthesis of α-substituted 3-ulosonic acids from aldonolactones

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Abstract—Zinc–silver/graphite mediated Reformatsky-reaction of furanoid aldonolactones with α-bromo-esters allows the synthesis of α-substituted 3-ulosonic acids in high yields.

1. Introduction

Recognition of the importance of ulosonic acid derivatives for the regulation of a great variety of biological phenomena has fueled the pronounced interest in these compounds over the last years.[1–3] Amongst the most essential members of this class of carbohydrate constituents of cellular and bacterial membranes are KDO (3-deoxy-D-manno-2-octulosonic acid), Neu5Ac (5-acetamido-3,5-dideoxy-D-glycero-D-galacto-2-nonulosonic acid) and KDN (3-deoxy-D-glycero-D-galacto-nonulosonic acid). In addition, the 2-(2-hydroxy-tetrahydro-pyran-2-yl)-propionic acid moiety has been found in various natural products including the fungicidal and cytotoxic macrolide soraphen A,[4,5] the insect toxin pederin[6–9] and several ionophore antibiotics.[10–14]

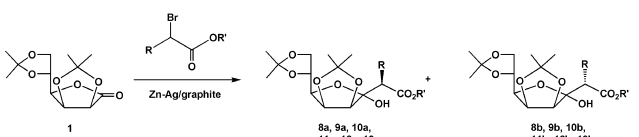
As a part of our studies on the synthetic utility of the highly active zinc–silver/graphite surface compound[15–17] we reported the application of a Reformatsky reaction to aldonolactones. Whereas Reformatsky reactions of lactones performed under classical conditions by and large[18–20] suffer from low yields, functional group incompatibility and low regio- and/or stereoselectivity the use of highly activated zinc species allows such chain elongation reactions to take place under very mild conditions with usually high yields even when the reactions are performed at low temperatures.[21]

In this study the condensation of furanoid as well as of pyranoid aldonolactones with organo zinc reagents from different simple halo alkanoates has been shown to afford chain extended 3-ulo-furanos (or 3-ulopyranos)onates in high yields. Alternatively a fluoride catalyzed synthesis of these compounds from α-silylesters,[22] trimethylsilyl ketene acetals[23,24] or most recently by use of a SmI_2-mediated Reformatsky-type reaction[25] has been suggested.

2. Results and discussion

Reaction of 2,3:5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone (**1**) with racemic or enantiomerically pure methyl 2-bromo-alkanoates **2**–**7** in the presence of the highly active zinc–silver/graphite surface compound at −20°C gave the chain-elongated products **8a**,**b**, **9a**,**b**, **10a**,**b**, **11a**,**b**, **12a**,**b**, and **13a**,**b**, respectively. No difference in yields or product distribution was observed upon using either racemic or enantiomerically pure α-bromo-alkanoates. All products were obtained as mixtures of epimers that were easily separated by column chromatography. These epimers differ in the absolute configuration at the newly created stereogenic centre C(2) with the anomeric hydroxy group pseudo-axially oriented. The signals of these hydroxy groups are found in the corresponding ^{1}H NMR spectra between δ 2.2–5.0 ppm and in the IR spectra a broad band at ν=3400–3500 cm^{-1}. In the ^{1}H and ^{13}C NMR spectra the chemical shifts for the carbohydrate parts are practically unchanged as compared to the starting material **1** except for the lactone carbonyl group that is missing in the ^{13}C spectra of the products. The e.i. MS spectra of all products show a characteristic M−15 peak (Scheme 1, Table 1).

In order to determine the absolute configuration at the newly created stereogenic centre C(2), suitable crystals of **9a** were



Scheme 1.

Keywords: Reformatsky reactions; aldonolactones.
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Table 1. Synthesis of ulosonic acids by *Reformatsky*-reactions

Ester	R′	R	Product	Yield [%]	(2*R*):(2*S*)
2	CH_3	$-CH_3$	**8**	82	39:41
3	CH_3	$-CH(CH_3)_2$	**9**	76	36:64
4	CH_3	$-CH_2-CH(CH_3)_2$	**10**	74	45:55
5	CH_3	$-C(CH_3)_3$	**11**	69	33:67
6	CH_3	$-CH_2-C_6H_5$	**12**	85	38:62
7	CH_3	$-C_6H_5$	**13**	75	43:57
14	$-C(CH_3)_3$	$-CH_3$	**15**	74	43:57
16	$-C(CH_3)_3$	$-H$	**17**	54	0:100

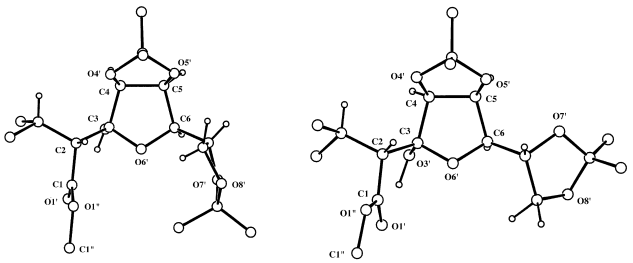


Figure 1. Crystal structure of **9a**. The unit cells contain two conformers that differ in the arrangement of the side chain. Selected data: orthorhombic, $P2_12_12_1$, a=8.737(2) Å, b=13.553(3) Å, c=34.615 Å, Z=8,1956 collected, R=0.041, C(2)–C(3)=1.519(8) Å, C(3)–O(6′)=1.415(6) Å, C(3)–C(4)=1.549(8) Å, C(4)–C(5)=1.516(8) Å, C(5)–C(6)=1.521(8) Å, C(6)–C(O6′)=1.453(6) Å.

grown and subjected to a single crystal X-ray analysis the results of which are depicted in Figure 1.

As shown from this X-ray analysis of **9a** the carbon C(2) possesses a (*R*) configuration hence for **9b** a (*S*)-configuration can be assumed. Since the crystallization of these compounds proved rather difficult and time consuming due to a concomitant deterioration of the compounds upon prolonged standing in solution a more convenient way for the determination of the absolute configuration at C(2) was needed. Upon comparison of the ^{1}H NMR spectroscopic data it was revealed that H–C(2) is found to be slightly shifted to a higher field for the (2*R*)-configurated compounds as compared to their corresponding (2*S*)-epimers. Similarly the signal of the anomeric hydroxy group is found at lower field for the (2*R*) stereomers. In the ^{13}C NMR spectra the position of the anomeric carbon C(3) seems indicative for the absolute configuration at C(2) since for all of the (2*R*)-configurated compounds δ C(3) was found at lower field as compared to the (2*S*)-stereoisomers.

The assignment of the absolute configuration at C(2) performed by the comparison of the NMR spectroscopic data parallels the results from the measurement of the specific optical rotation. This led to the assumption that CD spectra should allow an unambiguous assignment of the absolute configuration even for compounds obtained only as one single stereoisomer (where consequently the comparison of the NMR spectroscopic data is not possible at all). Representative CD spectra for the epimers **9a**,**b** are depicted in Figure 2.

Semiempirical AM1 calculations indicate that the (2*R*) isomer should be thermodynamically more stable than the (2*S*)-isomer that was always obtained as the major product

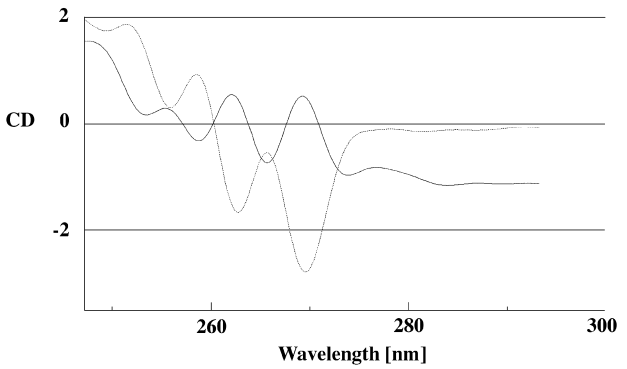
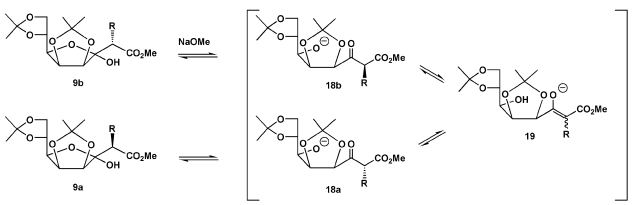


Figure 2. CD spectra for **9a** (···) and **9b** (—) in $CHCl_3$.

in these reactions. Thus, a kinetically controlled attack of the organozinc species onto the sterically less hindered *re*-face of the lactone carbonyl moiety seems reasonable resulting in the intermediary formation of β-configurated product that undergoes subsequently rapid anomerization leading to the thermodynamically more stable α-anomer.

