A Straightforward Stereoselective Synthesis of Spiro-epoxyoxindoles

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General experimental procedures

Chromatographic purification of compounds was achieved with Merck 60 silica gel (40-63 μm).¹ Thin layer chromatography was carried out on silica gel 60 F₂₅₄ (1.1 mm, Merck) with spot detection under UV light or phosphomolybdic acid or KMnO₄ oxidation. ¹H NMR spectra were recorded at 250 or 400 MHz. Data appear in the following order: chemical shifts in ppm, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant *J* in Hz, number of protons. ¹³C NMR spectra were acquired at 63 or 100 MHz operating with broad band ¹H decoupling. The hydrogen multiplicity were obtained by DEPT135 or JMod experiences. ¹⁹F NMR spectra were recorded at 235 MHz. Mp's stand

(1) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2924.

uncorrected. High-pressure liquid chromatography (HPLC) was performed with a diode array detector and a *Chiralpack AD-H Daicel* chiral column (length: 250 mm; i.d.: 4.6 mm; 5 μ m) with EtOH/MeCN (90/10) eluent at a flow rate of 1 mL/min at 20°C. A racemic sample of the oxiranes was run to check the retention times and the matching of the UV spectra of both enantiomers.

N-alkyl isatins were synthesized according to literature procedures² (RX, NaH in DMF) and the analyses were in agreement with the literature for the *N*-methyl,³ *N*-*p*-MeObenzyl,^{3c} *N*-Boc.⁴

(2) Da Settimo, F.; Primofiore, G.; Da Settimo, A.; La Motta, C.; Simorini, F.; Novellino, E.; Greco, G.; Lavecchia, A.; Boldrini, E. *J. Med. Chem.* **2003**, *46*, 1419.

(3) (a) Cheng, Y.; Ye, H.-L.; Zhan, Y.-H.; Meth-Cohn, O. *Synthesis* **2001**, 904. (b) Webber, S. E.; Tikhe, J.; Worland, S. T.; Fuhrman, S. A.; Hendrickson, T. F.; Matthews, D. A.; Love, R. A.; Patrick, A. K.; Meador, J. W.; Ferre, R. A.; Brown, E. L.; DeLisle, D. M.; Ford, C. E.; Binford, S. L. *J. Med. Chem.* **1996**, *39*, 5072. (c) Da Settimo, F.; Primofiore, G.; Da Settimo, A.; La Motta, C.; Simorini, F.; Novellino, E.; Greco, G.; Lavecchia, A.; Boldrini, E. *J. Med. Chem.* **2003**, *46*, 1419.

(4) Wille, G.; Steglich, W. *Synthesis* **2001**, 759.

I Optimization of the *N*-methyl isatin **1a** epoxidation

The best results were obtained in polar solvents like acetonitrile and cesium carbonate. Although the reaction could be run at room temperature, the process is slow. Much faster reactions were observed at 50°C (entry 7). A wet solvent from the bottle could be used with only a slight decrease in yield (entry 8), likely due to solvolysis of the α -bromo acetamide **2a**. However, isatin **1a** was not compatible with nucleophilic bases such as NaOH (entry 5).

entry ^a	thiolane (equiv)	Solvent	Base, additives	temp (°C)	time (h)	Yield ^b (Conv ^c)	dr ^d (<i>trans</i> : <i>cis</i>)
1	1	THF	2 K ₃ PO ₄ , 0.1 <i>n</i> -Bu ₄ NBr	rt	72	(17%)	> 96:4
2	1	THF	2 Cs ₂ CO ₃	rt	168	(70%)	> 96:4
3	1	MeCN	2 Cs ₂ CO ₃	rt	40	46% (69%)	> 96:4
4	1	MeCN	2 Cs ₂ CO ₃ , 0.2 <i>n</i> -Bu ₄ NI	rt	25	58% (73%)	> 96:4
5	1	MeCN:H ₂ O ^e	2 NaOH	rt	24	0% ^f	-
6	1	THF	2 K ₃ PO ₄ , 0.1 <i>n</i> -Bu ₄ NHSO ₄	50	96	(44%)	> 96:4
7	1	MeCN	2 Cs ₂ CO ₃	50	24	90% (100%)	> 96:4
8	1	MeCN ^g	2 Cs ₂ CO ₃	50	24	85%	> 96:4
9	0.2	MeCN	2 Cs ₂ CO ₃	50	24	(54%)	> 96:4
10	0.2	MeCN	2 Cs ₂ CO ₃	50	72	72%	> 96:4
11	0	MeCN	2 Cs ₂ CO ₃	50	24	0%	-
12	1 ^h	MeCN	2 Cs ₂ CO ₃	50	24	(20-25%)	

