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Preliminary communication

An approach to β-lactams from α,β-unsaturated sugar δ-lactones

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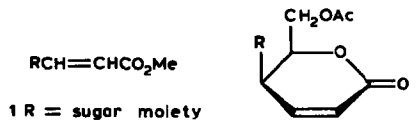
α,β-Unsaturated aldonates **1** have been employed as starting materials for the synthesis of natural products or their analogues[1–5]. Attention has been focussed on the Michael addition of alkoxides[1] and benzylamine[2], (4 + 2)-cycloaddition of cyclopentadiene[3,4], or a Wittig ylid addition[5]. Despite the acyclic structure of the substrates, marked asymmetric induction was observed due to the proximity of the chiral center.



2 R = H
3 R = OAc

We have shown that 6-acetoxymethyl-5,6-dihydro-2-pyrone (**2**) and 4,6-di-*O*-acetyl-2,3-dideoxy-D-*threo*-hex-2-enono-1,5-lactone (**3**), which are structurally related to **1**, display high stereoselectivity in 1,3-dipolar cycloaddition reactions with nitrones, even for **2** in which the stereocontrolling centre is in a homoallylic position with respect to the double bond[6].

During investigation of the utility of **2** and **3** in synthesis, attention was turned to the Michael addition of nitrogen nucleophiles with the intention of synthesising a β-lactam precursor of thienamycin.

Addition of *O*-benzylhydroxylamine (1 equiv.) to **2** (ethanol, room temp., 48 h) afforded the unstable *trans*-6-acetoxymethyl-3-benzyloxyamino-2-pyrone (**4**†, 70%) as the sole product; colourless syrup; ν_{max}^{film} 3470 (NH), 1750 cm^{-1} (C=O); ^1H-n.m.r. ($CDCl_3$): *inter alia*, δ 1.80 (ddd, 1 H, *J* 14.7, 11.3, and 5.0 Hz, H-4′), 1.91

†All new compounds gave satisfactory spectroscopic and analytical data. Formulae of compounds derived from **2** represent D compounds although in fact they are DL.

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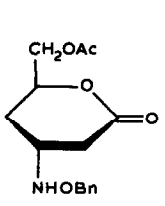
(ddt, 1 H, *J* 3.6, 3.2, and 1.2 Hz, H-4), 2.49 (ddd, 1 H, *J* 17.3 and 5.1 Hz, H-2), 2.68 (dd, 1 H, *J* 6.2 Hz, H-2′), 3.61 (m, 1 H, H-3), 4.66 (m, 1 H, H-5). Attempts to purify **4** converted it into **2**; hence, it was not purified but used immediately for the next step. Essentially the same stereochemical outcome was observed[7] on azide ion addition to **2**. Benzylamine or *N*-benzylhydroxylamine, used under similar conditions, attacked the carbonyl carbon atom of **2** to form acyclic amides which were not investigated further. In contrast to our findings, *O*-benzylhydroxylamine has been reported to open saturated lactones, producing *O*-benzylhydroxamates[8]. The observed regio- and stereo-selectivity in the formation of **4** is due to the enhanced nucleophilicity of *O*-benzylhydroxylamine because of the α-effect[9], and the preferred axial attack of the reagent.



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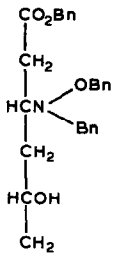

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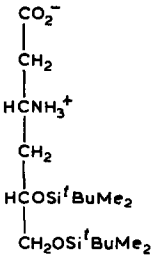

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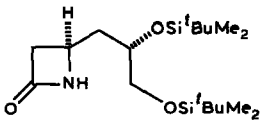

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The crude lactone **4** (2 mmol) was transformed into the benzyl ester **5** (30%). Thus, **4** was saponified (2 equiv. of KOH, aqueous methanol, room temp., 24 h) and the resulting potassium salt was treated (room temp., 72 h) with benzyl bromide in *N,N*-dimethylformamide in the presence of a catalytic amount of 18-crown-6. Chromatography then gave benzyl 3-(*N*-benzyl-*N*-benzyloxyamino)-2,3,4-trideoxy-DL-*erythro*-hexonate (**5**); colourless syrup; ν_{max}^{film} 3400 (OH), 1720 cm^{-1} (C=O); ^{1}H-n.m.r. ($CDCl_3$): *inter alia*, δ 1.51 (dt, 1 H, *J* 14.5, 3.0, and 3.0 Hz, H-4), 1.88 (dt, 1 H, *J* 10.4 and 10.4 Hz, H-4′), 2.46 (dd, 1 H, *J* 15.4 and 8.7 Hz, H-2), 3.00 (dd, 1 H, *J* 4.3 Hz, H-2′), ~3.7 (m, 1 H, H-3), 3.80 (m, 1 H, H-5). *tert*-Butyldimethylsilylation of **5** and hydrogenolysis of the product (methanol, 3 atm., H_2 Pd–C) afforded 3-amino-5,6-di(*tert*-butyldimethylsilyl)-2,3,4-trideoxy-DL-*erythro*-hexonic acid (**6**, 60%); colourless syrup; ν_{max}^{film} 3090, 2870, 2630, 2120 (NH_3^+), 1560, 1400 cm^{-1} (CO_2^-); ^{1}H-n.m.r. ($CDCl_3$): *inter alia*, δ 1.85 (m, 2 H, H-4,4′), 2.50 (m, 2 H, H-2,2′), 3.55 (m, 1 H, H-3), 3.85 (m, 1 H, H-5). Cyclisation of **6** (2 mmol), using 2-chloro-1-methylpyridinium iodide[11] (1.1 equiv., room temp., 2.2 equiv. of Et_3N, 2 h), gave (4*R**, 2′*S**)-4-[2′,3′-di(*tert*-butyldimethylsilyloxy)-propyl]aazetidin-2-one (**7**, 86%); colourless syrup; ν_{max}^{film} 3250 (NH), 1750 cm^{-1} (C=O); ^{1}H-n.m.r. ($CDCl_3$): *inter alia*, δ 1.78 (dt, 1 H, *J* 15.1 and 7.5 Hz, H-1′a), 1.94 (ddd, 1 H, *J* 6.0 and 4.1 Hz, H-1′b), 2.60 (ddd, 1 H, *J* 14.7, 2.6, and 1.5 Hz, H-3a), 3.08 (ddd, 1 H, *J* 5.0 and 1.6 Hz, H-3b), 3.39 (dd, 1 H, *J* 9.8 and 7.3 Hz, H-3′a), 3.57 (dd, 1 H, *J* 5.0 Hz, H-3′b), 3.77 (m, 2 H, H-2′,4); mass spectrum: *m/z* 373 (M^+).

Thus, readily available α,β-unsaturated lactones are attractive substrates for the synthesis of selected structures. Michael addition of nitrogen nucleophiles to the lactones **2** and **3** involves marked stereocontrol in the formation of the new chiral centre at C-3, and *O*-benzylhydroxylamine is an attractive soft nucleophile which attacks preferentially at the β-carbon atom of the α,β-unsaturated lactone system.

ACKNOWLEDGMENT

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