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SYNTHESIS OF HIGHLY SUBSTITUTED INDOLE ALKALOID SPECIES *VIA* [4 + 1] CYCLIZATION OF NUCLEOPHILIC CARBENES AND INDOLE ISOCYANATES

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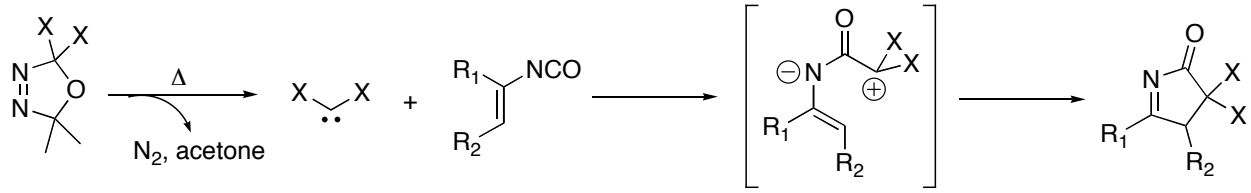
Abstract - Thermally induced [4 + 1] cyclization between indole isocyanates and dimethoxycarbene or bis(propylthio)carbene has been achieved with good chemical efficiency. The methodology provides rapid access to fused pyrroloindole substructures commonly found in a variety of indole alkaloid natural products.

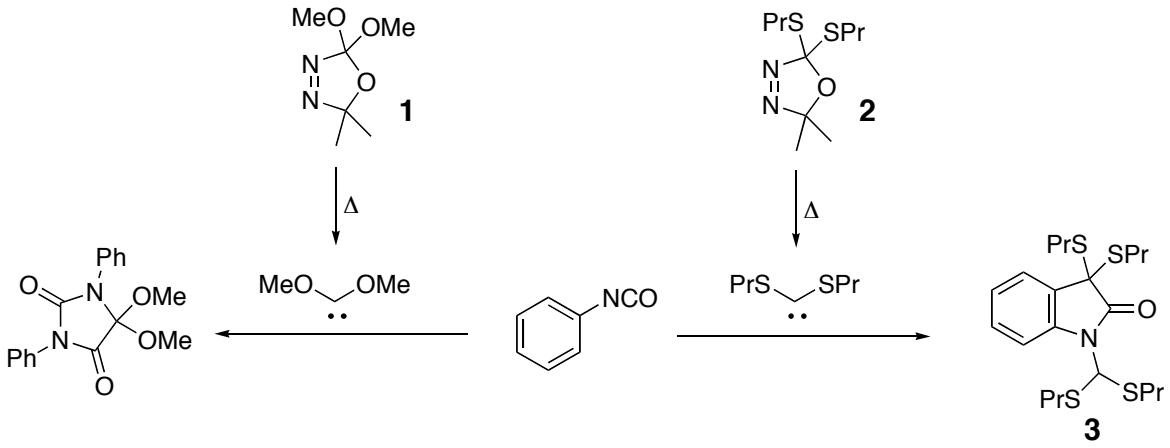
This paper is dedicated to Barry M. Trost on the occasion of his 65th birthday.

INTRODUCTION

Recently, vinyl isocyanates have been shown to exhibit considerable utility as building blocks for the formation of functionally elaborate five-membered nitrogen heterocycles *via* [4 + 1] cyclization with sulfur-, oxygen-, and nitrogen-based carbenes.[1-3] Nucleophilic carbenes, generated from the thermal decomposition of oxadiazolines, constitute powerful 1,1-dipole equivalents for constructing pyrrolidinone systems,[4-6] and this process has been utilized as a key strategy-level transformation in the total synthesis of the alkaloids tazettine and mesembrine.[7,8] The methodology has also been extended to include the construction of isatins *via* [4 + 1] cyclization with aryl isocyanates and bis(alkylthio)carbenes,[6,9] a process



that is generally inaccessible with dimethoxycarbene.[5,10] For example, bis(propylthio)carbene underwent [4 + 1] cyclization with phenyl isocyanate to provide isatin (**3**), while the corresponding reaction with dimethoxycarbene produces a hydantoin product (Scheme 1).[6,10]



Scheme 1. The differential reactivity of dimethoxy- and bis(propylthio)-carbenes with phenyl isocyanate.

The fused pyrroloindole ring (**A**) is a common structural motif present in many biologically active natural products (Figure 1). For example, the pyrrolo[2,3-*b*]indole moiety is found in brevianamide E,[11] sporidesmin A,[12] flustramine B,[13] and physostigmine;[14] and as a consequence, considerable effort has been expended to provide entries into these species.[15-17] In addition, other isomeric pyrroloindole fused ring systems are present in biologically relevant compounds;[18-20] rapid access to these substructures could provide key intermediates for the efficient syntheses of numerous indole alkaloids.

