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Diastereoselective Photochemical Synthesis of 3,3'-Disubstituted Indolines

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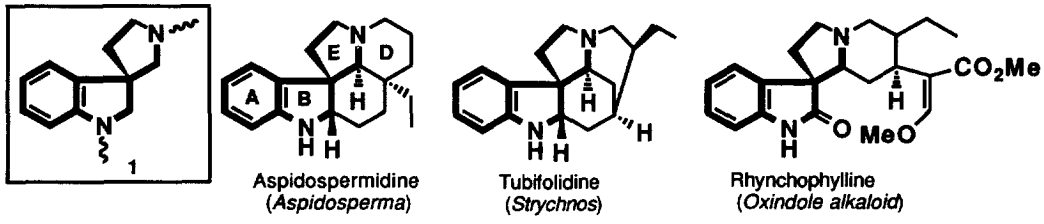
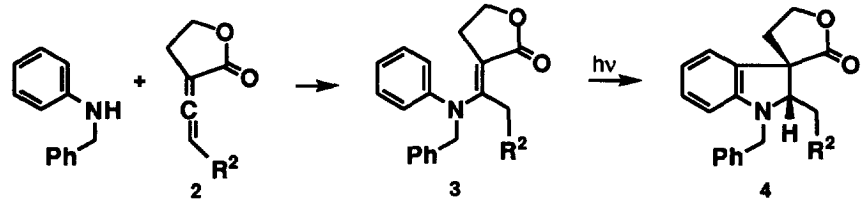
Abstract : Spiroindoline lactams **9** and imides **11** were efficiently and diastereoselectively prepared by photocyclization of *N*-arylenaminolactams **8** and esters **5** respectively. Imides **11** were conveniently transformed into the known indolines **13** and **14** which are key intermediates for the synthesis of (±)-vindorosine and *Aspidosperma* alkaloids. © 1997 Elsevier Science Ltd.

Great attention has been directed toward the synthesis of the spirocyclic structure **1**[1], a substructure commonly found in *Strychnos*, *Aspidosperma* and oxindole alkaloids (Scheme 1).



Scheme 1

We have recently reported[2] the efficient and diastereoselective synthesis of spiroindoline lactones **4** using, as a key step, the photochemical cyclization of *N*-protected enaminolactones **3**. These latter were prepared by condensation of *N*-benzylaniline with allenic lactones **2** (Scheme 2).



Scheme 2

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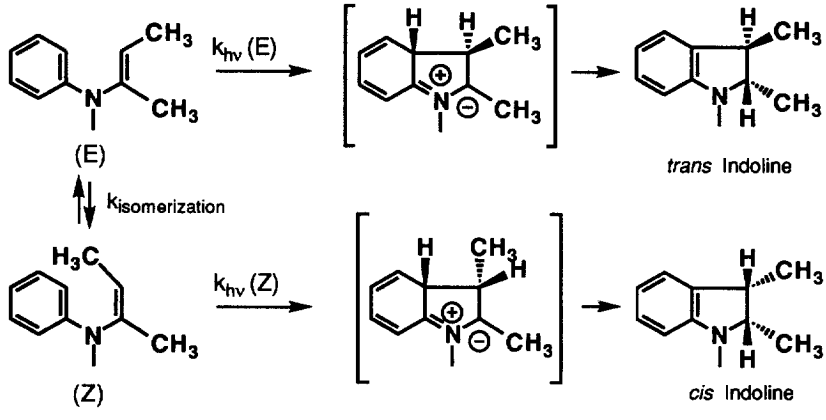
We wish to report in this article the application of our photochemical procedure to the preparation of nitrile esters **6** and **7** and of spiroindoline lactams **9** and **10** respectively from enaminoesters **5**[3,4] and enaminolactams **8**[3] in which R^2 is a protected alcohol or a protected ketone which could allow the subsequent formation of C ring of *Aspidosperma* or *Strychnos* alkaloids by intramolecular cyclization. We describe also the synthesis of spiroimides **11** and **12** from nitrile esters **6** and **7** together with their transformation into known key intermediates used for the synthesis of *Aspidosperma* alkaloids.

Synthesis of indoline esters 6 and 7

Photocyclization of arylenamines and arylenaminones is well documented.[5] Through a conrotatory process, it leads first to a zwitterion which, after suprafacial hydrogen [1,4] migration, gives stereospecifically and efficiently a *trans*-hexahydrocarbazole or a *trans*-hexahydrocarbazol-4-one.

When the same reaction is applied to the photocyclization of acyclic enamines, a mixture of *cis* and *trans* diastereoisomeric indolines is obtained, due to the photochemical *E/Z* isomerization of the double bond before the photocyclization step (Scheme 3).[6]



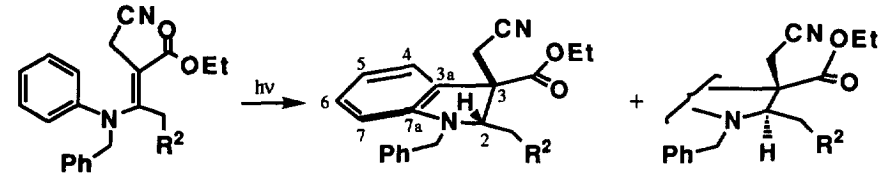
Scheme 3

Enaminoesters **5**[3] were irradiated, under nitrogen, in a pyrex immersion-well apparatus[7] with a 400-W medium pressure mercury lamp. The irradiation of **5a**[3] gave rapidly and with an excellent overall yield (Table 1), a *cis* [8] and *trans* indoline mixture (**6a** and **7a**) whose ratio was dependent on the solvent (Table 1) and which could be easily separated by flash chromatography (Scheme 4). We have already shown that the *cis/trans* ratio was solvent dependent[2] and that it was possible to control, to a certain extent, the stereochemistry of the photocyclization product by a carefull choice of the solvent.

Table 1: Irradiation of Enaminoester **5a**

Solvent	Time (h)	yield(%)	6a(%)	7a(%)
C_6H_6	0.75	80	35	55
C_6H_6/MeOH(1/1)	0.5	85	40	45
CH_3CN	0.5	90	60	30

Since indoline **6a** (*cis* C-2, C-3 relationship as observed in the natural series), was the major product obtained when the reaction was performed in acetonitrile, the irradiation of **5b**[3] and **5c**[3] was conducted in this solvent. Photocyclization of **5b** led after 40 minutes to **6b** and **7b** in a 90% yield and in a 2.6/1 ratio as deduced from ^{1}H NMR spectrum of the crude reaction mixture. In a same way, photocyclization of **5c**[4] afforded efficiently **6c** and **7c** in a 93% overall yield and in a 2/3 ratio. In this case, the *trans* isomer was the major product. The same result was observed when the reaction was conducted in other solvent such as C_6H_6 or C_6H_6/MeOH (1/1) (Scheme 4).



Scheme 4

The structure of **6** and **7** was established by using a combination of ^{1}H, ^{13}C and 2-D ^{1}H-^{1}H NMR correlation. The stereochemistry at C-2 and C-3 was unambiguously determined from n.O.e. data (Figure 1). Furthermore, the ^{1}H and ^{13}C-NMR spectra of **6** and **7** showed characteristic data in relation to their respective stereochemistry. In particular, H-2 proton consistently appeared at lower field in the *trans*- compared to the *cis*-series and the two CH_2CN diastereotopic protons resonated as an AB system at lower field and with a smaller $\Delta\nu$ in the *cis*-series (Table 2). In the ^{13}C NMR spectrum, carbon atoms C-3, $\underline{C}H_2CN$ and $\underline{C}H_2$C-2 were deshielded and the $N\underline{C}H_2$Ph were shielded in the *cis*-series (Table 3).

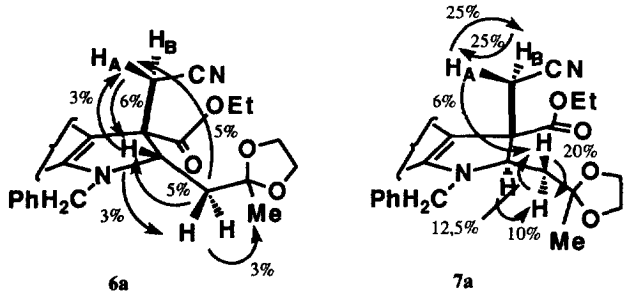


Figure 1. Selected n.O.e. for **6a** and **7a**

Table 2. Characteristic ^1H NMR Data for Isomers **6** and **7**.

	6a	**6b**	**6c**	**7a**	**7b**	**7c**
δH-2(ppm)	4.05 (dd)	4.03 (dd)	3.86 (t)	4.47 (dd)	4.49 (dd)	4.30-4.51 (m)
δCH_2CN (ppm)	3.37 (AB)	3.24 (AB)	2.90 (AB)	3.00 (AB)	3.25 (AB)	3.08 (AB)
$\Delta\nu$ CH_2CN	22.8 Hz	23.5 Hz	61 Hz	123.1 Hz	114.6 Hz	97.5 Hz

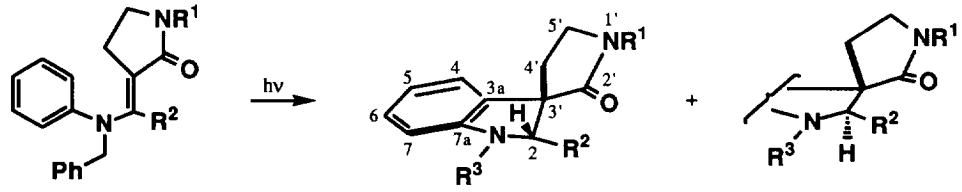
Table 3. Characteristic ^{13}C NMR Data for Isomers **6** and **7**.

