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Synthesis of 3-Deoxy-α-D-*manno*-oct-2-ulosonic Acid Glycoside (Kdo) and Its 2-Deoxy Analogue: A Horner–Emmons Approach†

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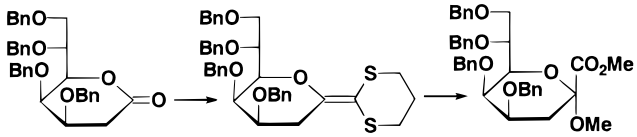
ABSTRACT



A very simple and potentially valuable synthetic approach to 3-deoxy-α-D-*manno*-oct-2-ulosonic acid glycoside is described. The key reaction in the synthesis is the construction of ketene dithioacetal from the corresponding 2-deoxy-D-*manno*-heptono-1,5-lactone and 1,3-dithianyl anion. The synthesis ends with a tandem oxidative hydrolysis of the dithianyl group/glycosylation process.

3-Deoxy-α-D-*manno*-oct-2-ulosonic acid glycoside (Kdo) is a component of all lipopolysaccharides (LPS) of Gram-negative bacteria playing a central role in their growth.[1] It occours also in many acidic exopolysaccharides (K-antigens) located at the cell surface of the bacteria[2] as well as in cell walls of plants.[3] Therefore, Kdo has generated considerable interest in its synthesis,[1,4] and it is still a current topic of research investigations.[5]

During the course of our synthetic studies toward ulosonic acids[6] we have reported on a unique stereocontrolled approach to the isomeric 3-deoxy-hept-2-ulosonic acids based on the reaction of sugar lactones with the 1,3-dithianyl anion

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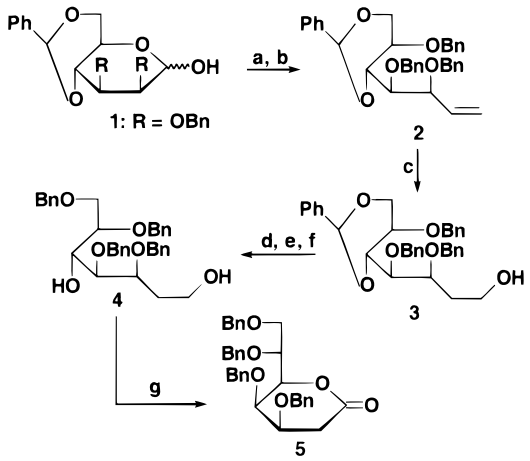
Scheme 1[a]



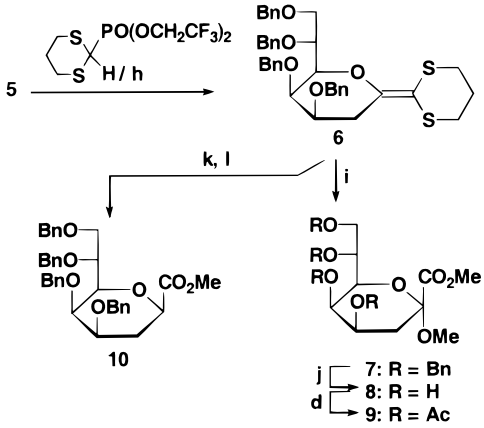
[a] (a) $Me_2PhSiCH_2MgCl$, THF, 90 °C; (b) KH, THF, 60 °C, then BnBr, rt; (c) 9-BBN, THF, then, H_2O_2 30%, $NaOH_{aq}$; (d) Ac_2O, Py; (e) TES, TFA, CH_2Cl_2, rt; (f) K_2CO_3, MeOH, rt; (g) PCC, dichloroethane, 60 °C.

to create ketene thioacetals as key intermediates.[7] In this Letter, we describe our synthetic design for the glycoside of 3-deoxy-α-D-*manno*-oct-2-ulosonic acid (Kdo) and its 2-deoxy analogue. A major problem for this synthesis is the efficient construction of the *O*-benzyl-protected 2-deoxy-D-*manno*-heptono-1,5-lactone moiety. The known 3,4:6,7-di-*O*-isopropylidene derivative[4o] was not suitable for the reaction with the 1,3-dithianyl anion due to its steric rigidity.[7]