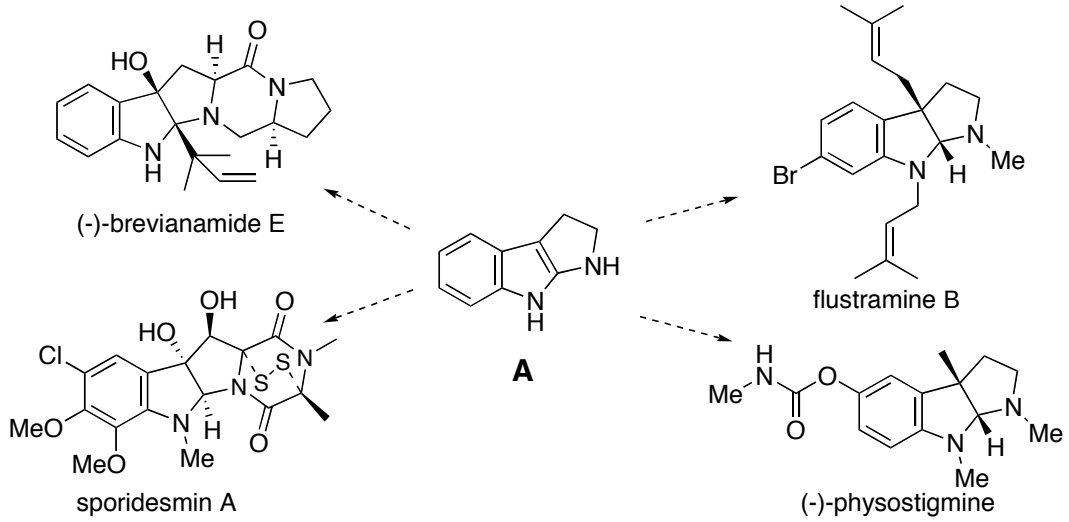


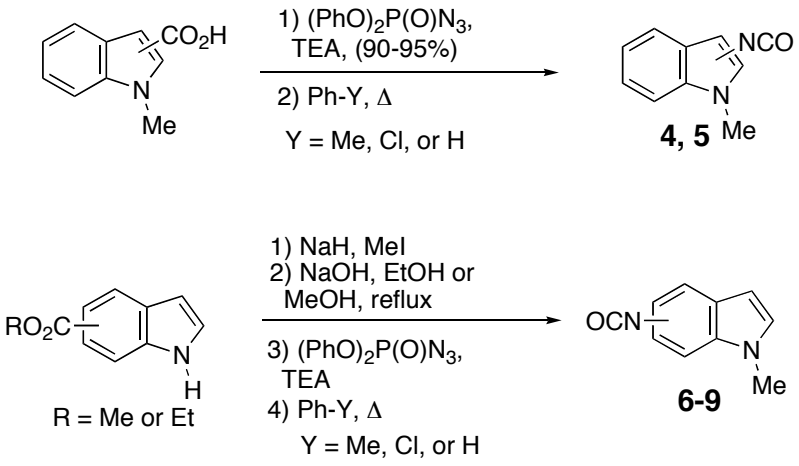
Figure 1. Natural products containing the pyrrolo[2,3-*b*]indole substructure.

This paper describes the construction of the fused pyrroloindole ring structure at various locations about the indole ring system *via* [4 + 1] cyclization between nucleophilic carbenes and indole isocyanates.

Dimethoxycarbene precursor (**1**) (Scheme 1), readily available *via* the procedures of Warkentin,[21,22] and bis(propylthio)carbene precursor (**2**), available from the published procedures of our laboratory,[6] were employed. The reaction sequence provides fused pyrroloindole species rich in functionality and well-suited for post-cyclization elaboration.

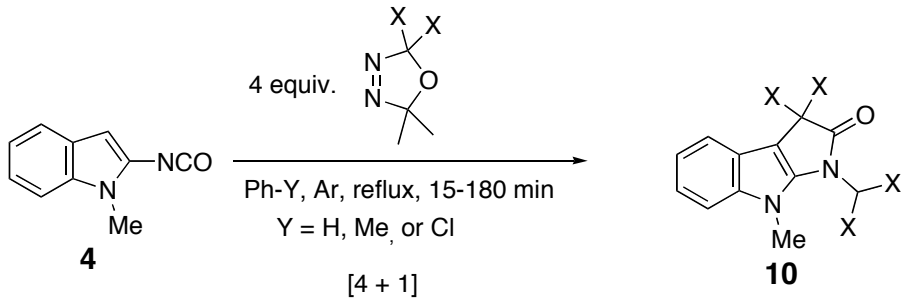
RESULTS AND DISCUSSION

Indole isocyanates (**4-9**) were prepared from commercially available indole acids or indole carboxylates as shown in Scheme 2. Methylindole-2-carboxylic acid and methylindole-3-carboxylic acid were treated



Scheme 2. Preparation of indole isocyanates.

