

A convenient synthesis of *trans*-3-hydroxy-L-proline

Surajit Sinha, Santosh Tilve,⁺ and Srinivasan Chandrasekaran^{*}

Department of Organic Chemistry, Indian Institute of Science, Bangalore-560012, India

E-mail: scn@orgchem.iisc.ernet.in

Dedicated to Professor S. Swaminathan on his 80th birthday

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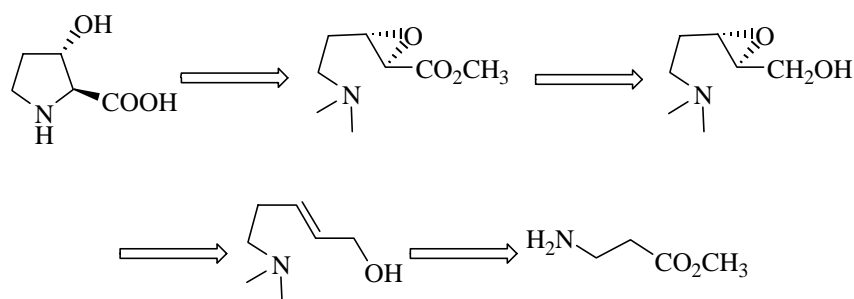
Abstract. A simple synthesis of *trans*-3-hydroxy-L-proline has been achieved starting from β -alanine making use of Sharpless asymmetric epoxidation as a key step in the synthesis.

Keywords: β -Alanine, Sharpless asymmetric epoxidation, hydroxyproline

Introduction

3-Hydroxyprolines are important components and chiral synthons for biologically active compounds such as cyclothialidine,¹ mucrorin-D,² telomycin³ and polyhydroxylated alkaloids⁴. *Trans*-3-hydroxy-L-proline **1** was isolated from bovine Achilles tendon collagen⁵. Several syntheses of 3-hydroxy prolines in general⁶ and *trans*-3-hydroxy-L-proline in particular⁷ have been reported. Most of the methods utilized enzymatic methods or chiron approach to get the optically pure product.

We decided to study a new approach to the asymmetric synthesis of *trans*-3-hydroxy-L-proline **1** using Sharpless asymmetric epoxidation as a key step in the synthetic strategy. A retrosynthetic analysis of this approach is depicted in scheme 1.



Scheme 1. Retrosynthetic analysis for compound **1**.

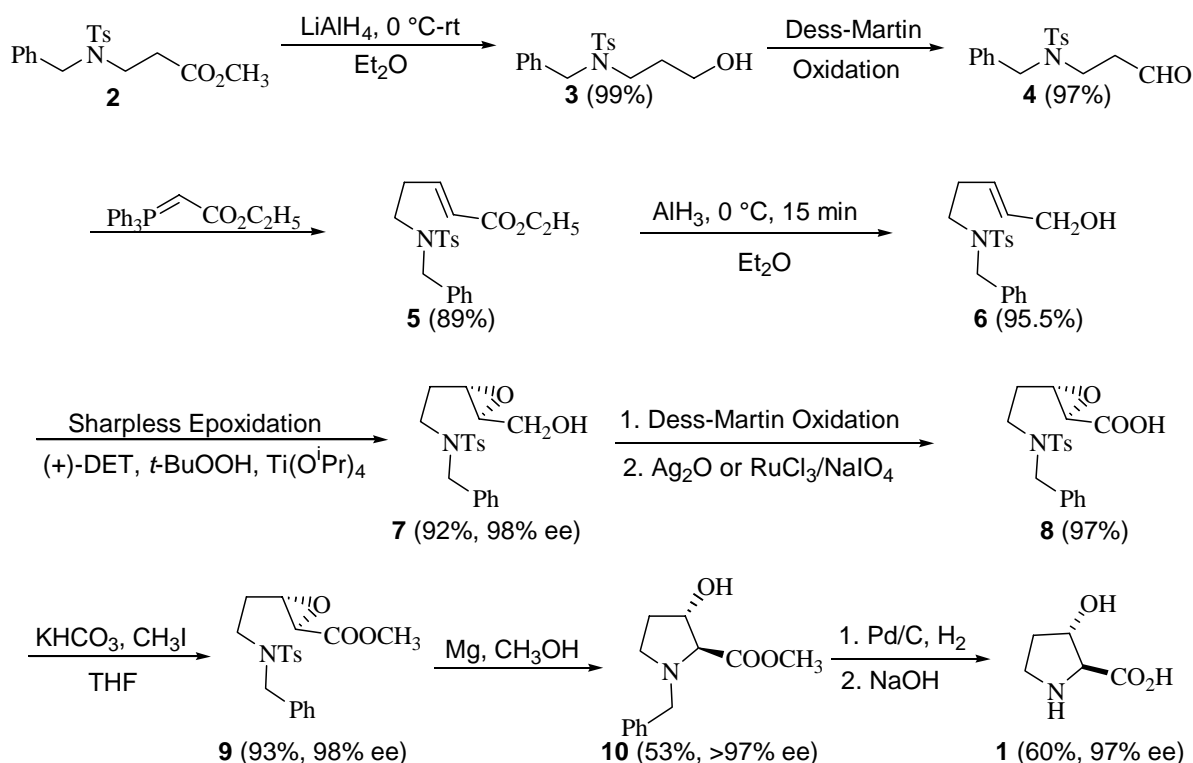
trans-3-Hydroxy proline can be derived by an intramolecular cyclisation of an amino epoxide. The chiral epoxide can be generated by Sharpless epoxidation of a suitable allylic alcohol. The allylic alcohol in turn can be derived from β -alanine by straightforward synthetic manipulations (Scheme 1).

