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Synthetic approach to 3-deoxy-D-*manno*-oct-2-ulosonic acid (Kdo) α-disaccharides via a ketene dithioacetal†

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Abstract

A unique strategy for the synthesis of Kdo α-disaccharides based on the ketene dithioacetal **4** (precursor of Kdo) as a 'glycosyl donor' has been developed. Direct, fully stereoselective addition of 6-, 7-, or 8-OH unprotected sugar units to the *exo*-anomeric double bond in **4**, promoted by trimethylsilyl triflate, led to the corresponding *O*-disaccharides **12** with the dithioacetal residue intact. Subsequent hydrolysis of the later afforded the title compounds in high yields.

1. Introduction

3-Deoxy-D-*manno*-oct-2-ulosonic acid (Kdo) is a key component of the core region lipopolysaccharides (LPS) of Gram-negative bacteria.[1] Kdo-α-(2→6)-GlcN disaccharide forms the glycosidic linkage between lipid A and inner core region,[2] which is composed of Kdo and L- and D-*glycero*-D-*manno*-heptoses.[3] Kdo units in this region are connected by α-(2→4) linkage, forming trisaccharides,[3] or by α-(2→8) linkage, as it occurs in the terminal part of LPS of *Chlamydia*.[4]

Synthetic analogues of Kdo and its disaccharides have attracted interest as potential inhibitors of Kdo incorporation into LPS inner core region.[5] Numerous syntheses of di- and oligosaccharides based on Kdo halides as glycosyl donors have been reported.[6] They, however, suffer from incomplete stereoselective outcome of the glycosylation reaction, often leading to the mixture of α/β anomers. In addition, the C-2–C-3 elimination product is usually formed.[6c]

Introduction at C-3 of the Kdo glycosyl donor the phenylselenyl moiety as a stereocontrolling auxiliary has allowed α-disaccharides to be achieved as sole products.[7] This glycosylselenation process involving phenylselenyl triflate as a reagent is quite capricious and one must take into account a reductive removal of C-3 substituent in the final step of synthesis.

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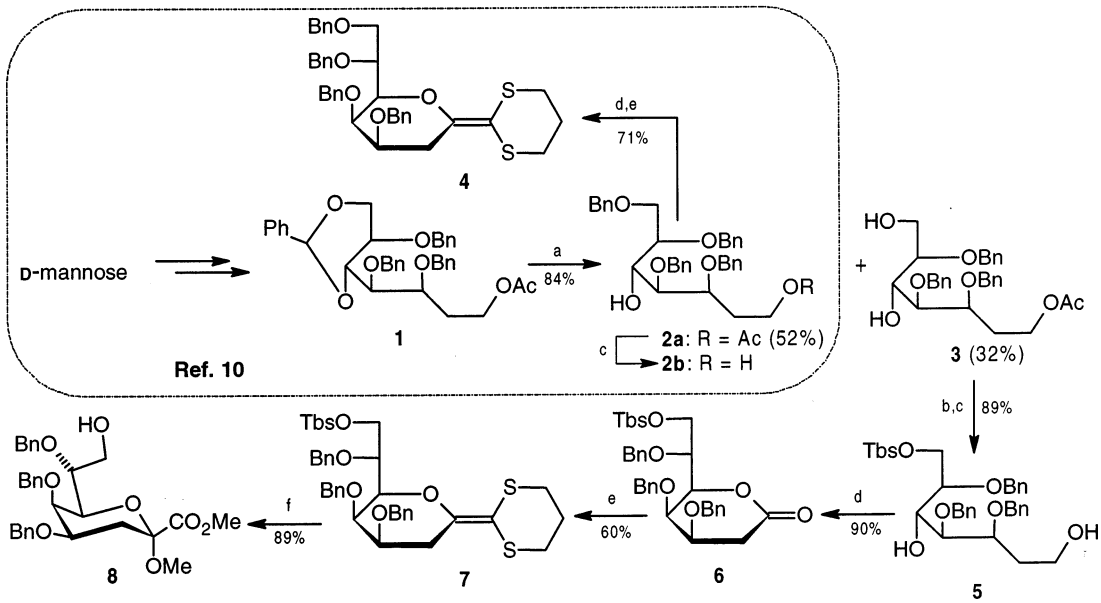
It occurred to us some time ago that replacement of ulosonic acid glycosyl donor by its precursor would be of interest in the search for stereoselective synthesis of disaccharides.[8] Such a precursor would correspond to the simple *exo*-glycal, which has been reported[9] to undergo iodonium mediated addition of alcohols to form *O*-glycosidic linkage. Following this reasoning we synthesized ketene dithioacetals of type **4**, hoping that dithianyl group located at the end of the *exo*-anomeric double bond should exert a steric hindrance for the attack from the dithianyl ring side. Therefore α-glycosidic linkage should be formed exclusively. Successful preparation of heptulosonic acid disaccharides in this way confirmed our expectations.[8]

2. Results and discussion

Ketene dithioacetal **4** being a precursor of Kdo molecule, was synthesized from D-mannose by a previously described route[10] (Scheme 1). One step of this route deserves, however, some comments: a mixture of products **2a** and **3** was obtained upon the reductive cleavage of 5,7-*O*-benzylidene ring in **1** with triethylsilane (TES)–trifluoroacetic acid (TFA) system, whereas such a reaction of the 4,6-*O*-benzylidene group in sugars leads to the 6-*O*-benzyl derivative as a sole product.[11]

