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# Studies on the Synthesis of (2*S*,3*R*)-3-Hydroxy-3-methylproline via $C_2-N$ Bond Formation

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A new efficient synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline (**3**) is reported. During the course of a recent study on the Lewis acid promoted intramolecular opening of an epoxide by a carbamate NH, a highly concerted rearrangement was unexpectedly observed. Further investigations of substrate generality show that δ-carbamate-α,β-epoxide esters commonly underwent similar rearrangements with the aid of Lewis acids. Retrosynthetic analysis of such a $C_2-N$ disconnection can lead to an efficient synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline (**3**) in high enantio purity. Stereochemistries were established by a Sharpless asymmetric dihydroxylation and a diastereoselective reductive amination.

## Introduction

The discovery of new and diverse natural products of potential clinical utility remains an important area of organic chemistry today. For example, during the past 50 years, more than 50% of anticancer drugs on the market were directly or indirectly developed from natural products.[1] Polyoxypeptins A (**1**) and B (**2**) are two recent examples that were isolated from *Streptomyces* culture broth by Umezawa and co-workers[2] in 1998 (Figure 1). Both compounds were believed to be potent inducers of apoptosis in apoptosis-resistant human pancreatic carcinoma adenocarcinoma AsPC-1 cells.[3] Structurally, polyoxypeptins present a variety of unique structural features, including six unusual amino acids in high oxidation states and one complex acyl side chain with five stereogenic centers. These structural complexities have drawn significant attention from the synthetic organic community. Related to this have been efforts focused on elegant syntheses of unusual amino acids, including (2*S*,3*R*)-3-hydroxy-3-methylproline (3-OH MePro, **3**). To date, three synthetic routes have been established toward this novel amino acid via different strategies. Kobayashi[4] and Hamada[5] achieved syntheses using palladium-catalyzed intramolecular *N*-allylation of alkenyloxirane and $SmI_2$-mediated diastereoselective cyclization reaction, respectively. Our own previous synthesis was carried out using a Sharpless asymmetric dihydroxylation, followed by a regioselective opening of a cyclic sulfate by sodium azide.[6]

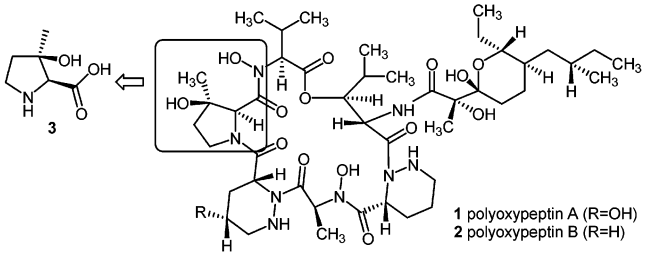


**FIGURE 1.** Structures of polyoxypeptins (**1** and **2**) and 3-OH MePro (**3**).

To meet material requirements for our study on total synthesis of polyoxypetins,[7] development of a more practical and scalable synthesis of **3** was desired. This prompted us to improve our original route[6] so as to make it more synthetically practical and economically usable. From a retrosynthetic perspective, the disconnection of the $C_2-N$ or $C_5-N$ bond of the pyrrolidine ring of **3** would lead to two different starting materials (Figure 2). Comparison with our previous report[6] (via $C_5-N$ disconnection) shows that the $C_2-N$ disconnection presents at least two pertinent points. One is that β-alanine and/or 3-amino-1-propanol starting materials are much less expensive than butan-4-yl-1-ol (which was used for the

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(2) (a) Umezawa, K.; Nakazawa, K.; Uemura, T.; Ikeda, Y.; Kondo, S.; Naganawa, H.; Kinoshita, N.; Hashizume, H.; Hamada, M.; Takeuchi, T.; Ohba, S. *Tetrahedron Lett.* **1998**, *39*, 1389−1392. (b) Umezawa, K.; Nakazawa, K.; Ikeda, Y.; Naganawa, H.; Kando, S. *J. Org. Chem.* **1999**, *64*, 3034−3038.

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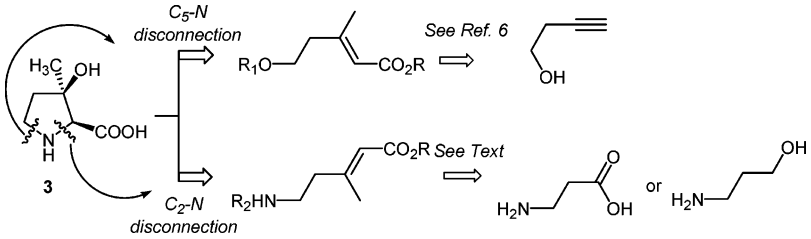
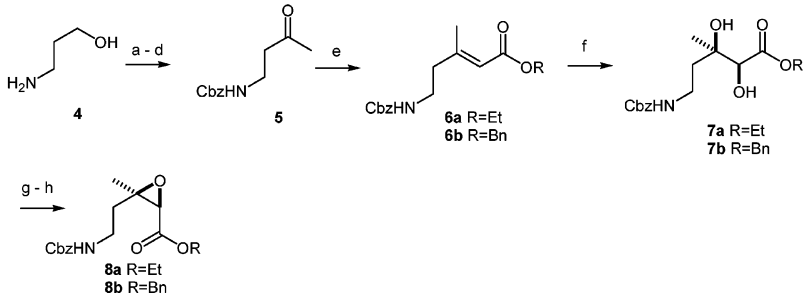



