SYNTHESIS OF 6-SUBSTITUTED 5,6,7,12-TETRAHYDROBENZO[4,5]-CYCLOHEPT[*b*]INDOL-12-ONE DERIVATIVES

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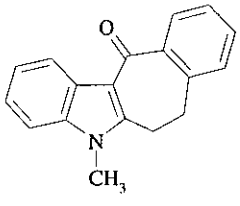
Abstract- The synthesis of 6-substituted 5,6,7,12-dihydrobenzo[4,5]cyclohept[*b*]-indole derivatives, through a regioselective alkylation of **1** in position-6, is reported. The antiproliferative activity of **18** was evaluated.

In our ongoing research to identify new effective chemotherapeutic agents, we have reported the preparation of 12-substituted 5,6,7,12-tetrahydrobenzo[4,5]cyclohept[*b*]indole derivatives[1] from the starting compound (**1**).[2] Of this new family, compound (**2**) was determined as the most active compound, exhibiting a modest *in vitro* cytotoxicity (IC_{50} L1210= 4.7 μM and IC_{50} LLC= 11.6 μM). As a continuation of our study of hydrobenzo[4,5]cyclohept[*b*]indole moiety as potential anticancer agent, we investigated the attachment position of the aminoalkyl chain, a group found in several anticancer agents,[3-5] on a seven membered ring.

In this paper, we describe the synthetic pathways and the preliminary antitumoral evaluation of a new series of 6-substituted 5,6,7,12-tetrahydrobenzo[4,5]cyclohept[*b*]indol-12-one derivatives (**A**).



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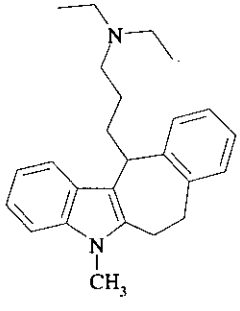

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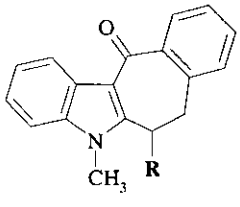
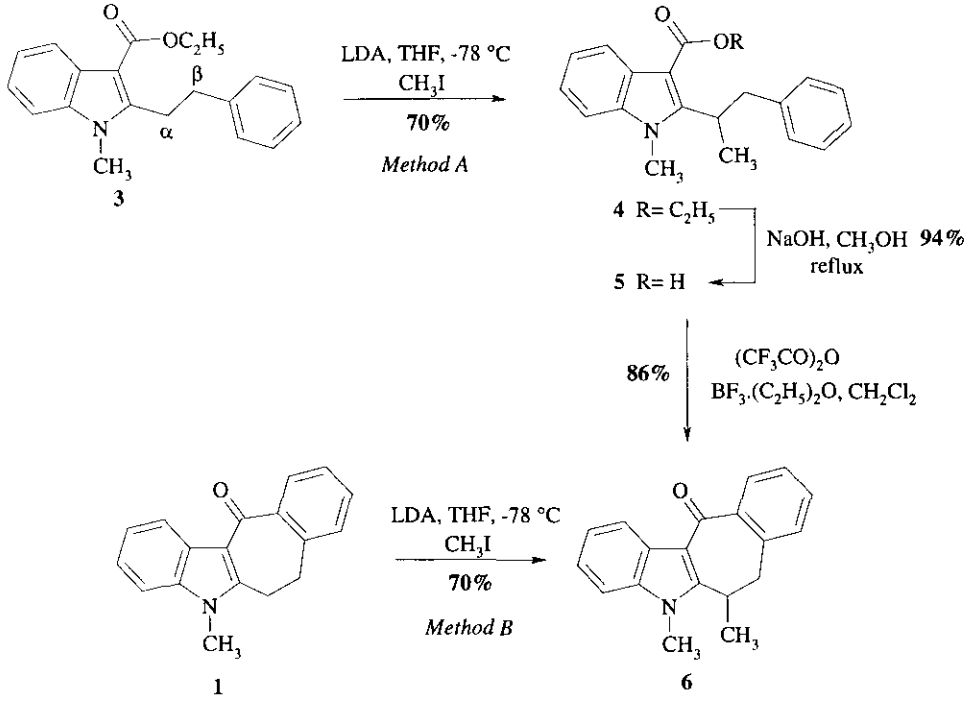


A

Two approaches have been investigated to obtain the model 6-methyl derivative (**6**) (Scheme 1). On one hand, the preparation of the tetracyclic compound (**6**) could be achieved from already methyl substituted precursors. On the other hand, the regioselective alkylation of the ketone (**1**) is an alternative way to obtain the same derivative (**6**).

