Efficient Diastereoselective Synthesis of (2*R*,3*R*,4*R*)-2-Amino-3-hydroxy-4,5-dimethylhexanoic Acid, the Lactone Linkage Unit of Homophymine A

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Received October 26, 2012; accepted November 14, 2012

For the total synthesis of novel cyclodepsipeptide homophymine A, (2*R*,3*R*,4*R*)-2-amino-3-hydroxy-4,5-dimethylhexanoic acid was successfully synthesized by Evans' asymmetric alkylation and the *anti*-selective asymmetric hydrogenation of a chiral *α*-amino-*β*-keto ester as the key steps.

Key words homophymine A; *β*-hydroxy-*α*-amino acid; *anti*-selective asymmetric hydrogenation; Evans' asymmetric alkylation

Homophymines (A–E and A1–E1), isolated from the New Caledonian sponge *Homophymia* species, are a new family of novel dimethylglutamine-containing cyclodepsipeptides with interesting biological activities[1–3] (Fig. 1). Homophymine A (**1**) is known to exhibit cytoprotective activity against human immunodeficiency virus-1 (HIV-1) infection and moderate cytotoxicity. As part of the study on synthesizing bioactive cyclodepsipeptides of marine origin,[4–8] we focused on homophymine A, which contains (2*R*,3*R*,4*R*,6*R*)-3-hydroxy-2,4,6-trimethyloctanoic acid[9] and novel amino acid residues: (2*S*,3*S*,4*R*)-3,4-dimethylglutamine,[10,11] (2*R*,3*R*,4*S*)-4-amino-2,3-dihydroxy-1,7-heptandioic acid, and (2*R*,3*R*,4*R*)-2-amino-3-hydroxy-4,5-dimethylhexanoic acid (**2**). In earlier studies, we demonstrated that the asymmetric hydrogenation of *α*-amino-*β*-keto esters using chiral catalysts *anti*-selectively proceeds to afford *anti β*-hydroxy-*α*-amino acids in a high diastereo- and enantioselective manner.[12–20] Following is an example of an efficient diastereoselective hydrogenation of a chiral substrate under the conditions of our developed *anti*-selective asymmetric hydrogenation, which provides an efficient synthesis of (2*R*,3*R*,4*R*)-2-amino-3-hydroxy-4,5-dimethylhexanoic acid (AHDMHA, **2**). Our synthesis is outlined by a retrosynthetic analysis in Chart 1.

Our synthesis commenced with the straightforward synthesis of (*R*)-2,3-dimethylbutanoic acid (**4**) (Chart 2). According to Evans' procedure, the oxazolidinones (**6a**, **6b**) were treated with *n*-butyl lithium at −78°C and the resulting lithium salts were acylated with isovaleryl chloride to give imides **7a** and **7b** in 98% and 75% yield, respectively. The imides **7a** and **7b** were treated with lithium diisopropylamide in tetrahydrofuran (THF) at −78°C followed by methylation of the resulting enolates with iodomethane to afford the methylated products **8a** and **8b** in 80% and 45% yield, respectively. In this asymmetric methylation, **7b** was inferior to **7a** in the diastereoselectivity. Although crude **8a** was a 93 : 7 mixture of diastereomers, the recrystallization of the crude material from *n*-hexane provided pure **8a** in diastereomeric purity and in 80% yield. The cleavage of the chiral auxiliary was accomplished by the treatment with alkaline hydrogen peroxide in aqueous THF.

In the next *β*-keto ester formation, it was found that the acid chloride derived from **4** was volatile. To prevent the loss of valuable **4**, we first attempted the modified procedure through the corresponding imidazolide of **4** (Table 1). The reaction of methyl *tert*-butoxycarbonylaminomalonate half ester (**11**)[21] with the imidazolide failed to give *α*-*tert*-butoxycarbonylamino-*β*-keto ester **10** (entry 1). To increase the acylating ability, *N*,*N*-dimethylaminopyridine (DMAP) or 4-(1-pyrrolidinyl)pyridine (PPY) was added, but it proved to be ineffective (entries 2, 3, respectively). Therefore, we examined the stepwise procedure using potassium methyl malonate (**12**).[22] Although the imidazolide with the magnesium methyl malonate generated from the potassium salt **12**, magnesium chloride, and triethylamine in THF hardly reacted (entry 4), an addition of 10 mol% DMAP in the above reaction mixture dramatically improved the chemical yield to afford the corresponding *β*-keto ester **9** in 95% yield (entry 5).

The *β*-keto ester **9** was converted to the oxime **13** by reaction with sodium nitrite in aqueous acetic acid, and the reduction of **13** with palladium on carbon and hydrogen afforded the key intermediate **3** in two steps and in 80% yield (Chart 3).

