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α–Amino Acids as Chiral Educts for Stereoselective Syntheses of Pyrrolidine and Pyrrolizidine Systems[1]

Ugo Chiacchio,[a]* Franco Casuscelli,[b] Antonino Corsaro,[a] Vito Librando,[a] Antonio Rescifina,[a] Roberto Romeo,[b] Giovanni Romeo[b]

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

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

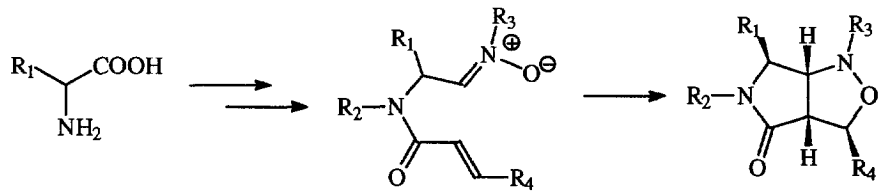
Abstract: Homochiral functionalized pyrrolidine and pyrrolizidine systems have been achieved by stereoselective intramolecular 1,3-dipolar cycloaddition of homochiral nitrones, starting from homochiral amino acids, and by subsequent reduction of the obtained cycloadducts.

Intramolecular 1,3-dipolar cycloadditions have recently been of considerable synthetic and mechanistic interest, especially in the formation of the intriguing carbon frameworks occurring in natural products and other complex molecules.[2]

Since the pioneering work of Le Bel,[3] the stereochemical aspects of these reactions have been investigated: the introduction of a chiral center in the starting nitrone causes an asymmetric induction giving rise to the formation of new chiral centers with definite configuration in the cycloadduct.[4] In particular, a stereocentre inserted at the α position to the nitrone mojety appears to give the best results in the control of the new formed chiral centers.[5]

This issue appears important because if the aldehyde precursor of the nitrone was derived from an optically active source (e.g. amino acid), the cycloaddition process would estabilish three new chiral centers whose absolute configuration would be dependent on the diastereoselectivity of the cycloaddition process.

As part of our program aimed at developing new methodologies for the synthesis of nitrogenous natural products,[6] we have been interested in the exploitation of the applicability of α-amino acids, as chiral educts, to the synthesis of homochiral cycloadducts via intermediate nitrone species.

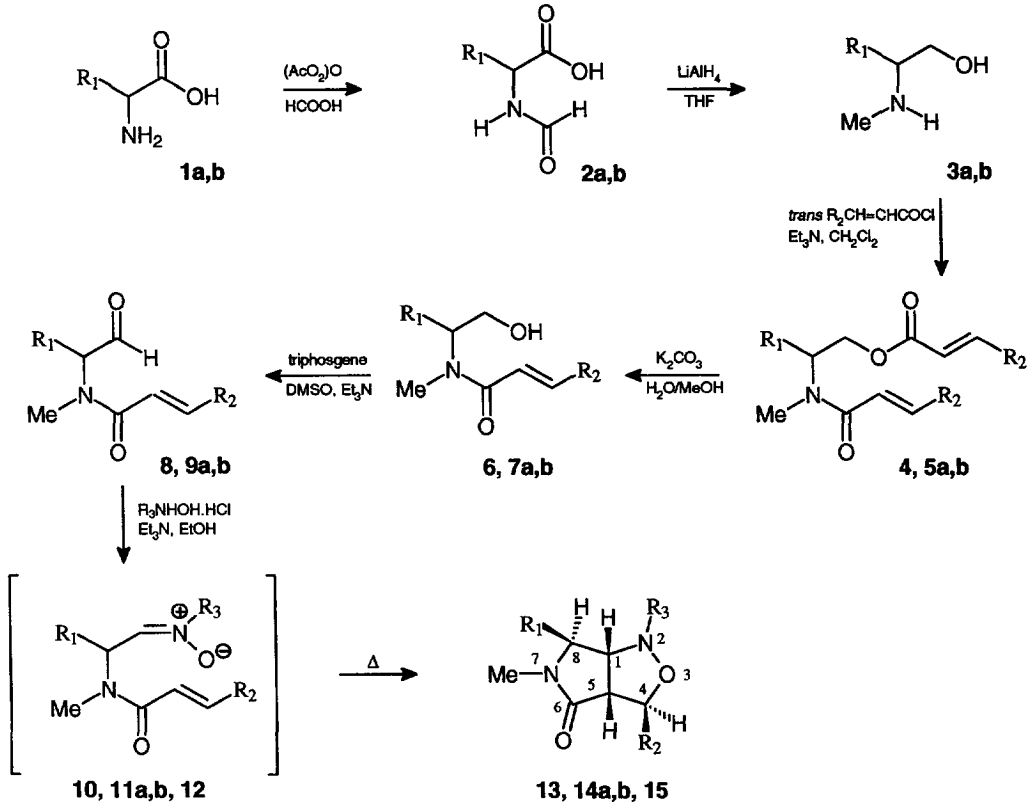


We report here the synthesis of a series of 3-oxa-2,7-diazabicyclo[3.3.0]octan-6-ones containing, four contiguous chiral centers, starting from homochiral amino acids.

The selective functionalization of the fused system by ring cleavage of the isoxazolidine ring represents a new easy entry to the stereoselective formation of pyrrolidine and pyrrolizidine systems with a very high diastereoisomeric and optical purity.

RESULTS AND DISCUSSION

Starting from L-alanine **1a** and L-phenylalanine **1b**, the β-aminoalcohols **3** were prepared according to the procedure of Huszthy.[7] The successive reaction with unsaturated acyl chlorides afforded the amido esters **4** and **5** which have been converted in the amido alcohols **6** and **7** by selective hydrolysis with K_2CO_3 in H_2O/MeOH.[8] Swern-like oxidation[9] of **6** and **7** led to the corresponding aldehydes **8** and **9**. Treatment of **8** and **9** with *N*-alkylhydroxylamine gave nitrones **10-12**, which spontaneously underwent intramolecular cycloaddition yielding the bicyclic compounds **13-15** (Scheme 1).



