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# A Facile Synthesis of Lentiginosine Analogues Based on a Highly Regio- and Diastereoselective Allylic Amination Using Chlorosulfonyl Isocyanate

In Su Kim,[a] Qing Ri Li,[b] Guang Ri Dong,[b] Yoo Chang Kim,[b] Yeon Ju Hong,[b] Momi Lee,[b] Ki-Whan Chi,[a] Joa Sub Oh,[b] and Young Hoon Jung*[b]

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The concise synthesis of the lentiginosine analogues pyrrolizidine alkaloid **2** and pyrroloazepine alkaloid **3** has been achieved from inexpensive and readily available D-lyxose. The key steps in the synthesis included regio- and diastereoselective amination, inter- or intramolecular olefin metathesis, and Appel cyclization. The *anti*-3,4-amino alcohol **6**, essential for the preparation of the title compounds **2** and **3**, was synthesized by the regio- and diastereoselective amination of *anti*-3,4-tribenzyl ether **7** using chlorosulfonyl isocyanate. The reaction of **7** with chlorosulfonyl isocyanate in toluene at 0 °C afforded **6** exclusively with a diastereoselectivity of 26:1 in 84 % yield. These results can be explained by the neighboring-group effect, which leads to retention of the stereochemistry.

## Introduction

Polyhydroxylated alkaloids (azasugars or iminosugars) are among the most interesting recent discoveries in the field of natural products. They are distributed widely in many plants and microorganisms[1] and have been reported to inhibit a range of glycosidases in a reversible or competitive manner due to their structural resemblance to the sugar moiety of natural substrates.[2] Most of these glycosidase inhibitors have attracted considerable interest and demand on account of their remarkable therapeutic potential in many diseases, such as viral or bacterial infections, diabetes, obesity, and cancer.[3] As a consequence, a variety of natural or non-natural analogues of polyhydroxylated alkaloids have been prepared and evaluated for clinical applications.[4] For example, two *N*-alkylated derivatives of deoxynojirimycin, miglitol (Glyset™) and *N*-butyldeoxynojirimycin (Zavesca™), are currently used as drugs for the treatment of type II diabetes and Gaucher's disease, respectively.[5]

As part of an ongoing research program aimed at the development of an amination methodology using chlorosulfonyl isocyanate (CSI)[6] and its application to the total synthesis of polyhydroxylated alkaloids,[7] we recently reported a facile approach to the construction of indolizidine alkaloid (–)-lentiginosine (**1**) based on the regio- and diastereoselective allylic amination of polybenzyl ethers using chlorosulfonyl isocyanate.[8]

[a] Department of Chemistry, University of Ulsan, Ulsan 680-749, Korea
[b] College of Pharmacy, Sungkyunkwan University, Suwon 440-746, South Korea
Fax: +82-31-290-7773
E-mail: yhjung@skku.ac.kr

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Although there has been considerable research in the area of natural alkaloids such as lentiginosine (5,6-ring system), unnatural analogues of lentiginosine, that is, pyrrolizidines (5,5-ring system) and pyrroloazepines (5,7-ring system), remain relatively unexplored. Consequently, the synthesis of polyhydroxylated pyrrolizidine and pyrroloazepine has attracted considerable attention. This study focused on the synthesis of pyrrolizidine alkaloid **2** and pyrroloazepine alkaloid **3** as new glycosidase inhibitors (Figure 1).

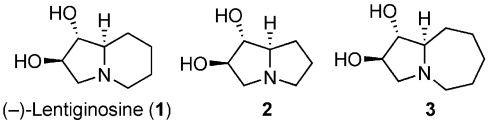
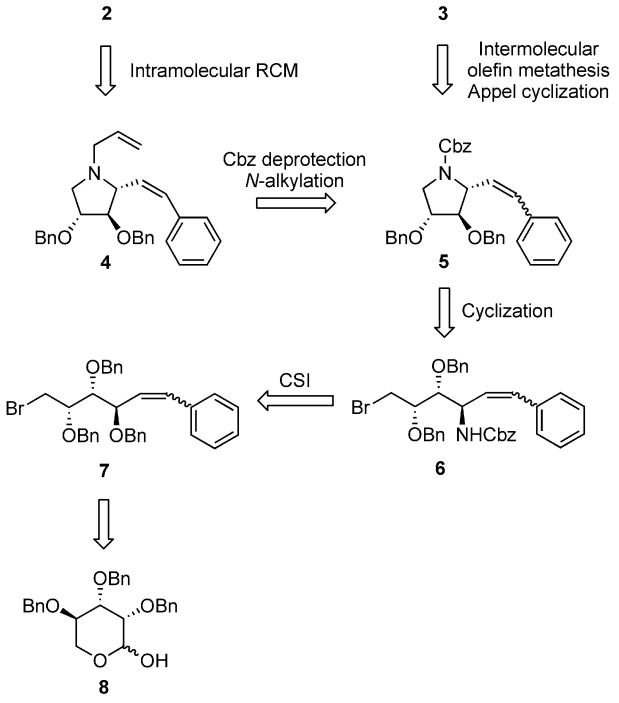



Figure 1. Structures of lentiginosine and its analogues.

