Pergamon

Tetrahedron Vol. 50, No. 18, pp. 5503-5514, 1994

0040-4020/94 $6.00+0.00

0040-4020(94)E0204-7

Stereoselective Synthesis of Fused γ-Lactams by Intramolecular Nitrone Cycloaddition

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Abstract: A series of nitrones **5** joined by amides to olefines were prepared *in situ* from the related aldehydes with *N*-methylhydroxylamine. The nitrones added intramolecularly to the olefin, and the cycloadditions gave fused γ-lactams **6** stereoselectively. A stereocentre located in position α to the nitronic functionality **13** completely controls the stereochemical course of the intramolecular cycloaddition, which exclusively affords compound **14** with simultaneous introduction of four stereocentres. The formation of this latter compound was also supported by PM3 calculations. Furthermore, simple heating of unsaturated oxime **17** led to compound **19** via intramolecular oxime olefin cycloaddition.

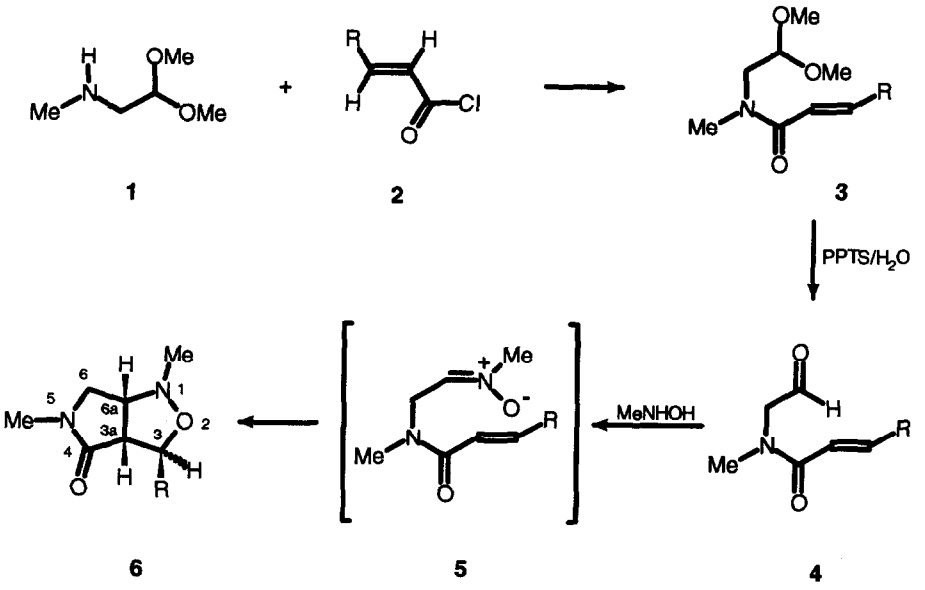
Intramolecular 1,3-dipolar cycloadditions have recently received a great deal of attention, especially in the synthesis of complex carbon frameworks.[1] Such reactions generate two new rings, one of which is a five-membered heterocyclic ring which can be cleaved and then led to the stereospecific introduction of two functional groups. Among the most useful systems in this regard are the nitrile oxide-olefin[2] and nitrone-olefin[3] cycloadditions which have shown considerable synthetic utility in natural product synthesis.[4]

In the course of work performed in this laboratory on nitrile oxide and nitrone-olefin cycloadditions as a useful tool towards the formation of new C-C bonds and the construction of target molecules showing synthetic and biological interest,[5] we wished to examine a novel general approach to functionalized γ-lactams by intramolecular nitrone cycloaddition of a series of unsaturated α-aminoaldehydes. Our interest in such reactions was further stimulated by the possibility of a selective functionalization of the fused systems by ring cleavage of isoxazolidine[6] and/or γ-lactam moieties.[7]

Results and Discussion

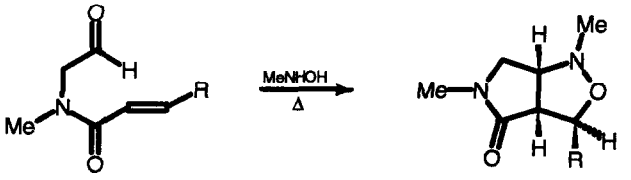
The overall synthetic approach is based on *N*-methylamino acetaldehyde dimethyl acetal **1** which has been reacted with unsaturated acyl chlorides **2** to give the corresponding amides **3**. Sequential treatment of derivatives **3** with pyridinium *p*-toluenesulfonate (PPTS)/H_2O and *N*-methyl hydroxylamine afforded the not isolated nitrones **5** which spontaneously underwent stereoselective intramolecular cycloaddition to fused five-membered ring

lactams **6** (Scheme 1, Table 1).



Scheme 1

Table 1. Reaction of **4a-d** with Methyl hydroxylamine in Ethanol at Reflux Temperature.



	R	Yield %
a	H	30
b	Me	72
c	Et	68
d	Ph	78

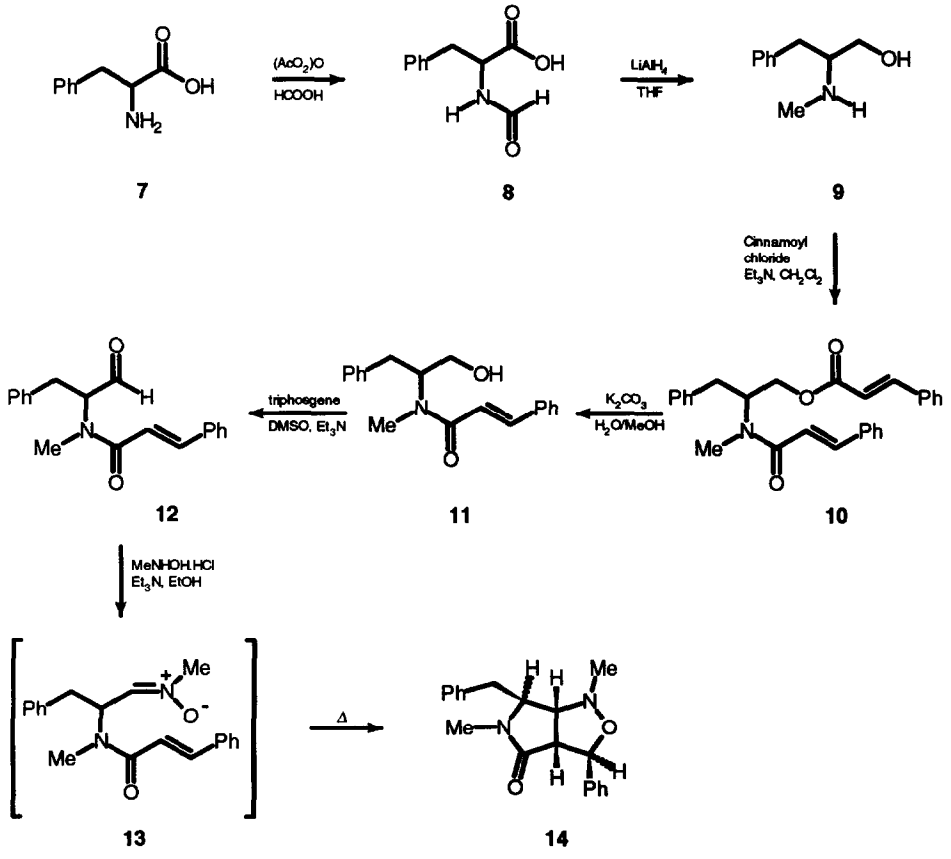
The obtained derivatives were characterized on the basis of analytical and spectroscopic data. High resolution mass spectra showed the correct molecular ions. The ir absorption of the carbonyl group is at 1685-1675 cm^{-1} in accord with γ-lactams. The ^1H nmr spectra showed the H_3 proton in the range 3.98-5.10 δ, while H_{3a} and H_{6a} protons resonate at 3.32-2.90 and 3.58-3.34 δ respectively. Moreover, the methylene protons at C_6 showed different chemical shifts, while their resonances are coincident in the amide precursors **3**.

