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A versatile route to benzocanthinones

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Abstract—Benzocanthinone (**1**) and five analogs (**10**, **12–15**) were prepared by radical-induced cyclizations of halo *N*-aroyl derivatives of β-carboline and carbazole.

1. Introduction

Benzocanthinone (**1**; 9*H*-benzo[*c*]indolo[3,2,1-*ij*][1,5]-naphthyridin-9-one), derived from *Calycanthus floridus* L., was first reported in 1938.[1] Both **1** and its tetracyclic analog, canthin-6-one (**2**; 6*H*-indolo[3,2,1-*e*][1,5]-naphthyridin-6-one), belong to a large family of β-carboline alkaloids, which exhibit a broad range of pharmacological activity.[2] Of the three reported syntheses of **1**, two proceeded in poor yields (0.4 and 9%),[1,3] and the third involved an isolation step unsuitable for scale-up purposes (filtration of mercury metal).[4] While new routes to **2** and its analogs continue to be developed,[5] there is to date no satisfactory route to pentacyclic alkaloids such as **1** (Fig. 1).

As part of our earlier interest in canthinones, we explored an intramolecular Diels–Alder pathway to **1**, which would simultaneously generate rings C and D.[6] The cycloaddition, however, could not be effected even under stringent conditions.[6a] Retrosynthetic analysis led us to consider the alternative paths shown in Scheme 1. Such disconnections generated β-carboline derivatives containing a pendent ring E. The final step would be closure of ring D by either amide formation or aryl–aryl coupling. Our interest was in devising a methodology not only for **1**, but also for a series of isomers, in which ring E contained the peripheral nitrogen atom. The three prior preparations of **1** were based on condensations of phthalic acid derivatives with tryptophan derivatives and thus, were incompatible with the latter objective.

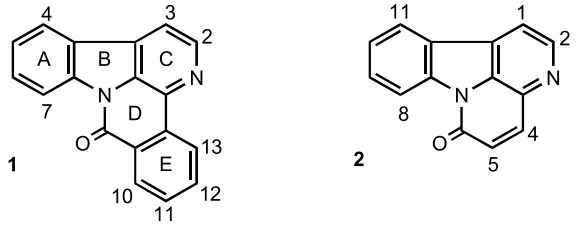

Figure 1. Benzocanthinone (**1**) and canthinone (**2**).

2. Results and discussion

We began by exploring path a and replicating Bracher and Hildebrand's conversion of 1-chloro-β-carboline (**3**) to 1-phenyl-β-carboline by Suzuki coupling.[7] In our hands, this reactivity could not be extended to 2-methoxycarbonylphenylboronic acid (**A**, X=OMe), 2-carboxyphenylboronic acid (**A**, X=OH), or 2-cyanophenylboronic acid (**A**, COX=CN). However, we anticipated that cyclization of either **B** or **C** could be effected by tributylstannane (path b), a process for which there was ample precedent.[8]

Our initial intermediate target was a type **C** molecule, given the ready availability of the starting materials. The subsequent radical-induced ring closure posed regioselectivity options at C(1) and C(8) of the β-carboline moiety, but the strong preference for radical attack at C(1) rather than at C(8) with isoquinoline augured well.[9] In the event, β-carboline (**4**) was converted to **5a–c**, which were subjected to radical, oxidative cyclization (Scheme 2). The reaction mixtures contained two coupling products, **1** and **6**, and, in the case of **5a** and **5c**, appreciable amounts of **4** resulting from reductive cleavage. GC–MS analysis

Keywords: Benzocanthinone; Pentacyclic alkaloids; Radical-induced cyclization.
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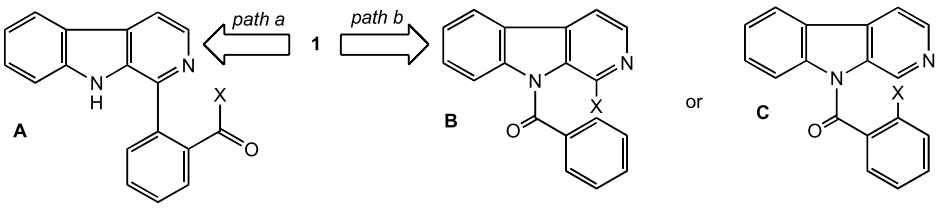
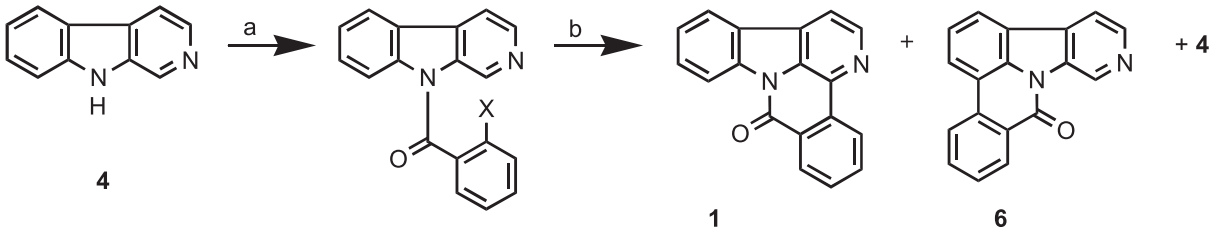


Scheme 1.



5a (X = Cl, 96%)
5b (X = Br, 71%)
5c (X = I, 76%)

Scheme 2. Reagents and conditions: (a) NaH, DMF, rt, then 2-halobenzoyl chloride, DMAP, DMF, 65 °C; (b) Bu_3SnH, ACN, toluene, reflux; see Table 1 for product conversions.

established that **1** and **6** had comparable retention times, identical masses, and the same fragmentation pattern. The identity of **1** was assigned by comparison with an authentic sample, and the structure of **6** was based on the above characteristics. The product ratios were a function of the halo substituent (Table 1). The regioselectivities related inversely to the aryl-halogen bond strengths,[10] whereby **5c** afforded the lowest energy aryl radical, which exhibited the highest selectivity between C(1) and C(8) of the β-carboline moiety.

The above results dictated that a type **B** intermediate was necessary for an unambiguous route to **1**. Accordingly, 1-chloro-β-carboline (**3**) was converted to amide **7**, which afforded **1** as the only observed product (Scheme 3).

