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TETRAHEDRON

Stereoselective Synthesis of 5-Alkyliden-6-aminotetrahydro-2-pyranones Through an Unexpected Isomerization of the Hydroxytetrahydro-2-pyridinones Obtained by the Selective Reduction of Acylated Enaminones.

Cristina Cimarelli and Gianni Palmieri *

Dipartimento di Scienze Chimiche, via S. Agostino 1, I-62032 Camerino, Italy

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Abstract: A convenient methodology for the stereoselective preparation of 5-alkyliden-6-aminotetrahydro-2-pyranone **4** is reported. The synthesis of 2-pyranone **4** occurs through an unknown isomerization mechanism of the hydroxytetrahydro-2-pyridinone **3**, an accessible starting material obtained by mild and selective reduction of the 5-acyltetrahydro-2-pyridinone **2**. The isomerization mechanism and the stereoselectivity in the synthesis of 2-pyranone **4** was investigated and rationalized.

The development of new selective methodologies applied to β-dicarbonyl compounds and to their derivatives, constitutes an active area of investigation in synthetic organic chemistry. The ease of preparation of enaminones, whose the regio- and the stereoselective synthesis and functionalization have been subject of our research for some time,[1] makes them attractive intermediates for organic synthesis. Enamino ketones and enamino esters can be reduced to γ-aminoalcohols or β-aminoacids, important classes of organic compounds of proved biological and pharmacological activity. The problematic reduction of enaminones is possible through a previous treatment with an acylating agent which allows the carbonyl group to become electrophilic enough to be attacked by hydride.[2] Acylation may be performed through the aza-annulation of enaminones with α,β-unsaturated acid chlorides or esters, recently reported to be a very efficient method for the formation of nitrogen heterocycles such as piperidine, indolizidine, and quinolizidine, contained in alkaloids.[3]

In this paper, we have found that both cyclic N-acylenaminones **2a-l** or acyclic ones **5a-c** can be reduced regioselectively under mild conditions with sodium borohydride in methanol to the corresponding β-hydroxyenamides **3a-l** and **6a-c** respectively (see table 1 and 2). In addition the β-hydroxyenamide **3** isomerize in acetic acid with the stereoselective formation of the 5-alkyliden-6-aminotetrahydro-2-pyranone **4**. It is noteworthy that homochiral 2-pyranone skeletons are present in a wide variety of natural products and used as chiral building blocks.[4] Generally low *d.e.* (5-20 %) were obtained in the reduction of the acylenaminones **2k,l** and **5b,c**, in the standard conditions, where enantiopure (*R*)-1-phenylethylamine is used for the preparation of the starting enaminone. Better *d.e.* were obtained lowering the reaction temperature (see note d table 1).

Treatment of alcohols **6a** and **6b** with acetic acid for 1 h at 40 °C affords to the 4-hydroxy-2-pentanone and the imine **7b** respectively (see Scheme 1). The formation of the imine **7b** occurs through the intramolecular transfer of the benzoyl group to the oxygen atom and successive elimination of benzoic acid.

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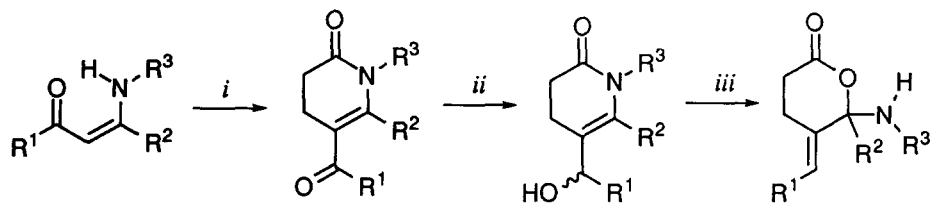
Table 1. Regioselective reduction of the cyclic N-acylenaminones **2a-l** to the hydroxyenamides **3a-l** and isomerization of them to the 5-alkyliden-6-aminotetrahydro-2-pyranones **4b-f,k,l**.



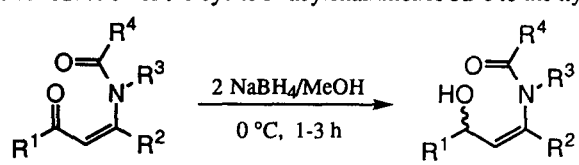
1a-l **2a-l** **3a-l** **4b-e,k,l**

i: acryloyl chloride/THF, reflux; *ii*: 2 $NaBH_4$/MeOH, 0 °C, 1-3 h; *iii*: AcOH, 40 °C, 1 h.

2	R^1	R^2	R^3	3	Yield (%) [a]	*d.e.*	4	Yield (%) [a]	*d.e.*
2a	Me	Me	H	**3a**	84				
2b	Me	Me	Me	**3b**	97		**4b**	53	
2c	Me	Me	Ph	**3c**	95		**4c**	70	
2d	Me	Me	Bn	**3d**	86		**4d**	67	
2e	Ph	Me	Bn	**3e**	82		**4e**	85	
2f	Ph	Me	Ph	**3f**	87		**4f**	73	
2g	$(CH_2)_3$		Me	**3g**	60				
2h	$(CH_2)_3$		Ph	**3h**	31				
2i	CH_2-CMe_2-CH_2		Me	**3i**	20				
2j	CH_2-CMe_2-CH_2		Ph	**3j**	30				
2k	Me	Me	(*R*)-PhMeCH	**3k**	95 [b]	20 [c,d]	**4k**	72	> 98 [c]
2l	Ph	Me	(*R*)-PhMeCH	**3l**	87 [b]	18 [c,d]	**4l**	83	> 98 [c]

[a] Calculated on pure isolated products. [b] Isolated as mixtures of the two diastereomers. [c] Determined by HPLC and ^{1}HNMR of purified but unaltered reaction mixtures of the two diastereomers (configuration of the major diastereomer unknown). [d] The *d.e.* = 60 % is obtained when the reaction were performed at -60 °C for 1 h.

