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Regioselective Reductions of Various 3-Aminosuccinimides; Application to the Synthesis of two Heterocyclic Systems.

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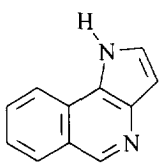
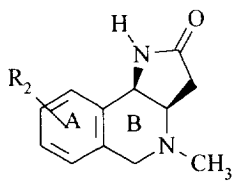
Abstract *:* The synthesis of novel pyrrolo[3,2-c]isoquinolines is investigated starting from 3-aminosuccinimides. Various known routes leading to 3-aminosuccinimides were tested but a new approach *via* nucleophilic addition of arylalkylamines on maleimide gave better results. The regioselectivity of the reduction of these compounds was shown to depend on the degree of substitution of the concerned 3-aminosuccinimide. The hydroxylactams are formed *in-situ*, then converted into the ethoxylactams. The latter, after generation of an iminium salt, afforded the target pyrroloisoquinolines and two further derivatives of another new heterocyclic system: the 3,6-methano-2,5-benzodiazocine.

During the course of our investigations concerning synthetic receptors for carboxylic acids and amines, we were interested in the synthesis of tricyclic compounds possessing two nitrogen atoms, derived from the pyrrolo[3,2-c]isoquinoline structure. For our purpose, molecular modelling studies and molecular models examination showed that these potential receptors must possess both a lactam group and a tertiary amine group able to hydrogen bond with the guest and a functional group on the benzene ring (Scheme 1). The latter group might be used to install a flexible side chain possessing a supplementary carboxamide moiety leading to further hydrogen bonding with the guest. The synthesis and the complexation properties of a part of the above described receptor (i. e. the A,B moiety with R_2 = 2-pyridyl-NH-CO-CH_2-) have been described in a previous paper.[1] To our knowledge,[2] only a few derivatives of the pyrrolo[3,2-c]isoquinoline structure have been reported in the literature.



Pyrrolo[3,2-c]isoquinoline



Host precursor

Scheme 1

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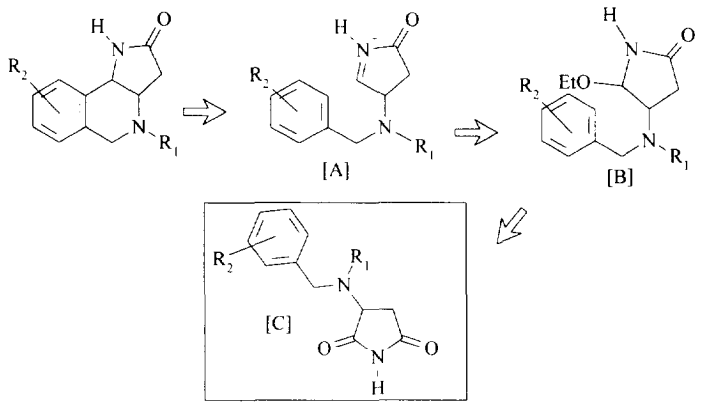
The disconnection approach presented on Scheme 2 showed that a choice precursor for this kind of structure may be the iminium salt [A] which could cyclize under S_EAr2 conditions.[3] The required iminium salt may be generated by acid treatment of the ethoxylactam [B] obtained by regioselective reduction of the succinimide [C] followed by ethanolysis of the intermediate hydroxy lactam. The required 3-aminosuccinimides are not described in the literature. However, some potential precursors like 3-hydroxy or 3-acetoxysuccinimides are known and their regioselective reduction occurred generally on the C=O located on the same side as the 3-substituent.[4]

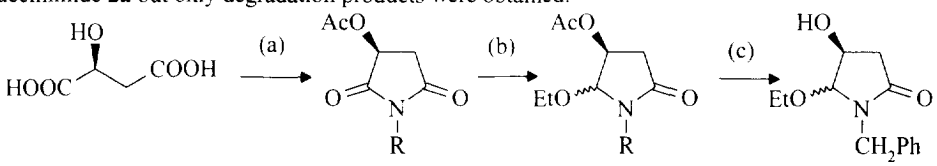


Scheme 2

The aim of this paper is to report the synthesis of various 3-aminosuccinimides, to study the parameters for the regioselective reduction of these compounds and to use the products obtained from the reduction to build the new pyrrolo[3,2-*c*]isoquinoline structures.

Synthesis of aminosuccinimides and first reductions

There are only a few reports dealing with the synthesis of 3-aminopyrrolidinones[5] or their precursors, the 3-hydroxysuccinimides.[6] We first tried the malic acid route known to afford hydroxysuccinimides via acetoxy derivatives. These hydroxy derivatives could be further converted into the target amino compounds using Mitsunobu conditions[6] or via the mesylates.[7] Starting from (S)-malic acid, the acetoxysuccinimide **2a** was obtained according to a recent protocol described by Lee *et al.*[4b] We tried $LiBH_4$[8] or $NaBH_4$ reductions of succinimide **2a** but only degradation products were obtained.

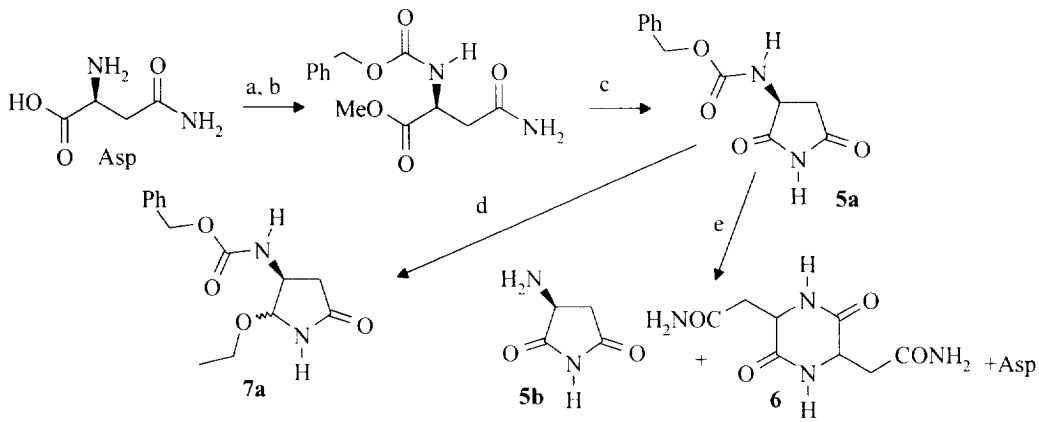


(a): 1) AcCl, 2) RNH_2, 3) AcCl. (b) 1) $NaBH_4$/EtOH, -15 °C/15 min, 2)H^+. (c): EtOH/EtONa

