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Highly stereoselective synthesis and structural characterization of new amino sugar derivatives

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Abstract—2-*C*-Nitroalkyl-1,4:3,6-dianhydromannitols were synthesized via a Henry reaction of nitroalkyls with 1,4:3,6-dianhydrofructose. Catalytic hydrogenation then afforded the corresponding vicinal amino alcohols. Oximation of 1,4:3,6-dianhydrofructose with hydroxylamine, followed by hydrogenation, gave 2-amino-1,4:3,6-dianhydro-2-deoxymannitol. All compounds were elucidated by their HRMS, ^{1}H NMR, ^{13}C NMR, and IR spectra. The absolute configurations of the amino sugar derivatives were confirmed by single-crystal X-ray analysis or NOESY spectral studies. The possible mechanism for hydrogenation of the nitro 2-*C*-nitroalkyl sugar is proposed. The conformations of the fused furan rings of nitro and amino sugar derivatives are presented.

Keywords: 1,4:3,6-Dianhydro-D-fructose; Isomannide; Amino sugar; Vicinal amino alcohols; X-ray crystallographic study

1. Introduction

Amino sugars are an important class of compounds having a broad spectrum of applications in the chemical, biochemical, medicinal, and pharmaceutical fields,[1,2] especially for the amino sugar-containing antibiotics.[3–6] In particular, most potent glycosidase inhibitors are basic amino sugars,[7] and some antibiotics such as tunicamycin[8] contain an amino sugar backbone. As such, a variety of stereoselective synthetic methods have been developed.

1,4:3,6-Dianhydro-D-fructose (DAF) consists of two fused tetrahydrofuran rings having the cis-arrangement at the ring junctions, giving a V-shaped molecule. The compound has an *endo*-hydroxyl group at C-5 with respect to the V-shaped molecule and a highly reactive carbonyl group at C-2, which allows good control in diastereoselectivity of such reactions as nucleophilic addition to the carbonyl group. In our previous paper, we reported the preparation of DAF from sucralose and asymmetric synthesis of novel polycyclic tetrahydroquinolines by reaction of the obtained DAF with anilines.[9] In the synthesis of tetrahydroquinolines, the DAF moiety played an important role for stereocontrol of the reaction. Thus, we are interested in the design of other diastereoselective reactions of DAF and the synthesis of the corresponding amino derivatives that may have desired biological activities.

In the present paper, 2-*C*-aminomethyl-1,4:3,6-dianhydromannitol (2-*C*-aminomethylisomannide, **3**), 2-*C*-[(1*R*)-aminoethyl]-1,4:3,6-dianhydromannitol (2-*C*-[(1*R*)-aminoethyl]isomannide, **5**), and 2-amino-1,4:3,6-dianhydro-2-deoxymannitol (2-amino-2-deoxyisomannide, **10**) were synthesized from DAF, and the configurations of their newly formed stereogenic centers were established by X-ray crystallographic analysis or NOESY studies.

2. Results and discussion

2.1. Synthetic transformations

Without a doubt, the sequence of addition of a nitro alkyl group to a carbonyl group, followed by the

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conversion of the nitro group into the amino group via catalytic hydrogenation, is among the most powerful approaches to amino alcohol derivatives. The generation of an anion α to nitrogen is an actively pursued area of research toward the synthesis of vicinal amino alcohols.[10] A typical example is the Henry reaction.[11]

Reaction of DAF (**1**) with nitromethane in the presence of Et_3N at ambient temperature afforded 2-*C*-nitromethyl-1,4:3,6-dianhydrohexitol (**2**), followed by hydrogenation of **2** in ethanol with Pd/C gave the corresponding amino derivative (**3**). Compounds **2** and **3** were elucidated by their HRMS, ^{1}H NMR, ^{13}C NMR, and IR spectra. The *R*-configuration of the newly formed stereogenic center at C-2 was established by X-ray crystallographic analysis of a suitable crystal of **2** after recrystallization from ethanol (as shown in Fig. 1 and Table 1). Thus compound **2** was 2-*C*-nitromethylisomannide and **3** was consequently 2-*C*-aminomethylisomannide (as depicted in Scheme 1). When nitromethane was replaced by nitroethane in the reaction, the corresponding nucleophilic adduct **4** was available. Catalytic hydrogenation of compound **4** under the above-mentioned conditions gave 2-*C*-[(1*R*)-aminoethyl]isomannide (**5**) (as shown in Scheme 1). The stereochemistry for the chiral center α to amino group of compound **5** was confirmed by X-ray crystallographic analysis of compound **5** (as shown in Fig. 2 and Table 1).