^a All reactions were performed on 0.75 mmol of *N*-methyl isatin **1a** with α -bromo acetamide **2a** (2 equiv), thiolane, base (2 equiv) in anhydrous solvent with respect to the general procedure (see § II). ^b Isolated yield of the *trans* epoxide **4a** after column chromatography. ^c Conversion in epoxide **4a** with respect to *N*-methyl isatin **1a**. ^d Estimated on the ¹H NMR of the crude product. ^e MeCN:H₂O (90/10). ^f *N*-Methyl isatin **1a** was decomposed. ^g Reaction run in an open-vessel with the solvent directly taken from the bottle. ^h Ethyl bromoacetate or *tert*-butyl bromoacetate (2 equiv) were used instead of α -bromo acetamide **2a** (*vide infra*).

Remark: In order to compare with sulfonium ylide derived from α -bromo acetamide **2a**, ethyl bromoacetate or *tert*-butyl bromoacetate were also evaluated in the optimized epoxidation conditions (entry 7). These α -bromo acetates did react with *N*-methyl isatin (entry 12) but with a low conversion of 20-25 % (with respect to the recovered *N*-methyl isatin **1a**). We assume that the corresponding ester-epoxydes were formed, according to the literature ¹H NMR spectra.⁵ This result is in agreement with the known stability (and poor reactivity) of the ester-stabilized sulfonium ylides which only react with highly activated 1,2-dicarbonyl compounds,⁶ or in specific conditions.⁷

(5) Joshi, K. C.; Jain, R.; Garg, S. *J. Heterocyclic Chem.* **1984**, *21*, 977.

(6) Payne, G. B. *J. Org. Chem.* **1968**, *33*, 3517.

(7) (a) Borredon, E.; Clavellinas, F.; Delmas, M.; Gaset, A. J.; Sinisterra, V. *J. Org. Chem.* **1990**, *55*, 501. (b) Aggarwal, V. K.; Charmant, J. P. H.; Fuentes, D.; Harvey, J. N.; Hynd, G.; Ohara, D.; Picoul, W.; Robiette, R.; Smith, C.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc.* **2006**, *128*, 2105 and references therein for a background knowledge.

II General procedure for the synthesis of 1-alkyl-3'-pyrrolidinocarbonylspiro[3*H*-indole-3,2'-oxiran]-2(1*H*)-one compounds **4**

Thiolane (0.066 mL, 0.75 mmol, 1 equiv) was introduced to a solution of *N*-alkyl isatin **1** (0.75 mmol, 1 equiv) and α -bromo acetamide **2** (1.5 mmol, 2 equiv) in anhydrous acetonitrile (1.5 mL) at room temperature under nitrogen. Then, cesium carbonate (489 mg, 1.5 mmol, 2 equiv) was added in one portion. The solution was stirred at 50°C (oil bath temperature) for 24 hours. The reaction mixture was allowed to stand at room temperature and the remaining solid was filtered and washed with CH_2Cl_2 . The filtrate was concentrated *in vacuo*. Purification by flash column chromatography (by default ether/methanol 20:1, otherwise indicated) afforded the desired *trans* epoxides as described in the following characterizations. *Remark*: the obtained solids tend to retain solvents such as methanol, AcOEt and CH_2Cl_2 , so they have to be dried for long period of time under vacuum.

The C_2 symmetrical sulfides were used instead of thiolane for the asymmetric protocol.

