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Benzyl 2-Cyano-3,3-Dimethyl-1-pyrrolidinecarboxylate, a Versatile Intermediate for the Synthesis of 3,3-Dimethylproline Derivatives

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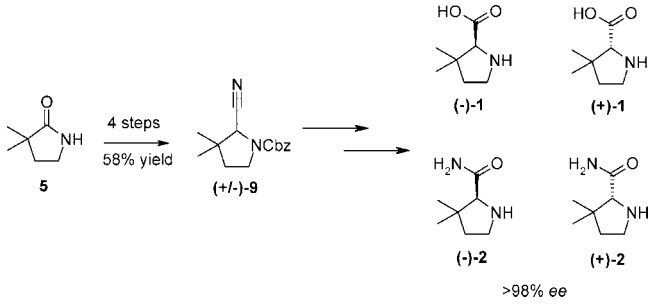
Received December 20, 2007



The synthesis of racemic nitrile (±)-**9** was accomplished in four steps and 58% overall yield from the known pyrrolidinone **5**. Nitrile (±)-**9** was resolved via preparative chiral HPLC to afford optically pure nitriles (+)-**9** and (−)-**9**, from which 3,3-dimethylprolines (+)-**1** and (−)-**1** and 3,3-dimethylprolinamides (+)-**2** and (−)-**2** could be accessed in nearly quantitative yield, without loss of optical purity. The absolute configurations of the resolved prolines and prolinamides were determined by correlation with an intermediate of known absolute stereochemistry.

Among the naturally occurring amino acids, proline has a unique conformationally restricted structure resulting from its side chain and the α-amino group being contained within a five-membered ring. Consequently, proline can induce a reversal in the direction of the peptide backbone and can impart a dramatic effect on the secondary structure of many peptides and proteins, directing and switching peptide chains into favorable topologies.[1] Expanded interest in the effect of proline congeners on protein structure and stability led to the preparation of analogues that were incorporated into peptides to study their structural and biological properties.[2] The use of proline congeners is also common in the small molecule peptide arena. For instance, β-alkylprolines have been used to develop enzyme inhibitors and peptidomimetics exhibiting improved bioactivity and metabolic stability.[3] In particular, replacement of proline by 3,3-dimethylproline has been proposed as a strategy for reducing the rate of N-terminal amide isomerization in peptides.[4]

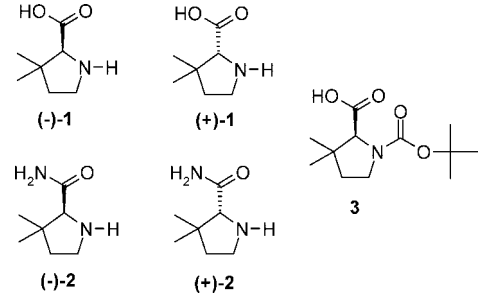


FIGURE 1. 3,3-Dimethylproline derivatives.

As part of a medicinal chemistry program,[5] we required access to multigram quantities of both enantiomers of 3,3-dimethylproline ((+)-**1** and (−)-**1**) and 3,3-dimethylprolinamide ((+)-**2** and (−)-**2**) (Figure 1). During the course of this work, the only 3,3-dimethylproline derivative commercially available was the expensive Boc protected (*S*)-enantiomer **3**.[6] Although the synthesis of **3** (in eight steps and 41% overall yield from 4-hydroxy-*S*-proline) was reported,[3b] we chose to pursue a route using the nitrile (±)-**9** as a common late-stage intermediate which enables rapid access to (±)-**1**,[7] (±)-**2**,[5,6] and their respective enantiomers with an additional resolution step. This also provided the opportunity to develop analytical HPLC methods for the determination of the optical purity of the compounds prepared.

As outlined in Scheme 1, alkylation of the lithium enolate of *N*-TBS-protected 3-pyrrolidinone **4**[8] with methyl iodide, followed by treatment with TBAF, provided 3,3-dimethylpyrrolidin-2-one (**5**)[9] in 46% overall yield. Deprotonation of **5** with LHMDS, followed by addition of benzyl chloroformate, afforded

(1) (a) Che, Y.; Marshall, G. R. *Biopolymers* **2006**, *81*, 392. (b) Richardson, J. S. *Adv. Protein Chem.* **1981**, *34*, 167.

