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A Photoredox Catalysis Approach for the Synthesis of Both the ABDE and the ABCD Cores of Tronocarpine

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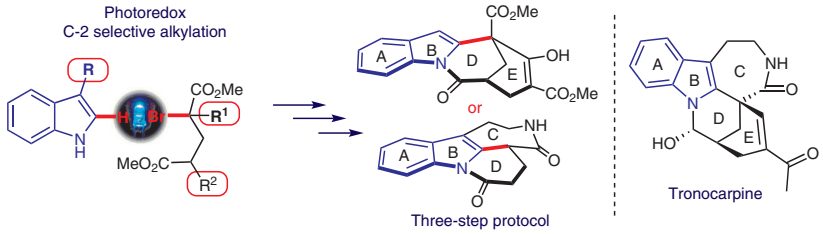
Dedicated to Dr. Joseph M. Muchowski on the occasion of his 82nd birthday



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Abstract A general strategy for the facile construction of both the ABDE and ABCD cores of tronocarpine, chippiine and dippinine alkaloids through the retrosynthetic disconnection of the polycyclic motifs into an indole or tryptamine fragment and a suitably functionalized alkyl chain is presented. The approach is enabled by an efficient Ir(III)-catalyzed, photoredox-mediated radical addition of tetramethyl 1-bromopentane-1,1,3,5-tetracarboxylate and dimethyl 2-bromopentanedioate selectively at C-2 of the indole. Subsequent intramolecular cyclization events furnish the desired ABDE and ABCD polycyclic cores in good preparative yields.

Key words indoles, alkaloids, radicals, photoredox catalysis, tronocarpine

Tabernaemontana (Apocynaceae) is a genus of plants with more than one hundred species known, which are distributed throughout the tropical regions, mainly in America, Africa, and Asia, where they have been used in traditional medicine for the treatment of hypertension, sore throats and abdominal pain.[1,2] Among monoterpene indole alkaloids isolated from this species (*Tabernaemontana sp.*) are tronocarpine (**1**),[3] 10,11-demethoxychippiine (**2**),[4] dippinine B (**3**) and dippinine C (**4**),[5,6] which are presumably biosynthesized from iboganes.[7] *In vitro* assays showed appreciable cytotoxic activity of **2** against KB cells, while compounds **3** and **4** were able to reverse multidrug resistance in vincristine-resistant KB cells.[8] These four alkaloids share a very similar pentacyclic ABCDE ring system, with the main difference between **1** and **2**–**4** being a rearranged junction of the E ring (Figure 1). Other important shared structural features are the presence of a hemiaminal function in the D ring and a quaternary carbon fusing the CDE rings. These intriguing structures have motivated some research groups to develop synthetic approaches to such monomeric post-iboga alkaloids. Several contributions to the syntheses of the ABCD core of tronocarpine (**1**) have been reported to date.[9] On the other hand, the tetracyclic ABDE substructure **5** was achieved in 2009 by Sapeta and Kerr using an intramolecular Mn(III)-mediated malonate oxidative cyclization as the pivotal step.[10] In 2014, Martínez et al. reported the most advanced approach towards the full tronocarpine framework, featuring an intermolecular oxidative xanthate-based radical addition to *N*-Boc-tryptamine to install a malonate unit, which was linearly elaborated further into the ABCDE pentacycle **6**.[11] Recently, in 2019, Han's group reported the semi-synthesis of the pentacyclic alkaloid (+)-dippinine B (**3**) from commercially available (+)-catharanthine via a biosynthetically inspired route.[12]

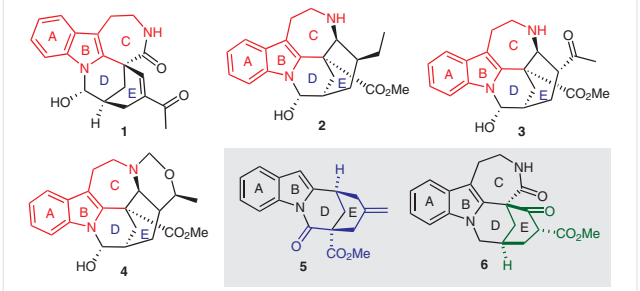

Figure 1 Tronocarpine (**1**), 10,11-demethoxychippiine (**2**), dippinine B (**3**), dippinine C (**4**) and advanced intermediates reported for tronocarpine

Closer examination of compounds **1**–**4**, and many other related indole monoterpenoid alkaloids, reveals a C-2 alkylated tryptamine basic structure (Figure 1, highlighted in red). Accordingly, a direct C–H alkylation (C–C bond formation) at C-2 of the indole nucleus (e.g., tryptamine) with a suitably functionalized alkyl skeleton would yield valuable synthetic intermediates for practical entries into this type

