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Efficient, "Tin-Free" Radical Cyclization to Aromatic Systems. Synthesis of 5,6,8,9,10,11-Hexahydroindolo[2,1-*a*]isoquinolines

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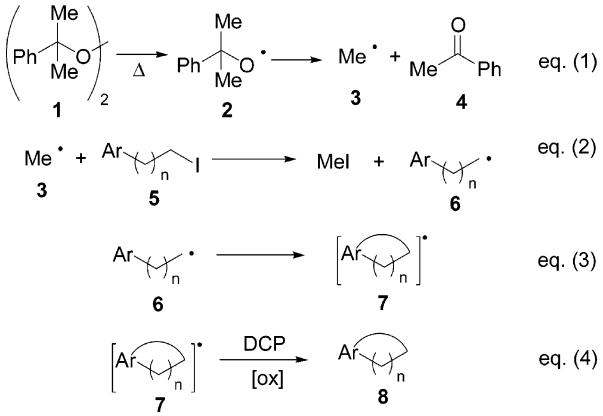
Abstract: Efficient radical cyclization of alkyl iodides to various aromatic systems including pyrrole, indole, isoquinolone, pyridone, and benzene, mediated by dicumyl peroxide, is described. The methodology was used to provide access to 5,6,8,9,10,11-hexahydroindolo[2,1-*a*]isoquinoline derivatives.

During the past several years, the addition of radicals to aromatic nuclei followed by oxidation to restore the aromatic systems has received considerable attention and is frequently of preparative value.[1−5] Several methods have been devised to effect such cyclizations, with $^{n}Bu_3$-SnH-mediated reactions being the most explored. This methodology has been used to annulate five-, six-, and seven-membered rings to various aromatic systems including derivatives of benzene, pyrrole, indole, pyridine, imidazole, benzimidazole, thiophene, and quinoline. Oxidative intramolecular additions to aromatic systems mediated by Mn(III),[2] Fe(III),[3] Cu(II),[4] Ce(IV),[3,4] which proceed with varying degrees of efficiency, have also been reported and recently Zard and co-workers[5] have annulated five-, six-, and seven-membered rings to an aromatic nucleus, exploiting xanthate based radical chemistry. As a long-term goal we have been interested in finding efficient tin-free methods for effecting oxidative radical cyclization to aromatic systems. In this context, we have been exploring the possibility of effecting oxidative homolytic cyclization of primary alkyl iodides to aromatic systems using environmentally friendly organic peroxides as the sole reagent. This paper describes the application of such methodology to the synthesis of several potentially cytotoxic indolo[2,1-*a*]isoquinoline derivatives.

SCHEME 1. Proposed Mechanism for the Radical Cyclization to Aromatic Systems Using DCP



The thermal fragmentation of dicumyl peroxide (DCP) was of special importance for our purposes, since the very reactive methyl radical species is produced (Scheme 1, eq 1). Thus, on the basis of the known favorable equilibrium of eq 2 (Scheme 1),[6] radical **6** is expected to be generated from the methyl radical **3** and alkyl iodide **5** and then add intramolecularly to the aromatic nucleus (Scheme 1, eq 3). Restoration of the aromatic system by DCP would then complete the sequence (eq 4).[7] Thus, since DCP would be acting both as the initiator and the oxidant,[4] a stoichiometric amount of the peroxide would be required to complete the reaction. In a pioneering work, Renaud et al. reported that dilauroyl peroxide induces a similar process; nevertheless, only an α-iodoacetamide derivative which produces a stabilized radical was tested.[8]

The initial experiments were carried out on the 3-acylindoles **9**, the oxidative radical cyclization which had been

