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3-Indolylacyl Radical Cyclizations upon Pyridines and Tetrahydropyridines: Access to Ergoline-Related Indole [*cd*]-fused Isoquinolines

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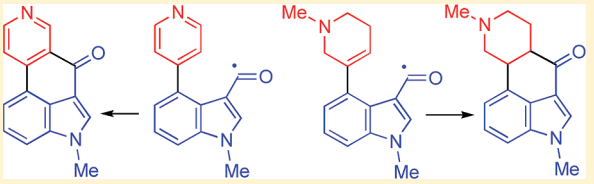
Supporting Information

ABSTRACT: Cyclizations of selenoester-derived 3-indolylacyl radicals, involving the homolytic acylation of pyridines or the addition to double bonds included in tetrahydropyridine rings, have been used to synthesize indole [*cd*]-fused isoquinolines related to the natural ergoline system.

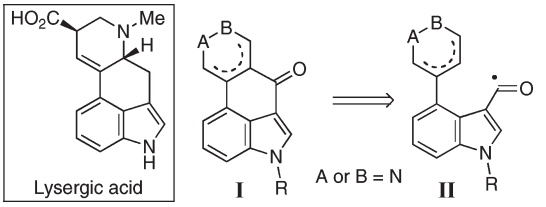


In the last years we have been working on the implementation of a novel indole annulation procedure taking advantage of the reactions of selenoester-derived 2-indolylacyl radicals.[1,2] We have shown that these reactive intermediates participate in cyclizations upon alkenes[3−6] and (hetero)aromatic systems,[7−9] leading to a great variety of polycyclic indolyl ketones of interest in the synthesis of natural products and related bioactive compounds.[10] On the basis of these results, we considered using the regioisomeric 3-indolylacyl radicals[11] in similar reactions for the construction of indole [*cd*]-fused isoquinolines **I**, which are structurally related to the ergoline system present in the biologically important ergot alkaloids (for example, lysergic acid, Scheme 1). We specifically wanted to study if cyclizations of pyridine- or tetrahydropyridine-containing 3-indolylacyl radicals of general formula II, involving either aromatic substitution or alkene addition processes, would serve to close the central carbocyclic 6-membered ring, thus giving direct access to the target tetracyclic systems.

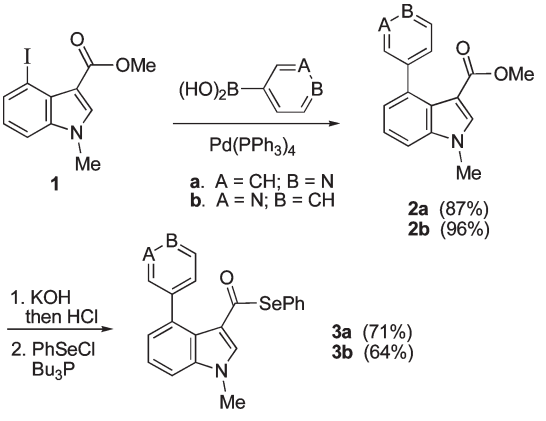
Intramolecular homolytic aromatic substitutions have become a useful tool for the construction of otherwise inaccessible polycyclic systems, in particular with the advent and application of tin-based reagents.[12] However, the use of electron-deficient pyridines as substrates toward nucleophilic acyl radicals, which represents the umpolung of the Friedel−Craft reaction, has been scarcely studied.[8,9,13] Indeed, most reported examples of such homolytic acylations are conducted in acidic media under oxidative protocols (Minisci reactions).[14]

Selenoesters **3a** and **3b** (Scheme 2), bearing 4- or 3-pyridyl moieties attached at the indole 4-position, were selected as the radical precursors to study cyclizations leading to pyrido-fused systems.[15] These compounds were efficiently prepared by Suzuki coupling of methyl 4-iodo-3-indolecarboxylate **1** with 4- or 3-pyridylboronic acid, followed by hydrolysis of the ester function and phenylselenation of the resulting carboxylic acid according to the Batty and Crich protocol.[16]

Scheme 1. Synthetic Strategy



Scheme 2. Synthesis of Selenoesters 3



Treatment of selenoester **3a** with *n*-Bu_3SnH as the radical mediator and AIBN as the initiator in refluxing benzene for 20 h

