SYNTHESIS AND STRUCTURAL ASSIGNMENT OF DIASTEREOMERICALLY PURE N-SUBSTITUTED 4-ALKYLPYRROLIDIN-2-ONES, INTERMEDIATES FOR THE PREPARATION OF 3-ALKYLPYRROLIDINES IN BOTH ENANTIOMERICALLY PURE FORMS

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Abstract - By radical cyclisation of N-[(S)-1-phenylethyl]-N-allyl-iodoacetamides **(6a-d)**, 4-substituted pyrrolidin-2-ones **(7a-d)** and **(8a-d)** were prepared as diastereomeric equimolar mixtures which were separated by column chromatography. The preferred conformation of **7a-d** and **8a-d** was determined by molecular mechanics methods and the configuration of the newly introduced stereogenic center was assigned by ^{1}H nmr data and further confirmed by NOE experiments. Compounds **(7a-d)** and **(8a-d)** can be converted into 3-alkylpyrrolidines in both enantiomerically pure forms following procedures reported in the literature.

The pyrrolidine ring and its monosubstituted derivatives are components of a number of natural and synthetic products with biological activity. [1] In addition, enantiomerically pure pyrrolidines are efficiently employed as chiral auxiliaries [2] and intermediates of a variety of non-racemic compounds [3] such as Rolipram **(1)**, [4] an antidepressant and inhibitor of phosphodiesterase, the hypolipidemic **(2)** [5] and 3-pyrrolidineacetic acid **(3)**, [6] which acts as an inhibitor of GABA transfer in neurons and glial cells.
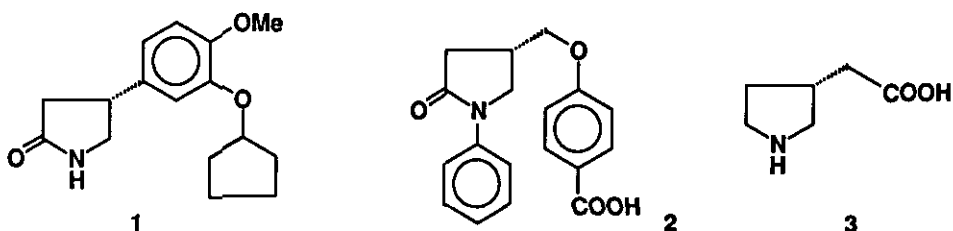
Although a number of synthetic approaches to racemic 3-substituted pyrrolidines have been reported, [7] methods for the preparation of these compounds in both the enantiomerically pure forms are scarcely found in the literature. [8]

As part of a program directed towards the synthesis of naturally occurring compounds with biological activity containing the 3-substituted pyrrolidine ring, we recognised that a pyrrolidin-2-one bonded to a chiral auxiliary that could be readily removed, should be exploitable as a latent pyrrolidine structure.

Thus, the present paper deals with the synthesis of 4-alkylpyrrolidin-2-ones (7a-d) and (8a-d) containing the (S)-1-phenylethylamine moiety [9] as almost equimolar diastereomeric mixtures, which can be separated to give the pure diastereomers. Moreover the configuration of the newly introduced stereogenic centre can be assigned on the basis of ^{1}H nmr data and NOE experiments. We envisioned that diastereomeric equimolar mixtures of 4(R,S)-alkyl-1-[(S)-phenyleth-1'-yl)]pyrrolidin-2-ones (7) and (8) could be obtained by intramolecular radical cyclisation of either N-allyl-N-[(S)-phenyleth-1-yl]iodo- or phenylselenoamides.
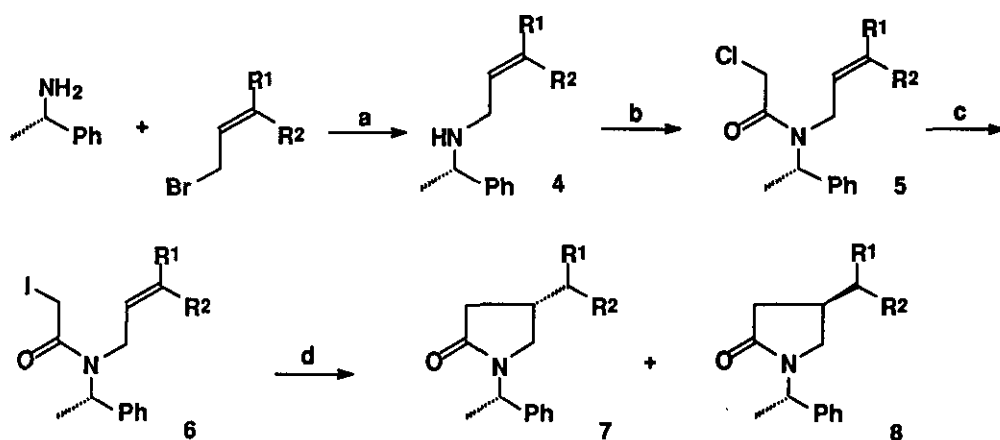
Scheme 1. *Reagents and conditions:* a. Dichloromethane, 12 h, room temperature. b. Ethyl acetate, Et₃N, DMAP, chloroacetyl chloride, 0 °C, 3 h. c. Acetone, NaI, room temperature, 12 h. d. Bu₃SnH, AIBN, refluxing benzene, column chromatography.

