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A STEREOCONTROLLED FORMAL ASYMMETRIC SYNTHESIS OF PSEUDODISTOMIN C

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Abstract – An efficient and stereocontrolled formal asymmetric synthesis of pseudodistomin C has been achieved by employing intramolecular transamidation reaction**,** *exo*-methylenation**,** and highly stereoselective hydroboration. The resulting 2-hydroxymethylpiperidine derivative (**15**) was further converted into the key intermediate (**2**) for the synthesis of pseudodistomin C.

Pseudodistomin C (**1**)**,** isolated in 1995 from the Okinawan tunicate *Pseudodistoma kanoko* by Kobayashi *et al*., is a piperidine alkaloid possessing 2,4,5-trisubstituted structure and shown to have cytotoxicity against L1210 and human epidermoid carcinoma KB cells *in vitro*.[1] The relative stereochemistry of the three functional groups on the piperidine ring of **1** was elucidated on the basis of spectral data and the whole structure of **1** was unambiguously determined in 1996 by Kobayashi co-workers[2] *via* asymmetric total synthesis. The three functional groups on the piperidine ring of **1** are placed in all *cis* orientations (Figure 1).

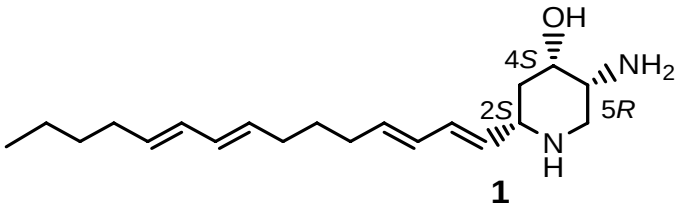

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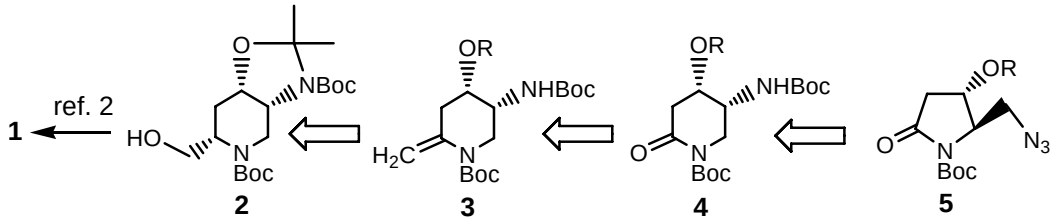
Figure 1. The structure of pseudodistomin C

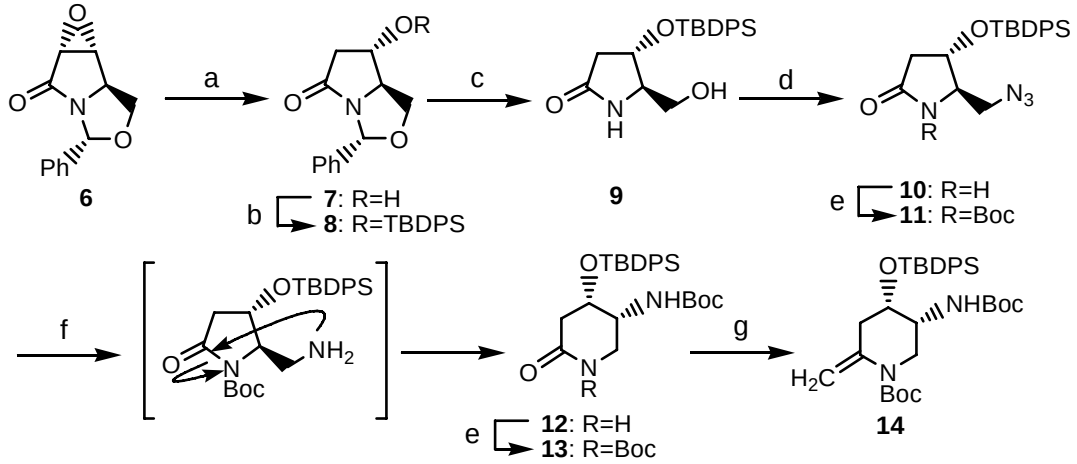
Despite interesting pharmacological activity and unique structural feature, to our knowledge, only two approaches for the synthesis of pseudodistomin C have been reported to date. Kobayashi and co-workers[2] have reported the first total synthesis *via* intramolecular amidomercuration of homochiral *N*-alkenylurethane available from *D*-serine as a chiral source. On the other hand, Langlois[3] have reported the formal synthesis, in which 6-benzenelsulfonylmethylpyrrolidine derivative, Kobayashi's synthetic precursor, was synthesized *via* intramolecular transamidation (IT)[4] of 5-azidomethyl-γ-lactam derivative

derived from (*S*)-pyroglutaminol followed by selective ring opening of the resulting δ-lactam derivative by organometallic reagent and subsequent ring closure. Recently, we have reported the syntheses of conformationally restricted surrogates of the 2,4-diaminobutanoyl-(Dab)-Gly dipeptide based on IT reaction.[4j,k] As an extension of our going program utilizing this reaction on the synthesis of biologically active compounds, we herein report the stereocontrolled formal asymmetric synthesis of pseudodistomin C.



