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Asymmetric Synthesis of 4-Substituted Prolines as Conformationally Constrained Amino Acid Analogues

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Abstract

Treatment of readily available chiral building block **1** with (2*R*)-2,3-*O*-isopropylideneglyceraldehyde (**5**) provides a new route for asymmetric synthesis of 2,4-disubstituted pyrrolidines. Several proline-amino acid chimeras: proline-leucine, proline-lysine, proline-arginine and proline-glutamic acid, are synthesized in highly diastereomerically pure forms.

Keywords: peptidomimetics, chimeras, 4-substituted prolines, 2,4-disubstituted pyrrolidines

This paper is dedicated to Professor A. Ian Scott on the occassion of his 70th birthday.

Introduction

In recent years, the design, synthesis, and utilization of peptidomimetics have attracted multidisciplinary interest in an effort to develop new pharmaceutical agents with improved pharmacokinetic properties and to firmly establish three dimensional structure-bioactivity relationships. Induction of conformational constraint into bioactive peptides has been regarded as a useful means to evaluate conformational prerequisites for biological activities [1,2,3,4]. Among numerous possibilities to attain conformational rigidity, incorporation of proline-amino acid chimeras [5] into bioactive peptides is particularly interesting [6,7]. Previously, we have reported efficient stereodivergent methodologies for the asymmetric synthesis of 2,3- and 2,5-disubstituted pyrrolidine derivatives starting from the readily available chiral synthon **1** [8,9,10,11]. In conjunction with our ongoing research program, we have been equally interested in developing a novel route to the asymmetric synthesis of 2,4-disubstituted pyrrolidines, in particular, 4-substituted proline derivatives. Although the widely available *trans*-4-hydroxy-L-proline has been employed in the synthesis of many 4-substituted proline derivatives [12], yet general and efficient protocols for the asymmetric synthesis of 2,4-disubstituted pyrrolidines have been noticeably rare and are thus in high demand [13,14,15]. With the molecular diversity in mind, compound **2** (Figure 1) with two discernible hydroxy functionalities was chosen as our primary synthetic target. Homologation of the unprotected hydroxy group should *a priori* provide a range of 4-substituted proline

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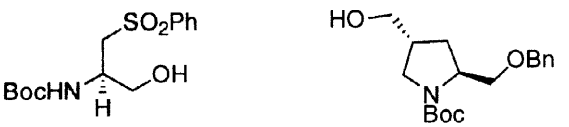
derivatives. In this paper we describe an efficient synthesis of compound **2** as well as proline-leucine, proline-lysine, proline-arginine and proline-glutamic acid chimeras as conformationally constrained amino acid analogues in enantiomerically pure form [16].



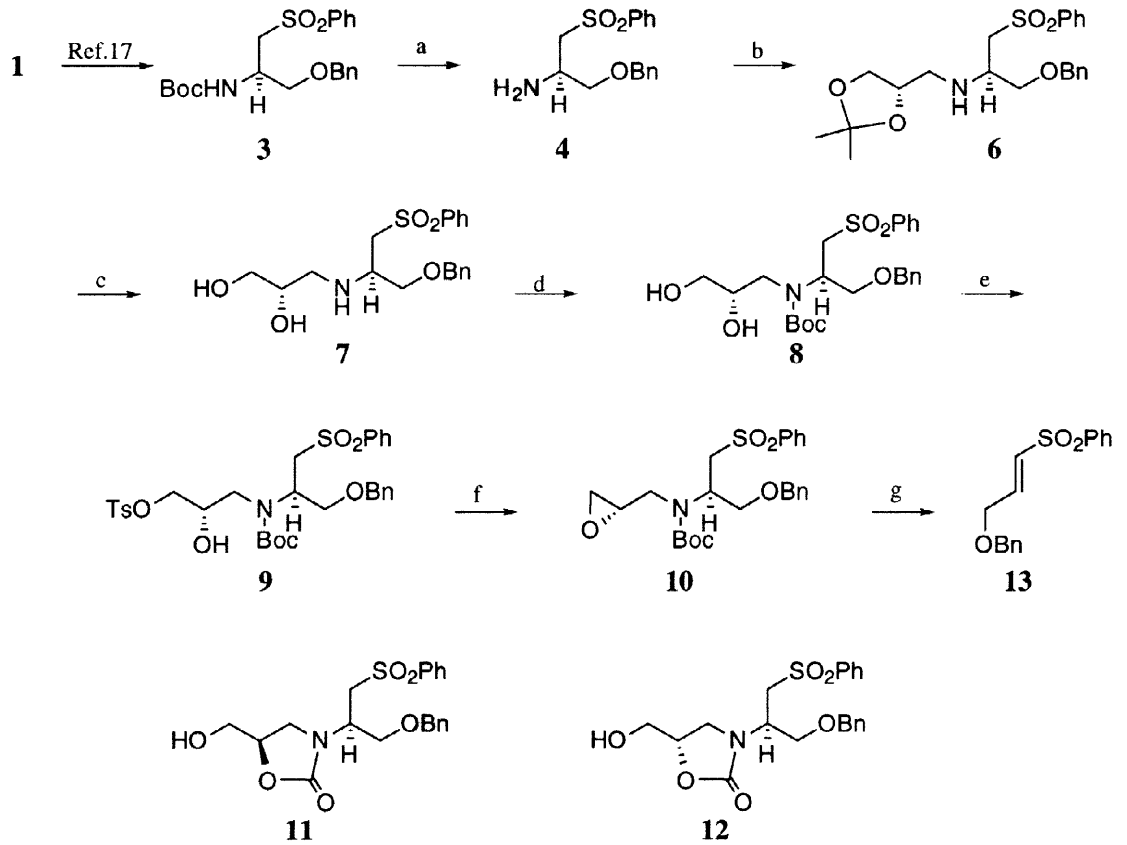
1 **2**

Figure 1

Results and Discussion

Synthesis of (2*S*,4*R*)-*N*-Boc-2-benzyloxymethyl-4-hydroxymethylpyrrolidine (2). Our initial investigations were focused on the preparation and subsequent cyclization of **10** (Scheme 1). Selective *O*-benzylation of synthon **1** [17] followed by removal of the *N*-Boc function under mild acidic conditions gave the primary amine **4**. Reductive alkylation of **4** with (2*R*)-2,3-*O*-isopropylideneglyceraldehyde (**5**) in the presence of $Ti(O^iPr)_4$ [18] furnished the secondary amine **6** in 68% yield. Hydrolysis of **6** afforded diol **7**, which was reprotected by treatment with Boc_2O in DMF to give **8** in high yield. Tosylation of the amino diol **8** under conventional conditions (TsCl, Py, rt, 24 h) afforded the monotosylate **9** with an excellent regioselectivity. Bistosylate was not formed even in the presence of excess of TsCl, probably due to the steric hindrance around the secondary alcohol. Treatment of **9** with potassium carbonate in wet DMF afforded the epoxide **10** which was found to be relatively unstable. Thus, upon standing at room temperature or during flash chromatography on silica gel, partial degradation occurred to give the oxazolidinone **11**. The formation of this oxazolidinone was readily explained by nucleophilic attack of the carbamate oxygen onto the epoxide with the inversion of configuration at the secondary hydroxy carbon. The stereochemistry of oxazolidinone **11** was confirmed by the preparation of its epimer **12**. On the other hand, treatment of diol **8** with K_2CO_3 in MeOH lead to the formation of the oxazolidinone **12** resulting from the nucleophilic attack of secondary alcohol onto the carbonyl function of *N*-Boc group.

With the compound **10** in hand, formation of pyrrolidine *via* the 5-*exo* cyclization of the corresponding sulfonyl stabilized carbanion was attempted. Unfortunately, treatment of **10** with LDA in THF at -70°C for 3 h did not afford the desired compound. Instead, degradation occurred to give a complex reaction mixture from which the olefin **13** was found as the only isolable product. Under various reaction conditions, we were unable to trigger the desired cyclization.

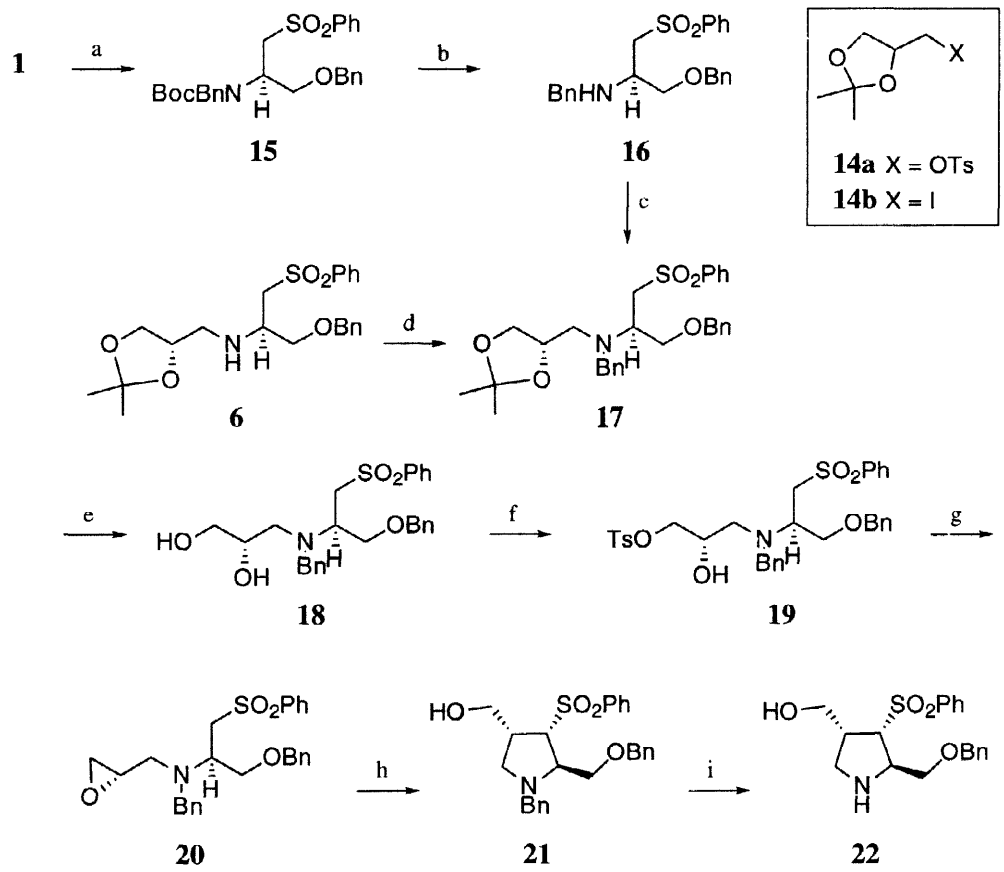


Reagents and conditions: a) 3N HCl-EtOAc, rt, 2 h, 94%; b) (2*R*)-2,3-*O*-isopropylideneglyceraldehyde (**5**), $Ti(O^iPr)_4$, rt, 1h; $NaBH_3CN$, MeOH, rt, overnight, 68%; c) 0.5 N HCl-MeOH, rt, 5 h, 96%; d) Boc_2O, DMF, rt, 48 h, 93%; e) TsCl, Py, rt, 24 h, 74%; f) K_2CO_3, wet DMF, rt, 24 h, 54%; g) LDA, THF, -70°C, 3 h, 30%.

Scheme 1

Assuming that the presence of *N*-Boc protecting group is responsible for the undesired β-elimination process leading to olefin **13**, we presumed that the replacement of *N*-Boc by an *N*-alkyl group could prevent this competing reaction by decreasing the amine's capacity as a leaving group. This proved to be rewarding and a successful synthesis of (2*S*,4*R*)-*N*-Boc-*trans*-2-benzyloxymethyl-4-hydroxymethylpyrrolidine **2** was accomplished as shown in Scheme 2. The *N,O*-bisbenzylation of (*R*)-**1** (NaH, $^nBu_4NI$, BnBr, THF) followed by the removal of the *N*-Boc function provided the secondary amine **16** (82% for two steps). Reductive alkylation of **16** with (2*R*)-2,3-*O*-isopropylideneglyceraldehyde **5** using sodium triacetoxyborohydride as reductant in 1,2-dichloroethane at room temperature afforded the tertiary amine **17** in 97% yield [19]. Alternatively, compound **17** can be synthesized by benzylation of **6** (BnBr, K_2CO_3, DMF, 80°C, 48 h, 63%; or PhCHO, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, rt, 6 h, 90%). However, the direct alkylation of the secondary amine **16** or the primary amine **4** with compound **14a** or **14b** was inefficient. Either starting material was recovered (K_2CO_3, HMPA, 80°C, 24 h), or degradation occurred at higher temperature

(120°C). Hydrolysis of acetonide under mild acidic conditions furnished the diol **18** (94%) which was then converted to the epoxide **20** by a straightforward two-step sequence *via* monotosylate **19** in excellent overall yield [20].



