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A new approach to construction of isoindolo[1,2-*a*]isoquinoline alkaloids *Nuevamine*, *Jamtine*, and *Hirsutine* via IMDAF reaction

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ABSTRACT

The interaction between 1-furyl-1,2,3,4-tetrahydroisoquinolines and unsaturated acids derivatives (acryloyl, methacryloyl, and crotonoyl chloride, maleic and citraconic anhydride) was studied. It was shown that the reaction proceeds via amide formation and subsequent intramolecular Diels–Alder reaction of the furan (IMDAF). The [4+2] cycloaddition proceeded under mild reaction conditions (25–80 °C) and afforded only the *exo*-adduct in a high yield. With this method, a new approach to the isoindolo[1,2-*a*]isoquinoline system, the basic structural element of alkaloids *Jamtine*, *Hirsutine*, and *Nuevamine*, is proposed.

1. Introduction

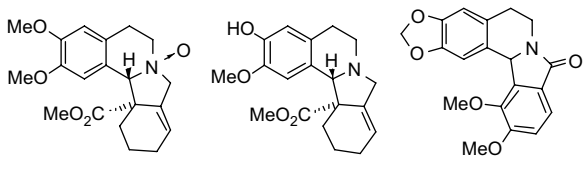
Recently our group has proposed several efficient approaches to potentially bioactive substances such as hydrogenated hydroxyisoquinolines,[1] isoindolo[2,1-*a*]quinolines,[2] and isoindolo[2,1-*b*]benzazepines[3] using commercially available furfurylamines as starting materials. The intramolecular furan Diels–Alder reaction (IMDAF)[4] between unsaturated acid derivatives and the furan core of the amines was the key step of the transformations mentioned above.

Trying to apply our chemistry to target natural products we were attracted to isoindoloisoquinoline alkaloids. There are three known natural products containing the isoindolo[2,1-*a*]isoquinoline skeleton. These are the alkaloids *Nuevamine*, *Jamtine* (and its *N*-oxide), and *Hirsutine* (Chart 1).

The lactams of (±)-*Nuevamine*, the first known isoindoloquinoline alkaloids, were isolated in 1984[5] by Berberis Darwinii Hook (Southern Chile). Their structure was established one year later[6] and there are several published methods of their synthesis.[7]

(±)-*Jamtine* is probably the best-known substance amongst isoindoloquinoline alkaloids. Its isolation was reported in 1987.[8] It is produced by the climbing shrub *Cocculus Hirsutus*,[9] that grows in Pakistan and India and is widely used in folk medicine.[10]

From all appearances *Jamtine* together with other bioactive substances is responsible for the antihyperglycemic activity of



Jamtine-N-oxide *Hirsutine* from Cocculus hirsutus (L.)

Nuevamine from Berberis darwinii Hook

Chart 1.

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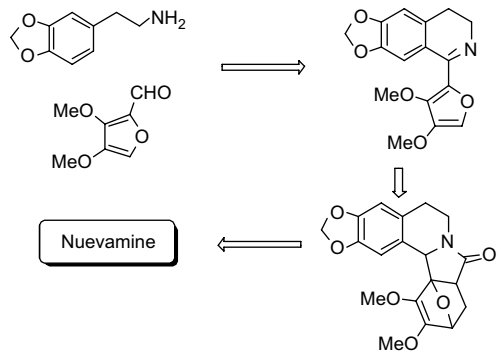


Chart 2.

aqueous extract of *C. Hirsutus* leaves (L.).[11] The first synthesis of this unusual alkaloid was reported by Padwa's research group in 2002.[12]

Isolation of the isoindoloisoquinoline alkaloid (±)-*Hirsutine* was first reported in 1991[13] (also from *C. Hirsutus*). We were surprised to have found no published synthesis of this substance. Possibly it can be explained by the fact that another *Corynanthe* alkaloid of indolo[2,3-*a*]quinolizidine series has the same name.[14]

2. Results and discussion

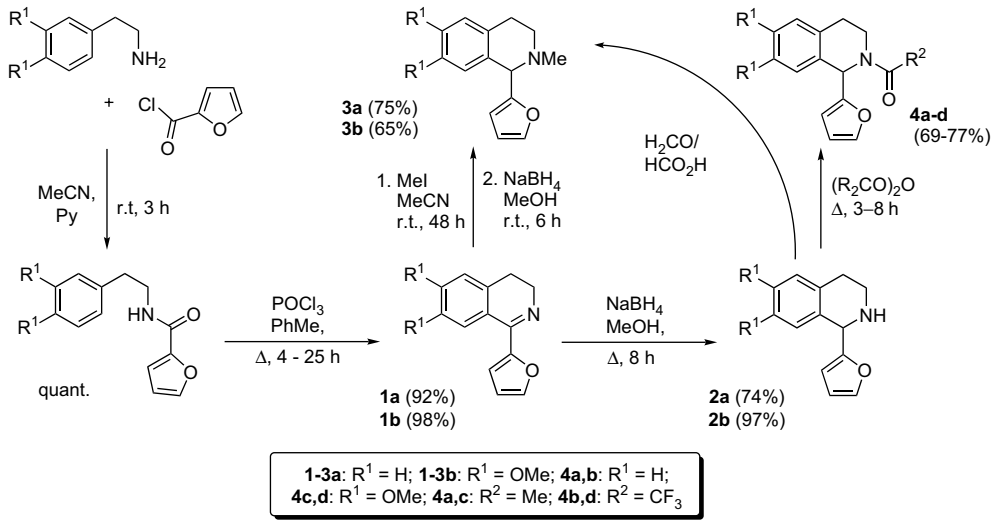
Our approach to the construction of isoindolo[1,2-*a*]isoquinol ine frame involves three basic steps (Chart 2): Bischler–Napieralski synthesis of 3,4-dihydro-1-furylisoquinoline, reduction, and then cycloaddition of the resulting tetrahydroisoquinoline with either maleic anhydride or an unsaturated acid chloride. Subsequent transformations of the Diels–Alder adducts can lead to various products including *Nuevamine*.

The initial 1-furylisoquinolines **2**–**4** were obtained by a three-step procedure, which involves acylation of phenethylamines with furoylchloride followed by Bischler–Napieralski reaction.[15] Condensation of furoylamides in an excess of phosphorus oxychloride in boiling toluene gave the desired imines **1** in good overall yields. Dimethoxy derivative **1b** formed much faster (3–5 h) and in higher yields (95–98%) than its unsubstituted analogue **1a** (24–26 h, 85–92%), that can be explained by the electron-donor effect of the methoxy groups.

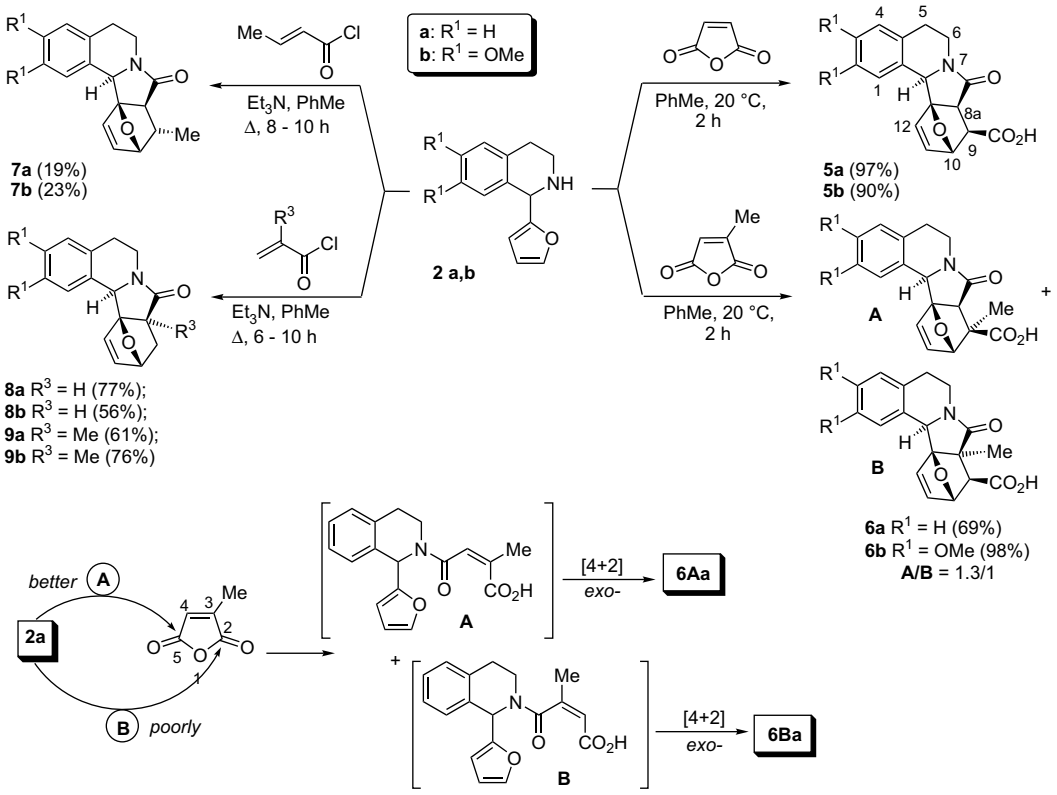
In both cases no resinification occurs. Subsequent alkylation/reduction or reduction/acylation processes gave *N*-methyltetrahydroisoquinolines **3** and amides **4** (Scheme 1). It should be mentioned that the two-stage procedure for preparation of 2-methyl-1,2,3,4-tetrahydroisoquinolines **3**, including alkylation with methyl iodide and reduction under sodium borohydride, turned out to be preferable (65–77% overall yield) over the single-stage reaction of formic acid/formaldehyde mixture (45–55%).

The next step of our study implied the construction of the isoindolo[1,2-*a*]isoquinoline skeleton based on the interaction between tetrahydroisoquinolines **2a**,**b** and maleic (citraconic) anhydride. Both reactions went smoothly and stereospecifically under mild reaction conditions. As shown in Scheme 2 by an example of adding citraconic anhydride to 1-furyl-1,2,3,4-tetrahyd roisoquinoline **2a**, the reaction ran via an initial maleinamides **A** (**B**) formation (that was not isolated) followed by the stereoselective intramolecular [4+2] *exo*-cycloaddition reaction. The Diels–Alder adducts—5,8,8a,9,10,12b-hexahydro-6*H*-10,12a-epoyisoindolo[2,1-*a*]isoquinolines **5** (**6**), occur with the form of single diastereoisomer with the *cis*-orientation[2,13,16] of the 10,12a-epoxy bridge and substituents at C-8a and C-9 ($J_{8a\text{-}exo,9\text{-}exo}$=8.8–9.3 Hz, $J_{9exo,10}$=0 Hz). The H-8a and H-12b protons have the *cis*-configuration as well. This conclusion was confirmed by ^{1}H NMR NOE values indicating the increase of H_i signal intensity when H_j signal was saturated ($\eta_{H_i}\{H_j\}$, %). The values of $\eta_{H\text{-}12b}\{H\text{-}8a\}$=4–6.5% and $\eta_{H\text{-}8a}\{H\text{-}12b\}$=4.5% proved that H-8a and H-12b atoms in adducts **5a**,**b** are situated on the same side of the central pyrrolidone ring. In the case of citraconic anhydride, a mixture of two regioisomers, which differ in the position of the methyl group (at C-8a or C-9), was isolated from the reaction mixture. Both isomeric pairs **6aA**/**6aB** and **6bA**/**6bB** contained predominantly the regioisomers with Me group at the position C-9. The ratio of isomers **A**/**B** was ~1.3:1 according to the ^{1}H NMR spectroscopic data (see Experimental section) (Scheme 2). These results could be explained by the fact that the nucleophilic attack of **2a** by nitrogen atom occurs preferentially at the C-5 carbon atom of citraconic anhydride rather than at C-2. The latter is sterically bulkier and bears a lesser partial positive charge resulting from the electron-donating effect of the Me-3 group.

For *Nuevamine* synthesis it is necessary to be able to obtain the isoindolo[1,2-*a*]isoquinoline skeleton without the carboxylic group at C-9. To this end we had to turn to the interaction between tetrahydroisoquinolines **2** and chloranhydrides of acrylic acid derivatives. The acylation and following cycloaddition of crotonoyl, methacryloyl, and acryloyl chlorides with 1,2,3,4-tetrahydro-1-furylisoquinolines **2a**,**b** required more drastic reaction conditions (Scheme 2) compared to maleic anhydride. While the maleic



Scheme 1.



Scheme 2.

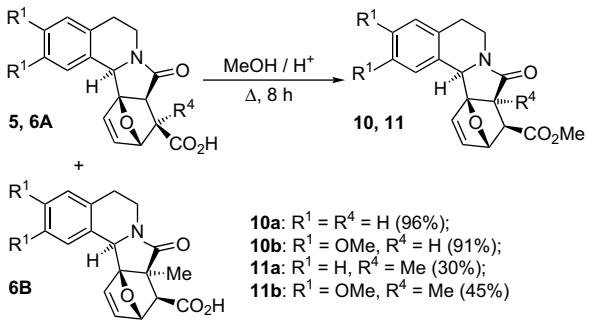
anhydride, the cycloaddition proceeded at room temperature for 2 h, the reaction with acryloyl chloride derivatives required 8–10 h heating at 110 °C in toluene. In the case of the acylation of tetrahydroisoquinolines **2a**,**b** with crotonoyl and acryloyl chlorides, the reactions proceeded smoothly to give the corresponding 10,12b-epoxyisoindolo[1,2-*a*]isoquinolines **8**,**9** in moderate yields (56–77%) and with a high level of stereoselectivity. After solvent removal a simple purification process by recrystallization allowed us to obtain pure *exo*-pentacycles **8a**,**b** and **9a**,**b**. The substituent R^3 (Me-8a) in compounds **9** has *endo*-orientation, that was established from the large NOE values of $\eta_{H\text{-}12b}\{Me\text{-}8a\}$ or vice versa equal to 12–14%.

Unexpectedly, the analogous procedure with the initial product **2** and crotonoyl chloride under chosen reaction conditions gave the target isoindoloisoquinolines **7** in poor yields (no more than 25%). We cannot provide any acceptable explanation of this fact. The structure of compounds **7** was established relying on the ^1H NMR spectroscopic data. In particular, the H-8a and H-9 atoms of the oxabicycloheptene fragment in these compounds gave the doublet signals at δ 2.18–2.20 ppm and the doublet-doublet-quartet signals at δ 2.62–2.64 ppm with spin–spin coupling constants $J_{8a\text{-}endo,9\text{-}exo}$= 3.8 Hz and $J_{10,9\text{-}exo}$=4.5 Hz.

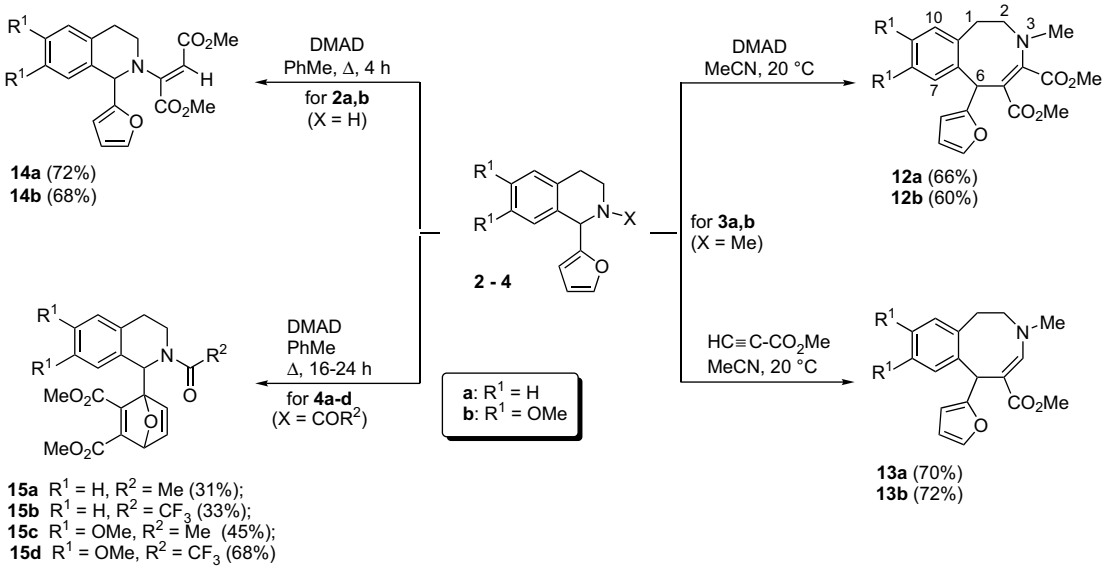
The carboxylic acids **5**, **6** are colourless crystalline substances, sparingly soluble in most organic solvents, and therefore hardly analyzable by NMR. In this connection we carried out their esterification (Scheme 3) that permitted us to obtain the corresponding esters **10**, **11** and interrogate their spatial structures using ^1H–^1H and ^{13}C NMR methods. It was interesting to note that after esterification of the regioisomer mixture **6A**/**6B** and isolation of esters **11**, the unique derivatives **11a** (**11b**) with *endo*-orientation of the Me-8a groups were obtained. Probably the purification by recrystallization protocol led to enrichment of less soluble Me-8a regioisomers, and thus, we were unable to isolate the corresponding Me-9 analogue.

In the second part of our investigation we were interested in the interaction between isoquinolines **1**–**4** and activated alkynes. Since the isoquinolines **1**–**4** possess simultaneously the dienophilic furan fragment and the nucleophilic nitrogen atom in their molecules, two competing ways of the reaction are theoretically possible: the Diels–Alder cycloaddition to the furan ring and the Michael addition to nitrogen.

We presume, that the formation of the tetrahydrobenzo[*d*]azocines derivatives **12a,b** proceeds via the Michael addition of the saturated nitrogen atom of isoquinolines **3a,b** to the triple bond of the DMAD (dimethyl acetylenedicarboxylate) molecule, followed by the intramolecular SN reaction, leading to the tetrahydropyridine ring expansion (Scheme 4). In a similar manner, methyl propiolate addition to amines **3a**,**b** led to the regioselective Michael addition and subsequent cycle expansion to form benzo[*d*]azocines **13a**,**b**. In either case, according to chromatography–mass spectrometry data, no [4+2] cycloaddition adduct was observed in the crude reaction mixture. The formation mechanism of octatomic cycles **12** and **13** is exemplified in our previous papers.[17]



Scheme 3.



