New Cascade 2-Indolylacyl Radical Addition−Cyclization Reactions

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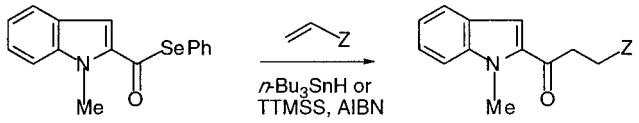
Over the last several years, radical cyclizations involving aromatic species have received considerable synthetic attention.[1] In particular, the cyclization of aryl radicals often constitutes the key step in the construction of polycyclic systems incorporating an aromatic ring.[2] However, in the chemistry of indoles and related heterocycles, the cyclization of indolyl (and other heteroaryl) radicals has been comparatively less studied.[3] In contrast, there are several reports dealing with the alternative approach that involves the addition of radical species to the indole nucleus. Most of them make use of reductive (*n*-Bu_3SnH−AIBN) conditions,[4] and they result in the formation of 1,2-fused indoles by radical cyclization onto the indole 2-position.[5] Whereas in some cases the indole nucleus is recovered in its 2,3-dihydro (indoline) form after the final reduction of the resultant 3-indolyl radical,[6] the reestablishment of the aromatic indole nucleus has been more commonly observed either from 2-unsubstituted (*n*-Bu_3SnH-mediated oxidative radical cyclizations)[7] or from 2-substituted indoles (radical *ipso*-substitutions).[8]

Scheme 1



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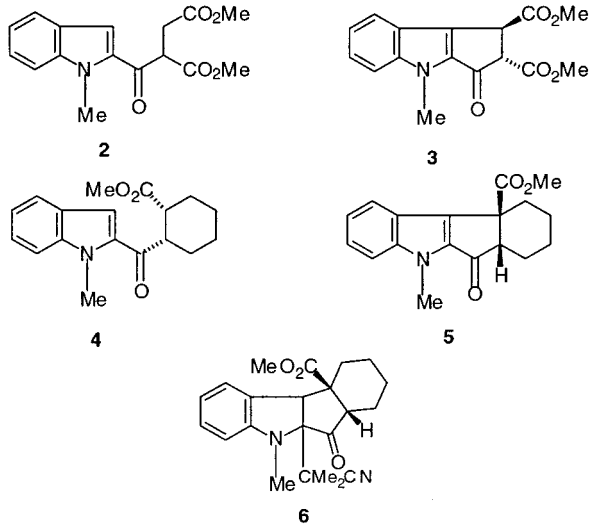
In the context of our studies on the synthesis of 2-acylindole alkaloids, we have recently described the generation and intermolecular reactions of 2-indolylacyl radicals.[9] We have shown that 2-indolylacyl radicals derived from the corresponding phenyl selenoesters (e.g., **1**, Scheme 1) undergo addition to a variety of alkene acceptors under reductive conditions providing access to 1,4-dicarbonyl compounds bearing the 2-acylindole moiety.

In some cases, under the standard *n*-Bu_3SnH−AIBN conditions, the yields of the corresponding acylindole adducts were low. For instance, from selenoester **1** and dimethyl fumarate, the desired adduct **2** was obtained in a modest 24% yield.[9] A further investigation of this reaction has revealed an interesting result. When the poorer hydrogen-atom donor tris(trimethylsilyl)silane (TTMSS)[10] was used as the radical mediator in order to minimize the competitive reduction of the intermediate 2-indolylacyl radical, the cyclopenta[*b*]indol-3-one **3** was obtained (26%) along with adduct **2** (26%). Similarly, methyl 1-cyclohexenecarboxylate, an unreactive acceptor under *n*-Bu_3SnH conditions, afforded a 1:1:1 mixture of adduct **4**, tetracycle **5**, and the 2-substituted indoline derivative **6** in 45% overall yield.



2 **3** **4** **5** **6**

The unexpected formation of these cyclized products can be rationalized by considering the cascade reactions depicted in Scheme 2. The electrophilic radical **A**, coming from the intermolecular addition of the nucleophilic 2-indolylacyl radical to the acceptor, has a comparatively long effective lifetime under TTMSS conditions and, in part, can intramolecularly react at the indole 3-position

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(2) Yet, L. *Tetrahedron* **1999**, *55*, 9349−9403.

(3) (a) Sundberg, R. J.; Cherney, R. J. *J. Org. Chem.* **1990**, *55*, 6028−6037. (b) Mohanakrishnan, A. K.; Srinivasan, P. C. *Tetrahedron Lett.* **1996**, *37*, 2659−2662. (c) Dobbs, A.; Jones, K.; Veal, K. T. *Tetrahedron* **1998**, *54*, 2149−2160 and references therein. (d) For the cyclization of 2-quinolyl radicals, see: Comins, D. L.; Hong, H.; Jianhua, G. *Tetrahedron Lett.* **1994**, *35*, 5331−5334.

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(6) (a) Ziegler, F. E.; Jeroncic, L. O. *J. Org. Chem.* **1991**, *56*, 3479−3486. (b) Ziegler, F. E.; Harran, P. G. *J. Org. Chem.* **1993**, *58*, 2768−2773. (c) Ziegler, F. E.; Belema, M. *J. Org. Chem.* **1994**, *59*, 7962−7967. For synthetic applications, see: (d) Ziegler, F. E.; Belema, M. *J. Org. Chem.* **1997**, *62*, 1083−1094. (e) Ziegler, F. E.; Berlin, M. Y. *Tetrahedron Lett.* **1998**, *39*, 2455−2458.