Compounds	R_1	R_2	R_3
1a-14a	Me	Ph	Me
1b-14b	$PhCH_2$	Ph	Me
4,6,8,10,13	$PhCH_2$	Me	Me
12,15	Me	Ph	Cyclohexyl

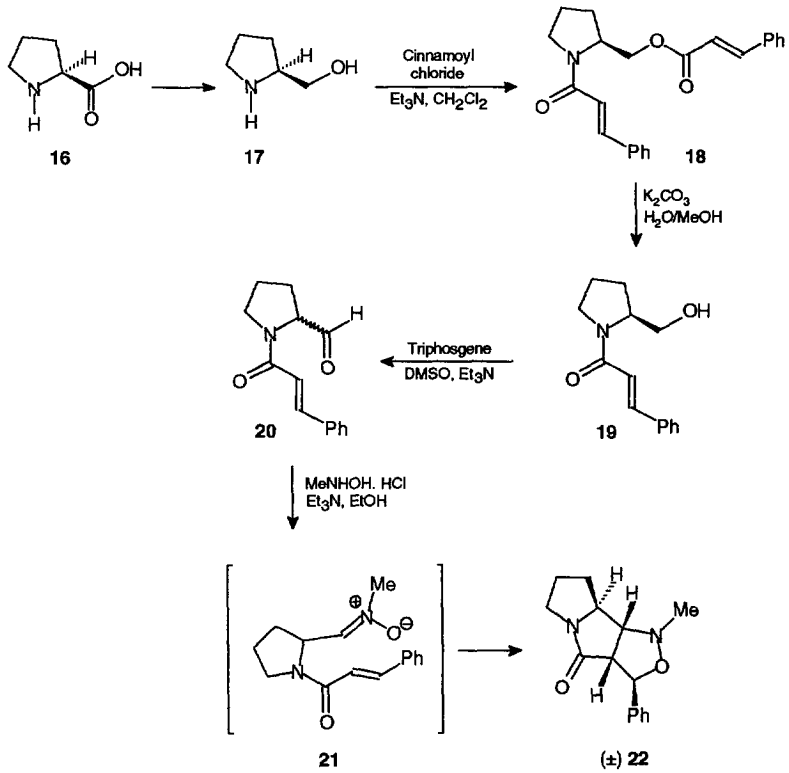
Scheme 1

The investigated 1,3-dipolar cycloaddition reactions showed high regioselectivity: according to similar intramolecular processes, no bridged adducts have been detected in the crude reaction mixture.[10]

The cycloaddition process was found to proceed diastereoselectively furnishing homochiral compounds **13-15** from homochiral starting material. In fact, the ^1H nmr spectrum of **13-15** 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. The stereochemical information present in the dipolarophile is 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 betwen the isoxazolidine and the lactam five-membered rings is always *cis* as confirmed by coupling constants values. The proposed stereochemistry for the obtained adducts **13-15** has been confirmed by NOE difference spectroscopy. In particular, irradiation of methyl group at C_8, in compounds **14a** and **15** resulted in a positive enhancement of the signals for H_1 and H_5; in contrast, when H_4 was irradiated, a positive NOE was detected only for the resonance of H_8. These results are clearly indicative of a *syn* relationship between H_1, H_5 and the methyl group at C_8. Similarly, in derivatives **13, 14b** the NOE observed for H_1 and methylene protons of the benzylic substituent at C_8 on irradiation of the H_5 resonance, agrees with the proposed configurations which show H_1, H_5, and benzylic protons on the same side of the pentatomic ring.

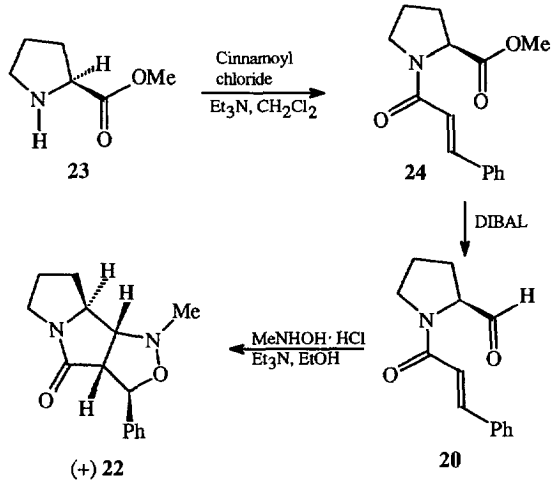
Thus, in the reaction at hand, the stereocentre at the α position with respect to the nitronic functionality can effectively control the formation of the new contiguous stereocentres and one of the 8 possible stereoisomers is produced in a highly selective fashion.



Scheme 2

In a similary way L-proline **16** was converted in 1-methyl-3-phenyl-4-oxo-1,3,3a,8b-tetrahydropyrrolizidino[3,2-c]isoxazole **22** (Scheme 2); however compound **22** is obtained as a racemic mixture, which has been resolved by HPLC using a semipreparative chiral column Chiralcel OJ, with a 6:1 hexane/isopropanol mixture as eluent. The accurate examination of the individual reaction steps revealed that complete racemization occurred at the level of formation of the aldehyde **20**.[11]

This stereochemical problem was overcome by an alternative synthetic procedure.[12] The homochiral aldehyde **20** was synthesized by converting the proline methyl ester **23** to the amido ester **24** which was subsequently reduced with 1 equivalent of DIBAL in dry toluene at -78 °C. Furthermore treatment of **20** with *N*-methyl hydroxylamine in anhydrous EtOH at reflux gave the enantiomerically pure compound **22** (Scheme 3).



