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Intramolecular Nitrone Cycloaddition: Stereoselective Synthesis of Piperidine Systems

Ugo Chiacchio,[a*] Antonio Rescifina,[a] Francesco Casuscelli,[b] Anna Piperno,[b] Vincenzo Pisani,[b] and Roberto Romeo[c]

[a]Dipartimento di Scienze Chimiche, Università, 95125 Catania, Italy

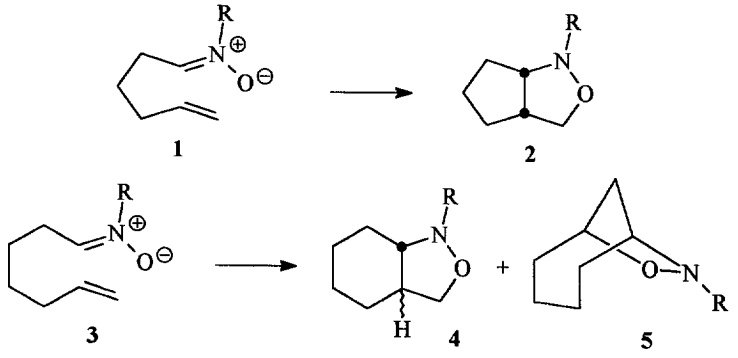
[b]Dipartimento Farmaco-Chimico, Università, 98168 Messina, Italy

[c]Dipartimento di Chimica, Università, 87036 Arcavacata di Rende, Italy

Abstract: A synthetic approach to isomerically functionalized piperidine systems has been designed by intramolecular nitrone cycloaddition, starting from β-enamidoaldehydes, and by subsequent reductive ring-opening of the obtained fused δ-lactams. Copyright © 1996 Published by Elsevier Science Ltd

Intramolecular 1,3-dipolar cycloadditions have recently received considerable synthetic and mechanistic interest as a convenient tool for the rapid construction of the complex carbon frameworks occurring in natural products and biological molecules.[1,2]

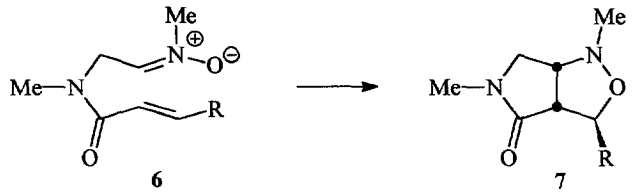
A significant body of information regarding the regiochemistry and the stereochemistry of the process has been collected since the studies of Le Bel.[3] The intramolecular 1,3-dipolar cycloaddition can be viewed as a competitive process between the bridged and fused modes of cycloaddition, controlled by a suitable interplay of factors such as alkene polarity, ring strain and other non-bonded interactions.[4]



Scheme 1

5-Hexen-1-imino-*N*-oxides **1** react with high regio- and stereoselectivity to give the fused 3-oxa-2-azabicyclo[3.3.0]octanes (*cis*) **2** as exclusive products, while 6-hepten-1-imino-*N*-oxides **3** gave predominantly fused products 8-oxa-7-azabicyclo[4.3.0]nonanes **4** (*cis* and *trans* fusion), together with the bridged 7-oxa-8-azabicyclo[4.2.1]nonanes **5** (Scheme 1). However, the obtained results suggest that steric effects at the reacting carbon termini may operate against fused-product regiochemistry.[5]

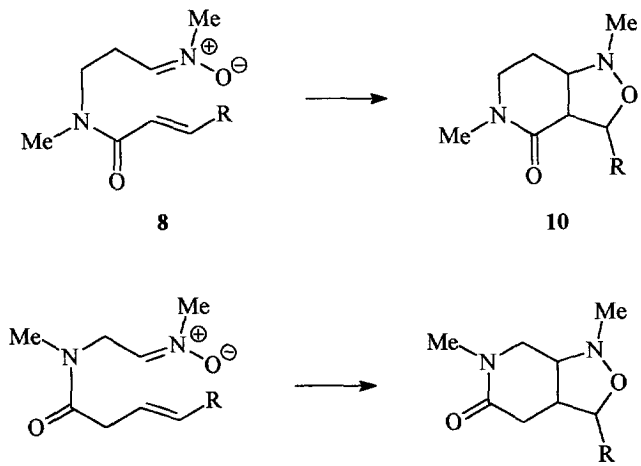
To gain a better understanding of the factors which control the balance between the two reaction courses, we have extended the process to a series of compounds in which an amido group has been inserted in the tether connecting the nitrone moiety to the dipolarophilic double bond. Recently we have reported that 5-hexen-3-*N*-methyl-4-oxo-1-imino-*N*-oxides **6** lead stereoselectively to *cis* fused γ-lactams **7** (Scheme 2).[6]



6 **7**

Scheme 2

In this paper, we describe a novel general approach to functionalized fused δ-lactams **10** and **11** by intramolecular nitrone cycloaddition of 6-hepten-4-*N*-methyl-5-oxo-1-imino-*N*-oxides **8** and 6-hepten-3-*N*-methyl-4-oxo-1-imino-*N*-oxides **9** (Scheme 3).



