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Carbohydrate Research 295 (1996) 69–75

CARBOHYDRATE RESEARCH

A novel chemical synthesis of a 3-deoxy-D-*arabino*-heptulosonic acid 7-phosphate (DAHP) derivative and its 2-deoxy analogue

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Received 28 May 1996; accepted 21 August 1996

Abstract

Using 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl cyanide as a precursor, methyl (methyl 3-deoxy-α-D-*arabino*-hept-2-ulopyranosid)onate (**6**) and its 2-deoxy analogue (**10**) were prepared. The synthesis involved an elimination of one molecule of acetic acid from C-2–C-3 and transformation of the CN group into COOMe, followed by methoxymercuration with subsequent reductive removal of the mercuri residue to give **6** or hydrogenation of the double bond to give **10**. Phosphorylation of the 7-OH group led to the title compounds. © 1996 Elsevier Science Ltd.

Keywords: DAHP; D-*arabino*-Heptulosonic acid; 2-Deoxy-D-*arabino*-heptulosonic acid

1. Introduction

Its well known that all micro-organisms and plants synthesise the aromatic amino acids (phenylalanine, tyrosine, tryptophan) from 3-deoxy-D-*arabino*-hept-2-ulosonic acid 7-phosphate (DAHP) by enzyme-catalysed transformations (shikimic pathway) [1]. To investigate the mechanism of this transformation the synthetic compounds were required. Two approaches, chemical [2] and enzymatic [3], for the synthesis of DAHP have been reported. The chemical syntheses of this compound are usually based on 2-deoxy-D-*arabino*-hexose diethyl dithioacetal [2].

A more general approach to the ulosonic acids has been demonstrated by Crich and Ritchie, who used glycals for the C-1 carbon elongation [4]. In an anionic–free-radical process, utilising the reactivity of the C-1 phenyl sulphones, they introduced COOH and

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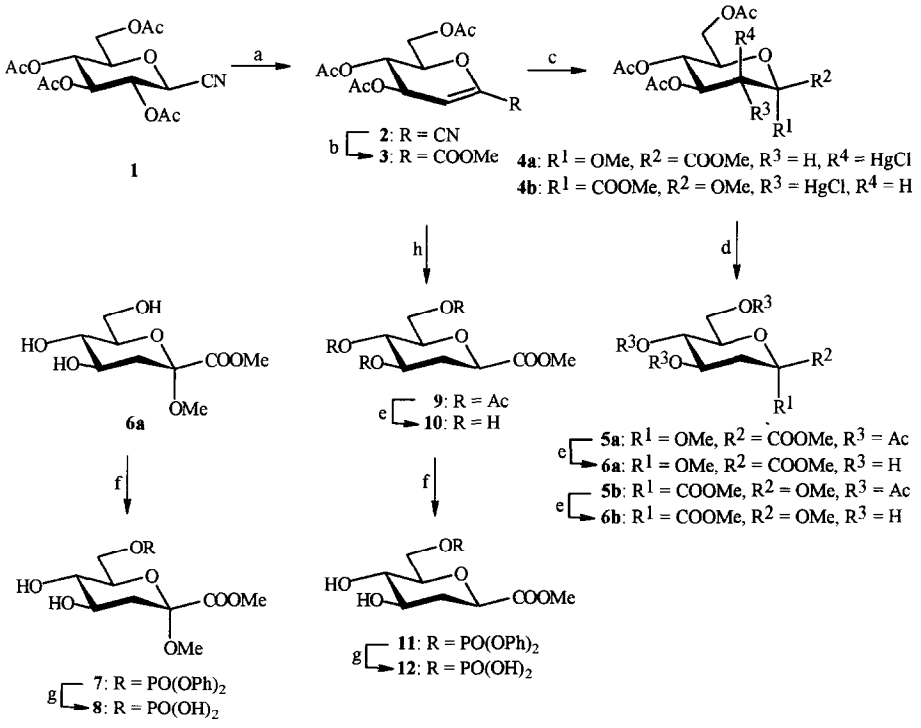
PII S0008-6215(96)00227-3

OH groups at C-1 of the pyranoses. The present paper describes an addition reaction to the 1-cyanoglucal derivative as a route to the title compounds.