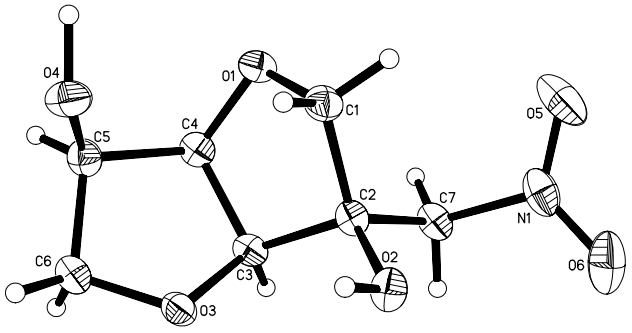
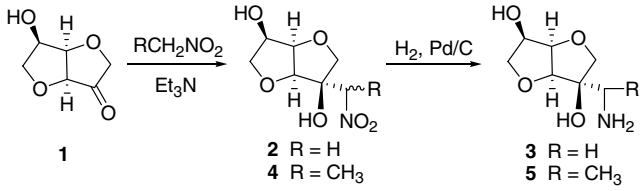


Figure 1. X-ray crystal structure for compound **2**.

It is worth noting that, according to ^{1}H and ^{13}C NMR spectra, compound **4** is a mixture (molar ratio 1:1) of two stereoisomers at the α-C to the nitro group due to lack of stereoselectivity in the generation of a carbon anion from the CH_2 group of nitroethane. However, there is only one *R*-isomer with respect to corresponding carbon atom in the hydrogenation product **5**. That is to say, in the process of conversion, either the *S*- or *R*-isomer of **4** is transformed to the *R*-isomer of compound **5**. Thus, according to the mechanism for the reduction of nitro compounds,[12] we speculate that the hydrogenation reaction must have gone through the process of formation of a C=N intermediate. The possible pathway for the transformation is proposed in Scheme 2 as follows: Two hydrogen atoms are added to nitro compound **4**, followed by elimination of a molecule of H_2O, furnishing the corresponding nitroso compound **6**. Under the influence of the intramolecular H-bond with the 2-OH group, the nitroso compound readily isomerizes to the oxime and forms relatively stable six-membered cyclic intermediate **7**. Hydrogen atoms anchored to the catalyst surface then attack the C=N bond from the less-hindered face, resulting in the stereoselective formation of 2-*C*-[(1*R*)-hydroxylaminoethyl]isomannide (**8**). Subsequent further hydrogenation

Table 1. Single-crystal X-ray data and structure refinement for compounds **2** and **5**

	2	**5**
Empirical formula	$C_7H_{11}NO_6$	$C_8H_{15}NO_4$
Formula weight	205.17	189.21
Crystal system	Orthorhombic	Orthorhombic
Space group	*P*2(1)2(1)2(1)	*P*2(1)2(1)2(1)
Unit cell dimensions		
a (Å)	5.509(1)	5.698(1)
b (Å)	7.183(1)	10.056(2)
c (Å)	22.380(5)	16.330(3)
V (Å^3)	885.7(3)	935.8(3)
Z	4	4
D_{calcd} (Mg/m^3)	1.539	1.343
Absorption coefficient (mm^{-1})	0.136	0.107
F(000)	432	408
Crystal size (mm^3)	$0.20 \times 0.20 \times 0.18$	$0.20 \times 0.18 \times 0.17$
θ Range for data collection (°)	1.82–25.00	2.38–24.99
Index ranges	$-6 \leqslant h \leqslant 6$, $0 \leqslant k \leqslant 8$, $-26 \leqslant l \leqslant 26$	$-6 \leqslant h \leqslant 6$, $0 \leqslant k \leqslant 11$, $-19 \leqslant l \leqslant 19$
Reflections collected/unique	2647/1451 [*R*(int) = 0.0775]	2803/1534 [*R*(int) = 0.0712]
Completeness to $2\theta = 24.99$	93.5%	95.5%
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	1451/0/136	1534/0/135
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0617$	$R_1 = 0.0413$
R Indices (all data)	$wR_2 = 0.1531$	$wR_2 = 0.0980$
Goodness-of-fit on F^2	1.028	1.019



Scheme 1. Synthesis of β-amino alcohol derivatives of isomannide.

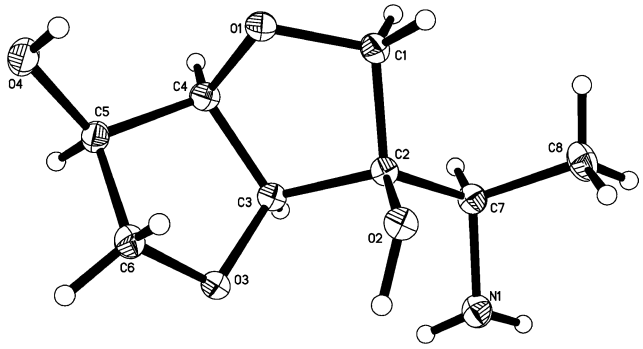


Figure 2. X-ray crystal structure for compound **5**.

and elimination of H_2O affords a 2-*C*-[(1*R*)-aminoethyl]isomannide (**5**).

