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A proline-catalyzed aldol approach to the synthesis of 1-*N*-iminosugars of the D-glucuronic acid type

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Abstract

A new synthetic route to 1-*N*-iminosugars of glucuronic acid type (e.g., **1**) has been developed employing proline-catalyzed aldol reaction as a key step.
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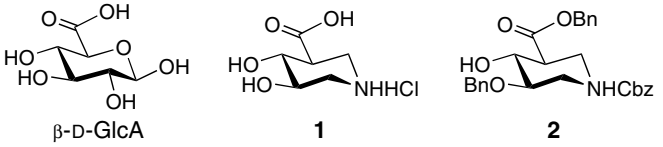
Keywords: 1-*N*-Iminosugar; Aldol reaction; Proline-catalyzed; Glucuronidase inhibitor; Synthesis

1-*N*-Iminosugars, saccharide analogs with a nitrogen in place of the anomeric carbon, have been disclosed as potent inhibitors of β-glycosidases, due to their good mimicry of the transition state involving in equatorial glycoside cleavage.[1–4] Thus, the D-glucuronic acid (GlcA)-type 1-*N*-iminosugar (**1**) is found to be a potent and specific inhibitor of β-D-glucuronidase from bovine liver ($K_i = 79$ nM).[2] Incorporation of this GlcA mimic into the reducing end of a heparan sulfate (HS) oligosaccharide could provide a potent and specific inhibitor of heparanase,[5] the unique mammalian endo-β-D-glucuronidase, which has become a promising target of anticancer therapy.[6] To this end, we first required a properly protected derivative of the 1-*N*-iminosugar **1** (e.g., **2**, with only the 4-OH free). Concise approaches to the synthesis of compound **1** have been reported by Ichikawa and co-workers[2c] and Ganem and co-workers;[3] and a number of synthetic approaches toward the analogous 1-*N*-iminosugars are available in the literatures;[4] however, modification of these methods to the synthesis of compound **2** requires lengthy transformations. Herein, we report a new and concise approach to the synthesis of 1-*N*-iminosugars, as exemplified by the synthesis of compounds **1** and **2**, using proline-catalyzed aldol reaction as a key step.



Organocatalyzed enantioselective aldol reaction has recently been an intensive research topic, which provides a biomimetic approach to the synthesis of saccharides.[7] Applying this new technology to the preparation of 1-*N*-iminosugars (e.g., **1** and **2**) would require the aldol coupling of a β-amino-aldehyde and a glyceric aldehyde (e.g., **3** and **4**, for the preparation of the GlcA-type **1** and **2**). Thus, direct cross aldol condensation of aldehydes **3**[8] and **4**[9] was examined in the presence of proline (Scheme 1). The use of 0.1 equiv of proline in DMF at room temperature gave the best results (Table 1, entry 2): the mechanistically expected *anti*-product **5** was predominately formed in a 6:1 ratio to a stereoisomer (**6**) in a total yield of 48%. Oxidation of the unstable aldols **5** and **6** with sodium chlorite followed by benzyl ester formation provided esters **7** and **8**, which were separated by careful chromatography on silica gel. However, the exact stereochemistry in these products was not determined at this stage.

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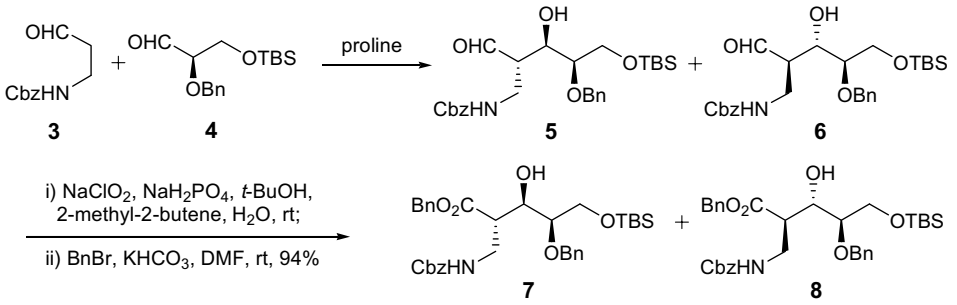


Scheme 1.

Table 1
Proline-catalyzed aldol reaction of aldehydes **3** and **4**[a]

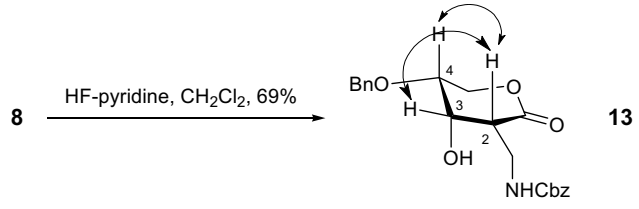
Entry	Solvent	Catalyst loading (equiv)	Temperature	Yield (%)	**5/6**
1	DMF	0.05	rt	<20	—
2	DMF	0.1	rt	48	6/1
3	DMF	0.3	rt	31	1/1
4	DMF	0.1	0 °C	<20	3/1
5	DMSO	0.1	rt	45	5/1

