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A Versatile Route to β-Enamino Esters by Acylation of Lithium Enamines with Diethyl Carbonate or Benzyl Chloroformate.

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Abstract: A versatile route to β -enamino esters 1, using accessible starting materials, was developed. Lithiated enamines are allowed to react with diethyl carbonate or benzyl chloroformate with the formation of the β -enamino esters 1a or 1b. The reaction is rather general from a wide array of ketimines and aldimines. Products included cyclic β -enamino esters 1aa-ac, very useful for the synthesis of natural products.

 β -Enamino acid derivatives, particularly β -enamino esters (1), are important building blocks in organic synthesis.¹ β -Enamino esters are a highly versatile class of intermediates in the synthesis of biologically active compounds such as β -aminoacids (2) or γ -aminoalcohols (3), easily obtainable by reduction (see Scheme 1).²

Scheme 1



In particular the cyclic β -enamino esters **1aa-ac** (R¹-R² = (CH₂)_n; n = 3, 4 and 5) have been used for the synthesis of many natural products such as pyrrolizidines, indolizidines, quinolizidines and others alkaloids.^{1c-f} Several methods are known for the preparation of these vinilogous urethanes, *e.g.* Eschenmoser coupling reaction.³ Among them, a two step sequence starting from carbonyl compounds *via C*-alkoxycarbonylation of enolate anions, followed by condensation of the β -keto ester thus obtained with ammonia or amines in an aromatic solvent with azeotropic removal of water formed, appears to be the most practical and frequently employed procedure.⁴ However, the success of this approach requires a strict control of the reaction conditions in order to ensure effective *C*-regioselectivity in the enolate anion acylation and, in most instances, it is also highly dependent on the nature of starting materials. In addition, the direct condensation procedure often fails when less reactive amines and sterically hindered ketones are employed.⁵

Scheme 2



Reagents and Conditions: a) LDA (2 equiv.), THF, 0 °C, 30 min. b) (EtO)₂CO (2 equiv.), THF, -80 °C, 1 h. c) EtOCOCl (1.2 equiv.), THF, -80 °C, 1 h. d) saturated aqueous NH₄Cl.

Entry	Imine	R1	R ²	R ³	Product	Yields (%) ^a
1	4 a	(CH ₂	2)3	Н	laa	70
2	4b	(CH ₂) ₄		Н	1ab	59
3	4 c	(CH ₂)5		Н	1ac	72
4	4d	Pr ⁱ	Н	Me	lad	59
5	4 e	Pr ⁱ	Н	Et	lae	43
6	4f	Pr ⁱ	Me	Н	laf	62
7	4g	(R)-PhMeCH	Me	Н	lag	61
8	4h	(R)-PhMeCH	Pr ⁱ	Н	1ah	57
9	4i	(R)-PhMeCH	Bu ^t	Н	1ai	75
10	4j	(R)-PhMeCH		(CH ₂) ₄	1aj	70
11	4k	Pr ⁱ		(CH ₂) ₃	lak	45
12	41	(R)-PhMeCH	Ph	Н	1al	66
13	4m	Ph	Me	Н	1am	42
14	4a	(CH ₂) ₃		Н	1ba	76
15	4c	(CH ₂) ₅		Н	1bc	48
16	4d	Pr ⁱ	Н	Me	1bd	34
17	4 e	Pr ⁱ	Н	Et	1be	43
18	4f	Pr ⁱ	Me	Н	1bf	53
19	41	(R)-PhMeCH	Ph	Н	1bl	67
20	4n	(R)-PhMeCH		(CH ₂)3	1bn	63

a- Yields related to the starting imines 4.

β-Enamino esters

In order to find a general entry to β -enamino esters 1a or 1b and as an extention of our previous results on the preparation of β -enamino ketones with a general and regiospecific method (by acylation of lithiated enamine with esters),⁷ we tried this method for the reaction of lithiated enamine 5 with carbonates or chloroformates. α -Metallated imines are versatile nucleophiles capable of carbon-carbon bond formation⁶ and a useful tool for the introduction of a masked carbonyl function in β -position with respect to an electrophilic carbon. When lithiated enamine 5, prepared from imines 4, according to standard methods,⁸ were allowed to react with diethyl carbonate or benzyl chloroformate at - 80 °C in tetrahydrofuran, the corresponding β -enamino esters 1a or 1b were obtained in good to moderate yields. An overall twofold excess of base is required for the reaction to go to completion, thus indicating that a second equivalent of the lithium derivative preferentially metalates the β -enamino esters 1a or 1b as soon as they are formed. Obviously, the anionic form 6 protects it from a further nucleophilic attack by the imine anions 5.