δ(ppm)	**6a**	**6b**	**6c**	**7a**	**7b**	**7c**
C-2	61.6	67.0	69.1	61.9	66.3	69.7
C-3	56.6	56.3	56.1	55.3	55.3	55.8
$\underline{C}H_2CN$	23.6	23.6	26.0	22.5	22.5	22.2
$\underline{C}H_2C$-2	38.5	42.6	30.5	36.7	41.8	28.2
$N\underline{C}H_2Ph$	50.4	50.3	51.3	51.8	51.8	51.7

Synthesis of spiroindoline lactams 9 and 10

Similarly to enaminoesters **5**, enaminolactams **8**[3] were irradiated in dry acetonitrile in a pyrex immersion-well apparatus using a 400W-medium pressure mercury lamp. Irradiation of **8a**[3] led, after 30 minutes, to a mixture of debenzylated spiroindolines **9a** and **10a** in a 68% overall yield and in a 2.4/1 ratio (^1H NMR) (Scheme 5).

The two indolines were separated by flash chromatography. In the same conditions, photocyclization of **8b**[3] led exclusively to the spirocompound **9b** (62% yield) and irradiation of **8c**[3] gave, after 30 minutes, a mixture of spiroindolines lactams **9c** and **10c** (65% yield and 3.3/1 ratio).



8a $R^1 = n$-Bu; $R^2 = CH_2OCH_2Ph$
8b $R^1 = CH_2Ph$; $R^2 = CH_2OCH_2Ph$
8c $R^1 = CH_2Ph$; $R^2 = CH{=}CH_2$

9a $R^1 = n$-Bu; $R^3 = H$; $R^2 = CH_2OCH_2Ph$
9b $R^1 = R^3 = CH_2Ph$; $R^2 = CH_2OCH_2Ph$
9c $R^1 = R^3 = CH_2Ph$; $R^2 = CH{=}CH_2$

10a $R^1 = n$-Bu; $R^3 = H$; $R^2 = CH_2OCH_2Ph$
10c $R^1 = R^3 = CH_2Ph$; $R^2 = CH{=}CH_2$

Scheme 5

The structures of **9** and **10** were assigned on the basis of ^1H, ^{13}C and ^1H-^1H NMR spectra. The stereochemistry of spiroindolines **9a** and **10a** was determined by n.O.e. data (Figure 2).

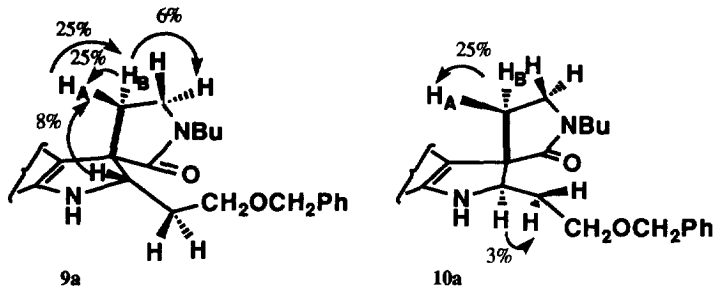


Figure 2 : Selected n.O.e. data for **9a** and **10a**

As observed for indolines **6** and **7**, the chemical shifts of H-2, C-4', C-2, and C-2-CH and the Δν values of the two H-4' were in good agreement with the proposed *cis* and *trans* stereochemistry of spiroindolines **9** and **10**. In the *trans*-series, the hydrogen H-2 was deshielded and the Δν of the H-4' hydrogens was larger. In the *cis*-series, the carbon atoms C-2, C-4' and C-2-CH were deshielded (Tables 4 and 5).

Table 4. Characteristic ^{1}H NMR Data for Isomers **9** and **10**.

	9a	**9b**	**9c**	**10a**	**10c**
δH-2 (ppm)	3.85-3.90 (m)	2.22 (dd)	3.93 (d)	3.75-3.88 (m)	4.50 (d)
Δν H-4'(ppm)	0.1	0.02	0.2	0.5	0.5

Table 5. Characteristic ^{13}C NMR Data for Isomers **9** and **10**.

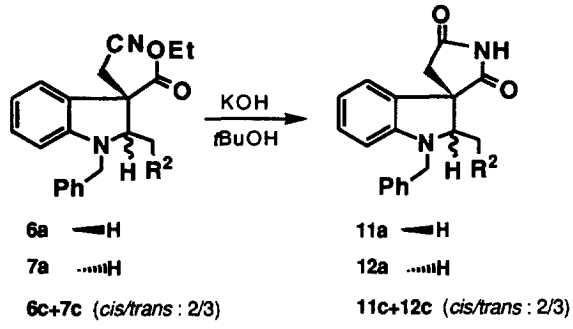
δ(ppm)	**9a**	**9c**	**10a**	**10c**
C-2	66.9	77.7	63.8	73.6
C-4'	30.8	32.1	29.7	29.0
C-2-CH	33.1	138.3	30.8	134.9

In the case of **8a** N_a-debenzylation was observed. We have previously demonstrated that loss of benzyl group occured after photocyclization in the case of enaminolactones.[2] This deprotection could be explained by the formation of an iminium ion and subsequent loss of benzaldehyde. All attempts to trap this postulated intermediate with trimethylsilylcyanide[9] known to afford α-aminonitrile failed, probably because of the short life time or the steric crowding of the iminium ion.

Synthesis of spiroimides 11 and 12 : Access to Speckamp and Hiemstra intermediates 13[1n] and 14[1m]

Spiroindoline imides **11** and **12** were quantitatively prepared by treatment of indoline esters **6** and **7** in basic medium.[10] Hydrolysis of the nitrile function led to an amide which spontaneously cyclized on the ester function (Scheme 6). When the reaction was conducted on the 2/3 mixture of **6c** and **7c**, diastereoisomers **11c**

and **12c** were obtained in the same ratio. Compounds **11c** and **12c** could not be efficiently separated and only **12c** was isolated in pure form.

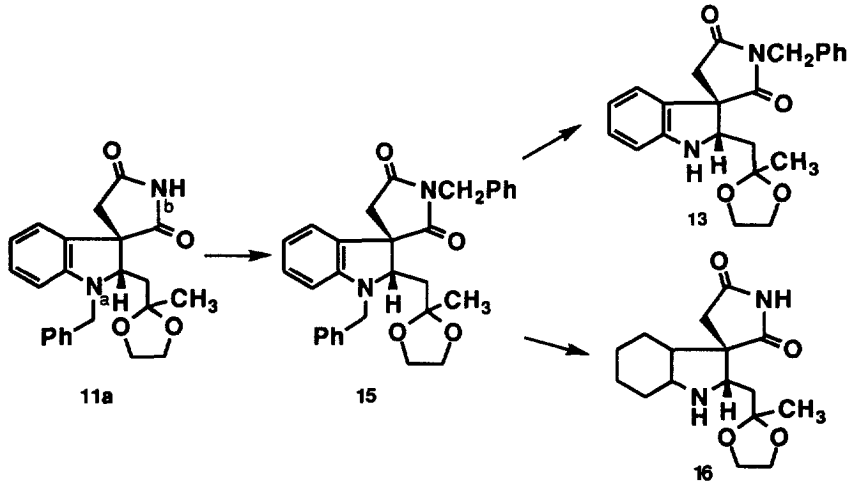


Scheme 6

Spiroindoline imides **11a,c** could be considered as direct precursors of the Speckamp and Hiemstra intermediates **13**[1n] and **14**[1m].

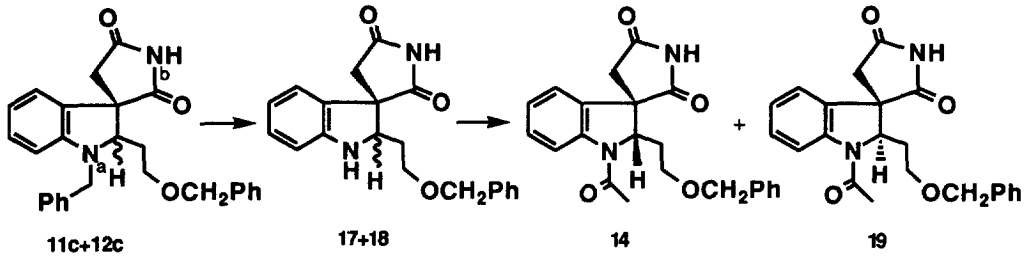
Spiroimide **11a** was easily transformed, in two steps, into **13** by benzylation of the imide function followed by regiospecific N_a-deprotection of the indoline benzyl group.

Imide **15** was prepared by treatment of **11a** with benzylic alcohol, DEAD and PPh_3 in anhydrous THF using the Mitsunobu procedure with 83% yield. Hydrogenolysis of **15** in a Parr apparatus under 3 atm in the presence of PtO_2 or Rh/Al_2O_3 in dry methanol or ethanol only yielded unreacted starting material. However, use of Pd/C or $Pd(OH)_2$[11] as catalyst under the same conditions afforded indoline **16** in 61% and 68% yield respectively (Scheme 7). Interestingly, when a solution of **15** in dry methanol was treated under argon with ammonium formate[12] and Pd/C as catalyst, indoline **13**[1n] was quantitatively isolated (Scheme 7).



