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, respectively8) (Scheme 1). These
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 NaN₃ 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 NaClO₂ oxidation in 72% yield through 2 steps. Conversion of azido-carboxylic acid 12 to amide 13 was achieved by treatment with H₂ and Pd(OH)₄/EtOH 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 K₂CO₃ in 97% yield, cleavage of the silyl ether by employing (n-Bu)₃NF was performed to give (S)-(hydroxyethyl)piperidine 3 in 76% yield. The NMR spectrum agreed with that in the literature.5) 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.

(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.3) 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.

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conversion of (S)-alcohol 3 to selenide 16 by employing 2-nitrophenyl selenocyanate and (n-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 CH2Cl2 and a phosphate buffer (pH 8), optically pure (S)-vinylpiperidine 2 (>99% ee) was obtained. Employing H2O2 or NaO4 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 of (S)-2, (R)-2, and (R)-3 were also obtained as >99% ee.

The syntheses of optically pure (S)-vinylpiperidine 2 and (R)-hydroxypiperidine 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 aloperine5,7) 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-butylidihydroxyisiloxyl)-7-trityloxyheptane (9). To a solution of (R)-trityl ether 7 (31.5 g, 8.41 mmol) in ether (55 ml) was added HCO2H (55 ml) at 0°C. The reaction solution was stirred at 0°C for 1 h before additions of EtOAc and H2O. The organic solution was separated, washed with brine, and dried (Na2SO4). 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, [α]D20 = +1.8 (c 1.4, CHCl3). 1H-NMR (CDCl3) δ 1.05 (9H, s, tert-Bu), 1.38–1.56 (5H, m, 1H, m), 1.73 (1H, m), 3.07 (2H, t, J = 6.6 Hz, 7-H2), 3.53 (1H, m, 3-H), 3.72 (1H, dd, J = 10.7, 10.5, 5.4 Hz, 1-HH), 3.80 (1H, dd, J = 10.7, 8.3, 5.4 Hz, 1-HH), 7.20–7.30 (9H, m, ArH), 7.34–7.45 (12H, m, ArH), 7.64–7.67 (4H, m, ArH). 13C-NMR (CDCl3) δ 19.2, 22.9, 26.8, 29.8, 34.5, 37.0, 59.7, 60.5, 63.2, 86.4, 126.8, 126.79, 126.71, 128.7, 129.7, 133.5, 133.7, 135.49, 135.53, 144.4. IR max (CHCl3): 3073, 2934, 2103, 1113, 1088, 909 cm−1. Anal. Calcd. for C23H32O2N3Si: C, 77.4; H, 7.34; N, 6.43. Found: C, 77.37; H, 7.35; N, 6.36. (R)-9, [α]D20 = −1.8 (c 1.7, CHCl3).

(S)-3-Azido-7-(tert-butylidihydroxyisiloxyl)-1-heptanone (10). To a solution of (S)-trityl ether 9 (5.50 g, 8.41 mmol) in ether (55 ml) was added HCO2H (55 ml) at 0°C. The reaction solution was stirred at 0°C for 1 h before additions of EtOAc and H2O. The organic solution was separated, successively washed with a sat. aq. NaHCO3 solution and brine, and dried (Na2SO4). 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, [α]D20 = +3.3 (c 4.0, CHCl3). 1H-NMR (CDCl3) 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-H2), 3.74 (1H, dd, J = 10.5, 10.5, 5.6 Hz, 7-HH), 3.80 (1H, dd, J = 10.5, 8.1, 5.4 Hz, 7-HH), 7.37–7.43 (6H, m, ArH), 7.65–7.67 (4H, m, ArH). 13C-NMR (CDCl3) 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, 135.4, 135.5. IR max (CHCl3): 3050, 2934, 2103, 1429, 1113, 1092, 909, 824. Anal. Calcd. for C23H32O2N3Si: C, 76.11; H, 8.08; N, 10.21. Found: C, 76.23; H, 8.16; N, 10.09. (R)-10, [α]D20 = −3.3 (c 3.4, CHCl3).

