Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 8031–8035

Stereoselective synthesis of protected (2*S*,3*S*)-*N*-methyl-5-hydroxyisoleucine, a component of halipeptins

Sousuke Hara, Kazuishi Makino and Yasumasa Hamada*

Graduate School of Pharmaceutical Sciences, Chiba University, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

Received 28 May 2004; revised 16 June 2004; accepted 24 June 2004

Available online 29 July 2004

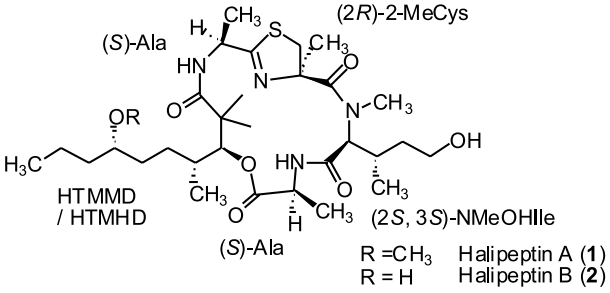
Abstract—The stereocontrolled synthesis of the protected (2*S*,3*S*)-*N*-methyl-5-hydroxyisoleucine, a component of halipeptins A and B with potent anti-inflammatory activity, has been achieved. The key steps include (i) installation of a double bond to bicyclic lactam **4** using *N*-*tert*-butyl phenylsulfinimidoyl chloride, (ii) highly *exo*-selective Michael reaction with lithium dimethylcuprate in the presence of chlorotrimethylsilane, and (iii) Ru-catalyzed oxidative deprotection of *N*,*O*-benzylidene acetal to the acid anhydride.

1. Introduction

Halipeptins A (**1**) and B (**2**)[1] are novel 17-membered cyclic depsipeptides isolated from the marine sponge *Haliclona* sp. collected in waters off the Vanuatu Islands by Gomez-Paloma and co-workers in 2001. In 2002, Gomez-Paloma et al. corrected the original assignments for halipeptins and reported the structural revision of an oxazetidine ring to the thiazoline unit in halipeptins A and B (Fig. 1).[2] Halipeptin A is known to show strong anti-inflammatory activity in vivo, causing 60% reduction of edema in mice at the dose of 300 μg/kg. In addition to their potent biological activities, their intriguing structures containing (2*S*,3*S*)-*N*-methyl-5-hydroxyisoleucine (*N*MeOHIle) and other unusual units prompted us and another group to initiate efforts directed towards the total synthesis. Very recently, Izzo and Riccardis reported the first synthesis of the *N*MeOHIle derivative in 10 steps and 1.1% overall yield, in which a diastereoselective silyl-assisted [3,3]-sigmatropic rearrangement was employed as a key step.[3] We required a practical synthesis of *N*MeOHIle for production of halipeptins and their analogues. Herein, we describe an enantioselective synthesis of protected (2*S*,3*S*)-*N*MeOHIle (**3**) based on the strategy of stereocontrolled transformation of chiral bicyclic lactam **4** and novel Ru-catalyzed oxidative deprotection of the benzylidene acetal originally developed by us.[4j]

2. Results and discussion

As the starting material for synthesis of (2*S*,3*S*)-*N*-methyl-5-hydroxyisoleucine, we chose bicyclic lactam **4** derived from



