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An efficient synthesis of L-allono-1,4-lactone from 2,3:5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone

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Dedicated to Professor Leo A. Paquette on the occasion of his 70th birthday

Abstract—We reported herein an efficient synthesis of L-allono-1,4-lactone from 2,3:5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone in five steps. The key feature of this method involved a one-pot, 'double inversion' procedure at the stereocenters of C-4 and C-5 of D-mannono-1,4-lactone to afford the target molecule.

The recent two papers have been demonstrated the efficient routes to synthesize L-ribose by Ikegami[1] and Kim[2] groups, respectively. It is noteworthy that the Kim's group employed 2 equiv of piperidine for opening the γ-lactone then inverted C-4 stereochemistry in a one-pot procedure after aqueous work up.[2] An early report had described the selective conversion of the mesylated D-ribonolactone into L-lyxono-1,4-lactone derivative under strong aqueous potassium hydroxide condition.[3] The above strategies were all used to invert only the C-4 stereochemistry on furanoses. In conjunction with our ongoing project associated with the efficient preparations of a series of L-sugars, we will report herein a synthesis of L-allono-1,4-lactone **8** from 2,3:5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone **2**. This method was also via a one-pot procedure but invert two stereocenters at C-4 and C-5 of **2** under NaH/80% DMF (aq) condition through twice the internal S_N2 reaction.

Our synthetic strategy is depicted in Scheme 1. 2,3:5,6-Di-*O*-isopropylidene-D-mannono-1,4-lactone **2** was obtained from the oxidation of **1** by *N*-iodosuccinimide/*n*-tetrabutylammonium iodide condition in 75% yield.[4] Compound **2** was subject to selective acid removal (80% aq AcOH) of protecting group to afford **3** in 86% yield after silica gel chromatography. The C-6 hydroxyl group of **3** was protected with TBSCl to provide the silyl ether **4**[5] in 68% yield. This moderate yield was due to inevitable receiving the bissilyl ether of **3**. The C-5 hydroxy group of **4** was mesylated to afford **5**[6] in 83% yield. The resulting compound was dissolved in wet DMF followed by the addition of 2.1 equiv of sodium hydride (60% in mineral oil).[7] This reaction was completed within 5 min to provide **6** along with **7**.[8] A higher yield (85%) of **7** could be achieved by treating the mixture with Amberlite-120 (H^+) resin 5 min after the addition of sodium hydride in order to complete the removal of silyl ether of **6**. Not only **7** is the higher R_f value (EtOAc/Hex = 2:1) relative to **3**, but also is its ^1H NMR of H_3–H_4 distinct from **3**, **4**, and **5**. No coupling between H_3 and H_4 of **7** has been detected. Furthermore, the relative stereochemistry of protons between C-3 and C-4 of **7** is proven to be opposite sense by no observance of NOE on the basis of NOESY spectrum. Finally, the protecting group of **7** was removed by Amberlite-120 (H^+) to afford the target molecule, L-allono-1,4-lactone **8**,[9] in 76% isolated yield. The optical rotation value and melting point of 8 are all consistent with the reported data.[10–12]

The plausible mechanism of transformation from **5** to **7** is illustrated in Scheme 2. The similar mechanism could also be found in the Varela et al. in their preparation of aldopentono-1,4-thiolactones.[13] When compound **5** was dissolved in 80% DMF (aq), the sodium hydroxide was generated in situ after sodium hydride was added. The epoxide formation was through S_N2 displacement of C-5-OMs by oxygen anion on C-4 under this basic

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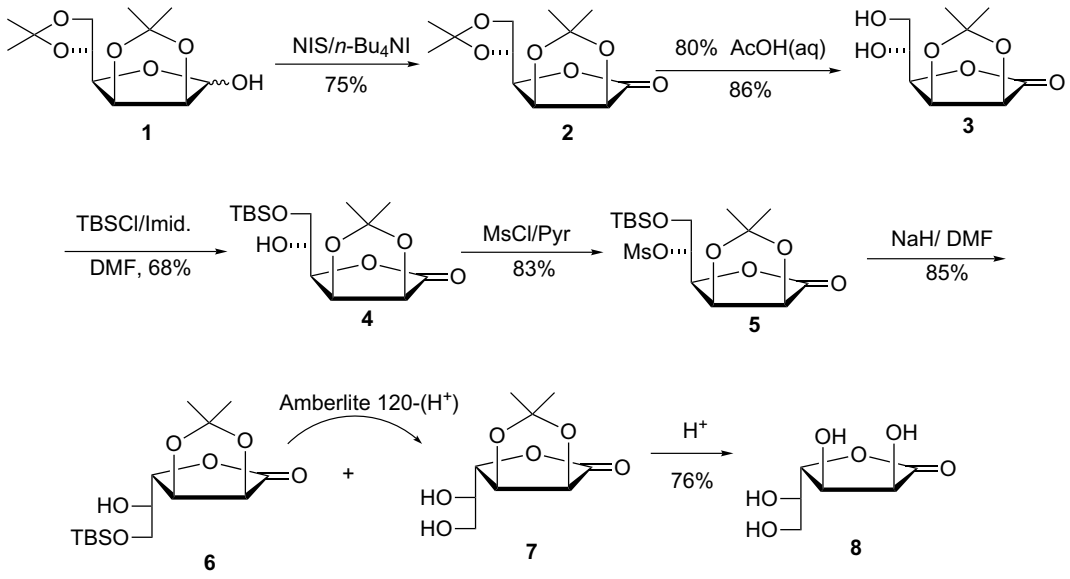
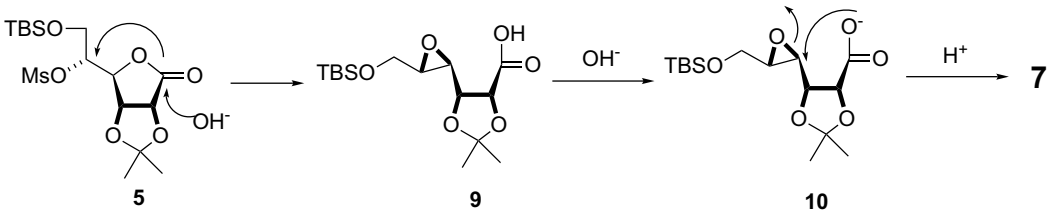


Scheme 1.