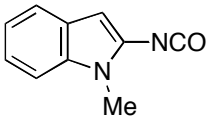
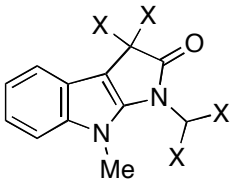
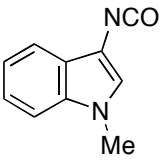
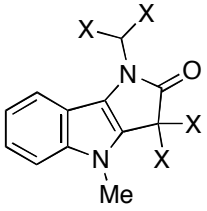
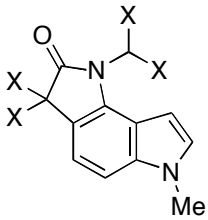
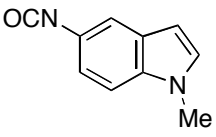
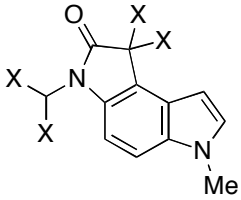
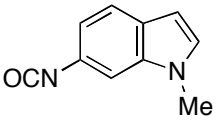
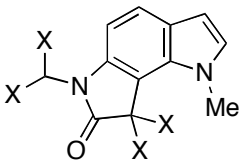
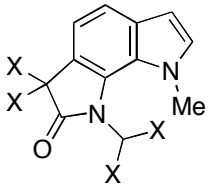
with diphenylphosphorazidate in the presence of TEA to afford the corresponding acyl azides in good yield. The analogous indole isocyanates at positions 4-7 were accessed from the corresponding indole carboxylates. The carboxylates were *N*-methylated with sodium hydride and methyl iodide, prior to saponification with sodium hydroxide; the liberated acids were then converted to the requisite acyl azides. The indole acyl azides underwent smooth thermally-induced Curtius rearrangement to the isocyanates (**4-9**) in benzene, toluene, or chlorobenzene.



Scheme 3. [4 + 1] cycloaddition of indole-2-isocyanate with nucleophilic carbene.

With the indole precursors in hand, attention turned to the [4 + 1] cyclization reactions. A typical example employing indole-2-isocyanate (**4**) is shown in Scheme 3. The reactions were performed with four equiv. of carbene to account for the formation of carbene dimer, a ubiquitous side-product of these reactions.[4,23,24] Consistent with related results,[3,9] the reactions yielded 2:1 adducts, with the second carbene equivalent inserting into the N-H bond of the incipient pyrrolidinone ring. Complete results are compiled in Table 1. In all cases, dimethoxycarbene reacted with good efficiency in yields ranging from 55-75%, and for **12**-**15** the reported yields are over 4 steps from the starting indole carboxylates. However, bis(propylthio)carbene performed poorly relative to dimethoxycarbene with the indole

Table 1. [4 + 1] cyclization reaction of indole isocyanates with dimethoxycarbene (**1**) and bis(propylthio)carbene (**2**).

entry		isocyanate	product	yield*
1	**4**			**10a**, X=OMe, 65% **10b**, X=SPr, trace
2	**5**			**11a**, X=OMe, 57% **11b**, X=SPr, 21%
3	**6**			**12a**, X=OMe, 75% **12b**, X=SPr, 68%
4	**7**			**13a**, X=OMe, 55% **13b**, X=SPr, 53%
5	**8**			**14a**, X=OMe, 57% **14b**, X=SPr, 58%
6	**9**			**15a**, X=OMe, 65% **15b**, X=SPr, decomp.

*Yields for **12**-**15** are over 4 steps from the commercially available indole carboxylates.

isocyanates substituted at the 2-, 3-, and 7-positions. Cycloadducts (**10b**) and (**11b)** were only obtained in trace amounts and 24% yield respectively, compared to 65% and 57% yields in the analogous reactions with dimethoxycarbene. Furthermore, decomposition was observed in the reaction with indole isocyanate (**9**) and bis(propylthio)carbene; whereas the corresponding reaction between dimethoxycarbene produced the desired cycloadduct (**15a)** in 65% yield. Indole substrates with isocyanate substituents in the 4-6 positions reacted with both dimethoxy- and bis(propylthio)carbene providing cycloadducts (**12**-**14)** in good yields. The observed regioselectivity for cycloadducts (**13**) and (**14**) is consistent with the frontier electron density of indole for electrophilic substitution, as calculated by the LCAO-MO method.[25]

In addition to the natural products shown above in Figure 1, this methodology also provides rapid access to isomeric pyrroloindole substructures found in other biologically active compounds. A few illustrative examples are shown in Figure 2. "Twist-free" indolactam-V has been shown to represent the reactive conformation of the teleocidins - a class of tumor promoters.[26] The synthesis of "twist-free" indolactam-V and related analogues could be efficiently achieved through the elaboration of cycloadduct (**12**). Likewise, 5-hydroxytryptamine (5-HT) receptor antagonists[19] - a class of molecules that represent potential therapeutics for psychiatric disorders like anxiety, depression, and migraine - could be rapidly assembled *via* cycloadduct (**14**). CC-1065 has been shown to possess potent *in vitro* and *in vivo* antitumor activity, as well as antimicrobial activity.[18] The structure consists of three pyrroloindole units, represented by **B**, which could be prepared in an analogous manner to cycloadduct (**13**).

