Pergamon

Tetrahedron, Vol. 52, No. 3, pp. 1069-1084, 1996

0040-4020/96 $15.00 + 0.00

0040-4020(95)00939-6

A Convenient Approach to Diastereomerically Pure 1,3,4-Trisubstituted Pyrrolidin-2-ones by Intramolecular Cyclisation of *N*-(2-Alken-1-yl)amides Mediated by Mn(III). An Entry to Both (*R*)- and (*S*)-3-Pyrrolidineacetic Acid

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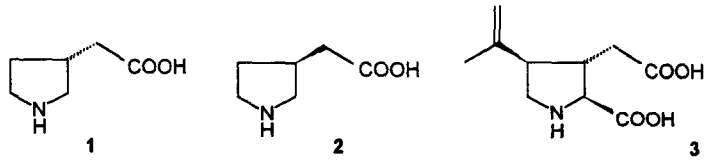
Abstract: The oxidative cyclisation of a series of either (*S*)-*N*-(2-alken-1-yl)-*N*-(1-phenyleth-1-yl)-acetoacetamides **5a-d** and methoxycarbonylacetamides **6a-b**, performed by using $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OAc)_2 \cdot H_2O$ in acetic acid, has been examined. The reaction proceeds regioselectively through a 5-*exo*-mode, leading to 1,3,4-trisubstituted pyrrolidin-2-ones **7a-d**,**8a-d** and **9a-b**,**10a-b** as diastereomeric mixtures in about 2:1 ratio, which are easily separated by silica gel chromatography. The configuration of the pure diastereomers is assigned from ^1H NMR data and confirmed by NOE experiments. The observed asymmetric induction has been explained on the basis of molecular mechanics calculations. This cyclisation constitutes a useful tool for the synthesis of biologically active amino acids containing the pyrrolidine ring in both enantiomerically pure forms, such as (*R*)- and (*S*)-3-pyrrolidineacetic acid, **1** and **2**.

A number of synthetic studies was recently directed towards new approaches to the enantiomerically pure forms of non-proteinogenic amino acids containing the pyrrolidine ring, such as (*S*)- and (*R*)-3-pyrrolidineacetic acid, **1** and **2**, which deserve attention as inhibitors of synaptosomal γ-aminobutyric acid (GABA) uptake. [1] In fact GABA is an inhibitory neurotransmitter and diminished levels can lead to the development of certain neurological and psychiatric disorders. [2] Stimulation of GABA receptors, inhibition of GABA uptake or inactivation of GABA transaminase, the enzyme responsible for GABA biodegradation, can be used as a means for treating such diseases. [3] Moreover the pyrrolidine ring constitutes the distinctive feature of kainoids, a class of non-proteinogenic amino acids with potent neuroexcitatory properties, such as (+)-*allo*-kainic acid **3**. [4]



1 **2** **3**

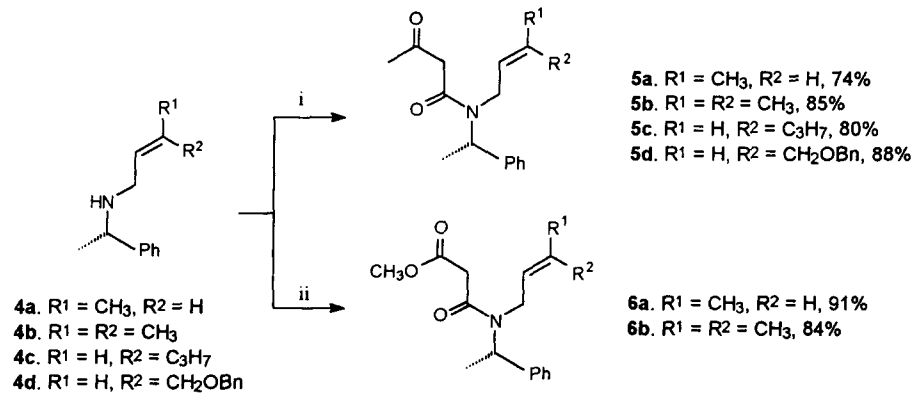
A previous report from this laboratory described the radical initiated cyclisation of (*S*)-*N*-(2-alken-1-yl)-*N*-(1-phenyleth-1-yl)iodoacetamides to give diastereomeric mixtures of 4-substituted pyrrolidin-2-ones, which after separation could be easily converted into 3-substituted pyrrolidines. [5] As a subsequent development in this area, we devised to obtain pyrrolidin-2-ones bearing at either C-3 or C-4 chains susceptible of further

transformations by intramolecular cyclisation mediated by Mn(III) [6] of *N*-(2-alken-1-yl)-*N*-(1-phenyleth-1-yl)acetoacetamides and methoxycarbonylacetamides. The intramolecular cyclisation of unsaturated β-oxoesters mediated by Mn(III) constitutes a powerful method for the construction of cyclic compounds starting from acyclic precursors and modifications of this procedure exploiting chiral auxiliaries are a subject of current interest in synthetic organic chemistry. [7,8] However, the cyclisation was generally performed with either 2-substituted acetoacetates [6] or acetoacetamides, [8] in order to minimize the formation of overoxidation products, and no examples concern the cyclisation of amides derived from the (*S*)-phenylethylamine as the chiral auxiliary.

Therefore *trans*-3,4-disubstituted pyrrolidin-2-ones containing the (*S*)-phenylethylamine moiety were prepared in high diastereomeric purity and we wish to report here the results obtained and the structural assignment of the products, together with a discussion on the stereochemical features of the reaction.

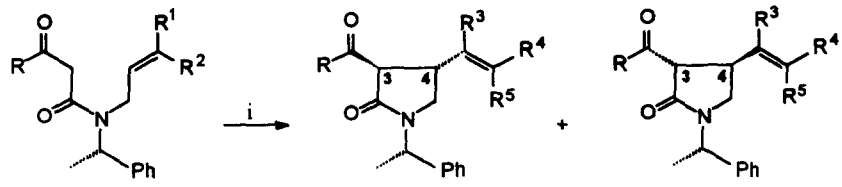
RESULTS AND DISCUSSION

The preparation of *N*-(2-alken-1-yl)acetoacetamides **5a-d** and methoxycarbonylacetamides **6a-b** is outlined in Scheme 1. (*S*)-Phenylethylamine reacted with the appropriate allylic halides or methanesulphonates to give the secondary amines **4a-d**. [5] Subsequent treatment of **4a-d** with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one in refluxing toluene afforded in good yield the acetoacetamides **5a-d**. On the other hand, by reaction of **4a-b** with methyl malonyl chloride the corresponding methoxycarbonylacetamides **6a-b** were obtained. All the amides were obtained as rotameric mixtures, as evidenced by their ^1H and ^{13}C NMR spectra.



Scheme 1. ***Reagents and conditions:*** **i.** 2,6,6-Trimethyl-4*H*-1,3-dioxin-4-one, refluxing toluene, 1 h. **ii.** Methyl malonyl chloride, Et_3N, DMAP, ethyl acetate, 0 °C, 1 h.

The oxidative cyclisation of the amides **5a-d** and **6a-b** was carried out by treating with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv. of $Cu(OAc)_2 \cdot H_2O$ in acetic acid for 6 h at room temperature. The reaction proceeded with total regioselection through a 5-*exo* closure, affording in moderate to good yields diastereomeric mixtures of pyrrolidin-2-ones **7a-d**,**8a-d**, and **9a-b**,**10a-b**. [9,10]



R = R¹ = CH_3, R^2 = H, **5a**

R = R¹ = R^2 = CH_3, **5b**

R = CH_3, R¹ = H, R^2 = n-C_3H_7, **5c**

R = CH_3, R¹ = H, R^2 = CH_2OCH_2Ph, **5d**

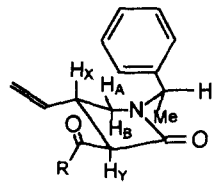
R = CH_3O, R¹ = CH_3, R^2 = H, **6a**

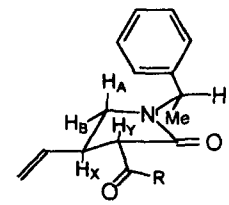
R = CH_3O, R¹ = R^2 = CH_3, **6b**

R = CH_3, R^3 = R^4 = R^5 = H
7a+8a, 70%, d.r. 68:32
R = R^3 = CH_3, R^4 = R^5 = H
7b+8b, 68%, d.r. 67:33
R = CH_3, = R^3 = R^5 = H, R^4 = C_2H_5
7c+8c, 52%, d.r. 68:32
R = CH_3,= R^3 =R^4 = H, R^5 = OCH_2Ph
7d+8d, 46%, d.r. 68:32
R = CH_3O, R^3 = R^4 = R^5 = H
9a+10a, 53%, d.r. 70:30
R = CH_3O, R^3 = CH_3, R^4 = R^5 = H
9b+10b, 49%, d.r. 68:32

Scheme 2. ***Reagents and conditions:*** **i.** $Mn(OAc)_3 \cdot 2H_2O$ (2 equiv), $Cu(OAc)_2 \cdot H_2O$ (1 equiv), AcOH, r.t.