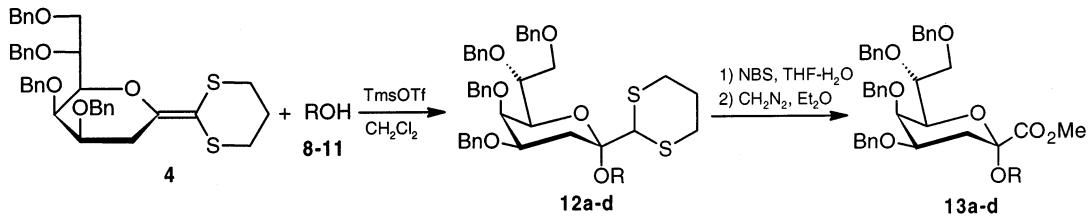


Scheme 1. Reagents and conditions: (a) TFA–TES, CH_2Cl_2, rt; (b) TbsCl, Im, CH_2Cl_2, DMAP, rt; (c) K_2CO_3, MeOH, rt; (d) PCC, dichloroethane, 60°C; (e) 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]-1,3-dithiane, KHMDS, THF, −78°C→rt; (f) NBS, MeOH, CH_2Cl_2, rt

Fortunately, we found this unexpected product **3** to be very useful for the preparation Kdo as a glycosyl acceptor in Kdo–Kdo disaccharide synthesis. With this aim compound **3**, after selective protection of the 7-OH group with *tert*-butyldimethylsilyl ether (Tbs) and subsequent hydrolysis of the 1-OAc residue, underwent oxidative cyclization by treatment with PCC in dichloroethane to give 2-deoxy-heptonolactone **6**. This was reacted with the 1,3-dithianyl anion generated from 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]-1,3-dithiane and potassium

bis(trimethylsilyl)amide (KHMDS) in THF,[10] leading to ketene dithioacetal **7**. Efficient transformation of **7** into the glycosyl acceptor **8** was performed in one step using *N*-bromosuccinimide in methanol–dichloromethane.[10] Under these conditions the Tbs group was simultaneously removed.

Following our purpose of employing ketene dithioacetal template **4** toward the synthesis of varied Kdo disaccharides (Scheme 2), we investigated firstly the reaction with the known 6-*O*-unprotected glucose derivative **9** (Table 1). Direct addition of **9** to the double bond of ketene dithioacetal afforded disaccharide **12a** in high yield (Scheme 2, Table 1). The reaction was conducted in dichloromethane at −78→−30°C using trimethylsilyl triflate (TmsOTf) as a promoter.[8] Similar results, and an even higher yield of the desired disaccharide **12b**, were obtained applying the 7-*O*-unprotected L-*glycero*-D-*manno*-heptose derivative **10**.[12]



Scheme 2.

In contrast, glucosamine derivative **11** as a glycosyl acceptor needed more severe conditions, i.e. higher temperature (~0°C), longer reaction time and a stoichiometric amount of TmsOTf promoter. As a result disaccharide **12c** was obtained in about 40% yield.

We were pleased to find that the addition of Kdo derivative **8** to Kdo precursor **4** proceeded smoothly giving (2→8) linked disaccharide **12d** in 72% yield.

In all reactions performed disaccharides were isolated as the only products, leaving the dithianyl ring intact. This last one was easily transformed into the methyl ester by an oxidative hydrolysis with 10-fold excess of NBS in aqueous THF solution (9:1),[13] to give the α-linked Kdo disaccharides **13a–d** with full stereoselectivity (Scheme 2, Table 1). Evidently, the 1,3-dithianyl ring due to its capacity fulfills a steric control on the addition reaction stage.

The α-configuration of the glycosidic linkage was established by comparison of NMR data with those reported[14] (Table 1). The distance between H-3ax and H-3eq (about 0.05 ppm) established unambiguously α configuration. In the β anomers the distance is larger than 0.25 ppm. In one case (compound **13a**) the configuration was additionally confirmed by NMR identity of per-*O*-acetylated derivative **14** with the literature data.[15]

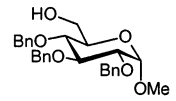
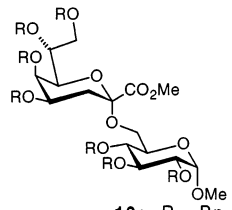
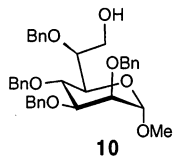
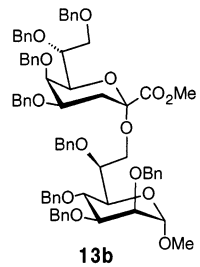
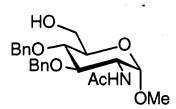
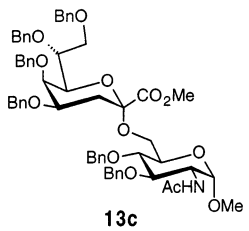
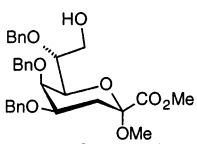
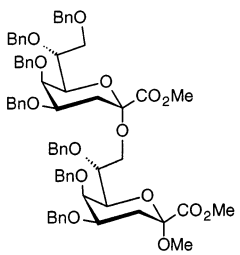
In summary, we have demonstrated the unique ketene dithioacetal precursor of Kdo as a versatile 'glycosyl donor' for the fully stereoselective construction of Kdo α-disaccharides.

