

*Supplementary material for:*

**Dearomatising Anionic Cyclisation of Substituted N-Cumyl-N-benzylbenzamides on Treatment with LDA: Synthesis of Partially Saturated Substituted Isoindolones**

Jonathan Clayden, Christel J. Menet and Darren J. Mansfield

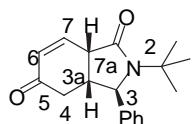
*Department of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, U.K., and Aventis CropScience SA, Centre de Recherche de La Dargoire, 14-20 rue Pierre Baizet - BP 9163, 69263 Lyon Cedex 09, France*

**General experimental**

All non-aqueous reactions were performed under an atmosphere of dry nitrogen at temperatures which were those of an external bath. Proton nuclear magnetic resonance ( $^1\text{H}$  NMR) spectra were recorded on Varian Gemini 200 (200MHz) or Varian XL 300 (300 MHz) spectrometers with residual non-deuterated solvent as the internal standard. Chemical shifts are quoted in parts per million (ppm) down-field from tetramethylsilane.  $J$  values are quoted in Hertz (Hz). Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn), sextet (sx), septet (sp), doublet of doublets (dd), multiplet (m) and broad (b). The solvent used was deuterated chloroform or dimethylsulfoxide. The infrared spectra were recorded on an ATI Matteson Genesis Series FTIR spectrometer or a Perkin Elmer 1710 FT spectrometer, as evaporated films from chloroform except where stated. Absorption maxima ( $\nu_{\max}$ ) are quoted in wave numbers ( $\text{cm}^{-1}$ ). Abbreviations are as follows: broad (b), weak (w), aryl (ar) and alkyl (al). Mass spectra were recorded on Kratos MS25, Kratos Concept and Fisons VG Trio 2000 spectrometers using both electron impact (EI) and chemical ionisation (CI) with ammonia. Tetrahydrofuran (THF) and diethyl ether were dried over sodium/benzophenone and distilled under dry nitrogen prior to use. Water refers to distilled water. Dimethylformamide (DMF) was distilled from calcium hydride and stored over 4 Å molecular sieves. Petrol refers to the fraction of petroleum ether that boils

between 40 and 60 °C and was distilled before use. Dichloromethane was dried over phosphorus pentoxide and distilled before use. Ether refers to diethyl ether. Flash chromatography was carried out using Merck silica gel 60H (40-60µm, 230-400 mesh). Thin layer chromatography (TLC) was carried out on aluminium-backed Kieselgel 60 F<sub>254</sub> silica plates. Visualisation was achieved using ultraviolet light, iodine adsorbed on silica gel, or 10% dodecamolybdophosphoric acid in ethanol followed by heating. Melting points were determined on a Kofler microscope melting point machine and are uncorrected.

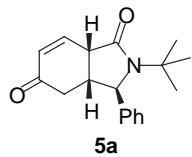
### Isoindolone numbering:



### General procedure for cyclisation with LDA

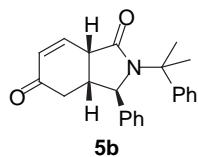
A solution of the benzamide (typically ca. 0.25 g) in THF was added to a solution of freshly prepared LDA (1.3 eq.) in THF at 0 °C. The reaction was stirred at room temperature for 1.5 h. Saturated ammonium chloride solution (10 ml) and (for the synthesis of enones by hydrolysis of enol ethers) dilute hydrochloric acid (20 ml) were added to the mixture. The aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub> and evaporated under reduced pressure to afford the crude product.

*[3(RS),3a(RS),7a(SR)]-2-tert-Butyl-3-phenyl-2,3,3a,7a-tetrahydro-4H-isoindole-1,5-dione 5a*



