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Intramolecular Hetero Diels–Alder Routes to γ-Carboline Alkaloids

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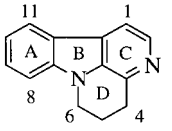
Abstract—Concise and efficient routes to the carboline alkaloids isocanthine (**3**), isocanthin-6-one (**4**), 1-methylisocanthine (**5**), and 1-methylisocanthin-6-one (**6**) are reported. In each case, the key synthetic step was an intramolecular hetero Diels–Alder reaction of a 1-aza-1,3-diene with an acetylenic dienophile.

Introduction

Canthines are tetracyclic β-carboline alkaloids (general structure **1**), several dozen of which have been isolated from natural sources, characterized, and screened for a broad range of pharmaceutical activity.[1] One representative example is 6*H*-indolo[3,2,1-*de*][1,5]-naphthyridine-6-one (**2**, canthin-6-one), which has been isolated from several Asian and Australian plants and has shown both antimicrobial and anti-tumorigenic properties.[2] Traditionally, compounds such as **2** have been prepared by Bischler–Napieralski reactions or Pictet–Spengler condensations of tryptamine derivatives.[3] However, an alternate approach to the synthesis of **2** and related β-carboline systems was reported by Li and Snyder whereby rings C and D were simultaneously constructed via an intramolecular Diels–Alder cycloaddition utilizing the C(2)–C(3) double bond of indole as dienophile and a 1,2,4-triazine tethered to N(1) of indole as diene.[4] Syntheses of γ-carboline analogs and γ-carboline alkaloids such as 5,6-dihydro-4*H*-indolo[3,2,1-*ij*]naphthyridine (**3**, isocanthine) have typically employed electrocyclic ring closures of 1-azatrienes.[5] For example, Gilchrist et al. prepared **3** in a seven-step synthesis using an electrocyclic pathway wherein closure of an oxime derivative efficiently generated the C-pyridine ring.[6]



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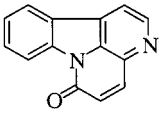

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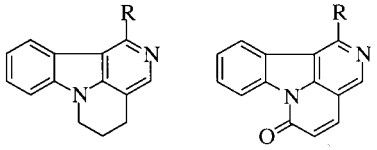

3 R=H
5 R=Me

4 R=H
6 R=Me

Studies in this laboratory have also involved syntheses of both β- and γ-carboline alkaloids utilizing Diels–Alder pathways. While our initial efforts towards **1** and **2** led only to their carbocyclic analogs,[7] we recently reported a preliminary account of a concise and efficient four-step synthesis of isocanthin-6-one (**4**), a new member of the γ-carboline series, in which the key step was an intramolecular hetero Diels–Alder reaction of a 1-aza-1,3-diene with an acetylene dienophile.[8] Herein we provide a full account of the initial methodology developed to synthesize **4**, as well as its general extension to prepare three other γ-carboline alkaloid analogs: isocanthine (**3**), 1-methylisocanthine (**5**), and 1-methylisocanthin-6-one (**6**). Since both **4** and **6** are structural congeners of the pharmacologically-active **2**, their synthesis allows additional exploration of structure–activity relationships (SAR) in the carboline alkaloid series. The 1-methyl derivatives (**5** and **6**) were chosen in particular because the presence of a functional group α to the nitrogen atom in the fused pyridine ring of **2** has previously been shown to increase dramatically its biological activity.[9]

Results and Discussion

The overall route to isocanthin-6-one (**4**) is summarized in Scheme 1. Coupling of indole-3-carboxaldehyde (**7**) with 4-pentynoic acid to generate **8** was readily effected using

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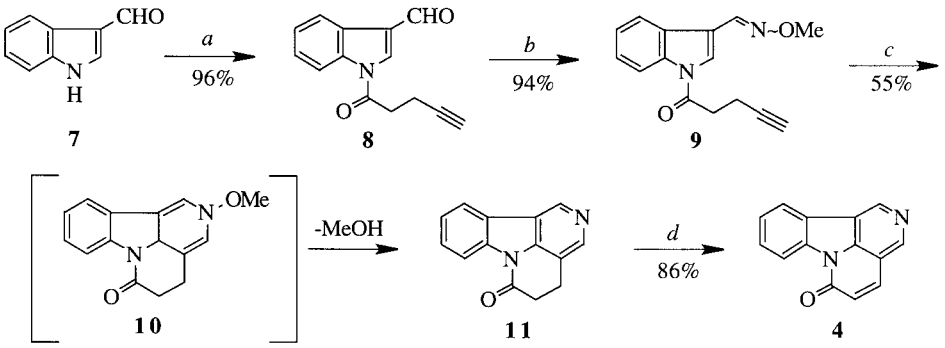


