

A Short-Step Synthesis of (2*S*,3*R*)-3-Hydroxy-3-methylproline, a Component of Polyoxypeptins, Using a Tandem Michael–Aldol Reaction and Optical Resolution

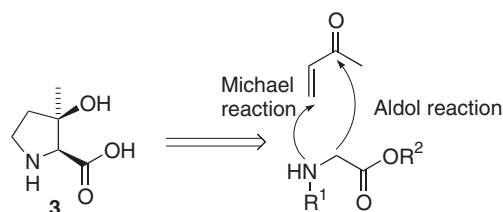
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A short-step synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline, a component of polyoxypeptins, using a tandem Michael–aldol reaction followed by its optical resolution using (–)-cinchonidine has been achieved.

Polyoxypeptins A (**1**) and B (**2**) are novel 19-membered cyclic hexadepsipeptides isolated from the culture broth of *Streptomyces* species by Umezawa and co-workers in 1998 (Fig. 1).¹ They are known to show strong anticancer activity through the induction of apoptosis against apoptosis-resistant human pancreatic adenocarcinoma AsPC-1 cells. In addition to their potent biological activities, the structural complexity containing a novel (2*S*,3*R*)-3-hydroxy-3-methylproline (**3**, HOMEPro) and other unusual amino acids have led several groups,² including ours,³ to investigate the total synthesis of polyoxypeptins and structurally related cyclodepsipeptides. We and others have already reported the stereoselective synthesis of HOMEPro.^{3c} However, these methods require multi steps and give low overall yields, and there is still need of a concise method for large-scale production of this unique component. Recently, we explored a concise synthetic route to racemic HOMEPro utilizing a tandem Michael–aldol reaction (Scheme 1).⁴ The reaction was originally reported by Terry in 1962^{5a} and subsequently Lash in 1991^{5b} as a part of pyrrole synthesis. However, no further investigation on the stereoselectivity and/or the transformation to optically active HOMEPro derivatives was made. Herein, we describe a short-step synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline from *N*-tosylglycine esters through optical resolution using (–)-cinchonidine.



Scheme 1.

Results and Discussion

Our synthetic plan for racemic HOMEPro is shown in Scheme 1. The key reaction is the diastereoselective construction of the multi-substituted pyrrolidine ring in a single step using a tandem Michael–aldol reaction between *N*-protected glycine ester and 3-buten-2-one. We first searched for this type of reaction under several conditions utilizing a phase-transfer catalyst or a combination of various Lewis acids and bases. All attempts failed, however, the reaction progressed in the presence of a base (Table 1). Thus, the reaction of *N*-tosylglycine ethyl ester and 3-buten-2-one using a catalytic amount of *t*-BuOK (0.2 eq) in *t*-BuOH–Et₂O afforded the Michael–aldol adducts as a diastereomeric mixture of 55:45 in 49% combined yield (entry 1). It is crucial to protect the amino group as a sulfonamide in this reaction (entry 2). To improve the chemical yield and diastereoselectivity, the effect of the ester group was examined. The use of *N*-tosylglycine *t*-butyl ester was effective in terms of yield (68%) but no diastereoselectivity was observed (entry 3). The introduction of a benzyl group to *N*-tosylglycine increased the product selectivity (**5c**:**6c** = 69:31) in good yield (entry 4). The treatment of **4c** with 1,8-diazabicyclo[5.4.0]undec-7-ene^{5b} (DBU, 1.0 equivalent) instead of *t*-BuOK provided the Michael–aldol adducts with some improvement in yield (82% yield, **5c**:**6c** = 69:31, entry 5). Furthermore, we observed that this reaction progressed with a catalytic amount of DBU (0.2 eq) with a similar yield (81%) and diastereoselectivity (**5c**:**6c** = 66:34, entry 6). We also investigated various solvents under conditions using DBU as a base. Besides THF, other solvents such as PhCH₃, DME, and 1,4-dioxane could be used for this reaction with similar results (en-

