STEREOSELECTIVE SYNTHESIS OF ENANTIOMERICALLY *PURE ISOXAZOLIDINE-FUSED* δ-LACTAMS

Ugo Chiacchio,*[a] Antonino Corsaro,[a] Anna Piperno,[b] Antonio Rescifina,[a] Giovanni Romeo,[b] and Roberto Romeo[b]

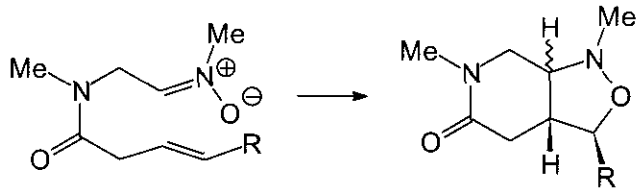
[a]Dipartimento di Scienze Chimiche, Università di Catania, Italy
[b]Dipartimento Farmaco-Chimico, Università di Messina, Italy
*uchiacchio@dipchi.unict.it

Abstract - Enantiomerically pure isoxazolidine-fused δ-lactams have been obtained by intramolecular nitrone cycloaddition starting from homochiral amido aldehydes. The stereocenter of the homochiral precursor controls the stereochemical course of the process.

Developing methods, that efficiently construct polyheterocyclic ring systems possessing several stereocenters, are of great interest in synthetic chemistry.[1] In recent years much attention has been focused on reactions that affect formation of heterocycles through the intramolecular version of [3+2] cycloaddition, especially in the synthesis of the intriguing carbon frameworks occurring in natural products and other stereochemically complicated molecules.[2]

Among these, the 1,3-dipolar cycloaddition of nitrones occupies a uniquely important position due to their synthetic as well as theoretical significance.[3] Introduction of a heteroatom in the tether connecting the nitrone and the alkene groups considerably extends the synthetic potential of the process:[4] such reactions assume, in fact, great interest in the synthesis of pyrrolidines, pyrrolizidines, indolizidines, furans and thiophenes.[5] In particular, a chiral center in the starting substrate could cause an asymmetric induction giving rise to the formation of new chiral centers with definite configuration in the cycloadducts.[6]

Our interest in the chemistry of nitrone-olefin cycloaddition[7] stems from the exploitation of isoxazolidines as valuable intermediate in organic synthesis of target molecules showing synthetic and biological interest. On this basis, we have previously extended the process to a series of compounds in which an amido group has been inserted in the tether connecting the nitrone moiety to the dipolarophile double bond and we have reported that 6-hepten-3-*N*-methyl-4-oxo-1-imino-*N*-oxides (**1**) lead to *cis*- and *trans*-fused δ-lactams (**2**) according to the nature of the substituents present on the double bond (Scheme 1).[8]



Scheme 1

In the present paper we report the effects associated to the insertion of a chiral center in α-position with respect to nitrone functionality: starting from homochiral aminoacids, homochiral δ-lactams containing four contiguous chiral centers have been synthesized. The selective functionalization of the fused systems by ring cleavage of the isoxazolidine rings constitutes a new easy entry to the stereoselective formation of piperidine and indolizidine derivatives with a very high diastereoselection and optical purity.

RESULTS AND DISCUSSION

The bicyclic compounds (**9a-c**) have been obtained as reported in Scheme 2. Reaction of (*S*)-(+)-3-phenyl-2-(*N*-methylamino)propanol (**3**)[7] with β,γ-unsaturated acyl chlorides (**4**) led to the corresponding amido esters (**5**), which have been converted into the α-amido aldehydes (**7**) by sequential hydrolysis (K_2CO_3) and Swern oxidation. The subsequent treatment with *N*-methylhydroxylamine furnished nitrones (**8**) which spontaneously underwent intramolecular cycloaddition to 7-benzyl-1,6-dimethylperhydro-isoxazolo[3,4-*c*]pyridin-5-ones (**9**).

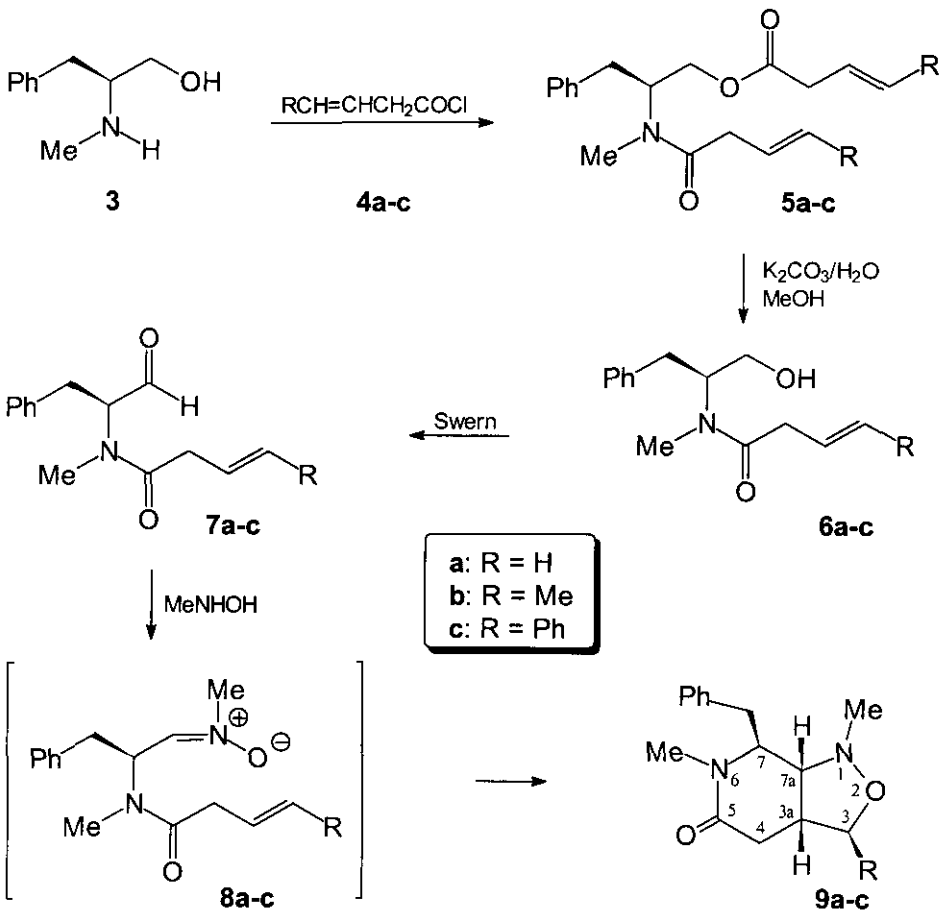
The structure of obtained compounds was confirmed by analytical and spectrometric data. High resolution MS spectra showed the correct molecular ions for all the examined compounds. The ^{1}H NMR showed in compounds (**9a-c**) the diagnostic resonance of H3 protons which appear for **9a**, as two doublets of doublet at δ 3.48 and 4.14; as a doublet of quartet at δ 3.65 for **9b** and as a doublet (J = 8.8 Hz) at δ 4.47 for **9c**. Instead H3a appear as multiplets centered at δ 3.10, 2.50 and 2.91 respectively.

