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A Route to 3-Deoxy-4-O-methyl-D-*manno*-oct-2-ulosonic Acid (4-O-Methyl-KDO) and Its D-*gluco* Isomer Derivatives

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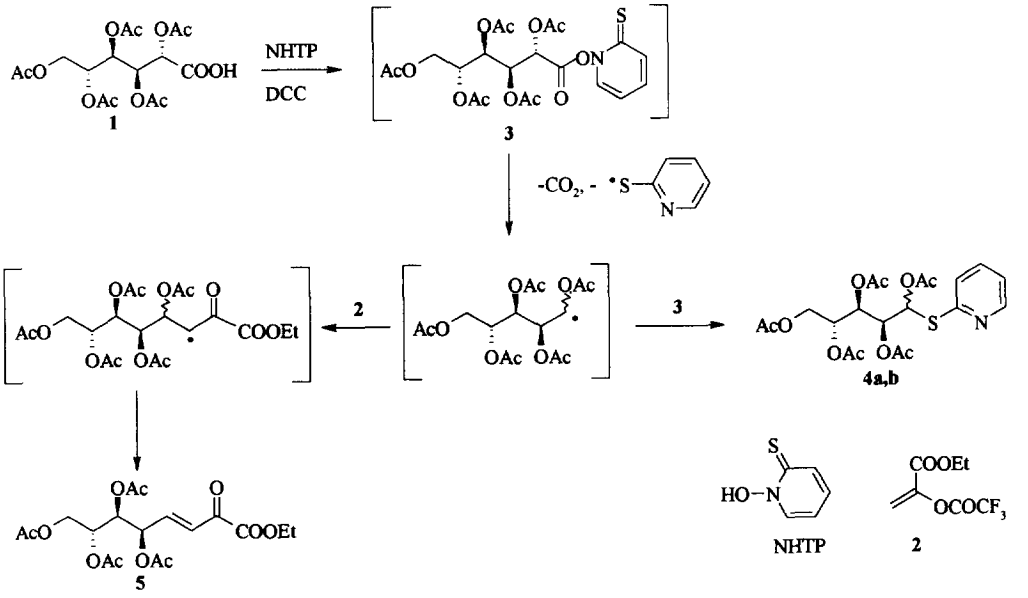
Abstract: *Methoxymercuration of α,β-unsaturated ketoester **5** (readily obtained from peracetylated D-gluconic acid **1** via Barton ester) led to a separable mixture of KDO derivative **9** and its D-gluco isomer **10**.* © 1997 Elsevier Science Ltd. All rights reserved.

3-Deoxy-D-*manno*-oct-2-ulosonic acid (KDO), a common component of the inner core of Gram-negative bacterial lipopolysaccharides (LPS), is one of the most enticing synthetic targets in sugar chemistry. A number of chemical syntheses of KDO have been elaborated[1]. For the large scale preparation of ammonium salt of KDO the classical method of Cornforth[2a], recently optimized by Shirai and Ogura is used[2b]. Reviews on the chemistry of KDO have been also published[2a,3].

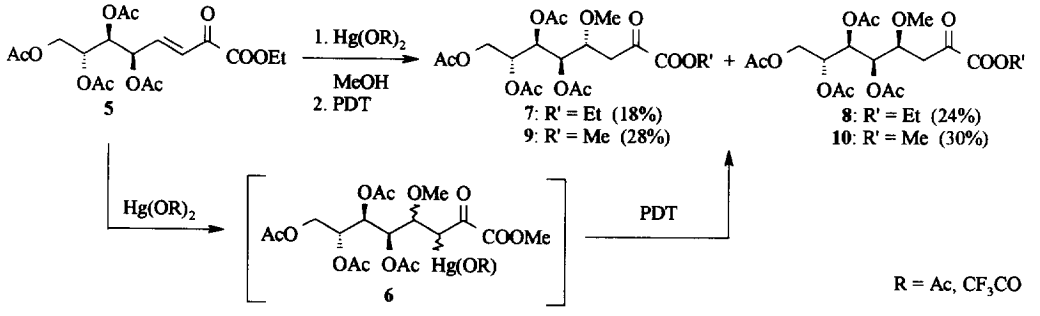
In our approach to KDO we were led by the recently published general synthesis of α-ketoesters basing on the photochemical reaction of Barton's esters [1-O-acyl-2-thiopyridone, acylated N-hydroxy-2-thiopyridone][4] with ethyl 2-trifluoroacetylacrylate (**2**). Our target compound should be formed from the readily available D-gluconic acid (in form of peracetylated derivative **1**) converted to Barton's ester **3** and subsequently



