Synthesis of the AB-DE Ring System Present in the Alstoscholarine Alkaloids

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Abstract: A practical protocol is presented for the construction of the AB-DE rings present in (19,20)-(*E*)- and (19,20)-(*Z*)-alstoscholarine alkaloids from the commercially available glutamic acid 5-methyl ester, employing only a six-step synthetic sequence. The main features include the synthesis of the alkynylindolizinone core and the use of Sonogashira cross-coupling and base-mediated cyclization to afford a 2-substituted indole without the use of protecting groups.

Key words: alkaloids, indoles, pyrroles, cross-coupling, heterocycles

The monoterpene indole alkaloids form a group of compounds of great structural diversity,[1] which have demonstrated important pharmacological activities.[2] One of the main sources of this type of alkaloid is the *Alstonia* (Apocynaceae) sp. genus, which is distributed mainly in Asia and Africa, with about 60 species reported.[3] The extensive study of the constituents of this genus has led to the isolation of more than 400 compounds, many of them monoterpene indole alkaloids. Usually, these alkaloids have 18 or 19 carbon atoms at the core, and various biological properties have been assigned to them, including anticancer and antibacterial activities, among others.[1a] In 2007, Luo and co-workers isolated (19,20)-(*E*)- and (19,20)-(*Z*)-alstoscholarine (**1** and **2**), novel alkaloids from the aerial part of *Alstonia scholaris*, a Chinese plant used in traditional medicine against dysentery and malaria (Figure 1).[4] These novel pentacyclic structures include a pyrrole- and indole-fused system with three stereogenic centers and two additional carbons atoms with respect to other monoterpene indole alkaloids (Figure 1). Recently, Zhu and coworkers reported the first total synthesis of both diastereomers using a protecting-group-free strategy, featuring a Pictet–Spengler cyclization for the construction of the pentacyclic core.[5] Interestingly, in the structure of alstoscholarines **1** and **2**, a single carbon atom joins the pyrrole and indole nuclei, with the pyrrole being part of an 8-oxo-5,6,7,8-tetrahydroindolizine ring system. The indolizine and indolizinone ring systems are the main core of a large alkaloid family widely distributed in nature,[6] and several members of this family of compounds display biological activities[7] against cancer[8] and against Alzheimer's disease and Parkinson's disease.[9]

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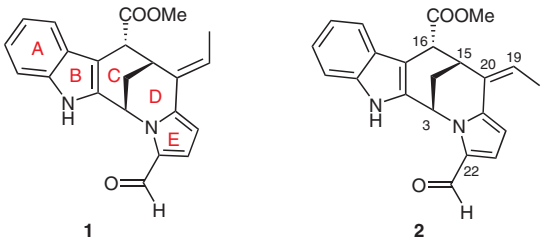
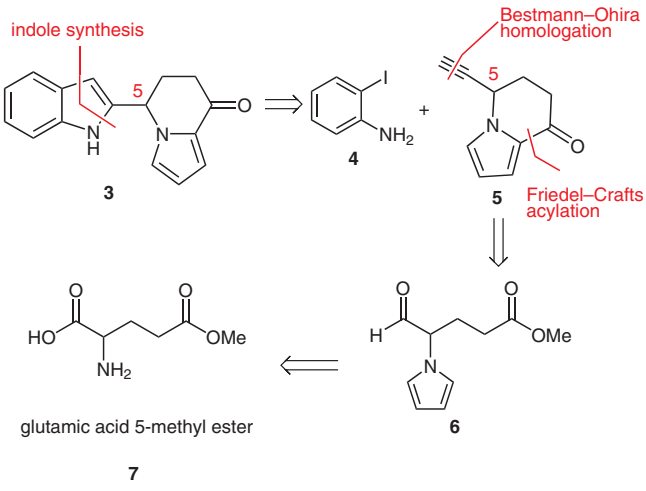


Figure 1 (19,20)-(*E*)-Alstoscholarine (**1**) and (19,20)-(*Z*)-alstoscholarine (**2**)

