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# Diastereomerically Pure Pyrrolidin-2-ones by Intramolecular Michael Reaction. Synthesis of Both (*S*)- and (*R*)-3-Pyrrolidineacetic Acid

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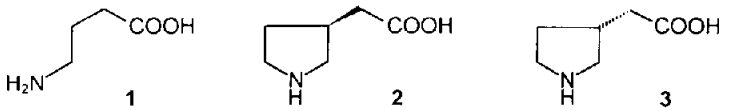
***Abstract***: By intramolecular conjugate addition of their derived enolates, the amides **5** and **6** gave diastereomeric mixtures of pyrrolidin-2-ones **10**,**11** and **12**,**13**, in good yield and 80:20 d.r. After chromatographic separation, the configuration of pure diastereomers was assigned from $^1$H NMR data. The usefulness of this intramolecular cyclisation was proven by conversion of either **10** or **12** into pyrrolidin-2-one **14** which through simple steps gave (*S*)-3-pyrrolidineacetic acid, **2**. Following the same synthetic scheme, but starting from either **11** or **13**, (*R*)-3-pyrrolidineacetic acid **3** was obtained.

γ-Aminobutyric acid (GABA) **1** is a major neurotransmitter in mammals, and disfunctioning of GABA-ergic synapses has been invoked for Parkinson's disease, Huntington's chorea, epilepsy and some forms of schizofrenia. [1a-c] One of the possible ways to palliate GABA deficiency lies in the inibition of uptake mechanisms of this neurotransmitter. Recently the non-proteinogenic amino acids (*S*)- and (*R*)-pyrrolidineacetic, **2** and **3**, proved to be potent inhibitors of glial as well neuronal GABA uptake. Moreover both enantiomers **2** and **3** bind to GABA receptor sites with opposite stereochemistry, since the (*S*)-enantiomer **2** is more potent than the (*R*)-enantiomer **3** as inhibitor of $GABA_B$ receptor binding, whereas the $GABA_A$ receptor affinity deals with the (*R*)-enantiomer **3**, exclusively. [1d] Thus it appears attractive to prepare both enantiomers **2** and **3** in high enantiomeric purity.

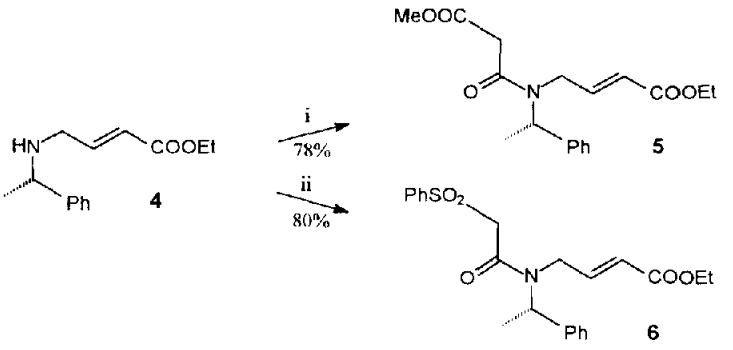



As part of a project aimed to synthesize non-proteinogenic as well as unusual amino acids containing the pyrrolidine ring, we recently reported a convenient approach to diastereomerically pure 4-substituted pyrrolidin-2-ones by radical induced cyclisation of *N*-allyl iodoacetamides. [2] Since the carbonyl group of pyrrolidin-2-ones can be easily removed, [3] this method resulted in a useful route to 3-substituted pyrrolidines.

With the aim of obtaining both enantiomers of 3-pyrrolidineacetic acid, **2** and **3**, we envisioned that substituted pyrrolidin-2-ones with defined configuration could arise from an intramolecular Michael reaction, starting from amides derived from (*S*)-phenylethylamine. [4] Intramolecular conjugate addition of anions to α,β-

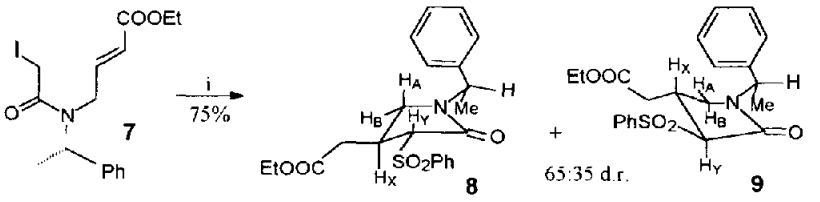
unsaturated esters has been studied in recent years, and a great deal of attention has been devoted to reactions leading to heterocyclic rings. [5] On the other hand, to the best of our knowledge, no examples are reported of intramolecular conjugated additions of amide enolates to α,β-unsaturated esters, in order to obtain substituted pyrrolidin-2-ones in high diastereomeric purity.

Therefore we prepared the methoxycarbonylacetamide **5** by acylation of the amino ester **4** with methyl malonyl chloride. On the other hand, the benzenesulphonylacetamide **6** was obtained by reaction of benzenesulphonylacetic acid with the amino ester **4** in the presence of DCC.




**Scheme 1.** ***Reagents and conditions:*** **i.** Methyl malonyl chloride, $Et_3N$, DMAP, $CH_2Cl_2$, 0 °C. **ii.** Benzenesulphonylacetic acid, DCC, THF, 0 °C.