Scheme 7

Imide **14**[1m] was synthesized by N_a-debenzylation then acylation of **11c**. Debenzylation of the 2/3 mixture of spiroindolines **11c** and **12c** in anhydrous methanol with ammonium formate and Pd/C as catalyst furnished quantitatively the mixture of indolines **17** and **18** which were directly and quantitatively acetylated (acetic anhydride in dry methylene chloride). The two obtained spiroindoline imides **14** and **19** were cleanly separated by flash chromatography on silica gel. The key intermediate **14**[1m] was obtained in 36% yield whereas its epimer **19** was isolated with a 58% yield (Scheme 8).



Scheme 8

The five spiroindoline imides **13**, **14**, **15**, **16** and **19** were fully characterized by their NMR spectroscopic data (see experimental part). Moreover, the spectroscopic data of indoline **14** were in good agreement with those reported in the literature.[1m] In particular, each of the two H-4' appeared as a doublet at δ 2.72 and 3.30 (J = 18 Hz) for **14** whilst they appeared as an AB system centered at δ 3.10 ppm for isomer **19**. The H-2 proton was detected as a doublet of doublet at δ 4.77 for **14** and as a multiplet at δ 4.80-5.00 for **19**. The singlet corresponding of the two protons of the OCH_2Ph group was observed at δ 4.77 in the case of **14** and δ 4.42 for its isomer **19**.

Conclusion

The results presented here describe an efficient and diastereoselective synthesis of numerous *cis* and *trans* 3,3'-disubstituted indoline esters, lactams and imides by photochemical cyclization of enaminoesters and lactams. The spiroindoline imides **11a** and **11c** were converted in two steps and 80% and 36% yields respectively into the known intermediates **13** and **14** that have been shown to be very useful for the synthesis of *Aspidosperma* alkaloids. Further work in this area is currently underway and will be described in due course.

EXPERIMENTAL

General. ^1H and ^{13}C NMR spectra were recorded on a *Bruker* AC 400 (400 and 100 MHz respectively) spectrometer in $CDCl_3$. All chemical shifts are reported in parts per million and are referenced against internal tetramethylsilane. Coupling constant (J) are given in Hz. The high resolution mass spectra (HRMS) were carried out at the Service Central d'Analyse of Vernaison (France) and the relative peak intensities are given as a percentage of the base peak. EIMS and microanalyses were performed at the Service Central d'Analyse of Vernaison (France). IR spectra were recorded on a *Perkin Elmer 815* spectrophotometer in CCl_4 or $CHCl_3$

solution. Column chromatography was carried out on 200-400 mesh Silica Gel 60 (*Merck*). Melting points (mp) were taken on a *Reichert* hot stage microscope and are uncorrected.

Typical procedure for the photocyclization step
A solution of enaminoesters or enaminolactams in dry solvent was irradiated under nitrogen in a pyrex immersion-well apparatus[7] with a 400-W medium pressure mercury lamp. After removal of the solvent the residue was purified by flash chromatography using a mixture of AcOEt-Hexane as eluent.

Photocyclization of 5a
Photocyclization of **6a** (1.90 mmol in 200 ml of solvent : see Table 1) gave **6a** and **7a**.
***cis-N*-benzyl-3-carboethoxy-3-cyanomethyl-2-(2,2-ethylenedioxy)propyl-2,3-dihydroindole 6a** : m.p. : 101-102°C (ether). **IR** (CCl_4) ν_{max} : 2250, 1730 cm^{-1}. **^1H NMR** : δ = 1.28 (t, 3H, J = 7 Hz, $CH_2\underline{CH_3}$); 1.30 (s, 3H,$C\underline{H_3}$); 2.23 (dd, 1H, ABX system, B part, J_{BX} = 6 Hz, J_{AB} = 15 Hz); 2.30 (dd, 1H, ABX system, A part, J_{AX} = 3 Hz, J_{AB} = 15 Hz); 3.27 (2H, AB system, J = 17 Hz, $\Delta\nu$ = 22.8 Hz , $C\underline{H_2}CN$); 3.85-4.00 (m, 4H, O-$C\underline{H_2}C\underline{H_2}$-O); 4.05 (dd, 1H, ABX system, X part, J_{AX} = 3 Hz, J_{BX} = 6 Hz, H-2); 4.10-4.20 (q, 1H, J = 7 Hz, $C\underline{H_2}CH_3$); 4.20-4.30 (m, 1H, O-$C\underline{H_2}$); 4.45 (2H, AB system, J = 17 Hz, $\Delta\nu$ = 163.6 Hz, $NC\underline{H_2}Ph$); 6.32 (d, 1H, J = 8 Hz, H-7); 6.72 (t, 1H, J = 7,5 Hz, H-5); 7.08-7.01 (m, 2H, H-6 and H-4); 7.20-7.40 (m, 5H, Aromatic). **^{13}C NMR** : δ = 14.0 ($CH_2\underline{C}H_3$); 23.6 ($\underline{C}H_2CN$), 24.1 ($\underline{C}H_3$), 38.5 ($\underline{C}H_2C$-2), 50.4 (N-$\underline{C}H_2Ph$), 56.6 (C-3), 61.6 (C-2), 64.5 (O-$\underline{C}H_2\underline{C}H_2$-O), 67.3 ($\underline{C}H_2CH_3$), 108.3 (C-acetal), 108.5 (C-7), 117.8 (CN), 118.3 (C-5), 122.5 (C-4), 126.7, 126.8, 127.5 (C-3a), 128.5, 129.8 (C-6), 139.0 (C-*ipso*), 152.3 (C-7a), 171.0 ($\underline{C}O_2Et$). **Anal.** calc. for $C_{23}H_{28}NO_4$: C, 71.41; H, 6.71; N, 6.66. Found C, 70.96; H, 6.44; N, 6.17.

***trans-N*-benzyl-3-carboethoxy-3-cyanomethyl-2-(2,2-ethylenedioxy)propyl-2,3-dihydroindole 7a** : m.p. : 172-173 °C (AcOEt). **IR** (CCl_4) ν_{max} : 2255, 1730 cm^{-1} .**^1H NMR** : δ = 1.27 (s, 3H,$C\underline{H_3}$); 1.32 (t, 3H, J = 7 Hz, $CH_2\underline{CH_3}$); 2.20 (dd, 1H, ABX system, B part, J_{BX} = 10.5 Hz, J_{AB} = 15 Hz); 2.30 (dd, 1H, ABX system, A part, J_{AX} = 2.25 Hz, J_{AB}= 15 Hz); 3.00 (2H, AB system, J = 16 Hz, $\Delta\nu$ = 123.1 Hz, $C\underline{H_2}CN$); 3.80-3.95 (m, 4H, O-$C\underline{H_2}$-$C\underline{H_2}$-O); 4.42 (2H, AB system, J = 17 Hz, $\Delta\nu$ = 104.4 Hz, N-$C\underline{H_2}Ph$); 4.28 (q, 2H, J = 7 Hz, $C\underline{H_2}CH_3$); 4.47 (dd, 1H, ABX system, X part, J_{AX} = 2.25 Hz, J_{BX} = 10.5 Hz, H-2); 6.42 (d, 1H, J = 7.5 Hz, H-7); 6.75 (t, 1H, J = 7.5 Hz, H-5); 7.12 (t, 1H, J = 7.5 Hz, H-6); 7.17 (d, 1H, J = 7.5 Hz, H-4); 7.25-7.40 (m, 5H, Aromatic). **^{13}C NMR** : δ = 14.2 ($CH_2\underline{C}H_3$), 22.5 ($\underline{C}H_2CN$), 23.9 ($\underline{C}H_3$), 36.7 ($\underline{C}H_2$-C-2), 51.8 (N-$\underline{C}H_2Ph$), 55.3 (C-3), 61.9 (C-2), 64.0 (O-$\underline{C}H_2CH_2$-O), 64.5 (O-$CH_2\underline{C}H_2$-O), 66.5 ($\underline{C}H_2CH_3$), 108.3 (C-acetal), 108.9 (C-7), 118.1 (CN), 119.0 (C-5), 123.2 (C-4), 126.9, 127.1, 128.7, 129.0 (C-3a), 130.0 (C-6), 138.7 (C-*ipso*), 151.2 (C-7a), 171.7 ($\underline{C}O_2Et$). **Anal.** calc. for $C_{23}H_{28}NO_4$: C, 71.41; H, 6.71; N, 6.66. Found C, 71.03; H, 6.83; N, 6.56.

