[4+2] Cycloaddition of α,β-Unsaturated Acid Anhydrides to 2-Furylpiperidin-4-ones: The Short Route to Annulated 8,10a-Epoxypyrido[2,1-*a*]isoindoles

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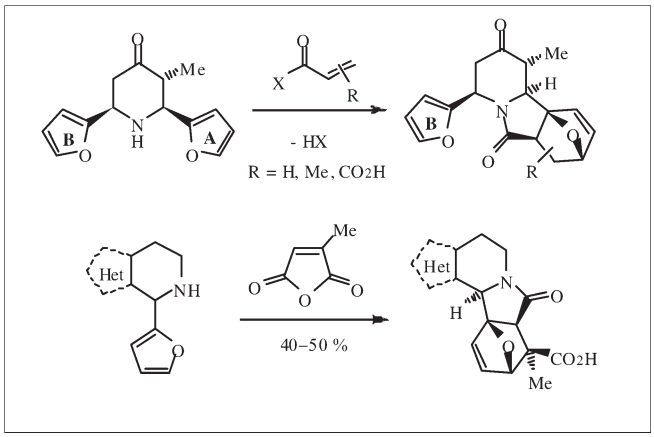
Received August 8, 2009
DOI 10.1002/jhet.316
Published online 4 March 2010 in Wiley InterScience (www.interscience.wiley.com).



A one-step preparation procedure of 8,10a-epoxypyrido[2,1-*a*]isoindoles and their 7-carboxylic derivatives is reported. The key synthetic step includes the intramolecular *exo*-Diels–Alder reaction (IMDAF) of *N*-furfurylacrylamide, produced *in situ* from 2-furylpiperidin-4-ones and α,β-unsaturated acid anhydrides. The synthesis of the title compounds can be performed under mild conditions with a high level of regio- and stereoselectivity. The same strategy has been successfully used for the synthesis of 9,11a-epoxyimidazo[4′,5′:3,4]pyrido[2,1-*a*]isoindole-8-carboxylic acid from maleic anhydride and the spinacine derivatives – 4-(2-furyl)-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridines.

J. Heterocyclic Chem., **47**, 400 (2010).

INTRODUCTION

Substituted and hydrogenated pyrido[2,1-*a*]isoindoles possess a wide range of pharmacological activity. For example, they are known to have a protective effect against nitrogen-induced hypoxia [1] and are potential inhibitors of tumor cell proliferation [2]. It is known as well that compounds containing heterocyclic fragments of spinacine and β-carboline are of great biological importance. Thus, the aminoacid spinacine (separated first from shark liver [3], found also in ginseng roots [4] and cheese [5]) shows the properties of an inhibitor of γ-aminobutyric acid uptake in neurons [6]. The heterocyclic structure of β-carboline serves as a framework for well-known alkaloids: *Elaeagnine*, *Harman*, and *Harmine* [7] (Fig. 1).

Therefore, one of the aims of this work was the development of a convenient method of synthesis for potentially biologically active heterocycles—benzo[1,2]indolizino[8,7-*b*]indole and imidazo[4′,5′:3,4]pyrido[2,1-*a*]isoindole, combining the above fragments into one structure.

To achieve the aforementioned goal, we used an intramolecular variant of the Diels-Alder reaction in the piperidone series (IMDAF), containing the unsaturated moiety [8–10]. We have used the same strategy before for various preparations of heterocyclics – particularly for isoindolo[2,1-*a*]quinolines [11], isoindolo[2,1-*b*][2]benzazepines [12], and isoindolo[1,2-*a*]isoquinolines [13], with the structure close to natural alkaloids.

RESULTS AND DISCUSSION

Starting materials for pyrido[2,1-*a*]isoindoles preparation, the furfuryl amines **1**, were synthesized from readily accessible ketones and from furfural (5-methylfurfural), according to the known method [14] with small variations

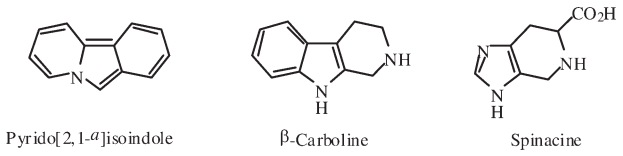


Figure 1. Some of the targeted alkaloid-like structures.

(see Experimental section). The piperidones **1a–d** were separated after the recrystallization in moderate yield (Scheme 1) as individual *all-e*-diastereoisomers.

It should be noted that the yields of symmetrically substituted amino ketones **1b**,**d** turned out ~20% higher than for unsymmetric **1a**,**c**.

Interaction of α,β-unsaturated acid derivatives (methacrylic and cinnamic acid chlorides) with symmetric furfuryl amines **1b**,**d** proceeds smoothly in boiling toluene (Scheme 2). It was established during experiment that after initial acylation on the nitrogen atom, a spontaneous intramolecular [4+2] cycloaddition of an unsaturated fragment to the furan ring occurs in intermediate *N*-acryloyl amides. The final products of the reaction are hydrogenated 2*H*-8,10a-epoxypyrido[2,1-*a*]isoindole-2,6(6a*H*)-diones **2**, **3**. The substituent's size in olefin moiety exerts a considerable influence on the yield of adducts **2**, **3**—the yield of 6a-methylsubstituted derivatives **2** is 15–30% higher compared to their more sterically hindered 7-phenyl analogues **3**.

In both cases the Diels-Alder reaction occurs stereoselectively as *exo*-[4+2]-cycloaddition with *endo*-position of methyl (phenyl) group in oxabicyclo[2.2.1]heptene fragment of adducts **2** and **3**. Axial-axial constant of piperidine ring protons $^3J_{1,10b} = 11.8-12.2$ Hz and vicinal constant of bicyclic fragment's low-field protons $^3J_{9,10} = 5.5-6.2$ Hz are most evident in their ^{1}H NMR spectra.

Acylation of piperidones **1b**,**d** by citraconic anhydride proceeds in both carbonyl groups, leading to the formation of stereoisomers **4bA**,**4dA/4bB**,**4dB** mixtures with different methyl group positions (see Scheme 2 for the total yield of stereoisomeric mixture). 7-Methylsubstituted isomers **4bA**, **4dA** dominate in crude reaction mixtures; the A/B ratio fluctuates in different experiments and is usually within the 4:1–3:1 interval. Major isomers **4bA**, **4dA** were separated as individual compounds by fractional recrystallization from *i*-PrOH–DMF mixture (their yields are summarized in Experimental section).

Cycloaddition of methacryloyl chloride, crotonyl chloride, and cinnamoyl chloride to unsymmetric difurylpiperidines **1a**,**c** proceeds stereoselectively as well as regioselectively, giving *exo*-products of Diels-Alder **2a**,**c**, **3a**,**c**,**e** with moderate yield (Scheme 3). Citraconic anhydride, being added to piperidones **1a**,**c**, forms diastereomeric mixtures, from which we could separate only major adducts **4aA**, **4cA** after the recrystallization.

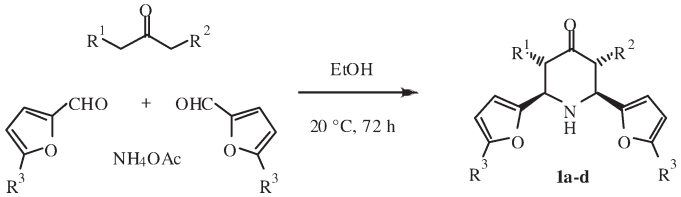
It should be noted if the three-fold excess of dienophile is used in reaction with furfuryl amines **1**, the cycloaddition of a second alkene molecule to the free furan nucleus of isoindoles **2–4** does not occur.

Interestingly enough, from two furan fragments (**X** and **Y**) present in unsymmetrical piperidones **1a**,**c**, [4+2]-cycloaddition passes regiospecifically to 2-furyl ring **Y**. In our opinion, such selectivity is related to the fact that the furan cycle **Y** in intermediate lactam **4*** (Scheme 4) is fixed strictly favorably to the Diels-Alder reaction (due to steric interaction with 3-alkyl substituent). Alternative 6-furyl substituent (**X**) can rotate freely, and is consequently less predisposed to cycloaddition.

Cycloaddition adducts of 2,6-dioxo-8,10a-epoxypyrido[2,1-*a*]isoindole-7-carboxylic acids (**4**) are white powders with low solubility in most organic solvents, so for the unequivocal determination of their spatial structure we have synthesized methyl ester **5** from the acid **4aA** (Scheme 5). Slow recrystallization of this ester from a hexane-ethyl acetate mixture gave us a monocrystal suitable for X-ray analysis.

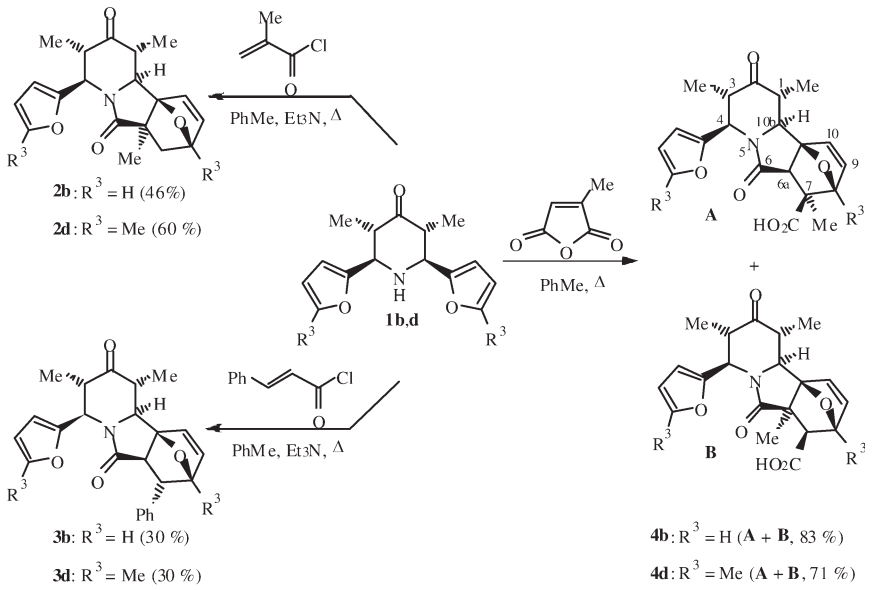
Adduct **5** comprises a fused tetracyclic system containing three five-membered (pyrrolidinone, dihydro- and tetrahydrofurans) rings and one six-membered ring (piperidinone) (Fig. 2). The five-membered rings have the usual *envelope* conformation. The six-membered ring adopts a *twist-boat* conformation (the C3 and C10B carbon atoms are out of the mean plane as defined by the other atoms of the ring by 0.577 and 0.559 Å, respectively). The N5 nitrogen atom has a trigonal-planar geometry (the sum of the bond angles about N5 is 359.5°). The dihedral angle between the planes of the pyrrolidinone and piperidinone rings is 19.1°. The methyl substituent at the C1 carbon atom is in equatorial position, whereas the furyl substituent at the C4 carbon

Scheme 1. Synthesis of the initial piperidones **1a-d**.



Comp.	R^1	R^2	R^3	Yield (%)
1a	H	Me	H	34
1b	Me	Me	H	63
1c	H	Et	H	33
1d	Me	Me	Me	41

Scheme 2. Cycloaddition with symmetrical substituted piperidones **1b**,**d**.

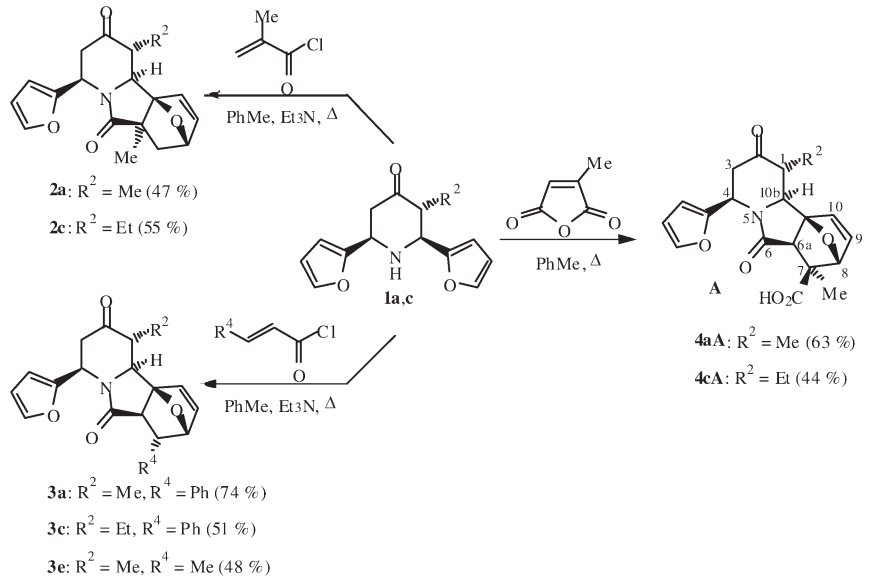


atom is in axial position. The sterically unfavorable axial arrangement of the furyl substituent is apparently explained by both the structure of the initial compound **1a** and the structure of the [4+2] cycloaddition reaction intermediate.

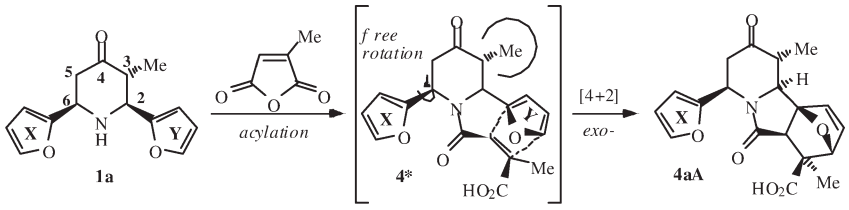
The synthesis of 2,6-unsymmetrically substituted piperidine-4-ones by condensation of α,β-unsaturated ketone, an aldehyde and ammonia was described earlier for the dendrobatid frog alkaloid 241D [15]. In this case the yield of target piperidine-4-ones did not exceed 10−12%. We used this method for the synthesis of 6-aryl-2-furylpiperidine-4-ones **6** (Scheme 6). The reaction conditions were standard [14c,15], and furfural and 5-methylfurfural were used as aldehydes. The usual work-up gives a mixture of products, from which the target piperidones **6** can be separated easily (although with low yield) as hydrochlorides (see Experimental section). 2-Furylpiperidones **6a-c** react smoothly with acryloyl chloride and maleic anhydride in boiling toluene, giving *exo*-products of cycloaddition—2*H*-8,10a-epoxypirido[2,1-*a*]isoindoles (**8**) and their 7-carboxylic acids (**7**)—with moderate yields.

The most low-field chemical shifts of C-2 (δ 208−211 ppm) and C-6 (δ 170−176 ppm) carbon atoms, together with well-identified C-10a and C-8 (δ

Scheme 3. Cycloaddition with unsymmetrical substituted piperidones **1a**,**c**.



Scheme 4. Mechanistic explanation for the high regioselectivity of Diels-Alder reaction.



79−91 ppm) carbon atom signals are the most characteristic in ^{13}C NMR spectra of cycloaddition products **2**−**5**, **7**, **8**.

A large number of methods for pentacyclic indolizinoindole core synthesis are known [16], and the similarity of this heterocyclic system to some alkaloids encourages further research. Several short studies [17] dedicated to the synthesis of benzo[1,2]indolizino[8,7-*b*]indol-4-carboxylic acids of type **10** from maleic anhydride and *N*-furfurylidene(indol-3-yl)ethanamines have been published recently. An elegant reaction sequence (acylation/ Pictet-Spengler/ IMDAF) proceeds in mild conditions (Scheme 7). To build some alkaloid-like polycyclic structures by Suzuki coupling, we needed to synthesize 3-halosubstituted adducts **10**.

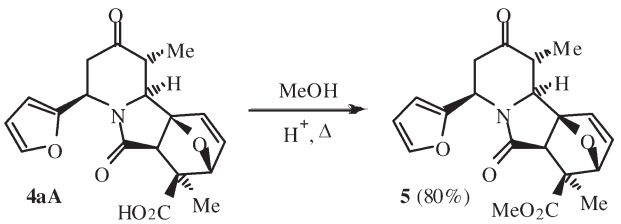
As was shown earlier [17], the condensation of *N*-furfurylidenetriptamines **9a**,**b** with maleic anhydride proceeds stereoselectively, yielding the single *exo*-diastereoisomer **10a**,**b**. Analogous interaction of azomethine **9c** with citraconic anhydride leads with good yield to the mixture of polycycles **12A** and **12B** (in approximatively equal amounts), isomeric by methyl group position, that we could not separate by recrystallization.

Haloderivatives **10a**,**b** are white powders, low soluble even in DMSO, so to determinate their structure by ^{1}H and ^{13}C NMR we have synthesized esters **11**. The spatial structure of these latter was established by NOE spectra, in which we can observe a significant change of H-13b proton integral intensity, while irradiating H-4a (and *vice versa*). This fact indicated the spatial closeness (*cis*-orientation) of the above protons.

In the last part of our work we have applied an analogous method for the synthesis of spinacines annelated with epoxyisoindole moiety. The condensation of histamine with aromatic aldehydes in an alkaline medium leading to spinacines (Fig. 1) was already described [18]. However, no examples of 4-furyl substituted imidazo[4,5-*c*]pyridines have been published until now. Furylspinacines **13** were synthesized with moderate yield according to modified method [18b] (Scheme 8).

