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Intramolecular Nitrile Oxide Cycloaddition (INOC) of Substituted Amido-Oximes[1]

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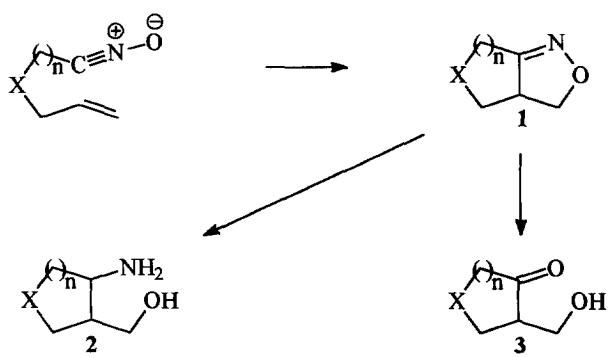
Abstract: Functionalized enantiomerically pure 3,4-dehydropyrrolidin-2-one and 1,2-dehydropyrrolizidin-3-one systems have been achieved by intramolecular nitrile oxide cycloaddition, starting from enamido-oximes, and by subsequent reduction of the obtained cycloadducts.

In recent years the intramolecular 1,3-dipolar cycloaddition reaction has received a great deal of synthetic and mechanistic attention especially in the synthesis of the intriguing carbon frameworks occurring in natural and complex molecules.[2] In particular, among these reactions, intramolecular nitrile oxide-olefin cycloadditions (INOC) give a [n.3.0] bicyclic system **1** where the resulting isoxazoline ring can serve as a precursor to 1,3-aminoalcohols **2**, hydroxy ketones **3** or other functional groups[3] (Scheme 1).



Scheme 1

To the best of our knowledge, no reports on systems where the olefin double bond is linked to the nitrile oxide moiety by a tether containing an amido group are present in literature. The *N-O* bond cleavage in these

systems can represent an easy synthetic entry to functionalized lactams which are potentially of interest in medicinal chemistry;[4] this is particularly true if these compounds can be prepared in a stereoselective manner.

In this paper we wished to exploit the scope and synthetic possibilities of the intramolecular nitrile oxide cycloaddition of a series of amido-oximes as a versatile approach for the synthesis of 3,4-dehydropyrrolidin-2-one system with potential for functionalization into target molecules showing synthetic and biological interest.[5] With this aim we have also exploited the effect of a stereocentre in α to the nitrile oxide moiety to influence the relative stereochemistry of the newly formed stereogenic centres in the products.

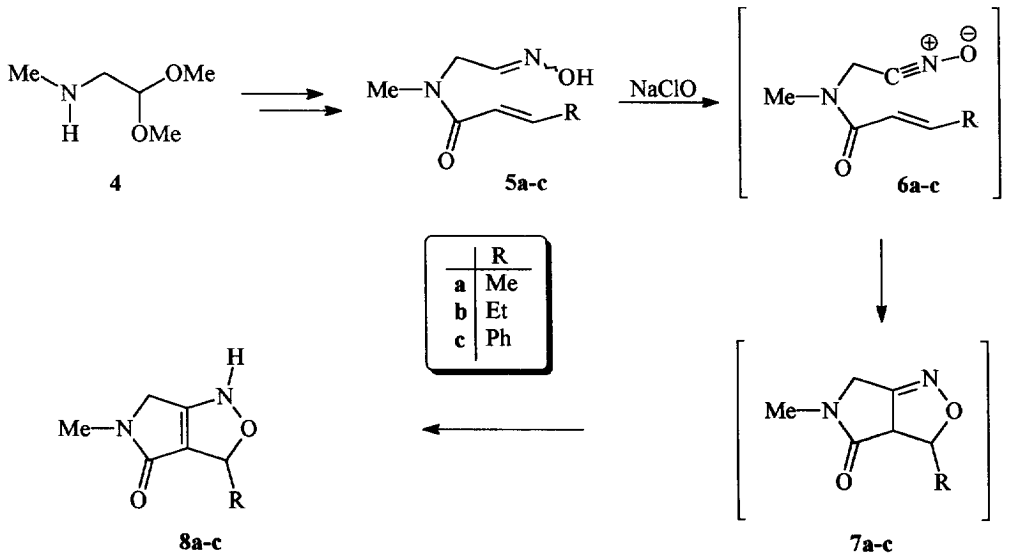
RESULTS AND DISCUSSION

Substrates **5a-c**, that possess properly situated aldoxime functionalities, were prepared, as described before,[6] from *N*-methylamino acetaldehyde dimethyl acetal **4**.

Treatment of derivatives **5a-c** with sodium hypochlorite in dichloromethane solution at 0 °C gave the bicyclic 2H-3-oxa-4-substituted-7-methyl-2,7-diazabicyclo[3.3.0]oct-1,5-en-6-ones **8a-c** in moderate to good yields (Scheme 2). The obtained derivatives have been characterized on the basis of analytical and spectroscopic data. High resolution mass spectra showed the correct molecular ions. IR spectra show the carbonyl absorption at 1650 cm^{-1}, in accord with a conjugated γ-lactam carbonyl group, and the characteristic sharp band at 3350 cm^{-1} of the secondary amino group.