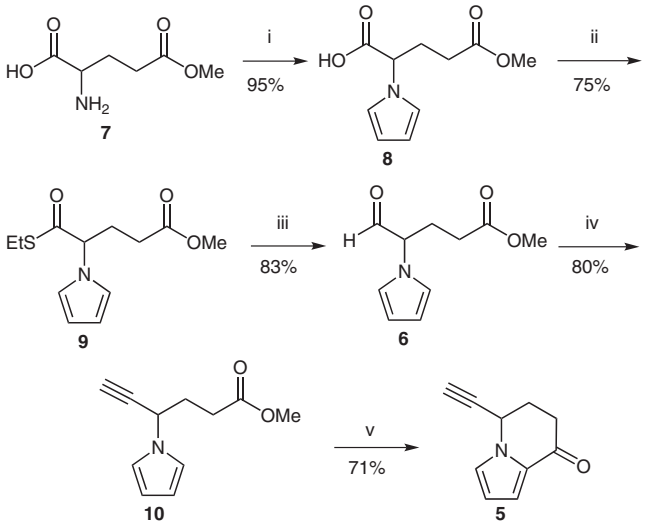
In this context, we envisioned that the dihydroindolizinone **3**, which includes a 2-indolyl substituent at C-5, a motif present in **1** and **2**, might be assembled starting from the commercially available glutamic acid 5-methyl ester (**7**), using the synthesis of indolizinones reported by Jefford and co-workers,[10] followed by transformation of the alkyne **5** into the corresponding 2-substituted indole **3** (Scheme 1). This practical synthetic sequence might allow the construction of the AB-DE ring system present in **1** and **2**. The implementation of this approach is reported herein.



Scheme 1 Retrosynthetic analysis of the AB-DE rings present in alstoscholarines

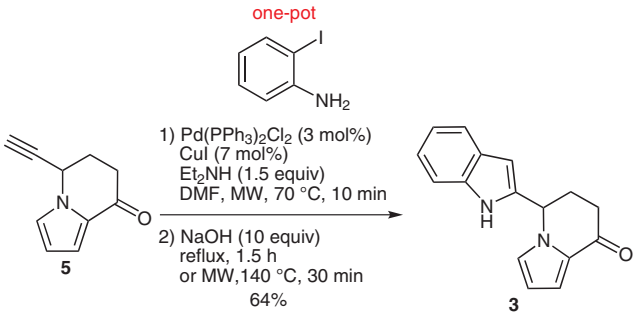
We started with synthesis of the pyrrole nucleus by reacting the commercially available glutamic acid 5-methyl ester (**7**) with 2,5-dimethoxytetrahydrofuran. Previously reported conditions[10a] [such as neat AcOH, H_2O–AcOH–DCE (1:2:3), or H_2O–DCE (1:1) systems] proved to be ineffective as only trace amounts of the desired pyrrole were

observed; however, the use of 2,5-dimethoxytetrahydrofuran and a catalytic amount of acetic acid, in a 1:1 mixture of water–1,2-dichloroethane (DCE) at reflux for one hour, afforded the pyrrole **8**. Then, we focused our efforts on the reduction of the carboxylic acid to the corresponding aldehyde without affecting the ester functionality. To this end, we elected to prepare the thioester **9**, and then to reduce it to the α-amino aldehyde as in the protocol reported by Fukuyama and co-workers.[11] Thus, treatment of the carboxylic acid **8** with ethyl chloroformate, triethylamine and ethanethiol in dichloromethane at 0 °C for 3.5 hours afforded the thioester **9**. The aldehyde **6** was obtained in good yield upon treatment of the thioester **9** with triethylsilane and 10% Pd/C in tetrahydrofuran. Despite our efforts to avoid racemization of the chiral center, **6** was always obtained as a racemic mixture. In a straightforward manner, alkyne **10** was obtained in good yield using the Bestmann–Ohira reagent[12] (dimethyl 1-diazo-2-oxopropylphosphonate). The anticipated cyclization of **10** into the alkynylindolizinone **5** was efficiently accomplished using boron tribromide in dichloromethane, under reaction conditions described previously by Jefford and co-workers[10] (Scheme 2).



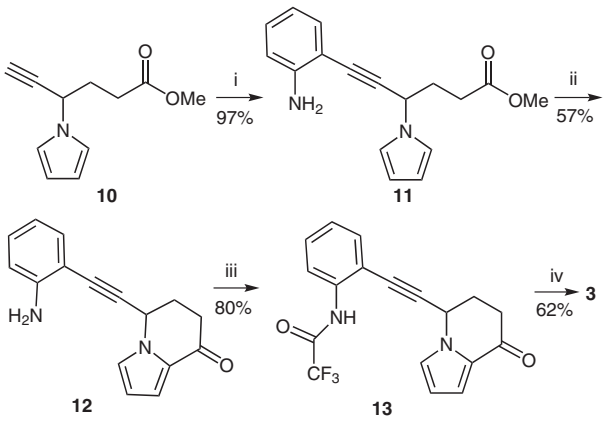
Scheme 2 Synthesis of alkyne **5**. *Reagents and conditions*: i) 2,5-dimethoxytetrahydrofuran (1.1 equiv), AcOH (cat.) (0.1 equiv), H_2O–DCE (1:1), reflux, 1 h, 95%; ii) ClCOOEt (1.2 equiv), Et_3N (2 equiv), EtSH (2.2 equiv), CH_2Cl_2, 0 °C, 3.5 h, 75%; iii) Et_3SiH (1.5 equiv), 10% Pd/C (0.05 equiv), THF, 3.5 h, 83%; iv) dimethyl 1-diazo-2-oxopropylphosphonate (1.3 equiv), K_2CO_3 (2.0 equiv), MeOH, r.t., 8 h, 80%; v) BBr_3 (2 equiv), CH_2Cl_2, r.t., 0.5 h, 71%.

