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4-Benzyl-2,3-didehydroprolinate as a Homochiral Template for Michael Additions. Synthesis of Enantiopure α-Allokainoids, β-Kainoids, 2,3-Methanoprolines and other 3,4-Disubstituted Prolines

Jesús Ezquerra, Ana Escribano and Almudena Rubio*

Centro de Investigación Lilly, S. A. Paraje de la Cruz S/N, 28130 Valdeolmos, Madrid, Spain.

Modesto Jesús Remuiñán and Juan José Vaquero

Departamento de Química Orgánica, Universidad de Alcalá, 28871 Alcalá de Henares, Madrid, Spain.

Abstract: Ethyl (4*R*)-*N*-methoxycarbonyl-4-benzyl-2,3-didehydroprolinate **10a** undergoes Michael additions with stabilized carbanions and cuprates giving exclusively the enantiopure all-*trans* 3,4-disubstituted prolinates. The high stereoselection observed in this reaction is driven by the C-4 substituent of the Michael acceptor. This methodology has been applied to the synthesis of the enantiopure β-kainoid **5a** and the 2,3-methanoproline **15**.

The family of natural products with a 4-substituted pyrrolidinedicarboxylic acid structure are known as kainoids.[1] The major representatives of these non-proteinogenic amino acids are domoic acid,[2] acromelic acids,[3] α-kainic acid **1**[4] and its C-4 epimer, α-allokainic acid (**2**)[5] (Figure 1). All these compounds exhibit powerful Central Nervous System (CNS) effects mediated through high affinity for the kainate receptors.[6] The need to develop pharmacological tools for the better understanding of glutamate receptors, have led to the synthesis of several kainoid analogues[7,8] . One of these kainoid analogues, the β-kainic acid[9] **3**, has been reported to have anticonvulsant activity.[10] Since the biological activity of these compounds is affected by configurational and conformational changes, the development of synthetic strategies to control the relative stereochemistry is an important synthetic challenge in the discovery of new biologically active compounds.

As a part of our interest in the development of new excitatory amino acid receptor ligands, we have recently reported the enantioselective synthesis of α-allokainoids **4** by Michael addition of the diethyl malonate anion to chiral 4-substituted 2,3-didehydroprolinates.[11]

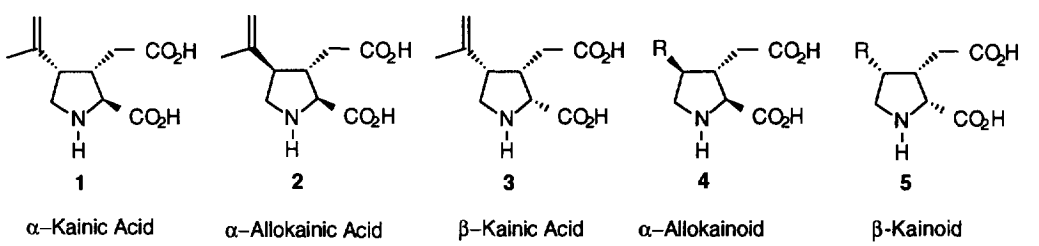
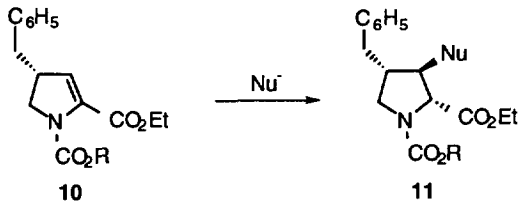


Figure 1

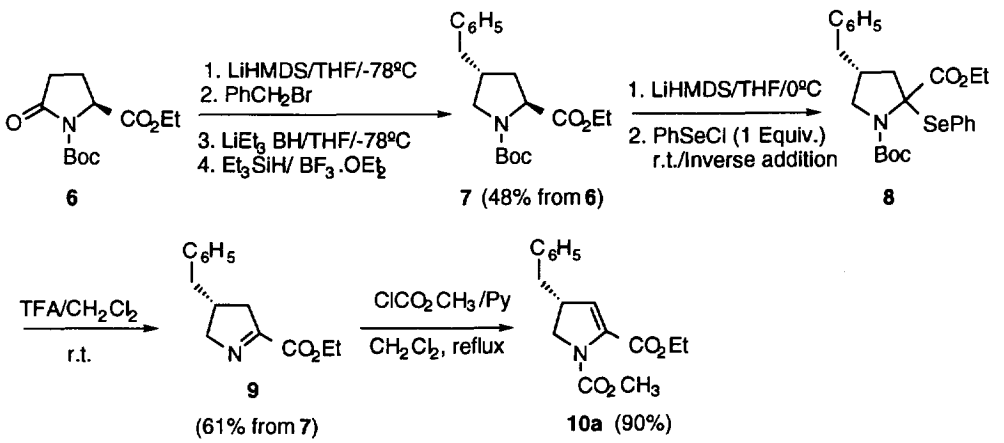
In this paper we report on the scope and limitations of this Michael addition reaction with different nucleophiles[12] and its application to the synthesis of enantiopure β-kainoid (**5**) and other 3,4-disubstituted

prolines. The main feature of this approach is the high degree of stereocontrol that the C-4 substituent of the Δ^2-pyrrolines **10** (Scheme 1) exercises during the Michael addition over the newly created C-2 and C-3 stereogenic centres.



Scheme 1

The Michael acceptor **10a** (Scheme 2) was prepared starting from ethyl *N*-Boc pyroglutamate **6**, following the same reaction pathway recently reported by us.[11]

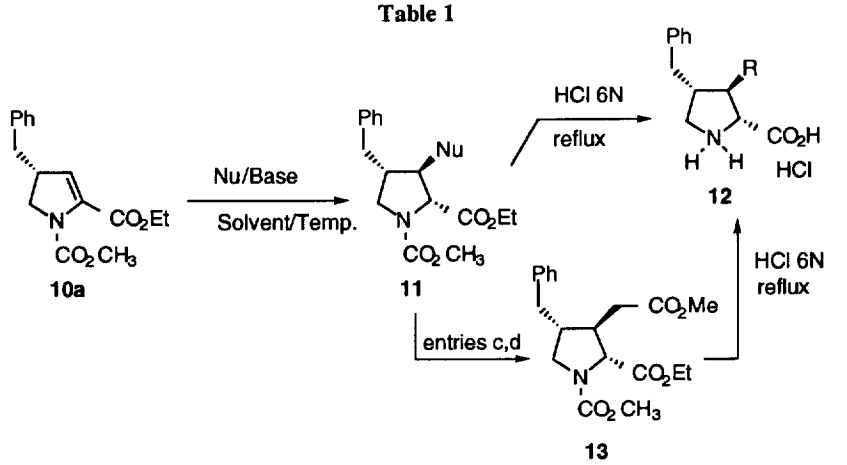


Scheme 2

With the Michael acceptor **10a** in hands we decided to explore its reactivity with different nucleophiles. We studied the effect of the base (NaH, KHMDS, Cs_2CO_3), solvent (Et_2O, THF, toluene), reaction time and temperature. Thus, **10a** reacts with stabilized carbanions such as diethyl malonate or ethyl acetoacetate (Table 1, entries a, b), in good to moderate yields, using NaH as base in THF. For other stabilized carbanions such as methyl phenylsulfonylacetate or methyl phenylthioacetate (Table 1, entries c, d) it was necessary to change the base and the Michael adducts were obtained in moderate yields. The reaction could not be extended to other nucleophiles such as methyl *p*-tolylsulfinylacetate. In this case the Michael conjugate addition gave complex mixtures of the reagent's degradation products and starting material. On the other hand, cuprates such as dimethyl or diphenyl cuprate (table 1, entries e, f) gave the Michael addition in 15 min.