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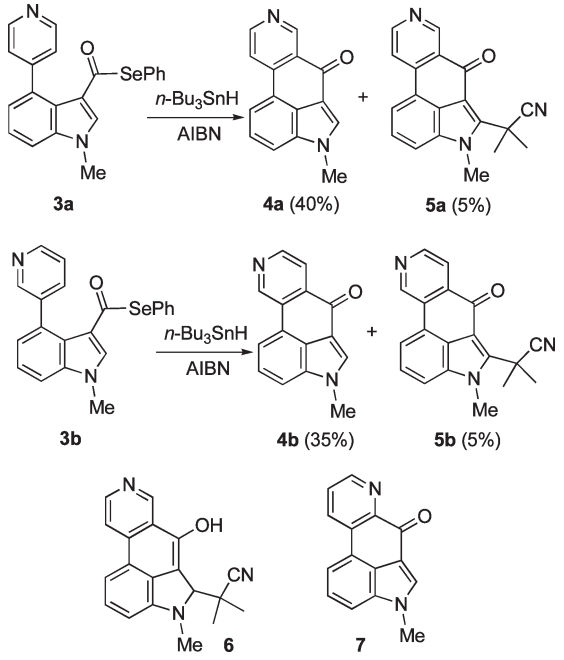
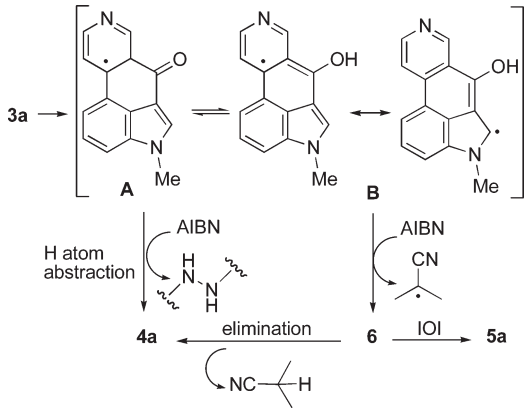
Scheme 3. Cyclization of Selenoesters 3



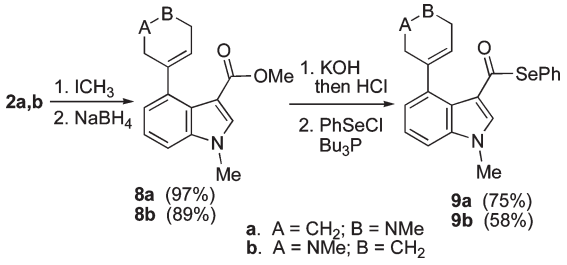
Scheme 4. Likely Mechanism (4-Pyridyl Series)



led to the target indolo[4,3-*fg*]isoquinoline **4a** (40% yield, Scheme 3) along with minor amounts of tetracycle **5a** (5%), which additionally incorporated the 2-cyano-2-propyl moiety of the initiator at the indole 2-position. Significant amounts (25%) of unreacted selenoester, indicative of a poor chain, were recovered, but no trace of aldehyde coming from the premature reduction of the initially formed acyl radical was observed. An entirely parallel cyclization course was observed in the 3-pyridyl series, as selenoester **3b** led to the indolo[3,4-*gh*]isoquinoline **4b** (35%) on exposure to the above conditions, with minor amounts (5%) of the corresponding 2-(2-cyano-2-propyl)indole **5b** also being formed. It should be noted that the cyclization took place regioselectively at the 4-position of the pyridine ring and no trace of the product coming from the alternative attack at the 2-position, i.e., the *natural* ergoline **7**, was detected.

At this stage of the work, we assumed that tetracycles **4a,b** were the result of a hydrogen atom abstraction from the

Scheme 5. Synthesis of Selenoesters 9



intermediate cyclized radical (for the 4-pyridyl series, **A**, Scheme 4), most probably at the hands of the initiator AIBN,[17,18] which is present in stoichiometric amounts. However, formation of byproduct **5a,b** could not be readily explained.

To gain further insight into the mechanistic course of the above cyclizations, we briefly examined the behavior of selenoester **3a** under tris(trimethylsilyl)silane (TTMSS)-AIBN conditions. After 18 h at reflux we obtained a complex crude reaction mixture, in which the major product was shown by ^{1}H NMR to be a dihydro derivative of indole **5a**, i.e., indoline **6**. No trace of tetracycle **4a** was detected. As expected considering its dihydroaromatic structure, indoline **6** proved to be unstable during the extractive workup and column chromatography, mainly undergoing oxidation to **5a**. We were nevertheless able to obtain a pure sample and confirm its highly conjugated enol structure by ^{1}H NMR. Significantly, it was fully converted into indoles **4a** and **5a** (1:3 ratio) after 12 h in the NMR tube (CD_3OD).

The formation of indoline **6** can be rationalized by considering that, after cyclization of the initially formed 3-indolylacyl radical upon the pyridine ring, the resulting highly delocalized azacyclohexadienyl radical **A**, or its tautomeric form **B**, is intercepted by 2-cyano-2-propyl radicals coming from the breakdown of AIBN[19] (Scheme 4). It is likely that this route is also operative under *n*-Bu_3SnH conditions, which would easily explain the isolation of the minor byproduct **5a**.[20] On the other hand, the major product **4a** might be generated by elimination of 2-methylpropanenitrile from **6**,[21] which would constitute an alternative route to the direct hydrogen atom abstraction from radical **A**. A similar mechanistic rationale can account for the formation of products **4b** and **5b** in the 3-pyridyl series (not depicted).