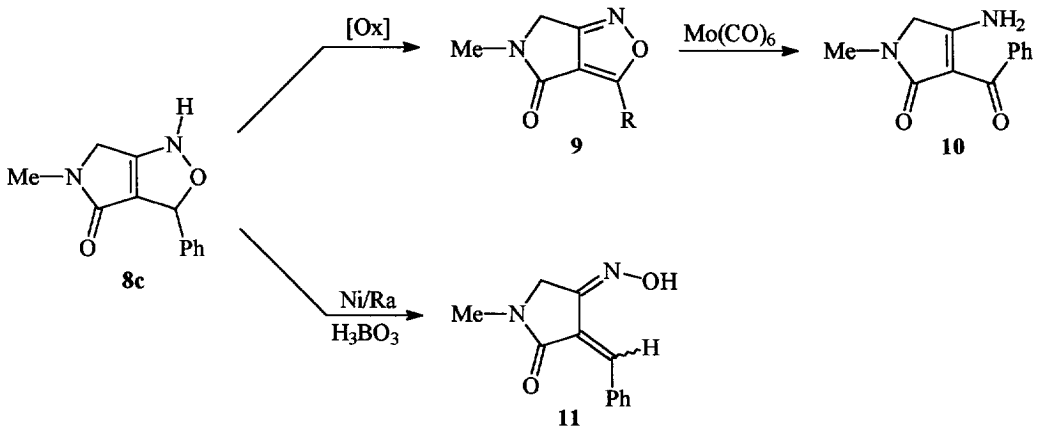
On the other hand, the ^1H nmr shows only the resonance of H_4 besides the resonance corresponding to methylene protons at C_8 which gives rise to a doublet in the range 4.05-4.39 ppm.

Formation of compounds **8**, can be explained on the basis of the isomerization of an initial, not isolated cycloadduct **7**, arising from the intramolecular nitrile oxide-olefin cycloaddition process of an intermediate 1,3-dipole **6**. The double bond migration is ascribed to an easy 1,3-prototropic hydrogen shift rationalizable on the basis of an increased thermodynamic stability due to the extension of conjugation.



Scheme 2

The chemistry of the resulting fused five-membered ring system **8** has been investigated. The reaction of **8c** with chloranil in toluene at reflux temperature yields the isoxazole derivative **9** which has been reduced with molybdenum hexacarbonyl in acetonitrile and transformed into *N*-methyl-3-benzoyl-4-amino-3,4-dehydro-pyrrolidin-2-one **10**. Attempts to reductively ring open cycloadduct **8c** failed: however, treatment of **8c** with Ni-Raney and H_3BO_3 in MeOH/H_2O leads to the formation of the oxime **11** (25% yields) (Scheme 3).



Scheme 3

The stereochemical aspects of these intramolecular cycloadditions have been further investigated. Intramolecular nitrone cycloadditions with a stereocentre inserted in the tether connecting dipole and dipolarophile have already been object of recent research.[6,7]

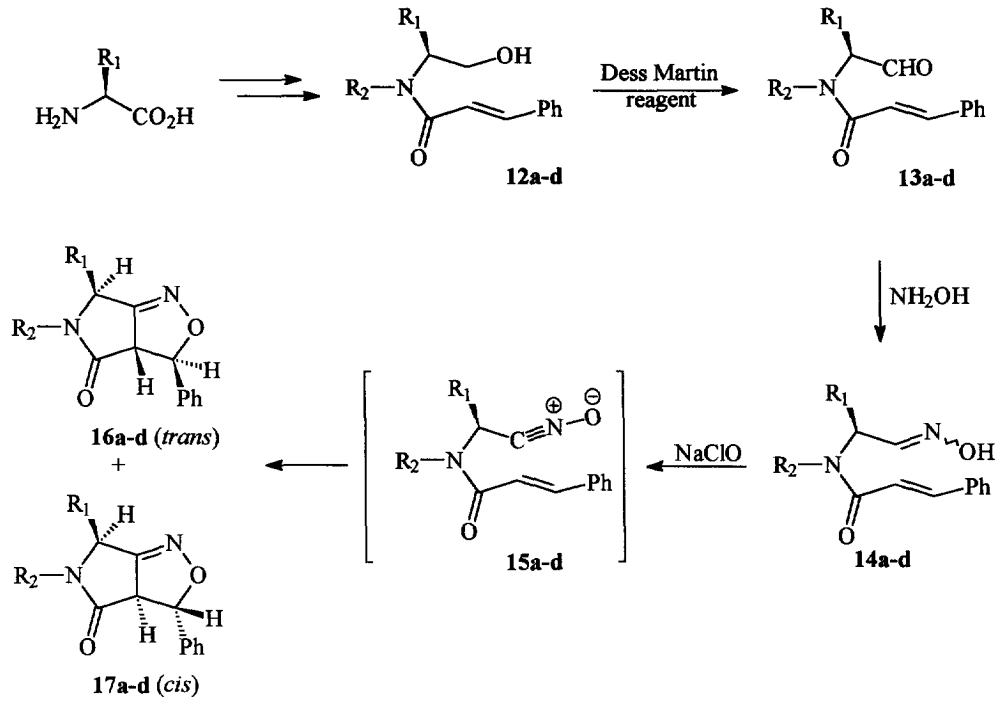
In this view, we examined the effect of a stereocentre located in position α to the nitrile oxide to influence the stereochemical course of the intramolecular nitrile oxide cycloaddition to α,β-unsaturated amides.

The reaction of homochiral oximes **14a-d**, obtained by the already reported procedure,[6,7] with NaClO afforded directly, through the intermediate, not isolated nitrile oxide **15**, a mixture of diastereoisomeric 3-oxa-4-phenyl-2,7-diazabicyclo[3.3.0]oct-1-en-6-ones **16** and **17** which have been separated by semipreparative HPLC ($CHCl_3$/hexane 1:1 as eluent) (Scheme 4). The obtained derivatives have been 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_4 proton in the range 4.31-4.39 δ, while H_5 protons resonate as a doublet at 3.02-3.33 δ; moreover H_8 protons give rise to two doublets in the range 3.54-3.67 δ.

The stereochemical assignments to the obtained products have been determinated by ^1H nmr and NOE experiments. The stereochemical informations present in the dipolarophile moiety are completely retained in the cycloadducts and the relative stereochemistry at C_4 and C_5 in the formed Δ^2-isoxazoline ring is predeterminated by the alkene geometry. Furthermore, the positive NOE effect observed for methylene protons at C_8, in compound **16** (*trans*), when irradiating H_5 is clearly indicative of their *cis* relationship. On the contrary, in compound **17** (*cis*) irradiation of the same proton give rise to an enhancement of H_8 resonance.

