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Base catalysed isomerisation of aldoses of the *arabino* and *lyxo* series in the presence of aluminate

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Abstract

Base-catalysed isomerisation of aldoses of the *arabino* and *lyxo* series in aluminate solution has been investigated. L-Arabinose and D-galactose give L-*erythro*-2-pentulose (L-ribulose) and D-*lyxo*-2-hexulose (D-tagatose), respectively, in good yields, whereas lower reactivity is observed for 6-deoxy-D-galactose (D-fucose). From D-lyxose, D-mannose and 6-deoxy-L-mannose (L-rhamnose) are obtained mixtures of ketoses and C-2 epimeric aldoses. Small amounts of the 3-epimers of the ketoses were also formed. 6-Deoxy-L-*arabino*-2-hexulose (6-deoxy-L-fructose) and 6-deoxy-L-glucose (L-quinovose) were formed in low yields from 6-deoxy-L-mannose and isolated as their *O*-isopropylidene derivatives. Explanations of the differences in reactivity and course of the reaction have been suggested on the basis of steric effects.

Keywords: L-*erythro*-2-Pentulose; 6-Deoxy-D-*lyxo*-2-hexulose; D-Xylulose; D-Fructose; 6-Deoxy-L-fructose; D-Xylose; D-Glucose; L-Quinovose

1. Introduction

Base-catalysed isomerisation of D-glucose to D-fructose in aluminate solution was reported in a patent in 1964.[1] Since then, this method has been applied in isomerisation, also of reducing disaccharides, lactulose has been prepared from lactose[2] and maltose has been converted to maltulose in aluminate solution[3] and on aluminate resin.[4] A possible mechanism of the isomerisation of glucose to fructose has been suggested[5] on the basis of the known capability of aluminate to form complexes with monosaccharides.[6] A 9% conversion of L-arabinose in aluminate solution to L-*erythro*-2-pentulose (L-ribulose), determined by an enzymatic assay, has also been reported.[7] During previous, unpublished work on aldol reactions, we needed D- or L-*erythro*-2-pentulose as starting material and decided to prepare the L enantiomer from L-arabinose on the basis of the reported isomerisation in aluminate solution. We found that considerably more than the reported 9% of the pentulose could be obtained in this reaction.

Through the last few years, much attention has been focused on D-*lyxo*-2-hexulose (tagatose), the "novel hexose", as a potential therapeutic adjunct in the management of type 2 diabetes mellitus[8,9] and as a non-calorific sweetener in food. It has been found recently that D-*lyxo*-2-hexulose may be produced from D-galactose by the action of the same enzyme, L-*arabinose isomerase*, that isomerises the aldopentose to L-*erythro*-2-pentulose.[10–13] The growing interest in D-*lyxo*-2-hexulose and the similarity in the effect of L-*arabinose isomerase* on L-arabinose and its higher homologue D-galactose, gave us the idea to compare also the effect of aluminate on the same two sugars as well as on 6-deoxy-D-galactose (D-fucose) as a third member of the L-*arabino* series.

Mannose, unlike glucose, is known to undergo C-2 epimerisation in aluminate solution in addition to aldose–ketose isomerisation.[5] Mannose belongs to the *lyxo* series with *erythro* configuration at C-2–C-3, whereas the aldoses of the *arabino* series, as well as glucose have threo configuration at these carbon atoms. In order to get further information on the importance of configuration in the reaction of aldoses in aluminate solution, we decided to include three aldoses of the *lyxo* series, D-lyxose, D-mannose and 6-deoxy-L-mannose (L-rhamnose) in our investigation.

