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Note

Sugar β-ketoesters: new chirons in the synthesis of 6-deoxyheptulosurono-7,4-lactones

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The development of new strategies for the formation of such a molecular skeleton as a tetrahydrofuran ring cis-fused to a γ-lactone is a topic of current interest in organic synthesis [1]. This structural unit constitutes the main component of a number of biologically active natural products such as piptosidin, dilaspirolactone [1], (+)-delesserine [2], goniofufurone [3], and polyether antibiotics [4]. In the present communication, we report the synthesis of hitherto unknown sugar β-ketoesters **2a–c** and demonstrate the first example of the application of these β-ketoesters in the synthesis of 6-deoxyheptulofuranosid-urono-7,4-lactones **3a–c** with methoxyl functionality at the ring junction.

A convenient method for the synthesis of β-ketoesters is the reaction of aldehydes with ethyl diazoacetate (EDA) in the presence of a Lewis acid [5]. However, sugar aldehydes are known to give these products only in low yields [6–8]. As a part of our interest in the synthesis of new chirons from sugars [9], we have investigated the same reaction with certain sugar dialdoses and optimized the conditions to obtain high yields of hitherto unknown β-ketoesters. Thus, reaction of dialdose **1a** with EDA, in the presence of 50 mol% BF_3 etherate in dry dichloromethane, afforded the β-ketoester **2a** in 85% yield. Our attempts to use other Lewis acids, such as tin(II) chloride, tin(IV) chloride, zinc chloride, and zinc bromide, in variable amounts (10 mol% to 1 mol equiv) and with different reaction conditions (0–20°C) and solvents, gave low yields (< 50%) of **2a**. The reaction (with 50 mol% BF_3 etherate) was found to be general and high yields of β-ketoes-

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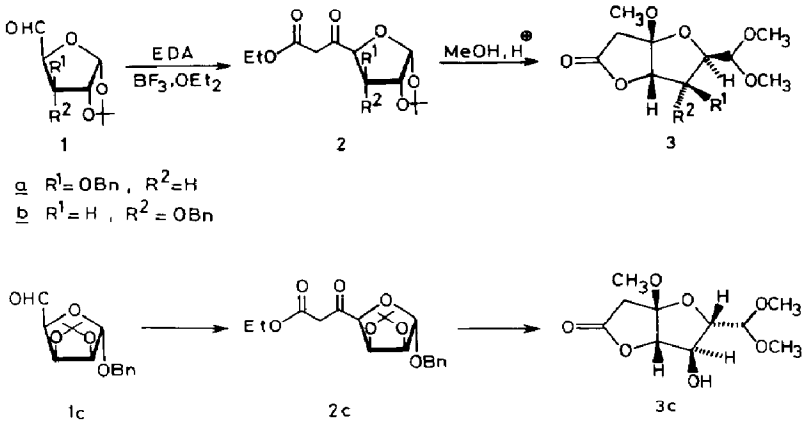
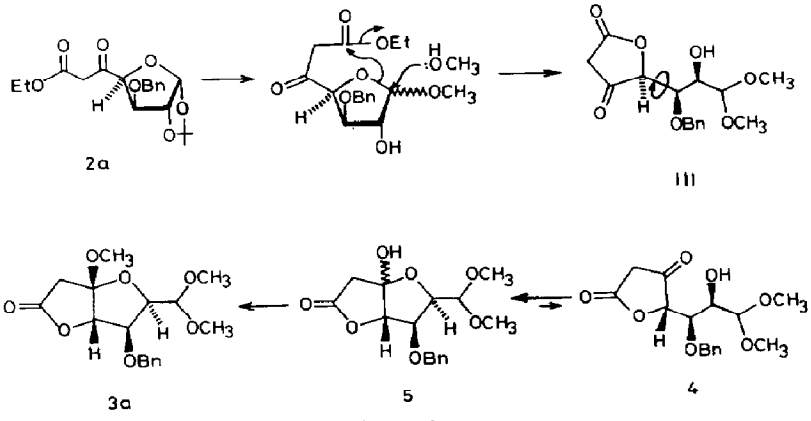


Scheme 1.

ters **2b** and **2c** were obtained from the easily available dialdoses **1b** and **1c**, respectively [10,11].