The corresponding 2-substituted indole **3** was prepared using a one-pot two-step process: initial Sonogashira cross-coupling between alkyne **5** and *o*-iodoaniline (**4**), and subsequent intramolecular base-mediated cyclization of the *o*-alkynylaniline intermediate.[13] Interestingly, this last step could be carried out under reflux or microwave conditions (Scheme 3). Other conditions[14] [such as reaction with $Pd(PPh_3)_2Cl_2$, CuI and Et_3N in DMF for 24 h at r.t. or under reflux] were not successful in providing the desired indole.



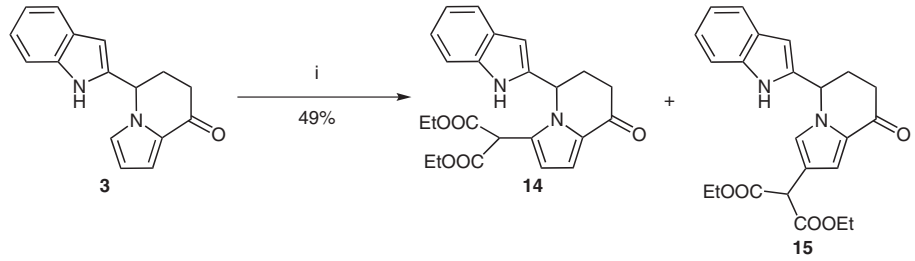
Scheme 3 Synthesis of the AB-DE rings of alstoscholarines

In an ancillary study, we successfully undertook a related synthetic approach for the synthesis of 2-substituted indole **3**, as depicted in Scheme 4. Treatment of the terminal alkyne **10** and *o*-iodoaniline under Sonogashira cross-coupling conditions[14] afforded the *o*-alkynylaniline **11** in excellent yield. Subsequent intramolecular Friedel–Crafts acylation[10] and N-trifluoromethylamidation[15] using trifluoroacetic anhydride furnished the *o*-alkynyltrifluoroacetanilide **13** in good yield. Previously reported cyclization conditions (such as *t*-BuOK, NMP, r.t., 5 h,[16] or $InBr_3$, toluene, reflux, 3 h[17]) proved to be inefficient to give the desired indole **3**. In contrast, under the Castro indole synthesis conditions,[18] which use inexpensive copper(I) iodide and triethylamine in ethylene glycol–*N*,*N*-dimethylformamide at reflux for 22 hours, the indole **3** was afforded in good yield (Scheme 4). Additionally, the structure of compound **3** was proved by X-ray crystallography[19] (Figure 2).



Scheme 4 Synthesis of the 2-substituted indole **3**. *Reagents and conditions*: i) *o*-iodoaniline, $Pd(PPh_3)_2Cl_2$ (3 mol%), CuI (7 mol%), Et_2NH (1.5 equiv), DMF, MW, 70 °C, 1 h, 97%; ii) BBr_3 (2 equiv), CH_2Cl_2, r.t., 1 h, 57%; iii) TFAA (2 equiv), THF, 0 °C, 24 h, 80%; iv) CuI (1 equiv), Et_3N (2 equiv), ethylene glycol–DMF (1:5.3), reflux, 22 h, 62%.

In a preliminary study, we examined the introduction of the diethyl malonate group into the indole at C-3 using diethyl diazomalonate[20] under reaction conditions described in the literature.[21] Surprisingly, the reaction of **3** did not afford the expected C-3-substituted indole, but instead



Scheme 5 Efforts toward alkylation at the indole 3-position. *Reagents and conditions*: i) diethyl diazomalonate (1.5 equiv), $Rh_2(OAc)_4$ (3 mol%), CH_2Cl_2, reflux, 15 h, 49% (1:1 mixture).

