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Green aldose isomerisation: 2-*C*-methyl-1,4-lactones from the reaction of Amadori ketoses with calcium hydroxide

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Abstract—Saccharinic acids, branched 2-*C*-methyl-aldonic acids, may be accessed via a green procedure from aldoses by sequential conversion to an Amadori ketose and treatment with calcium hydroxide; D-galactose and D-glucose are converted to 2-*C*-methyl-D-*lyxono*-1,4-lactone (with a small amount of 2-*C*-methyl-D-*xylono*-1,4-lactone) and 2-*C*-methyl-D-*ribono*-1,4-lactone. Inversion of configuration at C-4 of the branched lactones allows access to 2-*C*-methyl-L-*ribono*-1,4-lactone and 2-*C*-methyl-L-*lyxono*-1,4-lactone, respectively. D-Xylose affords 2-*C*-methyl-D-*threono*-1,4-lactone and 2-*C*-methyl-D-*erythrono*-1,4-lactone, whereas L-arabinose, under similar conditions, gave the enantiomers 2-*C*-methyl-L-*threono*-1,4-lactone and 2-*C*-methyl-L-*erythrono*-1,4-lactone.

At present, all commercially available carbohydrate scaffolds contain linear carbon chains.[1] The Kiliani cyanide ascensions[2,3] on unprotected ketohexoses—D-fructose, L-sorbose,[4] D-tagatose and D-psicose[5]—provide an accessible set of derivatives bearing a C-2 hydroxymethyl group of value in the efficient synthesis of complex homochiral targets;[6] the Kiliani reaction of the C-2 branched sugars[7,8] gives C-3 branched sugars. The isomerisation of aldoses or ketoses into 2-*C*-methyl-aldonic acids by calcium hydroxide in very low yields is one of the oldest[9] and most complex organic reactions with typically less than 0.5% of branched 2-*C*-methyl-aldonic acids being formed;[10] after optimisation of the reaction of fructose with calcium hydroxide a yield of around 11% of 2-*C*-methyl-D-ribonic acid **3D** can be obtained in several weeks.[11] This letter establishes the generality of the calcium hydroxide isomerisations of Amadori ketoses, derived from cheap aldoses, to 2-*C*-methyl-branched aldonic acids as a new strategy for the synthesis of branched sugar chirons.

The sole previous report of this transformation (Scheme 1) is the conversion of D-glucose **1** with dimethylamine to fructosamine **2**, which with aqueous calcium hydroxide gives the branched ribose derivative **3D**, isolated as its lactone;[12] a practical procedure is given below for the transformation of D-galactose **6** via the Amadori ketose **5** to 2-*C*-methyl-lyxonic acid **4D**. Although the yields are modest, the low cost of glucose and galactose make **3D** and **4D** accessible starting materials for homochiral targets with methyl-branched carbon chains. There are currently no cheaply available L-aldohexoses; however, inversion of configuration at C-4 of 1,4-lactones can be accomplished efficiently on a multi-kilogram scale.[13] Thus the epimerisations of D-*ribono*-**3D** to L-*lyxono*-**4L** and of D-*lyxono*-**4D** to L-*ribono*-**3L** allow both enantiomers to be synthesised.

Pentoses also undergo the same transformation (Scheme 2). Thus, D-xylose **7** was converted to Amadori derivative **8**; subsequent reaction of **8** with calcium oxide allows the isolation of both 2-*C*-methyl-D-*erythrono*-**9D** and D-*threono*-**10D** acids. L-Arabinose **12**, the only readily available L-pentose, allows the formation of enantiomers **9L** and **10L** from L-ribulosamine **11**.