As shown in **Table 1**, the reaction is rather general as regards the amine residue [$R = Pr^i$, Ph, (R)-PhMeCH] and shows good yields not only with the methyl ketimines ($R^3=H$) but on a wide array of ketimines [$R^2-R^3 = (CH_2)_3$; (CH_2)₄] and aldimines ($R^2 = H$; $R^3 = Me$, Et).

The better yields have been obtained in the case of β -enamino esters **1aa-ac**, very useful starting material in the synthesis of some alkaloids.¹ In order to simplify the method, we tried to obtain the β -enamino esters without purification of the ketimine or aldimine intermediates. This "one pot" procedure takes place successfully under the same reaction conditions (yield 63 % for **1aj** based on the starting carbonyl compound). The low yield observed in some case could be due to the instability of β -enamino esters with partial hydrolysis on work-up to give the parent keto ester. The reaction occurs with total regioselectivity, the *C*-acylated derivatives **1a** or **1b** being the sole isolated product and no N-acylated compounds were detected. In addition it is worth noting that good results can be obtained for the synthesis of hindered β -enamino esters such as **1a**. In this specific entry the direct condensation of the 1-phenylethylamine with the ethyl benzoylacetate in benzene, at reflux for 6 h, furnished the expected β -enamino esters as **1a** in low yield (see **Scheme 3**). The β -keto amide **9** is obtained as the major product in addition to the β -enamino amide **10**, *via* an unusual aminolysis of the ester function.⁵

Scheme 3



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Sometimes side products such as urethanes derived from the reaction of LDA with diethyl carbonate or benzyl chloroformate were also present in the reaction mixture but these side products can be easily removed by flash chromatography. To avoid the formation of urethanes, more sterically hindered bases such as lithium tetramethylpiperidide or lithium hexamethyldisilazide can be advantageously used but without any improvement of the reaction yields.

β-Enamino esters synthesized from ketimines adopt the (*Z*)-*s*-*cis* conformation (see **laf** in **Scheme 4**), stabilized by hydrogen bonding as indicated by a strongly shifted downfield resonance of the amide proton (δ = 7.30-9.40 ppm in the CDCl₃ ¹H NMR spectrum). Products **lad, ae, bd, be**, obtained from aldimines (R² = H), have two conformations of comparable stability and more stable with respect to the other possible conformers.⁹ The relative stability of the four possible conformers can be evaluated by PM3 semi-empirical computational method¹⁰. As outlined in the experimental section the spectroscopic data for these compounds show that the conformers present are only the (*Z*)-*s*-*cis* and (*E*)-*s*-*cis* (see **lad** in **Scheme 4**). Structural assignment of C=C double bond geometry were confirmed by NOE difference spectroscopy which shows a significant nuclear Overhauser effect between the vinyl and allylic protons for only the (*Z*)-isomers.

Scheme 4



Benzylic enamino esters **1b**, are sometime preferable to other β -enamino esters because of the hydrogenolysable benzyl group that allows a simplified work up for the isolation of the corresponding β -amino acid. This is the case of the synthesis of the antibiotic antifungine cispentacin [(1R,2S)-2-amino-1-cyclopentanecarboxylic acid] as showed, for its enantiomer, in the Scheme 5 where the free amino acid can be obtained easily by filtration and evaporation of the hydrogenation mixture.^{2e}



To summarize, we have developed a useful and versatile access to vinylogous urethanes using easily accessible starting materials This procedure may complement those existing in the literature for the synthesis of β -enamino esters.

EXPERIMENTAL

General Remarks

Solvents were dried and purified according to known procedure. THF was dried by refluxing over sodium wire until the blue color of benzophenone ketyl persisted and then distilled into a dry receiver under nitrogen atmosphere. All reagents were distilled prior to use or were of commercial quality from freshly opened containers. Analytical TLC plates (silica gel 60 F254) and silica gel (230-400 mesh) were purchased from Merck, Darmstadt. All melting points (determined with a Köfler hot-stage microscope) are uncorrected. Microanalyses were obtained with a Fisons Intruments (EA 1108). IR-spectra were recorded on a Perkin-Elmer spectrophotometer. ¹H and ¹³C-NMR spectra were measured on a Varian VXR 300 (300 and 75 MHz) in CDCl₃ solutions. GLC-MS analysis were performed on a Hewlett Packard 59970 work station equipped with a methyl silicone capillary column and by an HP-5970 mass detector. Cyclic ketimines **4a-c** were prepared from lactams according to literature.¹¹