(2) (a) Zhang, K.; Schweizer, F. *Synlett* **2005**, 3111. and references cited therein. (b) Che, Y.; Marshall, G. R. *J. Org. Chem.* **2004**, *69*, 9030. (c) Quancard, J.; Labonne, A.; Jacquot, Y.; Lavielle, S.; Karoyan, P. *J. Org. Chem.* **2004**, *69*, 7940. (d) Cavelier, F.; Vivet, B.; Martinez, J.; Aubry, A.; Didierjean, C.; Vicherat, A.; Marraud, M. *J. Am. Chem. Soc.* **2002**, *124*, 2917. (e) Halab, L.; Lubell, W. D. *J. Am. Chem. Soc.* **2002**, *124*, 2474. (f) Tam, J. P.; Miao, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9013. (g) An, S. S. A.; Lester, C. C.; Peng, J.-L.; Y, J.; Rothwarf, D. M.; Welker, E.; Thannhauser, T. W.; Zhang, L. S.; Tam, J. P.; Scheraga, H. A. *J. Am. Chem. Soc.* **1999**, *121*, 11558. (h) Beausoleil, E.; Lubell, W. D. *J. Am. Chem. Soc.* **1996**, *118*, 12902. (i) Delaney, N. G.; Madison, V. J. *J. Am. Chem. Soc.* **1982**, *104*, 6635.

(3) (a) Raghavan, S.; Lu, Z.; Beeson, T.; Chapman, K. T.; Schleif, W. A.; Olsen, D. B.; Stahlhut, M.; Rutkowski, C. A.; Gabryelski, L.; Emini, E.; Tata, J. R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5432. (b) Sharma, R.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 202 and references cited therein.

(4) Beausoleil, B.; Sharma, R.; Michnick, S. W.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 6572.

(5) Axten, J. M.; Medina, J. R. Patent WO 2007016364 A 2 2007.

(6) After this work was completed, 3,3-dimethylprolinamide (±)-**2** became commercially available (see the Supporting Information).

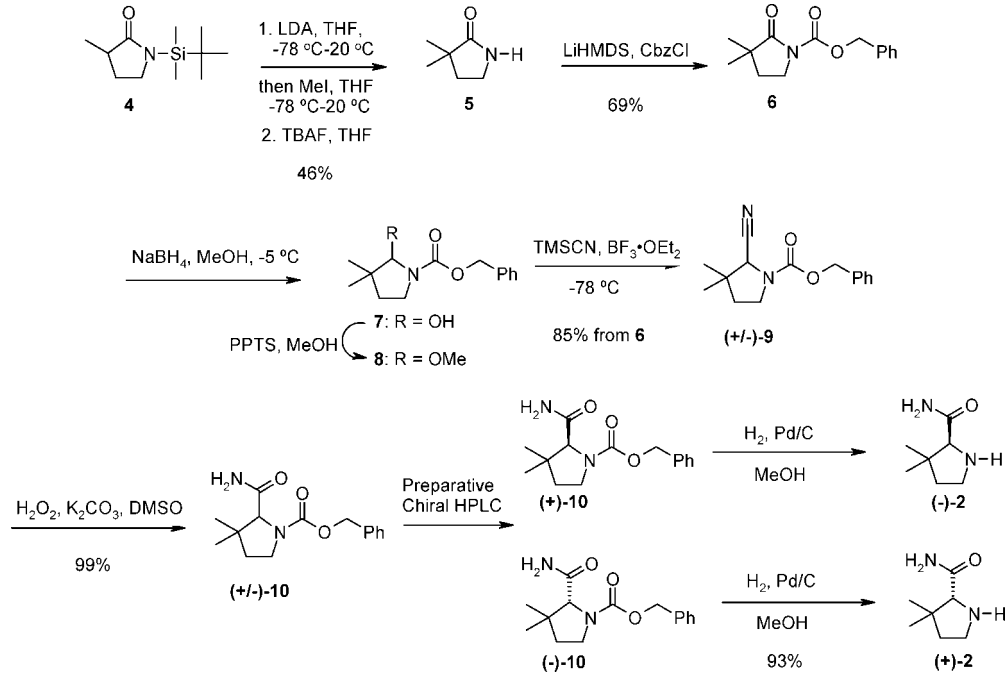
(7) (a) Robl, J. A.; Sulsky, R. B.; Augeri, D. J.; Magnin, D. R.; Hamann, L. G.; Betebenner, D. A. Patent WO 2001068603 A2 2001. (b) Morgan, B. A.; Schafer, D. J. Patent DE 260915 4 1976.

