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PAPER

Decarboxylative Claisen rearrangement reactions: synthesis and reactivity of alkylidene-substituted indolines†

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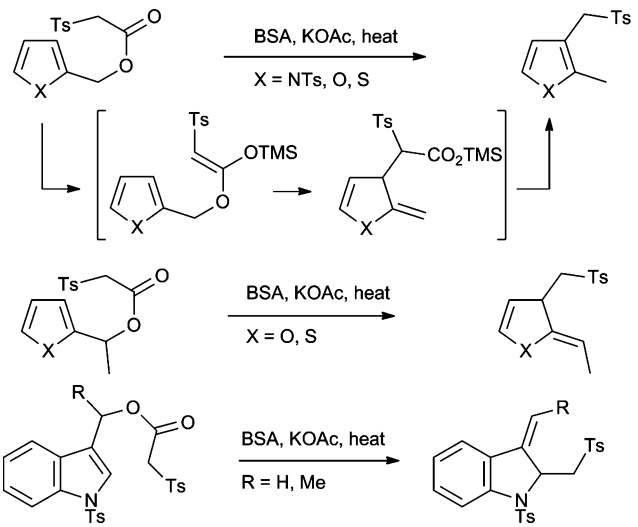
Microwave-assisted decarboxylative Claisen rearrangement (dCr) reactions of substituted acetate derivatives of 3-(hydroxyalkyl)indoles give de-aromatised products. The reactivity of the resultant compounds was evaluated.

Introduction

The decarboxylative Claisen rearrangement (dCr) reaction developed in our laboratory[1] is a variant of the Ireland–Claisen rearrangement,[2–4] in which allylic tosylacetates undergo *in situ* silyl ketene acetal formation, [3,3]-sigmatropic rearrangement, and desilylation–decarboxylation on exposure to *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and KOAc in a cycle catalysed by acetate. We have applied this transformation to reactants possessing heteroaromatic rings in place of the more conventional allylic moieties: thiophene-, pyrrole- and furan-containing substrates gave dCr reaction products in good yields, by a mechanism involving de-aromatisation of the heterocyclic nucleus.[5,6] In some instances the de-aromatised compounds could be isolated and characterised (Scheme 1).[7] In the case of furan derivatives, these non-aromatic species entered into aldol-type reactions characteristic of enol ethers.[8] This article describes de-aromatising dCr reactions of a range of indole-containing substrates, and shows that compounds possessing quaternary centres may be accessed *via* this unusual pathway.

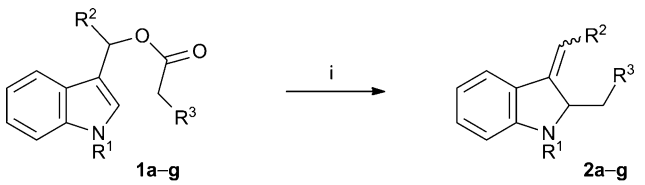
Results and discussion

In the first part of this study, the versatility of de-aromatising dCr reactions of indole-containing esters with respect to the electron-withdrawing group α- to the ester and the indole *N*-substituent was evaluated. Substrates **1a–g** were synthesised from the corresponding alcohols using standard methods. Treatment



Scheme 1 De-aromatising dCr reactions of heteroaromatic substrates.[5,8]

of 0.4 M toluene[9] solutions of **1** with BSA and stoichiometric KOAc under microwave conditions gave the alkylidene-substitued indolines **2** in moderate to good yields; the use of alternating sequences of microwave heating followed by cooling was found to be optimal.[1f,10] The reactions are depicted in Scheme 2, and the results collected in the Table 1.



Scheme 2 De-aromatising dCr reactions of indoles **1a–g**. *Reagents and conditions*: (i) BSA (1.5 equiv.), KOAc (1.0 equiv.), PhMe (0.4 M solution of reactants), microwave, 150 °C.

Several features of the dCr reactions depicted above are noteworthy. Initial experiments showed that *N*-Boc indoles gave higher yields than the *N*-tosyl analogues (entries 1, 2). Substrates having cyano substituents α- to the ester gave similar yields to the

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† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of compounds **1–12**, and further information concerning the X-ray crystallographic analysis of *Z*-**3**. CCDC reference number 775144. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob06212c

Table 1 De-aromatising dCr reactions of indoles **1a–g**

Entry	Substrate	R^1	R^2	R^3	Conditions[a]	Product	Yield (%)[b]
1	**1a**	Ts	H	Ts	5 × 1 min	**2a**	32
2	**1b**	Boc	H	Ts	4 × 1 min	**2b**	68
3	**1c**	Boc	H	CN	4 × 1 min	**2c**	70
4	**1d**	Boc	H	CO_2Et	4 × 1 min	**2d**	22[c]
5	**1e**	Boc	Me	Ts	4 × 1 min	**2e**	87[d]
6	**1f**	Boc	Me	CN	5 × 1 min	**2f**	82[d]
7	**1g**	Boc	Me	CO_2Et	4 × 1 min	**2g**	53[d]

[a] All reactions were carried out at 150 °C, with 1 min cooling between the stated number of heating cycles. [b] Isolated yield following chromatographic purification on silica gel. [c] Prolonged exposure of product **2d** to silica gel resulted in re-aromatisation to the isomeric indole, which was fully characterised. [d] Product was obtained as a mixture of geometric isomers.

α-tosyl analogues (entries 2, 3 and 5, 6). The efficiency of dCr reaction of ester-containing substrates **1d** and **1g** was diminished in part by the instability on silica gel of the products **2d** and **2g**; in the case of **2d** significant quantities of the indolic product of re-aromatisation were observed. With $R^2 = CH_3$ in **1**, an increase in the yield of **2** was observed relative to the less highly substituted compound (compare entries 2 and 5, 3 and 6, 4 and 7).

One of the de-aromatising dCr reaction substrates studied showed markedly different behaviour from that of **1a–g**. Exposure of indolic ester **1h** to the standard reaction conditions gave in good yield two products which were isomeric with the expected ethylidene-substituted indoline **2h**; The structure of **3** followed from extensive NMR experimentation, and was confirmed by X-ray crystallographic analysis of the major (2 : 1) isomer (Fig. 1).[11] Additionally, ozonolysis of **3** with mildly reductive work-up gave 3-oxoindoline **4**. Under the milder dCr reaction conditions studied previously[5] we had observed conversion of **1h** into **2h** in good yields. Therefore, it seems likely in the present case that elimination of the elements of tolylsulfinic acid from **2h** gives a bis(alkylidene)indoline, which undergoes re-aromatisation *via* a [1,5]-sigmatropic hydrogen shift and/or protonation–deprotonation. Protonation at C2 then gives a delocalised cationic intermediate, which is intercepted by tolylsulfinate anion to give **3**.[12] Support for this mechanistic interpretation came from the observation that subjection of **2h** synthesised under the milder conditions to the standard microwave procedure resulted in the formation of **3**. The formation of **3**, together with the mechanism postulated for its generation are shown in Scheme 3.