This series of experiments established that a stereogenic centre in the nitrile oxide/olefin tether[8] can affect only in a low degree olefin face selectivity which, in turn, increases with the steric requirements of R at C_8

(increases face selectivity with increasing steric bulk). In fact, comparable face selectivity has been experienced with R = benzyl and isobutyl, whereas 3:1 (*trans* versus *cis*) mixtures have been obtained with R = isopropyl and in the proline derivatives **16d** and **17d**, the *trans/cis* ratio increases to 4:1.



Scheme 4

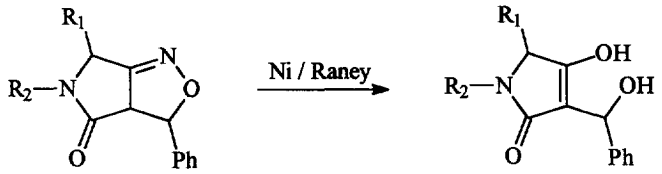
	R_1	R_2	Yield%	16:17 Ratio
a	isopropyl	Me	80	3:1
b	isobutyl	Me	90	1:1
c	Benzyl	Me	60	1:1
d	$-(CH_2)_3-$		60	4:1

The obtained results parallel the data already reported in the literature for 1,3-dipolar intramolecular cycloadditions of nitrile oxides.[9]

Raney-Nickel reduction of compound **16c** and **17c** afforded 3-phenylmethanol-4-hydroxy-3,4-dehydro-pyrrolidin-2-ones **18c** and **19c** while reduction of compound **17d** afforded 1-hydroxy-2-phenylmethanol-1,2-dehydropyrrolizidin-3-one **19d** (Scheme 5). The enolic structure appears to be stabilized by the extended conjugation and by the intramolecular hydrogen bonding involving the hydroxy groups at C_3 and on the substituent at position 2.

The molecular structure of the reaction products was assigned on the basis of analytical and spectroscopic

data (see experimental).



16c, 17c,d **18c, 19c,d**

Scheme 5

In conclusion, the intramolecular nitrile oxide-olefin cycloaddition process afforded functionalized enantiomerically pure 3,4-dehydropyrrolidin-2-one and 1,2-dehydropyrrolizidin-3-one systems, with specific absolute stereochemistry. Moreover, this ring closure offers the possibility of usefully synthetic manipulation directed towards the synthesis of natural compounds.

EXPERIMENTAL

Mp 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. ^{1}H Nmr spectra were measured on a Bruker WP 200 SY instrument in $CDCl_3$ as solvent. Chemical shifts are in ppm (δ) from TMS as internal standard. NOE difference spectra were obtained by subtracting alternatively right-off-resonance free induction decays (FIDS) from right-on-resonance-induced FIDS. Merck silica gel 60H was used for preparative short-column chromatography. Optical rotations were measured on a PF 241 MC Polarimeter (Perkin Elmer). Compounds **5a-c** and **12-14c,d** have been previously reported by us.[6,7]

Preparation of 2H-3-oxa-4-substituted-7-methyl-2,7-diazabicyclo[3.3.0]oct-1,5-en-6-one 8a-c.

General procedure. To a mixture containing 50 mmol of compound **5a-c** in 100 ml of dichloromethane was added dropwise 10 ml of sodium hypochlorite (7% solution) at 0 °C under vigorous stirring. After 3h the reaction mixture was evaporated and the residue subjected to silica flash-chromatography (MeOH/$CHCl_3$ 3:97) gave bicycloadducts **8a-c**.

*Reaction of **5a***. First fractions gave 2H-3-oxa-4,7-dimethyl-2,7-diazabicyclo[3.3.0]oct-1,5-en-6-one **8a**. Light yellow oil (25% yield); ir (neat): 3350, 2980, 2960, 1670, 1450, 1370, 1220, 1110, 970, 850, 680 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 1.27 (d, 3H, J = 7.3 Hz), 2.98 (s, 3H, N-CH_3), 4.06 (d, 1H, H_{8a}, J = 13.2 Hz), 4.34 (d, 1H, H_{8b}, J = 13.2 Hz), 4.61 (q, 1H, H_4, J = 7.3 Hz). ^{13}C Nmr: δ ($CDCl_3$) 17.48, 30.95, 48.05, 79.15, 115.27, 159.98, 165.37. Exact mass calculated for $C_7H_{10}N_2O_2$: 154.0742. Found: 154.0737.

*Reaction of **5b***. First eluted fractions gave 2H-3-oxa-4-ethyl-7-methyl-2,7-diazabicyclo[3.3.0]oct-1,5-en-6-one **8b**. Light yellow oil (30% yield); ir (neat): 3450, 2980, 2960, 1650, 1450, 1220, 1110, 980, 860, 750, 680 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 1.09 (t, 3H, J = 7.4 Hz), 1.42 (m, 2H), 1.61 (bs, 1H, NH), 3.01 (s, 3H, N-CH_3), 4.10 (d, 1H, H_{8a}, J = 13.3 Hz), 4.39 (d, 1H, H_{8b}, J = 13.3 Hz), 4.77 (dd, 1H, H_4, J = 8.9 and 4.4 Hz). ^{13}C Nmr: δ

($CDCl_3$) 9.85, 22.87, 32.58, 46.45, 72.05, 113.24, 158.93, 162.64. Exact mass calculated for $C_8H_{12}N_2O_2$: 168.0898. Found: 168.0907.