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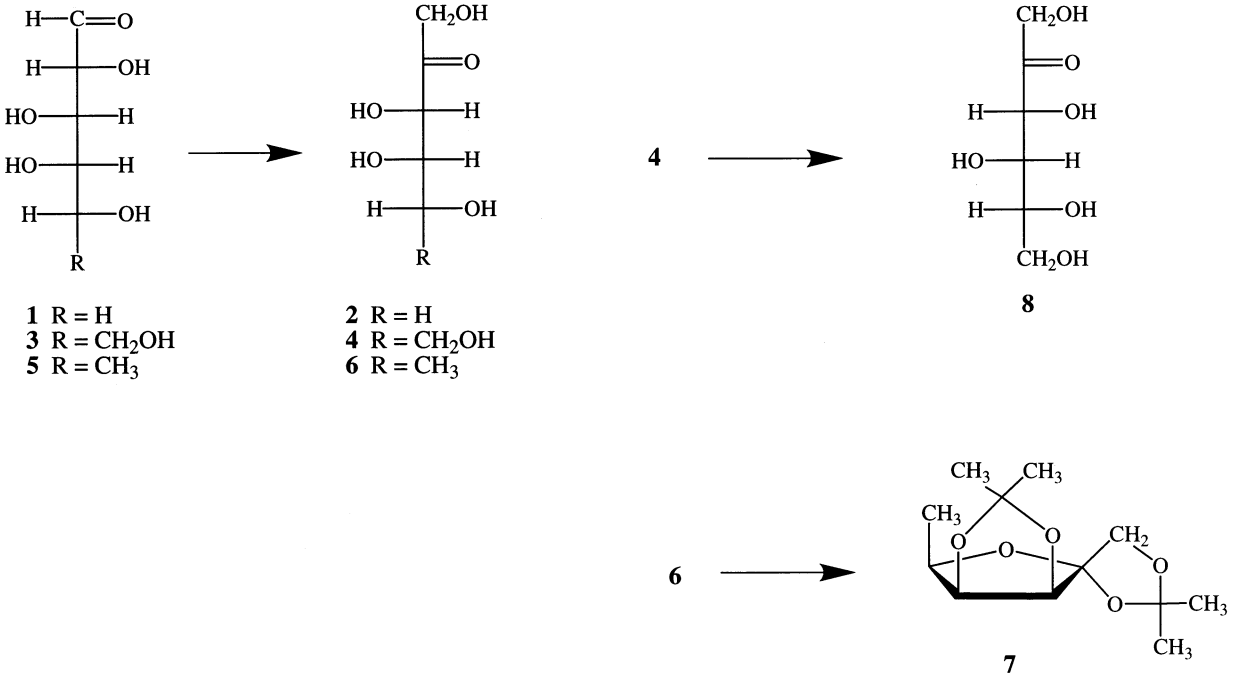
2. Results and discussion

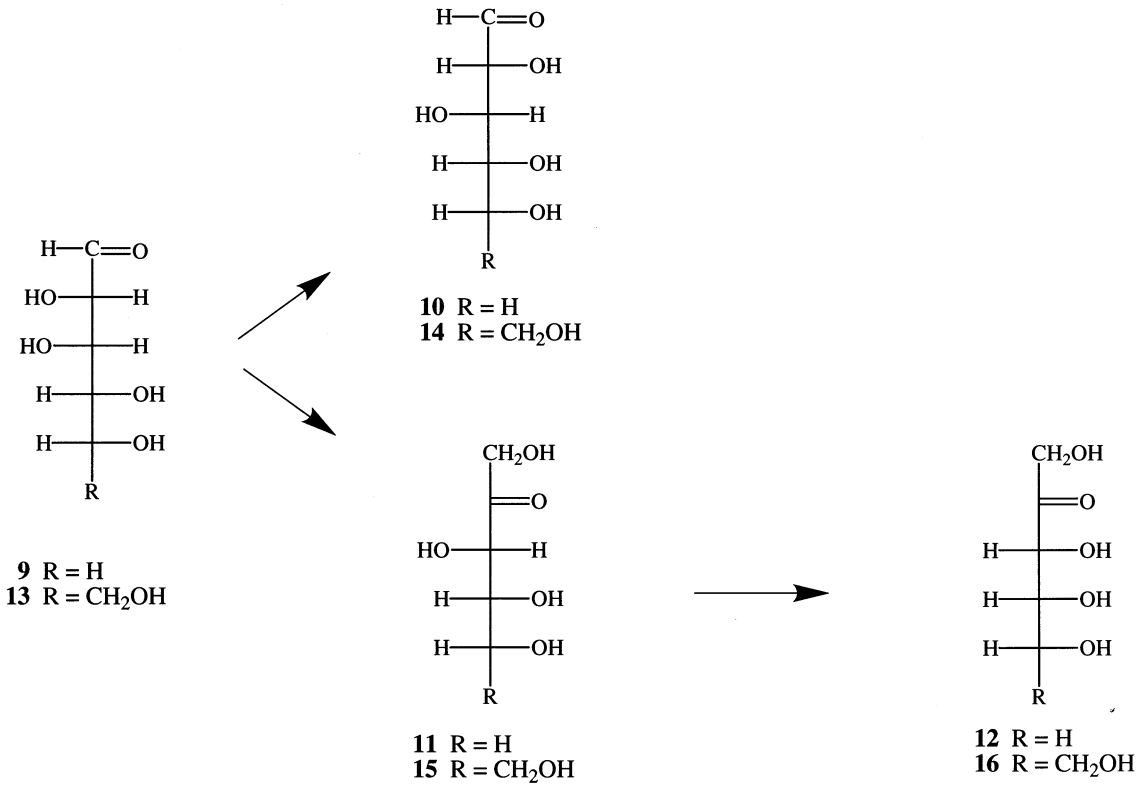
When a sodium aluminate solution of L-arabinose (**1**) was kept at 35 °C for 20 h, GC–MS analysis of the isopropylidene derivatives of the sugars[14,15] revealed a reaction mixture containing L-*erythro*-2-pentulose (**2**) and **1** in a ratio of about 2:3, whereas similar treatment of D-galactose (**3**) resulted in about 70% conversion to D-*lyxo*-2-hexulose (**4**). From 6-deoxy-D-galactose (**5**) only about 20% had isomerised to 6-deoxy-D-*lyxo*-2-hexulose (**6**) after 20 h under the same conditions, determined by GC–MS as its 1,2:3,4-di-*O*-isopropylidene derivative (**7**). Whereas isomerisation of L-arabinose (**1**) gave almost exclusively **2**, small amounts of D-*xylo*-2-hexulose (**8**) (D-sorbose), and the 3-epimer of **4** was formed during isomerisation of D-galactose (**3**) (Scheme 1).