Reagents and conditions: a) NaH, THF, 0°C, 30 min; then BnBr, $^{n}Bu_4NI$, 0°C, 24 h, 86%; b) 3N HCl-EtOAc; rt, 1 h, 95%; c) (2*R*)-2,3-*O*-isopropylideneglyceraldehyde (**5**), $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, rt, overnight, 97%; d) Procedure A: BnBr, K_2CO_3, DMF, 80°C, 48 h, 63%; Procedure B: PhCHO, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, rt, 6 h, 90%; e) 4N HCl-THF, rt, 3 h, 94%; f) TsCl, Py, 0°C, 24 h, 85%; g) K_2CO_3, wet DMF, rt, 24 h, 99%; h) $Ti(O^{i}Pr)_4$, THF, -70°C, 10 min, then KHMDS, -70°C, 2 h, 73%; i) H_2 (1 atm), 10% Pd/C, MeOH, rt, 21 h, 62%.

Scheme 2

Cyclization of the epoxy sulfone **20** was found to be more difficult than expected. Thus, treatment of the epoxy sulfone **20** in THF with LDA at room temperature did not afford the desired cyclic product and only the starting material was recovered. The result was nevertheless encouraging since the competing β-elimination process was indeed avoided in this manner. This allowed us to carry out a more detailed survey of reaction conditions and some of the results varying the base, the Lewis acid additive, and the reaction temperature are summarized in Table 1.

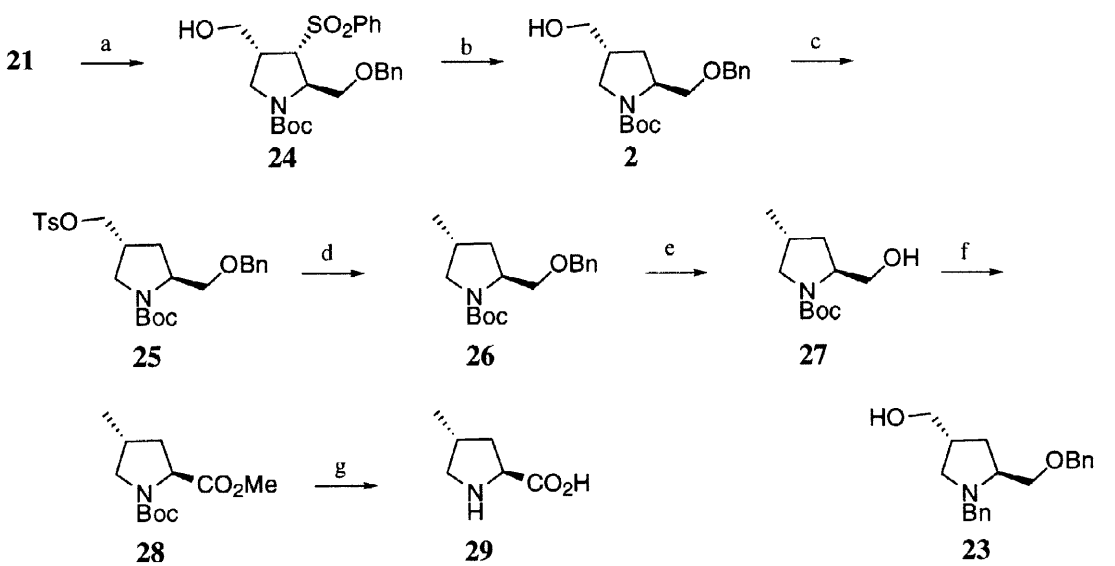
Table 1 Suvey of cyclization conditions[a]

Entry	Base	Lewis acid	Temperature	Yield of **21**
1	LDA	——	-70°C then 0°C	0%
2	KHMDS	——	-70°C then 0°C	8%[b]
3	KHMDS	BF_3OEt_2	-70°C	44%[c]
4	KHMDS	$ZnCl_2$	-70°C then rt	44%[b]
5	KHMDS	$Ti(O^iPr)_4$	-70°C	73%[c]

[a]THF was used as solvent; [b]mixture of two diastereoisomers; [c]single stereoisomer

As can be seen, the desired 5-*exo* cyclization can indeed be performed although both the yield and the stereoselectivity were quite sensitive to the different reaction parameters. When KHMDS was used as base without Lewis acid additive (entry 2) or in the presence of $ZnCl_2$ (entry 4), a mixture of two diastereoisomers was produced. These two stereoisomers differed from each other at the C-3 carbon center since removal of the phenylsulfonyl group afforded a single diastereoisomer (*vide infra*). The optimal conditions found in our hand involved the treatment of the epoxy sulfone **20** in THF with KHMDS in the presence of 2 equiv of $Ti(O^iPr)_4$ at -70°C (entry 5). Under these conditions, pyrrolidine **21** was isolated in 73% yield as a single diastereomer. The exclusive 5-*exo* cyclization mode was in accord with the literature precedents [21,22]. The stereochemistry of cyclic product was determined from detailed NMR analysis. Initial studies were carried out with compound **21**. Although resolution of the ^1H NMR spectrum was good, the overlap of H-4 signals with others made the stereochemical assignment difficult. Therefore the *N*-benzyl group of **21** was removed selectively by hydrogenolysis [H_2 (1 atm), 10% Pd/C, MeOH, rt, 21 h, 62%] to afford compound **22**. The ^1H NMR signals of this compound could be fully assigned from 2D ^1H-^1H COSY, HMBC and 2D NOESY experiments. An intense NOE observed between H-3 and H-4, between H-3 and CH_2OBn and the lack of a cross peak between H-2 and H-4 in NOESY were in accord with the stereochemistry shown in Scheme 2. A weak NOE was also observed between H-2 and H-3. While the stereochemistry of C-3 was of no consequence as it will become achiral at the later stage, that of C-4 was further confirmed by its conversion into the natural products **29** and **42** (*vide Infra*). It is worthy noting that the issue of the stereochemistry of C-4 was uncertain at the outset of this work due to the possible participation of nitrogen atom leading to a double S_N2 process (retention at C-4) [23]. Experimentally, this was not observed and we hypothesized that the coordination of Lewis acid to the nitrogen atom decreased significantly its nucleophilicity favoring thus the direct attack of carbanion onto the epoxide (inversion at C-4).

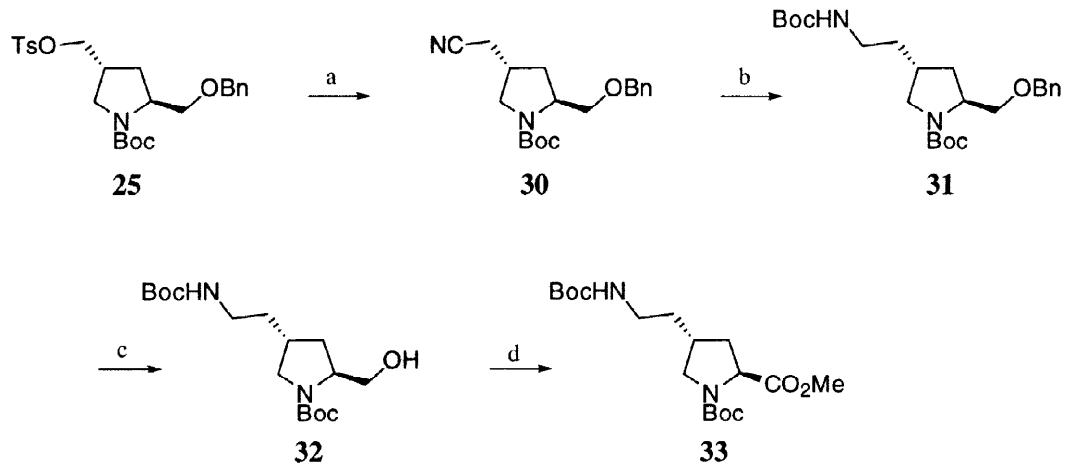
Synthesis of (2*S*,4*R*)-4-methylproline (proline-leucine chimera) (29). This amino acid has been isolated from young apple fruits [24]. It is also a component of a number of natural products, such as monamycins, a depsipeptide antibiotic isolated from *Streptomyces jamaicensis* [25]. Our synthesis starting from compound **21** was shown in Scheme 3. One pot deprotection-protection of compound **21** (10% Pd/C, H_2, 1atm, MeOH, Boc_2O) [26] afforded compound **24** in 95% yield. It is interesting to note that the *N*-benzyl group was selectively removed without affecting the *O*-benzyl function. Treatment of compound **24** with 6% Na-Hg in the presence of 3 equiv of Na_2HPO_4 in MeOH at 0°C gave the desired (2*S*,4*R*)-*N*-Boc-*trans*-2-benzyloxymethyl-4-hydroxymethylpyrrolidine **2** in 96% yield. We noted that desulfonylation of compound **21** under the same conditions was troublesome. Although compound **23** was isolable, the reaction proceeded sluggishly leading to unreproducible results. We suspected that the *N*-benzyl group could be sensitive under these reductive conditions. The primary alcohol was reduced to a methyl group by a two step sequence. The hydroxyl goup of **2** was first converted into the tosylate **25** (TsCl, DMAP, Py, 0°C, 30 min; rt, 24 h, 85%) which was then reduced by $NaBH_4$ in DMSO to give **26** (87%). Debenzylation by hydrogenolysis (92%), oxidation (TEMPO, NaOCl) [27] followed by esterification of the resulting carboxylic acid with diazomethane furnished the methyl ester **28** (88%) as a mixture of two rotamers. Finally, treatment of **28** with HCl followed by propylene oxide gave free (2*S*,4*R*)-4-methylproline **29** (100%) whose physical data including the optical rotation were in good agreement with those reported in the literature [25].



Reagents and conditions: a) 10% Pd/C, H_2 (1 atm), Boc_2O, MeOH, rt, 3 h, 95%; b) 6% Na-Hg, Na_2HPO_4, MeOH, 0°C, 2 h, 100%; c) TsCl, DMAP, Py, 0°C, 30 min, rt, 24 h, 85%; d) $NaBH_4$, DMSO, 45°C, 16 h, 87%; e) 10% Pd/C, H_2 (1 atm), MeOH, rt, 18 h, 92%; f) i) TEMPO, NaOCl, KBr, 5% $NaHCO_3$, acetone, 0°C, 2 h; ii) CH_2N_2, 88%; g) i) 1N HCl, rfx, 3 h; ii) EtOH, propylene oxide, heat, 100%.

Scheme 3

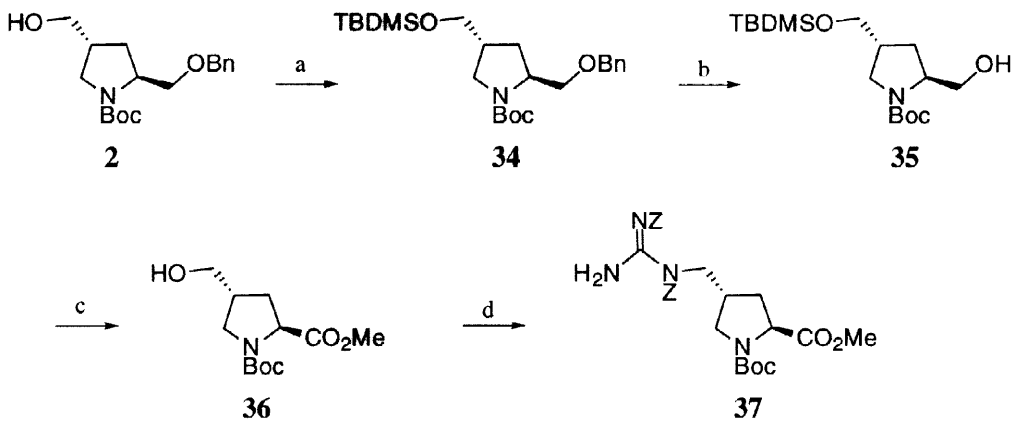
Synthesis of (2*S*,4*R*)-*N*-Boc-4-(*N'*-Boc-2'-aminoethyl)proline methyl ester (33). This proline-lysine chimera was synthesized as shown in Scheme 4 starting from tosylate **25**. One carbon homologation was achieved by displacement of **25** with cyanide (KCN, DMSO, 80°C, 3 h, 96%) to give nitrile **30**. Reduction of nitrile group (BH_3·THF, THF, rfx, overnight), and protection with *tert*-butoxycarbonyl group gave the di-Boc protected compound **31** (77%). Debenzylation by hydrogenolysis, oxidation of the primary alcohol (TEMPO catalyzed NaOCl) [27] and esterification with diazomethane afforded **33** in quantitative yield.