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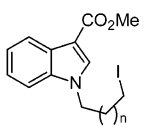
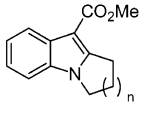
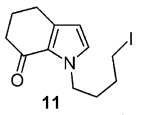
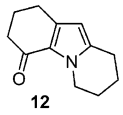
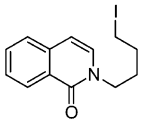
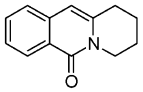
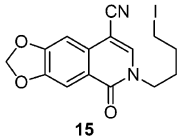
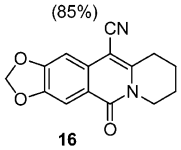
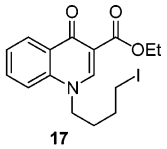
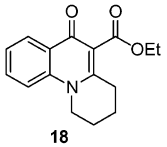
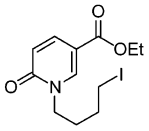
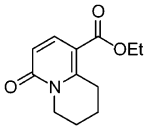
TABLE 1. Oxidative-Radical Cyclization Using Dicumyl Peroxide[a]

Entry	Starting material	Product (Yield)
1	 **9a** n = 1 **9b** n = 2	 **10a** n = 1 (90%) **10b** n = 2 (85%)
2	 **11**	 **12** (91%)
3	 **13**	 **14** (85%)
4	 **15**	 **16** (76%)
5	 **17**	 **18** (89%)
6	 **19**	 **20** (37%)

[a] Conditions: dicumyl peroxide (1.5 equiv), chlorobenzene, reflux.

studied previously under conditions different from those described herein.[3,1j] Thus, portionwise addition of DCP (1.5 equiv) to refluxing solutions of the indoles **9a** and **9b** gave the expected tricyclic products **10a** and **10b** in excellent yields (Table 1) along with considerable amounts of acetophenone and 2-phenylpropan-2-ol derived from DCP.[4] Under the same conditions, the pyrrole derivative **12**, the isoquinolin-1-ones **14** and **16**, and the 4-quinolone derivative **18** were all produced in high yields from the corresponding iodo compounds **11**, **13**, **15**, and **17**. Even the 2-pyridone derivative **19** underwent cyclization to **20**, albeit in modest yield. It should be noted that such cyclizations have been reported to fail in the case of Bu_3SnH/AIBN- mediated reactions.[9]

Indolo[2,1-*a*]isoquinoline **21** is the basic skeleton found in the dibenzopyrrocoline alkaloids cryptaustoline **22a** and cryptowoline **22b** isolated from the bark of *Cryptocarya bowiei* (Figure 1). It has been observed that such bases display important antileukemic and antitumor activities.[10,11] We have recently initiated a program

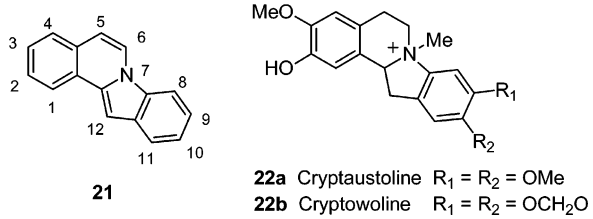
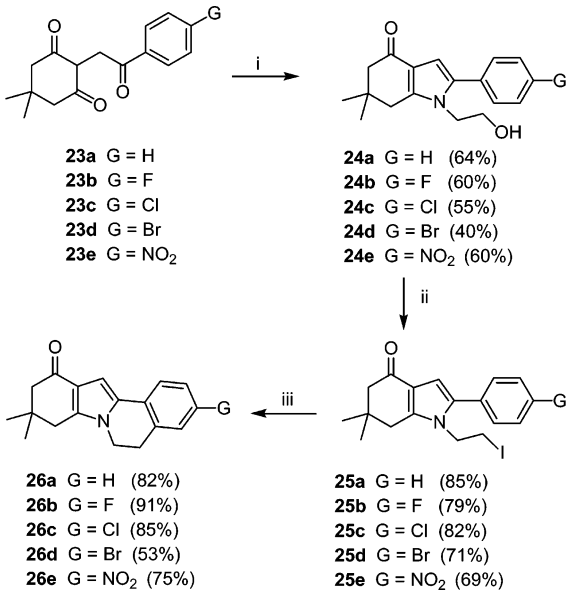


FIGURE 1. Dibenzopyrrocoline alkaloids from *Cryptocarya bowiei*.