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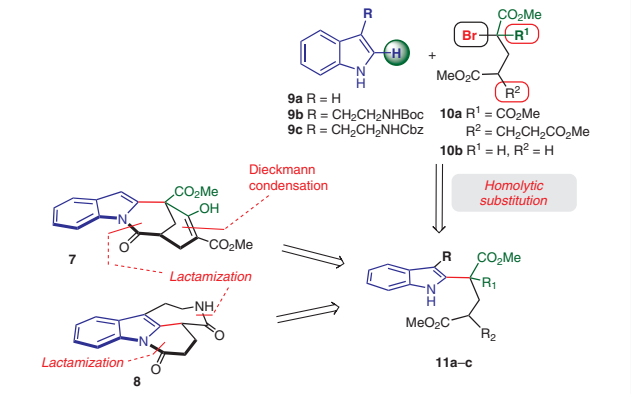
of molecules (see Scheme 1). Incidentally, the innate C-2 installation of selected alkyl moieties via direct radical oxidative addition onto the indole nucleus, either with or without substitution at C-3, has been well documented.[13] This issue is in sharp contrast with the classic electrophilic substitution at C-3. In 2003, we reported an efficient xanthate-based radical oxidative addition for the direct installation of an acetate moiety at C-2 of the indole nucleus.[13c] Extension to malonyl radicals to functionalize *N*-Boc-tryptamine was further described by us in 2009.[9e] In the last decade photoredox catalysis has become a powerful and promising tool that makes feasible several reactions that were once considered difficult to achieve.[14] In this context, the research group of Stephenson reported the catalytic photoredox C-2 selective functionalization of indoles employing bromomalonates as the source of secondary[15] and tertiary[16] malonyl radicals.

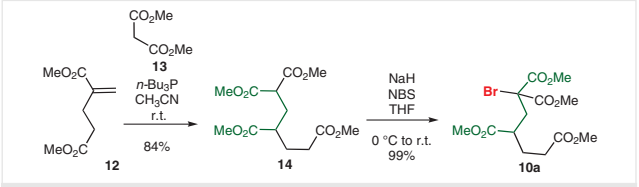
Based on these precedents, the present study was designed to test the hypothesis that indole derivatives **9** might be homolytically alkylated with dimethyl 2-bromoglutarate derivatives **10** under photocatalytic conditions. Should this hypothesis prove to be realizable, the resulting adducts **11** will contain the complete basic functionality to be advanced to either the common ABDE skeleton (through a Dieckmann condensation/lactamization sequence) or to the ABCD framework (via a double lactamization sequence) present in the alkaloids **1**–**4**, as depicted retrosynthetically in Scheme 1.



Scheme 1 Retrosynthesis of the polycyclic systems **7** and **8**

Thus, our work commenced with the synthesis of bromomalonate **10a** by a phosphine-catalyzed Michael addition of dimethyl malonate (**13**) to the α,β-unsaturated ester **12**.[17,18] Next, bromination of the elongated-chain malonate **14** with *N*-bromosuccinimide in a basic medium furnished the desired bromomalonate **10a** on gram scale and in practically quantitative yield (Scheme 2).

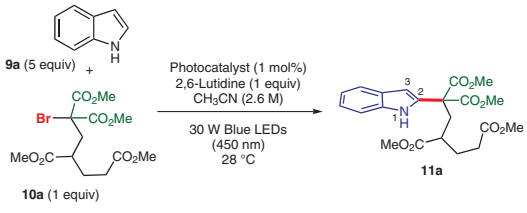
The visible-light photoredox radical addition to indole (**9a**) employing bromomalonate **10a** as a radical precursor proved to be a very efficient route for generating the (generally regarded as challenging[19]) quaternary carbon adja-



Scheme 2 Synthetic route to bromomalonate **10a**

cent to the position 2 of the heterocyclic ring, as shown in Table 1. The source of monochromatic visible light was a 30 W hand-made apparatus constructed with an array of blue LEDs (450–452 nm), which kept the irradiation chamber at a constant temperature of 28 °C with the aid of a fan.[20] The reactions were carried out in 4 mL glass vials and indole (**9a**) was used in excess with the intention to efficiently trap the fleeting malonyl radical (Table 1, entries 1 and 3). Gratifyingly, when $Ru(bpy)_3Cl_2·6H_2O$ was used, the expected 2-substitued indole **11a** was obtained in 79% yield (Table 1, entry 1); however, a dramatic drop in the yield (33%) was observed when the reaction was scaled up (Table 1, entry 2), probably due to decreased photon penetration into the round-bottomed flask in comparison to the vials, which hampered the excitation of the photocatalyst and therefore the formation of the malonyl radical. Finally, when $Ir(ppy)_3$ was used as the photocatalyst, the desired product **11a** was obtained in quantitative yield (Table 1, entry 3). It is important to note that the excess starting indole could be recovered by flash column chromatography to be reused with no detriment to the observed yields. On the contrary, attempts to carry out this photoredox radical addition failed with 3-substituted indoles such as *N*-Boc-tryptamine (**9b**) and *N*-Cbz-tryptamine (**9c**).

