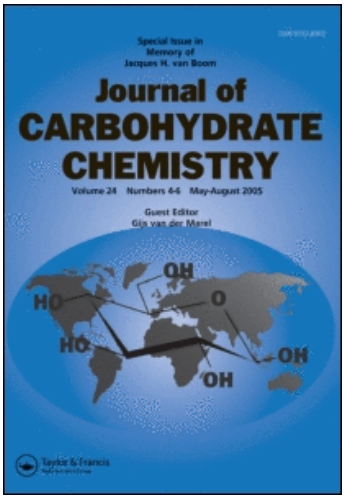

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NI(II)-CATALYSED REACTIONS OF FREE D-FRUCTOSE DERIVATIVES MODIFIED AT POSITIONS C-5 AND/OR C-6

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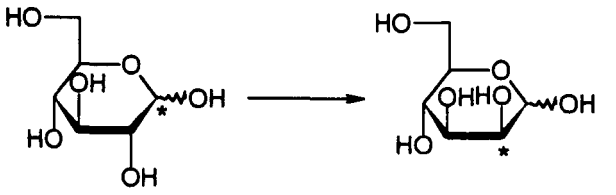
ABSTRACT

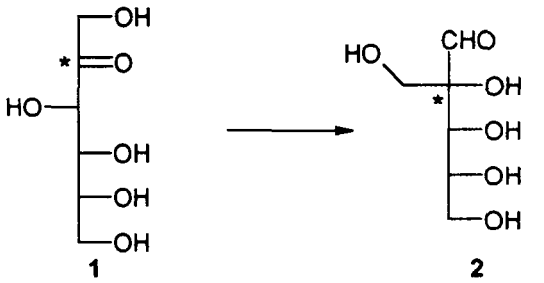
The nickel(II) catalysed isomerisation reactions of D-fructose derivatives modified at positions 5 and/or 6 were investigated. 5,6-Dimodified open-chain D-fructose derivatives as well as an open-chain derivative of D-xylulose reacted to give complex mixtures containing no major product. 5-Modified ketohexoses invariantly were degraded to the corresponding methyl pentonates upon loss of C-1. 6-Modified D-fructofuranose furnished the desired rearrangement into a branched-chain derivative of D-ribose. In marked contrast to previous belief, from these results it appears that 5-OH plays an important role in the productive co-ordination of the D-fructose derivatives to the nickel-ethylenediamine complexes under consideration.

INTRODUCTION

Nickel(II) complexes with various *N*-substituted derivatives of 1,2-diaminoethane and 1,3-diaminopropane in methanol as the solvent. These compounds have recently been discovered to be capable of isomerising aldoses into their corresponding epimers at C-2.[1] Remarkably, in the course of the rearrangement reaction, carbons C-1 and C-2 as well as the substituents attached, quantitatively interchange their positions as was demonstrated



Scheme 1

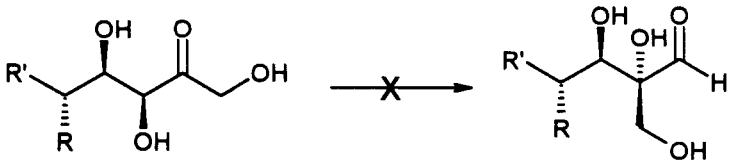


Scheme 2

with the aid of aldoses regioselectively substituted with stable isotopes such as ^{2}H and ^{13}C in NMR experiments (Scheme 1).[2]

Following the fate of ketoses under the reaction conditions, Yoshikawa and co-workers discovered an exciting extension of the rearrangement.[3] When D-fructose (**1**) was subjected to the reaction conditions, D-hamamelose (2-*C*-hydroxymethyl-D-ribose, **2**) was found to be the product of the isomerisation reaction (Scheme 2). In the latter, C-1 had become the hydroxymethyl side-chain as was demonstrated in experiments employing 2-[^{13}C]-D-fructose.

Furthermore, it was found that a *threo* relationship between C-3 and C-4 in the ketohexose is a prerequisite for obtaining preparatively useful yields.[4] This particularly interesting outcome and its preparative potential for our glycosidase inhibitor syntheses prompted us to conduct experiments with various modified D-fructose derivatives. These compounds contained azidodeoxy groups or other non-natural sustituents at positions 5 and/or 6 which, according to the proposed mechanism of the rearrangement, do not take part in the co-ordination process and, consequently, should be able to be modified.