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(8) (a) Caddick, S.; Aboutayab, K.; Jenkins, K.; West, R. I. *J. Chem. Soc., Perkin Trans. 1* **1996**, 675−682. (b) Caddick, S.; Shering, C. L.; Wadman, S. N. *Tetrahedron* **2000**, *56*, 465−473. See also: (c) Aldabbagh, F.; Bowman, W. R. *Tetrahedron* **1999**, *55*, 4109−4122. (d) Miranda, L. D.; Cruz-Almanza, R.; Alvarez-García, A.; Muchowski, J. M. *Tetrahedron Lett.* **2000**, *41*, 3035−3038.

(9) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *Org. Lett.* **2001**, *3*, 1697−1700.

(10) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188−194.

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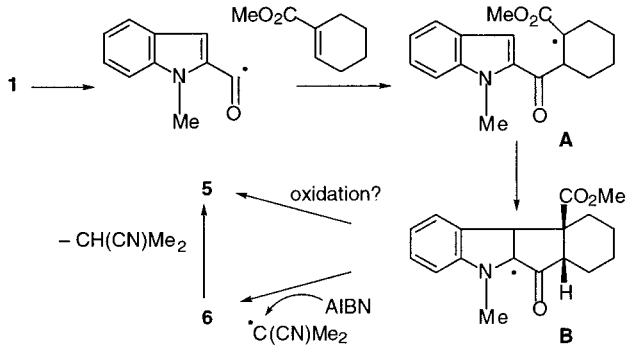
Scheme 2

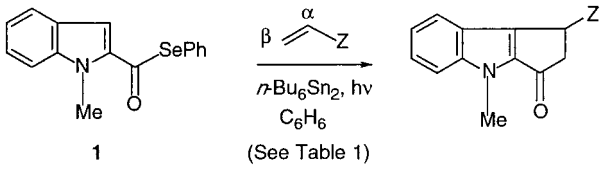


(formally a 5-endo cyclization)[11] to give a new stabilized captodative[12] radical **B**, which would undergo oxidation to indole **5**. Full equivalents of TTMSS and AIBN were required in these reactions, suggesting that AIBN or 2-cyano-2-propyl radicals could act as the required oxidant.[13] Although different explanations involving "pseudo $S_{RN}1$" mechanisms[7d,14] (proton loss from **B** followed by SET or, alternatively, SET from **B** followed by proton loss) can also be taken into account, the isolation in this particular case of tetracycle **6**, coming from the reaction of **B** with AIBN, might be indicative of the participation of the initiator in the oxidative process. Furthermore, **6** was partially converted into **5** under purification (SiO_2 column chromatography) conditions.

In the literature, there are several examples of cascade reactions comprising intramolecular homolytic aromatic substitutions with nucleophilic alkyl radicals, generated under oxidative conditions by addition of an electrophilic radical to an alkene.[15,16] However, the analogous process involving the final reaction between an electrophilic radical such as **A** and an aromatic or heteroaromatic ring under nonoxidative conditions is less common.[17] In the context of the present work, it is relevant to mention the formation of cycloalkano[*a*]pyrroles from 1-(ω-iodoalkyl)-pyrroles and activated olefins under electroreductive conditions[18] and the *n*-Bu_6Sn_2-mediated formation of pyrido[1,2-*a*]indoles from 1-(2-iodoethyl)indoles and methyl acrylate.[19]

To further develop the synthetic possibilities of 2-indolylacyl radicals, we decided to explore the question of whether or not the above annulation process from phenyl selenoester **1** and suitable electron-deficient alkenes could be of preparative interest, thus allowing access to the cyclopenta[*b*]indole nucleus present in several indole alkaloids.[20] To minimize the formation of the simple addition products (e.g., **2** or **4**), we used nonreductive conditions (*n*-Bu_6Sn_2, *hν*, C_6H_6, Scheme 3). The results are summarized in Table 1.

Scheme 3



Satisfactorily, heating a benzene solution of phenyl selenoester **1** (1 mol) and dimethyl fumarate (4 mol) in the presence of *n*-Bu_6Sn_2 (1.2 mol) under sun-lamp irradiation gave the expected cyclized aromatic product **3** in 45% yield (entry 1). No trace of adduct **2** was detected. In a similar manner, tetracycle **5**, with the hexahydroindeno[2,1-*b*]indole skeleton characteristic of the alkaloid yuehchukene,[21] was obtained in 53% yield as the only reaction product from methyl 1-cyclohexenecarboxylate (entry 2).

The above cascade reactions probably involve the initial homolytic cleavage of *n*-Bu_6Sn_2 to generate the intermediate 2-indolylacyl radical. As in the above TTMSS–AIBN conditions, this radical would undergo the addition–cyclization–oxidation[22] sequence depicted in Scheme 2, which would now be favored in the absence of potential competitive reactions.

To investigate the scope and efficiency of the process, the same protocol was applied to other alkene acceptors varying either the substitution pattern or the electron-withdrawing groups.[23] From methyl crotonate (entry 3), the corresponding cyclopenta[*b*]indole **7** was isolated in the highest yield in this series (71%). Interestingly, minor amounts (8%) of adduct **8** were formed. Similarly, when phenyl selenoester **1** reacted with α,β-unsaturated lactam ester **9**, the pyridocyclopenta[1,2-*b*]indole **10** was obtained in 41% yield along with significant amounts (27%) of adduct **11** (entry 4). On the other hand, adducts **12** (52%) and **13** (55%) were the only isolated products (entries 5 and 6, respectively) when 2-cyclohexenone or 2-cyclopentenone was used as an acceptor.[9] These adducts were obtained in similar yields (40–50%) when these reactions were carried out in solvents other than benzene such as cyclohexane or acetonitrile.