8 **10**

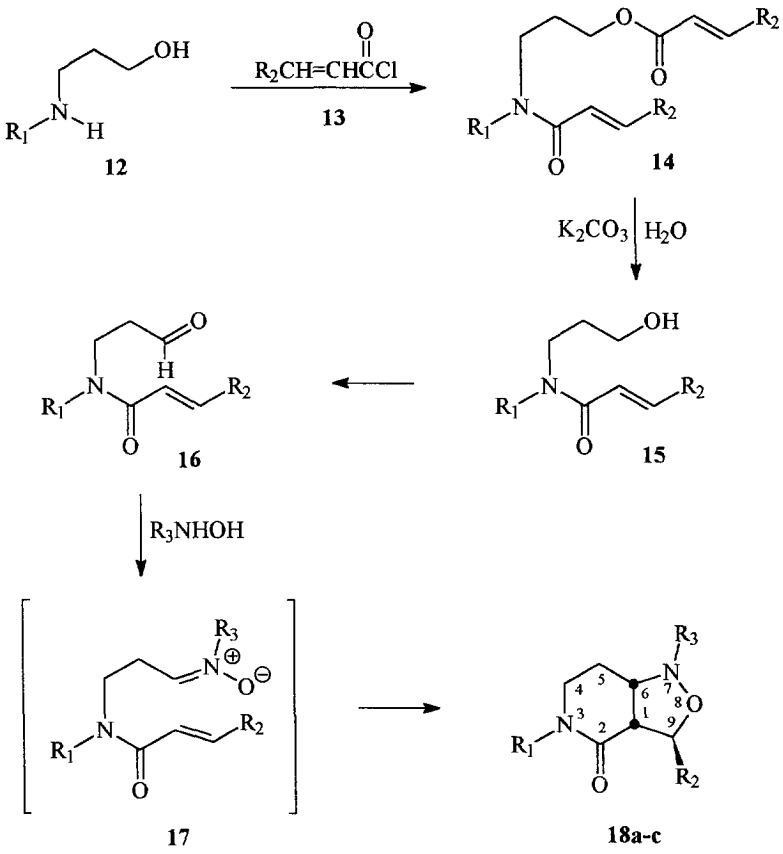
9 **11**

Scheme 3

Our interest in these reactions is further promoted by the possibility of a selective functionalization of the obtained fused systems, by ring cleavage of isoxazolidine moiety, to give piperidine derivatives, which occur widely in a number of alkaloids.[7]

RESULTS AND DISCUSSION

The β-amido aldehydes **16** required for this study were synthesized as reported in scheme 4. The reaction of 3-(*N*-substituted-amino)propanol **12**[8] with α,β-unsaturated acyl chlorides **13** led to the corresponding amidoesters **14** which have been converted into the amido alcohols **15** by selective hydrolysis with K_2CO_3 in H_2O/MeOH. Swern-like oxidation of **15** afforded the corresponding aldehydes **16** which have been transformed by reaction with hydroxylamine derivatives to the corresponding 8-oxa-3,7-diazabicyclo[4.3.0]nonan-2-ones **18**, *via* the not isolated nitrones **17**, as exclusive products (Scheme 4).



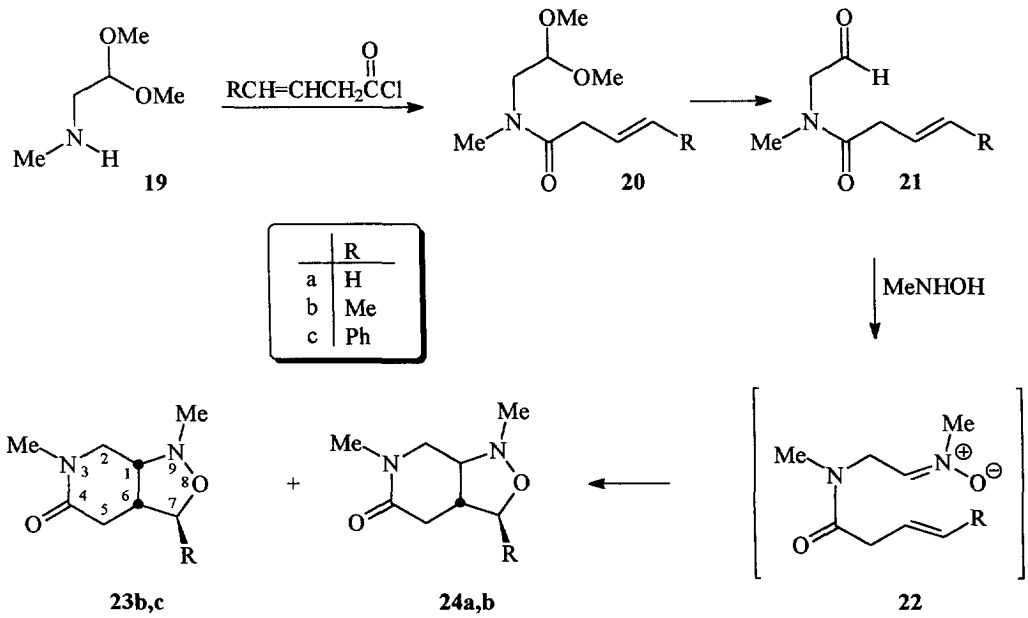
	R_1	R_2	R_3	Yield %
a	Isoprop	Ph	Ph	65
b	Bn	Ph	Me	65
c	Isoprop	Me	Me	70

Scheme 4

The obtained derivatives were characterized on the basis of analytical and spectroscopic data. High resolution mass spectra showed the correct molecular ions. Ir absorptions of carbonyl groups are at 1685-1675 cm^{-1} in accord with δ-lactams. The ^1H NMR spectra showed the H_9 proton in the range 3.89-5.27 δ, while H_1 and H_6 protons resonate at 2.80-3.50 δ. The methylene protons at C_4 showed different chemical shifts in the range 3.10-3.20 and 3.40-3.60 δ, while their resonances are coincident in the precursor amidoaldehydes **16**; methylene protons at C_5 give rise to an indistinct multiplet centered at 1.80 δ.

The investigated 1,3-dipolar cycloaddition showed a complete regioselectivity: no bridged adducts have been detected in the crude reaction mixtures. The reactions have also been found to be stereospecific; intramolecular cycloadducts **18** were obtained stereochemically pure, with no evidence in the nmr spectra or tlc of the crude products of any diastereomers. The relative stereochemistry at C_1-C_9 in the formed isoxazolidine ring is predetermined by the alkene geometry; furthermore, the ring junction between isoxazolidine and lactam 6-membered rings is always *cis*, as evidenced by NOE experiments. In fact, in compound **18a-c,** irradiation of the upfield resonance corresponding to methylene protons at C_4 resulted in the observation of a signal enhancement for H_1 and H_6; similarly, when the resonance for H_6 was irradiated, a positive NOE effect was observed for H_1 and the ortho protons of the phenyl substituent at C_9, in compounds **18 a,b**, and for H_1 and the methyl group at C_9, in compound **18c**. On the contrary, irradiation of H_9 gives rise, in compounds **18a,b**, to a NOE effect only for H_1 and the aromatic protons at C_9.

These results are in agreement with the structure of stereoisomers **18a-c** which show H_1 and H_6 in a *syn* relationship.