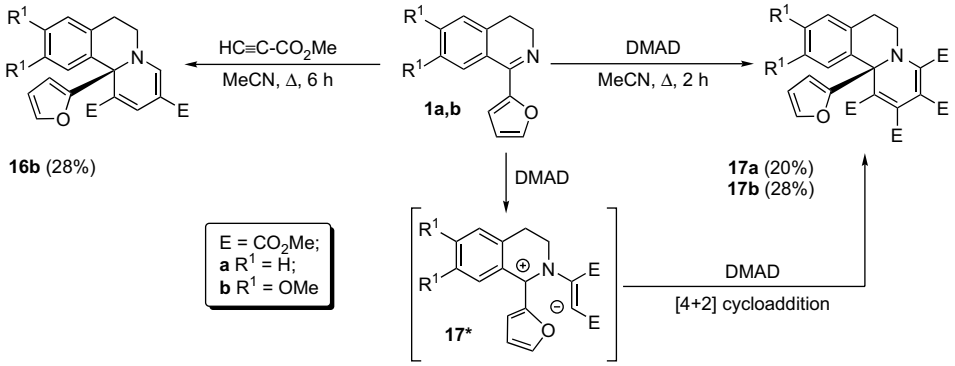
Scheme 4.

The interaction between 1-furyl-1,2,3,4-tetrahydroisoquinol ines **2a**,**b** and double molar excess of DMAD proceeded smoothly in boiling toluene (Scheme 4). Initially we expected alkylation of nitrogen with alkyne to the *N*-vinyl derivative **14** that would undergo further the [4+2] cycloaddition with the second DMAD molecule. But practically, only the first stage was realized (most likely, owing to the steric hindrance of the bulky *N*-vinyl fragment). In much the same way *N*-acylated isoquinolines **4** cyclized in the presence of DMAD giving adducts **15** in satisfactory yields. The latter was isolated as a mixture of two geometrical isomers differing in the orientation of the H-1 relative to the 1′,4′-oxabridge. The ratio of the two isomers was ~6:1 according to the ^{1}H NMR spectroscopic data.

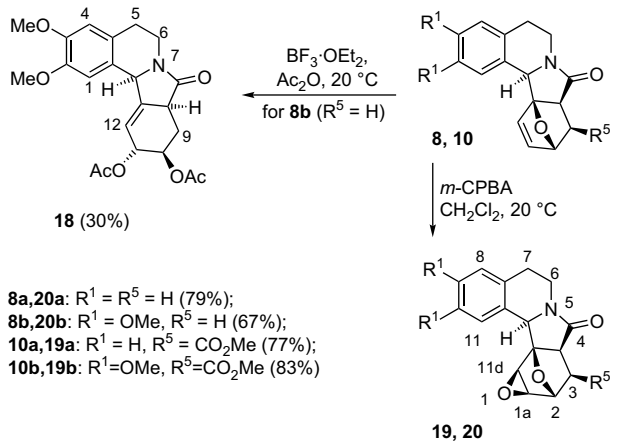
The reaction of 3,4-dihydroisoquinolines **1** with an excess of DMAD or methyl propiolate gives an unusual reaction. In that case the attack of acetylenedicarboxylate at the nitrogen atom of the imines **1** led to the relatively stable zwitterion **17***. The subsequent [4+2] cycloaddition of the next DMAD molecule to this ion closes the six-membered cycle and forms product **17**.[18] Methyl propiolate reacts with **1** in the same way. No products of furan cycloaddition or cycle expansion were isolated from the reaction mixture (Scheme 5).

The last part of this article concerns the modification of the oxabicycloheptene moiety in epoxyisoindolo[1,2-*a*]isoquinolines **8**,**10**. First, in the presence of $BF_3 \cdot OEt_2$ in acetic anhydride epoxide **8b** was transformed into diacetyl compound **18** (Scheme 6). This reaction was a result of opening of the oxabridge with subsequent migration of the double bond. Its structure was established by ^{1}H and ^{13}C NMR spectroscopic data. Double bond migration to C-12-position was proved by the presence of the quaternary carbon C-12a at δ 141.9 ppm. It is a painful conclusion for us, since we relied on the fact that the conjugate double bond would arise at the C-8a–C-9 position (*Jamtine* skeleton). A relatively high (for diacetoxy-substituted fragments) coupling constant $^3J_{10\text{-H},11\text{-H}}$=7.9 Hz indicated the pseudoaxial positions of H-10 and H-11. It means that the acetoxy groups had the *trans*-configuration. This statement was confirmed by ^{1}H NMR NOE values $\eta_{\text{H-12b}}${H-8a}=6%, on the one hand, and $\eta_{\text{H-10}}${H-8a}=5%, on the other hand, proved that the H-12b, H-10, and H-8a atoms were situated on the same side of the central pyrrolidone plane.

Then, the epoxidation of the double bond in **8a**,**b** and **10a**,**b** with *m*-chloroperoxybenzoic acid was accomplished. The yields of diepoxides **19**, **20** were 65–85% (Scheme 6). As expected,[1a,19] oxirane ring of heptacycles **19**, **20** was *exo*-annulated to the oxabicycloheptane fragment. The *endo*-configuration of H-1a, H-3(*endo*), H-3a, and H-11d of the compound **19**, **20** was concluded from the similarity of the vicinal constants $^3J_{1a,11d}$=2.9–3.3 Hz, $^3J_{3a,3A(endo)}$=8.9–9.2 Hz, and $^3J_{2,3A(endo)}$=$^3J_{2,1a(endo)}$=0 Hz with the literature data for analogous bridged systems with reliably established configurations.[20] According to these data, the coupling



Scheme 5.



Scheme 6.

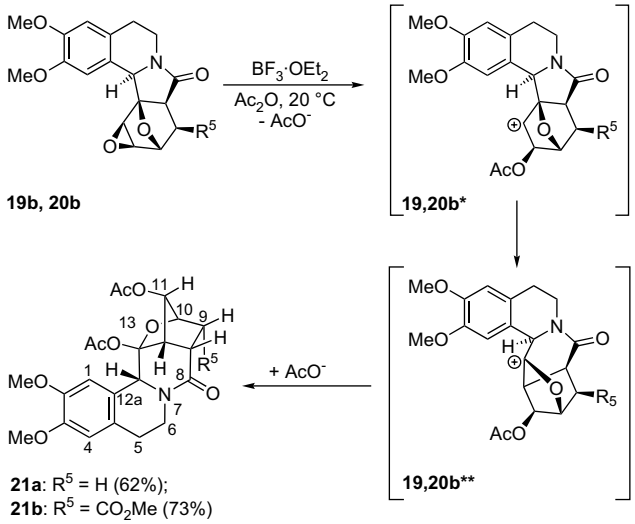
constant of the proton in the bridgehead (H-2) is very small (<1 Hz) for R-*endo*-H, but it is higher than 3 Hz for R-*exo*-H, so the observed spin coupling constants unambiguously prove the *endo*-orientation of H-1a and H-3A(*endo*).

The exposure of diepoxides **19b**, **20b** to $BF_3 \cdot OEt_2$ in the presence of acetic anhydride led to the opening of the oxirane ring in accordance with the original Wagner–Meerwein skeleton rearrangement (Scheme 7). As a result polycycles **21a**,**b** (with quite good yield) were formed via intermediate cations **19**, **20b*** and **19**, **20b****. The formation mechanism of compounds **21a**,**b** looks like a typical Wagner–Meerwein rearrangement and it is exemplified in Scheme 7.

^1H and ^{13}C NMR data for the compounds **21a**,**b** confirm their structural similarity with the 4,6-epoxycyclopenta[*c*]pyridine skeleton. But the absence of literature analogy of the structure of the compounds **21a**,**b** did not allow us to make a decisive choice between several possible alternative structures relying only on NMR data. Particularly the relative configuration of hydrogen atoms at C-11 and C-12a remained unclear.

Single crystals of **21a** were grown by crystallization from a mixture of ethanol with dimethylformamide, and its molecular structure was unambiguously elucidated by X-ray data (Fig. 1).

Compound **21a** comprises a fused pentacyclic system containing two five-membered (cyclopentane and tetrahydrofuran) and three



Scheme 7.

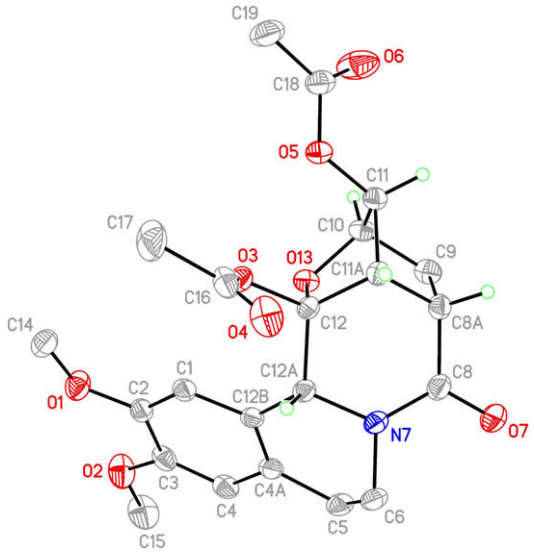


Figure 1. Molecular structure of **21a** (only hydrogen atoms at the asymmetric centers are shown).

six-membered (tetrahydropyridinone, tetrahydropyridine and benzene) rings (Figs. 1 and 2). Both five-membered rings of the bicyclic fragment have usual *envelope* conformations, and the two central six-membered rings adopt the *sofa* (tetrahydropyridinone, the C11A carbon atom is out of the plane through the other atoms of the ring by 0.672 Å) and nonsymmetrical *half-chair* (tetrahydropyridine, the C6 carbon and N7 nitrogen atoms are out of the plane through the other atoms of the ring by −0.544 and 0.238 Å, respectively) conformations. The nitrogen N7 atom has the trigonal-planar geometry (sum of the bond angles is 359.4°). The dihedral angle between the planes of the tetrahydropyridinone and tetrahydropyridine rings is 131.3°. It is interesting to point out that the two carboxylate substituents are in the sterically unfavourable *syn*-periplanar configuration relative to the tetrahydrofuran ring. Such a disposition is explained by both the structure of the initial epoxy compound **19b** and the direction of the Wagner–Meerwein rearrangement.

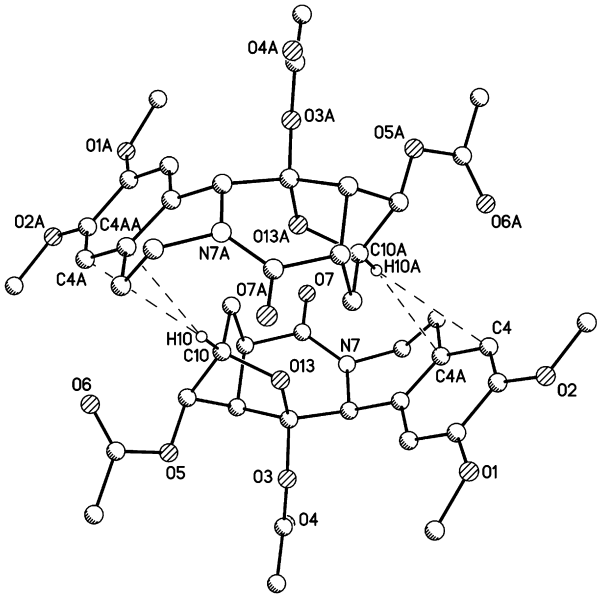


Figure 2. The H-bonded dimers of **21a** (most hydrogen atoms are omitted for clarity); hydrogen bonds are shown by dashed lines.

The molecules of **21a** are diastereomers and possess six asymmetric centers at the C8A, C10, C11, C11A, C12, and C12A carbon atoms. The crystal of **21a** is racemate and consists of enantiomeric pairs with the relative configuration of the centers *rac*-8A*R**,10*S**,11*R**,11A*R**,12*R**,12A*S**. In the crystal, the enantiomers of **21a** form the centrosymmetrical dimers via intermolecular C10–H···π(C4–C4A) [−*x*, 1−*y*, −*z*] hydrogen bonds (H···C4 3.04 Å, ∠C10–H···C4 131°; H···C4A 2.79 Å, ∠C10–H···C4A 151°) (Fig. 2). The dimers are packed in stacks along the *a* axis (see Supplementary data).

Thus, herein we reported a facile new procedure, which enables the synthesis of isoindolo[1,2-*a*]isoquinolines in three synthetic steps with high levels of diastereoselectivity, from readily available precursors: furfural, phenethylamines, and maleic anhydride. Some reactions of the adducts obtained have been performed, and the regioselectivity of the reaction of activated alkynes with hydrogenized 1-furylisoquinolines has been investigated. The suggested strategy for the isoindolo[1,2-*a*]isoquinoline construction offers a new short synthetic route to the alkaloid *Nuevamine* and closely related structural analogs of the alkaloids *Jamtine* and *Hirsutine*.

3. Experimental

3.1. General

All reagents were purchased from Acros Chemical Co. All solvents were used without further purification. Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were obtained in KBr pellets for solids or in thin film for oils using an IR-Fourier spectrometer Infralum FT-801. ^{1}H (400 or 600 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded for solutions (2–5%) in deuteriochloroform or DMSO-d_6 (**6b** and **19a**) at 30 °C and traces of chloroform (^{1}H NMR δ 7.26 ppm) or DMSO-d_5H (^{1}H NMR δ 2.49 ppm and ^{13}C NMR 39.43 ppm) were used as the internal standard. Mass spectra were measured either on Thermo Focus DSQ II (electron ionization, 70 eV, ion source temperature was 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). The purity of the substances obtained 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.

3.2. X-ray crystal structure determination

The crystal of **21a** ($C_{22}H_{25}NO_8$, M=431.43) is triclinic, space group *P*-1, at T=293 K: a=9.5010(19), b=10.792(2), c=11.173(2) Å, α=87.60(3), β=74.90(3), γ=68.31(3)°, V=1025.9(4) Å^3, Z=2, d_{calcd}=1.397 g/cm^3, F(000)=456, μ=0.107 mm^{-1}. 4041 total reflections (3794 unique reflections, R_{int}=0.012) were measured on an Enraf-Nonius CAD-4 four-circle automated diffractometer (λ(Mo Kα)-radiation, β-filter, $\omega/2\theta$ scan mode, $2\theta_{max}$=51°). The structure was determined by direct methods and refined by full-matrix least squares technique with anisotropic displacement parameters for non-hydrogen atoms. The hydrogen atoms were placed in calculated positions and refined within riding model with fixed isotropic displacement parameters (U_{iso}(H)=1.5U_{eq}(C) for the CH_3-groups and U_{iso}(H)=1.2U_{eq}(C) for the other groups). The final divergence factors were R_1=0.031 for 2553 independent reflections with $I>2\sigma(I)$ and wR_2=0.091 for all independent reflections, S=1.039. All calculations were carried out using the SHELXTL (PC version 6.12) program.[21] Crystallographic data for **21a** have been deposited with the Cambridge Crystallographic Data Center, CCDC 694217. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

3.3. 1-(2-Furyl)-3,4-dihydroisoquinoline (1a), 1-(2-furyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (1b)

3.3.1. Compound *1a*

Phosphoryl chloride (72 mL, 1 mol) was slowly added with cooling to a stirred solution of amide **1a** (43 g, 0.20 mol) in absolute toluene (250 mL). The reaction mixture was then refluxed for 24–26 h. At the end of reaction, the reaction mixture was cooled and poured into 300 mL ice and treated with 25% aqueous ammonia to pH 9–10. Then the organic products were extracted with ethyl acetate (3×150 mL), the organic layers were combined, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on Al_2O_3 (eluent ethyl acetate–hexane 1:10) to give dihydroisoquinoline **1a** as dark oil. Yield 33.3 g (92%); R_f (ethyl acetate) 0.35; IR 1735 (C=N) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M$^+$ 197 (87), 168 (100), 154 (11), 141 (57), 128 (14), 115 (82), 102 (16), 89 (31), 77 (43), 63 (58), 51 (64), 38 (99). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (1H, dd, $J_{8,6}$ 1.4, $J_{8,7}$ 7.4 Hz, H-8), 7.58 (1H, br d, $J_{5',4'}$ 2.0 Hz, H-5′), 7.41 (1H, dt, $J_{6,5}$=$J_{6,7}$ 7.4, $J_{6,8}$ 1.4 Hz, H-6), 7.33 (1H, dt, $J_{7,5}$ 1.5, $J_{7,6}$=$J_{7,8}$ 7.4 Hz, H-7), 7.26 (1H, br dd, $J_{5,6}$ 7.4, $J_{5,7}$ 1.5 Hz, H-5), 6.85 (1H, br d, $J_{3',4'}$ 3.4 Hz, H-3′), 6.52 (1H, dd, $J_{4',3'}$ 3.4, $J_{4',5'}$ 2.0 Hz, H-4′), 3.82 (2H, t, $J_{3,4}$ 7.4 Hz, H-4), 2.74 (2H, t, $J_{3,4}$ 7.4 Hz, H-3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 156.9 ($C_{2'}$), 151.7 (C_1), 143.9 ($C_{5'}$), 138.8 (C_{4a}), 130.7 (C_6), 127.53 (C_{8a}), 127.45 (C_8), 126.8 and 126.7 (C_5 and C_7), 113.0 and 111.2 ($C_{3'}$ and $C_{4'}$), 47.2 (C_3), 26.3 (C_4). Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.20; H, 5.60; N, 7.11.

3.3.2. Compound *1b*

Phosphoryl chloride (13.1 mL, 0.18 mol) was slowly added dropwise with cooling to a stirred solution of amide **1a** (10.0 g, 0.036 mol) in absolute toluene (70 mL). The reaction mixture was then refluxed for 3–5 h. After cooling, it was poured into 100 mL of broken ice and basified with 25% aqueous ammonia to pH 9–10. The mixture was extracted with ethyl acetate (3×100 mL). The extract was dried over $MgSO_4$ and concentrated in vacuo. The crude product was recrystallized from mixture of hexane–ethyl acetate to give dihydroisoquinoline **1b** as pale-yellow rhombic crystals. Yield 9.0 g (98%); mp 99–101 °C; R_f (ethyl acetate) 0.41; IR 1717 (C=N) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M$^+$ 257 (100), 242 (18), 228 (17), 212 (13), 184 (6), 115 (7), 77 (9), 63 (6), 51 (7), 39 (13). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (1H, dd, $J_{5',3'}$ 0.8, $J_{5',4'}$ 1.3 Hz, H-5′), 7.24 (1H, s, H-8), 6.82 (1H, dd, $J_{3',4'}$ 3.4, $J_{3',5'}$ 0.8 Hz, H-3′), 6.74 (1H, s, H-5), 6.51 (1H, dd, $J_{4',3'}$ 3.4, $J_{4',5'}$ 1.3 Hz, H-4′), 3.92 (3H, s, H–OMe), 3.85 (3H, s, H–OMe), 3.77 (2H, t, $J_{3,4}$ 7.4 Hz, H-3), 2.65 (2H, t, $J_{4,3}$ 7.4 Hz, H-4). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 156.2 ($C_{2'}$), 151.9 (C_6), 150.9 (C_7), 147.2 (C_1), 143.6 ($C_{5'}$), 131.7 (C_{4a}), 120.2 (C_{8a}), 112.4 (C_5), 111.1 (C_8), 110.7 ($C_{3'}$), 110.3 ($C_{4'}$), 56.1 and 55.8 (OMe×2), 47.0 (C_3), 22.7 (C_4). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.05; H, 5.85; N, 5.42.