A possible rationale for the above results is as follows. We can consider that the cyclization of radical adduct **C** (Scheme 4) to give a five-membered ring fused to the indole nucleus is relatively slow, particularly in the reactions described in entries 4–6 of Table 1 because of the strain associated with the resulting tetracyclic systems. In this situation, reduction becomes a competitive reaction. Although the transfer of a hydrogen atom from the solvent cannot be ruled out, this reduction might also

(11) For a related example, see: Gribble, G. W.; Fraser, H. L.; Badenock, J. C. *Chem. Commun.* **2001**, 805–806.

(12) Stella, L.; Harvey, J. N. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 360–380.

(13) Curran, D. P.; Yu, H.; Liu, H. *Tetrahedron* **1994**, *50*, 7343–7366.

(14) Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119–10128.

(15) (a) Chuang, C.-P.; Wang, S.-F. *Synth. Commun.* **1994**, *24*, 1493–1505. (b) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339–363. See also: (c) Wang, S. F.; Chuang, C. P.; Lee, J.-H.; Liu, S. T. *Tetrahedron* **1999**, *55*, 2273–2288.

(16) For similar addition–cyclization sequences, but involving two separate steps, see: (a) Liard, A.; Quiclet-Sire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 1759–1762. (b) Kaoudi, T.; Quiclet-Sire, B.; Seguin, B.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2000**, *39*, 731–733.

(17) (a) Araneo, S.; Fontana, F.; Minisci, F.; Recupero, F.; Serri, A. *Tetrahedron Lett.* **1995**, *36*, 4307–4310. (b) Beckwith, A. L. J.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1995**, 977–978.

(18) Ozaki, S.; Mitoh, S.; Ohmori, H. *Chem. Pharm. Bull.* **1996**, *44*, 2020–2024.

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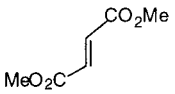
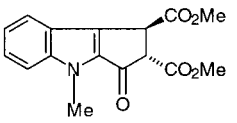
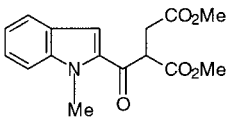
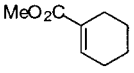
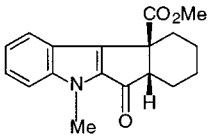
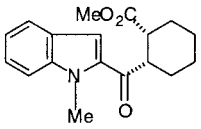
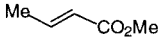
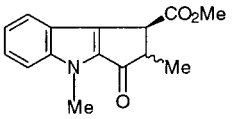
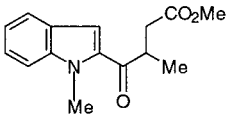
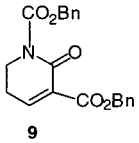
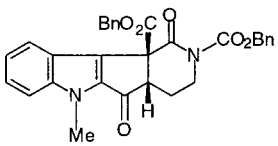
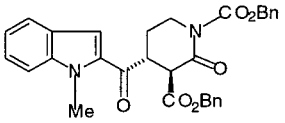
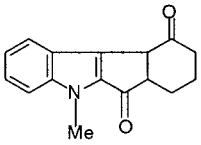
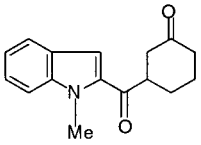
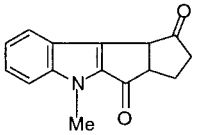
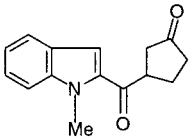
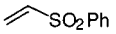
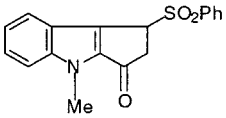
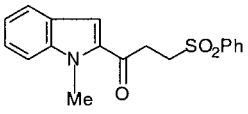
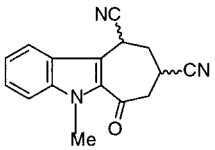
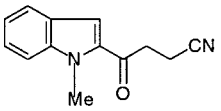
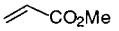
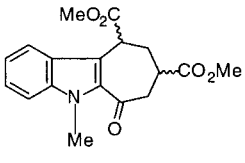
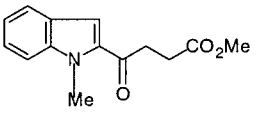
(20) Bergman, J.; Venemalm, L. *Tetrahedron* **1990**, *46*, 6067–6084 and references therein.

(21) Ishikura, M.; Imaizumi, K.; Katagiri, N. *Heterocycles* **2000**, *53*, 553–556 and references therein.

(22) The oxidative cyclization mechanism mediated by Me_6Sn_2 has been discussed: (a) Josien, H.; Ko, S. B.; Bom, D.; Curran, D. P. *Chem. Eur. J.* **1998**, *4*, 67–83. (b) Bowman, W. R.; Bridge, C. F.; Cloonan, M. O.; Leach, D. C. *Synlett* **2001**, 765–768. See also ref 19.

(23) The use of styrene and other electron-rich alkenes was unsuccessful.

