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High-Yielding One-Step Conversion of D-Glucose and D-Galactose to the Corresponding α and β Methyl-D-glucofuranosides and Galactofuranosides

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## HIGH-YIELDING ONE-STEP CONVERSION OF D-GLUCOSE AND D-GALACTOSE TO THE CORRESPONDING $\alpha$ AND $\beta$ METHYL-D-GLUCOFURANOSIDES AND GALACTOFURANOSIDES.

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Abstract : D-Glucose and D-Galactose are transformed to the corresponding  $\alpha$  and  $\beta$ -Methyl D-Glucofuranosides in good yields using methanol and Ferric chloride as catalyst.

Most of the time, the synthesis of furanosides is accomplished in several stages<sup>1</sup> starting from sugar derivatives protected in the furanoid form, for example via 1,2-0-isopropylidene- $\alpha$ -D-glucofuranose-5,6-carbonate,<sup>2</sup> D-glucurono-3,6-lactone<sup>3</sup> or  $\alpha$ -D-Glucofuranose 1,2:3,5-bis-(benzeneboronate)<sup>4</sup>.

Furanosides are the kinetically controlled products of the acid-catalyzed alcoholysis of monosaccharides and ring-expand to the thermodynamically more stable pyranosides.<sup>5-7</sup> It has been shown that the relative proportions of furanosides and pyranosides, as well as  $\alpha$  and  $\beta$  isomers, produced by the Fischer glycosidation<sup>8</sup> of monosaccharides such as D-allose, may be changed<sup>9</sup> by the presence of alkaline-earth metal ions such as calcium and strontium with form

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complexes. We now report on the acid-catalysed glycosidation of D-glucose and D-glactose in the presence of ferric chloride.

When D-glucose was treated at room temperature for 7 days, with anhydrous methanol containing a slight excess of anhydrous ferric chloride, t.l.c revealed almost quantitative conversion into methyl  $\alpha$  and  $\beta$  D-glucofuranosides 1 and 2. Only few amounts if not traces of methyl D-Glucopyranosides and unreacted D-Glucose were detected. When the reaction was carried out under the same conditions using zing chloride or aluminium chloride as catalysts complex reaction mixtures were obtained.



Buchanan<sup>10</sup> synthesised **1** and **2**, by the original Fischer method. In these conditions, only poor yields were obtained. This indicated that ring expansion is prevented by the presence of ferric ions in the reaction mixture. The methyl D-glucofuranosides formed in the presence of ferric chloride were isolated in 75% yields as a colorless gum exhibiting an optical rotation<sup>2,11</sup> of -14°. Thus, the  $\alpha$ , $\beta$ -ratio for the mixture was 32:68. This result was confirmed by both <sup>1</sup>H<sup>1,12</sup> and <sup>13</sup>C<sup>13</sup> n.m.r spectra which were in good agreement with the literature data.

Surprisingly, in contrary with D-glucose, D-galactose did not react at room temperature with methanol in the presence of ferric chloride even after 4 days. It was necessary to heat to bring the reaction to completion. T.l.c indicated that the reaction mixture contained two major products, the  $\alpha$  and  $\beta$  D-galactofuranosides **3** and **4** and small quantities of methyl D-galactopyranosides as a slower migrating single spot. Flash chromatography afforded the pure  $\beta$  anomer **4** in 40% yields and 35% of a 45-55  $\alpha$ , $\beta$ -mixture of **3** and **4**. Optical rotations, <sup>14</sup> <sup>1</sup>H n.m.r<sup>1,12</sup> and <sup>13</sup>C<sup>13</sup> n.m.r were in good agreement with published data.

## **Experimental section**

General methods. n.m.r. spectra were recorded with a Brucker AM200 spectrometer. <sup>1</sup>H n.m.r. spectra were recorded in pyridine d<sub>5</sub> using tetramethylsilane as internal standard and <sup>13</sup>C n.m.r. spectra in D<sub>2</sub>O using the signal of dioxanne fixed at  $\delta$  67.4 as reference. The progress of reactions and purity of samples were checked by t.l.c on silica gels plates with mixtures of dichloromethane-methanol (7:3) as eluant.

