An Efficient Synthesis of 1,2,9,9a-Tetrahydrocyclopropa[c]benz[e]indol-4-one (CBI): An Enhanced and Simplified Analog of the CC-1065 and Duocarmycin Alkylation Subunits

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An efficient synthesis of **4**, the immediate precursor to *N*-BOC-CBI and related analogs of CC-1065 incorporating the 1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one alkylation subunit, is described based on a Tempo trap of a 5-*exo-trig* aryl radical–alkene cyclization with direct introduction of a 3-(hydroxymethyl)indoline using an unfunctionalized alkene acceptor.

(+)-CC-1065 (**1**)[1] and the duocarmycins[2,3] represent the initial members of a class of exceptionally potent antitumor antibiotics that derive their biological effects through the reversible, sequence selective alkylation of duplex DNA.[4–13] Subsequent to their disclosure, extensive efforts have been devoted to establish their duplex DNA alkylation selectivity and its structural origin,[4–13] to establish the link between DNA alkylation and the ensuing biological properties,[14] and to define the fundamental principles underlying the relationships between structure, chemical reactivity, and biological properties.[15–24] The preceding and current studies of the natural enantiomers of the CBI-based analogs of (+)-CC-1065 have shown that they are chemically more stable (4×), biologically more potent (4×), and considerably more synthetically accessible than the corresponding agents incorporating the natural CPI (cyclopropapyrroloindolone) alkylation subunit of CC-1065.[20] Moreover, the natural enantiomers of the CBI-based analogs alkylate DNA with an unaltered sequence selectivity at an enhanced rate and with a greater efficiency than the

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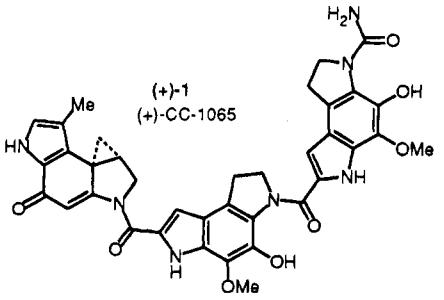
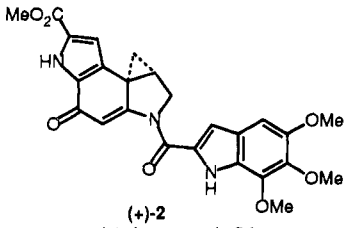
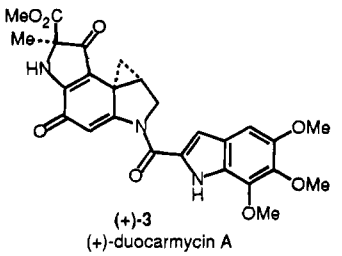
corresponding CPI analogs, indicating that they possess characteristics that make them especially attractive to pursue. These observations have prompted us to study the CBI-based analogs of CC-1065 in detail.