3.4. 1-(2-Furyl)-1,2,3,4-tetrahydroisoquinoline (2a), 1-(2-furyl)-6,7-dimethoxy-1,2,3,4-terahydroisoquinoline (2b). Typical procedure

2-Fold molar excess of $NaBH_4$ (3.33 g, 0.088 mol) was added to an alcohol solution (150 mL, MeOH) of the corresponding dihydroisoquinoline (0.044 mol). The reaction mixture was then refluxed for 6–10 h (monitoring by TLC). At the end of the reaction, the mixture was diluted with water (400 mL) and extracted with

chloroform (5×50 mL). The extract was dried over $MgSO_4$ and concentrated in vacuo to give 1,2,3,4-tetrahydroisoquinolines **2a**,**b**.

*3.4.1. Compound **2a***

White powder, yield 6.42 g (74%); mp 39–41 °C; R_f (50% ethyl acetate–hexane) 0.68; IR 3235 (NH) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 199 (100), 170 (67), 141 (76), 130 (42), 115 (52), 103 (18), 77 (31), 55 (36), 39 (43). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38 (1H, br d, $J_{5',3'}$ 0.7, $J_{5',4'}$ 1.8 Hz, H-5′), 7.10–7.20 (3H, m, H-5, H-6, and H-7), 7.02 (1H, d, $J_{8,7}$ 8.1 Hz, H-8), 6.29 (1H, dd, $J_{4',3'}$ 3.0, $J_{4',5'}$ 1.8 Hz, H-4′), 5.98 (1H, dd, $J_{3',4'}$ 3.0, $J_{3',5'}$ 0.7 Hz, H-3′), 5.22 (1H, s, H-1), 3.06–3.14 (2H, m, H-3), 2.86 (2H, m, H-4), 2.33 (1H, br s, NH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 156.8 ($C_{2'}$), 142.0 ($C_{5'}$), 135.3 and 135.1 (C_{4a} and C_{8a}), 129.3, 127.8, 126.8, 125.6 ($C_{5,6,7,8}$), 109.9 and 108.3 ($C_{3'}$ and $C_{4'}$), 58.0 (C_1), 42.2 (C_3), 29.0 (C_4). Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.36; H, 6.59; N, 6.99.

*3.4.2. Compound **2b***

Viscous pale-red oil, yield 10.95 g (97%); R_f (50% ethyl acetate–hexane) 0.50; IR 3330 (NH) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 259 (85), 258 (100), 244 (30), 230 (29), 228 (27), 201 (16), 192 (13), 115 (11), 77 (5). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39 (1H, br d, $J_{5',3'}$ 0.8, $J_{5',4'}$ 1.8 Hz, H-5′), 6.61 (1H, s, H-5), 6.51 (1H, s, H-8), 6.29 (1H, dd, $J_{4',3'}$ 3.2, $J_{4',5'}$ 1.8 Hz, H-4′), 5.98 (1H, dd, $J_{3',4'}$ 3.2, $J_{3',5'}$ 0.8 Hz, H-3′), 5.15 (1H, s, H-1), 3.87 (3H, s, OMe), 3.76 (3H, s, OMe), 3.01–3.13 (2H, m, H-3), 2.86–2.71 (2H, m, H-4), 2.34 (1H, br s, NH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 156.9 ($C_{2'}$), 148.3 and 147.7 (C_6 and C_7), 141.9 ($C_{5'}$), 127.5 and 126.9 (C_{4a} and C_{8a}), 111.7 (C_5), 110.7 (C_8), 109.9 and 108.2 ($C_{3'}$ and $C_{4'}$), 55.9 and 55.8 (OMe×2), 54.0 (C_1), 40.3 (C_3), 28.8 (C_4). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.51; H, 6.58; N, 5.42.

3.5. 1-(2′-Furyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (3a), 1-(2′-furyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (3b)

Method A. To a solution of corresponding isoquinoline **1a**,**b** (1.9 mmol) in 35 mL of acetonitrile was added 0.12 mL (1.9 mmol) of methyl iodide. The reaction mixture was stirred at room temperature for 2 days (monitoring by TLC). At the end of the reaction the solvent was evaporated. The residue was crystallized in ethyl acetate to give intermediate *N*-methylisoquinoline iodides as yellow solids (yield 84%).

Sodium borohydride 0.12 g (3.2 mmol) was slowly added to the stirred solution of *N*-methy-3,4-dihydrolisoquinoline iodide (1.6 mmol) in 30 mL of methanol at room temperature. The reaction progress was monitored by TLC (until disappearance of the starting compound's spot). At the end of the reaction (36 h) the mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3×25 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated to give brown oil. The residue was purified by the column chromatography on alumina (Al_2O_3, 45×1 cm), eluent: hexane, then hexane–ethyl acetate (10:1, 5:1, 1:1) to give *title compound* **3**.

Method B. Paraform 0.27 g (9.0 mmol) was added to a solution of corresponding isoquinoline (9.0 mmol) in 20 mL of formic acid. The reaction mixture was refluxed for 4–6 h until the complete dissolution of paraformaldehyde. After the reaction mixture was cooled an additional 1.08 g (0.036 mol) of paraform was added. The resulted mixture was refluxed additionally for 4–6 h. The formic acid was removed under reduced pressure. The residue, brown oil, was dissolved in ethyl acetate (50 mL) and washed with saturated solution of sodium carbonate (2×20 mL). The organic layer was separated, washed with water (2×20 mL), dried ($MgSO_4$), and concentrated. The residue, brown oil, was purified by the column chromatography on alumina (Al_2O_3, 45×1 cm), eluent: hexane, then hexane–ethyl acetate (10:1, 5:1, 1:1) to give the corresponding compounds **3**.

*3.5.1. Compound **3a***

Brown oil, yield: *method A*—0.31 g (92%), *method B*—0.79 g (41%); R_f (30% ethyl acetate–hexane) 0.63; IR 1451 (C=C) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 213 (70), 185 (6), 170 (73), 140 (100), 128 (13), 114 (35), 89 (7), 77 (7), 42 (13). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38 (1H, dd, $J_{5',3'}$ 0.8, $J_{5',4'}$ 1.6 Hz, H-5′), 7.09–7.15 (1H, m, H-5, 6, and 7), 6.88 (1H, br d, $J_{8,7}$ 8.0 Hz, H-8), 6.34 (1H, dd, $J_{4',5'}$ 1.6, $J_{4',3'}$ 3.0 Hz, H-4′), 6.21 (1H, dd, $J_{3',5'}$ 0.8, $J_{3',4'}$ 3.0 Hz, H-3′), 4.60 (1H, s, H-1), 3.11 (2H, m, H-3), 2.92 (1H, m, H-4A), 2.68 (m, 1H, H-4B), 2.38 (3H, s, NMe). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 155.1 ($C_{2'}$), 142.2 ($C_{5'}$), 135.3 and 134.4 (C_{4a} and C_{8a}), 128.7 (C_5), 127.7, 126.5, 125.7 ($C_{6,7,8}$), 109.8 and 109.6 ($C_{3'}$ and $C_{4'}$), 63.1 (C_1), 50.3 (C_3), 43.8 (Me-2), 28.6 (C_4). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.82; H, 7.08; N, 6.56.

*3.5.2. Compound **3b***

Brown oil, yield: *method A*—0.34 g (77%), *method B*—1.28 g (52%); R_f (ethyl acetate) 0.38; IR 1464 (C=C) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 273 (77), 258 (13), 230 (100), 206 (54), 187 (17), 144 (17), 115 (33), 81 (44), 42 (58). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35 (1H, dd, $J_{5',3'}$ 0.8, $J_{5',4'}$ 1.8 Hz, H-5′), 6.60 (1H, s, H-8), 6.32 (1H, s, H-5), 6.30 (1H, dd, $J_{4',5'}$ 1.8, $J_{4',3'}$ 3.2 Hz, H-4′), 6.15 (1H, dd, $J_{3',5'}$ 0.8, $J_{3',4'}$ 3.2 Hz, H-3′), 4.51 (1H, s, H-1), 3.83 (3H, s, OMe), 3.68 (3H, s, OMe), 3.04 (1H, m, H-3A), 2.94 (1H, m, H-3B), 2.79 (1H, m, H-4A), 2.63 (1H, m, H-4B), 2.34 (3H, s, NMe). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 155.1 ($C_{2'}$), 148.1 and 147.4 (C_6 and C_7), 142.4 ($C_{5'}$), 127.0 and 126.6 (C_{4a} and C_{8a}), 111.3 and 110.7 (C_5 and C_8), 109.9 and 109.7 ($C_{3'}$ and $C_{4'}$), 62.5 (C_1), 56.0 and 55.9 (OMe×2), 50.1 (C_3), 43.6 (Me-2), 28.0 (C_4). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.28; H, 7.00; N, 5.11.

3.6. 2-Acetyl-1-(2′-furyl)-1,2,3,4-tetrahydroisoquinoline (4a), 6,7-dimethoxy-2-acetyl-1-(2′-furyl)-1,2,3,4-tetrahydroisoquinoline (4c). Typical procedure

The corresponding tetrahydroisoquinoline **2a**,**b** (0.014 mol) was dissolved in 20 mL of acetic anhydride. The reaction mixture was then refluxed for 3 h. At the end of the reaction the mixture was diluted with water (100 mL) and neutralized by saturated solution of sodium carbonate (40 mL). Then the organic layer was extracted with ethyl acetate (3×25 mL) and the extract was dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on Al_2O_3 (1×45 cm, eluent: hexane).

*3.6.1. Compound **4a***

Yellow viscid oil, yield 2.33 g (69%); R_f (30% ethyl acetate–hexane) 0.38; IR 1654 (NCO) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 241 (41), 212 (40), 198 (18), 182 (16), 170 (67), 141 (37), 130 (25), 115 (48), 103 (16), 77 (23), 63 (17), 51 (23), 43 (100). ^1H NMR mixture of two amide rotamers, data for *major* isomer ($CDCl_3$, 400 MHz) δ 7.32 (1H, dd, $J_{5',3'}$ 0.8, $J_{5',4'}$ 1.8 Hz, H-5′), 7.16–7.25 (4H, m, C_6H_4), 6.84 (1H, s, H-1), 6.26 (1H, dd, $J_{4',5'}$ 1.8, $J_{4',3'}$ 3.2 Hz, H-4′), 6.03 (1H, dd, $J_{3',5'}$ 0.8, $J_{3',4'}$ 3.2 Hz, H-3′), 3.83 (1H, m, H-3A), 3.61 (1H, m, H-3B), 2.75–3.06 (2H, m, H-4), 2.19 (3H, s, MeCO). ^{13}C NMR mixture of two amide rotamers ($CDCl_3$, 100.6 MHz) δ 169.2 (*C*OMe), 154.8 and 154.3 ($C_{2'}$), 142.8 and 142.4 ($C_{5'}$), 135.5 and 134.1 (C_{4a}), 126.2 and 126.5 (C_6), 129.4, 128.9, 128.5, 128.1, 127.8, 127.4 ($C_{5,7,8,8a}$), 110.2 and 110.1, 109.0 and 108.8 ($C_{3'}$ and $C_{4'}$), 55.1 and 49.9 (C_1), 41.3 and 36.1 (C_3), 29.1 and 28.3 (C_4), 21.9 and 21.7 (CO*Me*). Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.68; H, 6.25; N, 5.82.

*3.6.2. Compound **4c***

White large crystals, yield 3.12 g (74%); mp 122–124 °C; R_f (ethyl acetate) 0.46; IR 1649 (NCO) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity):

M^+ 301 (19), 272 (22), 230 (10), 200 (10), 128 (9), 115 (17), 77 (12), 63 (10), 51 (13), 43 (100), 39 (15). ^{1}H NMR mixture of two amide rotamers, data for *major* isomer ($CDCl_3$, 400 MHz) δ 7.34 (1H, dd, $J_{5',3'}$ 0.8, $J_{5',4'}$ 1.8 Hz, H-5′), 6.76 (1H, s, H-8), 6.65 (1H, s, H-5), 6.27 (1H, dd, $J_{4',5'}$ 1.8, $J_{4',3'}$ 3.2 Hz, H-4′), 5.91 (1H, br dd, $J_{3',5'}$ 0.8, $J_{3',4'}$ 3.2 Hz, H-3′), 5.91 (1H, s, H-1), 4.63 (1H, m, $J_{3A,3B}$ 14.1 Hz, H-3A), 3.87 (3H, s, OMe), 3.79 (3H, s, OMe), 3.54 (1H, m, $J_{3B,3A}$ 14.1 Hz, H-3B), 2.91 (1H, m, H-4A), 2.77 (1H, m, H-4B), 2.18 (3H, s, COMe). ^{13}C NMR mixture of two amide rotamers ($CDCl_3$, 100.6 MHz) δ 169.2 and 168.7 (*C*OMe), 154.7 and 154.2 ($C_{2'}$), 148.5, 148.2, 147.6, 147.8 (C_6 and C_7), 142.5 and 142.2 ($C_{5'}$), 127.5, 126.1, 125.3, 124.1 (C_{4a} and C_{8a}), 111.4, 111.2, 110.9, 110.7, 110.0, 109.8, 108.8, 108.6 (C_5, C_8, $C_{3'}$, $C_{4'}$), 55.93, 55.87, 55.77 (OMe×2), 54.4 and 49.2 (C_1), 40.9 and 35.6 (C_3), 28.4 and 27.6 (C_4), 21.7 and 21.4 (CO*Me*). Anal. Calcd for $C_{17}H_{19}NO$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.77; H, 6.35; N, 4.67.

3.7. 2-Trifluoracetyl-1-(2′-furyl)-1,2,3,4-tetrahydroisoquinoline (4b), 6,7-dimethoxy-2-trifluoracetyl-1-(2′-furyl)-1,2,3,4-tetrahydroisoquinoline (4d). Typical procedure

The corresponding isoquinoline **2a**,**b** (0.039 mol) was dissolved in 50 mL of dichloromethane and then triethylamine (8.2 mL, 0.06 mol) was added in one portion to this solution. The resulted mixture was ice-cooled and trifluoroacetic anhydride (7.0 mL, 0.05 mol) was added drop-wise. The reaction mixture was vigorously stirred at room temperature for one day (TLC monitoring). Then it was diluted with water (100 mL), neutralized by saturated solution of sodium carbonate (15 mL), and then extracted with dichloromethane (3×50 mL). The extract was dried over $MgSO_4$. After solvent evaporation, the residue was crystallized in ether to give isoquinolines **4a**,**b** as white solids.

3.7.1. Compound *4b*

Colourless oil, yield 8.81 g (77%); R_f (10% ethyl acetate–hexane) 0.85; IR 1692 (NCO) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 295 (100), 266 (69), 226 (14), 198 (49), 183 (17), 169 (19), 154 (16), 141 (26), 115 (53), 77 (13). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (1H, dd, $J_{5',3'}$ 0.8, $J_{5',4'}$ 1.8 Hz, H-5′), 7.16–7.30 (4H, m, C_6H_4), 6.73 (1H, s, H-1), 6.31 (1H, dd, $J_{4',5'}$ 1.8, $J_{4',3'}$ 2.6 Hz, H-4′), 6.12 (1H, dd, $J_{3',5'}$ 0.8, $J_{3',4'}$ 2.6 Hz, H-3′), 4.08 (1H, m, $J_{3A,3B}$ 12.7 Hz, H-3A), 3.67 (1H, m, $J_{3B,3A}$ 12.7 Hz, H-3B), 3.10 (1H, m, H-4A), 2.92 (1H, m, H-4B). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 155.9 (q, $^2J_{C,F}$=35.2 Hz, *C*OCF$_3$), 153.0 ($C_{2'}$), 143.2 ($C_{5'}$), 133.4 and 131.8 (C_{4a} and C_{8a}), 129.0, 128.4, 127.9, 126.8 ($C_{5,6,7,8}$), 116.6 (q, $^1J_{C,F}$=288.0 Hz, CO*C*F$_3$), 110.2 and 110.1 ($C_{3'}$ and $C_{4'}$), 51.5 (C_1), 40.4 (br s, C_3), 29.2 (C_4). Anal. Calcd for $C_{15}H_{12}F_3NO_2$: C, 61.02; H, 4.10; N, 4.74. Found: C, 61.11; H, 4.09; N, 4.79.

3.7.2. Compound *4d*

White needle crystals, yield 9.88 g (71%); mp 106 °C; R_f (15% ethyl acetate–hexane) 0.29; IR 1698 (NCO) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 355 (100), 326 (49), 311 (14), 286 (16), 258 (37), 243 (21), 199 (10), 128 (8), 115 (13), 77 (6). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (1H, dd, $J_{5',3'}$ 0.8, $J_{5',4'}$ 1.8 Hz, H-5′), 6.73 (1H, s, H-1), 6.66 (1H, s, H-8), 6.62 (1H, s, H-5), 6.33 (1H, dd, $J_{4',5'}$ 1.8, $J_{4',3'}$ 3.2 Hz, H-4′), 6.15 (1H, dd, $J_{3',5'}$ 0.8, $J_{3',4'}$ 3.2 Hz, H-3′), 4.04 (1H, m, $J_{3A,3B}$ 13.5 Hz, H-3A), 3.90 (3H, s, OMe), 3.82 (3H, s, OMe), 3.63 (1H, m, $J_{3B,3A}$ 13.5 Hz, H-3B), 3.06 (1H, m, H-4A), 2.85 (1H, m, H-4B). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 155.6 (q, $^2J_{C,F}$=35.2 Hz, *C*OCF$_3$), 153.0 ($C_{2'}$), 148.8 and 148.0 (C_6 and C_7), 143.1 ($C_{5'}$), 125.5 and 123.5 (C_{4a} and C_{8a}), 119.4 (q, $^1J_{C,F}$=287.0 Hz, CO*C*F$_3$), 111.2 and 110.7 (C_5 and C_8), 110.1 and 110.0 ($C_{3'}$ and $C_{4'}$), 56.0 and 55.9 (OMe×2), 51.1 (C_1), 40.2 (q, $^4J_{C,F}$=4.5 Hz, C_3), 28.6 (C_4). Anal. Calcd for $C_{17}H_{16}F_3NO_4$: C, 57.47; H, 4.54; N, 3.94. Found: C, 57.44; H, 4.55; N, 3.94.

