Stereoselective Allyl Amine Synthesis through Enantioselective Addition of Diethylzinc and [1,3]-Chirality Transfer: Synthesis of Lentiginosine and Polyoxamic Acid Derivative

Yoshiyasu Ichikawa,*[a] Takashi Ito,[b] and Minoru Isobe[b]

Abstract: A new synthetic method for the preparation of allyl amines has been developed. The key steps of this method are enantioselective addition of diethylzinc and [1,3]-chirality transfer through the [3.3] sigmatropic rearrangement of allyl cyanates. Stereocontrolled syntheses of lentiginosine (**1**) and polyoxamic acid derivative **2** from a common intermediate **7** derived from D-tartaric acid (**8**), have been accomplished.

Keywords: asymmetric synthesis · natural products · rearrangement · synthesis design · total synthesis

Introduction

As part of our research program aimed at the development of [3.3] sigmatropic rearrangements of allyl cyanates for the synthesis of natural products,[1] we recently proposed an approach for stereoselective allyl amine synthesis as shown in Figure 1.[2] An enantioselective addition of diethylzinc (Et_2Zn) to α,β-unsaturated aldehyde **A** would furnish allyl alcohol **B** with predictable stereoselectivity. This allyl alcohol **B** would then be transformed into allyl cyanate **C**, which would undergo a concerted [3.3] bond reorganization to afford allyl isocyanate **D** with a high degree of [1,3]-chirality transfer.[3] Treatment of the resultant allyl isocyanate **D** with alcohol would provide the corresponding carbamate **E**. It should be noted that it is possible to chose the most appropriate carbamate as a protecting group for allyl amine.[4] Further manipulation—ring-closing methathesis (RCM) of **F**, for example—would offer the nitrogen-containing heterocycle **G**, whereas oxidative cleavage of the double bond in **E** could furnish the nonproteinogenic amino acid **H**.

In this synthetic protocol, when the R^1 group in **A** has stereogenic centers, a matched-mismatched problem might be expected to arise during the synthesis of the allyl alcohol (**A**→**B**).[5] In fact, it is well known that the stereochemical outcome of asymmetric synthesis will often be to some extent dependent on the relationship between the absolute configuration of the chiral ligand and that of the substrate. We envisioned that such a problem could be circumvented in our case, because enantioselective addition of Et_2Zn would be carried out at the remote position, where the effect of the R^1 group should become negligible. Moreover, since the transfer of chirality through allyl cyanate-to-isocyanate rearrangement (**C**→**D**) is quite reliable, due to its concerted six-membered transition state, we might accomplish

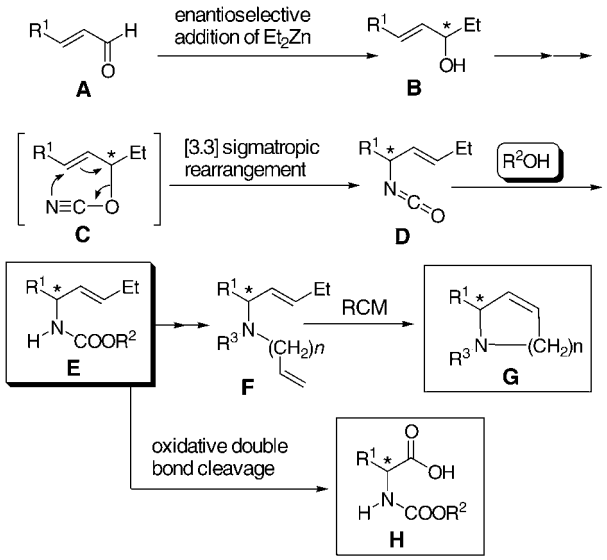

Figure 1. A plan for stereoselective allyl amine synthesis.

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the construction of a stereogenic center bearing an N-substituent in proximity to the R^1 group.

To demonstrate the efficiency of this stereoselective allyl amine synthesis, we planned to synthesize lentiginosine (**1**) and the polyoxamic acid derivative **2** (Figure 2). Lentiginosine was isolated in 1990 from the leaves of *Austragalus lentiginosus*, and this dihydroxylated indolizine alkaloid is a strong inhibitor of the fungal α-glucosidase amyloglucosidase, an enzyme that hydrolyzes 1,4- and 1,6-α-glucosidic linkages.[6] Polyoxamic acid (**3**) is known to be a structural constituent of polyoxins,[7] a class of peptidyl-nucleoside antifungal antibiotics.[8] This unusual amino acid has three contiguous stereocenters, and the polyoxamic acid derivative **2** is an intermediate for the synthesis of polyoxin J (**4**).[9] Here we describe syntheses of lentiginosine (**1**) and the polyoxamic acid derivative **2** by the stereoselective allyl amine synthesis represented in Figure 1.

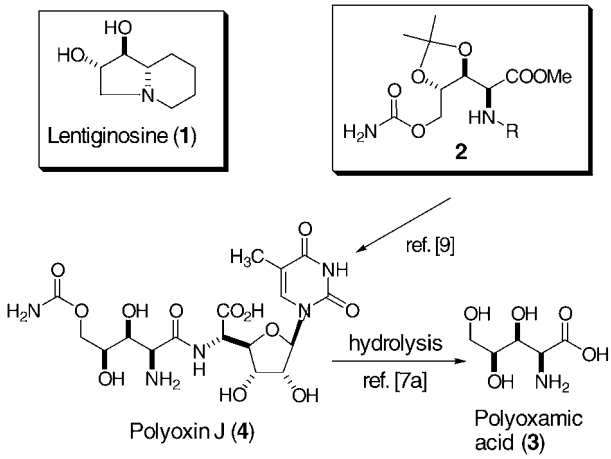


Figure 2. Two target molecules: lentiginosine (**1**) and the polyoxamic acid derivative **2**.

Results and Discussion

Synthetic plan: Our synthetic analysis demonstrating how the two target molecules, lentiginosine (**1**) and the polyoxamic acid derivative **2**, could be prepared from a common intermediate **7** derived from D-tartaric acid (**8**) is shown in Figure 3.[10] It should be noted that the stereogenic center of the nitrogen-bearing carbon in the intermediate **5** for lentiginosine is the opposite of that in **6** for the polyoxamic acid derivative **2**. Consequently, this synthetic plan offers an appropriate situation to test our expectation that the nitrogen-bearing stereocenter could be constructed diastereoselectively at the position adjacent to the other stereogenic centers.

Stereoselective synthesis of allyl amine intermediates: Our initial efforts focused on the enantioselective addition of Et_2Zn to the α,β-unsaturated aldehyde **9** in the presence of

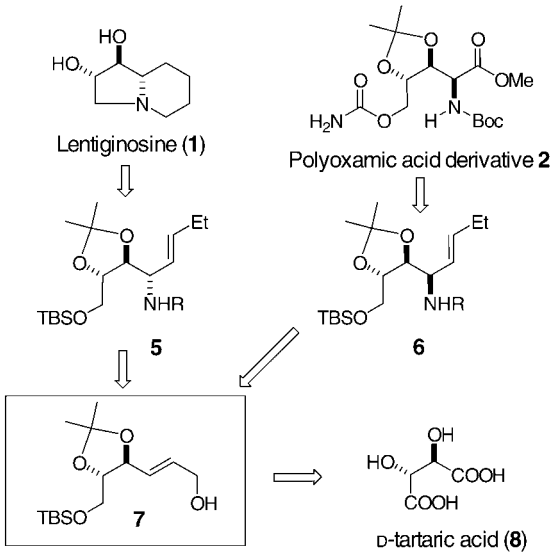
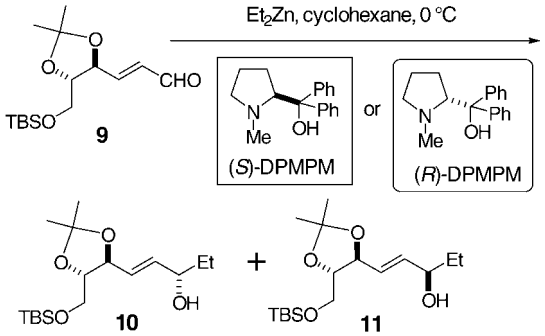


Figure 3. Retrosynthetic analysis of **1** with a common intermediate.

diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM), first reported by Soai,[11] and the results are depicted in Figure 4. Treatment of the aldehyde **9**[12] with Et_2Zn in the presence of a catalytic amount of (*R*)-DPMPM (6 mol%) in cyclohexane at 0°C for 7 h provided the allyl alcohol **10** in 91% yield with a high 93:7 diastereoselectivity (entry A, determined by ^{1}H NMR).