Table 1 Screened Conditions for the Photoredox-Initiated Radical Addition of **10a** to Indole

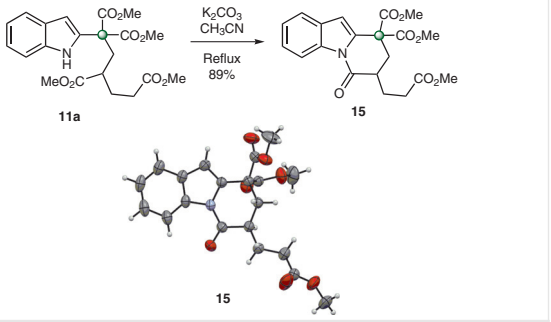


Entry	Catalyst	Time (h)	Yield (%)
1	$Ru(bpy)_3Cl_2·6H_2O$	17	79[a]
2	$Ru(bpy)_3Cl_2·6H_2O$	20	33[b]
3	$Ir(ppy)_3$	17	100[a]

[a] Indole (**9a**) (0.26 mmol) was used.
[b] Indole (**9a**) (13 mmol) was used.

With the quaternary indolyl-malonate **11a** in hand, experimentation towards the construction of the title alkaloid polycyclic substructures was carried out. To this end, intra-

molecular cyclization of coupled indole **11a** promoted by potassium carbonate gave the indole-lactam **15** in 89% yield (Scheme 3). This compound was unambiguously characterized by NMR spectroscopy and single-crystal X-ray analysis.[21]

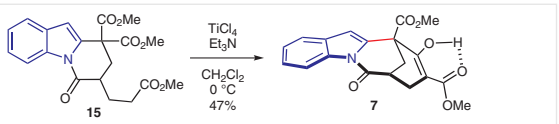


Scheme 3 Synthesis and X-ray crystal structure of intermediate **15**

Subsequently, to complete the target ABDE system, an intramolecular Dieckmann condensation on the tricycle **15** mediated by $TiCl_4/Et_3N$ was performed (Scheme 4). In this way, the desired tetracycle **7** was obtained as a unique diastereomer in moderate yield after flash column chromatography. Interestingly, the presence of a single signal in the ^1H NMR spectrum at 12.15 ppm confirmed that the tetracycle **7** was found mostly as the enol tautomer, since the keto tautomer was unidentifiable in the spectrum.

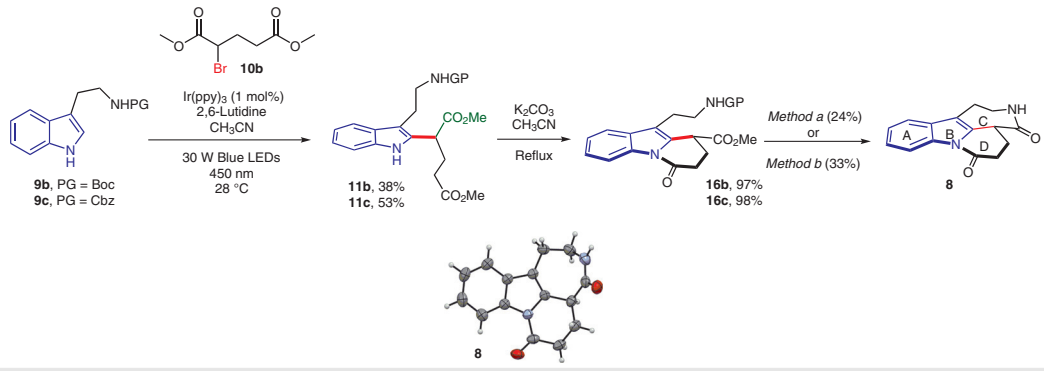
In order to explore the capacity of this strategy to construct the ABCD core of tronocarpine (**1**), we reacted *N*-Boc-tryptamine (**9b**)[22a] and *N*-Cbz-tryptamine (**9c**)[22b] with the L-glutamic acid derived bromoester **10b**[23] using the previously optimized conditions [see Table 1: $Ir(ppy)_3$, 2,6-lutidine, blue LEDs] (Scheme 5). Again, only the products **11b** and **11c** of C-2 indole alkylation were observed, and only in moderate yields. To our delight, cyclization of the coupled indoles **11b** and **11c** in basic medium furnished the pyridoindoles **16b** and **16c**, respectively, in excellent yields. Finally, removal of the protecting group in **16b** or **16c** led to spontaneous lactamization to yield the desired ABCD tetracycle **8** in moderate isolated yields. Moreover, a single crystal of **8** was secured allowing its unequivocal structural assessment by X-ray crystallography.[21]

