

From Pyrrolidin-2-ones to 3-Aza-2-oxobicyclo[3.2.0]heptanes. Synthesis of Both Enantiomers of *cis*-2-Aminomethylcyclobutane carboxylic Acid, a Conformationally Restricted Analogue of GABA

Roberta Galeazzi, Giovanna Mobbili, Mario Orena *

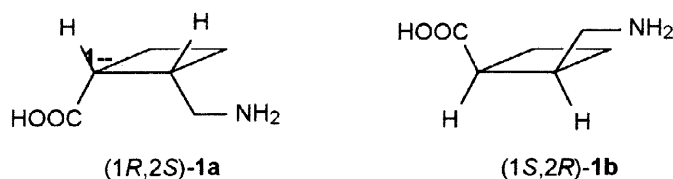
Dipartimento di Scienze dei Materiali e della Terra - Università di Ancona. Via Breccie Bianche - I-60131 Ancona,
Italy

Received 7 September 1998; revised 16 October 1998; accepted 29 October 1998

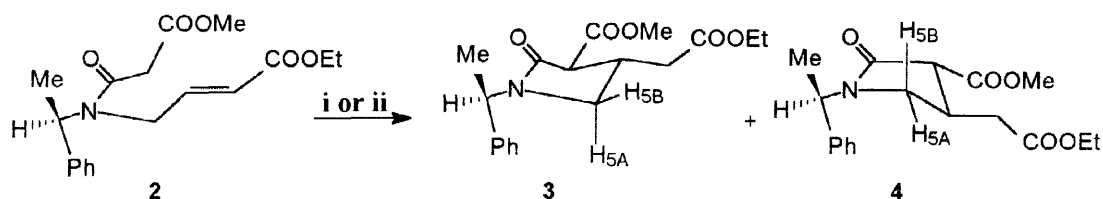
Abstract: By changing the cyclisation conditions (NaH in THF or NaOEt in EtOH), an enantiopure malonamide containing an enoate acceptor afforded either diastereomeric pyrrolidin-2-one **3** or **4** as the major product of the intramolecular conjugate addition. After separation, both diastereomers were converted through simple steps into the corresponding 3-aza-2-oxobicyclo[3.2.0] heptane which eventually led to each enantiomer of *cis*-2-aminomethylcyclobutanecarboxylic acid, **1**, a conformationally restricted analogue of GABA, in both enantiomerically pure form. © 1998 Elsevier Science Ltd. All rights reserved.

Non-proteinogenic amino acids containing small rings can be used to mimic backbone and side chain conformations of peptides. In fact introduction of rigidity into bioactive peptides has been considered as a useful means to study conformational requisites for their biological activities.¹ Moreover, conformationally constrained analogues of GABA, the main inhibitory neurotransmitter in the mammalian central nervous system, are currently employed in order to investigate the active conformers of GABA and the structural features of GABA receptors.² Among them, cyclopropane containing amino acids have been frequently reported,³ whereas the cyclobutane containing ones and their derivatives are scarcely reported in the literature.⁴

Our continuing interest in the preparation of non proteinogenic amino acids with biological activity prompted us to realize the synthesis of both enantiomers of *cis*-2-aminomethylcyclobutanecarboxylic acid, (1*R*,2*S*)-**1a** and (1*S*,2*R*)-**1b**, conformationally restricted analogues of GABA.

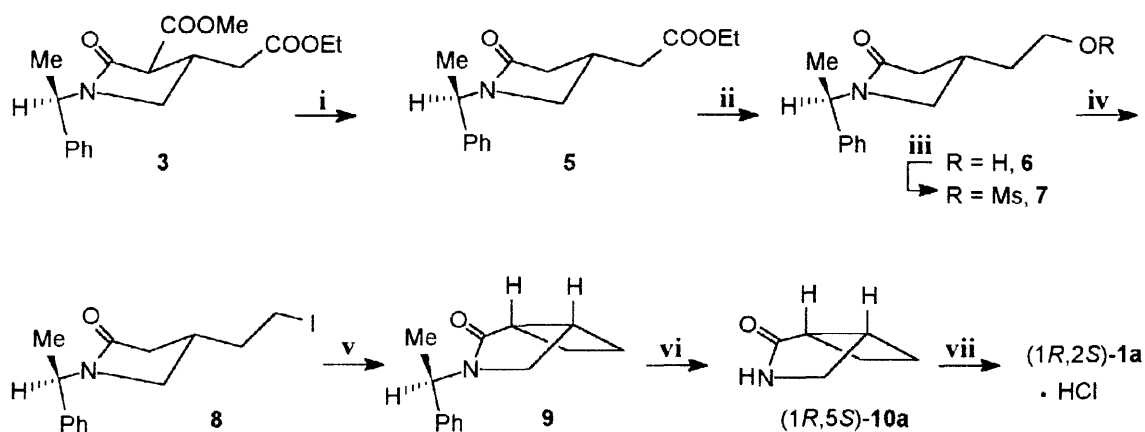


We recently reported a stereoselective approach to pyrrolidin-2-ones exploiting an intramolecular conjugate addition of a chiral amide enolate to an α,β -unsaturated ester.^{5,6} Now we disclose that the diastereoselection of this reaction can be changed by selecting proper conditions for the enolate formation. Thus, the cyclisation of amide **2**, carried out in dry THF at $-78\text{ }^\circ\text{C}$ by using NaH as the base, led mainly to 3,4-*trans*-disubstituted pyrrolidin-2-one **3** (d.r. **3:4** 80:20).⁵ On the contrary, when the amide enolate was generated with sodium ethoxide in dry ethanol at $-78\text{ }^\circ\text{C}$, a reversal of diastereoselection was observed, and pyrrolidin-2-one **4** was the major component of the diastereomeric mixture (d.r. **3:4** 30:70).⁷



Scheme 1. Reagents and conditions: **i.** NaH, THF, $-78\text{ }^\circ\text{C}$, 80%, d.r. 80:20. **ii.** NaOEt, EtOH, $-78\text{ }^\circ\text{C}$, 82%, d.r. 30:70.