Scheme 3

This may be attributed to the instability of the intermediate α-hydroxylactam probably leading to ring opening reactions followed by degradation. We thus tried the same reduction with the *N*-benzylsuccinimide **2b**

obtained by replacing ammonia with benzylamine in the second step of the synthesis. [9] In this case, the reduction proceeded smoothly[4a], the work-up was easier and 5-ethoxy-4-hydroxypyrrolidin-2-one **4b** was obtained after cleavage of the acetyloxy protection with sodium ethoxide in a 37 % yield (calculated from initial succinimide **2b**). Unfortunately, the conversion of the 4-hydroxy moiety into an azide group failed under modified Mitsunobu's conditions.[6] The asparagine route was then investigated (Scheme 4).



a) Cl-COOCH$_2$Ph, KHCO$_3$. b) SOCl$_2$, MeOH. c) NaOH then aqueous HCl. d) NaBH$_4$. e) H$_2$/ Pd-C in methanol

Scheme 4

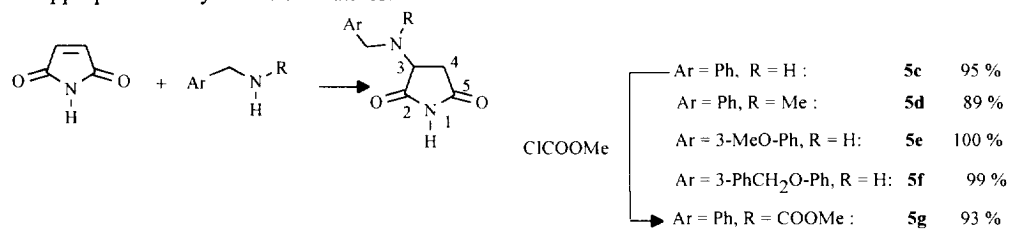
(S)-Asparagine (Asp) was first protected[10] with a benzyloxycarbonyl group and esterified.[5] The *N*-protected 3-aminosuccinimide **5a** was obtained after ring closure with sodium hydroxide and subsequent treatment with hydrochloric acid.[11] The protecting group was then removed by catalytic hydrogenolysis to afford a mixture of the required 3-aminopyrrolidine-2,5-dione **5b**, the diketopiperazine **6** and a small amount of asparagine. The piperazinedione **6** resulted from ring opening followed by self condensation of the aminosuccinimide and occurred during the work-up and the recrystallisation steps in aqueous solvents. We always obtained random ratios for **6**/**5b**, depending on the actual conditions, and recrystallisation from a diethyl ether/ dimethylformamide mixture[12] did not improve the results. With the synthesis of the free amine being tedious, we decided to reduce directly the *N*-protected aminosuccinimide **5a**. Reduction of **5a** with a large excess of sodium borohydride at -15 °C for 15 min occurred at the C=O situated on C(2) and subsequent quenching with sulfuric acid at lower temperature (-25 °C) gave the ethoxylactam **7a** in a 45 % yield (identified by ^{1}H NMR spectroscopy with selective irradiation as described below).

This first series of experiments clearly showed that: The synthesis of 3-aminosuccinimides is rather difficult using the published procedures and the use of carbamates **7a** or **5a** is tedious owing to the above described side reactions. Their regioselective reduction seems to be possible despite the instability of the intermediate hydroxylactam. There is a lack of a method leading to the desired arylalkylaminosuccinimides.

Synthesis of 3-Arylalkylaminosuccinimides via Nucleophilic Addition of Amines on Maleimide

Considering the difficulties incured for the synthesis of aminosuccinimides and in order to open a new route to this class of compounds we decided to study the nucleophilic addition of an appropriate amine on maleimide. This kind of approach has been rarely used in the literature. On one hand, a related method

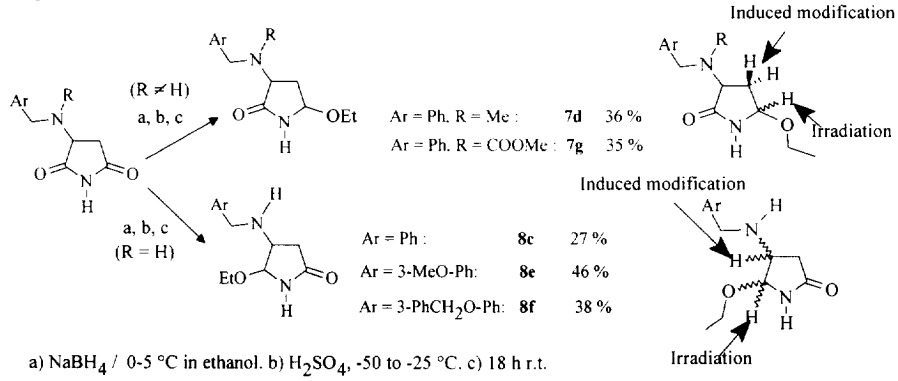
involving conjugate addition of amines to enantiopure (R)-5-isopropoxy-3-pyrrolidin-2-one has been described by Speckamp *et al.*[3b] These addition reactions were clean and afforded 4-nitrogen-substituted 5-alkoxypyrrolidin-2-ones in both nice yields and good optical purity. On the other hand, only a few papers reported nucleophilic addition of amines on *N*-substituted maleimides[13] or the addition of phenylhydroxylamine on maleimide.[14] No preparative use of this reaction has been mentioned and polymerisation side reactions are observed when the nitrogen is not substituted. Despite these facts, we observed clean reactions when a solution of maleimide in ethyl acetate was treated, at room temperature, by the appropriate benzylamine derivatives.



Scheme 5

The corresponding 3-aminosuccinimides **5c-f** were obtained in good to quantitative yields (Scheme 5). For the synthesis of compound **5f**, possessing a benzyloxy group, it was necessary to find a method leading to 3-benzyloxybenzylamine, not commercially available and only mentioned in three patents.[15] This synthesis was achieved by reaction of 3-benzyloxybenzaldehyde with hydroxylamine, quick isolation of the formed oxime and subsequent reduction with a nickel/aluminium alloy in a mixture of aqueous sodium hydroxide and ethanol. On the other hand, classical treatment of the amine **5c** with methyl chloroformate afforded carbamate **5g** in a 93 % yield. The structures of compounds **5c-g** were confirmed by ^{1}H NMR spectroscopy. The two benzylic protons and the two H-C(4) of the pyrrolidine ring are not magnetically equivalent leading to the observation of *gem*-coupling constants (13 and 18 Hz, respectively).

