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A formal approach to the cyanobacterial sunscreen indole, prenostodione

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Dedicated to Dr. Gordon W. Gribble in recognition of his outstanding contributions to the field of indole chemistry

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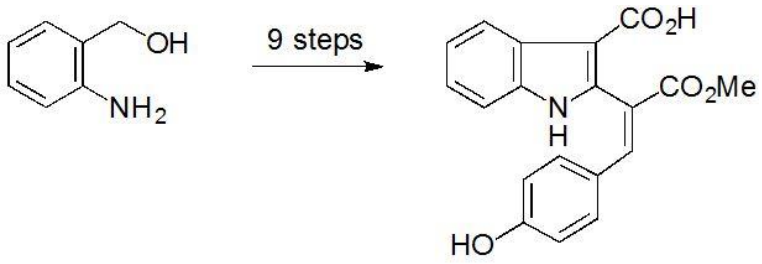
Abstract

The synthesis of the indole sunscreen pigment prenostodione was attempted via an LDA-initiated condensation of *N*-carbamate indole-2-methyl ester **22** with 4-[(*t*-butyldimethylsilyl)oxy]benzaldehyde (**14**) and a late-stage Vilsmeier–Haack formylation. Difficulties with the ensuing oxidation required installation of a C-3 carboxylic acid necessitating the use of a recently reported protocol and thus a formal synthesis of the natural product was realized from 2-aminobenzyl alcohol (**17**) in nine steps.



17 **3**

Keywords: Prenostodione, isoprenostodione, scytonemin, cyanobacteria, Pinnick–Lindgren oxidation

Introduction

The ubiquitous indole skeleton continues to feature prominently in alkaloids isolated from diverse terrestrial and marine sources.[1-2] One such source of novel, and in many cases bioactive, indole-based isolates is cyanobacteria.[3-5] These oxygenic photoautotrophic prokaryotes, commonly referred to as blue-green algae, date back as far as 3.5 billion years[6] and adopt filamentous, unicellular, or aggregated morphologies generally reflective of the habitats to which they have adapted.[7-8]

From those alkaloids reported in the last few decades, members of the classes of hapalindoles,[9-21] fischerindoles,[9,17-18,22] ambiguines,[23,36-37] and welwitindolinones[9,18,22,25-29] have received significant attention from the synthetic community, with over 10 groups rendering total or formal protocols – many with enantioselective precision – since their first isolation in 1984.[30] The sunscreen indole pigments scytonemin (**1**),[31] nostodione A (**2**),[32-34] and prenostodione (**3**),[33] isolated from a variety of cyanobacterial species including Scytonema sp., Nostoc sp., and Scytonema hofmanni, however, have not garnered the same level of interest. While a few total syntheses of these three species are available,[35-39] the focus has been on the exploration of their bioactivity and their enzymatically determined biosynthetic pathways.[40-48] More interestingly, the syntheses of four recently isolated and structurally-related derivatives – scytonine (**4**), dimethoxyscytonemin (**5**), tetramethoxyscytonemin (**6**),[49] and scytonemin-3a-imine (**7**)[50] – remain unreported (Figure 1).