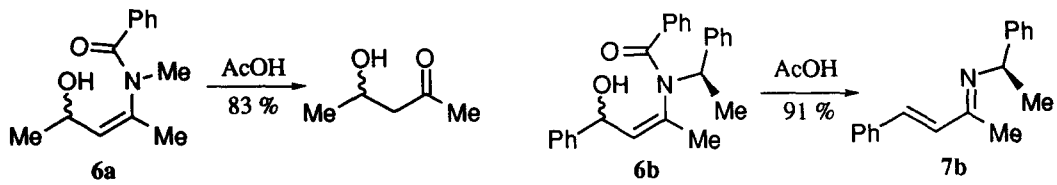
Table 2. Regioselective reduction of the cyclic N-acylenaminones **5a-c** to the hydroxyenamides **6a-c**.



5a-c **6a-c**

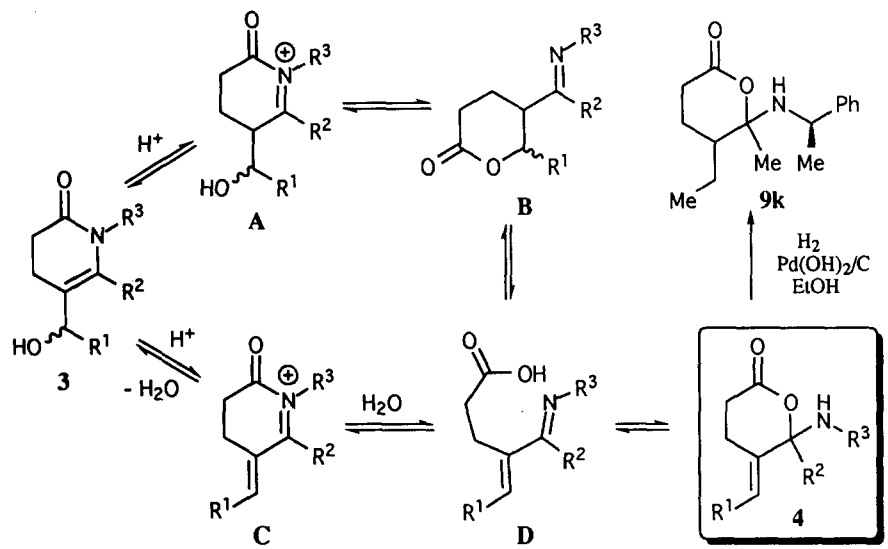
5	R^1	R^2	R^3	R^4	6	Yield (%) [a]	*d.e.*
5a	Me	Me	Me	Ph	**6a**	86	-
5b	Ph	Me	(*R*)-PhMeCH	Ph	**6b**	91 [b]	9 [c]
5c	Me	Me	(*R*)-PhMeCH	Me	**6c**	92 [b]	5 [c]

[a] Calculated on pure isolated products. [b] Isolated as mixtures of the two diastereomers. [c] Determined by HPLC and 1 HNMR of purified but unchanged reaction mixtures of the two diastereomers (configuration of the major diastereomer unknown).



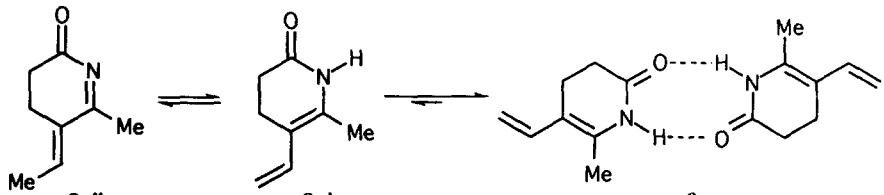
Scheme 1. Acidic treatment of the acyclic β-hydroxyenamide **6a,b**.

Otherwise to the acyclic compounds **6a-c**, the treatment of the cyclic alcohols **3b-f,k,l** with acetic acid for 1 h at 40 °C allows the formation of the 5-alkyliden-6-aminotetrahydro-2-pyranone **4**. This molecular rearrangement can occur through two alternative mechanism hypothesis showed in Scheme 2. In the first more probable mechanism hypothesis, the protonated intermediate **A**, through an intramolecular nucleophilic substitution at the acyl group, leads to the lactone **B**. An alternative mechanism provides the hydrolysis of the product of elimination **C**. Both the alternative pathways afford to δ-imino acid **D**, that cyclizes to the 5-alkyliden-6-aminotetrahydro-2-pyranone **4**. Unique exception to this behaviour is the alcohol **3a** (R^3= H), that affords only to the elimination product **8a**. Treating the bicyclic alcohols **3g-j** with the standard acidic conditions affords only to unaltered starting material. This different experimental behaviour may depend on the constrained (restricted) geometry of the starting materials **3g-j** in which the hydroxy group (intermediate **A**) is too far from the amide function for a nucleophilic attack to take place. This experimental evidence indirectly confirms the first mechanism hypothesis.



Scheme 2. Mechanism hypothesis for the isomerization of the hydroxyenamide **3** to the 5-alkyliden-6-aminopyran-2-one **4**.

Spectroscopic characterization shows that the compound **8a** is present only in the enaminic form (**8a'**), that can exist in a more stable dimeric structure. The stability of the dimeric form (**8a**) is due to the two intermolecular hydrogen bonds. This behaviour is in accord with the calculated (PM3) relative heat of formation[5] of the tautomeric structures (see Scheme 3).