Acylation of spinacines **13** with maleic anhydride at room temperature occurs exclusively on the *N*-5 nitrogen atom of the tetrahydropyridine ring – products of anhydride addition to imidazole cycle were not found in the reaction mixture. Acylation (same as in previous cases) is accompanied by simultaneous [4+2] cycloaddition giving *exo*-adducts **14**. We suppose the *cis*-position of H-7a and H-11b protons by analogy with adducts **2**-**4**, **7**, **8**, and **10**. Cycloaddition products are extremely hard-soluble and hard-crystallizing tawny powders. The low-field singlet signal of H-2 proton at δ ∼7.5 ppm and broaded one of H-11b at δ ∼5.3 ppm, as well as associated *exo*-protons H-7a, H-8 with $^{3}J_{7a,8}$ = 8.9−9.1 Hz (at δ 2.5−3.0 ppm), can be considered as characteristic. In the carbon spectrum, C-2 and C-11a peaks at δ 135−136 and 90−91 ppm, respectively, are remarkable.

Scheme 5. Esterification of the carboxylic acid **4aA**.



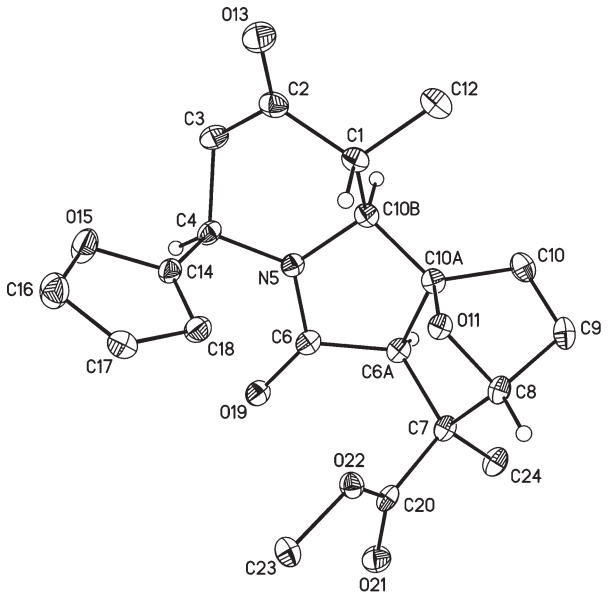
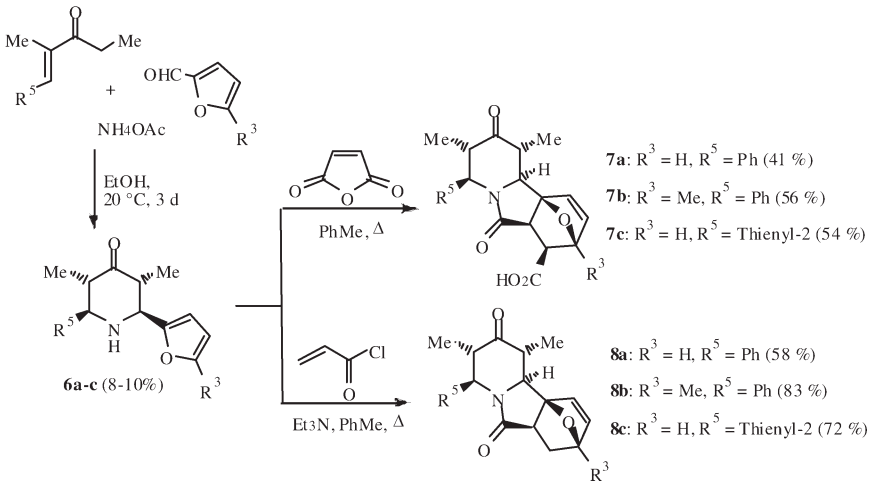


Figure 2. Molecular structure of ester **5**, depicting anisotropic displacement ellipsoids at the 50% probability level. Only hydrogen atoms at the asymmetric centers are shown.

Scheme 6. Synthesis and [4+2] cycloaddition of 2-aryl-6-furylpiperidine-4-ons **6**.

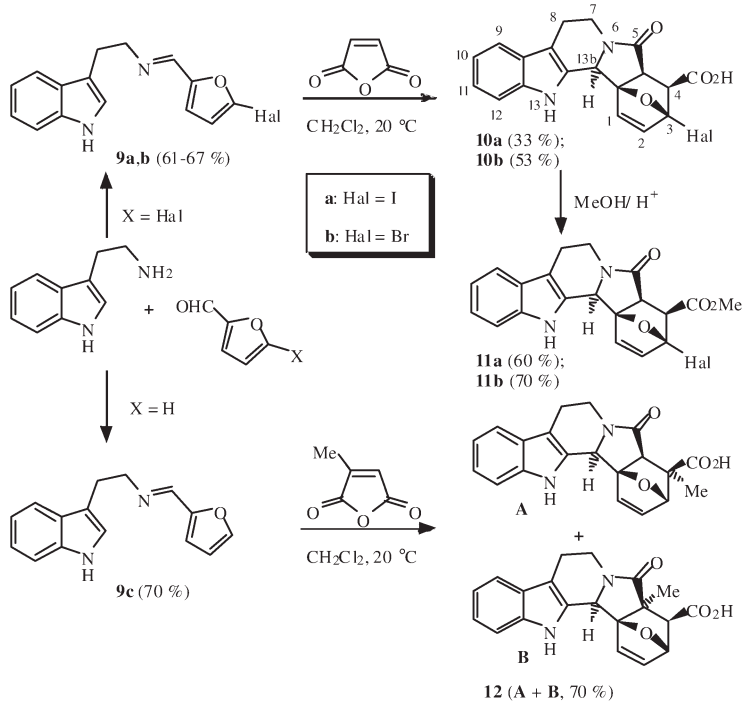


Therefore, in the current study we have demonstrated the possibility of synthesis of various heterocyclic systems condensed with an epoxyisoindole fragment: 8,10a-epoxypyrido[2,1-*a*]isoindoles, 3,13c-epoxybenzo[1,2]indolizino[8,7-*b*]indoles and 9,11a-epoxyimidazo[4′,5′:3,4]pyrido[2,1-*a*]isoindoles, based on IMDAF-reaction of annelated furfuryl amines with α,β-unsaturated acid anhydrides. It was shown that in the majority of cases the Diels-Alder reaction proceeds with a high degree of regio- and stereoselectivity as *exo*-[4+2] cycloaddition.

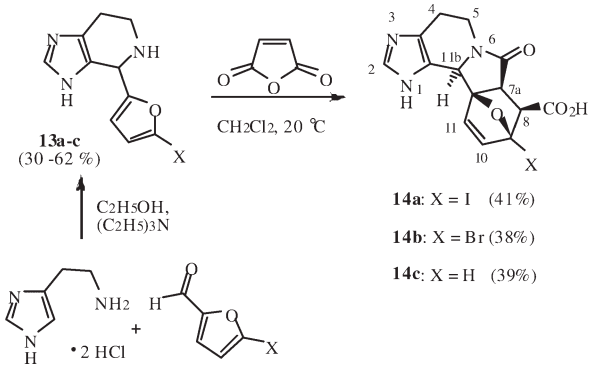
EXPERIMENTAL

All reagents were purchased from Acros Chemical Co. All solvents were used without further purification. Melting points were determined using SMP10 and are uncorrected. IR spectra were obtained in KBr pellets using an IR-fourier spectrometer Infralum FT-801. ^{1}H and ^{13}C NMR spectra were recorded on Jeol JNM-ECA 600 (600 MHz for ^{1}H and 150.9 MHz for ^{13}C) or Bruker Uniti + (400 MHz for ^{1}H and 100.6 MHz for ^{13}C) spectrometers in $CDCl_3$ or DMSO-d_6 at 27°C, and residual signals of chloroform (^{1}H NMR δ 7.26 ppm and ^{13}C NMR 76.9 ppm) or DMSO-d_5H (^{1}H NMR δ 2.49 ppm and ^{13}C NMR 39.4 ppm) were used as the internal standard. Mass spectra

Scheme 7. Synthesis of 3,13c-epoxybenzo[1,2]indolizino[8,7-*b*]indol-4-carboxylic acids **10-12**.



Scheme 8. Synthesis of 9,11a-epoxyimidazo[4′,5′:3,4]pyrido[2,1-*a*]isoindole-8-carboxylic acids **14a-c**.



were measured either on Thermo Focus DSQ II (electron ionization, 70 eV, ion source temperature 200°C, gas chromatographic inlet with Varian FactorFour VF-5ms column) or on Thermo Trace DSQ (electron ionization, 70 eV, ion source temperature was 200°C, direct inlet probe) spectrometers. Positive-ion electrospray ionization (ESI+) mass spectra were acquired using an API4000 instrument (Applied Biosystems) in the ESI+ mode (sample MeOH-H_2O solution). Nitrogen was used as nebulizer and argon as collision gas, needle voltage was set at 3000 V with ion source at 100°C. The purity of the obtained substances and the composition of the reaction mixtures were controlled by TLC Sorbfile plates. The separation of the final products was carried out by column chromatography on Al_2O_3 (activated, neutral, 50–200 mm) or by fractional crystallization. Microanalyses were performed for C, H, N on a Vario Macro Cube C,H,N,O,S-analyser and were within ±0.4% of theoretical values.

The crystal of ester **5** ($C_{20}H_{21}NO_6$, M = 371.38) is monoclinic, space group $P2_1/c$, at T = 100 K: a = 18.8819(12), b = 8.6778(5), c = 10.7027(7) Å, β = 102.2460(10)°, V = 1713.77(18) Å^3, Z = 4, d_{calc} = 1.439 g/cm^3, $F(000)$ = 784, μ = 0.107 mm^{-1}. 19,911 total reflections (4560 unique reflections, R_{int} = 0.053) were measured on a Bruker SMART APEX II CCD diffractometer (λ(MoK$_\alpha$)-radiation, graphite monochromator, ω and ϕ scan mode, $2\theta_{max}$ = 58°). The structure was determined by direct methods and refined by full-matrix least squares technique on F^2 with anisotropic displacement parameters for nonhydrogen atoms. The hydrogen atoms were placed in calculated positions and refined within the riding model with fixed isotropic displacement parameters (U_{iso}(H) = 1.5 U_{eq}(C) for the CH_3-groups and U_{iso}(H) = 1.2 U_{eq}(C) for the other groups). The final divergence factors were R_1 = 0.043 for 3182 independent reflections with $I > 2\sigma$ (I) and wR_2 = 0.083 for all independent reflections, S = 1.007. All calculations were carried out using the *SHELXTL* program [19]. CCDC No. 741777 contains the supplementary crystallographic data for this article. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033).

General procedure for preparation of piperidones 1a-d. A solution of corresponding furaldehyde (~25 mL, 0.3 mol) and ammonium acetate (23 g, 0.3 mol) in ethanol (150 mL) was added to a solution of ketone **1a–d** (0.15 mol) in ethanol (50 mL). The resulting clear mixture was allowed to remain at room temperature for 3 d. Then the obtained brown mixture was diluted with diethyl ether (400 mL) and washed with water (3 × 200 mL). The organic layer was separated, dried ($MgSO_4$), filtered, evaporated, and purified by column chromatography on alumina (eluant: hexane) to give corresponding piperidones **2a-d** as white prisms in good to moderate yields.

(2S*,3R*,6R*)-2,6-Di(2-furyl)-3-methylpiperidin-4-one (1a). Yield 34%; mp 63−64°C (hexane-ethyl acetate) lit. [14b]: 40°C; ir: NH 3317, C=O 1706 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, $J_{3,Me}$ = 6.5 Hz, 3 H, CH_3-3), 2.35 (brs, 1 H, *N*H), 2.71 (dd, $J_{5B,6}$ = 3.0, $^2J_{5,5}$ = 13.6 Hz, 1 H, H-5B), 2.84 (dq, $J_{3,2}$ = 10.7, $J_{3,Me}$ = 6.5 Hz, 1 H, H-3), 2.85 (dd, $J_{5A,6}$ = 12.1, $^2J_{5,5}$ = 13.6 Hz, 1 H, H-5A), 3.80 (d, $J_{2,3}$ = 10.7 Hz, 1 H, H-2), 4.17 (dd, $J_{6,5A}$ = 12.1, $J_{6,5B}$ = 3.0 Hz, 1 H, H-6), 6.21 (brd, $J_{\beta',\beta}$ = 3.2 Hz, 1 H, H-β*)†, 6.29 (dd, $J_{\alpha,\beta}$ = 1.8, $J_{\beta',\beta}$ = 3.2 Hz, 1 H, H-β), 6.32 (m, 2 H, H-β′ and H-β′*), 7.36 (dd, $J_{\beta',\alpha}$ = 0.8, $J_{\alpha,\beta}$ = 1.8 Hz, 1 H, H-α), 7.39 (dd, $J_{\beta',\alpha}$ = 0.6, $J_{\alpha,\beta}$ = 1.8 Hz, 1 H, H-α*); ms (EI, 70 eV): *m/z* 245 (28) [M]$^+$, 175 (3), 174 (10), 150 (2), 146 (2), 136 (5), 123 (14), 122 (31), 108 (10), 95 (30), 94 (100), 93 (97), 79 (31), 66 (40), 65 (35), 56 (23), 40 (12). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.48; H, 6.20; N, 5.93.

(2R*,3S*,5R*,6S*)-2,6-Di(2-furyl)-3,5-dimethylpiperidin-4-one (1b). Yield 63%; mp 73.5–74.5°C (hexane-ethyl acetate) lit. [14b]: 57°C; ir: NH 3315, C=O 1705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, $J_{Me,3(Me,5)}$ = 6.6 Hz, 6 H, CH_3-3 and CH_3-5), 2.27 (brs, 1 H, *N*H), 2.95 (dq, $J_{2,3(5,6)}$ = 10.8, $J_{Me,3(Me,5)}$ = 6.6 Hz, 2 H, H-3 and H-5), 3.76 (d, $J_{2,3(5,6)}$ = 10.8 Hz, 2 H, H-2 and H-6), 6.27 (dd, $J_{\alpha,\beta'}$ = 0.8, $J_{\beta',\beta}$ = 3.2 Hz, 2 H, H-β′), 6.31 (dd, $J_{\alpha,\beta}$ = 1.8, $J_{\beta',\beta}$ = 3.2 Hz, 2 H, H-β), 7.38 (dd, $J_{\beta',\alpha}$ = 0.8, $J_{\alpha,\beta}$ = 1.8 Hz, 2 H, H-α); ms (EI, 70 eV): *m/z* (%) 259 (13) [M]$^+$, 174 (14), 146 (3), 136 (29), 123 (23), 108 (100), 96 (16), 80 (16), 79 (54), 77 (27), 55 (14), 53 (15), 39 (42). Anal. Calcd for $C_{17}H_{15}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.30; H, 6.51; N, 5.61.

(2S*,3R*,6R*)-3-Ethyl-2,6-di(2-furyl)piperidin-4-one (1c). Yield 33%; mp 45–47°C (hexane-ethylacetate) lit. [14b]: 47°C; ir: NH 3316, CO 1707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, $J_{CH2,Me}$ = 7.0 Hz, 3 H, CH_3), 1.28 (m, 1 H, CH_2ACH$_3$), 1.60 (m, 1 H, CH_2BCH$_3$), 2.31 (brs, 1 H, *NH*), 2.70 (dd, $J_{5B,6}$ = 2.5, $^2J_{5,5}$ = 13.0 Hz, 1 H, H-5B), 2.73 (m, 1 H, H-3), 2.84 (dd, $^2J_{5,5}$ = $J_{5A,6}$ = 13.0 Hz, 1 H, H-5A), 3.91 (d, $J_{2,3}$ = 10.9 Hz, 1 H, H-2), 4.15 (dd, $J_{6,5B}$ = 2.5, $J_{6,5A}$ = 13.0 Hz, 1 H, H-6), 6.21 (brd, $J_{\beta',\beta}$ = 3.1 Hz, 1 H, H-β′), 6.31 (m, 3 H, H-β, H-β*, H-β′*), 7.35 (brd, $J_{\alpha,\beta}$ = 1.6 Hz, 1 H, H-α), 7.39 (brd, $J_{\alpha,\beta}$ = 1.6 Hz, 1 H, H-α*); ms (EI, 70 eV): *m/z* (%) 259 (15) [M]$^+$, 174 (10), 149 (3), 137 (9), 122 (21), 107 (6), 96 (14), 94 (100), 77 (8), 65 (10), 55 (14), 39 (27). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.39; H, 6.55; N, 5.45.

(2R*,3S*,5R*,6S*)-3,5-Dimethyl-2,6-bis(5-methyl-2-furyl)-piperidin-4-one (1d). Yield 41%; mp 85–86°C (hexane-ethyl acetate); ir: NH 3282, C=O 1704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, $J_{Me,3(Me,5)}$ = 6.5 Hz, 6 H, CH_3-3 and CH_3-5), 2.27 (d, $J_{Me,\beta'}$ = 0.6 Hz, 6 H, CH_3-Fur and CH_3-Fur*), 2.75 (brs, 1 H, *N*H), 2.90 (dq, $J_{3,2\ (5,6)}$ = 10.8 Hz, $J_{Me,3(Me,5)}$ = 6.5 Hz, 2 H, H-3 and H-5), 3.66 (d, $J_{3,2(5,6)}$ = 10.8 Hz, 2 H, H-2 and H-6), 5.88 (dq, $J_{Me,\beta'}$ = 0.6, $J_{\beta',\beta}$ = 3.0 Hz, 2 H, H-β′ and H-β′*), 6.12 (brd, $J_{\beta',\beta}$ = 3.0 Hz, 2 H, H-β and H-β*); ms (EI, 70 eV): *m/z* (%) 287 (35) [M]$^+$, 244 (5),

† α*, β* and β′*—the protons of the second furan ring.

202 (20), 150 (40), 137 (13), 122 (100), 110 (20), 101 (8), 79 (7), 77 (6), 43 (7). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.98; H, 7.50; N, 4.75.

