Convenient Synthesis of Highly Functionalized, 3,4-Disubstituted Indole Building Blocks

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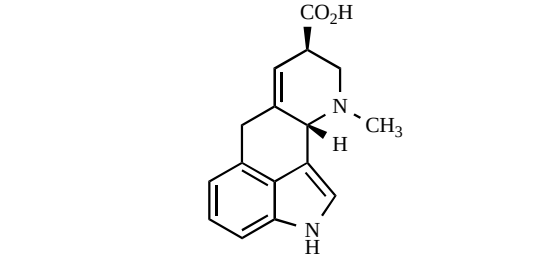
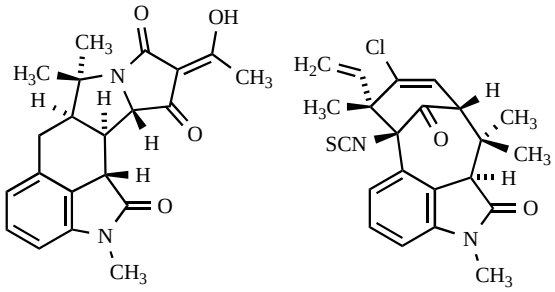
Abstract: Several 3,4-disubstituted indole building blocks were synthesized, containing a one-carbon functional group at C-4 and a three-carbon chain bearing at least one ω functional group. A C-4 functionalized indole derivative was prepared by application of the Leimgruber-Batcho reaction. Several three-carbon chains were subsequently installed at the indole C-3 position. In the first strategy employed, a Mannich reaction was followed by the creation of a C-C bond by phosphine-induced generation of a 3-methyleneindolenine species, which was trapped by diethyl malonate. Alternatively, a Vilsmeier formylation at C-3 was followed by Knoevenagel or Wittig reactions or by treatment with ethyl diazoacetate in the presence of a Lewis acid. Direct introduction of the three-carbon chain at C-3 using a Lewis acid-catalyzed Michael reaction was also achieved. Further functionalization of the benzylic position attached to C-4 by attachment of a nitro group was carried out, but preparation of a tricyclic welwistatin fragment by intramolecular nitroalkane acylation or intramolecular Henry reactions was not possible.

INTRODUCTION

Many bioactive natural and unnatural products contain 3,4-disubstituted indole or oxindole frameworks. The structures of a few representative examples are shown in Fig. **1**, including ergotamine-type alkaloids such as lysergic acid [1], the antibiotic spearadine [2] and the MDR inhibitor and antimicrotubule agent welwistatin [3], a product of the metabolism of the cyanobacteria *Wetsiella intricata* and *Hapalosiphon welwtschii* [4].



Lysergic acid



Speradine A

Welwistatin

Fig. (1). Structures of some bioactive alkaloids containing a 3,4-disubstituted indole or oxindole fragment.

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A large number of methods are known that allow the synthesis of substituted indoles [5,6,7]. Nevertheless, the preparation of 3,4-disubstituted indole systems is still a very challenging task, and the difficulties found in this endeavour can be partly attributed to the low nucleophilicity of the indole C-4 position. Although some methodologies involving the use of transition metal complexes or anionic benzyne cyclizations have been created for this purpose [8], the development of efficient methods leading to 3,4-disubstituted indoles from simple starting materials continues to be of great interest. We describe in this paper our route to several highly functionalized building blocks containing this structural motif.

RESULTS AND DISCUSSION

The starting material that we chose for our study was ethyl indole-4-carboxylate, which was obtained using the Leimgruber-Batcho indole synthesis [9], based on the treatment of 2-nitrotoluene derivatives with dimethylformamide acetals. As shown in Fig. **2**, treatment of commercially available methyl-2-methyl-3- nitrobenzoate with dimethylformamide diethylacetal gave a 95% yield of compound **1**, where enamine formation was accompanied by transesterification by the ethanol liberated from the DMF acetal. Its reductive cyclization in the presence of Ni Raney afforded indole **2a**, which was *N*-methylated to **2b** by treatment with sodium hydride and methyl iodide. Compounds **2a** and **2b** were efficiently reduced by exposure to lithium aluminium hydride to give alcohols **3a** and **3b**, respectively, which were finally protected as *tert*-butyldiphenylsilyl ethers **4a** and **4b**.

The Mannich reaction allows the easy creation of a carbon-carbon bond at the indole C-3 position, and the dimethylamino group can be subsequently displaced to give highly electrophilic 3-methyleneindolenine species. For this reason we treated an acetic acid solution of compounds **3a**,**b** with formaldehyde and dimethylamine, yielding Mannich bases **5a**,**b**. In order to facilitate displacement of the dimethylamino group we methylated compounds **5** to give gramine

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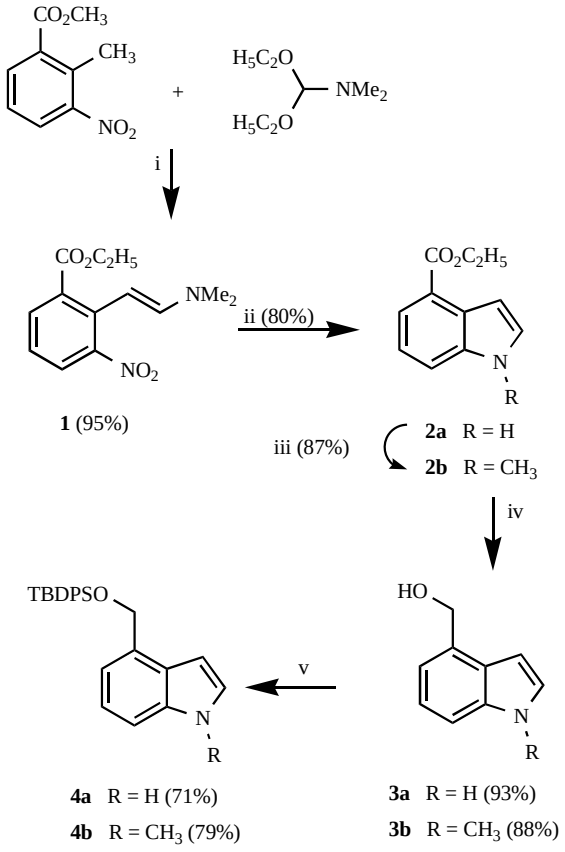
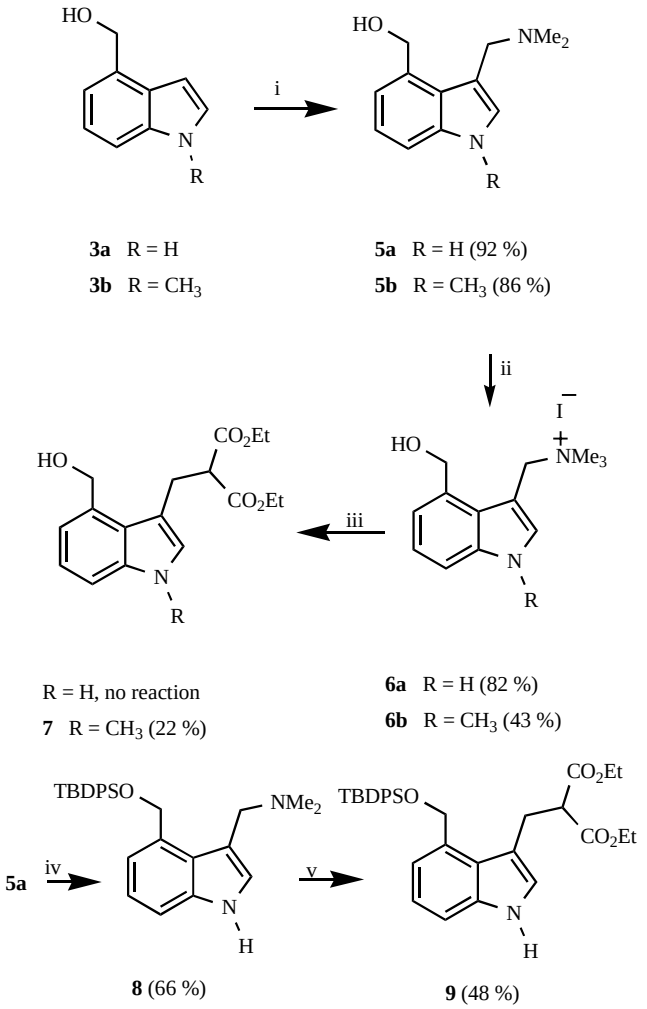
derivatives **6a**,**b**, whose reactivity towards the diethyl malonate anion was subsequently studied. Although we hoped that use of an excess of anion would allow the use of hydroxyl-unprotected starting materials, the reaction of the sodium derivative of diethyl malonate with **6a** proved to be not possible. On the other hand, we achieved limited success (22% yield of compound **7b**) by treatment of **6b** with an ethanolic solution of diethyl malonate in the presence of sodium ethoxide. Numerous attempts to improve this result by changing the base (NaH), the solvent (DMF) and the reaction conditions (time, temperature, excess of malonate anion) were unsuccessful. In view of these problems, compound **5a** was transformed into its *O*-silyl protected derivative **8**, which was treated with diethyl malonate in the presence of tributylphosphine as a catalyst [10], giving compound **9** in an acceptable 48% yield (Fig. **3**).



Reagents and conditions: i. DMF, 110 °C, 48 h, ii. NH_2-$NH_2.H_2O$, Ni Raney, CH_3OH-THF, r.t., 45 min. iii. NaH, DMF, r.t., 5 min, then ICH_3, DMF, r.t., 1 h: iv. $LiAlH_4$, THF, r.t., 12 h for **3**a, 48 h for **3**b; v. TBDPSCl, Et_3N, DMAP, Cl_2CH_2, r.t., 12 h.

Fig. (2). Synthesis of 4-substituted indoles as starting materials.

Another approach to the functionalization of the C-3 position involved the use of the Vilsmeier-Haack formylation. Treatment of compound **4b** with phosphorous oxychloride in dimethylformamide afforded an iminium salt **10** that could be isolated or hydrolyzed *in situ* under basic conditions (pH 8, 60 °C) to yield aldehyde **11**, while the use of harsher basic conditions (pH 12, 60 °C) led to the deprotected hydroxy aldehyde **12**. Both **11** and **12** gave the classical Knoevenagel reaction with diethyl malonate, albeit in moderate yields, affording compounds **13** and **14**, respectively (Fig. **4**).

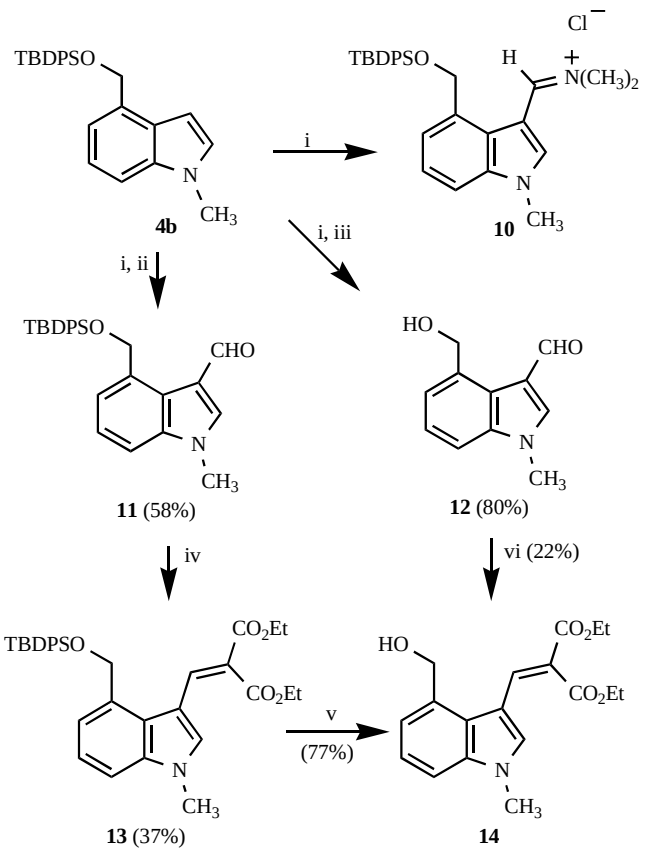


Reagents and conditions: i. $(CH_3)_2NH$, HCHO, H_2O, AcOH, r.t., 3 h. ii. ICH_3, THF, 4 °C, 12 h. iii. NaOEt, diethyl malonate, EtOH, reflux, 12 h; iv. TBDPSCl, Et_3N, DMAP, Cl_2CH_2, r.t., 12 h; v. Diethyl malonate, PBu_3, THF, 80 °C, 24 h

Fig. (3). Synthesis of 3,4-disubstituted indoles based on the Mannich reaction of compounds **3**.

