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Synthesis of a Heteroannulated Furanose *via* Intramolecular Michael Addition in an ω-Hydroxy α,β-Unsaturated Nitrile†

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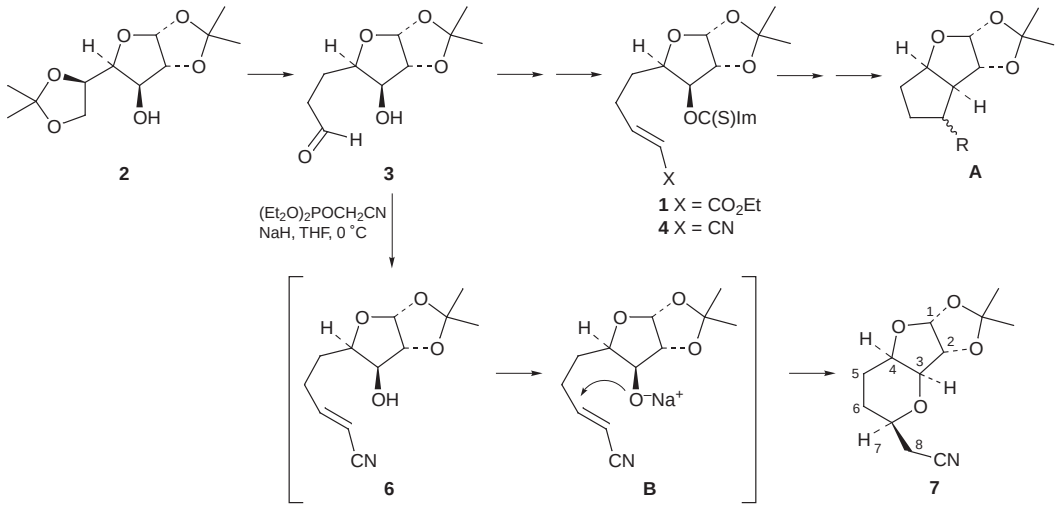
An highly stereospecific Michael addition in the ω-hydroxy α,β-unsaturated nitrile **4**, obtained from 'diacetone glucose' **2**, leading to annulated furanose **7** is reported.

For a number of years we have been actively working in the synthesis and reactivity of 'annulated furanoses.' These compounds are key intermediates for the preparation of enantiomerically pure building blocks[1] and natural products,[2] and have been prepared by using free radical cyclizations[3] on conveniently substituted radical precursors derived from sugars.[4]

In the course of these studies, some years ago we described the synthesis of the radical precursor **1** from 'diacetone glucose' **2**, *via* Wittig reaction of aldehyde **3** followed by thiocarbonyl imidazolide formation (Scheme 1).[5] In connection with these studies, and in the context of a current project under progress in our laboratory, aimed at developing practical routes for the synthesis of chiral cyclopentanes (**A**; Scheme 1) from these intermediates, we wanted to prepare the analogous intermediate **4** from aldehyde **3**. In this contribution we report the unexpected result obtained during the olefination of aldehyde **3** that has resulted in the formation of the branched-chain sugar derivative **7** in very good yield and in an highly stereospecific manner.

Starting with aldehyde **3**,[5] after treatment with diethyl cyanomethylphosphonate and sodium hydride, in dry THF at room temperature (see Experimental section), after work-up and chromatography we isolated product **7**, as a white solid in 88% yield. ^{1}H NMR analysis of the crude reaction mixture clearly demonstrated that this product was a mixture of two isomers in a 9:1 ratio. After recrystallization the major isomer was isolated in almost pure form. The major compound **7** showed analytical data [we obtained a correct elemental analysis for $C_{12}H_{17}NO_4$ and a mass spectrum with the molecular ion at 240 ($M^+ + 1$, 1%) and a significant fragmentation ion at 224 ($M^+ - 15$: $M^+ - CH_3$, for 62%)] consistent for the expected nitrile **6** (Scheme 1), but whose IR and ^{1}H NMR spectroscopic data did not correspond with this structure. In the IR spectrum a weak signal at 2250 cm^{-1} could be attributed to a simple alkyl nitrile, but not to an α,β-unsaturated nitrile. In agreement with this, in the high field ^{1}N NMR spectrum the expected presumed deshielded vinyl protons in compound **6** were absent; by contrast, in addition to the signals for the furanose nucleus (H1, 2, 3 and 4), new signals were detected at δ 3.59 (ddt) for one proton and at δ 2.52 (d) for two protons. These data strongly pointed out that the structure of product **7** was a tetrahydropyran-like molecule obtained, as shown in Scheme 1, by basic mediated intramolecular Michael *O*-cyclization of the unisolated intermediate, unsaturated nitrile **6** (Scheme 1). The proton at δ 3.59 was assigned to H7 and the doublet ($J_{7ax,8} = 6.1$ Hz) at δ 2.52 to the cyanomethylene group. Very interestingly, the measured vicinal coupling constants for H7: $J_{7ax,6ax} = 10.1$ Hz, $J_{7ax,6ax} = 2.0$ Hz, $J_{7,8} = 6.1$ Hz, allowed us to determine the absolute configuration as *R* at the newly formed stereocenter (H7); in fact, large and small vicinal coupling constants, in a chair-like conformation, are only possible for this arrangement. Additional NOE experiments in the ^{1}H NMR spectrum between H3 and H7 confirmed the assigned stereochemistry.