In this way, amide **1a** (0.25 g, 0.84 mmol) in THF (15 ml) and LDA (1.1 mmol) in THF (5 ml) gave, after purification by flash chromatography (7:3 petroleum ether:ethyl acetate), the title compound as a white solid (0.17 g, 73 %), mp 131-134 °C;  $R_f$  0.15;  $\nu_{\max}$  2975 (CH), 1678 (C=O);  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) 7.5-7.2 (5H, m, Ph), 6.92 (1H, dd,  $J$  5.5, 10, H7), 6.05 (1H, dd,  $J$  1.5, 10, H6), 4.19 (1H, s, H3), 3.7-3.5 (1H, m, H7a), 2.8-2.5 (3H, m, H4, H3a), 1.39 (3H, s, *tert*-butyl);  $\delta_C$  (75 MHz,  $\text{CDCl}_3$ ) 196.69, 171.60, 144.49, 141.51, 130.19, 129.09, 127.96, 125.26, 66.25, 55.52, 42.0, 41.75, 39.93, 27.92;  $m/z$ (EI) 284 ( $M + \text{H}^+$ , 36 %), 95 (100 %). Found:  $M^+$  283.1573;  $\text{C}_{18}\text{H}_{21}\text{NO}_2$  requires  $M$  283.15722.

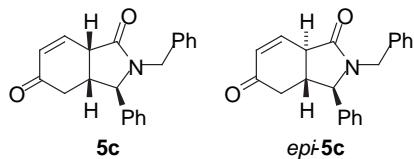
*[3(RS),3a(RS),7a(SR)]-2-(1-Methyl-1-phenylethyl)-3-phenyl-2,3,3a,4,5,7a-hexahydro-1H-1,5-isoindoledione 5b*



In the same way, amide **1b** (0.2 g, 0.56 mmol) and LDA (0.73 mmol) in THF (15 ml) gave, after purification by flash chromatography (7:3 petroleum ether: ethyl acetate), the title compound as a white solid (1.03 g, 53 %), mp 127-128 °C;  $R_f$  0.15;  $\nu_{\max}$  2978 (CH), 1680 (C=O);  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) 7.34 (10H, m, ArH), 6.92 (1H, dd,  $J$  5,  $J$  10, H7),

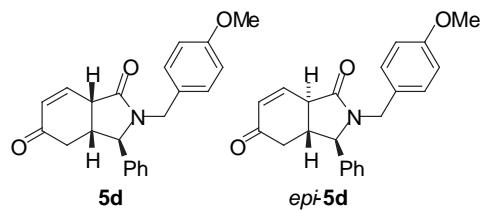
6.16 (1H, dd, *J* 2, *J* 10, H6), 4.47 (1H, d, *J* 2.5, H3), 3.67 (1H, m, H7a), 2.66 (3H, m, H4, H3a), 1.85 (3H, s, CH<sub>3</sub>), 1.52 (3H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 196.52, 171.48, 145.87, 144.33, 141.46, 130.25, 128.99, 128.09, 126.90, 125.80, 125.20, 67.25, 59.91, 42.38, 41.47, 39.04, 28.21, 27.14; m/z (CI) 346 (M+H<sup>+</sup>, 100 %). Found: M<sup>+</sup> 345.1732; C<sub>23</sub>H<sub>23</sub>NO<sub>2</sub> requires *M* 345.17287.

[3(RS),3a(RS),7a(SR)]- and [3(RS),3a(RS),7a(RS)]-2-Benzyl-3-phenyl-2,3,3a,4,5,7a-hexahydro-1*H*-1,5-isoindoledione **5c** and *epi*-**5c**



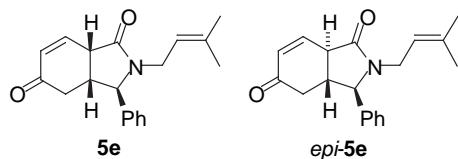
In the same way, amide **1c** (0.25 g, 0.75 mmol) and LDA (0.98 mmol) in THF (15 ml) gave, after purification by flash chromatography (7:3 petroleum ether:ethyl acetate), the title compounds as a colourless oil (0.12 g, 50 %). <sup>1</sup>H NMR shows two diastereoisomers in a ratio of 3:1; R<sub>f</sub> 0.16;  $\nu_{\text{max}}$  = 1686.14, 1678.36 (C=O);  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 7.13 (11H, m, Ph), 6.23 (1H, dd, *J* 2.5, *J* = 10.2, H6), 5.14 and 3.54 (2H, d, *J* 14.5, CH<sub>2</sub>Bn<sup>major</sup>), 5.21 and 3.58 (2H, d, *J* 14.5, CH<sub>2</sub>Bn<sup>minor</sup>), 4.07 (1H, d, *J* 6.5, H3), 3.99 (1H, d, *J* 8, H3), 3.67 (1H, m, H7a), 2.88 (1H, m, H3a), 2.69 (2H, dd, *J* 5, *J* 14.5, H4<sup>minor</sup>), 2.56 (1H, dd, *J* 6, *J* 17, H4a<sup>major</sup>), 2.38 (1H, dd, *J* 6, J17, H4b<sup>major</sup>);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>), 175.15, 172.12, 153.14, 138.64, 135-124 (ArH), 113.71, 89.70, 69.38, 54.25, 44.29, 43.26, 41.58.