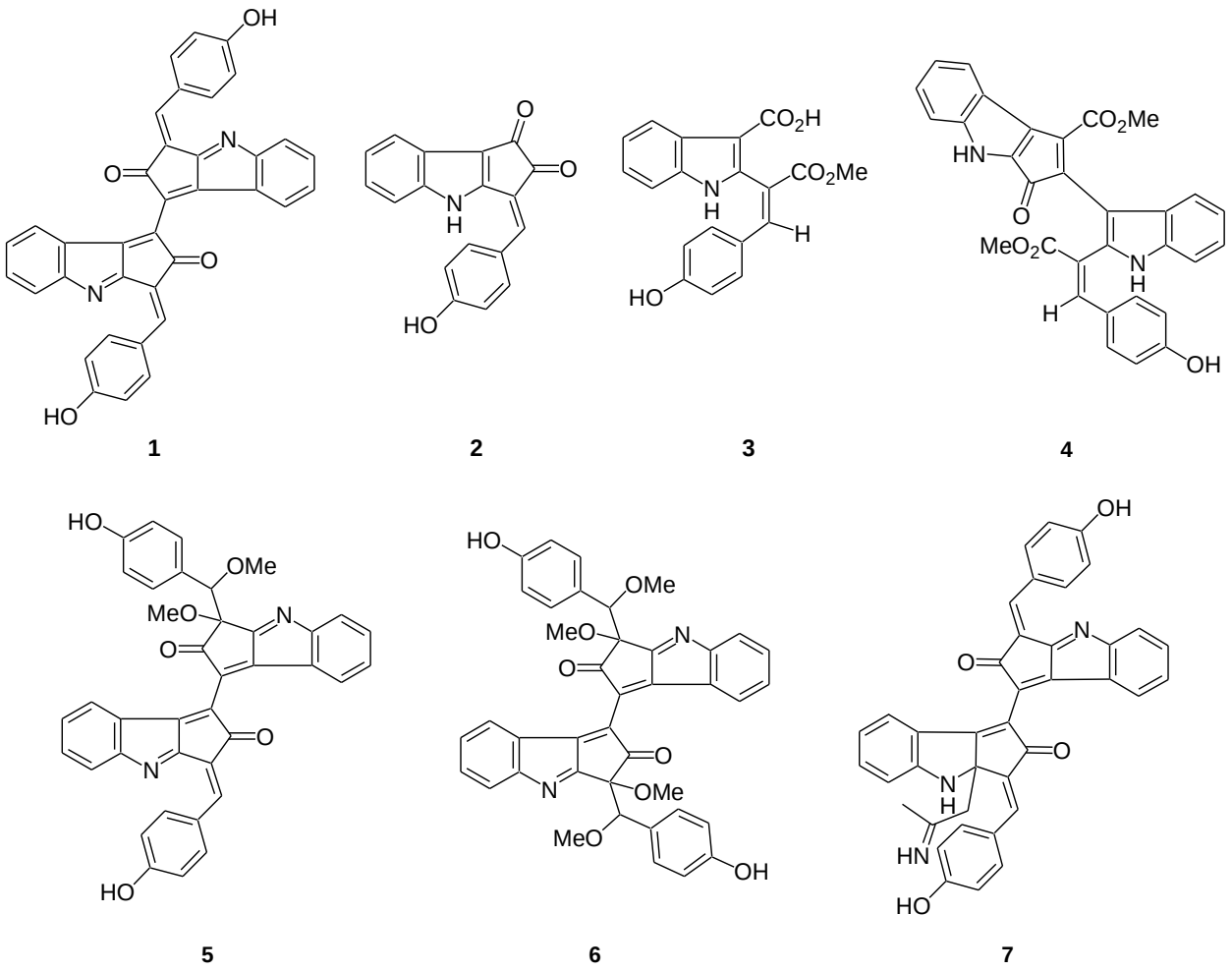
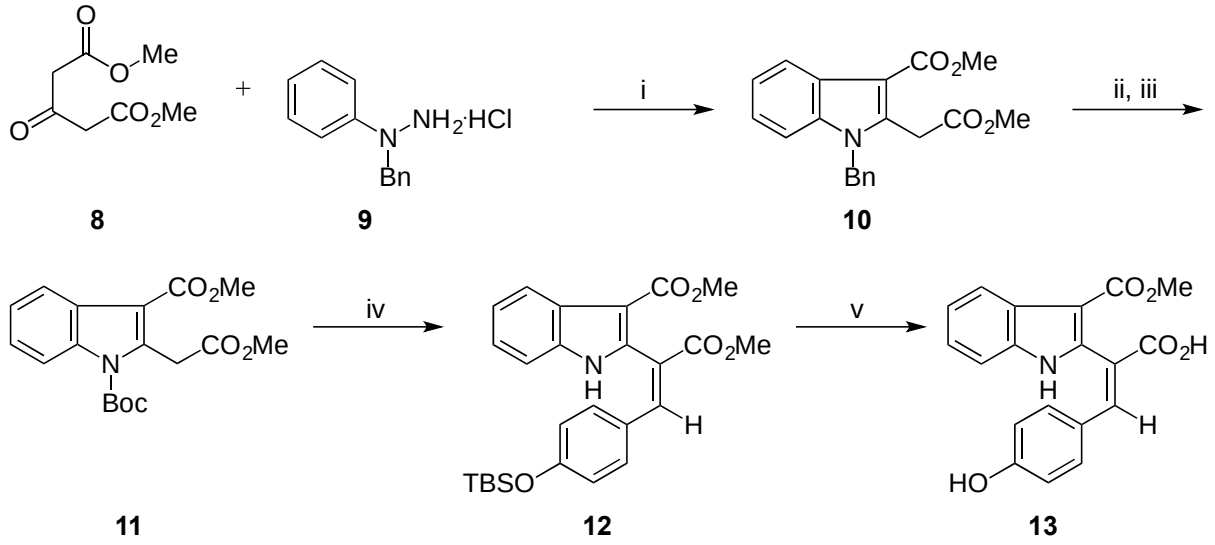


Figure 1. Cyanobacterial alkaloids of interest.