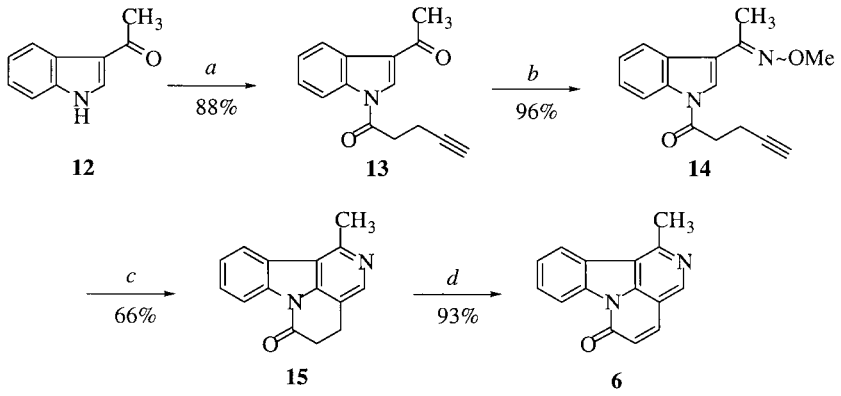
Scheme 1. (a) $HC{\equiv}CCH_2CH_2CO_2H$, DCC, DMAP, CH_2Cl_2, rt, 5 h. (b) $MeONH_2{\cdot}HCl$, C_5H_5N, 95% EtOH, Δ, 3.5 h. (c) toluene,180°C, 4 days. (d) 30% Pd/C, sulfolane, 285°C, 2 h.

1,3-dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-dimethylaminopyridine (DMAP). Subsequent conversion of **8** to its methoxime derivative (**9**) was achieved by standard methodologies. Probes of the intramolecular Diels–Alder reaction were carried out in refluxing diglyme, xylenes, and mesitylene before it was discovered that toluene was the solvent of choice (180°C, sealed tube, 4 days). Thus, cycloaddition of **9** simultaneously constructed rings C and D to give intermediate **10**; subsequent loss of methanol afforded the desired adduct **11**. Similar thermolysis was also achieved in refluxing sulfolane (285°C, 2 h), albeit in lower yield (37%). Interestingly, attempts to promote this cycloaddition through use of various Lewis acid catalysts, such as $TiCl_4$ and $Sc(OTf)_3$, were ineffectual. The methoxime 1-aza-1,3-diene derivative was selected in particular for this synthetic methodology based upon its successful application in intermolecular hetero Diels–Alder routes to γ-carboline analogs.[10] However, neither the oxime nor benzylimine analogs of **9** underwent Diels–Alder cycloaddition under similar reaction conditions, despite literature precedent for their participation in hetero Diels–Alder reactions.[5,11] In the case of the oxime variant of **9** dehydration to the 3-cyano-1-(4-pentynoyl)-indole derivative occurred instead of cycloaddition; the benzylimine variant gave only decomposition products based upon GC–MS analysis.

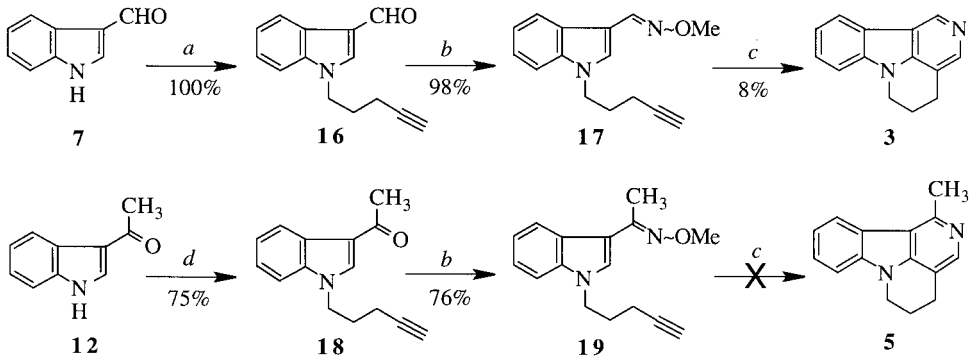
Initial attempts to oxidize **11**–**4** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were unsuccessful, although no such difficulties were experienced during an analogous oxidation to generate the carbocyclic analog of **11**.[7] The oxidation of **11** was effected with palladium on activated carbon (Pd/C) in refluxing sulfolane. Use of less than a full equivalent of Pd/C did not achieve complete conversion to **4**. To our knowledge, this final step represents the first dehydrogenation in sulfolane via palladium. Although diphenyl ether is more typically utilized as the reaction solvent, the ease of sulfolane removal makes this method preferable. The overall yield of isocanthin-6-one (**4**) from this four-step preparation was 43%.

This methodology was readily extended to synthesize 1-methylisocanthin-6-one (**6**), as shown in Scheme 2. Comparable yields were achieved in each step, with the exception of the Diels–Alder cycloaddition. Interestingly, heating in toluene at 180°C in a sealed tube for four days afforded **15** in only 23% yield. Since GC–MS analysis showed only recovered **14** in addition to cycloadduct **15**, extension of the reaction time to seven days substantially increased the yield. Thermolysis of **14** in refluxing sulfolane (285°C, 2 h) provided **15** in 45% yield. Oxidation using Pd/C in refluxing sulfolane completed the synthesis of 1-methylisocanthin-6-one (**6**) in an overall yield of 52%.

