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Thermodynamic *vs.* kinetic control in the stereoselective intramolecular conjugate addition of amide enolates leading to chiral *trans*-3,4-disubstituted pyrrolidin-2-ones

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Abstract

Intramolecular conjugate addition of amide enolates to α,β-unsaturated esters was found to give either of the diastereomeric *trans*-3,4-disubstituted pyrrolidin-2-ones **6, 10** or **7, 11** as the major products, by choosing the appropriate reaction conditions. The cyclisation performed with NaH in THF afforded mainly **6** and **10**, whereas by using sodium ethoxide in ethanol the major products of the cyclisation were isomers **7** and **11**, with the opposite configuration at both C-3 and C-4. This behaviour was explained by thermodynamic *vs.* kinetic control and supported by molecular mechanics and quantomechanical calculations.

Keywords: pyrrolidinones, cyclisation, stereoselection, Michael reaction

Introduction

In the last few years we have investigated new procedures for the stereoselective synthesis of pyrrolidin-2-ones[1-3] which are useful intermediates to a number of bioactive compounds[2e,4] and we report herein the stereodivergent preparation of 1,3,4-trisubstituted pyrrolidin-2-ones **3**[5] depending on the reaction conditions employed. In fact, we intended that these compounds can lead to substituted azetidinones such as **1**[6] through the ring contraction of the derivative **2**, which is currently being studied in our laboratory. The continued interest for the stereoselective synthesis of the β-lactam ring stems from the variety of antibiotics featuring a β-lactam moiety, in particular carbapenems[7] such as (+)-PS-5,[8] thienamycin[9] and its 1β-methyl derivative.[10] Thus, we were interested in the stereoselective synthesis of pyrrolidin-2-ones **3**, suitable for conversion into **1**, a key intermediate for the preparation of carbapenems.[6]

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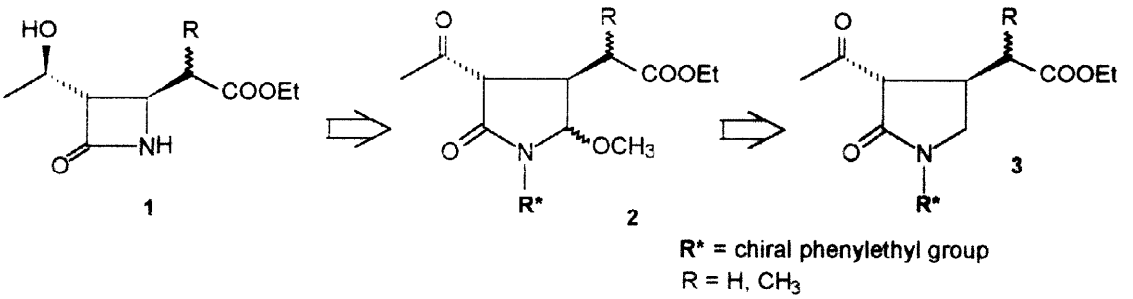
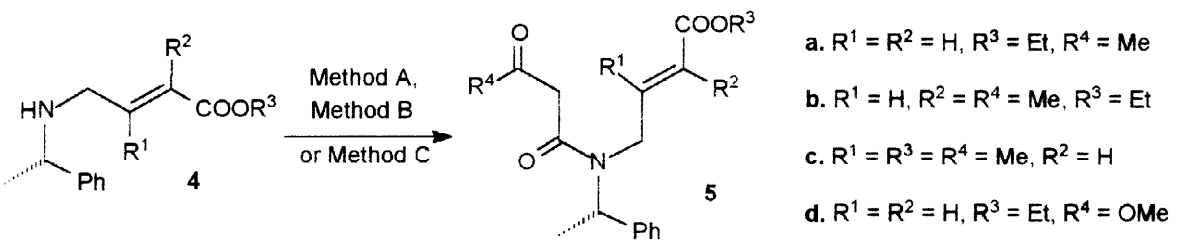


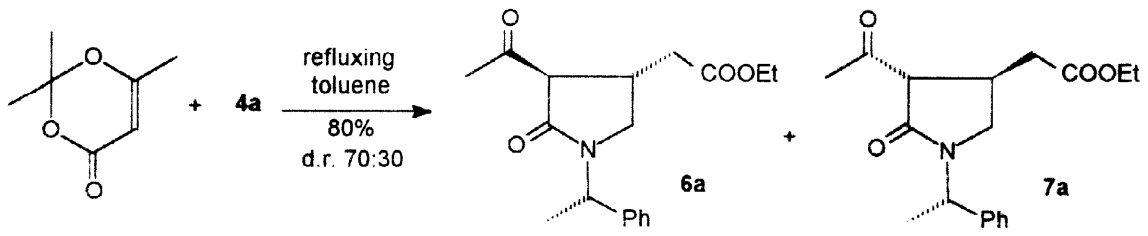
Results and discussion

In a previous paper[3] we reported on the stereoselective synthesis of *trans*-3,4-disubstituted pyrrolidin-2-ones *via* intramolecular conjugate addition. In our strategy we tethered an enolate anion to an α,β-unsaturated ester, in order to benefit from the entropic advantage associated with constraining the two reacting partners in close proximity.[11] As an extension of this methodology, we planned to study the diastereoselection of the conjugate addition varying the cyclisation conditions. Thus, upon treatment of the amino esters **4a-c** with diketene, the corresponding amides **5a-c** were obtained in good yield. On the other hand, the amides **5b,c** could be prepared also by treatment of **4b,c** with 2,2,6-trimethyl-4*H*-dioxin-4-one in refluxing toluene.[2b] Eventually, the amide **5d** was synthesized by reaction of **4a** with a mixed anhydride.



Scheme 1. ***Reagents, conditions and yields*****: Method A:** Diketene, DMAP, THF, -15 °C. **a.** 77%. **b.** 77%. **c.** 78%. **Method B:** 2,2,6-Trimethyl-4*H*-dioxin-4-one, refluxing PhMe. **b.** 83%. **c.** 83%. **Method C:** $MeO_2CCH_2CO_2K$, Me_3CCOCl, CH_2Cl_2, 20 °C. **d.** 87%.