reacting with **2**. Per-O-acetylated D-gluconic acid (**1**) was obtained from the cheap D-gluconic acid δ-lactone[5]. Its reaction with N-hydroxy-2-thiopyridone (NHTP) in the presence of dicyclohexylcarbodiimide (DCC) at low temperature (-20°C) did not lead to the corresponding ester **3**. Instead, an epimeric mixture of D-arabinose 1-S-(2-pyridine)-1-O-acetates (**4a,b**) was obtained in very good yield (88%). Lowering the temperature of the esterification to -70°C did not change the outcome of the reaction. When the esterification reaction was performed at -20°C in the presence of **2**, a known α,β-unsaturated ester, ethyl E-5,6,7,8-tetra-O-acetyl-3,4-dideoxy-D-*arabino*-oct-2-ulos-3-enoate[6-8] (**5**) was obtained in 78% isolated yield. The O,S-acetal **4** was formed as a side product in a low (7%) yield. Evidently, coupling reaction of the transiently formed Barton's ester **3** with **2** is connected with elimination of an acetic acid molecule. Mechanism proposed in scheme above, follows Barton's suggestion[9].

Compound **5** was obtained earlier by a Wittig reaction between tetra-O-acetyl-*aldehydo*-D-arabinose and (ethoxyoxalyl)methylenetriphenylphosphorane[6], by ring opening of C-(D-arabinosyl)-substituted pyruvate[7] and by reaction of per-O-acetyl-D-arabino-1-cobaloxime with methyl 1-(trimethylsilyloxy)acrylate[8].

In continuation of our synthesis we decided to employ **5** as the substrate for a formal water molecule addition across the double bond. This addition was described by Kochetkov[10], however the final yield of his multi-step procedure is very low. Compound **5** was also used for the synthesis of 4-deoxy-KDO by hydrogenation of the double bond[6]. Because the alkoxymercuration of α,β-unsaturated carbonyl compounds is well documented and is known to proceed with high regioselectivity, the RO group being added in the β-position and the mercury atom in α-position[11], we decided to employ alkoxymercuration as the method for addition of an alcohol molecule across the double bond. Treatment of **5** with mercuric acetate or mercuric trifluoroacetate in methanol followed by demetalation of the organomercurial **6** formed with propane-1,3-dithiol (PDT) under weakly basic conditions led in good yield to two stereoisomeric products, **7** and **8** (or **9** and **10** - depending on demetalation procedure), of the proper regiochemistry, i.e. both having the OMe group at C-4. Regioisomers with OMe group at C-3 carbon atom were not detected. Benzyloxymercuration of **5** under similar conditions did not lead to any well-defined products.

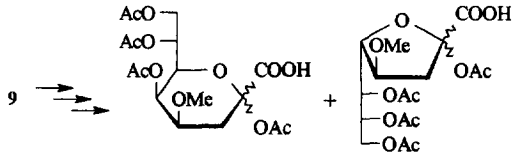


It is important to note, that during the alkoxymercuration process in methanol solution, complete transesterification occurred and methyl esters **6** were formed. When the demetalation reaction was carried out in ethanol solution according to the method C (see Experimental), a second transesterification process followed. When the demetalation reaction was performed at short reaction times, the mixture of methyl and ethyl esters was obtained. Pure ethyl esters could be produced at prolonged reaction times, however at cost of lower yields. Demetalation procedure D (see Experimental) retained methyl ester and gave higher yield of products.

