Efficient Synthesis of the First *N*-Methyloxoarcyriaflavin Including an Original Central Seven-Membered Cycle

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Abstract: A new route to the first *N*-methyloxoarcyriaflavin was designed. The compound was obtained by a palladium-catalyzed Stille cross-coupling reaction, followed by an electrophilic cyclization onto a C-2 indolic position as a key step.

Key words: indole, tropone, palladium, electrophilic cyclization, rearrangement

Over the last decades, several groups have been interested in the synthesis of diverse indolocarbazoles because of their diverse biological and pharmacological activities.[1] Among them, the naturally occurring arcyriaflavin A (**I**) (Figure 1) exhibits moderate cyclin-dependent kinases (CDKs) inhibition.[2] With the aim of finding more potent activities against cancer cells, the structure of arcyriaflavin A (**I**) has been modulated, mainly by replacement of one of the indole cores by diverse (hetero)aromatic moities: thiophene, azaindole, naphthalene, phenyl, etc.,[3] or by design of unfused indolocarbazole analogues.[4] In another study of our own, we introduced a carbonyl group between the indole moiety and a phenyl group, leading to compounds of type **III**.[5] The tropone core, a central seven-membered ring, was directly inspired by caulersine (**IV**), a natural bisindolic molecule isolated from the alga *Caulerpa serrulata*.[6]

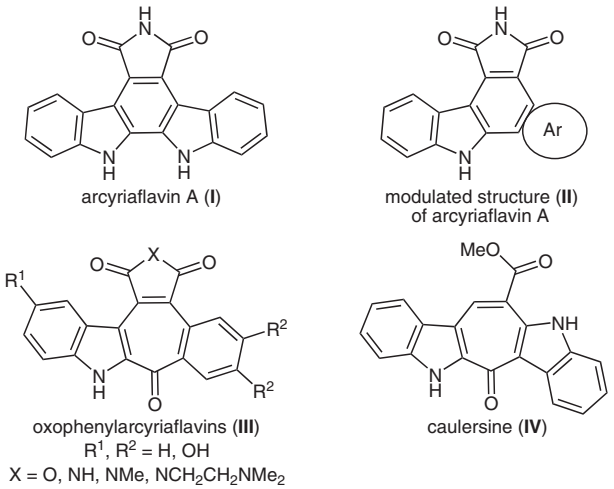

Figure 1 Arcyriaflavin A and modulated-structure compounds

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In continuation of our work, it appeared as a challenge to design compound **1** (Scheme 1), a bisindolic analogue of compounds of type **III**. Currently, only few bisindolic compounds bearing a central seven-membered ring have been synthesized. The two main compounds are homoarcyriaflavin (**V**)[7] and arcyriacyanin A (**VI**) (Figure 2).[8] Homoarcyriaflavin was obtained by a double 1,4-Michael addition starting from a bisindolic scaffold and dibromomaleimide in basic medium, whereas three ways of synthesis were described for arcyriacyanin A, two out of three including Heck palladium-catalyzed reactions.

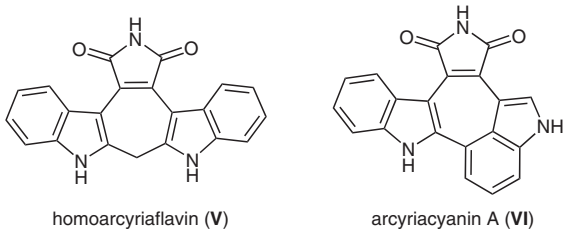


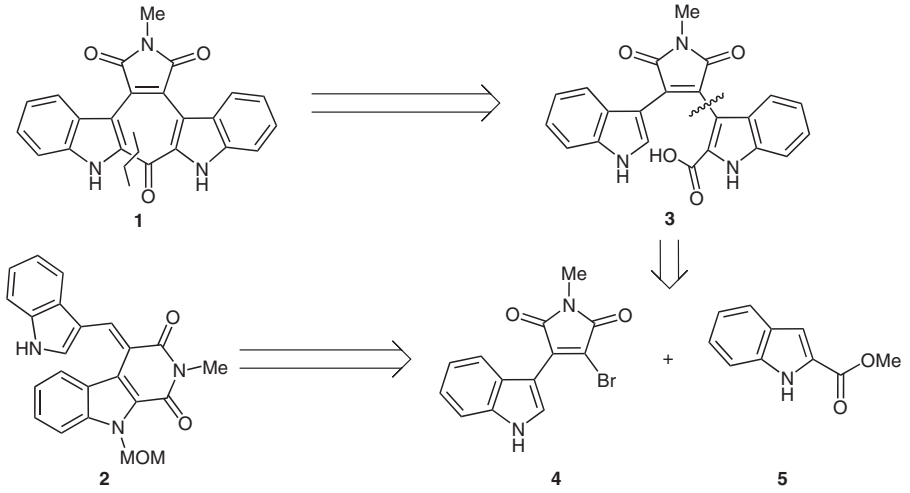
Figure 2 Bisindoles bearing a seven-membered central ring

In this article, we describe an original synthesis of the first *N*-methyloxoarcyriaflavin (**1**) in only few efficient steps starting from the well known 3-bromo-4-indolyl-*N*-methylmaleimide (**4**)[9] and indole-2-carboxylic acid methyl ester (**5**).[10] During the course of this work, an unexpected rearranged 4-ethylidene β-carboline **2** was isolated, whose structure has been confirmed by a different synthetic pathway (Scheme 1).

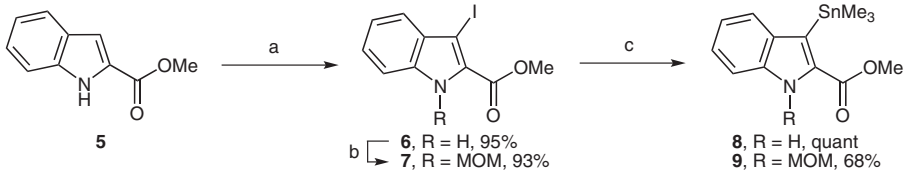
Following our previous strategy,[5] the central tropone of the *N*-methyloxoarcyriaflavin (**1**) can be generated through an intramolecular electrophilic cyclization in C-2 of an indole. The opened bisindolic precursor **3** would be formed by a Stille cross-coupling reaction between 3-bromo-4-indolyl-*N*-methylmaleimide (**4**) and a C-3 tin derivative of **5**.