We then focus our attention on the assembly of indole [*cd*]-fused isoquinolines by intramolecular addition of 3-indolylacyl radicals to double bonds included in tetrahydropyridine rings under reductive conditions. To this end, we selected selenoesters **9a** and **9b** (Scheme 5), from which the central carbocyclic ring of the target system would be closed by 6-*endo* cyclization upon 1,2,5,6-tetrahydro-4- or -3-pyridyl moieties, respectively. These compounds were easily prepared from esters **2a** or **2b** by quaternization with methyl iodide, reduction of the resulting pyridinium salts with $NaBH_4$, and subsequent phenylselenation of the tetrahydropyridine esters **8a** or **8b** through the corresponding carboxylic acid as in the above series.

We were pleased to find that cyclization of selenoester **9a** smoothly took place under the standard *n*-Bu_3SnH conditions, using AIBN as the initiator in refluxing benzene. The reaction was completed in 4 h and did not require slow addition techniques, leading to the expected tetracycle **10a** in

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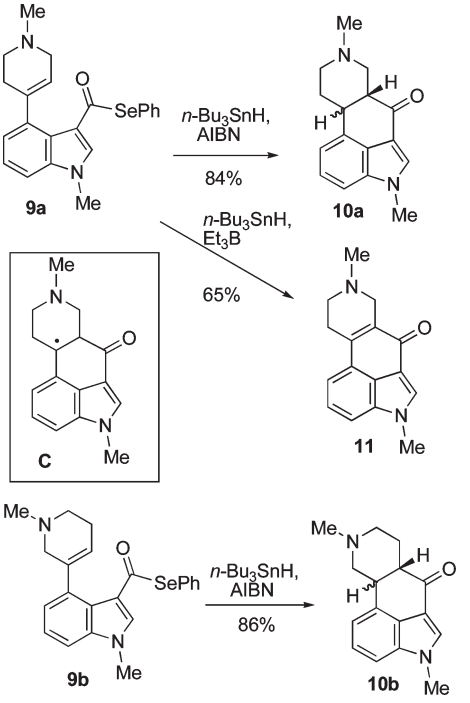
Scheme 6. Cyclization of Selenoesters 9



high yield (84%) as a 1.2:1 mixture of trans−cis stereoisomers (Scheme 6). Its formation was consistent with the predicted 6-*endo* attack of the initially formed acyl radical at the 3-position of the tetrahydropyridine ring and the subsequent reduction of the resulting tetracyclic radical **C** by nonstereoselective hydrogen abstraction from the tin hydride. Similarly, selenoester **9b** on exposure to the above conditions led to tetracycle **10b** in 86% yield (1.5:1 mixture of trans−cis stereoisomers).

With the aim of improving the above stereoselectivity, we decided to switch from AIBN initiation to Et_3B, which allows *n*-Bu_3SnH-mediated reactions to be performed at room (or lower) temperatures.[22] However, when **9a** was subjected to this new radical protocol, tetracycle **11**, which retained the original double bond, was isolated in 65% yield. Minor amounts (10%) of byproduct coming from adventitious nucleophilic addition (phenylselenolate, H_2O) to the enone moiety were also formed. The formation of **11** was striking since it indicated that the nucleophilic benzyl-type radical **C** resulting from the 6-endo cyclization, instead of being intercepted by the tin hydride, underwent oxidation by loss of a hydrogen atom, for instance at the hands of ethyl radicals from the initiator.

In summary, we have shown that selenoester-derived 3-indolylacyl radicals undergo cyclization upon pyridine rings attached at the indole 4-position under *n*-Bu_3SnH-AIBN conditions to give indole [*cd*]-fused isoquinolines in moderate yields. There is evidence to suggest that reaction of 2-cyanopropyl radicals with the initially formed cyclized radical and subsequent elimination could be a contributory mechanism for the homolytic aromatic substitution process. From the synthetic standpoint, the best yields of the target tetracyclic systems are obtained by 6-*endo* radical cyclizations upon tetrahydropyridine double bonds.

EXPERIMENTAL SECTION

Methyl 4-Iodo-1-methyl-3-indolecarboxylate (1). A solution of methyl 4-iodo-3-indolecarboxylate[23] (1.30 g, 4.32 mmol) in anhydrous THF (17 mL) was added dropwise under Ar to an ice-cooled suspension of NaH (5.18 mmol) in anhydrous THF (10 mL). After the solution was stirred 1 h at 0 °C, iodomethane (1.20 mL, 19.44 mmol) was added dropwise and the mixture was allowed to warm to rt for 4 h. The mixture was poured into H_2O, acidified with 1 M aqueous HCl, and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give **1** (1.35 g, 99%) as an oil, which crystallized on standing. An analytical sample was obtained by crystallization from MeOH: mp 80−2 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 3.79 (s, 3H), 3.87 (s, 3H), 6.95 (t, J = 7.8 Hz, 1H), 7.43 (dd, J = 8.1, 0.9 Hz, 1H), 7.76 (dd, J = 7.8, 0.9 Hz, 1H), 7.88 (s, 1H); ^{13}C NMR (CD_3OD, 75.4 MHz) δ 33.6 (CH_3), 51.5 (CH_3), 85.1 (C), 109.1 (C), 111.4 (CH), 124.8 (CH), 129.6 (C), 135.7 (CH), 138.1 (CH), 139.2 (C), 166.2 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{11}H_{11}INO_2$ 315.9829, found 315.9827.

