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Facile Synthesis of a New Type of Iminosugar: a Nitrogen Atom is in the Anomeric Position

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Abstract—A new type of iminosugar in which a nitrogen atom is in the place of the anomeric carbon was synthesized in a stereoselective manner from mannose via 4-*C*-hydroxymethyl-2,3-*O*-isopropylidene-1,5'-anhydro-L-ribofuranose derivative.

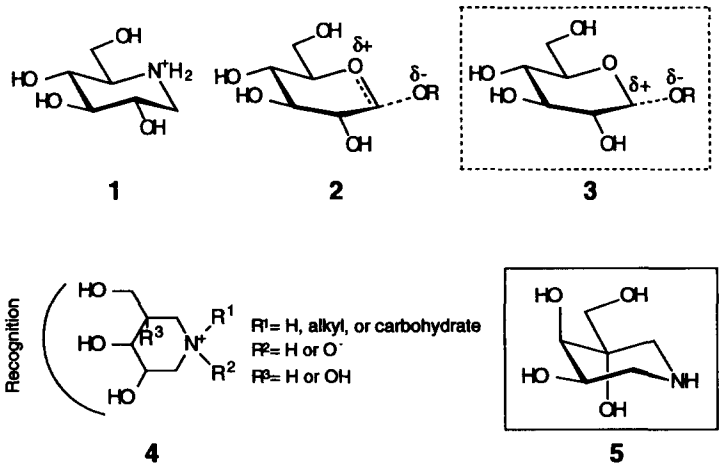
Introduction

Compounds that inhibit oligosaccharide biosynthesis represent valuable tools for analyzing the role of complex carbohydrates in biological processes.[1] In particular, glycosidase inhibitors, iminosugars such as deoxynojirimycin (**1**), have been used to dissect specific cellular events[2,3] and are now emerging synthetic targets as potential therapeutic agents to treat a variety of metabolic and infectious diseases.[3,4] These azasugar have been considered to mimic the intermediate of glycoside-cleaving reaction **2** in which the positive charge is located at the position of the ring oxygen. A variety of naturally occurring and designed iminosugars have been synthesized based on this assumption.[3,5] Another structure, **3**, was proposed by us as the intermediate in the glucose-cleaving reaction where the positive charge is located at the anomeric carbon instead of the ring oxygen.[6] Recently Bols *et al.*, reported the synthesis of isofagomine where a nitrogen atom is located at the anomeric position.[7] This prompted us to report our synthesis of a galactose-type iminosugar which has a nitrogen atom in the place of the anomeric carbon.