The β-ketoesters **2a–c** could represent versatile intermediates as they provide a polyoxygenated carbon framework with multiple avenues of chirality, as well as an access for functional group transformation on the active methylene group. To demonstrate this fact, our original plan was to synthesize five-membered carbocyclic compounds by treating **2a** with acidic methanol to give the anomeric methyl glycosides and convert the free HO-2 group into a good leaving group. Base-catalyzed intramolecular alkylation (attack of the active methylene carbon at C-2) would then have led to the required five-membered carbocyclic skeleton. However, when **2a–c** were each treated with methanolic 2.5% H_2SO_4, under reflux, we isolated 6-deoxyheptulosidurono-γ-lactones **3a–c** (Scheme 1). The IR band at 1790 cm^{-1} and the AB quartet in the region δ 2–3, with J_{gem} 17.5 Hz, for 6-deoxy protons in the ^1H NMR spectrum confirmed the formation of the five-membered lactone. The spectral and analytical data coupled with the mode of formation



Scheme 2.

(Scheme 2) require these compounds to have the tetrahydrofuran ring cis-fused with the γ-lactone and having methoxyl functionality at the ring junction.

The formation of 6-deoxyheptulosiduronolactones can be explained via the intermediate **4**, obtained by acetal exchange to give dimethyl acetal functionality and the requisite lactone ring formation. Intermediate **4** is then converted into a hemiacetal **5** by ring closure from the hydroxyl at C-2 and then into the acetal **3** (Scheme 2).

In conclusion, we have devised a direct method for two-carbon homologation of dialdoses, leading to sugar β-ketoesters in high yield, and a facile one-step conversion of these β-ketoesters into bicyclic heptulosiduronolactones with methoxyl functionality at the ring junction.

1. Experimental

General methods.—^{1}H NMR spectra of $CDCl_3$ solutions were recorded with Jeol FX 90 Q (90 MHz) and Bruker AC 200 (200 MHz) spectrometers. Chemical shifts are reported in ppm (δ) relative to internal Me_4Si. IR spectra were recorded with a Perkin–Elmer Model 337 spectrophotometer. Optical rotations were measured at 25°C with a Perkin–Elmer 241 polarimeter. C,H analyses were performed on a Hosli Carbon–Hydrogen analyser. All the reactions were conducted in oven-dried glassware under dry N_2. Flash chromatography was carried out using Kieselgel 60 (230–400 mesh) with petroleum ether (bp 40–60°C)–EtOAc as eluent. All solvents were purified and dried before use. The dialdoses **1a–c** were prepared according to literature procedures [10,11]. Ethyl diazoacetate and BF_3 etherate were purchased from Aldrich.

*Ethyl 3-O-benzyl-6-deoxy-1,2-O-isopropylidene-α-*D-xylo-*heptofuranuronate-5-ulose* (**2a**).—A solution of **1a** (0.56 g, 2 mmol) and ethyl diazoacetate (0.34 g, 3 mmol) in dry CH_2Cl_2 (18 mL) was cooled to 0°C under N_2. BF_3 etherate (0.14 g, 1 mmol) in CH_2Cl_2 (2 mL) was added drop by drop, controlling the N_2 evolution at a low steady rate. The reaction was allowed to warm gradually, stirred at 15°C for 3 h, and quenched with aq 10% $NaHCO_3$. The resulting mixture was extracted with diethyl ether (3 × 20 mL), and the ether extract washed with brine, dried over anhyd Na_2SO_4, and evaporated (rotary evaporator) to give an oil. Flash chromatography using 19:1 petroleum ether–EtOAc afforded **2a** (0.62 g, 85%) as a colourless oil; $[\alpha]_D$ −98.2° (*c* 1, $CHCl_3$); IR: ν_{max} 1730, 1752 cm^{-1}; ^{1}H NMR: δ 1.24 (t, 3 H, *J* 7.5 Hz, CH_2CH_3), 1.31 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 3.46 (d, 1 H, $J_{6a,6b}$ 17 Hz, H-6a), 3.71 (d, 1 H, H-6b), 4.16 (q, 2 H, CH_2CH_3), 4.26 (d, 1 H, $J_{3,4}$ 3.4 Hz, H-3), 4.52 (bs, 2 H, OCH_2Ph), 4.55 (d, 1 H, H-4), 4.68 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-2), 6.04 (d, 1 H, H-1), 7.15–7.42 (m, 5 H, Ph). Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.62; H, 6.64, Found: C, 62.49; H, 6.58.