We began with the synthesis of the stannylated esters **8** and **9**, as building blocks for the cross-coupling reaction (Scheme 2). The esterification of the commercially available indole-2-carboxylic acid was conducted in refluxing methanol for 24 hours with either 1.2 equivalents of acetyl chloride or 1.5 equivalents of sulfuric acid to afford **5** in 96 and 99% yield, respectively.[11]

The iodination was performed at room temperature using KOH as a base and provided **6** in an excellent yield after



Scheme 1 Retrosynthetic pathway toward *N*-methyloxoarcyriaflavin (**1**)



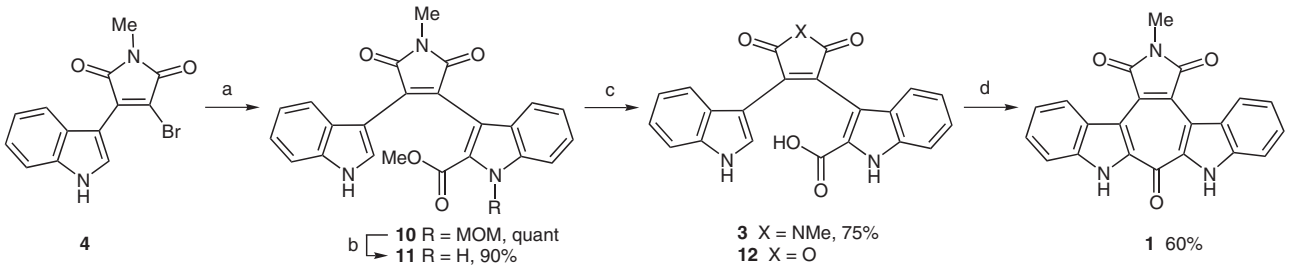
Scheme 2 *Reagents and conditions*: a) KOH (4.0 equiv), DMF, r.t., 10 min, then I_2, DMF, r.t., 1.25 h, 95%; b) NaH (1.3 equiv), DMF, 0 °C, 30 min, then MOMCl (4.0 equiv), 0 °C to r.t., 2 h, 93%; c) from **6**, Sn_2Me_6 (1.2 equiv), $Pd(PPh_3)_4$ (0.1 equiv), toluene, reflux, 6 h, **8** (quant); from **7**, Sn_2Me_6 (1.5 equiv), $Pd(PPh_3)_4$ (0.2 equiv), toluene, reflux, 8 h, **9** 68%.

only 1.25 hours. Compound **6** was then protected using a large excess of MOMCl (4.0 equiv) from 0 °C to room temperature for two hours, affording **7** in 93% yield.[12] First attempts of halogen–metal exchange carried out on compound **6** with Sn_2Bu_6 led only to a mixture of starting material and compound **5**. The exchange was then tried with Sn_2Me_6, which afforded compound **8** as a crude product quantitatively; attempts to purify led to the cleavage of the stannyl group on the chromatographic column (either with silica gel or neutral aluminum oxide). Using the same conditions, compound **7** led to **9** in 47% yield. It appears that **9** was less sensitive than **8** and could be purified by flash chromatography on silica gel. However, 20% of compound **9** was destannylated during the purification. An increase of the quantities of both Sn_2Me_6 and $Pd(PPh_3)_4$ produced **9** in an improved yield of 68%.

Having the coupling partners **8** and **9** in hand, we next tried the Stille cross-coupling reaction with unprotected indole derivative **4** under previously optimized conditions (Scheme 3).[5] Starting from **8**, hydrodestannylation occurred and **5** was isolated, whereas the palladium-catalyzed coupling reaction of **4** with **9** afforded **10** quantitatively.

At this stage two strategies can be adopted: first removing the indolic nitrogen atom protecting group of **10** and then performing the saponification of the ester; or proceeding the opposite way. We envisioned in the first place the MOM cleavage of **10** in acidic media and isolated **11** in 90% yield (Scheme 3). To obtain the acid function needed for the electrophilic cyclization, several conditions were attempted. As indicated in Table 1 (entries 1–3), Lewis acid conditions,[12] saponification in diluted basic media[5] and transesterification assay[13] appeared as unfruitful.

Facing failures with traditional systems, we turned our attention to unconventional methods. In a previous work concerning the deprotection of carbamates with Bu_4NF, we observed, in some cases, a quantitative hydrolysis of



Scheme 3 *Reagents and conditions*: a) **9** (1.5 equiv), CuI (0.1 equiv), $PdCl_2(PPh_3)_4$ (0.2 equiv), dioxane, reflux, 3.5 h, quant; b) aq 2 N HCl, MeOH, reflux, 16 h, 90%; c) LiOOH (5.0 equiv), dioxane, 0 °C to r.t., 1 h, then reflux, 4.5 h, 75%; d) from **3**, PPA, P_2O_5, 130 °C, 4 h, 60%.

Table 1 Synthesis of the Acid **3** Starting from the Ester **11**

Entry	Conditions	Time	Yield (%)
1	BBr_3 (25.0 equiv), CH_2Cl_2, 0 °C, then r.t.	0.5 h	**11** (95)
2	KOH 15% (3.6 equiv), acetone, r.t.	14.5 h	**11** (60)
3	$Ti(O\textit{i}\text{-}Pr)_4$ (0.5 equiv), $CH_2{=}CHCH_2OH$, reflux	3 d	**11** (86)
4	Bu_4NF (1 M in THF, 20 equiv), microwave, 140 °C	0.25 h	**3** (55)
5	LiOOH (5.0 equiv), THF, 0 °C, then r.t.	89 h	**3** (19) + **12** (13)
6	a) LiOOH (5.0 equiv), THF, 0 °C, then r.t. b) heating to 70 °C	a) 1 h b) 15.5 h	**3** (19) + **12** (24)
7	a) LiOOH (5.0 equiv), dioxane, 0 °C to r.t. b) heating to reflux	a) 1 h b) 4.5 h	**3** (75)

ester functions as a side-reaction.[14] Indeed, using Bu_4NF in large excess and heating the mixture with microwaves for 15 min led to **3** in 55% yield (entry 4).

In parallel, we also tried LiOOH, prepared from LiOH/H_2O_2 (entries 5–7).[15] This method presents two advantages: a less basic media than with KOH or LiOH; the use of the nucleophilic character of the HOO^- anion. Because of this nucleophilicity, the maleimide part was opened and first attempts led to a mixture of **3/12** in a 6:4 ratio as well as degradation due to the long reaction time (entry 5). Optimizing the conditions afforded compound **3** alone in the best yield of 75% without any trace of **12** (entry 7).

The last step of the synthesis was the electrophilic cyclization onto position C-2 of the indole. Our usual conditions, $BF_3{\cdot}Et_2O$ at reflux in dichloroethane,[5] led to an inseparable mixture of **1** and an unidentified compound. Fortunately, the cyclization could be conducted in a mixture of polyphosphoric acid and P_2O_5, providing the final and pure compound **1** in 60% yield.

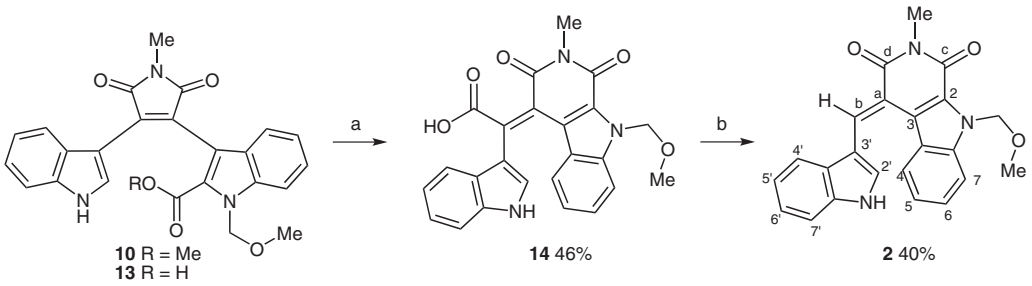
In a second set of experiments, we wanted to try the other strategy consisting of hydrolyzing first the ester function of the protected compound **10** (Scheme 4). But in presence of the methoxymethyl group, the saponification did not afford the expected protected acid **13**. Instead, the reaction led to a surprising rearranged product, which was suspected, after complete analysis to be **14**, nevertheless with ambiguous structural assignment due to a poor solubility in NMR solvents. This compound **14** was presumably formed by maleimide opening in basic media. The liberated amide reacted thus with the acid to form the thermodynamically stable β-carboline.