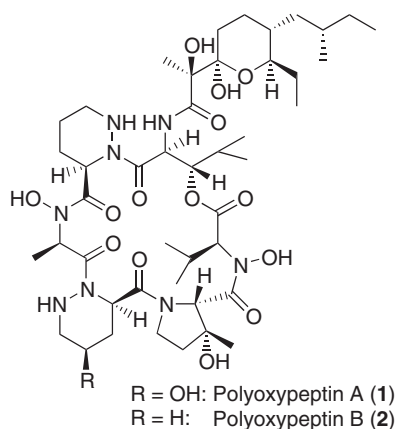


Fig. 1. Structure of polyoxypeptins.

Table 1. Diastereoselective Construction of Pyrrolidine Ring Using Tandem Michael–Aldol Reaction

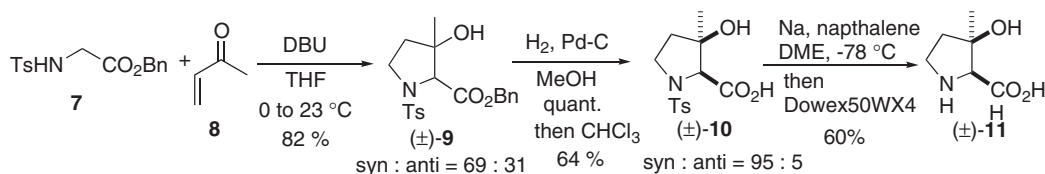
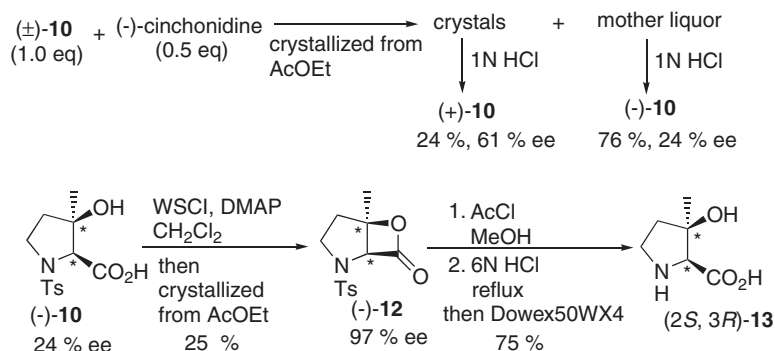
$R^1HN-CH_2-CO-OR^2 + CH_2=CH-C(=O)CH_3 \xrightarrow[\text{solvent, 0 to 23 } ^\circ C]{\text{base}}$

4a: R = Et **4b:** R = *t*-Bu
4c: R = Bn

5 syn **6** anti

Entry	R ¹	R ²	Base/eq	Solvent	Time/h	Yield/% ^{a)}	Ratio ^{b)} syn:anti
1	Ts	Et	<i>t</i> -BuOK (0.2)	<i>t</i> -BuOH–Et ₂ O	73	49	55:45
2	Boc	Et	<i>t</i> -BuOK (0.2)	<i>t</i> -BuOH–Et ₂ O	73	N.R. ^{c)}	—
3	Ts	<i>t</i> -Bu	<i>t</i> -BuOK (0.2)	<i>t</i> -BuOH–Et ₂ O	73	68	50:50
4	Ts	Bn	<i>t</i> -BuOK (0.2)	<i>t</i> -BuOH–THF	73	65	65:35
5	Ts	Bn	DBU (1.0)	THF	14	82	69:31
6	Ts	Bn	DBU (0.2)	THF	64	81	66:34
7	Ts	Bn	DBU (1.0)	CH ₂ Cl ₂	25	75	39:61
8	Ts	Bn	DBU (1.0)	DMF	14	81	43:57
9	Ts	Bn	DBU (1.0)	PhCH ₃	22	74	66:34
10	Ts	Bn	DBU (1.0)	DME	22	82	60:40
11	Ts	Bn	DBU (1.0)	1,4-dioxane	24	81	63:37

a) Yields of isolated products. b) Determined by ¹H NMR. c) No reaction.