a, R¹ = R² = H
b, R¹ = Me, R² = H
c, R¹ = R² = Me
d, R¹ = COOMe, R² = H

First, by treatment with a number of allylic bromides, (S)-1-phenylethylamine was converted into the corresponding secondary allylic amines (4a-d). [10] The subsequent acylation, performed with chloroacetyl chloride, afforded the chloroacetamides (5a-d) which gave without isolation the iodoamides (6a-d) by reaction with NaI in acetone at room temperature. Although the ir and mass spectra of 6a-d were consistent with the assigned structure, ^{1}H and ^{13}C nmr spectra showed two sets of signals, corresponding to the <u>anti</u> and <u>syn</u> conformers, respectively, owing to the restricted rotation around the amidic bond. [11] In fact, by recording the ^{1}H nmr spectra at 80 °C, the separate sets of signals coalesce into a unique set. The rotameric <u>anti</u>:<u>syn</u> ratios observed in ^{1}H and ^{13}C nmr spectra were in good agreement with molecular mechanics calculations performed by using the force field MMX. [12] The <u>anti</u> conformer was found to be less stable than the <u>syn</u> one, owing to a high Van der Waals interaction between the phenyl group and the iodometyl group, and the energy differences range from 0.53 to 1.67 Kcal mole^{-1} (Table 1).
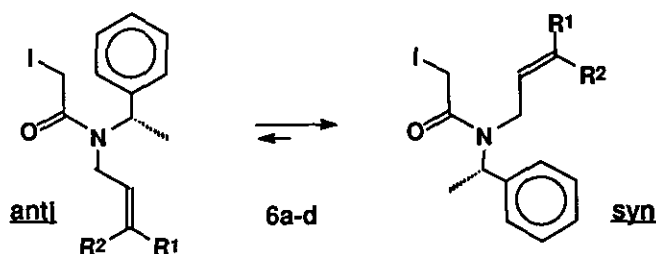
At the cyclisation temperature (353 K), the <u>anti</u>:<u>syn</u> ratio increases, although the <u>syn</u> conformer always remains the prevalent one. Table 1 reports the relative population ratios determined from ^{1}H and ^{13}C nmr spectra, and the calculated ratios at 298 K and 353 K, together with the calculated total steric energy differences and Van der Waals energy differences between the <u>anti</u> and <u>syn</u> conformers of (6a-d).

Table 1. Experimentally observed and calculated <u>anti</u>:<u>syn</u>: ratios for iodoacetamides (6a-d).

Product	Observed ratio (298 K)	Calculated ratio (298 K)	Calculated ratio (353 K)	Total steric <u>anti-syn</u> ΔE (Kcal mole^{-1})	Van der Waals <u>anti-syn</u> ΔE (Kcal mole^{-1})
(6a)	24:76	22:78	30:70	0.8	0.53
(6b)	20:80	14:86	17:83	1.11	0.70
(6c)	12:88	14:86	18:82	1.08	0.77
(6d)	35:65	39:61	41:59	0.26	1.67

The cyclisation, performed with Bu₃SnH-AIBN in refluxing benzene, [13] gave diastereomeric equimolar mixtures of 4-substituted pyrrolidin-2-ones (7a-d) and (8a-d) in moderate to good yield, together with little amounts of the acetamides which arise from the reductive cleavage of the C-I bond. As previously reported, [14] only the syn conformer can cyclise to give the pyrrolidin-2-one, whereas the anti one leads to the corresponding acetamide, via dehalogenation reaction, since the radical formation is much faster than the conformational interconversion by rotation around the amidic bond. This is in agreement with the experimental results, since increasing yields were observed with increasing syn:anti ratios.

Moreover, by treatment of the chloroacetamides (5a) and (5c) with phenylselenolate anion, [15] the corresponding phenylselenamides (9a) and (9b) were prepared in good yield. It is noteworthy that by cyclisation of 9a, performed with Bu₃SnH-AIBN in refluxing benzene, the pyrrolidin-2-ones (7a) and (8a) were obtained in 75:25 diastereomeric ratio, although the reasons of the observed asymmetric induction are difficult to explain. On the contrary, the cyclisation of 9b, performed under the same conditions, led to an equimolar mixture of 7c and 8c, in analogy with the cyclisation of 6c.

The diastereomeric mixtures were separated by column chromatography and the configuration of the stereogenic center at C-4 was first assigned from the chemical shifts and the coupling constant (J) values of the protons at C-5 (H$_a$ and H$_b$). First of all the more stable conformations of the pyrrolidin-2-ones (7) and (8) were determined from molecular mechanics calculations performed by using the force field MM+ (Figure 1). [16] In the lowest energy conformations the dihedral angle O-C(2)-N-C(1')-H ranges between 3° and -8° for 7a-d and between 27° and 41° for 8a-d, respectively.

a. O-C(2)-N-C(1')-H = 3°; H-C(1')-C(1")-C(2") = -46°
b. O-C(2)-N-C(1')-H = 3°; H-C(1')-C(1")-C(2") = -46°
c. O-C(2)-N-C(1')-H = 4°; H-C(1')-C(1")-C(2") = -46°
d. O-C(2)-N-C(1')-H = -8°; H-C(1')-C(1")-C(2") = -50°

a. O-C(2)-N-C(1')-H = 28°; H-C(1')-C(1")-C(2") = -14°
b. O-C(2)-N-C(1')-H = 27°; H-C(1')-C(1")-C(2") = -15°
c. O-C(2)-N-C(1')-H = 29°; H-C(1')-C(1")-C(2") = -14°
d. O-C(2)-N-C(1')-H = 41°; H-C(1')-C(1")-C(2") = -4°

Figure 1. Preferred conformations and selected dihedral angles for diastereomers (7a-d) and (8a-d).

In addition the plane of the phenyl group turns always towards H_a since H-C(1')-C(1")-C(2") ranges between -50° and -4°. As a consequence, in diastereomers (7a-d), either H_a and H_b experience a single shielding effect, due to the phenyl ring and the alkyl group, respectively. On the other hand, in diastereomers (8a-d), in which both the phenyl group and the alkyl group lie on the same side of H_a, H_a experiences two shielding effects, whereas H_b experiences no shielding effect (Table 2). Moreover, for the diastereomers (7a-d), the values [9] of $J(H_a,H_x)$ and $J(H_b,H_x)$ suggest a syn relationship between H_a and H_x and an anti relationship between H_b and H_x. On the contrary, the reverse trend of coupling constants is observed for diastereomers (8a-d), and the $J(H_a,H_x)$ and $J(H_b,H_x)$ values suggest an anti relationship between H_a and H_x, and a syn relationship between H_b and H_x, respectively. Thus on the basis of the chemical shift values and the J values the configuration at C-4 either in 7a-d and in 8a-d was assigned (Table 2).

In addition, the results of NOE experiments performed on the diastereomers (7a-d) and (8a-d) confirmed the stereochemical assignment. In fact the irradiation of the protons α to C-4 in diastereomers (7a-d) produced an enhancement of the signals of H_b and H_z, so that these protons must lie syn to the CHR^1R^2 group. On the other hand, when the protons α to C-4 in diastereomers (8a-d) were irradiated, both H_a and H_y signals were enhanced, thus confirming a syn relationship between these protons and the CHR^1R^2 group. Following this approach, the configuration at C-4 of either 7a-d and 8a-d was unequivocally assigned.