II.1 1-methyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one: **4a**

Following the general procedure, the *trans* epoxide **4a** was obtained as a pale yellow solid in 90% yield after purification (> 96:4 *trans*:*cis* ratio was determined on the ^1H NMR of the

crude product). M.p. 127-133 °C. ^1H NMR (CDCl_3 , 250 MHz) δ 1.78-2.00 (m, 4H), 3.19-3.25 (m, 1H), 3.29 (s, 3H), 3.47-3.63 (m, 3H), 4.29 (s, 1H), 6.91 (d, J = 6.9 Hz, 1H), 7.02-7.08 (m, 1H), 7.31-7.35 (m, 2H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 23.8 (CH_2), 26.1 (CH_2), 26.9 (CH_3), 45.9 (CH_2), 46.2 (CH_2), 59.8 (C), 61.0 (CH), 108.9 (CH), 120.0 (C), 123.3 (CH), 124.7 (CH), 131.0 (CH), 145.5 (C), 162.6 (C), 170.5 (C). IR (powder) ν 1721, 1652, 1615, 1451, 1376, 1338, 921, 755 cm^{-1} . HRMS m/z calcd for $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 273.1239, found: 273.1228. Anal. Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 65.83; H, 6.33; N, 10.21. HPLC: The enantiomers of the *trans* epoxide: 4.5 min (the *levo* (-) isomer) and 9.4 min (the *dextro* (+) isomer), with UV maximum absorption: 220 nm (according the HPLC method described in the general experimental procedures). The rotation measurements were made with the enantio-enriched samples in CH_2Cl_2 .

II.2 1-methyl-3'-(morpholin-4-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one: **4b**

Following the general procedure, the *trans* epoxide **4b** was obtained as a orange solid in 45% yield after purification (ether/methanol 10:1) by flash column chromatography (> 96:4 *trans*:*cis* ratio determined on the ^1H NMR of the crude product). M.p. 164-165 °C. ^1H NMR (CDCl_3 , 250 MHz) δ 3.12-3.29 (m, 2H), 3.29 (s, 1H), 3.48-3.83 (m, 6H), 4.33 (s, 1H), 6.94 (d, J = 7.8 Hz, 1H), 7.04-7.10 (m, 1H), 7.17 (d, J = 7.2 Hz, 1H), 7.39-7.44 (m, 1H). ^{13}C NMR (CDCl_3 , 63 MHz) δ 26.9 (CH_3), 42.2 (CH_2), 45.4 (CH_2), 59.9 (C), 60.4 (CH), 66.4 (CH_2), 66.7 (CH_2), 109.1 (C), 119.6 (CH), 123.3 (CH), 124.0 (CH), 131.2 (CH), 145.3 (C), 162.8 (C), 170.01 (C). IR (powder) ν (cm^{-1}) 1738, 1639, 1618, 1467, 1348, 1275, 1248, 1106, 925,

849, 748. Anal. Calcd for C₁₅H₁₆N₂O₄: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.62; H, 5.77; N, 9.91.

II.3 1-(4-methoxybenzyl)-3'-pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one: 4c

Following the general procedure, the *trans* epoxide **4c** was obtained as a orange solid in 88% yield after purification (ether/methanol 10:1) by flash column chromatography (> 96:4 *trans:cis* ratio determined on the ¹H NMR of the crude product). M.p. 175-178 °C (CH₂Cl₂). ¹H NMR (CDCl₃, 250 MHz) δ 1.79-1.89 (m, 4H), 3.19-3.23 (m, 1H), 3.48-3.62 (m, 3H), 3.78 (s, 1H), 4.34 (s, 1H), 4.90 (s, 2H), 6.81-6.87 (m, 3H), 6.95-7.03 (m, 1H), 7.24-7.34 (m, 4H). ¹³C NMR (CDCl₃, 63 MHz) δ 23.8 (CH₂), 26.0 (CH₂), 43.9 (CH₂), 45.8 (CH₂), 46.2 (CH₂), 55.3 (CH₃), 59.8 (C), 61.2 (CH), 109.9 (CH), 114.3 (CH), 119.9 (C), 123.2 (CH), 124.6 (CH), 127.2 (C), 128.9 (CH), 130.8 (CH), 144.5 (C), 159.3 (C), 162.5 (C), 170.5 (C). IR (powder) ν (cm⁻¹) 1719, 1662, 1614, 1513, 1351, 1251, 1027, 783. HRMS *m/z* calcd for C₂₂H₂₃N₂O₄ [M+H]⁺: 379.1658, found: 479.1660.

A crystalline compound was obtained by slow evaporation of a CH₂Cl₂ solution and the X-Ray crystal structure determination is reported as a CIF file.

