Indolecarbonyl Coupling Reactions Promoted by Samarium Diiodide. Application to the Synthesis of Indole-Fused Compounds

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By the assistance of an *N*-sulfonyl group or a cyano group at the C-2 position, hydroxyalkylations of indole-3-carbonyls were achieved by the promotion of samarium diiodide. The indolecarbonyl coupling reactions proceeded in high stereoselectivity via chelate transition states. Intramolecular indolecarbonyl couplings of 1-(3-oxopropyl)indole-3-carboxaldehydes were realized as the indolecarbonyl group was more reactive toward SmI_2 than the aliphatic carbonyl group. Elaboration of the coupling products with oxidizing agents, acid, phosphorus pentasulfide (or Lawesson's reagent), amines, and hydrazine led to a variety of indole derivatives and indole-fused polycyclic compounds of synthetic interest and pharmaceutical uses.

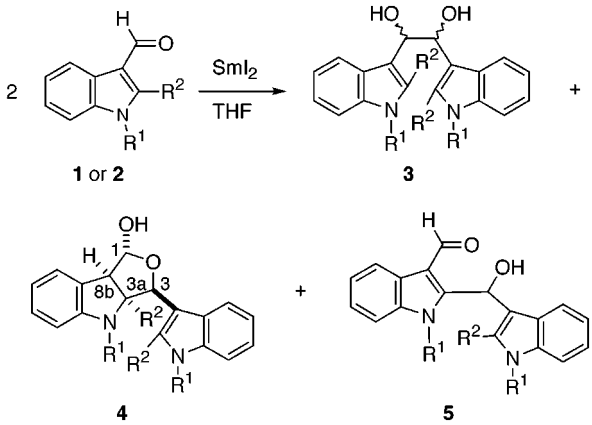
Introduction

The chemistry of indole compounds[1] has been extensively studied, partly due to their uses in pharmaceutical and industrial products. However, most studies of indole-3-carbonyls are limited to the conventional reactions, such as reductions, oxidations (for indole-3-carboxaldehydes), nucleophilic reactions of organometallic reagents, condensations with active methylene compounds, and aldol reactions (for 3-acetylindoles), similar to those found in common aromatic aldehydes and ketones. In a previous paper,[2] we demonstrated a new method for hydroxyalkylations at the C-2 positions of indole-3-carbonyls by the SmI_2-promoted coupling reactions. We report herein the scope and application of this method.

Results and Discussion

On treatment with SmI_2 (2 equiv) in THF at ambient temperature for 1 h, 1-(methylsulfonyl)indole-3-carboxaldehyde (**1b**) underwent a reductive coupling reaction to give **4b** in 66% yield (Table 1). According to the ^1H NMR analysis, compound **4b** consisted of three isomers (92:6:2), of which the major isomer was isolated and determined to have the (1*R**,3*S**,3a*S**,8b*R**) configuration by X-ray diffraction. The large coupling constant (8.5 Hz) between H-3a and H-8b was in agreement with their cis relationship. The analogous indolecarboxaldehydes **1c** and **1d** containing *p*-tolylsulfonyl or phenylsulfonyl groups at the 1-position also underwent similar self-coupling reactions to give **4c** and **4d** in 50% and 37% yields, respectively. Some pinacolic coupling products **3c** (15%) and **3d** (6%) were also found.[3] Under similar reaction conditions, 1-(*tert*-butoxycarbonyl)indole-3-carboxaldehyde (**1e**) only yielded a small amount (9%) of self-coupling product **4e**, while a large amount (36%) of the starting material was recovered. The reaction of 1-methylindole-3-carboxaldehyde (**1a**) was very sluggish; no apparent reaction occurred on treatment with SmI_2 in

Table 1. Self-Coupling Reactions of Indole-3-carboxaldehydes Promoted by SmI_2 in THF Solution



entry	reactant	R^1	R^2	HMPA equiv	products (yield/%)
1[a]	**1a**	Me	H	8	**3a** (44)
2[a]	**1b**	$MeSO_2$	H	0	**4b** (66)
3[a]	**1b**	$MeSO_2$	H	8	**4b** (15)[b]
4[a]	**1c**	*p*-$MeC_6H_4SO_2$	H	0	**3c** (15) + **4c** (50)
5[a]	**1d**	$C_6H_5SO_2$	H	0	**3d** (6) + **4d** (37)
6[a]	**1e**	*t*-BuOCO	H	0	**4e** (9)[c]
7[a]	**2a**	Me	CN	8	**5** (30)[d]
8[e]	**2a**	Me	CN	8	**5** (62)

[a] The THF solution of reactant (**1** or **2a**) was added to the freshly prepared SmI_2 solution. [b] The starting material **1b** (11%) and its desulfonylation product, indole-3-carboxaldehyde (42%), were also obtained. [c] The starting material **1e** (36%) was recovered. [e] The SmI_2-HMPA solution was added to the THF solution of **2a**.

(1) (a) Remers, W. A. In *Heterocyclic Compounds*; Houlihan, W. J., Ed.; Wiley: New York, 1979; Vol. 25, Part III, pp 357−527. (b) Saxton, J. E. In *The Chemistry of Heterocyclic Compounds*; Academic Press: New York, 1983; Vol. 25, Part 4. (c) Gribble, G. W. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1990; Vol. 39, p 239. (d) Sundberg, R. J. *Indoles*; Academic Press: New York, 1996.

(2) (a) Shiue, J.-S.; Fang, J.-M. *J. Chem. Soc., Chem. Commun.* **1993**, 1277. For related study on the phenyl and thiophene systems: (b) Shiue, J.-S.; Lin, C.-C.; Fang, J.-M. *Tetrahedron Lett.* **1993**, *34*, 335. (c) Yang, S.-M.; Fang, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2669. (d) Yang, S.-M.; Fang, J.-M. *Tetrahedron Lett.* **1997**, *38*, 1589. (e) Shiue, J.-S.; Lin, M.-H.; Fang, J.-M. *J. Org. Chem.* **1997**, *62*, 4643.

(3) To our knowledge, there is no report on the pinacolic coupling reaction of indolecarboxaldehydes. For general pinacolic coupling reactions promoted by SmI_2, see: Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

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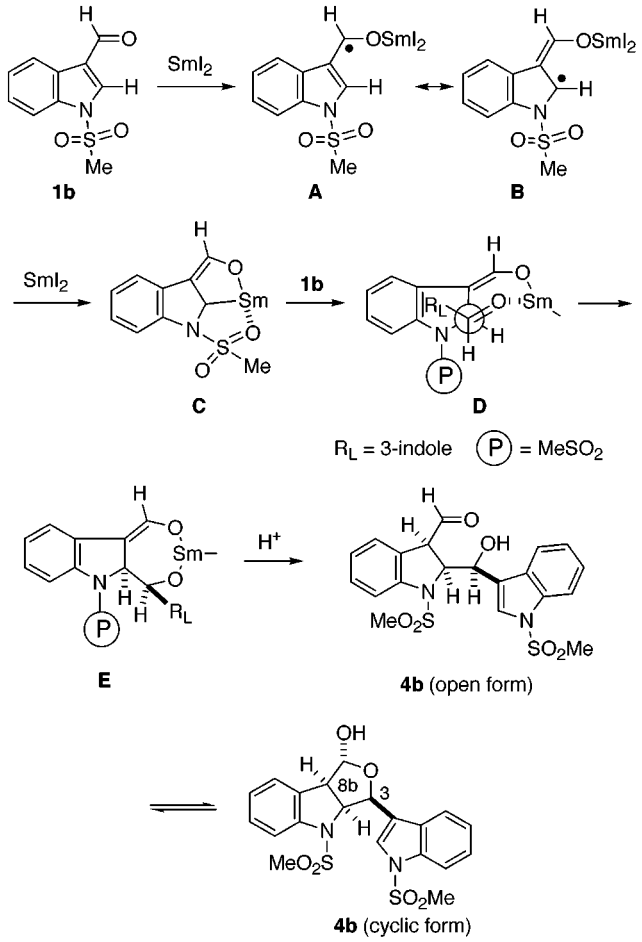
Scheme 1



THF for a similar period (1 h). However, a pinacol **3a** (diastereomeric ratio 10:1) could be isolated after stirring for 7 days in the presence of a dipolar cosolvent HMPA, which is often used to enhance the reactivity of SmI_2.[4] When **1b**−**d** were treated with SmI_2 in the presence of HMPA, severe cleavage of the sulfonyl groups occurred to give the corresponding indole-3-carboxaldehyde as the main product.[5]

A reaction mechanism, as exemplified by the formation of **4b** (Scheme 1), is proposed to account for the stereochemistry observed in the self-coupling reactions. The reaction was presumably initiated by one-electron transfer from SmI_2 to the indolecarbonyl group of **1b**. The intermediate C-2 radical anion **B** was further reduced by SmI_2 to give an organosamarium **C**, which was stabilized by the adjacent sulfonyl group.[6a] Addition of a second molecule of **1b** to the intermediate **C** might proceed with a chelate transition state **D**.[2] The alternative transition state by placing the indole ring (R_L) adjacent to the sulfonyl group (P) was less favorable due to the steric effect. Protonation of the samarium enolate **E** should occur on the less hindered exo face to furnish **4b** (open form), which existed as a thermodynamically stable cyclic form of hemiacetal. On the other hand, such stabilization at C-2 would be void in the case of **1a** with a 1-methyl group. Thus, no coupling reaction at the C-2 position of **1a** could occur.