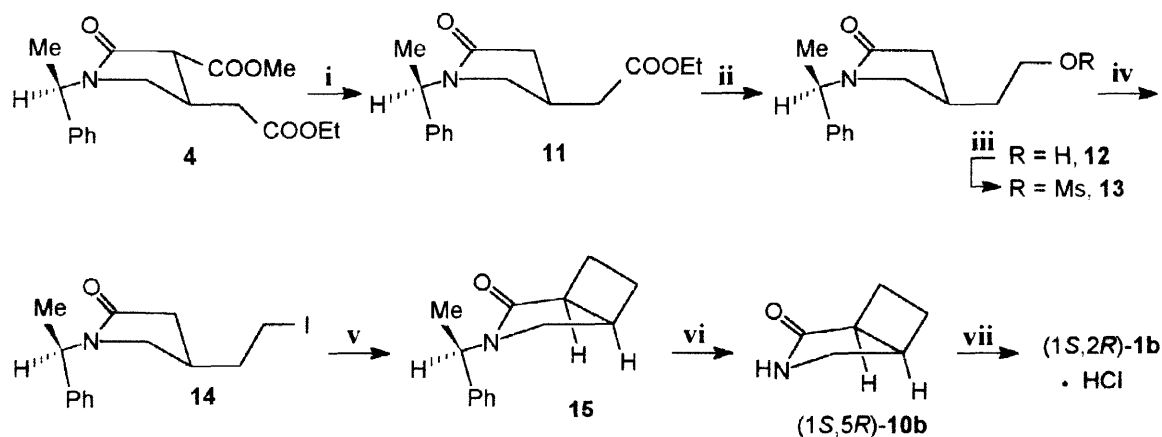
First, the diastereomers were easily separated by silica gel chromatography and the configurations were assigned on the basis of ^1H NMR spectra.⁸ In fact the minimum energy conformations of both diastereomers **3** and **4** were calculated and it resulted that the phenyl group lies under the plane of the pyrrolidin-2-one ring.⁹ Thus, in compound **3** $\text{H}_{5\text{A}}$ experiences a double shielding effect, since the alkyl group at C_4 which lies on the same side of the phenyl group. On the contrary, in compound **4** $\text{H}_{5\text{A}}$ experiences a single shielding effect, since the alkyl group at C_4 which lies on the opposite side with respect to the phenyl group. Therefore, the chemical shifts and coupling constants values of both $\text{H}_{5\text{A}}$ and $\text{H}_{5\text{B}}$ proved diagnostics in order to assign the configuration at C_4 , which was further confirmed by n.O.e. experiments.



Scheme 2. Reagents and conditions: **i.** Wet DMF, NaCl, $80\text{ }^\circ\text{C}$, 78%. **ii.** LiBH_4 , THF, $0\text{ }^\circ\text{C}$, 89%. **iii.** MsCl, Et_3N , DMAP, CH_2Cl_2 , $0\text{ }^\circ\text{C}$, 93%. **iv.** NaI, acetone, r.t., 91%. **v.** LiHMDS, THF, $-15\text{ }^\circ\text{C}$, 12 h, 83%. **vi.** Li-NH_3 , $-78\text{ }^\circ\text{C}$, 79%. **vii.** 1M HCl, $80\text{ }^\circ\text{C}$, 12 h, 78%.

With the stereodivergent synthesis of either **3** or **4** in hand, starting from the acyclic amide **2**, the next challenge was the preparation of the enantiomers (1*R*,2*S*)-**1a** and (1*S*,2*R*)-**1b**, starting from pyrrolidin-2-ones **3** and **4**, respectively. In fact, upon treatment of **3** with NaCl in wet DMF at 80 °C, the 4-substituted pyrrolidin-2-one **5** was obtained in good yield.¹⁰ Reduction of **5**, performed with LiBH₄ in THF at 0 °C, afforded the alcohol **6**, which was subsequently converted first into the corresponding mesylate **7** and then into the iodo derivative **8**.¹¹ By addition of Li-hexamethyldisilazide in THF at -15 °C, the 3-aza-2-oxo[3.2.0]bicycloheptane **9** was obtained in good yield as a sole diastereomer, whose configuration was confirmed by analysis of the ¹H NMR spectrum.⁸ The phenylethyl group was then removed by treatment with Li-NH₃ at -78 °C, to give the bicyclic amide **10a** in good yield. Eventually, hydrolysis of this compound, performed with 1M HCl at 80 °C, allowed preparation of the amino acid (1*R*,2*S*)-**1a** as the corresponding hydrochloride (Scheme 2).

On the other hand, following the same synthetic pathways (Scheme 3), the enantiomeric amino acid (1*S*,2*R*)-**1b** was prepared with nearly identical yield. Further studies are in progress both to test the conformational biases imposed by incorporating the amino acids (1*R*,2*S*)-**1a** and (1*S*,2*R*)-**1b** into peptide sequences and to determine their biological activities.



Scheme 3. Reagents and conditions: i. Wet DMF, NaCl, 80 °C, 76%. ii. LiAlH₄, THF, 0 °C, 86%. iii. MsCl, Et₃N, DMAP, CH₂Cl₂, 0 °C, 90%. iv. NaI, acetone, r.t., 88%. v. LiHMDS, THF, -15 °C, 12 h, 85%. vi. Li-NH₃, -78 °C, 77%. vii. 1M HCl, 80 °C, 12 h, 76%.

Experimental

Melting points were measured on a Electrothermal IA 9000 apparatus and are uncorrected. IR spectra were recorded in CHCl₃ on a Nicolet Fourier Transform Infrared 20-SX spectrophotometer. Diastereomeric ratios were determined by GC analysis using a Chrompack 9001 instrument equipped with a Chrompack 7720 capillary column (50 m x 0.25 mm i.d.; stationary phase CP-Sil-5 CB). ¹H and ¹³C NMR spectra were recorded at 200 MHz and 50 MHz, respectively, on a Varian Gemini 200 spectrometer, using CDCl₃ as a solvent. Chemical shifts (δ) are reported in ppm relative to TMS and coupling constants (J) in Hz.