It seems most likely that the proximal oxygenated substituents on the carbohydrate thereby act as directing groups during the addition of the zincorganic reagents by steric effects than by chelation.

In order to find an experimental proof for the calculated higher thermodynamic stability of the (2*R*)-configurated products the reaction of **9b** in CD_3OD with catalytical amounts of CD_3ONa was studied. After stirring at room temperature for 30 min a 4:1 mixture of **9a/9b** was obtained (Scheme 2).



Scheme 2.

^{1}H NMR spectroscopic analysis revealed a deuterium exchange rate of 88% at C(2) for both **9a** and **9b** thus indicating a base induced ring opening of **9a** to afford **18** that undergoes an enolization to **19**. Intermediate **19** is re-protonated to afford the thermodynamically more stable **9b**. The ^{13}C NMR spectra of these deuterated derivatives show the carbon atom C(2) as a triplet at δ=53.44 ppm with a coupling constant $J_{C(2),D}$=20.4 Hz.

Comparison of the chemical shift δ(C2) shows a deuterium induced shift to higher fields ($|\Delta\delta|$=0.38 ppm) whereas for C(1) a downfield shift ($|\Delta\delta|$=0.14 ppm) was observed.

Treatment of the D-erythrono-1,4-lactone derived compound **20** with C_2D_5OD with catalytical amounts of C_2D_5ONa for 24 h at room temperature resulted in the formation of a 36% deuterated **21** (from ^{1}H integration). The diastereotopic protons $H_{A,B-C(2)}$ were exchanged by deuterium in a similar extend. Again in the ^{13}C NMR δC(2) in **21** is shifted to higher fields ($|\Delta\delta|$=0.26 ppm with

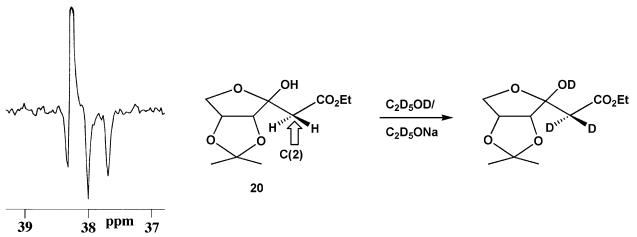


Figure 3. Part of the ^{13}C NMR spectrum of **20** after treatment with C_2D_5OD/cat. C_2D_5ONa showing C(2) with its typical deuterium-induced high field shift ($|\Delta\delta|$=0.26 ppm and $J_{C(2),D}$=20.1 Hz).

$J_{C(2),D}$=20.1 Hz) whereas C(1) is shifted to lower fields ($|\Delta\delta|$=0.10 ppm); no deuterium-induced shift was observed for C(3) (Fig. 3).

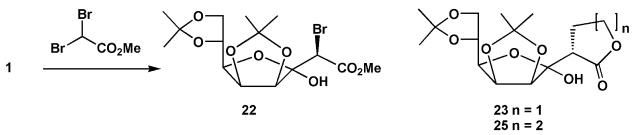
Upon treatment of **9a** or **9b** with the Lewis acid $ZnCl_2$ in THF for a prolonged period of time no epimerization took place. Hence, it seems reasonable that the ratio of (2*S*): (2*R*) configurated material formed during the reaction rather reflects the kinetical control of this reaction than the thermodynamic equilibrium between these two compounds.

Treatment of either **9a** or **9b** with strong acids does not result in any epimerization but partial cleavage of the isopropylidene acetals as well as cleavage of the ester followed by a decarboxylation reaction (ketonic cleavage) as described earlier.[26]

To gain further insights in this zinc-mediated Reformatsky reaction *tert* butyl bromo-acetate was allowed to react with Zn–Ag/graphite at −70°C for 10 min, then the reaction mixture was filtered under argon and equal stoichiometric amounts of **1** were added both to the filtrate and to the graphite pad that was re-suspended in anhydrous THF prior to the addition of a solution of **1**. Whereas for the filtrate a clean formation of **17** was observed within several minutes hardly any reaction was observed for the re-suspended graphite hence clearly indicating the formation of soluble Reformatsky reagents that are not longer absorbed or attached to the graphite surface. Therefore, the presence of the Zn–Ag/graphite allows a very fast und quantitative formation of the Reformatsky reagent even at very low temperature due to the huge surface of the Zn–Ag couple finely dispersed on the graphite surface whereas the presence of the graphite is no longer necessary nor significant for the reaction of the zincorganic species with the carboxyl group.

Upon addition of elemental sulfur (10 mol% in a minimum of CS_2) as a radical scavenger to a suspension of Zn–Ag/graphite followed by the simultaneous addition of *tert* butyl bromo-acetate and **1** no reaction occurred even at room temperature within 24 h whereas upon addition of sulfur (10 mol% in a minimum of CS_2) to a preformed Reformatsky reagent from Zn–Ag/graphite and *tert* butyl bromo-acetate followed by the addition of **1** only led to a significantly slowing of the reaction but it came to completion within 24 h. These results indicate the Reformatsky reaction to proceed similar to the SmI_2 induced analogues reaction of α-halo-alkanoates with carbonyl compounds via a SET mechanism. Possibly in a first step the bromo-ester is reduced via a first single electron transfer at the surface of the Zn–Ag/graphite to the corresponding radical that is reduced to an organozinc species after a second electron transfer. These experiments, however, do not allow to decide whether the fine dispersion of the Zn–Ag-couple or the graphite additionally acting as a supporter of the first single electron transfer is the main reason for the rather high reactivity of this reagent.

Whereas the Reformatsky reaction of **1** with *tert* butyl-dibromoacetate gave a 1:1 mixture of the (2*R*)/(2*S*) configurated products the reaction of **1** with ethyl dibromo-acetate gave a 72:18 mixture in favor of the (2*R*) epimer (by ^1H NMR); only the (2*R*) isomer **22** was obtained, however, from the reaction of **1** with methyl dibromo-acetate albeit at a somewhat lowered yield of 64% (Scheme 3).



Scheme 3.

In analogy to the products possessing a carbon substituent at C(2) from the CD spectrum for **22** a (2*R*) configuration was predicted; this prediction matched perfectly to the results from a single crystal X-ray analysis whose results are depicted in Figure 4.

The exclusive formation of **22** can be rationalized from an of the *si*-face of the (*Z*)-zinc enolate with the *re*-face of the lactone carbonyl moiety followed by a zinco[3.3] sigma-tropic rearrangement of the chair-like six-membered transition state followed by a fast anomerization of the hydroxyl group at C(3).[17]

Reaction of **1** with α-bromo-γ-butyrolactone (**24**) in the

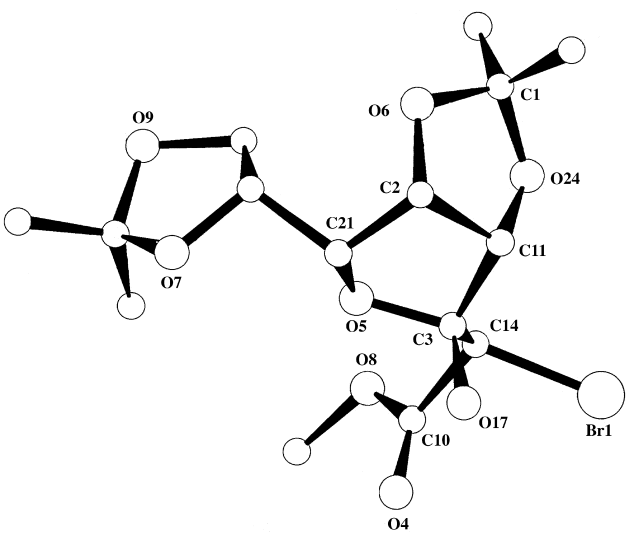


Figure 4. Single crystal X-ray analysis of **22**; selected data: monoclinic, *P*2sub1, *a*=7.80(2) Å, *b*=7.367(13) Å, *c*=15.90(4) Å, α=90°, β=87.7°, γ=90°, 3587 reflections collected, 2371 independent reflections, full-matrix least-squares on F^2, goodness-of-fit on F^2=0.885; Br(1)–C(14)=19.946(9) Å, C(3)–O(5)=1.428(9) Å, C(3)–O(17)=1.421(10) Å, C(3)–C(11)=1.521(11) Å, C(2)–C(11)=1.528(12) Å, C(2)–C(21)=1.522(13) Å, O(5)–C(21)=1.439(10) Å, C(3)–C(14)=1.516(12) Å.