[3(RS),3a(RS),7a(SR)]- and [3(RS),3a(RS),7a(RS)]-3-Benzyl-2-(4-methoxybenzyl)-2,3,3a,4,5,7a-hexahydro-1*H*-1,5-isoindoledione **5d** and *epi*-**5d**



In the same way, amide **1d** (2 g, 5.54 mmol) and LDA (7.0 mmol) in 50 ml of THF gave, after purification by flash chromatography (1:1 petroleum ether:ethyl acetate), the title compounds as a yellow oil (1.2 g, 62 %).  $^1\text{H}$  NMR shows two diastereoisomers (ratio 7:1);  $R_f = 0.17$ ;  $\nu_{\text{max}}$  1679 (C=O);  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.6-6.6 (9H, m, ArH), 6.23 (1H, d,  $J$  10.5, H5<sup>minor</sup>), 6.09 (1H, dd,  $J$  2.5,  $J$  8, H5<sup>major</sup>), 5.03 (1H, d,  $J$  14.5, H1'a<sup>minor</sup>), 4.96 (1H, d,  $J$  14.5, H1'a<sup>major</sup>), 3.92 (1H, d,  $J$  8, H3<sup>minor</sup>), 3.84 (1H, d,  $J$  8, H3<sup>major</sup>), 3.70 (3H, s,  $\text{CH}_3\text{O}$ ), 3.5-3.6 (1H, m, H7a), 3.46 (1H, d,  $J$  14.5, H1'b<sup>minor</sup>), 3.36 (1H, d,  $J$  14.5, H1'b<sup>major</sup>), 3.0-2.9 (1H, m, H3a), 2.65 (1H, dd,  $J$  8, 15, H4a<sup>minor</sup>), 2.53 (1H, dd,  $J$  6.5, 17, H4a<sup>major</sup>), 2.34 (1H, dd,  $J$  7, 15.5, H4b<sup>major</sup>);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 196.06, 171.84, 159.03, 143.34, 137.09, 130.89, 130.093, 129.52, 113.94, 113.85, 64.61, 55.10, 43.97, 43.50, 40.40, 35.83.

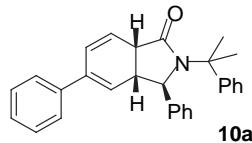
*[3(RS),3a(RS),7a(SR)]- and [3(RS),3a(RS),7a(RS)]-3-Benzyl-2-(3-methylbut-2-enyl)-2,3,3a,4,5,7a-hexahydro-1H-1,5-isoindoledione **5e** and epi-**5e***



In the same way, amide **1e** (0.5 g, 1.6 mmol) and LDA (2.08 mmol) gave, after purification by flash chromatography (3:1 petroleum ether:ethyl acetate, the title compounds as an orange oil (0.235 g, 47 %).  $^1\text{H}$  NMR shows two diastereoisomers (ratio x:x).  $R_f = 0.17$ ;  $\nu_{\text{max}}$  2930 (CH), 1680 (C=O);  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.6-7.1 (5H, m, ArH),