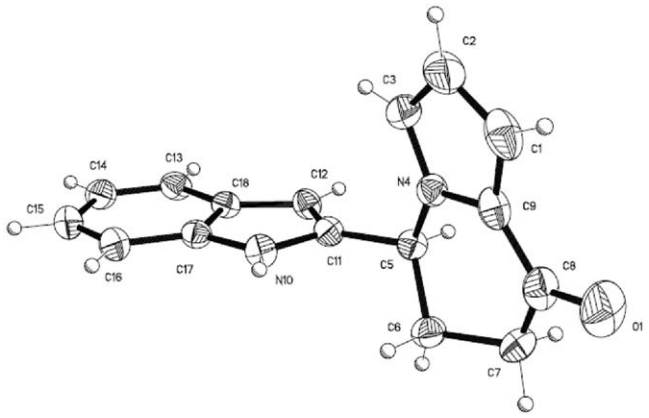


Figure 2 X-ray crystal structure of compound **3**

produced the two isomers **14** and **15** in a 1:1 mixture that resulted from alkylation of the pyrrole (Scheme 5). In principle, the pyrrole nucleus bearing an acyl substituent would be less reactive than the indole system. The regioselectivity observed may be attributed to steric factors in the vicinity of the C-3 position of the indole nucleus.[21a]

In summary, we have developed a practical protocol for the construction of the AB-DE rings present in the alstoscholarine alkaloids from the commercially available glutamic acid 5-methyl ester (**7**), employing a six-step synthetic sequence. The main features include the synthesis of the alkynylindolizinone core **5** and the use of Sonogashira cross-coupling/base-mediated cyclization to afford the 2-substituted indole **3** without the use of protecting groups.

^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini FT 200A (200 MHz), Varian Unity (300 MHz), Bruker Avance (300 MHz), Bruker Avance III (400 MHz) and Varian Unity Inova (500 MHz) spectrometers; TMS was used as the internal reference. Low-resolution mass spectra were recorded on a Jeol JMS AX-505 HA instrument (EI, 70 eV) and HRMS on a Jeol SX-102A instrument. IR spectra were measured on a Bruker Tensor 27 spectrophotometer. X-ray crystal structure analysis was undertaken on a Bruker Smart Apex diffractometer (CCD detector). The microwave-assisted reactions were performed using a CEM Discover Synthesis™ Unit (CEM Corp., Matthews, NC) with a monomodal open-vessel system. Reaction progress was monitored by TLC on precoated Merck silica gel Kieselgel 60 F254 plates; the spots were visualized under UV light (254 nm). Flash chromatography was conducted on silica gel (230–400 mesh). Melting points were determined on a Fisher–Johns instrument. General starting materials are commercially available, and were acquired from Sigma-Aldrich and used without further purification. DMF and CH_2Cl_2 were dried over CaH_2, THF over Na, and MeOH over Mg, then vacuum-distilled and stored over molecular sieves. Dimethyl 1-diazo-2-oxopropylphosphonate[12] and diethyl diazomalonate[20] were obtained according to the methods described in the literature.

5-Methoxy-5-oxo-2-(1*H*-pyrrol-1-yl)pentanoic Acid (8)

A soln of glutamic acid 5-methyl ester (**7**; 0.5 g, 3.1 mmol), 2,5-dimethoxytetrahydrofuran (0.45 g, 3.4 mmol) and AcOH (0.31 mmol) in a H_2O–DCE mixture (1:1, 10 mL) was refluxed for 1 h. The reaction mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture was separated by silica gel column chromatography (EtOAc) to give **8** (0.623 g, 95%) as a brown oil.

R_f = 0.2 (hexane–EtOAc, 1:1).

IR ($CHCl_3$): 3007, 2954, 1734, 1236 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.20–2.60 (m, 4 H), 3.65 (s, 3 H), 4.75 (m, 1 H), 6.17 (dd, *J* = 2.2, 2.2 Hz, 2 H), 6.69 (dd, *J* = 2.2, 2.2 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.6, 29.6, 51.8, 60.5, 109.0, 129.1, 172.9, 175.5.

MS (EI, 70 eV): *m*/*z* (%) = 211 (66) [M]$^+$, 180 (51), 106 (100).

HRMS–FAB: *m*/*z* [M]$^+$ calcd for $C_{10}H_{13}NO_4$: 211.0845; found: 211.0851.