A surprising result was observed when we treated the amino ester **4a** and 2,2,6-trimethyl-4*H*-dioxin-4-one in refluxing toluene, with the aim to prepare the amide **5a**; instead a diastereomeric 70:30 mixture of pyrrolidin-2-ones **6a** and **7a** was obtained (Scheme 2). The reaction probably proceeds through the initial attack of the amino group of **4a** on the carbonyl group of 2,2,6-trimethyl-4*H*-dioxin-4-one, followed by ring closure *via* conjugate addition of the resulting amide enolate anion. It is noteworthy, however, that both **4b** and **4c** under the same conditions afforded amides **5b** and **5c** exclusively and this behaviour can be ascribed to steric hindrance of the substituents on the double bond during the cyclisation.



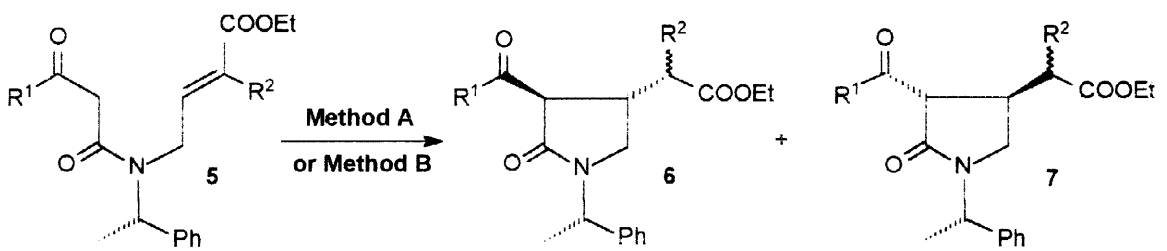
Scheme 2

The cyclisation of the amides **5a,b,d** was carried out first by treating with NaH in THF at -78 °C. Under these conditions, the pyrrolidin-2-ones **6a,b,d** and **7a,b,d** were obtained in high yield, the products **7** being the major components (Scheme 3). Both **6b** and **7b** were inseparable mixture of epimers 70:30 at C-2 of the propanoate chain, but the configuration of the major isomer was not assigned. However, the configuration of this centre did not affect the structural assignment of the centres at the pyrrolidin-2-one ring.[12]

The reaction was then performed by using sodium ethoxide in ethanol at -78 °C, and the cyclisation proceeded with good yield and diastereoselection, leading to **6a,b,d** and **7a,b,d.** with **6a,b,d** the major products in this case.

By treatment at -78 °C with either NaH in THF or sodium ethoxide in ethanol, the amide **5c** gave a complex, inseparable mixture of products.

The diastereomeric mixtures of 3,4-*trans*-disubstituted pyrrolidin-2-ones were easily separated by silica gel chromatography, to give isolated **6a,b,d** and **7a,b,d** and the absolute configuration of all the products were determined by ^{1}H NMR data supported by molecular mechanics calculations.[1-3]



a. R^1 = Me, R^2 = H; **b.** R^1 = R^2 = Me; **d.** R^1 = MeO, R^2 = H

Scheme 3. ***Reagents, conditions and yields*****: Method A:** NaH, THF, -78 °C. **a.** 77%, d.r. 28:72. **b.** 76%, d.r. 30:70. **d.** 82%, d.r. 20:80. **Method B:** EtONa, EtOH, -78 °C. **a.** 84%, d.r. 85:15. **b.** 82%, d.r. 84:16. 80%, d.r. 70:30.

Moreover, the configuration of products **6a** and **7a** could be also proved by n.O.e. experiments. In fact a positive n.O.e. between H_Y and CH_2 of the chain at C-4 was observed for both **6a** and **7a**, thus confirming the *trans*-configuration. Eventually, structural assignment was confirmed by positive n.O.e. between H_A and H_X for **6a**, and between H_A and CH_2 of the chain at C-4 for **7a** (Figure 1).

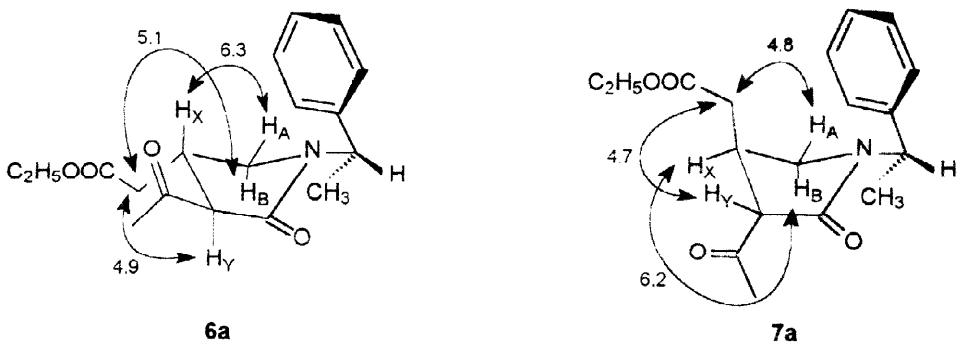
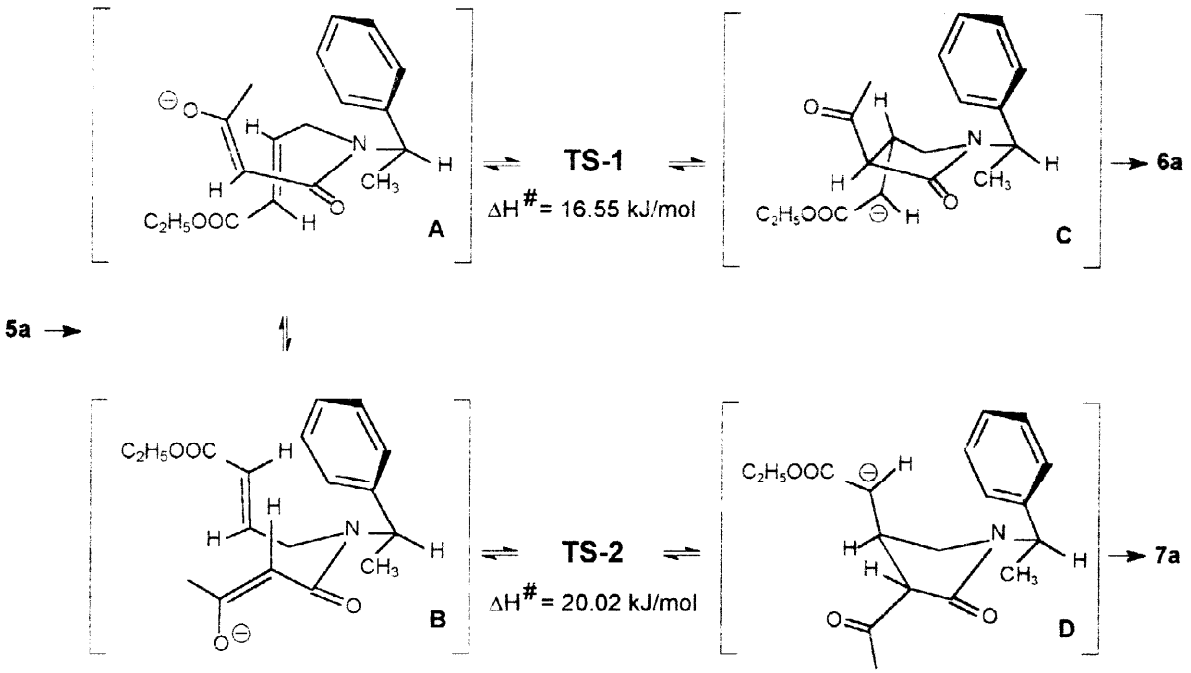