In the examined compounds H7 resonates as multiplets in the range δ 3.31-3.40; H7a as doublets (J = 11.0 Hz) in the range δ 2.78-3.10; the methylene protons at C4 appear at δ 2.34-2.54 as doublets (J = 10.2-16.4 Hz) and at 2.28-2.53 δ as doublets of doublets (J = 1.5-4.4 and 10.2-16.4 Hz).

The nitrone cycloaddition process was regiospecific leading to the exclusive formation of fused compounds as indicated by the presence of diagnostic ^{1}H NMR absorptions expected for isoxazolidine protons at C3: no bridged products were detected in the crude reaction mixtures.

The reactions have been also found to be stereospecific: the stereochemical information present in the dipolarophile moiety is completely retained in the obtained cycloadducts and the relative stereochemistry

at C3-C3a, in the formed isoxazolidine rings, is predetermined by the alkene geometry. The ring junction between the isoxazolidine ring and the lactam six-membered rings is always *cis*, as confirmed by coupling constants and ROE measurements.



3 4a-c 5a-c 6a-c 7a-c 8a-c 9a-c

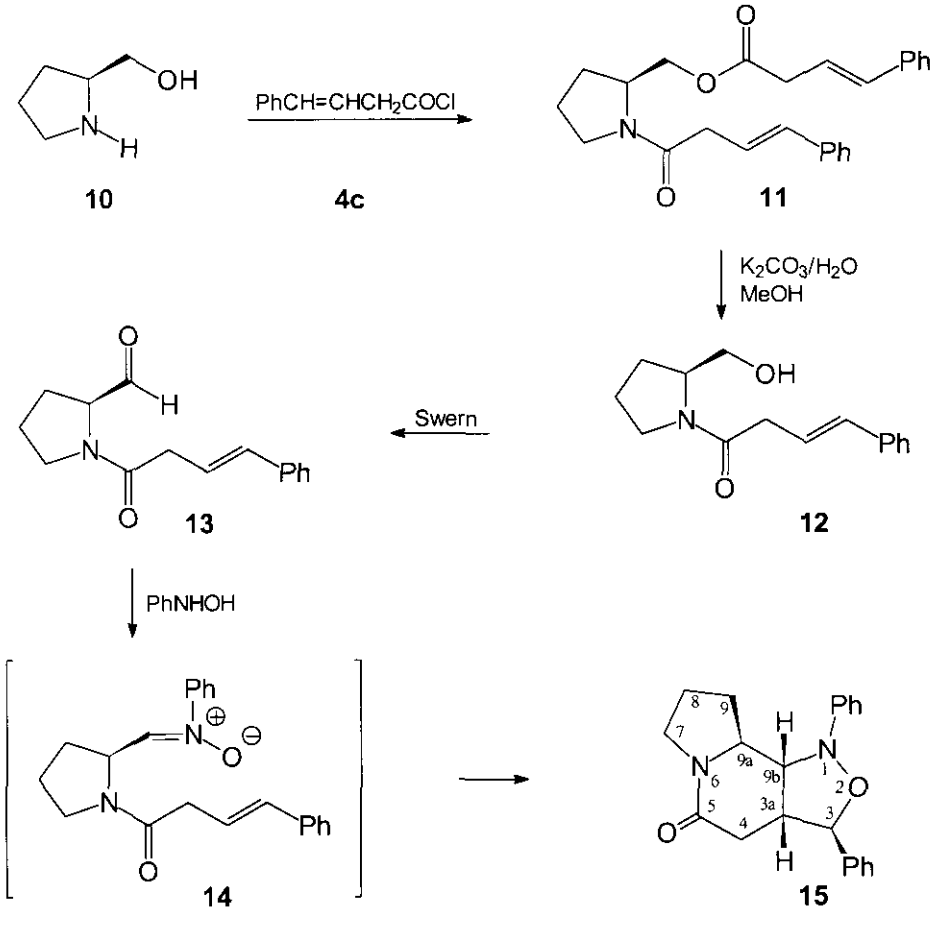
Scheme 2

In particular, for **9a**, T-Roesy data show ROE enhancements between H3a with H7a and H3"; between H4" with H3a and the benzylic protons at C7 (according to a boat conformation); and between H4· with H3', so confirming the *cis* ring fusion and the *syn* relationship between H7a and the benzylic group at C7. On the contrary T-Roesy experiments on **9b,c** show ROE enhancements between H3a with H7a and H4"; H3 with H4·; H7a with H3a and the benzylic protons at C7. The obtained data clearly indicate a *cis* ring fusion arrangement.

With respect to the stereochemical outcome verified in the analogous intramolecular cycloaddition performed on achiral substrates,[8] where with a methyl group inserted at the terminal carbon atom of the alkene moiety a 70:30 mixture of *cis*- and *trans*-fused cycloadducts is obtained, the presence of the benzylic group at C7 promotes a totally diastereoselective process with the exclusive formation of the

enantiomerically pure cycloadducts (**9a-c**).

The described synthetic approach can represent an interesting route for functionalized polycyclic systems. In this context, the L-prolinol (**10**) was reacted with the *trans* styrylacetic chloride (**4c**), to give, according the procedure above reported, the corresponding aldehyde (**13**). The subsequent reaction with *N*-phenylhydroxylamine afforded the enantiomerically pure tricyclic compound (**15**) (*cis-anti*), as a single adduct, in 51% yield (Scheme 3).