With the key intermediate, we examined the diastereoselective hydrogenation of **3** under the conditions of our developed *anti*-selective asymmetric hydrogenation, which proceeds through dynamic kinetic resolution (DKR) (Table 2). Catalytic asymmetric hydrogenation through DKR is one of the most efficient methods for the preparation of optically active compounds.[23–26] The hydrogenation of **3** using the 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)-Ru catalyst under the standard conditions produced, after *N*-*tert*-butoxycarbonyl protection, the desired *anti β*-hydroxy-*α*-amino acid ester **15** with a 90 : 10 diastereoselectivity

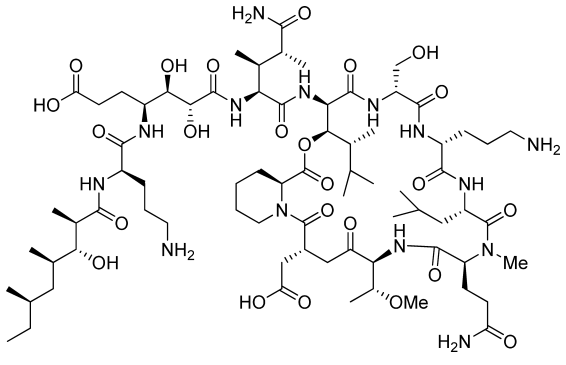

Fig. 1. Structure of Homophymine A (**1**)

The authors declare no conflict of interest.

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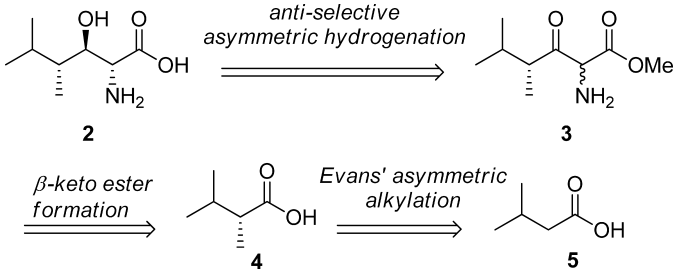


Chart 1. Retrosynthetic Analysis of (2*R*,3*R*,4*R*)-2-Amino-3-hydroxy-4,5-dimethylhexanoic Acid (**2**)

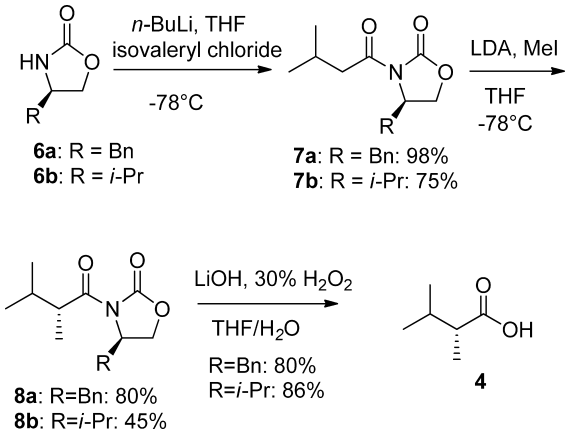


Chart 2. Synthesis of (*R*)-2,3-Dimethylbutanoic Acid (**4**)

(judged by ^{1}H-NMR analysis) in 70% conversion yield (entry 1). Because of the bulkiness of the substituent adjacent to the carbonyl functionality, the reaction was incomplete even after 72 h at 50°C. Although the recrystallization of the crude product furnished the diastereomerically pure **15** in 51% yield, the chemical yield was unsatisfactory. However, using an increased amount of the catalyst provided a better diastereoselectivity and improved the yield of pure **15** (entry 2). We also disclosed that Iridium-MeO-2,2′-dimethoxy-5,5′-bis(diphenylphosphinio)biphenyl (BIPHEP) is an efficient catalyst for the *anti*-selective asymmetric hydrogenation of alkyl substrate with a bulky group at the 4 position.[15–17] Therefore, we attempted the hydrogenation of **3** using the Ir catalyst, but no reaction was observed. Nevertheless, it is noteworthy that, although the starting **3** is a mixture of diastereomers, the highly stereoselective hydrogenation proceeds in a reagent-controlled manner to afford the *anti* product in a satisfactory yield and diastereoselectivity.

For the confirmation of stereochemistry, **15** was converted to the acetonide **16** using 2,2-dimethoxypropane and boron trifluoride etherate (Chart 4). The acid hydrolysis of **16** in refluxing 6 M hydrochloric acid furnished (2*R*,3*R*,4*R*)-2-amino-3-hydroxy-4,5-dimethylhexanoic acid (**2**) in 94% yield. Its NMR spectrum was identical with that of the natural **2** derived from homophymine A.

In addition, the *anti*-stereochemistry of **15** was unambiguously determined by the nuclear Overhauser effect (NOE) experiment of **16** and comparisons of their *J*-values with the congener **18** derived from known (2*R*,3*R*)-3-hydroxyleucine (**17**) as shown in Fig. 2.