Table 1. Percent composition of product mixtures in Schemes 2–9[a]

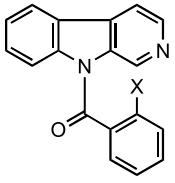
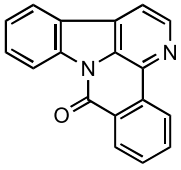
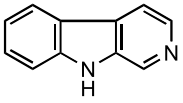
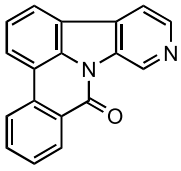
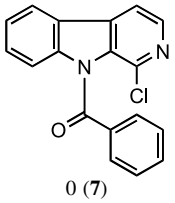
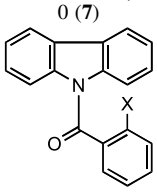
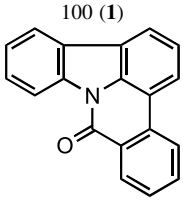
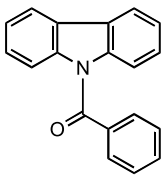
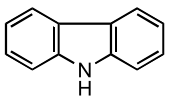
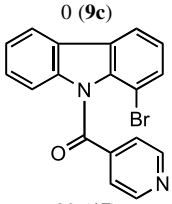
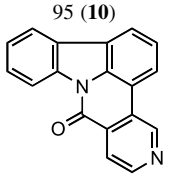
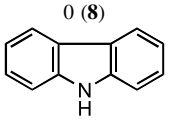
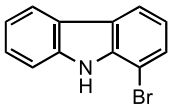
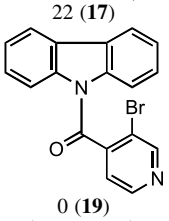
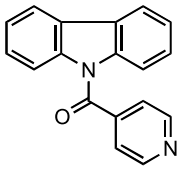
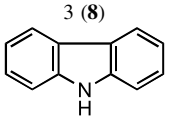
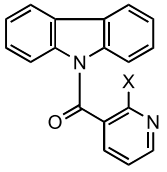
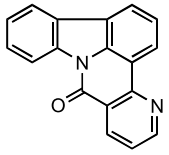
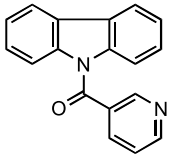
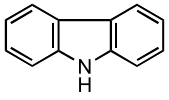
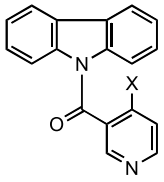
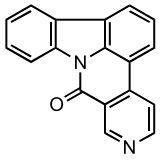
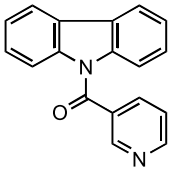
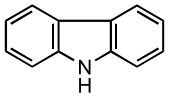
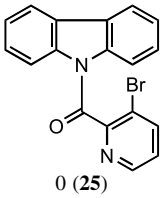
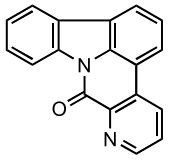
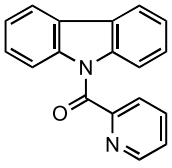
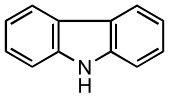
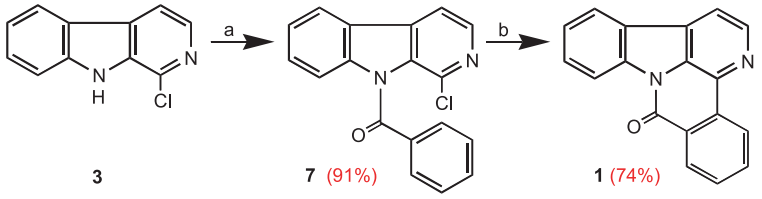
	Amide	Cyclization	Dehalogenation	Amide cleavage	Other
					
X					
Cl	51 (**5a**)	13 (**1**)		22 (**4**)	14 (**6**)
Br	0 (**5b**)	69 (**1**)		0 (**4**)	31 (**6**)
I	0 (**5c**)	42 (**1**)		51 (**4**)	7 (**6**)
					
	0 (**7**)	100 (**1**)			
					
X					
Cl	75 (**9a**)	18 (**10**)	0 (**11**)	7 (**8**)	
Br	0 (**9b**)	>99 (**10**)	0 (**11**)	0 (**8**)	

Table 1 (*continued*)

	Amide	Cyclization	Dehalogenation	Amide cleavage	Other
I	0 (**9c**) 	95 (**10**) 	5 (**11**)	0 (**8**) 	
	22 (**17**) 	69 (**13**)		3 (**8**) 	6 (**16**)
	0 (**19**) 	93 (**13**) 	3 (**20**) 	4 (**8**) 	
X Cl Br	6 (**21a**) 0 (**21b**) 	90 (**12**) 99 (**12**) 	2 (**22**) 1 (**22**) 	2 (**8**) 0 (**8**) 	
X Cl Br	67 (**24a**) 9 (**24b**) 	28 (**14**) 88 (**14**) 	3 (**22**) 2 (**22**) 	2 (**8**) 1 (**8**) 	
	0 (**25**)	37 (**15**)	13 (**26**)	5 (**8**)	16 (**27a**)[b] 14 (**27b**)[b] 8 (**27c**)[b]

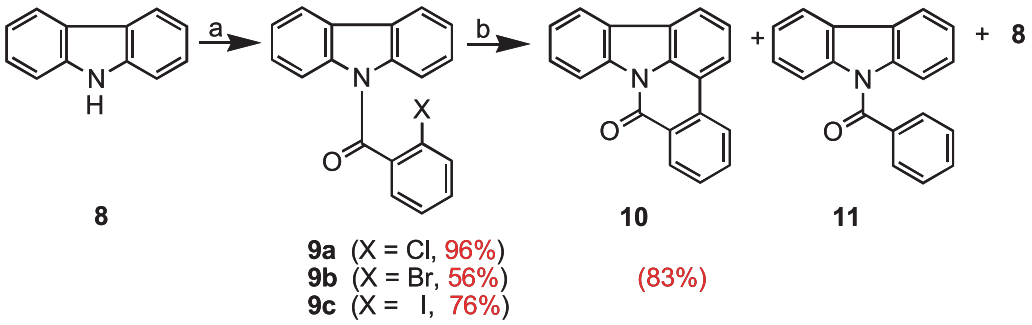
[a] Standard conditions: see Section 4.4.1.
[b] Values not calibrated.