*Ethyl 3-O-benzyl-6-deoxy-1,2-O-isopropylidene-α-*D-ribo-*heptofuranuronate-5-ulose* (**2b**).—Treatment of dialdose **1b** (0.56 g, 2 mmol) in CH_2Cl_2 as described above, at 0–10°C, for 2 h gave **2b** (0.60 g, 83%) as a colourless oil; $[\alpha]_D$ + 38.5° (*c* 1, $CHCl_3$); IR: ν_{max} 1735, 1755 cm^{-1}; ^{1}H NMR: δ 1.2 (t, 3 H, *J* 7.7 Hz, CH_2CH_3),

1.34 (s, 3 H, CH_3), 1.57 (s, 3 H, CH_3), 3.47 (d, 1 H, $J_{6a,6b}$ 16.7 Hz, H-6a), 3.67 (d, 1 H, H-6b), 3.94 (dd, 1 H, $J_{3,4}$ 5.1, $J_{2,3}$ 9.5 Hz, H-3), 4.15 (q, 2 H, CH_2CH_3), 4.34–4.95 (m, 4 H, H-2,4 and OCH_2Ph), 5.78 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 7.34 (s, 5 H, Ph). Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.62; H, 6.64, Found: C, 62.72; H, 6.60.

*Ethyl (benzyl 6-deoxy-2,3-*O*-isopropylidene-α-*D*-lyxo-heptofuranosid)uronate-5-ulose* (**2c**).—Treatment of dialdose **1c** (0.56 g, 2 mmol) and ethyl diazoacetate (0.34 g, 3 mmol) with BF_3 etherate (0.14 g, 1 mmol) in CH_2Cl_2 as described above, for 4 h, gave **2c** (0.57 g, 78%) as a colourless oil; $[\alpha]_D$ + 2.0° (*c* 1, $CHCl_3$); IR: ν_{max} 1730, 1750 cm^{-1}; ^1H NMR: δ 1.24 (s, 3 H, CH_3), 1.27 (t, 3 H, *J* 7.4 Hz, CH_2CH_3), 1.40 (s, 3 H, CH_3), 3.46 (d, 1 H, $J_{6a,6b}$ 16 Hz, H-6a), 3.75 (d, 1 H, H-6b), 4.20 (q, 2 H, CH_2CH_3), 4.35–4.77 (m, 4 H, H-2,4 and OCH_2Ph), 5.02 (dd, 1 H, $J_{3,4}$ 4.0, $J_{2,3}$ 6.0 Hz, H-3), 5.21 (s, 1 H, H-1), 7.42 (s, 5 H, Ph). Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.62; H, 6.64. Found: C, 62.83; H, 6.78.

