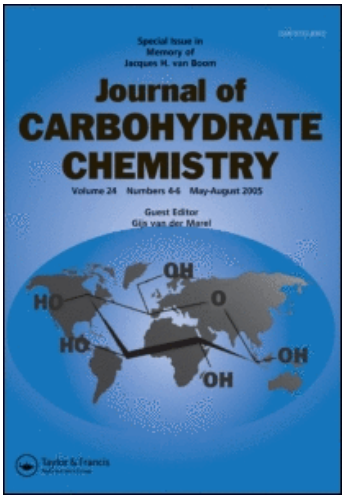

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SYNTHESIS OF 2,6-DIDEOXY-6-THIO DERIVATIVES OF KDO

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ABSTRACT

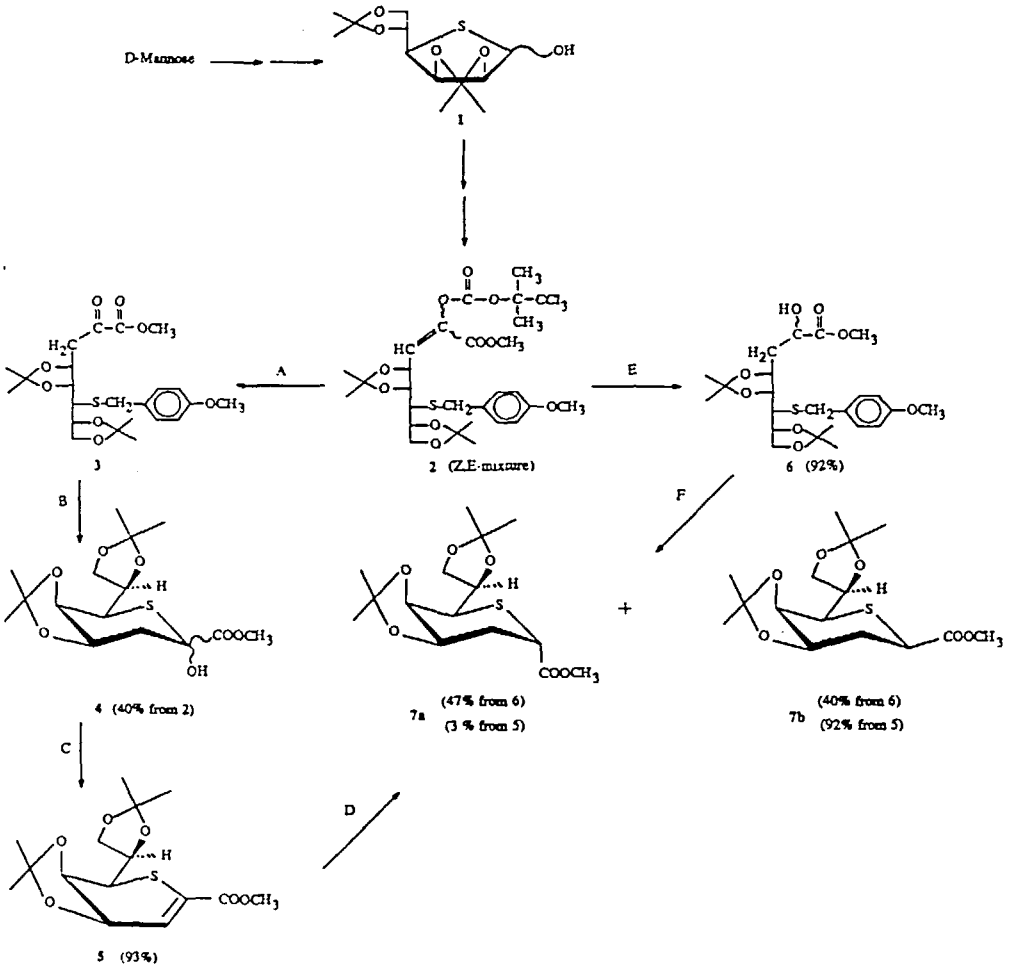
Ammonium 2,3,6-trideoxy-2,6-epithio-D-*manno*-2-octenoate (**8**), ammonium 2,3,6-trideoxy-2,6-epithio-D-*glycero*-D-*talo*-octanoate (**10a**), ammonium 2,3,6-trideoxy-2,6-epithio-D-*glycero*-D-*galacto*-octanoate (**10b**) and ammonium 2,3,6-trideoxy-2,6-epithio-oxa-D-*glycero*-D-*galacto*-octanoate (**13**) have been synthesised as potential inhibitors of the enzyme CMP-KDO synthetase. The key step in the synthesis of **8** was the elimination of water from methyl 3,6-dideoxy-4,5:7,8-di-*O*-isopropylidene-6-thio-D-*manno*-2-octulosonate (**4**) using chlorodiphenylphosphine, imidazole and bromine to give the unsaturated methyl 2,3,6-trideoxy-2,6-epithio-4,5:7,8-di-*O*-isopropylidene-D-*manno*-2-octenoate (**5**). For the synthesis of **10a** and **10b**, zinc reduction of methyl 3,6-dideoxy-4,5:7,8-di-*O*-isopropylidene-6-*S*-(4-methoxybenzyl)-6-thio-2-*O*-(trichloro-*tert*-butoxycarbonyl)-D-*manno*-2-octenoate (**2**) gave an epimeric mix-