Entry	Catalyst	Yield [%]	**10**:**11** ratio
A	(*S*)-DPMPM	91	93:7
B	(*R*)-DPMPM	87	7:93

Figure 4. Enantioselective addition of Et_2Zn to aldehyde **9**.

The structure for **10** was initially assigned by the Soai empirical rule and finally confirmed by Mosher–Kusumi MTPA ester analysis, which has been widely used to determine the absolute configurations of secondary alcohols (Figure 5).[13] Thus, the secondary alcohol **10** was transformed into the corresponding (*S*)- and (*R*)-MTPA esters **12**, and their chemical shift differences ($\Delta\delta$ values: $\Delta\delta = \delta_S - \delta_R$) were calculated.[13] The protons with positive $\Delta\delta$ values are placed on the right side in the configurational correlation model and those

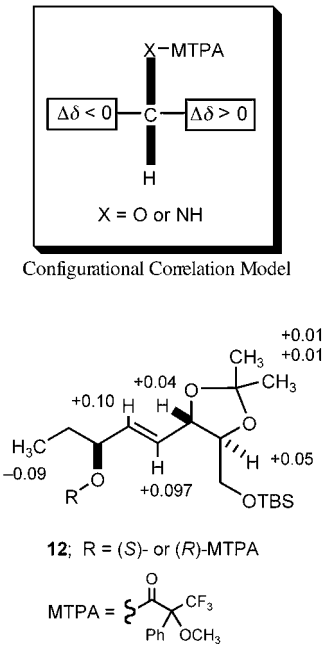
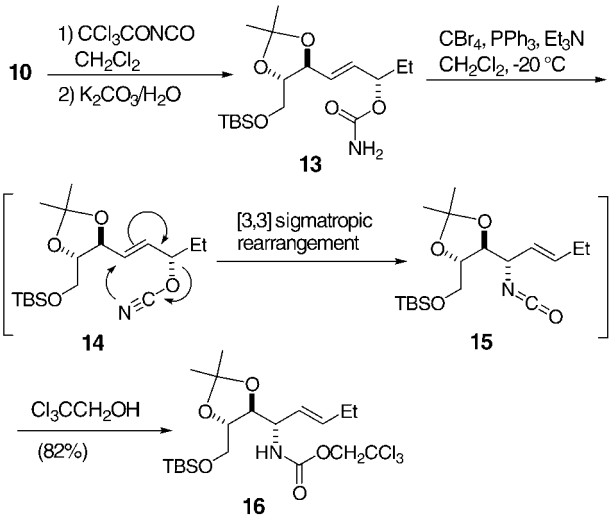


Figure 5. Mosher–Kusumi MTPA ester analysis: configurational correlation model and $\Delta\delta$ values for the Mosher ester derivative **12** ($\Delta\delta = \delta_S - \delta_R$).

with negative $\Delta\delta$ on the left side. This procedure elucidated the absolute stereochemistry of secondary alcohol **10** as the *S* configuration.

With 6 mol% of (*S*)-DPMPM as catalyst, enantioselective addition of Et_2Zn to aldehyde **9** proceeded smoothly with good face selectivity to furnish predominantly the product **11** (93:7, ^{1}H NMR) in 87% yield (entry B; see Figure 4). Since the yields and selectivities in entries A and B are comparable, it is evident that the stereochemical outcome of this Soai protocol is independent of the relationship between the respective absolute configurations of aldehyde **9** and DPMPM and that reagent control is dominant in this reaction.

Having obtained two allyl alcohols, we next turned our attention to the preparation of allyl amine intermediates by way of the allyl cyanate-to-isocyanate rearrangement (Scheme 1). Treatment of allyl alcohol **10**[14] with trichloroacetyl isocyanate, followed by hydrolysis with potassium carbonate in aqueous methanol, gave the carbamate **13**. Dehydration of **13** with triphenylphosphine, carbon tetrabromide, and triethylamine at −20 °C gave the allyl cyanate **14**, which underwent a [3.3] sigmatropic rearrangement to afford the allyl isocyanate **15**. Since isolation of **15** by aqueous workup is difficult, due to the hydrolysis of the isocyanate group, the reaction mixture was treated in situ with 2,2,2-trichloroethanol. The trichloroethoxy (Troc) carbamate **16** was isolated after



Scheme 1. Synthesis of allyl amine intermediate **16** for lentiginosine.

workup and chromatographic purification in a good 82% yield from allyl alcohol **10**.

The stereochemical outcome of this [1,3]-chirality transfer process was determined by the Kusumi MTPA-amide method (Figure 6).[15] Thus, the Troc-carbamate **16** was

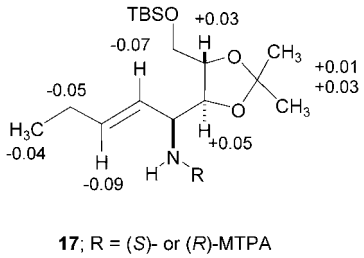


Figure 6. Kusumi MTPA amide analysis of **17**.

transformed into the corresponding (*S*)- and (*R*)-MTPA amides **17**, and analysis of their $\Delta\delta$ values in terms of the configurational correlation model depicted in Figure 5 confirmed the asymmetric carbon bearing the nitrogen substituent to have the *S* configuration. Figure 7 shows the cyclic transition state through which the allyl cyanate-to-isocyanate rearrangement may pass. The stereochemistry of the newly formed stereogenic center in **15** is consistent with the concerted six-membered cyclic transition state **B**→**C** in

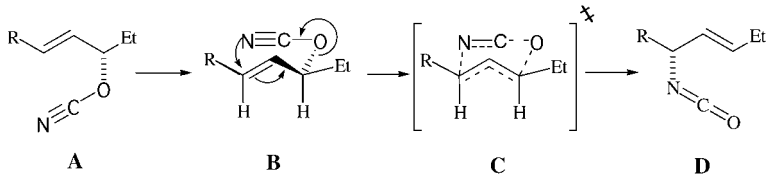
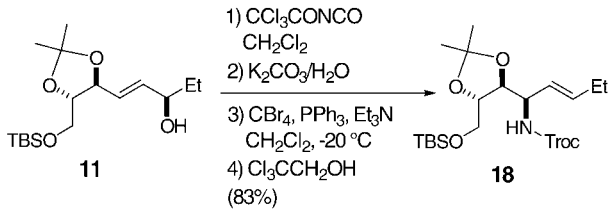


Figure 7. The cyclic six-membered transition state **C** through which the allyl cyanate-to-isocyanate rearrangement **A**→**D** may pass.

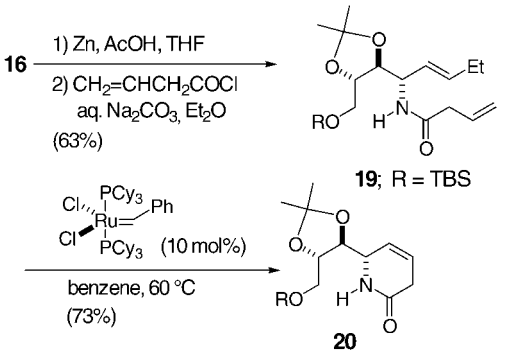
which the ethyl group adopts a pseudoequatorial orientation.[16]

For the synthesis of the polyoxamic acid derivative, it was necessary to prepare the diastereomer of **16**, namely **18**, which was also accomplished by a procedure similar to that shown in Scheme 1. Accordingly, [1,3]-chirality transfer in allyl alcohol **11** was achieved through the [3.3] sigmatropic rearrangement of the allyl cyanate to afford ally carbamate **18** in 83% overall yield (Scheme 2).



Scheme 2. Preparation of the allyl amine intermediate **18** for the polyoxamic acid derivative.