Scheme 1 illustrates the synthesis of the required lactone **5** from the mannose **1**[8] using for the elongation reaction a protocol similar to that developed by Nicotra et al.[9] Modifying their procedure we applied $Me_2PhSiCH_2MgCl$ as the most convenient Grignard reagent. Addition of this reagent to **1** gave the intermediate silyl derivative as a mixture of two separable isomers. These, without separation, underwent an elimination reaction with KH to afford the sole product. Its sequential benzylation provided the terminal olefin **2**.[10] The stage was now set for a terminal hydroxylation. This was succeeded by the standard reaction with 9-BBN to give the alcohol **3**.[11] Attempted direct conversion of **3** into **4** was unsuccessful. Therefore, **3** was first acetylated and then 5-OH was regioselectively deprotected using a TES−TFA mixture.[12] Subsequent hydrolysis of the acetyl residue furnished the diol **4**.[13] Finally, **4** was cyclized to the lactone **5** in nearly quantitative yield, employing PCC as a reagent.[14]

The elaboration of the *O*-benzyl-protected lactone **5** into the required Kdo **7** is shown in Scheme 2. Formation of the

Scheme 2[a]



[a] (h) KHMDS, THF, −78 °C/rt; (i) NBS, MeOH, CH_2Cl_2, rt; (j) Pd−C, H_2, EtOH; (k) $LiBH_4$, TMSCl, THF, 50 °C; (l) NBS, THF_{aq}, rt, then CH_2N_2, Et_2O.

ketene dithioacetal **6** was best achieved using a Horner−Emmons reaction, with 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]-1,3-dithiane[15] as a reagent.

Presumably, the strong electron-withdrawing character of the trifluoroethoxy substituent enhances the elimination step of the Horner−Emmons reaction, thus avoiding a comparative elimination process in the carbohydrate ring.[7] To generate the dithianyl anion, potassium bis(trimethylsilyl)-amide was used, according to the previously described procedure.[7] Addition of **5** at −78 °C (1.0 mmol scale), then

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(10) To a stirred suspension of magnesium (390 mg, 16.05 mmol) with a few crystals of sublimate in dry tetrahydrofuran (25 mL) was added dropwise (chloromethyl)dimethylphenylsilane (2.96 mL, 16.05 mmol) under reflux. After the Grignard reagent formation was complete (the appearance of the dark-graphite color of the mixture), a solution of mannose **1** (2.4 g, 5.35 mmol) in dry THF was added and the mixture was refluxed for 3−4 h. The reaction mixture was diluted with ethyl ether and quenched with a saturated aqueous solution of NH_4Cl and brine. After drying and evaporation of the solvents, column chromatography (hexane−ether, 1:1) gave an intermediate silyl derivative (two separable isomers; HR-MS (LSIMS) calcd for $C_{36}H_{42}O_6Si$ $[M + Na]^+$ 621.2648 found 621.2654). Both addition products (∼2 g) were dissolved in dry THF (20 mL) and treated with an excess of potassium hydride (∼13.4 mmol suspension in mineral oil) at 0 °C. The solution was stirred for 1 h at 50 °C (TLC). The reaction mixture was then recooled to 0 °C, and benzyl bromide (0.83 mL, 7 mmol) was added dropwise. After 1 h at room temperature the mixture was diluted with ethyl ether, and methanol was cautiously added, followed by washing with brine. Evaporation of solvents left a syrup which after column chromatography (hexane−ether, 5:1) afforded **2** (1.75 g, 62%) as a colorless syrup: $[\alpha]_D$ −30.3 (*c* 1.08); ^1H NMR (200 MHz, $CDCl_3$) δ 3.64 (t, 1H, J = 10.3 Hz), 3.90 (m, 1H), 4.10−4.50 (m, 4H), 4.50−4.80 (3 × ABq, 3 × 2H, CH_2Ph), 5.24−5.56 (m, 2H, H-1a, H-1b), 5.35 (s, 1H, benzylidene), 5.80−6.06 (m, 1H, H-2), 7.15−7.50 (m, 20H, Ar); HR-MS (LSIMS) calcd for $C_{35}H_{36}O_5$ $[M + Na]^+$ 559.2460, found 559.2476.