SCHEME 2[a]



[a] Conditions: (i) 2-aminoethanol, AcOH, 60 °C; (ii) Ph_3P, I_2, imidazole; (iii) dicumyl peroxide, chlorobenzene, reflux.

involving the preparation and testing of structurally novel cytotoxic substances,[12] and in this regard, it was of interest to develop efficient synthetic strategies to derivatives of the heterocyclic system **21**.

The synthesis started with the synthesis of the 1,4-dicarbonyl compounds **23a**−**e** according to the procedure reported previously[13] (Scheme 2). After generation of the pyrrole nucleus by condensation of these compounds with 2-aminoethanol, followed by reaction of the hydroxyethyl compounds so produced with triphenylphosphine and iodine, the desired iodo compounds **26a**−**e** were obtained in moderate overall yields (Scheme 2). Cyclization of these iodides under the above-described conditions gave excellent yields of the tetracyclic compounds **26a**−**e** with the *p*-fluoro **26b** compound being generated most efficiently. It is important to point out that **25d**, which bears a bromine substituent in the para position, is converted into **26d** in which the bromine atom is retained. Such a process would be difficult, if not impossible, to accomplish using tin-based radical chemistry.

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In closing, it has been demonstrated that the intramolecular oxidative radical cyclization of primary alkyl iodides to aromatic nuclei can be efficiently effected using DCP. Not only are these reactions conducted in the absence of heavy metals and under tin-free conditions, but also the well-known problem of the premature reduction of the radical intermediate, frequently encountered in $^{n}Bu_3SnH$-mediated reactions, is easily avoided. The present methodology was also adapted to provide rapid access to derivatives of the pharmacologically important 5,6,8,9,10,11-hexahydroindolo[2,1-*a*]isoquinolines.

Experimental Section

General Procedure for the Synthesis of 1-(2-Hydroxyethyl)tetrahydroindolones (24a−e). To a vigorously stirred suspension of triketone **19** (1 g, 3.88 mmol) in acetic acid (5 mL) was added ethanolamine (0.36 mL, 5.82 mmol). The resulting slurry was heated to 60 °C under an atmosphere of N_2 until no more starting material was observed by TLC, and then the reaction mixture was allowed to warm to room temperature and spilled over ice−water (10 mL). The solid was filtered and washed with cooled water. The crude mixture was purified by column chromatography on neutral aluminum oxide using a gradient of 30−50% EtOAc in hexane as eluant. Evaporation of the collected fractions gave 1-(2-hydroxyethyl)indolones.

1-(2-Hydroxyethyl)-6,6-dimethyl-2-phenyl-1,5,6,7-tetrahydroindol-4-one (24a): yield 64% as a white solid; mp 172−74 °C; IR (KBr, cm^{-1}) ν_{max} 3325, 2955, 2883, 1624, 1475, 1061, 779, 703; ^1H NMR (300 MHz, $CDCl_3$ + DMSO) δ 1.16 (s, 6H), 2.32 (s, 2H), 2.79 (s, 2H), 3.54 (t, J = 6.2 Hz, 2H), 4.02 (t, J = 6.1 Hz, 3H), 6.42 (s, 1H), 7.41 (d, J = 4.6 Hz, 5H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO) δ 28.2, 34.9, 35.9, 46.1, 51.5, 60.2, 104.6, 118.3, 127.2, 128.2, 128.8, 132.1, 135.4, 144.1, 192.4; MS (EI) *m*/*z* (rel intensity) 283 (M^+, 67), 183 (100); HRMS (FAB+) calcd for $C_{18}H_{22}O_2N$ 284.1651, found 284.1642.