Table 1. *n*-Bu_6Sn_2-Mediated Reactions of Phenyl Selenoester 1 with Alkene Acceptors

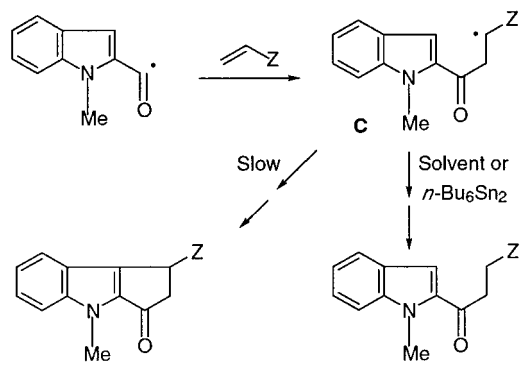
entry	alkene acceptor	addition-cyclization product		Yield[a] (%)	addition product		Yield[a] (%)
1			**3**	45[b]		**2**[c]	0
2			**5**	53		**4**	0
3			**7**	71[d]		**8**[c]	8
4	 **9**		**10**	41		**11**	27
5				0		**12**[c]	52
6				0		**13**[c]	55
7			**14**	22		**15**	<5
8			**16**	42[e]		**17**[c]	0
9			**18**	61[f]		**19**[c]	0

[a] Isolated yields of chromatographically pure material. [b] Yield of 41% from dimethyl maleate. [c] From ref 9. [d] A 4:3 mixture of cis/trans stereoisomers. [e] A 4:1 mixture of cis/trans stereoisomers. [f] A 3:1 mixture of cis/trans stereoisomers.

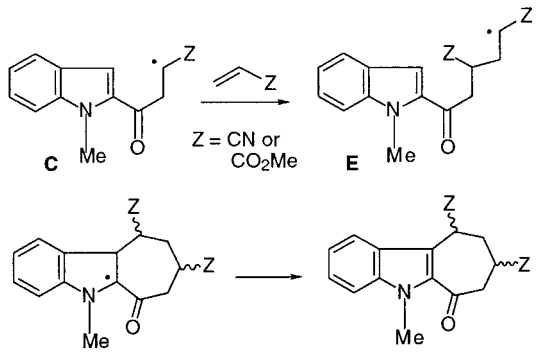
take place via the reaction of **C** with excess *n*-Bu_6Sn_2 to give a tin enolate, which would undergo hydrolysis during the workup.

The behavior of β-unsubstituted electron-deficient alkenes in the *n*-Bu_6Sn_2-mediated 2-indolylacyl radical addition−cyclization sequence from phenyl selenoester **1** also deserves comment. Thus, vinyl sulfone (entry 7) was not an efficient acceptor, the corresponding cyclopenta[*b*]indole **14** being obtained in a modest 22% yield along with trace amounts of the initially formed adduct **15**, which was the main product (38%) under *n*-Bu_3SnH−AIBN conditions (see Experimental Section). On the other hand, the use of the more reactive alkene acceptors acrylonitrile or methyl acrylate (entries 8 and 9) resulted

Scheme 4



Scheme 5



in the formation of the bis-addition−cyclization products **16** and **18**. Surprisingly, **16** and **18** were also the predominant products when the reactions were performed with smaller amounts (1 or 1.5 mol) of the alkene. This result is another reflection of the slow cyclization of the radical adduct **C** to give a strained cyclopenta[*b*]indole. It seems reasonable to asume that **C** reacts faster with a second molecule of alkene acceptor to give a new radical adduct **E**, which would undergo a more favorable cyclization to the cyclohepta[*b*]indole **16** or **18** (Scheme 5).

In summary, an unprecedented radical cascade reaction comprising an intermolecular 2-indolylacyl radical addition−oxidative cyclization sequence from phenyl selenoester **1** and a series of electron-deficient alkenes has been developed. When α,β-unsaturated esters are used as acceptors, this annulation process provides straightforward access to cyclopenta[*b*]indoles and, in some cases, cyclohepta[*b*]indoles in acceptable yields.

Experimental Section

General Procedures. Reaction courses and product mixtures were routinely monitored by TLC on silica gel (precoated F_{254} Merck plates). Drying of organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of the solvents was accomplished under reduced pressure with a rotatory evaporator. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.04−0.06 mm). Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ solution, using TMS as the internal reference. Microanalyses and HRMS analyses were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona.

Reaction of Phenyl Selenoester 1 and Dimethyl Fumarate under TTMSS−AIBN Conditions. TTMSS (0.4 mL, 1.28 mmol) and AIBN (0.21 g, 1.28 mmol) in C_6H_6 (4 mL) were added over a period of 2 h (syringe pump) to a heated (reflux) solution of selenoester **1** (0.2 g, 0.64 mmol) and dimethyl fumarate (0.46 g, 3.2 mmol) in C_6H_6 (12 mL). After an additional 3 h at reflux, the solution was concentrated under reduced pressure, and the resulting residue was chromatographed.