Scheme 5

A different route has been exploited towards the synthesis of the analogous 8-oxa-3,9-diazabicyclo-[4.3.0]nonan-4-ones. The reaction pathway reported in scheme 5 starts from *N*-methylaminoacetaldehyde dimethylacetal **19** which was converted in the α-amido aldehydes **21** according to previously reported

procedure.[6] Treatment of **21** with *N*-methyl hydroxylamine afforded a mixture of fused (*cis* and *trans*) compounds **23** and **24** (Scheme 5).

The structural assignments to obtained cycloadducts were readily made by MS, ^1H and ^{13}C NMR analytical data (see Experimental).

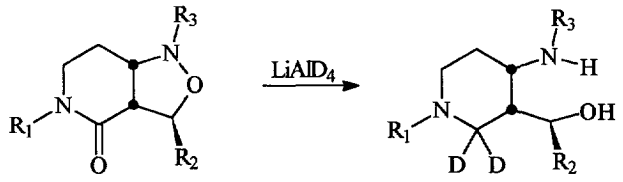
The intramolecular cycloaddition process is always regiospecific leading to the exclusive formation of fused compounds as indicated by the presence of diagnostic ^1H NMR absorptions expected for isoxazolidine protons at C_7: no bridged products were detected in the crude reaction mixture either chromatographically or spectroscopically.

The stereochemical outcome of the intramolecular cycloaddition process appears of some interest: the nature of the ring fusion stereochemistry in isoxazolidines **23** (*cis*) and **24** (*trans*) is linked to the substitution pattern at the alkene carbon C_7 (R); thus, *cis* adducts result as major (*cis*/*trans* ratio = 70:30) or nearly exclusive products (*cis*/*trans* ratio = 99:1), when a methyl or a phenyl group respectively is incorporated at R; on the contrary, when R is an hydrogen atom, only *trans* adducts are obtained.

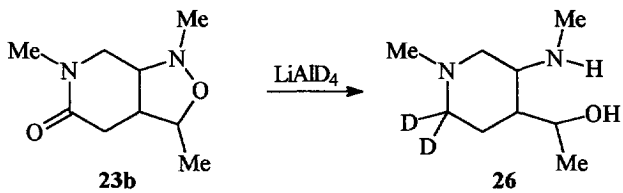
The proposed stereochemical features have been determined by analysis of ^1H NMR spectra and by NOE difference spectroscopy. In *cis* compounds **23b,c**, irradiation of the upfield H_2 resonance gives rise to a positive NOE effect on H_1 and H_6, so indicating a *cis* relationship between these protons. Furthermore, when H_6 is irradiated, a comparable NOE for H_1 and the methyl or phenyl substituent at C_7 and, in a lesser degree, for the adjacent H_7 is observed. Analogously, irradiation of H_7 causes an enhancement of the resonance of the substituent at C_7 and a lesser effect for the hydrogen atom at C_6.

On the contrary, in compound **24b**, when H_7 is irradiated, a 3% NOE on H_1 is observed, so suggesting that these protons are topologically close in a *trans* ring fusion arrangement.

The stereochemical characteristics of *trans* compound **24a** cannot be easily determined by NOE measurements and have been assigned by analysis of ^1H NMR data: in fact, the ^1H NMR spectrum shows a nearly coincident chemical shift for H_1 and H_6 (3.00 δ), besides a downfield resonance (4.20 δ) for one of the protons at C_7. These features can be considered diagnostic of a *trans* ring fusion in this kind of compounds as confirmed by the analysis of the ^1H NMR spectra of analogous compounds **23b** and **24b**; in fact, H_1 and H_6 resonate with different chemical shifts (2.47 δ) and (3.01 δ) in *cis* compound **23b** and nearly at the same chemical shift in the *trans* isomer **24b**; moreover H_7 in **24b** resonate at lower field (4.44 δ) with respect to the analogous proton in *cis* derivative **23b** (3.69 δ).



18b,c **25b,c**



23b **26**

Scheme 6

Functionalization of the obtained compounds **18**, **23** and **24** have been performed by ring cleavage of isoxazolidine nucleus towards the formation of substituted piperidines. Thus, reduction of **18b**, as model compound, with $LiAlD_4$, in anhydrous THF at reflux for 4 h, afforded the corresponding piperidine **25** in high yields (Scheme 6).

The obtained compounds gave satisfactory elemental analysis. The presence of NH and OH groups was indicated by IR absorptions at 3295 and 3420 cm^{-1} respectively and by the presence of a broad singlet in the ^1H NMR spectrum integrating as two protons and exchangeable with D_2O.

In conclusion, a new synthetic approach to isomerically functionalized piperidine systems has been designed by intramolecular nitrone cycloaddition. The amino and alcoholic functionalities present in the so obtained compounds, in a definite stereochemical relationship, offers the possibility of usefully synthetic manipulations directed towards the synthesis of natural alkaloids.

EXPERIMENTAL

Mps were measured on a Kofler apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer elemental analyzer. Infrared spectra were recorded on a Perkin-Elmer 377 instrument. ^1H NMR spectra were measured on a Varian 300 Gemini instrument in $CDCl_3$ as solvent. Chemical shifts are in ppm (δ) from TMS as internal standard. NOE difference spectra were obtained by substracting alternatively right-off-resonance free induction decays (FIDs) from right-on-resonance-induced FIDs. 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).

Preparation of *E*-enamido esters derivatives 14a-c.

General procedure. A solution (165 mmol) of trans acyl chloride 13 in 150 ml of anhydrous carbon tetrachloride was added dropwise, at 0 °C, to a stirred solution containing 75 mmol of **12a,b** and 22.5 ml (165 mmol) of Et_3N in 150 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 filtrates were washed with water, dried with sodium sulfate, filtered, and the solvent was removed under reduced pressure. The residue was subjected to silica flash-chromatography using a methanol/chloroform 3:97 mixture as eluent.