**FIGURE 2.** Analysis of disconnection of C−N bonds of pyrrolidine.

**SCHEME 1** [a]



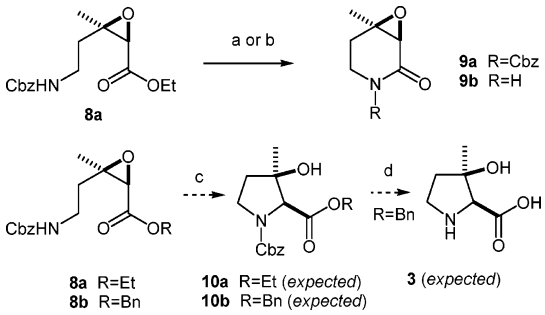

[a] Reagents and conditions: (a) CbzCl, $Na_2CO_3$, $H_2O$, 92%. (b) $(COCl)_2$, DMSO, $CH_2Cl_2$, −60 °C, 83%. (c) $CH_3MgI$, THF, −78 °C, 77%. (d) $(COCl)_2$, DMSO, $CH_2Cl_2$, −60 °C, 85%. (e) **6a**: $(EtO)_2P(O)(CH_2COOEt)$, NaH, THF, 0 °C to reflux, 88%. **6b**: $(EtO)_2P(O)(CH_2COOBn)$, NaH, DMF, 0 °C to rt, 80%. (f) AD-mix-*β*, $CH_3SO_2NH_2$, *t*-BuOH−$H_2O$, 0 °C. **7a**: 94% yield, 98% ee by HPLC. **7b**: 80% yield. (g) $Et_3N$, TsCl, $CH_2Cl_2$, 83%. (h) **8a**: $K_2CO_3$, EtOH, 90%. **8b**: $Et_3N$, TsCl, $CH_2Cl_2$, then DBU, 90% from **7b**, 95% ee by HPLC.

route via a $C_5$−N disconnection[6]) and are commercially available in larger quantities. A second point is that the preexisting nitrogen unit of *β*-alanine or 3-amino-1-propanol reduces steps needed to introduce nitrogen functionality in later stages of the synthesis. This could potentially save time and raise the overall yield. Herein we report our study on the above-mentioned $C_2$−N disconnection. Unexpectedly a concerted rearrangement was found during the course of our efforts that furnished the desired pyrrolidine ring by a Lewis acid promoted intramolecular expoxide opening reaction.

**Synthesis of (2*S*,3*R*)-3-Hydroxy-3-methylproline.** Synthesis started from inexpensive commercially available 3-amino-1-propanol (**4**). Protection of the free amine with CbzCl followed by Swern oxidation of the alcohol and treatment of the resultant aldehyde with methylmagnesium iodide at −78 °C gave the ketone **5** in 50% overall yield in four steps after oxidation of the newly afforded alcohol (Scheme 1). Wittig−Horner reaction of **5** with triethyl phosphonoacetate in the presence of NaH gave the (*E*)-olefin **6a**. Sharpless asymmetric dihydroxylation[8] of trisubstituted olefin **6a** yielded the diol **7a** with the desired stereochemistry (94% yield, 98% ee by HPLC). Selective tosylation of the α-hydroxyl followed by treatment with $K_2CO_3$ resulted in the key precursor, epoxide **8a**.

With **8a** in hand, two routes to the pyrrolidine ring were possible. Owing to the weak acidity of the carbamate NH, basic conditions were initially tried to open the epoxide intramolecularly (Scheme 2). However, the lactimide **9a** was generated under strong basic conditions (NaH, etc.). On the other hand, using weakly basic conditions ($K_2CO_3$, $Et_3N$), no reaction was observed. To enhance the nucleophilicity of nitrogen, the *N*-Cbz protection was removed. Unfortunately, direct hydrogenolysis of **8a** quickly produced the lactam **9b**. With these disappointing results obtained under basic conditions, Lewis acid promoted cyclization reactions were examined next. Similar methods are frequently used for the preparation of THF-containing derivatives.[9] Initially, a mild Lewis acid, $Yb(OTf)_3$, was utilized as a promoter; however, the reaction was quite slow even when 1 equiv of $Yb(OTf)_3$ was used, Using $BF_3{\cdot}Et_2O$ instead, the reaction of **8a** was carried out quickly in dichloromethane at −78 °C, providing a single TLC spot that corresponded to the expected product **10a**. However, subsequent attempts to hydrolyze the ethyl ester of **10a** gave a surprisingly complex mixture. To obtain the acid **3** more clearly, benzyl ester **8b** was employed (Scheme 1). Treatment of **8b** with $BF_3{\cdot}Et_2O$ in dichloromethane at −78 °C resulted