GC–MS analysis after acetonation of the products from the aldoses of the *lyxo* series showed more complex mixtures. D-Lyxose (**9**) gave D-xylose (**10**) by epimerisaton at C-2 in addition to isomerisation to D-*threo*-2-pentulose (**11**) which further partly isomerised to its 3-epimeric 2-pentulose (**12**). From D-mannose (**13**) was formed D-glucose (**14**) in addition to the main product D-fructose (**15**) as expected.[5] Minute amounts of the 3-epimer of **15,** D-*ribo*-2-hexulose (psicose) (**16**) were also observed after prolonged reaction time (Scheme 2). Traces of the *arabino*- and *ribo*-3-hexuloses were also formed. The major products from the aldoses **9** and **13** were the ketoses **11** and **15**. 6-Deoxy-L-mannose (**17**) also gave mainly ketose as a product, but in addition to the formation of 6-deoxy-L-*arabino*-2-hexulose (6-deoxy-L-fructose) (**18**), relatively more C-2 epimerisation occurred than with **9** and **13**, leading to substantial amounts of 6-deoxy-L-glucose (L-quinovose) (**19**). C-3 epimerisation of **18** was also observed, giving the *ribo*-isomer (**20**) (Scheme 3). Table 1 shows the relative proportions of epimerisation and isomerisation products from the aldoses after different reaction times.

On a preparative scale, and after prolonged reaction time, the ketoses **2**, **4** and **6** were obtained in 64, 78 and 42% yield, respectively, after oxidation of remaining aldoses by bromine and removal of the resulting aldonic acids by ion-exchange resin. The product of aldose–ketose isomerisation of **17**, 6-deoxy-L-*arabino*-2-hexulose (**18**) was isolated as its *O*-isopropylidene derivative. The isomerisation mixture was treated with acetone–sulfuric acid and the products partitioned between hexane and water. The compounds in the water phase were subjected to mild-acid hydrolysis, and only the relatively stable 2,3-*O*-isopropylidene-6-deoxy-β-L-*arabino*-2-hexulofuranose (**21**) was resistant and could be extracted as a single compound in $CHCl_3$. Its mass spectrum revealed a M-$CH_3]^+$ peak at m/z 189, a high-intensity peak at m/z 173 due to C-1–C-2 cleavage and the characteristic fragment ion pair at m/z 130 and 115 for a 2,3-*O*-isopropylidene derivative of a 2-ketose,[16,17] which is only formed from ketoses with *threo* configuration at C-3–C-4.[17] The ^1H and ^{13}C NMR spectra are in agreement with the structure. It is expected from the dihedral angles that no coupling is observed between H-3 and H-4, and between H-4 and



Scheme 1.

