NOVEL ROUTE TO THE SYNTHESIS OF HYDROXYLATED PYRROLIDINE DERIVATIVES *VIA* THE INTRAMOLECULAR REACTION OF γ-AMINOALLYLSTANNANE WITH ALDEHYDE. TOTAL SYNTHESIS OF (+)-PREUSSIN

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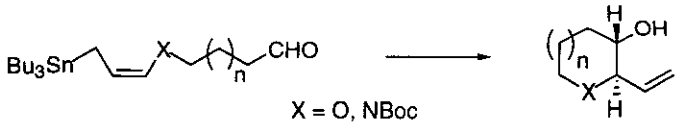
Abstract-The thermal cyclization of γ-aminoallylstannane (**8**) having an aldehyde group gave β-hydroxypyrrolidine derivative (**9a**) as a sole product. This methodology was applied successfully to the total synthesis of (+)-preussin.

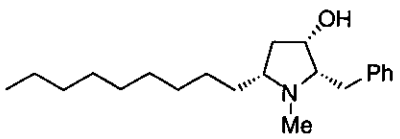
INTRODUCTION

Recently, we have developed an efficient method for the synthesis of medium sized cyclic ether *via* the intramolecular reaction of γ-alkoxyallylstannane with aldehyde (eq 1; X = O, n = 1, 2).[1] The usefulness of this methodology has been demonstrated by the total synthesis of hemibrevetoxin B[2] and related polycyclic ethers.[3]

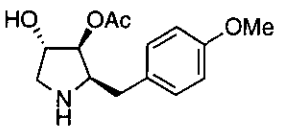


(1)

It occurred to us that replacement of the oxygen to nitrogen would produce the corresponding β-hydroxy nitrogen heterocycle (eq 1, X = NBoc). The structural framework of hydroxylated nitrogen heterocycle is widely found in alkaloids such as (+)-preussin (**1**)[4] and anisomycin (**2**).[5] In this paper, we wish to report the stereoselective synthesis of β-hydroxypyrrolidine derivatives *via* the intramolecular reaction of γ-aminoallylstannane with aldehyde[6] and its application to the total synthesis of **1**. To the best of our knowledge, this is the first example of a successful use of γ-aminoallylstannane in organic synthesis.[7]



1: (+)-Preussin

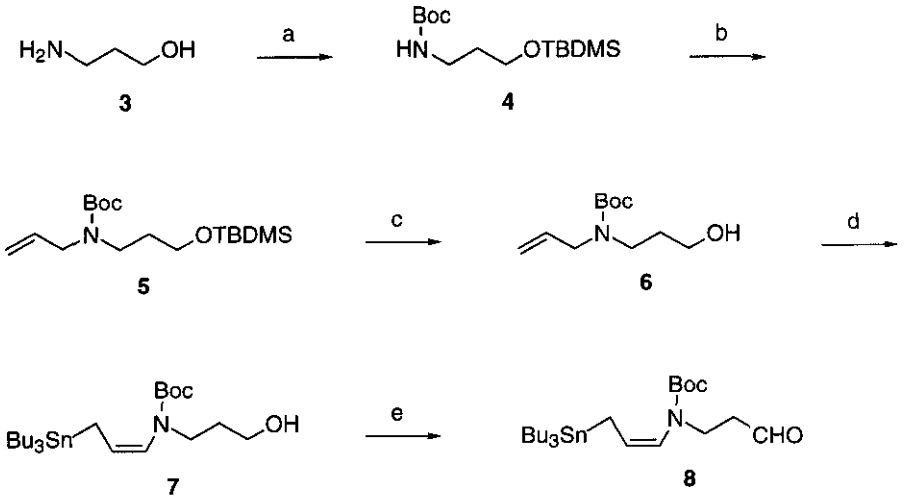


2: (-)-Anisomycin

INTRAMOLECULAR REACTION OF γ-AMINOALLYLSTANNANE WITH ALDEHYDE

The γ-aminoallylstannane (**8**), bearing formyl group at the terminus of the carbon chain, was prepared as shown in Scheme 1. Reaction of 4-amino-1-propanol (**3**) with TBDMSCl/Et_3N followed by the treatment with Boc_2O gave *N*-protected silyl ether (**4**) in 91% yield. Allylation of **4** was performed with allyl bromide/KH to give **5** in 96% yield. Desilylation of **5** with TBAF afforded primary alcohol (**6**) in 96% yield. Treatment of **6** with *sec*-BuLi/TMEDA followed by trapping with *n*-Bu_3SnCl gave *Z*-γ-amino-allylstannane (**7**) in 43% yield. Oxidation of alcohol (**7**) produced aldehyde (**8**) in 73% yield.

Scheme 1



Reagents and Conditions: (a) TBDMSCl, Et_3N, CH_2Cl_2, 0 ℃, 1 h, then Boc_2O, 0 ℃, 1 h, 91%; (b) KH, THF, 0 ℃, 20 min, then allyl bromide, rt, 96%; (c) TBAF, THF, rt, 96%; (d) *sec*-BuLi, TMEDA, THF, -78 ℃, then *n*-Bu_3SnCl, -78 ℃ → rt, 43%; (e) SO_3·py, DMSO, Et_3N, CH_2Cl_2, rt, 73%.

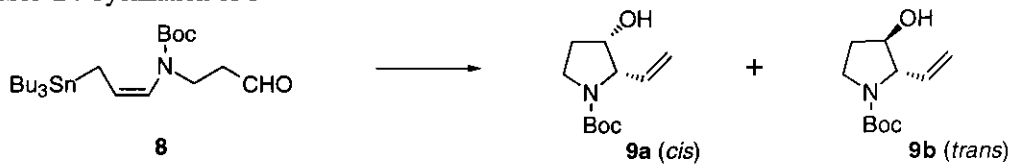
The results of the cyclization of **8** are summarized in Table 1. All reactions were carried out immediately after preparation of the substrate (**8**) owing to its low stability. Although the Lewis and protic acid mediated reactions gave unsatisfactory results (entries 1-6), very high stereoselectivity was observed in the thermal cyclization. Thus, the reaction of **8** in refluxing toluene afforded **9a** in 67% yield as a sole product (entry 7).

The stereochemistries of **9a** and **9b** were confirmed by the ^{1}H-NMR analysis and NOE experiments of the corresponding acetate (**10**)[8] and (**11**) (Figure 1).[9] The *cis* stereochemistry of **10** was determined by observing NOEs between H_α (δ 3.88) and H_β (δ 5.25). Strong NOEs between H_β (δ 5.00) and an olefinic proton H_γ (δ 5.78) was observed, indicating the *trans* stereochemistry of **11**. Irradiation of H_β of **11** gave also a significant enhancement of the resonance at H_α (δ 4.32), as usually observed in the case of 5-membered cyclic compounds.