Methyl 5-(Ethylthio)-5-oxo-4-(1*H*-pyrrol-1-yl)pentanoate (9)

A soln of **8** (0.60 g, 2.8 mmol) in anhyd CH_2Cl_2 (5 mL) was cooled to 0 °C, and then ethyl chloroformate (0.37 g, 3.4 mmol) and Et_3N (0.28 g, 2.8 mmol) were added dropwise, under an argon atmosphere, and the mixture was stirred for 30 min. Then, EtSH (0.38 g, 6.22 mmol) and Et_3N (0.28 g, 2.8 mmol) were added and the mixture was stirred at 0 °C for 3.5 h. The resulting solution was diluted with CH_2Cl_2 (5 mL) and washed consecutively with 1 M HCl (1 × 6 mL), H_2O (1 × 6 mL), 1 M NaOH (1 × 6 mL), H_2O (1 × 6 mL) and brine (1 × 6 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was separated by silica gel column chromatography (hexane–EtOAc, 9:1) to afford **9** (0.544 g, 75%) as a yellow oil.

R_f = 0.6 (hexane–EtOAc, 8:2).

IR ($CHCl_3$): 3562, 2953, 1734, 1680, 1277, 1171 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.2 Hz, 3 H), 2.15–2.37 (m, 3 H), 2.45–2.62 (m, 1 H), 2.85 (q, *J* = 7.2 Hz, 2 H), 3.66 (s, 3 H), 4.71–4.79 (m, 1 H), 6.24 (dd, *J* = 2.2, 2.2 Hz, 2 H), 6.70 (dd, *J* = 2.2, 2.2 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 23.5, 27.1, 29.6, 51.8, 67.4, 109.3, 120.5, 172.7, 199.0.

MS (EI, 70 eV): *m*/*z* (%) = 255 (15) [M]$^+$, 166 (80), 106 (100).

HRMS–FAB: *m/z* $[M]^+$ calcd for $C_{12}H_{17}NO_3S$: 255.0929; found: 255.0926.

Methyl 5-Oxo-4-(1*H*-pyrrol-1-yl)pentanoate (6)

To a soln of thioester **9** (0.055 g, 0.22 mmol) and Pd/C (10% wt. dry basis) (0.011 g, 5 mol%) in freshly distilled THF (0.21 mL), Et_3SiH (0.069 mL, 0.31 mmol) was added dropwise, under an argon atmosphere, using a syringe pump (1 h total time of addition). The resulting solution was stirred at r.t. for 3.5 h and then filtered over a Celite® pad and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (hexane–EtOAc, 8:2) to afford **6** (0.035 g, 83%) as a brown oil.

R_f = 0.2 (hexane–EtOAc, 8:2).

IR ($CHCl_3$): 2953, 1732, 1439, 1231, 1173 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.00–2.60 (m, 4 H), 3.66 (s, 3 H), 4.63 (m, 1 H), 6.27 (dd, *J* = 2.2, 2.2 Hz, 2 H), 6.66 (dd, *J* = 2.2, 2.2 Hz, 2 H), 9.67 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.0, 29.2, 51.8, 66.4, 110.0, 119.9, 172.8, 197.6.

MS (EI, 70 eV): *m/z* (%) = 195 (45) $[M]^+$, 166 (50), 106 (100).

HRMS–FAB: *m/z* $[M + H]^+$ calcd for $C_{10}H_{14}NO_3$: 196.0974; found: 196.0976.

Methyl 4-(1*H*-Pyrrol-1-yl)hex-5-ynoate (10)

To a soln of aldehyde **6** (0.800 g, 4.10 mmol) and K_2CO_3 (1.134 g, 8.20 mmol) in anhyd MeOH (6 mL), a soln of dimethyl 1-diazo-2-oxopropylphosphonate (1.023 g, 5.33 mmol) in MeOH (1 mL) was added under an argon atmosphere. The reaction mixture was stirred at r.t. over an 8 h period. Then, the resulting solution was diluted with CH_2Cl_2 (5 mL) and washed with 10% aq $NaHCO_3$ (1 × 5 mL) and H_2O (1 × 5 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture was separated by silica gel column chromatography (hexane–EtOAc, 8:2) to give **10** (0.628 g, 80%) as a yellow oil.

R_f = 0.5 (hexane–EtOAc, 8:2).

IR ($CHCl_3$): 3307, 3004, 1733, 1439, 1272, 1170 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.20–2.40 (m, 4 H), 2.51 (d, *J* = 2.4 Hz, 1 H), 3.67 (s, 3 H), 4.94 (m, 1 H), 6.17 (dd, *J* = 2.2, 2.2 Hz, 2 H), 6.80 (dd, *J* = 2.2, 2.2 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.7, 32.9, 49.9, 51.7, 74.1, 80.7, 108.7, 119.2, 172.9.