2. Results and discussion

As a continuation of our studies aimed at the synthesis of 3-deoxy-2-ulosonic acids, we recently reported [5] the use of 1-cyanoglycals [6,7] as masked synthons for carboxyl and hydroxyl functions. This approach seemed to be especially suitable for the synthesis of 3-deoxy-D-*arabino*-heptulosonic acid 7-phosphate (DAHP), starting from 1-cyano-D-glucal, which contains all the structural and stereochemical features of the natural DAHP, except those at the anomeric centre and at C-7.

Slightly modifying a previously elaborated procedure for the elimination of one molecule of acetic acid from glycopyranosyl cyanides [7], the D-*gluco* derivative **1** was treated with 1,8-diazabicyclo[5.4.0]undec-7ene (DBU), leading to 4,5,7-tri-*O*-acetyl-2,6-anhydro-3-deoxy-D-*arabino*-hept-2-enononitrile (**2**) in a 70% yield (Scheme 1). Previously, compound **2** has been obtained by Buchanan et al. from 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl cyanide, using a similar procedure [8]. Although the sub-



Scheme 1. (a) DBU, CH_2Cl_2; (b) 1. $NaOH_{aq}$-EtOH, 2. Ac_2O-Py, 3. CH_2N_2-Et_2O; (c) 1. $Hg(CF_3COO)_2$-MeOH, 2. KCl; (d) Ph_3SnH, toluene; (e) Me_3SiCl, MeOH, or $NaHCO_3$, MeOH; (f) $(PhO)_2POCl$-Py; (g) PtO_2, H_2, EtOH; (h) Pd-C, H_2, EtOH.

strate described [8], having the *trans*-diaxial arrangement of H-1 and AcO-2, should be more favourable for an elimination of acetic acid, there is a precedent in the literature which suggests that the stereochemistry at C-1–C-2 is not crucial for this process [9].

Hydrolysis of **2** with 1 M aqueous ethanolic NaOH at ~ 90 °C, then acetylation, and esterification of the carboxyl group, using diazomethane, afforded methyl 4,5,7-tri-*O*-acetyl-2,6-anhydro-3-deoxy-D-*arabino*-hept-2-enonate (**3**) in 91% yield.

Glycosidation of the glycal **3** was promoted by a mercuric salt. Thus, treatment of **3** with mercuric trifluoroacetate in methanol followed by potassium chloride gave a mixture of two diastereomers of α-D-*manno* (**4a**) and β-D-*gluco* (**4b**) configuration. To provide a proof of the stereochemistry at C-2 of **4a** and **4b**, the isomers were separated by flash chomatography on silica gel. Their structures were established by ^{1}H NMR data. The 500-MHz spectrum of the major product **4a** (the ratio of **4a**:**4b** = 4:1) exhibited a well-defined doublet at δ 3.36 for H-3 with a $J_{3,4}$ value of 5.2 Hz, supporting a *cis* axial–equatorial arrangement between the 3-chloromercuri substituent and the adjacent 4-acetoxy group. In contrast, the upfield shift to δ 2.53 (doublet) for H-3 in **4b**, as well as the $J_{3,4}$ value of 12.0 Hz, consistent with a *trans* equatorial–equatorial arrangement of the 3-chloromercuri and 4-acetoxy substituents, confirmed unambiguously the β-anomeric configuration of **4b**. A prevalence of the *trans*-diaxial addition product **4a** over the *trans*-diequatorial **4b** is comparable to previous findings on glycosidation of 1-methoxycarbonylglycals (sialic acid series) with *N*-bromo- and *N*-iodo-succinimide in methanol [10].