In search for an alternative, more efficient procedure to create a three-carbon chain at C-3, we carried out the reaction of compound **11** with ethyl diazoacetate in the presence of a Lewis acid [11] and obtained compound **15** in moderate yield. The most efficient method for the installation of the three-carbon chain proved to be the Wittig reaction of aldehydes **11** or **12** with ethoxycarbonylmethylene-triphenylphosphorane, which afforded good to excellent yields of compounds **16** and **17**, respectively. Interestingly, the Wittig reaction leading to **16** could also be carried out from iminium salt **10**, although a longer reaction time was required. Catalytic hydrogenation of **16** and **17** furnished **18** and **19**, respectively, in quantitative yields, and compound **19** could also be obtained very efficiently by fluoride-induced deprotection of **18** (Fig. **5**).

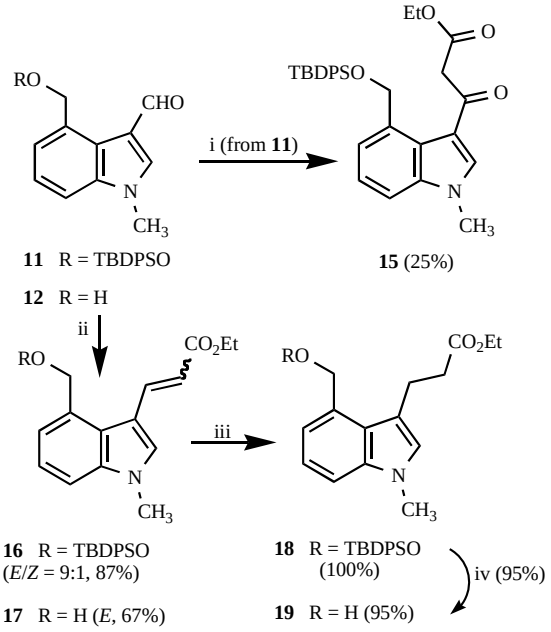
In order to allow the generation of a nucleophilic center at the benzylic position attached to C-4, we planned the introduction of a nitro group by displacement of a suitable halide with sodium nitrite. This transformation proved troublesome, since the application of published procedures for the transformation of halides into nitroalkanes [12, 13] to the



Reagents and conditions: i. $POCl_3$, DMF, 0 °C, 30 min, 0°C to r.t., 45 min. ii. NaOH-H_2O, pH = 8, 60 °C, 30 min; iii. NaOH-H_2O, pH = 12, 60 °C, 30 min; iv. Diethyl malonate, pyridine-piperidine, 180 °C, 40 h. v. Diethyl malonate, pyridine-piperidine, 180 °C, 4 days; vi. HF, CH_3CN, r.t., 24 h

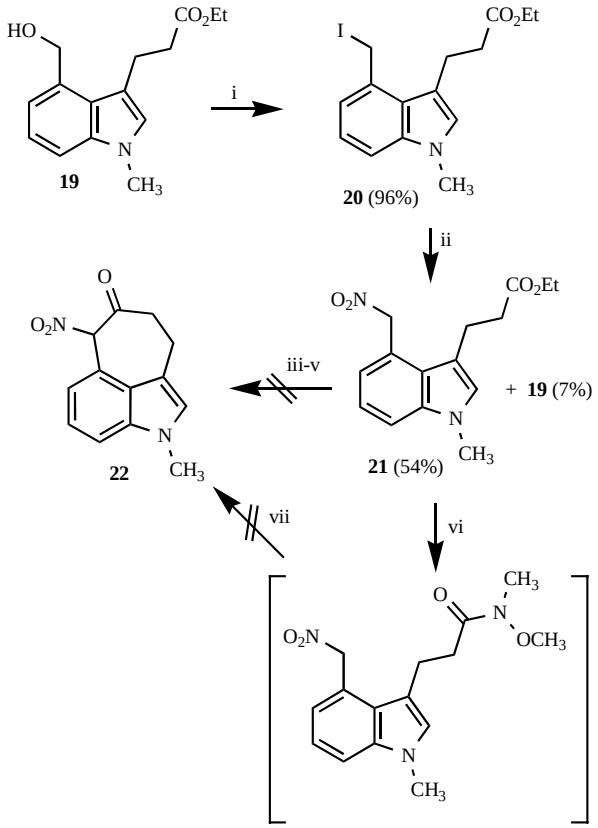
Fig. (4). Initial attempts at the installation of a three-carbon chain at the indole C-3 position using the Knoevenagel reaction.

reaction between sodium nitrite and benzyl bromide, used as a model, did not lead to the expected phenylnitromethane but to benzyl nitrite as the only product. This problem could be overcome by addition of urea to the reaction mixture in order to increase the solubility of sodium nitrite in the dimethylformamide used as solvent [14], and under the new conditions (-20 °C, urea, DMF) the model reaction gave phenylnitromethane in 80% yield. This result was further improved by the use of benzyl iodide as the substrate, which led to the desired nitro derivative in 99% yield after 5 h at -20 °C. For this reason, alcohol **19** was transformed into iodide **20** using the one-pot protocol developed by Olah, involving treatment with trimethylsilyl chloride and potassium iodide [15,16]. The reaction of iodide **20** with sodium nitrite was carried out under similar conditions, although at a lower reaction temperature, and gave nitro derivative **21** in 54% yield, together with a small amount of alcohol **19**, presumably from hydrolysis of the iodide. Unfortunately, all attempts to induce a 7-*exo*-*trig* cyclization from the anion of **21**, prepared using several bases including DBU in acetonitrile [17], KF-alumina suspended in THF [18] and BuLi in THF-DMU [19], were unsuccessful. An attempt to facilitate the cyclization by activating the ester group in **21** *via* its transformation into the corresponding Weinreb amide [20] was also unsuccessful (Fig. **6**).



Reagents and conditions: i. N_2CHCO_2Et, BF_3-Et_2O, CH_2Cl_2, r.t., 4 h; ii. Ph_3PCHCO_2Et, EtOH, reflux, 48 h; iii. H_2, Pd-C, CH_3OH, 9 h; iv. TBAF, THF, r.t., 10 h.

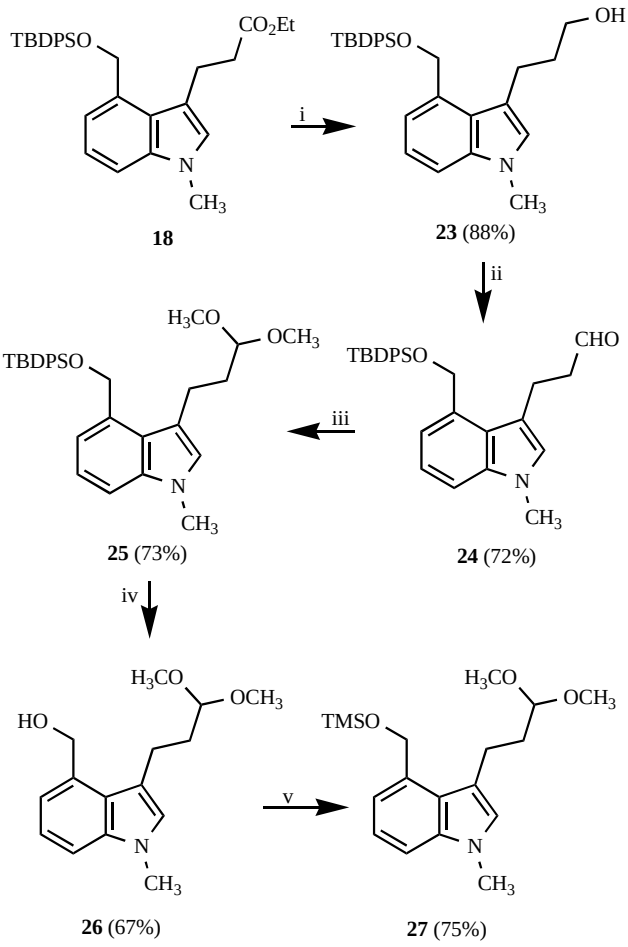
Fig. (5). Installation of a three-carbon chain at the indole C-3 position using diazoalkane and phosphorous ylide chemistry.



Reagents and conditions: i. NaI (2 eq.), TMSCl (2 eq.), CH_3CN, -75 to -40 °C, 2 h. ii. $NaNO_2$, urea, DMF, - 75 °C to - 40 °C, 2 h; iii. DBU, CH_3CN, several conditions; iv. KF-alumina, THF, several conditions; v. BuLi, THF, DMU, several conditions; vi. $(CH_3)_2AlCl$, $H_3CONHCH_3.HCl$, CH_2Cl_2, r.t., 4 h; vii. DBU, THF, several conditions.

Fig. (6). Further functionalization of compound **19** and attempts at the preparation of a welwistatin tricyclic fragment.

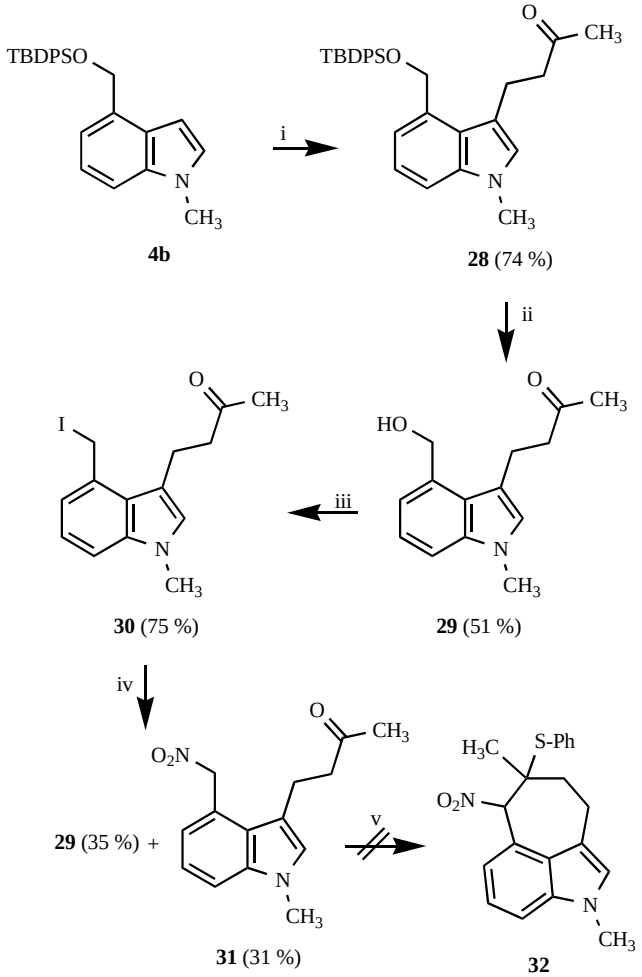
In an effort to achieve the desired cyclization by an intramolecular Henry reaction, ester **18** was treated with lithium aluminium hydride to give primary alcohol **23**, which was then oxidized to aldehyde **24** by exposure to the Ley-Griffith TPAP reagent [21]. Since an attempt at the deprotection of the hydroxyl group in **24** led to a complex mixture of products, a decision was made to protect its aldehyde group as a dimethyl acetal, which was prepared using the mild conditions described by Noyori [22] in order to avoid decomposition of the indole ring. Acetal **25** thus prepared could be deprotected in the presence of fluoride to give compound **26**, but all attempts to transform this compound into the corresponding iodide using Olah's conditions led only to complex mixtures of decomposition products. The intermediate of this reaction, *i.e.*, trimethylsilyl ether **27**, was isolated by carrying out the procedure in the presence of triethylamine (Fig. **7**), but again this compound could not be transformed into the desired iodide.