Assignments were aided by decoupling and homonuclear two-dimensional experiments. Specific rotations were measured on a Perkin Elmer 241 polarimeter. GC-MS analyses were performed with a Hewlett-Packard spectrometer 5890, series II, using a HP-5 capillary column (30 m x 0.25 mm i.d.; stationary phase 5% phenyl methyl silicone). Flash chromatography was performed with silica gel 60 (230–400 mesh). (*R*)-Phenylethylamine, 2 M LiBH₄ solution in THF and 1 M solution of Li-hexamethyldisilazide in THF-hexanes were purchased from Aldrich. According to our already reported procedure^{5,8i} compound **2** was prepared starting from ethyl (*E*)-4-bromo-2-butenate and (*R*)-phenylethylamine: $[\alpha]_D^{25} +32.8$ (c 1, CHCl₃). GC-MS (EI, 70 eV): *m/z* 233 (M⁺), 218, 204, 190, 172, 144, 128, 105, 77. Anal. Calcd for C₁₄H₁₉NO₂: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.02; H, 8.17; N, 5.96.

Preparation of ethyl (3*S*,4*S*,1'*R*)-[1-(1'-phenyleth-1'-yl)-3-methoxycarbonyl-2-oxopyrrolidin-4-yl]acetate (3) and its isomer (3*R*,4*R*,1'*R*), (4), by cyclisation of (2) carried out with NaH.

A solution containing the amide **2** (2.3 g, 10 mmol) in dry THF (30 ml) was slowly added at -78 °C to a suspension of NaH (0.48 g; 10 mmol; 50% dispersion in mineral oil) in dry THF (20 ml). After 1 h solid NH₄Cl (5g) was added¹¹ and the temperature raised to 20 °C. The mixture was poured in water (50 ml) and after extraction with ethyl acetate (2 x 100 ml) and drying (Na₂SO₄), the organic layer was evaporated under reduced pressure. The residue was chromatographed by silica gel chromatography (cyclohexane:ethyl acetate 7:3) to give the diastereomers **3** and **4** as colorless oils in 80% overall yield and 80:20 d.r. **Isomer (3*S*,4*S*,1'*R*)-3**: 64% yield. IR: 1742, 1665 cm⁻¹. ¹H NMR: 1.16 (t, 3H, J = 7.2), 1.51 (d, 3H, J = 7.0), 2.26 (dd, 1H, J = 7.7, J = 16.1), 2.42 (dd, 1H, J = 6.6, J = 16.1), 2.57 (dd, 1H, H_{5A}, J_{4,5} = 6.4, J_{AB} = 9.6), 2.91 - 3.14 (m, 1H, H₄), 3.19 (d, 1H, H₃, J = 7.7), 3.66 (dd, 1H, H_{5B}, J_{4,5} = 8.9, J_{AB} = 9.6), 3.76 (s, 3H), 4.03 (q, 2H, J = 7.2), 5.44 (q, 1H, J = 7.0), 7.18 - 7.39 (m, 5 ArH). ¹³C NMR: 14.6, 16.5, 32.9, 37.9, 46.7, 50.1, 53.2, 55.1, 61.3, 127.6, 128.1, 128.2, 129.0, 129.1, 139.9, 168.7, 170.3, 171.4. $[\alpha]_D^{25} +87.1$ (c 0.5, CHCl₃). GC-MS (EI, 70 eV): *m/z* 333 (M⁺), 318, 288, 274, 242, 214, 188, 132, 120, 105, 91, 77. Anal. Calcd for C₁₈H₂₃NO₅: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.77; H, 6.91; N, 4.23. **Isomer (3*R*,4*R*,1'*R*)-4**: 16% yield. IR: 1744, 1665 cm⁻¹. ¹H NMR: 1.23 (t, 3H, J = 7.1), 1.53 (d, 3H, J = 7.1), 2.43 (dd, 1H, J = 7.2, J = 16.2), 2.55 (dd, 1H, J = 6.1, J = 16.2), 2.84 - 3.09 (m, 2H, H₄ + H_{5A}), 3.23 - 3.32 (m, 2H, H₃ + H_{5B}), 3.79 (s, 3H), 4.11 (q, 2H, J = 7.1), 5.47 (q, 1H, J = 7.1), 7.18 - 7.38 (m, 5 ArH). ¹³C NMR: 14.6, 16.6, 33.0, 38.1, 46.8, 50.0, 53.2, 55.1, 61.4, 127.4, 128.1, 129.1, 139.8, 168.9, 170.3, 171.4. $[\alpha]_D^{25} +129.8$ (c 1, CHCl₃). GC-MS (EI, 70 eV): *m/z* 333 (M⁺), 318, 288, 274, 242, 214, 188, 132, 120, 105, 91, 77. Anal. Calcd for C₁₈H₂₃NO₅: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.82; H, 6.97; N, 4.19.

Preparation of ethyl (3*S*,4*S*,1'*R*)-[1-(1'-phenyleth-1'-yl)-3-methoxycarbonyl-2-oxopyrrolidin-4-yl]acetate (3) and its isomer (3*R*,4*R*,1'*R*), (4), by cyclisation of (2) carried out with NaOEt.