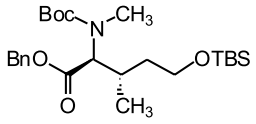
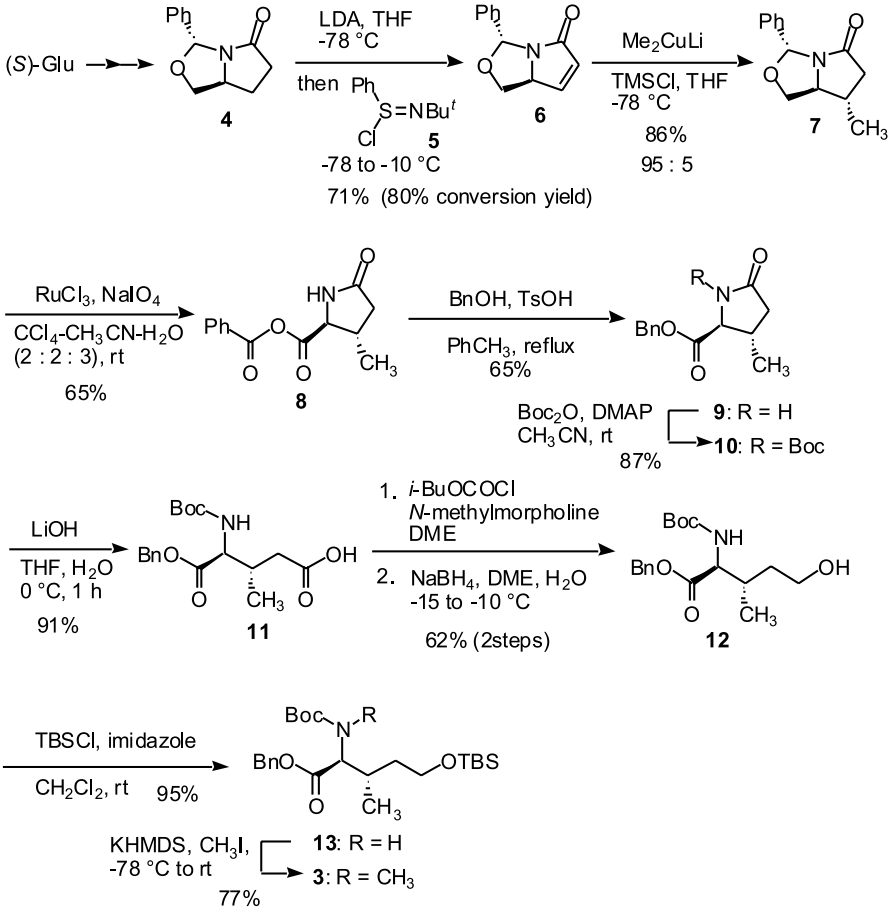


Figure 1. Structure of halipeptins.

Keywords: Halipeptin; Bicyclic lactam; *N*-*tert*-Butyl phenylsulfinimidoyl chloride; (2*S*,3*S*)-*N*-Methyl-5-hydroxyisoleucine.
* Corresponding author. Tel./fax: +81-4-3290-2987; e-mail: hamada@p.chiba-u.ac.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.111

(*S*)-glutamic acid (Scheme 1). Bicyclic lactam **4** is a versatile synthon in the synthesis of a variety of natural products[4] and was prepared from (*S*)-pyroglutamic acid according to Thottathil's procedure.[5] First, introduction of a double bond to the lactam was performed by two-step conversion, phenylselenylation-phenylselenoxide elimination, developed by us.[4a,b] This method, however, requires highly toxic and expensive phenylselenium bromide or chloride, and in addition its reproducibility is sometimes problematic in large-scale production. In search of a solution for this problem we investigated the possibility of direct conversion using other less toxic reagents for the synthesis of the bicyclic unsaturated lactam. However, dehydrogenation of the lactam to give the unsaturated lactam proved difficult. For example, use of Saegusa method[6] and IBX oxidation[7] developed by Nicolaou for preparation of α,β-unsaturated ketones gave no desired product and/or recovery of the starting material. After several experiments, *N*-*tert*-butyl phenylsulfinimidoyl chloride (**5**) originally developed for ketonic compounds by Mukaiyama and Matsuo[8] was found to be effective and reliable for large-scale production of highly strained α,β-unsaturated lactam **6**. Thus, **4** was deprotonated with lithium diisopropylamide in tetrahydrofuran (−78 °C, 30 min) and treated with **5** (−78 to −10 °C, 8 h) to afford, in addition to a small amount of the starting material (11%), **6** in 71% isolated yield (80% conversion yield, 4.5 g scale). As expected, purification of **6** using silica gel column chromatography was difficult due to contamination of **4** with similar polarity. Fortunately, the latent methyl derivative **7** was found to be easily purified. Stereoselective introduction of the methyl group at the 6 position of the bicyclic lactam was carried out by using Hanessian's procedure.[9] Treatment of **6** with lithium dimethylcuprate (Me_2CuLi) in the presence of chlorotrimethylsilane[10] at −78 °C afforded methylated product **7** in 86% yield in a diastereomeric ratio of 95:5. The stereochemistry of the newly formed stereocenter was unambiguously assigned by NOE experiment using ^1H NMR.[4i] For removal of *N*,*O*-benzylidene acetal, we employed direct conversion to the acid anhydride using oxidative cleavage developed by us.[4j] Thus, acetal **7** was oxidized with a catalytic amount of ruthenium chloride (5 mol%) in the presence of sodium periodate in acetonitrile–carbon tetrachloride–water (2:2:3)[11] to give acid anhydride **8** in 65% yield, which was transformed to benzyl ester **9** by treatment with benzyl alcohol in the presence of *p*-toluenesulfonic acid in toluene under refluxing conditions. For selective cleavage of the lactam ring under coexistence of the benzyl ester, the nitrogen of the lactam was protected with di-*tert*-butyl dicarbonate (Boc_2O) in the presence of *N*,*N*-dimethylaminopyridine (DMAP) to produce *tert*-butoxycarbonyl imide **10** in 87% yield. Functional group selective hydrolysis of the γ-lactam ring in **10** was carried out by using lithium hydroxide in aqueous THF to afford carboxylic acid **11** in excellent yield. Then **11** was converted to the mixed acid anhydride by treatment with isobutyl chloroformate in the presence of *N*-methylmorpholine and reduced to (2*S*,3*S*)-5-