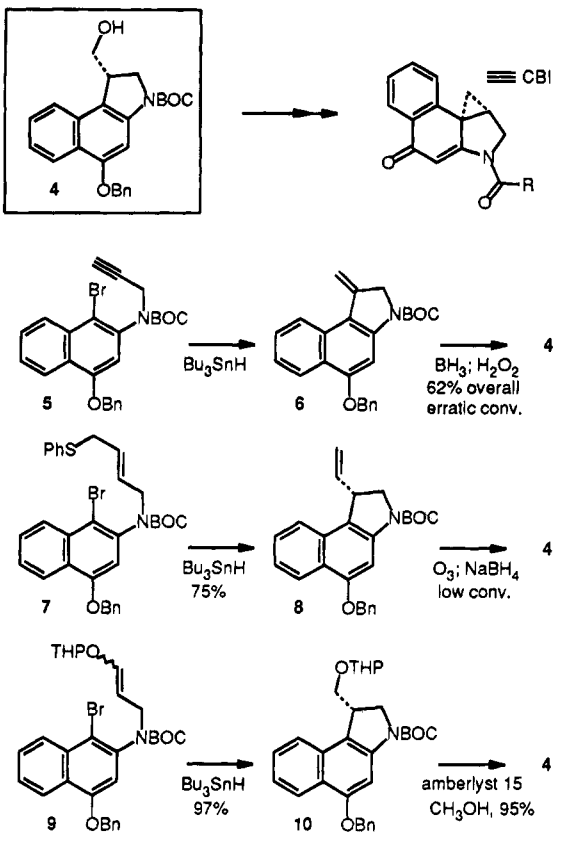






In the course of efforts on the evaluation of structural analogs of CC-1065 and the duocarmycins incorporating the 1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (CBI) alkylation subunit,[20] we have devised a more efficient synthesis of the immediate precursor **4**. Not only does this significant improvement provide straightforward access to CBI, its precursors, and subsequent analogs of **1**–**3** in substantial quantity but the approach has proven generally applicable to related new or existing alkylation subunits as well.[25,26]

Scheme 1



In our initial efforts, the 3-(hydroxymethyl)indoline **4** was derived from a 5-*exo-dig* aryl radical–alkyne cyclization of **5** followed by immediate hydroboration–oxidation of the inherently unstable 3-methyleneindoline **6** (Scheme 1).[20d] Although satisfactory conversions to **4** were achieved under carefully defined reaction conditions (50–62%), the isomerization of **6** to the corresponding indole could not be eliminated completely. Nonetheless, this proved more successful than an indirect approach based on a self terminating 5-*exo-trig* aryl radical–alkene cyclization of **7** in which the subsequent conversion of **8** to **4** proved lengthy and problematic. In more recent efforts, this was effectively addressed with use of **9** and a 5-*exo-trig* aryl radical–alkene cyclization to provide **10** (97%) which incorporates the necessary functionality directly in the free radical cyclization substrate.[20h] Not only did this solve the problem of postcyclization functionalization but also reinforced the inherent regioselectivity of the free radical cyclization by virtue of the use of an activated acceptor alkene. The natural limitation of this latter approach is the requirement to incorporate the product functionality into the acceptor alkene of the free radical cyclization substrate and for **9** this entailed a carefully defined ozonolysis and subsequent Wittig reaction with a functionalized methylenetriphenylphosphorane.

Herein, we report a more efficient and simpler preparation of **4** based on the successful Tempo trap of an aryl radical–alkene 5-*exo-trig* cyclization of an unactivated and unfunctionalized alkene that replaces this need for pre- or post-cyclization functionalization. Although pre-

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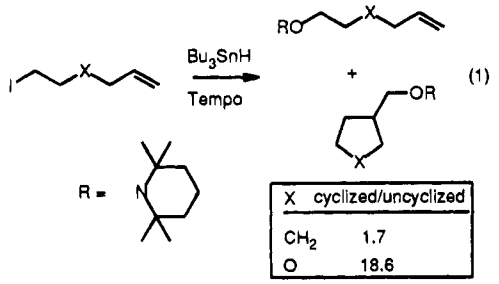
ceding studies have effectively utilized a Tempo trap of free radicals generated even under reductive conditions,[27] descriptions of its use to terminate free radical cyclization reactions have been limited.[28-30] However, Bergman and co-workers have described studies that included radical trapping experiments of a vanadium hydride species and compared the resulting hydrogen atom donating ability of this complex to Bu_3SnH.[29] In efforts to determine rate constants for hydrogen atom transfer, various radical clock reactions were employed including the cyclization reactions of the two 5-hexenyl radicals shown in eq 1. The surprisingly high ratios of cyclized to uncyclized Tempo-trapped product[31] at the reported concentrations in the presence of Bu_3SnH and the significantly faster cyclization rates of related aryl radicals,[32] prompted us to investigate an analogous reaction for the preparation of CBI.



This was first examined in detail with **11** where treatment of the aryl iodide **11a** with Bu_3SnH (3 equiv) in the presence of Tempo (5 equiv, C_6H_6, 70 °C, 1 h, 83%) provided **12** directly in excellent conversion (Scheme 2). As expected, hydrogen atom abstraction by a primary radical from Bu_3SnH ($k \approx 10^6$ M^{-1} s^{-1})[33] does not effectively compete with rapid coupling of the cyclization product radical with Tempo ($k \approx 10^9$ M^{-1} s^{-1}). However, the desired reaction did not proceed to completion until approximately 3 equiv of Bu_3SnH had been added to the reaction mixture (Table 1). This result is presumably a consequence of the competing reaction of the generated tributyltin radical with Tempo. The rate constant for halogen abstraction from an aryl iodide by tributyltin radical ($k \approx 8 \times 10^8$ M^{-1} s^{-1} at 80 °C)[34] is of the same order of magnitude as the rate constant for reaction of a tertiary carbon-centered radical with Tempo ($k \approx 7.6 \times 10^8$ M^{-1} s^{-1} at 25 °C).[35]