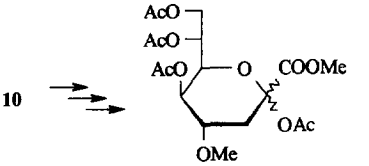
Compounds **9** and **10** were chromatographically separated and their configuration was determined by comparison of the coupling constants between H-4 and methylene protons (H-3 and H-3') with known, similar

compounds. For the 4,5-*erythro* compound **9** the coupling constants are: $J_{3,4}$ = 5.5 Hz, $J_{3',4}$ = 6.9 Hz. Literature data for ethyl 3-deoxy-5,6:7,8-di-O-isopropylidene-D-*manno*-oct-2-ulonate[1c] are: $J_{3,4}$ 4.9 Hz, $J_{3',4}$ = 7.8 Hz. For the 4,5-*threo* compound **10** coupling constants are: $J_{3,3'}$ = 17.2 Hz, $J_{3,4}$ = 7.1 Hz, $J_{3',4}$ = 4.8 Hz compared with $J_{3,3'}$ = 17.2 Hz, $J_{3,4}$ = 8.1 Hz and $J_{3',4}$ = 3.9 Hz for methyl 3-deoxy-4,5,6,7,8,9-hexa-O-benzyl-D-*glycero*-D-*galacto*-non-2-ulonate[1d].

For final assignment of configuration at C-4 we converted esters **9** and **10** to pyranose forms **11** and **12**. Deacetylation of **9** by treatment with $NaHCO_3$ in methanol[12], followed by cyclization in the presence of D-(+)-camphorsulfonic acid and acetylation under standard conditions, gave **11a,b** in 37% yield as a mixture (probably furanose and pyranose forms) with one dominating product (**11a**) identified as free acid. Similar transformation of **10** gave a mixture of two anomeric esters **12** (28%). Reaction conditions leading to **11** and **12** were not optimized.



11a **11b**



12

The coupling constants for **11a,** indicative of configuration, are as follows: $J_{3,3'}$ = 14.0 Hz, $J_{3,4}$ = 9.5 Hz, $J_{3',4}$ = 4.1 Hz, $J_{4,5}$ 4.1 Hz. Literature values are generally similar, e.g.: for per-O-acetylated methyl ester of KDO[13]: $J_{3,3'}$ = 13.0 Hz, $J_{3,4}$ = 12.0 Hz, $J_{3',4}$ = 6.0 Hz and $J_{4,5}$ = 3.0 Hz; for methyl (methyl 4,5,7,8-tetra-O-acetyl-3-deoxy-β-D-*manno*-oct-2-ulo)pyranosonate[2a]: $J_{3,3'}$ = 12.5 Hz, $J_{3,4}$ = 12.5 Hz, $J_{3',4}$ = 5.5 Hz and $J_{4,5}$ = 2 Hz; for α-anomer of the former compound[14]: $J_{3,3'}$ = 14.8 Hz, $J_{3,4}$ = 8.1 Hz, $J_{3',4}$ = 2.7 Hz, and $J_{4,5}$ = 6.2 Hz.

Similar data for **12** are as follows: $J_{3,3'}$ = 13.5 Hz, $J_{3,4}$ = 6.9 Hz, $J_{3',4}$ = 7.4 Hz, $J_{4,5}$ 5.8 Hz for one of the anomers, and $J_{3,3'}$ = 14.7 Hz, $J_{3,4}$ = 7.2 Hz, $J_{3',4}$ = 3.1 Hz, $J_{4,5}$ 3.8 Hz for the other. Literature data for ethyl 2,4,5,7,8-penta-O-acetyl-3-deoxy-D-*gluco*-oct-2-ulopyranosonate[15]: $J_{3,3'}$ = 14.2 Hz, $J_{3,4}$ = 3.5 Hz, $J_{3',4}$ = 3.1 Hz, $J_{4,5}$ = 5.0 Hz.

Spectral data obtained for **11** and **12** are in agreement with literature data cited above, and well corroborate the configuration of our products. The present method provides a short and simple way to 4-O-methyl-KDO and to its D-*gluco* isomer. During the experimentation described in this paper an article[1a] on the same subject appeared. Reacting peracetylated D-gluconic acid, NHTP and **2,** followed by addition of phenylhydrazine, the authors could obtain KDO and its *gluco* stereoisomer in form of phenylhydrazones. A return to the keto group did not succeed.