II.4 5-iodo-1-methyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one: **4e**

Following the general procedure, the *trans* epoxide **4e** was obtained as a yellow solid in 75% yield after purification (> 96:4 *trans:cis* ratio determined on the ^1H NMR of the crude product). M.p. 183-185 °C. ^1H NMR (CDCl_3 , 250 MHz) δ 1.62-2.04 (m, 4H), 3.27 (s, 3H), 3.22-3.32 (m, 1H), 3.52-3.66 (m, 3H), 4.30 (s, 1H), 6.70 (d, $J = 8.3$ Hz, 1H), 7.62 (d, $J = 1.8$ Hz, 1H), 7.70-7.73 (dd, $J = 1.8$ and 8.2 Hz, 1H). ^{13}C NMR (CDCl_3 , 63 MHz) δ 23.9 (CH₂), 26.2 (CH₂), 27.0 (CH₃), 46.1 (CH₂), 46.5 (CH₂), 59.3 (C), 61.1 (CH), 85.9 (C), 110.9 (CH), 122.3 (C), 133.5 (CH), 139.8 (CH), 145.2 (C), 162.3 (C), 169.8 (C). IR (powder) ν (cm⁻¹) 1726, 1652, 1607, 1339, 1128, 814. HRMS m/z calcd for C₁₅H₁₅N₂O₃INa [M+Na]⁺: 421.0025, found: 421.0045.

II.5 5-bromo-1-methyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one: **4f**

Following the general procedure, the *trans* epoxide **4f** was obtained as a pale yellow-orange solid in 53% yield after purification (> 96:4 *trans:cis* ratio determined on the ^1H NMR of the crude product). M.p. 168-170 °C. ^1H NMR (CDCl_3 , 250 MHz) δ 1.85-2.05 (m, 4H), 3.22-3.34 (m, 1H), 3.28 (s, 3H), 3.51-3.66 (m, 3H), 4.30 (s, 1H), 6.80 (d, $J = 8.2$ Hz, 1H), 7.49-7.55 (m, 2H). ^{13}C NMR (CDCl_3 , 63 MHz) δ 23.9 (CH₂), 26.2 (CH₂), 27.0 (CH₃), 46.1 (CH₂), 46.5 (CH₂), 59.5 (C), 61.1 (CH), 110.4 (CH), 116.2 (C), 122.1 (C), 128.0 (CH), 133.9 (CH), 144.5

(C), 162.2 (C), 170.0 (C). IR (powder) ν (cm⁻¹) 1732, 1646, 1608, 1336, 1127, 903, 807. HRMS m/z calcd for C₁₅H₁₅N₂O₃BrNa [M+Na]⁺: 373.0164, found: 373.0172.

II.6 5-fluoro-1-methyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1H)-one:

4g

Following the general procedure, the *trans* epoxide **4g** was obtained as a pale yellow-orange solid in 79% yield after purification (> 96:4 *trans:cis* ratio determined on the ¹H NMR of the crude product). M.p. 149-151 °C. ¹H NMR (CDCl₃, 250 MHz) δ 1.83-2.01 (m, 4H), 3.28-3.32 (m, 1H), 3.31 (s, 3H), 3.51-3.65 (m, 3H), 4.30 (s, 1H), 6.84 (dd, J = 4.0 Hz and 8.5 Hz, 1H), 7.05-7.19 (m, 2H). ¹³C NMR (CDCl₃, 63 MHz) δ 23.8 (CH₂), 26.0 (CH₂), 26.9 (CH₃), 45.9 (CH₂), 46.3 (CH₂), 59.6 (C), 60.9 (CH), 109.5 (d, J = 8.1 Hz, CH), 112.9 (d, J = 26.4 Hz, CH), 117.2 (d, J = 23.2 Hz, CH), 121.5 (d, J = 8.8 Hz, C), 141.3 (C), 159.2 (d, J = 242.2 Hz, C), 162.1 (C), 170.1 (C). IR (powder) ν (cm⁻¹) 1734, 1652, 1615, 1469, 1455, 1338, 1124, 883. HRMS m/z calcd for C₁₅H₁₆N₂O₃F [M+H]⁺: 291.1145, found: 291.1138. Anal. Calcd for C₁₅H₁₅N₂O₃F: C, 62.06; H, 5.21; N, 9.65. Found: C, 62.05; H, 5.43; N, 9.67.