Treatment of compound **1** with hydroxylamine gave 1,4:3,6-dianhydrofructose oxime (**9**). Subsequent catalytic hydrogenation of the oxime in the presence of Raney Ni furnished 2-amino-2-deoxyisomannide (**10**) (Scheme 3). The configuration of the newly formed chiral center (C-2) was established by a NOESY study with correlations of the H atoms as shown in Figure 3.

In conclusion, by utilization of the stereocontrol of the V-shaped sugar ring, vicinal amino alcohol and amino derivatives of 1,4:3,6-dianhydromannitol were stereoselectively synthesized. It is indicated that DAF is an appropriate chiral building block or intermediate in asymmetric synthesis. The use of the amino alcohols and amino sugars in asymmetric catalysis and drug development is under study.

2.2. X-ray crystallographic analysis

Details of the crystal structure determinations for compounds **2** and **5** are summarized in Table 1. Selected torsion angles are presented in Table 2. In compound **2**, the first furan ring adopts the ^1E conformation: four atoms, C-2, C-3, C-4, and O-1 are coplanar with a torsion angle of $-0.4(3)°$. The flap atom C-1 is puckered in the *endo* direction. Cremer–Pople puckering parameters[13] for this ring are $Q = 0.348(3)$ Å and $\Phi = 218.2\ (6)°$. The same conformation, E_6, is found in the second furan ring: O-3, C-3, C-4, and C-5, are coplanar with a torsion angle of $-6.4(3)°$, the atom C-6 flaps toward the *exo* direction. Corresponding Cremer–Pople puckering parameters are $Q = 0.367(3)$ Å and $\Phi = 152.0(6)°$. Two furan rings fused along the C-3–C-4 bond, allowed a V-shaped molecule with a torsion angle within 115.6–122.3° between two planes: C-2–C-3–C-4–O-1 of ring 1 and O-3–C-3–C-4–C-5 of ring 2. Different from **2**, compound **5** possesses two *T*-form furan rings, ring 1 twisted on O-1–C-1 and ring 2 on C-5–C-6, respectively. Interestingly, C-1 and C-6, flapping to the *endo* and *exo* direction, respectively, in compound **2**, pucker to the opposite directions in **5**. That is, C-1 goes in the *exo* (T_1) and C-6 to the *endo* (^6T) directions. Cremer–Pople pucke-ring parameters for ring 1 are $Q = 0.379(2)$ Å, $\Phi = 18.0(3)°$, and those for ring 2 are $Q = 0.377(2)$ Å, $\Phi = 309.8(4)°$.

The interaction between the molecules of compound **2** in stacking is shown in Figure 4. The molecules are

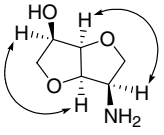
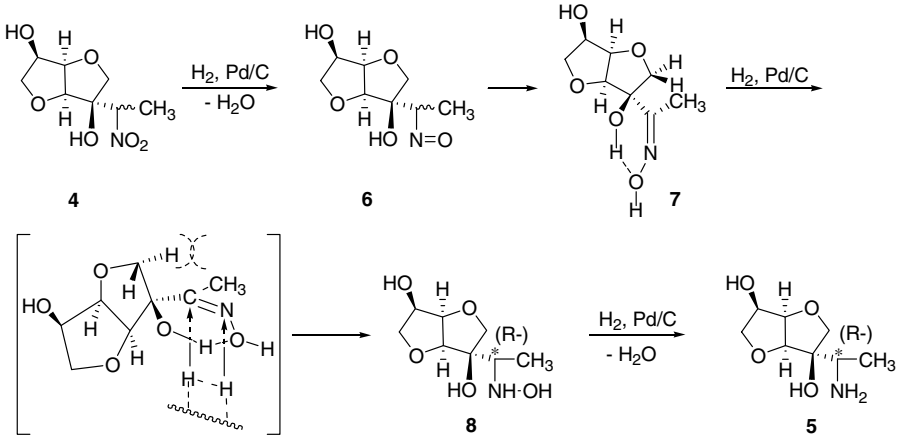
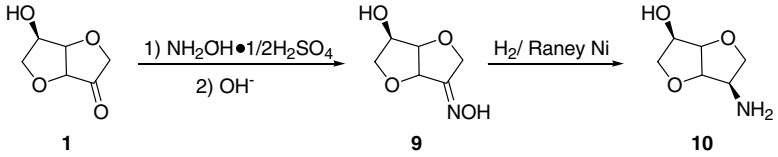


Figure 3. Correlation of H atoms in NOESY spectrum for compound **10**.



Scheme 2. Proposed pathway for the formation of compound **5**.