**SCHEME 2** [a]




[a] Reagents and conditions: (a) NaH, DMF or THF. (b) $H_2$, 10% Pd−C, MeOH. (c) $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, −78°C to rt, 80% for **10a** (expected) and 70% for **10b** (expected). (d) $H_2$, 10% Pd−C, MeOH, 95% for **3** (expected).

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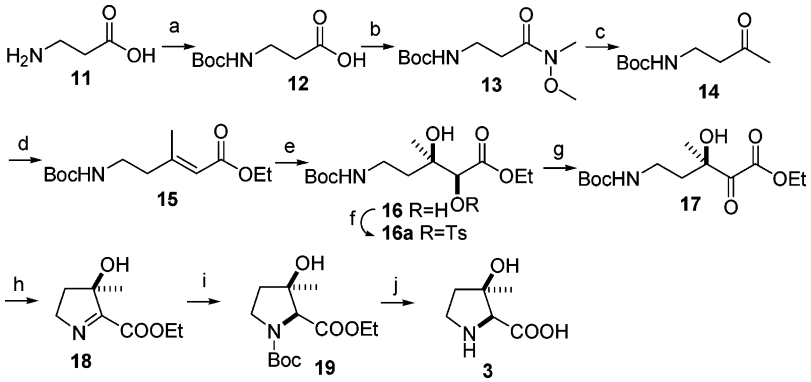
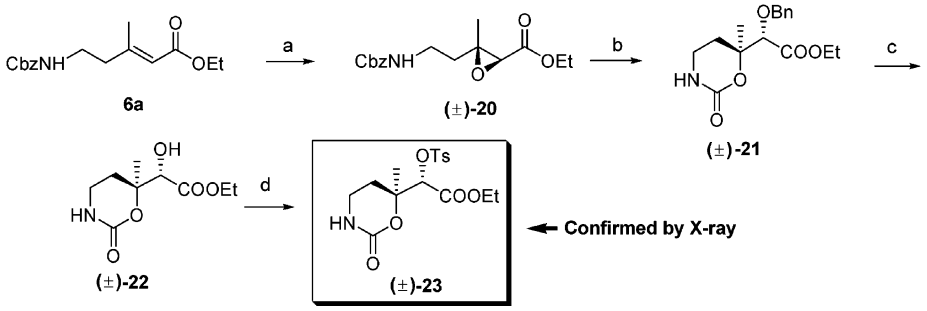
(9) (a) Sivakumar, M.; Borhan, B. *Tetrahedron Lett.* **2003**, *44*, 5547. (b) Hatakeyama, S.; Sakurai, K.; Numata, H.; Ochi, N.; Takano, S. *J. Am. Chem. Soc.* **1988**, *110*, 5201−5203. (c) Fujiwara, K.; Tokiwano, T.; Murai, A.; *Tetrahedron Lett.* **1995**, *36*, 8063−8066.

**SCHEME 3** [a]




[a] Reagents and conditions: (a) $K_2CO_3$, $H_2O$, dioxane, 98%. (b) $CH_2Cl_2$, −15 °C to rt, 80%. (c) THF, MeMgI, −78 °C to rt, 72%. (d) $(EtO)_2P(O)(CH_2COOEt)$, NaH, THF, 0 °C to reflux, 66.3%. (e) AD-mix-$\beta$, $CH_3SO_2NH_2$, *t*-BuOH−$H_2O$, 0 °C, 89%. (f) TsCl, $Et_3N$, $CH_2Cl_2$, rt, 82%, 98% ee by HPLC. (g) DMSO, $SOCl_2$, $CH_2Cl_2$, −78 °C, 88%. (h) TFA, $CH_2Cl_2$, 0 °C, 2 h, then $Et_3N$, $CH_2Cl_2$, 0 °C to rt, 78%. (i) $Boc_2O$, EtOH, 10% Pd−C, 78% for **19**. (j) LiOH·$H_2O$, rt, 6 h, then TFA, $CH_2Cl_2$, 0 °C to rt, 2 h, 81%.