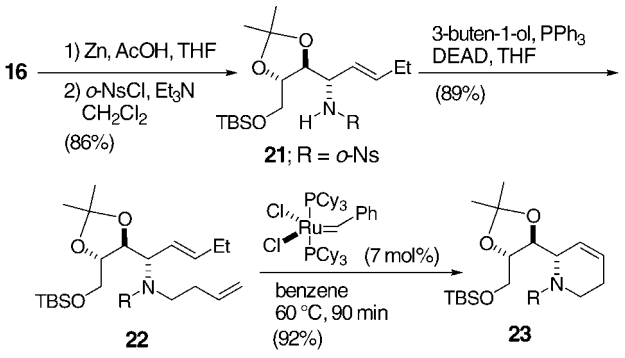
Synthesis of lentiginosine: Having established an efficient route for the preparation of allyl amine intermediate **16**, which possesses the three stereogenic centers necessary for lentiginosine synthesis, we next turned to the construction of the lactam ring through RCM (Scheme 3). Deprotection of



Scheme 3. Synthesis of the unsaturated lactam **20** by RCM.

16 with zinc and acetic acid in THF, followed by treatment of the resulting amine with but-3-enoyl chloride, furnished amide **19** as an oil. A ruthenium-catalyzed RCM in the presence of 10 mol% of Grubbs' catalysis (Grubbs I; benzylidene-bis(tricyclohexylphosphine)dichlororuthenium)[17] in benzene at 60 °C afforded the unsaturated lactam **20** in 73% yield.

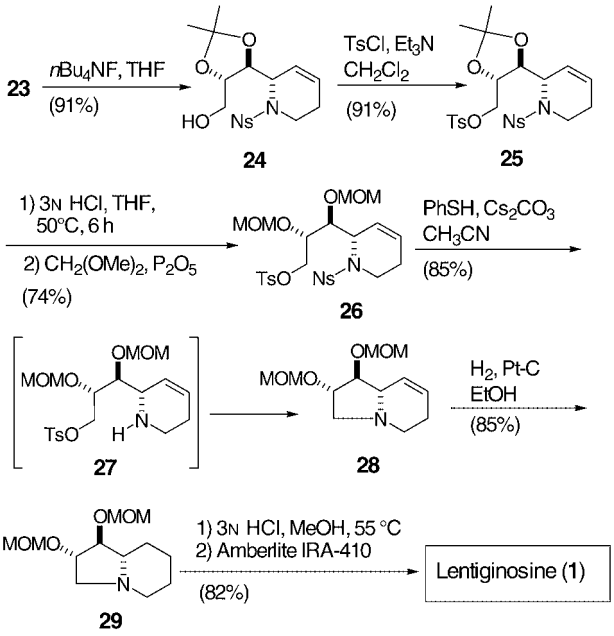
At this stage we felt it was unfortunate that there had been no opportunity to separate the minor isomer arising from enantioselective addition of Et_2Zn over the steps from allyl alcohol **10**. To solve this problem, we elected to prepare the *o*-nitrobenzenesulfonamide derivative, in view of the pronounced tendency of such derivatives to crystallize (Scheme 4). Thus, the *o*-nosyl amide **21** was prepared by deprotection of **16** and subsequent treatment of the resultant



Scheme 4. Synthesis of the nosyl intermediate **22** and its cyclization by RCM to give **23**.

amine with *o*-nitrobenzenesulfonyl chloride and triethylamine. Fortunately, diastereomerically pure **21** was obtained in 86% yield after recrystallization from a mixture of AcOEt and hexane, and the minor isomer could readily be removed at this stage. Following the Fukuyama method for the synthesis of secondary amines,[18] the *o*-nosyl amide **21** was treated with 3-buten-1-ol under Mitsunobu conditions (PPh_3, DEAD, benzene) to furnish the 1,7-diene **22** in 89% yield. A ruthenium-catalyzed RCM of **22** in the presence of Grubbs I catalysis (7 mol%) in benzene at 60 °C for 90 min successfully constructed the tetrahydropyridine ring to afford the cyclized product **23** in good yield (92%). The higher yield in this RCM reaction relative to that shown in Scheme 3 may be explained by the buttressing effect of the *o*-nitrobenzenesulfonyl group.[19]

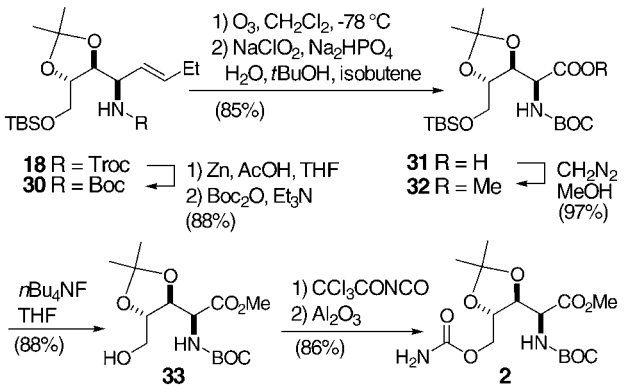
The next task was the preparation of the dihydroxylated five-membered ring of the lentiginosine framework (Scheme 5). Removal of the silyl protecting group in **23** with



Scheme 5. Synthesis of lentiginosine (**1**).

tetra-*n*-butylammonium fluoride, followed by tosylation of the resulting primary alcohol **24**, furnished the tosylate **25** in 83% yield over two steps. Since removal of the *o*-nosyl group in **25** gave no cyclized product,[20] the acetonide group used for diol protection in **25** was transformed into a bis-(methoxymethyl) (MOM) system by acid-catalyzed hydrolysis of the acetonide group with HCl (3 N) in aqueous THF, followed by MOM protection of the resulting diol with dimethoxymethane in the presence of phosphorous pentoxide[21] to afford **26** in 74% yield over the two steps. Removal of the *o*-nosyl group (**26**→**27**) with concomitant construction of a pyrrolidine ring (**27**→**28**) was achieved by treatment of **26** with thiophenol and cesium carbonate in acetonitrile, giving the cyclized product **28** in 85% yield. Catalytic hydrogenation of alkene **28** with platinum in ethanol afforded the indolizine **29** in 85% yield. Finally, removal of the two MOM groups in **29** with HCl (3 N) in hot aqueous MeOH (55 °C), followed by treatment with ion-exchange resin (Amberlite IRA 410), furnished an 82% yield of lentiginosine (**1**), the ^{1}H and ^{13}C NMR spectroscopic properties of which were in good agreement with those previously reported by Greene.[6l]

Synthesis of polyoxamic acid: The synthesis of the polyoxamic acid derivative **2** started with removal of the Troc group in **18** with zinc and acetic acid in THF (Scheme 6).



Scheme 6. Synthesis of the polyoxamic acid derivative **2**.

Reprotection of the resulting amine with di-*tert*-butyl dicarbonate and triethylamine provided the Boc-carbamate **30** in 88% yield. Oxidative cleavage of the double bond in **30** was carried out by ozonolysis, and the aldehyde produced was immediately subjected to sodium chlorite oxidation to furnish the protected polyoxamic acid **31** in 85% yield (two steps). Treatment of this acid **31** with diazomethane in methanol provided the methyl ester **32** in 97% yield. Removal of the silyl group in **32** by Ghosh's procedure with tetrabutylammonium fluoride and carbamoylation of **33** by treatment with trichloroacetyl isocyanate and aluminium oxide[22] furnished the Boc-protected carbamoylpolyoxamic acid ester **2** in 86% yield.

Conclusion

We have established a highly efficient synthetic method for allyl amines by a sequence of steps involving enantioselective addition of Et_2Zn and [3.3] sigmatropic rearrangement of allyl cyanates. As demonstrated in the synthesis of lentiginosine (**1**) and the polyoxamic acid **2**, the asymmetric center bearing the nitrogen substituent could be constructed without the problems of substrate/reagent matching and mismatching. Further applications of this method to the synthesis of natural products are under investigation in our group.