Experimental

General methods. The solvents were purified and dried according to literature methods. TLC was performed on Silica Gel HF-254 and column chromatography on Silica Gel 230 - 400 mesh (Merck). ^{1}H NMR spectra were recorded with a Varian AC-200 (200 MHz) and Bruker AM-500 (500 MHz) spectrometers in deuterochloroform ($CDCl_3$) with Me_4Si as internal standard. High resolution mass spectra (HR-MS) were measured with an AMD-604 mass spectrometer. Optical rotations were measured with a JASCO DIP-360 automatic polarimeter.

1,2,3,4,5-penta-O-acetyl-D-arabinose S-(2-pyridyl)-thioacetal (4)

Compound **4** was obtained by slow addition of **1** (3.25 g, 8.0 mM) in dichloromethane (20 mL) into solution of DCC (1.65 g, 8.0 mM) and NHTP (1.02 g, 8.0 mM) in dichloromethane (20 mL) at 0°C. The

mixture was allowed to attain room temperature, and stirring was continued for 1 h. The whole mixture was filtered through short column filled with silica gel (dichloromethane as eluent), the solvents were evaporated and the remaining syrup was purified by column chromatography (hexane - ethyl acetate, 2 : 1) to afford 3.32 g (88%) of **4** as a 1.4 : 1.0 mixture of epimers identified on the basis of spectral data. Compound **4a**: ^{1}H NMR ($CDCl_3$), δ 8.43 - 8.49, 7.50 - 7.55, 7.17 - 7.24 and 7.05 - 7.10 (4m, 4H, Ar); 7.10 (d, 1H, $J_{1,2}$ 7.1 Hz, H-1); 5.69 - 5.72 (m, 2H, H-2,3); 5.13 - 5.18 (m, 1H, H-4); 4.34 (dd, 1H, $J_{5,4}$ 3.2, $J_{5,5'}$ 12.4 Hz, H-5); 4.10 (dd, 1H, $J_{5',4}$ 6.3 Hz, H-5'). ^{13}C NMR ($CDCl_3$), δ 75.71 (C-1); 70.60 and 68.83 (C-2,3); 68.77 (C-4); 61.83 (C-5). Compound **4b**: ^{1}H NMR ($CDCl_3$), δ 6.99 (d, 1H, $J_{1,2}$ 6.8 Hz, H-1); 5.67 (dd, 1H, $J_{2,3}$ 2.9 Hz, H-2); 5.59 (dd, 1H, $J_{3,4}$ 8.6 Hz, H-3); 5.13 - 5.18 (m, 1H, H-4); 4.25 (dd, 1H, $J_{5,4}$ 2.9, $J_{5,5'}$ 12.5 Hz, H-5); 4.14 (dd, 1H, $J_{5',4}$ 5.2 Hz, H-5'). ^{13}C NMR ($CDCl_3$), δ 76.41 (C-1); 69.83 (C-2); 68.22 (C-4); 68.01 (C-3); 61.74 (C-5). HR-MS(EI) calc. for $C_{20}H_{25}NO_{10}S$ $(M)^+$: 471.1199. Found: 471.1198.

Ethyl E-5,6,7,8-tetra-O-acetyl-3,4-dideoxy-D-arabino-*oct-2-ulos-3-enoate (5)*

To a cooled (-17°C) solution of ethyl 1-(trifluoroacetoxy)acrylate[4] (**2**, 3.20 g, 15.0 mM), dicyclohexylcarbodiimide (DCC, 1.03 g, 5.0 mM) and NHTP (662 mg, 5.2 mM) in dichloromethane (5 mL) a solution of per-O-acetylated D-gluconic acid[5] (2.07 g, 5.1 mM) in dichloromethane (10 mL) slowly added under argon atmosphere while stirring. The mixture was allowed to attain room temperature and stirring was continued for 3 h. The solvents were evaporated and to the residue was added ethyl ether (15 mL). Dicyclohexylurea was filtered off, the solvents were evaporated, and the remaining syrup was purified by column chromatography (hexane - ethyl acetate, 2 : 1) to afford 1.62 g (78%) of **5** and 165 mg (7 %) of **4**.

