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Synthesis of an Optically Pure Synthetic Intermediate of Aloperine from a Yeast-Reductive Product

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Optically pure (*S*)- and (*R*)-vinylpiperidine 2 and (*S*)- and (*R*)-(hydroxyethyl)piperidine 3, which were key intermediates for the synthesis of aloperine, were synthesized from yeast-reductive products.

Key words: piperidine; aloperine; yeast-reductive product

Piperidine derivatives are important synthetic intermediates for the synthesis of alkaloids, and some reviews on the synthesis of piperidine are known.[1,2] Aloperine (**1**) has been isolated from plants which were used as the traditional Chinese medicine for the treatment of inflammation.[3] The structure of aloperine (**1**) containing its absolute configuration has been determined,[4] and two synthetic studies are known (Fig. 1). L. E. Overman and co-workers have synthesized aloperine (**1**) with 97% ee from (*R*)-vinylpiperidine **2** of 97% ee.[5] D. Passarella and coworkers have prepared (*R*)-(hydroxyethyl)piperidine **3** with 90% ee,[6] and then converted to aloperine with 90% ee.[7] These reports demonstrate that the ee values of key intermediates **2** and **3** determined the ee value of aloperine in these synthetic processes. The preparation of **2** or **3** with a higher ee value will lead to the synthesis of aloperine with a correspondingly higher ee value.

The application of yeast-reductive products **4** and **5** to preparing **2** and **3** is described in this report. Compounds **4** and **5** had already been converted to (*R*)-**7** and (*S*)-**7** *via* (*R*)-**6** and (*S*)-**6**, respectively[8] (Scheme 1). These

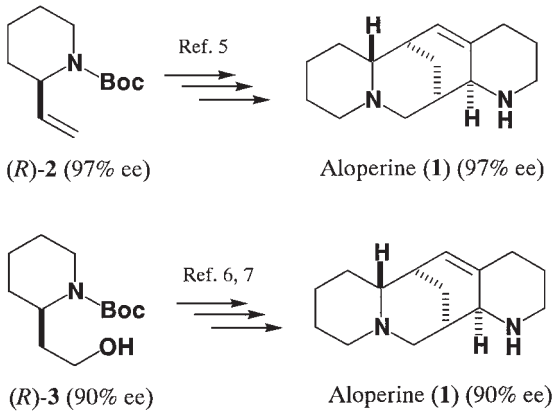
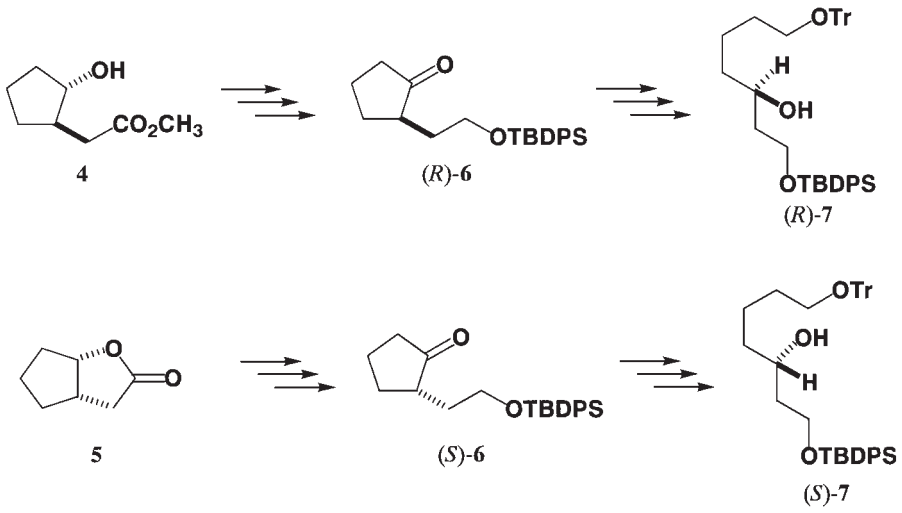


Fig. 1. Previous Synthetic Study of (+)-Aloperine (**1**).



