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# 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 Brecce Bianche - I-60131 Ancona, Italy

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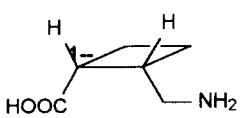
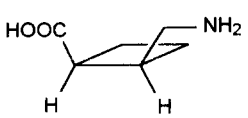
**Abstract:** By changing the cyclisation conditions (NaH in THF or NaOEt in EtOH), an enantiopure malonamide containing an enoate acceptor afforded either diastereomeric pyrrolidin-2-one **3** or **4** as the major product of the intramolecular conjugate addition. After separation, both diastereomers 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. 

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.




(1*R*,2*S*)-**1a**




(1*S*,2*R*)-**1b**

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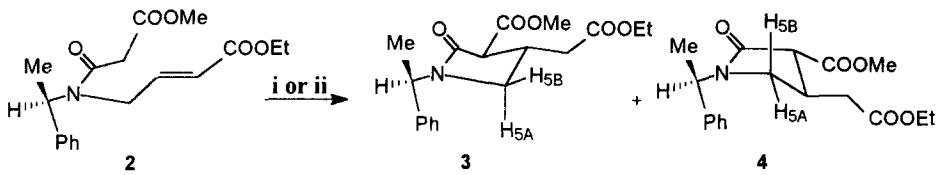
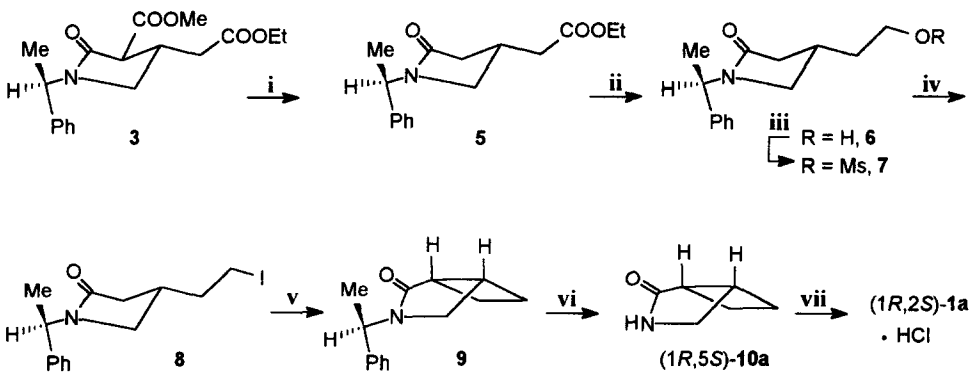
We recently reported a stereoselective approach to pyrrolidin-2-ones exploiting an intramolecular conjugate addition of a chiral amide enolate to an α,β-unsaturated ester.[5,6] Now we disclose that the diastereoselection of this reaction can be changed by selecting proper conditions for the enolate formation. Thus, the cyclisation of amide **2**, carried out in dry THF at -78 °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 °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 °C, 80%, d.r. 80:20. **ii.** NaOEt, EtOH, -78 °C, 82%, d.r. 30:70.

