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LACTAM & AMIDE ACETALS XXI. USE OF PYROGLUTAMIC ACID AND PROLINE IN CHIRAL SYNTHESIS OF CONFORMATIONALLY CONSTRAINED PIPERAZINONES

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ABSTRACT: *Making use of amide activation chiral synthesis of (+)-(1S,5R)- and (-)-(1R,5S)-3,8-diazabicyclo[3.2.1]octan-2-ones (1 and 2) has been achieved from L- and D-pyroglutamates, and of (-)-(2R,6S)-, (-)-(2S,6S)-, (+)-(2S,6R)- and (+)-(2R,6R)-2-methyl-1,4-diazabicyclo[4.3.0]nonan-5-ones (3a, 3b, 4a and 4b) from L & D-proline methyl esters respectively. The key step of the synthesis involves a stereo-selective catalytic hydrogenation, accompanied with spontaneous cyclisation, of the nitroenamines 11, 14, 17 and 19. While this reaction was stereospecific in the case of pyro-Glu derived nitroenamines (11 and 14), with N-acetyl-proline derived nitroenamines (17 and 19) both 2R and 2S diastereoisomers were obtained with 40% d.e. of the diastereomer with 2-CH_3 oriented cis to the 6-H. The piperazinones 1 and 2 on treatment with methanolic HCl at room temperature yielded the corresponding optically pure 5-aminomethylprolines 12 and 15 respectively.*

Suitably activated lactams and amides possess great synthetic utility for construction of nitrogen heterocycles. Among the activated lactams, lactam acetals are particularly useful as these react with both nucleophiles and electrophiles at C_1 and C_2 respectively, and thus also with bifunctional reagents to form annulated products[1]. What is of special significance is that the reactions take place under very mild conditions and without the addition of external base which makes these reactions specially suitable for substrates having sensitive substituents and centers prone to epimerisation[1,2]. In our continuing studies on the synthetic utility of lactam and amide acetals it was considered of interest to explore the application of lactams derived from α-amino acids for the chiral syntheses of conformationally restricted piperazines. Piperazine structure is a common pharmacophore in a number of biologically active compounds acting on the CNS[3,4], CVS[5,6] and as anthelmintics[7,8]. Although a variety of heterocyclic systems incorporating the piperazine moiety have been synthesized both in our laboratory[4,8,9] and elsewhere[10-12], little attention has been paid to the asymmetric synthesis of bicyclo-piperazines possessing constrained conformations, which would help to define the

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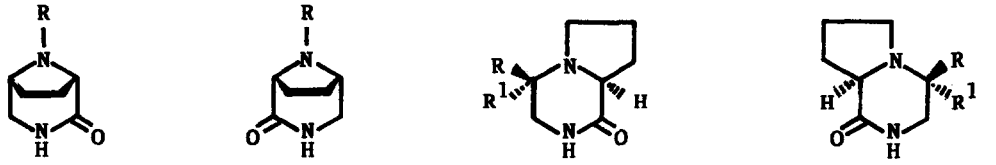
Dedicated to Prof.Gabor Fodor for his 75th birthday.

spatial coordinates of piperazines for different biological activities. This paper describes chiral syntheses of semirigid piperazinones 1 and 2 from L- and D-pyroglutamates and of 3a,3b,4a and 4b from N-acetyl L- and D-proline methyl esters (Fig.1).

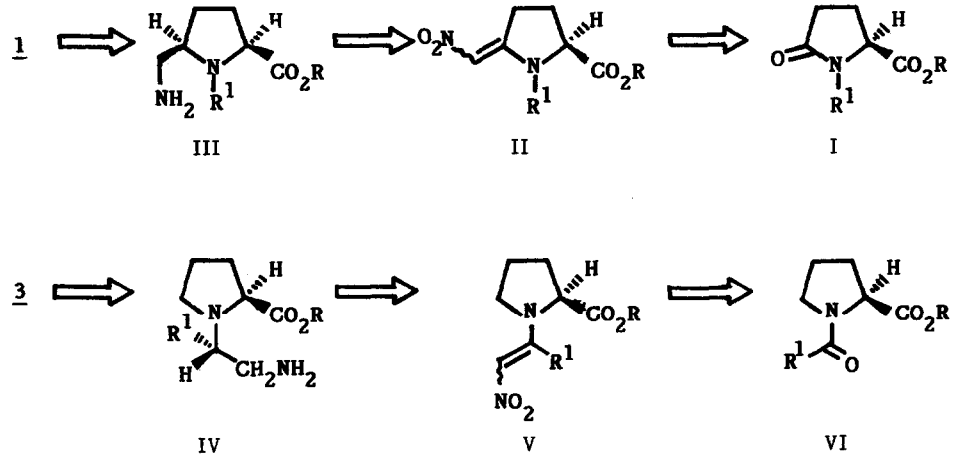


1a, R=H 2a, R=H 3a, R=H, R^1=Me 4a, R=H, R^1=Me

1b, R=Bn 2b, R=Bn 3b, R=Me, R^1=H 4b, R=Me, R^1=H

FIGURE - 1

A retrosynthetic analysis of these structures (Scheme 1) indicated the possibility of constructing the piperazine ring through stereocontrolled reduction of enantiomerically pure nitroenamines of type II & V, which could in turn be generated from pyroglutamates I and N-acylproline esters VI respectively, by selective activation of the amide function followed by condensation with nitromethane under conditions which would not affect the stereochemistry at C-2.