Scheme 3. Reagents and conditions: (a) NaH, DMF, rt, then benzoyl chloride, DMAP, DMF, 120 °C; (b) Bu_3SnH, ACN, toluene, reflux; see Table 1 for product conversion.

With this new route to **1** achieved, we extended the methodology to analogs and isomers of **1**. Our next objective was **10** (9*H*-indolo[3,2,1-*de*]phenanthridin-9-one), the carbocyclic analog of **1**. It had previously been prepared from carbazole (**8**) via Pschorr cyclization in 1% yield and from the photochemical rearrangement of 9-(2-halobenzoyl)-carbazoles in 23 and 67% yields.[11] Since the latter process paralleled the present route, we prepared three derivatives (**9a–c**) of **8** and converted them to **10** (Scheme 4). Under our standard conditions **9b** and **9c** gave high conversion rates to **10**, but **9a** was poorly reactive. In some cases, minor amounts of carbazole (**8**) and dehalogenated amide (**11**) were generated. The latter process is frequently observed in such cyclizations.[8]

The major application of this methodology was to a family



Scheme 4. Reagents and conditions: (a) NaH, DMF, rt, then 2-halobenzoyl chloride, DMAP, DMF, 65 °C; (b) Bu_3SnH, ACN, toluene, reflux; see Table 1 for product conversions.

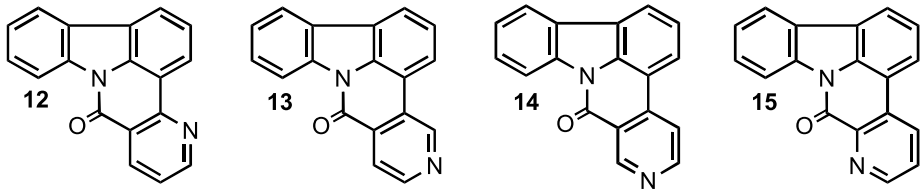


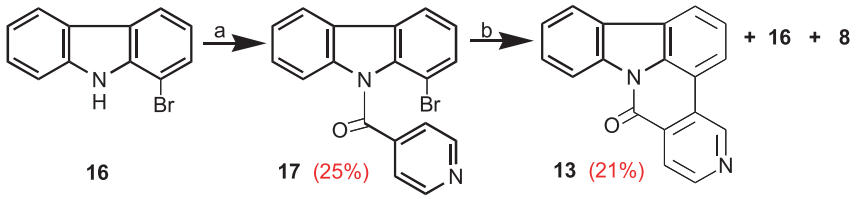
Figure 2.

of isomers **12**–**15**,[12] suitable for structure–activity relationship studies (Fig. 2). Retrosynthetically, the least complicated target was **13**, since the symmetry of the 4-pyridinyl ring E accommodated both type **B** and **C** precursors. The former route, starting from 1-bromocarbazole (**16**), afforded **13** in good yield accompanied by only minor amounts of amide-cleaved side products (Scheme 5). The product mixture contained only a single product (**13**) with *m*/*z* 270. The structure was consistent with a mechanistic process involving 6-*endo* radical cyclization. Although, a 5-*exo* route has been detected in related cyclizations,[13] in the present case such a pathway could only be operative if the spiro radical intermediate never rearranged to **14**. The alternate route to **1** via a type **C** precursor proceeded without ambiguity, starting from 3-bromo-4-pyridinecarboxylic acid (**18**) (Scheme 6).

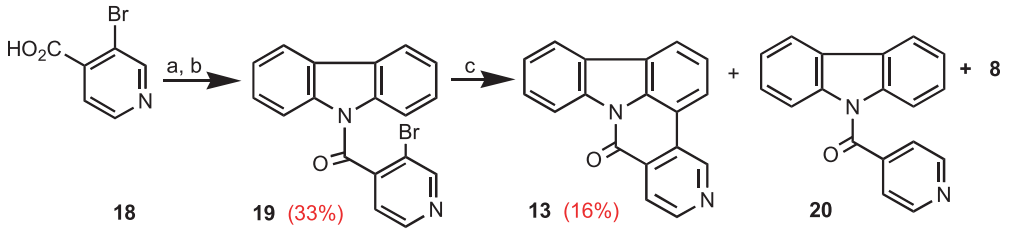
Routes to the remaining isomers (**12**, **14**, **15**) were feasible only with type **C** precursors. For **12**, amide **21a** was converted to **21b** by the method of Schlosser and Cottet.[14] Both amides were readily cyclized to **12** (Scheme 7).

The analogous route to **14** required 4-chloro-3-pyridinecarboxylic acid (**23**). It was converted to **24a** and **24b** and both precursors afforded **14** (Scheme 8).

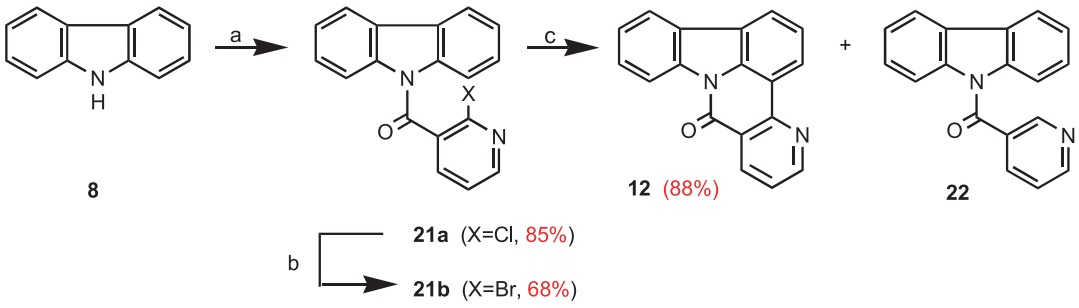
Finally, the standard protocol was utilized for the preparation of **15**. 3-Bromo-2-pyridinecarboxylic acid was