Scheme 1. Retrosynthetic analysis for pseudodistomin C

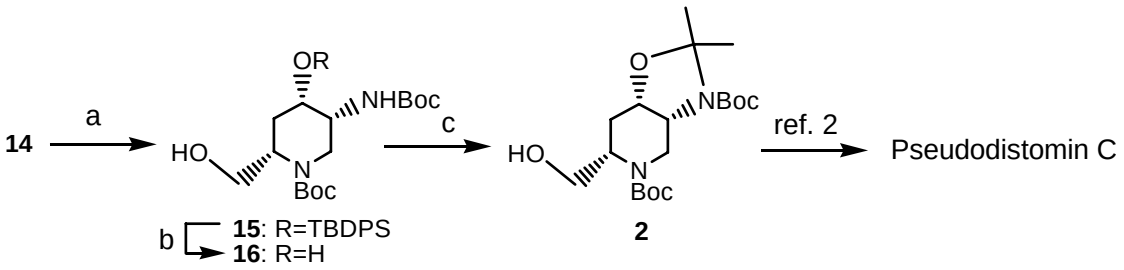
Our retrosynthetic strategy for the synthesis of pseudodistomin C is outlined in Scheme 1. We envisioned that Kobayashi's intermediate (**2**) could arise from *exo*-methylene compound (**3**) *via* stereoselective hydroboration. Compound (**3**) in turn may be prepared by titanium-mediated carbonyl olefination of δ-lactam derivative (**4**). Compound (**4**) could be constructed by IT reaction of 5-azidomethyl pyrrolidin-2-one derivative (**5**).



Scheme 2. Reagents and conditions: (a) ($PhSe)_2$, $NaBH_4$, AcOH, EtOH, rt, 86%; (b) TBDPS-Cl, Im, DMF, 0°C to rt; (c) H_2NNH_2-H_2O, 10% Pd-C, MeOH, reflux, 86% (2 steps); (d) (i) MsCl, Et_3N, CH_2Cl_2, 0°C; (ii) NaN_3, DMF, 80°C; (e) Boc_2O, 4-DMAP, CH_2Cl_2, rt, 88% (3 steps); (f) H_2, 10% Pd-C, MeOH-H_2O (12:1), 3 atm, rt, 92%; (g) Cp_2TiMe_2, toluene, 105°C, 78%.

Thus, we started from known α,β-epoxylactam (**6**),[5] which was prepared from (*S*)-pyroglutaminol as a homochiral source (Scheme 2). For the conversion of **6** into the known hydroxyl lactam (**7**),[5a,c] a few methods for the regioselective reductive ring-opening of α,β-epoxylactams have been reported.[5a,c,6] In view of mild reaction conditions at room temperature, we decided to explore the $(PhSe)_2/NaBH_4$/AcOH system developed by Miyashita[6] to prepare the compound (**7**). Thus, **6** was treated with borane complex $Na[PhSeB(OEt)_3]$ generated *in situ* with $(PhSe)_2$ and $NaBH_4$ in EtOH at room temperature to afford the

desired hydroxyl lactam (**7**) as a sole product in 86% yield. Protection of hydroxy group in **7** with *tert*-butylchlorodiphenylsilane (TBDPS-Cl) and then removal of benzylidene acetal group in **8** employing the transfer hydrogenation[7] by the use of hydrazine hydrate as a hydrogen source and 10% Pd-C in MeOH gave *N*-unsubstituted γ-lactam (**9**) in 86% overall yield from **7**. Sequential mesylation of the resulting alcohol (**9**) with methanesulfonyl chloride (MsCl) and triethylamine (Et_3N) in CH_2Cl_2, azidation with NaN_3, and *N*-protection with Boc_2O and 4-dimethylaminopyridine (4-DMAP) afforded azido-γ-lactam (**11**) in 88% overall yield from **9**. Next, intramolecular transamidation of the azido γ-lactam (**11**) was performed using our previous reported reaction conditions.[4j,k] Thus, a catalytic hydrogenation of the azido group in **11** in the presence of 10% Pd-C in MeOH-H_2O (12:1) at room temperature under 3 atm hydrogen atmosphere for 48 h afforded the expected *N*-unsubstituted δ-lactam (**12**) in 92% yield. After protection of the lactam ring nitrogen of **12** with Boc_2O and 4-DMAP, we turn out our attention on the titanium-mediated carbonyl olefination of the resulting *N*-Boc-δ-lactam (**13**). Compound (**13**) was reacted with 1.4 equiv. of dimethyltitanocene (Cp_2TiMe_2)[8] in toluene at 105°C, affording the desired *exo*-methylene compound (**14**) in 78% yield without isomerization to the endocyclic unsaturated compound.[9] Compound (**14**) was stable during a few days.



Scheme 3. Reagents and conditions: (a) (i) 9-BBM, THF, rt; (ii) H_2O_2, NaOH, 75%; (b) n-Bu_4NF, THF, rt; (c) $Me_2C(OMe)_2$, *p*-TsOH,acetone, rt, 79% (2 steps).