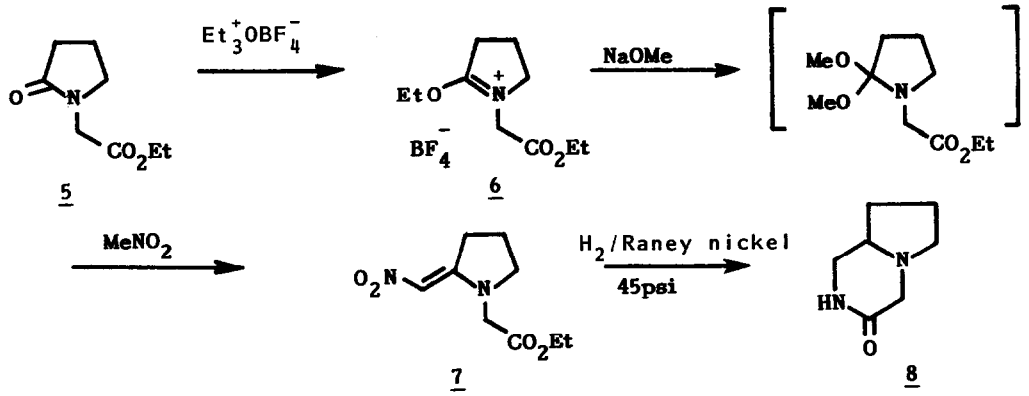
III II I

IV V VI

SCHEME - 1

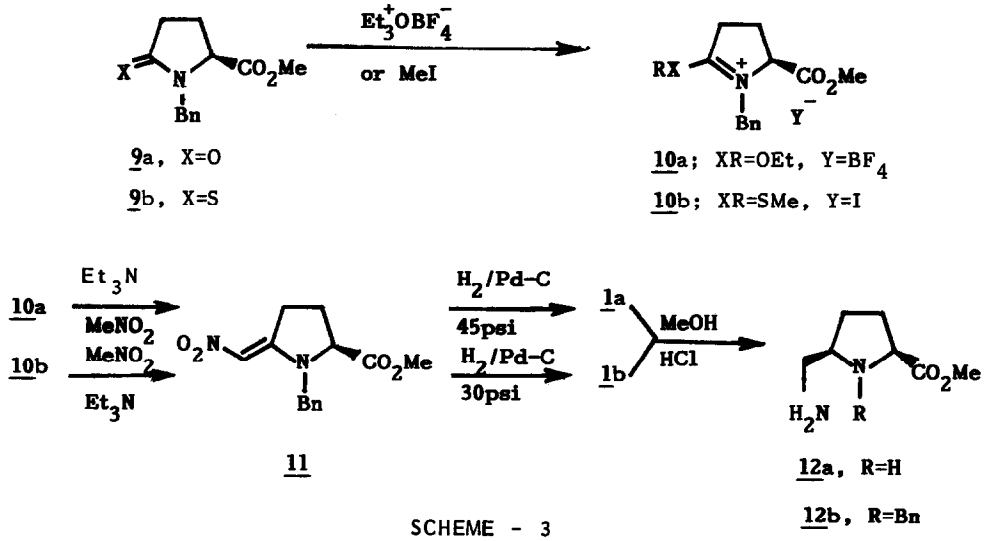
With a view to establish the feasibility of this approach 1,4-diazabicyclo[4.3.0]nonan-3-one 8 was first synthesised as a model compound. N-Ethoxycarbonylmethyl-2-pyrrolidone on treatment with Meerwein

reagent[13] followed by treatment with NaOMe of the adduct thus formed gave the corresponding lactam acetal, which without isolation was condensed with nitromethane to yield the nitroenamine 7 in 60% overall yield. 7 underwent ready reduction accompanied with by spontaneous cyclisation when hydrogenated over Raney nickel at 45 psi to furnish 8. The piperazinone 8 had been synthesized earlier by Schmidt reaction on 1-azabicyclo [3.3.0]octan-3-one[14] (Scheme 2).