Reagents and conditions: a) KCN, DMSO, 80°C, 3 h, 96%; b) i) BH_3.THF, THF, rfx, overnight; ii) HCl-MeOH, rt, 3 h; iii) Boc_2O, THF, rt, overnight, 77%; c) H_2 (1 atm), 10% Pd-C, EtOAc, rt, 6 h, 100%; d) i) TEMPO, NaOCl, KBr, 5% $NaHCO_3$, acetone, 0°C, 2 h; ii) CH_2N_2, 100%.

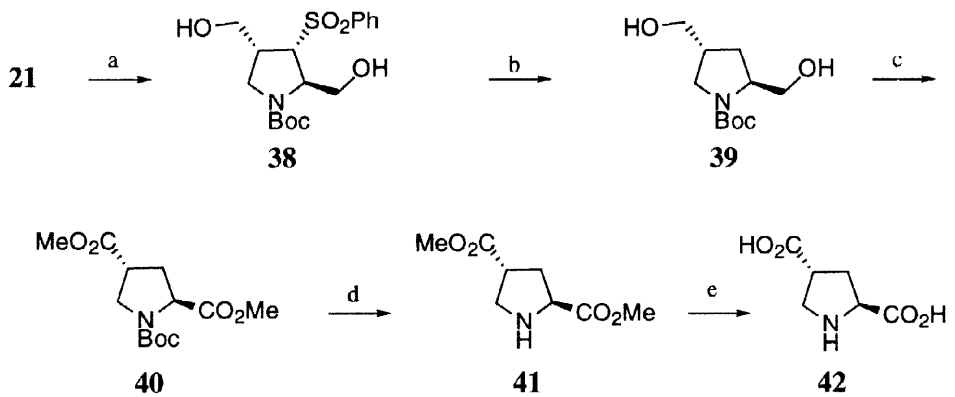
Scheme 4

Synthesis of (2*S*,4*R*)-*N*-Boc-4-(*N'*,N^G-bisbenzyloxycarbonyl-guanidino-methyl)proline methyl ester (37). This proline-arginine chimera was prepared starting from compound **2** (Scheme 5). Protection of the primary hydroxy group as TBDMS ether was realized under classic conditions to give compound **34** (100%), which was hydrogenated to give alcohol **35** (93%). Sequential TEMPO catalyzed oxidation [27], esterification with diazomethane and removal of the TBDMS group yielded primary alcohol **36** in 84% yield. Guanylation of **36** under Mitsunobu conditions [28] gave the desired compound **37** (80%) which existed as a mixture of two rotamers.



Reagents and conditions: a) TBDMSCl, imidazole, DMF, rt, 1 h, 100%; b) 10% Pd/C, H_2 (1 atm), EtOAc, rt, 7 h, 93%; c) i) TEMPO, NaOCl, KBr, 5% $NaHCO_3$, acetone, 0°C, 2 h; ii) CH_2N_2, 88%; iii) $^nBu_4NF$, THF, rt, overnight, 79%; d) $ZN{=}C(NHZ)NH_2$, $(CH_3)_2CHO_2CN{=}NCO_2CH(CH_3)_2$, PPh_3, THF, rt, 24 h. 80%.

Scheme 5



Reagents and conditions: a) 10% Pd/C, H_2 (60 psi), Boc_2O, MeOH, rt, overnight, 89%; b) 6% Na-Hg, Na_2HPO_4, MeOH, 0°C, 2 h, 96%. c) i) TEMPO, NaOCl, KBr, 5% $NaHCO_3$, acetone, 0°C, 2 h; ii) CH_2N_2, 84%; d) CH_2Cl_2-TFA, rt, 1 h, 100%; e) i) 1N HCl, rfx, 3 h; ii) EtOH, propylene oxide, heat, 100%.

Scheme 6

Synthesis of (2*S*,4*R*)-4-carboxy-proline (42). This amino acid (proline-glutamic acid chimera) has been isolated from the seeds of *Afzelia bella* [29] and has been demonstrated to be a potent competitive glutamate transport inhibitor [30]. Our synthesis was accomplished as shown in Scheme 6. Simultaneous removal of *N*- and *O*-benzyl groups from **21** and *in situ* derivatization of the secondary amine was performed by hydrogenolysis at 60 psi in the presence of 10% Pd/C and Boc_2O. Desulfonylation of **38** under standard conditions gave the diol **39** in 96% yield. Jones oxidation (0°C, 1 h) followed by treatment with diazomethane gave the dicarboxylic ester **40** in low yield (23%). However, when TEMPO catalyzed NaOCl oxidation [27] was employed, the diester **40** was isolated in 84% yield as a mixture of two

rotamers. Removal of *N*-Boc group (CH_2Cl_2-TFA, rt, 1 h, 100%) provided **41** as a single diastereoisomer based on the ^1H and ^{13}C NMR spectra. Finally sequential treatment of **41** with HCl followed by propylene oxide gave (2*S*,4*R*)-4-carboxy-proline (**42**) whose physical data including the optical rotation were in good agreement with those reported in the literature [30,31,32].

In summary, we have developed a new efficient method for the synthesis of a series of 4-substituted prolines ready for incorporation into peptide. The synthesis is highly flexible and can be stereodivergent. In fact, the (2*S*,4*S*), (2*R*,4*R*), (2*R*,4*S*) diastereomers of **2** were readily accessible by using the antipodes of **1** and **5** or by manipulating the diol function of intermediate **18**. Application of these amino acid chimeras in the design and synthesis of peptidomimetics are currently underway in our laboratory.

Experimental Section

General

Infrared (IR) spectra were recorded on a Nicolet-205 spectrometer. ^1H and ^{13}C NMR spectra were measured on Brucker AM-400, AM-300 and AC-250 (400, 300 and 250 MHz, respectively) spectrometers with tetramethylsilane as internal standard (δ ppm). Flash chromatography was performed using Kieselgel 60 (230-400 mesh, E. Merck) and usually employed a stepwise solvent polarity gradient, correlated with TLC mobility. Solvents and reagents were purified according to standard laboratory techniques. Optical rotations were determined on a Perkin-Elmer automatic polarimeter at room temperature. Mass spectra were run on AEI MS-50 (EI), AEI MS-9 (CI) and Kratos MS-80 (FAB), respectively. Elemental analyses were carried out by the microanalytical laboratory at the ICSN. All reactions requiring anhydrous conditions or in an inert atmosphere were conducted under an atmosphere of Argon.

(2*R*)-1-Benzyloxy-2-amino-3-phenylsulfonylpropane (4). To a solution of **3** (493 mg, 1.22 mmol) in EtOAc (9 mL) was added conc. HCl (3 mL). The reaction mixture was stirred at room temperature for 2 h, then neutralized with 30% K_2CO_3 solution, extracted with EtOAc. The EtOAc extracts were washed with brine, dried over Na_2SO_4 and evaporated. Flash column chromatography on silica gel (CH_2Cl_2/MeOH = 20/1) afforded compound **4** (350 mg, 94%): $[\alpha]_D$ -6 (*c* 4.0, $CHCl_3$); IR ($CHCl_3$) 3550, 3388, 3075, 3031, 3006, 2863, 1588, 1456, 1369, 1300, 1219, 1144, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93-7.91 (m, 2H), 7.69-7.64 (m, 1H), 7.59-7.54 (m, 2H), 7.36-7.24 (m, 5H), 4.47 (s, 2H), 3.61-3.54 (m, 1H), 3.45-3.37 (m, 2H), 3.30 (dd, *J* = 14.1, 3.0 Hz, 1H), 3.14 (dd, *J* = 14.1, 8.8 Hz, 1H), 1.81 (s, 2H, NH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.4, 137.5, 133.6, 129.2, 128.2, 127.6, 127.4, 73.5, 72.9, 60.2, 46.5; MS (CI) *m/z* 306 $[M+H]^+$, 164, 107; HRMS calcd for $C_{16}H_{20}NO_3S$ (M+H) 306.1164, found 306.1166.

(2*R*,2'*S*)-1-Benzyloxy-2-*N*-(2',3'-*O*-isopropylidene-2',3'-dihydroxypropyl)amino-3-phenylsulfonylpropane (6). To a solution of aldehyde **5** (1.71 g, 13.11 mmol) and amine **4** (4.0 g, 13.11 mmol) in absolute ethanol (20 mL) was added titanium (IV) isopropoxide (4.84 g, 17.04 mmol). After being stirred at room temperature for 1 h, sodium cyanoborohydride (826 mg, 13.11 mmol) was added, and the resulting reaction mixture was stirred overnight. The reaction was quenched by addition of a few drops of water and the volatiles were removed under reduced pressure. To the residue was added EtOAc and the resulting inorganic precipitate was removed by filtration through a short pad of Celite and washed with EtOAc. The filtrate was then evaporated, and then purified by flash chromatography on silica gel (heptane/EtOAc = 1/1) to give **6** (3.75 g, 68%): $[\alpha]_D$ -7 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3338, 2988, 2938, 2869, 1450, 1381, 1313, 1231, 1150, 1094, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93-7.89 (m, 2H), 7.67-7.52 (m, 3H), 7.36-7.24 (m, 5H), 4.46 (s, 2H), 4.11-4.03 (m, 1H), 3.97 (dd, *J* = 7.9, 6.3 Hz, 1H), 3.60 (dd, *J* = 7.9, 6.4 Hz, 1H), 3.55 (dd, *J* = 9.5, 4.6 Hz, 1H), 3.50 (dd, *J* = 9.5, 4.1 Hz, 1H), 3.39-3.20 (m, 3H), 2.68 (dd, *J* = 11.7, 6.5 Hz, 1H), 2.61 (dd, *J* = 11.7, 4.9 Hz, 1H), 1.88 (br s, 1H), 1.39 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.6, 137.5, 133.4, 128.9, 128.1, 127.6, 127.5, 127.3, 108.8, 75.0, 72.8, 70.2, 67.1, 57.5, 53.0, 49.5, 26.6, 25.1; MS (CI) *m/z* 420 $[M+H]^+$; HRMS calcd for $C_{22}H_{30}NO_5S$ (M+H) 420.1845, found 420.1825.

(2*R*,2'*S*)-1-Benzyloxy-2-*N*-(2',3'-dihydroxypropyl)amino-3-phenylsulfonylpropane (7). A solution of **6** (2.87 g, 6.85 mmol) in 0.5 N HCl-MeOH (65 mL) was stirred at room temperature for 5 h. After evaporation of the solvent, the residue was redissolved in 30% aqueous K_2CO_3 solution and EtOAc. The aqueous layer was extracted with EtOAc. The EtOAc extracts were washed with brine, dried and evaporated. Flash chromatography on silica gel (CH_2Cl_2/MeOH = 20/1) gave diol **7** (2.48 g, 96%): $[\alpha]_D$ -7 (*c* 2.0, MeOH); IR ($CHCl_3$) 3475, 3025, 1456, 1300, 1212, 1156, 1094 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94-7.90 (m, 2H), 7.69-7.54 (m, 3H), 7.37-7.24 (m, 5H), 4.46 (s, 2H), 3.70-3.64 (m, 2H), 3.55-3.46 (m, 3H), 3.36-3.21 (m, 1H), 3.33 (dd, *J* = 14.6, 3.9 Hz, 1H), 3.24 (dd, *J* = 14.6, 8.3 Hz, 1H), 2.74 (dd, *J* = 12.4, 3.8 Hz, 1H), 2.63 (dd, *J* = 12.4, 7.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.6, 137.5, 133.7, 129.3, 128.4, 127.7, 73.1, 70.3, 69.9, 65.0, 57.6, 52.8, 49.1; MS (CI) *m/z* 380 $[M+H]^+$, 290, 92; HRMS calcd for $C_{19}H_{26}NO_5S$ (M+H) 380.1532, found 380.1541.