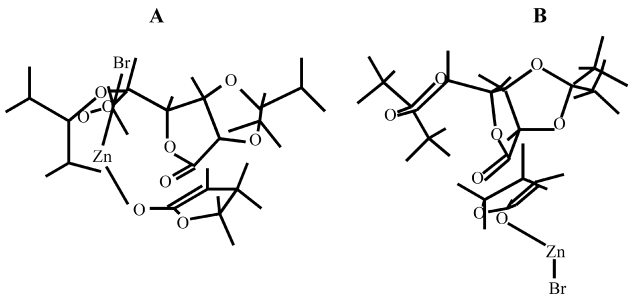


Figure 5. Simulation [software CAChe 3.8; individual conformation optimized by AM1 calculations (after having performed a systematic conformational search by application of a MM2 force field)] of the approach of the organozinc species from α-bromo-γ-butyrolactone (neglecting THF molecules as possible ligands) to the zinc core) onto the *re*-face of the lactone carbonyl group of **1** to afford **23**. **A**: disfavoured *re*–*re*-approach; **B**: favored *si*–*re* approach.

presence of Zn–Ag/graphite at −20°C resulted in the exclusive formation of one single stereoisomer **23** out of possible 4 (including the anomers). The formation of only one epimer can be rationalized by the formation of an intermediary (*E*)-zinc-enolate that reacts with its *si*-face onto the *re*-face of the lactone carbonyl group via a transition state **B** (Fig. 5) to result in the formation of a (2*S*)-configurated product.

Inspection of Dreiding models and calculations indicated that the transition state **A** (resulting from a *re*–*re* attack) should be disfavored due to the occurrence of unfavourable steric interactions of the substituents of the two five-membered rings. **23** shows similar IR and NMR spectroscopic as well as chirooptical properties in comparison to previously prepared **25** whose absolute configuration at the newly created stereogenic centres has been deduced unambiguously by a single crystal X-ray analysis.[27]

3. Experimental

3.1. General

The melting points are uncorrected (Reichert hot stage microscope), optical rotations were obtained using a Perkin–Elmer 243B polarimeter (1 cm micro-cell), NMR spectra (internal Me_4Si) were recorded using either a Bruker AM250 or a Varian XL300 instrument (δ given in ppm, J in Hz), IR spectra (film or KBr pellet) on a Perkin–Elmer 298 instrument, MS spectra were taken either on a MAT311A or a Varian-112S instrument; for elemental analysis a Foss–Heraeus Vario EL instrument was used. TLC was performed on silica gel (Merck 5554, detection by dipping in a solution containing 10% sulfuric acid (400 ml), ammonium molybdate (20 g) and cerium$^{(IV)}$ sulfate (20 mg) followed by heating to 150°C. The tetrahydrofuran used throughout for all reactions was freshly distilled from sodium/benzophenone; all reactions were performed under dry argon.

3.2. General procedure for Reformatsky reactions

Degassed graphite (Fluka, 1.56 g, 130 mmol, 150°, 30 min) and clean, freshly cut potassium (0.66 g, 16.88 mmol) were stirred at 150°C under argon. To the resulting bronze-coloured C_8K suspended in THF (100 ml) a mixture of anhydrous zinc chloride (1.1 g, 8.2 mmol) and silver acetate (0.12 g, 0.72 mmol) was added in several portions at room temperature with vigorous stirring. The addition of these salts caused the solvent to boil; heating and reflux was continued for an additional 25 min, the suspension was cooled to −78°C and a solution of **1** and of the halo ester (for quantities vide infra) in abs. THF (15 ml) was added slowly. After stirring for the period and temperature given (vide infra) the mixture was filtered over a pad of Celite, diluted with ethyl acetate (150 ml) and extracted with ice water (10 ml) and brine (10 ml). The organic layer was dried over sodium sulfate, the solution was evaporated below 35°C and the remaining residue subjected to column chromatography to afford the corresponding products.

3.2.1. (2*R*) Methyl 2-deoxy-4,5;7,8-di-*O*-isopropylidene-2-methyl-α-D-manno-3,6-furanoso-3-octulosonate (8a) and (2*S*) methyl 2-deoxy-4,5;7,8-di-*O*-isopropylidene-2-methyl-α-D-manno-3,6-furanoso-3-octulosonate (8b). The reaction of **1** (1.03 g, 4.0 mmol) with methyl 2-bromo-propionate (**2**) (1.33 g, 8.0 mmol) at −78→0°C for 4 h followed by column chromatography (hexane/ethyl acetate 5:1) gave **8a** (0.44 g, 32%) and **8b** (0.69 g, 50%).

Data for **8a**. Oil, $[\alpha]_D=-7.5°$ (c=1.3, $CHCl_3$), R_f=0.31 (hexane/ethyl acetate 3:1); IR (film) ν=3480m, 3470m, 2990s, 2950s, 1720s, 1460m, 1440m, 1370s, 1380s, 1345m, 1260m, 1240m, 1210s, 1185m, 1175m, 1115m, 1065s, 1040s; ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.30 (d, J=7.2 Hz, 3H, H–C(2′)), 1.32, 1.37, 1.42, 1.47 (each s, 3H, Me), 2.95 (q, J=7.2 Hz, 1H, H–C(2)), 3.72 (s, 3H, OMe), 3.96 (dd, J=4.8, 8.6 Hz, 1H, H_A–C(8), 4.04 (dd, J=6.1, 8.6 Hz, 1H, H_B–C(8)), 4.10 (dd, J=3.8, 7.7 Hz, 1H, H–C(6)), 4.35 (ddd, J=4.8, 6.1, 7.7 Hz, 1H, H–C(7)), 4.47 (d, J=5.9 Hz, 1H, H–C(4), 4.57 (s, 1H, OH), 4.83 (dd, J=3.8, 5.9 Hz, 1H, H–C(4)); ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.68 (q, C(2′)), 24.42, 25.43, 25.84, 26.73 (each q, Me (isopropylidene)), 42.05 (d, C(2)), 51.83 (q, OMe), 66.70 (t, C(8)), 73.06, 79.18, 79.94, 84.08 (each d, C(4,5,6,7)), 106.24 (s, C(3)), 108.89, 112.51 (each s, C_q (isopropylidene)), 176.46 (s, C(1)); MS (e.i., 80 eV, 85°C): m/z=331 (56.0), 315 (4.9), 273 (6.5), 259 (2.3), 245 (7.9), 213 (8.4), 187 (13.8), 181 (11.1), 158 (19.2), 141 (29.6), 133 (15.2), 126 (118.5), 115 (40.2), 101 (100.0). Anal. calcd for $C_{16}H_{26}O_8$ (346.38): C, 55.48; H, 7.57. Found: C, 55.54; H, 7.62.

Data for **8b**. Colorless oil, $[\alpha]_D=-4.0°$ (c=1.2, $CHCl_3$), R_f=0.21 (hexane/ethyl acetate 3:1); IR (film): ν=3460bm, 2980s, 2960m, 2900m, 1740s, 1455m, 1370s, 1340m, 1260s, 1205s, 1160s, 1110m, 1075s, 1065s; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.30 (s, 3H, Me (isopropylidene)), 1.31 (d, J=7.3 Hz, 3H, H–C(2′)), 1.37, 1.43, 1.44 (each s, 3 H, Me (isopropylidene)), 3.03 (q, J=7.3 Hz, 1H, H–C(2)), 3.73 (s, 3H, OMe), 3.84 (s, 1H, OH), 3.99–4.09 (m, 2H, H–C(8)), 4.12 (dd, J=3.8, 7.4 Hz, 1H, H–C(6)), 4.31–4.37 (m, H–C(7)), 4.59 (d, J=5.8 Hz, 1H, H–C(4)), 4.8S (dd, J=3.8, 5.8 Hz, 1H, H–C(5)); ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.24 (q, C(2′)), 24.50, 24.51, 25.86, 26.80 (each q, Me (isopropylidene)), 42.55 (d, C(2)), 51.95 (q, OMe), 66.65 (t, C(8)), 73.11, 79.46, 79.97, 86.39 (each d, C(4,5,6,7)), 104.85 (s, C(3)), 108.93, 112.55 (each s, C_q (isopropylidene)), 175.62 (s, C(1)); MS (e.i., 80 eV, 80°C): m/z=331

(34.7), 315 (3.0), 273 (3.9), 253 (3.4), 213 (6.6), 187 (5.1), 181 (9.3), 156 (8.4), 141 (30.1), 126 (15.9), 115 (39.8), 101 (100.0). Anal. calcd for $C_{16}H_{26}O_8$ (346.38): C, 55.48; H, 7.56. Found: C, 55.40; H, 7.53.