Reaction of **12a** *with cinnamoyl chloride*. First fractions gave *(E,E)-3-(N-isopropyl-N-cinnamoylamino)-propyl cinnamoate* **14a**. Oil (95%); two rotamers; ir (neat) 3060, 2935, 1750, 1645, 1450, 1375, 1250, 1100, 980, 860 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.22 (d, 3H, CH_3, J = 6.3 Hz), 1.28 (d, 3H, CH_3, J = 6.6 Hz), 2.09 (m, 2H, CH_2), 3.46 (m, 2H, N-CH_2), 4.29 (m, 2H, OCH_2), 4.87 (ept, 1H, $CH(CH_3)_2$, J = 6.3 and 6.6 Hz), 6.44, 6.47 (d, total 1H, =CH, J = 15.9 Hz), 6.89, 6.92 (d, total 1H, =CH, J = 15.9 Hz), 7.26-7.53 (m, 10H, ArH), 7.61-7.69 (m, total 2H, =CHPh). ^{13}C Nmr: δ ($CDCl_3$) 22.35, 25.50, 30.45, 42.35, 47.30, 64.50, 118.15, 119.10, 127.70, 127.85, 128.10, 130.50, 130.85, 132.25, 133.50, 135.64, 143.77, 146.92, 168.95, 170.92. MS: m/e (M^+) 377. (Found: C, 76.12; H, 7.38; N, 3.69%. Calc. for $C_{24}H_{27}NO_3$: C, 76.35; H, 7.22; N, 3.71%).

Reaction of **12b** *with cinnamoyl chloride*. First fractions gave *(E,E)-3-(N-benzyl-N-cinnamoylamino)-propyl cinnamoate* **14b**. Oil (95%); two rotamers; ir (neat) 3040, 2980, 1740, 1640, 1600, 1550, 1180, 970, 860, 760 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 2.05 (m, 2H, CH_2), 3.55 (m, 2H, N-CH_2), 4.35 (m, 2H, OCH_2), 4.76 (s, 2H, $PhCH_2$), 6.42, 6.45 (d, total 1H, =CH, J = 15.6 Hz), 6.85, 6.89 (d, total 1H, =CH, J = 15.6 Hz), 7.20-7.55 (m, 10H, ArH), 7.78 (m, total 2H, =CHPh). ^{13}C Nmr: δ ($CDCl_3$) 47.53, 50.50, 64.30, 64.54, 116.86, 117.37,

127.55, 127.91, 128.56, 129.33, 130.20, 134.10, 142.02, 142.70, 145.13, 166.38, 166.80. MS: m/e (M^+) 425. (Found: C, 79.10; H, 6.41; N, 3.29%. Calc. for $C_{28}H_{27}NO_3$: C, 79.02; H, 6.40; N, 3.29%).

Reaction of **12a** *with crotonyl chloride*. First fractions gave *(E,E)-3-(N-isopropyl-N-but-2-enoylamino)-propyl but-2-enoate* **14c**. Oil (98%); two rotamers; ir (neat) 3350, 2940, 1750, 1665, 1620, 1440, 1375, 1240, 1170, 1095, 970,750 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.20 (d, 3H, CH_3, J = 6,3 Hz), 1.26 (d, 3H, CH_3, J = 6.6 Hz), 1.68, 1.85 (d, total 6H, CH_3, J = 6.8 Hz), 2.15 (m, 2H, CH_2), 3.40 (m, 2H, N-CH_2), 4.45 (m, 2H, OCH_2), 4.86 (ept, 1H, CH, J = 6.3 and 6.6 Hz), 5.71,5.92 (m, total 2H, =CH), 6.55, 6.85 (m, total 2H, =CH). ^{13}C Nmr: δ ($CDCl_3$) 22.20, 24.35, 26.89, 45.50, 47.45, 50.01, 118.85, 120.05, 139.50, 140.30, 170.70, 171.20. MS: m/e (M^+) 2.53. (Found: C, 65.98; H, 9.15; N, 5.54%. Calc. for $C_{14}H_{23}NO_3$: C, 66.36; H, 9.16; N, 5.53%).

Preparation of *(E)*-enamido-propanol derivatives 15a-c.

General procedure. To a stirred solution containing 50 mmol of **12a-c** in 280 ml of methanol, 6% aqueous K_2CO_3 (150 ml) was added. The mixture was stirred overnight; after removal of the solvent under reduced pressure, the residue was subjected to silica flash-chromatography (MeOH/$CHCl_3$ 4:96).

Reaction of **14a** *with* K_2CO_3. First eluted product was *(E)-N-isopropyl-N-(3-propanol)cinnamamide* **15a**. Oil (90%); ir (neat) 3600-3200, 2970, 1660, 1570, 1400, 1375, 1060, 980,760 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.26 (d, 6H, CH_3, J = 6.6 Hz), 1.71 (m, 2H, CH_2), 3.51 (m, 4H, OCH_2, NCH_2), 4.29 (sept, 1H, C<u>H</u>$(CH_3)_2$, J = 6.6 Hz), 6.88 (d, 1H, =CH, J = 15.1 Hz), 7.32-7.50 (m, 5H, ArH), 7.65 (d, 1H, =CH, J = 15.1 Hz). ^{13}C Nmr: δ ($CDCl_3$) 22.35, 25.50, 30.45, 42.35, 47.30, 64.50, 118.15, 119.10, 127.70, 127.85, 128.10, 130.50, 130.85, 132.25, 133.50, 135.64, 143.77, 146.92, 168.95, 170.92. MS: m/e (M^+) 247. (Found: C, 73.12; H, 8.53; N, 5.69%. Calc. for $C_{15}H_{21}NO_2$: C, 72.83; H, 8.56; N, 5.67%).

Reaction of **14b** *with* K_2CO_3. First eluted product was *(E)-N-benzyl-N-(3-propanol)cinnamamide* **15b**. Oil (85%); ir (neat) 3600-3200, 3060, 2980, 1675, 1600, 1400, 1300, 1090, 980, 700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.73 (m, 2H, CH_2), 3.48 (bs, 2H, NCH_2), 3.58 (bs, 2H, OCH_2), 4.20 (bs, 1H, OH), 4.60 (s, 2H, NCH_2Ph), 6.74 (d, 1H, =CH, J = 15.3 Hz), 7.17-7.37 (m, 10H, ArH), 7.72 (d, 1H, =CH, J = 15.3 Hz). ^{13}C Nmr: δ ($CDCl_3$) 31.75, 42.73, 44.81, 51.87, 117.10, 125.39, 127.82, 127.91, 128.73, 128.79, 128.96, 129.72, 135.13, 137.52, 143.74, 167.50. MS: m/e (M^+) 295. (Found: C, 77.23; H, 7.18; N, 4.74%. Calc. for $C_{19}H_{21}NO_2$: C, 77.25; H, 7.17; N, 4.74%).