II.7 1-methyl-3'-(pyrrolidin-1-ylcarbonyl)-5-(trifluoromethoxy)spiro[indole-3,2'-oxiran]-2(1H)-one: **4h**

Following the general procedure, the *trans* epoxide **4h** was obtained as a yellow solid in 79% yield after purification (> 96:4 *trans:cis* ratio determined on the ^1H NMR of the crude product). M.p. 169-170 °C. ^1H NMR (CDCl_3 , 250 MHz) δ 1.82-2.00 (m, 4H), 3.25-3.30 (m, 1H), 3.28 (s, 3H), 3.50-3.64 (m, 4H), 4.32 (s, 1H), 6.89-6.93 (m, 1H), 7.26-7.30 (m, 2H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 23.8 (CH₂), 26.1 (CH₂), 27.0 (CH₃), 45.9 (CH₂), 46.3 (CH₂), 59.4 (C), 61.0 (CH), 109.5 (CH), 118.9 (CH), 120.5 (q, $J = 257.2$ Hz, C), 121.5 (C), 124.1 (CH), 144.0 (C), 145.0 (C), 162.0 (C), 170.2 (C). ^{19}F NMR (CDCl_3 , 235 MHz) δ -58.5. IR (powder) ν (cm^{-1}) 1737, 1669, 1652, 1615, 1464, 1247, 1216, 1156, 1116, 819, 694. HRMS m/z calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_4\text{F}_3$ $[\text{M}+\text{H}]^+$: 357.1062, found: 357.1046. Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_4\text{F}_3$: C, 53.94; H, 4.24; N, 7.86. Found: C, 54.09; H, 4.25; N, 7.89.

II.8 1,5-dimethyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1H)-one: **4i**

Following the general procedure, the *trans* epoxide **4i** was obtained as a yellow solid in 88% yield after purification (> 96:4 *trans:cis* ratio determined on the ^1H NMR of the crude product). M.p. 122-124 °C. ^1H NMR (CDCl_3 , 250 MHz) δ 1.81-1.99 (m, 4H), 2.30 (s, 3H), 3.21-3.27 (m, 1H), 3.27 (s, 3H), 3.51-3.63 (m, 3H), 4.29 (s, 1H), 6.80 (d, $J = 7.8$ Hz, 1H), 7.16-7.21 (m, 2H). ^{13}C NMR (CDCl_3 , 63 MHz) δ 21.2 (CH₃), 24.0 (CH₂), 26.1 (CH₂), 27.0 (CH₃), 46.0, (CH₂), 46.3 (CH₂), 60.0 (C), 61.1 (CH), 108.7 (CH), 120.9 (C), 125.4 (CH), 131.3 (CH), 133.1 (C), 143.2 (C), 162.7 (C), 170.5 (C). IR (powder) ν (cm^{-1}) 1716, 1657, 1622, 1601, 1343, 1121, 819, 718. HRMS m/z calcd for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 287.1386, found: 287.1404.

II.8 1-methyl-5-nitro-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1H)-one: **4j**

Following the general procedure, the *trans* epoxide **4j** was obtained as a pale reddish solid in 64% yield after purification (95:5 *trans:cis* ratio determined on the ^1H NMR of the crude product). M.p. 177-179 °C. ^1H NMR (CDCl_3 , 250 MHz) δ 1.90-2.02 (m, 4H), 3.34 (s, 1H), 3.20-3.72 (m, 4H), 4.37 (s, 1H), 7.02 (d, 1H, $J = 8.7$ Hz), 8.17 (d, 1H, $J = 2.3$ Hz), 8.36 (dd, 1H, $J = 2.3$ Hz and 8.7 Hz). ^{13}C NMR (CDCl_3 , 63 MHz) δ 23.9 (CH_2), 26.3 (CH_2), 27.4 (CH_3), 46.4 (CH_2), 46.7 (CH_2), 59.3 (C), 61.4 (CH), 108.7 (CH), 120.8 (CH), 121.3 (C), 127.8 (CH), 144.0 (C), 150.7 (C), 161.9 (C), 170.8 (C). IR (powder) ν (cm^{-1}) 1745, 1650, 1615, 1516, 1338, 1293, 1121, 919, 750. HRMS m/z calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$: 340.0909, found: 430.0919.