Reagents and conditions: i. $LiAlH_4$, THF, r.t., 16 h; ii. TPAP, NMO, CH_3CN, r.t., 3 h; iii. TMSOTf, methoxytrimethylsilane, CH_2Cl_2, - 78 °C, 3 h; iv. $Bu_4N^+ F^-$, THF, r.t., 32 ; v. NaI, TMSCl-Et_3N, - 78 °C to - 40 °C, 90 min.

Fig. (7). Functionalization of compound **18**.

In order to avoid the use of carbonyl-protecting groups, an alternative approach involving the use of a ketone group in the side chain was conceived. As shown in Fig. **8**, the ytterbium triflate-catalyzed [23] Michael reaction of **4b** with methyl vinyl ketone afforded compound **28**, which in this case could be deprotected to **29** by treatment with fluoride. Exposure of **29** to the previously employed Olah's conditions allowed the preparation of iodide **30**, which furnished nitro derivative **31** in moderate yield, together with alcohol **29**, upon treatment with sodium nitrite and urea in dimethylformamide. Compound **31** was then submitted to literature conditions that allow to carry out the Henry reaction between nitroalkanes and ketones by displacing the unfavourable equilibria through reaction of the nitroaldol adduct with a thiol [24]. Unfortunately, all our attempts at translating these conditions into an intramolecular reaction allowing the preparation of compound **32** from **31** were unsuccessful.



Reagents and conditions: i. Methyl vinyl ketone, $Yb(OTf)_3.3\ H_2O$, r.t., 16 h; ii. $Bu_4N^+ F^-$, THF, r.t., 12 h; iii. NaI, TMSCl, CH_3CN, -78 ° C to - 40 °C, 90 min; iv. $NaNO_2$, urea, DMF, - 78 °C to - 40 °C, 2.5 h; v. Piperidine, thiophenol, 4 Å powdered molecular sieves, benzene, reflux, 23 h.

Fig. (8). Direct introduction of a three-carbon chain and attempts at an intramolecular Henry reaction.

CONCLUSIONS

The synthesis of several highly functionalized 3,4-disubstituted indole building blocks was achieved from a C-4 functionalized indole derivative obtained by application of the Leimgruber-Batcho reaction. Because of their relationship with a tricyclic welwistatin fragment, these compounds contained a one-carbon functional group at C-4 and a three-

carbon chain bearing ω alcohol, aldehyde, ketone, acetal or ester groups, while the benzylic position was functionalized by ester, hydroxy or protected hydroxy, halide or nitro groups. The compounds obtained constitute synthetically relevant materials that will hopefully find use in the preparation of bioactive indole derivatives.

EXPERIMENTAL SECTION

General Information

All reagents were of commercial quality (Aldrich, Fluka, SDS, Probus) and were used as received. Solvents (from SDS) were dried and purified using standard techniques. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230-40 mesh). Melting points were measured with a Reichert 723 hot stage microscope, and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrophotometer, with all compounds examined as films on a NaCl disk. NMR spectra were obtained on a Bruker Avance instrument (250 MHz for ^{1}H, 62.9 MHz for ^{13}C), which is maintained by CAI de Resonancia Magnética Nuclear, Universidad Complutense, with $CDCl_3$ as solvent. Combustion elemental microanalyses were determined by CAI de Microanálisis Elemental, Universidad Complutense, using a Leco 932 CHNS microanalyzer.

Ethyl 2-(2-dimethylaminovinyl)-3-nitro-benzoate (1)

To a solution of methyl 2-methyl-3-nitrobenzoate (4.1 g, 20 mmol) in dimethylformamide (16 mL) was added *N,N*-dimethylformamide diethylacetal (10 g, 83.9 mmol). The reaction mixture was refluxed under an argon atmosphere for 48 h, poured on water and extracted with ethyl ether (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated, leaving a residue that was identified as compound **1**, as a reddish viscous oil (5.025 g, 95 %). ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.82 (m, 2H, H-6, H-4); 7.15 (t, 1H, *J* = 7.9 Hz, H-5); 6.41 (d, 1H, *J* = 13.6 Hz, H-2'); 5.75 (d, 1H, *J* = 13.6 Hz, H-1'); 4.45 (q, 2H, *J* = 7.2 Hz, CH_2); 2.90 (s, 6H, $N(CH_3)_2$); 1.45 (t, 3H, *J* = 7.1 Hz, CH_3) ppm. ^{13}C-RMN ($CDCl_3$, 250 MHz) δ: 168.8 ($\underline{C}O_2CH_2CH_3$); 149.1 (C-3'); 146.0 (C-2'); 134.2 (C-1'); 133.1 (C-4); 132.0 (C-2'); 126.6 (C-6); 122.9 (C-5); 88.9 (C-1'); 61.4 ($CO_2\underline{C}H_2CH_3$); 40.5 (NMe_2); 14.2 ($CO_2CH_2\underline{C}H_3$) ppm. Anal. Calcd. for $C_{13}H_{16}N_2O_4$, M = 264: C, 59.08; H, 6.10; N, 10.60. Found: C, 58.95; H, 5.97; N, 10.52.

Ethyl indole-4-carboxylate (2a)

To a solution of compound **1** (1.597 g, 6 mmol) in methanol (12 mL) and tetrahydrofuran (12 mL) was added 80% hydrazine hydrate (0.450 g, 9 mmol). The mixture was protected with a calcium chloride tube and stirred at room temperature while a 50% suspension of Raney Ni in water (0.12 mL) was added portionwise. The resulting suspension was stirred at room temperature and filtered through celite, which was washed with dichloromethane. The combined filtrates were dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by chromatography on silica gel, eluting with a 2:1 petroleum ether-ethyl acetate mixture, to yield 907 mg (80 %) of indole **2**. IR (NaCl) ν: 3314.8 (NH); 1686.1 (CO); 1275.3 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.47 (s, 1H, NH); 7.91 (d, 1H, *J* = 7.5 Hz, H-5); 7.58 (d, 1H, *J* = 8.1 Hz, H-7); 7.33 (t, 1H, *J* = 3.0 Hz, H-6); 7.24 (d, 1H, *J* = 5.1 Hz, H-2); 7.18 (d, 1H, *J* = 2.3 Hz, H-3); 4.44 (q, 2H, *J* = 7.1 Hz, CH_2); 1.45 (t, 3H, *J* = 7.1 Hz, CH_3) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 167,8 ($\underline{C}O_2CH_2CH_3$); 136.7 (C-7a); 127.5 (C-3a); 126.3 (C-2); 123.5 (C-5); 122.0 (C-4); 121.3 (C-6); 115.9 (C-7); 104.1 (C-3); 60.7 ($CO_2\underline{C}H_2CH_3$); 14,58 ($CO_2CH_2\underline{C}H_3$) ppm. Analysis: Calcd. for $C_{11}H_{11}NO_2$, M = 189: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.56; H, 5.44; N, 7.40.

Ethyl 1-methylindole-4-carboxylate (2b)

A commercial suspension of sodium hydride in paraffins (60%, 138 mg, 5.76 mmol) was washed with dry petroleum ether (3 x 10 mL), under an argon atmosphere. A solution of compound **2** (907 mg, 4.8 mmol) in dry dimethylformamide (3 mL) was added, and the resulting suspension was stirred at room temperature for 5 min. Methyl iodide (2 g, 14.4 mmol) was added and stirring at room temperature was maintained for 1 h. The reaction mixture was poured on crushed ice (10 g) and extracted with ethyl acetate (3x10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated, and the residue was chromatographed on silica gel, eluting with a 2:1 petroleum ether-ethyl acetate mixture, to yield 850 g (87%) of indole **3**. IR (NaCl) ν: 1702,5 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.91 (d, 1H, *J* = 7.5 Hz; H-5); 7.51 (d, 1H, *J* = 8.2 Hz, H-7); 7.25 (t, 1H, *J* = 8.4 Hz, H-6); 7.17 (d, 1H, *J* = 3.1 Hz, H-2); 7.09 (d, 1H, *J* = 3.1 Hz, H-3); 4.44 (q, 2H, *J* = 14.2 Hz, CH_2); 3.82 (s, 3H, CH_3); 1.45 (t, 3H, *J* = 7.1 Hz, CH_3) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 167.8 (CO); 137.6 (C-7a); 130.9 (C-3a); 128.1 (C-2); 123.0 (C-5); 122.0 (C-4); 120.7 (C-6); 114.0 (C-7); 102.4 (C-3); 60.6 ($CO_2\underline{C}H_2CH_3$); 33,1 (N-CH_3); 14.6 ($CO_2CH_2\underline{C}H_3$) ppm. Analysis: Calcd. for $C_{12}H_{13}NO_2$, M = 203: C, 70.92; H-6.45; N, 6.89. Found: C-70.80; H, 6.45; N, 6.80.

(Indol-4-yl)methanol (3a)

To a stirred suspension of lithium aluminium hydride (115 mg, 3 mmol) in ethyl ether (10 mL) and tetrahydrofuran (10 mL), kept under an argon atmosphere and cooled to 0 °C, was added dropwise a solution of **2a** (370 mg, 2.11 mmol) in the same solvent mixture (10 mL). The suspension was stirred at room temperature for 48 h. Excess lithium aluminium hydride was destroyed by addition of ethyl acetate followed by a few drops of water, maintaining initially the reaction mixture in a bath at 0 °C and then at room temperature for 30 min. Solid sodium bicarbonate was then added until a white solid was formed, which was filtered and washed with ethyl acetate. The filtrate was dried over anhydrous Na_2SO_4 and evaporated, and the pale brown residue was identified as alcohol **3a** (234 mg, 93%). Anal. Calcd. for C_9H_9NO, M = 147: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.10; H, 6.40; N, 9.23.

(1-Methylindol-4-yl)methanol (3b)

The same method described for the preparation of **3a**, starting from 439 mg (2.32 mmol) of compound **2b**, afforded 330 mg (88%) of alcohol **3b**. IR (NaCl) ν: 3363.7 (OH) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7,30-7,10 (m, 3H, H-5, H-6, H-7); 7.08 (d, 1H, *J* = 3.2 Hz, H-2); 6.59 (d, 1H, *J* = 3.2 Hz, H-3); 4.97 (s, 2H, C_4-CH_2); 3.80 (s, 3H, N-CH_3); 1.67 (s, 1H, OH) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 136.9 (C-7a);

132.9 (C-4); 129.1 (C-2); 126.8 (C-3a); 121.7 (C-5); 118.0 (C-6); 109.2 (C-7); 99.1 (C-3); 64.1 (C_4-$\underline{C}H_2$); 33.1 (N-CH_3) ppm. Anal. Calcd. for $C_{10}H_{11}NO$, M = 161: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.38; H, 6.74; N, 8.32.

4-(*tert*-Butyldiphenylsilyloxy)indole (4a)

To a solution of indole **3a** (68 mg, 0.463 mmol) in dry dichlorometane (0.6 mL), kept under an argon atmosphere and cooled at 0 °C, was added triethylamine (65 μL, 0.55 mmol). After stirring for 5 min at 0 °C, *tert*-butyldiphenylsilyl chloride (140 μL, 0.55 mmol) and 4-dimethylaminopyridine (25 mg, 0.2 mmol) were added. The reaction mixture was left to warm to room temperature and stirred for 12 h, poured onto water (10 mL) and extracted with chloroform (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated, leaving a residue that was chromatographed on silica gel, eluting with a 10:1 petroleum ether-ethyl acetate mixture, to yield 126 mg (71%) of compound **4a**, as a colourless viscous oil. IR (NaCl) ν: 3316.8 (NH) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.12 (br s, 1H, NH); 7.77 (m, 4H, H-2",6"); 7.44-7.25 (m, 8H, H-7,5,3",4",5"); 7.20 (t, 1H, *J* = 7.5 Hz, H-6); 7.15 (t, 1H, *J* = 2.8 Hz, H-2); 6.52 (m, 1H, H-3); 5.11 (s, 2H, H-α); 1.12 (s, 9H, C($C\underline{H}_3$)$_3$) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 135.8 (C-7a); 135.8 (C-2",6"); 133.8 (C-1"); 133.1 (C-4); 129.8 (C-4"); 129.7 (C-2); 127.9 (C-3",5"); 123.9 (C-3a); 122.1 (C-5); 117.0 (C-6); 110.1 (C-7); 100.9 (C-3); 64.5 (C-α); 27.03 (C($\underline{C}H_3$)$_3$); 19.7 ($\underline{C}$(CH_3)$_3$) ppm. Anal. Calcd. for $C_{25}H_{27}NOSi$, M = 385: C, 77.88; H, 7.06; N, 3.63. Found: C, 77.57; H, 7.03; N, 3.52.