## Results and Discussion

The retrosynthetic analysis of **2** and **3** is outlined in Scheme 1. The five-membered ring of the pyrrolizidine core would be constructed from pyrrolidine **4** by intramolecular ring-closing metathesis after chemoselective Pd-catalyzed deprotection of the *N*-Cbz moiety in **5** and *N*-alkylation with allyl bromide. However, the ring-closing metathesis protocol was far less effective in the synthesis of the pyrroloazepine core. Therefore, it was envisaged that the seven-membered ring of the pyrroloazepine core could be prepared by Appel cyclization after intermolecular olefin metathesis between compound **5** and its alkene partner. The common intermediate **5** could be prepared by the intramolecular cyclization of compound **6**, which, in turn, would come from the regio- and diastereoselective introduction of

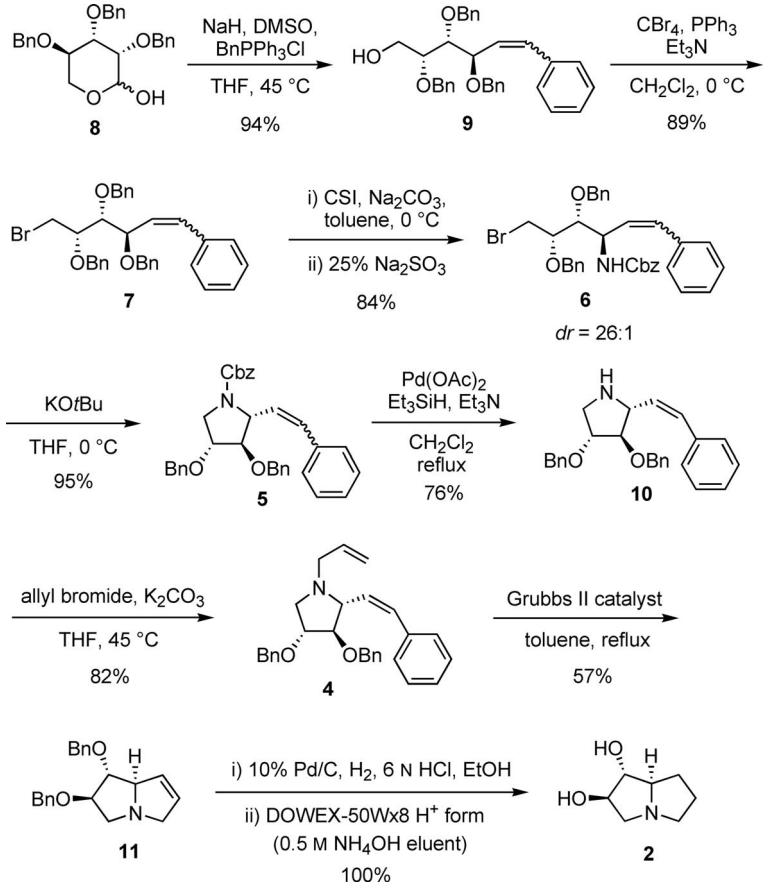



Scheme 1. Retrosynthetic analysis of **2** and **3**.

NHCbz into cinnamyl polybenzyl ether **7** using chlorosulfonyl isocyanate. This approach would allow the two dihydroxylated alkaloids to be generated from the same intermediate **5** in relatively few synthetic steps.

The total synthesis of pyrrolizidine alkaloid **2** was achieved by starting from the benzylated pyranose **8** prepared from commercially available D-lyxose according to a methodology reported in the literature.[9] Wittig reaction of compound **8** with the DMSO anion in THF at 45 °C afforded the olefin **9** as a 3.1:1 mixture of (*Z*)/(*E*) isomers in 94% yield (Scheme 2). The hydroxy moiety of compound **9** was then converted into the bromide **7** with carbon tetrabromide, triphenylphosphane, and triethylamine in 89% yield. Treatment of the *anti*-3,4-tribenzyl ether **7** with chlorosulfonyl isocyanate in toluene at 0 °C for 24 h followed by desulfonylation using an aqueous solution of 25% sodium sulfite afforded the *anti*-3,4-amino alcohol **6** with an excellent diastereoselectivity of 26:1 in 84% yield.