Scheme 1. Stereoselective synthesis of (2*S*,3*S*)-*N*-methyl-5-hydroxyisoleucine (*N*MeOHlle).

hydroxyisoleucine **12** with sodium borohydride in 62% yield. After protection of the hydroxy group as a *tert*-butyldimethylsilyl ether, *N*-methylation of **13** using iodomethane and potassium hexamethyldisilazide (KHMDS) in THF furnished protected (2*S*,3*S*)-*N*MeOHIle **3** in 77% yield.

3. Conclusion

In conclusion, we have achieved the stereoselective synthesis of protected (2*S*,3*S*)-*N*-methyl-5-hydroxyisoleucine **3** in 9.9% overall yield by stereoselective transformation of chiral bicyclic lactam **4** based on (i) installation of a double bond using *N*-*tert*-butyl phenylsulfinimidoyl chloride, (ii) highly *exo*-selective Michael reaction in the presence of chlorotrimethylsilane, and (iii) Ru-catalyzed oxidative deprotection of *N*,*O*-benzylidene acetal **7** to acid anhydride **8** as the key steps. Further investigation toward the total synthesis of halipeptins is actively under way.

4. Experimental

4.1. General

Melting points were measured with a SHIBATA NEL-270 melting point apparatus. IR spectra were recorded on a JASCO FT/IR-230 spectrometer. NMR spectra were recorded on JEOL JNM GSX400A and JNM ECP400 spectrometers. FAB mass spectra were obtained with a JEOL JMS-HX-110A spectrometer. Optical resolutions were determined on a JASCO DIP-140 and JASCO P-1020 polarimeter. Column chromatography was carried out with silica gel BW-820MH (Fuji silysia). Analytical thin layer chromatography was performed on Merck Kieselgel 60F254 0.25 mm thickness plates.

4.1.1. (2*R*,5*S*)-2-Phenyl-1-aza-3-oxabicyclo[3.3.0]oct-6-en-8-one (6). To a solution of diisopropylamine (3.4 mL, 24.3 mmol) in THF (82 mL) at 0 °C was added dropwise a solution of *n*-butyllithium in hexane (1.6 mol/L, 15.5 mL, 24.8 mmol) under argon atmosphere. After stirring at the same temperature for 30 min, the solution was cooled to −78 °C and a solution of **4** (4.49 g, 22.1 mmol) in THF (14 mL) was added dropwise via canula. After 30 min, a solution of *N*-*tert*-butyl benzenesulfinimidoyl chloride (9.63 g, 44.6 mmol) in THF (14 mL) was added in one portion. The reaction mixture was gradually warmed to −10 °C. After 8.5 h, the reaction was quenched by addition of saturated aqueous NH_4Cl (100 mL) and diluted with ethyl acetate (100 mL). The aqueous layer was extracted with ethyl acetate (1×100 mL). The organic extract was washed with saturated brine (100 mL), dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (200 g, *n*-hexane/ethyl acetate=1/1 to ethyl acetate only) to give **6** (3.33 g, 71%, conversion yield 80%) as a brown oil along with a small amount of the starting material **4** (0.506 g, 11.3%). The spectra of **6** were identical with those of the reference.[4b]