Reaction of 5c. First eluted fractions gave 2H-3-oxa-4-phenyl-7-methyl-2,7-diazabicyclo[3.3.0]oct-1,5-en-6-one **8c**. White solid, mp 151-154 °C (75% yield); ir (KBr): 3350, 3060, 3040, 2980, 1715, 1650, 1500, 1490, 1400, 1300, 1260, 1040, 865, 770, 740, 700, 680 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.59 (bs, 1H, NH), 2.83 (s, 3H, N-CH_3), 4.05 (d, 1H, H_{8a}, J = 13.4 Hz), 4.35 (d, 1H, H_{8b}, J = 13.4 Hz), 5.92 (s, 1H, H_4), 7.32 (s, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 30.68, 45.38, 74.72, 92.40, 126.33, 128.62, 129.23, 132.14, 156.29, 163.16. Exact mass calculated for $C_{12}H_{12}N_2O_2$: 216.0898. Found: 216.0911.

Preparation of compounds 9-11.

Oxidation of compound 8c with chloranil. A solution of 50 mmol of **8c** and 100 mmol of chloranil in dry toluene was refluxed for 4 h; at the end of this time the solvent was evaporated and the residue subjected to silica flash-chromatography (cyclohexane/ethyl acetate 7:3) gave 3-Oxa-4-phenyl-7-methyl-2,7-diazabicyclo[3.3.0] octa-1,4-dien-6-one **9**. White solid, mp 170-171 °C (70% yield); ir (KBr): 3080, 3060, 2960, 2940, 1690, 1680, 1650, 1500, 1460, 1400, 1250, 1150, 910, 780, 760, 690 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 3.17 (s, 3H, N-CH_3), 4.48 (s, 2H), 7.51-7.53 (m, 3H, aromatic protons), 8.29-8.33 (m, 2H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 30.14, 46.42, 112.93, 125.93, 127.69, 129.09, 131.72, 161.05, 164.96, 167.55. Exact mass calculated for $C_{12}H_{10}N_2O_2$: 214.0742. Found: 214.0735.

Reduction of compound 9 with molybdenum hexacarbonyl. A solution of 50 mmol of **9** and 25 mmol of molybdenum hexacarbonyl[10] in dry acetonitrile was refluxed for 3 h; at the end of this time the solvent was evaporated and the residue subjected to silica flash-chromatography (ethyl acetate) gave *1-Methyl-3-benzoyl-4-amino-3,4-dehydropyrrolidin-2-one* ***10***. Light yellow solid, mp 191-194 °C (85% yield); ir (Kbr):3280, 3180, 3060, 2980, 1630, 1510, 1450, 1400, 1330, 1250, 1220, 1000, 930, 890, 750, 700, 660 cm^{-1}. ^1H Nmr: δ (CD_3OD) 2.88 (s, 3H, N-CH_3), 4.10 (s, 2H, H_5), 7.34-7.87 (m, 5H, aromatic protons). ^{13}C Nmr: δ (CD_3OD) 28.80, 50.58, 101.21, 128.38, 129.60, 131.39, 140.82, 171.64, 173.73, 193.63. Exact mass calculated for $C_{12}H_{12}N_2O_2$: 216.0898. Found: 216.0891.

Reduction of compound 8c with Raney-Nickel. To a solution of isoxazoline 8c (170 mg, 0.8 mmol) in 5/1 methanol/water (10 ml) was added boric acid (97 mg, 1.6 mmol) and 30 mg of W2 Nickel-Raney.[11] The solution was placed under hydrogen atmosphere and stirred vigorously for 3 h. At the end of this time the solution was filtered through Celite, the aqueous layer was extracted with CH_2Cl_2 and the organic solution was dryed over Na_2SO_4. The solvent was evaporated and the residue subjected to silica flash-chromatography (cyclohexane/ethyl acetate 5:5) gave *N-Methyl-3-benzyliden-4-hydroxyiminopyrrolidin-2-one* ***11***. White solid, mp 225-228 °C (65% yield); ir (KBr): 3350, 3250, 3040, 2960, 2940, 1680, 1620, 1500, 1450, 1270, 1220, 1130, 1040, 970, 920, 760, 680 cm^{-1}. ^1H Nmr: major isomer δ ($DMSO-d_6$) 2.96 (s, 3H, N-CH_3), 4.17 (s, 2H, H_5), 7.38 (s, 1H, $H_{3'}$), 7.44-7.46 (m, 3H, aromatic protons), 8.29-8.33 (m, 2H, aromatic protons), 11.99 (s, 1H, OH). ^{13}C Nmr: δ ($DMSO-d_6$) 29.38, 47.78, 123.14, 128.36, 130.38, 131.61, 134.03, 134.43, 151.27, 166.48. Exact mass calculated for $C_{12}H_{12}N_2O_2$: 216.0898. Found: 216.0904.

Preparation of amidoalcohols 12a,b.

The above compounds were prepared according to the general method already reported by us,[6,7] yield and spectroscopic date being shown below.

Trans (S)-(-)-[N-methyl-N-(1-isopropyl-1-ethan-2-ol)] cinnamamide ***12a***. Light yellow oil (88% yield); $[\alpha]_D^{25}$ - 51.3° (c = 0.78, $CHCl_3$); two rotamers, population 1:1; ir (neat): 3600-3200, 3080, 3060, 2980, 2960, 1650, 1600, 1450, 1400, 1360, 1170, 1070, 970, 920, 850, 760, 710, 680 cm^{-1}. ^1H nmr: δ ($CDCl_3$) 0.80, 0.83 (d, total 3H, *J* = 6.5 Hz), 0.93, 0.94 (d, total 3H, *J* = 6.5 Hz), 1.76 (m, total 1H), 2.88, 3.02 (s, total 3H, N-CH_3), 3.71 (m, total 3H), 6.91, 7.08 (d, total 1H, *J* = 15.4 Hz), 7.23-7.51 (m, total 5H, aromatic protons), 7.56, 7.64 (d, total 1H, *J* = 15.4 Hz). ^{13}C Nmr: δ ($CDCl_3$) 19.87, 19.91, 26.48, 27.51, 27.55, 30.99, 59.87, 60.91, 62.08, 65.12, 118.03, 119.57, 126.73, 127.03, 128.15, 128.57, 128.94, 129.07, 134.89, 135.21, 141.13, 142.50, 167.49, 169.15. Exact mass calculated for $C_{15}H_{21}NO_2$: 247.1572. Found: 247.1567.

