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An Asymmetric Approach to Pyrrolidinone and Pyrrolizidinone Systems by Intramolecular Oxime-Olefin Cycloaddition[1]

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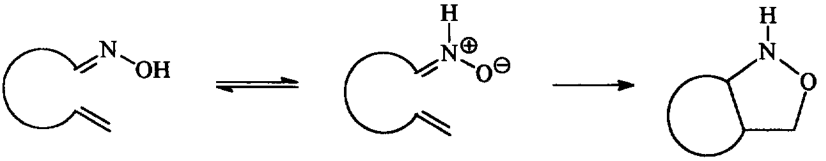
Abstract: Homochiral functionalized pyrrolidinone and pyrrolizidinone systems have been achieved by stereoselective intramolecular oxime-olefin cycloaddition starting from homochiral amino acids, and by subsequent reduction of the obtained fused isoxazolidines. Copyright © 1996 Elsevier Science Ltd

Formation of intriguing carbon frameworks occurring in natural and complex molecules has received considerable synthetic and mechanistic interest by pericyclic addition of nitrones to alkenes. [2,3] When both reactants are part of the same molecule, the intramolecular nature of this synthetic scheme allows a direct access to highly functionalized systems in a regioselective and stereocontrolled manner: a stereocentre on the dipole is often able to influence the relative stereochemistry of the newly formed stereogenic centers in the products. In particular, stereoselection at C_3 of the acyclic substrate appears to give the best control of the new formed stereogenic centers.[4] Among the most useful systems in this regard are the nitrile oxide-olefin and nitrone-olefin cycloaddition which proceed with a variable degree of stereoselectivity.

It has been reported that the intramolecular oxime-olefin cycloadditions (IOOC) afford fused 5-membered isoxazolidines.[5] These reactions proceed with a remarkable degree of stereoselectivity and are postulated to occur *via* cycloaddition of a reactive NH nitrone species to the olefinic double bond.



1 2 3

Figure 1

In fact, the conversion of **1** in **2** can be explained in terms of a thermal tautomeric equilibrium of the oxime with its 1,3-dipolar tautomer **2**, which subsequently undergoes an intramolecular 1,3-dipolar cycloaddition to isoxazolidine derivative **3** (Figure 1).[6]

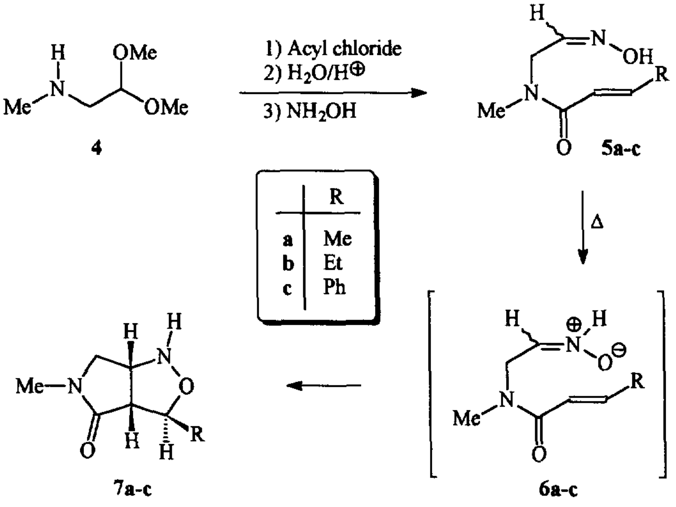
As part of our ongoing research into the exploitation of the intramolecular version of 1,3-dipolar cycloaddition in the synthesis of a wide variety of heterocyclic compounds,[7] we have investigated the scope of oxime-nitrone isomerization as a versatile approach for the synthesis of isoxazolidine systems, with potential for functionalization into target molecules showing synthetic and biological interest.[8] With this aim we have explored the effect of an amido group, in the tether connecting the oxime and dipolarophilic double bond moieties, to promote the tautomerization process[5] (see intermediate 2) in these reactions.

We report here that a facile oxime-nitrone isomerization takes place in the α-amidoxime systems, to give fused five-membered isoxazolidine systems. Furthermore, the selective isoxazolidine ring opening reaction offers a valuable asymmetric approach to homochiral pyrrolidinone and pyrrolizidinone systems, according to the presence of a chiral centre in the oxime functionality.

RESULTS AND DISCUSSION

Substrates **5a-c**, that possess properly situated aldoxime functionalities, were prepared, as decribed before,[7] from *N*-methylamino acetaldehyde dimethyl acetal **4**, by reaction with the suitable acyl chloride, followed by hydrolysis and successive reaction with hydroxylamine.