MS (EI, 70 eV): *m/z* (%) = 191 (35) $[M]^+$, 101 (100).

HRMS–FAB: *m/z* $[M]^+$ calcd for $C_{11}H_{13}NO_2$: 191.0946; found: 191.0952.

5-Ethynyl-6,7-dihydroindolizin-8(5*H*)-one (5)

To a soln of alkyne **10** (0.149 g, 0.78 mmol) in CH_2Cl_2 (1 mL), 1 M BBr_3 in CH_2Cl_2 (1.56 mL, 1.56 mmol) was added dropwise. The reaction mixture was stirred under an argon atmosphere at r.t. for 30 min. The reaction crude was diluted with H_2O (4 mL) and neutralized with 10% aq $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The product was purified by silica gel column chromatography (hexane–EtOAc, 6:4) to afford **5** (0.088 g, 71%) as a pale brown solid.

Mp 74–75 °C; R_f = 0.5 (hexane–EtOAc, 8:2).

IR ($CHCl_3$): 3306, 1659, 1534, 1463, 1202 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.32–2.67 (m, 3 H), 2.55 (d, *J* = 2.4 Hz, 1 H), 2.76–2.91 (m, 1 H), 5.02 (m, 1 H), 6.31 (d, *J* = 4.0 Hz, 1 H), 7.06 (d, *J* = 4.0 Hz, 1 H), 7.13 (d, *J* = 4.0 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.1, 34.4, 46.6, 74.2, 79.7, 110.8, 114.9, 125.5, 129.9, 186.1.

MS (FAB^+): *m/z* (%) = 159 (7) $[M]^+$, 136 (30), 91 (24), 73 (100).

HRMS–FAB: *m/z* $[M + H]^+$ calcd for $C_{10}H_{10}NO$: 160.0762; found: 160.0757.

5-(1*H*-Indol-2-yl)-6,7-dihydroindolizin-8(5*H*)-one (3)

To a deoxygenated soln of Et_2NH (0.02 mL, 0.19 mmol) in anhyd DMF (0.4 mL), 2-iodoaniline (0.029 g, 0.13 mmol), $Pd(PPh_3)_2Cl_2$ (0.0027 g, 3 mol%), CuI (0.0017 g, 7 mol%) and alkyne **5** (0.031 g, 0.20 mmol) were added. The resulting solution was heated to 70 °C under microwave irradiation for 10 min. Then, freshly powdered NaOH (0.052 g, 1.3 mmol) and additional DMF (0.26 mL) were added and the mixture was then refluxed under conventional heating (1.5 h) or under microwave irradiation (140 °C, 30 min). The mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with H_2O (15 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The product was purified by silica gel column chromatography (hexane–EtOAc, 7:3) to afford **3** (0.021 g, 64%) as a yellow solid.

Mp 215–218 °C; R_f = 0.2 (hexane–EtOAc, 6:4).

IR (KBr): 3277, 1643, 1530, 1463, 1297, 1073 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 2.56–2.70 (m, 4 H), 5.56 (dd, *J* = 5.0, 3.2 Hz, 1 H), 6.31 (dd, *J* = 2.6, 1.6 Hz, 1 H), 6.46 (s, 1 H), 6.76 (s, 1 H), 7.10–7.24 (m, 2 H), 7.13 (s, 1 H), 7.33 (d, *J* = 4.8 Hz, 1 H), 7.59 (d, *J* = 4.8 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 30.7, 34.6, 53.7, 102.5, 111.0, 111.1, 114.8, 120.5, 120.7, 122.8, 124.2, 126.0, 127.9, 135.5, 186.7.

MS (EI, 70 eV): *m/z* (%) = 250 (100) $[M]^+$, 193 (40), 156 (64), 94 (33).

HRMS–FAB: *m/z* $[M]^+$ calcd for $C_{16}H_{14}N_2O$: 250.1106; found: 250.1104.

Methyl 6-(2-Aminophenyl)-4-(1*H*-pyrrol-1-yl)hex-5-ynoate (11)

To a deaerated soln of Et_2NH (0.35 mL, 3.45 mmol) in anhyd DMF (6.3 mL), 2-iodoaniline (0.504 g, 2.30 mmol), $Pd(PPh_3)_2Cl_2$ (0.048 g, 3 mol%), CuI (0.030 g, 7 mol%) and alkyne **10** (0.659 g, 3.45 mmol) were added. The resulting solution was heated to 70 °C under microwave irradiation for 60 min. The mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 16 mL). The combined organic layers were washed with H_2O (1 × 16 mL) and dried (Na_2SO_4). The crude mixture was separated by silica gel column chromatography (hexane–EtOAc, 9:1) to afford **11** (0.637 g, 97%) as a pale brown oil.