The intramolecular cyclization of compound **6** with potassium *tert*-butoxide provided the corresponding pyrrolidine **5** in 95% yield. Various deprotection conditions, such as $BBr_3$,[10] hydrogenation, and KOH[11] were attempted for the chemoselective removal of the Cbz moiety on the pyrrolidine ring in **5**, but with limited/no success. Pd-catalyzed

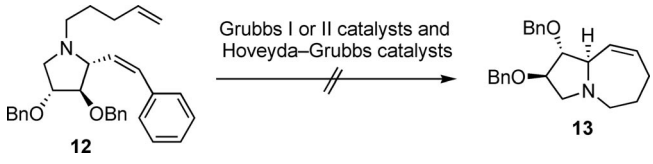



Scheme 2. Total synthesis of (1*R*,2*R*,7a*R*)-1,2-dihydroxypyrrolizidine (**2**).

*N*-Cbz deprotection with triethylsilane gave the desired product **10**, concomitant with the isomerization of the (*Z*)/(*E*) olefin mixtures **5** to produce the (*Z*) olefin exclusively.[12,13] Allylation of the pyrrolidine **10** under standard conditions (allyl bromide, $K_2CO_3$, and THF) proceeded cleanly to afford in 82% yield the diene compound **4** required for ring-closing metathesis. Treatment of compound **4** with Grubbs II catalyst in toluene at reflux afforded the pyrrolizidine core **11** in 57% yield. Finally, catalytic hydrogenation provided the pyrrolizidine alkaloid (1*R*,2*R*,7a*R*)-1,2-dihydroxypyrrolizidine (**2**) in quantitative yield. The spectroscopic data ($^1$H and $^{13}$C NMR) and specific rotation of the synthetic sample are identical to those reported in the literature.[14]

According to previous work, Grubbs II catalyst was first used with compound **12** under a range of reaction conditions to give the pyrroloazepine core **13**. However, these attempts were unsuccessful and led to the recovery of the starting material and a small amount of intermolecular olefination byproducts. Extended reaction times resulted in decomposition of the starting material. Similar results were obtained when the reaction was carried out with Grubbs I and Hoveyda–Grubbs catalysts (Scheme 3, Figure 2).[15] In view of these unsuccessful results, we turned our attention to the intermolecular metathesis reaction between the common intermediate **5** and alkene partners **14** and **15**. The reaction conditions for the intermolecular olefination reaction were then optimized, and the results are summarized in Table 1.




Scheme 3. Ring-closing metathesis approach for the synthesis of **13**.

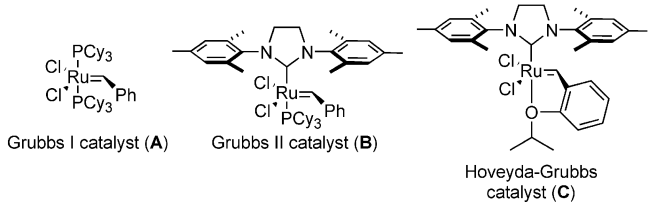
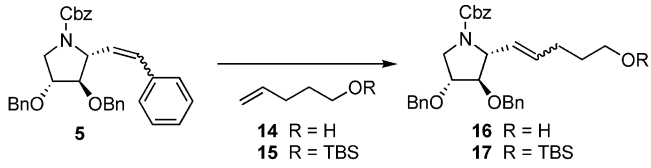



Figure 2. Grubbs I and II catalysts and Hoveyda–Grubbs catalyst for intermolecular olefin metathesis.

The reaction of compound **5** and 4-penten-1-ol (**14**) under Grubbs I, II or Hoveyda–Grubbs catalysis gave the corresponding product **16** in low yield (Entries 1–3). However, the desired product **17** was obtained in 44% yield when the terminal olefin **15** was used with 20 mol-% of Grubbs II catalyst (Entry 4). An increased loading of compound **15** was more effective under otherwise identical conditions (Entry 5). Finally, when 30 mol-% of Grubbs II catalyst was used in toluene at 100 °C, the disubstituted alkene **5** was converted into the corresponding alkene **17** as a 3:1 mixture of (*E*)/(*Z*) isomers in 63% yield (Entry 6).

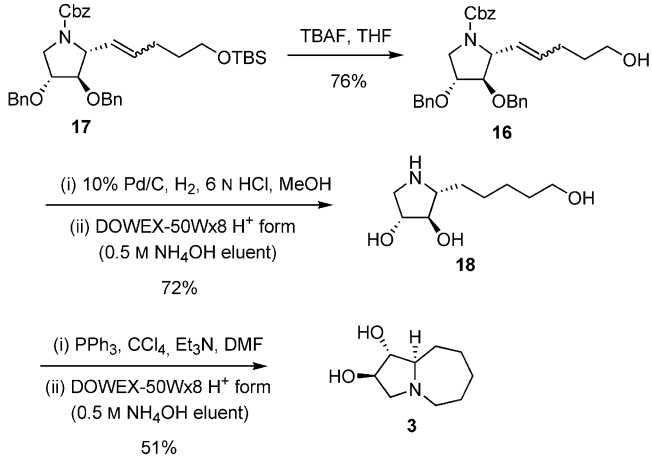
Table 1. Intermolecular olefin metathesis of the disubstituted alkene **5** and terminal olefins **14** and **15**.[a]