Dimethyl 2-(1-Methyl-2-indolylcarbonyl)butanedioate (2): 0.05 g (26%); elution with 9:1 hexanes−AcOEt; ^{1}H NMR (200 MHz) δ 3.09 (d, J = 7.2 Hz, 2H), 3.70 and 3.71 (2 s, 6H), 4.06 (s, 3H), 4.83 (t, J = 7.2 Hz, 1H), 7.17 (m, 1H), 7.40 (m, 2H), 7.51 (s, 1H), 7.72 (dt, J = 1.2, 8 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 32.3 (CH_3), 33.2 (CH_2), 50.9 (CH), 52.1 (CH_3), 52.9 (CH_3), 110.4 (CH), 113.4 (CH), 120.9 (CH), 123.3 (CH), 125.7 (C), 126.6 (CH), 133.6 (C), 140.6 (C), 169.4 (C), 171.6 (C), 186.6 (C); HRMS calcd for $C_{16}H_{16}NO_5$ 302.1028, found 302.1024.

Dimethyl *trans*-4-Methyl-3-oxocyclopenta[*b*]indole-1,2-dicarboxylate (3): 0.05 g (26%); elution with 8:2 hexanes−AcOEt; ^{1}H NMR (300 MHz, assignment aided by NOE and HMQC) δ 3.83 (2 s, 6H, OMe), 3.90 (s, 3H, NMe), 4.51 (d, J = 2.9 Hz, 1H, 2-H), 4.78 (d, J = 2.9 Hz, 1H, 1-H), 7.22 (m, 1H, 7-H), 7.38 (d, J = 8 Hz, 1H, 5-H), 7.40 (m, 1H, 6-H), 7.88 (d, J = 8 Hz, 1H, 8-H); ^{13}C NMR (75.4 MHz, assignment aided by HMQC and HMBC) δ 30.2 (NMe), 42.8 (C-1), 52.7 and 53.0 (OMe), 60.5 (C-2), 111.0 (C-5), 121.1 (C-7), 122.4 (C-8a), 122.6 (C-8), 127.6 (C-6), 136.0 (C-3a), 139.6 (C-8b), 145.2 (C-4a), 168.5 and 170.1 (CO), 184.9 (C-3); HRMS calcd for $C_{16}H_{15}NO_5$ 301.0950, found 301.0956.

Reaction of Phenyl Selenoester 1 and Methyl 1-Cyclohexenecarboxylate under TTMSS−AIBN Conditions. Operating as above, from selenoester **1** (0.20 g, 0.64 mmol) and 1-cyclohexenecarboxylate (0.43 g, 3.2 mmol), the following compounds were obtained after flash chromatography of the resultant residue.

Methyl *cis*-2-(*N*-Methyl-2-indolylcarbonyl)cyclohexanecarboxylate (4): 0.03 g (15%); elution with 95:5 hexanes−AcOEt; ^{1}H NMR (600 MHz, assignment aided by HMQC) δ 1.40 (m, 1H, 4-H_{eq}), 1.50 (m, 2H, 5-H), 1.78 (m, 1H, 4-H_{ax}), 1.86 (m, 1H, 3-H_{ax}), 1.92 (m, 1H, 6-H_{eq}), 2.15 (m, 1H, 3-H_{eq}), 2.41 (m, 1H, 6-H_{ax}), 2.83 (ddd, J = 4.2, 4.8, 8.6 Hz, 1H, 1-H_{ax}), 3.61 (s, 3H, OMe), 3.78 (q, J = 5.4, 1H, 2-H_{eq}), 4.04 (s, 3H, NMe), 7.18 (m, 1H, indole 5-H), 7.22 (s, 1H, indole 3-H), 7.38 (m, 2H, indole 6-H, 7-H), 7.72 (d, J = 8 Hz, 1H, 4-H); ^{13}C NMR (75.4 MHz, assignment aided by HMQC) δ 23.1 (C-5), 24.0 (C-4), 26.1 (C-6), 28.1 (C-3), 32.1 (NMe), 43.4 (C-1), 46.3 (C-2), 51.6 (OMe), 109.9 (indole C-3), 110.3 (indole C-7), 120.5 (indole C-5), 122.6 (indole C-4), 125.4 (indole C-6), 125.7 (indole C-3a), 134.3 (indole C-7a), 139.7 (indole C-2), 174.3, 196.1 (CO); HRMS calcd for $C_{18}H_{21}NO_3$ 299.1521, found 299.1517.

Methyl *cis*-6,6a,7,8,9,10,10a-Hexahydro-6*H*-5-methyl-6-oxoindeno[2,1-*b*]indole-10a-carboxylate (5): 0.03 g (15%); elution with 9:1 hexanes−AcOEt; ^{1}H NMR (500 MHz, assignment aided by HMQC) δ 1.2−1.5 (m, 4H, 8-H, 9-H), 1.65 and 2.42 (2 m, 2H, 10-H), 1.80 and 2.05 (2 m, 2H, 7-H), 3.59 (dd, J = 4.8, 6.2 Hz, 1H, 6a-H), 3.79 (s, 3H, OMe), 3.93 (s, 3H, NMe), 7.20 (m, 1H, 2-H), 7.40 (m, 2H, 3-H, 4-H), 7.87 (d, J = 8 Hz, 1H, 1-H); ^{13}C NMR (50.3 MHz, assignment aided by HMQC and HMBC) δ 19.2 (C-8), 19.9 (C-9), 22.1 (C-7), 30.3 (NMe), 32.7 (C-10), 49.0 (C-10a), 52.5 (OMe), 55.3 (C-6a), 111.0 (C-4), 120.6 (C-2), 122.1 (C-10c), 122.5 (C-1), 126.6 (C-3), 137.1 (C-5a), 143.9 (C-10b), 144.5 (C-4a), 174.7 (CO), 194.8 (C-6); HRMS calcd for $C_{18}H_{19}NO_3$ 297.1364, found 297.1356.