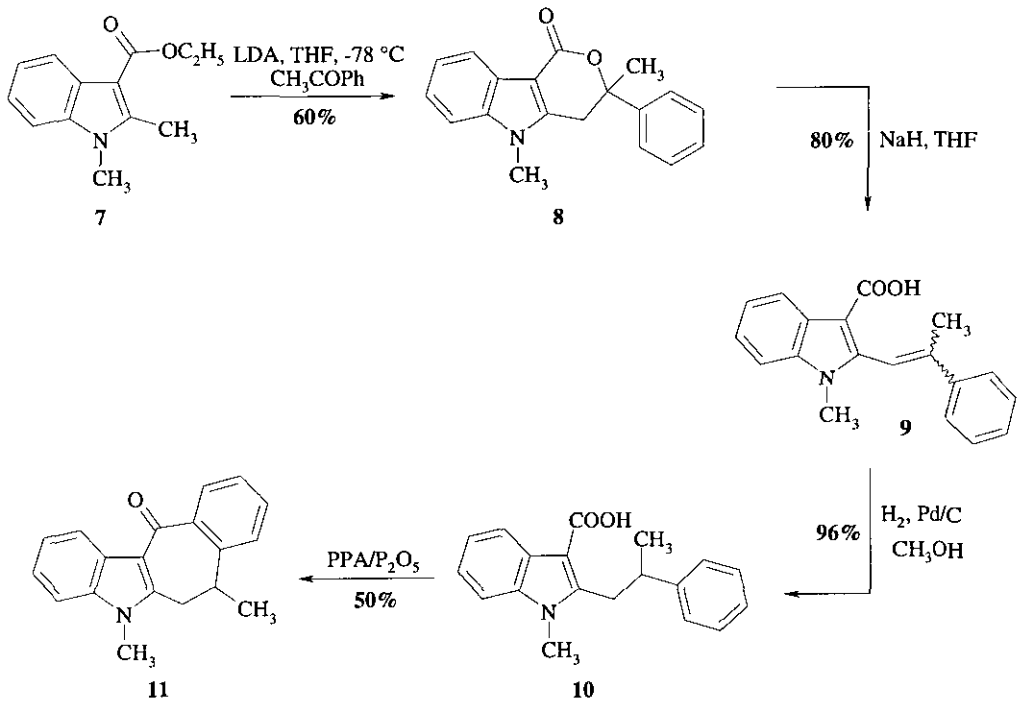
The ethyl 1-methyl-2-phenylethylindole-3-carboxylate (**3**)[2] was regioselectively lithiated in position-α on the phenyl chain with LDA in THF at -78 °C, followed by quenching of the carbanion obtained by addition of iodomethane affording **4** in 70% yield. The regioselectivity of this alkylation in position-α, despite the benzylic position-β, was determined by 2D NMR experiments. Saponification of ester (**4**) with a methanolic sodium hydroxide solution at reflux (24 h) afforded the corresponding acid (**5**) in 94% yield. Finally, the cyclization of **5** in the presence of trifluoroacetic anhydride and boron trifluoride diethyl ether in dichloromethane gave the tetracyclic ketone (**6**) in 86% yield.



Scheme 1

In order to firmly confirm the site of alkylation, the isomeric tetracyclic ketone (**11**) has been prepared according to a methodology developed by Macor (Scheme 2).[6,7] The anion generated from the starting material (**7**)[8] using LDA at -78 °C is quenched with acetophenone to form the lactonic compound (**8**) in 60% yield. Treatment of **8** with base led to the opening of the lactonic ring followed by a dehydration to affording **9** as a *E/Z* mixture (ratio 1.5:1) in 80% yield. Catalytic hydrogenation of **9** under 40 psi of

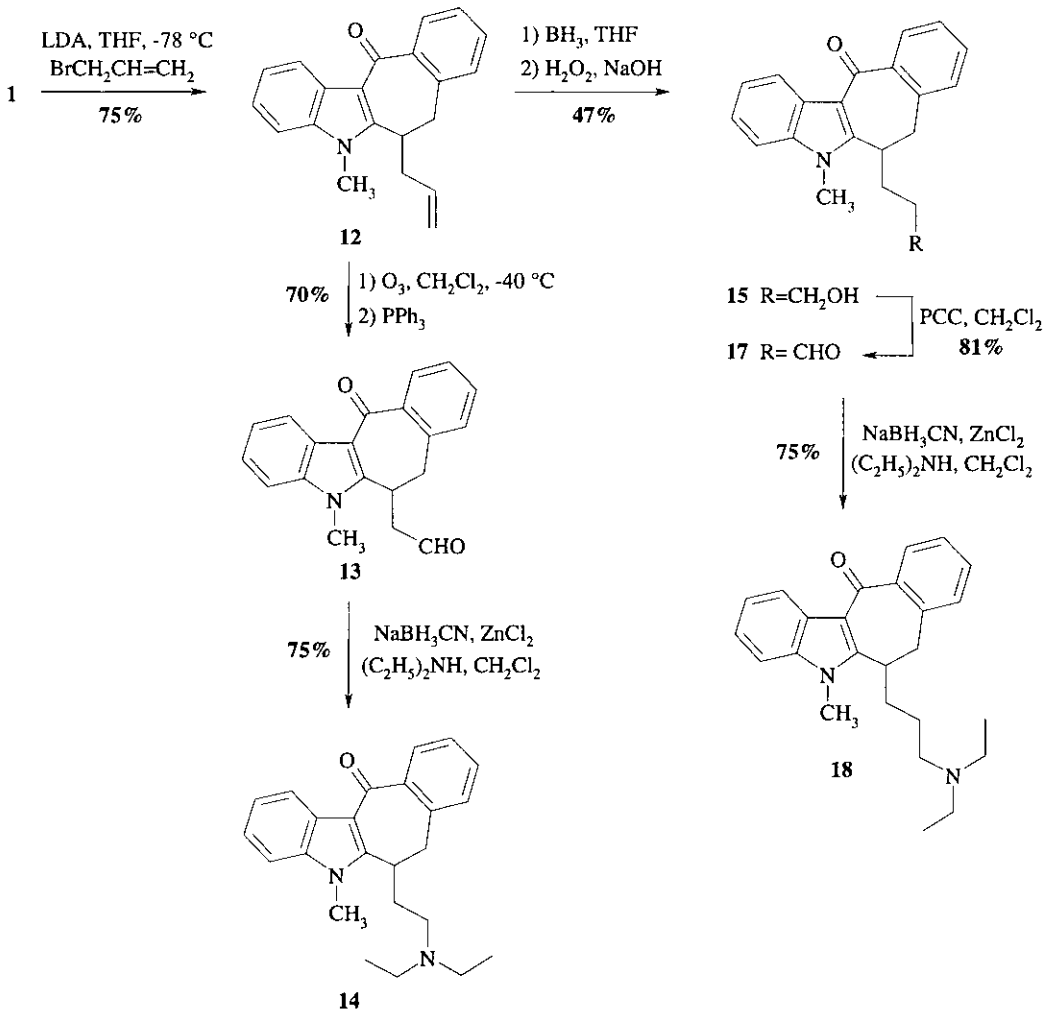
hydrogen using palladium on carbon (10%) gave compound (**10**) in 96% yield. Final cyclization of **10** with PPA/P_2O_5 at 110 °C gave in 50% yield of the ketone (**11**). Compound (**11**) and its isomer (**6**) were obviously different comparing their NMR data. The ^1H NMR spectrum of **11** showed a doublet signal for the methyl at δ 1.43 ppm (J = 7.1 Hz) whereas for **6** the methyl was highshielded at δ 1.11 ppm (d, J = 7.2 Hz).