3. Experimental

3.1. General information

Optical rotations were measured with a JASCO Dip-360 Digital Polarimeter at room temperature. ^{1}H NMR spectra were recorded on Bruker AM-500 (500 MHz) spectrometers with Me_4Si as internal standard. High resolution mass spectra were taken on a Mariner PerSeptive

Table 1

ROH	dithiane	disaccharide	(H-3eq) – (H-3ax) [ppm]
 **9**	**12a** (76%)	 1) H_2/Pd-C, EtOH 2) Ac_2O, Py → **13a**: R = Bn; **14**: R = Ac	0.07
 **10**	**12b** (86%)	 **13b**	0.07
 **11**	**12c** (39%)	 **13c**	0.07
 **8**	**12d** (72%)	 **13d**	< 0.10

Biosystems mass spectrometer with time-of-flight (TOF) detector. IR spectra were taken with a Perkin–Elmer FT-IR-1600 spectrophotometer. Reactions were controlled using TLC on silica [Merck alu-plates (0.2 mm)].

All reagents and solvents were purified and dried according to common methods. All organic solutions were dried over $MgSO_4$. Reaction products were purified by flash chromatography using Merck's Kieselgel 60 (240–400 mesh or 70–230 mesh).

3.2. 1-O-*Acetyl*-3,4,6,7-*tetra*-O-*benzyl*-2-*deoxy*-D-manno-*heptitol* **2a** *and* 1-O-*acetyl*-3,4,6-*tri*-O-*benzyl*-2-*deoxy*-D-manno-*heptitol* **3**

To a vigorously stirred solution of benzylidene heptitol **1**[10] (1.70 g, 2.70 mmol) in dry CH_2Cl_2 were added triethylsilane (2.0 mL, 12.55 mmol) and trifluoroacetic acid (0.86 mL, 11.30 mmol) at 0°C under Ar. The temperature was allowed to rise to room temperature during 1 h with stirring (TLC). The mixture was diluted with ethyl ether and washed with $NaHCO_3$ and water. After solvent evaporation the residue was chromatographed on silica gel to give 7-*O*-benzyl derivative **2a** (52%); mp 47°C; $[\alpha]_D$ −10.5 (*c* 1.00 in $CHCl_3$); IR (film) $\nu_{\text{inter alia}}$: 3488, 3031, 2867, 1773, 1496, 1454, 1245, 1098 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.90–2.00 (m, 2H, 2×H-2), 1.96 (s, 3H, Ac), 3.15 (d, 1H, OH-5, *J* 5.8 Hz), 3.56–3.69 (m, 2H), 3.70–3.82 (m, 2H), 3.82–3.92 (m, 2H), 4.10–4.20 (m, 2H), 4.30–4.80 (4×ABq, 4×2H, C<u>H</u>$_2$Ph), 7.20–7.40 (m, 20H, Ar); HR-MS (ESI) calcd for $C_{37}H_{42}O_7$ $[M+Na]^+$ 621.2823; found 621.2858.

Eluted second was 5,7-*O*-deprotected compound **3** (32%); colourless oil: $[\alpha]_D$ −25.1 (*c* 0.98 in $CHCl_3$); IR (film) $\nu_{\text{inter alia}}$: 3465, 2875, 1733, 1497, 1454, 1245, 1096, 1058 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.90–1.97 (m, 2H, 2×H-2), 1.97 (s, 3H, Ac), 2.29–2.32 (m, 1H, OH-7), 3.30 (d, 1H, OH-5, *J* 5.3 Hz), 3.49–3.52 (m, 1H), 3.77 (dd, 1H, H-4, *J* 1.5, 3.0 Hz), 3.80–3.90 (m, 4H), 4.10–4.18 (m, 2H), 4.20–4.70 (3×ABq, 3×2H, C<u>H</u>$_2$Ph), 7.20–7.35 (m, 15H, Ar); HR-MS (ESI) calcd for $C_{30}H_{36}O_7$ $[M+Na]^+$ 531.2353; found 531.2364.

3.3. 3,4,6-*Tri*-O-*benzyl*-7-O-tert-*butyldimethylsilyl*-2-*deoxy*-D-manno-*heptitol* **5**