In fact, we were pleased to find that, by refluxing the iodoacetamide **7** in methanol with 2 equiv of sodium benzenesulphinate, in order to prepare **6**, [6] a diastereomeric mixture of pyrrolidin-2-ones **8** and **9** was directly formed in 75% yield and 65:35 d.r., as determined by $^{13}C$ NMR spectrum of the crude reaction mixture. The reaction mechanism involves the nucleophilic displacement of iodine by the benzenesulphinate anion to give **6**, followed by intramolecular conjugate addition in which the benzenesulphinate anion acts as a base. In fact, by treating **6** with sodium benzenesulphinate in refluxing methanol, **8** and **9** were obtained in 75% yield and 65:35 d.r. The diastereomeric mixture was easily separated by silica gel chromatography and the structures of diastereomers **8** and **9** were assigned on the basis of $^1H$ NMR data. Thus, the minimum energy conformations of both diastereomers **8** and **9** were calculated by using the MM+ force field [7] (Scheme 2) and showed that the phenyl group lies above the plane of the heterocycle ring and the hydrogen $H_A$ either in both **8** and **9** experiences the shielding effect by the phenyl group.




**Scheme 2.** ***Reagents and conditions:*** **i.** $PhSO_2Na$ (2 equiv), refluxing methanol.

Therefore, the chemical shifts and the coupling constants values of $H_A$ and $H_B$ proved diagnostics for the configurational assignment of C-4. [8] The *trans*-relationship between the substituents at C-3 and C-4 was established by either $J_{XY}$ value and a large NOE effect between $H_Y$ and the methylenic protons of $CH_2COOEt$ at C-4, so that the configurations of **8** and **9** were assigned as 3*R*,4*S*,1'*S* and 3*S*,4*R*,1'*S*, respectively. The configuration of **9** was eventually confirmed by X-ray diffraction analysis.

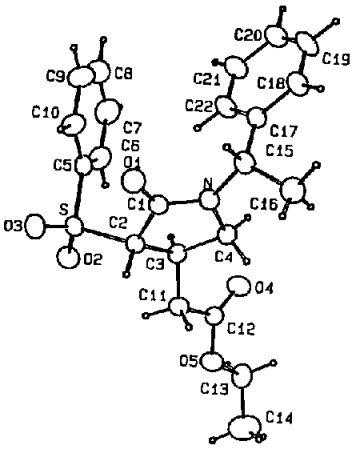
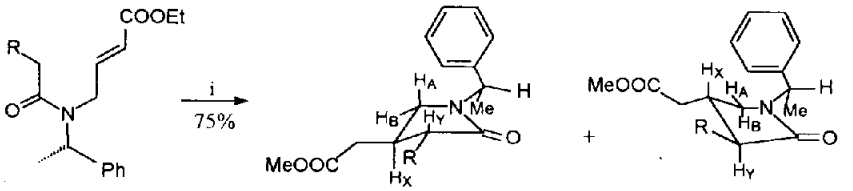



**Figure 1.** Perspective drawing (ORTEP) of **9**. The numbering is that used for the X-ray analysis.

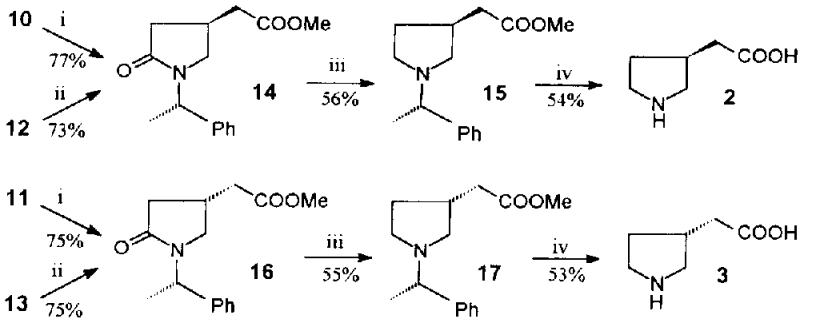
The observed d.r. was in good agreement with the calculated steric energies for diastereomers **8** and **9**, ($\Delta E$ = 0.73 kcal/mol), as determined by using MM+ force field [7] and in order to increase the diastereoselection of the cyclisation, we devised to carry out the reaction at diminished temperature. Thus both **5** and **6** were treated with NaH in THF at -78 °C. [9] Since during the work-up the ester functionality was cleaved to an extent of about 30%, the crude reaction mixtures were treated with 2M NaOH for 1 h, then acidified and the acids were esterified with $CH_2N_2$ (Scheme 3). Following this procedure, diastereomeric mixtures of pyrrolidin-2-ones **10**,**11** and **12**,**13**, respectively, were obtained in 75% yield and 80:20 d.r., [10] as determined by g.l.c. analysis and $^{13}C$ NMR spectra of the crude reaction mixtures. After chromatographic separation, the configuration at either C-3 and C-4 of pure diastereomers was assigned on the basis of $^1H$ NMR data, [8] as well as for diastereomers **8** and **9**.




