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Efficient enantioselective synthesis of (2*R*,3*R*)- and (2*S*,3*S*)-3-hydroxyleucines and their diastereomers through dynamic kinetic resolution

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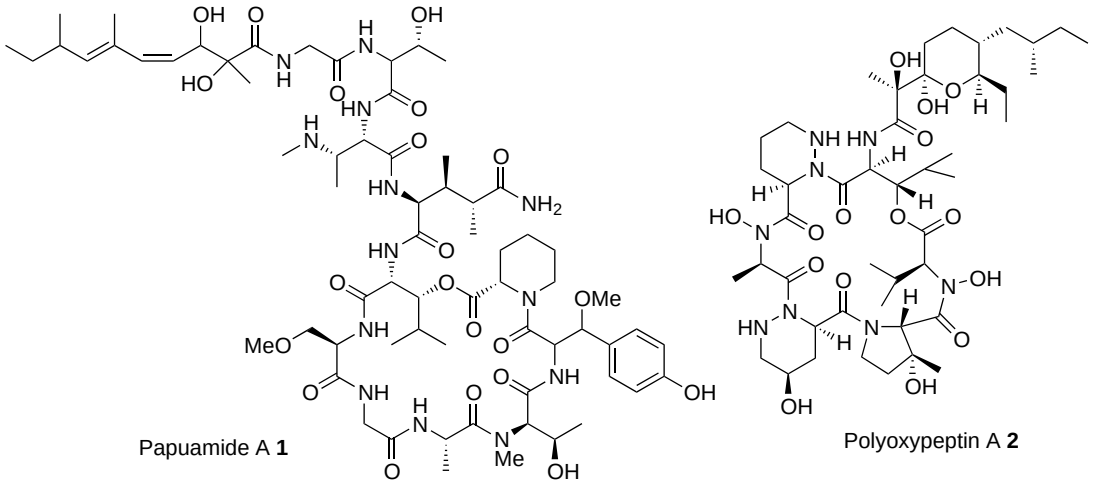
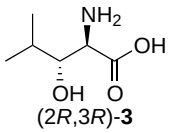
Abstract—(2*R*,3*R*)- and (2*S*,3*S*)-3-Hydroxyleucines, components of cyclodepsipeptides, papuamides and polyoxypeptins, were efficiently synthesized along with their diastereomers from the corresponding β-keto-α-amino acid ester through dynamic kinetic resolution using $RuCl_2$(binap)-catalyzed hydrogenation. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Naturally occurring (2*R*,3*R*)- and (2*S*,3*S*)-3-hydroxyleucines are found as components of the ester tether linkage in cyclodepsipeptides, such as papuamides[1] of marine origin and polyoxypeptins[2] of microbial origin (Fig. 1). The (2*R*,3*S*)-diastereomer has also been used as a building block in the synthesis of lactacystin, a neurotrophic agent.[3e]

Several groups have already reported enantioselective approaches to these important 3-hydroxyleucines,[3,4]




(2*R*,3*R*)-**3**

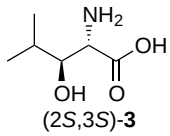

(2*S*,3*S*)-**3**

Figure 1.