Reductive demercuration of the individual isomers **4a** and **4b** with triphenyltin hydride in the presence of an excess of NaOAc [11] resulted in the formation of methyl (methyl 4,5,7-tri-*O*-acetyl-3-deoxy-α-D-*arabino*-hept-2-ulopyranosid)onate (**5a**, DAH derivative) and its β anomer **5b**, respectively. The configuration of the products **5a** and **5b** was a final proof for *trans*-diaxial and *trans*-diequatorial addition of the methoxy–chloromercuri groups across the double bond in **3**.

It is worth noting that DAH accompanies DAHP produced by different strains of *Escherichia coli*. Assuming, however, that DAHP is formed from phosphoenol pyruvate and D-erythrose 4-phosphate in a condensation mediated by DAHP synthase, DHA may rather be a product of dephosphorylation of DAHP [2].

To introduce the phosphate group at O-7, deacetylation of **5**, leaving the C-1 methoxycarbonyl group untouched, was necessary. It was done by treatment of a methanolic solution of **5** with dry $NaHCO_3$ at room temperature over a 1-h period; the desired compound **6** was then isolated in high yield as the sole product. This sensitivity of the acetyl residues in **6** towards $NaHCO_3$ was very useful. Similar sensitivity of these acetates in **5** and **9** was observed in the presence of chlorotrimethylsilane in methanol to give **6** and **10**, respectively.

Further steps, leading to the DAHP derivative, were as follows: phosphorylation of **6a** with diphenyl phosphonate in pyridine [2] at −20 °C followed by flash chromatography on silica gel afforded the 7-phosphate derivative **7** in 95% yield. Diphenyl ester groups were removed by hydrogenolysis using Adams' catalyst, to give the phosphate **8**, isolated as a very hygroscopic white solid.

Methyl 4,5,7-tri-*O*-acetyl-2,6-anhydro-3-deoxy-D-*arabino*-hept-2-enonate (**3**), due to the unsaturation, is a potential precursor of modified heptulosonic acids. The simplest

modification that we performed was the hydrogenation of **3**. Compound **9** thus obtained, being a 2-deoxy analogue of DAH, is a known molecule [12]. By the route described above for DAHP synthesis, we prepared its 7-phosphate analogue **12**.

In summary, a convenient synthon for both DAH and DAHP, as well as for their 2-deoxy analogues, was prepared. Further investigations into the utilisation of 1-cyanoglycals in the synthesis of the 3-deoxy-2-ulosonic acids are now in progress.

3. Experimental

General methods.—Optical rotations were measured with a JASCO DIP Digital Polarimeter at room temperature. ^{1}H NMR spectra were recorded on Bruker AM-500 (500 MHz) and Varian AC-200 (200 MHz) spectrometers with Me_4Si as internal standard. Mass spectra were taken on an AMD-604 mass spectrometer. Reactions were monitored by TLC on silica gel [Merck alu-plates (0.2 mm)]. All reagents and solvents were purified and dried according to common methods [12]. Pyridine (used for phosphorylation reactions) was dried by distillation over KOH, CaH_2, and TsCl, successively, and left over CaH_2 in a dark glass bottle with serum cap. All organic solutions were dried over $MgSO_4$. Reaction products were purified by flash column chromatography, using Merck Kieselgel 60 (240–400 or 70–230 mesh).