4.1.2. (2*R*,5*S*,6*S*)-6-Methyl-2-phenyl-1-aza-3-oxabicyclo[3.3.0]octan-8-one (7). To a suspension of CuI (11.4 g, 59 mmol) in THF (344 mL) at −78 °C under argon atmosphere was added a solution of MeLi in ether (0.8 M, 105 mL, 84 mmol) and the mixture was stirred at 0 °C for 30 min. The resulting colorless solution was cooled to −78 °C and a solution of Me_3SiCl (7.57 mL, 59 mmol) and enone **6** (4.0 g, 19 mmol) in THF (30 mL) was added. After stirring for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (250 mL). The aqueous phase was extracted with ether (3×120 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (3×100 mL), water (100 mL), and saturated brine (150 mL), dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (120 g, *n*-hexane/ethyl acetate=2/1) to give **7** (3.78 g, 86%) as a colorless oil: $[\alpha]_D^{22}=+228$ (*c* 0.64, $CHCl_3$) (lit.[9] (6*R*)-enantiomer: $[\alpha]_D=-2.3$ (*c* 1.47, $CHCl_3$)); IR (neat) 2962, 1710, 1453, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (3H, d, $J=6.8$ Hz), 2.33–2.39 (1H, m), 2.46–2.69 (2H, m), 3.60 (1H, dd, $J=7.0$, 8.0 Hz), 3.62–6.77 (1H, m), 4.20 (1H, dd, $J=6.3$, 8.3 Hz), 6.35 (1H, s), 7.30–7.44 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.16, 34.77, 42.31, 66.04, 70.77, 87.08, 125.95, 128.38, 128.49, 138.5, 177.5. HRMS (FAB, NBA) calcd for $C_{13}H_{16}NO_2$: 218.1181 ($M+H^+$). Found: 218.1185.

4.1.3. (2*S*,3*S*)-3-Methyl-5-oxo-pyrrolidine-2-carboxylic benzoic anhydride (8). To a solution of bicyclic lactam **7** (0.351 g, 1.62 mmol) and $NaIO_4$ (2.08 g, 9.72 mmol) in carbon tetrachloride (2 mL), and H_2O (3 mL) was added a solution of added $RuCl_3\cdot nH_2O$ (91% purity, 18.5 mg, 81.2 μmol) in acetonitrile (2 mL). After stirring at room temperature for 24 h, the reaction mixture was filtered through a pad of celite, and the filtrate was extracted with ethyl acetate, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by recrystallization (ethyl acetate/*n*-hexane) to give **8** (0.260 g, 1.05 mmol, 65%) as colorless solids: mp 172–174 °C; $[\alpha]_D^{23}=-18.9$ (*c* 1.06, $CHCl_3$); IR (KBr) 3854, 3821, 3745, 3676, 2966, 1741, 1680, 1291, 1247, 1212, 708, 633 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (3H, d, $J=7.1$ Hz), 2.29 (1H, dd, $J=5.4$, 17.8 Hz), 2.62–2.66 (1H, m), 2.92 (1H, dd, $J=8.5$, 17.8 Hz), 4.53 (1H, d, $J=4.9$ Hz), 7.41–7.45 (2H, m), 7.53–7.57 (1H, m), 7.66–7.68 (2H, m); ^{13}C NMR ($CDCl_3$) δ 20.0, 30.2, 39.9, 65.3, 127.9, 129.2, 132.5, 133.5, 170.7, 172.7, 175.2. Anal. calcd for $C_{13}H_{13}NO_4$: C, 63.15, H, 5.30, N, 5.67. Found: C, 63.29, H, 5.39, N, 5.69.