5: $[\alpha]_D^{22}$ +22.7° (c 5.13, chloroform); lit.[6]: $[\alpha]_D^{22}$ +24.4° (c 1.1, chloroform). ^{1}H NMR ($CDCl_3$), δ 7.00 (dd, 1H, $J_{4,5}$ 4.3, $J_{4,3}$ 15.9 Hz, H-4); 6.75 (dd, 1H, $J_{3,5}$ 1.7 Hz, H-3); 5.78 (m, 1H, H-5); 5.44 (dd, 1H, $J_{6,5}$ 2.7, $J_{6,7}$ 8.9 Hz, H-6); 5.22 (m, 1H, $J_{7,8}$ 2.7, $J_{7,8'}$ 4.4 Hz, H-7), 4.35 (q, 2H, J 7.1 Hz, OCH_2), 4.26 (dd, 1H, $J_{8,8'}$ 12.8 Hz, H-8); 4.16 (dd, 1H, H-8'); 2.17 and 2.08 (2s, 6H, 2 × OAc); 2.07 (s, 6H, 2 × OAc); 1.38 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$), δ 182.14, 170.55, 169.75, 169.61 and 169.38 (C=O); 145.51 and 125.66 (C-3,4); 70.09, 69.40 and 68.17 (C-5,6,7); 62.74 and 61.70 (CH_2 and C-8); 20.81, 20.72, 20.62 and 20.54 (OAc); 14.04 (CH_3). HR-MS(EI) calc. for $C_{18}H_{24}O_{11}$ $(M)^+$: 416.1318. Found: 416.1319.

Methoxymercuration of **5**

Method A: a mixture of **5** (416 mg, 1.0 mM) and mercuric acetate (440 mg, 1.4 mM) in methanol (10 mL) was stirred at 30 - 35°C for 48 h. The solvents were evaporated to give crude **6**.

Method B: a mixture of **5** (416 mg, 1.0 mM), mercuric trifluoroacetate (600 mg, 1.4 mM) and mercuric oxide (220 mg, 1.0 mM) in methanol (10 mL) was stirred at 0°C for 24 h. The solvents were evaporated to give crude **6**.

Demercuration of **6**

Method C[16]: Crude **6** was dissolved in ethanol (7 mL), cooled to 0°C, and sodium hydrogencarbonate (1.5 eq calculated for mercury salts) and propanedithiol (PDT, 1.1 eq) were added. The mixture was stirred at 0°C for 0.5 h and 12 h at room temperature. Mercuric acetate (approx. 100 mg) was added to complex any residual thiol and the mixture was concentrated to dryness. To the residue water (20 mL) was added and the products were extracted with dichloromethane (3 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography (hexane - ethyl acetate, 2 · 1) of the residue gave an inseparable mixture

of **7** and **8** (190 mg, 42 %) in proportion 1.0 : 1.4. HR-MS(EI) calc for $C_{16}H_{23}O_{10}$ $(M\text{-}COOEt)^+$: 375.1291. Found: 375.1287.

Ethyl 5,6,7,8-tetra-O-acetyl-3-deoxy-4-O-methyl-D-manno-*oct-2-ulonate (7)*: ^{1}H NMR ($CDCl_3$), δ 5.47 (dd, 1H, $J_{6,5}$ 4.2, $J_{6,7}$ 7.1 Hz, H-6); 5.23 (dd, 1H, $J_{5,4}$ 5.3 Hz, H-5); 5.16 (m, 1H, H-7); 4.33 (q, 2H, J 7.1 Hz, $COOCH_2CH_3$) ; 4.27 (dd, 1H, $J_{8,7}$ 2.9, $J_{8,8'}$ 12.4 Hz, H-8); 4.15 (dd, 1H, $J_{8',7}$ 5.5 Hz, H-8'); 3.95 (m, 1H, $J_{4,3}$ 7.1, $J_{4,3'}$ 5.3 Hz, H-4); 3.38 (s, 3H, OCH_3); 3.12 (m, 2H, H-3,3'); 1.38 (t, 3H, $COOCH_2CH_3$).