The thermal IOOC reaction of amidoximes **5a-c** was then accomplished by simple heating in ethanol at reflux. In this way the bicyclic 2H-3-oxa-4-substituted-7-methyl-2,7-diazabicyclo[3.3.0]octan-6-ones **7a-c** were isolated in 90-95% yield (Scheme 1). The intramolecular cycloaddition apparently proceeds *via* the NH nitrone tautomer **6a-c** which undergoes a stereoselective 1,3-dipolar cycloaddition.[6]



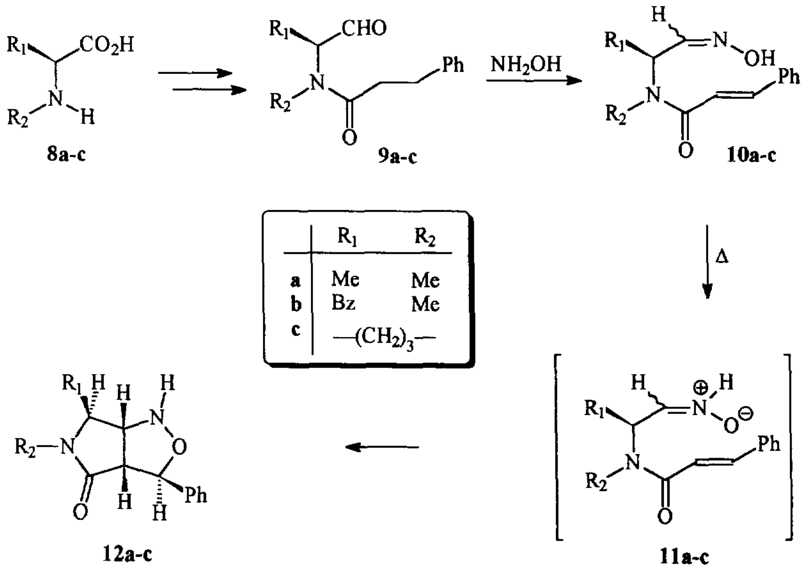
Scheme 1

The derivatives thus obtained 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; moreover ir spectra show the characteristic sharp band at 3350 cm^{-1} of secondary amino group. The ^{1}H nmr spectra showed the H_4 proton in the range 4.31-5.44 δ, while H_5 and H_1

protons resonate at 3.02-3.63 and 4.12-4.17 δ respectively. The 1,3-dipolar cycloaddition investigated showed high regioselectivity; no bridged adducts have been detected in the crude reaction mixture.[9] The reactions have been also found to be stereospecific; intramolecular cycloadducts **7a-c** were obtained stereochemically pure, with no evidence in the nmr spectra or tlc of the crude products of any diastereomers.

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 isoxazolidine ring is predetermined by the alkene geometry. Furthermore, the ring junction between the isoxazolidine and lactam five-membered rings is always *cis*,[9] as indicated by coupling constant values and NOE measurements. For instance, in compound **7a** the coupling constant for the *cis* ring fusion ($J_{1,5}$) is 7.5 Hz, indicative of a nearly eclipsed dihedral angle between H_1 and H_5. Irradiation of H_5 gives rise to a positive NOE effect for H_1, the methyl group at C_4 and the downfield resonance relative to methylene protons at position 8: these results clearly indicate a *cis* relationship between these protons. Likewise, when H_1 was irradiated, the signals corresponding to H_5 and methylene protons at C_8 were enhanced.

We have further investigated the generality and the stereochemical aspects of these intramolecular cycloadditions: IOOC processes, with a stereocentre located in the tether connecting dipole and dipolarophile moiety, have already been the subject of a recent research.[10] On this basis, we examined the ability of a stereocentre located in position α to the oxime to completely control the stereochemical course of the intramolecular oxime tautomer cycloaddition to α,β-unsaturated amides. Starting from L-alanine, L-phenylalanine and L-proline, **8a-c**, the corresponding aldehydes **9a-c** have been prepared as previously reported.[11] By reaction of **9a-c** with hydroxylamine, oximes **10a-c** have been obtained as mixtures of *syn/anti* stereoisomers. Further heating of the unsaturated amidoximes **10a-c** leads to products **12a-c** derived from the IOOC reaction *via* the intermediate not isolated nitrones **11a-c**. The bicyclic compounds **12a-c** are the only obtained cycloadducts (Scheme 2).



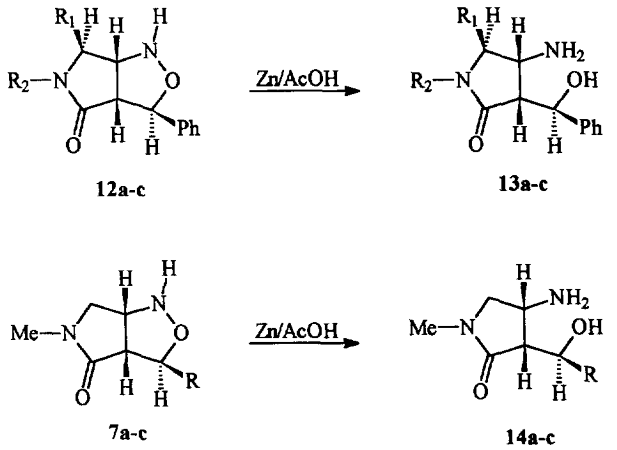
	R_1	R_2
a	Me	Me
b	Bz	Me
c	—(CH$_2$)$_3$—	

Scheme 2

The cycloaddition process was found to proceed diastereoselectively furnishing homochiral compounds **12a-c** from homochiral starting materials. In fact, the ^{1}H nmr spectrum of **12a-c**, 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 expected shifts induced by the paramagnetic reagent.

Thus, in the reactions at hand, the stereocentre at the α position with respect to the oxime 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.

