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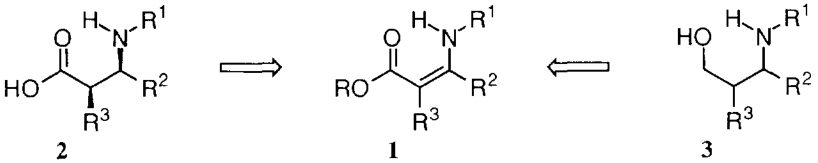
Abstract: A versatile route to β-enamino esters **1**, using accessible starting materials, was developed. Lithiated enamines are allowed to react with diethyl carbonate or benzyl chloroformate with the formation of the β-enamino esters **1a** or **1b**. The reaction is rather general from a wide array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

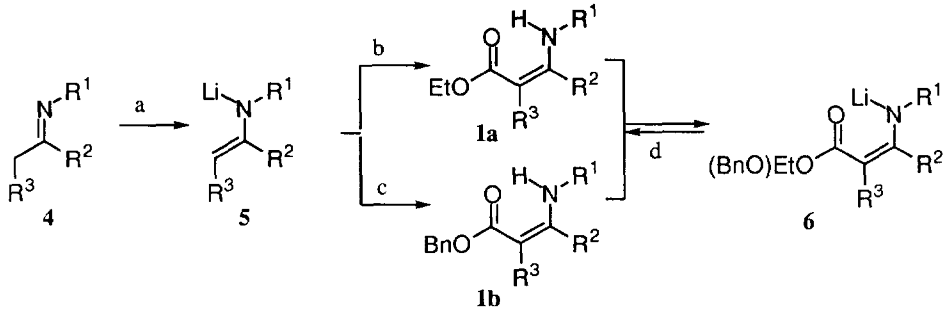
β-Enamino acid derivatives, particularly β-enamino esters (**1**), are important building blocks in organic synthesis.[1] β-Enamino esters are a highly versatile class of intermediates in the synthesis of biologically active compounds such as β-aminoacids (**2**) or γ-aminoalcohols (**3**), easily obtainable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

Scheme 1



In particular the cyclic β-enamino esters **1aa-ac** (R^1-R^2 = $(CH_2)_n$; 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 NH_4Cl.

Table 1. Acylation of imines **4** to β-enamino esters **1a** and **1b**.

Entry	Imine	R^1	R^2	R^3	Product	Yields (%)[a]
1	**4a**	$(CH_2)_3$		H	**1aa**	70
2	**4b**	$(CH_2)_4$		H	**1ab**	59
3	**4c**	$(CH_2)_5$		H	**1ac**	72
4	**4d**	Pr^i	H	Me	**1ad**	59
5	**4e**	Pr^i	H	Et	**1ae**	43
6	**4f**	Pr^i	Me	H	**1af**	62
7	**4g**	(*R*)-PhMeCH	Me	H	**1ag**	61
8	**4h**	(*R*)-PhMeCH	Pr^i	H	**1ah**	57
9	**4i**	(*R*)-PhMeCH	Bu^t	H	**1ai**	75
10	**4j**	(*R*)-PhMeCH	$(CH_2)_4$		**1aj**	70
11	**4k**	Pr^i	$(CH_2)_3$		**1ak**	45
12	**4l**	(*R*)-PhMeCH	Ph	H	**1al**	66
13	**4m**	Ph	Me	H	**1am**	42
14	**4a**	$(CH_2)_3$		H	**1ba**	76
15	**4c**	$(CH_2)_5$		H	**1bc**	48
16	**4d**	Pr^i	H	Me	**1bd**	34
17	**4e**	Pr^i	H	Et	**1be**	43
18	**4f**	Pr^i	Me	H	**1bf**	53
19	**4l**	(*R*)-PhMeCH	Ph	H	**1bl**	67
20	**4n**	(*R*)-PhMeCH	$(CH_2)_3$		**1bn**	63