General procedure for preparation of 6a-methylepoxypyrido[2,1-*a*]isoindolones 2a-d. A mixture of corresponding piperidone **1a-d** (4.0 mmol), methacryloyl chloride (0.6 mL, 6.0 mmol) and triethylamine (1.7 mL, 12.0 mmol) in toluene (25 mL) was refluxed for 4 h. The reaction progress was monitored by TLC (until disappearance of the starting compound's spot). At the end of the reaction the mixture was poured into water (100 mL), an aq. (5%) solution of HCl added until pH ~6 and organic substances extracted with ethyl acetate (3 × 80 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated to give crude products. Further crystallization from hexane-ethyl acetate gave corresponding compounds **2a-d** as white needles.

(1R*,4R*,6aR*,8S*,10aS*,10bS*)-4-(2-Furyl)-1,3,4,7,8,10b-hexahydro-1,6a-dimethyl-2H-8,10a-epoxypyrido[2,1-a]isoindole-2,6(6aH)-dione (2a). Yield 47%; mp 136–138°C (hexane-ethyl acetate); ir: NH 3282, C=O 1724, N–C=O 1695 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 1.09 (brs, 3 H, CH_3-6a), 1.11 (d, $J_{1,Me\text{-}1}$ = 6.8 Hz, 3 H, CH_3-1), 1.12 (d, $J_{7endo,7exo}$ = 11.8 Hz, 1 H, H-7*endo*), 2.45 (dd, $J_{7exo,8}$ = 4.8, $J_{7exo,7endo}$ = 11.8 Hz, 1 H, H-7*exo*), 2.91 (dq, $J_{1,10b}$ = 11.9, $J_{1,Me\text{-}1}$ = 6.8 Hz, 1 H, H-1), 2.91 (dd, $J_{3B,4}$ = 6.2, $^2J_{3,3}$ = 17.2 Hz, 1 H, H-3B), 2.99 (dd, $J_{3A,4}$ = 2.1, $^2J_{3,3}$ = 17.2 Hz, 1 H, H-3A), 4.20 (d, $J_{10b,1}$ = 11.9 Hz, 1 H, H-10b), 5.00 (dd, $J_{8,9}$ = 1.7, $J_{8,7exo}$ = 4.8 Hz, 1 H, H-8), 5.32 (brdd, $J_{4,3B}$ = 2.1, $J_{4,3A}$ = 6.2 Hz, 1 H, H-4), 6.20 (dd, $J_{4',5'}$ = 1.8, $J_{4',3'}$ = 3.2 Hz, 1 H, H-4′), 6.25 (dd, $J_{3',5'}$ = 0.7, $J_{3',4'}$ = 3.2 Hz, 1 H, H-3′), 6.33 (d, $J_{10,9}$ = 5.8 Hz, 1 H, H-10), 6.43 (dd, $J_{9,8}$ = 1.7 Hz, $J_{9,10}$ = 5.8 Hz, 1 H, H-9), 7.23 (dd, $J_{5',3'}$ = 0.7, $J_{5',4'}$ = 1.8 Hz, 1 H, H-5′); ^{13}C nmr (100.6 MHz, $CDCl_3$): δ = 208.1 (C_2), 177.1 (C_6), 152.6 ($C_{2'}$), 142.1 ($C_{5'}$), 137.0 and 131.6 (C_9 and C_{10}), 110.4 and 107.7 ($C_{3'}$ and $C_{4'}$), 92.7 (C_{10a}), 78.6 (C_8), 57.9 (C_4), 52.7 (C_{6a}), 46.2 and 44.3 (C_1 and C_{10b}), 41.8 (C_3), 36.6 (C_7), 20.0 (CH_3-6a), 10.3 (CH_3-1); ms (EI, 70 eV): *m*/*z* (%) 313 [M^+] (22), 228 (20), 176 (9), 162 (12), 149 (19), 121 (10), 108 (38), 94 (52), 69 (48), 66 (26), 41 (100). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.89; H, 6.21; N, 4.51.

(1R*,3S*,4R*,6aR*,8S*,10aS*,10bS*)-4-(2-Furyl)-1,3,4,7,8,10b-hexahydro-1,3,6a-trimethyl-2H-8,10a-epoxypyrido[2,1-a]isoindole-2,6(6aH)-dione (2b). Yield 46%; mp 134–136°C (hexane-ethyl acetate); ir: C=O 1717, N–C=O 1678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 3 H, CH_3-6a), 1.14 (d, *J* = 6.6 Hz, 3 H, CH_3-1), 1.18 (d, $J_{7exo,7endo}$ = 11.7 Hz, 1 H, H-7*exo*), 1.39 (d, $J_{3,Me\text{-}3}$ = 7.6 Hz, 3 H, CH_3-3), 2.51 (dd, $J_{7exo,8}$ = 4.8, $J_{7exo,7endo}$ = 11.7 Hz, 1 H, H-7*exo*), 3.00 (dq, $J_{1,Me\text{-}1}$ = 6.6, $J_{1,10b}$ = 12.0 Hz, 1 H, H-1), 3.10 (dq, $J_{3,Me\text{-}3}$ = 7.6, $J_{3,4}$ = 2.0 Hz, 1 H, H-3), 4.21 (d, $J_{10b,1}$ = 12.0 Hz, 1 H, H-10b), 5.03 (dd, $J_{4,3'}$ = 0.6, $J_{4,3}$ = 2.0 Hz, 1 H, H-4), 5.07 (dd, $J_{8,9}$ = 1.7, $J_{8,7exo}$ = 4.8 Hz, 1 H, H-8), 6.25 (dd, $J_{4',5'}$ = 1.8, $J_{4',3'}$ = 3.2 Hz, 1 H, H-4′), 6.32 (dt, $J_{3',5'}$ = $^4J_{4,3'}$ = 0.6, $J_{3',4'}$ = 3.2 Hz, 1 H, H-3′), 6.40 (d, $J_{10,9}$ = 5.9 Hz, 1 H, H-10), 6.49 (dd, $J_{9,8}$ = 1.8, $J_{9,10}$ = 5.9 Hz, 1 H, H-9), 7.28 (dd, $J_{5',3'}$ = 0.6, $J_{5',4'}$ = 1.8 Hz, 1 H, H-5′); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 210.6 (C_2), 178.0 (C_6), 152.5 ($C_{2'}$), 142.0 ($C_{5'}$), 136.9 and 131.5 (C_9 and C_{10}), 110.3 and 107.6 ($C_{3'}$ and $C_{4'}$), 93.0 (C_{10a}), 78.7 (C_8), 57.6 (C_4), 52.8 (C_{6a}), 52.6 (C_{10b}), 46.4 and 43.8 (C_1 and C_3), 36.6 (C_7), 20.0 (CH_3-6a), 17.5 (CH_3-3), 10.3 (CH_3-1); ms (EI, 70 eV): *m*/*z* (%) 327 [M^+] (86), 312 (13), 242 (85), 176 (100), 163 (90), 148 (38), 108 (74), 79 (43), 69 (46). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 4.28; N, 6.47. Found: C, 69.42; H, 4.32; N, 6.73.

(1R*,4R*,6aR*,8S*,10aS*,10bS*)-1-Ethyl-4-(2-furyl)-1,3,4,7,8,10b-hexahydro-6a-methyl-2H-8,10a-epoxypyrido[2,1-a]isoindole-2,6(6aH)-dione (2c). Yield 55%; mp 140°C (hexane-ethyl acetate); ir: C=O 1720, N–C=O 1698 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 0.93 (t, $J_{CH2,Me}$ = 7.3 Hz, 1 H, CH_2CH_3), 1.12 (s, 3 H, CH_3-6a), 1.14 (d, $J_{7endo,7exo}$ = 12.1 Hz, 1 H, H-7*endo*), 1.58 (m, 1 H, $CH_{2(B)}CH_3$), 1.93 (m, 1 H, $CH_{2(A)}CH_3$), 2.47 (dd, $J_{7exo,8}$ = 5.0, $^2J_{7exo,7endo}$ = 12.1 Hz, 1 H, H-7*exo*), 2.89 (dd, $J_{3B,4}$ = 6.2, $^2J_{3,3}$ = 17.0 Hz, 1 H, H-3B), 2.89 (m, 1 H, H-1), 3.00 (brd, $^2J_{3,3}$ = 17.0 Hz, 1 H, H-3A), 4.46 (d, $J_{10b,1}$ = 12.1 Hz, 1 H, H-10b), 5.02 (brd, $J_{8,7exo}$ = 5.0 Hz, 1 H, H-8), 5.30 (brd, $J_{3B,4}$ = 6.2 Hz, 1 H, H-4), 6.23–6.25 (m, 2 H, H-3′ and H-4′), 6.41 (d, $J_{10,9}$ = 6.0 Hz, 1 H, H-10), 6.45 (brd, $J_{9,10}$ = 6.0 Hz, 1 H, H-9), 7,25 (brd, $J_{4',5'}$ =1.6 Hz, 1 H, H-5′); ^{13}C nmr (100.6 MHz, $CDCl_3$): δ = 207.9 (C_2), 177.1 (C_6), 152.6 ($C_{2'}$), 142.2 ($C_{5'}$), 137.2 (C_{10}), 131.3 (C_9), 110.4 and 107.6 ($C_{3'}$ and $C_{4'}$), 92.6 (C_{10a}), 78.7 (C_8), 55.0, 49.6, 46.29 (C_1, C_{10b}, and C_4), 52.8 (C_{6a}), 42.9 (C_3), 36.6 (C_7), 20.1 (CH_3-6a), 18.4 (CH_2CH_3), 10.4 (CH_2CH_3); ms (EI, 70 eV): *m*/*z* (%) 327 [M^+] (100), 300 (12), 256 (15), 242 (25), 162 (31), 148 (63), 122 (40), 94 (56), 67 (42), 41 (49). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; N, 6.47; H, 4.28. Found: C, 69.51; N, 6.59; H, 4.62.

(1R*,3S*,4R*,6aR*,8S*,10aS*,10bS*)-4-(5-Methyl-2-furyl)-1,3,4,7,8,10b-hexahydro-1,3,6a,8-tetramethyl-2H-8,10a-epoxypyrido[2,1-a]isoindole-2,6(6aH)-dione (2d). Yield 60%; mp 182°C (hexane-ethyl acetate); ir: C=O 1713, N–C=O 1688 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 1.04 (s, 3 H, CH_3-6a), 1.05 (d, $J_{1,Me\text{-}1}$ = 6.8 Hz, 3 H, CH_3-1), 1.19 (d, $^2J_{7exo,7endo}$ = 12.1 Hz, 1 H, H-7*exo*), 1.31 (d, $J_{3,Me\text{-}3}$ = 7.7 Hz, 3 H, CH_3-3), 1.56 (s, 3 H, CH_3-8), 2.13 (s, 3 H, CH_3-5′), 2.17 (d, $^2J_{7endo,7exo}$ = 12.1 Hz, 1 H, H-7*endo*), 2.90 (dq, $J_{1,Me\text{-}1}$ = 6.8, $J_{1,10b}$ = 12.2 Hz, 1 H, H-1), 3.03 (dq, $J_{3,Me\text{-}3}$ = 7.7, $J_{3,4}$ = 1.0 Hz, 1 H, H-3), 4.06 (d, $J_{10b,1}$ = 12.2 Hz, 1 H, H-10b), 4.93 (brs, 1 H, H-4), 5.74 (brd, $J_{4',3'}$ = 2.9 Hz, 1 H, H-4′), 6.10 (brd, $J_{3',4'}$ = 2.9 Hz, 1 H, H-3′), 6.22 (d, $J_{9,10}$ = 6.1 Hz, 1 H, H-10), 6.30 (d, $J_{9,10}$ = 6.1 Hz, 1 H, H-9); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 211.2 (C_2), 178.3 (C_6), 151.6 and 150.7 ($C_{2'}$ and $C_{5'}$), 140.1 (C_9), 132.1 (C_{10}), 107.9 ($C_{3'}$), 106.3 ($C_{4'}$), 86.8 (2C, C_{10a} and C_8), 57.6, 56.0 and 52.5 (C_{6a}, C_{10b}, and C_4), 46.7, 43.8 and 42.9 (C_1, C_3, and C_7), 19.8, 19.1 and 17.7 (CH_3-5′, CH_3-6a and CH_3-8), 13.5 (CH_3-3), 10.3 (CH_3-1); ms (EI, 70 eV): *m*/*z* (%) 355 [M^+] (67), 270 (86), 242 (9), 190 (100), 162 (29), 149 (36), 122 (95), 107 (30), 93 (14), 79 (39), 69 (22), 41 (66). Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 3.94; N, 7.09. Found: C, 70.88; H, 3.89; N, 7.13.

General procedure for preparation of 7-phenylepoxypyrido[2,1-*a*]isoindolones 3a-d. A mixture of corresponding piperidone **1a-d** (4.0 mmol), cinnamoyl chloride (1.0 g, 6.0 mmol) and triethylamine (1.7 mL, 12.0 mmol) in toluene (25 mL) was refluxed for 5–6 h. The reaction progress was monitored by TLC (until disappearance of the starting compound's spot). At the end of the reaction the mixture was poured into water (100 mL), an aq. (5%) solution of HCl added until pH ~6 and extracted with ethyl acetate (3 × 80 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated to give crude products. Further crystallization from hexane-ethyl

acetate gave corresponding compounds **3a–d** as colourless needles.

(1R*,4R*,6aR*,8S*,10aS*,10bS*)-4-(2-Furyl)-1,3,4,7,8,10b-hexahydro-1-methyl-7-phenyl-2H-8,10a-epoxypyrido[2,1-a]isoindole-2,6(6aH)-dione (3a). Yield 74%; mp 137−138°C (hexane-ethyl acetate); ir: C=O 1724, N─C=O 1692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (d, $J_{1,Me\text{-}1}$ = 6.8 Hz, 3 H, CH_3-1), 2.83 (d, $J_{6a,7}$ = 4.4 Hz, 1 H, H-6a), 2.97 (dd, $J_{3A,4}$ = 5.6, $^2J_{3,3}$ = 16.8 Hz, 1 H, H-3A), 2.99 (dq, $J_{1,Me\text{-}1}$ = 6.9, $J_{1,10b}$ = 11.8 Hz, 1 H, H-1), 3.02 (dd, $J_{3B,4}$ = 2.5, $^2J_{3,3}$ = 16.8 Hz, 1 H, H-3B), 3.84 (t, $J_{7exo,8} = J_{6a,7}$ = 4.4 Hz, 1 H, H-7*exo*), 4.37 (d, $J_{10b,1}$ = 11.8 Hz, 1 H, H-10b), 5.25 (dd, $J_{8,9}$ = 1.9, $J_{8,7exo}$ = 4.4 Hz, 1H, H-8), 5.39 (dd, $J_{4,3B}$ = 2.5, $J_{4,3A}$ = 5.6 Hz, 1 H, H-4), 6.29 (dd, $J_{4',5'}$ = 1.9, $J_{4',3'}$ = 3.1 Hz, 1 H, H-4′), 6.34 (brd, $J_{3',4'}$ = 3.1 Hz, 1 H, H-3′), 6.30 (dd, $J_{9,8}$ = 1.9, $J_{9,10}$ = 6.2 Hz, 1 H, H-9), 6.57 (d, $J_{10,9}$ = 6.2 Hz, 1 H, H-10), 7.29–7.15 (m, 6H, H-Ph, and H-5′); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 207.8 (C_2), 172.9 (C_6), 152.5 ($C_{2'}$), 142.1 ($C_{5'}$), 138.8 ($C_{1''}$), 135.4 and 134.0 (C_9 and C_{10}), 128.3 and 127.8 (each by 2C, $C_{2''}$, and $C_{6''}$, $C_{3''}$ and $C_{5''}$), 126.8 ($C_{4''}$), 110.3 and 107.5 ($C_{3'}$ and $C_{4'}$), 91.9 (C_{10a}), 82.3 (C_8), 59.2 and 55.6 (C_{10b} and C_4), 47.4, 46.2 and 44.3 (C_1, C_{6a}, and C_7), 41.8 (C_3), 10.2 (CH_3-1); ms (EI, 70 eV): *m*/*z* (%) 375 [M^+] (9), 307 (2), 245 (5), 238 (13), 228 (50), 224 (11), 210 (5), 169 (5), 162 (12), 148 (17), 131 (81), 108 (59), 103 (86), 94 (100), 77 (79), 66 (41), 65 (26), 55 (14), 39 (23). Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.73; H, 5.37; N, 4.04.

