A Facile and General Synthesis of Rare L-Sugar Lactones

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Abstract: A facile and general synthesis of rare L-sugar lactones from D-sugars by selectively inverting C-5 was developed. Selective 1-deacylation of sugar perpivaloates by hydroxylamine is described. More practically, β-D-glucose pentaacetate could be transformed to L-*idono*-1,4-lactones by this simple procedure.

Key words: L-sugar, aldonolactone, 1-deacylation

Except for a few configurations such as arabinose and xylose, L-sugars are rare in nature. Some such as L-iduronic acid, L-rhamnose and L-fucose[1] are important components in biological systems although they are found in very low abundance. Some L-nucleosides have shown great potent as antiviral agents.[2] Practical and general methods for the synthesis of L-sugars are therefore of interest. Ikegami et al. developed a useful method of synthesizing L-hexoses by inverting C-5 of D-glycono-1,5-lactones[3a] and a related synthesis of L-ribose.[3b] The starting materials involved in this synthesis, however, are relatively expensive. The separation of side products in Mitsunobu reactions is always another issue. Lee et al. employed mesylate substitution to invert certain position of sugar lactones to prepare rare sugar such as L-ribose.[4] Here we introduce a general and facile synthesis of L-sugar lactones from D-sugars.

2,3,4,6-Tetra-*O*-trimethylacetyl-D-glucose (**1**) was treated with hydroxylamine (Scheme 1) hydrochloric acid salt in pyridine to give an aldoxime **2**. Treatment of **2** with methanesulfonyl chloride afforded 5-*O*-methanesulfonyl-2,3,4,6-tetra-*O*-pivaloyl D-gluconitrile (**3**) with the 5-position derivatized to a good leaving group. Hydrolysis of this orthogonally protected and derivatized D-gluconitrile with hydrochloric acid in ethanol yielded L-*idono*-1,4-lactone **4**.

The acidic displacement of the mesyl (-OMs) group could result from the attack of neighboring pivaloyl carbonyl groups or the possible carboxylic acid/amide from nitrile hydrolysis. To probe the reaction mechanism, compound **3** was refluxed in methanol–water for 24 hours and the solution turned acidic. NMR analyses of this hydrolysate (Figure 1) indicated that the OMs group had been

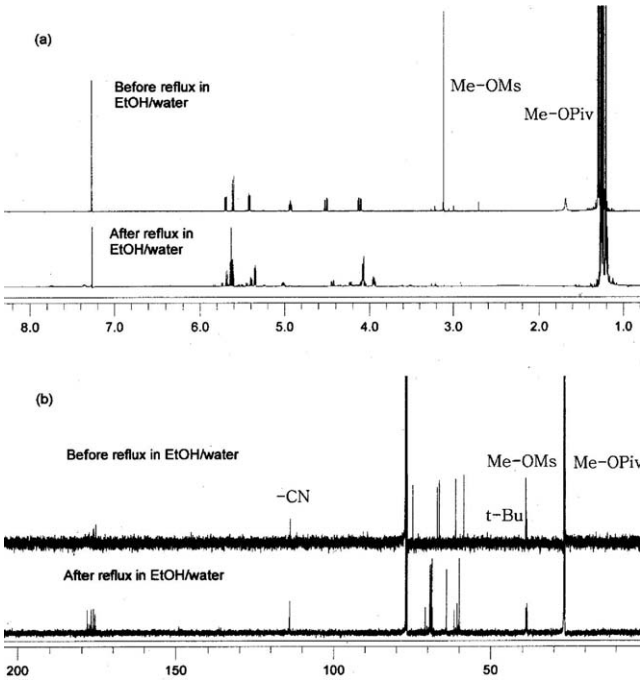
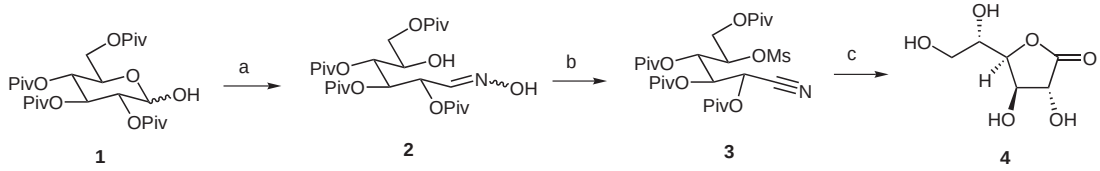