(11) To a solution of **2** (1.7 g, 3.17 mmol) in dry THF (20 mL) was added dropwise 9-BBN (20 mL, ∼0.5 M solution in THF, 9.5 mmol) at room temperature. The mixture was stirred for 5 h at room temperature and then diluted with tetrahydrofuran (30 mL); 30% H_2O_2 was then added (30 mL) at 0 °C, followed by aqueous NaOH 4% (30 mL). The reaction mixture was warmed to room temperature and stirred for 1 h, then diluted with $CHCl_3$, washed with water, and dried. Removal of the solvents under reduced pressure and chromatography of the residue (hexane−ether, 1:1) afforded **3** (1.0 g, 57%) as a colorless syrup: $[\alpha]_D$ −11.5 (*c* 1.60); ^1H NMR (200 MHz, $CDCl_3$) δ 1.85−2.15 (m, 2H, H-2a, H-2b), 3.64 (t, 1H, J = 9.9 Hz), 3.75 (m, 1H), 3.82−4.10 (m, 6H), 4.42−4.85 (3 × ABq, 3 × 2H, CH_2Ph), 5.42 (s, 1H, benzylidene), 7.20−7.50 (m, 20H, Ar). Anal. Calcd for $C_{35}H_{38}O_6$ [554.68]: C, 75.79; H, 6.91. Found: C, 75.69; H, 6.90.

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mainting the reaction mixture at room temperature for about 3 h afforded, after usual workup ketene dithioacetal **6** in 71% yield.[16]

A tandem oxidative hydrolysis of the dithianyl group/glycosylation reaction by NBS−MeOH in CH_2Cl_2 provided the glycoside of the Kdo derivative **7** in 91% yield, with full stereoselectivity.[17] The benzyl residues were readily removed by hydrogenolysis to give **8**.[18] The NMR spectra of *O*-acetyl derivative **9**[19] were similar to those reported by Unger.[20]

Conversion of **6** to the 2-deoxy-Kdo derivative **10** required three operations: (i) reduction of the olefinic linkage in **6** ($LiBH_4$−TMSCl), (ii) oxidative hydrolysis of the 1,3-dithianyl residue (NBS−THF−H_2O), (iii) esterification of the resulting carboxyl function (CH_2N_2 in Et_2O). The 2-deoxy-Kdo derivative **10**[21] was isolated as the sole product. Its structure was confirmed by NMR data comparable to those of an analogous benzyl derivative of 2-deoxy-D-*lyxo*-heptulosonic acid methyl ester.[7]

In summary, we have succeeded in the preparation of a fully protected *O*-benzyl 2-deoxy-D-*manno*-heptono-1,5-lactone, utilized in the unique two-step synthesis of the methyl glycoside of Kdo. This approach may have value for the synthesis of disaccharides and other more complex glycosides by analogy to the preparation of α-glycosides/disaccharides of 3-deoxy-D-*lyxo*-hept-2-ulosonic acid.[22]

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(13) Compound **3** (1.5 g, 2.70 mmol) was acetylated in the usual way at room temperature with an Ac_2O−Py system. After evaporation of the reagents with toluene, the resulting acetate was dissolved in CH_2Cl_2 (10 mL). Triethylsilane (2.0 mL, 12.55 mmol) and then trifluoroacetic acid (0.86 mL, 11.3 mmol) were added dropwise at 0 °C. 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. The solvents were evaporated, and the residue was filtered through a short column of silica gel. The crude product dissolved in methanol (10 mL) was stirred with an excess of K_2CO_3 at room temperature for 30 min. The reaction mixture was filtered through Celite and then through a column of silica gel to give **4** (780 mg, 52%): mp 49 °C; $[\alpha]_D$ −20.3 (*c* 0.62); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.90−2.10 (m, 3H, H-2a, H-2b, OH), 3.12 (d, 1H, J = 5.9 Hz, OH), 3.60−3.98 (m, 8H), 4.32−4.79 (4 × ABq, 4 × 2H, C*H*$_2$Ph), 7.20−7.50 (m, 20H, Ar); HR-MS (LSIMS) calcd for $C_{35}H_{40}O_6$ $[M + Na]^+$ 579.2723, found 579.2743.

(14) A mixture of PCC (700 mg, 3.24 mmol) and heptitol **5** (450 mg, 0.81 mmol) was stirred in 1,2-dichloroethane (20 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 **5** in almost quantitative yield (440 mg) as an oil: $[\alpha]_D$ −4.2 (*c* 1.09); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.90 (dd, 1H, J = 7.17, 17.8 Hz, H-2eq), 2.96 (dd, 1H, J = 10.8, 17.7 Hz, H-2ax), 3.70 (dd, 1H, J = 3.5, 10.8 Hz, H-7a), 3.85 (dd 1H, J = 2.01, 10.9 Hz, H-7b), 3.89−3.94 (m, 2H, H-3, H-6), 4.36 (dd, 1H, J = 1.5, 9.3 Hz, H-5), 4.39 (bs, 1H, H-4), 4.35−5.07 (4 × ABq, 4 × 2H, C*H*$_2$Ph), 7.23−7.36 (m, 20H, Ar); ^{13}C NMR ($CDCl_3$) δ 33.1, 67.4, 70.3, 70.8, 71.8, 73.5, 74.0, 74.8, 75.5, 76.3, 127.3−128.6 and 137.3−138.3 (Ar), 169.0; HR-MS (LSIMS) calcd for $C_{35}H_{36}O_6$ $[M + Na]^+$ 575.2410, found 575.2455.