Scheme 3. Calculated (PM3) relative heat of formation[5] of the tautomeric structures for **8a**.

The isomerization of the hydroxytetrahydro-2-pyridinone **3**, to the 6-aminotetrahydro-2-pyranone **4** in acetic acid, occurs with high diastereoselectivity when chiral group are bonded to N atom as in the case of the alcohols **3k,l**. The reaction performed indifferently either on the pure, isolated diastereomers of the **3k** and of the **3l** or on the mixture of diastereomers such as obtained from the reduction of **2k,l** afforded to only one epimeric product **4k,l**. This behaviour can be confirmed performing, on the polarimetric cell, the reaction of the pure isolated diastereomer **3lM** (major diastereomer) or **3lm** (minus diastereomer) in acetic acid at 20 °C, and recording the optical activity as showed in the figure 1 for **3l**.

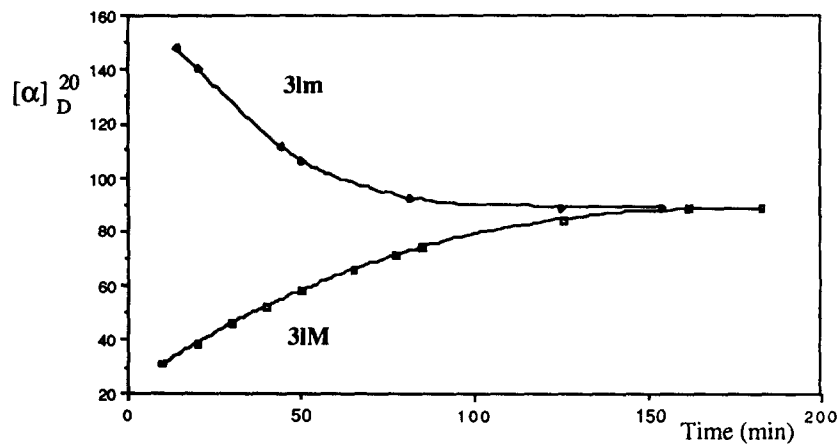


Figure 1. Optical activity showed from the hydroxytetrahydro-2-pyridinone **3lM** (major diastereomer) or **3lm** (minus diastereomer) in acetic acid at 20 °C

The crystals obtained for **4k,l** are not suitable for the determination of the absolute configuration by X-ray diffraction. At the time, different methodologies for the determination of the absolute configuration for **4k,l** are not feasible. Semiempirical molecular modelling calculation (PM3/H_2O) of the heat of formation[5] of the more

stable conformer for the two epimers (6*R*)- and (6*S*)-**4k,l** make possible to attribute teorically the configuration (6*R*) to the new stereogenic centre formed in **4k,l** (see Scheme 4). Thus the cyclization must occur with the nucleophylic attack of the carboxylic group on the *re* face of iminic function in the intermediate **D**.

(6*R*)-**4k,l** (6*S*)-**4k,l**

4k: R^1 = Me	0.0 Kcal/mol	1.7 Kcal/mol
4l: R^1 = Ph	0.0 Kcal/mol	1.3 Kcal/mol

Scheme 4. Calculated (PM3/H_2O) heat of formation[5] of the more stable conformer for the two epimers **4k,l**.

In the attempt to hydrogenolize the chiral group bound at the N atom we have performed the catalytic reduction of the pyranone **4k** with palladium hydroxide on carbon at room temperature for 15 h. We have found that the compound is resistant to the hydrogenolytic conditions applied and only the double bond C=C is reduced with the formation of the pyranone **9k** (see experimental section).

In conclusion we have found a mild and convenient methodology for the stereoselective preparation of 5-alkyliden-6-aminotetrahydro-2-pyranone **4**. The synthesis of 2-pyranone **4** occurs through an unknown isomerization mechanism of the hydroxytetrahydro-2-pyridinone **3**, an accessible starting material obtained by mild and selective reduction of the acylated enaminone **2**.

EXPERIMENTAL SECTION

^1H and ^{13}C-NMR spectra were recorded with a Varian VXR 300 instrument. Chemical shifts are given in ppm downfield from Me_4Si in $CDCl_3$ solution. Coupling constants are given in Hertz. IR spectra were recorded with a Perkin-Elmer 257 spectrometer. GC-MS analyses were performed with an HP 59970 workstation formed by an HP-5890 gas chromatograph equipped with a methyl silicone capillary column and by an HP-5970 mass detector. Optical rotations were measured with a Perkin-Elmer 241 polarimeter using 10 cm cells. THF was dried by refluxing over sodium wires until the blue colour of benzophenone ketyl persisted and then distilled into a dry receiver under nitrogen atmosphere. Commercial methyllithium and butyllithium solutions (Aldrich) were employed under dry atmosphere. Commercial HMPA, TMEDA and TMP (Aldrich) were dried and distilled before use. The (*R*)-(+)-1-phenylethylamine 98% $[\alpha]^{23}_D$ +38°(neat) were purchased from Aldrich and used without further purification.

Preparation of starting enaminones 1a-l, 2a-l and 5a-c.

The enaminones **1a-l** were prepared from the appropriate β-diketone and amine according to described procedure.[6] The enaminones **5a** and **5b** were prepared by benzoylation of **1b** and **1l** respectively while the enaminone **5c** was prepared by acetylation of **1k**. Tetrahydro-2-pyranones **2a-l** were prepared following the general procedure for aza-annulation of the enaminones **1a-l** under the milder conditions reported in literature.[7] The characterization of some enaminones follows.

