A New Short and Efficient Route to 3-Deoxy-D-*manno*-oct-2-ulosonic Acid (KDO) and 3-Deoxy-D-*arabino*-hept-2-ulosonic Acid (DAH)

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Abstract: An efficient synthesis of lactones **5** and **6**, known intermediates towards KDO and DAH, respectively, has been achieved by a short and highly efficient route. Homologation of protected D-mannose and D-arabinose was performed by a Peterson reaction with 2-lithio-2-trimethylsilyldithiane or the corresponding bis(methylsulfanyl) derivative, followed by the cyclization of the resulting ketene dithioacetal under very smooth conditions. An oxidative treatment with iodine gave the lactones **5** and **6** in a three-step sequence with high yields. Interestingly, this approach can be considered as a general method for the synthesis of various 2-deoxysugar lactones.

Key words: carbohydrates, natural products, lactones, ketene, dithioacetal

Higher 3-deoxy-2-ulosonic acids are a family of widely distributed natural high-carbon carbohydrates. Among this family, 3-deoxy-D-*arabino*-hept-2-ulosonic acid (DAH **1**), 3-deoxy-D-*manno*-oct-2-ulosonic acid (KDO **2**), 3-deoxy-D-*glycero*-D-*galacto*-non-2-ulosonic acid (KDN), and 5-acetamido-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-ulosonic acid (*N*-acetylneuraminic acid or sialic acid) are the most common members (Figure 1).

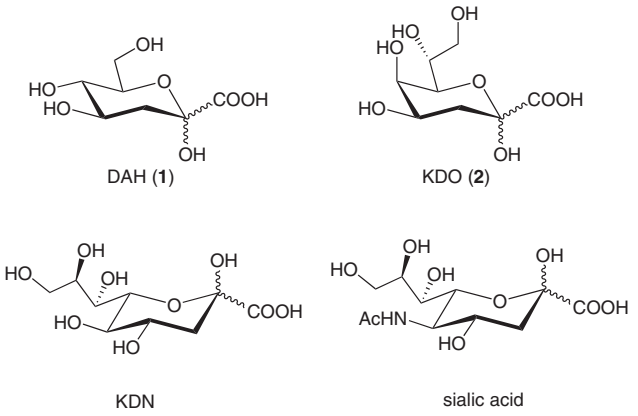
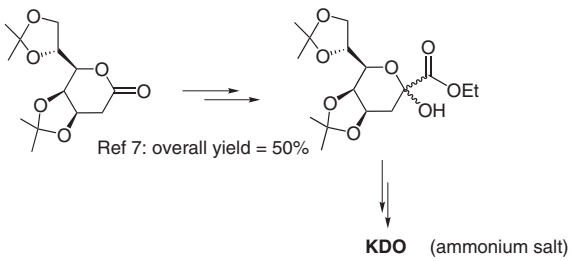


Figure 1 Molecular structures of the most common 3-deoxy-2-ulosonic acids

DAH (**1**) plays an important role in the biosynthesis of aromatic amino acids in plants and micro-organisms as a key intermediate in the shikimate pathway.[1] KDO (**2**) is an essential constituent of lipopolysaccharides (LPS) and acidic exopolysaccharides (K antigens) found in the cell surface of Gram-negative bacteria.[2] The difficulty of their isolation from the biological material as well as the desire to study their biological functions led to an increasing interest in short and efficient syntheses of chemically pure KDO and DAH.

With this aim, many enzymatic and chemical syntheses of KDO and DAH have been developed, starting from easily available carbohydrates.[3] Among them, carbohydrate-based chemical synthesis via a two-carbon elongation is the most reliable approach. In particular, very general, short and efficient strategies for the synthesis of various 2-ulosonic acids have been developed from the corresponding sugar lactones[4–7] as exemplified for KDO in Scheme 1.



Scheme 1

Protected sugar lactone **5** as precursor for KDO has been previously described.[8] However, the different approaches involved a large number of steps (from 4[8a] to 8[8b]) and as a result low overall yields were obtained (38%[8b] to 48%[8a]).

Herein, we describe a novel short and efficient method for the synthesis of the two protected sugar lactone precursors of KDO and DAH. Our strategy involved the cyclization of a ketene dithioacetal as the sequence key step. Some years ago, during the course of our investigations on radical perfluoroalkylation of carbohydrate-derived ketene dithioacetals, we observed a spontaneous cyclization reaction of the ketene dithioacetal derived from diacetone D-mannose.[9] It was interesting to exploit and to optimize this reaction in order to develop a new strategy for the synthesis of 2-deoxylactones.