(S)-5-Azido-7-(tert-butylidihydroxyisiloxyl)-1-heptanone (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,
7.65–7.67 (4H, m, ArH).

(5)-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-buten (13.2 ml, 125 mmol) and NaH2PO4•2H2O (4.42 g, 28.3 mmol) in tert-ButOH (70 ml) and H2O (20 ml) was added NaClO2 (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 CHCl3, the mixture was acidified with a 1 M aq. HCl solution. The organic solution was separated, washed with H2O and brine, and dried (Na2SO4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/6) gave (S)-acid 12 (11.7 g, 25.5 mmol, 97%) as a colorless oil, [α]D20 = +2.8 (c 5.3, CHCl3). 1H-NMR (CDCl3) 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-H2), 3.60 (1H, m, 5-H), 3.74 (1H, ddd, J = 10.7, 10.7, 5.4 Hz, 7-HH), 3.80 (1H, ddd, J = 10.7, 7.8, 4.9 Hz, 7-HH), 7.37–7.45 (6H, m, ArH), 7.65–7.67 (4H, m, ArH). 13C-NMR (CDCl3) δ 19.2, 21.2, 26.8, 33.6, 33.8, 36.9, 59.4, 60.3, 127.3, 129.7, 133.4, 133.6, 135.49, 135.53, 179.1. IRmax (CHCl3): 2932, 2105, 1713, 1113, 1092, 909. Anal. Calcd. for C23H33O2Si2: C, 64.91; H, 7.34; N, 9.87. Found: C, 65.11; H, 7.39; N, 9.76. (R)-12, [α]D20 = −2.8 (c 1.8, CHCl3).

(5)-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 H2 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 being 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, [α]D20 = +3.8 (c 4.8, CHCl3). 1H-NMR (CDCl3) 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-HH), 2.39 (1H, m, 3-HH), 3.60 (1H, m, 6-H), 3.72–3.80 (2H, m, CH2OTBBDPS), 6.31 (1H, br. s, NH), 7.38–7.46 (6H, m, ArH), 7.65–7.66 (4H, m, ArH). 13C-NMR (CDCl3) 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, 131.3, 133.2, 135.5, 171.8. IRmax (CHCl3): 3376, 2934, 1649, 1472, 1113, 1092, 909. Anal. Calcd. for C23H33O2Si2: C, 72.39; H, 8.19; N, 3.67. Found: C, 72.35; H, 8.14; N, 3.73. (R)-13, [α]D20 = −3.8 (c 1.3, CHCl3).

(S)-2-[2-(tert-Butyldiphenylsilyloxy)ethyl]piperidine (14). To a solution of (S)-amide 13 (3.26 g, 8.54 mmol) in CH2Cl2 (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. NH4Cl solution was added. The organic solution was separated, washed with brine, and dried (Na2SO4). Concentration followed by silica gel column chromatography (CHCl3/MEOH/ Et3N = 19/1/1) gave (S)-piperidine 14 (1.50 g, 4.08 mmol, 48% yield, 51% of amide was recovered) as a colorless oil, [α]D20 = −3.2 (c 2.2, CHCl3). 1H-NMR (CDCl3) 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-HH), 2.66 (1H, m, 6-HH), 3.00 (1H, m, 2-H), 3.74 (2H, t, J = 6.3 Hz, CH2OTBBDPS), 7.26–7.44 (6H, m, ArH), 7.65–7.67 (4H, m, ArH). 13C-NMR (CDCl3) 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. IRmax (CHCl3): 2934, 2859, 1732, 1429, 1111. Anal. Calcd. for C25H35ONSi: C, 75.15; H, 9.05; N, 3.81. Found: C, 74.85; H, 8.90; N, 3.77. (R)-14, [α]D20 = +3.2 (c 2.2, CH2Cl2).

