



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.

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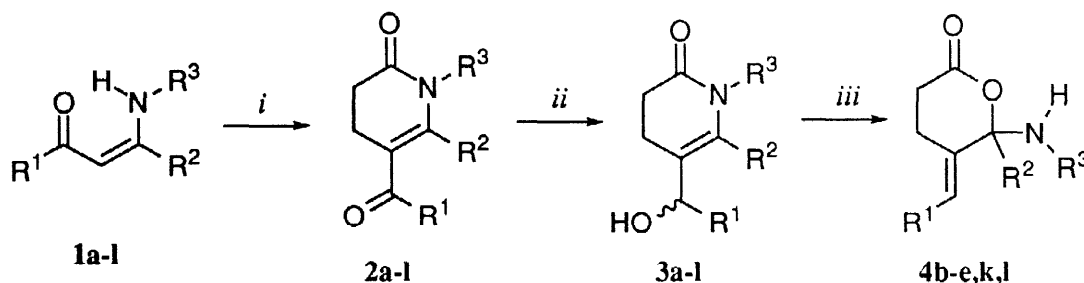
Abstract: A convenient methodology for the stereoselective preparation of 5-alkyliden-6-aminotetrahydro-2-pyranone **4** is reported. The synthesis of 2-pyranone **4** occurs through an unknown isomerization mechanism of the hydroxytetrahydro-2-pyridinone **3**, an accessible starting material obtained 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.

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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).

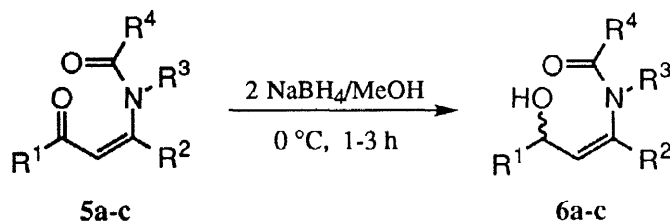
Treatment of alcohols **6a** and **6b** with acetic acid for 1 h at 40 °C affords to the 4-hydroxy-2-pentanone and the imine **7b** respectively (see Scheme 1). The formation of the imine **7b** occurs through the intramolecular transfer of the benzoyl group to the oxygen atom and successive elimination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

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**.

i: acryloyl chloride/THF, reflux; *ii*: 2 NaBH₄/MeOH, 0 °C, 1-3 h; *iii*: AcOH, 40 °C, 1 h.

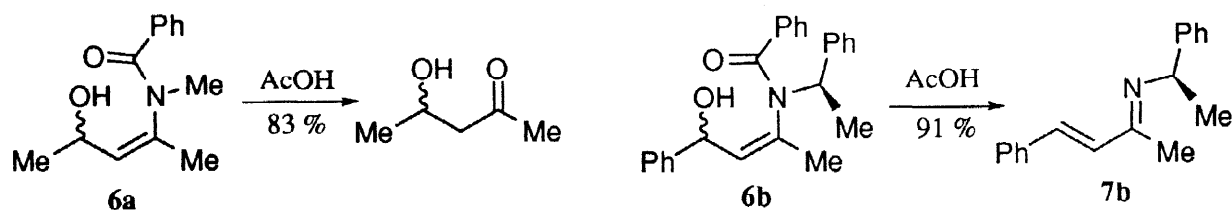
2	R ¹	R ²	R ³	3	Yield (%) ^a	<i>d.e.</i>	4	Yield (%) ^a	<i>d.e.</i>
2a	Me	Me	H	3a	84				
2b	Me	Me	Me	3b	97		4b	53	
2c	Me	Me	Ph	3c	95		4c	70	
2d	Me	Me	Bn	3d	86		4d	67	
2e	Ph	Me	Bn	3e	82		4e	85	
2f	Ph	Me	Ph	3f	87		4f	73	
2g		(CH ₂) ₃	Me	3g	60				
2h		(CH ₂) ₃	Ph	3h	31				
2i		CH ₂ -CMe ₂ -CH ₂	Me	3i	20				
2j		CH ₂ -CMe ₂ -CH ₂	Ph	3j	30				
2k	Me	Me	(<i>R</i>)-PhMeCH	3k	95 ^b	20 ^{c d}	4k	72	> 98 ^c
2l	Ph	Me	(<i>R</i>)-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 ¹HNMR 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**.