R = MeOOC, **5** **10** d.r. 80:20 **11**
R = $PhSO_2$, **6** **12** d.r. 80:20 **13**

**Scheme 3.** ***Reagents and conditions:*** **i.** NaH, THF, -78 °C, then 2 M NaOH, 2M HCl, $CH_2N_2$.

In order to test the synthetic usefulness of the cyclisation, the pure pyrrolidin-2-ones were used to prepare both (*R*)- and (*S*)-3-pyrrolidineacetic acids, **2** and **3**. Thus treatment of either **10** and **11** with NaCl in wet DMF at reflux provided in good yield the pyrrolidin-2-ones **14** and **16**, respectively.[11] The same compounds **14** and **16** were obtained when **12** and **13**, respectively, were treated with Na-Hg in methanol.[12] The pyrrolidin-2-one **14**, by treatment with $BH_3$ in THF, was converted into the corresponding amino ester **15**[3] which, following literature methods,[1d] gave (*S*)-3-pyrrolidineacetic acid **2** in 54% yield. The same synthetic sequence, but carried out starting from **16**, led to (*R*)-3-pyrrolidineacetic acid, **3**, in 53% yield (Scheme 4).




**Scheme 4.** ***Reagents and conditions:*** **i.** NaCl, wet DMF, Δ. **ii.** Na-Hg, MeOH, 0 °C. **iii.** $BH_3$-THF. **iv.** (a) $H_2$, 10% Pd-C. (b) Amberlite IRA 400 (OH form), followed by elution with AcOH-$H_2O$.

## Experimental

**General Methods.** Melting points were determined on Electrothermal 5000 apparatus and are uncorrected. IR spectra were recorded 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, unless otherwise stated. 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. The NMR tubes were degased with the freeze-pump-thaw technique before running NOE 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). The solvents were distilled under argon before use. (*S*)-1-phenylethylamine was purchased from Aldrich.

**(*S*)-*N*-[3-Ethoxycarbonyl-2(*E*)-propen-1-yl]-*N*-(1-phenyleth-1-yl)amine 4.** The title compound was prepared in 75% yield starting from ethyl 4-bromo-2(*E*)-butenoate and (*S*)-phenylethylamine.[2] IR ($CHCl_3$): 3345, 1725 $cm^{-1}$; $^1H$ NMR: 1.28 (t, 3H, J = 7.0), 1.36 (d, 3H, J = 6.6), 1.54 (bs, 1H, NH), 3.24 (dd, 2H, J =

5.5, J = 1.8), 3.79 (q, 1H, J = 6.6), 4.18 (q, 2H, J = 7.0), 5.96 (dt, 1H, J = 15.8, J = 1.8), 6.97 (dt, 1H, J = 15.8, J = 5.5), 7.18 - 7.25 (m, 5 ArH); $^{13}$C NMR: 14.8, 24.8, 48.5, 58.1, 60.8, 121.8, 127.0, 127.5, 129.0, 145.5, 147.5, 167.0; $[\alpha]_D$ -32.6 (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, 72.03; H, 8.17; N, 5.96.

**(*S*)-*N*-[3-Ethoxycarbonyl-2(*E*)-propen-1-yl]-*N*-(1-phenyleth-1-yl)methoxycarbonylacetamide 5.** To a solution of (*S*)-*N*-[3-ethoxycarbonyl-2(*E*)-propen-1-yl]-*N*-(1-phenyleth-1-yl)amine **4** (7.0 g; 30 mmol) in dichloromethane (120 ml) containing triethylamine (3.4 g, 33 mmol) and *N,N*-dimethylaminopyridine (0.37 g; 3 mmol) at 0 °C, methyl malonyl chloride (4.5 g; 33 mmol) in dichloromethane (50 ml) was added and the mixture was stirred at 0 °C for 1 h. The reaction mixture was poured into ethyl acetate (150 ml) and the organic phase was washed with 2 M HCl (50 ml) and then with 10% aqueous $Na_2CO_3$ (100 ml). After drying over $Na_2SO_4$, the organic layer was removed in vacuo and the residue was purified by flash chromatography (cyclohexane:ethyl acetate 70:30) to give **5** in 78% yield as a colorless oil; IR ($CHCl_3$): 1745, 1725, 1668 cm$^{-1}$; $^1$H NMR: 1.26 (t, 3H, 46%, J = 7.1), 1.28 (t, 3H, 54%, J = 7.1), 1.52 (d, 3H, 54%, J = 7.1), 1.62 (d, 3H, 46%, J = 7.1), 3.41 (s, 2H), 3.65 - 3.88 (m, 2H), 3.76 (s, 3H, 54%), 3.85 (s, 3H, 46%), 4.14 (q, 2H, 46%, J = 7.1), 4.17 (q, 2H, 54%, J = 7.1), 5.09 (q, 1H, 46%, J = 7.1), 5.75 (dt, 1H, 46%, J = 15.7, J = 1.7), 5.80 (dt, 1H, 54%, J = 15.7, J = 1.7), 6.11 (q, 1H, 54%, J = 7.1), 6.66 (dt, 1H, J = 15.7, J = 4.8), 6.75 (dt, 1H, 46%, J = 15.7, J = 4.8), 7.15 - 7.42 (m, 5 ArH), $^{13}$C NMR: 14.6, 16.9 (54%), 19.0 (46%), 41.8, 44.2 (54%), 45.3 (46%), 52.1 (54%), 53.0 (46%), 56.9, 60.8 (46%), 61.2 (54%), 122.6 (46%), 123.2 (54%), 127.1, 128.0, 128.3, 18.5, 129.1, 129.4, 139.8 (54%), 140.2 (46%), 144.1 (46%), 144.3 (54%), 165.9 (46%), 166.6 (54%), 167.3 (46%), 168.4 (54%); $[\alpha]_D$ - 83.2 (c 1, $CHCl_3$); GC-MS (EI, 70eV) *m/z* 333 ($M^+$), 318, 286, 210, 186, 168, 160, 133, 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, 6.91; N, 4.16.