(2*R*,2'*S*)-1-Benzyloxy-2-*N*-[(2',3'-dihydroxypropyl)(*tert*-butoxycarbonyl)]amino-3-phenylsulfonylpropane (8). To a solution of **7** (889 mg, 2.34 mmol) in DMF (8 mL) was added Boc_2O (563 mg, 2.58 mmol). The reaction mixture was stirred at room temperature for 48 h, diluted with water, extracted with Et_2O. The ether extracts were washed with water and brine, dried and evaporated. Flash column chromatography on silica gel (heptane/EtOAc = 1/2) afforded **8** as two rotamers (1.043 g, 93%): $[\alpha]_D$ -22 (*c* 2.2, $CHCl_3$); IR ($CHCl_3$) 3436, 3024, 3017, 1689, 1477, 1457, 1417, 1404, 1370, 1331, 1304, 1251, 1151, 1105, 1085, 1025 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.91-7.88 (m, 2H), 7.65-7.52 (m, 3H), 7.35-7.24 (m, 5H), 4.60-4.48 (m, 2H), 4.11-2.89 (m, 12H), 2.69 (br s, OH), 2.18 (br s, OH), 1.77 (br s, OH), 1.38 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 155.2, 154 1, 139.3, 139.2, 136.7, 133.7, 133.5,

129.1, 129.0, 128.2, 127.7, 127.6, 127.4, 81.2, 80.2, 73.0, 71.2, 70.5, 69.7, 69.1, 63.9, 63.4, 56.0, 54.9, 54.3, 28.0; MS (CI) *m/z* 480 $[M+H]^+$, 436, 424, 380, 238, 143; HRMS calcd for $C_{24}H_{34}NO_4S$ (M+H) 480.2056, found 480.2064.

(2*R*,2'*S*)-1-Benzlyoxy-2-*N*-[(3'-tosyl-2',3'-dihydroxypropyl)(*tert*-butoxycarbonyl]-amino-3-phenylsulfonylpropane (9). To a stirred solution of diol **8** (170 mg, 0.36 mmol) in pyridine (2 mL) at 0°C was added *p*-toluenesulfonyl chloride (81 mg, 0.43 mmol, 1.2 equiv) in one portion. The reaction mixture was stirred at room temperature for 24 h, diluted with water, extracted with Et_2O. The ether extracts were washed with 1N HCl, water, saturated aqueous $NaHCO_3$ solution, brine, dried, and evaporated. Flash chromatography on silica gel (heptane/EtOAc = 2/1) gave the monotosylate **9** (166 mg, 74%): $[\alpha]_D$ -12 (*c* 1.8, $CHCl_3$); IR ($CHCl_3$) 3416, 3024, 2984, 2931, 2871, 1689, 1596, 1483, 1457, 1370, 1304, 1178, 1151, 1098, 1085, 985, 912, 832 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98-7.25 (m, 15H), 4.45 (s, 2H), 4.05-3.25 (m, 7H), 3.22-3.02 (m, 1H), 2.98-2.80 (m, 1H), 2.42 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.8, 144.7, 139.3, 136.5, 133.8, 133.6, 132.3, 130.0, 129.1, 128.3, 127.9, 127.7, 127.4, 81.3, 80.6, 73.1, 31.3, 70.7, 69.7, 68.9, 68.5, 68.3, 56.1, 54.8, 28.0, 21.4; MS (FAB) *m/z* 640 $[M+Li]^+$.

(2*R*,2'*S*)-1-Benzyloxy-2-*N*-[(2',3'-epoxypropyl)(*tert*-butoxycarbonyl)]amino-3-phenylsulfonylpropane (10). To a solution of **9** (74 mg, 0.12 mmol) in DMF (1 mL) in the presence of water (1 drop) was added K_2CO_3 (49 mg, 0.35 mmol). After being stirred at room temperature for 24 h, the reaction mixture was diluted with water, extracted with Et_2O. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and evaporated. Preparative TLC on silica gel (heptane/EtOAc = 1/1) gave epoxide **10** as two rotamers (29 mg, 54%): $[\alpha]_D$ -36 (*c* 0.75, $CHCl_3$); IR ($CHCl_3$) 3031, 2981, 2931, 1688, 1481, 1456, 1394, 1369, 1306, 1263, 1206, 1156, 1081 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95-7.90 (m, 2H), 7.70-7.52 (m, 3H), 7.35-7.24 (m, 5H), 4.47 (s, 2H), 4.43-4.30 (m, 1H), 4.06-3.94 (m, 1H), 3.83-3.53 (m 4H), 3.40-3.24 (m, 1H), 3.08-2.88 (m, 1H), 2.78-2.75 (m, 1H), 2.57, 2.44 (two br s, 1H), 1.40 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.4, 139.9, 137.7, 133.5, 129.8, 129.7, 129.1, 128.3, 127.8, 127.6, 81.1, 80.6, 72.8, 70.0, 56.3, 55.2, 53.8, 51.7, 50.7, 50.3, 46.0, 45.7, 28.3; MS (CI) *m/z* 462 $[M+H]^+$, 406, 322, 266, 232, 176, 143, 107; HRMS calcd for $C_{24}H_{32}NO_6S$ (M+H) 462.1950, found 462.1943.

Oxazolidinone 11: $[\alpha]_D$ -38 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3588, 3569, 3044, 2981, 2938, 2869, 1750, 1488, 1450, 1375, 1313, 1225, 1206, 1156, 1100, 1081, 1050 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.95-7.92 (m, 2H), 7.70-7.55 (m, 3H), 7.38-7.23 (m, 5H), 4.49 (d, *J* = 11.9 Hz, 1H), 4.43 (d, *J* = 11.9 Hz, 1H), 4.42-4.30 (m, 2H), 3.80-3.51 (m, 7H), 3.28 (dd, *J* = 14.8, 3.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.8, 138.8, 137.2, 134.1, 129.4, 128.5, 128.1, 127.7, 74.0, 73.3, 70.1, 63.0, 53.8, 49.1, 44.4; MS (CI) *m/z* 406 $[M+H]^+$, 266, 264, 176, 143, 107; HRMS calcd for $C_{20}H_{24}NO_6S$ (M+H) 406.1324, found 406.1329.

Oxazolidinone 12: $[\alpha]_D$ +13 (*c* 2.1, $CHCl_3$); IR ($CHCl_3$) 3594, 3512, 3031, 2944, 2875, 1750, 1494, 1450, 1313, 1231, 1150, 1113, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95-7.92 (m, 2H), 7.70-7.54 (m, 3H), 7.38-7.23 (m, 5H), 4.55-4.47 (m 1H), 4.48 (d, *J* = 11.9 Hz, 1H), 4.42 (d, *J* = 11.9 Hz, 1H), 4.35-4.27 (m, 1H), 3.81-3.61 (m, 6H), 3.55 (dd, *J* = 18.4, 6.1

Hz, 1H), 3.29 (dd, J = 14.8, 3.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.0, 138.5, 137.1, 133.9, 129.3, 128.3, 127.8, 127.7, 127.5, 74.0, 72.9, 69.7, 62.8, 53.3, 48.7, 44.2 MS (CI) *m/z* 406 $[M+H]^+$, 280, 266, 176, 143, 107; HRMS calcd for $C_{20}H_{24}NO_6S$ (M+H) 406.1324, found 406.1321.

(*E*)-3-Phenylsulfonyl-allyl benzyl ether (13): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.91-7.87 (m, 2H), 7.65-7.50 (m, 3H), 7.38-7.26 (m, 5H), 7.01 (dt, J = 15.0, 3.4 Hz, 1H), 6.67 (dt, J = 15.0, 2.2 Hz, 1H), 4.55 (s, 2H), 4.21 (dd, J = 3.4, 2.2 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.5, 140.2, 137.1, 133.3, 130.2, 129.2, 128.4, 128.0, 127.6, 127.5, 73.0, 67.5; MS (CI) *m/z* 289 $[M+H]^+$, 107.

(2*R*)-1-Benzyloxy-2-*N*-[(*tert*-butoxycarbonyl)(benzyl)]amino-3-phenylsulfonylpropane (15). To a suspension of NaH (55-65% in mineral oil, 1.635 g, 40.89 mmol) in THF (60 mL) at 0°C was added **1** (5.6 g, 17.78 mmol) in THF (30 mL). After being stirred for 30 min, benzyl bromide (6.39 g, 4.44 mL, 37.33 mmol) and a catalytic amount of ^{n}Bu$_4$NI (66 mg, 0.178 mmol, 1%) were added, successively. The reaction mixture was stirred at 0°C for 24 h. The reaction was quenched by addition of water and extracted with ether. The combined ether layers were washed with brine, dried, and evaporated. Flash chromatography on silica gel (heptane/EtOAc = 5/1) afforded compound **15** (7.6 g, 86%): $[\alpha]_D$ -26 (*c* 4.1, $CHCl_3$); IR ($CHCl_3$) 3094, 3069, 3019, 2981, 2931, 2806, 1688, 1456, 1375, 1306, 1250, 1206, 1150, 1119, 1081 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.9-7.8 (m, 2H), 7.7-7.5 (m, 3H), 7.4-7.1 (m, 10H), 4.64-4.58 (m, 1H), 4.28-3.24 (m, 8H), 1.37 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.34, 139.44, 138.07, 137.29, 133.22, 128.85, 128.50, 128.03, 127.89, 127.58, 127.26, 127.07, 126.86, 79.96, 72.24, 69.93, 55.07, 53.21, 52.11, 27.87; MS (CI) *m/z* 496 $[M+H]^+$, 440, 396, 143, 107; HRMS Calcd for $C_{28}H_{34}NO_5S$ (M+H) 496.2201, found 496.2158.

(2*R*)-1-Benzyloxy-2-*N*-(benzyl)amino-3-phenylsulfonylpropane (16). A solution of **15** (869 mg, 1.76 mmol) in 3N HCl-EtOAc (20 mL) was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue was redissolved in aqueous 30% K_2CO_3 and extracted with EtOAc. The combined organic extracts were washed with brine, dried, and evaporated. Flash chromatography on silica gel (heptane/EtOAc = 3/1) gave amine **16** (659 mg, 95%): mp 64-65°C; $[\alpha]_D$ -21 (*c* 2.8, $CHCl_3$); IR ($CHCl_3$) 3625, 3331, 3063, 3031, 2975, 2931, 2863, 1494, 1456, 1450, 1306, 1200, 1150, 1081 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.84-7.81 (m, 2H), 7.65-7.59 (m, 1H), 7.53-7.47 (m, 2H), 7.37-7.18 (m, 10H), 4.43 (s, 2H), 3.68 (s, 2H), 3.59-3.49 (m, 2H), 3.44-3.23 (m, 2H), 2.02 (br s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 139.28, 137.53, 133.29, 128.92, 128.09, 127.83, 127.53, 127.44, 127.37, 126.71, 72.77, 70.17, 57.49, 52.04, 50.69; MS (CI) *m/z* 396 $[M+H]^+$, 394, 143, 107. Anal. Calcd for $C_{23}H_{25}NO_3S$: C 70.03; H, 6.13; N, 3.55; S, 8.13. Found: C, 70.19; H, 6.36; N, 3.55; S, 8.01.