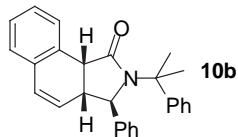
6.92 (1H, dd, *J* 3.5, *J* 10, H7<sup>major</sup>), 6.26 (1H, dd, *J* 2.5, *J* 10, H6<sup>major</sup>), 5.04 (1H, m, CH<sub>2</sub><sup>minor</sup>), 4.90 (1H, m, CH<sub>2</sub><sup>major</sup>), 4.42 (1H, d, *J* 5.5, H3<sup>minor</sup>), 4.36 (1H, d, *J* 5.4, H3<sup>major</sup>), 4.17 (1H, dd, *J* 8, *J* 14.5, CH=), 3.58 (1H, m, H7a), 3.34 (1H, dd, *J* 8.5, *J* 14.5, CH<sub>2</sub><sup>minor</sup>), 3.22 (1H, dd, *J* 9, *J* 14.5, CH<sup>major</sup>), 2.82 (1H, m, H3a), 2.63 (1H, dd, *J* 6, *J* 17, H4), 2.50 (1H, dd, *J* 3.5, *J* 17, H4), 1.67 (3H, s, CH<sub>3</sub><sup>minor</sup>), (3H, s, CH<sub>3</sub><sup>major</sup>), 1.26 (3H, s, CH<sub>3</sub><sup>minor</sup>), 1.20 (3H, s, CH<sub>3</sub><sup>major</sup>); m/z (EI) 295 (M<sup>+</sup>, 100 %). Found: M<sup>+</sup> 295.1576; C<sub>19</sub>H<sub>21</sub>NO<sub>2</sub> requires *M* 295.15722.

*[3(RS),3a(RS),7a(SR)]-2-(1-Methyl-1-phenylethyl)-3,5-diphenyl-2,3,3a,7a-tetrahydro-1H-1-isoindolone 10a*



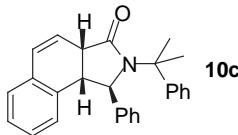
In the same way, amide **9a** (0.25 g, 0.64 mmol) and LDA (0.83 mmol) in THF (15 ml) gave, after purification by flash chromatography (4:1 petroleum ether:ethyl acetate), the title compound as a waxy yellow solid (0.22 g, 88 %); R<sub>f</sub>=0.24;  $\nu_{\text{max}}$  2979, 1688, 1600;  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 7.6-7.0 (15H, m, ArH), 6.40 (1H, d, *J* 10, H6), 6.05 (1H, dd, *J* 5, 10, H7), 5.95 (1H, d, *J* 3, H4) 4.94 (1H, d, *J* 2.5, H3), 3.64 (1H, dd, *J* 5.5, 11.5, H7a), 3.26 (1H, dt, *J* 11.5, H3a), 1.88 (1H, 3H, CH<sub>3</sub>), 1.45 (3H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 174.87, 147.12, 143.59, 140.08, 136.02, 128.96, 128.48, 128.05, 127.75, 127.53, 127.30, 126.32, 125.62, 125.58, 125.28, 124.79, 123.96, 122.93, 70.62, 60.20, 43.80, 40.40, 29.94, 26.97; m/z (CI) 406 (M+H<sup>+</sup>, 75 %), 119 (100 %). Found: M<sup>+</sup> 405.2088; C<sub>29</sub>H<sub>27</sub>NO requires *M* 405.20925.

*[3(RS),3a(RS),7a(RS)]-2-(1-Methyl-1-phenylethyl)-3-phenyl-2,3,3a,9b-tetrahydro-1H-benzo[e]isoindol-1-one 10b*



In the same way, amide **9b** (0.25 g, 0.66 mmol) and LDA (0.83 mmol) in THF (15 ml) gave, after purification by flash chromatography (4:1 petroleum ether:ethyl acetate), the title compound as a yellow solid (0.22 g, 88 %), mp 170-171 °C;  $R_f$  = 0.21;  $\nu_{\max}$  2978, 1689, 1655;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.1-7.6 (14H, m, ArH), 7.06 (1H, dd, H), 6.59 (1H, dd,  $J$  2.5, 10, H5), 5.91 (1H, dd,  $J$  2.5, 9.5, H4), 4.88 (1H, s, H3), 4.01 (1H, d,  $J$  9, H9b), 3.24 (1H, d,  $J$  8.5, H3a), 1.87 (3H, s,  $\text{CH}_3$ ), 1.52 (1H, s,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 173.84, 146.50, 142.94, 131.33, 130.23, 129.60, 129.15, 128.91, 128.04, 127.88, 127.86, 127.76, 127.62, 126.53, 126.46, 125.65, 125.20, 68.65, 59.87, 44.32, 44.09, 28.97, 27.17; m/z (CI) 380 ( $\text{M}+\text{H}^+$ , 100 %), 119 (30 %). Found C, 85.4; H, 6.7; N, 3.6,  $M^+$  379.1941;  $\text{C}_{27}\text{H}_{25}\text{NO}$  requires C, 85.4; H, 6.6; N, 3.6;  $M$  379.1938.

