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A New Short Synthesis of 3-Substituted 5-Amino-1-(chloromethyl)-1,2-dihydro-3*H*-benzo[*e*]indoles (Amino-CBIs)

Shangjin Yang and William A. Denny*

Auckland Cancer Society Research Centre, School of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland 1000, New Zealand

b.denny@auckland.ac.nz

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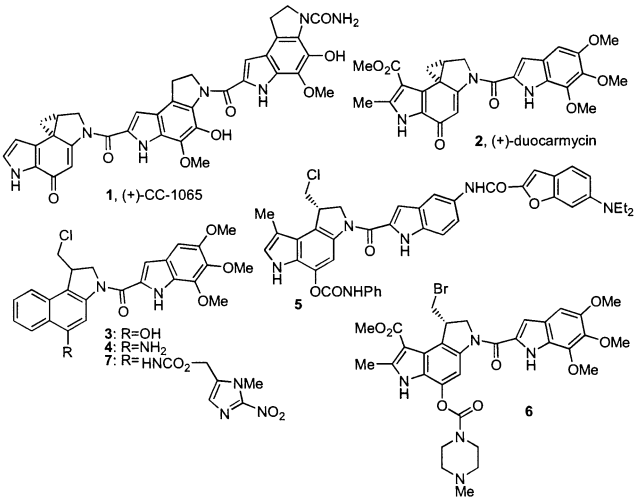
A new short synthesis of 3-substituted 5-amino-1-(chloromethyl)-1,2-dihydro-3*H*-benzo[*e*]indoles from Martius Yellow is disclosed. The key steps of the synthesis were three efficient regioselective reactions (iodination, 5-exo-trig aryl radical−alkene cyclization and carboxylation).

Introduction

The cyclopropylindole antitumor antibiotics, exemplified by the natural products (+)-CC-1065 (**1**) and (+)-duocarmycin SA (**2**), are extremely cytotoxic DNA-alkylating agents with subnanomolar potencies in cell culture.[1] This class of compounds has been extensively investigated to understand the mechanism of the alkylation step, the basis for their DNA sequence selectivity, and their potent cytotoxicity.[2] The simplified and more synthetically accessible benzo[*e*]indoles such as CBI-TMI[3] and the corresponding open-chain 5-hydroxy-1,2-dihydro-3*H*-benzo[*e*]indole (5-hydroxyCBI-TMI; 3)[4] retain the potency and biological properties characteristic of the more complex natural products, binding in the minor groove of DNA and alkylating at the N3 of adenine in a highly regio- and sequence-selective manner.[5,6] There are now efficient syntheses of these hydroxy-CBIs, where the key indoline ring is constructed via radical cyclization of an aryl radical onto a tethered alkene.[4] Analogues in which the 5-hydroxy group is protected as a carbamate, including carzelesin (**5**)[7] and KW-2189 (**6**),[8] are less toxic forms that are cleaved by rapid and nonspecific enzymatic hydrolysis.



To obtain more stable prodrugs in this class, we have developed the corresponding 5-amino-1,2-dihydro-*3H*-benzo[*e*]indoles (amino-CBI-TMI, e.g., **4**) (Scheme 1).[9] These show similar biological properties to the 5-hydroxy compounds, but form more stable carbamate prodrugs (e.g., **7**)[10] that have been of interest to us as prodrugs for gene-directed enzyme-prodrug therapy (GDEPT) in conjunction with the minor aerobic nitroreductase (NTR) from *E. coli*.[11]

The radical cyclization method[4] used previously for the hydroxy analogues could not be used in our previous

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(2) For recent contributions, see: (a) Boger, D. L.; Schmitt, H. W.; Fink, B. E.; Hedrick, M. P. *J Org. Chem.* **2001**, *66*, 6654. (b) Boger, D. L.; Hughes, T. V.; Hedrick, M. P. *J. Org. Chem.* **2001**, *66*, 2207. (c) Boger, D. L.; Santillan, A., Jr.; Searcey, M.; Brunette, S. R.; Wolkenberg, S. E.; Hedrick, M. P.; Jin, Q. *J Org. Chem.* **2000**, *65*, 4101. (d) Boger, D. L.; Boyce, C. W. *J. Org. Chem.* **2000**, *65*, 4088. (e) Boger, D. L.; Searcey, M.; Tse, W. C.; Jin, Q. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 495. (f) Baraldi, P. G.; Cacciari, B.; Romagnoli, R.; Spalluto, G.; Boyce, C. W.; Boger, D. L. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3087. (g) Boger, D. L.; Stauffer, F.; Hedrick, M. P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2021. (h) Boger, D. L.; Yun, W. *J. Am. Chem. Soc.* **1994**, *116*, 7996. (i) Boger, D. L.; Munk, S. A. *J. Am. Chem. Soc.* **1994**, *116*, 7996.