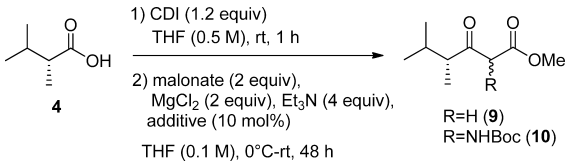
In conclusion, we succeeded in the first synthesis of (2*R*,3*R*,4*R*)-2-amino-3-hydroxy-4,5-dimethylhexanoic acid employing the diastereoselective hydrogenation of a chiral substrate under the conditions of our developed *anti*-selective asymmetric hydrogenation as a key step. This key step proceeds with reagent-control to afford the *anti*-hydroxyamino acid in excellent diastereoselectivity and yield.

Experimental

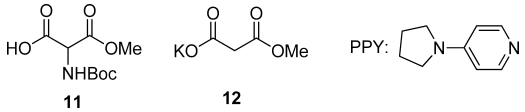
Melting points were measured with a SIBATA NEL-270 melting point apparatus. Optical rotations were measured on a JASCO DIP-14-polarimeter and JASCO P-1020 polarimeter with a sodium lamp (589 nm). Infrared spectra were recorded on a JASCO FT/IR-230 fourier transform infrared spectrophotometer. NMR spectra were recorded on JEOL JNM-GSX 400α (400 MHz) and JNM ECP400 spectrometers (400 MHz), unless otherwise indicated. Chemical shifts are recorded in parts per million (ppm) downfield from tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL HX-110A (LRFAB, LREI) spectrometer. HPLC analyses were carried out on a chiral column indicated in each experiment. Column chromatography was performed with silica gel BW-820MH (Fuji Davison Co.). All reactions were carried out in oven-dried glassware with magnetic stirring unless otherwise noted.

(*R*)-4-Benzyl-3-(3-methylbutanoyl)oxazolidin-2-one (7a) To a stirred solution of (*R*)-Evans oxazolidinone **6a** (3.54 g, 20 mmol) in THF (100 mL) at −78°C was added a 1.6 M solution of *n*-BuLi (in *n*-hexane, 13.1 mL, 21 mmol). After stirring the reaction mixture for 30 min, isovaleryl chloride (2.7 mL, 22 mmol) was added at −78°C and the reaction mixture was stirred for 1 h. The reaction mixture was quenched with a satd NH_4Cl solution. (100 mL) and separated. The aqueous layer was extracted with EtOAc (200 mL). The combined organic layers were washed with a satd $NaHCO_3$ solution (100 mL), water (100 mL), and brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a colorless residue. The crude product was purified by silica gel column chromatography (*n*-hexane–EtOAc=4 : 1) to give **7a** (5.1 g, 98%) as a colorless solid: $[\alpha]_D^{20}$ −45.2 (c=0.76, $CHCl_3$); mp 41–42°C; IR (neat) ν 2958, 2926, 1780, 1698, 1389, 1306, 1210 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.01 (3H, d, J=6.8 Hz), 1.02 (3H, d, J=6.8 Hz), 2.22 (1H, sept., J=6.8 Hz), 2.75 (1H, m), 2.77 (1H, dd, J=9.6, 6.8 Hz), 2.89 (1H, dd, J=6.8, 16.0 Hz), 3.31 (1H, dd, J=3.2, 13.2 Hz), 4.14–4.21 (2H, m), 4.65–4.71 (1H, m), 7.21–7.35 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 23.4, 22.5, 25.0, 37.9, 43.9, 55.1, 66.0, 127.3, 128.9, 129.4, 135.3, 153.4, 172.6; high resolution (HR)-MS (electrospray ionization-time-of-flight (ESI-TOF)) Calcd for $C_{15}H_{20}NO_3$ $[M+H]^+$ 262.1443, Found 262.1440.

Table 1. Synthesis of β-Keto Esters



Entry	Malonate	Product	Additive	Yield[a)]
1	**11**	**10**	—	NR
2	**11**	**10**	DMAP	NR
3	**11**	**10**	PPY	NR
4	**12**	**9**	—	~10%
5	**12**	**9**	DMAP	95%



a) Isolated yield. NR: no reaction.

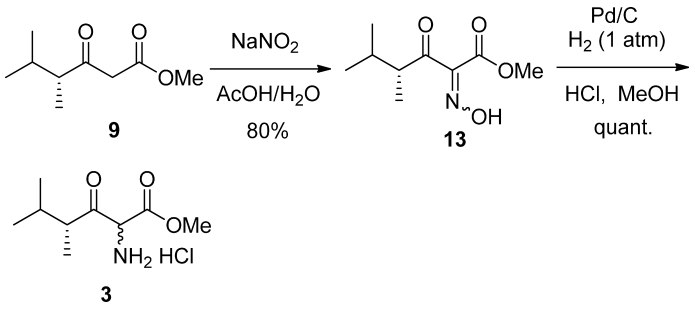
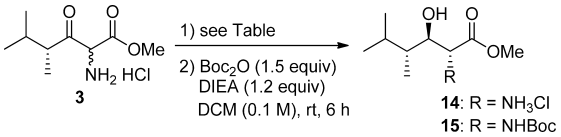