As previously described,[9] treatment of diacetone D-mannose with the lithium derivative of commercially available 2-trimethylsilyl-1,3-dithiane led directly, in one step,

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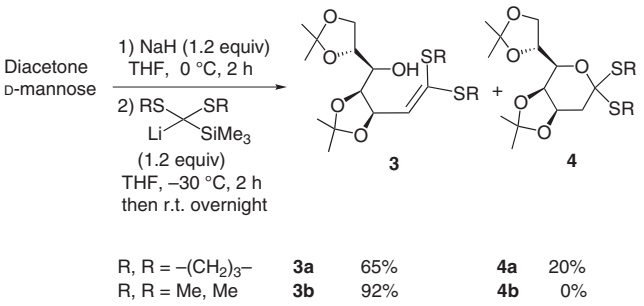
to the linear ketene dithioacetal **3a** in 65% yield. However, 20% of cyclized product **4a** was also isolated. Formation of **4a** during the purification step is due to the instability of **3a** over silica gel. On the other hand, with the lithio derivative of bis(methylsulfanyl)trimethylsilylmethane, the ketene dithioacetal **3b** was prepared and isolated in 92% yield without formation of **4b** (Scheme 2).

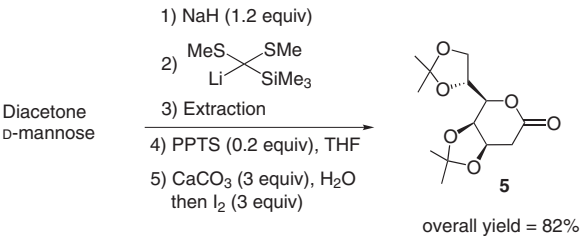


Scheme 2

Having observed the formation of the cyclized by-product **4a** during the purification step over silica gel, we were keen to study and develop suitable conditions to obtain this compound as the major product of the reaction. Cyclization of **3a** and **3b** was performed in very smooth acidic conditions using a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) in dichloromethane[10] at r.t. to give **4a** and **4b** in 89 and 76% yields, respectively. The lower yield obtained for **4b** is mainly due to the longer reaction time required, leading to a minor amount of lactone **5**. Finally, deprotection of the thioacetal group of **4a** and **4b** under classical conditions, using iodine in a buffered aqueous medium, allowed the formation of lactone **5** as precursor of KDO **2** in 91 and 93% yield, respectively (Scheme 3).

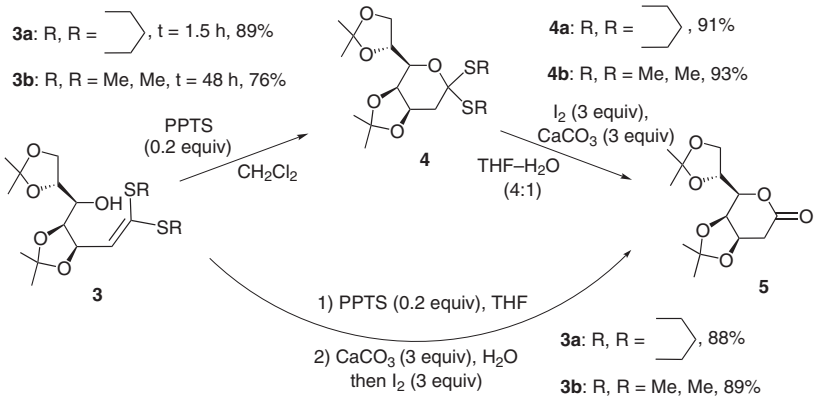
Interestingly, this reaction sequence can be performed in a 'one-pot' reaction. Treatment of ketene dithioacetals **3a** and **3b** with a catalytic amount of PPTS in THF followed by addition of excess calcium carbonate, water, and iodine gave directly lactone **5** with a 88–89% overall yield (Scheme 3).

The preparation of the key lactone **5** was then optimized and performed in a direct procedure from diacetone D-mannose. Compound **5** was obtained in an 82% overall yield by the sequence depicted in Scheme 4, without any intermediate purification.

