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Synthesis of 6-amino-6-deoxy-D-gulono-1,6-lactam and L-gulono-1,6-lactam derived from corresponding 5,6-*O*-sulfinyl hexono-1,4-lactones

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Abstract—Syntheses of 6-amino-6-deoxy-2,3-*O*-isopropylidene-D-gulono- and L-gulono-1,6-lactams **3** and **4** from corresponding glycono-1,4-lactones are described. Activation of the primary hydroxyl group requires 5,6-cyclic sulfite intermediate to obtain 6-azido-6-deoxy derivatives, which are cyclized after reduction.

1. Introduction

Intracyclic nitrogen-based sugar analogues named azasugars or iminosugars have been discovered as natural products. These compounds have been of considerable interest because many of them show specific inhibition against glycosidases and glycosyltransferases, being potential therapeutic agents for viral, proliferative and metabolic diseases.[1] Thus, these properties have stimulated intensive work directed on their synthesis, usually towards the five- and six-member iminosugars.

Nevertheless, only few reports have appeared on the synthesis of seven-member iminosugars (polyhydroxyazepanes), which have also been shown to possess potent inhibitory activities.[2] In some of those reported, they have often been obtained in admixture with their corresponding six-member ring derivatives, requiring separation.[3]

Polyhydroxyheptonolactams have been reported as tetrahydroxycaprolactam derived, potentially useful monomers for the preparation of novel oligomeric and polymeric materials.[4a]

Polyhydroxyheptonolactams are also precursors of polyhydroxyazepanes, and have been described from protected lactones as starting materials.[4] Our group has recently described an improved synthesis of 6-amino-6-deoxy-D-galactono- and D-mannono-1,6-lactams **1** and **2** via corresponding 6-bromo-6-deoxy-1,4-lactones (Fig. 1).[5]

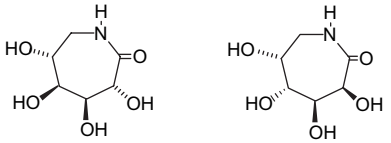

Figure 1.

In previous work, we have shown the usefulness of cyclic sulfites for stereoselective *N*-glycosylation, *O*-glycosylation and *C*-glycosylation reactions of hexoses and pentoses.[6] In the continuation of our interest in the synthesis of azasugars,[5,7] we now describe a synthetic route to 6-amino-6-deoxy-D- and L-gulono-1,6-lactams **3** and **4** (Fig. 2) from D- and L-gulono-1,4-lactones involving 5,6-cyclic sulfite as activating group of the primary hydroxyl.

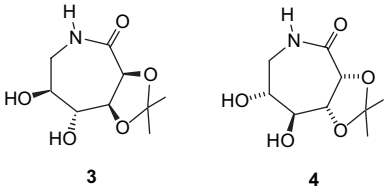

Figure 2.

Keywords: D-Gulono-1,4-lactone; L-Gulono-1,4-lactone; 5,6-*O*-Sulfinyl-1,4-lactone; 6-Amino-6-deoxy-D-gulonolactam; 6-Amino-6-deoxy-L-gulonolactam.
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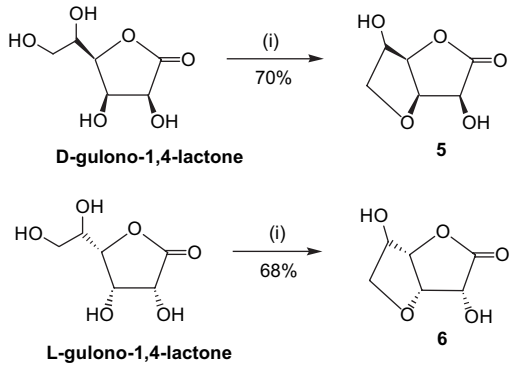
2. Results and discussion