5-Acetyl-6-methyl-1,2,3,4-tetrahydro-2-pyridinone (2a): mp 130-132 °C (CH_2Cl_2/n-hexane); IR (nujol) 1685, 1580, 1375, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (s, 3 H), 2.26 (s, 3 H), 2.45-2.56 (m, 2 H), 2.62-2.73 (m, 2 H), 8.33 (br s, 1 H); MS *m/z* 153 (M^+, 60), 138 (100), 110 (42); Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.86; H, 7.18; N, 9.26.

5-Acetyl-1,6-dimethyl-1,2,3,4-tetrahydro-2-pyridinone (2b): oil; IR (film) 1655, 1580, 1300, 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.19 (s, 3 H), 2.30 (s, 3 H), 2.38-2.54 (m, 4 H), 3.11 (s, 3 H); MS *m/z* 167 (M^+, 72), 152 (100) 124 (76) 110 (18); Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.42; H, 7.59; N, 8.51.

5-Benzoyl-1-benzyl-6-methyl-1,2,3,4-tetrahydro-2-pyridinone (2e) [7]: mp 73-75 °C (CH_2Cl_2/n-hexane); IR (nujol) 1675, 1605, 1450, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92 (s, 3 H), 2.55-2.78 (m, 4 H), 5.03 (s, 2 H), 7.15-7.73 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 17.02, 23.13, 31.24, 44.21, 117.44, 125.82, 126.83, 128.22, 128.39, 128.42, 132.37 137.24, 138.18, 142.85, 170.37, 196.73; MS *m/z* 305 (M^+, 31), 304 (38), 276 (6), 214 (7); Anal. Calcd. for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.78; H, 6.35; N, 4.42.

5-Benzoyl-6-methyl-1-phenyl-1,2,3,4-tetrahydro-2-pyridinone (2f): mp 98-100 °C (CH_2Cl_2/n-hexane); IR (nujol) 1680, 1620, 1450, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66 (s, 3 H), 2.65-2.84 (m, 4 H), 7.15-7.85 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 19.31, 24.37, 32.48, 117.27, 128.86, 129.19, 129.29, 129.52, 129.85, 133.19, 138.30, 139.10, 144.26, 171.09, 197.73; Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.54; H, 5.96; N, 4.63.

1-Methyl-1,2,3,4,5,6,7,8-octahydro-2,5-quinolinedione (2g): oil; ^1H NMR ($CDCl_3$) δ 1.90-2.06 (m, 2 H), 2.24-2.55 (m, 8 H), 3.08 (s, 3 H); Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.81; H, 7.54; N, 7.64.

1-Phenyl-1,2,3,4,5,6,7,8-octahydro-2,5-quinolinedione (2h): oil; ^1H NMR ($CDCl_3$) δ 1.86-2.14 (m, 4 H), 2.40 (t, 2 H, J = 6.5 Hz), 2.66-2.78 (m, 4 H), 7.09-7.53 (m, 5 H); MS *m/z* 241 (M^+, 47), 212 (100), 184 (17); Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.89; H, 6.03; N, 5.62.

1,7,7-Trimethyl-1,2,3,4,5,6,7,8-octahydro-2,5-quinolinedione (2i): oil; IR (film) 1680, 1600, 1445, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (s, 6 H), 2.27 (s, 2 H), 2.43 (s, 2 H), 2.50-2.58 (m, 4 H), 3.19 (s, 3 H); Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.41; H, 8.12; N, 6.53.

7,7-Dimethyl-1-phenyl-1,2,3,4,5,6,7,8-octahydro-2,5-quinolinedione (2j): oil; ^1H NMR ($CDCl_3$) δ 0.99 (s, 6 H), 1.96 (s, 2 H), 2.27 (s, 2 H), 2.66-2.78 (m, 4 H), 7.08-7.53 (m, 5 H); Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.73; H, 7.21; N, 5.42.

5-Acetyl-6-methyl-1-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydro-2-pyridinone (2k): oil; IR (film) 1665, 1580, 1280, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.78 (d, 3 H, J = 7.3 Hz), 2.09 (s, 3 H), 2.26 (s, 3 H), 2.45-

2.69 (m, 4 H), 5.92 (q, 1 H, J = 7.3 Hz), 7.15-7.41 (m, 5 H); MS m/z 257 (M^+, 53), 153 (91), 138 (100), 110 (23); Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.89; H, 7.35; N, 5.21.

***N*1-methyl-*N*1-[(*Z*)-1-methyl-3-oxo-1-butenyl]benzamide (5a)**: oil ; IR (film) 1640, 1345, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.96 (s, 3 H), 2.25 (s, 3 H), 3.27 (s, 3 H), 5.76 (s, 1 H), 7.23-7.52 (m, 5 H); Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.99; H, 7.19; N, 6.22.

***N*1-(1-methyl-3-oxo-3-phenyl-1-propenyl]-*N*1-[(1*R*)-1-phenylethyl]benzamide (5b)**: oil ; IR (film) 1630, 1590, 1310, 1225 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C) δ 1.77 (d, 3 H, J = 7.1 Hz), 2.06 (s, 3 H), 6.18 (q, 1 H, J = 7.1 Hz), 6.32 (s, 1 H), 7.10-7.65 (m, 15 H); Anal. Calcd. for $C_{25}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 79.69; H, 6.54; N, 4.01.

General procedure for the reduction with $NaBH_4$/MeOH of the acylated enaminones 2a-l and 5a-c to hydroxytetrahydro-2-pyridinones 3a-l and δ-hydroxyenamides 6a-c.