4-(*tert*-Butyldiphenylsilyloxy)-1-methylindole (4b)

The same method described for the preparation of **4a**, starting from 4.845 g, 30 mmol) of compound **3b**, afforded 9.470 g (79%) of **4b**, as a white solid. Mp 60 °C. IR (NaCl) ν: 1111.8 (C-O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.75 (m, 4H, H-2",6"); 7.43-7.34 (m, 6H, H-,3",4",5"); 7.25-7.23 (m, 3H, H-5,6,7); 7.01 (d, 1H, *J* = 2.5 Hz, H-3); 6.42 (d, 1H, *J* = 5.0 Hz, H-2); 5.07 (s, 2H, H-α); 3.78 (s, 3H, N-CH_3); 1.10 (s, 9H, C($C\underline{H}_3$)$_3$) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 136.7 (C-7a); 135.8 (C-2",6"); 133.9 (C-1"); 133.1 (C-4); 129.7 (C-4"); 128.6 (C-2); 127.8 (C-3",5"); 125.9 (C-3a); 121.6 (C-5); 116.6 (C-6); 108.3 (C-7); 99.2 (C-3); 64.4 (C-α); 33.1 (N-CH_3); 27.0 (C($\underline{C}H_3$)$_3$); 19.6 ($\underline{C}$(CH_3)$_3$) ppm. Anal. Calcd. for $C_{26}H_{29}NOSi$: C, 78.15; H, 7.31; N, 3.51. Found: 77.89; H, 7.13; N, 3.42.

(3-(Dimethylaminomethyl)indol-4-yl)methanol (5a)

To a cooled (0 °C) solution of compound **3a** (235 mg, 1.6 mmol) in glacial acetic acid (0.8 mL), maintained under an argon atmosphere, was added a 37% aqueous solution of formaldehyde (0.13 mL, 1.6 mmol) and a 25% aqueous solution of dimethylamine (0.18 mL, 1.6 mmol). The solution was left to warm to room temperature and stirred for 1.5 h, poured onto 30% aqueous sodium hydroxide (10 mL) and extracted with chloroform (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated, yielding 298 mg (92%) of compound **5a** as a pale green, viscous oil. IR (NaCl) ν: 3210.5 (broad signal, NH and OH). ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.28 (s, 1H, NH); 7.26 (d, 1H, *J* = 7.5 Hz; H-7); 7.13 (t, 1H, *J* = 7.5 Hz, H-6); 7.05 (d, 1H, *J* = 1.0 Hz, H-5); 6.97 (d, 1H, *J* = 7.5 Hz, H-2); 4.84 (s, 2H, H-α); 3.76 (s, 2H, H-α'); 2.24 (s, 6H, N($C\underline{H}_3$)$_2$) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 138.0 (C-7a); 135.0 (C-4); 124.3 (C-3a); 125.3 (C-2); 122.4 (C-5); 121.1 (C-6); 112.1 (C-3); 111.6 (C-7); 68.6 (C-α); 57.4 (C-α'); 44.5 (N($\underline{C}H_3$)$_2$) ppm. Anal. Calcd. for $C_{12}H_{16}N_2O$, M = 204: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.23; H, 7.64; N, 13.39.

(3-(Dimethylaminomethyl)-1-methylindol-4-yl)methanol (5b)

The same method described for the preparation of **5a**, starting from 400 mg (3.1 mmol) of compound **3b**, afforded 438 mg (86%) of **5b**. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.22 (d, 1H, *J* = 7.1 Hz, H-7); 7.15 (t, 1H, *J* = 6.9 Hz, H-6); 6.99 (d, 1H, *J* = 6.9 Hz, H-5); 6.91 (s, 1H, H-2); 4.84 (d, 2H, CH_2OH); 3.73 (s, 5H, N-CH_3 and $C\underline{H}_2$-N(CH_3)$_2$); 2.24 (s, 6H, N(CH_3)$_2$) ppm. ^{13}CNMR ($CDCl_3$, 62.9 MHz) δ: 138.6 (C-7a); 135.6 (C-4); 129.6 (C-2); 124.8 (C-3a); 122.2 (C-5); 120.9 (C-6); 111.1 (C-3); 109.6 (C-7); 64.4 (CH_2OH); 44.7 (N(CH_3)$_2$; 32.9 (N-CH_3) ppm. Anal. Calcd. for $C_{13}H_{18}N_2O$, M = 218: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.26; H, 7.97; N, 12.46.

(4-Hydroxymethyl-3-indolylmethyl) trimethylamonium iodide (6a)

To a cooled (0 °C), stirred solution of compound **5a** (200 mg, 0.98 mmol) in dry tetrahydrofuran (4 mL), maintained under an argon atmosphere, was slowly added neat methyl iodide (2.75 mL), maintaining the temperature of the bath at 0 °C. The resulting solution was stirred at room temperature for 30 min and then kept at 4 °C for 14 h and filtered, affording 235 mg (82 %) of salt **6a**, as a pale brown solid. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.88 (s, 1H, H-2); 7.77 (d, 1H, *J* = 7.5 Hz, H-7); 7.47 (t, 1H, *J* = 7.5 Hz, H-6); 7.33 (d, 1H, *J* = 7.0 Hz, H-5); 5.34 (s, 2H, CH_2-N); 4.97 (s, 2H, $C\underline{H}_2$OH); 3.24 (s, 9H, N(CH_3)$_3$) ppm. Anal. Calcd. for $C_{13}H_{19}IN_2O$, M = 346: C, 45.10; H, 5.53; N, 8.09. Found: C, 44.81; H, 5.32; N, 5.26.

(4-Hydroxymethyl-1-methyl-3-indolylmethyl) trimethylammonium iodide (6b)

To a cooled (0 °C), stirred solution of compound **5a** (565 mg, 2.6 mmol) in dry tetrahydrofuran (10 mL), maintained under an argon atmosphere, was slowly added neat methyl iodide (7.3 mL), maintaining the temperature of the bath at 0 °C. The resulting solution was stirred at room temperature for 30 min and then kept at 4 °C for 14 h and filtered. The precipitate was washed with methanol, leaving an insoluble residue. The methanol washings were evaporated, affording 410 mg (43%) of salt **6b**, as a pale orange solid. Mp 60 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.57 (s, 1H, H-2); 7.24 (overlapped with $CHCl_3$, H-7); 7.19 (t, 1H, *J* = 7.1 Hz, H-6); 7.10 (d, 1H, *J* = 6.8 Hz, H-5); 5.18 (s, 2H, CH_2-N); 4.95 (s, 2H, CH_2-OH); 3.73 (s, 3H, CH_3); 3,22 (s, 9H, N(CH_3)$_3$) ppm. Anal. Calcd. for $C_{14}H_{21}IN_2O$, M = 360: C, 46.68; H, 5.88; N, 7.78. Found: C, 46.38; H, 5.68; N, 7.32.

Ethyl 2-((4-hydroxymethyl-1-methyl-3-indolyl)methyl)malonate (7)

To an ethanolic solution of sodium ethoxide, freshly prepared from sodium (50 mg, 2.18 mmol) in absolute ethanol (3.3 mL), was added freshly distilled diethyl malonate (347 mg, 2.18 mmol) and the solution was stirred at room temperature for 15 min, under an argon atmosphere. A solution of compound **6b** (239 mg, 0.664 mmol) in absolute ethanol (2 mL) was prepared by brief reflux, cooled and added to the

sodium diethyl malonate solution. The reacting mixture was refluxed under an argon atmosphere for 12 h, cooled and evaporated to dryness. The residue was dissolved in water (5 mL) and the solution was extracted with chloroform (3 x 10 mL). The remaining aqueous phase was acidified to pH 4 with 36% HCl and extracted with chloroform (4 x 10 mL). The combined chloroform phases from the second extraction were dried over anhydrous Na_2SO_4 and evaporated, leaving a residue that was purified by chromatography on silica gel, eluting with a petroleum ether-ethyl acetate gradient, to yield 50 mg (23%) of compound **7**. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.24 (m, H-7'); 7,14 (t, 1H, *J* = 6.9 Hz, H-6'); 7.02 (d, 1H, *J* = 6.7 Hz, H-5'), 6.93 (s, 1H, H-2'); 4.99 (q, 2H, *J* = 12.2 Hz, CH_2OH); 4.20 (m, 4H, 2 CH_2); 3,91 (t, 1H, *J* = 7.2 Hz, H-2); 3.69 (s, 3H, $N_{1'}$-CH_3); 3.53 (d, 2H, *J* = 6.1 Hz, H-α); 1.23 (m, 6H, $2CH_3$) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 167.4 ($\underline{C}O_2CH_2CH_3$); 137.6 (C-7a'); 132.1 (C-4'); 128.6 (C-2'); 124.9 (C-3a'); 121.3 (C-5'); 120.5 (C-6'); 110.1 (C-3'); 109.9 (C-7'); 64.2 (CH_2OH); 61.9 and 61.6 (2 ($CO_2\underline{C}H_2CH_3$); 53.5 (C-2); 40.4 (C-α); 32.7 (N-CH_3); 13.9 and 13.9 ($CO_2CH_2\underline{C}H_3$) ppm. Anal. Calcd. for $C_{18}H_{23}NO_5$, M = 333: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.58; H, 6.78; N, 4.07.

*3-Dimethylamino-4-(*tert*-butyldiphenylsilyloxymethyl) indole (8)*

To a solution of alcohol **5b** (67 mg, 0.328 mmol) in dry dichloromethane (0.5 mL), cooled to 0 °C and in an argon atmosphere, was added triethylamine (50 μL, 0.39 mmol). The mixture was stirred for 5 min at 0 °C and *tert*-butyldiphenylsilyl chloride (100 μL, 0.39 mmol) and 4-dimethylaminopyridine (25 mg, 0.2 mmol) were added. The reaction was left to reach room temperature and stirring was maintained for 12 h. The reaction mixture was poured on water (10 mL) and extracted with chloroform (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated, leaving a residue that was purified by chromatography on silica gel, eluting with a 8:1 mixture of petroleum ether and ethyl acetate, affording 96 mg (66%) of compound **8**, as a white solid. IR (NaCl) ν: 3064 (NH) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.02 (s, 1H, NH); 7.72 (dd, 4H, *J* = 7.5 and 2.5 Hz, H-2",6"); 7.43-7.26 (m, 8H, H-5,7,3",4",5"); 7.16 (t, 1H, *J* = 7.5 Hz, H-6); 7.01 (s, 1H, H-2); 5.36 (s, 2H, H-α); 3.38 (s, 2H, H-α'); 1.99 (s, 6H, $N(CH_3)_2$); 1.09 (s, 9H, $C(CH_3)_3$) ppm. Anal. Calcd. for $C_{28}H_{34}N_2OSi$, M = 442: C, 75.97; H, 7.74; N, 6.33. Found: C, 75.95; H, 7.58; N, 6.30.