The synthetic route was started with the readily available and inexpensive β -alanine. A suitable protective group for the amino group was needed which will be stable to Sharpless epoxidation conditions later in the sequence. It is well documented in the literature⁸ that the *tert*-butoxycarbonyl or benzyloxycarbonyl protected amines usually lead to the formation of cyclic urethane derivatives under these conditions. Various type of N-protecting groups that would encourage cyclization through nitrogen, namely *N*-tosyl, *N*-trityl, and even unprotected derivatives have been tried but in all the cases the reaction leads to a complex mixture of products. All the problems are taken care of when nitrogen is protected both with tosyl as well as benzyl group.⁹

The synthetic route adopted to achieve the synthesis of **1** is presented in Scheme 2. The methyl ester of β -alanine was readily converted to the *N*-protected methylester **2**, which on reduction with lithium aluminium hydride in ether (0°C) provided the alcohol **3** in quantitative yield. The alcohol **3** was then oxidized with Dess-Martin periodinane to afford the aldehyde **4** in 97% yield, while the Swern oxidation of the same compound gave the product only in 69% yield. The aldehyde **4** was allowed to react with triethylphosphono acetate¹⁰ and the E-olefinic ester **5** was obtained in 89% yield. Initially the reduction of the unsaturated ester **5** was tried with lithium aluminium hydride in ether but it led to a mixture of allylic alcohol **6** and the corresponding saturated alcohol. However, when the reduction of **5** was carried out with AlH₃, generated *in situ*, the allylic alcohol **6** was the only product obtained in quantitative yield.

Now the stage was set for carrying out Sharpless asymmetric epoxidation. The allyl alcohol **6** was treated with titanium tetrakisopropoxide, *tert*-butyl hydroperoxide, and L-(+)-diethyl tartarate¹¹ and the epoxy alcohol **7** was obtained in 92% yield with 98% e.e. The enantiomeric excess was estimated by NMR shift reagent [Eu(hfc)₃] experiments.

Initially, the direct oxidation of the epoxy alcohol **7** to the epoxy acid **8** with RuCl₃/NaIO₄¹² was carried out but the yield obtained in this reaction was generally poor (45% of corresponding methyl ester). Therefore, the epoxy alcohol **7** was first oxidized to the aldehyde with Dess-Martin periodinane, followed by oxidation with Ag₂O to get the epoxy carboxylic acid **8** (91%). Compound **8** was converted to its methyl ester **9** on treatment with methyl iodide in high yield. NMR experiments with chiral shift reagent [Eu(hfc)₃] revealed the product **9** to have optical purity of 98% e.e.