To a solution of **3** (1.20 g, 2.36 mmol) in anhydrous CH_2Cl_2 (10 mL) were added triethylamine (0.42 mL, 3.0 mmol), 4-dimethylaminopyridine (20 mg) and *tert*-butyldiphenylsilyl chloride (380 mg, 2.5 mmol). The solution was stirred overnight at room temperature, then evaporated. The crude product was redissolved in methanol (20 mL) and K_2CO_3 (500 mg) was added. The resulting suspension was stirred at rt for 1 h (TLC). The mixture was then diluted with CH_2Cl_2 and filtered through a short column of silica gel to give **5** (1.2 g, 87%) as a colourless oil: $[\alpha]_D$ −19.3 (*c* 1.15, $CHCl_3$); IR (film) $\nu_{\text{inter alia}}$: 3461, 3031, 2929, 2857, 1454, 1253, 1094 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.07, 0.08 (2×s, 2×3H, ^{t}BuM<u>e</u>$_2$Si), 0.91 (s, 9H, ^{t}B<u>u</u>Me$_2$Si), 1.84–1.94 (m, 2H, 2×H-2), 1.95–1.98 (m, 1H, OH-1), 3.09 (d, 1H, OH-5, *J* 6.0 Hz), 3.55 (ddd, 1H, H-6, *J* 3.2, 5.4, 8.4 Hz), 3.68–3.72 (m, 2H, 2×H-1), 3.76 (m, 1H, H-5), 3.84 (dd, 1H, H-7a, *J* 5.4, 11.1 Hz), 3.87–3.91 (m, 1H, H-3), 3.91 (dd, 1H, H-4, *J* 1.8, 3.5 Hz), 4.03 (dd, 1H, H-7b, *J* 3.2, 11.0 Hz), 4.37–4.80 (3×ABq, 3×2H, C<u>H</u>$_2$Ph), 7.20–7.35 (m, 15H, Ar); HR-MS (ESI) calcd for $C_{34}H_{48}O_6Si$ $[M+Na]^+$ 603.3112; found 603.3122.

3.4. 3,4,6-*Tri*-O-*benzyl*-7-O-tert-*butyldimethylsilyl*-2-*deoxy*-D-manno-*heptono*-1,5-*lactone* **6**

A mixture of PCC (1.80 g, 8.50 mmol) and heptitol **5** (1.30 g, 2.2 mmol) was stirred in 1,2-dichloroethane solution (30 mL) at 60°C for 1 h and then poured onto a column of silica gel prepared in hexane. Elution with hexane–ether (3:2) gave lactone **6** with 90% yield. Colourless oil: $[\alpha]_D$ −7.3 (*c* 1.13, $CHCl_3$); IR (film) $\nu_{\text{inter alia}}$: 3031, 2952, 2929, 2857, 1747, 1455, 1224, 1099 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.06, 0.07 (2×s, 2×3H, ^{t}BuM<u>e</u>$_2$Si), 0.90 (s, 9H, ^{t}B<u>u</u>Me$_2$Si), 2.91 (dd, 1H, H-2eq, *J* 6.8, 17.8 Hz), 2.96 (dd, 1H, H-2ax, *J* 10.8, 17.7 Hz), 3.28–3.86 (m, 2H, H-7a, H-7b), 3.92 (ddd, 1H, H-3, *J* 1.8, 7.0, 10.8 Hz), 4.03 (dd, 1H, H-6, *J* 3.6, 12.8 Hz), 4.26 (dd, 1H, H-5, *J* 1.5, 8.5 Hz), 4.37 (bs, 1H, H-4), 4.36–5.06 (3×ABq, 3×2H, C<u>H</u>$_2$Ph), 7.26–7.37 (m, 15H, Ar); HR-MS (ESI) calcd for $C_{34}H_{44}O_6Si$ $[M+Na]^+$ 599.2799; found 599.2806.

3.5. 2,6-Anhydro-4,5,7-tri-O-benzyl-8-O-tert-butyldimethylsilyl-1-(propane-1,3-diyl-dithioacetal)-1,3-dideoxy-D-manno-oct-1-enitol **7**

A solution of potassium bis(trimethylsilyl)amide (3.4 mL, 1.70 mmol ~0.5 M solution in toluene) was added dropwise to 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]-1,3-dithiane (620 mg, 1.70 mmol) dissolved in anhydrous THF (10 mL) at −78°C under Ar. The temperature was maintained at −78°C for 1 h and then a solution of **6** (500 mg, 0.87 mmol) in THF (1–2 mL) was added dropwise. The reaction was stirred for ~3 h while the temperature was allowed to raise to rt. The reaction was then neutralized with TFA, and the crude product was purified by flash chromatography (hexane–ether, 9:1) to give 350 mg of **7** (60%) as a light yellow oil: $[\alpha]_D$ +85.8 (*c* 1.23, $CHCl_3$); IR (film) $\nu_{\text{inter alia}}$: 3030, 2952, 2927, 2856, 1596, 1454, 1355, 1237, 1098 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.08, 0.09 (2×s, 2×3H, ^{t}Bu$\underline{Me}_2$Si), 0.91 (s, 9H, $^t\underline{Bu}Me_2Si$), 2.08–2.14 (m, 2H, H-2″ax, H-2″eq), 2.58 (dd, 1H, H-3ax, *J* 11.9, 14.0 Hz), 2.70–2.86 (m, 4H, H-1″ax, H-1″eq, H-3″ax, H-3″eq), 3.33 (ddd, 1H, H-3eq, *J* 1.1, 5.0, 14.0 Hz), 3.55 (dd, 1H, H-6, *J* 1.1, 9.0 Hz), 3.64 (ddd, 1H, H-4, *J* 2.2, 5.1, 11.9 Hz), 3.88–3.93 (m, 2H, H-8a, H-8b), 4.20–4.23 (m+bs, 2H, H-7, H-5), 4.38–5.06 (3×ABq, 3×2H, C$\underline{H}_2$Ph), 7.23–7.35 (m, 15H, Ar); HR-MS (ESI) calcd for $C_{38}H_{50}O_5S_2$ $[M+Na]^+$ 701.2767; found 701.2742.