Photocyclization of 5b. It was carried out in CH_3CN (150 ml) from **5b** (1.04 mmol) and gave a mixture of **6b** and **7b** in 90% yield in a 2.6/1 ratio.
***cis-N*-benzyl-3-carboethoxy-3-cyanomethyl-2-(2,2-ethylenedioxy-3-carboethoxy)propyl-2,3-dihydroindole 6b** : m.p. : 116-117°C (ether). **IR** ($CHCl_3$) ν_{max} : 1730 cm^{-1}. **^1H NMR** : δ = 1.26 (t, 3H, J = 7 Hz, $CH_2\underline{CH_3}$); 2.50 (dd, 1H, ABX system, B part, J_{BX} = 5.5 Hz, J_{AB} = 16.5 Hz); 2.56 (dd, 1H, ABX system, A part, J_{AX} = 3 Hz, J_{AB} = 16,5 Hz); 2.62 (s, 2H, $C\underline{H_2}$-CO_2CH_3); 3.24 (2H, AB system, J = 16.5 Hz, $\Delta\nu$ = 23.5 Hz, $C\underline{H_2}CN$); 3.62 (s, 3H, O-$C\underline{H_3}$); 3.86-4.33 (m, 6H, O-$C\underline{H_2}$-$C\underline{H_2}$-O et $C\underline{H_2}CH_3$); 4.03 (dd, 1H, ABX system, X part, J_{BX} = 5.5 Hz, J_{AX} = 3 Hz, H-2); 4.45 (2H, AB system, J = 17 Hz, $\Delta\nu$ = 163.1 Hz, N-$C\underline{H_2}Ph$); 6.33 (d, 1H, J = 8 Hz, H-7); 6.72 (t, 1H, J = 7.5 Hz, H-5); 7.06 (d, 1H, J = 7.5 Hz, H-4); 7.08 (t, 1H, J = 7.5 Hz, H-6); 7.20-7.40 (m, 5H, Aromatic). **^{13}C NMR** : δ = 14.1 ($CH_2\underline{C}H_3$), 23.6 ($\underline{C}H_2CN$), 36.8 ($\underline{C}H_2$-CO_2CH_3), 42.6 ($\underline{C}H_2$-C-2), 50.3 (NCH_2Ph), 51.8 (O-$\underline{C}H_3$); 56,7 (C-3), 61.8 ($\underline{C}H_2CH_3$), 65.0 and 65.2 (O-$\underline{C}H_2\underline{C}H_2$-O), 67.0 (C-2), 107.8 (C-acetal), 108.5 (C-7); 117,9 (CN), 118.4 (C-5), 122.6 (C-4), 126.7, 126.8, 128.5, 127.4 (C-3a), 129.9 (C-6), 139.1 (C-*ipso*), 152,4 (C-7a), 169.4 ($\underline{C}O_2Et$), 171.0 ($\underline{C}O_2CH_3$). **MS** (EI): *m/z* = 479 (M+1, 4), 478 (M^+, 15), 392 (4), 320 (3), 319 (15), 246 (3), 220 (15), 146 (7), 145 (100), 115 (2), 103 (18), 92 (6), 91 (78). **HRMS** for $C_{27}H_{30}N_2O_6$: M^+ , calc. 478.2100; found 478.2103.

***trans-N*-benzyl-3-carboethoxy-3-cyanomethyl-2-(2,2-ethylenedioxy-3-carboethoxy)propyl-2,3-dihydroindole 7b** : m.p. : 238-239°C (ether). **IR** ($CHCl_3$) ν_{max} : 1730 cm^{-1}. **^1H NMR** : δ = 1.32 (t, 3H, J = 7 Hz, $CH_2\underline{CH_3}$); 2.45-2.56 (m, 2H, $C\underline{H_2}$-C-2); 2.65 (2H, AB system, J = 14.5 Hz, $\Delta\nu$ = 17.5 Hz, $C\underline{H_2}$-CO_2CH_3); 3.05 (2H, AB system, J = 16.5 Hz, $\Delta\nu$ = 114.6 Hz, $C\underline{H_2}CN$); 3.67 (s, 3H, O-$C\underline{H_3}$); 3.84-3.98 (m, 4H, O-$C\underline{H_2}$-$C\underline{H_2}$-O); 4.21-4.34 (m, 2H, $C\underline{H_2}CH_3$); 4.39 (2H, AB system, J = 17 Hz, $\Delta\nu$ = 110.5

Hz, N-C$\underline{H}_2$Ph); 4.49 (dd, 1H, ABX system, X part, J = 4 Hz, J = 9 Hz, H-2); 6.43 (d, 1H, J = 8 Hz, H-7); 6.76 (t, 1H, J = 7.5 Hz, H-5); 7.12 (t, 1H, J = 8 Hz, H-6); 7.16 (d, 1H, J = 7.5 Hz, H-4); 7.23-7.40 (m, 5H, Aromatic). **^{13}C NMR** δ = 14.2 (CH$_2\underline{C}$H$_3$), 22.5 ($\underline{C}$H$_2$CN), 34.6 ($\underline{C}$H$_2$CO$_2$CH$_3$), 41.8 ($\underline{C}$H$_2$C-2), 51.8 (NCH$_2$Ph), 51.9 (OCH$_3$), 55.3 (C-3), 62.0 ($\underline{C}$H$_2$CH$_3$), 64.5 and 65.9 (O-$\underline{C}$H$_2\underline{C}$H$_2$-O), 66.3 (C-2), 107.6 (C-acetal), 108.9 (C-7), 118.1 (CN), 119.0 (C-5), 123.2 (C-4), 126.9, 127.0, 128.6, 128.9 (C-3a), 130.0 (C-6), 138.8 (C-*ipso*), 151.1 (C-7a), 169.5 ($\underline{C}$O$_2$Et), 171.6 ($\underline{C}$O$_2$CH$_3$). **MS** (EI): *m/z* = 479 (M+1, 5), 478 (M$^+$, 18), 433 (2), 392 (5), 376 (2), 360 (2), 343 (3), 333 (3), 320 (3), 319 (15), 246 (3), 220 (12), 146 (7), 145 (100), 130 (2), 103 (19), 92 (5), 91 (70). **HRMS** for C$_{27}$H$_{30}$N$_2$O$_6$: M$^+$, calc. 478.2100; found 478.2103.

Photocyclization of 5c. It was carried out in CH$_3$CN (150 ml) from **5c** (1.04 mmol) and gave 93% of a mixture of **6c** and **7c** in a 2/3 ratio.

***cis-N*-benzyl-3-carboethoxy-3-cyanomethyl-2-(2-benzyloxy)ethyl-2,3-dihydroindole 6c** : Oil; **IR** (CHCl$_3$) ν_{max} : 2255, 1730 cm^{-1}. **^{1}H NMR** : δ = 1.20 (t, 3H, J = 8 Hz, CH$_2\underline{C}$H$_3$); 2.00-2.07 (m, 2H, $\underline{C}$H$_2$CH$_2$OCH$_2$Ph); 2.90 (2H, AB system, J = 16.8 Hz, Δν = 61 Hz, $\underline{C}$H$_2$CN); 3.46 (t, 2H, J = 6 Hz, CH$_2\underline{C}$H$_2$OCH$_2$Ph); 3.86 (t, 1H, J = 6.2 Hz, H-2); 4.08-4.50 (m, 4H, N-C$\underline{H}_2$Ph and C$\underline{H}_2$CH$_3$); 4.40 (s, 2H, O-C$\underline{H}_2$Ph); 6.41 (d, 1H, J = 8 Hz, H-7); 6.71 (t, 1H, J = 8 Hz, H-5); 7.10 (t, 1H, J = 8 Hz, H-6); 7.23-7.33 (m, 11H, Aromatic and H-4). **^{13}C NMR** δ = 14.1 (CH$_3$), 26.0 ($\underline{C}$H$_2$CN), 30.5 ($\underline{C}$H$_2$CH$_2$OCH$_2$Ph); 51.3 (N-CH$_2$Ph), 56.5 (C-3), 61.8 ($\underline{C}$H$_2$CH$_3$), 66.6 (CH$_2\underline{C}$H$_2$OCH$_2$Ph), 69.1 (C-2), 73.1 (OCH$_2$Ph), 108.2 (C-7), 117.4 (CN), 118.4 (C-5), 123.6 (C-4), 125.3 (C-3a), 126.8, 127.0, 127.2, 127.9, 128.4, 128.6, 139.3 (C-*ipso*), 139.8 (C-*ipso*), 151.6 (C-7a), 170.9 ($\underline{C}$O$_2$Et).

***trans-N*-benzyl-3-carboethoxy-3-cyanomethyl-2-(2-benzyloxy)ethyl-2,3-dihydroindole 7c** : Oil ; **IR** (CHCl$_3$) ν_{max} : 2255, 1730 cm^{-1}. **^{1}H NMR** : δ = 1.21 (t, 3H, J = 8 Hz, CH$_2\underline{C}$H$_3$); 2.00-2.10 (m, 2H, $\underline{C}$H$_2$CH$_2$OCH$_2$Ph); 3.08 (2H, AB system, J = 16.4 Hz, Δν = 97.5 Hz, $\underline{C}$H$_2$CN); 3.46-3.51 (m, 1H, CH$_2\underline{C}$H$_2$OCH$_2$Ph); 3.55-3.61 (m, 1H, CH$_2\underline{C}$H$_2$OCH$_2$Ph); 3.98-4.05 (m, 1H, CH$_2\underline{C}$H$_3$); 4.19-4.29 (m, 1H, CH$_2\underline{C}$H$_3$); 4.30-4.51 (m, 5H, NCH$_2$Ph, OCH$_2$Ph, H-2); 6.48 (d, 1H, J = 8 Hz, H-7); 6.79 (t, 1H, J = 8 Hz, H-5); 7.12 (t, 1H, J = 8 Hz, H-6); 7.20-7.40 (m, 11H, Aromatic and H-4). **^{13}C NMR** : δ = 14.1 (CH$_3$), 22.2 ($\underline{C}$H$_2$CN), 28.2 ($\underline{C}$H$_2$CH$_2$OCH$_2$Ph), 51.7 (NCH$_2$Ph), 55.8 (C-3), 62.1 ($\underline{C}$H$_2$CH$_3$), 67.6 (CH$_2\underline{C}$H$_2$OCH$_2$Ph), 69.7 (C-2), 73.1 (OCH$_2$Ph), 108.8 (C-7), 118.2 (CN), 119.1 (C-5), 123.5 (C-4), 125.8 (C-3a), 138.6 (C-*ipso*), 139.4 (C-*ipso*), 152.3 (C-7a), 170.7 ($\underline{C}$O$_2$Et).