D-Galactose **6** on reaction with dibenzylamine in acetic acid/ethanol (Scheme 3) underwent the Amadori rearrangement to give tagatosamine **5**, which crystallised as the α-anomer,[14] in 88% yield.[15] Treatment of Amadori ketose **5** with calcium oxide in water, followed

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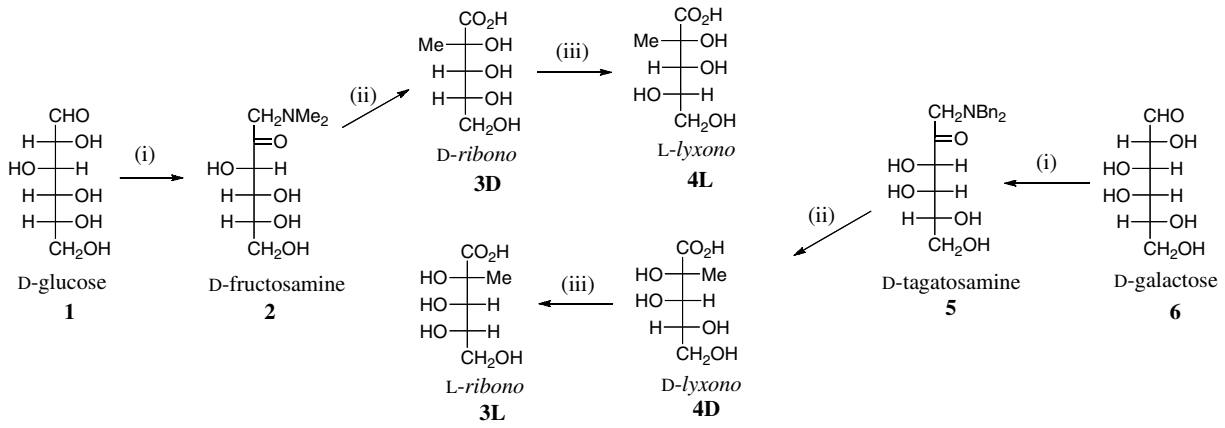
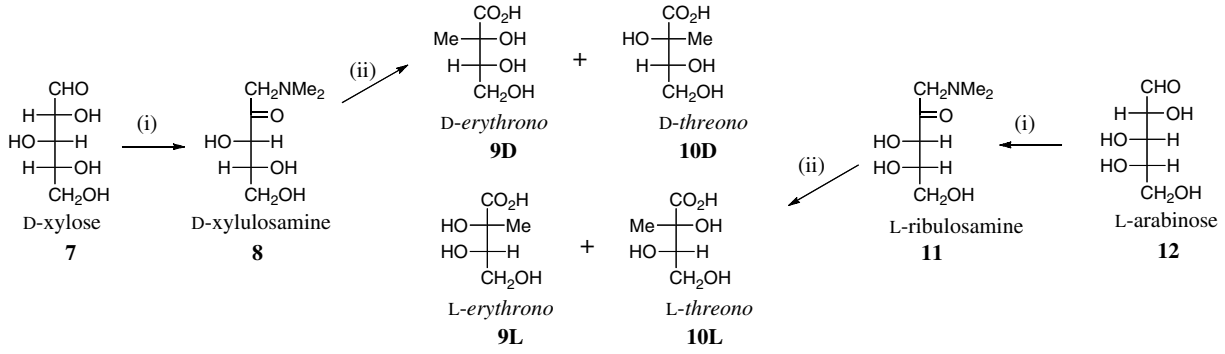
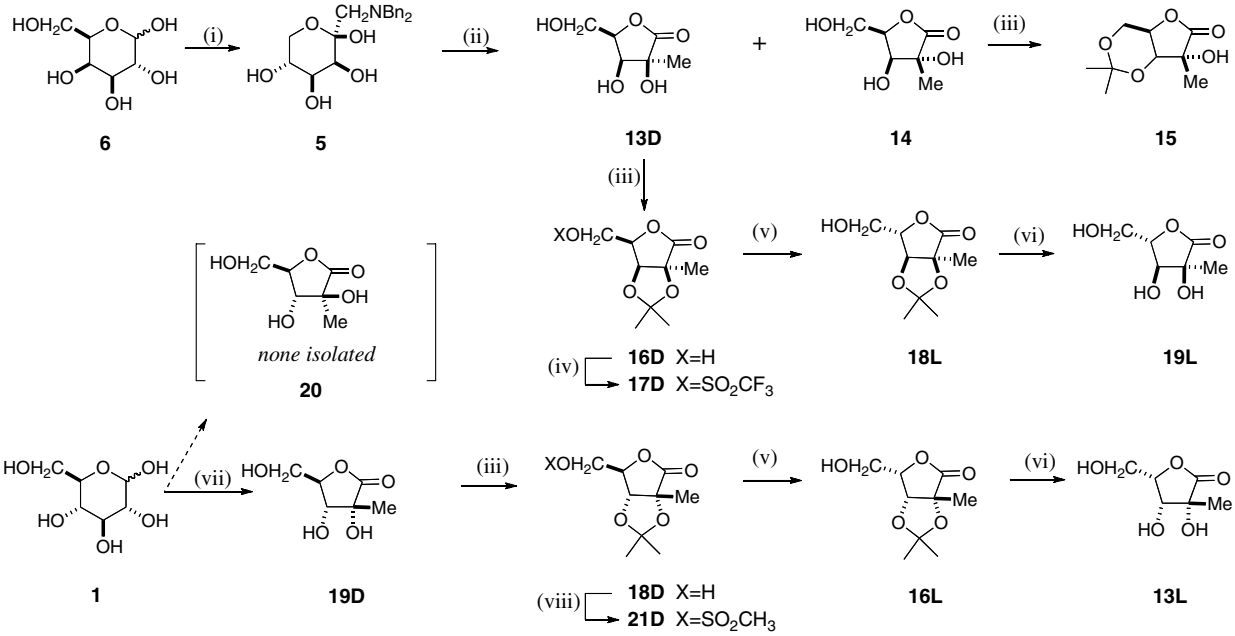