2-(4-Fluorophenyl)-1-(2-hydroxyethyl)-6,6-dimethyl-1,5,6,7-tetrahydroindol-4-one (24b): yield 60% as a white solid; mp 161−63 °C; IR (KBr, cm^{-1}) ν_{max} 3340, 2954, 2879, 1629, 1481, 1058, 847; ^1H NMR (300 MHz, $CDCl_3$ + DMSO) δ 1.16 (s, 6H), 2.34 (s, 2H), 2.77 (s, 2H), 3.56 (t, J = 6.3 Hz, 2H), 3.98 (t, J = 6.3 Hz, 2H), 4.36 (s, 1H), 6.43 (s, 1H), 7.11 (t, J = 8.7 Hz, 2H), 7.41 (dd, J = 5.4, 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO) δ 28.2, 34.8, 35.9, 45.9, 51.4, 60.3, 104.7, 114.7, 115.0, 118.3, 128.1, 130.7, 130.8, 134.3, 143.9, 160.1, 163.3, 192.8; MS (EI) *m*/*z* (rel intensity) 301 (M^+, 100), 201 (96); HRMS (FAB+) calcd for $C_{18}H_{21}O_2NF$ 302.1556, found 302.1554.

2-(4-Chlorophenyl)-1-(2-hydroxyethyl)-6,6-dimethyl-1,5,6,7-tetrahydroindol-4-one (24c): yield 55% as a white solid; mp 165−66 °C; IR (KBr, cm^{-1}) ν_{max} 3255, 2958, 2870, 1627, 1477, 1062, 820; ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 6H), 2.23 (s, 2H), 2.70 (s, 2H), 2.77 (s,1H), 3.69 (d, J = 3.0 Hz, 2H), 4.02 (t, J = 6.0 Hz, 2H), 6.50 (s, 1H), 7.38 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.7, 35.4, 36.7, 46.5, 51.5, 61.4, 106.1, 119.2, 128.9, 130.7, 130.8, 134.0, 135.1, 144.9, 194.1; MS (EI) *m*/*z* (rel intensity) 317 (M^+, 98), 217 (100); HRMS (FAB+) calcd for $C_{18}H_{21}O_2NCl$ 318.1261, found 318.1251.

2-(4-Bromophenyl)-1-(2-hydroxyethyl)-6,6-dimethyl-1,5,6,7-tetrahydroindol-4-one (24d): yield 40% as a white solid; mp 159−160 °C; IR (KBr, cm^{-1}) ν_{max} 3258, 2953, 2872, 1628, 1475, 1063, 819; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 6H), 2.21 (s, 2H), 2.69 (s, 2H), 2.88 (s,1H), 3.71 (t, J = 5.5 Hz, 2H), 4.02 (t, J = 5.5 Hz, 2H), 6.49 (s, 1H), 7.32 (dd, J = 8.6, 1.9 Hz, 2H); 7.54 (dd, J = 8.6, 1.8 Hz, 2H,); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.7, 35.4, 36.6, 46.6, 51.3, 56.9, 61.3, 106.1, 119.0, 122.2, 131.0, 131.1, 131.8, 135.2, 145.4, 194.2; MS (EI) *m*/*z* (rel intensity) 361 (M^+, 100) 363 (M^+ + 2, 99); HRMS (FAB+) calcd for $C_{18}H_{21}O_2NBr$ 362.0756, found 362.0742.

1-(2-Hydroxyethyl)-6,6-dimethyl-2-(4-nitrophenyl)-1,5,6,7-tetrahydroindol-4-one (24e): yield 60% as a yellow solid; mp 184−86 °C; IR (KBr, cm^{-1}) ν_{max} 3444, 2957, 2873, 1656, 1595, 1516, 1475, 1342, 859; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 6H), 1.95 (s, 1H), 2.30 (s, 2H), 2.74 (s, 2H), 3.75 (t, J = 5.7 Hz, 2H), 4.12 (t, J = 5.7 Hz, 2H), 6.66 (s, 1H), 7.64 (d, J = 9.0 Hz, 2H), 8.26 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.7, 35.4, 36.8, 46.7, 51.6, 61.5, 108.0, 119.8, 124.0, 129.5, 134.1, 138.9, 146.0, 146.9, 193.9; MS (EI) *m*/*z* (rel intensity) 328 (M^+, 80); 228 (100), HRMS (FAB+) calcd for $C_{18}H_{21}O_4N_2$ 329.1501, found 329.1508.