While the diastereoselectivity of the cyclisation was moderate and varied only slightly depending on the alkyl chain at C-4 (Scheme 2), the diastereomeric products were readily separated by silica gel chromatography and were obtained in optically pure form, suitable for use in a variety of asymmetric syntheses. [11] The stereochemical assignment of these compounds was developed by means of ^1H NMR spectroscopy and difference NOE experiments.





R = CH_3, **7a**

H-C(1')-N-C(2)-O = -3.7°
H_A-C(5)-C(4)-H_X = -34.8°
H_B-C(5)-C(4)-H_X = -159.0°
H_X-C(4)-C(3)-H_Y = 160.0°

R = CH_3, **8a**

H-C(1')-N-C(2)-O = -2.1°
H_A-C(5)-C(4)-H_X = 159.6°
H_B-C(5)-C(4)-H_X = 35.8°
H_X-C(4)-C(3)-H_Y = -161.8°

R = OCH_3, **9a**

H-C(1')-N-C(2)-O = -2.0°
H_A-C(5)-C(4)-H_X = -34.6°
H_B-C(5)-C(4)-H_X = -158.7°
H_X-C(4)-C(3)-H_Y = 159.2°

R = OCH_3, **10a**

H-C(1')-N-C(2)-O = -2.0°
H_A-C(5)-C(4)-H_X = 159.7°
H_B-C(5)-C(4)-H_X = 35.9°
H_X-C(4)-C(3)-H_Y = -160.5°

Figure 1. Preferential conformations and selected dihedral angles for **(7a)**, **(8a)**, **(9a)** and **(10a)** determined by molecular mechanics calculations (MM+).

Table 1. Selected chemical shift and coupling constant (J) values for diastereomers **(7a-d)**, **(8a-d)**, **(9a-b)** and **(10a-b)**.

Compound	δH_A	δH_B	J_{AX}	J_{BX}	J_{XY}
7a	3.15	3.03	7.8	7.2	8.1
7b	3.15	3.07	7.7	7.1	7.4
7c	3.12	2.98	7.9	7.5	8.3
7d	3.19	2.98	8.1	7.0	8.1
9a	3.05	3.18	9.5	6.3	8.5
9b	3.20	3.20	- [a]	- [a]	8.2
8a	2.71	3.45 [b]	5.1	- [b]	- [b]
8b	2.74	3.44 [b]	4.9	- [b]	- [b]
8c	2.66	3.39 [b]	6.1	- [b]	- [b]
8d	2.64	3.50	6.5	8.2	7.5
10a	2.71	3.52	7.5	8.1	- [c]
10b	2.74	3.52	6.9	8.0	8.4

[a] H_A, H_B and H_X have similar chemical shift value and only a complex multiplet is observed.
[b] H_B, H_X and H_Y have similar chemical shift value, and only a complex multiplet is observed.
[c] H_X and H_Y have similar chemical shift value and only a complex multiplet is observed.

First the preferred conformation of the diastereomers **7a**,**8a** and **9a**,**10a** was calculated by using MM+ force field, [12] and it appeared that the C-H bond is almost coplanar with the carbonyl group, so that the phenyl group of the phenylethylamine moiety lies above the plane of the heterocyclic ring (Figure 1).

As a consequence, the chemical shifts of H_A and H_B resulted to be diagnostic for assignment of the configuration at C-4 (Table 1). In fact, when a *cis*-relationship occurs between H_B and the substituent at C-4, both H_A and H_B experience a shielding effect by the phenyl group and the substituent at C-4, respectively, and their chemical shift values are similar. In this case the signals were assigned to H_A or H_B on comparison of the coupling constants values (J_{AX} and J_{BX}), since the *cis*-coupling constant is always greater than the *trans*-one, in five membered rings (isomers **7** and **9**). By contrast, H_A is always more shielded than H_B when H_B and the chain at C-4 are *trans* each other, owing to the combined shielding effects of the phenyl and the alkyl group at C-4 (isomers **8** ad **10**). [13]

The configurational assignment of the stereogenic centre at C-4 was eventually confirmed by difference NOE experiments performed on **7a** and **8a**. In fact, on irradiation at the vinyl proton H_Z in the chain of **7a**, a large NOE enhancement of H_B occurred, indicating the *cis*-relationship between H_B and the substituent at C-4, whereas a small enhancement was observed for H_A, thus confirming the configurational assignment of C-4 (Figure 2). The inverted trend was observed for **8a**, in which a NOE effect was observed between H_A and the vinyl proton H_Z in the chain, so that also for **8a** the configurational assignment of C-4 was confirmed. Analogous results were observed for **9a** and **10a**.

In order to assign the configuration at C-3, the relationship between the substituents at C-3 and C-4 was determined on the basis of the value of the coupling constant J_{XY}.

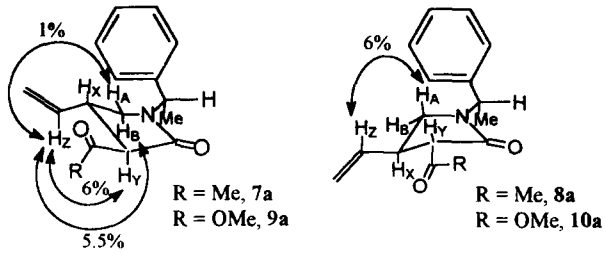


Figure 2. Selected difference NOE experiments.

The observed value (about 8 Hz) suggested a *trans*-relationship, and this result was confirmed by difference NOE experiments. In fact, on irradiation of H_Y in **7a** and **9a**, a large NOE enhancement was observed for the vinylic proton H_Z, and vice-versa, thus indicating a *cis*-relationship between H_Y and the substituent at C-4. As a consequence, both C-3 and C-4 configurations were established.

Moreover, the formation of the double bond in the chain at C-4 proceeds with total stereoselection. In fact, even starting from the (*Z*)-amide **5c**, only the diastereomers **7c** and **8c** with (*E*)-configuration at the double bond were observed, as proven by the coupling constant value (J = 15.2 Hz). On the contrary, when the benzyl enol ethers **7d** and **8d** were prepared starting from **5d**, the double bond configuration resulted to be *Z*, as determined from the value of the coupling constant of the vinylic protons (J = 6.2 Hz) and difference NOE experiments, although a rationale for this behaviour is hard to find.

Eventually, in order to explain the significant level of diastereofacial control achieved in this reaction (d.r. about 2:1), we first examined the molar fractions obtained from MM+ calculations. In fact, from the steric energy of diastereomers **7a,8a** (ΔE = 0.53 kcal/mol) and **9a,10a** (ΔE = 0.54 kcal/mol), respectively, a 0.71:0.29 ratio was calculated at 298 K, in good agreement with experimental findings. [14]

Then, since molecular mechanics calculations and transition state models resulted useful for stereochemical analysis, [15] we constructed transition state models for the cyclisation reaction mediated by Mn(III) by using the MM+ force field. In fact the rate-determining step of the cyclisation is believed to be the formation of a Mn(III) enolate which rapidly converts into a carbon-centered radical [16] and the subsequent 5-*exo* cyclisation can proceed through a chair-like transition structure, with attack to either the *si*-face (**TS-1**) or the *re*-face (**TS-2**) of the double bond.