β-Amino α,β-Unsaturated Esters 1aa-am; General Procedure:

A three necked, round-bottomed flask equipped with dropping funnel and septum inlet was flame-dried under nitrogen atmosphere and charged with butyl lithium (20 mmol, 1.6 M in hexane), then a solution of diisopropylamine (20 mmol, 2.8 ml) in anhydrous tetrahydrofuran (5 ml) was added at 0 °C. After 10 min at this temperature a solution of the imine 4 (10 mmol) in THF (5 ml) was added and the resulting bright yellow solution was stirred for 30 min at 0 °C then cooled to - 80 °C. At this temperature a solution of diethyl carbonate (2.42 ml, 20 mmol) in THF (5 ml) is slowly added (1 h) and the mixture is allowed to rise to room temperature (2 h). Dilution with 50 ml CH₂Cl₂ is followed by water hydrolysis (10 ml saturated aq. NH₄Cl). The organic layer is dried over Na₂SO₄, the product is isolated as an orange oil by removal of solvent under reduced pressure. Crude products **1aa-am** are purified by flash chromatography on a silica gel column (70-230 mesh) using a mixture of hexane / EtOAc (95:5) as eluent.

The benzyl enamino esters 1b were prepared and purified by the same procedure, but using benzylchloroformate (12 mmol) instead of diethyl carbonate.

Ethyl Azacyclopentane-2-ylideneacetate (1aa): m.p. 61-62 °C (CH₂Cl₂/hexane); IR (nujol) 3340, 1645, 1580, 1230, 1135, 1050 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.24 (t, 3H, *J* = 7.1 Hz), 1.95 (quint, 2H, *J* = 7.3 Hz), 2.56 (t, 2H, *J* = 7.7 Hz), 3.50 (t, 2H, *J* = 7.3 Hz), 4.09 (q, 2H, *J* = 7.1 Hz), 4.50 (s, 1H), 7.90 (brs, 1H) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ 15.18, 22.50, 32.67, 47.51, 58.86, 77.06, 166.96 (q), 171.21 (q) ppm; MS (m/z): 155 (M⁺, 31), 110 (100), 83 (91); Anal. Calcd for C₈H₁₃NO₂: C, 61.91; H, 8.44; N, 9.03%. Found: C, 62.04; H, 8.40; N, 9.14%.

Ethyl Azacyclohexane-2-ylideneacetate (1ab): oil; IR (neat) 3265, 1645, 1580, 1220, 1150, 1050 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.22 (t, 3H, *J* = 7.1 Hz), 1.57-1.83 (m, 4H), 2.36 (t, 2H, *J* = 6.4 Hz), 3.27 (td, 2H, *J* = 6.3, 2.3 Hz), 4.06 (q, 2H, *J* = 7.1 Hz), 4.33 (s, 1H), 8.71 (brs, 1H) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ 15.16, 20.42, 23.29, 29.60, 41.71, 58.63, 80.64, 163.21 (q), 171.15 (q) ppm; MS (m/z): 169 (M⁺, 80), 124 (95), 97 (100); Anal. Calcd for C9H₁₅NO₂: C, 63.88; H, 8.93; N, 8.28%. Found: C, 63.97; H, 8.81; N, 8.21%.

Ethyl Azacycloheptane-2-ylideneacetate (1ac): 55-56 °C (MeOH); IR (nujol) 3295, 1640, 1595, 1245, 1155, 1045 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.25 (t, 3H, *J* = 7.1 Hz), 1.51-1.75 (m, 6H), 2.23-2.32 (m, 2H), 3.24-3.34 (m, 2H), 4.08 (q, 2H, *J* = 7.1 Hz), 4.44 (s, 1H), 8.85 (brs, 1H) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ 15.15, 26.97, 30.60, 30.94, 35.60, 44.72, 58.77, 81.22, 168.99 (q), 171.33 (q) ppm; MS (m/z): 183 (M⁺, 51), 138 (73), 111 (100); Anal. Calcd for C₁₀H₁₇NO₂: C, 65.54; H, 9.35; N, 7.64%. Found: C, 65.62; H, 9.49; N, 7.76%.