General Procedure for the Preparation of 1-(2-Iodoethyl)tetrahydroindolones (25a−e). Triphenylphosphine (1.5 equiv) and imidazole (1.5 equiv) were dissolved in dry CH_2Cl_2 (1.5 mL/mmol). The mixture was cooled in an ice bath, and iodine (1.5 equiv) was added with vigorous stirring over 10 min. The resulting slurry was warmed to room temperature, and a solution of hydroxyethyl tetrahydroindolone **(24)** (1.0 equiv) in CH_2Cl_2 was added dropwise over 15 min. The mixture was stirred for 1 h under atmosphere of N_2. The solvent was removed, and the crude residue was purified by column chromatography on neutral aluminum oxide using Hex/EtOAc as eluent.

1-(2-Iodoethyl)-6,6-dimethyl-2-phenyl-1,5,6,7-tetrahydroindol-4-one (25a): yield 85% as a white solid; mp 143−45 °C; IR (KBr, cm^{-1}) ν_{max} 2952, 2923, 2867, 1656, 1471, 772, 705; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 6H), 2.40 (s, 2H), 2.71 (s, 2H), 3.03 (t, J = 8.1 Hz, 2H), 4.23 (t, J = 8.1 Hz, 2H), 6.56 (s, 1H), 7.34−7.47 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.7, 28.9, 35.6, 36.4, 46.4, 51.9, 106.2, 119.7, 128.2, 128.9, 129.0, 132.0, 135.4, 143.0, 193.6; MS (EI) *m*/*z* (rel intensity) 393 (M^+, 100); HRMS (FAB+) calcd for $C_{18}H_{21}ONI$ 394.0668, found 394.0666.

2-(4-Fluorophenyl)-1-(2-iodoethyl)-6,6-dimethyl-1,5,6,7-tetrahydroindol-4-one (25b): yield 79% as a white solid; mp 140−41 °C; IR (KBr, cm^{-1}) ν_{max} 2952, 2925, 2861, 1658, 1469, 851; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 6H), 2.39 (s, 2H), 2.67 (s, 2H), 3.02 (t, J = 7.9 Hz, 2H), 4.20 (t, J = 7.9 Hz, 2H), 6.53 (s, 1H), 7.14 (dd, J = 8.8, 2.9 Hz, 2H), 7.33 (dd, J = 5.3, 2.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.5, 28.8, 35.6, 36.4, 46.3, 51.9, 106.4, 115.8, 116.1, 119.6, 130.8, 130.9, 134.2, 142.9, 193.5; MS (EI) *m*/*z* (rel intensity) 411 (M^+, 100); HRMS (FAB+) calcd for $C_{18}H_{20}ONFI$ 412.0574, found 412.0582.

2-(4-Chlorophenyl)-1-(2-iodoethyl)-6,6-dimethyl-1,5,6,7-tetrahydroindol-4-one (25c): yield 82% as a white solid; mp 125−26 °C; IR (KBr, cm^{-1}) ν_{max} 2957, 2929, 2872,1651,1472, 803; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 6H), 2.39 (s, 2H), 2.70 (s, 2H), 3.03 (t, J = 7.9 Hz, 2H), 4.22 (t, J = 7.9 Hz, 2H), 6.56 (s, 1H), 7.28 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H,); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8, 35.6, 36.4, 46.4, 51.9, 106.6, 119.8, 129.1, 130.1, 130.5, 134.1, 134.3, 143.2, 193.5; MS (EI) *m*/*z* (rel intensity) 427 (M^+, 100); HRMS (FAB+) calcd for $C_{18}H_{20}ONClI$ 428.0278, found 428.0285.