Scheme 2. Synthesis of *rac*-(2*S*^{*},3*R*^{*})-3-hydroxy-3-methylproline.Scheme 3. Optical resolution of *rac*-(2*S*^{*},3*R*^{*})-3-hydroxy-3-methylproline.

tries 9–11). Interestingly, the use of CH₂Cl₂ or DMF gave the anti isomer **6c** as a major product (entries 7 and 8). With the Michael–aldol adducts in hand, we next examined the separation of their diastereomers and transformation to (2*S*^{*},3*R*^{*})-HOMePro (Scheme 2). After hydrogenolysis of the benzyl ester in quantitative yield, diastereomeric purification was achieved utilizing the difference in solubility in CHCl₃ between the syn and anti diastereomers. The syn isomer was more soluble in CHCl₃ than the anti isomer. Thus, after the mixture (syn:anti = 69:31) was suspended in CHCl₃ and heated to reflux, the insoluble solid was filtered off, and the filtrate was concentrated in vacuo to give the syn-rich mixture. This cycle was repeated five times to give the diastereomerically enriched (±)-**10** (syn:anti = 95:5) in 65% yield.

Deprotection of the tosyl group was attained by using sodium naphthalenide in DME. After treatment of the crude mixture with Dowex 50WX4 ion exchange resin (H⁺ form) eluted with 2 M aqueous pyridine, the eluant was concentrated, and the residue was recrystallized from H₂O to give (2*S*^{*},3*R*^{*})-HOMePro as diastereomerically pure crystals.

Having established the short-step synthesis of 3-hydroxy-3-methylproline as a racemic form, we next investigated the optical resolution using a chiral amine (Scheme 3). The resolution was carried out by dissolving 1 equivalent of racemic (±)-**10** and 0.5 equivalent of (–)-cinchonidine in various solvents with heating, followed by precipitating by cooling. It seemed that the crystallization solvents were critical for the formation of molecular crystals. In a solvent such as MeOH,

EtOH, Et₂O, THF, and acetone, no crystallization was observed. The solubility of (±)-**10** in CH₃CN, CHCl₃, CH₂Cl₂, *i*-PrOH, *n*-PrOH, and hexane was too poor to be used as the solvent for the recrystallization. After a survey of several solvents, we found that partial optical resolution occurred with the use of ethyl acetate. The solids crystallized from ethyl acetate were collected by filtration and treated with 1 M hydrochloric acid to liberate (+)-**10** ([α]_D²³ +52.9 (*c* 0.52, CHCl₃), 61% ee) in 24% yield. The mother liquor containing the desired (2*S*,3*R*)-stereoisomer was washed with 1 M hydrochloric acid and evaporated in vacuo to yield (−)-**10** ([α]_D −20.9 (*c* 1.1, CHCl₃), 24% ee) as solids in 76% yield. For further enantiomeric enrichment, (−)-**10** was converted to β-lactone **12**, which was recrystallized from ethyl acetate to give highly optically enriched (−)-**12** with 97% ee in 25% yield. Methanolysis of the β-lactone ring under acidic conditions and the subsequent deprotection of the *N*-tosyl group with 6 M hydrochloric acid furnished (2*S*,3*R*)-HOMEPro **13** as a *p*-toluenesulfonic acid salt. Purification of the crude salt with Dowex 50WX4 using 1 M aqueous pyridine as an eluant afforded pure (2*S*,3*R*)-**13** in 75% yield.

Conclusion

In conclusion, we have developed a concise method to construct the multi-substituted pyrrolidine ring in one step using a tandem Michael–aldol reaction catalyzed by DBU, and achieved a short-step synthesis of racemic (2*S**,3*R**)-3-hydroxy-3-methylproline. The enantiometrically pure (2*S*,3*R*)-3-hydroxy-3-methylproline was obtained by partial optical resolution using (−)-cinchonidine and enantiomeric enrichment by the recrystallization of its β-lactone derivative. Further studies directed towards the total synthesis of polyoxypeptins are in progress.