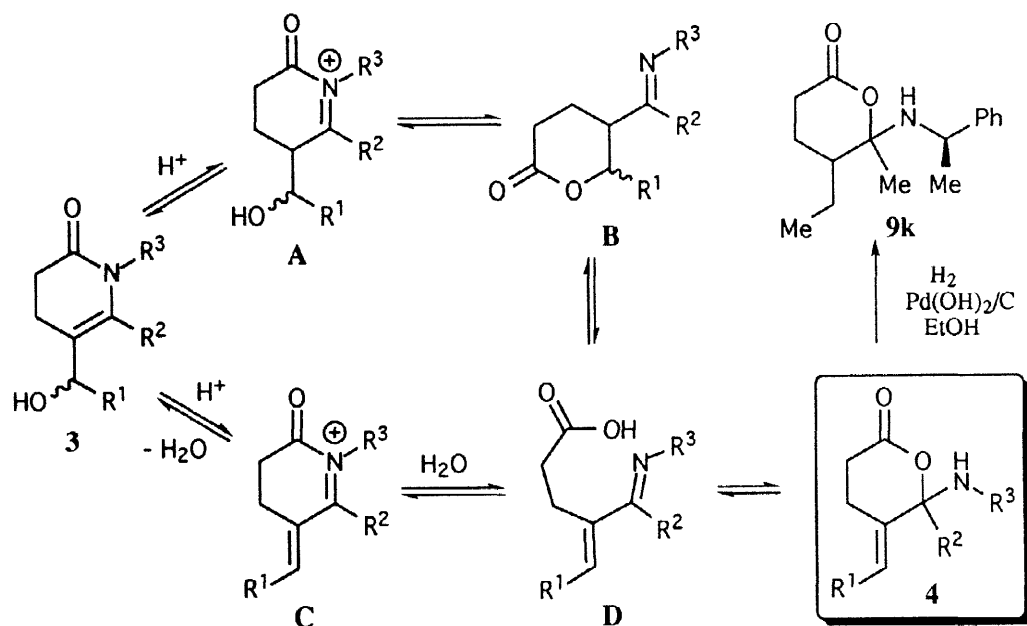
5	R ¹	R ²	R ³	R ⁴	6	Yield (%) ^a	<i>d.e.</i>
5a	Me	Me	Me	Ph	6a	86	-
5b	Ph	Me	(<i>R</i>)-PhMeCH	Ph	6b	91 ^b	9 ^c
5c	Me	Me	(<i>R</i>)-PhMeCH	Me	6c	92 ^b	5 ^c

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



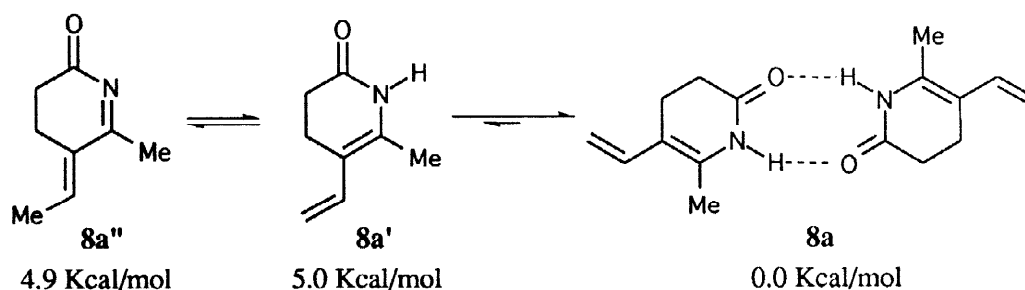
Scheme 1. Acidic treatment of the acyclic β -hydroxyenamide **6a,b**.

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 formation⁵ of the tautomeric structures (see Scheme 3).



Scheme 3. Calculated (PM3) relative heat of formation⁵ 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 **3IM** (major diastereomer) or **3Im** (minus diastereomer) in acetic acid at 20 °C, and recording the optical activity as showed in the figure 1 for **3l**.