4.1.4. (2*S*,3*S*)-3-Methyl-5-oxo-pyrrolidine-2-carboxylic acid benzyl ester (9). To a solution of **8** (0.197 g, 0.797 mmol) and benzyl alcohol (0.83 mL, 8.02 mmol) in toluene (4 mL) was added $TsOH\cdot H_2O$ (18.6 mg, 0.098 mmol). The reaction mixture was heated to reflux for 14.5 h. After cooling, the reaction was quenched by addition of saturated aqueous sodium hydrogen carbonate and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=1/1 to $CHCl_3/CH_3OH$=4/1) to afford **9** (0.121 g, 65%) as a brown oil. The analytical sample was obtained by recrystallization (*n*-hexane/ether) as colorless needles: mp 79 °C; $[\alpha]_D^{19}=+21.1$ (*c* 0.66, $CHCl_3$); IR (KBr) 3218, 1701, 1669, 1457, 1264, 1090, 1005, 752, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (3H, d, $J=$

6.6 Hz), 1.98–2.08 (1H, m), 2.53–2.65 (2H, m), 3.86 (1H, d, J=5.4 Hz), 5.18 (1H, d, J=12.2 Hz), 5.22 (1H, d, J=12.2 Hz), 5.94 (1H, s), 7.33–7.41 (5H, m); ^{13}C NMR ($CDCl_3$) δ 20.1, 34.1, 37.8, 62.4, 67.3, 128.3, 128.6, 128.7, 135.1, 171.4, 176.7. Anal. calcd for $C_{13}H_{15}NO_3$: C, 66.94, H, 6.48, N, 6.00. Found: C, 66.97, H, 6.51, N, 5.96.

4.1.5. (2*S*,3*S*)-3-Methyl-5-oxo-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-*tert*-butyl ester (10). A solution of **9** (0.200 g, 0.857 mmol), Boc_2O (0.565 g, 2.59 mmol), and DMAP (21.8 mg, 0.178 mmol) in CH_3CN (4.3 mL) was stirred at room temperature. After 9.5 h, the reaction mixture was diluted with ethyl acetate, washed with saturated brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=1/1) to give **10** (0.249 g, 87%) as a colorless oil: $[\alpha]_D^{22}=-14.7$ (c 1.03, $CHCl_3$); IR (neat) 2977, 1793, 1752, 1715, 1499, 1456, 1369, 1314, 1154, 1087, 1021, 911, 839, 750, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, d, J=6.8 Hz), 1.42 (9H, s), 2.14 (1H, dd, J=4.2 Hz, 17.3 Hz), 2.31–2.40 (1H, m), 2.77 (1H, dd, J=8.5, 17.3 Hz), 4.22 (1H, d, J=3.4 Hz), 5.19 (1H, d, J=12.2 Hz), 7.33–7.40 (5H, m); ^{13}C NMR ($CDCl_3$) δ 20.5, 27.8, 29.7, 39.4, 66.0, 67.3, 83.7, 128.5, 128.6, 128.7, 135.0, 149.3, 170.7, 172.7. HRMS (FAB, NBA) calcd for $C_{18}H_{24}NO_5$: 334.1654 ($M+H^+$). Found: 334.1628.

4.1.6. (2*S*,3*S*)-2-*tert*-Butoxycarbonylamino-3-methyl-1,5-pentanedioic acid 1-benzyl ester (11). To a solution of **10** (0.249 g, 0.747 mmol) in THF (3.2 mL) and water (0.8 mL) at 0 °C was added $LiOH\cdot H_2O$ (36.3 mg, 0.865 mmol) and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was neutralized by addition of acetic acid and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3/CH_3OH$=9/1) to give **11** (0.238 g, 91%) as a yellow oil: IR (neat) 3330, 2976, 1718, 1560, 1508, 1457, 1369, 1160, 1069, 1017, 753, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.982 (3 H, d, J=6.4 Hz), 1.43 (9H, s), 2.21–2.22 (1H, m), 2.42–2.46 (2H, m), 4.34 (1H, brs), 5.09–5.22 (3H, m), 7.30–7.39 (5H, m); ^{13}C NMR ($CDCl_3$) δ 16.5, 28.2, 33.5, 57.6, 67.2, 77.2, 80.2, 128.4, 128.5, 128.6, 135.1, 155.5, 171.6; $[\alpha]_D^{22}=+5.49$ (c 1.52, $CHCl_3$). HRMS (EI) calcd for $C_{18}H_{25}NO_6$: 351.1682. Found: 351.1693.