To a solution containing the amide **3** (2.3 g; 10 mmol) in dry ethanol (30 ml) was slowly added at -78° a solution containing sodium ethoxide [10 mmol; prepared by dissolving Na (240 mg, 10 mmol)] in dry ethanol (20 ml). After 1 h solid NH₄Cl (5.0 g)¹² was added and the temperature raised to 20 °C. The mixture was

poured in water (50 ml), extracted with ethyl acetate (3 x 100 ml) and then the organic layer was dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography, to give the diastereomeric pyrrolidin-2-ones **3** and **4** as colorless oils in 82% overall yield and 30:70 d.r. **Isomer (3*S*,4*S*,1'*R*)-3**: 25% yield. $[\alpha]_D^{25} +87.1$ (c 0.5, CHCl_3). GC-MS (EI, 70 eV): m/z 333 (M^+), 318, 288, 274, 242, 214, 188, 132, 120, 105, 91, 77. Anal. Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.81; H, 6.93; N, 4.22. **Isomer (3*R*,4*R*,1'*R*)-4**: 57% yield. $[\alpha]_D^{25} +129.8$ (c 1, CHCl_3). GC-MS (EI, 70 eV): m/z 333 (M^+), 318, 288, 274, 242, 214, 188, 132, 120, 105, 91, 77. Anal. Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.79; H, 6.99; N, 4.15.

Ethyl (4*R*,1'*R*)-[1-(1'-phenyleth-1'-yl)-2-oxopyrrolidin-4-yl]acetate (5)

A solution containing the pyrrolidin-2-one **3** (3.3 g, 10 mmol), NaCl (0.68 g, 10 mmol) and H_2O (0.18 g, 10 mmol) in DMF (10 ml) was heated at 80 °C for 3 h. Then the solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (100 ml). The organic layer was washed with brine (30 ml) and dried (Na_2SO_4). After removal of the solvent in vacuo, the product was purified by silica gel chromatography (cyclohexane:ethyl acetate 60:40), to give the title compound in 78% yield as a colorless oil. IR: 1743, 1664 cm^{-1} . ^1H NMR: 1.20 (t, 3H, $J = 7.2$), 1.52 (d, 3H, $J = 7.2$), 2.04 - 2.15 (m, 1H, H_{3A}), 2.23 (dd, 1H, $J = 7.8$, $J = 16.2$), 2.37 (dd, 1H, $J = 6.3$, $J = 16.2$), 2.55 - 2.79 (m, 3H, $\text{H}_{3B} + \text{H}_4 + \text{H}_{5A}$), 3.53 (dd, 1H, H_{5B} , $J = 7.1$, $J = 9.4$), 4.07 (q, 2H, $J = 7.2$), 5.51 (q, 1H, $J = 7.2$), 7.21 - 7.42 (m, 5 ArH). ^{13}C NMR: 14.6, 16.6, 28.7, 38.1, 39.0, 48.1, 49.4, 61.1, 127.6, 128.0, 129.1, 140.3, 172.1. $[\alpha]_D^{25} +108.6$ (c 0.5, CHCl_3). GC-MS (EI, 70 eV): m/z 275 (M^+), 260, 232, 230, 184, 170, 160, 146, 132, 126, 105, 91, 77. Anal. Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.75; H, 7.72; N, 5.12.

(4'*S*,1'*R*)-2-[1'-(1''-Phenyleth-1''-yl)-2'-oxopyrrolidin-4'-yl]ethanol (6)

To a solution containing the ester **5** (5.5 g, 20 mmol) in dry THF (80 ml) under argon atmosphere, LiBH_4 was added (6 mmol; 3 ml of a 2M solution in THF) at 0 °C. After 2 h methanol (1 ml) and H_2O (30 ml) were added and the mixture was poured into a Na_2SO_4 saturated aqueous solution (50 ml). After extraction of the reaction mixture with ethyl acetate (3 x 100 ml) and drying (Na_2SO_4), the solvent was removed under reduced pressure. The residue was then purified by silica gel chromatography (ethyl acetate), to give the title compound in 89% yield as a colorless oil. IR: 3345, 1665 cm^{-1} . ^1H NMR: 1.52 (d, 3H, $J = 7.2$), 1.49 - 1.63 (m, 2H), 1.75 (br s, 1H, OH), 2.13 (dd, 1H, H_{3A} , $J_{3,4} = 6.9$, $J_{AB} = 15.8$), 2.39 - 2.56 (m, 1H, H_4), 2.62 (dd, 1H, H_{3B} , $J_{3,4} = 8.2$, $J_{AB} = 15.8$), 2.63 (dd, 1H, H_{5A} , $J_{4,5} = 6.2$, $J_{AB} = 9.4$), 3.46 (dd, 1H, H_{5B} , $J_{4,5} = 7.5$, $J_{AB} = 9.4$), 3.59 (t, 2H, $J = 6.3$), 5.50 (q, 1H, $J = 7.2$), 7.23 - 7.41 (m, 5 ArH). ^{13}C NMR: 16.7, 29.3, 37.5, 38.5, 48.4, 49.3, 61.1, 127.6, 128.0, 129.0, 140.5, 174.3. $[\alpha]_D^{25} +133.6$ (c 0.5, CHCl_3). GC-MS (EI, 70 eV): m/z 233 (M^+), 218, 160, 146, 142, 105, 91, 77. Anal. Calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.04; H, 8.17; N, 6.03.

(4*S*,1'*R*)-1-(1'-Phenyleth-1'-yl)-4-(2''-methanesulfonyloxyeth-1''-yl)pyrrolidin-2-one (7)

To a solution containing the compound **6** (4.7 g, 20 mmol) triethylamine (3.9 ml; 27 mmol) and DMAP