Photocyclization of 8a. It was carried out in CH$_3$CN (150 ml) from **8a** (1.04 mmol) and gave a mixture of **9a** and **10a** in 68% yield in a 2.4/1 ratio.

***cis-N'*-butyl-2-(2-benzyloxy)ethylspiro-[3,3'-(2,3-dihydroindole)pyrrolidin-2'-one] 9a** : Oil ; . **IR** (CCl$_4$) ν_{max} : 3375, 1690 cm^{-1}. **^{1}H NMR** : δ = 0.95 (t, 3H, J = 7.5 Hz, C$\underline{H}_3$); 1.32 (st, 2H, J = 7.5 Hz, C$\underline{H}_2$CH$_3$); 1.50 (qt, 2H, J = 7.5 Hz, C$\underline{H}_2$CH$_2$CH$_3$); 1.75-1.85 (m, 1H, C$\underline{H}_2$CH$_2$-OCH$_2$Ph); 2.10-2.25 (m, 2H, C$\underline{H}_2$CH$_2$OCH$_2$Ph and H-4'); 2.35-2.45 (m, 1H, H-4'); 3.25-3.35 (m, 2H, NC$\underline{H}_2$CH$_2$CH$_3$)*; 3.37-3.50 (m, 2H, H-5')*; 3.62 (t, 2H, J = 7.5 Hz, CH$_2\underline{C}$H$_2$OCH$_2$Ph); 3.85-3.90 (m, 1H, H-2); 4.53 (2H, AB system, J = 12.5 Hz, Δν = 19 Hz, O-C$\underline{H}_2$Ph); 6.62 (d, 1H, J = 8 Hz, H-7); 6.72 (t, 1H, J = 8 Hz, H-5); 6.98 (d, 1H, J = 8 Hz, H-4); 7.07 (t, 1H, J = 8 Hz, H-6); 7.25-7.40 (m, 5H, Aromatic). **^{13}C NMR** : δ = 13.8 ($\underline{C}$H$_3$), 20.1 ($\underline{C}$H$_2$CH$_3$), 29.4 ($\underline{C}$H$_2$CH$_2$CH$_3$), 30.8 (C-4'), 33.1 ($\underline{C}$H$_2$-CH$_2$OCH$_2$Ph), 42.6 (C-5')*, 43.4 (N-$\underline{C}$H$_2$)*, 57.2 (C-3'), 66.9 (C-2), 67.1 (CH$_2\underline{C}$H$_2$OCH$_2$Ph), 73.0 (O-$\underline{C}$H$_2$Ph), 110.2 (C-7), 119.2 (C-5), 122.9 (C-4), 128.9 (C-6), 128.3, 128.5, 129.1, 132.4 (C-3a), 138.2 (C-*ipso*), 150.7 (C-7a), 173.3 (C-2'). **MS** (EI) : *m/z* = 379 (M+1, 13), 378 (M$^+$; 46), 33 (2), 315 (3), 300 (2), 287 (6), 272 (11), 270 (16), 257 (6), 244 (18), 243 (100), 229 (4), 213 (5), 199 (6), 186 (5), 170 (17), 156 (26), 156 (10), 144 (96), 130 (39), 117 (11), 103 (5), 91 (99). **HRMS** for C$_{24}$H$_{30}$N$_2$O$_2$: M$^+$, calc. 378.2307; found 378.2310.

***trans-N'*-butyl-2-(2-benzyloxy)ethylspiro-[3,3'-(2,3-dihydroindole)pyrrolidin-2'-one] 10a** : Oil, **IR** (CCl$_4$) ν_{max} : 3400, 1690 cm^{-1}. **^{1}H NMR** : δ = 1.00 (t, 3H, J = 7.5 Hz, C$\underline{H}_3$); 1.30-1.40 (m, 2H, C$\underline{H}_2$CH$_3$); 1.50-1.60 (qt, 2H, J = 7.5 Hz, C$\underline{H}_2$CH$_2$CH$_3$); 1.70-1.85 (m, 2H, C$\underline{H}_2$CH$_2$O-CH$_2$Ph et H-4'); 1.90-2.00 (m, 1H, C$\underline{H}_2$CH$_2$OCH$_2$Ph); 2.35-2.45 (m, 1H, H-4'); 3.15-3.30 (m, 2H, NC$\underline{H}_2$CH$_2$CH$_3$); 3.40-3.50 (m, 2H, H-5'); 3.55-3.65 (m, 2H, CH$_2\underline{C}$H$_2$OCH$_2$Ph); 4.22 (dd, J = 3 Hz and J = 9.5 Hz, 1H, H-2); 4;55 (s, 2H, OC$\underline{H}_2$Ph); 6.62 (d, 1H, J = 8 Hz, H-7); 6.70 (t, 1H, J = 8 Hz, H-5); 6.98 (d, 1H, J = 8 Hz, H-4); 7.03 (t, 1H, J = 8 Hz, H-6); 7.25-7.40 (m, 5H, Aromatic). **^{13}C NMR** : δ = 13.9 (CH$_3$), 20.3 ($\underline{C}$H$_2$CH$_3$), 28.0 ($\underline{C}$H$_2$CH$_2$CH$_3$), 29.7 (C-4'), 30.8 ($\underline{C}$H$_2$CH$_2$OCH$_2$Ph), 42.8 (C-5')*, 44.3 (N-$\underline{C}$H$_2$)*, 55.5 (C-3), 63.8

(C-2), 69.1 ($CH_2\underline{C}H_2OCH_2Ph$), 73.2 ($O\underline{C}H_2Ph$), 109.9 (C-7), 119.2 (C-5), 122.3 (C-4), 127.7 (C-6), 127.8, 128.4, 128.5, 133.1 (C-3a), 138.2 (C-*ipso*), 149.8 (C-7a), 175.0 (C-2').
* interchangeable attribution.

Photocyclization of 8b. It was carried out in CH_3CN (150 ml) from **8b** (1.04 mmol) and gave **9b** in 62% yield.
***cis*-*N*,*N'*-dibenzyl-2-(2-benzyloxy)ethylspiro-[3,3'-(2,3-dihydroindole)pyrrolidin-2'-one] 9b:** Oil; **IR** (CCl_4) ν_{max} : 1695 cm^{-1}. **^{1}H NMR** : δ = 1.50-1.88 (m, 1H, H-4'); 1.90-2.05 (m, 1H, H-4'); 2.38-2.50 (m, 1H, H-5'); 2.50-2.60 (m, 2H, H-5'); 3.00-3.10 (m 1H, $C\underline{H}_2CH_2OCH_2Ph$); 3.15-3.40 (m, 2H, $C\underline{H}_2CH_2OCH_2Ph$ and $CH_2C\underline{H}_2OCH_2Ph$); 3.62-3.75 (m, 1H, $CH_2C\underline{H}_2OCH_2Ph$); 3.75-3.88 (m, 1H, H-2); 4.42 (2H, AB system, J = 17 Hz, Δν = 40 Hz, $NC\underline{H}_2Ph$)*; 4.50 (s, 2H, $OC\underline{H}_2Ph$)*; 4.52 (2H, AB system, J = 17 Hz, Δν = 125.8 Hz, $NC\underline{H}_2Ph$)*; 6.60 (d, 1H, J = 8 Hz, H-7); 6.65 (t, 1H, J = 8 Hz, H-5); 6.75 (d, 1H, J = 8 Hz, H-4); 7.02 (t, 1H, J = 8 Hz, H-6); 7.20-7.40 (m, 15H, Aromatic).
* interchangeable attribution.

Photocyclization of 8c. It was carried out in CH_3CN (150 ml) from **8c** (1.04 mmol) and gave a mixture of **9c** and **10c** in 65% yield in a 3.3/1 ratio.
***cis*-*N*,*N'*-dibenzyl-2-vinylspiro-[3,3'-(2,3-dihydroindole)pyrrolidin-2'-one] 9c** : Oil; **IR** (CCl_4) ν_{max} : 1700 cm^{-1}. **^{1}H NMR** : δ = 2.10-2.20 (m, 1H, H-4'); 2.45-2.55 (m, 1H, H-4'); 3.20-3.35 (m, 2H, H-5'); 3.93 (d, 1H, J = 9.5 Hz, H-2); 4.28 (2H, AB system, J = 16 Hz, Δν =13.4 Hz, $NC\underline{H}_2Ph$); 4.50 (s, 2H, $NC\underline{H}_2Ph$); 5.25 (d, 1H, J = 10 Hz, $C\underline{H}_2$=CH); 5.30 (d, 1H, J = 17 Hz, $C\underline{H}_2$=CH); 6.25 (ddd, 1H, J = 9.5 Hz, J = 10 Hz and J = 17 Hz, CH_2=$C\underline{H}$); 6.44 (d, 1H, J = 7.5 Hz, H-7); 6.70 (t, 1H, J = 7.5 Hz, H-5); 6.97 (d, 1H, J = 7.5 Hz, H-4); 7.08 (t, 1H, J = 7.5 Hz, H-6); 7.20-7.40 (m, 10 H, Aromatic). **^{13}C NMR** : δ = 32.1 (C-4'), 43.9 (C-5'), 47.0 ($N\underline{C}H_2Ph$), 50.0 ($NC\underline{H}_2Ph$), 57.2 (C-3), 77.7 (C-2), 108.0 (C-7), 118.1 (C-5), 120.9 ($\underline{C}H_2$=CH), 122.5 (C-4), 128.4 (C-6), 131.6 (C-3a), 135.9 (C-*ipso*), 136.5 (C-*ipso*), 138.3 (CH_2=$\underline{C}H$), 151.8 (C-7a), 173.0 (C-2'). **MS** (EI) : *m/z* = 395 (6), 394 (20), 303 (14), 262 (10), 246 (5), 232 (2), 220 (4), 170 (11), 156 (5), 128 (2), 117 (3), 92 (8), 91 (100). **HRMS** for $C_{27}H_{26}N_2O$: $M^+_\bullet$, calc. 394.2045; found 394.2040.

