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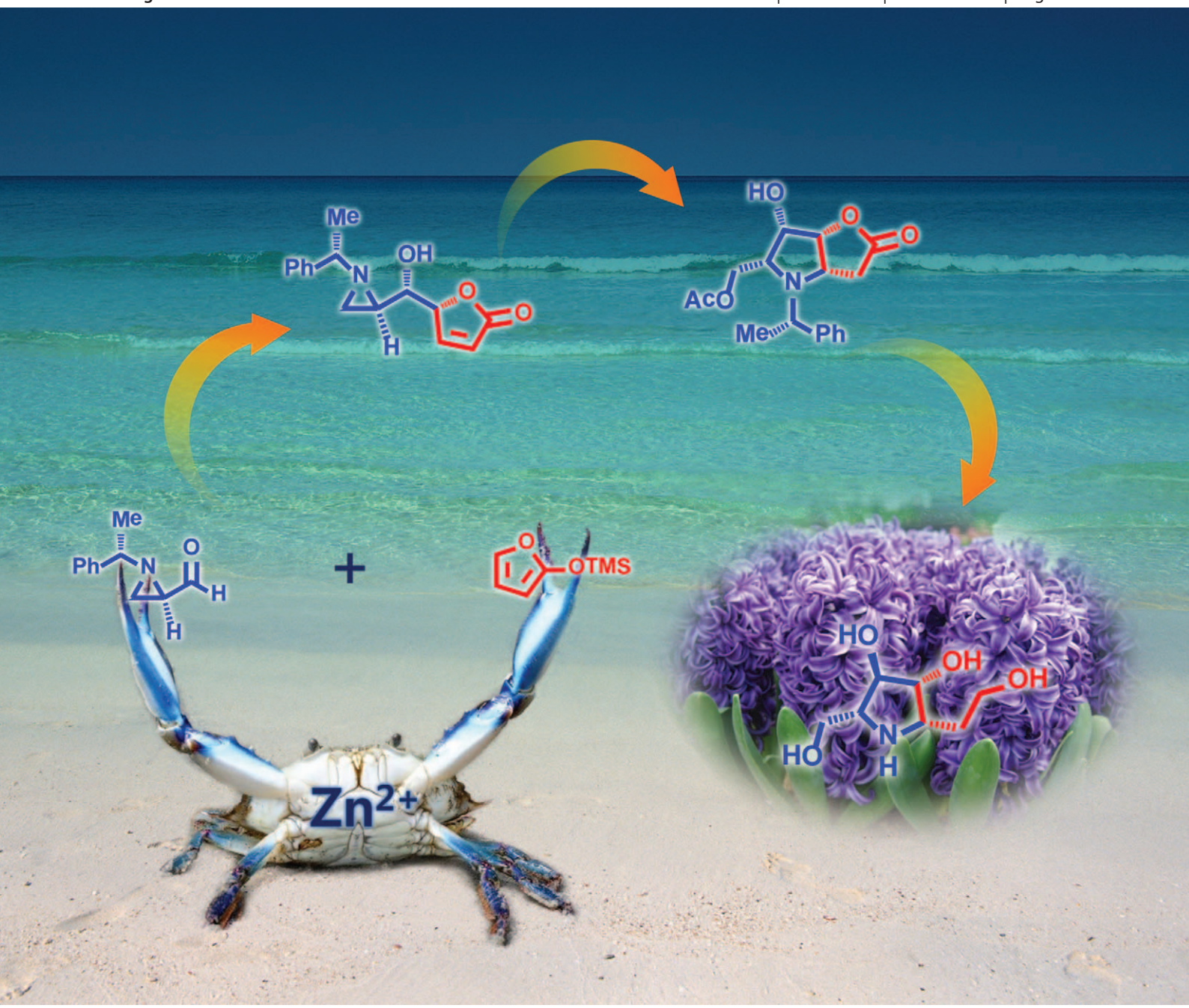

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Won Koo Lee, Hyun-Joon Ha *et al.*

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Highly stereoselective directed reactions and an efficient synthesis of azafuranoses from a chiral aziridine†

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Hogyu Lee,[a] Jun Hee Kim,[a] Won Koo Lee,*[a] Jaeheung Cho,[b] Wonwoo Nam,[c] Jaedeok Lee[d] and Hyun-Joon Ha*[d]

