Synthesis of 4-*cis*-Phenyl-L-proline via Hydrogenolysis

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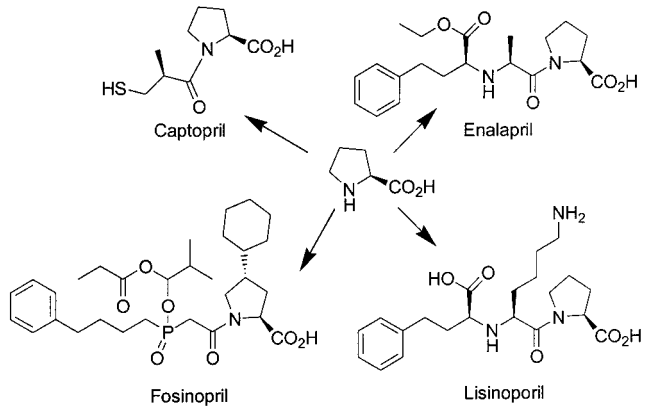
Introduction

Proline is an important amino acid in many naturally occurring bioactive peptides such as gramicidin[1,2] and α-melanotropin,[3,4] both of which have important biological activities. In addition, proline and its 4-substituted derivatives have been extensively used in the pharmaceutical industry, such as in angiotensin-converting enzyme (ACE) inhibitors, including Captopril,[5] Enalapril,[6] Fosinopril,[7] and Lisinopril[6] (Chart 1), which are widely introduced to treat hypertension and congestive heart failure. Furthermore, among the 20 naturally occurring amino acids proline is the only residue found in proteins that is cyclic and a secondary amine, providing novel constraints. Hence, its unique structural properties and medicinal potentials have directed our research to the design and synthesis of novel proline derivatives. It has been found that appropriate conformational constraints provide a powerful method for the design of peptide ligands with potent bioactivities and selectivities.[8−17] In this regard, proline provides a special structure for stabilizing turns and other secondary structures in compounds that incorporate it.[18−22] In searching for novel constrained amino acids for our design of selective and potent ligands, we have found a simple method for substitution at the 4-position of proline starting from 4-*trans*-hydroxy-proline (**2**), a naturally abundant amino acid.

Chart 1. Examples of Proline-Related ACE Inhibitors



Results

More than a decade ago, it was reported that 4-*cis*-phenylproline (**1**) can be made by hydrogenation (Scheme 1, Path A) of the double bond in compound **3**.[7] However, attempts to repeat the literature methods were not successful in our hands. To make this compound readily available for our ongoing investigation of its application in biological research, we have investigated a new and practical route to this compound, which has been successfully synthesized by hydrogenolysis (Scheme 1, Path B) of the 4-*cis*-hydroxy-4-*trans*-phenylproline derivative (**7**). Initially, hydroxy proline (**2**) was esterified in dry methanol saturated with dry hydrogen chloride gas to give **5** (Scheme 2) in a quantitative yield. The N^{α}-amino group was then Boc protected, and the hydroxyl group was oxidized by CrO_3 in a rather low yield (ca. 40%).[23] Attempts to optimize this procedure by slow addition of the oxidant did not improve the yield significantly, and lowering the temperature did not either. By applying PDC as the oxidant, a slightly improved yield (50%) for **6b** was achieved.

