NEW SYNTHETIC APPROACH TO 1-AZABICYCLO[x.y.0]ALKANE SKELETONS FROM β-ENAMINO DIESTERS DERIVED FROM MELDRUM'S ACID

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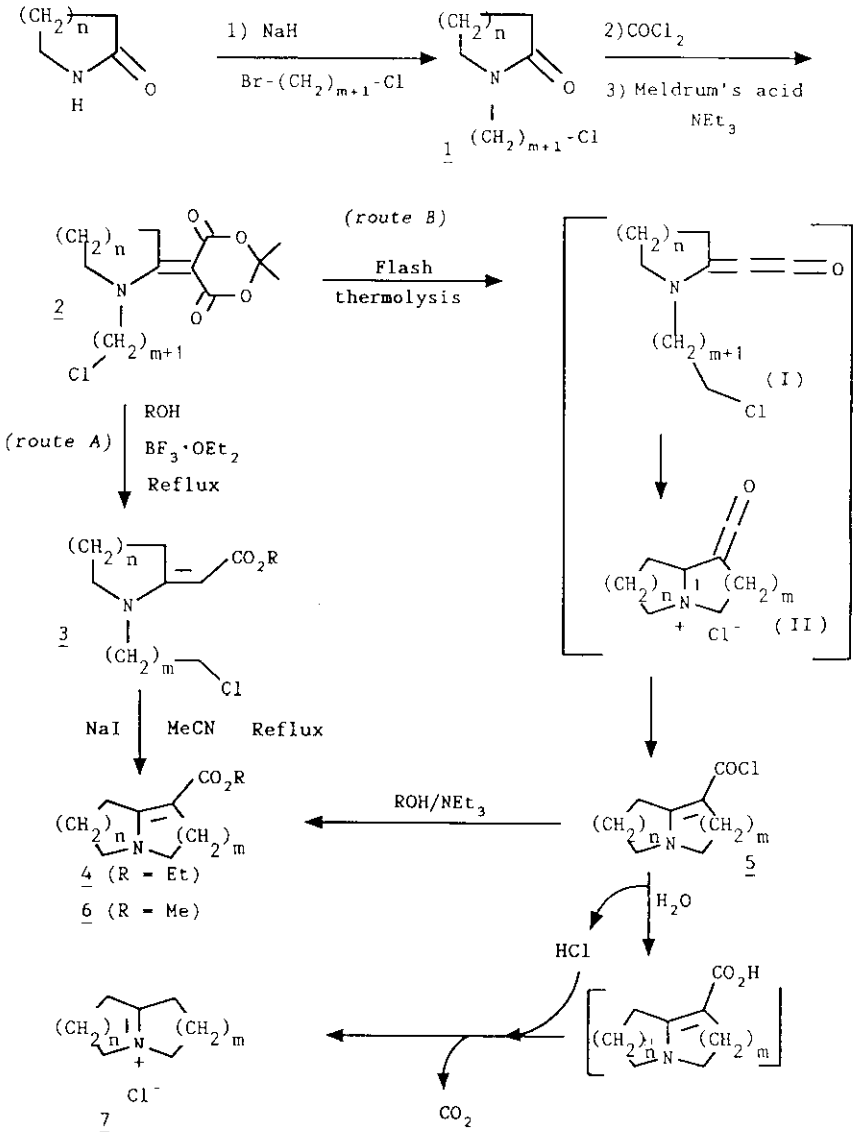
Abstract - Two complementary methods for the synthesis of title compounds (4 and 6), namely, monodecarboxylating transesterification of β-enamino esters 2 followed by intramolecular cyclization of 3, and direct cyclization of 2 under flash vacuum thermolysis conditions , have been elaborated. Further investigations allowed the identification of β-enamino acid chloride 5 as a stable intermediate in the direct cyclization of 2 into 6. Azabicyclic compounds 4 were stereospecifically converted to bicyclic β-amino alcohols 9 by means of stereocontrolled carbon-carbon double bond catalytic hydrogenation followed by ester moiety reduction.