4,5,7-Tri-O-*acetyl-2,6-anhydro-3-deoxy*-D-arabino-*hept-2-enononitrile* (**2**).—To a stirred solution of cyanide **1** (2.0 g, 5.60 mmol) [6] in dry CH_2Cl_2 (50 mL) was added DBU (2.0 mL, 13.3 mmol) at −20 °C. Stirring was continued at this temperature for 5 h, and the mixture was left overnight at −5 °C. TLC (1:1 hexane–ether) showed that some starting material remained. Since a prolonged reaction time or a higher temperature led to the destruction of the substrate, the reaction was interrupted and, after processing, the mixture was separated by chromatography on silica gel. Elution with 2:3 hexane–ether removed the unchanged **1**, and gave the desired **2** (1.2 g, 70%); mp 78–80 °C; $[\alpha]_D$ −42.4° (*c* 2.0, $CHCl_3$); lit. [8] mp 79–81 °C, $[\alpha]_D$ −46.6° ($CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.08, 2.10, 2.12 (3 s, 9 H, 3 × OAc), 4.19 (m, 1 H, H-7a), 4.38–4.50 (m, 2 H, H-6, H-7b), 5.22 (dt, 1 H, H-5), 5.38 (dd, 1 H, H-4), 5.72 (d, 1 H, H-3); $J_{3,4}$ 3.7, $J_{4,5}$ 5.5, $J_{5,6}$ 5.8 Hz, $J_{6,7a}$, $J_{6,7b}$, and $J_{7a,7b}$ - unresolved. Anal. Calcd for $C_{13}H_{15}NO_7$: C, 52.53; H, 5.09; N, 4.71. Found: C, 52.34; H, 5.11; N, 4.73.

Methyl 4,5,7-tri-O-*acetyl-2,6-anhydro-3-deoxy*-D-arabino-*hept-2-enonate* (**3**).—To a solution of nitrile **2** (3.0 g, 10.0 mmol) in EtOH (100 mL) was added 1 M aq NaOH (80 mL). The reaction mixture was heated to ~ 90 °C for 20 h, then cooled to room temperature and neutralised with AcOH. After evaporation under reduced pressure, the solid was treated with an excess of 1:1 Ac_2O–pyridine for 12 h. The mixture was then poured into ice–water, acidified with aq HCl to pH ~ 3, and extracted with EtOAc. The organic layers were washed with water, dried, and concentrated. The resulting syrup was redissolved in MeOH and treated with a solution of CH_2N_2 in ether. Filtration through a short column of silica gel (7:3 hexane–acetone) gave **3** (3.0 g, 91%) as a colourless oil; $[\alpha]_D$ −55.7° (*c* 0.69, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.07, 2.08, 2.10 (3 s, 9 H, 3 × OAc), 3.83 (s, 3 H, COOMe), 4.22 (dd, 1 H, H-7a), 4.44 (m, 1 H, H-6), 4.47 (t, 1 H, H-7b), 5.25 (dd, 1 H, H-5), 5.44 (m, 1 H, H-4), 6.04 (d, 1 H, H-3); $J_{3,4}$ 3.7, $J_{3,5}$

0.3, $J_{4,5}$ 5.4, $J_{4,6}$ 0.8, $J_{5,6}$ 6.7, $J_{6,7a}$ 2.8, $J_{6,7b}$ 5.8, $J_{7a,7b}$ 11.8 Hz. Anal. Calcd for $C_{14}H_{18}O_9$: C, 50.91; H, 5.49. Found: C, 51.20; H, 5.62.