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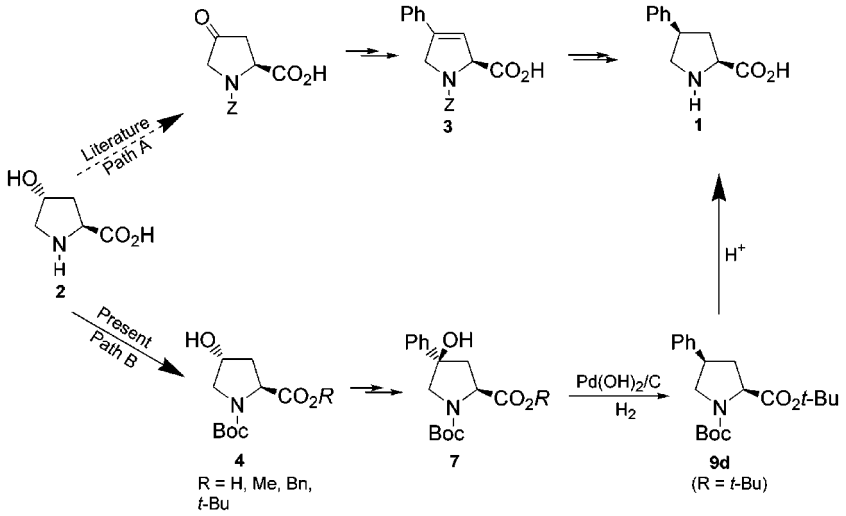
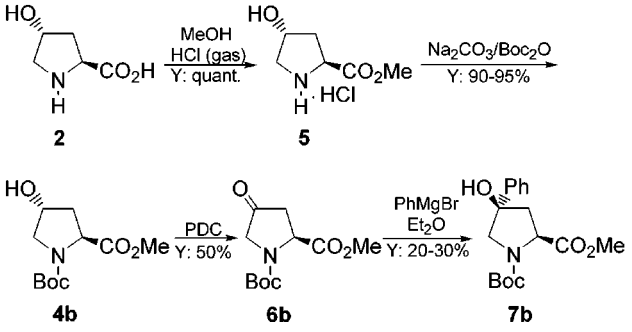
Scheme 1. Procedures to Synthesize 4-*cis*-Ph-Proline



Scheme 2. Synthesis of 7b



Scheme 3. Synthesis of 7d

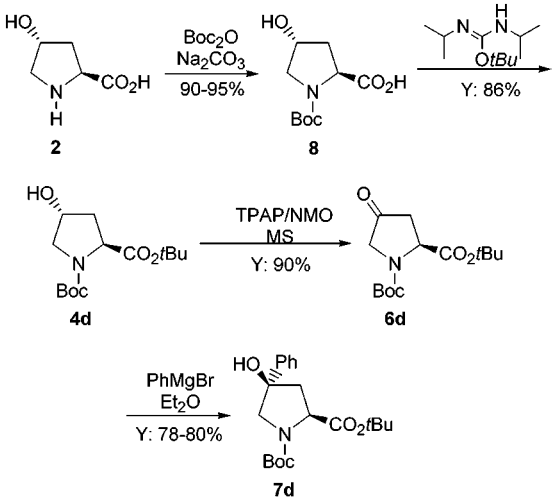
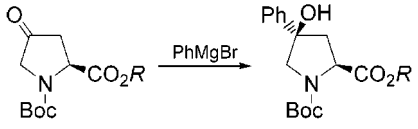


Table 1. Grignard Addition of 6 with PhMgBr



product	R	yield (%)[a]
7a	H	40−45[b]
7b	CH_3	20−30
7c	Bn	36[c]
7d	*t*-Bu	78−80

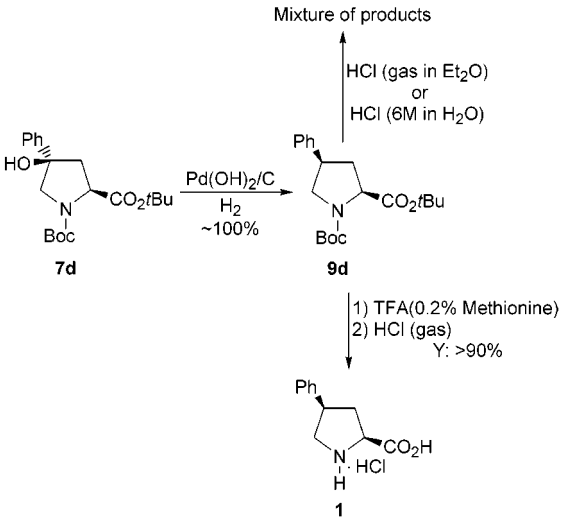
[a] Isolated yields. [b] THF was the reaction media. [c] When THF was used as the solvent, no desired product was obtained.