Experimental Section

Melting points were recorded on a micro melting point apparatus and are not corrected. Optical rotations are given in units of 10^{-1}deg cm^2 g^{-1}. Infrared spectra are reported as wavenumbers (cm^{-1}). ^{1}H NMR data are reported as follows: chemical shift (δ), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broadened, m = multiplet), coupling constants (J, given in Hz). ^{13}C NMR chemical shifts (δ) are recorded in parts per million (ppm) relative to $CDCl_3$ (δ = 77.0), CD_3OD (δ = 49.0), or *t*BuOH (δ = 30.29, in D_2O) as internal standards. High-resolution mass spectra (HRMS) are reported in m/z. Reactions were run under nitrogen when sensitive to moisture or oxygen. Dichloromethane was dried over molecular sieves (3 Å). Pyridine and triethylamine were stocked over anhydrous KOH. All other commercially available reagents were used as received.

(2*E*,4*S*,5*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-4,5-(isopropylidenedioxy)hex-2-enal (9): IBX (*o*-iodoxybenzoic acid, 250 mg) was added portionwise at 0 °C to a solution of allyl alcohol **7** (208 mg, 0.69 mmol) in DMSO (7.0 mL). After stirring at room temperature for 4 h, the reaction mixture was diluted with hexane and ether. The resulting suspension was poured into ice-cooled water and then filtered through a pad of Hyflo Super Cell. The separated aqueous layer was extracted with Et_2O, and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt/hexane 1:30) to afford aldehyde **9** (187 mg, 90%) as a colorless oil : $[\alpha]_D^{28}$ −3.2 (c = 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.08 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.43 (s, 3H), 1.45 (s, 3H), 3.72–3.90 (m, 3H), 4.63 (ddd, J = 8, 5, 1.5 Hz, 1H), 6.39 (ddd, J = 15.5, 8, 1.5 Hz, 1H), 6.83 (dd, J = 15.5, 5 Hz, 1H), 9.59 ppm (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = −5.5, −5.4, 18.3, 25.8, 26.7, 26.9, 63.0, 78.1, 80.7, 110.2, 131.9, 153.3, 193.1 ppm; IR (KBr): $\tilde{\nu}$ = 2932, 1699, 1096 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{28}O_4Si$: C 59.96, H 9.39; found: C 59.93, H 9.26.

(3*S*,4*E*,6*S*,7*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-6,7-(isopropylidenedioxy)-oct-4-en-3-ol (10): A solution of (*S*)-(+)-DPMPM (122 mg, 0.46 mmol) and aldehyde **9** (2.30 g, 7.65 mmol) dissolved in cyclohexane (26.0 mL) was heated at reflux for 30 min under nitrogen atmosphere, and was then cooled to 0 °C. Diethylzinc (1.02 M solution in hexane, 16.5 mL, 16.8 mmol) was added, and the mixture was stirred at 0 °C for 7 h. The reaction mixture was diluted with Et_2O and then poured into aqueous $KHSO_4$ solution (1 M), and the separated aqueous layer was extracted with Et_2O. The combined organic layer was washed with water, saturated aqueous $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt/hexane 1:20) to afford allyl alcohol **10** (2.31 g, 91%) as a colorless oil: $[\alpha]_D^{27}$ +1.71 (c = 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.07 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 0.94 (t, J = 7 Hz, 3H), 1.41 (s, 3H), 1.42 (s, 3H), 1.52–1.61 (m, 2H), 3.68–3.81 (m, 3H), 4.02–4.12 (m, 1H), 4.36 (t, J = 7 Hz, 1H), 5.72 (ddd, J = 15.5, 7, 1 Hz, 1H), 5.84 ppm (dd, J = 15.5, 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = −5.5, −5.3, 9.6, 18.3, 25.9, 26.9, 27.1, 29.9, 62.4,

73.2, 78.3, 81.5, 109.0, 127.9, 136.8 ppm; IR (KBr): $\tilde{\nu}$ = 3431, 2959, 2932, 1254, 1092 cm^{-1}.

(3*R*,4*E*,6*S*,7*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-6,7-(isopropylidenedioxy)-oct-4-en-3-ol (11): A solution of (*R*)-(−)-DPMPM (83 mg, 0.31 mmol) and aldehyde **9** (1.56 g, 5.19 mmol) dissolved in cyclohexane (18.0 mL) was heated at reflux for 30 min under nitrogen, and was then cooled to 0 °C. Diethylzinc (1.02 M solution in hexane, 11.2 mL, 11.42 mmol) was added dropwise, and the solution was stirred at 0 °C for 4 h. The reaction mixture was diluted with Et_2O and poured into aqueous $KHSO_4$ solution (1 M). The separated aqueous layer was extracted with Et_2O, and the combined organic layer was washed with water, saturated aqueous $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt/hexane 1:20) to afford allyl alcohol **11** (1.50 g, 87 %) as a colorless oil: $[\alpha]_D^{24}$ −10.7 (*c* = 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.06 (s, 3H), 0.07 (s, 3H), 0.90 (s, 9H), 0.93 (t, *J* = 7.5 Hz, 3H), 1.41 (s, 3H), 1.43 (s, 3H), 1.50–1.63 (m, 2H), 3.68–3.80 (m, 3H), 4.06 (q, *J* = 6.0 Hz, 1H), 4.36 (t, *J* = 7.0 Hz, 1H), 5.70 (ddd, *J* = 15.5, 7.0, 1.0 Hz, 1H), 5.83 ppm (ddd, *J* = 15.5, 6.0, 0.5 Hz, 1H); ^{13}C NMR (100 MHz): δ = −5.5, −5.3, 9.7, 18.3, 25.9, 26.9, 27.1, 29.9, 62.4, 73.5, 78.3, 81.5, 109.1, 128.1, 136.9 ppm; IR (KBr): $\tilde{\nu}$ = 3409, 2931, 1252 cm^{-1}.

(3*E*,5*S*,6*S*,7*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-6,7-(isopropylidenedioxy)-5-[(2,2,2-trichloroethoxycarbonyl)amino]-oct-3-ene (16): Trichloroacetyl isocyanate (650 μL, 5.46 mmol) was added at 0 °C to a solution of the allyl alcohol **10** (903 mg, 2.73 mmol) in CH_2Cl_2 (12.0 mL). After stirring at 0 °C for 20 min, the reaction mixture was concentrated under reduced pressure, and the resulting residue was dissolved in MeOH (7.0 mL). Water (11.0 mL) and potassium carbonate (2.26 g, 16.4 mmol) were added to the reaction mixture at 0 °C, and the cooling bath was removed. After the mixture had been stirred at room temperature for 7 h, the separated aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with aqueous $KHSO_4$ (1 M), water, saturated aqueous $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt/hexane 1:4) to afford allyl carbamate **13** (972 mg, 95 %) as a colorless oil.

Carbon tetrabromide (316 mg, 0.95 mmol) in CH_2Cl_2 (2.0 mL) was added at −20 °C under nitrogen to the allyl carbamate **13** (91 mg, 0.24 mmol), triphenylphosphine (223 mg, 0.85 mmol), and triethylamine (185 μL, 1.32 mmol) in CH_2Cl_2 (3.0 mL). The reaction mixture was allowed to warm to 0 °C over 20 min and was then treated with 2,2,2-trichloroethanol (260 μL, 2.68 mmol). After the mixture had been stirred at 0 °C for 1 h, the cooling bath was removed. After the mixture had then been stirred at room temperature for 2 h, ether and aqueous $KHSO_4$ (1 M) were added, and the separated aqueous layer was extracted with Et_2O. The combined organic layer was washed with water, saturated aqueous $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt/hexane 1:20) to afford Troc-carbamate **16** (106 mg, 86 %) as a colorless oil: $[\alpha]_D^{28}$ −12.2 (*c* = 1.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.08 (s, 6H), 0.91 (s, 9H), 1.00 (t, *J* = 7.5 Hz, 3H), 1.39 (s, 6H), 2.08 (dq, *J* = 7.5, 6.5 Hz, 2H), 3.68 (dd, *J* = 10, 6 Hz, 1H), 3.80 (dd, *J* = 10, 4.5 Hz, 1H), 3.84–3.91 (m, 1H), 4.02 (dd, *J* = 7.5, 4 Hz, 1H), 4.24–4.31 (m, 1H), 4.72 (2H, s), 5.43 (br d, *J* = 7.5 Hz, 1H), 5.49 (dd, *J* = 15.5, 7.5 Hz, 1H), 5.78 ppm (dt, *J* = 15.5, 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = −5.4, 13.3, 18.4, 25.3, 25.9, 26.9, 27.1, 54.9, 63.9, 74.6, 78.0, 80.7, 95.6, 109.5, 123.9, 137.0, 153.8 ppm; IR (KBr): $\tilde{\nu}$ = 3321, 2933, 1745, 1509, 1252, 1092 cm^{-1}.