Thus we examined the modes of attack of the radical to the double bond (Figure 3) and by molecular mechanics calculations we obtained the steric energies for each transition states **TS'-1(A,B)**, **TS''-1(A,B)**, **TS'-2(A,B)** and **TS''-2(A,B)**. We used the transition state parameters for the geometry of the system radical-double bond, [17] whereas standard MM+ force field parameters were employed for the rest of the molecule. Hence, both **TS'-2(A)** and **TS'-2(B)**, which lead to the minor diastereomer **8a**, resulted at higher energy than the corresponding **TS'-1(B)**, which leads to the major diastereomer **7a** (ΔE about 0.5 kcal/mol). An analogous trend (ΔE about 0.4 Kcal/mol) was observed for **TS''-2(B)** with respect to **TS''-1(B)** leading to **10a** and **9a**, respectively, and these results were in agreement with the observed d.r. [18]

The most important factor responsible for steric energy difference stems from the non-bonding interactions. In fact the observed ΔE_{nb} is 0.47 kcal/mol for **TS'** and 0.44 kcal/mol for **TS''**, whereas the values of all the remaining contributions are very similar and counterbalance each other.

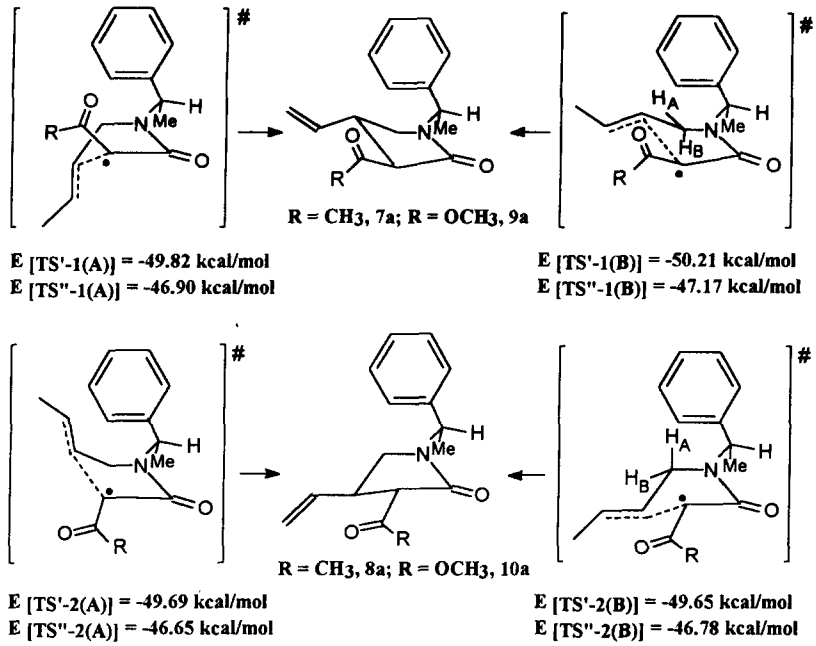
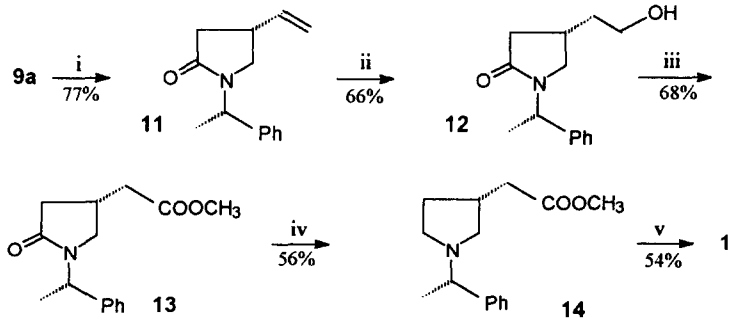


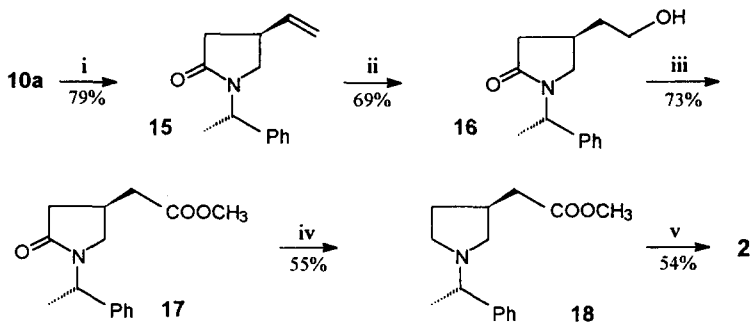
Figure 3. Lowest energy transition states (R = CH_3, **TS'**; R = OCH_3, **TS"**) for cyclisations leading to diastereomers **(7a,8a)** and **(9a,10a)**.

This result could be tentatively ascribed to a non-bonding interaction between the pseudo-axial hydrogen H_A and the phenyl group in **TS'-2(B)** and **TS"-2(B)**. Moreover, the differences in diastereoselection observed were quite small (Scheme 2) on increasing the bulkiness of the substituent at C-4. This suggests that in the C-C bond-forming transition state the group at C-4 is far removed from the reaction centres and it does not affect the stereochemical outcome of the cyclization.



Scheme 3. ***Reagents and conditions:*** **i.** NaCl, wet DMF, Δ. **ii.** 9-BBN, THF. **iii.** PDC-DMF, then CH_2N_2. **iv.** BH_3-THF. **v.** a) H_2-10% Pd-C; b) Amberlite IRA 400 (OH form), then elution with AcOH-H_2O.

To show the usefulness of this synthetic method, compounds **9a** and **10a** were converted into the (*R*)- and (*S*)-3-pyrrolidineacetic acid, **1** and **2**, respectively. The methoxycarbonyl group of **9a** was removed on treatment with NaCl in refluxing wet DMF, to give the corresponding 4-ethenylpyrrolidin-2-one **11** in good yield. [19] Hydroboration performed with 9-BBN in THF, followed by oxidation of the intermediate borane with H_2O_2, gave the alcohol **12**. [20] By oxidation with PDC in DMF, the corresponding acid was obtained, which was directly esterified with CH_2N_2 to give the ester **13**. Removal of the carbonyl group was carried out with with BH_3 in THF [21] and the amino ester **14** was converted into (*R*)-3-pyrrolidineacetic acid **1** following literature methods (Scheme 3). [3a] On the other hand the same synthetic sequence, carried out starting from **10a**, allowed to prepare (S)-3-pyrrolidineacetic acid **2** in comparable yield (Scheme 4).



Scheme 4. ***Reagents and conditions:*** **i.** NaCl, wet DMF, Δ. **ii.** 9-BBN, THF. **iii.** PDC-DMF, then CH_2N_2. **iv.** BH_3-THF. **v.** (a) H_2-10% Pd-C. (b) Amberlite IRA 400 in the OH^- form, then elution with AcOH-H_2O.

In summary, the method reported herein allows to prepare a number of pyrrolidin-2-ones, which are versatile intermediates for synthesizing both enantiomers of biologically active compounds containing the pyrrolidine ring: The mild reaction conditions, coupled with the operational simplicity, make this method attractive and further applications to the synthesis of (+)-*allo*-kainic acid **3** and pyrrolizidine alkaloids will be reported in due course.

EXPERIMENTAL

General Methods. 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. $Mn(OAc)_3{\cdot}2H_2O$, $Cu(OAc)_2{\cdot}H_2O$, (*E*)-1-bromo-2-butene, (*Z*)-2-hexen-1-ol, (*Z*)-4-benzyloxy-2-buten-1-ol, 9-BBN solution and (*S*)-1-phenylethylamine were purchased from Aldrich.

Preparation of (*S*)-*N*-(2-Alken-1-yl)-*N*-(1-phenyleth-1-yl)amines (4a-d). General Procedure. A solution of allylic bromide or *p*-toluenesulphonate (40 mmol) and (*S*)-1-phenylethylamine (8.6 g; 70 mmol) in dichloromethane (120 ml) was stirred at room temperature for 5 h and then washed with saturated aqueous $NaHCO_3$ solution (100 ml). The organic layer was separated, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (70:30 cyclohexane:ethyl acetate), to give the secondary allylic amines **4a-d** as colorless oils.