3: R = N_3; R' = CH_2F
5: R = OMe; R' = CH_2OMe
6: R = H; R' = H

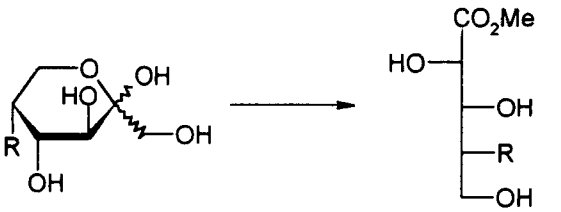
4

Scheme 3

RESULTS AND DISCUSSION

In initial experiments, an attempt to isomerise the known[5] open-chain 5-azido-5,6-dideoxy-6-fluoro-D-fructose (**3**) into the corresponding 4,5-dimodified derivative of D-hamamelose **4** was carried out with the aim of gaining access to a new series of branched chain pyrrolidines as potential glycosidase inhibitors. Despite all efforts made, the reaction was difficult to follow by TLC as several spots could be detected without the indication of major product formation. Upon work-up, inseparable multi-component mixtures were obtained from which only starting material could be recovered in very low yields. This was also found to be the case when 5,6-di-*O*-methyl-D-fructose (**5**), available by enzymatic isomerisation of 5,6-di-*O*-methyl-D-glucofuranose,[6] was employed as a more readily available model compound. The same problem also arose with the simple 5-deoxy-D-*threo*-pentulose[7] (5-deoxy-D-xylulose, **6**), synthesized in 70% yield by enzymatic isomerisation of 5-deoxy-D-xylose,[8] as the starting material. In none of these sets of experiments could defined products of the hamamelose type be unambiguously detected by NMR methods or isolated from the reaction mixtures (Scheme 3).

To gain a better understanding of the chemistry involved and in order to find out which of the non-natural substituents at C-5 and C-6 might be responsible for the somewhat disappointing results, we turned our attention to 5-modified D-fructose derivatives as starting materials for the isomerisation reaction. 5-Azido-5-deoxy-D-fructopyranose[9] (**7**) was subjected to the isomerisation reaction conditions in order to obtain the corresponding 4-azidodeoxy derivative of D-hamamelose, this being a precursor



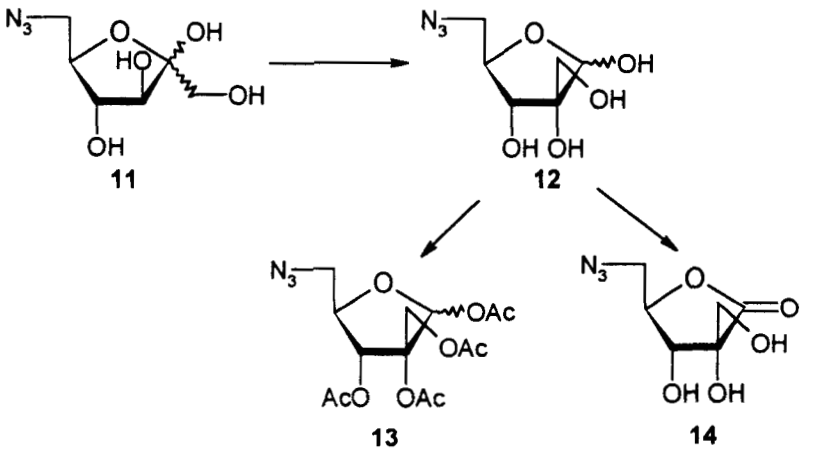
7: R = N_3
9: R = OBn

8: R = N_3
10: R = OBn

Scheme 4

to highly functionalised pyrrolidines. When exposed to the reported standard reaction conditions employing complexes of Ni(II) with *N,N'*-diethylethylenediamine or *N,N'*-diethylpropylenediamine as the catalysts, a slow but clean reaction took place leading to a less polar product. This turned out not to be the desired 4-azidodeoxy derivative of D-hamamelose but could instead be identified as methyl 4-azido-4-deoxy-D-arabinonate (**8**). When 5-*O*-benzyl-D-fructopyranose[9] (**9**) was chosen as the starting material, an analogous outcome of the reaction was observed. Formation of the desired 4-*O*-benzyl-D-hamamelose could not be detected. Instead, the ketose was converted into methyl 4-*O*-benzyl-D-arabinonate (**10**) in 47% isolated yield (Scheme 4). These results parallel recently made observations[10] with 5-azidodeoxy- as well as 5-deoxyfluoro-L-sorbopyranoses which were degraded to the corresponding methyl L-xylonates in 38 and 20% isolated yields, respectively. As observed previously,[10] the reactions proceeded equally well under an atmosphere of argon and the presence of nickel(II) was found to be essential.

