Efficient Synthesis of 3-Deoxy-D-*arabino*-2-heptulosonate (DAH) and -D-*gluco*-2-heptulosonate by a Two-Carbon Chain Elongation of D-Arabinose

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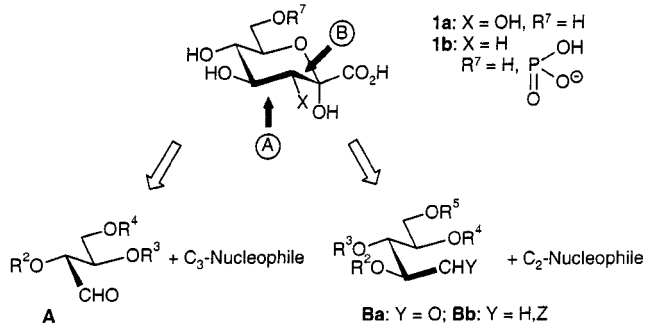
Keywords: Carbohydrates / Deoxy sugars / Ketoses / Mercaptals / Heptulosonates / Synthesis / Asymmetric induction

Reaction of α-lithiated methyl glyoxylate diethyl mercaptal (**3**) with 2,3,5-tri-*O*-benzyl-D-arabinose (**2**) stereoselectively afforded the D-*gluco*-2-heptulosonate derivative **4**. Mercaptal cleavage led to the corresponding pyranose **5a** which could be directly transformed into unprotected D-*gluco*-2-heptulosonic acid (**1a**), one of the target molecules. Deoxygenation of **5a** at C-3 could also be readily accomplished as its 3-hydroxy group is unprotected. Thus, the second target molecule, **1b**, was obtained in just a few steps.

Introduction

The biosynthesis of the aromatic amino acids phenylalanine, tyrosine, and tryptophan in plants and microorganisms is based on the shikimate pathway.[1] The first metabolic intermediate in this pathway is 3-deoxy-D-*arabino*-2-heptulosonate 7-phosphate [Scheme 1; **1b**: $R^7 = PO_2(OH)^- =$ DAHP] which, in an interesting sequence of reactions brought about by the enzyme dehydroquinate synthase, is ring-closed to dehydroquinate, a cyclohexanonecarboxylate derivative.[2] The biosynthesis of DAHP is based on chain extension of D-erythrose 4-phosphate as a C_4 electrophile with phosphoenolpyruvate as a C_3 nucleophile; thus, Nature follows retrosynthetic pathway **A** shown in Scheme 1. This reaction correlates with the biosynthesis of the corresponding 3-deoxy-2-glyculosonates Kdo and Neu5Ac, which are generated on reaction of D-arabinose 5-phosphate or *N*-acetyl-D-mannosamine 6-phosphate, respectively, with phosphoenolpyruvate.[3] In all these reactions, a new stereogenic centre is introduced at C-4. Several chemical syntheses of Kdo and Neu5Ac follow the same strategy, and DAH (**1b**: $R^7 = H$) has also been obtained by this route.[4−6] Thus, face-selective addition of the nucleophile to the erythrose carbonyl group is required. Because of this problem, as an alternative, retrosynthetic pathway **B** leading to intermediates **Ba** and **Bb** has also been investigated. Thus, reaction of either the carbonyl group (**Ba**) with a suitable Wittig reagent or of an alkylating agent (**Bb**) with a C_2 nucleophile is required in order to construct the carbon skeleton of 3-deoxy-2-glyculosonates with the correct stereochemistry of the functional groups.



Scheme 1. Strategies for the synthesis of **1a** and **1b** (Z = leaving group)

Recently, it was found that not only Kdo but also Ko (D-*glycero*-D-*talo*-2-octulosonate, also termed 2-keto-octosonate) occurs in nature.[7] We were able to develop an efficient synthesis of this compound as well as of the desired α-glycosides.[8] This synthesis is based on *syn*-selective addition of α-lithiated methyl glyoxylate mercaptal as a C_2 nucleophile to a D-mannose derivative as a C_6 electrophile. Application of this reaction protocol to the synthesis of DAH (**1b**: $R^7 = H$) and to the corresponding D-*gluco*-2-heptulosonate (**1a**) is reported herein.[9]