*Methyl 3-*O*-benzyl-6-deoxy-β-*D*-xylo-hept-5-ulo-5,2-furanosidurono-7,4-lactone dimethyl acetal* (**3a**).—A solution of **2a** (0.4 g, 1.1 mmol) in methanolic 2.5% H_2SO_4 (8 mL) was refluxed for 2 h. The solution was neutralized with aq satd $NaHCO_3$. Methanol was removed under reduced pressure and the residue was extracted with $CHCl_3$ (3 × 20 mL). Flash chromatographic purification using 19:1 petroleum ether–EtOAc gave **3a** as a colourless oil (0.28 g, 75%); $[\alpha]_D$ + 3.9° (*c* 1, $CHCl_3$); IR (neat): ν_{max} 1792, 1447, 1356, 1193 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.88 (d, 1 H, $J_{6a,6b}$ 18.1 Hz, H-6a), 3.00 (d, 1 H, H-6b), 3.40 (s, 3 H, OCH_3), 3.43 (s, 3 H, OCH_3), 3.45 (s, 3 H, OCH_3), 4.15–4.21 (m, 2 H, H-2,3), 4.59–4.80 (m, 4 H, $-OCH_2Ph$, H-1,4), 7.36 (s, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 22.5 MHz): δ 39.3 (C-6), 51.4, 52.6, 54.6 (OCH_3), 72.9 (OCH_2Ph), 80.7 (C-3), 87.0, 88.0 (C-4,2), 101.9 (C-1), 111.7 (C-5), 127.4, 137.1 (Ph), 171.7 (C-7). Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.34; H, 6.55. Found: C, 60.07; H, 6.67.

*Methyl 3-*O*-benzyl-6-deoxy-β-*D*-ribo-hept-5-ulo-5,2-furanosidurono-7,4-lactone dimethyl acetal* (**3b**).—Treatment of **2b**, as described for **2a**, gave **3b** as a colourless oil (0.24 g, 65%); $[\alpha]_D$ −70.6° (*c* 1, $CHCl_3$); IR (neat): ν_{max} 1795, 1450, 1305, 1200, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.78 (d, 1 H, $J_{6a,6b}$ 17.5 Hz, H-6a), 3.02 (d, 1 H, H-6b), 3.36 (s, 3 H, OCH_3), 3.41 (s, 3 H, OCH_3), 3.42 (s, 3 H, OCH_3), 4.18–4.35 (m, 3 H, H-1,2,3), 4.58 (d, 1 H, *J* 11.8 Hz, OCH_2Ph), 4.66 (d, 1 H, $J_{4,3}$ 4.7 Hz, H-4), 4.75 (d, 1 H, OCH_2Ph), 7.42 (bs, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 22.5 MHz): δ 39.3 (C-6), 51.1, 53.9, 55.1 (OCH_3), 72.8 (OCH_2Ph), 78.4 (C-3), 83.2, 84.1 (C-2,4), 104.2 (C-1), 111.7 (C-5), 127.8, 128.2, 137.4 (Ph), 172.3 (C-7). Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.34; H, 6.55. Found: C, 60.60; H, 6.45.

*Methyl 6-deoxy-β-*D*-lyxo-hept-5-ulo-5,2-furanosidurono-7,4-lactone dimethyl acetal* (**3c**).—A solution of **2c** (0.4 g, 1.098 mmol) in methanolic 2.5% H_2SO_4 (8 mL) was refluxed for 3 h. Work up as above gave a residue which, on chromatographic purification with 4:1 petroleum ether–EtOAc, gave **3c** as a colourless oil (0.17 g, 62%); $[\alpha]_D$ −29.8° (*c* 1, $CHCl_3$); IR (neat) 3700–3200, 1765, 1453, 1355, 1201 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz), δ 2.30–2.62 (bs, 1 H, exchanges with D_2O, OH), 2.81 (d, 1 H, $J_{6a,6b}$ 17.4 Hz, H-6a), 2.96 (d, 1 H, H-6b), 3.45 (s, 3 H, OCH_3), 3.47 (s, 3 H, OCH_3), 3.50 (s, 3 H, OCH_3), 4.11 (t, 1 H, $J_{1,2} = J_{2,3} = 6.5$ Hz, H-2), 4.35 (dd, 1 H, $J_{3,4}$ 1.8 Hz, H-3), 4.44 (d, 1 H, H-1), 4.71 (d, 1 H, H-4); ^{13}C NMR

($CDCl_3$, 22.5 MHz): δ 38.8 (C-6), 51.6, 54.3, 55.8 (OCH_3), 85.4, 91.3, 91.4 (C-2,3,4), 104.8 (C-1), 111.3 (C-5), 171.8 (C-7). Anal. Calcd for $C_{10}H_{16}O_7$: C, 48.38; H, 6.50. Found: C, 48.32; H, 6.65.

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