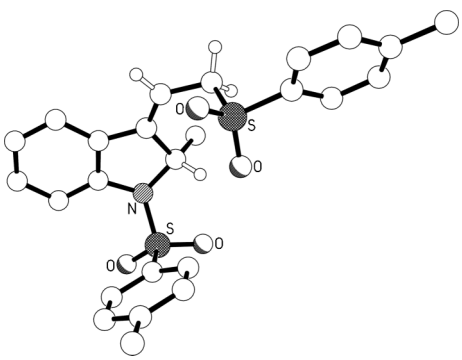
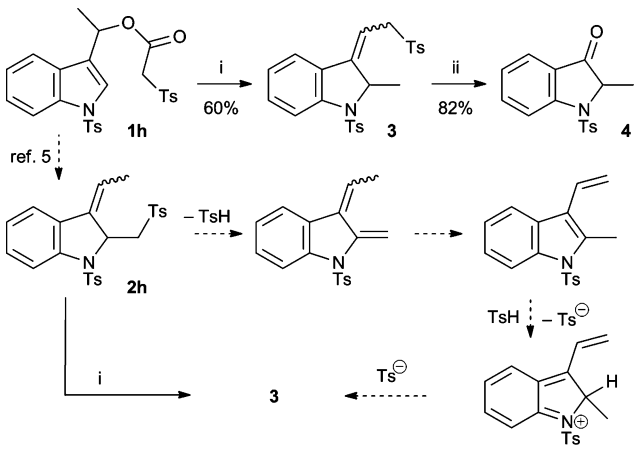


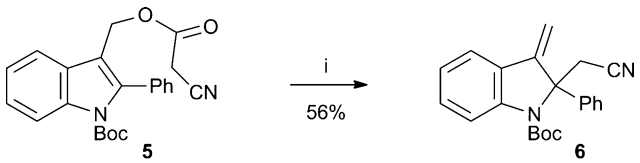
Fig. 1 The molecular structure of *Z*-**3**.

The final dCr substrate studied in this work was selected to ascertain whether more sterically congested indolines could be



Scheme 3 Unusual dCr reaction of **1h**, and postulated mechanism. *Reagents and conditions*: (i) BSA (1.5 equiv.), KOAc (1.0 equiv.), PhMe (0.4 M solution of reactants), microwave, 150 °C, 5 × 1 min; (ii) O_3, CH_2Cl_2, –78 °C, 5 min; SMe_2.

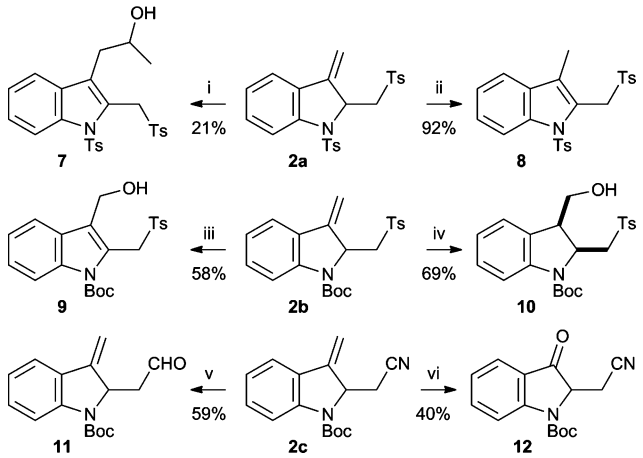
accessed using the de-aromatising transformation. Subjection of the cyanoacetate ester **5** to the usual dCr conditions gave in 56% yield the *N*-Boc-substituted 3-methyleneindoline **6**, which possesses a quaternary centre at C2 (Scheme 4).



Scheme 4 De-aromatising dCr reaction of **5**. *Reagents and conditions*: (i) BSA (1.5 equiv.), KOAc (1.0 equiv.), PhMe (0.4 M solution of reactants), microwave, 150 °C, 4 × 1 min.

The second phase of this work was directed towards developing the utility of the exocyclic methylene group for further synthetic manipulation post-dCr reaction. De-aromatised indoles have been subjected to hydroboration–oxidation,[13] imino-ene,[14] ozonolysis[15] and ring-closing metathesis[15] reactions. Exposure of 3-methyleneindoline **2a** to ethanal in the presence of $ZnCl_2$ at 0 °C gave in low yield the re-aromatised secondary alcohol **7**; at room temperature, high-yielding isomerisation to indole **8** was the sole pathway observed. Oxidation of **2b** with *m*CPBA gave the re-aromatised alcohol **9**, while hydroboration–oxidation gave indoline **10**. Finally, treatment of dCr product **2c** with

DIBAL-H gave aldehyde **11**, with no evidence of re-aromatisation. Compound **2c** also was subjected to ozonolytic cleavage, giving 3-oxoindoline **12** (Scheme 5).



Scheme 5 Derivatisation reactions of 3-methyleneindolines **2a–c**. *Reagents and conditions*: (i) MeCHO, $ZnCl_2$, CH_2Cl_2, 0 °C; (ii) MeCHO, $ZnCl_2$, CH_2Cl_2, rt; (iii) *m*CPBA, CH_2Cl_2, rt; (iv) $BH_3{\cdot}SMe_2$; H_2O_2, NaOH, 0 °C–rt; (v) DIBAL-H, PhMe, −78 °C–rt; (vi) O_3, CH_2Cl_2 (0.007 M), −78 °C; Me_2S, rt.

Conclusions

In summary, we have demonstrated that the de-aromatising dCr reaction of indole-containing substituted esters is an effective method for the generation of 3-alkylideneindolines, and that these products may be usefully elaborated in a variety of ways. In particular, we note the amenability of this approach to the generation of products containing quaternary centres. Ongoing work is concerned with developing asymmetric versions of this process, and applications to natural products synthesis. The results of these studies will be reported in due course.

Experimental

General

Infrared spectra were recorded on a Mattson 5000 FT-IR spectrometer and on a Perkin–Elmer Spectrum RX FT-IR System. Proton magnetic resonance (^{1}H NMR) and carbon magnetic resonance (^{13}C NMR) spectra were recorded in $CDCl_3$ unless otherwise stated on a Bruker AV-400 spectrometer. Chemical shifts are in parts per million (ppm) and are referenced relative to the residual proton-containing solvent (^{1}H NMR: 7.26 ppm for $CDCl_3$; ^{13}C NMR: 77.0 ppm for $CDCl_3$). The following abbreviations are used to indicate the multiplicities: s, singlet, br s, broad signal; d, doublet; t, triplet; m multiplet. Mass spectra (CI) were recorded using Micromass AutoSpec-Q, Micromass Platform II or Micromass AutoSpec Premier instruments. Analytical thin layer chromatography (TLC) was performed on pre-coated aluminium-backed Merck Kiesegel 60 F_{254} plates. Visualisation was effected with ultraviolet light, potassium permanganate or vanillin as appropriate. Flash chromatography was performed using BDH (40-63 μm) silica gel unless otherwise stated. CH_2Cl_2 were distilled under nitrogen from CaH_2 prior to use. All other solvents were reagent-grade. Petrol refers to the fraction of petroleum ether with bp_{760} 40–60 °C. KOAc was oven-dried at 120 °C for several days prior to use. All other reagents were purchased from Aldrich, Fluka, Acros, Alfa Aesar, Lancaster and used as such unless otherwise stated. Microwave-assisted reactions were carried out in a Biotage Initiator instrument. Ozonolyses were performed with an Ozonia Triogen LAB2B ozone generator.

(1-Tosyl-1*H*-indol-3-yl)methyl 2-tosylacetate (1a)

To a stirred solution of (1-tosyl-1*H*-indol-3-yl)methanol (2.3 g, 7.6 mmol) in dry CH_2Cl_2 (75 mL) at rt were added Et_3N (5.3 mL, 38.2 mmol) and chloroacetyl chloride (1.8 mL, 22.8 mmol) and the resultant solution was stirred at rt for 5 min. CH_2Cl_2 (50 mL) and brine (50 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (7 : 3 petrol : EtOAc with 1% Et_3N) to afford (1-tosyl-1*H*-indol-3-yl)methyl 2-chloroacetate (1.89 g, 66%). ν_{max} (film) 3189, 2923, 2852, 1741, 1659, 1632, 1597, 1469, 1410, 1372, 1326, 1291, 1189, 1174, 1150, 1122, 1084, 973, 813, 747, 722, 703, 672 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.69 (s, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.35–7.30 (m, 1H), 7.31–7.24 (m, 3H), 5.37 (s, 2H), 4.08 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 145.1, 134.9, 129.1, 126.8, 126.2, 125.1, 123.4, 119.5, 116.2, 113.6, 59.2, 40.7, 21.4; HRMS-ES+: [M±CO_2CH_2Cl] calcd for $C_{16}H_{14}NO_2S$, 284.0745; found, 284.0743.