Scheme 2. Synthesis of *trans*-3-hydroxy-L-proline.

It was then decided to deprotect the N-benzyl group, which then can be cyclized on treatment with $\text{K}_2\text{CO}_3/\text{MeOH}$. Unfortunately, the reaction of compound **9** with $\text{Pd/C}/\text{H}_2$ did not effect the hydrogenolysis as desired. Even under forcing conditions at higher hydrogen pressure the hydrogenolysis could not be accomplished efficiently. The next strategy was to remove the tosyl protective group of **9** with $\text{Na}/\text{naphthalene}$.⁹ Here again, the reaction was not very clean. Finally detosylation of **9** was carried out successfully by reacting it with Mg/MeOH .¹³ Under these conditions, not only did the tosyl group undergo cleavage but it also underwent *in situ* cyclisation to give the *N*-benzylated 3-hydroxy-L-proline derivative **10** (33% overall yield from β -alanine; based on recovered starting material). The ^1H NMR of **10** did not give any indication as to whether it was the *cis*- or the *trans*- isomer. However, it was found to be a single diastereomer with 97% e.e. as confirmed by NMR chiral shift reagent $[\text{Eu}(\text{hfc})_3]$ experiment as well as HPLC analysis on a chiral column [cyclodex α -pm, solvent: 10% water containing 1% tetraethyl ammonium acetate buffer in MeOH, flow rate 0.4, retention time 5.99 min]. For purposes of characterization, compound **10** was converted to the corresponding *para*-toluene sulfonate salt. In the ^1H NMR of this salt, the α -H appeared as a clear doublet at δ 3.18 with a coupling constant of 1.7 Hz indicating it to be the *trans* product. Compound **10** on hydrogenolysis ($\text{Pd/C}/\text{H}_2$) followed by saponification gave a residue which was purified by resin bead column chromatography (elution with 1.5-2M aq. NH_3 solution) to afford **1** as a white solid with the melting point (228-236°C) (lit.^{7a, 7b} 228-235°C) and optical rotation $[\alpha] = -18.3^\circ$ {lit.⁷ $[\alpha] = -$

18.8} data identical to those, reported in the literature for *trans*-3-hydroxy-L-proline. Its optical purity was found to be >97% e.e.

In conclusion it has been demonstrated that starting from inexpensive achiral β -alanine, the 13-step synthesis of enantiopure *trans*-3-hydroxy-L-proline **1** has been achieved using Sharpless asymmetric epoxidation as a key-step.

Experimental Section

Preparation of TsBnNCH₂CH₂CH₂OH (3). To a stirred solution of TsBnNCH₂CH₂CO₂Me **2** (15 g, 0.04 mol) in anhydrous Et₂O (150 mL), lithium aluminum hydride (2 g, 0.052 mol) was added at 0°C over a period of 30 min and the reaction mixture was stirred at that temperature for another 30 min. The reaction mixture was quenched with moist Et₂O and filtered through a pad of Celite. The organic layer was washed with 1N HCl (2 × 40 mL), brine, dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure. The product **3** was obtained as a colorless liquid after column chromatography on silica gel (13.78 g, 99%).

IR (neat, cm⁻¹): 3500-3300; 1590; 1450; 1490; 1320; 1150; ¹H NMR (CDCl₃, 90 MHz) δ : 1.40 (m, 2H, -CH₂CH₂CH₂-); 1.60 (br s, 1H, -OH); 2.40 (s, 3H, Ar-CH₃); 3.20 (t, *J* = 6 Hz, 2H, -CH₂N-); 3.50 (t, *J* = 6 Hz, 2H, -CH₂O-); 4.25 (s, 2H, -CH₂Ph); 7.25 (m, 7H, aromatic protons); 7.70 9d, *J* = 7.7 Hz, 2H, aromatic protons).