Next, hydroboration of the olefin moiety in **14** using the sterically demanding 9-borabicyclo[3,3,1]-nonane (9-BBN) described by Herdeis *et al.*[10] followed by treatment with hydrogen peroxide afforded the corresponding primary alcohol (**15**) as a single diastereoisomer in 75% yield, in which the three substituents at C2-, C4-, and C5-positions are all *cis* to each other (Scheme 3). This structure was assigned by its NOESY spectrum, in which marked NOEs between C2-H and C4-H, and C4-H and C5-H were observed. Thus, the absolute configuration of **15** was unambiguously determined as (2*S*,4*S*,5*R*)-**15**. Hydroboration of **14** occurred exclusively from less hinder β-side. The stereoselectivity could be explained by the fact that the α-side of both conformers of **14A** and **14B** is shielded by the sterically bulky *tert*-butyldiphenylsilyloxy and *tert*-butyloxycarbonylamino groups respectively. In both half-chair-like conformers of **14A** and **14B** 1,3-diaxial interactions are operating, so a roughly 1:1 equibrium mixture of these conformers is present. Therefore, the sterically bulky borane reagent, 9-BBN, attacked the olefin moiety of **14** from less hinder β-side (Figure 2).

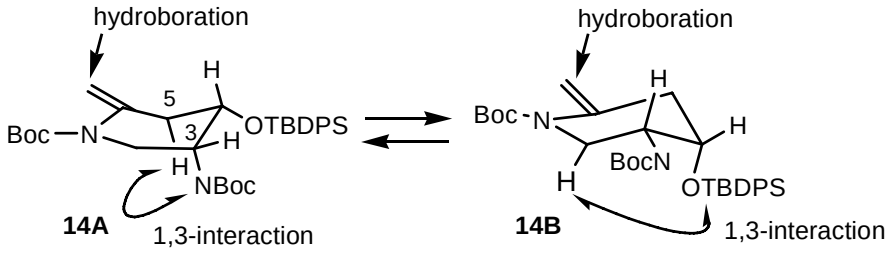


Figure 2.

For the synthesis of Kobayashi's intermediate (**2**), removal of the *O*-TBDPS group in **15** with n-Bu_4NF followed by simultaneous protection of the hydroxy and *N*-*tert*-butoxycarbonylamino groups with 2,2-dimethoxypropane and *p*-TsOH gave the known oxazolidine (**2**) [mp 104-105°C, $[\alpha]^{24}_D$ -10.8° (c=1.30, $CHCl_3$); lit.,[2] mp 104°C, $[\alpha]^{24}_D$ -7.3° (c=1.0, $CHCl_3$)] in 79% overall yield from **15**, which was already converted into pseudodistomin C triacetate by Kobayashi *et al*.[2] The spectral data were good agreement with those reported.[2]

In summary, an efficient and stereocontrolled formal synthesis of pseudodistomin C (**1**) has been developed. This route featured intramolecular transamidation reaction of azido-γ-lactam (**11**), *exo*-methylenation of the resulting δ-lactam (**13**), and highly stereoselective hydroboration of **14**.

EXPERIMENTAL

Melting points were measured on a Yanako MP-S3 micromelting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-370 automatic digital polarimeter. IR spectra were recorded with a HORIBA FT-720 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were measured with a JNM-ECP-500 spectrometer. Chemical shifts are expressed in ppm (δ) downfield from tetramethylsilane as internal standard in $CDCl_3$ solutions. EIMS, FABMS, and high resolution fast atom bombardment MS spectra were obtained with JMS-SX-102A spectrometer. Routine monitoring of reaction was carried out using Merck TLC aluminum sheet silica gel 60 F254. Flash column chromatography was performed with indicated solvents on Merck silica gel, 230-400 mesh. All solvents were dried and purified before use. (2*R*,5*R*,6*R*,7*R*)-6,7-Epoxy-2-phenyl-3-oxa-1-azabicyclo[3,3,0]octane-8-one (**6**) was prepared according to a literature procedure.[5]

(2*R*,5*R*,6*S*)-6-Hydroxy-2-phenyl-3-oxa-1-azabicyclo[3,3,0]octan-8-one (**7**)

To a mixture of $(PhSe)_2$ (8.8 g, 27.6 mmol) in EtOH (50 mL) at rt under nitrogen atmosphere, $NaBH_4$ (2.09 g, 55.2 mmol) was added and the mixture was vigorously stirred for 20 min. The reaction mixture was cooled to 0°C, to which AcOH (4.2 mL, 73.6 mmol) was added. The resulting mixture was stirred for 5 min at 0°C, and then added to a solution of an α,β-epoxylactam (**6**) (4.0 g, 18.4 mmol) in EtOH (30 mL) under nitrogen atmosphere. The mixture was stirred for 30 min and then diluted with AcOEt (40 mL), in which oxygen was passed for 5 min. The mixture was washed with brine and the extract was dried over

Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography [$CHCl_3$-MeOH (20:1, v/v)] to give **7** (3.47 g, 86%) as a colorless solid. Recrystallization from AcOEt-isopropyl ether gave an analytical sample of **7** as a colorless needles; mp132-133°C; $[\alpha]^{25}_D$ +231° (c=1.02, $CHCl_3$). [lit.,[5] mp 132-133°C; $[\alpha]^{20}_D$ +228° (c=0.204, $CHCl_3$)].