Chart 3. Synthesis of α-Amino-β-keto Ester **3**

Table 2. Asymmetric Hydrogenation of α-Amino-β-keto Ester **3** through Dynamic Kinetic Resolution



Entry	Conditions	Temp. and time	dr[a)]	Yield[b)] (in two steps)
1	$[RuCl_2(C_6H_6)]_2$ (3 mol%), (*R*)-BINAP (6 mol%), H_2 (100 atm), DCM (0.3 M)	50°C, 72 h	90 : 10	51%[c)]
2	$[RuCl_2(C_6H_6)]_2$ (5 mol%), (*R*)-BINAP (10 mol%), H_2 (100 atm), DCM (0.3 M)	50°C, 72 h	95 : 5	76%
3	$[IrCl(cod)]_2$ (0.5 mol%), (*R*)-MeO-BIPHEP (1.3 mol%), NaBARF (1 mol%), AcONa (1 eq), H_2 (4.5 atm), AcOH (0.2 M)	25°C, 96 h	—	NR[d)]

a) Diastereomeric ratio was determined by ^{1}H-NMR analysis after Boc protection. *b*) Isolated yield of **15** after diastereomeric purification by recrystallization. *c*) The conversion yield of the first step was 70% (judged by ^{1}H-NMR analysis of the crude reaction mixture). *d*) No reaction.

(*R*)-4-Benzyl-3-((*R*)-2,3-dimethylbutanoyl)oxazolidin-2-one (8a) To a stirred solution of lithium diisopropylamide (LDA) (23.4 mmol) in THF (100 mL) at −78°C was added **7a** (5.1 g, 19.5 mmol). After stirring the mixture for 30 min, iodomethane (1.46 mL, 23.4 mmol) was added and the reaction mixture was allowed to warm to 0°C and stirred at 0°C for 3 h. The reaction mixture was quenched with a satd NH_4Cl solution (100 mL) and separated. The aqueous layer was extracted with EtOAc (200 mL). The combined organic layers were washed with a satd $NaHCO_3$ solution (100 mL), water (100 mL), and brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product in a 93 : 7 diastereoselectivity (judged by ^{1}H-NMR spectrum). The crude product was purified by silica gel column chromatography (*n*-hexane–EtOAc=4 : 1) followed by recrystallization from *n*-hexane to give diastereomerically pure **8a** (4.65 g, 80%) as colorless needles: $[\alpha]_D^{20}$ −86.4 (*c*=1.00, $CHCl_3$); mp 52–53°C; IR (neat) *v* 2965, 2918, 1776, 1696, 1455, 1384, 1348, 1209 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.94 (3H, d, *J*=6.8 Hz), 0.95 (3H, d, *J*=6.8 Hz), 1.17 (3H, d, *J*=6.8 Hz), 1.99 (1H, octet, *J*=

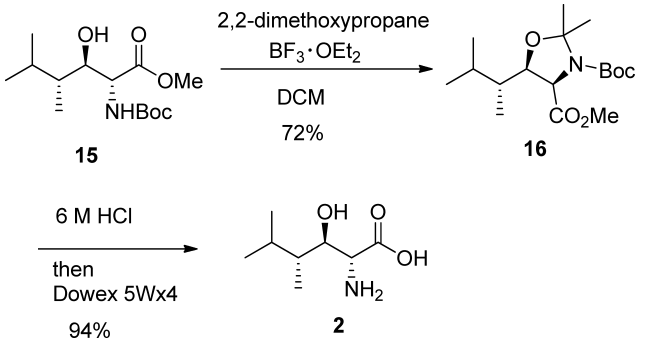


Chart 4. Synthesis of (2*R*,3*R*,4*R*)-2-Amino-3-hydroxy-4,5-dimethylhexanoic Acid (**2**)

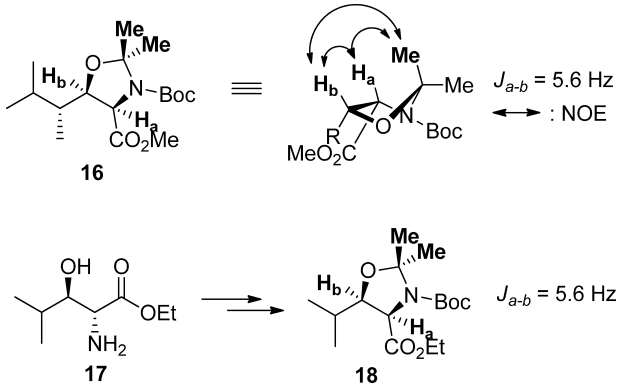


Fig. 2. NOE Experiment of **16**

6.8 Hz), 2.77 (1H, dd, *J*=9.6, 13.2 Hz), 3.29 (1H, dd, *J*=3.2, 13.2 Hz), 3.60 (1H, quint., *J*=6.8 Hz), 4.14–4.70 (2H, m), 4.67 (1H, m), 7.21–7.35 (5H, m),; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.8, 18.6, 21.2, 30.6, 37.9, 43.5, 55.5, 65.9, 127.3, 128.9, 129.4, 135.4, 153.1, 177.1; HR-MS (ESI-TOF) Calcd for $C_{16}H_{22}NO_3$ $[M+H]^+$ 276.1600, Found 276.1588.