Driven by our desire to access scytonemin (**1**) we sought an initial approach to prenostodione (**3**), proposed by Pluotno and Carmeli[33] to be the precursor of both nostodione A (**2**) and scytonemin (**1**). This indole-3-carboxylic acid derivative is substituted with a *p*-hydroxybenzylidene group appended at the C-2 position of the indole and was determined to have *E*-geometry around the exocyclic double bond. We herein outline our endeavors towards this target compound along with the interesting detours which resulted in a synthesis of an isomer of the natural product, dubbed *iso*prenostodione (**13**).[51]

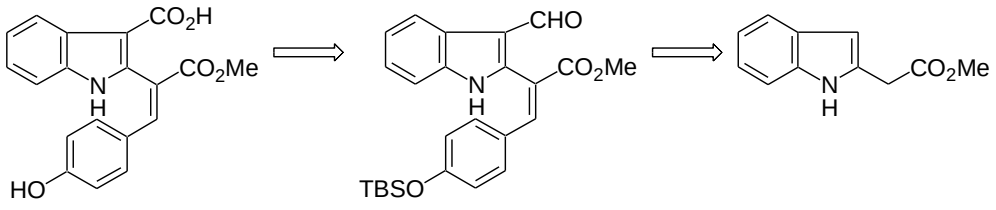
Results and Discussion

A previous account described our initial strategy, which was centered on the installation of the vinyl appendage at the methylene position of an indole diester, and revealed a correlation between the choice of ester and the geometry observed in the coupling.[52] The indole methyl diester **10**, accessed via a Fischer indole synthesis, was therefore smoothly converted into vinyl indole **12** after reaction with 4-[(TBS)oxy]benzaldehyde (**14**) in the presence of base – LDA then CaH_2. A final selective hydrolysis, though not without precedent,[53] proved problematic in this system and regrettably dimethyl ester **12** underwent cleavage at the C-2 position rather than at the intended C-3 site (Scheme 1).



Scheme 1. Reagents and Conditions: i. MeOH, Δ, 12 h (57%); ii. $AlCl_3$, PhH, Δ, 0.5 h (85%); iii. Boc_2O, DMAP, THF, rt (100%); iv. *n*-BuLi, $((CH_3)_2CH)_2NH$, 4-$TBSOC_6H_4CHO$ (**14**), -78 °C; CaH_2, Δ, 1 h (46%); v. KOH, MeOH, Δ, 4 h (23%).

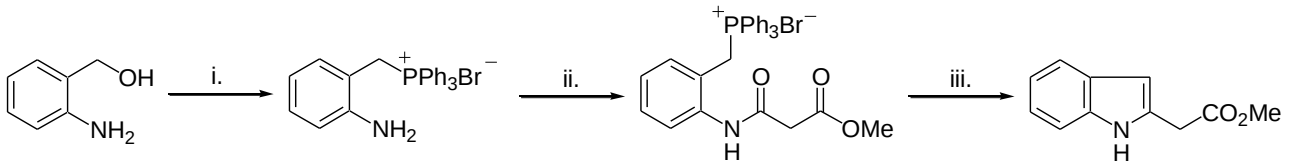
This disappointing result caused us to consider a new approach which was aimed at introducing the C-3 acid in the terminal stages of the synthesis. Furthermore, it was envisioned that, when used in tandem with the base-catalyzed coupling protocol[54] used in our previous attempt at prenostodione (**3**),[51] a late-stage Vilsmier–Haack formylation[55] could introduce an oxidizable C-3 formyl group (Scheme 2).



3 **15** **16**

Scheme 2. Revised retrosynthetic strategy to prenostodione (**3**).

Consequently, treatment of 2-aminobenzyltriphenylphosphonium bromide (**18**), obtained from reaction of commercially obtained 2-aminobenzyl alcohol (**17**) and triphenylphosphonium hydrogen bromide, with methyl malonyl chloride, resulted in the isolation of 1,3-dicarbonyl intermediate **19** as a white powder in 79% yield.[56] Construction of the indole ring was realized when **19** was treated with slightly more than stoichiometric amounts of potassium *tert*-butoxide resulting in indole ester **16** – the product of an intramolecular Wittig condensation (Scheme 3).[57]