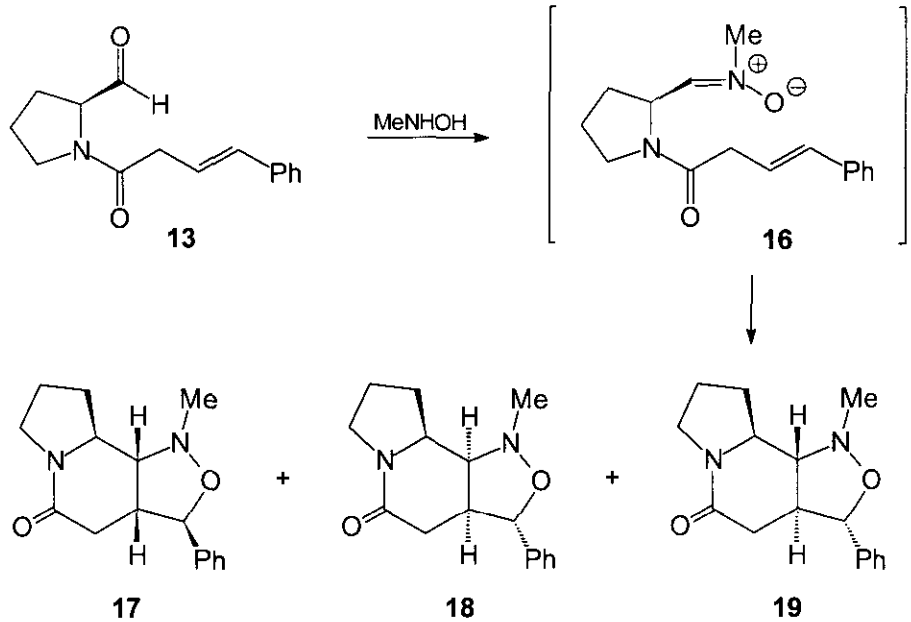
Scheme 3

Compound (**15**) was characterized by analytical and spectroscopic data. The magnitude of the vicinal coupling constant, exhibited by H3a and H9b (9.8 Hz), is consistent with a dihedral angle of *ca.* 3.2° on the basis of the Karplus equation[9] and hence a *cis* junction between indolizidine and isoxazolidine rings is evidenced. This hypothesis is supported by NOE experiments: the NOE effect observed between H9b and H3a (*ca.* 6%) provide conclusive evidence of their spectral proximity, arising from a *cis* relationship.

Furthermore, the 9.7 Hz coupling constant between H9a and H9b indicates an *anti* stereochemistry between these protons; in fact, in structurally similar indolizidino-isoxazolidine compounds[10] a vicinal

coupling constant of 3 Hz is indicative of a gauche dihedral angle and, then, of a *syn* stereochemistry. Thus, in reaction at hand, the stereocenter of the homochiral precursor appears to effectively control the stereochemical course of the process with the formation of one of eight possible stereoisomers in a highly stereoselective fashion.

However, different results were obtained when aldehyde (**13**) was reacted with *N*-methylhydroxylamine: the intramolecular cycloaddition process of the intermediate, not isolated, nitrone (**16**) afforded a mixture of *cis-anti* **17** and *cis-syn* **18** fused adducts in a relative ratio 2.3:1, together with traces of the *trans-anti*-fused isomer (**19**) (in the relative ratio 69:30:1) (Scheme 4).



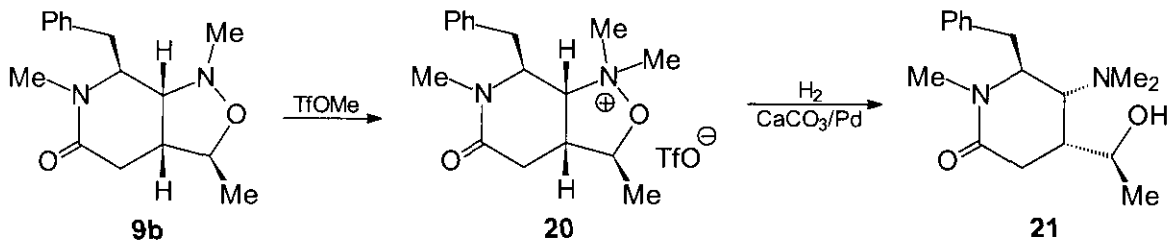
Scheme 4

Compounds (**17**) and (**18**) were characterized by spectroscopic data. In **18** irradiation of the H9b resonance at δ 3.23, as a doublet of doublets, induces a very relevant enhancement of the H3a and H9a signals, so suggesting that these protons are topologically close together in a *syn* relationship. On the contrary, irradiation of the analogous proton in **17** (δ 3.35, m) gives rise to a positive NOE for H3a, together with a less relevant effect on H4.

Ring closure to six-membered rings fused to the isoxazolidine nucleus, as part of an indolizidine or quinolizidine systems, have been previously reported,[10] according to an intramolecular oxime-olefin cycloaddition process, with the formation of the *cis-syn* stereoisomers. In the case at hand, the intramolecular nitrone cycloaddition promoves a different stereochemical decourse leading to the *cis-anti* stereoisomer as the major (**17**) or the exclusive cycloadduct (**15**).

The selective ring cleavage of the isoxazolidine nucleus affords a synthetic approach to homochiral

functionalized piperidine and indolizidine systems. Thus, piperidinone (**21**) has been obtained by reaction of **9b** respectively with methyl trifluoromethanesulfonate, in dry CCl_4 at 0 °C, followed by hydrogenolysis with 5% palladium on $CaCO_3$ in dry MeOH at 60 °C for 12 h (yields 95%) (Scheme 5).



9b **20** **21**

Scheme 5

In conclusion, the intramolecular nitrone cycloaddition reaction, starting from homochiral aminoacids precursors, leads to homochiral functionalized piperidine systems, with specific absolute stereochemistry. Moreover, the overall process offers the possibility of usefully synthetic manipulations directed towards the synthesis of natural compounds.

EXPERIMENTAL

Elemental analyses were performed with a Perkin-Elmer elemental analyzer. IR spectra were recorded on a Perkin-Elmer 377 instrument. ^{1}H NMR spectra were measured on a Varian 300 Gemini and on a Varian 500 Unity INOVA instruments in $CDCl_3$ as solvent. Chemical shifts are in ppm (δ) from TMS as internal standard. Reaction mixtures were analyzed by TLC on silica gel GF 254 (Merck) and the spots were detected under UV light (254 nm). Flash chromatography was carried out with Kieselgel 60 (Merck). Optical rotations were measured on a PF 241 MC polarimeter (Perkin Elmer).

Preparation of (*E*)-enamido esters derivatives.

General procedure. A solution (165 mmol) of acyl cloride in 150 mL of anhydrous carbon tetrachloride was added dropwise, at 0 °C, to a stirred solution containing 75 mmol of **3**, **10** and 22.5 mL of Et_3N in 150 mL of anhydrous carbon tetrachloride. The reaction mixture was stirred at 0 °C for 30 min and then at 25 °C for 6 h. The mixture was filtered and washed with 50 mL of carbon tetrachloride. The combined filtrates were washed with water, dried with sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was subjected to silica flash chromatography using a methanol-chloroform 2:98 mixture as eluent.