Tetracycle 6: 0.03 g (15%); elution with 9:1 hexanes−AcOEt; ^{1}H NMR (200 MHz) δ 0.9−1.1 (m, 4H), 1.26 and 1.35 (2 s, 6H), 1.2−1.4 (m, 3H), 2.20 (m, 1H), 3.16 (s, 3H), 3.25 (m, 1H), 3.79 (s, 1H), 3.90 (s, 3H), 6.43 (d, J = 7.8 Hz, 1H), 6.72 (td, J = 0.9, 7.2 Hz, 1H), 7.10 (d, J = 7.2 Hz, 1H), 7.18 (td, J = 1.2, 7.5 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 21.1 (CH_2), 21.9 (CH_2), 22.2 (CH_2), 22.4 ($2CH_3$), 28.1 (CH_2), 31.4 (CH_3), 39.6 (C), 49.8 (C), 52.7 (CH_3), 54.6 (CH), 54.8 (CH), 77.2 (C), 106.2 (CH), 118.0 (CH), 123.1 (C), 124.4 (C), 125.0 (CH), 129.4 (CH), 151.1 (C), 175.4 (C), 208.9 (C).

General Procedure for the *n*-Bu_6Sn_2-Mediated Reactions of Phenyl Selenoester 1 with Alkene Acceptors. A solution of selenoester **1** (0.65 mmol), the alkene acceptor (2.60 mmol), and *n*-Bu_6Sn_2 (0.80 mmol) in C_6H_6 (30 mL) was refluxed under sun-lamp irradiation (300 W) for 24 h. The solution was concentrated under reduced pressure; the residue was partitioned between hexanes (15 mL) and acetonitrile (15 mL), and the polar layer was washed with hexanes (3 × 15 mL) to remove

tin compounds. The solvent was removed, and the crude product was chromatographed (flash, hexanes−AcOEt). The results are given in Table 1. Eluents, melting points, NMR data, and HRMS or elemental analyses are given below.

Methyl 2,4-Dimethyl-3-oxocyclopenta[*b*]indole-1-carboxylate (7). Major cis isomer: 8:2 hexanes−AcOEt; mp 59−60 °C; ^{1}H NMR (200 MHz, assignment aided by NOE and HMQC) δ 1.32 (d, J = 7.8 Hz, 3H, CH_3), 3.35 (q, J = 7.4 Hz, 1H, 2-H), 3.75 (s, 3H, NMe), 3.94 (s, 3H, OMe), 4.42 (d, J = 7 Hz, 1H, 1-H), 7.18 (m, 1H, 7-H), 7.40 (m, 2H, 5-H, 6-H), 7.64 (dt, J = 1.2, 7.8 Hz, 1H, 8-H); ^{13}C NMR (50.3 MHz, assignment aided by HMQC) δ 13.0 (CH_3), 30.2 (NMe), 43.7 (C-1), 49.8 (C-2), 52.1 (OMe), 111.1 (C-5), 120.8 (C-7), 121.7 (C-8), 122.6 (C-8a), 126.9 (C-6), 138.1 and 139.2 (C-3a, C-8b), 144.9 (C-4a), 171.8 (CO), 194.7 (C-3); HRMS calcd for $C_{15}H_{15}NO_3$ 257.1052, found 257.1045. Minor trans isomer: 9:1 hexanes−AcOEt; ^{1}H NMR (200 MHz, assignment aided by NOE) δ 1.45 (d, J = 7.4 Hz, 3H, CH_3), 3.42 (qd, J = 2.8, 7.8 Hz, 1H, 2-H), 3.81 (s, 3H, NMe), 3.90 (d, J = 2.8 Hz, 1H, 1-H), 3.92 (s, 3H, OMe), 7.21 (m, 1H, 7-H), 7.40 (m, 2H, 5-H, 6-H), 7.80 (dt, J = 1.2, 7.8 Hz, 1H, 8-H); ^{13}C NMR (50.3 MHz) δ 16.3 (CH_3), 30.2 (CH_3), 47.3 (CH), 50.9 (CH), 52.4 (CH_3), 111.0 (CH), 120.8 (CH), 122.2 (CH), 122.6 (C), 126.9 (CH), 137.3 and 138.1 (2C), 144.9 (C), 172.2 (C), 195.0 (C); HRMS calcd for $C_{15}H_{15}NO_3$ 257.1052, found 257.1050.

Methyl 3-Methyl-4-(*N*-methyl-2-indolyl)-4-oxobutanoate (8): 95:5 hexanes−AcOEt; ^{1}H NMR (300 MHz) δ 1.30 (d, J = 7.2 Hz, 3H), 2.45 (dd, J = 6, 16.4 Hz, 1H), 2.97 (dd, J = 8.2, 16.4 Hz, 1H), 3.65 (s, 3H), 3.90 (m, 1H), 4.06 (s, 3H), 7.18 (m, 1H), 7.40 (m, 3H), 7.75 (d, J = 8 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 18.9 (CH_3), 32.2 (CH_3), 37.4 (CH_2), 39.1 (CH), 51.7 (CH_3), 110.3 (CH), 111.5 (CH), 120.7 (CH), 123.0 (CH), 125.8 (C), 126.0 (CH), 133.8 (C), 140.3 (C), 172.7 (C), 196.4 (C); HRMS calcd for $C_{15}H_{17}NO_3$ 257.1208, found 257.1214.