*Diethyl 2-((4'-*tert*-butyldiphenylsilyloxymethyl-1'-methyl-3'-indolyl)methyl) malonate (9)*

To a solution of compound **8** (50 mg, 0,113 mmol) in dry tetrahydrofuran (2 mL), under an inert atmosphere, was added a solution of tributylphosphine (28 μL, 0.113 mmol) in dry tetrahydrofuran (1 mL). The mixture was stirred for 5 min and diethyl malonate (30 μL, 0,136 mmol) was added. The reaction mixture was refluxed for 24 h, cooled and poured on water (5 mL) containing a few drops of 0.5 M aqueous HCl. After extraction with a 95:5 dichloromethane-methanol mixture (3 x 5 mL), the combined organic layers were washed with brine (10 mL) dried over anhydrous Na_2SO_4 and evaporated. The residue was chomatographed on silica gel, eluting with a 1:1 petroleum ether-ethyl acetate mixture, affording 30 mg (48%) of compound **9** as a pale yellow oil. IR (NaCl) ν: 3404.0 (NH); 1730.3 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.03 (s, 1H, NH); 7.66 (dd, 4H, *J* = 7.5 and 2.5 Hz, H-2",6"); 7.43-7.23 (m, 8H, H-5',7',3",4",5"); 7.07 (t, 1H, *J* = 7.5 Hz, H-6'); 6.99 (s, 1H, H-2'); 5.14 (s, 2H, H-α); 4.07 (q, 2H, *J* = 7.5 Hz, $C\underline{H}_2CH_3$); 3.72 (t, 2H, *J* = 7.5 Hz, H-2); 3.51 (d, 2H, *J* = 7.5 Hz, H-α'); 1.12 (t, 3H, *J* = 7.5 Hz, $CH_2C\underline{H}_3$); 1.04 (s, 9H, $C(C\underline{H}_3)_3$) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 169.3 (CO); 136.9 (C-7a'); 135.8 (C-2",6"); 133.8 (C-1"); 133.1 (C-4'); 129.7 (C-4"); 127.7 (C-3",5"); 124.5 (C-3a'); 123.2 (C-2'); 121.9 (C-5'); 119.3 (C-6'); 112.8 (C-3'); 110.8 (C-7'); 64.8 (C-α); 61.7 ($\underline{C}H_2CH_3$); 53.7 (C-2); 27.0 ($C(\underline{C}H_3)_3$); 26.3 (C-α'); 19.4 ($\underline{C}(CH_3)_3$); 14.1 ($CH_2\underline{C}H_3$) ppm. Anal. Calcd. for $C_{33}H_{39}NO_5Si$, M = 557: C, 71.06; H, 7.05; N, 2.51. Found: C, 70.86; H, 6.86; N, 2.35.

*(4'-*tert*-Butyldiphenylsilyloxymethyl-1'-methylindol-3'-yl) methylene)dimethyl-ammonium chloride (10)*

A solution of phosphorous oxychloride (0.3 mL, 3.05 mmol) in anhydrous dimethylformamide (0.7 mL) was stirred at 0 °C for 30 min under an argon atmosphere. A solution of compound **4b** (976 mg, 2.45 mmol) in anhydrous dimethylformamide (5 mL) was added dropwise. The reaction mixture was stirred at room temperature for 45 min and poured on water (10 mL). After stirring for 30 min, the mixture was cooled to 0 °C, giving a precipitate that was filtered and dried under reduced pressure in the presence of phosphorous pentoxide to yield 973 mg (80%) of compound **10**, as a white solid. Mp 128-129 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 9.22 (s, 1H, H-α'); 7.54 (d, 4H, *J* = 7.5 Hz, H-2",6"); 7.47-7.19 (m, 9H, H-5,6,7,3",4",5"); 6.82 (d, 1H, *J* = 7.5 Hz, H-2); 5.00 (s, 2H, H-α); 4.13 (s, 3H, N'CH_3); 3.86 (s, 3H, N-CH_3); 3.55 (s, 3H, N'-CH_3); 0,96 (s, 9H, $C(C\underline{H}_3)_3$) ppm ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 160.6 (C-α'); 142.4 (C-2); 138.3 (C-7a); 135.6 (C-2",6"); 132.7 (C-1"); 131.9 (C-4); 130.3 (C-4"); 128.1 (C-3",5"); 126.7 (C-3a); 125.5 (C-5); 124.6 (C-6); 111.8 (C-7); 105.9 (C-3); 65.9 (C-α); 50.4 and 44.2 (2N'-CH_3); 35.0 (N-CH_3); 26.9 ($C(\underline{C}H_3)_3$); 19.4 ($\underline{C}(CH_3)_3$) ppm. Anal. Calcd. for $C_{29}H_{35}ClN_2OSi$, M = 490: C, 70.92; H, 7.14; N, 5.70. Found: C, 71.19; H, 7.28; N, 5.89.

*1-Methyl-4-(*tert*-butyldiphenylsilyloxymethylindole)-3-carbaldehyde (11)*

A solution of phosphorous oxychloride (0.27 mL, 2.91 mmol) in anhydrous dimethylformamide (1.3 mL) was stirred at 0 °C for 30 min under an argon atmosphere. A solution of compound **4b** (933 mg, 2.34 mmol) in anhydrous dimethylformamide (5 mL) was added dropwise. The reaction mixture was stirred at room temperature for 30 min and cooled to 0 °C. Water (10 mL) was added and 20% aqueous NaOH was added dropwise until pH = 8. The solution was heated at 60 °C for 30 min. The precipitate obtained upon cooling was filtered and dissolved in chloroform. This solution was dried over anhydrous Na_2SO_4 and evaporated to yield aldehyde **11** (891 mg, 89%), as a yellow solid. Mp 92-95 °C. IR (NaCl) ν: 1669.1 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 9.97 (s, 1H, CHO); 7.77 (s, 1H, H-2); 7.71-7.67 (m, 4H, H-2",6"); 7.47-7.25 (m, 9H, H-5,6,7,3",4",5"); 5.30 (s, 2H, H-α); 3.85 (s, 3H, N-CH_3); 1.07 (s, 9H, $C(C\underline{H}_3)_3$) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 185.4 (CHO); 138.2 (C-7a); 137.8 (C-2); 135.7 (C-2",6"); 133.7 (C-1"); 134.9 (C-4); 129.8 (C-3",5"); 129.7 (C-4"); 123.6 (C-3a); 122.7

(C-5); 120.7 (C-6); 118.9 (C-3); 109.2 (C-7); 65.7 (C-α); 34.0 (N-CH_3); 27.0 (C($\underline{C}H_3)_3$); 19.5 ($\underline{C}(CH_3)_3$) ppm. Anal. Calcd. for $C_{27}H_{29}NO_2Si$, M = 428: C, 75.84; H, 6.84; N, 3.28. Found: C, 75.53; H, 6.91; N, 3.29.

1-Methyl-4-hydroxymethylindole-3-carbaldehyde (12)

Method A

The same procedure described for the preparation of **11**, starting from 7.825 g (15.94 mmol) of compound **10** and basifying the aqueous solution to pH 12 prior to heating at 60 °C, gave 7.337 g (80%) of compound **12**, as a white solid. Mp 109-113 °C. IR (NaCl) ν: 3380.8 (OH); 1644.6 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 9.68 (s, 1H, CHO); 7.74 (s, 1H, H-2); 7.36-7.19 (m, 3H, H-5,6,7); 4.87 (s, 2H, H-α); 3.85 (s, 3H, N-CH_3); 1.03 (s, 1H, OH) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 185.4 (CHO); 144.5 (C-2); 139.6 (C-7a); 136.6 (C-4); 124.7 (C-5); 124.5 (C-6); 122.6 (C-3a); 118.6 (C-3); 110.1 (C-7); 65.0 (C-α); 34.2 (N-CH_3) ppm. Anal. Calcd. for $C_{11}H_{11}NO_2$, M = 189: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.50; H, 6.01; N, 7.10.

Method B

To a solution of compound **11** (3.410 g, 7.97 mmol) in acetonitrile (1 mL), was added dropwise, at 0 °C, a 48% aqueous solution of HF (0.14 mL, 7.97 mmol). The solution was stirred at room temperature for 24 h. After this time, the reaction mixture was poured onto a saturated aqueous solution of sodium bicarbonate (15 mL) and extracted with chloroform (3 x 15 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel, eluting with a 2:1 petroleum ether-ethyl acetate mixture, yielding 2.626 g (77%) of compound **12**, as a white solid.

Diethyl 2-((4'-*tert*-butyldiphenylsilyloxy-methyl-1'-methyl-3'-indolyl)methylene)malonate (13)

To a solution of diethyl malonate (0,17 mL) in pyridine (2 mL), under an argon atmosphere, was added compound **12** (200 mg, 0.47 mmol), piperidine (0.28 mL) and 4 Å molecular sieves. The reacting mixture was heated at 180 °C for 48 h, cooled poured on acidic water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel, eluting with 10:1 petroleum ether-ethyl acetate, yielding 133 mg (37%) of compound **13**, as a yellow solid. Mp 105-106 °C. IR (NaCl) ν: 1718.8 (CO); 1608.9; 1242.8; 1201.4 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.47 (s, 1H, H-α'); 7.70-7.66 (m, 4H, H-2",6"); 7.60 (s, 1H, H-2'); 7.43-7.36 (m, 6H, H-3",4",5"); 7.23 (d, 1H, *J* = 7,5 Hz, H-5'); 7.12 (t, 1H, *J* = 7,5 Hz, H-6'); 6.92 (d, 1H, *J* = 7,5 Hz, H-7'); 5.13 (s, 2H, H-α); 4.32 (q, 2H, *J* = 7,5 Hz, $C\underline{H}_2CH_3$); 4.18 (q, 2H, *J* = 7.5 Hz, $C\underline{H}_2CH_3$); 3.79 (s, 3H, N-CH_3); 1.31 (t, 3H, *J* = 7.5 Hz, $CH_2C\underline{H}_3$); 1.19 (t, 3H, *J* = 7.5 Hz, $CH_2C\underline{H}_3$); 1.03 (s, 9H, C($C\underline{H}_3)_3$) ppm ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 168.6 ($\underline{C}O_2Et$); 165.0 ($\underline{C}O_2Et$); 138.1 (C-α'); 137.5 (C-7a'); 135.9 (C-2",6"); 133.8 (C-1"); 133.5 (C-4'); 131.7 (C-2'); 129.7 (C-4"); 127.7 (C-3",5"); 125.7 (C-3a'); 122.5 (C-5'); 121.3 (C-6'); 120.5 (C-2); 110.2 (C-3'); 109.6 (C-7'); 65.2 (C-α); 61.5 ($\underline{C}H_2CH_3$); 60.9 ($\underline{C}H_2CH_3$); 33.7 (N-CH_3); 26.9 (C($\underline{C}H_3)_3$); 19.4 ($\underline{C}(CH_3)_3$); 14.4 ($CH_2\underline{C}H_3$); 14.2 ($CH_2\underline{C}H_3$) ppm. Anal. Calcd. for $C_{34}H_{39}NO_5Si$, M = 569: C, 71.67, H, 6.90, N, 2.46. Found: C, 71.69, H, 7.08, N, 2.31.

Diethyl 2-((4'-hydroxymethyl-1'-methyl-3'-indolyl)methylene)malonate (14)

Method A

The same procedure described for the preparation of **13**, starting from 367 mg (1.94 mmol) of compound **12**, afforded 115 mg (22%) of **14**, as a yellow solid. Mp 75 °C. IR (NaCl) ν: 3464.0 (OH); 1717.8 (CO); 1605.4; 1241.9; 1202.4 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.47 (s, 1H, H-α'); 7.65 (s, 1H, H-2'); 7.31-7.21 (m, 3H, H-5',6',7'); 5.05 (d, 2H, *J* = 5 Hz, H-α); 4.36-4.23 (m, 4H, $2C\underline{H}_2CH_3$); 3.80 (s, 3H, N-CH_3); 1.34-1.22 (m, 6H, $2CH_2C\underline{H}_3$); 1.90 (s, 1H, OH) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 168.3 ($\underline{C}O_2Et$); 165.5 ($\underline{C}O_2Et$); 137.6 (C-α'); 137.6 (C-7a'); 133.4 (C-4'); 132.2 (C-2'); 126.0 (C-3a'); 122.8 (C-5'); 122.0 (C-6'); 120.1 (C-2); 110.2 (C-7'); 110.0 (C-3'); 64.2 (C-α); 61.5 ($\underline{C}H_2CH_3$); 61.2 ($\underline{C}H_2CH_3$); 33.7 (N-CH_3); 26.9 (C($\underline{C}H_3)_3$); 14.4 ($CH_2\underline{C}H_3$); 14.2 ($CH_2\underline{C}H_3$) ppm. Anal. Calcd. for $C_{18}H_{21}NO_5$, M = 331: C, 65.24; H, 6.39; N, 4.23. Found: C, 64.96; H, 6.25; N, 4.09.