Low yields (ca. 20−30%) were obtained for the Grignard addition with phenylmagnesium bromide to **6b**, and quite a few side products were detected by TLC. We postulated that the problem might arise from a competitive reaction with the carbonyl groups in **6b**. Hence, the carboxyl group was protected in the form of several esters (Table 1). With a benzyl group as the protecting group, the yield improved to 36%. Though the phenyl group can provide steric protection, its electron-withdrawing property may increase the electrophilicity of the carbonyl group and the combined effect may lead to only a small improvement in the yield. Surprisingly, when no protection was used for the acid group, the Grignard addition gave a modestly improved isolated yield of 40−45%, presumably because the negative ion reduced electrophilicity of the acid carbonyl group. When the bulky *tert*-butyl group was used for ester protection (Scheme 3), its steric effect and electron-donating character made the carbonyl much less electrophilic and resulted in a greatly improved yield (ca. 80%, Table 1) for the Grignard reaction. Only a single diastereoisomer, 4-*cis*-hydroxyl-4-phenyl-L-proline derivative (**7d**), was obtained. In addition, the *tert*-butyl ester protecting group made the final deprotecting step easier, since both N^{α}-Boc and *tert*-butyl ester groups could be removed under mild condition by trifluoroacetic acid (TFA) in one step.

The diastereoselectivity of the Grignard addition of phenylmagnesium bromide to **6** was assessed. For compound **6b** (R = Me), only one diastereoisomer, methyl 4-*cis*-hydroxyl-4-phenyl-L-prolinate (**7b**), was obtained. Neither high-resolution NMR nor HPLC with a diode array detector were able to detect any of the other diastereoisomer. An X-ray structure of compound **7b** demonstrated that the hydroxyl group is *cis* to the acid group (see Supplementary Information). Hence, the phenyl group attacked the carbonyl group only *trans* to the acid group. Similarly, for other analogues, **7a**, **7c,** and **7d**, only one diastereoisomer, which has a hydroxyl group *cis* to the acid group, was obtained.

Hydrogenolysis of **7d** by hydrogen with $Pd(OH)_2$ in methanol led to almost pure dehydroxyl product **9d** (Scheme 4) with a de > 95%. In addition, the chiral center at the 4-position was inverted, as can be seen from the X-ray structure of **9d** (see Supplementary Information).

Scheme 4. Synthesis of 1



We were not able to separate any intermediate. In fact, when TLC was used to monitor the reaction, only the starting material **7d** and the product **9d** were detected. Further investigation is needed for the identification of the reaction mechanism for this step.

Attempts to deprotect both amino and acidic groups of **9d** were carried on in hydrogen chloride gas in ethyl ether or hydrochloric acid (6 M in water) and gave mixtures of products. However, deprotection in almost pure TFA (with 0.2% methionine, Scheme 4) provided essentially pure amino acid **1** as an oil. Upon treatment with hydrogen chloride gas in deionized water, 4-*cis*-phenyl-L-proline hydrogen chloride (**1**) was obtained, after extraction with diethyl ether and subsequent evaporation of the aqueous solution, as a white powder that was pure on the basis of NMR, TLC and HPLC.

Conclusion

A practical new pathway to the synthesis of 4-*cis*-phenyl-L-proline (**1**) has been developed. A key step involving a regio- and diastereoselective Grignard reaction has been thoroughly investigated. All of the steps are easily scalable. Currently, we are investigating other aryl-substituted prolines using the procedures reported here.

Experimental Section

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Analytical thin-layer chromatography was carried out on precoated silica gel plates. Flash column chromatography was performed using E. Merck Silica gel (230 mesh). Independent analysis of purity for synthetic products was achieved using analytical HPLC system (column, Vydac C18; detector, diode array; flow rate, 1.0 mL/min; gradient, 10−90% acetonitrile, 90−10% water (0.1% TFA) over 40 min. High-resolution mass spectra (HR-MS) were obtained at the University of Arizona Mass Spectroscopy Facility in the Department of Chemistry. All NMR spectra were obtained on a 500 MHz spectrometer. Optical rotations were measured on a polarimeter using a 0.5-dm cell. X-ray crystallography was performed at the University of Arizona Crystallography Facility.