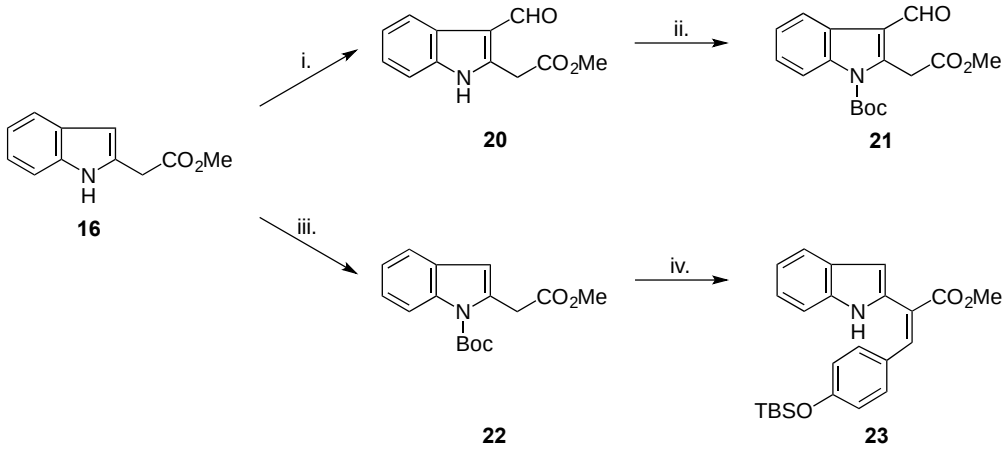
17 **18** **19** **16**

Scheme 3. Reagents and Conditions: i. PPh_3•HBr, CH_3CN (88%); ii. MeO_2CCH_2COCl, CH_2Cl_2, 3 h (79%); iii. 1.1 eq. KO*t*-Bu, PhMe, Δ, 6 h (74%).

With sights firmly set on accessing vinyl indole **15**, a Vilsmeier Haack formylation of indole **16** resulted in 3-formylindole derivative **20** but suffered from low yields after purification. Resultantly, and notwithstanding the successful conversion of **20** to the *N*-Boc-indole **21**, the order of the installation of the functional groups was re-engineered with a view to improving the product yields. Accordingly, coupling of *t*-butoxycarbamate **22**, obtained by protection of indole **16** in almost quantitative yield, with 4-[(TBS)oxy]benzaldehyde (**14**), in the presence of LDA and NaH, led to the isolation of alkene **23** as a yellow solid in 44% yield as outlined in Scheme 4. Although alkene **23** was observed to undergo rapid decomposition in deuterated chloroform, we were able to confirm its identity using NMR spectroscopy. Moreover, 2D NOESY and 1D NOE experiments, conducted on **23**, did not reveal any correlation between the NH proton (δ 8.41) and the vinyl proton at δ 7.85 and consequently gave support to the assignment of an *E*-geometry at the exocyclic double bond.[58]

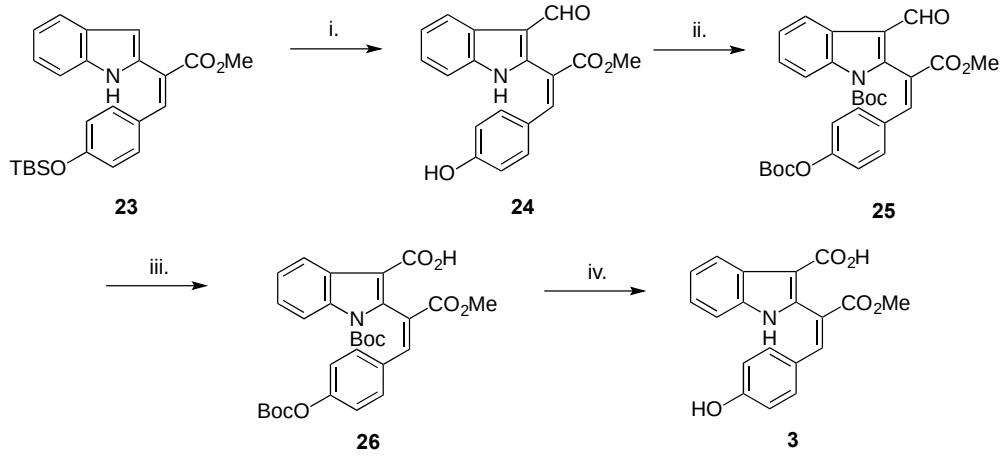
The introduction of the C-3 aldehyde via Vilsmeier–Haack formylation, this time in the absence of an alkali in the hydrolysis step,[59] also resulted in the cleavage of the silyl ether functional group and therefore completion of the strategy would have only required oxidation of the aldehyde to a carboxylic acid (Scheme 5). Unfortunately, a carboxylic acid did not result from reaction under Pinnick–Lindgren oxidation conditions,[60,61] nor upon using other oxidants such as $AgNO_3$, $KMnO_4$, and DDQ. During the ensuing lull in progression, we were fatefully made aware of a recent paper by Biswas *et al*. which outlined the conversion of methyl 2-(3-formyl-1*H*-indole-2-yl)acetate into prenostodione (**3**).[37] Their approach, while synthetically unmatched, was strikingly similar to our proposed route and involved the coupling of methyl ester aldehyde **20** with *p*-hydroxybenzaldehyde, in the presence of the catalyst L-proline, to generate aldehyde **24**. There was

also a notable absence of a direct oxidation protocol which was indicative of the incompatibility of the indole NH and/or the phenol OH with oxidation conditions.