The synthesis of bicyclic alkaloids characterized by 1-azabicyclo[x.y.0]alkane framework continues to be the focus of research due to their occurrence in some plants[2-7] and also for their biological activities.[8-10] As a part of an investigation on fused heterocycles, we have been engaged in the preparation of bridgehead heterocycles.[11,12] Recently we reported a stereospecific synthesis of isoretronecanol, trachelanthamidine, lupinine, and epilupinine.[3] For this purpose we employed a method which displays two key steps (Scheme 1). Preparation of bicyclic β-enamino esters 4 (or 6) by ring closure of β-enamino esters obtained from Meldrum's acid derivatives 2, and stereospecific carbon-carbon double bond reduction of 4. In this paper we wish to describe the results obtained in extending this methodology to the synthesis of 1-azabicyclo[x.y.0]alkane skeletons of various size and to compare chemical versus catalytic hydrogenation of β-enamino esters 4 in order to prepare some natural products and their analogues. The precursors 2 are readily prepared from commercially available lactams by a sequence which implicates N-chloroalkylation then imidoylation reactions.[13]

In the route A we adopted a strategy which proceeds through two stages. Firstly, a monodecarboxylating transesterification of 2 in the presence of boron trifluoride etherate in boiling ethanol, provides the corresponding (E) N-chloroalkyl β-enamino ester 3.

Secondly, 3 refluxed in acetonitrile solution containing sodium iodide, affords the bicyclic β-enamino ester 4 by intramolecular alkylation (Scheme 1, path A). This annelation constitutes a valuable access to indolizidine and quinolizidine skeletons (Table 1). However this reaction does not take place in the case of the pyrrolizidine homologue precursor (n=m=1), probably because of conformational factors.



Scheme 1

On the other hand, we have been studying the aminomethylene ketene thermal reactivity in gas phase.[12,14] We have established that N-alkylaminomethylene ketenes, generated in situ by thermal extrusion of carbon dioxide and acetone from Meldrum's acid derivatives 2 (X =

halide), undergo 1,4-hydrogen shift followed by electrocyclization (6 π-electrons) leading to β-enaminones[12] under flash vacuum thermolysis conditions. The introduction of chlorine atom into the N-alkyl chain shows up the enaminic character of the corresponding aminomethylene ketene[15] with no more 1,4-hydrogen migration reaction. Flash pyrolyses of Meldrum's acid derivatives 2 were performed at 580°C (10^{-4} - 10^{-5} torr) and the crudes were condensed on cold finger covered with methanol (-196°C). Once the thermolysis completed, the pyrolyzate was allowed to reach room temperature and then neutralized with triethylamine. The only isolated products were the corresponding β-enamino esters 6 (Table 1). However, when the pyrolyzate of 2b was received on cold deuterated chloroform without triethylamine, we were able to identify the β-enamino acid chloride 5b whose structure was assigned on the basis of ^{1}H and ^{13}C-nmr under inert atmosphere.[15] After treatment with a mixture of methanol and triethylamine, the product 5b leads to the adduct 6b, whereas addition of water instead of methanol and triethylamine gives the imminium salt 7b.[16] These results can be rationalized by assuming that the N-chloroalkyl aminomethylene ketene (I) cyclization occurs through an intramolecular nucleophilic displacement of chlorine atom by the enamine moiety of the heterocumulene (I) affording 5 [(II) is probably the first bicyclic intermediate] which is easily esterified into 6 (Scheme 1, route B). Compared to the first route (A), this method is shorter and the cyclization takes place in the case of m = n = 1, allowing the preparation of pyrrolizidine system as well. However we could not get the β-enamino ester 6e (n = 3, m = 2) by flash thermolysis method.

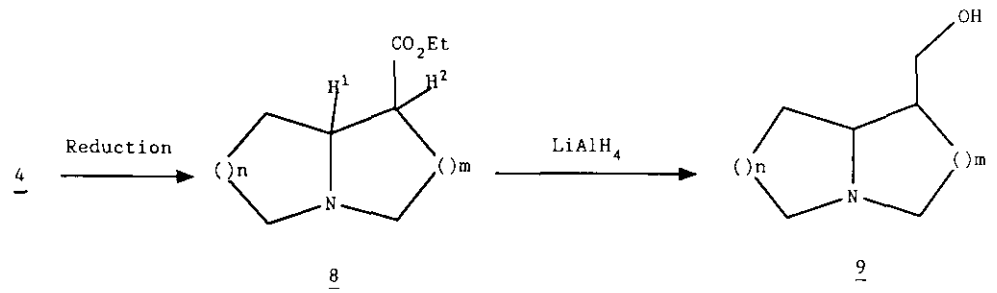
Table 1: Preparation of β-Enamino Esters 4 (route A) and 6 (route B)