Scheme 3. Preparation of 2-amino-2-deoxyisomannide.

Table 2. Selected torsion angles (°) for compounds **2** and **5**

	2	5
O(1)–C(1)–C(2)–C(3)	−35.0(3)	32.7(2)
C(4)–O(1)–C(1)–C(2)	36.8(3)	−43.2(2)
C(2)–C(3)–C(4)–O(1)	−0.4(3)	−13.2(2)
C(1)–C(2)–C(3)–C(4)	21.1(3)	−11.3(2)
C(1)–O(1)–C(4)–C(3)	−22.5(3)	34.5(2)
O(3)–C(3)–C(4)–C(5)	−6.4(3)	−8.9(2)
C(3)–C(4)–C(5)–C(6)	−17.2(3)	28.9(2)
C(4)–C(5)–C(6)–O(3)	35.2(3)	−39.4(2)
C(3)–O(3)–C(6)–C(5)	−41.1(3)	35.3(2)
C(6)–O(3)–C(3)–C(4)	29.3(3)	−16.3(2)
O(3)–C(3)–C(4)–O(1)	115.7(3)	107.09(17)
C(2)–C(3)–C(4)–C(5)	−122.3(3)	−129.18(17)

firstly lined in a row through a hydrogen bond between the 4-OH group of one molecule and O-3 of next one. Then a column packing is assembled by two rows of molecules through intermolecular hydrogen bonds between the 2-OH group of one molecule and O-4 of neighboring one in the next row (as listed in Table 3). Finally, the columns are bounded by the supramolecular interactions among molecules to form a regular three-dimensional network. Different to **2**, compound **5** makes contacts with four neighboring molecules through 2-OH···O-1, 4-OH···N-1, 1-N–H(E)···O-4, and 1-N–H(F)···O-4, respectively, as listed in Table 3, which results in a reticular molecular packing (as shown in Fig. 5). Perhaps it is the different intermolecular hydrogen bonds due to different substitution at C-7 (nitro and amino groups) that lead to the opposite puckering direction of C-1 and C-6 in the two compounds.

3. Experimental

3.1. General methods

^{1}H and ^{13}C NMR spectra were acquired on Bruker AVANCE DPX-400 spectrometer at 25 °C. The ^{1}H and ^{13}C NMR chemical shifts (δ), given in parts per million, were referenced to internal tetramethylsilane (Me_4Si). Melting points were determined on a WC-1 melting-point apparatus and are uncorrected. Optical

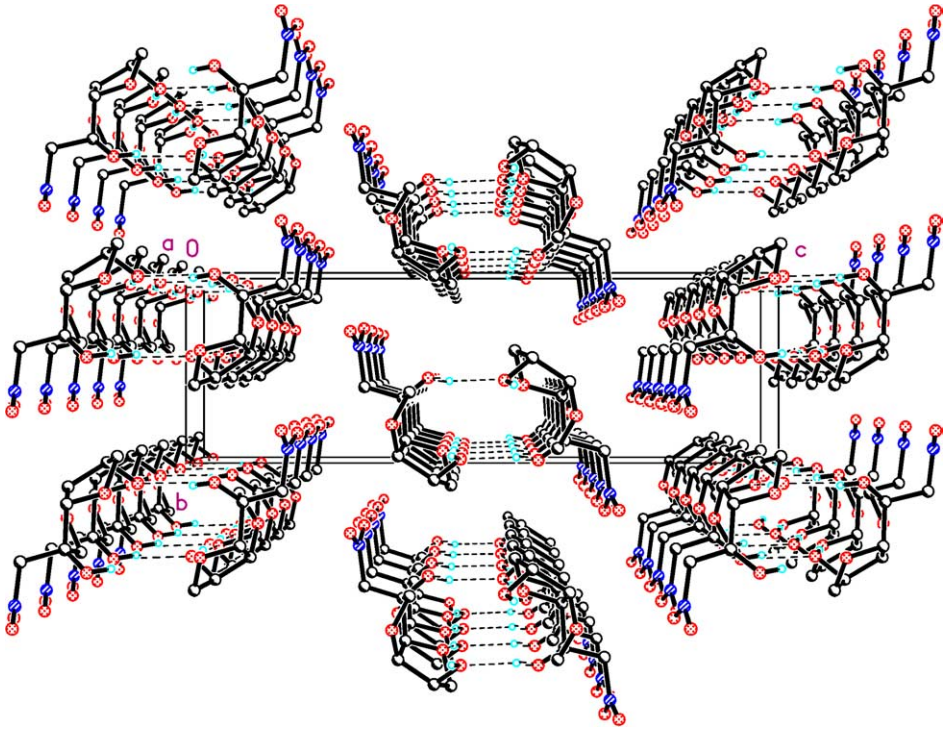


Figure 4. Molecular stacking of compound **2** along the *a*-axis showing the intermolecular hydrogen bonds.