Finally, an analogous synthesis of both isocanthine (**3**) and 1-methylisocanthine (**5**) was pursued via a three-step route, utilizing an intramolecular hetero Diels–Alder reaction of a 1-aza-1,3-diene with an alkyl-tethered acetylenic dienophile instead of the amide-tethered variant employed earlier. As shown in Scheme 3, both **7** and **12** were readily *N*-alkylated



Scheme 2. (a) $HC{\equiv}CCH_2CH_2CO_2H$, DCC, DMAP, CH_2Cl_2, rt, 5 h. (b) $MeONH_2{\cdot}HCl$, C_5H_5N, 95% EtOH, Δ, 3.5 h. (c) toluene, 180°C, 7 days. (d) 30% Pd/C, sulfolane, 285°C, 2 h.

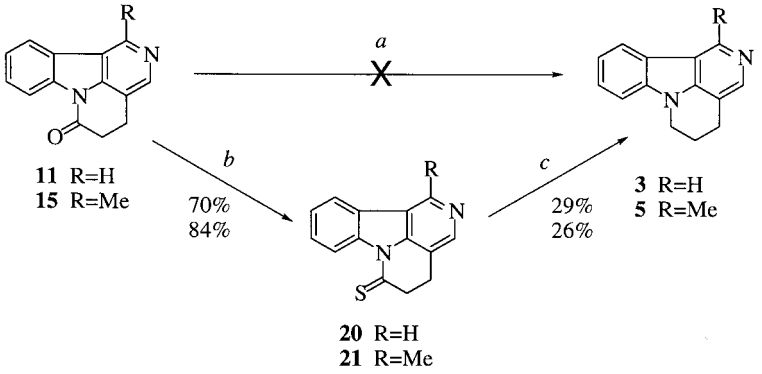


Scheme 3. (a) $HC{\equiv}CCH_2CH_2CH_2CH_2Cl$, NaH, DMF, 75°C, 5 h. (b) $MeONH_2{\cdot}HCl$, C_5H_5N, 95% EtOH, Δ, 3.5 h. (c) sulfolane, 285°C, 2 h. (d) $HC{\equiv}CCH_2CH_2CH_2CH_2Cl$, K_2CO_3, DMF, 75°C, 23 h.

with 5-chloro-1-pentyne in THF using either K_2CO_3 or NaH as base to generate **16** and **18**. These adducts were then readily converted to their corresponding methoxime derivatives (**17** and **19**). Unfortunately, Diels–Alder cycloaddition proved quite difficult to achieve. Heating in toluene as performed earlier (180°C, sealed tube, 4 days) led only to recovered starting material in both cases. Heating **17** in refluxing sulfolane (285°C, 2 h) provided an isolated yield of **3** in only 8% yield; GC–MS analysis of the crude product mixture showed a substantial amount (37%) of a compound whose mass was consistent with 3-cyano-1-(4-pentynyl)-indole. Similar treatment of **19** to generate **5** led solely to degradation products based upon GC–MS analysis. Use of additional Lewis acid catalysts (ZnI_2, $LiClO_4$) as well as other reaction solvents (ethylene glycol, benzene, pyridine) failed to provide either **3** or **5**. An attempt with Wilkinson's catalyst [$(PPh_3)_4RuCl$] in refluxing trifluoroethanol was similarly ineffectual.

Although the attempted Diels–Alder cyclizations of **17**–**3** and **19**–**5** involved the same diene and dienophile equivalents as utilized earlier to prepare **4** and **6**, the greater difficulty in achieving cyclization can be attributed to the absence of the amide carbonyl in **17** and **19** that was present in **9** and **13**. Because the π-system of the amide linkage must be coplanar with the aromatic indole system, the tethered pentynoyl fragment is restricted in its orientations, one of which places the acetylenic dienophile in the direction of the 1-aza-1,3-diene moiety, facilitating more favorable geometry compared to the freely rotating alkyl tether of **17** and **19**. Further, the amide linkage might facilitate the cycloaddition based upon potential delocalization of the indole nitrogen lone pair. Delocalization towards the methoxime group effectively disrupts the 1-aza-1,3-diene moiety, whereas delocalization towards the amide carbonyl maintains the 1-aza-1,3-diene system.