Results and Discussion

The synthesis of **1a** and **1b** starts from the known diethylmercaptal of methyl glyoxylate **3**[10] and commercially available 2,3,5-tri-*O*-benzyl-D-arabinose (**2**)[11] (Scheme 2). α-*C*-Lithiation of **3** with lithium diisopropylamide (LDA) in THF, addition of freshly prepared magnesium bromide, followed by addition of **2** stereoselectively furnished the desired open-chain D-*gluco*-2-heptulosonate **4** in high yield. Thus, stereoselective *syn* addition of **3** to the aldehyde group of **2** was again achieved. Treatment of **4** with *N*-iodosuccinimide (NIS) in aqueous acetone afforded the corresponding 2-heptulopyranosonate derivative **5a**, as indicated

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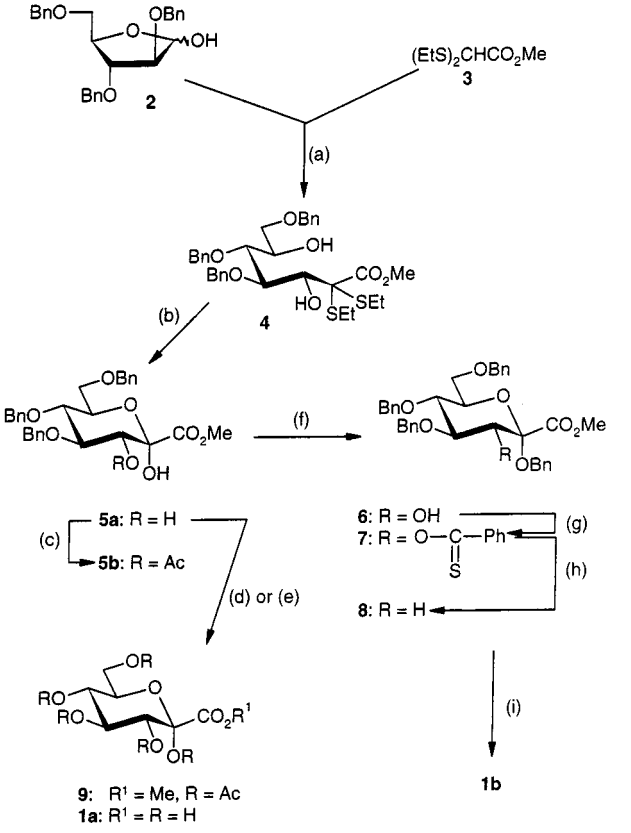
  1434−193X/02/0101−0057 $ 17.50+.50/0

by its ^{1}H NMR spectroscopic data ($^3J_{3,4}$ = 9.2 Hz). The physical data for **5a** were also in accordance with those reported for material obtained by a different route.[12] *O*-Acetylation of **5a** with acetyl chloride in pyridine, followed by treatment with aqueous $NaHCO_3$, afforded the 3-*O*-acetyl derivative **5b**, as indicated by the chemical shift of 3-H (**5a**: δ = 4.04; **5b**: δ = 5.30). Hydrogenation of **5a** with palladium on carbon as catalyst in methanol, followed by ester saponification with sodium hydroxide and ion-exchange with H^+, afforded target molecule **1a** in only three steps from the starting materials. Hydrogenolysis of the benzyl groups of **5a** and subsequent *O*-acetylation with acetic anhydride in pyridine in the presence of Steglich's reagent (DMAP) furnished per-*O*-acetyl derivative **9**, for which a full structural assignment could be made on the basis of its ^{1}H NMR spectroscopic data.



Scheme 2. Synthesis of **1a** and **1b** from **2** and **3**; reagents and conditions: (a) **3**, LDA, $MgBr_2$, THF; 79%; (b) NIS, acetone; 72%; (c) AcCl, pyridine, CH_2Cl_2; 89%; (d) Pd/C, H_2 (4 bar), MeOH; 0.1 M NaOH; quant.; (e) Pd/C, H_2 (4 bar); Ac_2O, pyridine, DMAP; 92%; (f) BnBr, NaH, DMF; MeOH, NaOMe; 78%; (g) PhC(Cl)=NMe_2Cl, pyridine, CH_2Cl_2; H_2S; 96%; (h) Bu_3SnH, AIBN, toluene; 64%; (i) Pd/C, H_2 (4 bar); 0.1 M NaOH; quant.

