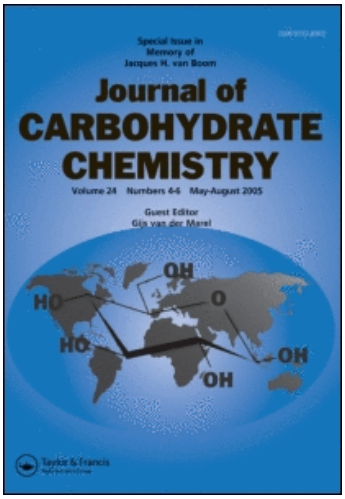

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A Chemical Synthesis of 3-Deoxy-D-*manno*-2-octulosonic Acid from D-mannose

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A chemical synthesis of Kdo was achieved via the condensation of a protected D-mannofuranose-5,6-cyclic sulfate with ethyl 1,3-dithiane-2-carboxylate, which is an efficient equivalent for installing an α-ketoester unit as a key step.

INTRODUCTION

2-Keto-3-deoxy-D-*manno*-octulosonic acid (Kdo, **1**) is a component in the outer membrane lipopolysaccharide (LPS) or lipo-oligosaccharide (LOS) produced by gram-negative bacteria.

Its chemical and enzymatic syntheses from D-arabinose and D-mannose have been reported by several groups.[1–3] Among them, two-carbon elongation at the anomeric position of the starting D-mannose derivative is reliable.[4] In the chemical synthesis from D-mannose, all groups put emphasis on the elaboration of the two-carbon unit, which is later converted to α-ketocarboxylic acid moiety.

Inspired by studies in which a nucleophilic substitution of cyclic sulfates with dithianyl compounds afforded corresponding carbon elongated products,[4c,4e,5] we designed a different approach to Kdo, which was the treatment of cyclic sulfate **2** with glyoxylate equivalent **3** to give the two-carbon elongated product **4** at the C-6 position, which might be transformed to Kdo (Fig. 1). In this paper the synthesis of Kdo ammonium salt using the alkylation of the cyclic sulfate **2** at the C-6 position with the ethyl dithiane-2-carboxylate anion is described.

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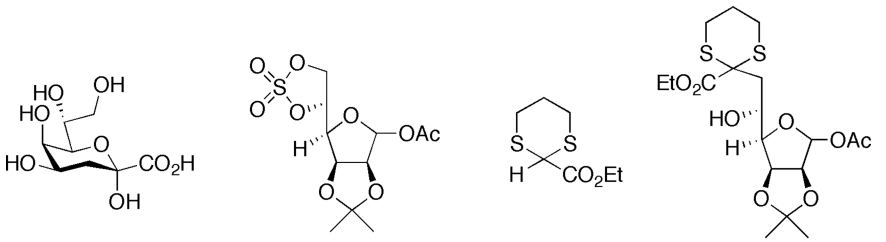
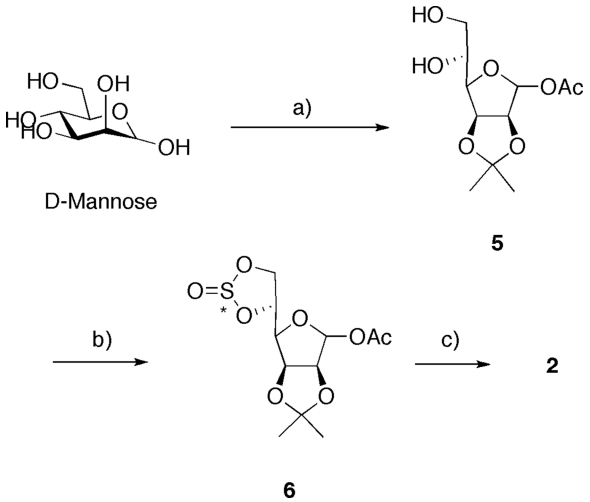