Scheme 1. Reagents and conditions: (i) Me_2NH or Bn_2NH; (ii) CaO, H_2O; (iii) invert at C-4.



Scheme 2. Reagents: (i) Me_2NH; (ii) CaO, H_2O.



Scheme 3. Reagents: (i) Bn_2NH, AcOH, EtOH; (ii) CaO, H_2O; (iii) Me_2CO, $CuSO_4$, concd H_2SO_4; (iv) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2; (v) KOH, diaoxane, H_2O; (vi) CF_3COOH, H_2O; (vii) Ref. 12; (viii) CH_3SO_2Cl, pyridine, DMAP.

by an acid work-up, gave as the easily isolated and separated products 2-*C*-methyl-branched *lyxono*-**13D** (12% yield) and *xylono*-**14** (2% yield) lactones. There is a significant preference for the formation of *cis*-diol **13D** rather than *trans*-isomer **14**; in contrast, when glucose **1** was subjected to the same procedure only the *cis*-diol *ribono*-lactone **19D** was formed with none of the epimeric *trans*-diol *arabino*-lactone **20** being formed.[12]

A practical method for the synthesis of branched D-lyxonolactone **13D** (the lactone derived from **4D**) is as follows: A suspension of the Amadori ketose **5** (41.2 g, 115 mmol) in water (750 mL) was stirred at 70 °C with calcium oxide (32 g, 570 mmol) for 24 h. The reaction mixture was cooled to room temperature, filtered through Celite® and then passed through Amberlite® IR-120 H^+ ion exchange resin, using water as the eluant. The water was then removed under reduced pressure to afford a crude orange oil which was purified by flash column chromatography (ethyl acetate/cyclohexane, (6:1) → ethyl acetate) to afford 2-*C*-methyl-D-*lyxono*-1,4-lactone **13D** (1.98 g, 12%)[16] and D-*xylono*-epimer **14** (338 mg, 2%).[17] The structure of the unprotected *lyxono*-lactone **13D** was confirmed by X-ray crystallographic analysis;[18] reaction of *xylono*-epimer **14** with acetone in the presence of anhydrous copper sulfate and acid gave 3,5-acetonide **15** (mp 155–158 °C, $[\alpha]_D^{23}$ +82.2 (*c* 0.67, $CHCl_3$)), an X-ray structure of which was also determined.[19] It is easy to distinguish between the diastereomers by their ^{13}C spectra; the chemical shift of the 2-*C*-methyl group of *lyxono*-isomer **13D** (δ 20.7) where the diol unit is *cis* is at a significantly lower field than *xylono*-isomer **14** (δ 16.8), where the diol unit is *trans*.

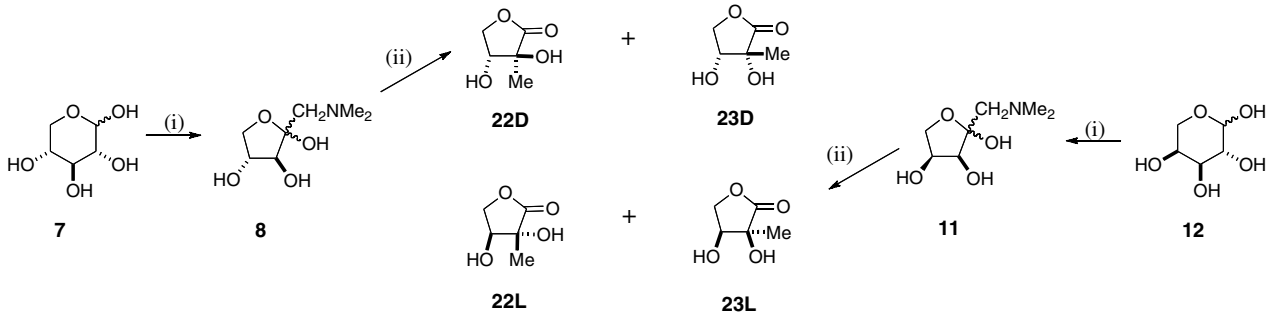
The branched D-*lyxono*-lactone **13D** was converted into L-*ribono*-lactone **19L**, epimeric at C-4. Acetonation of **13D** gave the 5 ring 2,3-*O*-isopropylidene derivative **16D** (mp 64–66 °C, $[\alpha]_D^{23}$ +77.2 (*c* 1.75, Me_2CO)) in 99% yield; in contrast to the reaction of lyxonolactone itself,[20] none of the 6 ring 3,5-ketal was formed. Esterification of the free alcohol in **16D** with triflic anhydride in dichloromethane in the presence of pyridine gave triflate **17D** (mp 79–81 °C, $[\alpha]_D^{21}$ +60.9 (*c* 0.60, Me_2CO)) in 100% yield. Reaction of the triflate **17D** with potassium hydroxide in aqueous dioxane caused ring opening and subsequent epoxide formation; work-up with acid gave inversion of configuration at C-4 and closure to the protected lactone **18L** (mp 52–54 °C, $[\alpha]_D^{22}$ +34.2 (*c* 1.05, Me_2CO)) in 82% yield. Removal of the ketal from **18L** with aqueous trifluoroacetic acid gave the unprotected L-*ribono*-lactone **19L** (mp 160–162 °C, $[\alpha]_D^{22}$ −87.7 (*c* 0.60, water) {lit.[11] for the D-enantiomer **19D** mp 160–161 °C, $[\alpha]_D^{22}$ +93 (water)}) in 90% yield. The overall yield for the conversion of D-*lyxono*-lactone **13D** (the lactone of **4D**) to L-*ribono*-lactone **19L** (the lactone of **3L**) was 73%.