In a third series of experiments, the behaviour of 6-modified D-fructose derivatives was investigated employing 6-azido-6-deoxy-D-fructofuranose[11] (**11**), easily available from sucrose in three steps, as the starting material. Reaction of ketofuranose **11** with the catalyst system at 30 °C was allowed to proceed for one to two hours. After this period of time the reaction was quenched and the crude mixture of products was acetylated to allow an easier separation of the components. Examination of the components gratifyingly showed that 5-azidodeoxy-D-hamamelose (**12**), which was isolated as the tetra-*O*-acetate



Scheme 5

(**13**), had been formed in the isomerisation process, albeit in a yield of less than 10%. Assignment of the configuration at C-2 based on NMR experiments was made by comparison with published data.[4,12] Even lower yields were obtained in attempts to isolate the desired branched-chain sugar *via* oxidation to the corresponding lactone **14** (Scheme 5). Optimisation experiments are currently being carried out to obtain compound **14** in a preparatively more useful yield. It should be noted that with D-fructose (**1**) as the starting material and the selected Ni-complexes employed for this study, results published[3] by the discoverers of this particular rearrangement could be reproduced.

In conclusion, the experiments reported here suggest that the currently accepted mechanism for the nickel(II)/ethylenediamine catalysed rearrangement of the 2-ketose D-fructose into the branched chain aldose D-hamamelose does not apply for derivatives bearing modifications at C-5 and, consequently, neither for analogues with alterations at both, C-5 and C-6. The outcome of the reaction is independent of the diamine ligands selected and of reaction times between 45 min and 2 hours as employed in this study. This infers that in the catalytic process with 2-ketoses the hydroxyl group at C-5 plays a similarly essential role as does C-4 in aldoses. Further experiments will clearly be necessary to establish this point as well as to evaluate any preparative potential of the method for natural product synthesis.

EXPERIMENTAL

General Methods. Melting points were determined on a Tottoli apparatus (Büchi 300) and are uncorrected. Optical rotations were measured with a JASCO DIP-360 Digital Polarimeter at 589 nm at ambient temp. NMR spectra were recorded at 300.13 or 200 MHz (^{1}H) as well as 75.47 or 50.29 MHz (^{13}C). Residual non-deuterated solvent was used as internal standard for determination of chemical shifts. The signals of protecting groups are in the expected regions and are not listed explicitly. TLC was performed on precoated aluminum plates (Merck 5554) employing 5% vanillin/sulfuric acid as well as ceric ammonium molybdate as staining agents. For column chromatography, silica gel 60, 230-400 mesh (Merck 9385), was used.

General Procedure for Isomerisation Reactions. To a 10% solution of nickel(II) chloride hexahydrate (1 equiv) and *N,N'*-diethylethylenediamine or *N,N'*-diethyl-1,3-propylenediamine (2 equiv) in dry methanol, a 20% solution of the respective starting material (1 equiv) was added, and the mixture was stirred at ambient temp for 45 min after which period of time the solution was diluted with distilled water (1:1, v/v) followed by adjustment of the pH of the mixture to 7 with 0.5 M sulfuric acid. After having been stirred for one additional hour, the mixture was treated with acidic ion exchange resin Amberlite IR 120 and weakly basic Amberlite IRA 68. The resulting solution was concentrated under reduced pressure. The residue was chromatographed on silica gel or on Dowex 50 W X 2, 100-200 mesh (Ca^{2+}). For TLC, ethyl acetate/MeOH 4:1 was employed. Chromatography on silica gel was performed with ethyl acetate as the mobile phase.

5,6-Di-*O*-methyl-D-fructose (5). To a 5% aqueous solution of 5,6-di-*O*-methyl-D-glucofuranose (1.5 g, 7.2 mmol; prepared from 3-*O*-benzyl-1,2-*O*-isopropylidene-5,6-di-*O*-methyl-α-D-glucofuranose by the method of Freudenberg and Plankenhorn:[6] $[\alpha]_D^{20}$ +1.3° (*c* 3.0, MeOH); ^{13}C NMR δ 104.5, 98.3 (C-1/α,β), 82.2, 81.7, 79.5, 79.1, 78.8 78.0, 77.4, 76.6 (C-2, C-3, C-4, C-5/α,β), 73.6, 73.4 (C-6/α,β), 59.6 (2 C), 58.6, 58.5) a few drops of a 1% aqueous $MgSO_4$ solution and immobilised glucose isomerase (EC 5.3.1.5, Sweetzyme T, 4 g) were added and the mixture was stirred at 60 °C for 4-6 h after which period of time solids were removed by filtration. To the filtrate, $BaCO_3$ (2

