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Amadori ketoses with calcium hydroxide and the Kiliani reaction on 1-deoxy ketoses: two approaches to the synthesis of saccharinic acids

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Abstract—Saccharinic acids (2-*C*-methyl aldonic acids) may be formed by treatment of Amadori ketoses with calcium hydroxide or by the Kiliani reaction of 1-deoxy ketoses with cyanide. Thus (i) *N*,*N*-dibenzyl or *N*,*N*-dimethyl-1-amino-1-deoxy-D-fructose with aqueous calcium hydroxide afforded 2-*C*-methyl-D-ribono-1,4-lactone under green conditions and (ii) reaction of methyl magnesium bromide with 2,3-*O*-isopropylidene-D-erythronolactone gave 1-deoxy-3,4-*O*-isopropylidene-D-ribulose, which on subsequent treatment with aqueous sodium cyanide and hydrolysis, formed 2-*C*-methyl-D-arabinono-1,4-lactone. Such branched sugar lactones are likely to be of value as chirons containing branched carbon chains.
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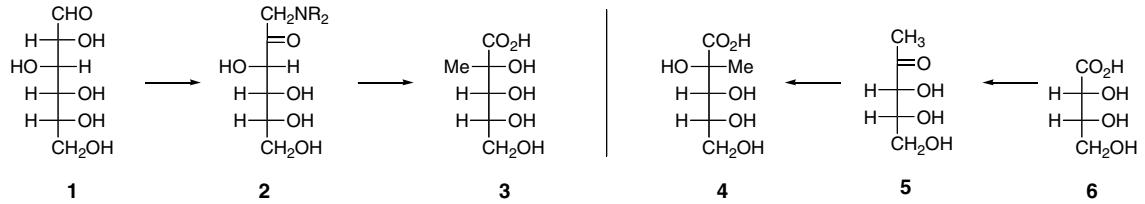
1. Introduction

Although almost all readily available carbohydrate scaffolds contain linear carbon chains,[1] the Kiliani ascension[2] on unprotected ketoses[3] provides access to branched carbohydrate lactones under environmentally friendly conditions; the convenient preparations of branched carbon chain diacetonides from D-fructose, L-sorbose,[4] D-tagatose and D-psicose[5] suggest that a new family of carbohydrate chirons containing branched carbon chains will be useful for the efficient synthesis of complex homochiral targets.[6] The Kiliani reaction on ketohexoses limits the branch at C-2 to a hydroxymethyl group. This letter exemplifies two hitherto unexplored approaches to carbohydrate lactones bearing a methyl branch at C-2 to form saccharinic acids (2-*C*-methyl aldonic acids). The strategies are most clearly seen using Fischer projection formulae (Scheme 1).

The first approach involved the reaction of D-glucose **1** with a secondary amine to give the corresponding fructosamine **2** by the Amadori reaction; treatment of the Amadori ketohexose **2** with calcium hydroxide in water gave the branched ribonic acid **3**, isolated as its lactone. The overall reaction is simply an isomerisation between



Scheme 1. Approaches to 2-*C*-methyl aldonic acids.

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the six carbon sugar glucose **1** and the saccharinic acid **3**. No protection is needed during the transformation. Alternatively two sequential one carbon nucleophilic additions to a four carbon sugar provided access to a six carbon saccharinic acid. Thus addition of methyl magnesium bromide to a lactone derived from **6** afforded a protected 1-deoxy-D-ribulose **5**; subsequent addition of cyanide resulted in a Kiliani chain extension to give 2-*C*-methyl-D-arabinonic acid **4**.