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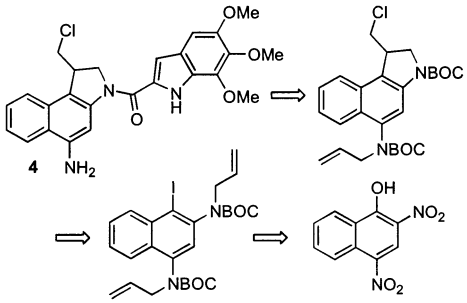
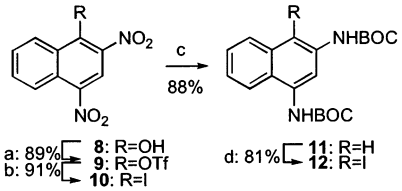
SCHEME 1



SCHEME 2. Synthesis of Iodide 10[a]



[a] Reagents and conditions: (a) 1.3 equiv of Tf_2O/2.6 equiv of Et_3N, CH_2Cl_2, 0 °C then rt, 2 h; (b) 34 equiv of NaI, EtOAc, reflux, 2 h; (c) 15 equiv of $SnCl_2$, EtOAc, reflux, 30 min, basic workup then 4.7 equiv of BOC_2O, THF, reflux, 5 h; (d) 1.37 equiv of NIS/2.0 equiv of TsOH, 1:1 THF−MeOH, −78 °C then rt over 4 h.

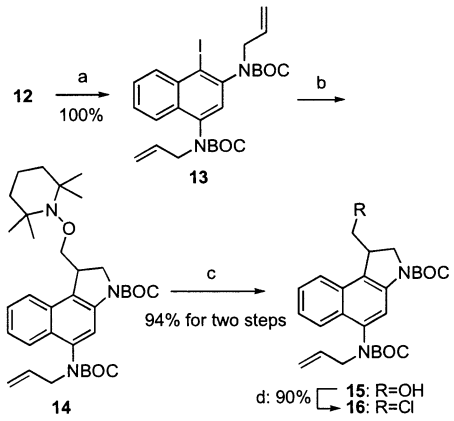
synthesis of the aminoCBIs,[9] where instead the 5-amino group was protected throughout the synthesis as a nitro group and an alternative method via formation of the corresponding lactam was employed. By this route, **4** was synthesized from 1-hydroxynaphthalene-2-carboxylic acid in 15 steps, in an overall yield of 3%. We now describe a new and more convenient synthesis of racemic **4** and analogues, based on the regioselective 5-exo-trig aryl radical−alkene cyclization, using allylamine as the amine equivalent.

Results and Discussion

As envisaged in the retrosynthesis in Scheme 1, the indoline was formed via radical cyclization of the naphthalenyl radical onto the neighboring allyl group, while the second allyl was a protecting group for the incipient 5-amino moiety. As an inexpensive starting material we chose the commercially available 2,4-dinitro-1-hydroxynaphthalene Martius Yellow (**8**), which was converted to iodide **10** through trifluoromethanesulfonate **9** (Scheme 2). Attempts to reduce the two nitro groups in the presence of the iodine using many of the standard reagents (Fe, Ni_2B, $SnCl_2$, H_2)[12] resulted in extensive deiodination. The desired iodide **12** was thus prepared in two steps from **10** in 71% overall yield, by reduction/deiodination with $SnCl_2$ and protection of the amines with BOC anhydride to give **11**, followed by electrophilic iodination of this with NIS.[4] Reduction/deiodination using hydrogenation (H_2/Pd−C, EtOAc) gave the same product but with lower yield (69% compared to 88%).

