Synthesis of 3-Deoxy-D-*manno*-octulosonic Acid (KDO)

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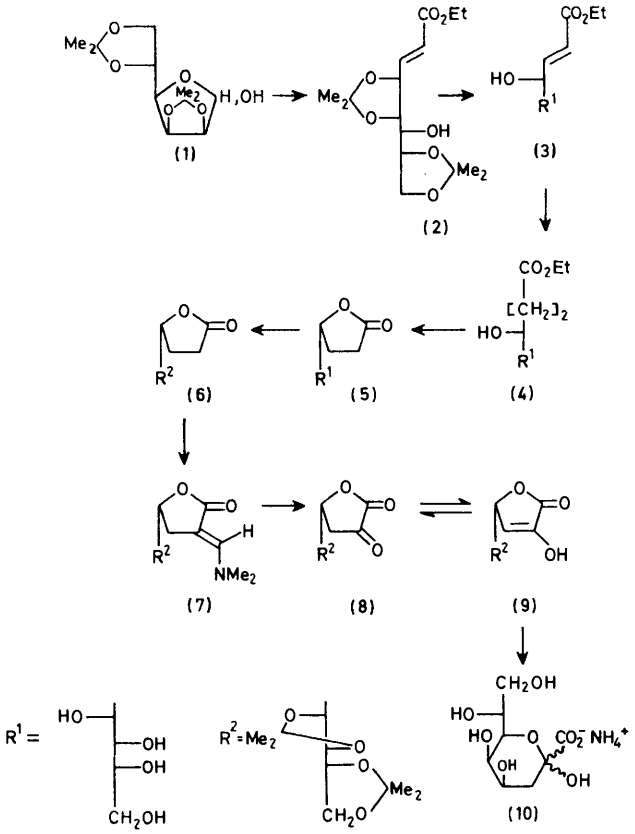
Summary 2,3:5,6-Di-*O*-isopropylidene-D-mannose has been converted by five sequential reactions (Wittig reaction, deacetonation, hydrogenation, lactonisation, and isopropylidenation) into 2,3-dideoxy-5,6:7,8-di-*O*-isopropylidene-D-octonolactone which in a Wasserman reaction gave an α-ketolactone from which KDO could readily be obtained by hydrolysis.

3-DEOXY-D-*manno*-OCTULOSONIC ACID (KDO), a constituent of most Gram-negative bacterial cell envelopes, is generally synthesised by addition of oxalacetic acid or its di-t-butyl ester[1] to D-arabinose or by condensing D-arabinose tetraacetate and (t-butoxyoxalyl)methylenetriphenylphosphorane.[2] D-Mannose has also been chain-lengthened to give KDO by subjecting it to sequential Nef and Kiliani reactions.[3] In these reactions, pairs of stereoisomers are generated and this hampers the purification of intermediates.

Now, we report a practical, high yielding synthesis of KDO from D-mannose in which intermediates with new centres of asymmetry are not formed and chromatography is not required.

2,3:5,6-Di-*O*-isopropylidene-D-mannose[4] (**1**) and (ethoxycarbonylmethylene)triphenylphosphorane when heated for 6 h in benzene under reflux gave the ethyl octenoate (**2**)† {$[\alpha]_D^{20}$ +14·6°; ν_{max} 3500, 1720, and 1660 cm^{-1}; λ_{max} 210, ϵ 6·9 × 10^3}. This was deacetonated with 10% trifluoroacetic acid in aqueous ethanol to afford compound (**3**) {m.p. 134—135 °C; $[\alpha]_D^{22}$ +31·9°} which in ethanol was hydrogenated over palladium-on-charcoal to yield the ethyl octonate (**4**) {m.p. 116—117 °C; $[\alpha]_D^{22}$ +10° (EtOH)}. Lactonisation and re-acetonation gave respectively the