[a] For a typical operation: A solution of 3-benzyloxycarbonylaminopropanal **3** (145 mg, 0.700 mmol) in DMF (1.5 mL) was added slowly over a course of 24 h to a stirring suspension of 2-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-D-glyceraldehyde **4** (296 mg, 1.00 mmol) and L-proline (9 mg, 0.08 mmol) in DMF (1.5 mL) at room temperature. The mixture was stirred for an additional 2 h at room temperature, and then was concentrated in vacuo. Flash chromatography (4:1 hexanes–ethyl acetate) afforded a 6:1 mixture of diastereoisomers **5** and **6** as a colorless oil (167 mg, 48%).

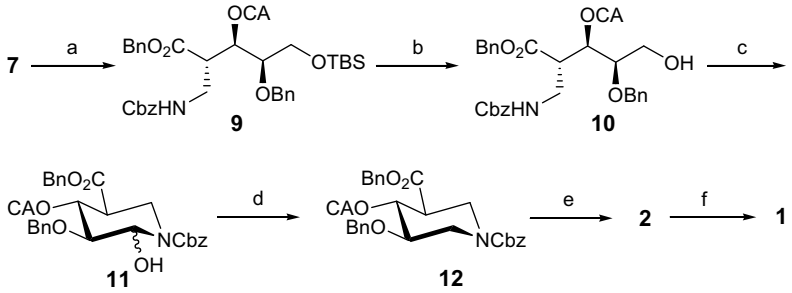
Conversion of compound **7** into the desired 1-*N*-iminosugars **1** and **2** was achieved concisely as shown in Scheme 2. Thus, the free hydroxyl group in **7** was protected with an easily removable chloroacetyl (CA) group, providing **9** in high yield. Attempts to remove the primary TBS ether in **9** with tetrabutyl ammonium fluoride (TBAF)/acetic acid or hydrogen fluoride–pyridine complex led to the formation of the 1,5-lactone and migration of the CA group. Hydrofluoric acid was found effective to cleave the TBS group cleanly. The resulting alcohol **10** was then subjected to Swern oxidation; automatic intramolecular aminal formation afforded the piperidine derivative **11**. This epimeric mixture was then subjected to reduction with triethylsilane/boron trifluoride diethyl etherate to provide the fully protected 1-*N*-iminosugar derivative **12** in good yield (71% for three steps). Finally, the CA group in **12** was selectively deprotected with thiourea/2,6-lutidine, providing the desired **2** in an excellent 95% yield. It should be noted that the removal of an acetyl group at this stage was found problematic under either acidic or basic conditions, leading to the corresponding 4,5-elimination product. Further removal of the benzyl and Cbz protection with Pd/C catalyzed hydrogenation afforded the known 1-*N*-iminosugar **1**. The analytical data of **1** are identical to those reported,[2c] thus confirming the proposed stereochemistry in the major aldol product **5**.

The stereochemistry of the minor aldol product **6** was implied by NOE analysis of its lactone derivative **13** (Scheme 3).[10]

In summary, the GlcA-type 1-*N*-iminosugar derivatives (e.g., **1** and **2**) were concisely synthesized from the aldol adduct (e.g., **5**) in high yields, demonstrating a new route



Scheme 3.



Scheme 2. Reagents and conditions: (a) Chloroacetic anhydride, pyridine, DMAP, CH_2Cl_2, 91%; (b) HF (40%), CH_3CN; (c) $(COCl)_2$, DMSO, −65 °C, CH_2Cl_2; (d) triethylsilane, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 71% (3 steps); (e) thiourea, 2,6-lutidine, MeOH, 95%; (f) H_2, Pd/C (10%), MeOH; then HCl (1 N), 90%.

to the synthesis of 1-*N*-iminosugars of biological significance. There is certainly room for improvement in the proline-catalyzed aldol coupling with aldehydes **3** and **4** and the likes as partners, that has not been examined before. Incorporation of the present GlcA-type 1-*N*-iminosugar into the reducing end of heparan sulfate (HS) oligosaccharides and the test of their heparanase inhibitions are our current projects and will be reported in due course.