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 (−)-methyl chloroformate (17.5 µl, 81.6 µmol). The reaction mixture was stirred at room temperature for 2 h, and then CHCl3 and H2O were added. The organic solution was separated, successively washed with a 1 M aq. HCl solution, sat. aq. NaHCO3 solution, and brine, and then dried (Na2SO4). After concentration, the residue was applied to HPLC (Cica-Merk Lichrospher Si60, 2% EtOAc in hexane, 2.0 ml/min, detected at 270 nm, tR = 20 min) to determine >99% de. Product from (R)-14, tR = 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. K2CO3 solution (10 ml) was stirred at 0 °C for 2 h before additions of EtOAc and H2O. The organic solution was separated, washed with brine, and dried (Na2SO4). 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,
[α]D20 = −16 (c 0.5, CHCl3). 1H-NMR (CDCl3) 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’), 3.60 (1H, ddd, J = 10.3, 8.3, 5.9 Hz, CHOTBBDPS), 3.70 (1H, ddd, J = 10.3, 8.3, 6.3 Hz, CHJOTBBDPS), 3.90 (1H, m, 6-H’), 4.27 (1H, m, 2-H), 7.34–7.43 (6H, m, ArH), 7.65–7.67 (4H, m, ArH). 13C-NMR (CDCl3) δ 19.05, 19.14, 25.6, 26.9, 28.4, 28.7, 32.8, 38.9, 47.4, 79.0, 127.6, 129.7, 129.54, 133.8, 135.5, 154.9. IR max (CHC13): 2934, 1676, 1428, 1279, 1244, 1169, 1116, 1090. Anal. Calcd. for C37H43O5N3Si: C, 71.90; H, 8.84; N, 2.99. Found: C, 71.85; H, 8.85; N, 3.04. (R)-15, [α]D20 = +16 (c 1.4, CHCl3).

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)3NF (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, [α]D20 = −22 (c 1.2, CHCl3), lit.56 [α]D20 = −18.9 (c 1, CHCl3), (R)-3, [α]D20 = +22 (c 1.0, CHCl3), lit.57 [α]D20 = +19.3 (c 1, CHCl3). The spectra data agreed with those in the literature.56

tert-Butyl (S)-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)3P (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, [α]D20 = −25 (c 1.0, CHCl3). 1H-NMR (CDCl3) 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’), 2.80–2.92 (2H, m, CH2SePh), 4.02 (1H, m, 6-HH’), 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). 13C-NMR (CDCl3) 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. IR max (CHCl3): 2947, 1670, 1517, 1417, 1333, 1150. Anal. Calcd. for C18H16O2SeN2: C, 52.30; H, 6.34; N, 6.78. Found: C, 52.60; H, 6.34; N, 6.76. (R)-16, [α]D20 = +25 (c 1.0, CHCl3).

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 CH2Cl2 (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. Na2SO4 solution, the organic solution was separated, washed with brine, and dried (Na2SO4). 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, [α]D20 = −37 (c 0.5, CHCl3). (R)-2, [α]D20 = +37 (c 0.6, CHCl3), lit.53 (α)D20 = +35.3 (c 1.0, CHCl3). The spectra data agreed with those in the literature.53

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 CF3CO2H (17 μl, 0.23 mmol) in CH2Cl2 (5 ml) was stirred at room temperature for 6 h, sat. aq. NaHCO3 and CH2Cl2 were added. The organic solution was separated, washed with brine, and dried (Na2SO4). After concentration, the resulting residue was dissolved in pyridine. To this solution was added (−)-methyl chloroformate (57 μl, 0.27 mmol) at 0°C. The reaction solution was stirred at room temperature for 2 h before additions of CHCl3 and a 1 m aq. HCl solution. The organic solution was separated, successively washed with a sat. aq. NaHCO3 solution and brine, and dried (Na2SO4). After concentration, the residue was applied to HPLC (Chiralpak AD-H, 2% iso-PrOH in hexane, 0.5 ml/min, detected at 210 nm, tR = 18 min) to determine >99% de. Product from (R)-2, tR = 14 min, >99% de.

Acknowledgments

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References

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