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A NOVEL APPROACH TO HEX-2-ENOS-4-ULOSES FROM GLYCALS. SYNTHESIS OF CHIRAL 6-HYDROXY-(2R)-2-HYDROXYMETHYL-2H--PYRAN-3(6H)-ONE (1) AND ITS TRITYL DERIVATIVE (2)

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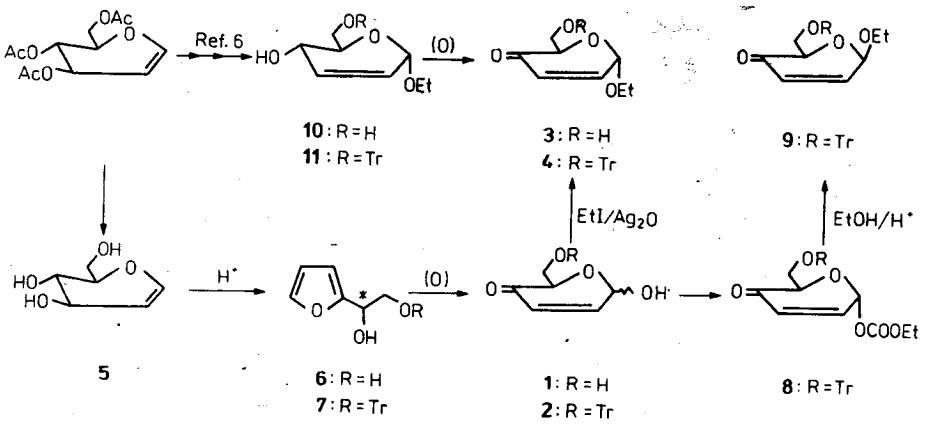
Racemic derivatives of hexenulose (**1**) prepared by oxidation of 2-furyl carbinols, have been used for the synthesis of monosaccharides [1] and several "deformed" sugars [2]. Optically pure compound **1** prepared in low yield *via* (2-furyl)-glycolic acid [3], by a multistep procedure, has merited little attention as a chiral synthon [4]. On the other hand, chiral glycoside **3**, as well as its trityl derivative **4**, are among the most widely used chiral templates for the synthesis of a great number of natural products (e.g. amino sugars [5a,b,c,d], antibiotic components [5e,f,g], pheromones [5h], annulated pyranosides [5k], chrysanthemum dicarboxylic acids [5l], the Prelog-Djerassi lactonic acid [5m] etc.). However, the reported reaction sequence [6] for preparation of glycosides **3** and **4** from tri-O-acetyl-D-glucal, leaves the pyranoid ring intact and yields only α-glycosides. Thus we decided to pyranoid ring intact and as a consequence yields only α-glycosides. Thus we decided to develop a more efficient methodology for preparing chiral hex-2-enos-4-uloses.



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In the approach presented here, the pyranoid ring of a glycal (e.g. **5**), is first transformed to a furanoid one (e.g. **6**), which is finally oxidatively rearranged to the pyran ring of an hexenulose (e.g. **1**), with retention of configuration at C-5 [8]. Chiral hex-2-enopyranos-4-uloses (alternatively named: 6-hydroxy-2H-pyran-3(6H)-ones) are thus derived in high yield. These products have the same α,β-enone system as the valuable synthons **3** and **4** and, in addition, a hemiacetalic hydroxy group, suitable for further functionalisation [7].

Both anomeric glycosides were prepared in good yield from compound **2**, demonstrating the versatility of our procedure. It should be also noted that the direct preparation of 6-O-derivatives of compound **1**, which otherwise presents difficulties due to the instability of **1** in basic media, can easily proceed by this methodology. Thus the considerably more stable under basic conditions compound **6**, is first derivatized and then converted to the 6-O-protected hexenulose (e.g. **6** → **7** → **2**).