To a stirred solution of (1-tosyl-1*H*-indol-3-yl)methyl 2-chloroacetate (950 mg, 2.5 mmol) in MeCN (25 mL) at rt were added Et_3N (0.70 mL, 5.0 mmol) and sodium *p*-toluenesulfinate hydrate (530 mg, 3.0 mmol) and the resultant solution was stirred at rt for 12 h. EtOAc (50 mL) and brine (50 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (7 : 3 petrol : EtOAc with 1% Et_3N) to afford (1-tosyl-1*H*-indol-3-yl)methyl 2-tosylacetate (**1a**, 890 mg, 72%), which had data in agreement with those reported;[5] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.0 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.61–7.57 (m, 3H), 7.44–7.42 (m, 1H), 7.37–7.33 (m, 1H), 7.22–7.20 (m, 3H), 7.06–7.04 (m, 2H), 5.23 (s, 2H), 4.13 (s, 2H), 2.32 (br s, 3H), 2.28 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 145.1, 135.1, 134.6, 129.8, 129.4, 129.0, 128.0, 126.6, 126.2, 124.9, 123.3, 119.5, 115.8, 113.3, 60.7, 58.8, 21.3, 21.2.

tert-Butyl 3-((2-tosylacetoxy)methyl)-1*H*-indole-1-carboxylate (1b)

To a stirred solution of *tert*-butyl 3-(hydroxymethyl)-1*H*-indole-1-carboxylate (2.0 g, 8.0 mmol) in dry CH_2Cl_2 (80 mL) at rt were added Et_3N (5.6 mL, 40.4 mmol) and chloroacetyl chloride (1.9 mL, 24.0 mmol) and the resultant solution was stirred at rt for 5 min. CH_2Cl_2 (50 mL) and brine (50 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (7 : 3 petrol : EtOAc with 1% Et_3N) to afford *tert*-butyl 3-((2-chloroacetoxy)methyl)-1*H*-indole-1-carboxylate (1.91 g, 74%). ν_{max} (film) 3440, 3125, 2979, 2935, 1738, 1731, 1610, 1477, 1455, 1392, 1307, 1257, 1229, 1156, 1090,

1018, 958, 855, 768, 747, 579 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.0 Hz, 1H), 7.71 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.40–7.36 (m, 1H), 7.32–7.28 (m, 1H), 5.40 (s, 2H), 4.09 (s, 2H), 1.70 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 149.2, 135.4, 128.9, 126.1, 124.7, 122.8, 118.9, 115.2, 114.4, 84.0, 59.5, 40.7, 28.0; HRMS-ES+: [M±Boc/-CO_2CH_2Cl] calcd for C_9H_7N, 130.0657; found, 130.0646.

To a stirred solution of 3-((2-chloroacetoxy)methyl)-1*H*-indole-1-carboxylate (200 mg, 0.62 mmol) in MeCN (6.0 mL) at rt were added Et_3N (0.17 mL, 1.2 mmol) and sodium *p*-toluenesulfinate hydrate (130 mg, 0.74 mmol) and the resultant solution was stirred at rt for 2 d. EtOAc (50 mL) and brine (50 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (7 : 3 petrol : EtOAc with 1% Et_3N) to afford *tert*-butyl 3-((2-tosylacetoxy)methyl)-1*H*-indole-1-carboxylate (**1b**, 185 mg, 67%). ν_{max} (film) 3054, 2980, 2937, 2258, 1738, 1716, 1597, 1455, 1385, 1329, 1274, 1229, 1150, 1097, 912, 814, 768, 733, 648, 515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.63 (s, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.40–7.36 (m, 1H), 7.29–7.25 (m, 1H), 7.15 (d, J = 8.4 Hz, 2H), 5.29 (s, 1H), 4.14 (s, 2H), 3.82 (s, 3H), 1.70 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 149.2, 145.1, 135.37, 135.30, 129.5, 128.8, 128.2, 126.2, 124.7, 122.8, 119.0, 115.1, 114.1, 84.0, 60.8, 59.3, 28.0, 21.4. HRMS-ES+: [M+Na] calcd for $C_{23}H_{25}NO_6SNa$, 466.1300; found, 466.1293.

tert-Butyl 3-((2-cyanoacetoxy)methyl)-1*H*-indole-1-carboxylate (1c)

To a stirred solution of *tert*-butyl 3-formyl-1*H*-indole-1-carboxylate (9.0 g, 36.5 mmol) in MeOH (100 mL) at 0 °C was added sodium borohydride (6.9 g, 183 mmol) and the resultant solution was stirred at rt for 1 h. Acetone (100 mL) was added and the solvent was removed under reduced pressure. Brine (100 mL) and CH_2Cl_2 (100 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure to give *tert*-butyl 3-(hydroxymethyl)-1*H*-indole-1-carboxylate, which was used without further purification. ν_{max} (film) 3390, 2980, 2933, 2874, 1737, 1715, 1608, 1455, 1372, 1308, 1257, 1223, 1157, 1087, 1018, 911, 856, 767, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 7.6 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.59 (s, 1H), 7.37–7.33 (m, 1H), 7.29–7.25 (m, 1H), 4.84 (s, 2H), 2.09 (br s, 1H), 1.68 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 135.7, 129.2, 124.6, 123.7, 122.7, 120.5, 119.3, 115.3, 83.7, 57.1, 28.2, 27.9; HRMS-ES+: [M±Boc/-OH] calcd for C_9H_7N, 130.0657; found, 130.0647.

To a stirred solution of the above alcohol (720 mg, 2.9 mmol) in dry CH_2Cl_2 (30 mL) at rt were added Et_3N (0.91 mL, 6.5 mmol), *N*,*N*′-diisopropylcarbodiimide (0.55 mL, 3.5 mmol), DMAP (cat.) and cyanoacetic acid (300 mg, 3.5 mmol) and the resultant solution was stirred at rt for 2 d. CH_2Cl_2 (50 mL) and brine (50 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (6 : 4 petrol : EtOAc with 1% Et_3N) to afford *tert*-butyl 3-((2-cyanoacetoxy)methyl)-1*H*-indole-1-carboxylate (**1c**, 510 mg, 55% over 2 steps). ν_{max} (film) 3458, 3056, 2980, 2933, 2264, 2112, 1755, 1734, 1716, 1610, 1477, 1455, 1392, 1359, 1300, 1258, 1157, 1091, 1010, 984, 855, 767, 748, 581 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.4 Hz, 1H), 7.73 (s, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.42–7.38 (m, 1H), 7.34–7.29 (m, 1H), 5.43 (s, 2H), 3.49 (s, 2H), 1.70 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 149.3, 135.5, 128.9, 126.6, 125.0, 123.1, 119.0, 115.4, 114.0, 112.8, 84.3, 60.4, 60.2, 28.1, 24.7; HRMS-ES+: [M±Boc/-CO_2CH_2CN] calcd for C_9H_7N, 130.0657; found, 130.0650.