Preparation of TsBnNCH₂CH₂CHO (4). Procedure A. Anhydrous DMSO (2.7 mL, 37.60 mmol) was added drop-wise to oxalyl chloride in anhydrous CH₂Cl₂ (40 mL) at -60°C under argon. It was stirred for 5 min and then the alcohol **3** (2 g, 6.26 mmol) in CH₂Cl₂ (10 mL) was added over a period of 15 min. The reaction mixture was stirred for another half an hour (-60°C) after which Et₃N (5.5 mL, 40 mmol) was added dropwise and it was allowed to warm to room temperature (25°C) over a period of 1 h. The reaction mixture was washed with 1N HCl (15 mL), brine (25 mL) and dried over anhydrous Na₂SO₄. The solvent was removed *in vacuo*. After purification by column chromatography on silica gel (using 15% EtOAc in hexane as eluent), the pure aldehyde **4** was obtained as a colorless liquid (1.37 g, 69%).

Procedure B. Oxidation of alcohol 3 with Dess Martin periodinane. To a stirred solution of periodinane (4.0 g, 8.4 mmol) in CH₂Cl₂ (15 mL) was added a solution of alcohol **3** (2.0 g, 6.26 mmol) in CH₂Cl₂ (10 mL). Within 5 min, a white precipitate appeared. The heterogeneous reaction mixture was stirred for 40 min. It was diluted with diethyl ether (75 mL) and the resulting suspension of iodine was added to 1.3M NaOH (30 mL). After the mixture was stirred for 10 min, the ether layer was washed successively with 1.3M NaOH (30 mL) solution, and brine (20 mL), dried over anhydrous sodium sulfate and concentrated to give the crude product. This, on purification on a silica gel column gave the pure aldehyde **4** as a colorless oil (1.93 g, 97%).

IR (neat, cm^{-1}): 1690; 1600; 1440; 1330. ^1H NMR (CDCl_3 , 90 MHz) δ : 2.40 (s, 3H, $-\text{ArCH}_3$); 2.60 (t, $J = 6$ Hz, 2H, $-\text{CH}_2\text{CHO}$); 3.40 (t, $J = 6$ Hz, 2H, $-\text{CH}_2\text{N-}$); 4.20 (s, 2H, $-\text{CH}_2\text{Ph}$); 7.30 (m, 7H, aromatic protons); 7.75 (d, $J = 7.7$ Hz, 2H, aromatic protons); 9.90 (s, 1H, $-\text{CHO}$). **EIMS**: 317(M^+).

Preparation of (E)-TsBnNCH₂CH₂CH=CHCO₂Et (5). The mixture of aldehyde **4** (0.242 g, 0.76 mmol), K_2CO_3 (0.21 g, 1.52 mmol), triphenylphosphon-acetate (182 μL , 0.91 mmol) and water (0.16 mL) was stirred for 16 h at room temperature. EtOAc (10 mL) was added and the reaction mixture was washed with water (5 mL), and brine, dried over anhydrous Na_2SO_4 , filtered, and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel (using 10% EtOAc in hexane as eluent) yielded **5** as a colorless liquid (0.262 g, 89%).

IR (neat, cm^{-1}): 1720; 1590; 1490; 1450; 1325; 1150. ^1H NMR (CDCl_3 , 300 MHz) δ : 1.26 (t, $J = 6.9$ Hz, 3H, $-\text{OCH}_2\text{CH}_3$); 2.23 (m, 2H, $-\text{CH}_2\text{CH=}$); 2.45 (s, 3H, ArCH_3); 3.18 (t, $J = 7.5$ Hz, 2H, $-\text{NCH}_2-$); 4.16 (q, $J = 6.9$ Hz, 2H, $-\text{OCH}_2\text{CH}_3$); 4.30 (s, 2H, $-\text{CH}_2\text{Ph}$); 5.62 (dd, $J_1 = 15.45$ Hz, $J_2 = 1.6$ Hz, 1H, $-\text{CH=CHCO-}$); 6.64 (dt, $J_1 = 15.6$ Hz, $J_2 = 7.2$ Hz, 1H, $-\text{CH}_2\text{CH=CH-}$); 7.30 (m, 7H, aromatic protons); 7.73 (d, $J = 8$ Hz, 2H, aromatic protons). LRMS m/z (%): 386 [(M^+-1) , 1.4]; 364 (4.4); 342 (22); 274 (100); 181 (16); 155 (24); 92 (100). Elemental Analysis: Calculated for $\text{C}_{21}\text{H}_{25}\text{O}_4\text{SN}$: C=65.11; H=6.46; N=3.62; Found: C=64.92; H=6.31; N=3.54.