Pyridines 2a,b. A mixture of iodoindole **1** (0.53 g, 1.68 mmol), the respective pyridylboronic acid (90%, 0.28 g, 2.03 mmol), $Pd(PPh_3)_4$ (78 mg, 0.067 mmol), and 1 M aqueous Na_2CO_3 (3.9 mL) in DME (16 mL) was stirred at reflux temperature for 24 (**1a**) or 4 h (**1b**). The reaction mixture was partitioned between AcOEt and H_2O. The organic layer was concentrated to dryness and the crude product was chromatographed (SiO_2, AcOEt) to give the pure product.

Methyl 1-methyl-4-(4-pyridyl)-3-indolecarboxylate (2a): 0.39 g (87%); mp 134−6 °C; ^{1}H NMR (acetone-d_6, 300 MHz) δ 3.28 (s, 3H), 3.96 (s, 3H), 7.14 (dd, J = 6.9, 0.9 Hz, 1H), 7.28 (d, J = 6.3 Hz, 2H), 7.38 (dd, J = 8.1, 7.2 Hz, 1H), 7.58 (dd, J = 8.1, 0.9 Hz, 1H), 8.01 (s, 1H), 8.56 (d, J = 6 Hz, 2H); ^{13}C NMR (acetone-d_6, 75.4 MHz) δ 33.7 (CH_3), 50.4 (CH_3), 108.0 (C), 111.4 (CH), 123.4 (CH), 123.6 (C), 124.2 (CH), 124.4 (CH), 134.1 (C), 137.9 (CH), 139.2 (C), 149.6 (CH), 151.3 (C), 164.6 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{16}H_{15}N_2O_2$ 267.1128, found 267.1132. Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.38; H, 5.42; N, 10.43.

Methyl 1-methyl-4-(3-pyridyl)-3-indolecarboxylate (2b): 0.43 g (96%); mp 114−6 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.37 (s, 3H), 3.89 (s, 3H), 7.16 (dd, J = 6.3, 1.8 Hz, 1H), 7.34 (ddd, J = 7.8, 5.1, 0.9 Hz, 1H), 7.40 (m, 2H), 7.73 (td, J = 7.2, 1.8 Hz, 1H), 7.87 (s, 1H), 8.59 (dd, J = 5.1, 1.8 Hz, 1H), 8.65 (d, J = 2.1, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 33.5 (CH_3), 50.9 (CH_3), 107.5 (C), 109.6 (CH), 122.3 (CH), 122.7 (CH), 123.4 (C), 124.3 (CH), 132.4 (C), 135.5 (CH), 136.8 (CH), 138.0 (C), 138.4 (C), 147.5 (CH), 149.5 (CH), 164.4 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{16}H_{15}N_2O_2$ 267.1128, found 267.1132. Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71;81 H, 5.29; N, 10.08.

Phenyl Selenoesters 3a,b. A solution of the respective carboxylic ester **2a** or **2b** (0.27 g, 1.0 mmol) in a 1:1:1 mixture of 2 N aqueous KOH−MeOH−dioxane (5 mL) was heated at reflux for 24 h. MeOH was evaporated and 1 N aqueous HCl was added until pH 7. The precipitated carboxylic acid was collected by filtration, washed with H_2O, and dried over P_4O_{10}. A suspension of this material in a 1:1 mixture of CH_2Cl_2−MeOH (8 mL) was treated with Et_3N (0.24 mL, 1.70 mmol). After 30 min at rt, the mixture was concentrated under reduced pressure to give the respective triethylammonium salt. In another flask, tributylphosphine (0.52 mL, 2.12 mmol) was added under Ar to a solution of PhSeCl (0.41 g, 2.12 mmol) in anhydrous THF (4 mL), and the mixture was stirred at rt for 10 min. The resulting yellow solution was added to a suspension of the above triethylammonium salt in THF (4 mL) and the resulting mixture was stirred at rt overnight. The reaction mixture was partitioned between CH_2Cl_2 and H_2O, and extracted with CH_2Cl_2. The solvent was removed and the crude product was purified as indicated below.

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Phenyl 1-methyl-4-(4-pyridyl)-3-indolecarboselenoate (3a): 0.28 g (71%, after crystallization on standing in the fridge and washing with Et_2O); mp 192−4 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.92 (s, 3H), 7.23 (dd, J = 5.5, 3 Hz, 1H), 7.32 (m, 5H), 7.44 (m, 4H), 8.03 (s, 1H), 8.60 (d, J = 5.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 33.9 (CH_3), 110.3 (CH), 117.8 (C), 121.3 (C), 123.7 (CH), 124.0 (CH), 124.4 (CH), 126.9 (C), 128.5 (CH), 129.1 (CH), 133.3 (C), 135.6 (CH), 136.6 (CH), 138.6 (C), 148.1 (CH), 149.7 (C), 182.5 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{21}H_{17}N_2OSe$ 393.0500, found 393.0503. Anal. Calcd for $C_{21}H_{16}N_2OSe$: C, 64.45; H, 4.12; N, 7.16. Found: C, 63.99; H, 4.20; N, 6.97.