ture of an α-hydroxyester **6** which was ring closed by *in situ* activation of the hydroxyl group using triphenylphosphine and triiodoimidazole followed by cleavage of the *p*-methoxybenzyl group to give **7a** and **7b**, which then were deprotected to give **10a** and **10b**.

INTRODUCTION

KDO[1] (3-deoxy-D-*manno*-2-octulosonic acid) is a constituent of the lipopolysaccharide (LPS)[2] of Gram-negative bacteria and links the polysaccharide to lipid A. The enzyme CMP-KDO synthetase[3] catalyzes the formation of CMP-KDO from KDO and cytidine triphosphate. This is believed to be the rate-limiting step in LPS biosynthesis in gram-negative bacteria.[3] CMP-KDO synthetase is thus an attractive target for the direct inhibition of KDO metabolism and for the development of novel antibiotics based on the concept of enzyme inhibition. We have previously reported on the synthesis of 6-deoxy-6-thio-KDO.[4] This analog gave low inhibition of CMP-KDO synthetase. In the synthesis only one anomer was formed, probably with the α configuration. Since β-KDO is the natural substrate,[5] this would account for the low inhibition observed.

2-Deoxy-β-KDO derivatives have been shown to be potent inhibitors of CMP-KDO synthetase.[6] From these results, the C-2 epimeric pairs of 2,6-dideoxy-6-thio-KDO (**10a**, **10b**) were considered as interesting target molecules. It has been postulated that the low inhibitory activity of the carbocyclic analogue of KDO[7] is partially due to lack of hydrogen bonding at the position of the ring oxygen.[8] As a sulfoxide would be a hydrogen bond acceptor, the preparation of the corresponding sulfoxides of **10a** and **10b** were attempted. Although the reactions proceeded uneventfully, only the "α-anomer" **13** could be isolated. The acidic proton at C-2 probably establishes an equilibrium favouring the thermodynamically most stable epimer. The 2,3-unsaturated analogue of KDO has previously been prepared[9] and was shown to be inactive as an inhibitor of CMP-KDO synthetase.[10] In the present work the corresponding analogue in which the ring oxygen has been replaced by sulfur was prepared.

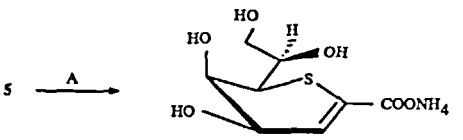


a: A. see ref. 4; B. see ref. 4; C. $(Ph)_2PCl$, imidazole, Br_2, toluene; D. Pd/H_2; E. Zn, Et_2O-HOAc; F. $(Ph)_3P$, triiodoimidazole, toluene, 90 °C

Scheme I[a]