3.2.2. (2*R*) Methyl-2-deoxy-2-isopropyl-4,5;7,8-di-*O*-isopropylidene-α-D-manno-3,6-furanoso-3-octulosonate (9a) and (2*S*) methyl-2-deoxy-2-isopropyl-4,5;7,8-di-*O*-isopropylidene-α-D-manno-3,6-furanoso-3-octulosonate (9b). The reaction of **1** (1.03 g, 4.0 mmol) with methyl 2-bromo-2-methyl-butanoate (**3**) (1.56 g, 8 mmol) at −20⟶ −5°C for 5 h followed by column chromatography (hexane/ethyl acetate 5:1) gave **9a** (0.40 g, 27%) and **9b** (0.73 g, 49%).

Data for **9a**. Mp 73–74°C, $[\alpha]_D$=−23.4° (c=1.0, $CHCl_3$), R_f=0.50 (hexane/ethyl acetate 3:1); IR (film): ν=3470bs, 3000s, 2970s, 2940s, 2880m, 1750s, 1460m, 1440m, 1380s, 1320w, 1300w, 1270m, 1210s, 1170s, 1135s, 1070s, 1035s, 1010s; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.95, 1.07 (each d, J=6.8 Hz, 3H, Me–C(2′)), 1.31, 1.36, 1.41, 1.47 (each s, 3H, Me (isopropylidene), 2.17 (dqq, J=6.8, 6.8, 6.1 Hz, 1H, H–C(2′)), 2.79 (d, J=6.1 Hz, 1H, H–C(2)), 3.71 (s, 3H, OMe), 3.94 (dd, J=4.7, 7.5 Hz, 1H, H_A–C(8)), 4.03 (dd, J=5.8, 7.5 Hz, 1H, H_B–C(8)), 4.05 (dd, J=3.8, 6.5 Hz, 1H, H–C(6)), 4.35 (ddd, J=4.7, 5.8, 6.5 Hz, 1H, H–C(7)), 4.48 (d, J=5.8 Hz, 1H, H–C(4)), 4.51 (s, 1H, OH), 4.82 (dd, J=3.8, 5.8 Hz, 1H, H–C(5)); ^{13}C NMR (63 MHz, $CDCl_3$): δ=19.96 (d, C(2′), 22.22, 24.44 (each q, C(2″)), 25.39, 25.85, 26.71, 27.81 (each q, Me (isopropylidene)), 51.40 (q, OMe), 53.74 (q, C(2)), 66.68 (t, C(8)), 73.18, 78.42, 80.25, 84.70 (each d, C(4,5,6,7)), 106.48 (s, C(3)), 108.87, 112.55 (s, C_q (isopropylidene)), 174.96 (s, C(1)); MS (e.i., 80 eV, 94°C): m/z=359 (56.6), 343 (3.7), 301 (5.8), 273 (12.4), 241 (5.6), 215 (13.0), 186 (22.7), 143 (44.8), 141 (29.3), 126 (18.4), 116 (26.5), 101 (100.0). Anal. calcd for $C_{18}H_{30}O_8$ (374.43): C, 57.74; H, 8.08. Found: C, 58.04; H, 8.17.

Data for **9b**. Colorless oil, $[\alpha]_D$=−20.9° (c=1.1, $CHCl_3$), R_f=0.36 (hexane/ethyl acetate 3:1); IR (film): ν=3490bm, 2980s, 2960s, 2940s, 2880m, 1715s, 1460s, 1440s, 1380s, 1370s, 1260m, 1210s, 1160m, 1090s, 1065s, 1040s; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.95 (d, J=6.8 Hz, 3H, Me–C(2′)), 1.11 (d, J=6.9 Hz, 3H, Me–C(2′)), 1.28, 1.38, 1.43, 1.44 (each s, 3H, Me), 2.40 (ddq, J=4.5, 6.8, 6.9 Hz, 1H, H–C(2′)), 2.77 (d, J=4.5 Hz, 1H, H–C(2)), 3.73 (s, 1H, OH), 3.75 (s, 3H, OMe), 4.04 (dd, J=4.3, 7.5 Hz, 1H, H_A–C(8)), 4.09 (dd, J=5.7, 7.5 Hz, 1H, H_B–C(8)), 4.14 (dd, J=3.8, 7.9 Hz, 1H, H–C(6)), 4.35 (ddd, J=4.3, 5.7, 7.9 Hz, 1H, H–C(7)), 4.44 (d, J=5.8 Hz, 1H, H–C(4)), 4.82 (dd, J=3.8, 5.8 Hz, 1H, H–C(5)); ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.53 (d, C(2′)), 23.54, 24.64 (each q, C(2″)), 25.50, 25.92, 26.59, 26.62 (each q, Me (isopropylidene)), 51.47 (q, OMe), 53.63 (d, C(2)), 66.84 (t, C(8)), 73.11, 79.66, 79.91, 87.50 (each q, C(4,5,6,7)), 105.55 (s, C(3)), 109.03, 112.70 (each s, C_q (isopropylidene)), 175.2 (s, C(1)); MS (e.i., 80 eV, 106°C): m/z=359 (20.9), 343 (0.6), 301 (2.7), 281 (1.6), 269 (0.7), 241 (5.0), 215 (2.8), 209 (6.4), 181 (3.2), 173 (3.7), 161 (14.1), 141 (31.7), 126 (17.7), 115 (10.0), 101 (89.8), 98 (39.5). Anal. calcd for $C_{18}H_{30}O_8$ (374.43): C, 57.74; H, 8.08. Found: C, 57.89; H, 8.19.

3.2.3. (2*R*) Methyl 2-deoxy-2-isobutyl-4,5;7,8-di-*O*-isopropylidene-α-D-manno-3,6-furanoso-3-octulosonate (10a) and (2*S*) methyl 2-deoxy-2-isobutyl-4,5;7,8-di-*O*-isopropylidene-α-D-manno-3,6-furanoso-3-octulosonate (10b). The reaction of **1** (1.03 g, 4.0 mmol) and methyl 2-bromo-4-methyl-heptanoate (**4**) (1.67 g, 8 mmol) at −20⟶ −5°C for 6 h followed by column chromatography (hexane/ethyl acetate 5:1) gave **10a** (0.51 g, 33%) and **10b** (0.63 g, 41%) erhalten.

Data for **10a**. Colorless oil, $[\alpha]_D$=+16.9° (c=2.0, $CHCl_3$), R_f=0.48 (hexane/ethyl acetate 3:1); IR (film): ν=3480m, 2990s, 2960s, 2900m, 2880m, 1715s, 1455m, 1445m, 1380s, 1370s, 1210s, 1170s, 1130m, 1115m, 1060s, 1040s; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.91 (d, J=5.1 Hz, 3H, Me–C(2″)), 0.93 (d, J=5.0 Hz, 3H, Me–C(2″)), 1.30–1.40 (m, 1H, H–C(2″)), 1.32, 1.37, 1.40, 1.46 (each s, 3H, Me (isopropylidene)), 1.67–1.79 (m, 2H, H–C(2′)), 2.99 (d, J=2.6, 11.8 Hz, 1H, H–C(2)), 3.71 (s, 3H, OMe), 3.94 (dd, J=5.1, 8.7 Hz, 1H, H_A–C(8)), 4.00–4.16 (m, 2H, H_B–C(8) and H–C(6)), 4.35 (ddd, J=5.1, 6.1, 7.2 Hz, 1H, H–C(7)), 4.44 (s, 1H, OH), 4.46 (d, J=5.9 Hz, 1H, H–C(4)), 4.81 (dd, J=3.7, 5.9 Hz, 1H, H–C(5)); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.18 (d, C(2″)), 23.70, 24.64 (each q, Me–C(2″)), 25.65, 25.93, 26.40, 26.80 (each q, Me (isopropylidene)), 37.81 (t, C(2′)), 46.48 (q, OMe), 51.84 (d, C(2)), 66.72 (t, C(8)), 73.25, 79.01, 80.20, 84.31 (each d, C(4,5,6,7)), 106.51 (s, C(3)), 108.99, 112.71 (each s, C_q (isopropylidene)), 176.50 (s, C(1)); MS (e.i., 80 eV, 72°C): m/z=388 (0.1), 373 (51.7), 357 (3.1), 315 (6.6), 287 (8.2), 255 (6.2), 229 (10.6), 200 (6.6), 175 (13.9), 157 (32.0), 144 (29.7), 126 (19.6), 101 (100.0); MS (FAB, glycerine+LiCl): m/z=395 (M+Li), 373, 313. Anal. calcd for $C_{19}H_{32}O_8$ (388.46): C, 58.75; H, 8.30. Found: C, 58.79; H, 8.20.