Experimental

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. HPLC analyses were performed using JASCO UV-970 and PU-980 high pressure liquid chromatograph with an optically active column. 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. 3-Buten-2-one, 1,8-diazabicyclo[5.4.0]undec-7-ene, potassium *tert*-butoxide, (−)-cinchonidine, 4-dimethylaminopyridine, acetyl chloride, and hydrochloric acid were purchased from Wako pure chemical industries, Ltd. 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (WSCl) was purchased from Kokusan Chemical, Ltd. *N*-Tosylglycine benzyl ester is commercially available from Sigma-Aldrich Chemical Company, Inc., or is easily prepared from glycine in 2 steps: a) TsCl, Na₂CO₃, Et₂O, H₂O, 122 h, 23 °C, 91%; b) BnOH, TsOH, PhH, reflux, 22 h, quant.

(2*S,3*R**)- and (2*R**,3*S**)-Benzyl 3-Hydroxy-3-methyl-1-(*p*-tolylsulfonyl)-pyrrolidine-2-carboxylates (±)-**9**.** To a stirred solution of Ts–Gly–OBn **7** (3.00 g, 9.39 mmol) and 3-buten-2-one (1.20 mL, 14.4 mmol) in THF (38 mL) at 23 °C was added drop-

wise DBU (1.40 mL, 9.38 mmol). After 14 h, the reaction was quenched with 1 M HCl, and the resulting mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, saturated aqueous NaHCO₃ solution and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by silica-gel chromatography (hexane:ethyl acetate = 1:1) to give the Michael–aldol adducts (±)-**9** (3.66 g, 7.70 mmol, syn:anti = 69:31, 82%) as a pale yellow oil. The analytical samples were obtained by purification using silica-gel chromatography (hexane:ethyl acetate = 20:1). Syn adduct: ¹H NMR (400 MHz, CDCl₃) δ 1.27 (3H, s, CH₃), 1.74 (1H, ddd, *J* = 12.5, 7.5, 6.8 Hz, CH₂), 2.08 (1H, ddd, *J* = 12.5, 7.3, 6.0 Hz, CH₂), 2.23 (1H, s, OH), 2.42 (3H, s, CH₃), 3.39 (1H, ddd, *J* = 9.9, 7.7, 6.0 Hz, CH₂), 3.56 (1H, ddd, *J* = 9.9, 7.3, 6.8 Hz, CH₂), 4.12 (1H, s, CH), 5.20 (2H, s, CH₂), 7.28 (2H, d, *J* = 8.6 Hz, Ar), 7.31–7.42 (5H, m, Ar), 7.74 (2H, dt, *J* = 8.4, 1.8 Hz, Ar); ¹³C NMR (100 MHz, CDCl₃) δ 21.6, 26.4, 38.9, 46.2, 67.3, 69.1, 79.0, 127.5, 128.3, 128.4, 128.6, 129.7, 135.0, 135.3, 143.8, 169.8; IR (neat, cm^{−1}) 3497, 3063, 3033, 2976, 2893, 1744, 1598, 1496, 1454, 1385, 1344, 1158, 1094; HRMS (FAB); calcd for C₂₀H₂₄NO₅S (M + H) 390.1375, found 390.1360. Anti adduct: ¹H NMR (400 MHz, CDCl₃) δ 1.17 (3H, s, CH₃), 1.76 (1H, s, OH), 1.82 (1H, dd, *J* = 13.0, 6.6 Hz, CH₂), 2.07 (1H, ddd, *J* = 12.8, 10.6, 8.6 Hz, CH₂), 2.40 (3H, s, CH₃), 3.41 (1H, ddd, *J* = 10.6, 8.8, 6.6 Hz, CH₂), 3.62 (1H, dt, *J* = 8.8, 1.6 Hz, CH₂), 4.11 (1H, s, CH), 5.12 (1H, d, *J* = 12.3 Hz, CH₂), 5.17 (1H, d, *J* = 12.3 Hz, CH₂), 7.27 (2H, d, *J* = 8.1 Hz, Ar), 7.32–7.40 (5H, m, Ar), 7.72 (2H, dt, *J* = 8.2, 1.8 Hz, Ar); ¹³C NMR (100 MHz, CDCl₃) δ 21.5, 22.9, 38.2, 46.4, 67.2, 71.6, 79.9, 127.5, 128.5, 128.5, 128.6, 129.6, 134.7, 135.1, 143.6, 170.1; IR (neat, cm^{−1}) 3499, 3064, 3033, 2979, 2890, 1742, 1598, 1496, 1455, 1384, 1337, 1261, 1163, 1095; HRMS (FAB); calcd for C₂₀H₂₄NO₅S (M + H) 390.1375, found 390.1344.