(8) Padwa, A.; Coats, S. J.; Harring, S. R.; Hadjiarapoglou, L.; Semones, M. A. *Synthesis* **1995**, *8*, 973.

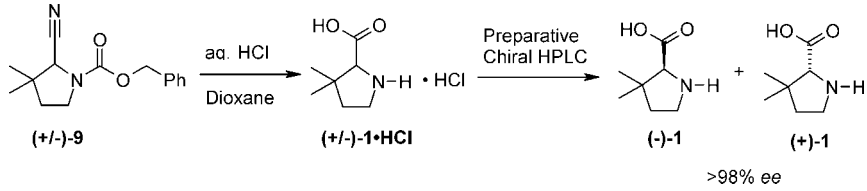
(9) Although 3,3-dimethylpyrrolidin-2-one **5** can be prepared in a one-pot procedure from *N*-TMS-protected pyrrolidinone, we preferred to work with the less moisture-sensitive TBS-protected material. Ahn, Y.; Cardenas, G. I.; Yang, J.; Romo, D. *Org. Lett.* **2001**, *3*, 751.

10.1021/jo7027163 CCC: $40.75
Published on Web 04/23/2008

SCHEME 1. Synthetic Route to 3,3-Dimethylproline Derivatives



SCHEME 2. Synthesis and Resolution of 3,3-Dimethylproline ((±)-1)

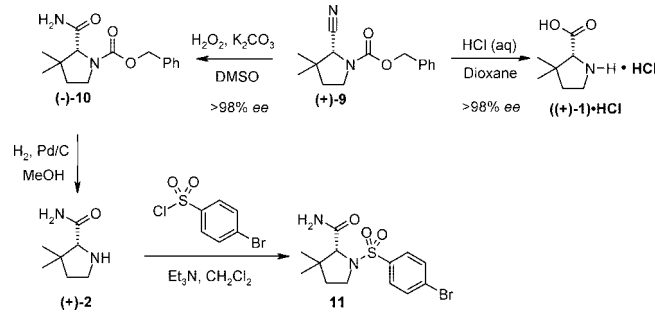


the protected lactam **6** in 69% yield. Reduction[10] to the hemiaminal **7** was accomplished by the slow addition of $NaBH_4$ to lactam **6** at −5 °C. Treatment of **7** with catalytic PPTS in methanol smoothly formed **8**, which was reacted with trimethylsilyl cyanide in the presence of $BF_3 \cdot OEt_2$[11] to afford racemic nitrile (±)-**9** in 85% overall yield from **6**. Following the Katritzky protocol,[12] nitrile (±)-**9** was converted to carboxamide (±)-**10**, which was resolved in gram quantities by preparative chiral HPLC (Chiralpak AD column) to afford (+)-**10** and (−)-**10** in >98% ee.[13] The Cbz group was removed by hydrogenolysis using 10% Pd/C in MeOH under a hydrogen atmosphere to afford 3,3-dimethylprolinamides (−)-**2** and (+)-**2** in 93% yield.

We also examined the direct conversion of nitrile (±)-**9** to racemic 3,3-dimethylproline ((±)-**1**), followed by resolution to (+)-**1** and (−)-**1** (Scheme 2). Treatment of (±)-**9** with aqueous HCl in dioxane hydrolyzed the nitrile and carbamate groups to afford (±)-**1·HCl**. Racemic (±)-**1·HCl** was resolved by chiral HPLC (Chirobiotic T column) to provide the amino acid enantiomers (−)-**1** and (+)-**1** in >98% optical purity.[13]

Although we had reliable methods for the resolution of prolinamides (±)-**10** and prolines (±)-**1**, we investigated the resolution of the versatile intermediate nitrile (±)-**9**. This would allow access to the proline derivatives (−)-**1** and (+)-**1** and prolinamides (−)-**2** and (+)-**2** from (±)-**9** using a single resolution step, provided that the optical purity would not be compromised during the subsequent chemical transformation.