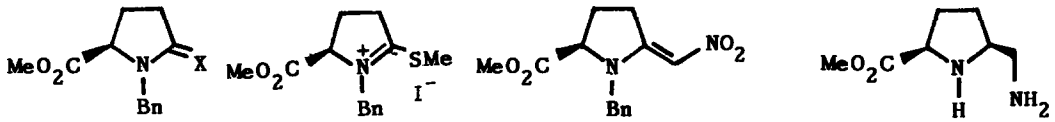
SCHEME - 2

With the feasibility of the approach established, studies with L- and D-pyroglutamates were initiated. The required methyl L-pyroglutamate 9a and thiopyroglutamate 9b were prepared from L-glutamic acid essentially as described in literature[15] with some modification of the experimental conditions to improve the yields as described in the experimental section. The pyroglutamate 9a was converted to ethoxyimonium salt 10a with Meerwein reagent, which on condensation with nitromethane in presence of triethylamine (TEA) yielded the nitroenamine 11 in 40% yield. Alternatively the thiolactam 9b yielded thiomethylimonium iodide 10b with excess MeI in 98% yield, which on condensation with nitromethane in DMF and excess TEA afforded 11in 56% yield. The nitroenamine 11 appeared to be thermodynamically stable as the E-isomer as shown by NMR studies; irradiation of the olefinic proton resulted in 9% NOE enhancement for the benzylic protons. Reduction and cyclization of nitroenamine 11 to bicyclopiperazine-2-one 1a was readily realized with a powerful 1,3-asymmetric induction under Pd-C hydrogenation at 45 psi for 24 h; 1a was obtained as a single product in 91% yield. Interestingly, when the hydrogenation was carried out at 30 psi N-benzyl-bicyclopiperazine-2-one 1b was obtained selectively in 81% yield. Following a similar sequence of reactions, methyl D-pyroglutamate 13a was converted to (1R, 5S)-bicyclopiperazine-2-one 2a and its N-benzylated derivative 2b. This



SCHEME - 3

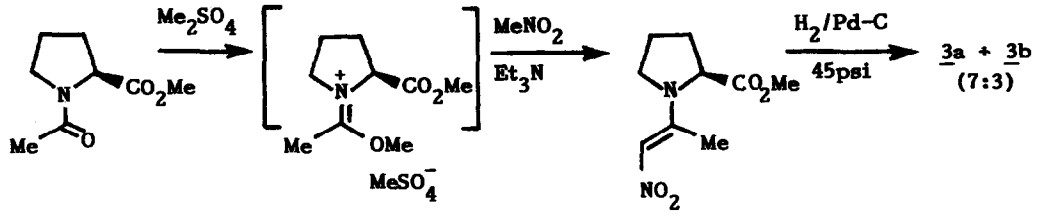
ring system had been synthesised earlier[10-12] but without any consideration to chirality. The piperazinones 1 and 2 on treatment with methanolic HCl at room temperature yielded (2S,5R)- and (2R,5S)-5-aminomethylproline methyl esters (12 and 15) respectively. This provides a useful approach to obtain chiral 5-cis-substituted prolines and thus to 2,5-cis-substituted pyrrolidines (Scheme 3).



13a, X=O
13b, X=S
13c
14
15

FIGURE - 2

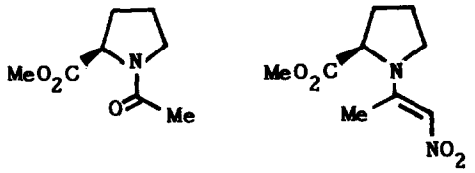
In a similar set of reactions methyl L- & D-N-acetylproline methyl esters on reaction with dimethyl sulfate gave the corresponding imonium methosulfates, which without isolation were condensed with nitromethane to provide the nitroenamines 17 and 19 respectively. These nitroenamines were found to be rather unstable and deteriorated even on column chromatography. So without much manipulation the nitroenamines were subjected to catalytic hydrogenation over 10% Pd-C at 45 psi to yield 2-methyl-1,4-diazabicyclo[4.3.0]nonan-5-ones, obtained as a mixture of diastereomers in 7:3 ratio [40% de.] as determined by tlc scanning or by integration of the 2-methyl signals in the NMR of the mixture. The structural



16 17

SCHEME - 4

assignments were made by COSY NMR while the 2-Me stereochemistry was decided on the basis of NOE between the 2-CH_3 and 6-H as discussed below; the major isomer 3a and 4a had the 2-CH_3 and 6-H cis-oriented (2R,6S or 2S,6R).



