An Alternative Synthesis of 3,6-Dideoxy-D-*xylo*-hexose (Abequose)

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In our continued efforts at synthesizing *Salmonella* antigens comprising a 3,6-dideoxyhexosyl containing disaccharide unit covalently linked to an immunogenic protein,[1,2] it became necessary to find a convenient route to abequose (3,6-dideoxy-D-*xylo*-hexose) derivatives benzylated in the 2-position, suitable for use in glycoside synthesis.

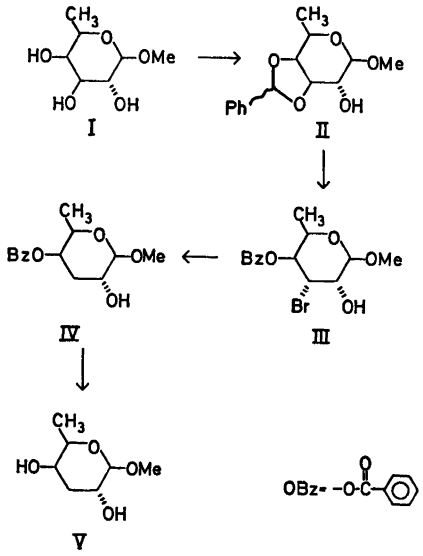
We now report the synthesis of a new abequose derivative IV, useful for this purpose. The key step is the reaction between *N*-bromosuccinimide and a benzylidene acetal devised by Hanessian and Plessas.[3] Siewert and Westphal[4] have previously described a convenient synthesis of abequose from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside.

Methyl β-D-fucopyranoside[5] (I) was prepared from methyl 4,6-*O*-benzylidene-2,3-di-*O*-benzoyl-β-D-galactopyranoside[6] by reaction with *N*-bromosuccinimide, followed by calalytic hydrogenation and debenzoylation.[3] The overall yield of isolated crystalline material was 58 %. Treatment of I with benzylidene bromide and pyridine[7] afforded the 3,4-benzylidene derivative II as a crystalline mixture of stereoisomers. Reaction of II with *N*-bromosuccinimide[3] afforded the bromo compound III which was hydrogenated to give the 3,6-dideoxyhexose IV. Debenzoylation of IV gave methyl β-abequoside (V) in an overall yield of 21 % from I.

The benzylation of IV in the 2-position[8] followed by exchange of the benzoyl group in the 4-position with a *p*-nitrobenzoyl group affords a derivative, useful in synthesis of α-abequosides. This will be described in a forthcoming paper.

Experimental. General methods were essentially the same as those described in a previous paper.[9] GLC-MS was performed using a Varian MAT 311 instrument with a connected Varian 2700 gas chromatograph (ionization potential 70 eV, ionization current 1000 μA and ion source temperature 180 °C). Preparative separations were performed on Merck silica gel 60 prepacked columns for liquid chromatography.

Methyl 3,4-O-benzylidene-6-deoxy-β-D-galacto-hexopyranoside (II). A solution of methyl β-D-fucopyranoside (I) (2.5 g) and benzylidene bromide (3.3 ml) in pyridine (45 ml) was refluxed for 2 h. The reaction mixture was diluted with chloroform and the chloroform solution was washed with water, dried over sodium sulfate, filtered and concentrated to a syrup. TLC (toluene-ethyl acetate 1:1) showed the presence of a major component which was isolated by column chromatography using the same solvent system to yield II (2.45 g) which crystallized from diethyl ether-hexanes, m.p. 97 – 99 °C, $[\alpha]_D$ +2° (*c*, 0.6, chloroform). (Found: C 63.0; H 6.95. $C_{14}H_{18}O_5$ requires: C 63.1; H 6.81). NMR ($CDCl_3$): δ 1.45 and 1.47 (3 H, both d, both $J_{5,6}$ 6.5 Hz, isomeric H-6), 3.54, 3.53 (3 H, both s, OCH_3), 5.93 and 6.17 (1 H, both s, isomeric PhCH), 7.3 – 7.6 (5 H, C_6H_5).



Methyl 4-O-benzoyl-3-bromo-3,6-dideoxy-D-gulo-hexose (III). *N*-Bromosuccinimide (1.1 g) was added to II (1.5 g) and barium carbonate (2.2 g) in carbon tetrachloride (115 ml).[3] The suspension was refluxed with stirring for 1 h, diluted with chloroform and filtered. The filtrate was washed with water and the organic phase dried over sodium sulfate, filtered and concentrated to a syrup. TLC (toluene-ethyl acetate 4:1) showed the presence of one major component which was isolated by column chromatography using the same solvent system yielding pure III (1.23 g) $[\alpha]_D$ +9° (*c*, 0.5, chloroform) NMR ($CDCl_3$): δ 1.28 (3 H, d, $J_{5,6}$ 6.5 Hz, H-6), 2.72 (1 H, broad s, OH), 3.62 (3 H, s, OCH_3), 3.76 (1 H, dd, $J_{1,2}$ 7.5 Hz, $J_{2,3}$ 4 Hz, H-2), 4.42 – 4.75 (2 H, m, H-3, H-5), 4,67 (1 H, d, $J_{1,2}$ 7.5 Hz, H-1), 5.35 (1 H, dd, *J* 1.5 Hz, *J* 3.5 Hz, H-4); 7.43 – 7.70 (3 H, C_6H_5); 8.03 – 8.23 (2 H, C_6H_5). The assignments were confirmed by spin decoupling experiments. The axial disposition of the bromine atom is indicated by the coupling constants and is in agreement with the inversion mechanism suggested for this reaction.[3]