Ethyl 3-(N-isopropyl)amino-2-methyl-2-propenoate (1ad): oil; IR (neat) 3320, 1660, 1600, 1210, 1110 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) (the two conformer are present in the ratio of about 3:2) δ 1.16 (d, 6H, J = 6.5 Hz), 1.25 (t, 3H, J = 7.1 Hz), 1.67 (s, 3H), 3.33 (octet, 1H, J = 6.5 Hz), 4.13 (q, 2H, J = 7.1 Hz), 6.58 (d, 1H, J = 13.2 Hz), 7.50 (br m, 1H) ppm [(Z)-s-cis major conformer]; 1.18 (d, 6H, J = 6.4 Hz), 1.23 (t, 3H, J = 7.1 Hz), 1.63 (d, 3H, J = 1.0 Hz), 3.45 (octet, 1H, J = 6.4 Hz), 3.92 (br m, 1H), 4.13 (q, 2H, J = 7.1 Hz), 7.38 (dd, 1H, J = 13.9, 1.0 Hz) ppm [(E)-s-cis minus conformer]; ¹³C NMR (CDCl₃, 75 MHz) (in parenthesis the value of the minus conformer) δ 9.85 (14.42), 15.10 (15.95), 24.54 (24.61), 49.59 (49.63), 59.19 (59.59), 89.03 (93.64), 149.46 (145.32), 171.19 (169.99) ppm; MS (m/z): 171 (M⁺, 26), 156 (25), 126 (29), 110 (100); Anal. Calcd for C9H₁₇NO₂: C, 63.13; H, 10.01; N, 8.18%. Found: C, 63.02; H, 10.16; N, 8.03%.

Ethyl 3-(N-isopropyl)amino-2-ethyl-2-propenoate (1ae): oil; IR (neat) 3310, 1660, 1600, 1370, 1200, 1115 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) (the two conformer are present in the ratio of about 3:1) δ 0.99 (t, 3H, J = 7.3 Hz), 1.18 (d, 6H, J = 6.5 Hz), 1.26 (t, 3H, J = 7.1 Hz), 2.08 (q, 2H, J = 7.3 Hz), 3.32 (octet, 1H, J = 6.5 Hz), 4.13 (q, 2H, J = 7.1 Hz), 6.58 (d, 1H, J = 13.0 Hz), 7.57 (br m, 1H) ppm [(*Z*)-*s*-*cis* major conformer]; 0.95 (t, 3H, J = 7.3 Hz), 1.19 (d, 6H, J = 6.5 Hz), 1.24 (t, 3H, J = 7.1 Hz), 2.13 (q, 2H, J = 7.3 Hz), 3.45 (octet, 1H, J = 6.5 Hz), 3.98 (br m, 1H), 4.12 (q, 2H, J = 7.1 Hz), 7.35 (d, 1H, J = 14.0 Hz) ppm [(*E*)-*s*-*cis* minus conformer]; ¹³C NMR (CDCl₃, 75 MHz) (in parenthesis the value of the minus conformer) δ 14.56, 15.75, 17.61, 24.02 (23.44), 49.21 (49.13), 58.55 (58.97), 95.66 (83.57, q), 148.68 (144.22), 170.52 (169.03, q) ppm; MS (m/z): 185 (M⁺, 38), 170 (100), 140 (27), 124 (62); Anal. Calcd for C₁₀H₁₉NO₂: C, 64.83; H, 10.34; N, 7.56 %. Found: C, 64.71; H, 10.39; N, 7.43 %.

Ethyl 3-(N-isopropyl)amino-2-butenoate (1af): oil; IR (neat) 3260, 1640, 1600, 1260, 1150, 1050 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.17 (d, 6H, J = 6.3 Hz), 1.21 (t, 3H, J = 7.1 Hz), 1.90 (s, 3H), 3.65 (d sept, 1H, J = 9.0, 6.4 Hz), 4.04 (q, 2H, J = 7.1 Hz), 4.35 (s, 1H), 8.45 (br d, 1H, J = 9.0 Hz) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ 14.50, 18.95, 23.94, 44.24, 57.92, 81.70, 160.62 (q), 170.40 (q) ppm; MS (m/z): 171 (M⁺, 70), 126

(58), 110 (100), 98 (61), 84 (97); Anal. Calcd for C₉H₁₇NO₂: C, 63.13; H, 10.01; N, 8.18 %. Found: C, 62.96; H, 10.19; N, 8.27 %.