18 19

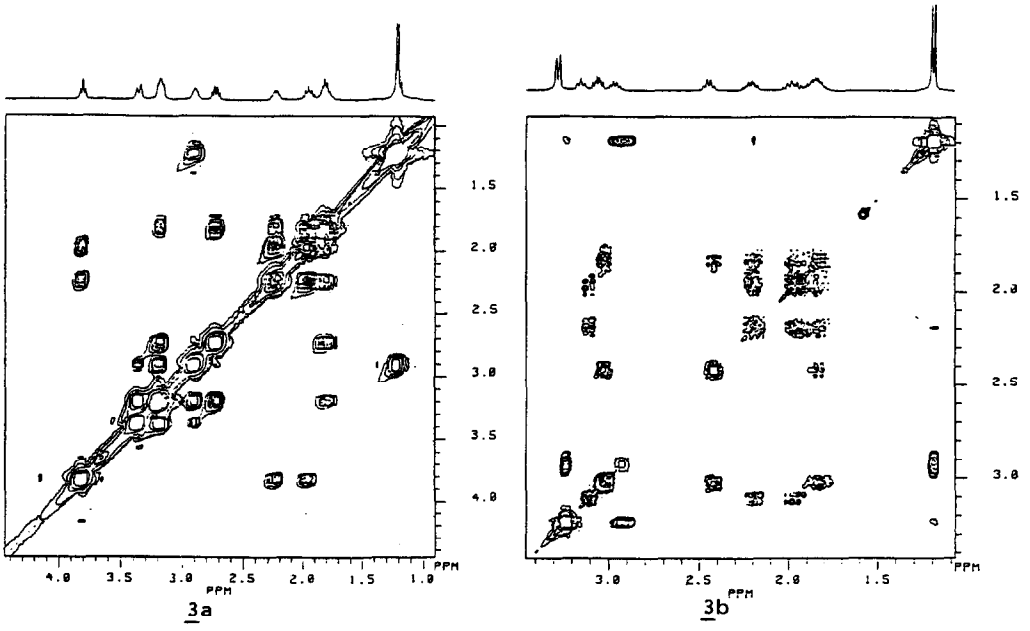
FIGURE - 3

NMR Assignments: For assigning the stereostructures to the products ^{1}H NMR spectra at 400 MHz were recorded. The spectra of 1 and 2 and of all the intermediates therein, had the expected well resolved signals, and unambiguous assignments of all the protons could be made by decoupling experiments; the spectral data are described in the experimental section. The ^{1}H NMR spectra of compounds 3a and 3b (and of 4a and 4b) (Table 1), however, showed some overlaping and upfield shifting of α-CH signals, and assignment by first order analysis proved difficult. Therefore, for unambiguous assignment of the signals, 2D COSY spectra of 3a,3b,4a and 4b in $CDCl_3$ were analysed; the COSY spectra of 3a and 3b are described as a contour plot in Fig.4 underneath the one dimensional spectra. The most downfield signal at δ3.77 in the spectrum of 3a is attributed to H-6 (C_α-H of proline moiety), which showed two cross peaks at δ 2.25 and 1.99 assigned to H-7 and H-7' protons. Similar connectivities could be traced as an unbroken sequence till H-9 and H-9' respectively. The assignment of the signals for secondary CH_3 and its relayed connectivities was straightforward from the 2D spectrum. The ^{1}H NMR spectrum of 3b showed considerable difference from that of 3a particularly in the chemical shift of H_2-3 and H-6 protons; the signals for the

TABLE 1: ^{1}H NMR Chemical Shifts, Coupling Constants for 3a and 3b

	3a		3b	
Protons	δ_H ($CDCl_3$)	J(H,H) (Hz)	δ_H ($CDCl_3$)	J(H,H) (Hz)
C-C<u>H</u>$_3$	1.22	d; 7.0	1.19	d; 7.0
N-<u>H</u>	6.70	brs	6.30	brs
2	2.90	ddd; 7.0,8.0,4.0	2.92	ddd; 7.0
3	3.42	ddd; 4.0,13.2,4.0	3.29	brs
3'	3.20	ddd[e];8.0,13.2,4.0	3.25	brs
6	3.77	dd; 7.8,6.2	3.10	dd;8.0,9.0
7	2.25	m	2.19	m
7'	1.99	m	1.96	m
8	1.84	m[e]	1.83	m[e]
9	3.13	m[e]	3.02	ddd;5.0,8.0, 10.0
9'	2.74	ddd;6.2,8.6,11.0	2.41	ddd;6.2,8.6, 11.0

e; overlapped with the other signals.



2D COSY Spectra of 3a and 3b

FIGURE-4

latter were shifted considerably upfield. In the case of 3b it was found more useful to first assign the $C\underline{H}_3$ signals and its connectivities, and then identify those of the proline moiety. The H_2-3 signals indicate a complex coupled spin system, tending towards magnetic equivalence. Since the molecule is rigid, the relative orientation of the $C\underline{H}_3$ appears to be playing an important role in the above phenomenon. To determine the orientation of the CH_3 group the NOE difference spectra were studied; in 3a H-6 showed NOE with H-7 and the 2-$C\underline{H}_3$ only indicating that these protons are in the same plane. In 3b no NOE was observed between H-6 and 2-$C\underline{H}_3$. It was therefore concluded that in 3a the 6-H and 2-CH_3 are relatively *cis* to each other, whereas in 3b these are *trans* oriented.

The spectra of 4a and 4b as expected were superimposable with those of their counterparts 3a, 3b with similar NOE effects, thus indicating that 4a and 4b are enantiomers of 3a and 3b respectively.

EXPERIMENTAL

Melting points were taken in an electrically heated instrument and are uncorrected. Compounds were routinely checked for their purity on silica gel-G TLC plates and their spots were visualized by exposing them to iodine vapour, by spraying with Dragendorff and $KMnO_4$ reagents. IR spectra (λ max in cm^{-1}) were recorded either on Perkin-Elmer 157 or Acculab-1 models and ^1H NMR spectra were recorded on Bruker WM-400 MHz instruments using TMS as internal reference and chemical shifts are in δ units. Mass spectra were run on Jeol JMS D300 instrument using direct inlet system. Optical rotations were taken on Perkin-Elmer 241 Polarimeter.