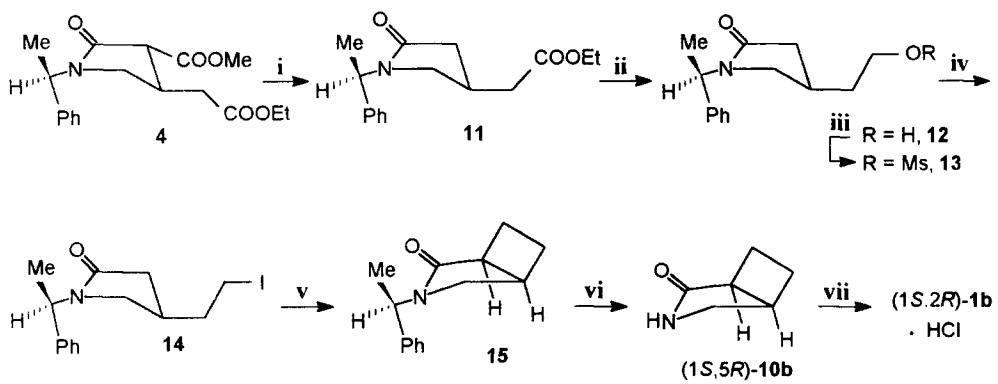
First, the diastereomers were easily separated by silica gel chromatography and the configurations were assigned on the basis of $^1$H NMR spectra.[8] In fact the minimum energy conformations of both diastereomers **3** and **4** were calculated and it resulted that the phenyl group lies under the plane of the pyrrolidin-2-one ring.[9] Thus, in compound **3** $H_{5A}$ 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** $H_{5A}$ 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 $H_{5A}$ and $H_{5B}$ 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 °C, 78%. **ii.** $LiBH_4$, THF, 0 °C, 89%. **iii,** MsCl, $Et_3N$, DMAP, $CH_2Cl_2$, 0 °C, 93%. **iv.** NaI, acetone, r.t., 91%. **v.** LiHMDS, THF, -15 °C, 12 h, 83%. **vi.** Li-$NH_3$, -78 °C, 79%. **vii.** 1M HCl, 80 °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 $LiBH_4$ 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-$NH_3$ 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.** $LiAlH_4$, THF, 0 °C, 86%. **iii,** MsCl, $Et_3N$, DMAP, $CH_2Cl_2$, 0 °C, 90%. **iv.** NaI, acetone, r.t., 88%. **v.** LiHMDS, THF, -15 °C, 12 h, 85%. **vi.** Li-$NH_3$, -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 $CHCl_3$ 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 $^{13}C$ NMR spectra were recorded at 200 MHz and 50 MHz, respectively, on a Varian Gemini 200 spectrometer, using $CDCl_3$ 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 $LiBH_4$ solution in THF and 1 M solution of Li-hexamethyldisilazide in THF-hexanes were purchased from Aldrich. According to our already reported procedure[5,8j] compound **2** was prepared starting from ethyl (*E*)-4-bromo-2-butenoate and (*R*)-phenylethylamine: $[\alpha]_D$ +32.8 (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 233 ($M^+$), 218, 204, 190, 172, 144, 128, 105, 77. Anal. Calcd for $C_{14}H_{19}NO_2$: 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 $NH_4Cl$ (5g) was added[11] 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 ($Na_2SO_4$), 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, $H_4$), 3.19 (d, 1H, $H_3$, 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). $^{13}C$ 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. $[\alpha]_D$ +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 $C_{18}H_{23}NO_5$: 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, $H_4$ + $H_{5A}$), 3.23 - 3.32 (m, 2H, $H_3$ + $H_{5B}$), 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). $^{13}C$ 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. $[\alpha]_D$ +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 $C_{18}H_{23}NO_5$: 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 $NH_4Cl$ (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. $[\alpha]_D$ +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 $C_{18}H_{23}NO_5$: 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. $[\alpha]_D$ +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 $C_{18}H_{23}NO_5$: 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, $H_{3B}$ + $H_4$ + $H_{5A}$), 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. $[\alpha]_D$ +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 $C_{16}H_{21}NO_3$: 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 pured 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. $[\alpha]_D$ +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 $C_{14}H_{19}NO_2$: 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 $H_2O$ (50 ml) and extracted with ethyl acetate (3 x 100 ml). The organic layer was dried ($Na_2SO_4$) 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, $H_4$), 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). $^{13}C$ 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. $[\alpha]_D$ +105.8 (c 0.5, $CHCl_3$). GC-MS (EI, 70 eV): *m z* 311 ($M^+$), 296, 220, 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, 57.84; 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 $Na_2S_2O_3$ (50 ml), and dried ($Na_2SO_4$). 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, $H_{3B}$ + $H_4$ + $H_{5A}$), 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). $^{13}C$ 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. $[\alpha]_D$ +98.3 (c 0.5, $CHCl_3$). GC-MS (EI, 70 eV): *m z* 343 ($M^+$), 328, 310, 309, 252, 161, 160, 135, 127, 118, 105, 91, 77. Anal. Calcd for $C_{14}H_{18}NOI$: 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 $H_2O$-ice and extracted with ethyl acetate (3 x 100 ml). The organic layer was dried ($Na_2SO_4$) 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, $H_5$), 3.00 –3.12 (m, 1H, $H_1$), 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). $^{13}C$ 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. $[\alpha]_D$ +130.7 (c 0.5, $CHCl_3$). GC-MS (EI, 70 eV): *m z* 215 ($M^+$), 200, 187, 174, 172, 124, 120, 105, 104, 91, 77. Anal. Calcd for $C_{14}H_{17}NO$: 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 $NH_3$ (about 100 ml) was condensed at -78 °C and then Li (0.49 g; 70 mmol) was added. When the metal dissolved in $NH_3$, 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 $NH_4Cl$ (7 g) was added and the mixture was extracted with ethyl acetate (3 x 150 ml). The organic layer was dried ($Na_2SO_4$) 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). $^{13}C$ NMR: 24.4, 26.7, 33.8, 40.9, 49.2, 182.3. $[\alpha]_D$ -58.0 (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, 64.80; 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 $H_2O$ 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 ($CD_3OD$): 1.75 - 1.98 (m, 1H), 2.12 - 2.41 (m, 2H), 2.72 - 3.11 (m, 2H), 3.14 - 3.51 (m, 3H). $^{13}C$ NMR ($CD_3OD$): 22.9, 24.0, 36.1, 41.4, 42.8, 177.4. $[\alpha]_D$ -24.5 (c 0.5, $CH_3OH$). MS (EI, 70 eV): *m/z* 130 ($MH^+$), 129, 113, 112, 99, 97, 90, 85, 83, 68. Anal. Calcd for $C_6H_{12}NO_2Cl$: 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). $^{13}C$ 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. $[\alpha]_D$ +118.9 (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 $C_{16}H_{21}NO_3$: 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, $H_4$), 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). $^{13}C$ 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. $[\alpha]_D$ +85.8 (c 0.5, $CHCl_3$). 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. $[\alpha]_D$ +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, $H_{5A}$ + $C\underline{H}_2I$), 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. $[\alpha]_D$ +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. $[\alpha]_D$ 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**. $[\alpha]_D$ +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. $[\alpha]_D$ 24.1 (c 0.4, $CH_3OH$). **Anal. Calcd for $C_6H_{12}NO_2Cl$**: C, 43.51; H, 7.30; N, 8.46. Found: C, 43.45; H, 7.26; N, 8.51.

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**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.; Ohfune, 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.; Munoz, 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. *$GABA_B$ Receptors in Mammalian Function*: John Wiley & Sons: New York, 1990. f) Nielsen, L.; Brehm, L.; Krogsgaard-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.**; Ohfune, 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.; Ohfune, 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 coniugate 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 previouly observed partial hydrolysis (see ref. 5) of the ester group was suppressed.