The investigated 1,3-dipolar cycloadditions showed high regioselectivity; according to similar intramolecular processes, no bridged adducts have been detected in the crude reaction mixture.[3d, 8]

The reactions have been also found to be stereospecific; intramolecular cycloadducts **6** were obtained stereochemically pure, with no evidence in the nmr spectra or tlc of the crude products of any diastereoisomers. The stereochemical informations present in the dipolarophile moiety are completely retained in the cycloadducts and the relative stereochemistry at C_3 and C_{3a} in the formed isoxazolidine ring is predetermined by the alkene geometry.

Furthermore, the ring junction between the isoxazolidine ring and the lactam five-membered ring is always *cis*[8] as confirmed by coupling constants and NOE measurements.

For instance, in compound **6b** the coupling constant for the cis ring junction protons ($J_{3a,6a}$) is 8.1 Hz, indicative of a nearly eclipsed dihedral angle between H_{3a} and H_{6a}. Irradiation of H_{3a} gives rise to a positive NOE effect for H_{6a}, so indicating a *cis* relationship between these protons; likewise, when H_{6a} was irradiated, the signals corresponding to H_{3a} and methylene protons at C_5 were enhanced.



Scheme 2

The stereochemical aspects of these intramolecular cycloadditions have been further investigated. Intramolecular cycloadditions with a stereocentre inserted on the nitrone nitrogen or in the tether connecting dipole and dipolarophile have already been the subjects of recent research.[9] Stereoselection at C_3 of the acyclic substrate appears to give the best results in the control of the stereochemistry of the new formed chiral centres.

We examined the ability of a stereocentre located in position α to the nitrone to completely control the stereochemical course of an intramolecular nitrone cycloaddition to α,β-unsaturated amides. Starting from L-phenylalanine **7**, the β-amidoalcohol **11** has been obtained by standard methods;[10] the subsequent Swern oxidation[11] of **11** afforded aldehyde **12**. By reaction of **12** with *N*-alkylhydroxylamine, nitrone intermediate **13** was formed which spontaneously cyclized to the bicyclic compound **14** as the only obtained cycloadduct (Scheme 2). The stereochemistry of **14** has been assigned on the basis of NOE measurements.

The cycloaddition process was found to proceed diastereoselectively furnishing homochiral compound **14** from homochiral starting material. In fact, the ^1H nmr spectrum of **14**, recorded in the presence of increasing amounts of the chiral shift reagent [Eu(tfc)$_3$] does not show any change of the single resonances, apart from the expectable shifts induced by the paramagnetic reagent.

Thus, in the reaction at hand, the stereocentre at the α position with respect to the nitronic functionality can effectively control the formation of the new contiguous stereocentres and one of the 8 possible stereoisomers is produced in a highly selective fashion. The observed result was also confirmed by semiempirical calculations.

From inspection of Dreiding models are possible two different conformers **13** and **15**, both in *E* or *Z* form, which lead to compounds **14** and **16** respectively (Figure 1).[12]

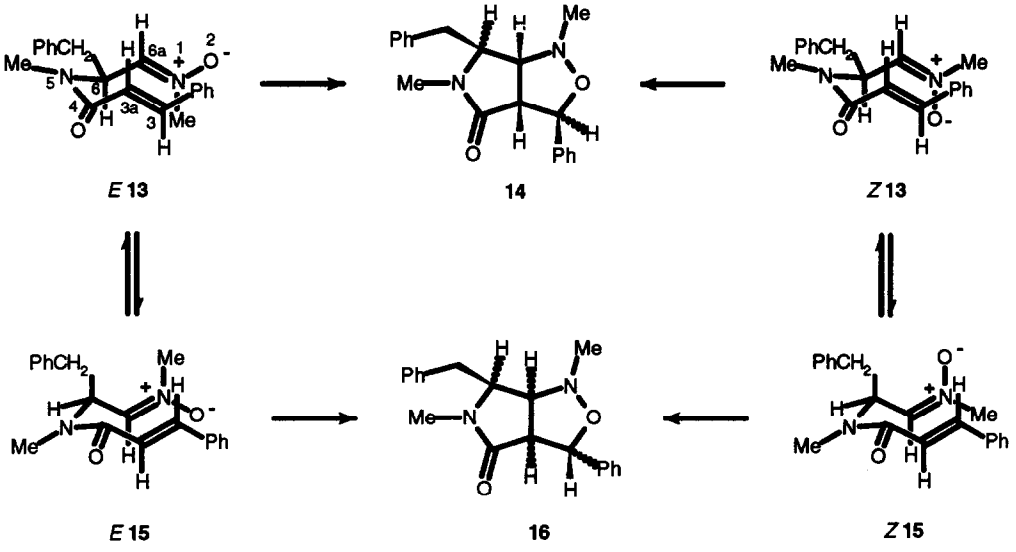


Figure 1

Since **14** is the only cyclic compound of the reaction products, one must expect that *Z* **15** and *E* **15** are energetically unfavoured. In order to have quantitative informations, *Z* **13**, *E* **13**, *Z* **15** and *E* **15**, having the CH_2Ph group in the equatorial or axial accomodations, as well as **14** and **16**, were fully optimized by means of the semiempirical PM3 method using the MOPAC computational package furnished by QCPE.[13]

Table 2. Optimized Geometries (PM3 Calculations) of the Transition States *Z* **13**, *E* **13**, *Z* **15** and *E* **15** (Distances in Å, Angles in Degrees).