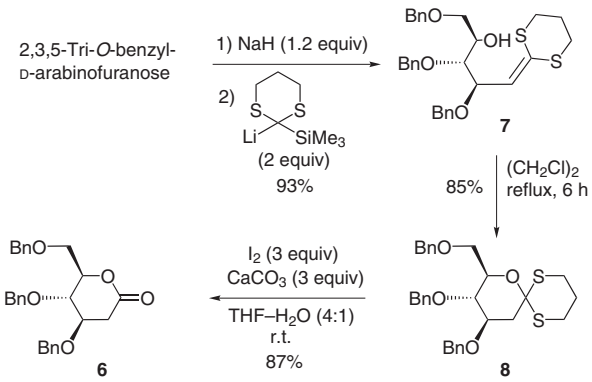


Scheme 4

The protected sugar lactone **6** as precursor of DAH (**1**) was previously prepared by oxidation of tri-*O*-benzyl-D-glucal using PCC.[11] The same reaction conditions as for ketene dithioacetals **3a** and **3b** were applied starting from the commercially available 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose. Surprisingly, results were disappointing and yields remained very low (less than 30%). After some attempts, we found that crystallization and co-evaporation from toluene of the commercial sugar and then its reaction with an excess (2 equiv) of lithium 2-trimethylsilyl-1,3-dithiane were required to obtain ketene dithioacetal **7** in very good yield (93%). However, cyclization of **7** under acidic conditions reported above led mainly to a decomposition of the starting material during the reaction. Unfortunately, the use of other acidic reaction conditions was unsuccessful. Finally, the cyclization of **7** was performed by heating it in dichloromethane or 1,2-dichloroethane. Under these reaction conditions, cyclized compound **8** was isolated in good yield (85%). Then, dethioacetalization was easily done under the previously described conditions affording **6** in 87% yield. After these three steps, the synthesis of lactone **6** was achieved in an overall yield of 69% (Scheme 5).



Scheme 3



Scheme 5

In summary, we have found a convenient and efficient synthesis of the lactones **5** and **6** as precursors for KDO (**2**) and DAH (**1**) from commercially available protected sugars. According to the reported conversions of lactones **5** and **6** into KDO (**2**) and DAH (**1**), this approach corresponds to a significant improvement of the synthesis of these two interesting compounds. This synthetic approach can be considered as a general method for the formation of 2-deoxysugar lactones with a one-carbon homologation.

All air- and moisture-sensitive reactions were carried out under argon. THF was distilled over Na/benzophenone and CH_2Cl_2 was distilled over CaH_2. All reported NMR spectra were recorded with a Bruker AC 250 spectrometer. Chemical shifts are reported as δ values relative to $CHCl_3$ peak defined at δ = 7.27 (^{1}H NMR) or δ = 77.00 (^{13}C NMR). IR spectra were recorded as film between NaCl plates or as KBr pellets on an AVATAR 320 FT-IR spectrometer. Mass spectra were obtained on a THERMOQUEST Trace GC 2000 Series instrument. Optical rotations were recorded using a Perkin-Elmer 241 polarimeter with a thermally jacketed 10 cm cell. Elementary analyses were taken on a Perkin-Elmer CHN 2400 elementary analysis instrument. Melting points were determined with a Büchi apparatus in open capillary tubes and are uncorrected. Analytical TLC was performed on Merck 60 PF_{254} silica gel pre-coated plates. Preparative flash silica gel chromatography was performed using Merck Kieselgel 60 (40–63 μm). All commercially available chemicals were used as received unless otherwise noted. Petroleum ether (PE) used refers to the fraction boiling at 40–60 °C.

The commercially available 2-trimethylsilyl-1,3-dithiane was purified by distillation (bp 78 °C/0.7 mbar).

2,3:4,5-Di-*O*-isopropylidene-α-D-mannofuranose (Diacetone D-Mannose)

Diacetone D-mannose was prepared according to the literature procedure.[9] Recrystallization: PE–EtOAc (95:5).

Yield: 70%; colorless solid; mp 124 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.33 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 1.46 (s, 6 H, 2 CH_3), 4.03 (d, 2 H, $^3J_{6,5} = {}^3J_{6',5} = 5.1$ Hz, H-6, H-6′), 3.98–4.08 (m, 1 H, OH), 4.13 (dd, 1 H, $^3J_{4,5} = 7.1$ Hz, $^3J_{4,3} = 3.6$ Hz, H-4), 4.37 (dt, 1 H, $^3J_{5,4} = 7.1$ Hz, $^3J_{5,6} = {}^3J_{5,6'} = 5.1$ Hz, H-5), 4.56 (d, 1 H, $^3J_{2,3} = 5.8$ Hz, H-2), 4.77 (dd, 1 H, $^3J_{3,2} = 5.8$ Hz, $^3J_{3,4} = 3.6$ Hz, H-3), 5.33 (d, 1 H, $^3J_{1,OH} = 2.5$ Hz, H-1).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 24.3 (CH_3), 25.0 (CH_3), 25.7 (CH_3), 26.6 (CH_3), 66.3 (C-6), 73.2 (C-5), 79.5 (C-3), 79.8 (C-4), 85.3 (C-2), 101.0 (C-1), 109.0 [$C(CH_3)_2$], 112.5 [$C(CH_3)_2$].

Bis(methylsulfanyl)trimethylsilylmethane

To a solution of bis(methylthio)methane (21.2 g, 196 mmol) in anhyd THF (100 mL) was added slowly a solution of *n*-BuLi 1.6 M (1.2 equiv, 146.9 mL) in *n*-hexane at –78 °C. The mixture was stirred for 4 h at –78 °C and chlorotrimethylsilane was added. The mixture was stirred overnight while the temperature was allowed to rise to r.t., and then extracted with petroleum ether. The organic extract was washed with brine and dried ($MgSO_4$). The crude product was purified by distillation; bp 42 °C/0.2 mbar; yield: 26.2 g (74%); colorless oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.18 [s, 9 H, $Si(CH_3)_3$], 2.16 (s, 6 H, SCH_3), 2.86 (s, 1 H, CH).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = –1.7 [$Si(CH_3)_3$], 14.9 (2 SCH_3), 41.6 (CH).