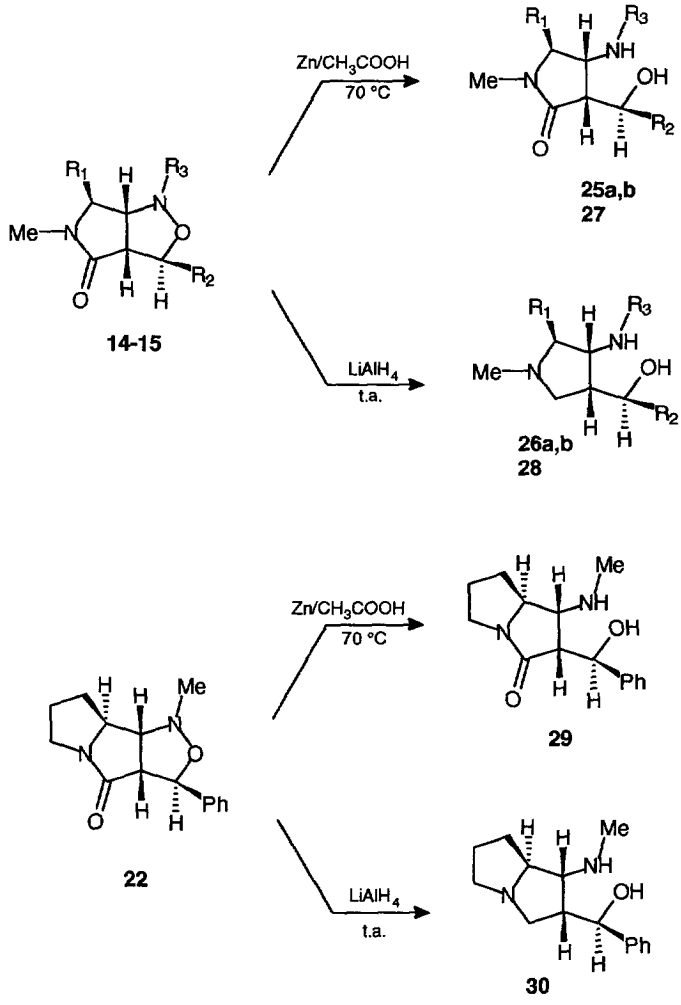
Scheme 3

Reduction of compounds **14, 15**, and **22** with zinc in acetic acid and water at 70 °C resulted in the formation of the homochiral functionalized pyrrolidin-2-ones **25, 27**, and pyrrolizidin-3-one **29** in almost quantitative yields. Furthermore, treatment of the above isoxazolidines with $LiAlH_4$ afforded the corresponding enantiomerically pure pyrrolidines **26, 28**, and pyrrolizidine **30** in high yield (Scheme 4).

The obtained compounds give satisfactory elemental analysis. The presence of NH and OH groups in **25-30** was indicated by i.r. absorptions at 3295 and at 3420 cm^{-1} respectively and by the presence of a broad singlet in the ^1H nmr spectrum integrating as two protons which was exchanged with deuterium oxide. The lactam carbonyl groups for compounds **25a,b 27, 29** is furthermore evidenced by i.r. absorption at 1645 cm^{-1} and by the presence of a resonance at 172.5 δ in the ^{13}C nmr.

Furthermore, as expected, the stereochemical features acquired in the cycloaddition process have been retained in compounds **25-30**, as confirmed by coupling constants and NOE measurements. For instance, irradiation of the methyl group at C_5 in **25a** taken as model compound, induces a very relevant enhancement of the H_3 and H_4 signals, 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 at C_4 together with a less relevant effect on H_4.

Our initial goal, directed towards the design of a new synthetic approach to homochiral functionalized pyrrolidine and pyrrolizidine systems, widely diffused in natural alkaloids, has been therefore reached by selective ring cleavage of the isoxazolidine ring.



Scheme 4

In conclusion, variously functionalizated pyrrolidine and pyrrolizidine derivatives can be obtained, with specific absolute stereochemistry, by intramolecular nitrone cycloaddition, starting from homochiral amino acids.

Furthermore, the amino and the alcohol functions present in compounds **25-30** offer the possibility of usefully synthetic manipulations directed towards the synthesis of natural alkaloids.

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 P.F. 241 MC Polarimeter (Perkin Elmer). Compounds **1b-14b** have been already reported in literature.[10]

Preparation of (1R,4R,5R,8S)-3-oxa-2,7-diazabicyclo[3.3.0]octan-6-ones 13, 14a, 15.

The above compounds were prepared according to the general method already reported by us,[10] yields and spectroscopic data being shown below.

(S)-(+)-2-(N-formylamino)-propanoic acid ***2a***. White crystalline solid, mp 125-127 °C (87%); $[\alpha]_D^{25}$ + 193.0° (c = 1.5, THF); ir (KBr): 3400, 3100-2500, 1750-1680, 1450, 1300, 1220, 1140, 870, 650 cm^{-1}. ^1H Nmr: δ (DMSO-d_6) 1.26 (d, 3H, *J* = 7.3 Hz), 4.26 (dq, 2H, *J* = 7.3 and 7.0 Hz), 7.98 (s, 1H, CHO), 8.38 (d, 1H, *J* = 7.0 Hz, slowly disappeared in D_2O). ^{13}C Nmr: δ (DMSO-d_6) 17.43, 46.25, 160.82, 173.83; ms: m/e (M^+) 117; exact mass calculated for $C_4H_7NO_3$: 117.0427. Found: 117.0425. (Found: C, 41.13; H, 6.01; N, 11.87%. Calc. for $C_4H_7NO_3$: C, 41.03; H, 6.03; N, 11.96%).

(S)-(+)-2-(N-methylamino)propanol ***3a***. Oil (95%); $[\alpha]_D^{25}$ + 43.0° (c = 4.5, $CHCl_3$); ir (neat): 3600-3200, 2980, 1450, 1380, 1350, 1160, 1070, 1030, 800 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.02 (d, 3H, *J* = 6.4 Hz), 2.41 (s, 3H, N-CH_3), 2.67 (m, 3H, N-CH, NH and OH), 3.30 (dd, 1H, *J* = 10.7 and 7.2 Hz), 3.58 (dd, 1H, *J* = 10.7 and 3.9 Hz). ^{13}C Nmr: δ ($CDCl_3$) 16.15, 33.44, 56.03, 85.22; ms: m/e (M^+) 89; exact mass calculated for $C_4H_{11}NO$: 89.0840. Found: 89.0852. (Found: C, 53.85; H, 12.35; N, 15.87%. Calc. for $C_4H_{11}NO$: C, 53.90; H, 12.44; N, 15.71%).