	E 13	*Z* 13	*Z* 15	*E* 15		*E* 13	*Z* 13	*Z* 15	*E* 15
$r_{N1\text{-}C2}$	1.245	1.243	1.247	1.249	$\delta_{3a\text{-}C4\text{-}N5}$	119.5	119.6	123.8	124.0
$r_{C3\text{-}C3a}$	1.338	1.337	1.338	1.339	$\delta_{C4\text{-}N5\text{-}C6}$	120.6	120.5	128.8	122.4
$r_{C3a\text{-}C4}$	1.486	1.486	1.486	1.484	$\delta_{N5\text{-}C6\text{-}C6a}$	109.3	109.0	113.4	113.2
$r_{C4\text{-}N5}$	1.422	1.419	1.414	1.419	$\delta_{C6a\text{-}N1\text{-}O2}$	124.4	126.8	127.4	122.1
$r_{N5\text{-}C6}$	1.500	1.502	1.508	1.511	$\delta_{C6\text{-}N5\text{-}CH_3}$	119.4	119.8	114.1	114.4
$r_{C3\text{-}Ph}$	1.461	1.462	1.462	1.461	$\delta_{C6a\text{-}C6\text{-}CH_2Ph}$	106.9	107.6	113.2	117.0
$r_{C4\text{-}O}$	1.224	1.225	1.229	1.227	$\delta_{C3a\text{-}C4\text{-}O}$	122.1	121.9	119.7	120.3
$r_{N5\text{-}CH_3}$	1.476	1.476	1.487	1.489	$\delta_{C6a\text{-}N1\text{-}CH_3}$	118.4	115.7	115.6	123.1
$r_{C6\text{-}CH_2Ph}$	1.547	1.543	1.549	1.549	$\delta_{C3a\text{-}C3\text{-}Ph}$	123.1	123.0	123.1	123.2
r_{CH_2Ph}	1.497	1.497	1.496	1.495					
$r_{C6a\text{-}N1}$	1.331	1.331	1.330	1.331	$\omega_{C3\text{-}C3a\text{-}C4\text{-}C5}$	- 90.0[a]	- 90.0[a]	90.0[a]	90.0[a]
$r_{N1\text{-}CH_3}$	1.499	1.504	1.503	1.496	$\omega_{CH_3\text{-}N5\text{-}C6\text{-}CH_2Ph}$	0.0[a]	0.0[a]	50.9	47.3
$r_{C3a\text{-}C6a}$	2.949	2.929	2.790	2.817	$\omega_{C3a\text{-}C4\text{-}N5\text{-}C6}$	0.0[a]	0.0[a]	0.0[a]	0.0[a]
					$\omega_{CH_3\text{-}N5\text{-}C4\text{-}O}$	0.0[a]	0.0[a]	0.0[a]	0.0[a]
ΔHf[b]	42.26	43.48	49.06	53.75	$\omega_{C4\text{-}C3a\text{-}C3\text{-}Ph}$	180.0[a]	180.0[a]	180.0[a]	180.0[a]
					$\omega_{C4\text{-}N5\text{-}C6\text{-}C6a}$	- 60.1	- 59.4	0.0[a]	0.0[a]
					$\omega_{CH_3\text{-}N1\text{-}C6a\text{-}C6}$	- 1.1	- 177.3	- 174.3	9.6

[a]Assumed Values. [b]Kcal/mol.

In order to avoid deviations towards absolute minima (which do not represent transition states) during optimization of *Z* **13**, *E* **13**, *Z* **15** and *E* **15**, the C_6, N_5, C_4 and C_{3a} atoms were obliged to lie on the same plane; moreover the torsion angle of the CHPh group around the C_{3a}-C_4 bond was frozen to 90°. The phenyl frameworks were assumed to be regular hexagons having $r_{C\text{-}C}$ = 1.97 Å and $r_{C\text{-}H}$ = 1.085 Å.

The most significant optimized geometrical parameters are reported in tables 2 and 3.

Analysis of these data points out that bond lengths and bond angles of the four transition states are nearly equal so that their energy difference is to be attributed to different non bonded interactions. On the contrary, they are remarkably different from those of the cyclic products.

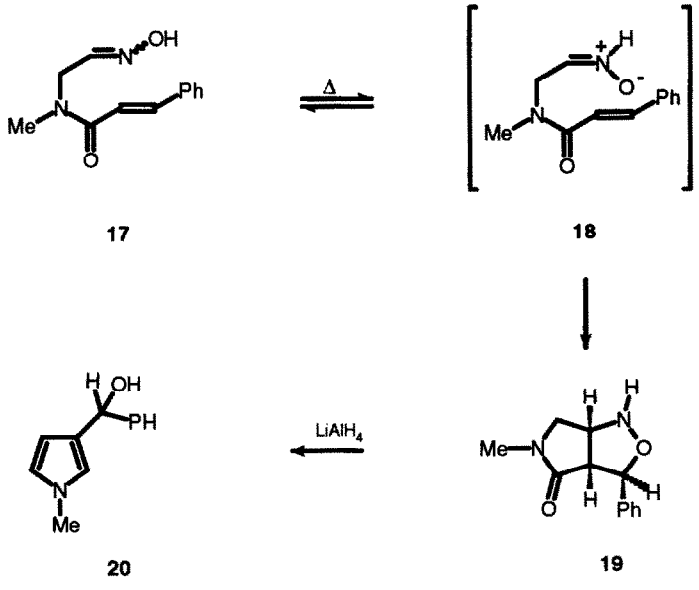
Both compounds **14** and **16** have the pentatomic rings not planar and is folded along the C_3-C_{3a} bond, but **16** is about 5.9 Kcal mol^{-1} less stable than **14**. The transition state *E* **13** is energetically favoured with respect to *Z* **13** and both of them are more stable than *E* **15** and *Z* **15**. According to the Boltzman equation and to the ΔE predicted by calculations, the conformational equilibrium would be: *E* **13** = 88% and *Z* **13** = 12% while *E* **15** and *Z* **15** are absent. On this ground, compound **14** is expected to be the only product of the reaction, in agreement with experimental findings.

Furthermore, we found that simple heating of the unsaturated amidooxime **17**, obtained from **4d** by treatment with PPTS/H_2O and hydroxylamine hydrochloride, led to cycloaddition product **19** derived from the intramolecular oxime olefin cycloaddition reaction[14] *via* the intermediate nitrone **18**. Compound **19**, moreover was transformed by $LiAlH_4$ reduction in the *N*-methyl-3-(phenylmethanol)pyrrole **20**, in 75% yield (Scheme 3).

Table 3. Optimized Geometries (PM3 Calculations) of the Cyclic Compounds **14** and **16** (Distances in Å, Angles in Degrees).