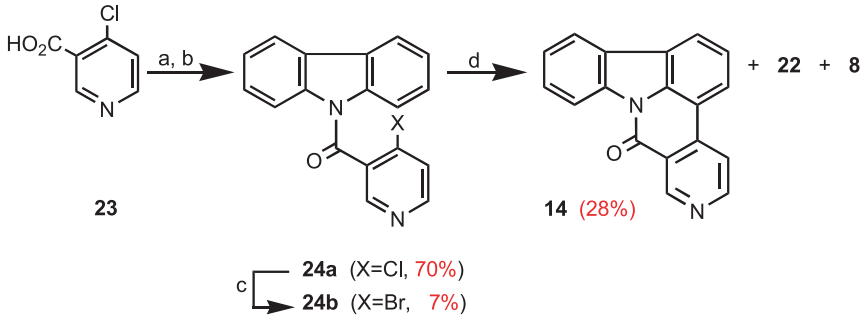
Scheme 5. Reagents and conditions: (a) NaH, DMF, rt, then 4-pyridinecarbonyl chloride, DMAP, DMF, 75 °C; (b) Bu_3SnH, ACN, toluene, reflux; see Table 1 for product conversions.



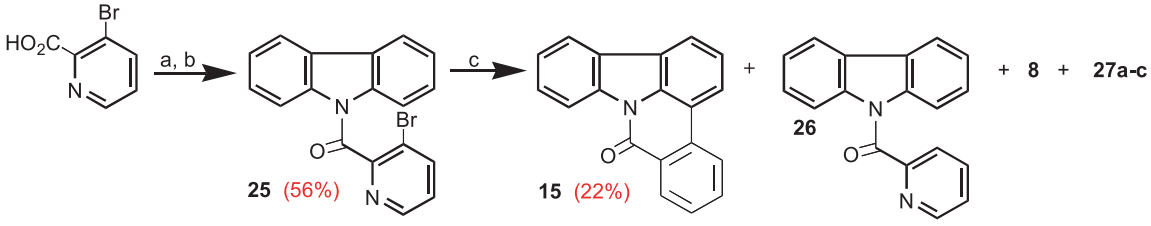
Scheme 6. Reagents and conditions: (a) $SOCl_2$, reflux; (b) **8**, NaH, DMF, rt, then DMAP, DMF, 65 °C; (c) Bu_3SnH, ACN, toluene, reflux; see Table 1 for product conversions.



Scheme 7. Reagents and conditions: (a) NaH, 15-crown-5, THF, rt, then 2-chloro-3-pyridinecarbonyl chloride, DMAP, DMF, rt; (b) Me_3SiBr, EtCN, reflux; (c) Bu_3SnH, ACN, toluene, reflux; see Table 1 for product conversions.



Scheme 8. Reagents and conditions: (a) $SOCl_2$, reflux; (b) **8**, NaH, 15-crown-5, THF, rt, then DMAP, rt; (c) Me_3SiBr, EtCN, reflux; (d) Bu_3SnH, ACN, toluene, reflux; see Table 1 for product conversions.



Scheme 9. Reagents and conditions: (a) $SOCl_2$, reflux; (b) **8**, NaH, 15-crown-5, THF, rt, then DMAP, rt; (c) Bu_3SnH, ACN, toluene, reflux; see Table 1 for product conversions.

converted without difficulty to amide **25**, but the cyclization step afforded an appreciable amount of side products (Scheme 9). Although the side products (**27a–c**) were not isolated, by GC–MS analysis they consisted of three compounds with the same mass (*m*/*z* 362) and comparable retention times. The reduced amount of **15** (37%) and the increased amounts of **26** (13%) and **27a–c** (38%) can be attributed to the intermediate pyridinyl radical adopting a conformation, which facilitated intermolecular processes leading to **26** and **27a–c** via reaction with tributylstannane and solvent, respectively. This more reactive conformer reflected the reduction in nonbonded interaction between H(1) of the carbazole moiety and the nitrogen atom of ring E compared to all other cases in this study. It was noteworthy that in none of the other five cyclizations was a side product observed with *m*/*z* 362. The isomeric **27a–c** were considered to have resulted from radical pyridinylation of toluene.

3. Conclusion

A short route to a series of isomeric benzocanthinones has been developed. In each case, the key step was an intramolecular, radical-induced, oxidative cyclization. The best reactivities were obtained when the halogen substituent (Br > Cl) was alpha to a pyridinyl nitrogen or a carbonyl group. The conversations, except for **15**, were good to excellent; the isolated yields were poor to good.

4. Experimental

4.1. General procedures

Melting points were taken on a modified Hershberg apparatus with matched Anschütz thermometers and are uncorrected. NMR spectra were measured in $CDCl_3$ on a Bruker Avance DRX 500 spectrometer with a Hewlett Packard (HP) ×1100 Workstation running under XWINMR version 3.5; chemical shifts are reported in ppm downfield relative to internal tetramethylsilane, and coupling constants are reported in hertz (Hz). GC–MS analyses were performed on a HP 6890 gas chromatography system with a HP-5MS crosslinked diphenyl(5%) dimethyl(95%)polysiloxane capillary column (30 m × 0.25 mm × 0.25 μm film), a 5973 mass selective detector,

and a HP Kayak XA computer. FT-IR spectra were recorded on a Perkin Elmer Spectrum One spectrophotometer with a Dell Optiplex GX1 computer. HRMS analyses were performed by the Nebraska Center for Mass Spectrometry at the University of Nebraska-Lincoln. Elemental microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Liquid injections were made with a KD Scientific 100 Series syringe pump. Tetrahydrofuran (THF) and toluene were purified by the method of Grubbs and co-workers;[15] dimethylformamide (DMF, 99.8%) was sparged with argon for 3 h and stored over 4A molecular sieves. Products were purified by recrystallization or by medium-pressure liquid chromatography with silica gel as stationary phase and hexanes–ethyl acetate as mobile phase; all compounds were determined to be >98% pure by capillary GLC and ^{1}H NMR spectroscopy.

4.2. Starting materials

Compounds **3**,[7] **9ac**,[11] **11**,[11] **16**,[16] **18**,[17] and **24**[18] were prepared by literature procedures; their physical and spectral data matched the reported values. 3-Bromo-2-pyridinecarboxylic acid was a gift from Aventis Pharmaceutical Co. All other chemicals used in this study were commercially available.