Since the presence of rotamers, and in some cases (**11b-d**) the generation of an additional stereogenic centre complicates the NMR analysis of compounds **11**, the stereochemical outcome of the reaction was established on the final 3,4-disubstituted prolines **12.** Thus, acid hydrolysis of Michael adducts **11a,b,e,f** gave the corresponding prolines **12a,b,e,f** as single diastereomers. The all-*trans* stereochemistry was ascertained by nOe experiments[13] . On the other hand, Michael adducts **11c** and **11d** were transformed into the α-allokainoid **12a**. Removal of the phenylsulfonyl group [Na(Hg)] in **11c** and phenylthio group [Ni-

Table 1



Entry	Nu	Base	Solvent	Temp(°C)/ Time(Hrs.)	Yield[a,b] 11 (%)	R	Yield[a, b] 12 (%)
a	$(EtO_2C)_2CH_2$	NaH	THF	0 to r.t./7	70 (**11a**)	CH_2CO_2H	60 (**12a**)
b	$CH_3COCH_2CO_2Et$	NaH	THF	40/6	50 (**11b**)	CH_2COCH_3	72 (**12b**)
c	$PhSO_2CH_2CO_2Me$	Cs_2CO_3	THF	20/96	55 (**11c**)	CH_2CO_2H	50 (**12a**)[c]
d	$PhSCH_2CO_2Me$	KHMDS	Toluene	-40 to 0/1.5	40 (**11d**)	CH_2CO_2H	50 (**12a**)[d]
e	Me_2CuLi		THF/Et_2O	-40/0.25	88 (**11e**)	CH_3	44 (**12e**)
f	Ph_2CuLi		THF/Et_2O	-40/0.25	52 (**11f**)	Ph	53 (**12f**)

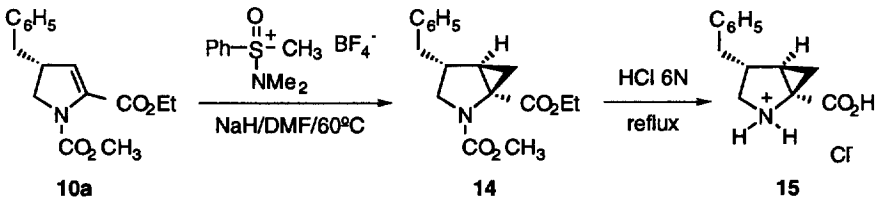
[a] Isolated yield. [b] Compound in brackets. [c] Compound **11c** was reduced with Na(Hg) (23% yield) giving rise to the corresponding diester **13**. Yield from **13**. [d] Compound **11d** was desulfurated with Ni-Raney in ethanol (79% yield) giving the corresponding diester **13**. Yield from **13**.

Raney] in **11d** followed by acid hydrolysis of the resulting diester **13** gave exclusively the α–allokainoid **12a**[11] [$[\alpha]_D$ = +10.4 (c, 0.22, H_2O)].

The stereochemical outcome of this conjugate addition is controlled by the substituent at C-4 of the Michael acceptor. Selective *trans* attack by the nucleophile from the opposite less hindered face of the Δ^2-pyrroline **10a**, followed by protonation of the anion intermediate resulted in the formation of the all-*trans* prolinates **11a-f**. Recently, other closely related methodologies, based on the Michael conjugate addition to different 3,4-didehydropyroglutamate derivatives, where the carboxylic moiety was transformed into a protected alcohol[7c,14] or as its *N,O*-acetal,[15] have been described. While in these transformations the protected alcohol or the *N,O*-acetal functionality are responsible for the stereochemical reaction outcome, in our approach the reaction stereocontrol is driven by the C-4 substituent of the Michael acceptor. Since we have previously reported[11] the synthesis of the corresponding enantiomer of **10a** starting from pyroglutamate **6**, the present methodology constitutes a useful enantiodivergent approach for the synthesis of 3,4-disubstituted prolines.

Due to the high level of stereocontrol observed in this conjugate additon, we decided to explore the cyclopropanation of **10a** in order to obtain the 4-substituted 2,3-methanoproline **15** (Scheme 3)[16]. Reaction of **10a** with dimethylsulfoxonium methylide in DMSO at room temperature led to a 5% yield of the cyclopropane adduct **14** (Scheme 3). However, cyclopropanation with (dimethylamino) phenyloxosulfonium methylide at 60°C in DMF for 48 hrs., allowed us to obtain **14** in 30% yield together with some starting

material (70% conversion). Finally, **14** was hydrolysed under acid conditions (HCl 6N), and the (2*R*, 3*R*, 4*R*)-4-benzyl-2,3-methanoproline **15** was isolated in 72% yield. The stereochemical assignment was confirmed by nOes experiments.[13]

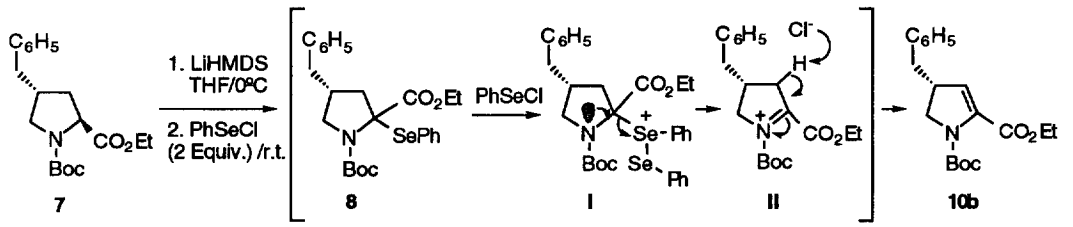


Scheme 3

While the synthesis and resolution of racemic 2,3-methanoproline have been described recently[17], this new approach is applicable to more highly substituted enantiopure compounds.

After having developed an efficient synthesis of enantiopure α-allokainoids, we turned our attention to applying this methodology to the synthesis of β-kainoids **5**. It was envisioned that the configuration at C-3 could be inverted in the Michael adduct **11a** through double bond formation followed by stereoselective hydrogenation.

In preparing the Michael acceptor **10a**, we discovered that, when the lithium enolate of the 4-benzylprolinate **7** was treated with an excess of PhSeCl (2 equivalents), the α-selenated derivative **8** was not isolated, but instead, in situ formation of the α,β-unsaturated compound **10b** took place (Scheme 4). An explanation of this unexpected result could involve selenation of the selenide **8** by a second equivalent of electrophile, giving rise to the unstable intermediate **I** that quickly eliminates with the assistance of the nitrogen lone pair to the N-acyliminium ion **II**. Finally, prototopic displacement assisted by chloride would give **10b**. We have noticed that chloride ions are necessary for this reaction to take place. In fact, when PhSeCl was replaced by the more electrophilic selenation reagent *N*-(phenylseleno)phthalimide (N-PSP)[18] and under the same reaction conditions, no olefin formation was observed in the crude mixture.

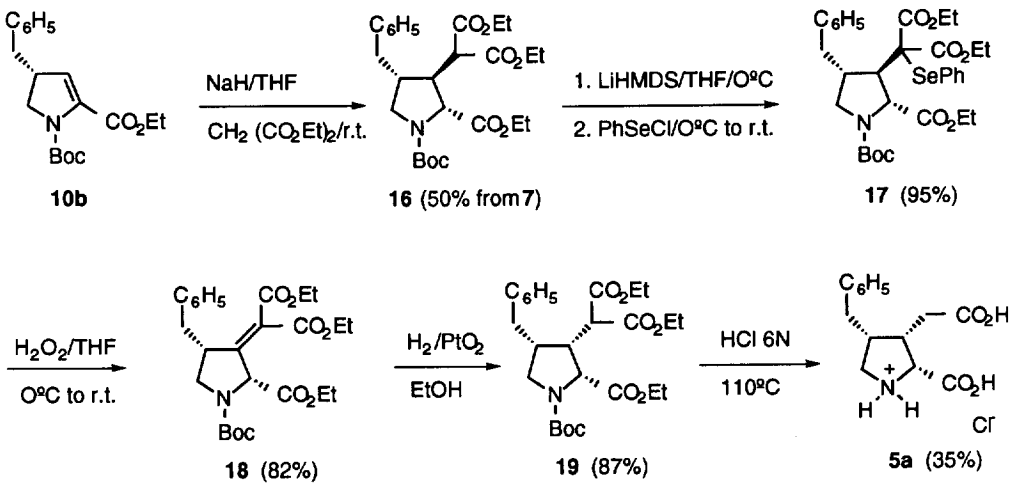


Scheme 4

In the literature,[12,19] N-urethane 2,3-didehydroprolinates have been obtained from the corresponding N-protected prolinates through a four steps sequence [nitrogen deprotection, N-chlorination (tBuOCl), dehydrochlorination (Et_3N) and treatment of the resulting pyrroline with ethyl or benzyl chloroformate]. This method has the limitation of being restricted to N-ethoxycarbonyl and N-benzyloxycarbonyl derivatives. The fact that the didehydroprolinate **10b** can be obtained in just one step from the prolinate **7** constitutes a significant advantage. In addition, this transformation is more valuable if one considers that the reported method cannot be applied for the synthesis of N-Boc 2,3-didehydroprolinates[7d].

