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CHEMISTRY OF 5-YLIDENE-1,3-DIOXOLAN-4-ONES. SYNTHESES OF 3-DEOXY-D-ARABINO-2-HEPTULOSONIC ACID (DAH) AND 3-DEOXY-D-MANNO-2-OCTULOSONIC ACID (KDO)

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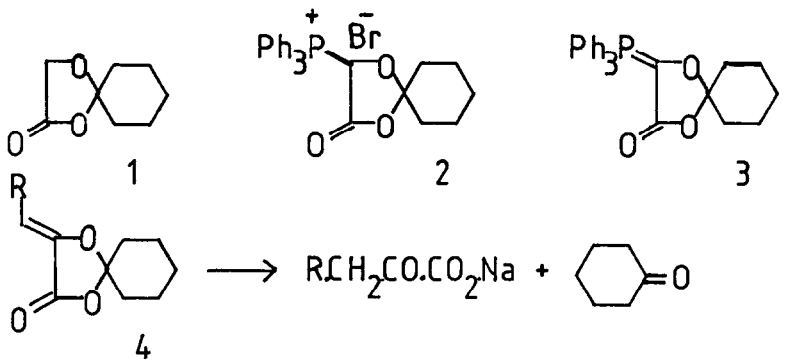
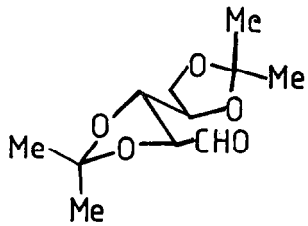
Summary. 3-Deoxy-D-arabino-2-heptulosonic acid and 3-deoxy-D-manno-2-octulosonic acid have been synthesised in chiral form from D-arabinose and D-mannose respectively, *via* 5-ylidene-1,3-dioxolan-4-one intermediates. The α-keto acid function in the products is liberated under mild basic hydrolysis conditions.

Previous studies[1] have shown the utility of the Wittig reagent (3) for the synthesis of 5-ylidene-1,3-dioxolan-4-ones (4) which can be employed as intermediates for the synthesis of α-keto carboxylic acids. The merit in this approach derives from the nature of the heterocyclic ring system in (4), which is moderately stable to acid, but which may be hydrolysed by alkali under very mild conditions to afford the salt of the α-keto carboxylic acid with the expulsion of cyclohexanone. It was considered, therefore, that this strategy would provide a versatile and general approach to the chiral synthesis of sugar acids of biosynthetic importance starting from readily available protected aldehydo sugars.



The 7-phosphate of 3-deoxy-D-arabino-2-heptulosonic acid (DAH)[2] (8) occurs as the first C7 intermediate in the biosynthesis of aromatic amino acids by the shikimate pathway, which is found in plants and bacteria but not in mammals.[3] Thus synthesis of shikimate metabolites has been the subject of much research because of the potential for the development of



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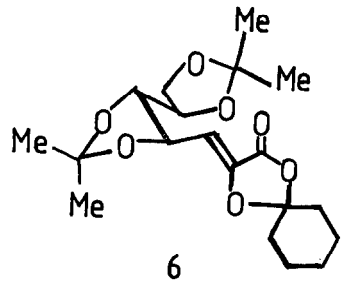

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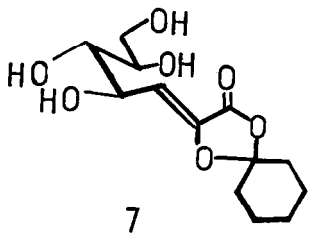

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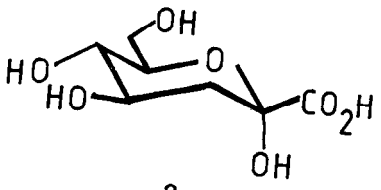

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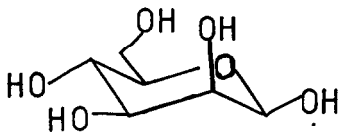
herbicides and antibacterials which would be non-toxic to mammals.

