Synthesis and Olefination Reactions of an α-Enal from Diacetone Glucose

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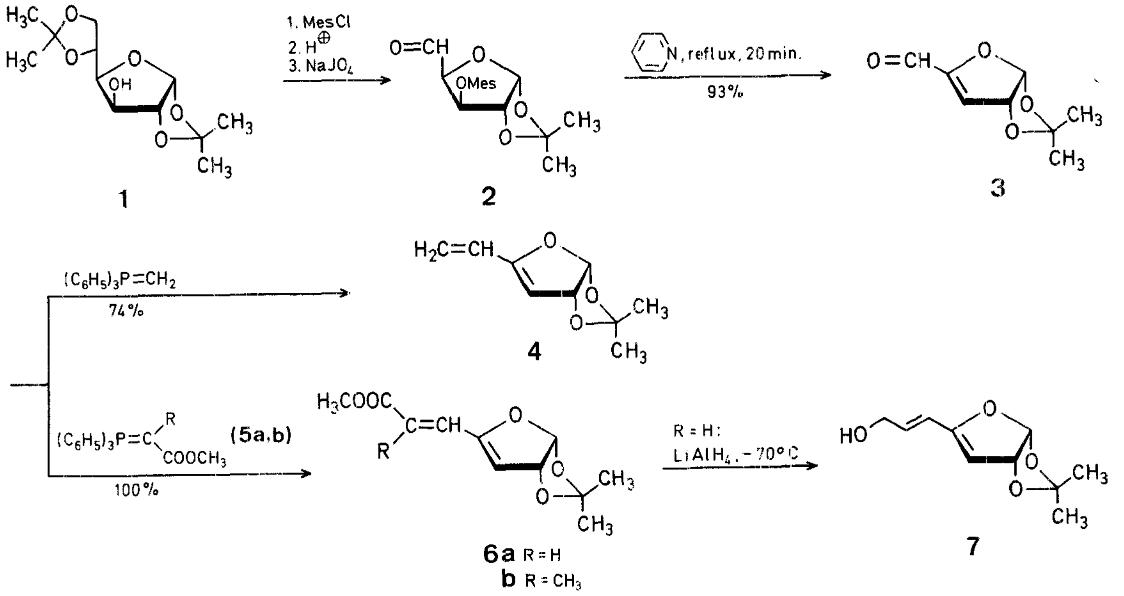
The preparation of unsaturated sugars, particularly those of the α-enone[1,2] and conjugated diene[3] varieties, has been of major interest in our laboratory, and others, and the value of these derivatives has been demonstrated for syntheses of complex and modified sugars (e.g. disaccharide[4], antibiotic[5,6], and amino[7]), natural products (prostanoids[8,9], sex pheromones[10]), and carbocyclic systems[11]. In the past, these unsaturated sugars have been derived from pyranosides, but we have recently been exploring the utility of furanoses[12] and in developing this line of interest we report on some systems that can be obtained simply, rapidly, and efficiently from 1,2-5,6-di-*O*-isopropylidene-D-glucofuranose (**1**; diacetone glucose)[13].

Sulfonation of **1** followed by selective hydrolysis and periodate cleavage afforded **2** in ~95% yield, as a mixture of the free aldehyde and its hydrated form. The fact that epimerisation had not occurred was established by reducing **2** with sodium borohydride. The material obtained quantitatively, 1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-α-D-xylofuranose, was identical to that prepared by sulfonation of 5-*O*-*t*-butyldimethylsilyl-1,2-*O*-isopropylidene-α-D-xylofuranose[12b] followed by treatment with fluoride ion.

The attempted use of alkoxides for the β-elimination leading to **3** proved unworkable and this was not surprising in view of past evidence implicating **3** as a transient intermediate in reactions of analogous systems[14]. However, refluxing of **2** with pyridine followed by evaporation and elution through silica with diethyl ether led to a nearly quantitative yield of **3** as a mobile oil. Compound **3** tends to photodecompose if left exposed on the bench, but it is stable indefinitely in the refrigerator.