(2*R*,2'*S*)-1-Benzyloxy-2-*N*-[(2',3'-*O*-isopropylidene-2',3'-dihydroxypropyl)(benzyl)]-amino-3-phenylsulfonylpropane (17) from 16. To a solution of **5** (414 mg, 3.18 mmol, 1.1 equiv) and amine **16** (1.143 g, 2.89 mmol) in 1,2-dichloroethane (15 mL) was added sodium triacetoxyborohydride (95%, 904 mg, 4.05 mmol, 1.4 equiv). The reaction mixture was stirred at room temperature under an Ar atmosphere overnight. After addition of saturated aqueous $NaHCO_3$ solution, the reaction mixture was extracted with Et_2O. The ether extracts

were washed with brine, dried over Na_2SO_4, and evaporated. Purification by column chromatography on silica gel (heptane/EtOAc = 3/1) gave **17** (1.43 g, 97%): $[\alpha]_D$ +1 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) 2988, 2938, 2875, 1450, 1388, 1313, 1244, 1156, 1113, 1081, 1069, 1025 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.88-7.85 (m, 2H), 7.67-7.61 (m, 1H), 7.55-7.49 (m, 2H), 7.36-7.15 (m, 10H), 4.40 (s, 2H), 4.02 (quintet, *J* = 6.2 Hz, 1H), 3.92 (dd, *J* = 8.0, 6.1 Hz, 1H), 3.79 (d, *J* = 14.2 Hz, 1H), 3.66 (m, 2H), 3.59-3.27 (m, 5H), 2.74 (dd, *J* = 13.3, 6.5 Hz), 1H), 2.68 (dd, *J* = 13.3, 5.7 Hz, 1H), 1.31 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 139.4, 138.9, 137.6, 133.1, 128.8, 128.1, 127.9, 127.8, 127.3, 127.1, 126.6, 108.4, 74.4, 72.6, 71.0, 67.7, 55.7, 54.7, 53.7, 53.2, 26.4, 25.1; MS (CI) *m/z* 510 $[M+H]^+$, 452, 420. Anal. Calcd for $C_{29}H_{35}NO_5S$: C 68.34; H, 6.92; N, 2.75; S, 6.29. Found: C, 68.08; H, 7.05; N, 2.77; S, 6.44.

Compound 17 from 6*via* Procedure A. To a solution of **6** (38 mg, 0.09 mmol) in DMF (1 ml) were added potassium carbonate (25 mg, 0.18 mmol) and benzyl bromide (31 mg, 0.18 mmol), successively. After being stirred at 80°C for 48 h, the reaction mixture was diluted with water and extracted with Et_2O. The ether extracts were washed with water and brine, dried and evaporated. Purification by preparative TLC on silica gel (heptane/EtOAc = 3/1) afforded **17** (29 mg, 63%).

Compound 17 from 6 *via* Procedure B. To a solution of benzaldehyde (19 mg, 0.18 mmol) and amine **6** (67 mg, 0.16 mmol) in 1,2-dichloroethane was added sodium triacetoxyborohydride (47 mg, 0.22 mmol). After being stirred at room temperature under an Ar atmosphere for 6 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The ether extracts were washed with brine, dried over Na_2SO_4 and evaporated. Purification by preparative TLC on silica gel (heptane/EtOAc = 3/1) gave **17** (73 mg, 90%).

(2*R*,2'*S*)-1-Benzyloxy-2-*N*-[(2',3'-dihydroxypropyl)(benzyl)]amino-3-phenylsulfonylpropane (18). A solution of **17** (7.67 g, 15.07 mmol) in 4N HCl-THF (50 mL conc. HCl + 150 mL THF) was stirred at room temperature for 3 h. After evaporation of the solvent, the residue was redissolved in 30% K_2CO_3 aqueous solution and EtOAc. The aqueous layer was extracted with EtOAc. The EtOAc extracts were washed with brine, dried and evaporated. Flash chromatography on silica gel (heptane/EtOAc = 1/1 then 1/3) gave diol **18** (6.65 g, 94%): $[\alpha]_D$ -53 (*c* 2.6, $CHCl_3$); IR ($CHCl_3$) 3465, 3072, 2937, 2860, 1499, 1454, 1396, 1357, 1312, 1203, 1151, 1113, 1087, 1061, 1029 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.77-7.74 (m, 2H), 7.65-7.58 (m, 1H), 7.52-7.46 (m, 2H), 7.37-7.21 (m, 10H), 4.41 (s, 2H), 3.82 (d, *J* = 13.6 Hz, 1H), 3.68 (d, *J* = 13.6 Hz, 1H), 3.69-3.34 (m, 7H), 3.17 (dd, *J* = 14.3, 3.8 Hz, 1H), 2.75 (dd, *J* = 13.4, 9.6 Hz, 1H), 2.57 (dd, *J* = 13.4, 3.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.1, 138.2, 137.4, 133.4, 129.1, 128.2, 127.6, 127.4, 127.2, 72.9, 68.3, 68.0, 64.1, 56.0, 54.7, 54.4, 52.2; MS (CI) *m/z* 470 $[M+H]^+$, 328. 289, 238, 182, 143, 107; HRMS calcd for $C_{26}H_{32}NO_5S$ (M+H) 470.2001, found 470.2008.

(2*R*,2'*S*)-1-Benzyloxy-2-*N*-[(3'-tosyl-2',3'-dihydroxypropyl)(benzy)]amino-3-phenylsulfonylpropane (19). To a stirred solution of diol **18** (3.136 g, 6.69 mmol) in pyridine (45 mL) at 0°C was added TsCl (1.40 g, 7.36 mmol, 1.1 equiv) in one portion. The reaction

mixture was stirred at this temperature for 24 h. Pyridine was removed by evaporation *in vacuo*. The residue was taken into water and extracted with EtOAc. The aqueous layer was extracted with EtOAc. The combined EtOAc extracts were washed with brine, dried over Na_2SO_4 and evaporated. Flash chromatography on silica gel (heptane/EtOAc = 1/1 then 1/3) gave the monotosylate **19** (3.55 g, 85%) and the starting material **18** (208 mg, 6.6%). Compound **19**: $[\alpha]_D$ -35 (*c* 2.2, $CHCl_3$); IR ($CHCl_3$) 3456, 3025, 2931, 2863, 1500, 1450, 1363, 1306, 1219, 1175, 1150, 1106, 1088, 988 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.79-7.73 (m, 4H), 7.65-7.58 (m, 1H), 7.54-7.46 (m, 2H), 7.39-7.22 (m, 12H), 4.42 (s, 2H), 3.92 (d, *J* = 5.1 Hz, 2H), 3.76 (d, *J* = 13.7 Hz, 1H), 3.64 (d, *J* = 13.7 Hz, 1H), 3.71-3.46 (m, 4H), 3.33 (dd, *J* = 14.3, 7.8 Hz, 1H), 3.12 (dd, *J* = 14.3, 3.9 Hz, 1H), 2.71 (dd, *J* = 13.6, 4.1 Hz, 1H), 2.63 (dd, *J* = 13.6, 8.3 Hz, 1H), 2.42 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 144.5, 138.0, 133.3, 132.3, 129.5, 129.0, 128.8, 128.0, 127.5, 127.4, 127.3, 127.2, 72.7, 71.3, 68.2, 66.0, 55.9, 54.6, 54.5, 52.6, 21.2; MS (FAB) *m/z* 624 $[M+H]^+$. Anal. Calcd for $C_{33}H_{37}NO_7S_2$: C 63.54; H, 5.98; N, 2.25; S, 10.28. Found: C, 63.53; H, 5.99; N, 2.31; S, 10.26.

(2*R*,2'*S*)-1-Benzyloxy-2-*N*-[(2',3'-epoxypropyl)(benzyl)]amino-3-phenylsulfonyl propane (20). To a solution of **19** (2.888 g, 4.64 mmol) in DMF (46 mL) in the presence of water (417 mg, 23.18 mmol) was added K_2CO_3 (1.922 g, 13.91 mmol). After being stirred at room temperature for 24 h, the reaction mixture was diluted with water, extracted with Et_2O. The combined organic extracts were washed with water and brine, dried over Na_2SO_4 and evaporated. Column chromatography on silica gel (heptane/EtOAc = 3/1) gave epoxide **20** (2.077 g, 99%): $[\alpha]_D$ -21 (*c* 2.8, $CHCl_3$); IR ($CHCl_3$) 3069, 3025, 2925, 2869, 1494, 1450, 1394, 1363, 1306, 1219, 1150, 1113, 1081 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.89-7.86 (m, 2H), 7.67-7.60 (m, 1H), 7.56-7.49 (m, 2H), 7.37-7.20 (m, 10H), 4.44 (s, 2H), 3.89 (d, *J* = 14.1 Hz, 1H), 3.65 (d, *J* = 14.1 Hz, 1H), 3.70-3.60 (m, 3H), 3.46 (dd, *J* = 14.2, 6.2 Hz, 1H), 3.36 (dd, *J* = 14.2, 4.8 Hz, 1H), 2.85 (m, 1H), 2.84 (dd, *J* = 15.2, 3.9 Hz, 1H), 2.61 (dd, *J* = 4.9, 3.9 Hz, 1H), 2.52 (dd, *J* = 15.2, 7.1 Hz, 1H), 2.34 (dd, *J* = 4.9, 2.5 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 140.0, 139.3, 137.9, 133.5, 129.2, 128.5, 128.4, 128.2, 127.9, 127.6, 127.0, 73.2, 70.6, 56.3, 55.5, 54.9, 53.4, 51.4, 45.6; MS (CI) *m/z* 452 $[M+H]^+$, 396, 362, 143, 107; HRMS calcd for $C_{26}H_{30}NO_4S$ (M+H) 452.1896, found 452.1896.

(2*R*,3*S*,4*R*)-1-Benzyl-2-benzyloxymethyl-3-phenylsulfonyl-4-hydroxymethyl pyrrolidine (21). To a stirred solution of epoxide **20** (464 mg, 1.03 mmol) in THF (20 mL) at -70°C was added $Ti(O^iPr)_4$ (877 mg, 919 μL, 3.09 mmol). After being stirred at the same temperature for 10 min, a solution of KHMDS in toluene (0.5 M, 6.18 mL, 3.09 mmol) was added, and stirring was continued for 2 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution and the reaction mixture was extracted with Et_2O. The ether layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography on silica gel (heptane/EtOAc = 1/1) to furnish **21** (340 mg, 73%): $[\alpha]_D$ -92 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 3536, 3072, 2952, 2896, 2861, 2404, 1497, 1455, 1448, 1303, 1293, 1234, 1198, 1142, 1084, 1073, 1028 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.83-7.79 (m, 2H), 7.59-7.52 (m, 1H), 7.47-7.40 (m, 2H), 7.33-7.23 (m, 10H), 4.35 (dd, *J* = 12.5, 9.9 Hz,

1H), 4.17 (d, J = 12.0 Hz, 1H), 4.04 (d, J = 12.0 Hz, 1H), 3.95 (d, J = 12.8 Hz, 1H), 3.85 (dd, J = 12.5, 4.7 Hz, 1H), 3.80 (dd, J = 8.0, 3.1 Hz, 1H), 3.66 (d, J = 12.8 Hz, 1H), 3.17-3.11 (m, 1H), 3.03-2.93 (m, 3H), 2.79 (dd, J = 9.9, 4.3 Hz, 1H), 2.73 (dd, J = 11.6, 8.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.7, 138.3, 137.7, 133.7, 129.0, 128.8, 128.6, 128.2, 127.6, 127.2, 72.8, 70.8, 66.6, 65.4, 60.1, 59.5, 55.5, 45.7; MS (CI) *m/z* 452 $[M+H]^+$, 143, 107; HRMS calcd for $C_{26}H_{30}NO_4S$ (M+H) 452.1896, found 452.1889. Anal. Calcd for $C_{26}H_{29}NO_4S$: C, 69.15 ; H, 6.47; N, 3.10; S, 7.10; Found: C, 68.87; H, 6.61; N, 3.11; S, 6.82.

(2*R*,3*S*,4*R*)-2-Benzyloxymethyl-3-phenylsulfonyl-4-hydroxymethylpyrrolidine (22). A suspension of **21** (108 mg, 0.24 mmol) and Pd/C (10%, 22 mg) in MeOH was hydrogenated at 1 atm for 21 h. The reaction mixture was filtered through a short pad of Celite, the filtrate was evaporated *in vacuo* and purified by preparative TLC on silica gel (CH_2Cl_2/MeOH = 20/1) to afford **22** (54 mg, 62%): $[\alpha]_D$ +3 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3538, 3006, 2950, 2894, 2869, 1450, 1400, 1363, 1306, 1288, 1144, 1106, 1088, 1075, 1063, 1025 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.80 (m, 2H), 7.63-7.58 (m, 1H), 7.50-7.45 (m, 2H), 7.35-7.26 (m, 3H), 7.11-7.08 (m, 2H), 4.28 (d, J = 12.0 Hz, 1H), 4.25 (dd, J = 12.5, 8.6 Hz, 1H), 4.13 (d, J = 12.0 Hz, 1H), 3.99 (dd, J = 12.5, 4.8 Hz, 1H), 3.77 (dd, J = 8.6, 4.7 Hz, 1H), 3.56 (q, J = 4.6 Hz, 1H), 3.07 (m, 3H), 2.82 (m, 1H), 2.71 (dd, J = 9.7, 4.4 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.7, 137.6, 133.9, 129.3, 128.4, 128.2, 127.8, 127.6, 73.0, 70.4, 66.5, 61.5, 60.7, 50.5, 48.4; MS (CI) *m/z* 362 $[M+H]^+$, 220, 143, 130, 107. Anal. Calcd for $C_{19}H_{23}NO_4S$: C, 63.14 ; H, 6.41; N, 3.88; S, 8.87; Found: C, 62.94; H, 6.67; N, 3.99; S, 8.69.