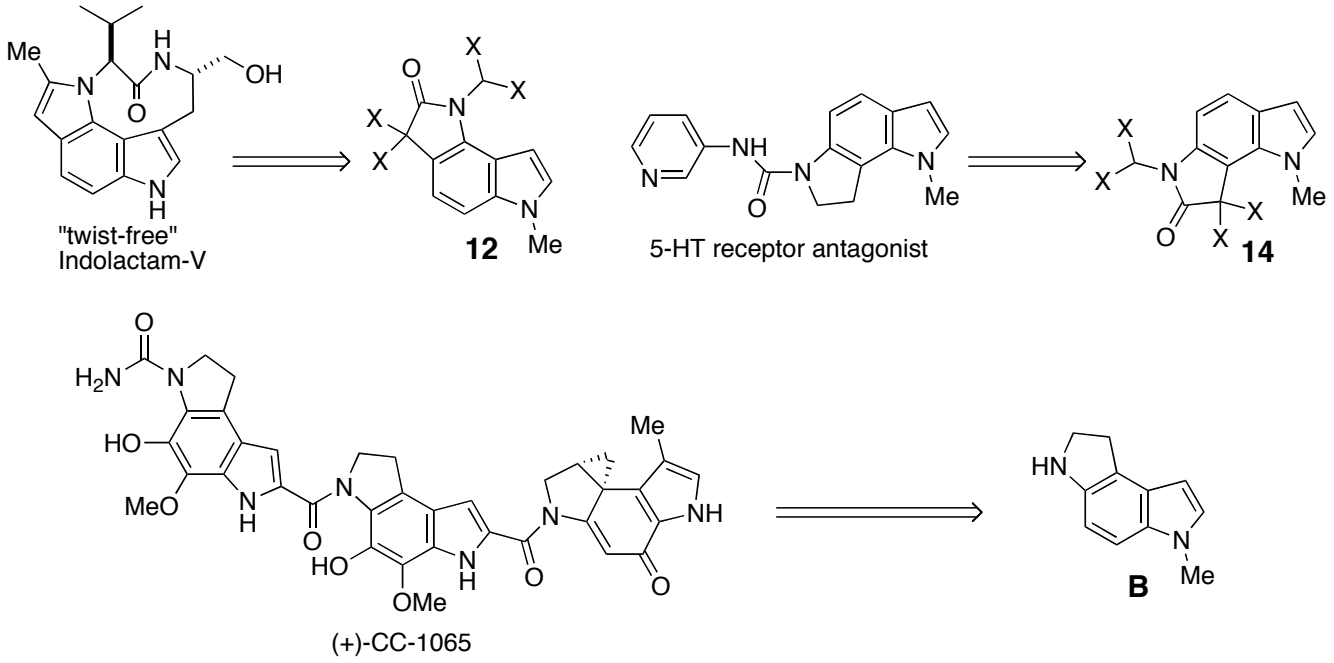


Figure 2. Potential synthetic targets containing isomeric fused pyrroloindole ring systems

In summary, dimethoxy- and bis(propylthio)carbene have been shown to effectively participate in [4 + 1] cyclization reactions with indole isocyanates. The reaction provides fused pyrroloindole structures rich in functionality, and poised for further elaboration into various classes of indole alkaloids. Significantly, these results also provide an example of successful [4 + 1] cyclization between dimethoxycarbene and aryl isocyanates, a process that commonly produces unwanted hydantoin products.[5,10]

EXPERIMENTAL

General

All reactions were performed in oven-dried glassware. ^{1}H and ^{13}C NMR spectra were collected on a 500 MHz Varian Unity-500 or 400 MHz Varian Mercury-400 spectrometer; IR spectra were collected on a Perkin Elmer Spectrum RX-1 FT-IR system. Chemical shifts are reported relative to C_6D_6 (^{1}H: δ 7.15 ppm, ^{13}C: δ 128.0 ppm). Analytical TLC was performed on silica gel 60 F_{254} precoated glass plates; compounds were purified by flash chromatography using 60 Å Purisil silica gel 230-400 mesh. New compounds exhibited spectral (^{1}H NMR, ^{13}C NMR, and IR) and analytical (HRMS) data consistent with the assigned structures. Dimethoxycarbene[21,22] and bis(propylthio)carbene[6] oxadiazoline precursors were prepared as previously described.