In conclusion, we have demonstrated our retrosynthetic concept that dissects the *Tabernaemontana* and related alkaloids into an indole fragment and a designed hydrocarbon fragment suitable to accommodate the monoterpenoid skeleton through judicious application of posterior intramolecular cyclizations. Iridium(III) photoredox catalysis proved to be an amenable method for the direct coupling of indole derivatives and the elaborated bromo esters **10**. In the first case, the coupling of indole with bromomalonate **10a** yielded the quaternary indolyl-malonate **11a**, which led to the construction of ABDE core **7** in 42% overall yield via just two further cyclization events. In the second case, the tetracycle ABCD **8** was also straightforwardly synthesized in yields of 24–33% from the coupled diester-tryptamines **11b**,**c** by way of two successive lactamizations. Further investigation towards the total synthesis of indole monoterpenoid alkaloids using this approach is currently underway.



Scheme 4 Synthesis of tetracycle **7**

Moisture-sensitive reactions were performed under an argon atmosphere and glassware was flame-dried in an oven. THF was dried over sodium metal (benzophenone as indicator) and distilled prior to use. CH_2Cl_2 was dried over calcium hydride and distilled prior to use. Unless otherwise noted, all reagents were obtained commercially and used without further purification. The reactions were monitored by TLC using Kieselgel 60 GF_{254} plates, eluting with hexane/EtOAc solvent systems. Chromatographic spots were detected by irradiation of the TLC plates with UV light (254 nm), followed by exposure to vanillin, phosphomolybdic acid or potassium permanganate stains with



Scheme 5 Synthesis and X-ray crystal structure of **8**. *Method a* (for **16b**): (1) CF_3COOH, CH_2Cl_2, r.t.; (2) K_2CO_3, MeOH, 40 °C. *Method b* (for **16c**): Pd/C (10%), H_2, MeOH, r.t.

further careful heating. Column chromatography was performed with Sigma-Aldrich silica gel (200–300 mesh) under positive pressure. The melting points were measured on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were obtained with a Bruker Tensor 27 FT-IR spectrophotometer, as thin films held between KBr cells. ^{1}H and ^{13}C NMR spectra were recorded on Jeol Eclipse-300 MHz and Bruker Avance III-400 MHz spectrometers in $CDCl_3$. Chemical shift data are reported in ppm with TMS (0 ppm, ^{1}H), $CDCl_3$ (76.9 ppm, ^{13}C) and DMSO-d_6 (39.5 ppm, ^{13}C) as internal standards. Standard abbreviations are used to report signal splitting patterns. Coupling constants (J) are reported in hertz (Hz). High-resolution mass spectrometry was performed using a Jeol JMS-T100LC spectrometer employing the DART$^+$ technique in positive ion mode. X-ray diffraction studies were performed on a Bruker AXS diffractometer. CIF files were processed using Mercury software provided by the CCDC. For the photoredox experiments, a handmade 30 W reactor was used; this device emits 1536 lumens of monochromatic blue light (450–452 nm).[20]

Tetramethyl Pentane-1,1,3,5-tetracarboxylate (14)

Unsaturated ester **12** (3.41 g, 19.8 mmol), dimethyl malonate (**13**) (7.84 g, 59.41 mmol), CH_3CN (46 mL) and *n*-tributylphosphine (0.41 g, 0.51 mL, 1.98 mmol) were placed into a round-bottomed flask. The solution was stirred under an argon atmosphere for 23 h at room temperature followed by evaporation of CH_3CN under reduced pressure. The resulting greenish oil was purified by column chromatography using hexane/EtOAc (8:2) to elute the excess of dimethyl malonate (**13**), followed by hexane/EtOAc (8:2) to give malonate **14** (5.04 g, 16.55 mmol, 84%) as a clear oil.

R_f = 0.1 (hexane/EtOAc, 8:2).

IR (film): 3456, 3002, 2956, 2848, 1735, 1437, 1330, 1246, 1203, 1159, 1046 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.72 (s, 3 H), 3.71 (s, 3 H), 3.66 (s, 3 H), 3.64 (s, 3 H), 3.42 (dd, J_1 = 9.0 Hz, J_2 = 5.9 Hz, 1 H), 2.48–2.41 (m, 1 H), 2.34–2.30 (m, 2 H), 2.23–2.15 (m, 1 H), 2.11–2.04 (m, 1 H), 1.97–1.79 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6, 173.0, 169.2, 169.2, 52.7, 52.6, 51.8, 51.6, 49.5, 42.2, 31.3, 30.6, 27.2.

HRMS (DART$^+$): m/z [M + H]$^+$ calcd for $C_{13}H_{21}O_8$: 305.12364; found: 305.12373.