Reaction of **14c** *with* K_2CO_3. First eluted product was *(E)-N-isopropyl-N-(3-propanol)but-2-enamide* **15c**. Oil (80%); ir (neat) 3600-3200, 2980, 1670, 1560, 1400, 1375, 1300, 1060, 970, 875 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.25 (d, 6H, CH_3, J = 6.6 Hz), 1.65 (m, 2H, CH_2), 1.80 (dd, 3H, CH_3, J = 1.6 and 6.5 Hz), 3.50 (m, 4H, NCH_2 and OCH_2), 3.67 (bs, 1H, OH), 4.27 (sept, 1H, CH, J = 6.6 Hz), 6.09 (d, 1H, =CH, J = 15.0 Hz), 6.40 (dq, 1H, =CH, J = 6.5 and 15.0 Hz). ^{13}C Nmr: δ ($CDCl_3$) 22.53, 24.87, 25.50, 30.40, 41.35, 47.20, 64.50, 119.65, 148.70, 165.60. MS: m/e (M^+) 185. (Found: C, 64.57; H, 10.33; N, 7.58%. Calc. for $C_{10}H_{19}NO_2$: C, 64.82; H, 10.34; N, 7.56%).

Preparation of *(E)*-enamide-propanal derivatives 16a-c.

General procedure. 8.5 ml (120 mmol) of anhydrous DMSO were added, at -78 °C, to a stirred solution of bis(trichloromethyl)carbonate (20 mmol) in 50 ml of dry dichloromethane at -78 °C. The reaction mixture was stirred for 15 min and then a solution of **15a-c** (8 mmol) in 80 ml of dichloromethane was slowly added at the same temperature. After 15 min of stirring, triethylamine (19.7 ml, 140 mmol) in 100 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 bath was removed. The reaction mixture was stirred at rt for 2 h and the solvent was removed under reduced pressure. The obtained residue was extracted with dichloromethane, washed with water, dried with sodium sulfate and silica flash chromatographated ($MeOH/CHCL_3$ 3:97).

First eluted product was *(E)-3-N-isopropyl-N-(3-propanal)cinnamamide* ***16a***. Oil (60%); ir (neat) 3050, 3020, 2980, 1735, 1660, 1600, 1500, 1375, 1130, 980, 760 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.23 (d, 3H, CH_3, J = 6.3 Hz), 1.28 (d, 3H, CH_3, J = 6.6 Hz), 2.70 (m, 2H, CH_2), 3.48 (m, 2H, NCH_2), 4.20 (sept, 1H, NCH, J = 6.3 and 6.6 Hz), 6.60 (d, 1H, =CH, J = 16.2 Hz), 7.22-7.58 (m, 2H, ArH and =CH), 9.76 (s, 1H, CHO). ^{13}C Nmr: δ ($CDCl_3$) 22.30, 24.45, 36.34, 59.10, 64.30, 120.51, 127.53, 128.64, 129.49, 134.64, 140.75, 166.96, 201.51. MS: m/e (M^+) 245. (Found: C, 72.68; H, 7.78; N, 5.70%. Calc. for $C_{15}H_{19}NO_2$: C, 73.43; H, 7.81; N, 5.71%).

First eluted product was *(E)-3-N-benzyl-N-(3-propanal)cinnamamide* ***16b***. Oil (55%); ir (neat) 3060, 3000, 1730, 1660, 1400, 1130, 990, 770 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 2.77 (m, 2H, CH_2), 3.50 (m, 2H, NCH_2), 5.01 (s, 2H, NCH_2Ph), 6.59 (d, 1H, =CH, J = 15.1 Hz), 7.20 (m, 6H, ArH and =CH), 9.76 (s, 1H, CHO). ^{13}C Nmr: δ ($CDCl_3$) 36.31, 43.64, 59.15, 123.91, 127.62, 127.78, 128.53, 128.84, 129.10, 129.76, 134.60, 135.39, 139.23, 201.50. MS: m/e (M^+) 293 (Found: C, 77.24; H, 6.50; N, 4.77%. Calc. for $C_{19}H_{19}NO_2$: C, 77.78; H, 6.53; N, 4.78%).

First eluted product was *(E)-3-N-isopropil-N-(3-propanal)but-2-enamide* ***16c***. Oil (60%); ir (neat) 3050, 3010, 2980, 1730, 1670, 1500, 1375, 1130, 970, 830 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.24 (d, 3H, CH_3, J = 6.3 Hz), 1.28 (d, 3H, CH_3, J = 6.6 Hz), 1.80 (d, 3H, CH_3, J = 6.8 Hz), 2.68 (m, 2H, CH_2), 3.48 (m, 2H, CH_2), 4.25 (sept, 1H, CH, J = 6.3 and 6.6 Hz), 6.26 (d, 1H, =CH, J = 15.1 Hz), 6.88 (m, 1H, =CH), 9.75 (s, 1H, CHO). ^{13}C Nmr: δ ($CDCl_3$) 22.40, 24.35, 25.60, 36.45, 59.60, 64.80, 118.96, 137.27, 168.19, 206.34. MS: m/e (M^+) 183 (Found: C, 65.70; H, 9.20; N, 7.66%. Calc. for $C_{10}H_{17}NO_2$: C, 65.51; H, 9.35; N, 7.64%).

Preparation of 8-oxa-3,7-diazabicyclo[4.3.0]nonan-2-ones 18a-c.

General procedure. A mixture containing 7.5 mmol of compound **16a-c**, 11.5 ml (8.25 mmol) of triethylamine, 8.25 mmol of *N*-substituted hydroxylamines in 200 ml of absolute ethanol was refluxed for 36 h. At the end of this time the solvent was evaporated under reduce pressure and the residue subjected to silica flash-chromatography ($MeOH/CHCl_3$ 2:98).