RESULTS AND DISCUSSION

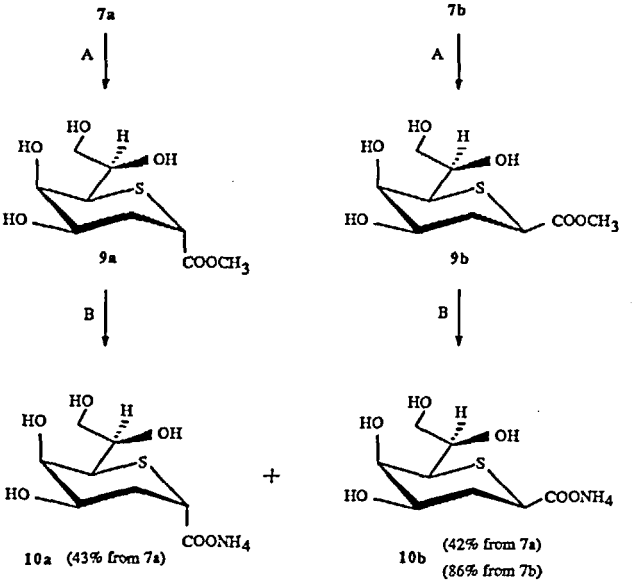
The preparation of methyl 3,6-dideoxy-4,5:7,8-di-*O*-isopropylidene-6-thio-D-*manno*-2-octulopyranosonate (4) starting from D-mannose and proceeding via 1 and 2 has previously been described.[4] Thus, starting from 2 the trichloro-*tert*-butoxycarbonyl group was cleaved using zinc in acetic acid-diethyl ether, followed by removal of the *p*-methoxybenzyl group using dichlorodicyanobenzoquinone to give 4. Several routes for the elimination of water



8 (74%)

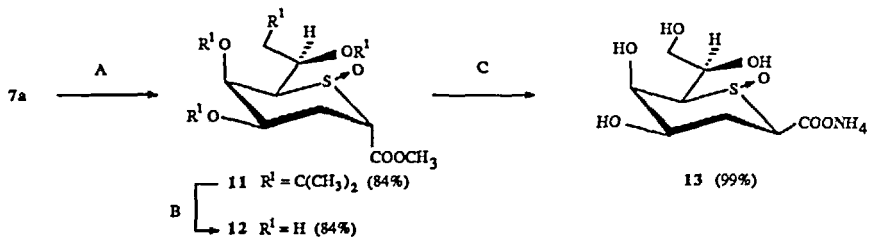
a: A. (1) CF_3COOH, CH_3OH, H_2O; (2) KOH, H_2O;
(3) Dowex 50 NH_4^+

Scheme II[a]



a: A. CF_3COOH, CH_3OH, H_2O; B. (1) KOH, H_2O, (2) Dowex 50 NH_4^+

Scheme III[a]



a: A. (1) MCPBA, EtOAc, -40 °C; B. CF_3COOH, CH_3OH
C. (1) KOH, H_2O, (2) Dowex 50 NH_4^+

Scheme IV[a]

to introduce the 2,3-unsaturation were examined, and eventually a procedure useful for preparing alkylhalides from alcohols was found to work.[11] Thus reaction of **4** with chlorodiphenylphosphine, bromine and imidazole in toluene at room temperature produced the unsaturated **5** in 93 % yield. Catalytic hydrogenation of **5** using palladium in ethanol gave an entry to the corresponding saturated derivatives **7a** and **7b**. The face selectivity was high giving 92 % of **7b** and 3 % of **7a**. Compound **5** was deprotected to give **8** using standard procedures.

A shorter and more efficient route to epimers **7a** and **7b** starting from **2** was explored. In a modification of the trichloro-*tert*-butoxycarbonyl deprotecting procedure used for the conversion of **2** to **3**, the amount of acetic acid in diethyl ether was increased from 3 % to 5 % (v/v) and the time of reaction increased from 1 h to 4 h. Using this procedure the α-hydroxyester **6** (chirality at C-2 unspecified) was obtained in 92 % yield directly from **2**. Subjecting **6** to triphenylphosphine and triiodoimidazole in toluene gave the expected ring closed product.[12] The C-2 epimers were separated on a silica gel column to give **7a** and **7b** in 47 % and 40 % yield, respectively. Standard deprotecting procedures provided the target compounds **10a** and **10b**. Compound **9a** isomerized partially during the basic hydrolysis, indicating that the equatorial oriented carboxyl group ("α-anomer") is thermodynamically favoured.