General procedure for N-methylation

The indole carboxylates were dissolved in dry DMF (100 mM) under an Ar atmosphere and cooled to 0 °C. Two equiv. of sodium hydride, as a 60% dispersion in mineral oil, was then added and stirring continued for 1 h at 0 °C. One equiv. of methyl iodide was then added and the reaction was stirred for 30 min at 0 °C, followed by 2 h at room temperature, at which time TLC revealed complete consumption of starting material. Workup was achieved through the addition of 60 mL 1 M $NaHCO_3$ and 60 mL ethyl acetate. The aqueous phase was extracted 3x with 60 mL diethyl ether; the combined organics were then dried with Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude products as a clear, colorless oil. The products were used without further purification.

General procedure for saponification of indole carboxylates

N-Methylated indole methyl (or ethyl) carboxylates were dissolved in a 1 M sodium hydroxide solution consisting of 80% methanol/ethanol (depending on ester) and 20% water to a concentration of 90 mM. The reaction mixture was refluxed for 8 h, at which time TLC revealed consumption of starting material. The reaction was then added to 80 mL 1 M HCl and the aqueous phase was extracted 4x with 100 mL dichloromethane; the combined organics were washed 1x with 100 mL saturated sodium chloride, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the acid as a white solid, which was used without further purification.

General procedure for the preparation of indole acyl azides

To a solution of the indole carboxylic acid dissolved in anhydrous benzene (0.2 M) was added one equiv. of distilled triethylamine. The solution was stirred at rt for 15 min under Ar; one equiv. of diphenylphosphorazidate (DPPA) was then added and stirring was continued for 1 h, at which time TLC revealed complete conversion. The reaction mixture was then purified by silica gel chromatography (various ratios of hexanes:ethyl acetate) to afford indole acyl azide. In three cases (**6**-**8**) the acyl azide was inseparable from the DPPA byproduct. Therefore, the yields for **12**-**15** are reported over 4 steps from the commercially available indole carboxylates.

General procedure for the [4 + 1] cyclization of indole isocyanates with dimethoxycarbene

The indole acyl azide was dissolved in anhydrous chlorobenzene or toluene to a concentration of 10 mM and refluxed for 1 h under Ar to effect thermal Curtius rearrangement to the corresponding indole isocyanate. To the refluxing mixture was added 4 equiv. of oxadiazoline (**1**) *via* syringe. Following addition, refluxing continued until reaction was complete, typically 15-60 min in chlorobenzene, or 60-180 min in toluene. The reaction was allowed to cool to room temperature; the solvent was then removed *in vacuo*. The crude residue was purified by silica gel chromatography in varying ratios of hexanes:ethyl acetate containing 2% triethylamine to yield the pure product as a light yellow, oily residue. The pure products were characterized by NMR spectroscopy in C_6D_6. Note: In two cases (**11a** and **15a**) the best results were obtained by heating the corresponding indole acyl azides to reflux in the presence of the carbene oxadiazoline precursor.

General procedure for the [4 + 1] cyclization of indole isocyanates with bis(propylthio)carbene

The indole acyl azide was dissolved in anhydrous benzene to a concentration of 10 mM and refluxed for 1 h under Ar to effect thermal Curtius rearrangement to the corresponding indole isocyanate. To the refluxing mixture was added 4 equiv. of oxadiazoline (**2**) as a 1 M solution in hexanes in five portions over 1 h. The oxadiazoline stock solution was kept at 0 °C over the course of the addition. Following addition, refluxing continued until reaction was complete, typically 60-120 min. The reaction was allowed to cool to room temperature; the solvent was removed *in vacuo*. The crude residue was then purified by silica gel chromatography in varying ratios of hexanes and ethyl acetate containing 1% triethylamine, yielding pure product as a light orange, oily residue. The pure products were characterized by NMR spectroscopy in C_6D_6.

3,3-Dimethoxy-1-dimethoxymethyl-8-methylpyrrolo[2,3-*b*]indol-2(1*H*,3*H*,8*H*)-one (10a). The corresponding acyl azide (51 mg, 0.25 mmol) precursor to **4**, in the presence of dimethoxycarbene precursor (**1**) (166 mg, 1.0 mmol), was heated to reflux in chlorobenzene. After 15 min, TLC revealed consumption of starting material. Pyrrolodinoindole (**10a**) (52 mg, 65%) was obtained as an oily residue after column chromatography with 90:8:2 hexanes:ethyl acetate:TEA. TLC (SiO_2, 4:1 hexanes/ethyl

acetate): R_f = 0.61. ^{1}H NMR (500 MHz): δ 2.91 (s, 6H), 3.42 (s, 3H), 3.58 (s, 6H), 5.87 (s, 1H), 6.92 (d, J = 7.5 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H). ^{13}C NMR (125 MHz): δ 175.1, 143.9, 138.0, 124.4, 121.8, 120.1, 118.4, 110.3, 102.4, 100.8, 95.7, 54.2, 51.7, 31.6. IR (neat): υ 2943, 1753, 1556, 1522, 1457, 1107, 1065 cm^{-1}. HRMS calculated for $C_{16}H_{20}N_2O_5$ 320.1372, found 320.1385.