	14	**16**		**14**	**16**
$\delta_{N1\text{-}O2\text{-}C3}$	106.1	106.6	$\omega_{N1\text{-}O2\text{-}C3\text{-}C3a}$	27.6	- 27.1
$\delta_{O2\text{-}C3\text{-}C3a}$	107.3	107.2	$\omega_{O2\text{-}C3\text{-}C3a\text{-}C6a}$	- 12.6	18.6
$\delta_{C3\text{-}C3a\text{-}C6a}$	105.7	106.3	$\omega_{C3\text{-}C3a\text{-}C6a\text{-}N1}$	- 7.7	- 2.0
$\delta_{C6a\text{-}C3a\text{-}C4}$	105.6	105.5	$\omega_{C3a\text{-}C6a\text{-}N1\text{-}O2}$	- 33.0	26.4
$\delta_{C3a\text{-}C4\text{-}N5}$	109.9	110.0	$\omega_{C6a\text{-}N1\text{-}O2\text{-}C3}$	- 33.0	26.4
$\delta_{C4\text{-}N5\text{-}C6}$	110.0	109.6	$\omega_{C6a\text{-}C3a\text{-}C4\text{-}N5}$	- 6.3	0.1
$\delta_{N5\text{-}C6\text{-}C6a}$	105.6	105.0	$\omega_{C3a\text{-}C4\text{-}N5\text{-}C6}$	13.3	15.1
$\delta_{C6\text{-}C6a\text{-}C3a}$	106.9	105.1	$\omega_{C4\text{-}N5\text{-}C6\text{-}C6a}$	- 14.5	- 23.8
$\delta_{C6a\text{-}N1\text{-}O2}$	106.0	107.8	$\omega_{N5\text{-}C6\text{-}C6a\text{-}C3a}$	10.2	23.2
$\delta_{N1\text{-}C6a\text{-}C3a}$	104.9	104.6	$\omega_{C6\text{-}C6a\text{-}C3a\text{-}C4}$	- 2.6	- 14.4
$\delta_{C6\text{-}N5\text{-}CH_3}$	116.7	117.4	$\omega_{CH_3\text{-}N5\text{-}C6\text{-}CH_2Ph}$	83.7	70.6
$\delta_{C6a\text{-}C6\text{-}CH_2Ph}$	111.0	116.0	$\omega_{CH_3\text{-}N5\text{-}C4\text{-}O}$	- 29.7	- 29.2
$\delta_{H\text{-}C6a\text{-}C3a}$	111.9	112.3	$\omega_{C4\text{-}C3a\text{-}C3\text{-}Ph}$	- 133.3	137.2
$\delta_{C6a\text{-}C3a\text{-}H}$	111.9	112.4	$\omega_{CH_3\text{-}N1\text{-}C6a\text{-}Ca}$	28.0	- 19.1
$\delta_{C3a\text{-}C4\text{-}O}$	127.6	127.3	$\omega_{C3\text{-}C3a\text{-}C4\text{-}C5}$	- 121.3	115.4
$\delta_{C3a\text{-}C3\text{-}Ph}$	115.2	110.8	$\omega_{H\text{-}C6a\text{-}C3a\text{-}H}$	-0.4	- 12.7
ΔHf (Kcal/mol)	7.75	13.60			

[a]Bond lengths are practically equal in the two isomers. Those of **14** are: N1-O2 = 1.525; O2-C3 = 1.417; C3-C3a = 1.547; C3a-C4 = 1.518; C4-N5 = 1.435; N5-C6 = 1.500; C3-Ph = 1.515; C4-O = 1.216; N5-CH_3 = 1.472; N1-CH3 = 1.467; C6-CH_2-Ph = 1.536; CH_2-Ph = 1.496; C6a-N1 = 1.491; C3a-C6a = 1.542.



Scheme 3

In conclusion, we have presented new examples of intramolecular 1,3-dipolar cycloadditions which allow a stereoselective synthesis of fused γ-lactams. These ring closures are of potential interest in the stereospecific formation of highly functionalized carbon frameworks that can be considered useful precursors of various cyclic and acyclic molecules.

Extensions of the scope and synthetic potential of these cycloadditions are being further investigated.

Experimental

Mp were determined on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer elemental analyzer. Infrared spectra were recorded on a Perkin-Elmer 225 spectrophotometer and ^1H and ^{13}C nmr on Bruker WP 200 SY instrument; chemical shifts are reported in ppm from internal Me_4Si and refer to $CDCl_3$ solutions. Reaction mixtures were analyzed by tlc on silica gel GF 254 (Merck) and the spots were detected under uv light (254 nm). Flash chromatography was carried out with Kieselgel 60 (Merck). Optical rotation were measured on a P.F. 241 MC Polarimeter (Perkin Elmer).

Preparation of *trans N*-methyl-*N*-(acetaldehyde dimethyl acetal)enamides 3a-d.

General procedure. To a stirred solution containing 50 mmol of methylamino acetaldehyde dimethyl acetal **1**, and 7.5 ml of triethylamine in 50 ml of dry carbon tetrachloride was added dropwise a solution of 55 mmol of corresponding acyl chloride in 50 ml of dry carbon tetrachloride at 0 °C. The solution was stirred at 25 °C for 6 h and then filtered. The obtained solid was washed with 30 ml of carbon tetrachloride, the combined filtrate washed with 10 ml of water, and dried with sodium sulfate. The solvent was removed at reduced pressure, and the residue was subjected to silica flash chromatography using a methanol/chloroform 2:98 mixture as eluent.

Reaction of **1** *with propenoyl chloride* **2a**. First fractions gave *N*-methyl-*N*-(acetaldehyde dimethyl acetal)propenamide **3a**, 98% yield; light yellow oil; ir (neat) 2940, 2840, 1735, 1660, 1460, 1410, 1280, 1190, 1105, 1075, 980, 800, 725 cm^{-1}. ^1H NMR:[15] δ ($CDCl_3$) 3.08, 3.12 (s, total 3H, N-CH_3), 3.43 (s, 6H, O-CH_3), 3.77 (d, 2H, N-CH_2, J = 5.4 Hz), 4.48, 4.51 (t, total 1H, O-CH, J = 5.4 Hz), 6.23-6.48 (m, 1H), 6.58-6.73 (m, 2H). (Found: C, 55.63; H, 8.67; N, 8.14%. Calc. for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09%).