Kdo, 1 2 3 4

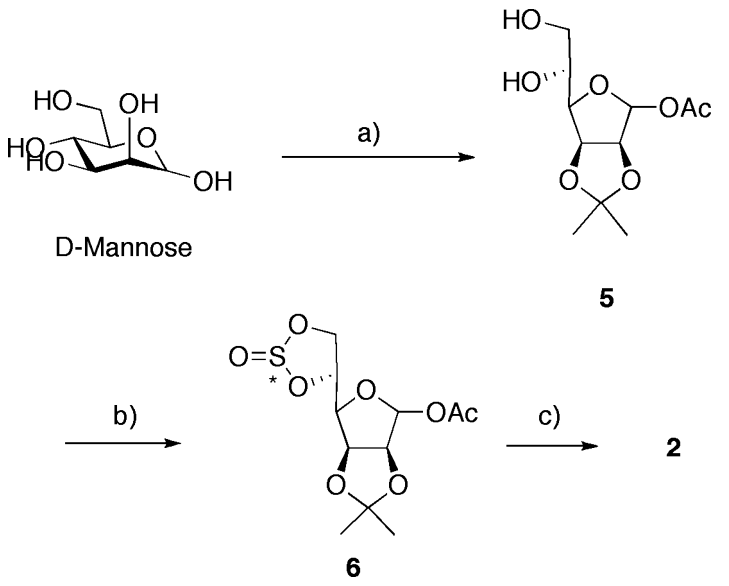
Figure 1:

RESULTS AND DISCUSSIONS

The key cyclic sulfate **2** for this study was prepared from diol **5**, which was easily synthesized from D-mannose in the following procedures (Scheme 1): acetalation of D-mannose,[6] acetylation of the anomeric hydroxyl group,[7] and acidic hydrolysis of 5,6-acetonide[8] (>95% in three steps). Diol **5** was treated with thionyl chloride and triethylamine in dichloromethane to give cyclic sulfinates **6** in 99% yield as a 2:1 mixture of diastereomers. Although these diasteromers could be easily separated by silica gel column chromatography, they did not necessarily have to be separated due to the continuing oxidation to get the key cyclic sulfate **2**. Oxidation of the mixture of cyclic sulfites **5** with $RuCl_3$-nH_2O and $NaIO_4$[9] afforded cyclic sulfate **2** as a colorless solid in 92% yield. Compound **2** was stable under argon at –20°C for 6 months.



Scheme 1: Conditions: a) i) acetone, I_2,[6] 99%, ii) Ac_2O, Py[7], 99%, iii) 60% AcOH[9], 99%; b) $SOCl_2$, Et_3N, CH_2Cl_2, 95%; c) $RuCl_3nH_2O$, $NaIO_4$, acetone, H_2O, 92%.



Scheme 2:

Ethyl 1,3-dithiane-2-carboxylate **3** was chosen as a suitable glyoxylate unit. The key alkylation of **2** with **3** was carried out as follows (Scheme 2). To a solution of the anion **3** (prepared with NaHMDS or NaH and a catalytic amount of t-butanol at 0°C) was added the cyclic sulfate **2**. The mixture was stirred at rt for 3 h, neutralized by the addition of a 1.0 equiv. of sulfuric acid and water, and separated by size exclusion chromatography (Sephadex LH-20, chloroform-methanol) and purified by silica gel column chromatography to give sulfate **7** and sulfate hemiacetal **7a**. Acid hydrolysis of **7** and **7a** gave a mixture of hydroxy ester **8**, lactone **9** (38%, 23% from **2**), and trace amounts of hemiacetals (**8a** and **9a**). Although these compounds could be separated by silica gel column chromatography, they converged into lactone **9** after acetylation of the anomeric hydroxyl group and intramolecular lactonization. Accordingly, compound **9** was obtained in 64% yield from cyclic sulfate **2** by sequentially carrying out acid hydrolysis, acetylation, and subsequent lactone formation without isolating **7**, **8**, and **9**.