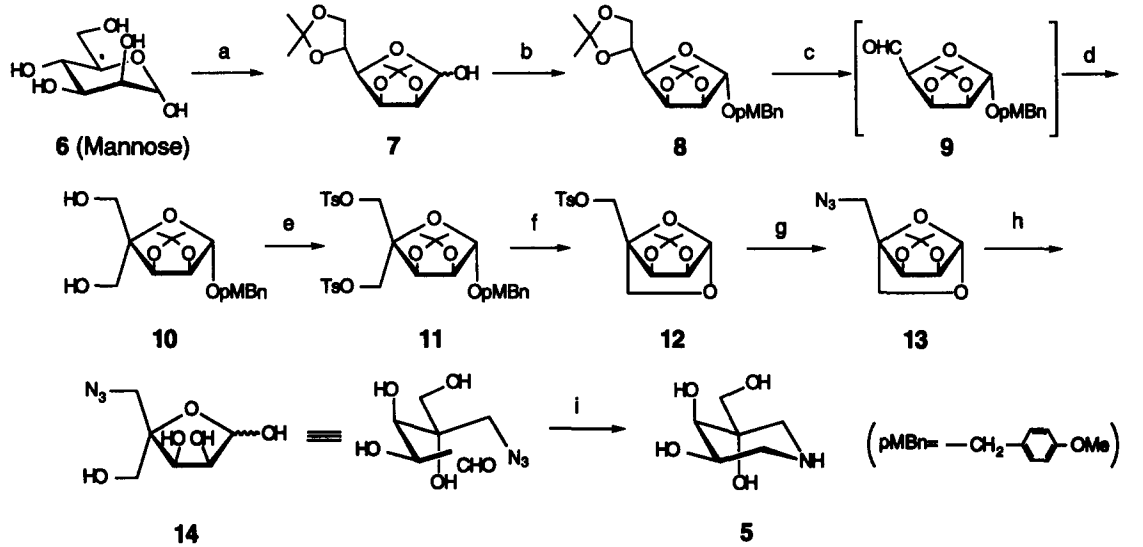
Results and Discussion

Our inhibitor design was based on the cationic intermediate structure **3**: a nitrogen atom, located in the place of the anomeric carbon would generate a positive charge, and the hydroxyl groups are for the recognition by the enzyme, as depicted by the general structure **4**. The designed inhibitor of galactosidase is shown as **5**, which has an extra OH group on the C-5 carbon like a glucosidase inhibitor valiolamine.[8]

The synthesis started with 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**7**) which is readily obtainable from D-mannose (Scheme 1).[9] Protection of the anomeric hydroxyl group of **7** with *p*-methoxybenzyl (*p*MBn) group with Ag_2O, KI, and *p*MBnCl in DMF gave an α-glycoside **8** as a major product (α:β = 8:1).[10] The 5,6-*O*-isopropylidene group of **8** was selectively hydrolyzed with 70% AcOH, and the vicinal diol moiety was oxidatively cleaved with $NaIO_4$ to give an aldehyde **9**. The aldehyde **9** was subjected to the Moffatt's Aldol–Cannizzaro reaction with HCHO and NaOH[11] to give a C-4 branched furanoside **10**.



1 **2** **3** **4** **5**



Scheme 1. Synthesis of inhibitor **5**. Reagents and conditions: (a) Ref 9; (b) Ag_2O/*p*-methoxybenzyl chloride (*p*MBnCl)/DMF/rt/overnight (74%); (c) (i) 70% AcOH/rt/4h, (ii) $NaIO_4$/MeOH–H_2O/0 °C/30 min; (d) NaOH/37% aq. HCHO solution/THF–H_2O/rt/overnight (32% overall from **8**); (e) TsCl/pyr/rt/overnight (81%); (f) (i) DDQ/CH_2Cl_2–H_2O/rt/overnight (81%), (ii) NaH/DMF/0 °C/2 h (90%); (g) NaN_3/DMF/130 °C/4 h (89%); (h) 60% CF_3CO_2H/rt/overnight; (i) H_2/10% Pd/C/$NaHCO_3$/H_2O/rt/overnight (76% overall from **13**).

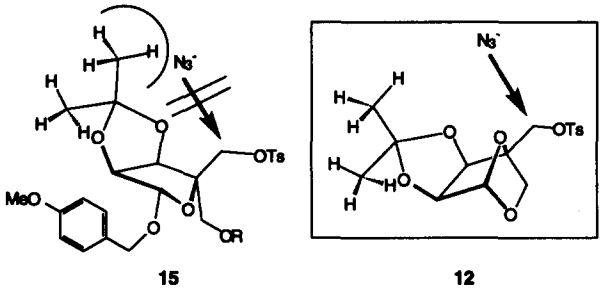


Figure 1. S_N2 substitution with N_3^-.

Several attempts to differentiate these two primary hydroxyl groups (5- and 5'-OH) with selective protection such as silylation, benzylation or acylation were not successful, and resulted in a mixture of products. We therefore planned to form an anhydro ring via 1,5 or 1,5' for the differentiation of the 5- and 5'-positions. Di-*O*-tosylation of **10** with an excess of TsCl gave a high yield of 5,5'-di-*O*-tosyl derivative **11**. The *p*MBn group was removed by the Oikawa procedure with DDQ[12] to generate the anomeric OH, which was then treated with NaH[13] to give a single product in high yield. The structure of the product was tentatively assigned to be the 1,5'-anhydro derivative **12**, and was finally proved by ^1H NMR experiment of **5**.