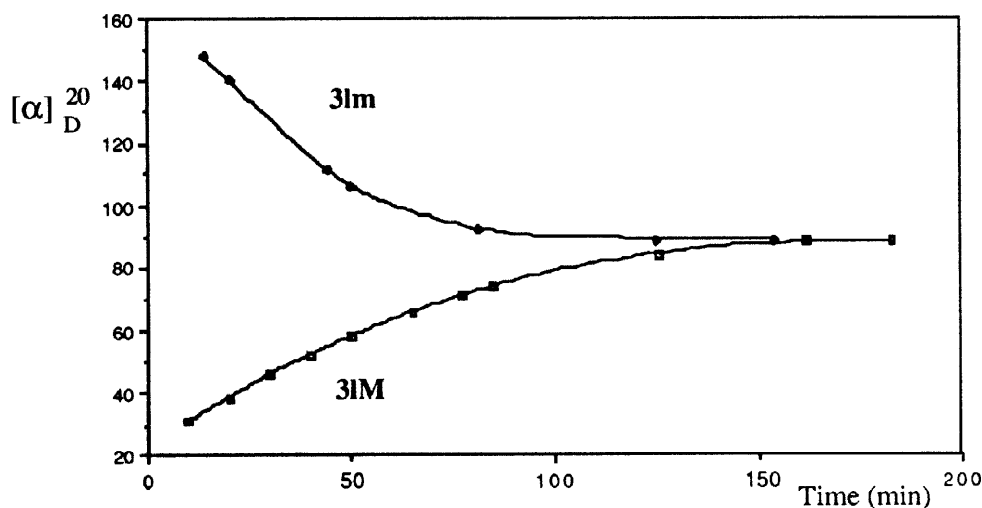
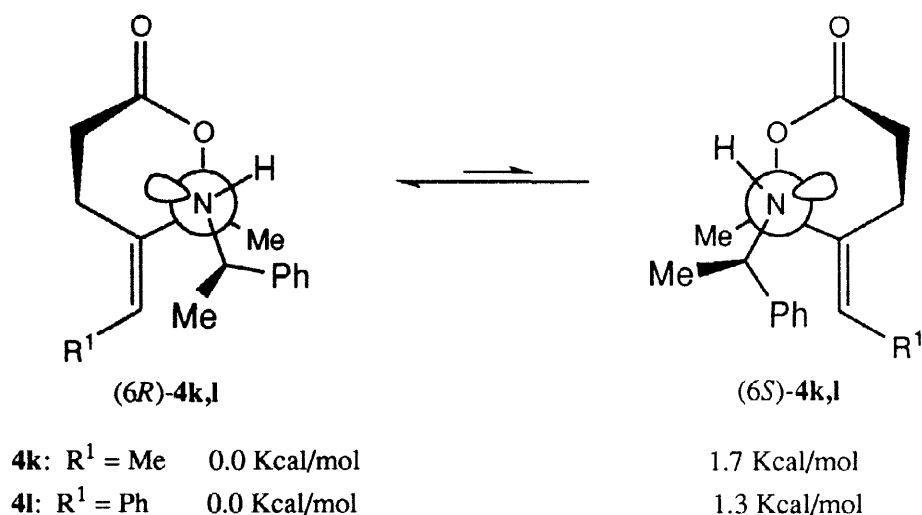


Figure 1. Optical activity showed from the hydroxytetrahydro-2-pyridinone **3IM** (major diastereomer) or **3Im** (minus diastereomer) in acetic acid at 20 °C

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/H₂O) of the heat of formation⁵ 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 nucleophilic attack of the carboxylic group on the *re* face of iminic function in the intermediate D.



Scheme 4. Calculated (PM3/H₂O) heat of formation⁵ 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 ¹³C-NMR spectra were recorded with a Varian VXR 300 instrument. Chemical shifts are given in ppm downfield from Me₄Si in CDCl₃ 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% [α]_D²³ +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 benzylation 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 (CH₂Cl₂/n-hexane); IR (nujol) 1685, 1580, 1375, 1200 cm⁻¹; ¹H NMR (CDCl₃) 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 C₈H₁₁NO₂: 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 (CDCl₃) 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 C₉H₁₃NO₂: 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): mp 73–75 °C (CH₂Cl₂/n-hexane); IR (nujol) 1675, 1605, 1450, 1190 cm⁻¹; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₂₀H₁₉NO₂: 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 (CH₂Cl₂/n-hexane); IR (nujol) 1680, 1620, 1450, 1200 cm⁻¹; ¹H NMR (CDCl₃) δ 1.66 (s, 3 H), 2.65–2.84 (m, 4 H), 7.15–7.85 (m, 10 H); ¹³C NMR (CDCl₃) 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 C₁₉H₁₇NO₂: 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 (CDCl₃) δ 1.90–2.06 (m, 2 H), 2.24–2.55 (m, 8 H), 3.08 (s, 3 H); Anal. Calcd. for C₁₀H₁₃NO₂: 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 (CDCl₃) 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 C₁₅H₁₅NO₂: 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 (CDCl₃) 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 C₁₂H₁₇NO₂: 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 (CDCl₃) 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 C₁₇H₁₉NO₂: 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 (CDCl₃) 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.