Scheme 2

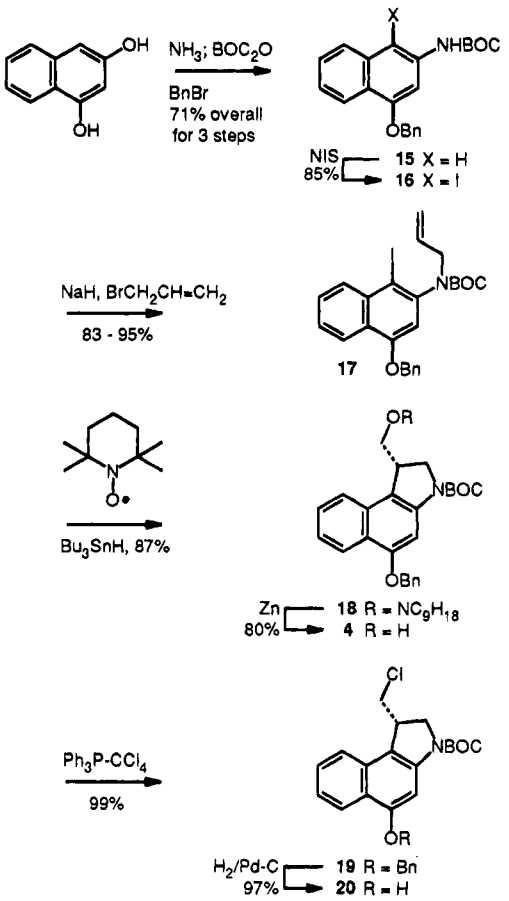


Table 1. Sequential Radical Cyclization Tempo-Trap of 11a[a]

equivalents		% isolated yield		
Bu_3SnH	Tempo	**12**	**13**	**11a**
1	1	21	5	52
1	2	27	0	68
2	2	64	2[b]	23
3	5	83	0	0

[a] Reactions were performed at an initial substrate (**11a**) concentration of 0.03–0.05 M. An equivalent of Bu_3SnH was added to a mixture of **11a** and Tempo in benzene and the solution was warmed at 70 °C. Additional equivalents of Bu_3SnH were added at 15 min intervals and the reaction progress ceased ≤45 min following the final Bu_3SnH addition. [b] Estimated from the ^1H NMR spectrum of the crude reaction mixture.

In addition to Bu_3SnH, $(Me_3Sn)_2$ under sunlamp irradiation and $(Me_3Si)_3SiH$ also proved effective for promoting the cyclization reaction (eq 3). Incomplete reaction in the case of $(Me_3Sn)_2$ may have been a function of the sunlamp and additional tin reagent or a more powerful lamp may likely have allowed the reaction to reach completion. The increased Si–H bond strength of $(Me_3Si)_3SiH$ relative to Bu_3SnH[36] manifests itself in the

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(31) The second order rate constant for reaction of a primary radical with Tempo is solvent dependent with $k = 6.7 \times 10^8$ M^{-1} s^{-1} in benzene and $k = 1.9 \times 10^8$ M^{-1} s^{-1} in acetonitrile at 18 °C. The first order cyclization rate constants at 80 °C for X = CH_2 and X = O are 1.3×10^6 s^{-1} and 2.6×10^7 s^{-1}, respectively, see Beckwith, A. L. J.; Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4983 and references cited therein.

(32) For example, the cyclization rate of the 2-(allyloxy)phen-1-yl radical has been estimated to be >600 times that of the 3-oxa-5-hexen-1-yl radical (i.e. X = O in eq 1), see Beckwith, A. L. J.; Glover, S. A. *Aust. J. Chem.* **1987**, *40*, 157 and Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. However, the accuracy of the cyclization rate constant for the phenyl radical is currently under question, see ref 33.