Figure 1. Selected n.O.e. for compounds **6a** and **7a**.

The reversal of the diastereofacial selection depending on the reaction conditions could be explained by inspection of the reaction course. First we calculated the energies for diastereomers **6a** and **7a**, and **7a** was found to be more stable by 3.59 kJ/mol.[13,14] From this value the expected products ratio for a thermodynamic process must be 10:90, in agreement with the observed results. Then we considered the rotamers **A** and **B** of the anion generated from **5a**, and we found that **B** is more stable than **A** by 2.05 kJ/mol.[13,14] In addition, the $\Delta H^{\#}$ values were calculated for transition states of the steps **A** → **C** and **B** → **D** (**TS-1** and **TS-2**), respectively, and the first process was found to be kinetically favoured, $\Delta\Delta H^{\#}$ between the two steps being 3.47 kJ/mol (Scheme 4).[15,16] In this case the products ratio must be 89:11, calculated on the basis of $\Delta\Delta H^{\#}$ of the steps **A** → **C** and **B** → **D**. Thus, both **A** and **B** give rise to the conjugate addition, leading to the anions **C** and **D**, respectively. However, when the cyclisation is carried out in THF by using NaH as the base, the conjugate addition is reversible, since a proton source is missing in the reaction mixture. Equilibration can take place and the major product of the cyclisation is **7a**, which has the lower energy.[17] On the contrary, when the reaction is carried out in ethanol by using sodium ethoxide as the base, the anions **C** and **D** cannot equilibrate. In fact, they immediately undergo protonation by the solvent and under these conditions the d.r. of the products **6a** and **7a** relies on both the rotameric distribution of the starting acyclic anions **A** and **B** and the $\Delta\Delta H^{\#}$ of the processes leading to **TS-1** and **TS-2** respectively. Thus, the major product is **6a**, which forms first though it has the higher energy and the reversal of the diastereoselection of the conjugate addition can be explained in terms of thermodynamic *versus* kinetic control. To support this hypothesis, an 85:15 mixture of **6a** and

7a was treated in dry THF at -78 °C in the presence of an excess of NaH (2 equiv) and a 25:75 d.r. **6a**:**7a** was obtained. Also, when **4a** and 2,2,6-trimethyl-4*H*-dioxin-4-one were refluxed in toluene, the pyrrolidin-2-one **6a** was the major product of the cyclisation. In this case the conjugate addition clearly proceeds under irreversible conditions, and the major product of the cyclisation, **6a**, is the same obtained by cyclisation of **5a** with EtONa in EtOH.

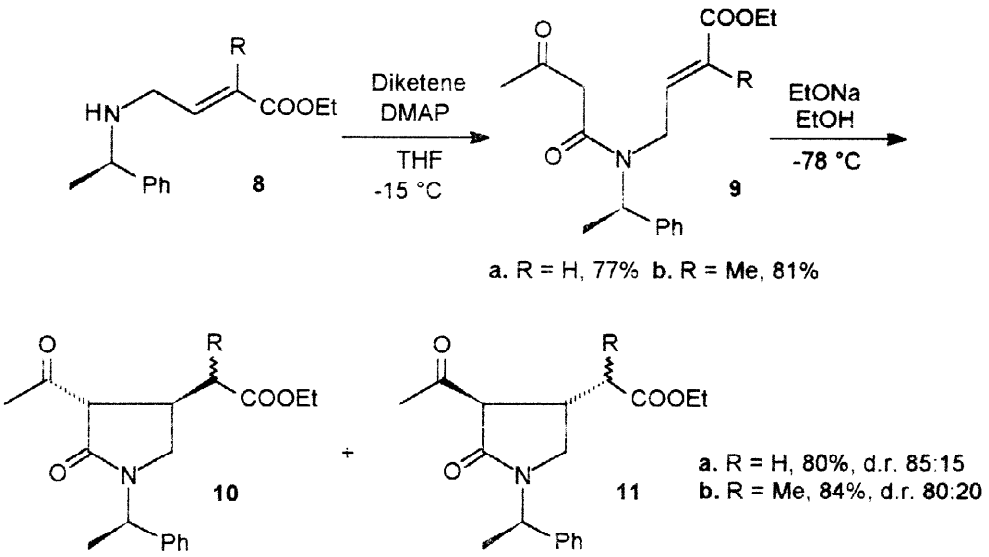


Scheme 5

Our goal, however, was to synthesize *trans*-3,4-disubstituted pyrrolidin-2-ones suitable to be converted into **1**. Since better d.r. were observed carrying out the cyclisation with sodium ethoxide in ethanol, we first prepared the amides **9a,b** which were then cyclised at -78 °C to give **10a**,**11a** and **10b**,**11b**, respectively. As before, both **10b** and **11b** were a mixture of epimers 70:30 at C-2 of the propanoate chain (Scheme 6).[12]

Conclusion

From the above results, we have shown that a stereodivergent synthesis of 3,4-disubstituted pyrrolidin-2-ones can be realised simply by changing the reaction conditions. Moreover, starting from the amides **9**, in which the configuration at C-1' is *R*, we obtained with the highest yield and d.r. the pyrrolidin-2-ones **10**, suitable for conversion into **1**. Work aimed at this goal is in progress in our laboratory,[18] and will be reported in due course.