R_f = 0.3 (hexane–EtOAc, 8:2).

IR ($CHCl_3$): 3496, 3006, 2954, 2224, 1732, 1615, 1490, 1290 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.20–2.62 (m, 4 H), 3.67 (s, 3 H), 5.01 (t, *J* = 6.4 Hz, 1 H), 6.18 (dd, *J* = 4.0, 2.0 Hz, 2 H), 6.66–6.74 (m, 2 H), 6.75 (t, *J* = 2.0 Hz, 1 H), 6.87 (t, *J* = 2.2 Hz, 1 H), 7.14 (t, *J* = 7.2 Hz, 1 H), 7.28 (d, *J* = 6.6 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.9, 33.4, 50.9, 51.8, 82.7, 91.2, 106.6, 108.6, 109.0, 114.3, 117.8, 119.2, 130.1, 132.4, 148.0, 172.9.

MS (EI, 70 eV): *m/z* (%) = 282 (91) $[M]^+$, 216 (62), 184 (94), 156 (100), 91 (57).

HRMS–FAB: *m/z* $[M]^+$ calcd for $C_{17}H_{18}N_2O_2$: 282.1368; found: 282.1361.

5-[(2-Aminophenyl)ethynyl]-6,7-dihydroindolizin-8(5*H*)-one (12)

To a soln of *o*-alkynylaniline **11** (1.723 g, 6.17 mmol) in CH_2Cl_2 (17 mL), 1 M BBr_3 in CH_2Cl_2 (12.3 mL, 12.3 mmol) was added dropwise. The reaction mixture was stirred under an argon atmosphere at r.t. for 1 h. The crude material was diluted with H_2O (10 mL) and neutralized with 10% aq $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture was separated by silica gel column chromatography (hexane–EtOAc, 6:4) to give **12** (0.879 g, 57%) as a yellow oil.

R_f = 0.25 (hexane–EtOAc, 6:4).

IR ($CHCl_3$): 3352, 2222, 1656, 1620, 1459, 1307, 749 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.45–2.95 (m, 4 H), 5.28 (dd, *J* = 5.2, 2.8 Hz, 1 H), 6.32 (dd, *J* = 2.6, 1.6 Hz, 1 H), 6.69 (s, 1 H), 6.71 (s, 1 H), 7.06–7.29 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.7, 34.8, 47.7, 82.9, 90.2, 110.8, 114.5, 115.0, 118.1, 121.4, 125.5, 130.1, 130.4, 132.5, 148.0, 186.1.

MS (EI, 70 eV): *m*/*z* (%) = 250 (100) $[M]^+$, 195 (28), 130 (26), 94 (79).

HRMS–FAB: *m*/*z* $[M]^+$ calcd for $C_{16}H_{14}N_2O$: 250.1106; found: 250.1111.

2,2,2-Trifluoro-*N*-{2-[(8-oxo-5,6,7,8-tetrahydroindolizin-5-yl)ethynyl]phenyl}acetamide (13)

A soln of *o*-alkynylaniline **12** (0.879 g, 3.51 mmol) in anhyd THF (7.5 mL) was cooled to 0 °C and TFAA (0.97 mL, 7.02 mmol) was added dropwise, over 0.5 h. After a stirring period of 24 h at 0 °C, the reaction mixture was diluted with sat. aq $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (hexane–EtOAc, 9:1) to afford **13** as the main product (0.969 g, 80%) as an orange oil.

R_f = 0.2 (hexane–EtOAc, 6:4).

IR ($CHCl_3$): 3389, 1742, 1660, 1536, 1460, 1401, 1289, 1152 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.48–2.91 (m, 4 H), 5.33 (m, 1 H), 6.35 (dd, *J* = 4.2, 2.7 Hz, 1 H), 7.05–7.24 (m, 3 H), 7.39–7.49 (m, 2 H), 8.27 (d, *J* = 8.4 Hz, 1 H), 8.51 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.1, 34.2, 47.1, 79.9, 93.5, 111.3, 112.0, 115.2, 120.2, 125.2, 125.7, 130.0, 130.7, 132.3, 136.3, 154.1, 154.6, 185.7.

MS (EI, 70 eV): *m*/*z* (%) = 346 (100) $[M]^+$, 277 (86), 134 (16), 94 (68).