Ethyl 3-[N-(*R*)-1-phenylethyl]-amino-2-butenoate (1ag): oil; IR (neat) 3280, 1645, 1605, 1265, 1145, 700 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.28 (t, 3H, *J* = 7.1 Hz), 1.52 (d, 3H, *J* = 6.8 Hz), 1.77 (s, 3H), 4.13 (q, 2H, *J* = 7.1 Hz), 4.48 (s, 1H), 4.63 (m, 1H), 7.18-7.39 (m, 5H), 8.98 (br s, 1H) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ 15.15, 20.18, 25.43, 53.32, 58.87, 83.62, 125.90, 127.55, 129.28, 145.45 (q), 161.98 (q), 171.15 (q) ppm; MS (m/z): 233 (M⁺, 20), 172 (15), 145 (16), 105 (100); Anal. Calcd for C₁₄H₁₉NO₂: C, 72.07; H, 8.21; N, 6.00 %. Found: C, 72.18; H, 8.29; N, 5.84 %.

Ethyl 3-[N-(*R*)-1-phenylethyl]-amino-4-methyl-2-pentenoate (1ah): oil; IR (neat) 3250, 1635, 1595, 1245, 1030, 695 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 0.79 (d, 3H, *J* = 6.8 Hz), 1.12 (d, 3H, *J* = 6.8 Hz), 1.28 (t, 3H, *J* = 7.1 Hz), 1.52 (d, 3H, *J* = 6.8 Hz), 2.51 (sept, 1H, *J* = 6.8 Hz), 4.13 (q, 2H, *J* = 7.1 Hz), 4.55 (s, 1H), 4.69 (m, 1H), 7.15-7.37 (m, 5H), 9.15 (br d, 1H, *J* = 8.0 Hz) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ 15.13, 21.34, 22.97, 25.70, 29.36, 52.50, 58.89, 79.29, 125.86, 127.51, 129.21, 145.89, 171.91, 172.24 ppm; MS (m/z): 261 (M⁺, 17), 246 (7), 188 (11), 173 (17), 105 (100); Anal. Calcd for C₁₆H₂₃NO₂: C, 73.53; H, 8.87; N, 5.36 %. Found: C, 73.69; H, 9.02; N, 5.28 %.

Ethyl 3-[N-(*R*)-1-phenylethyl]-amino-4,4-dimethyl-2-pentenoate (1ai): oil; IR (neat) 3320, 1685, 1520, 1245, 1055, 695 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.19 (s, 9H), 1.30 (t, 3H, *J* = 7.1 Hz), 1.52 (d, 3H, *J* = 6.7 Hz), 4.15 (q, 2H, *J* = 7.1 Hz), 4.68 (s, 1H), 5.07 (dq, 1H, *J* = 10.9, 6.7 Hz), 7.15-7.42 (m, 5H), 9.40 (br d, 1H, *J* = 10.9 Hz) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ 14.58, 25.97, 27.71, 29.62, 32.95, 54.01, 58.53, 60.31, 80.69, 125.32, 126.71, 128.56, 145.20, 169.32, 171.85 ppm; MS (m/z): 275 (M⁺, 2), 260 (2), 187 (6), 105 (100); Anal. Calcd for C₁₇H₂₅NO₂: C, 74.14; H, 9.15; N, 5.09 %. Found: C, 74.08; H, 9.27; N, 5.18 %.

2-[N-(*R***)-1-phenylethyl]-amino-1-carboethoxycyclohexene (1aj)**: oil; IR (neat) 3240, 1630, 1580, 1435, 1210, 690 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.29 (t, 3H, *J* = 7.1 Hz), 1.47 (d, 3H, *J* = 6.8 Hz), 1.40-2.40 (m, 8H), 4.17 (q, 2H, *J* = 7.1 Hz), 4.63 (quint, 1H, *J* = 7.1 Hz), 7.16-7.38 (m, 5H), 9.40 (br d, 1H, *J* = 7.6 Hz) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ 15.17, 22.68, 23.07, 24.29, 25.85, 27.11, 52.47, 59.19, 91.01 (q), 125.91, 127.27, 129.16, 146.33 (q), 159.56 (q), 171.44 (q) ppm; MS (m/z): 273 (M⁺, 52), 258 (20), 212 (49), 105 (100); Anal. Calcd for C₁₇H₂₃NO₂: C, 74.69; H, 8.48; N, 5.12%. Found: C, 74.61; H, 8.63; N, 4.92%.