Table 3. Hydrogen bonds for compounds **2** and **5** [Å and °]

D–H	*d*(D–H)	*d*(H···A)	*d*(D···A)	∠(DHA)	A	
2						
O(2)–H(2A)	0.82	1.96	2.759(3)	164.3	O4	$x+1/2, -y+1/2, -z$
O(4)–H(4E)	1.02(7)	1.72(7)	2.739(3)	173(6)	O3	$x-1, y, z$
5						
O(2)–H(2E)	0.97(4)	1.92(4)	2.862(3)	164(3)	O(1)	$-x+2, y-1/2, -z+3/2$
O(4)–H(4E)	0.89(4)	2.00(3)	2.851(3)	160(3)	N(1)	$-x+2, y+1/2, -z+3/2$
N(1)–H(1F)	0.96(3)	2.32(3)	3.257(3)	165(2)	O(4)	$-x+5/2, -y+2, z+1/2$
N(1)–H(1E)	0.83(4)	2.55(4)	3.356(3)	163(4)	O(4)	$-x+3, y-1/2, -z+3/2$

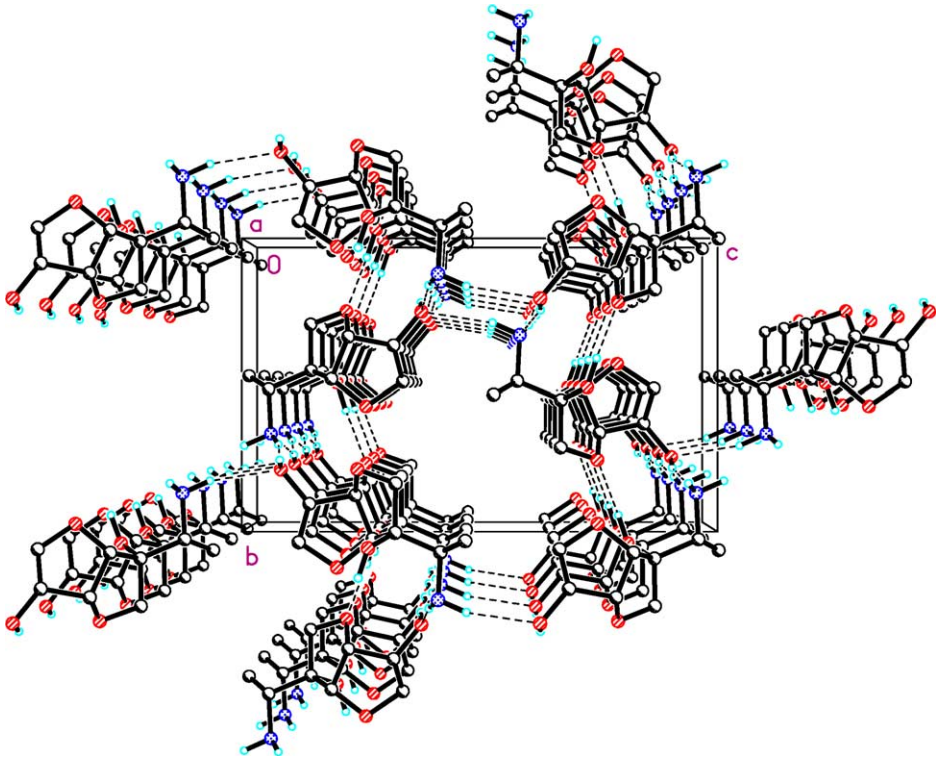


Figure 5. Molecular stacking of compound **5** along the *a*-axis showing the intermolecular hydrogen bonds.

rotations were measured on a Perkin–Elmer 341 Polarimeter. HRMS (high-resolution mass spectra) were taken with a Q-Tof Micromass spectrometer. Thin-layer chromatography (TLC) was performed on glass plates precoated with silica gel (5–40 μm) to monitor the reactions and certify the purity of the reaction products. Visualization was accomplished by spraying the chromatograms with 10% ethanolic sulfuric acid and charring them on a hot plate.

3.2. X-ray diffraction experiment

X-ray diffraction analysis was carried out on a Rigaku RAXIS-IV imaging plate with graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). An orthorhombic crystal was selected and mounted on a glass fiber. All data were collected at a temperature of 291(2) K and corrected for Lorentz polarization effects. The structure was solved via direct methods and expanded using the Fourier technique. The non-hydrogen atoms were refined with anisotropic thermal parameters. Hydroxyl hydrogen atoms were refined with isotropic thermal parameters. Other hydrogen atoms were included but not refined. All calculations were performed using the SHELX-97 crystallographic software package.[14] Atomic coordinates and equivalent isotropic displacement parameters for compounds **2** and **5** are presented in Table 4.