Trying to prove this structure, and also to facilitate the NMR analysis, we treated **14** with hydrogen over Pd/C in order to reduce the double bond. Despite a long reaction time, the expected hydrogenated compound **15** was never observed. Instead, an unexpected decarboxylation occurred and compound **2** was the sole isolated product in 40% yield. Unfortunately, NMR 2D experiments were still not satisfactory to confirm the structure of **2**.

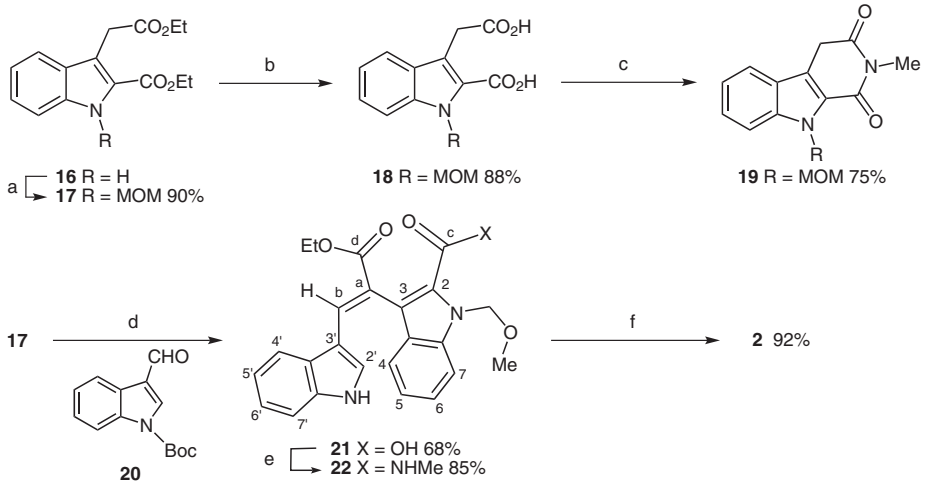
So, we decided to prepare **2** in an unequivocal route (Scheme 5; method B, see experimental). Such a structure suggests an aldolization/crotonization sequence between formylindole and a β-carboline. Starting from the ketoglutyric acid and phenylhydrazine, the indole **16** was obtained under Fischer type conditions[16] in 68% yield and a further MOM protection led easily to **17** in 90% yield (Scheme 5).

A double saponification generated the diacid **18** in 88% yield, which was involved in a direct condensation of aqueous methylamine in refluxing *n*-propanol to afford the expected carboline **19** in a good yield.[17] Nevertheless, all attempts to realize the condensation between **19** and 3-formyl-*N*-Boc-indole (aldolization or Knovenaegel condensation) failed.

We next envisioned performing such a reaction on the diester **17**. In the presence of sodium hydride (5.0 equiv) and using a slight excess of 3-formyl-*N*-Boc-indole (**20**), the alkene **21** was isolated in 68% yield (Scheme 5).[18]



Scheme 4 *Reagents and conditions*: a) from **10**, aq 45% KOH (3.6 equiv), acetone, r.t., 21 h, then concd HCl, r.t. 12 h, 46%; b) Pd/C, H_2 (50 psi), DMF, 3 d, 40%.



Scheme 5 *Reagents and conditions*: a) NaH (1.2 equiv), MOMCl (1.5 equiv), DMF, 0 °C to r.t. 6.5 h, 90%; b) KOH (2.2 equiv), H_2O–EtOH (1:1), THF, 50 °C, 8 h, 88%; c) $MeNH_2$ (4.0 equiv), H_2O–PrOH, reflux, 12 h, 75%; d) NaH (5.0 equiv) 1 h, then **20** (1.2 equiv), r.t., THF, 15 h, 68%; e) EDCI (1.1 equiv), HOBt (1.1 equiv), 30 min, then $MeNH_2$ (1.2 equiv), DMF, r.t., 5 h, 85%; f) Et_3N (cat.), MeOH, r.t., 2 h, 92%.

During the reaction, a mono and regioselective saponification occurred concomitantly. The *E*-configuration of the double bond was established by NMR experiment, by measurement of the long-range hetero ^{13}C–^{1}H coupling constant, between H_b and CO_d ($^3J_{H,CO}$ = 3.0 Hz).[19] Then, the amidification of **21** in the presence of methylamine led under peptidic conditions to the amide **22** in 85% yield.[20] Fortunately, the spontaneous cyclization of **22** occurred in the presence of a catalytic amount of triethylamine in methanol at room temperature and led to **2** in 92% yield.

After analysis, all data were in concordance with the previously supposed compound. The supposed β-carboline structure of compound **2** was thus confirmed, as well as the synthetic sequence starting from **10**, leading to **14** and then to **2** (Scheme 4).

In conclusion, we have reported here the synthesis of the first *N*-methyloxoarcyriaflavine in only four efficient steps involving a Stille cross coupling and a final electrophilic cyclization. Our investigations provided an unexpected β-carboline which was synthesized by another straightforward route. All structures were confirmed and further investigations are in progress using these two original structures for designing new potential antitumor drugs.

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 500, 400, or DPX 250 instruments using $CDCl_3$ or DMSO-d_6. The chemical shifts are reported in ppm (δ scale) and all *J* values are in Hz. Melting points are uncorrected. IR absorption spectra were recorded on a Perkin-Elmer FT PARAGON 1000 PC and values are reported in cm^{-1}. MS spectra (ion spray) were performed on a Perkin-Elmer SCIEX API 300 spectrometer. HRMS analyses were realized by the Centre Régional de Mesures Physiques de l'Ouest (CRMPO, Rennes) or by the Centre Régional de Mesure Physique (CRMP, Clermont Ferrand). Monitoring of the reactions was performed using silica gel TLC plates (Merck 60 F_{254}). Spots were visualized by UV light at 254 and 365 nm. Column chromatography was performed using silica gel 60 (40–63 μm, Merck). Petroleum ether (PE) used refers to the fraction boiling in the range 30–60 °C.

3-Iodo-1-methoxymethyl-1*H*-indole-2-carboxylic Acid Methyl Ester (7)

To a suspension of NaH (690 mg, 17.3 mmol, 60% in oil) in DMF (48 mL), under argon and at 0 °C, was added over 50 min a solution of **6** (4.0 g, 13.3 mmol) in DMF (48 mL). The mixture was stirred at 0 °C for 0.5 h and MOMCl (4.0 mL, 53.1 mmol) was added dropwise. The solution was then stirred for 2 h and quenched with iced H_2O (10 mL). The precipitate was filtered through a Millipore filter, washed with H_2O (2 × 30 mL), and dried under vacuum to give **7** as a white solid (4.3 g, 93%); mp 61–62 °C; R_f = 0.38 (PE–EtOAc, 9:1).

IR (NaCl): 3020, 2953, 1712, 1654, 1500 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 3.26 (s, 3 H, CH_3OCH_2), 4.00 (s, 3 H, CO_2CH_3), 5.94 (s, 2 H, CH_3OCH_2), 7.27–7.31 (m, 1 H, H-5), 7.43 (t, *J* = 7.1 Hz, 1 H, H-6), 7.52 (d, *J* = 8.5 Hz, 1 H, H-7), 7.60 (d, *J* = 8.2 Hz, 1 H, H-4).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 51.9 (CO_2CH_3), 56.3 (CH_3OCH_2), 70.4 (C-3), 75.7 (CH_3OCH_2), 111.3 (CH-7), 122.4 (CH-5), 124.2 (CH-4), 126.9 (CH-6), 128.7 (C_q), 130.7 (C_q), 139.1 (C_q), 161.7 (CO_2CH_3).