3.8. (8a*S**,9*R**,10*S**,12a*R**,12b*R**)-8-Oxo-5,8,8a,9,10,12b-hexahydro-6*H*-10,12a-epoxyisoindolo[1,2-*a*]isoquinoline-9-carboxylic acid (5a), (8a*S**,9*R**,10*S**,12a*R**,12b*R**)-2,3-dimethoxy-8-oxo-5,8,8a,9,10,12b-hexahydro-6*H*-10,12a-epoxyisoindolo[1,2-*a*]isoquinoline-9-carboxylic acid (5b), (8a*S**,9*R**,10*S**,12a*R**,12b*R**)-9-methyl-8-oxo-5,8,8a,9,10,12b-hexahydro-6*H*-10,12a-epoxyisoindolo[1,2-*a*]isoquinoline-9-carboxylic acid (6a), (8a*S**,9*R**,10*S**,12a*R**,12b*R**)-9-methyl-2,3-dimethoxy-8-oxo-5,8,8a,9,10,12b-hexahydro-6*H*-10,12a-epoxyisoindolo[1,2-*a*]isoquinoline-9-carboxylic acid (6b). Typical procedure

The toluene (15 mL) solution of maleic anhydride (8.0 mmol) in case of **5a**,**b** or citraconic anhydride (8.0 mmol) in case of **6a**,**b** was added to the toluene solution (15 mL) of the corresponding tetrahydroisoquinoline **2a**,**b** (7.10 mol). The reaction mixture was stirred for 2–3 h at room temperature. At the end of the reaction toluene was removed in vacuo, ether (10–20 mL) was added to the residue, and the precipitate was filtered off to give acids **5**–**6a**,**b** as white solids.

3.8.1. Compound *5a*

White powder, yield 1.96 g (97%); mp 219–221 °C; IR 1657 (NCO) and 1730 (CO_2H) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 297 (9), 279 (14), 251 (40), 224 (42), 198 (100), 184 (27), 170 (52), 132 (40), 103 (35), 76 (30), 54 (36), 43 (34). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.05 (br s, CO_2H), 7.11–7.17 (4H, m, C_6H_4), 6.88 (1H, d, $J_{12,11}$ 5.7 Hz, H-12), 6.45 (1H, dd, $J_{11,10}$ 1.6, $J_{11,12}$ 5.7 Hz, H-11), 5.44 (1H, br s, H-12b), 4.83 (1H, d, $J_{10,11}$ 1.6 Hz, H-10), 4.00 (1H, ddd, $J_{6A,5B}$ 2.4, $J_{6A,5A}$ 5.7, $J_{6A,6B}$ 12.9 Hz, H-6A), 3.01 (1H, m, H-6B), 2.97 (1H, br d, $J_{9endo,8a}$ 9.1 Hz, H-9$_{endo}$), 2.71 (1H, m, H-5A), 2.60 (1H, m, H-5B), 2.48 (1H, d, $J_{8a,9endo}$ 9.1 Hz, H-8a). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.3 (C_8), 169.6 (C–CO_2H), 137.7 (C_{11}), 135.7 (C_{12}), 135.1 (C_{4a}), 132.9 (C_{12c}), 129.3 (C_4), 126.6–127.0 (C_1–C_3), 92.2 (C_{12a}), 81.2 (C_{10}), 56.3 (C_{12b}), 51.3 (C_{8a}), 45.5 (C_9), 36.9 (C_6), 28.7 (C_5). Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.90; H, 4.85; N, 4.48.

3.8.2. Compound *5b*

White powder, yield 2.18 g (90%); mp 230–232 °C; IR 1677 (NCO) and 1715 (CO_2H) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 357 (4), 258 (100), 244 (16), 228 (25), 187 (50), 141 (20), 76 (26), 54 (91), 43 (80). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (br s, CO_2H), 6.92 (1H, d, $J_{12,11}$ 5.7 Hz, H-12), 6.71 (1H, s, H-4), 6.65 (1H, s, H-1), 6.47 (1H, br d, $J_{11,12}$ 5.7 Hz, H-11), 5.35 (1H, br s, H-12b), 4.84 (1H, br s, H-10), 4.04 (1H, m, H-6A), 3.70 (3H, s, OMe), 3.64 (3H, s, OMe), 3.40 (1H, m, H-6B), 2.98 (1H, br d, $J_{9endo,8a}$ 8.9 Hz, H-9$_{endo}$), 2.71 (1H, m, H-5A), 2.60 (1H, m, H-5B), 2.53 (1H, d, $J_{8a,9endo}$ 8.9 Hz, H-8a). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.4 (C_8), 169.6 (CO_2H), 148.1 (C_2), 147.8 (C_3), 137.8 (C_{11}), 135.6 (C_{12}), 127.2 (C_{4a}), 124.4 (C_{12c}), 112.6 (C_4), 110.1 (C_1), 92.3 (C_{12a}), 81.2 (C_{10}), 56.1 and 56.0, 56.1 (C_{12b} and C_2-OMe, C_3-OMe), 51.3 (C_{8a}), 45.5 (C_9), 37.0 (C_6), 28.2 (C_5). Anal. Calcd for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 63.59; H, 5.09; N, 4.20.

3.8.3. Compound *6a*

Regioisomer mixture **6Aa**/**6Ba** 1.3:1 (according to ^{1}H NMR), white powder, yield 1.46 g (69%); mp 178–182 °C; IR (broad band) 1694 (NCO and CO_2H) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 311 (4), 266 (7), 198 (73), 170 (45), 141 (31), 115 (61), 101 (19), 76 (36), 68 (100), 63 (35), 59 (64), 43 (38). ^{1}H NMR for *major* isomer **A** ($CDCl_3$, 400 MHz) δ 12.02 (br s, CO_2H), 7.13–7.19 (4H, m, C_6H_4), 6.92 (1H, d, $J_{12,11}$ 5.7 Hz, H-12), 6.55 (1H, dd, $J_{11,10}$ 1.8, $J_{11,12}$ 5.7 Hz, H-11), 5.44 (1H, br s, H-12b), 4.76 (1H, d, $J_{10,11}$ 1.8 Hz, H-10), 4.02 (1H, ddd, $J_{6A,5B}$ 2.8, $J_{6A,5A}$ 6.0, $J_{6A,6B}$ 12.9 Hz, H-6A), 3.02 (1H, m, $J_{6B,5B}$ 3.9, $J_{6B,5A}$ 11.2, $J_{6B,6A}$ 12.9 Hz, H-6B), 2.74 (1H, m, $J_{5A,6A}$ 6.0, $J_{5A,6B}$ 11.2, $J_{5,5}$ 12.0 Hz, H-5A), 2.63 (1H, ddd, $J_{5B,6A}$ 2.8, $J_{5B,6B}$ 3.9, $J_{5,5}$ 12.0 Hz, H-5B),

2.09 (1H, s, H-8a), 1.18 (3H, s, Me). ^{13}C NMR for *major* isomer **A** ($CDCl_3$, 100.6 MHz) δ 173.3 (C_8), 173.2 (CO_2H), 138.3 (C_{11}), 135.3 (C_{4a}), 133.7 (C_{12}), 132.9 (C_{12c}), 129.3 (C_4), 126.6, 126.7, 127.0 (C_1, C_2, C_3), 94.5 (C_{12a}), 80.7 (C_{10}), 57.26 (C_9), 54.9 (C_{8a}), 53.7 (C_{12b}), 36.9 (C_6), 28.7 (C_5), 21.7 (C_9-Me). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.14; H, 5.72; N, 4.26.

3.8.4. Compound ***6b***

Regioisomer mixture **6Ab**/**6Bb** 1.25:1 (according to ^{1}H NMR), white powder, yield 2.47 g (98%); mp 189–192 °C; IR (broad band) 1673 (NC=O) and 1738 (CO_2H) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): [M$^+$−46] 325 (2), 258 (81), 244 (36), 230 (67), 214 (30), 201 (58), 192 (47), 176 (38), 159 (35), 144 (34), 128 (33), 115 (60), 68 (100), 59 (83), 43 (86). ^{1}H NMR for *major* isomer **A** ($CDCl_3$, 400 MHz) δ 12.02 (br s, CO_2H), 6.98 (1H, d, $J_{12,11}$ 5.7 Hz, H-12), 6.73 (1H, s, H-4), 6.70 (1H, s, H-1), 6.53 (1H, dd, $J_{11,10}$ 1.8, $J_{11,12}$ 5.7 Hz, H-11), 5.44 (1H, br s, H-12b), 4.76 (1H, d, $J_{10,11}$ 1.8 Hz, H-10), 4.04 (1H, ddd, $J_{6A,5B}$ 2.6, $J_{6A,5A}$ 5.8, $J_{6A,6B}$ 12.7 Hz, H-6A), 3.72 (3H, s, OMe), 3.67 (3H, s, OMe), 2.95 (1H, dt, $J_{6B,5B}$ 4.0, $J_{6B,6A}$ 12.7 Hz, H-6B), 2.72 (1H, m, $J_{5A,6A}$ 5.8 Hz, H-5A), 2.50 (1H, m, $J_{5B,6A}$ 2.6, $J_{5B,6B}$ 4.0 Hz, H-5B), 2.08 (1H, s, H-8a), 1.18 (3H, s, Me). ^{13}C NMR for *major* isomers **A** (DMSO-d_6, 100.6 MHz) δ 172.6 and 172.3 (CO_2H and C_8), 147.8 and 147.5 (C_2 and C_3), 137.7 and 133.0 (C_{11} and C_{12}), 127.2 and 124.0 (C_{4a} and C_{12c}), 112.6 and 110.3 (C_1 and C_4), 93.8 (C_{12a}), 80.0 (C_{10}), 56.5 (C_{12b}), 55.8 and 55.6 (OMe×2), 54.1 and 53.4 (C_{8a} and C_9), 36.4 (C_6), 27.5 (C_5), 20.9 (Me-1). Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.35; H, 5.48; N, 4.01.

3.9. (8a*S**,9*S**,10*S**,12a*R**,12b*R**)-9-Methyl-5,9,10,12b-tetrahydro-6*H*-10,12a-epoxyisoindolo[1,2-*a*]isoquinolin-8(8a*H*)-one (7a), (8a*S**,9*S**,10*S**,12a*R**,12b*R**)-2,3-dimethoxy-9-methyl-5,9,10,12b-tetrahydro-6*H*-10,12a-epoxyisoindolo[1,2-*a*]isoquinolin-8(8a*H*)-one (7b), (8a*S*,10*R*,12a*R*,12b*R*)-5,9,10,12b-tetrahydro-6*H*-10,12a-epoxyisoindolo[1,2-*a*]isoquinolin-8(8a*H*)-one (8a), (8a*S**,10*R**,12a*R**,12b*R**)-2,3-dimethoxy-5,9,10,12b-tetrahydro-6*H*-10,12a-epoxyisoindolo[1,2-*a*]isoquinolin-8(8a*H*)-one (8b), (8a*S**,10*R**,12a*R**,12b*R**)-8a-methyl-5,9,10,12b-tetrahydro-6*H*-10,12a-epoxyisoindolo[1,2-*a*]isoquinolin-8(8a*H*)-one (9a), (8a*S**,10*R**,12a*R**,12b*R**)-2,3-dimethoxy-8a-methyl-5,9,10,12b-tetrahydro-6*H*-10,12a-epoxyisoindolo[1,2-*a*]isoquinolin-8(8a*H*)-one (9b). Typical procedure**

The corresponding isoquinoline **2a**,**b** (~1.0 g, 3.90 mmol) was dissolved in benzene (in case of **8a**,**b**) or toluene (for **7a**,**b** and **9a**,**b**). Triethylamine (1.1 mL, 7.80 mmol) was added in one portion to the solution, then acryloyl chloride (0.47 mL, 5.80 mmol) in case of **8a**,**b** (crotonoyl chloride in case of **7a**,**b** and methacryloyl chloride in case of **9a**,**b**) was rapidly added to the solution. The reaction mixture was refluxed for 10 h (TLC monitoring). At the end of the reaction it was diluted with water (50 mL) and extracted with ethyl acetate (4×30 mL). The extract was dried over $MgSO_4$ and concentrated in vacuo. The residue solidified on standing and further crystallization from hexane–ethyl acetate gave the corresponding isoindoloisoquinolines **7**–**9a**,**b** as white solids.

3.9.1. Compound ***7a***

White rhombic crystals, yield 0.29 g (19%); mp 141–143 °C; R_f (ethyl acetate) 0.71; IR 1680 (NC=O) and 1615 (C=C) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M$^+$ 267 (59), 238 (100), 210 (9), 198 (22), 184 (55), 170 (39), 141 (29), 115 (25), 69 (71). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.16–7.26 (4H, m, C_6H_4), 6.89 (1H, d, $J_{12,11}$ 5.8 Hz, H-12), 6.47 (1H, dd, $J_{11,10}$ 1.5, $J_{11,12}$ 5.8 Hz, H-11), 5.42 (1H, s, H-12b), 4.83 (1H, dd, $J_{10,11}$ 1.5, $J_{10,9}$ 4.4 Hz, H-10), 4.38 (1H, ddd, $J_{6A,5B}$ 2.3, $J_{6A,5A}$ 5.8, $J_{6A,6B}$ 12.9 Hz, H-6A), 3.08 (1H, m, $J_{5A,6A}$ 5.8 Hz, H-5A), 2.95 (1H, m, $J_{5B,6A}$ 2.3 Hz, H-5B), 2.75 (1H, dt, $J_{6B,6A}$ 12.9 Hz, H-6B), 2.64 (1H, ddq, $J_{9,8a}$ 3.8, $J_{9,10}$ 4.4, $J_{Me,9}$ 7.1 Hz, H-9), 2.20 (d, 1H, $J_{8a,12b}$ 0.8, $J_{8a,9}$ 3.8 Hz, H-8a), 1.02 (3H, d, $J_{Me,9}$ 7.1 Hz, Me). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.0 (C_8), 136.0 (C_{11}), 134.7 (C_{4a}), 134.0 (C_{12}), 131.5 (C_{12c}), 129.3 (C_4), 126.0, 126.6, 127.2 (C_1, C_2, C_3), 93.1 (C_{12a}), 82.5 (C_{10}), 57.8 (C_{12b}), 56.1 (C_{8a}), 37.1 (C_6), 36.6 (C_9), 28.6 (C_5), 17.1 (Me). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.69; N, 5.01. Found: C, 76.62; H, 6.69; N, 5.01.

3.9.2. Compound ***7b***

White rhombic crystals, yield 0.44 g (23%); mp 149–151 °C; R_f (ethyl acetate) 0.57; IR 1682 (NCO) and 1611 (C=C) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M$^+$ 327 (32), 298 (55), 270 (12), 258 (21), 244 (100), 115 (11), 69 (47), 41 (27). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.75 (1H, d, $J_{12,11}$ 5.7 Hz, H-12), 6.61 (1H, s, H-4), 6.59 (1H, s, H-1), 6.45 (1H, dd, $J_{11,10}$ 1.4, $J_{11,12}$ 5.7 Hz, H-11), 5.28 (1H, br s, H-12b), 4.83 (1H, dd, $J_{10,11}$ 1.4, $J_{10,9}$ 4.5 Hz, H-10), 4.38 (1H, ddd, $J_{6A,5B}$ 1.8, $J_{6A,5A}$ 5.6, $J_{6A,6B}$ 12.7 Hz, H-6A), 3.83 (3H, s, OMe), 3.82 (3H, s, OMe), 3.02 (1H, m, $J_{5A,6A}$ 5.6 Hz, H-5A), 2.88 (1H, m, $J_{5B,6A}$ 1.8 Hz, H-5B), 2.62 (1H, m, H-6B), 2.62 (1H, ddd, $J_{9,8a}$ 3.7, $J_{9,10}$ 4.5, $J_{Me,9}$ 7.0 Hz, H-9), 2.18 (1H, br d, $J_{8a,9}$ 3.7 Hz, H-8a), 1.01 (3H, d, $J_{Me,9}$ 7.0 Hz, Me). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.0 (C_8), 148.1 (C_2), 147.9 (C_3), 136.3 (C_{11}), 133.7 (C_{12}), 127.0 (C_{4a}), 131.5 (C_{12c}), 111.8 (C_4), 108.7 (C_1), 93.0 (C_{12a}), 82.4 (C_{10}), 56.1 (C_{12b}), 57.6, 55.8, and 55.9 (C_{8a}, C_2-OMe, and C_3-OMe), 37.1 (C_6), 36.6 (C_9), 28.1 (C_5), 17.1 (Me). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.45; H, 6.25; N, 4.56.

3.9.3. Compound ***8a***

White rhombic crystals, yield 1.13 g (77%); mp 118–120 °C; R_f (ethyl acetate) 0.36; IR 1682 (NC=O) and 1619 (C=C) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M$^+$ 253 (21), 224 (50), 185 (11), 141 (21), 115 (27), 94 (53), 85 (71), 76 (86), 66 (46), 55 (100), 42 (35). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.13–7.24 (4H, m, C_6H_4), 6.68 (1H, d, $J_{12,11}$ 5.8 Hz, H-12), 6.45 (1H, dd, $J_{11,10}$ 1.7, $J_{11,12}$ 5.8 Hz, H-11), 5.42 (1H, s, H-12b), 5.00 (1H, dd, $J_{10,9exo}$ 4.6, $J_{10,11}$ 1.7 Hz, H-10), 4.37 (1H, ddd, $J_{6A,5A}$ 5.6, $J_{6A,6B}$ 12.9, $J_{6A,5B}$ 2.4 Hz, H-6A), 3.09 (1H, m, $J_{6B,6A}$ 12.9 Hz, H-6B), 2.93 (1H, m, $J_{5A,6A}$ 5.6 Hz, H-5A), 2.74 (1H, m, $J_{5B,6A}$ 2.4 Hz, H-5B), 2.66 (1H, dd, $J_{8a,9exo}$ 3.5, $J_{8a,9endo}$ 8.8 Hz, H-8a), 2.23 (1H, ddd, $J_{9exo,8a}$ 3.5, $J_{9exo,10}$ 4.6, $J_{9exo,9endo}$ 11.8 Hz, H-9$_{exo}$), 1.61 (1H, dd, $J_{9endo,8a}$ 8.8, $J_{9endo,9exo}$ 11.8 Hz, H-9$_{endo}$). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.1 (C_8), 137.8 (C_{11}), 134.7 (C_{4a}), 132.8 (C_{12}), 131.6 (C_{12c}), 129.3 (C_4), 126.0, 126.7, 127.2 (C_1, C_2, C_3), 92.5 (C_{12a}), 79.0 (C_{10}), 57.8 (C_{12b}), 48.4 (C_{8a}), 37.2 (C_6), 28.6 (C_5), 28.2 (C_9). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.52; H, 5.64; N, 5.26.