Scheme 1

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To our knowledge, this is the first case described in the literature showing base mediated *O*-cyclization in ω-hydroxy α,β-unsaturated nitriles to give a tetrahydropyran.[7] Similar results for analogous, chiral ω-hydroxy α,β-unsaturated esters are known.[6] This result paves the way for the synthesis of new useful building blocks as these annulated furanoses *via* heteroatom mediated Michael intramolecular cyclizations.

Experimental

Reactions were monitored by TLC using precoated silica gel alumina plates containing a fluorescent indicator (Merck, 5539). Detection was by UV (254 nm) followed by charring with sulfuric–acetic acid spray, 1% aqueous potassium permanganate solution or 0.5% phosphomolybdic acid in 95% EtOH. Anhydrous $MgSO_4$ was used to dry organic solutions during work-ups. Flash column chromatography was performed using Kieselgel 60 (230–400 mesh, Merck). The melting point was determined in a Kofler apparatus and is uncorrected. Optical rotation was determined with a Perkin-Elmer 257 instrument. The ^{1}N NMR spectrum was recorded with a Varian VXR-300S spectrometer.

Synthesis of Compound **7**.—To a suspension of sodium hydride (107 mg, 4.46 mmol, 2.4 equiv, 60% dispersion in oil) in dry THF (5 mL diethyl cyanomethylenephosphonate (0.72 mL, 4.46 mmol, 2.4 equiv.) was slowly added at room temperature and stirred for 15 min. The mixture was cooled in an ice bath and a solution of aldehyde **3**[5] (402 mg, 1.86 mmol) in dry THF (1 mL) was added dropwise. After 3 h, the reaction was complete (TLC analysis), saturated aqueous ammonium chloride was added, the solvent was removed and the residue dissolved in ethyl acetate, washed with water, dried, filtered and evaporated. The residue was submitted to flash chromatography [hexane–ethyl acetate (4:1)] to give compound **7** (403 mg, 88%, as a mixture of isomers in a 9:1 ratio). Recrystallization from hexane–ethyl acetate gave a pure sample of major isomer of **7** (C-7*R*): mp 118–120 °C; $[\alpha]_D^{25} = 20$ (c 0.49, $CHCl_3$); IR (KBr) 2990, 2950, 2250, 1380, 1375 and 1080 cm^{-1}; $\delta_H(CDCl_3)$ 5.90 (d, $J_{1,2} = 3.8$ Hz, 1H, H1), 4.51 (d, 1H, H2), 4.19 (q, $J = 2.5$ Hz, 1H, H4), 3.98 ($J = 1.6$ Hz, 1H, H3), 3.59 (ddt, $J_{7ax,8} = 6.1$ Hz, $J_{7ax,6ax} = 10.1$ Hz, $J_{7ax,6eq} = 2.0$ Hz, 1H, H7ax), 2.52 (d, 2H, 2 H8), 2.22 (br dq, $J_{5ax,5eq} = 12.3$ Hz, $J = 2.5$ Hz, 1H, H5eq), 1.90–1.45 (m, 3H, H5ax, 2 H6) 1.49, 1.31 [s, s, 3H, 3H, –$OC(CH_3)_2O$–]; MS (70 eV) m/z 240 ($M^+ + 1$, 1), 224 ($M^+ - 15$), 18: (79), 164 (10), 123 (27), 81 (30), 43 (100%). Anal. Calc. for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C 60.51; H, 7.30; N, 5.78%.

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