IS-MS: *m*/*z* = 363.5 $[M + NH_4]^+$.

3-Trimethylstannyl-1*H*-indole-2-carboxylic Acid Methyl Ester (8)

To a solution of **6** (250.0 mg, 0.83 mmol) in distilled toluene (10 mL) was added Sn_2Me_6 (0.20 mL, 1.00 mmol). After degassing the mixture with argon for 0.5 h, $Pd(PPh_3)_4$ (96 mg, 0.08 mmol) was introduced. The flask was immersed in a preheated oil bath (125 °C) and the mixture was refluxed for 5.5 h. The solution was quenched with a mixture of hexane/sat. aq KF (1:1, 20 mL) and stirred for 0.5 h. The salts were filtered over Celite and the organic layer dried under vacuum to afford crude **8** as an orange solid (366 mg, quant); R_f = 0.64 (PE–EtOAc, 9:1).

^1H NMR (250 MHz, $CDCl_3$): δ = 0.41 [t, *J* = 28.0 Hz, 9 H, $Sn(CH_3)_3$], 3.94 (s, 3 H, CO_2CH_3), 7.14 (t, *J* = 7.5 Hz, 1 H, H-5), 7.28–7.40 (m, 1 H, H-6), 7.45 (d, *J* = 8.1 Hz, 1 H, H-7), 7.81 (d, *J* = 8.3 Hz, 1 H, H-4), 9.1 (br, 1 H, NH).

3-Trimethylstannyl-1-methoxymethyl-1*H*-indole-2-carboxylic Acid Methyl Ester (9)

Compound **9** was obtained as described for **8** starting from **7** (1.0 g, 2.90 mmol), toluene (50 mL), Sn_2Me_6 (0.9 mL, 4.35 mmol), $Pd(PPh_3)_4$ (670 mg, 0.58 mmol), and refluxing for 8 h. After treat-

ment with aq KF, a purification by chromatography on silica gel (PE, then PE–EtOAc, 98:2) afforded **9** as a colorless oil (752 mg, 68%); R_f = 0.49 (PE–EtOAc, 9:1).

IR (NaCl): 3000, 2950, 1714 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 0.39 [t, *J* = 27.2 Hz, 9 H, $Sn(CH_3)_3$], 3.30 (s, 3 H, CH_3OCH_2), 3.91 (s, 3 H, CO_2CH_3), 5.97 (s, 2 H, CH_3OCH_2), 7.18 (t, *J* = 7.5 Hz, 1 H, H-5), 7.38 (t, *J* = 7.7 Hz, 1 H, H-6), 7.56 (d, *J* = 8.5 Hz, 1 H, H-7), 7.83 (d, *J* = 7.9 Hz, 1 H, H-4).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = –6.5 [$Sn(CH_3)_3$], 51.6 (CO_2CH_3), 56.1 (CH_3OCH_2), 75.0 (CH_3OCH_2), 111.1 (CH-7), 121.1 (CH-5), 123.8 (C_q), 124.4 (CH-4), 125.5 (CH-6), 133.1 (C_q), 133.5 (C_q), 140.9 (C_q), 162.6 (CO_2CH_3).

IS-MS: *m*/*z* = 380.5, 382.5, 384.5, 386.5, 388.5 $[M + H]^+$ for ^{116}Sn, ^{118}Sn, ^{120}Sn, ^{122}Sn, and ^{124}Sn isotopes.

3-[4-(1*H*-Indol-3-yl)-1-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl]-1-methoxymethyl-1*H*-indole-2-carboxylic Acid Methyl Ester (10)

A solution of **4** (27.0 mg, 0.09 mmol), **9** (52 mg, 0.13 mmol), and CuI (2.0 mg, 0.01 mmol) in dioxane (5 mL) was degassed under argon for 0.5 h. Then $PdCl_2(PPh_3)_2$ (12.0 mg, 0.02 mmol) was added and the flask was immersed in a preheated oil bath (120 °C). The mixture was refluxed under argon for 3.75 h, then cooled to r.t., and filtered over Celite. The filtrate was evaporated and the crude product purified by chromatography on silica gel (PE–CH_2Cl_2, 1:1, then PE–CH_2Cl_2–EtOAc, 2:2:1) to provide **10** as an ochre solid (40 mg, quant); R_f = 0.44 (PE–EtOAc, 6:4); mp 181–183 °C (dec.).

IR (KBr): 3320, 2951, 1754, 1715, 1695, 1634, 1531 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 3.06 (s, 3 H, NCH_3), 3.17 (s, 3 H, CH_3OCH_2), 3.75 (s, 3 H, CO_2CH_3), 5.88–6.06 (m, 2 H, CH_3OCH_2), 6.52 (t, *J* = 7.5 Hz, 1 H, H-5′), 6.69 (d, *J* = 8.2 Hz, 1 H, H-4′), 6.80 (t, *J* = 7.5 Hz, 1 H, H-5), 6.89–6.96 (m, 2 H, H-4/H-6′), 7.20 (t, *J* = 7.7 Hz, 1 H, H-6), 7.32 (d, *J* = 7.9 Hz, 1 H, H-7′), 7.71 (d, *J* = 8.2 Hz, 1 H, H-7), 8.03 (d, *J* = 1.9 Hz, 1 H, H-2′), 11.86 (br s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 24.2 (NCH_3), 52.1 (CO_2CH_3), 55.4 (CH_3OCH_2), 74.3 (CH_3OCH_2), 105.2 (C_q-3′), 111.5 (CH-7), 112.0 (CH-7′), 113.6 (C_q-3), 119.7 (CH-5′), 120.1 (CH-4′), 121.1 (CH-4), 121.3 (CH-5), 122.0 (CH-6′),124.1 (C_q), 125.1 (C_q-9 + C_q-9′), 125.5 (CH-6), 127.3 (C_q-2), 130.5 (CH-2′), 132.7 (C_q), 136.1 (Cq-8′), 138.0 (C_q-8), 161.7 (CO_2CH_3), 170.6 (NC=O), 171.3 (NC=O).

IS-MS: *m*/*z* = 461.5 $[M + NH_4]^+$, 466.5 $[M + Na]^+$, 442.5 $[M – H]^–$.

3-[4-(1*H*-Indol-3-yl)-1-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl]-1*H*-indole-2-carboxylic Acid Methyl Ester (11)

To a solution of **10** (1.0 g, 2.26 mmol) in MeOH (150 mL) was added aq 6 N HCl (100 mL). The mixture was refluxed for 18 h and then cooled to r.t. The precipitate was filtered through a Millipore filter, washed with H_2O (3 × 30 mL), and then dissolved in EtOAc (4 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered through a plug of cotton wool, and evaporated under vacuum to give **11** as an orange solid (827 mg, 92%); R_f = 0.32 (PE–CH_2Cl_2–EtOAc, 9:9:2); mp 251–253 °C (dec.).