2-(N-isopropyl)-amino-1-carboethoxycyclopentene (1ak): oil; IR (neat) 3300, 1650, 1590, 1250, 1115, 1040 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.17 (d, 6H, *J* = 6.4 Hz), 1.24 (t, 3H, *J* = 7.1 Hz), 1.72-1.89 (m, 2H), 2.42-2.60 (m, 4H), 3.53 (d sept, 1H, *J* = 9.2, 6.4 Hz), 4.12 (q, 2H, *J* = 7.1 Hz), 7.32 (brs d, *J* = 9.2, 1H Hz) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ 14.74, 21.07, 24.32, 28.81, 31.83, 58.28, 67.62, 91.98 (q), 163.87 (q), 168.50 (q) ppm; MS (m/z): 197 (M⁺, 40), 182 (15), 150 (40), 136 (100); Anal. Calcd for C₁₁H₁₉NO₂: C, 66.97; H, 9.71; N, 7.10 %. Found: C, 66.81; H, 9.78; N, 7.18 %.

Ethyl 3-[N-(*R*)-1-phenylethyl]-amino-3-phenyl-2-propenoate (1al): oil; IR (neat) 3260, 1640, 1595, 1470, 1275, 1160 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.30 (t, 3H, *J* = 7.1 Hz), 1.47 (d, 3 H, *J* = 6.8 Hz), 4.19 (q, 2 H, *J* = 7.0 Hz), 4.45 (dq, 1 H, *J* = 9.5, 6.7 Hz), 4.62 (s, 1 H), 7.03-7.42 (m, 10 H), 8.93 (br d, 1 H, *J* = 9.5 Hz) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ 14.59, 24.60, 53.80, 58.78, 86.65, 125.62, 126.84, 127.72, 128.14, 128.49, 129.06, 136.34 (q), 144.80 (q), 164.27 (q), 170.39 (q) ppm; MS (m/z): 295 (M⁺, 57), 280 (9), 207 (60), 105 (100); Anal. Calcd for C₁₉H₂₁NO₂: C, 77.26; H, 7.17; N, 4.74 %. Found: C, 77.18; H, 7.21; N, 4.56 %.

Ethyl 3-anilino-2-butenoate (1am): oil; IR 3250, 1640, 1605, 1260, 1150, 695 (neat) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.29 (t, 3H, J = 7.2 Hz), 1.99 (s, 3H), 4.16 (q, 2H, J = 7.2 Hz), 4.70 (s, 1H), 7.04-7.38 (m,

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5H), 10.40 (br s, 1H) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ 14.58, 20.34, 58.74, 85.99, 124.38, 124.89, 129.03, 139.30 (q), 158.93 (q), 170.38 (q) ppm; MS (m/z): 205 (M⁺, 88), 160 (78), 132 (89), 118 (100); Anal. Calcd for C₁₂H₁₅NO₂: C, 70.22; H, 7.37; N, 6.82 %. Found: C, 70.34; H, 7.28; N, 6.69 %.

Benzyl Azacyclopentane-2-ylideneacetate (1ba): m.p. 75-76 °C (CH₂Cl₂/hexane); IR (neat) 3360, 1635, 1590, 1450, 1230, 1135 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.88-2.05 (m, 2H), 2.59 (t, 2H, *J* = 7.7 Hz), 3.51 (t, 2H, *J* = 7.0 Hz), 4.62 (s, 1H), 5.13 (s, 2H), 7.23-7.42 (m, 5H), 7.95 (brs, 1H) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ 22.51, 32.77, 47.59, 64.84, 76.79, 128.09, 128.25, 128.90, 138.16 (q), 167.46 (q), 170.89 (q) ppm; MS (m/z): 217 (M⁺, 15), 110 (34), 91 (100), 83 (85); Anal. Calcd for C₁₃H₁₅NO₂: C, 71.87; H, 6.96; N, 6.45 %. Found: C, 71.98; H, 7.05; N, 6.49 %.

Benzyl Azacycloheptane-2-ylideneacetate (1bc): m.p. 56-57 °C (CH₂Cl₂/hexane); IR (nujol) 3300, 1640, 1595, 1450, 1150, 690 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.52-1.77 (m, 6H), 2.25-2.34 (m, 2H), 3.25-3.36 (m, 2H), 4.54 (s, 1H), 5.19 (s, 2H), 7.21-7.42 (m, 5H), 8.87 (brs, 1H) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ 26.90, 30.53, 30.95, 35.63, 44.77, 64.73, 81.01, 128.12, 128.29, 128.90, 138.09 (q), 169.41 (q), 170.95 (q) ppm; MS (m/z): 245 (M⁺, 18), 138 (22), 111 (100), 91 (82); Anal. Calcd for C₁₅H₁₉NO₂: C, 73.44; H, 7.81; N, 5.71 %. Found: C, 73.57; H, 7.94; N, 5.56 %.