3.9.4. Compound ***8b***

White rhombic crystals, yield 1.02 g (56%); mp 140–142 °C; R_f (ethyl acetate) 0.42; IR 1715 (NC=O) and 1620 (C=C) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M$^+$ 313 (54), 284 (100), 258 (20), 244 (64), 228 (7), 191 (11), 176 (13), 115 (7), 55 (16). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.66 (1H, d, $J_{12,11}$ 5.8 Hz, H-12), 6.60 (1H, s, H-4), 6.59 (1H, s, H-1), 6.45 (1H, dd, $J_{11,10}$ 1.5, $J_{11,12}$ 5.8 Hz, H-11), 5.35 (1H, br s, H-12b), 5.00 (1H, dd, $J_{10,9exo}$ 4.4, $J_{10,11}$ 1.5 Hz, H-10), 4.38 (1H, ddd, $J_{6A,5A}$ 5.5, $J_{6A,6B}$ 12.6, $J_{6A,5B}$ 1.8 Hz, H-6A), 3.83 (3H, s, OMe), 3.81 (3H, s, OMe), 3.03 (1H, dt, $J_{6B,6A}$ 12.6, $J_{6B,5B}$ 4.0 Hz, H-6B), 2.87 (1H, m, $J_{5A,6A}$ 5.5 Hz, H-5A), 2.66 (1H, dd, $J_{8a,9endo}$ 8.8, $J_{8a,9exo}$ 3.6 Hz, H-8a), 2.64 (1H, m, $J_{5B,6A}$ 1.8, $J_{5B,6B}$ 4.0 Hz, H-5B), 2.22 (1H, ddd, $J_{9exo,8a}$ 3.6, $J_{9exo,9endo}$ 11.8, $J_{9exo,10}$ 4.4 Hz, H-9$_{exo}$), 1.60 (1H, dd, $J_{9endo,8a}$ 8.8, $J_{9endo,9exo}$ 11.8 Hz, H-9$_{endo}$). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.1 (C_8), 148.2 and 148.0 (C_2 and C_3), 138.1 (C_{11}), 132.5 (C_{12}), 123.2 and 127.0 (C_{4a} and C_{12c}), 111.9 (C_4), 108.7 (C_1), 92.4 (C_{12a}), 79.0 (C_{10}), 57.6 (C_{12b}), 55.8 and 55.9 (OMe×2), 48.4 (C_{8a}), 37.2 (C_6), 28.2 and 28.1 (C_9 and C_5). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.70; H, 5.92; N, 4.25.

3.9.5. Compound ***9a***

White rhombic crystals, yield 0.94 g (61%); mp 160–162 °C; R_f (ethyl acetate) 0.70; IR (broad band) 1675 (NC=O) cm^{-1}; EIMS

(70 eV) *m*/*z* (rel intensity): M^+ 267 (100), 238 (50), 224 (26), 210 (20), 199 (40), 183 (37), 168 (23), 141 (46), 130 (42), 115 (30), 69 (48), 59 (29), 43 (38). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.16–7.26 (4H, m, C_6H_4), 6.68 (1H, d, $J_{12,11}$ 5.9 Hz, H-12), 6.52 (1H, dd, $J_{11,10}$ 1.5, $J_{11,12}$ 5.9 Hz, H-11), 5.34 (1H, s, H-12b), 4.90 (1H, dd, $J_{10,9exo}$ 4.9, $J_{10,11}$ 1.5 Hz, H-10), 4.38 (1H, ddd, $J_{6A,5A}$ 5.6, $J_{6A,6B}$ 12.7, $J_{6A,5B}$ 2.3 Hz, H-6A), 3.11 (1H, br dt, $J_{6B,6A}$ 12.7, $J_{6B,5A}$ 11.6, $J_{6B,5B}$ 3.8 Hz, H-6B), 2.94 (1H, m, $J_{5A,6A}$ 5.6, $J_{5A,5B}$ 15.6, $J_{5A,6B}$ 11.6 Hz, H-5A), 2.75 (1H, ddd, $J_{5B,6A}$ 2.3, $J_{5B,5A}$ 15.6, $J_{5B,6B}$ 3.8 Hz, H-5B), 2.50 (1H, dd, $J_{9exo,10}$ 4.9, $J_{9exo,9endo}$ 11.8 Hz, H-9$_{exo}$), 1.20 (3H, br s, Me), 1.15 (1H, d, $J_{9endo,9exo}$ 11.8 Hz, H-9$_{endo}$). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 177.1 (C_8), 138.1 (C_{11}), 135.0 (C_{4a}), 131.7 (C_{12c}), 131.3 (C_{12}), 129.3 (C_4), 126.0, 126.7, 127.2 (C_1, C_2, C_3), 94.7 (C_{12a}), 78.8 (C_{10}), 56.4 (C_{12b}), 53.4 (C_{8a}), 37.2 (C_6), 36.4 (C_9), 28.74 (C_5), 20.4 (Me). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.15; H, 6.65; N, 5.51.

3.9.6. Compound **9b**

White rhombic crystals, yield 1.44 g (76%); mp 59–61 °C; R_f (50% ethyl acetate–hexane) 0.52; IR 1686 (NCO) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 327 (100), 312 (24), 298 (57), 284 (15), 258 (47), 244 (21), 69 (34). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.67 (1H, d, $J_{12,11}$ 5.8 Hz, H-12), 6.63 (1H, s, H-4), 6.62 (1H, s, H-1), 6.53 (1H, dd, $J_{11,10}$ 1.7, $J_{11,12}$ 5.8 Hz, H-11), 5.28 (1H, br s, H-12b), 4.91 (1H, dd, $J_{10,9exo}$ 4.8, $J_{10,11}$ 1.7 Hz, H-10), 4.38 (1H, ddd, $J_{6A,5A}$ 5.7, $J_{6A,6B}$ 13.1, $J_{6A,5B}$ 2.1 Hz, H-6A), 3.85 (3H, s, OMe), 3.84 (3H, s, OMe), 3.03 (1H, m, $J_{5A,6A}$ 5.7 Hz, H-5A), 2.89 (1H, m, H-5B), 2.65 (1H, m, H-6B), 2.50 (1H, dd, $J_{9exo,9endo}$ 11.8, $J_{9exo,10}$ 4.8 Hz, H-9$_{exo}$), 1.19 (3H, s, Me), 1.15 (1H, d, $J_{9endo,9exo}$ 11.8 Hz, H-9$_{endo}$). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 177.0 (C_8), 148.1 (C_2), 147.9 (C_3), 138.4 (C_{11}), 130.9 (C_{12}), 127.2 (C_{4a}), 123.2 (C_{12c}), 111.8 (C_4), 108.6 (C_1), 94.6 (C_{12a}), 78.7 (C_{10}), 56.2 (C_{12b}), 55.8 and 55.8 (C_2-OMe and C_3-OMe), 53.4 (C_{8a}), 37.2 (C_6), 36.4 (C_9), 28.2 (C_5), 20.4 (Me_8). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.48; H, 4.85; N, 4.02.

3.10. Methyl (8a*S**,9*R**,10*S**,12a*R**,12b*R**)-8-oxo-5,8,8a,9,10,12b-hexahydro-6*H*-10,12a-epoxyisoindolo[1,2-*a*]isoquinoline-9-carboxylate (10a), methyl (8a*S**,9*R**,10*S**,12a*R**,12b*R**)-2,3-dimethoxy-8-oxo-5,8,8a,9,10,12b-hexahydro-6*H*-10,12a-epoxyisoindolo[1,2-*a*]isoquinoline-9-carboxylate (10b), methyl (8a*S**,9*R**,10*S**,12a*R**,12b*R**)-9-methyl-8-oxo-5,8,8a,9,10,12b-hexahydro-6*H*-10,12a-epoxyisoindolo[1,2-*a*]isoquinoline-9-carboxylate (11a), methyl (8a*S**,9*R**,10*S**,12a*R**,12b*R**)-9-methyl-2,3-dimethoxy-8-oxo-5,8,8a,9,10,12b-hexahydro-6*H*-10,12a-epoxyisoindolo[1,2-*a*]isoquinoline-9-carboxylate (11b). Typical procedure

Adduct **5**–**6a**,**b** (5.0 mmol) was then refluxed in methanol (20 mL) for 8 h in the presence of catalytic amount of concentrated H_2SO_4. Then the reaction mixture was poured into 150 mL of water and extracted with chloroform (3×70 mL). The extract was dried over $MgSO_4$ and concentrated in vacuo. The crude product was recrystallized from mixture of hexane–ethyl acetate to give esters **10**–**11a**,**b** as white solids.

3.10.1. Compound **10a**

White powder, yield 1.50 g (96%); mp 199–201 °C; IR 1701 (NC═O) and 1724 (CO_2Me) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 311 (10), 280 (10), 251 (45), 223 (25), 198 (100), 168 (17), 141 (26), 130 (45), 115 (60), 84 (15), 55 (64), 43 (32). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.13–7.23 (4H, m, C_6H_4), 6.76 (1H, d, $J_{12,11}$ 5.7 Hz, H-12), 6.50 (1H, dd, $J_{11,10}$ 1.6, $J_{11,12}$ 5.7 Hz, H-11), 5.38 (1H, s, H-12b), 5.10 (1H, d, $J_{10,11}$ 1.6 Hz, H-10), 4.31 (1H, ddd, $J_{6A,6B}$ 12.7, $J_{6A,5A}$ 5.4, $J_{6A,5B}$ 2.9 Hz, H-6A), 3.75 (3H, s, CO_2Me), 3.06 (1H, m, $J_{6B,6A}$ 12.7 Hz, H-6B), 2.99 (1H, br d, $J_{9endo,8a}$ 9.2 Hz, H-9$_{endo}$), 2.95 (1H, m, $J_{5A,5B}$ 15.6, $J_{5A,6A}$ 5.4 Hz, H-5A), 2.75 (1H, d, $J_{8a,9endo}$ 9.2 Hz, H-8a), 2.72 (1H, dt, $J_{5B,5A}$ 15.6, $J_{5B,6A}$ 2.9 Hz, H-5B). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.2 (C_8), 169.6 (CO_2Me), 137.7 (C_{12}), 135.0 (C_{4a}), 134.8 (C_{11}), 131.2 (C_{12c}), 129.4 (C_4), 125.9, 126.6, 127.3 (C_1, C_2, C_3), 92.0 (C_{12a}), 81.3 (C_{10}), 57.0 (C_{12b}), 52.1 (C_{8a}), 51.8 (OMe), 45.3 (C_9), 37.4 (C_6), 28.8 (C_5). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.78; H, 5.23; N, 4.25.

3.10.2. Compound **10b**

White powder, yield 1.69 g (91%); mp 162–164 °C; IR 1691 (NC═O) and 1738 (CO_2Me) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 371 (8), 339 (6), 310 (20), 258 (100), 243 (13), 176 (18), 144 (30), 113 (60), 84 (95), 59 (98), 43 (50). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.77 (1H, d, $J_{12,11}$ 5.8 Hz, H-12), 6.61 (1H, s, H-4), 6.58 (1H, s, H-1), 6.52 (1H, dd, $J_{11,10}$ 1.7, $J_{11,12}$ 5.8 Hz, H-11), 5.33 (1H, br s, H-12b), 5.12 (1H, d, $J_{10,11}$ 1.7 Hz, H-10), 4.34 (1H, ddd, $J_{5A,5A}$ 5.6, $J_{6A,5B}$ 3.4, $J_{6A,6B}$ 12.8 Hz, H-6A), 3.83 (3H, s, OMe), 3.81 (3H, s, OMe), 3.75 (3H, s, H-CO_2Me), 3.03 (1H, m, $J_{5A,6A}$ 5.6 Hz, H-5A), 3.00 (1H, d, $J_{9endo,8a}$ 9.1 Hz, H-9$_{endo}$), 2.90 (1H, m, H-5B), 2.75 (1H, d, $J_{8a,9endo}$ 9.1 Hz, H-8a), 2.64 (1H, m, $J_{6B,6A}$ 12.8, $J_{6B,5B}$ 3.6 Hz, H-6B). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.1 (C_8), 169.6 (CO_2Me), 148.3 (C_3), 147.9 (C_2), 138.0 (C_{12}), 134.6 (C_{11}), 127.3 (C_{12c}), 122.8 (C_{4a}), 111.9 (C_4), 108.7 (C_1), 92.0 (C_{12a}), 81.3 (C_{10}), 56.8 (C_{12b}), 55.9 and 56.0 (C_2-OMe and C_3-OMe), 52.1 (C_{8a}), 51.7 (CO_2*Me*), 45.3 (C_9), 37.4 (C_6), 28.3 (C_5). Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.41; H, 5.42; N, 3.55.

3.10.3. Compound **11a**

White powder, yield 0.49 g (30%); mp 172–174 °C; IR 1690 (NC═O), 1740 (CO_2Me) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 325 (3), 296 (5), 266 (15), 198 (100), 168 (14), 141 (37), 130 (29), 115 (23), 84 (48), 69 (45), 59 (61), 43 (42). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.16–7.25 (4H, m, C_6H_4), 6.85 (1H, d, $J_{12,11}$ 5.8 Hz, H-12), 6.57 (dd, 1H, $J_{11,10}$ 1.8, $J_{11,12}$ 5.8 Hz, H-11), 5.36 (1H, s, H-12b), 4.99 (1H, d, $J_{10,11}$ 1.8 Hz, H-10), 4.35 (ddd, 1H, $J_{6A,5A}$ 5.5, $J_{6A,5B}$ 2.5, $J_{6A,6B}$ 12.8 Hz, H-6A), 3.73 (3H, s, CO_2Me), 2.96 (1H, m, $J_{5A,6A}$ 5.5 Hz, H-6B), 2.76 (1H, m, H-5A), 2.55 (1H, m, H-5B), 1.91 (1H, s, H-9), 1.30 (3H, s, Me-8a). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.7 (C_8), 172.4 (CO_2Me), 138.1 (C_{11}), 135.2 (C_{4a}), 133.0 (C_{12}), 131.3 (C_{12c}), 129.3 (C_4), 125.9, 126.6, 127.3 (C_1, C_2, C_3), 92.4 (C_{12a}), 80.6 (C_{10}), 57.7 (C_{8a}), 55.7 (C_{12b}), 53.5 (C_{9a}), 52.1 (CO_2*Me*), 37.3 (C_6), 28.8 (C_5), 21.3 (Me_{8a}). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.38; H, 5.64; N, 4.53.

3.10.4. Compound **11b**

White powder, yield 0.90 g (45%); mp 154–156 °C; IR 1697 (NCO), 1737 (CO_2Me) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 385 (10), 326 (14), 258 (100), 242 (16), 214 (13), 127 (37), 84 (34), 59 (35), 43 (27). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.70 (1H, d, *J* 5.8 Hz, H-12), 6.57 (1H, s, H-4), 6.54 (1H, s, H-1), 6.54 (1H, dd, *J* 5.8, $J_{10,11}$ 1.8 Hz, H-11), 5.17 (1H, br s, H-12b), 4.96 (1H, d, $J_{10,11}$ 1.8 Hz, H-10), 4.25 (1H, ddd, $J_{6A,6B}$ 12.5, $J_{5A,6A}$ 5.4, $J_{5B,6A}$ 2.3 Hz, H-6A), 3.76 (3H, s, OMe-3), 3.71 (3H, s, CO_2Me), 3.78 (3H, s, OMe-2), 2.96 (1H, ddd, $J_{6A,6B}$ 12.5, $J_{5A,6B}$ 11.6, $J_{5B,6B}$ 3.6 Hz, H-6B), 2.84 (1H, ddd, *J* 15.3, $J_{5A,6B}$ 11.6, $J_{5A,6A}$ 5.4 Hz, H-5A), 2.57 (1H, dt, $J_{5A,5B}$ 15.3, $J_{5B,6B}$ 3.0, $J_{5B,6A}$ 3.0 Hz, H-5B), 1.89 (1H, s, H-9), 1.28 (3H, s, Me-8a). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.4 and 172.1 (s, C_8 and 9-CO), 148.0 and 147.6 (s, C_2 and C_3), 138.1 (d, *J* 177.5 Hz, C_{11}), 132.5 (d, *J* 176.5 Hz, C_{12}), 127.2 and 122.5 (s, C_{4a} and C_{12c}), 111.7 (d, *J* 156.2 Hz, C_4), 108.3 (d, *J* 154.7 Hz, C_1), 94.1 (s, C_{12a}), 8.3 (d, *J* 168.5 Hz, C_{10}), 57.5 (s, C_{8a}), 55.7 and 55.6 (q, *J* 144.5 Hz, C_2-OMe and C_3-OMe), 55.2 (d, *J* 139.5 Hz, C_{12b}), 53.2 (d, *J* 138.0 Hz, C_{9a}), 51.8 (q, *J* 146.5 Hz, CO_2*Me*), 37.0 (t, *J* 142.0 Hz, C_6), 28.0 (t, *J* 129.5 Hz, C_5), 21.0 (q, *J* 129.0 Hz, Me_{8a}). Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.68; H, 5.82; N, 3.40.

3.11. Dimethyl 6-(2′-furyl)-3-methyl-1,2,3,6-tetrahydro-3-benzoazocine-4,5-dicarboxylate (12a)

Isoquinoline **3a** (2.78 g, 0.013 mol) was dissolved in 50 mL of acetonitrile and then DMAD (1.76 mL, 0.014 mol) was added in one portion to the solution. The reaction mixture was stirred at room

temperature for 7–10 days (TLC monitoring). After removal of the solvent and recrystallization from mixture of hexane–ethyl acetate benzoazocine **12a** was obtained as white crystals.