Scheme 2.

condition to provide **9**. Consequently the stereocenter of C-4 of **9** was inverted by the resulting carboxylate **10** through, again, a S_N2-type reaction to furnish **7**. At this stage, both the stereochemistry of C-4 and C-5 have been altered to afford the derivative of L-allono-1,4-lactone sequence.

In conclusion, L-allono-1,4-lactone **8**, was efficiently synthesized from 2,3:5,6-di-*O*-isopropylidene-D-manno-1,4-lactone **2** via a one-pot, 'double inversion' fashion reaction in five steps. The resulting product **8** clearly supports our proposed mechanism that the formation of epoxide is the first step in this transformation. The merit of this type of reaction is able to invert the stereochemistry of both C-4 and C-5 in D-furanoses simultaneously. Thus it will provide a more diversified and efficient strategy to prepare other L-furanoses. Further employment of this kind of method in pursuit of preparing a series of L-sugars is under investigation.

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5. Compound **4**: a clear syrup. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.93 (1H, dd, $J = 5.2$, 3.6 Hz), 4.82 (1H, d, $J = 5.2$ Hz), 4.37 (1H, dd, $J = 8.9$, 3.6 Hz), 3.97 (1H, ddd, $J = 8.9$, 4.0, 3.1 Hz), 3.86 (1H, dd, $J = 10.6$, 3.1 Hz), 3.77 (1H, dd, $J = 10.6$, 4.0 Hz), 1.49 (3H, s), 1.44 (3H, s), 0.91 (9H, s), 0.10 (3H, s), 0.09 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 114.2, 76.8, 76.2, 76.0, 68.6, 63.4, 26.8, 25.9, 25.8, 18.2, −5.5. LRMS (*m*/*z*) 333 (M+H, 5%), 275 (17%), 247 (23%), 189 (35%), 117 (100%), 89 (28%), 75 (100%).
6. Compound **5**: a pale white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83–4.91 (3H, m), 4.76 (1H, dd, $J = 8.1$, 2.9 Hz), 4.14 (1H, dd, $J = 12.3$, 2.1 Hz), 3.94 (1H, dd, $J = 12.3$, 3.7 Hz), 3.10 (3H, s), 1.49 (3H, s), 1.41 (3H, s), 0.90 (9H, s), 0.11 (3H, s), 0.09 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 114.6, 78.9, 75.9, 75.5, 74.7, 62.1, 38.7, 26.8, 25.9, 25.8, 18.3, −5.5. LRMS (*m*/*z*) 411 (M+H, 3%), 183 (36%), 153 (100%), 135 (31%). $[\alpha]_D^{26}$ +5.2° (*c* 0.2, MeOH). Mp 116–119 °C.
7. The addition of 2.1 equiv of NaH is necessary to allow the reaction to be complete within 5 min. The reaction was extremely slow while the reaction was conducted under 1.1, 1.25 or 1.5 equiv of NaH, respectively.

8. Typical procedure: All of the reactions were conducted on the basis of 0.1–0.2 M. To a solution of compound **5** in 80% DMF (aq) was added 2.1 equiv 60% NaH at ambient temperature. The reaction was complete within 5 min and followed by addition of Amberlite-120 (H^+) to quench the reaction as well as to cleave the silyl ether. The resulting mixture was filtered, evaporated and purified by column chromatography (230–400 mesh SiO_2, EtOAc/Hex = 2:1). Compound **7**: a pale white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 4.91 (1H, d, $J = 5.6$ Hz), 4.77 (1H, d, $J = 5.6$ Hz), 4.65 (1H, d, $J = 2.7$ Hz), 3.82 (1H, ddd, $J = 6.6$, 5.6, 2.5 Hz), 3.69 (1H, dd, $J = 11.3$, 5.6 Hz), 3.61 (1H, dd, $J = 11.3$, 6.6 Hz), 1.41 (3H, s), 1.36 (3H, s). ^{13}C NMR (75 MHz, CD_3OD) δ 176.8, 113.9, 85.2, 77.8, 76.9, 72.3, 63.4, 27.1, 25.6. LRMS (m/z) 219 (M+H, 8%), 203 (100%), 115 (40%), 59 (62%). $[\alpha]_D^{25}$ +54.3° (c 0.1, MeOH). Mp 124 °C.
9. Compound **8**: Crystallized from MeOH/CH_2Cl_2. a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 4.57 (d, $J = 5.4$ Hz, 1H), 4.41 (d, $J = 5.4$ Hz, 1H), 4.40 (d, $J = 3.9$ Hz, 1H), 3.79 (ddd, $J = 6.1$, 5.5, 3.9 Hz, 1H), 3.60 (d, $J = 6.1$ Hz, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ 178.6, 87.5, 72.2, 70.3, 69.3, 63.8. $[\alpha]_D^{25}$ +5.8° (c 0.03, H_2O). lit.[10] $[\alpha]_D^{20-25}$ +6.32° to +4.34° (H_2O). lit.[11] $[\alpha]_D^{20-25}$ +3.7° (H_2O). Mp 128–129 °C. lit.[10] mp 130 °C.
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