(*R*)-2,3-Dimethyl-butyric Acid (4) To a solution of **8a** (2.47 g, 10.9 mmol) in THF–H_2O (1 : 1, 50 mL) at 23°C was added LiOH H_2O (684 mg, 16.3 mmol) followed by a 30% H_2O_2 solution (2.2 mL, 20 mmol). After stirring the mixture at 23°C for 6 h, the reaction mixture was acidified with a 1 M $KHSO_4$ solution (25 mL) and extracted with EtOAc (150 mL×2). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a colorless residue. The crude product was purified by silica gel column chromatography (*n*-hexane–EtOAc=4 : 1) to give **4** (1.02 g, 81%) as a colorless oil: $[\alpha]_D^{20}$ −22.3 (*c*=0.74, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.93 (3H, d, *J*=6.8 Hz), 0.97 (3H, d, *J*=6.8 Hz), 1.13 (3H, d, *J*=6.8 Hz), 1.95 (1H, octet, *J*=6.8 Hz), 2.27 (1H, quintet, *J*=6.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.3, 18.9, 20.6, 30.7, 46.0, 182.9. The spectroscopic data for **4** were consistent with those of the literature.[27]

(*R*)-4,5-Dimethyl-3-oxo-hexanoic Acid Methyl Ester (9) To a stirred solution of carboxylic acid **4** (423 mg, 3.64 mmol) in THF (50 mL) was added carbonyldiimidazole (885 mg, 5.46 mmol) at 23°C. After stirring the mixture for 6 h, the reaction mixture was quenched with water (50 mL) and extracted with EtOAc (50 mL×2). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give the crude imidazolide as a colorless oil. A suspension of potassium methyl malonate (1.1 g, 7.0 mmol), powdered $MgCl_2$ (666 mg, 7.0 mmol), and Et_3N (2 mL, 14 mmol) in THF (35 mL) was stirred at 23°C for 2 h. The crude imidazolide (499 mg, 3.0 mmol) and DMAP (37 mg, 0.3 mmol) were added at 23°C and the reaction mixture was stirred for 48 h. The reaction was quenched with a satd NH_4Cl solution (25 mL) and extracted with EtOAc (50 mL×2). The combined organic layers were washed with a satd $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product. The crude product was purified by silica gel column chromatography (*n*-hexane–EtOAc=4 : 1) to give **9** (583 mg, 93% as a 78 : 22 mixture of keto and enol tautomers) as a colorless oil: $[\alpha]_D^{20}$ −23.9 (*c*=0.8, $CHCl_3$); IR (neat) *v* 2961, 2875, 2138, 1716, 1655, 1309, 1210 cm^{-1}; ^{1}H-NMR (keto form, 400 MHz, $CDCl_3$) δ: 0.87 (3H, d, *J*=6.8 Hz), 0.94 (3H, d, *J*=6.8 Hz), 1.05 (3H, d, *J*=6.8 Hz), 1.98 (1H, octet, *J*=6.8 Hz), 2.44 (1H, quint., *J*=6.8 Hz), 3.49 (2H, s), 3.74 (3H, s); ^{13}C-NMR (keto form, 100 MHz, $CDCl_3$) δ: 12.3, 18.5, 21.2, 29.9, 48.1, 52.2, 53.0, 167.7, 206.5; HR-MS (ESI-TOF) Calcd for $C_9H_{16}NaO_3$ $[M+Na]^+$ 195.0997, Found 195.0994.

(*R*)-2-Hydroxyimino-4,5-dimethyl-3-oxo-hexanoic Acid Methyl Ester (13) To a stirred solution of β-ketoester **9** (270 mg, 1.57 mmol) in AcOH (4 mL) at 0°C was added a $NaNO_2$ solution (325 mg, 4.7 mmol, in 4 mL water). After stirring the mixture at 23°C for 2 h, the reaction mixture was quenched with a satd $NaHCO_3$ solution and extracted with EtOAc (100 mL×2). The combined organic layers were washed with a satd $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product. The crude product was purified by silica gel column chromatography (*n*-hexane–EtOAc=4 : 1) to give **13** (249 mg, 80%) as a colorless oil: $[\alpha]_D^{20}$ −16.1 (*c*=3.85, $CHCl_3$); IR (neat) *v* 3342, 2963, 2875, 1731, 1677, 1435, 1292, 1212 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.89 (3H, d, *J*=6.8 Hz), 0.92 (3H, d, *J*=6.8 Hz), 1.07 (3H, d, *J*=6.8 Hz), 2.02 (1H, octet, *J*=6.8 Hz), 3.21 (1H, quint., *J*=6.8 Hz), 3.91 (3H, s), 9.13–9.32 (1H, brs); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 12.8, 18.9, 21.2, 30.6, 46.8, 52.8, 150.6, 162.1, 200.0; HR-MS (ESI-TOF) Calcd for $C_9H_{15}NNaO_4$ $[M+Na]^+$ 224.0899, Found 224.0892.

