

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.[3e] 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.

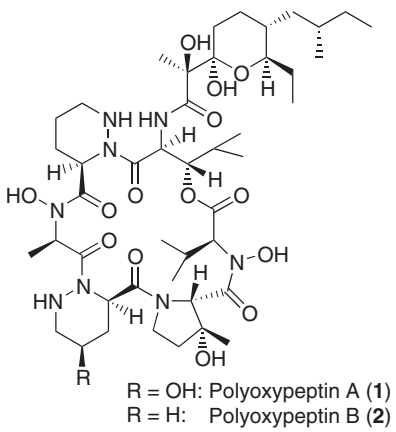
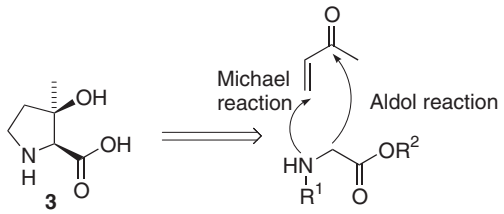


Fig. 1. Structure of polyoxypeptins.



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–Et_2O 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 $PhCH_3$, DME, and 1,4-dioxane could be used for this reaction with similar results (en-

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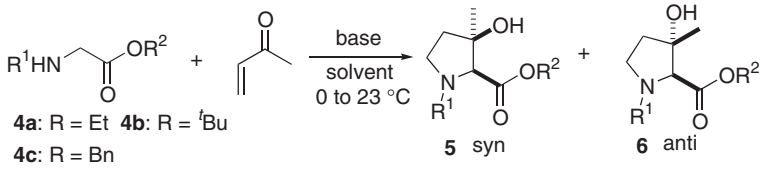
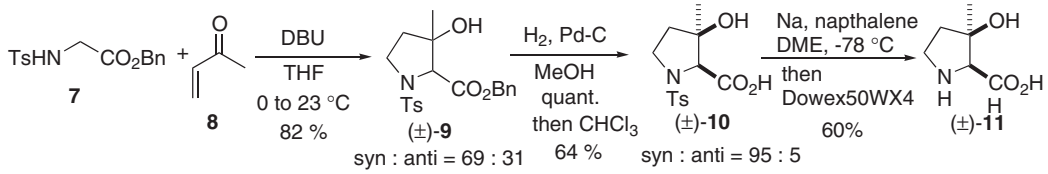
Table 1. Diastereoselective Construction of Pyrrolidine Ring Using Tandem Michael–Aldol Reaction