4.3. Typical procedures for the preparation of amides

4.3.1. 9-Benzoyl-1-chloro-β-carboline (7). Method A. To a stirred solution of 1-chloro-β-carboline (**3**)[7] (1.317 g, 6.50 mmol) in DMF (100 mL) under argon was added sodium hydride (0.432 g of 60% dispersion in mineral oil; 0.259 g, 10.6 mmol). The slurry was stirred at room temperature for 20 min and to it was added dropwise a solution of benzoyl chloride (1.096 g, 7.80 mmol) and 4-dimethylaminopyridine (DMAP) (0.079 g, 0.65 mmol) in DMF (25 mL). The reaction mixture was stirred at 70 °C for 15 h, concentrated at reduced pressure, diluted with water (150 mL), neutralized with saturated aqueous sodium bicarbonate, and extracted with chloroform. The combined extract was washed with water, dried over anhydrous Na_2SO_4, and evaporated at reduced pressure to give a viscous, residual liquid (1.81 g, 91%), which was crystallized to give the analytical sample of **5a**: mp 137.0–138.0 °C (2-propanol); IR (film) 1699 cm^{-1}; ^{1}H NMR δ 8.40 (1H, d, J=5.0 Hz), 8.10 (1H, dd, J=8.0, 0.6 Hz), 7.94 (1H, d, J=5.0 Hz), 7.85 (2H, dd, J=8.0, 1.2 Hz), 7.70 (1H, t, J=7.5 Hz), 7.56–7.47 (3H, m), 7.44–7.37 (2H, m); ^{13}C NMR δ 168.6, 142.1, 141.2, 137.1, 135.0, 134.8, 134.3, 133.5, 130.3, 129.9, 129.2, 123.3, 122.9, 121.7, 113.9, 113.8; MS (*m*/*z*) 308 (M$^+$ ^{37}Cl, 8%), 306 (M$^+$ ^{35}Cl, 24), 105 (100), 77 (37). Calcd for $C_{18}H_{11}Cl\cdot N_2O$: C, 70.48; H, 3.62; N, 9.13. Found: C, 69.79; H, 3.77; N; 9.03.

4.3.2. 9-(2-Chlorobenzoyl)-β-carboline (5a). Colorless solid (0.286 g, 96%): mp 157.0–158.0 °C; IR (film) 1686 cm^{-1}; ^{1}H NMR δ 8.73 (1H, br s), 8.60 (1H, d, J=5.0 Hz), 8.07 (1H, dd, J=10.0, 1.0 Hz), 7.90 (1H, dd, J=5.0, 1.0 Hz), 7.62–7.55 (3H, m), 7.54–7.43 (4H, m); ^{13}C NMR δ 166.1, 144.1, 139.1, 135.7, 135.1, 132.9, 132.4, 131.3, 130.7, 130.0, 128.8, 127.9, 124.6, 121.3, 114.2; MS (*m*/*z*) 308 (M$^+$ ^{37}Cl, 6%), 306 (M$^+$ ^{35}Cl, 18), 141 (34), 139 (100), 111 (25). HRMS for $C_{18}H_{12}Cl\cdot N_2O$ [M+H]$^+$ requires: 307.0638. Found: 307.0642.

4.3.3. 9-(2-Bromobenzoyl)-β-carboline (5b). Pale yellow solid (0.254 g, 71%): mp 139.4–140.0 °C; IR (film) 1685 cm^{-1}; ^{1}H NMR δ 8.61 (1H, s), 8.07 (1H, d, J=8.0 Hz), 7.91 (1H, d, J=4.0 Hz), 7.74 (1H, d, J=8.0 Hz), 7.57 (1H, d, J=4.0 Hz), 7.55–7.51 (4H, m), 7.50–7.43 (3H, m); ^{13}C NMR δ 166.8, 144.0, 139.0, 137.8, 133.8, 132.9, 132.5, 130.1, 128.8, 128.5, 124.6, 121.3, 119.7, 116.3; MS (*m*/*z*) 352 (M$^+$ ^{81}Br, 13%), 350 (M$^+$ ^{79}Br, 13), 185 (99), 183 (100), 157 (23), 155 (24). HRMS for $C_{18}H_{12}Br\cdot N_2O$ [M+H]$^+$ requires: 351.0133. Found: 351.0141.

4.3.4. 9-(2-Iodobenzoyl)-β-carboline (5c). Colorless solid (0.125 g, 76%): mp 135.8–137.0 °C; IR (film) 1684 cm^{-1}; ^{1}H NMR δ 8.68 (1H, br s), 8.59 (1H, d, J=5.0 Hz), 8.04 (1H, d, J=8.0 Hz), 7.96 (1H, d, J=8.0 Hz), 7.87 (1H, d, J=5.0 Hz), 7.58 (1H, t, J=7.4 Hz), 7.53–7.40 (3H, m), 7.32 (1H, t, J=7.7 Hz); ^{13}C NMR δ 168.3, 144.1, 141.7, 140.2, 139.1, 138.0, 135.1, 132.9, 132.3, 130.0, 129.1, 128.5, 124.7, 124.6, 121.3, 116.4, 114.2; MS (*m*/*z*) 398 (M$^+$, 13%), 231 (100), 203 (22). HRMS for $C_{18}H_{12}I\cdot N_2O$ [M+H]$^+$ requires: 398.9994. Found: 398.9981.

4.3.5. 1-Bromo-9-(4-pyridinecarbonyl)-carbazole (17). Pale yellow solid (0.050 g, 25%): mp 129.0–130.5 °C; IR (film) 1697 cm^{-1}; ^{1}H NMR δ 8.81 (2H, d, J=3.9 Hz), 8.03 (2H, m), 7.58 (3H, m), 7.40 (3H, m), 7.29 (1H, m); ^{13}C NMR δ 167.9, 151.1, 151.0, 142.8, 140.3, 138.4, 131.7, 129.1, 127.9, 125.1, 125.0, 123.7, 122.8, 120.6, 120.5, 119.3, 113.4, 108.7; MS *m*/*z* 352 (M$^+$ ^{81}Br, 41%), 350 (M$^+$ ^{79}Br, 43), 165 (21), 164 (22), 106 (100), 78 (33). Calcd for $C_{18}H_{11}Br\cdot N_2O$: C, 61.56; H, 3.16; N, 7.98. Found: C, 61.50; H, 3.39; N, 7.90.