The 2,3-unsaturated **5** was deprotected using standard conditions to give **8** in 74 % yield. For the synthesis of the sulfoxide derivative **13**, the sulfide **7a** was oxidized using *m*-chloroperbenzoic acid at -40 °C to give **11** in 84 % yield. Deprotection with trifluoroacetic acid gave **12** in 84 % yield. Saponification of 12 resulted in isomerisation at C-2 to give 13 in 99 % yield. The chirality of the sulfoxide was not determined.

These compounds were tested *in vitro* for antibacterial activity using the methods described by Pring *et. al.*[13] Compound **10a** exhibited weak activity, whereas the other compounds tested were without activity.

EXPERIMENTAL

General methods. Concentrations were performed under diminished pressure (1-2 kPa) at a bath temperature not exceeding

40 °C. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. NMR spectra were recorded at 25 °C with a JEOL GSX-270 instrument. Chemical shifts are given in ppm downfield from tetramethylsilane when using $CDCl_3$, and from acetone (^{13}C, δ 31.0) or sodium 3-trimethylsilylpropanoate-d_4 (^1H) when using D_2O. ^1H-NMR data were obtained by one- or two-dimensional spectroscopy (COSY). NMR spectra for all compounds were in accordance with the postulated structures. All reactions were monitored by TLC using precoated silica gel plates (F 250 Merck). Spots were visualized by UV light and/or charring with 8% sulfuric acid. Column chromatography was performed using silica gel 60 (0.040-0.063 mm Merck). The loadings were in the range 1/25-1/100 (w/w). Organic phases were dried over anhydrous magnesium sulfate. The yields given are for purified products. Chlorodiphenylphosphine was obtained from Aldrich Chemical Co. and distilled (bp 130 °C at 0.5 Pa) before use. Satisfactory elemental analyses for some of the compounds could not be obtained, but their purity was judged, using chromatographic techniques and by NMR spectroscopy, to be >90%.

Methyl 2,3,6-Trideoxy-2,6-epithio-4,5:7,8-di-*O*-isopropylidene-D-*manno*-2-octenoate (5). To a mixture of methyl 3,6-dideoxy-4,5:7,8-di-*O*-isopropylidene-6-thio-D-*manno*-2-octulosonate[4] (4) (0.5 g, 1.44 mmol) and imidazole (0.24 g, 3.59 mmol) in toluene (10 mL) was added a solution of chlorodiphenylphosphine (0.38 g, 1.72 mmol) and bromine (0.28 g, 1.72 mmol) in toluene (5 mL) at room temperature. The reaction mixture was stirred for 30 min and then poured into an equal volume of 1 M sodium hydroxide in a separating funnel. The funnel was shaken for 5 min with portionwise addition of iodine until the toluene phase remained iodine-coloured. The aqueous phase was separated and the toluene phase was washed with aqueous sodium thiosulfate to remove excess iodine and then washed with water, dried and concentrated. The residue was purified by column chromatography (ethyl acetate-toluene, 1:3) to yield compound 5 (0.44 g, 93%): $[\alpha]^{22}_D$ +17° (*c* 0.93, chloroform): ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 25.5, 26.6, 26.8, 27.7 (4 CH_3), 46.4 (C-6), 52.8 (OCH_3), 67.4 (C-8), 70.7, 71.8, 75.0, 109.6, 110.2 [2 $C(CH_3)_2$], 128.2 (C-3), 130.6 (C-2), 164.4 (C-1); ^1H NMR ($CDCl_3$) δ 3.46 (dd, $J_{5,6}$ = 1.45 Hz, $J_{6,7}$ = 6.78 Hz,

H-6), 3.81 (s, OCH_3), 3.96 (dd, $J_{7,8}$ = 8.8 Hz, $J_{8,8'}$ = 6.05 Hz, H-8), 4.08 (dd, $J_{7,8'}$ = 8.8 Hz, H-8'), 4.40 (ddd, H-7), 4.56 (dd, $J_{4,5}$ = 5.68 Hz, H-5), 4.76 (dd, H-4), 6.84 (d, $J_{3,4}$ = 3.67 Hz, H-3).

Anal. Calcd for $C_{15}H_{22}O_6S$: C, 54.5; H, 6.7; S, 9.7. Found: C, 54.7; H, 6.7; S, 9.2.