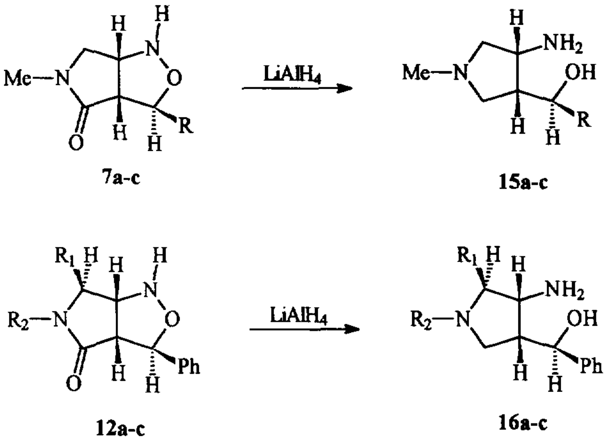
Our final goal, directed towards the design of a new synthetic approach to homochiral functionalized pyrrolidinone and pyrrolizidinone systems, widely diffused in natural products,[12] has been reached by selective cleavage of the isoxazolidine ring. Reduction of compounds **12a-c** with zinc in acetic acid and water at 70 °C resulted in the formation of the homochiral functionalized pyrrolidin-2-ones **13a,b** and pyrrolizidin-3-one **13c** in almost quantitative yields. Analogous treatment of compounds **7a-c** gives rise to pyrrolidinones **14a-c** (Scheme 3).



Scheme 3

The compounds thus obtained gave satisfactory elemental analysis. The presence of NH_2 and OH groups in **13** and **14** was indicated by ir absorptions at 3250 and 3450 cm^{-1} respectively and by the presence of a broad singlet in the ^{1}H NMR spectrum, integrating as three protons, which was exchanged with deuterium oxide. The lactam carbonyl group for these compounds is evidenced by ir absorptions at 1680 cm^{-1} and by the presence of a resonance at 173.00 δ in the ^{13}C nmr. As expected, the stereochemical features acquired in the cycloaddition process have been retained in compounds **13** and **14**, as confirmed by coupling constants and NOE experiments. For instance, irradiation of the methyl group at C_5 in **13a**, taken as model compound, induces a very relevant enhancement of the H_3 and H_4 signals, so suggesting that these protons are topologically close together. In contrast, when H_5 was irradiated, a NOE was observed for the resonance of the *N*-CH_3 group, together with a less relevant effect on H_4. Reduction of **7a-c** with $LiAlH_4$ affords[13] the corresponding pyrrolidines **15a-c**, while reduction of **12a-c** affords the enantiomerically pure pyrrolidines **16a,b** and pyrrolizidine **16c** in high yield (Scheme 4).

The molecular structure of the reaction products were assigned on the basis of analytical and spectroscopic data (see experimental).



Scheme 4

In conclusion, the intramolecular oxime-olefin cycloaddition process, starting from homochiral aminoacid precursors, affords homochiral functionalized pyrrolidinone and pyrrolizidinone 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 **5c** and **7c** have been previously reported by us.[7]

Preparation of *trans N*-methyl-*N*-(acetaldoxime)enamides 5a,b.

General procedure. A mixture containing 2.5 mmol of *trans N*-methyl-*N*-(acetaldehyde)enamides **5** in 30 ml of 95% aqueous ethanol, 2.6 mmol of hydroxylamine hydrochloride and 10.5 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 ($MeOH/CHCl_3$ 2:98) gave as a *syn-anti* mixture of oxime derivatives **5a,b**.

Reaction of N-methyl-N-(acetaldehyde)but-2-enamide[7] *with hydroxylamine hydrochloride.* First fractions gave *trans N*-methyl-*N*-(acetaldoxime)but-2-enamide **5a**. Light yellow oil (90% yield); ir (neat): 3600-3250, 2960, 1660, 1600, 1480, 1450, 1410, 1280, 1140, 960, 830 cm^{-1}. Major isomer ^{1}H nmr: δ ($CDCl_3$) 1.90 (dd, 3H, J = 6.6 and 1.2 Hz), 3.05 (s, 1H, N-CH_3), 4.18 (d, 2H, J = 5.8 Hz), 6.27 (dq, 1H, J = 15.0 and 1.2 Hz), 6.94 (dq, 1H, J = 15.0 and 6.6 Hz), 7.38 (t, 1H, J = 5.8 Hz). ^{13}C Nmr: δ ($CDCl_3$) 21.37, 37.05, 47.18, 117.94, 145.35, 149.73, 167.71.

Reaction of N-methyl-N-(acetaldehyde) pent-2-enamide[7] *with hydroxylamine hydrochloride.* First fractions gave *trans* *N*-methyl-*N*-(acetaldoxime)pent-2-enamide **5b**. Light yellow oil (90% yield); ir (neat): 3450-3250, 2960, 2940, 1650, 1600, 1450, 1390, 1270, 1110, 960, 900, 840, 720 cm^{-1}. Major isomer ^{1}H nmr: δ ($CDCl_3$) 1.07 (t, 3H, *J* = 7.4 Hz), 2.24 (m, 2H), 3.05 (s, 3H, N-CH_3), 4.17 (d, 2H, *J* = 5.7 Hz), 6.23 (dt, 1H, *J* = 15.1 and 1.1 Hz), 6.99 (dt, 1H, *J* = 15.1 and 6.3 Hz), 7.38 (t, 1H, *J* = 5.7 Hz). ^{13}C Nmr: δ ($CDCl_3$) 12.35, 25.51, 35.02, 46.44, 118.45, 146.14, 149.23, 167.50.