Preparation of (E)-TsBnNCH₂CH₂CH=CHCH₂OH (6). AlCl_3 (4.1 g, 0.031 mol) was added portion wise over a period of 20 min to a stirred solution of lithium aluminum hydride (4.1 g, 0.11 mol) in Et_2O (300 mL) at 0°C . It was stirred for 5 min and the ester **5** (10.5 g, 0.027 mol) in Et_2O (80 mL) was added drop-wise through a dropping funnel (10 min) at 0°C . Then the reaction mixture was quenched with moist Et_2O . The organic layer was separated and the aqueous layer was washed with Et_2O (50 mL). The combined organic layer was washed with 2N HCl (100 mL), brine (60 mL) and dried over anhydrous Na_2SO_4 . The solvent was removed *in vacuo*. Purification by column chromatography on silica gel (using 30% EtOAc in hexane as eluent) yielded the allylic alcohol **6** as a colorless liquid (8.9 g, 95.5%).

IR (neat, cm^{-1}): 3400-3200; 1600; 1445; 1325; ^1H NMR (CDCl_3 , 300 MHz) δ : 1.65 (br s, 1H, $-\text{OH}$); 2.05 (m, 2H, $-\text{CH}_2\text{CH}_2\text{CH=}$); 2.44 (s, 3H, Ar-CH_3); 3.15 (t, $J = 7.5$ Hz, 2H, $-\text{NCH}_2-$); 3.95 (d, $J = 5.4$ Hz, 2H, $=\text{CHCH}_2\text{OH}$); 4.30 (s, 2H, $-\text{CH}_2\text{Ph}$); 5.46 (m, 2H, $-\text{CH=CH-}$); 7.30 (m, 7H, aromatic protons); 7.72 (d, $J = 8.4$ Hz, 2H, aromatic protons); LRMS (m/z , %): 344 [(M^+-1) , 5]; 274 (100); 258 (8); 181 (80); 155 (29); 106 (29); 91 (100).

Procedure for Sharpless epoxidation of allylic alcohol (6)

A two neck round bottomed flask (500 mL) equipped with a magnetic stirring bar, and molecular sieves (0.700 g, powder), was oven dried, then fitted with a septum and flushed with argon. The flask was charged with anhydrous CH_2Cl_2 (200 mL) and cooled to -24°C . Then the following liquids were added sequentially via syringe: titanium tetrakisopropoxide (7.55 mL, 25 mmol), L-