(2*R*,5*R*,6*S*)-6-(*tert*-Butyldiphenylsilyloxy)-3-oxa-2-phenyl-1-azabicyclo[3,3,0]octan-8-one (**8**)

To a stirred solution of **7** (2.0 g, 6.25 mmol) in dry DMF (40 mL) at 0°C were successively added imidazole (1.88 g, 1.87 mmol) and TBDPS-Cl (2.06g, 7.50 mmol) and the mixture was stirred at rt for 8 h. The reaction mixture was diluted with H_2O and extracted with AcOEt (40 mL). The extract was washed with brine, dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography [hexane-AcOEt (4:1, v/v)] to give **8** (3.97 g, 95%) as a colorless oil. $[\alpha]^{26}_D$ +103.6° (c=1.00, $CHCl_3$); IR (neat) 3070, 2890, 1712; ^{1}H-NMR ($CDCl_3$) δ 1.06 (9H, s, $(CH_3)_3CSi$), 2.68 (1H, dd, J=16.5, 7.80 Hz, C7-H), 2.96 (1H, dd, J=16.5, 8.20 Hz, C7-H), 3.04 (1H, dd, J=8.70, 6.80 Hz, C4-H), 3.62 (1H, dd, J=8.70, 6.70 Hz, C4-H), 4.01 (1H, m, C5-H), 4.31 (1H, m, C6-H), 6.21 (1H, s, C2-H), 7.34-7.62 (15H, m, Ph-H); ^{13}C-NMR ($CDCl_3$) δ 18.96 (s, $(CH_3)_3CSi$), 26.77 (q, $(CH_3)_3CSi$), 43.93 (t, C7), 67.13 (d, C5), 69.47 (t, C4), 72.88 (d, C6), 87.00 (d, C2), 125.96, 128.01, 128.42, 130.27, 130.34, 135.56, 135.59 (Ph), 174.90 (s, lactam C=O); HRFABMS Calcd for $C_{28}H_{32}NO_3Si$: 458.2152. Found: 458.2153.

(4*S*,5*R*)-5-Hydroxymethyl-4-(*tert*-butyldiphenylsilyloxy)pyrrolidin-2-one (**9**)

To a stirred solution of **8** (1.5 g, 3.3 mmol) in EtOH (40 mL) was added 10% Pd-C (1.65 g) and 100% H_2NNH_2-H_2O (3.3 mL) at rt under nitrogen atmosphere. The suspension was refluxed with vigorously stirring for 10 h. The catalyst was filtered and washed with EtOH. The combined filtrates were evaporated in vacuo and then the residue was purified by column chromatography [$CHCl_3$-MeOH (15:1, v/v)] to give **9** (1.1 g, 90%) as a colorless viscous oil. $[\alpha]^{24}_D$ +8.91° (c=1.28, $CHCl_3$); IR (neat) 3072, 2931, 2885, 1693; ^{1}H-NMR ($CDCl_3$) δ 1.05 (9H, s, $(CH_3)_3CSi$), 2.27 (1H, dd, J=17.4, 3.2 Hz, C3-H), 2.41 (1H, dd, J=17.4, 7.3 Hz, C3-H), 2.96 (1H, dd, J=11.9, 5.5 Hz, CH_2OH), 3.28 (1H, dd, J=11.4, 3.3 Hz, CH_2OH), 3.51-3.53 (1H, m, C5-H), 4.20-4.21 (1H, m, C4-H), 7.59-7.63 (10H, m, Ph-H); ^{13}C-NMR ($CDCl_3$) δ 19.00 (s, $(CH_3)_3CSi$), 26.85 (q, $(CH_3)_3CSi$), 40.93 (t, C3), 53.42 (t, CH_2OH), 62.91 (d, C5), 70.66 (d, C4), 127.88, 130.04, 133.05, 135.69 (Ph), 177.30 (s, lactam C=O); FABMS m/z 370 $(M+1)^+$; HRFABMS Calcd for $C_{21}H_{28}NO_3Si$ $(M+1)^+$: 370.1839. Found: 370.1840.

(4*S*,5*R*)-5-Azidomethyl-4-(*tert*-butyldiphenylsilyloxy)pyrrolidin-2-one (**10**)

To a stirred solution of **9** (3.21 g, 8.68 mmol) and Et_3N (1.32 g, 13.0 mmol) in CH_2Cl_2 (40 mL) was added MsCl (1.2 g, 10.4 mmol) under nitrogen atmosphere and stirred for 12 h. Saturated aqueous citric