Method	A	A	A	A	B	B	B	B	B	B
Products	4a	4b	4d	4e	4a	6a	6b	6c	6d	6e
R	Et	Et	Et	Et	Et	Me	Me	Me	Me	Me
n	1	1	2	3	1	1	1	1	2	3
m	1	2	2	2	1	1	2	3	2	2
Yields(%)	0	60	70	60	45	42	45	10	34	0

The combined results of both routes (A and B) demonstrate that our method constitutes an efficient and rapid approach to 1-azabicyclo[x.y.0]alkane frameworks whose structures are often encountered in alkaloids. For the completion of this study the diastereospecific carbon-carbon double bond reduction was investigated in order to prepare β-amino esters 8 (Scheme 2).

The literature only reports chemical reduction of ethyl 1,10-dehydrolupinate 4d leading

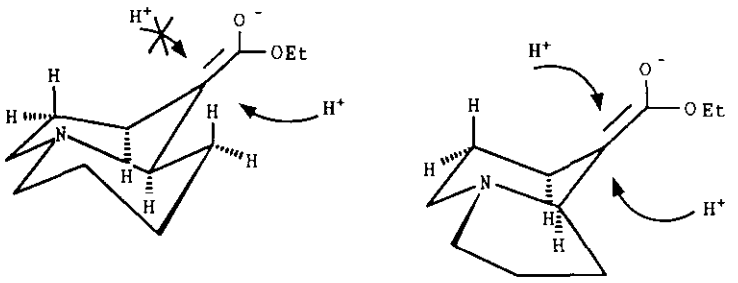
stereospecifically to the cis-ethyl lupinate 8d.[17] The same conditions applied to the homologue 4e (n=3, m=2) give the same selectivity (Table 2), while 4b (n=1, m=2) leads to a mixture of both isomers (cis/trans = 2/3). This difference of selectivity can be explained by examining steric hindrance of both α and β faces of enolates [(IIIb) and (IIId)] formed after hydride attack as shown by Golberg and coworkers.[17]



4 → 8 → 9

Scheme 2

In the case of (IIId) (n = m = 2), the enolate moiety presents two 1,3-diaxial interactions with hydrogen atoms and another one with the nitrogen lone-pair on the β-face, therefore making the protonation easier from the α-face as pictured on Scheme 3 and leading exclusively to the cis isomer. The same arguments are valid in the case of 5e also. However, because of the five member ring planarity, the indolizidine enolate (IIIb) presents a single 1,3-diaxial hydrogen interaction on the β-face which becomes more accessible (Scheme 3) and therefore the stereoselectivity of the protonation falls down.



(IIId) (IIIb)

Scheme 3

On the other hand, we have found that catalytic hydrogenation on Raney nickel at 100°C exclusively yields the cis isomer in various cases of our fused ring systems and we have observed that the hydrogenation at 200°C on Raney nickel specifically gives the trans isomer. Moreover, the cis isomers are quantitatively isomerized into the trans ones just by heating at 200°C (neither hydrogen nor nickel are needed). The results of this study are summarized in Table 2. The stereospecificity of these reductions is evaluated on the basis of 500 MHz ^{1}H-nmr data (J_{cis}< 4 Hz and J_{trans}> 10 Hz) which provide a clear criterion in the case of 8b,d,e.[13] We used bidimensional nmr techniques also (COSY, ^{13}C-^{1}H

δ-δ correlations,...) to confirm the structural assignments. Because of the relative planarity of pyrrolizidine systems, these techniques were not helpful to clearly assign the stereochemistry of 8a. However a significant nuclear Overhauser effect (nOe) was observed between H-1 and H-2 in the case of cis isomer. Meanwile no significant nOe was observed in the case of trans isomer.