Benzyl 3-(N-isopropyl)-amino-2-methyl-2-propenoate (1bd): oil; IR (neat) 3320, 1660, 1600, 1100, 690 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) (the two conformer are present in the ratio of about 1:1) δ 1.20 (d, 3H, *J* = 6.5 Hz), 1.21 (d, 3H, *J* = 6.5 Hz), 1.70 (d, 1.5 H, *J* = 0.9 Hz), 1.77 (d, 1.5 H, *J* = 0.7 Hz), 3.27-3.55 (m, 1H), 3.95 (m, 0.5 H), 5.16 and 5.17 (two s, 2H), 6.65 (dd, 0.5H, *J* = 12.8, 0.7 Hz), 7.26-7.43 (m, 5 H), 7.48 (dd, 0.5H, *J* = 13.8, 0.9 Hz), 7.57 (m, 0.5 H) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ (in parenthesis the value of the minus conformer) ppm 15.50 (9.46), 24.06 (24.15), 49.30 (49.20), 64.50 (65.03), 88.15 (92.30, q), 127.41 (Ph), 127.56 (Ph), 127.58 (Ph), 127.76 (Ph), 128.35 (Ph), 128.37 (Ph), 137.47 (137.60, q, Ph), 149.50 (145.40), 170.27 (169.23, q); MS (m/z): 233 (M⁺, 13), 218 (3), 142 (5), 91 (100); Anal. Calcd for C₁₄H₁₉NO₂: C, 72.07; H, 8.21; N, 6.00 %. Found: C, 71.93; H, 8.28; N, 6.22 %.

Benzyl 3-(N-isopropyl)-amino-2-ethyl-2-propenoate (1be) (the two conformer are present in the ratio of about 7:3): oil; IR (neat) 3300, 1645, 1590, 1250, 1110, 1040 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.05 (t, 3H, J = 7.4 Hz), 1.21 (d, 6H, J = 6.5 Hz), 2.17 (q, 2H, J = 7.4 Hz), 3.35 (octet, 1H, J = 6.5 Hz), 5.19 (s, 2H), 6.66 (d, 1H, J = 14.1 Hz), 7.25-7.50 (m, 5H), 7.65 (m, 1H) ppm [(*Z*)-*s*-*cis* major conformer]; ¹³C NMR (CDCl₃, 75 MHz) δ 15.94, 24.04, 49.37, 64.49, 69.70, 95.25 (q), 128.31, 128.52, 128.57, 137.49 (q), 149.26, 170.14 (q) ppm (major conformer); MS (m/z): 247 (M⁺, 20), 232 (34), 156 (7), 91 (100); Anal. Calcd for C₁₅H₂₁NO₂: C, 72.84; H, 8.56; N, 5.66 %. Found: C, 72.66; H, 8.48; N, 5.49 %.

Benzyl 3-(N-isopropyl)-amino-2-butanoate (1bf): oil; IR (neat) 3270, 1640, 1590, 1260, 1150, 695 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.22 (d, 6H, *J* = 6.4 Hz), 1.95 (s, 3H), 3.69 (d sept, 1H, *J* = 9.0, 6.4 Hz), 4.49 (s, 1H), 5.10 (s, 2H), 7.23-7.42 (m, 5H), 8.50 (br d, 1H, *J* = 9.0 Hz) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ 19.24, 24.08, 44.51, 64.10, 81.42, 128.36, 128.56, 128.61, 137.52 (q), 166.91 (q), 170.16 (q) ppm; MS (m/z): 233 (M⁺, 30), 142 (32), 124 (22), 91 (100); Anal. Calcd for C₁₄H₁₉NO₂: C, 72.07; H, 8.21; N, 6.00%. Found: C, 72.21; H, 8.18; N, 5.82 %.

Benzyl 3-[N-(*R***)-1-phenylethyl]-amino-3-phenyl-2-propenoate (1bl**): oil; IR (neat) 3260, 1640, 1580, 1270, 1150, 1120 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.49 (d, 3H, *J* = 6.9 Hz), 4.48 (dq, 1H, *J* = 9.5, 6.9 Hz), 4.73 (s, 1H), 5.19 and 5.23 (two d, 2H, *J*_{AB} = 12.5 Hz), 6.98-7.48 (m, 15H), 8.94 (br d, 1H, *J* = 9.5 Hz) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ 24.58, 53.87, 64.67, 86.31, 125.64, 126.90, 127.72, 127.79, 127.89, 128.19,

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128.46, 128.52, 129.14, 136.24 (q), 137.13 (q), 144.70 (q), 164.62 (q), 169.99 (q) ppm; MS (m/z): 357 (M⁺, 32), 249 (43), 231 (25), 220 (100), 77 (52); Anal. Calcd for C₂₄H₂₃NO₂: C, 80.64; H, 6.49; N, 3.92 %. Found: C, 80.51; H, 6.67; N, 3.70 %.