*Methyl (methyl 4,5,7-tri-*O*-acetyl-3-chloromercuri-3-deoxy-α-*D*-manno-* (**4a**) *and methyl (methyl 4,5,7-tri-*O*-acetyl-3-chloromercuri-3-deoxy-β-*D*-gluco-hept-2-ulopyranosid)onate* (**4b**).—To a stirred solution of ester **3** (3.0 g, 9.08 mmol) in MeOH (60 mL) was added stepwise mercuric trifluoroacetate (7.8 g, 18.16 mmol) at 0 °C under Ar. Stirring was continued at room temperature. After 0.5 h, when TLC (3:2 hexane–acetone) showed that **3** was all consumed, KCl (2 g) was added, and the mixture was left overnight. Column chromatography of the product (1:3 hexane–ether) gave pure two diastereoisomers in a ratio $\alpha:\beta = 4:1$ (overall yield 80%). Eluted first was the β-D-*gluco* isomer (**4b**) (16%); mp 61–63°C; $[\alpha]_D$ +75.3° (*c* 1.7, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.03, 2.07, 2.10 (3 s, 9 H, 3 × OAc), 2.53 (dd, 1 H, H-3), 3.37 (s, 3 H, OMe), 3.89 (ddd, 1 H, H-6), 3.93 (s, 3 H, COOMe), 4.13–4.35 (m, 2 H, H-7, H-7a), 4.93–5.15 (m, 2 H, H-4, H-5); $J_{3,4}$ 12.0, $J_{4,5}$ 9.2, $J_{5,6}$ 9.9, $J_{6,7}$ 2.5, $J_{6,7a}$ 4.3, $J_{7,7a}$ 12.4 Hz. Eluted second was the α-D-*manno* isomer (**4a**) (64%); mp 145 °C; $[\alpha]_D$ −25.2° (*c* 1.75, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.05, 2.06, 2.14 (3 s, 9 H, 3 × OAc), 3.33 (s, 3 H, OMe), 3.36 (d, 1 H, H-3), 3.88 (s, 3 H, COOMe), 3.98 (ddd, 1 H, H-6), 4.18 (dd, 1 H, H-7a), 4.28 (dd, 1 H, H-7b), 4.98 (dd, 1 H, H-5), 5.81 (dd, 1 H, H-4); $J_{3,4}$ 5.2, $J_{4,5}$ 8.7, $J_{5,6}$ 9.9, $J_{6,7a}$ 2.5, $J_{6,7b}$ 4.3, $J_{7a,7b}$ 12.4 Hz.

*Methyl (methyl 4,5,7-tri-*O*-acetyl-3-deoxy-α-*D*-arabino-hept-2-ulopyranosid)onate* (**5a**).—A mixture of **4a** (3.2 g, 5.36 mmol) and dry NaOAc (2.1 g, 25 mmol) in dry toluene (50 mL) was treated with triphenyltin hydride (solution in toluene) (2.1 g, 6.0 mmol) and azobis(isobutyronitrile) (10 mg) at 0 °C under Ar. The reaction was stirred overnight; TLC (1:3 hexane–ether) showed that **4a** was all consumed. Evaporation left a residue which was dissolved in ether, treated with aq 30% KF, and stirred overnight. After filtration through Celite, the organic phase was separated, dried, and evaporated. Column chromatography of the residue (2:3 hexane–ether) gave **5a** as a colourless oil (1.7 g, 90%); $[\alpha]_D$ +46.4° (*c* 1.04, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.87 (dd, 1 H, H-3ax), 2.01, 2.05, 2.09 (3 s, 9 H, 3 × OAc), 2.52 (dd, 1 H, H-3eq), 3.29 (s, 3 H, OMe), 3.81 (s, 3 H, COOMe), 3.90 (ddd, 1 H, H-6), 4.15 (dd, 1 H, H-7a), 4.32 (dd, 1 H, H-7b), 5.04 (t, 1 H, H-5), 5.34 (m, 1 H, H-4); $J_{3ax,3eq}$ 13.0, $J_{3ax,4}$ 11.5, $J_{3eq,4}$ 5.4, $J_{4,5}$ 9.7, $J_{5,6}$ 10.0, $J_{6,7a}$ 2.4, $J_{6,7b}$ 5.2, $J_{7a,7b}$ 12.3 Hz. Anal. Calcd for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12. Found: C, 49.52; H, 6.30.