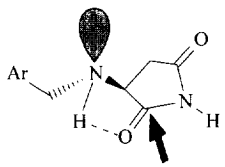
Reduction of the obtained aminosuccinimides



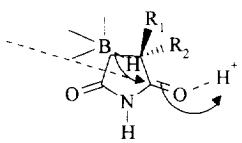
Scheme 6

The regioselectivity of the reduction of 3-alkyl or 3,3-dialkyl succinimides has been extensively studied by Speckamp *et al.*[16] These authors used particular conditions : during the course of the sodium borohydride reduction in ethyl alcohol, a few drops of hydrochloric acid were added every 15 min in order to adjust the pH

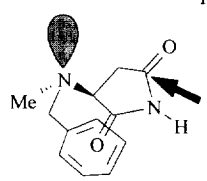
of the reaction mixture. After completion of the reaction, the hydroxylactam was converted into the ethoxylactam under more strongly acidic conditions. Under these conditions, the reduction often took place at the most substituted C=O in the succinimides. The explanation proposed consists in the approach of the hydride ion via the less hindered C=O and addition on the C atom of the more hindered one virtually along a straight line along the C=O bond (Scheme 7). Other papers[17] showed that the regioselectivity observed is not so clear and depends on the reducing agent. Although the steric factor was frequently invoked, the involvement of the amino H atom and the α-carbonyl-O-atom in an inter or intramolecular hydrogen bond was suspected to cause preferential activation of the α-carbonyl group towards hydride attack.[17b]



Reduction of the more hindered C=O
Intermolecular H-bond also possible



Reduction under Speckamp's conditions



Reduction on the less hindered C=O

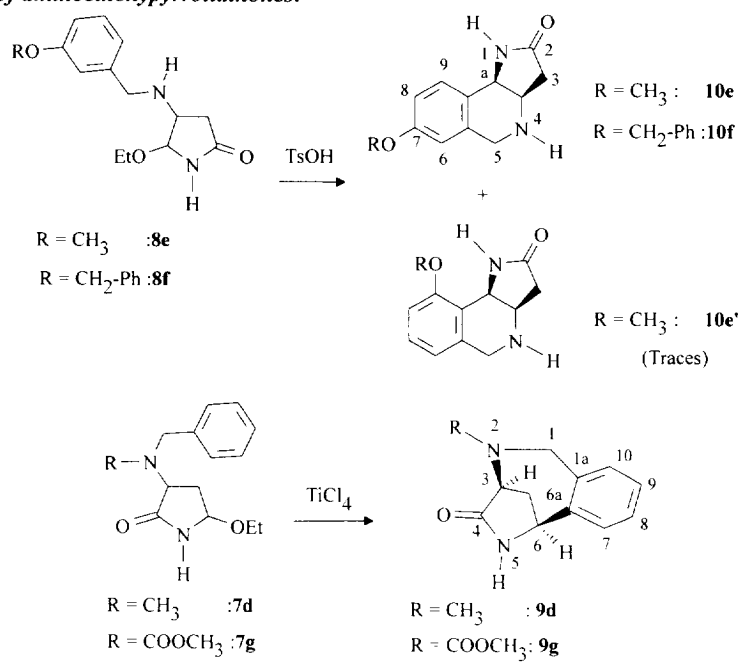
Scheme 7

In the case of 3-aminosuccinimides, Speckamp's conditions led to poor results (only 2 % reduction products, 10 % starting material and degradation products) probably because the amine group underwent protonation during the acidification process. Better results were obtained under classical conditions using an excess of sodium borohydride in ethyl alcohol. After reduction, the ethanolysis reaction was performed under acidic conditions, at low temperature. In the crude reaction mixture, starting material was always observed (from 15 to 30 % after purification, depending on the starting aminosuccinimide) besides very small amounts of other non-identified products having spectral characteristics different from those of the other regioisomer. The increasing of the reaction time always resulted in diminishing the proportion of starting material but the yields in reduction products were significantly lower. So, these reduction experiments gave average but reproducible yields and the results are summarized in Scheme 6. The regioselectivity of the reductions was established using ^{1}H NMR spectroscopy and selective irradiation of the H-(C5) giving a signal at 4.80 ppm (Scheme 6). Careful examination of the side-products did not detect traces of the other regioisomer. It can be seen that the regioselectivity observed depended on the degree of substitution of the amine group. While with tertiary aminosuccinimide **5d** and carbamate **5g** the reduction occurred at the less hindered C=O, the more hindered C=O was reduced in the case of secondary aminosuccinimides **5c**, **5e**, **5f** or carbamate **5a**. We think that when an N-H bond is present, a hydrogen bond may be created with the oxygen atom of the carbonyl group promoting the reduction at the more hindered C=O (Scheme 7). If there is no N-H bond, the amino group is bulkier and a stacking interaction between the phenyl ring and the carbonyl group[18] could be possible promoting the reduction on the less hindered C=O (Scheme 7). Semi-empirical calculations performed on

these amino succinimides showed no significant differences between the two C=O (charges and MO coefficients) whereas molecular mechanics calculations and CPK models confirmed the importance of the steric factor.[19]

The NMR spectra of the reduction products **7d-g** were complicated by the presence of the two C(5) epimers. As described in the literature[20], a method used for the assignment of the stereochemistry of 2,3-disubstituted pyrrolidines is based on the vicinal coupling constant J_{vic} between H-C(2) and H-C(3). The trans coupling constant is usually 0-1 Hz while for the corresponding cis-substituted compound J_{vic} is about 5-6 Hz. The two coupling constants were observed for **7c-g** but it was impossible to identify all the signals because most of them were superimposed. Moreover, as we will see below, the spectra of the cyclized compounds will be easier to interpret.

Ring closure of aminoethoxypyrrolidinones:



Scheme 8

Various catalysts may be used in order to promote the iminium ion cyclization of **7c-g** type ethoxylactams. These are Lewis acids[21] ($TiCl_4$, BF_3, $ZnCl_2$), sulfonic acids [21,22], trimethylsilyl triflate[23], trifluoroacetic acid[23], formic acid[4a] or polyphosphoric acid [24]. Whatever the conditions and as already observed with a similar product under $TiCl_4$ catalysis by Speckamp *et al*,[3b] no ring closure was observed in the case of compound **8c**. Alternatively, this ring closure proceeded smoothly in the case of lactams **8e,f** through refluxing in dichloromethane with p-toluenesulfonic acid, but not under Lewis acid catalysis. The required new pyrrolo[3,2-c]isoquinoline derivatives **10e,f** were obtained in good yields. The coupling constant between the protons 1a and 3a was about 5 Hz showing a cis ring-junction between the 5 and the 6-membered rings.[20] In the case of the cyclization of **8e**, the NMR spectrum of the final product showed a small amount of the other isomer **10e'** whereas **10f** was isolated as a single isomer (within the limits of the NMR accuracy).