EXPERIMENTAL

Deacylation of tri-O-acetyl-D-glucal (30 g, 200 ccm MeOH, 0.5 g KCN, 3 hrs, small column filtration), yielded D-glucal (**5**) quantitatively, which upon treatment with $HgSO_4$ in dilute H_2SO_4 [8], yielded 12.7 g of compound **6** (90% yield). Oxidation of **6** with *m*-CPBA (1 g of **6**, 50 ccm CH_2Cl_2, 1.3 eqs *m*-CPBA, water extraction, neutralization with Dowex MR-12 and removal of the water under reduced pressure), afforded 780 mg (70% yield) of compound **1**, as a colorless oil *. Preparation of the more attractive trityl derivative **2**, has been accomplished through the tritylated alcohol **7** (8 g of **6**, 100 ccm of dry pyridine, 17 g of Ph_3CCl, 24 hrs, extraction with CH_2Cl_2, column purification, 17.5 g of **7** **, 75% yield). Oxidation of **7** (10 g) by the NBS method [9] (100 ccm THF/H_2O 4 : 1, 1.2 eqs NBS, extraction with 1.5 dm^3 of ether, successive washings with concentrated solutions of KI, $Na_2S_2O_3$, $NaHCO_3$ and finally H_2O), afforded after crystallization from CH_2Cl_2 — hexane 8.3 g (80% yield of analytically pure compound **2**) ***.

Treatment of **2** with EtI/Ag_2O in acetone [10] afforded a mixture of compounds **4** and **9** (ratio 7 : 3), which after chromatographic separation, using AcOEt — hexane (1 : 9) as eluant, afforded pure **4** **** in 45% yield (25% overall yield based on

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* Compound **1**: ^1H NMR, 60 MHz (DMSO-d_6), δ: 3.60 (m, 2H, $H_{6,6'}$), 3.42 (s) and 4.61 (m, 1H+1H, disappeared on addition of D_2O, —OH), 4.12 (t) and 4.31 (t, 1H (two anomers), J = 4.1 Hz, H_5), 5.56 (m, 1H, H_1), 5.95 (m, 1H, H_3), 6.95 (m, 1H, H_2); IR (film), ν_{max}: 3400 (broad), 1690 cm^{-1}.

** Compound **7**: ^1H NMR, 60 MHz ($CDCl_3$), δ: 2.75 (d, 1H, J = 4.8 Hz, disappeared on addition of D_2O, —OH), 3.42 (d, 2H, J = 5.6 Hz, $H_{6,6'}$), 4.75 (dt, 1H, J_{CH-CH_2} = = 5.6 Hz, $J_{H,OH}$ = 4.8 Hz, —CH—), 6.15 (d, 1H, J = 1.5 Hz, furan β-H), 7.20 (m, 17H (15H from trityl, 2H from furan)); m.p. 109—111°C; IR (KBr), ν_{max}: 3450 (narrow), 885, 740 cm^{-1}; satisfactory elemental analysis.

*** Compound **2**: ^1H NMR, 60 MHz ($CDCl_3$), δ: 3.16 (d, 1H, J = 5.8 Hz, disappeared on addition of D_2O, —OH), 3.53 (d, 2H, J = 4.2 Hz, $H_{6,6'}$), 4.62 (t, 1H, J = 4.2 Hz, H_5), 5.65 (broad 1H, (d after adding D_2O, J = 3.1 Hz), H_1), 6.15 (d, 1H, $J_{3,2}$ = 10.1 Hz, $J_{3,1}$ = 0 Hz, H_3), 6.75 (dd, 1H, $J_{2,3}$ = 10.1 Hz, $J_{2,1}$ = 3.1 Hz, H_2), 7.2 (m, 15H, trityl); m.p. 152—154°C; IR (KBr), ν_{max}: 3370 (narrow), 1680 cm^{-1}, satisfactory elemental analysis.