Table 2. [1]H Nmr Data for 4-Alkylpyrrolidin-2-ones (7a-d) and (8a-d).

Product	δH_a	δH_b	$J(H_a,H_x)$	$J(H_b,H_x)$
(7a)	3.07	2.84	7.6	6.2
(7b)	3.14	2.96	7.8	6.6
(7c)	3.01	3.01	— [a]	— [a]
(7d)	3.21	3.02	7.5	5.8
(8a)	2.54	3.41	5.9	7.3
(8b)	2.53	3.39	6.5	7.8
(8c)	2.59	3.03	7.7	8.1
(8d)	— [b]	3.52	- [b]	7.2

[a] H_a and H_b are superimposed at 3.01 δ, and either $J(H_a,H_x)$ and $J(H_b,H_x)$ cannot be determined
[b] H_a and H_z are superimposed at 2.54-2.74 δ, and $\delta(H_a)$ and $J(H_a,H_x)$ cannot be determined
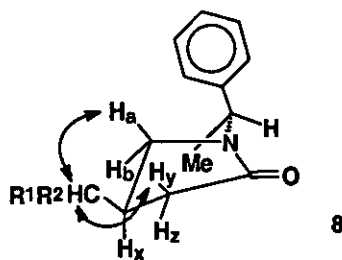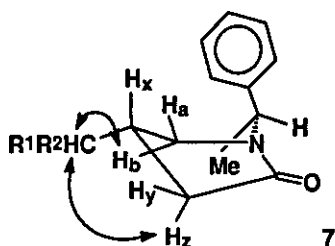
The conversion of pyrrolidin-2-ones (7) and (8) into the corresponding enantiomerically pure pyrrolidines can be performed by subsequent removal of both the carbonyl group [17] and benzylic group [18] following literature methods, which proceed without racemisation at the stereogenic center, so that 7 and 8 allow a convenient access to enantiomerically pure 3-alkylpyrrolidines (9) and (10) with biological activity. [6]

a, R1 = R2 = H
b, R1 = Me, R2 = H
c, R1 = R2 = Me
d, R1 = COOMe, R2 = H
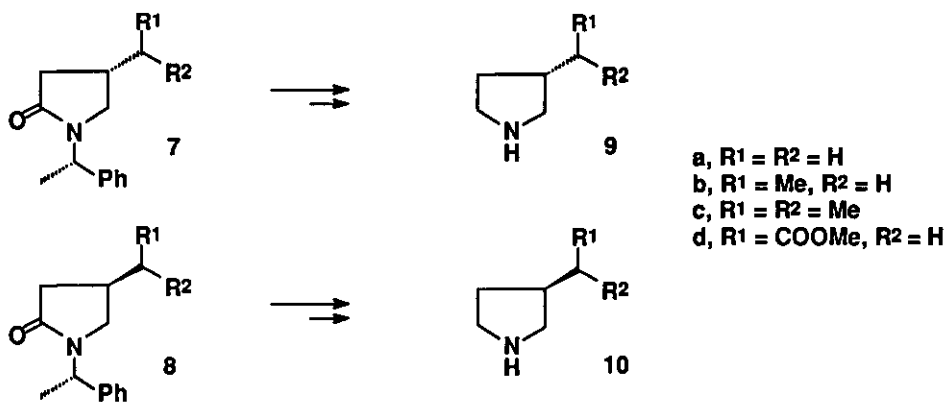
EXPERIMENTAL

General Methods. Ir spectra were recorded on a Nicolet Fourier Transform Infrared 20-SX spectrophotometer. ^{1}H Nmr 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. The nmr tubes containing samples of 7a-d and 8a-d 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 cross linked methyl silicone column and were recorded on a Carlo Erba QMD 1000 spectrometer. Flash chromatography was performed with silica gel 60 (230-400 mesh). The solvents were distilled under argon before use. (S)-1-Phenylethylamine was purchased by Aldrich and distilled before use.

Preparation of *N*-[(*S*)-1-phenylethyl]-*N*-allylamines (4a-d). **General Procedure.** A solution of allylic bromide (30 mmol) and (*S*)-1-phenylethylamine (7.3 g; 60 mmol) in dichloromehane (75 ml) was stirred at room temperature for 5 h and then washed with saturated aqueous NaHCO₃ solution (50 ml). The organic layer was separated, dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatogaphy (70:30 cyclohexane:ethyl acetate), to afford the secondary allylic amines as colorless oils.

N-[(*S*)-1-Phenyleth-1-yl]-*N*-allylamine (4a). The title product was prepared in 75% yield as colorless oil starting from allyl bromide and (*S*)-1-phenylethylamine; ^{1}H nmr: 1.38 (d, 3H, J = 6.5), 1.55 (br s, 1H, NH), 3.12 (d, 2H, J = 6.1), 3.82 (q, 1H, J = 6.5 Hz), 5.02 - 5.21 (m, 2H), 5.81 - 6.01 (m, 1H), 7.32 (m, 5 ArH); ^{13}C nmr: 24.7, 50.7, 58.0, 116.2, 127.1, 127.4, 128.9, 137.4, 145.9; [α]$_D$ -63.0° (c 1, CHCl₃); m/z 161 (M⁺), 146, 105, 91, 77. Anal. Calcd for C₁₁H₁₅N: C, 81.94; H, 9.38. Found: C, 81.90; H, 9.35.

N-[(*S*)-1-Phenyleth-1-yl]-*N*-[2(*E*)-buten-1-yl)]amine (4b). The title compound was prepared in 72% yield as colorless oil starting from 1-bromo-2(*E*)-butene and (*S*)-1-phenylethylamine; ^{1}H 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, 1H, 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; [α]$_D$ -76.0° (c 1, CHCl₃); m/z 175 (M⁺), 160, 106, 105, 91, 77. Anal. Calcd for C₁₂H₁₇N: C, 82.23; H, 9.78. Found: C, 82.19; H, 9.74.

N-[(*S*)-1-Phenyleth-1-yl]-*N*-(3-methyl-2-buten-1-yl)amine (4c). The title compound was prepared in 76% yield as colorless oil starting from 1-bromo-3-methyl-2-butene and (*S*)-1-phenylethylamine; ^{1}H 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),7.31 (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; [α]$_D$ -70.5° (c 1, CHCl₃); m/z 189 (M⁺), 174, 146, 120, 106, 105, 91, 77; Anal. Calcd for C₁₃H₁₉N: C, 82.48; H, 10.12. Found: C, 82.43; H, 10.08.