Data for **10b**. Colorless oil, $[\alpha]_D$=−11.6° (c=2.2, $CHCl_3$), R_f=0.27 (hexane/ethyl acetate 3:1); IR (film): ν=3480m, 2980s, 2950s, 1735s, 1455m, 1440m, 1380s, 1370s, 1260s, 1210s, 1160s 1100m, 1060s, 1045s; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.91–0.92 (m, 6H, Me–C(2″)), 1.30, 1.38, 1.43, 1.46 (each s, 3H, Me (isopropylidene)), 1.54–1.71 (m, 3H, H–C(2′) and C(2″)), 2.97–3.02 (m, 1H, HC(2)), 3.74 (s, 3H, OMe), 3.93 (s, 1H, OH), 4.02 (dd, J=5.2, 8.8 Hz, 1H, H_A–C(8)), 4.07 (dd, J=6.1, 8.8 Hz, 1H, H_B–C(8)), 4.13 (dd, J=3.7, 7.6 Hz, 1 H, H–C(6)), 4.30–4.37 (m, 1H, H–C(7)), 4.48 (d, J=5.8 Hz, 1H, H–C(4)), 4.84 (dd, J=3.7, 5.8 Hz, 1H, H–C(5)); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.80 (d, C(2″)), 23.13, 24.66 (each q, Me–C(2″)), 25.48, 25.96, 26.22, 26.80 (each q, Me (isopropylidene)), 35.78 (t, C(2′)), 46.00 (q, OMe), 51.87 (d, C(2)), 66.73 (t, C(8)), 73.11, 79.88, 79.89, 86.84 (each d, C(4,5,6,7)), 105.16 (s, C(3)), 108.98, 112.74 (each s, C_q (isopropylidene)), 176.21 (s, C(1)); MS (e.i., 80 eV, 104°C): m/z=373 (24.0), 357 (0.9), 315 (3.7), 299 (1.1), 295 (3.6), 283 (0.6), 255 (5.1), 243 (6.4), 229 (3.5), 223 (5.4), 195 (2.7), 179 (3.5), 175 (12.2), 157 (26.3), 141 (31.2), 126 (17.5), 101 (100.0). Anal. calcd for $C_{19}H_{32}O_8$ (388.46): C; 58.75; H, 8.30. Found: C, 58.51; H, 8.25.

3.2.4. (2*R*) Methyl 2-*tert* butyl-2-deoxy-4,5;7,8-di-*O*-isopropylidene-α-D-manno-3,6-furanoso-3-octulosonate (11a) and (2*S*) methyl 2-*tert* butyl-2-deoxy-4,5;7,8-di-*O*-isopropylidene-α-D-manno-3,6-furanoso-oct-3-ulosonate (11b). The reaction of **1** (1.03 g, 4.0 mmol) and methyl 2-bromo-3,3-dimethyl-butanoate (1.68 g, 8.0 mmol) at

−78⟶−5°C for 4 h followed by column chromatography (hexane/ethyl acetate 5:1) gave **11a** (0.36 g, 23%) and **11b** (0.71 g, 46%).

Data for **11a**. Colorless oil, $[\alpha]_D$=−6.4° (*c*=1.0, $CHCl_3$), R_f=0.45 (hexane/ethyl acetate 3:1); IR (film): ν=3460bs, 2980s, 2960s, 2900s, 1725s, 1480m, 1450m, 1430m, 1370s, 1330s, 1270m, 1230m, 1210s, 1150s, 1060s, 1040s, 1000s; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.10 (s, 9H, Me (*tert* butyl)), 1.30, 1.36, 1.40, 1.47 (each s, 3H, Me (isopropylidene)), 2.91 (s, 1H, H−C(2)), 3.68 (s, 3H, OMe), 3.92 (dd, *J*=5.1, 8.7 Hz, 1H, H_A−C(8)), 4.01 (dd, *J*=6.2, 8.7 Hz, 1H, H_B−C(8)), 4.00–4.04 (m, 1H, H−C(6)), 4.22 (s, 1H, OH), 4.30–4.33 (m, *J*=5.1, 6.2 Hz, 1H, H−C(7)), 4.52 (d, *J*=5.8 Hz, 1H, H−C(4)), 4.83 (dd, *J*=4.1, 5.8 Hz, 1H, H−C(5)); ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.40, 25.54, 25.83, 26.65 (each q, Me (isopropylidene)), 29.57 (q, Me (*tert* butyl)), 32.80 (s, C_q (*tert* butyl)), 51.20 (q, OMe), 56.01 (d, C(2)), 66.48 (t, C(8)), 73.23, 77.35, 80.43, 84.46 (each d, C(4,5,6,7)); 106.25 (s, C(3)), 108.77, 112.14 (each s, C_q (isopropylidene)), 174.30 (s, C(1)); MS (e.i., 80 eV, 114°C): *m*/*z*=373 (14.9), 357 (1.9), 342 (4.3), 299 (3.8), 287 (5.8), 285 (4.0), 199 (8.3), 173 (5.9), 157 (14.2), 141 (13.3), 126 (6.3), 115 (10.4), 101 (72.4). Anal. calcd for $C_{19}H_{32}O_8$ (388.46): C, 58.75; H, 8.30. Found: C, 58.78; H, 8.35.

Data for **11b**. Colorless oil, $[\alpha]_D$=−15.5° (*c*=2.3, $CHCl_3$), R_f=0.39 (hexane/ethyl acetate 3:1); IR (film): ν=3460bs, 2990s, 2960s, 2910m, 2880m, 1705s, 1480m, 1450m, 1435m, 1370s, 1260m, 1210s, 1160s, 1110s, 1070s, 1050s, 1010s; ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.12 (s, 9H, Me (*tert* butyl)), 1.28, 1.38, 1.44, 1.45 (each s, 3H, Me (isopropylidene)), 2.85 (s, 1H, H−C(2)), 3.74 (s, 3H, OMe), 4.02 (dd, *J*=5.1, 8.6 Hz, 1H, H_A−C(8)), 4.08 (dd, *J*=6.1, 8.6 Hz, 1H, H_B−C(8), 4.15 (dd, *J*=3.8, 7.7 Hz, 1H, H−C(6)), 4.18 (s, 1H, OH), 4.33 (d, *J*=5.8 Hz, 1H, H−C(4)), 4.34–4.37 (m, 1H, H−C(7)), 4.78 (dd, *J*=3.8, 5.8 Hz, 1H, H−C(5)); ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.69, 25.40, 26.02, 26.90 (each q, Me (isopropylidene)), 30.13 (q, Me (*tert* butyl)), 34.26 (s, C_q (*tert* butyl)), 51.55 (q, OMe), 55.63 (d, C(2)), 66.88 (t, C(8)), 73.05, 78.97, 80.15, 88.52 (each d, C(4,5,6,7)), 106.09 (s, C(3)), 109.09, 112.71 (each s, C″ (isopropylidene)), 175.47 (s, C(1)); MS (e.i., 80 eV, 51°C): *m*/*z*=373 (25.2), 357 (1.2), 315 (2.6), 299 (1.4), 259 (11.9), 231 (7.8), 227 (7.3), 199 (4.3), 185 (2.4), 175 (12.6), 157 (17.1), 141 (34.4), 126 (18.4), 115 (13.8), 101 (100.0). Anal. calcd for $C_{19}H_{32}O_8$ (388.46): C, 58.75; H, 8.30. Found: C, 58.66; H, 8.29.