Scheme 1. Conversion of Yeast-Reductive Products **4** and **5** to (*R*)-**7** and (*S*)-**7**.[8]

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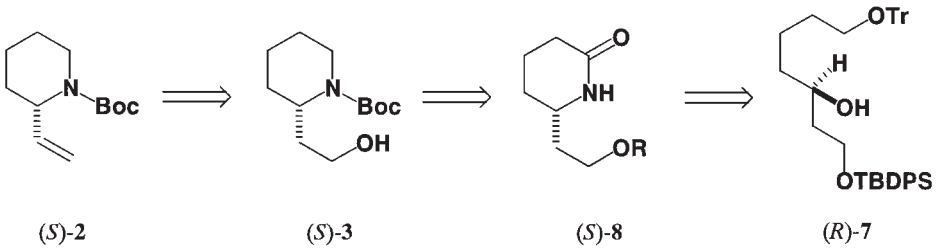
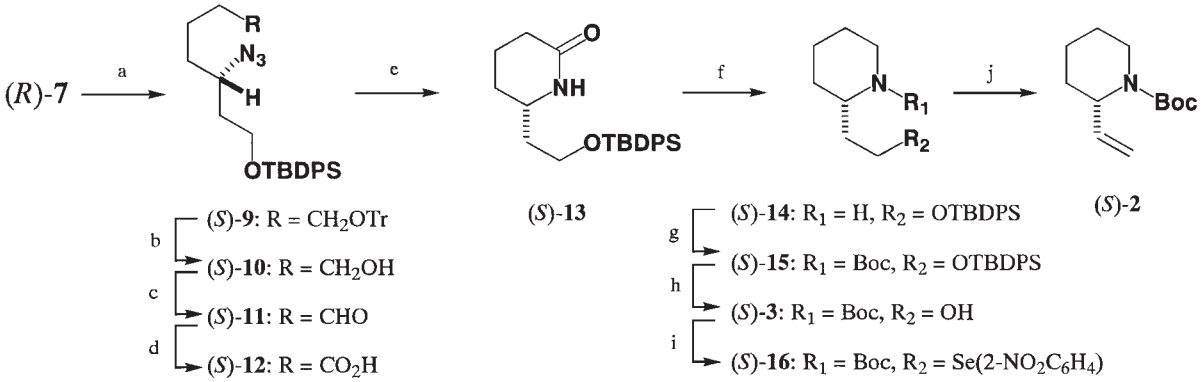


Scheme 2. Retrosynthetic Analysis of (*S*)-**2**.



Scheme 3. Synthesis of (*S*)-**2**.

(a) (1) MsCl, Et_3N, CH_2Cl_2, r.t., 12 h; (2) NaN_3, DMF, 100 °C, 1 h (99%, 2 steps); (b) HCO_2H, ether, 0 °C, 1 h (91%); (c) PCC, NaOAc, MS 4A, CH_2Cl_2, r.t., 15 h (74%); (d) 2-methyl-2-butene, $NaH_2PO_4 \cdot 2H_2O$, $NaClO_2$, aq. *tert*-BuOH, 0 °C, 1 h (97%); (e) (1) H_2, $Pd(OH)_2$, EtOH, r.t., 4 h; (2) toluene, reflux, 1 h (90%, 2 steps); (f) DIBAL-H, CH_2Cl_2, 0 °C, 1 h (48%); (g) $(Boc)_2O$, K_2CO_3, aq. THF, 0 °C, 2 h (97%); (h) $(n\text{-}Bu)_4NF$, THF, 0 °C, 8 h (76%); (i) $(2\text{-}NO_2C_6H_4)SeCN$, $(n\text{-}Bu)_3P$, THF, r.t., 12 h (92%); (j) MCPBA, phosphate buffer at pH 8, CH_2Cl_2, 0 °C, 30 min (81%).