4.3.6. 9-(3-Bromo-4-pyridinecarbonyl)-carbazole (19). Tan solid (0.175 g, 33%): mp 125.5–126.0 °C; IR (film) 1678 cm^{-1}; ^{1}H NMR δ 8.94 (1H, s), 8.79 (1H, d, J=4.2 Hz), 8.00 (2H, d, J=7.8 Hz), 7.47 (1H, d, J=4.2 Hz), 7.44–7.27 (6H, m); ^{13}C δ 164.7, 153.2, 149.3, 145.4, 138.2, 127.6, 127.0, 124.8, 122.5, 120.1, 115.8; MS *m*/*z* 352 (M$^+$ ^{81}Br, 64%), 350 (M$^+$ ^{79}Br, 67), 271 (60), 186 (88), 184 (100), 166 (25), 158 (26), 140 (28). Calcd for $C_{18}H_{11}Br\cdot N_2O$: C, 61.56; H, 3.16; N, 7.98. Found: C, 62.02; H, 3.44; N, 7.86.

4.3.7. 9-(2-Bromobenzoyl)-carbazole (9b). Method B. To a stirred slurry of sodium hydride (0.084 g of a 60% dispersion in mineral oil; 0.0504 g, 2.10 mmol) in THF (20 mL) under argon were added a solution of carbazole (0.334 g, 2.00 mmol) and 15-crown-5 (0.463 g, 2.10 mmol) in THF (8 mL). The slurry was stirred at room temperature for 30 min and to it was added dropwise a solution of 2-bromobenzoyl chloride (0.483 g, 2.20 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 17 h, concentrated at reduced pressure, diluted with brine (20 mL), neutralized with saturated aqueous sodium bicarbonate, and extracted with dicloromethane. The combined extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated at reduced pressure to give an orange solid, which was recrystallized to give **9b** (0.394 g, 56%): mp 102.5–103.0 °C (95% ethanol);

IR (KBr) 1678 cm^{-1}; ^1H NMR δ 8.01–8.00 (1H, m), 7.99–7.97 (1H, m), 7.73 (1H, dm, $J=7.6$ Hz), 7.55–7.45 (4H, m), 7.41–7.29 (5H, m); ^{13}C NMR δ 167.2, 138.5, 138.4, 133.6, 132.0, 128.8, 128.2, 127.3, 126.7, 124.2, 119.8, 115.9; MS *m/z* 351 (M^+ ^{81}Br, 30%), 349 (M^+ ^{79}Br, 29), 185 (94), 183 (100), 157 (27), 155 (29), 140 (21). Calcd for $C_{19}H_{12}Br{\cdot}NO$: C, 65.16; H, 3.45; N, 4.00. Found: C, 64.88; H, 3.68; N. 4.08.

4.3.8. 9-(4-Pyridinecarbonyl)-carbazole (20). Colorless solid (0.052 g, 21%): mp 184.5–185.0 °C; IR (film) 1679 cm^{-1}; ^1H δ 8.85 (2H, d, $J=5.0$ Hz), 7.98 (2H, d, $J=7.0$ Hz), 7.54 (2H, d, $J=5.0$ Hz), 7.49 (2H, d, $J=8.0$ Hz), 7.37 (2H, t, $J=7.0$ Hz), 7.32 (2H, d, $J=8.0$ Hz); ^{13}C δ 167.4, 151.1, 143.4, 138.7, 127.3, 126.6, 124.3, 122.3, 120.2, 116.0; MS *m/z* 272 (M^+48%), 106 (100), 78 (50). HRMS for $C_{18}H_{13}N_2O$ $[M+H]^+$ requires: 273.1028. Found: 273.1018.

4.3.9. 9-(2-Chloro-3-pyridinecarbonyl)-carbazole (21a). Tan solid (0.987 g, 85%): mp 129.0–131.0 °C; IR (film) 1677 cm^{-1}; ^1H δ 8.67 (1H, dd, $J=5.0$, 2.0 Hz), 8.03–7.97 (2H, m), 7.90 (1H, dd, $J=7.6$, 2.0 Hz), 7.53–7.45 (2H, m), 7.44–7.30 (4H, m); ^{13}C NMR δ 164.7, 151.5, 147.9, 138.2, 137.8, 132.9, 127.5, 126.8, 124.5, 123.0, 120.0, 115.6; MS *m/z* 308 (M^+ ^{37}Cl, 7%), 306 (M^+ ^{35}Cl, 19), 142 (28), 140 (100), 112 (34). Calcd for $C_{18}H_{11}Cl{\cdot}N_2O$: C, 70.48; H, 3.62; N, 9.13. Found: C, 70.26; H, 3.67; N, 9.04.

4.3.10. 9-(2-Bromo-3-pyridinecarbonyl)-carbazole (21b). Prepared from **21a** by the method of Schlosser and Cottet.[14] Tan solid (0.238 g, 68%): mp 143.5–144.5 °C; IR (film) 1686 cm^{-1}; ^1H NMR δ 8.63 (1H, dd, $J=5.0$, 2.0 Hz), 8.00 (2H, d, $J=7.0$ Hz), 7.83 (1H, dd, $J=7.0$, 2.0 Hz), 7.51 (1H, dd, $J=7.0$, 5.0 Hz), 7.40 (2H, t, $J=8.0$ Hz), 7.34 (2H, t, $J=7.0$ Hz); ^{13}C NMR δ 165.3, 151.9, 139.2, 138.5, 137.5, 135.9, 127.7, 127.0, 124.8, 123.4, 120.2, 116.0; MS *m/z* 352 ($M^+$$^{81}Br$, 53%), 350 ($M^+$ ^{79}Br, 54), 186 (96), 184 (100), 158 (29), 156 (30). Calcd for $C_{18}H_{11}Br{\cdot}N_2O$: C, 61.56; H, 3.16; N, 7.98. Found: C, 60.91; H, 3.34; N, 7.90.