The differences observed in the reactivities of ethoxylactams **8c** and **8e,f** are typical of isoquinoline chemistry. For example, Pommeranz-Fritsch cyclisations are known to occur only when the benzene ring is substituted by at least one electron donating group able to activate the position involved in the ring closure. However, we were very surprised to observe the easier ring closure of 5-ethoxylactams **7d,g** under titanium tetrachloride catalysis, because in these compounds the benzene ring is not substituted by an electron donating group. The spectral properties of the two compounds **9d,g** thus obtained led us to think that they are the first derivatives of a new heterocyclic system, 3,6-methano-2,5-benzodiazocin-4-one, never before prepared to our knowledge. Contrary to compounds **10e,f**, a lot of duplicate signals are observed in the ^{1}H and ^{13}C NMR spectra and this duplication cannot be attributed to a cis-trans isomerism because compounds **9d,g** must have the cis-configuration (for C(3)-H and C(6)-H) for geometry reasons. It was necessary to perform a ^{1}H-^{13}C COSY NMR experiment to attribute unambigously some signals. (see experimental part). To rationalize this easy ring closure, we performed molecular mechanics calculations[19] on the iminium salts, modelling intermediates for the six and seven-membered rings but no significant results could be obtained.

Compounds **10e-f**, are valuable intermediates of the targeted hosts. These hosts could be obtained by cleavage of the ether bond, followed by an appropriate coupling reaction leading to an acetamide derivative connected to (C7) of the isoquinoline ring. This work is now in progress and the complexation studies of the new hosts with acids and amines will be undertaken as soon as possible.

Acknowledgment. This work was supported by a research grant from the *Région Haute Normandie*. We thank Dr. J. Maddaluno for helpful dicussions.

EXPERIMENTAL

The infrared spectra were recorded on a Beckman IR 4250 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded either on a 200 MHz or a 400 MHz Bruker apparatus. Spectra were recorded in deuteriochloroform or in hexadeuterio dimethyl sulfoxide (DMSO-d_6). Chemicals were purchased from Aldrich Co or Janssen Co and, unless ortherwise stated, were used without further purification. Flash chromatographies were performed with silica 60 (70-230 mesh from Merck) and monitored with silica plates (Merck, kieselgel 60 F_{254}).

(3S)-N-Benzyloxycarbonylasparagine. (S)-Asparagine monohydrate (15 g, 99.9 mmol) was dissolved at 60 °C in aqueous potassium hydrogen carbonate (1M solution, 250 ml). After cooling to room temperature, benzyl chloroformate (18.8 ml, 124.9 mmol) was added dropwise over 2 h with efficient stirring. The excess of chloroformate was then extracted with diethyl ether and the aqueous layer was acidified (pH = 2, pH testing paper) with concentrated hydrochloric acid. The solid material was filtered and recrystallized from hot water. The yield was 51 % of a white solid. mp = 166 °C (lit[10] 163 °C). ^{1}H NMR (60 MHz, DMSO-d6) : 7.2 (s, 5H, Ph) ; 6.8 (m, 2H, NH_2 amide) ; 5.0 (s, 2H, CH_2-Ph) ; 4.2 (m, 1H, chiral CH) ; 2.4 (m, 2H, CH_2). IR (cm^{-1}) : 3412, 3338 (NH, NH_2) ; 1700 (C=O acid) ; 1645(C=O amide, carbonate).

3-(S)-N-Benzyloxycarbonylaminopyrrolidine-2,5-dione ***5a***. A suspension of the above protected asparagine (13.6 g, 51.1 mmol) in methanol (170 ml) at 0-5°C, was treated dropwise within about 15 min with thionyl chloride (11.1 ml, 152.5 mmol). Methanol was removed under reduced pressure and the eventual excess of thionyl chloride was co-distilled with toluene. The white solid was thoroughly washed with diethyl ether and yielded 88 % of a white solid. mp = 150 °C (lit[5] 153 °C). ^{1}H NMR (60 MHz, DMSO-d6) : 7.45 (m, 2H, NH_2 amide) ; 7.4 (s, 5H, phenyl ring) ; 5.0 (s, 2H, CH_2-Ph) ; 4.5 (m, 1H, chiral CH) ; 3.6 (s, 3H, CH_3 ester) ; 2.6 (m, 2H, CH_2). IR : 3410, 3310 (NH, NH_2) ; 1740 (C=O ester) ; 1645 (C=O amide, carbamate).

The above ester (8.5 g, 30.3 mmol) was dissolved in water (40 ml) and 0.5 M aqueous sodium hydroxide (60.6 ml) was added dropwise. After 40 min stirring at room temperature, the solution was acidified with 1 M aqueous hydrochloric acid (30.3 ml, pH = 3 testing paper). After ice cooling, the solid material was filtered and washed with a small amount of cold water. Recrystallization from ethyl acetate/cyclohexane afforded a white solid in a 68 % yield. mp = 79 °C (lit[5] 80-81 °C). ^{1}H NMR (200 MHz, $CDCl_3$) : 9.00 (m, 1H, NH); 7.33 (s, 5H, Ph) ; 5.82 (d, 1H, J = 6.9 Hz, NH carbamate) ; 5.10 (s, 2H, CH_2Ph) ; 4.38 (pseudo-q, 1H, H_3) ; 3.05 (dd, 1H, J = 8.8 and J = 18 Hz, one CH_2 proton) ; 2.80 (dd, 1H, J = 5.5 and J = 18.0 Hz, the other CH_2 proton). IR (cm^{-1}) : 3360, 3065 (NH) ; 1720 (C=O imide, carbamate).

3-Benzyloxybenzylamine. This procedure was adapted from the three patents reported in the literature.[15] To a solution of 3-benzyloxybenzaldehyde (30 g, 138.6 mmol) in water (580 ml) and ethanol (28 ml) were added hydroxylamine hydrochloride (13.96 g, 200.9 mmol) and sodium acetate (27.38 g, 336.2 mmol). The mixture was heated to reflux for 4 h. After cooling to room temperature, the solution was extracted with dichloromethane (4x400 ml). The mixed organic layers were dried on $MgSO_4$ and afforded the oxime as a white solid which was used for the next step without further purification. The yield was quantitative. ^{1}H NMR ($CDCl_3$, 200 MHz): 8.19 (s, 1H, H_9); 7.80 (m, 1H, H_{10}); 7.60-7.00 (m, 9H, aromatic protons); 5.11 (s, 2H). To a cooled solution (0-5 °C) of this crude oxime (12.82 g, 56 mmol) in ethanol (127 ml) and aqueous 2M sodium hydroxide (127 ml), nickel-aluminium alloy (10 g) was added in two equivalent portions within 15 min. The solution was stirred at room temperature for 18 h and then extracted with dichloromethane (6x200 ml). The mixed organic layers were dried on $MgSO_4$ and concentrated under reduced pressure to afford a 77 % yield as an oil which crystallized slowly. ^{1}H NMR ($CDCl_3$, 200 MHz): 7.44-7.20 (m, 6H); 7.00-6.80(m, 3H); 5.09(s, 2H); 3.87(s, 2H); 2.53(m, 2H).

General procedure for the nucleophilic addition of amines on maleimide.

To a solution of maleimide in ethyl acetate (concentration range : 0.64-0.78M), the appropriate amine (1.1equiv) was added dropwise at room temperature. The resulting mixture was stirred for 20 h at room temperature and the solvent was removed under reduced pressure. The resulting crude product was recrystallized or chromatographed on a silica column.