Figure 1 ^{1}H and ^{13}C NMR spectra of the starting material (compound **3**) and the hydrolysis intermediate after refluxing in MeOH–H_2O for 24 h. (a) ^{1}H NMR spectra comparison; (b) carbon NMR spectra comparison. The H-5 signal in the proton spectrum of the unhydrolyzed compound is at δ = ca. 5 ppm and the H-6 signals are between δ = 4.0 and 4.6 ppm. Note the disappearance of the H-6 signals in (a) and the appearance of new signals at δ = ca. 4.1 ppm in (b). Note also the shift of the C-6 signal in the ^{13}C spectrum from δ = ca. 61 ppm to δ = ca. 63 ppm.



Scheme 1 Synthesis of L-*idono*-1,4-lactone from 2,3,4,6-tetra-*O*-trimethylacetyl-D-glucose (**1**). *Reagents and conditions*: a) hydroxylamine hydrogen chloride salt, pyridine, 90%; b) MsCl, pyridine, 88%; c) HCl, EtOH–H_2O, 85%.

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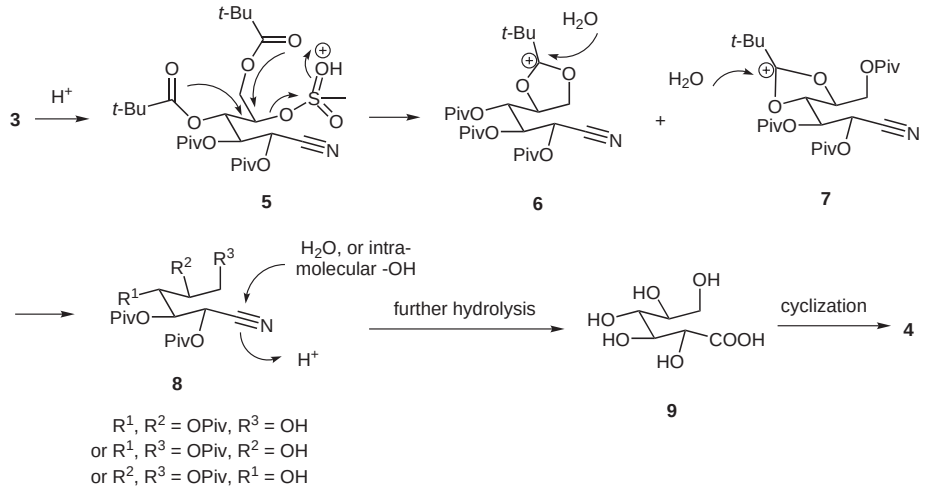


Scheme 2 The proposed mechanism of formation of L-*idono*-1,4-lactone **4** by a simple acidic treatment of 5-*O*-methanesulfonyl-2,3,4,6-tetra-*O*-pivaloyl D-gluconitrile **3**.

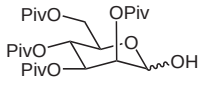
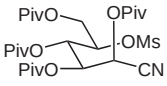
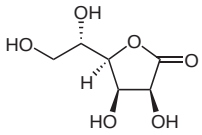
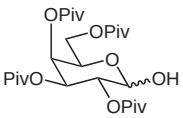
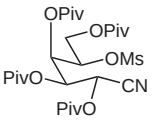
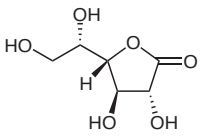
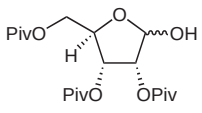
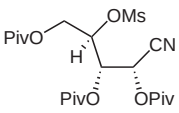
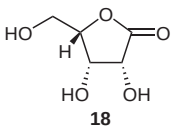
removed but the nitrile group was still unchanged. This indicated that the OMs group was displaced by a neighboring pivaloyl groups.