(3*R*,4*E*,6*S*,7*S*)-3-[(Aminocarbonyl)oxy]-8-[(*tert*-butyldimethylsilyl)oxy]-6,7-(isopropylidenedioxy)-oct-4-ene (18): Trichloroacetyl isocyanate (96 μL, 0.80 mmol) was added at 0 °C to a solution of the allyl alcohol **11** (133 mg, 0.40 mmol) in CH_2Cl_2 (7.0 mL). After stirring at 0 °C for 20 min, the solution was concentrated under reduced pressure, and the resulting residue was dissolved in MeOH (3.0 mL). Water (3.0 mL) and potassium carbonate (388 mg, 2.8 mmol) were added at 0 °C, and the stirring was continued at room temperature for 6 h. The separated aqueous layer was extracted with Et_2O, and the combined organic layer was washed with aqueous $KHSO_4$ (1 M), water, saturated aqueous $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. Concentration under reduced pressure provided the residue, which was purified by silica gel chromatography (AcOEt/hexane 1:5) to afford allyl carbamate (147 mg, 97 %) as a colorless oil.

Carbon tetrabromide (502 mg, 1.51 mmol) in CH_2Cl_2 (2.0 mL) was added at −10 °C under nitrogen to a solution of the allyl carbamate (147 mg, 0.39 mmol), triphenylphosphine (356 mg, 1.36 mmol), and triethylamine (352 μL, 2.52 mmol) in CH_2Cl_2 (5.0 mL). The reaction mixture was stirred at −10 °C for 20 min, and was then treated with 2,2,2-trichloroethanol (1.50 mL, 15.6 mmol). After the solution had been allowed to warm to room temperature, the stirring was continued for 8 h. The mixture was diluted with Et_2O and aqueous $KHSO_4$ (1 M), and the separated aqueous layer was extracted with Et_2O. The combined organic layer was washed with water, saturated aqueous $NaHCO_3$, and brine, and was dried over anhydrous Na_2SO_4. Concentration under reduced pressure afforded the residue which was purified by silica gel chromatography (AcOEt/hexane 1:20) to afford Troc-carbamate **18** (168 mg, 86 %) as a colorless oil: $[\alpha]_D^{22}$ +2.9 (*c* = 1.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.10 (s, 6H), 0.91 (s, 9H), 0.99 (t, *J* = 7.5 Hz, 3H), 1.38 (s, 3H), 1.42 (s, 3H), 2.03–2.13 (m, 2H), 3.69 (dd, *J* = 11.5, 7.0 Hz, 1H), 3.78–3.90 (m, 1H), 3.84 (dd, *J* = 11.5, 7.5 Hz, 1H), 4.01 (dd, *J* = 7.5, 2.5 Hz, 1H), 4.38–4.45 (m, 1H), 4.72 (d, *J* = 11.5 Hz, 1H), 4.76 (d, *J* = 11.5 Hz, 1H), 5.48 (ddt, *J* = 15.5, 6.0, 1.5 Hz, 1H), 5.71 (br d, *J* = 9.0 Hz, 1H), 5.75 ppm (dtd, *J* = 15.5, 6.5, 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = −5.4, 13.3, 18.4, 25.3, 25.3, 25.9, 26.9, 27.0, 52.5, 63.5, 74.5, 81.0, 95.7, 109.1, 125.6, 134.8, 154.2 ppm; IR (KBr): $\tilde{\nu}$ = 3337, 2932, 1748, 1508, 1252, 1081 cm^{-1}.

(3*E*,5*S*,6*S*,7*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-6,7-(isopropylidenedioxy)-5-[(2-nitrobenzenesulfonyl)amino]-oct-3-ene (21): Zinc powder (750 mg, 11.4 mmol) was added at room temperature to a solution of Troc-carbamate **16** (340 mg, 0.67 mmol) and AcOH (270 μL, 4.7 mmol) in THF (17.0 mL). After vigorous stirring for 4 h, the resulting suspension was diluted with AcOEt, and filtered through a pad of Hyflo Super Cell®. The filtrate was concentrated, and the resulting residue was dissolved in CH_2Cl_2. This solution was washed with saturated aqueous $NaHCO_3$, water, and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The resulting crude amine was dissolved in CH_2Cl_2 (18.0 mL), and saturated aqueous $NaHCO_3$ (17.0 mL) and 2-nitrobenzenesulfonyl chloride (450 mg, 2.02 mmol) were added at 0 °C. After vigorous stirring at 0 °C for 2 h, the organic layer was separated and the aqueous layer was extracted with AcOEt. *N*,*N*-Dimethyl-1,3-propanediamine (0.19 mL, 1.51 mmol) was added at 0 °C to the combined organic layer to quench excess 2-nitrobenzenesulfonyl chloride. The solution was washed with water and brine, dried over anhydrous Na_2SO_4, and then concentrated to give a residue, which was purified by recrystallization (AcOEt and hexane) to afford *o*-nosylamide **21** (285 mg, 86 %) as colorless needles: mp 67–68 °C; $[\alpha]_D^{28}$ +114.2 (*c* = 1.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.08 (s, 3H), 0.09 (s, 3H), 0.71 (t, *J* = 7.5 Hz, 3H), 0.92 (s, 9H), 1.32 (s, 3H), 1.34 (s, 3H), 1.72–1.84 (m, 2H), 3.65–3.83 (m, 3H), 4.05 (dd, *J* = 7.5, 3.5 Hz, 1H), 4.12 (td, *J* = 9.0, 3.5 Hz, 1H), 5.22 (ddt, *J* = 15.5, 9.0, 1.5 Hz, 1H), 5.48 (dt, *J* = 15.5, 6.0 Hz, 1H), 5.82 (d, *J* = 9.0 Hz, 1H), 7.65–8.08 ppm (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = −5.5, −5.4, 12.8, 18.3, 24.9, 25.9, 26.8, 26.9, 58.5, 63.8, 77.5, 81.0, 109.4, 123.0, 125.2, 131.3, 132.5, 133.1, 135.5, 138.2, 147.8 ppm; IR (KBr): $\tilde{\nu}$ = 3363, 2933, 1542, 1363, 1172, 1084, 743 cm^{-1}; elemental analysis calcd (%) for $C_{23}H_{38}N_2O_7SSi$: C 53.67, H 7.44, N 5.44; found: C 53.69, H 7.49, N 5.36.

(3*E*,5*S*,6*S*,7*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-6,7-(isopropylidenedioxy)-5-[(2-nitrobenzenesulfonyl)(pent-3-enyl)amino]-oct-3-ene (22): Diethyl azodicarboxylate (40 % toluene solution, 1.40 mL, 0.36 mmol) was added dropwise at 0 °C to a solution of the *o*-nosylamide **21** (372 mg, 0.72 mmol), but-3-en-1-ol (217 μL, 2.53 mmol), and triphenylphosphine (950 mg, 3.61 mmol) in benzene. After having been stirred at room temperature for 7 h, the resulting mixture was concentrated under reduced pressure to afford the residue, which was purified by silica gel chromatography (AcOEt/hexane 1:7) to furnish the alkene **22** (367 mg, 89 %) as a colorless oil: $[\alpha]_D^{27}$ +20.7 (*c* = 2.92, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.09 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 0.90 (t, *J* =

7.0 Hz, 3H), 1.36 (s, 3H), 1.37 (s, 3H), 1.98 (dq, J = 12.0, 7.0 Hz, 2H), 2.45 (td, J = 8.0, 7.0 Hz, 2H), 3.38 (dt, J = 15.5, 8.0 Hz, 1H), 3.52 (dt, J = 15.5, 8.0 Hz, 1H), 3.73 (td, J = 8.5, 4.0 Hz, 1H), 3.77–3.81 (m, 2H), 4.13 (dd, J = 8.5, 2.0 Hz, 1H), 4.44 (dd, J = 7.5, 2.0 Hz, 1H), 4.98–5.08 (m, 2H), 5.51–5.65 (m, 2H), 5.73 (ddt, J = 12.0, 10.0, 7.0 Hz, 1H), 7.57–7.99 ppm (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = −5.5, −5.4, 13.1, 18.4, 25.5, 25.9, 26.9, 35.3, 45.4, 60.3, 63.3, 79.2, 81.1, 109.5, 116.7, 120.8, 124.0, 130.6, 131.3, 133.2, 134.1, 135.0, 139.5, 148.4 ppm; IR (KBr): $\tilde{\nu}$ = 2933, 1547, 1373, 1171, 778 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{44}N_2O_7SSi$: C 57.01, H 7.80, N 4.93; found: C 56.92, H 7.77, N 5.12.