The tolerance of **3** to chemical transformations has been examined by looking at a variety of Wittig olefination reactions. Treatment with 1.5 equivalents of methylenetriphenylphosphorane for 15 min led to a 72% yield of the diene **4**. This yield was encouragingly high since we have found that **3** is very sensitive to basic media.

Reaction of **3** with the stabilised phosphoranes **5a** and **5b** in dichloromethane at room temperature was rapid – indeed exothermic in the case of **5b**. Isolation after 5 min afforded the corresponding dienic esters, **6a** and **6b**, respectively, in quantitative yields. The complete absence of the (*Z*)-isomers in these reactions is noteworthy. The dienic esters may be reduced to the corresponding alcohols, if due care is taken. Thus treatment of **6a** in diethyl ether with lithium aluminium hydride at −70 to −50 °C afforded the dienol **7** in 88% yield. Further study of these systems is currently underway and will be reported in due course.

^{1}H-N.M.R. spectra were run on a Varian T-60 and I.R. spectra on a Beckman model IR-10 spectrometer. Low resolution mass spectra were run on a Hitachi RMU-6E or a Varian MAT CH7 spectrometer and a VG 7070F instrument was used for high resolution spectra. Optical rotations were determined on a Carl Zeiss model LEP no. 37074 instrument. T.L.C. was done on aluminium sheets precoated with silica gel 60 (HF 254, Merck) to a thickness of 0.25 mm. For column chromatography, Merck silica gel (0.063–0.20 mm 70–230 mesh A.S.T.M.) was used.

1,2-*O*-Isopropylidene-3-*O*-methanesulfonyl-α-D-*xylo*-pentodialdo-1,4-furanose (2):

1,2:5,6-*O*-isopropylidene-α-D-glucofuranose (diacetone glucose)[13] (**1**; 40 g, 0.15 mol) is dissolved in dry pyridine (500 ml) and the solution cooled to 0 °C. To this solution, methanesulfonyl chloride (20 g, 0.17 mol) in dichloromethane (50 ml) is added and the reaction mixture is stirred for 2 h at ambient temperature and then poured into ice/water. The aqueous layer is extracted with dichloromethane (3 × 400 ml). The combined organic layers are washed first with aqueous sodium hydrogen carbonate solution then with brine. The solvent is removed under reduced pressure and the residue azeotroped with toluene a few times. The product (53 g, 100% yield) is dissolved in methanol (2.1 l) and water (300 ml), then aqueous sulfuric acid (10% w/w, 100 ml) is added and the reaction mixture is stirred at room temperature for 36 h by which time, as shown by T.L.C., no starting material is left. The solution is made neutral by addition of 5% aqueous sodium hydroxide, then sodium metaperiodate (60 g, 0.28 mol) is added, and the reaction mixture is stirred vigorously for 45 min. After filtering, the solvent is removed under reduced pressure, leaving **2** as a light yellow syrup which is satisfactory for use in the next step. The material exists partially in the hydrated form, the concentration of which varies; yield: 40 g; R_f (ether): 0.29; $[\alpha]_D^{20}$: −38.37° (*c* 4.8, chloroform).

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$C_9H_{14}O_7S \cdot 1/8\,H_2O$	calc.	C 40.26	H 5.31	S 11.93
(268.5)	found	40.30	5.44	11.84

M.S.: $m/e = 251$ ($M^+ - CH_3$).

I.R. (film): $\nu = 3500, 1740$ cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$, 60 MHz) *(free aldehyde)*: $\delta = 1.27$ (s, 3 H); 1.47 (s, 3 H); 3.05 (s, 3 H); 4.6–5.0 (m, 2 H); 5.26 (d, 1 H, $J_{3,4} = 2.8$ Hz); 6.15 (d, 1 H, $J_{1,2} = 3.8$ Hz); 9.66 ppm (s, 1 H).