2-(4-Bromophenyl)-1-(2-iodoethyl)-6,6-dimethyl-1,5,6,7-tetrahydroindol-4-one (25d): yield 71% as a white solid; mp 119−20 °C; IR (KBr, cm^{-1}) ν_{max} 2955, 2871, 1654, 1466, 805; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 6H), 2.39 (s, 2H), 2.70 (s, 2H), 3.03 (t, J = 7.9 Hz, 2H), 4.22 (t, J = 7.9 Hz, 2H), 6.56 (s, 1H), 7.23 (dd, J = 9.0, 1.8 Hz, 2H), 7.57 (dd, J = 8.5, 2.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.5, 28.8, 35.6, 36.4, 46.4, 51.9, 106.7, 119.8, 122.5, 130.4, 131.0, 132.1, 134.1, 143.3, 193.5; MS (EI) *m*/*z* (rel intensity) 471 (M^+, 06), 473 (M^+ + 2, 07), 83 (100); HRMS (FAB+) calcd for $C_{18}H_{20}ONBrI$ 471.9773, found 471.9782.

1-(2-Iodoethyl)-6,6-dimethyl-2-(4-nitrophenyl)-1,5,6,7-tetrahydroindol-4-one (25e): yield 69% as a yellow solid; mp 150−51 °C; IR (KBr, cm^{-1}) ν_{max} 2954, 2926, 2867, 1656, 1599, 1518, 1470, 1342, 856; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 6H), 2.42 (s, 2H), 2.73 (s, 2H), 3.06 (t, J = 7.5 Hz, 2H), 4.31 (t, J = 7.5 Hz, 2H), 6.72 (s, 1H), 7.53 (d, J = 9.0 Hz, 2H), 8.31 (d, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.1, 28.8, 35.6, 36.5, 46.6, 51.9, 108.6, 120.4, 124.3, 128.9, 133.1, 138.5, 144.6, 147.1, 193.4; MS (EI) *m*/*z* (rel intensity) 438 (M^+, 100); HRMS (FAB+) calcd for $C_{18}H_{20}O_3N_2I$ 439.0519, found 439.0521.

General Procedure for Radical Cyclization Using Dicumyl Peroxide. To a degassed solution of the corresponding iodo derivative (1.0 equiv) in refluxing chlorobecene (7 mL/mmol) was added dicumyl peroxide (1.5 equiv) portionwise (0.3 equiv/1.5 h). The reaction was carried out under an atmosphere of N_2 during 7.5 h. Then, the mixture was allowed to warm to room

temperature and evaporated to dryness. The crude residue was purified by column chromatography on silica gel (EtOAc/Hex).

2,3,6,7,8,9-Hexahydro-1*H*-pyrido[1,2-*a*]indol-4-one (12): yellow oil; IR ($CHCl_3$, cm^{-1}) ν_{max} 2936, 2862, 1640, 1491, 1438, 1322; ^1H NMR (300 MHz, $CDCl_3$) δ 1.75−1.83 (m, 2H), 1.90−1.97 (m, 2H), 1.99−2.07 (m, 2H), 2.50 (dd, J = 6.4, 6.4 Hz, 2H), 2.69 (dd, J = 6.1, 6.1 Hz, 2H), 2.78 (dd, J = 6.4, 6.4 Hz, 2H), 4.32 (dd, J = 6.15, 6.15 Hz, 2H), 5.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 22.9, 23.0, 23.7, 23.8, 24.9, 38.14, 45.7, 105.8, 119.3, 125.4, 139.4, 140.4, 187.1; MS (EI) *m*/*z* 189 (M^+, 100); HRMS (FAB+) calcd for $C_{12}H_{15}NO$ 189.1213, found 189.1231.

1,2,3,4-Tetrahydropyrido[1,2-*b*]isoquinolin-6-one (14). Eluted with hexanes−ethyl acetate (6:4): 85% yield as a white solid; mp 99−100 °C (lit.[14] 100−103 °C); IR (KBr, cm^{-1}) ν_{max} 2952, 2855, 1650, 1630, 1600; ^1H NMR (300 MHz, $CDCl_3$) δ 1.81−1.88 (m, 2H), 1.93−1.99 (m, 2H), 2.82 (t, J = 6.8 Hz, 2H), 4.12 (t, J = 6.2 Hz, 2H), 6.32 (s, 1H), 7.36−7.42 (m, 2H), 7.55−7.60 (m, 1H), 8.40 (d, J = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 22.4, 28.8, 41.0, 103.8, 124.9, 125.5, 125.6, 127.8, 132.0, 136.8, 140.9, 162.9; MS (EI) *m*/*z* (rel intensity) 199 (M^+, 100); HRMS (FAB+) calcd for $C_{13}H_{14}NO$ 200.1075, found 200.1072.