Another reason for forming the 1,5'-anhydro ring is that a substitution reaction of the 5-OTs was considered difficult because the 5-tosyloxymethyl group of a substrate such as **15** is a "neopentyl" type which is known to have difficulty in undergoing an S_N2 type substitution reaction (Fig. 1).[14] Additionally, **15** has a bicyclic system, in which the 5-OTs is in the concave face, therefore, the S_N2 reaction of the 5-OTs with N_3^- would be more difficult. On the other hand, the tricyclic structure of **12** may stretch the 5-OTs group away from the steric problem caused by the substituents on C-2 and -3, and also away from the concave face; thereby the azido substitution reaction of the 5-OTs is expected to give the 5-azido derivative **13**.

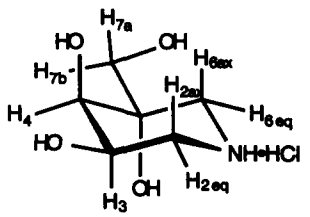


Figure 2. Inhibitor 5•HCl salt.

Table 1. Inhibitory potency of **5**

Glycosidases	IC_{50} (μM)
β-galactosidase	17.5
α-galactosidase	610
β-glucosidase	420
α-glucosidase	>2000

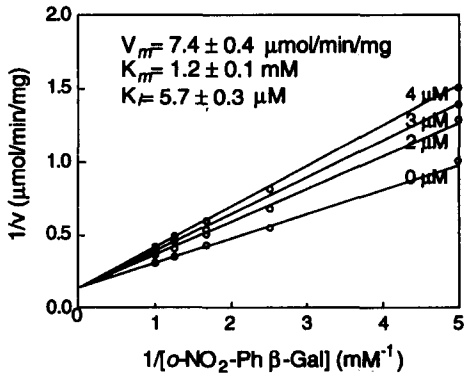


Figure 3. Inhibition of β-galactosidase with **5**.

The reaction of **12** with NaN_3 proceeded smoothly to give the 5-azido derivative **13** in 4 h. Hydrolysis of the 1,5-anhydro ring and the 2,3-*O*-isopropylidene group of **13** with 60% CF_3CO_2H followed by the reductive amination in a buffered solution (pH 8) gave **5** after purification with Dowex 50W-X8 [H^+] resin. The structure of **5** (Fig. 2) was confirmed by ^1H NMR spectrum, where H_{2ax} appears as a triplet with a large coupling constant ($J_{2ax,3}$ = 11.82 Hz), and H_4 appears as a doublet with a small coupling ($J_{3,4}$ = 2.84 Hz).

The inhibitory potency of **5** was examined[15] against several glycosidases, including β-galactosidase (from *Aspergillus oryzae*, Sigma G 7138), α-galactosidase (from green coffee beans, Sigma G 8507), β-glucosidase (from almonds, Sigma G 4511), and α-glucosidase (from yeast, Sigma G 7256). As expected, compound **5** strongly inhibits β-galactosidase (K_i 5.7 μM) in a competitive manner (Fig. 3), and shows a high specificity to the enzyme when compared to other glycosidases examined (Table 1). Interestingly **5** weakly inhibits α-galactosidase (IC_{50} 610 μM), whereas 1-deoxygalactonojirimycin inhibits α-galactosidase (from green coffee beans) much more strongly (K_i 1.6 nM)[16] than β-galactosidase (*Aspergillus wentii*) with K_i 0.16 μM.[16] β-Galactosylamine was reported to inhibit β-galactosidase (*A. wentii*) with K_i 13.4 μM,[16] and it is as potent as 1-*N*-iminosugar **5**; however, β-galactosylamine is unstable and hydrolyzed easily. Overall, these inhibition data suggested that 1-*N*-iminogalactose (**5**) is a potent inhibitor of β-galactosidase, and was distinguished by α- and β-galactosidases.