1-Ethoxycarbonylmethyl-2-pyrrolidone (5)

A solution of 2-pyrrolidone (17 g, 0.2 mol) in anhydrous benzene (60 ml) was added to a suspension of sodium hydride (0.22 mol, prewashed with anhydrous benzene) in anhydrous benzene (200 ml) and the reaction mixture was refluxed for 16 hr. It was cooled, a solution of ethyl bromoacetate (33.4 g, 0.2 mol) in anhydrous benzene (100 ml) was added and the mixture refluxed for another 6 hr. The reaction mixture was filtered. The filtrate thus obtained was washed with water and concentrated to give 5 as an oil, which was distilled under reduced pressure; yield 21.5 g, (63%), bp 125°/10 mm. IR(Neat): 2900, 1730, 1680, 1435, 1280, 1200, 1160, 1025, 760. ^1H NMR(CCl_4): 1.25 (t, 3H, C-$C\underline{H}_3$), 1.88-2.40 (m, 4H, 3-$C\underline{H}_2$ and 4-$C\underline{H}_2$), 3.38 (t, 2H, 5-$C\underline{H}_2$), 3.88 (s, 2H, N-$C\underline{H}_2CO$) and 4.19 (q, 2H, O-$C\underline{H}_2$). MS m/z: 171 (M^+). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.14; H, 7.60; N, 8.19. Found: C, 55.84; H, 7.72; N, 8.43.

1-Ethoxycarbonylmethyl-2-nitromethylenepyrrolidine (7)

A solution of 5 (1.71 g, 0.01 mol) in dry methylene chloride (5 ml) was added to a solution of triethyloxonium tetrafluoroborate (2.28 g, 0.012 mol) in dry methylene chloride (5 ml) and the reaction mixture was stirred for 6 hr. Methylene chloride was removed under reduced pressure, the residue taken up in methanol (5 ml), cooled to 0°C, sodium methoxide solution (prepared from 0.28 g, 0.012 g atom, of sodium) was added and the solution stirred for 3 hr. Nitromethane (0.67 g, 0.011 mol) was added to the reaction mixture and refluxed for 2 hr. Methanol was distilled off and the residue taken up in methylene chloride and filtered. The filtrate was concentrated to give an oil which was chromatographed on silica column. Elution with ethyl acetate-hexane (50:50) gave the compound 7, which was crystallized from methylene chloride; yield 1.0 g (47%), m.p.105°. IR(KBr): 2960, 1745, 1580, 1360, 1235, 1200, 1080, 775, 740, 720. ^{1}H NMR($CDCl_3$): 1.23 (t, 3H, C-CH_3), 2.05 (quint., 2H, 4-CH_2), 3.40 (t, 2H, 3-CH_2), 3.58 (t, 2H, 5-CH_2), 3.89 (s, 2H, NCH_2CO), 4.14 (q, 2H, O-CH_2) and 6.49 (s, 1H, olefinic H). MS m/z: 214 (M^+). Anal. Calcd. for $C_9H_{14}N_2O_4$: C, 50.45; H, 6.58; N, 13.08. Found: C, 50.32; H, 6.67; N, 13.21.

1,4-Diazabicyclo[4.3.0]nonan-3-one (8)

The nitroenamine 7 (250 mg) in anhydrous ethanol (20 ml) was hydrogenated in presence of Raney nickel catalyst at 45 psi hydrogen pressure for 4 hr. The catalyst was filtered off and the filtrate on concentration furnished 8, which was crystallised from ethyl acetate; yield 120 mg (73%), mp 118° (lit.[14] 120-121.5°). IR(KBr): 3350, 3130, 2900, 1660, 1485, 1100, 805. MS m/z: 140 (M^+). Anal. Calcd for $C_7H_{12}N_2O$: C, 59.96; H, 8.63; N, 19.98. Found: C, 60.15; H, 8.48; N, 19.80.

(S)-(+)-1-Benzyl-5-oxoproline methyl ester (9a)

A solution of L-1-benzylpyroglutamic acid (43.8 g, 0.20 mol) and a few drops of concentrated sulphuric acid in 300 ml of absolute methanol was refluxed for 10 hr. The solution was cooled to room temperature and methanol removed under reduced pressure. The residue was dissolved in ethyl acetate (500 ml), washed with saturated aqueous $NaHCO_3$ solution (3x50 ml), water (2x50 ml) and then with saturated NaCl solution (2x50 ml). The ethyl acetate layer was dried over Na_2SO_4 and concentrated to give 9a as a colourless thick oil; yield 45.90 g (98%). $[\alpha]_D^{25}$ +2.85 (c 1.75, MeOH).