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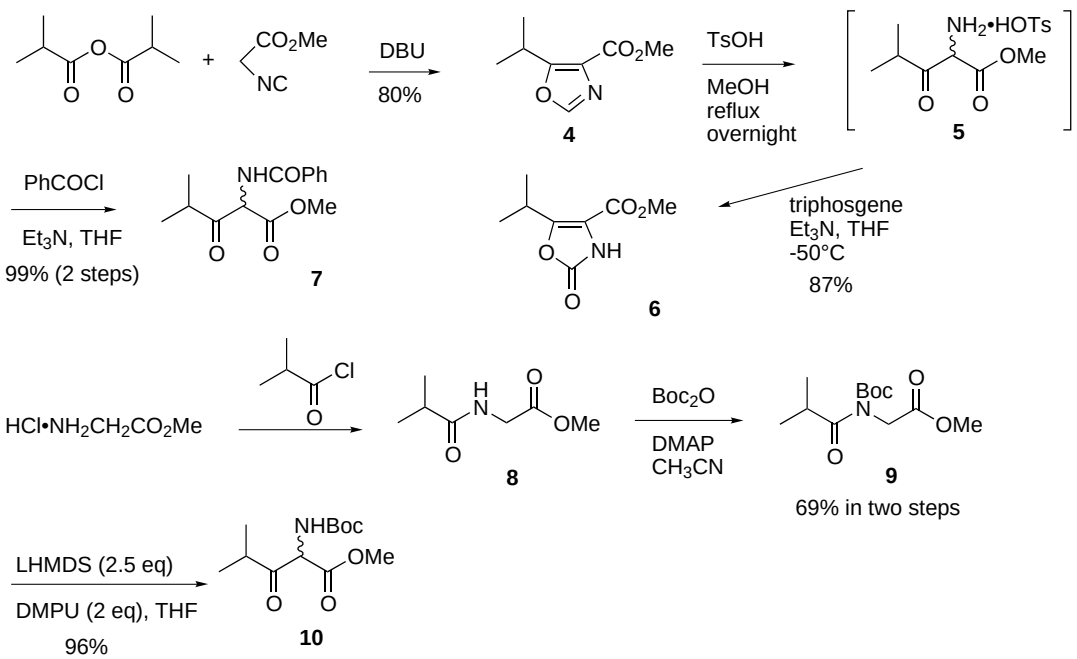
including Sharpless asymmetric epoxidation,[3a,e,4a] enantioselective aldol condensation,[3b,i] diastereoselective aldol condensation,[3c,h] Sharpless asymmetric dihydroxylation,[3d,4c] alkylation of the serinal derivatives,[3f,g] alkylation of chiral 2-hydroxyisobutyraldehyde,[3j] Sharpless asymmetric aminohydroxylation[4b] and asymmetric Strecker methods.[4d] Some of these methods are stereoselective but require careful handling and problems with the use of some large-scale processes remain to be solved. In connection with our efforts to synthesize papuamides, cyclodepsipeptides with anti-HIV and cytotoxic activities, and polyoxypeptins, cyclodepsipeptides with apoptosis-inducing activity, we needed (2*R*,3*R*)- and (2*S*,3*S*)-3-hydroxyleucines in large quantities. Herein, we report a simple and efficient method for the preparation of (2*R*,3*R*)- and (2*S*,3*S*)-3-hydroxyleucines and their diastereomers from the corresponding β-keto-α-amino acid ester through dynamic kinetic resolution using $RuCl_2$(binap)-catalyzed hydrogenation.