Trans, trans (S)-(-)-2-(N-methyl-N-but-2-enoylamino)-3-phenylpropyl but-2-enoate ***4***. Oil (78%); $[\alpha]_D^{25}$ - 38.0° (c = 1.0, THF); two rotamers, population 4:6; ir (neat): 3030, 2940, 1740, 1660, 1620, 1450, 1400, 1250, 1170, 1095, 970, 920, 750, 700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.74, 1.88 (d, total 6H, *J* = 6.8 Hz), 2.78-3.08 (m, 2H), 2.86, 2.88 (s, total 3H, N-CH_3), 4.03-4.49 (m, 2H), 5.09-5.17 (m, 2H), 5.71-5.92 (m, 1H), 5.94, 6.14 (d, total 1H, *J* = 15.0 Hz), 6.55, 6.85 (m, total 1H), 7.10-7.31 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 18.06, 26.89, 31.17, 34.86, 35.47, 38.86, 53.64, 57.00, 63.19, 63.68, 118.57, 118.86, 122.05, 126.44, 126.83, 128.40, 128.66, 129.44, 129.87, 136.89, 137.11, 140.34, 141.71, 167.16, 171.03; ms: m/e (M^+) 301; exact mass calculated for $C_{18}H_{23}NO_3$: 301.1678. Found: 301.1675. (Found: C, 71.70; H, 7.58; N, 4.69%. Calc. for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65%).

Trans, trans (S)-(-)-2-(N-methyl-N-cinnamoylamino)-propyl cinnamoate ***5a***. Oil (88%); $[\alpha]_D^{25}$ - 88.3° (c = 2.4, $CHCl_3$); two rotamers, population 1:1; ir (neat): 3060, 3040, 2980, 1720, 1650, 1600, 1500, 1400, 1180, 970, 860, 760, 710, 680 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.24, 1.31 (d, total 3H, *J* = 6.7 Hz), 2.97, 3.06 (s, total 3H, N-CH_3), 4.15-4.73 (m, 2H), 5.22 (m, 1H), 6.35, 6.41 (d, total 1H, *J* = 15.5 Hz), 6.91, 7.01 (d, total 1H, *J* = 15.5 Hz), 7.18-7.59 (m, 10H, aromatic protons), 7.61-7.82 (m, 2H). ^{13}C Nmr: δ ($CDCl_3$) 14.02, 15.17, 26.62, 29.60, 47.53, 50.76, 64.14, 64.54, 116.86, 117.37, 127.55, 127.91, 128.56, 129.33, 130.19, 133.99, 135.05, 142.14, 142.70, 145.13, 145.50, 166.38, 166.80; ms: m/e (M^+) 349; exact mass calculated for $C_{22}H_{23}NO_3$: 349.1678. Found: 349.1674. (Found: C, 75.66; H, 6.60; N, 4.00%. Calc. for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01%).

Trans (S)-(-)-[N-methyl-N-(1-benzyl-1-ethan-2-ol)]but-2-enamide ***6***. Oil (96%); $[\alpha]_D^{25}$ - 45.3° (c = 1.5, THF); two rotamers, population 6:4; ir (neat): 3380, 3030, 2925, 1710, 1660, 1600, 1450, 1400, 1365, 1220, 1090, 965, 920, 750, 700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.66, 1.83 (d, total 3H, *J* = 5.8 Hz), 2.76 (m, 2H), 2.83, 2.84 (s, total 3H, N-CH_3), 3.68 (m, 3H), 4.22, 4.64 (m, total 1H), 6.04, 6.13 (d, total 1H, *J* = 15.0 Hz), 6.47, 6.86 (m, total 1H), 7.07-7.32 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 18.12, 26.91, 32.26, 84.39, 35.29, 53.34, 58.85, 60.85, 62.10, 62.81, 122.24, 122.39, 126.24, 126.51, 128.34, 128.71, 137.47, 138.00, 139.94, 141.93, 168.16, 168.80; ms: m/e (M^+) 233; exact mass calculated for $C_{14}H_{19}NO_2$: 233.1415. Found: 233.1426. (Found: C, 72.00; H, 8.26; N, 5.99%. Calc. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00%).

Trans (S)-(-)-[N-methyl-N-(2-propanol)] cinnamoate ***7a***. Oil (95%); $[\alpha]_D^{25}$ - 25.4° (c = 2.2, $CHCl_3$); two rotamers, population 3:7; ir (neat): 3380, 3080, 3040, 2920, 1650, 1590, 1400, 1360, 1120, 1060, 980, 760 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.18, 1.24 (d, total 3H, *J* = 6.5 Hz), 2.92, 3.04 (s, total 3H, N-CH_3), 3.32, 3.48 (m, total 3H), 4.31, 4.72 (m, total 1H), 6.87, 7.03 (d, total 1H, *J* = 15.2 Hz), 7.25-7.58 (m, 5H, aromatic protons), 7.63, 7.68 (d, total 1H, *J* = 15.2 Hz). ^{13}C Nmr: δ ($CDCl_3$) 13.78, 14.96, 26.66, 30.30, 52.19, 54.52, 63.60, 64.59, 118.05, 118.58, 127.75, 128.73, 129.35, 129.64, 142.03, 143.06, 168.22; ms: m/e (M^+) 219; exact mass calculated for $C_{13}H_{17}NO_2$: 219.1259. Found: 219.1242. (Found: C, 77.14; H, 7.77; N, 6.42%. Calc. for $C_{13}H_{17}NO_2$: C, 72.21; H, 7.81; N, 6.39%).