† All new compounds gave satisfactory elemental analyses and well resolved ^1H and ^{13}C n.m.r. spectra. ^1H Spectra were measured at 100 MHz and ^{13}C spectra at 15 MHz. Unless stated otherwise optical rotations were measured for chloroform solutions.

lactones (**5**) and (**6**) {respectively m.p. 156—157 °C; $[\alpha]_D^{18}$ −16·6° and m.p. 88—88·5 °C; $[\alpha]_D^{20}$ +6·6°; ν_{max} 1765 cm^{-1} (CO)}. We find that on the 0·06 mole scale compound (**1**) can be converted into compound (**6**) without purification of the intermediates (**2**), (**3**), (**4**), and (**5**) in 77% overall yield.

The di-*O*-isopropylidene-lactone (**6**) was converted into an α-keto-lactone by the method of Wasserman.[5] Compound (**6**) and tris(dimethylamino)methane were stirred at 70 °C under nitrogen for 5 days to afford the 2-(dimethylaminomethylene)-lactone (**7**) after the crude dried initial product in ethyl acetate–ether (1:1) had been passed through a pad of silica gel. Compound (**7**) was obtained in 94% yield with m.p. 86—87·5 °C; $[\alpha]_D^{22}$ −66·4°; ν_{max} 1630 and 1730 cm^{-1} (C=C, C=O); λ_{max} 294 nm (ϵ 6·71 × 10^4); δ_H (250 MHz in C_6D_6) 2·13 (s, 6H, NMe_2), 2·98 (ddd, $J_{3,3'}$ 14, $J_{3,4}$ 5·3, $^4J_{3,v}$ 1·7 Hz), 2·74 (ddd, $J_{3',3}$ 14, $J_{3',4}$ 8·8, $^4J_{3,v}$ 1·7 Hz), 7·05 [t, vinyl H(v), $J_{v,3}$ 1·7, $J_{v,3'}$ 1·7 Hz]; δ_C 174·9 (C-1), 87·2 (C-2), and 41·7 p.p.m. (NMe_2). Oxygen was passed through a solution of compound (**7**) in dichloromethane which contained Methylene Blue. The mixture was maintained at −72 °C and irradiated for 1 h with a tungsten filament 500 W photoflood lamp (Philips PF 308 E121) and then worked up to give the blocked α-keto-lactone (**8** ⇌ **9**) (93%) {m.p. 102—104 °C; $[\alpha]_D^{22}$ +56·7°; ν_{max} 3250 (OH), 1735, 1737 (C=O), and 1650 cm^{-1} (C=C)} which in solution was preponderantly in the enol form (**9**) {δ_H (250 MHz, $CDCl_3$–C_6D_6, 4:1) 2·71 (dd, $J_{3,3'}$ 18·7, $J_{3,4}$ 3·8 Hz), 2·44 (dd, $J_{3',3}$ 18·7, $J_{3',4}$ 8·3 Hz) [*ca.* 33% of compound (**8**)] and 6·08 (d, $J_{3,4}$ 1·8 Hz) [*ca.* 66% of compound (**9**)]; δ_C 159·5 (C-1), 191·7 (C-2), and 33·6 (C-3) due to (**8**) and 169·9 (C-1), 143·5 (C-2), and 115·7 (C-3) p.p.m. due to (**9**)}. Hydrolysis of this material with aqueous trifluoroacetic acid gave KDO as an amorphous solid in 85% yield, m.p. 140—142 °C (decomp.), $[\alpha]_D^{21}$ +47·5° (in H_2O) which was converted into the ammonium salt of KDO (**10**) in 75% yield from (**8** ⇌ **9**), m.p. 120—121 °C, undepressed when mixed with authentic material; $[\alpha]_D^{21}$ +58·7° (7 min) → +40·1° (45 min); ^{13}C n.m.r. spectrum in close agreement with those in the literature.[6,7] This route gives better yields for the chemical synthesis of KDO than others reported in the literature.[1–3,6]

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