Phenyl 1-methyl-4-(3-pyridyl)-3-indolecarboselenoate (3b): 0.25 g (64%, after flash chromatography, SiO_2, hexanes and 4:6 hexanes−AcOEt); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.93 (s, 3H), 7.22 (dd, J = 6, 2.7 Hz, 1H), 7.30 (m, 4H), 7.45 (m, 4H), 7.67 (ddd, J = 8.1, 2.4, 1.8 Hz, 1H), 8.04 (s, 1H), 8.56 (dd, J = 5.1, 1.8 Hz, 1H), 8.74 (dd, J = 2.1, 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 33.7 (CH_3), 109.6 (CH), 117.7 (C), 121.8 (C), 122.4 (CH), 123.6 (CH), 124.7 (CH), 127.1 (C), 128.3 (CH), 128.9 (CH), 132.6 (C), 135.7 (CH), 135.8 (CH), 136.6 (CH), 136.8 (C), 138.4 (C), 147.9 (CH), 149.5 (CH), 182.4 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{21}H_{17}N_2OSe$ 393.0500, found 393.0502. Anal. Calcd for $C_{21}H_{16}N_2OSe$: C, 64.45; H, 4.12; N, 7.16. Found: C, 64.20; H, 4.21; N, 7.01.

Radical Cyclization of Selenoesters 3. A solution of n-Bu_3SnH (0.14 mL, 0.52 mmol) and AIBN (84 mg, 0.52 mmol) in C_6H_6 (2 mL) was added over a period of 20 h to a heated (reflux) suspension of the respective selenoester **3a** or **3b** (0.10 g, 0.26 mmol) in C_6H_6 (10 mL). After an additional 2 h at reflux, the reaction mixture was concentrated, the resulting residue was partitioned between hexanes (15 mL) and acetonitrile (15 mL), and the polar layer was washed with hexanes. The solvent was removed, and the crude mixture was chromatographed (SiO_2, AcOEt and 98:2 AcOEt−MeOH) to give the pure products.

From 3a: 4-Methylindolo[4,3-*fg*]isoquinolin-6-one (4a): 24 mg (40%); ^1H NMR (DMSO-d_6, 300 MHz) δ 4.07 (s, 3H), 7.57 (t, J = 7.8 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 8.29 (d J = 7.5 Hz, 1H), 8.39 (d, J = 5.1 Hz, 1H), 8.57 (s, 1H), 8.84 (d, J = 5.4 Hz, 1H), 9.43 (s, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 34.2 (CH_3), 112.7 (C), 114.8 (CH), 117.9 (CH), 119.1 (CH), 120.6 (C), 124.2 (CH), 126.7 (C), 128.2 (C), 135.2 (C), 136.1 (CH), 142.3 (C), 149.8 (CH), 151.9 (CH), 177.1 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{15}H_{11}N_2O$ 235.0866, found 235.0866.

5-(2-Cyano-2-propyl)-4-methylindolo[4,3-*fg*]isoquinolin-6-one (5a): 4 mg (5%); ^1H NMR ($CDCl_3$, 500 MHz) δ 2.29 (s, 6H), 4.39 (s, 3H), 7.61 (dd, J = 8, 7 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 8.12 (d J = 7 Hz, 1H), 8.17 (d, J = 5 Hz, 1H), 8.85 (broad s, 1H), 9.68 (s, 1H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 26.7 (CH_3), 33.9 (CH_3), 34.2 (C), 111.2 (C), 113.8 (CH), 117.1 (CH), 119.3 (CH), 120.9 (C), 123.3 (C), 124.6 (CH), 126.5 (C), 129.5 (C), 135.6 (C), 147.6 (C), 149.7 (2 CH), 176.9 (C), one quaternary C not observed; ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{16}N_3O$ 302.1288, found 302.1289.

From 3b: 4-Methylindolo[3,4-*gh*]isoquinolin-6-one (4b): 21 mg (35%); mp 246−8 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.07 (s, 3H), 7.55 (m, 2H), 8.12 (m, 1H), 8.13 (s, 1H), 8.31 (d, J = 5 Hz, 1H), 8.80 (d, J = 5 Hz, 1H), 9.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 34.4 (CH_3), 111.8 (CH), 113.7 (C), 117.3 (CH), 120.6 (CH), 121.8 (C), 124.5 (CH), 126.3 (C), 129.8 (C), 134.2 (CH), 135.1 (C), 139.7 (C), 146.6 (CH), 148.7 (CH), 177.8 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{15}H_{11}N_2O$ 235.0866, found 235.0865. Anal. Calcd for $C_{15}H_{10}N_2O \cdot H_2O$: C, 71.41; H, 4.79; N, 11.10. Found: C, 71.30; H, 4.36; N, 10.75.