equiv) and bromine (1.4 equiv) were added and the brown mixture was stirred at ambient temp until TLC ($CHCl_3$/MeOH 5:1, v/v) indicated no more change. Excess Br_2 was removed with compressed air, the solution was concentrated under reduced pressure and the residue was subjected to chromatography on silica gel (ethyl acetate) to give 940 mg (62%) of open-chain ketose **5**: $[\alpha]_D^{20}$ -74.0° (*c* 0.2, MeOH); ^{1}H NMR (MeOH-d_4) δ 4.51 (d, 1 H, $J_{1,1'}$ 19.2 Hz, H-1), 4.44 (d, 1 H, H-1'), 4.41 (d, 1 H, $J_{3,4}$ 1.8 Hz, H-3), 3.93 (dd, 1 H, $J_{4,5}$ 9.1 Hz, H-4), 3.75 (dd, 1 H, $J_{5,6}$ 2.4 Hz, $J_{6,6'}$ 10.6 Hz, H-6), 3.61 (dd, 1 H, $J_{5,6'}$ 4.4 Hz, H-6'), 3.40 (m, H-5), 3.44 (s, 3 H, OMe), 3.38 (s, 3 H, OMe); ^{13}C NMR δ 214.2 (C-2), 80.6 (C-3), 76.9 (C-4), 72.2, 72.1, 67.9 (C-1, C-5, C-6), 59.5, 58.4 (2 OMe).

Anal. Calcd for $C_8H_{16}O_6$ (208.21): C, 46.15; H, 7.75. Found: C, 45.90; H, 7.92.

5-Deoxy-D-*threo*-pentulose (6). 5-Deoxy-D-xylofuranose[8] (1.22 g, 9.1 mmol) was subjected to immobilised glucose isomerase (Sweetzyme T, 4 g) following the procedure given for the preparation of ketose **5**. After chromatography (ethyl acetate), open-chain pentulose **6** (860 mg, 70%) was obtained as a faintly yellow oil: $[\alpha]_D^{20}$ -25.4° (*c* 1.5, MeOH); ^{1}H NMR (D_2O) δ 4.67 (d, 1 H, $J_{1,1'}$ 19.5 Hz, H-1), 4.55 (d, 1 H, H-1'), 4.30 (d, 1 H, $J_{3,4}$ 2.6 Hz, H-3), 4.24 (dt, 1 H, $J_{4,5}$ 6.2 Hz, H-4), 1.36 (d, 3 H, 3 H-5); ^{13}C NMR δ 213.8 (C-2), 79.4 (C-3), 68.9, 67.0 (C-1, C-4), 18.9 (C-5).

Anal. Calcd for $C_5H_{10}O_4$ (134.13): C, 44.77; H, 7.51. Found: C, 44.61; H, 7.65.

Methyl 4-Azido-4-deoxy-D-arabinonate (8). Following the general procedure for isomerisation reactions, reaction of azidodeoxyfructose[9] **7** (111 mg, 0.54 mmol) with the catalyst gave a faster moving product. After 24 h, all starting material had been consumed. Following work-up, the product could be isolated (27 mg, 24%) by chromatography and was identified as methyl 4-azido-4-deoxy-D-arabinonate **8**: $[\alpha]_D^{20}$ -22.0° (*c* 1.4, MeOH); ^{1}H NMR (MeOH-d_4) δ 4.41 (d, 1 H, $J_{2,3}$ 1.7 Hz, H-2), 4.15 (dd, 1 H, $J_{3,4}$ 10.5 Hz, H-3), 3.86-3.55 (m, 6 H, H-4, H-5, H-5', OMe); ^{13}C NMR δ 175.0 (C-1), 72.6, 72.3 (C-2, C-3), 65.3, 63.5 (C-4, C-5), 52.7 (OMe).

Anal. Calcd for $C_6H_{11}N_3O_5$ (205.17): C, 35.13; H, 5.40. Found: C, 35.30; H, 5.55.

Methyl 4-*O*-Benzyl-D-arabinonate (10). Applying the general procedure to 5-*O*-benzyl-D-fructopyranose[9] (**9**, 38 mg, 0.14 mmol) gave product **10** (18 mg, 47%) as a colourless oil: $[\alpha]_D^{20}$ -10.6° (*c* 0.9, MeOH); ^{1}H NMR (MeOH-d_4) δ 4.49 (d, 1 H, $J_{2,3}$ 1.8

Hz, H-2), 4.01 (dd, 1 H, $J_{3,4}$ 9.3 Hz, H-3), 3.95 (dd, 1 H, $J_{4,5}$ 2.8 Hz, $J_{5,5'}$ 9.2 Hz, H-5), 3.75 (s, 3 H, OMe), 3.74 (m, 1 H, H-5'), 3.61 (ddd, 1 H, $J_{4,5'}$ 4.0 Hz, H-4); ^{13}C NMR δ 175.2 (C-1), 80.4, 73.7, 72.4, 72.2 (C-2, C-3, C-4, $\underline{C}H_2Ph$), 61.7 (C-5).