Although isocanthine (**3**) was prepared in an overall yield of 8% by the initial three-step methodology (Scheme 3), an alternative path to **3** and **5** was clearly needed. Initially, based upon the literature precedent[12] for the direct reduction of amides to amines with $LiAlH_4$, we anticipated that both **11** and **15** could be converted to **3** and **5**, respectively, completing their overall synthesis in four steps from **7** and **12** (Scheme 4). However, this transformation could not be achieved; others have also been unable to reduce *N*-aryl amides to amines with $LiAlH_4$.[13] Direct hydrogenation using Adam's catalyst (PtO_2) was equally ineffective. Successful preparation of both **3** and **5** was achieved by reverting to a two-step preparation from **11** and **15** in which the amides were converted to the corresponding thioamides (**20** and **21**) using Lawesson's reagent in toluene (100°C, 24 h). GC–MS analysis confirmed formation of the thioamides based upon significant peaks at both $[M^+]$ and $[M-33]^+$, due to loss of an HS radical.[14] IR analysis of the thioamides confirmed the absence of the carbonyl groups. The carbon-sulfur bonds of **20** and **21** were subsequently cleaved and replaced with hydrogen upon treatment with Raney nickel, providing **3** and **5** in 20% and 22% yield from **11** and **15**, respectively. Overall yields of **3** and **5** in five steps from **7** and **12** were 10 and 12%, respectively.



Scheme 4. (a) $LiAlH_4$, THF, rt, 18 h. (b) Lawesson's reagent, toluene, 100°C, 24 h. (c) Raney Ni, 95% EtOH, Δ, 3.5 h.

Thus, we have developed a general methodology to generate γ-carboline alkaloids concisely and efficiently via intramolecular hetero Diels–Alder reactions of 1-aza-1,3-dienes with acetylenic dienophiles. Additionally, we have demonstrated the importance of the amide linkage for the tethered alkynyl moiety in facilitating the cycloaddition step.

Experimental

General methods

Melting points were obtained in open capillary tubes and are uncorrected. IR spectra were recorded for solids (KBr pellet) and liquids (neat between NaCl plates) on a Nicolet-Magna 550 FT spectrometer and are reported in wavenumbers (cm^{-1}). NMR spectra were obtained on a Bruker DPX 300 spectrometer; chemical shifts are reported in ppm downfield relative to tetramethylsilane, and coupling constants are reported in hertz (Hz). GC–MS analyses were performed on a Hewlett–Packard 5890 Series II gas chromatograph with a capillary SPB-5 polydiphenyl(5%)-dimethyl(95%)siloxane column (30 m×200 μm film) and a Hewlett–Packard 5791A mass spectrometer (EI, 70 eV). All chemicals were obtained from commercial sources and used as received unless indicated. All solvents were dried over molecular sieves prior to use. R_f values for thin layer chromatography (TLC) were obtained on silica gel sheets with ethyl acetate as eluent. Flash chromatography was carried out on silica gel (40 μm) with ethyl acetate as eluent. Column chromatography was carried out on alumina (neutral, super I) with chloroform as eluent. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. High resolution mass spectra were performed at Eli Lilly & Co., Indianapolis, IN.

3-Formyl-1-(4-pentynoyl)-indole (8). To an argon-swept Erlenmeyer flask fitted with a drying tube were added DCC (4.54 g, 22.0 mmol), CH_2Cl_2 (70 mL), DMAP (0.244 g, 2.0 mmol) and indole-3-carboxaldehyde (2.90 g, 20.0 mmol). A solution of 4-pentynoic acid (2.36 g, 24.0 mmol) in CH_2Cl_2 (30 mL) was added dropwise and the mixture was stirred at room temperature for 5 h. Upon completion, based on TLC analysis, the DCU was removed by gravity filtration and the filtrate was washed with a saturated solution of $NaHCO_3$ (2×25 mL), dried over sodium sulfate, and concentrated in vacuo to give **8** (4.332 g, 96%) as a white solid: mp 137–138°C (ethanol); R_f 0.63; IR ν 1730, 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.15 (s, 1H, C*H*O), 8.44 (d, 1H, *J*=7.2 Hz, *H*-7), 8.30 (d, 1H, *J*=7.1 Hz, *H*-4), 8.13 (s, 1H, *H*-2), 7.45 (qd, 2H, *J*=7.3, 1.6 Hz, *H*-5, *H*-6), 3.29 (t, 2H, *J*=7.2 Hz, COCH_2), 2.78 (td, 2H, *J*=7.2, 2.6 Hz, CH_2C≡CH), 2.07 (t, 1H, *J*=2.6 Hz, C≡C*H*); ^{13}C NMR ($CDCl_3$) δ 13.83, 34.90, 69.96, 81.70, 111.48, 116.43, 122.01, 124.44, 125.56, 127.01, 134.16, 136.44, 169.45, 185.52; MS *m*/*z* 224 $[M-H]^+$. Anal. Calcd for $C_{14}H_{11}NO_2$, 0.5 H_2O: C, 71.78; H, 5.16; N, 5.98. Found: C, 71.83; H, 4.66; N, 5.91.