5-(2-Cyano-2-propyl)-4-methylindolo[3,4-*gh*]isoquinolin-6-one (5b): 4 mg (5%); mp 236−8 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.28 (s, 6H), 4.38 (s, 3H), 7.58 (m, 2H), 8.16 (m, 1H), 8.28 (d, J = 5 Hz, 1H), 8.80 (d, J = 5 Hz, 1H), 9.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 26.7 (CH_3), 33.8 (CH_3), 34.2 (C), 111.0 (C), 111.8 (CH), 117.8 (CH), 120.8 (CH), 121.5 (C), 123.4 (C), 124.8 (CH), 125.1 (C), 129.0 (C), 135.5 (C), 139.9 (C), 146.4 (CH), 147.3 (C), 148.7 (CH), 177.0 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{16}N_3O$ 302.1288, found 302.1293.

Indoline 6: ^1H NMR (CD_3OD, 300 MHz) δ 1.32 (s, 3H), 1.65 (s, 3H), 3.34 (s, 3H), 5.25 (s, 1H), 6.92 (d, J = 7.5 Hz, 1H), 7.61 (dd, J = 8.4, 7.5 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 8.77 (d, J = 6.6 Hz, 1H), 9.03 (d, J = 6.6 Hz, 1H), 9.80 (s, 1H).

Tetrahydropyridines 8a,b. Iodomethane (0.70 mL, 11.80 mmol) was added to a solution of the respective pyridines **2a** or **2b** (0.31 g, 1.16 mmol) in anhydrous acetone (7 mL) and anhydrous C_6H_6 (0.7 mL). After the mixture was stirred at rt for 24 h, the corresponding pyridinium salt was collected by filtration. $NaBH_4$ (0.11 g, 2.91 mmol) was added in three portions to an ice-cooled suspension of the pyridinium salt in MeOH (10 mL). After the soluton was stirred at rt for 7 h, the solvent was removed and the resulting residue was partitioned between CH_2Cl_2 and a saturated aqueous Na_2CO_3 solution, and extracted with CH_2Cl_2. The organic extracts were dried and concentrated and the crude product was chromatographed (SiO_2, 95:5:1 CH_2Cl_2−MeOH−diethylamine) to give the pure product.

Methyl 1-methyl-4-(1-methyl-1,2,5,6-tetrahydro-4-pyridyl)-3-indolecarboxylate (8a): 0.32 g (97%); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.46 (s, 3H), 2.51 (m, 2H), 2.78 (t, J = 5.7 Hz, 2H), 3.17 (q, J = 2.7 Hz, 2H), 3.81 (s, 3H), 3.83 (s, 3H), 5.64 (m, 1H), 7.09 (m, 1H), 7.25 (m, 2H), 7.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 31.4 (CH_2), 33.1 (CH_3), 45.8 (CH_3), 51.0 (CH_3), 51.9 (CH_2), 54.5 (CH_2), 107.0 (C), 108.4 (CH), 120.9 (CH), 122.4 (CH), 122.5 (CH), 123.0 (C), 135.8 (CH), 137.2 (C), 137.6 (C), 138.2 (C), 164.1 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{17}H_{21}N_2O_2$ 285.1598, found 285.1597.

Methyl 1-methyl-4-(1-methyl-1,2,5,6-tetrahydro-3-pyridyl)-3-indolecarboxylate (8b): 0.29 g (89%); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.41 (s, 3H), 2.38 (m, 2H), 2.68 (t, J = 5.7 Hz, 2H), 3.22 (q, J = 2.7 Hz, 2H), 3.81 (s, 3H), 3.84 (s, 3H), 5.65 (m, 1H), 7.09 (m, 1H), 7.26 (m, 2H), 7.76 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 26.0 (CH_2), 33.2 (CH_3), 45.6 (CH_3), 51.1 (CH_2 and CH_3), 58.6 (CH_2), 107.4 (C), 108.4 (CH), 121.3 (CH), 122.4 (CH), 122.6 (CH), 123.4 (C), 135.7 (CH and C), 137.6 (C), 138.0 (C), 164.5 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{17}H_{21}N_2O_2$ 285.1598, found 285.1595.

Phenyl 1-Methyl-4-(1-methyl-1,2,5,6-tetrahydro-4-pyridyl)-3-indolecarboselenoate (9a). Methyl ester **8a** (0.31 g, 1.09 mmol) was subjected to the protocol described for the preparation of **3a,b**. The crude oily residue crystallized on standing in the fridge. After washing with Et_2O, the resulting white solid (selenoester **9a** hydrochloride, mp 192−4 °C) was partitioned between 2 N aqueous Na_2CO_3 and CH_2Cl_2 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give selenoester **9a**: 0.33 g (75%); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.48 (s, 3H), 2.55 (m, 2H), 2.80 (t, J = 5.6 Hz, 2H), 3.20 (m, 2H), 3.77 (s, 3H), 5.66 (broad s, 1H), 7.16 (d, J = 6.8 Hz, 1H), 7.24 (d, J = 8.8 Hz, 1H), 7.32 (t, J = 8 Hz, 1H), 7.43 (m, 3H), 7.67 (m, 2H), 7.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 30.7 (CH_2), 33.4 (CH_3), 45.4 (CH_3), 51.4 (CH_2), 54.2 (CH_2), 108.5 (CH), 117.4 (C), 121.5 (C), 121.9 (CH), 122.7 (CH), 123.4 (CH), 127.4 (C), 128.2 (CH), 128.9 (CH), 135.8 (CH), 136.0 (CH), 136.6 (C), 137.3 (C), 138.1 (C), 182.3 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{22}H_{23}N_2OSe$ 411.0970, found 411.0971. For **9a**·HCl: Anal. Calcd for $C_{22}H_{22}N_2OSe \cdot HCl \cdot {}^3/_2H_2O$: C, 55.88; H, 5.54; N, 5.92. Found: C, 55.62; H, 5.36; N, 5.75.