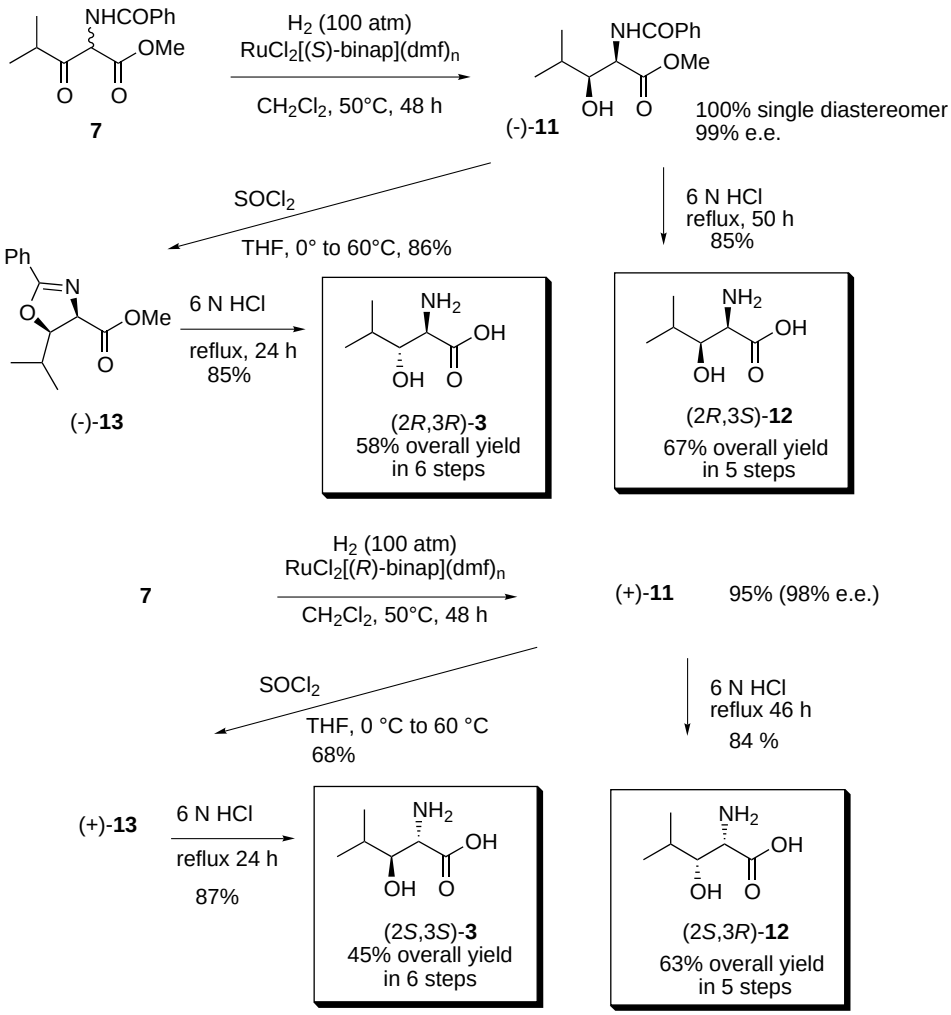
2. Results and discussion

The key features of our synthesis are (1) the preparation of the β-keto-α-amino acid esters from the 4-methoxycarbonyloxazole or by novel acyl migration of the *N*,*N*-diacylglycine ester (Scheme 1) and (2) stereoselective reduction of the β-keto-α-amino acid ester using the $RuCl_2$(binap)-catalyzed hydrogenation methodology developed by Noyori,[5] as illustrated in Scheme 2. Treatment of isovaleric anhydride with methyl isocyanoacetate in the presence of diazabicyclo-[4.3.0]undecene (DBU) afforded the oxazole **4**[6] in 80% yield, which was also obtained from isovaleric acid and methyl isocyanoacetate by use of diphenyl phosphorazidate and potassium carbonate sesquihydrate with similar efficiency.[7] Acid-catalyzed cleavage of **4** with *p*-toluenesulfonic acid (TsOH) proceeded cleanly under reflux in methanol and gave the β-keto-α-amino acid ester **5** in quantitative yield. First, we attempted the formation and stereoselective hydrogenation of the oxazolone **6**, which directly produces the desired stereochemistry of the 3-hydroxyleucine. Reaction of **5** with triphosgene in the presence of triethylamine in THF at −50°C gave the oxazolone **6** in 87% yield. Unfortunately, the stereoselective hydrogenation of **6** using several catalysts, such as Rh-BINAP and Rh-DIOP, was sluggish and failed to afford the *erythro*-3-hydroxyleucine derivative in productive yield.

Next, we focussed on the stereoselective reduction of the β-keto-α-amino acid ester **5**. Protection of **5** using benzoyl chloride and triethylamine in tetrahydrofuran (THF) at the nitrogen function provided the 2-benzoylamino-3-oxopentanoate **7** in 99% yield. Alternatively, the *N*-*tert*-butoxycarbonyl derivative of **7** was obtained by N–C acyl migration reaction developed by us.[8] The double acylated substrate **9** for the migration was prepared by acylation of methyl glycinate hydrochloride with isovaleryl chloride and subsequent *N*-*tert*-butoxycarbonylation with di-*tert*-butyl dicarbonate in the presence of *N*,*N*-dimethylaminopyridine (DMAP) in acetonitrile in 69% yield. N–C Acyl migration of **9** was carried out by treatment with lithium hexamethyldisilazide (2.5 equiv.) in the presence of *N*,*N*-dimethylpropyleneurea (DMPU) in THF at −78°C to afford the β-keto-α-amino acid ester **10** in 96% yield. Interestingly, the *tert*-butoxycarbonyl group in the double acylated substrate **9** was observed to serve as a non-transfer group.



Scheme 1.