(1R*,3S*,4R*,6aR*,8S*,10aS*,10bS*)-4-(2-Furyl)-1,3,4,7,8,10b-hexahydro-1,3-dimethyl-7-phenyl-2H-8,10a-epoxypyrido[2,1-a]isoindole-2,6(6aH)-dione (3b). Yield 30%; mp 153−155°C (hexane-ethyl acetate); ir: C=O 1724, N─C=O 1683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (d, $J_{3,Me\text{-}3}$ = 6.9 Hz, 3 H, CH_3-3), 1.35 (d, $J_{1,Me\text{-}1}$ = 7.5 Hz, 3 H, CH_3-1), 2.83 (d, $J_{6a,7}$ = 4.4 Hz, 1 H, H-6a), 3.11−2.96 (m, 2 H, H-1 and H-3), 3.85 (t, $J_{7,6a} = J_{7,8}$ = 4.4 Hz, H-7), 4.30 (d, $J_{1,10b}$ = 12.5 Hz, H-10b), 5.00 (d, $J_{3,4}$ = 2.5 Hz, 1 H, H-4), 5.26 (dd, $J_{8,9}$ = 1.3, $J_{8,7}$ = 4.4 Hz, 1 H, H-8), 6.28 (dd, $J_{9,8}$ = 1.3, $J_{9,10}$ = 6.2 Hz, 1 H, H-9), 6.27 (dd, $J_{4',5'}$ = 1.8, $J_{4',3'}$ = 3.1 Hz, 1 H, H-4′), 6.56 (d, $J_{10,9}$ = 6.2 Hz, 1 H, H-10), 7.30–7.13 (m, 5 H, H-Ph), 7.30 (brd, $J_{4',5'}$ = 1.8 Hz, H-5′); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 210.3 (C_2), 173.8 (C_6), 152.3 ($C_{2'}$), 142.1 ($C_{5'}$), 138.8 ($C_{1''}$), 135.5 and 134.0 (C_9 and C_{10}), 128.4 and 127.9 (each by 2C, $C_{2''}$ and $C_{6''}$, $C_{3''}$, and $C_{5''}$), 126.8 ($C_{4''}$), 110.3 and 107.7 ($C_{3'}$ and $C_{4'}$), 92.1 (C_{10a}), 82.4 (C_8), 59.4, 55.6, 53.0, 47.6, 46.5 and 43.9 (C_{10b}, C_4, C_1, C_{6a}, C_7, and C_3), 17.0 (CH_3-3), 10.2 (CH_3-1); ms (EI, 70 eV): *m*/*z* (%) 389 [M^+] (21), 281 (8), 256 (19), 242 (75), 238 (11), 207 (9), 191 (6), 174 (12), 162 (45), 146 (18), 131 (85), 108 (100), 103 (97), 94 (18), 77 (84), 75 (84), 65 (16). Anal. Calcd for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60. Found: C, 73.76; H, 5.88; N, 3.37.

(1R*,4R*,6aR*,7S*,8S*,10aS*,10bS*)-1-Ethyl-4-(2-furyl)-7-phenyl-1,3,4,7,8,10b-hexahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-2,6(6aH)-dione (3c). Yield 51%; mp 140°C (hexane-ethyl acetate); ir: C=O 1715, N─C=O 1689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, $J_{CH2,Me}$ = 7.5 Hz, 3H, $CH_2\underline{CH_3}$), 1.62 (m, 1 H, $CH\underline{H_B}CH_3$), 1.97 (m, 1 H, $C\underline{H_A}HCH_3$), 2.81 (d, $J_{6a,7}$ = 4.4 Hz, 1 H, H-6a), 2.90 (dd, $J_{3A,4}$ = 1.8, $^2J_{3A,3B}$ = 16.2 Hz, 1 H, H-3A), 2.91 (m, 1 H, H-1), 2.91 (dd, $J_{3B,4}$ = 6.2, $^2J_{3B,3A}$ = 16.2 Hz, 1 H, H-3B), 3.82 (t, $J_{7,6a} = J_{7,8}$ = 4.4 Hz, 1 H, H-7), 4.61 (d, $J_{1,10b}$ = 11.8 Hz, 1 H, H-10b), 5.24 (dd, $J_{8,9}$ = 1.8, $J_{7,8}$ = 4.4 Hz, 1 H, H-8), 5.35 (dd, $J_{4,3A}$ = 1.8, $J_{4,3B}$ = 6.2 Hz, 1 H, H-4), 6.26 (dd, $J_{4',5'}$ = 1.8, $J_{4',3'}$ = 3.2 Hz, 1 H, H-4′), 6.29 (dd, $J_{9,8}$ = 1.8, $J_{9,10}$ = 6.2 Hz, 1 H, H-9), 6.30 (dd, $J_{3',5'}$ = 0.7, $J_{3',4'}$ = 3.2 Hz, 1 H, H-3′), 6.59 (d, $J_{10,9}$ = 6.2 Hz, 1 H, H-10), 7.26–7.14 (m, 5 H, H″-Ph), 7.28 (brd, $J_{3',5'}$ = 1.8 Hz, 1 H, H-5′); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 207.7 (C_2), 173.1 (C_6), 152.6 ($C_{2'}$), 142.4 ($C_{5'}$), 138.9 ($C_{1''}$), 135.9 and 133.8 (C_9 and C_{10}), 128.5 (2C, $C_{3''}$ and $C_{5''}$), 128.0 (2C, $C_{2''}$, and $C_{6''}$), 127.0 ($C_{4''}$), 110.5 ($C_{3'}$), 107.7 ($C_{4'}$), 91.9 (C_{10a}), 82.5 (C_8), 56.7, 55.9, 49.8, 47.6 and 46.5 (C_1, C_4, C_{6a}, C_7, and C_{10b}), 43.1 (C_3), 18.5 ($\underline{CH_2}CH_3$), 10.5 ($CH_2\underline{CH_3}$); ms (EI, 70 eV): *m*/*z* (%) 389 [M^+] (11), 360 (2), 321 (3), 266 (7), 258 (11), 242 (98), 238 (81), 210 (8), 176 (10), 148 (58), 131 (100), 122 (35), 103 (54), 94 (31), 77 (37), 65 (10). Anal. Calcd for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60. Found: C, 74.31; H, 5.68; N, 3.91.

(1R*,3S*,4R*,6aR*,8S*,10aS*,10bS*)-1,3,8-Trimethyl-4-(5-methyl-2-furyl)-7-phenyl-1,3,4,7,8,10b-hexahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-2,6(6aH)-dione (3d). Yield 30%; mp 160°C (hexane-ethyl acetate); ir: C=O 1722, N─C=O 1683 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 1.15 (d, $J_{Me\text{-}1,1}$ = 6.6 Hz, 3 H, CH_3-1), 1.35 (d, $J_{Me\text{-}3,3}$ = 7.7 Hz, 3 H, CH_3-3), 1.57 (s, 3 H, CH_3-8), 2.19 (brs, 3 H, CH_3-5″), 2.95 (d, $J_{6a,7exo}$ = 3.9 Hz, 1 H, H-6a), 2.98 (dq, $J_{1,Me\text{-}1}$ = 6.6, $J_{1,10b}$ = 12.1 Hz, 1 H, H-1), 3.05 (dq, $J_{3,4}$ = 2.5, $J_{3,Me\text{-}3}$ = 7.7 Hz, 1 H, H-3), 3.99 (d, $J_{7exo,6a}$ = 3.9 Hz, 1 H, H-7*exo*), 4.24 (d, $J_{10b,1}$ = 12.1 Hz, H-10b), 4.97 (brd, $J_{4,3}$ = 2.5 Hz, 1 H, H-4), 5.82 (dq, $J_{4',Me\text{-}5'}$ = 1.1, $J_{4',3'}$ = 3.1 Hz, 1 H, H-4′), 6.05 (d, $J_{10,9}$ = 5.5 Hz, 1 H, H-10), 6.19 (brd, $J_{3',4'}$ = 3.1 Hz, 1 H, H-3′), 6.60 (d, $J_{9,10}$ = 5.5 Hz, 1 H, H-9), 7.11 (m, 2 H, H-2″ and H-6″), 7.25–7.18 (m, 3 H, H-3″−H-5″); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 210.9 (C_2), 173.9 (C_6), 151.8 and 150.7 ($C_{2'}$ and $C_{5'}$), 138.8 and 134.2 (C_9 and C_{10}), 128.2 (5C, $C_{2''}$−$C_{6''}$), 127.1 ($C_{1''}$), 108.0 ($C_{3'}$), 106.3 ($C_{4'}$), 91.4 and 90.5 (C_8 and C_{10a}), 59.44, 59.40, 53.3 and 53.0 (C_{10b}, C_{6a}, C_7, and C_4), 46.8 (C_3), 44.0 (C_1), 17.7 (CH_3-5′), 17.5 (CH_3-8), 13.6 (CH_3-3), 10.4 (CH_3-1); ms (EI, 70 eV): *m*/*z* (%) 417 [M^+] (3), 270 (100), 252 (45), 224 (10), 176 (22), 150 (16), 149 (10), 131 (49), 122 (24), 107 (7), 103 (23), 79 (8), 77 (17). Anal. Calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.66; H, 6.49; N, 3.21.

(1R*,4R*,6aR*,8S*,10aS*,10bS*)-4-(2-Furyl)-1,7-dimethyl-1,3,4,7,8,10b-hexahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-2,6(6aH)-dione (3e). A mixture of piperidone **1a** (0.98 g, 4.0 mmol), crotonyl chloride (0.6 mL, 6.0 mmol) and triethylamine (1.7 mL, 12.0 mmol) in toluene (25 mL) was refluxed for 6 h. The reaction progress was monitored by TLC. At the end of the reaction the mixture was poured into water (100 mL), an aq. (5%) solution of HCl added until pH ∼6 and extracted with ethyl acetate (3 × 80 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated to give crude product. Further crystallization from hexane-ethyl acetate gave compound **3e** as white needles. Yield 48%, mp 160 °C (hexane-ethyl acetate); ir: C=O 1722, N─C=O 1687 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 0.97 (d, $J_{7,Me\text{-}7}$ = 7.1 Hz, 3 H, CH_3-7), 1.11 (d, $J_{1,Me\text{-}1}$ = 6.9 Hz, 3 H, CH_3-1), 2.04 (d, $J_{6a,7}$ = 3.8 Hz, 1 H, H-6a), 2.58 (dq, $J_{1,Me\text{-}1}$ = 6.9, $J_{1,10b}$ = 11.9 Hz, 1 H, H-1), 2.89 (ddq, $J_{7,6a}$ = 3.8, $J_{7,8}$ = 4.5, $JMe_{\text{-}7,7}$ = 7.1 Hz, 1 H, H-7), 2.90 (dd, $J_{3B,4}$ = 6.2, $^2J_{3B,3A}$ = 17.1 Hz, 1 H, H-3B), 2.97 (dd, $J_{3A,4}$ = 2.0, $^2J_{3A,3B}$ = 17.1 Hz, 1 H, H-3A), 4.23 (d, $J_{10b,1}$ = 11.9 Hz, 1 H, H-10b), 4.90 (dd, $J_{8,9}$ = 1.6, $J_{8,7exo}$ = 4.5 Hz, 1H, H-8), 5.31 (dd, $J_{3A,4}$ = 2.0,

$J_{4,3B}$ = 6.2 Hz, 1 H, H-4), 6.20 (dd, $J_{4',5'}$ = 1.8, $J_{4',3'}$ = 3.2 Hz, 1 H, H-4′), 6.23 (brdd, $J_{3',4'}$ = 3.2, $J_{3',5'}$ = 0.5 Hz, 1 H, H-3′), 6.35 (dd, $J_{9,8}$ = 1.6, $J_{9,10}$ = 5.8 Hz, 1 H, H-9), 6.45 (d, $J_{10,9}$ = 5.8 Hz, 1 H, H-10), 7.24 (dd, $J_{3',5'}$ = 0.5, $J_{4',5'}$ = 1.8 Hz, 1 H, H-5′); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 208.0 (C_2), 173.4 (C_6), 152.5 ($C_{2'}$), 142.1 ($C_{5'}$), 134.8 and 134.1 (C_9 and C_{10}), 110.3 and 107.4 ($C_{3'}$ and $C_{4'}$), 91.3 (C_{10a}), 82.1 (C_8), 59.3 and 55.5 (C_{10b} and C_4), 46.1, 44.3 and 37.0 (C_{6a}, C_7, and C_1), 41.7 (C_3), 17.0 (CH_3-7), 10.1 (CH_3-1); ms (EI, 70 eV): *m/z* (%) 313 [M^+] (25), 228 (22), 176 (10), 162 (13), 149 (20), 148 (14), 108 (33), 94 (55), 79 (41), 69 (44), 66 (25), 65 (20), 41 (100). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.89; H, 6.07; N, 4.52.

General procedure for preparation of carboxylic acids 4a-d. A solution of piperidone **1a-d** (4.0 mmol) and citraconic anhydride (0.54 mL, 6.0 mmol) in toluene (30 mL) was refluxed for 4−6 h. At the end of the reaction the resulting mixture was cooled, and formation of white, yellow, or brown solids was observed. The crystals were filtered off, washed first with toluene (2 × 30 mL), then with acetone (2 × 20 mL) and air-dried to give corresponding acids **4a-d** as regioisomer mixtures (total yields of isomers **4b**,**dA** and **4b**,**dB** given on the Scheme 2). After recrystallization from isopropanol-DMF mixture the major isomers **4a-dA** were isolated as white powders.

(1R*,4R*,6aR*,7S*,8R*,10aS*,10bS*)-4-(2-Furyl)-1,7-dimethyl-2,6-dioxo-1,3,4,6,6a,7,8,10b-octahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-7-carboxylic acid (4aA). Yield 63%; mp 168−170°C; ir: C=O 1722, CO_2H 1698 and N−C=O 1674 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.00 (d, $J_{1,Me-1}$ = 7.5 Hz, 3 H, CH_3-1), 1.11 (s, 3 H, CH_3-7), 2.49 (s, 1 H, H-6a), 2.50 (dq, $J_{1,10b}$ = 11.8, $J_{1,Me-1}$ = 7.5 Hz, 1 H, H-1), 2.73 (dd, $J_{3B,4}$ = 1.9, $^2J_{3,3}$ = 16.8 Hz, 1 H, H-3B), 3.27 (dd, $J_{3A,4}$ = 6.2, $^2J_{3,3}$ = 16.8 Hz, 1 H, H-3A), 4.58 (d, $J_{10b,1}$ = 11.8 Hz, 1 H, H-10b), 5.02 (d, $J_{8,9}$ = 1.2 Hz, 1 H, H-8), 5.18 (dd, $J_{4,3B}$ = 1.9, $J_{4,3A}$ = 6.2 Hz, 1 H, H-4), 6.27 (dd, $J_{4',5'}$ = 1.8, $J_{4',3'}$ = 3.1 Hz, 1 H, H-4′), 6.37 (brd, $J_{3',4'}$ = 3.1 Hz, 1 H, H-3′), 6.52 (dd, $J_{8,9}$ = 1.2, $J_{9,10}$ = 5.6 Hz, 1 H, H-9), 6.65 (d, $J_{9,10}$ = 5.6 Hz, 1 H, H-10), 7.49 (brd, $J_{5',4'}$ = 1.8 Hz, 1 H, H-5′); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 208.6 (C_2), 174.8 (CO_2H), 170.0 (C_6), 153.2 ($C_{2'}$), 142.3 ($C_{5'}$), 136.2 and 135.4 (C_9 and C_{10}), 110.4 and 107.0 ($C_{3'}$ and $C_{4'}$), 84.0 (C_8), 79.2 (C_{10a}), 58.9 (C_{6a}), 57.1, 46.0 and 44.0 (C_1, C_4, and C_{10b}), 50.4 (C_7), 42.1 (C_3), 22.1 (Me-7), 10.0 (Me-1); ms (EI, 70 eV): m/z (%) 357 [M^+] (3), 245 (39), 228 (14), 176 (9), 174 (13), 122 (21), 108 (16), 96 (10), 94 (100), 79 (11), 77 (9), 68 (22), 66 (12), 65 (13), 39 (14). Anal. Calcd for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 63.91; H, 5.51; N, 4.26.

(1R*,3S*,4R*,6aR*,7S*,8R*,10aS*,10bS*)-4-(2-Furyl)-1,3,7-trimethyl-2,6-dioxo-1,3,4,6,6a,7,8,10b-octahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-7-carboxylic acid (4bA). Yield 63%; mp 206−208°C; ir: C=O and CO_2H brd 1704, N−C=O 1638 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.08 (d, 3H, $J_{Me-1,1}$ = 6.7 Hz, CH_3-1), 1.11 (s, 3H, CH_3-7), 1.32 (d, 3H, $J_{Me-3,3}$ = 7.8 Hz, CH_3-3), 2.52 (s, 1H, H-6a), 2.63 (dq, 1H, $J_{1,10b}$ = 11.8, $J_{1,Me-1}$ = 6.7 Hz, H-1), 2.93 (dq, 1H, $J_{3,4}$ = 2.5, $J_{3,Me-3}$ = 7.8 Hz, H-3), 4.54 (d, 1H, $J_{1,10b}$ = 11.8 Hz, H-10b), 4.92 (brd, 1H, $J_{3,4}$ = 2.5 Hz, H-4), 5.06 (d, 1 H, $J_{8,9}$ = 1.9 Hz, H-8), 6.28 (dd, 1 H, $J_{3',4'}$ = 3.1, $J_{4',5'}$ = 1.9 Hz, H-4′), 6.48 (dt, 1 H, $J_{3',4'}$ = 3.1, $^4J_{3',4}$ = $J_{3',5'}$ = 0.9 Hz, H-3′), 6.53 (dd, 1 H, $J_{9,10}$ = 5.6, $J_{8,9}$ = 1.9 Hz, H-9), 6.66 (d, 1 H, $J_{9,10}$ = 5.6 Hz, H-10), 7.51 (dd, 1 H, $J_{5',4'}$ = 1.9, $J_{3',5'}$ = 0.9 Hz, H-5′), 12.31 (brs, 1H, CO_2H); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 210.1 (C_2), 176.3 (CO_2H), 172.1 (C_6), 151.6 ($C_{2'}$), 142.2 ($C_{5'}$), 136.1 and 135.0 (C_9 and C_{10}), 110.6 and 108.1 ($C_{3'}$ and $C_{4'}$), 91.3 (C_{10a}), 84.9 (C_8), 59.2, 58.7, 53.1, 46.4 and 43.9 (C_1, C_{6a}, C_4, C_3, C_{10b} and C_{6a}), 52.4 (C_7), 22.5 (Me-7), 17.4 (Me-3), 10.2 (Me-1); ms (EI, 70 eV): m/z (%) 371 [M^+] (16), 327 (3), 290 (15), 258 (31), 242 (92), 235 (7), 217 (22), 190 (51), 176 (38), 162 (20), 136 (54), 123 (74), 108 (100), 95 (23), 78 (83), 68 (25), 58 (34), 43 (66), 39 (76), 33 (96). Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: 64.51; H, 5.31; N, 3.98.