(+)-diethyl tartrate (4.5 mL, 26.5 mmol), allyl alcohol **6** (7.3 g, 21 mmol, the mixture was stirred for 5 min before the addition of **6**) and finally *tert*-butyl hydroperoxide (12.6 mL, 63 mmol, 3 eq, 5 molar solution in toluene). The resulting homogeneous solution was then stirred for 22 h at -24°C. Aqueous tartaric acid solution (10% 65 mL) was added while stirring and, after 30 min, the cooling bath was removed and stirring was continued at room temperature for approximately 1 h until the aqueous layer became clear. After separation of the aqueous layer, the organic layer was washed once with water [M14], dried over anhydrous sodium sulfate, filtered, and concentrated to afford a colorless oil with an odor revealing contamination by *tert*-butyl hydroperoxide. This oil was diluted with ether (150 mL), the resulting solution was cooled in an ice bath, and then 1*N* sodium hydroxide solution (70 mL) was added. This produced a two-phase mixture which was stirred at 0°C for 30 min. The ether layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. After purification by column chromatography on silica gel (using 30% EtOAc in hexane as eluent), the pure epoxy alcohol **7** was obtained as a colorless viscous liquid (7 g, 92%). $[\alpha]_D^{25} = -9$ ($c = 1$ in CH_2Cl_2). IR (neat, cm^{-1}): 3500-3200; 1590; 1490; 1440; 1320; 1150. ^1H NMR (CDCl_3 , 300 MHz) δ : 1.55 (2H, m, $-\text{CH}_2\text{CH}_2\text{CH}(\text{O})-$); 1.88 (br s, $-\text{OH}$); 2.45 (s, 3H, ArCH_3); 2.80 (m, 2H, $-\text{NCH}_2\text{CH}_2$); 3.25 (m, 2H, $-\text{CH}(\text{O})\text{CH}_2\text{OH}$); 3.65 (m, 1H, $-\text{CH}_2\text{CH}(\text{O})-$); 3.72 (m, 1H, $-\text{CH}(\text{O})\text{CH}_2\text{OH}$); 4.30 (s, 2H, $-\text{CH}_2\text{Ph}$); 7.30 (m, 7H, aromatic protons); 7.70 (d, $J = 8.0$ Hz, 2H, aromatic protons); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 21.2; 30.5; 45.1; 51.9; 52.4; 58.0; 61.5; 126.8; 127.8; 128.1; 128.3; 129.5; 135.9; 143.3; LRMS (m/z , %): 359 [$\text{M}^+ - 2$, 0.50]; 343 (0.70); 274 (80); 206 (100); 181 (7); 155 (10); 91 (100). Elemental analysis: Calculated for $\text{C}_{19}\text{H}_{23}\text{O}_4\text{SN}$: C=63.16, H=6.37, N=3.88; Found: C=62.89, H=6.64, N=4.01.

Conversion of epoxy alcohol **7** to epoxy ester **9**

To a stirred solution of periodinane (2 g, 4.21 mmol) in CH_2Cl_2 (15 mL) was added a solution of alcohol **7** (1.16 g, 3.21 mmol) in CH_2Cl_2 (10 mL). Within 5 min a white precipitate appeared. The heterogeneous reaction mixture was stirred for 40 min, diluted with ether (75 mL) and the resulting suspension of iodine was added to 1.3*M* NaOH (30 mL). After the mixture was stirred for 10 min, the ether layer was washed with 1.3*M* NaOH (30 mL) solution, and brine (20 mL), dried over anhydrous sodium sulfate and filtered. Removal of the solvent gave the corresponding the aldehyde as a colorless oil (1.15 g, 99.8%).

Silver nitrate (1.6 g, 9.5 mmol) in water (40 mL) was added to well stirred solution of sodium hydroxide (0.750 g, 18.75 mmol) in water (40 mL). A solution of the crude epoxy aldehyde (obtained as described above) (1.15 g, 3.20 mmol) in THF (10 mL) was added drop-wise to the suspension and stirred at room temperature for 3 h. The residue was filtered through a pad of Celite and washed with water (5 mL). After washing with ether (15 mL), the aqueous layer was acidified with cold 1*N* HCl and the white precipitate was extracted with ether (2×30 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield the carboxylic acid **8** as a colorless liquid (1.17 g, 97%).

IR (neat, cm^{-1}): 3400-2800; 1720; 1600; 1450; 1330; 1150. ^1H NMR (CDCl_3 , 300 MHz) δ : 1.50 (m, 1H, $-\text{CH}_2\text{CH}(\text{H})\text{CH}(\text{O})-$); 1.80 (m, 1H, $-\text{CH}_2\text{CH}(\text{H})\text{CH}(\text{O})-$); 2.46 (s, 3H, ArCH_3); 3.0 (m, 1H, $-\text{CH}_2\text{CH}(\text{H})\text{N}-$); 3.10 (d, $J = 2.1$ Hz, 1H, $-\text{CH}_2\text{CH}(\text{O})-$); 3.25 (m, 1H, $-\text{CH}_2\text{CH}(\text{H})\text{N}-$); 4.30 (s, 2H, $-\text{CH}_2\text{Ph}$); 7.30 (m, 7H, aromatic protons); 7.75 (d, $J = 8.7$ Hz, 2H, aromatic protons).