Reaction of **1** *with trans but-2-enoyl chloride* **2b**. First fractions gave *trans N*-methyl-*N*-(acetaldehyde dimethyl acetal)but-2-enamide **3b**, 85% yield; light yellow oil; ir (neat) 2970, 2820, 1655, 1400, 1120, 1070, 970, 875 cm^{-1}. ^1H NMR:[15] δ ($CDCl_3$) 1.88 (dd, 3H, CH_3, J = 1.5 and 6.6 Hz), 3.08, 3.12 (s, total 3H, N-CH_3), 3.41 (s, 6H, O-CH_3), 3.44 (d, 2H, N-CH_2, J = 5.4 Hz), 4.45, 4.50 (t, total 1H, CH-O, J = 5.4 Hz), 6.29 (d, 1H, =CH, J = 15.0 Hz), 6.95 (dq, 1H, =CH, J = 6.6 and 15.0 Hz). ^{13}C NMR: δ ($CDCl_3$) 24.87, 33.13, 52.37, 55.48, 104.32, 119.68, 148.80, 165.68. (Found: C, 57.57; H, 9.23; N, 7.22%. Calc. for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48%).

Reaction of **1** *with trans pent-2-enoyl chloride* **2c**. First fractions gave *trans N*-methyl-*N*-(acetaldehyde dimethyl acetal)pent-2-enamide **3c**, 93% yield; ligth yellow oil; ir (neat) 2980, 2960, 1665, 1620, 1400, 1130, 1070, 970 cm^{-1}. ^1H NMR:[15] δ ($CDCl_3$) 1.06 (t, 3H, CH_3, J = 7.3 Hz), 2.24 (m, 2H, CH_2), 3.05, 3.11 (s, total 3H, N-CH_3), 3.39 (s, 6H, O-CH_3), 3.49 (d, 2H, N-CH_2, J = 5.4 Hz), 4.40, 4.51 (t, total 1H, CH- O, J = 5.4 Hz), 6.23, 6.26 (d, total 1H, =CH, J = 15.0 Hz), 6.93 (dt, 1H, =CH, J = 6.3 and 15.0 Hz). ^{13}C NMR: δ ($CDCl_3$) 13.26, 26.25, 31.63, 51.21, 55.51, 104.02, 119.72, 148.83, 165.28. (Found: C, 59.59; H, 9.54; N, 6.63%. Calc. for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96%).

Reaction of **1** *with trans cinnamoyl choloride* **2d**. First fractions gave *trans N*-methyl-*N*-(acetaldehyde dimethyl acetal)cinnamamide **3d**, 96% yield; yellow oil; ir (neat) 2920, 2820, 1645, 1610, 1400, 1190, 1120, 1070, 980, 760 cm^{-1}. ^1H NMR:[15] δ ($CDCl_3$) 3.11, 3.24 (s, total 3H, N-CH_3), 3.43 (s, 6H, O-CH_3), 3.58 (d, 2H, N-CH_2, J = 5.3 Hz), 4.48, 4.58 (t, total 1H, CH-O, J = 5.3 Hz), 6.90, 6.96 (d, total 1H, =CH, J = 15.4 Hz), 7.35-7.54 (m, 5H, aromatic protons), 7.70 (d, 1H, =CH, J = 15.4 Hz). ^{13}C NMR: δ ($CDCl_3$) 35.48, 37.37, 50.70, 52.74, 55.13, 58.85, 103.31, 103.76, 117.14, 117.56, 127.76, 128.71, 129.58, 129.61, 135.12, 142.39, 142.77, 167.45, 168.02. (Found: C, 67.39; H, 7.72; N, 5.62%. Calc. for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62%).

Preparation of trans *N*-methyl-*N*-(acetaldehyde)enamides 4a-d.

General procedure. 50 mmol of compounds **3a-d** were dissolved in 100 ml of acetone, then 5 gr of pyridinium *p*-toluensulfonate (PPTS) and 10 ml of water were added to the mixture. The reaction mixture was allowed to reflux for 48 h. The solvent was removed under reduced pressure and the residue was subjected to silica flash chromatography using a methanol/chloroform 3:97 mixture as eluent.

Reaction of **3a** *with PPTS.* First eluted product was *N*-methyl-*N*-(acetaldehyde)propenamide **4a**, 40% yield; yellow oil; ir (neat) 2940, 2850, 1650, 1560, 1195, 1130, 1080, 985 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 3.09 (s, 3H, N-CH_3), 4.24 (s, 2H, N-CH_2), 6.12-6.14 (m, 1H), 6.37-6.48 (m, 2H), 9.59 (s, 1H, CHO). (Found: C, 56.97; H, 7.09; N, 10.67%. Calc. for $C_6H_9NO_2$: C, 56.68; H, 7.14; N, 11.02%).

Reaction of **3b** *with PPTS.* First eluted product was *trans N*-methyl-*N*-(acetaldehyde)but-2-enamide **4b**, 60% yield; yellow oil; ir (neat) 2920, 2820, 2720, 1730, 1665, 1610, 1400, 1290, 1230, 1100, 975, 835 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.92 (dd, 3H, CH_3, J = 1.6 and 6.8 Hz), 3.15 (s, 3H, N-CH_3), 4.22 (s, 2H, N-CH_2), 6.34 (dd, 1H, =CH, J = 1.6 and 14.9 Hz), 6.98 (dq, 1H, =CH, J = 6.8 and 14.9 Hz), 9.56 (s, 1H, CHO). ^{13}C NMR: δ ($CDCl_3$) 24.31, 38.35, 58.32, 119.75, 149.38, 167.32, 197.53. (Found: C, 59.34; H, 7.95; N, 10.28%. Calc. for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92%).

Reaction of **3c** *with PPTS.* First eluted product was *trans N*-methyl-*N*-(acetaldehyde)pent-2-enamide **4c**, 70% yield; yellow oil; ir (neat) 2985, 2970, 2940, 1740, 1665, 1605, 1490, 1400, 1380, 1115, 1060, 975, 850 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.19 (t, 3H, CH_3, J = 7.0 Hz), 2.26 (m, 2H, CH_2), 3.17 (s, 3H, N-CH_3), 4.22 (s, 2H, N-CH_2), 6.24 (d, 1H, =CH, J = 15.0 Hz), 6.97 (dt, 1H, =CH, J = 6.9 and 15.0 Hz), 9.60 (s, 1H, CHO). ^{13}C NMR: δ ($CDCl_3$) 12.35, 25.49, 37.96, 58.28, 119.55, 149.44, 167.13, 197.35. (Found: C, 62.05; H, 8.36; N, 8.75%. Calc. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03%.

Reaction of **3d** *with PPTS.* First eluted product was *trans N*-methyl-*N*-(acetaldehyde)cinnamamide **4d**, 68% yield; yellow oil; ir (neat) 3060, 2980, 2960, 1735, 1645, 1600, 1400, 1200, 970, 760, 700, 680 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 3.23 (s, 3H, N-CH_3), 4.28 (s, 2H, N-CH_2), 6.93 (d, 1H, =CH, J = 15.4 Hz), 7.35-7.54 (m, 5H, aromatic protons), 7.21 (d, 1H, =CH, J = 15.4 Hz), 9.62 (s, 1H, CHO). ^{13}C NMR: δ ($CDCl_3$) 36.85, 58.47, 115.97, 127.81, 128.68, 129.82, 134.70, 143.80, 167.20, 197.11. (Found: C, 71.22; H, 6.38; N, 6.79%. Calc. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89%).