3.2.5. (2*R*) Methyl 2-benzyl-2-deoxy-4,5;7,8-di-*O*-isopropylidene-α-D-manno-3,6-furanoso-3-octulosonate (12a) and (2*S*) methyl 2-benzyl-2-deoxy-4,5;7,8-di-*O*-isopropyliden-α-D-manno-3,6-furanoso-3-octulosonate (12b). The reaction of **1** (1.03 g, 4.0 mmol) and methyl 2-bromo-3-phenyl-propanoate (**6**) (1.94 g, 8.0 mmol) at −20⟶−5°C for 6 h followed by column chromatography (hexane/ethyl acetate 5:1) gave **12a** (0.54 g, 32%) and **12b** (0.89 g, 53%).

Data for **12a**. Mp 74–75°C, $[\alpha]_D$=+30.9° (*c*=1.4, $CHCl_3$), R_f=0.40 (hexane/ethyl acetate 3:1); IR (film): ν=3470s, 3040m, 3000s, 2950s, 1720s, 1500m, 1460m, 1440m, 1380s, 1270w, 1220s, 1170s, 1120m, 1070s, 1040s; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.40 (s, 6H, Me (isopropylidene)), 1.43, 1.56 (each s, 3H, Me (isopropylidene)), 2.19 (s, 1H, OH), 2.91–3.01 (m, 1H, H−C(2)), 3.11–3.24 (m, 2H, H−C(2′)), 3.49 (s, 3H, OMe), 3.98 (dd, *J*=5.0, 8.7 Hz, 1H, H_A−C(8)), 4.06 (dd, *J*=6.2, 8.7 Hz, 1H, H_B−C(8)), 4.16 (dd, *J*=3.7, 7.3 Hz, 1H, H−C(7)), 4.35–4.40 (m, 1H, H−C(7)), 4.62 (d, *J*=9.0 Hz, 1 H, H−C(4)), 4.90 (dd, *J*=3.7, 5.9 Hz, 1H, H−C(5)), 7.19–7.33 (m, 5H, CH_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.49, 25.651, 25.90, 26.65 (each q, Me (isopropylidene)), 35.09 (t, C(2′)), 50.64 (q, OMe), 51.51 (d, C(2)), 66.58 (t, C(8)), 73.11, 79.08, 80.12, 84.22 (each d, C(4,5,6,7)), 105.99 (s, C(3)), 108.88, 112.75 (each s, C_q (isopropylidene)), 126.36, 128.19, 128.56, (each d, CH_{arom}), 138.28 (s, $C_{q\ arom}$), 175.35 (s, C(1)); MS (e.i., 80 eV, 109°C): *m*/*z*=422 (0.1), 407 (43.6), 404 (5.0), 345 (0.9), 329 (4.3), 263 (6.3), 234 (10.2), 216 (12.3), 209 (10.8), 191 (11.4), 159 (32.4), 141 (28.2), 131 (25.4), 126 (16.3), 101 (92.9), 91 (100.0). Anal. calcd for $C_{22}H_{30}O_8$ (422.48): C, 62.55; H, 7.16. Found: C, 62.33; H, 6.99.

Data for **12b**. Colorless oil, $[\alpha]_D$=−13.8° (*c*=1.7, $CHCl_3$), R_f=0.20 (hexane/ethyl acetate 3:1); IR (film): ν=3480bm, 3100w, 3070w, 3040m, 2990s, 2960s, 2940s, 1740s, 1610w, 1500m, 1455m, 1440m, 1375s, 1260s, 1215s, 1165s, 1120s, 1050s; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.29, 1.38 (each s, 3H, Me (isopropylidene)), 1.45 (s, 6H, Me (isopropylidene)), 2.90–3.01 (m, 1H, H−C(2)), 3.19–3.27 (m, 2H, H−C(2′)), 3.51 (s, 3H, OMe), 3.61 (s, 1H, OH) 3.98–4.10 (m, 2H, H−C(8)), 4.15 (dd, *J*=3.7, 7.8 Hz, 1H, H−C(6)), 4.32–4.40 (m, 1H, H−C(7)), 4.50 (d, *J*=5.9 Hz, 1H, H−C(4)), 4.86 (dd, *J*=3.7, 5.9 Hz, 1H, H−C(5)), 7.16–7.29 (m, 5H, CH_{arom})); ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.52, 25.42, 25.92, 26.97 (each q, Me (isopropylidene)), 33.04 (t, C(2′)), 50.27 (q, OMe), 51.69 (d, C(2)), 66.79 (t, C(8)), 73.01, 79.81, 79.88, 86.64 (each d, C(4,5,6,7)), 104.78 (s, C(3)), 109.06, 112.81 (each s, C_q (isopropylidene)), 126.18, 128.08, 128.80 (each d, CH_{arom}), 138.96 (s, $C_{q\ arom}$), 175.00 (s, C(1)); MS (e.i., 80 eV, 118°C): *m*/*z*=407 (27.8), 404 (2.4), 364 (1.4), 349 (3.8), 329 (4.4), 234 (5.8), 209 (12.4), 191 (11.2), 163 (16.3), 156 (14.2), 141 (28.3), 131 (18.4), 104 (11.7), 101 (100.0). Anal. calcd for $C_{22}H_{30}O_8$ (422.48): C, 62.55; H, 7.16. Found: C, 62.35; H, 7.39.

3.2.6. (2*R*) Methyl 2-deoxy-2-phenyl-4,5;7,8-di-*O*-isopropylidene-α-D-manno-3,6-furanoso-3-octulosonate (13a) and (2*S*) methyl 2-deoxy-2-phenyl-4,5;7,8-di-*O*-isopropylidene-α-D-manno-3,6-furanoso-3-octulosonate (13b). The reaction of **1** (1.03 g, 4.0 mmol) and methyl 2-bromo-2-phenyl-acetate (**7**) (1.83 g, 8.0 mmol) at −20⟶−5°C for 5 h followed by column chromatography (hexane/ethyl acetate 10:1) gave **13a** (0.54 g, 33%) and **13b** (0.69 g, 42%).

Data for **13a**. Mp 100–102°C, $[\alpha]_D$=+58.1° (*c*=1.1, $CHCl_3$), R_f=0.58 (hexane/ethyl acetate 3:1); IR (KBr): ν=3480bs, 2990s, 2960s, 2940m, 2920w, 1720s, 1500m, 1455m, 1380s, 1355s, 1320m, 1275m, 1250s, 1240m, 1230m, 1215s, 1175s, 1155m, 1115m, 1070s, 1030s, 1010s, 1000m; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.21, 1.38, 1.43, 1.54 (each s, 3H, Me (isopropylidene)), 3.66 (s, 3H, OMe), 4.03 (dd, *J*=4.8, 8.7 Hz, 1H, H_A−C(8)), 4.07–4.17 (m, 3H, H−C(2), H−C(4) and H_B−C(8)), 4.14 (dd, *J*=3.9, 7.8 Hz, 1H, H−C(6)), 4.39 (ddd, *J*=4.8, 6.0, 7.8 Hz, 1H, H−C(7)), 4.76 (dd, *J*=3.9, 5.8 Hz, 1H,

H–C(5)), 5.00 (s, 1H, OH), 7.26–7.54 (m, 5H, CH_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.28, 25.35, 25.82, 26.72 (each q, Me (isopropylidene)), 52.11 (q, OMe), 52.69 (d, C(2)), 66.66 (t, C(8), 73.04, 79.19, 79.88, 83.85 (each d, C(4,5,6,7)); 106.03 (s, C(3)), 108.84, 112.28 (each s, C_q (isopropylidene)), 127.54, 127.95, 129.62 (each d, CH_{arom}), 132.95 (s, $C_{q\ arom}$), 173.48 (s, C(1)); MS (e.i., 80 eV, 80°C): *m/z*=408 (0.8), 393 (49.3), 377 (4.0), 335 (6.6), 315 (2.9), 259 (12.7), 249 (8.5), 215 (6.5), 214 (11.6), 195 (19.4), 177 (13.8), 156 (18.2), 150 (80.1), 141 (33.0), 126 (22.0), 118 (31.1), 101 (84.3); MS (ci, isobutane): *m/z*=409, 390. Anal. calcd for $C_{21}H_{28}O_8$ (408.45): C, 61.75; H, 6.91. Found: C, 61.93; H, 6.75.