(1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)methyl ethyl malonate (1d)

To a stirred solution of *tert*-butyl 3-(hydroxymethyl)-1*H*-indole-1-carboxylate (1.35 g, 5.5 mmol) in dry CH_2Cl_2 (5.0 mL) at rt were added Et_3N (1.7 mL, 12.1 mmol), DIC (0.98 mL, 6.6 mmol), DMAP (cat.) and ethyl hydrogen malonate (0.78 mL, 6.6 mmol) and the resultant solution was stirred at rt for 2 d. CH_2Cl_2 (50 mL) and brine (50 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (8 : 2 petrol : EtOAc containing 1% Et_3N) to afford (1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)methyl ethyl malonate (**1d**, 1.65 g, 84%). ν_{max} (film) 2979, 2934, 1737, 1732, 1454, 1370, 1259, 1162, 1090, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18–8.16 (m, 1H), 7.70–7.55 (m, 2H), 7.38–7.25 (m, 3H), 5.37 (s, 2H), 4.17 (q, J = 7.2 Hz, 2H), 3.45 (s, 2H), 1.70 (br s, 9H), 1.24 (t, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 166.3, 149.4, 135.6, 129.1, 125.9, 124.8, 122.9, 119.2, 115.3, 114.9, 84.0, 61.5, 60.3, 59.1, 59.0, 41.6, 41.5, 28.1, 14.2; HRMS-ES+: [M+Na] calcd for $C_{19}H_{23}NO_6Na$, 384.1423; found, 384.1414.

tert-Butyl 3-(1-(2-tosylacetoxy)ethyl)-1*H*-indole-1-carboxylate (1e)

To a stirred solution of 1*H*-indole-3-carbaldehyde (2.25 g, 15.5 mmol) in dry CH_2Cl_2 (50 mL) at rt were added DMAP (cat.), Et_3N (3.2 mL, 23.2 mmol) and BOC_2O (5.3 mL, 23.2 mmol) and the resultant solution was stirred at rt overnight. Brine (50 mL) and CH_2Cl_2 (50 mL) were added. The organic layer was dried over magnesium sulfate, the solvent removed under reduced pressure to give *tert*-butyl 3-formyl-1*H*-indole-1-carboxylate (3.8 g, 100%), which was used without further purification and had spectra identical to that reported in the literature;[16] ^1H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.31 (d, J = 6.9 Hz, 1H), 8.26 (s, 1H), 8.17 (d, J = 7.7 Hz, 1H), 7.45–7.28 (m, 2H), 1.73 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.8, 148.8, 136.5, 135.9, 126.1, 124.6, 122.1, 121.5, 115.1, 85.6, 28.1.

To a stirred solution of the above crude aldehyde (1.3 g, 5.3 mmol) in dry THF (50 mL) at 0 °C was added MeMgCl (3.8 mL, 2.8 M solution in THF, 10.6 mmol) and the resultant solution was stirred for 1 h at 0 °C. Brine (40 mL) and EtOAc (40 mL) were added. The organic layer was dried over magnesium sulfate, the solvent removed under reduced pressure to give *tert*-butyl 3-(1-hydroxyethyl)-1*H*-indole-1-carboxylate, which was used without further purification.^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.56 (s, 1H), 7.36–7.33 (m, 1H), 7.28–7.25 (m, 1H), 5.19 (q, 6.8 Hz, 1H), 2.00 (br s, 1H), 1.69 (s, 9H), 1.67 (d, J = 6.8 Hz, 3H).

To a stirred solution of the above crude alcohol (5.0 mmol) in dry CH_2Cl_2 (20 mL) at rt were added Et_3N (1.5 mL, 11.0 mmol), DIC (0.93 mL, 6.0 mmol) and tosylacetic acid (1.2 g, 5.0 mmol)

and the resultant mixture was stirred at rt for 2 d. Brine (50 mL) and CH_2Cl_2 (50 mL) were added. The organic layer was dried over magnesium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (7 : 3 petrol : EtOAc with 1% Et_3N) to afford *tert*-butyl 3-(1-(2-tosylacetoxy)ethyl)-1*H*-indole-1-carboxylate (**1e**, 1.2 g, 52%). ν_{max} (film) 2981, 2934, 1738, 1732, 1455, 1371, 1257, 1152, 1025, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.57 (s, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.33–7.29 (m, 1H), 7.21–7.18 (m, 1H), 7.13 (d, J = 8.0 Hz, 2H), 6.21 (q, J = 6.8 Hz, 1H), 4.12 (s, 2H), 2.33 (s, 3H), 1.66 (s, 9H), 1.62 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 149.5, 145.3, 135.7, 129.7, 128.5, 128.1, 124.8, 123.7, 122.8, 119.7, 115.4, 84.1, 68.3, 61.2, 28.2, 21.7, 20.2; HRMS-ES+: [M+] calcd for $C_{24}H_{27}NO_6SNa$, 480.1457; found, 480.1456.

tert-Butyl 3-(1-(2-cyanoacetoxy)ethyl)-1*H*-indole-1-carboxylate (1f)

To a stirred solution of *tert*-butyl 3-formyl-1*H*-indole-1-carboxylate (2.7 g, 11.0 mmol) in dry THF (100 ml) at 0 °C was added MeMgCl (7.9 mL, 2.8 M solution in THF, 22.0 mmol) and the resultant solution was stirred at 0 °C for 1 h. A saturated aqueous solution of ammonium chloride (50 mL) and EtOAc (50 mL) were added. The organic layer was dried over magnesium sulfate, the solvent removed under reduced pressure to give *tert*-butyl 3-(1-hydroxyethyl)-1*H*-indole-1-carboxylate, which was used without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.56 (s, 1H), 7.36–7.33 (m, 1H), 7.28–7.25 (m, 1H), 5.19 (q, 6.8 Hz, 1H), 2.00 (br s, 1H), 1.69 (s, 9H), 1.67 (d, J = 6.8 Hz, 3H).

To a stirred solution of the above crude alcohol (2.5 g, 9.57 mmol) in dry CH_2Cl_2 (25 mL) at rt were added Et_3N (2.9 mL, 21.0 mmol), DIC (1.8 mL, 11.5 mmol) and cyanoacetic acid (980 mg, 11.5 mmol) and the resultant solution was stirred at rt for 4 d. CH_2Cl_2 (50 mL) and brine (50 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (7 : 3 petrol : EtOAc with 1% Et_3N) to afford *tert*-butyl 3-(1-(2-cyanoacetoxy)ethyl)-1*H*-indole-1-carboxylate (**1f**, 2.25 g, 72% over 2 steps). ν_{max} (film) 2981, 2934, 1733, 1730, 1455, 1371, 1319, 1257, 1225, 1152, 1098, 1025, 855, 767, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.0 Hz, 1H), 7.66–7.65 (m, 2H), 7.38–7.35 (m, 1H), 7.31–7.27 (m, 1H), 6.31 (q, J = 6.8 Hz, 1H), 3.47 (s, 2H), 1.78 (d, J = 6.8 Hz, 3H), 1.70 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 149.4, 135.7, 128.0, 124.8, 123.8, 122.9, 119.5, 115.5, 113.0, 84.2, 69.1, 28.1, 24.9, 20.3; HRMS-ES+: [M±Boc/-CO_2CH_2CN] calcd for $C_{10}H_{10}N$, 144.0813; found, 144.0804.