The enaminone (3.0 mmol) dissolved in methanol (10 mL) was treated with $NaBH_4$ (6.0 mmol) at 0 °C and the reaction monitored by TLC. After the reduction was complete (1-3 h) the reaction mixture was partitioned, at room temperature, between water (50 ml) and dichloromethane (100 mL). The organic layer was dried (Na_2SO_4), evaporated under reduced pressure and the residue obtained was submitted to column chromatography (10 to 50 % ethyl acetate on cyclohexane as eluent). The yields of the pure isolated hydroxytetrahydro-2-pyridinone **3a-l** and δ-hydroxyenamides **6a-c** are reported in Table 1.

5-(1-Hydroxyethyl)-6-methyl-1,2,3,4-tetrahydro-2-pyridinone (3a): mp 141-143 °C (CH_2Cl_2-hexane); IR (nujol) 3400, 1650, 1385, 1065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (d, 3H, J = 6.4 Hz), 1.72 (br s, 1 H), 1.84 (t, 3 H, J = 1.4 Hz), 2.10-2.63 (m, 4 H), 4.75 (q, 1 H, J = 6.4 Hz), 7.47 (br s, 1 H). MS m/z 155 (M^+,);^{13}C NMR ($CDCl_3$) δ 15.24, 18.79, 21.27, 30.80, 65.53, 115.27, 127.55, 171.80. Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.18; H, 8.66; N, 9.25.

5-(1-Hydroxyethyl)-1,6-dimethyl-1,2,3,4-tetrahydro-2-pyridinone (3b): oil; IR (film) 3400, 1640, 1390, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (d, 3 H, J = 6.4 Hz), 1.91 (t, 3 H, J = 1.5 Hz), 2.05-2.42 (m, 5 H), 3.04 (s, 3 H), 4.73 (q, 1 H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 14.53, 18.79, 21.77, 29.56, 32.31, 66.43, 120.95, 131.37, 171.66; MS m/z 151 (M^+-18, 100), 122 (68), 108 (64); Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.96; H, 8.76; N, 8.03.

5-(1-Hydroxyethyl)-6-methyl-1-phenyl-1,2,3,4-tetrahydro-2-pyridinone (3c): oil; IR (film) 3400, 1655, 1370, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (d, 3 H, J = 6.4 Hz), 1.55 (t, 3 H, J = 1.5 Hz), 2.21 (br s, 1 H), 2.25-2.65 (m, 4 H), 4.76 (q, 1 H, J = 6.4 Hz), 7.00-7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 15.95, 19.16, 21.89, 32.98, 66.66, 121.33, 128.17, 129.29, 129.51, 131.75, 139.07, 171.41; MS m/z 213 (M^+-18, 100, 184 (34), 170 (60), 118 (26) ;Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.89; H, 7.63; N, 5.81.

1-Benzyl-5-(1-hydroxyethyl)-6-methyl-1,2,3,4-tetrahydro-2-pyridinone (3d): oil; IR (film) 3400, 1650, 1395, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (d, 3 H, J = 6.4 Hz), 1.68 (s, 3 H), 1.95-2.50 (m, 4 H), 3.40 (br s, 1 H), 4.57 (q, 1 H, J = 6.4 Hz), 4.72 and 4.86 (two d, 2 H, J = 16.5 Hz), 6.98-7.25 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.34, 18.89, 21.85, 32.47, 44.98, 66.01, 122.56, 126.57, 127.35, 129.03, 130.62, 138.58, 171.79; MS m/z 227 (M^+-18, 67), 212 (16), 198 (41), 184 (25), 91 (100);Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.31; H, 7.94; N, 5.47.

1-Benzyl-5-[hydroxy(phenyl)methyl]-6-methyl-1,2,3,4-tetrahydro-2-pyridinone (3e): oil; IR (film) 3400, 1650, 1395, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.93 (s, 3 H), 2.40-2.60 (m, 4 H), 3.23 (br s, 1 H), 4.81 and 5.03 (two d, 2 H, J = 16.5 Hz), 5.63 (s, 1 H), 7.05-7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 14.99, 19.68, 32.44, 45.12, 71.60, 121.54, 125.87, 126.66, 127.51, 127.58, 128.75, 129.15, 132.80, 138.52, 142.83, 171.69; MS *m/z* 289 (M^+-18, 75), 260 (62), 198 (29), 91 (100);Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.92; H, 7.03; N, 4.69.

5-[Hydroxy(phenyl)methyl]-6-methyl-1-phenyl-1,2,3,4-tetrahydro-2-pyridinone (3f): oil; IR (film) 3400, 1650, 1395, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 (s, 3 H), 2.25-2.60 (m, 4 H), 4.02 (br s, 1 H), 5.60 (s, 1 H), 7.05-7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 16.46, 19.84, 32.79, 71.53, 121.12, 125.99, 127.54, 128.17, 128.78, 129.28, 129.52, 132.90, 139.10, 143.26, 171.54; MS *m/z* 293 (M^+, 67), 250 (91), 201 (100), 173 (96); Anal. Calcd. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.93; H, 6.68; N, 4.59.

5-Hydroxy-1-methyl-1,2,3,4,5,6,7,8-octahydro-2-quinolinone (3g): oil; IR (film) 3400, 1630, 1360, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60-2.53 (m, 11 H), 3.02 (s, 3 H), 4.12 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ ; MS *m/z* 163 (M^+-18, 100), 134 (43), 120 (32); Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.39; H, 8.46; N, 7.54.