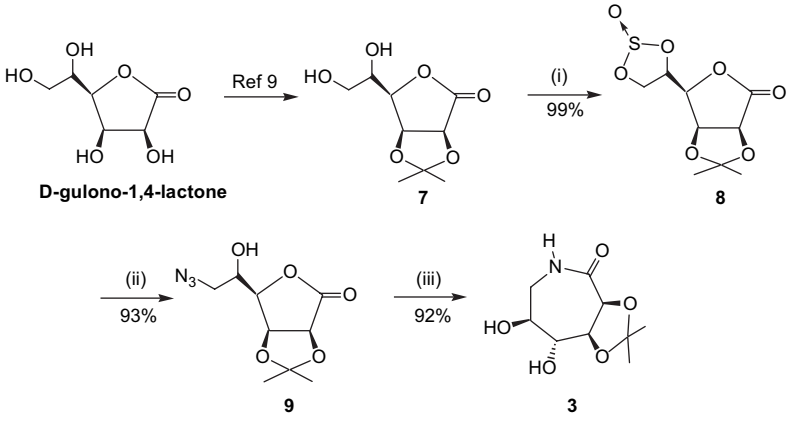
We first selected the D-gulono-1,4-lactone as starting material. D-Gulono-1,4-lactone was subjected to bromination, with the intention to prepare 6-bromo-6-deoxy-D-gulono-1,4-lactone, by using carbon tetrabromide–triphenylphosphine system in pyridine.[5] In spite of many attempts with other solvents such as DMF or higher temperatures, we never obtained the 6-bromo-6-deoxy derivative. With this reagent, D-gulono-1,4-lactone gave a 3,6-anhydro derivative **5** (70%). This reaction applied to L-gulono-1,4-lactone gave the same result, the 3,6-anhydro compound **6** was isolated in only 38% yield, in this case more starting lactone was retrieved (Scheme 1). The formation of 3,6-anhydro compound has already been described in the literature for structures with cis-relationship between the 3-OH group and the side chain at C-4. This anhydridation was observed by heating 6-bromo-6-deoxy-D-mannono and D-idono-1,4-lactone.[8]



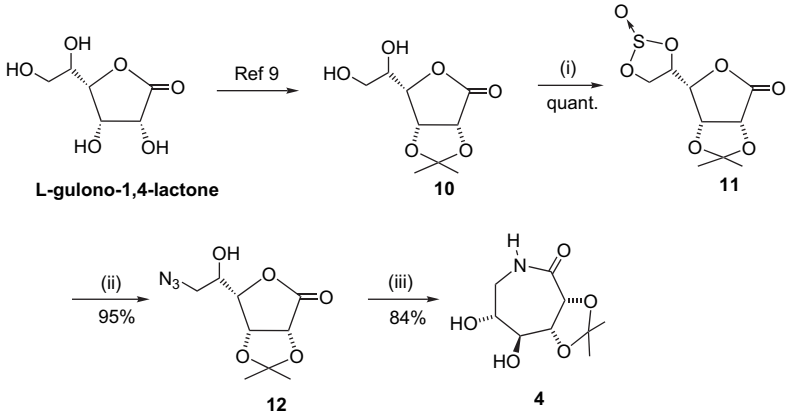
Scheme 1. (i) Conditions: PPh_3, CBr_4, pyridine.

Therefore, we turned to the cyclic sulfite as activating group. 5,6-Cyclic sulfite derivative **8** of D-gulono-1,4-lactone was obtained from 2,3-*O*-isopropylidene-D-gulono-1,4-lactone **7**,[9] which was synthesized in two steps from commercial D-gulono-1,4-lactone (Scheme 2). Sulfinylation of **7** by thionyl chloride in THF in the presence of pyridine afforded 5,6-cyclic sulfite D-gulono-1,4-lactone **8** in 99% in 5–10 min. Treatment of **8** with sodium azide in DMF gave the corresponding 6-deoxy-6-azido compound **9** in 93% yield. The one-pot reduction of the azido group and subsequent N-heterocyclization was realized by catalytic hydrogen transfer with ammonium formate as hydrogen donor and palladium on charcoal (10%) as catalyst in ethyl acetate at 70 °C.[10] The 6-amino-6-deoxy-D-gulono-1,6-lactam **3** was isolated in 92% yield.

This strategy was also applied to the L-gulono-1,4-lactone. 2,3-*O*-Isopropylidene-L-gulono-1,4-lactone **10** was prepared as described in the literature.[9] Sulfinylation of **10** was quantitative. Then azidation of **11** afforded the product **12** in 95% yield. The reduction–cyclization steps by catalytic hydrogen transfer produced 6-amino-6-deoxy-L-gulono-1,6-lactam **4** in 84% yield from **12** (Scheme 3).