In summary, we have accomplished an efficient synthesis of a new type of glycosidase inhibitor (1-*N*-iminosugar) in which a nitrogen atom is in the place of the anomeric carbon, in a stereoselective manner from a readily available mannose derivative. The 1-*N*-iminogalactose has proven to be a potent inhibitor of β-galactosidase, and the 1-nitrogen atom can be used to conjugate with other molecules to be an inhibitor of other glycoenzymes. Synthesis of other types of 1-*N*-iminosugars and their further modification are in progress in our laboratory.

Experimental

4'-Methoxybenzyl 2,3:5,6-di-O-isopropylidene-α-D-mannofuranoside (8)

4-Methoxybenzyl chloride (*p*MBnCl) (5.71 g, 36.5 mmol; 4.94 mL) was added dropwise to a cold suspension of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside[9] (**7**) (7.3 g, 28.0 mmol), KI (5.58 g, 33.7 mmol) and Ag_2O (8.45 g, 36.5 mmol) in DMF (70 mL) at 0–5 °C, and the mixture was stirred for 10 h at room temperature. TLC analysis showed that a major product, α-anomer **8** and its β-anomer formed with R_f = 0.61 and 0.42 in toluene:EtOAc (2:1), respectively. The reaction mixture was diluted with EtOAc (200 mL) and filtered with Celite. Saturated NaCl solution (50 mL) was added to the filtrate and the precipitate was filtered off with Celite and rinsed with EtOAc. The filtrate was extracted with EtOAc and the combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel, with toluene:EtOAc (10:1), to give **8** (7.91 g, 74%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.29, 1.37, 1.44, 1.45 (*s*, 3H each, 4 × CH_3 of di-*O*-isopropylidene), 3.74 (*s*, 3H, OCH_3 of pMBn), 3.96 (*dd*, 1H, *J* = 3.59, 7.68 Hz, H-4), 4.00 (*dd*, 1H, *J* = 4.61, 8.66 Hz, H-6a), 4.10 (*dd*, 1H, *J* = 6.19, 8.66 Hz, H-6b), 4.39 (*d*, 1H, *J* = 11.49 Hz, benzylic), 4.40 (*ddd*, 1H, *J* = 1.33, 1.61, 5.77 Hz, H-5), 4.56 (*d*, 1H, *J* = 11.50 Hz, benzylic), 4.60 (*d*, 1H, *J* = 5.98 Hz, H-2), 4.74 (*dd*, 1H, *J* = 3.61, 5.90 Hz, H-3), 5.04 (*br s*, 1H, H-1), 6.85 (*d*, 2H, *J* = 8.70 Hz, aromatic), 7.22 (*d*, 2H, *J* = 8.65 Hz, aromatic); ^{13}C NMR (75.2 MHz, $CDCl_3$) δ 24.47, 25.18, 25.77, 26.59, 66.76, 68.57, 108.88, 112.36, 107.93, 112.36, 113.39, 129.38, 129.46, 160.27; HRMS (CI) calcd for $C_{20}H_{32}NO_7$ ($M + NH_4^+$) 398.2179, found 398.2183.

4'-Methoxybenzyl 4-(hydroxymethyl)-2,3-O-isopropylidene-β-L-erythropentofuranoside (10)

A solution of **8** (7.30 g, 19.2 mmol) in 70% AcOH (100 mL) was stirred for 4 h at room temperature. TLC analysis showed that **8** (R_f = 0.72 in toluene:EtOAc, 1:1) was converted to the product (R_f = 0.11) concomitant with a further hydrolyzed product on the baseline. The reaction mixture was concentrated, and the residue was chromatographed on silica gel, with toluene:EtOAc (3:1), to give the diol (5.62 g, 86%).