acid (30 mL) and CH_2Cl_2 (30 mL) were added and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated in vacuo to afford colorless oil. To a solution of this oil in DMF (30 mL), NaN_3 (1.7 g, 26.1 mmol) was added and the mixture was heated at 80°C for 6 h. H_2O (20 mL) and AcOEt (40 mL) were added and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography [hexane-AcOEt 1:1 (v/v)] to give **10** (3.02 g, 88%) as a colorless viscous oil. $[\alpha]^{24}_D$ +30.19° (c=1.10, $CHCl_3$); IR (neat) 3250, 2104, 1705; ^{1}H-NMR ($CDCl_3$) δ 1.07 (9H, s, $(CH_3)_3CSi$), 2.37 (1H, dd, J=17.9, 3.7 Hz, C3-H), 2.51 (1H, dd, J=17.9, 5.9 Hz, C3-H), 2.76 (1H, dd, J=12.6, 6.0 Hz, CH_2N_3), 3.02 (1H, dd, J=12.4, 4.1 Hz, CH_2N_3), 3.42-3.58 (1H, m, C5-H), 4.02-4.32 (1H, m, C4-H), 7.40-7.66 (10H, Ph-H); ^{13}C-NMR ($CDCl_3$) δ 18.98 (s, $(CH_3)_3CSi$), 26.81 (q, $(CH_3)_3CSi$), 40.26 (t, C3), 53.02 (t, CH_2N_3), 62.99 (d, C5), 70.95 (d, C4), 127.94, 127.96, 130.14, 130.21, 135.66, 135.68 (Ph), 176.30 (s, lactam C=O); FABMS m/z 395 $(M+1)^+$; HRFABMS Calcd for $C_{21}H_{29}N_4O_2Si$ $(M+1)^+$: 395.1903. Found : 395.1905.

(4*S*,5*R*)-5-Azidomethyl-1-*tert*-butoxycarbonyl-4-(*tert*-butyldiphenylsilyloxy)pyrrolidin-2-one (**11**)
To a solution of **10** (2.86 g, 7.25 mmol) and 4-DMAP (0.18 g, 1.45 mmol) in CH_2Cl_2 (40 mL) was added Boc_2O (3.16 g, 14.5 mmol) at rt. After being stirred for 8 h, the mixture was quenched by saturated aqueous citric acid and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography [hexane-AcOEt 2:1 (v/v)] to give **11** (3.45 g, 96%) as a colorless viscous oil. $[\alpha]^{24}_D$ -27.6° (c=1.08, $CHCl_3$); IR (neat) 3072, 2933, 2108, 1789, 1758, 1716; ^{1}H-NMR ($CDCl_3$) δ 1.06 (9H, s, $(CH_3)_3CSi$), 1.59 (9H, s, $(CH_3)_3CO$), 2.48 (1H, br d, J=17.9 Hz, C3-H), 2.78 (1H, dd, 17.9, 6.0 Hz, C3-H), 2.92 (1H, dd, J=12.8, 2.8 Hz, CH_2N_3), 3.36 (1H, dd, J=12.8, 5.5 Hz, CH_2N_3), 3.99 (1H, dd, J=5.1, 2.8 Hz, C5-H), 4.13-4.15 (1H, m, C4-H), 7.40-7.65 (10H, m, Ph-H); ^{13}C-NMR ($CDCl_3$) δ 18.96 (s, $(CH_3)_3CSi$), 26.74 (q, $(CH_3)_3CSi$), 28.00 (q, $(CH_3)_3CO$), 41.93 (t, C3), 51.10 (t, CH_2N_3), 66.04 (d, C5), 68.24 (d, C4), 127.98, 130.22, 132.57, 132.95, 135.61 (Ph), 149.75 (s, urethane C=O), 172.28 (s, lactam C=O); FABMS m/z 495 $(M+1)^+$; HRFABMS Calcd for $C_{26}H_{34}N_4O_4Si$ $(M+1)^+$: 495.2427. Found: 495.2424.

(4*S*,5*R*)-5-(*tert*-Butoxycarbonylamino)-4-(*tert*-butyldiphenylsilyloxy)piperidin-2-one (**12**)
A mixture of **11** (1.2 g, 2.4 mmol) and 10% Pd-C (0.3 g) in MeOH-H_2O (65 mL, 12/1 (v/v)) was stirred for 48 h at rt under hydrogen atmosphere (3 atm). The catalyst was filtered off and the filtrate was concentrated in vacuo to give a residue, which was partitioned between $CHCl_3$ and H_2O. The aqueous layer was backwashed with $CHCl_3$. The combined organic layer was dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography [$CHCl_3$-MeOH 10:1 (v/v)] to give **12** (1.05 g, 92%) as a colorless viscous oil. $[\alpha]^{24}_D$ +32.5° (c=0.90, MeOH); IR (neat) 3450,

3072, 2964, 1716, 1662; ^{1}H-NMR ($CDCl_3$) δ 1.01 (9H, s, $(CH_3)_3CSi$), 1.41 (9H, s, $(CH_3)_3CO$), 2.31-2.45 (2H, m, C3-H), 3.25-3.32 (1H, m, C6-H),3.45-3.55 (1H, m, C6-H), 3.86-3.97 (1H, m, C5-H), 4.11-4.21 (1H, m, C4-H), 4.76 (1H, d, J=7.40 Hz, NHBoc), 7.04 (1H, m, NHCO), 7.37-7.67 (10H, m, Ph-H); ^{13}C-NMR ($CDCl_3$) δ 19.31 (s, $(CH_3)_3CSi$), 26.97 (q, $(CH_3)_3CSi$), 28.29 (q, $(CH_3)_3CO$), 38.34 (t, C3), 41.79 (t, C6), 48.52 (d, C5), 68.27 (d, C4), 79.74 (s, $(CH_3)_3CO$), 127.94, 127.99, 130.15, 132.89, 135.67, 135.70 (Ph), 155.75 (s, urethane C=O), 170.14 (s, lactam C=O); FABMS m/z 469 $(M+1)^+$; HRFABMS Calcd for $C_{26}H_{37}N_2O_4Si$ $(M+1)^+$: 469.2522. Found: 469.2521.