The observed stereoselectivities are well explained by the similar mechanism as that proposed for the reaction of allylstannane with aldehyde.[10] It is widely accepted that the thermal reaction of allylic stannane with aldehyde proceeds *via* a cyclic transition state as shown in Scheme 2. Owing to the high stability of

cis fused 5-6 system such as **12**, **8** cyclized to give *cis* isomer (**9a**), predominantly. Scheme 3 illustrates the acyclic transition state model for the Lewis acid mediated reaction of **8**. Perhaps, the small energy gap between **13** and **14** would cause the low stereoselectivity.

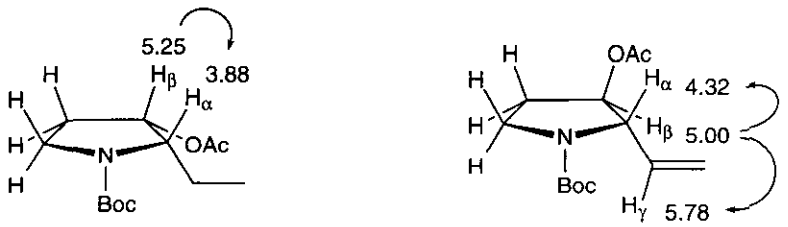
Table 2. Cyclization of **8**[a]



8 **9a** (*cis*) **9b** (*trans*)

entry	reagent (equiv)	temp (℃)	time (h)	ratio (**9a**:**9b**)[b]	yield (%)[c]
1	$TiCl_4$ (1.2)	-78	0.5	59:41	38
2	$BF_3 \cdot OEt_2$ (1.2)	-78	0.5	36:64	70
3	$SnCl_4$ (1.2)	-78	0.5	76:24	52
4	$AlCl_3 \cdot OEt_2$ (1.2)	-78	0.5	67:33	66
5	$MgBr_2 \cdot OEt_2$ (1.2)	-78	0.5	59:41	63
6	CF_3CO_2H (2.0)	-78	0.5	49:51	70
7	-[d]	110	1.0	>98:2	67

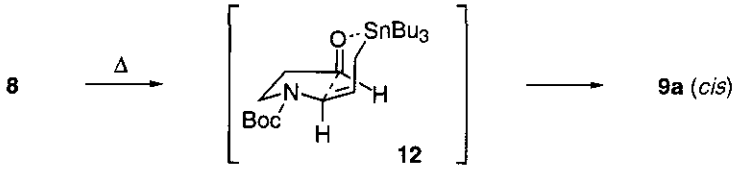
[a]The reactions were carried out with 0.1 M substrate in CH_2Cl_2 under the conditions indicated in the Table, and quenched with aqueous saturated $NaHCO_3$ at the reaction temperature. [b]Ratios were determined by a capillary GC analysis [c]Isolated yields [d]Toluene was used as a solvent.



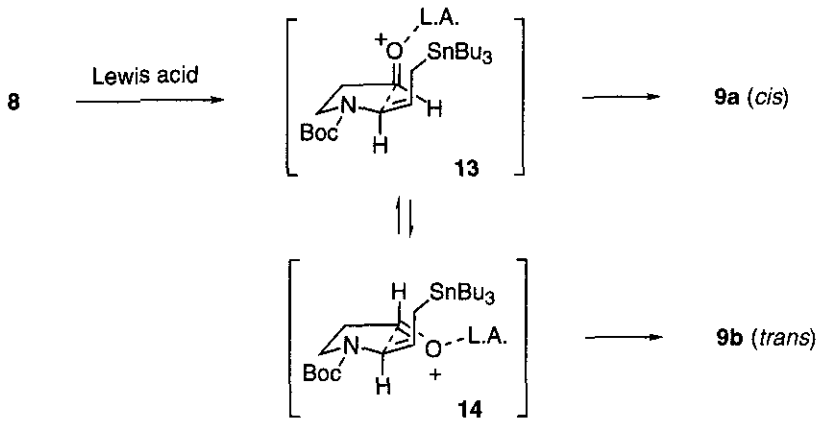
10 **11**

Figure 1. Chemical shifts of representative protons of **10** and **11**. Observed NOEs are shown by arrows.

Scheme 2. Cyclic Transition State Model for the Thermal Cyclization of **8**



Scheme 3. Acyclic Transition State Model for the Lewis Acid Mediated Cyclization of **8**

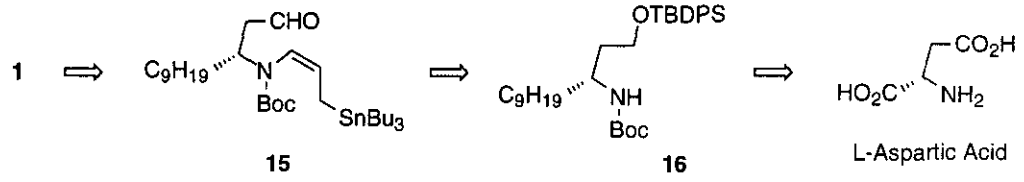


The stereoselective formation of the *cis* isomer (**9a**) is highly promising for the synthesis of nitrogen heterocycles, since (+)-preussin possesses *cis*-sterochemistry between α- and β-substituents.

TOTAL SYNTHESIS OF (+)-PREUSSIN

(+)-Preussin (**1**), isolated from fermentation broths of both *Aspergillus ochraceus* and *Preussia* sp. in the late 1980s, is a novel pyrrolidine alkaloid which shows a broader spectrum of antifungal activity against yeasts and filamentous fungi.[4] Since the first total synthesis of **1** was reported by Pak and co-workers in 1991,[11] several synthetic methods have became available.[12] Our synthetic strategy is outlined in Scheme 4. Accordingly, it was envisaged that **1** would be preparable *via* the stereoselective cyclization of **15**, this latter precursor being derived from **16**. Based on this retrosynthetic analysis, L-aspartic acid was chosen as a starting material.