**(*S*)-*N*-[3-Ethoxycarbonyl-2(*E*)-propen-1-yl]-*N*-(1-phenyleth-1-yl)benzenesulphonylacetamide 6.** To a solution of benzenesulphonylacetic acid (6.0 g, 30 mmol) dissolved in THF (50 ml), was slowly added dicyclohexylcarbodiimide (6.2 g; 30 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 min, and then a solution of (*S*)-*N*-[3-ethoxycarbonyl-2(*E*)-propen-1-yl]-*N*-(1-phenyleth-1-yl)amine **4** (5.25 g; 30 mmol) in THF (40 ml) was slowly added. Stirring was continued for 2 h, and the mixture was allowed to warm to rooom temperature. The solid dicyclohexylurea was filtered off and the solvent removed under reduced pressure. Flash chromatography of the residue (cyclohexane:ethyl acetate 60:40) gave the title product in 80% yield as white crystals: m.p. 118 - 120 °C; IR ($CHCl_3$): 1720, 1665 cm$^{-1}$; $^1$H NMR: 1.27 (t, 3H, 57%, J = 7.1), 1.29 (t, 3H, 43%, J = 7.1), 1.48 (d, 3H, 57%, J = 7.1), 1.68 (d, 3H, 43%, J = 7.1), 3.65 - 4.53 (m, 6H), 5.48 (q, 1H, 43%, J = 7.1), 5.77 (dt, 1H, 57%, J = 15.8, J = 1.9), 5.79 (dt, 1H, 43%, J = 15.8, J = 1.9), 5.93 (q, 1H, 57%, J = 7.1), 6.67 (dt, 1H, 43%, J = 15.8, J = 5.3), 6.69 (dt, 1H, 57%, J = 15.8, J = 5.3), 7.21 - 7.42 (m, 5 ArH), 7.51 - 774 (m, 3 ArH), 7.86 (m, 2 ArH); $^{13}$C NMR: 14.7 (57%), 14.8 (43%), 17.1 (57%), 19.4 (43%), 44.4 (43%), 45.3 (57%), 52.7 (57%), 57.4 (43%), 60.5 (43%), 60.9 (43%), 61.0 (57%), 61.3 (57%), 122.9 (43%), 123.4 (57%), 127.2, 128.0, 129.1, 129.2, 129.5, 129.7, 1219.8, 134.7 (57%), 134.9 (43%), 139.8, 143.4 (43%), 144.1 (57%), 162.1 (43%), 162.4 (57%), 165.8 (57%), 166.4 (43%); $[\alpha]_D$ -116.1 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z* 400 ($M^+$ - $CH_3$), 274 ($M^+$ - $C_6H_5SO_2$), 228, 186, 172, 105, 91, 77. Anal. Calcd for $C_{22}H_{25}NO_5S$: C, 63.60; H, 6.06; N, 3.37. Found: C, 63.56; H, 6.03; N, 3.34.

**(*S*)-*N*-[3-Ethoxycarbonyl-2(*E*)-propen-1-yl]-*N*-(1-phenyleth-1-yl)iodoacetamide 7.** According to ref. 2, the title compound **7** was obtained as a yiellow oil in 75% yield starting from (*S*)-*N*-[3-ethoxycarbonyl-2(*E*)-propen-1-yl]-*N*-(1-phenyleth-1-yl)amine **4** and bromoacetyl bromide; IR ($CHCl_3$): 1718, 1667 $cm^{-1}$; $^1H$ NMR: 1.25 (t, 3H, 63%, J = 7.1), 1.28 (t, 3H, 37%, J = 7.1), 1.51 (d, 3H, 63%, J = 7.0), 1.66 (d, 3H, 37%, J = 7.0), 3.45 - 4.15 (m, 4H), 4.18 (q, 2H, 63%, J = 7.1), 4.21 (q, 2H, 37%, J = 7.1), 5.24 (q, 1H, 37%, J = 7.0), 5.72 (d, 1H, 37%, J = 15.7), 5.79 (d, 1H, 63%, J = 15.7), 6.04 (q, 1H, 63%, J = 7.0), 6.72 (dt, 1H, 63%, J = 15.7, J = 5.4), 6.91 (dt, 1H, 37%, J = 15.7, J = 5.4), 7.31 (m, 5 ArH); $^{13}C$ NMR: -3.4 (63%), -1.9 (37%), 14.5, 16.7 (63%), 18.8 (37%), 44.3 (37%), 45.8 (63%), 50.3 (37%), 52.4 (37%), 52,5 (63%), 57.5 (63%), 122.0 (37%), 122.5 (67%), 127.3, 128.4,139.8, 144.5 (37%), 144.8 (63%), 166.1, 169.4; $[\alpha]_D$ -87.2 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z* 232 ($M^+$ - $COCH_2I$), 162, 127, 105, 91, 77. Anal Calcd for $C_{16}H_{20}NO_3I$: C, 47.90; H, 5.02; N, 3.49. Found: C, 47.82; H, 4.97; N, 3.43.