Tetramethyl 1-Bromopentane-1,1,3,5-tetracarboxylate (10a)

A solution of malonate **14** (5.03 g, 16.55 mmol) dissolved in anhydrous THF (120 mL) was placed into a round-bottomed flask under argon. The solution was cooled with an ice–water bath followed by the addition of NaH (95%, 0.5 g, 19.86 mmol). The bubbling suspension was vigorously stirred for 15 min whilst maintaining cooling with the ice bath. Subsequently, recrystallized *N*-bromosuccinimide (3.24 g, 18.21 mmol) was added in one portion and the mixture was stirred at 0 °C for 5 min. The suspension was warmed to room temperature and stirred for an additional 30 min, after which distilled H_2O (180 mL) was added. The resulting mixture was extracted with EtOAc (2 × 180 mL) and the combined organic phases were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was adsorbed on silica gel. Purification by column chromatography using hexane/EtOAc (7:3) gave bromomalonate **10a** (6.32 g, 16.49 mmol, 99%) as an orange oil.

R_f = 0.3 (hexane/EtOAc, 7:3).

IR (film): 3654, 3457, 3003, 2954, 2848, 2599, 2042, 1735, 1435, 1380, 1249, 1198, 1164, 1092, 1051, 1022, 987, 836 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.81 (s, 3 H), 3.78 (s, 3 H), 3.67 (s, 6 H), 2.90 (dd, J_1 = 15.1 Hz, J_2 = 9.0 Hz, 1 H), 2.76–2.70 (m, 1 H), 2.40–2.33 (m, 3 H), 2.00–1.84 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.7, 172.8, 167.2, 166.8, 60.6, 54.0, 51.9, 51.7, 41.7, 39.7, 31.2, 28.7.

HRMS (DART$^+$): m/z [M + H]$^+$ calcd for $C_{13}H_{20}BrO_8$: 383.03415; found: 383.03404.

Tetramethyl 1-(1*H*-Indol-2-yl)pentane-1,1,3,5-tetracarboxylate (11a)

Bromomalonate **10a** (0.1 g, 0.26 mmol), indole (**9a**) (0.15 g, 1.3 mmol), 2,6-lutidine (0.028 g, 0.03 mL, 0.26 mmol) and Ir(ppy)$_3$ (1.7 mg, 0.0026 mmol) were added to a 4 mL vial equipped with a stir bar under an argon atmosphere. Afterwards, deoxygenated CH_3CN (0.5 mL) was added to the vial and degassing was performed using the freeze-pump-thaw technique. The vial was irradiated in a blue LED photoreactor for 17 h at a constant temperature of 28 °C. After that time, the solution was adsorbed on silica gel. Purification by flash column chromatography using hexane/EtOAc (7:3) gave **11a** (0.109 g, 0.259 mmol, 100%) as an orange oil which crystallized slowly as a slightly brown solid.

Mp 93–96 °C; R_f = 0.2 (hexane/EtOAc, 7:3).

IR (film): 3407, 3002, 2954, 2847, 1735, 1454, 1436, 1233, 1207, 1169, 1091, 1071, 751 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ = 9.52 (s, 1 H), 7.47 (d, J = 7.8 Hz, 1 H), 7.31 (d, J = 7.6 Hz, 1 H), 7.13–7.07 (m, 1 H), 7.03–6.97 (m, 1 H), 6.29–6.28 (m, 1 H), 3.68 (s, 6 H), 3.51 (s, 3 H), 3.28 (s, 3 H), 2.85 (dd, J_1 = 14.4 Hz, J_2 = 9.7 Hz, 1 H), 2.45–2.30 (m, 2 H), 2.17 (t, J = 7.7 Hz, 2 H), 1.88–1.69 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.0, 172.9, 170.1, 169.9, 135.7, 132.7, 127.5, 122.2, 120.4, 119.9, 111.3, 101.8, 57.3, 53.3, 51.6, 40.8, 38.7, 31.2, 28.8.

HRMS (DART$^+$): m/z [M + H]$^+$ calcd for $C_{21}H_{26}NO_8$: 420.16584; found: 420.16500.

Dimethyl 7-(3-Methoxy-3-oxopropyl)-6-oxo-7,8-dihydropyrido-[1,2-*a*]indole-9,9(6*H*)-dicarboxylate (15)

Tetramethyl 1-(1*H*-indol-2-yl)pentane-1,1,3,5-tetracarboxylate (**11a**) (1.42 g, 3.4 mmol) and potassium carbonate (95%, 1.9 g, 13.6 mmol) were placed into a round-bottomed flask under argon. The mixture was dissolved in CH_3CN (170 mL) and heated at reflux for 18 min, after which the solution was allowed to cool to room temperature. The CH_3CN was evaporated under reduced pressure and distilled H_2O (130 mL) was added to the resulting brown oil. The aqueous phase was extracted with CH_2Cl_2 (2 × 130 mL) and the combined organic phases were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was adsorbed on silica gel. Purification by column chromatography using hexane/EtOAc (8:2) gave *N*-acylated indole **15** (1.17 g, 3.04 mmol, 89%) as an orange crystalline solid.