*Methyl (methyl 4,5,7-tri-*O*-acetyl-3-deoxy-β-*D*-arabino-hept-2-ulopyranosid)onate* (**5b**).—Processing was similar to that described for the preparation of **5a**, to give **5b** as a colourless oil (89%); $[\alpha]_D$ +46.5° (*c* 1.49, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.94 (dd, 1 H, H-3ax), 2.03, 2.04 2.10 (3 s, 9 H, 3 × OAc), 2.65 (dd, 1 H, H-3eq), 3.36 (s, 3 H, OMe), 3.86 (s, 3 H, COOMe), 4.01 (ddd, 1 H, H-6), 4.20 (dd, 1 H, H-7a), 4.31 (dd, 1 H, H-7b), 4.99 (m, 1 H, H-4), 5.05 (t, 1 H, H-5); $J_{3ax,3eq}$ 13.2, $J_{3ax,4}$ 11.1, $J_{3eq,4}$ 5.0, $J_{4,5}$ 9.2, $J_{5,6}$ 9.4, $J_{6,7a}$ 2.6, $J_{6,7b}$ 4.4, $J_{7a,7b}$ 12.3 Hz. HR-MS (LSIMS): Calcd for $C_{15}H_{22}O_{10}$ [M + Na]: *m/z* 385.1111. Found: *m/z* 385.1116.

*Methyl (methyl 3-deoxy-α-*D*-arabino-hept-2-ulopyranosid)onate* (**6a**).—To a solution of ester **5a** (2.0 g, 5.52 mmol) in MeOH (10 mL) was added $NaHCO_3$ (2 g) and the resulting suspension was stirred at room temperature for 1 h (TLC, 9:1 CH_2Cl_2–MeOH). The mixture was filtered through Celite and a short column of silica gel to give **6a**

(white crystals, 1.2 g, 90%); mp 146–147 °C; $[\alpha]_D$ +79.4° (*c* 0.90, MeOH); ^{1}H NMR (500 MHz, D_2O): δ 1.75 (dd, 1 H, H-3ax), 2.36 (dd, 1 H, H-3eq), 3.25 (s, 3 H, OMe), 3.42 (t, 1 H, H-5), 3.59 (ddd, 1 H, H-6), 3.84 (dd, 1 H, H-7b), 3.87 (s, 3 H, COOMe), 3.91–3.98 (m, 2 H, H-4, H-7a); $J_{3ax,3eq}$ 13.4, $J_{3ax,4}$ 11.6, $J_{3eq,4}$ 5.2, $J_{4,5}$ 9.5, $J_{5,6}$ 10.0, $J_{6,7a}$ 2.3, $J_{6,7b}$ 5.5, $J_{7a,7b}$ 12.4 Hz.

*Methyl (methyl 3-deoxy-β-*D-arabino-*hept-2-ulopyranosid)onate* (**6b**).—Processing was similar to that described for the preparation of **6a**, to give **6b** as a colourless oil (95%); $[\alpha]_D$ +44.3° (*c* 0.89, MeOH); ^{1}H NMR (500 MHz, D_2O): δ 1.63 (dd, 1 H, H-3ax), 2.45 (dd, 1 H, H-3eq), 3.22 (s, 3 H, OMe), 3.25 (t, 1 H, H-5), 3.40–350 (m, 2 H, H-4, H-6), 3.64 (dd, 1 H, H-7b), 3.72 (s, 3 H, COOMe), 3.76 (dd, 1 H, H-7a); $J_{3ax,3eq}$ 12.9, $J_{3ax,4}$ 11.9, $J_{3eq,4}$ 4.8, $J_{4,5}$ 9.2, $J_{5,6}$ 9.7, $J_{6,7a}$ 2.3, $J_{6,7b}$ 5.0, $J_{7a,7b}$ 12.4 Hz.