2. Reaction of Amadori ketoses with calcium hydroxide

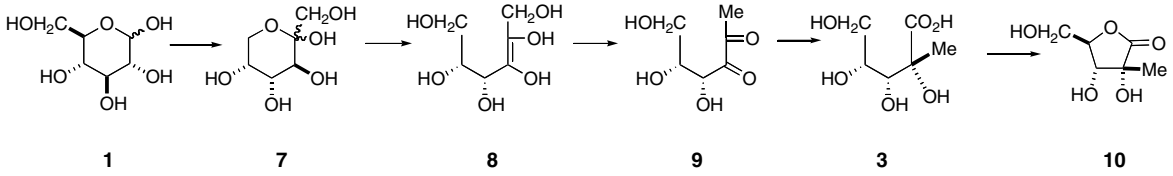
The reaction of glucose with aqueous base to give saccharinic acids[7] is one of the oldest reactions known; it is also one of the most complicated.[8] More than 50 compounds have been identified from the reaction of glucose with aqueous calcium hydroxide with only a trace of the saccharinic acid **3** being formed.[9] A plausible pathway for the isomerisation of **1** to **3** is illustrated in Scheme 2;[10] an initial Lobry de Bruyn rearrangement[11] of glucose **1** to fructose **7** is followed by formation of ene-diol **8**. Base catalysed dehydration of **8** to an enol, followed by tautomerism, affords the diketone **9**. A subsequent benzilic acid rearrangement of **9** leads to the branched ribonic acid **3**, invariably isolated as its crystalline lactone **10**.

Although the yield of the branched ribonolactone **10** from reaction of glucose with calcium hydroxide was only 0.4%,[9] treatment of fructose with calcium hydroxide under carefully optimised conditions of temperature and time allowed the isolation of **10** in a yield of around 11%.[12] The time of the reaction, together with the need to remove large volumes of water, make the production of **10** a troublesome procedure. The key step for the generation of diketone **9** is the base-catalysed elimination of water from **8**. However, the introduction of leaving groups at C-1 other than the hydroxyl function is lengthy and cumbersome.

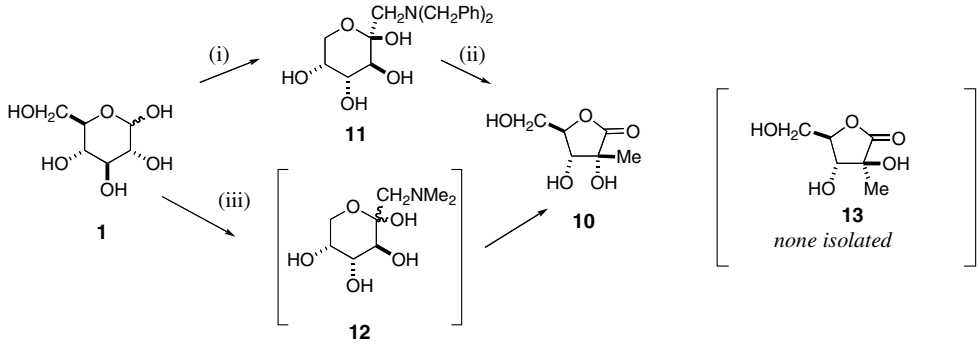
The Amadori rearrangement is the principal mechanism for non-enzymatic conjugation of proteins to carbohydrates; this directly introduces an amino function as an alternative leaving group to the hydroxide ion at C-1 of the ketose.[13] The reaction of dibenzylamine with glucose **1** in ethanol in the presence of acetic acid gave the Amadori ketose **11** as a crystalline material[14] in 86% yield.[15] Subsequent treatment of the dibenzyl ketoseamine **11** with calcium hydroxide in water afforded, after acidic work-up, the branched ribono-1,4-lactone **10** in 16% yield. This represented a significant increase in yield in comparison to that obtained in the base treatment of fructose and, more importantly, reduced the time and effort in preparing **10** (Scheme 3).

The insolubility of the dibenzylamine **11** in water presented some practical problems in the reaction with calcium hydroxide. Thus attempts were made to synthesise a water-soluble Amadori compound using dimethylamine as the amine component for the rearrangement. The isolation of the water-soluble dimethylamine Amadori ketose **12** proved challenging; however, both ^{13}C NMR spectroscopy (in the formation of a new quaternary C and of an additional methylene group) and mass spectrometry provided evidence for the formation of **12** together with the absence of glucose. Subsequent calcium hydroxide treatment of crude **12** afforded 2-*C*-methyl-D-ribono-1,4-lactone **10** in a 19% overall yield from D-glucose.