IR (KBr): 3373, 3283, 1759, 1717, 1693, 1635, 1543, 1385, 741 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 3.07 (s, 3 H, NCH_3), 3.73 (s, 3 H, CO_2CH_3), 6.56–6.62 (m, 2 H, H-4′/H-5′), 6.79 (t, *J* = 7.5 Hz, 1 H, H-5), 6.94 (t, *J* = 7.6 Hz, 1 H, H-6′), 7.02 (d, *J* = 8.1 Hz, 1 H, H-4), 7.16 (t, *J* = 7.6 Hz, 1 H, H-6), 7.33 (d, *J* = 8.1 Hz, 1 H, H-7′), 7.44 (d, *J* = 8.3 Hz, 1 H, H-7), 7.96 (d, *J* = 2.7 Hz, 1 H, H-2′), 11.78 (br s, 1 H, $NH_{ind'}$), 12. 31 (br s, 1 H, NH_{ind}).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 24.1 (NCH_3), 51.8 (CO_2CH_3), 105.5 (C_q-3′), 110.9 (C_q-3), 111.9 (CH-7′), 112.7 (CH-7), 119.8 (CH-5′), 120.3 (CH-4′), 120.4 (CH-5), 121.1 (CH-4), 121.9 (CH-6′), 124.5 (C_q), 124.9 (C-9′ + CH-6), 126.2 (C_q-9 + C_q), 130.4 (CH-2′), 133.1 (C_q), 136.1 (C_q-8), 136.2 (C_q-8′), 161.4 (CO_2CH_3), 170.5 (NC=O), 171.4 (NC=O).

IS-MS: *m*/*z* = 400.5 $[M + H]^+$, 422.5 $[M + Na]^+$, 398 $[M – H]^–$.

3-[4-(1*H*-Indol-3-yl)-1-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl]-1*H*-indole-2-carboxylic Acid (3)

To aq 1 M LiOH (1.25 mL, 1.25 mmol) cooled to 0 °C was added dropwise H_2O_2 (0.63 mL). The mixture was stirred at 0 °C for 0.5 h, then added dropwise at 0 °C to a solution of **10** (100 mg, 0.25 mmol) in dioxane (4 mL). The mixture was warmed up to r.t. over 1 h and refluxed for 4.5 h. After cooling to r.t., the solution was diluted with H_2O (20 mL), acidified with concd HCl (6 mL) and stirred overnight at r.t. The precipitate was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with H_2O (50 mL), dried ($MgSO_4$), filtered through a plug of cotton wool, and evaporated under vacuum to afford **11** as an orange solid (73 mg, 75%); R_f = 0.48 (EtOAc–MeOH, 8:2); mp 223–225 °C (dec.).

IR (KBr): 3342, 3059, 2928, 1759, 1697, 1446, 1385, 1245 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 3.05 (s, 3 H, NCH_3), 6.59 (t, *J* = 8.1 Hz, 1 H, H-5′), 6.70 (d, *J* = 8.1 Hz, 1 H, H-4′), 6.77 (t, *J* = 7.6 Hz, 1 H, H-5), 6.94 (t, *J* = 8.1 Hz, 1 H, H-6′), 6.99 (d, *J* = 8.1 Hz, 1 H, H-4), 7.12 (t, *J* = 7.7 Hz, 1 H, H-6), 7.31 (d, *J* = 8.1 Hz, 1 H, H-7′), 7.41 (d, *J* = 8.3 Hz, 1 H, H-7), 7.92 (d, *J* = 2.9 Hz, 1 H, H-2′), 11.75 (br s, 1 H, $NH_{ind'}$), 12.13 (br s, 1 H, NH_{ind}).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 24.1 (NCH_3), 105.5 (C_q-3′), 110.2 (C_q-3), 111.9 (CH-7′), 112.6 (CH-7), 119.8 (CH-5′), 120.2 (CH-5), 120.4 (CH-4′), 120.7 (CH-4), 121.8 (CH-6′), 124.4 (CH-6), 125.0 (C_q-9′), 126.4 (C_q-9), 130.2 (CH-2′), 132.9 (C_q-a), 135.8 (C_q-8), 136.1 (C_q-8′), 139.9 (C_q-b), 142.4 (C_q-2), 162.4 (CO_2H), 170.5 (NC=O), 171.5 (NC=O).

IS-MS: *m*/*z* = 384 $[M – H]^–$.

Indolo[2′,3′-3,4]indolo[2′,3′-6,7]cyclohepta[1,2-*c*]-1-methylpyrrol-1,3,9-trione (1)

To a mixture of polyphosphoric acid (5.0 g, large excess) and P_2O_5 (770 mg, large excess), heated to 130 °C, was added **11** (50 mg, 0.13 mmol). After heating for 4 h at 130 °C and cooling to r.t., the mixture was diluted with H_2O (50 mL) and neutralized to pH 7 with sat. aq $NaHCO_3$ (70 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with H_2O (3 × 50 mL), dried ($MgSO_4$), and filtered through a plug of cotton wool. Removal of the solvents afforded **1** as an orange solid (29 mg, 60%); R_f = 0.14 (PE–CH_2Cl_2–EtOAc, 9:9:2); mp 193–195 °C (dec.).

IR (KBr): 3228, 2923, 1766, 1705, 1550, 1493, 1459, 1387 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 3.12 (s, 3 H, NCH_3), 7.33 (t, *J* = 7.1 Hz, 2 H, H-5), 7.55 (t, *J* = 7.1 Hz, 2 H, H-6), 7.75 (d, *J* = 8.0 Hz, 2 H, H-7), 9.11 (d, *J* = 8.5 Hz, 2 H, H-4), 13.06 (br s, 2 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 24.3 (NCH_3), 112.7 (2 × CH-7), 114.3 (2 × C_q-3), 121.3 (2 × CH-5), 123.9 (2 × C_q-9), 125.0 (2 × C_q), 127.6 (2 × CH-4), 127.7 (2 × CH-6), 138.6 (2 × C_q-8), 140.3 (2 × C_q-2), 167.9 (C=O), 170.0 (2 × NC=O).

HRMS: *m*/*z* calcd for $C_{22}H_{13}N_3O_3$: 367.09569; found $[M^{+\bullet}]$: 367.0961.

(*Z*)-2-(1*H*-Indol-3-yl)-2-(9-methoxymethyl-2-methyl-1,3-(2*H*)-dioxo-4,9-dihydro-1*H*-pyrido[3,4-*b*]indol-4-ylidene)acetic Acid (14)

To a solution of **10** (150 mg, 0.34 mmol) in acetone (7.5 mL) was added 0.5 mL of aq KOH (69 mg, 1.23 mmol). The mixture was

stirred at r.t. for 21 h. After evaporation of the acetone, the mixture was diluted with H_2O (15 mL), then acidified with concd HCl (15 mL), and stirred overnight at r.t. The precipitate was filtered through a Millipore filter, washed with H_2O (2 × 20 mL), and purified by chromatography on silica gel (EtOAc, then EtOAc–MeOH, 6:4) to give **14** as a brown solid (67 mg, 46%); R_f = 0.21 (EtOAc–MeOH, 8:2); mp 157–159 °C (dec.).