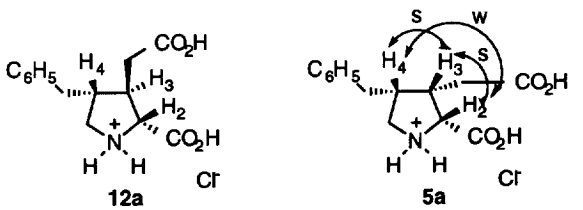
As compound **10b** (Scheme 5) turned out to be quite unstable, it was used in the Michael conjugate additon with diethyl malonate without any purification, yielding **16** (50% overall yield from **7**). The next

steps were directed at the epimerization of the C-3 stereogenic centre of the prolinate system. Therefore, selective methine deprotonation of the malonate moiety with LiHMDS in THF at O°C and reaction with PhSeCl[20], yielded the selenide **17** (95% yield). Oxidation with H_2O_2/THF at O°C, followed by selenoxide *syn* elimination at room temperature, afforded the olefin **18** (82% yield). Catalytic hydrogenation (PtO_2) on the less sterically hindered face of **18**, gave exclusively the all-*cis* prolinate **19** (87% yield). Finally, acid hydrolysis and decarboxylation gave the β-kainoid hydrochloride **5a** in 35% isolated yield.



Scheme 5

The stereochemical assignment of the β-kainoid **5a** was made on the basis of n.O.e experiments and coupling constant analysis (Figure 2). By n.O.e. irradiation it was possible to correlate all the *cis* protons of the system. On the other hand, the comparison of coupling constants and chemical shifts of both α-allokainoid **12a** and β-kainoid **5a** fit the kainoids NMR pattern reported by Ohfune,[3d] where regardless of the C-4 substituent, the proton at C-2 appears under 4.2 ppm when the 2,3-substituents are *trans* , while if the substituents are *cis* it appears higher than 4.2 ppm.



$J_{2,3}$= 5.8 Hz
δH_2 = 3.91 ppm

$J_{2,3}$= 7.7 Hz
δH_2 = 4.56 ppm

Figure 2

The enantiomeric purity of all the amino acids reported here was established by ^{1}H-NMR (detection limit was determined by doping experiments) of the Mosher's amides[21] of the corresponding methyl esters. Thus, esterification of the final amino acids (CH_3OH/HCl(g)), followed by Mosher amide formation ((S)-(+)- and (R)-(-)-methoxy-α-(trifluoromethyl)phenylacetyl chloride in the presence of propylene oxide) gave an *ee* ≥95% in all cases.

In summary, ethyl (4*R*) *N*-methoxycarbonyl-4-benzyl-2,3-didehydroprolinate **10a** undergoes a highly stereoselective Michael addition with stabilized carbanions and cuprates giving rise to enantiopure all-*trans* 3,4-disubstituted prolinates. This methodology has been applied to the synthesis of the enantiopure β-kainoids and 2,3-methanoproline derivatives, thus providing a new enantioselective synthesis of these highly functionalised prolines.

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EXPERIMENTAL

Materials and Methods. All solvents and reagents were purchased from commercial sources and used as received, unless otherwise indicated. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. ^{1}H-NMR and ^{13}C-NMR data were recorded on a Bruker AC-200P (200 MHz). IR spectra were obtained on Nicolet 510 P-FT (film and KBr). High Resolution Mass Spectra (HRMS) were measured on a VG-Autospec spectrometer. Melting points were determined on a Büchi apparatus and are not corrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Analytical TLC was performed on Merck TLC glass plates precoated with F_{254} silica gel 60 (UV, 254 nm and Iodine). Chromatographic separations were performed by using 230-400 mesh silica gel (Merck). Elemental analyses were performed by the Universidad de Alcalá de Henares de Madrid.

Ethyl (4*R*)-4-benzylpyrroline-2-carboxylate 9: To a solution of **7**[22] (1.5 g, 4.5 mmol) in 25 mL of THF at 0°C, was added under nitrogen atmosphere 5.4 mL of a 1M solution of LiHMDS in THF (5.4 mmol). After stirring for 30 min., the enolate was added over a solution of PhSeCl (0.94 g, 4.9 mmol) in 10 mL of THF. The reaction mixture was stirred at room temperature for 12 h. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl ether (3 x 50 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under vacuum. The crude mixture was dissolved in 50 mL of CH_2Cl_2 and trifluoroacetic acid (4 mL) was added at room temperature. After 12 hours, the crude mixture was washed with $NaHCO_3$ saturated solution (75 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness. The crude was purified by flash chromatography (EtOAc/hexane 1:2). 61% yield. $[\alpha]_D$= +24.5 (c 0.9, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 7.33-7.11 (m, 5H, Ph), 4.30 (q, 2H, J=7.1 Hz, CH_2-CH_3), 4.20-4.07 (m, 1H, CH_2N), 3.90-3.78 (m, 1H,CH_2N), 2.99-2.55 (m, 5H), 1.34 (t, 3H, J=7.1 Hz, CH_3-CH_2). ^{13}C-RMN ($CDCl_3$): 168.0 (CO_2), 162.6 (C=N), 139.7, 128.6 (2C), 128.5 (2C), 126.2, 67.4 (CH_2C=N), 61.8 (CO_2CH_2), 41.1 (CH_2), 40.5 (CH_2), 37.9 (CH), 14.0 (CH_3). IR (film): 1722, 1454, 1265, 1107 cm^{-1}. EIMS m/e 231 (M^+, 1), 202 (2), 156 (6), 140 (11), 117 (19), 91 (100), 57 (4).

Ethyl (4*R*)-*N*-(methoxycarbonyl)-4-benzyl-2,3-didehydroprolinate 10a: Over a solution of the Δ^1-pyrroline **9** (0.8 g, 34 mmol) and pyridine (0.62 mL, 7 mmol) in 10 mL of CH_2Cl_2, previously cooled at -30°C; was added methyl chloroformate (0.6 mL, 7 mmol). The reaction mixture was stirred for 15 min. at -30°C and 1 hour at reflux. The reaction was quenched with saturated ammonium chloride solution (25 mL) and extracted with CH_2Cl_2 (2 x 50 mL). After dried with Na_2SO_4 and filtered, the solvent was removed under vacuum. The crude was purified by flash chromatography (EtOAc/hexane 1:3). 90% yield. $[\alpha]_D$= +2.3 (c 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 7.35-7.13 (m, 5H, Ph), 5.76 (d, 1H, J= 2.7 Hz, HC=C), 4.28 (q, 2H, J=7.1 Hz, CH_2-CH_3), 3.98 (dd, 1H, J=11.4 and 9.7 Hz, CH_2N), 3.70 (s, 3H, NCO_2CH_3), 3.68 (dd, 1H, J= 11.4 and 6.2 Hz, CH_2N), 3.35-3.18 (m, 1H, H_4), 2.85-2.63 (m, 2H, CH_2Ph), 1.31 (t, 3H, J=7.1 Hz, CH_3-CH_2). ^{13}C-RMN

($CDCl_3$): 161.9 (CO_2), 153.9 (NCO_2), 138.4, 136.1 (C=CH), 128.7 (2C), 128.5 (2C), 126.4, 122.6 (HC=C), 61.2 (CO_2CH_2), 53.7 (CH_2N), 52.8 (CO_2CH_3), 43.1 (CH), 40.2 (CH_2), 14.0 (CH_3). IR (film): 1717, 1447, 1356, 1182 cm^{-1}. CIMS m/e 290 (M^+ +1).

Ethyl (4*R*)-*N*-(tert-butoxycarbonyl)-4-benzyl-2,3-didehydroprolinate 10b: To a solution of **7** (1.5 g, 4.5 mmol) in 25 mL of THF at 0°C, was added under nitrogen atmosphere a 1M solution of LiHMDS in THF (5.4 mL, 5.4 mmol). After stirring for 30 min., the lithium enolate was added slowly over a solution of PhSeCl (1.72 g, 9 mmol) in 10 mL of THF. The reaction mixture was stirred at room temperature for 12 h. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl ether (3 x 50 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under vacuum. $[\alpha]_D$= -29.5° (c 1.2, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 7.39-7.12 (m, 5H, Ph), 5.68 (d, 1H, J= 2.7 Hz, HC=C), 4.25 (q, 2H, J=7.1 Hz, CH_2-CH_3), 3.96 (dd, 1H, J=11.5 and 9.7 Hz, CH_2N), 3.65 (dd, 1H, J= 11.5 and 6.3 Hz, CH_2N), 3.30-3.12 (m, 1H, H_4), 2.83-2.64 (m, 2H, CH_2Ph), 1.44 (s, 9H, $C(CH_3)_3$), 1.32 (t, 3H, J=7.1 Hz, CH_3-CH_2). ^{13}C-RMN ($CDCl_3$): 162.3 (CO_2), 152.6 (NCO_2), 138.7, 136.6 (C=CH), 128.8 (2C), 128.5 (2C), 126.4, 122.0 (HC=C), 81.1 ($C(CH_3)_3$), 61.1 (CO_2CH_2), 53.8 (CH_2N), 42.9 (CH), 40.4 (CH_2), 28.1 ($C(CH_3)_3$), 14.1 (CH_3). IR (film): 1738, 1705, 1392, 1367, 1167 cm^{-1}. HRMS calcd for $C_{19}H_{26}NO_4$ (M^++1) 332.1862, found 332.1857.