3.6. Methyl (methyl 4,5,7-tri-O-benzyl-3-deoxy-α-D-manno-oct-2-ulopyranosid)onate **8**

A solution of **7** (350 mg, 0.52 mmol) in CH_2Cl_2 (10 mL) was treated with methanol (3 mL) and NBS (280 mg, 1.56 mmol). The mixture was stirred at rt for ~0.5 h, and then filtered through a short column of silica gel and evaporated. The residue was purified by chromatography (hexane–ether, 1:1) on silica to give the desired ester **8** as a colourless oil (250 mg, 89%): $[\alpha]_D$ +13.7 (*c* 0.83, $CHCl_3$); IR (film) $\nu_{\text{inter alia}}$: 3529, 3031, 2923, 1749, 1454, 1273, 1162, 1085, 1063 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.23 (dd, 1H, H-3ax, *J* 11.8, 12.4 Hz), 2.32 (ddd, 1H, H-3eq, *J* 0.8, 4.4, 12.5 Hz), 2.30 (m, 1H, OH), 3.23 (s, 3H, OMe), 3.75 (dd, 1H, H-6, *J* 1.1, 8.9 Hz), 3.79 (s, 3H, CO_2Me), 3.85–3.88 (m, 2H, H-8a, H-8b), 3.94 (m, 1H, H-7), 4.00 (ddd, 1H, H-4, *J* 2.4, 4.6, 11.6 Hz), 4.06 (bs, 1H, H-5), 4.30–5.05 (3×ABq, 3×2H, C$\underline{H}_2$Ph), 7.23–7.35 (m, 15H, Ar); HR-MS (ESI) calcd for $C_{38}H_{50}O_5S_2$ $[M+Na]^+$ 559.2302; found 559.2305.

3.7. 4,5,7,8-Tetra-O-benzyl-3-deoxy-1-(propane-1,3-diyl-dithioacetal)-α-D-manno-octopyranosyl-(2→6)-(methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside) **12a**

Trimethylsilyl triflate (10 μL) was added to a stirred solution of enitol **4**[10] (200 mg, 0.31 mmol) and glucose derivative **9** (150 mg, 0.35 mmol) in dry CH_2Cl_2 (5 mL) at −78°C under Ar. The reaction mixture was stirred for 1 h while the temperature was allowed to rise to −30°C. The reaction was then recooled to −78°C, and neutralized with a methanolic solution of NH_3. After evaporation of the solvents the crude product was purified by flash chromatography (hexane–ether, 3:2) giving dithiane **12a** as a colourless oil (260 mg, 76%): $[\alpha]_D$ +22.5 (*c* 0.55, $CHCl_3$); IR (film) $\nu_{\text{inter alia}}$: 3030, 2952, 2927, 2856, 1596, 1454, 1355, 1237, 1098 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.72–1.82 and 1.99–2.06 (2×m, 2×1H, H-2″ax, H-2″eq), 2.23 (dd, 1H, H-3eq, *J* 4.1, 12.4 Hz), 2.38 (dd, 1H, H-3ax, *J* 12.0, 12.1 Hz), 2.66–2.82 (m, 4H,

H-1″ax, H-1″eq, H-3″ax, H-3″eq), 3.01 (dd, 1H, H-4′, *J* 8.8, 10.2 Hz), 3.18 (s, 3H, OMe), 3.32 (dd, 1H, H-2′, *J* 3.6, 9.6 Hz), 3.36 (dd, 1H, H-6a′, *J* 8.5, 9.9 Hz), 3.63 (dd, 1H, H-8b, *J* 4.4, 10.7 Hz), 3.75–3.81 (m, 2H, H-8a, H-5′), 3.29–4.93 (m, 3H, H-4, H-6, H-3′), 3.95 (ddd, 1H, H-7, *J* 1.9, 4.3, 9.0 Hz), 4.00 (dd, 1H, H-6′b, *J* 1.5, 10.0 Hz), 4.09 (bs, 1H, H-5), 4.41 (s, 1H, H-1), 4.51 (d, 1H, H-1′, *J*∼3 Hz), 4.35–5.13 (7×ABq, 7×2H, C$\underline{H}_2$Ph), 7.20–7.37 (m, 35H, Ar); HR-MS (ESI) calcd for $C_{67}H_{74}O_{11}S_2$ $[M+Na]^+$ 1141.4565; found 1141.4618.

3.8. 4,5,7,8-Tetra-O-*benzyl-3-deoxy-1-(propane-1,3-diyl-dithioacetal)-α-D*-manno-*octopyranosyl-(2→7)-(methyl 2,3,4,6-tetra*-O-*benzyl-L*-glycero-*α-D*-manno-*heptopyranoside)* **12b**