Scheme 6

Experimental

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); mass spectra were obtained by electron impact at 70 eV. Flash chromatography was performed with silica gel 60 (230-400 mesh). THF was distilled from sodium benzophenone ketyl under argon before use. (*S*)- and (*R*)-1-Phenylethylamine were purchased from Aldrich. Compounds **4a** and **4d** were prepared according the reported procedures.[1]

(*E*,*S*)-*N*-(3-Ethoxycarbonyl-2-butenyl)-*N*-(1-phenylethyl)amine (4b). According the literature method,[1] compound **4b** was obtained in 80% yield as a yellow oil starting from ethyl (*E*)-4-bromo-2-methyl-2-butenoate and (*S*)-phenylethylamine. IR: 3340, 1715 cm^{-1}. ^1H NMR: 1.27 (t, 3H, J = 7.1), 1.36 (d, 3H, J = 6.6), 1.51 (br s, 1H, NH), 1.71 (s, 3H), 3.23 (d, 2H, J = 6.7), 3.79 (q, 1H, J = 6.6), 4.17 (q, 2H, J = 7.1), 6.77 (t, 1H, J = 6.7), 7.15-7.35 (m, 5 ArH). ^{13}C NMR: 13.1, 14.7, 24.8, 45.9, 58.4, 61.0, 127.1, 127.5, 129.0. 129.3, 140.6, 145.5, 168.3. $[\alpha]_D$

-52.5 (c 1, $CHCl_3$). GC-MS: *m/z* 247 (M^+), 232, 167, 115, 105, 91, 77. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84, H, 8.56, N, 5.66. Found: C, 72.79; H, 8.50; N, 5.63.

(*E,S*)-*N*-(3-Methoxycarbonyl-2-methyl-2-butenyl)-*N*-(1-phenylethyl)amine (4c). According the literature method,[1] the title compound was obtained in 83% yield as a colorless oil starting from methyl (*E*)-4-bromo-3-methyl-2-butenoate and (*S*)-phenylethylamine. IR: 3348, 1710 cm^{-1}. ^1H NMR: 1.35 (d, 3H, J = 6.9), 2.11 (s, 3H), 3.13 (s, 2H), 3.74 (q, 1H, J = 6.9), 3.81 (s, 3H), 5.93 (s, 1H), 7.18 - 7.35 (m, 5 ArH). ^{13}C NMR: 18.0, 25.0, 51.4, 55.4, 57.9, 115.1, 127.0, 127.5, 129.0, 145.7, 158.6, 167.7. $[\alpha]_D$ - 27.5 (c 1, $CHCl_3$). GC-MS: *m/z* 234 (MH^+), 218, 186, 158, 128, 113, 105, 77. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07, H, 8.21, N, 6.00. Found: C, 71.99; H, 8.19; N, 5.94.

(*E,R*)-*N*-(3-Ethoxycarbonyl-2-propenyl)-*N*-(1-phenylethyl)amine (8a). According to the literature method,[1] the title compound was obtained in 73% yield starting from ethyl (*E*)-4-bromo-2-butenoate and (*R*)-phenylethylamine. $[\alpha]_D$ 33.1 (c 1, $CHCl_3$). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.09; H, 8.18; N, 5.94.

(*E,R*)-*N*-(3-Ethoxycarbonyl-2-butenyl)-*N*-(1-phenylethyl)amine (8b). According to the literature method,[1] the title compound was prepared in 73% yield starting from ethyl (*E*)-4-bromo-2-methyl-2-butenoate and (*R*)-phenylethylamine. $[\alpha]_D$ 53.1 (c 1, $CHCl_3$). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84, H, 8.56, N, 5.66. Found: C, 72.78; H, 8.52; N, 5.62.

Preparation of 3-oxobutanamides (5a-c) and (9a-b). Method A. A solution containing **4a-c** or **8a-b** (20 mmol) and *N,N*-dimethylaminopyridine (0.3 g) in dry THF (70 ml) at -15 °C was slowly added to a solution containing diketene (1.8 g; 22 mmol) in dry THF (20 ml). After 1 h the solvent was removed under reduced pressure at 20 °C and the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 7:3) to give the amides **5a-c** or **9a-b** (rotameric mixtures) as colorless oils.

Preparation of 3-oxobutanamides (5b-c). Method B. A solution containing **4b-c** (20 mmol) and 2,2,6-trimethyl-4*H*-dioxin-4-one (3.2 g; 23 mmol) in toluene (100 ml) was refluxed for 1 h. After removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 7:3) to give the amides **5b-c** (rotameric mixtures) as colorless oils.[2b]

(*E,S*)-*N*-(3-Ethoxycarbonyl-2-propenyl)-*N*-(1-phenylethyl)-3-oxobutanamide (5a). Following Method A, the title compound was obtained in 77% yield starting from **4a**. IR:

1725, 1665 cm^{-1}. ^1H NMR: 1.24 (t, 3H, 40%, J = 7.1), 1.27 (t, 3H, 60%, J = 7.1), 1.50 (d, 3H, 60%, J = 6.9), 1.60 (d, 3H, 40%, J = 6.9), 2.28 (s, 3H, 60%), 2.31 (s, 3H, 40%), 3.48 - 3.94 (m, 2H), 3.50 (s, 2H, 60%), 3.71 (s, 2H, 40%), 4.14 (q, 2H, 40%, J = 7.1), 4.16 (q, 2H, 60%, J = 7.1), 5.05 (q, 1H, 40%, J = 6.9), 5.77 (ddd, 1H, J = 15.8, J = 1.7, J = 1.6), 6.08 (q, 1H, 60%, J = 6.9), 6.65 (dt, 1H, 60%, J = 15.8, J = 4.8), 6.73 (dt, 1H, 40%, J = 15.8, J = 4.8), 7.18 - 7.42 (m, 5 ArH). ^{13}C NMR: 14.7, 16.7 (40%), 17.1 (60%) 30.3 (40%), 30.9 (60%), 44.1 (40%), 45.2 (60%), 50.7 (60%), 51.9 (40%), 56.8 (60%), 60.8 (40%), 61.2 (60%), 61.9 (40%), 122.7 (40%), 123.1 (60%), 127.1 (60%), 127.3 (40%), 128.0 (60%), 128.3 (40%), 128.5 (40%), 129.2 (60%), 140.0 (40%), 140.3 (60%), 144.2 (40%), 144.6 (60%), 166.1 (60%), 166.5 (40%), 167.1 (40%), 167.8 (60%), 172.1 (40%), 172.7 (60%). $[\alpha]_D$ -111.9 (c 1, $CHCl_3$). GC-MS: *m/z* 317 (M^+), 302, 274, 260, 246, 230, 188, 166, 155, 132, 105, 91, 77. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.08; H, 7.18, N, 4.38.