(R)-(-)-1-Benzyl-5-oxoproline methyl ester (13a)

This was prepared in a similar manner from D-1-benzylpyroglutamic acid, yield 98%; $[\alpha]_D^{25}$ -3.03 (c 1.3, MeOH).

(S)-(+)-1-Benzyl-5-thioxoproline methyl ester (9b)

To a solution of 9a (44.0 g, 0.190 mol) in anhydrous THF (400 ml) Lawesson's reagent[16] (38.15 g, 0.095 mol) was added under vigorous stirring. After 30 min THF was evaporated and the residue was taken up in ethyl acetate (600 ml), washed successively with saturated $NaHCO_3$ solution (3x150 ml), saturated aqueous NaCl solution (2x100 ml) and the aqueous phase back extracted with ethyl acetate (2x50 ml). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated to give a light yellow coloured crystalline product which was recrystallized from $CHCl_3$:Hexane giving the thiolactam 9b. Yield 45.0 g (96%), mp 62°, $[\alpha]_D^{25}$ +152.5 (c 0.8, MeOH).

(R)-(-)-1-Benzyl-5-thioxoproline methyl ester (13b)

This was prepared in a similar manner from methyl D-1-benzylpyroglutamate (13a); mp 49°, yield 93%, $[\alpha]_D^{25}$ -150.6 (c 0.7, MeOH).

(S)-(+)-1-Benzyl-2-ethoxy-5-methoxycarbonyl-1-pyrrolinium fluoroborate(10a)

9a (5.12 g, 0.022 mol) in anhydrous CH_2Cl_2 (10 ml) was added dropwise to a stirred solution of Meerwein reagent (triethyloxonium tetrafluoroborate) (4.59 g, 0.024 mol) in anhydrous dichloromethane (20 ml) kept under nitrogen atmosphere. Stirring was continued for 6 hr, CH_2Cl_2 removed in vacuo and the residue dried under reduced pressure over P_2O_5 to yield 10a as a thick colourless oil, yield 6.8 g (89%).

(S)-(+)-1-Benzyl-2-thiomethoxy-5-methoxycarbonyl-1-pyrrolinium iodide(10b)

A solution of the thiolactam 9b (76.0 g, 0.30 mol) and methyl iodide (216.5 g, 1.50 mol) was stirred at room temperature for 2 hr, the formation of a yellow precipitate indicates the formation of the thiomethyl imonium iodide. The excess of methyl iodide was removed under reduced pressure, the residue taken up in dry benzene, stirred for 10 min, the solid which separated was filtered, washed well with dry benzene and dry ether and dried under vacuum over P_2O_5 to give 10b as yellow solid; yield 118 g (98%), mp 157°.

(R)-(-)-1-Benzyl-2-thiomethoxy-5-methoxycarbonyl-1-pyrrolinium iodide(13c)

This was prepared in a similar manner from 13b, yield 97%, mp 125°.

(S)-(+)-1-Benzyl-5-nitromethyleneproline methyl ester (11)

Method A: To a stirred solution of 10a (6.96 g, 0.020 mol) in 50 ml of anhydrous dichloromethane, dry Et_3N (2.22 g, 0.022 mol) was added under nitrogen atmosphere. After 10 min dry nitromethane (6.1 g, 0.10 mol) was added and the reaction mixture was stirred for 24 hr at room temp-

erature. The excess of nitromethane and CH_2Cl_2 were removed in vacuo and the residue dissolved in chloroform (100 ml). The organic phase was washed successively with 10% aqueous HCl solution (2x10 ml), water (2x10 ml), saturated aqueous NaCl solution (3x10 ml), dried (anhydrous Na_2SO_4) and concentrated to give 11 which was purified by silica gel column chromatography using $CHCl_3$/MeOH (99/1) to give the nitroenamine 11 as yellow coloured crystalline solid, yield 2.22 g (40%), mp 101-102°.

Method B: To a stirred solution of 10b (7.82 g, 0.020 mol) in dry DMF (50 ml), dry Et_3N (2.22 g, 0.022 mol) and anhydrous nitromethane (6.1 g, 0.100 mol) were added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 12 hr. DMF and excess of nitromethane were removed under reduced pressure (bath temperature 80°C) and the residue was purified by silica gel column chromatography using $CHCl_3$/MeOH as eluent. On evaporation of the solvent a thick dark red coloured residue was left which on trituration with $CHCl_3$:ether gave yellow coloured crystals of 11, yield 3.10 g (56%), mp 101°. IR(KBr): 1738, 1580, 1320. ^1H NMR($CDCl_3$): 2.16-2.38 (m, 3H, 4-C$\underline{H}_2$ & 3-C$\underline{H}$), 3.32-3.46 (m, 1H, 3-C$\underline{H}$), 3.75 (s, 3H, -$CO_2C\underline{H}_3$), 4.26 (dd, 1H, J=9.0 & 4.0 Hz, 2-C$\underline{H}$), 4.30 & 4.50 (d, 1H, J=16.0 Hz, Benzylic-$\underline{H}$), 6.80 (s, 1H, olefinic-$\underline{H}$), 7.0-7.35 (m, 5H, Ar-$\underline{H}$). MS m/z: 276 (M^+). $[\alpha]_D^{25}$ +176.4 (c 1, MeOH). Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.85; H, 5.83; N, 10.14. Found: C, 60.87; H, 5.56; N, 10.01.