3-Formyl-1-(4-pentynoyl)-indole methoxime (9). To an argon-swept flask were added **8** (0.450 g, 2.0 mmol), methoxylamine hydrochloride (0.334 g, 4.0 mmol), pyridine (8 mL), and 95% EtOH (8 mL). The solution was stirred at reflux for 3.5 h, and the solvent was concentrated in vacuo to give a pale yellow residual oil. The crude product was dissolved in chloroform (20 mL) and washed with water (4×75 mL); the combined organic phase was dried over sodium sulfate and concentrated in vacuo to give **9** (0.477 g, 94%) as a white solid: mp 144–145°C (ethanol); IR ν 1733, 1623 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.46 (d, 1H, *J*=8.0 Hz, *H*-7), 8.23 (s, 1H, *HC*=NOMe), 8.18 (d, 1H, *J*=7.7 Hz, *H*-4), 7.62 (s, 1H, *H*-2), 7.40 (m, 2H, *H*-5, *H*-6), 4.04 (s, 3H, $NOCH_3$), 3.21 (t, 2H, *J*=7.3 Hz, COCH_2), 2.75 (td, 2H, *J*=7.3, 2.6 Hz, CH_2C≡CH), 2.04 (t, 1H, *J*=2.6 Hz, C≡C*H*); ^{13}C NMR ($CDCl_3$) δ 13.82, 34.85, 62.21, 69.62, 82.15, 116.43, 122.55, 124.58, 125.53, 126.36, 127.02, 136.37, 142.52, 169.03; MS *m*/*z* 254$[M^+]$. Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.98; H, 5.65; N, 10.96.

4,5-Dihydroisocanthin-6-one (11). To an argon-swept thick-walled ampule was added a solution of **9** (0.050 g, 0.197 mmol) in toluene (2.0 mL). The sealed ampule was placed in an oven preheated at 180±2°C for four days. The tube was opened without pressure release, and the liquid was concentrated in vacuo to give a residual yellow oil (0.046 g). Flash chromatography gave **11** (0.024 g, 55%) as a tan solid: mp 170–171°C; R_f=0.34; IR ν 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.10 (s, 1H, *H*-1), 8.50 (br s, 1H, *H*-3), 8.46 (d, 1H, *J*=8.2 Hz, *H*-8), 8.04 (d, 1H, *J*=7.6 Hz, *H*-11), 7.52 (dt, 2H, *J*=3.2, 7.6 Hz, *H*-9, *H*-10), 3.34 (t, 2H, *J*=8.5 Hz, CH_2); 3.10 (t, 2H, *J*=7.4 Hz, CH_2); ^{13}C NMR (DMSO-d_6) δ 20.96, 32.32, 111.48, 115.41, 119.95, 120.57, 121.68, 124.51, 126.44, 128.28, 140.66, 143.53, 143.73, 173.63; MS *m*/*z* 222 $[M^+]$. HRMS for $C_{14}H_{11}N_2O$ $[M+H]^+$ requires: 223.0871. Found: 223.0873.

Isocanthin-6-one (4). To an argon-swept conical vial were added **11** (0.020 g, 0.090 mmol), palladium (30%) on activated carbon (0.015 g, 0.090 mmol of Pd), sulfolane (2.0 mL), and a spin vane. The reaction flask was capped and placed in a preheated aluminum block at 285±2°C for 2 h. The cooled mixture was diluted with ether (3 mL) and gravity filtered to remove insoluble particulates. The filtrate was diluted with water (100 mL) and extracted with ether (3×25 mL). The combined organic phase was washed with water (4×100 mL), dried over sodium sulfate, and concentrated in vacuo to give a residual yellow solid (0.020 g). Flash chromatography gave **4** (0.017 g, 86%) as a white solid: mp 191–192°C; R_f 0.33; IR ν 1690 cm^{-1}; ^1H NMR ($CDCL_3$) δ 9.35 (br s, 1H, *H*-1), 8.99 (br s, 1H, *H*-3), 8.73 (d, 1H *J*=7.9 Hz, *H*-8), 8.18 (d, 1H, *J*=8.0 Hz, *H*-11); 7.97 (d, 1H, *J*=9.5 Hz, *H*-5), 7.63 (dt, 2H, *J*=3.0, 7.6 Hz, *H*-9, *H*-10), 6.90 (d, 1H, J-9.6 Hz, *H*-4); ^{13}C NMR (DMSO-d_6) δ 113.69, 116.15, 121.49, 122.54, 123.84, 124.68, 125.78, 128.40, 128.94, 136.97, 141.13, 143.32, 144.49, 145.61; MS *m*/*z* 220 $[M^+]$. HRMS for $C_{14}H_9N_2O$ $[M+H]^+$ requires: 221.0715. Found: 221.0713.