III Epoxidation with the in situ preformed sulfonium salt

III.1 sulfonium salt **2c**

Thiolane (0.087 mL, 0.99 mmol) was added to a solution of α -bromo acetamide **2a** (189.2 mg, 0.99 mmol, 1 equiv) in D_2O (0.540 mL) into an NMR tube. The solution is stirred at 20°C by means of a small magnetic stirrer. The ^1H NMR spectrum was taken after 30 minutes (77:23 sulfonium: α -bromo acetamide) and after 90 minutes (99:1 sulfonium: α -bromo acetamide). The original biphasic mixture becomes homogenous along with the sulfonium salt formation.

For comparison, we prepared an NMR tube with thiolane (10.6 mg, 0.12mmol), α -bromo acetamide **2a**, D₂O (0.066 mL) and CD₃CN (600 mL), namely with a D₂O:CD₃CN (10:90), and the ¹H NMR spectrum was taken after 80 minutes (23:77 sulfonium: α -bromo acetamide), 16 hours (89:11 sulfonium: α -bromo acetamide) and 28 hours (99:1 sulfonium: α -bromo acetamide). Although there are concentration differences, this shows that the rate of the sulfonium formation (indeed the equilibrium) is significantly enhanced in water.

III.2 NMR of the sulfonium salt **2c**

The original ^1H NMR (400 MHz) of α -bromo acetamide **2a** in D_2O

The same NMR tube after 90 minutes of the addition of thiolane.

III.2 Formation of 3'-pyrrolidinocarbonylspiro[3*H*-indole-3,2'-oxiran]-2(1*H*)-one **4k** (and **4l**) from the sulfonium salt **2c**

Thiolane (0.174 mL, 2.0 mmol, 1.1 equiv) was added to a solution of α -bromo acetamide **2a** (378 mg, 2.0 mmol, 1.1 equiv) in water (1 mL) at room temperature. The mixture (thiolane is not soluble so there are initially two layers) was vigorously stirred for 90 minutes resulting thereby in a homogenous solution (formation of the sulfonium salt **2c**). Acetonitrile, isatin (263 mg, 1.8 mmol), *n*-Bu₄NHSO₄ (65 mg, 0.19 mmol, 0.1 equiv) and K₃PO₄ (1045 mg, 4.9 mmol, 2.7 equiv) were subsequently added to the solution which became rapidly black. The mixture was vigorously stirred for 3 days at room temperature and, then, diluted with a saturated aqueous NH₄Cl solution. The aqueous layer was extracted by dichloromethane and the combined organic layers were dried over MgSO₄, filtrated and concentrated *in vacuo* (> 96:4 *trans*:*cis* ratio determined on the ¹H NMR of the crude product). Purification by flash column chromatography (AcOEt) afforded **4l** (41%) as a pale yellow solid. The *N*-alkylated product **4k** was eluted by a mixture a AcOEt/EtOH (4/1) afforded a pale yellow solid (10% yield). Remark: the obtained solids tend to retained solvents such as methanol, AcOEt and CH₂Cl₂ so they have to be dried for long period of time under vacuum. Product **4l**. M.p. 171-174 °C (CH₂Cl₂). ¹H NMR (CDCl₃, 400 MHz) δ 1.82-1.89 (m, 3H), 1.91-2.05 (m, 1H), 3.25-3.29 (m, 1H), 3.51-3.64 (m, 3H), 4.30 (s, 1H), 6.90 (d, *J* = 8 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 7.26-7.31 (m, 2H), 8.83 (brs, 1H). ¹³C NMR (CDCl₃, 100 MHz) δ 23.7 (CH₂), 25.9 (CH₂), 45.9 (CH₂), 46.2 (CH₂), 60.1 (C), 70.0 (CH), 111.4 (CH), 119.8 (C), 122.8 (CH), 124.2 (CH) 130.9 (CH), 143.2 (C), 162.9 (C), 172.3 (C). IR (powder) ν 2967 (br), 2982 (br), 1743, 1711,