Trans (S)-(-)-[N-methyl-N-(1-isobutyl-1-ethan-2-ol)] cinnamamide ***12b***. White solid, mp 84-86 °C (90% yield); $[\alpha]_D^{25}$ - 13.9° (c = 1.15, $CHCl_3$); two rotamers, population 1:1; ir (KBr): 3350-3150, 3080, 3060, 2980, 2960, 1650, 1580, 1470, 1410, 1370, 1270, 1140, 1040, 1000, 870, 770, 720, 690, 650 cm^{-1}. ^1H nmr: δ ($CDCl_3$) 0.81 (d, total 3H, *J* = 6.4 Hz), 0.88 (d, total 3H, *J* = 6.4 Hz), 1.17 (m, total 1H), 1.43 (m, totla 2H), 2.85, 2.98 (s, total 3H, N-CH_3), 3.62 (m, total 2H), 4.22, 4.82 (m, total 1H), 6.88, 7.12 (d, total 1H, *J* = 15.4 Hz), 7.23-7.50 (m, total 5H, aromatic protons), 7.55, 7.65 (d, total 1H, *J* = 15.4 Hz). ^{13}C Nmr: δ ($CDCl_3$) 21.56, 21.85, 23.04, 24.19, 24.66, 26.60, 29.59, 36.78, 37.35, 53.61, 57.32, 62.40, 62.94, 117.86, 118.74, 127.39, 127.49, 128.31, 128.44, 128.93, 129.28, 141.40, 142.44, 167.76, 168.51. Exact mass calculated for $C_{16}H_{23}NO_2$: 261.1728. Found: 261.1739.

Preparation of *trans N*-methyl-*N*-(substitutedacetaldehyde)cinnamamides 13a,b.

General procedure. 20 ml of wet CH_2Cl_2 (10 µl H_2O in 10 ml di CH_2Cl_2) was added slowly to a vigorously stirring solution of amidoalcohol **12** (1 mmol) and DMP[12] (Dess Martin Periodinane) (640 mg, 1 mmol) in 6 ml of dry CH_2Cl_2 and allowed to stirring for 30 m. The mixture was then diluted with ether, and concentrated into a few ml of solvent by rotary evaporator. The residue was taken up in 50 ml of ether and then washed with 30 ml of 1:1 10% $Na_2S_2O_3$:saturated aqueous $NaHCO_3$, followed by 10 ml of H_2O and 10 ml of brine. The aqueous washings were back-extracted with 20 ml of ether, and this organic layer was washed with H_2O and brine. The combined organic layers were dried with Na_2SO_4, and the solvent removed under reduced pressure. The residue was then subjected to silica flash-chromatography using a methanol/chlorophorm 3:97 mixture as eluent.

Trans (S)-(+)-N-methyl-N-(1-isopropylacetaldehyde) cinnamamide ***13a***. Light yellow oil (75% yield); $[\alpha]_D^{25}$ + 1.5° (c = 1.35, $CHCl_3$); ir (neat): 3080, 3060, 2975, 2960, 1730, 1650, 1600, 1500, 1450, 1400, 1260, 1130, 970, 850, 760, 710, 685 cm^{-1}. ^1H nmr: δ ($CDCl_3$) 0.95 (d, 3H, *J* = 6.7 Hz), 1.18 (d, 3H, *J* = 6.7 Hz), 2.41 (dsect, 1H, *J* = 9.8 and 6.7 Hz), 3.14 (s, 3H, N-CH_3), 4.47 (d, 1H, *J* = 9.8 Hz), 6.92 (d, 1H, *J* = 15.4 Hz), 7.36-7.55 (m, 5H, aromatic protons), 7.75 (d, 1H, *J* = 15.4 Hz), 9.70 (s, 1H, CHO). ^{13}C Nmr: δ ($CDCl_3$) 19.53, 20.23, 26.53, 34.48, 70.20, 116.25, 127.88, 128.75, 129.87, 134.87, 144.08, 167.24, 198.32. Exact mass calculated for $C_{15}H_{19}NO_2$: 245.1415. Found: 245.1411.

Trans (S)-(-)-N-methyl-N-(1-isobutylacetaldehyde) cinnamamide ***13b***. Light yellow oil (75% yield); $[\alpha]_D^{25}$ - 41.0° (c = 1.40, $CHCl_3$); ir (neat): 3060, 3040, 2960, 2940, 2860, 2750, 1730, 1650, 1600, 1500, 1450, 1400, 1320, 1300, 1260, 1200, 1130, 1100, 1020, 970, 850, 760, 700, 680 cm^{-1}. ^1H nmr: δ ($CDCl_3$) 0.95 (d, 6H, *J* = 6.3 Hz), 1.65 (m, 3H), 3.09 (s, 3H, N-CH_3), 4.89 (dd, 1H, *J* = 9.8 and 4.6 Hz), 6.90 (d, 1H, *J* = 15.4 Hz), 7.31-7.53 (m, 5H, aromatic protons), 7.71 (d, 1H, *J* = 15.4 Hz), 9.53 (s, 1H, CHO). ^{13}C Nmr: δ ($CDCl_3$) 21.56, 22.99, 24.80, 26.67, 33.18, 34.60, 63.12, 116.35, 127.73, 128.62, 129.72, 134.76, 143.28, 143.77, 167.07, 199.29. Exact mass calculated for $C_{16}H_{21}NO_2$: 259.1572. Found: 259.1580.