*Reaction of **3** with vinylacetic chloride (**4a**).* First fraction gave (2*S*)-2-[3-butenoyl(methyl)amino]-3-phenylpropyl 3-butenoate (**5a**), (85%). Oil, two rotamers; $[\alpha]_D^{25}$ -10.3° (c = 5.8, $CHCl_3$). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.75; H, 7.68; N, 4.66. IR (neat) 2940, 2840, 1735, 1690, 1570, 1060, 980, 760 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.78 and 2.81 (s, total 3H, NCH_3), 2.91 (m, 2H, CH_2Ph), 3.08 (m, 4H, CH_2C=), 4.25 (m, 2H, CH_2O), 5.10 (m, 5H, CH_2= and CH), 5.85 (m, 2H, CH=), 7.15-7.35 (m, 5H, ArH). ^{13}C NMR: δ ($CDCl_3$) 21.83, 35.38, 35.93, 39.75, 63.40, 76.03, 117.93, 119.03, 126.07, 126.92, 128.38, 128.73, 128.93, 137.10, 127.23, 137.51, 171.82, 173.25. Exact MS calculated for $C_{18}H_{23}NO_3$: 301.1678. Found: 301.1680.

*Reaction of **3** with **4b**.* First fraction gave (2*S*)-2-(methyl((*E*)-3-pentenoyl)amino)-3-phenylpropyl (*E*)-3-pentenoate (**5b**) (90%). Oil, two rotamers. Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.80; H, 8.24; N, 4.26. IR (neat): 3060, 2935, 1750, 1640, 1570, 1375, 1060, 980, 750 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.64 (d, 3H, CH_3, J = 1.5 Hz), 1.68 (d, 3H, CH_3, J =1.5 Hz), 2.79 and 2.87 (s, total 3H, N-CH_3), 2.92 (m, 2H, CH_2-Ph), 3.05 (m, 4H, CH_2-C=), 4.07 and 4.19 (m, total 2H, CH_2O), 4.70 and 5.10 (m, total 1H, CH), 5.61 (m, 2H, CH=), 5.59 (m, 2H, CH=), 7.20-7.32 (m, 10H, ArH). ^{13}C NMR: δ ($CDCl_3$) 18.56, 18.57, 27.62, 37.69, 38.52, 38.93, 58.08, 64.62, 122.56, 123.85, 127.19, 127.64, 129.00, 129.08, 129.27, 129.45, 129.85, 137.66, 172.48, 175.89. Exact MS calculated for $C_{20}H_{27}NO_3$: 329.1991. Found: 329.1990.

*Reaction of **3** with **4c**.* First fraction gave (2*S*)-2-methyl[(*E*)-4-phenyl-3-butenoyl]amino-3-phenylpropyl (*E*)-4-phenyl-3-butenoate (**5c**) (95%). Oil, two rotamers; $[\alpha]_D^{25}$ - 21.9° (c = 3.65, $CHCl_3$). Anal. Calcd for $C_{30}H_{31}NO_3$: C, 79.44; H, 6.89; N, 3.09. Found: C, 79.51; H, 6.71; N, 3.07. IR (neat): 3040, 2975, 1740, 1760, 1605, 1540, 1410, 1200, 1040, 970, 860, 760 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.79 and 2.86 (s, total 3H, N-CH_3), 2.85 (m, 2H, CH_2-Ph), 3.13 (d, 2H, CH_2-C=, J = 6.2 Hz), 3.23 (d, 2H, CH_2-C=, J = 6.8 Hz), 4.16 and 4.30 (m, total 2H, CH_2O), 5.15 (m, 1H, CH=), 6.27 (m, 4H, CH=), 7.11-7.34 (m, 15H, ArH). ^{13}C NMR: δ ($CDCl_3$) 32.01, 35.09, 36.06, 38.38, 59.07, 62.81, 123.37, 124.20, 126.93, 127.14, 127.30, 127.45, 127.94, 128.10, 128.27, 128.43, 128.52, 128.72, 129.13, 129.41, 129.50, 129.79, 129.90, 133.15, 133.46, 137.59, 137.72, 138.46, 173.43, 173.64. Exact MS calculated for $C_{30}H_{31}NO_3$: 453.2304. Found: 453.2303.

*Reaction of **10** with **4c**.* First fraction gave (2*S*)-1-[(*E*)-4-phenyl-3-butenoyl]tetrahydro-1*H*-2-pyrrolylmethyl (*E*)-4-phenyl-3-butenoate (**11**) (90%). Oil. Anal. Calcd for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 77.18; H, 6.95; N, 3.62. IR (neat) 3040, 3015, 1723, 1655, 1600, 1450, 1150, 980, 760, 710 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.90 (m, 4H), 3.10 (d, 2H, CH_2C=, J = 6.0 Hz), 3.30 (d, 2H, CH_2=, J = 6.2 Hz), 3.45 (m, 3H), 4.20 (m, 2H, CH_2O), 6.45 (m, 4H, CH=), 7.03-7.28 (m, 10H, ArH). ^{13}C NMR: δ ($CDCl_3$) 24.16, 26.86, 36.06, 38.48, 55.40, 55.94, 63.81, 123.82, 124.75, 126.91, 127.21, 123.30, 128.32,

128.55, 126.69, 129.40, 129.51, 129.90, 129.95, 133.46, 133.83, 142.35, 143.80, 173.02, 173.43. Exact MS calculated for $C_{25}H_{27}NO_3$: 389.1991. Found: 389.1988.

Preparation of (*E*)-enamido alcohols.

General procedure. To a stirred solution containing 50 mmol of amido esters in 280 mL of MeOH was added 6% aqueous K_2CO_3 (150 mL). The mixture was stirred until TLC showed the disappearance of the starting material; after removal of the solvent under reduced pressure, the residue was subjected to silica flash chromatography (MeOH/$CHCl_3$ 4:96).

*Reaction of **5a** with K_2CO_3/MeOH for 2 h*. First fraction gave *N*1-[(1*S*)-1-benzyl-2-hydroxyethyl]-*N*1-methyl-3-butenamide (**6a**) (100%). Oil, $[\alpha]_D^{25}$ - 7.4° (c = 10.7, $CHCl_3$), two rotamers. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.00; H, 8.19; N, 6.01. IR (neat) 3400, 2970, 1690, 1280, 1075, 980, 800, 725 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.55 (br s, 1H, OH), 2.78 (s, 3H, N-CH_3), 2.92 (m, 2H, CH_2-Ph), 3.07 (d, 2H, CH_2C=, *J* = 6.6 Hz), 3.75 (dd, 2H, CH_2OH, *J* = 3.75 and 11.4 Hz), 4.12 and 4.53 (m, total 1H, CH), 5.08 (m, 2H, CH_2=), 5.82 (m, 1H, CH=), 7.13-7.35 (m, 5H, ArH). ^{13}C NMR: δ ($CDCl_3$) 25.32, 34.71, 39.78, 58.80, 63.91, 118.01, 127.30, 128.42, 128.52, 128.93, 133.21, 138.52, 172.50. Exact MS calculated for $C_{14}H_{19}NO_2$: 233.1416. Found: 233.1419.