N-[(*S*)-1-Phenyleth-1-yl]-*N*-[3-methoxycarbonyl-2(*E*)-propen-1-yl]amine (4d). The title compound was prepared in 70% yield as colorless oil starting from methyl 4-bromo-2(*E*)-butenoate and (*S*)-1-phenylethylamine; ^{1}H nmr: 1.38 (d, 3H, J = 6.6), 1.52 (br s, 1H, NH), 3.25 (dd, 2H, J = 5.5, J = 1.8), 3.73 (s, 3H), 3.79 (q, 1H, J = 6.6), 5.97 (dt, 1H, J = 15.7, J = 1.8), 6.97 (dt, 1H, J = 15.7, J = 5.5), 7.31 (m, 5 ArH); ^{13}C nmr: 24.8, 48.5, 52.0, 58.1, 121.4, 127.6, 128.8, 128.9, 145.5, 147.8, 167.4; [α]$_D$ -48.5° (c 1, CHCl₃); m/z 219 (M+), 204, 144, 114, 105, 91, 77. Anal. Calcd for C₁₃H₁₇NO₂: C, 71.21; H, 7.81. Found: C, 71.17; H, 7.76.

Preparation of iodoacetamides (6a-d). General Procedure. To a solution of the secondary allylic amine (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, chloroacetyl chloride (3.7 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 2 M HCl (100 ml) and then with 10% aqueous Na_2CO_3 (100 ml). After drying over Na_2SO_4, the organic layer was removed in vacuo to give the crude chloroacetamides (5a-d) as an oil which was dissolved in acetone (100 ml). To the solution, NaI (9.0 g; 60 mmol) was added and the mixture was stirred overnight. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate (150 ml). The organic phase was subsequently washed with 10% aqueous $Na_2S_2O_3$ (50 ml) and with brine. After drying over Na_2SO_4 and removal of the solvent, the residue was purified by flash chromatography (cyclohexane:ethyl acetate 70:30), to give the iodoacetamides (6a), (6b) and (6d) as yellow oils, whereas 6c was a yellow solid.

N-[(*S*)-1-Phenyleth-1-yl]-*N*-allyliodoacetamide (6a). The title compound was obtained in 91% yield as colorless oil; ir (CHCl₃): 1658 cm⁻¹; ¹H nmr: 1.50 (76%, d, 3H, J = 6.5), 1.69 (24%, d, 3H, J = 6.5), 3.35 - 3.91 (m, 2H), 3.76 (s, 2H), 4.96 - 5.18 (m, 2H), 5.65 - 5.75 (m, 1H), 6.04 (q, 1H, J = 6.5), 7.32 (m, 5 ArH); ¹³C nmr: -1.6 (24%), -1.5 (76%), 16.7 (76%), 18.9 (24%), 46.1 (24%), 47.4 (76%), 52.1 (76%), 57.6 (24%), 116.7 (24%), 117.0 (76%), 127.9, 128.0, 128.9, 134.3 (24%), 135.4 (76%), 140.7, 169.2; $[\alpha]_D$ -121.1° (c 1, CHCl₃); m/z 178 (M^+ - CH_2I), 143, 127, 105, 91, 77. Anal. Calcd for $C_{13}H_{16}NOI$: C, 47.43; H, 4.90. Found: C, 47.39; H, 4.86.:

N-[(*S*)-1-Phenyleth-1-yl]-*N*-[2(*E*)-buten-1-yl)iodoacetamide (6b). The title compound was obtained in 87% yield as colorless oil; ir (CHCl₃): 1662 cm⁻¹; ¹H nmr: 1.51 (80%, d, 3H, J = 6.5), 1.66 (d, 3H, J = 4.2), 1.69 (20%, d, 3H, J = 6.5), 3.35 - 3.85 (m, 2H), 3.78 (ABq, 2H, J = 6), 5.08 (20%, q, 1H, J = 6.5), 5.15 - 5.65 (m, 2H), 6.02 (80%, q, 1H, J = 6.5), 7.33 (m, 5 ArH); ¹³C nmr: -1.65 (20%), -1.15 (80%), 16.5(20%), 16.7 (80%), 18.0 (80%), 18.2 (20%), 45.6 (20%), 46.8 (80%), 52.0 (80%), 57.5 (20%), 127.0 (20%), 127.2 (80%), 127.9, 128.2, 128.4 (80%), 128.6 (20%), 128.9, 140.8, 169.1; $[\alpha]_D$ -112.9° (c 1, CHCl₃); m/z 202 (M^+ - CH_2I), 157, 127, 105, 91, 77 . Anal. Calcd for $C_{14}H_{18}NOI$: C, 48.99; H, 5.29. Found: C, 48.95; H, 5.27.

N-[(*S*)-1-Phenyleth-1-yl]-*N*-(3-methyl-2-buten-1-yl)iodoacetamide (6c). The title compound was obtained in 89% yield; mp 78 °C (from ether); ir (CHCl₃): 1655 cm⁻¹; ¹H nmr: 1.51 (88%, d, 3H, J = 6.5), 1.58 (s, 3H), 1.65 (s, 3H), 1.69 (12%, d, 3H, J = 6.5), 3.41 - 3.85 (m, 2H), 3.75 (ABq, 2H, J = 7), 4.86 (88%, t, 1H, J = 6.1), 5.05 (12%, t, 1H, J = 6.1), 5.10 (12%, q, 1H, J = 6.5), 5.98 (88%, q, 1H, J = 6.5), 7.31 (m, 5 ArH); ¹³C nmr: -2.2 (12%), -1.9 (88%), 16.6, 18.3 (88%), 18.4 (12%), 26.1, 41.0 (12%), 43.3 (88%), 51.9 (88%), 57.3 (12%), 121.7 (12%), 122.7 (88%), 127.9, 128.9, 129.2, 132.1 (12%), 135.6 (88%), 140.9, 168.9; $[\alpha]_D$ -112.2° (c 1, CHCl₃); m/z 216 (M^+ - CH_2I), 171, 127, 105, 91, 77. Anal. Calcd for $C_{15}H_{20}NOI$: C, 50.43; H, 5.64. Found: C, 50.39; H, 5.61.