Methyl iodide (0.4 mL, 6.24 mmol) was added to a stirred mixture of crude epoxy carboxylic acid **8** (1.17 g, 3.12 mmol) and KHCO_3 (0.406 g, 4 mmol) in anhydrous DMF (8 mL). The reaction mixture was stirred at room temperature for 12 h. DMF was removed under reduced pressure, Et_2O (50 mL) was added to the residue and the mixture was washed with water (10 mL), sodium thiosulfate solution (10 mL, 20%), and brine. The organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in vacuo*. After purification by column chromatography on silica gel (using 20% EtOAc in hexane as eluent), the pure epoxy ester **9** was obtained as a colorless liquid (1.13 g, 93%). Overall yield of **9** from alcohol **7** was 91%.

$[\alpha]_D^{25} = -23.34$ ($c = 1.5$ in CH_2Cl_2). IR (neat, cm^{-1}): 1730; 1590; 1500; 1460; 1340; 1200; 1150. ^1H NMR (CDCl_3 , 300 MHz) δ : 1.56 (m, 1H, $-\text{CH}_2\text{CH}(\text{H})\text{CH}(\text{O})-$); 1.65 (m, 1H, $-\text{CH}_2\text{CH}(\text{H})\text{CH}(\text{O})-$); 2.45 (s, 3H, ArCH_3); 2.98 (m, 1H, $-\text{CH}_2\text{CH}(\text{H})\text{N}-$); 3.07 (d, $J = 1.8$ Hz, 1H, $-\text{CH}_2\text{CH}(\text{O})-$); 3.22 (m, 1H, $-\text{CH}_2\text{CH}(\text{H})\text{N}-$); 3.75 (s, 3H, $-\text{COOCH}_3$); 4.30 (s, 2H, $-\text{CH}_2\text{Ph}$); 7.30 (m, 7H, aromatic protons); 7.72 (d, $J = 8.4$ Hz, 2H, aromatic protons); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 20.6; 30.1; 4.1; 5.9; 52.1; 52.6; 55.0; 126.4; 127.2; 127.6; 127.9; 129.0; 135.3; 135.5; 142.7; 168.3. LRMS (m/z , %): 274 [$\text{TsBnN}^+=\text{CH}_2$], 15]; 234 [M^+-Tos], 12]; 155 (2); 118 (4); 91 (100). Elemental analysis: Calculated for $\text{C}_{20}\text{H}_{23}\text{O}_5\text{NS}$: C=61.69, H=5.91, N=3.60. Found: C=61.42, H=5.83, N=3.46.

Detosylation followed by cyclisation of **9** with Mg/MeOH

To a suspension of Mg (0.388 g, 16 mmol) in anhydrous MeOH (40 mL) was added a solution of the epoxy ester **9** (0.91 g, 2.35 mmol) in anhydrous MeOH (20 mL). The resulting suspension was stirred at room temperature for 12 h. MeOH was removed *in vacuo* and the residue was diluted with CHCl_3 (60 mL) and filtered through a pad of Celite®. The CHCl_3 layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. After purification by column chromatography on silica gel (using MeOH: *tert*-BuOMe: hexane 0.5: 2: 3.5 as eluent), proline derivative **10** was obtained as a colorless liquid (0.293 g, 53%); $[\alpha]_D^{25} = -22.1$ ($c = 0.6$ in CH_2Cl_2). Starting material **9** (0.110 g, 31%) was recovered from the reaction.