**SCHEME 4** [a]




[a] Reagents and conditions: (a) *m*-CPBA, $CH_2Cl_2$, reflux, 24 h, 71%. (b) $BF_3$·$Et_2O$, $CH_2Cl_2$, −78 °C to rt, 80%. (c) Pd−C, EtOH, quant. (d) TsCl, pyridine, 92%.

in the expected structure **10b** in 70% isolated yield (Scheme 2). Hydrogenolysis of **10b** proceeded smoothly to yield **3** (expected) as a white solid in satisfactory yield. However, analyses of the $^1H$ and $^{13}C$ NMR spectra of **3** showed that its structure was completely different than expected.[2] This was despite the fact mass spectra (EI) indicated that the precursors **10a** and **10b** as well as **3** itself provided the expected molecular weights. The most probable explanation for these facts was that a rearrangement occurred in step c of Scheme 2, which efficiently generated a new structure without loss of any components from reactants **8a** and **8b**.

With knowledge of the above failed cyclization reaction, the original synthetic strategy for 3-hydroxy-3-methyl proline (**3**) was modified to avoid acidic or basic conditions. In this new route, formation of the $C_2$−N bond was achieved by an intramolecular reductive amination through a key intermediate, the α-ketoester **17**. The synthetic route was executed as detailed in Scheme 3. $\beta$-Alanine (**11**) was protected with $Boc_2O$ and then converted to amide **13**,[10] which was treated with methylmagnesium iodide at −78 °C to afford ketone **14**. The (2*E*)-α,$\beta$-unsaturated ester **15** was prepared by condensation of ketone **14** with triethyl phosphonoacetate in the presence of NaH in THF. Next, Sharpless asymmetric dihydroxylation[8] of trisubstituted olefin **15** gave diol **16** in 89% yield with the desired stereochemistries. Enantiomeric purity (98% ee) was determined by HPLC measurement of tosylate **16a**. Selective oxidation of diol **16** under Swern conditions[11] provided α-ketoester **17** in 88% yield. Of note, other oxidative conditions (PDC, Dess−Martin periodinane, etc.) led to cleavage of diol **16** to give **14**. Deprotection of the *N*-Boc group of **17** using TFA followed by treatment with $Et_3N$ resulted in the stable cyclic α-iminoester **18**. Hydrogenation of **18** in the presence of $Boc_2O$[12] gave **19** (78%) as well as its $C_2$-epimer (20%). Both of these could be well separated by routine flash chromatography. Finally, hydrolysis of the ethyl ester (LiOH) and removal of the *N*-Boc group (TFA) afforded the free amino acid **3** in 90% yield. All physical data of **3** were in complete agreement with previous reports.[2,4−6]

**Studies on the $BF_3$·$OEt_2$-Promoted Rearrangement.** As mentioned above, NMR and mass spectral data of **10a** and **10b** were not unambiguous; **10b** was converted into a stable analogue, which could be easily crystallized and subjected to X-ray crystallographic analysis. To expeditiously prepare sufficient material for the synthesis of a large number of derivatives, the racemic epoxide ester (±)-**20** was obtained by epoxidation of (*E*)-

(10) (a) Hodgson, D. M.; Glen, R.; Redgrave, A. J. *Tetrahedron Lett.* **2002**, *43*, 3927−3930. (b) Toyooka, N.; Okumura, M.; Himiyama, T.; Nakazawa, A.; Nemoto, H. *Synlett* **2003**, 55−58.

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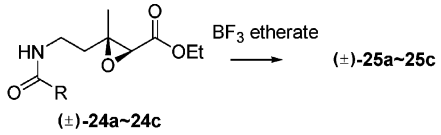
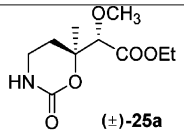
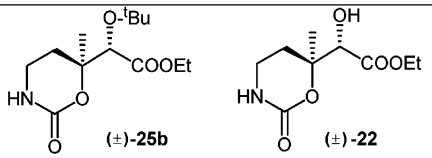
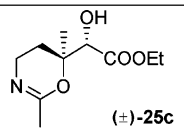
(12) Andrus, M. B.; Li, W.; Keyes, R. F. *J. Org. Chem.* **1997**, *62*, 5542−5549.