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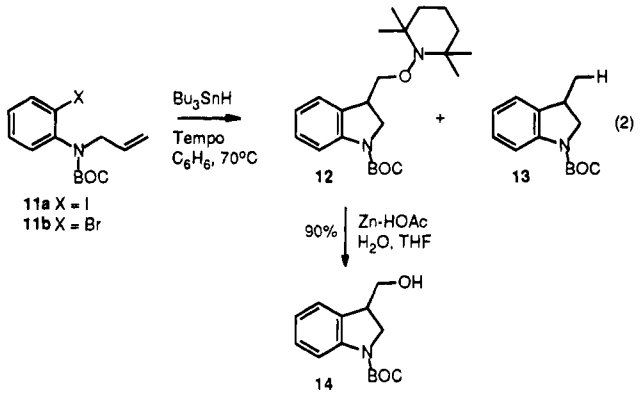
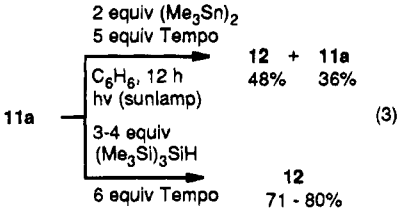


increased reaction time required with this reagent since the rate-determining step of the reaction is likely to involve hydrogen atom abstraction from Bu_3SnH or $(Me_3Si)_3SiH$ by Tempo.[29] The corresponding aryl bromide **11b** proved less effective in this cyclization–Tempo trap and provided much lower conversions to **12** (15%) and substantial (40%) recovered starting material under identical conditions. Similarly, efforts to trap the cyclization product radical derived from **11a** under comparable conditions with O_2[37] (air or O_2 balloon) provided only low conversions to **14** (15–27%) and afforded principally the reduction product **13**[38] (72%). In addition to benzene, toluene, acetonitrile, and methanol were also found to be compatible solvents for the cyclization reaction with toluene and acetonitrile providing slightly higher yields of **12** under comparable conditions. Although reactions were typically run from 0.03 to 0.05 M in **11**, reactions run at concentrations of 0.10–0.5 M provided **12** without significant byproducts and in only slightly lower yields than reactions run under more dilute conditions. Reductive cleavage of **12** to provide **14** was effected cleanly by treatment with Zn[39] ($HOAc–H_2O$–THF, 70 °C, 2 h, 90%) while Ra-Ni[40] (H_2, $AlCl_3$ or $B(OH)_3$), 10% Pd–C (H_2),[41] and SmI_2 (*t*-BuOH) provided only recovered **12**, eq 2.



The extension of the observations to the preparation of **4** proved straightforward (Scheme 2). Selective C4 iodination of **15**, readily accessible in three steps from commercially available[42] 1,3-dihydroxynaphthalene (71% overall),[20h] effected by low-temperature treatment with NIS in the presence of an acid-catalyst (1.1 equiv NIS, cat. H_2SO_4, 1:1 THF–CH_3OH, −78 °C, 3 h) cleanly provided **16** (85%). Subsequent alkylation of the sodium salt of the carbamate **16** (1.2 equiv NaH, DMF, 25 °C, 45 min) with allyl bromide (3.0 equiv, DMF, 25 °C, 3 h) provided **17** (83–95%) and the required substrate for implementation of the key 5-*exo*-*trig* aryl radical–alkene cyclization. Treatment of a mixture of **17** and Tempo (6.0 equiv) in C_6H_6 with Bu_3SnH (5 equiv, C_6H_6, 70 °C, 1 h) provided **18** in excellent conversions (87%). Addition of fewer equivalents of Bu_3SnH resulted in recovered starting material, and the reaction progress was typically monitored following addition of the last 2 equiv of Bu_3SnH to ensure complete reaction. Consistent with observations made with **11**, substrate **17** also cyclized to provide **18** in excellent yield (84%) with toluene as solvent and $(CH_3Si)_3SiH$ (6 equiv) substituted for Bu_3SnH. Reductive cleavage of **18** to provide **4** (80%) was effected by treatment with activated Zn powder in HOAc–THF–H_2O (3:1:1, 70 °C, 2 h).