3-Acetyl-1-(4-pentynoyl)-indole (13). 13 (0.454 g, 88%) was prepared by the procedure described for **8** on a 2.0 mmol scale to give a white solid: mp 117.5–118.0°C (ethanol); IR ν 1729, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.42 (dd, 1H, *J*=3.0, 13 Hz, *H*-7), 8.35 (dd, 1H, *J*=3.0, 13 Hz, *H*-4), 8.11 (s, 1H *H*-2), 7.45 (m, 2H, *H*-5, H-6), 3.29 (t, 2H, *J*=7.0 Hz, COCH_2), 2,80 (td, 2H, *J*=5.0,

2.5 Hz, $CH_2C{\equiv}CH$), 2.61 (s, 3H, CH_3), 2.09 (t, 1H, J=7.0 Hz, $C{\equiv}CH$); ^{13}C NMR ($CDCl_3$) δ 13.80, 27.92, 34.94, 69.84, 81.89, 116.16, 122.12, 122.56,125.30, 126.36, 127.14, 130.18, 136.03, 169.45, 193.57; Ms m/z 239 [M^+].Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.23; H, 5.85. Found: C, 75.18; H, 5.52; N, 5.84.

3-Acetyl-1-(4-pentynoyl)-indole methoxime (14). 14 (0.123 g, 96%) was prepared by the procedure described for **9** on a 0.5 mmol scale to give a white solid; mp 158–159°C (ethanol); IR ν 1719, 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.46 (d, 1H, J=7.2 Hz, H-7), 8.35 (d 1H, J=7.5 Hz, H-4), 7.63 (s, 1H, H-2), 7.39 (m, 2H, H-5 H-6), 4.09 (s, 3H, $NOCH_3$), 3.24 (t, 2H, J=7.0 Hz, $COCH_2$), 2.77 (td, 2H, J=7.3, 2.6 Hz, $CH_2C{\equiv}CH$), 2.28 (s, 3H, CH_3), 2.07 (t, 1H, J=2.6 Hz, $C{\equiv}CH$); ^{13}C NMR ($CDCl_3$) δ 12.76, 13.83, 34.91, 62.13, 69.56, 82.30, 116.21, 120.20, 123.60, 123.69, 124.47, 126.00, 127.37, 136.46, 150.25, 169.02; MS m/z 268 [M^+]. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.56; H, 5.96; N, 10.43. Found: C, 71.42; H, 5.98; N, 10.36.

4,5-Dihydro-1-methylisocanthin-6-one (15). 15 (0.052 g, 66%) was prepared by the procedure described for **11** on a 0.17 mmol scale, with heating at 180±2°C for seven days. Flash chromatography gave a tan solid: mp 162–163°C; R_f 0.37; IR ν 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.55 (d, 1H, J=7.9 Hz, H-7.9), Hz, H-8), 8.39 (br, s, 1H, H-3), 8.10 (d, 1H, J=7.2 Hz, H-11), 7.55 (dt, 2H, J=1.8, 7.9 Hz, H-9, H-10), 3.33 (t, 2H, J=7.5 Hz, CH_2), 3.11 (t, 2H, J=7.7 Hz, CH_2), 3.01 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 20.67, 22.84, 32.45, 111.36, 115.31, 120.03, 121.97, 122.49, 124.55, 125.84, 127.67, 136.66, 142.59, 150.30, 167.82: MS m/z 236 [M^+]. HRMS for $C_{15}H_{13}N_2O$ [M+H]$^+$ requires: 237.1028. Found: 237.1034.

1-Methylisocanthin-6-one (6). 6 (0.046 g, 93%) was prepared by the procedure described for **4** on a 0.21 mmol scale. Flash chromatography gave a white solid: mp 219–220°C (dec.); R_f 0.35; IR ν 1676 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.86 (br s, 1H, H-3), 8.78 (d, 1H, J=8.2 Hz, H-8), 8.18 (d, ^{1}H J=7.2 Hz, H-11), 7.94 (d, 1H, J=9.6 Hz, H-5), 7.64 (dt, 2H, J=2.3, 7.5 Hz, H-9, H-10), 6.90 (d,1H, J=9.6 Hz, H-4), 3.15 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 23.16, 112.15, 116.14, 122.55, 123.14, 124.36, 125.80, 128.30, 128.94, 136.99, 145.09, 145.61, 154.05, 159.65; MS m/z 234 [M^+]. HRMS for $C_{15}H_{11}N_2O$ [M+H]$^+$ requires: 235.0871. Found: 235.0859.

3-Formyl-1-(4-pentynyl)-indole (16). Indole-3-carboxaldehyde (6.34 g, 44.0 mmol) was converted by the method of Eberle et al. to a tan solid (9.3 g, 100%). Column chromatography gave **16** as a white solid: mp 55–56°C (lit.[15] 53–54°C); IR ν 1646 cm^{-1};^{1}H NMR ($CDCl_3$) δ 9.99 (s, 1H, CHO), 8.24 (d, 1H, H-7), 8.13 (s, 1H, H-2), 7.60 (d, 1H, H-4), 7.30 (m, 2H, H-5, H-6), 4.44 (t, 2H, NCH_2), 2.49 (t, 1H, $C{\equiv}CH$), 2.3–2.0 (m, 4H, $CH_2CH_2C{\equiv}CH$); ^{13}C NMR ($CDCl_3$) δ 13.80, 27.92, 34.94, 69.84, 81.89, 116.16, 12.12, 122.56, 125.30, 126.36, 127.14, 130.18, 136.03, 169.45, 193.57, MS m/z 211 [M^+].