**TABLE 1. Results of Rearrangement of Epoxides 24a−c**




| Entry | Reactant **24** | Product **25** | Isolated Yield |
|---|---|---|---|
| 1 | **24a**: R=$OCH_3$ |  (±)-**25a** | 73% |
| 2 | **24b**: R=O-*t*-Bu |  (±)-**25b** (±)-**22** | 34% (**25b**) 48% (**22**) |
| 3 | **24c**: R=$CH_3$ |  (±)-**25c** | 78% |

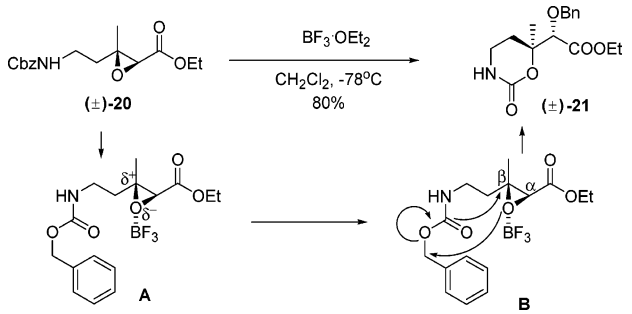



**FIGURE 3.** Proposed mechanism of $BF_3$ etherate promoted rearrangement.

olefin **6a** using *m*-CPBA (Scheme 4). Treatment of (±)-**20** with 1.2 equiv of $BF_3{\cdot}Et_2O$ in $CH_2Cl_2$ at −78 °C afforded (±)-**21** in 80% isolated yield. After benzyl deprotection by catalytic hydrogenolysis, the resultant solid (±)-**22** was immediately converted into the corresponding tosylate (±)-**23**, which was highly crystalline in a variety of solvents. Results of single-crystal X-ray crystallographic analysis of (±)-**23** (CIF data and an enlarged color picture) are provided in Supporting Information.

Having determined the nature of the unexpected rearrangement, a pathway for this reaction was proposed as shown in Figure 3. Because (±)-**21** was single product (80% isolated yield), the rearrangement must be highly concerted (**B**). Under $BF_3{\cdot}Et_2O$ assistance, epoxide activation first occurred (**A**). Subsequently, attack of the carbon-$\beta$ by the carbamate C═O formed an oxazinanone ring with reversion of configuration of the C-$\beta$ center. Simultaneously, the alkoxide anion resluting from the ring opening immediately sequestered the leaving benzyl cation to form a benzyl ether, resulting in (±)-**21** neatly.

Because benzyl cations are chemically stable species, significant uncertainty exists concerning the substrate-generality of such a rearrangement. To explore the generality and stereochemistry of alkyl migration, three additional substrates (**24a−c**) were synthesized and treated with $BF_3{\cdot}Et_2O$. Results are shown in Table 1. In the case of R = $OCH_3$ (entry 1), a satisfying yield of α-methoxy ester was isolated. Because methyl cations are unstable, it is obvious that this result is due to a rapid and concerted process. The second example is a *N*-Boc-protected derivative. Following routine workup and purification, two related compounds (**25b** and **22**) were obtained in 82% total yield. This result could be explained by the partial transformation of *tert*-butyl ether **25b** into the corresponding alcohol **22** (deprotection) under the acidic reaction conditions. Acetamide **24c** is distinct in that it would not be able to provide an alkyl for the migration step. In support of our previously proposed mechanism, the six-member heterocycle **25c** was obtained with reversed C-$\beta$ stereochemistry. The highly efficient stereoinversion of trisubstituted alcohol derivatives by this rearrangement could potentially be of great utility in organic synthesis.

## Conclusion

In summary, a new inexpensive and scalable synthesis of (2*S*,3*R*)-3-hydroxyl-3-methylproline (**3**) based on a $C_2$−N disconnection protocol was achieved. Initial stereochemistry was introduced in high enantiomeric excess by Sharpless asymmetric dihydroxylation. Subsequent intramolecular diastereoselective reductive amination afforded the pyrrolidine ring of **3** bearing the desired functionality. During the course of our studies on Lewis acid promoted intramolecular epoxide-opening/cyclization, an unexpected rearrangement was observed. Upon investigation this was found to be a concerted and highly stereospecific process. Further studies on the incorporation of **3** into polyoxypeptins and extensive exploration of the potential uses of the newly found rearrangement are in progress.

## Experimental Section

**5-Benzyloxycarbonylamino-3-methyl-pent-2-enoic Acid Ethyl Ester (6a).** To a suspension of NaH (60%, 0.131 g, 3.2 mmol) in anhydrous THF (6 mL) at 0 °C under nitrogen was

added triethyl phosphonoacetate (0.76 g, 3.3 mmol) in anhydrous THF (2 mL). After the mixture was stirred for 30 min at 0 °C, ketone **5** (0.5 g, 2.2 mmol) in THF (2 mL) was added. The reaction was allowed to stir overnight at room temperature and then quenched by aqueous $NH_4Cl$. Most of the solvent was removed in vacuo, and the residue was poured into water and extracted with EtOAc (20 mL × 3). The combined extracts were washed with brine and dried over $MgSO_4$. Concentration and flash chromatography gave **6a** as a colorless oil (0.52 g, 78%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.34 (m, 5H), 5.68 (s, 1H), 5.10 (s, 2H), 4.81 (br, 1H), 4.14 (q, $J$ = 7.5 Hz, 2H), 3.36 (q, $J$ = 6.9 Hz, 2H), 2.34 (t, $J$ = 6.9 Hz, 2H), 2.16 (s, 3H), 1.27 (t, $J$ = 7.5 Hz, 3H). MS (EI, $m/z$): 292 ($M^+ + 1$). IR (neat, $cm^{-1}$): 3355, 1713, 1649, 1532, 775, 737, 698. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.11; H, 7.57; N, 4.53.