(*R*)- and (*S*)-**7** were selected as intermediates for the syntheses of (*S*)-**2** and (*S*)-**3**, and (*R*)-**2** and (*R*)-**3**. Scheme 2 shows the retrosynthetic analysis. (*S*)-Vinylpiperidine **2** would have been obtained from (*S*)-(hydroxyethyl)piperidine **3** by dehydration, and the reduction of (*S*)-amide **8** would have then give a (*S*)-piperidine **3**. (*R*)-Alcohol **7** could be converted to (*S*)-amide **8** by SN2 introduction of an amino group, deprotection followed by oxidation to carboxylic acid. (*R*)-Vinylpiperidine **2** and (*R*)-(hydroxyethyl)piperidine **3** could be obtained from (*S*)-alcohol **7**. It can be assumed that direct conversion of **6** to amide **8** by Beckmann rearrangement under acidic condition would be difficult because of selection of the protective group. Since reported yeast-reductive products **4** and **5** each have a high ee value, syntheses of vinylpiperidine **2** and (hydroxyethyl)piperidine **3** with higher ee value could be expected. The purpose of this project is to synthesize (*S*)-**2** and (*S*)-**3** with a high ee value, as well as (*R*)-**2** and (*R*)-**3**. The success of this project will make it possible to synthesize (−)- and (+)-aloperine with high ee value and contribute to biological research. Kibayashi has succeeded in the preparation of enantiopure (*R*)-(2-hydroxyethyl)piperidine by using a chiral auxiliary.[9] Our challenge is to synthesize enantiopure (*R*)- and (*S*)-**2** and (*R*)- and (*S*)-**3** by using yeast-reductive products obtained from one racemic compound.

Results and Discussion

Scheme 3 shows the synthesis of (*S*)-**3** and (*S*)-**2**. (*R*)-Alcohol **7**, which was prepared from yeast-reductive product **4**,[8] was converted to a corresponding mesylate by using mesyl chloride and triethylamine, and the crude mesylate was then converted to azide **9** by employing NaN_3 in 99% yield through 2 steps. After cleavage of the trityl ether using formic acid in ether in 91% yield, resulting alcohol **10** was oxidized to carboxylic acid **12** by pyridinium chlorochromate and subsequent $NaClO_2$ oxidation in 72% yield through 2 steps. Conversion of azido-carboxylic acid **12** to amide **13** was achieved by treatment with H_2 and $Pd(OH)_2/C$ followed by heating in toluene in 90% yield. DIBAL-H reduction of amide **13** gave (*S*)-piperidine **14** in 48% yield, amide **13** being recovered in 51%. The enantiomeric excess of (*S*)-piperidine **14** was determined as >99% after the reaction with (−)-menthyl chloroformate.

After introduction of *tert*-butoxycarbonyl (Boc) group by using $(Boc)_2O$ and K_2CO_3 in 97% yield, cleavage of the silyl ether by employing $(n\text{-}Bu)_4NF$ was performed to give (*S*)-(hydroxyethyl)piperidine **3** in 76% yield. The NMR spectrum agreed with that in the literature.[6] Dehydration of (*S*)-**3** to (*S*)-vinylpiperidine **2** by the Chugaev reaction failed to give any useful products. However, dehydration *via* selenide **16** gave **2**. After

Table 1. Conversion of (*S*)-Selenide **16** to (*S*)-Vinylpiperidine **2**

Reaction condition	Yield	ee
a) 30% H_2O_2/THF (0.3/5), 0 °C to r.t., 12 h	92%	54%
b) 30% H_2O_2/CH_2Cl_2 (1/1), 0 °C to r.t., 2 h	85%	92%
c) 2 eq. $NaIO_4$, THF/H_2O (1/1.2), 0 °C to r.t., 12 h	85%	93%
d) 2.3 eq. MCPBA, CH_2Cl_2/phosphate buffer at pH 8 (1/1), 0 °C, 30 min	81%	>99%

conversion of (*S*)-alcohol **3** to selenide **16** by employing 2-nitrophenyl selenocyanate and $(n\text{-Bu})_3P$[10] in 92% yield, the reaction conditions for oxidation and elimination were examined to give optically pure (*S*)-**2** (Table 1). When selenide **16** was treated with *m*-chloroperbenzoic acid in CH_2Cl_2 and a phosphate buffer (pH 8), optically pure (*S*)-vinylpiperidine **2** (>99% ee) was obtained. Employing H_2O_2 or $NaIO_4$ did not give optically pure (*S*)-**2**. There is the possibility for a radical or anion to be formed at the C-2 allylic position in the presence of some oxidants. It was assumed that this was the reason for racemization, so the buffer was employed to avoid the production of a radical or anion. The NMR spectrum agreed with that in the literature.[5] The optical purity was determined by a modification of the described method.[5] After removal of the Boc group and reaction with (−)-menthyl chloroformate, the resulting product was applied to a chiral column. (*R*)-Vinylpiperidine **2** and (*R*)-(hydroxyethyl)piperidine **3** were also obtained from (*S*)-**7**, which had been prepared from yeast-reductive product **5**, by the same synthetic process as that for (*S*)-**2** and (*S*)-**3**. The optical purity of (*R*)-**2** and (*R*)-**3** was also determined as >99% ee.