(2*S*)-(1′*S*,2′*S*)-3′-[(*tert*-Butyldimethylsilyl)oxy]-[1′,2′-(isopropylidenedioxy)propyl]-*N*-(2-nitrobenzenesulfonyl)-3,4-dehydro-piperidine (23): A dry Schlenk flask was charged with **22** (211 mg, 0.37 mmol) and benzene (19.0 mL) and the solution was degassed by three freeze-thaw cycles. After the Schlenk flask had been cooled to −78 °C, benzylidenebis(tricyclohexylphosphine)dichlororuthenium (21 mg, 0.026 mmol) was placed on the resulting solidified mixture. The Schlenk flask was evacuated and then heated at 60 °C for 90 min. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt/hexane 1:10) to afford cyclized lactam **23** (175 mg, 92%) as a colorless oil: $[\alpha]_D^{26}$ −193.5 (c = 1.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.08 (s, 6H), 0.90 (s, 9H), 1.38 (s, 3H), 1.40 (s, 3H), 1.85–2.01 (m, 2H), 3.41 (ddd, J = 15.0, 11.0, 5.5 Hz, 1H), 3.97 (dd, J = 15.0, 5.5 Hz, 1H), 4.04–4.10 (m, 1H), 4.14 (dd, J = 7.0, 6.5 Hz, 1H), 4.47–4.52 (m, 1H), 5.79–5.92 (m, 2H), 7.55–8.00 ppm (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = −5.5, −5.4, 18.3, 23.1, 25.9, 27.1, 27.2, 40.1, 55.7, 63.0, 79.2, 79.7, 109.3, 124.0, 124.6, 126.6, 130.3, 131.5, 133.5, 134.2, 148.2 ppm; IR (KBr): $\tilde{\nu}$ = 2932, 1547, 1373, 1171, 747 cm^{-1}; elemental analysis calcd (%) for $C_{23}H_{36}N_2O_7SSi$: C 53.88, H 7.08, N 5.46; found: C 53.83, H 6.90, N 5.22.

(2*S*)-(1′*S*,2′*S*)-3′-Hydroxy-[1′,2′-(isopropylidenedioxy)-propyl]-*N*-(2-nitrobenzenesulfonyl)-3,4-dehydro-piperidine (24): A solution of tetrabutylammonium fluoride (1 M solution in THF, 360 μL, 0.36 mmol) was added to a solution of silyl ether **23** (134 mg, 10.3 mmol) in CH_3CN (5.0 mL). The reaction mixture was stirred at room temperature for 6 h and was then concentrated under reduced pressure. Purification of the resulting residue by silica gel chromatography (AcOEt/hexane 1:1) afforded alcohol **24** (94 mg, 91%) as a colorless oil: $[\alpha]_D^{23}$ −301.2 (c = 0.94, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.42 (s, 3H), 1.43 (s, 3H), 1.87–2.03 (m, 2H; H-2), 3.29–3.39 (m, 1H), 3.72 (ddd, J = 12.0, 8.0, 4.0 Hz, 1H), 3.88 (dt, J = 12.0, 4.0 Hz, 1H), 4.06 (t, J = 7.5 Hz, 1H), 4.19 (dt, J = 7.5, 3.5 Hz, 1H), 4.44–4.50 (m, 1H), 5.79–5.86 (m, 1H), 5.91 (dq, J = 10.5, 2.0 Hz, 1H), 7.57–8.02 ppm (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.8, 27.0, 27.1, 39.9, 55.8, 62.3, 78.5, 79.7, 109.5, 124.1, 124.9, 126.3, 130.4, 131.6, 133.7, 133.8, 148.1 ppm; IR (KBr): $\tilde{\nu}$ = 3447, 1545, 1373, 1168, 748 cm^{-1}; HRMS (FAB): found: 399.1232 $[M+H]^+$; $C_{17}H_{23}O_7N_2S$ calcd 399.1226; elemental analysis calcd (%) for $C_{17}H_{22}N_2O_7S$: C 51.25, H 5.57, N 7.03; found: C 51.27, H 5.42, N 6.98.

(2*S*)-{(1′*S*,2′*S*)-1′,2′-(Isopropylidenedioxy)-3′-[(*p*-toluenesulfonyl)oxy]-propyl}-*N*-(2-nitrobenzenesulfonyl)-3,4-dehydropiperidine (25): A solution of alcohol **24** (175 mg, 0.44 mmol) and Et_3N (1.1 mL, 7.92 mmol) in CH_2Cl_2 (12.0 mL) was treated at 0 °C with *p*-toluenesulfonyl chloride (755 mg, 3.96 mmol). After the mixture had been stirred at room temperature for 4 h, *N*,*N*-dimethyl-1,3-propanediamine (550 μL, 4.4 mmol) was added to quench the excess *p*-toluenesulfonyl chloride. The mixture was diluted with ether and poured into water. The aqueous layer was extracted with AcOEt. The combined organic extract was washed with aqueous $KHSO_4$ (1 M), water, saturated aqueous $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. Concentration under reduced pressure provided a residue, which was purified by silica gel chromatography (AcOEt/hexane 1:2) to furnish the tosylate **25** (221 mg, 91%) as a colorless oil: $[\alpha]_D^{26}$ −172.6 (c = 1.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.35 (s, 3H), 1.39 (s, 3H), 1.83–1.90 (m, 2H), 2.45 (s, 3H), 3.20–3.31 (m, 1H), 3.88–3.95 (m, 1H), 4.06 (t, J = 7.5 Hz, 1H), 4.19 (d, J = 3.5 Hz, 2H), 4.26 (td, J = 7.5, 3.5 Hz, 1H), 4.39–4.44 (m, 1H), 5.77–5.89 (m, 2H), 7.33–8.00 ppm (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.6, 22.7, 26.8, 27.0, 39.9, 55.7, 69.0, 77.0, 78.2, 110.2, 124.1, 124.6, 126.6, 128.1, 129.9, 130.4, 131.7, 132.6, 133.6, 133.8, 145.0, 148.1 ppm; IR (KBr): $\tilde{\nu}$ = 1546, 1372, 1178, 853, 747 cm^{-1}; elemental analysis calcd (%) for $C_{24}H_{28}N_2O_9S_2$: C 52.16, H 5.11, N 5.07; found: C 52.15, H 5.21, N 5.11.

(2*S*)-{(1′*S*,2′*S*)-1′,2′-Dihydroxy-3′-[(*p*-toluenesulfonyl)oxy]propyl}-*N*-(2-nitrobenzenesulfonyl)-3,4-dehydropiperidine (26): A solution of acetonide **25** (340 mg, 0.62 mmol) in a mixture of THF (15.0 mL) and HCl (3 N, 10.0 mL) was heated at 50 °C for 5 h. The reaction mixture was concentrated, and the resultant aqueous layer was extracted with AcOEt. The combined extract was washed with water, saturated aqueous $NaHCO_3$, and brine, and was dried over anhydrous Na_2SO_4. After concentration under reduced pressure, purification of the resulting oil by silica gel chromatography (AcOEt/hexane 1:1) furnished the corresponding diol (289 mg, 92%).