Methyl (4*R*)-2-Amino-4,5-dimethyl-3-oxohexanoate Hydrochloride (3) A suspension of oxime **13** (210 mg, 1.04 mmol), 2 M HCl–MeOH (1.6 mL, 3.2 mmol), and 2.8 wt% Pd–C (40 mg, 0.01 mmol) in MeOH (5 mL) was stirred under hydrogen atmosphere (1 atm) at 23°C for 6 h. The reaction mixture was filtered through a celite pad and the filtrate was concentrated *in vacuo* to give **3** (232 mg, quant. as a 1 : 1 mixture of diastereomers) as a colorless solid: $[\alpha]_D^{20}$ 17.1 (*c*=1.20, MeOH); mp 123–125°C; IR (neat) *v* 2962, 2875, 2624, 1752, 1726, 1585, 1508, 1439, 1369, 1277, 1139 cm^{-1}; ^{1}H-NMR (1 : 1 diastereomers, 400 MHz, $CDCl_3$) δ: 0.80 (3H, d, *J*=6.8 Hz), 0.87 (3H, d, *J*=6.8 Hz), 0.90 (3H, d, *J*=6.8 Hz), 1.01 (6H, d, *J*=6.4 Hz), 1.20 (3H, d, *J*=7.2 Hz), 1.93–2.02 (1H, m), 2.15–2.23 (1H, m), 2.85–2.92 (1H, m), 2.98–3.05 (1H, m), 3.88 (3H, s), 3.91 (3H, s), 5.30 (1H, s), 5.38 (1H, s); ^{13}C-NMR (1 : 1 diastereomers 100 MHz, $CDCl_3$) δ: 11.1, 14.4, 17.9, 18.9, 21.1, 21.3, 29.3, 30.3, 49.5, 50.6, 54.1, 54.4, 61.2, 61.4, 163.3, 163.5, 201.4; HR-MS (ESI-TOF) Calcd for $C_9H_{18}NO_3$ $[M+H]^+$ 188.1287, Found 188.1315.

Methyl (2*R*,3*R*,4*R*)-2-Amino-3-hydroxy-4,5-dimethylhexanoate Hydrochloride (14) Ru-(*R*)-BINAP complex was

prepared from $[RuCl_2(C_6H_6)]_2$ (48 mg, 0.096 mmol) and (*R*)-BINAP (121 mg, 0.195 mmol) according to the literature procedure.[28] The resulting red-brown catalyst was dried *in vacuo* at 50°C for 2 h. A degassed solution of *α*-amino-*β*-keto ester hydrochloride **3** (449 mg, 1.9 mmol) in dichloromethane (DCM) (6 mL) was added to the catalyst under an argon atmosphere. The reaction was carried out in a glassware placed in a stainless autoclave apparatus. The mixture was hydrogenated at 50°C under 100 atm of hydrogen for 72 h. The solvent was removed *in vacuo* to leave crude **14** and the residue was recrystallized from DCM–EtOAc to give pure *β*-hydroxyamino acid **14** as colorless crystals (347 mg, 81%, >99%dr): $[\alpha]_D^{20}$ −14.4 (*c*=1.0, MeOH); mp 178–179°C; IR (neat): *ν* 3342, 2959, 1747, 1508, 1234, 1033 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3OD) *δ*: 0.83 (3H, d, *J*=6.8 Hz), 0.88 (3H, d, *J*=6.8 Hz), 0.99 (3H, d, *J*=6.8 Hz), 1.75–1.86 (1H, m), 2.16–2.28 (1H, m), 3.67–3.76 (1H, m), 3.88 (3H, s), 4.12–4.26 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 10.5, 15.7, 22.6, 28.1, 42.6, 54.3, 58.1, 75.3, 171.8; HR-MS (ESI-TOF) Calcd for $C_9H_{20}NO_3$ $[M+H]^+$ 190.1443, Found 190.1465. The diastereomeric ratio of crude **14** was determined by the analysis of its ^{1}H-NMR spectrum to be 95 : 5.