(*E,S*)-*N*-(3-Ethoxycarbonyl-2-butenyl)-*N*-(1-phenylethyl)-3-oxobutanamide (5b). Starting from (*E,S*)-*N*-[3-ethoxycarbonyl-2-butenyl]-*N*-(1-phenylethyl)amine **4b**, the title compound was obtained in 77% yield following Method A and in 83% yield following Method B. IR: 1715, 1701, 1663, 1630 cm^{-1}. ^1H NMR: 1.22 (t, 3H, J = 7.2, 30%), 1.23 (t, 3H, J = 7.2, 70%), 1.49 (d, 3H, J = 7.0, 70%), 1.57 (d, 3H, J = 7.0, 30%), 1.66 (s, 3H, 70%), 1.92 (s, 3H, 30%), 2.25 (s, 3H, 70%), 2.28 (s, 3H, 30%), 3.46 (s, 2H, 70%), 3.55 - 3.84 (m, 2H), 3.68 (s, 2H, 30%), 4.10 (q, 2H, J = 7.2, 30%), 4.12 (q, 2H, J = 7.2, 70%), 5.05 (q, 1H, J = 7.2, 30%), 6.05 (q, 1H, J = 7.2, 70%), 6.29 (t, 1H, J = 6.0, 70%), 6.43 (t, 1H, J = 6.0, 30%), 7.15 - 7.41 (m, 5 ArH). ^{13}C NMR: 12.8 (30%), 12.9 (70%), 14.7 (70%), 16.8 (30%), 18.8 (30%), 22.6 (70%), 30.9, 41.6 (30%), 42.7 (70%), 50.7 (70%), 51.7 (30%), 56.6 (70%), 61.0 (30%), 61.2 (70%), 61.3 (30%), 127.2, 127.3, 127.5, 127.8, 128.0, 128.2, 128.4, 128.7, 129.0, 129.1, 129.3 (70%), 129.8 (30%), 138.6 (70%), 139.0 (30%), 140.0 (30%), 140.3 (70%), 167.1 (30%), 167.4 (70%), 176.3. $[\alpha]_D$ -93.1 (c 1, $CHCl_3$). GC-MS: *m/z* 331 (M^+), 316, 288, 230, 202, 180, 152, 126, 105, 77. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.81; H, 7.55; N, 4.18.

(*E,S*)-*N*-(3-Methoxycarbonyl-2-butenyl)-*N*-(1-phenylethyl)-3-oxobutanamide (5c). Starting from **4c**, the title compound was obtained in 78% yield following Method A and in 83% yield following Method B. IR: 1715, 1710, 1655, 1625 cm^{-1}. ^1H NMR: 1.47 (d, 3H, J = 7.0, 60%), 1.58 (d, 3H, J = 7.0, 40%), 1.93 (s, 3H, 40%), 2.00 (s, 3H, 60%), 2.06 (s, 3H, 40%), 2.28 (s, 3H, 60%), 3.30 - 3.75 (m, 4H), 3.64 (s, 3H, 40%), 3.68 (s, 3H, 60%), 4.78 (s, 1H, 40%), 5.05 (q, 1H, J = 7.0, 40%), 5.69 (s, 1H, 60%), 6.06 (q, 1H, J = 7.0, 60%), 7.16 - 7.44 (m, 5 ArH). ^{13}C NMR: 17.1 (60%), 17.2 (40%), 19.1 (60%), 22.6 (40%), 27.4, 30.9 (40%), 31.0 (60%), 50.9 (60%), 51.1 (40%), 51.7 (40%), 52.2 (60%),57.1, 114.9 (40%), 115.6 (60%), 126.9 (40%), 127.9 (60%), 128.1, 128.2, 128.5 (60%), 129.1 (60%), 129.3 (40%), 129.4 (40%),

140.4, 154.9 (40%), 155.0 (60%), 166.8 (60%), 166.9 (40%), 167.3 (40%), 168.3 (60%) 205.2. $[\alpha]_D$ -121.5 (c 1, $CHCl_3$). GC-MS: *m/z* 317 (M^+), 302, 274, 244, 233, 201, 174, 140, 133, 105, 98, 77. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.09; H, 7.25; N, 4.38.

Preparation of (*E,S*)-N-(3-ethoxycarbonyl-2-propenyl)-*N*-(1-phenylethyl)methoxycarbonylacetamide (5d). Method C. To a suspension of potassium monomethyl malonate (4.7 g; 30 mmol) in dichloromethane (50 ml) pivaloyl chloride (3.6 g; 30 mmol) was added at 20 °C and the mixture was stirred for 1 h. Then a solution containing the amine **4a** (7.0 g; 30 mmol) in dichloromethane (30 ml) was added at 20 °C and stirred for 3 h. Water (50 ml) was added and the mixture was extracted with ethyl acetate (3 x 150 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 70:30) to give the amide **5d** in 87% yield as colorless oil.

(*E,R*)-*N*-(3-Ethoxycarbonyl-2-propenyl)-*N*-(1-phenylethyl)-3-oxobutanamide (9a). Following Method A, the title compound was obtained in 77% yield as a colorless oil starting from **8a**. $[\alpha]_D$ 112.3 (c 1, $CHCl_3$). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.06; H, 7.22, N, 4.37.