The syntheses of optically pure (*S*)-vinylpiperidine **2** and (*S*)-(hydroxyethyl)piperidine **3**, which are key intermediates for the synthesis of (−)-aloperine, were achieved from yeast-reductive products. Optically pure (*R*)-**2** and (*R*)-**3** were also obtained. The optical purity of these synthetic compounds was higher than that of compounds reported in the literature.[5–7] This is a new synthetic route to a piperidine derivative, which is an intermediate for the synthesis of aloperine[5,7] and other alkaloids,[6,9] from yeast-reductive products.

Experimental

Melting point (mp) data are uncorrected. NMR data were measured by a JNM-EX400 spectrometer, IR spectra were determined with a Shimadzu FTIR-8100 spectrophotometer and optical rotation values were evaluated with a Horiba SEPA-200 instrument. The silica gel used was Wakogel C-300 (Wako, 200–300 mesh). HPLC analyses were performed with Shimadzu LC-6AD and SPD-6AV instruments.

*(S)-3-Azido-1-(tert-butyldiphenylsilyloxy)-7-trityloxyheptane (**9**).* To a solution of (*R*)-trityl ether **7** (31.5 g, 50.1 mmol) and Et_3N (7.67 ml, 55.0 mmol) in CH_2Cl_2 (50 ml) was added MsCl (4.26 ml, 55.0 mmol) at 0 °C, and then the resulting reaction solution was stirred at room temperature for 12 h. After addition of H_2O, the organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration gave a crude mesylate. A reaction solution of the crude mesylate and NaN_3 (6.47 g, 99.5 mmol) in DMF (300 ml) was stirred at 100 °C for 1 h before additions of H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/9) gave (*S*)-azide **9** (32.4 g, 49.5 mmol, 99%) as a colorless oil, $[\alpha]^{20}_D = +1.8$ (*c* 1.4, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.05 (9H, s, *tert*-Bu), 1.38–1.56 (5H, m), 1.57–1.68 (2H, m), 1.73 (1H, m), 3.07 (2H, t, J = 6.6 Hz, 7-H_2), 3.53 (1H, m, 3-H), 3.72 (1H, ddd, J = 10.7, 10.7, 5.4 Hz, 1-*H*H), 3.80 (1H, ddd, J = 10.7, 8.3, 5.4 Hz, 1-H*H*), 7.20–7.30 (9H, m, ArH), 7.34–7.45 (12H, m, ArH), 7.64–7.67 (4H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ 19.2, 22.9, 26.8, 29.8, 34.5, 37.0, 59.7, 60.5, 63.2, 86.4, 126.8, 127.69, 127.71, 128.7, 129.7, 133.5, 133.7, 135.49, 135.53, 144.4. IR ν_{max} ($CHCl_3$): 3073, 2934, 2103, 1113, 1088, 909 cm^{-1}. *Anal*. Calcd. for $C_{42}H_{47}O_2N_3Si$: C, 77.14; H, 7.24; N, 6.43. Found: C, 77.37; H, 7.35; N, 6.36. (*R*)-**9**, $[\alpha]^{20}_D = -1.8$ (*c* 1.7, $CHCl_3$).