The structures of **8** and **9** were determined by 2-D NMR spectroscopy (DQF-COSY, HMQC, and HMBC). The assignments of ring proton and carbon signals of both **8** and **9** were confirmed by comparing their NMR data to those of 1,5,6-tri-*O*-acetyl-2,3-*O*-isopropylidenemannofuranose.[10]

The structure of hydroxy ester **8** was determined by confirming that the carbon atom at C-9 and the quaternary carbon of dithioacetal are connected. In the HMBC spectrum, the presence of the cross-relay peak due to C-1 and the methylene protons of the ethyl group confirmed that the ^{13}C satellite signal

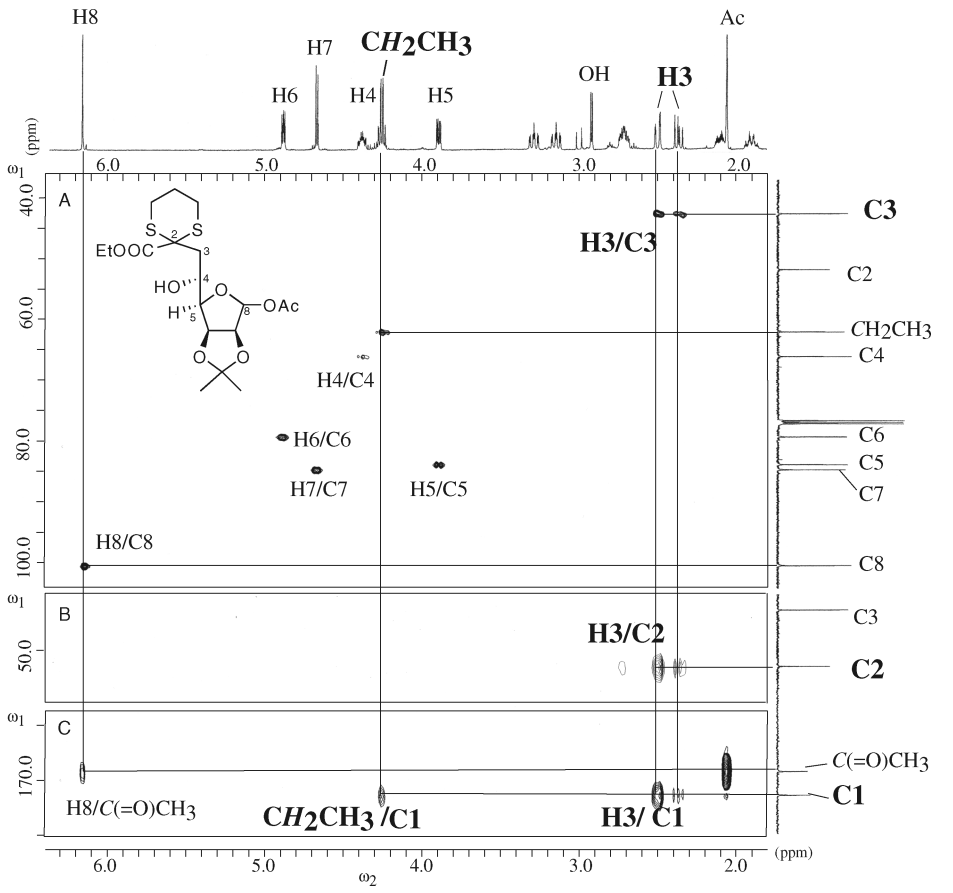


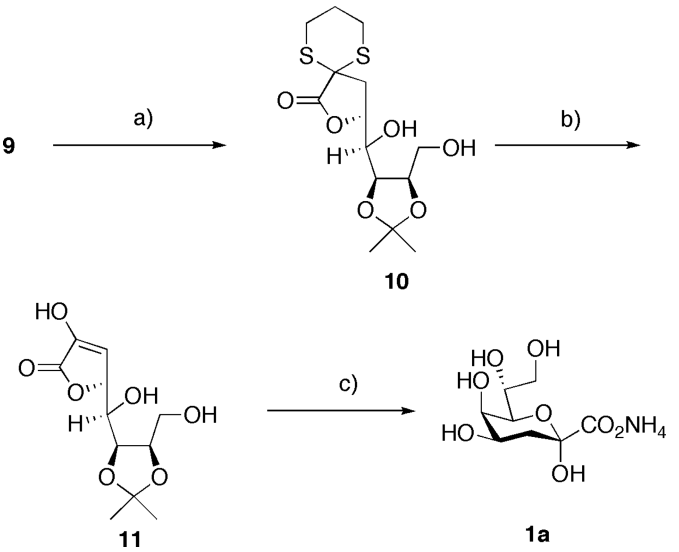
Figure 2: Partial HMQC (panel A) and HMBC (panels B and C) spectra of compound **8** recorded in $CDCl_3$ at 25°C. Only partial $^{13}C/^{1}H$ cross-peaks (A) and cross-relay peaks (B and C) are labeled.

at 169.2 ppm is C-1. In addition, the presence of two sets of cross-relay peaks ascribed to H-3/C-1 and H-3/the quaternary carbon of the dithiane group (C-2) was confirmed (Fig. 2). Thus, we determined that a dithiane **3** is connected to a cyclic sulfate **2** at the C-6 position.