IR (neat, cm^{-1}): 3400-3100; 1730; 1450; 1200; ^1H NMR (CDCl_3 , 300 MHz) δ : 1.75 (m, 1H, $-\text{CH}(\text{H})\text{CH}(\text{OH})-$); 1.95 (m, 1H, $-\text{CH}(\text{H})\text{CH}(\text{OH})-$); 2.0 (br s, $-\text{OH}$); 2.80 (t, $J = 6.6$ Hz, 2H, $-\text{CH}_2\text{N}-$); 3.27 (m, 1H, $-\text{CH}_2\text{CH}(\text{OH})-$); 3.28 (d, $J = 1.8$ Hz, 1H, $-\text{CH}(\text{COOCH}_3)\text{N}-$); 3.77 (s, 3H, $-\text{COOCH}_3$); 3.80 (s, 2H, $-\text{CH}_2\text{Ph}$); 7.30 (m, 5H, aromatic protons). ^1H NMR ($\text{CDCl}_3+\text{D}_2\text{O}$, 300 MHz) δ : 1.75 (m, 1H); 1.95 (m, 1H); 2.82 (t, $J = 6.6$ Hz, 2H); 3.27 (m, 1H); 3.28 (d, $J = 1.8$ Hz, 1H); 3.78 (s, 3H); 3.80 (s, 2H); 7.30 (m, 5H). LRMS (m/z , %): 236 [M^++1], (3.5)]; 176 (8); 146 (100); 117 (5); 91 (100); 65 (14); Elemental Analysis: Calculated for $\text{C}_{20}\text{H}_{25}\text{O}_6\text{SN}$: C 58.97, H 6.14, N 3.44. Found C 58.89, H 6.29, N 3.60.

Data for *p*-toluene sulfonate salt of **10**: mp: 151-153°C.

¹H NMR (CDCl₃, 200 MHz) δ: 1.82 (m, 1H, -CH(H)CH(OH)-); 2.35 (m, 1H, -CH(H)CH(OH)-); 2.40 (s, 3H, ArCH₃); 2.95 (t, *J* = 7.8 Hz, 2H, -CH₂N-); 3.14 (m, 1H, -CH₂CH(OH)-); 3.18 (d, *J* = 1.7 Hz, 1H, -CH(COOCH₃)N-); 3.73 (s, 3H, -COOCH₃); 4.13 (s, 2H, -CH₂Ph); 7.35 (m, 7H, aromatic protons); 7.70 (d, *J* = 8.1 Hz, 2H, aromatic protons); 9.14 (br s, -NH(CH₂Ph)-).

¹H NMR (CDCl₃+D₂O, 200 MHz) δ: 1.90 (m, 1H); 2.25 (m, 1H); 2.38 (s, 3H); 2.95 (t, *J* = 7.8 Hz, 2H); 3.14 (m, 1H); 3.20 (d, *J* = 1.7 Hz, 1H); 3.73 (s, 3H); 4.14 (s, 2H); 7.35 (m, 7H); 7.70 (d, *J* = 8.1 Hz, 2H).

Preparation of *trans*-3-hydroxy-L-proline (**1**)

A mixture of the hydroxy ester **10** (0.045 g, 0.19 mmol) and 10% Pd-C (16 mg) in 15% HCO₂H in MeOH (4 mL) was hydrogenated at room temperature for 24 h under an atmosphere of hydrogen. The catalyst was filtered off and the solvent was evaporated under reduced pressure to give the debenzylated product as a brown oil. This crude product was taken up in a mixture of MeOH (0.6 mL) and aq. 2*N* NaOH (200 μL) and stirred at room temperature for 4 h. Then the reaction mixture was acidified with 1*N* HCl to pH ~2 and the solvent was removed *in vacuo*. The residue was dissolved in water (1 mL) and purified by ion-exchange chromatography [Dowex resin, 1.5-2*M* aq. NH₃ solution]. After evaporation of the solvent the *trans*-3-hydroxy-L-proline **1** was obtained as a colorless solid (0.015g, 60%). mp: (228-236°C decomp.) (lit.⁷ 228-235°C); [α]_D²⁵-18.3 (c-0.2, H₂O); lit.⁷ [α]_D²⁰-18.8

IR (KBr): 3410, 2920; ¹H-NMR(D₂O, 300 MHz) δ: 2.0 (2H, m, -CH₂CH(OH)-), 3.4(1H, m, -CH(CH₂)NH-), 3.5 (1H, m, -CH(CH₂)NH-), 4.1(1H, s, -CH(OH)-), 4.6 (1H, m, -CH(COOH)NH-); EIMS: 131 (M⁺).

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References and Notes

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