**Ethyl (3*R*,4*S*,1'*S*)-[3-benzenesulphonyl-2-oxo-1-(1'-phenyleth-1'-yl)-pyrrolidin-4-yl]acetate 8 and its (3*S*,4*R*,1'*S*)-isomer 9.** To a solution containing **7** (4.0 g; 10 mmol) in methanol (50 ml), sodium benzenesulphinate (3.3 g; 20 mmol) was added and the solution was refluxed for 3 h. After removal of the solvent under reduced pressure, the residue was dissolved in ethyl acetate (100 ml) and washed with water and brine. After drying ($Na_2SO_4$), the solvent was removed in vacuo and the residue was chromatographed on silica gel (cyclohexane:ethyl acetate 70:30 as eluant) to give pure diastereomers **8** and **9** in 75% overall yield and 65:35 d.r. IR ($CHCl_3$): 1745, 1664 $cm^{-1}$. **(3*R*,4*S*,1'*S*)-Isomer 8:** colorless oil; $R_f$ 0.42; $^1H$ NMR: 1.17 (t, 3H, J = 7.0), 1.45 (d, 3H, J = 7.1), 2.35 (dd, 1H, J = 16.4, J = 8.6), 2.58 (dd, 1H, $H_A$, $J_{AB}$ = 10.1, $J_{AX}$ = 4.7), 2.60 (dd, 1H, H = 16.4, J = 6.8), 3.34 (m, 1H, $H_X$), 3.63 (dd, 1H, $H_B$, $J_{AB}$ = 10.1, $J_{BX}$ = 8.1), 3.89 (d, 1H, $H_Y$, $J_{XY}$ = 5.2), 4.05 (q, 2H, J = 7.0), 5.39 (q, 1H, J = 7.1), 7.15 - 7.33 (m, 5 ArH), 7.51 - 7.73 (m, 3 ArH), 7.95 - 8.04 (m, 2 ArH); $^{13}C$ NMR: 14.6, 16.3, 29.9, 38.4, 46.5, 50.4, 61.4, 71.2, 127.5, 127.7, 128.4, 128.9, 129.0, 134.8, 138.2, 139.4, 164.7, 171.0; $[\alpha]_D$ - 69.7 (c 1, $CHCl_3$) **(3*S*,4*R*,1'*S*)-Isomer 9:** white solid: m.p.132 °C; $R_f$ = 0.36; $^1H$ NMR: 1.26 (t, 3H, J = 7.2), 1.47 (d, 3H, J = 7.0), 2.59 (dd, 1H, J = 16.4, J = 8.1), 2.80 (dd, 1H, J = 16.4, J = 4.7), 2.96 (dd, 1H, $H_A$, $J_{AB}$ = 14.0, $J_{AX}$ = 9.2), 3.23 (m, 1H, $H_X$), 3.26 (dd, 1H, $H_B$, $J_{AB}$ = 14.0, $J_{BX}$ = 8.0), 3.96 (d, 1H, $H_Y$, $J_{XY}$ = 6.4), 4.23 (q, 2H, J = 7.2), 5.38 (q, 1H, J = 7.0), 7.09 - 7.18 (m, 2 ArH), 7.20 - 7.41 (m, 3 ArH), 7.49 -7.75 (m, 3 ArH), 7.95 - 8.05 (m, 2 ArH); $^{13}C$ NMR: 14.6, 16.5, 30.0, 38.4, 46.3, 50.1, 61.5, 70.9, 127.6, 128.2, 129.1, 129.5, 130.2, 134.7, 137.9, 139.2, 164.7, 171.2; $[\alpha]_D$ -130.8 (c 1, $CHCl_3$). GC-MS (EI, 70eV) *m z* 274 ($M^+$ - $C_6H_5SO_2$), 258, 228, 172, 160, 120, 105, 91, 77. Anal. Calcd for $C_{22}H_{25}NO_5S$: C, 63.60; H, 6.06; N, 3.37. Found: C, 63.55, H, 6.03; N, 3.33.