Finally, the reduction of ester moiety was readily achieved with lithium aluminum hydride in good yields, leading to β-amino alcohols 9 among which we can recognize; lupinine,[8,13,17] isoretronecanol[10,11,13] and their trans isomers; epilupinine[6,13,18] and trachelanthamidine[10,11,13] which exhibit the same structural data with those reported in literature.

Table 2: Reduction of Bicyclic β-Enamino Esters 4:

Reduction System	Yields (%)	n	m	8 (cis) (%)	8 (trans) (%)
$NaBH_4$	88	1	2	40	60
	94	2	2	100	—
	71	3	2	100	—
H_2/Ni-Raney 200°C-6 h	90	1	1	—	100
	88	1	2	—	100
	89	2	2	—	100
	90	3	2	—	100
H_2/Ni-Raney 100°C-6 h	90	1	1	100	—
	88	1	2	100	—
	89	2	2	100	—
	90	3	2	100	—

In conclusion, we described in this paper a new access to 1-azabicyclic systems by intramolecular cyclization of β-enamino esters derived from Meldrum's acid by means of two complementary routes, whose combination allows the access to 5-5, 5-6, 5-7, 6-6 and 6-7 membered fused rings. Furthermore, we investigated the reduction of β-enamino esters 4 and succeeded in the stereospecific hydrogenation of their carbon-carbon double bond reduction under mild conditions, preparing either cis or trans isomers.

Experimental Section.

Melting points were determined in open capillaries using a Büchi apparatus and are uncorrected. ^{1}H-Nmr and ^{13}C-nmr spectra were run on a Varian A60-A and Brucker 80, 250

and 500 MHz spectrometers for the structural assignment in the case of β-amino esters 8. Chemical shifts are given in δ units downfield from internal trimethylsilane as the reference. Multiplicities are reported with the following abbrevation: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, m = multiplet, br = broad. Infrared spectra were recorded on a Beckman IR 20. The mass spectra were determined on a JEOL D 300 spectrometer. Column chromatography was performed on silica gel, Merck Kieselgel 60 (0.040-0.063 mm). Thin-layer chromatography (tlc) was performed by using Merck Kieselgel $60F_{254}$ coated plates in the denoted solvent.

I) Preparation of N-Chloroalkyllactams 1 : Following the procedure previously reported.[13]

1-(3-Chloropropyl)-2-pyrrolidinone. 1b (n=1, m=2):

92% yield; $bp_{0.05}$ 95°C; ir (neat) 1650 cm^{-1}; ^1H-nmr ($CDCl_3$) δ 1.71-2.56 (6H, m), 3.26-3.71 (6H, m). Anal. Calcd for $C_7H_{12}NOCl$: C, 51.97; H, 7.43; N, 8.66. Found: C, 51.73, H, 7.73; N, 8.94.

1-(4-Chlorobutyl)-2-pyrrolidinone. 1c (n=1, m=3):

95% yield; $bp_{0.01}$ 93°C; ir (neat) 1675 cm^{-1}; ^1H-nmr ($CDCl_3$) δ 1.50-2.61 (8H, m), 3.16-3.75 (6H, m). Anal. Calcd for $C_8H_{14}NOCl$: C, 54.70; H, 8.03; N, 7.97. Found: C, 54.38; H, 7.95; N, 8.11.

1-(3-Chloropropyl)caprolactam. 1e (n=3, m=2):

91% yield; $bp_{0.01}$ 99°C; ir (neat) 1640 cm^{-1}; ^1H-nmr ($CDCl_3$) δ 1.46-2.28 (8H, m), 2.30-2.68 (2H, m), 3.20-3.70 (6H, m). Anal. Calcd for $C_9H_{16}NOCl$: C, 56.98; H, 8.50; N, 7.38. Found: C, 56.84; H, 8.62; N, 7.38.

II) β-Enamino Diesters 2 were prepared by imidoylation of lactams 1 according to the procedure previously reported by our group.[11-13]

5-[1-(3-Chloropropyl)-2-pyrrolidinylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione. 2b (n=1, m=2):

60% yield; mp 170°C (EtOH); ir ($CHBr_3$) 1700, 1650 cm^{-1}; ^1H-nmr ($CDCl_3$) δ 1.71 (6H, s), 1.85-2.51 (4H, m), 3.35-4.16 (8H, m). Anal. Calcd for $C_{13}H_{18}NO_4Cl$: C, 54.26; H, 6.30; N, 4.86. Found: C, 53.97; H, 6.34; N, 5.01.