2-[N-(*R***)-1-phenylethyl]-amino-1-carbobenzoxycyclopentene (1bn)**: oil; IR (neat) 3320, 1660, 1600, 1270, 1130, 710 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.51 (d, 3H, *J* = 6.8 Hz), 1.60-1.87 (m, 2H), 2.15-2.34 (m, 1H), 2.45-2.64 (m, 3H), 4.56 (dq, 1H, *J* = 7.4, 6.7 Hz), 5.20, 5.23 (two d, 2H, *J* AB = 13.0 Hz), 7.20-7.46 (m, 10 H), 7.80 (br d, 1H, *J* = 7.4 Hz) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ 21.46, 25.39, 29.41, 32.89, 54.84, 64.77, 93.65 (q), 128.04, 128.82, 128.90, 129.03, 129.08, 129.22, 135.67, (q) 138.07 (q), 165.18 (q), 168.57 (q) ppm; MS (m/z): 321 (M⁺, 12), 277 (18), 207 (14), 105 (100) ; Anal. Calcd for C₂₁H₂₃NO₂: C, 78.47; H, 7.21; N, 4.36 %. Found: C, 78.59; H, 7.43; N, 4.18 %.

Condensation of the (R)-1-phenylethylamine with the ethyl benzoylacetate: A solution of (R)-1-phenylethylamine (1.21 g, 10mmol), ethyl benzoylacetate (1.92 g, 10 mmol) and a catalytic amount of *p*-toluenesulfonic acid in 20 mL of benzene was refluxed under a nitrogen atmosphere with continuous removal of water by means of a Dean-Stark trap during 6 h. The reaction mixture was cooled in an ice bath and subsequently washed with 25 mL of an aqueous sodium bicarbonate solution. After drying over sodium sulfate and removal of the solvent, the resulting oily residue was submitted to column chromatographic separation (10 to 50 % AcOEt on cyclohexane). The amides 9 and 10 reported in the Scheme 3 were isolated and characterized.

N-[(*R***)-1-phenylethyl]-benzoylacetamid (9)**: mp 108-110 °C (CH₂Cl₂/n-hexane); IR (nujol) 3320, 1640, 1550, 1205, 755 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.51 (d, 3H, 7.0 Hz), 2.23 (br s, 1H), 3.89 and 3.95 (two d, 2H, $J_{AB} = 17.0$ Hz), 5.15 (m, 1H), 7.23-7.74 (m, 8H), 7.98 (d, 2H, 7.1 Hz) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ 22.12, 45.26, 49.03, 126.06, 127.29, 128.53, 128.65, 128.84, 134.04, 136.17 (q), 143.08 (q), 164.83 (q), 196.19 (q) ppm; MS (m/z): 267 (M⁺, 12), 120 (100), 105 (90), 77 (62); Anal. Calcd for C₁₇H₁₇NO₂: C, 76.38; H, 6.41; N, 5.24 %. Found: C, 76.53; H, 6.55; N, 5.02 %.

N,N'-[di-(*R***)-1-phenylethyl]-3-amino-3-phenyl-2-propenamid (10)**: mp 46-48 °C (CH₂Cl₂/n-hexane); IR (nujol) 3270, 1610, 1300, 1205, 760, 690 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.46 (d, 3H, 6.9 Hz), 1.53 (d, 3H, 6.7 Hz), 4.39 (dq, 1H, 9.6, 6.8 Hz), 4.50 (s, 1H), 5.15-5.48 (m, 2H), 7.07-7.42 (m, 15H), 9.40 (br d, 1H, 9.6 Hz) ppm; ¹³C NMR (CDCl₃, 75 MHz) δ 22.50, 24.72, 48.04, 53.77, 89.87, 125.77, 126.10, 126.57, 127.05, 127.79, 128.03, 128.33, 128.59, 128.73, 136.95 (q), 144.15 (q), 145.28 (q), 161.60 (q), 169.34 (q) ppm; MS (m/z): 370 (M⁺, 6), 249 (47), 231 (49), 220 (100), 132 (26), 105 (92); Anal. Calcd for C₂₅H₂₆N₂O: C, 81.05; H, 7.07; N, 7.56 %. Found: C, 81.19; H, 7.18; N, 7.38 %.

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