Preparation of 2,7-dimethyl-3-oxa-4-substituted-2,7-diazabicyclo[3.3.0]octan-6-ones 6a-d.

General procedure. A mixture containing 10 mmol of compound **4a-d**, 1.5 ml of triethylamine, 11mmol of methyl hydroxylamine hydrochloride in 50 ml of absolute ethanol was refluxed for 36 h. At the end of this time the solvent was evaporated under reduced pressure and the residue extracted with dichloromethane, washed with water and dried with sodium sulfate. Evaporation of the solvent and flash chromatography (MeOH/$CHCl_3$ 3:97) gave cycloadducts **6a-d**.

Reaction of **4a** *with methyl hydroxylamine.* First fractions gave 2,7-dimethyl-3-oxa-2,7-diazabicyclo[3.3.0]-octan-6-one **6a**, 30% yield; light yellow oil; ir (neat): 2980, 2965, 2915, 1680, 1480, 1270, 920 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.73 (s, 3H, N-CH_3), 2.87 (s, 3H, N-CH_3), 3.03-3.09 (m, 1H, H_{3a}), 3.14-3.19 (m, 2H, H_6), 3.55-3.66 (m, 1H, H_{6a}), 4.08-4.21 (m, 2H, H_3). ^{13}C NMR: δ ($CDCl_3$) 29.84, 43.88, 50.52, 63.04, 67.25, 71.22, 173.20. Exact mass calculated for $C_7H_{12}N_2O_2$: 156.0899. Found: 156.0894. (Found: C, 53.79; H, 7.84; N, 17.74%. Calc. for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.74; N, 17.94%).

Reaction of **4b** *with methyl hydroxylamine.* First fractions gave 2,7-dimethyl-3-oxa-4-methyl-2,7-diaza-bicyclo[3.3.0]octan-6-one **6b**, 72% yield; white solid, mp 75-78 °C; ir (KBr): 2980, 2960, 2920, 1680, 1490, 1280 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.42 (d, 3H, CH_3, J = 6.2 Hz), 2.73 (s, 3H, N-CH_3), 2.85 (s, 3H, N-CH_3), 2.96 (dd, 1H, H_{3a}, J = 5.7 and 8.1 Hz), 3.18-3.21 (m, 2H, H_6), 3.48-3.53 (m, 1H, H_{6a}), 4.14 (dq, 1H, H_3, J = 5.7 and 6.2 Hz). ^{13}C NMR: δ ($CDCl_3$) 20.57, 30.62, 44.42, 52.27, 59.64, 66.81, 77.97, 173.21. Exact mass calculated for $C_8H_{14}N_2O_2$: 170.1055. Found: 170.1056. (Found: C, 56.31; H, 8.35; N, 16.60%. Calc. for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46%).

Reaction of **4c** *with methyl hydroxylamine.* First fractions gave 2,7-dimethyl-3-oxa-4-ethyl-2,7-diaza-bicyclo[3.3.0]octan-6-one **6c**, 68% yield; light yellow oil; ir (neat): 2950, 2910, 2860, 1675, 1490, 1400, 1300,

1100 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.03 (t, 3H, CH_3, J = 7.4 Hz), 1.66-1.81 (m, 2H, CH_2), 2.73 (s, 3H, N-CH_3), 2.85 (s, 3H, N-CH_3), 2.99 (dd, 1H, H_{3a}, J = 5.7 and 8.3 Hz), 3.11-3-22 (m, 2H, H_6), 3.47-3.55 (m, 1H, H_{6a}), 3.93-4.02 (m, 1H, H_3). ^{13}C NMR: δ ($CDCl_3$) 9.74, 26.99, 29.53, 43.26, 51.10, 56.79, 65.56, 81.76, 173.00. Exact mass calculated for $C_9H_{16}N_2O_2$: 184.1212. Found: 184.1216. (Found: C, 58.82; H, 8.69; N, 15.09%. Calc. for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21%).

Reaction of **4d** *with methyl hydroxylamine.* First fractions gave 2,7-dimethyl-3-oxa-4-phenyl-2,7-diazabicyclo[3.3.0]octan-6-one **6d**, 78% yield; white solid, mp 97-99 °C; 78% yield; ir (KBr): 3080, 2920, 2900, 2850, 1685, 1490, 1440, 1290, 1050, 1020, 750, 700 cm^{-1}; ^1H NMR: δ ($CDCl_3$) 2.84 (s, 3H, N-CH_3), 2.89 (s, 3H, N-CH_3), 3.25 (d, 1H, H_6, J = 11.1 Hz), 3.22-3.34 (m, 2H, H_{3a} and H_{6a}), 3.54 (dd, 1H, H_6, J = 5.1 and 11.1 Hz), 5.10 (d, 1H, H_3, J = 4.8 Hz), 7.31-7.50 (m, 5H, aromatic protons). ^{13}C NMR: δ ($CDCl_3$) 30.73, 44.13, 51.98, 60.74, 67.01, 82.81, 127.38, 129.00, 129.56, 139.89, 173.00. Exact mass calculated for $C_{13}H_{16}N_2O_2$: 232.1212. Found: 232.1189. (Found: C, 67.60; H, 6.86; N, 11.95%. Calc. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06%).

Preparation of (1R, 4R, 5S, 8S)-(-)-2,7-dimethyl-3-oxa-4-phenyl-8-benzyl-2,7-diazabicyclo[3.3.0]-octan-6-one 14.

To a stirred solution of 27 g (165 mmol) of (S)-(+)-2-amino-3-phenylpropanoic acid **7** in 200 ml of 80% formic acid was added dropwise 106.3 ml of acetic anhydride at 0 °C. After the reaction mixture was stirred at 0 °C for 10 min and at rt for 4 h, it was treated with 70 ml of water. The solvent was removed under reduced pressure and the residue was recrystallized from water to give 24.40 g (76%) of (S)-(+)-2-(*N*-formylamino)-3-phenyl-propanoic acid **8**, mp 168-169 °C; $[\alpha]_D^{25}$ + 99.5° (c = 1.0, THF); ir (KBr): 3356, 3026, 2949, 2854, 2732, 2490, 1912, 1719, 1605, 1523, 1377, 1254, 1080, 875, 697, 610 cm^{-1}. ^1H NMR: δ (DMSO-d_6) 2.85 (dd, 1H, Ph-CH, J = 9.2 and 13.8 Hz), 3.07 (dd, 1H, Ph-CH, J = 4.9 and 13.8 Hz), 4.45-4.56 (m, 1H, N-CH), 7.17-7-32 (m, 5H, aromatic protons), 7.95 (s, 1H, NH), 8.39 (bs, 1H, N-CHO), 12.86 (bs, 1H, OH). ^{13}C NMR: δ (DMSO-d_6) 36.72, 51.98, 126.51, 128.22, 129.12, 137.29, 160.95, 172.57. (Found: C, 62.32; H, 5.68; N, 7.14%. Calc. for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.14%.