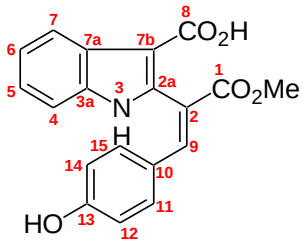
Scheme 4. Reagents and Conditions: i. $POCl_3$, DMF, 0 °C, 1 h; $NaHCO_3$, NaOH (33%); ii. Boc_2O, DMAP, THF, rt (65%); iii. Boc_2O, DMAP, THF, rt (96%); iv. LDA, 4-TBSOC_6H_4CHO (**14**), THF -78 °C, 1 h; NaH, Δ, 2 h (44%).

Given this regretful turn of events, we decided to complete a formal synthesis of prenostodione (**3**) using this reported protocol[37] and reprotected both the -NH and -OH functional groups, by stirring aldehyde **24** with 2.5 equivalents of Boc_2O in the presence of catalytic amounts of DMAP at room temperature for 4 hours (Scheme 5). The ensuing Pinnick–Lindgren oxidation required the sequential addition of sodium chlorite and monosodium phosphate to the heterogeneous mixture of aldehyde **25** and sulfamic acid in *t*-BuOH/H_2O, and afforded di-Boc-acid **26** as a pale yellow solid in 87% yield (over 2 steps). The identity of **26** was confirmed by the disappearance of the aldehyde signals found at δ 9.81 and δ 186.7 in ^{1}H- and ^{13}C-NMR spectra, respectively. In a final effort to secure the coveted natural product prenostodione (**3**), diBoc-acid **26** was treated with TFA in CH_2Cl_2 at 0 °C to facilitate deprotection and the natural product was obtained as a yellow oil, albeit in a modest 24% yield. The NMR spectra of the synthetic product were comparable to literature values for the natural product but revealed minor deviations from those of *iso*prenostodione (13) previously reported (**Table 1**).[33]



Scheme 5. *Reagents and Conditions:* i. $POCl_3$, DMF, Δ, 1 h (79%); ii. Boc_2O, DMAP, CH_2Cl_2, rt (100%); iii. NH_2SO_3H, $NaClO_2$, NaH_2PO_4, *t*-BuOH/H_2O (3:1), rt, 8 h (87%); iv. TFA, CH_2Cl_2, 0 °C, 8 h (24%).

Table 1. Comparison of ^{1}H- and ^{13}C-NMR data for the naturally occurring prenostodione (**3**) (N.P.), synthetic prenostodione (S.P.) and isoprenostodione (**13**) (I.P)[33,51]



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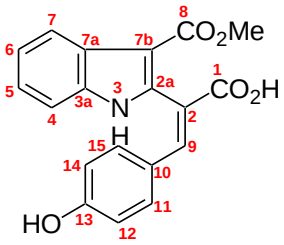

13

Position	N.P. (δ_C)[a]	S.P. (δ_C)[b]	I.P. (δ_C)[a]	N.P. (δ_H)[a]	S.P. (δ_H)[b]	I.P. (δ_H)[a]
1	166.9	166.8	167.8			
1-OMe	52.1	52.0	50.8	3.63 s	3.64 s	3.69 s
2	120.4	120.3	120.5			
2a	139.3	139.2	140.9			
3				11.82 s	11.84	11.93 s
3a	135.8	135.7	135.8			
4	112.1	112.0	112.2	7.37 d (8.8 Hz)	7.37-7.38 d (6.7 Hz)	7.38 -7.41 m
5	122.5	122.4	122.8	7.20 m	7.18-7.20 m	7.22-7.18 d (8.0 Hz)
6	121.2	121.1	121.1	7.18 m		
7	121.2	121.1	121.6	8.03 d (8.7 Hz)	8.04-8.05 d (6.7 Hz)	8.03-8.00 d (8.7 Hz)
7a	127.1	127.0	126.7			
7b	105.8	105.7	104.8			
8	165.8	165.7	165.0			
9	142.3	142.1	141.9	7.78 s	7.79 s	7.77 s
10	124.8	124.7	125.1			
11, 15	132.3	132.2	132.2	6.84 d (8.7 Hz)	6.84-6.85 d (8.3 Hz)	6.84-6.81 d (8.6 Hz)
12, 14	115.8	115.6	115.8	6.58 d (8.7 Hz)	6.58-6.59 d (8.3 Hz)	6.60-6.57 d (8.6 Hz)
13	159.6	159.4	159.4			
13-O				9.99 s	10.05 s	10.04 s

[a] NMR experiments conducted in DMSO-d_6; [b] NMR experiments conducted in $CDCl_3$

Conclusions

We have completed a formal synthesis of prenostodione (**3**) in nine steps from commercially available 2-aminobenzyl alcohol. Efforts geared towards improving the yield of the hydrolysis step and developing synthesis of other similar indole pigments continue in our laboratory.