*Reaction of **5b** with K_2CO_3*. First fraction gave *N*1-[(1*S*)-1-benzyl-2-hydroxyethyl]-*N*1-methyl-(*E*)-3-pentenamide (**6b**) (85%). Oil, two rotamers. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.85; H, 8.57; N, 5.66. IR (neat) 3380,. 3080, 3040, 2920, 1680, 1590, 1400, 1360, 1110, 1050, 980, 760 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.62 and 1.70 (d, total 3H, CH_3, *J* = 2.4 Hz), 2.77 and 2.89 (s, total 3H, N-CH_3), 2.91 (m, 2H, CH_2-Ph), 3.20 (br s, 1H, OH), 3.75 (m, 2H, CH_2O), 4.11 and 4.51 (m, 1H, CH), 5.40 (m, 2H, CH=), 7.11-7.32 (m, 5H, ArH). ^{13}C NMR: δ ($CDCl_3$) 17.97, 32.35, 34.31, 38.53, 59.35, 63.09, 123.50, 126.41, 126.59, 128.40, 128.69, 128.85, 129.03, 137.90, 173.49. Exact MS calculated for $C_{15}H_{21}NO_2$: 247.1572. Found: 247.1574.

*Reaction of **5c** with K_2CO_3*. First fraction gave *N*1-[(1*S*)-1-benzyl-2-hydroxyethyl]-*N*1-methyl-(*E*)-4-phenyl-3-butenamide (**6c**) (92%). Oil, two rotamers; $[\alpha]_D^{25}$ - 36.4° (c = 11.5, $CHCl_3$). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.68; H, 7.50; N, 4.53. IR (neat) 3385, 3380, 3030, 1675, 1600, 1400, 1350, 1130, 980, 760 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.67 (s, 3H, N-CH_3), 2.75 (m, 2H, CH_2-Ph), 3.16 (dd, 2H, CH_2-CH=, *J* = 1.2 and 6.4 Hz), 3.72 (m, 2H, CH_2OH), 4.15 and 4.55 (m, total 1H, CH), 6.15 (m, 1H, CH=), 6.32 (dd, 1H, CH=, *J* = 1.2 and 15.9 Hz), 7.17-7.40 (m, 10H, ArH). ^{13}C NMR: δ ($CDCl_3$) 32.53, 34.31, 38.88, 59.30, 61.14, 122.61, 126.21, 126.80, 127.24, 127.39, 128.03, 128.41, 128.45, 128.74, 128.81, 129.13, 132.43, 132.79, 137.81, 172.84. Exact MS calculated for $C_{20}H_{23}NO_2$: 309.1729. Found: 309.1726.

*Reaction of **11** with K_2CO_3.* First fraction gave (*E*)-1-[(2*S*)-2-(hydroxymethyl)tetrahydro-1*H*-1-pyrrolyl]-4-phenyl-3-buten-1-one (**12**) (80%). Oil. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.58; H, 7.78; N, 5.73. IR (neat) 3375, 3058, 2960, 1670, 1590, 1420, 1050, 980, 760 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.85 (m, 4H), 3.2 (d, 2H, CH_2CH=, J = 6.0 Hz), 3.63 (m, 4H, CH_2O and CH_2N), 4.18 (m, 1H, CH), 5.20 (br s, 1H, OH), 6.42 (m, 2H, CH=), 7.20-7.35 (m, 5H, ArH). ^{13}C NMR: δ ($CDCl_3$), 27.59, 27.98, 45.88, 58.60, 60.70, 65.09, 118.80, 118.85, 127.32, 128.95, 129.02, 129.4, 141.10, 142.3, 173.02. Exact MS calculated for $C_{15}H_{19}NO_2$: 245.1416. Found: 245.1417.

Preparation of (*E*)-enamide aldehydes derivatives.

General procedure. 8.5 mL (120 mmol) of anhydrous DMSO was added, at – 78 °C, to a stirred solution of bis(trichloromethyl)carbonate (20 mmol) in 50 mL of dry dichloromethane at – 78 °C. The reaction mixture was stirred for 15 min and then a solution of amido alcohols (8 mmol) in 80 mL of dichloromethane was slowly added at the same temperature. After 15 min of stirring, triethylamine (19.7 mL, 140 mmol) in 100 mL of dichloromethane was added dropwise maintaining the temperature below – 70 °C. After the addition, the resulting suspension was stirred at – 78 °C for 5 min and then the acetone-dry bath was removed. The reaction mixture was stirred at rt for 2 h and the solvent was removed under reduced pressure. The obtained residue was extracted with dichloromethane, washed with water, dried with sodium sulfate and silica flash chromatographated (MeOH/$CHCl_3$ 3:97).

*Reaction of **6a** with DMSO.* First fraction gave *N*1-[(1*S*)-1-benzyl-2-oxoethyl]-*N*1-methyl-3-butenamide (**7a**) (70%). Oil, two rotamers. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.78; H, 7.45; N, 6.04. IR (neat) 2940, 2860, 1730, 1680, 1600, 1580, 1180, 1150, 1090, 980, 760 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.73 (s, 3H, N-CH_3), 3.23 (m, 2H, CH_2-Ph), 3.35 and 3.45 (d, total 2H, CH_2CH=, J = 6.4 Hz), 4.38 (m, 1H, CH), 5.15 (m, 2H, CH_2=), 6.92 (m, 1H, CH=), 7.20-7.35 (m, 5H, ArH), 9.60 (s, 1H, CHO). ^{13}C NMR: δ ($CDCl_3$) 19.51, 29.82, 32.85, 38.37, 78.02, 118.03, 128.04, 128.57, 128.82, 128.34, 131.30, 147.3, 169.20, 198.23. Exact MS calculated for $C_{14}H_{17}NO_2$: 231.1259. Found: 231.1261.