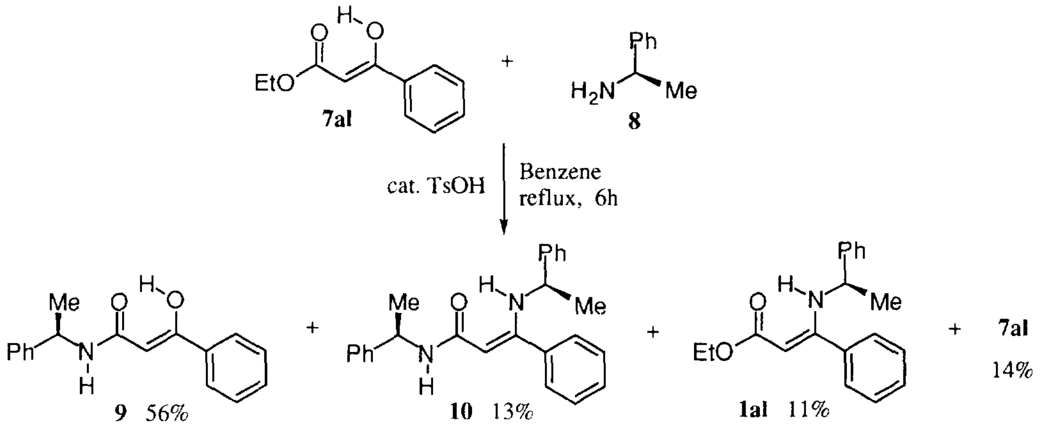
[a] Yields related to the starting imines **4**.

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 formation[6] 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 **1al**. 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 **1al** 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]

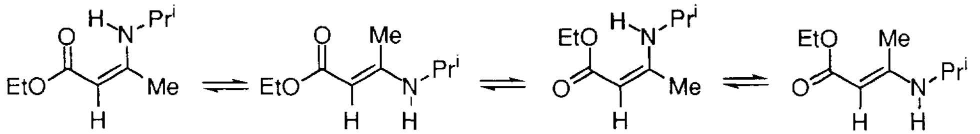
Scheme 3



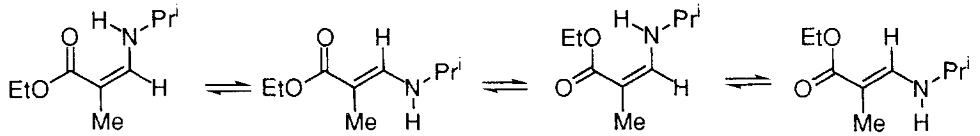
Sometimes side products such as urethanes derived from the reaction of LDA with diethyl carbonate or benzyl chloroformate were also present in the reaction mixture but these side products can be easily removed by flash chromatography. To avoid the formation of urethanes, more sterically hindered bases 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 **1af** 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 $CDCl_3$ ^1H NMR spectrum). Products **1ad, ae, bd, be**, obtained from aldimines (R^2 = 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 method[10]. 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 **1ad** 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



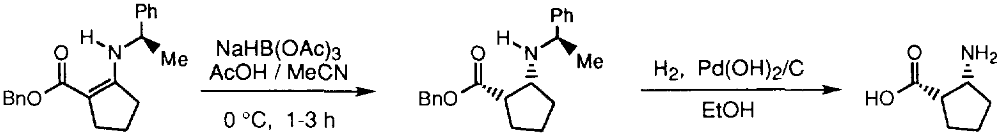
1af	(*Z*)-*s*-*cis*	(*E*)-*s*-*cis*	(*Z*)-*s*-*trans*	(*E*)-*s*-*trans*
	0.00 Kcal/mol	2.08 Kcal/mol	2.11 Kcal/mol	3.49 Kcal/mol



1ad	(*Z*)-*s*-*cis*	(*E*)-*s*-*cis*	(*Z*)-*s*-*trans*	(*E*)-*s*-*trans*
	0.19 Kcal/mol	0.00 Kcal/mol	1.25 Kcal/mol	0.52 Kcal/mol

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]

Scheme 5



1bn

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. ^{1}H and ^{13}C-NMR spectra were measured on a Varian VXR 300 (300 and 75 MHz) in $CDCl_3$ 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] Imines **4d-m** were prepared by condensation of aldehydes or ketones with the appropriate amine according to literature.[12]