***tert*-Butyl N^{α}-Boc-4-*trans*-hydroxy-L-prolinate (4d).** *O*-*tert*-Butyl *N*,*N*′-diisopropylisourea[24] (2.98 g, 13 mmol) was added dropwise to a solution of N^{α}-Boc-4-*trans*-hydroxy-L-proline (**8**, 3.00 g, 13 mmol) in THF (30 mL) over a period of 10 min at room temperature, and then the mixture was heated to 55−60 °C for 4 h. Additional *O*-*tert*-butyl *N*,*N*′-diisopropylisourea (2.98 g, 13 mmol) was added to the mixture, and stirring was continued overnight. After the mixture cooled, the precipitated urea was filtered off and the filtrate was evaporated in vacuo to give a solid residue, which was purified by flash column chromatography (hexanes/ethyl acetate = 1:1, v/v) to give the corresponding *tert*-butyl ester. Yield, 3.2 g (86%), mp 62−64 °C. $[\alpha]^{25}_{D} = -64.8$ (*c* = 1.3, $CHCl_3$). HR-MS calcd for $C_{14}H_{26}NO_5$: $[M + H]^+$ 288.1857, found 288.1821. $R_f = 0.58$ ($CHCl_3$/MeOH = 9:1). ^{1}H NMR ($CDCl_3$): 4.44 (hump, 1H), 4.30−4.23 (m, 1H), 3.62−3.49 (m, 2H), 2.33−2.20 (m, 1H), 2.07−1.99 (m, 1H), 1.45−1.43 (3s, 18H). ^{13}C NMR ($CDCl_3$): 172.14, 154.21, 81.07, 80.12, 69.06, 58.52, 54.53, 39.10, 38.34, 28.28, 27.94, 27.87.

***tert*-Butyl N^{α}-Boc-4-keto-L-prolinate (6d).** Tetrapropylammonium perruthenate (TPAP, 63 mg) was added in one portion to a stirred mixture of N^{α}-Boc-4-*trans*-hydroxy-L-proline (**4d**, 1 g, 3.47 mmol), *N*-methylmorpholine *N*-oxide (0.62 g, 15.6 mmol), and powdered molecular sieves (4 Å, 1.78 g) in dichloromethane (7 mL) at room temperature under Ar. The mixture was stirred for 3 h and then filtered and evaporated in vacuo to give a black residue. The product was purified by flash column (CH_2Cl_2/EtOAc = 1:1, v/v) and recrystallized from ether and hexane to give the corresponding ketone **6d**. Yield, 0.9 g (90%), mp 66−67 °C (lit. 67−68 °C).[23] $[\alpha]^{25}_{D} = +11.2$ (*c* 1.2, $CHCl_3$), lit. $[\alpha]^{25}_{D} = 10.65$ (*c* 1.23, $CHCl_3$).[23] HR-MS calcd for $C_{14}H_{24}NO_5$ $[M + H]^+$ 286.1703, found 286.1665. $R_f = 0.55$ (hexane/EtOAc = 7:3). ^{1}H NMR ($CDCl_3$): 4.70−4.58 (q, *J* = 10.4 Hz, 1H), 3.81−3.88 (m, 2H), 3.06−2.85 (m, 1H), 2.58−2.48 (d, *J* = 18.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): 208.88, 208.07, 170.82, 154.31, 153.62, 82.31, 80.97, 57.02, 56.56, 52.92, 52.48, 41.37, 40.84, 28.21, 27.86.