General procedure for Michael addition of diethyl malonate to compounds 10: To a suspension of sodium hydride (63 mg, 2.6 mmol) in anhydrous THF (15 mL) was added diethylmalonate (0.43 mL, 2.8 mmol) at 0°C. After 30 min, a solution of **10** (784 mg, 2.36 mmol) in THF (10 mL) was added at 0°C. The reaction mixture was stirred for 7 hours at room temperature. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl ether (3 x 10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under vacuum.

Diethyl [(2*R*,3*S*,4*R*)-*N*-(methoxycarbonyl)-4-benzyl-2-(ethoxycarbonyl)pyrrolidin-3-yl]malonate 11a: Purified by flash chromatography (EtOAc/hexane 1:3). 70% yield. $[\alpha]_D$=+12.4 (c 0.5, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 305°K): 7.32-7.10 (m, 5H, Ph), 4.38 (d, 1H, J=5.0 Hz, H_2), 4.29-4.13 (m, 6H, CH_2-CH_3), 3.64 (s, 3H, NCO_2CH_3), 3.57-5.53 (m, 1H, CH_2N), 3.55 (d, 1H, J=6.5 Hz, $CH(CO_2Et)_2$), 3.26 (dd, 1H, J=10.9 and 6.5 Hz, CH_2N), 2.94-2.81 (m, 2H), 2.58 (dd, 1H, J= 12.7 and 9.8 Hz, CH_2Ph), 2.48 (m, 1H), 1.33-1.22 (m, 9H, CH_3-CH_2). ^{13}C-RMN ($CDCl_3$): Mixture of rotamers: 171.9 (CO_2), 167.6 (2C, CO_2), 155.1 and 154.7 (NCO_2), 139.4 and 139.2, 128.6 (2C), 128.5 (2C), 126.4 (CH), 62.4 (CO_2CH_2), 61.8 (2C, CO_2CH_2), 61.4 and 61.3 (NCHCO2), 53.6 and 53.4 ($CH(CO_2Et)_2$), 52.6 (NCO_2CH_3), 51.1 and 50.6 (CH_2N), 47.9 and 46.9 (CH), 43.3 and 42.6 (CH), 39.2 and 39.1 (CH_2Ph), 14.1, 13.9 (2C, CH_3). IR (film): 1732, 1713, 1454, 1388, 1196 cm^{-1}. EIMS m/e 403 (M^+-EtOH, 1), 376 (5), 223 (5), 117 (21), 91 (100).

Diethyl [(2*R*, 3*S*, 4*R*)-*N*-(tert-butoxycarbonyl)-4-benzyl-2-(ethoxycarbonyl)pyrrolidin-3-yl]malonate 16: Purified by flash chromatography (EtOAc/hexane 1:6). 50% yield from **7**. $[\alpha]_D$= +11.0 (c 0.3, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 313°K): 7.30-7.09 (m, 5H, Ph), 4.31 (d, 1H, J=5.3 Hz, H_2), 4.27-4.13 (m, 6H, CH_2-CH_3), 3.54 (d, 1H, J=6.3 Hz, $CH(CO_2Et)_2$), 3.51 (m, 1H, CH_2N), 2.90 (dd, 1H, J=13.1 and 4.9 Hz, CH_2N), 2.84-2.64 (m, 2H), 2.58 (dd, 1H, J= 11.6 and 9.7 Hz, CH_2Ph), 2.45 (m, 1H), 1.40 (s, 9H, $C(CH_3)_3$), 1.33-1.22 (m, 9H, CH_3-CH_2). ^{13}C-RMN ($CDCl_3$, 313°K): 172.0, 167.4, 167.3 (CO_2), 153.4 (NCO_2), 139.3, 128.5 (2C), 128.3 (2C), 126.1, 79.8 ($C(CH_3)_3$), 62.1, 61.4 (2C, CO_2CH_2), 60.8 ($NCHCO_2$) , 53.4 (CH_2N), 50.7 ($CH(CO_2Et)_2$), 47.9 (CH), 42.5 (CH), 38.9 (CH_2Ph), 28.0 ($C(CH_3)_3$), 13.9, 13.7 (2C) (CH_3). IR (film): 1732, 1705, 1397, 1368, 1258, 1171 cm^{-1}. EIMS m/e 435 (M^+-^{t}Bu, 3), 418 (2), 390 (4), 362 (16), 318 (44), 140 (27), 117 (15), 91 (53), 57 (100).

Ethyl [(2*R*, 3*S*, 4*R*)-N-(methoxycarbonyl)-4-benzyl-2-(ethoxycarbonyl)pyrrolidin-3-yl]acetylacetate 11b: Over a suspension of sodium hydride (10 mg, 0.41 mmol) in 2 mL of THF at 0°C was added under nitrogen atmosphere ethyl acetoacetate (54 mL, 0.41 mmol). After stirring for 15 min., a solution of **10a** (0.1 g, 1.5 mmol) in 2 mL of THF was added. The mixture was stirred at 40°C for 6 hours. The reaction was quenched with saturated ammonium chloride solution (10 mL) and extracted with ethyl ether (3 x 25 mL). After usual treatment, the solvent was removed under vacuum and the residue was purified by flash

chromatography (EtOAc/hexane 1:4). 50% yield. ^{1}H-NMR ($CDCl_3$, 333°K): Mixture of two diastereomers: 7.31-7.03 (m, 10H, Ph), 4.36-4.13 (m, 10H, H-2 and CH_2-CH_3), 3.65 (s, 3H, NCO_2CH_3), 3.64 (s, 3H, NCO_2CH_3), 3.65-3.54 (m, 2H, CH_2N), 3.59 (d, 1H, J= 6.9 Hz, CHCO), 3.48 (d, 1H, J= 7.1 Hz, CHCO), 3.32-3.22 (m, 2H, CH_2N), 2.92-2.78 (m, 4H, CH_2Ph), 2.68-2.52 (m, 2H, H-3), 2.44-2.29 (m, 2H, H-4), 2.21 (s, 3H, $COCH_3$), 2.11 (s, 3H, $COCH_3$), 1.33-1.20 (m, 12H, CH_3-CH_2). IR (film): 1740, 1713, 1451, 1391, 1149 cm^{-1}. EIMS m/e 419 (M^+, 0.5), 373 (2), 346 (25), 198 (37), 117 (24), 91 (100), 59 (40).

Michael addition of methyl phenylsulfonylacetate to compound 10a: Over a suspension of cesium carbonate (0.31 g, 2.35 mmol) and methyl phenylsulfonylacetate (0.46 g, 2.13 mmol) in 6 mL of THF at 0°C under nitrogen atmosphere, was added a solution of **10a** (0.31 g, 1.07 mmol) in 6 mL of THF. After 96 hours at room temperature, the reaction was quenched with saturated ammonium chloride solution (10 mL) and extracted with ethyl ether (3 x 25 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/hexane 1:3), rending compound **11c** as a mixture of diastereomers (55%) and unreacted starting material (22%).