N-[(*S*)-1-Phenyleth-1-yl]-*N*-[3-methoxycarbonyl-2(*E*)-propen-1-yl]iodoacetamide (6d). The title compound was obtained in 83% yield as colorless oil; ir (CHCl$_3$): 1744, 1660 cm^{-1}; ^{1}H nmr: 1.49 (65%, d, 3H, J = 6.5), 1.68 (35%, d, 3H, J = 6.5), 3.5 - 4.05 (m, 4H), 3.81 (35%, s, 3H), 3.86 (65%, s, 3H), 5.15 (35%, q, 1H, J = 6.5), 5.75 (35%, d, 1H, J = 15.6), 5.84 (65%, d, 1H, J = 15.6), 6.05 (65%, q, 1H, J = 6.5), 6.85 (m, 1H), 7.3 (m, 5 ArH); ^{13}C nmr: -3.3 (65%), -1.9 (35%), 16.7 (65%), 18.8 (35%), 44.1 (35%), 45.8 (65%), 50.2 (35%), 52.2 (35%), 52.3 (65%), 57.5 (65%), 122.0 (35%), 122.4 (65%), 127.1, 128.0, 128.4, 139.8, 144.3 (35%), 144.9 (65%), 166.2, 169.3; [α]$_D$ -79.1° (c 1, CHCl$_3$); m/z 218 (M$^+$ - COCH$_2$I), 162, 127, 105, 91, 77. Anal. Calcd for C$_{15}$H$_{18}$NO$_3$I: C, 46.53; H, 4.69. Found: C, 46.49; H, 4.66.

Cyclisation of iodoacetamides (6a-d). General Procedure. To a refluxing solution of the iodoacetamide (6a-d) (15 mmol) in benzene (350 ml), was added a solution of Bu$_3$SnH (5.2 g; 18 mmol) and AIBN (2.9 g; 18 mmol) in benzene (35 ml) *via* a syringe during 4 h, and the mixture was heated at reflux for an additional hour. After removal of the solvent in vacuo, ether (50 ml) and saturated KF aqueous solution (10 ml) were added to the residue, and the mixture was stirred vigorously at room temperature for 1 h. The organic layer was separated, dried over Na$_2$SO$_4$ and concentrated. The residue was chromatographed on silica gel (cyclohexane:ethyl acetate 70:30), to give the pure diastereomers (7a-d) and (8a-d) as colorless oils.

(4*S*,1'*S*)-4-Methyl-1-(phenyleth-1'-yl)pyrrolidin-2-one (7a) and (4*R*,1'*S*)-4-methyl-1-(phenyleth-1'-yl)pyrrolidin-2-one (8a). An equimolar diastereomeric mixture of 7a and 8a was recovered in 54% yield as a colorless oil; ir (CHCl$_3$): 1668 cm^{-1}; **(4*S*,1'*S*)-Isomer (7a):** R$_f$ = 0.32; ^{1}H nmr: 1.06 (d, 3H, J = 6.7), 1.49 (d, 3H, J = 7.2), 2.04 (dd, 1H, H$_y$, J = 7.3, J = 15.7), 2.29 (m, 1H, H$_x$), 2.54 (dd, 1H, H$_z$, J = 8.1, J = 15.7), 2.84 (dd, 1H, H$_b$, J = 6.2, J = 9.5), 3.07 (dd, 1H, H$_a$, J = 7.6, J = 9.5), 5.47 (q, 1H, J = 7.2), 7.32 (m, 5 ArH); ^{13}C nmr: 16.6, 20.0, 27.1, 40.3, 49.2, 50.1, 127.5, 127.9, 128.9, 140.8, 174.4. [α]$_D$ -106.3° (c 1, CHCl$_3$). **(4*R*,1'*S*)-Isomer (8a):** R$_f$ = 0.30; ^{1}H nmr: 0.94 (d, 3H, J = 6.7), 1.49 (d, 3H, J = 7.2), 2.01 (dd, 1H, H$_y$, J = 6.7, J = 16.2), 2.33 (m, 2H, H$_x$+H$_z$), 2.54, (dd, 1H, H$_a$, J = 5.9, J = 9.4), 3.41 (dd, 1H, H$_b$, J = 7.3, J = 9.4), 5.49 (q, 1H, J = 7.2), 7.33 (m, 5 ArH); ^{13}C nmr: 16.6, 20.1, 26.8, 40.3, 49.2, 49.9, 127.5, 127.9, 128.9, 140.8, 174.4; [α]$_D$ -132.2° (c 1, CHCl$_3$). M/z 203 (M$^+$), 189, 146, 105, 91, 77. Anal. Calcd for C$_{13}$H$_{17}$NO: C, 76.81; H, 8.43. Found: C, 76.77; H, 8.39.

(4*S*,1'*S*)-4-Ethyl-1-(phenyleth-1'-yl)pyrrolidin-2-one (7b) and (4*R*,1'*S*)-4-ethyl-1-(phenyleth-1'-yl)pyrrolidin-2-one (8b). An equimolar diastereomeric mixture of 7b and 8b was recovered in 65% yield as a colorless oil; ir (CHCl$_3$): 1671 cm^{-1}; **(4*S*,1'*S*)-Isomer (7b):** R$_f$ = 0.34; ^{1}H nmr: 0.88 (t, 3H, J = 7.3), 1.50 (d, 3H, J = 7.1), 2.12 (m, 3H), 2.54 (dd, 1H, H$_z$, J = 11.1, J = 19.0), 2.96 (dd, 1H, H$_b$, J = 6.6 J = 9.6), 3.14 (dd,

1H, H$_a$, J = 7.8, J = 9.6), 5.48 (q, 1H, J = 7.1), 7.3 (m, 5 ArH); ^{13}C nmr: 16.6, 27.9, 33.9, 38.3, 48.3, 49.2,

127.5, 127.6, 128.9, 140.8, 174.4; [α]$_D$ -75.4° (c 1, CHCl$_3$). **(4R,1'S)-Isomer (8b):** R$_f$ = 0.31; ^{1}H nmr: 0.80 (t,

3H, J = 7.3), 1.42 (d, 3H, J = 7.1), 2.11 (m, 3H), 2.51 (dd, 1H, H$_z$, J = 6.0, J = 19.0), 2.53 (dd, 1H, H$_a$, J = 6.5,

J = 9.6), 3.39 (dd, 1H, H$_b$, J = 7.8, J = 9.6), 5.49 (q, 1H, J = 7.1), 7.32 (m, 5 ArH); ^{13}C nmr: 12.1, 16.5, 27.8,

33.8, 38.3, 48.1, 49.1, 127.5, 127.6, 128.8, 140.6, 174.4; [α]$_D$ -91.5° (c 1, CHCl$_3$). M/z 217 (M$^+$), 202, 160,

105, 91, 77. Anal. Calcd for C$_{14}$H$_{19}$NO: C, 77.38; H, 8.81. Found: C, 77.33, H, 8.78.