1659, 1640, 1620, 1468, 1455, 1335, 1215, 931, 771, 755 cm^{-1} . HRMS m/z calcd for $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 259.1083, found: 259.1090. 1-(2-oxo-2-pyrrolidin-1-ylethyl)-3'-pyrrolidin-1-ylcarbonylspiro[indole-3,2'-oxiran]-2(1*H*)-one **4k**. M.p. 77-93 °C (the melting point is not clear-cut). ^1H NMR (CDCl_3 , 400 MHz) δ 1.76-2.12 (m, 8H), 3.19-3.24 (m, 1H), 3.46-3.59 (m, 7H), 3.51-3.64 (m, 3H), 4.30 (s, 1H), 4.31 (d, J = 16.0 Hz, 1H), 4.69 (d, J = 16.0 Hz, 1H), 6.88-6.90 (m, 1H), 7.01-7.05 (m, 1H), 7.31-7.36 (m, 2H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 23.7 (CH₂), 24.0 (CH₂), 25.9 (CH₂), 26.2 (CH₂), 45.7 (CH₂), 45.6 (CH₂), 46.0 (CH₂), 46.1 (CH₂), 46.2 (CH₂), 59.6 (C), 61.2 (CH), 109.5 (CH), 119.4 (C), 123.2 (CH), 124.2 (CH), 130.9 (CH), 144.6 (C), 162.3 (C), 163.9 (C), 170.5 (C). IR (powder) ν 1732, 1651, 1615, 1446, 1188, 754 cm^{-1} . HRMS m/z calcd for $\text{C}_{20}\text{H}_{24}\text{N}_3\text{O}_4$ $[\text{M}+\text{H}]^+$: 370.1774, found: 370.1767.

IV Synthesis of 3'-benzoylspiro[indole-3,2'-oxiran]-2(1*H*)-one **5a**

The phenyllithium (0.365 mL, 1.6 M in *n*-Bu₂O, 0.58 mmol, 2.5 equiv) was added dropwise to a solution of epoxide **4a** (60.1 mg, 0.23 mmol) in anhydrous THF (1.9 mL) at -78 °C.⁸ The solution was stirred for 90 minutes at -78 °C and quenched by a mixture of a saturated aqueous NH₄Cl solution and THF (2 mL, 1:1 ratio). The mixture was allowed to stand at room temperature, then the aqueous layer was extracted by dichloromethane and the combined organic layers were dried over MgSO₄, filtrated and concentrated *in vacuo*. Purification by flash column chromatography (AcOEt:Hept 1:1) afforded **5a** (79%) as a

⁸ Meth-Cohn, O.; Chen, Y. *Tetrahedron Lett.* **1999**, 40, 6069.

yellow solid. *Remark:* the obtained solids tend to retained solvents such as methanol, AcOEt and CH₂Cl₂ so they have to be dried for long period of time under vacuum. M.p. 146-152 °C (MeOH). ¹H NMR (CDCl₃, 400 MHz) δ 4.98 (s, 1H), 6.93-6.98 (m, 2H), 7.12 (d, J = 7.6 Hz, 1H), 7.31-7.27 (m, 1H), 7.46-7.50 (m, 2H), 7.60-7.64 (m, 1H), 7.95-7.97 (m, 2H), 8.16 (brs, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ 61.3 (C), 63.9 (CH), 111.4 (CH), 119.6 (C), 123.5 (CH), 124.8 (CH), 128.5 (CH), 129.2 (CH), 131.3 (CH), 134.7 (CH) 135.1 (C), 142.7 (C), 172.8 (C), 190.7 (C). IR (powder) ν 3171 (br), 1729, 1711, 1693, 1619, 1470, 1341, 1455, 1228, 1215, 1015, 752, 703 cm⁻¹. HRMS m/z calcd for C₁₆H₁₂N₁O₃ [M+H]⁺: 266.0817, found: 266.0815. A crystalline compound was obtained by slow evaporation of a MeOH solution and the X-Ray crystal structure determination is reported as a CIF file.