SCHEME 3. Synthesis of (−)-10, (+)-1•HCl, and 11 from Optically Pure (+)-9



Chiral HPLC resolution of nitrile (±)-**9** was accomplished using a Chiralcel OJ column to afford (+)-**9** and (−)-**9** in 99% ee and 97% ee, respectively.[13] When nitrile (+)-**9** (>99% ee) was converted to the carboxamide derivative (−)-**10**, analytical HPLC analysis indicated the product to be >98% ee (Scheme 3). Likewise, when nitrile (+)-**9** was converted to dimethylproline (+)-**1•HCl**, HPLC analysis indicated that this compound had an optical purity of >98% ee. Furthermore, the free base was identical (HPLC analysis) to the reference sample (+)-**1** described in Scheme 2.

Finally, the absolute configurations of enantiomers (−)-**2**/(+)-**2**, (−)-/(+)-**1**, and (−)-**9**/(+)-**9** were determined by cor-

(10) Wijnberg, J. B. P. A.; Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 179.

(11) (a) Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S. *Tetrahedron* **1994**, *50*, 6221. (b) For a review of the chemistry of *N*-acyliminium ions, see: Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

(12) Katritzky, A. R.; Pilarski, B.; Urogdi, L. *Synthesis* **1989**, 949.

(13) See the Supporting Information.

relation with the stereochemistry of compound **11**. Sulfonylation of enantiomer (+)-**2**, derived from the hydrogenolysis of (−)-**10**, produced the crystalline compound **11** (Scheme 3), which upon X-ray analysis indicated *R*-stereochemistry.[13]

In summary, a short and practical preparation of the enantiomers of 3,3-dimethylproline and 3,3-dimethylprolinamide, starting from 3,3-dimethylpyrrolidinone and based on the resolution of (±)-**9**, was accomplished. The conversion of the optically enriched nitriles to the corresponding carboxamide and carboxylic acid derivatives occurs without loss of optical purity, as determined by chiral HPLC analysis. The absolute configurations of the proline and prolinamides prepared were confirmed by correlation with an intermediate of known absolute stereochemistry as determined by X-ray crystallography. The methods described herein can be performed on gram scale, making nitriles (−)-**9** and (+)-**9** valuable and versatile intermediates for the synthesis of optically pure 3,3-dimethylproline analogues.

Experimental Section

3,3-Dimethyl-2-pyrrolidinone (5). To a solution of diisopropylamine (17.9 g, 177 mmol) in THF (300 mL) at 0 °C was added *n*-butyllithium (77.1 mL, 193 mmol, 2.5 M solution in hexanes) over 5 min. After 0.5 h, the reaction mixture was cooled to −78 °C, and a solution of **4** (34.3 g, 161 mmol) in THF (80 mL) was added dropwise, keeping the reaction temperature below −60 °C. The reaction mixture was warmed to 20 °C and stirred at this temperature for 1 h. The reaction was cooled back to −78 °C, and a solution of iodomethane (25.1 g, 177 mmol) in THF (10 mL) was added dropwise over 10 min. The reaction was warmed to 20 °C and stirred for 16 h. The reaction mixture was quenched by addition of saturated NH_4Cl (300 mL), the layers were separated, and the aqueous phase was extracted with EtOAc (2 × 150 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The resulting crude oil was purified by silica gel flash chromatography (EtOAc/hexanes) to provide the desired dimethylpyrrolidinone derivative as a yellow oil. This oil was immediately dissolved in THF (250 mL), the resulting solution was cooled to 5 °C, and tetrabutylammonium fluoride (194 mL, 194 mmol, 1 M solution in THF) was added over 30 min. The reaction mixture was warmed to 20 °C, stirred for 2 h, and then concentrated. The resulting crude oil was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH) to afford product **5** (8.13 g, 46%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.52 (bs, 1H), 3.32 (t, J = 6.8 Hz, 2H), 1.97 (t, J = 6.8 Hz, 2H), 1.18 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.2, 36.4, 38.7, 39.6, 183.8.

Benzyl 3,3-Dimethyl-2-oxo-1-pyrrolidinecarboxylate (6). To a solution of **5** (8.13 g, 72 mmol) in THF (200 mL) at −78 °C was added LHMDS (79 mL, 79 mmol, 1 M solution in THF) over 15 min. The solution was stirred for 30 min, benzyl chloroformate (13.5 g, 79 mmol) was added, and the reaction mixture was warmed to room temperature. After 16 h, the reaction was concentrated to 1/3 total volume and diluted with EtOAc (500 mL). The organic solution was washed sequentially with 1 M HCl (2 × 200 mL), H_2O (200 mL), and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography on silica gel (EtOAc/hexanes) provided product **6** (12.3 g, 69%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (m, 2H), 7.30−7.43 (m, 3H), 5.31 (s, 2H), 3.75 (t, J = 7.0 Hz, 2H), 1.89 (t, J = 7.1 Hz, 2H), 1.22 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.2, 32.9, 42.1, 42.7, 67.9, 128.0, 128.3, 128.5, 135.3, 151.8, 178.8. MS *m/e* 270.2 $[M + Na]^+$. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.00; H, 7.06; N, 5.73.