Trimethylsilyl triflate (20 μL) was added to a stirred solution of enitol **4**[10] (230 mg, 0.35 mmol) and heptose derivative **10**[12] (150 mg, 0.25 mmol) in dry CH_2Cl_2 (5 mL) at −78°C under Ar. The reaction mixture was stirred for 1 h while the temperature was allowed to rise to −40°C. The reaction was then recooled to −78°C, and neutralized with a methanolic solution of NH_3. Evaporation of the solvents and chromatography (hexane–ether, 3:2) gave **12b** as a colourless oil (230 mg, 86%): $[\alpha]_D$ +14.8 (*c* 1.00, $CHCl_3$); IR (KBr) $\nu_{\text{inter alia}}$: 3437, 3029, 2900, 1952, 1496, 1453, 1362, 1111, 1060 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.74–1.84 and 2.00–2.08 (2×m, 2×1H, H-2″ax, H-2″eq), 2.27 (dd, 1H, H-3eq, *J* 4.2, 12.6 Hz), 2.42 (dd, 1H, H-3ax, *J* 12.0, 12.5 Hz), 2.69–2.86 (m, 4H, H-1″ax, H-1″eq, H-3″ax, H-3″eq), 3.19 (s, 3H, OMe), 3.62–3.67 (m, 2H), 3.70–3.73 (m, 2H), 3.74 (m, 1H, H-2″), 3.80–3.87 (m, 3H), 3.97 (ddd, 1H, H-7, *J* 1.8, 4.7, 9.1 Hz), 4.07 (dd, 1H, *J* 6.3, 10.1 Hz), 4.10 (bs, 1H, H-5), 4.12 (dd, 1H, *J* 1.0, 4.9 Hz), 4.16 (t, 1H, H-4′, *J* 9.4 Hz), 4.41 (s, 1H, H-1), 4.75 (d, 1H, H-1′, *J* 1.7 Hz), 4.30–5.15 (8×ABq, 8×2H, C$\underline{H}_2$Ph), 7.20–7.37 (m, 40H, Ar); HR-MS (ESI) calcd for $C_{75}H_{82}O_{12}S_2$ $[M+Na]^+$ 1261.5145; found 1261.5175.

3.9. 4,5,7,8-Tetra-O-*benzyl-3-deoxy-1-(propane-1,3-diyl-dithioacetal)-α-D*-manno-*octopyranosyl-(2→6)-(methyl 3,4-di*-O-*benzyl-2-deoxy-2*-N-*acetamide-α-D-glucopyranoside)* **12c**

Trimethylsilyl triflate (20 μL) was added to a stirred solution of enitol **4**[10] (100 mg, 0.15 mmol) and glucosamine derivative **11** (62 mg, 0.15 mmol) in dry CH_2Cl_2 (3 mL) at −20°C under Ar. The reaction mixture was stirred for 2 h while the temperature was allowed to rise to 0°C and stirred for 2 h at this temperature. The reaction was then recooled to −20°C, and neutralized with methanolic solution of NH_3. Evaporation of the solvents and chromatography (hexane–ether, 1:1) gave dithiane **12c** as a colourless oil (65 mg, 39%): $[\alpha]_D$ +60.8 (*c* 0.49, $CHCl_3$); IR (film) $\nu_{\text{inter alia}}$: 3299, 3030, 2901, 1657, 1496, 1453, 1362, 1120, 1058 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.83 (s, 3H, NAc), 2.02–2.09 (m, 2H, H-2″ax, H-2″eq), 2.23 (dd, 1H, H-3eq, *J* 4.2, 12.3 Hz), 2.40 (dd, 1H, H-3ax, *J* 12.0, 12.2 Hz), 2.71–2.86 (m, 4H, H-1″ax, H-1″eq, H-3″ax, H-3″eq), 3.09 (s, 3H, OMe), 3.17 (dd, 1H, H-4′, *J* 9.0, 9.9 Hz), 3.42 (dd, 1H, H-6′b, *J* 8.9, 9.9 Hz), 3.60 (dd, 1H, H-3′, *J* 8.8, 10.4 Hz), 3.66 (dd, 1H, H-8b, *J* 4.7, 10.7 Hz), 3.73 (m, 1H, H-5′), 3.82 (dd, 1H, H-8a, *J* 1.8, 10.7 Hz), 3.88 (ddd, 1H, H-4, *J* 2.2, 4.5, 9.9 Hz), 3.89 (d, 1H, H-6, *J* 9.9 Hz), 3.97 (ddd, 1H, H-7, *J* 1.8, 4.5, 9.0 Hz), 4.02 (dd, 1H, H-6′a, *J* 1.1, 9.9 Hz), 4.11 (bs, 1H, H-5), 4.14 (dd, 1H, H-2′, *J* 3.7, 10.2 Hz), 4.36–5.11 (6×ABq, 6×2H, C$\underline{H}_2$Ph) and (s, 1H, H-1) and (d, 1H, H-1′), 5.26 (d, 1H, NH, *J* 9.4 Hz), 7.20–7.37 (m, 30H, Ar); HR-MS (ESI) calcd for $C_{62}H_{71}O_{11}NS_2$ $[M+Na]^+$ 1092.4366; found 1092.4335.