Scheme 2.

The key hydrogenation of **7** using $RuCl_2$((*S*)-binap) in methylene chloride was found to be sluggish and required higher temperature (Scheme 2). Finally, the reaction at 50°C for 48 h gave the (2*R*,3*S*)-3-hydroxyleucine derivative (−)-**11** in 100% yield. The enantiomeric excess (e.e.) of **11** was shown to be 99% by HPLC analysis using a chiral column. The absolute stereostructure of **11** was unambiguously determined after conversion to the corresponding 3-hydroxyleucine. Thus, (−)-**11** was hydrolyzed with 6N aqueous hydrochloric acid under reflux for 50 h to give (2*R*,3*S*)-3-hydroxyleucine (+)-**12**, which was confirmed by comparison with the values reported by others.[3e] Inversion of the C(3) stereochemistry of (−)-**11** was effected by treatment with thionyl chloride in THF at 0°C and then heating to 60°C to furnish the oxazoline (−)-**13** with the stereochemistry (2*R*,3*R*)-3-hydroxyleucine in 86% yield. The thus obtained (−)-**13** was hydrolyzed with 6N aqueous hydrochloric acid under reflux to afford (2*R*,3*R*)-3-hydroxyleucine ((−)-**3**) in 85% yield which was identical with that reported.[3e] The overall yields of (−)-**3** and (+)-**12** are 58% and 67%, respectively. (2*S*,3*S*)-3-Hydroxyleucine (+)-**3** and the (2*S*,3*R*)-diastereoisomer (−)-**12** were also synthesized with similar efficiency by use of an analogous procedure.

3. Conclusion

We have succeeded in the efficient synthesis of (2*R*,3*R*)- and (2*S*,3*S*)-3-hydroxyleucines applicable to large-scale production in six steps with high overall yields. Using the same procedure, the (2*R*,3*S*)- and (2*S*,3*R*)-3-hydroxyleucines, are also available with high overall yields in five steps.

4. Experimental

Melting points are uncorrected. IR spectra were recorded on a JASCO FT/IR-230 spectrometer. NMR spectra were recorded on JEOL JNM GSX400A, JNM GSX500A, and JNM ECP400 spectrometers. FAB mass spectra were obtained with a JEOL JMS-HX-110A spectrometer. Optical rotations were determined on a JASCO DIP-140 polarimeter. Column chromatography was carried out with silica gel BW-820MH (Fuji silysia).

4.1. 4-Methoxycarbonyl-5-(1-methylethyl)-1,3-oxazole 4

Prepared according to the literature procedure.[6]

4.2. Methyl 2-benzoylamino-4-methyl-3-oxopentanoate 7

A mixture of the oxazole (**4**, 958 mg, 5.66 mmol) and $TsOH \cdot H_2O$ (2.14 g, 11.26 mmol) in MeOH (15 mL) was heated under reflux overnight. The mixture was cooled to rt and concentrated in vacuo. The residue was triturated with ether and filtered to afford methyl 2-amino-4-methyl-3-oxopentanoate toluenesulfonic acid salt (2.46 g, quant.) as colorless solids. The crude material was used for the next step without further purification.

A suspension of the TsOH salt **5** (2.46 g) in THF (15 mL) was cooled to 0°C. Benzoyl chloride (0.7 mL, 6.03 mmol) and triethylamine (2.4 mL, 17.2 mmol) was slowly added. After stirring overnight, the reaction mixture was quenched with water (1 mL) and diluted with ethyl acetate–*n*-hexane (5:1). The mixture was washed with aqueous hydrochloric acid (1N), water, saturated aqueous sodium hydrogen carbonate, and saturated brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography (30 g, ethyl acetate–*n*-hexane = 1:2.5 to 1:1) to give *N*-benzoyl derivative **7** as a colorless oil (1.43 g, 99%); IR (neat): 3409, 1754, 1660, 1516, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (3H, d, $J = 6.8$ Hz), 1.26 (3H, d, $J = 7.1$ Hz), 3.14 (1H, heptet, $J = 6.8$ Hz), 3.84 (3H, s), 5.62 (1H, d, $J = 6.8$ Hz), 7.31 (1H, d, $J = 5.4$ Hz), 7.44–7.50 (2H, m), 7.52–7.56 (1H, m), 7.84–7.87 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.6, 18.8, 37.7, 53.2, 61.0, 127.2, 128.6, 132.0, 133.0, 166.7, 166.9, 205.0. HRMS calcd for $C_{14}H_{18}NO_4$: 264.1236 (M^++1). Found: 264.1237.