4.1.7. (2*S*,3*S*)-2-*tert*-Butoxycarbonylamino-5-hydroxy-3-methylpentanoic acid benzyl ester (12). To a solution of **11** (0.126 g, 0.359 mmol) in 1,2-dimethoxyethane (DME, 0.5 mL) at −15 °C were successively added a solution of *N*-methyl morpholine (40.9 mg, 0.404 mmol) in DME (0.5 mL) and isobutyl chloroformate (53.9 mg, 0.395 mmol) in DME (0.5 mL), and the reaction mixture was stirred at −15 to −10 °C for 15 min. The precipitated *N*-methyl morpholine hydrochloride was removed by filtration and washed with DME, and the combined filtrates were chilled to −15 °C in an ice–salt bath. Then, a solution of $NaBH_4$ (41.0 mg, 1.08 mmol) in water (0.5 mL) was added in one portion at −15 °C. After stirring at −15 to −10 °C for 10 min, the reaction was quenched by addition of saturated aqueous NH_4Cl, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=1/1) to give **12** (75.5 mg, 62%) as a colorless oil: $[\alpha]_D^{22}=+5.49$ (c 1.52, $CHCl_3$); IR (neat) 3382, 2974, 1710, 1560, 1499, 1457, 1366, 1250, 1163, 1057, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.916 (3H, d, J=6.8 Hz), 1.43 (9H, s), 1.55–1.63 (1H, m), 2.16–2.17 (2H, m), 3.59 (1H, m), 3.70 (1H, m), 4.34–4.37 (1H, m), 5.13 (1H, d, J=12.2 Hz), 5.22 (1H, d, J=12.2 Hz), 5.36 (1H, d, J=7.8 Hz), 7.31–7.37 (5H, m); ^{13}C NMR ($CDCl_3$) δ 16.0, 28.3, 33.2, 35.0, 57.3, 60.0, 67.0, 77.2, 79.9, 128.4, 128.5, 128.6, 135.3, 155.7, 171.9. HRMS (EI) calcd for $C_{18}H_{28}NO_5$: 338.1967 (MH^+). Found: 338.1935.

4.1.8. (2*S*,3*S*)-2-*tert*-Butoxycarbonylamino-5-(*tert*-butyldimethylsiloxy)-3-methylpentanoic acid benzyl ester (13). To a solution of TBSCl (0.230 g, 1.53 mmol) and imidazole (0.180 g, 2.64 mmol) in CH_2Cl_2 (1 mL) was added a solution of **12** (0.171 g, 0.507 mmol) in CH_2Cl_2 (1.5 mL) via cannula and the reaction mixture was stirred at room temperature for 10.5 h. The reaction was diluted with ethyl acetate, washed with saturated brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=5/1) to give **13** (0.218 g, 95%) as a colorless oil: $[\alpha]_D^{24}=+1.72$ (c 0.99, $CHCl_3$); IR (neat) 3356, 2929, 1718, 1560, 1499, 1365, 1255, 1163, 1099, 836, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.030 (6H, s), 0.876 (9H, s), 0.940 (3H, d, J=7.0 Hz), 1.28–1.36 (1H, m), 1.43 (9H, s), 1.53–1.60 (2H, m), 2.17 (1H, m), 3.54–3.60 (1H, m), 3.62–3.67 (1H, m), 4.25–4.28 (1H, m), 5.13 (1H, d, J=12.5 Hz), 5.18 (1H, d, J=12.5 Hz), 5.32 (1H, d, J=8.8 Hz), 7.32–7.36 (5H, m); ^{13}C NMR ($CDCl_3$) δ −5.43, −5.40, 16.3, 18.3, 25.9, 28.3, 32.9, 35.0, 58.3, 60.5, 66.8, 79.6, 128.3, 128.5, 135.5, 155.7, 172.2. HRMS (FAB, NBA) calcd for $C_{24}H_{42}NO_5Si$: 452.2832 ($M+H^+$). Found: 452.2838.