Ammonium 2,3,6-Trideoxy-2,6-epithio-D-*manno*-2-octenoate (8). Compound **5** (0.44 g, 1.33 mmol) was dissolved in trifluoroacetic acid-methanol-water (15 mL, 9:6:0.2). After the solution was stirred for 3 h at room temperature, it was concentrated and residual acid was removed by three azeotropic distillations with toluene. The residue was purified by column chromatography (ethyl acetate-methanol-water, 85:10:5) to yield *methyl 2,3,6-trideoxy-2,6-epithio-D-manno-2-octenoate* (0.27 g), $[\alpha]^{22}_D$ -15° (*c* 2.36, methanol): ^{13}C NMR (67.5 MHz, DMSO-d_6) δ 46.3 (C-6), 52.3 (OCH_3), 62.5, 63.2, 68.7, 70.0, 126.1 (C-3), 135.4 (C-2), 163.7 (C-1); ^1H NMR (D_2O) δ 3.36 (m, H-6), 3.54 (dd, H-8'), 3.65-3.76 (m, H-5, H-7, H-8 and OCH_3), 4.20 (m, H-4), 6.59 (dd, H-3). A solution of this material (25 mg, 0.1 mmol) in 0.2 M potassium hydroxide (3.0 mL) was kept for 3 h at room temperature. The solution was passed through a column of Dowex 50 NH_4^+ eluted with water, and lyophilised to yield compound **8** (23 mg, 74 %): $[\alpha]^{22}_D$ +3° (*c* 3.8, water): ^{13}C NMR (67.5 MHz, D_2O) δ 46.5 (C-6), 64.0, 64.2, 70.1, 71.1, 129.0 (C-3), 133.8 (C-2), 171.5 (C-1); ^1H NMR (D_2O) δ 3.47 (d, H-6), 3.62 (dd, H-8), 3.78-3.94 (m, H-7 and H-8), 4.34 (ddd, H-5), 4.49 (ddd, H-4), 6.41 (dd, H-3).

Anal. Calcd for $C_8H_{15}NO_6S$ x 0.78 SiO_2: C, 32.02; H, 5.04. Found: C, 32.02; H, 4.71.

Methyl 2,3,6-Trideoxy-2,6-epithio-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*talo*-octanoate (7a) and Methyl 2,3,6-Trideoxy-2,6-epithio-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*galacto*-octanoate (7b). ROUTE A: **5** (0.25 g, 0.76 mmol) was hydrogenated over 10% palladium on charcoal (0.85 g) at 400 kPa in 95% ethanol (30 mL) for 15 h. The mixture was filtered and the filtrate was concentrated to a residue which was purified on column chromatography (ethyl acetate-toluene, 1:2) to yield **7a** (7 mg, 3 %) and **7b** (0.23 g, 92 %). **ROUTE B:** To a stirred solution of methyl 3,6-dideoxy-4,5:7,8-di-*O*-isopropylidene-6-*S*-(4-