8,9-Methylenedioxy-1,2,3,4-tetrahydro-11-cyanopyrido-[1,2-*b*]isoquinolin-6-one (16). Eluted with hexanes−ethyl acetate (1:1): 76% yield as a white solid; mp 277−279 °C; IR (KBr, cm^{-1}) ν_{max} 2941, 2212, 1654, 1616, 1562; ^1H NMR (300 MHz, $CDCl_3$) δ 1.86−2.05 (m, 4H), 3.13 (t, J = 6.8 Hz, 2H), 4.09 (t, J = 6.6 Hz, 2H), 6.11 (s, 1H), 7.14 (s, 1H), 7.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4, 21.9, 28.2, 42.4, 88.9, 101.6, 102.2, 105.8, 116.4, 118.7, 131.2, 148.2, 149.8, 153.1, 161.0; MS (EI) *m*/*z* (rel intensity) 268 (M^+, 100); HRMS (FAB+) calcd for $C_{15}H_{13}N_2O_3$ 269.0926, found 269.0924.

Ethyl 1,2,3,4-Tetrahydropyrido[1,2-*a*]quinolin-6-one-5-carboxylate (18). Eluted with hexanes−ethyl acetate (1:2): 89% yield as a white solid; mp 132−133 °C (lit.[15] mp 132−135 °C); IR (KBr, cm^{-1}) ν_{max} 2953, 1716, 1620, 1600, 1540; ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (t, J = 7.2 Hz, 3H), 1.83−1.92 (m, 2H), 2.06−2.15 (m, 2H), 3.01 (t, J = 6.6 Hz, 2H), 4.10 (t, J = 6.6 Hz, 2H), 4.39 (q, J = 7.2 Hz, 2H), 7.37 (td, J = 7.6, 0.9 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.63 (td, J = 7.2, 1.6 Hz), 8.44 (dd, J = 8.1, 1.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 18.4, 22.5, 27.6, 46.4, 61.2, 114.7, 116.8, 124.0, 126.7, 126.8, 132.2, 140.9, 149.9, 167.5, 173.5; MS (EI) *m*/*z* (rel intensity) 271 (M^+, 20), 199 (100); HRMS (FAB+) calcd for $C_{16}H_{18}NO_3$ 272.1287, found 272.1275.

Ethyl 4-Oxo-6,7,8,9-tetrahydro-4H-quinolizine-1-carboxylate (20). Eluted with hexanes−ethyl acetate (6:4): 37% yield as a white solid; mp 54−56 °C (lit.[16] 52−53 °C); HRMS (FAB+) calcd for $C_{12}H_{16}NO_3$ 222.1130, found 222.1123.

9,9-Dimethyl-5,8,9,10-tetrahydro-6*H*-indolo[2,1-*a*]isoquinolin-11-one (26a): yield 82% as a white crystalline solid; mp 148−50 °C; IR (KBr, cm^{-1}) ν_{max} 2957, 2871, 1647, 1486, 762; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (s, 6H), 2.38 (s, 2H), 2.65 (s, 2H), 3.08 (t, J = 6.6, 2H), 3.97 (t, J = 6.6, 2H), 6.87 (s, 1H), 7.12−7.28 (m, 3H), 7.53 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8, 35.3, 35.6, 41.0, 52.1, 99.9, 119.8, 122.9, 126.6, 127.5, 127.9, 128.7, 130.3, 131.2, 142.1, 193.3; MS (EI) *m*/*z* (rel intensity) 265 (M^+, 81), 181 (100); HRMS (FAB+) calcd for $C_{18}H_{20}ON$ 266.1545, found 266.1545.