*3.11.1. Compound **12a***

White cubic crystals, yield 3.05 g (66%), mp 138 °C, R_f (20% ethyl acetate–hexane) 0.37; IR 1738 and 1679 (CO_2Me) cm^{-1}; EIMS (70 eV) *m/z* (rel intensity): M^+ 355 (69), 323 (24), 296 (72), 266 (24), 236 (100), 208 (13), 181 (18), 165 (27), 152 (19), 141 (12), 115 (19), 58 (26). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.31 (1H, dd, $J_{7,8}$ 7.3, $J_{7,9}$ 1.6 Hz, H-7), 7.26 (1H, dd, $J_{5',3'}$ 0.9, $J_{5',4'}$ 1.9 Hz, H-5′), 7.22 (1H, dt, $J_{9,7}$ 1.6, $J_{9,8}$=$J_{9,10}$=7.3 Hz, H-9), 7.20 (1H, dt, $J_{8,9}$=$J_{8,9}$=7.3, $J_{8,10}$ 1.6 Hz, H-8), 7.12 (1H, br d, $J_{10,8}$ 1.6, $J_{10,9}$ 7.3 Hz, H-10), 6.27 (1H, dd, $J_{4',3'}$ 3.2, $J_{4',5'}$ 1.9 Hz, H-4′), 5.90 (1H, s, H-6), 5.89 (1H, dd, $J_{3',4'}$ 3.2, $J_{3',5'}$ 0.9 Hz, H-3′), 3.76 (3H, s, CO_2Me), 3.71 (3H, s, CO_2Me), 3.59 (1H, ddd, $J_{2A,1A}$ 11.6, $J_{2A,1B}$ 6.5, $J_{2A,2B}$ 15.1 Hz, H-2A), 3.19 (1H, ddd, $J_{2B,1A}$ 7.8, $J_{2B,1B}$ 1.6, $J_{2B,2A}$ 15.1 Hz, H-2B), 2.96 (1H, ddd, $J_{1A,1B}$ 15.9, $J_{1A,2A}$ 11.6, $J_{1A,2B}$ 7.8 Hz, H-1A), 2.81 (1H, ddd, $J_{1B,1A}$ 15.9, $J_{1B,2A}$ 6.5, $J_{1B,2B}$ 1.6 Hz, H-1B), 2.53 (3H, s, NMe). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 167.0 and 169.3 (CO_2Me×2), 157.1 ($C_{2'}$), 155.9 (C_4), 141.0 ($C_{5'}$), 137.4 (C_{6a}), 137.2 (C_{10a}), 133.2 (C_{10}), 131.1 (C_7), 127.5 (C_8), 127.4 (C_9), 110.5 ($C_{3'}$), 105.0 ($C_{4'}$), 101.9 (C_5), 55.0 (C_2), 51.9 and 52.6 (CO_2Me×2), 47.0 (NMe), 38.0 (C_6), 34.4 (C_1). Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.70; H, 5.95; N, 3.93.

3.12. Dimethyl 6-(2′-furyl)-8,9-dimethoxy-3-methyl-1,2,3,6-tetrahydro-3-benzoazocine-4,5-dicarboxylate (12b)

Isoquinoline **3b** (0.33 g, 1.20 mmol) was dissolved in 30 mL of acetonitrile and 0.15 mL (1.20 mmol) of DMAD was added in one portion to the solution. The reaction mixture was stirred at room temperature for 7–10 days (monitoring by TLC). After removal of the solvent and recrystallization from mixture of hexane–ethyl acetate benzoazocine **12b** was obtained as white crystals.

*3.12.1. Compound **12b***

White cubic crystals, yield 0.30 g (60%), mp 138–140 °C, R_f (50% ethyl acetate–hexane) 0.40; IR 1729 and 1685 (CO_2Me) cm^{-1}; EIMS (70 eV) *m/z* (rel intensity): M^+ 415 (15), 358 (32), 326 (10), 296 (9), 243 (9), 229 (8), 197 (14), 181 (14), 164 (22), 151 (24), 58 (100), 42 (12). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.28 (1H, dd, $J_{5',3'}$ 0.8, $J_{5',4'}$ 1.8 Hz, H-5′), 6.81 (1H, s, H-10), 6.62 (1H, s, H-7), 6.28 (1H, dd, $J_{4',3'}$ 3.2, $J_{4',5'}$ 1.8 Hz, H-4′), 5.90 (1H, dd, $J_{3',4'}$ 3.2, $J_{3',5'}$ 0.8 Hz, H-3′), 5.82 (1H, s, H-6), 3.90 (3H, s, OMe), 3.88 (3H, s, OMe), 3.79 (3H, s, CO_2Me), 3.73 (3H, s, CO_2Me), 3.56 (1H, m, $J_{2A,1B}$ 6.0, $J_{2A,2B}$ 15.2 Hz, H-2A), 3.19 (1H, ddd, $J_{2B,1A}$ 7.6, $J_{2B,1B}$ 1.8, $J_{2B,2A}$ 15.2 Hz, H-2B), 2.90 (1H, m, $J_{1A,1B}$ 16.2, $J_{1A,2B}$ 7.6 Hz, H-1A), 2.79 (1H, ddd, $J_{1B,1A}$ 16.2, $J_{1B,2A}$ 6.0, $J_{1B,2B}$ 1.8 Hz, H-1B), 2.53 (3H, s, NMe). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 167.0 and 169.4 (CO_2Me×2), 157.2 ($C_{2'}$), 155.8 (C_4), 147.7 (C_8), 147.6 (C_9), 141.0 ($C_{5'}$), 129.4 (C_{6a}), 129.2 (C_{10a}), 116.2 (C_{10}), 114.2 (C_7), 110.5 ($C_{3'}$), 104.9 ($C_{4'}$), 101.9 (C_5), 55.9 and 56.0 (OMe×2), 55.0 (C_2), 51.9 and 52.6 (CO_2Me×2), 46.7 (NMe), 38.1 (C_6), 34.1 (C_1). Anal. Calcd for $C_{22}H_{25}NO_7$: C, 63.60; H, 6.07; N, 3.37. Found: C, 63.60; H, 6.09; N, 3.38.

3.13. Methyl 6-(2′-furyl)-3-methyl-1,2,3,6-tetrahydro-3-benzoazocine-5-carboxylate (13a)

Isoquinoline **3a** (2.22 g, 0.01 mol) was dissolved in 50 mL of acetonitrile. Then methyl propiolate (0.93 mL, 0.01 mol) was added in one portion to the solution. The reaction mixture was stirred at room temperature for 10–12 days (monitoring by TLC). After removing of the solvent, residue was chromatographed on Al_2O_3 (eluent: hexane, ethyl acetate–hexane 1:10) to give benzoazocine **13a** as white crystals.

*3.13.1. Compound **13a***

White rhombuses, yield 2.08 g (70%), mp 84–86 °C, R_f (20% ethyl acetate–hexane) 0.30; IR 1678 (CO_2Me), 1615 (C=C) cm^{-1}; EIMS (70 eV) *m/z* (rel intensity): M^+ 297 (100), 266 (17), 238 (84), 210 (22), 194 (25), 180 (24), 165 (28), 152 (17), 128 (38), 115 (15), 81 (8), 42 (19). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.62 (1H, s, H-4), 7.33 (1H, s, H-7), 7.31 (1H, dd, $J_{5',3'}$ 0.8, $J_{5',4'}$ 1.8 Hz, H-5′), 7.20–7.23 (3H, m, H-8, 9, and 10), 6.30 (1H, dd, $J_{4',3'}$ 3.1, $J_{4',5'}$ 1.8 Hz, H-4′), 5.99 (1H, br s, H-6), 5.86 (1H, dd, $J_{3',4'}$ 3.1, $J_{3',5'}$ 0.8 Hz, H-3′), 3.75 (3H, s, CO_2Me), 3.65 (1H, ddd, $J_{2A,1B}$ 6.3, $J_{2A,1A}$ 12.0, $J_{2A,2B}$ 17.9 Hz, H-2A), 3.08 (1H, m, $J_{2B,1B}$ 2.6, $J_{2B,2A}$ 17.9 Hz, H-2B), 3.08 (1H, m, $J_{1A,1B}$ 15.0, $J_{1A,2A}$ 12.0 Hz, H-1A), 2.94 (3H, s, NMe), 2.92 (1H, ddd, $J_{1B,1A}$ 15.0, $J_{1B,2A}$ 6.3, $J_{1B,2B}$ 2.6 Hz, H-1B). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.4 (CO_2Me), 159.1 ($C_{2'}$), 153.6 (C_4), 140.8 ($C_{5'}$), 138.5 (C_{6a}), 136.8 (C_{10a}), 133.1 (C_{10}), 131.9 (C_7), 127.3 (C_8), 126.9 (C_9), 110.7 ($C_{3'}$), 103.9 ($C_{4'}$), 96.2 (C_5), 51.42 (CO_2Me), 51.1 (C_2), 45.0 (NMe), 43.94 (C_6), 36.6 (C_1). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.83; H, 6.40; N, 4.69.

3.14. Methyl 6-(2′-furyl)-8,9-dimethoxy-3-methyl-1,2,3,6-tetrahydro-3-benzoazocine-5-carboxylate (13b)

Isoquinoline **3b** (1.92 g, 7.0 mmol) was dissolved in 50 mL of acetonitrile. Then the methyl propiolate (0.70 mL, 7.8 mmol) was added in one portion to the solution. The reaction mixture was stirred at room temperature for 10–12 days (TLC monitoring). After removal of the solvent and recrystallization from mixture of hexane–ethyl acetate benzoazocine **13b** was obtained as white crystals.

*3.14.1. Compound **13b***

White rhombuses, yield 1.81 g (72%), mp 126–128 °C, R_f (50% ethyl acetate–hexane) 0.42; IR 1671 (CO_2Me) and 1610 (C=C) cm^{-1}; EIMS (70 eV) *m/z* (rel intensity): M^+ 357 (100), 342 (15), 326 (13), 314 (10), 298 (89), 282 (10), 270 (14), 255 (17), 243 (25), 212 (11), 164 (22), 128 (15), 42 (13). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.61 (1H, s, H-4), 7.30 (1H, dd, $J_{5',3'}$ 0.7, $J_{5',4'}$ 1.8 Hz, H-5′), 6.78 (1H, s, H-10), 6.66 (1H, s, H-7), 6.27 (1H, dd, $J_{4',3'}$ 3.0, $J_{4',5'}$ 1.8 Hz, H-4′), 5.85 (1H, s, H-6), 5.82 (1H, dd, $J_{3',4'}$ 3.0, $J_{3',5'}$ 0.7 Hz, H-3′), 3.90 (3H, s, OMe), 3.88 (3H, s, OMe), 3.74 (3H, s, CO_2Me), 3.59 (1H, m, H-2A), 3.00 (2H, m, H-1), 2.96 (3H, s, NMe), 2.88 (1H, m, H-1B). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.5 (CO_2Me), 159.2 ($C_{2'}$), 153.4 (C_4), 147.5 (C_8), 147.2 (C_9), 140.8 ($C_{5'}$), 130.7 (C_{6a}), 128.7 (C_{10a}), 116.1 (C_{10}), 115.0 (C_7), 110.6 ($C_{3'}$), 103.9 ($C_{4'}$), 96.3 (C_5), 55.9 and 55.9 (OMe×2), 51.4 (CO_2Me), 51.0 (C_2), 44.5 (NMe), 43.9 (C_6), 36.3 (C_1). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.20; H, 6.47; N, 3.89.

3.15. Dimethyl (2*E*)-2-[1-(2-furyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]but-2-enedioate (14a), dimethyl (2*E*)-2-[1-(2-furyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl]but-2-enedioate (14b). Typical procedure

Acetylenedicarboxylic ester (DMAD) (5 mL, 0.04 mol) was added to a solution of isoquinolines **2a**,**b** (0.01 mol) in 30 mL of toluene. The resulted mixture was boiled for 2–6 h. The reaction progress was monitored by TLC (until disappearance of the starting compound). At the end of the reaction the mixture was cooled and the solvent was evaporated. The residue was purified by column chromatography on alumina (eluent ethyl acetate–hexane 1:10) to give white crystals of isoquinolines **14a**,**b**.

*3.15.1. Compound **14a***

White plates, yield 2.54 g (72%), mp 97–99 °C, R_f (25% ethyl acetate–hexane) 0.47; IR 1700 and 1747 (CO_2Me) cm^{-1}; EIMS (70 eV) *m/z* (rel intensity): M^+ 341 (13), 310 (15), 282 (100), 250 (15), 222 (48), 210 (6), 198 (8), 141 (17), 115 (13). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34 (1H, br d, $J_{5'',4''}$ 1.8 Hz, H-5″), 7.12–7.23 (4H, m, H–Ar), 6.27 (1H, dd, $J_{4'',3''}$ 3.2, $J_{4'',5''}$ 1.8 Hz, H-4″), 6.06 (1H, dd, $J_{3'',4''}$ 3.2, $J_{3'',5''}$ 0.8 Hz, H-3″), 5.64 (1H, s, H-1), 5.01 (1H, s, H-3′), 3.63 and 3.94 (3H, s, OMe), 3.42–3.59 (2H, m, H-3), 3.06 (1H, m, H-4A), 2.83 (1H, m,

H-4B). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 168.2 ($C_{4'}$ in CO_2Me), 165.9 (CO_2Me-2′), 152.9 and 153.6 ($C_{2'}$, $C_{2''}$), 142.8 ($C_{5''}$), 132.8 and 134.1 (C_{4a}, C_{8a}), 126.5, 127.8, 127.8, and 128.8 (C_5,C_6, C_7, and C_8), 110.2 ($C_{3''}$), 109.0 ($C_{4''}$), 86.0 ($C_{3'}$), 55.9 (C_1), 53.9 and 53.0 (OMe×2), 43.2 (C_3), 28.3 (C_4). Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.63; H, 5.45; N, 3.99.

*3.15.2. Compound **14b***

White plates, yield 2.71 g (68%), mp 130–132 °C, R_f (ethyl acetate) 0.56; IR 1683 and 1743 (CO_2Me) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 401 (10), 386 (8), 370 (14), 343 (21), 342 (100), 340 (18), 326 (8), 282 (17), 258 (12), 191 (14). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (1H, dd, $J_{5'',3''}$ 0.8, $J_{5'',4''}$ 1.6 Hz, H-5″), 6.60 (1H, s, H-5), 6.57 (1H, s, H-8), 6.27 (1H, dd, $J_{3'',4''}$ 3.2, $J_{3'',5''}$ 0.8 Hz, H-3″), 6.06 (1H, dd, $J_{4'',3''}$ 3.2, $J_{4'',5''}$ 1.8 Hz, H-4″), 5.55 (1H, s, H-1), 5.02 (1H, s, H-3′), 3.62, 3.78, 3.85, 3.94 (3H, four singlets, OMe×4), 3.40–3.56 (2H, m, H-3), 3.00 (1H, m, H-4B), 2.70 (1H, m, H-4A). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 168.2 and 166.0 (CO_2Me×2), 147.7, 148.6, 153.1, and 153.6 (C_6, C_7, $C_{2'}$, and $C_{2''}$), 142.9 ($C_{5''}$), 124.4 and 126.3 (C_{4a}, C_{8a}), 110.4 and 111.2 (C_5 and C_8), 110.2 ($C_{3''}$), 109.2 ($C_{4''}$), 85.8 ($C_{3'}$), 55.9 and 56.1 (OMe×2), 55.4 (C_1), 53.1 and 50.9 (CO_2Me×2), 43.1 (C_3), 27.9 (C_4). Anal. Calcd for $C_{21}H_{23}NO_7$: C, 62.83; H, 5.78; N, 3.49. Found: C, 62.95; H, 5.96; N, 3.69.

3.16. Dimethyl (1*R**,4*S**)-1-[2-acetyl-1,2,3,4-tetrahydroisoquinoline-1-yl]-7-oxabicyclo[2.2.1]hepta-2,5-dien-2,3-dicarboxylate (15a), dimethyl (1*R**,4*S**)-1-[2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (15b), dimethyl (1*R**,4*S**)-1-[6,7-dimethoxy-2-acetyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (15c), dimethyl (1*R**,4*S**)-1-[6,7-dimethoxy-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (15d). Typical procedure

DMAD (0.49 mL, 4.0 mmol) was added to the solution of corresponding tetrahydroisoquinoline **13a–d** (1.6 mmol) in 30 mL of toluene. The resulted mixture was refluxed for 2–3 days (TLC monitoring). At the end of the reaction the mixture was cooled and toluene was evaporated. The residue was treated with ether (7–10 mL) to give white solids. The obtained crystals were filtered-off and washed with ether. Further crystallization from hexane–ethyl acetate gave the corresponding adducts **15** as a colourless crystals.

*3.16.1. Compound **15a***

White powder, yield 0.19 g (31%); mp 184–186 °C, R_f (30% ethyl acetate–hexane) 0.26; IR 1735, 1717 (CO_2Me), 1644 (NCO) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): 354 [M^+−29] (16), 312 (22), 280 (27), 248 (13), 198 (8), 174 (23), 132 (100), 117 (16), 103 (13), 77 (17), 59 (13), 43 (87); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 (1H, d, $J_{6',5'}$ 5.2 Hz, H-6′), 7.10–7.24 (1H, m, H-5, 6, 7, and 8), 7.09 (1H, dd, $J_{5',4'}$ 1.8, $J_{5',6'}$ 5.2 Hz, H-5′), 6.60 (1H, s, H-1), 5.65 (1H, d, $J_{4',5'}$ 1.8 Hz, H-4′), 4.06 (1H, m, H-3A), 3.84 (3H, s, CO_2Me), 3.78 (1H, m, H-3B), 3.76 (3H, s, CO_2Me), 2.88 (1H, m, H-4B), 2.88 (1H, m, H-4A), 2.15 (3H, s, NCOMe). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.1 (NCOMe), 162.3 and 164.7 (CO_2Me×2), 156.7 ($C_{2'}$), 149.6 ($C_{3'}$), 144.8 ($C_{5'}$), 144.1 ($C_{6'}$), 134.5 (C_{4a}), 132.6 (C_{8a}), 129.1 (C_5), 127.7 (C_6), 127.5 (C_7), 126.1 (C_8), 102.5 ($C_{1'}$), 83.7 ($C_{4'}$), 52.4 and 52.6 (CO_2Me×2), 50.0 (C_1), 41.7 (C_3), 28.5 (C_4), 21.1 (NCOMe). Anal. Calcd for $C_{21}H_{21}NO_6$: C, 65.79; H, 5.52; N, 3.65. Found: C, 65.78; H, 5.50; N, 3.60.