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(16) A solution of potassium bis(trimethylsilyl)amide (1.8 mL, 0.90 mmol ~0.5 M solution in toluene) was added dropwise to 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]-1,3-dithiane (330 mg, 0.9 mmol) dissolved in anhydrous THF (5 mL) at −78 °C under Ar. The temperature was maintained at −78 °C for 1 h, and then a solution of **5** (250 mg, 0.45 mmol) in THF (1−2 mL) was added dropwise. The reaction was stirred for ~3 h while the temperature was allowed to rise to room temperature. The reaction was neutralized with TFA, and the crude product was purified by flash chromatography (hexane−ether, 4:1) to give 215 mg of **6** (72%): $[\alpha]_D$ +61.4 (*c* 0.70); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.12−2.17 (m, 2H, H-2′ax, H-2′eq), 2.63 (dd, 1H, J = 11.0, 13.9 Hz, H-3ax), 2.75−2.90 (m, 4H, H-1′ax, H-1′eq, H-3′ax, H-3′eq), 3.37 (ddd, 1H, J = 0.8, 5.0, 14.0 Hz, H-3eq), 3.69 (ddd, 1H, J = 2.1, 5.0, 11.9 Hz, H-4), 3.74 (d 1H, J = 9.5 Hz, H-6), 3.84 (dd, 1H, J = 4.2, 10.7 Hz, H-8a), 4.00−4.05 (m, 2H, H-7, H-8b), 4.27 (bs, 1H, H-5), 4.41−5.11 (4×ABq, 4 × 2H, C*H*$_2$Ph), 7.25−7.40 (m, 20H, Ar); ^{13}C NMR ($CDCl_3$) δ 25.58, 27.9, 29.6, 30.2, 69.1, 70.4, 72.0, 72.1, 73.5, 74.0, 76, 0, 76.7, 77.5, 77.7, 127.3−128.4 and 138.1−139.0 (Ar), 150.3; HR-MS (LSIMS) calcd for $C_{39}H_{42}O_5S_2$ $[M]^+$ 654.2474, found 654.2490.

(17) A solution of **6** (160 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) was treated with methanol (0.5 mL) and NBS (88 mg, 0.50 mmol). The mixture was stirred at room temperature for ~0.5 h and then filtered through a short column of silica gel and evaporated. The residue was purified by chromatography (hexane−ether, 4:1) on silica to give the desired ester **7** as a colorless oil (140 mg, 91%): $[\alpha]_D$ +12.8 (*c* 1.00); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23−2.27 (m, 2H, H-3ax, H-3eq), 3.18 (s, 3H, OMe), 3.74 (dd, 1H, J = 3.4, 10.7 Hz), 3.77 (s, 3H, CO_2Me), 3.83−3−87 (m, 2H), 3.96−4.02 (m, 2H), 4.16 (bs, 1H, H-5), 4.33−5.04 (4 × ABq, 4 × 2H, C*H*$_2$Ph), 7.21−7.34 (m, 20H, Ar); ^{13}C NMR ($CDCl_3$) δ 32.9, 50.9, 52.4, 67.7, 70.5, 71.0, 71.7, 72.1, 73.3, 74.0, 75.5, 75.9, 99.3, 127.2−128.3 and 138.2−139.2 (Ar), 168.6; HR-MS (LSIMS) calcd for $C_{38}H_{42}O_8$ $[M + Na]^+$ 649.2777, found 649.2778.