A solution of $NaIO_4$ (4.94 g, 23.1 mmol) in water (100 mL) was added dropwise to a cooled solution of the above diol (5.62 g, 16.5 mmol) in methanol (150 mL) at 0–5 °C, and the mixture was stirred for 30 min at 0–5 °C. TLC analysis showed that the diol (R_f = 0.11 in toluene:EtOAc, 1:1) was converted to the aldehyde **9** (R_f = 0.45) as a sole product. The reaction mixture was concentrated and the residue was dissolved in EtOAc and water, and the aqueous layer was extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give the aldehyde **9**, which was used for the next step without further purification.

Sodium hydroxide solution (1 N, 50 mL) was added dropwise to a cooled solution of the above aldehyde **9** in THF (34 mL), water (34 mL) and 37% aqueous formaldehyde (13 mL) at 0–5 °C, and the mixture was stirred overnight at room temperature. TLC analysis showed two products formed: a faster moving spot (R_f = 0.59 in hexane:acetone, 1:1) was the desired product **10** and a slower moving spot (R_f = 0.47) was an eliminated product, and the ratio was *ca* 1:1. The reaction mixture was neutralized by the addition of HCO_2H, and concentrated. The residue

was dissolved in water and EtOAc, and the aqueous layer was extracted with EtOAc. The combined organic extracts were, without being washed with water, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel, with toluene:acetone (5:1) to give **10** (2.13 g, 32% overall): mp 118–119 °C (from EtOAc–Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31, 1.50 (*s*, 3H each, 2 × CH_3 of *O*-isopropylidene), 2.54 (*q*, 1H, *J* = 6.36 Hz, 5-OH), 3.39 (*dd*, 1H, *J* = 3.65, 9.87 Hz, 5'-OH), 3.63–3.84 (*m*, 4H, H-5a,5b,5'a,5'b), 3.79 (*s*, 3H, OCH_3 of *p*MBn), 4.48 (*d*, 1H, *J* = 11.40 Hz, benzylic), 4.70 (*d*, 1H, *J* = 11.40 Hz, benzylic), 4.71 (*d*, 1H, *J* = 5.96 Hz, H-2), 4.84 (*d*, 1H, *J* = 6.07 Hz, H-3), 5.17 (*s*, 1H, H-1); ^{13}C NMR (75.2 MHz, $CDCl_3$) δ 24.30, 25.98, 55.26, 63.44, 66.00, 69.88, 82.05, 86.62, 90.68, 107.03, 112.55, 114.08, 128.46, 129.89, 159.66; HRMS (CI) calcd for $C_{17}H_{28}NO_7$ (M + NH_4^+) 358.1866, found 358.1861.

4'-Methoxybenzyl 2,3-O-isopropylidene-5-O-p-toluenesulfonyl-4-(p-toluenesulfonyloxymethyl)-β-L-erythropentofuranoside (11)

