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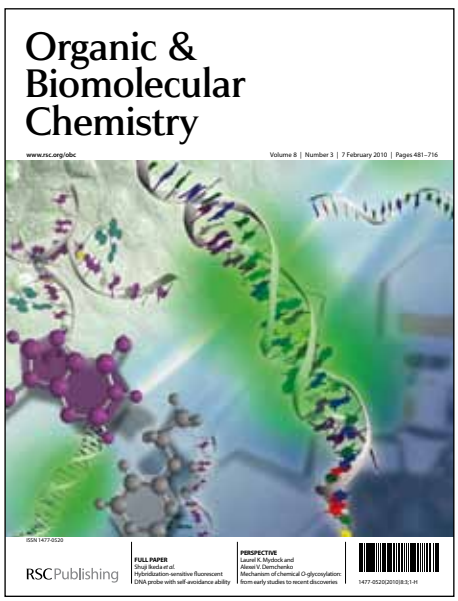

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ARTICLE TYPE

Highly Stereoselective Directed Reactions and an Efficient Synthesis of Azafuranose from a Chiral Aziridine

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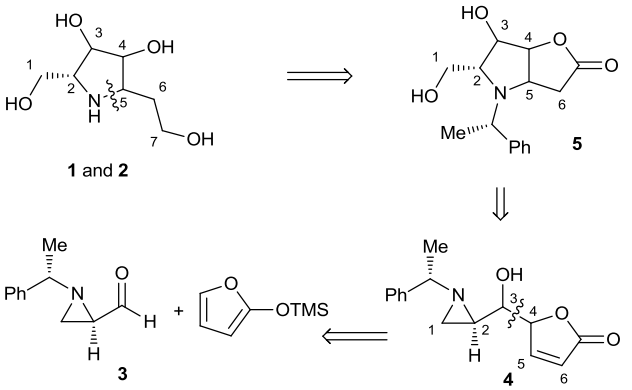
Polyhydroxylated pyrrolidines, as biologically important azafuranose represented by the natural product (+)-2,5-imino-2,5,6-trideoxy-*gulo*-heptitol and its C(3)-epimer, were elaborated from a commercially available enantiomerically pure (2*R*)-hydroxymethylaziridine by highly stereoselective directed reactions in more than 61% overall yield. At first, the nucleophile trimethylsilyloxyfuran was directed to (2*R*)-aziridine-2-carboxaldehyde by $ZnBr_2$ to yield the unusual *anti*-addition product as a single isomer rose from the chelation-controlled transition. The ring-opening of aziridine was followed by conjugate addition to give a *cis*-fused bicycle, which was converted to the target molecule after required reductive operations.

Introduction

Syntheses and structural evaluations of azasugars have attracted great attention due to their biological activities, such as glycosidase and glycosyltransferase inhibitors in the sugar metabolism.[1] Recently, (+)-2,5-imino-2,5,6-trideoxy-*gulo*-heptitol (**1**) and its stereoisomers were isolated from *Hyacinthus orientalis*, and they were found to show specific glycosidase-inhibiting properties.[2] An efficient and stereoselective synthesis of aza-sugars[3] is still needed to overcome the drawbacks of most reported methods[4] including the difficulties of obtaining starting materials and the formation of unwanted diastereoisomers. Most synthetic pathways required to introduce an hydroxyethyl side chain or its equivalent whose stereoselectivity was poor.[4] As part of our chiral aziridine program, we succeeded in the asymmetric synthesis of azapyranose sugar.[5] This time, we would like to develop highly efficient and stereoselective synthesis of azafuranose, specifically, (+)-2,5-imino-2,5,6-trideoxy-*gulo*-heptitol (**1**) and its C(3)epimer **2** through the highly stereoselective directed reactions.



Scheme 1 Retrosynthetic analysis of (+)-2,5-imino-2,5,6-trideoxy-*gulo*-heptitol

The target azafuranose, (+)-2,5-imino-2,5,6-trideoxy-*gulo*-heptitol (**1**), includes a pyrrolidine ring, which could be elaborated by the intramolecular conjugated addition of the amine liberated from the aziridine ring-opening reaction of the synthetic intermediate **4** (Scheme 1). The compound **3**, bearing all necessary carbons, should be derived from the addition reaction of 2-trimethylsilyloxyfuran to aziridine-2-carboxaldehyde. Other than the stereochemistry at C5 of the pyrrolidine ring, all stereocenters, including C2, C3, and C4, should be generated from the reactions, including the addition of 2-trimethylsilyloxyfuran to the aziridne-2-carboxaldehyde (**3**) and the subsequent intramolecular conjugate addition of the amine to the 2,5-didhydrofuran-2-one in the compound **4**. Our previous study[6] encouraged us to apply the highly stereoselective directed reactions. The stereochemistry of alcohol in the compound **4** will