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 CH_2Cl_2 is followed by water hydrolysis (10 ml saturated aq. NH_4Cl). The organic layer is dried over Na_2SO_4, 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 (CH_2Cl_2/hexane); IR (nujol) 3340, 1645, 1580, 1230, 1135, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 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; ^{13}C NMR ($CDCl_3$, 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 $C_8H_{13}NO_2$: 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 ($CDCl_3$, 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; ^{13}C NMR ($CDCl_3$, 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 $C_9H_{15}NO_2$: 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 ($CDCl_3$, 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; ^{13}C NMR ($CDCl_3$, 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 $C_{10}H_{17}NO_2$: 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 ($CDCl_3$, 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]; ^{13}C NMR ($CDCl_3$, 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 $C_9H_{17}NO_2$: 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 ($CDCl_3$, 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]; ^{13}C NMR ($CDCl_3$, 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 $C_{10}H_{19}NO_2$: 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 ($CDCl_3$, 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; ^{13}C NMR ($CDCl_3$, 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 $C_9H_{17}NO_2$: 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}; ^{1}H NMR (CDCl$_3$, 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; ^{13}C NMR (CDCl$_3$, 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 $C_{14}H_{19}NO_2$: 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}; ^{1}H NMR (CDCl$_3$, 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; ^{13}C NMR (CDCl$_3$, 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 $C_{16}H_{23}NO_2$: 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}; ^{1}H NMR (CDCl$_3$, 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; ^{13}C NMR (CDCl$_3$, 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 $C_{17}H_{25}NO_2$: 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}; ^{1}H NMR (CDCl$_3$, 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; ^{13}C NMR (CDCl$_3$, 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 $C_{17}H_{23}NO_2$: 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}; ^{1}H NMR (CDCl$_3$, 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; ^{13}C NMR (CDCl$_3$, 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 $C_{11}H_{19}NO_2$: 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}; ^{1}H NMR (CDCl$_3$, 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; ^{13}C NMR (CDCl$_3$, 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 $C_{19}H_{21}NO_2$: 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}; ^{1}H NMR (CDCl$_3$, 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, 5H), 10.40 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 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 $C_{12}H_{15}NO_2$: 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 (CH_2Cl_2/hexane); IR (neat) 3360, 1635, 1590, 1450, 1230, 1135 cm^{-1}; ^{1}H NMR ($CDCl_3$, 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; ^{13}C NMR ($CDCl_3$, 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 $C_{13}H_{15}NO_2$: 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 (CH_2Cl_2/hexane); IR (nujol) 3300, 1640, 1595, 1450, 1150, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 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; ^{13}C NMR ($CDCl_3$, 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 $C_{15}H_{19}NO_2$: 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}; ^{1}H NMR ($CDCl_3$, 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 = O.9 Hz), 1.77 (d, 1.5 H, J = O.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, O.7 Hz), 7.26-7.43 (m, 5 H), 7.48 (dd, 0.5H, J = 13.8, O.9 Hz), 7.57 (m, 0.5 H) ppm; ^{13}C NMR ($CDCl_3$, 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 $C_{14}H_{19}NO_2$: 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}; ^{1}H NMR ($CDCl_3$, 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]; ^{13}C NMR ($CDCl_3$, 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 $C_{15}H_{21}NO_2$: 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}; ^{1}H NMR ($CDCl_3$, 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; ^{13}C NMR ($CDCl_3$, 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 $C_{14}H_{19}NO_2$: 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}; ^{1}H NMR ($CDCl_3$, 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; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.58, 53.87, 64.67, 86.31, 125.64, 126.90, 127.72, 127.79, 127.89, 128.19, 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 $C_{24}H_{23}NO_2$: 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 ($CDCl_3$, 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; ^{13}C NMR ($CDCl_3$, 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 $C_{21}H_{23}NO_2$: 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 (CH_2Cl_2/n-hexane); IR (nujol) 3320, 1640, 1550, 1205, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 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; ^{13}C NMR ($CDCl_3$, 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 $C_{17}H_{17}NO_2$: 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 (CH_2Cl_2/n-hexane); IR (nujol) 3270, 1610, 1300, 1205, 760, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 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; ^{13}C NMR ($CDCl_3$, 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 $C_{25}H_{26}N_2O$: C, 81.05; H, 7.07; N, 7.56 %. Found: C, 81.19; H, 7.18; N, 7.38 %.

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