(1R*,4R*,6aR*,7S*,8R*,10aS*,10bS*)-1-Ethyl-4-(2-furyl)-7-methyl-2,6-dioxo-1,3,4,6,6a,7,8,10b-octahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-7-carboxylic acid (4cA). Yield 44%; mp 160 °C; ir: C=O 1719, CO_2H 1678 and N−C=O 1675 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.86 (t, $J_{CH2,Me}$ = 7.5 Hz, 3 H, CH_2CH_3), 1.11 (s, 3 H, CH_3-7), 1.48 (m, 1 H, CH_2ACH_3), 1.70 (m, 1 H, CH_2BCH_3), 2.47 (m, 1 H, H-1), 2.46 (s, 1 H, H-6a), 2.73 (dd, $J_{3B,4}$ = 1.9, $^2J_{3,3}$ = 16.2 Hz, 1 H, H-3B), 3.25 (dd, $J_{3A,4}$ = 6.2, $^2J_{3,3}$ = 16.2 Hz, 1 H, H-3A), 4.77 (d, $J_{10b,1}$ = 11.8 Hz, 1 H, H-10b), 5.02 (d, $J_{8,9}$ = 1.9 Hz, 1 H, H-8), 5.16 (dd, $J_{4,3B}$ = 1.9, $J_{4,3A}$ = 6.2 Hz, 1 H, H-4), 6.26 (dd, $J_{4',5'}$ = 1.9, $J_{4',3'}$ = 3.1 Hz, 1 H, H-4′), 6.35 (brd, $J_{3',4'}$ = 3.1 Hz, 1 H, H-3′), 6.53 (dd, $J_{8,9}$ = 1.9, $J_{9,10}$ = 5.6 Hz, 1 H, H-9), 6.69 (d, $J_{9,10}$ = 5.6 Hz, 1 H, H-10), 7.48 (brd, $J_{5',4'}$ = 1.9 Hz, 1 H, H-5′); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 208.6 (C_2), 174.8 (CO_2H), 170.0 (C_6), 153.2 ($C_{2'}$), 142.4 ($C_{5'}$), 136.3 and 135.3 (C_9 and C_{10}), 110.4 ($C_{3'}$), 107.0 ($C_{4'}$), 84.0 (C_8), 79.2 (C_{10a}), 59.0 (C_{6a}), 54.8, 49.5 and 46.1 (C_1, C_4 and C_{10b}), 50.4 (C_7), 43.1 (C_3), 22.2 (Me-7), 18.3 (CH_2CH_3), 10.5 (CH_2CH_3); ms (EI, 70 eV): m/z (%) 371 [M^+] (24), 259 (17), 258 (28), 242 (87), 204 (26), 176 (80), 175 (35), 148 (16), 138 (15), 136 (30), 135 (18), 122 (69), 107 (16), 94 (100), 79 (18), 77 (18), 66 (19), 65 (19). Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.71; H, 5.37; N, 3.81.

(1R*,3S*,4R*,6aR*,7S*,8R*,10aS*,10bS*)-1,3,7,8-Tetramethyl-4-(5-methyl-2-furyl)-2,6-dioxo-1,3,4,6,6a,7,8,10b-octahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-7-carboxylic acid (4dA). Yield 55%; mp 136−140°C; ir: C=O 1721, CO_2H 1698, N−C=O 1672; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 0.99 (d, $J_{1,Me-1}$ = 6.8 Hz, 3 H, CH_3-1), 1.05 (s, 3 H, CH_3-7), 1.27 (d, $J_{3,Me-3}$ = 7.7 Hz, 3 H, CH_3-3), 1.50 (s, 3 H, CH_3-8), 2.18 (brs, 3 H, CH_3-5′), 2.56 (s, 1 H, H-6a), 2.61 (brdq, $J_{1,Me-1}$ = 6.8, $J_{1,10b}$ = 12.2 Hz, 1 H, H-1), 2.87 (dq, $J_{3,Me-3}$ = 7.7, $J_{3,4}$ = 2.2 Hz, 1 H, H-3), 4.45 (d, $J_{10b,1}$ = 12.2 Hz, 1 H, H-10b), 4.80 (d, $J_{4,3}$ = 2.2 Hz, 1 H, H-4), 5.86 (dq, $J_{4',3'}$ = 3.0, $J_{4',Me-5'}$ = 1.0 Hz, 1 H, H-4′), 6.32 (d, $J_{9,10}$ = 5.5 Hz, 1 H, H-10), 6.41 (brd, $J_{3',4'}$ = 3.0 Hz, 1 H, H-3′), 6.62 (d, $J_{9,10}$ = 5.5 Hz, 1 H, H-9); ^{13}C nmr (DMSO-d_6, 100.6 MHz): δ = 210.7 (C_2), 173.8 (CO_2H), 170.9 (C_6), 151.2 and 150.6 ($C_{2'}$ and $C_{5'}$), 139.2 (C_9), 136.2 (C_{10}), 108.1 and 106.4 ($C_{3'}$ and $C_{4'}$), 91.4 and 89.4 (C_8 and C_{10a}), 61.9 and 57.2 (C_4 and C_{10b}), 53.2 (C_7), 52.2, 47.1 and 43.7 (C_1, C_3, and C_{6a}), 22.1 (Me-7), 16.6, 14.6, 13.3 (Me-3, Me-8, and Me-5″), 10.1 (Me-1); ms (EI, 70 eV): m/z (%) 399 [M^+] (5), 304 (3), 287 (44), 270 (51), 244 (14), 204 (65), 202 (53), 190 (21), 162 (15), 150 (60), 136 (50), 122 (100), 110 (59), 95 (60), 77 (62), 68 (49), 55 (65), 44 (44). Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.18; H, 6.45; N, 3.78.

Methyl (1R*,4R*,6aR*,7S*,8R*,10aS*,10bS*)-4-(2-furyl)-1,7-dimethyl-2,6-dioxo-1,3,4,6,6a,7,8,10b-octahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-7-carboxylate (5). A mixture of acid **4a** (5.0 g, 13.0 mmol) and sulphuric acid (0.5 mL) in methanol (80 mL) was refluxed for 12 h. At the end, the mixture was cooled, poured into water (400 mL), and extracted with CH_2Cl_2 (5 × 80 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated to give crude product. Further crystallization from hexane-ethyl acetate gave ester **5** as colourless prisms. Yield 80%; mp 168 °C; ir: CO_2Me 1739, C=O 1720, N─C=O 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.14 (d, $J_{1,Me\text{-}1}$ = 6.9 Hz, 3 H, CH_3-1), 1.27 (s, 3 H, CH_3-7), 2.42 (s, 1 H, H-6a), 2.91 (dd, $J_{3A,4}$ = 6.2, $^2J_{3,3}$ = 16.8 Hz, 1 H, H-3A), 2.96 (dq, $J_{1,10b}$ = 11.8, $J_{1,Me\text{-}1}$ = 6.9 Hz, 1 H, H-1), 3.02 (dd, $J_{3B,4}$ = 1.9, $^2J_{3,3}$ = 16.8 Hz, 1 H, H-3B), 3.58 (s, 3 H, CO_2CH_3), 4.25 (d, $J_{10b,1}$ = 11.8 Hz, 1 H, H-10b), 5.09 (d, $J_{8,9}$ = 1.7 Hz, 1 H, H-8), 5.32 (dd, $J_{4,3B}$ = 1.9, $J_{4,3A}$ = 6.2 Hz, 1 H, H-4), 6.26 (dd, $J_{4',5'}$ = 1.8, $J_{4',3'}$ = 3.1 Hz, 1 H, H-4′), 6.40 (brd, $J_{3',4'}$ = 3.1 Hz, 1 H, H-3′), 6.50 (dd, $J_{8,9}$ = 1.7, $J_{9,10}$ = 5.6 Hz, 1 H, H-9), 6.52 (d, $J_{9,10}$ = 5.6 Hz, 1 H, H-10), 7.27 (dd, $J_{5',4'}$ = 1.8, $J_{5',3'}$ = 0.7 Hz, 1 H, H-5′); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 207.8 (C_2), 173.9 ($\underline{C}O_2Me$), 170.3 (C_6), 152.2 ($C_{2'}$), 142.4 ($C_{5'}$), 136.7 and 134.9 ($\overline{C}_9$ and C_{10}), 110.4 ($C_{4'}$), 107.8 ($C_{3'}$), 90.9 (C_8), 84.4 (C_{10a}), 59.4 and 58.7 (C_{6a} and C_7), 52.4 ($CO_2\ \underline{C}H_3$), 46.3, 44.6 and 41.8 (C_1, C_3 and C_4), 22.1 (CH_3-7), 10.1 ($\overline{C}H_3$-1); ms (EI, 70 eV): m/z (%) 371 (40) $[M]^+$, 343 (9), 295 (12), 244 (46), 228 (90), 190 (62), 176 (100), 127 (54), 122 (65), 99 (25), 79 (16), 53 (19). Anal. Calcd for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 63.91; H, 5.42; N, 3.87.

(2S*,3R*,5S*,6R*)-2-(2-Furyl)-3,5-dimethyl-6-phenylpiperidin-4-one (6a). A homogeneous solution of furfural (7.5 mL, 9.0 mmol), 2-methyl-1-phenylpent-1-en-3-on (15.7 g, 9 mmol), ammonium acetate (13.0 g, 1.8 mmol) and NH_3 (5 mL of 25% aqueous solution) in ethanol (100 mL) was stirred for a week at room temperature. The resulting mixture was put into water (400 mL), extracted with ethyl acetate (3 × 100 mL), and the organic layer separated, dried ($MgSO_4$), filtered, and evaporated. The residue (viscous brown oil) was transferred into oxalate by the following method: to the residue, dissolved in 200 mL of absolute ether, a saturated ether solution of the anhydrous oxalic acid (∼100 mL) was added until the end of the pale-brown precipitate formation. Obtained residue was filtered off, washed with acetone (2 × 70 mL), and then boiled in 100 mL of acetone. Remaining solids were filtered off and air-dried to give oxalate of piperidone **6a** as white powder. For further transformations, the obtained oxalate was dissolved in water (80 mL), a 10% solution of NH_4OH was added until pH 9−10, and free base was extracted with ether (3 × 70 mL). The organic layers were separated, dried ($MgSO_4$), filtered, and evaporated to give a pale-yellow viscous oil, which crystallized when left to stand into **c**olourless needles; yield 8%; mp 68−69°C (hexane-ethyl acetate); ir: NH 3312, C=O 1704 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 0.80 and 0.99 (two d, $J_{3(5),Me\text{-}3(Me\text{-}5)}$ = 6.7 Hz, each to 3 H, CH_3-3 and CH_3-5), 2.12 (brs, 1 H, *N*H), 2.76 (ddq, $^4J_{3,5}$ = 1.2, $J_{3,2}$ = 10.6, $J_{3,Me\text{-}3}$ = 6.7 Hz, 1 H, H-3), 2.95 (ddq, $^4J_{3,5}$ = 1.2, $J_{5,6}$ = 10.7, $J_{5,Me\text{-}5}$ = 6.7 Hz, 1 H, H-5), 3.55 (d, $J_{3,2}$ = 10.6 Hz, 1 H, H-2), 3.78 (d, $J_{5,6}$ = 10.7 Hz, 1 H, H-6), 6.25 (dd, $J_{3',4'}$ = 3.2, $J_{5',3'}$ = 0.6 Hz, 1 H, H-3′), 6.30 (dd, $J_{3',4'}$ = 3.2, $J_{4',5'}$ = 1.8 Hz, 1 H, H-4′), 7.37 (dd, $J_{5',3'}$ = 0.6, $J_{5',4'}$ = 1.8, 1 H, H-5′), 7.26−7.44 (m, 5H, H-Ph); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 210.6 (C_4), 154.5 ($C_{2'}$), 142.2 ($C_{5'}$), 141.6 ($C_{1''}$), 128.7 (2C, $C_{2''}$ and $C_{6''}$), 128.2 ($C_{4''}$), 127.8 (2C, $C_{3''}$ and $C_{5''}$), 110.2 ($C_{4'}$), 107.5 ($C_{3'}$), 68.6 (C_6), 61.9 (C_2), 51.9 and 49.9 (C_3 and C_5), 10.65 and 10.62 (CH_3-1 and CH_3-3); ms (EI, 70 eV): m/z (%) 269 (21) $[M]^+$, 184 (20), 146 (17), 123 (21), 117 (30), 108 (44), 79 (42), 77 (36), 56 (100). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.43; H, 7.30; N, 5.05.

(2S*,3R*,5S*,6R*)-3,5-Dimethyl-2-(5-methyl-2-furyl)-6-phenylpiperidin-4-one (6b). A homogeneous solution of 5-methyl furfural (9.80 mL, 9.7 mmol), 2-methyl-1-phenylpent-1-en-3-one (17.05 g, 9.7 mmol), ammonium acetate (15.09 g, 19.6 mmol) and NH_3 (5 mL of 25% aqueous solution) in ethanol (80 mL) was stirred for a week at room temperature. The resulting mixture was treated as stated earlier for compound **6a**. Piperidone **6b** was obtained as colourless needles; yield 8%; mp 105−106°C (hexane-ethyl acetate); ir: NH 3317, C=O 1703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 0.81 and 0.95 (two d, $J_{3(5),Me\text{-}3(Me\text{-}5)}$ = 6.9 Hz, each to 3 H, CH_3-3 and CH_3-5), 2.11 (brs, *N*H), 2.27 (d, $^4J_{4',Me\text{-}5'}$ = 1.2 Hz, 3 H, CH_3-5′), 2.75 (dq, $J_{3,2}$ = 11.2, $J_{3,Me\text{-}3}$ = 6.9 Hz, 1 H, H-3), 2.94 (dq, $J_{5,6}$ = 10.6, $J_{5,Me\text{-}5}$ = 6.9 Hz, 1 H, H-5), 3.55 (d, $J_{5,6}$ = 10.6 Hz, 1 H, H-6), 3.71 (d, $J_{3,2}$ = 11.2 Hz, 1 H, H-2), 5.88 (dq, $J_{3',4'}$ = 3.1, $^4J_{4',Me\text{-}5'}$ = 1.2 Hz, 1 H, H-4′), 6.12 (d, $J_{3',4'}$ = 3.1 Hz, 1 H, H-3′), 7.25−7.54 (m, 5H, H-Ph); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 210.8 (C_4), 152.7 and 151.8 ($C_{2'}$ and $C_{5'}$), 141.6 ($C_{1''}$), 128.6 (2C, $C_{2''}$ and $C_{6''}$), 128.7 (2C, $C_{3''}$ and $C_{5''}$), 128.0 ($C_{4''}$), 108.2 ($C_{3'}$), 106.1 ($C_{4'}$), 68.5 (C_6), 62.0 (C_2), 51.8 (C_1), 49.7 (C_1), 13.7 (CH_3-5′), 10.7 and 10.6 (CH_3-3 and CH_3-5); ms (EI, 70 eV): m/z (%) 283 (54) $[M]^+$, 240 (3), 226 (3), 198 (20), 149 (9), 137 (47), 122 (100), 117 (30), 104 (16), 91 (35), 79 (34), 57 (16), 56 (93), 43 (83). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.43; H, 7.26; N, 5.01.

(2S*,3R*,5S*,6R*)-2-(2-Furyl)-3,5-dimethyl-6-(2-thienyl)piperidin-4-one (6c). A homogeneous solution of furfural (4.2 mL, 51.4 mmol), 2-methyl-1-(α-thienyl)pent-1-en-3-one (9.22 g, 51.4 mmol), ammonium acetate (7.9 g, 100 mmol) and NH_3 (2.2 mL of 25% aqueous solution) in ethanol (40 mL) was stirred for 72 h at room temperature. The resulting mixture was treated as stated earlier for piperidone **6a**. Piperidone **6c** was obtained as colourless needles; yield 10%; mp 86−88°C (hexane-ethyl acetate); ir: NH 3307, C=O 1704 cm^{-1}; ^{1}HNMR (600 MHz, $CDCl_3$): δ 0.93 and 0.95 (two d, $J_{3(5),Me\text{-}3(Me\text{-}5)}$ = 6.7 Hz, each to 3 H, CH_3-3 and CH_3-5), 2.35 (brs, 1 H, *N*H), 2.73 (ddq, $J_{3,2}$ = 10.7, $J_{3,Me\text{-}3}$ = 6.7, $^4J_{3,5}$ = 1.2 Hz, 1 H, H-3), 2.98 (ddq, $J_{5,6}$ = 10.6, $J_{5,Me\text{-}5}$ = 6.7, $^4J_{3,5}$ = 1.2 Hz, 1 H, H-5), 3.81 (d, $J_{2,3}$ = 10.6 Hz, 1 H, H-2), 3.95 (d, $J_{5,6}$ = 10.6 Hz, 1 H, H-6), 6.31 (dd, $J_{5',3'}$ = 0.7, $J_{4',5'}$ = 3.2 Hz, 1 H, H-3′furyl), 6.35 (dd, $J_{5',4'}$ = 1.8, $J_{4',3'}$ = 3.2 Hz, 1 H, H-4′furyl), 6.96 (dd, $J_{5',4'}$ = 5.1, $J_{3',4'}$ = 3.5 Hz, 1 H, H-4′thienyl), 7.02 (dd, $J_{5',3'}$ = 1.1, $J_{4',3'}$ = 3.5 Hz, 1 H, H-3′thienyl), 7.28 (dd, $J_{5',3'}$ = 5.1, $J_{5',4'}$ = 1.1 Hz, 1 H, H-5′thienyl),7.41 (dd, $J_{5',4'}$ = 1.8, $J_{5',3'}$ = 0.7 Hz, 1 H, H-5′furyl); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 209.3 (C_4), 154.2 ($C_{2'furyl}$), 145.3 ($C_{2'thienyl}$), 142.1 ($C_{5'furyl}$), 126.3, 125.2, and 125.0 ($C_{3'thienyl}$, $C_{4'thienyl}$, and $C_{5'thienyl}$), 110.2 and 107.4 ($C_{3'furyl}$ and $C_{4'furyl}$), 63.7 (C_2), 61.4 (C_6), 53.1 (C_5), 49.7 (C_3), 10.6 and 10.5 (CH_3-3 and CH_3-5); ms (EI, 70 eV): m/z (%)275 (4) $[M]^+$, 228 (2), 190 (19), 163 (5), 152 (25), 124

(97), 108 (100), 96 (42), 79 (70), 77 (43), 55 (28), 45 (35), 41 (40), 39 (72). Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09; S, 11.64. Found: C, 65.23; H, 6.31; N, 5.42.