(2*S,3*R**)-3-Hydroxy-3-methyl-1-(*p*-tolylsulfonyl)-pyrrolidine-2-carboxylic Acids (±)-**10**.** A mixture of the Michael–aldol adducts (3.66 g, 9.39 mmol, syn:anti = 69:31) and 5% Pd/C (360 mg) in MeOH (38 mL) was stirred under a hydrogen atmosphere (1 atm) at 23 °C for 14 h. The reaction mixture was filtered and concentrated in vacuo to give the carboxylic acid (**10**, 2.81 g, 9.39 mmol, quant.) as a pale yellow solid. After the crude carboxylic acid was suspended in CHCl₃ and heated to reflux, the insoluble solid (anti product) was filtered off. The filtrate was concentrated in vacuo to give the syn-rich mixture. This cycle was repeated five times to give the syn product (±)-**10** (1.80 g, 6.01 mmol, 64%, syn:anti = 95:5). Syn product: Mp 95–96 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.29 (3H, s, CH₃), 1.58 (1H, dt, *J* = 12.6, 7.7 Hz, CH₂), 2.06 (1H, ddd, *J* = 12.6, 6.8, 5.3 Hz, CH₂), 2.23 (1H, s, OH), 2.44 (3H, s, CH₃), 3.38 (1H, ddd, *J* = 10.4, 7.7, 5.1 Hz, CH₂), 3.64 (1H, dt, *J* = 10.4, 7.1 Hz, CH₂), 4.01 (1H, s, CH), 7.35 (2H, d, *J* = 8.1 Hz, Ar), 7.74 (2H, dt, *J* = 8.2, 2.0 Hz, Ar); ¹³C NMR (100 MHz, CDCl₃) δ 21.6, 26.1, 38.9, 46.8, 69.4, 79.5, 127.6, 129.9, 134.0, 144.3, 172.7; IR (neat, cm^{−1}) 3437, 3355, 2981, 2875, 2648, 2550, 1694, 1419, 1387, 1343, 1281, 1246, 1207, 1159; HRMS (FAB); calcd for C₁₃H₁₈NO₅S (M + H), 300.0906, found 300.0876. Anti product: Mp 195–196 °C (dec); ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.17 (3H, s, CH₃), 1.71 (1H, dd, *J* = 12.3, 6.0 Hz, CH₂), 1.88 (1H, dt, *J* = 12.1, 8.2 Hz, CH₂), 2.39 (3H, s, CH₃), 3.16 (1H, ddd, *J* = 11.0, 8.2, 6.4 Hz, CH₂), 3.42 (1H, t, *J* = 8.1 Hz, CH₂), 3.79 (1H, s, CH), 4.98 (1H, s, OH), 7.40 (2H, d, *J* = 8.4 Hz, Ar), 7.66 (2H, d, *J* = 8.2 Hz, Ar), 12.78 (1H, bs, OH); ¹³C NMR

(100 MHz, DMSO-*d*₆) δ 19.9, 22.1, 36.7, 45.4, 70.6, 77.0, 126.1, 128.5, 133.5, 142.0, 170.8; IR (neat, cm⁻¹) 3478, 3063, 2978, 2936, 2892, 2651, 2562, 1714, 1462, 1434, 1377, 1326, 1270, 1149, 1093; HRMS (FAB); calcd for C₁₃H₁₈NO₅S (M + H), 300.0906, found 300.0886.