(0.3 g) in ethyl acetate (70 ml), at 0 °C, methanesulfonyl chloride (3.1 g; 27 mmol) dissolved in ethyl acetate (10 ml) was slowly added. After 3 h the suspension was poured in H₂O (50 ml) and extracted with ethyl acetate (3 x 100 ml). The organic layer was dried (Na₂SO₄) and then the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate) to give the title compound in 93% yield as colorless oil. IR: 1664 cm⁻¹. ¹H NMR: 1.52 (d, 3H, J = 7.1), 1.70 (dt, 2H, J = 6.4, J = 6.9), 2.13 (dd, 1H, H_{3A}, J_{3,4} = 6.6, J_{AB} = 15.9), 2.40 - 2.56 (m, 1H, H₄), 2.61 (dd, 1H, H_{5A}, J_{4,5} = 6.2, J_{AB} = 9.6), 2.65 (dd, 1H, H_{3B}, J_{3,4} = 8.3, J_{AB} = 15.9), 3.47 (dd, 1H, H_{5B}, J_{4,5} = 7.4, J_{AB} = 9.6), 4.14 (t, 2H, J = 6.2), 5.50 (q, 1H, J = 7.1), 7.20 - 7.39 (m, 5 ArH). ¹³C NMR: 16.6, 29.1, 34.1, 37.9, 38.1, 47.9, 49.4, 67.9, 127.6, 128.1, 129.0, 140.3, 173.6. [α]_D +105.8 (c 0.5, CHCl₃). GC-MS (EI, 70 eV): *m/z* 311 (M⁺), 296, 220, 160, 146, 105, 104, 91, 79, 77. Anal. Calcd for C₁₅H₂₁NO₄S: C, 57.86; H, 6.80; N, 4.50. Found: C, 57.84; H, 6.77; N, 4.48.

(4*S*,1'*R*)-1-(1'-Phenyleth-1'-yl)-4-(2''-iodoeth-1''-yl)pyrrolidin-2-one (8)

To a solution containing the compound 7 (4.7 g; 15 mmol) in acetone (70 ml), NaI (4.5 g; 30 mmol) was added and the mixture was stirred for 12 h at 20 °C. The solvent was then removed under reduced pressure and the residue was dissolved in ethyl acetate (150 ml). The organic layer was then washed with a 10% aqueous solution of Na₂S₂O₃ (50 ml), and dried (Na₂SO₄). After removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 70:30), to give the title compound in 91% yield as colorless oil. IR: 1667 cm⁻¹. ¹H NMR: 1.53 (d, 3H, J = 7.1), 1.75 - 1.87 (m, 2H), 2.08 (dd, 1H, H_{3A}, J_{3,4} = 6.3, J_{AB} = 15.8), 2.35 - 2.71 (m, 3H, H_{3B} + H₄ + H_{5A}), 3.04 (t, 2H, J = 7.0), 3.45 (dd, 1H, H_{5B}, J_{4,5} = 7.2, J_{AB} = 9.3), 5.51 (q, 1H, J = 7.1), 7.24 - 7.43 (m, 5 ArH). ¹³C NMR: 3.3, 16.6, 33.0, 37.6, 38.2, 47.5, 49.4, 127.6, 128.1, 129.1, 140.3, 173.7. [α]_D +98.3 (c 0.5, CHCl₃). GC-MS (EI, 70 eV): *m/z* 343 (M⁺), 328, 310, 309, 252, 161, 160, 135, 127, 118, 105, 91, 77. Anal. Calcd for C₁₄H₁₈NOI: C, 48.99; H, 5.29; N, 4.08. Found: C, 49.05; H, 5.24; N, 4.14.

(1*R*,5*S*, 1'*R*)-3-(1'-Phenyleth-1'-yl)-3-aza-2-oxobicyclo[3.2.0]heptane (9)

To a solution containing the compound 8 (5.1 g; 15 mmol) in dry THF (50 ml) at -15 °C Li-hexamethyldisilazide (15 mmol; 15 ml of 1 M solution in THF-hexane) was added and the solution was stirred at -15 °C for 12 h. The mixture was poured in H₂O-ice and extracted with ethyl acetate (3 x 100 ml). The organic layer was dried (Na₂SO₄) and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 50:50) to give the title compound in 83% yield as white crystals. M.p. 61 - 63 °C. IR: 1664 cm⁻¹. ¹H NMR: 1.53 (d, 3H, J = 7.2), 1.57 - 1.73 (m, 1H), 2.03 - 2.27 (m, 2H), 2.35 - 2.50 (m, 1H), 2.73 (d, 1H, H_{4A}, J_{AB} = 10.1), 2.79 - 2.96 (m, 1H, H₅), 3.00 - 3.12 (m, 1H, H₁), 3.43 (dd, 1H, H_{4B}, J_{4,5} = 6.9, J_{AB} = 10.1), 5.57 (q, 1H, J = 7.2), 7.23 - 7.43 (m, 5 ArH). ¹³C NMR: 16.1, 24.9, 26.5, 30.4, 42.5, 49.0, 49.2, 67.9, 127.4, 127.8, 127.9, 129.0, 141.0, 177.4. [α]_D +130.7 (c 0.5, CHCl₃). GC-MS (EI, 70 eV): *m/z* 215 (M⁺), 200, 187, 174, 172, 124, 120, 105, 104, 91, 77. Anal. Calcd for C₁₄H₁₇NO: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.12; H, 8.01; N, 6.46.

(1*R*,5*S*)-3-Aza-2-oxobicyclo[3.2.0]heptane (10a)

In a flask under argon atmosphere NH₃ (about 100 ml) was condensed at -78 °C and then Li (0.49 g; 70 mmol) was added. When the metal dissolved in NH₃, a solution containing the compound **9** (3.2 g, 15 mmol) in THF - *t*-BuOH (30 ml of a 90:10 mixture) was quickly added. After 10 min powdered NH₄Cl (7 g) was added and the mixture was extracted with ethyl acetate (3 x 150 ml). The organic layer was dried (Na₂SO₄) and, after evaporation under reduced pressure, the residue was purified by silica gel chromatography (ethyl acetate), to give the title compound in 79% yield as a colorless oil. IR: 3351, 1667 cm⁻¹. ¹H NMR: 1.91 - 2.18 (m, 2H), 2.21 - 2.53 (m, 2H), 2.81 - 2.94 (m, 1H), 2.95 - 3.09 (m, 1H), 3.17 (d, 1H, J = 10.2), 3.47 (dd, 1H, J = 6.9, J = 10.2), 7.25 (br s, 1H, NH). ¹³C NMR: 24.4, 26.7, 33.8, 40.9, 49.2, 182.3. [α]_D -58.0 (c 0.5, CHCl₃). GC-MS (EI, 70 eV): *m/z* 111 (M⁺), 83, 82, 68, 67, 55. Anal. Calcd C₆H₉NO: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.80; H, 8.13; N, 12.64.