4.1.9. (2*S*,3*S*)-2-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)-5-(*tert*-butyldimethylsiloxy)-3-methyl pentanoic acid benzyl ester (3). To a solution of **13** (52.9 mg, 0.117 mmol) in THF (1 mL) under Ar atmosphere was added 0.5 M solution of KHMDS in toluene (0.26 mL, 0.130 mmol) at −78 °C and the mixture was stirred at the same temperature for 30 min. Then iodomethane (0.070 mL, 1.12 mmol) was added and the reaction temperature was gradually warmed to room temperature. After 18.5 h, the reaction was quenched by addition of saturated aqueous NH_4Cl, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=5/1) to give **3** (42.0 mg, 77%) as a colorless oil: $[\alpha]_D^{19}=-42.2$ (c 0.52, $CHCl_3$); IR (neat) 2930, 1740, 1700, 1473, 1366, 1313, 1256, 1172, 1096, 1004, 836, 775, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C) δ 0.031 (6H, s), 0.880 (9H, s), 0.928 (3H, d, J=6.6 Hz), 1.20–1.26 (1H, m), 1.43 (9H, s), 1.65–1.67 (1H, m), 2.21 (1H, m), 2.80–2.84 (3H, m), 3.59–3.72 (3H, m), 5.12 (1H, d, J=12.7 Hz), 5.17 (1H, d, J=12.4 Hz), 7.28–7.33 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$, 45 °C, a mixture of conformational isomers) δ −5.40, −5.34, 16.3, 16.5, 18.3, 25.5, 25.7, 25.9, 28.4, 29.1, 30.3, 33.1, 35.2, 35.6, 51.5, 60.5, 60.7, 61.0, 62.4, 64.1, 66.2, 66.8, 80.1, 128.0, 128.1, 128.3, 128.5, 135.9, 155.7, 171.2.

HRMS (FAB, NBA) calcd for $C_{25}H_{44}NO_5Si$: 466.2989 ($M+H^+$). Found: 466.2945. Anal. calcd for $C_{25}H_{43}NO_5Si$: C, 64.48, H, 9.31, N, 3.01. Found: C, 64.21, H, 9.31, N, 3.04.

References and notes

1. Randazzo, A.; Bifulco, G.; Giannini, C.; Bucci, M.; Debitus, C.; Cirino, G.; Gomez-Paloma, L. *J. Am. Chem. Soc.* **2001**, *123*, 10870–10876.
2. Monica, C. D.; Randazzo, A.; Bifulco, G.; Cimino, P.; Aquino, M.; Izzo, I.; Riccardis, F. D.; Gomez-Paloma, L. *Tetrahedron Lett.* **2002**, *43*, 5707–5710.
3. Izzo, I.; Avallone, E.; Corte, L. D.; Maulucci, N.; Riccardis, F. D. *Tetrahedron: Asymmetry* **2004**, *15*, 1181–1186.
4. (a) Hamada, Y.; Kawai, A.; Kohno, Y.; Hara, O.; Shioiri, T. *J. Am. Chem. Soc.* **1989**, *111*, 1524–1525. (b) Hamada, Y.; Hara, O.; Kawai, A.; Kohno, Y.; Shioiri, T. *Tetrahedron* **1991**, *47*, 8635–8652. (c) Uno, H.; Baldwin, J. E.; Russel, A. T. *J. Am. Chem. Soc.* **1994**, *116*, 2139–2140. (d) Herdeis, C.; Hubmann, H. P.; Lotter, H. *Tetrahedron: Asymmetry* **1994**, *5*, 119–128. (e) Griffart-Brunet, D.; Langlois, N. *Tetrahedron Lett.* **1994**, *35*, 119–122. (f) Ogawa, A. K.; DeMattei, J. A.; Scarlato, G. R.; Tellew, J. E.; Chong, L. S.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6153–6161. (g) Zhang, R.; Brownewell, F.; Madalengoitia, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 3894–3902. (h) Hara, O.; Takizawa, J.; Yamatake, T.; Makino, K.; Hamada, Y. *Tetrahedron Lett.* **1999**, *40*, 7787–7790. (i) Okamoto, N.; Hara, O.; Makino, K.; Hamada, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1353–1358. (j) Makino, K.; Shintani, K.; Yamatake, T.; Hara, O.; Hatano, K.; Hamada, Y. *Tetrahedron* **2002**, *58*, 9737–9740.
5. (a) Thottathil, J. K.; Przybyla, C.; Malley, M.; Gougoutas, J. Z. *Tetrahedron Lett.* **1986**, *27*, 1533–1536. (b) Thottathil, J. K.; Moniot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissick, T. P. *J. Org. Chem.* **1986**, *51*, 3140–3143.
6. Ito, Y.; Hirai, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013.
7. Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596–7597.
8. Matsuo, J.; Iida, D.; Tatani, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn* **2002**, *75*, 223–234.
9. Hanessian, S.; Ratovelomanana, V. *Synlett* **1990**, 501–503.
10. Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047–1050.
11. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.