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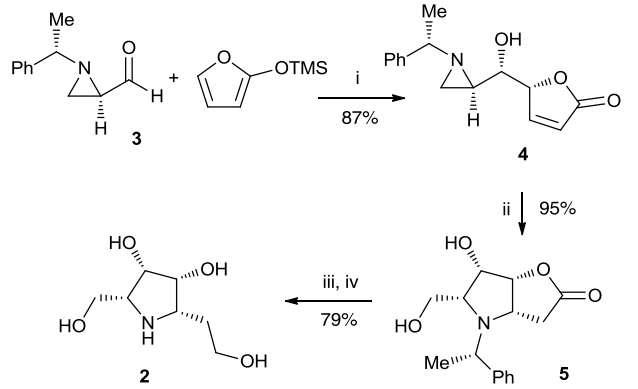
be generated from the chelation-controlled addition of the nucleophile whose alignment will guide the facial selectivity of 2-trimethylsilyloxyfuran to establish the configuration of a lactone ring. The aziridine ring opening by an oxygen nucleophile and the subsequent conjugate addition of the released amine to α,β-unsaturated lactone ring yield the bicyclic adduct **5**, with the final C-N bond formation for the pyrrolidine ring. All necessary carbons with proper stereochemistry in the compound **5** will afford the targets after necessary reductive operations.

Results and discussion

The starting material (1*S*)-phenylethylaziridine-(2*R*)-carboxaldehyde (**3**) was prepared from the commercially available corresponding alcohol in 95% yield.[7] The addition of 2-trimethylsilyloxyfuran to the aldehyde **3** in the presence of $ZnBr_2$ (1.5 eq) in THF at 0 °C provided the coupled product **4** as a single isomer in 87% yield. The absolute configurations of the secondary alcohol in **4** can be predicted based on our previously known metal-catalyzed addition reaction of 2-acyl- and 2-iminoaziridines with chelation-controlled transition states.[8] However, the absolute configuration of the lactone site was not clear at this stage. Therefore, we proceeded with regioselective aziridine ring-opening reaction using trifluoroacetic acid in H_2O:THF (4:1) to obtain the bicyclic compound **5** in 95% yield.[9] The product **5** bearing the [5,5']-fused ring system was generated from the intramolecular cyclization of the amine derived from the aziridine ring-opening reaction to the α,β-unsaturated lactone ring. The stereochemistry of the newly formed C-N bond for the ring was controlled only by the configuration of the lactone to lead to [5,5']-bicyclic compound (Scheme 2). Obtaining a good crystalline derivative of this bicycle for X-ray analysis the two hydroxyl groups were reacted with *p*-nitrobenzoyl chloride and Et_3N in CH_2Cl_2 to yield the corresponding ester **6** as a solid in 90% yield.



Scheme 2 Synthesis of the C(3) epimer of the natural product (+)-2,5-imino-2,5,6-trideoxy-*gulo*-heptitol. Reagents and conditions: (i) $ZnBr_2$ (1.5 eq.), THF (0.1 M; (ii) TFA (5 eq.), H_2O:THF (4:1); (iii) $BH_3{\cdot}SMe_2$ (4 eq.) THF; (iv) H_2 (1 atm), $Pd(OH)_2$, MeOH (0.1 M).

The compound **6** was purified by recrystallization and we obtained X-ray crystalline structure (Figure 1) to confirm the absolute configurations of the consecutive four carbon centres. The crystalline structure clearly shows *cis*-fused [5,5']-bicycle with the configuration at carbon centres as 2*R*, 3*S*, 4*R* and 5*S*. This stereochemical outcome clearly indicates that the configurations of the secondary alcohol and its adjacent lactone ring in the compound **4** are *S* and *R*, respectively.

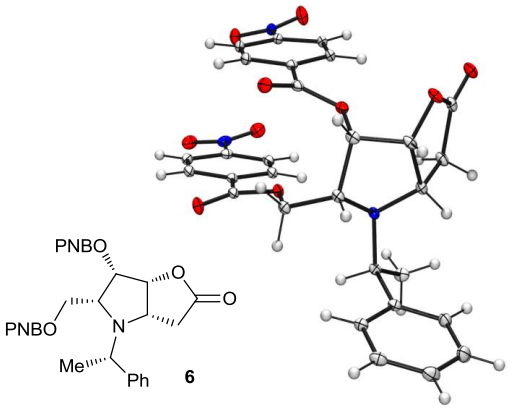
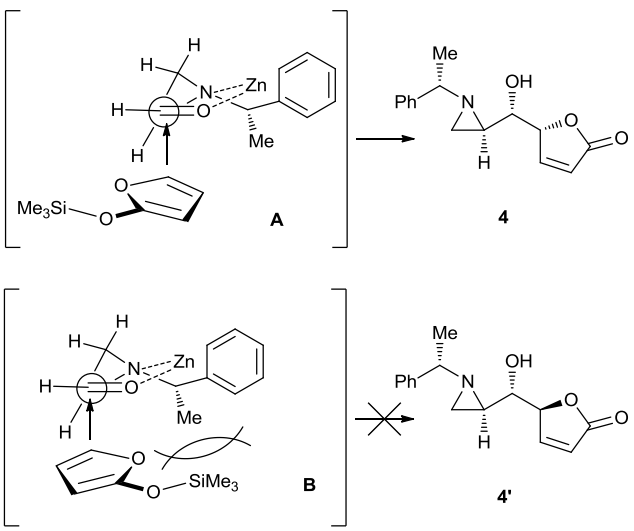