As stabilization of the C-2 radical or anion is a prerequisite factor to achieve the indolecarbonyl coupling reaction, we consider that introduction of a cyano substituent at C-2 may exert a beneficial effect. Indeed, the coupling reaction of 2-cyano-1-methylindole-3-carboxaldehyde (**2a**), followed by in situ elimination of HCN, occurred on treatment with SmI_2−HMPA in THF to give a 30% yield of compound **5** (entry 7, Table 1). A significant amount of starting material **2a** (23%) was recovered. The yield of **5** was improved to 62% by an inverse addition of the SmI_2−HMPA solution to the substrate **2a**. By inverse addition, the radical anion of **2a** could be generated and reacted instantly with the remaining molecules of **2a**. The cyano group was selected as the C-2 substituent for three reasons: (i) the electron-withdrawing property and resonance effect of cyano group can stabilize the C-2 anion,[6a] (ii) together with the amino group, they can exert a captodative effect to enhance the formation of C-2 radical,[6b,c] and (iii) the cyano group is of a small enough size to minimize the steric effect in the addition of a second indolecarbonyl. Compound **2a** was prepared by a Vilsmeier reaction[7] of 2-cyano-1-methylindole, which was efficiently obtained by cyanation of 1-methylindole using an electrochemical method.[8]

Cross-coupling reactions of indole-3-carboxaldehydes (**1b** and **2a**) with various aromatic and aliphatic carbonyl compounds were also carried out to afford **7a**−**d** and **8a**−**f** (Table 2). On treatment of **1b** with SmI_2 in the absence of HMPA, the self-coupling reaction (giving **4b**) competed with the cross-coupling reaction. Side products formed by pinacolic couplings of aromatic aldehydes, giving **6a**,**b**, were also found in entries 1 and 2 (Table 2). Compound **1b** failed to undergo cross-coupling with acetophenone; instead, the self-coupling product **4b** was obtained in 81% yield. According to the NOE studies, the indolecarbonyl coupling products **7b** and **7d** also had (1*R**,3*S**,3a*S**,8b*R**) configurations, like **4b**. Thus, irradiation of H-3a (at δ 5.26, dd, J = 8.5, 5.9 Hz) in compound **7b** caused 19% enhancement of H-3 (at δ 5.49, d, J = 5.9 Hz) and 16% enhancement of H-8b (at δ 4.19, d, J = 8.5 Hz). Irradiation of H-3a (at δ 4.84, dd, J = 8.5, 5.8 Hz) in compound **7d** caused 14% enhancement of H-3 (at δ 4.34, ddd, J = 9.4, 5.8, 3.1 Hz) and 12% enhancement of H-8b (at δ 4.11, d, J = 8.5 Hz). The coupling reaction of **1b** with *p*-methoxybenzaldehyde in the absence of HMPA gave **7a** as a single isomer with a (1*R**,3*S**,3a*S**,8b*R**) configuration. However, the reaction in the presence of HMPA gave **7a** and two isomers in a ratio of 43:29:29. The two minor products had

(4) The original paper for the effect of HMPA on reduction of organic halides with SmI_2: (a) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485. For reviews for various reactions of SmI_2 and the effect of HMPA, see: (b) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573. (c) Inanaga, J. *J. Synth. Org. Chem.* **1989**, *47*, 200. (d) Soderquist, J. A. *Aldrichim. Acta* **1991**, *24*, 15. (e) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (f) Brandukova, N. E.; Vygodskii, Y. S.; Vinogradova, S. V. *Russ. Chem. Rev.* **1994**, *63*, 345. (g) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307.

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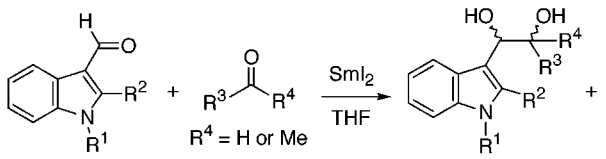
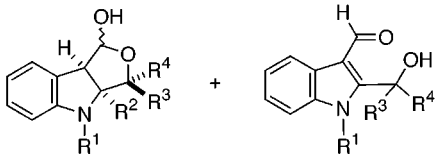
Table 2. SmI_2-Promoted Cross-Coupling Reactions of Indole-3-carboxaldehydes with Other Carbonyl Compounds



1b $R^1 = MeSO_2$, $R^2 = H$
2a $R^1 = Me$, $R^2 = CN$

6



7 **8**

entry	reactants	HMPA (equiv)	products (yield/%)
1[a]	**1b** + *p*-$MeOC_6H_4CHO$	0	**6a** (4) + **7a** (42)
2[a]	**1b** + *p*-$CH_3C_6H_4CHO$	0	**6b** (14) + **7b** (38)
3[a]	**1b** + CH_3CH_2CHO	0	**7c** (51)
4[a]	**1b** + $CH_3(CH_2)_4CHO$	0	**7d** (31)
5	**2a** + *p*-$MeOC_6H_4CHO$	0	**8a** (63)
6	**2a** + *p*-$CH_3C_6H_4CHO$	8	**8b** (73)
7	**2a** + CH_3CHO	8	**8c** (38)
8	**2a** + $CH_3(CH_2)_4CHO$	8	**8d** (51)
9	**2a** + $C_6H_5COCH_3$	8	**8e** (75)
10	**2a** + $C_2H_5COCH_3$	8	**8f** (67)

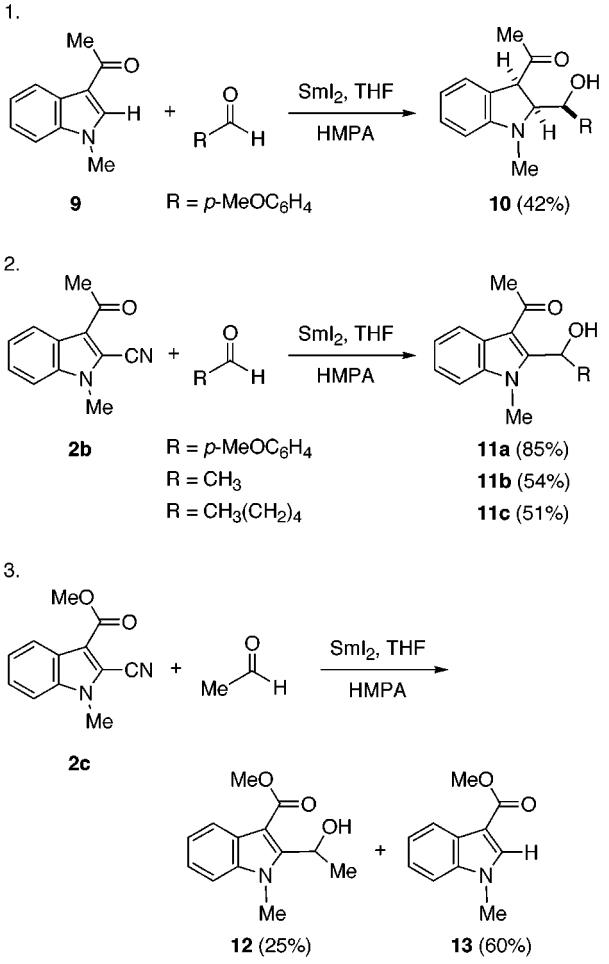
[a] The self-coupling product **4b** was also obtained in significant amounts (40−46%).