*(S)-5-Azido-7-(tert-butyldiphenylsilyloxy)-1-heptanol (**10**).* To a solution of (*S*)-trityl ether **9** (5.50 g, 8.41 mmol) in ether (55 ml) was added HCO_2H (55 ml) at 0 °C. The reaction solution was stirred at 0 °C for 1 h before additions of EtOAc and H_2O. The organic solution was separated, successively washed with a sat. aq. $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/9) gave (*S*)-alcohol **10** (3.15 g, 7.65 mmol, 91%) as a colorless oil, $[\alpha]^{20}_D = +3.3$ (*c* 4.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.06 (9H, s, *tert*-Bu), 1.40–1.62 (6H, m), 1.66 (1H, m), 1.76 (1H, m), 3.58 (1H, m, 5-H), 3.66 (2H, t, J = 6.3 Hz, 1-H_2), 3.74 (1H, ddd, J = 10.5, 10.5, 5.6 Hz, 7-*H*H), 3.80 (1H, ddd, J = 10.5, 8.1, 5.4 Hz, 7-H*H*), 7.37–7.43 (6H, m, ArH), 7.65–7.67 (4H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ 19.2, 22.4, 26.8, 32.4, 34.4, 37.0, 50.7, 60.5, 62.7, 127.7, 129.7, 133.5, 133.6, 135.50, 135.54. IR ν_{max} ($CHCl_3$): 3500, 2934, 2103, 1429, 1113, 1092, 909, 824. *Anal*. Calcd. for $C_{23}H_{33}O_2N_3Si$: C, 67.11; H, 8.08; N, 10.21. Found: C, 67.23; H, 8.16; N, 10.09. (*R*)-**10**, $[\alpha]^{20}_D = -3.3$ (*c* 3.4, $CHCl_3$).

*(S)-5-Azido-7-(tert-butyldiphenylsilyloxy)heptanal (**11**).* A reaction mixture of (*S*)-alcohol **10** (17.6 g, 42.8 mmol), PCC (10.1 g, 46.9 mmol), NaOAc (3.86 g,

47.1 mmol) and MS 4A (0.3 g) in CH_2Cl_2 (300 ml) was stirred at room temperature for 15 h before filtration. The resulting filtrate was concentrated, and the residue was applied to silica gel column chromatography (EtOAc/hexane = 1/9) to give (*S*)-aldehyde **11** (13.0 g, 31.7 mmol, 74%) as a colorless oil, $[\alpha]^{20}_D = +3.1$ (*c* 1.3, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.06 (9H, s, *tert*-Bu), 1.46–1.62 (2H, m), 1.62–1.85 (4H, m), 2.47 (2H, td, J = 7.1, 1.5 Hz, 2-H_2), 3.59 (1H, m, 5-H), 3.74 (1H, ddd, J = 10.7, 10.7, 5.4 Hz, 7-*H*H), 3.80 (1H, ddd, J = 10.7, 7.8, 4.9 Hz, 7-H*H*), 7.37–7.45 (6H, m, ArH), 7.64–7.67 (4H, m, ArH), 9.77 (1H, d, J = 1.5 Hz, CHO). ^{13}C-NMR ($CDCl_3$) δ 18.7, 19.2, 26.8, 33.9, 36.9, 43.4, 59.4, 60.3, 127.7, 129.7, 133.5, 133.6, 135.50, 135.54, 201.8. IRν_{max} ($CHCl_3$): 3073, 2932, 2103, 1725, 1113, 909, 824. *Anal*. Calcd. for $C_{23}H_{31}O_2N_3Si$: C, 67.44; H, 7.63; N, 10.26. Found: C, 67.47; H, 7.67; N, 10.09. (*R*)-**11**, $[\alpha]^{20}_D = -3.1$ (*c* 1.6, $CHCl_3$).

*(S)-5-Azido-7-(tert-butyldiphenylsilyloxy)heptanoic acid (**12**).* To an ice-cooled solution of (*S*)-aldehyde **11** (11.6 g, 28.3 mmol), 2-methyl-2-butene (13.2 ml, 125 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (4.42 g, 28.3 mmol) in *tert*-BuOH (70 ml) and H_2O (20 ml) was added $NaClO_2$ (8.70 g, 96.2 mmol), and then the resulting reaction solution was stirred in an ice-cooled bath for 1 h. After addition of $CHCl_3$, the mixture was acidified with a 1 M aq. HCl solution. The organic solution was separated, washed with H_2O and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/6) gave (*S*)-acid **12** (11.7 g, 27.5 mmol, 97%) as a colorless oil, $[\alpha]^{20}_D = +2.8$ (*c* 5.3, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.05 (9H, s, *tert*-Bu), 1.50–1.60 (2H, m), 1.60–1.85 (4H, m), 2.39 (2H, t, J = 7.3 Hz, 2-H_2), 3.60 (1H, m, 5-H), 3.74 (1H, ddd, J = 10.7, 10.7, 5.4 Hz, 7-*H*H), 3.80 (1H, ddd, J = 10.7, 7.8, 4.9 Hz, 7-H*H*), 7.37–7.45 (6H, m, ArH), 7.65–7.67 (4H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ 19.2, 21.2, 26.8, 33.6, 33.8, 36.9, 59.4, 60.3, 127.7, 129.7, 133.4, 133.6, 135.49, 135.53, 179.1. IRν_{max} ($CHCl_3$): 2932, 2105, 1713, 1113, 1092, 909. *Anal*. Calcd. for $C_{23}H_{31}O_3N_3Si$: C, 64.91; H, 7.34; N, 9.87. Found: C, 65.11; H, 7.39; N, 9.76. (*R*)-**12**, $[\alpha]^{20}_D = -2.8$ (*c* 1.8, $CHCl_3$).