Fig 1 ORTEP Drawing of the bicyclic compound **6**

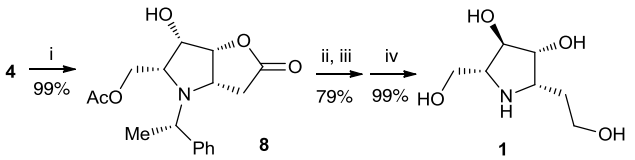
The addition of the nucleophile 2-trimethylsilyloxyfuran to the aziridine-2-carboxaldehyde was directed by the chelation-controlled transition state as expected. However, the stereochemistry of the alcohol and the lactone ring had an unusual *anti*-relationship. Most cases of vinylogous aldol reactions[10] with silyloxyfuran yield the *syn*-adduct with "Diels-Alder-like" orientation of the two reactants in the s-*trans* conformation.[11] This unusual *anti*-relationship can possibly be explained by the formation of the pre-associated chelation-controlled transition state between aziridine and aldehyde (Scheme 3). Once this was generated the transition state **A** leading to the unusual *anti*-adduct **4** is more favourable to avoid the non-bonding interaction between the 2-phenylethyl group and the silicon substituent rather than the "Diels-Alder-like" transition state **B**.



Scheme 3 Possible transition structures of the addition of 2-trimethylsilyloxyfuran to aziridine-2-carboxaldehyde

The next operation was the aziridine ring opening[12] by the oxygen nucleophile to release the amine which is ready to react with the β-position of the α,β-unsaturated lactone via conjugate addition.[13] The stereochemical pathway of this conjugate addition was pre-determined by the configuration of the lactone to lead *cis*-fused [5,5']-bicyclic compound **5** without any other choice. The whole sequence of the reactions was directed as one by one, i.e. the first chelation-controlled transition of the nucleophilic addition in aziridine-2-carboxaldehyde directed the facial selectivity of the silyloxyfuran ring and then this adduct lead the stereochemical pathway of the conjugate addition.[14] After establishment of the absolute configuration, the lactone moiety of **5** was reduced with $BH_3{\cdot}SMe_2$ in THF to the corresponding tetraol **7** in 79% yield and the following hydrgenolytic cleavage of the *N*-benzyl group provided the C(3)-epimer **2** of the natural product **1** in quantitative yield (Scheme 2). We also synthesized the enantiomer of **2** (**ent-2**) starting from the enantiomer of starting material, (1*R*)-phenylethylaziridine-(2*S*)-carboxaldehyde.

The target natural product, (+)-2,5-imino-2,5,6-trideoxy-*gulo*-heptitol (**1**), has 3*R* configuration of the hydroxide which is opposite stereochemistry in the initial adduct **4**. We succeeded the synthesis of the natural product involving the inversion of the hydroxy configuration by the Mitsunobu reaction (Scheme 4).



Scheme 4 Synthesis of the natural product (+)-2,5-imino-2,5,6-trideoxy-*gulo*-heptitol. Reagents and conditions: (i) AcOH (5 eq.), CH_2Cl_2; (ii) 1) PPh_3 (2 eq.) PNBA (2 eq.) DIAD (2 eq.), Toluene, RT to 100 °C, (iii) $BH_3{\cdot}SMe_2$ (15 eq.), THF; (iv) H_2 (1 atm), $Pd(OH)_2$, MeOH (0.1M).

For the convenience of the Mitsunobu reaction to invert the configuration of C3 of the bicycle we performed regioselective aziridine ring-opening reaction[12] of **4** with AcOH (5 eq.) in CH_2Cl_2 instead of H_2O to provide the fused lactone **8** in quantitative yield.[15] The reaction of **8** with Ph_3P (2 eq.) and *p*-nitrobenzoic acid (PNBA, 2 eq.) in the presence of DIAD (2 eq.) in toluene at 100 °C provided an inversion product[16] as the benzoate which was reduced in the aforementioned method with $BH_3{\cdot}SMe_2$ in THF (15 eq.) at 50 °C to result in the tetraol **9** in 78% yield. The reductive cleavage of the *N*-benzyl group by catalytic hydrogenation with $Pd(OH)_2{\cdot}C$ in MeOH produced the target molecule **1** as a free base in 99% yield. The enantiomer of the target molecule (**ent-1**) was also prepared from the (1*R*)-phenylethylaziridine-(2*S*)-carboxaldehyde.