Scheme 2

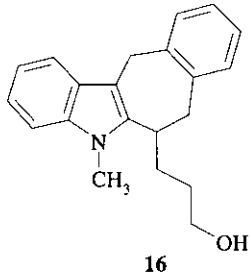
Considering this regioselective alkylation of **3**, we have applied this strategy to the ketone (**1**) (Scheme 1). Thus, compound (**6**) was directly prepared in 70% yield through a lithiation in position-6 of **1** with LDA in THF at -78 °C followed by addition of iodomethane in the medium.

The second pathway involving the direct alkylation of **1** allowed us to prepare several 6-substituted derivatives (Scheme 3). Initial alkylation attempts with ethyl bromoacetate as electrophile were fruitless. Therefore, we chose to introduce the allyl moiety, which can be a good precursor for the aminoalkyl chain. Reaction of **1** with LDA in THF, followed by addition of 3-bromopropene gave compound (**12**) in 75% yield. Ozonolysis of **12** in the presence of triphenylphosphine afforded the aldehyde derivative (**13**). Reductive amination of **13** was performed with zinc chloride and sodium cyanoborohydride in the presence of diethylamine to afford the aminoalkyl product (**14**) in 75% yield.



Scheme 3

Hydroboration of **12** with borane-tetrahydrofuran complex or borane-methyl sulfide complex, followed by an oxidation with hydrogen peroxide in basic medium afforded the alcohol (**15**) in 47% yield. Using an excess of the reducing reagent involved an over reduction of the keto group to the alcohol (**16**) (89% yield).



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Oxidation of **15** in the presence of pyridinium chlorochromate in dichloromethane afforded the aldehyde derivative (**17**). Reductive amination of **17** gave the desired compound (**18**) in 75% yield.

Compound (**18**) was evaluated for growth inhibitory property, measured as IC_{50} value, against the murine leukemia L1210 cell line.[9] The biological result was compared with the reference compound adriamycine (IC_{50} L1210= 0.024 μM). Weak *in vitro* cytotoxicity was observed for **18** (IC_{50} L1210= 31.7 μM).

This study represents an effective route to 6-substituted derivatives through a regioselective alkylation of the seven-membered ring. Unfortunately, the cytotoxicity of these derivatives (e.g. compound (**18**)) was *significantly less compared to adriamycine.*

EXPERIMENTAL

Melting points were determined using a Büchi SMP-20 melting point apparatus and are uncorrected. The IR spectra of compounds were recorded on a Perkin Elmer FTIR paragon 1000 spectrophotometer. NMR spectra were recorded at 300 °K in $CDCl_3$ or DMSO-d_6 on a Bruker Avance DPX 250. Chemical shifts are expressed in parts per million and referenced to TMS. MS spectra were recorded on Perkin-Elmer SCIEX API 300 using ionspray methodology. Thin layer chromatography was performed on precoated plate of silica gel $60F_{254}$ (Merck) and the spots visualised using a UV lamp. Flash chromatography was performed with Merck silica gel 60 (0.040 mm-0.063 mm) as the stationary phase. All air- and moisture sensitive reactions were conducted under a prepurified argon atmosphere. Anhydrous solvents or reagents were transferred *via* syringe.