4.3.11. 9-(3-Pyridinecarbonyl)-carbazole (22). Colorless solid (0.054 g, 22%): mp 126.0–126.5 °C; IR (film) 1676 cm^{-1}; ^1H NMR δ 8.94 (1H, s), 8.88 (1H, d, $J=5.0$ Hz), 8.05–7.99 (3H, m), 7.54–7.45 (3H, m), 7.40–7.32 (4H, m); ^{13}C NMR δ 167.5, 153.2, 150.2, 139.0, 136.8, 131.9, 127.2, 126.5, 124.1, 123.8, 120.3, 115.9; MS *m/z* 272 (M^+46%), 106 (100), 78 (45). HRMS for $C_{18}H_{13}N_2O$ $[M+H]^+$ requires: 273.1028. Found: 273.1033.

4.3.12. 9-(4-Chloro-3-pyridinecarbonyl)-carbazole (24a). Tan solid (0.147 g, 70%): mp 130.5–131.5 °C; IR (film) 1676 cm^{-1}; ^1H NMR δ 8.76 (1H, s), 8.73 (1H, d, $J=5.0$ Hz), 7.95 (2H, d, $J=8.0$ Hz), 7.48 (1H, d, $J=7.0$ Hz), 7.38–7.30 (5H, m); ^{13}C NMR δ 164.1, 152.4, 149.6, 141.6, 138.3, 132.7, 127.6, 126.8, 125.3, 124.7, 120.2, 115.6; MS *m/z* 308 (M^+ ^{37}Cl, 19%), 306 (M^+ ^{35}Cl, 54), 142 (30), 140 (100), 112 (26). HRMS for $C_{18}H_{12}Cl{\cdot}N_2O$ $[M+H]^+$ requires: 307.0638. Found: 307.0624.

4.3.13. 9-(4-Bromo-3-pyridinecarbonyl)-carbazole (24b). Prepared from **24a** by the method Schlosser and Cottet.[14] Tan solid (0.011 g, 6.9%): mp 143.0–144.0 °C; IR (film) 1670 cm^{-1}; ^1H NMR δ 8.73 (1H, s), 8.66 (1H, d, $J=5.0$ Hz), 8.01 (2H, d, $J=7.0$ Hz), 7.71 (1H, d, $J=6.0$ Hz), 7.58–7.43 (1H, m), 7.40 (2H, t, $J=7.0$ Hz), 7.34 (2H, t, $J=7.0$ Hz); ^{13}C NMR 165.1, 152.1, 149.3, 138.5, 135.2, 130.9, 128.6, 127.7, 127.0, 124.8, 120.3, 115.9; MS *m/z* 352 (M^+ ^{81}Br, 98%), 350 (M^+ ^{79}Br, 97), 186 (98), 184 (00), 166 (31), 158 (88), 156 (90), 140 (38). HRMS for $C_{18}H_{12}Br{\cdot}N_2O$ $[M+H]^+$ requires: 351.0133. Found: 351. 0143.

4.3.14. 9-(3-Bromo-2-pyridinecarbonyl)-carbazole (25). Colorless solid (0.301 g, 56%): mp 142.5–143.0 °C; IR (film) 1683 cm^{-1}; ^1H NMR δ 8.71 (1H, d, $J=5.0$ Hz), 8.09 (1H, d, $J=8.0$ Hz), 7.98 (2H, d, $J=8.0$ Hz), 7.44 (1H, dd, $J=8.0$, 5.0 Hz), 7.38 (2H, t, $J=8.0$ Hz), 7.32 (2H, t, $J=8.0$ Hz); ^{13}C NMR δ 165.4, 154.0, 148.7, 141.5, 138.4, 127.5, 127.0, 126.5, 124.5, 120.1, 118.0, 115.9; MS *m/z* 352 (M^+ ^{81}Br, 90%), 350 (M^+ ^{79}Br, 88), 186 (98), 184 (100), 166 (31), 158 (88), 156 (90), 140 (38). HRMS for $C_{18}H_{12}Br{\cdot}N_2O$ $[M+H]^+$ requires: 351.0133. Found: 351. 0136.

4.3.15. 9-(2-Pyridinecarbonyl)-carbazole (26). Colorless solid (0.145 g, 59%): mp 132.0–132.5 °C; IR (film) 1681 cm^{-1}; ^1H NMR δ 8.71 (1H, d, $J=4.0$ Hz), 8.00–7.95 (3H, m), 7.87 (1H, d, $J=8.0$ Hz), 7.56 (1H, dd, $J=7.0$, 4.0 Hz), 7.38–7.28 (6H, m); ^{13}C NMR δ 168.0, 153.7, 149.9, 139.1, 137.8, 127.0, 126.7, 126.5, 124.3, 124.0, 120.0, 116.1; MS *m/z* 272 (M^+100%), 271 (76), 106 (51), 78 (99). HRMS for $C_{18}H_{13}N_2O$ $[M+H]^+$ requires: 273.1028. Found: 273.1033.

4.4. Typical procedure for cyclization

The procedure reported below was used in all cases. Composition of the crude product mixtures was determined by GC–MS analysis. Detector responses were calibrated with independently prepared samples of all observed products; the percent conversions in Table 1 reflect the normalized values. The reaction conditions were optimized. Product yields were not optimized, since the hexane trituration step to remove tin-containing compounds partially dissolved the desired products.