Conclusions

In conclusion we successfully synthesized the natural product (+)-2,5-imino-2,5,6-trideoxy-*gulo*-heptitol and its C(3)-epimer from an enantiomerically pure commercial (2*R*)-hydroxymethylaziridine by the highly stereoselective directed reactions in more than 61% overall yield. The key steps include the nucleophilic *anti*-addition of 2-trimethylsilyloxyfuran to (2*R*)-aziridine-2-carboxaldehyde with $ZnBr_2$, and the conjugate addition of the amine released from the ring-opening reaction of aziridine.

Experimental

General experimental procedures

All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Air sensitive reagents and solutions were transferred via syringe and were introduced to the apparatus through rubber septa. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Dichloromethane was distilled from calcium hydride. MeOH was commercial grade reagents (99.9 % assay) and used without further purification. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, or by immersion in solutions of ninhydrin, *p*-anisaldehyde, or phosphomolybdic acid (PMA) followed by heating on a hot plate for about 10 sec. Purification of reaction products was carried out by flash chromatography using Kieselgel 60 Art 9385 (230-400 mesh). ^{1}H-NMR and ^{13}C-NMR spectra were obtained using a Varian Vnmr-400 (400 MHz for ^{1}H, and 100 MHz for ^{13}C), or a Varian Inova-500 (500 MHz for ^{1}H, and 125 MHz for ^{13}C) spectrometer. Chemical shifts are reported relative to chloroform (δ = 7.26) for ^{1}H NMR and chloroform (δ = 77.2) for ^{13}C NMR. Data are reported as (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.) Coupling constants are given in Hz. Ambiguous assignments were resolved on the basis of standard one dimensional proton decoupling experiments. Optical rotations were determined at 589 nm at 26°C. Data are reported as follows: $[\alpha]_D^{24}$, concentration (c in g/100 mL), and solvent. Elemental analyses were performed using a Carlo Erba EA 1180 elemental analyzer. High resolution mass spectra were recorded on a 4.7 Tesla IonSpec ESI-FOFMS and JEOL (JMS-700). All commercially available compounds were used as received unless stated otherwise.

(*R*)-5-((*S*)-hydroxy((*R*)-1-((*S*)-1-phenylethyl)aziridin-2-yl)methyl)furan-2(5H)-one (4)

To a solution of zinc bromide (1427 mg, 6.34 mmol) in 35.0 mL in THF of under nitrogen atmosphere at 0 ℃ was added 2-(trimethylsilyloxy)furan (0.93 mL, 5.50 mmol). The mixture was stirred for 10 min and then treated with (*R*)-1-((*S*)-1-phenylethyl)aziridine-2-carbaldehyde **3** (740 mg, 4.23 mmol) in 7.0 mL of THF *via* cannula at 0 ℃. The mixture was stirred for 1 h 30 min at 0 ℃ and then treated with sat'd sodium bicarbonate solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc (40.0 mL × 4). The combined extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed and purification by silica gel flash chromatography (EtOAc:hexane, 50:50) gave 4 in 952 mg (87 %) yield as yellow solid: (**4**) $[\alpha]_D^{24}$ = -17.6 (c = 1.00, in $CHCl_3$), (ent-4) $[\alpha]_D^{24}$ = +19.4 (c = 1.20, in $CHCl_3$); mp 115-117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H, arom. H), 7.30-7.24 (m, 1H, C5), 6.01 (m, 1H, C6), 3.87 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H, C3), 3.23 (t, J = 7.6 Hz, 1H, C4), 2.87 (d, J = 7.2, 1H, C2), 2.68 (q, 1H, -$CHCH_3$), 2.08 (m, 1H, C2), 1.97 (dd, J_1 = 6.4 Hz, J_2 = 0.8 Hz, 1H, C1), 1.65 (dd, J_1 = 6.4 Hz, J_2 = 0.4 Hz, 1H, C1), 1.48 (dd, J_1 = 6.4 Hz, J_2 = 0.8 Hz, 3H, -$CHCH_3$). ^{13}C NMR (100 MHz,

$CDCl_3$): δ 182.9, 155.7, 143.6, 128.7, 127.9, 127.1, 121.7, 84.8, 69.4, 68.6, 38.3, 30.5, 21.9; Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.42; H, 6.68; N, 5.35.

(3a*S*,5*R*,6*S*,6a*R*)-6-hydroxy-5-(hydroxymethyl)-4-((*S*)-1-phenylethyl)hexahydro-2H-furo[3,2-b]pyrrol-2-one (5).