Experimental Section

General. Melting points were determined on a Sanyo Gallenkamp capillary melting point apparatus, in open capillaries and are uncorrected. Thin layer chromatography (TLC) was performed on Whatman brand 20 x 20 cm aluminum backed silica plates with fluorescent indicator. Plates were visualized by 254 nm UV light. Flash chromatography was carried out using Silicycle ultra-pure silica gel 60 Å (230 - 400 mesh). Preparative TLC (PTLC) was performed with Merck precoated TLC plates silica gel 60 F_{254}. ^{1}H (300 MHz), ^{1}H (600 MHz), ^{13}C (75 MHz), ^{13}C (150 MHz) NMR spectra were recorded on Bruker-300 and -600 Fourier transform spectrometers. The chemical shifts are reported in δ (ppm) using the δ 7.26 signal of $CDCl_3$ (^{1}H-NMR) and the δ 77.16 signal of $CDCl_3$ (^{13}C-NMR), the δ 2.50 signal of $(CD_3)_2SO$ (^{1}H-NMR) and the δ 39.50 signal of $(CD_3)_2SO$ (^{13}C-NMR). Ultraviolet (UV) spectra were recorded on a Hewlett-Packard 8451A Diode Array UV spectrophotometer and are reported in nanometers. Infrared spectra (IR) were recorded on a Shimadzu IR Affinity-1 FTIR spectrophotometer and are referenced to the 1601 cm^{-1} band of polystyrene. IR spectra were obtained using solid potassium bromide pellets (KBr) and are reported in reciprocal centimeters.

[2-(Methoxycarbonylacetamido)benzyl]triphenylphosphonium bromide (19). Methyl malonyl chloride (1.02 mL, 1.29 g, 9.48 mmol, 1 eq.) was added to a stirring solution of 2-aminobenzyltriphenylphosphonium bromide (**18**) (4.12 g, 9.48 mmol, 1 eq.) in CH_2Cl_2 (20 mL). After 3 h, the solvent was removed and the residue was recrystallized from hot MeOH to give phosphonium bromide **19** (4.10 g, 79%) as a white solid; mp 235 °C (dec) (lit.[62] mp 238-239 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.44 (s, 1H), 7.60-7.80 (m, 17H), 6.81-6.86 (m, 1H), 6.70-6.74 (m, 1H), 5.46-5.51 (d, *J* 14.4 Hz, 2H), 3.65 (s, 3H), 3.52 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.6, 165.5, 138.0, 135.2, 134.4, 131.6, 130.3, 129.3, 127.2, 125.3, 120.1, 118.4, 117.3, 52.1, 43.4. IR ν (KBr) 3433, 3101, 1744, 1682, 1435, 1242, 1157, 1111, 748 cm^{-1}; UV λ_{max} (MeOH) 204, 241, 292 nm.

Methyl 2-(1*H*-indol-2-yl)acetate (16). Potassium *tert*-butoxide (835 mg, 7.44 mmol, 1.1 eq.) was added to a stirring suspension of phosphonium bromide **19** (3.71 g, 6.77 mmol, 1 eq.) in toluene (17 mL) at reflux. After 6 h, the reaction was poured onto H_2O and stirred for a further 10 min. The mixture was extracted with CH_2Cl_2 (3 x 30 mL) and the organic extracts were combined, washed with brine (1 x 30 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (2:1 hexanes : EtOAc) gave the desired indole **16** (947 mg, 74%) as a pale yellow solid: mp 65-67 °C (lit.[62] mp 68-69 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.54-7.56 (d, 1H, *J* 7.74 Hz), 7.34-7.37 (d, 1H, *J* 7.98 Hz), 7.06-7.19 (m, 2H), 6.36 (s, 1H), 3.85 (s, 2H), 3.76 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.1, 136.5, 130.5, 128.3, 121.9, 120.3, 120.0, 110.9, 102.0, 52.5, 33.9; IR ν (KBr) 3356, 2847, 1728, 1543, 748 cm^{-1}; UV λ_{max} (MeOH) 219, 271, 290, 389 nm.