**[2-(Methoxymethylcarbamoyl)-ethyl]carbamic Acid *tert*-Butyl Ester (13).**[13] To a stirred solution of *N*-Boc $\beta$-alanine **12** (25.0 g, 132 mmol) and *N*-methylmorpholine (32 mL, 0.29 mol) in $CH_2Cl_2$ (150 mL) was added dropwise isobutyl chloroformate (19.1 mL, 145 mmol) at −15 °C, and the mixture was stirred for 15 min. *N*,*O*-Dimethyl hydroxylamine hydrochloride (14.2 g, 145 mmol) was then added, and the reaction continued to stir at −15 °C for 15 min and then was allowed to remain at room temperature for 36 h. The mixture was washed with 10% aqueous potassium bisulfate (50 mL). The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were washed with $H_2O$ and brine and dried ($MgSO_4$). Concentration and flash chromatography gave amide **13** as a colorless oil (25.5 g, 80%). $^1$H NMR (300 MHz, $CD_3OD$): $\delta$ 6.71 (br, 1H), 3.61 (s, 3H), 3.13 (m, 2H), 3.04 (s, 3H), 2.47 (br, 2H), 1.33 (s, 9H). MS (EI, $m/z$): 201 ($M^+ - 31$). IR (film, $cm^{-1}$): 3353, 2987, 2939, 1716, 1654, 1508.

**(3-Oxo-butyl)-carbamic Acid *tert*-Butyl Ester (14).**[14] To a solution of **13** (14.5 g, 62.5 mmol) in dry THF (400 mL) was added MeMgI (1.65 M in ether, 114 mL, 188 mmol) dropwise under an argon atmosphere at −78 °C. After completion of addition, the reaction mixture was allowed to warm to 0 °C and stirred for 2 h until aqueous $NH_4Cl$ (100 mL) was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with EtOAc (200 mL × 3). The combined organic layers were washed with $H_2O$ and brine and dried ($MgSO_4$). Concentration and flash chromatography afforded **14** as a colorless oil (8.3 g, 72%). $^1$H NMR (300 MHz, $CDCl_3$):$\delta$ 5.05 (s, 1H), 3.35 (q, $J$ = 6.0 Hz, 2H), 2.67 (t, $J$ = 6.0 Hz, 2H), 2.16 (s, 3H), 1.42 (s, 9H). MS (EI, $m/z$): 187 ($M^+$). IR (film, $cm^{-1}$): 3366, 2979, 1713, 1521, 1317, 1169.

**5-*tert*-Butoxycarbonylamino-3-methylpent-2-enoic Acid Ethyl Ester (15).** Compound **15** was prepared according to the procedure for compound **6a**. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.68 (s, 1H), 4.53 (br, 1H), 4.18 (q, $J$ = 7.5 Hz, 2H), 3.30 (q, $J$ = 6.6 Hz, 2H), 2.32 (t, $J$ = 6.6 Hz, 2H), 2.17 (s, 3H), 1.43 (s, 9H), 1.29 (t, $J$ = 7.5 Hz, 3H). MS (EI, $m/z$): 201 ($MH^+ - C_4H_9$). IR (neat, $cm^{-1}$): 3375, 2980, 2936, 1717, 1651, 1172, 1151. Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.76; H, 8.85; N, 5.38.