***trans*-*N*,*N'*-dibenzyl-2-vinylspiro-[3,3'-(2,3-dihydroindole)pyrrolidin-2'-one] 10c** : Oil; **IR** (CCl_4) ν_{max} : 1700 cm^{-1}. **^{1}H NMR** : δ = 1.92-2.00 (m, 1H, H-4'); 2.50-2.60 (m, 1H, H-4'); 3.18-3.28 (m, 1H, H-5'); 3.32-3.40 (m, 1H, H-5'); 4.28 (2H, AB system, J = 16 Hz, Δν =117.6 Hz, $NC\underline{H}_2Ph$); 4.50 (d, 1H, J = 8.5 Hz, H-2); 4.60 (2H, AB system, J = 14.5 Hz, Δν = 60.6 Hz, NCH_2Ph); 5.31 (d,1H, J = 10.5 Hz, $C\underline{H}_2$=CH); 5.41 (d, 1H, J = 16.5 Hz, $C\underline{H}_2$=CH); 5.92 (ddd, 1H, J = 10.5 Hz, J = 8.5 Hz and J = 16 Hz, CH_2=$C\underline{H}$); 6.35 (d, 1H, J = 7.5 Hz, H-7); 6.65 (t, 1H, J = 7.5 Hz, H-5); 6,83 (d, 1H, J = 7.5 Hz, H-4); 7.02 (t, 1H, J = 7.5 Hz, H-6); 7.20-7.40 (m, 5 H, Aromatic). **^{13}C NMR** δ = 29.0 (C-4'), 44.1 (C-5'), 47.5 (NCH_2Ph), 51.2 (NCH_2Ph), 56.1 (C-3), 73.6 (C-2), 108.4 (C-7), 118.7 (C-5), 121.3 ($\underline{C}H_2$=CH), 122.5 (C-7), 128.2 (C-6), 133.0 (C-3a), 134.9 (CH_2=$\underline{C}H$), 137.2 (C-*ipso*), 138.8 (C-*ipso*), 151.4 (C-7a), 173.0 (C-2'). **MS** (EI) : *m/z* = 395 (4), 394 (15), 353 (2), 318 (4), 303 (6), 279 (3), 262 (7), 246 (3), 220 (4), 188 (2), 170 (5), 156 (3), 149 (5), 130 (2), 105 (4), 92 (8), 91 (100). **HRMS** for $C_{27}H_{26}N_2O$: $M^+_\bullet$, calc. 394.2045; found 394.2040.

Typical procedure for the synthesis of spiroimides
To a stirred solution of indoline ester (1 mmol) in *tert*-butylalcohol (40 ml) was added, under Ar, 3 equivalents of finely powdered KOH. The resulting mixture was refluxed for 3 days. After cooling, the solvent was evaporated and 50 ml of an aqueous solution of sodium chloride was added. The solution was extracted with $CHCl_3$ (three times 20 ml). The organic layer was washed with an aqueous saturated solution of sodium chloride, and then dried over anhydrous $MgSO_4$. Removal of the solvent under vacuum gave the pure spiroimides quantitatively.

***cis*-*N*-benzyl-2-(2,2-ethylenedioxy)propylspiro-[3,3'-(2,3-dihydroindole)pyrrolidine-2',5'-dione] 11a.** It was prepared quantitatively from 0.42g of **6a** using the general procedure described above. Oil; **IR** (CCl_4) ν_{max} : 3420, 1720,1785 cm^{-1}. **^{1}H NMR** : δ = 1.30 (s, 3H, CH_3); 2.25 (dd, 1H, ABX system, B part, J_{BX} = 1;1 Hz, J_{AB} = 14.4 Hz); 2;65 (dd, 1H, ABX system, A part, J_{AX} = 10.3 Hz, J_{AB} = 14.3 Hz); 3.05 (2H, AB system, J = 20.5 Hz, Δν = 51.4 Hz , H-4'); 3.85 (dd, 1H, ABX system, X part, J_{AX} = 10.2 Hz, J_{BX} = 1.2 Hz, H-2); 3.95 (s, 4H, O-$C\underline{H}_2C\underline{H}_2$-O); 4.32 (2H, AB system, J = 20.5 Hz, Δν = 123.5 Hz, NCH_2Ph); 6.42 (d, 1H, J = 8 Hz, H-7); 6.72 (t, 1H, J = 7.5 Hz, H-5); 7.01 (d, 1H, J = 8 Hz, H-4); 7.22 (t, 1H, J = 7.5 Hz, H-6); 7.35 (s, 5H, Aromatic); 8.00-8.10 (bs, 1H, NH). **^{13}C NMR** : δ = 23.9 (CH_3), 37.5 ($C\underline{H}_2$C-2), 45.3 (C-4'), 51.3 (NCH_2Ph), 56.4 (C-3'), 64.1, 64.5 (O-$\underline{C}H_2\underline{C}H_2$-O), 68.7 (C-2), 108.6 (C-acetal, C-7),

118.7 (C-5), 121.9 (C-4), 127.8, 128.7, 129.7 (C-6), 130.2 (C-3a), 138.0 (C-*ipso*), 151.6 (C-7a), 176.5 (C-2'), 177.8 (C-5'). **MS** (EI) : *m/z* = 393 (M+1, 5), 392 (M^+, 18), 334 (2), 392 (18), 291 (9), 276 (2), 220 (24), 143 (2), 130 (2), 115 (2), 91 (55), 87 (100). **HRMS** for $C_{23}H_{24}N_2O_4$: M^+ , calc. 392.1736; found 392.1721. **Anal.** calc. for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14. found C, 70.12; H, 6.73; N, 6.91.

***trans-N*-benzyl-2-(2,2-ethylenedioxy)propylspiro-[3,3'-(2,3-dihydroindole)pyrrolidine-2',5'-dione] 12a.** It was prepared from 0.56 g of **7a** using the general procedure described above. Oil; **IR** (CCl_4) ν_{max} : 3420, 1715, 1785 cm^{-1}. **^{1}H NMR** : δ = 1.30 (s, 3H, CH_3); 2.11 (dd, 1H, ABX system, B part, J_{BX} = 11 Hz, J_{AB} = 15.5 Hz); 2.37 (dd, 1H, ABX system, A part, J_{AX} = 2 Hz, J_{AB} = 15.5 Hz); 2.50 (d, 1H, *J* = 18 Hz, H-4'); 3.35 (d, 1H, *J* = 18 Hz, H-4'); 3.80-3.95 (m, 4H, O-CH_2CH_2-O); 4;31 (dd, 1H, ABX system, X part, J_{AX} = 2 Hz, J_{BX} = 11Hz, H-2); 4.36 (2H, AB system, *J* = 16.5 Hz, Δν = 85.3 Hz, NCH_2Ph); 6.39 (d, 1H, *J* = 8 Hz, H-7); 6.72 (t, 1H, *J* = 7.5 Hz, H-5); 7.02 (d, 1H, *J* = 7.5 Hz, H-4); 7.08 (t, 1H, *J* = 8 Hz, H-6); 7.25-7.40 (m, 5H, Aromatic); 8.20-8.30 (bs, 1H, NH). **^{13}C NMR** : δ = 24.3 (CH_3), 38.3 (CH_2C-2), 41.0 (C-4'), 52.5 (NCH_2Ph), 57.6 (C-3'), 64.0 (C-2), 64.4 (O-CH_2CH_2-O), 108.3 (C-acetal), 108.9 (C-7), 119.5 (C-5), 121.4 (C-4), 127.0, 127.2, 128.7, 129.6 (C-6), 131.9 (C-3a), 138.7 (C-*ipso*), 151.0 (C-7a), 176.4 (C-2'), 179.8 (C-5'). **MS** (EI) : *m/z* = 392 (M^+, 22), 393 (M+1, 6), 347 (2), 291 (11), 276 (3), 246 (2), 220 (31), 143 (2), 130 (4), 115 (2), 102 (2), 91 (80), 87 (100). **HRMS** for $C_{23}H_{24}N_2O_4$: M^+ , calc. 392.1736; found 392.1740.

Spiroimides 11c and 12c : They were quantitatively prepared from a mixture of **6c** and **7c** in a 2/3 *cis/trans* ratio using the general procedure.