Ethyl 5,6,7,8-tetra-O-acetyl-3-deoxy-4-O-methyl-D-gluco-*oct-2-ulonate (8)*: ^{1}H NMR ($CDCl_3$), δ 5.51 (dd, 1H, $J_{6,5}$ 3.2, $J_{6,7}$ 8.1 Hz, H-6); 5.26 (dd, 1H, $J_{5,4}$ 6.2 Hz, H-5); 5.08 (m, 1H, H-7); 4.35 (q, 2H, J 7.1 Hz, $COOCH_2CH_3$); 4.28 (dd, 1H, $J_{8,7}$ 3.0, $J_{8,8'}$ 12.5 Hz, H-8); 4.13 (dd, 1H, $J_{8',7}$ 5.3 Hz, H-8'); 3.93 (m, 1H, H-4); 3.37 (s, 3H, OCH_3); 3.18 (dd, 1H, $J_{3,4}$ 7.1, $J_{3,3'}$ 17.3 Hz, H-3); 2.94 dd, 1H, $J_{3',4}$ 4.9 Hz, H-3'); 1.39 (t, 3H, $COOCH_2CH_3$).

Method D[16]: Crude **6** was dissolved in dichloromethane (10 mL), cooled to 0°C and then triethylamine (1.5 eq calculated for mercury salts) and propanedithiol (PDT, 1.1 eq) were added. The mixture was stirred at 0°C for 0.5 h and 2 h at room temperature. Mercuric acetate (approx. 100 mg) was added to complex any residual thiol and the mixture was filtered through a silica gel pad and eluted with hexane - ethyl acetate (2 : 1) mixture. The solvents were evaporated. Column chromatography (hexane - ethyl acetate, 2 : 1) of the residue gave **10** (132 mg, 30 %) followed by **9** (120 mg, 28 %). HR-MS(LSIMS) for the mixture of **9** and **10** calc for $C_{16}H_{23}O_{10}$ $(M\text{-}COOCH_3)^+$: 375.1291. Found: 375.1301.

Methyl 5,6,7,8-tetra-O-acetyl-3-deoxy-4-O-methyl-D-manno-*oct-2-ulonate (9)*: $[\alpha]_D^{20}$ +28.1° (c 1.08, chloroform). ^{1}H NMR ($CDCl_3$), δ 5.42 (dd, 1H, $J_{6,5}$ 4.2, $J_{6,7}$ 7.0 Hz, H-6); 5.19 (dd, 1H, $J_{5,4}$ 5.3 Hz, H-5); 5.13 (m, 1H, H-7); 4.24 (dd, 1H, $J_{8,7}$ 3.0, $J_{8,8'}$ 12.4 Hz, H-8); 4.10 (dd, 1H, $J_{8',7}$ 5.6 Hz, H-8'); 3.91 (dt, 1H, $J_{4,3} \cong$ 5.5, $J_{4,3'} \cong$ 6.9 Hz, H-4); 3.84 (s, 3H, $COOCH_3$); 3.33 (s, 3H, OCH_3); 3.08 (m, 2H, H-3,3'). ^{13}C NMR ($CDCl_3$), δ 191.26 (C-1); 170.63, 170.19, 170.00, 169.83 (C-2, OAc); 75.23; 70.31; 69.12; 68.78; 61.67 (C-8); 58.79 ($COOCH_3$); 53.21 (OCH_3); 39.96 (C-3).