Mp 88–90 °C; R_f = 0.24 (hexane/EtOAc, 8:2).

IR (film): 3451, 3007, 2954, 1748, 1734, 1695, 1452, 1437, 1383, 1327, 1276, 1233, 1194, 1069, 766 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 8.39 (d, J = 8.2 Hz, 1 H), 7.49–7.44 (m, 1 H), 7.30–7.25 (m, 1 H), 7.22–7.18 (m, 1 H), 6.62 (s, 1 H), 3.83 (s, 3 H), 3.71 (s, 3 H), 3.62 (s, 3 H), 2.76–2.56 (m, 2 H), 2.54–2.41 (m, 3 H), 2.38–2.29 (m, 1 H), 1.97–1.88 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 169.8, 169.2, 168.5, 135.2, 132.4, 129.2, 125.5, 124.3, 120.7, 116.6, 109.2, 55.5, 39.1, 33.7, 31.3, 25.3.

HRMS (DART$^+$): m/z [M + H]$^+$ calcd for $C_{20}H_{22}NO_7$: 388.13963; found: 388.13973.

Dimethyl 10-Hydroxy-6-oxo-6,7,8,11-tetrahydro-7,11-methanoazocino[1,2-*a*]indole-9,11-dicarboxylate (7)

A solution of *N*-acylated indole **15** (0.056 g, 0.146 mmol) dissolved in anhydrous CH_2Cl_2 (9 mL) was placed into a round-bottomed flask under argon. The solution was cooled to about 0 °C in an ice–water bath followed by dropwise addition of titanium tetrachloride (0.083 g, 0.048 mL, 0.439 mmol); the solution acquired an orange color immediately. Subsequent dropwise addition of triethylamine (0.052 g, 0.072 mL, 0.512 mmol) led to the solution turning gray. After stirring for 4 h at 0 °C, the now black solution was quenched by adding distilled H_2O (40 mL). The mixture was extracted twice with CH_2Cl_2 (2 × 15 mL) and the combined organic phase was dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting oil was adsorbed on silica gel. Purification by column chromatography using hexane/EtOAc (8:2) gave tetracyclic indole **7** (0.024 g, 0.0683 mmol, 47%) as a yellow oil.

R_f = 0.3 (hexane/EtOAc, 8:2).

IR (film): 3014, 2952, 2855, 1749, 1700, 1659, 1616, 1438, 1349, 1322, 1229, 1072, 746 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ = 12.15 (s, 1 H), 8.43 (d, J = 7.9 Hz, 1 H), 7.57–7.54 (m, 1 H), 7.36–7.25 (m, 2 H), 7.12 (s, 1 H), 3.90 (s, 3 H), 3.74 (s, 3 H), 3.32 (q, J = 3.8 Hz, 1 H), 2.81 (d, J = 4.2 Hz, 2 H), 2.62 (d, J = 3.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1, 170.4, 169.3, 166.8, 134.8, 129.7, 125.5, 123.5, 110.6, 108.4, 99.9, 95.7, 95.6, 53.0, 51.1, 47.9, 32.8, 26.7.

HRMS (DART$^+$): m/z [M + H]$^+$ calcd for $C_{19}H_{18}NO_6$: 356.11341; found: 356.11340.

Dimethyl 2-{3-[2-(*tert*-Butoxycarbonylamino)ethyl]-1*H*-indol-2-yl}pentanedioate (11b)

Dimethyl 2-bromopentanedioate (**10b**) (0.08 g, 0.33 mmol), *N*-Boc-tryptamine (**9b**) (0.13 g, 0.50 mmol), 2,6-lutidine (0.038 mL, 0.032 g, 0.33 mmol) and Ir(ppy)$_3$ (2 mg, 0.064 mmol) were added to a 4 mL vial equipped with a stir bar under an argon atmosphere. Afterwards, deoxygenated CH_3CN (1 mL) was added to the vial and degassing was performed using the freeze-pump-thaw technique. The vial was irradiated in a blue LED photoreactor for 12 h at a constant temperature of 28 °C. After that time, the solution was adsorbed on silica gel. Purification by flash column chromatography using hexane/EtOAc (85:15) gave **11b** (0.0528 g, 0.126 mmol, 38%) as a yellow oil.

R_f = 0.11 (hexane/EtOAc, 85:15).