Benzyl *cis*-2-(Benzyloxycarbonyl)-3,4,4a,10c-tetrahydro-2*H*-6-methyl-1,5-dioxopyrido[3′,4′:3,4]cyclopenta[1,2-*b*]indole-10c-carboxylate (10): 6:4 hexanes−AcOEt; ^{1}H NMR (200 MHz, assignments aided by HMQC) δ 2.40 (m, 2H, 4-H), 3.40 and 4.0 (2 m, 2H, 3-H), 3.53 (dd, J = 5.2, 5.4 Hz, 1H, 4a-H), 3.92 (s, 3H, NMe), 5.17 and 5.34 (2 d, J = 16 Hz, 2H, CH_2Ph), 5.20 (s, 2H, CH_2Ph), 7.20−7.45 (m, 13H), 8.05 (d, J = 8.4 Hz, 1H, 10-H); ^{13}C NMR (50.3 MHz, assignment aided by HMQC and HMBC) δ 25.0 (C-4), 30.4 (NMe), 43.5 (C-3), 56.4 (C-4a), 59.4 (C-10c), 68.1 (CH_2Ph), 68.8 (CH_2Ph), 110.8 (C-7), 121.7 (C-9), 122.9 (C-10a), 124.2 (C-10), 127.8 (C-8), 127.9−128.5 (6CH), 134.9 and 135.0 (2C), 137.9 (C-5a), 138.3 (C-10b), 145.4 (C-6a), 153.1 (CO), 166.6 (C-1), 169.1 (CO), 190.9 (C-5); HRMS calcd for $C_{31}H_{26}N_2O_6$ 522.1790, found 522.1778.

***trans*-1,3-Bis(benzyloxycarbonyl)-4-(*N*-methyl-2-indolylcarbonyl)-2-piperidone (11):** 7:3 hexanes−AcOEt; ^{1}H NMR (300 MHz) δ 2.05 and 2.35 (2 m, 2H), 3.75 and 4.0 (2 m, 2H), 4.0 (s, 3H), 4.18 (d, J = 9.6 Hz, 1H), 4.23 (dt, J = 6.5, 7.5, 10.4 Hz, 1H), 5.15 and 5.19 (2 d, J = 16 Hz, 2H), 5.33 (s, 2H), 7.20−7.45 (m, 13H), 7.75 (d, J = 8.4 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 26.9 (CH_2), 32.2 (CH_3), 43.8 (CH), 44.0 (CH_2), 52.6 (CH), 67.5 (CH_2), 69.0 (CH_2), 110.4 (CH), 112.7 (CH), 121.1 (CH), 123.2 (CH), 125.7 (C), 126.7 (CH), 128.1−128.6 (6CH), 132.7 (C), 135.1 (2C), 140.7 (C), 153.4 (C), 167.0 (C), 168.3 (C), 191.8 (C); HRMS calcd for $C_{31}H_{28}N_2O_6$ 524.1947, found 524.1957.

3-(*N*-Methyl-2-indolylcarbonyl)cyclohexanone (12): 8:2 hexanes−AcOEt; ^{1}H NMR (200 MHz) δ 1.88−2.20 (m, 4H), 2.42 (m, 2H), 2.49 (dd, J = 4.8, 14.5 Hz, 1H), 2.75 (dd, J = 10.8, 14.5 Hz, 1H), 3.79 (m, 1H), 4.08 (s, 3H), 7.17 (m, 1H), 7.33 (s, 1H), 7.40 (m, 2H), 7.70 (dt, J = 1.2, 8.2 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 24.9 (CH_2), 29.3 (CH_2), 32.4 (CH_3), 41.0 (CH_2), 43.6 (CH_2), 47.1 (CH), 110.4 (CH), 111.7 (CH), 120.9 (CH), 123.0 (CH), 125.6 (C), 126.3 (CH), 133.1 (C), 140.4 (C), 194.1 (C), 210.4 (C); HRMS calcd for $C_{16}H_{17}NO_2$ 255.1259, found 255.1247.

3-(*N*-Methyl-2-indolylcarbonyl)cyclopentanone (13): 7:3 hexanes−AcOEt; ^{1}H NMR (300 MHz) δ 2.17−2.43 (m, 4H), 2.46 (dd, J = 8.4, 15.6 Hz, 1H), 2.73 (dd, J = 8, 15.6 Hz, 1H), 4.09 (m, 1H), 4.09 (s, 3H), 7.18 (m, 1H), 7.37 (s, 1H), 7.40 (m, 2H), 7.71 (d, J = 8 Hz, 1H); ^{13}C NMR (75.4 MHz) δ 27.9 (CH_2), 32.3 (CH_3), 37.5 (CH_2), 41.4 (CH_2), 44.7 (CH), 110.4 (CH), 111.7 (CH), 120.9 (CH), 122.9 (CH), 125.6 (C), 126.3 (CH), 133.6 (C), 140.3 (C), 193.9 (C), 216.8 (C); HRMS calcd for $C_{15}H_{15}NO_2$ 241.1103, found 241.1095.