The presence of the unprotected 3-hydroxy group in **5a** also allowed ready access to DAH (**1b**: R^7 = H). To this end, anomeric *O*-alkylation[13] of derivative **5b** with benzyl bromide using sodium hydride as base was carried out; subsequent cleavage of the 3-*O*-acetyl group under Zemplén conditions furnished benzyl ketoside **6** in high yield. 3-Deoxygenation was performed according to Barton's procedure.[14] Thus, treatment of **6** with α-chloro-*N*,*N*-dimethylbenzimidium chloride[14] in the presence of pyridine and then with hydrogen sulfide led to the 3-*O*-thiobenzoyl derivative **7** in quantitative yield. Treatment of **7** with tributyltin hydride and azoisobutyronitrile (AIBN) afforded the fully protected DAH derivative **8**. Hydrogenolytic removal of all *O*-benzyl groups, saponification of the ester moiety with sodium hydroxide, followed by ion exchange with H^+ afforded DAH (**1b**) in quantitative yield. Its physical data were in full accordance with those reported previously.[4a,15]

Conclusion

In conclusion, two-carbon chain elongation of C_5 aldehyde **2** as an electrophile with **3** as a C_2 nucleophile occurred with complete *syn* stereoselectivity, directly furnishing the D-*gluco* stereoisomer. This could be transformed into D-*gluco*-2-heptulosonic acid (**1a**) in two steps. The absence of 3-*O*-protection in the C_7 intermediates also allowed ready access to biologically important 3-deoxy-D-*arabino*-2-heptulosonic acid (DAH, **1b**).

Experimental Section

General: Solvents were purified and dried in the usual way. Thin-layer chromatography (TLC): Merck foil plates coated with silica gel 60 F_{254}. Preparative flash chromatography: J. T. Baker silica gel 60 (30−60 μm) at a pressure of 0.3−0.4 bar. Melting points: Gallenkamp metal block; uncorrected values. Optical rotation: Perkin−Elmer polarimeter 241/MS; 1-dm cell; temperature: 20 °C. MALDI-MS: Kratos Analytical Kompac MALDI 2; matrix: 2,5-dihydroxybenzoic acid. NMR spectra: Bruker AC 250 Cryospek (250 MHz) and Bruker DRX 600 (600 MHz); solvents: $CDCl_3$ and D_2O; internal standard: residual chloroform (δ = 7.24) and $Si(CH_3)_4$; chemical shifts and coupling constants were partially obtained from COSY spectra. Elemental analyses: Heraeus CHNO-rapid.

2,3,5-Tri-*O*-benzyl-D-*arabino*-furanose (2): This compound is commercially available.

Methyl Glyoxylate Diethyl Mercaptal (3): This compound was synthesized according to a published procedure.[10]

Methyl 2-Deoxy-4,5,7-tri-*O*-benzyl-D-*gluco*-heptulosonate Diethyldithioacetal (4): A solution of diisopropylamine (27.6 mL, 196.4 mmol) in dry THF (250 mL) was treated with *n*BuLi (123 mL, 1.6 M in hexane, 197 mmol) at −20 °C. After stirring for 15 min, methyl glyoxylate diethyl mercaptal (**3**) (34.6 g, 178.6 mmol) was slowly added. The dark-red solution was kept at −20 °C for 2 h and then added to a cold (0 °C) solution of $MgBr_2$ in dry THF (250 mL), prepared from magnesium (6.5 g, 267.8 mmol) and 1,2-dibromoethane (20.5 mL, 238.1 mmol). 2,3,5-Tri-*O*-benzyl-D-*arabino*-furanose (**2**) (25 g, 59.5 mmol) was then added without a solvent. The reaction mixture was allowed to warm to room temperature over a period of 3 h, poured into ice-cold saturated aqueous NH_4Cl solution, and extracted with EtOAc. The combined extracts were washed with water, dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by flash chromatography (toluene/EtOAc, 8:1) to afford **4** (28.8 g, 79%) as a light brownish syrup. TLC (toluene/EtOAc, 6:1): R_f = 0.22, $[\alpha]_D^{25}$ = −34.2 (c = 0.25, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$):