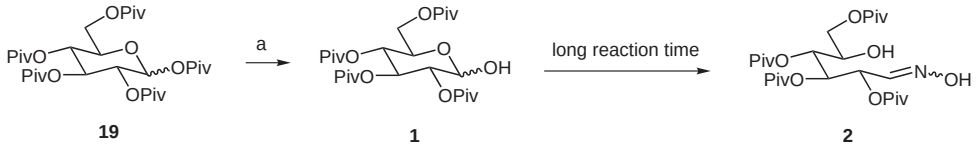
The proposed mechanism of the inversion of the 5-position under acidic condition is shown in Scheme 2. It is possible that the 5-position OMs is attacked intramolecularly by the neighboring 4- or 6-pivaloyl group to give a mixture of *tert*-butyl-1,3-dioxolanylium cations **6** and **7**. Intermediates **6** and **7** are quenched by water to give a mixture of three possible D-gluconitrile tetrapivaloates. Neighboring group participation in the displacement of OMs group has been reported by Acton et al.,[5] although under basic condition. Both the pivaloyl groups and the nitrile group are then completely hydrolyzed to give L-idonic acid, which spontaneously cyclize to L-*idono*-1,4-lactone. It is clear from Figure 1 that the participation of the 6-pivaloyl group is dominant because of the shift of both the proton and C-13 signals for this position.

The procedure described above is essentially applicable to all aldoses and should constitute a practical route towards L-aldonolactones since no expensive reagents and tedious separations are involved. Some other abundant aldoses were also subjected to this procedure and several other rare L-sugar lactones were synthesized (Table 1).

We also explored the possibility of directly using sugar perpivaloates as the starting materials. Hydrazine is widely used in the selective 1-O-deacylation of protected sugars. Based on the structure similarity of hydrazine and hydroxylamine, we proposed that hydroxylamine might also act as a deacylating reagent. Therefore it is possible that sugar oximes could be obtained directly from sugar perpivaloate **19** by combining deacylation and oxime for-

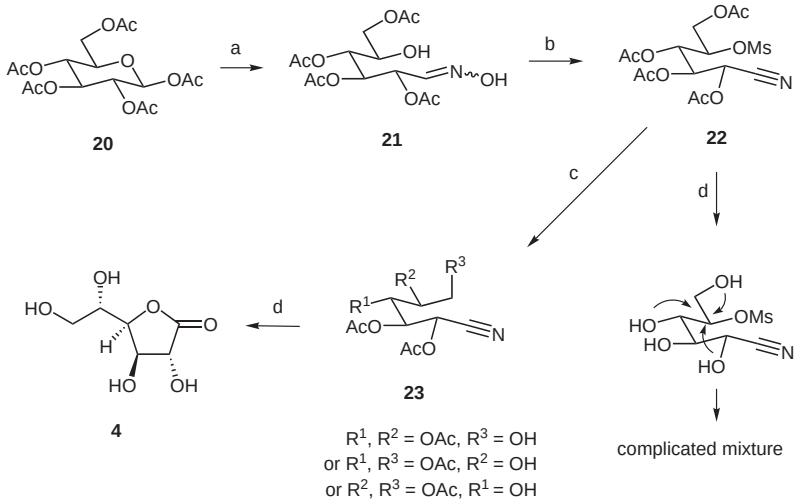
Table 1 Synthesis of L-Sugar Lactones from Sugar Pivaloates

Entry	Substrate	Intermediate	Product	Yield (%)
1	 **10**	 **13**	 **16**	76
2	 **11**	 **14**	 **17**	72
3	 **12**	 **15**	 **18**	69



19 **1** **2**

Scheme 3 Treatment of glucose pentapivaloate with hydroxylamine. *Reagents and conditions*: a) freshly prepared hydroxylamine, pyridine, r.t., 24 h, 85%.



20 **21** **22** **4** **23**

Scheme 4 Synthesis of L-*idono*-1,4-lactone from β-D-glucose pentaacetate. *Reagents and conditions*: a) hydroxylamine hydrogen chloride, pyridine; 88%; b) MsCl, pyridine; 90%; c) MeCN–H_2O, reflux; d) HCl, EtOH, H_2O; 75%.

mation in the same step without separation of **1**. Compound **19** was successfully transformed into compound **1** by treatment with hydroxylamine (Scheme 3) within 1 day. However, formation of glucose oxime **2** from hydroxylamine is much slower than that from hydroxylamine hydrochloride salt. This is not a surprise since it is well known that oxime formation is favored by lower pH value.[6] A similar result was observed with D-mannose and D-galactose pentapivaloates.