(*E,R*)-*N*-(3-Ethoxycarbonyl-2-butenyl)-*N*-(1-phenylethyl)-3-oxobutanamide (9b). Following Method A, the title compound was obtained in 81% yield as a colorless oil starting from **8b**. $[\alpha]_D$ 93.6 (c 1, $CHCl_3$). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.83; H, 7.56; N, 4.33.

Ethyl (3*S*,4*R*,1'*S*)-[3-acetyl-2-oxo-1-(1'-phenylethyl)pyrrolidin-4-yl]acetate (6a) and its isomer (3*R*,4S,1'S) (7a). A solution containing **5a** (2.4 g; 10 mmol) and 2,2,6-trimethyl-4*H*-dioxin-4-one (1.6 g; 12 mmol) in toluene (50 ml) was refluxed for 3 h. Then the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography, to give **6a** and **7a** in 80% overall yield and 70:30 d.r. **Isomer (3*R*,4*S*,1'*S*)-6a**: 56% yield. IR: 1735, 1668 cm^{-1}. ^1H NMR: 1.19 (t, 3H, J = 6.5), 1.52 (d, 3H, J = 7.1), 2.23 (dd, 1H, J = 16.2, J = 8.4), 2.35 (dd, 1H, J = 16.2, J = 7.2), 2.44 (s, 3H), 2.58 (dd, 1H, H_A, J_{AB} = 9.7, J_{AX} = 6.1), 3.14 (m, 1H, H_X), 3.39 (d, 1H, H_Y, J = 7.2), 3.58 (dd, 1H, H_B, J_{AB} = 9.7, J_{BX} = 8.1), 4.06 (q, 2H, J = 6.5), 5.45 (q, 1H, J = 7.1), 7.21 - 7.42 (m, 5 ArH). ^{13}C NMR: 14.6, 16.6, 30.2, 30.8, 38.0, 46.5, 50.1, 61.2, 62.1, 127.6, 128.2, 129.1, 140.0, 168.9, 171.7. $[\alpha]_D$ -106.3 (c 1, $CHCl_3$). GC-MS: *m/z* 317 (M^+), 302, 274, 272, 230, 214, 188, 166, 132, 105, 91, 77. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.07; H, 7.27; N, 4.37. **Isomer (3*S*,4*R*,1'*S*)-**

7a: 24% yield. IR: 1735, 1670 cm^{-1}. ^{1}NMR: 1.23 (t, 3H, J = 6.5), 1.54 (d, 3H, J = 7.2), 2.38 (dd, 1H, J = 8.5, J = 2.8), 2.45 (s, 3H), 2.47 (dd, 1H, J = 8.5, J = 2.2), 2.95 (dd, 1H, H_A, J_{AB} = 8.8, J_{AX} = 6.3), 3.07 (m, 1H, H_X), 3.25 (dd, 1H, H_B, J_{AB} = 8.8, J_{BX} = 7.5), 3.46 (d, 1H, H_Y, J_{XY} = 7.4), 5.42 (q, 1H, J = 7.2), 7.22 - 7.41 (m, 5 ArH). ^{13}C NMR: 14.6, 16.7, 30.3, 30.8, 38.1, 46.5, 50.0, 61.2, 61.9, 127.3, 128.1, 129.1, 139.9, 169.0, 171.7. $[\alpha]_D$ -129.4 (c 1, $CHCl_3$). GC-MS: *m/z* 317 (M^+), 302, 274, 272, 230, 214, 188, 166, 132, 105, 91, 77. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.09; H, 7.33; N, 4.43.

Cyclisation of the 3-Oxobutanamides (5a-d) with NaH in THF (Method A). General Procedure. A solution containing amides **5a**, **5b**, or **5d** (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 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 **6a, 6b, 6d** and **7a, 7b, 7d** as colorless oils.

Ethyl (3*R*,4*S*,1'*S*)-[3-acetyl-2-oxo-1-(1'-phenylethyl)pyrrolidin-4-yl]acetate (6a) and its isomer (3*S*,4*R*,1'*S*) (7a). Following the cyclisation method A and starting from **5a**, the compounds **6a** and **7a** were obtained in 77% overall yield as colorless oils. D.r. **(3*R*,4*S*,1'*S*)-6a**:**(3*S*,4*R*,1'*S*)-7a** 28:72. **Isomer (3*R*,4*S*,1'*S*)-6a**: 23% yield. $[\alpha]_D$ -106.5 (c 1, $CHCl_3$). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.14; H, 7.25; N, 4.46. **Isomer (3*S*,4*R*,1'*S*)-7a**: 54% yield. $[\alpha]_D$ -129.2 (c 1, $CHCl_3$). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.16; H, 7.27; N, 4.45.

Ethyl (2*RS*,3'*R*,4'*S*,1''*S*)-2-[3'-acetyl-2'-oxo-1'-(1''-phenylethyl)pyrrolidin-4'-yl]propanoate (6b) and its isomer (2*RS*,3'*S*,4'*R*,1''*S*) (7b). Following the cyclisation method A and starting from **5b** the diastereomers **6b** and **7b** were obtained in 76% overall yield as colorless oils. D.r. **(2*RS*,3'*R*,4'*S*,1''*S*)-6b**:**(2*RS*,3'*S*,4'*R*,1''*S*)-7b** 30:70. (2*RS*) ratio (unassigned): 70:30. IR: 1725, 1710, 1668 cm^{-1}. **Isomer (2*RS*,3'*R*,4'*S*,1''*S*)-6b**: 23% yield. ^{1}H NMR: 1.09 (d, 3H, 70%, J = 7.1), 1.10 (d, 3H, 30%, J = 7.0), 1.22 (t, 3H, 70%, J = 7.1), 1.23 (t, 3H, 30%, J = 7.1), 1.51 (d, 3H, 70%, J = 7.1), 1.52 (d, 3H, 30%, J = 7.1), 2.38 - 2.52 (m, 1H), 2.42 (s, 3H, 30%), 2.44 (s, 3H; 70%), 2.90 - 3.19 (m, 3H, H_A + H_B + H_X), 3.56 (d, 1H, H_Y, 30%, J = 7.2), 3.61 (d, 1H, H_Y, 70%, J = 7.2), 4.06 (q, 2H, 30%, J = 7.1), 4.07 (q, 2H, 70%, J = 7.2), 5.40 (q, 1H, 30%, J = 7.1), 5.41 (q, 1H, 70%, J = 7.1), 7.15 - 7.38 (m, 5 ArH). ^{13}C NMR: 14.6 (70%), 14.7 (30%), 14.9 (70%), 15.2 (30%), 16.6, 30.9 (30%), 31.0 (70%), 35.6 (30%), 36.1 (70%), 42.4 (30%), 43.0 (70%), 44.5 (30%), 44.8 (70%), 49.9 (70%), 50.0 (30%), 60.2 (30%), 60.5 (70%), 61.2