p-Toluenesulfonyl chloride (3.95 g, 20.7 mmol) was added portionwise to a cooled solution of **10** (1.41 g, 4.14 mmol) in pyridine (50 mL) at 0–5 °C, and the reaction mixture was stirred for 10 h at room temperature. During this time, another portion of *p*-toluenesulfonyl chloride (3.95 g, 20.7 mmol) was added to the reaction mixture. TLC analysis showed a major product **11** (R_f = 0.75 in toluene:EtOAc, 2:1) concomitant with monotosylate (R_f = 0.55 and 0.48). The reaction mixture was poured onto ice-water, and extracted with EtOAc. The combined extracts were successively washed with ice-cold diluted HCl, aqueous $NaHCO_3$, and water, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel, with toluene:EtOAc (5:1), to give **11** (2.4 g, 89%): mp 115–118 °C (from EtOAc–Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20, 1.29 (*s*, 3H each, 2 × CH_3 of *O*-isopropylidene), 2.44, 2.46 (*s*, 3H each, CH_3 of 5- and 5'-OTs), 3.82 (*s*, 3H, OCH_3 of *p*MBn), 4.02 (*d*, 1H, *J* = 9.71 Hz, H-5a), 4.06 (*d*, 1H, *J* = 9.67 Hz, H-5b), 4.12 (*br s*, 2H, H-5'a,5'b), 4.29 (*d*, 1H, *J* = 11.36 Hz, benzylic), 4.55 (*d*, 1H, *J* = 11.36 Hz, benzylic), 4.55 (*d*, 1H, *J* = 5.96 Hz, H-2), 4.61 (*d*, 1H, *J* = 5.98 Hz, H-3), 5.03 (*s*, 1H, H-1); ^{13}C NMR (75.2 MHz, $CDCl_3$) δ 21.65, 21.70, 24.33, 25.62, 55.32, 67.35, 68.02, 69.37, 81.50, 85.28, 85.65, 106.53, 113.96, 128.03, 128.23, 128.62, 129.74, 129.85, 130.05, 132.19, 144.84, 145.25; HRMS (FAB) calcd for $C_{31}H_{32}NO_{11}S_2$ (M + NH_4^+) 666.2043, found 666.2051.

1,5'-Anhydro-2,3-O-isopropylidene-4-(p-toluenesulfonyloxymethyl)-α-L-erythropentofuranose (12)

A mixture of **11** (3.1 g, 4.78 mmol) and DDQ (2.17 g, 9.56 mmol) in CH_2Cl_2 (76 mL) and water (4.2 mL) was stirred for 10 h at room temperature. TLC analysis showed that a new spot appeared with R_f = 0.48 in toluene:EtOAc, 2:1. The reaction mixture was diluted with $CHCl_3$ and water, and extracted with $CHCl_3$. The combined extracts were washed with water, dried, and concentrated. The residue was chromatographed on silica gel, with toluene:EtOAc (5:1), to give the *O*-demethoxybenzylated product (*ca* 2.7 g) concomitant with unidentified colored substance.

NaH (60% mineral oil dispersion, 306 mg, 7.66 mmol) was added portionwise to a cold solution of the above product in DMF (50 mL) at 0–5 °C, and the mixture was stirred for 30 min at 0–5 °C. TLC analysis showed that a single product formed (R_f = 0.62 in toluene:EtOAc, 2:1). The reaction mixture was poured onto ice-water, and extracted with EtOAc. The combined extracts were successively washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel, with hexane:EtOAc (9:1), to give **12** (1.64 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24, 1.34 (*s*, 3H each, 2 × CH_3 of *O*-isopropylidene), 2.46 (*s*, 3H, CH_3 of 5-OTs), 3.34 (*d*, 1H, *J* = 7.40 Hz, H-5'a), 3.39 (*d*, 1H, *J* = 7.40 Hz, H-5'b), 4.26 (*d*, 1H, *J* = 5.44 Hz, H-2), 4.33 (*d*, 1H, *J* = 5.40 Hz, H-3), 4.42 (*d*, 1H, *J* = 10.85 Hz, H-5a), 4.55 (*d*, 1H, *J* = 10.86 Hz, H-5b), 5.37 (*s*, 1H, H-1); ^{13}C NMR (75.2 MHz, $CDCl_3$) δ 21.62, 25.47, 25.89, 64.79, 65.04, 78.89, 81.84, 83.59, 100.70, 112.90, 128.16, 129.96, 145.28; HRMS (CI) calcd for $C_{16}H_{24}NO_7S$ (M + NH_4^+) 374.1273, found 374.1272.