Methyl [(2*R*, 3*R*, 4*R*)-*N*-(methoxycarbonyl)-4-benzyl-2-(ethoxycarbonyl)pyrrolidin-3-yl]acetate 13: Over a solution of **11c** (50 mg, 0.11 mmol) and anhydrous sodium hydrogenphosphate (60 mg, 0.43 mmol) in methanol (2 mL) at 0°C and under nitrogen atmosphere, was added Na(Hg) (0.39 g, 1.1 mmol). After stirring for 1 hour, the reaction was quenched with saturated ammonium chloride solution (2 mL) and extracted with ethyl ether (3 x 10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by flash chromatography (EtOAc/hexane 1:1), giving rise to compound **13** (23%) and 30% of unreacted starting material. $[\alpha]_D$= +50.7 (c 0.4, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 333°K): 7.30-7.07 (m, 5H, Ph), 4.26-4.11 (m, 2H, CH_2-CH_3), 4.07 (d, 1H, J= 6.5 Hz, H-2), 3.76-3.61 (m, 1H, CH_2N), 3.66 (s, 3H), 3.63 (s, 3H), 3.21 (dd, 1H, J=10.8 and 8.6 Hz, CH_2N), 2.84 (dd, 1H, J=13.7 and 8.3 Hz, CH_2CO_2Me), 2.61-2.38 (m, 4H), 2.35-2.18 (m, 1H, H-4), 1.27 (t, 3H, J= 7.1 Hz, CH_3-CH_2). ^{13}C-RMN ($CDCl_3$, 333°K): 171.8, 171.4 (CO_2), 154.9 (NCO_2), 139.3 (C), 128.6 (4C), 126.5 (CH), 64.6 ($NCHCO_2$), 61.1 (CO_2CH_2), 52.3 (CH_3), 51.7 (CH_2N), 51.5 (CH_3), 45.4 (CH), 45.0 (CH), 38.2 (CH_2), 36.7 (CH_2), 14.1 (CH_3). IR (film): 1740, 1705, 1454, 1392, 1186 cm^{-1}. CIMS m/e 364 (M^+ + 1). Anal Calcd for: $C_{19}H_{25}NO_6$ C, 62.80; H, 6.93; N, 3.85. Found: C, 62.46; H, 7.03; N, 4.29.

Michael addition of methyl phenylthioacetate to compound 10a:

Over a 0.5 M solution of KHMDS in toluene (3.3 mL, 1.65 mmol) at -40°C under nitrogen atmosphere, was added methyl phenylthioacetate (0.23 mL, 1.52 mmol). After stirring for 15 min, a solution of **10a** (0.4 g, 1.38 mmol) in 8 mL of toluene was added. After 90 min at 0°C, the reaction was quenched with saturated ammonium chloride solution (20 mL) and extracted with ethyl ether (3 x 50 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/hexane 1:4), giving rise to compound **11d** as a mixture of diastereomers. 40% yield. Compound **11d** (0.1 g, 0.22 mmol) was dissolved in 10 mL of anhydrous ethanol and an excess of Raney Nickel (previously activated by washing the commercial reagent with ethanol) was added. The mixture was vigorously stirred under nitrogen at room temperature for 4 hours. The nickel was removed by filtration and washed with ethanol. The solvent was evaporated and the residue was purified by flash chromatography (EtOAc/hexane 1:3) giving compound **13**. 79% yield.

General procedure for Michael addition of R_2CuLi to compound 10a: Over a suspension of $CuBr{\cdot}SMe_2$ (0.71 g, 3.46 mmol) in 8 mL of ethyl ether at -20°C under nitrogen atmosphere was added a 1.6 M solution of MeLi or 2M solution of PhLi (6.9 mmol). After cooling at -40°C for 30 min., a solution of **10a** (0.2 g, 0.69 mmol) in 8 mL of THF was added over cuprate solution. After stirring for 15 min., the reaction was quenched with saturated ammonium chloride solution and extracted with ethyl ether (3 x 40 mL). After usual treatment, the solvent was removed under vacuum and the residue was purified by flash chromatography (EtOAc/hexane 1:5).

Ethyl (2*R*, 3*R*, 4*R*)-*N*-(methoxycarbonyl)-4-benzyl-3-methylprolinate 11e: 88% yield. $[\alpha]_D$= +91.9 (c 0.4, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 333°K): 7.30-7.08 (m, 5H, Ph), 4.26-4.15 (m, 2H, CH_2-CH_3), 3.83 (d, 1H, J=7.7 Hz, H-2), 3.73-3.62 (m, 1H, CH_2N), 3.62 (s, 3H, NCO_2CH_3), 3.17 (t, 1H, J=10.6 Hz, CH_2N), 2.89 (dd, 1H, J=13.8 and 4.5 Hz, CH_2Ph), 2.50 (dd, 1H, J=13.8 and 10.6 Hz, CH_2Ph), 2.09-1.92 (m, 2H, H-3 and H-4), 1.28 (t, 3H, J= 7.1 Hz, CH_3-CH_2), 1.19 (t, 3H, J= 6.3 Hz, CH_3-CH). ^{13}C-RMN ($CDCl_3$): Mixture of rotamers: 174.5 and 170.4 (CO_2), 155.1 and 154.7 (NCO_2), 139.6 and 139.5 (C), 128.6 (4C), 126.3 (CH), 66.6 and 66.4 ($NCHCO_2$), 61.1 and 60.9 (CO_2CH_2), 52.5 (NCO_2CH_3), 52.4 and 51.9 (CH_2N), 47.6 and 46.9 (CH), 45.0 and 44.1 (CH), 37.5 and 37.4 (CH_2), 16.5 and 16.3 ($CHCH_3$), 14.2 (CH_3). IR (film): 1747, 1705, 1454, 1392, 1153 cm^{-1}. CIMS m/e 306 (M^++1). Anal Calcd for: $C_{17}H_{23}NO_4$ C, 66.86; H, 7.59; N, 4.58. Found: C, 66.86; H, 7.71; N, 4.73.

Ethyl (2*R*, 3*S*, 4*R*)-*N*-(methoxycarbonyl)-4-benzyl-3-phenylprolinate 11f: 52% yield. $[\alpha]_D$=-2.0 (c 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 333°K): 7.31-7.07 (m, 8H), 6.97-6.93 (m, 2H), 4.21 (d, 1H, J=8.5 Hz, H-2), 4.14-3.99 (m, 2H, CH_2-CH_3), 3.82-3.68 (m, 1H, CH_2N), 3.58 (s, 3H, NCO_2CH_3), 3.24 (dd, 1H, J=10.6 and 9.6 Hz, CH_2N), 2.98 (t, 1H, J=8.8 Hz, CHPh), 2.68 (dd, 1H, J=12.5 and 3.6 Hz, CH_2Ph), 2.59-2.47 (m, 1H, H-4), 2.39 (dd, 1H, J=12.5 and 9.3 Hz, CH_2Ph), 1.07 (t, 3H, J=7.1 Hz, CH_3-CH_2). ^{13}C-RMN ($CDCl_3$): Mixture of rotamers: 172.1 (CO_2), 155.0 and 154.6 (NCO_2), 139.4 and 139.2 (C), 138.4 and 138.3 (C), 128.9 (2C), 128.5 (2C), 128.4 (2C), 127.7 (2C), 126.3 (2C, CH), 66.7 and 66.6 ($NCHCO_2$), 61.0 and 60.9 (CO_2CH_2), 56.4 and 55.5 (CHPh), 52.6 (NCO_2CH_3), 52.2 and 51.8 (CH_2N), 47.9 and 47.2 (CH), 37.5 and 37.4 (CH_2Ph), 14.2 and 14.1 (CH_3). IR (film): 1744, 1705, 1454, 1390, 1197 cm^{-1}. EIMS m/e 367 (M^+, 1), 294 (25), 202 (14), 17 (22), 91 (100), 59 (27).

Ethyl (2*R*, 3*R*, 4*R*)-*N*-(methoxycarbonyl)-4-benzyl-2,3-methanoprolinate 14: A solution of (dimetilamino)methylphenylsulfoxonium fluorborate (0.11 g, 0.41 mmol) in 2 mL of DMF was added over 0.21 g of sodium hydride (0.41 mmol). After stirring at room temperature for 15 min, was added a solution of **10a** (0.1 g, 0.34 mmol) in 2 mL of DMF. The mixture was heated at 60°C for 48 hours. The reaction was quenched with saturated ammonium chloride solution (10 mL) and extracted with ethyl ether (3 x 25 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/hexane 1:1), rending compound **14** in a 30% yield and recovered starting material (30%). $[\alpha]_D$=+42.6 (c 0.64, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 7.35-7.15 (m, 5H, Ph), 4.23 (m, 2H, CH_2-CH_3), 3.70-3.54 (m, 2H, CH_2N), 3.69 (s, 3H, NCO_2CH_3), 2.89 (dd, 1H, J= 13.9 and 7.9 Hz, CH_2Ph), 2.77 (dd, 1H, J= 13.9 and 7.8 Hz, CH_2Ph), 2.52 (m, 1H, H-4), 1.97 (dd, 1H, J= 9.2 and 4.8 Hz, CH_2, cyclopropyl), 1.88 (m, 1H, H-3), 1.27 (t, 3H, J=7.1 Hz, CH_3-CH_2), 1.10 (t, 1H, J= 5.1 Hz, CH_2, cyclopropyl). ^{13}C-RMN ($CDCl_3$): 170.7 (CO_2), 156.4 (NCO_2), 130.3, 128.7 (2C), 128.6 (2C), 126.5 (CH), 61.2 (CO_2CH_2), 56.9 (CH_2N), 52.7 (NCO_2CH_3), 47.6 ($NCCO_2$), 42.0 (CH), 40.4 (CH_2Ph), 35.4 (CH), 25.7 (CH_2, Cyclopropyl), 14.3 (CH_3). IR (film): 1715, 1449, 1386, 1184 cm^{-1}. EIMS m/e 303 (M^+, 2), 272 (2), 257 (26), 230 (40), 166 (28), 140 (31), 117 (38), 91 (100), 59 (39).