Data for **13b**. Colorless oil, $[\alpha]_D$=−65.2° (*c*=1.3, $CHCl_3$), R_f=0.23 (hexane/ethyl acetate 3:1); IR (film): ν=3472w, 3031w, 2987s, 2938m, 1795m, 1745s, 1498w, 1455m, 1436m, 1372s, 1350m, 1320m, 1259s, 1210s, 1162s, 1116m, 1069s, 1042s; ^1H NMR (300 MHz, $CDCl_3$): δ= 1.33 (s, 3H, Me (isopropylidene)), 1.34 (s, 6H, Me (isopropylidene)), 1.50 (s, 3H, Me (isopropylidene)), 3.69 (s, 1H, H–C(2)), 3.69 (s, 1H, OMe), 3.90 (dd, *J*=5.0, 8.7 Hz, 1H, H_A–C(8)), 4.00 (dd, *J*=6.3, 8.7 Hz, 1H, H_B–C(8)), 4.06 (dd, *J*=3.7, 7.1 Hz, 1H, H–C(6)); 4.20 (s, 1H, OH), 4.34–4.38 (m, 1H, H–C(7)), 4.75 (d, *J*=5.9 Hz, 1H, HC(4)), 4.84–4.88 (m, 1H, H–C(5)), 7.26–7.36 (m, 5H, CH_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.28, 25.35, 25.82, 26.72 (each q, Me (isopropylidene)), 52.11 (q, OMe), 52.69 (d, C(2)), 66.66 (t, C(8)), 73.04, 79.19, 79.88, 83.85 (each d, C(4,5,6,7)), 106.03 (s, C(3)), 108.84, 112.28 (each s, C_q (isopropylidene)), 127.54, 127.95, 129.62 (each d, CH_{arom}), 132.95 (s, $C_{q\ arom}$), 173.48 (s, C(1)); MS (e.i., 80 eV, 121°C): *m/z*=393 (2.8), 377 (0.5), 335 (0.4), 277 (0.4), 243 (30.7), 201 (2.7), 185 (3.5), 150 (29.7), 101 (45.1), 91 (100.0); MS (FAB, NBA): *m/z*=393, 391, 333, 275, 243, 233, 215; MS (FAB, NBA+LiCl): *m/z*=415, 393, 391, 341, 333, 275, 233, 221. Anal. calcd for $C_{21}H_{28}O_8$ (408.45): C, 61.75; H, 6.91. Found: C, 61.87; H, 6.81.

3.2.7. (2*R*)-*tert* Butyl-2-deoxy-2-methyl-4,5;7,8-di-*O*-isopropylidene-α-D-manno-3,6-furanoso-3-octulosonate (15a) and (2*S*)-*tert* butyl-2-deoxy-2-methyl-4,5;7,8-di-*O*-isopropylidene-α-D-manno-3,6-furanoso-3-octulosonate (15b). The reaction of **1** (1.03 g, 4.0 mmol) with *tert* butyl 2-bromo-propanoate (**14**) (1.75 g, 8 mmol) −78→0°C for 3 h followed by column chromatography (hexane/ethyl acetate 10:1) gave **15a** (0.50 g, 32%) and **15b** (0.65 g, 42%).

Data for **15a**. Mp 76–79°C, $[\alpha]_D$=+4.5° (*c*=1.1, $CHCl_3$) [Lit.:[25] mp 75–77°C, $[\alpha]_D$=+4.5° (*c*=0.8, $CHCl_3$)], R_f= 0.67 (hexane/ethyl acetate 3:1); IR (KBr): ν=3400s, 2992s, 2943s, 2906w, 2874m, 2694s, 1484m, 1461s, 1428m, 1377s, 1354s, 1333m, 1319w, 1297w, 1277s, 1253s, 1216s, 1153s, 1111s, 1067s, 1041s, 1004m; ^1H NMR (300 MHz, $CDCl_3$): δ=1.26 (d, *J*=7.4 Hz, 3H, H–C(2′)), 1.29, 1.36, 1.42, 1.44 (each s, 3H, Me (isopropylidene)), 1.46 (s, 9H, Me (*tert* butyl)), 2.88 (q, *J*=7.4 Hz, 1H, H–C(2)), 3.87 (s, 1H, OH), 4.02–4.07 (m, 2H, H–C(8)), 4.11 (dd, *J*=3.8, 7.8 Hz, 1H, H–C(6)), 4.30–4.36 (m, *J*= 7.8 Hz, 1H, H–C(7)), 4.55 (d, *J*=5.9 Hz, 1H, H–C(4)), 4.84 (dd, *J*=3.8, 5.9 Hz, 1H, H–C(5)); ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.30 (q, C(2′)), 24.49, 25.41, 25.87, 26.83 (each q, Me (isopropylidene)), 27.92 (q, Me (*tert* butyl)), 43.41 (d, C(2)), 66.72 (t, C(8)), 73.10, 79.56, 79.88, 86.64 (each d, C(4,5,6,7)), 81.26 (s, C_q (*tert* butyl)), 104.96 (s, C(3)), 108.96, 112.44 (each s, C_q (isopropylidene), 175.11 (s, C(1)); MS (e.i., 80 eV, 60°C): *m/z*=373 (29.9), 317 (8.2), 315 (13.6), 274 (9.0), 259 (11.2), 231 (20.1), 200 (8.6), 144 (11.6), 141 (23.9), 126 (18.4), 101 (82.9), 98 (35.5), 71 (20.1), 59 (78.6), 57 (100.0). Anal. calcd for $C_{19}H_{32}O_8$ (388.46): C, 58.75; H, 8.30. Found: C, 58 73; H, 7.95.

Data for **15b**. Mp 80–82°C, $[\alpha]_D$=+2.2° (*c*=1.4, $CHCl_3$) [Lit.:[25] mp 82–84°C, $[\alpha]_D$=+2.9° (*c*=1.0, $CHC1_3$)], R_f= 0.47 (hexane/ethyl acetate 3:1); IR (KBr): ν=3485m, 2981m, 2935m, 2874w, 1701s, 1460w, 1381s, 1371s, 1348w, 1329w, 1257m, 1220s, 1157s, 1115m, 1083s, 1070s, 1040*m*; ^1H NMR (300 MHz, $CDCl_3$): δ=1.26 (d, *J*=7.2 Hz, 3H, H–C(2′)), 1.31, 1.37, 1.42, 1.47 (each s, 3H, Me (isopropylidene)), 1.46 (s, 9H, Me (*tert* butyl)), 2.78 (q, *J*=7.2 Hz, 1H, H–C(2)), 3.96 (dd, *J*=4.7, 8.6 Hz, 1H, H_A–C(8)), 4.04 (dd, *J*=6.2, 8.6 Hz, 1H, H_B–C(8)), 4.09 (dd, *J*=3.8, 7.7 Hz, 1H, H–C(6)), 4.36–4.39 (m, 1H, H–C(7)), 4.45 (d, *J*=5.9 Hz, 1H, H–C(4)), 4.82 (dd, *J*=3.8, 5.9 Hz, 1H, H–C(4)), 4.89 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.65 (q, C(2′)), 24.37, 25.43, 25.84, 26.84 (each q, Me (isopropylidene)), 27.94 (q, Me (*tert* butyl)), 42.77 (d, C(2)), 66.66 (t, C(8)), 73.06, 79.02, 79.90, 84.14 (each d, C(4,5,6,7)), 81.59 (s, C_q (*tert* butyl)), 106.39 (s, C(3)), 108.92, 112.44 (each s, C_q (isopropylidene)), 175.59 (s, C(1)); MS (e.i., 80 eV, 65°C): *m/z*=388 (0.05), 373 (29.1), 317 (19.5), 315 (18.8), 274 (17.5), 259 (13.9), 239 (5.6), 231 (11.4), 215 (12.3), 199 (10.2), 181 (6.0), 173 (8.5), 156 (15.4), 141 (37.8), 126 (24.5), 101 (100.0). Anal. calcd for $C_{19}H_{32}O_8$ (388.46): C, 58.75; H, 8.13. Found: C, 58.60; H, 8.30.

3.2.8. *tert* Butyl 2-deoxy-4,5;7,8-di-*O*-issopropylidene-α-D-manno-3,6-furanoso-3-octulosonate (17). To a suspension of Zn–Ag/graphite (4.0 mmol) in abs. THF (30 ml) at 0°C *tert* butyl bromo-acetate (**16**) (0.82 g, 4.0 mmol) was added and stirred at 0°C for 10 min and filtered. The filter residue was rinsed with abs. THF (2×10 ml) and to the combined filtrates **1** (1.03 g, 4.0 mmol) was added. Stirring was continued for 30 min and **17** (0.40 g, 54%) was obtained after usual work up. The filter cake was resuspended in abs. THF (50 ml), **1** (1.03 g, 4.0 mmol) was added and stirring continued for 30 min; after work up **1** was recovered almost quantitatively.