5-[1-(4-Chlorobutyl)-2-pyrrolidinylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione. 2c (n=1, m=3):

73% yield; mp 123°C (EtOH); ir ($CHCl_3$) 1705, 1660 cm^{-1}; ^1H-nmr ($CDCl_3$) δ 1.73 (6H, s), 1.78-2.32 (6H, m), 3.41-3.92 (8H, m). Anal. Calcd for $C_{14}H_{20}NO_4Cl$: C, 55.72; H, 6.68; N, 4.64. Found: C, 55.52; H, 6.61; N, 4.47.

5-[1-(3-Chloropropyl)-2-hexahydroazepinylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione. 2e (n=3, m=2):

50% yield; mp 169°C (EtOH); ir ($CHBr_3$) 1690, 1640 cm^{-1}; ^1H-nmr ($CDCl_3$) δ 1.68 (6H, s), 1.70-2.48 (8H, m), 3.00-3.31 (2H, m), 3.32-4.16 (6H, m). Anal. Calcd for $C_{15}H_{22}NO_4Cl$: C, 57.04; H, 7.02; N, 4.43. Found C, 56.87, H, 7.16; N, 4.60.

III) Preparation of β-Enamino Monoesters 3 . As described in reference 13.

Ethyl [1-(2-chloroethyl)-2-pyrrolidinylidene]acetate. 3a (n=m=1):
74% yield; $bp_{0.01}$ 140°C; ir (neat) 1680 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.23 (3H, t, J=7 Hz), 1.50-2.23 (2H, m), 3.03-3.71 (8H, m), 4.10 (2H, q, J=7 Hz), 4.46 (1H, s). Anal. Calcd for $C_{10}H_{16}NO_2Cl$: C, 55.17; H, 7.40; N, 6.43. Found: C, 55.36; H, 7.22; N, 6.49.
Ethyl [1-(3-chloropropyl)-2-pyrrolidinylidene]acetate. 3b (n=1, m=2):
90% yield; $bp_{0.05}$ 115°C; ir (neat) 1670 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.23 (3H, t, J=7 Hz), 1.80-2.30 (4H, m), 3.00-3.70 (8H, m), 4.10 (2H, q, J=7 Hz), 4.55 (1H, s). Anal. Calcd for $C_{11}H_{18}NO_2Cl$: C, 57.01; H, 7.83; N, 6.04. Found: C, 56.99; H, 8.02; N, 6.21.
Ethyl [1-(3-chloropropyl)-2-hexahydroazepinylidene]acetate. 3e (n=3, m=2):
86% yield; mp 51-52°C (cyclohexane); ir ($CHBr_3$) 1670 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.23 (3H, t, J=7 Hz), 1.38-1.88 (6H, m), 1.89-2.36 (2H, m), 3.06-3.80 (8H, m), 4.08 (2H, q, J=7 Hz), 4.51 (1H, s). Anal. Calcd for $C_{13}H_{22}NO_2Cl$: C, 60.10; H, 8.53; N, 5.39. Found: C, 60.03; H, 8.52; N, 5.52.

IV) Preparation of Bicyclic β-Enamino Esters 4. As already reported.[13]
8-Carbethoxy-1,2,3,5,6,7-hexahydroindolizine. 4b (n=1, m=2):
60% yield; $bp_{0.05}$ 115°C; ir (neat) 1650, 1585 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.23 (3H, t, J=7 Hz), 1.58-2.56 (6H, m), 2.90-3.50 (6H, m), 4.11 (2H, q, J=7 Hz). Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.77; N, 7.17. Found: C, 67.64; H, 9.19; N, 6.96.
1-Carbethoxy-2,3,6,7,8,9-hexahydro-4H,10H-pyrido[1,2,a]azepine. 4e (n=3, m=2):
60% yield; $bp_{0.05}$ 105°C; ir (neat) 1650, 1585 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.23 (3H, t, J=7 Hz), 1.45-2.56 (10H, m), 2.91-3.58 (6H, m), 4.08 (2H, q, J=7 Hz). Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.91; H, 9.47; N, 6.27. Found: C, 69.65; H, 9.37; N, 6.54.

