Facile Synthesis of the Next Higher Ketoses from Aldoses

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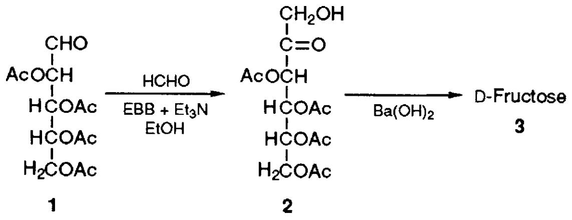
A novel and facile synthesis of the next higher ketohexoses in high yield is successfully achieved by treating aldopentoses with formaldehyde in the presence of 3-ethylbenzothiazolium bromide as a catalyst.

Much attention has recently been focused on the synthesis of higher-carbon carbohydrates partly because they are components of some antibiotics and partly because they can be chiral synthons for the preparation of natural products such as macrolide antibiotics.[1] Although a number of methods for lengthening carbohydrate chains have been reported,[2–10] the products have not been obtained in satisfactory yields and the methods require several steps and considerable skill. It is, thus, very desirable to develop a simple and high-yielding method of preparation.

We reported previously, a very interesting reaction, 'the selective cross-acyloin condensation', in which 1-hydroxy-2-ones were formed selectively from formaldehyde and a variety of other aldehydes by using a thiazolium salt as a catalyst.[11]



Scheme 1

The reaction has been examined as a carbon-chain lengthening reaction, and we have now succeeded in synthesizing readily the next higher ketohexoses in high yield by reacting aldopentoses with formaldehyde in the presence of 3-ethylbenzothiazolium bromide (EBB) as a catalyst.

The representative route, taking the case of synthesis of D-fructose (a ketohexose) from D-arabinose (an aldopentose) and formaldehyde by use of the selective cross-acyloin condensation, is illustrated in Scheme 1. Prior to cross-acyloin condensation, D-arabinose was converted into the diethyl dithioacetal, which was acetylated, and the resulting product was demercaptalated with aqueous cadmium carbonate/mercuric chloride to give 2,3,4,5-tetra-*O*-acetyl-*aldehydo*-D-arabinose **1** according to the published methods.[12a] In a 10 ml flask were placed **1** (1.57 mmol), paraformaldehyde (1.57 mmol as formaldehyde), 3-ethylbenzothiazolium bromide (3.14 mmol), ethanol (10 ml), and then triethylamine (3.14 mmol); dry nitrogen was bubbled through the mixture. The sealed reaction vessel was heated at 70 °C for 3 days. The reaction was quenched by cooling with ice water. The resulting mixture was concentrated by evaporation to give a dark syrup containing 3,4,5,6-tetra-*O*-acetyl-D-fructose **2** which was not isolated, followed by hydrolysis with barium hydroxide solution (50 ml, 0.3 mol dm^{-3}).[12b] After exact neutralizing and desalting, the solution was concentrated under reduced pressure at 40 °C to afford a syrupy product, which was solidified by adding absolute ethanol. The resulting solid was recrystallized from ethanol and a white crystalline product $\{[\alpha]^{20}_{\mathrm{D}} = -90.5°$ (*c* 4.0, H_2O), 80% yield based on **1**$\}$ was obtained, which was identified as D-fructose **3** by comparing the ^{1}H and ^{13}C NMR, and IR spectra of the isolated product with those of the authentic compound. The yield which was estimated by GC–IR technique after the oximated trimethylsilylation[13] was 88%. By the same procedure, the yield of L-fructose from 2,3,4,5-tetra-*O*-acetyl-*aldehydo*-L-arabinose was 72% (78% by GC–IR) and of D-sorbose from 2,3,4,5-tetra-*O*-acetyl-*aldehydo*-D-xylose 95% (100% by GC–IR), but the case of D-psicose from 2,3,4,5-tetra-*O*-acetyl-*aldehydo*-D-ribose proceeded in only 30% yield (34% by GC–IR), probably owing to the severity of the deacetylation (hydrolysis) step.

The conventional diazomethane method which affords a ketohexose from an aldehydo-form aldopentose included five steps and the total yield was only 43% in the case of synthesis of D-sorbose from 2,3,5,6-tetra-*O*-acetyl-*aldehydo*-D-xylose, although the yield in each step was considerably high.[4]

By using an aldohexose or an aldoheptose in place of an aldopentose, this reaction could be utilized for the preparation of the next higher ketoses, that is, a ketoheptose or a ketooctose. Furthermore, the use of glycoladehyde or glyceraldehyde instead of formaldehyde may enable us to synthesize readily the higher-carbon ketose with two or three additional carbons than the starting aldose.

Received, 31st December 1991; Com. 1/06526B

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