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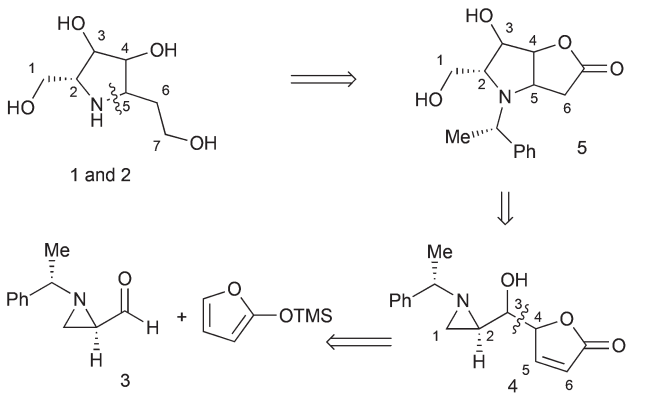
Polyhydroxylated pyrrolidines, such as biologically important azafuranoses represented by the natural product (+)-2,5-imino-2,5,6-trideoxy-*gulo*-heptitol and its C(3)-epimer, were elaborated from a commercially available enantiomerically pure (2*R*)-hydroxymethylaziridine by highly stereoselective directed reactions in more than 61% overall yield. At first, the nucleophile 2-trimethylsilyloxyfuran was directed to (2*R*)-aziridine-2-carboxaldehyde by $ZnBr_2$ to yield the unusual *anti*-addition product as a single isomer via 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 the required reductive operations.

Introduction

Syntheses and structural evaluations of aza-sugars have attracted great attention due to their biological activities, such as glycosidase and glycosyltransferase inhibitors in sugar metabolism.[1] Recently, (+)-2,5-imino-2,5,6-trideoxy-*gulo*-heptitol (**1**) and its stereoisomers have been 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 the introduction of a hydroxyethyl side chain or its equivalent the stereoselectivity of which was poor.[4] As part of our chiral aziridine program, we succeeded in the asymmetric synthesis of azapyranose sugars.[5] This time, we would like to develop highly efficient and stereoselective synthesis of azafuranoses, specifically (+)-2,5-imino-2,5,6-trideoxy-*gulo*-heptitol (**1**) and its C(3)epimer **2** through the highly stereoselective directed reactions.

The target azafuranose, (+)-2,5-imino-2,5,6-trideoxy-*gulo*-heptitol (**1**), included 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). Compound **4**, bearing all the necessary carbons, was 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, were generated from the addition of 2-trimethylsilyloxyfuran to the aziridine-2-carboxaldehyde (**3**). Our previous study[6] encouraged us to apply the highly stereoselective directed reactions. The stereochemistry of the alcohol in compound **4** was generated from the chelation-controlled addition of the nucleophile whose alignment guided the facial selectivity of 2-trimethylsilyloxyfuran to establish the configuration of the lactone ring.



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

[a]*Department of Chemistry, Sogang University, Seoul 121-742, Korea. E-mail: wonkoo@sogang.ac.kr*
[b]*Department of Emerging Materials Science, DGIST, Daegu 711-873, Korea. E-mail: jaeheung@dgist.ac.kr*
[c]*Department of Chemistry and Nano Science, Department of Bioinspired Science, Ewha Womans University, Seoul 120-750, Korea. E-mail: wwnam@mm.ewha.ac.kr*
[d]*Department of Chemistry and Protein Research Center for Bio-Industry, Hankuk University of Foreign Studies, Yongin 449-719, Korea. E-mail: hjha@hufs.ac.kr*

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The aziridine ring opening by an oxygen nucleophile and the subsequent conjugate addition of the released amine to the α,β-unsaturated lactone ring yielded the bicyclic adduct **5**, with the final C–N bond formation for the pyrrolidine ring. All the necessary carbons with proper stereochemistry in compound **5** afforded the targets after the 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 the regioselective aziridine ring-opening reaction using trifluoroacetic acid in H_2O–THF (4 : 1) to obtain the bicyclic compound **5** in 95% yield.[9] 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 the [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.

Compound **6** was purified by recrystallization and we obtained an X-ray crystalline structure (Fig. 1) to confirm the absolute configurations of the four consecutive carbon centres. The crystalline structure clearly shows a *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 compound **4** are *S* and *R*, respectively.