With these improvements incorporated into the full length synthesis, the penultimate CBI precursor **20** is available in 9 steps from commercially available 1,3-dihydroxynaphthalene in 33–38% overall yield in multigram quantities. When combined with the newly introduced direct chromatographic resolution of **20** on a preparative Chiralcel OD column,[20b] the synthesis of optically active CBI-based analogs of **1–3** has become suitably straightforward to accommodate their widespread use.

Experimental Section

[*N*-(*tert*-Butyloxycarbonyl)amino]-2-iodobenzene. A solution of 2-iodoaniline (1.10 g, 5.0 mmol) and di-*tert*-butyl dicarbonate (3.27 g, 15 mmol) in 20 mL of 1,4-dioxane was warmed at 95 °C for 12 h. The reaction mixture was cooled to 25 °C and poured into 20 mL of H_2O. The aqueous layer was extracted with EtOAc (4 × 15 mL). The organic layers were combined, washed with saturated aqueous NaCl (2 × 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Centrifugal TLC (4 mm Chromatotron plate, 0–5% EtOAc–hexanes gradient elution) provided the title compound (1.05 g, 66%) as a light-yellow oil: ^1H NMR ($CDCl_3$, 250 MHz) δ 8.03 (dd, 1H, J = 8.3, 1.4 Hz), 7.72 (dd, 1H, J = 8.0, 1.4 Hz), 7.29 (dt, 1H, J = 7.8, 1.4 Hz), 6.80 (br s, 1H), 6.75 (dt, 1H, J = 7.7, 1.5 Hz), 1.53 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.4, 138.7, 138.7, 129.1, 124.6, 120.1, 88.7, 80.9, 28.3; IR (film) 3393, 2978, 1733, 1587, 1572, 1515, 1431, 1246, 1221, 1155 cm^{-1}; FABHRMS (NBA–NaI) m/z 341.9972 ($C_{11}H_{14}INO_2$ + Na^+ requires 341.9967).

[*N*-(*tert*-Butyloxycarbonyl)-*N*-(2-propenyl)amino]-2-iodobenzene (11a). A solution of [*N*-(*tert*-butyloxycarbonyl)-amino]-2-iodobenzene (957 mg, 3.0 mmol) in 15 mL of DMF at 0 °C was treated with NaH (108 mg, 4.5 mmol) in several portions over 15 min. After 45 min, allyl bromide (1.09 g, 9.0 mmol) was added and the reaction mixture was warmed to 25 °C and stirred for 3 h. The reaction mixture was quenched by addition of 30 mL of saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with EtOAc (4 × 15 mL). The organic layers were combined, washed with saturated aqueous NaCl (2 × 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Centrifugal TLC (4 mm Chromatotron plate, 5% EtOAc–hexanes) provided **11a** (981 mg, 91%) as a white, crystalline solid (mixture of amide rotamers in $CDCl_3$): mp 66–67 °C; ^1H NMR ($CDCl_3$, 400 MHz) (major rotamer) δ 7.84 (d, 1H, J = 7.8 Hz), 7.29 (t, 1H, J = 7.5 Hz), 7.10 (d, 1H, J = 7.5 Hz), 6.95 (t, 1H, J = 7.5 Hz), 5.97–5.87 (m, 1H), 5.10–5.03 (m, 2H), 4.47 (dd, 1H, J = 15.1, 5.6 Hz), 3.74 (dd, 1H, J = 15.1, 7.1 Hz), 1.33 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major rotamer) δ 153.7, 144.1, 139.2, 133.5, 129.8, 128.6, 128.6, 117.8, 100.5, 80.2, 51.9, 28.4; IR (film) 3079, 2976, 2928, 1699, 1580, 1472, 1380, 1304, 1254, 1152, 1006 cm^{-1}; FABHRMS (NBA–NaI) m/z 360.0450 ($C_{14}H_{18}INO_2$ + H^+ requires 360.0461).