Preparation of *trans* *N*-methyl-*N*-(substitutedacetaldoxime)cinnamamides 14a,b.

The above compounds were prepared according to the general method already reported by us,[6,7] yield and spectroscopic date being shown below.

Trans (S)-N-methyl-N-(1-isopropylacetaldoxime) cinnamamide ***14a***. Light yellow oil (80% yield); *syn/anti* mixture 1:3; ir (neat): 3350-3250, 3080, 3060, 2980, ,2960, 1650, 1600, 1450, 1400, 1270, 1130, 1100, 970, 850, 760, 730, 700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) major isomer 0.76 (d, 3H, *J* = 6.8 Hz), 0.89 (d, 3H, *J* = 6.8 Hz), 1.21 (m, 1H), 2.83 (m, 1H), 2.92 (s, 3H, N-CH_3), 6.83 (d, 1H, *J* = 15.6 Hz), 7.28-7.51 (m, 6H, aromatic protons and CH=N), 7.70 (d, 1H, *J* = 15.6 Hz). ^{13}C Nmr: δ ($CDCl_3$) 14.79, 17.79, 28.37, 31.67, 56.80, 117.28, 127.73, 128.09, 128.64, 135.08, 143.39, 149.19, 167.08. Exact mass calculated for $C_{15}H_{20}N_2O_2$: 260.1524. Found: 260.1531.

Trans (S)-N-methyl-N-(1-isobutylacetaldoxime) cinnamamide ***14b***. Light yellow oil (75% yield); *syn/anti* mixture 1:4; ir (neat): 3600-3200, 3080, 3060, 2960, 1650, 1600, 1400, 1350, 1280, 1220, 1130, 1100, 970, 910, 850, 760, 700, 660 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) major isomer .93 (d, 6H, *J* = 6.0 Hz), 1.59 (m, 3H), 2.89 (m, 1H), 2.96 (s, 3H, N-CH_3), 6.84 (d, 1H, *J* = 15.4 Hz), 7.33-7.52 (m, 5H, aromatic protons), 7.73 (d, 1H, *J* = 15.4 Hz), 9.02 (s, 1H, CH=N). ^{13}C Nmr: δ ($CDCl_3$) 22.10, 23.15, 24.70, 30.63, 37.52, 51.19, 117.27, 127.88, 128.80, 129.77, 135.17, 143.74, 149.80, 167.22. Exact mass calculated for $C_{16}H_{22}N_2O_2$: 274.1681. Found: 274.1676.

Preparation of (4S,5S,8S)- and (4R,5R,8S)-3-oxa-4,8-disubstituted-7-methyl-2,7-diazabicyclo[3.3.0] oct-1-en-6-ones 16a-c and 17a-c and (3R,3aR,8aS)- and (3S,3aS,8aS)-(+)-3phenyl-4-oxo-3,3a-dihydro-pyrrolizidin[3,2-c]isoxazole 16,17d.

Reaction of ***14a*** *with NaClO*. First eluted fractions gave *(4S,5S,8S)-(+)-3-oxa-4-phenyl-7-methyl-8-isopropyl-2,7-diazabicyclo[3.3.0]oct-1-en-6-one* ***17a***. Light yellow solid, mp 68-74 °C (20% yield); $[\alpha]_D^{25}$ + 13.8° (c = 0.58, $CHCl_3$); ir (KBr): 3060, 3040, 2980, 1700, 1650, 1460, 1420, 1400, 1385, 1320, 1280, 1120, 1005, 960, 850, 820, 760, 700, 610 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.00 (d, 3H, *J* = 6.8 Hz), 1.31 (d, 3H, *J* = 7.0 Hz), 2.31 (m, 1H, $H_{8'}$), 2.91 (s, 3H, N-CH_3), 4.19 (dd, 1H, H_5, *J* = 12.8 and 1.9 Hz), 4.37 (dd, 1H, H_8, *J* = 3.8 and 1.9 Hz), 5.53 (d, 1H, H_4, *J* = 12.8 Hz), 7.31-7.56 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 14.28, 18.23, 27.59, 27.80, 61.41, 63.24, 85.55, 126.47, 128.45, 128.73, 136.78, 161.37, 167.63. Exact mass calculated for $C_{15}H_{18}N_2O_2$: 258.1368. Found: 258.1365. Further elution gave *(4R,5R,8S)-(-)-3-oxa-4-phenyl-7-methyl-8-isopropyl-2,7-diazabicyclo[3.3.0]oct-1-en-6-one* ***16a***. Light yellow oil (60% yield); $[\alpha]_D^{25}$ - 43.1° (c = 1.02, $CHCl_3$); ir (neat): 3070, 3040, 2960, 1705, 1650, 1460, 1400, 1320, 1290, 1220, 1070, 1050, 1000, 850, 750,

700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 0.91 (d, 3H, J = 6.8 Hz), 1.15 (d, 3H, J = 6.8 Hz), 2.25 (dsect, 1H, $H_{8'}$, J = 6.8 and 3.3 Hz), 2.95 (s, 3H, N-CH_3), 4.13 (d, 1H, H_5, J = 12.3 Hz), 4.17 (d, 1H, H_8, J = 3.3 Hz), 5.56 (d, 1H, H_4, J = 12.3 Hz), 7.30-7.54 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 16.69, 18.83, 28.59, 28.75, 60.86, 65.43, 85.99, 126.33, 128.41, 128.71, 136.99, 162.31, 167.66. Exact mass calculated for $C_{15}H_{18}N_2O_2$: 258.1368. Found: 258.1368.