3-Formyl-1-(4-pentynyl)-indole methoxime (17). 17 (0.236 g, 98%) was prepared by the procedure described for **9** on a 1.0 mmol scale to give a yellow oil: IR ν 1612 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.16 (d, 1H, H-7), 8.12 (s, 1H, H-2), 7.75 (d, 1H, H-4), 7.23 (m, 2H H-5, H-6), 4.26 (t, 2H, NCH_2), 3.98 (s, 3H, $NOCH_3$), 2.12 (t, 1H, $C{\equiv}CH$), 2.05 (m, 4H, $CH_2CH_3C{\equiv}CH$); ^{13}C NMR ($CDCl_3$) mixture of two diastereomers, E (62%) δ 15.61, 28.31, 44.74, 61.65, 69.87, 82.58, 108.91, 109.45, 120.93, 122.44, 122.93, 125.37, 130.29, 136.80, 143.97 and Z (37%) δ 15.75, 28.48, 45.01, 62.16, 69.78, 82.58, 105.94, 109.73, 118.37, 120.76, 122.44, 127.32, 133.72, 135.12, 138.56; MS m/z 240 [M^+]. HRMS for $C_{15}H_{17}N_2O$ [M+H]$^+$ requires: 241.1341. Found: 241.1330.

Isocanthine (3). To an argon-swept conical vial were added **17** (0.100 g, 0.42 mmol) and sulfolane (2.0 mL). The reaction flask was capped and placed in a preheated aluminum block at 285±2°C for 2 h. this reaction sequence was repeated three more times. The combined reaction mixtures were diluted with water (100 mL) and extracted with ether (4×25 mL). The combined organic phase was washed with water (4×100 mL) to remove residual sulfolane, dried over sodium sulfate, and concentrated in vacuo to give an orange–red oil (0.203 g). Flash chromatography gave **3** (0.027 g, 8%) as a tan solid: mp 268–270°C (dec.); (lit.[6b] 270°C with dec.); R_f 0.21; IR ν 2933, 1580, 1475, 1243, 1140, 777 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.15 (br s, 1H, H-1), 8.31 (br s, 1H, H-3), 8.15 (d, 1H, J=6.2 Hz, H-8), 7.53 (t, 1H, J=7.1 Hz, H-11), 7.41 (d, 1H, J=8.1 Hz, H-9), 7.32 (t, 1H, J=7.9 Hz H-10), 4.24 (t, 2H, J=5.7 Hz, NCH_2), 3.08 (t, 2H, J=6.2 Hz, CH_2), 2.39–2.29 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 21.97, 29.68, 41.01, 109.02, 116.66, 117,38, 120.77, 121.63, 126.91, 139.27, 139.46, 140.33, 142.75; MS m/z 208 [M^+]. HRMS for $C_{14}H_{13}N_2$ [M+H]$^+$ requires: 209.1077. Found: 209.1065.

4,5-Dihydroisocanthin-6-thione (20). To an argon-swept flask were added **11** (0.040 g, 0.170 mmol), Lawesson's reagent (0.034 g, 0.085 mmol), and toluene (3.0 mL). The reaction flask was fitted with a Vigreux column and a drying tube. The mixture was magnetically stirred for 24 h at 100°C, cooled, and concentrated in vacuo to give a residual yellow oil and orange solids. Flash chromatography gave **20** (0.030 g, 70% yield) as a yellow–orange solid: mp 121–123°C; R_f 0.32; IR ν 1648 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.40 (d, 1H, J=8.2 Hz), 8.73 (br s, 1H), 8.08 (m, 1H), 7.60 (dt, 2H, J=7.5, 15.3 Hz), 3.56 (m, 2H, CH_2), 3.18 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6) δ 23.56, 55.14, 112.46, 113.28, 113.52, 121.68, 127.61, 128.37, 132.19, 132.37, 135.71, 136.47, 161.06, 173.38, MS m/z 238 [M^+]. HRMS for $C_{14}H_{11}N_2S$ [M+H]$^+$ requires; 239.0643. Found: 239.0638.

Isocanthine (3). To an argon-swept flask were added **20** (0.020 g, 0.084 mmol) and 95% EtOH (5 mL). To the magnetically stirred solution was added via Pasteur pipette a suspension of Raney Ni (W-2, 50% dispersion in H_2O, in excess). The mixture was stirred at reflux for 3.5 h, cooled, and suction filtered through a pad of Celite (5.0 g). The solids were washed with 95% EtOH (3×10 mL) and the combined filtrate was concentrated in vacuo to give **3** as a white solid (0.005 g, 29%). Physical data were identical to the sample obtained above.