Reaction of **16a** *with N-phenyl hydroxylamine.* First fractions gave *7,9-diphenyl-3-isopropyl-8-oxa-3,7-diazabicyclo[4.3.0]nonan-2-one* **18a**. Oil (65%); ir (neat) 3050, 3010, 2980, 1690, 1600, 1375, 1130, 980, 750 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.07 (d, 3H, CH_3, J = 6.9 Hz), 1.14 (d, 3H, CH_3, J = 6.6 Hz), 1.95 (m, 2H, 5-CH_2), 3.13 (m, 1H, H_4), 3.41 (dd, 1H, H_1, J = 6.4 and 9.0 Hz), 3.42 (m, 1H, H_4), 3.82 (m, 1H, H_6), 4.86 (sept, 1H, CH, J = 6.6 and 6.9 Hz), 5.17 (d, 1H, H_9, J = 6.4 Hz), 7.13, 7.53 (m, 10H, ArH). ^{13}C Nmr: δ ($CDCl_3$) 19.29, 19.51, 36.46, 44.07, 56.41, 63.28, 81.88, 116.51, 118.24, 123.67, 126.65, 127.89, 128.40, 128.39, 128.92, 139.74, 148.10, 167.89. MS: m/e (M^+) 336. (Found: C, 74.92; H, 7.12; N, 8.31%. Calc. for $C_{21}H_{24}N_2O_2$: C, 74.96; H, 7.19; N, 8.33%).

Reaction of **16b** *with N-methyl hydroxylamine.* First fractions gave *3-benzyl-7-methyl-9-phenyl-8-oxa-3,7-diazabicyclo[4.3.0]nonan-2-one* **18b**. Oil (65%); ir (neat) 3010, 2970, 1680, 1610, 1350, 1130, 980, 760 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.76 (m, 1H, H_5), 1.94 (m, 1H, H_5), 2.75 (s, 3H, NCH_3), 3.06 (m, 2H, H_4 and H_6), 3.28 (dd, 1H, H_1, J = 6.4 and 8.4 Hz), 3.57 (ddd, 1H, H_4, J = 3.3, 8.1 and 12.0 Hz), 4.51 (d, 1H, CH_2Ph, J = 14.7 Hz), 4.73 (d, 1H, CH_2Ph, J = 14.7 Hz), 5.02 (d, 1H, H_9, J = 6.4 Hz), 7.23-7.56 (m, 10H, ArH). ^{13}C Nmr: δ ($CDCl_3$) 24.38, 42.55, 43.10, 50.35, 56.30, 66.16, 82.19, 126.73, 127.49, 127.94, 128.00, 128.39, 128.65, 136.68,

169.15. MS: m/e (M^+) 322. (Found: C, 74.40; H, 6.85; N, 8.70%. Calc. for $C_{20}H_{22}N_2O_2$: C, 74.50; H,6.88; N, 8.69%).

Reaction of **16c** *with N-methyl hydroxylamine.* First fractions gave *7,9-dimethyl-3-isopropyl-8-oxa-3,7-diazabicyclo[4.3.0]nonan-2-one* ***18c***. Oil (70%); ir (neat) 3020, 3000, 2980, 1680, 1600, 1375, 1130, 980 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.07 (d, 3H, CH_3, J = 4.5 Hz), 1.10 (d, 3H, CH_3, J = 4.5 Hz) 1.45 (d, 3H, CH_3, J = 6.0 Hz), 1.78 (m, 2H, CH_2), 2.68 (s, 3H, NCH_3), 2.80 (dd, 1H, H_1, J = 6.9 and 9.3 Hz), 2.88 (m, 1H, H_6), 3.08 (ddd, 1H, H_4, J = 3.9, 4.2 and 12.9 Hz), 3.38 (ddd, 1H, H_4, J = 3.6, 4.0 and 12.9 Hz), 3.80 (dq, 1H, H_9, J = 6.0 and 6.9 Hz), 4.87 (ept, 1H, NCH, J = 4.5 Hz). ^{13}C Nmr: δ ($CDCl_3$) 19.02, 19.39, 25.53, 35.58, 43.03, 43.52, 55.42, 65.65, 77.33, 168.14. MS: m/e (M^+) 212. (Found: C, 62.12; H, 9.39; N, 13.17%. Calc. for $C_{11}H_{20}N_2O_2$: C, 62.22; H, 9.50; N, 13.20%).

Preparation of 8-oxa-3,9-diazabicyclo[4.3.0]nonan-4-ones 23b,c and 24a,b.

General procedure. To a stirred solution containing 75 mmol of methylamino acetaldehyde dimethyl acetal **19**, and 11.25 of triethylamine in 50 ml of dry carbon tetrachloride was added dropwise a solution of 82.5 mmol of corresponding acyl chloride in 50 ml of dry carbon tetrachloride at 0 °C. The solution was strirred 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 subject to silica flash-chromatography using a methanol/chloroform 2:98 mixture as eluent.

N-Methyl-N-(acetaldehyde dimethyl acetal)but-3-enamide ***20a***. Oil (70%); ir (neat) 2940, 2840, 1690, 1460, 1410, 1280, 1190, 1105, 1075, 980, 800, 725 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 2.90, 3.00 (s, total 3H, N-CH_3), 3.20 (m, 2H, CH_2CO), 3.40, (s, 6H, OCH_3), 3.45 (d, 2H, NCH_2, J = 5.3 Hz), 4.35, 4.45 (t, total 1H, OCH, J = 5.3 Hz), 5.18 (m, 2H, =CH_2), 5.80 (m, 1H, =CH).). ^{13}C Nmr: δ ($CDCl_3$) 39.45, 39.51, 53.51, 55.86, 104.40, 118.89, 132.34, 172.30. MS: m/e (M^+) 187. (Found: C, 58.25; H, 9.17; N, 7.46%. Calc. for $C_9H_{17}NO_3$: C, 57.72; H, 9.16; N, 7.48%).

(E)-N-methyl-N-(acetaldehyde dimethyl acetal)pent-3-enamide ***20b***. Oil (80%); ir (neat) 2965, 2830, 1680, 1630, 1410, 1150, 1100, 960 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.68 (dd, 3H, CH_3, J = 6.3 and1.8 Hz), 2.96, 3.05 (s, total 3H, NCH_3), 3.18 (m, 2H, OCH_2), 3.39 (s, 6H, OCH_3), 3.42 (d, 2H, NCH_2, J = 5.1 Hz), 4.40, 4.50 (t, total 1H, OCH, J = 5.1 Hz), 5.55 (m, 2H, =CH). ^{13}C Nmr: δ ($CDCl_3$) 17.80, 37.10, 39.80, 54.40, 58.40, 105.30, 122.70, 137.00, 173.10. MS: m/e (M^+) 201. (Found: C, 59.60; H, 9.51; N, 6.96%. Calc. for $C_{10}H_{19}NO_3$: C, 59.66; H, 9.52; N, 6.96%).