Trans (S)-(-)-N-methyl-N-(2-propylaldehyde) ***9a***. Oil (77%); $[\alpha]_D^{25}$ - 22.6° (c = 1.6, $CHCl_3$); two rotamers, population 1:4; ir (neat): 3060, 3020, 2980, 2940, 2850, 2730, 1740, 1650, 1600, 1500, 1450, 1130, 980, 920, 760 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.21, 1.39 (d, total 3H, *J* = 7.3 Hz), 3.17 (s, 3H, N-CH_3), 4.12, 4.35 (dq, total 1H, *J* = 7.3 Hz, N-CH), 6.67, 6.90 (d, total 1H, *J* = 15.4 Hz), 7.28-7.62 (m, 5H, aromatic protons), 7.68, 7.71 (d, total 1H, *J* = 15.4 Hz), 9.54, 9.69 (s, total 1H, aldehydic proton). ^{13}C Nmr: δ ($CDCl_3$) 10.87, 33.89, 57.89, 61.57, 116.08, 119.62, 127.70, 128.60, 129.74, 134.61, 141.66, 143.74, 176.64, 197.67, 198.52; ms: m/e (M^+) 217; exact mass calculated for $C_{13}H_{15}NO_2$: 217.1102. Found: 217.1107. (Found: C, 71.80; H, 6.90; N, 6.51%. Calc. for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45%).

(1R, 4R, 5R, 8S)-(+)-2,4,7-trimethyl-3-oxa-8-benzyl-2,7-diazabicyclo[3.3.0]octan-6-one ***13***. Oil (62%); $[\alpha]_D^{25}$ + 1.2° (c = 1.7, $CHCl_3$); ir (neat): 3060, 3040, 2980, 1660, 1600, 1450, 1110, 970, 750, 700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.38 (d, 3H, *J* = 6.1 Hz), 2.32 (s, 3H, N-CH_3), 2.64 (dd, 1H, H_1, *J* = 8.5 and 4.5 Hz), 2.93 (s, 3H, N-CH_3), 2.89-3.15 (m, 3H, H_8 and benzylic protons), 3.49 (dd, 1H, H_5, *J* = 8.5 and 4.3 Hz), 4.06 (dq, 1H, H_4, *J* = 6.1 and 6.1 Hz), 7.13-7.41 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 19.35, 28.28, 37.84, 42.64, 57.35, 63.73, 70.43, 76.68, 127.26, 128.80, 129.39, 135.76, 173.13; ms: m/e (M^+) 260; exact mass calculated for $C_{15}H_{20}N_2O_2$: 260.1524. Found: 260.1532. (Found: C, 69.18; H, 7.75; N, 10.73%. Calc. for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76%).

(1R, 4R, 5R, 8S)-(+)-2,7,8-trimethyl-3-oxa-4-phenyl-2,7-diazabicyclo[3.3.0]octan-6-one ***14a***. Light yellow solid, mp 125-126 °C, (70%); $[\alpha]_D^{25}$ + 23.5° (c = 1.7, $CHCl_3$); ir (KBr): 3080, 3040, 2980, 1670, 1450, 1400, 1260, 1030, 760, 700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.25 (d, 3H, *J* = 6.7 Hz), 2.84 (s, 3H, N-CH_3), 2.87 (s, 3H, N-CH_3), 2.96 (d, 1H, H_1, *J* = 7.6 Hz), 3.36 (dd, 1H, H_5, *J* = 7.6 and 5.4 Hz), 3.39 (q, 1H, H_8, *J* = 6.7 Hz), 5.07 (d, 1H, H_4, *J* = 5.4 Hz), 7.26-7.50 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 18.13, 27.44, 43.19,

57.55, 58.43, 73.31, 81.30, 126.04, 127.64, 128.20, 139.22, 172.03; ms: m/e (M^+) 246; exact mass calculated for $C_{14}H_{18}N_2O_2$: 246.1368. Found: 246.1370. (Found: C, 68.22; H, 7.41; N, 11.33%. Calc. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37%).

(1R, 4R, 5R, 8S)-(+)-2-cyclohexyl-7,8-dimethyl-3-oxa-4-phenyl-2,7-diazabicyclo[3.3.0]octan-6-one ***15***. Light yellow solid, mp 121-123 °C, (76%); $[\alpha]_D^{25}$ + 31.7° (c = 1.7, $CHCl_3$); ir (KBr): 3080, 3040, 2980, 1680, 1490, 1450, 1400, 1050, 760, 690 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.18 (d, 3H, *J* = 6.7 Hz), 1.30 (m, 4H), 1.63 (m, 5H), 2.23 (m, 1H), 2.69 (m, 1H), 2.79 (s, 3H, N-CH_3), 3.20 (d, 1H, H_1, *J* = 8.6 Hz), 3.32 (dd, 1H, H_5, *J* = 8.6 and 6.1 Hz), 3.46 (q, 1H, H_8, *J* = 6.7 Hz), 4.96 (d, 1H, H_4, *J* = 6.1 Hz), 7.21-7.48 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 17.59, 24.44, 24.97, 25.61, 27.38, 30.28, 30.54, 58.18, 59.06, 65.90, 69.22, 80.32, 126.06, 127.47, 128.10, 139.48, 171.83; ms: m/e (M^+) 302; exact mass calculated for $C_{18}H_{26}N_2O_2$: 302.1994. Found: 302.1990. (Found: C, 71.38; H, 8.71; N, 9.30%. Calc. for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26%).

Trans, trans (S)-(-)-N-cinnamoyl-2-pyrrolidinmethanol cinnamoate ***18***. Sticky solid, (75%); $[\alpha]_D^{25}$ -16.0° (c = 2.5, THF); ir (nujol) 3080, 3060, 2980, 1710, 1650, 1600,1500, 1435,1315,1175, 975, 870, 765, 680 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.83-2.15 (m, 4H), 3.58-3.75 (m, 2H), 4.32-4.58 (m, 3H), 6.44 (d, 1H, *J* = 15.9 Hz), 6.75 (d, 1H, *J* = 15.5 Hz), 7.32-7.78 (m, 12H). ^{13}C Nmr: δ ($CDCl_3$) 21.73, 24.16, 26.86, 27.38, 28.71, 46.02, 47.21, 55.40, 55.94, 63.81, 65.21, 117.11, 117.75, 118.61, 128.02, 128.74, 129.54, 130.20, 133.92, 134.25, 135.13, 142.14, 142.34, 145.03, 145.65, 163.63; ms: m/e (M^+) 361; exact mass calculated for $C_{23}H_{23}NO_3$: 361.1678. Found: 361.1670. (Found: C, 77.28; H, 6.15; N, 3.90%. Calc. for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88%).