5-Hydroxy-1-phenyl-1,2,3,4,5,6,7,8-octahydro-2-quinolinone (3h): oil; IR (film) 3450, 1645, 1355, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45-1.77 (m, 6 H), 2.10-2.70 (m, 5 H), 4.15 (br s, 1 H), 7.00-7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 18.23, 22.42, 27.23, 31.41, 32.13, 67.37, 123.01, 127.74, 127.91, 128.96, 129.45, 135.62, 170.61; MS *m/z* 225 (M^+-18, 100), 196 (17), 182 (23), 168 (16); Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.27; H, 7.21; N, 5.51.

5-Hydroxy-1,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydro-2-quinolinone (3i): oil; IR (film) 3350, 1620, 1370, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (s, 3 H), 0.98 (s, 3 H), 0.85-2.48 (m, 9 H), 2.95 (s, 3 H), 4.19 (br t, 1 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 20.79, 26.26, 28.31, 30.81, 30.89, 31.42, 39.66, 44.51, 67.64, 115.79, 132.99, 170.89; MS *m/z* 191 (M^+-18, 13), 176 (100), 148 (15), 120 (11); Anal. Calcd. for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.61; H, 9.31; N, 6.84.

5-Hydroxy-7,7-dimethyl-1-phenyl-1,2,3,4,5,6,7,8-octahydro-2-quinolinone (3j): oil; IR (film) 3450, 1635, 1365, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91, (s, 3 H), 1.01, (s, 3 H), 1.78-2.74 (m, 9 H), 3.50-3.62 (m, 1 H), 6.98-7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 17.02, 27.97, 28.18, 31.42, 41.64, 43.52, 49.99, 68.10, 118.73, 128.65, 128.86, 129.53, 137.19, 140.38, 171.02; MS *m/z* 253 (M^+-18, 100), 236 (86), 208 (37), 168 (72);Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.42; H, 7.96; N, 4.93.

5-(1-Hydroxyethyl)-6-methyl-1-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydro-2-pyridinone (3kM) (major diastereomer): oil; IR (film) 3400, 1640, 1390, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (d, 3 H, J = 6.5 Hz), 1.62 (s, 3 H), 1.68 (d, 3 H, J = 7.2 Hz), 2.13-2.50 (m, 5 H), 4.66 (q, 1 H, J = 6.5 Hz), 5.85 (q, 1 H, J = 7.2 Hz), 7.12-7.33 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 15.47, 18.31, 18.81, 21.83, 33.72, 50.83, 66.08, 124.63, 126.42, 127.01, 128.82, 131.69, 142.76, 172.41; MS *m/z* 241 (M^+-18, 76), 226 (46), 198 (52), 105 (100); Anal. Calcd. for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.02; H, 8.34; N, 5.59.

3km (minus diastereomer): oil; IR (film) 3400, 1630, 1390, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, 3 H, 6.3 Hz), 1.60 (s, 3 H), 1.73 (d, 3 H, 7.1 Hz), 1.83 (br s, 1 H), 2.15-2.55 (m, 4 H), 4.68 (q, 1 H, J = 6.3 Hz), 5.90 (q, 1 H, J = 7.1 Hz), 7.14-7.37 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 15.47, 18.78, 18.86, 21.76, 33.82, 50.94, 66.26, 124.51, 126.44, 127.04, 128.79, 131.95, 142.43, 172.30; MS *m/z* 241 (M^+-18, 28), 226 (6), 198 (9), 137 (100);Anal. Calcd. for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.94; H, 8.29; N, 5.63.

5-[1-Hydroxy(phenyl)methyl]-6-methyl-1-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydro-2-pyridinone (3lM) (major diastereomer): mp 144-145 °C (CH_2Cl_2-hexane); $[\alpha]^{20}_D$ +33.45 (c = 1.6, $CHCl_3$); IR (nujol) 3400, 1645, 1390, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (br s, 1 H), 1.76 (d, 3 H, J = 7.0 Hz), 1.83 (s, 3 H), 2.20-2.57 (m, 4 H), 5.70 (s, 1 H), 5.99 (q, 1 H, J = 7.0 Hz), 7.20-7.40 (m, 10 H). ^{13}C NMR ($CDCl_3$) δ 15.56, 17.96, 19.19, 33.15, 50.32, 71.22, 122.69, 125.30, 125.95, 126.59, 127.29, 128.40, 128.43, 133.53, 142.02, 142.18, 171.61; MS *m/z* 303 (M^+-18, 68), 274 (73), 198 (100), 170 (35); Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.51; H, 7.12; N, 4.11.

(de = 24)

3lm (minus diastereomer): oil; IR (film) 3400, 1650, 1390, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70 (br s, 1 H), 1.77 (d, 3 H, J = 7.2 Hz), 1.83 (s, 3 H), 2.20-2.57 (m, 4 H), 5.66 (s, 1 H), 6.05 (q, 1 H, J = 7.2 Hz), 7.20-7.40 (m, 10 H). ^{13}C NMR ($CDCl_3$) δ 15.50, 18.39, 19.02, 33.10, 50.50, 70.43, 124.01, 125.37, 126.13, 126.71, 126.99, 128.16, 128.36, 132.80, 141.51, 142.18, 172.10; MS *m/z* 303 (M^+-18, 51), 274 (46), 198 (100), 170 (29); Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.58; H, 7.04; N, 4.14.

N1[(*Z*)-3-hydroxy-1-methyl-1-butenyl]-N1-methylbenzamide (6a): mp 69-70 °C (CH_2Cl_2-hexane); IR (nujol) 3400, 1610, 1365, 1055 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, 3 H, J = 6.3 Hz), 1.67 (br s, 1 H), 1.84 (s, 3 H), 3.16 (s, 3 H), 4.28 (dq, 1 H, J = 8.9, 6.3 Hz), 5.04 (d, 1 H, J = 8.9 Hz), 7.25-7.47 (m, 5 H); Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.43; H, 7.97; N, 6.18.