Ethyl 1-methyl-2-(1-methyl-2-phenylethyl)-1*H*-indole-3-carboxylate (4). To a suspension of ester (**3**) (1.6 g, 5.20 mmol) in anhydrous THF (100 mL), 2M lithium diisopropylamide in heptane (3.38 mL, 6.77 mmol) was added dropwise at -78 °C. After 30 min, a solution of iodomethane (0.65 mL, 10.40 mmol) in THF (5 mL) was added dropwise with vigorous stirring at -78 °C. The mixture was stirred 1 h at -78 °C, then 1 h at rt and THF was removed *in vacuo*. The residue was partitioned between ethyl acetate (30 mL) and 10% hydrochloric acid (30 mL), the aqueous phase separated and extracted with ethyl acetate (2 x 30 mL). The organic layers were combined, dried ($MgSO_4$) and evaporated *in vacuo*. The crude compound was purified by column chromatography (eluent: 9:1 petroleum ether/ethyl acetate) to afford 1.17 g (70%) of **4** as a white solid; mp 70 °C (ether-petroleum ether); IR (KBr): ν 1681 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ: 1.51 (t, 3H, J = 7.2 Hz, CH_3), 1.52 (d, 3H, J = 6.9 Hz, CH_3), 3.10 (dd, 1H, J = 7.7, 13.2 Hz, CH_2), 3.35-3.44 (m, 1H, CH_2), 3.59 (br s, 3H, CH_3), 4.10-4.30 (m, 1H, CH), 4.46 (q, 2H, J = 7.2 Hz, CH_2), 7.13-7.27 (m, 8H, H_{Ar}), 8.16-8.20 (m, 1H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ: 14.8 (CH_3), 18.0 (CH_3), 31.1 (CH_3), 33.8 (CH), 41.0 (CH_2), 59.7 (CH_2), 104.0 (q), 109.4, 121.8, 122.0, 122.2, 126.2, 127.0

(q), 128.4 (2), 129.1 (2), 136.7 (q), 140.6 (q), 152.1 (q), 166.0 (CO); MS: *m/z* 322 (M^++1); *Anal.* Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.18; H, 7.08; N, 4.45.

1-Methyl-2-(1-methyl-2-phenylethyl)-1*H*-indole-3-carboxylic acid (5). A solution of ester (**4**) (1.00 g, 3.11 mmol) in 95% methanol (40 mL) and sodium hydroxide (1.24 g, 31.1 mmol) was stirred at reflux for 48 h. The solvent was removed *in vacuo*, water (20 mL) was added to the residue and the *p*H was adjusted to 1 by careful addition of 10% hydrochloric acid. After extraction with methylene chloride (2 x 20 mL), the organic layer was dried ($MgSO_4$) and evaporated *in vacuo*. The residue was separated by column chromatography (eluent: 8:2 petroleum ether/ethyl acetate) to give 860 mg (94%) of **5** as a crystalline compound; mp 132 °C (ether-petroleum ether); IR (KBr): ν 3300-2500 (OH), 1690 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 1.56 (d, 3H, *J* = 7.2 Hz, CH_3), 3.11 (dd, 1H, *J* = 7.7, 13.2 Hz, CH_2), 3.35-3.52 (m, 1H, CH_2), 3.58 (br s, 3H, CH_3), 4.10-4.30 (m, 1H, CH), 7.12-7.31 (m, 8H, H_{Ar}), 8.31-8.35 (m, 1H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 18.0 (CH_3), 31.2 (CH_3), 33.9 (CH), 41.0 (CH_2), 103.3 (q), 109.4, 122.2, 122.3, 122.4, 126.3, 127.5 (q), 128.5 (2), 129.1 (2), 136.8 (q), 140.5 (q), 153.4 (q), 166.0 (CO); MS: *m/z* 294 (M^++1); *Anal.* Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 78.02; H, 6.68; N, 4.90.

5,6-Dimethyl-5,6,7,12-tetrahydrobenzo[4,5]cyclohepta[*b*]indol-12-one (6). *Method A*: To a solution of **5** (500 mg, 1.70 mmol) in 1,2-dichloroethane (15 mL) was added trifluoroacetic anhydride (0.60 mL, 4.26 mmol), and the mixture was stirred at rt for 1 h, then boron trifluoride etherate (0.21 mL, 1.70 mmol) was added. The reaction was carried out at 25 °C for 5 h. After cooling, water (20 mL) was added and the mixture was neutralized with 10% aqueous sodium hydroxide, then extracted with ethyl acetate (3 x 15 mL). The organic layer was dried ($MgSO_4$) then evaporated *in vacuo*. The crude residue was purified by column chromatography (eluent 9:1 petroleum ether/ethyl acetate) to give 400 mg (86%) of **6** as a solid; *Method B*: To a suspension of **1** (200 mg, 0.76 mmol) in anhydrous THF (15 mL), 2M lithium diisopropylamide in heptane (0.5 mL, 1.0 mmol) was added dropwise at -78 °C. After 30 min, a solution of iodomethane (0.1 mL, 1.52 mmol) in THF (2 mL) was added dropwise with vigorous stirring at -78 °C. The mixture was stirred 1 h at -78 °C, then 1 h at rt and THF was removed *in vacuo*. The residue was partitioned between ethyl acetate (15 mL) and 10% hydrochloric acid (15 mL), the aqueous phase separated and extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, dried ($MgSO_4$) and evaporated *in vacuo*. The crude compound was purified by column chromatography (eluent: 6:4 petroleum ether/methylene chloride) to afford 147 mg (70%) of **6** as a white solid; mp 176 °C (ether-petroleum ether); IR (KBr): ν 1610 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 1.11 (d, 3H, *J* = 7.2 Hz, CH_3), 2.95 (dd, 1H, *J* = 5.3, 13.8 Hz, CH_2), 3.42-3.53 (m, 1H, CH), 3.70-3.76 (m, 1H, CH_2), 3.73 (s, 3H, CH_3), 7.19-7.42 (m, 6H, H_{Ar}), 8.02-8.06 (m, 1H, H_{Ar}), 8.68-8.74 (m, 1H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 17.2 (CH_3), 30.1 (CH_3), 30.5 (CH), 40.4 (CH_2), 109.3, 114.1 (q), 123.2, 123.4 (2), 127.5, 127.9

(q), 130.1, 130.9, 131.2, 135.4 (q), 137.1 (q), 140.6 (q), 153.2 (q), 188.0 (CO); MS: *m/z* 276 (M^++1); *Anal.* Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 83.07; H, 6.03; N, 5.02.