IR (film): 3385, 3323, 2951, 2863, 1735, 1677, 1524, 1453, 1436, 1277, 1149, 962, 745, 619 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ = 8.42 (s, 1 H), 7.57–7.55 (m, 1 H), 7.34–7.31 (m, 1 H), 7.21–7.08 (m, 2 H), 4.75 (s, 1 H), 4.06–4.01 (m, 1 H), 3.72 (s, 3 H), 3.71–3.67 (m, 2 H), 3.62 (s, 3 H), 2.97–2.76 (m, 2 H), 2.40–2.19 (m, 4 H), 1.43 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 173.0, 155.9, 135.9, 130.7, 127.8, 122.3, 119.6, 118.8, 111.3, 110.9, 52.6, 51.7, 46.9, 45.7, 41.5, 41.1, 31.1, 28.4, 28.1.

HRMS (DART$^+$): m/z [M + H]$^+$ calcd for $C_{22}H_{31}N_2O_6$: 419.21821; found: 419.21638.

Dimethyl 2-{3-[2-(Benzyloxycarbonylamino)ethyl]-1*H*-indol-2-yl}pentanedioate (11c)

Dimethyl 2-bromopentanedioate (**10b**) (0.1199 g, 0.5015 mmol), *N*-Cbz-tryptamine (**9c**) (0.3476 g, 1.1809 mmol), 2,6-lutidine (0.6 mL, 0.555 g, 5.1795 mmol) and Ir(ppy)$_3$ (4 mg, 0.0051 mmol) were added to a 4 mL vial equipped with a stir bar under an argon atmosphere. Afterwards, deoxygenated CH_3CN (2.2 mL) was added to the vial and degassing was performed with the freeze-pump-thaw technique. The vial was irradiated in a blue LED photoreactor for 12 h at a constant temperature of 28 °C. After that time, the solution was adsorbed on silica gel. Purification by flash column chromatography using hexane/EtOAc (85:15) gave **11c** (0.1216 g, 0.2687 mmol, 53%) as a yellow oil.

R_f = 0.06 (hexane/EtOAc, 85:15).

IR (film): 3376, 3344, 3059, 3030, 2950, 1697, 1517, 1455, 1436, 1236, 1201, 1155, 1068, 986, 741, 697, 599 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ = 8.52 (s, 1 H), 7.54 (d, J = 8.9 Hz, 1 H), 7.32–7.29 (m, 7 H), 7.19–7.06 (m, 2 H), 5.09–5.05 (m, 3 H), 4.05–4.00 (m, 1 H), 3.59–3.56 (m, 6 H), 3.53–3.42 (m, 2 H), 3.04–2.82 (m, 2 H), 2.28–2.20 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 173.1, 156.5, 136.8, 136.0, 130.9, 128.6, 128.24, 128.21, 127.8, 122.5, 119.8, 118.7, 111.1, 109.4, 66.7, 52.6, 51.8, 41.6, 31.2, 28.1, 24.6, 14.2.

HRMS (DART$^+$): m/z [M + H]$^+$ calcd for $C_{25}H_{29}N_2O_6$: 453.20256; found: 453.20117.

Methyl 10-[2-(*tert*-Butoxycarbonylamino)ethyl]-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-9-carboxylate (16b)

Dimethyl 2-{3-[2-(*tert*-butoxycarbonylamino)ethyl]-1*H*-indol-2-yl}pentanedioate (**11b**) (0.2684 g, 0.6414 mmol) and potassium carbonate (95%, 0.54 g, 3.907 mmol) were placed into a round-bottomed flask under argon. The mixture was dissolved in CH_3CN (32 mL) and heated at reflux for 6 h, after which the solution was allowed to cool to room temperature. The CH_3CN was evaporated under reduced pressure and distilled H_2O (30 mL) was added to the resulting brown oil. The aqueous phase was extracted with EtOAc (2 × 30 mL) and the combined organic phases were dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford *N*-acylated indole **16b** (0.24 g, 0.621 mmol, 97%) as a yellow oil. The crude product was used in the following reaction without further purification.

IR (film): 3287, 3053, 2928, 2853, 1716, 1648, 1535, 1454, 1434, 1263, 1175, 736, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ = 8.49 (dd, J_1 = 7.3 Hz, J_2 = 1.2 Hz, 1 H), 7.60–7.53 (m, 1 H), 7.38–7.27 (m, 3 H), 4.18–4.16 (m, 1 H), 3.74 (s, 3 H), 3.50–3.33 (m, 2 H), 3.07–2.92 (m, 2 H), 2.86–2.76 (m, 2 H), 2.41–2.20 (m, 2 H), 1.43 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6, 168.3, 155.9, 134.9, 130.8, 129.6, 125.2, 124.0, 118.6, 116.7, 79.3, 52.9, 45.7, 39.9, 37.3, 30.9, 28.4, 24.2.

HRMS (DART$^+$): m/z [M + H]$^+$ calcd for $C_{21}H_{27}N_2O_5$: 387.19200; found: 387.19218.