4.3. 4-Methoxycarbonyl-5-(1-methylethyl)-1,3-oxazol-2-one 6

To a stirred mixture of the TsOH salt **5** (prepared as described above, 850 mg, 2.57 mmol) and Et_3N (1.07 mL, 7.70 mmol) in THF (8.8 mL) was cooled to −50°C and a solution of triphosgene (266 mg, 0.90 mmol) in THF (4.0 mL) was added via cannula. After stirring for 30 min, the reaction mixture was diluted with ether (90 mL) and saturated aqueous NH_4Cl (50 mL) was added. The aqueous phase was separated and extracted with ether (3×60 mL). The combined organic extracts were washed with brine (60 mL), dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (25 g, *n*-hexane–ethyl acetate = 2:1) to give the oxazolone **6** as colorless solids (411 mg, 87%); mp 74–76°C (ether–*n*-hexane); IR (KBr): 3226, 3143, 2979, 1762, 1721, 1661, 1316, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (6H, d, $J = 7.1$ Hz, $CH(CH_3)_2$), 3.50 (1H, septet, $J = 7.0$ Hz, $CH(CH_3)_2$), 3.88 (3H, s, CO_2CH_3), 8.70 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7, 25.4, 112.2, 154.4, 154.5, 159.1. HRMS calcd for $C_8H_{11}NO_4$: 185.0688. Found: 185.0692.

4.4. Methyl *N*-*tert*-butoxycarbonyl-*N*-isobutyrylglycinate 9

To a mechanically stirred suspension of methyl glycinate hydrochloride (10.11 g, 80.5 mmol) in ether (32 mL) at 0°C was added saturated aqueous potassium carbonate (64 mL) and isovaleroyl chloride (17 mL, 161 mmol), and the mixture was stirred at 0°C for 3 h. The reaction mixture was extracted three times with ether (150 mL) and the organic layer was washed with saturated aqueous sodium hydrogen carbonate, water, and saturated brine. The aqueous phase was saturated with sodium chloride and extracted with ethyl acetate (150 mL). The combined extracts were dried over sodium sulfate, filtered, and concentrated in vacuo to give the crude methyl *N*-isobutyrylglycinate **8** as a colorless oil (10.3 g), which was used directly in the next reaction.

The crude **8** was dissolved in acetonitrile (32.5 mL) at 20°C and di-*tert*-butyl dicarbonate (21.86 g, 100.2 mmol) followed by *N*,*N*-dimethylaminopyridine (807 mg, 6.6 mmol) was added. After stirring at 20°C for 6.5 h, the reaction mixture was condensed in vacuo and the residue was dissolved in ethyl acetate (300 mL). The organic layer was washed with potassium hydrogen sulfate (20 mL) and brine, then dried over sodium sulfate, filtered, and concentrated in vacuo to give the crude product (18.6 g) as a orange oil. Chromatographic purification (250 g, ethyl acetate–*n*-hexane = 1:6) gave the title compound **9** as a colorless oil (14.3 g, 69%); IR (neat): 1743, 1701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.19 (6H, d, $J = 7.0$ Hz), 1.50 (9H, s), 3.73 (3H, s), 3.74 (1H, septet, $J = 6.7$ Hz), 4.44 (2H, s). Anal. calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.56; H, 8.15; N, 6.01%.