δ = 1.07−1.17 (m, 6 H, SCH_2CH_3), 2.51−2.72 (m, 4 H, SCH_2CH_3), 3.10 (d, $J_{6,6\text{-OH}}$ = 4.2 Hz, 1 H, 6-OH), 3.35 (s, 3 H, $COOCH_3$), 3.62 (dd, $J_{6,7}$ = 5.4 Hz, $J_{7,7'}$ = 9.9 Hz, 1 H, 7-H), 3.69 (dd, $J_{6,7'}$ = 3.1 Hz, 1 H, 7′-H), 3.82−4.82 (m, 11 H, 3-, 4-, 5-, 6-H, 3-OH, CH_2Ph), 7.15−7.32 (m, 15 H, Ph). $C_{33}H_{42}O_7S_2$ (614.81): calcd. C 64.47, H 6.89; found C 64.25, H 6.96.

Methyl 4,5,7-Tri-*O*-benzyl-α-D-*gluco*-2-heptulopyranosonate (5a): A solution of mercaptal **4** (1.50 g, 2.44 mmol) in 98% acetone (60 mL) was treated with NIS (1.65 g, 7.33 mmol) at 15 °C and the reaction mixture was vigorously stirred for 30 min at room temperature. Triethylamine (2 mL), saturated aqueous $NaHCO_3$ solution, and saturated aqueous $Na_2S_2O_3$ solution were then added and the mixture was extracted several times with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (toluene/EtOAc, 5:2) gave **5a** (910 mg, 73%). The physical data were in full accordance with those reported previously.[12] TLC (toluene/EtOAc, 1:1): R_f = 0.53, $[\alpha]_D^{25}$ = +48.0 (c = 0.25, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.12 (d, $J_{3,3\text{-OH}}$ = 8.5 Hz, 1 H, 3-OH), 3.65 (dd, $J_{6,7}$ = 1.5 Hz, $J_{7,7'}$ = 11.1 Hz, 1 H, 7-H), 3.68 (dd, $J_{4,5}$ = 9.5 Hz, $J_{5,6}$ = 9.5 Hz, 1 H, 5-H), 3.74 (dd, $J_{6,7'}$ = 4.4 Hz, 1 H, 7′-H), 3.78 (dd, $J_{3,4}$ = 9.2 Hz, 1 H, 4-H), 3.87 (s, 3 H, $COOCH_3$), 4.03−4.06 (m, 2 H, 6-, 3-H), 4.31 (s, 1 H, 2-OH), 4.50−4.91 (m, 6 H, CH_2Ph), 7.18−7.38 (m, 15 H, Ph). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 53.7 (1 C, $COOCH_3$), 68.5 (1 C, C-7), 72.8 (1 C, C-6), 73.0 (1 C, C-3), 73.5−75.4 (3 C, CH_2Ph), 77.3 (1 C, C-5), 83.1 (1 C, C-4), 95.5 (1 C, C-2), 127.6−138.5 (18 C, Ph), 169.8 (1 C, C-1).

Methyl 3-*O*-Acetyl-4,5,7-tri-*O*-benzyl-α-D-*gluco*-2-heptulopyranosonate (5b): To a solution of **5a** (600 mg, 1.18 mmol) in dry CH_2Cl_2/pyridine (20:1; 20 mL) was added AcCl (130 μL, 1.77 mmol). After 90 min, the mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (toluene/EtOAc, 4:1) afforded **5b** (575 mg, 89%) as a colourless solid. TLC (toluene/EtOAc, 1:1): R_f = 0.65, $[\alpha]_D^{25}$ = +55.0 (c = 0.5, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.91 (s, 3 H, $COCH_3$), 3.63 (dd, $J_{6,7}$ = 2 Hz, $J_{7,7'}$ = 11.2 Hz, 1 H, 7-H), 3.70−4.09 (m, 7 H, 4-, 5-, 6-, 7′-H, $COOCH_3$), 4.20 (d, $J_{3,2\text{-OH}}$ = 1 Hz, 1 H, 2-OH), 4.47−4.84 (m, 6 H, CH_2Ph), 5.30 (dd, $J_{3,4}$ = 9.8 Hz, 1 H, 3-H), 7.12−7.38 (m, 15 H, Ph). $C_{31}H_{34}O_9 \cdot 25H_2O$ (555.11): calcd. C 67.08, H 6.26; found C 66.95, H 6.17.