3,3-Dimethoxy-1-dimethoxymethyl-4-methylpyrrolo[3,2-*b*]indol-2(1*H*,3*H*,4*H*)-one (11a). The corresponding acyl azide (34 mg, 0.17 mmol) precursor to **5** underwent Curtius rearrangement to the requisite isocyanate; indole isocyanate (**5**) and dimethoxycarbene precursor (**1**) (109 mg, 0.68 mmol) were heated to reflux in toluene for 180 min. Pyrrolodinoindole (**11a**) (31 mg, 57%) was obtained as an oily residue after column chromatography with 80:18:2 hexanes:ethyl acetate:TEA. TLC (SiO_2, 2:1 hexanes/ethyl acetate): R_f = 0.42. ^{1}H NMR (400 MHz): δ 3.10 (s, 6H), 3.23 (s, 3H), 3.43 (s, 6H), 6.09 (s, 1H), 6.95 (m, 1H), 7.18 (m, 2H), 8.21 (m, 1H), 7.59 (d, J = 7.5 Hz, 1H). ^{13}C NMR (100 MHz): δ 178.5, 139.2, 138.4, 123.5, 123.1, 121.7, 120.2, 116.4, 110.2, 101.7, 94.8, 53.8, 51.6, 30.6. IR (neat): υ 2945, 1732, 1467, 1365, 1222, 1186, 1069, 994 cm^{-1}. HRMS calculated for $C_{16}H_{20}N_2O_5$ 320.1372, found 320.1367.

1-(Bis(propylthio)methyl)-4-methyl-3,3-bis(propylthio)pyrrolo[3,2-*b*]indol-2(1*H*,3*H*,4*H*)-one (11b). The corresponding acyl azide (51 mg, 0.25 mmol) precursor to **5** underwent Curtius rearrangement to the requisite isocyanate; indole isocyanate (**5**) and bis(propylthio)carbene precursor (**2**) (1.0 mL, 1.0 mmol) were heated to reflux in benzene for 120 min. Pyrrolodinoindole (**11b**) (26 mg, 21%) was obtained as an oily residue after column chromatography with 98:2 hexanes:TEA. TLC (SiO_2, 4:1 hexanes/ethyl acetate): R_f = 0.64. ^{1}H NMR (400 MHz): δ 0.76 (m, 12H), 1.42 (m, 4H), 1.53 (m, 4H), 2.33 (m, 2H), 2.58 (m, 2H), 2.78 (m, 4H), 3.59 (s, 3H), 6.96 (d, J = 10 Hz, 1H), 7.00 (s, 1H), 7.13 (t, J = 10 Hz, 1H), 7.22 (t, J = 10 Hz, 1H), 8.63 (d, J = 10 Hz, 1H). ^{13}C NMR (125 MHz): δ 175.2, 139.4, 127.2, 122.7, 122.6, 120.5, 117.7, 116.1, 110.1, 73.7, 58.3, 34.9, 32.6, 30.2, 23.0, 22.8, 13.5, 13.4. IR (neat): υ 2961, 1708, 1462, 1404, 1277, 1014, 785 cm^{-1}. HRMS calculated for $C_{20}H_{36}N_2OS_4$ 496.1711, found 496.1714.

3,3-Dimethoxy-1-dimethoxymethyl-6-methylpyrrolo[2,3-*e*]indol-2(1*H*,3*H*,6*H*)-one (12a). The corresponding acyl azide (28 mg, 0.14 mmol) precursor to **6** underwent Curtius rearrangement to the requisite isocyanate; indole isocyanate (**6**) and dimethoxycarbene precursor (**1**) (90 mg, 0.56 mmol) was heated to reflux in toluene for 180 min. Pyrrolodinoindole (**12a**) (37 mg, 75% over 4 steps) was obtained as a crystalline solid after column chromatography with 70:28:2 hexanes:ethyl acetate:TEA. TLC (SiO_2, 2:1 hexanes/ethyl acetate): R_f = 0.31. ^{1}H NMR (500 MHz): δ 2.86 (s, 3H), 3.10 (s, 6H), 3.58 (s, 6H), 6.34 (s, 1H), 6.54 (d, J = 3.5 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 3.5 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H). ^{13}C NMR (125 MHz): δ 173.1, 140.1, 133.5, 128.5, 117.9, 115.9, 114.7, 104.4, 103.6, 102.4, 99.0,

54.0, 50.9, 32.2. IR (neat): υ 2942, 1735, 1622, 1477, 1301, 1111, 1071, 993 cm^{-1}. HRMS $[M + Na]^+$ calculated for $C_{16}H_{20}N_2O_5$ 343.1264, found 343.1271.