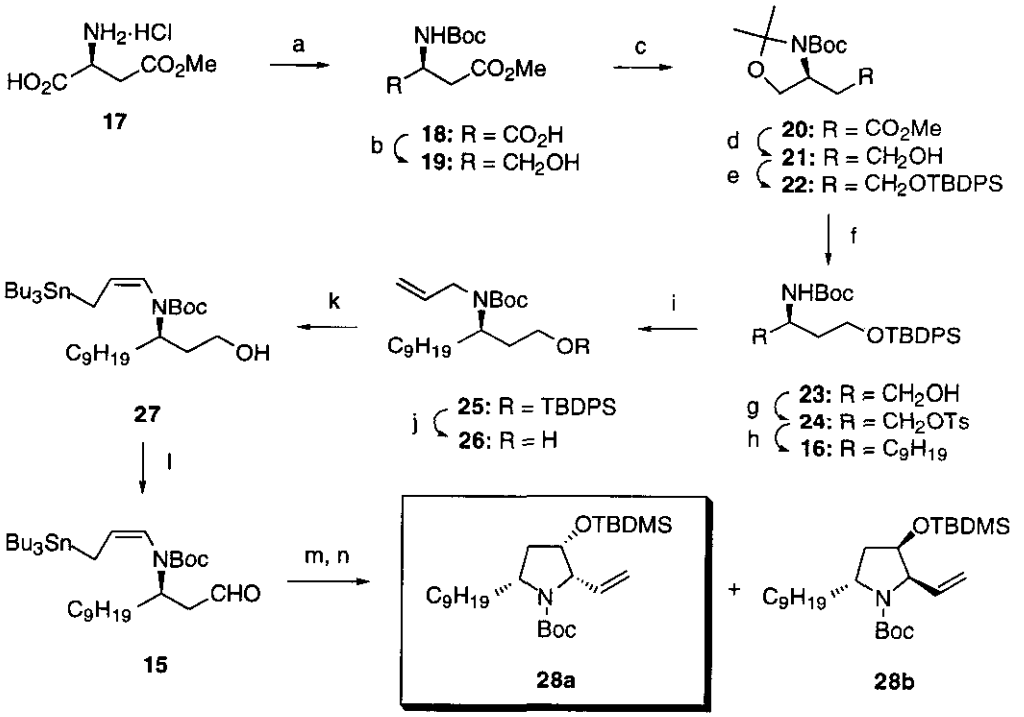
Scheme 4



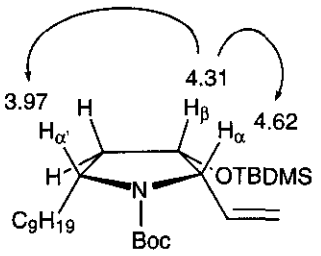
The construction of the hydroxylated pyrrolidine ring system is described in Scheme 5. Treatment of **17**[13] with Boc_2O under basic condition provided *N*-protected half ester (**18**) in good yield. Reduction of the hydroxycarbonyl group was performed by activated ester/reduction method.[14] Thus, the reaction of **18** with HOSu/DCC followed by treatment with $NaBH_4$ gave an alcohol (**19**), which was converted to acetonide (**20**) in 44% yield by 3 steps. Reduction of the ester (**20**) with $LiAlH_4$ followed by silyl protection gave **22** in quantitative yield. Selective hydrolysis of the acetonide was carried out with $PdCl_2(CH_3CN)_2$ to give **23** in 94% yield,[15] and the alcohol obtained was converted to the corresponding tosylate (**24**) in 86% yield. Alkylation of **24** with an excess amount of $C_8H_{17}Li$ in the presence of $CuBr \cdot SMe_2$ proceeded smoothly to afford **16** in 92% yield.[16] Allylation of the amino group, protected by

Boc, with allyl bromide/KH gave **25** in 91% yield. Deprotection of the TBDPS group was carried out with TBAF to give **26** in 97% yield. Formation of the corresponding allylic anion followed by trapping with *n*-Bu_3SnCl afforeded **27** in 25% yield along with 65% of the recovered starting material (**26**). Neither prolonged nor shorter reaction times gave a better result. Deprotonation of the bulky allylic ether (**26**) would possibly be very slow and the decomposition of the resulting allylic anion would compete if a prolonged reaction time was employed.[17] Oxidation with SO_3·py/DMSO/Et_3N followed by thermal cyclization in refluxing toluene gave an inseparable 1:1 diastereomeric mixture of pyrrolidine derivatives in 78% yield by 2 steps. The β-hydroxy group of the pyrrolidine derivatives was protected with TBDMSOTf/2,6-lutidine, and the resulting TBDMS derivatives could be separated by using silica gel column chromatography, giving a 1:1 mixture of **28a** and **28b** in 81% yield. The stereochemistry of **28a** was unambiguously determined by ^1H NMR analysis and NOE experiments as shown in Figure 2.[18] Thus, irradiation of the H_β (δ 4.31) produced a significant enhancement of H_α (δ 4.62) and H_α (δ 3.97). On the other hand, the NOE experiments on **28b** did not give a clear result as obtained in the case of **28a**. We assumed the *cis* relationship between the vinyl and OTBDMS group from the mechanism for the thermal cyclization.

Scheme 5



Reagents and Conditions: (a) Boc_2O, Na_2CO_3, dioxane, rt, 95%; (b) (i) *N*-hydroxysuccinimide, DCC, AcOEt, rt; (ii) $NaBH_4$, THF/EtOH (3:1), 0 ℃; (c) 2,2-dimethoxypropane, *p*-TsOH, CH_2Cl_2, rt, 44% (3 steps); (d) $LiAlH_4$, Et_2O, 0 ℃; (e) TBDPSCl, imidazole, CH_2Cl_2, rt, 100% (2 steps); (f) $PdCl_2(MeCN)_2$, MeCN, 80 ℃, 94%; (g) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 86%; (h) $C_8H_{17}Li$, CuBr·SMe_2, THF, -35 ℃, 92%; (i) allylbromide, KH, THF, 0 ℃ → rt, 91%; (j) TBAF, THF, rt, 97%; (k) *sec*-BuLi, TMEDA, THF, -78 ℃, then *n*-Bu_3SnCl, -78 ℃ → rt, 25% of **27**, 65% of **26**; (l) SO_3·py, DMSO, Et_3N, CH_2Cl_2, rt; (m) toluene, 110 ℃, 78% (2 steps); (n) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 ℃ → rt, 81%.

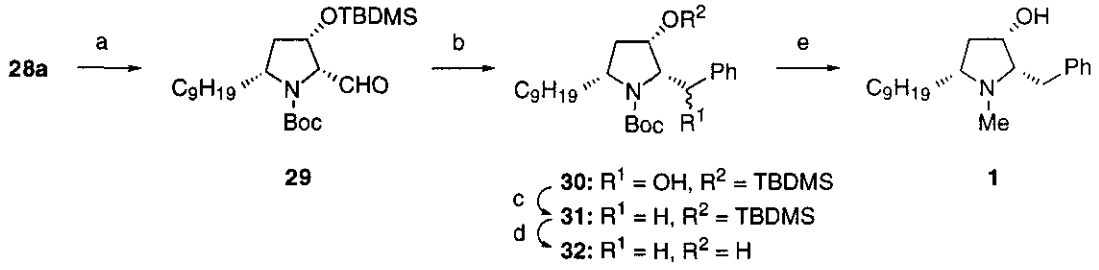


28a

Figure 2. Chemical shifts of representative protons of **28a**. Observed NOEs are shown by arrows.