3.10. 4,5,7,8-Tetra-O-benzyl-3-deoxy-1-(propane-1,3-diyl-dithioacetal)-α-D-manno-octo-pyranosyl-(2→8)-[methyl (methyl 4,5,7-tri-O-benzyl-3-deoxy-α-D-manno-oct-2-ulopyranosid)-onate] **12d**

Trimethylsilyl triflate (15 μL) was added to a stirred solution of enitol **4**[10] (200 mg, 0.30 mmol) and Kdo derivative **8** (130 mg, 0.24 mmol) in dry CH_2Cl_2 at −78°C under Ar. The reaction mixture was stirred for 2 h while the temperature was allowed to rise to −30°C. The reaction was then recooled to −78°C, and neutralized with a methanolic solution of NH_3, then evaporated and the residue was chromatographed (hexane–ether, 3:2) to give **12d** (200 mg, 72%). Colourless oil: $[\alpha]_D$ +21.9 (*c* 0.63, $CHCl_3$); IR (film) $\nu_{\text{inter alia}}$: 3030, 2898, 1748, 1496, 1453, 1361, 1109, 1062 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.72–1.81 and 1.95–2.03 (2×m, 2×1H, H-2″ax, H-2″eq), 2.20–2.26 (m, 3H, H-3eq, H-3′ax, H-3′eq), 2.42 (dd, 1H, H-3ax, *J* 12.1, 12.2 Hz), 2.64–2.90 (m, 4H, H-1″ax, H-1″eq, H-3″ax, H-3″eq), 3.12 (s, 3H, OMe), 3.38 (d, 1H, H-6′, *J* 9.0 Hz), 3.57 (dd, 1H, H-8′a, *J* 7.6, 11.0 Hz), 3.72 (dd, 1H, H-8a, *J* 4.2, 10.9 Hz), 3.74 (s, 3H, CO_2Me), 3.80–3.85 (m, 3H), 3.90 (d, 1H, H-6, *J* 9.1 Hz), 3.96 (ddd, 1H, H-7 or H-7′, *J* 1.8, 4.5, 9.0 Hz), 4.00 and 4.02 (2×bs, 2×1H, H-5 and H-5′), 4.19–4.26 (m, 2H), 4.33–5.08 (7×ABq, 7×2H, C$\underline{H}_2$Ph) and (s, 1H, H-1), 7.15–7.35 (m, 35H, Ar); HR-MS (ESI) calcd for $C_{70}H_{78}O_{13}S_2$ $[M+Na]^+$ 1213.4776; found 1213.4778.

3.11. General procedure for hydrolysis of the dithiane ring

Dithiane derivative (200 mg) was dissolved in a mixture of THF–water (9:1, 5 mL) and NBS (10 equiv.) was added in one portion at rt. The mixture was stirred until TLC showed disappearance of the substrate (0.5 h). The reaction was interrupted by addition of saturated aqueous Na_2SO_3 and diluted with AcOEt. The organic layer was washed with brine, dried and concentrated. The resulting crystals were redissolved in ether containing a few drops of methanol and treated with a solution of CH_2N_2 in ether. After evaporation, the residue was chromatographed to give the desired ester.

3.12. [Methyl (4,5,7,8-tetra-O-benzyl-3-deoxy-α-D-manno-oct-2-ulopyranosyl)onate]-(2→6)-(methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside) **13a**

Based on the general procedure for hydrolysis of the dithiane ring, compound **12a** was converted into ester **13a** (50%). Colourless oil: $[\alpha]_D$ +31.5 (*c* 1.22, $CHCl_3$); IR (film) $\nu_{\text{inter alia}}$: 3030, 2923, 1750, 1496, 1454, 1361, 1064 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.23 (dd, 1H, H-3ax, *J* 11.9, 12.2 Hz), 2.30 (dd, 1H, H-3eq, *J* 4.2, 12.5 Hz), 3.09 (dd, 1H, H-4′, *J* 9.5, 9.9 Hz), 3.21 (s, 3H, OMe), 3.36 (dd, 1H, H-2′, *J* 3.6, 9.6 Hz), 3.52 (dd, 1H, H-6a′, *J* 7.4, 10.9 Hz), 3.61–3.66 (m, 3H), 3.67 (s, 3H, CO_2Me), 3.80–3.84 (m, 2H), 3.60 (t, 1H, H-3′, *J* 9.4 Hz), 3.92 (ddd, 1H, H-4, *J* 2.3, 4.5, 11.5 Hz), 4.00 (ddd, 1H, H-7, *J* 1.9, 4.0, 9.2 Hz), 4.12 (bs, 1H, H-5), 4.51 (d, 1H, H-1′, *J* 3.7 Hz), 4.35–5.06 (7×ABq, 7×2H, C$\underline{H}_2$Ph), 7.19–7.35 (m, 35H, Ar); HR-MS (ESI) calcd for $C_{65}H_{70}O_{13}$ $[M+Na]^+$ 1081.4709; found 1081.4806.

Compounds **13a** after hydrogenolysis (H_2/Pd–C) and acetylation (Ac_2O–Py) was transformed into acetyl derivative **14**, identical by the NMR data with that synthesized by a previously elaborated methodology.[15]

3.13. [Methyl (4,5,7,8-tetra-O-benzyl-3-deoxy-α-D-manno-oct-2-ulopyranosyl)onate]-(2→7)-(methyl 2,3,4,6-tetra-O-benzyl-L-glycero-α-D-manno-heptopyranoside) **13b**