IR (KBr): 3393, 2930, 1757, 1686, 1648, 1575, 1476 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 3.21 (s, 3 H, CH_3OCH_2), 3.27 (s, 3 H, NCH_3), 6.05 (s, 2 H, CH_3OCH_2), 6.37 (d, *J* = 7.8 Hz, 1 H, H-4), 6.47 (t, *J* = 7.5 Hz, 1 H, H-5), 6.75 (t, *J* = 7.2 Hz, 1 H, H-5′), 6.97 (t, *J* = 7.5 Hz, 1 H, H-6′), 7.09 (t, *J* = 7.7 Hz, 1 H, H-6), 7.31 (d, *J* = 8.2 Hz, 1 H, H-7′), 7.44–7.55 (m, 3 H, H-2′/H-4′/H-7), 11.67 (br s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 26.4 (NCH_3), 55.2 (CH_3OCH_2), 73.7 (CH_3OCH_2), 110.2 (C_q), 111.2 (CH-7), 111.8 (CH-7′), 113.9 (C_q), 119.5 (CH-5′), 120.0 (CH-5), 120.6 (CH-4′), 121.5 (C_q-3), 121.6 (CH-6′), 122.1 (C_q-9), 123.4 (CH-4), 123.8 (C_q-2), 125.5 (CH-6), 125.9 (C_q-9′), 130.3 (CH-2′), 136.4 (C_q-8′), 139.7 (C_q-8), 159.4 (NC=O), 164.9 (NC=O).

IS-MS: *m*/*z* = 428 $[M - H]^-$.

(*E*)-4-[(1*H*-Indol-3-yl)methylene]-9-methoxymethyl-2-methyl-4,9-dihydro-1*H*-pyrido[3,4-*b*]indole-1,3(2*H*)-dione (2)

Method A: To a solution of **14** (50 mg, 0.12 mmol) in DMF (30 mL) was added Pd/C 10% (41 mg, 0.04 mmol). The mixture was stirred 4 d in a steel bomb at r.t. under H_2 (50 psi). The solution was filtered over Celite and washed with EtOAc (60 mL). The organic layer was washed with brine (3 × 50 mL) and H_2O (50 mL), dried ($MgSO_4$), and filtered through a plug of cotton wool. Removal of solvents provided **2** as an orange solid (18 mg, 40%).

Method B: To a stirred solution of compound **22** (100 mg, 0.23 mmol) in MeOH (5 mL) at r.t. was added a catalytic amount of Et_3N (3 drops) and the reaction mixture was stirred for 2 h. The precipitate was filtered through a Millipore filter, washed with MeOH (5 mL), and dried under reduced pressure to provide pure compound **2** as an orange solid (82 mg, 92%); R_f = 0.44 (PE–EtOAc, 1:1); mp 230–232 °C (dec.).

IR (KBr): 3278, 2925, 1672, 1632, 1488, 1372 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 3.23 (s, 3 H, CH_3OCH_2), 3.36 (s, 3 H, NCH_3), 6.11 (s, 2 H, CH_3OCH_2), 7.29–7.35 (m, 2 H, H-5′/H-6′), 7.47 (t, *J* = 7.6 Hz, 1 H, H-5), 7.55–7.59 (m, 2 H, H-6/H-7), 7.83 (d, *J* = 8.5 Hz, 1 H, H-7), 7.99 (d, *J* = 6.6 Hz, 1 H, H-4′), 8.39 (d, *J* = 8.3 Hz, 1 H, H-4), 8.65 (s, 1 H, H_b), 9.33 (d, *J* = 2.1 Hz, 1 H, H-2′), 12.28 (br s, 1 H, NH).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 26.5 (NCH_3), 55.5 (CH_3OCH_2), 73.9 (CH_3OCH_2), 111.5 (C_q-3′), 112.3 (CH-7), 112.7 (CH-7′), 114.7 (C_q), 117.8 (CH-4), 121.4 (C_q-9), 121.5 (CH-5′), 121.6 (C_q), 122.2 (C_q-2), 122.3 (CH-4), 122.7 (CH-5), 123.0 (CH-6′), 126.7 (CH-6), 129.0 (C_q-9′), 132.8 (CH_b), 135.1 (CH-2′), 136.1 (C_q-8′), 140.5 (C_q-8), 158.5(NC=O), 163.6 (NC=O).

HRMS: *m*/*z* calcd for $C_{23}H_{19}N_3O_3$: 385.14931; found $[M^{+}]$: 385.14264.

3-Ethoxycarbonylmethyl-1-methoxymethyl-1*H*-indole-2-carboxylic Acid Ethyl Ester (17)

Compound **16** (1.0 g, 3.63 mmol) was slowly added to a suspension of NaH (175 mg, 4.35 mmol, 60% in oil) in DMF (10 mL) at 0 °C. The mixture was stirred for 15 min at 0°C and then at r.t. for 15 min. Chloromethyl methyl ether (415 μL, 5.44 mmol) was added dropwise at 0 °C and the reaction mixture was stirred for 30 min at 0 °C and then 6 h at r.t. The mixture was diluted with H_2O (15 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with H_2O (10 mL), brine (10 mL), and dried (Na_2SO_4). After filtration and reduction of the volatiles under reduced pressure, silica gel column chromatographic purification (PE–EtOAc, 6:4) gave **17** as a colorless oil (1.04 g, 90%); R_f = 0.45 (PE–EtOAc, 6:4).

IR (ATR diamond): 2981, 1733, 1701, 1333, 1227 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 1.18 (t, *J* = 7.2 Hz, 3 H), 1.33 (t, *J* = 7.2 Hz, 3 H), 3.13 (s, 3 H), 4.04–4.11 (m, 4 H), 4.27–4.36 (q, *J* = 7.2 Hz, 2 H), 5.91 (s, 2 H), 7.20 (t, *J* = 7.5 Hz, 1 H), 7.40 (t, *J* = 7.7 Hz, 1 H), 7.71 (d, *J* = 8.2 Hz, 1 H), 7.77 (d, *J* = 7.9 Hz, 1 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.7 (CH_3), 14.0 (CH_3), 30.5 (CH_2), 55.2 (CH_2), 60.1 (CH_2), 60.5 (CH_2), 74.1 (CH_2), 111.1 (CH), 118.1 (C_q), 120.5 (CH), 120.8 (CH), 125.1 (C_q), 125.6 (CH), 126.6 (C_q), 138.2 (C_q), 161.2 (C=O), 163.7 (C=O).

IS-MS: *m*/*z* = 320 $[M + H]^+$.

HRMS: *m*/*z* calcd for $C_{17}H_{21}NO_5$ + Na $[M + Na^+]$: 342.1317; found: 342.1332.

3-Carboxymethyl-1-methoxymethyl-1*H*-indole-2-carboxylic Acid (18)

A solution of the diester **17** (200 mg, 0.62 mmol) in H_2O (5 mL) and EtOH (5 mL) was stirred for 8 h at r.t. in the presence of NaOH (55 mg, 1.37 mmol). H_2O (10 mL) was added and the suspension was extracted with CH_2Cl_2 (3 × 15 mL). The aqueous phase was acidified by the addition of concd HCl. The resulting white solid was filtered to give **18** (140 mg, 88%); mp >260 °C.

IR (ATR diamond): 2934, 1707, 1655, 1446, 1235, 1171 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.12 (s, 3 H), 4.03 (s, 2 H), 5.91 (s, 2 H), 7.16 (dd, *J* = 7.6, 7.2 Hz, 1 H), 7.36 (dd, *J* = 8.0, 7.2 Hz, 1 H), 7.66 (d, *J* = 7.6 Hz, 1 H), 7.71 (d, *J* = 8.0 Hz, 1 H), 12.72 (br s, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 30.6 (CH_2), 55.3 (CH_3), 74.1 (CH_2), 111.1 (CH), 118.5 (C_q), 120.5 (CH), 120.6 (CH), 125.2 (CH), 126.1 (C_q), 126.8 (C_q), 138.2 (C_q), 163.0 (C_q), 172.2 (C_q).