| Entry | Catalyst[b] | Mol-% | Olefin (equiv.) | *T* [°C] | Yield[c] [%] |
|---|---|---|---|---|---|
| 1 | **A** | 20 | **14** (5) | 80 | 5 |
| 2 | **B** | 20 | **14** (5) | 80 | 12 |
| 3 | **C** | 20 | **14** (5) | 80 | trace |
| 4 | **B** | 20 | **15** (5) | 100 | 44 |
| 5 | **B** | 20 | **15** (10) | 100 | 56 |
| 6 | **B** | 30 | **15** (10) | 100 | 63 |

[a] All reactions were carried out in toluene for 48 h. [b] See Figure 2 for the structures of the catalysts. [c] Isolated yield of the pure materials.

To complete the synthesis of pyrroloazepine **3**, the olefin **17** was treated with tetrabutylammonium fluoride (TBAF) to give the primary alcohol **16** (Scheme 4). One-pot debenzylation and reduction of the olefin **16** by hydrogenation provided trihydroxylated pyrrolidine alkaloid **18** in 72% yield. Finally, Appel cyclization[16] of compound **18** and subsequent resin purification provided the 5,7-bicyclic dihydroxylated alkaloid **3**. To the best of our knowledge this is the first report of the total synthesis of compound **3**.




Scheme 4. Total synthesis of (1*R*,2*R*,9a*R*)-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-1,2-diol (**3**).

## Conclusions

We have demonstrated the total synthesis of the lentiginosine analogues pyrrolizidine alkaloid **2** and pyrroloazepine alkaloid **3** starting from readily available D-lyxose by the regio- and diastereoselective allylic amination of *anti*-3,4-tribenzyl ether **7** using chlorosulfonyl isocyanate, intra- or intermolecular olefin metathesis, and Appel cyclization. It

is believed that this synthetic strategy can be applied to the preparation of a range of polyhydroxylated alkaloids or other natural products containing a ring nitrogen atom.

## Experimental Section

**General Procedures:** Commercially available reagents were used without additional purification unless otherwise stated. All anhydrous solvents were distilled from $CaH_2$, $P_2O_5$, or Na/benzophenone prior to reaction. All reactions were performed under nitrogen or argon. Melting points were measured with a Gallenkamp or Electrothermal IA9300 melting-point apparatus. NMR spectra ($^1H$ and $^{13}C$ NMR) were recorded with a Varian Unity Inova 500 MHz spectrometer in $CDCl_3$ solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ ($\delta_H$ = 7.26 ppm) and $CDCl_3$ ($\delta_C$ = 77.0 ppm) as internal standards. Resonance patterns are reported with the following notations: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation br. is used to indicate a broad signal. Coupling constants (*J*) are reported in Hertz (Hz). IR spectra were recorded with a Nicolet 205 or Bruker Vector 22 infrared spectrophotometer and are reported in $cm^{-1}$. Optical rotations were measured with a Jasco P1020 polarimeter. Thin-layer chromatography was carried out on plates coated with Kieselgel $60F_{254}$ (Merck). For flash column chromatography, E. Merck Kieselgel 60 (230–400 mesh) was used. High-resolusion mass spectra (HRMS) were recorded with a JEOL, JMS-505 or JMS-600 spectrometer.

**(*Z*)-(2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)-1-(prop-2-enyl)-2-styrylpyrrolidine (4):** Potassium carbonate (0.29 g, 2.08 mmol) and allyl bromide (0.18 mL, 2.08 mmol) were added to a stirred solution of **10** (0.20 g, 0.52 mmol) in anhydrous THF (1.7 mL) at room temperature under $N_2$. The reaction mixture was stirred at 45 °C for 4 h and quenched with $H_2O$ (1 mL). The aqueous layer was extracted with EtOAc (5 mL). The organic layer was washed with $H_2O$ and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 6:1) to afford 0.18 g (82%) of **4** as a colorless syrup. $R_f$ = 0.30 (hexanes/EtOAc, 5:1). $[\alpha]_D^{25}$ = –249.1 (*c* = 0.2, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 2.44–2.47 (br., 1 H), 2.55–2.58 (br., 1 H), 3.17–3.20 (br., 1 H), 3.39 (br. d, *J* = 10.0 Hz, 1 H), 3.49–3.53 (br., 1 H), 3.97–4.02 (br., 2 H), 4.49 (d, *J* = 12.0 Hz, 1 H), 4.56 (d, *J* = 11.5 Hz, 1 H), 4.59 (d, *J* = 11.5 Hz, 1 H), 4.62 (br. s, 1 H), 5.02 (br., 1 H), 5.08 (dd, *J* = 17.0, 1.0 Hz, 1 H), 5.72–5.81 (m, 2 H), 6.78 (d, *J* = 11.5 Hz, 1 H), 7.23–7.44 (m, 15 H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 56.58, 57.00, 71.48, 72.59, 82.10, 90.09, 117.57, 127.29, 127.91, 128.01, 128.16, 128.35, 128.55, 128.60, 129.16, 132.74, 133.98, 135.39, 138.26 ppm. IR (neat): $\tilde{\nu}$ = 3342, 2362, 1593, 1420, 1121, 1041 $cm^{-1}$. HRMS (FAB): calcd. for $C_{29}H_{32}NO_2$ $[M + H]^+$ 426.2433; found 426.2438.