To a solution of **4** (276 mg, 1.07 mmol) in 2.10 mL of H_2O and 8.50 mL of THF was added trifluoroacetic acid (0.41 mL, 1.13 mmol). The mixture was stirred for 15 h, and then treated with $NaHCO_3$ saturated solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc (5.0 mL × 4). The combined extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was concentrated and purification by silica gel flash chromatography (EtOAc:hexane, 70:30) gave **5** in 278 mg (95 %) yield as yellow liquid: (**5**) $[\alpha]_D^{24}$ = -4.0 (c = 1.56, in $CHCl_3$), (**ent-5**) $[\alpha]_D^{24}$ = +3.7 (c = 1.13, in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.34 (m, 2H, arom. H), 7.33-7.29 (m, 1H, arom. H), 7.28-7.24 (m, 3H, arom. H), 4.70 (dd, J_1 = 6.8 Hz, J_2 = 5.2 Hz, 1H, C4), 4.37 (q, J = 6.4 Hz, 1H, C3), 4.00 (q, J = 6.8 Hz, 1H, -$CHCH_3$), 3.88 (td, J_1 = 7.2 Hz, J_2 = 4.0 Hz, 1H, C5), 3.54-3.52 (m, 2H, C1), 3.22 (m, 1H, C2), 3.04 (d, J = 7.2 Hz, 1H, -OH), 2.69 (dd, J_1 = 17.6 Hz, J_2 = 6.8 Hz, 1H, C6), 2.60 (dd, J_1 = 17.6 Hz, J_2 = 4.0 Hz, 1H, C6), 2.34 (dd, J_1 = 7.6 Hz, J_2 = 4.8 Hz, 1H, -OH), 1.49 (d, J = 7.2 Hz, 3H, -$CHCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 141.0, 128.6, 127.8, 127.7, 82.1, 73.0, 62.7, 60.8, 57.9, 57.6, 38.7, 18.8; HRMS m/z calcd for $C_{15}H_{19}NO_4$: $[M+Na]^+$300.1206 Found 300.1210.

((3a*S*,5*R*,6*S*,6a*R*)-6-((4-nitrobenzoyl)oxy)-2-oxo-4-((*S*)-1-phenylethyl)hexahydro-2H-furo[3,2-b]pyrrol-5-yl)methyl 4-nitrobenzoate (6).

To a solution of **5** (66 mg, 0.238 mmol) in 2.40 mL of dichloromethane under nitrogen atmosphere at 0 ℃ was added p-nitrobenzoyl chloride (132 mg, 0.714 mmol), and triethylamine (0.10 mL, 0.729 mmol). The mixture was warmed to room temperature and stirred for 4 h, and then treated with ammonium chloride saturated solution. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (5.0 mL × 4). The combined extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was concentrated and purification by silica gel flash chromatography (dichloromethane:EtOAc, 50:1) gave **6** in 124 mg (90 %) yield as yellow solid: (**6**) $[\alpha]_D^{24}$ = -140.1 (c = 2.15, in $CHCl_3$), (**ent-6**) $[\alpha]_D^{24}$ = +135.4 (c = 1.13, in $CHCl_3$); mp 79-80 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26-8.12 (m, 6H, arom. H), 8.04-7.98 (m, 2H, arom. H), 7.42-7.28 (m, 5H, arom. H), 5.56 (dd, J_1 = 6.8 Hz, J_2 = 5.2 Hz, 1H, C4), 4.97 (dd, J_1 = 6.4 Hz, J_2 = 5.2 Hz, 1H, C3), 4.52-4.38 (m, 2H, C1), 4.11 (q, 1H, -CHCH3), 4.01 (td, J_1 = 6.8 Hz, J_2 = 7.2 Hz, 1H, C5), 3.89 (m, 1H, C2), 2.70 (dd, J_1 = 18.4 Hz, J_2 = 7.2 Hz, 1H, C6), 2.60 (dd, J_1 = 18.0 Hz, J_2 = 2.8 Hz, 1H, C6), 1.57 (d, J = 6.8 Hz, 3H, -$CHCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 164.1, 163.7, 150.8, 150.5, 140.5, 134.8, 134.1, 130.9, 130.6, 128.8, 128.2, 127.7, 123.7, 123.5, 80.7, 73.0, 59.7, 58.1, 38.8, 19.4, 14.2; Anal. Calcd for $C_{29}H_{25}N_3O_{10}$: C, 60.52; H, 4.38; N, 7.30. Found: C, 60.56; H, 4.51; N, 7.44.

(2*S*,3*R*,4*S*,5*R*)-2-(2-hydroxyethyl)-5-(hydroxymethyl)-1-((*S*)-1-phenylethyl)pyrrolidine-3,4-diol (7).