*(S)-6-[2-(tert-Butyldiphenylsilyloxy)ethyl]-2-piperidinone (**13**).* A reaction mixture of (*S*)-azide **12** (5.30 g, 12.5 mmol) and 20% $Pd(OH)_2/C$ (0.20 g) in EtOH (40 ml) was stirred under H_2 gas at ambient temperature for 4 h before filtration. The filtrate was concentrated, and the resulting residue was dissolved in toluene (80 ml), this reaction solution then beeing heated under reflux for 1 h. After concentration, the residue was applied to silica gel column chromatography (EtOAc/hexane = 1/1) to give (*S*)-amide **13** (4.29 g, 11.2 mmol, 90%) as colorless crystals, mp 94–95 °C, $[\alpha]^{20}_D = +3.8$ (*c* 4.8, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.07 (9H, s, *tert*-Bu), 1.32–1.41 (1H, m), 1.60–1.75 (3H, m), 1.80–1.91 (2H, m), 2.27 (1H, ddd, J = 17.8, 10.9, 5.9 Hz, 3-*H*H), 2.39 (1H, m, 3-H*H*), 3.60 (1H, m, 6-H), 3.72–3.80 (2H, m, CH_2OTBDPS), 6.31 (1H, br. s, NH), 7.38–7.46 (6H, m, ArH), 7.65–7.66 (4H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ 19.1, 19.9, 26.8, 29.0, 31.2, 39.0, 52.0, 61.8, 127.78, 127.80, 129.8, 129.9, 133.1, 133.2, 135.5, 171.8. IRν_{max} ($CHCl_3$): 3376, 2934, 1649, 1472, 1113, 1092, 909. *Anal*. Calcd. for $C_{23}H_{31}O_2NSi$: C, 72.39; H, 8.19; N, 3.67. Found: C, 72.35; H, 8.14; N, 3.73. (*R*)-**13**, $[\alpha]^{20}_D = -3.8$ (*c* 1.3, $CHCl_3$).

*(S)-2-[2-(tert-Butyldiphenylsilyloxy)ethyl]piperidine (**14**).* To a solution of (*S*)-amide **13** (3.26 g, 8.54 mmol) in CH_2Cl_2 (50 ml) was added DIBAL-H (18.8 ml, 1 M in toluene, 18.8 mmol) at 0 °C. After the reaction solution was stirred at 0 °C for 1 h, a sat. aq. NH_4Cl solution was added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography ($CHCl_3$/MeOH/Et_3N = 19/1/1) gave (*S*)-piperidine **14** (1.50 g, 4.08 mmol, 48% yield, 51% of amide was recovered) as a colorless oil, $[\alpha]^{20}_D = -3.2$ (*c* 2.2, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.04–1.15 (1H, m), 1.05 (9H, s, *tert*-Bu), 1.25–1.46 (2H, m), 1.54–1.68 (4H, m), 1.75 (1H, m), 2.02 (1H, br. s, NH), 2.60 (1H, ddd, J = 11.7, 11.7, 2.5 Hz, 6-*H*H), 2.66 (1H, m, 6-H*H*), 3.00 (1H, m, 2-H), 3.74 (2H, t, J = 6.3 Hz, CH_2OTBDPS), 7.26–7.44 (6H, m, ArH), 7.65–7.67 (4H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ 19.2, 24.9, 26.3, 26.8, 33.0, 39.6, 47.1, 54.8, 61.8, 127.6, 129.6, 133.7, 133.8, 135.5. IRν_{max} ($CHCl_3$): 2934, 2859, 1732, 1429, 1111. *Anal*. Calcd. for $C_{23}H_{33}ONSi$: C, 75.15; H, 9.05; N, 3.81. Found: C, 74.85; H, 8.90; N, 3.77. (*R*)-**14**, $[\alpha]^{20}_D = +3.2$ (*c* 2.2, $CHCl_3$).