Ketene Dithioacetals 3a,b and 7; General Procedure

A solution of *n*-BuLi (1.2 equiv) in *n*-hexane was added dropwise to a solution of the silyl reagent (1 equiv for diacetone D-mannose, 2 equiv for D-arabinose derivative) in anhyd THF (2 mL/mmol) at low temperature [–30 °C for the 2-trimethylsilyl-bis(methylthio)methane, 0 °C for the 2-trimethylsilyl-1,3-dithiane]. The resulting mixture was stirred for 2 h between 0 and –30 °C and was stabilized at 0 °C before being slowly added to a prepared solution of diacetone D-mannose [addition of a solution of protected sugar (1 equiv) in THF (1.2 mL/mmol) to a suspension of NaH (1.2 equiv) in THF (20 mL) at 0 °C and stirring for 2 h]. The mixture was stirred overnight while the temperature was allowed to rise to r.t. This mixture was then poured into sat. aq solution of NH_4Cl and extracted with Et_2O. The combined organic layers were washed with brine and dried ($MgSO_4$). After removal of the solvent, the crude product was submitted to flash chromatography over silica gel to give the pure ketene dithioacetal. A few drops of Et_3N could be added to the pure product to avoid its cyclization during storage.

2-(1′-Deoxy-2′,3′:5′,6′-di-*O*-isopropylidene-D-mannit-1-ylidene)-1,3-dithiane (3a)

Flash chromatography: PE–EtOAc (80:20).

Yield: 4.54 g (65%); colorless solid; mp 73 °C; $[\alpha]_D^{25}$ –80.3 (*c* 0.57, $CHCl_3$).

IR (KBr): 3491 (OH), 1585, 1115, 1053, 839 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.36 (s, 3 H, CH_3), 1.42 [s, 6 H, $C(CH_3)_2$], 1.52 (s, 3 H, CH_3), 2.13 (d, 1 H, $^3J_{4',OH} = 8.2$ Hz, OH), 2.20 (quint, 2 H, $^3J_{H,H} = 5.0$ Hz, CH_2 dithiane), 2.70–3.10 (m, 4 H, 2 SCH_2), 3.39 (ddd, 1 H, $^3J_{4',5'} = 8.8$ Hz, $^3J_{4',OH} = 8.2$ Hz, $^3J_{4',3'} = 1.2$ Hz, H-4′), 3.90–4.10 (m, 3 H, H-5′, H-6′, H-6″), 4.39 (dd, 1 H, $^3J_{3',2'} = 7.6$ Hz, $^3J_{3',4'} = 1.2$ Hz, H-3′), 5.29 (dd, 1 H, $^3J_{2',1'} = 8.1$ Hz, $^3J_{2',3'} = 7.6$ Hz, H-2′), 6.13 (d, 1 H, $^3J_{1',2'} = 8.1$ Hz, H-1′).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 24.8 (CH_2 dithiane), 24.9 (CH_3), 25.8 (CH_3), 27.1 (CH_3), 27.3 CH_3), 29.6 (SCH_2), 29.9 (SCH_2), 67.2 (C-6′), 70.8 (C-4′), 74.8 (C-2′), 76.6 (C-5′), 76.8 (C-3′), 108.4 [$C(CH_3)_2$], 109.1 [$C(CH_3)_2$], 126.4 (CH=), 134.1 [=C(SR)$_2$].

MS (EI): *m*/*z* (%) = 362 [M$^+$], 347, 273, 174, 145 (100).

Anal. Calcd for $C_{16}H_{26}O_5S_2$ (362.51): C, 53.01; H, 7.23. Found: C, 53.32; H, 7.09.

1,2-Dideoxy-1,1-bis(methylsulfanyl)-3,4:6,7-di-*O*-isopropylidene-D-*manno*-hept-1-enitol (3b)

Flash chromatography: PE–EtOAc (80:20).

Yield: 2.42 g (92%); colorless oil; $[\alpha]_D^{22}$ –105.0 (*c* 0.50, $CHCl_3$).