(E)-N-methyl-N-(acetaldehyde dimethyl acetal)-4-phenylbut-3-enamide ***20c***. Oil (90%); ir (neat) 2975, 2950, 1670, 1605, 1410, 1200, 1040, 980, 760 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 2.93, 3.03 (s, total 3H, NCH_3), 3.23 (d, 2H, CH_2CO, J = 6.6 Hz), 3.30, (s, 6H, OCH_3), 3.40 (d, 2H, NCH_2, J = 5.7 Hz), 4.37, 4.45 (t, total 1H, OCH), 6.28, 6.43 (m, 2H, =CH), 7.15-7.31 (m, 5H, ArH). ^{13}C Nmr: δ ($CDCl_3$) 38.37, 38.70, 50.94, 53.21, 55.21, 55.91, 103.55, 123.54, 124.19, 126.86, 128.05, 129.05, 133.41, 137.63, 167.40. MS: m/e (M^+) 263. (Found: C, 68.51; H, 8.10; N, 5.46%. Calc. for $C_{15}H_{21}NO_3$: C, 68.39; H, 8.04; N, 5.31%).

N-Methyl-N-(acetaldehyde)but-3-enamide ***21a***. Oil (40%); ir (neat) 2940, 2860, 1730, 1680, 1580, 1190, 1140, 1080, 985 cm^{-1}. ^1H Nmr: δ ($CDCl_3$), 2.98, 3.07 (s, total 3H, NCH_3), 3.21 (d, 2H, CH_2, J = 5.4 Hz) 4.18 (s, 2H, NCH_2), 5.15 (m, 2H, =CH_2), 5.89 (m, 1H, =CH), 9.55 (s, 1H, CHO). ^{13}C Nmr: δ ($CDCl_3$) 38.87, 54.41, 58.70, 118.70, 131.29, 168.30, 197.76. MS: m/e (M^+) 141. (Found: C, 58.12; H, 7.91; N, 9.94%. Calc. for $C_7H_{11}NO_2$: C, 59.54; H, 7.86; N, 9.93%).

(E)-N-methyl-N-(acetaldehyde)pent-3-enamide ***21b***. Oil (70%); ir (neat) 2930, 2870, 2730, 1735, 1670,

1405, 1295, 1230, 1110, 980, 830 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.70 (dd, 3H, CH_3, J = 1.8 and 6.3 Hz), 3.06 (s, 3H, NCH_3), 3.13 (m, 2H, CH_2), 4.17 (s, 2H, NCH_2), 5.54 (m, 2H, =CH), 9.54 (s, 1H, CHO) . ^{13}C Nmr: δ ($CDCl_3$) 18.48, 37.75, 54.41, 58.60, 123.70, 137.05, 173.10, 197.98. MS: m/e (M^+) 155. (Found: C, 61.92; H, 8.40; N, 9.10 %. Calc. for $C_8H_{13}NO_2$: C, 61.89; H, 8.45; N, 9.03 %).

(E)-N-Methyl-N-(acetaldehyde)-4-phenyl-but-3-enamide ***21c***. Oil (40%); ir (neat) 3060, 2980, 2950, 1740, 1650, 1400, 1200, 980, 760, 680 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 3.05 (s, 3H, NCH_3), 3.40 (d, 2H, CH_2, J = 5.4 Hz), 4.18 (s, 2H, NCH_2), 6.32 (m, 2H, =CH), 7.30-7.56 (m, 5H, ArH), 9.50 (s, 1H, CHO). ^{13}C Nmr: δ ($CDCl_3$) 38.70, 56.20, 58.30, 125.30, 128.76, 129.35, 133.41, 137.63, 168.50, 198.30. MS: m/e (M^+) 217. (Found: C, 71.80; H, 6.97; N, 6.45%. Calc. for $C_{13}H_{15}NO_2$: C, 71.85; H, 6.96; N, 6.45%).

3,7,9-Trimethyl-8-oxa-3,9-diazabicyclo[4.3.0]nonan-4-one ***23b***. Oil (40%); ir (neat) 2980, 2920, 1670, 1480, 1280, 1060 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.29 (d, 3H, CH_3, J = 6.1 Hz), 2.28 (dd, 1H, H_5, J = 3.6 and 15.3 Hz), 2.41 (dd, 1H, H_5, J = 6.3 and 15.3 Hz), 2.47 (m, 1H, H_6), 2.77 (s, 3H, NCH_3), 3.01 (m, 4H, NCH_3 and H_1), 3.13 (dd, 1H, H_2, J = 2.7 and 13.8 Hz), 3.48 (dd, 1H, $H_{2'}$, J = 3.6 and 13.8 Hz), 3.69 (dq, 1H, H_7, J = 4.0 and 6.1 Hz). ^{13}C Nmr: δ ($CDCl_3$) 17.55, 33.37, 36.10, 44.65, 48.58, 48.60, 50.30, 68.63, 78.69, 171.37. MS: m/e (M^+) 184. (Found: C, 58.61; H, 8.79; N, 15.18%. Calc. for $C_9H_{16}N_2O_2$: C, 58.66; H, 8.76; N, 15.21%).

3,9-Dimethyl-8-oxa-7-phenyl-3,9-diazabicyclo[4.3.0]nonan-4-one ***23c***. Oil (70%); ir (neat) 3080, 2920, 2900, 1670, 1480, 1440, 1290, 1050, 750, 700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 2.41 (m, 2H, H_5), 2.87 (m, 4H, NCH_3 and H_6), 3.05 (s, 3H, CH_3), 3.25 (m, 2H, H_1 and H_2), 3.54 (dd, 1H, $H_{2'}$, J = 3.6 and 14.8 Hz), 4.52 (d, 1H, H_7, J = 8.7 Hz), 7.21-7.41 (m, 5H, ArH). ^{13}C Nmr: δ ($CDCl_3$) 32.85, 36.70, 44.50, 49.46, 50.12, 68.54, 84.82, 126.81, 127.44, 129.14, 137.69, 173.10. MS: m/e (M^+) 246. (Found: C, 67.89; H, 7.39; N, 11.38%. Calc. for $C_{14}H_{18}N_2O_2$: C, 68.25; H, 7.37; N, 11.38%).