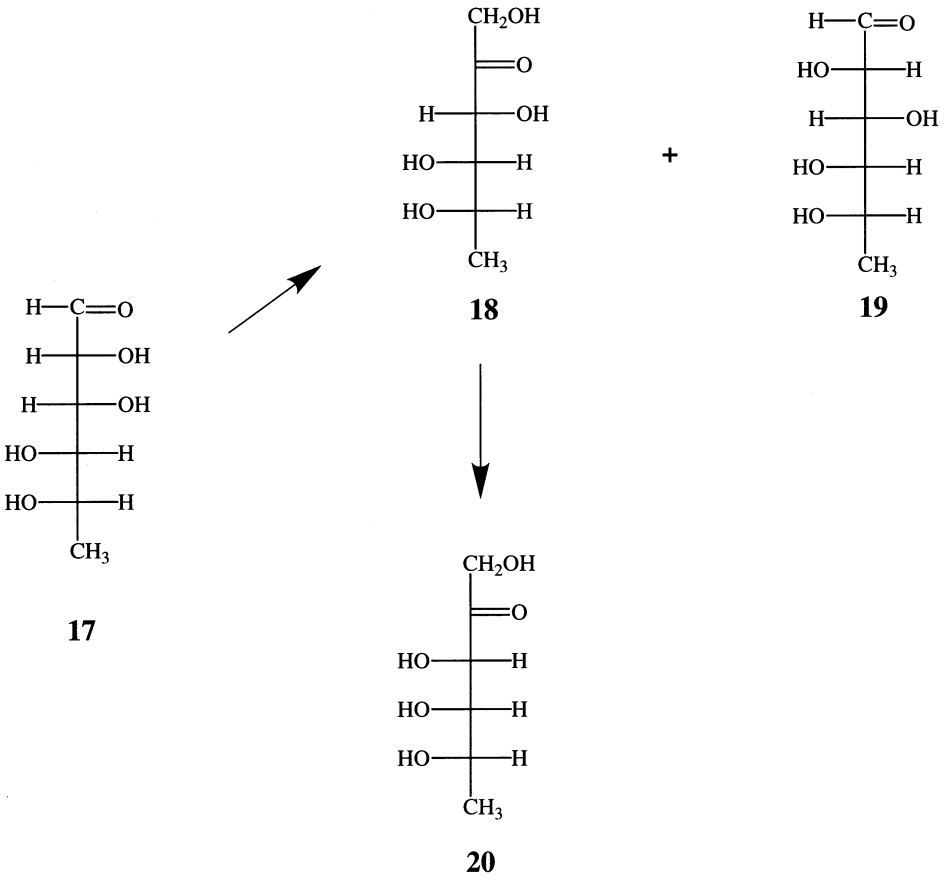


Scheme 2.

H-5 in the ^{1}H NMR spectrum, which by MM2 calculations are found to be 84° and 89°, respectively. From the hexane phase, the derivative of the aldose **19** could be isolated as the 1,2:3,5-di-*O*-isopropylidene derivative **22**. Advantage was taken of the great lability of the 3,5-*O*-isopropylidene group even with very mild-acid hydrolysis, which allowed selective hydrolysis to the monoisopropylidene derivative, separation from the di-*O*-isopropylidene derivative **23** of compound **20** by partitioning between hexane and water and re-acetonation of the monoisopropylidene derivative from the water phase. Compound **22** was characterised by MS and NMR spectrometry. The M-$CH_3]^+$ ion at *m*/*z* 229 in its electron impact mass spectrum shows that **22** is a di-*O*-isopropylidene derivative. The lack of the *m*/*z* 130–115 and 117–72 fragment ion pairs excludes the possibility of a 6-deoxy-2-hexulose.[16,17] Among the four 6-deoxy-L-aldohexoses known or expected to give only or mainly di-*O*-isopropylidene derivatives, those with *galacto* and *altro* configuration will give derivatives in pyranose form, and since the mass spectrum of **22** is very different from that of 1,2:3,4-di-*O*-isopropylidene-6-deoxy-α-L-galactopyranose, only *gluco* and the very unlikely *ido* configurations are possible for the compound. The ^{13}C NMR spectrum of **22** confirmed its identity. From its mass spectrum, compound **23** was identified as one of the anomers of 1,2:3,4-di-*O*-isopropylidene-6-deoxy-*ribo*-2-hexulofuranose, since the spectrum only differed from that of the *lyxo* isomer **7** in the relative abundance of some of the fragments, a fact that excludes other possibilities (Scheme 4).

From our own and other investigations of the effect of aluminate on aldoses, it appears that C-2 epimerisation requires an *erythro* configuration at C-2–C-3 and that the reactivity in aldose–ketose isomerisation also depends on the configuration of the aldoses, as well as that of the products. The ability of the ketoses to form stable aluminate complexes is important. Rendleman and Hodge[6] have shown that fructose, which dominates in the mannose–glucose–fructose isomerisation mixture, is much more retarded on an aluminate resin column than the aldohexoses; this is obviously due to the formation of a more stable complex. Sorbose is also retarded relatively to the aldoses, but much less than fructose. The suggested reason for the high yield of fructose obtained from glucose is the ability of the ketose to form a 1,3,6-tridentate aluminate complex in the α-furanose form.[5] Tagatose, unlike sorbose and psicose, also has a configuration allowing the formation of such a complex (Fig. 1). This may explain the high yield of D-tagatose obtained from D-galactose in our work and its limited further isomerisation to the 3-epimer D-sorbose (**8**). The similar C-3 epimerisation of fructose observed under isomerisation of mannose is also reported to occur when glucose is isomerised to fructose.[5] The theory of favourable complex formation