3-(N-Benzyl)aminosuccinimide ***5c***. According to general procedure, maleimide (0.7 g, 7.1 mmol) and benzylamine (0.81 ml, 7.4 mmol) in ethyl acetate (9 ml) afforded an oil which was chromatographed on a silica column (ethyl acetate, cyclohexane 3/1, R_f = 0.4). The yield was 95 % of a colourless oil which became a white solid after a long time. mp (decomposes) = 58 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) : 8.5 (m, 1H, NH) ; 7.4-7.2 (m, 5H, phenyl ring) ; 3.90 (d, 2H, J = 3.1 Hz, CH_2 benzyl) ; 3.84 (dd, 1H, J = 5.4 Hz and J = 8.3 Hz, H_3) ; 2.93 (dd, 1H, J = 8.3 Hz and J = 18.1 Hz, H_3) ; 2.61 (dd, 1H, J = 5.4 Hz and J = 18.1 Hz, $H_{3'}$) ; 2.08 (m, 1H, NH amine). ^{13}C NMR (200 MHz, $CDCl_3$) : 178.55 (C_2 or C_5) ; 175.75 (C_2 or C_5) ; 138.4 (quaternary phenylcarbon) ; 128.5, 128.15, 127.4 (phenyl ring) ; 56.4 (C_3) ; 51.5 (CH_2 benzyl) ; 37.1 (C_3). IR (cm^{-1}) : 3226 (NH) ; 1782 and 1713 (C=O). Anal. calcd for $C_{11}H_{12}N_2O_2$: C, 64.68 ; H, 5.93 ; N, 13.72. Found : C, 64.7 ; H, 6.08 ; N, 12.78.

3-(N-Benzyl-N-methyl)aminosuccinimide ***5d***. According to general procedure, maleimide (3 g, 30.3 mmol) and *N*-benzyl-*N*-methylamine (4.1 ml, 3.12 mmol) in ethyl acetate afforded an oil which was purified by flash chromatography (silica, ethyl acetate/cyclohexane 1/1, R_f = 0.4). The yield was 89 % of a white solid. mp = 105 °C. ^{1}H NMR (200 MHz, $CDCl_3$) : 8.74 (m, 1H, NH) ; 7.4-7.3 (m, 5H, phenyl ring) ; 3.95 (dd, 1H, J = 5.7 Hz and J = 8.6 Hz, H_3) ; 3.88 (d, 1H, J = 13.1 Hz, one H of CH_2-Ar) ; 3.72 (d, 1H, J = 13.1 Hz, the other H of CH_2-Ph) ; 2.84 (dd, 1H, J = 8.6 Hz and J = 18.7 Hz, H_4) ; 2.70 (dd, 1H, J = 5.7 Hz and J = 18.7 Hz, $H_{4'}$) ; 2.35 (s, 3H, N-CH_3). IR (cm^{-1}) : 3190 (NH) ; 1764 and 1708 (C=O). Anal. calcd for $C_{12}H_{14}N_2O_2$: C, 66.03 ; H, 6.48; N, 12.84. Found : C, 66.04 ; H, 6.7; N, 12.89).

3-N-[(3-Methoxyphenyl)methyl]aminosuccinimide ***5e***. According to general procedure, maleimide (1.59 g, 16.05 mmol) and 3-methoxybenzylamine (2.3 ml, 17.8 mmol) in ethyl acetate (25 ml) afforded an oil which was recrystallized from a mixture of ethyl acetate/cyclohexane (sometimes, the heavy oil precipitated after trituration). The yield was quantitative of a white solid. mp = 72 °C. An analytical sample was obtained after flash chromatography on silica (ethyl acetate/cyclohexane 1/1, R_f = 0.1). ^{1}H NMR (200 MHz, $CDCl_3$) : 8.20 (m, 1H, NH) ; 7.30 (d, 2H, J = 7.8 Hz, two phenyl protons) ; 7.00-6.80 (m, 3H, phenyl ring) ; 3.70-4.00 (m,

6H, CH_2-O, CH_2 benzyl and H_3) ; 2.94 (dd, 1H, J = 8.3 Hz and 18 Hz, H_4) ; 2.61 (dd, 1H, J = 5.3 Hz and J = 18 Hz, $H_{4'}$) ; 2.1 (m, 1H, NH amine). ^{13}C NMR (200 MHz, $CDCl_3$) ; 177.7 (C_2 or C_5) ; 174.7 (C_2 or C_5) ; 159.8 (quaternary phenyl carbon substitued by MeO group) ; 140.0 (quaternary phenyl carbon substitued by CH_2 group) ; 129.6, 120.3, 113.65 and 112.9 (phenyl group) ; 56.5 (C_3) ; 55.1 (methoxy group) ; 51.55 (CH_2 benzyle) ; 37.3 (C_4). IR (cm^{-1}) : 3288 (NH) ; 1718 (C=O). Anal. calcd for $C_{12}H_{14}N_2O_3$: C, 61.52 ; H, 6.04 ; N, 11.96. Found: C, 61.33 ; H, 6.3 ; N, 12.04.

3-N-[(3-Benzyloxyphenyl)methyl]aminosuccinimide ***5f***. According to general procedure, maleimide (3.6 g, 37 mmol) and 3-benzyloxybenzylamine (9.3 g, 43.6 mmol) in ethyl acetate (140 ml) afforded an oil which was purified by flash chromatography on silica (gradient elution with a mixture ethyl acetate/cyclohexane 2/5 then with a mixture of ethyl acetate/cyclohexane 3/2 in which the R_f of the product was 0.3). The yield was 99 % of a yellow oil. ^1H NMR (200 MHz, $CDCl_3$) : 8.20 (m, 1H, NH) ; 7.40-7.20 (m, 6H, aromatic protons); 7.00-6.80 (m, 3H, phenyl ring); 5.08(s, 2H); 3.94(d, J = 13.4 Hz; H_7) ; 3.80(d, 1H, J = 13.4 Hz, $H_{7'}$) ; 3.79(dd, 1H, J = 5.5 Hz and J = 8.2 Hz, H_3) ; 2.84 (dd, 1H, J = 8.3 and J = 18.1 Hz, H_4); 2.56 (dd, J = 5.4 and J = 18.1 Hz, $H_{4'}$); 2.00 (m, 1H, H_6). IR (cm^{-1}) : 3227 (NH) ; 1780, 1713 (C=O). Anal. calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.81; H, 5.81; N, 8.94.