*Determination of the enantiomeric excess of (S)-**14** and (R)-**14**.* To an ice-cooled solution of (*S*)-piperidine **14** (20 mg, 54.4 µmol) in pyridine (0.5 ml) was added (−)-menthyl chloroformate (17.5 µl, 81.6 µmol). The reaction mixture was stirred at room temperature for 2 h, and then $CHCl_3$ and H_2O were added. The organic solution was separated, successively washed with a 1 M aq. HCl solution, sat. aq. $NaHCO_3$ solution, and brine, and then dried (Na_2SO_4). After concentration, the residue was applied to HPLC (Cica-Merk Lichrospher Si60, 2% EtOAc in hexane, 2.0 ml/min, detected at 270 nm, t_R = 20 min) to determine >99% de. Product from (*R*)-**14**, t_R = 16 min, >99% de.

*tert-Butyl (S)-2-[2-(tert-butyldiphenylsilyloxy)]ethyl]-piperidine-1-carboxylate (**15**).* A reaction mixture of (*S*)-piperidine **14** (1.10 g, 2.99 mmol) and $(Boc)_2O$ (0.72 g, 3.30 mmol) in THF (10 ml) and a 2 M aq. K_2CO_3 solution (10 ml) was stirred at 0 °C for 2 h before additions of EtOAc and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/9) gave (*S*)-Boc-piperidine **15** (1.36 g, 2.91 mmol, 97%) as a colorless oil,

$[\alpha]^{20}_D = -16$ (*c* 0.5, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.05 (9H, s, *tert*-Bu), 1.35 (9H, s, *tert*-Bu), 1.40–1.58 (6H, m), 1.69 (1H, m), 1.97 (1H, m), 2.63 (1H, ddd, $J = 14.7$, 14.7, 3.6 Hz, 6-*H*H), 3.60 (1H, ddd, $J = 10.3$, 8.3, 5.9 Hz, C*H*HOTBDPS), 3.70 (1H, ddd, $J = 10.3$, 8.3, 6.3 Hz, CH*H*OTBDPS), 3.90 (1H, m, 6-H*H*), 4.27 (1H, m, 2-H), 7.34–7.43 (6H, m, ArH), 7.65–7.67 (4H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ 19.05, 19.14, 25.6, 26.9, 28.4, 28.7, 32.8, 38.9, 47.4, 61.9, 79.0, 127.6, 129.52, 129.54, 133.9, 135.5, 154.9. IRν_{max} ($CHCl_3$): 2934, 1676, 1428, 1279, 1244, 1169, 1146, 1111, 1090. *Anal*. Calcd. for $C_{28}H_{41}O_3NSi$: C, 71.90; H, 8.84; N, 2.99. Found: C, 71.85; H, 8.85; N, 3.04. (*R*)-**15**, $[\alpha]^{20}_D = +16$ (*c* 1.4, $CHCl_3$).

*tert-Butyl (S)-2-(2-hydroxyethyl)piperidine-1-carboxylate (**3**).* To an ice-cooled solution of (*S*)-Boc-piperidine **15** (0.65 g, 1.39 mmol) in THF (20 ml) was added (n-Bu)$_4$NF (1.53 ml, 1 M in THF, 1.53 mmol). The reaction solution was stirred at 0 °C for 8 h before concentration. The residue was applied to silica gel column chromatography (EtOAc/hexane = 1/19) to give (*S*)-(hydroxyethyl)piperidine **3** (0.24 g, 1.05 mmol, 76%) as a colorless oil, $[\alpha]^{20}_D = -22$ (*c* 1.2, $CHCl_3$), lit.:[6] $[\alpha]^{20}_D = -18.9$ (*c* 1, $CHCl_3$). (*R*)-**3**, $[\alpha]^{20}_D = +22$ (*c* 1.0, $CHCl_3$), lit.:[6] $[\alpha]^{20}_D = +19.3$ (*c* 1, $CHCl_3$). The spectra data agreed with those in the literature.[6]