**X-Ray Crystal Structure Analysis for 9.** Crystal Data: $C_{22}H_{25}NO_5S$, M = 415.51, Monoclinic, Space group $P2_1$, a = 11.958(4) Å, b = 8.263(1) Å, c = 11.968(4) Å, b = 116.71(2) °, V = 1056(1) $Å^3$, Z = 2, D(calc) = 1.306 $g/cm^3$. 2912 reflections were collected on a CAD4 Enraf-Nonius single crystal diffractometer at room temperature by ω scan technique by using graphite-monochromated $MoK_\alpha$ radiation (λ = 0.7107 Å). The structure was solved using direct methods and refined through full-matrix least-squares methods with unit weight for 1900 observed reflections with $I>3\sigma(I)$. [13] The non-hydrogen atoms were treated anisotropically. The hydrogen atoms were calculated from the carbon positions and added as fixed contributions with isotropic thermal parameters of 1.3 times the value of Beq of the atoms to which they are attached. A secondary extinction correction was applied [14] and the coefficient ($7.2(2)\ 10^{-7}$) was refined in least-squares. The final R

and $R_W$ values are 0.038 and 0.035 respectively. [15] The ORTEP drawing [16] is shown in Figure 1 together with the atom numbering scheme.

**Methyl (3*R*,4*R*,1'S)-[3-methoxycarbonyl-2-oxo-1-(1'-phenyleth-1'-yl)pyrrolidin-4-yl]acetate 10 and its (3*S*,4*S*,1'S)-isomer 11.** To a suspension of NaH (0.48 g; 50% in oil; 10 mmol) in dry THF (50 ml), a solution of **5** (3.3 g; 10 mmol) in dry THF (20 ml) was added at -78 °C. After 1 h 2 M NaOH (20 ml) was slowly added and the mixture stirred for 1 h at 20 °C. 2 M HCl (35 ml) was then added and the mixture was extracted with ethyl acetate (2 x 100 ml). The organic layer was dried ($Na_2SO_4$) and solvent was removed under reduced pressure. the residue was dissolved in methanol (30 ml) and treated with $CH_2N_2$ until the acids disappeared in t.l.c. The solvent was evaporated and the residue was chromatographed on silica gel (cyclohexane:ethyl acetate 70:30) to give pure pyrrolidin-2-ones **10** and **11** in 75% overall yield and 80:20 d.r. IR ($CHCl_3$): 1745, 1680 $cm^{-1}$. **(3*R*,4*R*,1'*S*)-Isomer 10**: $R_f$ 0.30; $^1H$ NMR: 1.53 (d, 3H, J = 7.1), 2.31 (dd, 1H, J = 16.6, J = 8.1), 2.47 (dd, 1H, J = 16.6, J = 6.3), 2.59 (dd, 1H, $H_A$, $J_{AX}$ = 6.7, $J_{AB}$ = 9.9), 3.08 (m, 1H, $H_X$), 3.22 (d, 1H, $H_Y$, $J_{XY}$ = 7.8), 3.61 (s, 3H), 3.65 (dd, 1H, $H_B$, $J_{BX}$ = 8.3, $J_{AB}$ = 9.9), 3.80 (s, 3H), 5.48 (q, 1H, J = 7.2), 7.2 - 7.45 (m, 5 ArH); $^{13}C$ NMR: 16.5, 32.9, 37.6, 46.7, 50.1, 52.3, 53.2, 55.1, 127.6, 128.3, 129.1, 139.9, 168.7, 170.2, 171.9; $[\alpha]_D$ -157.2 (c 1, $CHCl_3$). **(3*S*,4*S*,1'S)-Isomer 11**: $R_f$ 0.27; $^1H$ NMR: 1.53 (d, 3H, J = 7.1), 2.44 (dd, 1H, J = 16.6, J = 7.4), 2.56 (dd, 1H, J = 16.6, J = 6.2), 3.00 (m, 2H, $H_A$ + $H_X$), 3.30 (m, 2H, $H_B$ + $H_Y$), 3.63 (s, 3H), 3.81 (s, 3H), 5.45 (q, 1H, J = 7.1), 7.25 - 7.45 (m, 5 ArH); $^{13}C$ NMR: 16.6, 33.0, 37.8, 47.8, 49.9, 52.3, 53.1, 53.2, 55.1, 127.4, 127.6, 128.2, 139.8, 168.8, 170.3, 171.9; $[\alpha]_D$ -250.1 (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 319 ($M^+$), 304, 288, 272, 246, 230, 186, 160, 133, 105, 91, 77. Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.89; H, 6.60; N, 4.34.