3,5-Dimethyl-3-phenyl-1,3,4,5-tetrahydropyrano[4,3-*b*]indol-1-one (8). To a stirred solution of ethyl 1,2-dimethylindole-3-carboxylate (**7**)[8] (656 mg, 3.02 mmol) in anhydrous THF (20 mL), 2M lithium diisopropylamide in heptane (2.3 mL, 4.60 mmol) was added dropwise at -78 °C under nitrogen. After 30 min, a solution of acetophenone (0.62 mL, 5.31 mmol) in THF (2 mL) was added dropwise with vigorous stirring at -78 °C while maintaining the reaction temperature below -78 °C. The solution was then allowed to warm (usually to rt), and the course of the reaction was closely monitored by using TLC. When the formation of the lactone appeared to be optimized as indicated by TLC, the solution was quenched with water (20 mL), and this aqueous phase mixture was twice extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, dried ($MgSO_4$) and evaporated *in vacuo*. The crude compound was purified by column chromatography (eluent: 4:6 petroleum ether/methylene chloride) to afford 528 mg (60%) of **8** as a solid; mp 221 °C (MeOH); IR (KBr): ν 1691 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 1.83 (s, 3H, CH_3), 3.34 (d, 1H, *J* = 16.8 Hz, CH_2), 3.54 (d, 1H, *J* = 16.8 Hz, CH_2), 3.70 (s, 3H, CH_3), 7.21-7.33 (m, 6H, H_{Ar}), 7.47-7.50 (m, 2H, H_{Ar}), 8.06-8.08 (m, 1H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 30.1 (CH_3), 30.7 (CH_3), 33.3 (CH_2), 83.3 (q), 102.2 (q), 109.7, 120.9, 122.6, 123.1, 124.5 (2), 125.4 (q), 127.7, 128.7 (2), 137.7 (q), 144.5 (q), 145.4 (q), 163.1 (CO); MS: *m/z* 292 (M^++1). *Anal.* Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.15; H, 5.69; N, 4.94.

1-Methyl-2-(2-phenyl-1-propenyl)-1*H*-indole-3-carboxylic acid (9). To a solution of **8** (202 mg, 0.69 mmol) in anhydrous THF (5 mL), a solution of sodium hydride (104 mg, 2.6 mmol) in methanol (5 mL) was added at rt under nitrogen. The reaction solution was heated at reflux for 3 h. Water (10 mL) was then added, and the pH was adjusted to 3 with concentrated hydrochloric acid. The aqueous mixture was then extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, dried ($MgSO_4$) and evaporated *in vacuo*. The crude solid obtained was recrystallized from methanol to give 163 mg (80%) of **9** as a *E/Z* mixture (ratio ≈ 1.5:1); mp 214-216 °C (MeOH); IR (KBr): ν 3300-2500 (OH), 1648 (CO) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): δ 1.98 (d, 3H, *J* = 1.0 Hz, CH_{3E}), 2.35 (d, 3H, *J* = 1.3 Hz, CH_{3Z}), 3.04 (s, 3H, CH_{3Z}), 3.70 (s, 3H, CH_{3E}), 6.79 (d, 1H, *J* = 1.3 Hz, CH_Z=), 7.00 (d, 1H, *J* = 1.0 Hz, CH_E=), 7.05-7.48 (m, 12H, H_{ArE+Z}), 7.54-7.57 (m, 2H, H_{ArZ}), 7.67-7.70 (m, 2H, H_{ArE}), 8.00-8.04 (m, 1H, H_{ArZ}), 8.06-8.10 (m, 1H, H_{ArE}); ^{13}C NMR (62.90 MHz, DMSO-d_6): δ 17.7 (CH_{3E}), 24.7 (CH_{3Z}), 30.5 (CH_{3Z}), 30.8 (CH_{3E}), 104.5 (q), 104.7 (q), 110.3, 110.5, 117.1, 117.2, 120.8, 120.9, 121.4, 121.5, 122.0, 122.2, 125.9 (2), 126.4 (q), 126.6 (q), 127.3 (2), 127.6, 128.1, 128.3 (2), 128.5 (2), 136.4 (q), 136.8 (q), 140.6 (q), 141.1 (q), 142.1 (q), 142.9 (q), 143.5 (q), 143.6 (q), 165.9 (CO), 166.0. (CO); MS: *m/z* 292 (M^++1); *Anal.* Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.58; H, 6.03; N, 4.92.