(2*R*,3*S*,4*R*)-1-*tert*-Butoxycarbonyl-2-benzyloxymethyl-3-phenylsulfonyl-4-hydroxymethyl pyrrolidine (24). A suspension of **21** (1.31 g, 2.90 mmol), Boc_2O (760 mg, 3.48 mmol) and 10% Pd/C (131 mg) in MeOH was hydrogenated at 1 atm for 3 h. The reaction mixture was filtered through a short pad of Celite, the filtrate was evaporated *in vacuo* and purified by flash chromatography on silica gel (heptane/EtOAc = 1/1) to afford **24** as two rotamers (1.27 g, 95%): $[\alpha]_D$ -53 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$) 3688, 3631, 3550, 3006, 2981, 2900, 1694, 1475, 1450, 1394, 1369, 1313, 1244, 1206, 1144 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.85 (m, 2H), 7.67-7.46 (m, 3H), 7.33-7.27 (m, 3H), 7.05-7.03 (m, 2H), 4.36-4.09 (m, 4H), 3.96-3.88 (m, 2H), 3.56-3.17 (m, 5H), 1.46, 1.41 (ds, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 154.3, 153.5, 138.0, 137.7, 137.5, 137.4, 133.9, 133.8, 129.2, 128.4, 128.1, 127.4, 127.0, 80.0, 72.4, 69.1, 65.8, 65.2, 60.1, 58.9, 48.7, 48.1, 43.7, 42.6, 28.2; MS (CI) *m/z* 462 $[M+H]^+$, 406, 362, 143; HRMS calcd for $C_{24}H_{32}NO_6S$ (M+H) 462.1950, found 462.1978.

(2*S*,4*R*)-1-*tert*-Butoxycarbonyl-2-benzyloxymethyl-4-hydroxymethyl pyrrolidine (2). To a solution of **24** (740 mg, 1.60 mmol) in HPLC grade MeOH (5 mL) containing Na_2HPO_4 (912 mg, 6.42 mmol, 4 eq) was added 6% Na-Hg (1.84 g, 4.8 mmol, 3 eq) at 0°C. The mixture was vigorously stirred at 0°C for 2 h. Mercury was removed by decanting the reaction mixture. After evaporation of MeOH *in vacuo*, the residue was dissolved in water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with brine, dried and evaporated. Flash chromatography on silica gel

(heptane/EtOAc = 1/2) gave alcohol **2** as two rotamers (546 mg, 100%): $[\alpha]_D$ -43 (*c* 3.4, $CHCl_3$); IR ($CHCl_3$) 3681, 3631, 3456, 2981, 2938, 2869, 1681, 1481, 1456, 1406, 1369, 1250, 1169, 1131, 1094, 1109 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.34-7.28 (m, 5H), 4.52 (s, 2H), 4.07-3.95 (m, 1H), 3.68-3.36 (m, 5H), 3.18-3.11 (m, 1H), 2.52 (m, 1H), 2.21-1.68 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.5, 138.2, 128.3, 127.4, 79.4, 73.1, 71.0, 64.2, 56.6, 49.7, 49.1, 39.4, 38.6, 31.4, 30.7, 28.4; MS (CI) *m/z* 322 $[M+H]^+$, 266, 222; HRMS calcd for $C_{18}H_{28}NO_4$ (M+H) 322.2018, found 322.2013.

(2*S*,4*R*)-1-*tert*-Butoxycarbonyl-2-benzyloxymethyl-4-tosyloxymethyl pyrrolidine (25). To a stirred solution of alcohol **2** (280 mg, 0.87 mmol) and DMAP (11 mg, 0.087 mmol) in pyridine (9 mL) at 0°C was added TsCl (183 mg, 0.96 mmol, 1.1 equiv) in one portion. The reaction mixture was stirred at 0°C for 30 min then at room temperature for 24 h. The reaction mixture was taken into water and extracted with Et_2O. The aqueous layer was extracted with Et_2O. The combined ether extracts were washed with 1N HCl, water, saturated aqueous $NaHCO_3$ solution and brine, respectively, dried over Na_2SO_4 and evaporated. Flash chromatography on silica gel (heptane/EtOAc = 3/1) gave the tosylate **25** as two rotamers (350 mg, 85%): $[\alpha]_D$ -32 (*c* 2.6, $CHCl_3$); IR ($CHCl_3$) 3019, 2981, 2931, 2869, 1688, 1600, 1456, 1406, 1394, 1369, 1175, 1138, 1100, 975 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.80-7.76 (m, 2H), 7.36-7.27 (m, 8H), 4.49 (s, 2H), 4.01-3.95 (m, 3H), 3.52-3.36 (m, 3H), 3.08-3.01 (m, 1H), 2.70-2.69 (m, 1H), 2.45 (s, 3H), 2.05-2.03 (m, 1H), 1.69-1.60 (m, 1H), 1.43, 1.41 (two s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.0, 144.9, 138.2, 132.6, 129.9, 128.3, 127.8, 127.5, 127.4, 79.5, 73.1, 71.4, 71.0, 70.8, 56.4, 49.1, 48.6, 36.5, 35.6, 31.5, 30.5, 28.4, 21.6; MS (CI) *m/z* 476 $[M+H]^+$, 420, 376, 322, 276, 157, 107. Anal. Calcd for $C_{25}H_{33}NO_6S$: C, 63.14 ; H, 6.99; N, 2.95; S, 6.74; Found: C, 62.91; H, 7.21; N, 2.95; S, 6.88.

(2*S*,4*R*)-1-*tert*-Butoxycarbonyl-2-benzyloxymethyl-4-methyl pyrrolidine (26). To a solution of tosylate **25** (204 mg, 0.43 mmol) in DMSO (2 mL) was added $NaBH_4$ (81 mg, 2.15 mmo, 1 5 eq). The reaction mixture was stirred at 45°C for 16 h, diluted with water, extracted with Et2O. The ether extracts were washed with water and brine, dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography on silica gel (heptane/EtOAc = 1/1) to give **26** as two rotamers (114 mg, 87%): $[\alpha]_D$ -46 (*c* 2.1, $CHCl_3$); IR ($CHCl_3$) 3019, 2969, 2931, 2875, 1681, 1475, 1456, 1406, 1369, 1319, 1250, 1169, 1144, 1113 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 4.52 (s, 2H), 4.05-3.92 (m, 1H), 3.62-3.32 (m, 3H), 2.92-2.78 (m, 1H), 2.38-2.28 (m, 1H), 2.12-2.05 (m, 1H), 1.60-1.50 (m, 1H), 1.44, 1.42 (two s, 9H), 1.02 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.4, 138.4, 128.3, 127.4, 85.2, 73.1, 71.1, 70.9, 56.9, 54.0, 53.4, 37.0, 36.3, 31.4, 30.5, 28.5, 17.7; MS (CI) *m/z* 306 $[M+H]^+$, 250, 206, 107. Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59; Found: C, 70.71; H, 8.87; N, 4.71.

(2*S*,4*R*)-1-*tert*-Butoxycarbonyl-2-hydroxymethyl-4-methyl pyrrolidine (27). A suspension of **26** (100 mg, 0.33 mmol) and 10% Pd/C (10 mg) in MeOH was hydrogenated at 1 atm for 18 h. The reaction mixture was filtered through a short pad of Celite, the filtrate was evaporated *in vacuo* and purified by flash chromatography on silica gel (heptane/EtOAc = 2/1) to afford compound **27** as two rotamers (62 mg, 92%): $[\alpha]_D$ -40 (*c* 2.0, $CHCl_3$); IR

($CHCl_3$) 3381, 3006, 2969, 2931, 2881, 1663, 1475, 1456, 1412, 1369, 1331, 1250, 1169, 1156, 1119, 1025 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.50 (br s, 1H, OH), 4.05 (m, 1H), 3.61 (t, J = 5.2 Hz, 2H), 3.48 (dd, J = 10.7, 7.0 Hz, 1H), 2.94 (m, 1H), 2.32-2.21 (m, 1H), 1.72-1.56 (m, 2H), 1.47 (s, 9H), 1.02 (d, J= 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.1, 80.1, 67.6, 59.7, 54.5, 36.4, 31.6, 28.5, 17.8; MS (CI) m/z 216 $[M+H]^+$, 160, 116. Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37 ; H, 9.83; N, 6.51; Found: C, 61.55; H, 9.97; N, 6.59.

(2*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-4-methyl proline methyl ester (28). To a solution of **27** (30 mg, 0.14 mmol) in Me_2CO (2 mL) was added 5% aqueous $NaHCO_3$ solution (364 μL). This heterogeneous mixture was cooled to 0°C and treated sequentially with KBr (1.7 mg, 0.014 mmol) and TEMPO (24 mg, 0.15 mmol). Sodium hypochlorite (6% solution in water, 217 μL, 0.18 mmol) was then added dropwise while the mixture was vigorously stirred and maintained at 0°C. After 1 h, additional NaOCl (6% solution in water, 86 μL, 0.07 mmol) was added, and stirring was continued at 0°C for another 1 h followed by addition of 5% aqueous $NaHCO_3$ solution. After Me_2CO was removed on a rotary evaporator, the aqueous layer was washed twice with Et_2O, acidified to pH 6 with 10% $KHSO_4$ and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, concentrated and treated with excess diazomethane in Et_2O then evaporated. The residue was purified by flash chromatography on silica gel (heptane/EtOAc = 5/1 then 3/1) to give **28** as two rotamers (30 mg, 88%): $[\alpha]_D$ -33 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) 3013, 2981, 2931, 2875, 1744, 1688, 1456, 1406, 1375, 1238, 1200, 1181, 1163, 1144 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.36 (dd, J = 8.9, 2.3 Hz, 0.42H), 4.27 (dd, J = 8.8, 3.1 Hz, 0.58H), 3.78-3.64 (m, 1H), 3.72 (s, 3H), 3.00-2.86 (m, 1H), 2.46-2.34 (m, 1H), 2.11-2.02 (m, 1H), 1.91-1.77 (m, 1H), 1.46, 1.41 (two s, 9H), 1.04 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.3, 154.3, 153.6, 79.6, 59.0, 58.8, 53.4, 52.9, 51.9, 51.8, 38.3, 37.5, 31.9, 31.0, 28.3, 28.2, 17.3; MS (CI) m/z 244 $[M+H]^+$, 188, 144. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24 ; H, 8.70; N, 5.78; Found: C, 59.49; H, 8.66; N, 5.48.

(2*S*,4*R*)-4-methylproline (29). A solution of **28** (18 mg, 0.074 mmol) in 1N HCl (3 mL) was stirred at 100°C for 3 h. The volatile was evaporated. The residue was dissolved in EtOH. The solution was treated dropwise with propylene oxide under heating. Evaporation to dryness gave **29** (10 mg, 100%): $[\alpha]^{25}_D$ = -53 (*c* 0.4, H_2O) {lit.: $[\alpha]^{20}_D$ -52 (*c* 0.3, H_2O)[25]}; IR ($CHCl_3$) 3400, 2969, 2938, 2881, 2731, 1725, 1631, 1456, 1406, 1394, 1350, 1181, 1106, 1006, 975 cm^{-1}; ^1H NMR (250 MHz, D_2O) δ 4.31 (dd, J = 9.4, 4.4 Hz, 1H), 3.61 (dd, J = 11.3, 7.2 Hz, 1H), 2.90 (dd, J = 11.3, 8.8 Hz, 1H), 2.48-2.26 (m, 2H), 2.05-1.86 (m, 1H), 1.08 (d, J = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, D_2O) δ 175.0, 61.4, 53.1, 37.3, 32.8, 16.8; MS (CI) m/z 130 $[M+H]^+$, 84; HRMS calcd for $C_6H_{12}NO_2$ (M+H) 130.0868, found 130.0870.