(1*R**,3*R**,3a*S**,8b*R**) and (1*S**,3*R**,3a*S**,8b*R**) configurations, respectively, as determined by the NMR analyses and their subsequent transformations into an indoline lactone **23** (see Scheme 5). The indole-carbonyl coupling reaction of **1b** with propionaldehyde was less selective, giving **7c** as a mixture of three isomers (63:26:11). The preference of the (3*S**,3a*S**) relationship in the coupling products can be attributable to chelate transition states similar to that shown in Scheme 1 (R_L = *p*-$MeOC_6H_4$, *p*-$CH_3C_6H_4$, or butyl group). The dipolar cosolvent HMPA may interfere with the chelate transition state, and the coupling reaction may also proceed with an open transition state to give (3*R**,3a*S**) products. The selectivity in **7c** decreases as the incoming aldehyde becomes smaller (R_L = ethyl group).

The cross-coupling reactions of **2a** were facilitated by the cyano group at the C-2 position. The reactions proceeded smoothly with aromatic and aliphatic aldehydes and ketones, even in the presence of HMPA, to give simply the desired indolecarbonyl coupling products **8a**−**f** without interference of side reactions.

On treatment with SmI_2−HMPA in THF for 1 h, 1-methyl-3-acetylindole (**9**) underwent a cross-coupling reaction with *p*-methoxybenzaldehyde (Scheme 2); however, the reaction with acetophenone failed due to a competitive dimerization of acetophenone.[2e] The 2,3-cis configuration of the coupling product **10** was inferred from a large coupling constant of 8.7 Hz between H-2 and H-3 in the ^1H NMR spectrum.[6b,9] The cross-coupling reactions of 3-acetyl-2-cyano-1-methylindole (**2b**) with aromatic and aliphatic aldehydes were similarly carried

Scheme 2



out to give **11a**−**c** in better yields, presumably due to the beneficial effect of the cyano substituent. A cross-coupling reaction of methyl 2-cyano-1-methylindolecarboxylate (**2c**) with acetaldehyde, giving **12** (25%), also occurred after stirring for a prolonged period (12 h) at room temperature. However, a reductive decyanation predominated in such case to give **13** (60%).

Comins and Killpack[10] have reported the C-2 methylation of 1-methylindole-3-carboxaldehyde and 1-(methoxymethyl)indole-3-carboxaldehyde by sequential treatments with lithium *N*-methylpiperazine, BuLi (3 equiv), and MeI. It is suggested that addition of lithium piperazide onto the aldehyde group can form an aminal intermediate to induce the ortho-metalation (at C-2) and the subsequent alkylation. However, this procedure is somewhat tedious, and attempted metalations with *N*-(phenylsulfonyl)- or *N*-(*tert*-butoxycarbonyl)indole-3-carboxaldehydes (**1d** or **1e**) fail as decomposition occurs. This method is not applicable to introduction of C-2 substituents on indole ketones such as **2b** or **9**. For a comparison of our method with that using the ortho-metalation procedure,[11] we also investigated the transformation illustrated in Scheme 3. Metalation of 1-methylindole with BuLi and the subsequent hydroxyalkylation with CH_3CHO gave **15**, which reacted with BuLi and Ac_2O to give a low yield (24%) of the desired C-3 acetylation

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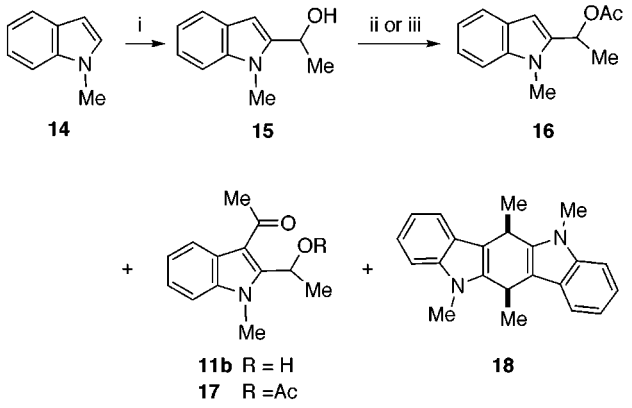
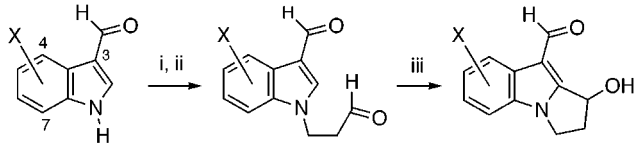
(11) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

Scheme 3[a]



[a] Reagents and conditions: (i) BuLi, THF, −78 °C (1 h) to 0 °C (2 h), then CH_3CHO, rt (6 h), 82%; (ii) BuLi, THF, −78 °C to rt (6 h), then Ac_2O, 0 °C to rt (12 h), **16** (70%), **17** (24%); (iii) $AlCl_3$, Ac_2O, CH_2Cl_2, 0 °C to rt (4 h), **11b** (13%), **18** (41%).

Scheme 4[a]



19a	X = H	**20a** (81%)	**21a** (64%)
19b	X = 5-OMe	**20b** (78%)	**21b** (78%)
19c	X = 7-Et	**20c** (75%)	**21c** (76%)

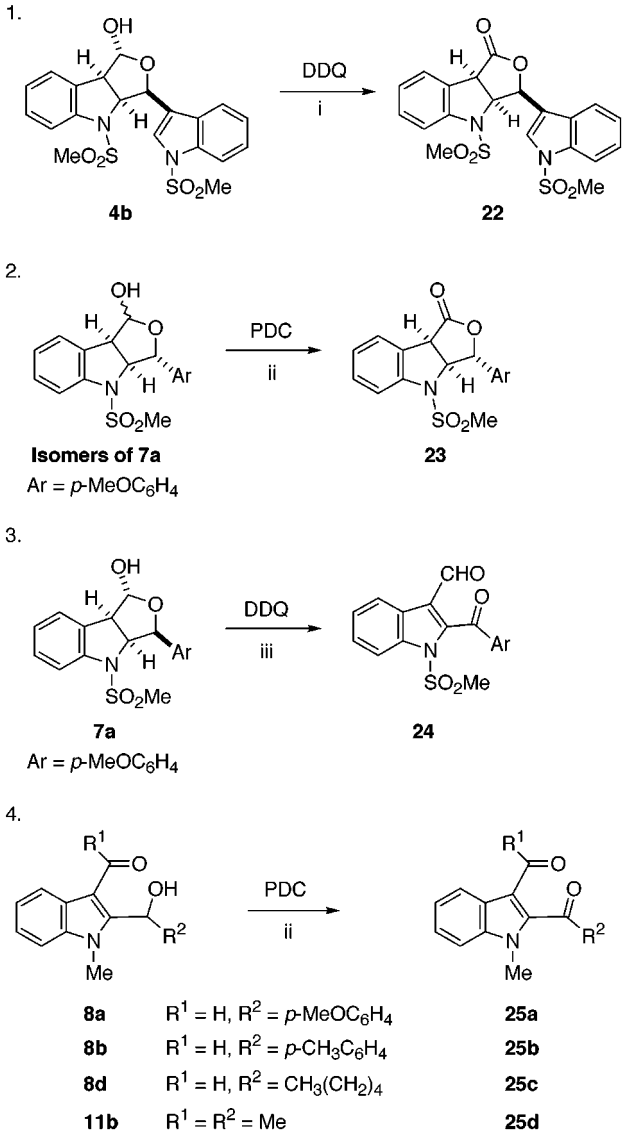
[a] Reagents and conditions: (i) NaH, THF, $BrCH_2CH_2CH[O(CH_2)_3O]$, 25 °C, 48 h; (ii) 70% aqueous AcOH, reflux 1 h; (iii) SmI_2, THF, HMPA, 0 °C (10 min) to 25 °C (1 h).

product **17**. Alternatively, alcohol **15** was treated with a mixture of Ac_2O and $AlCl_3$ to give the indole ketone **11b** (13%) and a dimeric condensation product **18**[12] (41%, cis/trans isomers = 83:17). Our method using SmI_2-promoted coupling reactions appeared to have the advantages of simple operation and good selectivity.