*3.16.2. Compound **15b***

White powder, yield 0.23 g (33%); mp 180–182 °C, R_f (20% ethyl acetate–hexane) 0.42; IR 1728 and 1710 (CO_2Me), 1689 (NCO) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 437 (1), 408 (6), 377 (14), 349 (12), 318 (16), 280 (23), 248 (15), 228 (100), 130 (21), 115 (38), 69 (14), 57 (9). ^{1}H NMR ($CDCl_3$, 400 MHz) complicated spectrum (mixture of two isomers in the ratio ~3:1), all data cite the *major* isomer δ 7.30 (1H, d, $J_{6',5'}$ 5.2 Hz, H-6), 7.14–7.27 (4H, m, H–Ar), 7.10 (1H, dd, $J_{5',4'}$ 2.0, $J_{6',5'}$ 5.2 Hz, H-5′), 6.47 (1H, s, H-1), 5.70 (1H, d, $J_{4',5'}$ 2.0 Hz, H-4′), 4.24 (1H, m, H-3A), 4.04 (1H, m, H-3B), 3.77 and 3.82 (3H, s, OMe), 2.93–3.08 (2H, m, H-4). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 162.7 and 164.2 (CO_2Me×2), 156.3 (q, $COCF_3$, $^2J_{C,F}$ 36.5 Hz), 153.0 and 153.7 ($C_{2'}$ and $C_{3'}$), 143.0 and 145.1 ($C_{6'}$ and $C_{5'}$), 133.8 (C_{4a}), 130.58 (C_{8a}), 126.9, 127.2, 128.0, 129.0 (C_5, C_6, C_7, and C_8), 116.6 (q, CF_3, $^1J_{C,F}$ 287.7 Hz), 101.2 ($C_{1'}$), 84.0 ($C_{4'}$), 52.8 (C_1), 52.0 and 52.5 (CO_2Me×2), 41.1 (C_3), 28.7 (C_4). Anal. Calcd for $C_{21}H_{18}F_3NO_6$: C, 57.67; H, 4.15; N, 3.20. Found: C, 57.76; H, 4.18; N, 3.09.

*3.16.3. Compound **15c***

White plates, yield 0.32 g (45%); mp 166–168 °C, R_f (ethyl acetate) 0.62; IR 1738, 1714 (CO_2Me), 1643 (NCO) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): 426 [M^+−17] (17), 384 (66), 352 (33), 301 (51), 272 (88), 258 (47), 230 (63), 192 (49), 176 (37), 111 (67), 79 (36), 59 (100); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26 (1H, d, $J_{6',5'}$ 5.4 Hz, H-6′), 7.11 (1H, dd, $J_{5',4'}$ 2.0, $J_{5',6'}$ 5.4 Hz, H-5′), 6.69 (1H, s, H-8), 6.57 (1H, s, H-5), 6.51 (1H, s, H-1), 5.68 (1H, d, $J_{4',5'}$ 2.0 Hz, H-4′), 4.02 (1H, m, H-3A), 3.84 (3H, s, OMe), 3.83 (3H, s, OMe), 3.82 (3H, s, CO_2Me), 3.78 (1H, m, H-3B), 3.76 (3H, s, CO_2Me), 2.81 (2H, m, H-4), 2.15 (3H, s, NCOMe). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.1 (NCOMe), 164.7 and 162.3 (CO_2Me×2), 156.7 and 149.5 ($C_{2'}$ and $C_{3'}$), 147.3 and 148.4 (C_7 and C_6), 144.2 and 144.5 ($C_{6'}$ and $C_{5'}$), 126.7 (C_{4a}), 124.2 (C_{8a}), 110.3 and 111.5 (C_8 and C_5), 102.5 ($C_{1'}$), 83.8 (C_4), 55.7 and 56.0 (OMe×2), 52.6 and 52.4 (CO_2Me×2), 49.6 (C_1), 41.6 (C_3), 27.9 (C_4), 21.1 (NCO*Me*). Anal. Calcd for $C_{23}H_{25}NO_8$: C, 62.30; H, 5.68; N, 3.16. Found: C, 62.28; H, 5.69; N, 3.17.

*3.16.4. Compound **15d***

White plates, yield 0.54 g (68%); mp 130 °C, R_f (50% ethyl acetate–hexane) 0.63; IR 1733 and 1696 (CO_2Me), 1634 (NCO) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 497 (9), 480 (16), 468 (13), 436 (21), 354 (41), 326 (19), 288 (100), 258 (19), 244 (11), 190 (11), 176 (26), 160 (6), 119 (6). ^{1}H NMR ($CDCl_3$, 400 MHz) complicated spectrum (mixture of two isomers in the ratio ~2:1), all data cite for *major* isomer δ 7.30 (1H, d, $J_{6',5'}$ 5.3 Hz, H-6′), 7.14 (1H, br d, $J_{5',6'}$ 5.3 Hz, H-5′), 6.72 (1H, s, H-8), 6.61 (1H, s, H-5), 6.40 (1H, s, H-1), 5.74 (br s, 1H, H-4′), 4.20 (1H, br dt, $J_{3A,3B}$ 14.0, $J_{3A,4A}$ 12.7, $J_{3A,4B}$ 4.7 Hz, H-3A), 4.05 (1H, dd, $J_{3B,3A}$ 14.0, $J_{3B,4A}$ 6.4 Hz, H-3B), 3.87 (3H, s, OMe), 3.85 (3H, s, OMe), 3.83 (3H, s, CO_2Me), 3.79 (3H, s, CO_2Me), 2.97 (1H, ddd, $J_{4A,3A}$ 12.7, $J_{4A,3B}$ 6.4, $J_{4A,4B}$ 16.8 Hz, H-4A), 2.83 (1H, dd, $J_{4B,3A}$ 4.7, $J_{4B,4A}$ 16.8 Hz, H-4B). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 164.6 and 162.1 (CO_2Me×2), 156.5 (q, $COCF_3$, $^2J_{C,F}$ 36.7 Hz), 150.1 and 155.1 ($C_{3'}$ and $C_{2'}$), 148.9 (C_6), 147.6 (C_7), 144.4 ($C_{5'}$), 143.7 ($C_{6'}$), 126.0 (C_{4a}), 122.6 (C_{8a}), 116.53 (q, CF_3, $^1J_{C,F}$ 288.3 Hz), 111.4 (C_5), 110.1 (C_8), 101.6 ($C_{1'}$), 83.9 ($C_{4'}$), 55.8 and 56.1 (OMe×2), 52.6 (C_1), 51.7 and 52.5 (CO_2Me×2), 41.1 (C_3), 28.2 (C_4). Anal. Calcd for $C_{23}H_{22}F_3NO_8$: C, 55.54; H, 4.46; N, 2.82. Found: C, 55.53; H, 4.44; N, 2.85.

3.17. Dimethyl 11b-(2′-furyl)-7,11b-dihydro-6*H*-pyrido[2,1-*a*]isoquinoline-1,3-dicarboxylate (16a), dimethyl 11b-(2′-furyl)-9,10-dimethoxy-7,11b-dihydro-6*H*-pyrido[2,1-*a*]isoquinoline-1,3-dicarbocylate (16b), tetramethyl 11b-(2′-furyl)-7,11b-dihydro-6*H*-pyrido[2,1-*a*]isoquinoline-1,2,3,4-tetracarboxylate (17a), tetramethyl 11b-(2′-furyl)-9,10-dimethoxy-7,11b-dihydro-6*H*-pyrido[2,1-*a*]isoquinoline-1,2,3,4-tetracarbocylate (17b). Typical procedure

DMAD (2.9 mL, 24.0 mmol, for **17**) or methyl propiolate (2.1 mL, 24.0 mmol, for **16**) was added to the solution of 12.0 mmol dihydroisoquinoline **1a**,**b** in 40 mL of acetonitrile at room temperature and the reaction mixture was refluxed for 2–6 h. The reaction

progress was monitored by TLC until disappearance of the starting compound's spot. At the end the solvent was evaporated to give viscous oil residue. Further purification by the column chromatography on alumina (Al_2O_3, 45×1 cm, eluent: hexane, ethyl acetate–hexane (1:10, 1:5, 1:1)) to give corresponding compounds **16** or **17**.

*3.17.1. Compound **16b***

White needles, yield 1.43 g (28%); mp 188–190 °C, R_f (ethyl acetate) 0.77; IR 1708 and 1684 (CO_2Me), 1604 (C=C) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 425 (59), 394 (4), 366 (100), 350 (16), 342 (11), 327 (6), 292 (3), 264 (3), 220 (2), 191 (2), 167 (3), 59 (2). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.76 (1H, s, H-4), 7.71 (1H, s, H-2), 7.33 (1H, dd, $J_{5',3'}$ 0.9, $J_{5',4'}$ 1.8 Hz, H-5′), 7.00 (1H, s, H-8), 6.54 (1H, s, H-11), 6.29 (1H, dd, $J_{4',3'}$ 3.3, $J_{4',5'}$ 1.8 Hz, H-4′), 5.91 (1H, dd, $J_{3',4'}$ 3.3, $J_{3',5'}$ 0.9 Hz, H-3′), 3.85 (3H, s, CO_2Me), 3.74 (3H, s, OMe), 3.70 (3H, s, OMe), 3.58 (1H, ddd, $J_{6A,6B}$ 13.5, $J_{6A,7A}$ 7.2, $J_{6A,7B}$ 2.3 Hz, H-6A), 3.51 (3H, s, CO_2Me), 3.51 (3H, s, CO_2Me), 3.48 (1H, ddd, $J_{6B,6A}$ 13.5, $J_{6B,7A}$ 10.7, $J_{6B,7B}$ 5.5 Hz, H-6B), 3.00 (1H, ddd, $J_{7A,6A}$ 7.2, $J_{7A,6B}$ 10.7, $J_{7A,7B}$ 16.4 Hz, H-7A), 2.86 (1H, ddd, $J_{7B,6A}$ 2.3, $J_{7B,6B}$ 5.5, $J_{7B,7A}$ 16.4 Hz, H-7B). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 164.3 and 167.1 (CO_2Me×2), 157.9 ($C_{2'}$), 155.3 (C_2 and C_4), 152.3 (C_1), 148.7 and 147.7 (C_9 and C_{10}), 142.3 ($C_{5'}$), 127.2 and 125.6 (C_{7a} and C_{11a}), 110.1, 110.8, 111.1, 112.2 ($C_{3'}$, C_3, C_8, C_{11}), 106.8 ($C_{4'}$), 104.1, 55.8, and 55.9 (OMe-Ar×2), 50.7 and 51.0 (CO_2Me×2), 41.9 (C_6), 29.8 (C_7). Anal. Calcd for $C_{23}H_{23}NO_7$: C, 64.93; H, 5.45; N, 3.29. Found: C, 65.11; H, 5.43; N, 3.26.

*3.17.2. Compound **17a***

White needles, yield 1.15 g (20%); mp 140 °C, R_f (50% ethyl acetate–hexane) 0.40; IR 1732 and 1712 (CO_2Me), 1597 (C=C) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 481 (10), 451 (53), 422 (100), 394 (21), 362 (33), 280 (24), 260 (62), 199 (54), 169 (23), 128 (24), 111 (42), 95 (43), 59 (92), 43 (57). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.07 (1H, d, $J_{11,10}$ 8.0 Hz, H-11), 7.38 (1H, dd, $J_{10,9}$ 7.6, $J_{10,11}$ 8.0 Hz, H-10), 7.27 (1H, t, $J_{9,8}$=$J_{9,10}$=7.6 Hz, H-9), 7.26 (1H, dd, $J_{5',3'}$ 0.8, $J_{5',4'}$ 1.7 Hz, H-5′), 7.08 (1H, d, $J_{8,9}$ 7.6 Hz, H-8), 6.38 (1H, dd, $J_{3',4'}$ 3.3, $J_{3',5'}$ 0.8 Hz, H-3′), 6.21 (1H, dd, $J_{4',3'}$ 3.3, $J_{4',5'}$ 1.7 Hz, H-4′), 3.98 (3H, s, CO_2Me), 3.74 (3H, s, CO_2Me), 3.72 (1H, m, $J_{6A,6B}$ 11.9 Hz, H-6A), 3.68 (3H, s, CO_2Me), 3.52 (3H, s, CO_2Me), 3.45 (1H, ddd, $J_{6B,6A}$ 11.9, $J_{6B,7A}$ 9.2, $J_{6B,7B}$ 4.9 Hz, H-6B), 2.88 (1H, m, $J_{7A,6B}$ 9.2 Hz, H-7A), 2.88 (1H, m, $J_{7B,6B}$ 4.9 Hz, H-7B). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 165.0 and 167.2 (CO_2Me×2), 164.2 (2C, CO_2Me×2), 152.4 ($C_{2'}$), 149.0 (C_4), 143.5 ($C_{5'}$), 135.2 (C_2), 134.6 (C_{7a}), 133.5 (C_{11a}), 126.42, 128.2, 128.6, 128.7 (four d, C_8–C_{11}), 116.6 (C_1), 112.7 ($C_{3'}$), 110.1 ($C_{4'}$), 99.9 (C_3), 62.8 (C_6), 51.7, 52.0, 52.5 and 53.3 (four q, CO_2Me×4), 46.5 (C_{11b}), 29.4 (C_7). Anal. Calcd for $C_{25}H_{23}NO_9$: C, 62.37; H, 4.82; N, 2.91. Found: C, 62.40; H, 4.83; N, 2.90.

*3.17.3. Compound **17b***

White needles, yield 1.82 g (28%); mp 196–197 °C, R_f (50% ethyl acetate–hexane) 0.33; IR 1735 and 1698 (CO_2Me), 1603 (C=C) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): M^+ 541 (3), 510 (6), 482 (100), 438 (4), 408 (3), 349 (3), 304 (3), 260 (3), 241 (7), 190 (2), 59 (5). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36 (1H, dd, $J_{5',3'}$ 0.8, $J_{5',4'}$ 1.8 Hz, H-5′), 6.64 (1H, s, H-11), 6.63 (1H, s, H-8), 6.44 (1H, dd, $J_{3',4'}$ 3.1, $J_{3',5'}$ 0.8 Hz, H-3′), 6.31 (1H, dd, $J_{4',3'}$ 3.1, $J_{4',5'}$ 1.8 Hz, H-4′), 3.93 (3H, s, OMe), 3.90 (3H, s, OMe), 3.82 (3H, s, CO_2Me), 3.74 (1H, m, $J_{6A,7A}$ 5.9 Hz, H-6A), 3.73 (3H, s, CO_2Me), 3.66 (3H, s, CO_2Me), 3.65 (1H, m, $J_{6B,7A}$ 12.4 Hz, H-6B), 3.45 (3H, s, CO_2Me), 3.13 (1H, ddd, $J_{7A,6A}$ 5.9, $J_{7A,6B}$ 12.4, $J_{7A,7B}$ 17.1 Hz, H-7A), 2.75 (1H, br d, $J_{7B,7A}$ 17.1 Hz, H-7B). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 164.2, 164.2, 165.2, 167.2 (CO_2Me×4), 147.4 (C_4), 148.7, 149.2, 152.5 ($C_{2'}$), 143.5 ($C_{5'}$), 134.7 (C_2), 126.9 (C_1), 125.2 (C_{7a}), 117.2 (C_{11a}), 112.6 (C_7), 111.8, 110.95 ($C_{3'}$), 110.1 ($C_{4'}$), 99.7 (C_3), 62.6 (C_{11b}), 55.9 (2C, q, OMe×2), 51.7, 52.2, 52.5, and 53.3 (four s, CO_2Me), 46.5 (C_6), 28.9 (C_7). Anal. Calcd for $C_{27}H_{27}NO_{11}$: C, 59.89; H, 5.03; N, 2.59. Found: C, 59.90; H, 5.02; N, 2.56.

3.18. (8a*S**,10*R**,11*R**,12b*S**)-10,11-Diacetoxy-2,3-dimethoxy-5,6,8,8a,9,10,11,12b-octahydroisoindolo[1,2-*a*]isoquinoline-8-one (18)

$BF_3 \cdot OEt_2$ 0.2 mL (1.6 mmol) was added to solution of 0.25 g (0.80 mmol) of isoindoloisoquinoline **8b** in 10 mL of acetic anhydride. The pale brown reaction mixture was stirred at 25 °C for 10 h. Then it was diluted with water (60 mL), neutralized with excess Na_2CO_3, and extracted with chloroform (3×30 mL). The organic phase was dried by $MgSO_4$. After solvent distillation, the substance was recrystallized from mixture of ethyl acetate–hexane to give 0.10 g (0.24 mmol) of compound **18**.

*3.18.1. Compound **18***

White rhombuses; yield (30%); mp 148–150 °C, R_f 0.69 (ethylacetate); IR 1685 (N–C=O), 1705 and 1729 (O–C=O) cm^{-1}; EIMS (70 eV) *m*/*z* (rel intensity): 415 [M^+] (39), 356 (100), 324 (34), 296 (56), 264 (34), 244 (39), 43 (22). ^1H NMR ($CDCl_3$, 400 MHz) δ 6.61 (1H, s, H-1), 6.60 (1H, s, H-4), 5.59 (1H, m, $J_{11,12}$ 3.1 Hz, H-12), 5.33 (1H, m, $J_{10,11}$ 7.9, $J_{11,12}$ 3.1 Hz, H-11), 5.23 (1H, br s, H-12b), 5.11 (1H, ddd, $J_{9B,10}$ 12.4, $J_{10,11}$ 7.9, $J_{9A,10}$ 4.0 Hz, H-10), 4.38 (1H, ddd, $J_{6A,6B}$ 12.7, $J_{5A,6A}$ 5.3, $J_{5B,6A}$ 1.5 Hz, H-6A), 3.81 (6H, s, 2-OMe, 3-OMe), 3.33 (1H, m, $J_{8a,9}$ 11.5 Hz, H-8a), 2.86 (1H, m, $J_{6A,6B}$ 12.7, $J_{5A,6B}$ 12.1, $J_{5B,6B}$ 3.4 Hz, H-6B), 2.71 (1H, m, $J_{5A,5B}$ 15.4, $J_{5A,6B}$ 12.1, $J_{5A,6A}$ 5.3 Hz, H-5A), 2.56 (1H, dd, $J_{5A,5B}$ 15.4, $J_{5B,6B}$ 3.4 Hz, H-5B), 2.45 (1H, ddd, $J_{9A,9B}$ 12.5, $J_{8a,9A}$ 5.3, $J_{9A,10}$ 4.0 Hz, H-9A), 2.01 (3H, s, OAc), 1.99 (3H, s, OAc), 1.54 (1H, ddd, $J_{9A,9B}$ 12.5, $J_{9B,10}$ 12.4, $J_{8a,9B}$ 11.5 Hz, H-9B). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.6 (s, C_8), 170.3 and 170.2 (s, C_{10} and C_{11}), 20.8 (q, 2C, *J* 130.0 Hz, OAc×2), 141.9 (s, C_{12a}), 28.3 (t, *J* 133.5 Hz, C_9), 148.1 and 147.7 (s, C_2 and C_3), 126.2 (s, C_{4a}), 123.0 (s, C_{12c}), 116.9 (d, *J* 165.0 Hz, C_{12}), 112.3 (d, *J* 156.5 Hz, C_4), 109.7 (d, *J* 155.0 Hz, C_1), 72.1 (d, *J* 149.0 Hz, C_{11}), 71.9 (d, *J* 148.5 Hz, C_{10}), 58.1 (d, *J* 140.5 Hz, C_{12b}), 56.1 (q, *J* 144.5 Hz, C_2-OMe), 55.7 (q, *J* 144.5 Hz, C_3-OMe), 42.0 (d, *J* 129.0 Hz, C_{8a}), 36.7 (t, *J* 142.0 Hz, C_6), 28.7 (t, *J* 130.5 Hz, C_5). Anal. Calcd for $C_{22}H_{25}NO_7$: C, 63.60; H, 6.07; N, 3.37; O, 26.96, Found: C, 63.61; H, 6.05; N, 3.37; O, 26.95.