(2*S*,4*R*)-1-*tert*-Butoxycarbonyl-2-benzyloxymethyl-4-cyanomethyl pyrrolidine (30). A solution of **25** (181 mg, 0.38 mmol) and KCN (50 mg, 0.76 mmol) in DMSO (2 mL) was heated at 80°C for 3 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution. The reaction mixture was extracted with Et_2O. The ether extracts were washed with water and brine, dried over Na_2SO_4 and evaporated. Flash column chromatography on silica gel (heptane/EtOAc = 3/1) afforded **30** as two rotamers (120 mg, 96%): $[\alpha]_D$ -49 (*c* 1.6,

$CHCl_3$); IR ($CHCl_3$) 3019, 2981, 2931, 2875, 1688, 1475, 1456, 1400, 1369, 1263, 1213, 1169, 1131, 1094 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20-7.09 (m, 5H), 4.35 (s, 2H), 3.90 (m, 1H), 3.46-3.40 (m, 3H), 2.95 (m, 1H), 2.53 (m, 1H), 2.24-2.21 (m, 2H), 2.03 (m, 1H), 1.65 (m, 1H), 1.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 138.3, 128.4, 127.6, 127.4, 118.0, 79.7, 73.2, 71.0, 70.8, 56.6, 51.2, 51.0, 34.4, 33.7, 32.8, 28.4, 20.6; MS (FAB) *m/z* 331 $[M+H]^+$, 275, 231. Anal. Calcd for $C_{19}H_{26}N_2O_3$: C 69.05; H, 7.94; N, 8.48. Found: C, 69.09; H, 7.84; N, 8.31.

(2*S*,4*R*)-1-*tert*-Butoxycarbonyl-2-benzyloxymethyl-4-[2'-*N*-(*tert*-butoxycarbonyl)-amino]ethyl pyrrolidine (31). To a solution of **30** (100 mg, 0.30 mmol) in anhydrous THF (3 mL) was introduced BH_3·THF (1M in THF, 3.0 mL, 3.0 mmol)) dropwise at room temperature. The resulting solution was heated to reflux overnight. After being cooled to 0°C, excess BH_3 was transformed into volatile trimethylborate by careful addition of anhydrous MeOH. The volatiles were removed *in vacuo* and the residue was redissolved in MeOH (5 mL) followed by slow addition of conc. aqueous HCl solution (5 mL). The reaction mixture was then stirred at room temperature overnight. The volatile was evaporated and the residue was dissolved in THF. To the above THF solution was added Et_3N (91 mg, 125 μL, 0.9 mmol) and Boc_2O (135 mg, 0.6 mmol). The mixture was stirred at room temperature overnight. After addition of water, the mixture was extracted with Et_2O. The ether extracts were washed with brine, dried over Na_2SO_4 and evaporated. Preparative TLC on silica gel (heptane/EtOAc = 2/1) gave **31** as two major rotamers (100 mg, 77%): $[\alpha]_D$ -27 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 3456, 3006, 2981, 2931, 2869, 1706, 1688, 1506, 1463, 1400, 1369, 1250, 1169, 1138, 1106 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.38-7.27 (m, 5H), 4.51 (s, 2H), 4.51 (s, 1H, NH), 4.04-3.92 (m, 1H), 3.54-3.31 (m, 3H), 3.13-3.10 (m, 2H), 2.92-2.89 (m, 1H), 2.28-2.12 (m, 2H), 1.59-1.19 (m, 3H), 1.44 (s, 18H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.0, 154.4, 138.5, 128.4, 127.6, 79.4, 73.2, 71.0, 56.7, 52.4, 52.0, 39.5, 35.0, 34.6, 34.4, 34.0, 33.7, 28.5; MS (CI) *m/z* 435 $[M+H]^+$, 379, 335, 107. Anal. Calcd for $C_{24}H_{38}N_2O_5$: C 66.33; H, 8.81; N, 6.45. Found: C, 65.69; H, 8.87; N, 6.28.

(2*S*,4*R*)-1-*tert*-Butoxycarbonyl-2-hydroxymethyl-4-[2'-*N*-(*tert*-butoxycarbonyl)amino] ethyl pyrrolidine (32). A suspension of **31** (58 mg, 0.13 mmol) and Pd/C (10%, 10 mg) in EtOAc was hydrogenated at 1 atm for 6 h. The reaction mixture was filtered through a short pad of Celite, the filtrate was evaporated *in vacuo* and purified by flash chromatography on silica gel (heptane/EtOAc = 1/1) to afford **32** as two rotamers (56 mg, 100%): $[\alpha]_D$ -13 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 3456, 3394, 3006, 2981, 2931, 2875, 1706, 1669, 1506, 1456, 1406, 1369, 1244, 1231, 1169 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.57 (br s, 1H), 4.29 (br s, 1H), 4.04 (br s, 1H), 3.61 (m, 2H), 3.53 (dd, *J* = 10.7, 7.3 Hz, 1H), 3.17-3.09 (m, 2H), 2.99 (t, *J* = 9.7 Hz, 1H), 2.22-2.19 (m, 1H), 1.73-1.49 (m, 4H), 1.47, 1.44 (ds, 18H); ^{13}C NMR (50 MHz, $CDCl_3$) (for the major rotamer) δ 156.9, 156.1, 80.3, 79.3, 67.2, 59.4, 52.7, 39.3, 34.7, 34.4, 33.8, 28.5; MS (CI) *m/z* 345 $[M+H]^+$, 301, 289, 245, 145; HRMS calcd for $C_{17}H_{33}N_2O_5$ (M+H) 345.2390, found 345.2381.

(2*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-4-[2'-*N*-(*tert*-butoxycarbonyl)amino]ethylproline methyl ester (33). Starting from **32** (29 mg, 0.084 mmol), the same procedure as described for the preparation of the methyl ester **28** provided **33**. Purification by flash chromatography on silica gel (heptane/EtOAc = 1/1) gave **33** as two rotamers (31 mg, 100%): $[\alpha]_D$ -13 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 3456, 3013, 2981, 2963, 2938, 1750, 1694, 1506, 1475, 1463, 1438, 1406, 1369, 1269, 1248, 1225 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.54 (br s, 1H), 4.37 (br d, *J* = 7.8 Hz, 0.47H), 4.26 (dd, *J* = 8.9, 2.2 Hz, 0.53H), 3.72 (s, 3H), 3.81-3.64 (m, 1H), 3.13-2.91 (m, 3H), 2.37-1.52 (m, 5H), 1.46, 1.44, 1.40 (three s, 18H); ^{13}C NMR (50 MHz, $CDCl_3$) (two major rotamers) δ 173.6, 173.4, 156.0, 153.7, 80.0, 79.3, 59.0, 58.7, 52.2, 52.0, 51.9, 51.5, 39.3, 36.4, 35.7, 35.1, 34.2, 33.5, 28.4, 28.3; MS (CI) *m/z* 373 $[M+H]^+$, 316, 273, 230, 172, 140; HRMS calcd for $C_{18}H_{33}N_2O_6$ (M+H) 373.2339, found 373.2336.

(2*S*,4*R*)-1-*tert*-Butoxycarbonyl-2-benzyloxymethyl-4-(*tert*-butyldimethylsilyloxy)-methyl pyrrolidine (34). To a solution of **2** (200 mg, 0.62 mmol) and imidazole (126 mg, 1.86 mmol) in DMF (6 mL) was added *tert*-butyldimethylsilyl chloride (103 mg, 0.69 mmol). The mixture was stirred at room temperature for 1 h. Water was added and the reaction mixture was extracted with Et_2O. The ether extracts were washed with water and brine, dried over Na_2SO_4 and evaporated. Flash column chromatography on silica gel (heptane/EtOAc = 20/1) afforded **34** as two rotamers (270 mg, 100%): $[\alpha]_D$ -35 (*c* 2.6, $CHCl_3$); IR ($CHCl_3$) 3006, 2956, 2931, 2894, 2863, 1688, 1475, 1456, 1406, 1369, 1263, 1256, 1169, 1138, 1112, 1094, 1013 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31(m, 5H), 4.52 (s, 2H), 4.05-3.94 (m, 1H), 3.60-3.40 (m, 5H), 3.14 (dd, *J* = 10.7, 8.2 Hz, 1H), 2.53-2.42 (m, 1H), 2.05-1.99 (m, 1H), 1.73-1.72 (m, 1H), 1.43 (s, 9H), 0.86 (s, 9H), 0.037 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.3, 138.4, 128.3, 127.4, 79.1, 73.1, 71.2, 64.8, 56.6, 49.3, 39.6, 38.7, 31.5, 30.7, 28.5, 25.9, 18.3, -5.4; MS (CI) *m/z* 436 $[M+H]^+$, 380, 336, 107. Anal. Calcd for $C_{24}H_{41}NO_4Si$: C, 66.16; H, 9.49; N, 3.22. Found: C, 65.92; H, 9.36; N, 3.28.

(2*S*,4*R*)-1-*tert*-Butoxycarbonyl-2-hydroxymethyl-4-(*tert*-butyldimethylsilyloxy)methyl pyrrolidine (35). A suspension of **34** (250 mg, 0.57 mmol) and Pd/C (10%, 50 mg) in EtOAc was hydrogenated at 1 atm for 7 h. The reaction mixture was filtered through a short pad of Celite, the filtrate was evaporated *in vacuo* and purified by flash chromatography on silica gel (heptane/EtOAc = 3/1) to afford **35** as two rotamers (183 mg, 93%): $[\alpha]_D$ -25 (*c* 3.4, $CHCl_3$); IR ($CHCl_3$) 3369, 3025, 3006, 2956, 2931, 2888, 2856, 1663, 1463, 1413, 1369, 1256, 1169, 1138, 1100, 838 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.61 (br s, 1H, OH), 4.02-4.01 (m, 1H), 3.63-3.25 (m, 6H), 2.38-2.33 (m, 1H), 1.88-1.55 (m, 2H), 1.47 (s, 9H), 0.89 (s, 9H), 0.045 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.0, 80.1, 67.3, 64.4, 59.4, 49.7, 39.4, 30.8, 28.4, 25.9, 18.3, -5.4; MS (CI) *m/z* 346 $[M+H]^+$, 302, 290, 246. Anal. Calcd for $C_{17}H_{35}NO_4Si$: C, 59.09 ; H, 10.21; N, 4.05; Found: C, 59.14; H, 9.98; N, 4.04.

(2*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-4-hydroxymethyl proline methyl ester (36). Starting from **35** (185 mg, 0.54 mmol), the same procedure as described for the preparation of the methyl ester **28** was employed. Thus obtained methyl ester was dissolved in THF and treated with $^nBu_4NF$ (1 M in THF, 540 μL, 0.54 mmol). The mixture was stirred at room temperature overnight, then diluted with Et_2O, washed with saturated $NaHCO_3$ solution and

brine, dried and evaporated. Flash column chromatography on silica gel (heptane/EtOAc = 1/3) gave **36** as two rotamers (110 mg, 79%): $[\alpha]_D$ -38 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) 3688, 3631, 3469, 2981, 2956, 2887, 1744, 1694, 1406, 1369, 1156, 1131, 1025 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.39 (dd, *J* = 8.0, 3.5 Hz, 0.42H), 4.29 (dd, *J* = 7.0, 5.5 Hz, 0.58H), 3.73 (s, 3H), 3.70-3.60 (m, 3H), 3.29-3.16 (m, 1H), 2.61-2.47 (m, 1H), 2.17-1.59 (m, 2H), 1.46, 1.41 (two s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.6, 173.5, 154.6, 154.0, 80.2, 80.1, 63.7, 63.5, 59.0, 58.7, 52.2, 52.0, 49.1, 48.7, 39.8, 39.0, 33.0, 32.3, 28.4, 28.3; MS (CI) *m/z* 260 $[M+H]^+$, 216, 204, 160. Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.59; H, 8.16; N, 5.40; Found: C, 54.95; H, 8.39; N, 5.15.