***tert*-Butyl 2-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (22).** To a solution of indole **16** (499 mg, 2.63 mmol, 1 eq.) in dry THF (17 mL) was added DMAP (14.9 mg, 0.122 mmol, 0.05 eq.) and di-*tert*-butyl dicarbonate (637 mg, 2.92 mmol, 1.1 eq.) with stirring. The reaction was allowed to stir at rt overnight before being poured onto ice H_2O (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 20 mL) and the organics were combined, dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (1:2 hexanes :

EtOAc) gave the protected indole **22** (0.735 g, 96%) as a pale yellow solid: mp 52-55 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.07-8.10 (d, *J* 7.8 Hz, 1H), 7.46-7.49 (m, 1H), 7.16-7.29 (m, 2H), 6.45 (s, 1H), 4.03 (s, 2H), 3.69 (s, 3H), 1.64 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.9, 150.6, 136.7, 133.3, 128.9, 124.1, 122.9, 120.4, 115.8, 110.5, 84.4, 52.1, 36.3, 28.2; IR ν (KBr) 3449, 1736, 1381, 1327, 748 cm^{-1}; UV λ_{max} (MeOH) 259, 282 nm.

(*E*)-Methyl 3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-(1*H*-indol-2-yl)acrylate (23). To a stirred solution of LDA (0.74 mL, 1.50 mmol, 1.5 eq., 2.0 M in hexanes) in dry THF (4 mL) at -75 °C was added a solution of ester **22** (286 mg, 0.99 mmol, 1 eq.) in dry THF (4 mL). The mixture stirred for 45 min before adding a solution of siloxy benzaldehyde **14** (260 mg, 1.10 mmol, 1.1 eq.) in dry THF (2 mL) and further stirred for 1 h at -75 °C before allowing the mixture to warm to rt slowly. NaH (27.8 mg, 1.2 mmol, 1.2 eq.) was added and the reaction mixture was stirred at reflux for 1 h. The solution was allowed to cool and poured onto H_2O (25 mL) with stirring. The aqueous mixture was extracted with CH_2Cl_2 (3 x 25 mL), and the combined organic extracts were washed with brine (1 x 25 mL), dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (5:1 hexanes : EtOAc) gave the desired alkene **23** (177 mg, 44%) as a yellow oil. Further purification by PTLC (5:1 hexanes : EtOAc) afforded a amorphous solid which was analyzed by HRMS: mp 68-70 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.86 (s, 1H), 7.58-7.60 (m, 1H), 7.33-7.34 (m, 1H), 7.18-7.20 (m, 1H), 7.14-7.15 (d, 2H, *J* 8.66 Hz) 7.10-7.13 (m, 1H), 6.68-6.70 (d, 2H, *J* 8.66 Hz) 6.56-6.57 (m, 1H) 3.84 (s, 3H), 0.96 (s, 9H), 0.19 (s, 6H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 168.1, 157.4, 142.2, 136.2, 132.0, 131.3, 128.5, 127.6, 122.4, 121.4, 121.0, 120.3, 120.0, 111.2, 104.7, 52.6, 25.7, 18.3, -4.3; IR ν (KBr) 3441, 1636, 1250, 1142, 902 cm^{-1}; UV λ_{max} (MeOH) 350, 300, 288 nm. HRMS calcd for $C_{24}H_{29}NO_3Si$ (M^+ +H) 408.1995. Found 408.2008.

(*E*)-methyl 2-(3-formyl-1*H*-indol-2-yl)-3-(4-hydroxyphenyl)acrylate (24). $POCl_3$ (0.109 g, 0.07 mL, 0.712 mmol, 1.2 equiv.) was added to DMF (0.052 g, 0.05 mL, 0.71 mmol, 1.2 equiv.) and after stirring for 15 min, alkene **23** (0.242 g, 0.595 mmol, 1 equiv.) in 1,2-dichloroethane (7 mL) was added. The reaction was heated to reflux for 1 h before it was poured onto an aqueous solution (1 mL) of NaOAc (0.464 g, 5.64 mmol, 9.5 equiv.) under ice-cooling and stirred overnight. The reaction mixture was diluted with H_2O (15 mL), the aqueous mixture was extracted by CH_2Cl_2 (3 x 15 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (1:1 hexanes : EtOAc) gave the desired product **24** (0.151 g, 79%) as yellow solid; mp 203 °C (dec); ^{1}H-NMR (600 MHz, DMSO-d_6) δ 12.27 (s, 1H), 10.19 (s, 1H), 9.70 (s, 1H), 8.10-8.12 (m, 2H), 7.48-7.50 (d, 1H, *J* 7.9 Hz), 7.26-7.29 (m, 2H), 6.93-6.95 (d, 2H, *J* 8.8 Hz), 6.60-6.62 (d, 2H, *J* 8.8 Hz), 3.72 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6) 184.5, 166.3, 160.1, 146.2, 144.0, 136.3, 132.6, 125.0, 123.9, 123.6, 122.4., 120.9, 116.4, 115.8, 113.9, 112.3, 52.4; IR ν (KBr) 3310, 2847, 1690, 1636, 1204, 748 cm^{-1}; UV λ_{max} (MeOH) 213, 245, 268, 303 nm.