Further transformations to provide **1** are shown in Scheme 6. Ozonolysis of **28a** afforded **29** in 65% yield. Treatment of **29** with PhMgBr gave **30** in 99% yield. Reaction of **30** with thiocarbonyldiimidazole gave the corresponding imidazolide, which was reacted with *n*-Bu_3SnH in the presence of AIBN to afford **31** in 47% yield. Desilylation of **31** with TBAF provided **32** in 98% yield; $[\alpha]^{25}_D$ -62.6° (lit.,[12c] $[\alpha]^{25}_D$ -56.6°). According to the reported procedure,[12c] **32** was converted to **1** in 68% yield by treatment with $LiAlH_4$ in refluxing THF. The spectroscopic and physical properties of the material obtained were in good agreement with those reported for natural[4] and previously synthesized (+)-preussin.[11,12]

Scheme 6



Reagents and Conditions: (a) O_3, MeOH, -78 °C, then Me_2S, -78 °C → rt, 65%, (b) PhMgBr, Et_2O, -78 °C → rt, 99%; (c) (i) (imidazole)$_2$C=S, toluene, 110 °C; (ii) *n*-Bu_3SnH, AIBN, toluene, 110 °C, 47% (2 steps); (d) TBAF, THF, rt, 98%; (e) $LiAlH_4$, THF, 65 °C, 68%.

CONCLUSION

A novel route to the synthesis of hydroxylated pyrrolidine derivatives *via* the intramolecular reaction of γ-aminoallylstannane with aldehyde was developed, and the usefullness of this method was demonstrated by the total synthesis of (+)-preussin. We believe that the presently developed strategy is widely applicable to the stereoselective synthesis of naturally occuring nitrogen heterocycles.

EEPERIMENTAL SECTION

General Procedure. ^{1}H- and ^{13}C-NMR spectra were recorded on JEOL GSX-270, JNM-LA300, and JNM-A500 spectrometers. Chemical shifts are reported in delta (δ) units, in part per million (ppm) downfield from tetramethylsilane or in ppm relative to the singlet at 7.26 ppm for chloroform. Coupling constants are reported in hertz (Hz). IR spectra (cm^{-1}) were measured with neat compounds on a SHIMADZU FTIR8200A infrared spectrophotometer. High resolution mass spectra were obtained with a JEOL JMS-HX110 spectrometer. Optical rotations were recorded on JASCO DIP-1000 polarimeter. Capillary GC analysis were performed with a SHIMADZU GC-14A flame ionization instrument with a CPB1-M25-025 column. All reactions were monitored by thin layer chromatography using Merck precoated aluminum plates (Kieselgel 60F_{254}, 0.2 mm). Column chromatography was done on Merck silica gel 60 (70-230 mesh ASTM), and for flash chromatography, Merck silica gel 60 (230-400 mesh ASTM) was employed. All solvents were dried immediately before use. Ether and THF were distilled from sodium/ benzophenone ketyl; dichloromethane, hexane, benzene, triethylamine, pyridine, DMF, DMSO, and TMEDA were distilled from CaH_2; methanol was distilled from $Mg(OMe)_2$. All reactions involving air- and/or moisture-sensitive materials were carried out in an argon atmosphere.

1-[*N*-(*tert*-Butoxycarbonyl)amino]-3-(*tert*-butyldimethylsiloxy)propane (4). To a stirred solution of 3-amino-1-propanol (5.0 mL, 65.4 mmol) and Et_3N (45.6 mL, 327 mmol) in CH_2Cl_2 (330 mL) at 0 ℃ was added TBDMSCl (10.8 g, 71.9 mmol). After 1 h, Boc_2O (17.1 g, 78.5 mmol) was added and the mixture was stirred at rt for 1 h. The reaction mixture was diluted with ether, washed with water, saturated aqueous $NaHCO_3$, and brine. Drying over $MgSO_4$, concentration, and silica gel column chromatography (hexane/AcOEt, 10:1) gave **4** (17.3 g, 91%): colorless oil; R_f = 0.29 (hexane/AcOEt, 10:1); IR (neat) 3350, 2970, 2943, 2898, 2870, 1700, 1510, 1474, 1465, 1258, 1178, 1100, 845, 780 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.14-5.02 (br s, 1H), 3.70 (t, J = 6.0 Hz, 2H), 3.23 (dt, J = 7.0, 6.0 Hz, 2H), 1.69 (quint, J = 7.0 Hz, 2H), 1.43 (s, 9H), 0.90 (s, 9H), 0.07 (s, 6H); Anal. Calcd for $C_{14}H_{31}NO_3Si$: C, 58.09; H, 10.79; N, 4.84. Found: C, 57.74; H, 10.75; N, 4.68.

1-[*N*-(*tert*-Butoxycarbonyl)-*N'*-(2-propenyl)amino]-3-(*tert*-butyldimethylsiloxy)propane (5). To a stirred suspension of KH (3.5 g of a 35% suspension in mineral oil, 31 mmol, prewashed with hexane) in THF (38 mL) at 0 ℃ were added allyl bromide (1.3 mL, 15 mmol) and a solution of **4** (3.0 g, 10 mmol) in THF (13 mL), and the mixture was stirred at rt. After 2 h, the reaction was quenched with MeOH followed by water at 0 ℃. The mixture was extracted with ether and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (hexane/AcOEt, 20:1) to give **5** (3.3 g, 96%): colorless oil; R_f = 0.31 (hexane/AcOEt, 20:1); IR (neat) 3090, 3020, 2970, 2940, 2900, 2864, 1604, 1465, 1410, 1370, 1252, 1180, 1105, 842, 780 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.76 (ddt, J = 17.0, 10.0, 6.0 Hz, 1H), 5.17-5.06 (m, 2H), 3.83 (br s, 1H), 3.62 (t, J = 6.0 Hz, 2H), 3.29-3.18 (m, 2H), 1.80-1.65 (m, 2H), 1.43 (s, 9H), 0.86 (s, 9H), 0.03 (s, 6H); Anal. Calcd for $C_{17}H_{35}NO_3Si$: C, 61.96; H, 10.70; N, 4.25. Found: C, 61.70; H, 10.73; N, 4.27.

3-[*N*-(*tert*-Butoxycarbonyl)-*N'*-(2-propenyl)amino]propan-1-ol (6). A mixture of 5 (2.7 g, 8.2 mmol) and TBAF (9.9 mL, 1.0 M in THF, 9.9 mmol) was stirred at rt overnight. The reaction mixture was diluted with AcOEt, washed with water and brine, dried over $MgSO_4$, and concentrated. Silica gel column chromatography (hexane/AcOEt, 4:1→2:1) gave **6** (1.7 g, 96%): colorless oil; R_f = 0.20 (hexane/AcOEt, 4:1); IR (neat) 3600-3100, 3095, 2975, 1702, 1678, 1482, 1413, 1373, 1252, 1166, 1062, 996, 920, 883, 776 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.78 (ddt, J = 17.0, 10.0, 5.5 Hz, 1H), 5.18-5.08 (m, 2H), 3.83-3.68 (m, 2H), 3.63-3.50 (m, 2H), 3.43-3.30 (m, 2H), 1.73-1.63 (m, 2H), 1.45 (s, 9H); Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 60.95; H, 9.68; N, 6.44.