To a stirred suspension of 27.5 g (720 mmol) of lithium aluminum hydride in 100 ml of dry tetrahydrofuran was added dropwise at 0 °C 17.20 g (89 mmol) of **8** dissolved in 350 ml of THF. The reaction mixture was stirred at 0 °C for 30 min, at rt for 3 h, and at reflux temperature for 9 h. The reaction mixture was cooled to 0 °C and 50 ml of 15% aqueous NaOH was slowly added. After the mixture was stirred overnight at rt, the solid was filtered and washed with THF. The combined filtrate and washing solutions were dried with sodium sulfate, filtered, and the solvent was removed under reduced pressure. The residue was recrystallized from cyclohexane to give 13.20 g (90%) of (S)-(+)-2-(*N*-methylamino)-3-phenylpropanol **9** as white crystals: mp 69-70 °C; $[\alpha]_D^{25}$ + 39.5° (c = 1.0, THF); ir (KBr): 3300, 3066, 2884, 1600, 1492, 1446, 1354, 1098, 1042, 955, 850, 785, 700 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.41 (s, 3H, N-CH_3), 2.60 (bs, 2H, disappeared in D_2O), 2.76-2.83 (m, 3H), 3.33 (dd, 1H, O-CH, J = 4.1 and 10.5 Hz), 3.65 (dd, 1H, O-CH, J = 3.2 and 10.5 Hz), 7.17-7.31 (m, 5H, aromatic protons). ^{13}C NMR: δ ($CDCl_3$) 33.57, 37.61, 61.71, 61.91, 126.38, 128.57, 129.15, 138.74. (Found: C, 73.04; H, 9.08; N, 8.17%. Calc. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48%.

To a stirred solution containing 8.25 g (50 mmol) of **9** and 15 ml (110 mmol) of Et_3N in 100 ml of anhydrous carbon tetrachloride was added dropwise, at 0 °C, a solution of trans cinnamoyl chloride 18 g (110 mmol) in 100 ml of anhydrous carbon tetrachloride. The reaction mixture was stirred at 0 °C for 30 min and then at 25 °C for 6 h. The mixture was filtered and washed with 50 ml of carbon tetrachloride. The combined filtrate was washed with water, dried with sodium sulfate, filtered, and the solvent was removed under reduced pressure to give 19 g (90%) of *trans, trans* (S)-(-)-2-(*N*-methyl-*N*-cinnamoylamino)-3-phenylpropyl cinnamoate **10** as a light yellow oil; $[\alpha]_D^{25}$ - 33.6° (c = 1.1, THF); ir (neat): 3069, 2928, 1750, 1642, 1451, 1310, 1259, 1100, 980, 860, 763 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.95 (dd, 2H, CH_2, J = 7.2 and 16.6 Hz), 3.01 (s, 3H, N-CH_3), 4.12- 4.67 (m, 3H), 6.31-6.83 (m, 2H), 7.18-7.64 (m, 12H). ^{13}C NMR: δ ($CDCl_3$) 36.29, 36.77, 58.73, 64.40, 64.80, 118.01, 118.65, 119.00, 119.20, 127.75-131.57, 142.77, 143.92, 146.47, 146.92, 166.28, 166.44, 167.02, 167.93. (Found: C, 78.95; H, 6.49; N, 3.65%. Calc. for $C_{28}H_{27}NO_3$: C, 79.03; H, 6.40; N, 3.29%.

To a stirred solution containing 8 g of **10** in 240 ml of methanol was added 120 ml of 6% aqueous K_2CO_3. After

the mixture was stirred overnight at rt, the solvent was removed under reduce pressure and the residue subjected to silica flash chromatography (MeOH/$CHCl_3$ 5:95) gave 5.25 g (95%) of *trans* (S)-(+)-[*N*-methyl-*N*-(1-benzyl-1-ethan-2-ol)]cinnamamide **11**, as a white solid, mp 86-88 °C; $[\alpha]_D^{25}$ + 28.0° (c = 1.0, THF); ir (KBr): 3450, 3200, 3080, 3060, 3030, 2980, 2950, 1650, 1600, 1400, 1260, 1090, 1030, 970, 800, 760, 700 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.77-2.97 (m, 2H), 2.95 (s, 3H, N-CH_3), 3.40 (bs, 1H, OH), 3.81 (m, 2H), 4.62 (m, 1H), 6.73 (d, 1H, =CH, J = 15.0 Hz). ^{13}C NMR: δ ($CDCl_3$) 27.07, 32.38, 34.36, 35.20, 59.25, 61.22, 62.13, 62.83, 117.77, 118.47, 126.22-129.51, 134.89, 135.11, 137.32, 137.78, 141.03, 142.72, 168.04, 168.68. (Found: C, 77.23; H, 7.22; N, 4.82%. Calc. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74%.

To a stirred solution of bis(trichloromethyl) carbonate (11.9 g, 40 mmol) in 120 ml of dry dichloromethane at -78 °C was added 17 ml (240 mmol) of anhydrous DMSO. The reaction mixture was stirred for 15 min and then a solution of **11** (4.70 g, 16 mmol) in 80 ml of dichloromethane was slowly added at the same temperature. After 15 min of stirring, triethylamine (39 ml, 280 mmol) in 160 ml of dichloromethane was added dropwise, maintaining the temperature below -70 °C. After the addition, the resulting suspension was stirred at - 78 °C for 5 min and then the acetone-dry ice bath was removed. The reaction mixture was stirred at rt for 2 h and the solvent was removed under reduced pressure. The residue obtenute was extracted with dichloromethane, washed with water, dried with sodium sulfate and silica flash chromatographated (MeOH/$CHCl_3$ 3:97) to gave 3.64 g (78%) of *trans* (S)-(-)-*N*-methyl-*N*-(benzylacetaldehyde)cinnamamide **12** as a light yellow oil; $[\alpha]_D^{25}$ - 9.5° (c = 1.7, THF); ir (neat): 3080, 3060, 3040, 2980, 2930, 1745, 1650, 1600, 1500, 1455, 1405, 1120, 970, 765, 700 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.87-3.04 (m, 2H, Ph-CH_2), 2.86 (s, 3H, N-CH_3), 4.19 (dd, 1H, CH-N, J = 4.8 and 10.2 Hz), 6.78 (d, 1H, =CH, J = 15.4 Hz), 7.17-7.60 (m, 5H, aromatic protons), 7.73 (d, 1H, =CH, J = 15.4 Hz), 9.62 (s, 1H, CHO). ^{13}C NMR: δ ($CDCl_3$) 32.66, 36.57, 69.64, 115.82, 126.61, 127.90, 128.65, 128.75, 128.97, 129.98, 134.68, 137.56, 144.13, 166.85, 197.19. (Found: C, 78.02; H, 6.53; N, 4.42%. Calc. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.42%).