IS-MS: *m*/*z* = 262 $[M - H]^-$.

9-Methoxymethyl-2-methyl-4,9-dihydro-1*H*-pyrido[3,4-*b*]indole-1,3(2*H*)-dione (19)

A solution of compound **18** (100 mg, 0.38 mmol) and a 4.0 molar ratio of $MeNH_2$ (40% in H_2O, 130 μL, 1.52 mmol) in H_2O–PrOH (6 mL, 1:2) was stirred at r.t. for 4 h and then heated at 90 °C for 12 h. The mixture was cooled to r.t. and the solvents were removed under reduced pressure. The crude product was recrystallized from MeOH–PE to yield **19** as a white solid (73 mg, 77%); mp 166–168 °C.

IR (ATR diamond): 2934, 1706, 1655, 1447, 1342, 1108 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 2.39 (s, 3 H), 3.11 (s, 3 H), 3.70 (s, 2 H), 5.96 (s, 2 H), 7.11 (dd, *J* = 7.2, 7.5 Hz, 1 H), 7.24 (dd, *J* = 8.2, 7.2 Hz, 1 H), 7.52 (d, *J* = 8.2 Hz, 1 H), 7.57 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.4 (CH_3), 33.2 (CH_2), 55.0 (CH_3), 73.6 (CH_2), 110.8 (CH), 112.0 (C_q), 119.0 (CH), 120.0 (CH), 123.0 (CH), 126.5 (C_q), 133.8 (C_q), 136.6 (C_q), 164.9 (C_q), 172.8 (C_q).

IS-MS: *m*/*z* = 258 $[M + H]^+$.

(*E*)-3-[3-Ethoxy-1-(1*H*-indol-3-yl)-3-oxoprop-1-en-2-yl]-1-methoxymethyl-1*H*-indole-2-carboxylic Acid (21)

A solution of compound **17** (1.0 g, 3.13 mmol) in THF (5 mL) was added under argon and at 0 °C to a suspension of NaH (627 mg, 15.65 mmol, 60% in oil) in THF (20 mL). The mixture was stirred at r.t. for 1 h and a solution of aldehyde **20** (922 mg, 3.76 mmol) in THF (5 mL) was added dropwise. The mixture was stirred at r.t. for

15 h. EtOH (2 mL) and then 50% aq AcOH (5 mL) were added. After extraction with EtOAc (2 × 30 mL), the organic layers were washed with sat. aq $NaHCO_3$ (20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was washed with Et_2O (3 × 10 mL) and the precipitate filtered through a Millipore filter to give **21** as a yellow solid (885 mg, 68%); mp 206–208 °C.

IR (ATR diamond): 3395, 2976, 1679, 1587, 1430, 1321 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.12 (t, *J* = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 3.19 (s, 3 H, CH_3OCH_2), 4.01–4.09 (m, 2 H, $CO_2CH_2CH_3$), 6.16–6.32 (m, 3 H, H-2′/ CH_3OCH_2), 6.87–6.91 (t, *J* = 7.5 Hz, 1 H, H-6′), 7.06–7.11 (m, 3 H, H-6/H-5/H-7′), 7.14–7.18 (t, *J* = 8.2 Hz, 1 H, H-5′), 7.28–7.30 (d, *J* = 8.8 Hz, 1 H, H-4′), 7.55 (d, *J* = 8.2 Hz, 1 H, H-7), 7.70 (d, *J* = 8.8 Hz, 1 H, H-4), 8.04 (s, 1 H, H_b), 11.35 (br s, 1 H, NH).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 14.2 ($CO_2CH_2CH_3$), 54.6 (CH_3OCH_2), 59.3 ($CO_2CH_2CH_3$), 73.6 (CH_3OCH_2), 110.7 (C_q-3′), 111.0 (CH-7), 111.7 (CH-4′), 114.2 (C_q), 117.6 (CH-4), 119.4 (CH-5), 119.7 (CH-6), 119.8 (CH-6′), 121.5 (C_q-9), 121.7 (CH-3′), 122.1 (CH-5′), 125.2 (C_q), 126.6 (C_q-2), 127.3 (CH-2′), 128.6 (CH_b), 135.1 (C_q), 136.0 (C_q), 137.0 (C_q), 165.5 (C=O_c), 168.2 (C=O_d).

HRMS: *m*/*z* calcd for $C_{24}H_{22}N_2O_5$ + Na [M + Na^+]: 441.1426; found: 441.1436.

(*E*)-Ethyl 3-(1*H*-Indol-3-yl)-2-(1-methoxymethyl-2-methylcarbamoyl-1*H*-indol-3-yl)acrylate (22)

To a stirred solution of compound **21** (100 mg, 0.24 mmol) in DMF (7 mL) at 0 °C were slowly added HOBt (39 mg, 0.28 mmol) and EDCI (51 mg, 0.26 mmol). The reaction mixture was stirred under inert atmosphere for 30 min. $MeNH_2$ (2 M in THF) (144 μL, 0.29 mmol) was added to the above mixture dropwise over 5 min and stirred for 5 h at r.t. The mixture was diluted with H_2O (3 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with H_2O (10 mL), brine (2 mL), dried ($MgSO_4$), and filtered. Concentration under vacuum and silica gel column chromatographic purification [CH_2Cl_2–MeOH (1%)] gave **22** as a yellow solid (87 mg, 85%); R_f = 0.45 (CH_2Cl_2–MeOH, 9:1); mp 120–122 °C (dec.).

IR (ATR diamond): 3394, 2976, 1678, 1588, 1431, 1367 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.30 (t, *J* = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 2.84 (d, *J* = 7.2 Hz, 3 H, CH_3NH), 3.29 (s, 3 H, CH_3OCH_2), 4.20–4.38 (m, 2 H, $CO_2CH_2CH_3$), 5.89–5.96 (m, 2 H, CH_3OCH_2), 6.25 (s, 1 H, H-2′), 7.01–7.07 (m, 2 H, H6′/*H*NCH_3), 7.20–7.27 (m, 3 H, H-4′/H-7′/H-5), 7.30–7.34 (m, 2 H, H-6/H-5′), 7.59 (d, *J* = 8.8 Hz, 1 H, H-7), 7.87 (d, *J* = 8.0 Hz, 1 H, H-4), 8.47 (br s, 1 H, NH), 8.53 (s, 1 H, H_b).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 14.3 ($CO_2CH_2CH_3$), 26.3 ($NHCH_3$), 55.9 (CH_3OCH_2), 61.2 ($CO_2CH_2CH_3$), 75.1 (CH_3OCH_2), 111.0 (CH-7), 111.2 (C_q), 111.5 (CH-5), 114.3 (C_q), 117.1 (C_q), 118.2 (CH-4), 121.1 (CH-6), 121.16 (CH-7′), 121.2 (CH-6′), 123.0 (CH-4′), 124.7 (CH-5′), 125.2 (C_q), 127.1 (CH-2′), 127.6 (C_q), 130.3 (C_q),135.1 (C_q), 135.4 (CH_b), 138.1 (C_q), 162.8 (C=O_c), 168.8 (C=O_d).