***tert*-Butyl N^{α}-Boc-*cis*-4-hydroxy-4-phenyl-L-prolinate (7d).** Phenylmagnesium bromide (3 M in Et_2O, 4.5 mL, 13.5 mmol) was added over a period of 15 min to a magnetically stirred solution of Boc-4-keto-L-proline-*tert*-butyl ester (**6d**, 1.5 g, 5.25 mmol) in dry diethyl ether (75 mL) at −60 °C. After 5 more minutes of stirring after the completion of the addition of PhMgBr, a saturated solution of ammonium chloride (15 mL) was added slowly to quench the reaction. Then the solution was stirred at room temperature for 1 h, and diethyl ether (50 mL) was added. The organic layer was successively washed with water (15 mL × 2) and brine (15 mL) and dried overnight over anhydrous $MgSO_4$. The solution was concentrated in vacuo. The resulting residue was recrystallized from hexanes. Yield of **7d**, 1.5 g (80%), mp 105−107 °C. $[\alpha]^{25}_{D} = -11.8$ (*c* 1.3, $CHCl_3$). HR-MS calcd for $C_{20}H_{30}NO_5$ $[M + H]^+$ 348.2175, found 348.2177. $R_f = 0.55$ (hexane/EtOAc = 7:3). ^{1}H NMR ($CDCl_3$): 7.54−7.28 (m, 5H), 4.44−4.36 (q, *J* = 10.1 Hz, 1H), 3.99−3.90 (m, 1H), 3.79−3.68 (q, *J* = 11.5 Hz, 1H), 2.74−2.67 (m, 1H), 2.32−2.26 (t, *J* = 14.2 Hz, 1H), 1.55−1.49 (4s, 18H). ^{13}C NMR ($CDCl_3$): 174.20, 173.99, 154.27, 153.80, 141.47, 141.36, 128.38, 127.60, 125.26, 82.82, 82.62, 80.46, 80.30, 80.06, 79.19, 61.42, 60.70, 59.45, 59.38, 44.39, 43.31, 28.35, 28.26, 27.95, 27.88.

***tert*-Butyl N^{α}-Boc-*cis*-4-phenyl-L-prolinate (9d).** *tert*-Butyl N^{α}-Boc-*cis*-4-hydroxy-*trans*-4-phenyl-L-prolinate (**7d**, 3.06 g, 8.40 mmol) was hydrogenated over $Pd(OH)_2$ (0.7 g) in methanol (70 mL) for 4 days at room temperature under a H_2 atmosphere (3 atm). The catalyst was filtered off, and the filtrate was concentrated in vacuo to give a residue, which was purified by recrystallization from hexane and ethyl acetate. Mp 92−94 °C, $[\alpha]^{25}_{D} = -45.4$ (*c* 1.0, $CHCl_3$). HR-MS calcd for $C_{20}H_{28}NO_4$, $[M + H]^+$ 348.2175, found 348.2177. $R_f = 0.68$ (hexane/EtOAc = 7:3). ^{1}H NMR ($CDCl_3$): 7.38−7.27 (m, 5H), 4.33−4.25 (m, 1H), 4.14−3.96 (m, 1H), 3.48−3.43 (m, 1H), 3.42−3.34 (m, 1H), 2.77−2.68 (m, 1H), 2.07−2.00 (m, 1H), 1.52−1.50 (3s, 18H).

***cis*-4-Phenylproline HCl Salt (1).** N^{α}-Boc-*trans*-4-phenyl-L-proline-*tert*-butyl ester (**9d**, 100 mg, 0.29 mmol) was dissolved in TFA (0.2% methionine, 4 mL), and the mixture was stirred for 2 h at room temperature. The solution was then concentrated. To the residue was added diethyl ether, and the resulting precipitate was filtered and dried in vacuo. The solid was then dissolved in water (20 mL). Pure HCl gas was bubbled into the solution. The solution was extracted with diethyl ether (20 mL), and the aqueous layer was then evaporated in vacuo to yield a white solid. Yield of **1**, 60 mg (90%), mp 175−177 °C, $[\alpha]^{25}_{D} =$

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+4.27 (*c* 0.5, MeOH). R_f = 0.42 (*n*-BuOH/AcOH/H_2O = 4:1:1). HR-MS calcd for $C_{11}H_{13}NO_2$ $[M + H]^+$ 192.1052, found 192.1018. ^1H NMR (D_2O): 7.36−7.26 (m, 5H), 4.50−4.47 (t, *J* = 9.0 Hz, 1H), 3.77−3.73 (t, *J* = 9.6 Hz, 1H), 3.62−3.58 (m, 1H), 3.36−3.31 (t, *J* = 11.3 Hz, 1H), 2.82−2.77 (m, 1H), 2.19−2.12 (m, 1H). ^{13}C NMR (D_2O): 171.72, 137.59, 129.01, 127.75, 127.13, 59.92, 50.92, 43.00, 35.58.