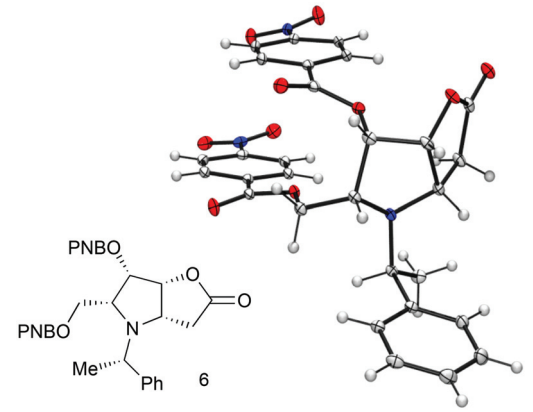
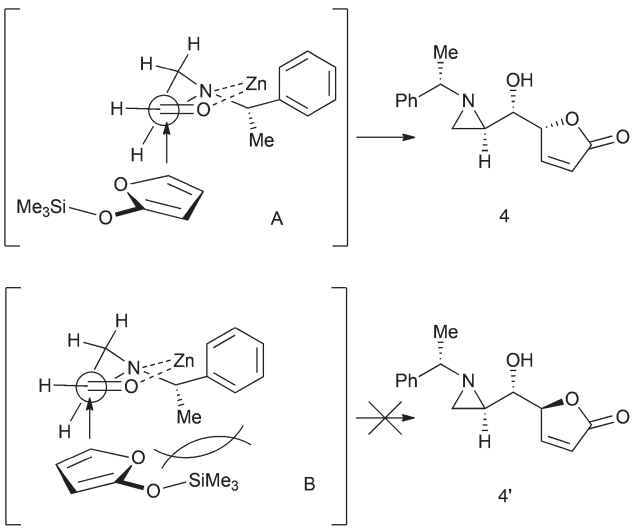
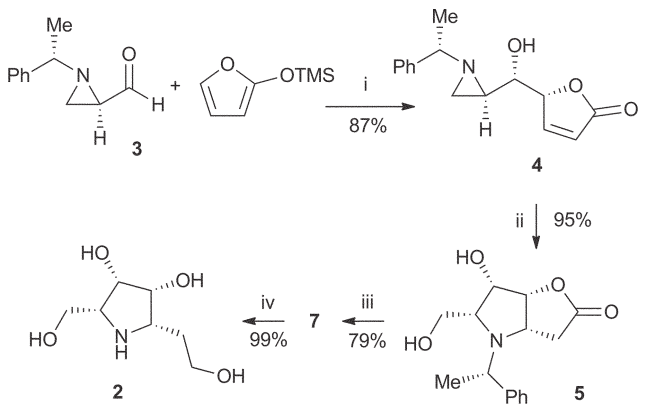


Fig. 1 ORTEP drawing of the bicyclic compound **6**.



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



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).

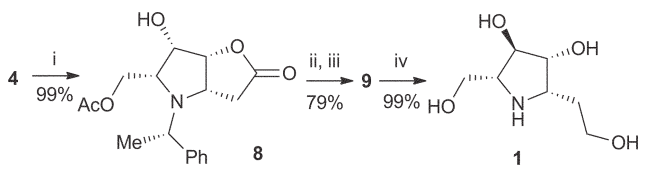
The addition of the nucleophile 2-trimethylsilyloxyfuran to the aziridine-2-carboxaldehyde was directed by the chelation-controlled transition state as expected. However, the stereochemistry of the alcohol and the lactone ring had an unusual *anti*-relationship. Most cases of vinylogous aldol reactions[10] 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 the aziridine and the aldehyde (Scheme 3). Once this was generated the transition state **A**

leading to the unusual *anti*-adduct **4** was 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**.

The next operation was the aziridine ring opening[12] by the oxygen nucleophile to release the amine which was 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 to the *cis*-fused [5,5′]-bicyclic compound **5** without any other choice. The whole sequence of the reactions was directed one by one, *i.e.* the first chelation-controlled nucleophilic addition to aziridine-2-carboxaldehyde directed the facial selectivity of the silyloxyfuran ring and then this adduct led 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 hydrogenolytic 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 the 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 to the stereochemistry in the initial adduct **4**. We succeeded in the synthesis of the natural product involving the inversion of the hydroxy configuration by the Mitsunobu reaction (Scheme 4).

For the convenience of the Mitsunobu reaction to invert the configuration of C3 of the bicycle, we performed the 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 by the aforementioned method with $BH_3{\cdot}SMe_2$ in THF (15 eq.) at 50 °C to result in the tetraol **9** in 79% 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.



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) 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 (0.1 M).

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 into the apparatus through rubber septa. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Dichloromethane was distilled from calcium hydride. MeOH was of commercial reagent grade (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 s. 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 a 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(5*H*)-one (4). To a solution of zinc bromide (1427 mg, 6.34 mmol) in 35.0 mL of THF under a nitrogen atmosphere at 0 °C 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 °C. The mixture was stirred for 1 h 30 min at 0 °C and then treated with saturated 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 a 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-2*H*-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 saturated $NaHCO_3$ 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 a 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-2*H*-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 a nitrogen atmosphere at 0 °C 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 saturated ammonium chloride 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 a 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 °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, –$CHCH_3$), 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 a 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 a 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 atmospheric pressure of H_2. The mixture was filtered and the filtrate was concentrated *in vacuo* to provide **2** in 17 mg (99%) yield as a 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-2*H*-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 a 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 saturated 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 a 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 °C; ^{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 a 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 °C 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 a nitrogen atmosphere at room temperature. The mixture was stirred for 4 h at 50 °C, 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 a 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 atmospheric pressure of H_2. The mixture was filtered and concentrated *in vacuo* to give **1** in 14 mg (99%) yield as a 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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