Data for **17**. Mp 104–106°C, $[\alpha]_D$=+9.9° (*c*=1.3, $CHCl_3$) [Lit.:[25] mp. 107°C, $[\alpha]_D$=+10.6° (*c*=1.0, $CHCl_3$)], R_f=0.32 (hexane/ethyl acetate 3:1); IR (KBr): ν=3440s, 2989m, 2943w, 1718s, 1381m, 1371s, 1257m, 1212s, 1162s, 1066s; ^1H NMR (300 MHz, $CDCl_3$): δ=1.08, 1.14, 1.20 (each s, 3H, Me (isopropylidene)), 1.24 (s, 12H, Me (isopropylidene) and Me (*tert* butyl)), 2.40, 2.49 (AB-system, *J*=16.3 Hz, 2H, $H_{A,B}$–C(2)), 3.76 (dd, *J*=4.7, 8.7 Hz, 1H, H_A–C(8)), 3.82 (dd, *J*=6.1, 8.7 Hz, 1H, H_B–C(8)), 3.86 (dd, *J*=3.7, 7.8 Hz, 1H, H–C(6)), 4.13 (ddd, *J*=4.7, 6.1, 7.8 Hz, 1H, H–C(7)), 4.25 (d, *J*=5.9 Hz, 1H, H–C(4)), 4.60 (dd, *J*=3.7, 5.9 Hz, 1H, H–C(5)), 4.86 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.44, 25.39, 25.87, 26.85 (each q, Me (isopropylidene)), 28.02 (q, Me (*tert* butyl)), 39.18 (t, C(2)), 66.78 (t, C(8)), 73.02, 79.18, 80.08, 85.65 (each d, C(4,5,6,7)), 82.05 (s, C_q (*tert* butyl)), 103.90 (s,

C(3)), 109.00, 112.64 (each s, C_q (isopropylidene)), 171.23 (s, C(1)); MS (e.i., 80 eV, 59°C): *m*/*z*=359 (29.9), 303 (15.0), 301 (16.0), 260 (9.3), 243 (11.6), 217 (19.3), 201 (9.3), 185 (8.6), 141 (24.8), 126 (16.1), 101 (88.8), 98 (34.6). Anal. calcd for $C_{18}H_{30}O_8$ (374.43): C, 57.62; H, 8.06. Found: C, 57.71; H, 7.79.

3.2.9. (2*R*) Methyl 2-bromo-2-deoxy-4,5;7,8-di-*O*-isopropylidene-α-D-manno-3,6-furanoso-3-octulosonate (22). The reaction of **1** (1.03 g, 4.0 mmol) and methyl dibromoacetate (1.86 g, 8.0 mmol) at mit. Dibromessigsäuremethylester (75) (3.71 g, 16 mmol) at −78→−40°C for 7 h followed by column chromatography (hexane/ethyl acetate 10:1) gave **22** (1.05 g, 64%), mp 97–99°C, $[\alpha]_D$=+60.0° (*c*=1.4, $CHCl_3$), R_f=0.42 (hexane/ethyl acetate 3:1); IR (KBr): ν=3500s, 3000s, 2990s, 2970s, 2940m, 2910m, 1730s, 1470m, 1440m, 1405m, 1390s, 1380s, 1330s, 1275s, 1290m, 1260m, 1215s, 1165s, 1115s, 1070s, 1050s, 1020s; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.35, 1.36, 1.41, 1.50 (each s, 3H, Me (isopropylidene)), 3.82 (s, 3H, OMe), 3.94 (dd, *J*=4.5, 8.7 Hz, 1H, H_A–C(8)), 4.03 (dd, *J*=6.1, 8.7 Hz, 1H, H_B–C(8)), 4.17 (dd, *J*=3.8, 7.8 Hz, 1H, H–C(6)), 4.35 (ddd, *J*=4.5, 6.1, 7.8 Hz, 1H, H–C(2)), 4.41 (s, 1H, OH), 4.61 (d, *J*=5.8 Hz, 1H, H–C(4)), 4.67 (s, 1H, H–C(2)), 4.85 (dd, *J*=3.8, 4.7 Hz, 1H, H–C(5)); ^{13}C NMR (63 MHz, $CDCl_3$): δ=24.35, 25.39, 25.84, 26.81 (each q, Me (isopropylidene)), 40.74 (q, OMe), 53.25 (d, C(2)); 66.67 (t, C(8)), 72.96, 79.89, 80.86, 84.52 (each d, C(4,5,6,7)); 104.98 (s, C(3)), 109.28, 113.12 (each s, C_q (isopropylidene)), 170.42 (s, C(1)); MS (e.i., 80 eV, 41°C): *m*/*z*=397 (34.4), 395 (34.1), 339 (2.4), 337 (2.8), 299 (1.3), 215 (3.0), 201 (7.3), 197 (5.2), 183 (3.9), 173 (4.8), 155 (7.5), 145 (9.6), 141 (9.9), 115 (10.1), 101 (74.7). Anal. calcd for $C_{15}H_{23}O_8Br$ (411.25): C, 43.81; H, 5.64; Br, 19.43. Found: C, 43.98; H, 5.50; Br, 19.62.

3.2.10. (2*S*)-2-Deoxy-2-(2′-hydroxyethyl)-4,5:7,8-di-*O*-isopropylidene-α-D-manno-3,6-furanoso-3-octulosonate-1,2′-lactone (23). Reaction of **1** (1.03 g, 4.0 mmol) with α-bromo-γ-butyrolactone (1.32 g, 8.0 mmol) at −78→−20°C for 6 h followed by column chromatography (hexane/ethylacetate 5:1→3:1) gave **23** (1.11 g, 81%), mp 128.5–131°C, $[\alpha]_D$=+21.0° (*c*=1.0, MeOH); R_f=0.07 (hexane/ethyl acetate 3:1); IR (KBr): ν=3360s, 2990s, 2960m, 2900w, 1750s, 1460w, 1385s, 1370m, 1340w, 1290w, 1260m, 1220s, 1175s, 1115m, 1100s, 1065s, 1050s, 1030s, 1010m; ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.32, 1.37, 1.44, 1.47 (each s, 3H, Me), 2.30–2.61 (m, 2H), 3.02 (dd, *J*=9.0, 11.6 Hz, 1H, H–C(2)), 3.95–4.25 (m, 4H), 4.28–4.93 (m, 2H), 4.60 (d, *J*=6.0 Hz, 1H), 4.87 (dd, *J*=3.9, 6.0 Hz, 1H, H–C(5)); 5.55 (s, 1H, exchangeable with D_2O); ^{13}C NMR (62 MHz, $CDCl_3$): δ=23.74, 25.21, 25.22 (each q, Me), 25.81 (t, C(1′)), 26.76 (q, Me), 43.07 (d, C(2)), 66.76, 67.27 (each t, C(2′, 8)), 72.92, 78.99, 79.94, 85.94 (each d, C(4,5,6,7)), 104.08 (s, C(3)), 109.11 (s, C^i_q), 112.73 (s, C^i_q), 178.56 (s, C(1)); MS (e.i., 112°C, 80 eV): *m*/*z*=329 (56), 271 (5.6), 251 (5.5), 225 (3.4), 211 (4.7), 193 (5.2), 185 (4.5), 179 (13.9), 156 (10.6), 145 (41.4). Anal. calcd for $C_{16}H_{24}O_8$ (344.36): C, 55.81; H, 7.02. Found: C, 55.84; H, 7.06.

3.2.11. Reaction of 1 with *tert* butyl bromo-acetate and Zn–Ag/graphite in the presence of sulfur. To a suspension of Zn–Ag/graphite (8.0 mmol) in anhydrous THF (50 ml) a solution of **16** (1.6 g, 8.0 mmol) containing sulfur (25 mg, 0.8 mmol), CS_2 (0.5 ml) and **1** (0.52 g, 2.0 mmol) in THF (15 ml) was added. After stirring for 1 h at 0°C and 20 h at 25°C the mixture was filtered over celite, the solvents were removed and the residue was subjected to column chromatography (hexane/ethyl acetate 3:1) to afford **1** in almost quantitative yield.

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