**** Compound **4**: amorphous solid from EtOH/H_2O (−5°C); m.p. 71—73°C; ^1H NMR, 60 MHz ($CDCl_3$), δ: 1.25 (t, 3H, J = 6.4 Hz, —CH_3), 3.30 (m, 2H, $H_{6,6'}$), 3.62 (m, 2H, —CH_2—), 4.27 (dd, 1H, J = 2.8 Hz, J = 3.0 Hz, H_5), 4.95 (d, 1H, $J_{1,2}$ = 3.2 Hz, H_1), 5.71 (d, 1H, $J_{3,2}$ = 10.1 Hz, $J_{3,1}$ = 0 Hz, H_3), 6.45 (dd, 1H, $J_{2,3}$ = 10.1 Hz, $J_{2,1}$ = 3.2 Hz, H_2), 6.90 (m, 15H, trityl); IR (film), ν_{max}: 1690 cm^{-1}; satisfactory elemental analysis.

tri-O-acetyl-D-glucal). Alternatively, esterification of compound **2** with ClCOOEt in dioxane — Et_3N * and subsequent solvolysis [10] with EtOH and $HClO_4$ (70%) yielded a mixture of compounds **4** and **9** (ratio 2 : 8), which after similar separation, afforded pure **9** in 60% yield, as a pale yellow oil **.

Finally, compound **4** was prepared according to the known method. In fact this preparation has not been published in detail, but it has been mentioned to proceed in an analogous manner with the preparation of **3** [11]. However oxidation of compound **11** could not be effected by activated MnO_2 *** and it was eventually performed by 10% excess of PDC in dry chloroform. The total yield from tri-O-acetyl-D-glucal was 15%. The product, thus obtained, gave identical NMR and IR spectra with **4**, and their $[\alpha]_D^{25}$ their $[\alpha]_D^{25}$ values were in close accordance ****,

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* Compound **8**, ^1H NMR, 60 MHz ($CDCl_3$), δ: 1.25 (t, 3H, $J = 6.4$ Hz, —CH_3), 3.40 (d, 2H, $J = 4.1$ Hz, $H_{6,6'}$), 4.12 (q, 2H, $J = 6.4$ Hz, —CH_2—), 4.43 (t, 1H, $J = 4.1$ Hz, H_5), 5.95 (d, 1H, $J_{3,2} = 10.1$ Hz, $J_{3,1} = 0$ Hz, H_3), 6.27 (d, 1H, $J_{1,2} = 3.4$ Hz, H_1), 6.60 (dd, 1H, $J_{2,3} = 10.1$ Hz, $J_{2,1} = 3.4$ Hz, H_2), 7.10 (m, 15H, trityl); IR (film), ν_{max}: 1755, 1700 cm^{-1}.

** Compound **9**, ^1H NMR, 60 MHz ($CDCl_3$), δ: 1.25 (t, 3H, $J = 6.2$ Hz, —CH_3), 3.35 (m, 2H, $H_{6,6'}$), 3.73 (q, 2H, $J = 6.2$ Hz, —CH_2—), 3.95 (m, 1H, H_5), 5.00 (m, 1H, H_1), 5.71 (dd, 1H, $J_{3,2} = 10.1$ Hz, $J_{3,1} = 1.2$ Hz, H_3), 6.42 (dd, 1H, $J_{2,3} = 10.1$ Hz, $J_{2,1} = 2.2$ Hz, H_2), 6.85 (m, 15H, trityl); IR (film), ν_{max}; 1695 cm^{-1}.

*** The same problem has also geen reported, for 6-O-*t*-butyldimethylsilyl derivative of **3**, which was eventually oxidized with PCC, see [12].

**** Product **4** prepared by our procedure gave $[\alpha]_D^{25} = -16.5$ ($C = 0.5$, $CHCl_3$), while that prepared according to the literature gave $[\alpha]_D^{25} = -15.6$ ($C = 0.5$, $CHCl_3$).

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