To a solution of **5** (42 mg, 0.152 mmol) in 0.51 mL of THF under nitrogen atmosphere at room temperature was added borane dimethyl sulfide complex (0.30 mL, 2.00 M) in THF. The mixture was stirred for 4 h at room temperature, and then treated with MeOH slowly. The solvent was removed and purification by silica gel flash chromatography (MeOH:EtOAc, 20:80) gave **7** in 34 mg (79 %) yield as yellow liquid: (**7**) $[\alpha]_D^{24}$ = +28.4 (c = 2.00, in $CHCl_3$), (**ent-7**) $[\alpha]_D^{24}$ = -27.1 (c = 4.81, in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.18 (m, 5H, arom. H), 4.21 (m, 1H), 4.12 (q, 1H), 4.03 (m, 1H), 3.82 (m, 2H, C1 or C7), 3.39 (d, J = 10.8 Hz, 1H), 3.25 (m, 2H, C1 or C7), 2.45 (dd, J_1 = 9.6 Hz, J_2 = 4.0 Hz, 1H), 2.01 (m, 2H, C6), 1.41 (d, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 128.4, 127.7, 127.3, 72.4, 72.3, 61.1, 60.0, 59.4, 58.8, 56.0, 32.0, 11.4; HRMS m/z calcd for $C_{15}H_{23}NO_4$: $[M+Na]^+$304.1519 Found 304.1530.

(2*S*,3*R*,4*S*,5*R*)-2-(2-hydroxyethyl)-5-(hydroxymethyl)pyrrolidine-3,4-diol (2).

To a solution of **7** (27 mg, 0.096 mmol) in 1.40 mL of MeOH was added palladium hydroxide on carbon (2.7 mg, 10 wt %). The resultant mixture was stirred for 7 h under at atmospheric pressure of H_2. The mixture was filtered and the filtrate was concentrated under vacuo to provide **2** in 17 mg (99 %) yield as yellow liquid: (**2**) $[\alpha]_D^{24}$ = +17.2 (c = 0.50, in MeOH), (**ent-2**) $[\alpha]_D^{24}$ = -18.4 (c = 0.63, in MeOH); ^{1}H NMR (400 MHz, D_2O): δ 4.38 (dd, J_1 = 7.2 Hz, J_2 = 4.8 Hz, 1H, C3), 4.11 (t, 1H, C4), 3.75 (dd, J_1 = 11.6 Hz, J_2 = 4.8 Hz, 1H, C1 or C7), 3.70-3.62 (m, 3H, C1 and C7), 3.33 (q, J = 6.4 Hz, 1H, C2), 3.17 (dd, J_1 = 11.6 Hz, J_2 = 7.2 Hz, 1H, C5), 1.95-1.85 (m, 1H, C6), 1.76 (m, J = 6.8 Hz, 1H, C6). ^{13}C NMR (100 MHz, D_2O): δ 71.83, 71.79, 71.67, 59.77, 59.04, 56.47, 30.61; HRMS m/z calcd for $C_7H_{15}NO_4$: $[M+Na]^+$200.0899 Found 200.0893.

((3a*S*,5*R*,6*S*,6a*R*)-6-hydroxy-2-oxo-4-((*S*)-1-phenylethyl)hexahydro-2H-furo[3,2-b]pyrrol-5-yl)methyl acetate (8).

To a solution of **4** (762 mg, 2.94 mmol) in 29.0 mL of dichloromethane under nitrogen atmosphere at room temperature was added acetic acid (14.7 mmol, 0.28 mL). The mixture was stirred for 15 h at room temperature, and then treated with sat'd sodium bicarbonate solution. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (5.0 mL × 4). The combined extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed and purification by silica gel flash chromatography (EtOAc:hexane, 50:50) gave **8** in 938 mg (100 %) yield as yellow solid: (**8**) $[\alpha]_D^{24}$ = -22.0 (c = 6.63, in CHCl3), (**ent-8**) $[\alpha]_D^{24}$ = +22.8 (c = 2.44, in $CHCl_3$); mp 112-114 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.25 (m, 5H, arom. H), 4.64 (dd, J_1 = 7.6 Hz, J_2 = 5.2 Hz, 1H, C4), 4.25 (m, 3H, C1 and C3), 4.01 (q, J = 3.4 Hz, 1H, -$CHCH_3$), 3.85 (dt, J_1 = 12 Hz, J_2 = 7.2 Hz, 1H, C5), 3.28 (dd, J_1 = 10.8 Hz, J_2 = 6.0 Hz, 1H, C2), 2.59 (m, 2H, C6), 2.08 (s, 3H, -$OCOCH_3$), 1.47 (d, J = 7.2 Hz, 3H, -$CHCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 171.322, 140.6, 128.5, 127.8, 127.7, 81.6, 71.3, 62.7, 61.8, 58.414, 57.139, 38.8, 21.0, 19.5; Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.97; H, 6.60; N, 4.40.