Preparation of 2H-3-oxa-4-substituted-7-methyl-2,7-diazabicyclo[3.3.0]octan-6-ones 7a,b.

General procedure. A mixture containing 50 mmol of compound **5a,b** in 100 ml of absolute ethanol was refluxed for 36 h. The reaction mixture was evaporated and the residue subjected to silica flash-chromatography (MeOH/$CHCl_3$ 3:97) gave bicycloadducts **7a,b**.

Reaction of 5a. First fractions gave 2H-3-oxa-4,7-dimethyl-2,7-diazabicyclo[3.3.0]octan-6-one **7a**. Yellow oil (68% yield); ir (neat): 3350, 2980, 2960, 1670, 1500, 1450, 1410, 1080, 840 cm $^{-1}$. ^{1}H Nmr: δ ($CDCl_3$) 1.31 (d, 3H, *J* = 6.4 Hz), 2.84 (s, 3H, N-CH_3), 3.02 (dd, 1H, H_5, *J* = 7.9 and 2.1 Hz), 3.35 (dd, 1H, H_{8a}, *J* = 11.3 and 2.4 Hz), 3.67 (dd, 1H, H_{8b}, *J* = 11.3 and 7.7 Hz), 4.14 (ddd, 1H, H_1, *J* = 7.9, 7.7 and 2.4 Hz), 4.47 (dq, 1H, H_4, *J* = 7.9 and 2.1 Hz). ^{13}C Nmr: δ ($CDCl_3$) 18.80, 29.45, 56.55, 57.87, 77.21, 81.03, 172.68. Exact mass calculated for $C_7H_{12}N_2O_2$: 156.0898. Found: 156.0896.

Reaction of 5b. First eluted fractions gave 2H-3-oxa-4-ethyl-7-methyl-2,7-diazabicyclo[3.3.0]octan-6-one **7b**. Yellow oil (72% yield); ir (neat): 3200, 2940, 2920, 1660, 1610, 1500, 1450, 1400, 1260 cm $^{-1}$. ^{1}H Nmr: δ ($CDCl_3$) 1.01 (t, 3H, *J* = 7.4 Hz), 1.59 (dq, 2H, *J* = 7.4 and 6.4 Hz), 2.85 (s, 3H, N-CH_3), 3.07 (dd, 1H, H_5, *J* = 8.1 and 2.6 Hz), 3.36 (dd, 1H, H_{8a}, *J* = 11.0 and 2.6 Hz), 3.67 (dd, 1H, H_{8b}, *J* = 11.0 and 7.7 Hz), 4.12 (ddd, 1H, H_1, *J* = 8.1, 7.7 and 2.6 Hz), 4.31 (m, 1H, H_4). ^{13}C Nmr: δ ($CDCl_3$) 10.01, 25.80, 29.48, 54.54, 56.43, 56.75, 86.49, 172.88. Exact mass calculated for $C_8H_{14}N_2O_2$: 168.0898. Found: 168.0902.

Preparation of *trans* *N*-methyl-*N*-[α-substituted-(acetaldoxime)]enamides 10a-c.

General procedure. See preparation of compounds **5a-c**. The titled compounds have been obtained as mixture of *syn/anti* isomers.

Reaction of trans (S)-(-)-*N-methyl-N-(2-propylaldehyde)cinnamoate*[11] ***9a*** *with hydroxylamine hydrochloride*. First fractions gave *trans* (S)-*N*-methyl-*N*-(2-propyloxime)cinnamoate **10a**. Sticky oil (98% yield); ir (neat): 3400-3200, 3080, 3060, 2980, 2940, 1675, 1650, 1600, 1450, 1400, 1340, 1110, 1030, 975, 950, 850, 760, 700, 680 cm^{-1}. Major isomer ^{1}H nmr: δ ($CDCl_3$) 1.30 (d, 2H, J = 6.7 Hz), 2.86 (s, 3H, N-CH_3), 3.70 (dq, 1H, J 0 6.7 and 5.5 Hz), 6.84 (d, 1H, *J* = 15.7 Hz), 7.28-7.52 (m, 6H, aromatic protons and HC=N), 7.71 (d, 1H, *J* = 15.7 Hz), 9.45 (bs, 1H, OH). ^{13}C Nmr: δ ($CDCl_3$) 18.95, 48.59, 117.31, 127.74, 128.69, 128.77, 135.03, 138.27 143.43, 149.94, 172.23. Exact mass calculated for $C_{13}H_{16}N_2O_2$: 232.1212. Found: 232.1214.

Reaction of trans (S)-(-)-*N-methyl-N-(3-phenyl-2-propylaldehyde)cinnamoate*[11] ***9b*** *with hydroxylamine hydrochloride*. First fractions gave *trans* (S)-*N*-methyl-*N*-(3-phenyl-2-propyloxime)cinnamoate **10b**. White solid, mp 93-5 °C (95% yield); ir (KBr): 3400-3200, 3080, 3060, 3020, 2920, 1680, 1660, 1600, 1490, 1450, 1400, 1250, 1180, 1020, 970, 840, 760, 740, 690 cm^{-1}. Major isomer ^{1}H nmr: δ ($CDCl_3$) 2.95-3.20 (m, 2H), 2.97 (s, 3H, N-CH_3), 5.40 (m, 1H), 6.70 (d, 1H, *J* = 15.2 Hz), 7.25-7.76 (m, 10H, aromatic protons), 7.81 (d, 1H, *J* = 4.5 Hz), 8.15 (d, 1H, *J* = 15.2 Hz), 8.57 (bs, 1H, OH). ^{13}C Nmr: δ ($CDCl_3$) 31.70, 35.04, 54.60, 117.12, 126.58, 127.81, 128.44, 128.71, 128.88, 129.73, 135.01, 139.43, 143.43, 149.26, 167.18. Exact mass calculated for $C_{19}H_{20}N_2O_2$: 308.1524. Found: 308.1528.