*Reaction of **6b** with DMSO.* First fraction gave *N*1-[(1*S*)-1-benzyl-2-oxoethyl]-*N*1-methyl-(*E*)-3-pentenamide (**7b**) (60%). Oil. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.38; H, 7.79; N, 5.73. IR (neat) 2930, 2875, 2725, 1740, 1680, 1295, 1335, 1110, 980, 720 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.75(dd, 3H, CH_3, J = 1.8 and 6.1 Hz), 2.71, (s, 3H, N-CH_3), 3.05 (d, 2H, CH_2, J = 5.1 Hz), 3.15 (dd, 1H, HCHPh, J = 4.8 and 12.5 Hz) 3.40 (dd, 1H, HCHPh, J = 10.5 and 12.5 Hz), 4.21 (m, 1H, CH), 5.55 (m, 2H, CH=), 7.17-7.30 (m, 5H, ArH), 9.56 (s, 1H, CHO). ^{13}C NMR: δ ($CDCl_3$) 18.36, 26.36, 37.29, 69.30, 123.70, 126.30, 126.76, 128.36, 128.65, 128.80, 137.05, 138.01, 174.11, 202.10. Exact MS calculated for $C_{15}H_{19}NO_2$: 245.1416. Found: 245.1411.

Reaction of ***6c*** *with DMSO.* First fraction gave *N*1-[(1*S*)-1-benzyl-2-oxoethyl]-*N*1-methyl-(*E*)-4-phenyl-3-butenamide (**7c**) (58%). Oil. Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.16; H, 6.89; N, 4.56. IR (neat) 2930, 2870, 1680, 1600, 1550, 1410, 1295, 1110, 980, 830 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.81 (s, 3H, N-CH_3), 3.02 (dd, 1H, HCHPh, *J* = 4.5 and 13.0 Hz), 3.12 (dd, 1H, HCHPh, *J* = 9.8 and 13.0 Hz), 3.32 (d, 2H, CH_2CH=, *J* = 6.9 Hz), 4.32 (m, 1H, CH), 6.25 (m, 1H, CH=), 6.49 (d, 1H, CH=, *J* = 15.0 Hz), 7.20-7.30 (m, 10H, ArH), 9.62 (s, 1H, CHO). ^{13}C NMR: δ ($CDCl_3$) 36.04, 39.83, 63.04, 65.05, 121.87, 122.47, 126.88, 127.15, 127.40, 127.57, 128.23, 129.31, 129.67, 130.84, 134.04, 135.18, 137.32, 137.92, 172.44, 198.22. Exact MS calculated for $C_{20}H_{21}NO_2$: 307.1572. Found: 307.1572.

Reaction of ***12*** *with DMSO.* First fraction gave (2*S*)-1-[(*E*)-4-phenyl-3-butenoyl]tetrahydro-1*H*-2-pyrrolecarbaldehyde (**13**) (60%). Oil. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.23; H, 7.00; N, 5.78. IR (neat) 3080, 3058, 2974, 2885, 1730, 1680, 1600, 1425, 1070, 980, 760 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.03 (m, 4H), 3.45 (d, 2H, CH_2C=, *J* = 6.0 Hz), 3.87 (m, 2H, CH_2N), 4.63 (m, 1H, CHN), 6.32 (m, 2H, CH=), 7.30-7.55 (m, 5H, ArH), 9.50 (s, 1H, CHO). ^{13}C NMR: δ ($CDCl_3$) 25.10, 25.43, 40.62, 58.81, 66.10, 121.83, 127.32, 125.15, 128.60, 129.12, 137.63, 140.31, 169.5, 198.51. Exact MS calculated for $C_{15}H_{17}NO_2$: 243.1259. Found: 243.1263.

Preparation of δ-lactams

General procedure. A mixture containing 7.5 mmol of amido aldehydes, 11.5 mL (8.25 mmol) of triethylamine, and 8.5 mmol of *N*-substituted hydroxylamines in 200 mL of absolute ethanol was refluxed for 24 h. At the end of this time the solvent was evaporated under reduce pressure and the residue subjected to silica flash chromatography (MeOH/$CHCl_3$ 3: 97).

Reaction of ***7a*** *with N-methylhydroxylamine.* First eluted fraction gave (3a*R*,7*S*,7a*R*)-7-benzyl-1,6-dimethylperhydroisoxazolo[3,4-*c*]pyridin-5-one (**9a**) (85%). Oil, $[\alpha]_D^{25}$ + 28.1° (c = 1.0, $CHCl_3$). Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.15; H, 7.72; N, 10.78. IR (neat) 2925, 2830, 1650, 1485, 1060, 1050, 800, 755, 700 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.34 (dd, 1H, H_4, *J* = 1.5 and 16.4 Hz) 2.53 (dd, 1H, H_4, *J* = 7.5 and 16.4 Hz) 2.60 (s, 3H, N-CH_3) 2.76 (s, 3H, N-CH_3), 2.78 (d, 1H, H_{7a}, *J* = 11.0 Hz) 2.83 (dd, 1H, CHPh, *J* = 7.8 and 14.0 Hz), 2.98 (dd, 1H, CHPh, *J* = 7.5 and 14.0 Hz) 3.10 (dddd, 1H, H_{3a}, J = 1.5, 7.5, 8.5 and 8.5 Hz) 3.40 (dd, 1H, H_7, *J* = 7.5 and 7.8 Hz), 3.44 (dd, 1H, H_3, *J* = 8.5 and 8.5 Hz) 4.10 (dd, 1H, H_3, *J* = 8.5 and 8.5 Hz), 7.17-7.35 (m, 5H, ArH). ^{13}C NMR: δ ($CDCl_3$) 31.74, 35.59, 37.96, 38.64, 39.44, 63.46, 68.64, 71.67, 127.15, 128.94, 128.96, 129.05, 129.20, 126.03, 168.95. Exact MS calculated for $C_{15}H_{20}N_2O_2$: 260.1525. Found: 260.1526.