Diethyl [(2*R*, 3*R*, 4*R*)-*N*-(tert-butoxycarbonyl)-4-benzyl-2-(ethoxycarbonyl)pyrrolidin-3-yl]phenylselenylmalonate 17: To a solution of **16** (450 mg, 0.91 mmol) in anhydrous THF (15 mL) was added a 1M solution of LiHMDS (1.0 mL, 1.0 mmol) at 0°C. After 30 min a solution of phenylselenyl chloride (208 mg, 1.09 mmol) in 12 mL of THF was added at 0°C. The mixture was stirred overnight at room temperature. The reaction was quenched and treated as above. The crude was purified by flash chromatography (EtOAc/hexane 1:6). 95% yield. $[\alpha]_D$= +17.9 (c 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 333°K): 7.68-7.64 (m, 2H), 7.40-7.08 (m, 8H), 4.85 (s broad, 1H, H-2), 4.27 (q, 2H, J=7.0 Hz, CH_2-CH_3), 4.14-4.00 (m, 4H, CH_2-CH_3), 3.44 (dd, 1H, J=10.7 and 7.3 Hz, CH_2N), 3.27 (dd, J=10.7 and 3.5 Hz, CH_2N), 3.17-2.76 (m, 3H), 2.59 (t, 1H, J=13.5 Hz, CH_2Ph), 1.44 (s, 9H, $C(CH_3)_3$), 1.34 (t, 3H, J=7.0 Hz, CH_3-CH_2), 1.27-1.12 (m, 6H,CH_3-CH_2). ^{13}C-RMN ($CDCl_3$, 333°K): 172.1, 167.8, 167.3 (CO_2), 153.6 (NCO_2), 139.7, 137.8 (2C), 129.6 (CH), 128.8 (2C), 128.6 (2C), 128.2 (2C), 126.7, 126.0 (CH), 79.7 ($C(CH_3)_3$), 64.1 (CSe), 62.2 (CO_2CH_2), 62.0 ($NCHCO_2$), 61.7,

60.9 ($CO_2\underline{C}H_2$), 54.2 (CH), 50.4 (CH_2N), 42.1 (CH), 41.8 (CH_2Ph), 28.1 ($C(CH_3)_3$), 14.0, 13.5, 13.4 (CH_3). IR (film): 1732, 1703, 1392, 1367, 1244 cm^{-1}. Anal Calcd for: $C_{32}H_{41}NO_8Se$ C, 59.44; H, 6.39; N, 2.17. Found: C, 59.63; H, 6.68; N, 2.25.

Diethyl [(2*R*, 4*R*)-*N*-(tert-butoxycarbonyl)-4-benzyl-2-(ethoxycarbonyl)pyrrolidin-3-ylidene]malonate 18: Hydrogen peroxide (0.34 mL) was added at 0°C to a solution of **17** (200 mg, 0.3 mmol) in 10 mL of THF. After 30 min, the reaction was warmed to room temperature and stirred overnight. The crude was purified by flash chromatography (EtOAc/hexane 1:6). 82% yield. $[\alpha]_D$= -88.5 (c 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 313°K): 7.31-7.16 (m, 5H), 5.48 (s, 1H, H_2), 4.44-4.14 (m, 6H, $C\underline{H}_2$-CH_3), 3.78-3.65 (m, 1H, H_4), 3.57 (dd, 1H, J=10.8 and 2.9 Hz, $C\underline{H}_2N$), 3.35 (dd, 1H, J=10.8 and 7.2 Hz, $C\underline{H}_2N$), 3.13 (dd, 1H, J=13.2 and 3.5 Hz, $C\underline{H}_2Ph$), 2.8 (dd, 1H, J=13.2 and 11.5 Hz, $C\underline{H}_2Ph$), 1.44 (s, 9H, $C(CH_3)_3$), 1.39-1.27 (m, 9H, $C\underline{H}_3$-CH_2). ^{13}C-RMN ($CDCl_3$, 313°K): 168.6, 164.3, 163.4 (CO_2), 157.6 (C=), 153.9 (NCO_2), 139.4, 129.1 (2C), 128.4 (2C), 126.4 (CH), 124.2 (C=), 80.4 ($\underline{C}(CH_3)_3$), 62.3 ($CO_2\underline{C}H_2$), 61.7 ($N\underline{C}HCO_2$), 61.4, 61.3 ($CO_2\underline{C}H_2$), 49.0 (CH), 44.6 (CH_2N), 39.2 (CH_2Ph), 28.2 ($C(CH_3)_3$), 13.9, 13.7 (CH_3). IR (film): 1750, 1713, 1393, 1250, 1190 cm^{-1}. EIMS m/e 389 (M^+-Boc, 1), 362 (3), 318 (6), 220 (48), 202 (30), 160 (44), 117 (4), 91 (60), 57 (100).

Diethyl [(2*R*, 3*R*, 4*R*)-*N*-(tert-butoxycarbonyl)-4-benzyl-2-(ethoxycarbonyl)pyrrolidin-3-yl]malonate 19: To a solution of **18** (160 mg, 0.32 mmol) in 10 mL of ethanol, was added platinum(IV) oxide (7 mg, 0.032 mmol). The reaction was allowed to proceed under hydrogen atmosphere at room temperature and atmospheric pressure for 4 hours. Filtration of the catalyst through celite gave compound **19**. Purification was achieved by flash chromatography (EtOAc/hexane 1:6). 87% yield. $[\alpha]_D$= +25.0 (c 0.6, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 333°K): 7.29-7.06 (m, 5H, Ph), 4.58 (d, 1H, J=8.9 Hz, H-2), 4.39-4.12 (m, 6H, $C\underline{H}_2$-CH_3), 3.58 (d, 1H, J=12.5 Hz, $C\underline{H}(CO_2Et)_2$), 3.52-3.22 (m, 3H), 2.78-2.42 (m, 3H), 1.42 (s, 9H, $C(CH_3)_3$), 1.34-1.23 (m, 9H, $C\underline{H}_3$-CH_2). ^{13}C-RMN ($CDCl_3$, 333°K): 171.2, 167.8, 167.2 (CO_2), 154.0 (NCO_2), 140.3, 129.0 (2C), 128.5 (2C), 126.1, 79.9 ($\underline{C}(CH_3)_3$), 61.8, 61.7, 61.0 ($CO_2\underline{C}H_2$), 59.9 ($N\underline{C}HCO_2$), 51.2 ($\underline{C}H(CO_2Et)_2$), 49.6 (CH_2N), 44.3 (CH), 40.6 (CH), 33.6 (CH_2Ph), 28.3 ($C(CH_3)_3$), 14.0, 13.9 (2C) (CH_3). IR (film): 1751, 1734, 1705, 1394, 1176 cm^{-1}. Anal Calcd for: $C_{26}H_{37}NO_8$ C, 65.53; H, 7.58; N, 2.85. Found: C, 64.26; H, 8.03; N, 2.28.

General procedure for hydrolisis of compounds 11, 13, 14 and 19: A mixture of the 3,4-disubstituted prolinates (0.2 mmol) and 6N HCl solution (8 mL) was refluxed for 2-4 days (for **11**, **13**, **14**) or 8 hours (for **19**). The resulting solution was evaporated to dryness, and the residue was triturated with ethyl ether. The final product was precipitated in acetone.

(2*R*, 3*R*, 4*R*)-(2-Carboxy-4-benzylpyrrolidin-3-yl)acetic acid hydrochloride 12a: 60% yield. M. p.: 58-60°C. $[\alpha]_D$= +10.4 (c 0.22, H_2O). ^{1}H NMR (D_2O): 7.19-6.97 (m, 5H, Ph), 3.91 (d, J = 5.8 Hz, 1H, H-2), 3.18 (dd, J = 6.3 and 11.1 Hz, 1H), 2.91 (dd, J = 8.3 and 11.1 Hz, 1H), 2.63 (dd, J = 5.1 and 13.4 Hz, 1H), 2.51-2.28 (m, 5H). ^{13}C NMR (D_2O) 176.0, 172.4, 139.3, 129.5 (2C), 129.4 (2C), 127.4, 64.4, 50.1, 44.7, 44.0, 37.2, 35.8. IR (KBr) 3422, 2924, 1724, 1406 cm^{-1}. Anal. Cald. for: $C_{14}H_{18}ClNO_4$ C, 56.08; H, 6.06; N, 4.67. Found: C, 55.85; H, 6.26; N, 4.43.