Benzyl *N*$^\alpha$-Boc-4-keto-prolinate (6c). To a solution of *N*$^\alpha$-Boc-4-*trans*-hydroxy-proline (**8**, 10 g, 43.2 mmol) and benzyl bromide (9.59 g, 56.2 mmol) in THF (40 mL) was added triethylamine (7.86 mL, 56.2 mmol) at 0 °C, and then the mixture was stirred overnight. After filtration, the filtrate was evaporated in vacuo to give a residue, which was subsequently purified by flash chromatography (hexane/ethyl acetate = 4:6, v/v) to give benzyl *N*$^\alpha$-Boc-4-*trans*-hydroxy-L-proline ester as a colorless oil. Yield, 12.6 g (91%). Benzyl *N*$^\alpha$-Boc-4-*trans*-hydroxy-proline ester (12.6 g, 39 mmol) was added to a solution of PDC (45 g, 120 mmol) in DMF (100 mL) at 0 °C, and the mixture was stirred for 8 h at room temperature. To this mixture was added water (50 mL), and the solution was extracted by ether (150 mL × 3). The solution was evaporated in vacuo to give a residue, which was purified by flash chromatography (hexanes/ethyl acetate = 7:3, v/v) to yield a colorless oil. Yield of **6c**, 8.0 g (64%), $[\alpha]^{25}_D$ = +0.73 (*c* 1.5, $CHCl_3$), lit. $[\alpha]^{20}_D$ = −5.4 (*c* 1, $CHCl_3$).[23] HR-MS calcd for $C_{17}H_{22}NO_5$: $[M + H]^+$ 320.1489, found 320.1496. R_f = 0.57 (hexane/EtOAc = 7:3). ^1H NMR ($CDCl_3$): 7.35 (s, 5H), 5.30−5.12 (m, 2H), 4.90−4.72 (2d, *J* = 9.8, 8.8 Hz, 1H), 3.95−3.87 (m, 2H), 3.03−2.91 (m, 1H), 2.65−2.56 (d, *J* = 8.8 Hz, 1H), 1.51 & 1.41 (2s, 9H). ^{13}C NMR ($CDCl_3$): 208.34, 207.54, 171.55, 171.51, 154.21, 153.39, 13.504, 134.92, 128.64, 128.57, 128.42, 128.09, 81.24, 67.47, 67.32, 67.31, 67.30, 67.28, 67.26, 67.25, 67.22, 56.26, 55.64, 52.80, 52.39, 41.12, 40.62, 40.54, 28.19, 28.01.

Benzyl *N*$^\alpha$-Boc-*cis*-4-hydroxy-4-phenyl-L-prolinate (7c). The coupling between benzyl *N*$^\alpha$-Boc-4-keto-L-prolinate (**6c**, 2.0 g, 6.23 mmol) and phenylmagnesium bromide was carried out by the same method (using dry diethyl ether as the solvent) outlined for the synthesis of *tert*-butyl **N**$^\alpha$-Boc-*cis*-4-hydroxy-4-phenyl-L-prolinate. (For this reaction, when THF was used as a solvent, we did not obtain any of the desired compound). After purification by flash chromatography, the titled compound was obtained as a colorless oil which crystallized as a white solid **7c** after long standing. Yield, 0.9 g (36%), mp 92−94 °C. $[\alpha]^{25}_D$ = −25.6 (*c* 0.36, $CHCl_3$), lit. $[\alpha]^{25}_D$ = −63.34 (*c* 1, $CHCl_3$).[23] HR-MS calcd for $C_{23}H_{28}NO_5$: $[M + H]^+$ 398.1967, found 398.1967. R_f = 0.50 (hexane/EtOAc = 7:3). ^1H NMR ($CDCl_3$): 7.48−7.28 (m, 10H), 5.36−5.15 (m, 2H), 4.61−4.48 (2d, *J* = 9.8 Hz, 1H), 3.96−3.68 (m, 2H), 2.70−2.65 (t, *J* = 11.8 Hz, 1H), 2.37−2.30 (q, *J* = 13.8 Hz, 1H), 1.46, 1.36 (2s, 18H).