3-Fluoro-9,9-dimethyl-5,8,9,10-tetrahydro-6*H*-indolo[2,1-*a*]-isoquinolin-11-one (26b): yield 91% as a white crystalline solid; mp 179−80 °C; IR (KBr, cm^{-1}) ν_{max} 2955, 2869, 1646, 1482, 826; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (s, 6H), 2.39 (s, 2H), 2.65 (s, 2H), 3.08 (t, J = 6.8, 2H), 3.98 (t, J = 6.8, 2H), 6.81 (s, 1H), 6.89−7.01 (m, 2H), 7.49 (dd, J = 5.6, 8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8, 28.9, 35.4, 35.6, 40.7, 52.1, 99.6, 114.7, 119.8, 124.6, 125.0, 130.6, 132.5, 142.1, 159.7, 163.0, 193.5; MS (EI) *m*/*z* (rel intensity) 283 (M^+, 100); HRMS (FAB+) calcd for $C_{18}H_{19}ONCl$ 284.1451, found 284.1452.

3-Chloro-9,9-dimethyl-5,8,9,10-tetrahydro-6*H*-indolo[2,1-*a*]-isoquinolin-11-one (26c): yield 85% as a white crystalline solid; mp 199−200 °C; IR (KBr, cm^{-1}) ν_{max} 2955, 2868, 1647, 1481, 829; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (s, 6H), 2.39 (s, 2H), 2.65 (s, 2H), 3.07 (t, J = 6.7, 2H), 3.97 (t, J = 6.7, 2H), 6.85 (s, 1H), 7.18−7.27 (m, 2H), 7.44 (d, J = 8.28 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.7, 28.8, 28.8, 35.3, 35.6, 40.7, 52.1, 100.4, 119.9, 124.2, 127.2, 127.7, 127.9, 130.3, 131.8, 131.9, 142.4, 193.4; MS (EI) *m*/*z* (rel intensity) 299 (M^+, 100); HRMS (FAB+) calcd for $C_{18}H_{19}ONCl$ 300.1155, found 300.1149.

3-Bromo-9,9-dimethyl-5,8,9,10-tetrahydro-6*H*-indolo[2,1-*a*]isoquinolin-11-one (26d): yield 53% as a white crystalline solid; mp 190−91 °C; IR (KBr, cm^{-1}) ν_{max} 2953, 2871, 1649, 1470, 825; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (s, 6H), 2.38 (s, 2H), 2.65 (s, 2H), 3.07 (t, J = 6.8 Hz, 2H), 3.97 (t, J = 6.7 Hz, 2H), 6.87 (s, 1H), 7.34 (s, 1H), 7.38 (d, J = 1.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.6, 28.8, 35.3, 35.6, 40.7, 52.1, 100.5, 119.8, 120.0, 124.5, 127.7, 130.4, 130.6, 130.8, 132.2, 142.4, 193.4; MS (EI) *m*/*z* (rel intensity) 343 (M^+, 76), 344 (M^+ + 2, 75), 259 (100); HRMS (FAB+) calcd for $C_{18}H_{19}ONBr$ 344.0650, found 344.0661.

9,9-Dimethyl-3-nitro-5,8,9,10-tetrahydro-6*H*-indolo[2,1-*a*]isoquinolin-11-one (26e): yield 75% as a yellow crystalline solid; mp 230−31 °C; IR (KBr, cm^{-1}) ν_{max} 2954, 2879, 1653, 1575, 1514, 1330, 807; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (s, 6H), 2.41 (s, 2H), 2.69 (s, 2H), 3.21 (t, J = 6.6 Hz, 2H), 4.06 (t, J = 6.6 Hz, 2H), 7.07 (s, 1H), 7.61 (d, J = 8.4 Hz, 1H), 8.10−8.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8, 28.8, 35.3, 35.7, 40.9, 52.1, 103.9, 120.8, 123.2, 123.6, 129.5, 130.8, 134.8, 143.7, 145.6, 193.2; MS (EI) *m*/*z* (rel intensity) 310 (M^+, 100); HRMS (FAB+) calcd for $C_{18}H_{19}O_3N_2$ 311.1396, found 311.1395.

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Supporting Information Available: ^1H and/or ^{13}C spectra for all compounds. Experimental details and full spectral data for the synthesis of compounds **13**, **15**, **17**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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