(4S,1'S)-4-(1'-Methyleth-1'-yl)-1-(phenyleth-1'-yl)pyrrolidin-2-one (7c) and (4R,1'S)-4-(1'-methyleth-1'-yl)-1-(phenyleth-1'-yl)pyrrolidin-2-one (8c). An equimolar diastereomeric mixture of **7c** and **8c** was

recovered in 81% yield as a colorless oil; ir (CHCl$_3$): 1669 cm^{-1}; **(4S,1'S)-Isomer (7c):** R$_f$ = 0.36; ^{1}H nmr: 0.84

(d, 3H, J = 6.6), 0.90 (d, 3H, J = 6.6), 1.48 (m, 1H), 1.51 (d, 3H, J = 6.9), 1.80 - 2.22 (m, 2H), 2.50 (dd, 1H, J

= 16.3, J = 8.5), 3.01 (m, 2H, H$_a$+H$_b$), 5.52 (q, 1H, J = 6.9), 7.32 (m, 5 ArH); ^{13}C nmr: 16.5, 20.5, 20.8, 33.0,

36.9, 39.4, 47.0, 49.2, 127.4, 127.8, 128.9, 140.8, 174.6.[α]$_D$ -121.4° (c 1, CHCl$_3$). **(4R,1'S)-Isomer 8c:** R$_f$ =

0.34; ^{1}H nmr: 0.70 (d, 3H, J = 6.6), 0.83 (d, 3H, J = 6.6), 1,48 (m, 1H), 1.50 (d, 3H, J = 6.9), 1.80 - 2.24 (m,

2H), 2.51 (dd, H, J = 16.3, J = 8.8), 2.59 (dd, 1H, H$_a$, J = 7.7, J = 9.6), 3.03 (dd, 1H, H$_b$, J = 8.1, J = 9.6), 5.51

(q, 1H, J = 6.9), 7.32 (m, 5 ArH); ^{13}C nmr: 16.6, 20.8, 20.9, 32.8, 36.9, 39.5, 46.8, 49.2, 127.7, 127.9, 128.8,

140.5, 174.6; [α]$_D$ -102.6° (c 1, CHCl$_3$). M/z 231 (M$^+$), 216, 160, 140, 105, 91, 77. Anal. Calcd for

C$_{15}$H$_{21}$NO: C, 77.88; H, 9.15. Found: C, 77.84, H, 9.11.

Methyl (4R,1'S)-[1-(phenyleth-1'-yl)-2-oxopyrrolidin-4-yl]acetate (7d) and methyl (4S,1'S)-[1-(phenyleth-1'-yl)-2-oxopyrrolidin-4-yl]acetate (8d). An equimolar diastereomeric mixture **7d** and **8d** was recovered in

48% yield as a colorless oil; ir (CHCl$_3$): 1745, 1665 cm^{-1}; **(4R,1'S)-Isomer (7d):** R$_f$ = 0.30; ^{1}H nmr: 1.51 (d,

3H, J = 7.2), 2.0 - 2.35 (m, 1H), 2.45 (m, 1H), 3.02 (dd, 1H, H$_b$, J = 5.8, J = 9.8), 3.21 (dd, 1H, H$_a$, J = 7.5, J =

9.8), 3.67 (s, 3H), 5.45 (q, 1H, J = 7.2), 7.31 (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; [α]$_D$ -103.6° (c 1, CHCl$_3$). **(4S,1'S)-Isomer (8d):** R$_f$ = 0.28; ^{1}H nmr:

1.51 (d, 3H, J = 7.2), 2.25 - 2.50 (m, 1H), 2.54 - 2.74 (m, 2H, H$_a$+H$_z$), 3.52 (dd, 1H, H$_b$, J = 7.2, J = 9.5), 3.63

(s, 3H), 5.48 (q, 1H, J = 7.2), 7.32 (m, 5 ArH); ^{13}C nmr: 17.2, 28.6, 38.2, 38.8, 48.0, 49.4, 52.3, 127.5, 128.0,

128.2, 140.5, 173.5, 195.1; [α]$_D$ -98.4° (c 1, CHCl$_3$). 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. Found: C, 68.89; H, 7.29.

Preparation of Phenylselenoacetamides (9a-b). General Procedure. To a solution of the secondary allylic

amine (4a) or (4c) (20 mmol) in ethyl acetate (50 ml), containing triethylamine (2.2 g; 21 mmol) and N,N-

dimethylaminopyridine (0.12 g; 1 mmol) at 0 °C, chloroacetyl chloride (2.4 g; 21 mmol) in ethyl acetate (20 ml)

was added and the mixture stirred at 0 °C for 1 h. The reaction mixture was poured into ethyl acetate (100 ml) and the organic phase was washed with 2 M HCl (100 ml) and then with 10% aqueous Na_2CO_3. After drying over Na_2SO_4, the organic layer was removed in vacuo to give the crude chloroacetamide (5a) or (5c) as an oil. Then, to a solution containing $NaBH_4$ (0.95 g; 25 mmol) in EtOH (50 ml) at 0°C, diphenyl diselenide (3.4 g; 11 mmol) was slowly added. The chloroacetamides (6a) or (6c) dissolved in EtOH (15 ml) was dropped into the colorless solution at 0°C and the mixture was stirred for 1 h at 0°C. The solvent was removed under reduced pressure, and ethyl acetate (100 ml) and H_2O (30 ml) were added to the residue. The organic layer was separated and the aqueous phase was further extracted twice with ethyl acetate (50 ml). After drying over Na_2SO_4 and removal of the solvent, the residue was chromatographed on silica gel (cyclohexane:ethyl acetate 70:30), to give in good yield the phenylselenoacetamides (9a-b) as yellow oils.