3-{*N*-(*tert*-Butoxycarbonyl)-*N'*-[(*Z*)-3-tributylstannyl-1-propenyl]amino}propan-1-ol (7). To a solution of **6** (1.0 g, 4.6 mmol) in THF (23 mL) at -78 ℃ were added *sec*-BuLi (9.5 mL, 1.07 M in cyclohexane, 10 mmol) and TMEDA (1.5 mL, 10 mmol), and the resulting yellow solution was stirred at the same temperature. After 1 h, *n*-Bu_3SnCl (1.5 mL, 5.6 mmol) was added, the cooling bath removed, and the reaction mixture was allowed to warm to rt. The mixture was quenched with water and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Silica gel column chromatography (hexane/AcOEt, 4:1) gave **7** (992 mg, 43%) and **6** (50%): colorless oil: R_f = (hexane/AcOEt, 4:1); IR (neat) 3600-3100, 2975, 2945, 2880, 2870, 1700, 1680, 1649, 1460, 1399, 1372, 1300, 1259, 1170, 1071, 882, 778 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.67 (dt, J = 8.0, 1.0 Hz, 1H), 5.24 (dt, J = 9.0, 8.0 Hz, 1H), 3.62-3.49 (m, 5H), 1.71-1.22 (m, 31H), 0.90 (s, 9H); Anal. Calcd for $C_{23}H_{47}NO_3Sn$: C, 54.78; H, 9.39; N, 2.78. Found: C, 54.69; H, 9.51; N, 2.85.

3-{*N*-(*tert*-Butoxycarbonyl)-*N'*-[(*Z*)-3-tributylstannyl-1-propenyl]amino}propan-1-al (8). To a stirred solution of **7** (202 mg, 0.4 mmol), DMSO (400 μL) and Et_3N (390 μL, 2.8 mmol) in CH_2Cl_2 (4 mL) at 0 ℃ was added SO_3·py (255 mg, 1.6 mmol), and the mixture was stirred at rt for 1 h. The reaction mixture was diluted with ether, washed with water and brine, dried over $MgSO_4$, and concentrated at 20 ℃ under reduced pressure. The crude aldehyde (**8**) was taken to the next cyclization without purification.

Typical Procedure of the Cyclization of 8. To a stirred solution of **8** (51 mg, 0.1 mmol) in CH_2Cl_2 at -78 ℃ was added BF_3·OEt_2 (120 μL, 1.0 M in CH_2Cl_2, 0.12 mmol). After 1 h, the reaction mixture was quenched with Et_3N, the cooling bath removed, and the reaction mixture was allowed to warm to rt. The mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$. The organic solution was vigorously stirred with saturated aqueous KF at rt overnight. The organic layer was dried over $MgSO_4$, concentrated, and subjected to silica gel column chromatography (hexane/AcOEt, 1:1) to give **9a** and **9b**.

(2*S,3*S**)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-2-vinylpyrrolidine (9a):** colorless oil: R_f = 0.31 (hexane/AcOEt, 1:1); IR (neat) 3600-3100, 3085, 2978, 2931, 2893, 1670, 1477, 1411, 1365, 1167, 1115, 1067, 897 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.80 (ddd, J = 17.0, 11.0, 6.0 Hz, 1H), 5.34 (br d, J = 11.0 Hz, 1H), 5.26 (br d, J = 17.0 Hz, 1H), 4.42-4.22 (m, 2H), 3.59-3.36 (m, 2H), 2.16-1.96 (m,

1H), 1.95-1.74 (m, 1H), 1.44 (s, 9H); Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.17; H, 9.05; N, 6.53; HRMS, calcd for $C_{11}H_{19}NO_3$: 213.1365 found: 213.1340.

(2*S,3*R**)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-2-vinylpyrrolidine (9b):** colorless oil; R_f = 0.31 (hexane/AcOEt, 1:1); IR (neat) 3600-3100, 3084, 2977, 2932, 2895, 1697, 1668, 1479, 1413, 1366, 1256, 1169, 1124, 989 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.80-5.77 (m, 1H), 5.23-5.02 (m, 2H), 4.35-4.10 (m, 2H), 3.65-3.40 (m, 2H), 2.10-1.95 (m, 1H), 1.90-1.75 (m, 1H), 1.40 (s, 9H); Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.86; H, 9.06; N, 6.27; HRMS, HRMS, calcd for $C_{11}H_{19}NO_3$: 213.1365 found: 213.1328.

(2*S,3*S**)-1-(*tert*-Butoxycarbonyl)-3-acetoxy-2-ethylpyrrolidine (10):** colorless oil; ^1H NMR (270 MHz, $CDCl_3$) δ 5.30-5.20 (m, 1H), 3.94-3.82 (m, 1H), 3.57-3.42 (m, 1H), 3.40-3.30 (m, 1H), 2.20-1.70 (m, 2H), 2.10 (s, 3H), 1.75 (m, 2H), 1.48 (s, 9H), 0.88 (t, J = 7.4 Hz, 3H).

(2*S,3*R**)-1-(*tert*-Butoxycarbonyl)-3-acetoxy-2-vinylpyrrolidine (11):** colorless oil; ^1H NMR (270 MHz, $CDCl_3$) δ 5.87-5.68 (m, 1H), 5.23-5.10 (m, 2H), 5.00 (d, J = 4.5 Hz, 1H), 4.42-4.21 (m, 1H), 3.75-3.45 (m, 2H), 2.18-2.00 (m, 1H), 2.07 (s, 3H), 1.99-1.89 (m, 9H).

***N*-(*tert*-Butoxycarbonyl)-L-aspartic acid 4-methyl ester (18).** To a mixture of **17** (15.4 g, 84 mmol) in dioxane (340 mL) and 0.5 M aqueous Na_2CO_3 at 0 ℃ was added Boc_2O (20.1 g, 92 mmol), and the mixture was stirred at rt overnight. Most of the solvent was evaporated under reduced pressure. The aqueous residue was then brought to pH 3 by addition of citric acid at 0 ℃, and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$, and concentrated. Silica gel column chromatography (CH_2Cl_2/EtOH, 5:1) gave **18** (19.7 g, 95%).