(*S*)-*N*-[2(*E*)-Buten-1-yl]-*N*-(1-phenyleth-1-yl)amine (4a). The title compound was prepared in 75% yield as colorless oil starting from 1-bromo-2(*E*)-butene. IR ($CDCl_3$): 3346 cm^{-1}; ^1H NMR: 1.35 (d, 3H, J = 6.6), 1.54 (br s, 1H, NH), 1.67 (d, 3H, J = 4.0), 3.04 (m, 2H), 3.78 (q, 1 H, J = 6.6), 5.55 (m, 2H), 7.30 (m, 5 ArH); ^{13}C NMR: 18.3, 24.7, 50.0, 58.0, 127.1, 127.7, 128.9, 130.0, 146.0; $[\alpha]_D$ -76.0 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z* 175 (M^+), 160, 106, 105, 91, 77. Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.17; H, 9.75; N, 7.95.

(*S*)-*N*-(3-Methyl-2-buten-1-yl)-*N*-[1-phenyleth-1-yl]amine (4b). The title compound was prepared in 76% yield as colorless oil starting from 1-bromo-3-methyl-2-butene. IR ($CDCl_3$): 3353 cm^{-1}; ^1H NMR: 1.36 (d, 3H, J = 6.6), 1.41 (br s, 1H, NH), 1.53 (s, 3H), 1.70 (s, 3H), 3.05 (d, 2H, J = 7.0), 3.79 (q, 1H, J = 6.6), 5.25 (t, 1H, J = 7.0), 7.3 (m, 5 ArH); ^{13}C NMR: 18.3, 24.8, 26.2, 45.7, 58.3, 123.5, 127.1, 127.4, 128.9, 134.8, 146.0; $[\alpha]_D$ -70.5 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z* 189 (M^+), 174, 146, 120, 106, 105, 91, 77. Anal. Calcd for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.44; H, 10.09; N, 7.35.

(*S*)-*N*-[2(*Z*)-Hexen-1-yl]-*N*-[1-phenyleth-1-yl]amine (4c). The title compound was prepared in 62% yield as colorless oil starting from 1-methanesulphonyloxy-2(*Z*)-hexene. IR ($CDCl_3$): 3346 cm^{-1}; ^1H NMR: 0.86 (t, 3H, J = 7.2), 1.31 (m, 2H), 1.36 (d, 3H, J = 6.6), 1.44 (br s, 1H, NH), 1.91 (m, 2H), 3.12 (d, 2H, J = 5.2), 3.81 (q, 1H, J = 6.6), 5,47 (m, 2H), 7.32 (m, 5 ArH); ^{13}C NMR: 14.2, 23.3, 24.8,29.9, 44.7, 58.2, 127.1, 127.6, 128.7, 128.9, 132.4, 145.1; $[\alpha]_D$ -82.2 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z* 203 (M^+), 188, 174, 158, 140, 120, 105, 91, 77. Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.66; H, 10.37; N, 6.84.

(*S*)-*N*-[4-Benzyloxy-2(*Z*)-buten-1-yl]-*N*-[1-phenyleth-1-yl]amine (4d). The title compound was prepared in 72% yield as colorless oil starting from 1-methanesulphonyloxy-4-benzyloxy-2(*Z*)-butene. IR ($CDCl_3$): 3350 cm^{-1}; ^1H NMR: 1.38 (d, 3H, J = 6.6), 1.83 (br s, 1H, NH), 3.12 (d, 2H, J = 5.3), 3.78 (q, 1H, J = 6.6), 3.96 (d, 2H, J = 4.9), 4.45 (s, 2H), 5.71 (m, 2H), 7.33 (m, 10 ArH); ^{13}C NMR: 24.4, 44.1, 54.9, 66.4, 75.9, 124.5, 127.1, 127.3, 127.6, 128.1, 128.3, 128.4, 137.2, 137.4; $[\alpha]_D$ -54.2 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z* 281 (M^+), 266, 212, 190, 173, 144, 131, 106, 91, 77. Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.04; H, 8.20; N, 4.95.

Preparation of (*S*)-*N*-(2-Alken-1-yl)-*N*-(1-phenyleth-1-yl)-3-oxobutanamides (5a-d). General Procedure. A solution of the appropriate secondary allylic amine **4a-d** (40 mmol) and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (6.4 g; 45 mmol) in toluene (100 ml) was refluxed for 2 h over oil bath. Then the solvent was removed under

reduced pressure and the residue was purified by flash chromatography on silica gel (cyclohexane:ethyl acetate 70:30) to give the amides **5a-d** as colorless oils.

(*S*)-*N*-[2(*E*)-Buten-1-yl]-*N*-(1-phenyleth-1-yl)-3-oxobutanamide (5a). The title compound was prepared in 74% yield starting from (*S*)-*N*-[2(*E*)-buten-1-yl]-*N*-(1-phenyleth-1-yl)amine **4a**: IR ($CDCl_3$): 1715, 1640 cm^{-1}; ^1H NMR: 1.51 (d, 3H, 80%, J = 7.0), 1.60 (d, 3H, J = 6.6), 1.66 (d, 3H, 20%, J = 7.0), 1.95 (s, 3H, 20%), 2.28 (s, 3H, 80%), 3.35 - 3.75 (m, 4H), 4.95 - 5.55 (m, 2H), 5.15 (q, 1H, 20%, J = 7.0), 6.05 (q, 1H, 80%, J = 7.0), 7.34 (m, 5 ArH); ^{13}C NMR: 17.1 (80%), 17.3 (20%), 18.1, 30.8 (20%), 30.9 (80%), 45.5 (20%), 46.3 (80%), 50.6 (20%), 50.8 (80%), 51.7 (20%), 51.8 (80%), 127.7, 127.8, 128.0, 128.1, 128.2, 128.4, 128.9, 129.2, 140.9, 168.1; $[\alpha]_D$ -152.5 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z* 259 (M^+), 244, 177, 175, 160, 146, 130, 118, 106, 91, 77. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.05; H, 8.12; N, 5.35.

(*S*)-*N*-(3-Methyl-2-buten-1-yl)-*N*-(1-phenyleth-1-yl)-3-oxobutanamide (5b). The title compound was prepared in 85% yield starting from (*S*)-*N*-(3-methyl-2-buten-1-yl)-*N*-(1-phenyleth-1-yl)amine **4b**: IR ($CHCl_3$): 1718, 1645 cm^{-1}; ^1H NMR: 1.51 (s, 3H), 1.54 (d, 3H, 55%, J = 6.6), 1.61 (s, 3H), 1.64 (d, 3H, 45%, J = 6.6), 1.95 (s, 3H, 45%), 2.28 (s, 3H, 55%), 3.38 - 3.74 (m, 4H), 4.85 (t, 1H, 45%, J = 6.0), 5.01 (t, 1H, 55%, J = 6.0), 5.09 (q, 1H, 45%, J = 6.6), 6.05 (q, 1H, 55%, J = 6.6), 7.33 (m, 5 ArH); ^{13}C NMR: 16.9 (55%), 18.0 (45%), 18.2 (55%), 18.6 (45%), 22.6, 25.9 (45%), 26.0 (55%), 30.8 (55%), 31.4 (45%), 41.9 (45%), 42.8 (55%), 50.6 (55%), 51.6 (45%), 122.5 (55%), 122.9 (45%), 127.7, 127.9, 128.9, 134.8, 141.0, 167.7, 177.2; $[\alpha]_D$ -148.2 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z* 273 (M^+), 258, 189, 174, 158, 146, 132, 120, 106, 91, 77. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.64; H, 8.44; N, 5.08.