(4*S*,5*R*)-1-*tert*-Butoxycarbonyl-5-(*tert*-butoxycarbonylamino)-4-(*tert*-butyldiphenylsilyloxy)piperidin-2-one (**13**)

Treatment of **12** (1.20 g, 2.56 mmol) in a similar manner to that described for the preparation of **11** from **10** gave **13** (1.31 g, 90%) as a pale yellow oil, after purification by column chromatography [hexane-AcOEt 3:1 (v/v)]. $[\alpha]^{24}_D$ +18.2° (c=0.95, MeOH); IR (neat) 3363, 1774, 1712; ^{1}H-NMR ($CDCl_3$) δ 1.09 (9H, s, $(CH_3)_3CSi$), 1.41 and 1.53 (18H, each s, $(CH_3)_3CO$), 2.50-2.55 (2H, m, C3-H), 3.70-3.75 (2H, m, C6-H), 3.90-4.00 (1H, m, C5-H), 4.10-4.20 (1H, m, C4-H), 4.72 (1H, d, J=7.40Hz, NHBoc), 7.39-7.63 (10H, m, Ph-H); ^{13}C-NMR ($CDCl_3$) δ 19.32 (s, $(CH_3)_3CSi$), 27.00 (q, $(CH_3)_3CSi$), 27.99 and 28.29 (each q, $(CH_3)_3CO$ x 2), 41.93 (t, C3), 45.34 (t, C6), 48.89 (d, C5), 68.41 (d, C4), 79.93 and 83.32 (each s, $(CH_3)_3CO$ x 2), 128.01, 128.07, 130.29, 135.69, 135.77 (Ph), 152.18 and 155.00 (each s, urethane C=O x 2), 168.31 (s, lactam C=O); FABMS m/z 569 $(M+1)^+$; HRFABMS Calcd for $C_{31}H_{45}N_2O_6Si$: 569.3047. Found: 569.3046.

(4*S*,5*R*)-1-*tert*-Butoxycarbonyl-5-(*tert*-butoxycarbonylamino)-4-(*tert*-butydiphenylsilyloxy)-2-methylene-piperidine (**14**)

To a solution of **13** (0.84 g, 1.47 mmol) in toluene (10 mL) was added Cp_2TiMe_2 (0.37 g, 1.8 mmol) and the mixture was heated at 105°C for 3 h. After evaporation of the solvent, the brown oil was diluted with pentane (20 mL) and the solution was filtered, and the filtrate was concentrated in vacuo. The orange colored oil residue was purified by column chromatography [hexane-AcOEt 5:1 (v/v)] to give **14** (0.65 g, 78%) as a yellow oil. $[\alpha]^{25}_D$ +24.5° (c=0.66, $CHCl_3$); IR (neat) 3450, 2875, 1716, 1655; ^{1}H-NMR ($CDCl_3$) δ 1.08 (9H, s, $(CH_3)_3CSi$), 1.42 and 1.45 (18H, each s, $(CH_3)_3CO$ x 2), 2.12-2.18 (2H, m, C3-H), 3.40-3.50 (1H, m, C6-H), 3.70-3.72 (1H, m, C6-H), 3.79 (1H, m, C5-H), 4.02-4.06 (1H, m, C4-H), 4.71 (1H, s, $=CH_E$), 4.76 (1H, d, J=7.40 Hz, NHBoc), 4.97 (1H, s, $=CH_Z$), 7.37-7.69 (10H, m, Ph-H); ^{13}C-NMR ($CDCl_3$) δ 19.42 (s, $(CH_3)_3CSi$), 27.07 (q, $(CH_3)_3CSi$), 28.26 and 28.37 (q, $(CH_3)_3CO$ x 2), 38.62 (t, C3), 44.81 (t, C6), 50.05 (d, C5), 69.95 (d, C4), 77.29 and 80.36 (each s, $(CH_3)_3CO$ x 2), 109.42 (t, $=CH_2$), 127.69, 127.85, 129.99, 133.56, 135.77, 135.86, 135.93 (Ph), 138.91 (s, C2), 153.77 and

155.09 (each s, urethane C=O); FABMS m/z 567 (M+1)+; HRFABMS Calcd for $C_{32}H_{47}N_2O_5Si$: 567.3254. Found: 567.3256.