V) Flash Pyrolysis of Derivatives 2.
General procedure: The pyrolysis apparatus used consists of a 60 x 3 cm quartz tube heated by an electric Herman-Moritz oven (580°C, measured by thermocouple at the midpoint of the furnace) and leading directly to a liquid nitrogen trap connected to the pumping system. This trap has an inlet behind the furnace (opposite to the vacuum system) to allow the introduction of solvent on the cold finger surface. The operating pressure ($p \approx 10^{-5}$ torr) was maintained with a CIT Alcatel (Crystal 100) two-stage oil diffusion pump capable of a vacuum of 10^{-3}-10^{-6} torr. The substrates 2 are sublimated (90-160°C) through the quartz tube and the emergent vapors collected in a trap cold with liquid nitrogen in a conventional manner.[20] For preparative experiments, methanol (EtOH in the case of 4a) was used as solvent and after warming up to room temperature, the pyrolyzate solution was neutralized by adding excess amounts of triethylamine. After evaporation of solvents (MeOH, NEt_3 and acetone) the residue was extracted with methylene chloride (3 x 5 ml) and water (5 ml), then dried over magnesium sulfate. For analytical experiments involving direct observation of intermediate 5b, deuterated chloroform was used instead of methanol and without triethylamine in order to identify the acid chloride 5b by nmr analysis under inert atmosphere.

8-Carbomethoxy-1,2,3,5,6,7-hexahydroindolizine. 6b (n=1, m=2, R=Me):
45% yield; mp 75°C (sublimation); ir ($CHCl_3$) 1660, 1585, 1440 cm^{-1}; ^1H-nmr ($CDCl_3$) δ 1.68-2.08 (4H, m), 2.28-2.31 (2H, m), 2.97-3.37 (6H, m), 3.62 (3H, s); ^{13}C-nmr ($CDCl_3$) δ 169.1 (s), 159.5 (s), 97.4 (s), 53.1 (t), 50.0 (q), 45.0 (t), 32.7 (t), 21.6 (t), 21.5 (t), 21.0 (t); mass spectrum, m/z (relative intensity) 181 (89), 180 (16), 166 (44), 150 (80), 123 (16), 122 (100), 120 (22), 58 (40). Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.39; H, 8.39; N, 7.82.
9-Carbomethoxy-2,3,5,6,7,8-hexahydro-1H-pyrrolo[1,2-a]azepine. 6c (n=1, m=3, R=Me):
Oil purified by flash chromatography (Et_2O/petrolum ether: 3/1); 10% yield; ir ($CHCl_3$) 1675, 1570 cm^{-1}; ^1H-nmr ($CDCl_3$) δ 1.65-2.05 (6H, m), 2.60 (2H, m), 3.00 (2H, t, J=7.5Hz), 3.32 (4H, m), 3.61 (3H, s); ^{13}C-nmr δ 170.4 (s), 165.9 (s), 94.5 (s), 56.1 (t), 50.4 (q), 49.7 (t), 35.1 (t), 27.4 (t), 25.9 (t), 25.5 (t), 22.2 (t). Anal. Calcd for $C_{11}H_{17}NO_2$: C, 66.67; H, 8.78; N, 7.17. Found : C, 67.41; H, 8.94, N, 7.26.
8-Chloroformyl-1,2,3,5,6,7-hexahydroindolizine. 5b (n=1, m=2):
^1H-Nmr ($CDCl_3$, 300 MHz) δ 1.76 (2H, dt, J=6.3, 5.7 Hz), 1.90 (2H, dt, J=7.4, 7.8 Hz), 2.36 (2H, t, J=6.3 Hz), 2.92 (2H, t, J=7.8 Hz), 3.13 (2H, t, J=5.7 Hz), 3.39 (2H, t, J=7.4 Hz); ^{13}C-nmr ($CDCl_3$) δ 165.8 (s), 163.7 (s), 89.4 (s), 54.1 (t), 44.9 (t), 33.9 (t), 23.9 (t), 21.0 (t), 19.8 (t).
2,3,5,6,7,8-Hexahydro-1H-indolizinium chloride.[16] 7b (n=1, m=2):
Ir ($CHCl_3$) 2930, 1685, 1625 cm^{-1}; ^1H-nmr ($CDCl_3$) δ 1.77-2.52 (6H, m), 2.96 (2H, m), 3.36 (2H, m), 3.85 (2H, m), 4.31 (2H, m); ^{13}C-nmr δ 60.9 (t), 48.3 (t), 39.1 (t), 28.0 (t), 20.4 (t), 18.2 (t), 16.8 (t).
Compounds 5b and 7b are only identified by their spectral data.