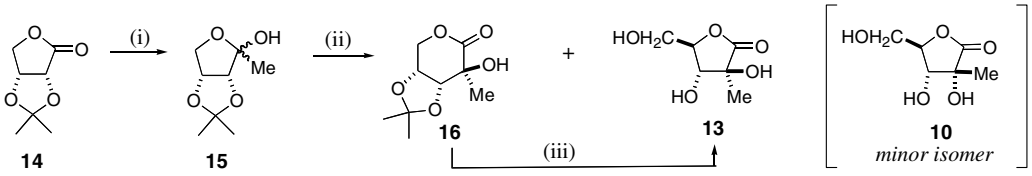
A practical method for the synthesis of lactone **10** is as follows: D-Glucose **1** (3.17 g, 17.6 mmol) suspended in ethanol (5 mL) and glacial acetic acid (1 mL) was treated with a solution of dimethylamine (33% solution in methylated spirits, 3.2 mL, 18.0 mmol) and the reaction



Scheme 2. Base catalysed isomerisations of glucose and fructose.



Scheme 3. Reagents and conditions: (i) $(PhCH_2)_2NH$, AcOH, EtOH; (ii) $Ca(OH)_2$, H_2O; then H^+; (iii) Me_2NH in EtOH/MeOH, AcOH; then $Ca(OH)_2$, H_2O; then H^+.



Scheme 4. Reagents and conditions: (i) MeMgBr, THF, −78 °C; (ii) NaCN, H_2O; then Amberlite IR 120 H^+; (iii) CF_3COOH, H_2O.

mixture stirred at 80 °C for 1.5 h. The resulting dark orange solution was concentrated in vacuo to afford a dark oil (6.55 g), which was dissolved in water (150 mL). The aqueous solution was stirred at 70 °C with calcium oxide (5.61 g, 100 mmol) for 24 h. Oxalic acid dihydrate (6.74 g, 53.5 mmol) was added to the suspension; the reaction mixture was filtered through Celite®. The filtrate was passed through Amberlite® IR 120 ion exchange resin. The residue obtained after removal of water was re-dissolved in water (50 mL) and heated at 40 °C for 15 min. The water was removed and the crude product purified by chromatography and subsequent crystallisation to afford the lactone **10** (534 mg, 19%).[16]

None of the epimeric arabinonolactone **13** was isolated during any of the reactions reported; a possible rationale for this exclusive diastereoselectivity is under investigation. Nonetheless this modification of the treatment of a ketose with base provides a much more convenient synthesis of the lactone **10** than has been hitherto available.

3. Kiliani reaction of 1-deoxy ketoses

An alternative approach to the synthesis of saccharinic acids is illustrated in Scheme 4 in which a six carbon saccharinic acid is prepared by two sequential additions of nucleophilic carbon to a four carbon sugar. Reaction of the protected D-erythronolactone **14**[17] with methyl magnesium bromide in THF afforded the lactol **15**, mp 82–85 °C (lit.[18] 87–89 °C), as a mixture of anomers in 99% yield. Treatment of the protected 1-deoxy ribulose **15** with aqueous sodium cyanide, followed by work-up with acid, gave the protected δ-lactone **16**[19] in 18% yield and a mixture of the deprotected γ-lactones **13**[20–22] and **10** in an approximate ratio of 5 to 1 and a combined yield of 45%. Recrystallisation of the mixture of γ-lactones afforded the pure arabinonolactone **13**.

The isopropylidene protecting group in **16** was removed in quantitative yield by treatment with aqueous trifluoroacetic acid to give 2-*C*-methyl-D-arabinono-1,4-lactone **13**. The structures of the protected[23] and unprotected[24] arabinonolactones were firmly established by X-ray crystallographic analysis.

4. Summary

The two complementary procedures provide practical access to the epimeric 2-*C*-methyl aldonolactones **10** and **13**, and the Kiliani reaction on 1-deoxy ketoses could potentially allow groups other than methyl to be introduced at C-2 of the lactone. In particular, the overall isomerisation of glucose **1** to 2-*C*-methyl-D-ribonic acid **3** by a green, environmentally friendly procedure indicates that a new class of chiron may be readily available. The scope and generality of the reaction of Amadori ketoses with calcium hydroxide is presently under investigation.[25]