In a similar manner, the absence of an ethyl signal due to COOEt in the ^{1}H NMR spectrum confirmed that the intramolecular cyclization took place to form a lactone structure. Therefore, we determined the structure of lactone **9**.

The deacetylation of lactone **9** with NaOMe and the reductive ring opening of the resulting hemiacetal with sodium borohydride ($NaBH_4$) at 0°C gave diol **10** in 86%. When the reduction was performed at rt, an undesired triol was given in 90% yield due to the reduction of the lactone function. The treatment

of **10** with N-bromosuccinimide (NBS) in aqueous acetone gave unsaturated lactone **11** in 78%. The isopropylidene group of **11** was cleaved with aqueous trifluoroacetic acid to give Kdo **1**, which was purified by ion-exchange column chromatography as its ammonium salt in 70% yield (Scheme 3).



Scheme 3: Conditions: a) NaOMe, MeOH, rt, then $NaBH_4$, 0°C, 86%; b) NBS, acetone, H_2O, 0°C, 78%; c) 90% TFA aq. rt, 15 min, 70%.

In summary, we successfully synthesized Kdo ammonium salt from easily available 1-*O*-acetyl-2,3-*O*-isopropylidene-α-D-mannofuranose in seven steps (overall 26%). This methodology for installing a glyoxylate dithioacetal unit onto the C-6 of D-mannose is convenient from the double points of view of the availability of the key α-ketoacid synthon (alkyl 1,3-dithiane-2-carboxylates are commercially available) and of the ready access to the desired ketoside carboxylic acid in four steps from the protected D-mannofuranose cyclic sulfate **2**. Furthermore, the synthetic intermediate **10** would be expected to convert into an acceptor that is suitable for the oligosaccharide synthesis, because it has two hydroxyl groups at the C-5 and C-8 positions, and each OH group will be able to connect with mono- or oligosaccharides to build inner core oligosaccharides of LOS/LPS. We are currently exploiting this intermediate **9** for the synthesis of core oligosaccharides of LOS as a glycosyl acceptor and will report the results in due course.

EXPERIMENTAL

General Methods

Optical rotations and melting points (uncorrected) were measured with a HORIBA SEPA-200 polarimeter and a YANAGIMOTO micro melting point apparatus, respectively. All NMR spectra were recorded at 25°C in $CDCl_3$ using a JEOL JNM-ECP 500-MHz NMR spectrometer equipped with a Silicon Graphics O_2 computer. Chemical shifts are reported in ppm relative to internal Me_4Si (δ_H 0.00) for ^1H NMR and $CDCl_3$ (δ_C 77.00) for ^{13}C NMR. Two-dimensional NMR data (DQF-COSY, HMQC, and HMBC) were processed using a Delta program (JEOL USA Inc.) in a similar manner as described previously.[11–13] Silica gel 60 (E. Merck) was used for flash column (0.040–0.063 mm) and open column (0.063–0.200 mm) chromatography. Silica gel 60 F_{254} (E. Merck) was used for thin-layer chromatography (TLC), and compounds were detected under UV light (254 nm) or by spraying with 10% conc. H_2SO_4 in MeOH and then heating the plates at 120°C for 5 min.