1,5'-Anhydro-4-(azidomethyl)-2,3-O-isopropylidene-α-L-erythropentofuranose (13)

A mixture of **12** (1.22 g, 3.43 mmol) and NaN_3 (2.23 g, 34.3 mmol) in DMF (50 mL) was heated for 4 h at 120 °C. TLC analysis showed that **12** (R_f = 0.51 in hexane:EtOAc, 2:1) was converted to a single product (R_f = 0.72). After cooling, the reaction mixture was diluted with EtOAc. The organic layer was successively washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel, with hexane:EtOAc (10:1), to give **13** (680 mg, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29, 1.45 (*s*, 3H each, 2 × CH_3 of *O*-isopropylidene), 3.32 (*d*, 1H, *J* = 7.28 Hz, H-5'a), 3.42 (*d*, 1H, *J* = 7.31 Hz, H-5'b), 3.78 (*d*, 1H, *J* = 13.05 Hz, H-5a), 3.86 (*d*, 1H, *J* = 13.03 Hz, H-5b), 4.26 (*d*, 1H, *J* = 5.48 Hz, H-2), 4.35 (*d*, 1H, *J* = 5.44 Hz, H-3), 5.41 (*s*, 1H, H-1); ^{13}C NMR (75.2 MHz, $CDCl_3$) δ 25.50, 25.99, 47.65, 65.41, 79.13, 82.03, 84.98, 100.51, 112.86; HRMS (CI) calcd for $C_9H_{17}N_4O_7$ (M + NH_4^+) 245.1250, found 245.1254.

(3R,4R,5R)-Trihydroxy-3(R)-hydroxymethylpyrolidine hydrochloride salt (5)

A solution of **13** (126 mg, 0.55 mmol) in 60% aqueous CF_3CO_2H (10 mL) was stirred for 10 h at room temperature. The starting material disappeared and formed a product (**14**) (R_f = 0.72, in

*i*PrOH:H_2O:NH_4OH 7:2:1). The reaction mixture was concentrated, and co-evaporated with EtOH twice. A solution of the residue in water (10 mL) was neutralized (pH 7) by the addition of saturated aqueous $NaHCO_3$ solution, and 10% Pd/C (60 mg) was added to the solution. The resulting suspension was stirred under a hydrogen atmosphere for 10 h at room temperature. TLC analysis showed that the starting material **14** (R_f = 0.72, in *i*PrOH:H_2O:NH_4OH 7:2:1) was converted to the product (**5**) (R_f = 0.34), which is stained well with ninhydrin but barely with anisaldehyde–sulfuric acid reagent. The reaction mixture was filtered with Celite, rinsed with water, and the filtrate was concentrated. The residue was dissolved in water (30 mL), and applied onto a column of Dowex 50W-X8 [H^+] (1.0 × 20 cm). The column was washed with water (50 mL) and the product was eluted with 5% NH_4OH. The fractions containing the product were pooled, concentrated, and further co-evaporated with water (× 2). To a solution of the residue in water (3 mL) was added N HCl solution (0.2 mL), and the resulting solution was lyophilized to give **5** as a HCl salt (76 mg, 86%): ^1H NMR (300 MHz, D_2O) δ 3.02 (*t*, 1 H, *J* = 11.82 Hz, H-2ax), 3.10 (*s*, 2H, H-7a,7b), 3.27 (*dd*, 1H, *J* = 5.04, 11.98 Hz, H-2eq), 3.61 (*d*, 1H, *J* = 12.15 Hz, H-6a), 3.69 (*d*, 1H, *J* = 12.18 Hz, H-6b), 3.89 (*d*, 1H, *J* = 2.84 Hz, H-4), 4.27 (*ddd*, 1H, *J* = 2.84, 5.10, 11.69 Hz, H-3); ^{13}C NMR (75.2 MHz, D_2O) δ 47.85, 50.03, 68.52, 69.47, 73.79, 78.33; HRMS (CI) calcd for $C_6H_{15}NO_4Cl$ ($M + H^+$) 164.0923, found 164.0925.

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