(1*R*,2*S*)-2-Aminomethylcyclobutanecarboxylic acid hydrochloride (1a)

A solution of compound **10a** (1.0 g, 9 mmol) in 1M HCl (30 ml) was stirred at 80 °C for 6 h. after removal of H₂O under reduced pressure, the solid residue was recrystallized (diethyl ether:ethanol) to give the title compound in 78% yield as white crystals. M.p.: 186-188 °C. ¹H NMR (CD₃OD): 1.75 - 1.98 (m, 1H), 2.12 - 2.41 (m, 2H), 2.72 - 3.11 (m, 2H), 3.14 - 3.51 (m, 3H). ¹³C NMR (CD₃OD): 22.9, 24.0, 36.1, 41.4, 42.8, 177.4. [α]_D -24.5 (c 0.5, CH₃OH). MS (EI, 70 eV): *m/z* 130 (MH⁺), 129, 113, 112, 99, 97, 90, 85, 83, 68. Anal. Calcd for C₆H₁₂NO₂Cl: C, 43.51; H, 7.30; N, 8.46. Found: C, 43.45; H, 7.26; N, 8.51.

Ethyl (4*S*,1'*R*)-[1-(1'-phenyleth-1'-yl)-2-oxopyrrolidin-4-yl]acetate (11)

Starting from **4**, the title compound was prepared in 76% yield as a colorless oil following the procedure above reported for compound **5**. IR: 1744, 1663 cm⁻¹. ¹H NMR: 1.28 (t, 3H, J = 7.1), 1.51 (d, 3H, J = 7.2), 2.10 - 2.26 (m, 1H, H_{3B}), 2.39 (dd, 1H, J = 7.9, J = 16.2), 2.49 (dd, 1H, J = 5.9, J = 16.2), 2.57 - 2.72 (m, 2H), 3.01 (dd, 1H, H_{5B}, J_{4,5} = 5.9, J_{AB} = 9.9), 3.20 (dd, 1H, H_{5A}, J_{4,5} = 7.5, J_{AB} = 9.9), 4.12 (q, 2H, J = 7.1), 5.49 (q, 1H, J = 7.2), 7.22 - 7.42 (m, 5 ArH). ¹³C NMR: 14.7, 16.6, 28.7, 38.1, 39.2, 48.1, 49.4, 61.2, 127.5, 128.0, 129.1, 140.4, 172.1, 173.6. [α]_D +118.9 (c 0.5, CHCl₃). GC-MS (EI, 70 eV): *m/z* 275 (M⁺), 260, 232, 230, 184, 170, 160, 146, 132, 126, 105, 91, 77. Anal. Calcd for C₁₆H₂₁NO₃: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.68; H, 7.74; N, 5.14.

(4'*R*,1'*R*)-2-[1'-(1''-Phenyleth-1''-yl)-2'-oxopyrrolidin-4'-yl]ethanol (12)

Starting from **11**, the title compound was prepared in 86% yield as a colorless oil following the procedure above reported for compound **6**. IR: 3345, 1664 cm⁻¹. ¹H NMR: 1.52 (d, 3H, J = 7.1), 1.70 (dt, 2H, J = 6.4, J = 6.9), 2.00 (br s, 1H, OH), 2.19 (dd, 1H, H_{3B}, J_{3,4} = 8.1, J_{AB} = 15.7), 2.28 - 2.51 (m, 1H, H₄), 2.62 (dd, 1H, H_{3A}, J_{3,4} = 8.0, J_{AB} = 15.7), 3.01 (dd, 1H, H_{5B}, J_{4,5} = 6.9, J_{AB} = 9.8), 3.15 (dd, 1H, H_{5A}, J_{4,5} = 7.7, J_{AB} = 9.8), 3.66 (t, 2H, J = 6.4), 5.49 (q, 1H, J = 6.9), 7.20 - 7.39 (m, 5 ArH). ¹³C NMR: 16.6, 29.6, 37.6, 38.5, 48.7, 49.4, 61.2, 127.4, 127.9, 129.0, 140.6, 174.3. [α]_D +85.8 (c 0.5, CHCl₃). GC-MS (EI, 70 eV): *m/z* 233 (M⁺), 218, 160,

146, 142, 105, 91, 77. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.11; H, 8.24; N, 5.98.

(4*R*,1'*R*)-1-(1'-Phenyleth-1'-yl)-4-(2''-methanesulfonyloxyeth-1''-yl)pyrrolidin-2-one (13)

Starting from **12**, the title compound was prepared in 90% yield as a colorless oil following the procedure above reported for compound **7**. IR: 1665 cm^{-1} . 1H NMR: 1.52 (d, 3H, $J = 7.0$), 1.89 (dt, 2H, $J = 5.8$, $J = 6.2$), 2.19 (dd, 1H, H_{3B} , $J_{3,4} = 8.0$, $J_{AB} = 15.8$), 2.31 - 2.51 (m, 1H, H_4), 2.65 (dd, 1H, H_{3A} , $J_{3,4} = 8.1$, $J_{AB} = 15.8$), 2.95 - 3.05 (m, 1H, H_{5B}), 2.99 (s, 3H), 3.16 (dd, 1H, H_{5A} , $J_{4,5} = 7.7$, $J_{AB} = 9.6$), 4.23 (t, 2H, $J = 5.8$), 5.48 (q, 1H, $J = 7.0$), 7.24 - 7.42 (m, 5 ArH). ^{13}C NMR: 16.6, 29.3, 34.2, 38.0, 38.1, 48.3, 49.5, 68.0, 127.5, 128.1, 129.1, 140.3, 173.7. $[\alpha]_D^{25} +96.4$ (c 0.5, $CHCl_3$). GC-MS (EI, 70 eV): m/z 311 (M^+), 296, 220, 200, 160, 146, 105, 104, 91, 79, 77. Anal. Calcd for $C_{15}H_{21}NO_4S$: C, 57.86; H, 6.80; N, 4.50. Found: C, 57.91; H, 6.75; N, 4.55.