(18) After hydrogenolysis of **7** with H_2 on Pd−C catalyst in an EtOH solution, **8** was obtained as an oil: ^{1}H NMR (500 MHz, D_2O) δ 1.98 (dd, 1H, J = 11.3, 12.9 Hz, H-3ax), 2.12 (ddd, 1H, J = 0.8, 5.1, 12.9 Hz, H-3eq), 3.28 (s, 3H, OMe), 3.71 (dd, 1H, J = 1.0, 9.0 Hz, H-6), 3.73 (dd, 1H, J = 6.1, 11.8 Hz, H-8a), 3.92 (s, 3H, CO_2Me), 3.97 (dd, 1H, J = 2.9, 11.8 Hz, H-8b), 4.02 (ddd, 1H, J = 3.2, 6.1, 9.0 Hz, H-7), 4.12 (m, 1H, H-5), 4.14 (ddd, 1H, J = 2.9, 5.1, 11.6 Hz, H-4); ^{13}C NMR (D_2O) δ 33.4, 51.1, 53.4, 62.8, 65.3, 65.7, 68.9, 71.6, 99.3, 170.3.

(19) Acetylation of **8** with acetic anhydride and pyridine gave **9**: $[\alpha]_D$ +65.7 (*c* 1.04); (lit.[20] +76.8, *c* 0.62); ^{1}H NMR (500 MHz, C_6D_6) δ 1.63, 1.67, 1.75, 1.80 (4s, 4 × 3H, 4Ac), 2.25 (dd, 1H, J = 11.9, 12.6 Hz, H-3ax), 2.30 (ddd, 1H, J = 0.8, 5.4, 12.6 Hz, H-3eq), 3.10 (s, 3H, OMe), 3.27 (s, 3H, CO_2Me), 3.90 (dd, 1H, J =1.4, 9.8 Hz, H-6), 4.16 (dd, 1H, J = 4.9, 12.2 Hz, H-8a), 4.66 (dd, 1H, J =2.4, 12.2 Hz, H-8b), 5.51 (ddd, 1H, J = 2.4, 4.8, 9.8 Hz, H-7), 5.56 (ddd, 1H, J = 3.0, 5.4, 11.9 Hz, H-4), 5.62 (m, 1H, H-5); ^{13}C NMR (C_6D_6) δ 20.1, 20.2, 20.3, 20.3, 32.5, 51.1, 51.9, 62.6, 64.7, 66.7, 67.9, 69.1, 99.6, 167.4, 169.3, 169.4, 169.7, 170.2.

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(21) To a mixture of $LiBH_4$ (11 mg, 0.5 mmol) in dry THF (2 mL) was added TMSCl (160 μL, 1.25 mmol) at room temperature under Ar, and the reaction was stirred for 1 h at room temperature. Then a solution of ketene dithioacetal **7** (65 mg, 0.1 mmol) in THF (2 mL) was added dropwise. The mixture was slowly warmed to 40−50 °C (TLC). Then methanol was cautiously added, followed by neutralization with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ether. After concentration, the crude product was redissolved in a mixture of THF−water (9:1, 3 mL) and NBS (178 mg, 1 mmol) was added in one portion at room temperature. The mixture was stirred until TLC showed disappearance of the substrate. The reaction was washed with saturated aqueous Na_2SO_3 and extracted with AcOEt. The organic layers were washed with brine, dried, and concentrated. The resulting crystals were redissolved in ether (with an excess of AcOEt) and treated with a solution of CH_2N_2 in ether. After evaporation, the residue was chromatographed on silica gel to give the desired 2-deoxy ester **10** (60%): $[\alpha]_D$ +3.6 (*c* 0.80); ^{1}H NMR (500 MHz, C_6D_6) δ 2.10 (m, 1H, H-3eq), 2.40 (dd, 1H, J = 12.6 Hz, H-3ax), 3.24 (ddd, 1H, J = 2.5, 4.4, 11.8 Hz, H-4), 3.32 (s, 3H, CO_2Me), 3.55 (dd, 1H, J = 1.0, 9.0 Hz, H-6), 3.73 (dd, 1H, J = 2.4, 12.1 Hz, H-2), 3.86 (m, 2H, H-8a, H-8b), 4.14 (dt, 1H, J = 2.9, 6.0, 8.9 Hz, H-7), 4.17 (m, 1H, H-5), 4.19−5.20 (4 × ABq, 4 × 2H, C*H*$_2$Ph), 7.05−7.24 (m, 20H, Ar); ^{13}C NMR (C_6D_6) δ 29.8, 51.3, 69.2, 70.2, 72.0, 73.0, 73.5, 74.7, 75.3, 77.5, 79.1, 96.4, 127.3−128.5 and 139.4−139.9 (Ar), 170.2; HR-MS (LSIMS) calcd for $C_{37}H_{40}O_7$ $[M]^+$ 619.2672, found 619.2680.

(22) Młynarski, J.; Banaszek, A. *Pol. J. Chem.* **1999**, *73*, 973.