3.19. Methyl (1a*R**,2*R**,3*R**,3a*S**,11b*R**,11c*R**,11d*R**)-4-oxo-1a,2,3,3a,4,7,11b,11d-octahydro-6*H*-2,11c-epoxireno-[6,7]isoindolo[1,2-*a*]isoquinolin-3-carboxylate (19a), methyl (1a*R**,2*R**,3*R**,3a*S**,11b*R**,11c*R**,11d*R**)-9,10-dimethoxy-4-oxo-1a,2,3,3a,4,7,11b,11d-octahydro-6*H*-2,11c-epoxireno-[6,7]isoindolo[1,2-*a*]isoquinoline-3-carboxylate (19b), (1a*R**,2*R**,3a*S**,11b*R**,11c*R**,11d*R**)-1a,3,3a,7,11b,11d-hexahydro-6*H*-2,11c-epoxireno[6,7]isoindolo[1,2-*a*]isoquinolin-4(2*H*)-one (20a), (1a*R**,2*R**,3a*S**,11b*R**,11c*R**,11d*R**)-9,10-dimethoxy-1a,3,3a,7,11b,11d-hexahydro-6*H*-2,11c-epoxireno[6,7]-isoindolo[1,2-*a*]isoquinolin-4(2*H*)-one (20b). Typical procedure

A mixture of 4.80 mmol of isoindoloisoquinoline **8** (**10**) and 15 mL of dichloromethane was added to solution of 2.07 g (12.0 mmol) of *m*-CPBA in 25 mL of dichloromethane. The resulted reaction mixture was boiled for 1–3 days (monitoring by TLC). Then it was cooled and diluted with water (50 mL), basified with $NaHCO_3$ to pH 9–10, and then extracted with CH_2Cl_2 (3×50 mL). The organic phase was dried over $MgSO_4$. After solvent distillation, the residue (brown oil) was treated with ether (10 mL). The obtained solids were filtered-off and were recrystallized from mixture of hexane–ethyl acetate to give corresponding diepoxides **19**–**20a**,**b** as white or pale-yellow crystals.

*3.19.1. Compound **19a***

White crystals, yield 1.21 g (77%); mp 258–260 °C; R_f (ethyl acetate) 0.32; IR 1707 (NC=O) and 1737 (CO_2Me) cm^{-1}; EIMS

(70 eV) *m/z* (rel intensity): M^+ 327 (80), 326 (100), 295 (30), 266 (8), 238 (15), 210 (12), 168 (13), 130 (37), 103 (10), 77 (7), 59 (5). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (1H, br d, $J_{10,11}$ 7.8 Hz, H-11), 7.28 (1H, br t, $J_{9,8}$=$J_{9,10}$=7.8 Hz, H-9), 7.21 (1H, br t, $J_{10,9}$=$J_{10,11}$=7.8 Hz, H-10), 7.13 (1H, br d, $J_{8,9}$ 7.8 Hz, H-8), 5.25 (1H, br s, H-2), 4.72 (1H, s, H-11b), 4.20 (1H, ddd, $J_{6A,6B}$ 12.7, $J_{6A,7A}$ 5.5, $J_{6A,7B}$ 3.0 Hz, H-6A), 3.72 (1H, d, $J_{1a,11d}$ 3.3 Hz, H-1a), 3.71 (3H, s, CO_2Me), 3.47 (1H, d, $J_{11d,1a}$ 3.3 Hz, H-11d), 3.18 (1H, br d, $J_{3endo,3a}$ 9.4 Hz, H-3$_{endo}$), 3.10 (1H, m, $J_{6B,6A}$ 12.7 Hz, H-6B), 2.94 (2H, d, $J_{3a,3endo}$ 9.4 Hz, H-3a), 3.00 (1H, m, H-7A), 2.74 (1H, m, $J_{7B,6A}$ 3.0 Hz, H-7B). ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 170.8 and 168.2 (CO_2H and C_4), 134.4 and 130.1 (C_{7a} and C_{11a}), 128.5 (C_8), 126.7, 126.2, 126.0 ($C_{9,10,11}$), 87.1 (C_{11c}), 77.1 (C_2), 55.6, 53.4, 51.2, 49.1, 48.5, 46.8 ($C_{1a,3,3a,11b,11d,CO2Me}$), 36.7 ($C_6$), 28.0 ($C_7$). Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 66.28; H, 5.01; N, 4.53.

3.19.2. Compound **19b**

White crystals, yield 1.54 g (83%); mp 158–160 °C; R_f (50% ethyl acetate–hexane) 0.32; IR 1708 (NC=O) and 1734 (CO_2Me) cm^{-1}; EIMS (70 eV) *m/z* (rel intensity): M^+ 387 (100), 372 (7), 356 (55), 258 (13), 190 (14), 43 (22). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.81 (1H, s, H-11), 6.59 (1H, s, H-8), 5.18 (1H, br s, H-2), 4.72 (1H, s, H-11b), 4.22 (1H, ddd, $J_{6A,6B}$ 13.0, $J_{6A,7A}$ 5.3, $J_{6A,7B}$ 3.0 Hz, H-6A), 3.88 (3H, s, OMe), 3.83 (3H, s, OMe), 3.71 (3H, s, CO_2Me), 3.71 (1H, d, $J_{1a,11d}$ 3.3 Hz, H-1a), 3.47 (1H, d, $J_{11d,1a}$ 3.3 Hz, H-11d), 3.18 (1H, dd, $J_{3endo,3a}$ 9.3, $J_{3endo,2}$ 0.7 Hz, H-3$_{endo}$), 3.08 (1H, m, $J_{6B,6A}$ 13.0 Hz, H-6B), 2.94 (1H, d, $J_{3a,3endo}$ 9.3 Hz, H-3a), 2.88 (1H, m, H-7A), 2.65 (1H, m, $J_{7B,6A}$ 3.0 Hz, H-7B). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.3 (C_4), 168.2 (CO_2Me), 148.0 and 148.4 (C_{10} and C_9), 126.5 (C_{11a}), 122.2 (C_{7a}), 111.6 (C_8), 108.7 (C_{11}), 87.3 (C_{11c}), 77.8 (C_2), 56.5 (C_{11b}), 56.0 and 55.9 (OMe×2), 53.9 (C_3), 52.2 (CO_2*Me*), 49.8 and 49.1 (C_{1a} and C_{11d}), 47.9 (C_{3a}), 37.6 (C_6), 28.0 (C_7). Anal. Calcd for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62. Found: C, 62.30; H, 5.22; N, 3.90.

3.19.3. Compound **20a**

Pale-yellow powder, yield 1.02 g (79%); mp 168–170 °C; IR 1682 (NC=O) cm^{-1}; EIMS (70 eV) *m/z* (rel intensity): M^+ 269 (100), 268 (98), 240 (17), 212 (7), 198 (7), 168 (6), 130 (21), 128 (7), 103 (8). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (1H, br d, $J_{10,11}$ 7.8 Hz, H-11), 7.33 (1H, br t, $J_{10,9}$=$J_{9,8}$=7.8 Hz, H-9), 7.23 (1H, br t, $J_{10,9}$=$J_{10,11}$=7.8 Hz, H-10), 7.17 (1H, br d, $J_{8,9}$ 7.8 Hz, H-8), 5.31 (1H, s, H-11b), 4.58 (1H, d, $J_{3exo,2}$ 4.9 Hz, H-2), 4.30 (1H, ddd, $J_{6A,6B}$ 12.8, $J_{6A,7A}$ 5.7, $J_{6A,7B}$ 2.8 Hz, H-6A), 3.71 (1H, d, $J_{1a,11d}$ 3.4 Hz, H-1a), 3.49 (1H, d, $J_{11d,1a}$ 3.4 Hz, H-11d), 3.15 (1H, m, $J_{6B,6A}$ 12.8 Hz, H-6B), 3.08 (1H, m, $J_{7A,6A}$ 5.7 Hz, H-7A), 2.95 (1H, dd, $J_{3a,3endo}$ 9.4, $J_{3a,3exo}$ 3.6 Hz, H-3a), 2.77 (1H, ddd, $J_{7B,6A}$ 2.8 Hz, H-7B), 2.25 (1H, ddd, $J_{3exo,2}$ 4.9, $J_{3exo,3endo}$ 12.7, $J_{3exo,3a}$ 3.6 Hz, H-3$_{exo}$), 1.88 (1H, dd, $J_{3endo,3exo}$ 12.7, $J_{3endo,3a}$ 9.4 Hz, H-3$_{endo}$). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 171.7 (C_4), 134.3 and 130.8 (C_{7a} and C_{11a}), 129.1 (C_8), 127.5, 126.9, 126.0 (C_9, C_{10}, C_{11}), 87.6 (C_{11c}), 75.5 (C_2), 57.3 (C_{11b}), 50.4, 50.1, 49.1 (C_{1a}, C_{11d}, C_{3a}), 37.4 (C_6), 30.9 (C_3), 28.5 (C_7). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.59; H, 5.39; N, 5.48.

3.19.4. Compound **20b**

Pale-yellow powder, yield 1.06 g (67%); mp 196–198 °C; IR 1690 (NC=O) cm^{-1}; EIMS (70 eV) *m/z* (rel intensity): M^+ 329 (100), 328 (73), 314 (8), 298 (67), 286 (5), 272 (4), 190 (6), 176 (7). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.84 (1H, s, H-11), 6.63 (1H, s, H-8), 5.23 (1H, s, H-11b), 4.58 (1H, d, $J_{3exo,2}$ 4.7 Hz, H-2), 4.29 (1H, ddd, *J* 1.5, 3.7, 12.8 Hz, H-6A), 3.91 (3H, s, OMe), 3.85 (3H, s, OMe), 3.70 (1H, d, $J_{1a,11d}$ 3.3 Hz, H-1a), 3.50 (1H, d, $J_{11d,1a}$ 3.3 Hz, H-11d), 3.09 (1H, m, H-6B), 2.89 (1H, dd, $J_{3exo,3a}$ 4.3, $J_{3endo,3a}$ 9.5 Hz, H-3a), 2.85–2.92 (1H, m, H-7A), 2.67 (1H, m, H-7B), 2.22 (1H, dt, $J_{3exo,2}$ 4.3, $J_{3exo,3endo}$ 12.4 Hz, H-3$_{exo}$), 1.87 (1H, dd, $J_{3endo,3exo}$ 12.4, $J_{3endo,3a}$ 9.5 Hz, H-3$_{endo}$). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 171.8 (C_4), 148.4 and 148.1 (C_{10} and C_9), 126.2 (C_{11a}), 122.5 (C_{7a}), 111.6 (C_8), 108.6 (C_{11}), 87.5 (C_{11c}), 75.5 (C_2), 57.1 (C_{11b}), 55.9 and 55.9 (OMe×2), 50.5, 50.1 and 49.0 (C_{1a}, C_{3a}, and C_{11d}), 37.4 (C_6), 31.0 (C_3), 27.9 (C_7). Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.90; H, 6.02; N, 4.51.

3.20. (8a*R**,10*S**,11a*R**,12*R**,12a*S**)-2,3-Dimethoxy-11-methyl-8-oxo-5,8,8a,9,10,11,11a,12a-octahydro-10,12-epoxycyclopenta[4,5]pyrido[2,1-*a*]isoquinoline-11,12-diylacetate (21a), methyl (8a*S**,9*S**,10*S**,11a*R**,12*R**,12a*S**)-11,12-bis(acetoxy)-2,3-dimethoxy-11-methyl-8-oxo-5,6,8,8a,9,10,11,11a,12,12a-decahydro-10,12-epoxycyclopenta[4,5]pyrido[2,1-*a*]isoquinoline-9-carboxilate (21b). Typical procedure

$BF_3 \cdot OEt_2$ (0.38 mL, 3.0 mmol) was added to solution of 1.50 mmol of corresponding epoxyisoindoloisoquinoline (**19b**, **20b**) in 10 mL of acetic anhydride with ice cooling. The mixture was stirred for 1 h at 2–4 °C and then at room temperature for 4 h (monitoring by TLC). At the end of the reaction, the reaction mixture was diluted with water (60 mL), and saturated sodium hydrocarbonate solution was added to pH 9–10. Three 70 mL extractions with chloroform were performed. The organic layers were combined, washed with water (2×30 mL), and dried over $MgSO_4$. After solvent distillation, the residue was crystallized in ether (5 mL) to give compounds **21a**,**b** as white powder. The subsequent recrystallization from ethyl acetate gives the analytically pure sample. A single crystal of the compound **21a** for X-ray analysis was obtained by slow crystallization from the mixture methanol–DMF.

3.20.1. Compound **21a**

White prisms, yield 0.4 g (62%); mp 262–264 °C (decomp.); IR 1645 (NC=O), 1730 and 1754 (OC=O) cm^{-1}; EIMS (70 eV) *m/z* (rel intensity): M^+ 431 (2), 388 (16), 372 (40), 343 (14), 312 (100), 300 (13), 284 (65), 272 (24), 258 (21), 192 (36), 176 (20), 43 (24). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (1H, s, H-1), 6.60 (1H, s, H-4), 5.44 (1H, br s, H-12a), 4.86 (1H, br d, $J_{11,11a}$ 1.4 Hz, H-11), 4.59 (1H, ddd, $J_{6A,5B}$ 2.5, $J_{6A,5A}$ 7.0, $J_{6A,6B}$ 10.5 Hz, H-6A), 4.57 (1H, br t, $J_{9B,10}$=$J_{11,10}$=1.0 Hz, H-10), 3.99 (1H, dd, $J_{11,11a}$ 1.4, $J_{8a,11a}$ 4.6 Hz, H-11a), 3.89 (3H, s, OMe), 3.84 (3H, s, OMe), 2.99 (1H, ddd, $J_{8a,9B}$ 4.0, $J_{8a,11a}$ 4.5, $J_{8a,9A}$ 11.8 Hz, H-8a), 2.92 (2H, m, H-5), 2.63 (1H, m, H-6B), 2.20 (1H, ddd, *J* 0.8, $J_{8a,9A}$ 11.8, $J_{9A,9B}$ 13.5 Hz, H-9A), 2.17 (3H, s, OAc), 2.14 (3H, s, OAc), 1.48 (1H, ddd, $J_{9B,10}$ 0.8, $J_{8a,9B}$ 4.0, $J_{9A,9B}$ 13.5 Hz, H-9B). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 168.2, 169.3, 170.1 (C_8, CO_2Me×2), 147.1 and 148.3 (C_3 and C_2), 128.9 (C_{4a}), 123.7 (C_{12b}), 111.6 (C_4), 110.3 (C_1), 107.2 (C_{12}), 80.0 (C_{11}), 77.8 (C_{10}), 58.9 (C_{12a}), 55.8 and 56.1 (OMe–Ar×2), 41.6 (C_{11a}), 41.0 (C_6), 35.4 (C_{8a}), 33.9 (C_9), 28.3 (C_5), 21.1 and 22.2 (OCO*Me*×2). Anal. Calcd for $C_{22}H_{25}NO_8$: C, 61.25; H, 5.84; N, 3.25. Found: C, 61.44; H, 5.68; N, 3.51.

3.20.2. Compound **21b**

White prisms, yield 0.10 g (73%); mp 241–243 °C; IR 1659 (NC=O), 1745 (OC=O) cm^{-1}; EIMS (70 eV) *m/z* (rel intensity): M^+ 489 (1), 430 (15), 429 (45), 371 (100), 342 (50), 272 (41), 192 (37), 176 (22), 60 (24), 43 (41). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 (1H, s, H-1), 6.62 (1H, s, H-4), 5.44 (1H, br s, H-12a), 4.94 (1H, br s, H-11), 4.80 (1H, m, H-9), 4.78 (1H, s, H-10), 4.13 (1H, dd, $J_{11,11a}$ 1.2, $J_{8a,11a}$ 3.7 Hz, H-11a), 3.90 (3H, s, OMe), 3.87 (3H, s, OMe), 3.39 (3H, s, CO_2Me), 3.18–3.25 (3H, m, H-6 and H-8a), 2.87 (1H, m, H-5A), 2.54 (1H, m, H-5B), 2.19 (3H, s, OAc), 2.17 (3H, s, OAc). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 164.9, 167.5, 169.2, 170.0 (C_8, CO_2Me, OCOMe×2), 146.7 and 147.9 (C_3 and C_2), 128.8 (C_{4a}), 123.3 (C_{12b}), 111.5 (C_1), 109.9 (C_4), 107.3 (C_{12}), 81.7 (C_8), 76.4 (C_{10}), 59.9 (C_{12a}), 55.8 and 56.0 (OMe–Ar), 51.9 (CO_2*Me*), 46.4 (C_{11a}), 42.8 (C_9), 41.3 (C_6), 38.4 (C_{8a}), 27.4 (C_5), 21.0 and 22.2 (OCO*Me*×2). Anal. Calcd for $C_{24}H_{27}NO_{10}$: C, 58.89; H, 5.56; N, 2.86. Found: C, 58.70; H, 5.82; N, 2.99.

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Supplementary data

Supplementary data containing tables of atom coordinates, bond lengths and angles, anisotropic displacement parameters, and crystal packing for **21a** are provided. Crystal data are also given as a CIF file. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.02.024.

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