IR (film): 3535 (OH), 2986, 1584 (C=C), 1372, 1213, 757 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.35 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 1.53 (s, 3 H, CH_3), 2.14 (d, 1 H, $^3J_{OH,5} = 8.6$ Hz, OH), 2.34 (s, 3 H, SCH_3), 2.37 (s, 3 H, SCH_3), 3.34

(m, 1 H, H-5), 3.90–4.10 (m, 3 H, H-7, H-7′, H-6), 4.43 (dd, 1 H, $^3J_{4,3}$ = 7.9 Hz, $^3J_{4,5}$ = 1.1 Hz, H-4), 5.44 (t, 1 H, $^3J_{3,2}$ = $^3J_{3,4}$ = 7.9 Hz, H-3), 5.91 (d, 1 H, $^3J_{2,3}$ = 7.9 Hz, H-2).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 16.6 (SCH_3), 17.1 (SCH_3), 24.3 (CH_3), 25.2 (CH_3), 26.5 (CH_3), 26.8 (CH_3), 66.7 (C-7), 70.4 (C-6), 75.5 (C-3), 76.1 (C-4), 76.5 (C-5), 108.3 [*C*(CH_3)$_2$], 109.2 [*C*(CH_3)$_2$], 125.7 (CH=), 138.7 [=*C*(SMe)$_2$].

MS (EI): *m*/*z* (%) = 350 [M$^+$], 303, 277, 162, 133 (100), 101.

Anal. Calcd for $C_{15}H_{26}O_5S_2$ (350.50): C, 51.40; H, 7.48. Found: C, 51.62; H, 7.46.

2-(1′-Deoxy-2′,3′,5′-tri-*O*-benzyl-D-arabinit-1-ylidene)-1,3-dithiane (7)

2,3,5-Tri-*O*-benzyl-β-D-arabinofuranose was dried by recrystallization from a mixture of PE–EtOAc (95:5), followed by co-evaporation with toluene. The reaction with D-arabinose derivative required the use of 2 equiv of silyl reagent and *n*-BuLi. Flash chromatography: PE–EtOAc (80:20).

Yield: 1.05 g (83%); colorless oil; [α]$_D^{23}$ –39.1 (*c* 0.55, $CHCl_3$).

IR (film): 3468 (OH), 3029, 2911, 1578, 1454 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.10–2.20 (m, 2 H, CH_2 dithiane), 2.70–2.80 (m, 1 H, SCH_2), 2.80–2.95 (m, 4 H, 3 H of SCH_2 and OH), 3.55–3.60 (m, 3 H, H-3′, H-5′, H-5″), 3.95–4.05 (m, 1 H, H-4′), 4.39 (d, 1 H, $^2J_{H,H}$ = 11.8 Hz, OCH_2), 4.45–4.55 (m, 4 H, 2 OCH_2), 4.63 (d, 1 H, $^2J_{H,H}$ = 11.6 Hz, OCH_2), 4.74 (dd, 1 H, $^3J_{2',1'}$ = 9.1 Hz, $^3J_{2',3'}$ = 3.8 Hz, H-2′), 6.03 (d, $^3J_{1',2'}$ = 9.1 Hz, H-1′), 7.27–7.31 (m, 15 H_{arom}).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 24.5 (CH_2 dithiane), 29.3 (SCH_2), 29.7 (SCH_2), 70.5 (C-4′), 70.9 (OCH_2), 71.2 (C-5′), 73.4 (OCH_2), 74.1 (OCH_2), 75.5 (C-2′), 80.4 (C-3′), 127.6–128.6 (15 CH_{arom}), 128.8 (CH=), 133.1 [=*C*(SR)$_2$], 138.5 (3 C_{arom}).

Anal. Calcd for $C_{30}H_{34}O_4S_2$ (522.72): C, 68.93; H, 6.56. Found: C, 68.56; H, 6.86.

Dithioortho Esters 4a,b; General Procedure

To a solution of the ketene dithioacetal **3a**,**b** (0.55 mmol) in anhyd CH_2Cl_2 (2.5 mL) was added pyridinium *p*-toluenesulfonate (PPTS, 0.11 mmol, 0.2 equiv). The resulting mixture was stirred (1.5 h for **3a** and 48 h for **3b**) at r.t. and extracted with Et_2O. The Et_2O extract was washed with aq $NaHCO_3$, brine and dried ($MgSO_4$). After removal of the solvent, the crude product was purified by flash chromatography.

1,2-Dideoxy-3,4:6,7-di-*O*-isopropylidene-1,1-dithianyl-D-*manno*-heptopyranose (4a)

Flash chromatography: PE–EtOAc (85:15).

Yield: 177 mg (89%); colorless solid; mp 81 °C; [α]$_D^{22}$ +110.2 (*c* 0.55, $CHCl_3$).