HRMS–FAB: *m*/*z* $[M]^+$ calcd for $C_{18}H_{13}F_3N_2O_2$: 346.3032; found: 346.3121.

2-Substituted Indole 3 from *o*-Alkynyltrifluoroacetanilide 13 (Scheme 4)

A deaerated soln of acetanilide **13** (0.360 g, 1.04 mmol), CuI (0.198 g, 1.04 mmol) and Et_3N (0.289 mL, 2.08 mmol) in ethylene glycol–DMF (1:5.3, 34 mL) was refluxed under an argon atmosphere for 22 h until complete consumption of the starting material. Then, the reaction mixture was diluted with H_2O (35 mL) and extracted with EtOAc (3 × 35 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (hexane–EtOAc, 7:3) to afford **3** (0.162 g, 62%) as a yellow solid.

Diethyl [5-(1*H*-Indol-2-yl)-8-oxo-5,6,7,8-tetrahydroindolizin-3-yl]malonate (14) and Diethyl [5-(1*H*-Indol-2-yl)-8-oxo-5,6,7,8-tetrahydroindolizin-2-yl]malonate (15)

To a refluxed soln of indole **3** (0.073 g, 0.29 mmol) and $Rh_2(OAc)_4$ (0.004 g, 3 mol%) in anhyd CH_2Cl_2 (2.5 mL), a soln of diethyl diazomalonate (0.08 g, 0.43 mmol) in CH_2Cl_2 (1 mL) was slowly added. The reaction mixture was stirred under an argon atmosphere for 15 h until complete consumption of the starting material. The solution was filtered over a Celite® pad and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (hexane–EtOAc, 8:2) to afford a 1:1 mixture of compounds **14** and **15** as a brown oil (0.058 g, 49%). These compounds were separated by preparative TLC.

Compound 14

Brown oil; R_f = 0.3 (hexane–EtOAc, 8:2).

IR ($CHCl_3$): 3545, 3447, 3292, 2930, 1735, 1659, 1539, 1305, 1185 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.09 (t, *J* = 7.2 Hz, 3 H), 1.15 (t, *J* = 7.2 Hz, 3 H), 2.53–2.62 (m, 4 H), 3.85–4.10 (m, 4 H), 4.67 (s, 1 H), 5.86 (br s, 1 H), 6.09 (s, 1 H), 6.52 (d, *J* = 4.4 Hz, 1 H), 7.08 (t, *J* = 8.0 Hz, 1 H), 7.14 (t, *J* = 8.0 Hz, 1 H), 7.18 (d, *J* = 4.4 Hz, 1 H), 7.29 (d, *J* = 8.2 Hz, 1 H), 7.49 (d, *J* = 8.2 Hz, 1 H), 7.96 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 13.7, 29.9, 32.0, 50.4, 50.9, 62.3, 62.5, 101.6, 111.0, 112.9, 114.8, 120.3, 120.3, 122.4, 128.1, 129.2, 131.7, 135.4, 136.1, 166.2, 166.3, 186.8.

MS (EI, 70 eV): *m*/*z* (%) = 408 (100) $[M]^+$, 362 (25), 261 (54), 252 (98).

HRMS–FAB: *m*/*z* $[M]^+$ calcd for $C_{23}H_{24}N_2O_5$: 408.1685; found: 408.1675.

Compound 15

Brown oil; R_f = 0.3 (hexane–EtOAc, 8:2).

IR ($CHCl_3$): 3502, 3458, 2931, 1730, 1660, 1484, 1399, 1303, 1156 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.11–1.20 (m, 6 H), 2.50–2.61 (m, 4 H), 3.85–4.10 (m, 4 H), 4.46 (s, 1 H), 5.40 (m, 1 H), 6.43 (s, 1 H), 6.78 (d, *J* = 4.0 Hz, 1 H), 7.08–7.30 (m, 4 H), 7.57 (d, *J* = 8.0 Hz, 1 H), 8.72 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 14.0, 30.3, 34.8, 50.8, 53.8, 61.8, 61.8, 102.6, 111.3, 114.7, 117.3, 120.2, 120.6, 122.6, 125.6, 127.7, 130.6, 135.1, 136.5, 168.0, 168.0, 188.8.

MS (EI, 70 eV): *m*/*z* (%) = 408 (100) $[M]^+$, 362 (25), 261 (54), 252 (98).

HRMS–FAB: *m*/*z* $[M]^+$ calcd for $C_{23}H_{24}N_2O_5$: 408.1685; found: 408.1678.

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