VI) Preparation of Bicyclic β-Amino Esters 8 (R=Et).

A) Reduction with $NaBH_4$.
General procedure: Sodium borohydride (1.33g , 0.035 mol) was added to ethanolic solution (30 ml) of β-enamino ester 4 (0.01 mol). The mixture was stirred for 12h at room temperature then water (30 ml) was added and the resulting mixture was neutralized (pH≈5) by adding aqueous 20% HCl dropwise. After stirring for 30 min at room temperature the solution was saturated with solid potassium carbonate, washed with chloroform (3 times 50 ml) and dried over sodium sulfate. Solvents were removed under vacuum and products were purified by distillation.
B) Catalytic reduction . As already described.[13]
N.B. In all cases cis and trans isomers exhibit the same carbonyl ir absorption and the same boiling point, but different Rf on silica gel tlc. Their stereochemistry was assigned on the basis of ^1H-nmr (500 MHz) data.

8-Carbethoxy-1,2,3,5,6,7,8,9-octahydroindolizine. 8b (n=1, m=2):
88% yield (either catalytic or chemical reduction); $bp_{0.01}$ 80°C (colorless oil); ir (neat), 1730 cm^{-1}.
Cis isomer: Rf = 0.46 (MeOH); ^1H-nmr ($CDCl_3$) δ 1.00 (3H, t, J=7 Hz), 1.17-1.29 (2H, m),

1.33-1.42 (1H, m), 1.46-1.64 (3H, m), 1.70-1.95 (5H, m), 2.49-2.53 (1H, m), 2.74-2.86 (2H, m), 3.90 (2H, q, J=7 Hz); ^{13}C-nmr ($CDCl_3$) δ 173.12, 64.55, 59.80, 54.86, 53.07, 44.77, 26.65, 26.31, 22.48, 20.69, 14.13. Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.96; H, 9.70; N, 7.10. Found: C, 67.05; H, 9.81; N, 6.96.

Trans isomer: Rf = 0.55 (MeOH); ^{1}H-nmr ($CDCl_3$) δ 1.10 (3H, t, J=7 Hz), 1.24-1.40 (2H, m), 1.43-1.69 (4H, m), 1.77-1.92 (4H, m), 1.95-2.02 (1H, m), 2.06-2.14 (1H, m), 2.88-2.96 (2H, m), 3.98 (2H, q, J=7 Hz); ^{13}C-nmr ($CDCl_3$) δ 174.32, 65.22, 60.14, 54.03, 52.28, 48.19, 29.25, 28.16, 24.83, 20.57, 14.24. Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.96, H, 9.70, N, 7.10; Found: C, 66.93; H, 9.88; N, 6.92.

1-Carbethoxy-1,2,3,4,6,7,8,9,10,11-decahydropyrido[1,2-a]azepines. 8e (n=3, m=2):

Yields: 90% (catalytic), 71% (chemical); $bp_{0.01}$ 85°C (colorless oil); ir (neat) 1730 cm^{-1}.

Cis isomer: Rf = 0.45 (MeOH); ^{1}H-nmr ($CDCl_3$) δ 1.24 (3H, t, J=7 Hz), 1.26-1.34 (1H, m), 1.35-1.84 (12H, m), 2.43-2.52 (1H, m), 2.61-2.72 (2H, m), 2.78-2.86 (1H, m), 2.88-2.97 (1H, m), 4.13 (2H, q, J=7 Hz); ^{13}C-nmr δ 173.72, 61.62, 50.92, 56.87, 48.63, 47.21, 28.05, 26.58, 26.14, 25.16, 24.99, 22.59, 14.30. Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.28; N, 6.21. Found: C, 68.93; H, 9.85; N, 6.34.