1-(*tert*-Butyloxycarbonyl)-3-[[(2′,2′,6′,6′-tetramethylpiperidino)oxy]methyl]-2,3-dihydroindole (12). A solu-

(37) Nakamura, E.; Inubushi, T.; Aoki, S.; Machii, D. *J. Am. Chem. Soc.* **1991**, *113*, 8980.
(38) For **13**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.82 (br s, 1H, C7-H), 7.14 (t, 1H, J = 7.6 Hz, C6-H), 7.11 (d, 1H, J = 7.5 Hz, C4-H), 6.93 (t, 1H, J = 7.4 Hz, C5-H), 4.12 (t, 1H, J = 10.1 Hz, C2–H), 3.48 (m, 1H, C2-H), 3.35 (m, 1H, C3-H), 1.54 (s, 9H, $C(CH_3)_3$), 1.30 (d, 3H, J = 6.8 Hz, $CHCH_3$).
(39) Shishido, Y.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 2876.
(40) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826.
(41) Gill, G. B.; Pattenden, G.; Reynolds, S. J. *Tetrahedron Lett.* **1989**, *30*, 3229.
(42) Commercially available from Sigma Chemical Co.

tion of **11a** (48 mg, 0.13 mmol) and Tempo (105 mg, 0.67 mmol) in 4 mL of benzene was treated with Bu_3SnH (39 mg, 0.13 mmol). The solution was warmed at 70 °C and an additional 1 equiv of Bu_3SnH (39 mg) was added twice during the next 30 min. After 1 h the solution was cooled and the volatiles were removed under reduced pressure. Centrifugal TLC (1 mm Chromatotron plate, 0–10% EtOAc–hexanes gradient elution) provided **12** (43 mg, 83%) as a colorless oil (mixture of amide rotamers in $CDCl_3$): ^1H NMR ($CDCl_3$, 400 MHz) (major rotamer) δ 7.82 (br s, 1H), 7.20 (d, 1H, J = 7.3 Hz), 7.16 (t, 1H, J = 7.8 Hz), 6.91 (dt, 1H, J = 7.5, 0.9 Hz), 4.02–3.92 (m, 2H, C2-H), 3.80 (dd, 1H, J = 11.4, 5.4 Hz), 3.80–3.77 (m, 1H), 3.54–3.49 (m, 1H), 1.54 (s, 9H), 1.42–1.23 (m, 6H), 1.10 (s, 12H), ^1H NMR (DMSO-d_6, 400 MHz, single amide rotamer) δ 7.68 (br s, 1H), 7.26 (d, 1H, J = 7.3 Hz), 7.16 (t, 1H, J = 7.7 Hz), 6.92 (t, 1H, J = 7.4 Hz), 3.95 (t, 1H, J = 10.5 Hz), 3.85–3.73 (m, 3H, C2-H), 3.51–3.45 (m, 1H), 1.48 (s, 9H), 1.44–1.22 (m, 6H), 1.07 (s, 3H), 1.04 (s, 3H), 1.00 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 151.5, 142.6, 132.5, 127.7, 124.8, 121.9, 114.0, 78.4, 59.4, 50.7, 39.1, 32.8, 32.6, 28.0, 19.8, 19.6, 16.5; IR (film) 2974, 2931, 1709, 1602, 1487, 1393, 1260, 1174, 1144, 1044, 1017 cm^{-1}; FABHRMS (NBA-NaI) m/z 389.2804 ($C_{23}H_{36}N_2O_3$ + H^+ requires 389.2796). Anal. Calcd for $C_{23}H_{36}N_2O_3$: C, 71.08; H, 9.34; N, 7.21. Found: C, 70.98; H, 9.07; N, 7.32.

1-(*tert*-Butyloxycarbonyl)-3-(hydroxymethyl)-2,3-dihydroindole (14). A solution of **12** (120 mg, 0.31 mmol) in 10 mL of a 3:1:1 mixture of HOAc–THF–H_2O was treated with zinc powder (242 mg, 3.71 g atoms), and the resulting suspension was warmed at 70 °C with vigorous stirring. After 2 h, the reaction mixture was cooled to 25 °C and the zinc was removed by filtration. The volatiles were removed under reduced pressure, and the resulting residue was dissolved in 15 mL of EtOAc and filtered. The solution was concentrated and subjected to centrifugal TLC (1 mm Chromatotron plate, 20% EtOAc–hexanes) to provide **14** (69 mg, 90%) as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.86 (br s, 1H), 7.19 (t, 1H, J = 8.0 Hz), 7.18 (d, 1H, J = 7.5 Hz), 6.94 (dt, 1H, J = 7.4, 0.8 Hz), 4.04 (t, 1H, J = 11.0 Hz), 3.87 (dd, 1H, J = 11.4, 4.9 Hz), 3.82–3.72 (m, 2H), 3.52–3.45 (m, 1H), 1.55 (s, 9H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 151.7, 142.8, 132.3, 127.6, 124.8, 121.9, 113.9, 79.8, 63.9, 50.9, 41.8, 28.2; IR (film) 3436, 2944, 1692, 1594, 1482, 1390, 1251, 1169, 1138 cm^{-1}; FABHRMS (NBA–NaI) m/z 250.1449 ($C_{14}H_{19}NO_3$ + H^+ requires 250.1443).