Methyl 2,4,5,7-Tetra-*O*-benzyl-α-D-*gluco*-2-heptulopyranosonate (6): NaH (74 mg, 3.11 mmol) was slowly added to a solution of **5b** (575 mg, 1.04 mmol) and BnBr (145 μL, 1.22 mmol) in dry DMF (15 mL). After 2 h at room temperature, the reaction mixture was treated with dry methanol (10 mL) and NaOMe (20 mg), and stirring was maintained for a further 2 h. After the usual workup (saturated aqueous NH_4Cl solution, EtOAc), the organic layer was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (toluene/EtOAc, 7:1) gave **6** (485 mg, 78%) as a colourless syrup. TLC (toluene/EtOAc, 6:1): R_f = 0.27, $[\alpha]_D^{25}$ = +30.6 (c = 0.5, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.45 (d, $J_{3,3\text{-OH}}$ = 8.4 Hz, 1 H, 3-OH), 3.63 (dd, $J_{4,5}$ = 9.0 Hz, $J_{5,6}$ = 9.3 Hz, 1 H, 5-H), 3.72−3.79 (m, 3 H, 6-, 7-, 7′-H), 3.81 (dd, $J_{3,4}$ = 8.9 Hz, 1 H, 4-H), 3.83 (s, 3 H, $COOCH_3$), 3.90 (dd, 1 H, 3-H), 4.53−4.97 (m, 8 H, CH_2Ph), 7.16−7.38 (m, 20 H, Ph). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 52.8 (1 C, $COOCH_3$), 65.8 (1 C, CH_2Ph), 68.6 (1 C, C-7), 73.4 (1 C, C-6), 75.2−75.5 (4 C, C-3, CH_2Ph), 77.0 (1 C, C-5), 83.3 (1 C, C-4), 99.4 (1 C, C-2), 127.6−138.6 (24 C, Ph), 167.9 (1 C, C-1). $C_{36}H_{38}O_8$ (598.69): calcd. C 72.22, H 6.40; found C 72.23, H 6.45.

Methyl 2,4,5,7-Tetra-*O*-benzyl-3-*O*-thiobenzoyl-α-D-*gluco*-2-heptulopyranosonate (7): α-Chloro-*N*,*N*-dimethylbenzimidium chloride (326 mg, 1.60 mmol) was added to a solution of **6** (480 mg, 0.80 mmol) in dry CH_2Cl_2/pyridine (20:1; 10 mL). The mixture was stirred overnight at room temperature and then treated with H_2S. After 10 min, saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with EtOAc. The organic layer was dried ($MgSO_4$), concentrated in vacuo, and the residue was purified by flash chromatography (toluene/EtOAc, 40:1) to afford **7** (555 mg, 96%) as a yellow syrup. TLC (toluene/EtOAc, 6:1): R_f = 0.67, $[\alpha]_D^{25}$ = +127.6 (c = 0.5, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.63 (s, 3 H, $COOCH_3$), 3.78−3.85 (m, 2 H, 7-, 7′-H), 3.88 (dd, $J_{4,5}$ = 9.0 Hz, $J_{5,6}$ = 9.8 Hz, 1 H, 5-H), 3.94 (ddd, $J_{6,7}$ = 2.0 Hz, $J_{6,7'}$ = 4.7 Hz, 1 H, 6-H), 4.35 (dd, $J_{3,4}$ = 9.5 Hz, 1 H, 4-H), 4.57−4.84 (m, 8 H, CH_2Ph), 6.44 (d, 1 H, 3-H), 7.08−8.22 (m, 25 H, Ph). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 53.1 (1 C, $COOCH_3$), 65.7 (1 C, CH_2Ph), 68.2 (1 C, C-7), 73.3−75.5 (4 C, C-6, CH_2Ph), 77.6 (1 C, C-5), 79.2 (1 C, C-3), 81.0 (1 C, C-4), 98.1 (1 C, C-2), 127.6−138.5 (30 C, Ph), 166.5 (1 C, C-1), 211.3 (1 C, C=S). $C_{43}H_{42}O_8S$ (718.86): calcd. C 71.85, H 5.89; found C 71.96, H 5.93.