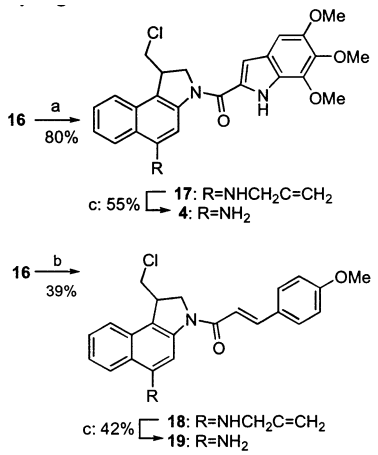
Allylation of **12** (NaH/allyl bromide) gave **13**, which underwent a Bu_3SnH-promoted 5-exo-trig free-radical cyclization[4] with in situ TEMPO to give **14** (Scheme 3). This was subsequently reduced (Zn/AcOH) to alcohol **15**, in 94% yield over the three steps. The alcohol was converted to chloride **16** with Ph_3P/CCl_4. The next task was to achieve an appropriate order of deprotection and reaction of the amine groups of **16**. The BOC groups were removed by acid-catalyzed deprotection (TFA), and coupling with 5,6,7-trimethoxyindole-2-carboxylic acid using EDCI proved to be highly regioselective, affording only the desired regioisomer **17** (Scheme 4). Deblocking of the allyl group proved to be difficult but was eventually effected using Grubb's carbene according to newly published work from Alcaide et al,[13] to give the desired amino-CBI-TMI (**4**) in 10 steps from **8**, with an overall yield of 22%.

SCHEME 3. Regioselective 5-Exo-trig Free-Radical Cyclization[a]



[a] Reagents and conditions: (a) 3.0 equiv of NaH, then 10.0 equiv of $CH_2{=}CHCH_2Cl$; (b) 7.0 equiv of TEMPO/5.0 equiv of Bu_3SnH added portionswise, benzene, 60 °C, 130 min; (c) 16 equiv of Zn powder, THF−HOAc−H_2O, 70 °C, 10 h; (d) 3.0 equiv of Ph_3P/10.0 equiv of CCl_4, CH_2Cl_2, rt, 2 h.

SCHEME 4. Regioselective Deprotection and Coupling[a]



[a] Reagents and conditions: (a) TFA, 0 °C, 2 h, removed the TFA, workup then 5,6,7-trimethoxyindole-2-carboxylic acid/EDCI; (b) TFA, 0 °C, 2 h, removed the TFA, workup then 4-methoxycinnamic acid/EDCI; (c) 10 mol % $Cl_2(PCy_3)_2Ru{=}CHPh$ added portionswise, toluene, 8 h, reflux.

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A similar synthesis gave cinnamate analogue **19** in 9% overall yield (the lower yield being largely due to a lower yield in the deallylation reaction. However, the original[14] preparation of this compound was also of lower yield, due to a longer route.

In summary, the above synthesis of 3-substituted 5-amino-1-(chloromethyl)-1,2-dihydro-3*H*-benzo[*e*]indoles from Martius Yellow, involving three efficient regioselective reactions (iodination, 5-exo-trig aryl radical−alkene cyclization, and carboxylation), is a considerable improvement (shorter and higher-yielding) over the original method.[9]

Experimental Section

2,4-Dinitro-1-naphthyl Trifluoromethanesulfonate (9). A solution of Martius Yellow (**8**) (5.0 g, 21.4 mmol) in CH_2Cl_2 (100 mL) was treated with Et_3N (8 mL, 57 mmol), and the resulting solution was cooled in an ice-salt bath and treated dropwise with trifluoromethanesulfonic anhydride (5 mL, 28 mmol). After the mixture was stirred at room temperature for 2 h, 0.5 N HCl (100 mL) was added in one portion, and the mixture was stirred for 30 min. The aqueous phase was separated and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were washed with saturated $NaHCO_3$ and brine, dried, and concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel. Elution with CH_2Cl_2, gave **9** (7.0 g, 89%) as yellow needles: mp (EtOAc/CH_2Cl_2) 105−107 °C; ^{1}H NMR [$(CD_3)_2$SO] δ 8.90 (s, 1 H), 8.59 (m, 1 H), 8.55 (m, 1 H), 7.98 (m, 1 H), 7.78 (m, 1 H); ^{13}C NMR δ 158.2, 135.1, 133.2, 127.9, 127.9, 127.7, 127.3, 125.5, 123.3, 122.4. Anal. Calcd for $C_{11}H_5F_3N_2O_7S$: C, 36.1; H, 1.4; N, 7.7. Found: C, 36.0; H, 1.3; N, 7.6.