***N*-(*tert*-Butyloxycarbonyl)-4-(benzyloxy)-1-iodo-2-naphthylamine (16).** A solution of **15**[20h] (1.28 g, 3.66 mmol) in 60 mL of a 1:1 mixture of THF–CH_3OH was cooled to −78 °C, and 20 μL of H_2SO_4 (or 20 mg TsOH·H_2O) in 0.5 mL of THF was added. *N*-Iodosuccinimide (910 mg, 4.03 mmol) in 5 mL of THF was then introduced by cannula over 5 min. Upon complete reaction (ca. 3 h at −78 °C), 10 mL of saturated aqueous $NaHCO_3$ and 50 mL of Et_2O were added. The reaction mixture was warmed to 25 °C, and solid NaCl was added to saturate the aqueous layer. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 10 mL). The organic layers were combined, washed with saturated aqueous $NaHCO_3$ (1 × 10 mL) and saturated aqueous NaCl (2 × 10 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by elution through a short column of SiO_2 (2 × 4 cm, 20% EtOAc–hexane) to provide **16** (1.48 g, 85%) as a white, crystalline solid: mp 111–112 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.21 (dd, 1H, J = 8.4, 0.8 Hz), 8.03 (s, 1H), 8.01 (d, 1H, J = 7.6 Hz), 7.55–7.33 (m, 7H), 7.30 (br s, 1H), 5.27 (s, 2H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.7, 152.8, 138.3, 136.6, 134.8, 131.2, 128.7, 128.6, 128.5, 128.1, 127.8, 124.5, 123.7, 122.7, 100.0, 81.2, 70.4, 28.4; IR (film) 3384, 2974, 2923, 1739, 1617, 1598, 1567, 1515, 1494, 1444, 1392, 1366, 1332, 1226, 1152, 1107, 1082 cm^{-1}; FABHRMS (NBA–CsI) m/z 607.9715 ($C_{22}H_{22}INO_3$ + Cs^+ requires 607.9699). Anal. Calcd for $C_{22}H_{22}INO_3$: C, 55.59; H, 4.67; N, 2.95. Found: C, 55.85; H, 4.43; N, 2.97.

2-[[*N*-(*tert*-Butyloxycarbonyl)-*N*-(2-propenyl)]amino]-4-(benzyloxy)-1-iodonaphthalene (17). A solution of **16** (1.38 g, 2.90 mmol) in 25 mL of DMF at 0 °C was treated with NaH (60% dispersion in oil, 139 mg, 3.5 mmol) in several portions over 15 min. After 45 min, allyl bromide (1.05 g, 8.70 mmol) was added and the reaction mixture was warmed to 25 °C and stirred for 3 h. The reaction mixture was quenched by addition of 20 mL of saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with EtOAc (4 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl (2 × 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Centrifugal TLC (2 mm Chromatotron plate, 20–50% CH_2Cl_2–hexanes) provided **17** (1.24 g, 83%, typically 80–95%) as a colorless oil (mixture of amide rotamers in $CDCl_3$): ^1H NMR ($CDCl_3$, 400 MHz) (major rotamer) δ 8.30 (d, 1H, J = 8.2 Hz), 7.29 (d, 1H, J = 8.2 Hz), 7.60–7.29 (m, 7H), 6.67 (s, 1H), 5.96–5.86 (m, 1H), 5.27–4.96 (m, 4H), 4.52 (dd, 1H, J = 15.0, 5.7 Hz), 3.79 (dd, 1H, J = 15.0, 7.2 Hz), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major rotamer) δ 154.9, 153.8, 143.0, 136.4, 135.3, 133.5, 132.7, 128.7, 128.6, 128.4, 128.1, 127.2, 126.1, 122.4, 117.9, 108.0, 95.0, 80.3, 70.2, 52.1, 28.3; IR (film) 3048, 2976, 2923, 1703, 1590, 1403, 1367, 1326, 1251, 1147, 1105 cm^{-1}; FABHRMS (NBA-NaI) m/z 538.0855 ($C_{25}H_{26}INO_3$ + Na^+ requires 538.0860).