Methyl 2,4,5,7-Tetra-*O*-benzyl-3-deoxy-α-D-*arabino*-2-heptulopyranosonate (8): A solution of **7** (300 mg, 418 mmol) in dry, degassed toluene (10 mL) was treated for 5 min with a stream of argon and warmed to 90 °C. Bu_3SnH (221 mL, 836 μmol) and AIBN (0.3 mg) were then added, the reaction mixture was stirred for 2 h at 90 °C and for a further 2 h at room temperature, and then concentrated to dryness. Flash chromatography of the residue (toluene/EtOAc, 14:1) gave **8** (155 mg, 64%) as a colourless syrup. TLC (toluene/EtOAc, 6:1): R_f = 0.43, $[\alpha]_D^{25}$ = +29.8 (c = 0.4, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.82 (dd, $J_{3,3'}$ = 13.0 Hz, $J_{3,4}$ = 11.1 Hz, 1 H, 3-H), 2.66 (dd, $J_{3',4}$ = 5.0 Hz, 1 H, 3′-H), 3.62 (dd, $J_{4,5}$ = 9.1, $^2J_{5,6}$ = 9.1 Hz, 1 H, 5-H), 3.75−3.82 (m, 5 H, 6-, 7-, 7′-H, $COOCH_3$), 4.06 (ddd, 1 H, 4-H), 4.43−4.89 (m, 8 H, CH_2Ph), 7.19−7.36 (m, 20 H, Ph). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 37.8 (1 C, C-3), 52.6 (1 C, $COOCH_3$), 65.6 (1 C, CH_2Ph), 68.6 (1 C, C-7), 71.8−75.1 (4 C, C-6, CH_2Ph), 77.5 (1 C, C-4), 77.6 (1 C, C-5), 98.9 (1 C, C-2), 127.5−138.3 (24 C, Ph), 168.8 (1 C, C-1). MS (MALDI, positive mode, matrix: DHB): m/z = 775 [M + DHB + K]$^+$, 621 [M + K]$^+$, 605 [M + Na]$^+$; 582.69 for $C_{36}H_{38}O_7$.

Methyl 2,3,4,5,7-Penta-*O*-acetyl-α-D-*gluco*-2-heptulopyranosonate (9): A suspension of 10% Pd/C (100 mg) in methanol (25 mL) was pre-treated with 4 bar of hydrogen for 30 min, **5a** (500 mg, 0.98 mmol) was then added, and the substrate was hydrogenated at 4 bar for 24 h. The reaction mixture was then filtered through Celite, the filtrate was concentrated to dryness, and the residue was redissolved in pyridine/Ac_2O (2:1; 20 mL). A catalytic amount of DMAP (10 mg) was added to this solution and the mixture was stirred overnight. After removal of the solvent, the residue was purified by flash chromatography (toluene/EtOAc, 2:1) to yield **9** (430 mg, 92%) as a colourless syrup. TLC (toluene/EtOAc, 1:1): R_f = 0.4, $[\alpha]_D^{25}$ = +60.0 (c = 0.1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.01, 2.04, 2.09, 2.23 (5 s, 15 H, $COCH_3$), 3.76 (s, 3 H, $COOCH_3$), 3.95 (ddd, $J_{6,7}$ = 2.1 Hz, $J_{6,7'}$ = 4.6 Hz, $J_{5,6}$ = 10.0 Hz, 1 H, 6-H), 4.10 (dd, $J_{7,7'}$ = 12.5 Hz, 1 H, 7-H), 4.33 (dd, 1 H, 7′-H), 5.19 (dd, $J_{4,5}$ = 9.8 Hz, 1 H, 5-H), 5.24 (d, $J_{3,4}$ = 9.8 Hz, 1 H, 3-H), 5.51 (dd, 1 H, 4-H). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 20.4−20.8 (5 C, $COCH_3$), 53.6 (1 C, $COOCH_3$), 61.3 (1 C, C-7), 67.7 (1 C, C-5), 69.5 (1 C, C-3), 70.2 (1 C, C-4), 70.5 (1 C, C-6), 95.3 (1 C, C-2), 164.5 (1 C, C-1), 167.8−170.7 (5 C, $COCH_3$). MS (MALDI, positive mode, matrix: DHB): m/z = 487 [M + K]$^+$, 471 [M + Na]$^+$. $C_{18}H_{24}O_{13} \cdot 1.5H_2O$ (475.40): calcd. C 45.48, H 5.72; found C 45.40, H 5.38.