Method B

To a solution of compound **13** (60 mg, 0.11 mmol) in dry dichloromethane (2 mL) was added a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (0.37 mL, 1.26 mmol). The reaction mixture was stirred at room temperature for 16 h, poured onto pH 7 aqueous buffer (0.5 mL) and extracted with ethyl ether (3 x 10 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel, eluting with 2:1 petroleum ether-ethyl acetate, yielding 27 mg (77%) of compound **14**.

Ethyl 3-(4'-*tert*-butyldiphenylsilyloxy-methyl-1'-methyl-indole-3'-yl)-3-oxopropanoate (15)

To a solution of ethyl diazoacetate (0.14 mL, 1.39 mmol) and BF_3-Et_2O complex (20 μL, 0.16 mmol) in dry dichloromethane (3 mL), cooled to 0 °C and under an argon atmosphere, was added a solution of aldehyde **12** (210 mg, 0.5 mmol). The reacting mixture was stirred at room temperature for 2.5 h, poured onto brine (10 mL) and extracted with diethyl ether (3 x 10 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel, eluting with 10:1 petroleum ether-ethyl acetate, yielding compound **15** 63 mg, 25%) as a pale yellow oil, formed by a *ca*. 1:2 mixture of *oxo* (**15a**) and *enol* (**15b**) tautomers. IR (NaCl) ν: 1731, 8 (CO) cm^{-1}. Anal. Calcd. for $C_{31}H_{35}NO_4Si$, M = 514: C, 72.48; H, 6.87; N, 2.73. Found: C, 72.27; H, 6.58; N, 2.44

^{1}H-NMR for **15a** ($CDCl_3$, 250 MHz) δ: 7.66-7.62 (m, 4H, H-2",6"); 7.40-7.22 (m, 10H, H-2',5',6',7',3",4",5"); 5.15 (d, 1H, *J* = 15.6 Hz, H-α); 4.85 (d, 1H, *J* = 15.6 Hz, H-α); 4.23-4.17 (m, 2H, $C\underline{H}_2CH_3$); 3.74 (s, 3H, N-CH_3); 3.07 (d, 1H, *J* = 15.5 Hz, H-2); 2.90 (d, 1H, *J* = 15.5 Hz, H-2); 1.11 (s, 9H, C($C\underline{H}_3)_3$); 0.84 (t, 3H, *J* = 7,5 Hz, $CH_2C\underline{H}_3$) ppm. ^{13}C-NMR for **15a** ($CDCl_3$, 62.9 MHz) δ: 197.0 ($\underline{C}O$); 173.2 ($\underline{C}O_2Et$); 137.0 (C-7a'); 135.6 (C-2",6"); 134.4 (C-1"); 133.6 (C-4'); 129.8 (C-4"); 129.7 (C-2'); 127.8 (C-3",5"); 124.5 (C-3a'); 122.0 (C-5'); 116.1 (C-6'); 108.1 (C-7'); 99.6 (C-3'); 68.3 (C-α); 61.2 ($\underline{C}H_2CH_3$), 39.6 (C-2); 33.0 (N-CH_3); 27.1 (C($\underline{C}H_3)_3$); 19.5 ($\underline{C}(CH_3)_3$); 14.1 ($CH_2\underline{C}H_3$) ppm.

^{1}H-NMR for **15b** ($CDCl_3$, 250 MHz) δ: 12.95 (s, 1H, OH); 7.80-7.66 (m, 1H, H-7'); 7.66-7.62 (m, 4H, H-2",6"); 7.40-7.22 (m, 8H, H-5',6',3",4",5"); 6.79 (s, 2H, H-2' y H-2); 5.15 (d, 1H, *J* = 15,6 Hz, H-α); 4,85 (d, 1H, *J* = 15.6 Hz, H-α); 4.23-4.17 (m, 3H, N-CH_3); 4.05-3.90 (m, 2H, $C\underline{H}_2CH_3$); 1.27 (t, 3H, *J* = 7.5 Hz, $CH_2C\underline{H}_3$); 1.13 (s, 9H, $C(C\underline{H}_3)_3$) ppm. ^{13}C-NMR for **15b** ($CDCl_3$, 62.9 MHz) δ: 169.3 ($\underline{C}O$); 168.8 ($\underline{C}O_2Et$); 137.0 (C-7a'); 135.6 (C-2",6"); 134.4 (C-1"); 133.8 (C-4'); 129.8 (C-4"); 129.7 (C-2'); 127.8 (C-3",5"); 124.5 (C-3a'); 122.0 (C-5'); 116.1 (C-6'); 108.1 (C-7'); 107.0 (C-3'); 67.8 (C-α); 60.9 ($\underline{C}H_2CH_3$); 33.0 (N-CH_3); 27.0 ($C(\underline{C}H_3)_3$); 19.4 ($\underline{C}(CH_3)_3$); 14.3 ($CH_2\underline{C}H_3$) ppm.

Ethyl 3-(4'-tert-butyldiphenylsilyloxy-methyl-1'-methyl-indol-3'-yl)-2-propenoate, E and Z isomers (16)

Method A

A solution of aldehyde 11 (5.758 g, 0.013 mol) and ethoxycarbonylmethylenetriphenylphosphorane (10.52 g, 0.03 mol) in absolute ethanol (20 mL) was refluxed for 9 h under an inert atmosphere. After the addition of an additional amount of phosphorane (10.52 g, 0.03 mol), reflux was maintained for 14 h. The reaction mixture was then cooled and the solvent was evaporated. Water (20 mL) was added and the suspension was extracted with ethyl acetate (3 x 20 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated. The residue was identified as a 9:1 mixture of the *E* and *Z* isomers of compound 16. Chromatography on silica gel, eluting with a 3:1 petroleum ether-ethyl acetate mixture, afforded 4.975 g (77%) of (*E*)-16, as a white solid, and 0.646 g (10%) of (*Z*)-16, as a pale yellow oil.

Data for (*E*)-**16**: Mp 110 °C. IR (NaCl) ν: 2930.9; 1698.1 (CO); 1619.9; 1530.4; 1257.7 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.31 (d, 1H, *J* = 15 Hz, H-3); 7.72-7.68 (m, 4H, H-2",6"); 7.48 (s, 1H, H-2'); 7.41-7.31 (m, 6H, H-3",4",5"); 7.24 (d, 1H, *J* = 7.5 Hz, H-5'); 7.13 (t, 1H, *J* = 7.5 Hz, H-6'); 6.96 (d, 1H, *J* = 7.5 Hz, H-7'); 6.18 (d, 1H, *J* = 15.0 Hz, H-2); 5.12 (s, 2H, H-α); 4.18 (q, 2H, *J* = 7.5 Hz, $C\underline{H}_2CH_3$); 3.80 (s, 3H, N-CH_3); 1.23 (t, 3H, *J* = 7.5 Hz, $CH_2C\underline{H}_3$); 1.04 (s, 9H, $C(CH_3)_3$). ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 167.5 ($\underline{C}O_2Et$); 139.6 (C-3); 137.7 (C-7a'); 135.7 (C-2",6"); 133.6 (C-1"); 133.3 (C-4'); 129.5 (C-4"); 128.4 (C-2'); 127.6 (C-3",5"); 124.7 (C-3a'); 122.0 (C-5'); 120.4 (C-6'); 113.4 (C-2); 112.5 (C-3'); 109.3 (C-7'); 65.0 (C-α); 59.8 ($\underline{C}H_2CH_3$), 33.3 (N-CH_3); 26.8 ($C(\underline{C}H_3)_3$); 19.2 ($\underline{C}(CH_3)_3$); 14.4 ($CH_2\underline{C}H_3$) ppm. Anal. Calcd. for $C_{31}H_{35}NO_3Si$, M = 497: C, 74.81; H, 7.09; N, 2.81. Found: C, 74.45; H, 7.33; N, 2.54.

Data for (*Z*)-**17**: IR (NaCl) ν: 1700.6 (CO); 1619.6; 1111.4; 1258.8 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.76 (s, 1H, H-2'); 7.75 (d, 1H, *J* = 12.5 Hz, H-3); 7.72-7.67 (m, 4H, H-2",6"); 7.45-7.32 (m, 6H, H-3",4",5"); 7.26 (d, 1H, *J* = 7.5 Hz, H-5'); 7.15 (t, 1H, *J* = 7.5 Hz, H-6'); 7.01 (d, 1H, *J* = 6.5 Hz, H-7'); 5.65 (d, 1H, *J* = 12.5 Hz, H-2); 5.03 (s, 2H, H-α); 4.19 (q, 2H, *J* = 7.5 Hz, $C\underline{H}_2CH_3$); 3.83 (s, 3H, N-CH_3); 1.31 (t, 3H, *J* = 7.5 Hz, $CH_2C\underline{H}_3$); 1.03 (s, 9H, $C(C\underline{H}_3)_3$) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 168.1 ($\underline{C}O_2Et$); 139.3 (C-3); 138.0 (C-7a'); 133.6 (C-4'); 129.0 (C-2'); 124.8 (C-3a'); 122.4 (C-5'); 121.1 (C-6'); 113.2 (C-2); 112.4 (C-3'); 110.1 (C-7'); 64.1 (C-α); 60.2 ($\underline{C}H_2CH_3$), 33.6 (N-CH_3); 14.6 ($CH_2\underline{C}H_3$). Anal. Calcd. for $C_{31}H_{35}NO_3Si$, M = 497: C, 74.81; H, 7.09; N, 2.81. Found: C, 74.41; H, 7.41; N, 2.43.

Method B

A solution of iminium salt **10** (170 mg, 0.35 mmol) and ethoxycarbonylmethylenetriphenylphosphorane (183 mg, 0.52 mmol) in 1,1,2-trichloroethane (2 mL) was refluxed for 12 h under an inert atmosphere. After the addition of an additional amount of ylide (10.52 g, 0.03 mol), reflux conditions were maintained for 4 days. After this time, the reaction mixture was cooled and the solvent was evaporated. Water (20 mL) was added and the suspension was extracted with ethyl acetate (3 x 20 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated. Silica gel chromatography of the residue, eluting with a 3:1 petroleum ether-ethyl acetate mixture, afforded 110 mg (64%) of (***E***)-**16** and 24 mg (14%) of (*Z*)-**16**.

(E)-Ethyl 3-(4'-hydroxymethyl-1'-methyl-indol-3'-yl)-2-propenoate (17)

The same method described for the preparation of **5a**, starting from 405 mg (2.14 mmol) of aldehyde **12**, afforded 361 mg (67%) of (*E*)-**17**, as a pale yellow solid. Mp 120-125 °C. IR (NaCl) ν: 3422.6 (OH); 1685.8 (CO); 1616.0; 1177.1 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 8.25 (d, 1H, *J* = 15.0 Hz, H-3); 7.47 (s, 1H, H-2'); 7.29-7.19 (m, 3H, H-5',6',7'); 6.19 (d, 1H, *J* = 15 Hz, H-2); 5.07 (s, 2H, H-α); 4.23 (q, 2H, *J* = 7.5 Hz, $C\underline{H}_2CH_3$); 3.79 (s, 3H, N-CH_3); 2.30 (s, 1H, OH); 1.31 (t, 3H, *J* = 7.5 Hz, $CH_2C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 168.1 ($\underline{C}O_2Et$); 139.3 (C-3); 138.0 (C-7a'); 133.6 (C-4'); 129.0 (C-2'); 124.8 (C-3a'); 122.4 (C-5'); 121.1 (C-6'); 113.2 (C-2); 112.4 (C-3'); 110.0 (C-7'); 64.1 (C-α); 60.2 ($\underline{C}H_2CH_3$), 33.6 (N-CH_3); 14.6 ($CH_2\underline{C}H_3$). Anal. Calcd. for $C_{15}H_{17}NO_3$, M = 259: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.24; H, 6.68; N, 5.34.