**(1*R*,2*R*,7a*R*)-1,2-Bis(benzyloxy)-2,3,5,7a-tetrahydro-1*H*-pyrrolizine (11):**[17] Second-generation Grubbs catalyst (24 mg, 0.028 mmol) was added to a stirred solution of **4** (0.12 g, 0.28 mmol) in anhydrous toluene (2.8 mL) under $N_2$. The reaction mixture was heated at reflux for 24 h. The resulting mixture was filtered through a Celite pad and concentrated in vacuo. The residue was purified by flash column chromatography ($CHCl_3$/MeOH, 15:1) to afford 52 mg (57%) of **11** as a pale-yellow oil. $R_f$ = 0.28 ($CHCl_3$/MeOH, 15:1). $[\alpha]_D^{25}$ = +20.6 (*c* = 0.1, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 2.74 (dd, *J* = 10.0, 7.0 Hz, 1 H), 3.41 (dd, *J* = 10.0, 5.0 Hz, 1 H), 3.48–3.53 (m, 1 H), 3.83–3.89 (m, 2 H), 4.17–4.21 (m, 2 H), 4.17–4.21 (m, 2 H), 4.56 (d, *J* = 12.0 Hz, 1 H), 4.62 (d, *J* = 12.0 Hz, 1 H), 4.65 (s, 2 H), 5.75 (s, 2 H), 7.27–7.39 (m, 10 H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 58.42, 62.90, 72.21, 72.26, 76.47, 83.66, 86.27, 127.79, 127.82, 127.88, 127.94, 127.96, 128.62, 128.67, 129.09, 138.44, 138.51 ppm. IR (neat): $\tilde{\nu}$ = 3344, 1592, 1418, 1121, 1041 $cm^{-1}$. HRMS (FAB): calcd. for $C_{21}H_{24}NO_2$ $[M + H]^+$ 322.1807; found 322.1812.

**(1*R*,2*R*,7a*R*)-1,2-Dihydroxypyrrolizidine (2):** A 6 N solution of aqueous HCl (1.5 mL) and 10% Pd/C (20 mg, 0.02 mmol) was added to a solution of **11** (45 mg, 0.14 mmol) in EtOH (7 mL). The reaction mixture was shaken in a Parr apparatus under hydrogen (60 psi) for 24 h. The resulting mixture was filtered through a Celite pad and concentrated in vacuo. The residue was purified by elution through a DOWEX-50Wx8 ($H^+$ form) ion-exchange resin by using 0.5 M aqueous $NH_4OH$ as eluent to afford 20 mg (100%) of **2** as a white solid. $R_f$ = 0.30 ($CH_2Cl_2$/MeOH/30%$NH_4OH$, 5:5:2). M.p. 166–167 °C. $[\alpha]_D^{25}$ = +10.1 (*c* = 1, MeOH). $^1H$ NMR (300 MHz, $D_2O$): $\delta$ = 1.75–1.80 (m, 1 H), 1.84–1.89 (m, 1 H), 1.91–1.99 (m, 1 H), 2.00–2.15 (m, 1 H), 2.89 (dd, *J* = 12.0, 5.7 Hz, 1 H), 2.96 (dd, *J* = 12.0, 5.1 Hz, 1 H), 3.28 (dt, *J* = 11.4, 5.7 Hz, 1 H), 3.51 (dd, *J* = 12.0, 5.7 Hz, 1 H), 3.59 (dd, *J* = 12.0, 7.2 Hz, 1 H), 3.94 (t, *J* = 4.8 Hz, 1 H), 4.20 (dd, *J* = 5.1, 4.8 Hz, 1 H) ppm. $^{13}C$ NMR (125 MHz, $D_2O$): $\delta$ = 25.14, 29.18, 56.50, 57.49, 71.93, 76.34, 79.20 ppm. HRMS (CI): calcd. for $C_7H_{14}NO_2$ $[M + H]^+$ 144.1024; found 144.1024.