**Methyl (3*R*,4*S*,1'*S*)-[3-benzenesulphonyl-2-oxo-1-(1'-phenyleth-1'-yl)-pyrrolidin-4-yl]acetate 12 and its (3*S*,4*R*,1'*S*)-Isomer 13.** Following the procedure reported for preparing the diastereomeric pair **(10),(11)**, but starting from **6**, the title compounds **12** and **13** were obtained in 75% overall yield and 80:20 d.r. IR ($CHCl_3$): 1745, 1675 $cm^{-1}$. **(3*R*,4*S*,1'*S*)-Isomer 12:** colorless oil; $R_f$ 0.41; $^1H$ NMR: 1.45 (d, 3H, J = 7.1), 2.37 (dd, 1H, J = 8.6, J = 16.5), 2.58 (dd, 1H, $H_A$, J = 4.3, J = 10.0), 2.63 (dd, 1H, J = 5.5, J = 16.5), 3.34 (m, 1H, $H_X$), 3.57 (s, 3H), 3.64 (dd, 1H, $H_B$, J = 8.1, J = 10.0), 3.90 (d, 1H, $H_Y$, J = 5.2), 5.39 (q, 1H, J = 7.1), 7.15 - 7.35 (m, 5 ArH), 7.51 - 7.73 (m, 3 ArH), 7.95 - 8.02 (m, 2 ArH); $^{13}C$ NMR: 16.3, 29.9, 38.2, 46.5, 50.5, 52.4, 71.2, 116.5, 127.6, 127.7, 128.1, 128.2, 128.3, 128.4, 129.2, 129.5, 129.9, 134.8, 138.1, 139.4, 164.7, 171.5; $[\alpha]_D$ -89.3 (c 1, $CHCl_3$). **(3*S*,4*R*,1'*S*)-Isomer 13:** white solid: m.p. 109 - 110 °C; $R_f$ 0.36; $^1H$ NMR: 1.46 (d, 3H, J = 7.1), 2.60 (dd, 1H, J = 8.2, J = 16.6), 2.81 (dd, 1H, J = 4.3, J = 16.6), 2.95 (dd, 1H, $H_A$, J = 9.2, J = 14.1), 3.23 (m, 2H, $H_X$ + $H_B$), 3.67 (s, 3H), 3.97 (d, 1H, $H_Y$, J = 6.4), 5.37 (q, 1H, J = 7.1), 7.05 - 7.16 (m, 2 ArH), 7.19 - 7.40 (m, 3 ArH), 7.48 - 7.74 (m, 3 ArH), 7.92 - 8.03 (m, 2 ArH); $^{13}C$ NMR: 16.45, 29.9, 38.2, 46.3, 50.1, 52.5, 70.9, 127.3, 128.2, 129.1, 129.5, 130.2, 134.7, 137.9, 139.2, 164.7, 171.7; $[\alpha]_D$ -160.7 (c 1, $CHCl_3$). GC-MS (EI, 70 eV): 260 ($M^+$ - $C_6H_5SO_2$), 244, 214, 160, 120, 105, 91, 77. Anal. Calcd for $C_{21}H_{23}NO_5S$: C, 62.83; H, 5.77; N, 3.49. Found: C, 62.78; H, 5.71; N, 3.43.

**Methyl (4*S*,1'*S*)-[2-oxo-1-(1'-phenyleth-1'-yl)pyrrolidin-4-yl]acetate 14.** The pyrrolidin-2-one **10** (1.6 g, 5 mmol), sodium chloride (0.58 g; 10 mmol) and water (180 mg; 10 mmol) were dissolved in DMF (10 ml) and the mixture was refluxed for 3 h. Then DMF was removed in vacuo and the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 60:40), to give **14** in 77% yield as a colorless oil. $R_f$ 0.27; IR ($CHCl_3$): 1745, 1665 $cm^{-1}$, $^1H$ NMR: 1.49 (d, 3H, J = 7.2), 2.25 - 2.38 (m, 2H), 2.45 (m, 1H), 2.55 - 2.75 (m,

3H), 3.53 (dd, 1H, $H_B$, J = 7.2, J = 9.5), 3.62 (s, 3H), 5.49 (q, 1H, J = 7.2), 7.21-7.45 (m, 5 ArH); $^{13}$C NMR: 17.2, 28.6, 38.2, 38.8, 48.1, 49.4, 52.3, 127.5, 128.0, 128.2, 140.5, 173.5, 195.1; $[\alpha]_D$ -98.6 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z* 261 ($M^+$), 246, 190, 136, 105, 91, 77. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.89; H, 7.26; N, 5.33.

**Methyl (4*R*,1'*S*)-[2-oxo-1-(1'-phenyleth-1'-yl)pyrrolidin-4-yl]acetate 16.** Following the same procedure employed for **14**, but starting from **11**, the title compound was obtained in 75% yield as a colorless oil: $R_f$ 0.30; IR ($CHCl_3$): 1745, 1665 cm$^{-1}$; $^1$H NMR: 1.51 (d, 3H, J = 7.2), 2.05-2.35 (m, 2H), 2.45 (m, 1H), 2.53-2.74 (m, 2H), 3.01 (dd, 1H, $H_B$, J = 5.8, J = 9.8), 3.21 (dd, 1H, $H_A$, J = 7.5, J = 9.5), 3.66 (s, 3H), 5.47 (q, 1H, J = 7.2), 7.25-7.45 (m, 5 ArH); $^{13}$C NMR: 16.6, 28.6, 38.1, 38.9, 48.1, 48.4, 52.3, 127.5, 128.1, 129.1, 140.5, 172.5, 195.0; $[\alpha]_D$ -103.8 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z* 261 ($M^+$), 246, 190, 136, 105, 91, 77. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.87; H, 7.24; N, 5.32.

**Desulphonylation Reaction of 12 and 13: General Procedure.** To a slurry of 6% Na(Hg) (7.9 g; 21 mmol) and disodium hydrogen phosphate (2.9 g; 21 mmol) in methanol (25 ml), were added the benzenesulphonyl derivatives **12** or **13** (5 mmol) dissolved in THF (5 ml). The mixture was stirred until the starting material disappeared, then water (30 ml)was added, followed by 6 M HCl (10 ml). After extraction with ethyl acetate (100 ml). the organic layer was dried ($Na_2SO_4$) and evaporated in vacuo to give a residue which was purified by silica gel chromatography (cyclohexane ethyl acetate 60:40), to give the pyrrolidin-2-ones **14** or **16** as colorless oils in 73% and 75% yield, respectively.