General procedure for preparation of carboxylic acids 7a-c. A solution of piperidone **6a-c** (21.0 mmol) and maleic anhydride (2.06 g, 21.0 mmol) in toluene (30 mL) was refluxed for 6–8 h. At the end of the reaction, the resulting mixture was cooled, and formation of yellow-brown solids was observed. The crystals were filtered off, washed first with toluene (2 × 30 mL), then with acetone (2 × 20 mL) and air-dried to give corresponding acids **7a–c**. Subsequent recrystallization from isopropanol-DMF mixture gave target products as colourless powders.

(1R*,3S*,4R*,6aR*,7S*,8R*,10aS*,10bS*)-1,3-Dimethyl-2,6-dioxo-4-phenyl-1,3,4,6,6a,7,8,10b-octahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-7-carboxylic acid (7a). Yield 41%; mp 224−225°C; ir: OH br 3245, CO_2H 1736, C=O 1718, N─C=O 1681 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 1.03 (d, $J_{1,Me\text{-}1}$ = 6.9 Hz, 3 H, CH_3-1), 1.42 (d, $J_{3,Me\text{-}3}$ = 7.5 Hz, 3 H, CH_3-3), 2.60 (d, $J_{6a,7}$ = 9.4 Hz, 1H, H-6a), 2.62 (dq, $J_{1,Me\text{-}1}$ = 6.9, $J_{1,10b}$ = 12.5 Hz, 1 H, H-1), 2.83 (dq, $J_{3,Me\text{-}3}$ = 7.5, $J_{3,4}$ = 1.8 Hz, 1 H, H-3), 3.01 (d, $J_{6a,7}$ = 9.4 Hz, 1 H, H-7), 4.69 (d, $J_{1,10b}$ = 12.5 Hz, 1 H, H-10b), 4.96 (brd, $J_{8,9}$ = 1.1 Hz, 1 H, H-8), 5.22 (d, $J_{3,4}$ = 1.8 Hz, 1 H, H-4), 6.49 (dd, $J_{8,9}$ = 1.1, $J_{9,10}$ = 5.6 Hz, 1 H, H-9), 6.65 (d, $J_{9,10}$ = 5.6 Hz, 1 H, H-10), 7.15 (brt, $J_{meta,para}$ = 7.5 Hz, 1 H, H-*para*), 7.21 (brt, $J_{meta,ortho}$ = $J_{meta,para}$ = 7.5 Hz, 2 H, H-*meta*), 7.40 (brd, $J_{ortho,meta}$ = 7.5 Hz, 2 H, H-*ortho*), 8.27 (s, 1 H, CO_2H); ^{13}C NMR (150.9 MHz, DMSO-d_6): δ = 211.6 (C_2), 173.5 (CO_2H), 171.3 (C_6), 142.0 ($C_{1'}$), 136.7 and 136.1 (C_9 and C_{10}), 128.6 (2C, $C_{2''}$, and $C_{6'}$), 127.0 ($C_{4'}$), 126.7 (2C, C_3, and $C_{5'}$), 90.9 (C_{10a}), 81.7 (C_8), 57.6 and 57.3 (C_4 and C_{10b}), 51.4, 51.3, 45.4 and 44.7 (C_1, C_3, C_7, C_{6a}), 18.6 (Me-3), 11.0 (Me-1); ms (EI, 70 eV): m/z (%) 367 (15) [M^+], 323 (13), 269 (19), 268 (77), 252 (56), 213 (19), 203 (19), 186 (53), 176 (74), 149 (22), 135 (22), 122 (32), 118 (69), 108 (100), 105 (32), 94 (22), 79 (26), 59 (35), 43 (47). Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.61; H, 5.81; N, 3.95.

(1R*,3S*,4R*,6aR*,7S*,8R*,10aS*,10bS*)-1,3,8-Trimethyl-2,6-dioxo-4-phenyl-1,3,4,6,6a,7,8,10b-octahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-7-carboxylic acid (7b). Yield 56%; mp 223−224 °C; ir OH br 3227, CO_2H 1740, C=O 1719, N─C=O 1679 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 1.03 (brd, $J_{1,Me\text{-}1}$ = 6.8 Hz, 3 H, CH_3-1), 1.35 (d, $J_{3,Me\text{-}3}$ = 7.5 Hz, 3 H, CH_3-3), 1.66 (s, 3 H, CH_3-8), 2.60 (d, $J_{6a,7}$ = 9.3 Hz, 1 H, H-6a), 2.64 (m, 1 H, H-3), 2.79 (m, 1 H, H-1), 3.01 (d, $J_{6a,7}$ = 9.3 Hz, 1 H, H-7), 4.60 (d, $J_{1,10b}$ = 11.8 Hz, 1 H, H-10b), 4.88 (brs, 1 H, H-4), 6.31 (d, $J_{10,9}$ = 5.3 Hz, 1 H, H-10), 6.68 (d, $J_{9,10}$ = 5.3 Hz, 1 H, H-9), 7.15 (brt, $J_{meta,para}$ = 7.5 Hz, 1 H, H-*para*), 7.22 (brt, $J_{meta,ortho}$ = $J_{meta,para}$ = 7.5 Hz, 2 H, H-*meta*), 7.44 (brd, $J_{ortho,meta}$ = 7.5 Hz, 2 H, H-*ortho*), 8.27 (s, 1 H, CO_2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 211.0 (C_2), 171.7 and 171.0 (CO_2H and C_6), 141.6 ($C_{1'}$), 139.3 and 136.7 (C_9 and C_{10}), 127.9 (2C, $C_{2'}$ and $C_{6'}$), 126.5 ($C_{4'}$), 126.4 (2C, $C_{3'}$ and $C_{5'}$), 89.6 and 88.6 (C_8 and C_{10a}), 79.2 (C_4), 57.7, 54.1, 51.0, 48.2 and 44.2 (C_1, C_3, C_{6a}, C_7, and C_{10b}), 17.5 and 16.0 (Me-8 and Me-3), 10.5 (Me-1); ms (EI, 70 eV): m/z (%) 381 (44) [M^+], 337 (10), 290 (30), 283 (56), 266 (67), 235 (23), 217 (29), 202 (21), 198 (53), 190 (97), 175 (78), 164 (22), 148 (70), 131 (62), 121 (98), 117 (100), 107 (68), 91 (82), 84 (23), 79 (96), 65 (39), 59 (46), 55 (77), 45 (12), 43 (47). Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.12; H, 6.11; N, 3.71.

(1R*,3S*,4R*,6aR*,7S*,8R*,10aS*,10bS*)-1,3-Dimethyl-2,6-dioxo-4-(2-thienyl)-1,3,4,6,6a,7,8,10b-octahydro-2H-8,10a-epoxypyrido[2,1-a]isoindole-7-carboxylic acid (7c). Yield 54%; mp 200−202°C; ir: OH 3221, CO_2H 1734, C=O 1718, N─C=O 1677 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 1.00 (d, $J_{1,Me\text{-}1}$ = 6.8 Hz, 3 H, CH_3-1), 1.40 (d, $J_{3,Me\text{-}3}$ =7.5 Hz, 3 H, CH_3-3), 2.61 (d, $J_{6a,7}$ = 9.1 Hz, 1 H, H-6a), 2.62 (dq (septet), $J_{1,Me\text{-}1}$ = 6.8, $J_{1,10b}$ = 12.4 Hz, 1 H, H-1), 2.89 (dq, $J_{3,Me\text{-}3}$ = 7.5, $J_{3,4}$ = 1.6 Hz, 1 H, H-3), 3.04 (d, $J_{6a,7}$ = 9.1 Hz, 1 H, H-7), 4.67 (d, $J_{1,10b}$ = 12.4 Hz, 1 H, H-10b), 5.17 (d, $J_{8,9}$ = 1.5 Hz, 1 H, H-8), 5.21 (d, $J_{3,4}$ = 1.6 Hz, 1 H, H-4), 6.48 (dd, $J_{8,9}$ = 1.5, $J_{9,10}$ = 5.7 Hz, 1 H, H-9), 6.61 (d, $J_{9,10}$ = 5.7 Hz, 1 H, H-10), 6.82 (dd, $J_{5',4'}$ = 4.8, $J_{3',4'}$ = 3.5 Hz, 1 H, H-4′), 7.17 (brd, $J_{3',4'}$ = 3.5 Hz, 1 H, H-3′), 7.36 (brd, $J_{4',5'}$ = 4.8 Hz, 1 H, H-α); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 211.2 (C_2), 173.6 (CO_2H), 171.4 (C_6), 145.1 ($C_{2'}$), 136.9 and 135.8 (C_9 and C_{10}), 127.0, 126.3 and 125.6 ($C_{3'}$, $C_{4'}$ and $C_{5'}$), 90.9 (C_{10a}), 81.7 (C_8), 57.1 (C_{10b}), 53.9 (C_4), 51.9, 51.3, 45.5 and 44.1 (C_1, C_3, C_7, C_{6a}), 17.9 (Me-3), 10.6 (Me-1); ms (EI, 70 eV): m/z (%) 373 (22) [M^+], 276 (20), 274 (40), 258 (70), 219 (71), 203 (32), 192 (85), 178 (52), 176 (100), 162 (50), 151 (68), 139 (64), 138 (83), 124 (84), 108 (74), 97 (50), 79 (40), 78 (81), 59 (32), 55 (83), 45 (54), 43 (75). Anal. Calcd for $C_{19}H_{19}NO_5S$: C, 61.11; H, 5.13; N, 3.75; S, 8.59. Found: C, 60.97; H, 5.09; N, 3.65.

General procedure for preparation of isoindolones 8a-c. A mixture of corresponding piperidone **6a-c** (10 mmol), acryloyl chloride (1.3 mL, 15 mmol) and triethylamine (2.5 mL, 20 mmol) in benzene (25 mL) was refluxed for 6 h. The reaction progress was monitored by TLC. At the end of the reaction, the mixture was poured into water (100 mL), an aq. (5%) solution of HCl added until pH ~6 and extracted with ethyl acetate (3 × 80 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated to give crude products. Further crystallization from hexane-ethyl acetate gave corresponding compounds **8a–c** as colourless prisms.

(1R*,3S*,4R*,6aR*,8S*,10aS*,10bS*)-1,3-Dimethyl-4-phenyl-1,3,4,7,8,10b-hexahydro-2H-8,10a-epoxypirido[2,1-a]isoindole-2,6(6aH)-dione (8a). Yield 58%; mp 161−162°C; ir: C=O br 1719, N─C=O 1680 and 1694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.16 (d, $J_{1,Me\text{-}1}$ = 6.2 Hz, 3 H, CH_3-1), 1.45 (d, $J_{3,Me\text{-}3}$ = 7.5 Hz, 3 H, CH_3-3), 1.66 (dd, $^2J_{7endo,7exo}$ = 11.8, $J_{7endo,6a}$ = 8.7 Hz, 1 H, H-7*endo*), 2.27 (ddd, $^2J_{7endo,7exo}$ = 11.8, $J_{6a,7exo}$ = 3.7, $J_{7exo,8}$ = 4.4 Hz, 1 H, H-7*exo*), 2.59 (dd, $J_{7endo,6a}$ = 8.7, $J_{6a,7exo}$ = 3.7 Hz, 1 H, H-6a), 2.85−2.94 (m, 2 H, H-1 and H-3), 4.41 (d, $J_{1,10b}$ = 12.5 Hz, 1 H, H-10b), 5.06 (d, $J_{3,4}$ = 1.9 Hz, 1 H, H-4), 5.22 (d, $J_{7exo,8}$ = 4.4 Hz, 1 H, H-8), 6.44 (s, 2 H, H-10 and H-9), 7.16−7.28 (m, 5H, H-Ph); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 210.8 (C_2), 174.5 (C_6), 140.8 ($C_{1'}$), 136.8 and 133.1 (C_9 and C_{10}), 128.7 (2C, $C_{2'}$ and $C_{6'}$), 127.3 ($C_{4'}$), 125.7 (2C, $C_{3'}$ and $C_{5'}$), 91.2 (C_{10a}), 79.1 (C_8), 59.4 and 58.3 (C_4 and C_{10b}), 51.0, 48.1 and 44.7 (C_1, C_3, C_{6a}), 28.6 (C_7), 18.9 (CH_3-3), 10.7 (CH_3-1); ms (EI, 70 eV): m/z (%) 323 (100) [M^+], 295 (5), 252 (17), 187 (7), 172 (9), 162 (23), 149 (12), 117 (25), 108 (12), 79 (17), 55 (70), 39 (5). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.32; H, 6.58; N, 4.29.

(1R*,3S*,4R*,6aR*,8S*,10aS*,10bS*)-1,3,8-Trimethyl-4-phenyl-1,3,4,7,8,10b-hexahydro-2H-8,10a-epoxypirido[2,1-a]isoindole-2,6(6aH)-dione (8b). Yield 83%; mp 185−186°C; ir: C=O and N─C=O br 1694 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$): δ = 1.15 (d, $J_{1,Me\text{-}1}$ = 6.9 Hz, 3 H, CH_3-3), 1.44 (d, $J_{3,Me\text{-}3}$ = 7.5 Hz, 3 H, CH_3-3), 1.72 (s, 3 H, CH_3-8), 1.74 (dd, $^2J_{7endo,7exo}$ = 12.0, $J_{7endo,6a}$ = 8.7 Hz, 1 H, H-7*endo*), 2.00 (dd, $J_{7endo,6a}$ = 8.7, $J_{6a,7exo}$ = 3.7 Hz, 1 H, H-6a), 2.68 (dd, $^2J_{7endo,7exo}$ = 12.0, $J_{6a,7exo}$ = 3.7 Hz, 1 H, H-7*exo*), 2.84−2.92 (m, 2 H, H-1 and H-3), 4.32 (d, $J_{1,10b}$ = 12.5 Hz, 1 H, H-10b), 5.05 (d, $J_{3,4}$ = 1.9 Hz, 1 H, H-4), 6.25 (d, $J_{9,10}$ = 5.6 Hz 1 H, H-10), 6.42 (d, $J_{9,10}$ = 5.6 Hz, 1 H, H-9), 7.17 (m, 1 H, H-Ph*para*), 7.23−7.21 (m, 4 H, H-Ph); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 208.5 (C_2), 172.3 (C_6), 138.5 ($C_{1'}$), 137.6 (C_9). 131.2 (C_{10}), 126.2 (2C, $C_{2'}$ and $C_{6'}$), 124.8 ($C_{4'}$), 123.4 (2C, $C_{3'}$ and $C_{5'}$), 88.6 (C_{10a}), 85.0 (C_8), 57.3 and 55.9 (C_4 and C_{10b}), 48.9, 48.6 and 42.3 (C_1, C_3, C_{6a}), 32.4 (C_7), 16.5 (2C, Me-3 and Me-8), 8.3 (Me-1); ms (EI, 70 eV): m/z (%) 337 (85) $[M]^+$, 309 (5), 266 (17), 246 (18), 191 (23), 176 (30), 122 (41), 117 (34), 55 (100), 25 (18). Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.79; H, 6.91; N, 4.08.