(*S*)-*N*-[2(*Z*)-Hexen-1-yl]-*N*-(1-phenyleth-1-yl)-3-oxobutanamide (5c). The title compound was prepared in 80% yield starting from (*S*)-*N*-[2(*Z*)-hexen-1-yl]-*N*-(1-phenyleth-1-yl)amine **4c**: IR ($CDCl_3$): 1716, 1644 cm^{-1}; ^1H NMR: 0.88 (t, 3H, J = 7.1), 1.34 (m, 2H), 1.51 (d, 3H, 85%, J = 7.0), 1.62 (d, 3H, 15%, J = 7.0), 1.88 (m, 2H), 1.94 (s, 3H, 15%), 2.28 (s, 3H, 85%), 3.45- 3.78 (m, 4H), 5.05 - 5.48 (m, 2H), 5.12 (q, 1H, 15%, J = 7.0), 6.07 (q, 1H, 85%, J = 7.0), 7.31 (m, 5 ArH); ^{13}C NMR: 14.1 (85%), 14.2 (15%), 16.6 (85%), 17.1 (15%), 22.5 (15%), 22.6 (85%), 27.3, 29.9 (85%), 30.1 (15%), 41.1 (15%), 41.8 (85%), 50.5 (15%), 50.8 (85%), 127.5, 127.9, 128.1, 128.8, 132.7, 140.9, 167.7, 172.5; $[\alpha]_D$ -133.2 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z* 287 (M^+), 203, 188, 174, 158, 146, 120, 105, 91, 77. Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.17; H, 8.74; N, 4.84.

(*S*)-*N*-[4-Benzyloxy-2(*Z*)-buten-1-yl]-*N*-(1-phenyleth-1-yl)-3-oxobutanamide (5d). The title compound was prepared in 88% yield starting from (*S*)-*N*-[4-benzyloxy-2(*Z*)-buten-1-yl]-*N*-(1-phenyleth-1-yl)amine **4d**: IR ($CHCl_3$): 1715, 1648 cm^{-1}; ^1H NMR: 1.51 (d, 3H, 38%, J = 6.8), 1.53 (d, 3H, 62%, J = 6.8), 2.23 (s, 3H, 38%), 2.58 (s, 3H, 62%), 3.51 - 3.83 (m, 4H), 3.91 (m, 2H), 4.45 (s, 2H), 5.05 (q, 1H, 38%, J = 6.8), 5.28 (m, 1H), 5.57 (m, 1H), 6.07 (q, 1H, 62%, J = 6.8),7.18 - 4.95 (m, 10 ArH); ^{13}C NMR: 16.9 (62%), 17.1 (38%), 24.5, 41.0 (38%), 42.1 (62%), 50.6 (62%), 51.7 (38%), 54.3 (62%), 56.8 (32%), 65.9 (62%), 66.1 (38%), 72.8 (38%), 73.3 (62%), 126.8 (62%), 127.3 (38%), 127.7, 128.0, 128.1, 128.3, 128.8, 129.0, 130.5 (38%), 131.0 (62%), 138.2 (38%), 140.3 (38%), 140.7 (62%), 143.2 (62%), 165.9 (38%), 167.9 (62%); $[\alpha]_D$ -87.5 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z* 365 (M^+), 281, 280, 266, 192, 190, 173, 147, 131, 118, 105, 91, 77. Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.54; H, 7.41; N, 3.79.

Preparation of (*S*)-*N*-(2-Alken-1-yl)-*N*-(1-phenyleth-1-yl)-methoxycarbonylacetamides (6a-b). General Procedure. To a solution of the secondary allylic amine **4a-b** (30 mmol) in ethyl acetate (70 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 ethyl acetate (30 ml) was added and the mixture stirred at 0 °C for 1 h. The reaction mixture was poured into ethyl acetate (150 ml) and the organic phase was washed with 2M HCl (100 ml) and then with 10% aqueous Na_2CO_3 (100 ml). After drying over Na_2SO_4, the organic layer was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (cyclohexane:ethyl acetate 70:30) to give the amides **6a-b** as colorless oils.

(*S*)-*N*-[2(*E*)-Buten-1-yl]-*N*-(1-phenyleth-1-yl)methoxycarbonylacetamide (6a). The title compound was prepared in 91% yield starting from (*S*)-*N*-[2(*E*)-buten-1-yl]-*N*-(1-phenyleth-1-yl)amine **4a**: IR ($CHCl_3$): 1735, 1638 cm^{-1}; ^1H NMR: 1.51 (d, 3H, 78%, J = 6.6), 1.62 (d, 3H, J = 6.4), 1.63 (d, 3H, 22%, J = 6.6), 3.43 - 3.65 (m, 4H), 3.75 (s, 3H), 5.04 (q, 1H, 22%, J = 6.6), 5.12 (dt, 1H, J = 15.4, J = 5.5), 5.45 (dq, 1H, J = 15.4, J = 6.4), 6.04 (q, 1H, 78%, J = 6.6) 7.3 (m, 5 ArH); ^{13}C NMR: 17.0 (78%), 18.0 (78%), 18.1 (22%), 19.5 (22%), 42.0 (78%), 42.1 (22%), 45.8 (22%), 46.3 (78%), 51.8, 52.8 (78%), 58.0 (22%), 127.2 (78%), 127.4 (22%), 128.0, 128.2, 128.8, 129.1 (78%), 130.0 (22%), 140.9, 167.3, 187.4; $[\alpha]_D$ -130.3 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z* 275 (M^+), 175, 160, 120, 106, 91, 77. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.74; H, 7.66; N, 5.05.

(*S*)-*N*-(3-Methyl-2-buten-1-yl)-*N*-(1-phenyleth-1-yl)methoxycarbonylacetamide (6b). The title compound was prepared in 84% yield starting from (*S*)-*N*-(3-methyl-2-buten-1-yl)-*N*-(1-phenyleth-1-yl)amine **4b**: IR ($CHCl_3$): 1739, 1641 cm^{-1}; ^1H NMR: 1.43 (s, 3H, 20%), 1.49 (s, 3H, 80%), 1.51 (d, 3H, 80%, J = 7.1), 1.59 (s, 3H, 20%), 1.60 (d, 3H, 20%), J = 7.1), 1.63 (s, 3H, 80%), 3.34 - 3.64 (m, 4H), 3.73 (s, 3H, 20%), 3.75 (s, 3H, 80%), 4.86 (t, 1H, 80%, J = 6.0), 5.01 (q, 1H, 20%, J = 7.1), 5.08 (t, 1H, 20%, J = 6.0), 6.05 (q, 1H, 80%, J = 7.1), 7.22 - 7.45 (m, 5 ArH); ^{13}C NMR: 16.8 (20%), 16.9 (80%), 18.2 (80%), 19.0 (20%), 26.0, 41.8 (80%), 42.0 (20%), 42.2 (20%), 42.7 (80%), 51.7, 52.8 (80%), 56.7 (20%), 121.9 (20%), 122.3 (80%), 128.0, 128.7, 128.9, 135.0, 141.0, 167.0, 168.9; $[\alpha]_D$ -129.2 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z* 289 (M^+), 257, 2.42, 214, 189, 174, 152, 106, 105, 91, 77. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.51; H, 7.98; N, 4.81.

Oxidative Cyclisation of *N*-(2-Alken-1-yl)amides (5a-d) and (6a-b). General Procedure. To a stirred suspension of $Mn(OAc)_3 \cdot 2H_2O$ (2.4 g; 9 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.9 g; 4.5 mmol) in glacial acetic acid (35 ml) was added the appropriate allylic amide (4.5 mmol), dissolved in glacial acetic acid (10 ml) and the reaction mixture was stirred for 12 h at room temperature. Water was added, and then $Na_2S_2O_3$ 10% solution (20 ml). The resulting solution was extracted with ethyl acetate (3 x 100 ml). the organic extracts were washed with saturated $NaHCO_3$ solution and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a residue which was purified by chromatography on silica gel (cyclohexane:ethyl acetate 70:30) to give pure diastereomers **7a-d**,**8a-d** and **9a-b**,**10a-b** as colorless oils.