1-*O*-acetyl-2,3-*O*-isopropylidene-5,6-sulfonylidene-α-D-mannofuranose (2)

To a solution of 1-*O*-acetyl-2,3-*O*-isopropylidenemannofuranose[8] **5** (1.70 g, 6.48 mmol) and triethylamine (3.6 mL, 26 mmol) in dry dichloromethane (25 mL), a solution of thionylchloride (0.90 mL, 13.0 mmol) was added at 0°C. After being stirred for 2 h, the mixture was diluted with EtOAc and added to saturated aqueous $NaHCO_3$. The aqueous layer was extracted with three portions of EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed on a column of silica gel (EtOAc:hexane = 3:2) to give a mixture of diastereomers as a colorless syrup **6** (1.99 g, 99%). A mixture of diastereomer was dissolved in a mixed solution of acetonitrile-dichloromethane-water (2:2:3, 49 mL), and then $NaIO_4$ (2.77 g, 13,0 mmol) and a catalytic amount of $RuCl_3 \cdot 7$ H_2O (6.0 mg) was added at rt. The reaction mixture was vigorously stirred for 20 min and then diluted with ethyl acetate and water. The aqueous layer was extracted with three portions of ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on a column of silica gel (hexane:ethyl acetate = 1:1) to afford a colorless solid, which was recrystallized from dichloromethane (1.93 g, 92%).

M.p. 90.3–91.3°C, $[\alpha]_D^{26}$ + 49.0 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$)δ 6.20 (brs, 1H, H-1), 5.36 (ddd, 1H, $J_{4,5}$ = 6.0, $J_{5,6a}$ = 6.5, $J_{5,6b}$ = 6.5 Hz, H-5), 4.90 (dd, 1H, $J_{2,3}$ = 5.5, $J_{3,4}$ = 3.5 Hz, H-3) 4.81 (dd, 1H, $J_{6a,6b}$ = 9.0 Hz, H-6a), 4.77 (dd, 1H, H-6b), 4.75 (d, 1H, H-2), 4.49 (dd, 1H, H-4), 2.10, (s, 3H, $COCH_3$), 1.48 and

1.33 (s each, 3H, CH_3). ^{13}C NMR ($CDCl_3$)δ 169.0 ($COCH_3$) 100.3 (C-1), 84.8 (C-2), 79.5 (C-4), 78.7 (C-3), 77.7 (C-5), 69.8 (C-6), 25.6 (CH_3), 24.1 (CH_3), 20.9 ($COCH_3$). Anal. calcd for $C_{11}H_{16}O_9S$; C, 40.74; H, 4.97; S, 9.89. Found C, 40.55; H, 4.85; S, 9.70.

(1S,2R,4R,5S,1′R)-4- {2′-[2-(ethoxycarbonyl)(1,3-dithian-2-yl)]-1′-hydroxyethyl}-7,7-dimethyl-3,6,8-trioxabicyclo[3.3.0]oct-2-yl acetate (8) and (1S,2R,4R,5S,3′R)-7,7-dimethyl-3,6,8-trioxa-4-(3′-oxa-4′-oxo-6′,10′-dithiaspiro[4.5]dec-2′-yl)bicyclo[3.3.0] oct-2-yl acetate (9)

Method A: To a solution of NaHMDS (0.6 M, 6.0 mL, 3.6 mmol) in dry DMF (10 mL), a solution of 1,3-dithiane-2-carboxylate (593 mg, 3.1 mmol) in DMF (5.0 mL) was added at 0°C. After stirring the mixture for 20 min, a solution of cyclic sulfonate **2** (500 mg, 1.54 mmol) in DMF (5.0 mL) was added, and the mixture was warmed up to rt. After being stirred for 3 h, 1 equiv. of conc. H_2SO_4 and water (1 equiv.) was added at 0°C, and the mixture was concentrated in vacuo. The residue was chromatographed on a column of Sephadex LH-20 ($CHCl_3$:MeOH = 3:1) to give corresponding sulfate esters **7** and **7a** as a colorless powder. The powder was dissolved in 1,4-dioxane (10.0 mL) and treated with a 100 μL of conc. H_2SO_4 and 100 μL of water at 0°C for 1 h. The mixture was neutralized with sat. $NaHCO_3$ aq. and diluted with ethyl acetate and filtrated through celite, and the filtrate was concentrated in vacuo. The residue was chromatographed on a column of silica gel (hexane:ethyl acetate = 1:1) to afford compounds **8** (255 mg, 38%) and **9** (140 mg, 23%).