3-Acetyl-1-(4-pentynyl)-indole (18). To an argon-swept test tube were added 5-chloro-1-pentyne (0.246 g,

2.4 mmol), 3-acetylindole (0.318 g, 2.0 mmol), anhydrous potassium carbonate (0.280 g, 2.0 mmol), and DMF (2 mL). The mixture was stirred for 23 h at 70–75°C in an oil bath, cooled, diluted with water (40 mL), and extracted with CH_2Cl_2 (3×10 mL). The combined organic phase was washed with water (4×20 mL), dried over sodium sulfate, and concentrated in vacuo to give a yellow oil. Flash chromatography gave **18** (0.337 g, 75%) as a yellow oil: IR ν 1643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.37 (m, 1H, *H*-7), 7.99 (s, 1H, *H*-2), 7.86 (d, 1H, *H*-4), 7.30 (m, 2H, *H*-5 *H*-6), 4.28 (t, 2H, NCH_2), 2.51 (s, 3H, CH_3), 2.15 (m, 1H C≡CH), 2.05–1.93 (m, 4H, CH_2CH_2C≡CH); ^{13}C NMR ($CDCl_3$) δ 15.53, 27.47, 28.03, 45.16, 70.11, 82.24, 109.66, 116.93, 122.42, 122.53, 123.19, 126.27, 134.94, 136.53, 192.83; MS *m/z* 225 [M^+]. HRMS for $C_{15}H_{16}NO$ $[M+H]^+$ requires: 226.1232. Found: 226.1226.

3-Acetyl-1-(4-pentynyl)-indole methoxime (19). 19 (0.763 g, 76%) was prepared by the procedure described for **9** on a 3.9 mmol scale to give a white solid: mp 61–62°C; IR ν 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.35 (m, 1H, *H*-7), 8.23 (s, 1H, *H*-2), 7.38 (d, 1H, *H*-4), 7.25 (m, 2H, *H*-5, *H*-6), 4.30 (t, 2H, NCH_2), 4.06 (s, 3H, NOCH_3), 2.28 (s, 3H, CH_3), 2.21 (m, 1H, C≡C*H*), 2.05 (m, 4H, CH_2CH_2C≡CH); ^{13}C NMR ($CDCl_3$) δ 12.65, 15.35, 28.16, 44.40, 61.39, 69.62, 82.54, 109.05, 112.53, 120.50, 122.38, 123.31, 125.09, 128.33, 136.67, 151.38; MS *m/z* 254 [M^+]. Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.39; H, 7.35; N, 10.81. An attempted conversion of **19** to **5** on a 0.39 mmol scale, following the initial procedure described for **3**, failed to provide the desired Diels–Alder adduct based on GC–MS analysis of the reaction products.

4,5-Dihydro-1-methylisocanthin-6-thione (21). 21 (0.072 g, 84%) was prepared by the procedure described for **20** on a 0.34 mmol scale. Flash chromatography gave a yellow–orange solid: mp 68–71°C; R_f 0.44; IR ν 1642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.45 (d, 1H, *J*=8.2 Hz), 8.58 (br s, 1H), 8.05 (d, 1H, *J*=7.4 Hz), 7.63 (dt, 2H, *J*=6.5, 19.0 Hz), 3.54 (t, 2H, *J*=7.4 Hz, CH_2), 3.17 (m, 2H, CH_2), 3.08 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 14.05, 23.06, 55.16, 112.65, 113.34, 113.59, 122.68, 132.23, 132.41, 132.79; MS *m/z* 252 [M^+]. HRMS for $C_{15}H_{13}N_2S$ $[M+H]^+$ requires: 253.0799. Found: 253.0791.

1-Methylisocanthine (5). 5 (0.009 g, 26% yield) was prepared by the procedure described for **3** on a 0.16 mmol scale to give a brown waxy oil: single component by TLC (R_f 0.21) and capillary GC; IR ν 2921, 1636, 1452, 1383, 1079, 753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.31 (br s, 1H, *H*-3), 8.16 (d, 1H, *J*=7.9 Hz, *H*-8), 7.57 (t, 1H, *J*=7.1 Hz, *H*-11), 7.50 (d, 1H, *J*=8.0 Hz, *H*-9), 7.42 (t, 1H, *J*=7.9 Hz, *H*-10) 4.28 (t, 2H, *J*=5.5 Hz, NCH_2), 3.09 (m, 2H, CH_2), 3.07 (s, 3H, CH_3), 2,36 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 14.10, 22.70, 29.65, 41.26, 109.84, 110.80 115.75, 116.00, 121.66, 122.42, 122.89, 127.94, 140.80, 143.70; MS *m/z* 222 [M^+]. HRMS for $C_{15}H_{15}N_2$ $[M+H]^+$ requires: 223.1235. Found: 223.1223.

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