(2*S,3*R**)-3-Hydroxy-3-methylprolines (±)-11.** To a dark green solution of Na (321 mg, 14.0 mmol) and naphthalene (2.86 g, 22.3 mmol) in DME (14 mL) at -78 °C was added dropwise a solution of *N*-tosylamide (±)-10 (1.09 g, 2.79 mmol) in DME (6.0 mL). After 15 min, the reaction was quenched with H₂O, and the resulting mixture was extracted with H₂O. After the combined aqueous extracts were neutralized with conc. HCl, the mixture was charged on Dowex 50WX4 resin (H⁺ form) and eluted with 1 M aqueous pyridine to afford brown-white solids (±)-11 (366 mg, 2.73 mmol, 98%). The solids could be further purified by recrystallization from H₂O to give colorless crystals (243 mg, 60%, 1.67 mmol). Mp 271 °C (dec); ¹H NMR (400 MHz, D₂O, 40 °C) δ 1.60 (s, 3H, CH₃), 2.12–2.17 (2H, m, CH₂), 3.45 (1H, ddd, *J* = 11.0, 7.1, 4.7 Hz, CH₂N), 3.55 (1H, dt, *J* = 11.7, 8.8 Hz, CH₂N), 3.85 (1H, s, CH); ¹³C NMR (100 MHz, D₂O, 60 °C) δ 24.3, 39.8, 43.8, 70.2, 78.8, 171.1; IR (KBr, cm⁻¹) 3225, 3117, 2935, 2701, 2632, 2563, 1641, 1464, 1412; Anal. Calcd for C₆H₁₁NO₃: C, 49.65; H, 7.64; N, 9.65%. Found: C, 49.44; H, 7.69; N, 9.54%.

(2*R*,3*S*)- and (2*S*,3*R*)-3-Hydroxy-3-methyl-1-(*p*-tolylsulfonyl)-pyrrolidine-2-carboxylic Acids (+)-10 and (-)-10. A mixture of racemic carboxylic acid (±)-10 (3.99 g, 13.3 mmol) and (-)-cinchonidine (1.96 g, 6.66 mmol) was dissolved in ethyl acetate (66.6 mL) with heating. After the clear solution was left for 12 h at 23 °C, colorless solids were precipitated. The solids were collected by filtration and treated with 1 M HCl to liberate (+)-(2*R*,3*S*)-10 ([α]_D²³ +52.9 (*c* 0.52, CHCl₃), 61% ee) as colorless solids. The filtrate was washed with 1 M HCl and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to give (-)-(2*S*,3*R*)-10 (3.03 g, 10.1 mmol, 76%, 24% ee) as colorless solids, which were used for the next reaction without further purification. The enantiomeric excess was determined by chiral HPLC analysis after transformation to the β -lactone 12.