Method B: To a suspension of NaH (258 mg, 6.17 mmol), t-BuOH (10 μL), and DMF (5 mL), a solution of compound **3** (1.19 g, 6.17 mmol) in DMF (7 mL) was added at 0°C. After stirring for 1 h, a solution of compound **2** (1.00 g, 3.08 mmol) in DMF (12 mL) was added to the mixture and it was stirred for 1.5 h. Sulfuric acid (320 μL) and water (110 μL) was added and then the reaction mixture was concentrated to remove DMF. The residue was dissolved in 1,4-dioxane (40 mL) and treated with sulfuric acid (650 μL) and water (220 μL) for 1 h at 0°C. The mixture was neutralized with sat. $NaHCO_3$ aq., diluted with dichloromethane, and separated. The aqueous solution was extracted with dichloromethane, and the combined extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated to a syrup. The residue was dissolved in pyridine (2.3 mL) and acetic anhydride (2.3 mL) and stirred for 12 h. The mixture was coevaporated with toluene several times to a residue. Purification by flash column chromatography (dichloromethane:hexane:ethyl acetate = 16:3:1) of the residue gave **9** as a colorless syrup (769 mg, 64%). **Compound 8**: $[\alpha]_D^{25}$+34.0 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$)δ 6.16 (brs, 1H, H-1), 4.89 (dd, 1H, $J_{5,6}$ = 3.5, $J_{6,7}$ = 6.0 Hz, H-6), 4.67, (brd, 1H, H-7), 4.34

(ddd, 1H, $J_{3a,4}$ = 9.5, $J_{3b,4}$ = 2.0, $J_{4,5}$ = 8.5 Hz, H-4), 4.26 (q, 2H, J = 7.0 Hz, CH_2CH$_3$), 3.90 (dd, 1H, H-5), 3.32–3.27 and 3.18–3.13 (m, 1H each, SCH_2), 2.49 (ddd, 1H, $J_{3a,3b}$ = 14.5 Hz, H-3a), 2.39 (ddd, 1H, H-3b), 2.15–2.08 (m, 2H, CH_2), 2.07 (s, 3H, Ac), 1.95–1.87 (m, 2H, CH_2), 1.48 and 1.33 (s, 3H each, CH$_3$), 1.34 (t, 3H, CH$_2$CH_3). ^{13}C NMR (CDCl$_3$)δ 171.4 (*C*OCH$_3$), 169.2 (C-1), 113.1 (C), 100.5 (C-8), 84.8 (C-7), 83.9 (C-5), 79.4 (C-6), 66.2 (C-4), 62.1 (*C*H$_2$CH$_3$), 51.9 (C-2), 42.7 (C-3), 27.7 (CH$_2$), 27.6 (CH$_2$), 25.9 (CH$_3$), 24.8 (CH$_3$), 24.4 (CH$_2$), 21.0 (CO*C*H$_3$), 13.9 (CH$_2$*C*H$_3$). Anal. calcd for C$_{11}$H$_{16}$O$_9$S; C, 49.52; H, 6.47. Found C, 49.28; H, 6.59. **Compound 9:** $[\alpha]_D^{25}$ –91.3 (*c* 1.0, CHCl$_3$). ^{1}H NMR (CDCl$_3$)δ 6.17 (brs, 1H, H-1), 4.86 (dd, 1H, $J_{5,6}$ = 3.5, $J_{6,7}$ = 6.0 Hz, H-6), 4.89 (ddd, 1H, $J_{3a,4}$ = 2.0, $J_{3b,4}$ =<0.5, $J_{4,5}$ = 6.0 Hz, H-4), 4.71, (brd, 1H, H-7), 4.24 (dd, 1H, H-5), 3.96–3.91 (m, 1H, SCH_2), and 3.48–3.39 (m, 1H, SCH_2), 2.66–2.57 (m, 2H, CH_2), 2.50–2.48 (m, 2H, CH_2, H-3), 2.15–2.08 (m, 1H, CH_2), 2.08 (s, 3H, Ac), 1.95–1.87 (m, 1H, CH_2), 1.47 and 1.32 (s, 3H each, CH$_3$). ^{13}C NMR (CDCl$_3$)δ 172.6 (C-1), 169.1 (*C*OCH$_3$), 113.5 (C), 100.5 (C-8), 84.9 (C-7), 81.9 (C-5), 79.0 (C-6), 73.2 (C-4), 44.3 (C-2), 40.4 (C-3), 27.0 and 26.9 (-S*C*H$_2$- each), 25.8 and 24.4 (*C*H$_3$, each), 24.1 (-*C*H$_2$-), 21.0 (CO*C*H$_3$). Anal. calcd for C$_{11}$H$_{16}$O$_9$S; C, 49.21; H, 5.68. Found C, 49.16; H, 5.67.