Methyl 10-[2-(Benzyloxycarbonylamino)ethyl]-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-9-carboxylate (16c)

Dimethyl 2-{3-[2-(benzyloxycarbonylamino)ethyl]-1*H*-indol-2-yl}-pentanedioate (**11c**) (0.2753 g, 0.6084 mmol) and potassium carbonate (95%, 0.5046 g, 3.46 mmol) were placed into a round-bottomed flask under an argon atmosphere. The mixture was dissolved in CH_3CN (31 mL) and heated at reflux for 6 h, after which the solution was allowed to cool to room temperature. The CH_3CN was evaporated

under reduced pressure and distilled H_2O (30 mL) was added to the resulting brown oil. The aqueous phase was extracted with EtOAc (2 × 30 mL) and the combined organic phases were dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford *N*-acylated indole **16c** (0.25 g, 0.5945 mmol, 98%) as a yellow oil. The crude product was used in the following reaction without further purification.

IR (film): 3375, 2953, 2921, 2850, 1732, 1697, 1511, 1455, 1365, 1317, 1245, 1159, 1170, 1037, 989, 751, 558 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$/TMS): δ = 8.48 (d, *J* = 8.0 Hz, 1 H), 7.53 (d, *J* = 7.4 Hz, 1 H), 7.37–7.28 (m, 8 H), 5.14–5.04 (m, 2 H), 4.97 (br s, 1 H), 3.68 (s, 3 H), 3.53–3.43 (m, 2 H), 3.04–2.72 (m, 4 H), 2.51–2.45 (m, 1 H), 2.24–2.14 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 168.4, 156.4, 136.6, 135.0, 130.9, 129.5, 128.6, 128.2, 125.4, 124.2, 118.5, 116.9, 116.5, 66.7, 52.9, 40.4, 37.5, 31.0, 24.9, 24.2, 14.3.

HRMS (DART$^+$): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{25}N_2O_5$: 421.17635; found: 421.17589.

2,3,5,6-Tetrahydroazepino[3,4,5-*hi*]benzo[*b*]indolizine-4,7(1*H*,4a*H*)-dione (8)

Method a

N-Acylated indole **16b** (0.1332 g, 0.3447 mmol) was placed into a round-bottomed flask under argon. Trifluoroacetic acid (1.028 mL, 1.53 g, 13.424 mmol) and CH_2Cl_2 (6 mL) were added and the mixture was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure followed by the addition of potassium carbonate (95%, 0.06 g, 0.4124 mmol) and anhydrous MeOH (6 mL). The suspension was heated at 40 °C for 2 h and then distilled H_2O (10 mL) was added. The aqueous phase was extracted with EtOAc (2 × 10 mL) and the combined organic phases were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the oily residue was adsorbed on silica gel. Purification by flash column chromatography using EtOAc/hexane (9:1) gave tetracycle **8** (0.0214 g, 0.0841 mmol, 24%) as a transparent crystalline solid.

Mp 223–224 °C; R_f = 0.25 (hexane/EtOAc, 9:1).

Method b

N-Acylated indole **16c** (0.0389 g, 0.0925 mmol) was placed into a round-bottomed flask followed by the addition of Pd/C (10%, 0.003 g) and MeOH (2.5 mL). A balloon containing hydrogen equipped with a syringe was fitted to the septum and the gas was bubbled into the suspension. The mixture was stirred at room temperature for 10 min and then filtered over Celite. The solvent was evaporated under reduced pressure and the residue transferred to a round-bottomed flask. Potassium carbonate (95%, 0.0382 g, 0.2626 mmol) and CH_3CN (3 mL) were added and the resulting suspension was heated at 40 °C for 2.5 h. Distilled H_2O (10 mL) was added and the aqueous phase was extracted with EtOAc (2 × 10 mL). The organic phases were combined and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the oily residue was adsorbed on silica gel. Purification by flash column chromatography using EtOAc/hexane (9:1) gave tetracycle **8** (0.0077 g, 0.0302 mmol, 33%) as a transparent crystalline solid.

IR (film): 3310, 3222, 2958, 2921, 1697, 1656, 1607, 1454, 1378, 1323, 1175, 1132, 764, 589, 547, 428 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6/TMS): δ = 8.33–8.30 (m, 1 H), 8.09–8.05 (m, 1 H), 7.49–7.46 (m, 1 H), 7.34–7.26 (m, 2 H), 4.44–4.37 (m, 1 H), 3.82–3.68 (m, 1 H), 3.41–3.39 (m, 1 H), 2.89–2.67 (m, 4 H), 2.20–2.09 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 172.8, 169.7, 134.1, 130.5, 130.0, 125.1, 124.2, 118.7, 116.3, 116.2, 38.5, 37.8, 32.8, 26.3, 22.5.

HRMS (DART$^+$): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{15}N_2O_2$: 255.11335; found: 255.11277.

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Supporting Information

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