for fructose and tagatose is supported by our observation that D-allose was isomerised only very slowly to D-psicose (**16**) in aluminate under the conditions used in this investigation. On the basis of the 1,3,6-tridentate theory, the much lower reactivity of D-fucose than D-galactose is expected because of the lack of a hydroxyl group at C-6. The formation of a 1,3-aluminate complex of the reacting aldose in the pyranose form has been proposed as an important early step in the reaction.[5] In the case of L-arabinose, the $^1C_4$ conformation is then expected to be preferred (Fig. 2(a)). In the same conformation of D-fucose, the methyl group will be axially oriented and experience *syn–axial* interactions with O-1 and O-3 (Fig. 2(b)). This may explain that the 6-deoxyaldose reacts also more slowly than L-arabinose. C-6 will be in the axial position in $^1C_4$ conformation also for D-glucose and D-galactose. However, the hydroxyl group at this carbon atom, with its capa-

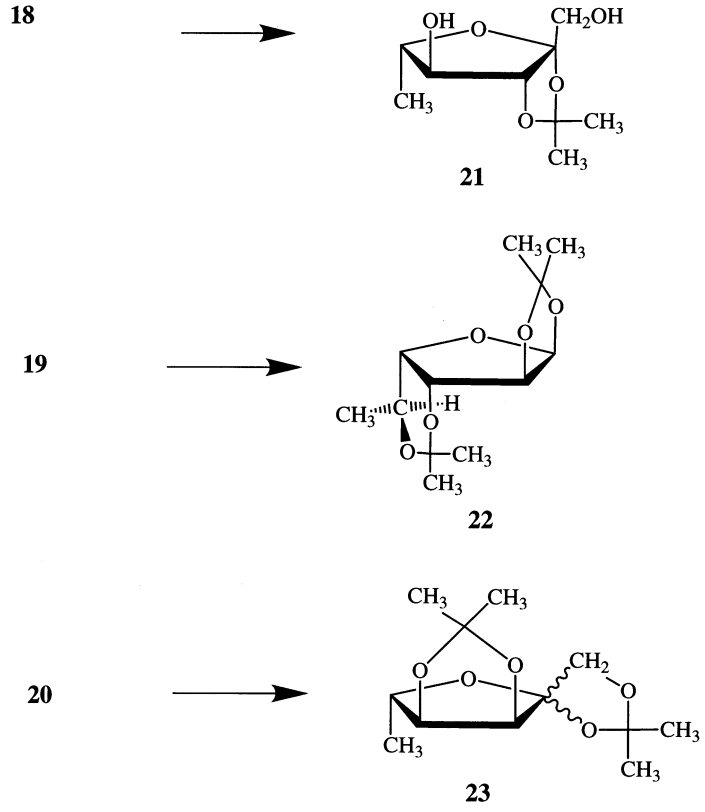


Scheme 3.

Table 1
Composition in percent in the reaction mixtures of unreacted aldose (A); ketose (K); 2-epimeric aldose (EA); and 3-epimeric ketose (EK) after different reaction times [a]

	3 h				20 h				40 h			
	A	K	EA	EK	A	K	EA	EK	A	K	EA	EK
L-Arabinose	93	7			60	40			31	69		
D-Galactose	83	17			30	69		1	10	85		5
6-Deoxy-D-galactose	97	3			80	20			62	38		
D-Lyxose	85	12	3		52	38	6	4	44	40	8	8
D-Mannose [b]	85	11	3	1	45	44	9	2	35	53	9	3
6-Deoxy-L-mannose	95	3	2		75	16	8	1	56	22	17	5

[a] Other products, which sometimes were formed in minor amounts, are not included.
[b] From mannose were formed small amounts of *arabino*- and *ribo*-3-hexulose.



Scheme 4.

bility to participate in 1,3,6-tridentate aluminate complex formation, may be a driving force in the aldose–ketose isomerisation instead of representing steric hindrance. That the order of reactivity in aldose–ketose isomerisation in the *lyxo* series is hexose > pentose > 6-deoxyhexose, just as observed for the sugars of the *arabino* series, supports the suggested explanations.