^{1}H-N.M.R. ($CDCl_3$, 60 MHz) *(hydrated aldehyde)*: $\delta = 1.27$ (s, 3 H); 1.47 (s, 3 H); 3.10 (s, 3 H); 4.1–4.3 (m, 1 H); 4.6–5.0 (m, 2 H); 5.02 (d, 1 H, $J_{3,4} = 3$ Hz); 5.95 ppm (d, 1 H, $J_{1,2} = 3.8$ Hz).

1,2-*O*-Isopropylidene-*α*-D-*glycero*-pent-3-enodialdo-1,4-furanose (3):

Compound **2** (40 g, 0.15 mol) is dissolved in dry pyridine and refluxed for 30 min. The solvent is removed under reduced pressure and the residue is extracted with diethyl ether which is then also evaporated. The brown syrup thus obtained is azotroped several times with toluene and eluted through a short column of silica gel with diethyl ether to give **3** as a light yellow syrup; yield: 24.8 g (96%); R_f (ether): 0.53; R_f (9:1 CH_2Cl_2/CH_3OH): 0.63; $[\alpha]_D^{20}$: $-88.59°$ (*c* 9.66, chloroform).

M.S.: $m/e = 170$ (M^+), 155 ($M^+ - CH_3$), 141 ($M^+ - CHO$).

^{1}H-N.M.R. ($CDCl_3$, 60 MHz): $\delta = 1.42$ (2 s, 6 H); 5.41 (dd, 1 H, $J_{2,3} = 2.8$ Hz); 6.13 (d, 1 H); 6.15 (d, 1 H, $J_{1,2} = 5.5$ Hz); 9.47 ppm (s, 1 H).

I.R. (film): $\nu = 1700, 1615$ cm^{-1}.

Semicarbazone of **3**; m.p. 182 °C (dec.).

$C_9H_{13}N_3O_4$	calc.	C 47.57	H 5.77	N 18.49
(227.2)	found	47.54	5.81	18.50

^{1}H-N.M.R. ($CDCl_3$, 60 MHz): $\delta = 1.36$ (s, 6 H); 5.34 (dd, 1 H, $J_{1,2} = 5$ Hz, $J_{2,3} = 2$ Hz); 5.65 (d, 1 H); 6.16 (d, 1 H); 6.28 (br s, 2 H); 7.40 (s, 1 H); 10.5 ppm (br s, 1 H).

3,5,6-Trideoxy-1,2-*O*-isopropylidene-*α*-D-*glycero*-hex-3,5-dienofuranose (4):

n-Butyllithium (40 mmol) is added to a suspension of methyltriphenylphosphonium bromide (15 g, 42 mmol) in dry tetrahydrofuran (250 ml) under an argon atmosphere at room temperature, and after stirring for 0.5 h, the aldehyde **3** (4.8 g, 28 mmol) in tetrahydrofuran (20 ml) is added. After 15 min, no starting material remains (T.L.C., ether) and the mixture is poured into water (100 ml) and extracted with ether (3 × 250 ml). The combined organic layers are washed with brine until neutrality, and processing in the usual way affords a residue which is passed through a silica gel column with ether to give **4** as a syrup; yield: 3.39 g (72%); R_f (ether): 0.72; R_f (3:2 benzene/ether): 0.42; $[\alpha]_D^{20}$: $-149.1°$ (*c* 1.06, chloroform).

M.S.: $m/e = 168.0775$ (calc. for $C_9H_{12}O_3$: 168.0786).

^{1}H-N.M.R. ($CDCl_3$, 60 MHz): $\delta = 5.10$ (d, 1 H, $J_{2,3} = 2$ Hz); 5.22 (t, 1 H, $J_{1,2} = 2$ Hz); 5.58 (d, 1 H); 5.67 (t, 1 H, $J_{5,6} = 2$ Hz); 5.98 (d, 1 H); 6.10 ppm (d, 1 H).