**Benzyl (2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)-2-[5-(*tert*-butyldimethylsilyloxy)pent-1-enyl]pyrrolidine-1-carboxylate (17):** *tert*-Butyldimethyl(pent-4-enyloxy)silane (**15**; 1.12 g, 5.58 mmol) and second-generation Grubbs catalyst (0.141 g, 0.167 mmol) were added to a stirred solution of **5** (0.29 g, 0.558 mmol) in anhydrous toluene (5.6 mL) under $N_2$. The reaction mixture was stirred at 100 °C for 48 h. The resulting mixture was filtered through a Celite pad and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 8:1) to afford 0.217 g (63%) of **17** as a pale-yellow oil. $R_f$ = 0.30 (hexanes/EtOAc, 6:1). $[\alpha]_D^{25}$ = +1.2 (*c* = 0.14, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 0.06 (s, 6 H), 0.88 (s, 9 H), 1.42–1.64 (m, 2 H), 2.00–2.16 (m, 2 H), 3.50–3.68 (m, 3 H), 3.75–3.80 (m, 2 H), 4.04 (t, *J* = 2.5 Hz, 1 H), 4.40–4.65 (m, 4 H), 5.09 (br. m, 1 H), 5.15 (d, *J* = 12.5 Hz, 1 H), 5.17 (d, *J* = 12.5 Hz, 1 H), 5.47–5.61 (m, 2 H), 7.26–7.37 (m, 15 H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = –5.04, –4.99, 18.56, 26.19, 26.20, 28.66, 29.93, 32.38, 36.14, 50.86, 62.73, 62.98, 64.88, 67.00, 71.62, 71.84, 76.67, 80.36, 81.41, 85.69, 86.87, 127.83, 127.89, 128.04, 128.05, 128.10, 128.59, 128.69, 128.71, 129.36, 132.81, 137.09, 137.88, 137.89, 155.44 ppm. HRMS (FAB): calcd. for $C_{37}H_{50}NO_5Si$ $[M + H]^+$ 616.3458; found 616.3456.

**Benzyl (2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)-2-(5-hydroxypent-1-enyl)pyrrolidine-1-carboxylate (16):** Tetrabutylammonium fluoride (0.71 mL, 0.714 mmol, 1.0 M in THF) was added to a stirred solution of **17** (0.22 g, 0.357 mmol) in anhydrous THF (1.8 mL) under $N_2$. The reaction mixture was stirred at room temperature for 8 h and quenched with a solution of aqueous saturated $NaHCO_3$ (1 mL). The aqueous layer was extracted with EtOAc (5 mL × 2). The organic layer was washed with $H_2O$ and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford 0.136 g (76%) of **16** as a colorless syrup. $R_f$ = 0.25 (hexanes/EtOAc, 2:1). $[\alpha]_D^{25}$ = +7.0 (*c* = 0.26, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 1.50–1.69 (m, 2 H), 2.00–2.20 (m, 3 H), 3.50–3.64 (m, 3 H), 3.71–3.91 (m, 2 H), 4.04 (d, *J* = 2.5 Hz, 1 H), 4.35–4.64 (m, 4 H), 5.01–5.22 (m, 3 H), 5.50–5.61 (m, 2 H), 7.20–7.39 (m, 15 H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 28.67, 32.06, 50.92, 62.55, 64.90, 67.05, 71.65, 80.34, 81.29, 85.54, 86.81, 127.89, 128.09, 128.13, 128.62, 128.71, 128.73, 128.99, 131.51, 132.24, 132.95, 137.09,

137.85, 155.12 ppm. HRMS (FAB): calcd. for $C_{31}H_{36}NO_5$ [M + H]$^+$ 502.2593; found 502.2599.

**(2*R*,3*R*,4*R*)-2-(5-Hydroxypentyl)pyrrolidine-3,4-diol (18):** A 6 N solution of aqueous HCl (1.2 mL) and 10% Pd/C (20 mg, 0.02 mmol) were added to a solution of **16** (0.12 g, 0.239 mmol) in MeOH (2.4 mL). The reaction mixture was shaken in a Parr apparatus under hydrogen (60 psi) for 24 h. The resulting mixture was filtered through a Celite pad and concentrated in vacuo. The residue was purified by elution through a DOWEX-50Wx8 ($H^+$ form) ion-exchange resin by using 0.5 M aqueous $NH_4OH$ as eluent to afford 32.5 mg (72%) of **18** as a white solid. $R_f$ = 0.26 ($CH_2Cl_2$/MeOH/30%$NH_4OH$, 5:5:0.8). $[\alpha]_D^{25}$ = –8.6 (*c* = 0.08, MeOH). $^1$H NMR (500 MHz, $D_2O$): $\delta$ = 1.27–1.52 (m, 7 H), 1.61–1.67 (m, 1 H), 2.79–2.85 (m, 2 H), 3.05 (dd, *J* = 12.0, 6.0 Hz, 1 H), 3.53 (t, *J* = 6.5 Hz, 2 H), 3.67 (dd, *J* = 5.5, 3.5 Hz, 1 H), 4.07 (dt, *J* = 6.0, 2.5 Hz, 1 H) ppm. $^{13}$C NMR (125 MHz, $D_2O$): $\delta$ = 25.11, 26.00, 31.29, 32.63, 50.61, 61.93, 64.48, 77.46, 82.30 ppm. HRMS (FAB): calcd. for $C_9H_{20}NO_3$ [M + H]$^+$ 190.1443; found 190.1448.