V NMR of 3'-spirooxiranyloxindoles

V.1 1-methyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one (¹H): 4a

V.1 1-methyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one (¹³C): 4a

V.1 1-methyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one (DEPT135): 4a

V.2 1-methyl-3'-(morpholin-4-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one (¹H): 4b

V.2 1-methyl-3'-(morpholin-4-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one (¹³C): 4b

V.2 1-methyl-3'-(morpholin-4-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one (DEPT): 4b

V.3 1-(4-methoxybenzyl)-3'-pyrrolidin-1-ylcarbonylspiro[indole-3,2'-oxiran]-2(1*H*)-one
(¹H): 4c

V.3 1-(4-methoxybenzyl)-3'-pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one

(¹³C): 4c

V.3 1-(4-methoxybenzyl)-3'-pyrrolidin-1-ylcarbonylspiro[indole-3,2'-oxiran]-2(1*H*)-one
(JMOD): 4c

V.4 5-iodo-1-methyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one
(¹H): 4e

V.4 5-iodo-1-methyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one
¹³C): 4e

V.4 5-iodo-1-methyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one
 (DEPT135): 4e

V.5 5-bromo-1-methyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one
(¹H): 4f

V.5 5-bromo-1-methyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one
 (¹³C): **4f**

V.5 5-bromo-1-methyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one
 (DEPT135): **4f**

V.6 5-fluoro-1-methyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one
(¹H): 4g

V.6 5-fluoro-1-methyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one

(¹³C): 4g

V.6 5-fluoro-1-methyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one

(DEPT135): 4g

V.7 1-methyl-3'-(pyrrolidin-1-ylcarbonyl)-5-(trifluoromethoxy)spiro[indole-3,2'-oxiran]-2(1*H*)-one (¹H): 4h

V.7 1-methyl-3'-(pyrrolidin-1-ylcarbonyl)-5-(trifluoromethoxy)spiro[indole-3,2'-oxiran]-2(1*H*)-one (¹³C): 4h

V.7 1-methyl-3'-(pyrrolidin-1-ylcarbonyl)-5-(trifluoromethoxy)spiro[indole-3,2'-oxiran]-2(1*H*)-one (DEPT135): 4h

V.8 1,5-dimethyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one (¹H):

4i

V.8 1,5-dimethyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one (¹³C):
4i

V.8 1,5-dimethyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one
(DEPT135): 4i

V.9 1-methyl-5-nitro-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one
(¹H): 4j

V.9 1-methyl-5-nitro-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one
¹³C): 4j

V.9 1-methyl-5-nitro-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one
 (DEPT135): 4j

V.10 **1-(2-oxo-2-pyrrolidin-1-ylethyl)-3'-pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one (¹H): 4k**

V.10 1-[2-pyrrolidinyl-2-oxoethyl]-3'-pyrrolidinocarbonylspiro[3*H*-indole-3,2'-oxiran]-2(1*H*)-one (¹H) (¹³C): 4k

V.10 1-[2-pyrrolidinyl-2-oxoethyl]-3'-pyrrolidinocarbonylspiro[3*H*-indole-3,2'-oxiran]-2(1*H*)-one (¹H) (DEPT135): 4k

V.11 3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one (¹H): 4l

V.11 3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one (¹³C): 4l

V.11 3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one (DEPT135): 4l

V.12 3'-benzoylspiro[indole-3,2'-oxiran]-2(1*H*)-one (¹H): 5a

V.12 3'-benzoylspro[indole-3,2'-oxiran]-2(1*H*)-one (¹³C): 5a

V.12 3'-benzoylspro[indole-3,2'-oxiran]-2(1*H*)-one (DEPT135): 5a

VI X-Ray crystal structures of 4a and 5a

VI.1 1-methyl-3'-(pyrrolidin-1-ylcarbonyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one: 4c

The X-Ray crystal structure of the *trans* epoxide **4a** showed that the pyrrolidine ring exhibits two defined conformations at the solid state (see CIF file for further information). Both of them are depicted in the ORTEP representation.

VI.2 3'-benzoylspiro[indole-3,2'-oxiran]-2(1*H*)-one: **5a**

The X-Ray crystal structure shows the *trans* relative configuration of the spiro-epoxyoxindoles **5a**. The crystal packing study shows that the epoxides are organized as pairs of enantiomers, the secondary lactam moieties are engaged in intermolecular hydrogen bonds, and both the oxindole sub-structures and the phenyl sub-structures display Π -stacking interactions (see CIF file for further information).