***cis-N*-benzyl-2-(2-benzyloxy)ethylspiro-[3,3'-(2,3-dihydroindole)pyrrolidine-2',5'-dione] 11c :** Oil; **IR** (CCl_4) ν_{max} : 3420, 1730, 1785 cm^{-1}. **^{1}H NMR** : δ = 2.08-2.20 (m, 1H, $CH_2CH_2OCH_2Ph$); 2.40-2.50 (m, 1H, $CH_2CH_2OCH_2Ph$); 3.01 (2H, AB system, *J* = 18.5 Hz, Δν = 46.3 Hz , H-4'); 3.35-3.50 (m, 2H, $CH_2CH_2OCH_2Ph$); 3.77 (dd, 1H, *J* = 10.3 Hz, *J* = 1.5 Hz, H-2); 4.21 (2H, AB system, *J* = 16.5 Hz, Δν = 67.2 Hz, NCH_2Ph); 4.42 (s, 2H, OCH_2Ph); 6.43 (d, 1H, *J* = 8 Hz, H-7); 6.70 (t, 1H, *J* = 7.5 Hz, H-5); 6.95 (d, 1H, *J* = 7.5 Hz, H-4); 7.08 (t, 1H, *J* = 8 Hz, H-6); 7.25-7.50 (m, 10H, Aromatic); 7.90-8.10 (bs, 1H, NH). **^{13}C NMR** : δ = 29.0 ($CH_2CH_2OCH_2Ph$), 44.4 (C-4'), 51.4 (NCH_2Ph), 56.2 (C-3'), 67.2 ($CH_2CH_2OCH_2Ph$), 71.6 (C-2), 73.3 (OCH_2Ph), 108.5 (C-7), 118.7 (C-5), 121.8 (C-4), 129.5 (C-6), 132.2 (C-3a), 137.5 (C-*ipso*), 138.0 (C-*ipso*), 151.8 (C-7a), 175.8 (C-2'), 177.3 (C-5').

***trans-N*-benzyl-2-(2-benzyloxy)ethylspiro-[3,3'-(2,3-dihydroindole)pyrrolidine-2',5'-dione] 12c :** m.p. : 128-129°C (ether). **IR** (CCl_4) ν_{max} : 3420, 1730, 1785 cm^{-1}. **^{1}H NMR** : δ = 2.03-2.10 (m, 2H, $CH_2CH_2OCH_2Ph$); 2.40 (d, 1H, *J* = 17.5 Hz, H-4'); 3.34-3.42 (m, 1H, CH_2CH_2-OCH_2Ph); 3.50 (d, 1H, *J* = 17.5 Hz, H-4'); 3.60-3.66 (m, 1H, $CH_2CH_2OCH_2Ph$); 4.21 (2H, AB system, *J* = 16.5 Hz, Δν = 67.2 Hz, NCH_2Ph); 4.31 (dd, 1H, *J* = 11 Hz, *J* = 2 Hz, H-2); 4.33 (2H, AB system, *J* = 11.5 Hz, Δν = 25.7 Hz, OCH_2Ph); 6.43 (d, 1H, *J* = 8 Hz, H-7); 6,69 (t, 1H, *J* = 7.5 Hz, H-5); 6.95 (d, 1H, *J* = 7.5 Hz, H-4); 7.08 (t, 1H, *J* = 8 Hz, H-6); 7.25-7.50 (m, 10H, Aromatic); 7.90-8.10 (bs, 1H, NH). **^{13}C NMR** : δ = 29.2 ($CH_2CH_2OCH_2Ph$), 40.9 (C-4'), 52.0 (NCH_2Ph), 57.6 (C-3'), 68.0 (C-2), 68.7 ($CH_2CH_2OCH_2Ph$), 73.4 (OCH_2Ph), 108.5 (C-7), 119.2 (C-5), 121.2 (C-4), 126.9, 127.0, 127.7, 127.9, 128.1, 128.4, 129.8 (C-6), 132.2 (C-3a), 137.3 (C-*ipso*), 138.5 (C-*ipso*), 150.7 (C-7a), 176.3 (C-2'), 179.5 (C-5'). **UV** (EtOH) : λ_{max} nm (ε) 303 (2720). **MS** (EI) : *m/z* = 427 (M+1, 5), 426 (M^+, 15), 335 (7), 320 (2), 292 (5), 291 (23), 264 (4), 250 (2), 234 (2), 162 (4), 144 (2), 130 (5), 120 (5), 92 (9), 91(100). **HRMS** for $C_{27}H_{26}N_2O_3$: M^+ , calc. 426.1943; found 426.1929. **Anal.** calc. for $C_{27}H_{26}NO_3$: C, 76.03; H, 6.15; N, 6.57. Found C, 75.66; H, 6.27; N, 6.41.

***cis-N,-N'*-dibenzyl-2-(2,2-ethylenedioxy)propylspiro-[3,3'-(2,3-dihydroindole)pyrrolidine-2',5'-dione] 15 :** To a solution of diethylazodicarboxylate (40 µl; 0.25mmol) in anhydrous THF (10 ml) was added, dropwise and under Ar at 0°C a solution of imide **11a** (0.1 g; 0.25 mmol) in THF (2 ml) followed by the benzylic alcohol (26.4 µl; 0.25 mmol) and a solution of triphenylphosphine (0.07 g; 0.25 mmol) in anhydrous THF (10 ml). After 10 minutes the solution was allowed to warm at room temperature and the stirring was continued for 12 hours. The solvent was then evaporated and the resulting residue dissolved in $CHCl_3$. The solution was washed twice with an aqueous solution of KOH (5%) and then twice with water. The organic layer was dried over $MgSO_4$ and the solvent evaporated under vacuum. Purification on silicagel with AcOEt-Hexane (1-9) as eluent gave 100 mg of **15** (yield = 83%). **IR** (CCl_4) ν_{max} : 1775, 1705 cm^{-1}. **^{1}H NMR** : δ = 1.15 (s, 3H, CH_3); 2.22 (dd, 1H, ABX system, B part, J_{BX} = 3.1 Hz, J_{AB} = 13.4 Hz); 2.57 (dd, 1H, ABX system, A part,J_{AX} = 5.1 Hz, J_{AB} = 13.4 Hz); 3.00 (2H, AB system, *J* = 20.5 Hz, Δν = 46.3 Hz , H-4'); 3.50-3.55 (m,

1H, O-C<u>H</u>2CH2-O); 3.65-3.75 (m, 3H, O-C<u>H</u>2C<u>H</u>2-O); 3.88 (dd, 1H, ABX, system, X part, J_{AX} = 5.3 Hz, J_{BX} = 3.0 Hz, H-2); 4.35 (2H, AB system, J = 15.5 Hz, $\Delta\nu$ = 36.0 Hz, N-C<u>H</u>2Ph); 4.72 (2H, AB system, J = 15.5 Hz, $\Delta\nu$ = 36.0 Hz, N1'-CH2Ph)*; 6.42 (d, 1H, J = 8 Hz, H-7); 6.67 (t, 1H, J = 8 Hz, H-5); 6.78 (d, 1H, J = 8 Hz, H-4); 7.07 (t, 1H, J = 8 Hz, H-6); 7.20-7.45 (m, 10H, Aromatic). **^{13}C NMR** : δ = 23.5 (CH_3), 29.7 (<u>C</u>H2C-2), 42.5 (N1'-<u>C</u>H2Ph), 44.2 (C-4'), 51.4 (N-<u>C</u>H2Ph), 55.0 (C-3), 63.9 (O-<u>C</u>H2CH2-O), 64.2 (O-CH2<u>C</u>H2-O), 68.8 (C-2), 108.3 (C-7), 108.5 (C-acetal); 118.6 (C-5), 121.7 (C-4), 127.0, 127.1, 128.7, 129.0, 129.2, 129.6 (C-6), 130.4 (C-3a), 136.0 (C-*ipso*), 138.2 (C-*ipso*), 151.6 (C-7a), 176.0 (C-2')*, 177.1 (C-5')*. **UV** (EtOH) : λ_{max} nm (ε) 311 (2290); 252 (7890). **MS** (EI) : *m/z* = 483 (M+1, 8), 482 (24), 395 (3), 381 (8), 277 (5), 221 (4), 220 (21), 219 (3), 149 (2), 130 (2), 119 (2), 105 (3), 91 (59), 87 (100). **Anal.** calc. for $C_{30}H_{30}N_2O_4$: C, 74.66; H, 6.27; N, 5.81. Found C, 74.98; H, 6.28; N, 6.26.
* interchangeable attribution.