Ethyl 3-(4'-*tert*-butyldiphenylsilyloxy-methyl-1'-methyl-indol-3'-yl)propanoate (18)

To a solution of compound **16** (1 g, 2.01 mmol) in methanol (20 mL) was added 10% Pd-C (60 mg). The suspension was stirred at room temperature under a hydrogen atmosphere for 8.5 h and filtered through celite, which was washed with dichloromethane. Evaporation of the solvent afforded 1.01 g (100%) of compound **18**, as a pale yellow oil. IR (NaCl) ν: 1731,8 (CO); 1111.7 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.70-7.67 (m, 4H, H-2",6"); 7.40-7.34 (m, 6H, H-3",4",5"); 7.17-7.11 (m, 3H, H-5',6',7'); 6.79 (s, 1H, H-2'); 5.11 (s, 2H, H-α); 4.05 (q, 2H, *J* = 7,5 Hz, $C\underline{H}_2CH_3$); 3.70 (s, 3H, N-CH_3); 3.12 (t, 2H, *J* = 7.5 Hz, H-3); 2.51 (t, 2H, *J* = 7.5 Hz, H-2); 1.16 (t, 3H, *J* = 7.5 Hz, $CH_2C\underline{H}_3$); 1.05 (s, 9H, $C(C\underline{H}_3)_3$) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 173.3 ($\underline{C}O_2Et$); 137.6 (C-7a'); 135.8 (C-2",6"); 133.8 (C-1"); 133.5 (C-4'); 129.7 (C-4"); 127.8 (C-3",5"); 126.8 (C-2'); 124.8 (C-3a'); 121.5 (C-5'); 118.1 (C-6'); 114.0 (C-3'); 108.7 (C-7'); 64.6 (C-α); 60.3 ($\underline{C}H_2CH_3$), 36.0 (C-2); 32.9 (N-CH_3); 27.0 ($C(\underline{C}H_3)_3$); 22.3 (C-3); 19.5 ($\underline{C}(CH_3)_3$); 14.3 ($CH_2\underline{C}H_3$) ppm. Anal. Calcd. for $C_{31}H_{37}NO_3Si$, M = 499: C, 74.51; H, 7.46; N, 2.80. Found: C, 74.25; H, 7.63; N, 2.74.

Ethyl 3-(4'-hydroxymethyl-1'-methyl-indol-3'-yl)propanoate (19)

Method A

The same method described for the preparation of **18**, starting from 200 mg (0.77 mmol) of compound **17**, afforded 192 mg (95%) of **19**, as a pale yellow oil. IR (NaCl) ν: 3428,0 (OH); 1727.9 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.23 (d, 1H, *J* = 7.5 Hz, H-5'); 7.16 (t, 1H, *J* = 7.5 Hz, H-6'); 7.06 (d, 1H, *J* = 7.5 Hz, H-7'); 6.87 (s, 1H, H-2'); 5.01 (s, 2H, H-α); 4.11 (q, 2H, *J* = 7.5 Hz, $C\underline{H}_2CH_3$); 3.72 (s, 3H, N-CH_3); 3.26 (t, 2H, *J* = 7.5 Hz, H-3); 2.70 (t, 2H, *J* = 7.5 Hz, H-2); 1.87 (s, 1H, OH); 1.21 (t, 3H, *J* = 7.5 Hz, $CH_2C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 173.6 ($\underline{C}O_2Et$); 137.6 (C-7a'); 133.2 (C-4'); 127.3 (C-2'); 125.0 (C-3a'); 121.6 (C-5'); 119.8 (C-6'); 113.8 (C-3'); 109.6 (C-7'); 64.3 (C-α); 60.5 ($\underline{C}H_2CH_3$); 35.9 (C-2); 32.9 (N-CH_3); 22.0 (C-3); 14.3 ($CH_2\underline{C}H_3$) ppm. Anal. Calcd. for $C_{15}H_{19}NO_3$, M = 261: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.51; H, 7.32; N, 5.19.

Method B

To a solution of compound **18** (891 mg, 1.79 mmol) in dry dichloromethane (6 mL) was added a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (6.22 mL, 21 mmol). The solution was stirred at room temperature for 16 h, poured onto pH 7 aqueous buffer (35 mL) and extracted with ethyl ether (3 x 20 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel, eluting with a 2:1 petroleum ether-ethyl acetate mixture, to yield 446 mg (95%) of compound **19**.

Ethyl 3-(4'-iodomethyl-1'-methylindol-3'-yl)propanoate (20)

To a solution of compound **19** (100 mg, 0.38 mmol) and oven-dried sodium iodide (115 mg, 0.77 mmol) in dry acetonitrile (1 mL), cooled to -78 °C and kept under an argon atmosphere, was added trimethylsilyl chloride (0.1 mL, 0.77 mmol). The temperature was raised to -40 °C and the reaction mixture was stirred at this temperature for 1.5 h. Addition of a 10% sodium thiosulfate aqueous solution caused the precipitation of a iodide **20** (136 mg, 96%), as a yellow solid. Mp 68-70 °C. IR (NaCl) ν: 1730.6 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.21-7.17 (m, 1H, H-5'); 7.12-7.05 (m, 2H, H-6',7'); 6.88 (s, 1H, H-2'); 4.89 (s, 2H, H-α); 4.14 (q, 2H, *J* = 7.5 Hz, $C\underline{H}_2CH_3$); 3.70 (s, 3H, N-CH_3); 3.41 (t, 2H, *J* = 7.5 Hz, H-3); 2.74 (t, 2H, *J* = 7.5 Hz, H-2); 1.24 (t, 3H, *J* = 7.5 Hz, $CH_2C\underline{H}_3$) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 173.6 ($\underline{C}O_2Et$); 137.6 (C-7a'); 133.1 (C-4'); 127.6 (C-2'); 124.8 (C-3a'); 121.6 (C-5'); 121.2 (C-6'); 113.8 (C-3'); 109.8 (C-7'); 60.4 ($\underline{C}H_2CH_3$), 35.8 (C-2); 32.9 (N-CH_3); 22.4 (C-3); 14.1 ($CH_2\underline{C}H_3$); 6.6 (C-α) ppm. Anal. Calcd. for $C_{15}H_{18}INO_2$, M = 371: C, 48.53; H, 4.89; N, 3.77. Found: C, 48.89; H, 5.12; N, 3.85.

Ethyl 3-(4'-nitromethyl-1'-methylindol-3'-yl)propanoate (21)

Sodium nitrite (55 mg, 0.8 mmol) and urea (62 mg, 1.04 mmol) were dried in an oven at 80 °C for 14 h. Both compounds were dissolved in dry dimethylformamide (4 mL), under an argon atmosphere. The solution was cooled to -78 °C and a solution of iodide **20** (128 mg, 0.35 mmol) in dry dimethylformamide (0.75 mL) was added dropwise. The bath temperature was left to raise to -40 °C and the reaction mixture was stirred at this temperature for 2 h and then warmed to room temperature. Water (5 mL) was added and the reaction mixture was extracted with ethyl acetate (3 x 10 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel, eluting with a 8:1 petroleum ether-ethyl acetate mixture, to yield 46 mg (54%) of nitro derivative **21**, as a pale yellow oil, and 5 mg (7%) of alcohol **19**, from hydrolysis of the starting iodide. IR (NaCl) ν: 1729.9 (CO); 1552.9 and 1373.3 (NO_2). ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.35 (d, 1H, *J* = 7.5 Hz, H-5'); 7.22 (t, 1H, *J* = 7.5 Hz, H-6'); 7.12 (d, 1H, *J* = 7.5 Hz, H-7'); 6.93 (s, 1H, H-2'); 5.84 (s, 2H, H-α); 4.12 (q, 2H, *J* = 7.5 Hz, $C\underline{H}_2CH_3$); 3.74 (s, 3H, N-CH_3); 3.19 (t, 2H, *J* = 7.5 Hz, H-3); 2.67 (t, 2H, *J* = 7.5 Hz, H-2); 1.22 (t, 3H, *J* = 7.5 Hz, $CH_2C\underline{H}_3$) ppm. Anal. Calcd. for $C_{15}H_{18}N_2O_4$, M = 290: C, 62.06; H, 6.25; N, 9.65. Found: C, 61.87; H, 5.97; N, 9.44.

3-(4'-*tert*-Butyldiphenylsilyloxymethyl-1'-methylindol-3'-yl) propanol (23)

A solution of compound **18** (150 mg, 0.3 mmol) in dry tetrahydrofuran (1.5 mL) was added dropwise to a suspension of lithium aluminium hydride (50 mg, 0.8 mmol) in the same solvent (1 mL), under an argon atmosphere and at 0 °C. The suspension was stirred at room temperature for 16 h. Excess lithium aluminium hydride was destroyed by addition of ethyl acetate followed by a few drops of water, maintaining initially the reaction mixture in a bath at 0 °C and then at room temperature for 30 min. Solid sodium bicarbonate was then added until a white solid was formed, which was filtered and washed with ethyl acetate. The organic solvent was dried over anhydrous Na_2SO_4 and evaporated, yielding compound **23** (120 mg, 88%) as a colourless oil. IR (NaCl) ν: 3355.1 (OH); 1111.6 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.73-7.70 (m, 4H, H-2",6"); 7.42-7.32 (m, 6H, H-3",4",5"); 7.25-7.18 (m, 3H, H-5',6',7'); 6.78 (s, 1H, H-2'); 5.14 (s, 2H, H-α); 3.71 (s, 3H, N-CH_3); 3.51 (t, 2H, *J* = 7.5 Hz, H-1); 2.77 (q, 2H, *J* = 7.5 Hz, H-3); 1.77-1.65 (m, 2H, H-2); 1.24 (s, 1H, OH); 1.08 (s, 9H, $C(C\underline{H}_3)_3$) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 137.5 (C-7a'); 135.8 (C-2",6"); 133.8 (C-1"); 133.8 (C-4'); 129.7 (C-4"); 127.8 (C-3",5"); 126.7 (C-2'); 124.8 (C-3a'); 121.5 (C-5'); 117.3 (C-6'); 114.8 (C-3'); 108.5 (C-7'); 64.4 (C-α); 62.6 (C-3); 34.6 (C-2); 32.8 (N-CH_3); 27.0 ($C(\underline{C}H_3)_3$); 23.1 (C-3); 19.5 ($\underline{C}(CH_3)_3$) ppm. Anal. Calcd. for $C_{29}H_{35}NO_2Si$, M = 457: C, 76.10; H, 7.71; N, 3.06. Found: C, 76.40; H, 7.43; N, 2.96.

3-(4'-*tert*-Butyldiphenylsilyloxymethyl-1'-methylindol-3'-yl)propanal (24)

To a solution of compound **23** (300 mg, 0.66 mmol) and *N*-methylmorfoline *N*-oxide (116 mg, 1 mmol) in dry acetonitrile (4 mL), under an argon atmosphere, was added activated powdered 4 Å molecular sieves and tetrapropylammonium perruthenate (TPAP) (24 mg, 0.066 mmol). The suspension was stirred at room temperature for 3 h and filtered through a pad of celite, which was washed with dichloromethane. Evaporation of the solvent followed by silica gel chromatography, eluting with a 3:1 petroleum ether-ethyl acetate mixture, afforded compound **24** (216 mg, 72%) as a pale green, viscous oil. IR (NaCl) ν: 1724.8 (CO); 1112.0 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.71-7.67 (m, 4H, H-

2",6"); 7.44-7.31 (m, 6H, H-3",4",5"); 7.21-7.14 (m, 3H, H-5',6',7'); 6.74 (s, 1H, H-2'); 5.09 (s, 2H, H-α); 3.70 (s, 3H, N-CH_3); 3.12 (t, 2H, *J* = 7.5 Hz, H-3); 2.60 (t, 2H, *J* = 7.5 Hz, H-2); 1.06 (s, 9H, C(C$\underline{H}_3$)$_3$) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 202.5 (CHO); 137.5 (C-7a'); 135.7 (C-2",6"); 133.6 (C-1"); 133.3 (C-4'); 129.7 (C-4"); 127.7 (C-3",5"); 126.8 (C-2'); 124.6 (C-3a'); 121.5 (C-5'); 118.1 (C-6'); 113.4 (C-3'); 108.7 (C-7'); 64.5 (C-α); 44.8 (C-2); 32.7 (N-CH_3); 26.9 (C($\underline{C}H_3$)$_3$); 19.3 (C-3); 19,03 ($\underline{C}$(CH$_3$)$_3$) ppm. Anal. Calcd. for $C_{29}H_{33}NO_2Si$, M = 455: C, 76.48; H, 7.25; N, 3.07. Found: C, 76.23; H, 7.13; N, 2.92.