Scheme 2. (i) Conditions: $SOCl_2$, pyridine, THF; (ii) NaN_3, DMF; (iii) Pd/C (10%), HCO_2NH_4, EtOAc.



Scheme 3. (i) Conditions: $SOCl_2$, pyridine, THF; (ii) NaN_3, DMF; (iii) Pd/C (10%), HCO_2NH_4, EtOAc.

In summary, we have described an access to 6-amino-6-deoxy-D- and L-gulono-1,6-lactam derived **3** and **4** from corresponding 2,3-*O*-isopropylidene-hexono-1,4-lactones. Attempts at 6-bromination of D- and L-gulono-1,4-lactones were unsuccessful. The azidation was efficient with a 5,6-cyclic sulfite as an alternative intermediate. Overall yields for the sulfinylation, azidation and reduction–cyclization are 84 and 80%, respectively, for the D- and L-isomers **3** and **4**.

3. Experimental

3.1. General

All chemicals were purchased from Aldrich or Acros (France). Carbon tetrabromide furnished by Aldrich was sublimed before use. Melting points were determined on a Büchi 535 apparatus and are uncorrected. Optical rotations were determined with a Jasco Dip 370 electronic micropolarimeter (10 cm cell) at 24 °C. ^{1}H NMR spectra were recorded on a Bruker 300 WB spectrometer at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz.

Thin layer chromatography (TLC) was performed on Merck glass plates silica gel 60 F254 stained with phosphomolybdic acid–H_2SO_4 reagent in ethanol. Column chromatography was carried out on silica gel (Merck, 230–400 mesh). All solvents were distilled before use.

3.1.1. 3,6-Anhydro-D-gulono-1,4-lactone (5). A solution of D-gulono-1,4-lactone (0.5 g, 2.8 mmol) in pyridine (10 mL) was treated with triphenylphosphine (1.47 g, 2 equiv) and carbon tetrabromide (0.93 g, 1 equiv). The mixture was stirred at room temperature for 2 h, then concentrated in vacuo and the residue was purified by column chromatography (EtOAc) to give **5** (0.314 g, 70%) as white solid. R_f 0.5 (EtOAc–MeOH 9:1), mp 146–147 °C, $[\alpha]_D$ −5.9 (*c* 0.4, MeOH), ^{1}H NMR (MeOD, 300 MHz) δ 4.52 (d, 1H, H-2, $J_{2,3}$=4.6 Hz), 4.43 (dd, 1H, H-3, $J_{3,4}$=2.9 Hz), 4.38 (dd, 1H, H-4, $J_{4,5}$=7.7 Hz), 4.15 (m, 1H, H-5), 3.78 (dd, 1H, H-6a, $J_{5,6a}$=4.2 Hz, $J_{6a,6b}$=11.5 Hz), 3.70 (dd, 1H, H-6b, $J_{5,6b}$=4.9 Hz). ^{13}C NMR (MeOD, 75 MHz) δ 176.4 (C-1), 85.0 (C-4), 78.7 (C-3), 75.2 (C-2), 74.2 (C-5), 69.9 (C-6).

3.1.2. 3,6-Anhydro-L-gulono-1,4-lactone (6). L-Gulono-1,4-lactone (0.5 g, 2.8 mmol) in pyridine treated with triphenylphosphine (2 equiv) and carbon tetrabromide as described above for **5**, gave **6** as white solid (0.172 g, 38%). R_f 0.5 (EtOAc–MeOH 9:1), mp 150–151 °C, $[\alpha]_D$ +5 (*c* 0.5, MeOH), ^{1}H NMR (MeOD, 300 MHz) δ 4.46 (dd, 1H, H-4, $J_{3,4}$=6.5 Hz), 4.39 (d, 1H, H-2, $J_{2,3}$=3.1 Hz), 4.32 (dd, 1H, H-3), 4.17 (m, 1H, H-5, $J_{4,5}$=5.0 Hz), 3.82 (d, 2H, H-6, $J_{5,6}$=7.2 Hz). ^{13}C NMR (MeOD, 75 MHz) δ 173.4 (C-1), 80.4 (C-3), 72.8 (C-6), 72.3 (C-4), 71.4 (C-5), 70.0 (C-2).