HRMS: *m*/*z* calcd for $C_{25}H_{25}N_3O_4$ + Na (M + Na^+): 454.1743; found: 454.1762.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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References

(1) (a) Sanchez, C.; Mendez, C.; Salas, J. A. *Nat. Prod. Rep.* **2006**, *23*, 1007. (b) Knölker, H.-J.; Reddy, K. R. In *The Alkaloids*, Vol. 65; Cordell, G. A., Ed.; Elsevier Academic Press: New York, **2008**, 1–430.

(2) (a) Sanchez-Martinez, C.; Shih, C.; Zhu, G.; Li, T.; Brooks, H. B.; Patel, B. K. R.; Schultz, R. M.; DeHahn, T. B.; Spencer, C. D.; Watkins, S. A.; Ogg, C. A.; Considine, E.; Dempsey, J. A.; Zhang, F. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3841. (b) Zhu, G.; Conner, S. E.; Zhou, X.; Shih, C.; Li, T.; Anderson, B. D.; Brooks, H. B.; Campbell, R. M.; Considine, E.; Dempsey, J. A.; Faul, M. M.; Ogg, C.; Patel, B.; Schultz, R. M.; Spencer, C. D.; Teicher, B.; Watkins, S. A. *J. Med. Chem.* **2003**, *46*, 2027.

(3) (a) Sanchez-Martinez, C.; Shih, C.; Faul, M. M.; Zhu, G.; Paal, M.; Somoza, C.; Li, T.; Kumrich, C. A.; Winneroski, L. L.; Xun, Z.; Brooks, H. B.; Patel, B. K. R.; Schultz, R. M.; DeHahn, T. B.; Spencer, C. D.; Watkins, S. A.; Considine, E.; Dempsey, J. A.; Ogg, C. A.; Campbell, R. M.; Anderson, B. A.; Wagner, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3835. (b) Engler, T. A.; Furness, K.; Malhotra, S.; Sanchez-Martinez, C.; Shih, C.; Xie, W.; Zhu, G.; Zhou, X.; Conner, S.; Faul, M. M.; Sullivan, K. A.; Kolis, S. P.; Brooks, H. B.; Patel, B.; Schultz, R. M.; DeHahn, T. B.; Kirmani, K.; Spencer, C. D.; Watkins, S. A.; Considine, E. L.; Dempsey, J. A.; Ogg, C. A.; Stamm, N. B.; Anderson, B. D.; Campbell, R. M.; Vasudevan, V.; Lytle, M. L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2261. (c) Zhu, G.; Conner, S.; Zhou, X.; Shih, C.; Brooks, H. B.; Considine, E.; Dempsey, J. A.; Ogg, C.; Patel, B.; Schultz, R. M.; Spencer, C. D.; Teicher, B.; Watkins, S. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1231. (d) Routier, S.; Peixoto, P.; Mérour, J.-Y.; Coudert, G.; Dias, N.; Bailly, C.; Pierré, A.; Léonce, S.; Caignard, D.-H. *J. Med. Chem.* **2005**, *48*, 1401. (e) Routier, S.; Mérour, J.-Y.; Dias, N.; Lansiaux, A.; Bailly, C.; Lozach, O.; Meijer, L. *J. Med. Chem.* **2006**, *49*, 789.

(4) (a) Caballero, E.; Adeva, M.; Calderon, S.; Sahagun, H.; Tomé, F.; Medarde, M.; Fernandez, J. L.; Lopez-Lazaro, M.; Ayuso, M. J. *Bioorg. Med. Chem.* **2003**, *11*, 3413. (b) Pews-Davtyan, A.; Tillack, A.; Ortinau, S.; Rolfs, A.; Beller M, *Org. Biomol. Chem.* **2008**, *6*, 992. (c) Levy, D. E.; Wang, D.-X.; Lu, Q.; Chen, Z.; Perumattam, J.; Xu, Y.-j.; Liclican, A.; Higaki, J.; Dong, H.; Laney, M.; Mavunkel, B.; Dugar, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2390.

(5) (a) Bourderioux, A.; Routier, S.; Bénéteau, V.; Mérour, J.-Y. *Tetrahedron Lett.* **2005**, *46*, 6071. (b) Bourderioux, A.; Routier, S.; Bénéteau, V.; Mérour, J.-Y. *Tetrahedron* **2007**, *63*, 9465. (c) Bourderioux, A.; Bénéteau, V.; Mérour, J.-Y.; Baldeyrou, B.; Ballot, C.; Lansiaux, A.; Bailly, C.; Le Guével, R.; Guillouzo, C.; Routier, S. *Org. Biomol. Chem.* **2008**, *6*, 2108.

(6) Su, J.-Y.; Zhu, Y.; Zeng, L.-M.; Xu, X.-H. *J. Nat. Prod.* **1997**, *60*, 1043.

(7) Mahboobi, S.; Burgemeister, T.; Dove, S.; Kuhr, S.; Popp, A. *J. Org. Chem.* **1999**, *64*, 8130.

(8) Brenner, M.; Mayer, G.; Terpin, A.; Steglich, W. *Chem. Eur. J.* **1997**, *3*, 70.

(9) (a) Steglich, W.; Steffan, B.; Kopanski, L.; Eckhardt, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 459. (b) Brenner, M.; Rexhausen, H.; Steffan, B.; Steglich, W. *Tetrahedron* **1988**, *44*, 2887. (c) Faul, M. M.; Sullivan, K. A.; Winneroski, L. L. *Synthesis* **1995**, 1511.

(10) Cruz, M. D.; Jimenez, F.; Delgado, F.; Tamariz, J. *Synlett* **2006**, 749.

(11) Martin, T.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 235.

(12) Mouaddib, A.; Joseph, B.; Hasnaoui, A.; Mérour, J.-Y. *Tetrahedron Lett.* **1999**, *40*, 5853.
(13) Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982**, 138.
(14) Jacquemard, U.; Bénéteau, V.; Lefoix, M.; Routier, S.; Mérour, J.-Y.; Coudert, G. *Tetrahedron* **2004**, *60*, 10039.
(15) (a) Lucas, H.; Basten, J. E. M.; Van Dinther, T. G.; Meuleman, D. G.; Van Aelst, S. F.; Van Boeckel, C. A. A. *Tetrahedron* **1990**, *46*, 8207. (b) Lopin, C.; Jacquinet, J.-C. *Angew. Chem. Int. Ed.* **2006**, *45*, 2574.
(16) (a) Robinson, J. R.; Good, N. E. *Can. J. Chem.* **1957**, *35*, 1578. (b) Sakamoto, T.; Nagano, T.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 2248.
(17) Yang, X.; Xu, X.; Ji, H. F. *J. Phys. Chem. B.* **2008**, *112*, 7196.
(18) Conchon, E.; Aboab, B.; Golsteyn, R. M.; Cruzalegui, F.; Edmonds, T.; Léonce, S.; Pfeiffer, B.; Prudhomme, M. *Eur. J. Med. Chem.* **2006**, *41*, 1470.
(19) (a) Vögeli, U.; Von Philipsborn, W.; Nagarajan, K.; Nair, M. D. *Helv. Chim. Acta* **1978**, *61*, 607. (b) Chezal, J. M.; Delmas, G.; Mavel, S.; Elakmaoui, H.; Métin, J.; Diez, A.; Blache, Y.; Gueiffier, A.; Rubiralta, M.; Teulade, J.-C.; Chavignon, O. *J. Org. Chem.* **1997**, *62*, 4085.
(20) Wakchaure, P. B.; Easwar, S.; Puranik, V. G.; Argade, N. P. *Tetrahedron* **2008**, *64*, 1786.