Application. Since the indolecarbonyl group in **20a**−**c** is considered to be more reactive toward SmI_2 than the aliphatic carbonyl group, the intramolecular coupling reactions can be anticipated to occur in the indolecarbonyl coupling manner. The indole dialdehydes **20a**−**c** were prepared by alkylation of the 3-formylindoles **19a**−**c** individually with 2-(2-bromoethyl)-1,3-dioxane followed by hydrolysis (Scheme 4). The desired intramolecular indolecarbonyl coupling proceeded smoothly on treatment with SmI_2 to give the pyrrolidino[1,2-*a*]indolecarboxaldehydes **21a**−**c** with a mytomycin skeleton.[13] Activation by a C-2 cyano group or *N*-sulfonyl group was unnecessary in such intramolecular cyclizations. The reaction involved a rearomatization of the indoline intermediate presumably via autoxidation on workup.

The hydroxyalkylated compounds obtained from intermolecular indolecarbonyl coupling reactions were subjected to oxidation with DDQ or PDC (Scheme 5). The indoline hemiacetal **4b** with (1*R**,3*S**,3a*S**,8a*R**)-configuration was oxidized by DDQ at room temperature to give the corresponding indoline lactone **22** with a (3*S**,3a*S**,8a*R**) configuration. Oxidation of a sample containing the (1*R**,3*R**,3a*S**,8b*R**) and (1*S**,3*R**,3a*S**,8b*R**) isomers of **7a** with PDC afforded a single indoline lactone **23** with a (3*R**,3a*S**,8a*R**) configuration. Compound **23** with a cis junction also exhibited a large coupling constant ($J_{3a,8b}$ = 10.0 Hz) comparable to that of **4b**. The coupling constant between H-3 and H-3a in **23** was small (1.7 Hz) by comparison with that of **4b** (5.7 Hz) or **22** (7.6 Hz), indicating that the orientation of the aryl group in **23** differs from that of **4b**. Oxidations of 2-(hydroxyalkyl)indoles **8a**,**b**,**d** and **11b** with PDC yielded the corresponding indole ketones **25a**−**d**. Vigorous oxidation of hemiacetal (1*R**,3*S**,3a*S**,8a*R**)-**7a** with DDQ in refluxing benzene also led to an indole ketone **24**.

Scheme 5[a]



[a] Reagents and conditions: (i) DDQ, PhH, rt, 16 h, **22**, 57%; (ii) PDC, sieves, CH_2Cl_2, rt, 4−15 h, **23**, 83%, **25a**, 94%, **25b**, 73%, **25c**, 62%, **25d**, 55%; (iii) DDQ, PhH, reflux, 2 h, **24**, 86%.

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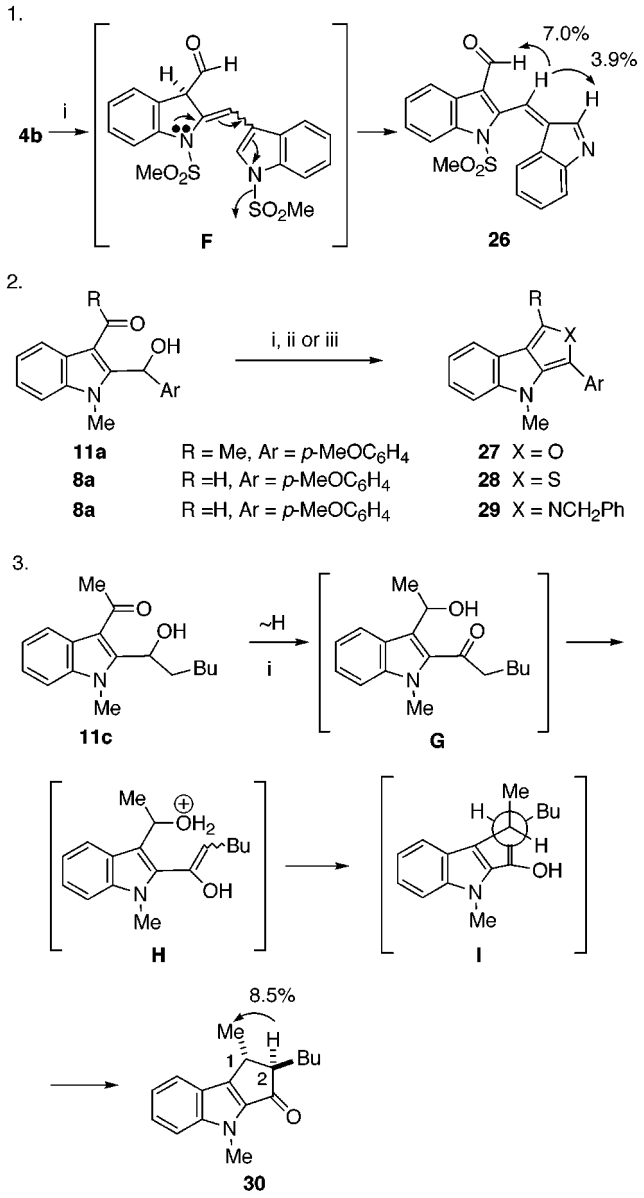
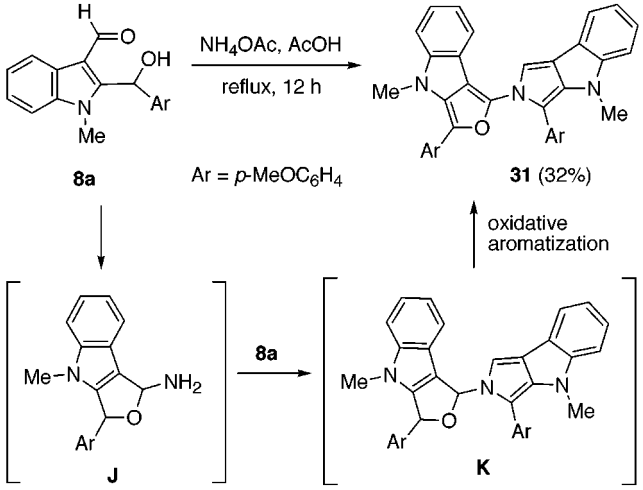
Scheme 6[a]



[a] Reagents and conditions: (i) *p*-TsOH, PhMe or PhH, reflux, 5−24 h; **26**, 85%, **27**, 82%, **30**, 63%; (ii) [*p*-$MeOC_6H_4P(=S)S]_2$, 1,4-dioxane, reflux, 4 h, **28**, 63%; (iii) $PhCH_2NH_2$, *p*-TsOH, PhMe, reflux, 6 days, **29**, 46%.

The indolecarbonyl coupling products were elaborated to a series of heterocycle-fused indoles.[14] Treatment of hemiacetal **4b** with *p*-TsOH in refluxing benzene afforded a single product **26** (85%), presumably via the dehydration intermediate **F** followed by elimination of a methylsulfonyl group (Scheme 6). The *E*-configuration of **26** was verified by an NOE experiment, i.e., irradiation of the vinyl proton (at δ 7.63), causing enhancements of the signals of the iminyl and formyl protons (at δ 9.17 and 10.32). The acid-catalyzed condensation of **11a** gave a furo[3,4-*b*]indole **27**. In a similar reaction mode, **8a** was treated with Lawesson's reagent or benzylamine to give thieno[3,4-*b*]indole **28** and pyrrolo[3,4-*b*]indole **29**. Compounds **27**−**29** are equivalents of indole-2,3-quinodimethane employed as diene substrates in Diels−Alder reactions.[14a−c] For example, the indolecarbonyl coupling product **11b** can be elaborated and utilized in a Diels−Alder reaction with pyridyne to give 6-methylellipticine.[14a−c] The acid-catalyzed reaction of **11c** proceeded differently to give a pentane[*b*]indole **30**. This reaction was presumably initiated by an intramolecular hydride shift[15] to give the intermediate **G**, which underwent an α-alkylation via the intermediate **H** to furnish the observed product. Compound **30** could be the thermodynamically favored product or obtained from a less steric demanding transition state **I**. The small coupling constant (J = 2.0 Hz) between H-1 and H-2 as well as an NOE experiment (as illustration) were in agreement with the trans configuration of **30**.

Scheme 7



The reaction of **8a** with NH_4OAc afforded a product **31** containing both pyrrolo[3,4-*b*]indole and furo[3,4-*b*]indole moieties (Scheme 7). The reaction was presumably initiated by formation of an aminal intermediate **J**, which could be trapped by a second molecule of **8a**. Subsequent oxidative aromatization of the intermediate **K** would furnish the observed product **31**.