1-Iodo-2,4-dinitronaphthalene (10). A solution of **9** (5.0 g, 13.7 mmol) and NaI (7.0 g) in EtOAc (200 mL) was heated under reflux for 2 h. After cooling to room temperature, the reaction mixture was washed with saturated $Na_2S_2O_3$, dried, and concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel. Elution with CH_2Cl_2 gave **10** (4.3 g, 91%) as yellow needles: mp (EtOAc/CH_2Cl_2) 194−195 °C; ^{1}H NMR [$(CD_3)_2$SO] δ 8.76 (s, 1 H, H-3), 8.54 (m, 1 H), 8.33 (m, 1 H), 8.00 (m, 2 H); ^{13}C NMR δ 151.8, 147.1, 135.0, 132.2, 131.2, 123.9, 123.3, 117.5, 102.7. Anal. Calcd for $C_{10}H_5IN_2O_4$: C, 34.9; H, 1.5; N, 8.1. Found: C, 34.8; H, 1.2; N, 7.9.

***N,N′*-Bis(*tert*-butyloxycarbonyl)-1,3-naphthalenediamine (11).** A suspension of **10** (1.0 g, 2.9 mmol) and $SnCl_2 \cdot 2H_2O$ (9.8 g, 43.6 mmol) in EtOAc (100 mL) was heated under reflux for 30 min. The white suspension was poured onto ice (ca. 100 g), and $NaHCO_3$ was added until the aqueous layer was basic to litmus. The mixture was extracted with EtOAc; the organic layer was washed with water and dried, and the solvent was removed under reduced pressure to give crude 1,3-naphthalenediamine. This was dissolved in THF (30 mL) and treated with $(BOC)_2O$ (3.0 g), and then the mixture was heated under reflux for 5 h. The solvent was removed, and the residue was purified by column chromatography on silica gel. Elution with CH_2Cl_2 gave **11** (0.916 g, 88%) as a brown solid: mp (petroleum ether) 129−131 °C; ^{1}H NMR ($CDCl_3$) δ 7.94 (s, 1 H), 7.78 (s, 1 H), 7.74 (m, 2 H), 7.41 (m, 2 H), 6.94 (s, 1 H), 6.69 (s, 1 H), 1.55 (s, 9 H), 1.54 (s, 9 H); ^{13}C NMR δ 153.1, 152.8, 135.8, 134.8, 133.7, 128.5, 126.5, 124.4, 122.3, 119.7, 110.6, 110.5, 80.9, 80.6, 28.3. Anal. Calcd for $C_{20}H_{26}N_2O_4$: C, 67.0; H, 7.3; N, 7.8. Found: C, 67.0; H, 7.3; N, 7.8.

***N,N′*-Bis(*tert*-butyloxycarbonyl)-1-iodo-2,4-naphthalenediamine (12).** A solution of **11** (8.63 g, 24.1 mmol) in THF/CH_3OH (200 mL, 1:1) at −78 °C was treated with *N*-iodosuccinimide (NIS, 8.5 g, 33.7 mmol) in THF (10 mL) followed by $TsOH \cdot H_2O$ (9.5 g, 50.2 mmol) in CH_3OH (10 mL). The reaction mixture was allowed to slowly warm to room temperature over 4 h and then diluted with 5% aqueous $Na_2S_2O_3$ and stirred at room temperature for 15 min. The reaction mixture was extracted with EtOAc (3 × 100 mL), dried, and concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel. Elution with CH_2Cl_2 and crystallization from EtOAc/petroleum ether afforded **12** (9.46 g, 81%) as a brown solid: mp 154−156 °C (dec); ^{1}H NMR ($CDCl_3$) δ 8.65 (s, 1 H), 8.12 (m, 1 H), 7.76 (m, 1 H), 7.52 (m, 1 H), 7.45 (m, 1 H), 7.19 (s, 1 H), 6.83 (s, 1 H), 1.57 (s, 9 H), 1.55 (s, 9 H); ^{13}C NMR δ 153.1, 152.6, 138.2, 134.8, 134.6, 132.6, 128.2, 125.3, 124.8, 121.3, 113.5, 81.3, 81.0, 28.3. Anal. Calcd for $C_{20}H_{25}IN_2O_4$: C, 49.6; H, 5.2; N, 5.8. Found: C, 49.8; H, 5.2; N, 5.8.