(R)-(-)-1-Benzyl-5-nitromethyleneproline methyl ester (14)

This was prepared in a similar manner from the corresponding (R)-2-thiomethoxypyrrolinium iodide: mp 103°, yield 52%. $[\alpha]_D^{25}$ -171.4 (c 1.0, MeOH). Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.85; H, 5.83; N, 10.14. Found: C, 61.01; H, 5.99; N, 10.47.

(1S,5R)-(+)-3,8-Diazabicyclo[3.2.1]octan-2-one (1a)

To a solution of 11 (500 mg, 0.0018 mol) in absolute methanol (10 ml), 10% Pd-C (500 mg) was added and the solution hydrogenated (45 psi of H_2) for 24 hr. The catalyst was removed by filtration and evaporation of the filtrate left a residue which on trituration with ether gave 1a as a light yellow coloured solid; yield 210 mg (91%), mp 185°. IR(KBr): 1650. ^1H NMR($CDCl_3$): 1.75 (m, 1H, 4-C$\underline{H}$), 2.05 (m, 3H, 4-C$\underline{H}$ & 5-C$\underline{H}_2$), 2.45 (bs, 1H, -N$\underline{H}$), 3.00 (dd, 1H, J=2.0 Hz & 9.0 Hz, 6-C$\underline{H}$), 3.48 (dd, 1H, J=4.0 Hz & 9.0 Hz, 3-C$\underline{H}$), 3.74 (m, 2H, 7-C$\underline{H}_2$), 6.35 (s, 1H, -N$\underline{H}$). MS m/z: 126 (M^+). $[\alpha]_D^{25}$ +26.6 (c 1, MeOH). Anal. Calcd for $C_6H_{10}N_2O$: C, 57.11; H, 7.98; N, 22.20. Found: C, 56.85; H, 7.69; N, 22.13.

(1R,5S)-(-)-3,8-Diazabicyclo[3.2.1]octan-2-one (2a)

This was prepared in a similar manner from 14; yield 90%, mp 191°, $[\alpha]_D^{25}$ -24.1 (c 1, MeOH).

(1S,5R)-(+)-8-Benzyl-3,8-diazabicyclo[3.2.1]octan-2-one (1b)

The above hydrogenation was carried out under 30 psi of hydrogen for 24 hr. The catalyst was removed by filtration. Evaporation of the filtrate left a residue which on trituration with hexane gave 1b yield 320 mg (80%), mp 113°. IR(KBr): 1655. ^{1}H NMR($CDCl_3$): 1.75 (m, 1H), 2.05 (m, 3H), 2.90 (d, 1H, J=10 Hz), 3.36-3.44 (m, 1H), 3.48-3.52 (m, 1H), 3.67 (dd, J=4.0 Hz, 10.0 Hz, 1H), 3.78 (s, 2H), 5.40 (bsr, NH), 7.26-7.40 (m, 5H). MS m/z: 216 (M^+). $[\alpha]_D^{25}$ +10.8 (c 1, MeOH).

(1R,5S)-(-)-8-Benzyl-3,8-diazabicyclo[3.2.1]octan-2-one (2b)

This was prepared from 14 by hydrogenation at 30 psi hydrogen pressure; yield 82%, mp 109°. $[\alpha]_D^{25}$ -9.6 (c 1, MeOH). Anal.Calcd for $C_{13}H_{16}N_2O$: C, 72.18; H, 7.45; N, 12.95. Found: C, 72.11; H, 7.56; N, 13.01.

(2S,5R)-(-)-5-Aminomethylproline methyl ester hydrochloride (12a)

A solution of 1a (100 mg) in 2N methanolic HCl (5.0 ml) was stirred at room temperature for 1 hr. Excess of methanol and HCl was removed in vacuo, the residue was dissolved in minimum amount of dry methanol, dry ether added under stirring, when a colourless crystaline solid separated out. The product was filtered, washed with ether and dried over P_2O_5 and KOH in desicator for 3 hr to give 12a, yield 175 mg (95%), mp 205°. IR(KBr): 1760. ^{1}H NMR(DMSO-d_6): 1.82 & 2.12 (m, 2H, 4-C$\underline{H}_2$), 2.12 & 2.25 (m, 2H, 3-C$\underline{H}_2$), 3.14 & 3.28 (m, 2H, 6-C$\underline{H}_2$), 3.74 (s, 3H,-OC$\underline{H}_3$), 3.84 (m, 1H, 5-C$\underline{H}$), 4.49 (m, 1H, 2-C$\underline{H}$), 8.58 (brs, 2H, -N$\underline{H}_2$), 10.05 (brs, 1H, N$\underline{H}$). MS m/z: 158 (M^+) (at 50 eV) and 128 $(M-30)^+$. $[\alpha]_D^{25}$ -24.5 (c 1, MeOH). Anal. Calcd for $C_7H_{14}N_2O_2.HCl.2H_2O$: C, 36.44; H, 8.30; N, 12.14. Found: C, 36.33; H, 8.22; N, 12.26.