Two molecules of **8a** condensed with one molecule of hydrazine to form a bishydrazone **32** (Scheme 8). Upon workup, compound **32** existed as a mixture of two isomers as shown by the ^1H NMR spectrum, but the isomeric mixture degenerated to a single isomer on standing at ambient temperature. We assumed that the (*E*,*E*)-isomer with hydrogen-bonded seven-membered rings was more stable than the (*Z*,*Z*)-isomer with hydrogen-bonded eight-membered rings. Treatment of **32** with DDQ or MnO_2 gave the corresponding diketone **33** (ca. 30%), along with a degradative product **25a** (ca. 12%). Diketone **25a** reacted with hydrazine afforded a 1:1 condensation product **34a**. The reaction of **25b** with hydrazine proceeded in a similar manner to give a pyridazino[4,5-*b*]indole **34b**. The reactions of **25a** and **25c** with P_2S_5 yielded mercaptothieno[2,3-*b*]indole **35** and thieno[2,3-*b*]indole-1-thione **36**, respectively. Upon treatment with

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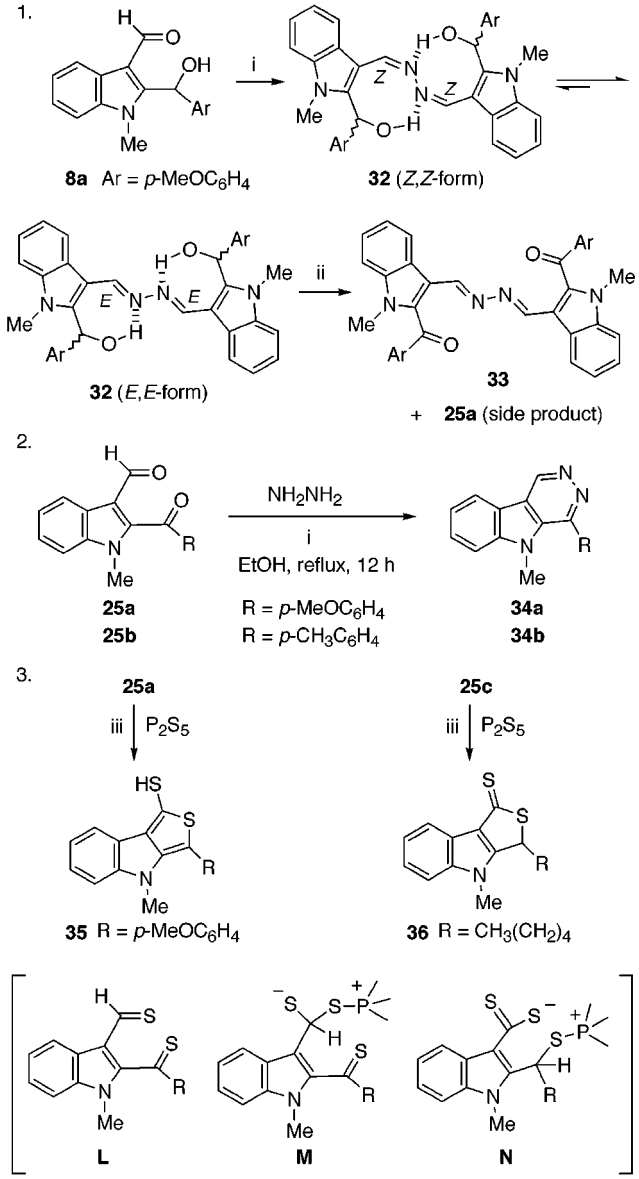
(15) Djerassi, C. *Org. React.* **1951**, *6*, 207.

Scheme 8[a]



[a] Reagents and conditions: (i) $N_2H_4 \cdot H_2O$, EtOH, reflux, 12 h, **32**, 84%, **34a**, 89%, **34b**, 82%; (ii) MnO_2 or DDQ, **33**, 30%; (iii) P_2S_5, 1,4-dioxane, reflux, 1−4 h, **35**, 51%, **36**, 68%.

P_2S_5, the two carbonyl groups in **25a** (or **25c**) might be converted to thiocarbonyls such as in the intermediate **L**. The thial group could react further with a second molecule of P_2S_5 to form a dithioacetal analogue **M**. The subsequent intramolecular hydride shift and cyclization would afford a thieno[2,3-*b*]indole-1-thione such as **36**. If the C-3 substituent R is an aromatic group such as that derived from **25a**, tautomerization could be facilitated to give a mercaptothieno[2,3-*b*]indole such as **35**. Compound **36** showed a resonance at δ 213.3 attributable to the thione group in the ^{13}C NMR spectrum,[16] but no carbonyl absorption in the IR spectrum was observed.

Conclusion. We have demonstrated in this study that indolecarbonyl coupling reactions can be achieved in two ways: (i) intramolecularly by monitoring the different reactivities of indolecarbonyl and aliphatic carbonyl groups toward SmI_2 as shown in Scheme 4 and (ii) intermolecularly by the assistance of an *N*-sulfonyl group or a cyano group at C-2. The coupling reactions appeared to proceed in high stereoselectivity via chelate transition states as illustrated in Scheme 1. Elaboration of the coupling products with oxidizing agents, acid, P_2S_5 (or Lawesson's reagent), amines, and hydrazine led to a variety of indole derivatives and indole-fused polycyclic compounds of synthetic interest and pharmaceutical uses. For example, furo[3,4-*b*]indole **27** can be utilized as an equivalent of indole-2,3-quinodimethane for Diels−Alder reactions.[14] Pyrrolidino[1,2-*a*]indolecarboxaldehydes **21a**−**c** construct a prototype of mytomycins.[13]

Experimental Section

Melting points are uncorrected. ^1H NMR spectra were recorded at 200, 300, or 400 MHz; ^{13}C NMR spectra were recorded at 50, 75, or 100 MHz. Tetramethylsilane and $CDCl_3$ were used as internal standards in ^1H and ^{13}C NMR spectra, respectively. Mass spectra were recorded at an ionizing voltage of 70 or 20 eV. Merck silica gel 60F sheets were used for analytical thin-layer chromatography. Column chromatography was performed on SiO_2 (70−230 mesh); gradients of EtOAc and *n*-hexane were used as eluents. High-pressure liquid chromatography was carried out on a liquid chromatograph equipped with a refractive index detector. The samples were analyzed and/or separated on a Hibar Lichrosorb Si 60 (7 μm) column (25 cm × 1 cm) with the indicated eluent with a 5 mL/min flow rate. THF was distilled from sodium benzophenone ketyl under N_2.

1-Methylindole-3-carboxaldehyde (**1a**, mp 68−69 °C),[8b] 1-(methylsulfonyl)indole-3-carboxaldehyde (**1b**, mp 169.5−170.5 °C),[14b] 1-(4-tolylsulfonyl)indole-3-carboxaldehyde (**1c**, mp 144.5−146 °C),[14b] 1-(phenylsulfonyl)indole-3-carboxaldehyde (**1d**, mp 156−158 °C),[14b] 1-(*tert*-butoxycarbonyl)indole-3-carboxaldehyde (**1e**, mp 125−126 °C),[14b] 3-formyl-1-methylindole-2-carbonitrile (**2a**, mp 165−166 °C),[8b] and 3-acetyl-1-methylindole-2-carbonitrile (**2b**, mp 152−154 °C)[8b] were prepared according to reported methods. Methyl 2-cyano-1-methylindole-3-carboxylate (**2c**), mp 141−143 °C, was prepared in 98% yield by treatment of the aldehyde **2a** with MnO_2/NaCN/HOAc in MeOH at room temperature for 17 h.[17] Indole-3-carboxaldehydes (**19a**−**c**) were treated with NaH and 2-(2-bromoethyl)-1,3-dioxane in THF, followed by hydrolysis in aqueous HOAc, to give 1-(3-oxopropyl)indole-3-carboxaldehydes (**20a**−**c**) in 75−81% yield.

General Procedure for the Reactions of Indolecarbonyls with SmI_2. Samarium metal (0.36 g, 2.4 mmol) and 1,2-diiodoethane (0.56 g, 2 mmol) in anhydrous THF (20 mL) were stirred at room temperature under an argon atmosphere for 1 h to give a deep blue solution. HMPA (1.4 mL, 8 mmol) was added in certain cases. The mixture was cooled to 0 °C in an ice bath, a THF solution (2 mL) of indolecarbonyl compound (1 mmol), along with an appropriate aldehyde (1−1.7 mmol) in the case of cross-coupling reactions, was added dropwise over a period of 2 min. The light green mixture was stirred at 0 °C for 30 min and warmed to room temperature over a period of 0.5−2 h. The serum cap was removed, and Et_2O (10 mL) was added. The mixture was then filtered and rinsed with EtOAc (15 mL). The

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organic phase was concentrated under reduced pressure and chromatographed on a silica gel column with elution of EtOAc/hexane to give products.