N1-methyl-N1-[(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.

N1-(1-methyl-3-oxo-3-phenyl-1-propenyl)-N1-[(1R)-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 ($\text{M}^+ - 18$, 75), 260 (62), 198 (29), 91 (100); Anal. Calcd. for $\text{C}_{20}\text{H}_{21}\text{NO}_2$: 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 $\text{C}_{19}\text{H}_{19}\text{NO}_2$: 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 ($\text{M}^+ - 18$, 100), 134 (43), 120 (32); Anal. Calcd. for $\text{C}_{10}\text{H}_{15}\text{NO}_2$: 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 ($\text{M}^+ - 18$, 100), 196 (17), 182 (23), 168 (16); Anal. Calcd. for $\text{C}_{15}\text{H}_{17}\text{NO}_2$: 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 ($\text{M}^+ - 18$, 13), 176 (100), 148 (15), 120 (11); Anal. Calcd. for $\text{C}_{12}\text{H}_{19}\text{NO}_2$: 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 ($\text{M}^+ - 18$, 100), 236 (86), 208 (37), 168 (72); Anal. Calcd. for $\text{C}_{17}\text{H}_{21}\text{NO}_2$: 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-[(1R)-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 ($\text{M}^+ - 18$, 76), 226 (46), 198 (52), 105 (100); Anal. Calcd. for $\text{C}_{16}\text{H}_{21}\text{NO}_2$: 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 ($\text{M}^+ - 18$, 28), 226 (6), 198 (9), 137 (100); Anal. Calcd. for $\text{C}_{16}\text{H}_{21}\text{NO}_2$: 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-[(1R)-1-phenylethyl]-1,2,3,4-tetrahydro-2-pyridinone (3IM) (major diastereomer): mp 144–145 °C (CH₂Cl₂-hexane); [α]_D²⁰ +33.45 (c = 1.6, CHCl₃); IR (nujol) 3400, 1645, 1390, 1180 cm⁻¹; ¹H NMR (CDCl₃) 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). ¹³C NMR (CDCl₃) 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 C₂₁H₂₃NO₂: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.51; H, 7.12; N, 4.11.

(de = 24)

3Im (minus diastereomer): oil; IR (film) 3400, 1650, 1390, 1190 cm⁻¹; ¹H NMR (CDCl₃) 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). ¹³C NMR (CDCl₃) 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 C₂₁H₂₃NO₂: 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 (CH₂Cl₂-hexane); IR (nujol) 3400, 1610, 1365, 1055 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₃H₁₇NO₂: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.43; H, 7.97; N, 6.18.

N1-[(Z)-3-hydroxy-1-methyl-3-phenyl-1-propenyl]-N1-[(1R)-1-phenylethyl]benzamide (6b) (major diastereomer): oil; IR (film) 3370, 1600, 1370, 1015 cm⁻¹; ¹H NMR (CDCl₃) 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 C₂₅H₂₅NO₂: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.62; H, 6.63; N, 3.59.

N1-[(Z)-3-hydroxy-1-methyl-1-butenyl]-N1-[(1R)-1-phenylethyl]acetamide (6c) (major diastereomer): oil; IR (film) 3370, 1610, 1380, 1060 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₅H₂₁NO₂: 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 CH₂Cl₂ (50 mL) was treated with Na₂CO₃ saturated solution. The organic layer was dried (Na₂SO₄), 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-2H-2-pyranone (4b): oil; IR (film) 3300, 1650, 1545, 1385 cm⁻¹; ¹H NMR (CDCl₃) 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). ¹³C NMR (CDCl₃) 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-2H-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-2H-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-2H-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-2H-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.

(6S)-5-[(E)ethylidene]-6-methyl-6-[(1R)-1-phenylethylamino]-tetrahydro-2H-2-pyranone (4k): mp 94–96 °C (CH_2Cl_2 -hexane); $[\alpha]_D^{20} + 88.5$ ($c = 4.1$, $CHCl_3$); 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.

(6S)-6-methyl-6-[(1R)-1-phenylethylamino]-5-[(E)-1-phenylmethylidene]tetrahydro-2H-2-pyranone (4l): mp 134–135 °C (CH_2Cl_2 -hexane); $[\alpha]_D^{20} + 83.3$ ($c = 3.2$, $CHCl_3$); 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-[(1R)-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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