Acknowledgements

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10. Selected data for the key compounds. Compound **1**: ^{1}H NMR (D_2O, 300 MHz): δ 2.79 (ddd, $J = 4.2$, 7.4, 7.8 Hz, 1H), 2.96 (dd, $J = 7.5$, 12.9 Hz, 1H), 3.26 (dd, $J = 7.8$, 13.2 Hz, 1H), 3.36 (dd, $J = 3.9$, 12.9 Hz, 1H), 3.40 (dd, $J = 5.1$, 13.2 Hz, 1H), 3.78 (dt, $J = 3.3$, 7.5 Hz, 1H), 3.96 (t, $J =$ 6.9 Hz, 1H). Compound **2**: $[\alpha]_D^{23}$ −18.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.55–2.67 (m, 1H), 2.64 (t, $J = 11.7$ Hz, 1H), 2.76–3.03 (br m, 2H), 3.21–3.39 (br m, 1H), 3.91 (t, $J = 9.3$ Hz, 1H), 4.21–4.55 (br m, 2H), 4.56–4.77 (m, 2H), 5.11 (s, 2H), 5.16 (s, 2H), 7.20–7.43 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 44.07, 45.39 (br), 47.99 (br), 66.71, 67.47, 72.27 (br), 73.57 (br), 77.69, 127.70, 127.84, 127.85, 127.94, 128.08, 128.19, 128.41, 128.44, 128.45, 135.27, 136.14, 137.69, 154.72, 170.85; ESIMS *m/z* 476.1 $[M+H]^+$, 498.0 $[M+Na]^+$; Anal. Calcd for $C_{28}H_{29}NO_6$: C, 70.72; H, 6.15; N, 2.95. Found: C, 70.79; H, 6.12; N, 2.77. Compound **7**: $[\alpha]_D^{23}$ −19.2 (*c* 0.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.045 (s, 3H), 0.048 (s, 3H), 0.88 (s, 9H), 2.92–2.98 (m, 1H), 2.97 (d, $J = 7.8$ Hz, 1H), 3.48 (t, $J = 6.1$ Hz, 2H), 3.52–3.58 (m, 1H), 3.73–3.86 (m, 2H), 3.90–3.97 (m, 1H), 4.50 (d, $J = 11.4$ Hz, 1H), 4.73 (d, $J = 11.4$ Hz, 1H), 4.93 (d, $J = 12.0$ Hz, 1H), 5.02 (d, $J = 12.0$ Hz, 1H), 5.06 (s, 2H), 5.07 (br s, 1H), 7.20–7.39 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.57, −5.55, 18.13, 25.80, 40.66, 48.38, 62.10, 66.50, 66.65, 70.48, 72.74, 79.77, 127.73, 127.95, 128.03, 128.06, 128.14, 128.18, 128.30, 128.33, 128.42, 128.44, 128.54, 128.57, 135.51, 136.34, 137.98, 156.21, 172.90; ESIMS *m/z* 608.3 $[M+H]^+$, 630.3 $[M+Na]^+$; Anal. Calcd for $C_{34}H_{45}NO_7Si$: C, 67.19; H, 7.46; N, 2.30. Found: C, 67.46; H, 7.31; N, 2.42. Compound **8**: $[\alpha]_D^{23}$ −20.2 (*c* 0.96, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.05 (s, 6H), 0.88 (s, 9H), 2.92–2.98 (m, 1H), 3.32 (d, $J = 6.6$ Hz, 1H), 3.44–3.49 (m, 1H), 3.56–3.72 (m, 2H), 3.76–3.87 (m, 2H), 4.03–4.09 (m, 1H), 4.42 (d, $J = 11.4$ Hz, 1H), 4.62 (d, $J = 11.4$ Hz, 1H), 5.01 (s, 2H), 5.07 (s, 2H), 5.28 (br t, $J = 6.3$ Hz, 1H), 7.22–7.33 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.60, −5.57, 18.09, 25.78, 39.85, 48.25, 62.65, 66.61, 66.77, 70.33, 72.85, 78.89, 127.72, 128.01, 128.05, 128.29, 128.33, 128.44, 128.52, 135.45, 136.34, 137.94, 156.68, 172.42; ESIMS *m/z* 608.4 $[M+H]^+$, 630.3 $[M+Na]^+$; Anal. Calcd for $C_{34}H_{45}NO_7Si$: C, 67.19; H, 7.46; N, 2.30. Found: C, 67.27; H, 7.43; N, 2.29. Compound **13**: $[\alpha]_D^{23}$ −43.0 (*c* 1.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.56 (dt, $J = 11.1$, 3.0 Hz, 1H); 3.56 (ddd, $J = 15.0$, 4.8, 2.1 Hz, 1H), 3.78–3.89 (m, 2H), 3.92 (dd, $J = 8.1$, 3.6 Hz, 1H), 4.33 (d, $J = 3.6$ Hz, 2H), 4.63 (d, $J = 11.7$ Hz, 1H), 4.73 (d, $J = 11.7$ Hz, 1H), 4.72 (d, $J = 4.5$ Hz, 1H), 5.11 (AB, 2H), 5.48 (m, 1H), 7.26–7.38 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 36.55, 47.66, 67.40, 68.40, 69.96, 71.46, 77.71, 127.79, 127.86, 128.00, 128.29, 128.44, 128.53, 135.83, 137.38, 158.43, 172.13; ESIMS *m/z* 408.2 $[M+Na]^+$; ESIHRMS *m/z* calcd for $C_{21}H_{23}NO_6$ $[M+Na]^+$: 408.1418; found, 408.1431.