*3-(4'-***tert***-Butyldiphenylsilyloxymethyl-1'-methylindol-3'-yl)propanal dimethyl acetal (25)*

To a solution of trimethylsilyl triflate (10 μL, 0.05 mmol) in dry dichloromethane (1 mL), at -78 °C and under an argon atmosphere, was added methoxytrimetylsilane (61 μL, 0.44 mmol). After stirring for 5 min at the same temperature, a solution of compound **24** (100 mg, 0.22 mmol) in dry dichloromethane (3 mL) was added and stirring at – 78 °C was maintained for 3 h. Pyridine (0.1 mL) was then added, and the reaction was left to warm to rom temperature, washed with a sodium bicarbonate saturated aqueous solution (15 mL), which was extracted with ethyl ether (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated, yielding 80 mg (73%) of compound **25**, as a colourless oil. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.75-7.71 (m, 4H, H-2",6"); 7.44-7.33 (m, 6H, H-3",4",5"); 7.21-7.19 (m, 3H, H-5',6',7'); 6.79 (s, 1H, H-2'); 5.17 (s, 2H, H-α); 4.31 (t, 1H, *J* = 7.5 Hz, H-1); 3.73 (s, 3H, N-CH_3); 3.24 (s, 6H, O($\underline{C}H_3$)$_2$); 2.83 (t, 2H, *J* = 7.5 Hz, H-3); 1.80 (t, 2H, *J* = 7.5 Hz, H-2); 1.09 (s, 9H, C(C$\underline{H}_3$)$_3$) ppm. Anal. Calcd. for $C_{31}H_{39}NO_3Si$, M = 502: C, 74.21; H, 7.83; N, 2.79. Found: C, 74.01; H, 7.67; N, 2.56.

3-(4'-Hydroxymethyl-1'-methylindol-3'-yl)propanal dimethyl acetal (26)

To a solution of silyl ether **25** (80 mg, 0.016 mmol) in dry dichloromethane (1 mL) was added a commercially available 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (0.6 mL, 1.92 mmol). The reacting mixture was stirred at room temperature for 16 h. After this time, it was poured onto pH 7 aqueous buffer (3 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel, eluting with a 10:1 petroleum ether-ethyl acetate mixture, to give 27 mg (67%) of compound **26**, as a colourless oil. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.27 (d, 1H, *J* = 7.5 Hz, H-5'); 7.19 (t, 1H, *J* = 7.5 Hz, H-6'); 7.09 (d, 1H, *J* = 7.5 Hz, H-7'); 6.88 (s, 1H, H-2'); 5.04 (s, 2H, H-α); 4.51 (t, 1H, *J* = 7.5 Hz, H-1); 3.75 (s, 3H, N-CH_3); 3.36 (s, 6H, 2 OCH_3); 3.00 (t, 2H, *J* = 7.5 Hz, H-3); 2.06-1.98 (m, 3H, H-2, OH) ppm. Anal. Calcd. for $C_{15}H_{21}NO_3$, M = 263: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.23; H, 7.91; N, 5.14.

3-(4'-Trimethylsilyloxymethyl-1'-methyl-indol-3'-yl)propanal dimethyl acetal (27)

Neat trimethylsilyl chloride (1 mL) and triethylamine (1 mL) were thoroughly mixed and the resulting suspension was centrifuged to eliminate triethylamine hydrochloride generated due to the presence of traces of hydrochloric acid in the commercial TMS chloride. 60 μL of the supernatant, containing about 0.22 mmol of trimethylsilyl chloride, were added to a solution of compound **26** (0,025 g, 0,11 mmol) and sodium iodide (33 mg, 0.22 mmol) in dry acetonitrile (1 mL), under an argon atmosphere at -78 °C. The temperature was risen to -40 °C and the reaction mixture was stirred at this temperature for 1.5 h. The reaction was warmed to room temperature, poured onto 10 % aqueous sodium thiosulfate (3 mL) and extracted with diethyl ether (4 x 5 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated, yielding 25 mg (75%) of compound **27** as a pale yellow oil. IR (NaCl) ν: 1250.4; 1072.1 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.24-7.09 (m, 3H, H-5',6',7'); 6.83 (s, 1H, H-2'); 5.08 (s, 2H, H-α); 4.50 (t, 1H, *J* = 7.5 Hz, H-1); 3.75 (s, 3H, N-CH_3); 3.36 (s, 6H, O(CH$_3$)$_2$); 2.96 (t, 2H, *J* = 7.5 Hz, H-3); 2.02-1.96 (m, 2H, H-2); 0.16 (s, 9H, Si(CH$_3$)$_3$) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 137.9 (C-7a'); 133.8 (C-4'); 126.9 (C-2'); 125.2 (C-3a'); 121.6 (C-5'); 118.6 (C-6'); 115.0 (C-3'); 109.1 (C-7'); 104.3 (C-1); 63.7 (C-α); 53.0 (OCH_3); 52.9 (OCH_3); 34.1 (C-2); 33.1 (N-CH_3); 22.2 (C-3); 0.0 (Si(CH$_3$)$_3$) ppm. Anal. Calcd. for $C_{18}H_{29}NO_3Si$, M = 335: C, 64.44; H, 8.71; N, 4.17. Found: C, 64.26; H, 8.54; N, 3.98.

*4-(4'-***tert***-Butyldiphenylsilyloxymethyl-1'-methylindol-3'-yl)-2-butanone (28)*

To a solution of compound **4b** (750 mg, 1.9 mmol) in dry acetonitrile (4 mL) was added ytterbium (III) triflate (50 mg, 0.081 mmol) and methyl vinyl ketone (0.7 mL, 8.41 mmol). The solution was stirred at room temperature for 16 h, under an argon atmosphere. The solvent was then evaporated and the residue was chromatographed on silica gel, eluting with 20:1 petroleum ether-diethyl ether, to give 1.153 g (74%) of compound **28**. IR (NaCl) ν: 1715.9 (CO); 1111.5 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.74-7.70 (m, 4H, H-2",6"); 7.44-7.34 (m, 6H, H-3",4",5"); 7.22-7.17 (m, 3H, H-5',6',7'); 6.79 (s, 1H, H-2'); 5.13 (s, 2H, H-α); 3.72 (s, 3H, N-CH_3); 3.04 (t, 2H, *J* = 7.5 Hz, H-4); 2.59 (t, 2H, *J* = 7.5 Hz, H-3); 1.98 (s, 3H, H-1); 1.09 (s, 9H, C(CH$_3$)$_3$) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 209.3 (CO); 136.1 (C-7a'); 136.0 (C-2",6"); 134.0 (C-1"); 133.7 (C-4'); 130.0 (C-4"); 128.1 (C-3",5"); 127.3 (C-2'); 125.0 (C-3a'); 121.8 (C-5'); 118.0 (C-6'); 113.4 (C-3'); 108.9 (C-7'); 64.7 (C-α); 45.7 (C-3); 33.1 (N-CH_3); 30.2 (C-1); 27.3 (C($\underline{C}H_3$)$_3$); 21.3 (C-4); 19.7 ($\underline{C}$(CH$_3$)$_3$) ppm. Anal. Calcd. for $C_{30}H_{35}NO_2Si$, M = 470: C, 76.71; H, 7.51; N, 2.98. Found: C, 76.42; H, 7.32; N, 2.72.

4-(4'-Hydroxymethyl-1'-methylindol-3'-yl)-2-butanone (29)

To a solution of compound **28** (621 mg, 1.32 mmol) in dry dichloromethane (4 mL), was added a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (4.6 mL, 15 mmol). The solution was stirred at room temperature for 16 h, poured onto pH 7 aqueous buffer (24 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel, eluting with a 10:1 petroleum ether-ethyl acetate mixture, to yield 155 mg (51%) of compound **29**, as a pale yellow solid. Mp 93 °C. IR (NaCl) ν: 3388.1 (OH); 1702.2 (CO); 747.1 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.27 (d, 1H, *J* = 7.5 Hz, H-5'); 7.19 (t, 1H, *J* = 7.5 Hz, H-6'); 7.08 (d, 1H, *J* = 7.5 Hz, H-7'); 6.87 (s, 1H, H-2'); 5.03 (s, 2H, H-α); 3.74 (s, 3H, N-CH_3); 3.24 (t, 2H, *J* = 7.5 Hz, H-4); 2.87 (t, 2H, *J* = 7.5 Hz, H-3); 2.16

(s, 3H, H-1); 1.84 (s, 1H, OH) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 209.4 (CO); 138.1 (C-7a'); 133.4 (C-4'); 127.7 (C-2'); 125.0 (C-3a'); 121.8 (C-5'); 120.1 (C-6'); 114.3 (C-3'); 110.0 (C-7'); 64.6 (C-α); 45.4 (C-3); 33.2 (N-$\underline{C}H_3$); 30.4 (C-1); 21.0 (C-4); 19.7 ($\underline{C}(CH_3)_3$) ppm. Anal. Calcd. for $C_{14}H_{17}NO_2$, M = 231: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.35; H, 7.30; N, 5.90.

4-(4'-Iodomethyl-1'-methylindol-3'-yl)-2-butanone (30)

To a solution of compound **29** (100 mg, 0.43 mmol) and sodium iodide (130 mg, 0.86 mmol) in dry acetonitrile (2 mL), kept at -78 °C and under an argon atmosphere, was added trimethylsilyl chloride (0.11 mL, 0.86 mmol). The temperature was risen to -40 °C and the reaction mixture was stirred at this temperature for 1.5 h. The reaction was warmed to room temperature and was poured onto 10 % aqueous sodium thiosulfate (3 mL). The yellow precipitate (110 mg, 75%) was identified as compound **30**. Mp: 70 °C. IR (NaCl) ν: 1710,8 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.23-7.06 (m, 3H, H-5',6',7'); 6.88 (s, 1H, H-2'); 4.92 (s, 2H, H-α); 3.72 (s, 3H, N-CH_3); 3.35 (t, 2H, *J* = 7.5 Hz, H-4); 2.92 (t, 2H, *J* = 7.5 Hz, H-3); 2.21 (s, 3H, H-1) ppm. ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 208.0 (CO); 138.1 (C-7a'); 133.4 (C-4'); 127.8 (C-2'); 125.0 (C-3a'); 121.6 (C-5'); 121.2 (C-6'); 113.5 (C-3'); 109.7 (C-7'); 45.0 (C-3); 32.7 (N-CH_3); 29.8 (C-1); 21.1 (C-4); 19.7 ($\underline{C}(CH_3)_3$); 6.7 (C-α) ppm. Anal. Calcd. for $C_{14}H_{16}INO$, M = 341: C, 49.28, H, 4.73; N, 4.11. Found: C, 48.91; H, 4.72; N, 4.08.

4-(4'-Nitromethyl-1'-methylindol-3'-yl)-2-butanone (31)

Sodium nitrite (50 mg, 0.7 mmol) and urea (55 mg, 0.9 mmol) were dried in an oven at 80 °C for 14 h. These compounds were dissolved in dry dimethylformamide (3 mL), under an argon atmosphere. The solution was cooled to -78 °C and a solution of iodide **30** (100 mg, 0.30 mmol) in dry dimethylformamide (1 mL). The bath temperature was raised to -40 °C and the reaction was stirred at this temperature for 2.5 h and extracted with dichloromethane (3 x 10 mL). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on silica gel, eluting with a 5:1 petroleum ether-ethyl acetate mixture, to yield 12 mg (35%) of hydroxy ketone **29** and 12 mg (31%) of compound **31**. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.38 (d, 1H, *J* = 7.5 Hz, H-5'); 7.23 (t, 1H, *J* = 5.0 Hz, H-6'); 7.15 (d, 1H, *J* = 7.5 Hz, H-5'); 6.84 (s, 1H, H-2'); 5.87 (s, 2H, H-α); 3.76 (s, 3H, N-CH_3); 3.17 (t, 2H, *J* = 7.5 Hz, H-4); 2.83 (t, 2H, *J* = 7.5 Hz, H-3); 2.17 (s, 3H, H-1) ppm. Anal. Calcd. for $C_{14}H_{16}N_2O_3$, M = 260: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.21; H, 5.93; N, 10.24.

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