(2*R*, 3*R*, 4*R*)-3-acetylmethyl-4-benzylproline hydrochloride 12b: 72% yield. M. p.: 141-143°C. $[\alpha]_D$= +11.6 (c 0.3, MeOH). ^{1}H-RMN (MeOH-d_4): 7.34-7.16 (m, 5H, Ph), 4.17 (d, 1H, J= 8.9 Hz, H-2), 3.58-3.30 (m, 1H, $C\underline{H}_2N$), 3.07 (dd, 1H, J= 11.5 and 8.5 Hz, $C\underline{H}_2N$), 2.94-2.81 (m, 3H), 2.72-2.47 (m, 3H), 2.08 (s, 3H, $COCH_3$). ^{13}C-RMN (MeOH-d_4): 208.8 (CO), 170.9 (CO_2H), 140.1, 129.8 (4C), 127.8 (CH), 64.4 ($N\underline{C}HCO_2$), 50.7 (CH_2N), 45.5, 44.1, 43.9, 38.5, 30.2. IR (KBr) 1711, 1601, 1375 cm^{-1}. HRMS calcd for $C_{15}H_{19}NO_3$.HCl (M^++1) 262.1443. Found 262.1441.

(2*R*, 3*R*, 4*R*)-4-Benzyl-3-methylproline hydrochloride 12e: 44% yield. M.p.: 160°C (dec.). $[\alpha]_D$= +47.0 (c 0.2, MeOH). ^{1}H-NMR (MeOH-d_4): 7.34-7.15 (m, 5H, Ph), 3.91 (d, 1H, J= 9.7 Hz, H-2), 3.26 (m, 1H, $C\underline{\ }_2N$), 3.03 (t, 1H, J= 11.6 Hz, $C\underline{H}_2N$), 2.97 (dd, 1H, J=9.7 and 5.1 Hz, $C\underline{H}_2Ph$), 2.61 (dd, 1H, J= 13.6 and 9.1 Hz, $C\underline{H}_2Ph$), 2.37-2.20 (m, 1H, H-4), 2.16-1.98 (m, 1H, H-3), 1.28 (d, 3H J=6.3 Hz, CH_3). ^{13}C-RMN (MeOH-d_4):

171.2 (CO_2H), 140.1, 129.8 (4C), 127.8, 66.8 ($NCHCO_2$), 50.9, 44.2, 37.8, 30.8, 16.6. IR (KBr): 2878, 1741, 1217, 1192. CIMS m/e 220 (M^++1). Anal Calcd for: $C_{13}H_{18}ClNO_2 \cdot H_2O$ C, 57.04 H, 7.36; N, 5.12. Found: C, 57.12 H, 7.16, N, 5.07.

(2*R*, 3*S*, 4*R*)-4-Benzyl-3-phenylproline hydrochloride 12f: 53% yield. M.p.: 78°C (dec.). $[\alpha]_D$= -13.5 (c 0.2, MeOH). ^{1}H-NMR (MeOH-d_4): 7.43-7.16 (m, 8H), 7.10-7.04 (m, 2H), 4.40 (d, 1H, J= 9.9 Hz, H-2), 3.42 (dd, 1H, J= 11.5 and 7.1 Hz, CH_2N), 3.25-3.14 (m, 2H), 2.84-2.76 (m, 1H, H-4), 2.75 (dd, 1H, J=13.7 and 3.6 Hz, CH_2Ph), 2.58 (dd, 1H, J= 13.7 and 10.1 Hz, CH_2Ph). ^{13}C-RMN (MeOH-d_4): 170.7 (CO_2H), 139.7, 138.6, 130.1 (2C), 129.7 (2C), 129.6 (2C), 129.2 (2C), 129.1, 127.7, 66.6 ($NCHCO_2$), 55.4, 51.3, 37.1, 24.2. IR (KBr): 2922, 1736, 1454. CIMS m/e 282 (M^++1). Anal Calcd for: $C_{18}H_{20}ClNO_2 \cdot H_2O$ C, 64.38; H, 6.60; N, 4.17. Found: C, 64.65 H, 6.43 N, 4.03.

(2*R*, 3*R*, 4*R*)-4-Benzyl-2,3-methanoproline hydrochloride 15: 72% yield. M.p.: 230°C (dec.). $[\alpha]_D$= +5.0 (c 0.2, MeOH). ^{1}H-NMR (MeOH-d_4): 7.37-7.21 (m, 5H, Ph), 3.22-3.13 (m, 2H, CH_2N), 2.84-2.71 (m, 3H, CH_2Ph and H-4), 2.23 (dd, 1H, H-4), 2.75 (dd, 1H, J=9.2 and 6.1 Hz), 1.71 (dd, 1H, J= 9.1 and 7.1 Hz), 1.61 (t, 1H, J= 6.2 Hz). ^{13}C-RMN (MeOH-d_4): 172.7 (CO_2H), 139.4, 130.1 (2C), 129.9 (2C), 127.9, 48.4, 47.7, 40.6, 39.6, 32.4, 15.8. IR (KBr): 3416, 2936, 1736, 1184. CIMS m/e 218 (M^++1).

(2*R*, 3*S*, 4*R*)-(2-Carboxy-4-benzylpyrrolidin-3-yl)acetic acid hydrochloride 5a: 35% yield. M.p.: 217-219°C. $[\alpha]_D$= +26.0 (c 0.2, MeOH). ^{1}H-NMR (MeOH-d_4): 7.32-7.22 (m, 5H, Ph), 4.56 (d, 1H, J= 7.7 Hz, H-2), 3.23 (m, 1H, H-3), 3.21 (m, 2H, CH_2N), 2.94 (m, 1H, H-4), 2.90 (m, 1H, CH_2Ph), 2.68 (dd, 1H, J= 17.0 and 7.2 Hz, CH_2CO_2H), 2.53 (dd, 1H, J= 17 and 7.0 Hz, CH_2CO_2H), 2.49 (m, 1H, CH_2Ph). ^{13}C-RMN (MeOH-d_4): 174.7, 170.4 (CO_2H), 140.2, 129.9 (2C), 129.8 (2C), 127.8 (CH), 63.7 ($NCHCO_2$), 49.9 (CH_2N), 44.0 (C-4), 41.0 (C-3), 35.0 (CH_2Ph), 31.2 CH_2CO_2H). IR (KBr): 3055, 1749, 1730, 1192, 1160. HRMS calcd for $C_{14}H_{17}NO_4$.HCl (M^++1) 264.1236. Found 264.1229.

General procedure for the optical purity determination. The final aminoacids (3-6 mg) were converted into the corresponding ester hydrochloride salts with a saturated HCl solution in dry MeOH (1 mL). The hydrochlorides were treated with (+) or (-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (2.2 eq) in THF in the presence of an excess of propylene oxide at room temperature. After stirring overnight, the solvent was evaporated and the residue was washed with a saturated $NaHCO_3$ solution and extracted with dichloromethane (3 x 5 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to dryness. The crude Mosher amides were analyzed by ^{1}H-NMR spectroscopy.

Methyl (2*R*, 3*R*, 4*R*, *S*) prolinate 12a-MTPA amide: ^{1}H-NMR ($CDCl_3$): 7.54-7.06 (m, 6H), 7.17-7.12 (m, 2H), 6.79-6.74 (m, 2H), 4.34 (d, 1H, J=8.0 Hz, H-2), 3.75 (s, 3H, CO_2CH_3), 3.63 (s, 3H, CO_2CH_3), 3.39 (q, 3H, J=1.3 Hz, OCH_3), 3.13-2.91 (m, 2H, CH_2N), 2.67 (dd, 1H, J=14.4 and 5.6 Hz), 2.45-2.26 (m, 5H)

Methyl (2*R*, 3*R*, 4*R*, *R*) prolinate 12a-MTPA amide: ^{1}H-NMR ($CDCl_3$): 7.60-7.51 (m, 2H), 7.44-7.33 (m, 4H), 7.18-7.13 (m, 2H), 6.77-6.70 (m, 2H), 4.30 (d, 1H, J=6.4 Hz, H-2), 3.79 (s, 3H, CO_2CH_3), 3.62 (s, 3H, CO_2CH_3), 3.58-3.44 (m, 2H, CH_2N), 3.39 (q, 3H, J=1.3 Hz, OCH_3), 2.59-2.15 (m, 6H).