**Methyl (3*S*,1'*S*)-[1-(1'-phenyleth-1'-yl)-pyrrolidin-3-yl] acetate 15.** To a solution containing **14** (1.3 g; 5 mmol) in dry THF (15 ml) under argon atmosphere, $BH_3$-THF (20 ml of 1.0 M solution, 20 mmol) was added at 0 °C. After completion of the addition, the mixture was refluxed for 1 h and then cooled at r.t. After addition of 4 M methanolic HCl (10 ml), the mixture was refluxed for an additional hour. Then the solvents were removed under reduced pressure and 4 M methanolic HCl (15 ml) was added to the residue and the solution was stirred for 12 h. The solvent was again removed in vacuo, the residue was dissolved in $H_2O$ (30 ml) and the solution was extracted with ethyl acetate (2 x 100 ml). After addition of solid $Na_2CO_3$ (10 g), the aqueous layer was extracted with ethyl acetate (2 x 100 ml), the combined extracts were dried ($Na_2SO_4$). The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (ethyl acetate), to give **15** in 56% yield as a colorless oil. IR ($CHCl_3$): 1740 cm$^{-1}$; $^1$H NMR: 1.35 - 1.51 (m, 1H), 1.37 (d, 3H, J = 6.6), 1.97 - 2.14 (m, 1H), 2.15 (dd, 1H, J = 6.2, J = 8.8), 2.30 - 2.77 (m, 5H); 2.68 (dd, 1H, J = 7.5, J = 8.8), 3.19 (q, 1H, J = 6.6), 3.64 (s, 3H), 7.19 - 7.39 (m, 5 ArH); $^{13}$C NMR: 23.6, 30.9, 34.1, 40.2, 51.9, 52.8, 59.1, 66.1, 127.4, 127.6, 128.8, 145.9, 173.8; $[\alpha]_D$ -34.2 (c 1, MeOH). GC-MS (EI, 70 eV): *m/z* 247 ($M^+$), 232, 217, 174, 172, 128, 105, 91, 77. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.75; H, 8.49; N, 5.58.

**(*S*)-3-Pyrrolidineacetic acid 2.** A solution of **15** (1.2 g; 5 mmol) in methanol (30 ml) was hydrogenated in a Parr hydrogenation apparatus (about 300 kPa) using 10% Pd-C (150 mg) as a catalyst. The reaction mixture was filtered and the solvent was evaporated in vacuo. The residue was dissolved in water (3 ml) and transferred to a column containing Amberlite IRA 400 in the OH form (20 g). After 2.5 h, elution with aqueous acetic acid (6%) gave **(2)** in 54% yield as a white solid: m.p. 163 °C [lit. [1d] 160 - 165 °C for the (*R*)-isomer]; $^1$H NMR ($D_2O$): 1.43 - 1.71 (m, 1H), 2.01 - 2.34 (m, 3H), 2.41 - 2.95 (m, 2H), 3.12 - 3.44 (m, 3H), $^{13}$C NMR ($D_2O$):

30.3, 34.2, 35.4, 37.2, 50.7, 177.2; $[\alpha]_D$ 9.2 (c 1, $H_2O$) [lit. [1d] 9.6 (c 1, $H_2O$)]. Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.70; H, 8.47; N, 10.75.

**Methyl (3*R*,1'*S*)-[1-(1'-phenyleth-1'-yl)-pyrrolidin-3-yl] acetate 17.** Following the same procedure employed for **15**, but starting from **16**, the title compound was obtained in 55% yield as a colorless oil: IR ($CHCl_3$): 1740 $cm^{-1}$; $^1H$ NMR: 1.32 - 1.51 (m, 1H), 1.37 (d, 3H, J = 6.6), 1.94 - 2.21 (m, 1H), 2.09 (dd, 1H, J = 6.2, J = 9.2), 2.34 - 2.76 (m, 5H), 2.87 (dd, 1H, J = 7.4, J = 9.2), 3.22 (q, 1H, J = 6.6), 3.64 (s, 3H), 7.15 - 7.38 (m, 5 ArH); $^{13}C$ NMR: 23.6, 30.9, 34.1, 40.3, 51.9, 52.0, 59.1, 66.1, 127.4, 127.6, 128.8, 145.8, 173.8; $[\alpha]_D$ -55.3 (c 1, MeOH). GC-MS (EI, 70 eV): *m/z* 247 ($M^+$), 232, 217, 174, 172, 128, 105, 91, 77. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.75; H, 8.51; N, 5.60.

**(*R*)-3-Pyrrolidineacetic acid 3.** Following the same procedure employed for **2**, but starting from **17**, the title compound was obtained in 53% yield as a white solid: m.p. 163 °C (lit. [1d] 160 - 165 °C); $[\alpha]_D$ -9.1 (c 1, $H_2O$) [lit. [1d] -9.3 (c 1, $H_2O$)]. Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.76; H, 8.45; N, 10.74.

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