(30%), 61.3 (70%), 127.3, 128.1, 129.1, 139.9, 169.2 (30%), 169.3 (70%), 174.7, 203.7 (30%), 203.8 (70%). GC-MS: *m/z* 331 (M^+), 318, 302, 274, 230, 202, 133, 126, 120, 105, 91, 77. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.83; H, 7.57; N, 4.20. **Isomer (2*RS*,3'*S*,4'*R*,1''*S*)-7b**: 53% yield. ^1H NMR: 0.97 (d, 3H, J = 7.0), 1.13 (t, 3H, 70%, J = 7.1), 1.15 (t, 3H, 30%, J = 7.1), 1.48 (d, 3H, 70%, J = 7.2), 1.49 (d, 3H, 30%, J = 7.2), 2.34 (dq, 1H, J = 7.1, J = 7.5), 2.42 (s, 3H, 30%), 2.45 (s, 3H, 70%), 2.63 (dd, 1H, H_A, 70%, J_{AX} = 6.3, J_{AB} = 9.9), 2.64 (dd, 1H, H_A, 30%, J_{AX} = 6.8, J_{AB} = 9.8), 2.87 - 3.20 (m, 1H, H_X), 3.43 (dd, 1H, H_B, 30%, J = 8.6, J = 9.8), 4.34 (dd, 1H, H_B, 30%, J_{BX} = 8.6, J_{AB} = 9.7), 3.47 (dd, 1H, H_B, 70%, J_{BX} = 8.8, J_{AB} = 9.8), 3.51 (d, 1H, H_Y, 70%, J = 7.2), 3.55 (d, 1H, H_Y, 30%, J = 7.2), 3.98 (q, 2H, 30%, J = 7.1), 4.00 (q, 2H, 70%, J = 7.1), 5.41 (q, 1H, 70%, J = 7.2), 5.42 (q, 1H, J = 7.2), 7.19 - 7.38 (m, 5 ArH). ^{13}C NMR: 14.6, 14.8 (30%), 14.9 (70%), 16.6, 31.0, 35.4 (70%), 36.0 (30%), 42.5 (70%), 42.8 (30%), 44.5 (30%), 44.9 (70%), 50.1 (30%), 50.2 (70%), 60.0 (70%), 60.7 (30%), 61.1 (30%), 61.2 (70%), 127.6, 128.2, 129.1, 139.9, 168.9 (70%), 169.2 (30%), 174.7, 203.7. GC-MS: *m/z* 331 (M^+), 318, 302, 274, 230, 202, 133, 126, 120, 105, 91, 77. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.79; H, 7.55; N, 4.19.

Ethyl (3*S*,4*S*,1'*S*)-3-[3-methoxycarbonyl-2-oxo-1-(1'-phenylethyl)pyrrolidin-4-yl]acetate (6d) and its (3*R*,4*R*,1'*S*)-isomer (7d). Following the cyclisation method A and starting from **5d** the diastereomers **6d** and **7d** were obtained in 80% overall yield as colorless oils. D.r. **(3*S*,4*S*,1'*S*)-6d** : **(3*R*,4*R*,1'*S*)-7d** 20:80. **Isomer (3*S*,4*S*,1'*S*)-6d**: 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), 3.23 - 3.32 (m, 2H), 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: *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, 64.88; H, 6.93; N, 4.24. **Isomer (3*R*,4*R*,1'*S*)-7d**: 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, J = 6.4, J = 9.6), 2.91 - 3.14 (m, 1H), 3.19 (d, 1H, J = 7.7), 3.66 (dd, 1H, J = 8.9, J = 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: *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, 64.87; H, 6.91; N, 4.23.

Cyclisation of the amides (5a,b,d) and (9a,b) with sodium ethoxide in ethanol (Method B). General Procedure. To a solution containing the amide **5a-c** and **9a,b** (20 mmol) in dry ethanol (30 ml) was slowly added at -78° a solution containing sodium ethoxide [20 mmol;

prepared by dissolving Na (480 mg; 20 mmol) in dry ethanol (20 ml)]. After 1 h solid NH_4Cl (5.0 g) was added and the temperature raised to 20 °C. After addition of water (50 ml), the mixture was extracted with ethyl acetate (3 x 100 ml) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography, to give the pyrrolidin-2-ones **6a**, **6b** and **6d**, **7a, 7b** and **7d**, **10a,b** and **11a,b** as colorless oils.

Ethyl (3*R*,4*S*,1'*S*)-[3-acetyl-2-oxo-1-(1'-phenylethyl)pyrrolidin-4-yl]acetate (6a) and its isomer (3*S*,4*R*,1'*S*) (7a). Following the cyclisation Method B and starting from **5a** the compounds **6a** and **7a** were obtained in 84% overall yield as colorless oils. D.r. **(3*R*,4*S*,1'*S*)-6a**:**(3*S*,4*R*,1'*S*)-7a** 85:15. **Isomer (3*R*,4*S*,1'*S*)-6a**: 71% yield. $[\alpha]_D$ -106.7 (c 1, $CHCl_3$). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.08; H, 7.34; N, 4.37. **Isomer (3*S*,4*R*,1'*S*)-7a**: 13% yield. $[\alpha]_D$ -129.2 (c 1, $CHCl_3$). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.15; H, 7.27; N, 4.43.