IR (KBr): 2992, 1458, 1375, 1243 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.36 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 1.97 (dtt, 1 H, $^2J_{2'ax,2'eq}$ = 14.0 Hz, $^3J_{2'ax,1'ax}$ = $^3J_{2'ax,3'ax}$ = 12.8 Hz, $^3J_{2'ax,3'eq}$ = 3.1 Hz, $^3J_{2'ax,1'eq}$ = 3.0 Hz, H-2′*ax*), 2.04 (dd, 1 H, $^2J_{2a,2b}$ = 14.3 Hz, $^3J_{2a,3}$ = 7.9 Hz, H-2a), 2.13 (dquint, 1 H, $^2J_{2'eq,2'ax}$ = 14.0 Hz, $^3J_{2'eq,1'ax}$ = $^3J_{2'eq,1'eq}$ = $^3J_{2'eq,3'ax}$ = $^3J_{2'eq,3'eq}$ = 2.8 Hz, H-2′*eq*), 2.16 (dd, 1 H, $^2J_{2b,2a}$ = 14.3 Hz, $^3J_{2b,3}$ = 6.0 Hz, H-2b), 2.60 (dt, 1 H, $^2J_{1'eq,1'ax}$ = 14.0 Hz, $^3J_{1'eq,2'ax}$ = $^3J_{1'eq,2'eq}$ = 3.0 Hz, H-1′*eq*), 2.66 (dt, 1 H, $^2J_{3'eq,3'ax}$ = 14.0 Hz, $^3J_{3'eq,2'ax}$ = $^3J_{3'eq,2'eq}$ = 3.1 Hz, H-3′*eq*), 3.00 (ddd, 1 H, $^2J_{1ax,1'eq}$ = 14.0 Hz, $^3J_{1'ax,2'ax}$ = 12.8 Hz, $^3J_{1'ax,2'eq}$ = 2.6 Hz, H-1′*ax*), 3.40 (ddd, 1 H, $^2J_{3'ax,3'eq}$ = 14.0 Hz, $^3J_{3'ax,2'ax}$ = 12,8 Hz, $^3J_{3'ax,2'eq}$ = 2.7 Hz, H-3′*ax*), 3.97 (dd, 1 H, $^3J_{5,6}$ = 7.4 Hz, $^3J_{5,4}$ = 2.3 Hz, H-5), 4,08 (dd, 1 H, $^2J_{7a,7b}$ = 8.6 Hz, $^3J_{7a,6}$ = 5.1 Hz, H-7a), 4.16 (dd, 1 H, $^2J_{7b,7a}$ = 8.6 Hz, $^3J_{7b,6}$ = 6.2 Hz, H-7b), 4.20 (dd, $^3J_{4,3}$ = 5.9 Hz, $^3J_{4,5}$ = 2.3 Hz, H-4), 4.45 (ddd, 1 H, $^3J_{6,5}$ = 7.4 Hz, $^3J_{6,7b}$ = 6.2 Hz, $^3J_{6,7a}$ = 5.1 Hz, H-6), 4.48 (ddd, 1 H, $^3J_{3,2a}$ = 7.9 Hz, $^3J_{3,2b}$ = 6.0 Hz, $^3J_{3,4}$ = 5.9 Hz, H-3).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 24.6 (CH_2), 25.5 (CH_3), 26.1 (CH_3), 26.2 (SCH_2), 26.9 (CH_3), 27.0 (SCH_2), 27.7 (CH_3), 39.5 (C-2), 66.8 (C-7), 69.9 (C-3), 71.0 (C-4), 72.0 (C-5), 74.3 (C-6), 85.6 (C-1), 109.2 [*C*(CH_3)$_2$], 109.3 [*C*(CH_3)$_2$].

MS (EI): *m*/*z* (%) = 362 [M$^+$], 347, 289, 273, 106, 58 (100).

Anal. Calcd for $C_{16}H_{26}O_5S_2$ (362.51): C, 53.01; H, 7.23. Found: C, 53.09; H, 7.13.

1,2-Dideoxy-3,4:6,7-di-*O*-isopropylidene-1,1-bis(methylsulfanyl)-D-*manno*-heptopyranose (4b)

Flash chromatography: PE–EtOAc (90:10).

Yield: 168 mg (76%); colorless oil; [α]$_D^{23}$ +134.0 (*c* 0.57, $CHCl_3$).

IR (film): 2985, 1455, 1370, 1058, 510 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.36 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 2.09 (s, 3 H, SCH_3), 2.14 (s, 3 H, SCH_3), 2.15 (dd, 1 H, $^2J_{2a,2b}$ = 14.6 Hz, $^3J_{2a,3}$ = 6.1 Hz, H-2a), 2.35 (dd, 1 H, $^2J_{2b,2a}$ = 14.6 Hz, $^3J_{2b,3}$ = 7.8 Hz, H-2b), 4.03 (dd, 1 H, $^2J_{7a,7b}$ = 8.8 Hz, $^3J_{7a,6}$ = 5.1 Hz, H-7a), 4.05 (dd, 1 H, $^3J_{5,6}$ = 6.3 Hz, $^3J_{5,4}$ = 2.3 Hz, H-5), 4.10 (dd, 1 H, $^2J_{7b,7a}$ = 8.8 Hz, $^3J_{7b,6}$ = 6.3 Hz, H-7b), 4.17 (dd, 1 H, $^3J_{4,3}$ = 6.1 Hz, $^3J_{4,5}$ = 2.3 Hz, H-4), 4.38 (dt, 1 H, $^3J_{6,7b}$ = $^3J_{6,5}$ = 6.3 Hz, $^3J_{6,7a}$ = 5.1 Hz, H-6), 4.46 (dt, 1 H, $^3J_{3,2}$ = 7.8 Hz, $^3J_{3,2'}$ = $^3J_{3,4}$ = 6.1 Hz, H-3).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 11.6 (SCH_3), 13.1 (SCH_3), 25.5 (CH_3), 26.0 (CH_3), 26.8 (CH_3), 27.9 (CH_3), 38.4 (C-2), 66.5 (C-7), 70.6 (C-3, C-4), 71.6 (C-5), 74.5 (C-6), 93.5 (C-1), 109.1 [*C*(CH_3)$_2$], 109.1 [*C*(CH_3)$_2$].