methoxybenzyl)-6-thio-2-*O*-(trichloro-*tert*-butoxycarbonyl)-D-*manno*-2-octenoate[4] (2) (0.50 g, 0.74 mmol) in diethyl ether containing acetic acid (5%, v/v, 20 mL) was added zinc dust (0.65 g, 14.9 mmol) at room temperature. After 4 h the mixture was filtered, the filtrate washed with saturated aqueous sodium hydrogen carbonate and water. The organic phase was dried and concentrated. The residue was purified by column chromatography (ethyl acetate-toluene, 1:4) to give **6** (0.32 g, 92 %): (Anal. Calcd for $C_{23}H_{34}O_8S$: C, 58.7; H, 7.3; S, 6.8. Found: C, 59.0; H, 7.3; S, 6.8). A mixture of **6** (0.29 g, 0.61 mmol), triphenylphosphine (0.80 g, 3.05 mmol) and triiodoimidazole[3] (0.82 g, 1.83 mmol) in toluene (15 mL) was stirred at 90 °C for 6 h. The mixture was diluted with toluene, washed with water, saturated aqueous sodium hydrogen carbonate and water, dried and concentrated. Column chromatography (ethyl acetate-toluene, 1:3) of the residue yielded **7a** (0.10 g, 47 %) and **7b** (0.08 g, 40 %): Compound **7a** had $[\alpha]^{22}_D$ +18° (*c* 4.25, methanol): ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 24.7, 25.6, 26.0, 26.9, (4 CH_3), 26.7 (C-3), 34.5 (C-2), 43.6 (C-6), 52.6 (OCH_3), 67.9 (C-8), 71.2, 71.4, 74.8, 108.8, 109.5, [2 $C(CH_3)_2$], 173.0 (C-1); ^1H NMR ($CDCl_3$) δ 1.97 (ddd, $J_{2,3a}$ = 11.7 Hz; $J_{3a,3e}$ = 15.0 Hz, H-3a), 2.30 (ddd, $J_{2,3e}$ = 4,8 Hz; $J_{3e,4}$ = 2.2 Hz, H-3e), 3.17 (dd, $J_{5,6}$ = 1.9 Hz, H-6), 3.74 (s, OCH_3), 3.86 (m, H-2, H-8) 4.02 (dd, $J_{7,8'}$= 6.1 Hz; $J_{8,8'}$= 8.8 Hz, H-8′), 4.16 (ddd, $J_{6,7}$ = 9.2 Hz, H-7), 4.52 (m, $J_{3a,4}$ = 4.1 Hz, H-4), 4.60 (dd, $J_{4,5}$ = 8.3 Hz, H-5): Compound **7b** had $[\alpha]^{22}_D$ -6° (*c* 3.41, methanol): ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 25.5, 26.5, 26.9, (4 CH_3), 28.9 (C-3), 40.2 (C-2), 45.6 (C-6), 52.8 (OCH_3), 67.7 (C-8), 71.5, 72.4, 75.0, 109.3, 109.4 [2 $C(CH_3)_2$], 171.6 (C-1); ^1H NMR ($CDCl_3$) δ 2.12 (m, $J_{2,3e}$ = 5.13 Hz; $J_{3e,4}$ = 3.6 Hz, H-3e), 2.48 (m, $J_{2,3a}$ = 6.6 Hz; $J_{3a,4}$ = 7.0 Hz; $J_{3a,3e}$ = 14.5 Hz, H-3a), 3.16 (dd, $J_{5,6}$ = 2.4 Hz; $J_{6,7}$ = 8.5 Hz, H-6), 3.72 (dd, H-2), 3.74 (s, OCH_3), 3.96 (dd, $J_{7,8}$ = 5.9 Hz; $J_{8,8'}$= 8.8 Hz, H-8), 4.06 (dd, J7,8′= 5.9 Hz, H-8′), 4.23 (dd, H-7), 4.31 (m, $J_{4,5}$ = 6.8 Hz, H-4), 4.46 (dd, H-5).

Anal. Calcd for $C_{15}H_{24}O_6S$: C, 54.2; H, 7.3; S, 9.6. Found: C, 54.7; H, 7.3; S, 9.4.

Ammonium 2,3,6-Trideoxy-2,6-epithio-D-*glycero*-D-*talo*-octanoate (10a) and Ammonium 2,3,6-Trideoxy-2,6-epithio-D-*glycero*-D-*galacto*-octanoate (10b). A solution of **7a** (0.10 g, 0.30 mmol) in trifluoroacetic acid-methanol-water (5 mL,