1-Methyl-2-(2-phenylpropyl)-1*H*-indole-3-carboxylic acid (10). To a solution of **9** (230 mg, 0.79 mmol) in anhydrous dioxane (20 mL) was added 10% Pd/C (50 mg). The reaction mixture was stirred overnight under 40 psi of hydrogen at rt. The catalyst was filtered through Celite and the filtrate was concentrated *in vacuo*. The crude solid was recrystallized from methanol to give 222 mg (96%) of **10** as white crystals; mp 190 °C; IR (KBr): ν 3300-2500 (OH), 1649 (CO) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): δ 1.26 (d, 3H, J = 6.5 Hz, CH_3), 3.18-3.34 (m, 2H, CH_2), 3.48 (s, 3H, CH_3), 3.55-3.63 (m, 1H, CH), 7.12-7.31 (m, 7H, H_{Ar}), 7.41-7.45 (m, 1H, H_{Ar}), 8.01-8.05 (m, 1H, H_{Ar}), 12.00 (br s, 1H, OH); ^{13}C NMR (62.90 MHz, DMSO-d_6): δ 20.4 (CH_3), 29.7 (CH_3), 33.7 (CH), 39.8 (CH_2), 103.7 (q), 110.0, 120.9, 121.1, 121.6, 126.3, 126.5 (q), 126.8 (2), 128.3 (2), 136.2 (q), 146.1 (q), 147.5 (q), 166.4 (CO); MS: *m/z* 294 (M^++1); *Anal.* Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.90; H, 6.60; N, 4.70.

5,7-Dimethyl-5,6,7,12-tetrahydrobenzo[4,5]cyclohepta[*b*]indol-12-one (11). Finely powdered **10** (200 mg, 0.68 mmol) was added to PPA/P_2O_5 (1 g/130 mg) with stirring under nitrogen at 90 °C. After the addition was complete, the mixture was stirred at 110 °C for 2 h. After cooling, ice was added, then the mixture was neutralized with saturated sodium hydrogenecarbonate, and extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. The crude residue was purified by column chromatography (eluent: 8:2 petroleum ether/ethyl acetate) to give 94 mg (50%) of **11** as a solid; mp 171 °C (ether-petroleum ether); IR (KBr): ν 1609 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 1.43 (d, 3H, J = 7.1 Hz, CH_3), 2.98 (dd, 1H, J = 7.7, 18.0 Hz, CH_2), 3.15 (dd, 1H, J = 3.0, 18.0 Hz, CH_2), 3.40-3.53 (m, 1H, CH), 3.61 (s, 3H, CH_3), 7.18-7.42 (m, 6H, H_{Ar}), 7.97-8.00 (m, 1H, H_{Ar}), 8.59-8.63 (m, 1H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 20.3 (CH_3), 30.0 (CH_3), 33.9 (CH_2), 37.0 (CH), 109.1, 114.7 (q), 122.8 (2), 123.1, 126.4, 127.2, 127.3 (q), 130.0, 131.2, 137.1 (q), 140.3 (q), 142.3 (q), 146.8 (q), 188.5 (CO); MS: *m/z* 276 (M^++1); *Anal.* Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.67; H, 6.15; N, 5.22.

5-Methyl-6-allyl-5,6,7,12-tetrahydrobenzo[4,5]cyclohepta[*b*]indol-12-one (12). Following the same procedure used for **6** (*method B*) but substituting iodomethane by 3-bromopropene, purification of the residue by column chromatography (eluent: 9:1 petroleum ether/ethyl acetate) gave **12** (75%) as a crystalline compound; mp 99 °C (methylene chloride-petroleum ether); IR (KBr): ν 1607 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 2.12-2.20 (m, 2H, CH_2), 3.16 (dd, 1H, J = 5.3, 14.4 Hz, CH_2), 3.37-3.45 (m, 1H, CH), 3.65 (br d, 1H, J = 14.4 Hz, CH_2), 3.77 (s, 3H, CH_3), 5.03 (d, 1H, J = 17.0 Hz, CH_2=), 5.13 (d, 1H, J = 10.0 Hz, CH_2=), 5.76-5.92 (m, 1H, CH=), 7.20-7.42 (m, 6H, H_{Ar}), 8.09-8.13 (m, 1H, H_{Ar}), 8.71-8.75 (m, 1H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 30.3 (CH_3), 35.6 (CH), 35.7 (CH_2), 37.4 (CH_2), 109.3, 114.5 (q), 118.1 (CH_2), 123.2, 123.4, 123.5, 127.5, 127.9 (q), 130.3, 131.1 (2), 135.1 (2), 137.1 (q),

140.3 (q), 151.8 (q), 187.4 (CO); MS: *m/z* 302 (M^++1); *Anal.* Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.77; H, 6.19; N, 4.52.