(3*R*,4*S*,1'*S*)-3-Acetyl-1-(1'-phenyleth-1'-yl)-4-ethenylpyrrolidin-2-one (7a) and its (3*S*,4*R*,1'*S*)-isomer (8a). The diastereomers were obtained in 70% overall yield as colorless oils starting from **5a**. Diastereomeric ratio **(7a)**:**(8a)** 68:32. IR ($CHCl_3$): 1718, 1644, 905 cm^{-1}; **(3*R*,4*S*,1'*S*)-Isomer (7a):** R_f = 0.32; ^1H NMR: 1.53 (d, 3H, J = 7.1), 2.46 (s, 3H), 3.03 (dd, 1H, H_B, J_{AB} = 9.5, J_{BX} = 7.2), 3.15 (dd, 1H, H_A, J_{AB} = 9.5, J_{AX} = 7.8), 3.35 (m, 1H, H_X), 3.50 (d, 1H, H_Y, J = 8.1), 5.11 (m, 2H), 5.42 (q, 1H, J = 7.1), 5.72 (ddd, 1H, J = 7.2, 10.2, 17.1), 7.32 (m, 5 ArH); ^{13}C NMR: 16.6, 31.2, 37.9, 46.2, 50.0, 61.9, 117.4, 127.3, 127.6, 128.1, 129.1, 137.5, 140.0, 169.2; $[\alpha]_D$ -163.3 (c 1, $CHCl_3$); **(3*S*,4*R*,1'*S*)-Isomer (8a):** R_f = 0.40; ^1H NMR: 1.51 (d, 3H, J = 7.1), 2.43 (s, 3H), 2.71 (d, 1H, H_A, J_{AB} = 7.9, J_{AX} = 5.1), 3.45 (m, 3H, H_B +H_X + H_Y), 5.02 (m, 2H), 5.45 (q, 1H, J

= 7.1), 5.61 (ddd, 1H, J = 7.1, J = 10.2, J = 17.2), 7.28 (m, 5 ArH); ^{13}C NMR: 16.7, 30.2, 31.1, 37.7, 46.2, 50.1, 62.2, 117.1, 127.6, 128.2, 129.1, 137.6, 140.0, 169.1; $[\alpha]_D$ -103.3 (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 257 (M^+), 242, 214, 200, 186, 173, 160, 132, 120, 105, 91, 77. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.64; H, 7.40; N, 5.40.

(3*R*,4*S*,1'*S*)-3-Acetyl-4-(2-methylpropen-2-yl)-1-(1'-phenyleth-1'-yl)pyrrolidin-2-one (7b) and its (3*S*,4*R*,1'*S*)-isomer (8b). The diastereomers were obtained in 52% overall yield as colorless oils starting from **5b**. Diastereomeric ratio **(7b)**:**(8b)** 67:33. IR ($CHCl_3$): 1716, 1641, 914 cm^{-1}. **(3*R*,4*S*,1'*S*)-Isomer (7b):** R_f = 0.34; ^{1}H NMR: 1.53 (d, 3H, J = 7.0), 1.71 (s, 3H), 2.47 (s, 3H), 3.07 (dd, 1H, H_B, J_{AB} = 9.3, J_{BX} = 7.1), 3.15 (dd, 1H, H_A, J_{AB} = 9.3, J_{AX} = 7.7), 3.35 (m, 1H, H_X), 3.59 (d, 1H, H_Y, J = 7.4), 4.77 (m, 2H), 5.47 (q, 1H, J = 7.0), 7.2 (m, 5 ArH); ^{13}C NMR: 16.6, 20.8, 31.1, 40.3, 45.7, 50.0, 60.9, 112.3, 127.3, 128.1, 129.1, 139.9, 144.0, 169.3; $[\alpha]_D$ -144.3 (c 1, $CHCl_3$). **(3*S*,4*R*,1'*S*)-Isomer (8b):** R_f = 0.41; ^{1}H NMR: 1.55 (d, 3H, J = 7.0), 1.69 (s, 3H), 2.45 (s, 3H), 2.74 (dd, 1H, H_A, J_{AB} = 8.6, J_{AX} = 4.9), 3.44 (m, 3H, H_B + H_X + H_Y), 4.65 (m, 2H), 5.47 (q, 3H, J = 7.0), 7.31 (m, 5 ArH); ^{13}C NMR: 16.5, 20.6, 31.0, 40.2, 45.6, 50.2, 61.3, 112.3, 127.7, 128.0, 128.3, 139.9, 144.2, 169.1; $[\alpha]_D$ -137.1 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z* 271 (M^+), 256, 228, 187, 172, 160, 124, 105, 91, 77. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.21; H, 7.77; N, 5.13.

(3*R*,4*S*,1'*S*)-3-Acetyl-4-(but-1'(*E*)-en-1'-yl)-1-(1'-phenyleth-1'-yl)pyrrolidin-2-one (7c) and its (3*S*,4*R*,1'*S*)-isomer (8c). The title diastereomers were obtained in 68% overall yield as colorless oils starting from **5c**. Diastereomeric ratio **(7c)**:**(8c)** 68:32. IR ($CHCl_3$): 1718, 1638 cm^{-1}. **(3*R*,4*S*,1'*S*)-Isomer (7c):** R_f = 0.33; ^{1}H NMR: 0.92 (t, 3H, J = 7.3), 1.51 (d, 3H, J = 7.0), 1.83 - 2.04 (m, 2H), 2.41 (s, 3H), 2.98 (dd, 1H, H_B, J_{AB} = 9.5, J_{BX} = 7.5), 3.12 (dd, 1H, H_A, J_{AB} = 9.5, J_{AX} = 7.9), 3.28 (m, 1H, H_X), 3.42 (d, 1H, H_Y, J = 8.3), 5.28 (dd, 1H, J = 7.3, J = 15.3), 5.41 (q, 1H, J = 7.0), 5.52 (dt, 1H, J = 6.2, J = 15.3), 7.16 - 7.39 (m, 5 ArH); ^{13}C NMR: 13.9, 16.7, 25.9, 31.2, 37.2, 46.8, 49.9, 62.5, 127.3, 127.7, 128.7, 128.9, 135.4, 140.1, 169.4; $[\alpha]_D$ -160.2 (c 1, $CHCl_3$). **(3*S*,4*R*,1'*S*)-Isomer (8c):** R_f = 0.39; ^{1}H NMR: 0.91 (t, 3H, J = 7.2), 1.49 (d, 3H, J = 7.1), 1.91 (m, 2H), 2.42 (s, 3H), 2.66 (dd, 1H, H_A, J_{AB} = 8.5, J_{AX} = 6.1), 3.39 (m, 3H, H_B + H_X + H_Y), 5.18 (dd, 1H, J = 7.2, J = 15.2), 5.42 (q, 1H, J = 7.1), 5.65 (dt, 1H, J = 6.3, J = 15.2), 7.21 - 7.42 (m, 5 ArH); ^{13}C NMR: 13.8, 16.7, 25.8, 31.2, 37.1, 46.8, 50.1, 62.8, 127.3, 127.5, 127.7, 127.9, 128.7, 135.4, 140.1, 169.5; $[\alpha]_D$ -131.6 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z* 285 (M^+), 270, 242, 214, 201, 194, 161, 160, 138, 120, 105, 91, 77. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91.