Methyl 5,6,7,8-tetra-O-acetyl-3-deoxy-4-O-methyl-D-gluco-*oct-2-ulonate (10)*: $[\alpha]_D^{20}$ +32.3° (c 0.96, chloroform). ^{1}H NMR ($CDCl_3$), δ 5.44 (dd, 1H, $J_{6,5}$ 3.2, $J_{6,7}$ 7.1 Hz, H-6); 5.20 (dd, 1H, $J_{5,4}$ 6.1 Hz, H-5); 5.02 (m, 1H, H-7); 4.23 (dd, 1H, $J_{8,7}$ 2.9, $J_{8,8'}$ 12.4 Hz, H-8); 4.08 (dd, 1H, $J_{8',7}$ 5.3 Hz, H-8'); 3.89 (m, 1H, H-4); 3.85 (s, 3H, $COOCH_3$); 3.31 (s, 3H, OCH_3); 3.14 (dd, 1H, $J_{3,4}$ 7.1, $J_{3,3'}$ 17.2 Hz, H-3); 2.90 (dd, 1H, $J_{3',4}$ 4.8 Hz, H-3'). ^{13}C NMR ($CDCl_3$), δ 191.21 (C-1); 170.63, 170.04; 169.65 (C-2, OAc); 75.42; 70.47; 68.61; 68.48; 61.79 (C-8); 58.31 ($COOCH_3$); 53.16 (OCH_3); 40.77 (C-3).

2,5,7,8-Tetra-O-acetyl-3-deoxy-4-O-methyl-D-manno-*oct-2-ulopyranosonic acid (11)*

To a suspension of **9** (124 mg, 0.28 mM) and $NaHCO_3$ (1.5 g) in methanol (5 mL), stirred for 24 h, dichloromethane (5 mL) was added and the mixture was filtered through silica gel (dichloromethane - methanol, 9 : 1 as eluent). The solvents were evaporated and the residue was stirred with methanol (5 mL) and D-(+)-camphorsulfonic acid (10 mg) for 24 h. The solvents were evaporated and the residue was acetylated (pyridine / acetic anhydride with DMAP as catalyst) overnight. The solvents were evaporated. Column chromatography (hexane - ethyl acetate, 1 : 1) of the residue gave 36 mg (28%) of **11**. **11a**: ^{1}H NMR ($CDCl_3$), δ 5.17 (m, $J_{7,6}$ 9.0 Hz, H-7); 4.68 (dd, $J_{5,6}$ 0.6, $J_{5,4}$ 4.1 Hz, H-5); 4.66 (d, H-6); 4.61 (dd, $J_{8,7}$ 2.8, $J_{8,8'}$ 12.4 Hz, H-8); 4.17 (dd, $J_{8',7}$ 3.8 Hz, H-8'); 3.97 (m, H-4); 3.42 (s, OMe); 2.53 (dd, $J_{3,4}$ 9.5, $J_{3,3'}$ 14.0 Hz, H-3); 2.30 (dd, $J_{3',4}$ 4.1 Hz, H-3').

*Methyl 2,5,7,8-tetra-O-acetyl-3-deoxy-4-O-methyl-D-*gluco*-oct-2-ulopyranosonate (12)*

This compound was obtained with 37% yield from **10** as described above for **11**. ^{1}H NMR ($CDCl_3$), δ 5.17 (m, $J_{7,6}$ 3.8 Hz, H-7a); 4.46 (t, $J_{5,6} \approx 3.7$ Hz, H-5b); 4.38 (dd, $J_{8,7}$ 3.7, $J_{8,8'}$ 12.5 Hz, H-8b); 4.34 (t, $J_{5,6} \approx 6$ Hz, H-5a); 4.31 (dd, $J_{8,7}$ 3.8, $J_{8,8'}$ 12.2 Hz, H-8a); 4.27 (dd, $J_{8',7}$ 6.5 Hz, H-8'a); 4.22 (dd, $J_{8',7}$ 6.0 Hz, H-8'b); 4.08 (m, $J_{4,5}$ 5.8 Hz, H-4a); 3.88 (m, $J_{4,5}$ 3.8 Hz, H-4b); 2.78(dd, $J_{3,4}$ 7.2, $J_{3,3'}$ 14.7 Hz, H-3b); 2.66 (dd, $J_{3',4}$ 6.9, $J_{3,3'}$ 13.5 Hz, H-3a); 2.41 (dd, $J_{3',4}$ 3.1 Hz, H-3'b); 2.35 (dd, $J_{3',4}$ 7.4 Hz, H-3'a).

References and notes

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