Methyl *N*$^\alpha$-Boc-4-*trans*-hydroxy-prolinate (4b). Methyl 4-*trans*-hydroxy-prolinate hydrochloride (**5**, 7.25 g, 50 mmol) was dissolved in a mixture of dioxane and water (2:1, v/v, 100 mL) at 0 °C. To the solution was added triethylamine (10.56 mL, 75 mmol) and Boc anhydride (14.53 g, 55 mmol). The reaction mixture was then stirred for 2 h at 20 °C and evaporated in vacuo. The resulting residue was washed with ethyl acetate (100 mL) and water (50 mL). The aqueous layer was successively washed with ethyl acetate (100 mL × 2). The combined organic layer was washed with HCl (0.5 M, 25 mL), water (25 mL × 2), sodium carbonate (5%, 25 mL), water (25 mL × 2), and brine (25 mL) and finally was dried overnight by anhydrous $MgSO_4$. The product was obtained as a colorless oil **4b** after the solvent was evaporated in vacuo and was used directly in the next step. Yield, 9.0 g (89%).

Methyl *N*$^\alpha$-Boc-4-keto-prolinate (6b). The synthesis (crude **4b** was used directly) was carried out by the same procedures used for the preparation of benzyl *N*$^\alpha$-Boc-4-keto-prolinate (**6c**). Methyl *N*$^\alpha$-Boc-4-keto-prolinate (**6b**) was isolated as a colorless oil. Yield, 5.4 g (50%). $[\alpha]^{25}_D$ = +9.82 (*c* 2.6, $CHCl_3$), lit. $[\alpha]^{26}_D$ = −21.7 (*c* 1.24, CH_3OH).[25] HR-MS calcd for $C_{11}H_{18}NO_5$: $[M + H]^+$ 244.1216, found 244.1191. R_f = 0.52 (hexane/EtOAc = 7:3). ^1H NMR ($CDCl_3$): 4.82−4.71 (dd, *J* = 9.3, 2.7 Hz, 1H), 3.91−3.88 (m, 2H), 3.77 (s, 3H), 2.99−2.89 (m, 1H), 2.60−2.56 (d, *J* = 18.7 Hz, 1H), 1.48−1.45 (3s, 9H). ^{13}C NMR ($CDCl_3$): 208.34, 207.54, 172.21, 154.26, 153.47, 81.26, 56.22, 55.50, 52.78, 52.45, 41.15, 40.71, 28.19, 27.88.

Methyl *N*$^\alpha$-Boc-*cis*-4-hydroxy-4-*trans*-phenyl-L-prolinate (7b). The reaction between *N*$^\alpha$-Boc-4-keto-proline methyl ester (**6b**, 490 mg, 2.0 mmol) and PhMgBr (2.0 M in Et_2O, 1.0 mL) was carried out by the same method outlined for the preparation of *tert*-butyl *N*$^\alpha$-Boc-*cis*-4-hydroxy-4-phenyl-L-prolinate. Yield, 200 mg (31%), mp 85−86 °C. $[\alpha]^{25}_D$ = −20.1 (*c* 0.8, $CHCl_3$). HR-MS calcd for $C_{17}H_{24}NO_5$: $[M + H]^+$ 322.1656, found 322.1655. R_f = 0.47 (hexane/EtOAc = 7:3). ^1H NMR ($CDCl_3$): 7.53−7.29 (m, 5H), 4.59−4.48 (dd, *J* = 9.4, 9.0 Hz, 1H), 4.00−3.71 (m, 5H), 2.73−2.67 (m, 1H), 2.39−2.33 (t, *J* = 15.6 Hz, 1H), 1.49−1.47 (3s, 9H). ^{13}C NMR ($CDCl_3$): 175.42, 175.17, 154.37, 153.58, 141.30, 141.23, 128.44, 128.42, 127.67, 125.22, 125.17, 80.63, 80.58, 79.21, 61.10, 60.20, 58.51, 58.31, 52.90, 52.59, 44.23, 43.26, 28.33, 28.24. A small portion of the product was recrystallized in a mixture of hexanes and ethyl acetate (95:5, v/v) and was used for the X-ray structural determination.