*Methyl (methyl 3-deoxy-α-*D-arabino-*hept-2-ulopyranosid)onate 7-(diphenyl phosphate)* (**7**).—The ester **6a** (100 mg, 0.42 mmol) was dissolved in dry pyridine (2 mL) and freshly distilled diphenyl phosphorochloridate (0.1 mL, 0.50 mmol) was added at −20 °C under Ar. The reaction mixture was stirred until all substrate **6a** was consumed (20–30 min) (TLC, EtOAc). The reaction mixture was then diluted with toluene and concentrated under reduced pressure. Pyridine was removed by evaporation with toluene. Flash chromatography (95:5 CH_2Cl_2–MeOH) of the mixture on silica gel yielded **7** (190 mg, 95%) as a light-yellow oil; $[\alpha]_D$ +14.5° (*c* 2.52, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.58 (dd, 1 H, H-3ax), 2.34 (dd, 1 H, H-3eq), 3.19 (s, 3 H, OMe), 3.24 (t, 1 H, H-5), 3.56 (m, 1 H, H-6), 3.81 (s, 3 H, COOMe), 3.94 (m, 1 H, H-4), 4.43 (td, 1 H, H-7a) 4.63 (m, 1 H, H-7b), 7.20–7.37 (m, 10 H, Ar); $J_{3ax,3eq}$ 13.1, $J_{3ax,4}$ 11.4, $J_{3eq,4}$ 5.1, $J_{4,5}$ 9.2, $J_{5,6}$ 9.7, $J_{6,7a}$ 2.0, $J_{6,7b}$ 3.5, $J_{7a,7b}$ 11.9, $J_{7a,P}$ 12.0, $J_{7b,P}$ 9.8 Hz.

*Methyl (methyl 3-deoxy-α-*D-arabino-*hept-2-ulopyranosid)onate 7-(dihydrogen phosphate)* (**8**).—The phosphate ester **7** (100 mg, 0.21 mmol) dissolved in EtOH (96%, 6 mL) was vigorously stirred with PtO_2 (50 mg) under H_2 for 12 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated. The residue was washed with ether to give **8** as a white, very hygroscopic solid (65 mg, 100%); $[\alpha]_D$ +51.5° (*c* 1.20, MeOH); ^{1}H NMR (500 MHz, D_2O): δ 1.77 (dd, 1 H, H-3ax), 2.35 (dd, 1 H, H-3eq), 3.25 (s, 3 H, OMe), 3.49 (t, 1 H, H-5), 3.70 (bdd, 1 H, H-6), 3.85 (s, 3 H, COOMe), 3.94 (m, 1 H, H-4), 4.12–4.22 (m, 2 H, H-7a, H-7b); $J_{3ax,3eq}$ 13.3, $J_{3ax,4}$ 11.6, $J_{3eq,4}$ 5.2, $J_{4,5}$ 9.2, $J_{5,6}$ 9.5, $J_{6,7a}$ 2.0, $J_{6,7b}$ 5.7, $J_{7a,7b}$ 11.7, $J_{7a,P}$ 5.7, $J_{7b,P}$ 7.0 Hz. HR-MS (LSIMS): Calcd for $C_9H_{17}O_{10}P$ [M + Na]: *m/z* 339.0457. Found: *m/z* 339.0453.

*Methyl 4,5,7-tri-*O*-acetyl-2,6-anhydro-3-deoxy-*D-gluco-*heptonate* (**9**).—The ester **3** (250 mg, 0.75 mmol) dissolved in EtOH (5 mL) was vigorously stirred with Pd–C (200 mg) under H_2 for 12 h. TLC (3:2 hexane–EtOAc) showed disappearance of the substrate. The mixture was filtered through Celite, and the filtrate was concentrated, to give **9** (250 mg, 100%) as a colourless oil; $[\alpha]_D$ −0.8° (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.63, 1.68, 1.69 (3 s, 9 H, 3 × OAc), 1.66 (dd, 1 H, H-3ax), 2.20 (ddd, 1 H, H-3eq), 3.15 (ddd, 1 H, H-6), 3.25 (s, 3 H, COOMe), 3.54 (dd, 1 H, H-2), 4.07 (dd, 1 H, H-7a), 4.33 (dd, 1 H, H-7b), 4.99 (m, 1 H, H-4), 5.18 (t, 1 H, H-5); $J_{2,3ax}$ 12.1, $J_{2,3eq}$ 2.2, $J_{3ax,3eq}$ 12.9, $J_{3ax,4}$ 9.5, $J_{3eq,4}$ 5.3, $J_{4,5}$ 9.8, $J_{5,6}$ 10.2, $J_{6,7a}$ 2.1, $J_{6,7b}$ 4.6, $J_{7a,7b}$ 12.4 Hz. Anal. Calcd for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07. Found: C, 50.48; H, 6.21.