The observation that L-*erythro*-2-pentulose (**2**) undergoes negligible C-3 epimerisation to the *threo* isomer in aluminate solution under the conditions applied in this investigation, whereas substantial amounts of the *erythro* isomer are formed from the latter, shows that the configuration of the 2-pentuloses is important for the stability of their aluminate complexes. This could indicate that OH-4 participates directly in a 1,3,4-aluminate complex of **2**, but despite the fact that the closely related borate ion is known to form complexes with vicinal hydroxyl groups,[18] such complexations with aluminate in carbohydrates have been considered as unlikely.[5]

The necessity of having an *erythro* configuration at C-2–C-3 in aldoses to give C-2 epimerisation in aluminate solution is in accordance with the model proposed by Shaw and Tsao[5] for the mannose–glucose isomerisation. The suggested common acyclic intermediate from two aldoses differing only in configuration at C-2, shown in Fig. 3, can only reform the aldose with *threo* configuration at C-2–C-3, no rotational orientation allows attack of OH-5 at C-1 from the side leading to the aldose with *erythro* configuration at these carbon atoms.

Other complexing agents such as borate[19,20] and Ca^{2+}, [21–23] alone or in combination with amines, as well as pentasilicate[24] have been applied in base catalysed aldose–ketose isomerisation. Ca^{2+} also effects C-2 epimerisation[22,23,25–27] with a mechanism involving C-1–C-2 interconversion as in the Bílik reaction with molybdate.[28] That aluminate gives some C-2 epimerisation for mannose, lyxose and rhamnose raises the question about the possibility of a similar C-1–C-2 interconversion mechanism operating also with this complexing agent. Mannose and lyxose are, however, reported to show considerable resistance to both C-2 epimerisation and aldose–ketose isomerisation with

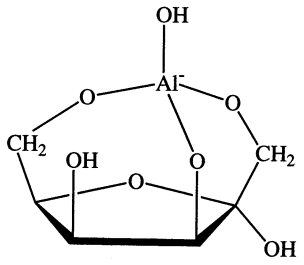


Fig. 1. 1,3,6-Tridentate aluminate complex of α-D-tagatofuranose.

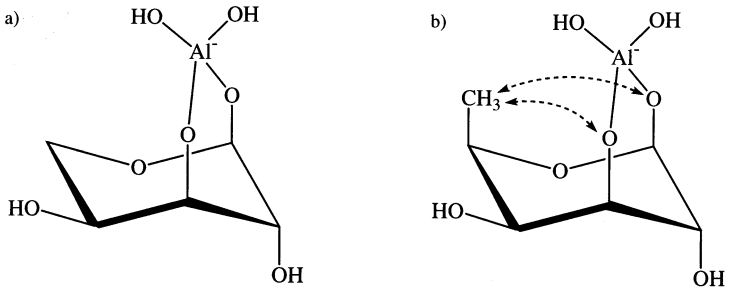


Fig. 2. 1,3-Bidentate aluminate complex of α-L-arabinopyranose (a) and β-D-fucopyranose (b) in $^1C_4$ conformation.

Ca^{2+}–amine combinations, whereas glucose undergoes extensive C-2 epimerisation to mannose.[23] This is the opposite order of reactivity to that observed in C-2 epimerisation in the presence of aluminate, which does not effect C-2 epimerisation of glucose. This fact argues against the possibility of similarities in the two epimerisation mechanisms. A suggested explanation for the resistance of mannose and lyxose to isomerisation and epimerisation in Ca^{2+} solution is the protection of these aldoses by a stable 1,2,3 *axial–equatorial–axial* complex,[23] very different from the proposed 1,3-bidentate aluminate complexes. It seems likely to us that aldose–ketose isomerisation in aluminate solution also occurs via the acyclic intermediate shown in Fig. 3 by OH-5 attack on C-2 instead of on C-1.

Aluminate is useful as a complexing agent in the preparation of ketoses from aldoses of the *arabino* series. In addition to galactose, the aldohexoses glucose and mannose also give good yields of ketose, presumably since fructose, like tagatose, may form a stable tridentate complex with aluminate. The complexity of the product mixtures from lyxose and 6-deoxymannose reduces the synthetic utility of base catalysed isomerisation in aluminate solution of these aldoses.