**(1*R*,2*R*,9a*R*)-Octahydro-1*H*-pyrrolo[1,2-*a*]azepine-1,2-diol (3):** $CCl_4$ (15 μL, 0.159 mmol), $PPh_3$ (42 mg, 0.159 mmol), and $Et_3N$ (22 μL, 0.159 mmol) were added to a stirred solution of **18** (15 mg, 0.079 mmol) in anhydrous DMF (0.6 mL) under $N_2$. The reaction mixture was stirred at room temperature for 36 h and quenched with MeOH (1 mL). The resulting mixture was concentrated in vacuo. The residue was purified by elution through a DOWEX-50Wx8 ($H^+$ form) ion-exchange resin by using 0.5 M aqueous $NH_4OH$ as eluent and flash column chromatography ($CH_2Cl_2$/MeOH/30%$NH_4OH$, 60:9:1) to afford 6.9 mg (51%) of **3** as a white solid. $R_f$ = 0.23 ($CH_2Cl_2$/MeOH/30%$NH_4OH$, 60:9:1). $[\alpha]_D^{25}$ = +27.7 (*c* = 0.2, MeOH). $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ = 1.60–1.93 (m, 7 H), 2.10–2.18 (m, 1 H), 2.85–2.92 (m, 1 H), 3.00–3.07 (m, 1 H), 3.20–3.33 (m, 3 H), 3.78 (dd, *J* = 4.5, 3.0 Hz, 1 H), 4.07 (dt, *J* = 4.5, 3.0 Hz, 1 H) ppm. $^{13}$C NMR (125 MHz, $CD_3OD$): $\delta$ = 25.37, 26.12, 26.67, 30.11, 55.35, 61.48, 73.08, 74.99, 82.83 ppm. HRMS (FAB): calcd. for $C_9H_{18}NO_2$ [M + H]$^+$ 172.1338; found 172.1337.

**Supporting Information** (see also the footnote on the first page of this article): $^1$H and $^{13}$C NMR spectra for compounds **2**–**4**, **11**, and **16**–**18**.