1-(Bis(propylthio)methyl)-6-methyl-3,3-bis(propylthio)pyrrolo[2,3-*e*]indol-2(1*H*,3*H*,6*H*)-one (12b). The corresponding acyl azide (48 mg, 0.24 mmol) precursor to **6** underwent Curtius rearrangement to the requisite isocyanate; indole isocyanate (**6**) and bis(propylthio)carbene precursor (**2**) (960 μL, 0.96 mmol) were heated to reflux in benzene for 90 min. Pyrrolodinoindole (**12b**) (90 mg, 68% over 4 steps) was obtained as an oily residue after column chromatography with 99:0:1 to 96:3:1 hexanes:ethyl acetate:TEA. TLC (SiO_2, 4:1 hexanes/ethyl acetate): R_f = 0.50. ^{1}H NMR (500 MHz): δ 0.77 (m, 12H), 1.47 (m, 4H), 1.59 (m, 4H), 2.43 (m, 2H), 2.64 (m, 2H), 2.82 (m, 5H), 2.90 (m, 2H), 6.58 (d, J = 3.5 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 7.30 (s, 1H), 7.60 (d, J = 3.5 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H). ^{13}C NMR (125 MHz): δ 175.6, 139.8, 132.4, 128.7, 118.8, 118.0, 115.3, 105.5, 104,5, 58.4, 57.4, 35.7, 32.8, 32.2, 23.1, 22.9, 13.6, 13.4. IR (neat): υ 2958, 1706, 1615, 1454, 1281, 1185, 715 cm^{-1}. HRMS calculated for $C_{20}H_{36}N_2OS_4$ 496.1711, found 496.1721.

8,8-Dimethoxy-6-dimethoxymethyl-3-methylpyrrolo[3,2-*e*]indol-7(3*H*,6*H*,8*H*)-one (13a). The corresponding acyl azide (60 mg, 0.30 mmol) precursor to **7** underwent Curtius rearrangement to the requisite isocyanate; indole isocyanate (**7**) and dimethoxycarbene precursor (**1**) (192 mg, 1.2 mmol) were heated to reflux in chlorobenzene for 15 min. Pyrrolodinoindole (**13a**) (53 mg, 55% over 4 steps) was obtained as a crystalline solid (mp = 88 °C) after column chromatography with 80:18:2 to 70:28:2 hexanes:ethyl acetate:TEA. TLC (SiO_2, 2:1 hexanes/ethyl acetate): R_f = 0.29. ^{1}H NMR (500 MHz): δ 2.81 (s, 3H), 3.14 (s, 6H), 3.63 (s, 6H), 6.24 (s, 1H), 6.50 (d, J = 3.0 Hz, 1H), 6.73 (d, J = 3.0 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 7.69 (d, J = 8.5 Hz, 1H). ^{13}C NMR (125 MHz): δ 172.1, 135.2, 133.6, 131.0, 125.6, 115.2, 111.0, 108.4, 102.8, 100.3, 99.7, 54.2, 51.6, 32.1. IR (neat): υ 2944, 1729, 1594, 1233, 1457, 1117, 1068 cm^{-1}. HRMS calculated for $C_{16}H_{20}N_2O_5$ 320.1372, found 320.1367.

1-(Bis(propylthio)methyl)-6-methyl-3,3-bis(propylthio)pyrrolo[2,3-*e*]indol-2(1*H*,3*H*,6*H*)-one (13b). The corresponding acyl azide (47 mg, 0.24 mmol) precursor to **7** underwent Curtius rearrangement to the requisite isocyanate; indole isocyanate (**7**) and bis(propylthio)carbene precursor (**2**) (960 μL, 0.96 mmol) were heated to reflux in benzene for 120 min. Pyrrolodinoindole (**13b**) (62 mg, 53% over 4 steps) was obtained as a light orange, oily residue after column chromatography with 99:0:1 to 96:3:1 hexanes:ethyl acetate:TEA. TLC (SiO_2, 4:1 hexanes/ethyl acetate): R_f = 0.50. ^{1}H NMR (500 MHz): δ 0.72 (t, J = 5.0 Hz, 6H), 0.79 (t, J = 5.0 Hz, 6H), 1.45 (m, 4H), 1.58 (m, 4H), 2.39 (m, 2H), 2.63 (m, 2H), 2.82 (m, 5H), 2.91 (m, 2H), 6.55 (d, J = 3.0 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 7.17 (s, 1H), 7.21 (d, J = 3.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H). ^{13}C NMR (125 MHz): δ 174.6, 135.5, 131.5, 130.5, 128.3, 125.1, 110.0, 108.7, 99.6, 58.4, 57.3, 35.1, 32.7, 32.1, 23.1, 22.9, 13.6, 13.4. IR (neat): υ 2960, 1704, 1589, 1421, 1282, 770 cm^{-1}. HRMS calculated for $C_{20}H_{36}N_2OS_4$ 496.1711, found 496.1709.