Benzyl 2-Cyano-3,3-dimethyl-1-pyrrolidinecarboxylate ((±)-9). To a solution of **6** (12.2 g, 49 mmol) in MeOH (100 mL) at −10 °C was added $NaBH_4$ (9.35 g, 25 mmol) in portions, maintaining an internal temperature below −5 °C. TLC (90:10 $CHCl_3$/EtOAc) confirmed that the reaction was complete. The reaction mixture was poured onto a slurry of saturated aqueous NH_4Cl (500 mL) and crushed ice. After being stirred for 16 h, the aqueous mixture was extracted with Et_2O (2 × 200 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to afford *N*,*O*-hemiacetal **7** (11.8 g) as a clear oil which was used without further purification. To *N*,*O*-hemiacetal **7** (11.8 g, 48 mmol) in MeOH (100 mL) was added PPTS (1.19 g, 4.8 mmol), and the solution was stirred for 45 min at 20 °C. The reaction was quenched with Et_3N (3 mL) and concentrated. The resulting crude oil was purified by flash chromatography on silica gel ($CHCl_3$/EtOAc) to provide methoxyaminal **8** (11.2 g) as a clear oil as a mixture of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (m, 5H), 5.08−5.29 (m, 2H), [4.68 (s) and 4.57 (s)] (1H), 3.47−3.58 (m, 2H), [3.31 (s) and 3.46 (s)] (3H), 1.94 (m, 1H), 1.49−1.67 (m, 1H), [1.11 (s) and 1.09 (s)] (3H), [0.95 (s) and 0.93 (s)] (3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.1, 25.0, (34.7 and 35.6), (42.0 and 42.8), (44.2 and 44.5), (56.5 and 57.0), (66.8 and 67.2), (95.4 and 95.8), (127.6 and 128.0), (128.0 and 128.0), 128.5, (136.6 and 136.8), (155.6 and 156.3). This compound was dissolved in CH_2Cl_2 (200 mL), and the solution was cooled to −78 °C. Trimethylsilyl cyanide (6.32 g, 64 mmol) was added followed by $BF_3 \cdot OEt_2$ (9.09 g, 64 mmol), and the reaction mixture was stirred for 1 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$,and the mixture was allowed to warm to 20 °C. After 2 h of vigorous stirring, the mixture was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to afford product (±)-**9** (10.8 g, 85% from **6**) as a clear oil as a mixture of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.52 (m, 5H), 5.21 (m, 2H), [4.25 (s) and 4.17 (s)] (1H), 3.46−3.71 (m, 2H), 1.97−2.06 (m, 1H), 1.77 (m, 1H), [1.37 (s) and 1.35 (s)] (3H), 1.16 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (24.0 and 24.1), (25.47 and 25.53), (36.9 and 37.8), (41.5 and 42.6), (44.8 and 45.1), (58.0 and 58.3), (67.5 and 67.8), (117.0 and 117.1), (127.9 and 128.0), 128.2, 128.5, (135.8 and 136.0), (153.9 and 154.5). HRMS: calcd for $C_{15}H_{19}N_2O_2$ (MH^+) 259.1441, found 259.1441. A portion of this material was resolved using preparative chiral HPLC (Chiralcel OJ column).[13]

Benzyl 2-(Aminocarbonyl)-3,3-dimethyl-1-pyrrolidinecarboxylate ((±)-10). To a solution of (±)-**9** (10.7 g, 41 mmol) in DMSO (30 mL) was added K_2CO_3 (2.14 g, 16 mmol), and the mixture was cooled to 10 °C (avoid freezing). A 30% aqueous solution of H_2O_2 (5.5 mL) was added dropwise, keeping the internal temperature <15 °C. After the reaction ceases to outgas (a bubbler was used to monitor gas evolution), it was allowed to warm to 20 °C and stirred for 2 h. The reaction was diluted with H_2O (300 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to provide carboxamide (±)-**10** (12.2 g) as a clear oil as a mixture of rotamers. This material was resolved using preparative chiral HPLC (Chiralpak AD column).[13]