(2*S*,4*S*,5*R*)-1-*tert*-Butoxycarbonyl-5-(*tert*-butoxycarbonylamino)-2-hydroxymethyl-4-(*tert*-butyldiphenylsilyloxy)piperidine (**15**)

To a solution of **14** (0.45 g, 0.79 mmol) in THF (40 mL) was added 0.5 M solution of 9-BBN (2.7 mL, 1.34 mmol) and the mixture was stirred at rt for 20 h. After addition of 30% hydrogen peroxide (4.0 mL, 39.5 mmol) and 3.0 M NaOH (4.0 mL, 12.0 mmol), the mixture was stirred at rt for 2 h. Potassium carbonate was added and the layers were separated. The aqueous layer was extracted with AcOEt and the combined organic layers were washed with brine, dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography [hexane-AcOEt 4:1 (v/v)] to give **15** (0.34 g, 75%) as a colorless solid. Recrystallization from AcOEt-isopropyl ether gave an analytical sample of **15** as a colorless needless; mp 103-104°C; $[\alpha]^{25}_D$ -3.27° (c=1.10, $CHCl_3$); IR (KBr) 3423, 1718, 1695; ^{1}H-NMR ($CDCl_3$) δ 1.10 (9H, s, $(CH_3)_3CSi$), 1.37 and 1.45 (18H, each s, $(CH_3)_3CO$ x 2), 1.66-1.70 (2H, m, C3-H), 2.60 (1H, br s, OH), 3.08-3.30 (1H, m, C6-H), 3.50-3.68 (2H, m, CH_2OH), 3.72-3.87 (1H, m, C6-H), 3.92-4.18 (3H, m, C2-, C4-, and C5-H), 4.67 (1H, br d, J=7.42 Hz, NHBoc), 7.37-7.70 (10H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ 19.36 (s, $(CH_3)_3CSi$), 27.19 (q, $(CH_3)_3CSi$), 28.34 and 28.36(each q, $(CH_3)_3CO$ x 2), 32.10 (t, C3), 38.81 (t, C6), 49.93 (d, C5), 51.40 (d, C2), 64.31 (t, CH_2OH), 69.02 (d, C4), 79.34 and 80.50 (each s, $(CH_3)_3CO$ x 2), 127.97, 130.09, 130.24, 132.68, 133.08, 135.85, 136.00 (Ph), 154.81 and 154.88 (each s, urethane C=O x 2); FABMS m/z 585 $(M+1)^+$; Anal. Calcd for $C_{32}H_{49}N_2O_6Si$: C, 65.72; H, 8.27; N, 4.79. Found: C, 65.58; H, 8.10; N, 4.62.

(2*S*,4*S*,5*R*)-1-*tert*-Butoxycarbonyl-5-(*tert*-butoxycarbonylamino)-2-hydroxymethyl-4-hydroxypiperidine (**16**)

Tetra-*n*-butylammonium fluoride (TBAF) in THF (1.0 M solution, 2.46 mL) was added dropwise to a stirred solution of **15** (0.48 g, 0.82 mmol) in THF (30 mL) at rt and the mixture was stirred for 6 h. The reaction mixture was concentrated in vacuo and the residue was purified by column chromatography (AcOEt) to give **16** (0.25 g, 88%) as a colorless viscous oil. $[\alpha]^{25}_D$ -14.3° (c=0.88, $CHCl_3$); IR (neat) 3444, 3336, 1722; ^{1}H-NMR ($CDCl_3$) δ 1.44 and 1.46 (18H, each s, $(CH_3)_3CO$), 1.93-2.08 (2H, m, C3-H), 2.59 and 2.78 (2H, each br s, OH x 2), 2.94-3.08 (1H, m, C6-H), 3.48-3.59 (1H, m, C6-H), 3.60-3.70 and 3.80-3.92 (2H, each m, CH_2OH), 3.92-4.08 (2H, m, C2- and C5-H), 4.12-4.28 (1H, m, C4-H), 5.29 (1H, br d, J=7.45 Hz, NHBoc); ^{13}C-NMR ($CDCl_3$) δ 28.22 and 28.38 (each q, $(CH_3)_3CO$ x 2), 33.16 (t, C3), 40.20 (t, C6), 49.67 (d, C5), 50.47 (d, C2), 64.85 (d, C4), 65.06 (t, CH_2OH), 77.37 and 80.46 (s, $(CH_3)_3CO$ x 2), 155.18 and 155.49 (each s, urethane C=O x 2); FABMS m/z 347 $(M+1)^+$; HRFABMS Calcd for $C_{16}H_{31}N_2O_6$: 347.2182. Found: 347.2187.

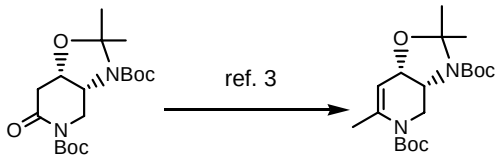
tert-Butyl (3a*R*,6*S*,7a*S*)-3-*tert*-Butoxycarbonyl-2,2-dimethyl-6-hydroxymethylperhydrooxazolo [4,5-*c*] pyridine-5-carboxylate (**2**)