Trans isomer: Rf = 0.52 (MeOH); ^{1}H-nmr ($CDCl_3$) δ 1.20 (3H, t, J=7 Hz), 1.37-1.71 (11H, m), 1.81-1.89 (1H, m), 2.21-2.44 (3H, m), 2.48-2.56 (1H, m), 2.66-2.74 (1H, m), 2.76-2.83 (1H, m), 4.07 (2H, q, J=7 Hz); ^{13}C-nmr ($CDCl_3$) δ 175.37, 64.51, 60.00, 56.80, 55.68, 48.62, 32.62, 28.80, 28.27, 27.79, 24.44, 14.24. Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.28; N, 6.21. Found: C, 69.02; H, 9.98; N, 6.42.

VII) **Preparation of β-Amino Alcohols 9**. As described by Golberg and coworkers.[17]

8-Hydroxymethyl-1,2,3,5,6,7,8,9-octahydroindolizine 9b (n=1, m=2):

90% yield; $bp_{0.04}$ 77°C; ir (neat) 3400 cm^{-1}.

Cis isomer: ^{1}H-Nmr (C_6D_6) δ 1.28-1.45 (4H, m), 1.48-152 (2H, m), 1.55-1.75 (3H, m), 1.80-1.92 (2H, m), 2.21-2.34 (1H, m), 2.68-2.74 (1H, m), 2.85-2.90 (1H, m), 3.82-3.88 (1H, m), 4.22-4.26 (1H, m); ^{13}C-nmr ($CDCl_3$) δ 66.58, 63.32, 54.87, 53.78, 37.12, 29.19, 26.02, 22.96, 21.10. Anal. Calcd for $C_6H_{17}NO$: C, 69.63; H, 11.03; N, 9.02. Found: C, 69.58; H, 10.92; N, 9.11.

Trans isomer: ^{1}H-Nmr (C_6D_6) δ 0.95-1.08 (1H, m), 1.42-1.62 (6H, m), 1.64-1.81 (3H, m), 1.80-1.92 (3H, m), 2.88-2.96 (1H, m), 3.36-3.42 (1H, m), 3.55-3.60 (1H, m); ^{13}C-nmr ($CDCl_3$) δ 66.98, 64.85, 54.43, 53.06, 4.96, 29.43, 28.33, 25.57, 21.19. Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.03; N, 9.02. Found: C, 69.45; H, 10.82; N, 9.08.

8-Hydroxymethyl-1,2,3,4,6,7,8,9,10,11-decahydropyrido[1,2-a]azepine 9e (n=3, m=2):

90% yield; $bp_{0.01}$ 135°C; ir (neat) 3400-3300 cm^{-1}.

Cis isomer: ^{1}H-Nmr (C_6D_6) δ 1.12-1.22 (8H, m), 1.64-1.78 (4H, m), 2.08-2.17 (2H, m), 2.21-2.32 (2H, m), 2.51-2.62 (2H, m), 3.65-3.70 (1H, m), 4.02-4.08 (1H, m); ^{13}C-nmr ($CDCl_3$) δ 67.45, 64.78, 57.13, 56.27, 42.36, 31.00, 29.57, 28.46, 27.13, 25.52, 24.46. Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.54; N, 7.84. Found: C, 72.09; H, 11.50; N, 7.84.

Trans isomer: ^{1}H-Nmr (C_6D_6) δ 1.22-1.28 (2H, m), 1.30-1.37 (2H, m), 1.39-1.52 (4H, m), 1.55-1.73 (5H, m), 2.30-2.39 (2H, m), 2.45-2.52 (1H, m), 2.55-2.62 (1H, m), 2.64-2.69 (1H,

m), 3.50-3.58 (2H, m); ^{13}C-nmr ($CDCl_3$) δ 65.69, 64.34, 55.10, 54.70, 41.97, 31.21, 28.76, 28.25, 27.88, 24.95, 24.83. Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.54; N, 7.84. Found: C, 72.21; H, 11.39; N, 7.94.

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