(2*S*,3*R*,4*R*,5*R*)-2-(2-hydroxyethyl)-5-(hydroxymethyl)-1-((S)-1-phenylethyl)pyrrolidine-3,4-diol (9).

To a solution of **8** (92 mg, 0.288 mmol) in 2.90 mL of toluene under nitrogen atmosphere at room temperature was added triphenylphosphine (151 mg, 0.576 mmol), diisopropyl azodicarboxylate (DIAD) (0.11 mL, 0.576 mmol), and *p*-

nitrobenzoic acid (96 mg, 0.576 mmol). The mixture was stirred for 5 h at 100 ℃ and cooled to room temperature, and then treated with water. The organic layer was separated, and the aqueous layer was extracted with EtOAc (5.0 mL × 4). The combined extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was concentrated and purification by silica gel flash chromatography (EtOAc:hexane, 30:70) gave the corresponding *p*-nitrobenzoate product. To the benzoate was added borane dimethyl sulfide complex in THF (2.20 mL, 2.00 M) under nitrogen atmosphere at room temperature. The mixture was stirred for 4 h at 50 ℃, and then treated with MeOH slowly. The organic layer was concentrated and purification by silica gel flash chromatography (MeOH:EtOAc, 20:80) gave **9** in 63 mg (78 %) yield as yellow liquid: **(9)** $[\alpha]_D^{24}$ = +11.0 (c = 3.67, in $CHCl_3$), **(ent-9)** $[\alpha]_D^{24}$ = -11.6 (c = 1.03, in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.28 (m, 4H), 7.28-7.24 (m, 1H), 4.50 (s, 4H), 4.02 (q, *J* = 6.4 Hz, 1H), 3.97 (m, 1H), 3.81 (t, *J* = 6.0, 1H), 3.72 (m, 1H), 3.63 (m, 1H), 3.33 (m, 2H), 2.95 (m, 2H), 1.84 (m, 1H), 1.70 (m, 1H), 1.44 (d, *J* = 6.4, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.6, 128.5, 127.8, 127.5, 77.6, 76.1, 64.1, 61.3, 60.0, 58.2, 32.4, 14.8; HRMS m/z calcd for $C_{15}H_{23}NO_4$: $[M+H]^+$ 282.1700, Found 282.1700.

2,5-Imino-2,5,6-trideoxy-*L-gulo*-heptitol (1).

To a solution of **9** (23 mg, 0.082 mmol) in 1.20 mL of MeOH was added palladium hydroxide on carbon (2.3 mg, 10 wt %). The mixture was stirred for 7 h under at atmospheric pressure of H_2. The mixture was filtered and concentrated under vacuo to give **1** in 14 mg (99 %) yield as yellow liquid: **(1)** $[\alpha]_D^{24}$ = +20.8 (c = 0.19, in MeOH), **(ent-1)** $[\alpha]_D^{24}$ = -21.5 (c = 0.69, in MeOH); ^{1}H NMR (400 MHz, D_2O): δ 3.95 (m, 1H), 3.85 (m, 1H), 3.74-3.60 (m, 4H), 3.20 (q, *J* = 7.6 Hz, 1H), 2.93 (q, *J* = 6.0 Hz, 1H), 1.89-1.76 (m, 1H), 1.75-1.65 (m, 1H). ^{13}C NMR (100 MHz, D_2O): δ 76.0, 75.5, 67.4, 60.2, 59.7, 58.3, 27.7; HRMS m/z calcd for $C_7H_{15}NO_4$: $[M+H]^+$178.1074, Found 178.1082.

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Notes and references

1 (a) G. Legler, in *Iminosugars as Glycosidase Inhibitors*, eds. A. E. Stütz, Wiley-VCH, Inc., New York, 1998, ch. 3, pp. 31-67. (b) N. Asano, in *Iminosugars*, eds. P. Compain and O. R. Martin, John Wiley and Sons, Inc., New York, 2007, Chap 1, pp. 7-24. (c) N. Asano, in *Modern Alkaloids*, eds. E. Fattorusso and O. Taglialatela-Scafati, Wiley-VCH, inc., Weinheim, 2008, ch. 5, pp. 111-138. (d) I. Robina, A. J. Moreno-Vargas, A.-T. Carmona abd P. Vogel, *Curr. Drug Metabol.*, 2004, **5**, 329. (e) M. S. M. Pearson, M. Mathé-Allainment, V. Fargeas and J. Lebreton, *Eur. J. Org. Chem.*, 2005, **11**, 2159.