A portion of the resulting diol (146 mg, 0.29 mmol) in dimethoxymethane (25.0 mL) was stirred at room temperature for 1.5 h in the presence of solid phosphorus pentoxide (ca. 20 mg). The reaction mixture was diluted with Et_2O and poured into water. The separated aqueous layer was extracted with AcOEt, and the combined organic extract was washed with saturated aqueous $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. After concentration under reduced pressure, the resulting residue was purified by silica gel chromatography (AcOEt/hexane 1:2) to give bis-methoxymethyl ether **26** (137 mg, 80%) as a white crystalline solid: Mp 115–118 °C; $[\alpha]_D^{23}$ −152.1 (c = 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.85–2.04 (m, 2H), 2.46 (s, 3H), 3.34 (s, 3H), 3.35 (s, 3H), 3.82 (dd, J = 6.0, 4.0 Hz, 1H), 4.23 (dd, J = 10.0, 6.0 Hz, 1H), 4.29 (dd, J = 10.0, 6.0 Hz, 1H), 4.62–4.73 (m, 5H), 5.73–5.79 (m, 1H), 5.79–5.85 (m, 1H), 7.34–7.99 ppm (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.6, 23.0, 39.8, 53.5, 55.9, 56.6, 68.6, 75.8, 80.1, 98.1, 98.5, 123.9, 124.3, 127.0, 128.0, 129.9, 130.4, 131.6, 132.7, 133.6, 133.6, 145.1, 148.1 ppm; IR (KBr): $\tilde{\nu}$ = 1545, 1362, 1178, 747 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{34}O_4Si$: C 49.99, H 5.37, N 4.66; found: C 50.00, H 5.11, N 4.65.

(1*S*,2*S*,8a*S*)-1,2-Bis(methoxymethoxy)-1,2,3,5,6,8a-hexahydro-indolizine (28): Thiophenol (16 μL, 0.16 mmol) was added to a suspension of **26** (32 mg, 0.053 mmol) and cesium carbonate (52 mg, 0.16 mmol) in acetonitrile (8.0 mL). After being stirred at room temperature for 1.5 h, the reaction mixture was filtered through a pad of Hyflo Super Cell®, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (dichloromethane/methanol, 30:1) to afford cyclized product **28** (11 mg, 85%) as a colorless oil: $[\alpha]_D^{26}$ −51.7 (c = 1.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.90–2.04 (m, 1H), 2.24–2.42 (m, 1H), 2.69 (ddd, J = 12.0, 10.0, 5.0 Hz, 1H), 2.92–3.04 (m, 3H), 3.08–3.16 (m, 1H), 3.38 (s, 3H), 3.40 (s, 3H), 3.84 (dd, J = 6.0, 3.0 Hz, 1H), 4.14 (ddd, J = 6.0, 4.5, 3.0 Hz, 1H), 4.64–4.80 ppm (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.8, 46.7, 55.4, 55.5, 56.5, 64.3, 81.6, 86.8, 95.9, 96.1, 126.1, 126.5 ppm; IR (KBr): $\tilde{\nu}$ = 1152, 1106, 1043 cm^{-1}; HRMS (FAB): found: 244.1571 $[M+H]^+$ $C_{12}H_{22}NO_4$ calcd 244.1549.

(1*S*,2*S*,8a*S*)-1,2-Bis(methoxymethoxy)indolizidine (29): A mixture of alkene **28** (14 mg, 0.058 mmol) and platinum on activated carbon (6 mg) in ethanol (6.0 mL) was vigorously stirred under hydrogen atmosphere for 2 h. The mixture was filtered through a pad of Hyflo Super Cell, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (dichloromethane/methanol 40:1) to afford indolizidine **29** (12 mg, 85%) as a colorless oil: $[\alpha]_D^{24}$ −30.0 (c = 0.73, $CHCl_3$) (lit.[6e] $[\alpha]_D^{20}$ −31, c = 1.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.12–1.48 (m, 2H), 1.54–2.02 (m, 5H), 1.90–2.02 (m, 1H), 2.38–2.46 (dd, J = 10.5, 5.5 Hz, 1H), 2.98–3.07 (m, 2H), 3.39 (s, 6H), 3.77 (dd, J = 8.0, 2.0 Hz, 1H), 4.01 (dd, J = 5.5, 2.0 Hz, 1H), 4.63–4.82 ppm (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.0, 24.7, 29.0, 53.3, 55.4, 55.5, 59.7, 68.8, 79.6, 87.6, 95.3, 95.9 ppm; IR (KBr): $\tilde{\nu}$ = 2936, 1152, 1107, 1041 cm^{-1}; HRMS (FAB): found: 246.1728 $[M+H]^+$; $C_{12}H_{24}NO_4$ calcd 246.1705.

Lentiginosine (1): A solution of indolizidine **29** (19 mg, 0.077 mmol) was dissolved in a mixture of methanol (6.0 mL) and HCl (3 N, 2.0 mL). After stirring at 55 °C for 5 h, the solution was concentrated under reduced pressure. The resulting hydrochloride was purified by silica gel chromatography (CH_2Cl_2/CH_3OH/28% aq. NH_3 85:14:1) to afford the residue, which was passed through an ion-exchange column of IRA-410 (H_2O) to furnish lentiginosine (**1**; 10 mg, 82%) as a white solid: $[\alpha]_D^{27}$ +1.06 (c = 0.47, MeOH) (lit.[6e] $[\alpha]_D^{20}$ +2.8, c = 0.28, MeOH) (lit.[6f] $[\alpha]_D^{25}$ +3.2, c =

0.27, MeOH) (lit.[6] $[\alpha]_D^{24}$ +3.1, c = 0.31, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.14–1.34 (m, 2H), 1.38–1.69 (m, 2H), 1.74–1.97 (m, 2H), 1.88–1.97 (m, 2H), 2.04 (td, J = 11.0, 3.0 Hz, 1H), 2.61 (dd, J = 11.0, 7.5 Hz, 1H), 2.82 (dd, J = 11.0, 2.0 Hz, 1H), 2.93 (br d, J = 11.0 Hz, 1H), 3.64 (dd, J = 9.0, 4.0 Hz, 1H), 4.06 ppm (ddd, J = 8.0, 4.0, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.8, 23.8, 27.4, 52.4, 60.1, 68.3, 75.5, 82.8 ppm; IR (KBr): $\tilde{\nu}$ = 3309 cm^{-1}; HRMS (FAB): found: 158.1210 $[M+H]^+$; $C_8H_{15}N_1O_2$ calcd 158.1181.

(3*E*,5*R*,6*S*,7*S*)-5-[(*tert*-Butoxycarbonyl)amino]-8-[(*tert*-butyldimethylsilyl)oxy]-6,7-(isopropylidenedioxy)-oct-3-ene (30): Zinc powder (863 mg, 13.2 mmol) was added at room temperature to a solution of allyl carbamate **18** (392 mg, 0.78 mmol) and AcOH (310 μL, 5.43 mmol) in THF (15.0 mL). After being stirred vigorously for 6 h, the suspension was diluted with AcOEt and was then filtered through a pad of Hyflo Super Cell. The filtrate was concentrated under reduced pressure to afford the crude allyl amine, which was dissolved in THF (20.0 mL). The solution was treated with Et_3N (140 μL, 1.01 mmol) and Boc_2O (230 μL, 1.01 mmol) at room temperature. After being stirred at room temperature for one day, the solution was concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography (AcOEt/hexane 1:8) to afford Boc-carbamate **30** (293 mg, 88%) as a colorless oil: $[\alpha]_D^{26}$ +1.3 (c = 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.09 (s, 6H), 0.91 (s, 9H), 0.99 (t, J = 7.5 Hz, 3H), 1.37 (s, 3H), 1.41 (s, 3H), 1.44 (s, 9H), 2.02–2.12 (m, 2H), 3.68–3.76 (m, 1H), 3.77–3.87 (m, 2H), 3.95–4.02 (m, 1H), 4.29 (br s, 1H), 5.18 (br s, 1H), 5.45 (dtd, J = 15.5, 6.0, 1.0 Hz, 1H), 5.68 ppm (dtd, J = 15.5, 7.0, 0.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = −5.5, −5.4, 13.4, 18.4, 25.3, 25.4, 26.0, 26.9, 27.0, 28.4, 63.3, 77.5, 79.3, 80.7, 108.9, 126.5, 134.0, 155.5 ppm; IR (KBr): $\tilde{\nu}$ = 2932, 1718, 1368, 1253, 1170 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{34}O_4Si$: C 61.50, H 10.09, N 3.26; found: C 61.51, H 10.28, N 3.11.