3.3. 2-*C*-Nitromethyl-1,4:3,6-dianhydromannitol (2-*C*-nitromethylisomannide, 2)

Nitromethane (2.0 mL) and a catalytic amount of Et_3N were added to a stirring solution of 1,4:3,6-dianhydrofructose (**1**, 1.44 g, 10 mmol) in EtOH (5 mL). The mixture was stirred at room temperature for 4 h, and

evaporated under reduced pressure to dryness. The residue was recrystallized with EtOH to give compound **2** as a white crystal (1.92 g, 93%): mp 112–113 °C, $[\alpha]_D^{20}$ +84.0 (*c* 0.26, CH_3OH); IR (KBr): 3341, 2987, 2917, 2884, 1543, 1430, 1070, 738, 661 cm^{-1}; ^1H NMR (400.1 MHz, D_2O): δ 4.72 (d, 2H, *J* 1.2 Hz, H-7), 4.54 (t, 1H, H-4), 4.51 (d, 1H, $J_{3,4}$ 5.2 Hz, H-3), 4.32 (ddd, 1H, $J_{4,5}$ 5.2, $J_{5,6b}$ 6.8, $J_{5,6a}$ 8.0 Hz, H-5), 3.98 (dd, 1H, $J_{5,6b}$ 6.8, $J_{6a,6b}$ 8.8 Hz, H-6b), 3.92 (d, 1H, $J_{1a,1b}$ 10.4 Hz, H-1a), 3.81 (d, 1H, $J_{1a,1b}$ 10.4 Hz, H-1b), 3.59 (t, 1H, $J_{6a,6b}$ 8.8 Hz, H-6a); ^{13}C NMR (100.6 MHz, D_2O): δ 82.6 (C-3), 80.8 (C-4), 78.2 (C-7), 77.8 (C-2), 73.8 (C-1), 70.9 (C-6), 70.1 (C-5); HRMS: calcd for $C_7H_{11}NO_6$: 205.0586, found: 228.0490 $[M+Na]^+$.

3.4. 2-*C*-Aminomethyl-1,4:3,6-dianhydromannitol (2-*C*-aminomethylisomannide, 3)

Compound **2** (1.5 g, 7.3 mmol) was dissolved in abs EtOH (150 mL) and 150 mg of Pd–C (10%) catalyst was added. The oscillating mixture was hydrogenated at 50 °C under 50 psi for 6 h. The resulting mixture was filtered and concentrated under reduced pressure to dryness, followed by recrystallization from 2-propanol, affording compound **3** as a white solid (1.15 g, 90%): mp 117–118 °C, $[\alpha]_D^{20}$ +97.0 (*c* 0.228, CH_3OH), IR (KBr): 3351, 3293, 2942, 2929, 2883, 1638, 1329, 1286, 1221, 1121, 1068, 1026, 977, 938, 869, 816, 746 cm^{-1}; ^1H NMR (400.1 MHz, D_2O): δ 4.51 (t, 1H, $J_{3,4}$ 4.8 Hz, H-4), 4.34 (m, 1H, H-5), 4.24 (d, 1H, $J_{3,4}$ 4.8 Hz, H-3), 3.98 (dd, 1H, $J_{5,6b}$ 6.4, $J_{6a,6b}$ 8.8 Hz, H-6b), 3.80 (d, 1H, $J_{1a,1b}$ 9.6 Hz, H-1a), 3.60 (d, 1H, $J_{1a,1b}$ 9.6 Hz, H-1b), 3.56 (t, 1H, $J_{6a,6b}$ 8.8 Hz, H-6a), 2.72 (s, 2H, H-7); ^{13}C NMR (100.6 MHz, D_2O): δ 83.7 (C-3), 81.7 (C-4), 80.6 (C-2), 73.9 (C-1), 71.9 (C-6), 71.7 (C-5), 45.2 (C-7); HRMS: calcd for $C_7H_{13}NO_4$: 175.0845, found: 176.0921 $[M+H]^+$, 198.0748 $[M+Na]^+$.