1-(1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)ethyl ethyl malonate (1g)

To a stirred solution of *tert*-butyl 3-(1-hydroxyethyl)-1*H*-indole-1-carboxylate (1.6 g, 6.1 mmol) in dry CH_2Cl_2 (15 mL) at rt were added Et_3N (1.9 mL, 13.5 mmol), DIC (1.1 mL, 7.4 mmol), DMAP (cat.) and ethyl hydrogen malonate (0.87 mL, 7.4 mmol) and the resultant solution was stirred at rt for 2 d. CH_2Cl_2 (50 mL) and brine (50 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (8 : 2 petrol : EtOAc with 1% Et_3N) to afford 1-(1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)ethyl ethyl malonate (**1g**, 1.57 g, 69%). ν_{max} (film) 2981, 2936, 1737, 1731, 1454, 1371, 1157, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18–8.16 (m, 1H), 7.66–7.63 (m, 2H), 7.37–7.33 (m, 1H), 7.29–7.25 (m, 1H), 6.30 (q, J = 6.4 Hz, 1H), 4.49 (q, J = 7.2 Hz, 2H), 3.41 (s, 2H), 1.75 (d, J = 6.4 Hz, 3H), 1.70 (br s, 9H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 166.0, 149.5, 135.7, 128.3, 124.6, 123.4, 122.7, 120.4, 119.7, 115.4, 83.9, 67.2, 61.5, 41.9, 28.1, 20.2, 14.0; HRMS-ES+: [M+Na] calcd for $C_{20}H_{25}NO_6Na$, 398.1580; found, 398.1577.

1-(1-Tosyl-1*H*-indol-3-yl)ethyl 2-tosylacetate (1h)

To a stirred solution of 1-tosyl-1*H*-indole-3-carbaldehyde (1.9 g, 6.4 mmol) in dry THF (100 ml) at 0 °C was added MeMgCl (4.5 mL, 2.8 M solution in THF, 12.7 mmol) and the resultant solution was stirred at 0 °C for 1 h. A saturated aqueous solution of ammonium chloride (50 mL) and EtOAc (50 mL) were added. The organic layer was dried over magnesium sulfate, the solvent removed under reduced pressure to give an alcohol, which was used without further purification.

To a stirred solution of the above crude alcohol (6.4 mmol) in dry CH_2Cl_2 (40 mL) at rt were added Et_3N (1.9 mL, 13.9 mmol), EDCI (1.4 g, 7.6 mmol) and tosylacetic acid (1.4 mg, 6.3 mmol) and the resultant solution was stirred at rt for 2 d. CH_2Cl_2 (50 mL) and brine (50 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (7 : 3 petrol : EtOAc with 1% Et_3N) to afford 1-(1-tosyl-1*H*-indol-3-yl)ethyl 2-tosylacetate (**1h**, 2.3 g, 71% over 2 steps). ν_{max} (film) 2936, 1740, 1653, 1596, 1494, 1448, 1327, 1175, 1152, 1129, 1086, 748 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 8.00–7.98 (m, 1H), 7.81–7.79 (m, 2H), 7.65–7.63 (m, 2H), 7.60 (s, 1H), 7.47–7.45 (m, 1H), 7.35–7.32 (m, 1H), 7.22–7.20 (m, 3H), 7.12–7.10 (m, 2H), 6.17 (q, J = 6.8 Hz, 1H), 4.14 (br s, 2H), 2.34 (br s, 3H), 2.28 (br s, 3H), 1.62 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 145.5, 145.2, 135.5, 135.0, 134.9, 130.0, 129.7, 128.3, 126.9, 125.0, 123.9, 123.4, 121.5, 120.2, 113.6, 67.9, 61.1, 21.6, 21.5, 20.2; HRMS-ES+: [M+Na] calcd for $C_{26}H_{25}NO_6S_2Na$, 534.1021; found, 534.1017.

3-Methylene-1-tosyl-2-(tosylmethyl)indoline (2a)

To a microwave vial containing (1-tosyl-1*H*-indol-3-yl)methyl 2-tosylacetate (**1a**, 880 mg, 1.8 mmol) at rt in dry toluene (4.5 ml, 0.4 M solution of reactants) were added KOAc (175 mg, 1.8 mmol) and BSA (0.65 mL, 2.7 mmol). The resultant mixture was exposed to 5 cycles of microwave irradiation of 1 min each at 150 °C with one minute of air assisted cooling between cycles. The solution was allowed to cool, and brine (30 mL) and CH_2Cl_2 (30 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (6 : 4 petrol : EtOAc with 1% Et_3N) to give 3-methylene-1-tosyl-2-(tosylmethyl)indoline (**2a**, 260 mg, 32%), which had data in agreement with that reported in the literature;[51] ^1H NMR

(400 MHz, $CDCl_3$) δ 7.87–7.85 (m, 2H), 7.71–7.69 (m, 1H), 7.51–7.49 (m, 2H), 7.39–7.35 (m, 2H), 7.33–7.31 (m, 1H), 7.29–7.27 (m, 1H), 7.19–7.17 (m, 2H), 7.11–7.07 (m, 1H), 5.59–5.57 (m, 2H), 5.03–5.00 (m, 1H), 4.06–4.02 (m, 1H), 3.73–3.67 (m, 1H), 2.49 (s, 3H), 2.35 (s, 3H); HRMS-ES+: [M+Na] calcd for $C_{22}H_{25}NO_4SNa$, 422.1402; found, 422.1390.

tert-Butyl 3-methylene-2-(tosylmethyl)indoline-1-carboxylate (2b)

To a microwave vial containing *tert*-butyl 3-((2-tosylacetoxy)-methyl)-1*H*-indole-1-carboxylate (**1b**, 1.5 g, 3.4 mmol) at rt in dry toluene (8.5 ml, 0.4 M solution of reactants) were added KOAc (330 mg, 3.4 mmol) and BSA (1.3 mL, 5.1 mmol). The resultant mixture was exposed to 4 cycles of microwave irradiation of 1 min each at 150 °C with one minute of air assisted cooling between cycles. The solution was allowed to cool, and brine (30 mL) and CH_2Cl_2 (30 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (8 : 2 petrol : EtOAc with 1% Et_3N) to give *tert*-butyl 3-methylene-2-(tosylmethyl)indoline-1-carboxylate (**2b**, 910 mg, 68%). ν_{max} (film) 2979, 2929, 1732, 1597, 1453, 1370, 1323, 1158, 1085, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (br s, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 7.6 Hz, 1H), 7.28–7.23 (m, 3H), 7.03–6.99 (m, 1H), 5.59 (d, J = 1.6 Hz, 1H), 5.32 (br s, 1H), 5.28 (br s, 1H), 3.86 (br s, 1H), 3.62–3.58 (m, 1H), 2.42 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 137.7, 129.9, 129.6, 127.8, 122.9, 120.6, 104.9, 82.2, 60.4, 59.0, 28.3, 21.6; HRMS-ES+: [M+Na] calcd for $C_{24}H_{23}NO_4S_2Na$, 476.0966; found, 476.0966.

tert-Butyl 2-(cyanomethyl)-3-methyleneindoline-1-carboxylate (2c)

To a microwave vial containing *tert*-butyl 3-((2-cyanoacetoxy)-methyl)-1*H*-indole-1-carboxylate (**1c**, 315 mg, 1.0 mmol) at rt in dry toluene (2.5 ml, 0.4 M solution of reactants) were added KOAc (49 mg, 0.5 mmol) and BR SA (0.37 mL, 1.5 mmol). The resulting mixture was exposed to 4 cycles of microwave irradiation of 1 min each at 150 °C with one minute of air assisted cooling between cycles. The solution was allowed to cool, and brine (30 mL) and EtOAc (30 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (7 : 3 petrol : EtOAc with 1% Et_3N) to give *tert*-butyl 2-(cyanomethyl)-3-methyleneindoline-1-carboxylate (**2c**, 190 mg, 70%). ν_{max} (film) 2979, 2931, 2253, 1728, 1456, 1370, 1357, 1329, 1231, 1133, 1119, 756 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.30–7.27 (m, 1H), 7.06–7.02 (m, 1H), 5.66 (s, 1H), 5.27 (s, 1H), 4.95 (br s, 1H), 3.05–2.90 (m, 2H), 1.61 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ *inter alia* [significant line broadening obr served] 130.5, 123.3, 120.8, 116.4, 115.9, 104.2, 59.4, 28.4; HRMS-ES+: [M±Boc] calcd for $C_{11}H_9N_2$, 169.0766; found, 169.0754.