N-[(S)-1-Phenyleth-1-yl]-N-allylphenylselenoacetamide (9a). The title compound was obtained in 81% yield as yellow oil; ir (CHCl₃): 1654 cm⁻¹; ¹H nmr: 1.51 (82%, d, 3H, J = 6.5), 1.62 (18%, d, 3H, J = 6.5), 3.35 - 3.87 (m, 2H), 3.73 (s, 2H), 4.93 - 5.13 (m, 2H), 5.14 (18%, q, 1H, J = 6.5), 5.48 - 5.65 (82%, m, 1H), 5.63 - 5.88 (18%, m, 1H), 6.07 (82%, q, 1H, J = 6.5), 7.32 (m, 3 ArH), 7.62 (m, 2 ArH); ¹³C nmr: 17.1 (82%), 19.4 (18%), 29.4 (18%), 29.5 (82%), 46.1 (18%), 46.8 (82%), 51.9 (82%), 57.1 (18%), 116.6 (18%), 117.1 (82%), 128.1, 128.2, 128.9, 129.6, 134.1 (18%), 135.5 (82%), 141.1, 170.8; $[\alpha]_D$ -119.2° (c 1, CHCl₃); m/z 358 (M⁺), 278, 202, 157, 105, 91, 77. Anal. Calcd for $C_{19}H_{21}NOSe$: C, 63.68; H, 5.91. Found: C, 63.64; H, 5.88.

N-[(S)-1-Phenyleth-1-yl]-N-(3-methyl-2-buten-1-yl)phenylselenoacetamide (9b). The title compound was obtained in 78% yield as yellow oil; ir (CHCl₃): 1649 cm⁻¹; ¹H nmr: 1.38 (s, 3H), 1.48 (80%, d, 3H, J = 6.5), 1.57 (s, 3H), 1.60 (20%, d, 3H, J = 6.5), 3.32 - 3.75 (m, 2H), 3.63 (s, 2H), 4.81 (80%, t, 1H, J = 6.2), 4.95 (20%, t, 1H, J = 6.2), 5.04 (20%, q, 1H, J = 6.5), 5.96 (80%, q, 1H, J = 6.5), 7.23 (m, 3 ArH), 7.58 (m, 2 ArH); ¹³C nmr: 16.5, 17.2 (80%), 19.3 (20%), 25.2, 29.3 (20%), 29.6 (80%), 46.2 (20%), 46.7 (80%), 51.7 (80%), 58.9 (20%), 115.8 (20%), 117.3 (80%), 128.2, 128.4, 129.1, 129.6, 134.1 (20%), 135.7 (80%), 139.9, 170.6; $[\alpha]_D$ -112.4° (c 1, CHCl₃); m/z 386 (M⁺), 306, 202, 157, 105, 91, 77. Anal. Calcd for $C_{21}H_{25}NOSe$: C, 65.28; H, 6.52. Found: C, 65.22; H, 6.48.

Cyclisation of phenylselenoacetamides. General Procedure. To a refluxing solution of the phenylselenoacetamide (10 mmol) in benzene (250 ml), was added a solution of Bu₃SnH (3.2 g; 11 mmol) and AIBN (1.8 g; 11 mmol) in benzene (20 ml) via a syringe during 3 h, and the mixture was heated at reflux for an additional hour. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel (cyclohexane:ethyl acetate 70:30), to give the pure diastereomers as colorless oils.

(4*R*,1'*S*)-4-Methyl-1-(phenyleth-1'-yl)pyrrolidin-2-one   (7a)   and   (4*S*,1'*S*)-4-methyl-1-(phenyleth-1'-yl)pyrrolidin-2-one   (8a). Starting from the phenylselenoacetamide (9a), a diastereomeric mixture of 7a and 8a in 70:30 ratio was obtained in 56% yield as colorless oil.

(4*R*,1'*S*)-4-(1'-Methyleth-1'-yl)-1-(phenyleth-1'-yl)pyrrolidin-2-one   (7c)   and   (4*S*,1'*S*)-4-(1'-methyleth-1'-yl)-1-(phenyleth-1'-yl)pyrrolidin-2-one   (8c). Starting from the phenylselenoacetamide (9b), an equimolar diastereomeric mixture of 7c and 8c was obtained in 86% yield as colorless oil.

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REFERENCES

1. K. Shiosaki and H. Rapoport, *J. Org. Chem.*, 1985, **50**, 1229; K.B.G. Torssell, 'Natural Product Chemistry', John Wiley & Sons, New York, 1983, Chapter 7; J.K. Thottathil, J.L. Moniot, R.H. Mueller, M.K.Y. Wong, and T.P. Kissick, *J. Org. Chem.*, 1986, **51**, 3141; Y. Hamada, A. Kawai, Y. Kohno, O. Hara, and T. Shioiri, *J. Am. Chem. Soc.*, 1989, **111**, 1524.

2. J.K. Whitesell and S.W. Felman, *J. Org. Chem.*, 1977, **42**, 1663; J.K. Whitesell and S.W. Felman, *J. Org. Chem.*, 1980, **45**, 755; J.K. Whitesell, *Acc. Chem. Res.*, 1985, **18**, 280; R.H. Schlessinger and E.J. Iwanowicz, *J. Org. Chem.*, 1986, **51**, 3070; N.A. Porter, D.M. Scott, I.J. Rosenstein, B. Giese, A. Veit, and H.G. Zeitz, *J. Am. Chem. Soc.*, 1991, **113**, 1791; L. Chen and L. Ghosez, *Tetrahedron: Asymmetry*, 1991, **2**, 1181; P.A. van Elburg, G.W.N. Honig, and D.N. Reinhoudt, *Tetrahedron Lett.*, 1987, **28**, 6397; A. Defoin and A. Brouillard-Poichet, J. Streith, *Helv. Chim. Acta*, 1991, **74**, 103.