3,3-Dimethyl-D-prolinamide ((+)-2). To a solution of (−)-**10** (0.11 g, 0.41 mmol) in MeOH (10 mL) was added Degussa type 10% palladium/carbon (5 mg), and the mixture was stirred for 3 h at 20 °C under atmospheric H_2. The catalyst was removed by filtration, and the filtrate was concentrated to afford the title compound (54 mg, 93%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6, TFA): δ 9.44 (bs, 1H), 8.59 (bs, 1H), 7.85 (s, 1H), 7.74 (s, 1H), 3.68 (m, 1H), 3.28 (m, 2H), 1.82 (m, 2H), 1.19 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, TFA): δ 22.2, 26.2, 38.3, 41.5, 42.9, 67.2, 167.9. HRMS: calcd for $C_7H_{15}N_2O$ (MH^+) 143.1184, found 143.1179. $[\alpha]^{20}_D$ = +24.5 (*c* 1.05, CH_3OH).

3,3-Dimethyl-L-prolinamide ((−)-2). $[\alpha]^{20}_D$ = −31.8 (*c* 1.00, CH_3OH).

3,3-Dimethylproline ((±)-1·HCl). Nitrile (±)-**9** (0.10 g, 0.29 mmol) was dissolved in dioxane (2 mL) and aqueous HCl (2 mL, 12 M), and the mixture was heated at 80 °C for 15 h. The solvents were evaporated, and the residue was triturated with acetonitrile to

afford the product (HCl salt, 68 mg, 99%) as an off-white solid. ^{1}H NMR (400 MHz, D_2O): δ 3.91 (m, 1H), 3.50 (m, 2H), 1.99 (m, 2H), 1.32 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (125 MHz, D_2O): δ 21.1, 25.5, 38.6, 41.6, 43.4, 68.4, 170.8. A portion of this material was resolved using preparative chiral HPLC (Chirobiotic T column).[13]

1-[(4-Bromophenyl)sulfonyl]-3,3-dimethyl-D-prolinamide (11). To a solution of (−)-**10** (0.20 g, 0.72 mmol) in MeOH (5 mL) was added Degussa type 10% palladium/carbon (0.02 g), and the mixture was stirred for 3 h at 20 °C under atmospheric H_2. The catalyst was filtered, and the reaction was concentrated to afford 3,3-dimethyl-D-prolinamide ((+)-**2**) (0.112 g) as a white solid. CH_2Cl_2 (10 mL) and Et_3N (0.2 mL, 1.4 mmol) were added followed by 4-bromobenzenesulfonyl chloride (0.18 g, 0.72 mmol), and the reaction mixture was stirred for 15 h at room temperature. The mixture was poured onto CH_2Cl_2 and saturated aqueous $NaHCO_3$, and the organic layer was separated, dried ($MgSO_4$), filtered, and concentrated to afford 238 mg of crude material. This material was recrystallized from EtOH/hexanes to afford X-ray quality crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70−7.76 (m, 4H), 6.43 (bs, 1H), 5.66 (m, 4H), 3.62−3.67 (m, 1H), 3.53 (s, 1H), 3.23−3.29 (m, 1H), 1.77−1.84 (m, 1H), 1.39−1.44 (m, 1H), 1.07 (s, 3H), 0.75 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.5, 27.5, 38.5, 42.7, 47.5, 71.6, 128.6, 129.3, 132.6, 134.7, 172.7. MS: *m/e* 361.0, 363.0 $[MH]^+$. HRMS: calcd for $C_{13}H_{18}N_2O_3S$ (MH^+) 361.0222, found 361.0215. $[\alpha]^{23}_D = +119$ (*c* 0.65, $CHCl_3$).

Acknowledgment. We thank Dr. Amy A. Sarjeant at Johns Hopkins University for the X-ray analysis of compound **11** as well as Dr. Jacques Briand for assistance with NMR experiments.

Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra, X-ray crystallographic data (CIF) for **11**, analytical details for the resolution of (±)-**1**, (±)-**9** and (±)-**10**, as well as the ee determination of their respective enantiomers. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7027163