*Reaction of **14b** with NaClO.* First eluted fractions gave *(4R,5R,8S)-(-)-3-oxa-4-phenyl-7-methyl-8-isobutyl-2,7-diazabicyclo[3.3.0]oct-1-en-6-one **16b***. Light yellow solid, mp 92-99 °C (45% yield); $[\alpha]_D^{25}$ - 86.5° (c = 0.18, $CHCl_3$); ir (KBr): 3080, 3060, 2980, 2960, 1700, 1470, 1400, 1250, 1120, 860, 830, 760, 700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 0.99 (d, 3H, J = 5.5 Hz), 1.02 (d, 3H, J = 5.5 Hz), 1.54 (m, 1H, $H_{8'a}$), 1.77 (m, 2H, $H_{8'b}$ and $H_{8''}$), 2.94 (s, 3H, N-CH_3), 4.21 (d, 1H, H_5, J = 11.9 Hz), 4.28 (dd, 1H, H_8, J = 9.6 and 3.7 Hz), 5.59 (d, 1H, H_4, J = 11.9 Hz), 7.36-7.54 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 21.91, 23.31, 25.31, 28.39, 38.68, 58.53, 59.31, 85.69, 126.35, 128.44, 128.75, 137.25, 162.86, 167.13. Exact mass calculated for $C_{16}H_{20}N_2O_2$: 272.1524. Found: 272.1525. Further elution gave *(4S,5S,8S)-(+)-3-oxa-4-phenyl-7-methyl-8-isobutyl-2,7-diazabicyclo[3.3.0]oct-1-en-6-one **17b***. Light yellow solid, mp 78-81 °C (45% yield); $[\alpha]_D^{25}$ + 90.6° (c = 0.26, $CHCl_3$); ir (KBr): 3080, 3060, 2960, 1720, 1700, 1500, 1470, 1450, 1420, 1370, 1250, 1050, 880, 840, 750, 690, 620 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.00 (d, 3H, J = 6.2 Hz), 1.03 (d, 3H, J = 6.2 Hz), 1.74 (m, 2H, $H_{8'a}$ and $H_{8''}$), 2.22 (m, 1H, $H_{8'b}$), 2.91 (s, 3H, N-CH_3), 4.18 (d, 1H, H_5, J = 11.9 Hz), 4.40 (ddd, 1H, H_8, J = 9.4, 4.4 and 2.1 Hz), 5.56 (d, 1H, H_4, J = 11.9 Hz), 7.33-7.53 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 21.65, 23.72, 24.96, 27.79, 38.92, 57.13, 61.13, 85.99, 126.38, 128.44, 128.74, 137.18, 164.65, 167.48. Exact mass calculated for $C_{16}H_{20}N_2O_2$: 272.1524. Found: 272.1526.

*Reaction of **14c** with NaClO.* First eluted fractions gave *(4S,5S,8S)-(-)-3-oxa-4-phenyl-7-methyl-8-benzyl-2,7-diazabicyclo[3.3.0]oct-1-en-6-one **17c***. White solid, mp 134-136 °C (30% yield); $[\alpha]_D^{25}$ - 2.0° (c = 1.00, THF); ir (KBr): 3080, 3060, 3020, 2960, 2940, 1715, 1500, 1450, 1410, 1390, 1370, 1315, 1100, 830, 750, 700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 2.84 (s, 3H, N-CH_3), 3.15 (dd, 1H, $H_{8'a}$, J = 14.6 and 5.3 Hz), 3.27 (dd, 1H, $H_{8'b}$, J = 14.6 and 7.1 Hz), 4.10 (dd, 1H, H_5, J = 12.1 and 0.7 Hz), 4.62 (ddd, 1H, H_8, J = 7.1, 5.3 and 0.7 Hz), 5.53 (d, 1H, H_4, J = 12.1 Hz), 7.24-7.49 (m, 10H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 28.45, 36.14, 59.54, 60.61, 86.04, 126.20, 127.02, 128.33, 128.50, 128.57, 129.25, 135.83, 136.93, 163.90, 163.34. Exact mass calculated for $C_{19}H_{18}N_2O_2$: 306.1368. Found: 306.1372. Further elution gave *(4R,5R,8S)-(-)-3-oxa-4-phenyl-7-methyl-8-benzyl-2,7-diazabicyclo[3.3.0]oct-1-en-6-one **16c***. White solid, mp 87-90 °C (30% yield); $[\alpha]_D^{25}$ - 133.0° (c = 1.50, THF); ir (KBr): 3060, 3040, 2960, 2940, 1700, 1650, 1490, 1450, 1400, 1370, 1310, 1250, 1115, 890, 820, 810, 750, 700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 2.95 (s, 3H, N-CH_3), 3.09 (d, 2H, $H_{8'}$, J = 4.6 Hz), 3.17 (d, 1H, H_5, J = 12.0 Hz), 4.53 (t, 1H, H_8, J = 4.6 Hz), 5.37 (d, 1H, H_4, J = 12.0 Hz), 7.11-7.30 (m, 10H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 28.26, 35.74, 59.31, 60.32, 85.54, 126.35, 127.47, 128.35, 128.47, 128.75, 129.15, 134.43, 136.60, 162.33, 167.36. Exact mass calculated for $C_{19}H_{18}N_2O_2$: 306.1368. Found: 306.1360.