4.4.1. 9*H*-Benzo[*c*]indolo[3,2,1-*ij*][1,5]naphthyridin-9-one (1). Under an argon atmosphere a solution of tributyltin hydride (0.350 mL, 0.378 g, 0.130 mmol) and azobis-(cyclohexanenitrile) (ACN) (0.244 g, 0.100 mmol) in toluene (5 mL) was added over 1 h via syringe pump to a stirred, refluxing solution of 9-benzoyl-1-chloro-β-carboline (**7**) (0.0306 g, 0.100 mmol) in toluene (50 mL). The reaction solution was stirred at reflux for an additional 2.5 h, and the solvent was removed at reduced pressure. The crude product mixture was analyzed by GC–MS and then triturated with hexanes. The remaining solid was collected, washed, and dried to give **1** (0.020 g, 74%): mp 227.5–229.5 °C [lit.[3] mp 226–227 °C]; IR (film) 1682 cm^{-1}; ^1H NMR δ 8.87 (1H, d, $J=5.0$ Hz), 8.86–8.81 (2H, m), 8.67 (1H, dd, $J=7.5$, 1.0 Hz), 8.16 (1H, d, $J=7.5$ Hz), 7.98 (1H, d, $J=5.0$ Hz), 7.93 (1H, td, $J=7.5$, 1.0 Hz), 7.79–7.73 (2H, m), 7.56 (1H, td, $J=7.5$, 1.0 Hz); ^{13}C NMR δ 159.5, 145.0, 139.3, 136.0, 134.8, 133.6, 130.7, 130.6, 130.4, 130.0, 129.4, 129.2, 125.4, 124.9, 122.5, 117.5, 115.2; MS *m/z* 270 (M^+100%).

4.4.2. 9*H*-Indolo[3,2,1-*de*]phenanthridin-9-one (10). Colorless solid (0.056 g, 83% from **5c**): mp 229.5–230.0 °C ($CHCl_3$–pet. ether) [lit.[11b] mp 227 °C]; IR (film) 1666 cm^{-1}; ^1H NMR δ 8.83 (1H, d, J=8.0 Hz), 8.68 (1H, d, J=7.7 Hz), 8.30 (1H, d, J=8.0 Hz), 8.15 (1H, d, J=7.7 Hz), 8.07–8.03 (2H, m), 7.81 (1H, t, J=7.0 Hz), 7.67–7.54 (3H, m), 7.49 (1H, t, J=7.4 Hz); ^{13}C NMR δ 160.1, 138.6, 134.2, 133.8, 133.0, 129.3, 128.3, 128.1, 127.8, 126.4, 125.0, 124.5, 124.1, 122.5, 121.0, 120.8, 120.3, 117.3, 117.2; MS *m/z* 269 (M^+100%).

4.4.3. 8*H*-[1,6]Naphthyridino[8,7,6-*jk*]carbazol-8-one (12). Yellow solid (0.057 g, 88%): mp 196.0–196.5 °C; IR (film) 1685 cm^{-1}; ^1H NMR δ 9.04 (1H, dd, J=4.6, 2.0 Hz), 8.89 (1H, dd, J=8.0, 2.0 Hz), 8.77 (1H, dt, J=8.0, 1.0 Hz), 8.58 (1H, dd, J=8.0, 1.0 Hz), 8.15 (1H, d, J=1.0 Hz), 8.13 (1H, d, J=1.0 Hz), 8.09–8.05 (1H, m), 7.67–7.47 (4H, m); ^{13}C NMR δ 159.6, 153.9, 151.1, 138.2, 137.2, 135.4, 128.2, 126.6, 125.4, 124.6, 124.2, 123.7, 123.1, 122.8, 122.3, 121.0, 118.2, 117.3; MS *m/z* 270 (M^+100%). HRMS for $C_{18}H_{11}N_2O$ $[M+H]^+$ requires: 271.0871. Found: 271.0861.

4.4.4. 8*H*-[2,6]Naphthyridino[4,3,2-*jk*]carbazol-8-one (13). Pale yellow solid (0.022 g, 16%): mp 249.5–250.0 °C; IR (film) 1677 cm^{-1}; ^1H NMR δ 9.77 (1H, s), 8.94 (1H, d, J=5.2 Hz), 8.84 (1H, d, J=8.0 Hz), 8.48 (1H, d, J=5.2 Hz), 8.34 (1H, d, J=8.0 Hz), 8.18 (1H, d, J=7.6 Hz), 8.13 (1H, d, J=7.5 Hz), 7.67 (2H, m), 7.56 (1H, d, J=7.5 Hz); ^{13}C NMR δ 149.0, 146.2, 138.5, 128.5, 126.6, 125.7, 124.9, 124.8, 122.0, 121.5, 121.0, 120.2, 117.5, 115.2; MS *m/z* 270 (M^+100%). Calcd for $C_{18}H_{10}N_2O$: C, 79.99; H, 3.73; N, 10.36. Found: C, 79.61; H, 3.80; N, 10.11.

4.4.5. 8*H*-[2,7]Naphthyridino[4,3,2-*jk*]carbazol-8-one (14). Colorless solid (0.035 g, 28%): mp 274.0–275.0 °C; IR (film) 1674 cm^{-1}; ^1H NMR δ 9.87 (1H, s), 8.97 (1H, d, J=2.0 Hz), 8.82 (1H, d, J=8.0 Hz), 8.21 (2H, t, J=7.0 Hz), 8.14–8.08 (2H, m), 7.65 (2H, t, J=8.0 Hz), 7.54 (1H, t, J=7.0 Hz); ^{13}C NMR δ 159.4, 152.8, 152.4, 140.6, 138.6, 135.7, 128.8, 126.3, 125.6, 125.2, 124.7, 123.6, 122.7, 121.4, 121.7, 117.6, 116.2, 115.3; MS *m/z* 270 (M^+100%), 242 (16). HRMS for $C_{18}H_{11}N_2O$ $[M^++H]$ requires: 271.0871. Found: 271.0864.

4.4.6. 8*H*-[1,7]Naphthyridino[5,6,7-*jk*]carbazol-8-one (15). Colorless solid (0.025 g, 22%): mp 252.0–255.0 °C with decomp.; IR (film) 1686 cm^{-1}; ^1H NMR δ 8.96 (1H, s), 8.81 (1H, d, J=8.5 Hz), 8.48 (1H, d, J=8.0 Hz), 7.93 (3H, q, J=7.0 Hz), 7.66 (1H, s), 7.58 (1H, t, J=8.0 Hz), 7.45 (2H, q, J=7.0 Hz); ^{13}C NMR δ 158.1, 150.5, 143.8, 138.5, 133.6, 131.0, 130.3, 128.4, 126.8, 126.1, 125.4, 124.5, 124.3, 122.0, 121.0, 120.4, 117.8, 115.1; MS *m/z* 270 (M^+100%), 242 (38), 121 (20). HRMS for $C_{18}H_{11}N_2O$ $[M^++H]$ requires: 271.0871. Found: 271.0859.

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