5-(Benzyloxy)-3-(*tert*-butyloxycarbonyl)-1-(2′,2′,6′,6′-tetramethylpiperidino)oxy]methyl]-1,2-dihydro-3*H*-benz[*e*]indole (18). A solution of **17** (1.85 g, 3.59 mmol) and Tempo (1.68 g, 10.8 mmol) in 120 mL of freshly distilled benzene (Na/benzophenone) under N_2 was treated with Bu_3SnH (1.045 g, 3.59 mmol). The solution was warmed at 70 °C and an additional 3 equiv of Tempo (3 × 0.56 g) and Bu_3SnH (4 × 1.045 g) were added sequentially in four portions over the next 45 min. After 1 h, the solution was cooled to 25 °C and the volatiles were removed under reduced pressure. Centrifugal TLC (4 mm Chromatotron plate, 0–10% EtOAc–hexanes gradient elution) followed by recrystallization from hexanes provided **18** (1.71 g, 87%, typically 70–90%) as white needles: mp 170–172 °C; ^1H NMR (C_6D_6, 400 MHz) δ 8.56 (d, 1H, J = 8.3 Hz), 8.38 (br s, 1H), 7.77 (d, 1H, J = 8.4 Hz), 7.35 (ddd, 1H, J = 8.3, 7.6, 1.2 Hz), 7.28 (d, 2H, J = 7.0 Hz), 7.20 (t, 1H, J = 7.6 Hz), 7.15 (t, 2H), 7.07 (t, 1H, J = 7.2 Hz), 4.36 (m, 1H), 4.12 (dd, 1H, J = 9.0, 4.5 Hz), 3.84 (m, 1H), 3.61 (m, 1H), 1.53 (s, 9H), 1.37–1.17 (m, 6H), 1.22 (s, 3H), 1.13 (s, 3H), 1.07 (s, 3H), 1.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.1, 151.4, 140.0, 135.8, 129.4, 127.3, 126.7, 126.3, 125.8, 121.9, 121.6, 121.4, 121.1, 114.8, 95.3, 79.2, 69.0, 58.5, 51.5, 38.4, 38.3, 37.2, 31.9, 27.3, 18.9, 15.8; IR (film) 2973, 2930, 1704, 1626, 1582, 1460, 1406, 1381, 1367, 1328, 1266, 1144, 1037, 787, 759 cm^{-1}; FABHRMS (NBA–CsI) m/z 677.2340 ($C_{34}H_{44}N_2O_4$ + Cs^+ requires 677.2355). Anal. Calcd for $C_{34}H_{44}N_2O_4$: C, 74.97; H, 8.14; N, 5.14. Found: C, 74.68; H, 8.37; N, 5.19.

5-(Benzyloxy)-3-(*tert*-butyloxycarbonyl)-1-(hydroxymethyl)-1,2-dihydro-3*H*-benz[*e*]indole (4). A solution of **18** (1.61 g, 2.95 mmol) in 70 mL of a 3:1:1 mixture of HOAc–THF–H_2O was treated with zinc powder (2.31 g, 35.4 g atoms), and the resulting suspension was warmed at 70 °C with vigorous stirring. After 2 h, the reaction mixture was cooled to 25 °C and the zinc was removed by filtration. The volatiles were removed under reduced pressure, and the resulting residue was dissolved in 40 mL of EtOAc and filtered. The solution was concentrated and subjected to centrifugal TLC (4 mm Chromatotron plate, 15–35% EtOAc–hexanes gradient elution) to provide **4** (0.96 g, 1.19 g theoretical, 80%) identical in all respects with authentic material.[20]

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Supplementary Material Available: Copies of the ^1H NMR spectra of [*N*-(*tert*-butyloxycarbonyl)amino]-2-iodobenzene, **11a**, **13**, **14**, **17**, and **4** (6 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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