Methyl (2*R*, 3*R*, 4*R*, *S*) prolinate 12)-MTPA amide: ^{1}H-NMR ($CDCl_3$): 7.57-6.73 (m, 10H), 4.18 (d, 1H, J= 8.6 Hz, H-2), 3.75 (q, 3H, J= 1.7 Hz, OCH_3), 3.72 (s, 3H, CO_2CH_3), 3.10 (dd, 1H, J= 11.6 and 7.1 Hz, CH_2N), 2.97 (t, 1H, J= 11.4 Hz, CH_2N), 2.63-2.34 (m, 6H), 2.02 (s, 3H, $COCH_3$).

Methyl (2*R*, 3*R*, 4*R*, *R*) prolinate 12b-MTPA amide: ^{1}H-NMR ($CDCl_3$): 7.58-7.50 (m, 2H), 7.45-7.39 (m, 3H), 7.18-7.13 (m, 3H), 6.79-6.74 (m, 2H), 4.18 (d, 1H, J= 6.9 Hz, H-2), 3.77 (s, 3H, CO_2CH_3), 3.58 (q, 3H, J= 1.6 Hz, OCH_3), 2.97 (t, 1H, J= 11.4 Hz, CH_2N), 2.50-2.19 (m, 8H), 1.99 (s, 3H, $COCH_3$).

Methyl (2*R*, 3*R*, 4*R*, *S*) prolinate 12e-MTPA amide: ^{1}H-NMR ($CDCl_3$): 7.43-7.16 (m, 5H), 7.15-7.11 (m, 3H), 6.79-6.73 (m, 2H), 4.11 (d, 1H, J= 8.9 Hz, H-2), 3.77 (s, 3H, CO_2CH_3), 3.75 (q, 3H, J= 1.5 Hz, OCH_3), 3.11 (dd, 1H, J= 11.3 and 6.5 Hz, CH_2N), 2.91 (t, 1H, J= 11.3 Hz, CH_2N), 2.71 (dd, 1H, J= 14.4 and 4.9 Hz, CH_2Ph), 2.30 (dd, 1H, J= 14.4 and 9.3 Hz,CH_2Ph), 1.87-1.73 (m, 1H, H-3), 1.59-1.45 (m, 1H, H-4), 1.10 (d, 3H, J= 6.5 Hz, CH_3).

Methyl (2*R*, 3*R*, 4*R*, *R*) prolinate 12e-MTPA amide: ^{1}H-NMR ($CDCl_3$): 7.58-7.50 (m, 2H), 7.44-7.37 (m, 3H), 7.20-7.41 (m, 3H), 6.83-6.76 (m, 2H), 4.05 (d, 1H, J= 7.5 Hz, H-2), 3.79 (s, 3H, CO_2CH_3), 3.53 (q, 3H, J= 1.5 Hz, OCH_3), 3.58-3.49 (m, 2H, CH_2N), 2.61 (dd, 1H, J= 13.5 and 4.9 Hz, CH_2Ph), 2.24 (dd, 1H, J= 13.9 and 8.1 Hz, CH_2Ph), 1.92-1.69 (m, 2H, H-3 and H-4), 1.10 (d, 3H, J= 6.4 Hz, CH_3).

Methyl (2*R*, 3*S*, 4*R*, *S*) prolinate 12f-MTPA amide ^{1}H-NMR ($CDCl_3$): 7.49-7.43 (m, 2H), 7.35-7.38 (m, 6H), 7.12-7.08 (m, 5H), 6.69-6.62 (m, 2H), 4.60 (d, 1H, J= 8.9 Hz, H-2), 3.79 (q, 3H, J= 1.8 Hz, OCH_3), 3.67 (s, 3H, CO_2CH_3), 3.27 (dd, 1H, J= 11.4 and 6.6 Hz, CH_2N), 3.07 (t, 1H, J= 10.9 Hz, CH_2N), 2.87 (t, 1H, J= 9.5 Hz, H-3), 2.56 (dd, 1H, J= 14.4 and 4.1 Hz, CH_2Ph), 2.29 (dd, 1H, J= 14.4 and 9.8 Hz, CH_2Ph), 2.15-1.99 (m, 1H, H-4).

Methyl (2*R*, 3*S*, 4*R*, *R*) prolinate 12f-MTPA amide: ^{1}H-NMR ($CDCl_3$): 7.59-7.54 (m, 2H), 7.46-7.42 (m, 3H), 7.34-7.28 (m, 3H), 7.15-7.10 (m, 5H), 6.70-6.60 (m, 2H), 4.52 (d, 1H, J= 8.4 Hz, H-2), 3.71 (s, 3H, CO_2CH_3), 3.67-3.65 (m, 2H, CH_2N), 3.59 (q, 3H, J= 1.5 Hz, OCH_3), 2.81 (t, 1H, J= 8.6 Hz, H-3), 2.54 (dd, 1H, J= 12.6 and 3.6 Hz, CH_2Ph), 2.47-2.37 (m, 1H, H-4), 2.30 (t, 1H, J= 12.6, CH_2Ph).

Methyl (2*R*, 3*R*, 4*R*, *S*) prolinate 15-MTPA amide: ^{1}H-NMR ($CDCl_3$): 7.47-7.41 (m, 2H), 7.39-7.32 (m, 3H), 7.21-7.15 (m, 3H), 6.99-6.93 (m, 2H), 3.82 (q, 3H, J=1.8 Hz, OCH_3), 3.74 (s, 3H, CO_2CH_3), 3.40 (dd, 1H, J=11.8 and 7.9 Hz, CH_2N), 3.10 (dd, 1H, J=11.8 and 6.9 Hz, CH_2N), 2.67-2.27 (m, 2H, CH_2Ph), 2.05 (dd, 1H, J=9.0 and 5.6 Hz, CH_2 cyclopropyl), 1.78 (ddd, 1H, J=9.0, 5.6 and 2.0 Hz, H-3), 0.95 (t, 1H, J=5.6 Hz, CH_2 cyclopropyl).

Methyl (2*R*, 3*R*, 4*R*, *R*) prolinate 15-MTPA amide: ^{1}H-NMR ($CDCl_3$): 7.67-7.60 (m, 2H), 7.46-7.41 (m, 3H), 7.20-7.16 (m, 3H), 6.81-6.76 (m, 2H), 3.81 (s, 3H, CO_2CH_3), 3.56 (q, 3H, J=1.5 Hz, OCH_3), 3.52-3.46 (m, 1H, CH_2N), 2.74 (dd, 1H, J=11.9 and 6.5 Hz, CH_2N), 2.54-2.40 (m, 3H), 2.05 (dd, 1H, J=9.2 and 6.0 Hz, CH_2 cyclopropyl), 1.73 (dd, 1H, J=9.2 and 6.0 Hz, H-3), 1.05 (t, 1H, J=6.0 Hz, CH_2 cyclopropyl).

Methyl (2*R*, 3*S*, 4*R*, *S*) prolinate 19-MTPA amide: ^{1}H-NMR ($CDCl_3$): 7.44-7.17 (m, 8H), 7.01-6.96 (m, 2H), 4.69 (d, 1H, J= 8.8 Hz, H-2), 3.83 (q, 3H, J= 1.6 Hz, OCH_3), 3.78 (s, 3H, CO_2CH_3), 3.68 (s, 3H, CO_2CH_3), 3.36 (dd, 1 H, J= 11.5 and 4.4 Hz, CH_2N), 3.23-2.88 (m, 1H), 2.71-2.29 (m, 6H)

Methyl (2*R*, 3*S*, 4*R*, *R*) prolinate 19-MTPA amide: ^{1}H-NMR ($CDCl_3$): 7.67-7.62 (m, 1H), 7.55-7.50 (m, 4H), 7.44-7.38 (m, 1H), 7.07-7.01 (m, 2H), 6.30-6.24 (m, 2H), 4.67 (d, 1H, J= 9.8 Hz, H-2), 3.82 (s, 3H, CO_2CH_3), 3.74 (s, 3H, CO_2CH_3), 3.58 (q, 3H, J= 1.7 Hz, OCH_3), 3.29-2.99 (m, 2H), 2.67-2.17 (m, 6H).

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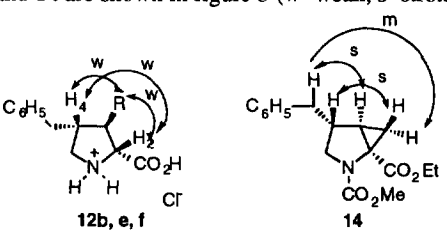

Figure 3

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