1,3,3a,8b-Tetrahydro-1-hydroxy-4-(methylsulfonyl)-3-[1-(methylsulfonyl)indol-3-yl]furo[3,4-*b*]indole (4b). According to the general procedure, treatment of 1-(methylsulfonyl)indole-3-carboxaldehyde (**1b**) with SmI_2 gave the self-coupling product (66%, three isomers (92:6:2)). The major isomer was isolated by recrystallization and determined to have the (1*R**,3*S**,3a*S**,8b*R**) configuration by an X-ray diffraction analysis: solid; mp 199−200 °C (from $CHCl_3$−cyclohexane); TLC (EtOAc/hexane (1:1)) $R_f = 0.18$; IR (neat) 3483, 2928, 1593, 1347, 1158 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.52 (3 H, s), 3.06 (3 H, s), 3.26 (1 H, s), 4.26 (1 H, d, $J = 8.5$ Hz), 5.07 (1 H, dd, $J = 8.5$, 5.7 Hz), 5.70 (1 H, s), 5.80 (1 H, d, $J = 5.7$ Hz), 7.06−7.35 (8 H, m), 7.89 (1 H, d, $J = 8.1$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.8, 40.4, 54.2, 68.4, 77.4, 102.3, 113.0, 115.0, 118.0, 120.9, 123.1, 124.8, 124.9, 125.3, 125.9, 129.2, 130.0 (2 C), 135.1, 142.2; MS *m*/*z* (rel intensity) 448 (10, M^+), 224 (64), 146 (59), 118 (100), 79 (6); HRMS calcd for $C_{20}H_{20}N_2O_6S_2$ 448.0763, found, 448.0766. The structure was confirmed by an X-ray diffraction.

3-Acetyl-2-[1-hydroxy-(4-methoxyphenyl)methyl]-1-methylindole (11a). According to the general procedure, treatment of 3-acetyl-1-methylindole-2-carbonitrile (**2b**) and *p*-methoxybenzaldehyde (1:1.5) with SmI_2 in the presence of HMPA gave the indolecarbonyl coupling product **11a** (85%): oil; TLC (EtOAc/hexane (3:7)) $R_f =$ 0.33; IR (neat) 3380, 1607, 1505, 1466, 1172, 972 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.70 (3 H, s), 3.72 (3 H, s), 3.73 (3 H, s), 6.25 (1 H, br s), 6.71 (2 H, d, $J = 8.7$ Hz), 7.11 (2 H, d, $J = 8.7$ Hz), 7.14−7.35 (3 H, m), 7.84−7.89 (1 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.8, 31.5, 55.2, 68.1, 110.5, 113.8 (2 C), 114.4, 120.8, 122.7, 122.8, 126.4, 127.3 (2 C), 133.2, 136.7, 150.7, 159.0, 196.4; MS *m*/*z* (rel intensity) 309 (100, M^+), 294 (20), 262 (7), 200 (10), 186 (26), 135 (15); HRMS calcd for $C_{19}H_{19}O_3N$ 309.1365, found 309.1363.

2,3-Dihydro-1-hydroxy-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (21a). According to the general procedure, a solution of **20a** (135 mg, 0.67 mmol) in THF (8 mL) was added via syringe pump to the SmI_2−HMPA solution over a period of 30 min to give **21a** (86 mg, 64%): solid; mp 113−115 °C; TLC (EtOAc/hexane (7:3)) $R_f = 0.34$; IR (KBr) 3351, 1632, 1567, 1428, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.58−2.72 (1 H, m), 2.98−3.09 (1 H, m), 4.01−4.14 (1 H, m), 4.28−4.39 (1 H, m), 5.59 (1 H, dd, $J = 7.7$, 6.2 Hz), 7.23−7.35 (3 H, m), 7.94−8.00 (1 H, m), 10.08 (1 H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 36.0, 44.2, 68.1, 110.1, 110.9, 119.5, 123.0, 123.2, 130.5, 132.5, 154.4, 185.0; MS *m*/*z* (rel intensity) 201 (100, M^+), 184 (22), 172 (14), 154 (15), 145 (20); HRMS calcd for $C_{12}H_{11}O_2N$ 201.0790, found 201.0792.

3a,8b-Dihydro-4-(methylsulfonyl)-3-[(1-methylsulfonyl)indol-3-yl]furo[3,4-*b*]indol-1-one (22). Hemiacetal (1*R**,3*S**,3a*S**,8b*R**)-**4b** (23 mg, 0.05 mmol) was treated with DDQ (45 mg, 0.2 mmol) in benzene (10 mL) at room temperature (27 °C) for 16 h. The mixture was concentrated and chromatographed on a silica gel column by elution with EtOAc/hexane (1:1) to give lactone (3*S**, 3a*S**,8b*R**)-**22** (13 mg, 57%): solid; mp 210−211 °C; TLC (EtOAc/hexane (2:3)) $R_f = 0.09$; IR (neat) 1753, 1361, 1158 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.64 (3 H, s), 3.03 (3 H, s), 4.61 (1 H, d, $J = 10.0$ Hz), 5.49 (1 H, dd, $J = 10.0$, 7.6 Hz), 6.20 (1 H, d, $J = 7.6$ Hz), 6.88−7.04 (3 H, m), 7.19−7.30 (4 H, m), 7.67 (1 H, d, $J = 7.2$ Hz), 7.86 (1 H, d, $J = 8.8$ Hz); ^{13}C NMR (CD_3CN, 50 MHz) δ 36.8, 41.4, 48.2, 66.4, 81.2, 114.0, 115.6, 118.3, 121.4, 124.0, 125.8, 126.0, 126.3, 127.2, 127.9, 130.0, 130.8, 136.0, 142.8, 175.5; MS *m*/*z* (rel intensity) 446 (18, M^+), 195 (98), 144 (68), 116 (100), 89 (25); HRMS calcd for $C_{20}H_{18}N_2O_6S_2$ 446.0606, found 446.0598.

3a,8b-Dihydro-4-(methylsulfonyl)-3-(4-methoxyphenyl)furo[3,4-*b*]indol-1-one (23). A mixture of the (1*R**,3*R**,3a*S**,8b*R**) and (1*S**,3*R**,3a*S**,8b*R**) isomers of **7a** (17 mg, 0.05 mmol) was treated with PDC (40 mg, 0.10 mmol) and molecular sieves (4 Å, 1 g) in CH_2Cl_2 (6 mL) at room temperature (25 °C) for 4 h. The mixture was concentrated and chromatographed on a silica gel column by elution with EtOAc/hexane (1:3) to give a lactone (3*R**,3a*S**,8b*R**)-**23** (14 mg, 83%): oil; TLC (EtOAc/hexane (3:7)) $R_f = 0.17$; IR (neat) 1781, 1355, 1251, 1164, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.86 (3 H, s), 3.80 (3 H, s), 4.39 (1 H, d, $J = 9.1$ Hz), 4.86 (1 H, dd, $J = 9.1$, 1.7 Hz), 5.87 (1 H, d, $J = 1.7$ Hz), 6.94 (2 H, d, $J = 8.8$ Hz), 7.17 (1 H, t, $J = 7.5$ Hz), 7.31−7.38 (1 H, m), 7.36 (2 H, d, $J = 8.8$ Hz), 7.46 (1 H, d, $J = 7.5$ Hz), 7.56 (1 H, d, $J = 7.5$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.6, 46.0, 55.3, 71.0, 87.0, 114.1, 114.4 (2 C), 125.1, 125.2, 126.0, 126.7 (2 C), 129.5, 130.3, 141.0, 160.0, 173.8; MS *m*/*z* (rel intensity) 359 (31, M^+), 315 (3), 280 (11), 236 (19), 195 (100), 144 (26), 116 (64); HRMS calcd for $C_{18}H_{17}NO_5S$ 359.0827, found 359.0835.