Methyl 3,5,6-Trideoxy-3,5(*E*)-dieno-1,2-*O*-isopropylidene-*α*-D-*glycero*-heptofuranouronate (6a):

Methyl (triphenylphosphoranylidene)-acetate (75 g, 0.22 mol) is added in small portions to a solution of aldehyde **3** (37 g, 0.22 mol) in dichloromethane (500 ml). The reaction is complete in 5 min (T.L.C., ether) and the solution is evaporated to dryness. The residue is passed through a short column of silica gel with ether to give **6a** as a syrup; yield: 49.5 g (100%); R_f (ether): 0.77; R_f (7:3 petroleum ether/ethyl acetate): 0.58; $[\alpha]_D^{20}$: $-118.6°$ (*c* 2.30, chloroform).

M.S.: $m/e = 226.0855$ (calc. for $C_{11}H_{14}O_5$: 226.0855).

^{1}H-N.M.R. ($CDCl_3$, 60 MHz): $\delta = 1.45$ (2s, 6 H); 3.77 (s, 3 H); 5.30 (dd, 1 H, $J_{1,2} = 5$ Hz, $J_{2,3} = 2.8$ Hz); 5.50 (d, 1 H); 6.07 (d, 1 H); 6.27 (d, 1 H, $J_{5,6} = 15.2$ Hz); 7.08 ppm (d, 1 H).
I.R. (film): $\nu = 1715, 1648, 1600$ cm^{-1}.

Methyl 3,5,6-Trideoxy-3,5(*E*)-dieno-1,2-*O*-isopropylidene-6-*C*-methyl-*α*-D-*glycero*-heptofuranouronate (6b):

The title compound **6b** is prepared as described above for the homologue **6a** using methyl 2-(triphenylphosphoranylidene)-propanoate and obtained as a syrup; yield: 100%; R_f (7:3 petroleum ether/ethyl acetate): 0.58; $[\alpha]_D^{20}$: $-98.26°$ (*c* 3.04, chloroform).

M.S.: $m/e = 240$ (M^+, $C_{12}H_{16}O_5$).

^{1}H-N.M.R. ($CDCl_3$, 60 MHz): $\delta = 1.43$ (2 s, 6 H); 2.17 (br s, 3 H); 3.75 (s, 3 H); 5.2–5.4 (m, 2 H); 5.85 (br s, 1 H); 6.04 ppm (d, 1 H, $J_{1,2} = 5$ Hz).

I.R. (film): $\nu = 1715, 1648, 1595$ cm^{-1}.

3,5,6-Trideoxy-3,5(*E*)-dieno-1,2-*O*-isopropylidene-*α*-D-*glycero*-heptofuranose (7):

To a solution of the ester **6a** (5.0 g, 22.1 mmol) in dry ether (500 ml) at −70 °C, lithium aluminium hydride (1.5 g) is added with vigorous stirring. The mixture is allowed to warm up to −50 °C and when the reaction is complete (T.L.C., ether) hydrated sodium sulfate is added to destroy the excess reagent. The mixture is then filtered and the ether processed in the usual way to afford **7** as a syrup; yield: 3.85 g (88%); R_f (ether): 0.6; $[\alpha]_D^{20}$: $-107.6°$ (*c* 6.14, chloroform).

$C_{10}H_{14}O_4$	calc.	C 60.60	H 7.07
(198.2)	found	60.43	7.16

M.S.: $m/e = 198.0897$ (calc. for $C_{10}H_{14}O_4$: 198.0892).

^{1}H-N.M.R. ($CDCl_3$, 60 MHz): $\delta = 1.45$ (2s, 6 H); 2.70 (t, 1 H, $J = 5$ Hz); 4.2 (m, 2 H); 5.10 (d, 1 H, $J_{2,3} = 2$ Hz); 5.29 (dd, 1 H, $J_{1,2} = 4$ Hz); 6.05 (d, 1 H); 6.1–6.3 ppm (m, 2 H).

I.R. (film): $\nu = 3400, 1650, 1610$ cm^{-1}.

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