Reaction of trans (S)-(-)-*N-cinnamoyl-prolinal*[11] ***9c*** *with hydroxylamine hydrochloride*. First fractions gave *trans* (S)-*N*-cinnamoyl-prolinaloxime **10c**. White solid, mp 55-8 °C (92% yield); ir (KBr): 3400-3150, 3080, 3020, 2980, 1650, 1580, 1500, 1450, 1250, 1180, 1030, 980, 900, 860, 760, 700, 680 cm^{-1}. Major isomer ^{1}H nmr: δ ($CDCl_3$) 1.90-2.07 (m, 2H), 2.23-2.41 (m, 1H), 3.68 (m, 2H), 4.71 (m, 1H), 4.79 (m, 1H), 6.71 (d, 1H, *J*

= 15.6 Hz), 9.30 (bs, 1H, OH). ^{13}C Nmr: δ ($CDCl_3$) 29.20, 31.31, 46.95, 56.51, 117.98, 127.92, 128.66, 129.59, 135.10, 142.88, 153.07, 169.84. Exact mass calculated for $C_{14}H_{16}N_2O_2$: 244.1211. Found: 244.1210.

Preparation of 2H-3-oxa-4-phenyl-2,7-diazabicyclo[3.3.0]octan-6-ones 12a-c.

General procedure. See preparation of compounds **7a-c**.

*Reaction of **10a***. First eluted fractions gave *(1R,4R,5R,8S)-(-)-2H-3-oxa-4-phenyl-7,8-dimethyl-2,7-diazabicyclo[3.3.0]octan-6-one **12a***. Light yellow solid, mp 108-10 °C (80% yield); $[\alpha]_D^{25}$ - 92.0 (c = 1.50, $CHCl_3$); ir (KBr): 3210, 3040, 2990, 2940, 1680, 1490, 1460, 1410, 1090, 770, 750, 710 cm^{-1}. ^{1}H Nmr: δ (DMSO-d$_6$) 1.22 (d, 3H, J = 6.7 Hz), 2.73 (s, 3H, N-CH$_3$), 3.42 (dq, 1H, H$_8$, J = 6.7 and 1.3 Hz), 3.56 (dd, 1H, H$_5$, J = 7.7 and 0.8 Hz), 3.74 (dd, 1H, H$_1$, J = 7.7 and 1.3 Hz), 4.96 (d, 1H, H$_4$, J = 0.8 Hz), 6.57 (bs, 1H, NH), 7.32-7.47 (m, 5H, aromatic protons). ^{13}C Nmr: δ (DMSO-d$_6$) 18.57, 27.16, 54.89, 57.51, 64.66, 84.54, 126.54, 127.83, 128.45, 139.58, 171.62. Exact mass calculated for $C_{13}H_{16}N_2O_2$: 232.1212. Found: 232.1205.

*Reaction of **10b***. First eluted fractions gave *(1R,4R,5R,8S)-(-)-2H-3-oxa-4-phenyl-7-methyl-8-benzyl-2,7-diazabicyclo[3.3.0]octan-6-one **12b***. Light yellow solid, mp 138-40 °C (75% yield); $[\alpha]_D^{25}$ - 31.4 (c = 0.70, $CHCl_3$); ir (KBr): 3220, 3060, 3040, 2960, 2880, 1690, 1600, 1500, 1460, 1410, 1250, 1060, 870, 750, 730, 700 cm^{-1}. ^{1}H Nmr: δ (DMSO-d$_6$) 2.74 (dd, 1H, H$_{8a}$, J = 13.5 and 7.3 Hz), 2.84 (s, 3H, N-CH$_3$), 3.05 (dd, 1H, H$_{8b}$, J = 13.5 and 3.5 Hz), 3.62 (dd, 1H, H$_8$, J= 7.3 and 3.5 Hz), 3.73 (d, 1H, H$_1$, J = 7.6 Hz), 3.81 (dd, 1H, H$_5$, J = 10.2 and 7.6 Hz), 4.82 (bs, 1H, NH), 6.65 (d, 1H, H$_4$, J = 10.2 Hz), 7.21-7.46 (m, 10H, aromatic protons). ^{13}C Nmr: δ (DMSO-d$_6$) 27.95, 36.98, 51.45, 57.96, 62.04, 64.74, 126.45, 127.85, 128.39, 128.91, 129.55, 130.48, 136.78, 139.43, 172.14. Exact mass calculated for $C_{19}H_{20}N_2O_2$: 308.1524. Found: 308.1522.