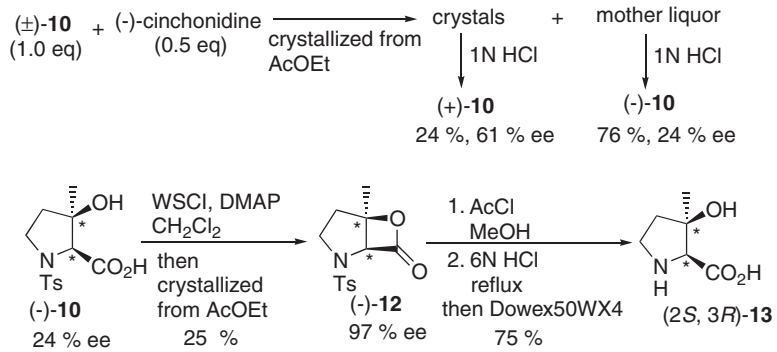


Entry	R^1	R^2	Base/eq	Solvent	Time/h	Yield/%[a]	Ratio[b] syn:anti
1	Ts	Et	*t*-BuOK (0.2)	*t*-BuOH–Et_2O	73	49	55:45
2	Boc	Et	*t*-BuOK (0.2)	*t*-BuOH–Et_2O	73	N.R.[c]	—
3	Ts	*t*-Bu	*t*-BuOK (0.2)	*t*-BuOH–Et_2O	73	68	50:50
4	Ts	Bn	*t*-BuOK (0.2)	*t*-BuOH–THF	73	65	65:35
5	Ts	Bn	DBU (1.0)	THF	14	82	69:31
6	Ts	Bn	DBU (0.2)	THF	64	81	66:34
7	Ts	Bn	DBU (1.0)	CH_2Cl_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 ^{1}H 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 CH_2Cl_2 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, diastereomerical purification was achieved utilizing the difference in solubility in $CHCl_3$ between the syn and anti diastereomers. The syn isomer was more soluble in $CHCl_3$ than the anti isomer. Thus, after the mixture (syn:anti = 69:31) was suspended in $CHCl_3$ 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 napthalenide 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 H_2O 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, Et_2O, THF, and acetone, no crystallization was observed. The solubility of (±)-**10** in CH_3CN, $CHCl_3$, CH_2Cl_2, *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** ($[\alpha]_D^{23}$ +52.9 (*c* 0.52, $CHCl_3$), 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** ($[\alpha]_D$ −20.9 (*c* 1.1, $CHCl_3$), 24% ee) as solids in 76% yield. For further enantiomerical 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 enantiometically pure (2*S*,3*R*)-3-hydroxy-3-methylproline was obtained by partial optical resolution using (−)-cinchonidine and enantiomerical 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 (WSCI) 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, Na_2CO_3, Et_2O, H_2O, 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 dropwise 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 $NaHCO_3$ solution and brine, dried over Na_2SO_4, 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: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, s, CH_3), 1.74 (1H, ddd, *J* = 12.5, 7.5, 6.8 Hz, CH_2), 2.08 (1H, ddd, *J* = 12.5, 7.3, 6.0 Hz, CH_2), 2.23 (1H, s, OH), 2.42 (3H, s, CH_3), 3.39 (1H, ddd, *J* = 9.9, 7.7, 6.0 Hz, CH_2), 3.56 (1H, ddd, *J* = 9.9, 7.3, 6.8 Hz, CH_2), 4.12 (1H, s, CH), 5.20 (2H, s, CH_2), 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{20}H_{24}NO_5S$ (M + H) 390.1375, found 390.1360. Anti adduct: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (3H, s, CH_3), 1.76 (1H, s, OH), 1.82 (1H, dd, *J* = 13.0, 6.6 Hz, CH_2), 2.07 (1H, ddd, *J* = 12.8, 10.6, 8.6 Hz, CH_2), 2.40 (3H, s, CH_3), 3.41 (1H, ddd, *J* = 10.6, 8.8, 6.6 Hz, CH_2), 3.62 (1H, dt, *J* = 8.8, 1.6 Hz, CH_2), 4.11 (1H, s, CH), 5.12 (1H, d, *J* = 12.3 Hz, CH_2), 5.17 (1H, d, *J* = 12.3 Hz, CH_2), 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{20}H_{24}NO_5S$ (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 $CHCl_3$ 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (3H, s, CH_3), 1.58 (1H, dt, *J* = 12.6, 7.7 Hz, CH_2), 2.06 (1H, ddd, *J* = 12.6, 6.8, 5.3 Hz, CH_2), 2.23 (1H, s, OH), 2.44 (3H, s, CH_3), 3.38 (1H, ddd, *J* = 10.4, 7.7, 5.1 Hz, CH_2), 3.64 (1H, dt, *J* = 10.4, 7.1 Hz, CH_2), 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{13}H_{18}NO_5S$ (M + H), 300.0906, found 300.0876. Anti product: Mp 195–196 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.17 (3H, s, CH_3), 1.71 (1H, dd, *J* = 12.3, 6.0 Hz, CH_2), 1.88 (1H, dt, *J* = 12.1, 8.2 Hz, CH_2), 2.39 (3H, s, CH_3), 3.16 (1H, ddd, *J* = 11.0, 8.2, 6.4 Hz, CH_2), 3.42 (1H, t, *J* = 8.1 Hz, CH_2), 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); ^{13}C 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 $C_{13}H_{18}NO_5S$ (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 napthalene (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 H_2O, and the resulting mixture was extracted with H_2O. 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 H_2O to give colorless crystals (243 mg, 60%, 1.67 mmol). Mp 271 °C (dec); ^{1}H NMR (400 MHz, D_2O, 40 °C) δ 1.60 (s, 3H, CH_3), 2.12–2.17 (2H, m, CH_2), 3.45 (1H, ddd, J = 11.0, 7.1, 4.7 Hz, CH_2N), 3.55 (1H, dt, J = 11.7, 8.8 Hz, CH_2N), 3.85 (1H, s, CH); ^{13}C NMR (100 MHz, D_2O, 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 $C_6H_{11}NO_3$: 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** ($[\alpha]_D^{23}$ +52.9 (*c* 0.52, $CHCl_3$), 61% ee) as colorless solids. The filtrate was washed with 1 M HCl and brine, dried over Na_2SO_4, 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 CH_2Cl_2 (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 $NaHCO_3$ solution and brine, dried over Na_2SO_4, 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. $[\alpha]_D^{24}$ −128 (*c* 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68 (3H, s, CH_3), 1.83 (1H, dt, J = 14.2, 11.5, 8.1 Hz, CH_2), 2.22 (1H, dd, J = 14.4, 5.9 Hz, CH_2), 2.44 (3H, s, CH_3), 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, CH_3), 7.34 (2H, d, J = 8.1 Hz, Ar), 7.79 (2H, d, J = 8.3 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{13}H_{17}NO_4S$ (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 μL, 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; $[\alpha]_D^{24}$ −52.5 (*c* 0.61, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, s, CH_3), 1.71 (1H, dt, J = 12.4, 6.8 Hz, CH_2), 2.10 (1H, dt, J = 12.4, 6.8 Hz, CH_2), 2.43 (3H, s, CH_3), 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, CH_3), 4.03 (1H, s, CH), 7.33 (2H, d, J = 8.0 Hz, Ar), 7.74 (2H, d, J = 8.0 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{14}H_{20}NO_5S$ (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. $[\alpha]_D^{25}$ −42.3 (*c* 1.1, H_2O). The spectral data were identical with our previous reported values.[3e]