2 (a) N. Asano, K. Yasuda, H. Kizu, A. Kato, J.-Q. Fan, R. J. Nash, G. W. J. Fleet and R. J. Molyneux, *Eur. J. Biochem.*, 2001, **268**, 35. (b) X. Kato, I. Adachi, M. Miyauchi, K. Ikeda, T. Komae, H. Kizu, Y. Kameda, A. A. Watson, R. J. Nash, M. R. Wormald, G. W. J. Fleet and N. Asano, *Carbohydrate Research*, 1999, **316**, 95. (c) T. Yamashita, K. Yasuda, H. Kizu, Y. Kameda, A. A. Watson, R. J. Nash, G. W. J. Fleet and N. Asano, *J. Nat. Prod.*, 2002, **65**, 1875. (d) N. Asano, R. J. Nash, R. J. Molyneux and G. W. Fleet, *Tetrahedron: Asymmetry*, 2000, **11**, 1645.

3 (a) N. Asano, R. J. Nash, R. J. Molyneux and G. W. Fleet, *Tetrahedron: Asymmetry*, 2000, **11**, 1645. (b) J.-B. Behr and G. Guillerm, *Tetrahedron: Asymmetry*, 2002, **13**, 111.

4 (a) J.-B. Behr, M. S. M. Pearson, C. Bello, P. Vogel and R. Plantier-Royon, *Tetrahedron: Asymmetry*, 2008, **19**, 1829. (b) M. Kummeter and U. Kazmaier, *Eur. J. Org. Chem*., 2003, **17**, 3330. (c) Y. Chikawa, Y. Igarashi, M. Ichikawa and Y. Suhara, *J. Am. Chem. Soc*., 1998, **120**, 3007. (d) A. Guaragna, S. D'Errico, D. D'Alonzo, S. Pedatella and G. Palumbo, *Org. Lett.*, 2007, **9**, 3473.

5 A. Singh, B. C. Kim, W. K. Lee and H.-J. Ha, *Org. Biomol. Chem.*, 2011, **9**, 1372.

6 (a) H. J. Yoon, Y.-W. Kim, B. K. Lee, W. K. Lee, Y. Kim and H.-J. Ha, *Chem. Commun*., 2007, **1**, 79. (b) H. G. Choi, J. H. Kwon, J. C. Kim, W. K. Lee, H. Eum and H.-J. Ha, *Tetrahedron Lett.*, 2010, **51**, 3284.

7 W. K. Lee and H.-J. Ha, *Aldrichimica Acta*, 2003, **36**, 57.

8 (a) J. M. Yun, T. B. Sim, H. S. Hahm, W. K. Lee and H.-J. Ha, *J. Org. Chem*., 2003, **68**, 7675. (b) M.-J. Suh, S. W. Kim, S. I. Beak, H.-J. Ha and W.-K. Lee, *Synlett.*, 2004, **3**, 489.

9 F. A. Davis and G. V. Reddy, *Tetrahedron Lett.*, 1996, **37**, 4349.

10 For reviews, see. (a) G. Casiraghi, L. Battistini, C. Curti, G. Rassu, and F. Zanardi, *Chem. Rev.*, 2011, **111**, 3076. (b) G. Casiraghi, F. Zanardi, G. Appendino and G. Rassu, *Chem. Rev*., 2000, **100**, 1929.

11 (a) R. K. Boeckman Jr., J. E. Pero and D. J. Boehmler, *J. Am. Chem. Soc.*, 2006, **128**, 11032. (b) M. Frings, I. Atodiresei, J. Runsink, G. Raabe and C. Bolm, *Chem. Eur. J*., 2009, **15**, 1566. (c) D. A. Evans, C. S. Burgey, M. C. Kozlowski and S. W. Tregay, *J. Am. Chem. Soc.*, 1999, **121**, 686. (d) M. De Rosa, L. Citro and A. Soriente, *Tetrahedron Lett*., 2006, **47**, 8507.

12 S. Stankovic, M. D'hooghe, S. Catak, H. Eum, M. Waroquier, V. Van Speybroeck, N. De Kimpe, and H.-J. Ha, *Chem. Soc. Rev*., 2012, **41**, 643.

13 D.-H. Yoon, H.-J. Ha, B. C. Kim and W. K. Lee, *Tetrahedron Lett.*, 2010, **51**, 2181.

14 The term "directed reaction" generally is used to explain that a certain major product favors among a number of possible products by certain functional groups in the starting material through the transient interaction of a substrate functional group with the incoming reagent. For reviews, see. (a) A. H. Hoveyda, D. A. Evans and G. C. Fu, *Chem. Rev.*, 1993, **93**, 1307. (b) B. Breit and Y. Schmidt, *Chem. Rev.*, 2008, **108**, 2928.

15 (a) C. S. Park, H. G. Choi, H. Lee, W. K. Lee and H.-J. Ha, *Tetrahedron: Asymmetry*, 2000, **11**, 3283. (b) H.-J. Ha, M. C. Hong, S. W. Ko, Y. W. Kim, W. K. Lee and J. Park, *Bioorg. Med. Chem. Lett*., 2006, **16**, 1880.

16 K. Hagiya, N. Muramoto, T. Misaki and T. Sugimura, *Tetrahedron*, 2009, **65**, 6109.