3. Experimental

General methods.—Optical rotations were measured with a Carl Zeiss Kreispolarimeter 0.01°. Pre-coated Silica Gel G plates were used for TLC with (A) 7:2:1 acetone–1-butanol–water and (B) 30:1 $CHCl_3$–CH_3OH as eluents. Spots were detected by spraying with diphenylamine–aniline–phosphoric acid[29] followed by H_2SO_4 in EtOAc and heating at 110 °C for 5 min. GC was performed with a Shimadzu GC-14B gas chromatograph, equipped with an open tubular fused silica column, 25 m × 0.32 mm ID, wall coated with CP-SIL 43 CB, programmed at 6°/min from 90 to 225 °C. For mass spectrometry, a JEOL JMX-DX 303 double focusing-mass spectrometer with EB geometry was used, equipped with a 10 kV post acceleration conversion dynode detector and an electron ionisation–chemical ionisation (EI–CI) ion source, operated in EI mode at 70 eV and an ion source temperature at 180 °C. A Carlo–Erba high-resolution gas chromatograph (HRGC) was applied for the GC–MS combination. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury instrument at 300 and 75 MHz, respectively. The assignments were based on COSY, HETCOR, NOESY and ROESY techniques. The spectra of the isopropylidene derivatives were recorded in $CDCl_3$ with $CHCl_3$ as the internal standard, while those of the free carbohydrates were recorded in D_2O with Me_2SO as internal standard (^{13}C NMR δ_{ref} 40.40 ppm).

Preparation of aluminate solution.—Aluminum powder or foil (3.40 g) was added to a solution of NaOH (5.00 g) in water (400 mL). When no more H_2 gas was evolved, small amounts of remaining solid were removed by filtration.

Isomerisation of aldoses, analysis of product mixtures.—Aluminate solution (3 mL) containing aldose (50 mg) was flushed with N_2 gas, corked and kept at 35 °C. Aliquots (0.5 mL) were withdrawn after 3, 20 and 40 h, diluted with water (5 mL) and deionized with Dowex 50 W (H^+) ion-exchange resin. After filtration of the solution and evaporation of the water under reduced pressure, the residue was stirred with 2% H_2SO_4 in acetone (3 mL) for 2 h. The solution was neutralised with solid $NaHCO_3$ and subjected to GC and GC–MS for identification and quantification of the aldoses,[14] 2-ketoses[15] and 3-hexuloses[30] in the product mixtures. The results are shown in Table 1.

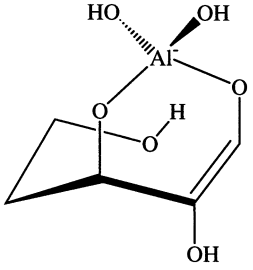


Fig. 3. Suggested intermediate in C-2 epimerisation of aldoses and in aldose–ketose isomerisation.

L-erythro-*2-Pentulose* (**2**).—L-Arabinose (**1**, 2.0 g) in aluminate solution (120 mL) was kept at 35 °C under N_2 for 48 h. After deionisation and filtration of the solution as describe above, was added $CaCO_3$ (1 g) and then Br_2 in small portions from a water solution under stirring in the dark until a faint brown colour remained for 1 h (total reaction time less than 2 h). The solution was then treated with Dowex 1 (HCO_3^-) ion exchange resin, filtered, treated with Dowex 50 W (H^+) and finally once more with Dowex 1 (HCO_3^-) resin. Filtration and evaporation of the solvent gave syrupy L-*erythro*-2-pentulose (**2**, 1.28 g, 64%), $[\alpha]_D^{20}$ +14° (*c* 2, water); lit.[31] +17°. The product was chromatographically homogeneous and indistinguishable from authentic **2** by TLC, R_f 0.45 (solvent A) and by GC after acetonation as described above, R_t 4.8 min. The ^1H and ^{13}C NMR spectra were in accordance with those reported for the D enantiomer.[32]

D-lyxo-*2-Hexulose* (**4**).—D-Galactose (**3**, 2.0 g) in aluminate solution (120 mL) was treated as described for compound **1**. The syrupy product crystallised slowly on addition of 96% EtOH to give **4** (1.56 g, 78%), mp 132–134 °C; lit. 131–132 °C.[33] $[\alpha]_D^{20}$ −3° (*c* 5, water); lit. −2°.[33] The product was chromatographically homogeneous and indistinguishable from authentic **4** by TLC, R_f 0.39 (solvent A) and by GC after acetonation, R_t 12.0 min. The ^1H and ^{13}C NMR spectra were identical with those of an authentic sample and in accordance with reported spectra.[34,35]

6-Deoxy-D-lyxo-*2-hexulose* (**6**).—Isomerisation of 6-deoxy-D-galactose (**5**, 0.50 g) and treatment of the product mixture with bromine as described for **1** and **3** gave syrupy **6** (0.21 g, 42%). $[\alpha]_D^{20}$ −3° (*c* 2, water); lit. −2°.[36] TLC (solvent A) showed a single spot, R_f 0.56. The ^1H and ^{13}C NMR data were in accordance with those reported for the L enantiomer.[37] After treatment of a small sample of **6** with acetone–H_2SO_4 as described above, GC showed the presence of almost exclusively one compound, 1,2:3,4-di-*O*-isopropylidene-6-deoxy-α-D-*lyxo*-2-hexulofuranose (**7**), with R_t 4.6 min; EIMS *m*/*z* (% rel. int.): 229 (100), 142 (80), 129 (19), 128 (27), 117 (97), 113 (86), 111 (53), 85 (25), 84 (71), 72 (36), 70 (28), 59 (89), 57 (24), 43 (82).