MS (EI): *m*/*z* (%) = 349 [M$^+$ – 1], 302, 287, 229, 169, 114 (100).

Anal. Calcd for $C_{15}H_{26}O_5S_2$ (350.50): C, 51.40; H, 7.48. Found: C, 51.41; H, 7.34.

1,2-Dideoxy-3,4,5-tri-*O*-benzyl-1,1-dithianyl-D-*arabino*-hexopyranose (8)

A solution of the ketene dithioacetal **7** (200 mg, 0.38 mmol) in 1,2-dichloroethane (10 mL) was refluxed for 3 h. After cooling, the solvent was evaporated in vacuo. The crude residue was chromatographed over silica gel to give pure dithioortho ester **8**. Flash chromatography: PE–EtOAc (90:10).

Yield: 170 mg (85%); colorless oil; [α]$_D^{22}$ +83.9 (*c* 0.53, $CHCl_3$).

IR (film): 2913, 1605, 1586, 1496, 1453 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.76–1.90 (m, 1 H, H-2a), 1.84 (m, 1 H, $^2J_{2'ax,2'eq}$ = 14.0 Hz, H-2′*ax*), 2.01 (m, 1 H, $^2J_{2'eq,2'ax}$ = 14.0 Hz, H-2′*eq*), 2.46 (m, 1 H, H-1′*eq*), 2.49 (dd, 1 H, $^2J_{2b,2a}$ = 13.2 Hz, $^3J_{2b,3}$ = 5.2 Hz, H-2b), 2.59 (m, 1 H, $^2J_{3'eq,3'ax}$ = 14.0 Hz, H-3′eq), 2.93 (ddd, 1 H, $^2J_{1'ax,1'eq}$ = 14.0 Hz, $^3J_{1'ax,2'eq}$ = 2.5 Hz, H-1′*ax*), 3.42 (t, 1 H, $^3J_{4,3}$ = $^3J_{4,5}$ = 9.5 Hz, H-4), 3.43 (ddd, 1 H, $^2J_{3'ax,3'eq}$ = 14.0 Hz, H-3′*ax*), 3.69 (d, 2 H, $^3J_{6a,5}$ = $^3J_{6b,5}$ = 9.5 Hz, H-6a, H-6b), 3.92–4.00 (m, 2 H, H-3, H-5), 4.47–4.60 (m, 5 H, 3 CH_2O), 4.82 (d, 1 H, $^2J_{H,H}$ = 10.9 Hz, CH_2O), 7.19–7.28 (m, 15 H_{arom}).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 25.2 (CH_2 dithiane), 25.8 (CH_2 dithiane), 27.4 (CH_2 dithiane), 42.5 (C-2), 69.3 (*C*H_2Ph), 71.9 (*C*H_2Ph), 73.2 (*C*H_2Ph), 74.7 (CH), 74.9 (C-6), 77.1 (CH), 78.5 (CH), 86.0 (C-1), 127.5–128.4 (15 CH_{arom}), 138.1–138.6 (C_{arom}).

Anal. Calcd for $C_{30}H_{34}O_4S_2$ (522.72): C, 68.93; H, 6.56. Found: C, 68.71; H, 6.94.

Lactones 5 and 6; General Procedure

$CaCO_3$ (0.83 mmol, 3 equiv) and I_2 (0.83 mmol, 3 equiv) were added successively to a solution of the dithioortho ester (0.28 mmol) in a mixture of THF–H_2O (4:1, 5 mL). The mixture was stirred at r.t.

until the disappearance of the starting material (1.5 h for **4a**,**b** and 3 h for **8**). The residue was diluted with Et_2O and the excess I_2 was reduced by the addition of sat. aq $Na_2S_2O_3$ solution. The aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$). After removal of the solvent, the crude product was purified by silica gel chromatography (PE–EtOAc) to give the pure lactones.

2-Deoxy-3,4:6,7-di-*O*-isopropylidene-D-*manno*-heptono-1,5-lactone (5)

Flash chromatography: PE–EtOAc (60:40).