(1R*,3S*,4R*,6aR*,8S*,10aS*,10bS*)-1,3-Dimethyl-4-(2-thienyl)-1,3,4,7,8,10b-hexahydro-2H-8,10a-epoxypirido[2,1-a]isoindole-2,6(6aH)-dione (8c). Yield 72%; mp 150−151°C; ir: C=O br 1716, N−C=O 1691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (d, $J_{1,Me\text{-}1}$ = 6.7 Hz, 3 H, CH_3-1), 1.42 (d, $J_{3,Me\text{-}3}$ = 7.7 Hz, 3 H, CH_3-3), 1.65 (dd, $J_{7,6a}$ = 8.8, $^2J_{7endo,7exo}$ = 11.9 Hz,1 H, H-7*endo*), 2.25 (dd, $J_{7exo,6a}$ = 3.5, $J_{8,7exo}$ = 4.5 Hz, 1 H, H-7*exo*), 2.57 (dd, $J_{7endo,6a}$ = 8.8, $J_{6a,7exo}$ = 3.5 Hz, 1 H, H-6a), 2.91 (dq, $J_{1,Me\text{-}1}$ = 6.7, $J_{1,10b}$ = 12.3 Hz, 1 H, H-1), 3.03 (dq, $J_{3,Me\text{-}3}$ = 7.7, $J_{3,4}$ = 1.5 Hz, 1 H, H-3), 4.34 (d, $J_{1,10b}$ = 12.3 Hz, 1 H, H-10b), 5.15 (dd, $J_{8,9}$ = 1.3, $J_{8,7exo}$ = 4.5 Hz 1 H, H-8), 5.30 (brd, $J_{3,4}$ = 1.5 Hz, 1 H, H-4), 6.38 (d, $J_{9,10}$ = 5.8 Hz, 1 H, H-10), 6.39 (dd, $J_{8,9}$ = 1.3, $J_{9,10}$ = 5.8 Hz, 1 H, H-9), 6.82 (dd, $J_{3',4'}$ = 3.5, $J_{5',4'}$ = 5.0 Hz, 1 H, H-4′), 6.93 (brdd, $J_{3',5'}$ = 1.0, $J_{3',4'}$ = 3.5 Hz, 1 H, H-3′), 7.12 (dd, $J_{5',4'}$ = 5.0, $J_{3',5'}$ = 1.0 Hz, 1 H, H-5′); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 210.6 (C_2), 174.7 (C_6), 144.7 ($C_{2'}$), 136.9 (C_9), 132.9 (C_{10}), 126.7, 124.88, and 124.91 ($C_{4'}$, $C_{3'}$ and $C_{5'}$), 91.1 (C_{10a}), 79.0 (C_8), 59.1 (C_{10b}), 54.1, 50.7, 48.1 and 44.1 (C_1, C_3, C_4, C_{6a}), 28.7 (C_7), 18.4 (Me-3), 10.5 (Me-1); ms (EI, 70 eV): *m/z* (%) 329 (7) $[M]^+$, 300 (1), 258 (8), 192 (4), 178 (19), 123 (20), 108 (36), 97 (19), 79 (34), 66 (22), 55 (100), 20 (43). Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25; S, 9.73. Found: C, 65.51; H, 5.57; N, 4.09.

General procedure for preparation of imines 9a-c. Powder of $MgSO_4$ (10 g, 83 mmol) was added to the solution of tryptamine (10.0 g, 62.5 mmol) and corresponding furfural (62.5 mmol) in dichloromethane (200 mL) at vigorous stirring. After 1 h, the reaction mixture was allowed to stay at room temperature for 24 h. Then $MgSO_4$ was filtered off, washed with dichloromethane (2 × 75 mL), the organic layers combined and evaporated. Further crystallization of solid residue from hexane-ethyl acetate gave the corresponding imines **9a-c**.

N-(5-Iodo-2-furyl)methylene-2-(1H-indol-3-yl)ethanamine (9a). Bright yellow needles, yield 67%; mp 138−140°C; ir: C=N 1643 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.20 (t, $J_{1,2}$ = 7.2 Hz, 2 H, H-2), 3.94 (dt, $J_{N=CH,1}$ = 0.8, $J_{1,2}$ = 7.2 Hz, 2 H, H-1), 6.58 (d, $J_{3',4'}$ = 3.3 Hz, 1 H, H-4′furyl), 6.63 (d, $J_{3',4'}$ = 3.3 Hz, 1 H, H-3′furyl), 7.01 (dd, $J_{2'',NH}$ = 2.1, $J_{2,2'}$ = 0.8 Hz, 1 H, H-2″), 7.15 (ddd, $^4J_{5'',7''}$ = 0.7, $J_{5'',4''}$ = 8.0, $J_{5'',6''}$ = 7.5 Hz, 1 H, H-5″), 7.22 (ddd, $^2J_{6'',4''}$ = 0.7, $J_{6'',5''}$ = 7.5, $J_{6'',7''}$ = 8.0 Hz, 1 H, H-6″), 7.37 (dd, $J_{7'',6''}$ = 8.0, $^4J_{5'',7''}$ = 0.7 Hz, 1 H, H-7″), 7.67 (brd, $J_{4'',5''}$ = 8.0 Hz, 1 H, H-4″), 7.84 (t, $J_{N=CH,1}$ = 0.8 Hz, 1 H, HC=N), 8.15 (brs, 1 H, *N*H). Anal. Calcd for $C_{15}H_{13}N_2OI$: C, 49.48; H, 3.61; I, 34.86; N, 7.70. Found: C, 49.73; H, 3.45; N, 7.65.

N-(5-Bromo-2-furyl)methylene-2-(1H-indol-3-yl)ethanamine (9b). Yellow needles, yield 61%; mp 138−140°C; ir: C=N 1645 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.19 (t, $J_{1,2}$ = 7.3 Hz, 2 H, H-2), 3.92 (dt, $J_{N=CH,1}$ = 0.8, $J_{1,2}$ = 7.3 Hz, 2 H, H-1), 6.40 (d, $J_{3',4'}$ = 3.5 Hz, 1 H, H-4′furyl), 6.63 (d, $J_{3',4'}$ = 3.5 Hz, 1 H, H-3′furyl), 7.01 (brd, $J_{2'',NH}$ = 2.2 Hz, 1 H, H-2″), 7.14 (ddd, $^4J_{5'',7''}$ = 1.0, $J_{5'',4''}$ = 8.1, $J_{5'',6''}$ = 7.7 Hz, 1 H, H-5″), 7.21 (dt, $^2J_{6'',4''}$ = 1.0, $J_{6'',5''}$ = $J_{6'',7''}$ = 7.7 Hz, 1 H, H-6″), 7.37 (brd, $J_{7'',6''}$ = 7.7 Hz, 1 H, H-7″), 7.67 (brd, $J_{4'',5''}$ = 7.7 Hz, 1 H, H-4″), 7.84 (d, $J_{N=CH,1}$ = 0.8 Hz, 1 H, HC=N), 8.18 (brs, 1 H, *N*H). Anal. Calcd for $C_{15}H_{13}N_2OBr$: C, 56.80; H, 4.13; Br, 25.19; N, 8.83. Found: C, 56.65; H, 4.29; N, 8.91.

N-(2-Furylmethylene)-2-(1H-indol-3-yl)ethanamine (9c). Bright yellow needles, yield 70%; mp 135−138°C; ir: C=N 1647 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.19 (dt, $J_{1,2}$ = 7.4, $J_{2'',2}$ = 0.7 Hz, 2 H, H-2), 3.91 (dt, $J_{N=CH,1}$ = 1.2, $J_{1,2}$ = 7.4 Hz, 2 H, H-1), 6.47 (dd, $J_{3',4'}$ = 3.4, $J_{5',4'}$ = 1.8 Hz, 1 H, H-4′furyl), 6.68 (dd, $J_{3',4'}$ = 3.4, $J_{3',5'}$ = 0.6 Hz, 1 H, H-3′furyl), 7.02 (brd, $J_{2'',NH}$ = 2.3 Hz, 1 H, H-2″), 7.12 (ddd, $^4J_{5'',7''}$ = 1.0, $J_{5'',4''}$ = 8.0, $J_{5'',6''}$ = 7.0 Hz, 1 H, H-5″), 7.19 (ddd, $^2J_{6'',4''}$ = 1.2, $J_{6'',5''}$ = 7.0, $J_{6'',7''}$ = 8.2 Hz, 1 H, H-6″), 7.36 (dd, $J_{7'',6''}$ = 8.2, $J_{7'',5''}$ = 1.0 Hz, 1 H, H-7″), 7.51 (dd, $J_{5',4'}$ = 1.8, $J_{3',5'}$ = 0.6 Hz, 1 H, H-5′furyl), 7.65 (dd, $J_{4'',5''}$ = 8.0, $J_{6'',4''}$ = 1.2 Hz, 1 H, H-4″), 7.96 (brt, $J_{N=CH,1}$ = 1.2 Hz, 1 H, HC=N), 8.04 (brs, 1 H, *N*H); ms (EI, 70 eV): m/z (%) 238 $[M^+]$ (10), 143 (5), 131 (16), 130 (100), 115 (7), 108 (16), 107 (16), 81 (26), 77 (31), 63 (7), 53 (25), 39 (21). Anal. Calcd for $C_{15}H_{14}NO_2$: C, 75.60; H, 5.93; N, 11.77. Found: C, 75.46; H, 5.72; N, 12.01.

General procedure for preparation of benzo[1,2]indolizino[8,7-*b*]indol-4-carboxylic acids 10a,b. A solution of azomethine **9a**,**b** (42.0 mmol) and maleic anhydride (4.5 g, 46 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 24 h. Formation of yellow solids was observed. The crystals were filtered off, washed first with CH_2Cl_2 (2 × 30 mL), then with acetone (2 × 20 mL) and air-dried. The corresponding acids **10a**,**b** were obtained as white powder.

(3R*,4S*,4aS*,13bR*,13cR*)-3-Iodo-5-oxo-3,4,4a,5,7,8,13,13b-octahydro-3,13c-epoxybenzo[1,2]indolizino[8,7-b]indole-4-carboxylic acid (10a). Yield 33%; mp >210°C (decomp.) (*i*-PrOH-DMF); ir: CO_2H 1687, N−C=O 16 and 1610 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.56 (m, 1 H, H-8B), 2.80 (m, 1 H, H-8A), 2.92 (d, $J_{4,4a}$ = 8.8 Hz, 1 H, H-4), 3.00 (m, 1 H, H-7B), 3.15 (d, $J_{4a,4}$ = 8.8 Hz, 1 H, H-4a), 4.28 (dd, *J* = 5.7, $^2J_{7,7}$ = 12.8 Hz, 1 H, H-7A), 5.63 (brs, 1 H, H-13b), 6.63 (d, $J_{2,1}$ = 5.4 Hz, 1 H, H-2), 6.80 (d, $J_{1,2}$ = 5.4 Hz, 1 H, H-1), 7.00 (brt, $J_{10,11} \sim J_{10,9}$ = 7.7 Hz, 1 H, H-10), 7.09 (brt, $J_{11,10} \sim J_{11,12}$ = 7.7 Hz, 1 H, H-11), 7.37 (brd, $J_{12,11}$ = 7.7 Hz, 1 H, H-12), 7.43 (brd, $J_{9,10}$ =7.7 Hz, 1 H, H-9), 10.95 (s, 1 H, *N*H), 12.44 (brs, 1 H, CO_2H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 170.4 and 168.0 (CO_2H and C_5), 142.9 (C_2), 137.2 (C_1), 136.5 (C_{12a}), 128.2 and 126.3 (C_{13a} and C_{8b}), 121.2, 118.6, 117.8 (C_9−C_{11}), 111.2 (C_{12}), 108.3 (C_{8a}), 89.7 (C_{13c}), 65.6 (C_3), 53.8, 53.2 and 52.9 (C_4, C_{4a} and C_{13b}), 37.1 (C_7), 20.9 (C_8); ms (EI, 70 eV): m/z (%) 364 $[M^+$-98] (26), 363 (40), 335 (32), 290 (29), 262 (8), 254 (52), 237 (47), 222 (26),

209 (65), 207 (57), 181 (47), 180 (97), 169 (46), 152 (32), 143 (46), 131 (70), 130 (100), 127 (90), 104 (24), 98 (77), 83 (96), 77 (77), 54 (98). Anal. Calcd for $C_{19}H_{15}IN_2O_4$: C, 49.37; H, 3.27; I, 27.45; N, 6.06. Found: C, 49.51; H, 3.32; N, 6.12.

(3R*,4S*,4aS*,13bR*,13cR*)-3-Bromo-5-oxo-3,4,4a,5,7,8,13,13b-octahydro-3,13c-epoxybenzo[1,2]indolizino[8,7-b]indole-4-carboxylic acid (10b). Yield 53%; mp >230°C (decomp.) (*i*-PrOH-DMF); ir: CO_2H 1745, N─C=O 1663 and 1644 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.58 (m, 1 H, H-8B), 2.80 (m, 1 H, H-8A), 3.02 (d, $J_{4,4a}$ = 8.9 Hz, 1 H, H-4), 3.02 (m, 1 H, H-7B), 3.23 (dd, $J_{4a,4}$ = 8.8, $J_{4a,13b}$ = 0.8 Hz, 1 H, H-4a), 4.29 (dd, J = 5.4, $^2J_{7,7}$ = 12.9 Hz, 1 H, H-7A), 5.63 (brs, 1 H, H-13b), 6.58 (d, $J_{2,1}$ = 5.6 Hz, 1 H, H-2), 6.98 (d, $J_{1,2}$ = 5.6 Hz, 1 H, H-1), 7.01 (brt, $J_{10,11} \sim J_{10,9}$ = 7.7 Hz, 1 H, H-10), 7.10 (brt, $J_{11,10} \sim J_{11,12}$ = 7.7 Hz, 1 H, H-11), 7.36 (brd, $J_{12,11}$ = 7.7 Hz, 1 H, H-12), 7.44 (brd, $J_{9,10}$ =7.7 Hz, 1 H, H-9), 10.98 (s, 1 H, *N*H), 12.46 (brs, 1 H, CO_2H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 170.1 and 168.4 (C_5 and CO_2H), 140.1 and 138.4 (C_2 and C_1), 136.9 (C_{12a}), 128.6 (C_{13a}), 126.8 (C_{8b}), 121.8 (C_{10}), 119.1 and 118.3 (C_9 and C_{11}), 111.7 (C_{12}), 108.8 (C_{8a}), 91.2 and 89.7 (C_{13c} and C_3), 54.62 and 54.57 (C_4 and C_{13b}), 51.7 (C_{4a}), 37.6 (C_7), 21.4 (C_8); ms (EI, 70 eV): m/z (%): 318 [M^+−98] (46), 316 (44), 290 (64), 288 (63), 261 (16), 237 (51), 229 (23), 223 (13), 220 (15), 208 (40), 191 (9), 180 (100), 169 (26), 154 (27), 152 (34), 144 (32), 130 (27), 128 (25), 115 (20), 102 (16), 98 (14), 89 (18), 81 (35), 79 (70), 59 (26), 54 (48), 43 (55). Anal. Calcd for $C_{19}H_{15}BrN_2O_4$: C, 54.96; H, 3.64; Br, 19.24; N, 6.75. Found: C, 54.89; H, 3.41; N, 6.93.

General procedure for preparation of esters 11a,b. Corresponding acid **10a**,**b** (10.5 mmol) was dissolved in methanol (130 mL) and sulphuric acid (0.5 mL) was added. The resulting solution was refluxed for 12 h. The reaction progress was monitored by TLC. At the end of the reaction the mixture was cooled, poured into water (400 mL) and extracted with CH_2Cl_2 (5 × 80 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated. Further crystallization of solid residue from ethanol gave the corresponding esters **11a**,**b** as pale-brown powders.

Methyl (3R*,4S*,4aS*,13bR*,13cR*)-3,4,4a,5,7,8,13,13b-octahydro-3-iodo-5-oxo-3,13c-epoxybenzo[1,2]indolizino[8,7-b]indole-4-carboxylate (11a). Pink powder, yield 60%; mp >215°C (decomp.); ir: CO_2Me 1752, N─C=O 1683 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.58 (m, 1 H, H-8B), 2.80 (brdd, J = 3.7, $^2J_{8,8}$ = 15.0 Hz, 1 H, H-8A), 2.99 (m, 1 H, H-7B), 3.10 (d, $J_{4,4a}$ = 9.3 Hz, 1 H, H-4), 3.20 (brd, $J_{4a,4}$ = 9.3 Hz, 1 H, H-4a), 3.58 (s, 3 H, CO_2CH_3), 4.29 (dd, J = 5.6, $J_{7,7}$ = 13.1 Hz, H-7A), 5.64 (s, 1 H, H-13b), 6.63 (d, $J_{1,2}$ = 5.3 Hz, 1 H, H-1), 6.82 (d, $J_{2,1}$ = 5.3 Hz, 1 H, H-2), 7.00 and 7.09 (two brt, $J \sim$ 7.5 Hz, each to1 H, H-10 and H-11), 7.36 (d, $J_{11,12}$ = 8.1 Hz, 1 H, H-12), 7.44 (brd, $J_{9,10}$ = 7.5 Hz, 1 H, H-9), 10.94 (brs, 1 H, *N*H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 169.8 and 168.1 (C_5 and $\underline{C}O_2CH_3$), 142.9 (C_2), 137.3 (C_1), 136.5, 128.1 and 126.3 (C_{12a}, C_{13a}, C_{8b}), 121.3 (C_{11}), 118.7 and 117.9 (C_9 and C_{10}), 111.3 (C_{12}), 108.4 (C_{8a}), 90.0 (C_{13c}), 64.9 (C_3), 53.9, 53.6, 53.0, and 51.4 (C_4, C_{4a}, $CO_2\underline{C}H_3$, and C_{13b}), 37.2 (C_7), 20.9 (C_8); ms (ESI+): m/z 499 [28, ($\overline{M}$+Na)$^+$], 477 [100, (M+H)$^+$]. Anal. Calcd for $C_{20}H_{17}IN_2O_4$: C, 50.44; H, 3.60; I, 26.65; N, 5.88. Found: C, 50.18; H, 3.51; N, 5.94.