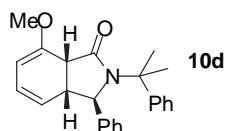
*[3(RS),3a(SR),7a(SR)]-2-(1-Methyl-1-phenylethyl)-1-phenyl-2,3,3a,9b-tetrahydro-1H-benzo[e]isoindol-3-one 10c*



In the same way, naphthamide **9c** (0.15 g, 0.40 mmol) and LDA (0.51 mmol) in THF (15 ml) gave, after purification by flash chromatography (4:1 petroleum ether:ethyl acetate), the title compound as a yellow solid (0.147 g, 98 %); m.p. 114-116 °C;  $R_f$  = 0.18;  $\nu_{\max}$  3029 (CH), 1692 (C=O);  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ), 7.26 (14H, m, ArH), 6.63 (2H, m, H1',

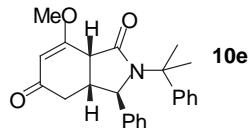
H6), 5.88 (1H, dd,  $J = 3.4, J = 9.7$ , H7), 4.87 (1H, d,  $J = 6.2$ , H2), 3.66 (1H, m, H3), 3.54 (1H, dd,  $J = 6.2, J = 9.9$ , H8), 1.79 (3H, s, CH<sub>3</sub>), 1.35 (3H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 175.43, 147.42, 142.97, 131.91, 131.66, 128.68, 128.14, 127.91, 127.83, 127.71, 127.60, 127.52, 127.37, 127.00, 126.22, 124.74, 123.25, 71.39, 60.59, 46.02, 44.15, 29.45, 27.80; m/z (EI) 380 (M+H<sup>+</sup>, 15 %), 119 (100 %). Found: M<sup>+</sup> 379.1937; C<sub>27</sub>H<sub>25</sub>NO requires M 379.1936.

*[3(RS),3a(RS),7a(RS)]-7-Methoxy-2-(1-methyl-1-phenylethyl)-3-phenyl-2,3,3a,7a-tetrahydro-1H-1-isoindolone 10d*



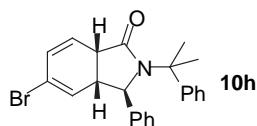
In the same way, amide **9d** (0.25 g, 0.70 mmol) and LDA (0.83 mmol) in THF (15 ml), using HCl during the work-up, gave, after purification by flash chromatography (4:1 petroleum ether:ethyl acetate) the title compound as a yellow solid (0.15 g, 60 %); m.p. 130-131 °C; R<sub>f</sub> = 0.10;  $\nu_{\text{max}}$  2980 (CH), 1692 (C=O), 1655 (C=O), 1595 (C=C);  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>), 7.30 (10H, m, ArH), 6.04 (1H, m, H5), 5.40 (1H, dd,  $J = 2, J = 9.5$ , H4), 4.96 (1H, d,  $J = 6.5$ , H6), 4.89 (1H, s, H3), 3.66 (3H, s, CH<sub>3</sub>O), 3.52 (1H, d,  $J = 9.5$ , H7a), 3.23 (1H, d,  $J = 9.5$ , H3a), 1.87 (3H, s, CH<sub>3</sub>), 1.48 (3H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 173.26, 154.58, 146.78, 142.83, 128.87, 127.96, 127.85, 126.35, 125.48, 125.34, 125.10, 119.42, 91.95, 68.85, 55.10, 46.11, 44.48, 29.56, 8.34, 26.76; m/z (EI) 359 (M<sup>+</sup>, 30 %), 242 (30 %), 119 (100 %). Found: M<sup>+</sup> 359.1884; C<sub>24</sub>H<sub>25</sub>NO<sub>2</sub> requires M 359.18852.