2-*N*-[(*tert*-Butoxycarbonyl)amino]-5-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-3,4-*O*-isopropylidene-L-xylonic acid (31): A solution of the alkene **30** (227 mg, 0.53 mmol) in methanol (15.0 mL) was cooled to −78°C. Ozone was passed through the solution until starting material had been consumed (TLC analysis). The resulting blue solution was purged with oxygen for 10 min, and dimethyl sulfide (270 μL, 3.70 mmol) was then added. After the mixture had been stirred at −78°C for 10 min, saturated aqueous $NaHCO_3$ was added. The separated aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure.

The resulting residue, dissolved in a mixture of *t*BuOH (20.0 mL) and H_2O (4.0 mL), was treated with Na_2HPO_4 (375 mg, 2.64 mmol), 2-methylbut-2-ene (1 drop), and $NaClO_2$ (143 mg, 1.58 mmol). After stirring at room temperature for 70 min, the mixture was poured into aqueous $KHSO_4$ (1M). The aqueous layer was extracted with CH_2Cl_2, and the combined organic extract was washed with brine and dried over anhydrous Na_2SO_4. Concentration under reduced pressure, followed by purification by silica gel chromatography (AcOEt/hexane/acetic acid 16:83:1), afforded carboxylic acid **31** (189 mg, 85%), which was further purified by recrystallization to yield an analytically pure sample as a white crystalline solid: m.p. 133–135°C; $[\alpha]_D^{27}$ +4.1 (c = 1.04, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz): δ = 0.06 (s, 3H), 0.07 (s, 3H), 0.97 (s, 9H), 1.25 (s, 3H), 1.27 (s, 3H), 1.39 (s, 9H), 3.70 (dd, J = 10.5, 5.5 Hz, 1H), 3.79 (dd, J = 10.5, 4.0 Hz, 1H), 4.07–4.14 (m, 1H), 10.40 ppm (br s, 1H); ^{13}C NMR (C_6D_6, 100 MHz): δ = −5.4, 18.5, 26.1, 26.9, 27.0, 28.3, 53.9, 63.2, 77.6, 78.7, 80.1, 109.7, 156.4, 175.4 ppm; IR (KBr): $\tilde{\nu}$ = 3399, 2932, 1749, 1718, 1165, 1090 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{34}O_4Si$: C 54.39, H 8.89, N 3.34; found: C 54.42, H 8.65, N 3.12.

Methyl 2-*N*-[(*tert*-butoxycarbonyl)amino]-5-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-3,4-*O*-isopropylidene-L-xylonate (32): A solution of carboxylic acid **31** (39 mg, 0.093 mol), dissolved in Et_2O (3.0 mL) and cooled to 0°C, was treated with an ethereal solution of diazomethane until a yellow-colored solution persisted. The excess diazomethane was quenched by dropwise addition of acetic acid until the color dissipated. The resulting reaction mixture was concentrated under reduced pressure to give a residue, which was purified by silica gel chromatography (AcOEt/hexane 1:10) to afford methyl ester **32** (39 mg, 97%) as a colorless oil: $[\alpha]_D^{27}$ +0.26 (c = 1.14, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz): δ = 0.06 (s, 3H), 0.07 (s, 3H), 0.97 (s, 9H), 1.25 (s, 3H), 1.30 (s, 3H), 1.41 (s, 9H), 3.21 (s, 3H), 3.71 (dd, J = 11.0, 5.5 Hz, 1H), 3.80 (dd, J = 11.0, 4.0 Hz, 1H), 4.15 (ddd, J = 8.0, 5.5, 4.0 Hz, 1H), 4.66 (dd, J = 8.0, 1.0 Hz, 1H), 4.86 (dd, J = 9.5, 1.0 Hz, 1H), 5.10 ppm (br d, J = 9.5 Hz, 1H); ^{13}C NMR (C_6D_6, 100 MHz): δ = −5.4, −5.4, 18.5, 26.1, 26.9, 27.2, 28.3, 52.0, 54.1, 63.3, 77.5, 79.0, 79.8, 109.6, 156.2, 171.0 ppm; IR (KBr): $\tilde{\nu}$ = 3448, 2933, 1757, 1720, 1253, 1165 cm^{-1}; HRMS (FAB): found: 434.2525 $[M+H]^+$; $C_{20}H_{40}NO_7Si$ calcd 434.2574.

Methyl 2-*N*-[(*tert*-butoxycarbonyl)amino]-2-deoxy-3,4-*O*-isopropylidene-L-xylonate (33): A solution of methyl ester **32** (17 mg, 0.039 mmol), dissolved in acetic acid (0.90 mL), THF (0.30 mL), and H_2O (0.30 mL), was stirred at room temperature for 2 days. THF was removed under reduced pressure, and the aqueous layer was extracted with AcOEt. The combined organic extract was washed with saturated aqueous $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Concentration under reduced pressure, followed by purification by silica gel chromatography (AcOEt/hexane 1:1), furnished alcohol **33** (11 mg, 88%) as a colorless oil: $[\alpha]_D^{27}$ +14.9 (c = 0.94, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.40 (s, 3H), 1.41 (s, 3H), 1.46 (s, 9H), 2.34 (br, 1H), 3.91 (dt, J = 8.0, 4.0 Hz, 1H), 4.37 (dd, J = 8.5, 1.5 Hz, 1H), 4.46 (dd, J = 9.0, 1.5 Hz, 1H), 5.41 ppm (br d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.8, 27.0, 28.3, 52.8, 53.1, 61.5, 76.9, 77.8, 80.5, 109.6, 156.1, 170.6 ppm; IR (KBr): $\tilde{\nu}$ = 3447, 2985, 1751, 1717, 1508, 1370, 1250, 1165 cm^{-1}; HRMS (FAB): found: 320.1688 $[M+H]^+$; $C_{14}H_{26}NO_7$ calcd 320.1709.

Methyl 5-*O*-(aminocarbonyl)-2-[*N*-*tert*-butoxycarbonyl]amino]-2-deoxy-3,4-*O*-isopropylidene-L-xylonate (2): Trichloroacetyl isocyanate (12 μL, 0.10 mmol) was added at 0°C to a solution of alcohol **33** (16 mg, 0.050 mmol) in CH_2Cl_2 (3.0 mL). After the mixture had been stirred at 0°C for 5 min, Al_2O_3 (400 mg) was added. The solvent was removed under reduced pressure, and the resulting solid was allowed to stand for 2 h and was then eluted with AcOEt. The eluent was concentrated and purified by silica gel chromatography (AcOEt/hexane, 2:1) to afford carbamate **2** (15 mg, 86%) as a colorless oil: $[\alpha]_D^{23}$ −2.2 (c = 0.54, CH_2Cl_2) (lit.[9] $[\alpha]_D^{23}$ −2.8, c = 0.84, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.39 (s, 3H), 1.42 (s, 3H), 1.46 (s, 9H), 3.80 (s, 3H), 4.02 (dt, J = 8.5, 5.0 Hz, 1H), 4.24–4.27 (m, 2H), 4.29 (dd, J = 8.5, 1.5 Hz, 1H), 4.51 (dd, J = 9.5, 1.5 Hz, 1H), 4.87 (br s, 2H), 5.30 ppm (br d, J = 9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.8, 26.8, 28.3, 52.8, 53.1, 64.1, 74.9, 78.3, 80.5, 110.1, 155.9, 156.1, 170.6 ppm; IR (KBr): $\tilde{\nu}$ = 3448, 3365, 1719, 1370, 1251, 1166, 1071 cm^{-1}. HRMS (FAB): found: 363.1721 $[M+H]^+$; $C_{15}H_{27}N_2O_8$ calcd 363.1767.

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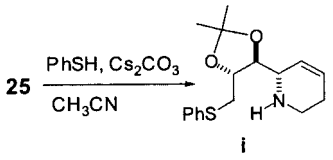

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