(3*R*,4*S*,1'*S*)-3-Acetyl-4-(2'-benzyloxy-1'(*Z*)-ethen-1'-yl)-1-(1'-phenyleth-1'-yl)pyrrolidin-2-one (7d) and its (3*S*,4*R*,1'*S*)-isomer (8d). The title diastereomers were obtained in 46% overall yield as colorless oils starting from **5d**. Diastereomeric ratio **(8d)**:**(9d)** 68:32. IR ($CHCl_3$): 1715, 1643 cm^{-1}. **(3*R*,4*S*,1'*S*)-Isomer (7d):** R_f = 0.38; ^{1}H NMR: 1.54 (d, 3H, J = 6.9), 2.60 (s, 3H), 2.98 (dd, 1H, H_B, J_{AB} = 9.5, J_{BX} = 7.0), 3.19 (dd, 1H, H_A, J_{AB} = 9.5, J_{AX} = 8.1), 3.50 (d, 1H, H_Y, J = 8.1), 3.62 (m, 1H, H_X), 4.36 (dd, 1H, J = 6.2, J = 7.7), 4.75 (s, 2H), 5.42 (q, 1H, J = 6.9), 6.07 (d, 1H, J = 6.2), 7.21 - 7.44 (m, 10 ArH); ^{13}C NMR: 16.7, 27.4, 30.8, 47.5, 49.9, 63.2, 74.6, 106.9, 126.7, 127.3, 128.0, 128.4, 128.6, 129.0, 129.1, 141.1, 143.0, 147.1, 169.8; $[\alpha]_D$ -148.3 (c 1, $CHCl_3$). **(3*S*,4*R*,1'*S*)-Isomer (8d):** R_f = 0.32; ^{1}H NMR: 1.50 (d, 3H, J = 7.0), 2.35 (s, 3H), 2.64 (dd, 1H, H_A, J_{AB} = 9.5, J_{AX} = 6.5), 3.44 (d, 1H, H_Y, J = 7.5), 3.50 (dd, 1H, H_B, J_{AB} = 9.5, J_{BX} = 8.2), 3.73 (m, 1H, H_X), 4.23 (dd, 1H, J = 6.2, J = 7.9), 4.74 (s, 2H), 5.44 (q, 1H, J = 7.0), 6.03 (d, 1H, J = 6.2), 7.15 - 7.42 (m, 10 ArH); ^{13}C NMR: 16.8, 30.6, 30.8, 47.4, 50.0, 63.4, 74.6, 107.0, 127.6, 127.7, 127.9, 128.0, 128.4, 128.5, 128.9, 129.0, 137.4, 140.3, 146.9, 169.8; $[\alpha]_D$ -166.2 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z*

363 (M^+), 348, 333, 318, 256, 229, 214, 186, 158, 144, 129, 105, 91, 77. Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.01; H, 6.93; N, 3.85. Found: C, 75.98; H, 6.89; N, 3.80.

(3*S*,4*S*,1'*S*)-4-Ethenyl-3-methoxycarbonyl-1-(1'-phenyleth-1'-yl)pyrrolidin-2-one (9a) and its (3*R*,4*R*,1'*S*)-isomer (10a). The title diastereomers were obtained in 53% overall yield as colorless oils starting from **6a**. Diastereomeric ratio **(9a):(10a)** 70:30. IR ($CHCl_3$): 1742, 1645, 915 cm^{-1}. **(3*S*,4*S*,1'*S*)-Isomer (9a):** R_f = 0.33; ^1H NMR: 1.53 (d, 3H, J = 7.1), 3.05 (dd, 1H, H_A, J_{AB} = 8.2, J_{AX} = 9.5), 3.18 (dd, 1H, H_B, J_{AB} = 8.2, J_{BX} = 6.3), 3.28 (m, 1H, H_X), 3.36 (d, 1H, H_Y, J = 8.5), 3.79 (s, 3H), 5.13 (m, 2H), 5.47 (q, 1H, J = 7.1), 5.76 (ddd, 1H, J = 17.1, J = 10.2, J = 6.9), 7.21 - 7.41 (m, 5 ArH); ^{13}C NMR: 16.6, 41.0, 46.5, 50.0, 53.2, 55.1, 117.9, 127.4, 128.1, 129.1, 136.7, 138.2, 169.0, 170.1; $[\alpha]_D$ -76.2 (c 1, $CHCl_3$). **(3*R*,4*R*,1'*S*)-Isomer (10a):** R_f = 0.40; ^1H NMR: 1.56 (d, 3H, J = 7.2), 2.71 (dd, 1H, H_A, J_{AB} = 9.4, J_{AX} = 7.5), 3.26 - 3.39 (m, 2H, H_X + H_Y), 3.52 (dd, 1H, H_B, J_{AB} = 9.4, J_{BX} = 8.1), 3.80 (s, 3H), 5.07 (m, 2H), 5.49 (q, 1H, J = 7.2), 5.64 (ddd, 1H, J = 17.1, J = 10.2, J = 6.8), 7.28 - 7.42 (m, 5 ArH); ^{13}C NMR: 16.6, 40.8, 46.4, 50.1, 53.1, 55.1, 117.7, 127.6, 128.2, 129.1, 136.7, 139.9, 169.0, 170.2; $[\alpha]_D$ -140.6 (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 273 (M^+), 258, 226, 214, 160, 132, 105, 91, 77. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.27; H, 6.98; N, 5.07.

(3*S*,4*S*,1'*S*)-3-Methoxycarbonyl-1-(1'-phenyleth-1'-yl)-4-(propen-2-yl)pyrrolidin-2-one (9b) and its (3*R*,4*R*,1'*S*)-isomer (10b). The title diastereomers were obtained in 49% overall yield as colorless oils starting from **6b**. Diastereomeric ratio **(9b):(10b)** 68:32. IR ($CHCl_3$): 1742, 1645, 910 cm^{-1}. **(3*S*,4*S*,1'*S*)-Isomer (9b)**: R_f = 0.39; ^1H NMR: 1.54 (d, 3H, J = 7.0), 1.70 (s, 3H), 3.11 - 3.32 (m, 3H, H_A + H_B + H_X), 3.48 (d, 1H, H_Y, J = 8.2), 3.79 (s, 3H), 4.67 - 4.85 (m, 2H), 5.49 (q, 1H, J = 7.0), 7.2 - 7.45 (m, 5 ArH); ^{13}C NMR: 16.6, 20.7, 43.4, 45.7, 49.9, 53.2, 53.9, 112.8, 127.4, 128.0, 128.3, 128.9, 140.0, 143.1, 164.5, 170.7; $[\alpha]_D$ -172.7 (c 1, $CHCl_3$). **(3*R*,4*R*,1'*S*)-Isomer (10b)**: R_f = 0.45; ^1H NMR: 1.53 (d, 3H, J = 7.2), 1.71 (s, 3H), 2.74 (dd, 1H, H_A, J_{AB} = 9.2, J_{AX} = 6.9), 3.31 (m, 1H, H_X), 3.41 (d, 1H, H_Y, J = 8.4), 3.52 (dd, 1H, H_B, J_{AB} = 9.2, J_{BX} = 8.0), 3.80 (s, 3H), 4.65 - 4.85 (m, 2H), 5.51 (q, 1H, J = 7.2), 7.24 - 7.44 (m, 5 ArH); ^{13}C NMR: 16.5, 20.6, 43.3, 45.6, 50.2, 53.2, 54.0, 112.7, 127.7, 128.1, 128.1, 128.9, 139.9, 143.1, 169.2, 170.7; $[\alpha]_D$ -147.6 (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 287 (M^+), 272, 256, 240, 228, 160, 132, 124, 105, 91, 77. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.95; H, 7.31; N, 4.81.

(4*R*,1'*S*)-4-Ethenyl-1-(1'-phenyleth-1'-yl)pyrrolidin-2-one (11). The pyrrolidin-2-one **9a** (2.7 g; 10 mmol), sodium chloride (0.68 g; 10 mmol) and water (0.18 g; 10 mmol) were dissolved in DMF (10 ml) and heated at reflux for 3 h. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate (100 ml). The organic layer was washed with water, dried over Na_2SO_4 and evaporated. The residue was then purified by silica gel chromatography (cyclohexane:ethyl acetate 60:40), to give **11** in 77% yield as a colorless oil. R_f 0.5; IR ($CHCl_3$): 1670, 915 cm^{-1}. ^1H NMR: 1.52 (d, 3H, J = 7.1), 2.33 (dd, 1H, J = 16.7, J = 8.5), 2.60 (dd, 1H, J = 16.7, J = 8.4), 2.84 (m, 1H, H_X), 3.08 (dd, 1H, H_A, J = 12.6, J = 9.9), 3.12 (dd, 1H, H_B, J = 12.6, J = 9.7), 5.07 (m, 2H), 5.48 (q, 1H, J = 7.1), 5.78 (ddd, 1H, J = 7.2, J = 10.2, J = 17.1), 7.22 - 7.44 (m, 5 ArH); ^{13}C NMR: 16.6, 36.6, 38.2, 48.0. 49.3, 116.2, 127.5, 128.0, 128.1, 129.0, 139.0, 140.7, 173.8; $[\alpha]_D$ -147.2 (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 215 (M^+), 200, 160, 146, 124, 105, 91, 77. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.01; H, 7.93; N, 6.44.