*Reaction of **7b** with N-methylhydroxylamine.* First eluted fraction gave (3*S*,3a*R*,7*S*,7a*R*)-7-benzyl-1,3,6-trimethylperhydroisoxazolo[3,4-*c*]pyridin-5-one (**9b**) (65%). Oil, $[\alpha]_D^{25}$ + 7.9° (c = 3.8, $CHCl_3$). Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.93; H, 8.07; N, 10.18. IR (neat) 2925, 2830, 1645, 1490, 1260, 1050, 800, 755, 700 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 1.25 (d, 3H, CH_3, *J* = 6.0 Hz), 2.28 (dd, 1 H, H_4, *J* = 4.2 and 15.0 Hz) 2.54 (m, 2H, $H_{4'}$ and H_{3a}) 2.58 (s, 3H, N-CH_3) 2.77 (s, 3H, N-CH_3), 2.82 (m, 2H, H_{7a} and CHPh) 2.95 (dd, 1H, CHPh, *J* = 7.3 and 13.0 Hz), 3.31 (dd, 1H, H_7, *J* = 5.5 and 7.3 Hz) 3.65 (dq, 1H, H_3, *J* = 6.0 and 7.2 Hz) 7.16-7.37 (m, 5H, ArH). ^{13}C NMR: δ ($CDCl_3$) 16.53, 29.64, 31.16, 35.69, 36.15, 38.35, 43.58, 46.71, 63.72, 69.64, 78.26, 127.30, 127.68, 128.96, 136.93, 169.20. Exact MS calculated for $C_{16}H_{22}N_2O_2$: 274.1681. Found: 274.1679.

*Reaction of **7c** with N-methylhydroxylamine.* First eluted fraction gave (3*R*,3a*R*,7*S*,7a*R*)-7-benzyl-1,6-dimethyl-3-phenylperhydroisoxazolo[3,4-*c*]pyridin-5-one (**9c**) (55%). Oil, $[\alpha]_D^{25}$ + 41.2° (c = 3.4, $CHCl_3$). Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 75.01; H, 7.20; N, 8.31. IR (neat) 3085, 2910, 2900, 1675, 1450, 1300, 1050, 750, 700 cm^{-1}. ^1H NMR: δ ($CDCl_3$) 2.36 (d, 1H, H_4, *J* = 10.2 Hz), 2.46 (dd, 1H, H_4, *J* = 4.5 and 10.2 Hz), 2.64 (s, 3H, N-CH_3), 2.82 (m, 1H, CHPh), 2.83 (s, 3H, N-CH_3), 2.89 (m, 1H, H_{3a}), 2.97 (dd, 1H, CHPh, *J* = 7.63 and 13.5 Hz), 2.98 (m, 1H, H_{7a}) 3.40 (dd, 1H, H_7, *J* = 3.5 and 4.5 Hz) 4.47 (d, 1H, H_3, *J* = 8.8 Hz) 7.17-7.38 (m, 10H, ArH). ^{13}C NMR: δ ($CDCl_3$), 29.61, 31.84, 37.70, 38.41, 43.63, 47.95, 63.67, 69.86, 84.63, 127.01, 127.10, 128.06, 128.59, 128.72, 128.90, 129.07, 129.29, 129.71, 130.96, 136.97, 137.09, 169.09. Exact MS calculated for $C_{21}H_{24}N_2O_2$: 336.1838. Found: 336.1839.

*Reaction of **13** with N-phenylhydroxylamine.* First eluted fraction gave (3*R*,3a*R*,9a*S*,9b*R*)-1,3-diphenyl-perhydroisoxazolo[4,3-*g*]indolizin-5-one (**15**) (51%). Oil, $[\alpha]_D^{25}$ + 8.0° (c = 0.25, $CHCl_3$). Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.58; H, 6.64; N, 8.41. ^1H NMR: δ ($CDCl_3$) 1.68 (m, 1H), 1.95 (m, 3H), 2.53 (dd, 1H, $H_{4'}$, *J* = 7.8 and 15.3 Hz), 2.54 (dd, 1H, $H_{4''}$, *J* = 9.3 and 15.3 Hz), 3.05 (dddd, 1H, H_{3a}, *J* = 7.8, 8.7, 9.3 and 9.8 Hz), 3.49 (m, 1H, $H_{7'}$), 3.63 (m, 1H, $H_{7''}$), 3.74 (dd, 1H, H_{9b}, *J* = 9.7 and 9.8 Hz), 3.90 (m, 1H, H_{9a}), 7.20-7.40 (m, 10H, ArH). ^{13}C NMR: δ ($CDCl_3$), 23.88, 27.05, 32.03, 34.60, 50.25, 55.28, 69.50, 83.75, 125.83, 126.16, 126.28, 126.37, 127.04, 128.32, 128.45, 128.49, 128.59, 137.50, 137.61, 169.51. Exact MS calculated for $C_{21}H_{22}N_2O_2$: 334.1681. Found: 334.1684.

*Reaction of **13** with N-metylhydroxylamine.* First eluted fraction gave (3*R*,3a*R*,9a*S*,9b*R*)-1-methyl-3-phenylperhydroisoxazolo[4,3-*g*]indolizin-5-one (**17**) (55.2%). Oil, $[\alpha]_D^{25}$ - 10.7° (c = 2.42, $CHCl_3$). Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.48; H, 7.40; N, 10.26. ^1H NMR: δ ($CDCl_3$) 1.95 (m, 1H), 2.01 (m, 3H), 2.50 (m, 2H, H_4), 2.86 (s, 3H, N-Me), 2.91 (m, 1H, H_{3a}), 3.21 (dd, 1H, H_{9b}, *J* = 7.5 and 11.0 Hz), 3.34 (m, 1H, H_{9a}), 3.70 (m, 2H), 4.67 (d, 1H, H_3, *J* = 7.5 Hz), 7.29-7.40 (m, 5H, ArH). ^{13}C NMR: δ ($CDCl_3$), 23.58, 27.53, 32.61, 34.56, 45.06, 50.36, 59.07, 74.95, 85.63,

125.87, 126.28, 127.04, 128.32, 128.45, 128.54, 137.35, 169.34. Exact MS calculated for $C_{16}H_{20}N_2O_2$: 272.1525. Found: 272.1524. Further eluted product was (3*S*,3a*S*,9a*S*,9b*S*)-1-methyl-3-phenylperhydroisoxazolo[4,3-*g*]indolizin-5-one (**18**) (24%). Oil, $[\alpha]_D^{25}$ - 16.0° (c = 0.37, $CHCl_3$). Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.63; H, 7.42; N, 10.31. ^{1}H NMR: δ ($CDCl_3$) 1.15 (m, 1H), 1.80 (m, 3H), 2.27 (dd, 1H, $H_{4'}$, J = 2.0 and 15.6 Hz), 2.32 (dd, 1H, $H_{4''}$, J = 5.5 and 15.6 Hz), 2.88 (s, 3H, N-Me), 2.95 (dddd, 1H, H_{3a}, J = 2.0, 5.5, 9.3 and 11.0 Hz), 3.24 (dd, 1H, H_{9b}, J = 3.5 and 11.0 Hz), 3.49 (m, 1H, H_{9a}), 3.64 (m, 2H), 4.41 (d, 1H, H_3, J = 9.5 Hz), 7.30-7.40 (m, 5H, ArH). ^{13}C NMR: δ ($CDCl_3$) 23.91, 27.03, 31.97, 34.57, 45.01, 50.11, 58.20, 69.06, 83.50, 125.87, 126.16, 127.04, 128.32, 128.59, 137.35, 169.03. Exact MS calculated for $C_{16}H_{20}N_2O_2$: 272.1525. Found: 272.1528.