Methyl (2*R*,3*R*,4*R*)-2-(*tert*-Butoxycarbonylamino)-3-hydroxy-4,5-dimethylhexanoate (15) To a stirred solution of **14** (300 mg, 1.33 mmol) in DCM (13 mL) at 23°C was added DIEA (0.35 mL, 2.0 mmol) and Boc_2O (440 mg, 2.0 mmol) and stirred for 12 h. Then the mixture was quenched with a 1 M $KHSO_4$ solution (20 mL) and extracted by DCM (20 mL). The organic layer was washed with a satd $NaHCO_3$ solution (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give crude product. The crude product was purified by silica gel column chromatography (*n*-hexane–EtOAc=4 : 1) to give **12** (361 mg, 94%) as a colorless solid: $[\alpha]_D^{20}$ −14.5 (*c*=1.00, $CHCl_3$); mp 70–71°C; IR (neat) *ν* 3403, 2959, 1716, 1506, 1366, 1163 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 0.77 (3H, d, *J*=6.8 Hz), 0.80 (3H, d, *J*=6.8 Hz), 0.92 (3H, d, *J*=6.8 Hz), 1.45 (9H, s), 1.44–1.55 (1H, m), 2.11–2.23 (1H, m), 2.50–2.60 (1H, m), 3.61 (1H, br d, *J*=8.8 Hz), 3.78 (3H, s), 4.48–4.50 (1H, m), 5.63 (1H, br d, *J*=6.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 9.4, 15.0, 21.2, 26.4, 28.3, 41.2, 52.3, 56.2, 75.9, 80.2, 155.6, 171.7; HR-MS (ESI-TOF) Calcd for $C_{14}H_{27}NNaO_5$ $[M+Na]^+$ 312.1787, Found 312.1772.

(4*R*,5*R*)-3-*tert*-Butyl-4-methyl-2,2-dimethyl-5-((*R*)-3-methylbutan-2-yl)oxazolidine-3,4-dicarboxylate (16) To a stirred solution of Boc-AHDMHA **15** (22 mg, 0.076 mmol) and 2,2-dimethoxypropane (47 *μ*L, 0.38 mmol) in DCM (0.8 mL) at 23°C was added $BF_3 \cdot OEt_2$ (0.5 *μ*L, 0.0038 mmol) and the reaction mixture was stirred for 30 min. Then the reaction mixture was diluted with EtOAc (5 mL) and washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give crude product. The crude product was purified by silica gel column chromatography (*n*-hexane–EtOAc=4 : 1) to give **16** (18 mg, 72%) as a colorless solid: $[\alpha]_D^{20}$ −2.9 (*c*=0.37, $CHCl_3$); mp 51–52°C; IR (neat) *ν* 2957, 1750, 1714, 1377, 1176 cm^{-1}; ^{1}H-NMR (*ca.* 6 : 4 rotamers, 400 MHz, C_6D_6) *δ*: 0.74 (3H, d, *J*=6.8 Hz), 0.77 (3H, d, *J*=6.8 Hz), 0.78 (1.2H, d, *J*=6.8 Hz), 0.79 (1.8H, d, *J*=6.8 Hz), 1.40 (3.6H, s), 1.42 (4.4H, s), 1.43 (1.2H, s), 1.53–1.58 (1H, m), 1.56 (1.8H, s), 1.89 (1.2H, s), 2.04 (1.8H, s), 2.25–2.32 (1H, m), 3.30 (1.2H, s), 3.32 (1.8H, s), 3.64 (0.4H, dd, *J*=5.6, 6.8 Hz), 3.67 (0.6H, dd, *J*=5.6, 6.8 Hz), 4.29 (0.6H, d, *J*=5.6 Hz), 4.50 (0.4H, d, *J*=5.6 Hz); ^{13}C-NMR (*ca.* 6 : 4 rotamers, 100 MHz, C_6D_6) *δ*: 10.6, 10.1, 15.7, 15.8, 21.0, 21.1, 24.9, 25.8, 26.3, 27.3, 27.9, 28.0, 28.9, 29.0, 39.1, 39.3, 51.8, 51.9, 63.6, 63.8, 79.4, 79.6, 80.3, 80.7, 94.3, 95.1, 151.9, 152.8, 171.3, 171.42; HR-MS (ESI-TOF) Calcd for $C_{17}H_{31}NNaO_5$ $[M+Na]^+$ 352.2100, Found 352.2060.

(2*R*,3*R*,4*R*)-2-Amino-3-hydroxy-4,5-dimethylhexanoic Acid (2) A solution of acetonide **16** (22 mg, 0.067 mmol) in a 6 M HCl solution (1 mL) was heated to reflux for 12 h. The resulting solution was concentrated *in vacuo* to give crude amino acid. The residue was purified with Dowex 50W-X4 ion-exchange resin (H^+ form) using a 2 M pyridine solution as an eluent to give the desalted (2*R*,3*R*,4*R*)-hydroxyamino acid **2** (11 mg, 94%) as a colorless powder: $[\alpha]_D^{20}$ −22.9 (HCl salt, *c*=0.55, MeOH); mp 195–197°C; IR (HCl salt, neat) *ν* 3411, 2962, 2875, 2632, 1752, 1726, 1594, 1508, 1439, 1369, 1277, 1139 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3OD) *δ*: 0.80 (3H, d, *J*=7.2 Hz), 0.85 (3H, d, *J*=7.2 Hz), 0.95 (3H, d, *J*=7.2 Hz), 1.81–1.89 (1H, m), 2.19–2.26 (1H, m), 3.65 (1H, dd, *J*=2.4, 10.4 Hz), 3.72 (1H, dd, *J*=2.4 Hz); ^{13}C-NMR (100 MHz, CD_3OD) *δ*: 9.5, 14.9, 21.4, 27.2, 41.2, 59.0, 74.0, 171.6; HR-MS (ESI-TOF) Calcd for $C_8H_{18}NO_3$ $[M+H]^+$ 176.1287, Found 176.1331. The NMR spectrum of natural AHDMHA: ^{1}H-NMR (500 MHz, CD_3OD) *δ*: 0.80 (3H, d, *J*=7.0 Hz), 0.85 (3H, d, *J*=6.9 Hz), 0.94 (3H, d, *J*=7.0 Hz), 1.84 (1H, m), 2.22 (1H, m), 3.65 (1H, dd, *J*=2.6, 10.0 Hz), 3.70 (1H, dd, *J*=2.6 Hz); ^{13}C-NMR (125 MHz, CD_3OD) *δ*: 9.5, 14.9, 21.4, 27.2, 41.2, 59.0, 74.0, 171.5.