3.5. 2-*C*-[(1*R*)-Nitroethyl]-1,4:3,6-dianhydromannitol [2-*C*-[(1*R*)-nitroethyl]isomannide, 4]

Treatment of 1,4:3,6-dianhydrofructose with nitroethane, according to the procedure described in Section 3.3, afforded a white solid (**4**, 89%). According to the assignment to the NMR data for the product, compound **4** was a pair of stereoisomers at α-C to the nitro group: mp 96–97 °C, $[\alpha]_D^{20}$ +138.8 (*c* 0.43, CH_3OH), IR (KBr): 3417, 2925, 2884, 1631, 1548, 1397, 1365, 1099, 1046 cm^{-1}; ^1H NMR (400.1 MHz, D_2O): δ 3.99 (d, 1H, *J* 10.0 Hz, H-1), 3.91 (d, 1H, *J* 10.0 Hz, H-1), 3.89 (d, 1H, *J* 10.4 Hz, H-1), 3.82 (d, 1H, *J* 10.4 Hz, H-1); 4.70 (d, 1H, *J* 5.6 Hz, H-3), 4.59 (d, 1H, *J* 5.6 Hz, H-3), 4.54 (t, 2H, *J* 5.6 Hz, H-4), 4.30 (m, 2H, H-5), 3.99 (dd, 2H, *J* 6.8, 8.8 Hz, H-6), 3.65 (t, 1H, *J* 8.8 Hz, H-6), 3.61 (t, 1H, *J* 8.8 Hz, H-6), 4.90 (d, 1H, *J* 6.8 Hz, $-CHNO_2$), 4.88 (d, 1H, *J* 6.8 Hz, $-CHNO_2$), 1.54 (d, 1H, *J* 6.8 Hz, CH_3), 1.51 (d, 1H, *J* 6.8 Hz, CH_3); ^{13}C NMR (100.6 MHz, D_2O): δ 76.7 (C-1), 74.9 (C-1), 81.0 (C-2), 80.8 (C-2), 86.1 (C-3), 86.0 (C-3), 84.3 (C-4), 83.5 (C-4), 70.6 (C-5), 70.5 (C-5), 72.2 (C-6), 71.8 (C-6), 82.2 ($-CHNO_2$), 82.1 ($-CHNO_2$), 13.1 (CH_3), 12.6 (CH_3); HRMS: calcd for $C_8H_{13}NO_6$: 219.0743, found: 242.0630 $[M+Na]^+$.

3.6. 2-*C*-[(1*R*)-Aminoethyl]-1,4:3,6-dianhydromannitol [2-*C*-[(1*R*)-aminoethyl]isomannide, 5]

Hydrogenation of compound **4**, according to the procedure described in Section 3.4, furnished compound **5** as a white solid (83%): mp 124–125 °C, $[\alpha]_D^{20}$ +73.0 (*c* 0.222, CH_3OH), IR (KBr): 3410, 3333, 2967, 2931, 2844, 1127, 1070, 1030 cm^{-1}; ^1H NMR (400.1 MHz, D_2O): δ 4.48 (t, 1H, $J_{3,4}$ 5.2 Hz, H-4), 4.39 (d, 1H, $J_{3,4}$ 5.2 Hz, H-3), 4.28 (m, 1H, H-5), 3.97 (t, 1H, $J_{6a,6b}$ 8.4 Hz, H-6a); 3.83 (d, 1H, $J_{1a,1b}$ 10.0 Hz, H-1a), 3.67 (d, 1H, $J_{1a,1b}$ 10.0 Hz,

Table 4. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for compounds **2** and **5**

Atoms	*x*	*y*	*z*	*U*(eq)	Atoms	*x*	*y*	*z*	*U*(eq)
2									
O(1)	−1828(4)	2754(3)	1413(1)	52(1)	C(1)	−613(6)	1193(5)	1146(2)	52(1)
O(2)	3592(4)	505(3)	876(1)	51(1)	C(2)	2082(6)	1498(4)	1272(1)	42(1)
O(3)	2929(4)	4167(3)	637(1)	49(1)	C(3)	2272(6)	3642(4)	1232(1)	44(1)
O(4)	−2262(5)	4420(4)	338(1)	64(1)	C(4)	−328(6)	4334(5)	1329(1)	47(1)
O(5)	867(7)	−1808(5)	2095(2)	102(1)	C(5)	−902(6)	5480(5)	758(2)	51(1)
O(6)	4679(9)	−2000(5)	1928(2)	105(1)	C(6)	1581(6)	5830(5)	502(2)	54(1)
N(1)	2806(8)	−1103(5)	1984(1)	64(1)	C(7)	2894(7)	958(4)	1899(1)	49(1)
5									
O(1)	11,693(2)	12,396(2)	7671(1)	37(1)	C(3)	12,962(3)	10,198(2)	7939(1)	30(1)
O(2)	8636(2)	10,068(2)	7921(1)	32(1)	C(4)	13,705(4)	11,547(2)	7593(1)	33(1)
O(3)	12,687(3)	9314(2)	7260(1)	38(1)	C(5)	14,194(4)	11,260(2)	6693(1)	35(1)
O(4)	14,004(3)	12,340(2)	6147(1)	44(1)	C(6)	12,545(4)	10,107(3)	6529(2)	41(1)
N(1)	10,514(4)	8409(2)	9214(2)	40(1)	C(7)	10,501(4)	9874(3)	9260(1)	34(1)
C(1)	10,568(4)	11,984(2)	8410(2)	35(1)	C(8)	8329(4)	10,301(3)	9730(2)	48(1)
C(2)	10,592(3)	10,476(2)	8402(1)	28(1)					

U(eq) is defined as one-third of the trace of the orthogonalized *Uij* tensor.