*[3(RS),3a(RS),7a(RS)]-7-Methoxy-2-(1-methyl-1-phenylethyl)-3-phenyl-2,3,3a,4,5,7a-hexahydro-1H-1,5-isoindoledione 10e*



In the same way, amide **9e** (0.25 g, 0.64 mmol) and LDA (0.83 mmol) in THF (15 ml), using HCl during the work-up, gave, after purification by flash chromatography (4:1 petroleum ether:ethyl acetate), the title compound as a yellow solid (0.15 g, 62 %); m.p. 178-180 °C;  $R_f$  = 0.14 (1:1 petroleum ether: ethyl acetate);  $\nu_{\max}$  2978 (CH), 1690 (C=O), 1655 (C=O), 1620 (C=C);  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.32 (10H, m, ArH), 5.21 (1H, s, H6), 4.46 (1H, s, H3), 3.76 (3H, s,  $\text{OCH}_3$ ), 3.69 (1H, m, H7a), 2.2-3.8 (3H, m, H3a, H4), 1.87 (3H, s,  $\text{CH}_3$ ), 1.57 (3H, s,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ), 196.18, 172.06, 169.53, 145.36, 140.76, 129.01, 128.11, 127.04, 125.58, 125.45, 102.91, 66.78, 59.64, 56.34, 44.68, 41.81, 38.92, 27.85, 26.87;  $m/z$  (EI) 375 ( $\text{M}^+$ , 30 %), 125 (100%), 119 (75 %). Found  $\text{M}^+$  375.1841;  $\text{C}_{24}\text{H}_{25}\text{NO}_3$  requires  $M$  375.18343.

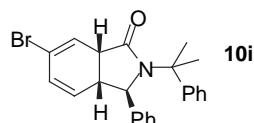
*[3(RS),3a(RS),7a(SR)]-5-Bromo-2-(1-methyl-1-phenylethyl)-3-phenyl-2,3,3a,7a-tetrahydro-1H-1-isoindolone 10h*



In the same way, amide **9h** (0.15 g, 0.37 mmol) and LDA (0.48 mmol) in THF (15 ml) gave, after purification by flash chromatography (4:1 petroleum ether:ethyl acetate), the title compound as an unstable yellow oil (0.089 g, 59 %);  $R_f$  = 0.19;  $\nu_{\max}$  2982 (CH), 1686 (C=O);  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.8-7.0 (10H, m, ArH), 6.1-5.8 (3H, m, H4, H6, H7),

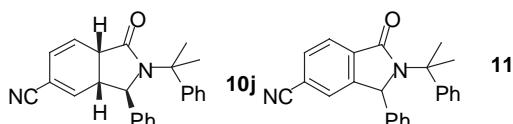
4.83 (1H, s, H3), 3.57 (1H, dd, *J* 5.5, 11.5, H7a), 3.18 (1H, m, H3a), 1.86 (3H, s, CH<sub>3</sub>), 1.44 (3H, s, CH<sub>3</sub>); m/z (CI) 408 (M+H<sup>+</sup>, 85 %), 328 (M<sup>+</sup>-Br, 100 %). Found: M<sup>+</sup> 407.0887; C<sub>23</sub>H<sub>22</sub>BrNO requires *M* 407.08852.

*[3(RS),3a(RS),7a(SR)]-6-Bromo-2-(1-methyl-1-phenylethyl)-3-phenyl-2,3,3a,7a-tetrahydro-1H-1-isoindolone 10i*



In the same way, amide **9i** (0.25 g, 0.61 mmol) and LDA (0.83 mmol) in THF (15 ml) gave, after purification by flash chromatography (4:1 petroleum ether:ethyl acetate) the title compound as an unstable yellow solid (0.11 g, 44 %); δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 7.33 (10H, m, ArH), 6.45 (1H, d, *J* 4.5, H7), 5.7-6.0 (2H, m, H4, H5), 5.44 (1H, s, H3), 3.74 (1H, dd, *J* 5.5, 11, H7a), 3.30 (1H, d, *J* 11.5, H3a); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 173.63, 146.58, 142.72, 128.91, 128.03, 127.83, 127.27, 126.54, 125.67, 124.90, 124.77, 122.78, 122.61, 68.23, 59.79, 50.17, 42.97, 29.32, 26.46.