3. J.T. Coyle and R. Schwarcz, *Nature*, 1976, **263**, 244; P.L. McGeer, *Nature*, 1976, **263**, 517; A.P. Kozikowski and A.H. Fauq, *Tetrahedron Lett.*, 1990, **31**, 2967; Y. Ohfune and M. Tomita, *J. Am. Chem. Soc.*, 1982, **104**, 3511; K. Konno, K. Hashimoto, Y. Ohfune, H. Shirahama, and T. Matsumoto, *J. Am. Chem. Soc.*, 1988, **110**, 4807; N. Langlois and R.Z. Andriamialisoa, *Tetrahedron Lett.*, 1991, **32**, 3057.

4. R. Schmiechen, R. Horowski, D. Palenschat, G. Paschelke, H. Wachtel, and W. Kehr, *Ger. Offen.* 2,413,935, 1975 (*U.S. Patent* 4,193,926, 1980)(*Chem. Abstr.*, 1976, **84**, 30878u); A.I. Meyers and L. Snyder, *J. Org. Chem.*, 1993, **58**, 36.

5. C.M. Marson, U. Grabowska, T. Walsgrove, D.S. Eggleston, and P.W. Baures, *J. Org. Chem.*, 1994, **59**, 284; S. Fujii, H. Kawamura, and S. Watanabe, *European Patent* 393,607, 1990 (*Chem. Abstr.*, 1991, **114**, 228741a).

6. P. Krogsgaard-Larsen, 'Amino Acids as Chemical Transmitters', ed. by F. Fonnum, Plenum, New York, 1978, pp. 347-355; L.M. Yunger, P.J. Fowler, P. Zarevics, P.E. Setler, O.M. Larsson, P. Thorbeck, P. Krogsgaard-Larsen, and A. Schusboe, *J. Neurochem.*, 1981, **37**, 1509; L. Nielsen, L. Brehm, and P. Krogsgaard-Larsen, *J. Med. Chem.*, 1990, **33**, 71.

7. J.W. Eckert, M.L. Rahm, and M.J. Kohlbezen, *J. Agr. Food Chem.*, 1972, **20**, 104; T.J. Hagen, *Synlett*, 1990, 63; S.E. Denmark and L.R. Marcin, *J. Org. Chem.*, 1993, **58**, 3857, and references cited therein.

8. G. Bettoni, C. Celluci, and F. Berardi, *J. Heterocycl. Chem.*, 1980, **17**, 603; A.I. Meyers and L. Snyder, *J. Org. Chem.*, 1993, **58**, 36; A.I. Meyers and L. Snyder, *J. Org. Chem.*, 1992, **57**, 3814; L.J. Westrum and A.I. Meyers, *Tetrahedron Lett.*, 1994, **35**, 973.

9. G. Cardillo, M. Orena, S. Sandri, and C. Tomasini, *Tetrahedron*, 1987, **43**, 2505; A. Bongini, G. Cardillo, M. Orena, G. Porzi, and S. Sandri, *Tetrahedron*, 1987, **43**, 4377; A. Bongini, G. Cardillo, M. Orena, G. Porzi, and S. Sandri, *Chem. Lett.*, 1988, 87; M. Orena, G. Porzi, and S. Sandri, *J. Chem. Res.*, *(S)*, 1990, 376; M. Orena, G. Porzi, and S. Sandri, *J. Org. Chem.*, 1992, **57**, 6532; G. Porzi and S. Sandri, *Tetrahedron: Asymmetry*, 1994, **5**, 453.

10. A. Barco, S. Benetti, G. Spalluto, A. Casolari, G.P. Pollini, and V. Zanirato, *J. Org. Chem.*, 1992, **57**, 6279.

11. A.L.J. Beckwith and C.H. Schiesser, *Tetrahedron*, 1985, **41**, 3925; D. Spellmeyer and K.N. Houk, *J. Org. Chem.*, 1987, **52**, 959; G. Stork and R. Mah, *Heterocycles*, 1989, **28**, 723; T. Sato, Y. Wada, M. Nishimoto, H. Ishibashi, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 1989, 879; D.P. Curran and J. Tamine, *J. Org. Chem.*, 1991, **56**, 2476; D. Curran and H. Liu, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1377.

12. The force field MMX used in PCMODEL is derived from MM2 (QCPE 395, 1977) by N.L. Allinger, with the pi-VESCF routines taken from MMP1 (QCPE 318, 1977) also by N.L. Allinger. We employed MMX force field to obtain optimized structures because it treats the electrostatic interactions in a different way from MM+ enclosed in the package Hyperchem, and it seems to work better in the cases examined by us.

13. P.F. Keusenkothen and M.B. Smith, *Tetrahedron Lett.*, 1989, **30**, 3369; J.L. Belletire and N.O. Mahmoodi, *Tetrahedron Lett.*, 1989, **30**, 4363

14. H. Nagashima, N. Ozaki, K. Seki, M. Ishii, and K. Itoh, *J. Org. Chem.*, 1989, **54**, 4497; S. Ozaki, H. Matsushita, and H. Ohmori, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2339.

15. H.J. Reich, F. Chow, and S.K. Shah, *J. Am. Chem. Soc.*, 1979, **101**, 6638.

16. The MM+ force field is an extension of MM2 which was developed by Allinger and co-workers. As references see: N.L. Allinger, *J. Am. Chem. Soc.*, 1977, **99**, 8127; N.L. Allinger and Y.H. Yuh, Quantum Chemistry Program Exchange, Bloomington, Indiana, Program #395, 'Molecular Mechanics', edd. U. Burkert and N.L. Allinger, ACS Monograph 177, American Chemical Society, Washington, D.C., 1982; J. Lii, S. Gallion, C. Bender, H. Wikstrom, N.L. Allinger, K.M. Flurchick and M.M. Teeter, *J. Comp. Chem.*, 1989, **10**, 503; K.B. Lipkowitz, QCPE Bulletin, Indiana University, 12, 1 (Feb., 1992). The program is enclosed in Hyperchem package, available from Hypercube Inc., Waterloo, Ont., Canada..

17. H.C. Brown and P. Heim, *J. Org. Chem.*, 1973, **38**, 912.

18. E. Marx, M. El Bouz, J.P. Célérier, and G. Lhommet, *Tetrahedron Lett.*, 1992, **33**, 4307; G. Haviari, J.P. Célérier, H. Petit, G. Lhommet, D. Gardette, and J.C. Gramain, *Tetrahedron Lett.*, 1992, **33**, 4311; B.V. Yang, D. O'Rourke, and J. Li, *Synlett*, 1993, 195.