Isomerisation of 6-deoxy-L-*mannose* (**17**).—Compound **17** (0.50 g) in aluminate solution (30 mL) was kept at 35 °C for 48 h. The solution was then treated with Dowex 50 W (H^+) ion-exchange resin, filtered and the water removed under reduced pressure. The residue was stirred with 2% H_2SO_4 in acetone (25 mL) for 2 h, then the solution was neutralised, filtered and concentrated. The residue was partitioned between water (15 mL) and hexane (20 mL) and the water phase was extracted with hexane (2 × 5 mL).

From the water phase the solvent was removed by evaporation. The residue was dissolved in 80% formic acid (2 mL) and then water (4 mL) was added and the solution was kept overnight at rt to allow selective hydrolysis of the 2,3-*O*-isopropylidene derivative of unreacted 6-deoxy-L-mannose. The solution was concentrated to a small volume (1 mL), diluted with water (5 mL) and evaporated to dryness. The residue was partitioned between water, made alkaline with $NaHCO_3$ (4 mL) and $CHCl_3$ (5 mL). The water solution was extracted with $CHCl_3$ (4 × 5 mL) and the combined $CHCl_3$ solutions were dried with Na_2SO_4. Filtration of the solution and evaporation of the solvent gave 2,3-*O*-isopropylidene-6-deoxy-β-L-*arabino*-2-hexulofuranose (**21**) as a syrup that crystallised on addition of Et_2O (128 mg, 21%); mp 110–112 °C; lit. 114–115 °C for the D enantiomer;[38] $[\alpha]_D^{20}$ −7° (*c* 2, EtOH); lit. +8° for the D enantiomer.[38] GC: R_t 14.6 min; TLC: R_f 0.25 (solvent B). EIMS: 189 (26), 173 (83), 171 (11), 130 (8), 129 (48), 115 (22), 111 (35), 71 (100), 59 (98), 43 (63). ^1H NMR: 1.21 (s, 3 H, *exo*-CH_3), 1.30 (d, *J* 6.9 Hz, 3 H, H-6), 1.43 (s, 3 H, *endo*-CH_3), 3.44 (bs, 2 H, OH), 3.56 (d, *J* 11.7 Hz, 1 H, H-1), 3.73 (d, *J* 11.7 Hz, 1 H, H-1), 3.91 (s, 1 H, H-4), 4.15 (q, 6.9 Hz, 1 H, H-5), 4.33 (s, 1 H, H-3); ^{13}C NMR: 20.49 (C-6), 26.11(*exo*-CH_3), 26.98 (*endo*-CH_3), 64.21 (C-1), 78.66 (C-4), 86.71 (C-5), 87.99 (C-3), 112.90 (CMe_2), 114.70 (C-2).

The combined hexane solutions from above were seen by GC to contain, in addition to compound **22**, minor amounts of **23** with R_t 5.0 min; EIMS: 229 (61), 142 (21), 129 (16), 128 (29), 117 (100), 113 (30), 111 (58), 85 (15), 84 (33), 72 (30), 70 (21), 59 (70), 43 (64). The hexane solution was evaporated, and 80% formic acid (1 mL) was added to the residue. After 15 min, water (10 mL) was added, and the water solution extracted with hexane (2 × 5 mL) and pH adjusted to 7 with $NaHCO_3$. After saturation with Na_2SO_4, the solution was extracted with $CHCl_3$ (5 × 6 mL). The $CHCl_3$ was evaporated, and the residue stirred for 20 min with 0.4% H_2SO_4 in acetone (10 mL). Neutralisation, filtration and evaporation followed by partitioning of the residue between water (5 mL) and hexane (10 mL) gave, after evaporation of the solvent from the hexane phase, 1,2:3,5-di-*O*-isopropylidene-6-deoxy-α-L-glucofuranose (**22**) as a syrup (66 mg, 9%). $[\alpha]_D^{20}$ −35° (*c* 0.5, $CHCl_3$); lit. +38° for the D enantiomer.[39] GC: R_t 6.1 min; TLC: R_f 0.80 (solvent B). EIMS: 229 (7), 171 (6), 142 (16), 129 (18), 113 (100), 100 (12), 85 (15), 84 (11), 71 (10), 59 (43), 43 (71). The ^{13}C NMR spectrum was in accordance with data reported for the D enantiomer.[40]

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