Methyl 4-O-benzoyl-3,6-dideoxy-β-D-xylo-hexopyranoside (IV). The 3-bromo compound

III (1.14 g) was hydrogenated at 420 kPa and room temperature with 10 % palladium on charcoal in ethanol (70 ml) containing triethylamine (0.6 ml) overnight.

Filtration and concentration gave a syrup which was dissolved in chloroform. The chloroform solution was washed with aqueous sodium hydrogen carbonate, water, dried over sodium sulfate, filtered and concentrated. The product was purified by column chromatography (toluene-ethyl acetate 1:1) to yield pure IV (0.52 g). $[\alpha]_D$ −105° (*c*, 0.8, chloroform). (Found: C 63.2; H 6.74. $C_{14}H_{18}O_5$ requires: C 63.1; H 6.81). NMR ($CDCl_3$): δ 1.27 (3 H, d, $J_{5,6}$ 6.5 Hz, H-6), 1.7–2.1 and 2.2–2.4 (2 H, m, H-3 and H-3'), 2.65 (1 H, broad s, OH), 3.60 (3 H, s, OCH_3), 3.67–4.05 (2 H, m, H-2 and H-5), 4.23 (1 H, d, $J_{1,2}$ 7.5 Hz, H-1), 5.13–5.33 (1 H, m, H-4), 7.40–7.67 (3 H, C_6H_5), 8.03–8.25 (2 H, C_6H_5).

*Methyl 3,6-dideoxy-β-*D*-xylo-hexopyranoside (V).* The 4-benzoate IV (75 mg) in methanol (10 ml) was treated with barium oxide (excess) at reflux temperature for 30 min. TLC (toluene-ethyl acetate 1:1) showed complete debenzoylation. The reaction mixture was neutralized with solid carbon dioxide, filtered and concentrated to a syrup (38 mg). The syrup was found to be chromatographically pure by TLC (ethyl acetate-methanol-water 85:10:5), having $[\alpha]_D$ −74° (*c*, 0.9, chloroform), $[\alpha]_D$ −66° (*c*, 0.5, methanol) and $[\alpha]_{546}$ −79° (*c*, 0.5, methanol) in agreement with previously recorded values.[10] An NMR spectrum ($CDCl_3$) was identical to that previously recorded for this substance.[10]

A small sample was hydrolyzed with 0.25 M aqueous sulfuric acid for 30 min at 100 °C, reduced with sodium borohydride and then acetylated.[11] The abequitol acetate thus obtained was indistinguishable from an authentic sample by GLC-MS.

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Bromination of Enamines from Methyl Isopropyl Ketone. II. A Convenient Preparation of Dibromomethyl Isopropyl Ketone

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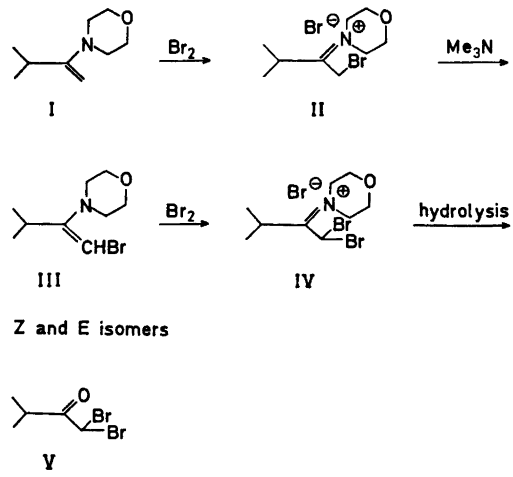
Dibromomethyl ketones, $CHBr_2COCHR_1R_2$, are rather difficult to prepare; generally they are obtained from the corresponding diazoketone with bromine.[1–3] However, this method is not very attractive for synthesis on a larger scale since it involves the use of excessive amounts of the noxious agent diazomethane. The preparation of bromomethyl isopropyl ketone from the morpholine enamine has recently been reported by us.[4] In our investigation of the scope of this reaction we have developed a convenient synthesis of dibromomethyl isopropyl ketone V; the reaction steps involved are summarized in



Scheme 1.