Based on the general procedure for hydrolysis of the dithiane ring, compound **12b** was converted into ester **13b** (53%). Colourless oil: $[\alpha]_D$ +34.4 (*c* 1.39, $CHCl_3$); IR (film) $\nu_{\text{inter alia}}$: 3030, 2916, 1752, 1496, 1453, 1117, 1063 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.25 (dd, 1H, H-3ax, *J* 11.9, 12.5 Hz), 2.32 (dd, 1H, H-3eq, *J* 4.5, 12.6 Hz), 3.15 (s, 3H, OMe), 3.63 (s, 3H, CO_2Me), 3.65 (dd, 1H, H-5′, *J* 1.0, 10.5 Hz), 3.69 (dd, 1H, H-8b, *J* 4.5, 10.8 Hz), 3.72–3.76 (m, 2H, H-2′, H-7′a), 3.80–3.88 (m, 4H, H-8a, H-6, H-7′b, H-3′), 3.92 (ddd, 1H, H-4, *J* 2.1, 4.5, 11.7 Hz), 3.95 (dd, 1H, H-6′, *J* 0.8, 6.7 Hz), 4.03 (ddd, 1H, H-7, *J* 1.5, 3.8, 9.2 Hz), 4.15 (dd, 1H, H-4′, *J* 9.1, 9.5 Hz), 4.16 (bs, 1H, H-5), 4.73 (d, 1H, H-1′, *J* 1.5 Hz), 4.28–5.07 (8×ABq, 8×2H, $C\underline{H}_2Ph$), 7.19–7.36 (m, 40H, Ar); HR-MS (ESI) calcd for $C_{73}H_{78}O_{14}$ $[M+Na]^+$ 1201.5284; found 1201.5252.

3.14. [Methyl (4,5,7,8-tetra-O-benzyl-3-deoxy-α-D-manno-oct-2-ulopyranosyl)onate]-(2→6)-(methyl 3,4-di-O-benzyl-2-deoxy-2-N-acetamide-α-D-glucopyranoside) **13c**

Based on the general procedure for hydrolysis of the dithiane ring, compound **12c** was converted into ester **13c** (53%). Colourless oil: $[\alpha]_D$ +56.5 (*c* 0.46, $CHCl_3$); IR (film) $\nu_{\text{inter alia}}$: 3064, 3031, 2923, 1772, 1750, 1714, 1545, 1454, 1292, 1185, 1121, 1062 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.84 (s, 3H, NAc), 2.25 (dd, 1H, H-3ax, *J* 11.9, 12.3 Hz), 2.32 (dd, 1H, H-3eq, *J* 4.3, 12.6 Hz), 3.14 (s, 3H, OMe), 3.69 (s, 3H, CO_2Me), 3.22 (dd, 1H, H-4′, *J* 9.2, 9.4 Hz), 3.55–3.71 (m, 5H, H-8a, H-3′, H-5′, H-6′a, H-6′b), 3.85 (dd, 1H, H-8b, *J* 1.8, 10.8 Hz), 3.90 (d, 1H, H-6, *J* 9.4 Hz), 3.92 (ddd, 1H, H-4. *J* 2.3, 4.5, 11.6 Hz), 4.02 (ddd, 1H, H-7, *J* 1.9, 4.06, 9.23 Hz), 4.13 (bs, 1H, H-5), 4.16 (dd, 1H, H-2′, *J* 3.8, 10.3 Hz), 3.79 (d, 1H, H-1′, *J* 3.8 Hz), 4.35–5.05 (6×ABq, 6×2H, $C\underline{H}_2Ph$), 5.31 (d, 1H, NH, *J* 9.4 Hz), 7.20–7.37 (m, 30H, Ar); HR-MS (ESI) calcd for $C_{60}H_{67}O_{13}N$ $[M+Na]^+$ 1032.4505; found 1032.4557.

3.15. [Methyl (4,5,7,8–tetra-O-benzyl-3-deoxy-α-D-manno-oct-2-ulopyranosyl)onate]-(2→8)-[methyl (methyl 4,5,7-tri-O-benzyl-3-deoxy-α-D-manno-oct-2-ulopyranosid)onate] **13d**

Based on the general procedure for hydrolysis of the dithiane ring, compound **12d** was converted into ester **13d** (50%). Colourless oil: $[\alpha]_D$ +20.9 (*c* 0.84, $CHCl_3$); IR (film) $\nu_{\text{inter alia}}$: 3063, 3030, 2949, 2917, 2866, 1748, 1496, 1454, 1272, 1161, 1113, 1064 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.17–2.24 (m, 3H, H-3ax, H-3′ax, H-3′eq), 2.35 (dd, 1H, H-3eq, *J* 4.3, 12.6 Hz), 3.06 (s, 3H, OMe), 3.38 (d, 1H, H-6′, *J* 9.0 Hz), 3.69 (dd, 1H, H-8′a, *J* 6.6, 11.1 Hz), 3.63 and 3.71 (2×s, 2×3H, 2×CO_2Me), 3.81–3.86 (m, 3H, H-4, H-4′, H-8′b), 3.88 (dd, 1H, H-8b, *J* 1.7, 10.8 Hz), 3.92 (d, 1H, H-6, *J* 9.4 Hz), 3.96 (ddd, 1H, H-7′, *J* 1.7, 6.6, 8.7 Hz), 3.98 (bs, 1H, H-5′), 4.02 (ddd, 1H, H-7, *J* 1.8, 3.9, 9.11 Hz), 4.06 (bs, 1H, H-5), 4.30–5.05 (7×ABq, 7×2H, $C\underline{H}_2Ph$), 7.15–7.35 (m, 35H, Ar); HR-MS (ESI) calcd for $C_{68}H_{74}O_{15}$ $[M+Na]^+$ 1153.4920; found 1153.4920.

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