4-Methyl-1-(phenylsulfonyl)cyclopenta[*b*]indol-3-one (14): 7:3 hexanes−AcOEt; mp 150−151 °C; ^{1}H NMR (200 MHz) δ 3.21 (dd, J = 3.6, 5.4 Hz, 2H), 3.86 (s, 3H), 5.06 (dd, J = 3.6, 4.8 Hz, 1H), 7.25 (m, 2H), 7.35−7.55 (m, 3H), 7.67 (m, 3H), 7.78 (d, J = 8 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 30.2 (CH_3), 43.2 (CH_2), 59.9 (CH), 111.0 (CH), 121.8 (CH), 122.7 (C), 123.2 (CH), 127.5 (CH), 129.1 (2CH), 134.0 (C), 134.1 (CH), 136.0 (C), 140.1 (C), 144.7 (C), 189.0 (C). Anal. Calcd for $C_{18}H_{15}NO_3S\cdot0.5H_2O$: C, 64.65; H, 4.82; N, 4.19. Found: C, 64.57; H, 4.54; N, 3.95.

5-Methyl-6-oxocyclohepta[*b*]indole-8,10-dicarbonitrile (16). Major trans isomer: 6:4 hexanes−AcOEt; ^{1}H NMR (500 MHz, assignment aided by HMQC) δ 2.46 (ddd, J = 3.8, 9, 14.6 Hz, 1H, 9-H_{ax}), 2.92 (dt, J = 5.5, 5.6, 14.2 Hz, 1H, 9-H_{eq}), 3.16 (dd, J = 8.2, 16.7 Hz, 1H, 7-H_{ax}), 3.53 (dd, J = 5, 16.5 Hz, 7-H_{eq}), 3.55 (m, 1H, 8-H), 4.01 (s, 3H, NMe), 4.73 (dd, J = 3.8, 5.5 Hz, 1H, 10-H), 7.28 (m, 1H, 2-H), 7.45 (m, 1H, 3-H), 7.47 (d, J = 8 Hz, 1H, 4-H), 7.75 (d, J = 8.4 Hz, 1H, 1-H); ^{13}C NMR (75.4 MHz, assignment aided by HMQC and HMBC) δ 23.8 (C-8), 25.5 (C-10), 32.4 (N−CH_3), 33.6 (C-9), 44.6 (C-7), 110.9 (C-4), 115.7 (C-10a), 118.1 and 119.6 (2CN), 119.8 (C-1), 121.9 (C-2), 124.5 (C-10b), 127.2 (C-3), 133.1 (C-5a), 138.8 (C-4a), 188.4 (C-6).

Dimethyl 5-Methyl-6-oxocyclohepta[*b*]indole-8,10-dicarboxylate (18). Major trans isomer: 1:1 hexanes−AcOEt; ^{1}H NMR (300 MHz, assignment aided by HMQC) δ 2.40 (ddd, J = 4.8, 9, 14.6 Hz, 1H, 7-H_{ax}), 2.85 (ddd, J = 4.5, 5.9, 14.5 Hz, 1H, 7-H_{eq}), 3.15 (dd, J = 4.8, 15.2 Hz, 1H, 7-H), 3.40 (dd, J = 6.6, 15.2 Hz, 1H, 7-H), 3.35 (m, 1H, 8-H), 3.65 and 3.67 (2 s, 6H, 2OMe), 3.97 (s, 3H, NMe), 4.55 (t, J = 4.5 Hz, 1H, 10-H), 7.17 (m, 1H, 2-H), 7.35 (m, 2H), 7.63 (d, J = 8.4 Hz, 1H, 1-H); ^{13}C NMR (75.4 MHz, assignment aided by HMQC and HMBC) δ 31.5 (C-9), 32.1 (NMe), 37.8 (C-8), 39.8 (C-10), 44.8 (C-7), 52.2 and 52.6 (2OMe), 110.4 (C-4), 120.4. (C-1), 120.7 (C-2), 122.9 (C-10b), 126.1 (C-3), 133.6 (C-5a), 138.8 (C-4a), 173.1 and 174.3 (2 CO), 192.5 (C-6); HRMS calcd for $C_{18}H_{19}NO_5$ 329.1263, found 329.1253.

3-(*N*-Methyl-2-indolyl)-3-oxopropyl Phenyl Sulfone (15). *n*-Bu_3SnH (0.21 mL, 0.8 mmol) in C_6H_6 (3 mL) was added over a period of 1 h (syringe pump) to a heated (reflux) solution of **1** (0.20 g, 0.64 mmol), phenyl vinyl sulfone (0.54 g, 3.2 mmol), and AIBN (0.1 mmol) in C_6H_6 (6 mL). After an additional 3 h at reflux, the solution was concentrated, and the resulting residue was chromatographed (flash, 8:2 hexanes−AcOEt) to give sulfone **15**: 0.08 g (38%); ^{1}H NMR (200 MHz) δ 3.53 (m, 4H), 3.98 (s, 3H), 7.18 (m, 1H), 7.35 (m, 3H), 7.59 (m, 3H), 7.70 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 8.4 Hz, 2H); ^{13}C NMR (50.3 MHz) δ 32.2 (CH_3), 32.4 (CH_2), 51.1 (CH_2), 110.4 (CH), 112.0 (CH), 121.0 (CH), 123.1 (CH), 125.6 (C), 126.4 (CH), 128.0 (CH), 129.3 (CH), 133.5 (C), 133.9 (CH), 138.9 (C), 140.2 (C), 188.5 (C); HRMS calcd for $C_{18}H_{17}NO_3S$ 327.0929, found 327.0927.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **2**−**8**, **10**−**13**, **15**, **16**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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