(S)-(-)-N-cinnamoyl-2-pyrrolidinmethanol ***19***. Oil, (83%); $[\alpha]_D^{25}$ - 31.3° (c = 1.8, THF); ir (neat) 3375, 3058, 2959, 2877, 1646, 1588, 1494, 1425, 1192, 1050, 980, 761 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.65-2.05 (m, 4H), 3.45-3.80 (m, 4H), 4.15-4.83 (m, 1H), 5.43 (bs, 1H, OH), 6.72 (d, 1H, *J* = 15.3 Hz), 7.28-7.72 (m, 6H, =CH and aromatic protons). ^{13}C Nmr: 21.51, 23.91, 27.59, 27.99, 45.88, 47.65, 58.65, 60.71, 63.92, 65.85, 118.04, 118.84, 127.54, 128.27, 128.44, 129.02, 129.49, 141.16, 142.35, 165.02, 166.42; ms: m/e (M^+) 231; exact mass calculated for $C_{14}H_{17}NO_2$: 231.1259. Found: 231.1265. (Found: C, 71.17; H, 6.98; N, 6.01%. Calc. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06%).

Preparation of (3R, 3aR, 8aS, 8bR)-(-)-1-methyl-3-phenyl-4-oxo-1,3,3a,8b-tetrahydropyrrolizidino-[3,2-c]isoxazole 22.

To a stirred solution containing 3.58 g (21.7 mmol) of (S)-proline methyl ester hydrochloride[13] **23** and 6 ml (43.4 mmol) of Et_3N in 20 ml of anhydrous carbon tetrachloride was added dropwise, at 0 °C, a solution of *trans* cinnamoyl chloride 3.6 g (21.7 mmol) in 10 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 30 ml of carbon tetrachloride. Tha combined filtrate was washed with water, dried with sodium sulfate, filtered, and solvent was removed under reduced pressure to give 4.5 g (80%) of *trans* (S)-(-)-*N*-cinnamoyl-proline methylester **24** as a light yellow oil; two rotamers, population 5:1; ir (neat) 3080, 3060, 2980, 1750, 1660, 1600, 1450, 1220, 1100, 750, 700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 2.02-243 (m, 4H), 3.76 (s, 3H, O-CH_3), 3.82 (m, 2H), 4.67 (dd, 1H, *J* = 9.5 and 4.5 Hz), 6.58, 6.81 (d, total 1H, *J* = 15.5 Hz), 7.33-7.61 (m, 5H, aromatic protons), 7.66, 7.78 (d, total 1H, *J* = 15.5 Hz). ^{13}C Nmr: 22.58, 24.74, 29.05, 31.30, 46.61, 46.84, 58.93, 59.29, 117.78, 127.63, 128.68, 129.66, 134.94, 142.03, 142.88, 164.78, 172.73; ms: m/e (M^+) 259; exact mass calculated for

$C_{15}H_{17}NO_3$: 259.1208. Found: 259.1200. (Found: C, 69.42; H, 6.58; N, 5.45%. Calc. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40%).

Diisobutylaluminum hydride (DIBAL) (13.2 mmol in toluene, 11 ml) was added dropwise with a syringe to a solution containing 2.7 g (10.4 mmol) of **24** in 25 ml of dry toluene at - 78 °C under an argon atmosphere. The reaction mixture was stirred for 2 h and was then quenched with 2 ml of methanol. The mixture was poured over 5% aqueous hydrochloric acid and ice, extracted with ether, washed with brine and concentrated under reduced pressure. The residue subjected to silica flash chromatography (cyclohexane/ethyl acetate 7:3) gave 1.66 g (70%) of *trans* (S)-(-)-*N*-cinnamoyl-prolinal **20**, as a light yellow oil; $[\alpha]_D^{25}$ - 86.4° (c = 2.5, $CHCl_3$); ir (neat) 3058, 2974, 2880, 1729, 1647, 1594, 1423, 1067, 980, 760 cm^{-1}. ^1H nmr: δ ($CDCl_3$) 1.82-2.33 (m, 4H), 3.63-3.85 (m, 2H), 4.50-4.62 (m, 1H, CH-N), 6.77 (d, 1H, *J* = 15.4 Hz), 7.36-7.57 (m, 5H, aromatic protons), 7.75 (d, 1H, *J* = 15.4 Hz), 9.60 (bs, 1H, CHO). ^{13}C nmr: δ ($CDCl_3$) 22.02, 24.37, 37.59, 68.81, 114.79, 118.62, 128.15, 129.12, 137.63, 140.31, 167.52, 198.04; ms: m/e (M^+) 229; exact mass calculated for $C_{14}H_{15}NO_2$: 229.1103. Found: 229.1109. (Found: C, 74.93; H, 6.75; N, 5.99%. Calc. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11%).

A mixture containing 1.5 g (6.5 mmol) of compound **20**, 1.36 ml (9.7 mmol) of triethylamine, 820 mg (9.7 mmol) of methylhydroxylamine hydrochloride in 200 ml of absolute ethanol was refluxed for 36 h. At the end of this time the solvent was evaporated under reduced pressure and the residue extracted with dichloromethane, washed with water and dried with sodium sulfate. Evaporation of the solvent and silica flash chromatography (cyclohexane/ethyl acetate 1:1) gave 1.27 g (75%) of (3R, 3aR, 8aS, 8bR)-(-)-1-methyl-3-phenyl-4-oxo-1,3,3a,8b-tetrahydropyrrolizidino[3,2-c]isoxazole **22**, as oil; $[\alpha]_D^{25}$ - 9.4° (c = 1.7, $CHCl_3$); ir (neat) 3080, 3040, 3000, 2980, 2850, 1690, 1460, 1400, 1210, 1040, 985, 770, 705 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.13-1.37 (m, 1H), 1.95-2.13 (m, 3H), 2.81 (s, 3H, N-CH_3), 3.03-3.16 (m, 1H), 3.47-3.55 (m, 2H), 3.62-3.76 (m, 2H), 5.18 (d, 1H, H_3, *J* = 5.6 Hz), 7.27-7.53 (m,, 5H, aromatic protons). ^{13}C Nmr: 25.50, 29.54, 41.86, 44.51, 61.42, 64.94, 71.93, 82.34, 125.88, 127.71, 128.35, 139.50. ms: m/e (M^+) 258; exact mass calculated for $C_{15}H_{18}N_2O_2$: 258.1368. Found: 258.1368. (Found: C, 68.47; H, 7.28; N, 10.91%. Calc. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84%).