Methyl (*S*)-2-[1-(*tert*-butoxycarbonyl)-2,2-dimethyl]oxazolin-5-ylacetate (20). A solution of **18** (1.0 g, 4.0 mmol) and *N*-hydroxysuccinimide (558 mg, 4.9 mmol) in CH_2Cl_2 (12 mL) at rt was treated with DCC (1.0 g, 4.9 mmol). After 3 h, anhydrous Na_2SO_4 was added, and the mixture was filtered through paper filter, and concentrated. The residue was dissolved in 20 mL of THF/EtOH (3:1). The mixture at 0 ℃ was treated with $NaBH_4$ (153 mg, 4.0 mmol). After 15 min, the reaction mixture was extracted with AcOEt. The organic layer was dried over Na_2SO_4, and concentrated to give crude **19**. To a mixture of **19** and 2,2-dimethoxypropane (1.5 mL, 12 mmol) in CH_2Cl_2 (40 mL) at rt was added a catalytic amount of *p*-TsOH, and the mixture was stirred overnight. The reaction mixture was quenched with powdered K_2CO_3, filtered through Celite pad, and concentrated. Silica gel column chromatography (hexane/AcOEt, 20:1→10:1) gave **20** (483 mg, 44%): colorless oil; R_f = 0.74 (hexane/AcOEt, 1:1); $[\alpha]^{27}_D$ +27.9°(c 1.0, $CHCl_3$); IR (neat) 2980, 2955, 2937, 2879, 1738, 1703, 1700, 1480, 1456, 1438, 1393, 1367, 1299, 1248, 1175, 1101, 1065, 845, 768 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.34-4.12 (m, 1H), 4.09-4.00 (m, 1H), 3.84 (dd, J = 6.0, 1.5 Hz, 1H), 3.70-3.62 (m, 3H), 3.00-2.72 (m, 1H), 2.60-2.43 (m, 1H), 1.59 (s, 3H), 1.52-1.44 (m, 12H); Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 56.91; H, 8.37; N, 5.13.

(*S*)-5-[2-(*tert*-Butyldimethylsiloxy)ethyl]-2-[1-(*tert*-butoxycarbonyl)]-2,2-dimethyloxazoline (22). To a stirred suspension of $LiAlH_4$ (746 mg, 20 mmol) in ether (100 mL) at 0 ℃ was added a solusion of **20** (5.4 g, 20 mmol) in ether (100 mL). After 20 min, the reaction mixture was quenched with saturated aqueous NaCl, filtered through Celite pad, and concentrated to give crude **21**. To a solution of **21** and imidazole (2.0 g, 30 mmol) in CH_2Cl_2 (200 mL) at 0 ℃ was added TBDPSCl (6.2 g, 24 mmol), and the mixture was stirred at rt overnight. The reaction mixture was diluted with ether, washed with water and brine, dried over $MgSO_4$, and concentrated. Silica gel column chromatography (hexane/AcOEt, 40:1→20:1) gave **22** (4.9 g, 100%): colorless oil; R_f = 0.71 (hexane/AcOEt, 2:1); $[\alpha]^{21}_D$ - 2.00° (c 1.0, $CHCl_3$); IR (neat) 3071, 3049, 2961, 2932, 2858, 1699, 1473, 1428, 1391, 1258, 1171, 1085, 702 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.68-7.62 (m, 4H), 7.44-7.34 (m, 6H), 4.00-3.78 (m, 3H), 3.76-3.66 (m, 2H), 2.05-1.95 (m, 1H), 1.88-1.70 (m, 1H), 1.58-1.38 (m, 15H), 1.05 (s, 9H); Anal. Calcd for $C_{28}H_{41}NO_4Si$: C, 69.53; H, 8.54; N, 2.90. Found: C, 69.37; H, 8.43; N, 2.72.

(*S*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-4-(*tert*-butyldiphenylsiloxy)butan-1-ol (23). A mixture of **22** (8.6 g, 18 mmol) and $PdCl_2(MeCN)_2$ (93 mg, 0.36 mmol) in MeCN (90 mL) was refluxed overnight. The reaction mixture was concentrated and the residue was subjected to silica gel column chromatography (hexane/AcOEt, 40:1→20:1) to give **23** (7.4 g, 94%): colorless oil; R_f = 0.46 (hexane/AcOEt, 2:1); IR (neat) 3600-3200, 3071, 3050, 2960, 2932, 2858, 1741, 1716, 1693, 1507, 1428, 1367, 1244, 1173, 1112, 703 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.68-7.64 (m, 4H), 7.48-7.36 (m, 6H), 5.52 (br s, 1H), 3.86-3.73 (m, 1H), 3.75 (t, J = 5.8 Hz, 2H), 3.73-3.65 (m, 2H), 3.28 (br s, 1H), 1.90-1.65 (m, 2H), 1.44 (s, 9H), 1.05 (s, 9H).

(*S*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-4-(*tert*-butyldiphenylsiloxy)butan-1-yl *p*-toluenesulfonate (24). A mixture of **23** (3.1 g, 7.0 mmol), Et_3N (2.0 mL, 14 mmol), TsCl (1.5 g, 7.7 mmol), and a catalytic amount of DMAP was stirred at rt overnight. The reaction mixture was diluted with ether, washed with water and brine, dried over $MgSO_4$, and concentrated. Silica gel column chromatography (hexane/AcOEt, 10:1→4:1) gave **24** (3.6 g, 86%): colorless oil; R_f = 0.31 (hexane/AcOEt, 4:1); $[\alpha]^{22}_D$ - 8.57° (c 1.0, $CHCl_3$); IR (neat) 3398, 3072, 3049, 2960, 2931, 2891, 2858, 1716, 1365, 1176, 1112, 786, 761, 704, 665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 8.4 Hz, 2H), 7.66-7.59 (m, 4H), 7.48-7.28 (m, 8H), 5.20-5.10 (m, 1H), 4.14-3.94 (m, 3H), 3.78-3.58 (m, 2H), 2.43 (s, 3H), 1.82-1.68 (m, 2H), 1.39 (s, 9H), 1.02 (s, 9H); Anal. Calcd for $C_{32}H_{43}NO_6SSi$: C, 64.29; H, 7.25; N, 2.34. Found: C, 64.09; H, 7.17; N, 2.59.

(*R*)-3-[*N*-(*tert*-Butoxycarbonyl)amino]-1-(*tert*-butyldiphenylsiloxy)dodecane (16). To a stirred suspension of CuBr·SMe_2 (514 mg, 2.5 mmol) in ether (2 mL) at -35 ℃ was added $C_8H_{17}Li$ (4.1 mL, 1.23 M in ether, 5.0 mmol), followed by a solution of **24** (300 mg, 0.5 mmol) in ether (2.0 mL), and the mixture was stirred at the same temperature for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, filtered through Celite pad, and extracted with ether. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. Silica gel column

chromatography (hexane/AcOEt, 100:1→20:1) gave **16** (249 mg, 92%): colorless oil; R_f = 0.66 (hexane/AcOEt, 4:1); IR (neat) 3423, 3357, 3071, 3049, 2929, 2856, 1718, 1701, 1502, 1365, 1174, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68-7.64 (m, 4H), 7.48-7.36 (m, 6H), 4.97-4.90 (m, 1H), 3.82-3.60 (m, 3H), 1.42 (s, 9H), 1.35-1.20 (m, 18H), 1.02 (s, 9H); Anal. Calcd for $C_{33}H_{53}NO_3Si$: C, 73.42; H, 9.90; N, 2.59. Found: C, 73.51; H, 10.47; N, 2.49.