(4*R*,1'*R*)-1-(1'-Phenyleth-1'-yl)-4-(2''-iodoeth-1''-yl)pyrrolidin-2-one (14)

Starting from **13**, the title compound was prepared in 88% yield as a colorless oil following the procedure above reported for compound **8**. IR: 1664 cm^{-1} . 1H NMR: 1.52 (d, 3H, $J = 7.2$), 1.96 (dt, 2H, $J = 7.1$, $J = 7.1$), 2.14 (dd, 1H, H_{3B} , $J_{3,4} = 7.4$, $J_{AB} = 15.8$), 2.28 - 2.45 (m, 1H, H_4), 2.62 (dd, 1H, H_{3A} , $J_{3,4} = 8.4$, $J_{AB} = 15.8$), 2.96 (dd, 1H, H_{5B} , $J_{4,5} = 6.6$, $J_{AB} = 9.6$), 3.07 - 3.20 (m, 3H, $H_{5A} + CH_2I$), 5.49 (q, 1H, $J = 7.2$), 7.22 - 7.42 (m, 5 ArH). ^{13}C NMR: 3.1, 16.6, 33.2, 37.6, 38.6, 47.8, 49.5, 127.5, 127.6, 128.1, 129.1, 140.4, 173.7. $[\alpha]_D^{25} +81.6$ (c 0.5, $CHCl_3$). GC-MS (EI, 70 eV): m/z 343 (M^+), 328, 310, 309, 252, 161, 160, 135, 127, 105, 91, 77. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.15; H, 8.03; N, 6.54.

(1*S*,5*R*,1'*R*)-3-(1'-Phenyleth-1'-yl)-3-aza-2-oxobicyclo[3.2.0]heptane (15)

Starting from **14**, the title compound was prepared in 85% yield as a colorless oil following the procedure above reported for compound **9**. IR: 1666 cm^{-1} . 1H NMR: 1.59 (d, 3H, $J = 7.1$), 1.81 - 1.99 (m, 1H), 2.03 - 2.21 (m, 1H), 2.22 - 2.64 (m, 3H), 2.75 - 2.94 (m, 1H, H_1), 2.98 - 3.12 (m, 2H), 5.58 (q, 1H, $J = 7.1$), 7.25 - 7.44 (m, 5 ArH). ^{13}C NMR: 16.8, 24.7, 27.0, 30.4, 42.5, 49.4, 49.6, 127.8, 127.9, 128.0, 129.0, 140.3, 177.3. $[\alpha]_D^{25} 209.1$ (c 0.5, $CHCl_3$). GC-MS (EI, 70 eV): m/z 215 (M^+), 200, 187, 174, 172, 120, 105, 91, 77. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.06; H, 7.91; N, 6.54.

(1*S*,5*R*)-3-Aza-2-oxobicyclo[3.2.0]heptane (10b)

Starting from **15**, the title compound was prepared in 77% yield as a colorless oil following the procedure above reported for compound **10a**. $[\alpha]_D^{25} +57.2$ (c 0.5, $CHCl_3$). GC-MS (EI, 70 eV): m/z 111 (M^+), 83, 82, 68, 67, 55. Anal. Calcd C_6H_9NO : C, 64.84; H, 8.16; N, 12.60. Found: C, 64.77; H, 8.19; N, 12.57.

(1*S*,2*R*)-2-Aminomethylcyclobutanecarboxylic acid hydrochloride (1b)

Starting from **16**, the title compound was prepared in 76% yield following the procedure above reported

for compound **1a**. M.p.: 190 - 191 °C. $[\alpha]_D^{25}$ 24.1 (c 0.4, CH₃OH). Anal. Calcd for C₆H₁₂NO₂Cl: C, 43.51; H, 7.30; N, 8.46. Found: C, 43.45; H, 7.26; N, 8.51.

Acknowledgement. This research was supported by M.U.R.S.T., (Rome) within the project "Chimica dei Composti Organici di Interesse Biologico". We thank Mr. Giandomenico Mariotti for valuable technical assistance.