Preparation of substituted pyrrolidin-2-ones 26, 28 and substituted pyrrolizidin-3-one 29.

General procedure. To a suspension of 0.4 mmol of substituted isoxazolidines **14**, **15** and **22** 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 efficent 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 extraced, and the organic extracts were combined, dried over sodium sulfate. Evaporation of the solvent gave compounds **25**, **27** and **29**.

(3R, 3'R, 4R, 5S)-(+)-3-(phenylmethanol-4-(N-methylamino)-5-methyl-N-methylpyrrolidin-2-one ***25a***. Oil (75%); $[\alpha]_D^{25}$ + 25.0° (c = 1.8, $CHCl_3$); ir (neat): 3420, 3295, 3040, 2960, 2840, 1670, 1500, 1460, 1100, 750, 700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.13 (d, 3H, *J* = 6.5 Hz), 2.30 (s, 3H, N-CH_3), 2.82 (s, 3H, N-CH_3), 2.92 (bs, 2H, H_3 and H_4), 3.48 (q, 1H, H_5, *J* = 6.5 Hz), 3.92 (bs, 2H, NH and OH), 5.40 (d, 1H, $H_{3'}$, *J* = 3.0 Hz), 7.21-7.45 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 16.49, 27.59, 34.16, 49.74, 59.40, 63.44, 70.81, 125.52, 127.03, 128.27, 142.93, 171.66; ms: m/e (M^+) 248; exact mass calculated for $C_{14}H_{20}N_2O_2$: 248.1524. Found: 248.1520. (Found: C, 67.69; H, 8.16; N, 11.30%. Calc. for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12; N, 11.28%).

(3R, 3'R, 4R, 5S)-(+)-3-(phenylmethanol-4-(N-methylamino)-5-benzyl-N-methylpyrrolidin-2-one ***25b***. Light yellow solid, mp 130-32 °C, (73%); $[\alpha]_D^{25}$ + 6.6° (c = 1.5, $CHCl_3$); ir (KBr): 3410, 3300, 3060, 2950, 2870, 1690, 1600, 1450, 1050, 750, 700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 2.02 (s, 3H, N-CH_3), 2.53-2.67 (m, 3H), 2.87-3.05 (m, 3H), 2.90 (s, 3H, N-CH_3), 3.44-3.52 (m, 1H, H_5), 5.27 (d, 1H, $H_{3'}$, *J* = 4.7 Hz), 7.08-7.36 (m, 10H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 28.70, 34.17, 37.21, 49.81, 60.90, 66.35, 71.26, 125.71, 126.98, 127.35, 128.21, 128.80, 129.00, 136.60, 142.99, 172.50; ms: m/e (M^+) 324; exact mass calculated for $C_{20}H_{24}N_2O_2$: 324.1837. Found: 324.1830. (Found: C, 73.98; H, 7.18; N, 8.71%. Calc. for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.46; N, 8.63%).

(3R, 3'R, 4R, 5S)-(+)-3-(phenylmethanol-4-(N-cyclohexylamino)-5methyl-N-methylpyrrolidin-2-one ***27***. Light yellow solid, mp 136-38 °C, (90%); $[\alpha]_D^{25}$ + 20.0° (c = 3.5, $CHCl_3$); ir (KBr): 3350, 3060, 2980, 2960, 1690, 1660, 1450, 1400, 1260, 1050, 700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.12 (m, 5H), 1.15 (d, 3H, *J* = 6.4 Hz), 1.67 (m, 5H), 2.22 (m, 1H), 2.85 (s, 3H, N-CH_3), 2.87 (dd, 1H, H_3, *J* = 6.9 and 4.3 Hz), 3.14 (dd, 1H, H_4, *J* = 6.9 and 2.1 Hz), 3.29 (dq, 1H, H_5, *J* = 6.4 and 2.1 Hz), 5.37 (d, 1H, $H_{3'}$, *J* = 4.3 Hz), 7.25-7.47 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 16.52, 24.76, 24.78, 25.72, 27.76, 33.02, 34.20, 49.80, 56.11, 59.20, 62.04, 71.50, 125.85, 127.01, 128.18, 143.36, 172.65; ms: m/e (M^+) 304; exact mass calculated for $C_{18}H_{28}N_2O_2$: 304.2150. Found: 304.2158. (Found: C, 71.08; H, 9.33; N, 9.12%. Calc. for $C_{18}H_{28}N_2O_2$: C, 71.02; H, 9.27; N, 9.20%).

(1R, 2R, 2'R, 8S)-(-)-1-(N-methylamino)-2-(phenylmethanol)pyrrolizidin-3-one ***29***. Oil (85%); $[\alpha]_D^{25}$ - 2.3° (c = 2.0, $CHCl_3$); ir (neat) 3430, 3300, 3080, 2950, 2880, 2800, 1675, 1600, 1450, 1060, 920, 750, 700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.35-1.52 (m, 1H), 1.87-2.18 (m, 3H), 2.20 (s, 3H, N-CH_3), 2.88-3.58 (m, 6H), 3.71-3.82 (m, 1H), 5.17 (d, 1H, $H_{3'}$, *J* = 4.7 Hz), 7.13-7.43 (m,, 5H, aromatic protons). ^{13}C Nmr: 26.64, 31.23, 35.19, 41.20, 56.82, 66.29, 66.67, 73.32, 125.70, 127.01, 128.09, 142.94, 173.13; ms: m/e (M^+) 260; exact mass calculated for $C_{15}H_{20}N_2O_2$: 260.1524. Found: 260.1528. (Found: C, 69.19; H, 7.78; N, 10.74%. Calc. for $C_{15}H_{20}N_2O_2$: C, 69.19; H, 7.75; N, 10.77%).