3:2:0.1) was stirred at room temperature for 3 h. The solution was concentrated and residual acid was removed by three azeotropic distillations with toluene. The residue was purified by column chromatography (ethyl acetate-methanol-water, 85:10:5) to yield *methyl 2,3,6-trideoxy-2,6-epithio-D-glycero-D-talo-octanoate* (**9a**) (65 mg): $[\alpha]^{22}_D$ +82° (*c* 0.95, methanol); ^{13}C NMR (67.5 MHz, D_2O) δ 27.9 (C-3), 40.3 (C-2), 45.4 (C-6), 52.6 (OCH_3), 63.2 (C-8), 65.7, 67.2, 69.7, 173.8 (C-1); ^1H NMR (D_2O) δ 2.20 (ddd, $J_{2,3a}$ = 5.1 Hz; $J_{3a,4}$ = 12.1 Hz, H-3a), 2.37 (ddd, $J_{2,3e}$ = 2.9 Hz; $J_{3e,4}$ = 4.4 Hz; $J_{3a,3e}$ = 12.1 Hz, H-3e), 3.38 (dd, $J_{5,6}$ = 1.3 Hz; $J_{6,7}$ = 9.0 Hz, H-6), 3.70 (dd, H-8′), 3.98 (dd, H-2), 4.05 (ddd, $J_{4,5}$ = 2.8 Hz, H-4), 4.38 (br s, H-5). **7b** (0.12 g, 0.36 mmol) was treated in the same way as **7a** to yield *methyl 2,3,6-trideoxy-2,6-epithio-D-glycero-D-galacto-octanoate* (**9b**, 80 mg): $[\alpha]^{22}_D$ +15° (*c* 0.76, methanol); ^{13}C NMR (67.5 MHz, D_2O): δ 30.3 (C-3), 43.1 (C-2), 47.1 (C-6), 52.6 (OCH_3), 63.0 (C-8), 65.0, 69.2, 70.3, 175.1 (C-1); ^1H NMR (D_2O) δ 1.93 (dd, $J_{2,3a}$ = 12.3 Hz; $J_{3a,4}$ = 12.3 Hz, H-3a), 2.25 (ddd, $J_{2,3e}$ = 3.4 Hz; $J_{3e,4}$ = 3.1 Hz; $J_{3a,3e}$ = 12.3 Hz, H-3e), 3.16 (dd, $J_{5,6}$ = 1.8 Hz; $J_{6,7}$ = 9.2 Hz, H-6), 3.9 (ddd, $J_{4,5}$ = 2.6 Hz, H-4), 4.20 (br s, H-5). A solution of **9a** (60 mg, 0.24 mmol) in 0.2 M potassium hydroxide (4 mL) was kept for 5 h at room temperature. The solution was neutralized using Dowex H^+, filtered and lyophilised. The residue containing **10a** and **10b** (as carboxylic acids) were separated by column chromatography (ethyl acetate-methanol-water-acetic acid, 7:3:1:1). The residues were separately passed through a column of Dowex 50 NH_4^+ eluted with water and lyophilised to yield **10a** (31 mg, 43 % from **7a**) and **10b** (30 mg, 42 % from **7a**). Compound **10a** had $[\alpha]^{22}_D$ +27° (*c* 2.25, water): ^{13}C NMR (67.5 MHz, D_2O) δ 31.2 (C-3), 45.0 (C-6), 46.6 (C-2), 64.6 (C-8), 67.6, 69.3, 71.3, 179.7 (C-1); ^1H NMR (D_2O) δ 2.07 (ddd, $J_{3a,3e}$ = 12.1 Hz; $J_{3a,2}$ = 5.1 Hz $J_{3a,4}$ = 12.1 Hz, H-3a), 2.22 (ddd, $J_{2,3e}$ = 3.8 Hz; $J_{3e,4}$ = 3.8 Hz, H-3e), 3.22 (dd, $J_{6,7}$ = 7.9 Hz; $J_{5,6}$ = 1.1 Hz, H-6), 3.64 (dd, H-8′), 4.22 (br s, H-5).

Ammonium 2,3,6-Trideoxy-2,6-epithio-D-*glycero*-D-*galacto*-octanoate (10b). **7b** (50 mg, 0.15 mmol) was treated the same way as **7a** to yield **10b** (50 mg, 86 %): $[\alpha]^{22}_D$ +23° (*c* 1.28, water); ^{13}C NMR (67.5 MHz, D_2O) δ 33.7 (C-3), 48.4 (C-6), 48.9 (C-2),

64.6 (C-8), 66.9, 70.9, 72.7, 178.5 (C-1); ^{1}H NMR (D_2O) δ 1.92 (ddd, $J_{3a,3e} = J_{3a,2} = J_{3a,4}$ = 12.5 Hz, H-3a), 2.29 (ddd, $J_{2,3e}$ = 2.6 Hz; $J_{3e,4}$ = 4.2 Hz, H-3e), 3.14 (dd, $J_{6,7}$ = 9.2 Hz, H-6), 4.25 (br s, H-5).

10a and **10b** were analysed as carboxylic acids; Anal. Calcd for: $C_8H_{14}O_6S$ x 1.2 SiO_2: C, 30.96; H, 4.55. Found: C, 30.97; H, 4.46.