2-(5-Methyl-12-oxo-5,6,7,12-tetrahydrobenzo[4,5]cyclohepta[*b*]indol-6-yl)ethanal (13). To a solution of **12** (200 mg, 0.66 mmol) in anhydrous methylene chloride (10 mL) was passed a slow stream of ozone at -40 °C. Consumption of the starting material was monitored by tlc. Triphenylphosphine (260 mg, 1 mmol) was then added and stirring was continued for 3 h at rt. Evaporation of the solvent followed by the purification of the crude residue by column chromatography (eluent: 9:1 petroleum ether/ethyl acetate) gave 116 mg (70%) of **13** as crystals; mp 172 °C (ether); IR (KBr): ν 1711 (CO), 1608 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 2.48 (dd, 1H, *J* = 3.2, 18.8 Hz, CH_2), 2.65 (dd, 1H, *J* = 5.7, 18.8 Hz, CH_2), 3.23 (dd, 1H, *J* = 5.5, 14.5 Hz, CH_2), 3.69 (d, 1H, *J* = 14.5 Hz, CH_2), 3.73 (s, 3H, CH_3), 4.00-4.07 (m, 1H, CH), 7.07-7.10 (m, 1H, H_{Ar}), 7.30-7.42 (m, 5H, H_{Ar}), 8.07-8.10 (m, 1H, H_{Ar}), 8.68-8.72 (m, 1H, H_{Ar}), 9.69 (s, 1H, CHO); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 29.4 (CH), 30.2 (CH_3), 37.2 (CH_2), 44.3 (CH_2), 109.4, 115.0 (q), 123.4, 123.5, 123.7, 127.8 (q), 127.9, 130.5, 130.6, 131.6, 134.8 (q), 137.0 (q), 140.1 (q), 150.5 (q), 187.2 (CO), 199.4 (CHO); MS: *m/z* 304 (M^++1); *Anal.* Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 78.97; H, 5.52; N, 4.47.

***6*-(3-Diethylaminoethyl)-5-methyl-5,6,7,12-tetrahydrobenzo[4,5]cyclohepta[*b*]indol-12-one (14)**. Aldehyde (**13**) (120 mg, 0.40 mmol), diethylamine (0.08 mL, 0.79 mmol), sodium cyanoborohydride (30 mg, 0.47 mmol) and zinc chloride (27 mg, 0.20 mmol) in methanol/methylene chloride (5:1 v/v, 12 mL) were stirred at rt for 1 h. After cooling and evaporation of solvent, the residue was partitioned between aqueous 10% HCl and methylene chloride and twice extracted. The organic phases were combined, dried ($MgSO_4$) and evaporated *in vacuo*. The crude compound was purified by column chromatography (eluent: 95:5 methylene chloride/methanol) to give 116 mg (81%) of **14** as a gum; IR (film): ν 1612 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 1.03 (t, 6H, *J* = 7.2 Hz, CH_3), 1.45-1.60 (m, 1H, CH_2), 1.69-1.82 (m, 1H, CH_2), 2.48-2.79 (m, 6H, CH_2), 3.06 (dd, 1H, *J* = 5.6, 14.5 Hz, CH_2), 3.49-3.55 (m, 1H, CH), 3.62 (d, 1H, *J* = 14.5 Hz, CH_2), 3.78 (s, 3H, CH_3), 7.20-7.43 (m, 6H, H_{Ar}), 8.04-8.10 (m, 1H, H_{Ar}), 8.65-8.71 (m, 1H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 11.8 (2 CH_3), 28.2 (CH_2), 30.1 (CH_3), 33.1 (CH), 36.9 (CH_2), 46.9 (2 CH_2), 52.2 (CH_2), 109.3, 114.3 (q), 123.1, 123.3, 123.4, 127.4, 128.0 (q), 130.4, 130.7, 131.2, 135.4 (q), 137.0 (q), 140.3 (q), 153.1 (q), 187.2 (CO); MS: *m/z* 361 (M^++1); *Anal.* Calcd for $C_{24}H_{28}N_2O$: C, 79.96; H, 7.83; N, 7.77. Found: C, 80.16; H, 7.77; N, 7.90.

6-(3-Hydroxypropyl)-5-methyl-5,6,7,12-tetrahydrobenzo[4,5]cyclohepta[*b*]indol-12-one (15). To a solution of **12** (140 mg, 0.46 mmol) in anhydrous THF (10 mL), was added 1M borane-tetrahydrofuran complex (0.3 mL, 0.30 mmol). The solution was stirred for 16 h at rt. Excess of reagent was hydrolyzed

with water, then 3M sodium hydroxide (2 mL) followed by 35% hydrogen peroxide (0.6 mL) were added. The final solution was stirred for 30 min at reflux. After cooling and neutralization with aqueous 10% HCl, the solution was extracted with ethyl acetate (2 x 10 mL). The organic phase was dried ($MgSO_4$) and evaporated *in vacuo*. The crude compound was purified by column chromatography (eluent: 2:8 petroleum ether/ethyl acetate) to afford 70 mg (47%) of **15** as a gum; IR (film): ν 3440 (OH), 1608 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 1.17-1.80 (m, 4H, CH_2), 2.03 (br s, 1H, OH), 3.04 (dd, 1H, *J* = 5.3, 14.4 Hz, CH_2), 3.24-3.31 (m, 1H, CH), 3.47-3.62 (m, 3H, CH_2), 3.64 (s, 3H, CH_3), 7.14-7.37 (m, 6H, H_{Ar}), 8.02-8.06 (m, 1H, H_{Ar}), 8.64-8.67 (m, 1H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 27.1 (CH_2), 30.0 (CH_2), 30.1 (CH_3), 34.9 (CH), 36.9 (CH_2), 62.1 (CH_2), 109.3, 114.1 (q), 123.1, 123.3, 123.4, 127.4, 127.8 (q), 130.2, 130.6, 131.2, 135.2 (q), 137.0 (q), 140.1 (q), 153.0 (q), 187.4 (CO); MS: *m/z* 320 (M^++1); *Anal.* Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 79.23; H, 6.81; N, 4.45.