(*R*)-3-[*N*-(*tert*-Butoxycarbonyl)-*N'*-(2-propenyl)amino]-1-(*tert*-butyldiphenylsiloxy)-dodecane (25). Allylation procedure was followed as described for compound (**5**). **25:** colorless oil: R_f = 0.26 (hexane/AcOEt, 20:1); $[\alpha]^{27}_D$ -5.11° (c 1.0, $CHCl_3$); IR (neat) 3071, 3050, 2958, 2929, 2856, 1694, 1462, 1428, 1365, 1247, 1176, 1112, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68-7.63 (m, 4H), 7.43-7.33 (m, 6H), 5.84-5.68 (m, 1H), 5.13-4.95 (m, 2H), 3.75-3.48 (m, 5H), 1.85-1.65 (m, 2H), 1.39 (s, 9H), 1.30-1.12 (m, 16H), 1.04 (s, 9H), 0.88 (t, J = 6.7 Hz, 3H); Anal. Calcd for $C_{36}H_{57}NO_3Si$: C, 74.56; H, 9.91; N, 2.42. Found: C, 74.71; H, 10.31; N, 2.21.

(*R*)-3-[*N*-(*tert*-Butoxycarbonyl)-*N'*-(2-propenyl)amino]dodecan-1-ol (26). Desilylation procedure was followed as described for compound (**6**). **26:** colorless oil; R_f = 0.26 (hexane/AcOEt, 4:1); $[\alpha]^{27}_D$ +10.5° (c 1.0, $CHCl_3$); IR (neat) 3600-3200, 3079, 3006, 2957, 2927, 2855, 1694, 1668, 1456, 1407, 1366, 1174, 1149, 1051, 919, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.90-5.73 (m, 1H), 5.19-5.04 (m, 2H), 4.32-4.20 (m, 1H), 3.64-3.36 (m, 5H), 1.73-1.38 (m, 2H), 1.46 (s, 9H), 1.25 (brs, 16H), 0.87 (t, J = 6.7 Hz, 3H); Anal. Calcd for $C_{20}H_{39}NO_3$: C, 70.34; H, 11.51; N, 4.10. Found: C, 70.10; H, 11.77; N, 4.11.

(*R*)-3-{*N*-(*tert*-Butoxycarbonyl)-*N'*-[(*Z*)-3-tributylstannyl-1-propenyl]amino}dodecan-1-ol (27). Experimental procedure was followed as described for compound **7**. **27:** colorless oil; R_f = 0.51 (hexane/AcOEt, 4:1); $[\alpha]^{21}_D$ +6.76° (c 1.0, $CHCl_3$); IR (neat) 3600-3100, 3007, 2956, 2925, 2871, 2855, 1694, 1667, 1642, 1456, 1407, 1366, 1253, 1156, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.52-5.35 (m, 2H), 4.35-4.13 (m, 1H), 3.64-3.50 (m, 2H), 1.73-1.22 (m, 41H), 1.00-0.76 (m, 18H); Anal. Calcd for $C_{32}H_{65}NO_3Sn$: C, 60.95; H, 10.39; N, 2.22. Found: C, 61.15; H, 10.15; N, 2.33.

28. To a mixture of **27** (2.5 g, 4.9 mmol), DMSO (5.0 mL), and Et_3N (4.8 mL, 35 mmol) in CH_2Cl_2 (50 mL) at 0 ℃ was added SO_3·py (3.2 g, 20 mmol), and the mixture was stirred at rt for 1 h. The reaction mixture was diluted with ether, washed with brine, dried over $MgSO_4$, and concentrated at 20 ℃ under reduced pressure to give crude **15**. A solution of **15** in toluene (50 mL) was stirred at 100 ℃ for 30 min, and concentrated. Silica gel column chromatography (hexane/AcOEt, 2:1→1:1) gave a 1:1 mixture of isomeric alcohols (510 mg, 78%). To a mixture of the above obtained alcohols (510 mg, 1.5 mmol) and 2,6-lutidine (350 μL, 3.0 mmol) in CH_2Cl_2 at 0 ℃ was added TBDMSOTf (520 μL, 2.3 mmol), and the mixture was stirred at rt for 1.5 h. The reaction mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. Flash column chromatography (hexane/ether, 40:1→20:1) gave **28a** and **28b** in 81% yield.

(2*S*, 3*S*, 5*R*)-1-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsiloxy)-5-nonyl-2-vinylpyrrolidine (28a): colorless oil; R_f = 0.51 (hexane/AcOEt, 10:1); $[\alpha]^{18}_D$ -31.6° (c 1.0, $CHCl_3$); IR (neat) 3084, 2957, 2928, 2856, 2361, 2341, 1699, 1464, 1389, 1256, 1142, 1094, 893, 837, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 100 ℃) δ 6.18 (ddd, J = 17.0, 10.5, 6.5 Hz, 1H), 5.50 (dt, J = 17.0, 1.5 Hz, 1H), 5.35 (dt, J = 10.5, 1.5 Hz, 1H), 4.62 (t, J = 6.5 Hz, 1H), 4.31 (dt, J = 8.0, 5.0 Hz, 1H), 3.97 (ddt, J = 9.0, 8.0, 4.0 Hz, 1H), 2.21 (dt, J = 12.5, 6.5 Hz, 1H), 1.81 (dt, J = 12.5, 8.0 Hz, 1H), 1.54-1.47 (m, 9H), 1.28 (t, J = 7.0 Hz, 3H), 1.10 (s, 12H), 0.20 (d, J = 1.5 Hz, 6H); Anal. Calcd for $C_{26}H_{51}NO_3Si$: C, 68.82; H, 11.33; N, 3.09. Found: C, 68.76; H, 10.95; N, 3.14.

(2*R*, 3*R*, 5*R*)-1-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsiloxy)-5-nonyl-2-vinylpyrrolidine (28b): colorless oil; R_f = 0.54 (hexane/AcOEt, 10:1); $[\alpha]^{22}_D$ +10.3° (c 1.0, $CHCl_3$); IR (neat) 3082, 2954, 2927, 2856, 1699, 1464, 1387, 1252, 1140, 1097, 895, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 100 ℃) δ 6.11 (ddd, J = 17.0, 10.6, 6.5 Hz, 1H), 5.36-5.31 (m, 2H), 4.62-4.56 (m, 2H), 4.08-4.01 (m, 1H), 2.30-2.12 (m, 2H), 1.98-1.92 (m, 1H), 1.60-1.43 (m, 24H), 1.10-1.03 (m, 12H), 0.22 (s, 6H); Anal. Calcd for $C_{26}H_{51}NO_3Si$: C, 68.82; H, 11.33; N, 3.09. Found: C, 68.64; H, 11.21; N, 3.22.