***N*1-[(*Z*)-3-hydroxy-1-methyl-3-phenyl-1-propenyl]-*N*1-[(1*R*)-1-phenylethyl]benzamide (6b)** (major diastereomer): oil; IR (film) 3370, 1600, 1370, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.49 (s, 3 H), 1.61 (d, 3 H, J = 7.2 Hz), 1.80 (br s, 1 H), 5.07 (d, 1 H, J = 8.4 Hz), 6.04 (q, 1 H, J = 7.2 Hz), 7.01-7.08 (m, 1 H), 7.17-7.47 (m, 15 H); Anal. Calcd. for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.62; H, 6.63; N, 3.59.

***N*1-[(*Z*)-3-hydroxy-1-methyl-1-butenyl]-*N*1-[(1*R*)-1-phenylethyl]acetamide (6c)** (major diastereomer): oil; IR (film) 3370, 1610, 1380, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (s, 3 H), 1.20 (d, 3 H, J = 6.2 Hz), 1.48 (d, 3 H, J = 7.0 Hz), 1.99 (s, 3 H), 3.23 (br s, 1 H), 4.27-4.46 (m, 1 H), 5.10-5.33 (m, 1 H), 5.82-5.97 (m, 1 H), 7.15-7.32 (m, 5 H); MS *m/z* 229 (M^+-18, 3), 202 (37), 186 (19), 124 (23), 105 (100); Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.71; H, 8.79; N, 5.48.

Isomerization of the hydroxytetrahydro-2-pyridinone 3 to 5-alkyliden-6-aminotetrahydro-2-pyranone 4

The alcohol **3** (1.0 mmol) dissolved in acetic acid (1.0 mL) was allowed to stand at 40 °C for 1 h. The reaction mixture dissolved in CH_2Cl_2 (50 mL) was treated with Na_2CO_3 satured solution. The organic layer was dried (Na_2SO_4), evaporated under reduced pressure and the residue obtained was submitted to column chromatography (30 % ethyl acetate on cyclohexane as eluent). The yields of the pure isolated 5-alkyliden-6-aminotetrahydro-2-pyranone **4** are reported in Table 1.

5-[(E)ethylidene]-6-methyl-6-(methylamino)tetrahydro-2*H*-2-pyranone (4b): oil; IR (film) 3300, 1650, 1545, 1385 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.89 (d, 3 H, J = 6.8 Hz), 2.12-2.23 (m, 2 H), 2.26 (s, 3 H), 2.50-2.61 (m, 2 H), 2.73 (d, 3 H, J = 4.8 Hz), 6.00 (br s, 1 H), 6.79 (q, 1 H, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ 15.27,

22.02, 25.97, 26.70, 35.90, 141.30, 142.11, 173.61, 200.14; MS *m/z* 154 (M^+-15, 8), 139 (24), 126 (100), 110 (22); Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 64.03; H, 8.81; N, 8.13.

6-Anilino-5-[(E)ethylidene]-6-methyltetrahydro-2*H*-2-pyranone (4c): oil; IR (film) 3500, 1655, 1535, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92 (d, 3 H, J = 7.1 Hz), 2.30 (s, 3 H), 2.40 (t, 2 H, J = 7.4 Hz), 2.68 (t, 2 H, J = 7.4 Hz), 6.84 (q, 1 H, J = 7.1 Hz), 7.00-7.60 (m, 5 H), 8.18 (br s, 1 H). ^{13}C NMR ($CDCl_3$) δ 15.41, 21.95, 26.02, 37.08, 120.32, 124.49, 129.35, 129.59, 138.72, 141.94, 171.51, 200.65; MS *m/z* 231 (M^+, 5), 188 (26), 139 (48), 111 (83), 93 (100); Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.83; H, 7.36; N, 5.87.

6-Benzylamino-5-[(E)ethylidene]-6-methyltetrahydro-2*H*-2-pyranone (4d): oil; IR (film) 3300, 1650, 1530, 1390 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (d, 3 H, J = 7.0 Hz), 2.20-2.30 (m, 2 H), 2.23 (s, 3 H), 2.54-2.66 (m, 2 H), 4.38 (d, 2 H, J = 5.9 Hz), 6.23 (br s, 1 H), 6.78 (q, 1 H, J = 7.0 Hz), 7.07-7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 15.31, 22.05, 25.95, 35.91, 43.99, 127.82, 128.26, 129.06, 138.96, 141.32, 142.03, 172.81, 200.08; MS *m/z* 245 (M^+, 5), 202 (26), 148 (13), 106 (100); Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.62; H, 7.97; N, 5.86.

6-Benzylamino-6-methyl-5-[(E)-1-phenylmethylidene]-tetrahydro-2*H*-2-pyranone (4e): oil; IR (film) 3300, 1635, 1450, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33-2.43 (m, 2 H), 2.44 (s, 3 H), 2.82-2.93 (m, 2 H), 4.43 (d, 2 H, J = 5.7 Hz), 6.05 (br m, 1 H), 7.20-7.48 (m, 10 H), 7.56 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.43, 26.43, 36.14, 44.08, 127.93, 128.29, 129.15, 129.29, 129.54, 129.82, 135.52, 138.83, 141.17, 141.98, 172.51, 200.81; MS *m/z* 307 (M^+, 2), 264 (11), 129 (22), 106 (47), 91 (100); Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.36; H, 7.03; N, 4.74.