References and Notes

1. a) Mapelli, C.; Turocy, G.; Switzer, F.L.; Stammer, C.H. *J. Org. Chem.*, **1989**, *54*, 145-149. b) Stammer, C.H. *Tetrahedron*, **1990**, *46*, 2231-2256. c) Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ohfuné, Y. *J. Org. Chem.*, **1991**, *56*, 4167-4176. d) Williams, R.M.; Fegley, G.J. *J. Am. Chem. Soc.*, **1991**, *113*, 8796-8806. e) Burgess, K.; Ho, K.-K. *J. Org. Chem.*, **1992**, *57*, 5931-5936. f) Koskinen, A.M.P.; Muñoz, L. *J. Org. Chem.*, **1993**, *58*, 879-886. g) Burgess, K.; Ho, K.-K.; Moye-Sherman, D. *Synlett*, **1994**, 575-583. h) Burgess, K.; Ho, K.-K. *J. Am. Chem. Soc.*, **1994**, *116*, 799-800. i) Burgess, K.; Li, W. *Tetrahedron Lett.*, **1995**, *36*, 2725-2728. j) Es-Sayed, M.; Devine, P.; Burgess, L.E.; de Meijere, A.; Meyers, A.I. *J. Chem. Soc. Chem. Commun.*, **1995**, 141-142.
2. a) Roberts, E.; Chase, T.N.; Tower, D.B. *GABA in Nervous System Function*; Raven Press, New York, **1976**. b) Sytinsky, I.A.; Sodatenkov, A.T.; Lajtha, A. *Prog. Neurobiol.*, **1978**, *10*, 89-96. c) Rando, R.R. *Acc. Chem. Res.*, **1975**, *8*, 281. d) Squires, R.F. *GABA and Benzodiazepine Receptors*; CRC Press: Boca Raton, **1988**, Vols 1 and 2. e) Bowery, N.G.; Bittiger, H.; Olpe, H.-R. *GABA_A Receptors in Mammalian Function*; John Wiley & Sons: New York, 1990. f) Nielsen, L.; Brehm, L.; Krosggaard-Larsen, P. *J. Med. Chem.*, **1990**, *33*, 71-77. g) Meldrum, B. *Nature*, **1995**, *376*, 122-123.
3. a) Allan, R.D.; Curtis, D.R.; Headley, P.M.; Johnston, G.A.R.; Lodge, D.; Twitchin, B. *J. Neurochem.*, **1980**, *34*, 652-656. b) Kennewell, P.D.; Matharu, S.S.; Taylor, J.B.; Westwood, R.; Sammes, P.G. *J. Chem. Soc., Perkin Trans. I*, **1982**, 2553-2562. c) Yongsiri, A.; Funase, K.; Takeuchi, H.; Shimamoto, K.; Ohfuné, Y. *Eur. J. Pharmacol.*, **1988**, *155*, 239-245. d) Paulini, K.; Reissig, H.-U. *Liebigs Ann. Chem.*, **1991**, 455-461. e) Morikawa, T.; Sasaki, H.; Hanai, R.; Shibuya, A.; Taguchi, T. *J. Org. Chem.*, **1994**, *59*, 97. f) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry*, **1997**, *8*, 133-137.
4. a) Avotins, F.; Bizdena, E. *Khim. Teknol. Biol. Aktiv. Soedin.*, **1983**, 34-48. *Chem. Abstr.*, **1984**, *100*, 210169w. b) Avotins, F.; Bizdena, E. *Khim. Teknol. Biol. Aktiv. Soedin.*, **1983**, 612-616. *Chem. Abstr.*, **1983**, *98*, 142988a. c) Burgess, K.; Li, S.; Rebenspies, J. *Tetrahedron Lett.*, **1997**, *38*, 1681-1684. d) Tsujishima, H.; Nakatani, K.; Shimamoto, K.; Shigeri, Y.; Yumoto, N.; Ohfuné, Y. *Tetrahedron Lett.*, **1998**, *39*, 1193-1196.
5. Galeazzi, R.; Geremia, S.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry*, **1996**, *7*, 79-88.
6. For some examples concerning stereoselective intramolecular conjugate additions leading to pyrrolidine or piperidine ring formation, see: a) Barco, A.; Benetti, S.; Casolari, A.; Pollini, G.P.; Spalluto, G. *Tetrahedron Lett.*, **1990**, *31*, 4917-4920. b) Barco, A.; Benetti, S.; Spalluto, G.; Casolari, A.; Pollini, G.P.; Zanirato, V. *J. Org. Chem.*, **1992**, *57*, 6279-6286. c) Hirai, Y.; Terada, T.; Yamazaki, T. *J. Am.*

- Chem. Soc.*, **1988**, *110*, 958-960. d) Hirai, Y.; Terada, T.; Yamazaki, T.; Momose, T. *J. Chem. Soc., Perkin Trans. I*, **1992**, 509-516.
7. Preliminary studies about the outcome of the reaction depending on the conditions employed suggest a thermodynamic vs. kinetic control. In fact, the calculated steric energies of compounds **3** and **4** resulted to be 0.00 and 0.53 kcal/mol, respectively.⁹ By using NaH in THF in the absence of a proton source, the conjugate addition leads to an equilibrium mixture and product **3**, more stable, is mainly formed under thermodynamic control. On the contrary, when sodium ethoxide in ethanol is employed, the anion arising from conjugate addition immediately undergoes protonation by the solvent, so that product **4** is mainly formed under kinetic control. Studies are in progress in order to attain a deeper insight about this behaviour and for possible extension of the method to the synthesis of bioactive compounds, and will be reported in due course.
8. a) Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *Tetrahedron*, **1987**, *43*, 2505-2512. b) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Tetrahedron*, **1987**, *43*, 4377-4383. c) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Chem. Lett.*, **1988**, 87-90. d) Bruni, E.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *Tetrahedron Lett.*, **1989**, *30*, 1679-1682. e) Orena, M.; Porzi, G.; Sandri, S. *J. Chem. Res., (S)*, **1990**, 376; *(M)*, **1990**, 2701-2711. f) Cardillo, G.; Orena, M.; Penna, M.; Sandri, S.; Tomasini, C. *Synlett*, **1990**, 543-544. g) Cardillo, G.; Orena, M.; Penna, M.; Sandri, S.; Tomasini, C. *Tetrahedron*, **1991**, *47*, 2263-2272. h) Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.*, **1992**, *57*, 6532-6536. i) Orena, M.; Porzi, G.; Sandri, S. *J. Chem. Res., (S)*, **1993**, 318-319; *(M)*, **1993**, 2125-2152. j) Cardillo, B.; Galeazzi, R.; Mobbili, G.; Orena, M.; Rossetti, M. *Heterocycles*, **1994**, *38*, 2663-2676. k) Cardillo, B.; Galeazzi, R.; Mobbili, G.; Orena, M. *Synlett*, **1995**, 1159-1160. l) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron*, **1996**, *52*, 1069-1084.
9. The search for the low energy conformations was run using BATCHMIN program implemented in MacroModel, software package Version 5.5. All the calculations were carried out on a Silicon Graphics Indigo 2 R10000 workstation. For a reference, see: Mohamadi, F.; Richards, N.G.J.; Guida, W.C.; Liskamp, R.; Lipton, M.; Canfield, C.; Chang, G.; Hendrickson, T.; Still, W.C. *J. Comput. Chem.*, **1990**, *11*, 440-448.
10. Stevens, R.V.; Lee, A.V.M. *J. Am. Chem. Soc.*, **1979**, *101*, 7032-7035.
11. The cyclisation was also performed starting from mesylate **8**, but in this case bicyclic compound **9** was isolated in only 53% yield.
12. Following this procedure the previously observed partial hydrolysis (see ref. 5) of the ester group was suppressed.