Preparation of substituted pyrrolidines 26, 28 and substituted pyrrolizidine 30.

General procedure. A suspension of 0.4 mmol of substituted isoxazolidines **14**, **15** and **22** and 3.2 mmol of lithium aluminum hydride in 15 ml of anhydrous tetrahydrofuran was stirred at 25 °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 the amino alcohols **26**, **28** and **30**.

(2S, 3R, 4R, 4'R)-(+)-2-methyl-3-(N-methylamino)-4-(phenylmethanol)-N-methyl-pyrrolidine ***26a***. Oil (70%); $[\alpha]_D^{25}$ + 1.2° (c = 3.5, $CHCl_3$); ir (neat) 3400, 3300, 3060, 2980, 1450, 1040, 750, 700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.10 (d, 3H, *J* = 6.4 Hz), 2.36 (s, 3H, N-CH_3), 2.65 (m, 2H, H_2 and $H_{5'}$), 2.77 (s, 3H, N-CH_3), 3.12 (m, 3H, H_3, H_4 and $H_{5''}$), 4.02 (bs, 2H, NH and OH), 4.81 (d, 1H, $H_{4'}$, *J* = 6.1 Hz), 7.25-7.43 (m,, 5H, aromatic protons). ^{13}C Nmr: 15.12, 38.91, 44.95, 55.16, 59.06, 63.93, 82.32, 85.37, 126.58, 127.97, 128.50, 139.89; ms: m/e (M^+) 246; exact mass calculated for $C_{15}H_{22}N_2O$: 246.1732. Found: 246.1738. (Found: C, 73.13; H, 8.92; N,

11.34%. Calc. for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37%).

(2S, 3R, 4R, 4'R)-(+)-2-benzyl-3-(N-methylamino)-4-(phenylmethanol)-N-methyl-pyrrolidine ***26b***. Oil (85%); $[\alpha]_D^{25}$ + 7.0° (c = 0.7, THF); ir (neat): 3380, 3295, 3060, 2950, 2860, 2780, 1600, 1450, 1040, 750, 700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 2.10 (s, 3H, N-CH_3), 2.42-253 (m, 1H), 2.51 (s, 3H, N-CH_3), 2.76-2.83 (m, 3H), 2.97-3.12 (m, 5H), 4.79 (d, 1H, $H_{4'}$, *J* = 4.1 Hz), 7.18-7.35 (m, 10H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 36.11, 39.29, 43.20, 55.91, 59.23, 70.37, 79.23, 74.60, 126.39, 126.58, 127.93, 128.46, 129.48, 138.72, 139.56; ms: m/e (M^+) 310; exact mass calculated for $C_{20}H_{26}N_2O$: 310.2045. Found: 310.2049. (Found: C, 77.11; H, 8.27; N, 9.07%. Calc. for $C_{20}H_{26}N_2O$: C, 77.37; H, 8.45; N, 9.03%).

(2S, 3R, 4R, 4'R)-(+)-2-methyl-3-(N-cyclohexylamino)-4-(phenylmethanol)-N-methyl-pyrrolidine ***28***. White solid, mp 76-8 °C, (83%); $[\alpha]_D^{25}$ + 4.7° (c = 2.1, $CHCl_3$); ir (KBr): 3400, 3300, 3020, 2960, 2940, 1450, 1340, 1160, 1040, 750, 700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.01 (d, 3H, *J* = 6.5 Hz), 1.27 (m, 5H), 1.73 (m, 5H), 2.17 (m, 1H), 2.36 (s, 3H, N-CH_3), 2.65 (m, 2H), 2.93 (m, 3H), 3.30 (m, 1H), 3.65 (m, 1H), 4.72 (d, 1H, $H_{4'}$, *J* = 7.1 Hz), 7.27-7.35 (m, 5H, aromatic protons). ^{13}C Nmr: δ ($CDCl_3$) 12.16, 24.77, 25.15, 25.94, 30.85, 37.95, 54.06, 56.50, 64.18, 65.96, 76.98, 84.78, 126.67, 127.84, 128.35, 139.51; ms: m/e (M^+) 288; exact mass calculated for $C_{18}H_{28}N_2O$: 288.2201. Found: 288.2214. (Found: C, 74.90; H, 9.73; N, 9.66%. Calc. for $C_{18}H_{28}N_2O$: C, 74.96; H, 9.78; N, 9.71%).

(1R, 2R, 2'R, 8S)-(-)-1-(N-methylamino)-2-(phenylmethanol)pyrrolizidine ***30***. Light yellow solid, mp 74-75 °C, (87%); $[\alpha]_D^{25}$ - 2.0° (c = 1.0, $CHCl_3$); ir (KBr) 3400, 3290, 3080, 2980, 1600, 1500, 1450, 1350, 1100, 1040, 750, 700 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 1.43-2.06 (m, 6H), 2.68-2.77 (m, 2H), 2.81 (s, 3H, N-CH_3), 2.94-3.38 (m, 5H), 4.83 (d, 1H, $H_{2'}$, *J* = 6.2 Hz), 7.24-7.41 (m,, 5H, aromatic protons). ^{13}C Nmr: 24.48, 28.55, 44.81, 53.28, 56.33, 57.09, 69.01, 80.34, 85.17, 126.66, 127.97, 128.50, 141.34; ms: m/e (M^+) 246; exact mass calculated for $C_{15}H_{22}N_2O$: 246.1732. Found: 246.1725. (Found: C, 72.93; H, 8.67; N, 11.43%. Calc. for $C_{15}H_{22}N_2O$: C, 73.12; H, 9.01; N, 11.38%).

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