Methyl  $\alpha$  and  $\beta$  –D-glucofuranosides 1 and 2. To a solution of ferric chloride (2.916 g, 18 mmoles) in anhydrous methanol (100 ml) was added Dglucose (3.240 g,18 mmoles) and the resulting mixture stirred for 6 days at room temperature (22°). T.l.c then showed the formation of one spot  $R_F$  0.50 and small amounts of starting material R<sub>F</sub>0.20. More ferric chloride was added (0.972 g, 6 mmoles) and the mixture stirred for 24 h. Celite was added, then a saturated aqueous solution of sodium hydrogencarbonate (10 g) to precipitate the ferric salts and the reaction mixture stirred one additional hour at room temperature. The precipitate obtained was filtered off through a pad of celite, washed with methanol and the filtrate evaporated. The resulting solid was extracted with boiling ethylacetate-ethanol (2:1, v/v, 4 x 80 ml) and the combined extracts evaporated. The residue was dissolved in THF, filtered and evaporated to afford a gum (2.9 g, 83%) pure enough to be used without any further purification. For analytical purposes the so obtained mixture of 1 and 2 was purified by flash chromatography with dichloromethane-methanol (94:6) as the eluant. Pure mixture of 1 and 2 was obtained as a colorless gum; yield 2.6 g (75%);  $[\alpha]_D^{22}$  -14 ° (c 3.8, water); <sup>1</sup>H n.m.r  $\delta$  3.45 (s, 3 H,  $\beta$ -CH<sub>3</sub>), 3.50 (s, 3 H,  $\alpha$ -CH<sub>3</sub>), 5.30 (d, 1 H, J<sub>1,2</sub> 4.2 Hz, α-H-1) 5.35 (d, 1 H, J<sub>1,2</sub> 1.0 Hz, β-H-1). <sup>13</sup>C n.m.r. δ 55.97 (β-OCH<sub>3</sub>), 56.75 (α-OCH<sub>3</sub>), 103.92 (α-C-1), 109.83 (β-C-1).

Methyl  $\alpha$  and  $\beta$  –D-galactofuranosides 3 and 4. A stirred suspension of Dgalactose (3.24g, 18 mmoles) in anhydrous methanol (100 ml) containing ferric chloride (2.91g, 18 mmoles) was heated at 60° for 24 h and then boiled under reflux for 4 h. After cooling at room temperature the reaction mixture was processed as described for 1 and 2 to remove the ferric salts. T.l.c of the residual gum (3.75g) showed the formation of two close spots, R<sub>F</sub> 0.50 and 0.46 corresponding to 4 and 3 respectively and a third one, R<sub>F</sub> 0.35 migrating as authentical samples of  $\alpha$  and  $\beta$ –D-galactopyranosides. Flash chromatography afforded first, pure **4** (1.41g, 40 %) as a colorless gum resistant to crystallisation :  $[\alpha]_D^{22}$  - 109 ° (*c* 4.3, water) [lit<sup>11,14</sup> [α]<sub>D</sub><sup>22</sup> - 112° (*c* 2, water)]; <sup>1</sup>H n.m.r δ 3.45 (s, 3 H, OCH<sub>3</sub>), 5.45 (d, 1 H, J<sub>1,2</sub> 2 Hz, H-1). <sup>13</sup>C n.m.r. δ 55.70 (β-OCH<sub>3</sub>), 108.94 (β-C-1). Further elution gave a pure 45:55 gummy α,β mixture (1.25 g, 35%) of **3** and **4** respectively. [α]<sub>D</sub><sup>22</sup> -14.3 ° (*c* 6, water); <sup>1</sup>H n.m.r. δ 3.45 (β-OCH<sub>3</sub>), 3.50 (α-OCH<sub>3</sub>), 5.15 (d, 1 H, J<sub>1,2</sub> 4.5 Hz, α-H-1), 5.45 (d, 1 H, J<sub>1,2</sub> 2 Hz, β-H-1). <sup>13</sup>C n.m.r. δ 55.70 (β-OCH<sub>3</sub>), 56.05 (α-OCH<sub>3</sub>),102.78 (α-C-1), 108.94 (β-C-1).

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