3-Deoxy-6,7-*O*-isopropylidene-D-*manno*-2-octulosonic acid γ-lactone, cyclic 2-(1,3-propanediyl dithioacetal) (10)

To a solution of compound **9** (243 mg, 0.70 mmol) in methanol (10 mL) was added a solution of sodium methoxide in methanol (0.45 M, 0.1 mL) at rt. After stirring for 12 h, sodium borohydride (106 mg, 2.8 mmol) was added to the mixture at 0°C. After stirring for 2 h, the reaction mixture was neutralized with acetic acid and concentrated to a syrup. Purification by flash column chromatography (ethyl acetate:methanol = 9:1) of the residue afforded **10** as a colorless amorphous solid (210 mg, 86%).

$[\alpha]_D^{25}$ –13.0 (*c* 1.0, CHCl$_3$). ^{1}H NMR (CDCl$_3$)δ 4.61 (ddd, 1H, $J_{3a,4}$ = 6.5, $J_{3b,4}$ = 8.5, $J_{4,5}$ = 8.0 Hz, H-4), 4.39 (dd,1H, $J_{5,6}$ =<0.5, $J_{6,7}$ = 7.5 Hz, H-6), 4.30 (ddd, 1H, H-7), 3.94 (dd, 1H, $J_{7,8a}$ = 4.0, $J_{8a,8b}$ = 12.0 Hz, H-8a), 3.82 (dd, 1H, $J_{7,8b}$ =<0.5 Hz, H-8b), 3.90 and 2.60 (m, 1H each, -SCH_2-), 3.78 (dd, 1H, H-5), 3.46 and 2.64 (m, 1H each, -SCH_2-), 2.53 (ddd, 1H, $J_{3a,3b}$ = 14.0 Hz, H-3b), 2.43 (ddd, 1H, H-3a), 2.19–2.25, and 1.85–1.96 (m, 1H each, -SCH$_2$CH_2-), 1.52 (s, 3H, CH_3), 1.39 (s, 3H, CH_3). ^{13}C NMR (CDCl$_3$)δ 173.1 (C-1), 108.6 (C), 76.6 (C-7), 76.0 (C-4), 75.5 (C-6), 70.5 (C-5), 60.6 (C-8), 44.5 (C-2), 40.8 (C-3), 27.0 (S*C*H$_2$-), 26.8(S*C*H$_2$-), 26.4 (*C*H$_3$), 24.6 (SCH$_2$*C*H$_2$-), 24.1(*C*H$_3$). Anal. calcd for C$_{14}$H$_{22}$O$_6$S$_2$; C, 47.98; H, 6.33. Found C, 47.82; H, 6.41.

Ammonium 3-deoxy-2-keto-D-*manno*-octlosonate (1a)

To a solution of the diol **10** (100 mg, 0.28 mmol) in 5.0 mL of the mixed solution (acetone/H$_2$O = 1/1) was added *N*-bromosuccinimide (152 mg, 0.85 mmol)

at 0°C. The mixture was stirred for 30 min and then 1.0 mL of 5% $Na_2S_2O_3$ aq. was added. After removal of the acetone, the mixture was diluted with chloroform and separated. The aqueous phase was extracted with chloroform and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on a column of silica gel ($CHCl_3$:MeOH = 2:1) to afford an amorphous syrup, and was treated with 90% aqueous trifluoroacetic acid (1 mL) at rt for 15 min. The mixture was concentrated under nitrogen, diluted with water, and neutralized by ammonia. The solution was passed through a Dowex 1 × 8-200 ion exchange resin. The combined filtrates were evaporated, and the residue was crystallized from ethanol-water to give 50 mg (70%) of colorless ammonium salt. m.p. 121–123°C; $[\alpha]_D^{25}$+39.2 (*c* 1.0, H_2O).[4g]

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