Yield: 69 mg (91% from **4a**), 69 mg (93% from **4b**); colorless solid; mp 121 °C; $[\alpha]_D^{22}$ +64.0 (*c* 0.54, $CHCl_3$) {Lit.[8a] $[\alpha]_D^{20}$ +64.0 (*c* 0.9, $CHCl_3$)}.

IR (KBr): 2994, 1752 (C=O), 1377, 1076, 839 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.37 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 2.52 (dd, 1 H, $^2J_{2a,2b}$ = 15.9 Hz, $^3J_{2a,3}$ = 3.5 Hz, H-2a), 2.90 (dd, 1 H, $^2J_{2b,2a}$ = 15.9 Hz, $^3J_{2b,3}$ = 2.1 Hz, H-2b), 3.92 (dd, 1 H, $^3J_{5,6}$ = 8.4 Hz, $^3J_{5,4}$ = 1.6 Hz, H-5), 4.09 (dd, 1 H, $^2J_{7a,7b}$ = 9.3 Hz, $^3J_{7a,6}$ = 5.8 Hz, H-7a), 4.16 (dd, 1 H, $^2J_{7b,7a}$ = 9.3 Hz, $^3J_{7b,6}$ = 4.0 Hz, H-7b), 4.37 (ddd, 1 H, $^3J_{6,5}$ = 8.4 Hz, $^3J_{6,7a}$ = 5.8 Hz, $^3J_{6,7b}$ = 4.0 Hz, H-6), 4,61 (dd, 1 H, $^3J_{4,3}$ = 7.8 Hz, $^3J_{4,5}$ = 1.6 Hz, H-4), 4.77 (ddd, 1 H, $^3J_{3,4}$ = 7.8 Hz, $^3J_{3,2'}$ = 3.5 Hz, $^3J_{3,2}$ = 2.1 Hz, H-3).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 24.1 (CH_3), 24.9 (CH_3), 25.8 (CH_3), 26.0 (CH_3), 34.6 (C-2), 66.6 (C-7), 71.1 (C-3), 71.3 (C-4), 72.7 (C-6), 77.7 (C-5), 109.7 [$C(CH_3)_2$], 109.7 [$C(CH_3)_2$], 168.8 (C=O).

MS (EI): *m*/*z* (%) = 273 [M^+ + 1], 259, 257, 157, 115, 101 (100).

Anal. Calcd for $C_{13}H_{20}O_6$ (272.29): C, 57.34; H, 7.40. Found: C, 56.95; H, 7.04.

2-Deoxy-3,4,6-tri-*O*-benzyl-D-*arabino*-hexono-1,5-lactone (6)

Flash chromatography: PE–EtOAc (80:20).

Yield: 72 mg (87% from **8**); colorless solid; mp 83–84 °C; $[\alpha]_D^{22}$ +48.0 (*c* 0.26, EtOH) {Lit.[11b] $[\alpha]_D$ +48.0 (*c* 1.0, EtOH) and Lit.[11a] $[\alpha]_D$ +47.0 (*c* 0.65, EtOH)}.

IR (KBr): 2890, 1745 (C=O), 1604, 1496, 1452, 734 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.76 (dd, 1 H, $^2J_{2a,2b}$ = 16.3 Hz, $^3J_{2a,3}$ = 5.4 Hz, H-2a), 2.86 (dd, 1 H, $^2J_{2b,2a}$ = 16.3 Hz, $^3J_{2b,3}$ = 4.3 Hz, H-2b), 3.71 (d, 2 H, $^3J_{6,5}$ = 4.0 Hz, H-6a, H-6b), 3.89 (dd, 1 H, $^3J_{4,3}$ = 7.1 Hz, $^3J_{4,5}$ = 4.3 Hz, H-4), 3.94 (ddd, 1 H, $^3J_{3,4}$ = 7.1 Hz, $^3J_{3,2a}$ = 5.4 Hz, $^3J_{3,2b}$ = 4.3 Hz, H-3), 4.30 (dt, 1 H, $^3J_{5,4}$ = 4.3 Hz, $^3J_{5,6a}$ = $^3J_{5,6b}$ = 4.0 Hz, H-5), 4.32–4.56 (m, 6 H, 3 CH_2O), 7.21–7.36 (m, 15 H_{arom}).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 33.8 (C-2), 68.8 (C-6), 71.1 (CH_2), 72.9 (CH_2), 73.5 (CH_2), 74.7 (C-3), 75.1 (C-4), 79.3 (C-5), 127.7–128.5 (15 CH_{arom}), 137.3 (2 C_{arom}), 137.7 (C_{arom}), 169.4 (C=O).

Anal. Calcd for $C_{27}H_{28}O_5$ (432.51): C, 74.98; H, 6.53. Found: C, 74.68; H, 6.73.

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