Catalytic hydrogenation and debenzylation of 15
To a solution of **15** (80 mg; 0.16 mmol) in anhydrous C_2H_5OH (10 ml) was added Pd/C (10%) (50 mg). The resulting solution was hydrogenated under 3 atm in a Parr apparatus during 3 days. The solution was filtered under celite and the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed twice with an aqueous solution of sodium carbonate (5%). The organic layer was dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude mixture was chromatographed on silica gel eluting with $CHCl_3$-MeOH (9-1) to afford 40 mg of **16** (yield = 61%). Compound **16** was obtained in a 68% yield from **15** (80 mg) under the same procedure using $Pd(OH)_2$ as catalyst. **16** : Oil; **IR** (CCl_4) ν_{max} : 3450 , 1770, 1700 cm^{-1}. **^{1}H NMR** : δ = 0.70-2.20 (m, 12H, H-3a, H-4, H-5, H-6, H-7, H-7a and <u>C</u>H2C-2); 1.25 (s, 3H, CH_3); 2.70 (2H, AB system, J = 17 Hz, $\Delta\nu$ = 32 Hz, H-4'); 2.92-3.05 (bs, 1H, NH); 3.15-3.25 (m, 2H, O-C<u>H</u>2CH2-O); 3.65-3.82 (m, 2H, O-C<u>H</u>2CH2-O and H-2); 4.63 (2H, AB system, J = 11.5 Hz, $\Delta\nu$ = 12.6 Hz, NCH2Ph); 7.20-7.40 (m, 5H, Aromatic). **^{13}C NMR** : δ = 19.8 (C-4)*, 21.7 (C-5)*, 21.9 (C-6)*, 23.8 (CH_3), 26.1 (C-7)*, 39.1 (<u>C</u>H2C-2), 41.4 (C-4'), 42.3 (NCH2Ph), 51.2 (C-3a), 56.4 (C-7a), 56.7 (C-3), 63.2 (C-2), 64.3, 64.4 (O-<u>C</u>H2<u>C</u>H2-O), 108.7 (C-acetal), 127.9, 128.6, 129.0, 136.1 (C-*ipso*), 175.9 (C-2')*, 178.8 (C-5')*. **MS** (EI) : *m/z* = 398 (2), 355 (6), 311 (6), 297 (6), 283 (3), 256 (4), 214 (3), 213 (4), 191 (7), 177 (6), 163 (7), 149(11), 135 (19), 125 (17), 123 (20), 111 (29), 109 (28), 107 (14), 97 (47), 91 (37), 87 (100). **HRMS** for $C_{23}H_{30}N_2O_4$: $M^+_{\bullet}$, calc. 398.2206; found 398.2210.
* interchangeable attribution.

Debenzylation of 15 : *cis-N'*-benzyl-2-(2,2-ethylenedioxy)propylspiro-[3,3'-(2,3-dihydroindole)pyrrolidine-2',5'-dione] 13. To a stirred suspension of imide **15** (100 mg; 0.21 mmol) in anhydrous CH_3OH (5 ml) was added, under Ar, an equal weight of Pd/C (10%) followed by anhydrous ammonium formate (65 mg; 1.04 mmol). The resulting reaction mixture was stirred at reflux during 30 minutes. After cooling, the catalyst was removed by filtration through a celite pad which was then washed with dry CH_3OH. The combined organic filtrate afforded on evaporation under reduced pressure the desired compound **13** which was purified by filtration on silica gel eluting with AcOEt-Hexane (1-1) (m = 80 mg; yield = 97%). **IR** (CCl_4) ν_{max} : 3420, 1770, 1710 cm^{-1}. **^{1}H NMR** : δ = 1.21 (s, 3H, CH_3); 1.76 (dd, 1H, ABX system, B part, J_{BX} = 3 Hz, J_{AB} = 14.5 Hz); 2.02 (dd, 1H, ABX system, A part, J_{AX} = 9 Hz, J_{AB} = 14.5 Hz); 2.92 (2H, AB system, J = 18.5 Hz, $\Delta\nu$ = 144.2 Hz, H-4'); 3.83-3.88 (m, 4H, O-C<u>H</u>2CH2-O); 3.97 (dd, 1H, ABX system, X part, J_{AX} = 9 Hz, J_{BX} = 3 Hz, H-2); 4.40-4.55 (bs, 1H, NH); 4.66 (2H, AB, system, J = 14 Hz, $\Delta\nu$ = 36.8 Hz, N-CH2Ph); 6.70 (d, 1H, J = 7.5 Hz, H-7); 6.71 (t, 1H, J = 7.5 Hz, H-5); 6.84 (d, 1H, J = 7.5 Hz, H-4); 7.12 (t, 1H, J = 7.5 Hz, H-6); 7.25-7.45 (m, 5H, Aromatic). **^{13}C NMR** : δ = 24.1 (CH_3), 38.8 (<u>C</u>H2C-2), 41.7 (C-4'), 42.5 (N'CH2Ph), 55.6 (C-3'), 64.4 (O-<u>C</u>H2CH2-O), 64.5 (O-CH2<u>C</u>H2-O), 65.3 (C-2), 109.1 (C-acetal), 110.3 (C-7), 119.3 (C-5), 122.3 (C-4), 128.0, 128.7, 128.9, 129.0 (C-3a), 129.6 (C-6), 136.0 (C-*ipso*), 150.9 (C-7a), 175.2 (C-2')*, 176.4 (C-5')*. **MS** (EI) : *m/z* = 392 (5), 391 (4), 291 (9), 220 (24), 186 (3), 144 (5), 130 (39), 103 (2), 91 (15), 87 (100). **HRMS** for $C_{30}H_{30}N_2O_4$: $M^+_{\bullet}$, calc. 392.1736 ; found 392.1740.
* interchangeable attribution.

***cis*- and *trans*-2-(2-benzyloxy)ethylspiro-[3,3'-(2,3-dihydroindole)pyrrolidine-2',5'-dione] 17 and 18.** Compounds **17+18** were quantitatively obtained as a mixture of *cis/trans* isomers in a 2/3 ratio using the same experimental protocol as described for compound **13** from a 2/3 mixture of **11c+12c** (25 mg; 0.058 mmol), Pd/C and ammonium formate (18 mg; 0.29 mmole) in anhydrous C_2H_5OH (5 ml). The mixture of compounds **17+18** was used in the next step without purification.

Preparation of spiroindolines 14 and 19

To a solution of **17+18** (20 mg; 0.059 mmol) in anhydrous CH_2Cl2 (5 ml) was added dropwise and under Ar, 10 equivalents of acetic anhydride (60 mg; 56 ml; 0.59 mmol). The resulting solution was stirred at room temperature for 12 hours. After removal of the solvent, the residue was extracted three times with Et_2O. The organic layer was washed with a saturated solution of sodium carbonate. Extracts were dried over anhydrous $MgSO_4$ prior to concentration under reduced pressure. Flash chromatography eluted with AcOEt-Hexane (1-1) led to 8 mg of **14** (yield = 36%) and to 13 mg of **19** (yield = 58%).

***cis*-*N*-acetyl-2-(2-benzyloxy)ethylspiro-[3,3'-(2,3-dihydroindole)pyrrolidine-2',5'-dione] 14 :** Oil; **IR** ($CHCl_3$) ν_{max} : 3400, 1785, 1730, 1655 cm^{-1}. ^1H **NMR** : δ = 1.80-1.85 (m, 1H, $CH_2CH_2OCH_2Ph$); 2.20-2.25 (m, 1H, $CH_2CH_2OCH_2Ph$); 2.30 (s, 3H, CH_3); 2.72 (d, 1H, J = 18 Hz, H-4'); 3.30 (d, 1H, J = 18 Hz, H-4'); 3.40-3.47 (m, 2H, $CH_2CH_2OCH_2Ph$); 4.44 (s, 2H, OCH_2Ph); 4.77 (dd, 1H, J = 8 Hz, J = 6 Hz, H-2); 7.00-7.50 (m, 9H, Aromatic); 11.68 (bs, 1H, NH). **MS** (EI) : m/z = 378 (4), 336 (5), 291 (2), 277 (1), 249 (1), 158 (6), 130 (61), 127 (1), 108 (6), 92 (10), 91 (100), 77 (25), 69(4), 51 (13), 28 (100). **HRMS** for $C_{22}H_{22}N_2O_4$: $M^+_\bullet$, calc. 378.1580; found 378.1580.

***trans*-*N*-acetyl-2-(2-benzyloxy)ethylspiro-[3,3'-(2,3-dihydroindole)pyrrolidine-2',5'-dione] 19:** Oil; **IR** ($CHCl_3$) ν_{max} : 3400, 1790, 1730, 1660 cm^{-1}. ^1H **NMR** : δ = 1.65-1.80 (m, 1H, $CH_2CH_2OCH_2Ph$); 2.05-2.18 (m, 1H, $CH_2CH_2OCH_2Ph$); 2.25 (s, 3H, CH_3); 3.10 (2H, AB system, J = 18 Hz, $\Delta\nu$ = 190.3 Hz, H-4'); 3.45-3.50 (m, 2H, $CH_2CH_2OCH_2Ph$); 4.32 (s, 2H, OCH_2Ph); 4.80-5.00 (m, 1H, H-2); 7.05-7.40 (m, 9H, Aromatic); 11.68 (bs, 1H, NH). ^{13}C **NMR** : δ = 23.4 (CH_3), 31.6 ($CH_2CH_2OCH_2Ph$), 37.3 (C-4'), 55.9 (C-3), 63.4 ($CH_2CH_2OCH_2Ph$), 66.3 (C-2), 73.3 (OCH_2Ph), 118.2 (C-7), 122.1 (C-5), 124.6 (C-4), 127.9, 128.0, 128.5, 128.8 (C-3a), 129.6 (C-6), 137.6 (C-*ipso*), 141.6 (C-7a), 169.4 ($NCOCH_3$), 175.2 (C-2')*, 178.4 (C-5')*. **MS** (EI) : m/z = 378 (5), 355 (1), 336 (2), 319 (1), 292 (4), 272 (3), 230 (5), 245 (3), 248 (11), 220 (11), 201 (5), 174 (3), 156 (4), 144 (5), 130 (22), 108 (8), 91 (100), 77 (15), 65(17), 43 (14). **HRMS** for $C_{22}H_{22}N_2O_4$: $M^+_\bullet$, calc. 378.1580; found 378.1580.

* interchangeable attribution.

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