Methyl 2,3,6-Trideoxy-2,6-epithiooxa-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*talo*-octanoate (11). To a solution of **7a** (200 mg, 0.60 mmol) in ethyl acetate (10 mL) was added a solution of 3-chloroperoxybenzoic acid (85 %, 122 mg, 0.60 mmol) in ethyl acetate (3 mL) at -40 °C. After 30 min at this temperature, the mixture was without prior work-up subjected to column chromatography (ethyl acetate-toluene, 1:3) to yield **11** (176 mg, 84 %): $[\alpha]^{22}_D$ +52° (*c* 0.32, methanol); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 23.7 (C-3), 25.6, 25.9, 26.6, 26.9 (4 CH_4), 52.9 (OCH_3), 55.5 (C-6), 65.2 (C-2), 67.9, 71.3, 71.9, 73.9, 108.8, 109.4 [2 $C(CH_3)_2$], 166.9 (C-1); ^{1}H NMR ($CDCl_3$) δ 2.32 (ddd, $J_{2,3a}$ = 12.2 Hz; $J_{3a,4}$ = 2.6 Hz; $J_{3a,3e}$ = 15.2 Hz, H-3a), 2.46 (ddd, $J_{2,3e}$ = 3.3 Hz; $J_{3e,4}$ = 2.9 Hz, H-3e), 2.85 (dd, $J_{5,6}$ = 1.8 Hz; $J_{6,7}$ = 9.2 Hz, H-6), 3.82 (s, OCH_3), 4.25 (dd, $J_{7,8} = J_{7,8'}$ = 6.2 Hz; $J_{8,8'}$ = 9.2 Hz, H-8), 4.76 (dd, $J_{4,5}$ = 7.7 Hz, H-5): MS (70 eV): m/z=348 (M^+); 333 (M^+-CH_3); 317 (M^+-OCH_3).

Methyl 2,3,6-Trideoxy-2,6-epithiooxa-D-*glycero*-D-*talo*-octanoate (12). Compound **11** (70 mg, 0.2 mmol) in trifluoroacetic acid-methanol-water (5 mL, 3:2:0.1) was kept at room temperature for 6 h. The solution was concentrated and residual acid was removed by three azeotropic distillations with toluene. The residue was purified by column chromatography (ethyl acetate-methanol-water, 85:10:5) to yield **12** (45 mg, 84 %): $[\alpha]^{22}_D$ +82° (*c* 0.95, methanol); ^{13}C NMR (67.5 MHz, CD_3OD) δ 27.7 (C-3), 53.2 (OCH_3), 57.6 (C-6), 63.3, 65.1, 67.8, 70.0 (C-2), 70.2, 175.5 (C-1); ^{1}H NMR ($CDCl_3$) δ 2.32 (m, H-3e and H-3a), 3.61 (dd, $J_{2,3a}$ = 4.0 Hz; $J_{2,3e}$ = 2.6 Hz, H-2), 3.77 (s, OCH_3).

Ammonium 2,3,6-Trideoxy-2,6-epithiooxa-D-*glycero*-D-*galacto*-octanoate (13). A solution of **12** (30 mg, 0.112 mmol) in 0.2 M potassium hydroxide (3 mL) was kept for 4 h at room temperature. The solution was passed through a column of Dowex

50 NH_4^+ eluted with water and lyophilised to yield **13** (30 mg, 99 %): $[\alpha]^{22}_D$ +23° (*c* 3.22, water); ^{13}C NMR (67.5 MHz, D_2O) δ 30.3 (C-3), 65.0, 65.6, 69.7, 70.0, 71.6 (C-2), 71.8, 175.5 (C-1); ^1H NMR (D_2O) δ 2.25 (m, H-3e and H-3a), 3.15 (dd, $J_{5,6}$ = 0.1 Hz; $J_{6,7}$ = 4.4 Hz, H-6), 3.68 (dd, $J_{2,3a}$ = 12.1 Hz; $J_{2,3e}$ = 4.4 Hz, H-2), 4.02 (ddd, $J_{3a,4}$ = 10.2 Hz; $J_{3e,4}$ = 5.9 Hz, H-4), 4.33 (dd, $J_{7,8}$ =$J_{7,8'}$= 5.1 Hz, H-7), 4.48 (br s, $J_{4,5}$ = 2.6 Hz, H-5).

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