8,8-Dimethoxy-6-dimethoxymethyl-1-methylpyrrolo[2,3-*g*]indol-7(1*H*,6*H*,8*H*)-one (14a). The corresponding acyl azide (63 mg, 0.31 mmol) precursor to **8** underwent Curtius rearrangement to the requisite isocyanate; indole isocyanate (**8**) and dimethoxycarbene precursor (**1**) (198 mg, 1.24 mmol) were heated to reflux in chlorobenzene for 30 min. Pyrrolodinoindole (**14a**) (58 mg, 57% over 4 steps) was obtained as a crystalline solid (mp = 131-132 °C) after column chromatography with 90:8:2 hexanes:ethyl acetate:TEA. TLC (SiO_2, 2:1 hexanes/ethyl acetate): $R_f = 0.47$. ^{1}H NMR (500 MHz): δ 3.11 (s, 6H), 3.39 (s, 6H), 3.65 (s, 3H), 6.20 (s, 1H), 6.39 (d, J = 3.0 Hz, 1H), 6.51 (d, J = 3.0 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H). ^{13}C NMR (125 MHz): δ 171.1, 136.2, 133.5, 130.0, 125.6, 123.8, 106.7, 105.8, 102.7, 102.5, 100.6, 54.1, 51.3, 47.5, 35.9. IR (neat): υ 2944, 1725, 1592, 1455, 1334, 1235, 1080 cm^{-1}. HRMS calculated for $C_{16}H_{20}N_2O_5$ 320.1372, found 320.1372.

6-(Bis(propylthio)methyl)-1-methyl-8,8-bis(propylthio)pyrrolo[2,3-*g*]indol-7(1*H*,6*H*,8*H*)-one (14b). The corresponding acyl azide (58 mg, 0.29 mmol) precursor to **8** underwent Curtius rearrangement to the requisite isocyanate; indole isocyanate (**8**) and bis(propylthio)carbene precursor (**2**) (1.2 mL, 1.2 mmol) were heated to reflux in benzene for 180 min. Pyrrolodinoindole (**14b**) (82 mg, 58% over 4 steps) was obtained as a light orange, oily residue after column chromatography with 99:0:1 hexanes:ethyl acetate:TEA. TLC (SiO_2, 4:1 hexanes/ethyl acetate): $R_f = 0.59$. ^{1}H NMR (500 MHz): δ 0.65 (t, J = 7.5 Hz, 6H), 0.73 (t, J = 7.5 Hz, 6H), 1.31 (m, 4H), 1.54 (m, 4H), 2.33 (m, 2H), 2.54 (m, 2H), 2.68 (m, 2H), 2.80 (m, 2H), 4.20 (s, 3H), 6.36 (d, J = 3.0 Hz, 1H), 6.52 (d, J = 3.0 Hz, 1H), 7.07 (s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H). ^{13}C NMR (125 MHz): δ 173.5, 134.8, 133.0, 130.9, 128.8, 122.8, 110.1, 107.4, 103.0, 58.6, 56.3, 39.1, 35.2, 32.7, 23.1, 22.8, 13.5, 13.4. IR (neat): υ 2959, 1704, 1584, 1448, 1284, 799 cm^{-1}. HRMS calculated for $C_{20}H_{36}N_2OS_4$ 496.1711, found 496.1686.

6,6-Dimethoxy-8-dimethoxymethyl-1-methylpyrrolo[3,2-*g*]indol-7(1*H*,6*H*,8*H*)-one (15a). The corresponding acyl azide (68 mg, 0.34 mmol) precursor to **9**, in the presence of dimethoxycarbene precursor (**1**) (218 mg, 1.36 mmol), was heated to reflux in chlorobenzene. After 30 min, TLC revealed consumption of starting material. Pyrrolodinoindole (**15a**) (71 mg, 65% over 4 steps) was obtained as a crystalline solid (mp = 198 °C d) after column chromatography with 80:18:2 hexanes:ethyl acetate:TEA. TLC (SiO_2, 2:1 hexanes/ethyl acetate): $R_f = 0.44$. ^{1}H NMR (500 MHz): δ 2.95 (s, 6H), 3.52 (s, 6H), 3.71 (s, 3H), 6.03 (s, 1H), 6.43 (d, J = 3.0 Hz, 1H), 6.57 (d, J = 3.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H). ^{13}C NMR (125 MHz): δ 175.4, 135.6, 133.7, 125.8, 120.4, 117.1, 116.3, 106.4, 102.6, 97.7, 73.7, 54.3, 50.9, 47.5, 37.5. IR (neat): υ 2940, 1737, 1467, 1303, 1183, 1071, 811 cm^{-1}. HRMS calculated for $C_{16}H_{20}N_2O_5$ 320.1372, found 320.1378.

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