A mixture containing 2.90 g (10 mmol) of compound **12**, 1.5 ml (11 mmol) of triethylamine, 920 mg (11mmol) of methyl hydroxylamine hydrochloride in 200 ml of absolute ethanol was refluxed for 36 h. At the end of this time the solvent was evaporated under reduced pressure and the residue extracted with dichloromethane, washed with water and dried with sodium sulfate. Evaporation of the solvent and silica flash chromatography (MeOH/$CHCl_3$ 3:97) gave 2.10 g (65%) of (1R,4R,5S,8S)-(-)-2,7-dimethyl-3-oxa-4-phenyl-8-benzyl-2,7-diaza-bicyclo[3.3.0]octan-6-one **14** as a light yellow oil; $[\alpha]_D^{25}$ - 2.0° (c = 2.5, $CHCl_3$); ir (neat): 3040, 3020, 2940, 2880, 1685, 1450, 1400, 1250, 1040, 750, 700 cm^{-1}. ^1H NMR: δ (DMSO-d_6) 2.35 (s, 3H, N-CH_3), 2.64-2.75 (m, 1H, H_6), 2.96 (dd, 1H, H_{3a}, J = 5.3 and 8.5 Hz), 2.85 (s, 3H, N-CH_3), 3.05-3.12 (m, 2H, CH_2), 3.58 (dd, 1H, H_{6a}, J = 4.0 and 8.5 Hz), 4.69 (d, 1H, H_3, J = 5.3 Hz), 7.22-7.36 (m, 10H, aromatic protons). ^{13}C NMR: δ (DMSO-d_6) 28.42, 37.88 42.71, 58.48, 63.79, 70.60, 81.63, 126.27, 127.24, 127.88, 128.43, 128.87, 129.35, 135.79, 139.10, 172.89. Exact mass calculated for $C_{20}H_{22}N_2O_2$: 322.1681. Found: 322.1677. (Found: C, 74.40; H, 6.93; N, 8.50%. Calc. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69%).

Preparation of 2H-3-oxa-4-phenyl-7-methyl-2,7-diazabiciclo[3.3.0]octan-6-one 19 and its reaction with Lithium Aluminum Hydride.

A mixture containing 1 g of *N*-methyl-*N*-(acetaldehyde)cinnamamide **4d** in 30 ml of 95% aqueous ethanol, 510 mg of hydroxylamine hydrochloride and 3 ml of 10% aqueous sodium hydroxide was stirred at 25 °C for 6 h. The solvent was evaporated at reduced pressure and the residue was extracted with dichloromethane, washed with water and dried over sodium sulfate. Evaporation of the solvent and silica flash chromatography (MeOH/$CHCl_3$ 3:97) gave 950 mg (88%) as a *syn-anti* mixture of *trans N*-methyl-*N*-(acetaldoxime)cinnamamide **17**, 85% yield; light yellow oil. Major isomer ^1H NMR: δ ($CDCl_3$) 3.12 (s, 3H, N-CH_3), 4.23 (d, 2H, N-CH_2, J = 5.2 Hz), 6.85 (d, 1H, J = 15.4 Hz), 7.35-7.53 (m, 6H), 7.72 (d, 1H, J = 15.4 Hz), 8.23 (bs, 1H, N=OH). Exact mass calculated for $C_{12}H_{14}N_2O_2$: 218.105528. Found: 218.106537.

A solution containing 1 g of above amide oxime **17** in 50 ml of absolute ethanol was refluxed for 36 h. The reaction mixture was subjected to silica flash chromatography (MeOH/$CHCl_3$ 5:95) to gave 870 mg (87%) of a light yellow oil, which was identified as 2H-3-oxa-4-phenyl-7-methyl-2,7-diazabicyclo[3.3.0]octan-6-one **19** on the basis of its spectral properties: ir (neat): 3190, 3040, 3020, 2920, 2890, 1680, 1500, 1440, 1300, 1100, 1040,

840, 750, 700 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.90 (s, 3H, N-CH_3), 3.47 (dd, 1H, H_6, J = 2.7 and 11.0 Hz), 3.63 (dd, 1H, J = 1.8 and 7.9 Hz, H_{3a}), 3.74 (dd, 1H, H_6, J = 7.3 and 11.0 Hz), 4.17 (ddd, 1H, H_{6a}, J = 2.7, 7.3 and 7.9 Hz), 5.44 (dd, 1H, H_3, J = 1.8 Hz), 7.31-7.48 (m, 5H, aromatic protons). ^{13}C NMR: δ ($CDCl_3$) 29.57, 55.45, 56.86, 57.23, 85.40, 125.95, 128.19, 128.84, 138.23, 172.37. Exact mass calculated for $C_{12}H_{14}N_2O_2$: 218.105528. Found: 218.105164. (Found: C, 66.35; H, 6.38; N, 12.59%. Calc. for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84%).

A suspension containing 700 mg of **19** and 500 mg of lithium aluminum hydride in 30 ml of anhydrous tetrahydrofuran was stirred at 25 °C for 24 h. At the end of this time the reaction was washed with water, and then dried with sodium sulfate. Removal of the solvent under reduced pressure was followed by silica flash chromatography to gave 450 mg of a yellow oil, 75% yield, which was identified as *N*-methyl-3-(phenylmethanol)--pyrrole **20**. IR (neat) 3400, 3080, 3040, 2950, 2920, 1610, 1560, 1510, 1500, 1455, 1425, 1165, 1020, 975, 780, 730, 705, 610 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.12 (bs, 1H, OH), 3.56 (s, 3H, N-CH_3), 5.77 (s, 1H, CH-O), 6.06 (dd, 1H, H_4, J = 1.8 and 2.4 Hz), 6.41 (dd, 1H, H_2, J = 1.8 and 1.8 Hz), 6.52 (dd, 1H, H_5, J = 1.8 and 2.4 Hz), 7.24-7.47 (m, 5H, aromatic protons). ^{13}C NMR: δ ($CDCl_3$) 36.07, 70.92, 107.11, 119.90, 122.18, 126.19, 127.07, 127.99, 128.14, 144.47. (Found: C, 77.32; H, 6.92; N, 7.12%. Calc. for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48%).

Acknowledgments

Authors are grateful to the Italian M. U. R. S. T. and C. N. R. for partial financial support.

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(*Received in UK* 24 *January* 1994; *revised* 24 *February* 1994; *accepted* 4 *March* 1994)