**(2*S*,3*R*)-5-*tert*-Butoxycarbonylamino-2,3-dihydroxy-3-methyl-pentanoic Acid Ethyl Ester (16).** A mixture of $K_3Fe(CN)_6$ (38.4 g, 117 mmol), $K_2CO_3$ (16.1 g, 117 mmol), $(DHQD)_2PHAL$ (1.71 g, 5 mol %), and $K_2OsO_2(OH)_4$ (143 mg, 1 mol %) in *t*-BuOH (200 mL) and $H_2O$ (200 mL) was stirred for 15 min at room temperature. $CH_3SO_2NH_2$ (3.7 g, 38.9 mmol) and olefin **15** (10.0 g, 38.9 mmol) were added at 0 °C, and the heterogeneous slurry was stirred vigorously for 12 h at 0 °C. The reaction was quenched by addition of $Na_2SO_3$ (50 g), and the mixture was allowed to warm to room temperature and stirred for 1 h. EtOAc (150 mL) was added, and the aqueous layer was extraceted with EtOAc (50 mL × 3). The combined organic layers were washed with brine and dried ($MgSO_4$). Concentration and flash chromatography afforded the diol **16** as a colorless oil (10.11 g, 89%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.13 (br, 1H), 4.32 (q, $J$ = 7.5 Hz, 2H), 4.03 (d, $J$ = 6.3 Hz, 1H), 3.33 (m, 2H), 3.22 (d, $J$ = 6.3 Hz, 1H), 2.97 (br, 1H), 1.80 (m, 2H), 1.44 (s, 9H), 1.33 (t, $J$ = 7.5 Hz, 3H), 1.18 (s, 3H). MS (ESI, $m/z$): 292 ($M^+ + 1$), 314 ($M^+ + Na$). IR (film, $cm^{-1}$): 3387 (br), 2981, 2937, 1694 (br), 1524, 1368, 1173. Anal. Calcd for $C_{13}H_{25}NO_6$: C, 53.59; H, 8.65; N, 4.81. Found: C, 53.70; H, 8.72; N, 4.79. $[\alpha]^{25}_D$ +10.1 (*c* 1.77, $CHCl_3$). A sample of tosylate **16a** was prepared by the reaction of **16** with TsCl and $Et_3N$ in $CH_2Cl_2$ at room temperature for 24h (82% yield). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.81 (d, $J$ = 8.7 Hz, 2H), 7.35 (d, $J$ = 8.1 Hz, 2H), 4.97 (br, 1H), 4.68 (s, 1H), 4.10 (q, $J$ = 6.9 Hz, 2H), 3.26 (m, 2H), 2.85 (br, 1H), 2.45 (s, 3H), 1.70 (m, 2H), 1.43 (s, 9H), 1.21 (s, 3H), 1.20 (t, $J$ = 6.9 Hz, 3H). HPLC of **16a**: 98% ee ($t_{1/2}$ = 16.1 min for the major enantiomer, $t_{1/2}$ = 21.6 min for the minor one, column AD; UV-detector, 254 nm; 20% 2-propanol in hexane; flow rate 0.7 mL/min).

**(3*R*)-5-*tert*-Butoxycarbonylamino-3-hydroxy-3-methyl-2-oxopentanoic Acid Ethyl Ester (17).** To a solution of oxalyl chloride (0.162 mL, 1.9 mmol) in $CH_2Cl_2$ (5.0 mL) under argon atmosphere was added dropwise anhydrous DMSO (0.268 mL, 3.8 mmol) in $CH_2Cl_2$ (8.0 mL) at −78 °C. After 15 min, the diol **16** (500 mg, 1.72 mmol) in $CH_2Cl_2$ (5.0 mL) was added dropwise over 10 min. The internal temperature was kept below −50 °C until the addition was completed. The reaction was stirred for an additional 2 h at −78 °C before triethylamine (0.5 mL) was added. After 5 min, the reaction was allowed to warm to room temperature. The mixture was diluted with EtOAc and washed with aqueous $NH_4Cl$ and brine. The organic phase was separated and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was purified by flash chromatography to give colorless oil **17** (438 mg, 88%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.97 (s, 1H), 4.29 (m, 2H), 3.60 (m, 2H), 3.28 (d, $J$ = 12.9, 1H), 2.03 (br, 2H), 1.42 (s, 9H), 1.32 (m, 3H),1.22 (s, 3H). MS (EI, $m/z$): 233 ($MH^+ - C_4H_9$). IR (film, $cm^{-1}$): 3480 (br), 2981, 2937, 2904, 1741, 1706, 1395, 1368, 1258, 1162, 1098. Anal. Calcd for $C_{13}H_{23}NO_6$: C, 53.97; H, 8.01; N, 4.84. Found: C, 53.69; H, 8.07; N, 4.80. $[\alpha]^{25}_D$ −20 (*c* 0.5, $CHCl_3$).

**(3*R*)-3-Hydroxy-3-methyl-4,5-dihydro-3*H*-pyrrole-2-carboxylic Acid Ethyl Ester (18).** To a stirred solution of α-ketoester **17** (2.5 g, 8.65 mmol) in $CH_2Cl_2$ (12.0 mL) was added TFA (6.0 mL) at 0 °C. After the mixture was stirred at room temperature for 2 h, the solvent was removed in a vacuum. To the resultant residue in $CH_2Cl_2$ (10 mL) was added $Et_3N$ (6 mL) at 0 °C. After being stirred for 2 h at room temperature, the mixture was diluted with EtOAc (50 mL), and the organic layer was washed with aqueous $NH_4Cl$, $H_2O$, and brine, successively, and dried ($MgSO_4$). Concentration and flash chromatography afforded **18** as a colorless oil (1.12 g, 78%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.39 (q, $J$ = 7.2 Hz, 2H), 4.12 (ddd, $J$ = 5.1, 7.5 Hz, 16.8 Hz, 1H), 3.90 (ddd, $J$ = 7.2, 7.8, 15.9 Hz, 1H), 3.05 (br, 1H), 2.08−2.20 (m, 2H), 1.55 (s, 3H), 1.42 (t, $J$ = 7.2 Hz, 3H). MS (EI, $m/z$): 171 ($M^+$). IR (film, $cm^{-1}$): 3376 (br), 2981, 2941, 1733, 1633, 1294, 1068. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.07; H, 7.89; N, 7.89. $[\alpha]^{25}_D$ +34.4 (*c* 0.55, $CHCl_3$).