Methyl (3R*,4S*,4aS*,13bR*,13cR*)-3-bromo-3,4,4a,5,7,8,13,13b-octahydro-5-oxo-3,13c-epoxybenzo[1,2]indolizino[8,7-b]indole-4-carboxylate acid (11b). Straw-coloured powder, yield 70%; mp >225°C (decomp.); ir: CO_2Me 1734, C=O 1662 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.60 (m, 1 H, H-8B), 2.80 (m, 1 H, H-8A), 3.00 (m, 1 H, H-7B) 3.19 (d, $J_{4,4a}$ = 9.0 Hz, 1 H, H-4), 3.29 (brd, $J_{4a,4}$ = 9.0 Hz, 1 H, H-4a), 3.58 (s, 3 H, CO_2CH_3), 4.29 (dd, J = 5.6, $J_{7,7}$ = 13.1 Hz, 1 H, H-7A), 5.65 (brs, 1 H, H-13b), 6.57 (d, $J_{1,2}$ = 5.6 Hz, 1 H, H-1), 7.00 (d, $J_{1,2}$ = 5.6 Hz, 1 H, H-2), 7.00 (brdd, $J_{10,11}$ = 7.5, $J_{11,12}$ = 8.1 Hz, 1 H, H-11), 7.09 (dt, $^4J_{10,12}$ = 1.2, $J_{10,11}$ = $J_{9,10}$ = 7.5 Hz, 1 H, H-10), 7.36 (brd, $J_{11,12}$ = 8.1 Hz, 1 H, H-12), 7.43 (brd, $J_{9,10}$ = 7.5 Hz, 1 H, H-9), 10.96 (s, 1 H, *N*H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 168.9 and 168.0 (C_5 and $\underline{C}O_2CH_3$), 139.6 and 138.0 (C_2 and C_1), 136.5, 127.9 and 126.3 (C_{12a}, C_{13a}, and C_{8b}), 121.4 (C_{10}), 118.7 and 117.9 (C_9 and C_{10}), 111.3 (C_{12}), 108.5 (C_{8a}), 90.3 and 89.5 (C_{13c} and C_3), 54.40, 54.26, 51.5, and 51.2 (C_4, C_{13b}, C_{4a}, $CO_2\underline{C}H_3$), 37.3 (C_7), 20.9 (C_8); ms (ESI+): m/z 452 [33, ($M+\overline{Na}$)$^+$, ^{81}Br], 450 [35, (M+Na)$^+$, ^{79}Br], 430 [98, (M+H)$^+$, ^{81}Br], 428 [100, (M+H)$^+$, ^{79}Br]. Anal. Calcd for $C_{20}H_{17}BrN_2O_4$: C, 55.96; H, 3.99; Br, 18.61; N, 6.53. Found: C, 55.94; H, 3.82; N, 6.82.

(3S*,4R*,4aS*,13bR*,13cR*)-3,4,4a,5,7,8,13,13b-Octahydro-4a-methyl-5-oxo-3,13c-epoxybenzo[1,2]indolizino[8,7-b]indole-4-carboxylic acid (12A) and (3S*,4R*,4aS*, 13bR*,13cR*)-4-methyl-5-oxo-3,4,4a,5,7,8,13,13b-octahydro-3,13c-epoxybenzo[1,2]indolizino[8,7-b]indole-4-carboxylic acid (12B). A solution of citraconic anhydride (7.6 mL, 84 mmol) in dichloromethane (10 mL) was added to a solution of imine **9c** (10 g, 42 mmol) in dichloromethane (30 mL). The reaction mixture was stirred at room temperature for 24 h. Obtained crystals were filtered off, washed with dichloromethane (3 × 20 mL) and air-dried to give corresponding acid as a mixture of the regioisomers **12A**:**12B**, in the ratio 1.3:1. Following data is cited for isomer mixture. White powder, yield 70%; mp >220°C (decomp.) (*i*-PrOH-DMF); ir: CO_2H 1725, C=O br 1667 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): **12A** maj: δ = 1.20 (s, 3 H, CH_3-4), 2.09 (s, 1 H, H-4a), 2.52 (m, 1 H, H-8B), 2.77 (m, 1 H, H-8A), 3.00 (m, 1 H, H-7B), 4.25 (m, 1 H, H-7A), 4.75 (d, $J_{2,3}$ = 1.6 Hz, 1 H, H-3), 5.53 (brs, 1 H, H-13b), 6.58 (dd, $J_{1,2}$ = 5.7, $J_{3,2}$ = 1.6 Hz, 1 H, H-2), 6.81 (d, $J_{2,1}$ = 5.7 Hz, 1 H, H-1), 6.98 (brt, $J_{10,11} \sim J_{10,9}$ = 7.7 Hz, 1 H, H-10), 7.07 (brt, $J_{11,10} \sim J_{11,12}$ = 7.7 Hz, 1 H, H-11), 7.34 (brd, $J_{12,11}$ = 8.0 Hz, 1 H, H-12), 7.41 (brd, $J_{9,10}$ = 7.7 Hz, 1 H, H-9), 10.86 (s, 1 H, *N*H), 12.10 (brs, 1 H, CO_2H); **12B** min: δ = 1.09 (s, 3 H, CH_3-4a), 2.54 (s, 1 H, H-4), 2.52 (m, 1 H, H-8B), 2.77 (m, 1 H, H-8A), 2.98 (m, 1 H, H-7B), 4.29 (m, 1 H, H-7A), 4.78 (d, $J_{2,3}$ = 1.6 Hz, 1 H, H-3), 5.54 (brs, 1 H, H-13b), 6.53 (dd, $J_{1,2}$ = 5.7, $J_{3,2}$ = 1.6 Hz, 1 H, H-2), 6.87 (d, $J_{2,1}$ = 5.7 Hz, 1 H, H-1), 6.98 (brt, $J_{10,11} \sim J_{10,9}$ = 7.7 Hz, 1 H, H-10), 7.07 (brt, $J_{11,10} \sim J_{11,12}$ = 7.7 Hz, 1 H, H-11), 7.34 (brd, $J_{12,11}$ = 8.0 Hz, 1 H, H-12), 7.41 (brd, $J_{9,10}$ = 7.7 Hz, 1 H, H-9), 10.86 (s, 1 H, *N*H), 12.10 (brs, 1 H, CO_2H); ^{13}C NMR **12A**+**12B** (100.6 MHz, DMSO-d_6): δ = 174.7, 172.8, 172.7, 169.4, 137.6, 136.5, 136.3, 135.7, 133.2, 129.00, 128.92, 126.4, 121.1 (2C), 118.6 (2C), 117.7 (2C), 111.2 (2C), 108.2 (2C), 92.6, 91.3, 84.0, 80.3, 79.2 (2C), 59.4, 57.0, 54.3, 53.1, 52.6, 50.2, 37.0, 36.8, 22.3, 21.4, 20.94, 20.86; ms (EI, 70 eV): *m*/*z* (%) 261 [M^+−89] (25), 259 (40), 257 (13), 203 (27), 201 (67), 199 (26), 180 (23), 178 (31), 121 (54), 119 (50), 101 (74), 98 (45), 82 (36), 72 (80), 59 (100), 57 (56), 55 (44), 43 (79). Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.53; H, 5.41; N, 8.12.

General procedure for preparation of 3*H*-imidazo[4,5-*c*]pyridines 13a-c. A solution of corresponding furfural (10.0 mmol) in ethanol (30 mL) was added to a mixture of histamine dihydrochloride (1.84 g, 10.0 mmol) and triethylamine (2.8 mL, 25.0 mmol) in ethanol (50 mL) while stirring. The resulting mixture was refluxed for 3 h. At the end of the reaction the solvent was evaporated, and obtained brown oil was triturated with acetone to give corresponding spinacine in moderate yield. Spinacine **13c** was used in the next step without further purification and spectral identification.

4,5,6,7-Tetrahydro-4-(5-iodo-2-furyl)- 3H-imidazo[4,5-c]pyridine (13a). Red powder, yield 30%, mp >150°C (decomp.) (*i*-PrOH-DMF); ir: NH 3414 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.51 (brt, $J_{6,7}$ = 5.7 Hz, 2 H, H-7), 2.90 (brt, $J_{6,7}$ = 5.7 Hz, 2 H, H-6), 4.94 (s, 1 H, H-4), 5.97 (d, $J_{3',4'}$ = 3.3 Hz, 1 H, H-3′), 6.57 (d, $J_{3',4'}$ = 3.3 Hz, 1 H, H-4′), 7.44 (s, 1 H, H-2); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 160.2 ($C_{2'}$), 134.9 (C_2), 129.4 and 126.6 (C_{3a} and C_{7a}), 120.5 ($C_{4'}$), 111.1 ($C_{3'}$), 90.2 ($C_{5'}$), 50.0 (C_4), 40.0 (C_6), 22.5 (C_7); ms (EI, 70 eV): m/z (%) 315 [M^+] (22), 314 (39), 286 (22), 251 (23), 188 (100), 159 (26), 132 (33), 131 (37), 104 (14), 95 (13), 79 (15), 77 (19), 51 (12), 45 (12). Anal. Calcd for $C_{10}H_{10}IN_3O$: C, 38.12; H, 3.20; I, 40.27; N, 13.34. Found: C, 38.39; H, 3.04; N, 13.58.

4-(5-Bromo-2-furyl)-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine (13b). Yellow powder, yield 62%, mp > 150°C (decomp.) (*i*-PrOH-DMF); ir: NH 3426 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.78 (m, 2 H, H-7), 3.20 (m, 2 H, H-6), 5.44 (brs, 1 H, H-4), 6.39 (d, $J_{3',4'}$ = 3.3 Hz, 1 H, H-3′), 6.57 (d, $J_{3',4'}$ = 3.3 Hz, 1 H, H-4′), 7.60 (s, 1 H, H-2); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 158.5 ($C_{2'}$), 133.5 (C_2), 130.1 and 126.7 (C_{3a} and C_{7a}), 119.6 ($C_{5'}$), 111.9 and 110.1 ($C_{3'}$ and $C_{4'}$), 50.1 (C_4), 39.9 (C_6), 23.1 (C_7); ms (ESI+): m/z 291 [17, $(M+Na)^+$, ^{81}Br], 389 [20, $(M+Na)^+$, ^{79}Br], 369 [95, $(M+H)^+$, ^{81}Br], 367 [100, $(M+H)^+$, ^{79}Br]. Anal. Calcd for $C_{10}H_{10}BrN_3O$: C, 44.80; H, 3.76; N, 15.67; Br, 29.80. Found: C, 44.66; H, 3.81; N, 15.71.

General procedure for preparation of imidazo[4′,5′:3,4]pyrido[2,1-*a*]isoindole-8-carboxylic acids 14a-c. A solution of maleic anhydride (0.57 g, 5.8 mmol) in ethanol (10 mL) was added to a solution of corresponding spinacine **13a–c** (5.3 mmol) in ethanol (20 mL). The reaction mixture was stirred at room temperature for 24 h. Formation of off-white precipitates was observed. At the end of the reaction the obtained solids were filtered off and washed with ethanol (3 × 20 mL) giving amino acids **14a-c** as poorly dissolved pale-yellow powders in most organic solvents.

(7aS*,8S*,9R*,11aR*,11bR*)-9-Iodo-1,4,5,7,7a,8,9,11b-octahydro-7-oxo-9,11a-epoxyimidazo[4′,5′:3,4]pyrido[2,1-a]isoindole-8-carboxylic acid (14a). Yield 41%, mp > 220°C (decomp.) (*i*-PrOH-DMF); ir: CO_2H 1756, C=O 1687 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.59 (m, 1 H, H-4B), 2.90−2.98 (m, 2 H, H-4A and H-5B), 2.88 (d, $J_{8,7a}$ = 8.1 Hz, 1 H, H-8), 3.06 (brd, $J_{7a,8}$ = 8.1 Hz, 1 H, H-7a), 4.20 (dd, $^2J_{5,5}$ = 13.1, $J_{5A,4B}$ = 5.6 Hz, 1 H, H-5A), 5.32 (brs, 1 H, H-11b), 6.54 (d, $J_{10,11}$ = 5.8 Hz, 1 H, H-11), 6.72 (d, $J_{11,10}$ = 5.8 Hz, 1 H, H-10), 7.51 (s, 1 H, H-2); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 170.8 and 168.7 (CO_2H and C_7), 143.4 (C_{10}), 137.8 (C_{11}) 135.1 (C_2), ∼114.4 (br 2C, C_{11c}, and C_{3a}), 90.2 (C_{11a}), 66.3 (C_9), 55.2 (C_{11b}), 53.6 and 53.5 (C_{7a} and C_8), 37.1 (C_5), 22.4 (C_4); ms (EI, 70 eV): m/z (%) 315 [M^+−98] (5), 314 (15), 286 (75), 182 (53), 127 (100), 98 (35); ms (ESI+): m/z 436 [23, $(M+Na)^+$], 414 [100, $(M+H)^+$]. Anal. Calcd for $C_{14}H_{12}IN_3O_4$: C, 40.70; H, 2.93; I, 30.72; N, 10.17. Found: C, 40.67; H, 2.86; N, 10.23.

(7aS*,8S*,9R*,11aR*,11bR*)-9-Bromo-1,4,5,7,7a,8,9,11b-octahydro-7-oxo-9,11a-epoxyimidazo[4′,5′:3,4]pyrido[2,1-a]isoindole-8-carboxylic acid (14b). Yield 38%, mp > 230°C (decomp.) (*i*-PrOH-DMF); ir: CO_2H 1761, C=O 1685 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.61 (m, 1 H, H-4B), 2.90−2.95 (m, 2 H, H-4A, and H-5B), 2.97 (d, $J_{8,7a}$ = 9.0 Hz, 1 H, H-8), 3.13 (brd, $J_{7a,8}$ = 9.0 Hz, 1 H, H-7a), 4.21 (dd, $^2J_{5,5}$ = 13.1, $J_{5A,4B}$ = 5.6 Hz, 1 H, H-5A), 5.32 (brs, 1 H, H-11b), 6.48 (d, $J_{10,11}$ = 5.3 Hz, 1 H, H-11), 6.91 (d, $J_{11,10}$ = 5.8 Hz, 1 H, H-10), 7.51 (s, 1 H, H-2); ^{13}C NMR (150.9 MHz, DMSO-d_6): δ = 170.0 and 168.6 (CO_2H and C_7), 140.1 (C_{10}), 138.4 (C_{11}), 135.1 (C_2), 113.6 (br 2C, C_{11c}, and C_{3a}), 90.2 (C_{11a}), 89.7 (C_9), 55.5 (C_{11b}), 54.5 and 51.8 (C_{7a} and C_8), 37.2 (C_5), 22.4 (C_4); ms (ESI+): m/z 389 [30, $(M+Na)^+$, ^{81}Br], 387 [29, $(M+Na)^+$, ^{79}Br], 367 [98, $(M+H)^+$, ^{81}Br], 365 [100, $(M+H)^+$, ^{79}Br]. Anal. Calcd for $C_{14}H_{12}BrN_3O_4$: C, 45.92; H, 3.30; Br, 21.82; N, 11.48. Found: C, 45.98; H, 3.55; N, 11.54.

(7aS*,8R*,9S*,11aR*,11bR*)-1,4,5,7,7a,8,9,11b-Octahydro-7-oxo-9,11a-epoxyimidazo[4′,5′:3,4]pyrido[2,1-a]isoindole-8-carboxylic acid (14c). Yield 39%, mp > 220°C (decomp.) (*i*-PrOH-DMF); ir: CO_2H and C=O br 1687 cm^{-1}; ^1H NMR (400 MHz, D_2O/$(CD_3)_2CO$ (5:1)/K_2CO_3 (5 mol %), traces of $(CD_3)COCD_2H$ at δ 2.06 ppm were used as the internal standard): δ = 2.34 (m, $^2J_{4,4}$ = 15.6, $J_{4B,5A}$ = 6.2, $J_{4B,5B}$ = 11.6, $^5J_{11b,Hb\text{-}4}$ = 2.2 Hz, 1 H, H-4B), 2.48 (m, $^2J_{4,4}$ = 15.6, $J_{4A,5B}$ = 4.8, J = 1.3 Hz, 1 H, H-4A), 2.50 (d, $J_{8,7a}$ = 9.3 Hz, 1 H, H-8), 2.90 (dddd, $^2J_{5,5}$ = 13.4, $J_{5B,4B}$ = 11.6, $J_{5B,4B}$ = 4.8, J = 1.4 Hz, 1 H, H-5B), 2.95 (dd, $J_{7a,8}$ = 9.3, $^4J_{11b,7a}$ = 1.3 Hz, 1 H, H-7a), 4.14 (dd, $^2J_{5,5}$ = 13.4, $J_{5A,4B}$ = 6.2 Hz, 1 H, H-5A), 4.84 (d, $J_{9,10}$ = 1.8 Hz, 1 H, H-9), 5.27 (brdd, $^5J_{11b,4B}$ = 2.2, $^4J_{11b,7a}$ = 1.3 Hz, 1 H, H-11b), 6.44 (dd, $J_{10,11}$ = 5.8, $J_{10,9}$ = 1.8 Hz, 1 H, H-10), 6.65 (d, $J_{11,10}$ = 5.8 Hz, 1 H, H-11), 7.50 (s, 1 H, H-2); ^{13}C NMR (100.6 MHz, D_2O/$(CD_3)_2CO$ (5:1)/K_2CO_3 (5 mol %), the signal of $(CD_3)_2CO$ at δ 29.2 ppm was used as the internal standard): δ = 178.9 (CO_2H), 172.6 (C_7), 137.5 (C_{10}), 135.6 (C_2), 133.5 (C_{11}), 127.7 (C_{11c}), 125.2 (C_{3a}), 90.40 (C_{11a}), 81.8 (C_9), 55.8 (C_{11b}), 50.8 (C_{7a}), 47.0 (C_8), 36.6 (C_5), 20.5 (C_4); ms (EI, 70 eV): m/z (%) 287 [M^+] (3), 241 (5), 225 (4), 189 (32), 188 (55), 161 (16), 160 (88), 159 (19), 133 (13), 132 (22), 131 (100), 120 (11), 104 (11), 95 (13), 77 (6), 54 (35), 44 (6), 28 (5), 26 (13). Anal. Calcd for $C_{14}H_{13}N_3O_4$: C, 58.54; H, 4.57; N, 14.64. Found: C, 58.58; H, 4.65; N, 14.81.

Acknowledgment. The authors are grateful to the Russian Foundation for Basic Research for the financial support of this work (grant no. 07-03-00083a).

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