tert-Butyl 2-(2-ethoxy-2-oxoethyl)-3-methyl-1*H*-indole-1-carboxylate (2d)

To a microwave vial containing (1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)methyl ethyl malonate (**1d**, 1.15 g, 3.2 mmol) at rt in dry toluene (8.0 ml, 0.4 M solution of reactants) were added KOAc (315 mg, 3.2 mmol) and BSA (1.2 mL, 4.8 mmol). The resulting mixture was exposed to 4 cycles of microwave irradiation of 1 min each at 150 °C with one minute of air assisted cooling between cycles. The solution was allowed to cool, and brine (30 mL) and EtOAc (30 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (7 : 3 petrol : EtOAc with 1% Et_3N) to give *tert*-butyl 2-(2-ethoxy-2-oxoethyl)-3-methyleneindoline-1-carboxylate (**2d**, 220 mg, 22%), which upon exposure to silica gel rearomatised to give *tert*-butyl 2-(2-ethoxy-2-oxoethyl)-3-methyl-1*H*-indole-1-carb-oxylate. ^1H NMR (400 MHz, $CDCl_3$) δ 8.12–8.10 (m, 1H), 7.51–7.49 (m, 1H), 7.33–7.24 (m, 2H), 4.22 (q, J = 7.2 Hz, 2H), 4.06 (s, 2H), 2.25 (s, 2H), 1.68 (br s, 9H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 150.6, 135.7, 130.3, 128.8, 124.0, 122.3, 118.4, 116.4, 115.6, 83.7, 60.8, 33.2, 28.2, 14.2, 8.7; HRMS-ES+: [M+Na] calcd for $C_{18}H_{23}NO_4Na$, 340.1525; found, 340.1512.

tert-Butyl 3-ethylidene-2-(tosylmethyl)indoline-1-carboxylate (2e)

To a microwave vial containing *tert*-butyl 3-(1-(2-tosylacetoxy)-ethyl)-1*H*-indole-1-carboxylate (**1e**, 1.1 g, 2.4 mmol) at rt in dry toluene (5.8 ml, 0.4 M solution of reactants) were added KOAc (225 mg, 2.4 mmol) and BSA (0.85 mL, 3.5 mmol). The resulting mixture was exposed to 4 cycles of microwave irradiation of 1 min each at 150 °C with one minute of air assisted cooling between cycles. The solution was allowed to cool, and brine (30 mL) and EtOAc (30 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (7 : 3 petrol : EtOAc with 1% Et_3N) to give *tert*-butyl 3-ethylidene-2-(tosylmethyl)indoline-1-carboxylate (**2e**, 860 mg, 87%) as a 1 : 0.6 mixture of alkene isomers. ν_{max} (film) 2976, 2929, 1710, 1701, 1597, 1477, 1392, 1318, 1165, 1140, 1086, 750 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 7.60–7.58 (m, 2H), 7.47–7.43 (m, 2.5 H), 7.29–7.22 (m, 3.5 H), 7.18–7.16 (m, 2H), 5.96–5.90 (m, 0.6H), 5.87–5.82 (m, 1H), 5.38 (br s, 0.6H), 5.23 (br s, 1H), 3.83 (br s, 1.2H), 3.61–3.50 (m, 2H), 2.42–2.41 (m, 5H), 1.95 (dd, J = 7, 2 Hz, 3H), 1.86 (br s, 1.8H), 1.55 (br s, 15H);^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 137.7, 137.3, 129.4, 129.2, 128.6, 128.4, 127.7, 127.6, 124.4, 122.7, 122.6, 120.3, 116.3, 115.8, 115.6, 81.9, 59.7, 28.2, 21.4, 14.8, 14.1; HRMS-ES+: [M+Na] calcd for $C_{23}H_{27}NO_4SNa$, 436.1559; found, 435.1547.

tert-Butyl 2-(cyanomethyl)-3-ethylideneindoline-1-carboxylate (2f)

To a microwave vial containing *tert*-butyl 3-(1-(2-cyanoacetoxy)-ethyl)-1*H*-indole-1-carboxylate (**1f**, 1.5 g, 4.5 mmol) at rt in dry toluene (10 ml, 0.4 M solution of reactants) were added KOAc (450 mg, 4.5 mmol) and BSA (1.69 mL, 6.8 mmol). The resulting mixture was exposed to 5 cycles of microwave irradiation of 1 min each at 150 °C with one minute of air assisted cooling between cycles. The solution was allowed to cool, and brine (30 mL) and EtOAc (30 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (8 : 2 petrol : EtOAc with 1% Et_3N) to give *tert*-butyl 2-(cyanomethyl)-3-ethylideneindoline-1-carboxylate (**2f**, 1.06 g, 82%) as a 1 : 1 mixture of alkene isomers. ν_{max} (film) 3446, 2977,

2926, 2854, 2253, 1732, 1599, 1478, 1455, 1371, 1289, 1256, 1150, 1119, 748 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.50 (br s, 1H), 7.40 (d, J = 7.2 Hz, 1H), 7.28–7.25 (m, 2H), 7.09–7.00 (m, 2H), 6.15 (br s, 1H), 5.91–5.85 (m, 1H), 5.27–5.16 (m, 1H), 4.89 (br s, 1H), 3.25 (br s, 1H), 3.05–2.75 (m, 3H), 2.10 (dd, J = 1.6, 7.6 Hz, 3H), 1.94 (d, J = 7.2 Hz, 3H), 1.63 (s, 9H), 1.61 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ *inter alia* [significant line broadening observed] 129.2, 124.8, 123.2, 120.0, 116.7, 115.8, 60.2, 57.6, 28.4, 14.4; HRMS-ES+: [M-BOC] calcd for $C_{12}H_{11}N_2$, 183.0922; found, 183.0914.

tert-Butyl 2-(2-ethoxy-2-oxoethyl)-3-ethylideneindoline-1-carboxylate (2g)

To a microwave vial containing 1-(1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)ethyl ethyl malonate (**1g**, 1.2 g, 3.2 mmol) at rt in dry toluene (8.0 ml, 0.4 M solution of reactants) were added KOAc (310 mg, 3.2 mmol) and BSA (1.2 mL, 4.8 mmol). The resulting mixture was exposed to 4 cycles of microwave irradiation of 1 min each at 150 °C with one minute of air assisted cooling between cycles. The solution was allowed to cool, and brine (30 mL) and EtOAc (30 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (7 : 3 petrol : EtOAc with 1% Et_3N) to give *tert*-butyl 2-(2-ethoxy-2-oxoethyl)-3-ethylideneindoline-1-carboxylate (**2g**, 560 mg, 53%) as a 2 : 1 mixture of alkene isomers. ν_{max} (film) 2977, 2931, 1734, 1709, 1464, 1391, 1163, 748 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (br s, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.20 (t, J = 10.9 Hz, 1H), 6.99 (t, J = 7.6 Hz, 1H), 5.68 (q, J = 7.2 Hz, 1H), 5.07 (br s, 1H), 4.11–4.03 (m, 2H), 2.87–2.65 (m, 2H), 2.00 (d, J = 7.2 Hz, 3H), 1.56 (br s, 9H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ *inter alia* [significant line broadening observed] 170.6, 128.7, 124.6, 122.5, 118.1, 115.5, 61.2, 60.4, 28.4, 14.3, 14.1; HRMS-ES+: [M+Na] calcd for $C_{19}H_{25}NO_4Na$, 354.1681; found, 354.1680.