*Reaction of **10c***. First eluted fractions gave *(3R,3aR,8aS,8bR)-(-)-1H-3-phenyl-4-oxo-1,3,3a,8b-tetrahydropyrrolizidin[3,2-c]isoxazole **12c***. White solid, mp 108-9 °C (90% yield); $[\alpha]_D^{25}$ - 8.0 (c = 1.60, $CHCl_3$); ir (KBr): 3220, 3080, 3060, 2980, 2900, 1680, 1600, 1450, 1330, 1170, 1020, 840, 730, 695 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 1.28-1.45 (m, 1H), 1.96-2.23 (m, 3H), 3.13 (ddd, 1H, H$_{8a}$, J = 11.8, 11.8 and 1.6 Hz), 4.03 (dd, 1H, H$_{3a}$, J = 8.1 and 1.7 Hz), 5.51 (d, 1H, H$_3$, J = 1.7 Hz), 5.72 (bs, 1H, NH), 7.35-7.41 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 25.44, 30.23, 41.65, 61.20, 64.13, 69.03, 85.51, 125.72, 128.09, 128.87, 138.65, 173.67. Exact mass calculated for $C_{14}H_{16}N_2O_2$: 244.1212. Found: 244.1216.

Preparation of substituted pyrrolidin-2-ones 13a,b, 14a-c and substituted pyrrolizidin-3-one 13c.

General procedure. To a suspension of 0.4 mmol of substituted isoxazolidines **7a-c** and **12a-c** in 9 ml of acetic acid/water (1:2) 1.6 mmol of zinc were added. The reaction mixture was heated at 70 °C for 48 h with efficient stirring and then cooled. Zinc salts were filtered off and the filtrate was concentrated. The residue was partitioned between 10% ammonium hydroxide/methylene chloride. The aqueous phase was further extracted and the combined organic extracts dried over sodium sulfate. Evaporation of the solvent and silica flash-chromatography (methanol/chloroform 3:97) gave compounds **13a-c** and **14a-c**.

*(3R,3'R,4R,5S)-(+)-3-(phenylmethanol)-4-amino-5-methyl-N-methylpyrrolidin-2-one **13a***. Oil (90% yield); $[\alpha]_D^{25}$+ 28.0 (c = 1.64, $CHCl_3$); ir (neat): 3500-3200, 3080, 3060, 2980, 2960, 1680, 1650, 1600, 1400, 1260, 1050, 1010, 750, 700 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 1.12 (d, 3H, J = 6.5 Hz), 2.82 (s, 3H, N-CH$_3$), 2.83 (dd, 1H, H$_4$, J= 7.5 and 6.2 Hz), 3.42 (dd, 1H, H$_3$, J = 7.5 and 4.0 Hz), 3.68 (dq, 1H, H$_5$, J = 7.5 and 6.2 Hz), 4.03 (bs, 3H, NH$_2$ and OH), 7.25-7.46 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 16.19, 27.61, 50.38, 54.71, 62.21, 70.74, 125.73, 127.35, 128.49, 142.54, 171.48. Exact mass calculated for $C_{13}H_{18}N_2O_2$: 234.1368. Found: 234.1366.

*(3R,3'R,4R,5S)-(+)-3-(phenylmethanol)-4-amino-5-benzyl-N-methylpyrrolidin-2-one **13b***. Oil (95% yield);

$[\alpha]_D^{25}$ + 59.4 (c = 0.64, $CHCl_3$); ir (neat): 3500-3300, 3080, 3060, 2980, 2920, 1675, 1600, 1490, 1455, 1400, 1060, 750, 730, 700 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 2.51 (bs, 3H, NH_2 and OH), 2.62 (dd, 1H, $H_{5'a}$, J = 13.7 and 8.1 Hz), 2.67 (dd, 1H, H_3, J = 7.1 and 4.1 Hz), 2.91 (s, 3H, N-CH_3), 2.98 (dd, 1H, $H_{5'b}$, J= 13.7 and 4.7 Hz), 3.96 (ddd, 1H, H_5, J = 8.1, 4.7 and 2.0 Hz), 3.49 (dd, 1H, H_4, J = 7.1 and 2.0 Hz), 5.28 (d, 1H, $H_{3'}$, J = 4.1 Hz), 7.10-7.41 (m, 10H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 28.58, 37.52, 50.36, 52.26, 69.77, 71.52, 125.46, 126.89, 126.99, 128.28, 128.84, 129.02, 136.38, 143.15, 172.80. Exact mass calculated for $C_{19}H_{22}N_2O_2$: 310.1681. Found: 310.1679.

(1R,2R,2'R,8S)-(-)-1-amino-2-(phenylmethanol)pyrrolizidin-3-one ***13c***. Oil (90% yield); $[\alpha]_D^{25}$ - 19.2 (c = 1.04, $CHCl_3$); ir (neat): 3450-3250, 3080, 3060, 2980, 2960, 1670, 1500, 1400, 1120, 940, 760, 700 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 1.32-1.47 (m, 1H), 1.96-2.17 (m, 3H), 2.82 (bs, 3H, NH_2 and OH), 2.93-3.08 (m, 2H), 3.54-3.76 (m, 3H), 5.26 (d, 1H, $H_{2'}$, J = 4.8 Hz), 7.27-7.45 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 26.43, 30.23, 41.73, 56.77, 57.52, 68.52, 72.79, 125.76, 127.06, 128.20, 142.84, 173.70. Exact mass calculated for $C_{14}H_{18}N_2O_2$: 246.1368. Found: 246.1364.