(2*R*, 3*S*, 5*R*)-1-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsiloxy)-2-formyl-5-nonylpyrrolidine (29). To a solution of **28a** (123 mg, 0.27 mmol) in MeOH (5.0 mL) at -78 ℃ was bubbled ozone until a blue color persisted. Excess ozone was removed by bubbling oxygen through the solution until it became colorless. To this solution at -78 ℃ was added Me_2S (50 mL), and the solution was warmed to rt and stirred overnight. The mixture was concentrated, dissolved in ether, washed with brine, and dried over $MgSO_4$. Concentration and silica gel column chromatography (hexane/AcOEt, 30:1→10:1) gave **29** (85 mg, 65%): colorless oil; R_f = 0.14 (hexane/AcOEt, 10:1); $[\alpha]^{20}_D$ +20.8° (c 1.0, C_6H_6); IR (neat) 2955, 2928, 2856, 1740, 1709, 1464, 1393, 1367, 1256, 1136, 837, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.47-9.38 (m, 1H), 4.67-4.61 (m, 1H), 4.15-3.78 (m, 2H), 2.12-1.95 (m, 2H), 1.87-1.70 (m, 2H), 1.55-1.20 (m, 23H); Anal. Calcd for $C_{25}H_{49}NO_4$: C, 65.89; H, 10.84; N, 3.07. Found: C, 66.48; H, 10.85; N, 3.15.

(2*R*, 3*S*, 5*R*)-1-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsiloxy)-2-(α-hydroxy-benzyl)-5-nonylpyrrolidine (30). To a solution of **29** (87 mg, 0.19 mmol) in ether (2.0 mL) at -78 ℃ was added PhMgBr (150 μL, 2.0 M in THF, 0.3 mmol), and the mixture stirred at same temperature for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Silica gel column chromatography (hexane/AcOEt, 20:1) gave **30** (101 mg, 99%): colorless oil; R_f = 0.20 (hexane/AcOEt, 10:1); $[\alpha]^{23}_D$ -34.8° (c 1.0, $CHCl_3$); IR (neat) 3449, 3063, 3030, 2955, 2928, 2856, 1693, 1674, 1464, 1391, 1335, 1254, 1174, 1140, 1086, 837, 777, 698, 665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.19 (m, 5H), 4.98-4.89 (br s, 1H), 4.42 (dt, J = 9.5, 7.7 Hz, 1H), 4.28-4.12 (m, 1H), 3.63 (ddt, J = 14.5, 9.5, 6.4 Hz, 1H), 2.31 (dt, J = 12.3, 7.9 Hz, 1H), 2.17 (m, 1H), 1.72 (ddd, J = 12.1, 9.4, 9.2 Hz, 1H), 1.56-1.02 (m, 24H), 0.97-0.85 (m, 12H), 0.18-0.00 (m, 6H); Anal. Calcd for $C_{31}H_{55}NO_4Si$: C, 69.74; H, 10.38; N, 2.62. Found: C, 69.94; H, 10.34; N, 2.74.

(2*S*, 3*S*, 5*R*)-1-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsiloxy)-2-benzyl-5-nonyl-pyrrolidine (31). A mixture of **30** (108 mg, 0.20 mmol) and 1,1'-thiocarbonyldiimidazole (144 mg, 0.81 mmol) in tolune (2.0 mL) was refluxed for 2 h. The mixture was filtered through silica gel, and concentrated. A mixture of the above obtained imidazolide, *n*-Bu_3SnH (60 mL, 0.23 mmol), and a catalytic amouny of AIBN was stirred at 90 ℃ for 40 min. Concentration and silica gel column chromatography (hexane/AcOEt, 20:1) gave **31** (49 mg, 47%): colorless oil; R_f = 0.66 (hexane/AcOEt, 4:1); $[\alpha]^{17}_D$ -52.2° (c 1.0, $CHCl_3$); IR (neat) 3028, 2956, 2928, 2856, 1693, 1464, 1389, 1258, 1142, 1090, 837, 795 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27-7.12 (m, 5H), 4.25 (dt, J = 9.9, 7.0 Hz, 1H), 4.08-3.95 (m, 1H), 3.70-3.50 (m, 1H), 2.62-2.10 (m, 2H), 1.66-1.51 (m, 1H), 1.43-1.07 (m, 25H), 0.91-0.87 (m, 6H); Anal. Calcd for $C_{31}H_{55}NO_3Si$: C, 71.90; H, 10.70; N, 2.70. Found: C, 71.37; H, 10.22; N, 2.84.

(2*S*,3*S*,5*R*)-1-(*tert*-Butoxycarbonyl)-2-benzyl-5-nonyl-3-pyrrolidinol (32). Desilylation procedure was followed as described for compound (**6**). **32:** colorless oil; R_f = 0.26 (hexane/AcOEt, 10:1); $[\alpha]^{25}_D$ -62.6° (c 1.0, CH_2Cl_2) [lit.,[12c] $[\alpha]^{25}_D$ -56.6° (c 1.0, CH_2Cl_2)]; IR (neat) 3600-3200, 3062, 3028, 2957, 2956, 2855, 1690, 1663, 1454, 1400, 1365, 1329, 1256, 1175, 1123, 1078, 779, 766, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.16 (m, 5H), 4.31 (ddd, J = 11.3, 7.2, 6.8 Hz, 1H), 4.14 (dt, J = 6.8, 6.8 Hz, 1H), 3.78-3.67 (m, 1H), 3.00-2.89 (m, 2H), 2.27 (ddd, J = 13.6, 7.2, 7.2 Hz, 1H), 2.13-1.90 (m, 1H), 1.70 (dt, J = 13.5, 6.8 Hz, 1H), 1.44-1.10 (m, 24H), 0.88 (t, J = 6.6 Hz, 1H); Anal. Calcd for $C_{25}H_{41}NO_3$: C, 74.40; H, 10.24; N, 3.47. Found: C, 73.94; H, 10.17; N, 3.56.

(2*S*,3*S*,5*R*)-1-Methyl-2-benzyl-5-nonyl-3-pyrrolidinol (1). To a suspension of $LiAlH_4$ (21 mg, 0.55 mg) in THF (0.3 mL) was added a solution of **32** (22 mg, 0.055 mmol) in THF (0.3 mL), and the mixture was refluxed for 4 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, and extracted ether. The extract was washed with brine, dried over $MgSO_4$, and concentrated. Silica gel column chromatography (hexane/AcOEt, 4:1→1:1) gave (+)-preussin (**1**) (12 mg, 68%): white solid; $[\alpha]^{25}_D$ +27.4° (c 1.0, CH_2Cl_2) [lit., natural[4] $[\alpha]^{25}_D$ +22.0° (c 1.0, $CHCl_3$); synthetic[11] $[\alpha]^{25}_D$ +31.1° (c 1.0, $CHCl_3$)].

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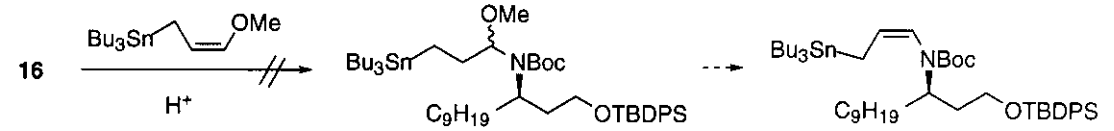

18 The ^{1}H NMR spectra were measured at 100 ℃ in toluene-d_8 because of the broading of the signals at rt.

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