(*E*)-*tert*-butyl-2-(1-(4-((*tert*-butoxycarbonyl)oxy)phenyl)-3-methoxy-3-oxoprop-1-en-2-yl)-3-formyl-1*H*-indole-1-carboxylate (25). To a stirred solution of compound **24** (61 mg 0.168 mmol, 1 equiv.) and DMAP (2.3 mg, 0.019 mmol, 0.1 equiv.) at 0 °C in CH_2Cl_2 (5 mL) was added Boc_2O (102.5 mg, 0.47 mmol, 2.5 equiv.). The stirring continued for 4 h at rt before the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL), quenched with dilute HCl and washed with H_2O. Evaporation of solvent afforded **25** as a crude white solid (98 mg, 100%) that was used without further purification: mp 102-105 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.31-8.32 (d, 1H, *J* 7.8 Hz), 8.27-8.28 (d, 1H, *J* 8.3 Hz) 8.14 (s, 1H), 7.44-7.46 (m, 1H), 7.38-7.40 (m, 1H), 7.13-7.15 (d, 2H, *J* 8.6 Hz), 7.04-7.05 (d, 2H, *J* 8.6 Hz), 3.78 (s, 3H), 1.57 (s, 9H), 1.50 (s, 9H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 186.7, 166.2, 152.5, 151.2, 149.2, 143.5, 143.4, 136.5, 131.5, 130.7, 126.2, 125.8, 124.9, 122.4, 122.0, 121.9, 118.2, 115.6, 86.4, 84.2, 52.8, 27.9, 27.1; IR ν (KBr) 2947, 2847, 1751, 1667, 1543, 1373, 756 cm^{-1}; UV λ_{max} (MeOH) 218, 314 nm.

(*E*)-1-(*tert*-butoxycarbonyl)-2-(1-(4-((*tert*-butoxycarbonyl)oxy)phenyl)-3-methoxy-3-oxoprop-1-en-2-yl)-1*H*-indole-3-carboxylic acid (26). To a heterogeneous mixture of aldehyde **25** (100 mg, 0.19 mmol, 1 equiv.) and

sulfamic acid (75 mg, 0.77 mmol, 4 equiv.) in *t*-BuOH:H_2O (3:1 = 4 mL) were added NaH_2PO_4 (69 mg, 0.58 mmol, 3 equiv.) and $NaClO_2$ (80%, 73 mg, 0.81 mmol, 3 equiv.), sequentially at room temperature. The reaction mixture was allowed to stir for 8 h then poured onto H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were concentrated in vacuo and purified by flash column chromatography (1:1 hexanes : EtOAc) to furnish acid **26** as a white solid (89 mg, 87%): mp 144-146 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.23-8.27 (m, 2H), 7.95 (s, 1H), 7.38-7.44 (m, 2H), 6.97-7.01 (m, 4H), 3.76 (s, 3H), 1.49 (s, 9H), 1.48 (s, 9H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 168.7, 166.6, 152.1, 151.3, 149.0, 141.6, 139.9, 136.2, 131.6, 130.9, 127.3, 125.6, 124.4, 124.1, 122.4, 121.7, 115.6, 111.3, 85.9, 84.0, 52.6, 27.9, 27.7; IR ν (KBr) 2978, 2932, 1751, 1674, 1373, 1150 cm^{-1}; UV λ_{max} (MeOH) 271, 272, 282 nm.

(*E*)-2-(1-(4-hydroxyphenyl)-3-methoxy-3-oxoprop-1-en-2-yl)-1*H*-indole-3-carboxylic acid (3). To a solution of di-Boc acid **26** (49.7 mg, 0.925 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) at 0 °C was added TFA (0.55 mL). The mixture was allowed to stir for 8 h before being concentrated by rotary evaporation to give the crude product. Purification by PTLC (1:2 hexanes : EtOAc) afforded the pure compound **3** as a yellow oil (7.6 mg, 24%): ^{1}H-NMR (600 MHz, DMSO-d_6) δ 11.84 (s, 1H), 10.05 (s, 1H), 8.04-8.05 (d, 1H, *J* 6.7 Hz), 7.79 (s, 1H), 7.37-7.38 (d, 1H, *J* 6.7 Hz), 7.18-7.20 (m, 2H), 6.84-6.85 (d, 2H, *J* 8.3 Hz), 6.58-6.59 (d, 2H, *J* 8.3 Hz), 3.64 (s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6) δ 166.8, 165.7, 159.4 142.1, 139.2, 135.7, 132.2, 127.0, 124.7, 122.4, 121.1, 121.1, 120.3, 115.6, 112.0, 105.7, 52.0; IR ν (KBr) 3549, 2924, 2855, 1643, 1574, 1512, 1443 cm^{-1}; UV λ_{max} (MeOH) 231, 286, 321 nm.

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