4-amino-3-(ethan-1-ol)-N-methylpyrrolidin-2-one ***14a***. Oil (70% yield); ir (neat): 3450-3250, 2990, 2970, 1670, 1500, 1450, 1400, 1250, 1080, 875, 820 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 1.47 (d, 3H, J = 6.3 Hz), 2.38 (dd, 1H, H_{5a}, J = 12.7 and 6.0 Hz), 2.59 (bs, 3H, NH_2 and OH), 2.87 (s, 3H, N-CH_3), 3.08 (dd, 1H, H_{5b}, J = 12.7 and 2.1 Hz), 3.57 (dd, 1H, H_3, J = 10.0 and 5.5 Hz), 3.85 (ddd, 1H, H_4, J = 10.0, 6.0 and 2.1 Hz), 4.20 (dq, 1H, $H_{3'}$, J = 6.3 and 5.5 Hz). ^{13}C Nmr: δ ($CDCl_3$) 21.86, 29.74, 48.02, 52.53, 57.59, 65.36, 173.03. Exact mass calculated for $C_7H_{14}N_2O_2$: 158.1055. Found: 158.1054.

4-amino-3-(propan-1-ol)-N-methylpyrrolidin-2-one ***14b***. Oil (73% yield); ir (neat) 3450-3250, 2980, 2960, 2940, 1675, 1500, 1450, 1400, 1300, 970 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 0.97 (t, 3H, J = 7.5 Hz), 1.51-1.68 (m, 1H), 1.85-1.98 (m, 1H), 2.37 (dd, 1H, J = 6.7 and 6.7 Hz), 2.75 (bs, 3H, NH_2 and OH), 2.82 (s, 3H, N-CH_3), 3.03 (dd, 1H, J = 10.0 and 2.1 Hz), 3.51 (dd, 1H, J = 10.0 and 6.0 Hz), 3.78 (bt, 1H, J = 5.2 Hz), 3.92-3.96 (m, 1H). ^{13}C Nmr: δ ($CDCl_3$) 10.06, 28.29, 47.89, 50.56, 57.46, 70.44, 70.55, 173.18. Exact mass calculated for $C_8H_{16}N_2O_2$: 172.1212. Found: 172.1214.

4-amino-3-(phenylmethanol)-N-methylpyrrolidin-2-one ***14c***. Oil (82% yield); ir (neat): 3450-3250, 3040, 3020, 2940, 2880, 1675, 1500, 1450, 1400, 1280, 1070, 930, 760, 710 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 2.74 (bs, 3H, NH_2 and OH), 2.84 (dd, 1H, H_{5a}, J = 10.7 and 1.9 Hz), 2.89 (s, 3H, N-CH_3), 3.01 (dd, 1H, H_{5b}, J = 10.7 and 2.5 Hz), 3.53 (dd, 1H, H_3, J = 10.1 and 3.8 Hz), 3.76 (ddd, 1H, H_4, J = 10.1, 2.5 and 1.9 Hz), 5.37 (d, 1H, $H_{3'}$, J = 3.8 Hz), 7.24-7.49 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 30.05, 47.92, 52.43, 57.82, 71.84, 125.84, 127.23, 128.61, 143.57, 173.24. Exact mass calculated for $C_{12}H_{16}N_2O_2$: 220.1212. Found: 220.1215.

Preparation of substituted pyrrolidines 15a-c, 16a,b and substituted pyrrolizidine 16c.

General procedure. A suspension mixture of 0.4 mmol of substituted isoxazolidines **7a-c** and **12a-c** and 3.2 mmol of lithium aluminium hydride in 15 ml of anhydrous tetrahydrofuran was stirred at 0 °C for 24 h. The reaction mixture was successively treated with 1 ml of water, 1 ml of a 10% sodium hydroxide solution, and 2 ml of water with cooling by ice-water. The precipitate was filtered off and washed with ether. The combined organic layer was concentrated under reduced pressure to afford, after flash chromatography under methanol/chloroform (3:97), amino alcohols **15a-c** and **16a-c**.

3-amino-4-(ethan-1-ol)-N-methylpyrrolidine ***15a***. Oil (65% yield); ir (neat): 3500-3250, 2980, 2960, 1450, 1370, 1050, 950, 880 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 1.08 (d, 3H, J = 6.1 Hz), 1.55-1.61 (m, 1H, H_4), 2.07-2.20 (m, 2H), 2.23 (s, 3H, N-CH_3), 2.79 (dd, 1H, J = 9.4 and 5.7 Hz), 3.15 (bs, 3H, NH_2 and OH), 3.49-3.59 (m, 2H), 3.74 (dq, 1H, $H_{4'}$, J = 9.5 and 6.1 Hz). ^{13}C Nmr: δ ($CDCl_3$) 21.64, 42.07, 48.75, 52.80, 58.22, 62.02, 67.72.

Exact mass calculated for $C_7H_{16}N_2O$: 144.1262. Found: 144.1259.