Anal. Calcd for $C_{13}H_{18}O_6$ (207.28): C, 75.33; H, 8.75. Found: C, 75.50; H, 8.86.

1,2,2',3-Tetra-*O*-acetyl-5-azido-5-deoxy-2-*C*-hydroxymethyl-D-ribose (1,2,2',3-Tetra-*O*-acetyl-5-azido-5-deoxy-D-hamamelose, 13). Following the general procedure for isomerisation reactions with Ni(II) complexes, 6-azido-6-deoxy-D-fructofuranose[11] (**11**, 936 mg, 4.56 mmol) was exposed to the respective complex for 1 hour at 30 °C. After concentration of the ion exchange resin treated solution, the residue was dissolved in pyridine (15 mL) and acetic anhydride (3 mL) followed by 4-dimethylaminopyridine (50 mg) were added to the solution. After quantitative conversion into a faster moving main product, the solution was concentrated under reduced pressure, the residue was dissolved in CH_2Cl_2 and the solution was consecutively washed with 5% aqueous HCl and sat. aqueous sodium bicarbonate. After drying (Na_2SO_4) and removal of the drying agent by filtration, the filtrate was concentrated under reduced pressure and the remaining material was chromatographed on silica gel to give desired hamamelose derivative **13** (145 mg, 8%) as a colourless oil: $[\alpha]_D^{20}$ +38.4° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.54 (s, 1 H, H-1), 5.22 (d, 1 H, $J_{3,4}$ 4.3 Hz, H-3), 4.67 (d, 1 H, $J_{2'a,2'b}$ 12.5 Hz, H-2'a), 4.54 (d, 1 H, H-2'b), 4.23 (ddd, 1 H, $J_{4,5}$ 3.5 Hz, $J_{4,5'}$ 4.3 Hz, H-5), 3.71 (dd, 1 H, $J_{5,5'}$ 13.3 Hz, H-5'); ^{13}C NMR δ 95.6 (C-1), 82.5 (C-4), 77.5, 71.3 (C-2, C-3), 61.7 (C-2'), 51.8 (C-5). In accordance with reported data,[4] only one anomer was obtained.

Anal. Calcd for $C_{14}H_{19}N_3O_9$ (373.32): C, 45.04; H, 5.13. Found: C, 44.89; H, 5.08.

5-Azido-5-deoxy-2-*C*-hydroxymethyl-D-ribono-1,4-lactone (5-Azido-5-deoxy-D-hamamelono-1,4-lactone, 14). 6-Azido-6-deoxy-D-fructofuranose[11] (**11**, 846 mg, 4.12 mmol) was exposed to the Ni(II) system according to the general procedure at 30 °C for 60 min. Following ion exchange resin treatment, $BaCO_3$ (2 equiv) and Br_2 (1.5 equiv) were added to the solution which was stirred at ambient temp until TLC (ethyl acetate/methanol 10:1, v/v) did not show any change in the distribution of components. Excess bromine was removed by blowing air through the mixture. Solids were filtered off,

the filtrate was concentrated under reduced pressure and the residue was chromatographed (cyclohexane/ethyl acetate 1:3, v/v) to give desired lactone **14** (30 mg, 3.5%) as a colourless syrup: $[\alpha]_D^{20}$ +74.7° (*c* 0.6, MeOH); ^{1}H NMR (D_2O) δ 4.66 (m, 1 H, H-4), 4.44 (d, 1 H, $J_{3,4}$ 7.4 Hz, H-3), 4.00 (dd, 1 H, $J_{4,5}$ 3 Hz, $J_{5,5'}$ 14.0 Hz, H-5), 3.90 (d, 1 H, H-2'a), 3.78 (d, 1 H, H-2'b), 3.73 (dd, 1 H, $J_{4,5'}$ 5.4 Hz, H-5'); ^{13}C NMR (acetone-d_6) δ 174.5 (C-1), 81.5 (C-4), 69.7 (C-3), 62.0 (C-2'), 52.1 (C-5).

Anal. Calcd for $C_6H_9N_3O_5$ (203.16): C, 35.47; H, 4.47. Found: C, 35.31; H, 4.61.

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