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References

1 a) K. Umezawa, K. Nakazawa, T. Uemura, Y. Ikeda, S. Kondo, H. Naganawa, N. Kinoshita, H. Hashizume, M. Hamada, T. Takeuchi, and S. Ohba, *Tetrahedron Lett.*, **39**, 1389 (1998). b) K. Umezawa, K. Nakazawa, Y. Ikeda, H. Naganawa, and S. Kondo, *J. Org. Chem.*, **64**, 3034 (1999).

2 a) Y. Noguchi, T. Yamada, H. Uchiro, and S. Kobayashi, *Tetrahedron Lett.*, **41**, 7499 (2000). b) Y. Noguchi, H. Uchihiro, T. Yamada, and S. Kobayashi, *Tetrahedron Lett.*, **42**, 5253 (2001). c) M. Lorca and M. Kurosu, *Tetrahedron Lett.*, **42**, 2431 (2001). d) D.-G. Qin, H.-Y. Zha, and Z.-J. Yao, *J. Org. Chem.*, **67**, 1038 (2002). e) D.-G. Qin and Z.-J. Yao, *Tetrahedron Lett.*, **44**, 571 (2003). f) Y. Aoyagi, Y. Saitoh, T. Ueno, M. Horiguchi, K. Takeya, and R. M. Williams, *J. Org. Chem.*, **68**, 6899 (2003). g) J.-W. Shen, D.-G. Qin, H.-W. Zhang, and Z.-J. Yao, *J. Org. Chem.*, **68**, 7479 (2003).

3 a) N. Okamoto, O. Hara, K. Makino, and Y. Hamada, *Tetrahedron: Asymmetry*, **12**, 1353 (2001). b) K. Makino, N. Okamoto, O. Hara, and Y. Hamada, *Tetrahedron: Asymmetry*, **12**, 1757 (2001). c) K. Makino, Y. Henmi, and Y. Hamada, *Synlett*, **2002**, 613. d) N. Okamoto, O. Hara, K. Makino, and Y. Hamada, *J. Org. Chem.*, **67**, 9210 (2002). e) K. Makino, A. Kondoh, and Y. Hamada, *Tetrahedron Lett.*, **43**, 4695 (2002). f) K. Makino, T. Suzuki, S. Awane, O. Hara, and Y. Hamada, *Tetrahedron Lett.*, **43**, 9391 (2002).

4 For excellent reviews of tandem reactions and Michael–

aldol reactions, see: a) L. F. Tietze, *Chem. Rev.*, **96**, 115 (1996). b) K. Takasu, *Yakugaku Zasshi*, **121**, 887 (2001).

5 a) W. G. Terry, A. H. Jackson, G. W. Kenner, and G. Komis, *J. Chem. Soc.*, **1965**, 4389. b) T. D. Lash and M. C. Hoehner, *J. Heterocycl. Chem.*, **28**, 1671 (1991).