*Reaction of **14d** with NaClO.* First eluted fractions gave *(3R,3aR,8aS)-(+)-3phenyl-4-oxo-3,3a-dihydropyrrolizidin[3,2-c]isoxazole **16d***. White solid, mp 148-149 °C (48% yield); $[\alpha]_D^{25}$ + 163.8° (c = 2.43, $CHCl_3$); ir (KBr): 3080, 3060, 2990, 2980, 2940, 1715, 1680, 1420, 1230, 1180, 840, 770, 750, 700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 2.11 (m, 4H), 3.06 (dt, 1H, H_{6a}, J = 11.7 and 5.7 Hz), 3.78 (dt, 1H, H_{6b}, J = 11.7 and 7.2 Hz),

4.42 (d, 1H, H_{3a}, J = 11.4 Hz), 4.64 (t, 1H, H_{8a}, J = 6.9 Hz), 5.57 (d, 1H, H_3, J = 11.4 Hz), 7.28-7.50 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 26.96, 27.15, 41.94, 60.06, 64.84, 85.18, 126.33, 128.42, 128.70, 137.37, 163.15, 168.01. Exact mass calculated for $C_{14}H_{14}N_2O_2$: 242.1055. Found: 242.1059. Further elution gave *(3S,3aS,8aS)-3-phenyl-4-oxo-3,3a-dihydropyrrolizidin[3,2-c]isoxazole* ***17d***. White sticky solid (12% yield); ir (KBr): 3080, 3060, 2980, 2960, 1710, 1680, 1400, 1220, 1150, 850, 760, 700, 680 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 2.13 (m, 4H), 2.94 (m, 1H, H_{6a}), 3.40 (m, 1H, H_{6b}), 4.57 (t, 1H, H_{8a}, J = 6.8 Hz), 4.94 (d, 1H, H_{3a}, J = 11.3 Hz), 5.82 (d, 1H, H_3, J = 11.3 Hz), 7.28-7.49 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 26.90, 27.64, 41.86, 58.45, 62.98, 84.22, 126.24, 128.49, 128.54, 135.47, 160.99, 165.77. Exact mass calculated for $C_{14}H_{14}N_2O_2$: 242.1055. Found: 242.1062.

Preparation of substituted 3,4-dehydropyrrolidin-2-ones 18c and 19c and substituted 1,2-dehydropyr-rolizidin-3-one 19d.

General procedure. A suspension mixture of 0.4 mmol of substituted isoxazolidines **16c** and **17c,d** and 50 mg of Nichel/Raney W2 in 15 ml solution of methanol/water 5/1 mixture was stirred at rt, for 24 h, under hydrogen atmosphere. The reaction mixture was successively filtered on celite and the filtrate was concentrated under reduced pressure to afford, after silica flash-chromatography under methanol/chloroform (3:97), compounds **18c** and **19c,d**.

(3'R,5S)-(+)-N-methyl-3-(phenylmethanol)-4-hydroxy-5-benzyl-3,4-dehydropyrrolidin-2-one ***18c***. White solid, mp 156-158 °C (75% yield); $[\alpha]_D^{25}$ + 17.1 (c = 0.17, $CHCl_3$); ir (KBr): 3400-3200, 3040, 3020, 2940, 1660, 1620, 1600, 1460, 1430, 1230, 1000, 760, 700 cm^{-1}. ^{1}H Nmr: δ (CD_3OD) 2.92 (s, 3H, N-CH_3), 2.97 (dd, 1H, $H_{5'a}$, J = 14.5 and 3.9 Hz), 3.23 (dd, 1H, $H_{5'b}$, J = 14.5 and 4.3 Hz), 4.11 (dd, 1H, H_5, J = 4.3 and 3.9 Hz), 5.43 (s, 1H, $H_{3'}$), 6.91-7.22 (m, 10H, aromatic protons). ^{13}C Nmr: δ (CD_3OD) 28.10, 37.29, 63.35, 69.23, 103.14, 127.14, 127.80, 129.08, 129.123, 130.74, 137.00, 144.98, 161.04, 175.74. Exact mass calculated for $C_{19}H_{19}NO_3$: 309.1365. Found: 309.1365.

(3'S,5S)-(+)-N-methyl-3-(phenylmethanol)-4-hydroxy-5-benzyl-3,4-dehydropyrrolidin-2-one ***19c***. White solid, mp 156-158 °C (70% yield); $[\alpha]_D^{25}$ + 12.3 (c = 0.32, $CHCl_3$); ir (KBr): 3400-3200, 3060, 3040, 2960, 2940, 1670, 1610, 1430, 1400, 1250, 1210, 1100, 790, 730, 700, 680 cm^{-1}. ^{1}H Nmr: δ (CD_3OD) 2.81 (s, 3H, N-CH_3), 3.00 (dd, 1H, $H_{5'a}$, J = 14.4 and 4.7 Hz), 3.23 (dd, 1H, $H_{5'b}$, J = 14.4 and 4.6 Hz), 4.16 (dd, 1H, H_5, J = 4.7 and 4.6 Hz), 4.52 (s, 1H, $H_{3'}$), 7.17-7.23 (m, 10H, aromatic protons). ^{13}C Nmr: δ (CD_3OD) 28.19, 37.10, 64.79, 79.25, 89.48, 127.74, 129.07, 130.67, 136.89, 167.18, 177.84. Exact mass calculated for $C_{19}H_{19}NO_3$: 309.1365. Found: 309.1367.

(3'R,5S)-(-)-1-hydroxy-2-(phenylmethanol)-1,2-dehydropyrrolizidin-3-one ***19d***. White solid, mp 105-106 °C (65% yield); $[\alpha]_D^{25}$ - 25.0 (c = 0.40, $CHCl_3$); ir (KBr): 3400-3200, 3060, 3040, 2980, 2960, 1630, 1600, 1450, 1430, 1370, 1300, 1090, 730, 700 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 2.09 (m, 4H), 3.07 (m, 1H), 3.42 (m, 1H), 3.97 (m, 1H, H_5), 4.86 (bs, 2H, OH), 5.13 (s, 1H, $H_{3'}$), 7.22-7.41 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 27.88, 28.83, 43.31, 56.77, 78.38, 101.35, 126.20, 127.19, 128.20, 141.02, 161.57, 179.01. Exact mass calculated for $C_{14}H_{15}NO_3$: 245.1052. Found: 245.1049.

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