Acknowledgment This work was financially supported in part by a Grant-in-Aid for Scientific Research (B) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References

1) Zampella A., Sepe V., Luciano P., Bellotta F., Monti M. C., D'Auria M. V., Jepsen T., Petek S., Adeline M.-T., Laprévôte O., Aubertin A.-M., Debitus C., Poupat C., Ahond A., *J. Org. Chem.*, **73**, 5319–5327 (2008).
2) Zampella A., Sepe V., Bellotta F., Luciano P., D'Auria M. V., Cresteil T., Debitus C., Petek S., Poupat C., Ahond A., *Org. Biomol. Chem.*, **7**, 4037–4044 (2009).
3) Bagavananthem Andavan G. S., Lemmens-Gruber R., *Marine Drugs*, **8**, 810–834 (2010).
4) Makino K., Nagata E., Hamada Y., *Tetrahedron Lett.*, **46**, 6827–6830 (2005).
5) Hara S., Makino K., Hamada Y., *Peptide Science*, **42**, 39–42 (2006).
6) Hara S., Makino K., Hamada Y., *Tetrahedron Lett.*, **47**, 1081–1085 (2006).
7) Hara S., Nagata E., Makino K., Hamada Y., *Peptide Science*, **44**, 27–30 (2008).
8) Ohtaka J., Hamajima A., Hamada Y., *Peptide Science*, **47**, 187 (2010).
9) Bellotta F., D'Auria M. V., Sepe V., Zampella A., *Tetrahedron*, **65**, 3659–3663 (2009).
10) Liang B., Carroll P. J., Joullié M. M., *Org. Lett.*, **2**, 4157–4160 (2000).
11) Okamoto N., Hara O., Makino K., Hamada Y., *Tetrahedron Asymmetry*, **12**, 1353–1358 (2001).
12) Makino K., Goto T., Hiroki Y., Hamada Y., *Angew. Chem. Int. Ed.*, **43**, 882–884 (2004).
13) Makino K., Goto T., Hiroki Y., Hamada Y., *Tetrahedron Asymmetry*, **19**, 2816–2828 (2008).
14) Makino K., Fujii T., Hamada Y., *Tetrahedron Asymmetry*, **17**, 481–485 (2006).

15) Makino K., Hiroki Y., Hamada Y., *J. Am. Chem. Soc.*, **127**, 5784–5785 (2005).
16) Makino K., Iwasaki M., Hamada Y., *Org. Lett.*, **8**, 4573–4576 (2006).
17) Maeda T., Makino K., Iwasaki M., Hamada Y., *Chemistry*, **16**, 11954–11962 (2010).
18) Hamada Y., Koseki Y., Fujii T., Maeda T., Hibino T., Makino K., *Chem. Commun.* (Camb.), **2008**, 6206–6208 (2008).
19) Hamada Y., Makino K., *J. Synth. Org. Chem. Jpn.*, **66**, 1057–1065 (2008).
20) Hamada Y., Makino K., "Asymmetric Synthesis and Application of α-Amino Acids," ed. by Soloshonok, V. A., Izawa, K., ACS Book, 2009, pp. 227–238.
21) Krysan D. J., *Tetrahedron Lett.*, **37**, 3303–3306 (1996).
22) Brooks D. W., Lu L. D.-L., Masamune S., *Angew. Chem. Int. Ed. Engl.*, **18**, 72–74 (1979).
23) Noyori R., Tokunaga M., Kitamura M., *Bull. Chem. Soc. Jpn.*, **68**, 36–55 (1995).
24) Ward R. S., *Tetrahedron Asymmetry*, **6**, 1475–1490 (1995).
25) Pellissier H., *Tetrahedron*, **59**, 8291–8327 (2003).
26) Pellissier H., *Tetrahedron*, **64**, 1563–1601 (2008).
27) Tanasova M., Borha B., *Eur. J. Org. Chem.*, **2012**, 3261–3269 (2012).
28) Kitamura M., Tokunaga M., Ohkuma T., Noyori R. *Org. Synth.*, *Coll.*, **9**, 589 (1998).