Acknowledgements

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(film): 3356 (s, br, O–H), 1773 (s, C=O) cm^{-1}; δ_H (CD_3OD, 400 MHz): 1.40 (3H, s, CH_3), 3.71 (1H, dd, H-5, $J_{5,4}$ 4.5, $J_{5,5'}$ 12.8), 3.90 (1H, d, H-3, $J_{3,4}$ 7.8), 3.94 (1H, dd, H-5′, $J_{5',4}$ 2.4, $J_{5',5}$ 12.8), 4.29 (1H, ddd, H-4, $J_{4,5}$ 4.5, $J_{4,5'}$ 2.4, $J_{4,3}$ 7.8); δ_C (CD_3OD, 100.6 MHz): 20.02 (CH_3), 60.03 (C-5), 72.55 (C-2), 72.64 (C-3), 83.43 (C-4), 176.97 (C-1); δ_H (DMSO-d_6, 400 MHz): 1.24 (3H, s, CH_3), 3.47–3.54 (1H, ddd, H-5, $J_{5,4}$ 5.2, $J_{5,OH}$ 5.9, $J_{5,5'}$ 12.7), 3.72 (1H, dd, H-3, $J_{3,OH}$ 7.4, $J_{3,4}$ 7.8), 3.72–3.77 (1H, ddd, H-5′, $J_{5',4}$ 2.3, $J_{5',OH}$ 5.2, $J_{5',5}$ 12.7), 4.13–4.17 (1H, m, H-4), 5.00–5.03 (1H, dd, OH-5, $J_{OH,5'}$ 5.4, $J_{OH,5}$ 5.9), 5.43 (1H, d, OH-3, $J_{OH,3}$ 7.3), 5.71 (1H, s, OH-2); δ_C (DMSO-d_6, 100.6 MHz): 20.9 (CH_3), 59.5 (C-5), 72.0 (C-2), 72.1 (C-3), 82.8 (C-4), 176.2 (C-1); *m*/*z* (ESI−): 161 ($M-H^+$, 100%).

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22. Selected data for **13**: mp 65–68 °C (from ethyl acetate/cyclohexane) [lit.[20] 89–91 °C; lit.[21] 63–65 °C (moist ethyl acetate)]; $[\alpha]_D^{21}$ +78.7 (*c* 1.02, H_2O) [lit.[20] $[\alpha]_D$ +69 (*c* 1.6, H_2O); lit.[21] $[\alpha]_D^{20}$ +82.5 (*c* 0.9, H_2O)]; ν_{max} (thin film): 3383 (s, br, O–H), 1771 (s, C=O); δ_H (CD_3OD, 500 MHz): 1.34 (3H, s, CH_3), 3.70 (1H, dd, H-5, $J_{5,4}$ 4.7, $J_{5,5'}$ 12.8), 3.90 (1H, dd, H-5′, $J_{5',4}$ 2.5, $J_{5',5}$ 12.8), 4.04–4.08 (1H, m, H-4), 4.16 (1H, d, H-3, $J_{3,4}$ 7.8); δ_C (CD_3OD, 100.6 MHz): 18.0 (CH_3), 60.9 (C-5), 75.13 (C-3), 76.9 (C-2), 82.1 (C-4), 179.3 (C-1); δ_H (DMSO-d_6, 400 MHz): 1.18 (3H, s, CH_3), 3.46–3.52 (1H, ddd, H-5, $J_{5,4}$ 4.8, $J_{5,OH}$ 5.8, $J_{5,5'}$ 12.7), 3.69–3.74 (1H, ddd, H-5′, $J_{5'4}$ 2.3, $J_{5',OH}$ 5.3, $J_{5',5}$ 12.7), 3.91–3.95 (1H, ddd, H-4, $J_{4,5'}$ 2.3, $J_{4,5}$ 4.7, $J_{4,3}$ 8.0), 3.99–4.02 (1H, dd, H-3, $J_{3,OH}$ 5.3, $J_{3,4}$ 8.0), 5.07 (1H, a-t, OH-5, $J_{OH,5}$ 5.6), 5.71 (1H, d, OH-3, $J_{OH,3}$ 5.2), 5.79 (1H, s, OH-2); δ_C (DMSO-d_6, 100.6 MHz): 18.0 (CH_3), 59.6 (C-5), 73.5 (C-3), 75.1 (C-2), 81.8 (C-4), 178.0 (C-1); *m*/*z* (ESI−): 161 ($M-H^+$, 100%).
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