To further improve the practicability of this procedure, acetyl group was employed as the protecting group. Interestingly, when β-D-glucose pentaacetate was treated with hydroxylamine hydrogen chloride in pyridine, the sugar oxime **21** was yielded directly, greatly improving the efficiency. Treatment with methanesulfonyl chloride afforded oxime dehydration and 5-O-mesylation in the same step to give **22**. When **22** was subjected to the same hydrolysis employed above for pivaloyl-protected sugar nitriles, however, a complicated mixture was obtained (Scheme 4). It is possible that under this condition, acetyl groups were deprotected in the same rate as that for mesyl groups, if not faster. This might trigger attack of the OMs group by neighboring hydroxy groups, yielding complicated anhydrosugars and products generated from their hydrolysis. This problem was successfully solved by refluxing **22** in acetonitrile and water first, which only displace the OMs group. The resulted mixture was then refluxed in acidic aqueous ethanol to yield L-*idono*-1,4-lactone **4** in a similar yield as that when pivaloyl group was used as the protecting group.

In summary, we developed a practical and general synthesis of L-aldono-1,4-lactones from aldose perpivaloates and peracetates by selectively inverting the C-5 positions. Several rare-L-sugar lactones were prepared conveniently. It is highly possible that this methodology could be applied in the synthesis of other rare sugars. It should be noted that the acid-catalyzed displacement of mesyl groups under similar conditions to form furans has been noted before.[7] The intramolecular base-catalyzed displacement of mesyl groups to form ethers is the norm.

General Experimental Procedure for L-Aldonolactone Synthesis

Anomeric-free sugar tetrapivaloates (for D-gluco, D-manno and D-galacto configurations) or tripivaloate (for D-ribo configuration) was dissolved in pyridine [5 mL/g starting material (SM)] with hydroxylamine hydrogen chloride salt (1.2 g/g SM). The solution was stirred at r.t. for 24 h. Then, CH_2Cl_2 (15 mL/g SM) was added and the mixture was filtered. The filtrate was washed with H_2O, dried and evaporated to afford the sugar oxime. The crude sugar oxime was dissolved in pyridine (5 mL/g) and cooled to 0 °C. Then, MsCl (2.5 equiv) was added slowly. The mixture was warmed to r.t. slowly and stirred for 8 h. It was then poured to cold $NaHCO_3$ solution and extracted by CH_2Cl_2. The organic layer was dried and evaporated to dryness. The residue was purified by flash column chromatography to afford the mesylated sugar nitrile. The mesylated sugar nitrile was refluxed in 1–3 N HCl in 1:1 mixture of EtOH and H_2O for 4–16 h. The solution was then evaporated to dryness to yield the L-sugar lactone. They can be purified by flash column chromatography. Their spectroscopic properties match those from literature.[8]

5-*O*-Methanesulfonyl-2,3,4,6-tetra-*O*-pivaloyl-D-gluconitrile (**3**): $[\alpha]_D$ +29.08 (*c* 0.8, $CHCl_3$). HRMS–FAB: *m/z* calcd for $C_{27}H_{45}NO_{11}S$: 591.2713; found: 592.2789 [MH^+]. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.24, 1.27, 1.29, 1.30 (4 × 9 H, 4 × s), 3.12 (3 H, s), 4.12 (1 H, dd, $J_{5,6'}$ = 4.6 Hz, $J_{6,6'}$ = 13.0 Hz, H-6′), 4.52 (1 H, dd, $J_{5,6}$ = 2.6 Hz, H-6), 4.93 (1 H, ddd, $J_{4,5}$ = 7.5 Hz, H-5), 5.42 (1 H, dd, $J_{2,3}$ = 7.0 Hz, $J_{3,4}$ = 2.4 Hz, H-3), 5.61 (1 H, d, H-2), 5.70 (1 H, dd, H-4). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.76, 27.00, 27.04, 38.89, 38.91, 39.08, 39.11, 39.21, 58.65, 61.23, 66.51, 67.08, 74.88, 113.94, 175.75, 176.38, 176.64, 177.82. IR: 2362, 2342, 1746, 1481, 1368, 1218 cm^{-1}.

5-*O*-Methanesulfonyl-2,3,4,6-tetra-*O*-pivaloyl-D-mannonitrile (**13**): $[\alpha]_D$ +0.95 (*c* 0.3, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.18, 1.21, 1.22, 1.28 (4 × 9 H, 4 × s), 3.11 (3 H, s), 4.09 (1 H, dd, $J_{5,6'}$ = 4.1 Hz, $J_{6,6'}$ = 13.1 Hz, H-6′), 4.43 (1 H, dd, $J_{5,6}$ = 2.4 Hz, H-6), 4.84 (1 H, ddd, $J_{4,5}$ = 8.1 Hz, H-5), 5.30 (1 H, d, $J_{2,3}$ = 7.3 Hz, H-2), 5.39 (1 H, dd, $J_{3,4}$ = 2.0 Hz, H-4), 5.42 (1 H, dd, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.71, 26.91, 26.93, 27.00, 38.81, 39.04, 39.10, 39.13, 59.3, 61.41, 66.51, 67.23, 74.48, 114.29, 175.66, 176.45, 176.52, 177.63. IR: 2363, 2344, 1744, 1215 cm^{-1}.