(2R,5S)-(+)-5-Aminomethylproline methyl ester hydrochloride (15)

This was obtained by treatment of 2a with methanolic HCl as described above for 12a; mp 185°. IR(KBr): 1760. MS m/z: 158 (M^+)(at 50 eV) and 128 $(M-30)^+$. $[\alpha]_D^{25}$ +23.7 (c 1, MeOH). Anal. Calcd for $C_7H_{14}N_2O_2.HCl.2H_2O$: C, 36.44; H, 8.30; N, 12.14. Found: C, 36.66; H, 8.50; N, 12.01.

(2S,5R)-(-)-1-Benzyl-5-aminomethylproline methyl ester hydrochloride(12b)

This was prepared under similar conditions described above from 1b, yield 240 mg (91%), mp 181°. IR(KBr): 1760. MS m/z: 248 $(M)^+$ (at 50 eV)

and 218 $(M-30)^+$. $[\alpha]_D^{25}$ -18.26 (c 1, MeOH).

(2R,6S)-(-)- and (2S,6S)-(-)-2-Methyl-1,4-diazabicyclo[4.3.0]nonan-5-ones (3a and 3b)

A mixture of L-N-acetylproline methyl ester[17] (1.71 g, 0.010 mol) and dimethyl sulphate (1.26 g, 0.010 mol) was heated under stirring at 80°C for 3 hr. The mixture was cooled to room temperature, dry $CHCl_3$ (10 ml) added followed by Et_3N (1.11 g, 0.011 mol) and nitromethane (6.1 g, 0.100 mol), and the reaction mixture was stirred at room temperature for 12 hr. The excess of nitromethane, Et_3N and chloroform were removed in vacuo and the residue was dissolved in minimum amount of water and extracted with ethyl acetate (3x50 ml). The combined organic phase was washed with saturated aqueous NaCl solution, dried over Na_2SO_4 and concentrated to dryness to give the nitroenamine 17 (1.13 g) as an oil. The solution of nitroenamine 17 (1.13 g) in 50 ml of absolute methanol was degassed (N_2), 10% Pd-C (600 mg) added and the mixture hydrogenated (45 psi, H_2) for 12 hr. The catalyst was removed by filtration and evaporation of the filtrate gave 3 (0.83 g; 54%). TLC showed it to be a mixture of two main products, one with a lower mobility designated 3a, and the other 3b. Their ratio was determined by scanning the iodine vapour exposed TLC plates or by integration of the 2-CH_3 signals in 400 MHz NMR spectra, and found to be 7:3 (40% d.e.). The products were separated in quantity by flash silica gel column chromatography using $CHCl_3$:MeOH (95:5) as eluant. 3a yield 580 mg (37%), low melting; $[\alpha]_D^{25}$-17 (c 1, MeOH). IR(KBr): 1680. MS m/z: 154 (M^+). TLC($CHCl_3$:MeOH, 9:1) Rf 0.41. Anal. Calcd for $C_8H_{14}N_2O$: C, 62.30; H, 9.14; N, 18.17. Found: C, 61.81; H, 8.71; N, 18.46.

3b: yield 252 mg (16%), mp 105°. $[\alpha]_D^{25}$ -34 (c 1, MeOH). IR(KBr): 1680. MS m/z: 154 (M^+). TLC($CHCl_3$:MeOH, 9:1) Rf 0.50. Anal. Calcd for $C_8H_{14}N_2O$: C, 62.30; H, 9.14; N, 18.17. Found: C, 62.45; H, 8.84; N, 18.04.

(2S,6R)-(+) and (2R,6R)-(+)-2-Methyl-1,4-diazabicyclo[4.3.0]nonan-5-ones (4a and 4b)

These were obtained in a similar ratio by hydrogenation of the nitroenamine 19 derived from D-N-acetylproline methyl ester.

4a: yield 182 mg (37%), mp 85°. $[\alpha]_D^{25}$ +15.6 (c 1, MeOH). IR(KBr): 1680. MS m/z: 154 (M^+). TLC ($CHCl_3$:MeOH, 9:1) Rf 0.41. Anal. Calcd for $C_8H_{14}N_2O$: C, 62.30; H, 9.14; N, 18.17. Found: C, 61.92; H, 9.04; N, 18.35.

4b: yield 78 mg (15%), mp 128°. $[\alpha]_D^{25}$ +35.6 (c 1, MeOH). IR(KBr): 1680.

MS m/z: 154 (M^+). TLC ($CHCl_3$: MeOH, 9:1) Rf 0.50. Anal. Calcd for $C_8H_{14}N_2O$: C, 62.30; H, 9.14; N, 18.17. Found: C, 62.11; H, 9.35; N, 17.96.

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