(2*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-4-[*N'*,N^G-bisbenzyloxycarbonyl)guanidino]methyl-proline methyl ester (37). To a solution of *N,N'*-bis(benzyloxycarbonyl)guanidine (51 mg, 0.154 mmol) and PPh_3 (30 mg, 0.116 mmol) in dry THF (3 mL) under argon was added **36** (20 mg, 0.077 mmol). The mixture was cooled to 0°C, and diisopropyl azodicarboxylate (25 mg, 0.116 mmol) was added dropwise. The reaction was stirred at room temperature for 24 h. Several drops of water were added, and the solvent was evaporated *in vacuo*. Preparative TLC on silica gel (toluene/EtOAc = 5/1) afforded **37** as two major rotamers (35 mg, 80%): $[\alpha]_D$ -11 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 3394, 3038, 3006, 2981, 2956, 1744, 1725, 1694, 1644, 1613, 1513, 1456, 1438, 1406, 1381, 1281, 1244, 1175, 1131, 1100, 1006, 900 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.45 (br s, 1H), 9.25 (br s, 1H), 7.42-7.28 (m, 10H), 5.32-5.08 (m, 2H), 4.35-4.25 (m, 1H), 4.20-3.92 (m, 2H), 3.69, 3.68 (two s, 3H), 3.65-3.56 (m, 1H), 3.22-3.05 (m, 1H), 2.69-2.61 (m 1H), 2.13-1.87 (m, 2H), 1.44, 1.38 (two s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.5, 173.2 163.8, 160.6, 155.8, 154.3, 153.7, 137.0, 134.4, 129.0, 128.9, 128.6, 128.5, 127.9, 80.0, 69.3, 67.0, 58.7, 58.5, 52.2, 52.0, 49.9, 49.5, 46.0, 45.8, 37.7, 36.8, 34.1, 33.6, 28.5, 28.3; MS (CI) *m/z* 569 $[M+H]^+$, 435, 91. Anal. Calcd for $C_{29}H_{36}N_4O_8$: C, 61.26; H, 6.38; N, 9.85; Found: C, 60.97; H, 6.29; N, 9.58.

(2*R*,3*S*,4*R*)-1-*tert*-Butoxycarbonyl-2-hydroxymethyl-3-phenylsulfonyl-4-hydroxy-methyl pyrrolidine (38). A suspension of **21** (230 mg, 0.51 mmol) and Pd/C (10%, 46 mg) in MeOH was hydrogenated at 60 psi overnight. The reaction mixture was filtered through a short pad of Celite, the filtrate was evaporated *in vacuo* and purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 20/1) to afford **38** (168 mg, 89%): $[\alpha]_D$ -86 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 3538, 3019, 2988, 2888, 1688, 1475, 1456, 1394, 1369, 1306, 1213, 1150, 1084 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.95-7.90 (m, 2H), 7.74-7.56 (m, 3H), 4.34-4.26 (m, 1H), 4.12-4.09 (m, 1H), 3.94-3.70 (m, 2H), 3.50-3.38 (m, 4H), 3.16-3.10 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.1, 137.7, 134.2, 129.4, 128.5, 80.6, 65.3, 63.0, 61.3, 60.2, 48.7, 43.8, 28.3; MS (CI) *m/z* 372 $[M+H]^+$, 316, 272, 232, 176, 143; HRMS calcd for $C_{17}H_{26}NO_6S$ (M+H) 372.1481, found 372.1442.

(2*S*,4*R*)-1-*tert*-Butoxycarbonyl-2-hydroxymethyl-4-hydroxymethyl pyrrolidine (39). To a solution of **38** (96 mg, 0.26 mmol) in HPLC grade MeOH (5 mL) containing Na_2HPO_4 (150 mg, 1.03 mmol, 4 eq) was added 6% Na-Hg (297 mg, 0.77 mmol, 3 eq) at 0°C. The mixture was vigorously stirred at 0°C for 2 h. Mercury was removed by decanting the reaction mixture. After evaporation of MeOH *in vacuo*, the residue was dissolved in water

and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with brine, dried and evaporated. Flash chromatography on silica gel (CH_2Cl_2/MeOH = 20/1) gave diol **39** (57 mg, 96%): $[\alpha]_D$ -32 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 3689, 3631, 3419, 3013, 2981, 2938, 2894, 1669, 1519, 1475, 1406, 1369, 1244, 1163, 1138, 1050 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.65 (br s, 1H), 4.00 (m, 1H), 3.62-3.44 (m, 5H), 3.20 (dd, *J* = 10.9, 7.5 Hz, 1H), 2.95 (br s, 1H), 2.50-2.35 (m, 1H), 1.85-1.70 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.98, 80.37, 67.32, 64.17, 59.37, 49.90, 39.36, 30.88, 28.42; MS (CI) *m/z* 232 $[M+H]^+$, 176, 132; HRMS calcd for $C_{11}H_{22}NO_4$ (M+H) 232.1549, found 232.1522.

(2*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-4-methoxycarbonyl proline methyl ester (40). Starting from **39** (40 mg, 0.17 mmol), exactly the same procedure as described for the preparation of compound **28** furnished **40** (42 mg, 84%): $[\alpha]_D$ -42 (*c* 0.45, $CHCl_3$); IR ($CHCl_3$) 2981, 2956, 1744, 1694, 1406, 1369, 1175, 1131 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.45 (dd, *J* = 8.8, 2.6 Hz, 0.45H), 4.35 (dd, *J* = 8.7, 3.8 Hz, 0.55 H), 3.87-3.54 (m, 2H), 3.74 (s, 3H), 3.72 (s, 3H), 3.34-3.14 (m, 1H), 2.57-2.37 (m, 1H), 2.26-2.13 (m, 1H), 1.46, 1.41 (ds, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.11, 172.83, 154.03, 153.40, 80.32, 58.72, 58.45, 52.19, 48.60, 41.85, 41.07, 33.33, 32.57, 28.35, 28.24; MS (CI) *m/z* 288 $[M+H]^+$, 232, 188; HRMS calcd for $C_{13}H_{22}NO_6$ (M+H) 288.1447, found 288.1475.

(2*S*,4*R*)-4-Methoxycarbonyl proline methyl ester (41). To a solution of **40** (30 mg, 0.104 mmol) in CH_2Cl_2 (1 mL) was added TFA (1 mL). The mixture was stirred at room temperature for 1 h. After evaporation of the solvent, the residue was dissolved in 30% aqueous K_2CO_3 solution and extracted with EtOAc. The EtOAc extracts were washed with brine, dried and evaporated to give **41** (20 mg, 100%): $[\alpha]_D$ -11 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) 3006, 2956, 2738, 2600, 1750, 1681, 1438, 1225, 1206, 1144 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 4.90 (br s, 1H), 4.55 (t, *J* = 8.2 Hz, 1H), 3.86 (s, 3H), 3.76 (s, 3H), 3.64 (d, *J* = 7.0 Hz, 2H), 3.41 (m, 1H), 2.66 (ddd, *J* = 13.8, 8.4, 5.3 Hz, 1H), 2.47 (dt, *J* = 13.8, 8.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.21, 168.72, 59.14, 53.80, 52.94, 47.50, 41.37, 31.43; HRMS calcd for $C_8H_{14}NO_4$ (M+H) 188.0923, found 188.0917.

(2*S*,4*R*)-4-Carboxyproline (42). A solution of **41** (12 mg, 0.042 mmol) was stirred at 100°C in 1N HCl (2 mL) for 3 h. The volatile was evaporated. The residue was dissolved in EtOH. The solution was treated dropwise with propylene oxide under heating. Evaporation to dryness gave **42** (7 mg, 100%): $[\alpha]^{25}_D$ -52 (*c* 0.9, H_2O) {lit.: $[\alpha]^{25}_D$ -54 (*c* 1.04, H_2O) [30]; $[\alpha]^{20}_D$ -46.6 (*c* 0.09, H_2O) [31]; $[\alpha]^{20}_D$ -46 (*c* 1, H_2O) [32]}; IR (KBr) 3419, 2925, 1719, 1619, 1413, 1388, 1363, 1338, 1288, 1225 cm^{-1}; ^1H NMR (250 MHz, D_2O) δ 4.29 (t, *J* = 7.9 Hz, 1H), 3.65-3.62 (m, 2H), 3.34 (quintet, *J* = 7.0 Hz, 1H), 2.60 (ddd, *J* = 14.2, 8.2, 5.9 Hz, 1H), 2.43 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 177.83, 175.10, 62.67, 49.25, 44.19, 34.02; MS (CI) *m/z* 160 $[M+H]^+$, 114; HRMS calcd for $C_6H_{10}NO_4$ (M+H) 160.0610, found 160.0606.

References

[1] Mosberg HI, Kroona HB. J. Med. Chem. 1992;35:4498-4500.

[2] Mosberg HI, Lomize AL, Wang C, Kroona H, Heyl DL, Sobczy-Kojiro K, Ma W, Mousigian C, Porreca F. J. Med. Chem. 1994;37:4371-4383.

[3] Ghose AK, Logan ME, Treasurywala AM, Wang H, Wahl RC, Tomczuk EF, Gowravaram MR, Jaegar EP, Wendoloski JJ. J. Am. Chem. Soc. 1995;117:4671-4682.

[4] Li W, Hanau CE, d'Avignon A, Moeller KD. J. Org. Chem. 1995;60:8155-8170.

[5] Lubell WD, Sharma R. J. Org. Chem. 1996;61:202-209.

[6] Holladay MW, Lin CW, May CS, Garvey DS, Witt DG, Miller TR, Wolfram CAW, Nadzan AM. J. Med. Chem. 1991;34:455-457.

[7] Kolodziej SA, Nikiforovich GV, Skeean R, Lignon M-F, Martinez J, Marshall GR. J. Med. Chem. 1995;38:137-149.

[8] Sasaki NA, Pauly R, Fontaine C, Chiaroni A, Riche C, Potier P. Tetrahedron Lett. 1994;35:241-244.

[9] Sasaki NA, Dockner M, Chiaroni A, Riche C, Potier P. J. Org. Chem. 1997;62:765-770.

[10] Sasaki NA, Sagnard I. Tetrahedron 1994;50:7093-7108.

[11] Dockner M, Sasaki NA, Potier P. Heterocycles 1996;42:529-532.

[12] Remuzon P. Tetrahedron 1996;52:13803-13835.

[13] Koskinen AMP, Rapoport H. J. Org. Chem. 1989;54:1859-1866 and references therein.

[14] Langlois N, Rojas A. Tetrahedron Lett. 1993;34:2477-2480.

[15] Pedregal C, Ezquerra J. Tetrahedron Lett. 1994;35:2053-2056.

[16] Wang Q, Sasaki NA, Potier P. Tetrahedron Lett. 1998;39:5755-5758: preliminary communication.

[17] Dockner M, Sasaki NA, Riche C, Potier P. Liebigs Ann./Recueil 1997;1267-1272.

[18] Mattson RJ, Pham KM, Leuck DJ, Cowen KA. J. Org. Chem. 1990;55:2552-2554.

[19] Abdel-Magid AF, Carson KG, Harris BD, Maryanoff CA, Shah RD. J. Org. Chem. 1996;61:3849-3862.

[20] Fleming PR, Sharpless KB. J. Org. Chem. 1991;56:2869-2875.

[21] Stork G, Cama LD, Coulson DR. J. Am. Chem. Soc. 1974;96:5268-5270.

[22] Stork G, Cohen JF. J. Am. Chem. Soc. 1974;96:5270-5272.

[23] Liu Q, Simms MJ, Boden N, Rayner CM. J. Chem. Soc.; Perkin Trans. I 1994;1363-1365.

[24] Hulme AC, Arthington W. Nature 1954;173:588-589.

[25] Dalby S, Kenner GW, Sheppard RC. Nature 1961;189:394-395.

[26] Sakaitani M, Hori K, Ohfune Y. Tetrahedron Lett. 1988;29:2983-2984.

[27] Reddy KL, Sharpless KB. J. Am. Chem. Soc. 1998;120:1207-1217.

[28] Dodd DS, Kozikowski AP. Tetrahedron Lett. 1994;35:977-980.

[29] Welter A, Marlier M, Dardenne G. Phytochem. 1978;17:131-134.

[30] Bridge RJ, Stanley MS, Anderson, MW, Cotman CW, Chamberlin AR. J. Med. Chem. 1991;34:717-725.

[31] Jones RCF, Howard KJ, Snaith JS. Tetrahedron Lett. 1996;37:1711-1714.

[32] Impellizzeri G, Piattelli M, Sciuto S, Fattorusso E. Phytochem. 1977;16:1601-1602.