3-(N-Benzyl-N-methoxycarbonyl)aminosuccinimide ***5g***. To a solution of *N*-benzylsuccinimide (0.897 g, 4.4 mmol) in dichloromethane (50 ml), methyl chloroformate (0.35 ml, 4.4 mmol) was added. The mixture was stirred at room temperature for 45 min. A white precipitate of amine hydrochloride appeared and triethylamine (0.62 ml, 4.4 mmol) was added dropwise within 45 min (the white precipitate disappeared). The mixture was further stirred for 30 min at room temperature and poured on ice cooled water (50 ml). The organic layer was separated and the aqueous layer extracted with dichloromethane (3x35 ml). The combined organic extracts were dried on magnesium sulfate and concentrated under reduced pressure to afford an oil which crystallized from a cyclohexane/ethyl acetate mixture. Yield 93 %. mp = 113 °C. TLC : R_f = 0.4 (ethyl acetate/cyclohexane 4/3). ^1H NMR (200 MHz, $CDCL_3$) : 8.49 (m, 1H, NH) ; 7.40-7.10 (m, 5H, phenyl group) ; 4.86 (dd, 1H, J = 15.6 and 15.9 Hz, one benzyl proton) ; 4.49 (dd, 1H, J = 15.6 and 15.7 Hz, the other benzyl proton) ; 4.04 (dd, 1H, J = 9 Hz et J = 6.1 Hz, H_3) ; 3.76 (2s, 3H) ; 2.86 (dd, 1H, J = 6.1 Hz and J = 17.9 Hz, H_4) ; 2.70 (dd, 1H, J = 9.1 Hz and J = 17.9 Hz, $H_{4'}$). Some small signals were partially masked by signals at 4.2. IR (cm^{-1}) : 3195 (NH) ; 1784 and 1724 (C=O) ; Anal. calcd for $C_{13}H_{14}N_2O_4$: C, 59.53 ; H, 5.39 ; N, 10.68. Found : C, 59.04, H, 5.35 ; N, 10.23.

General procedure for the reduction of aminosuccinimides :

We had some problems of reproducibility with a commercial sample of maleimide giving poor results in reductions after the nucleophilic addition of amines. These problems were solved after purification of the corresponding sample of maleimide by sublimation under reduced pressure. Sodium borohydride (3 to 5 equiv) was added in one or two portions to a solution of the appropriate imide in ethanol (concentration range : 0.031-0.062M) at 0-5°C, under stirring. The solution was stirred at 0-5°C during the appropriate time and then cooled at -50 °C. A solution of 1 M aqueous sulfuric acid was then added until pH = 3 (pH testing paper) the temperature being maintained under -25°C. After 18h stirring at room temperature, the mixture was basified with a minimal amount of a saturated aqueous solution of potassium hydrogen carbonate. After stirring for a few minutes, the insoluble material was removed by filtration. Ethanol was removed from the filtrate with a rotary evaporator and the remaining aqueous solution extracted with dichloromethane. The organic layers were dried on magnesium sulfate and concentrated under reduced pressure. The crude product was chromatographed on a silica column. The ethoxypyrrolidin-2-ones were rather unstable and, in most cases, no analytically pure sample could be obtained.

3-[N-Benzyloxycarbonyl]amino-5-ethoxypyrrolidin-2-one ***7a***. From 3-*N*-benzyloxycarbonylamino succinimide **5a** (0.5 g, 2 mmol) in ethanol (25 ml) and sodium borohydride (0.38 g, 10 mmol) at -15 °C for 15 min an oil was obtained. This oil was chromatographed on silica (ethyl acetate/cyclohexane 3/1, R_f = 0.2) to afford a 45% yield of a colourless oil containing the two C_5 epimers A and B. ^1H NMR (200 MHz, $CDCl_3$) : 8.10 (m, 1H, NH A/B) ; 7.80 (m, 1H, NH, A/B) ; 7.4-7.2 (s, 5H, phenyl ring) ; 5.85 (d, 1H, J = 5.9 Hz, NH carbonate A) ; 5.55 (d, 1H, J = 7.7 Hz, NH carbonate B) ; 5.12 (s, 2H, CH_2 benzyle +B) ; 4.86 (d, 1H, J = 4.7 Hz, H_5 B) ; 4.79 (s, 1H, H_5 A) ; 4.60-4.40 (m, 1H, H_4 B) ; 4.20-4.00 (m, 1H, $H_{4'}$ A) ; 3.7-3.2 (m, 2H, CH_2

ethyl group A+B) ; 2.93 (dd, 1H, J = 7.5 and J = 17.7 Hz, H_3 A) ; 2.66 (dd, 1H, J = 8.4 and J = 16.5 Hz, H_3 B) ; 2.29 (dd, 1H, J = 9.8 and J = 16.5 Hz, $H_{3'}$ B) ; 2.13(d, 1H, J = 17.7 Hz, $H_{3'}$ A) ; 1.35-1.10 (m, 3H, CH_3 ethyl group A+B). IR (cm^{-1}) : 3300 (NH carbonate) ; 1706 (C=O).

4-(N-Benzyl)amino-5-ethoxypyrrolidin-2-one ***8c***. From *N*-benzylaminosuccinimide **5c** (1 g, 4.9 mmol) in ethanol (160 ml) and two portions of sodium borohydride (0.76 g, 19.6 mmol) at 0-5 °C for 90 min, an oil (0.6 g) was obtained. The yield was 27% of a colourless oil which was purified by flash chromatography on silica. The starting material was eluted first with ethyl acetate (R_f = 0.55) and the final product was eluted with ethyl acetate/ethanol 1/1 (R_f = 0.6). Mixture of two C_5 epimers A and B. ^1H NMR (200 MHz, $CDCl_3$); 7.7-7.5 (m, 1H, NH A+B) ; 7.4-7.1 (m, 5H, phenyl group, A+B) ; 4.78 (d, 1H, H_5 A/B) ; 4.77 (s, 1H, H_5 A/B) ; 3.84 (2s, 2H, CH_2 benzyle A+B) ; 3.80-3.3 (m, 3H, H_4 and CH_2 ethyl group A+B) ; 2.79 (dd, 1H J = 7.2 and J = 17.4 Hz, H_3 A) ; 2.51 (dd, 1H, J = 7.9 and J = 16.6 Hz, H_3 B) ; 2.40 (m, 1H, NH), 2.26 (dd, 1H, J = 10.6 and J = 16.6 Hz, $H_{3'}$ B) ; 2.13 (dd, 1H, J = 2.4 and J = 17.4 Hz, $H_{3'}$ A) ; 1.25 (t, 3H, J = 7Hz, CH_3 ethyl A/B) ; 1.23 (t, 3H, J = 7Hz, CH_3 ethyl A/B). IR (cm^{-1}) : 3281 (NH) ; 1703 (C=O).