2-Methyl-1-tosyl-3-(2-tosylethylidene)indoline (3)

To a microwave vial containing 1-(1-tosyl-1*H*-indol-3-yl)ethyl 2-tosylacetate (**1h**, 2.0 g, 3.9 mmol) at rt in dry toluene (10 ml, 0.4 M solution of reactants) were added KOAc (380 mg, 3.9 mmol) and BSA (0.98 mL, 5.9 mmol). The resulting mixture was exposed to 5 cycles of microwave irradiation of 1 min each at 150 °C with one minute of air assisted cooling between cycles. The solution was allowed to cool, and brine (30 mL) and CH_2Cl_2 (30 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (6 : 4 petrol : EtOAc with 1% Et_3N) to give 2-methyl-1-tosyl-3-(2-tosylethylidene)indoline (**3**, 1.1 g, 60%) as a 2 : 1 mixture of alkene isomers. Data is for the major isomer. ν_{max} (film) 3408, 2979, 2927, 1598, 1463, 1352, 1168, 1086, 731 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 7.6 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.06–7.02 (m, 1H), 5.65 (dt, J = 2.0, 8.0 Hz, 1H), 4.97–4.93 (m, 1H), 3.99–3.82 (m, 2H), 2.45 (s, 3H), 2.32 (s, 3H), 1.40 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 145.0, 143.9, 142.8, 135.8, 134.5, 130.5, 129.8, 129.5, 128.7, 128.1, 126.9, 124.3, 121.0, 116.5, 104.3, 60.8, 56.6, 22.4, 21.5, 21.3; HRMS-ES+: [M+H] calcd for $C_{25}H_{26}NO_4S_2$, 468.1303; found, 468.1296.

2-Methyl-1-tosylindolin-3-one (4)

To a stirred solution of 2-methyl-1-tosyl-3-(2-tosylethylidene)-indoline (**3**, 285 mg, 0.61 mmol) in dry CH_2Cl_2 (20 mL) at −78 °C was bubbled though O_3/O_2 (30 min). Me_2S (1.0 mL) was added and the resultant mixture was stirred at rt overnight. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (6 : 4 petrol : EtOAc) to give 2-methyl-1-tosylindolin-3-one (**4**, 150 mg, 82%). ν_{max} (film) 3067, 2979, 2926, 1721, 1603, 1462, 1360, 1171, 1087, 954, 764, 661 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.4 Hz, 1H), 7.70–7.61 (m, 4H), 7.23–7.17 (m, 3H), 3.98 (q, J = 6.8 Hz, 1H), 2.34 (s, 3H), 1.66 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 152.6, 144.8, 137.2, 133.3, 131.0, 129.8, 127.0, 124.4, 123.8, 116.6, 63.2, 21.3, 17.7; HRMS-ES+: [M+H] calcd for $C_{16}H_{16}NO_3S$, 302.0851; found, 302.0836.

tert-Butyl 3-((2-cyanoacetoxy)methyl)-2-phenyl-1*H*-indole-1-carboxylate (5)

To a stirred solution of *tert*-butyl 3-(hydroxymethyl)-2-phenyl-1*H*-indole-1-carboxylate (2.1 g, 6.5 mmol) in dry CH_2Cl_2 (13 mL) at rt were added Et_3N (2.0 mL, 14.3 mmol), EDCI (1.5 g, 7.8 mmol), DMAP (cat.) and cyanoacetic acid (660 mg, 7.8 mmol) and the resultant solution was stirred for 2 d at rt. CH_2Cl_2 (50 mL) and brine (50 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (8 : 2 petrol : EtOAc with 1% Et_3N) to afford *tert*-butyl 3-((2-cyanoacetoxy)methyl)-2-phenyl-1*H*-indole-1-carboxylate (**5**, 1.5 g, 59%). ν_{max} (film) 3056, 2980, 2932, 2256, 1731, 1454, 1369, 1324, 1222, 1152, 1081, 911, 734, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.52–7.41 (m, 6H), 7.38–7.34 (m, 1H), 5.25 (s, 2H), 3.44 (s, 2H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 149.6, 139.8, 136.2, 132.5, 129.5, 128.2, 128.0, 127.9, 124.9, 123.1, 118.7, 115.2, 113.5, 112.8, 83.6, 59.8, 27.2, 24.5; HRMS-ES+: [M+Na] calcd for $C_{23}H_{22}N_2O_4Na$, 413.1477; found, 413.1481.

tert-Butyl 2-(cyanomethyl)-3-methylene-2-phenylindoline-1-carboxylate (6)

To a microwave vial containing *tert*-butyl 3-((2-cyanoacetoxy)-methyl)-2-phenyl-1*H*-indole-1-carboxylate (**5**, 1.0 g, 2.6 mmol) at rt in dry toluene (10.5 ml, 0.4 M solution of reactants) were added KOAc (410 mg, 3.4 mmol) and BSA (1.6 mL, 6.3 mmol). The resulting mixture was exposed to 4 cycles of microwave irradiation of 1 min each at 150 °C. The solution was allowed to cool, and brine (30 mL) and CH_2Cl_2 (30 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (8 : 2 petrol : EtOAc with 1% Et_3N) to give *tert*-butyl 2-(cyanomethyl)-3-methylene-2-phenylindoline-1-carboxylate (**6**, 500 mg, 56%). ν_{max} (film) 2979, 2932, 2350, 2341, 2264, 1736, 1453, 1389, 1259, 1157, 1091, 768 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (br s, 1H), 7.52–7.50 (m, 1H),

7.42–7.32 (m, 4H), 7.22–7.20 (m, 2H), 7.13–7.09 (m, 1H), 5.62 (s, 1H), 4.84 (s, 1H), 3.73 (br s, 1H), 3.45–3.41 (m, 1H), 1.22 (br s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 149.4, 144.0, 142.8, 130.6, 128.5, 127.5, 126.0, 123.8, 123.2, 120.6, 116.0, 115.4, 104.3, 82.0, 70.4, 28.3, 27.6; HRMS-ES+: [M+H] calcd for $C_{22}H_{23}N_2O_2$, 347.1760; found, 347.1756.

3-(2-Hydroxypropyl)-1-tosyl-2-(tosylmethyl)indole (7)

To a stirred solution of 3-methylene-1-tosyl-2-(tosylmethyl)-indoline (**2a**, 18 mg, 0.039 mmol) in dry CH_2Cl_2 (1.5 mL) at 0 °C were added acetaldehyde (0.004 mL, 0.079 mmol) and $ZnCl_2$ (10 mg, 0.079 mmol) and the resultant mixture was stirred at 0 °C for 3.5 h followed by stirring overnight at rt. Brine (10 mL) and CH_2Cl_2 (10 mL) were added. The organic layer was dried over magnesium sulfate, the solvent removed under reduced pressure and the residue was purified by preparative chromatography (6 : 4 petrol : EtOAc) to give 3-(2-hydroxypropyl)-1-tosyl-2-(tosylmethyl)indole (**7**, 4 mg, 21%). ν_{max} (film) 3524, 2964, 2925, 1596, 1451, 1360, 1168, 1147, 1086, 752, 659, 577 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8. Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.38–7.36 (m, 1H), 7.33–7.31 (m, 2H), 7.28–7.22 (m, 2H), 7.01 (d, J = 8.0 Hz, 2H), 5.25 and 5.05 (d, J = 14.4 Hz, both 1H), 3.43–3.40 (m, 1H), 2.86–2.83 (m, 1H), 2.70–2.65 (m, 1H), 2.48 (s, 3H), 2.25 (s, 3H), 0.36 (d, J = 6.0 Hz, 3H); HRMS-ES+: [M+Na] calcd for $C_{26}H_{27}NO_5S_2Na$, 520.1228; found, 520.1224.