**(2*S*,3*R*)-3-Hydroxy-3-methylpyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Ethyl Ester (19).** A mixture of imine **18** (310 mg, 1.88 mmol), $Boc_2O$ (1.2 g, 5.5 mmol) and 10% Pd−C (50 mg) in EtOH (10 mL) was hydrogenated (1 atm) for 12 h at room temperature. The solid was filtered, and the solution was concentrated in vacuo. Flash chromatography granted compound **19** as a colorless oil (400 mg, 78%) and its $C_2$-epimer as a white solid (100 mg, 20%) (HPLC analysis gave a ratio of 3.6:1). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.22 (q, $J$ = 6.9 Hz, 2H), 4.02 (s, 1H), 3.62 (m, 2H), 2.21 (br, 1H), 2.06 (m,-1H), 1.88 (m,1H), 1.49 (s, 3H), 1.41 (s, 9H), 1.33 (t, $J$ = 6.9 Hz, 3H). MS (EI, $m/z$): 273 ($M^+$). IR (film, $cm^{-1}$): 3448 (br),

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2979, 2936, 1745, 1704, 1683, 1405, 1369, 1188, 1164. Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 57.32; H, 8.82; N, 4.67. $[\alpha]^{25}_D$ −14.4 (*c* 0.75, $CHCl_3$). Data for the $C_2$-epimer: mp 108−110 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.22 (m, 2H), 4.05 (s, 1H), 3.60 (m, 2H), 2.09 (m, 1H), 1.95 (m, 1H), 1.83 (br, 1H), 1.46 (s, 3H), 1.41 (s, 9H), 1.32 (t, $J$ = 6.8 Hz, 3H). $[\alpha]^{25}_D$ −18.8 (c 0.52, $CHCl_3$).

**(2*S*,3*R*)-3-Hydroxy-3-methylpyrrolidine-2-carboxylic Acid (3).** To a stirred solution of **19** (78 mg, 0.28 mmol) in THF (2.0 mL) and water (1.0 mL) was added $LiOH\cdot H_2O$ (36 mg, 0.85 mmol) at room temperature. After being stirred for 6 h, the mixture was acidified by addition of aqueous $NaHSO_4$ (10%) to pH 3 and then extracted with EtOAc (15 mL × 3). The combined organic layers were concentrated in vacuo. The resultant residue was treated with TFA (2.0 mL) in $CH_2Cl_2$ (2.0 mL) at 0 °C. After the mixture was stirred at room temperature for 2 h, the solvent was removed in vacuo. The residue was taken up into water (1 mL), and the resultant aqueous solution was allowed to pass through a column (15 × 1 cm) of acidic ion-exchange resin (Dowex 50 × 2, 100−200 mesh), eluting first with water (100 mL) and then with aqueous ammonium hydroxide (2 M, 100 mL). The ammonia fraction was concentrated in vacuo to gave a colorless solid **3** (33 mg, 80% in two steps), mp 198−200 °C (dec). $^1$H NMR (300 MHz, $D_2O$): $\delta$ 3.86 (s, 1H), 3.54 (m, 1H), 3.47 (m, 1H), 2.15 (m, 2H), 1.58 (s, 3H). MS (EI, *m*/*z*): 145 ($M^+$). IR (KBr, $cm^{-1}$): 3349, 3108, 1626, 1577, 1417, 1323, 1209. $[\alpha]^{25}_D$ −42 (*c* 0.45, $H_2O$). {lit.[2] $[\alpha\alpha]^{25}_D$ −41.0 (*c* 0.40, $H_2O$); lit.[4] $[\alpha\alpha]^{25}_D$ −40.2 (*c* 0.42, $H_2O$); lit.[5] $[\alpha\alpha]^{25}_D$ −42 (*c* 1.30, $H_2O$); lit.[6] $[\alpha\alpha]^{25}_D$ −38.6 (*c* 0.40, $H_2O$)}.

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**Supporting Information Available:** Experimental details and physical data for compounds **20**−**23**, **25a**−**c**, and CIF data (X-ray) and an enlarged color picture for compound **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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