4.5. Methyl 2-*tert*-butoxycarbonylamino-4-methyl-3-oxopentanoate 10

To a stirred solution of methyl *N*-*tert*-butoxycarbonyl-*N*-isobutyrylglycinate (433 mg, 1.7 mmol) in THF at −78°C under an argon atmosphere was added DMPU (0.40 mL, 3.3 mmol) followed by lithium hexamethyldisilazide (1 M solution in THF, 4.25 mL, 4.25 mmol) over 10 min. After stirring at −78°C for 1.5 h, the reaction mixture was quenched with saturated aqueous ammonium chloride (24 mL). The mixture was extracted three times with ethyl acetate (50 mL). The organic layer was washed with water and saturated brine, dried over sodium sulfate, filtered, and concentrated in vacuo to give the crude product as a yellow oil. Chromatographic purification (90 g, ethyl acetate–*n*-hexane = 1:4) of the residue gave the title compound **10** (414 mg, 96%) as colorless crystals; mp 43–45°C (ethyl acetate–*n*-hexane); IR (KBr): 3320, 1729, 1720, 1687, 1535 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.10 (3H, d, $J = 6.7$ Hz), 1.19 (3H, d. $J = 7.0$ Hz), 1.44 (9H, s), 3.03 (1H, septet, $J = 6.7$ Hz), 3.80 (3H, s), 5.19 (1H, d, $J = 7.6$ Hz), 5.69 (1H, br s). Anal. calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.50; H, 8.15; N, 5.37%.

4.6. Methyl (2*R*,3*S*)-2-benzoylamino-3-hydroxy-4-methylpentanoate (−)-11

$RuCl_2[(S)\text{-binap}](dmf)_n$ was prepared from $[RuCl_2(C_6H_6)]_2$ (72 mg, 0.144 mmol) and (*S*)-binap (189 mg, 0.302 mmol) according to the literature.[5] The resulting red–brown catalyst was dried in vacuo at 60°C for 1 h. A degassed solution of *N*-benzoyl β-keto-α-amino ester **7** (7.60 g, 28.9 mmol) in dichloromethane (6.0 mL) was added to the catalyst under an argon atmosphere. The mixture was hydrogenated at 50°C under hydrogen pressure (100 atm) for 64 h. The solvent was removed in vacuo and the residue was purified by column chromatography (350 g, ethyl acetate–*n*-hexane = 1:3 to 1:2) to give methyl (2*R*,3*S*)-2-benzoylamino-3-hydroxy-4-methylpentanoate **11** as a yellow–green oil (7.66 g, 100%). An analytically pure sample was obtained by further purification using column chromatography. HPLC analysis using a CHIRALCEL OD-H and hexane–^{i}PrOH (85:15, 0.5 mL/min) as an eluent indicated to be 99% e.e. (retention times: (2*R*,3*S*): 10.1 min; (2*S*,3*R*): 16.6 min); $[\alpha]_D^{24} = -27.8$ (*c* 0.85, $CHCl_3$); IR (neat): 3388, 1747, 1650, 1531 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (3H, d, $J = 6.8$ Hz), 1.03 (3H, d, $J = 6.6$ Hz), 1.76 (1H, m), 2.80 (1H, m), 3.75 (3H, s), 3.84 (1H, m), 5.04 (1H, dd, $J = 2.0$, 9.3 Hz), 7.14 (1H, m), 7.40 (2H, m), 7.50 (1H, m), 7.84 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9, 31.1, 52.5, 54.7, 77.4, 127.2, 128.5, 131.8, 133.6, 167.8, 172.2. HRMS (FAB) calcd for $C_{14}H_{20}NO_4$: 266.1392 (M^++1). Found: 266.1370.

4.7. Methyl (2*S*,3*R*)-2-benzoylamino-3-hydroxy-4-methylpentanoate (+)-11

Prepared according to the procedure described above for (−)-**11**. Yield 95% (e.e. = 98%); $[\alpha]_D^{24} = +27.2$ (*c* 0.92, $CHCl_3$); IR (neat): 3417, 2598, 1747, 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.01 (3H, d, $J = 6.8$ Hz), 1.05 (3H, d, $J = 6.6$ Hz), 1.79 (1H, m), 2.22 (1H, d, $J = 4.4$ Hz), 3.79 (3H, s), 3.85 (1H, ddd, $J = 1.7$, 4.4, 9.0 Hz), 5.05 (1H, dd, $J = 1.7$, 9.0 Hz), 6.86 (1H, d, $J = 9.0$ Hz), 7.43–7.47 (2H, m), 7.51–7.55 (1H, m), 7.83–7.86 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9, 31.1, 52.5, 54.7, 74.4, 127.2, 128.5, 131.8, 133.7, 167.8, 172.2. HRMS (FAB) calcd for $C_{14}H_{20}NO_4$: 266.1392 (M^++1). Found: 266.1404.