***N*$^\alpha$-Boc-4-keto-proline (6a).** A mixture of pyridine (44 mL) in dry CH_2Cl_2 (100 mL) was cooled at 0 °C. To this mixture was added CrO_3 (26.4 g). Stirring was continued at 0 °C for 30 min, and then the mixture was allowed to warm to room temperature over a period of 30 min. A solution of *N*$^\alpha$-Boc-4-hydroxy-proline (**8**, 10.4 g, mmol) in CH_2Cl_2 (160 mL) was added over 5 min, and stirring was continued for 1 h. The reaction mixture was filtered and evaporated in vacuo. The residue was extracted with diethyl ether (250 mL × 3). The combined ether exacts were washed successively with HCl (5%, 2 × 100 mL) and NaCl (1 M, 3 × 50 mL) and then dried over $MgSO_4$ overnight. The organic solution was then decolorized with active charcoal, filtered, and evaporated to give a yellow oil. The residue was then recrystallized from a mixture of ethyl acetate and hexane to yield a colorless solid **6a**. Yield, 5.05 g (49%), mp 155−157 °C (decomp), lit. 160−162 °C (decomp.).[23] $[\alpha]^{25}_D$ = −16.5 (*c* 0.9, MeOH), lit. $[\alpha]^{24}_D$ = +20.9 (*c* 0.49, CH_3COCH_3).[23] HR-MS calcd for $C_{10}H_{16}NO_5$: $[M + H]^+$ 230.0990, found 230.1021. R_f = 0.28 ($CHCl_3$/MeOH = 7:3). ^1H NMR (CD_3OD): 4.74−4.69 (m, 1H), 3.92−3.76 (m, 2H), 3.15−3.06 (m, 1H), 2.60−2.50 (m, 1H), 1.50−1.45 (3s, 9H).

***N*$^\alpha$-Boc-*cis*-4-hydroxy-4-phenyl-L-proline (7a).** PhMgBr (3 M in THF, 1.33 mL, 4 mmol) was added over 15 min to a stirred solution of *N*$^\alpha$-Boc-4-keto-proline (**6a**, 230 mg, 1 mmol) in THF (15 mL) at −50 °C. The mixture was stirred at −50 °C for 1 h. Ammonium chloride solution (10%, 10 mL) was added slowly at −50 °C, acidified to pH 2 by HCl (6 M), extracted by ethyl acetate (30 mL × 3), and concentrated to give a brown residue. The residue was dissolved in NaOH (2%), and the solution was washed with ether (20 mL × 2). The aqueous solution was acidified by HCl (6 M) and workup (EtOAc) to give a residue, which was recrystallized from diethyl ether to afford a white solid. Yield, 145 mg (45%), mp 177−78 °C. $[\alpha]^{25}_D$ = −43.9 (*c* 0.5, MeOH). HR-MS calcd for $C_{16}H_{22}NO_5$: $[M + H]^+$ 308.1460, found 308.1489. R_f = 0.40 ($CHCl_3$/MeOH = 7:3). ^1H NMR (CD_3OD): 7.52−7.28 (m, 5H), 4.53−4.45 (m, 1H), 3.80−3.69 (m, 2H), 2.79−2.73 (m, 1H), 2.48−2.45 (d, *J* = 13.3 Hz, 1H), 1.50−1.48 (2s, 9H).

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Supporting Information Available: Detailed X-ray structural reports on compounds **7b** and **9d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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