1-(Methylsulfonyl)-2-(3*H*-indol-3-ylidene)methylindole-3-carboxaldehyde (26). Hemiacetal (1*R**,3*S**, 3a*S**,8b*R**)-**4b** (50 mg, 0.11 mmol) was treated with *p*-TsOH (21 mg, 0.11 mmol) in refluxing benzene (25 mL) for 24 h. A Dean−Stark apparatus was equipped for removal of water. The mixture was cooled, filtered through a pad of silica gel, and rinsed with EtOAc/hexane (1:1). The organic phase was concentrated and chromatographed on a silica gel column by elution with EtOAc/hexane (1:4) to give **26** (33 mg, 85%): oil; TLC (EtOAc/hexane (1:4)) $R_f = 0.10$; IR (neat) 2848, 1684, 1363, 1167, 1128 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.28 (3 H, s), 7.37−7.57 (3 H, m), 7.63 (1 H, s, vinyl H), 7.71−7.86 (2 H, m), 8.01 (1 H, d, $J = 8.0$ Hz), 8.21 (1 H, dd, $J = 8.0$, 1.5 Hz), 8.96 (1 H, dd, $J = 8.0$, 1.5 Hz), 9.17 (1 H, s, HC=N), 10.32 (1 H, s, CHO); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.4, 113.4, 116.2, 120.2, 123.2, 124.6, 125.3, 126.1, 127.1, 129.1, 129.7, 129.8, 130.1, 130.2, 134.8, 135.2, 148.4, 152.2, 193.2; MS *m*/*z* (rel intensity) 350 (35, M^+), 271 (100), 243 (61), 216 (33); HRMS calcd for $C_{19}H_{14}N_2O_3S$ 350.0725, found 350.0722.

1,4-Dimethyl-3-(4-methoxyphenyl)furo[3,4-*b*]indole (27). By a procedure similar to that for **26**, treatment of **11a** (20 mg, 0.065 mmol) with *p*-TsOH in refluxing benzene for 5 h gave **27** (15 mg, 82%): oil; TLC (EtOAc/hexane (3:7)) $R_f = 0.19$; IR (neat) 2937, 1608, 1513, 1460, 1263 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.49 (3 H, s), 3.63 (3 H, s), 3.85 (3 H, s), 6.50 (2 H, dd, $J = 7.0$, 2.0 Hz), 6.86 (2 H, dd, $J = 7.0$, 2.0 Hz), 7.25−7.38 (3 H, m), 7.90−7.93 (1 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.7, 30.9, 55.0, 110.5, 113.2 (2 C), 115.6, 120.8, 122.1, 122.4, 126.1, 129.5 (2 C), 129.9, 131.7, 133.9, 136.8, 145.9, 158.7; MS *m*/*z* (rel intensity) 291 (79, M^+), 279 (78), 224 (100), 197 (48), 143 (98); HRMS calcd for $C_{19}H_{17}O_2N$ 291.1259, found 291.1252.

3-(4-Methoxyphenyl)thieno[3,4-*b*]indole (28). Compound **8a** (35 mg, 0.12 mmol) was treated with Lawes-

son's reagent (65 mg, 0.16 mmol) in refluxing 1,4-dioxane (10 mL) for 4 h. The mixture was concentrated and partitioned between aqueous NaOH (10%, 10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The organic phase was dried (Na_2SO_4), concentrated and chromatographed on a silica gel column by elution with EtOAc/hexane (1:9) to give **28** (22 mg, 63%): oil; TLC (EtOAc/hexane (1:3)) R_f = 0.53; IR (neat) 2921, 2849, 1583, 1242 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.45 (3 H, s), 3.86 (3 H, s), 6.96 (2 H, dd, J = 8.6, 2.0 Hz), 7.07 (1 H, t, J = 7.6 Hz), 7.09 (1 H, d, J = 7.6 Hz), 7.36 (1 H, t, J = 7.6 Hz), 7.38 (1 H, s), 7.48 (2 H, dd, J = 8.6, 2.0 Hz), 7.78 (1 H, d, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 31.4, 55.3, 108.5, 109.0, 110.5, 113.8 (2 C), 118.7, 119.7, 121.0, 125.4, 126.4, 131.6 (2 C), 134.2, 141.6, 150.1, 159.0; MS *m*/*z* (rel intensity) 293 (100, M$^+$), 278 (41), 135 (12), 147 (13); HRMS calcd for $C_{18}H_{15}ONS$ 293.0874, found 293.0871.

2-(Phenylmethyl)-3-(4-methoxyphenyl)-4-methylpyrrolo[3,4-*b*]indole (29). Compound **8a** (26 mg, 0.08 mmol) was treated with benzylamine (0.02 mL) and *p*-TsOH (2 mg) in refluxing toluene (15 mL) for 6 days. A Dean−Stark apparatus was equipped for removal of water. The mixture was concentrated and chromatographed on a silica gel column by elution with EtOAc/hexane (1:9) to give **29** (12 mg, 46%) along with a 46% recovery of **8a**: oil; TLC (EtOAc/hexane (1:9)) R_f = 0.41; IR (neat) 2929, 1630, 1593, 1503, 1242, 740, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.33 (3 H, s), 3.67 (3 H, s), 5.07 (2 H, s), 6.80−7.22 (13 H, m), 7.62 (1 H, d, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 31.0, 51.4, 55.3, 107.8, 108.1, 109.1, 113.6 (2 C), 115.6, 117.6, 120.2, 120.4, 123.6, 123.9, 126.4 (2 C), 128.5 (2 C), 132.6 (2 C), 134.8, 139.3, 146.8, 158.9; MS (rel intensity) 366 (100, M$^+$), 275 (14); HRMS calcd for $C_{25}H_{22}N_2O$ 366.1732, found 366.1740.

2-Butyl-1,4-dimethylcyclopentane[*b*]indol-3-one (30). By a procedure similar to that for **26**, treatment of **11c** (51 mg, 0.19 mmol) with *p*-TsOH in refluxing benzene for 4 h gave **30** (trans, 30 mg, 63%): oil; TLC (EtOAc/hexane (1:9)) R_f = 0.36; IR (neat) 2957, 1679, 1483, 1204, 742 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.91 (3 H, t, J = 6.7 Hz), 1.25−1.65 (8 H, m), 1.88−2.01 (1 H, m), 2.49 (1 H, ddd, J = 9.0, 8.7, 2.0 Hz), 3.19 (1 H, qd, J = 7.0, 2.0 Hz), 3.89 (3 H, s), 7.10−7.74 (4 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 20.6, 22.9, 29.6, 30.1, 31.2, 35.1, 62.0, 111.0, 120.1, 121.9, 122.7, 126.5, 137.7, 145.0, 147.6, 196.9; MS *m*/*z* (rel intensity) 255 (43, M$^+$), 240 (5), 212 (27), 199 (100), 184 (21); HRMS calcd for $C_{17}H_{21}NO$ 255.1623, found 255.1631.

3-(4-Methoxyphenyl)-1-[3-(4-methoxyphenyl)-4-methylpyrrolo[3,4-*b*]indol-2-yl]-4-methylfuro[3,4-*b*]-indole (31). A mixture of **8a** (30 mg, 0.1 mmol) and ammonium acetate (400 mg, 5.2 mmol) in acetic acid (5 mL) was heated under reflux for 12 h. The mixture was cooled, and aqueous Na_2CO_3 (10%, 5 mL) and water (5 mL) were added. The mixture was extracted with EtOAc (15 mL × 3). The organic phase was dried (Na_2SO_4), concentrated, and chromatographed on a silica gel column by elution with EtOAc/hexane (1:9) to give **31** (9 mg, 32%): oil; TLC (EtOAc/hexane (1:3)) R_f = 0.28; IR (neat) 1592, 1246, 744 cm^{-1}; UV λ_{max} (ϵ) (MeOH) 373 (10 358), 273 (42 856), 226 (52 427) nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.41 (3 H, s), 3.58 (3 H, s), 3.88 (3 H, s), 3.89 (3 H, s), 6.47 (2 H, dd, J = 8.8, 2.0 Hz), 6.96 (2 H, dd, J = 8.8, 2.0 Hz), 7.24−7.39 (6 H, m), 7.44 (2 H, t, J = 8.0 Hz), 7.55 (1 H, t, J = 7.7 Hz), 7.68 (2 H, dd, J = 8.8, 2.0 Hz), 8.05 (1 H, s), 8.10 (1 H, d, J = 7.7 Hz), 8.16 (1 H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.2, 33.0, 55.2, 55.4, 109.7, 110.0, 113.0 (2 C), 113.1, 113.2 (2 C), 119.6, 121.0, 121.3, 121.4, 121.5, 124.2, 125.6, 128.2, 130.65, 130.7, 130.9 (2 C), 131.7, 131.9 (2 C), 132.1, 133.3, 134.4, 138.4, 142.3, 143.18, 143.24, 160.0, 162.7, 190.0; MS *m*/*z* (rel intensity) 551 (M$^+$, 100), 276 (1), 135 (17), 121 (6); FAB-MS *m*/*z* 552.2 (M$^+$ + 1); HRMS calcd for $C_{36}H_{29}N_3O_3$ 551.2208, found 551.2209.