4.8. (4*R*,5*R*)-4-Methoxycarbonyl-5-(1-methylethyl)-2-phenyl-1,3-oxazoline (−)-13

A solution of the ester (−)-**11** (300 mg, 1.13 mmol) in THF (11.3 mL) was cooled to 0°C. Thionyl chloride (88 μL, 1.21 mmol) was added to the solution at 0°C. The reaction mixture was allowed to warm gradually to 25°C. After stirring for 12 h, the mixture was heated to 60°C for 2.5 h with stirring. The reaction mixture was cooled to 0°C and quenched by addition of saturated aqueous sodium hydrogen carbonate (14 mL). The aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic extracts were washed with water (20 mL) and saturated brine (20 mL), dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (25 g, ethyl acetate–*n*-hexane = 1:3) to give the oxazoline **13** as a colorless oil (241 mg, 86%); $[\alpha]_D^{24} = -97.5$ (*c* 0.90, $CHCl_3$); IR (neat): 2964, 1747, 1645, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (3H, d, $J = 6.6$ Hz), 1.06 (3H, d, $J = 6.6$ Hz), 2.09 (1H, m), 3.77 (3H, s), 4.54 (1H, dd, $J = 7.9$, 9.9 Hz), 4.95 (1H, d, $J = 9.9$ Hz), 7.42 (2H, m), 7.50 (1H, m), 8.00 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 19.6, 29.2, 52.1, 70.6, 87.6, 127.2, 128.3, 128.5, 131.8, 166.6, 170.5. HRMS (FAB) calcd for $C_{14}H_{18}NO_3$: 248.1287 (M^++1). Found: 248.1289.

4.9. (4*S*,5*S*)-4-Methoxycarbonyl-5-(1-methylethyl)-2-phenyl-1,3-oxazoline (+)-13

Prepared according to the procedure described above for (−)-**13**. Yield 68%; $[\alpha]_D^{24} = +94.9$ (*c* 1.25, $CHCl_3$); IR (neat): 2964, 1746, 1644, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.02 (3H, d, $J = 6.6$ Hz), 1.06 (3H, d, $J = 6.3$ Hz), 2.09 (1H, m), 3.77 (3H, s), 4.54 (1H, dd, $J = 7.8$, 9.8 Hz), 4.95 (1H, d, $J = 9.8$ Hz), 7.40–7.43 (2H, m), 7.48–7.52 (1H, m), 7.98–8.00 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.8, 19.6, 29.3, 52.1, 70.6, 87.6, 127.2, 128.3, 128.5, 131.8, 166.6, 170.5. HRMS (FAB) calcd for $C_{14}H_{18}NO_3$: 248.1287 (M^++1). Found: 248.1272.

4.10. (2*R*,3*R*)-3-Hydroxyleucine (−)-3

A mixture of the oxazoline (−)-**13** (167 mg, 0.629 mmol) in 6N hydrochloric acid (11.5 mL) was heated to reflux for 24 h. The resulting solution was cooled to 25°C and washed with ether (20 mL). The aqueous layer was concentrated in vacuo. The residue was purified by Dowex 50W-X4 ion-exchange resin (H^+ form) using 2N pyridine as an eluant to give (2*R*,3*R*)-3-hydroxyleucine **3** as colorless powder (79 mg, 85%); mp 224–228°C (MeOH) (lit.[3e] 225–228°C); $[\alpha]_D^{26} = -21.6$ (*c* 1.15, H_2O) (lit.[3e] $[\alpha]_D^{26} = -22.0$ (*c* 0.96, H_2O)); IR (KBr): 3437, 3080, 2961, 1626 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 0.82 (3H, d, $J = 6.6$ Hz), 0.83 (3H, d, $J = 6.6$ Hz), 1.75–1.84 (1H, m), 3.39 (1H, dd, $J = 3.1$, 9.2 Hz), 3.77 (1H, d, $J = 3.1$ Hz); ^{13}C NMR (100 MHz, D_2O): δ 18.6, 30.2, 57.1, 76.1, 171.8. HRMS (FAB, glycerol matrix) calcd for $C_6H_{14}NO_3$: 148.0974 (M^++1). Found: 148.0963. Anal. calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.90; N, 9.52. Found: C, 48.78; H, 8.87; N, 9.25%.