A similarly efficient epimerisation of D-*ribono*-lactone **19D** (equivalent to the open chain aldonic acid **3D**) into L-*lyxono*-lactone **13L** (equivalent to the aldonic acid **4L**) was achieved in 68% overall yield. Lactone **19D**, prepared in 20% yield from D-glucose **1**,[12] was protected as its 2,3-acetonide **18D** (mp 52–54 °C; $[\alpha]_D^{21}$ −35.6 (*c* 1.42, Me_2CO)) in 100% yield. Reaction of **18D** with mesyl chloride in pyridine afforded mesylate **21D** (oil, $[\alpha]_D^{24}$ −24.7 (*c* 0.97, $CHCl_3$)) in 100% yield. Treatment of **21D** with potassium hydroxide in aqueous dioxane followed by an acid work-up gave inversion at C-4 to give the protected lactone **16L** (mp 64–66 °C, $[\alpha]_D^{22}$ −74.1 (*c* 0.64, Me_2CO), 91% yield) which was deprotected by aqueous trifluoroacetic acid to afford the branched L-*lyxono*-lactone **13L** (oil, $[\alpha]_D^{18}$ −77.3 (*c* 0.4, water)) in 75% yield.

2-*C*-Methyl-D-*erythrono*-1,4-lactone **23D**, the lactone of **9D**, was discovered as a natural product in *Astragalus lusitanicus*[21] and *Cicer ariatinum*;[22] D-*threono*-epimer **22D** was isolated from *Anthylis tetraphylla*[23] and also found in tobacco smoke.[24] 2-*C*-Methyl-D-erythritol was discovered in the petals of *Phlox subulata* and is involved in flower development.[25] The mevalonate-independent biosynthesis of isoprenoids via 2-*C*-methyl-D-erythritol phosphate is a target against malaria and pathogenic bacteria[26] and has increased the effort in the synthesis of 2-*C*-methyl tetroses.[27]

Previous syntheses of lactones **22D** and **23D**—all of which involve several steps and need protection of oxygen functional groups—include asymmetric aldol condensations[28,29] and use of protected chiral pool starting materials of lactic acid[30] and mannitol.[31] Although very small amounts of D-lactones **22D** and **23D** are obtained by the reaction of calcium hydroxide with D-xylose,[32] the sequential Amadori rearrangement-calcium hydroxide treatment of the pentoses D-xylose **7** and L-arabinose **12** produced enantiomeric lactones **22D** and **23D** or **22L** and **23L**, respectively, without any protection necessary.

Thus, D-xylose **7** was subjected to the Amadori rearrangement by treatment with ethanolic dimethylamine in acetic acid to give the xylulosamine **8** (Scheme 4); crude residue **8** obtained by removal of the solvent was treated with calcium oxide. After workup with acid ion exchange resin, a mixture of the branched D-*threono*-**22D** (10%)[33] and D-*erythrono*-**23D** (4%)[34] lactones was



Scheme 4. Reagents: (i) Me_2NH, AcOH, EtOH; (ii) CaO, H_2O; then H^+.

obtained. Neither of the lactones was crystalline; very careful chromatography was necessary to obtain pure samples of each separate diastereomer. The enantiomeric branched L-*threono*-**22L** and L-*erythrono*-**23L** lactones were obtained using an identical procedure from L-arabinose **12** via the intermediate ribulosamine **11**; the ratio of L-*threono*-**22L**/L-*erythrono*-**23L** was also approximately 3:1. Again the diastereomers could be differentiated by ^{13}C spectroscopy; the chemical shift of the 2-*C*-methyl group of the *cis*-diol *erythrono*-isomer **23** (δ 19.9) is at significantly lower field than the *trans*-diol *threono*-isomer **22** (δ 16.6).

It is noteworthy that the products from the aldohexoses (glucose and galactose) have a 2,3-*cis*-diol in the lactone ring as the major products, whereas the aldopentoses (xylose and arabinose) form predominantly the lactone with a *trans*-diol.