α-D-*gluco*-2-Heptulopyranosonic Acid (1a): A suspension of 10% Pd/C (200 mg) in methanol (50 mL) was pre-treated with 4 bar of hydrogen for 30 min, **5a** (1.00 g, 1.97 mmol) was then added, and the substrate was hydrogenated at 4 bar for 24 h. The reaction mixture was then filtered through Celite, the filtrate was concentrated to dryness, and the residue was redissolved in 0.1 N NaOH (10 mL). After stirring for 1 h, this solution was neutralized with Amberlite IR-120 (H^+) and filtered. Lyophilization yielded heptulosonic acid **1a** (510 mg, quant.) as a colourless solid. $[\alpha]_D^{25} = +35.5$ (c = 1.0, H_2O). ^1H NMR (600 MHz, D_2O): δ = 3.40 (dd, $J_{4,5}$ = 9.1 Hz, $J_{5,6}$ = 9.2 Hz, 1 H, 5-H), 3.59 (dd, $J_{3,4}$ = 9.6 Hz, 1 H, 4-H), 3.63 (d, 1 H, 3-H), 3.67−3.74 (m, 3 H, 6-, 7-, 7′-H). ^{13}C NMR (150.9 MHz, D_2O): δ = 60.0 (1 C, C-7), 68.8 (1 C, C-5), 71.9 (1 C, C-3), 72.9 (1 C, C-6), 73.0 (1 C, C-4), 95.8 (1 C, C-2), 172.8 (1 C, C-1). $C_7H_{12}O_8 \cdot 2H_2O$ (260.20): calcd. C 32.31, H 6.19; found C 32.25, H 5.94.

3-Deoxy-α-D-*arabino*-2-heptulopyranosonic Acid (1b): A suspension of 10% Pd/C (25 mg) in methanol/acetic acid (10:1, 20 mL) was pre-treated with 4 bar of hydrogen for 30 min, **8** (100 mg, 172 μmol) was then added, and the substrate was hydrogenated at 4 bar for 24 h. The reaction mixture was then filtered through Celite, the filtrate was concentrated to dryness, and the residue was purified by co-evaporation with toluene. The residue was then dissolved in 0.1 N NaOH (10 mL). After stirring for 1 h, this solution was neutralized with Amberlite IR-120 (H^+) and filtered. Lyophilization afforded **1b** (36 mg, quant.) as a colourless solid. The physical data were in full accordance with those reported previously.[4a,15] ^1H NMR (250 MHz, D_2O): δ = 1.77 (dd, $^2J_{3,3|}$ = 13.2, $^3J_{3,4}$ = 12 Hz, 1 H, 3-H), 2.20 (dd, $^3J_{3|,4}$ = 5.0 Hz, 1 H, 3′-H), 3.44 (dd, $^3J_{4,5}$ = 9.1, $^3J_{5,6}$ = 9.5 Hz, 1 H, 5-H), 3.75−3.98 (m, 4 H, 4-, 6-, 7-, 7′-H).

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. The help of Prof. Dr. Armin Geyer in the structural assignments by NMR experiments is gratefully acknowledged.

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Received July 10, 2001
[O01344]