(4*S*,1'*S*)-2-[2-Oxo-1-(1'-phenyleth-1'-yl)pyrrolidin-4-yl]ethanol (12). A solution of compound **(11)** (2.15 g; 10 mmol) in dry THF (20 ml) was slowly added under argon atmosphere to a solution of 9-BBN in THF (40 ml of a 0.5 M solution; 20 mmol) at 20 °C and the mixture was stirred overnight. The excess hydride was

carefully destroyed by dropwise addition of H_2O (5 ml). The hydroboration mixture was oxidised by adding at 0 °C 30% hydrogen peroxide (30 ml) and 2 M NaOH (20 ml), followed by stirring for 12 h. The aqueous layer was saturated with NaCl and extracted with ethyl acetate. After drying over Na_2SO_4 and removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (ethyl acetate:cyclohexane 85:15), to give the title compound **12** in 66% yield as a colorless oil. R_f 0.18; IR ($CHCl_3$): 3345, 1677 cm^{-1}; ^1H NMR: 1.48 (d, 3H, J = 7.1), 1.55 (br s, 1H, OH), 1.70 (m, 2H), 2.12 (dd, 1H, J = 8.0, J = 15.8), 2.34 (m, 1H, H_X), 2.55 (dd, 1H, J = 8.0, J = 15.8), 2.99 (dd, 1H, H_B, J = 6.9, J = 9.6), 3.14 (dd, 1H, H_A, J = 7.7, J = 9.6), 3.68 (t, 2H, J = 6.4), 5.44 (q, 1H, J = 7.1), 7.2 - 7.4 (m, 5 ArH); ^{13}C NMR: 16.6, 29.6, 37.5, 38.5, 438.7, 49.3, 60.9, 127.4, 127.9, 129.0, 140.6, 174.6; $[\alpha]_D$ -85.3 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z* 233 (M^+), 218, 188, 160, 142, 129, 105, 91, 77. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.98; H, 8.17; N, 5.95.

Methyl (4*R*,1'*S*)-[2-oxo-1-(1'-phenyleth-1'-yl)pyrrolidin-4-yl]acetate (13). To a solution containing pyridinium dichromate (7.5 g; 20 mmol) in dry DMF (15 ml) was slowly added the compound **12** (1.2 g; 5 mmol) dissolved in DMF (5 ml) at r.t. After stirring for 1 h, the mixture was diluted with H_2O (100 ml) and extracted (3 x 100 ml) with ethyl acetate and the organic layer was washed with 2 M HCl an brine. After drying over Na_2SO_4 and removal of the solvent under reduced pressure, the residue was dissolved in methanol (10 ml) and treated with an ethereal solution of CH_2N_2. The organic phase was evaporated in vacuo and the residue was chromatographed on silica gel (cyclohexane:ethyl acetate 70:30), to give **13** in 68% yield as a colorless oil. R_f 0.30; IR ($CHCl_3$): 1745, 1665 cm^{-1}; ^1H 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.

Methyl (3*R*,1'*S*)-[1-(1'-phenyleth-1'-yl)-pyrrolidin-3-yl] acetate (14). The compound **13** (1.3 g; 5 mmol) was dissolved in dry THF (15 ml) under argon atmosphere and BH_3-THF (20 ml of a 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. 4 M methanolic HCl (10 ml) was added and the mixture was refluxed for an additional hour. The solvents were removed under reduced pressure, 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) and the combined extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (ethyl acetate), to give **14** in 56% yield as a colorless oil. IR ($CHCl_3$): 1740 cm^{-1}; ^1H NMR: 1.37 (d, 3H, J = 6.6), 1.32 - 1.51 (m, 1H), 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, 52.8, 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, 8.47; N, 5.60.

(*R*)-3-Pyrrolidineacetic acid (1). A solution of **14** (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 **1** in 54% yield as a white solid: m.p. 163 °C (lit. [3a] 160 - 165 °C); ^{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; $[\alpha]_D$ -9.1 (c 1, H_2O) [lit. [3a] -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, 55.74; H, 8.61; N, 10.79.

(4*S*,1'*S*)-4-Ethenyl-1-(1'-phenyleth-1'-yl)pyrrolidin-2-one (15). Following the procedure above reported for compound **12**, but starting from **10a**, the title compound **15** was obtained in 79% yield as a colorless oil. R_f 0.44; IR ($CHCl_3$): 1670, 915 cm^{-1}. ^{1}H NMR: 1.51 (d, 3H, J = 7.2), 2.27 (dd, 1H, J = 16.6, J = 7.8), 2.61 (dd, 1H, J = 16.6, J = 8.5), 2.71 (dd, 1H, H_A, J = 9.6, J = 6.7), 2.92 (m, 1H, H_X), 3.44 (dd, 1H, H_B, J = 9.6, J = 7.7), 4.99 (m, 2H), 5.51 (q, 1H, J = 7.2), 5.66 (ddd, 1H, J = 7.1, J = 10.2, J = 17.2), 7.21 - 7.43 (m, 5 ArH); ^{13}C NMR: 16.7, 36.5, 38.2, 47.9, 49.3, 116.0, 127.6, 128.0, 128.1, 129.0, 139.0, 140.4, 173.8; $[\alpha]_D$ -133.4 (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 215 (M^+), 200, 160, 146, 124, 105, 91, 77. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.03; H, 7.90; N, 6.42.

(4*R*,1'*S*)-2-[2-Oxo-1-(1'-phenyleth-1'-yl)pyrrolidin-4-yl]ethanol (16). Following the procedure above reported for compound **11**, but starting from **15**, the title compound **16** was obtained in 69% yield as a colorless oil. R_f 0.15; IR ($CHCl_3$): 3350, 1675 cm^{-1}; ^{1}H NMR: 1.50 (d, 3H, J = 7.1), 1.56 (m, 2H), 2.01 (br s, 1H, OH), 2.11 (dd, 1H, J = 6.6, J = 15.5), 2.46 (m, 1H, H_X), 2.51 - 2.72 (m, 2H, H_A + H), 3.44 (dd, 1H, H_B, J = 7.4, J = 9.6), 3.57 (t, 2H, J = 6.5), 5.48 (q, 1H, J = 7.1), 7.18 - 7.42 (m, 5 ArH); ^{13}C NMR: 16.7, 29.3, 37.4, 38.5, 48.5, 49.4, 60.7, 127.5, 128.0, 129.0, 140.4, 174.6; $[\alpha]_D$ -132.5 (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 233 (M^+), 218, 200, 188, 172, 160, 142, 129, 105, 91, 77. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.97; H, 8.19; N, 6.02.

Methyl (4*S*,1'*S*)-[2-oxo-1-(1'-phenyleth-1'-yl)pyrrolidin-4-yl]acetate (17). Following the procedure above reported for compound **13**, but starting from **16**, the title compound **17** was obtained in 73% yield as a colorless oil.R_f 0.28; IR ($CHCl_3$): 1745, 1665 cm^{-1}; ^{1}H 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 (3*S*,1'*S*)-[1-(1'-phenyleth-1'-yl)-pyrrolidin-3-yl] acetate (18). Following the procedure employed for **14**, but starting from **17**, the title compound was obtained in 55% 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, 72.76; H, 8.50; N, 5.60.

(*S*)-3-Pyrrolidineacetic acid (2). Following the procedure employed for **1**, but starting from **18**, the title compound was obtained in white solid: m.p. 161-162 °C (lit. [3a] 160 - 165 °C); $[\alpha]_D$ 9.0 (c 1, H_2O) [lit. [3a] 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, 55.71; H, 8.51; N, 10.73.

ACKNOWLEDGEMENT

This research was supported by a research grant from Consiglio Nazionale delle Ricerche (C.N.R.), Italy. We thank also Sifavitor s.r.l. (Milano, Italy) for a fellowship to one of us (R.G.), and Miss Micaela Fabbri (Università di Bologna, Italy) for conducting GC-MS analyses.

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(*Received in UK* 28 *September* 1995; *accepted* 26 *October* 1995)