*[3(RS),3a(RS),7a(SR)]-2-(1-Methyl-1-phenylethyl)-1-oxo-3-phenyl-2,3,3a,7a-tetrahydro-1H-5-isoindolecarbonitrile 10j and 2-(1-Methyl-1-phenylethyl)-1-oxo-3-phenyl-2,3-dihydro-1H-5-isoindolyl cyanide 11*



In the same way, amide **9j** (0.15 g, 0.42 mmol) and LDA (0.55 mmol) in THF (15 ml) gave, after purification by flash chromatography (8:2 petroleum ether:ethyl acetate), the

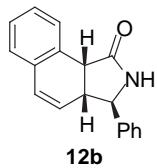
amide **10j** as a yellow solid (0.03 g, 20 %); m.p. 204-206 °C;  $R_f$  = 0.12;  $\nu_{\max}$  2924.30 (CH), 2250 (CN), 1686 (CO);  $\delta_H$  (300 MHz,  $CDCl_3$ ) 7.22 (10H, m, ArH), 6.40 (1H, d,  $J$  4, H8), 5.89 (1H, dd,  $J$  5,  $J$  9.5, H7), 5.88 (1H, d,  $J$  10, H6), 4.69 (1H, d,  $J$  3, H2), 3.53 (1H, qq,  $J$  1.5,  $J$  6.5, H3), 3.09 (1H, dt,  $J$  3.6, H8), 1.73 (3H, s,  $CH_3$ ), 1.35 (3H, s,  $CH_3$ );  $\delta_C$  (75 MHz,  $CDCl_3$ ) 173.08, 146.26, 142.42, 139-124 (ArH), 119.79, 117.66, 111.43, 69.44, 60.61, 42.89, 39.73, 29.03, 27.16; m/z (CI) 355 ( $M+H^+$ , 90 %), 119 (100%). Found:  $M^+$  354.1733;  $C_{24}H_{22}N_2O$  requires  $M$  354.1732.

Also obtained was amide **11**, mp = 178-180°C;  $R_f$  = 0.15;  $\nu_{\max}$  2980 (CH), 2230 (CN), 1692 (C=O);  $\delta_H$  (300 MHz,  $CDCl_3$ ) 7.77 (1H, d,  $J$  7.5, H6), 7.57 (1H, d,  $J$  7.5, H7), 7.3-6.9 (11H, m, ArH), 5.78 (1H, s, H3), 1.82 (3H, s,  $CH_3$ ), 1.54 (3H, s,  $CH_3$ );  $\delta_C$  (75 MHz,  $CDCl_3$ ) 167.45, 147, 05, 146.17, 138.27, 135.55, 131.95, 129.11, 128.54, 128.18, 126.91, 126.84, 126.74, 125.17, 124.23, 118.06, 115.13, 65.55, 60.75, 28.57, 27.96; m/z (CI) 353 ( $M+H^+$ , 100 %). Found:  $M^+$  352.1571;  $C_{24}H_{20}N_2O$  requires  $M$  352.15755.

### Procedure for deprotection

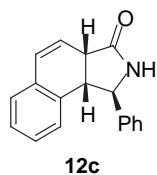
The amide **10** was treated with trifluoroacetic acid or a mixture of trifluoroacetic acid and dichloromethane and the mixture was refluxed for 3 h. Concentration under reduced pressure afforded a brown oil which was purified by flash chromatography.