H-1b), 3.60 (t, 1H, $J_{6a,6b}$ 8.4 Hz, H-6b), 2.89 (q, 1H, $J_{7,8}$ 6.8 Hz, H-7), 0.99 (d, 3H, H-8); ^{13}C NMR (100.6 MHz, D_2O): δ 84.4 (C-3), 82.7 (C-2), 82.1 (C-4), 74.8 (C-1), 71.5 (C-6), 71.0 (C-5), 50.3 (C-7), 15.9 (C-8); HRMS: calcd for $C_8H_{15}NO_4$: 189.1001, found: 190.1083 $[M+H]^+$, 212.0905 $[M+Na]^+$.

3.7. 1,4:3,6-Dianhydrofructose oxime (9)

A mixture of **1** (1.44 g, 10 mmol), hydroxylamine sulfate (984 mg, 6 mmol), and MeOH (20 mL) was stirred at ambient temperature for 10 h. Aq NaOH was added to adjust the pH value of the mixture to pH 7.0–7.5. Subsequent filtration, concentration, and recrystallization from MeOH furnished oxime **9** (1.46 g, 92%). Mp 143–145 °C, $[\alpha]_D^{20}$ +129.0 (*c* 0.486, CH_3OH), IR (KBr): 3367, 3298, 3134, 2956, 2873, 1468, 1399, 1110, 1078, 1043, 959, 827, 721 cm^{-1}; ^{1}H NMR (400.1 MHz, D_2O): δ 4.68 (d, 1H, $J_{1a,1b}$ 16.4 Hz, H-1a), 4.58 (d, 1H, $J_{1a,1b}$ 16.4 Hz, H-1b), 4.94 (d, 1H, $J_{3,4}$ 4.8 Hz, H-3), 4.67 (t, 1H, $J_{3,4}$ 4.8 Hz, H-4), 4.40 (m, 1H, H-5), 3.98 (dd, 1H, $J_{5,6a}$ 6.4, $J_{6a,6b}$ 8.8 Hz, H-6a), 3.60 (t, 1H, $J_{6a,6b}$ 8.4 Hz, H-6b); ^{13}C NMR (100.6 MHz, D_2O): δ 161.9 (C-2), 82.3 (C-4), 79.5 (C-3), 71.6 (C-5), 70.3 (C-6), 66.7 (C-1); HRMS: calcd for $C_6H_9NO_4$: 159.0532, found: 160.0607 $[M+H]^+$, 198.0190 $[M+K]^+$.

3.8. 2-Amino-1,4:3,6-dianhydro-2-deoxymannitol (2-amino-2-deoxyisomannide, 10)

Oxime **9** (1.11 g, 7.0 mmol) was dissolved in MeOH (120 mL), to which catalyst Raney Ni (0.55 g) was added. The mixture was hydrogenated at 40 °C under 50 psi for 8 h, followed by filtration and concentration, to give a residue. The residue was recrystallized from MeOH to afford product **10** as a white solid (0.83 g, 82%). Mp 117–118 °C, $[\alpha]_D^{20}$ +70.0 (*c* 0.218, CH_3OH); IR (KBr): 3428, 3183, 2947, 2881, 1650, 1621, 1544, 1505, 1411, 1044 cm^{-1}; ^{1}H NMR (400.1 MHz, D_2O): δ 4.53 (t, 1H, $J_{3,4}$ 5.2 Hz, H-3), 4.46 (dd, 1H, $J_{4,5}$ 4.4, $J_{3,4}$ 5.2 Hz, H-4), 4.23 (m, 1H, H-5), 4.00 (dd, 1H, $J_{1b,2}$ 7.2, $J_{1a,1b}$ 9.2 Hz, H-1b), 3.84 (dd, 1H, $J_{5,6a}$ 6.0, $J_{6a,6b}$ 9.2 Hz, H-6a), 3.68 (m, 1H, H-2), 3.56 (t, $J_{1a,1b}$ 8.8 Hz, H-1a), 3.46 (dd, 1H, $J_{5,6b}$ 7.2, $J_{6a,6b}$ 9.2 Hz, H-6b). ^{13}C NMR (100.6 MHz, D_2O): δ 82.6 (C-4), 80.5 (C-3), 72.5 (C-6), 71.3 (C-5), 70.6 (C-1), 52.8 (C-2); HRMS: calcd for $C_6H_{11}NO_3$: 145.0739, found: 146.0820 $[M+H]^+$.

4. Supplemental data

Complete crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 285771 (**2**) and CCDC No. 285772 (**5**). Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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