To a solution of **16** (0.15 g, 0.43 mmol) in acetone (10 mL) was added 2,2-dimethoxypropane (0.14 g, 1.3 mmol) and *p*-TsOH (15.0 mg, 0.08 mmol) at 0°C. After stirring at rt for 12 h, the same amount of 2,2-dimethoxypropane and *p*-TsOH were added and the mixture was stirred for 12 h. After addition of saturated solution of $NaHCO_3$, the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography [hexane-AcOEt 1:1 (v/v)] to give **2** (0.15 g, 90%) as a colorless solid. Recrystallization from AcOEt-isopropyl ether gave an analytical sample of **2** as a colorless needless; mp 104-105°C (lit.,[2] mp 104°C) ; $[\alpha]^{24}_D$ -10.8° (c=1.30, $CHCl_3$) (lit.,[2] $[\alpha]^{24}_D$ -7.3° (c=1.0, $CHCl_3$)); IR (KBr) 3457, 1710, 1674; ^{1}H-NMR ($CDCl_3$) δ 1.46 and 1.48 (18H, each s, $(CH_3)_3CO$ x 2), 1.51 and 1.64 (6H, each s, CH_3 x 2), 1.93-2.04 (2H, m, C7-H), 2.66 (1H, m, C4-H), 2.80-2.93 and 3.62-3.70 (2H, m, CH_2OH), 3.77-3.84 (1H, m, C7a-H), 3.86-3.95 (1H, m, C3a-H), 4.18-4.35 (2H, m, C4- and C6-H); ^{13}C-NMR ($CDCl_3$) δ 23.95 and 27.09 (each q, CH_3 x 2), 28.50 and 28.40 (each q, $(CH_3)_3CO$ x 2), 40.15 (t, C7), 49.63 (d, C6), 50.20 (t, C4), 53.50 (d, C3a), 62.97 (t, CH_2OH), 69.86 (d, C7a), 79.93 and 80.30 (each s, $(CH_3)_3CO$), 93.82 (s, C2), 151.60 and 155.70 (each s, urethane C=O x 2); FABMS m/z 387 $(M+1)^+$; Anal. Calcd for $C_{19}H_{34}N_2O_6$: C, 59.03; H, 8.87; N, 7.25. Found: C, 58.98; H, 8.64; N, 7.02.

REFERENCES AND NOTES

1. (a) J. Kobayashi, K. Naitoh, Y. Doi, K. Deki, and M. Ishibashi, *J. Org. Chem.*, 1995, **60**, 6941; (b) J. Kobayashi and M. Ishibashi, *Heterocycles*, 1996, **42**, 943; (c) I. Ninomiya, T. Kiguchi, and T. Naito, '*The Alkaloids*', Vol. 50, ed. by G. A. Cordell, Academic Press, Inc., London, 1998, pp. 317-342.
2. Y. Doi, M. Ishibashi, and J. Kobayashi, *Tetrahedron*, 1996, **52**, 4573.
3. N. Langlois, *Org. Lett.*, 2002, **4**, 185.
4. (a) U. Kramer, A. Guggisberg, M. Hesse, and H. Schmid, *Angew. Chem., Int. Ed. Engl.*, 1977, **16**, 861; (b) P. J. Murray, J. D. Starky, and J. E. Davies, *Tetrahedron Lett.*, 1998, **39**, 6721; (c) C. Dinsmore and C. B. J. Zartman, *Tetrahedron Lett.*, 2000, **41**, 6309; (d) A. Dinsmore, P. M. Doyle, P. B. Hitchcock, and D. W. Young, *Tetrahedron Lett.*, 2000, **41**, 10153; (e) H. H. Wasserman, H. Matsuyama, and R. P. Robinson, *Tetrahedron*, 2002, **58**, 7177; (f) N. Langlois, *Tetrahedron Lett.*, 2002, **43**, 9531; (g) K. Papadopoulos and D. W. Young, *Tetrahedron Lett.*, 2002, **43**, 3951; (h) B. K. Banik, S. Samajdar, and I. Banic, *Tetrahedron Lett.*, 2003, **44**, 1699; (i) T. Kouko, K. Matsumura, and T. Kawasaki, *Tetrahedron*, 2005, **61**, 2309; (j) K. Tanaka, H. Nemoto, and H. Sawanishi, *Tetrahedron:Asymmetry*, 2005, **16**, 809; (k) K. Tanaka, H. Nemoto, and H. Sawanishi, *Tetrahedron:Asymmetry*, 2005, **16**, 1989.

5. (a) C. Herdeis and H. P. Hummann, *Tetrahedron:Asymmetry*, 1994, **5**, 119; (b) C. Herdeis, A. Aschenbrenner, A. Kirfel, and F. Schwabenlander, *Tetrahedron:Asymmetry*, 1997, **8**, 2421; (c) S. K. Panday and N. Langlois, *Synth. Commun.*, 1997, **27**, 1373.
6. M. Miyashita, T. Suzuki, M. Hoshino, and A. Yoshikoshi, *Tetrahedron*, 1997, **53**, 12469.
7. (a) T. Bieg and W. Szeja, *Synthesis*, 1986, 317; (b) Y. Hamada, O. Hara, A. Kawai, Y. Kohno, and T. Shioiri, *Tetrahedron*, 1991, **47**, 8635.
8. N. A. Petasis and E. I. Bzowej, *J. Am. Chem. Soc.*, 1990, **112**, 6392.
9. Langlois have reported that treatment of a similar compound of **13**, *tert*-butyl (3a*R*, 7a*S*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-6-oxoperhydro[4,5-*c*]pyridine-5-carboxylate, with Cp_2TiMe_2 afforded only endocyclic unsaturated compound *via* isomerization of the created double bond. See ref. 3.



10. (a) C. Herdeis and E. Heller, *Tetrahedron:Asymmetry*, 1993, **4**, 2085; (b) C. Herdeis and E. Heller, *Tetrahedron:Asymmetry*, 1997, **8**, 1115.