*tert-Butyl (S)-2-[2-(2-Nitrophenylselenyl)ethyl]piperidine-1-carboxylate (**16**).* A reaction solution of (*S*)-(hydroxyethyl)piperidine **3** (0.21 g, 0.92 mmol), 2-nitrophenyl selenocyanate (0.25 g, 1.11 mmol), and (n-Bu)$_3$P (0.28 g, 1.38 mmol) in THF (20 ml) was stirred at room temperature for 12 h. After concentration, the resulting residue was applied to silica gel column chromatography (1% EtOAc in hexane) to give (*S*)-selenide **16** (0.35 g, 0.85 mmol, 92%) as a colorless oil, $[\alpha]^{20}_D = -25$ (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.40–1.70 (6H, m), 1.47 (9H, s, *tert*-Bu), 1.78 (1H, m), 2.20 (1H, m), 2.76 (1H, m, 6-*H*H), 2.80–2.92 (2H, m, CH_2SePh), 4.02 (1H, m, 6-H*H*), 4.42 (1H, m, 2-H), 7.29–7.33 (1H, m, ArH), 7.50–7.51 (2H, m, ArH), 8.29 (1H, d, $J = 7.8$ Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ 19.1, 22.8, 25.5, 28.5, 28.7, 28.8, 50.8, 60.4, 68.0, 79.6, 125.3, 126.5, 128.8, 131.5, 133.6, 155.2. IRν_{max} ($CHCl_3$): 2947, 1670, 1517, 1417, 1333, 1150. *Anal*. Calcd. for $C_{18}H_{26}O_4N_2Se$: C, 52.30; H, 6.34; N, 6.78. Found: C, 52.60; H, 6.34; N, 6.76. (*R*)-**16**, $[\alpha]^{20}_D = +25$ (*c* 1.0, $CHCl_3$).

*tert-Butyl (S)-2-vinylpiperidine-1-carboxylate (**2**).* A reaction mixture of (*S*)-selenide **16** (0.29 g, 0.70 mmol) and MCPBA (0.28 g, 1.62 mmol) in CH_2Cl_2 (10 ml) and a phosphate buffer at pH 8 (10 ml) was stirred at 0 °C for 30 min. After addition of a sat. aq. $Na_2S_2O_3$ solution, the organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (ether/petroleum ether = 1/9) gave (*S*)-vinylpiperidine **2** (0.12 g, 0.57 mmol, 81%) as a colorless oil, $[\alpha]^{20}_D = -37$ (*c* 0.5, $CHCl_3$). (*R*)-**2**, $[\alpha]^{20}_D = +37$ (*c* 0.6, $CHCl_3$), lit.[5] $[\alpha]^{20}_D = +35.3$ (*c* 1.0, $CHCl_3$). The spectra data agreed with those in the literature.[5]

*Determination of the enantiomeric excess of (S)- and (R)-vinylpiperidine **2**.* After a reaction mixture of (*S*)-vinylpiperidine **2** (47 mg, 0.22 mmol) and CF_3CO_2H (17 µl, 0.23 mmol) in CH_2Cl_2 (5 ml) was stirred at room temperature for 6 h, sat. aq. $NaHCO_3$ and CH_2Cl_2 were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After concentration, the resulting residue was dissolved in pyridine. To this solution was added (−)-menthyl chloroformate (57 µl, 0.27 mmol) at 0 °C. The reaction solution was stirred at room temperature for 2 h before additions of $CHCl_3$ and a 1 M aq. HCl solution. The organic solution was separated, successively washed with a sat. aq. $NaHCO_3$ solution and brine, and dried (Na_2SO_4). After concentration, the residue was applied to HPLC (Chiralpak AD-H, 2% *iso*-PrOH in hexane, 0.5 ml/min, detected at 210 nm, $t_R = 18$ min) to determine >99% de. Product from (*R*)-**2**, $t_R = 14$ min, >99% de.

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