5-*O*-Methanesulfonyl-2,3,4,6-tetra-*O*-pivaloyl-D-galactonitrile (**14**): ^1H NMR (500 MHz, $CDCl_3$): δ = 1.17, 1.19, 1.23, 1.28 (4 × 9 H, 4 × s), 3.15 (3 H, s), 4.08 (1 H, dd, $J_{5,6'}$ = 7.0 Hz, $J_{6,6'}$ = 11.9 Hz, H-6′), 4.16 (1 H, dd, $J_{5,6}$ = 5.8 Hz, H-6), 4.92 (1 H, ddd, $J_{4,5}$ = 1.8 Hz, H-5), 5.34 (1 H, d, $J_{2,3}$ = 2.3 Hz, H-2), 5.36 (1 H, dd, $J_{3,4}$ = 9.6 Hz, H-4), 5.63 (1 H, dd, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.68, 26.85, 26.90, 26.95, 38.72, 38.80, 38,96, 39.04, 39.08, 58.99, 61.86, 66.10, 66.76, 74.72, 114.00, 175.84, 176.10, 176.32, 177.62. IR: 2363, 2344, 1744, 1482, 1366, 1216 cm^{-1}.

4-*O*-Methanesulfonyl-2,3,5-tri-*O*-pivaloyl-D-ribonitrile (**15**): $[\alpha]_D$ +24.2 (*c* 2.4, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.23, 1.24, 1.26 (3 × 9 H, 3 × s), 3.18 (3 H, s), 4.21 (1 H, dd, $J_{4,5'}$ = 4.6 Hz, $J_{5,5'}$ = 12.9 Hz, H-5′), 4.53 (1 H, dd, $J_{4,5}$ = 3.1 Hz, H-5), 5.12 (1 H, ddd, $J_{3,4}$ = 6.7 Hz, H-4), 5.43 (1 H, dd, $J_{2,3}$ = 3.3 Hz, H-3), 5.79 (1 H, d, H-2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.76, 26.84, 27.01, 38.88, 38.91, 39.02, 60.55, 61.44, 68.17, 74.64, 113.75, 175.82, 176.02, 177.64. IR: 2363, 2344, 1748, 1482, 1367, 1215 cm^{-1}.

Preparation of L-*idono*-1,4-lactone from β-D-glucose-penta-acetate

It is essentially the same as the procedure described above except final hydrolysis step. 5-*O*-Methanesulfonyl-2,3,4,6-tetra-*O*-acetyl-D-gluconitrile (**22**) was first refluxed in MeCN–H_2O (4:1) for 12 h and then evaporated, the residue was refluxed in 2 N HCl in 1:1 mixture of EtOH and H_2O for 1 h to give L-*idono*-1,4-lactone.

5-*O*-Methanesulfonyl-2,3,4,6-tetra-*O*-acetyl-D-gluconitrile (**22**): $[\alpha]_D$ +28.1 (*c* 1.8, $CHCl_3$); HRMS–FAB: *m/z* calcd for $C_{15}H_{21}NO_{11}S$: 423.0835; found: 424.0911 [MH^+]. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.13, 2.19, 2.23, 2.24, (4 × 3 H, 4 × s), 3.11 (3 H, s), 4.26 (1 H, dd, $J_{5,6'}$ = 5.6 Hz, $J_{6,6'}$ = 12.8 Hz, H-6′), 4.41 (1 H, dd, $J_{5,6}$ = 2.8 Hz, H-6), 5.04 (1 H, ddd, $J_{4,5}$ = 8.0 Hz, H-5), 5.34 (1 H, dd, $J_{2,3}$ = 6.4 Hz, $J_{3,4}$ = 2.3 Hz, H-3), 5.61 (1 H, dd, H-4), 5.66 (1 H, d, H-2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.04, 20.45, 20.58, 20.62, 38.78, 58.23, 61.53, 66.49, 67.00, 74.50, 113.93, 167.99, 169.30, 169.70, 170.17. IR: 2362, 2340, 1756, 1372, 1216 cm^{-1}.

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