Phenyl 1-Methyl-4-(1-methyl-1,2,5,6-tetrahydro-3-pyridyl)-3-indolecarboselenoate (9b). A solution of methyl ester **8b** (0.25 g, 0.93 mmol) in a 1:1:1 mixture of 2 N aqueous KOH−MeOH−dioxane (6 mL) was heated at reflux for 24 h. The reaction mixture was concentrated, acidified with 1 N aqueous HCl until pH 4, and concentrated to dryness. The resulting residue was digested with anhydrous MeOH. The methanolic solution was concentrated to give the crude carboxylic acid hydrochloride. A suspension of this material in CH_2Cl_2 (4 mL) was treated with Et_3N (0.26 mL, 1.86 mmol) and the resulting triethylammonium salt was allowed to react with tributylphosphine (0.46 mL, 1.86 mmol) and PhSeCl (0.36 g, 1.86 mmol) as described for the preparation of selenoesters **3a,b**. After workup, the crude residue was chromatographed (SiO_2, CH_2Cl_2

and 96:4 CH_2Cl_2−MeOH). The resulting pale yellow oil (selenoester **9b** hydrochloride) was partitioned between 2 N aqueous Na_2CO_3 and CH_2Cl_2 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give selenoester **9b**: 0.22 g (58%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.45 (s, 3H), 2.38 (m, 2H), 2.69 (t, J = 6 Hz, 2H), 3.29 (q, J = 2.4 Hz, 2H), 3.81 (s, 3H), 5.68 (m, 1H), 7.16 (dd, J = 7.2, 1.2 Hz, 1H), 7.25 (dd, J = 8.4, 1.2 Hz, 1H), 7.32 (dd, J = 8.4, 7.2 Hz, 1H), 7.41 (m, 3H), 7.65 (m, 2H), 7.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.1 (CH_2), 33.5 (CH_3), 45.7 (CH_3), 50.7 (CH_2), 58.2 (CH_2), 108.5 (CH), 118.0 (C), 122.2 (C), 122.5 (CH), 123.3 (CH), 123.4 (CH), 127.7 (C), 128.4 (CH), 129.0 (CH), 135.7 (CH), 135.8 (CH), 135.9 (C), 136.1 (C), 138.3 (C), 182.5 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{22}H_{23}N_2OSe$ 411.0970, found 411.0977. Anal. Calcd for $C_{22}H_{22}N_2OSe$: C, 64.54; H, 5.42; N, 6.84. Found: C, 64.10; H, 5.42; N, 6.84.

Tetracycles 10a,b. A solution of the respective phenyl selenoester **9a** or **9b** (0.16 g, 0.39 mmol), *n*-Bu_3SnH (0.21 mL, 0.78 mmol), and AIBN (12 mg, 0.08 mmol) in C_6H_6 (11 mL) under Ar was heated at reflux for 4 h. The reaction mixture was concentrated, the resulting residue was partitioned between hexanes (15 mL) and acetonitrile (15 mL), and the polar layer was washed with hexanes. The solvent was removed and the crude product was chromatographed (SiO_2, CH_2Cl_2, 98:2 CH_2Cl_2−MeOH, and 97:2:1 CH_2Cl_2−MeOH−diethylamine) to give the pure product.

4,8-Dimethyl-6a,7,8,9,10,10a-hexahydroindolo[4,3-*fg*]-isoquinolin-6-one (10a): 83 mg (84%, 1.2:1 mixture of trans−cis stereoisomers); ^{1}H NMR ($CDCl_3$, 400 MHz, HSQC, HMBC, major trans isomer) δ 1.92 (qd, J = 12.4, 3.6 Hz, 1H, 10-H), 2.07 (t, J = 11.2 Hz, 1H, 7-H), 2.10 (td, J = 12, 2.8 Hz, 1H, 9-H), 2.42 (s, 3H, 8-Me), 2.52 (dm J = 12.8 Hz, 1H, 10-H), 2.79 (td, J = 11.6, 3.6 Hz, 1H, 6a-H), 3.02 (td, J = 11.6, 3.6 Hz, 1H, 10a-H), 3.08 (m, 1H, 9-H), 3.63 (dm, J = 11.6 Hz, 1H, 7-H), 3.85 (s, 3H, 4-Me), 7.10 (d, J = 7.2 Hz, 1H, 1-H), 7.22 (m, 1H, 3-H), 7.25 (m, 1H, 2-H), 7.55 (s, 1H, 5-H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, HSQC, HMBC, major trans isomer) δ 28.5 (C-10), 33.6 (4-Me), 41.4 (C-10a), 46.4 (8-Me), 52.0 (C-6a), 55.4 and 55.5 (C-7,9), 108.0 (C-3), 113.2 (C-5a), 115.5 (C-1), 123.8 (C-2), 127.6 (C-5), 129.0 (C-10c), 132.4 (C-10b), 134.8 (C-3a), 192.6 (C-6); ESI-HRMS $[M + H]^+$ calcd for $C_{16}H_{19}N_2O$ 255.1492, found 255.1491.