6-Anilino-6-methyl-5-[(*E*)-1-phenylmethylidene]tetrahydro-2*H*-2-pyranone (4f): oil; IR (film) 3300, 1635, 1450, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45-2.59 (m, 2 H), 2.49 (s, 3 H), 2.88-2.99 (m, 2 H), 7.01-7.61 (m, 11 H), 8.13 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.26, 26.50, 37.26, 120.23, 124.46, 129.33, 129.38, 129.66, 129.82, 135.42, 138.74, 141.04, 142.44, 171.22, 201.32; MS *m/z* 293 (M^+, 13), 250 (21), 201 (37), 173 (24), 93 (100); Anal. Calcd. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 78.04; H, 6.69; N, 4.52.

(6*S*)-5-[(E)ethylidene]-6-methyl-6-{[(1*R*)-1-phenylethyl]amino}-tetrahydro-2*H*-2-pyranone (4k): mp 94-96 °C (CH_2Cl_2-hexane); $[\alpha]^{20}_D$ + 88.5 (c = 4.1, $CHCl_3$); IR (nujol) 3500, 1650, 1530, 1275 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (d, 3 H, J = 7.0 Hz), 1.87 (d, 3 H, J = 7.0 Hz), 2.14-2.28 (m, 2 H), 2.26 (s, 3 H), 2.49-2.64 (m, 2 H), 5.08 (dq, 1 H, J = 7.9, 7.0 Hz), 6.02 (br d, 1 H, J = 7.9 Hz), 6.77 (q, 1 H, J = 7.0 Hz), 7.15-7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 15.32, 22.00, 22.31, 25.97, 36.08, 49.13, 126.66, 127.71, 129.05, 141.51, 141.98, 143.89, 171.91, 200.21; MS *m/z* 259 (M^+, 2), 216 (11), 139 (19), 120 (100); Anal. Calcd. for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.19; H, 8.07; N, 5.61.

(6*S*)-6-methyl-6-{[(1*R*)-1-phenylethyl]amino}-5-[(E)-1-phenylmethylidene]tetrahydro-2*H*-2-pyranone (4l): mp 134-135 °C (CH_2Cl_2-hexane); $[\alpha]^{20}_D$ + 83.3 (c = 3.2, $CHCl_3$); IR (nujol) 3320, 1635, 1520, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (d, 3 H, J = 7.0 Hz), 2.30-2.40 (m, 2 H), 2.42 (s, 3 H), 2.78-2.90 (m, 2 H), 5.10 (dq, 1 H, J = 7.9, 7.0 Hz), 6.31 (br d, 1 H, J = 7.9 Hz), 7.17-7.48 (m, 10 H), 7.52 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.39, 23.40, 26.47, 36.16, 49.17, 126.65, 127.71, 129.09, 129.27, 129.54, 129.88, 135.48, 141.18, 142.00, 143.89, 171.81, 200.99; MS *m/z* 321 (M^+, 9), 278 (12), 174 (36), 120 (67); Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.53; H, 7.03; N, 4.58.

N-[(E,2E)-1-methyl-3-phenyl-2-propenylidene]-N-[(1*R*)-1-phenylethyl]amine (7b): oil; ^1H NMR ($CDCl_3$) δ 1.70 (d, 3 H, J = 7.1 Hz), 2.40 (s, 3 H), 6.18 (q, 1 H, J = 7.1 Hz), 6.37 and 6.48 (two d, 2 H, J_{AB} =

17.1 Hz), 7.18-7.61 (m, 10 H); MS *m/z* 249 (M^+, 16), 248 (100), 205 (9), 105 (73); Anal. Calcd. for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62. Found: C, 86.93; H, 7.51; N, 5.39.

6-Methyl-5-vinyl-1,2,3,4-tetrahydro-2-pyridinone (8a) yields 86%: mp 113-116 °C (CH_2Cl_2-hexane); IR (nujol) 3200, 1685, 1640, 1385 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.94 (s, 3 H), 2.40-2.58 (m, 4 H), 4.90-5.10 (m, 2 H), 6.61 (dd, 1 H, J = 17.2, 10.8 Hz), 7.20 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.85, 20.93, 30.66, 110.59, 111.75, 131.47, 132.79, 172.75; MS *m/z* 137 (M^+, 100), 108 (57), 94 (79); Anal. Calcd. for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.16; H, 8.19; N, 10.06.

Reduction of pyranone 4k to 5-Ethyl-6-methyl-6-{[(1*R*)-1-phenylethyl]amino}tetrahydro-2*H*-2-pyranone (9k)

A mixture of the pyranone **4k** (0.52 g, 2.0 mmol) and 20% $Pd(OH)_2/C$ (50 mg) in EtOH (10 mL) was stirred under a hydrogen atmosphere (70 psi) at room temperature for 15 h. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to give the residue, which was chromatographed on a silica gel column (30% AcOEt on cyclohexane as eluent) to afford **9k** (0.48 g, 93%) as colourless oil; IR (film) 3260, 1620, 1520, 1335 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 and 0.84 (two t, 3 H, J = 7.20), 1.33-2.50 (m, 7 H), 1.45 (d, 3 H, J = 6.9 Hz), 2.07 and 2.10 (two s, 3 H), 5.08 (dq, 1 H, J = 7.9, 6.9 Hz), 6.11 (br d, 1 H, J = 7.9 Hz), 7.17-7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 12.03, 22.29, 25.01, 26.85, 29.23, 34.51, 49.19, 54.09, 126.63, 127.76, 129.09, 143.81, 171.84, 213.14; MS *m/z* 261 (M^+, 11), 163 (34), 141 (9), 120 (100); Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.76; H, 8.68; N, 5.21.

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