Bis{2-[1-hydroxy-(4-methoxyphenyl)methyl]-1-methylindole-3-carboxaldehyde} Hydrazone (32). A mixture of **8a** (42 mg, 0.14 mmol) and hydrazine monohydrate (0.1 mL, 2 mmol) in EtOH (10 mL) was stirred at room temperature (25 °C) for 1 h and then heated under reflux for 12 h. The mixture was concentrated and chromatographed on a silica gel column by elution with EtOAc/hexane (1:3) to give **32** (35 mg, 84%). The prepared sample consisted of two isomers, but it degenerated to one (*E*,*E*)-isomer on standing. (*Z*,*Z*)-Isomer: TLC (EtOAc/hexane (1:3)) R_f = 0.07; IR (neat) 3330, 1603, 1503, 1243 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.54 (6 H, s), 3.73 (6 H, s), 6.09 (2 H, s), 6.77 (4 H, dd, J = 8.7, 2.0 Hz), 7.15−7.25 (10 H, m), 7.81 (2 H, d, J = 6.7 Hz), 8.17 (2 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.4, 55.2, 68.0, 107.7, 109.5, 113.7, 113.9, 118.8, 120.6, 122.3, 126.4, 127.7, 127.8, 134.0, 136.5, 139.9, 141.3, 158.9. (*E*,*E*)-Isomer: solid; mp 233−235 °C dec; TLC (EtOAc/hexane (1:3)) R_f = 0.07; IR (KBr) 3284, 1598, 1503, 1245 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.67 (6 H, s), 3.72 (6 H, s), 6.18 (2 H, s), 6.76−6.82 (4 H, m), 7.22−7.32 (10 H, m), 7.78 (2 H, br s, OH), 7.92−7.94 (2 H, m), 8.90 (2 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.8, 55.2, 68.7, 107.6, 109.8, 113.9, 119.1, 121.6, 122.9, 127.6, 127.9, 133.8, 136.9, 145.1, 153.8, 159.1; MS *m*/*z* (rel intensity) 568 (2, M$^+$ − H_2O), 293 (100), 276 (46), 264 (80), 249 (72), 157 (29), 135 (34); FAB-MS *m*/*z* 587 (M$^+$ + 1), 569 (M$^+$ − H_2O + 1); HRMS calcd for $C_{36}H_{32}N_4O_3$ 568.2474 (M$^+$ − H_2O), found 568.2489.

Bis[2-(4-methoxybenzoyl)-1-methylindole-3-carboxaldehyde] Hydrazone (33). Diol **32** (34 mg, 0.058 mmol) was treated with MnO_2 (101 mg, 0.12 mmol) in refluxing benzene (10 mL) for 12 h. The mixture was cooled, filtered through a pad of Celite, and rinsed with EtOAc. The filtrate was concentrated and chromatographed on a silica gel column by elution with EtOAc/hexane (1:3) to give diketone **33** (8.3 mg, 25%). Treatment of **32** (17 mg) with DDQ (28 mg) in benzene at room temperature for 13 h gave **33** (5 mg, 30%): solid; mp 297−298 °C dec; TLC (EtOAc/hexane (1:3)) R_f = 0.15; IR (neat) 1622, 1604, 1582, 1253 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.77 (6 H, s), 3.88 (6 H, s), 6.96 (4 H, dd, J = 8.8, 1.8 Hz), 7.23−7.28 (2 H, m), 7.36−7.43 (4 H, m), 7.88 (4 H, dd, J = 8.8, 1.8 Hz), 8.45 (2 H, d, J = 8.0 Hz), 8.56 (2 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.8, 55.6, 109.9, 114.2 (2 C), 114.8, 122.3, 124.5, 124.8, 125.2, 131.6, 132.9 (2 C), 138.5, 139.3, 155.6, 164.4, 188.0; MS *m*/*z* (rel intensity) 582 (51, M$^+$), 447 (100), 291 (70), 264 (43), 249 (32), 135 (95); HRMS calcd for $C_{36}H_{30}N_4O_4$ 582.2267, found 582.2261.

4-(4-Methoxyphenyl)-5-methylpyridazino[4,5-*b*]-indole (34a). By a procedure similar to that for **32**, treatment of **25a** (64 mg, 0.22 mmol) with hydrazine monohydrate (0.02 mL, 0.41 mmol) in refluxing EtOH (10 mL) gave **34a** (52 mg, 82%): solid; mp 182−183 °C; TLC (MeOH/CH_2Cl_2 (1:19)) R_f = 0.24; IR (KBr) 3006, 2935, 1604, 1501, 1244, 829, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$,

200 MHz) δ 3.57 (3 H, s), 3.90 (3 H, s), 7.05−7.11 (2 H, m), 7.38−7.66 (5 H, m), 8.21 (1 H, d, J = 7.1 Hz), 9.73 (1 H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 32.6, 55.3, 110.2, 113.8 (2 C), 119.5, 119.8, 121.5, 121.6, 128.9, 131.0 (2 C), 134.9 (2 C), 141.7, 142.8, 148.4, 160.3; MS *m*/*z* (rel intensity) 289 (64, M^+), 288 (100), 273 (8), 246 (6), 217 (11), 203 (12); HRMS calcd for $C_{18}H_{15}N_3O$ 289.1215, found 289.1217.

1-Mercapto-4-methyl-3-(4-methoxyphenyl)thieno-[3,4-*b*]indole (35). By a procedure similar to that for **28**, treatment of **25a** (30 mg, 0.1 mmol) with P_2S_5 (32 mg, 0.14 mmol) in refluxing 1,4-dioxane (10 mL) for 1 h gave **35** (17 mg, 51%): deep red solid; mp 199−200 °C; TLC (EtOAc/hexane (3:7)) R_f = 0.25; IR (neat) 1600, 1527, 1489, 1464, 1244, 1032, 831 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.57 (1 H, s, SH), 3.13 (3 H, s), 3.87 (3 H, s), 6.69−6.79 (2 H, m), 6.95−6.98 (2 H, m), 7.09−7.14 (1 H, m), 7.36−7.40 (2 H, m), 7.53 (1 H, d, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.1, 55.4, 107.8, 113.9 (2 C), 118.2, 118.3, 119.3, 119.4, 120.9, 124.8, 126.5, 131.3 (2 C), 139.7, 141.4, 149.6, 159.4; MS *m*/*z* (rel intensity) 325 (100, M^+), 310 (24), 293 (30), 278 (19); HRMS calcd for $C_{18}H_{15}NOS_2$ 325.0595, found 325.0589.

4-Methyl-3-pentyl-3*H*-thieno[3,4-*b*]indole-3-thione (36). By a procedure similar to that for **28**, treatment of **25c** (59 mg, 0.22 mmol) with P_2S_5 (93 mg, 0.42 mmol) in refluxing 1,4-dioxane (15 mL) for 4 h gave **36** (45 mg, 68%): oil; TLC (EtOAc/hexane (1:4)) R_f = 0.27; IR (neat) 2927, 1503, 1469, 1201, 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (3 H, t, J = 6.8 Hz), 1.21−1.59 (6H, m), 1.92 (1 H, dtd, J = 9.6, 7.9, 3.2 Hz), 2.21 (1 H, tdd, J = 7.9, 3.4, 3.2 Hz), 3.76 (3 H, s), 4.63 (1 H, dd, J = 9.6, 3.2 Hz), 7.23−7.35 (3 H, m), 8.32−8.37 (1 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 22.3, 27.4, 31.4, 31.4, 33.0, 50.8, 109.9, 120.3, 121.8, 123.4, 124.3, 129.9, 142.9, 160.4, 213.3 (C=S); MS *m*/*z* (rel intensity) 289 (25, M^+), 232 (34), 218 (18), 71 (100); HRMS calcd for $C_{16}H_{19}NS_2$ 289.0959, found 289.0950.

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Supporting Information Available: Additional experimental procedures, ORTEP drawings and crystal data of compounds **4b** and **18**, and spectral data of new compounds (72 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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