Preparation of pyridinone 21

*Reaction of **9b** with methyl trifluoromethanesulfonate.* First eluted fraction gave (3*S*,3a*R*,7*S*,7a*R*)-7-benzyl-1,1,3,6-tetramethyl-5-oxoperhydroisoxazolo[3,4-*c*]pyridin-1-ium trifluoromethanesulfonate (**20**) (100%). Sticky solid. ^{1}H NMR: δ ($CDCl_3$) 1.46 (d, 3H, CH_3, J = 4.3 Hz), 2.33 (m, 1 H, $H_{4'}$) 2.61 (m, 1H, $H_{4''}$) 2.63 (s, 3H, N-CH_3) 2.95 (m, 1H, H_{3a}), 3.01 (m, 1H, $H_{7'}$), 3.30 (m, 1H, $H_{7''}$), 3.49 (s, 3H, N-CH_3), 3.55 (s, 3H, N-CH_3), 4.21 (m, 1H, H_3), 4.95 (m, 1H, H_{7a}), 7.27-7.30 (m, 5H, ArH). ^{13}C NMR: δ ($CDCl_3$) 14.60, 28.74, 33.90, 37.25, 43.32, 48.50, 56.50, 57.51, 76.09, 81.76, 126.41, 127.85, 128.27, 133.53, 166.67.

*Reduction of **20**.* Further eluted product was (4*R*,5*R*,6*S*)-6-benzyl-5-dimethylamino-4-[(1*S*)-1-hydroxyethyl]-1-methylhexahydro-2-pyridinone (**21**) (95%). Oil, $[\alpha]_D^{25}$ + 10.0° (c = 1.39, $CHCl_3$). Anal. Calcd for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.53; H, 9.00; N, 9.68. ^{1}H NMR: δ ($CDCl_3$) 1.24 (d, 3H, J = 6.3 Hz), 2.05 (dddd, 1H, H_4, J = 2.4, 4.6, 7.5 and 12.6 Hz), 2.09 (s, 6H, N-CH_3), 2.48 (dd, 1H, H_3, J = 7.5 and 19.5 Hz), 2.56 (dd, 1H, H_6, J = 3.9 and 4.3 Hz), 2.60 (br s, 1H, OH), 2.82 (dd, 1H, H_3, J = 12.6 and 19.5 Hz), 3.49 (m, 1H, H_{9a}), 3.00 (d, 1H, H_5, J = 4.6 Hz), 3.09 (s, 3H, N-CH_3), 3.16 (dd, 1H, $H_{6'}$, J = 4.3 and 13.5 Hz), 3.54 (dd, 1H, $H_{6''}$, J = 3.9 and 13.5 Hz), 3.80 (dq, 1H, $H_{4'}$, J = 2.4 and 6.3 Hz), 7.15-7.39 (m, 5H, ArH). ^{13}C NMR: δ ($CDCl_3$) 22.07, 32.27, 33.45, 36.58, 39.40, 42.93, 56.67, 58.70, 69.64, 127.09, 128.74, 137.16, 169.67. Exact MS calculated for $C_{17}H_{26}N_2O_2$: 290.1994. Found: 290.1992.

ACKNOWLEDGEMENTS

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

REFERENCES

1. T. Hudlicky, *Chem. Rev.*, 1996, **96**, 3.
2. R. Annunziata, M. Cinquini, F. Cozzi, and L. Raimondi, *Gazz. Chim. Ital.*, 1989, **119**, 253. A. Padwa and A.M. Schoffstall, "Advances in Cycloaddition," Vol. 2, ed. by D. P. Curran, JAI Press, Inc., Greenwich, 1990, pp. 2-28. A. Padwa, "Comprehensive Organic Synthesis," Vol. 4, ed. by V. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, p. 1111.
3. U. Chiacchio, A. Rescifina, and G. Romeo, "Targets in Heterocyclic Systems: Chemistry and Properties," Vol. 1, ed. by O. A. Attanasi and D. Spinelli, Società Chimica Italiana, Roma, 1997, p. 225. U. Chiacchio, F. Casuscelli, A. Corsaro, A. Rescifina, G. Romeo, and N. Uccella, *Tetrahedron*, 1994, **50**, 6671. R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, and L. Raimondi, *J. Org. Chem.*, 1995, **60**, 4697. J. J. Tufariello, "1,3-Dipolar Cycloaddition Chemistry," Vol. 2, Chapter 9, ed. by A. Padwa, John Wiley & Sons, New York, 1984, p. 83.
4. G. L'abbé, S. Emmers, W. Dehaen, and L. K. Dyall, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2553.
5. H. G. Aurich, M. Boutahar, H. Köster, K. D.; Möbus, and L. Ruits, *Chem. Ber.*, 1990, **123**, 1999. P. Bandiera, P. Bravo, L. Bruché, M. Zanda, and A. Arnone, *Gazz. Chim. Ital.*, 1996, **126**, 773. H. G. Aurich and F. Biesemeier, *Synthesis*, 1995, 1171.
6. M. Frederickson, *Tetrahedron*, 1997, **53**, 403.
7. U. Chiacchio, G. Buemi, F. Casuscelli, A. Procopio, A. Rescifina, and R. Romeo, *Tetrahedron*, 1994, **50**, 5503. U. Chiacchio, F. Casuscelli, A. Corsaro, V. Librando, A. Rescifina, R. Romeo, and G. Romeo, *Tetrahedron*, 1995, **51**, 5689. U. Chiacchio, F. Casuscelli, A. Corsaro, A. Rescifina, G. Romeo, and N. Uccella, *Tetrahedron*, 1994, **50**, 6671. U. Chiacchio, G. Romeo, and N. Uccella, "Trends in Heterocyclic Chemistry" 1995, Vol. 4, p. 261.
8. U. Chiacchio, A. Rescifina, F. Casuscelli, A. Piperno, V. Pisani, and R. Romeo, *Tetrahedron*, 1996, **52**, 14311.
9. D. H. Williams and I. Fleming, "Spectroscopic Methods in Organic Chemistry, 4th ed.", McGraw-Hill; London; 1987, p. 143.
10. A. Hassner, R. Maurya, A. Padwa, and W. H. Bullock, *J. Org. Chem.*, 1991, **56**, 2775.

Received, 23rd July, 1998