4.11. (2*S*,3*S*)-3-Hydroxyleucine (+)-3

Prepared according to the procedure described above for (−)-**3**. Yield 87%; mp 225–228°C (MeOH); $[\alpha]_D^{20} = +20.9$ (*c* 1.03, H_2O); IR (KBr): 3452, 3086, 1628, 1560 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 0.83 (3H, d, $J = 6.6$ Hz), 0.84 (3H, d, $J = 6.6$ Hz), 1.80 (1H, m), 3.40 (1H, dd, $J = 3.2$, 9.1 Hz), 3.78 (1H, d, $J = 3.1$ Hz); ^{13}C NMR (100 MHz, D_2O): δ 18.5, 18.6, 30.2, 57.1, 76.1, 171.8. HRMS (FAB, glycerol matrix) calcd for $C_6H_{14}NO_3$: 148.0974 (M^++1). Found: 148.0983. Anal. calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.90; N, 9.52. Found: C, 48.01; H, 9.00; N, 9.26%.

4.12. (2*R*,3*S*)-3-Hydroxyleucine (+)-12

A mixture of *N*-benzoyl-3-hydroxyleucine methyl ester (–)-**11** (100 mg, 1.131 mmol) in aqueous hydrochloric acid (6N, 6.9 mL) was heated under reflux for 50 h. The resulting solution was cooled to 25°C and washed with ether (10 mL). The aqueous layer was concentrated in vacuo. The residue was purified by Dowex 50W-X4 ion-exchange resin (H^+ form) using 2N pyridine as an eluant to give (2*R*,3*S*)-3-hydroxyleucine **12** as a colorless powder (47 mg, 85%): mp 202–205°C (MeOH) (lit.[3e] 213–214°C); $[\alpha]_D^{27}=+4.1$ (*c* 1.14, H_2O) (lit.[3e] $[\alpha]_D^{26}=+3.5$ (*c* 1, H_2O)); IR (KBr): 3316, 2961, 1637, 1509 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 0.78 (3H, d, $J=6.6$ Hz), 0.83 (3H, d, $J=6.4$ Hz), 1.53–1.62 (1H, m), 3.58 (1H, d, $J=8.4$ Hz), 3.65 (1H, s); ^{13}C NMR (100 MHz, D_2O): δ 17.4, 18.4, 30.2, 56.9, 75.1, 173.4. HRMS (FAB, glycerol matrix) calcd for $C_6H_{14}NO_3$: 148.0974 (M^++1). Found: 148.0986. Anal. calcd for $C_6H_{13}NO_3\cdot 6/5H_2O$: C, 42.69; H, 9.20; N, 8.30. Found: C, 42.98; H, 8.87; N, 8.23%.

4.13. (2*S*,3*R*)-3-Hydroxyleucine (–)-12

Prepared according to the procedure described above for (+)-**12**. Yield 84%; mp 203–206°C (MeOH) (lit.[3e] 213–214°C); $[\alpha]_D^{27}=-4.3$ (*c* 1.10, H_2O); IR (KBr): 3317, 2952, 1637, 1525 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 0.83 (3H, d, $J=6.6$ Hz), 0.88 (3H, d, $J=6.6$ Hz), 1.63 (1H, m), 3.63 (1H, dd, $J=3.9$, 7.8 Hz), 3.70 (1H, d, $J=3.9$ Hz); ^{13}C NMR (100 MHz, D_2O): δ 17.4, 18.4, 30.2, 56.9, 75.1, 173.4. HRMS (FAB, glycerol matrix) calcd for $C_6H_{14}NO_3$: 148.0974 (M^++1). Found: 148.0996. Anal. calcd for $C_6H_{13}NO_3\cdot H_2O$: C, 43.63; H, 9.15; N, 8.48. Found: C, 43.70; H, 9.21; N, 8.28%.

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