3.1.3. 2,3-*O*-Isopropylidene-5,6-*O*-sulfinyl-D-gulonolactone (8). To a solution of 2,3-*O*-isopropylidene-D-gulono-1,4-lactone **7**[9] (1 g, 4.6 mmol) in THF (20 mL) precooled to 0 °C, were added anhydrous pyridine (2.4 equiv) then dropwise thionyl chloride (1.2 equiv). The mixture was stirred at 0 °C under argon atmosphere for 10 min and pyridinium salts were filtrated and washed with cooled THF (3 mL). The filtrate was concentrated to give a yellow syrup, which was purified by flash chromatography on silica gel (EtOAc). The 5,6-*O*-sulfinyl derivative **8** was isolated as a mixture of *endo*/*exo* diastereoisomers (1.2 g, 99%) as a colourless syrup. R_f 0.46 (hexane–EtOAc 1:1), *endo*/*exo* mixture ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.16 (dd, 2H, H-1, H-3), 4.87 (m, 7H), 4.53–4.31 (2 dd, 4H, H-6 *endo*/*exo*), 1.40 (s, 3H, CH_3), 1.38 (s, 6H, $2CH_3$), 1.31 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.4 (C-1), 115.4 (C-*iso*), 82.1, 81.0 (C-4), 79.7, 79.0 (C-2), 76.0 (C-3), 75.8 (C-5), 68.5, 67.7 (C-6), 26.8, 25.8 ($2CH_3$).

3.1.4. 6-Azido-6-deoxy-2,3-*O*-isopropylidene-D-gulonolactone (9). To a solution of compound **8** (1 g, 3.78 mmol) in DMF (10 mL) was added sodium azide (369 mg, 1.5 equiv). The mixture was heated at 80 °C for 24 h under argon atmosphere. After evaporation of DMF under reduced pressure, the residue was purified by flash chromatography on silica gel (acetone) to furnish **9** (920 mg, 93%) as a syrup. R_f 0.7 (hexane–EtOAc 1:1), $[\alpha]_D$ −31 (*c* 1, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.97 (d, 1H, H-2, $J_{2,3}$=5.32 Hz), 4.87 (dd, 1H, H-3, $J_{3,4}$=3.45 Hz), 4.61 (dd, 1H, H-4, $J_{4,5}$=7.2 Hz), 4.08 (m, 1H, H-5, $J_{5,6a}$=5.5 Hz), 3.52 (dd, 1H, H-6a, $J_{6a,6b}$=13.06 Hz), 3.42 (dd, 1H, H-6b, $J_{5,6b}$=3.1 Hz), 1.42 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.2 (C-1), 114.1 (C-*iso*), 81.1 (C-4), 77.0 (C-2), 76.3 (C-3), 70.2 (C-5), 53.0 (C-6), 26.1, 25.0 ($2CH_3$).

3.1.5. 2,3-*O*-Isopropylidene-D-gulono-1,6-lactam (3). Compound **9** (200 mg, 0.822 mmol) in ethyl acetate (15 mL) was treated with palladium on charcoal (10%) in the presence of ammonium formate (10 equiv). The mixture was heated under argon atmosphere for 18 h, then filtered through a layer of Celite and concentrated in vacuo to give **3** as white crystals (165 mg, 92%). R_f 0.36 (hexane–EtOAc 4:6), $[\alpha]_D$ −15.5 (*c* 0.88, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.9 (d, 1H, H-2, $J_{2,3}$=5.34 Hz), 4.8 (dd, 1H, H-3, $J_{3,4}$=3.52 Hz), 4.55 (dd, 1H, H-4, $J_{4,5}$=7.28 Hz), 4.15 (m, 1H, H-5, $J_{5,6a}$=4.27 Hz), 3.53 (dd, 1H, H-6a, $J_{6a,6b}$= 12.9 Hz), 3.42 (dd, 1H, H-6b, $J_{5,6b}$=1.24 Hz), 1.32 (s, 3H, CH_3), 1.22 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.2 (C-1), 114.1 (C-*iso*), 81.1 (C-4), 77.9 (C-2), 77.0 (C-3), 70.2 (C-5), 53.5 (C-6), 26.1, 25.0 ($2CH_3$). Anal. Calcd for $C_9H_{15}O_5N$: C 49.76; H 6.96; N 6.45. Found (%): C 49.71; H 6.91; N 6.43.