*[3(RS),3a(RS),7a(RS)]-3-Phenyl-2,3,3a,9b-tetrahydro-1H-benzo[e]isoindol-1-one **12b***



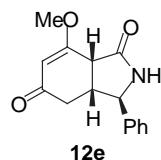
In this way, the amide **10b** (100 mg, 0.26 mmol) and trifluoroacetic acid (2 ml) gave, after purification by flash chromatography (2:1 petroleum ether:ethyl acetate) the amide **12b** (0.063 g, 94%) as a white solid, mp 166-167°C;  $R_f$  = 0.15;  $\nu_{\text{max}}$  3200 (NH), 3020 (CH), 1696 (C=O);  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.8-7.0 (9H, m, ArH), 6.59 (1H, d,  $J$  9.5, H5), 6.41 (1H, b, NH), 5.91 (1H, dd,  $J$  4.5,  $J$  9.5, H4), 4.57 (1H, d,  $J$  5.5, H3), 3.89 (1H, d,  $J$  9.5, H7a), 3.29 (1H, m, H3a);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 177.40, 140.80, 131.75, 128.93, 128.68, 128.64, 128.31, 128.19, 128.19, 128.13, 127.63, 126.97, 125.69, 125.46, 63.60, 45.72, 42.92;  $m/z$  (CI) 262 ( $\text{M}+\text{H}^+$ , 100 %). Found  $\text{M}^+$  261.1154;  $\text{C}_{18}\text{H}_{15}\text{NO}$  requires  $M$  261.11536.

*[3(RS),3a(SR),7a(SR)]-1-Phenyl-2,3,3a,9b-tetrahydro-1H-benzo[e]isoindol-3-one 12c*



In the same way, the amide **10c** (0.096 mg, 0.26 mmol), trifluoroacetic acid (1 ml) and dichloromethane (1 ml) gave, after purification by flash chromatography (2:1 petroleum ether:ethyl acetate), the amide **12c** (0.051 g, 76%) as a white solid, mp 166-167 °C;  $R_f$  = 0.23;  $\nu_{\max}$  3230 (NH), 3032 (CH), 1698 (C=O);  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) 7.4-6.8 (8H, m, ArH), 6.76 (1H, b, NH), 6.60 (1H, dd,  $J$  3, J 9.5, H6), 6.35 (1H, d,  $J$  7.5, ArH), 5.81 (1H, dd,  $J$  2.5, J 9.5, H7), 4.38 (1H, d,  $J$  9, H3), 3.58 (1H, dt,  $J$  2.5, J 9, H7a), 3.41 (1H, t,  $J$  9, H3a);  $\delta_C$  (75 MHz,  $\text{CDCl}_3$ ) 178.94, 138.56, 131.38, 130.56, 128.77, 128.56, 127.94, 127.76, 127.50, 127.45, 126.94, 121.33, 65.26, 48.59, 44.90;  $m/z$  (EI) 261 ( $M^+$ , 3%), 128 (100 %). Found:  $M^+$  261.1161;  $C_{18}\text{H}_{15}\text{NO}$  requires  $M$  261.11536.

*[3(RS),3a(RS),7a(RS)]-7-Methoxy-3-phenyl-2,3,3a,4,5,7a-hexahydro-1H-1,5-isoindoledione 12e*



In the same way, the amide **10c** (0.082 g, 0.22 mmol) and trifluoroacetic acid (2 ml) gave, after purification by flash chromatography (ethyl acetate) the amide **12c** (0.056 g, 100%) as an orange wax;  $R_f$  = 0.15;  $\nu_{\max}$  3230 (NH), 2916 (CH), 1707 (C=O), 1655 (C=O), 1603;  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) 7.5-7.0 (5H, m, ArH), 6.08 (1H, b, NH), 5.51 (1H, s, H6), 4.32 (1H, d,  $J$  6.5, H3), 3.74 (3H, s,  $\text{CH}_3\text{O}$ ), 3.43 (1H, d,  $J$  7.5, H7a), 2.86 (1H, m, H3a),

2.46 (2H, m, H4);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 195.89, 172.91, 169.75, 138.76, 129.11, 128.71, 126.05, 103.86, 61.43, 56.54, 44.65, 43.12, 35.85, 29.61;  $m/z$ (CI) 258 ( $\text{M}+\text{H}^+$ , 70 %), 72 (100 %). Found:  $\text{M}^+$  257.1048;  $\text{C}_{15}\text{H}_{15}\text{NO}_3$  requires  $M$  257.10519.