Methyl 2,6-anhydro-3-deoxy-D-gluco-*heptonate* (**10**).—To a cooled (−20 °C) solution of **9** (150 mg, 0.45 mmol) in MeOH (10 mL) was added dropwise Me_3SiCl (0.5 mL). The resulting mixture was stirred at room temperature overnight (TLC, 9:1 CH_2Cl_2–MeOH). The mixture was then neutralised with $NaHCO_3$ and filtered through a short column of silica gel to give **10** (85 mg, 95%) as white crystals; mp 139–141 °C, $[\alpha]_D$ +24.8° (*c* 0.9, MeOH); ^{1}H NMR (500 MHz, D_2O): δ 1.62 (dd, 1 H, H-3ax), 2.40 (ddd, 1 H, H-3eq), 3.31 (t, 1 H, H-5), 3.42 (ddd, 1 H, H-6), 3.76 (dd, 1 H, H-7b), 3.77 (m, 1 H, H-4), 3.80 (s, 3 H, COOMe), 3.92 (dd, 1 H, H-7a), 4.33 (dd, 1 H, H-2); $J_{2,3ax}$ 12.2, $J_{2,3eq}$ 2.3, $J_{3ax,3eq}$ 12.9, $J_{3ax,4}$ 12.3, $J_{3eq,4}$ 5.1, $J_{4,5}$ 9.2, $J_{5,6}$ 8.2, $J_{6,7a}$ 2.2, $J_{6,7b}$ 5.9, $J_{7a,7b}$ 12.4 Hz. Anal. Calcd for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.42; H, 7.04.

Methyl 2,6-anhydro-3-deoxy-D-gluco-*heptonate 7-(dihydrogen phosphate)* (**12**).—The ester **10** (100 mg, 0.48 mmol) was dissolved in dry pyridine (3 mL) and freshly distilled diphenyl phosphorochloridate (0.1 mL, 0.50 mmol) was added at −20 °C under Ar. The reaction mixture was stirred until TLC (EtOAc) showed disappearance of **10** (20–30 min). Further processing was similar to that described for the preparation of **8**, to give **12** (120 mg, 90%) as a white solid; $[\alpha]_D$ +17.5° (*c* 1.20, MeOH); ^{1}H NMR (500 MHz, D_2O): δ 1.63 (dd, 1 H, H-3ax), 2.38 (ddd, 1 H, H-3eq), 3.40 (t, 1 H, H-5), 3.53 (bdd, 1 H, H-6), 3.76 (ddd, 1 H, H-4), 3.78 (s, 3 H, COOMe), 4.08 (m, 1 H, H-7a), 4.17 (ddd, 1 H, H-7b), 4.33 (dd, 1 H, H-2); $J_{2,3ax}$ 12.2, $J_{2,3eq}$ 2.2, $J_{3ax,3eq}$ 12.9, $J_{3ax,4}$ 12.3, $J_{3eq,4}$ 5.1, $J_{4,5}$ 9.2, $J_{5,6}$ 9.5, $J_{6,7a}$ 1.8, $J_{6,7b}$ 5.1, $J_{7a,7b}$ 11.5, $J_{7a,P}$ 5.5 Hz. HR-MS (LSIMS): Calcd for $C_8H_{15}O_9P$ [M + Na]: *m/z* 309.0351. Found: *m/z* 309.0341.

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