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[1] A. A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux, R. J. Nash, *Phytochemistry* **2001**, *56*, 265–295.
[2] a) A. E. Stütz, *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*, Wiley-VCH, Weinheim, **1999**; b) T. D. Heightman, A. T. Vasella, *Angew. Chem. Int. Ed.* **1999**, *38*, 750–770; c) M. Bols, *Acc. Chem. Res.* **1988**, *21*, 1–8.
[3] a) P. Greimel, J. Spreitz, A. E. Stutz, T. M. Wrodnigg, *Curr. Top. Med. Chem.* **2003**, *3*, 513–523; b) L. Somsak, V. Nagya, Z. Hadady, T. Docsa, P. Gergely, *Curr. Pharm. Des.* **2003**, *9*, 1177–1189; c) Y. Nishimura, *Curr. Top. Med. Chem.* **2003**, *3*, 575–591; d) P. S. Johnson, H. E. Lebovitz, R. F. Coniff, D. C. Simonson, P. Raskin, C. L. Munera, *J. Clin. Endocrinol. Metab.* **1998**, *83*, 1515–1522; e) T. Tsuruoka, H. Fukuyasu, M. Ishii, T. Usui, S. Shibahara, S. Inouye, *J. Antibiot.* **1996**, *49*, 155–161; f) G. K. Ostrander, N. K. Scribner, L. R. Rohrschneider, *Cancer Res.* **1988**, *48*, 1091–1094; g) R. A. Gruters, J. J. Neefjes, M. Tersmette, R. E. Y. de Goede, A. Tulp, H. G. Huisman, F. Miedema, H. L. Ploegh, *Nature* **1987**, *330*, 74–77.
[4] V. H. Lillelund, H. H. Jensen, X. Liang, M. Bols, *Chem. Rev.* **2002**, *102*, 515–553, and references therein.
[5] a) B. Junge, M. Matzke, J. Stoltefuss in *Handbook of Experimental Pharmacology* (Eds.: J. Kuhlmann, W. Pils), Springer, Berlin, Heidelberg, New York, **1996**, vol. 119, pp. 411–482; b) P. L. McCormack, K. M. Goa, *Drugs* **2003**, *63*, 2427–2434; c) L. J. Scott, C. M. Spencer, *Drugs* **2000**, *59*, 521–549.
[6] a) G. R. Dong, Q. R. Li, S. H. Woo, I. S. Kim, Y. H. Jung, *Arch. Pharmacal Res.* **2008**, *31*, 1393–1398; b) J. D. Kim, I. S. Kim, C. H. Jin, O. P. Zee, Y. H. Jung, *Tetrahedron Lett.* **2005**, *46*, 1079–1082; c) Y. H. Jung, J. D. Kim, *Arch. Pharmacal Res.* **2005**, *28*, 382–390; d) J. D. Kim, O. P. Zee, Y. H. Jung, *J. Org. Chem.* **2003**, *68*, 3721–3724; e) J. D. Kim, G. Han, O. P. Zee, Y. H. Jung, *Tetrahedron Lett.* **2003**, *44*, 733–735; f) Y. H. Jung, J. D. Kim, *Arch. Pharmacal Res.* **2003**, *26*, 667–678; g) J. D. Kim, G. Han, L. S. Jeong, H.-J. Park, O. P. Zee, Y. H. Jung, *Tetrahedron* **2002**, *58*, 4395–4402; h) J. D. Kim, M. H. Lee, G. Han, H. Park, O. P. Zee, Y. H. Jung, *Tetrahedron* **2001**, *57*, 8257–8266; i) Y. H. Jung, J. D. Kim, *Arch. Pharmacal Res.* **2001**, *24*, 371–376; j) J. D. Kim, M. H. Lee, M. J. Lee, Y. H. Jung, *Tetrahedron Lett.* **2000**, *41*, 5073–5076; k) Y. H. Jung, J. D. Kim, *Arch. Pharmacal Res.* **2000**, *23*, 574–578.
[7] a) I. S. Kim, Q. R. Li, G. R. Dong, S. H. Woo, H.-j. Park, O. P. Zee, Y. H. Jung, *Synlett* **2008**, 2985–2988; b) I. S. Kim, C. B. Ryu, Q. R. Li, O. P. Zee, Y. H. Jung, *Tetrahedron Lett.* **2007**, *48*, 6258–6261; c) I. S. Kim, Q. R. Li, J. K. Lee, S. H. Lee, J. K. Lim, O. P. Zee, Y. H. Jung, *Synlett* **2007**, 1711–1714; d) I. S. Kim, H. Y. Lee, Y. H. Jung, *Heterocycles* **2007**, *71*, 1787–1800; e) I. S. Kim, S. J. Kim, J. K. Lee, Q. R. Li, Y. H. Jung, *Carbohydr. Res.* **2007**, *342*, 1502–1509; f) I. S. Kim, J. S. Oh, O. P. Zee, Y. H. Jung, *Tetrahedron* **2007**, *63*, 2622–2633; g) I. S. Kim, Y. J. Ji, Y. H. Jung, *Tetrahedron Lett.* **2006**, *47*, 7289–7293; h) I. S. Kim, J. D. Kim, C. B. Ryu, O. P. Zee, Y. H. Jung, *Tetrahedron* **2006**, *62*, 9349–9358; i) J. D. Kim, I. S. Kim, C. H. Jin, O. P. Zee, Y. H. Jung, *Org. Lett.* **2005**, *7*, 4025–4028.
[8] I. S. Kim, O. P. Zee, Y. H. Jung, *Org. Lett.* **2006**, *8*, 4101–4104.
[9] O. N. Nadein, A. Kornienko, *Org. Lett.* **2004**, *6*, 831–834.
[10] P. Pless, W. Bauer, *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 147–148.
[11] S. R. Angel, D. O. Arnaiz, *Tetrahedron Lett.* **1989**, *30*, 515–518.
[12] a) M. Sakaitani, N. Kurokawa, Y. Ohfune, *Tetrahedron Lett.* **1986**, *27*, 3753–3754; b) P. Wipf, Y. Uto, *Tetrahedron Lett.* **1999**, *40*, 5165–5169.
[13] I. S. Kim, G. R. Dong, Y. H. Jung, *J. Org. Chem.* **2007**, *72*, 5424–5426.
[14] a) V. D. Chaudhari, K. S. A. Kumar, D. D. Dhavale, *Tetrahedron* **2006**, *62*, 4349–4354; b) T. Ayad, Y. Génisson, M. Baltas, *Org. Biomol. Chem.* **2005**, *3*, 2626–2631; c) T. Ayad, Y. Génisson, M. Baltas, L. Gorrichon, *Chem. Commun.* **2003**, 582–583.
[15] S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.
[16] R. Appel, R. Kleinstück, *Chem. Ber.* **1974**, *107*, 5–12.
[17] For the spectroscopic data of the enantiomer of compound **17**, see; E. M. Sletten, L. J. Liotta, *J. Org. Chem.* **2006**, *71*, 1335–1343.

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