3-(N-Benzyl-N-methyl)amino-5-ethoxypyrolidin-2-one ***7d***. From 3-(*N*-methyl-*N*-benzyl)amino succinimide **5d** (3 g, 37 mmol) in ethanol (220 ml) and two portions of sodium borohydride (1.55 g ; 41.1 mmol, each time) at 0-5 °C for 1h, an oil was obtained after work-up. The product was chromatographed on silica : the starting material was eliminated after elution with ethyl acetate and the product was further eluted with ethyl acetate/ethanol 18/1 to yield 36% of an oil which crystallized slowly. mp = 76°C. TLC : R_f = 0.4 (AcOEt/EtOH 18/1). ^1H NMR (400 MHz, $CDCl_3$) : The two C_5 epimers A and B were observed. 7.54 (m, 1H, NH A+B) ; 7.36-7.20 (m, 5H, phenyl group A+B) ; 4.91-4.86 (m, 1H, H_5 A) ; 4.825 (ddd, 1H, J = 6.9 Hz, J = 3.4 Hz and J = 0.8 Hz, H_5 B) ; 3.85-3.33 (m, 5H, CH_2 benzyle, H_3, CH_2 ethyl A+B) ; 2.65-1.93 (m, 5H, CH_3 and H_3, H_3, A+B) ; 1.20 (t, 3H, J = 7 Hz, CH_3 ethyl group A/B) ; 1.17 (t, 3H, J = 7 Hz, CH_3 ethyl group A/B). In the complex signal occuring between 2.65-1.93, the following chemical shifts were attributed with ^1H COSY : 247 (ddd, 1H, J = 14.3, J = 6.9 and J = 9.9 Hz, H_4B) and 1.96 (ddd, 1H, J = 14.3, J = 3.4 and J = 6.5 Hz, $H_{4'}$ B). IR(cm^{-1}) : 3226(NH), 1707 (C=O). MS (CI, isobutane) : 249 (M+1) ; 203 (M+1-EtOH) ; 120 (Ph-CH_2-N-CH_3+). Anal. calcd for $C_{14}H_{20}N_2O_2$: C, 67.7 ; H, 8.13; N, 11.28. Found : C, 67.37 ; H, 8.29 ; N, 11.22.

3-[N-(3-Methoxybenzyl)]amino-5-ethoxypyrrolidin-2-one ***8e***. From imide **5e** (3.19 g, 15.6 mmol) in ethanol (300 ml) and two portions of sodium borohydride (1.57 g, 40.7 mmol) for 120 min at 0-5 °C, an oil (3.25 g) was obtained, in 46 % yield after flash chromatography on silica. The starting material was eluted first with ethyl acetate (R_f = 0.5) and the product with ethyl acetate/ethanol 10/2 (R_f = 0.4). Mixture of two C_5 epimers A and B. ^1H NMR (200 MHz, $CDCl_3$) : 7.7-7.5 (m, 1H, NH A+B) ; 7.25 (m, 1H, A+B) ; 6.70-7.00 (m, 3H, A+B) ; 4.80 (d, 1H, J = 5.1 Hz, H_5 A/B) ; 4.76 (d, 1H, J = 1.1 Hz, H_5 A/B) ; 3.7 (broad, 5H, MeO and CH_2 benzyle A+B) ; 3.70-3.30 (m, 3H, CH_2 ethyl group and H_4 A+B) ; 2.12 (dd, 1H, J = 2.5 and J = 17.4 Hz, H_3 A) ; 2.26 (dd, 1H, J = 10.5 and J = 16.6 Hz, H_3 B) ; 2.40 (m, 1H, NH) ; 2.51 (dd, J = 7.8 and J = 16.6 Hz, 1H, $H_{3'}$ B) ; 2.79 (dd, 1H, J = 7.3 and J = 17.4 Hz, $H_{3'}$ A) ; 1.35-1.15 (m, 3H, CH_3 ethyle A+B). IR (cm^{-1}) : 3280 (NH) ; 1703 (C=O)

3-[N-(3-Benzyloxyphenyl)methyl]amino-5-ethoxypyrrolidin-2-one ***8f***. From imide **5f** (2.95 g, 9.5 mmol) in ethanol (220 ml) and two portions of sodium borohydride (1.46 g, 37.7 mmol) for 120 min at 0-5 °C, an oil (2.91 g) was obtained, in 38 % yield after flash chromatography on silica. The starting material was eluted first with ethyl acetate and the product with ethyl acetate/ethanol 10/2 (R_f = 0.2). Mixture of two C_5 epimers A and B. ^1H NMR (200 MHz, $CDCl_3$) : 7.92 (m, NH, A/B); 7.50-7.20 (m, 5H, A+B) ; 7.0-6.80 (m, 4H, A+B) ; 5.08 (s, 2H, A+B) ; 4.74 (s, 1H, A+B) ; 3.8-3.3 (m, 5H, A+B) ; 2.75 (dd, 1H, A) ; 2.50 (dd, 1H, J = 7.9 and J = 16.5 Hz, H_3, B) ; 2.23 (dd, 1H, J = 10.5 and J = 16.6 Hz, H_3 B) ; 2.09 (dd, J = 9.5 and J = 17.5 Hz, 1H, B) ; IR (cm^{-1}) : 3220 (NH) ; 1715 (C=O)

3-(N-Benzyl-N-methoxycarbonyl)amino-5-ethoxypyrrolidin-2-one ***7g***. From the imide **5g** (0.153 g, 0.58 mmol) in ethanol (10 ml) and only one portion of sodium borohydride (0.11 g, 2.9 mmol) stirred for 70 min at 0-5 °C, an oil was obtained. A white solid was obtained after flash chromatography (silica, ethyl acetate, R_f = 0.3). Yield : 35 %. Mixture of two C_5 epimers A and B. ^1H NMR (200 MHz, $CDCl_3$) : 9.4 (m, 1H, NH A+B) ; 7.5-7.1 (m, 5H, phenyl group A+B) ; 5-3.9 (m, 5H, CH_2 benzyle, H_5 and H_3 A+B); 3.9-3.2 (m, 5H, CH_3, CH_2 ethyl A+B) ; 2.9-1.9 (m, 2H, H_4 and $H_{4'}$ A+B) ; 1.3-1.0 (m, 3H, CH_3 ethyl group A+B).