4,9-Dimethyl-6a,7,8,9,10,10a-hexahydroindolo[3,4-*gh*]-isoquinolin-6-one (10b): 85 mg (86%, 1.5:1 mixture of *trans-cis* isomers) [pure trans stereoisomer was obtained by digestion with Et_2O]; ^{1}H NMR ($CDCl_3$, 300 MHz, HSQC, HMBC) δ 1.77 (m, 1H, 7-H), 2.01 (td, J = 12.4, 2.8 Hz, 1H, 8-H), 2.23 (t, J = 10.8 Hz, 1H, 10-H), 2.39 (m, 2H, 6a-H, 7-H), 2.45 (s, 3H, 9-Me), 3.09 (dm J = 11.2 Hz, 1H, 8-H), 3.41 (td, J = 11.2, 3.6 Hz, 1H, 10a-H), 3.71 (m, 1H, 10-H), 3.88 (s, 3H, 4-Me), 7.06 (d, J = 7.2 Hz, 1H, 1-H), 7.24 (m, 1H, 3-H), 7.28 (m, 1H, 2-H), 7.57 (s, 1H, 5-H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, HSQC, HMBC) δ 25.4 (C-7), 33.7 (4-Me), 42.3 (C-10a), 46.3 (8-Me), 51.5 (C-6a), 55.8 (C-8), 58.4 (C-10), 108.1 (C-3), 113.3 (C-5a), 115.2 (C-1), 123.7 (C-2), 127.6 (C-5), 129.2 (C-10c), 131.0 (C-10b), 134.7 (C-3a), 193.3 (C-6); ESI-HRMS $[M + H]^+$ calcd for $C_{16}H_{19}N_2O$ 255.1492, found 255.1493.

4,8-Dimethyl-7,8,9,10-tetrahydroindolo[4,3-*fg*]isoquinolin-6-one (11). *n*-Bu_3SnH (0.31 mL, 1.16 mmol) and Et_3B (1 M in hexanes, 1.16 mmol) were added to a solution of phenyl selenoester **9a** (0.19 g, 0.46 mmol), previously dried azeotropically with anhydrous C_6H_6, in anhydrous C_6H_6 (16 mL). The reaction mixture was stirred at rt for 5 h with dry air constantly supplied by passing compressed air through a short tube of Drierite. *n*-Bu_3SnH (0.31 mL, 1.16 mmol) and Et_3B (1 M in hexanes, 1.16 mmol) were again added, and the reaction mixture was stirred at rt for 5 h. The solution was concentrated and the resulting residue was partitioned between hexanes (10 mL) and acetonitrile (10 mL), and the polar layer was washed with hexanes. The solvent was removed and the resulting residue was chromatographed (SiO_2, CH_2Cl_2, and 97:2:1 CH_2Cl_2−MeOH−DEA) to give tetracycle **11**: 76 mg (65%); ^{1}H NMR ($CDCl_3$, 300 MHz, HSQC and HMBC) δ 2.54 (s, 3H, 8-Me), 2.75 (t, J = 6 Hz, 2H, 9-H), 3.13 (m, 2H, 10-H), 3.57 (t, J = 1.8 Hz, 2H, 7-H), 3.99 (s, 3H, 4-Me), 7.39 (dd, J = 7.8, 7.2 Hz, 1H, 2-H), 7.48 (d, J = 7.8 Hz, 1H, 3-H), 7.54 (d, J = 7.2 Hz, 1H, 1-H), 7.96 (s, 1H, 5-H); ^{13}C NMR ($CDCl_3$−CD_3OD, 125.7 MHz, HSQC, HMBC) δ 25.7 (C-10), 34.0 (4-Me), 45.6 (8-Me), 51.1 (C-9), 53.1 (C-7), 112.3 (C-3), 113.9 (C-5a), 119.4 (C-1), 123.8 (C-2), 124.4 (C-10b), 125.3 (C-10c), 134.3 (C-3a, C-6a), 135.4 (C-5), 141.0 (C-10a), 179.4 (C-6); ESI-HRMS $[M + H]^+$ calcd for $C_{16}H_{17}N_2O$ 253.1335, found 253.1338.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) However, as pointed out by one of the reviewers, simple addition of 2-cyano-2-propyl radicals to the 2-position of the 3-acylindole moiety of **4a** cannot be ruled out under *n*-Bu_3SnH conditions.

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