3-amino-4-(propan-1-ol)-N-methylpyrrolidine ***15b***. Oil (68% yield); ir (neat): 3450-3250, 2980, 2960, 1450, 1360, 1050, 950, 880 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 0.95 (t, 3H, J = 7.2 Hz), 1.23-1.51 (m, 2H), 1.57-1.65 (m, 1H, H_3), 2.13-2.31 (m, 2H), 2.26 (s, 3H, N-CH_3), 2.79 (dd, 1H, J = 9.4 and 5.6 Hz), 3.18 (bs, 3H, NH_2 and OH), 3.33 (dd, 1H, J = 10.4 and 6.2 Hz), 3.46-3.56 (m, 1H), 4.03 (m, 1H, $H_{4'}$). ^{13}C Nmr: δ ($CDCl_3$) 12.35, 25.43, 43.04, 47.25, 52.85, 59.12, 63.43, 70.93. Exact mass calculated for $C_8H_{18}N_2O$: 158.1419. Found: 158.1422.

3-amino-4-(phenylmethanol)-N-methylpyrrolidine ***15c***. Oil (78% yield); ir (neat): 3400-3250, 3080, 3060, 2980, 2960, 2940, 1600, 1500, 1460, 1250, 1160, 1040, 910, 870, 760, 700 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 2.19-2.31 (m, 3H), 2.23 (s, 3H, N-CH_3), 2.61 (m, 1H), 2.87 (dd, 1H, J = 9.4 and 5.9 Hz), 3.20 (bs, 3H, NH_2 and OH), 3.68 (m, 1H), 4.66 (d, 1H, $H_{4'}$, J = 9.6 Hz), 7.24-7.41 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 42.41, 48.63, 53.10, 58.38, 67.10, 74.77, 127.08, 127.76, 128.56, 143.39. Exact mass calculated for $C_{12}H_{18}N_2O$: 206.1419. Found: 206.1421.

(2S,3R,4R,4'R)-(+)-2-methyl-3-amino-4-(phenylmethanol)-N-methylpyrrolidine ***16a***. Oil (84% yield); $[\alpha]_D^{25}$ + 10.0 (c = 1.60, $CHCl_3$); ir (neat): 3400-3200, 3080, 3060, 3020, 2960, 2920, 1600, 1490, 1450, 1380, 1220, 1050, 910, 760, 730, 700 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 1.11 (d, 3H, J = 6.1 Hz), 1.51-1.86 (m, 2H), 2.10 (s, 3H, N-CH_3), 2.39-2.58 (m, 2H), 3.08 (dd, 1H, H_3, J = 9.1 and 8.9 Hz), 3.24 (bs, 3H, NH_2 and OH), 4.52 (d, 1H, $H_{4'}$, J = 9.5 Hz), 7.18-7.31 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 16.14, 25.39, 29.89, 39.92, 45.40, 58.64, 59.65, 61.97, 70.74, 74.28, 126.69, 127.44, 128.16, 142.55. Exact mass calculated for $C_{13}H_{20}N_2O$: 220.1575. Found: 220.1576.

(2S,3R,4R,4'R)-(+)- 2-benzyl-3-amino-4-(phenylmethanol)-N-methylpyrrolidine ***16b***. Sticky oil (90% yield); $[\alpha]_D^{25}$ + 43.1 (c = 0.97, $CHCl_3$); ir (neat): 3600-3200, 3060, 3020, 2960, 1600, 1580, 1490, 1450, 1220, 1150, 920, 830, 750, 690 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 2.00 (dd, 1H, H_{5a}, J = 10.6 and 9.6 Hz), 2.08 (ddd, 1H, H_2, J = 7.8, 6.3 and 4.2 Hz), 2.20 (s, 3H, N-CH_3), 2.35 (dd, 1H, H_{5b}, J= 10.6 and 6.9 Hz), 2.46 (dddd, 1H, H_4, J = 10.6, 9.4, 6.9 and 6.3 Hz), 2.48 (dd, 1H, $H_{2'a}$, J = 13.3 and 7.8 Hz), 3.02 (dd, 1H, $H_{2'b}$, J = 13.3 and 4.2 Hz), 3.32 (dd, 1H, H_3, J = 9.4 and 6.3 Hz), 4.56 (d, 1H, $H_{4'}$, J = 9.4 Hz), 7.21-7.32 (m, 10H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 38.79, 40.48, 46.47, 57.42, 58.39, 73.29, 77.55, 126.16, 126.25, 127.24, 128.05, 128.39, 128.93, 138.40, 143.15. Exact mass calculated for $C_{19}H_{24}N_2O$: 296.1888. Found: 296.1887.

(1R,2R,2'R,8S)-(-)-1-amino-2-(phenylmethanol)pyrrolizidine ***16c***. Oil (85% yield); $[\alpha]_D^{25}$ - 2.0 (c = 1.00, $CHCl_3$); ir (neat): 3400-3200, 3060, 3020, 2960, 2880, 1600, 1450, 1100, 760, 700 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 1.48-1.86 (m, 4H), 2.12-2.63 (m, 4H), 3.33-3.51 (m, 2H), 3.73-3.85 (m, 1H), 4.36 (bs, 3H, NH_2 and OH), 4.87 (d, 1H, $H_{2'}$, J = 4.8 Hz), 7.32-7.43 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 25.41, 29.49, 30.39, 48.46, 54.50, 55.58, 57.51, 71.90, 73.76, 126.01, 127.48, 128.35, 143.84. Exact mass calculated for $C_{14}H_{20}N_2O$: 232.1575. Found: 232.1570.

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REFERENCES AND NOTES

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13. At 25 °C compound **7a** is converted into *N*-methyl-3-(phenylmethanol)pyrrole.[7]

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