3,9-Dimethyl-8-oxa-3,9-diazabicyclo[4.3.0]nonan-4-one ***24a***. Oil (60%); ir (neat) 2970, 2960, 1660, 1470, 1270, 920 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 2.26 (dd, 1H, H_5, J = 4.5 and 15.0 Hz), 2.37 (dd, 1H, $H_{5'}$, J = 5.7 and 15.0 Hz), 2.65 (s, 3H, NCH_3), 2.90 (s, 3H, NCH_3), 3.00 (m, 2H, H_1 and H_6), 3.14 (dd, 1H, H_2, J = 3.9 and 13.8 Hz), 3.41 (m, 1H, H_2), 3.44 (m, 1H, H_7), 4.07 (dd, 1H, $H_{7'}$, J = 7.5 and 8.4 Hz). ^{13}C Nmr: δ ($CDCl_3$) 20.10, 34.88, 36.16, 41.72, 44.95, 51.00, 67.58, 71.91, 171.71. MS: m/e (M^+) 170. (Found: C, 55.67; H, 8.21; N, 16.50%. Calc. for $C_8H_{14}N_2O_2$: C, 56.44; H, 8.29; N, 16.46%).

3,7,9-Trimethyl-8-oxa-3,9-diazabicyclo[4.3.0]nonan-4-one ***24b***. Oil (10%); ir (neat) 2980, 2910, 1675, 1470, 1280, 1060 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.18 (d, 3H, CH_3, J = 6.1 Hz), 2.23 (dd, 1H, H_5, J = 9.3 and 15.0 Hz) 2.39 (dd, 1H, $H_{5'}$, J = 9.6 and 15.0 Hz), 2.71 (s, 3H, NCH_3), 2.95 (m, 5H, NCH_3, H_1 and H_6), 3.34 (m, 2H, H_2), 4.44 (dq, 1H, H_7, J = 6.1 and 6.4 Hz). ^{13}C Nmr: δ ($CDCl_3$) 14.67, 23.45, 32.00, 37.80, 44.64, 52.24, 68.02, 72.10, 74.70, 172.62. MS: m/e (M^+) 184. (Found: C, 59.99; H, 8.70; N, 15.16%. Calc. for $C_9H_{16}N_2O_2$: C, 58.66; H, 8.76; N, 15.21%).

Preparation of piperidines derivatives.

The above compounds were prepared according to the general method already reported by us.

4-(N-Methylamino)-2-dideutero-3-hydroxybenzyl-N-benzylpiperidine ***25b***. Oil (60%); ir (neat) 3420, 3295, 3010, 2960, 1430, 1370, 1130, 1050, 980, 750 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.81-1.98 (m, 2H, H_5), 2.39-2.41 (m, 1H, H_6), 2.54, 2.67 (m, 2H, H_6 and H_3), 2.82 (s, 3H, NCH_3), 2.85-2.93 (m, 1H, H_4), 3.47 (d, 1H, CH_2Ph, J = 13.2 Hz), 3.58 (d, 1H, CH_2Ph, J = 13.2 Hz), 4.91(m, 1H, CHOH), 7.20-7.34 (m, 10H, ArH). ^{13}C Nmr: δ ($CDCl_3$) 27.51, 29.67, 45.19, 49.56, 50.27, 62.82, 64.27, 82.50, 127.04, 127.44, 128.08, 128.21, 128.31, 128.52, 128.62, 128.93, 138.41. MS: m/e (M^+) 312. (Found: C, 78.65; H, 7.59; D, 1.30; N, 9.00%. Calc. for

$C_{20}H_{24}D_2N_2O$: C, 76.88; H, 7.74; D, 1.29; N, 8.97%).

4-(N-Methylamino)-2-dideutero-3-(1-ethanol)-N-isopropylpiperidine ***25c***. Oil (50%); ir (neat) 3600-3290, 1450, 1140, 1050 cm^{-1}. ^1H Nmr: δ (DMSO d_6) 0.93 (d, 6H, CH_3, J = 6.6 Hz), 1,15 (d, 3H, CH_3, J = 6.3 Hz), 1.56 (m, 1H, H_5), 1,70 (m, 1H, $H_{5'}$), 2.20 (m, 1H, H_6), 2.30 (m, 2H, H_3 and $H_{6'}$), 2.64 (s, 3H, NCH_3), 2.66 (m, 2H, H_4 and CH^i), 3.33 (bs, 2H, OH and NH), 3.73 (m, 1H, CHOH). ^{13}C Nmr: δ (DMSO d_6) 17.88, 21.72, 26.03, 29.05, 30.46, 34.39, 47.81, 53.72, 63.55, 75.60. MS: m/e (M^+) 202. (Found: C, 65.21; H, 10.92; D, 1.98; N, 13.82%. Calc. for $C_{11}H_{22}D_2N_2O$: C, 65.30; H, 10.96; D, 1.99; N, 13.85%).

3-(N-Methylamino)-6-dideutero-4-(1-ethanol)-N-methylpiperidine **26**. Oil (40%); ir (neat) 3500-3200, 1470, 1150, 1060 cm^{-1}. ^1H Nmr: δ (DMSO-d_6) 1.20 (d, 3H, CH_3, J = 6.0 Hz), 1.71 (dd, 1H, H_5, J = 7.6 and 13.7 Hz), 1.89 (dd, 1H, $H_{5'}$, J = 6.4 and 13.7 Hz), 2.28 (m, 2H, H_3 and H_4), 2.60 (s, 6H, NCH_3), 2.94, 2.98 (m, 2H, H_2), 3.82 (dq, 1H, CHOH, J = 5.1 and 6.0 Hz). ^{13}C Nmr: δ (DMSO-d_6) 21.27, 23.36, 29.02, 31.05, 43.27, 44.02, 47.66, 63.20, 76.89. MS: m/e (M^+) 174. (Found: C, 61.78; H, 10.49; D, 2.30; N, 16.09%. Calc. for $C_9H_{18}D_2N_2O$: C, 62.03; H, 10.41; D, 2.31; N, 16.07%).

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