The starting dioxolanone (1) was prepared by a new method[4] which greatly improved the availability of the phosphonium salt (2). Liberation of the Wittig reagent (3), using 1,4-diazabicyclo[2,2,2]octane (DABCO) in toluene under an inert atmosphere, followed by immediate reaction with aldehyde (5) derived from D-arabinose[5] afforded the 5-ylidene-1,3-dioxolan-4-one (6) as a mixture of E and Z isomers. Although the configuration of the double bond is irrelevant to the final product, DAH (8), it was deemed better to proceed with a single isomer for characterisation purposes, thus the E/Z mixture was irradiated (500 W, tungsten) in the presence of I_2 to produce the Z isomer (6) (ν 1795 cm^{-1}; λ 251 nm, ϵ 10660) after chromatography (SiO_2:12% 40-60 petrol/ether). Removal of the acetonide protecting groups with trifluoroacetic acid (TFA) in aqueous ethanol afforded (7) (ν 1794; λ 248, ϵ 10840) which was subjected to hydrolysis using a 0.5 molar equivalent of $Ba(OH)_2$ in aqueous MeOH to yield DAH (8) as the barium salt; m.p. 185°C (d); $[\alpha]_D^{20}$ + 33.0 (C 1.0,H_2O); ^{13}C n.m.r. (100 MHz in D_2O), δ_C 177.35, 97.22, 74.50, 71.51, 69.72, 61.41, 40.03 (C 28.3, H 4.2; Calc. for $BaC_{14}H_{22}O_{14}.2H_2O$, C, 28.6; H, 4.4%).

3-Deoxy-D-manno-2-octulosonic acid (KDO) (14)[6,7] is recognised as a characteristic sugar component of the lipopolysaccharide (LPS) and acidic exopolysaccharide (K-antigen) which occur in the cell surface of Gram negative bacteria. LPS determines antigenicity, toxicity, adhesiveness, invasiveness and penetrability of the cell, thus KDO is an attractive target for chemotherapy since it has a crucial role in linking lipid A *via* a ketal to the end of the polysaccharide chain.

D-Mannose (9) was converted into the alcohol (10) by a known route[8] then oxidised, using a water soluble carbodiimide, to the aldehyde (11). Reaction with (3) afforded the E/Z mixture of products which were separated by chromatography (SiO_2: hexane/EtOAc, gradient elution) to afford (12) (ν 1792; λ 252, ϵ 11,440). Deprotection of the acid-labile functional groups

in (12) (90% aqueous HOAc; 90°C, 1 h) gave the pentahydroxy ylidene dioxolanone (13) (ν 1793; λ 248; ϵ 10,270) which was hydrolysed by a 0.5 molar equivalent of $Ba(OH)_2$ in aqueous MeOH to the barium salt of KDO (14) (C, 29.6; H, 4.6. Calc. for $BaC_{16}H_{26}O_{16}.2H_2O$, C, 29.7; H, 4.6%). This was converted into the known ammonium salt by reaction with a molar equivalent of $(NH_4)_2SO_4$ in aqueous ethanol to give the insoluble $BaSO_4$ and the soluble ammonium salt[9] which could be isolated as crystalline plates (85% aq. EtOH); m.p. 121-124°C; $[a]_D^{20}$ + 38.6 (C 1.1, H_2O); ^1H n.m.r. (200 MHz) in D_2O (Me_4Si ref)[7b] δ_H 4.56-4.42 (m), 4.16 (m), 4.09-3.99 (m), 3.93-3.55 (m), 2.57 (dd, J=14.2, 6.7 Hz), 2.33 (m), 2.09-1.81 (m). (C, 35.3; H, 7.1; N, 5.3. Calc. for $C_8H_{17}NO_8.H_2O$, C 35.2; H, 7.0; N, 5.1%).



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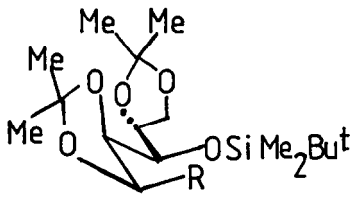

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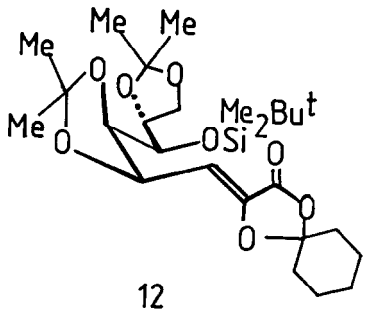
11 R = CHO



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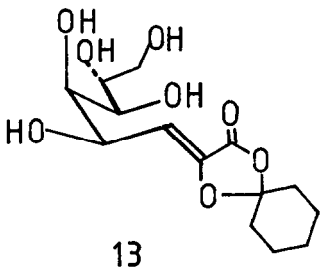

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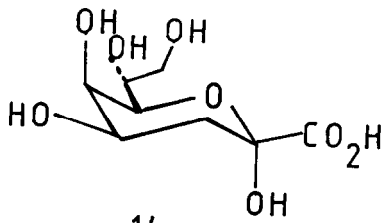

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The above syntheses illustrate the use of the Wittig reagent (3) for the synthesis of salts of 3-deoxy-2-keto carboxylic acids of biosynthetic importance, *via* intermediates having acid-labile protecting groups.

Acknowledgment

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