6-(3-Hydroxypropyl)-5-methyl-5,6,7,12-tetrahydrobenzo[4,5]cyclohepta[*b*]indole (16). The use of an excess of borane-tetrahydrofuran complex (2 eq for 1 eq of **14**) gave **16** in 89% yield as a gum; IR (film): ν 3380 (OH) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 1.20-138 (m, 1H, CH_2), 1.54-1.70 (m, 2H, CH_2), 1.72-1.85 (m, 1H, CH_2), 3.12 (dd, 1H, *J* = 6.3, 13.5 Hz, CH_2), 3.19-3.27 (m, 1H, CH), 3.45 (dd, 1H, *J* = 2.8, 13.5 Hz, CH_2), 3.59-3.64 (m, 2H, CH_2), 3.62 (s, 3H, CH_3), 4.07 (d, 1H, *J* = 16.6 Hz, CH_2), 4.17 (d, 1H, *J* = 16.6 Hz, CH_2), 7.08-7.28 (m, 7H, H_{Ar}), 7.60-7.64 (m, 1H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 29.8 (CH_2), 29.9 (CH_3), 30.0 (CH_2), 30.2 (CH_2), 35.3 (CH_2), 35.4 (CH), 62.8 (CH_2), 108.4 (q), 108.7, 117.7, 119.0, 121.1, 126.2, 126.7, 127.5 (q), 128.5, 130.2, 136.5 (q), 138.1 (q), 138.8 (q), 142.1 (q); MS: *m/z* 306 (M^++1); *Anal.* Calcd for $C_{21}H_{23}NO$: C, 82.59; H, 7.59; N, 4.59. Found: C, 82.36; H, 7.73; N, 4.50.

2-(5-Methyl-12-oxo-5,6,7,12-tetrahydrobenzo[4,5]cyclohepta[*b*]indol-6-yl)propanal (17). To a suspension of pyridinium chlorochromate (200 mg, 0.93 mmol) in methylene chloride (10 mL) was added in one portion the alcohol (**15**) (100 mg, 0.31 mmol) in methylene chloride (5 mL). The solution was stirred for 2 h at rt. The black solution was filtered through Celite and the filtrate was evaporated *in vacuo*. The crude residue was purified by column chromatography (eluent: 1:1 petroleum ether/ethyl acetate) to afford 79 mg (81%) of **17** as a gum; IR (film): ν 1720 (CO), 1607 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 1.43-1.58 (m, 1H, CH_2), 1.85-1.97 (m, 1H, CH_2), 2.55-2.64 (m, 2H, CH_2), 3.06 (dd, 1H, *J* = 5.7, 14.7 Hz, CH_2), 3.42-3.51 (m, 1H, CH), 3.66 (dd, 1H, *J* = 2.2, 14.7 Hz, CH_2), 3.85 (s, 3H, CH_3), 7.19-7.43 (m, 6H, H_{Ar}), 8.09-8.13 (m, 1H, H_{Ar}), 8.69-8.73 (m, 1H, H_{Ar}), 9.80 (s, 1H, CHO); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 23.2 (CH_2), 30.3 (CH_3), 33.7 (CH), 36.8 (CH_2), 40.7 (CH_2), 109.4, 114.3 (q), 123.3, 123.4, 123.5, 127.7, 127.9 (q), 130.4, 130.6, 131.4, 134.8 (q), 137.1 (q), 140.2 (q), 152.0 (q), 187.1

(CO), 201.3 (CHO); MS: *m/z* 318 (M^++1); *Anal.* Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.14; H, 5.87; N, 4.57.

6-(3-Diethylaminopropyl)-5-methyl-5,6,7,12-tetrahydrobenzo[4,5]cyclohepta[*b*]indol-12-one (18). Following the same procedure used for **14** but substituting **13** by **17**, purification of the residue by column chromatography (eluent: 95:5 methylene chloride/methanol) gave **18** (75%) as a gum; IR (film): ν 1610 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 1.15 (t, 6H, *J* = 7.2 Hz, CH_3), 1.21-1.47 (m, 2H, CH_2), 1.67-1.93 (m, 2H, CH_2), 2.48-2.70 (m, 2H, CH_2), 2.82 (q, 4H, *J* = 7.2 Hz, CH_2), 3.15 (dd, 1H, *J* = 5.6, 14.5 Hz, CH_2), 3.32-3.43 (m, 1H, CH), 3.65 (d, 1H, *J* = 14.5 Hz, CH_2), 3.77 (s, 3H, CH_3), 7.14-7.41 (m, 6H, H_{Ar}), 8.09-8.13 (m, 1H, H_{Ar}), 8.68-8.72 (m, 1H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 9.8 (2 CH_3), 23.3 (CH_2), 28.9 (CH_2), 30.4 (CH_3), 34.8 (CH), 37.3 (CH_2), 46.8 (2 CH_2), 52.3 (CH_2), 109.5, 114.3 (q), 123.2, 123.4, 123.5, 127.5, 127.9 (q), 130.5, 130.6, 131.3, 135.2 (q), 137.1 (q), 140.2 (q), 152.3 (q), 187.0 (CO); MS: *m/z* 375 (M^++1); *Anal.* Calcd for $C_{25}H_{30}N_2O$: C, 80.17; H, 8.07; N, 7.48. Found: C, 80.38; H, 8.00; N, 7.56.

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