Ring closure of the ethoxylactams

2-Methyl-1,2,5,6-tetrahydro-3,6-methano-2H-2,5-benzodiazocin-4-one ***9d***. Titanium tetrachloride (0.19 ml, 1.72 mmol) was slowly added to a stirred solution of the δ-ethoxylactam **7d** (0.102 g, 0.4 mmol) in dichloromethane (5 ml) at -73 °C under an argon atmosphere. The dry ice bath was then removed and the solution was stirred for 12 h at room temperature. The mixture was cooled at about 0 °C and an aqueous saturated solution of sodium hydrogen carbonate was added until pH = 7-8 (pH testing paper, caution, because the reaction is very exothermic). The organic layer was separated and the aqueous layer extracted with dichloromethane. The combined organic layers were dried on magnesium sulfate and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica (ethyl acetate/ethanol 18/1, R_f = 0.2). The yield was 37% of a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$) : 7.70 (m, 1H, NH) ; 7.4-7.0 (m, 4H, H_7, H_8, H_9, H_{10}); 5.32 (d, 1H, J = 5.9 Hz, H_6) ; 5.28 (m, 1H, H_6) ; 3.93-3.40 (m, 3H, CH_2 at 1 and H_3) ; 2.50-2.00 (m, 2H, bridgehead CH_2) ; 2.34 (s, 3H, N-CH_3) ; 2.77 (s, 3H, NCH_3). ^{13}C NMR (200 MHz, $CDCl_3$) : 30.85 and 31.4 (bridgehead CH_2); 38.0 and 38.6 (N-CH_3, correlated with protons at 2.34 and 2.77); 59.4 and 59.6, CH_2 at 1, correlated with protons at 3.40-3.93); 61.7 and 62.9 (C_3); 77.4 (C_6, correlated with proton at 5.32); 127.9, 128.9 and 129.7 (C_7, C_8, C_9, C_{10}); 138.5 (C_{1a} and C_{6a}); 176.6 and 178.2 (C=O). HRMS: Calcd for $C_{12}H_{14}N_2O$: M = 202.1106 g.mol^{-1}; Found: M = 202.1124 g.mol^{-1}.

2-Methoxycarbonyl-1,2,5,6-tetrahydro-3,6-methano-2H-2,5-benzodiazocin-4-one ***9g***. According to the procedure described above, δ-ethoxylactam **7g** (0.054 g, 0.18 mmol) in dichloromethane (4 ml) and titanium tetrachloride (1.09 mmol, 0.12 ml) afforded a 40% yield of an oil which was purified by flash chromatography on silica (ethyl acetate/ethanol 18/1, R_f = 0.2). Colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$) : 7.4-7.0 (m, 5H, NH, H_7, H_8, H_9, H_{10}) ; 5.30-4.21 (m, 4H, CH_2 at 1, H_3 and H_6) ; 3.74 (2s, 3H, CH_3 carbamate) ; 2.80-2.40 (dt, 2H, J = 6.5 and 13.0 Hz, bridgehead CH_2) ; 1.99 (dd, J = 6.7 and J = 13.0 Hz, bridgehead CH_2). ^{13}C NMR (200 MHz, $CDCl_3$) : 38.2 and 38.6 (bridgehead CH_2); 47.8 (CH_2 at 1); 53.4 (CH_3 carbamate); 57.4 (C_3); 59.8 (C_6); 128.0, 128.2; 128.9 (C_7, C_8, C_9, C_{10}); 136.6 (C_{1a} and C_{6a}); 155.9 (C=O carbamate); 174.3, 174.8 (C=O lactam).

1a,3a,4,5-Tetrahydro-7-methoxy-1H,3Hpyrrolo[3,2-c]isoquinolin-2-one ***10e***. A mixture of δ-ethoxylactam **8e** (0.0241 g, 0.091 mmol) and p-toluenesulfonic acid monohydrate (0.0355 g, 0.18 mmol) in dichloromethane (10 ml) was heated to reflux for 18 h. The cooled solution was washed with aqueous saturated sodium hydrogen carbonate (2x7 ml). The combined aqueous phases were extracted with dichloromethane (8 ml). The combined organic phases were dried on magnesium sulfate and concentrated under reduced pressure. The crude solid was purified by flash chromatography on silica. The side products were first eluted with ethyl acetate and the product was eluted with ethyl acetate/ethanol 1/1. The yield was 46% of a white solid. mp = 212 °C (in a sample containing no traces of the other isomer). ^{1}H NMR (400 MHz, $CDCl_3$) ; 7.13 (d, 1H, J = 8.4 Hz, H_9) ; 6.80 (dd, 1H, J = 2.6 and J = 8.4 Hz; H_8) ; 6.61 (d, 1H, J = 2.5 Hz, H_6) ; 6.18 (m, 1H, NH) ; 4.51 (d, 1H, J = 4.9 Hz, H_{1a}) ; 3.90 (s, 2H, 5-CH_2) ; 3.75 (m, 4H, H_{3a} and CH_3O) ; 2.82 (dd, 1H, J = 7.0 and 17.3 Hz, one proton of 3-CH_2) ; 2.28 (dd, 1H, J = 17.3 and 1.1 Hz, the other proton of 4-CH_2) ; 1.64 (m, 1H, NH). IR (cm^{-1}) : 3195 (NH lactam) ; 1694 (C=O). Anal. calcd for $C_{12}H_{14}N_2O_2$: C, 66.03 ; H, 6.48 ; N, 12.84. Found : C, 66.09 ; H, 6.41 ; N, 12.88. A small amount of the other isomer can be detected by careful study of the ^{1}H 400 MHz spectrum.

1a,3a,4,5-Tetrahydro-7-benzyloxy-1H,3Hpyrrolo[3,2-c]isoquinolin-2-one ***10f***. A mixture of δ-ethoxylactam **8f** (1.24 g, 3.6 mmol) and *p*-toluenesulfonic acid monohydrate (1.40 g, 7.2 mmol) in dichloromethane (80 ml) was heated to reflux for 18 h. The work-up described above for **10e** afforded 60% of a white solid. mp = 208 °C (from ethyl acetate/ cyclohexane). ^{1}H NMR (200 MHz, $CDCl_3$) ; 7.50-7.20 (m, 5H), 7.18 (d, J = 8.5 Hz, H_{12}) ; 6.90 (dd, 1H, J = 2.5 and J = 8.5 Hz; H_{11}) ; 6.70 (d, 1H, J = 2.5 Hz, H_9) ; 5.89 (m, 1H, NH) ; 5.07 (s, 2H); 4.56 (d, 1H, J = 4.9 Hz, H_{1a}) ; 3.93 (s, 2H, 5-CH_2) ; 3.80 (m, 1H, H_{3a}) ; 2.86 (dd, 1H, J = 7.0 and 17.3 Hz, one proton of 3-CH_2) ; 2.32 (dd, 1H, J = 17.3 and 1.2 Hz, the other proton of 4-CH_2) ; 1.68 (m, 1H, NH). IR (cm^{-1}) : 3185 (NH lactam) ; 1696 (C=O). Anal. calcd for $C_{18}H_{18}N_2O_2$, H_2O : C, 69.21 ; H, 6.45 ; N, 8.97. Found : C, 70.4 ; H, 6.15 ; N, 9.1. ^{13}C NMR (200 MHz, $CDCl_3$) : 39.4 (C_3); 46.35 (C_5); 53.1 and 54.1 (C_{1a} and C_{3a}, no attribution); 70.55 (O-CH_2-Ph); 112.6 and 114.7 (C_6 and C_8, no attribution); 127.8, 128.5, 129.1 and 130.8 (C_6 and tertiary carbon atoms of the phenyl ring on the benzyloxy group); 138.5 (quaternary carbon atom of the phenyl ring on the benzyloxy group); 159.5 (C_7); 175.9 (C=O).

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