Ethyl (2*RS*,3'*R*,4'*S*,1''*S*)-2-[3'-acetyl-2'-oxo-1'-(1''-phenylethyl)pyrrolidin-4'-yl]propanoate (6b) and its isomer (2*RS*,3'*S*,4'*R*,1''*S*) (7b). Following the cyclisation Method B and starting from **5b** the compounds **6b** and **7b** were obtained in 82% overall yield as colorless oils. D.r. **(2*RS*,3'*R*,4'*S*,1''*S*)-6b : (2*RS*,3'*S*,4'*R*,1''*S*)-7b** 84:16. **Isomer (2*RS*,3'*R*,4'*S*,1''*S*)-6b:** 69% yield. GC-MS: *m/z* 331 (M^+), 318, 302, 274, 230, 202, 133, 126, 120, 105, 91, 77. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.80 H, 7.54; N, 4.18. **Isomer (2*RS*,3'*S*,4'*R*,1''*S*)-7b:** 13% yield. GC-MS: *m/z* 331 (M^+), 318, 302, 274, 230, 202, 133, 126, 120, 105, 91, 77 Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.82: H, 7.55; N, 4.22.

Ethyl (3*S*,4*S*,1'*S*)-3-[3-methoxycarbonyl-2-oxo-1-(1'-phenylethyl)pyrrolidin-4-yl]acetate (6d) and its (3*R*,4*R*,1'*S*)-isomer (7d). Following the cyclisation Method B and starting from **5d** the diastereomers **6d** and **7d** were obtained in 80% overall yield as colorless oils. D.r. 70:30. **Isomer (3*S*,4*S*,1'*S*)-6d**: 56% yield. $[\alpha]_D$ -129.7 (c 1, $CHCl_3$). GC-MS: 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, 6.97; N, 4.18. **Isomer (3*R*,4*R*,1'*S*)-7d**: 24% yield. $[\alpha]_D$ -87.1 (c 0.5, $CHCl_3$). GC-MS: *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, 64.87; H, 6.91; N, 4.23.

Ethyl (3*S*,4*R*,1'*R*)-[3-acetyl-2-oxo-1-(1'-phenylethyl)pyrrolidin-4-yl]acetate (10a) and its isomer (3*R*,4*S*,1'*R*) (11a). Following the cyclisation Method B and starting from **9a** the compounds **10a** and **11a** were obtained as colorless oils, in 80% overall yield. D.r. **(3*S*,4*R*,1'*R*)-10a** : **(3*R*,4*S*,1'*R*)-11a** 85:15. **Isomer (3*S*,4*R*,1'*R*)-10a**: 68% yield. $[\alpha]_D$ 107.2 (c 1, $CHCl_3$).

GC-MS: *m/z* 317 (M^+), 302, 274, 272, 230, 214, 188, 166, 132, 105, 91, 77. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.09; H, 7.32; N, 4.42. **Isomer (3*R*,4*S*,1'*R*)-11a:** $[\alpha]_D$ 130.6 (c 1, $CHCl_3$). GC-MS: *m/z* 317 (M^+), 302, 274, 272, 230, 214, 188, 166, 132, 105, 91, 77. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.06; H, 7.26; N, 4.37.

Ethyl (2*RS*,3'*S*,4'*R*,1"*R*)-2-[3'-acetyl-2'-oxo-1'-(1"-phenylethyl)pyrrolidin-4'-yl]propanoate (10b) and its isomer (2*RS*,3'*R*,4'*S*,1"*R*) (11b). Following the cyclisation Method B and starting from **9b**, the compounds **10b** and **11b** were obtained in 80% overall yield. D.r. **(2*RS*,3'*S*,4'*R*,1"*R*)-10b** : **(2*RS*,3'*R*,4'*S*,1"*R*)-11b** 85:15. **Isomer (2*RS*,3'*S*,4'*R*,1"*R*)-10b:** 68% yield. GC-MS: *m/z* 331 (M^+), 318, 302, 274, 230, 202, 133, 126, 120, 105, 91, 77. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.88: H, 7.64; N, 4.26. **Isomer (2*RS*,3'*R*,4'*S*,1"*R*)-11b**: 12% yield. GC-MS: *m/z* 331 (M^+), 318, 302, 274, 230, 202, 133, 126, 120, 105, 91, 77. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.82: H, 7.55; N, 4.22.

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13. The search for the low energy conformations was run using BATCHMIN program implemented in MacroModel, software package Version 5.5 and MM2* force field. All the calculations were carried out on a Silicon Graphics Indigo 2 R10000 workstation. a) 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. b) Allinger, N.L. *J. Am. Chem. Soc.*, **1977**, *99*, 8127-8134, and subsequent versions, e.g. MM2-87, MM2-89, MM2-91. c) Lii, J.; Gallion, S.; Bender, C.; Wikstrom, H.; Allinger, N.L.; Flurchick, K.M.; Teeter, M.M. *J. Comput. Chem.*, **1989**, *10*, 503-511.
14. The relative energies of the two diastereomers were calculated by using the AM1 Hamiltonian. As references see: Dewar, M.J.S.; Zoebisch, E.G. Healy, E.F.; Stewart, J.J.P. *J. Am. Chem. Soc.*, **1985**, *107*, 3902-3909. The program is enclosed in Hyperchem package, release 5.01, available from Hypercube, Gainesville, Florida, U.S.A.
15. The reversibility of the conjugate addition allows for the formation of the lower energy product. See, for example: Chan, S.; Braish, T.F. *Tetrahedron*, **1994**, *50*, 9943-9950.
16. The functionalisation at C-5 of the pyrrolidin-2-one ring is currently studied: a) Murahashi, S.I.; Naota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.*, **1990**, *112*, 7820-7822. b) Cainelli, G.; Da Col, M.; Galletti, P.; Giacomini, D. *Synlett*, **1997**, 923-924.
17. The quadratic synchronous transit method (QST) was employed, which searches for a maximum along a parabola connecting reactants and products, and for a minimum in all directions perpendicular to the parabola. Stationary points on the potential energy surface (PES) were localised by minimising the energy gradient and evaluation of the transition states was achieved from the Hessian matrix. The nature of these stationary points was established by analytical calculations and diagonalisation of the matrix of the energy second derivatives, in order to identify the unique imaginay frequence. The normal mode analysis allowed to determine the normal mode of vibration corresponding to the coordinate of reaction, which consists in a synchronous motion of the two reaction centres. The frequency values are, for **TS-1** and for **TS-2**, -312.0 cm^{-1} and -354.46 cm^{-1}, respectively.
18. Peng, C.; Schlegel, H.B. *Isr. J. Chem.*, **1993**, *33*, 449-454.