(1*S*,5*R*)-(5-Methyl-2-(*p*-tolylsulfonyl)-6-oxa-2-aza-bicyclo-[3.2.0]heptan-7-one (-)-12. To a stirred solution of (-)-(2*S*,3*R*)-10 (2.96 g, 9.88 mmol) in CH₂Cl₂ (50 mL) at 0 °C was added WSCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) (2.08 g, 10.9 mmol) and DMAP (4-dimethylaminopyridine) (302 mg, 2.47 mmol). After stirring the mixture for 17 h at 23 °C, the reaction was quenched with 10% citric acid and extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous NaHCO₃ solution and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by silica-gel chromatography (hexane:ethyl acetate = 1:1) to give β -lactone as a colorless solid, which was recrystallized from ethyl acetate four times to give (-)-12 (700 mg, 2.47 mmol, 25%, 97% ee) as a colorless solid. [α]_D²⁴ -128 (*c* 0.13, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.68 (3H, s, CH₃), 1.83 (1H, dt, *J* = 14.2, 11.5, 8.1 Hz, CH₂), 2.22 (1H, dd, *J* = 14.4, 5.9 Hz, CH₂), 2.44 (3H, s, CH₃), 3.15 (1H, dt, *J* = 11.5, 5.9 Hz, CH), 4.00 (1H, dd, *J* = 11.2, 7.6 Hz, CH), 5.08 (1H, s, CH₃), 7.34 (2H, d, *J* = 8.1 Hz, Ar), 7.79 (2H, d, *J* = 8.3 Hz, Ar); ¹³C NMR (100 MHz, CDCl₃) δ 20.6, 21.6, 35.1, 46.7, 73.5, 87.3, 127.9, 130.0, 134.7, 144.5, 164.5; IR (neat, cm⁻¹) 3093, 3063, 2983, 2938, 1832, 1595, 1479, 1455, 1390, 1354, 1264; HRMS (FAB); calcd for C₁₃H₁₇NO₄S (M + H) 282.0800, found 282.0788. HPLC analysis: Daicel Chiralpac AD, flow 1.0

mL/min, hexane/*i*-PrOH = 65:35, retention times 10.1 min for (1*S*,5*R*)-(-)-12, 12.9 min for (1*R*,5*S*)-(+)-12.

(2*S*,3*R*)-3-Hydroxy-3-methylproline 13. To a stirred solution of (-)-12 (2.08 g, 7.39 mmol) in MeOH (37 mL) at 23 °C was added dropwise acetyl chloride (52.5 μ L, 0.739 mmol). After 21 h, the reaction mixture was concentrated in vacuo. The residue was purified by silica-gel chromatography (hexane:ethyl acetate = 3:2) to give the methyl ester (2.03 g, 7.31 mmol, 99%) as a colorless solid. Mp 134–135 °C; [α]_D²⁴ -52.5 (*c* 0.61, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.25 (3H, s, CH₃), 1.71 (1H, dt, *J* = 12.4, 6.8 Hz, CH₂), 2.10 (1H, dt, *J* = 12.4, 6.8 Hz, CH₂), 2.43 (3H, s, CH₃), 2.71 (1H, bs, OH), 3.35 (1H, dt, *J* = 11.2, 7.2 Hz, CH), 3.59 (1H, dt, *J* = 9.6, 8.8 Hz, CH), 3.74 (3H, s, CH₃), 4.03 (1H, s, CH), 7.33 (2H, d, *J* = 8.0 Hz, Ar), 7.74 (2H, d, *J* = 8.0 Hz, Ar); ¹³C NMR (100 MHz, CDCl₃) δ 21.5, 26.2, 38.7, 46.2, 52.3, 69.1, 78.7, 127.4, 129.6, 134.7, 143.8, 170.4; IR (neat, cm⁻¹) 3500, 2976, 2954, 2898, 1745, 1598, 1439, 1342, 1158, 1093; HRMS (FAB); calcd for C₁₄H₂₀NO₅S (M + H) 314.0984, found 314.1043.

A stirred mixture of the methyl ester (2.25 g, 7.18 mmol) in 6 M HCl (35 mL) was heated to reflux for 48 h. After cooling, the reaction mixture was concentrated in vacuo. The residue was charged on Dowex 50WX4 resin (H⁺ form) and eluted with 1 M aqueous pyridine to give pure 13 (782 mg, 5.39 mmol, 75%) as a colorless solid after evaporation. [α]_D²⁵ -42.3 (*c* 1.1, H₂O). The spectral data were identical with our previous reported values.^{3e}

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