In summary, the isomerisation of aldoses to saccharinic (2-*C*-methyl-aldonic) acids by an Amadori rearrangement followed by treatment with aqueous calcium oxide is shown to be general and provides access by green aqueous procedures to a group of hitherto unavailable branched carbohydrate chirons.

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16. *2-C-Methyl-D-lyxono-1,4-lactone* **13D**: mp 106–107 °C; $[\alpha]_D^{23}$ +70.4 (*c* 0.9, Me_2CO) ν_{max} (film): 3421, 1773 cm^{-1}; δ_H (CD_3OD, 400 MHz): 1.43 (3H, s, CH_3), 3.88 (2H, m, H-5 and H-5′), 4.07 (1H, d, $J_{3,4}$ 3.8 Hz, H-3), 4.54 (1H, ddd, $J_{4,5}$ 5.0 Hz, $J_{3,4}$ 3.8 Hz, $J_{4,5'}$ 5.9 Hz, H-4); δ_C (CD_3OD, 100.6 MHz): 20.7 (*C*H_3), 60.4 (C-5), 74.2 (C-3), 74.5 (C-2), 81.5 (C-4), 179.4 (C-1).
17. *2-C-Methyl-D-xylono-1,4-lactone* **14**: mp 161–162 °C; $[\alpha]_D^{23}$ +87.3 (*c* 0.5 in water); ν_{max} (film): 3254, 1776 cm^{-1}; δ_H (CD_3OD, 400 MHz): 1.39 (3H, s, CH_3), 3.82–3.90 (2H, m, H-5 and H-5′), 4.03 (1H, d, $J_{3,4}$ 3.7 Hz, H-3), 4.71 (1H, ddd, $J_{3,4}$ 3.7 Hz, $J_{4,5}$ 5.0 Hz, $J_{4,5'}$ 6.4 Hz, H-4); δ_C (CD_3OD, 100.6 MHz): 16.8 (*C*H_3), 60.4 (C-5), 75.3 (C-3), 76.5 (C-2), 82.9 (C-4), 178.2 (C-1).
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33. *2-C-Methyl-D-threono-1,4-lactone* **22D**: oil, $[\alpha]_D^{23}$ −18.8 (*c* 1.1, H_2O); ν_{max} (film): 3406, 1775 cm^{-1}; δ_H (CD_3OD, 400 MHz): 1.36 (3H, s, CH_3), 3.98 (1H, dd, $J_{3,4}$ 4.4 Hz, $J_{4,4'}$ 9.4 Hz, H-4), 4.19 (1H, m, H-3), 4.50 (1H, dd, $J_{3,4'}$ 5.4 Hz, $J_{4,4'}$ 9.4 Hz, H-4′); δ_C (CD_3OD, 100.6 MHz): 16.6 (*C*H_3), 71.8 (C-4), 74.5 (C-3), 74.9 (C-2), 179.0 (C-1).
34. *2-C-Methyl-D-erythrono-1,4-lactone* **23D**: oil, $[\alpha]_D^{22}$ −35.0 (*c* 0.3, H_2O); ν_{max} (film): 3398, 1774 cm^{-1}; δ_H (CD_3OD, 400 MHz): 1.41 (3H, s, CH_3), 4.06 (1H, dd, $J_{3,4}$ 1.8 Hz, $J_{3,4'}$ 4.1 Hz, H-3), 4.16 (1H, dd, $J_{3,4}$ 1.85 Hz, $J_{4,4'}$ 10.2 Hz, H-4), 4.45 (1H, dd, $J_{3,4'}$ 4.1 Hz, $J_{4,4'}$ 10.2 Hz, H-4′); δ_C (CD_3OD, 100.6 MHz): 19.9 (*C*H_3), 72.3 (C-4), 73.4 (C-2), 73.5 (C-3), 179.4 (C-1).