3-Methyl-1-tosyl-2-(tosylmethyl)indole (8)

To a stirred solution of 3-methylene-1-tosyl-2-(tosylmethyl)-indoline (**2a**, 24 mg, 0.05 mmol) in dry CH_2Cl_2 (0.5 mL) at rt were added acetaldehyde (0.006 mL, 0.10 mmol) and $ZnCl_2$ (14 mg, 0.1 mmol) and the resultant mixture was stirred at rt for 3.5 h. Brine (10 mL) and CH_2Cl_2 (10 mL) were added. The organic layer was dried over magnesium sulfate, the solvent removed under reduced pressure and the residue was purified by preparative chromatography (6 : 4 petrol : EtOAc) to give 3-methyl-1-tosyl-2-(tosylmethyl)indole (**8**, 22 mg, 92%). ν_{max} (film) 3063, 2925, 1597, 1452, 1371, 1319, 1190, 1144, 1088, 753 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.0 Hz, 1H), 7.32–7.27 (m, 4H), 7.11 (d, J = 8.0 Hz, 2H), 5.08 (s, 2H), 2.45 (s, 3H), 2.29 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 144.7, 135.7, 129.6, 129.5, 128.8, 126.4, 125.7, 1238, 119.4, 115.4, 98.4, 53.8, 21.7, 21.5, 20.6; HRMS-ES+: [M+Na] calcd for $C_{24}H_{23}NO_4S_2Na$, 476.0966; found, 476.0959.

tert-Butyl 3-(hydroxymethyl)-2-(tosylmethyl)-1*H*-indole-1-carboxylate (9)

To a stirred solution of *tert*-butyl 3-methylene-2-(tosylmethyl)-indoline-1-carboxylate (**2b**, 90 mg, 0.23 mmol) in dry CH_2Cl_2 (3 mL) at rt was added *m*CPBA (85 mg, 50% by weight, 0.25 mmol) and the resultant mixture was stirred at rt for 12 h. A saturated aqueous solution of sodium sulfate (10 mL), a saturated aqueous solution of sodium bicarbonate (10 mL) and CH_2Cl_2 (20 mL) were added. The organic layer was dried over sodium sulfate,[15] the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1 : 1 petrol : EtOAc) to afford *tert*-butyl 3-(hydroxymethyl)-2-(tosylmethyl)-1*H*-indole-1-carboxylate (**9**, 55 mg, 58%). ν_{max} (film) 3444, 2926, 2360, 1732, 1597, 1453, 1325, 1159, 1128, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.37–7.24 (m, 4H), 5.30 (s, 2H), 4.74 (s, 2H), 2.42 (s, 3H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 144.9, 136.3, 135.5, 129.7, 128.6, 125.5, 125.0, 124.4, 123.2, 119.4, 115.8, 84.4, 54.9, 53.8, 29.7, 28.0, 22.7, 21.6; HRMS-ES+: [M$^+$ -BOC/-OH] calcd for $C_{17}H_{16}NO_2S$, 298.0902; found, 298.0888.

tert-Butyl 3-(hydroxymethyl)-2-(tosylmethyl)indoline-1-carboxylate (10)

To a stirred solution of *tert*-butyl 3-methylene-2-(tosylmethyl)-indoline-1-carboxylate (**2b**, 130 mg, 0.32 mmol) in dry THF (6 mL) at 0 °C was added borane-dimethylsulfide complex (0.8 mL, 2.0 M solution in THF, 1.6 mmol) and the resultant mixture was stirred at rt for 1.5 h then cooled to 0 °C. Water (1.5 mL), 1 M NaOH (1.5 mL) and 30% H_2O_2 (0.50 mL) were added and the solution was stirred at rt for 12 h. EtOAc (50 mL) and brine (50 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (7 : 3 petrol : EtOAc) to afford *tert*-butyl 3-(hydroxymethyl)-2-(tosylmethyl)indoline-1-carboxylate (**10**, 90 mg, 69%). ν_{max} (film) 3497, 2975, 2926, 2854, 1704, 1598, 1482, 1386, 1317, 1288, 1252, 1145, 1086, 1017, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 2H), 7.60–7.59 (m, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.21–7.14 (m, 2H), 7.01–6.97 (m, 1H), 5.19–5.16 (m, 1H), 4.34 (dd, J = 4.0, 12.4 Hz, 1H), 4.13–4.09 (m, 1H), 3.87–3.82 (m, 2H), 3.53–3.49 (m, 1H), 2.44 (s, 3H), 1.56 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 144.9, 142.0, 137.2, 129.9, 128.2, 127.7, 123.4, 123.1, 115.7, 82.1, 60.0, 57.3, 55.9, 46.2, 28.3, 21.6; HRMS-ES+: [M+Na] calcd for $C_{22}H_{26}NO_5SNa$, 440.1508; found, 440.1519.

tert-Butyl 3-methylene-2-(2-oxoethyl)indoline-1-carboxylate (11)

To a stirred solution of *tert*-butyl 2-(cyanomethyl)-3-methyl-eneindoline-1-carboxylate (**2c**, 140 mg, 0.51 mmol) in dry toluene (5 mL) at –78 °C was added DIBAL-H (0.48 mL, 1.2 M in toluene, 0.57 mmol) and the resultant solution was stirred at 0 °C for 3 h and then at rt for 2 d. Brine (50 mL) and EtOAc (50 mL) were added. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure and the residue was purified by preparative TLC (8 : 2 petrol : EtOAc) to give *tert*-butyl 3-methylene-2-(2-oxoethyl)indoline-1-carboxylate (**11**, 82 mg, 59%). ν_{max} (film) 2976, 1707, 1478, 1468, 1382, 1167, 1146, 1118, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, J = 1 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.29 (br t, J = 8 Hz, 1H), 7.03 (t, J = 8 Hz, 1H), 5.57 (d, J = 2 Hz, 1H), 5.27 (br s, 1H), 5.10 (br s, 1H), 3.08–2.90 (m, 2H), 1.60 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ *inter alia* [significant line broadening observed] 199.6, 151.5, 151.2, 145.2, 145.1, 130.2, 127.8, 122.9, 120.5, 115.9, 102.9, 82.1, 59.0, 50.5, 28.3; HRMS-ES+: [M-BOC] calcd for $C_{11}H_{10}NO$, 172.0762; found, 172.0758.

***tert*-Butyl 2-(cyanomethyl)-3-oxoindoline-1-carboxylate (12)**

Through a stirred solution of *tert*-butyl 2-(cyanomethyl)-3-ethylideneindoline-1-carboxylate (**2c**, 300 mg, 1.11 mmol) in dry CH_2Cl_2 (150 mL) at −78 °C was bubbled O_3/O_2 (15 min). Me_2S (2.0 mL) was added and the resultant mixture was stirred at rt overnight. The solvent removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (7 : 3 petrol : EtOAc) to give *tert*-butyl 2-(cyanomethyl)-3-oxoindoline-1-carboxylate (**12**, 120 mg, 40%). ν_{max} (film) 2979, 1716, 1606, 1466, 1370, 1286, 1152, 1078, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (br s, 1H), 7.79 (d, $J = 8.0$ Hz, 1H), 7.73–7.69 (m, 1H), 7.29 (s, 1H), 7.24–7.21 (m, 1H), 4.37 (br s, 1H), 3.40 (br s, 1H), 3.12 (dd, $J = 3.2$, 16.8 Hz, 1H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 153.2, 150.4, 137.8, 124.1, 123.5, 122.8, 116.8, 114.8, 83.8, 60.1, 28.0, 19.7; HRMS-ES+: [M+H] calcd for $C_{15}H_{17}N_2O_3$, 273.1239; found, 273.1232.

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