3.1.6. 2,3-*O*-Isopropylidene-5,6-*O*-sulfinyl-L-gulonolactone (11). Reaction of 2,3-*O*-isopropylidene-L-gulono-1,4-lactone **10**[9] (1 g, 4.61 mmol) in THF (20 mL), with anhydrous pyridine (2.4 equiv) and thionyl chloride (1.2 equiv), as in case of **7**, gave quantitatively **11** as a colourless syrup in *endo*/*exo* mixture. R_f 0.46 (hexane–EtOAc 1:1), *endo*/*exo* mixture ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.23 (dd, 1H, H-3), 4.76 (m, 6H), 4.46–4.35 (2 dd, 4H, H-6 *endo*/*exo*), 1.42 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.31 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.4 (C-1), 115.4 (C-*iso*), 82.3, 82.1 (C-4), 79.6, 79.1 (C-2), 76.4 (C-3), 75.8 (C-5), 68.5, 67.7 (C-6), 26.9, 26.0 ($2CH_3$).

3.1.7. 6-Azido-6-deoxy-2,3-*O*-isopropylidene-L-gulonolactone (12). Reaction of **11** (720 mg, 2.724 mmol) with sodium azide (1.5 equiv) in DMF, as in case of **8**, gave **12**

as a colourless syrup (630 mg, 95%). R_f 0.73 (hexane–EtOAc 1:1), $[\alpha]_D$ +23 (*c* 1, $CHCl_3$), ^1H NMR ($CDCl_3$, 300 MHz) δ 4.9 (d, 1H, H-2, $J_{2,3}$=5.34 Hz), 4.9 (dd, 1H, H-3, $J_{3,4}$=3.52 Hz), 4.55 (dd, 1H, H-4, $J_{4,5}$=7.28 Hz), 4.15 (m, 1H, H-5, $J_{5,6a}$=4.27 Hz), 3.53 (dd, 1H, H-6a, $J_{6a,6b}$=12.9 Hz), 3.42 (dd, 1H, H-6b, $J_{5,6b}$=2.98 Hz), 1.42 (s, 3H, CH_3), 1.34 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.0 (C-1), 114.9 (C-*iso*), 80.2 (C-4), 76.8 (C-2), 76.3 (C-3), 70.3 (C-5), 52.8 (C-6), 27.1, 26.1 ($2CH_3$).

3.1.8. 2,3-*O*-Isopropylidene-L-gulono-1,6-lactam (4). Reaction of **12** (200 mg, 0.822 mmol) in ethyl acetate with palladium on charcoal (10%) in the presence of ammonium formate (10 equiv), as in the case of **9**, gave **4** as white crystals (150 mg, 84%). R_f 0.36 (hexane–EtOAc 4:6), $[\alpha]_D$ +17 (*c* 2.5, $CHCl_3$), ^1H NMR (MeOD, 300 MHz) δ 4.3 (d, 1H, H-2, $J_{2,3}$=7.8 Hz), 3.9 (dd, 1H, H-3, $J_{3,4}$=4.1 Hz), 3.45 (dd, 1H, H-4, $J_{4,5}$=7.28 Hz), 4.15 (m, 1H, H-5, $J_{5,6a}$= 4.27 Hz), 3.53 (dd, 1H, H-6a, $J_{6a,6b}$=12.9 Hz), 3.42 (dd, 1H, H-6b, $J_{5,6b}$=1.24 Hz), 1.32 (s, 3H, CH_3), 1.22 (s, 3H, CH_3). ^{13}C NMR (MeOD, 75 MHz) δ 175.2 (C-1), 114.1 (C-*iso*), 81.1 (C-4), 77.9 (C-2), 77.0 (C-3), 70.2 (C-5), 53.5 (C-6), 26.1, 25.0 ($2CH_3$). Anal. Calcd for $C_9H_{15}O_5N$: C 49.76; H 6.96; N 6.45. Found (%): C 49.73; H 6.89; N 6.40.

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