***N,N′*-Bis[allyl(*tert*-butyloxycarbonyl)]-1-iodo-2,4-naphthalenediamine (13).** A solution of **12** (4.86 g, 10.0 mmol) in anhydrous DMF (150 mL) under nitrogen was treated with NaH (1.2 g, 30 mmol, 60% oil dispersion), and the reaction mixture was stirred for 30 min at 0 °C. Allyl bromide (12.1 g, 100 mmol) was added dropwise over 5 min, and the solution was allowed to warm to room temperature and stirred for 2 h. Saturated aqueous $NaHCO_3$ (100 mL) was added, and the aqueous phase was extracted with EtOAc (3 × 100 mL), dried, and concentrated under reduced pressure; the residue was purified by column chromatography on silica gel. Elution with EtOAc/petroleum ether (from 1:10 to 1:5) and crystallization from EtOAc/petroleum ether afforded **13** (5.64 g, 100%) as a white solid: mp 150−152 °C; ^{1}H NMR ($CDCl_3$) δ 8.23 (m, 1 H), 7.77 (m, 1 H), 7.58 (m, 2 H), 7.10 (m, 1 H), 5.93 (m, 2 H), 5.07 (m, 4 H), 4.62 (m, 2 H), 3.87 (m, 2 H), 1.33 (m, 10 H), 1.25 (m, 8 H); ^{13}C NMR δ 154.7, 153.7, 133.6, 133.5, 131.6, 128.1, 127.3, 127.3, 123.4, 123.3, 120.5, 118.3, 80.4, 52.8, 28.1. Anal. Calcd for $C_{26}H_{33}IN_2O_4$: C, 55.3; H, 5.9; N, 5.0. Found: C, 55.6; H, 5.9; N, 5.1.

5-[Allyl(*tert*-butyloxycarbonyl)amino]-3-(*tert*-butyloxycarbonyl)-1-{[(2′,2′,6′,6′-tetramethylpiperidino)oxy]methyl}-1,2-dihydro-3*H*-benzo[*e*]indole (14). A solution of **13** (2.82 g, 5.0 mmol) in benzene (200 mL) was treated sequentially with TEMPO (3.0 equiv) and Bu_3SnH (1.0 equiv), and the reaction mixture was warmed to 60 °C and kept there for an additional 135 min. Additional Bu_3SnH (1 equiv) was added after 30, 60, and 90 min, and additional TEMPO (2 equiv) was added after 60 and 90 min. The solvent was then removed by evaporation, and the residue was purified by column chromatography on silica gel. Elution with EtOAc/petroleum ether (from 1:20 to 1:5) afforded **12** (2.97 g, 100%), which was sufficiently pure for the next step reaction as a pale yellow gum: ^{1}H NMR ($CDCl_3$) δ 8.09 (vbr, 1H), 7.76 (m, 2 H), 7.43 (m, 1 H), 7.32 (m, 1 H), 5.95 (m, 1 H), 5.07 (m, 2 H), 4.40−4.23 (m, 3 H), 4.09 (m, 2 H), 3.86 (m, 2 H), 1.59−1.0 (m, 36 H); ^{13}C NMR δ 152.5, 134.0, 133.8, 129.9, 128.9, 126.4, 126.0, 123.8, 123.4, 117.5, 80.0, 59.9, 52.4, 39.7, 33.1, 28.5, 28.2, 20.1, 17.1; HRMS *m*/*z* required for $C_{35}H_{51}N_2O_8$ 593.3828, found 593.3819.

5-[Allyl(*tert*-butyloxycarbonyl)amino]-3-(*tert*-butyloxycarbonyl)-1-(hydroxymethyl)-1,2-dihydro-3*H*-benzo[*e*]indole (15). A solution of **14** (2.97 g, 5.0 mmol) in THF/AcOH/H_2O (3:1:1, 200 mL) was treated with Zn powder (30 g, 80 equiv), and the mixture was warmed at 70 °C for 10 h. The Zn powder was removed by filtration through Celite, and the mixture was concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 (3 × 100 mL), dried, and concentrated under reduced pressure, and the crude product was purified by column chromatography on silica gel. Elution with EtOAc/petroleum ether (from 1:4 to 1:1), and crystallization from EtOAc/petroleum ether afforded **15** (2.13 g, 94%): mp 125−128 °C; ^{1}H NMR ($CDCl_3$) δ 8.14 (vbr, 1 H), 7.75 (m, 1 H), 7.43 (m, 1 H), 7.34 (m, 1 H), 5.98 (m, 1 H), 5.11 (m, 2 H), 4.20 (m, 2 H), 4.11 (m, 2 H), 3.90 (m, 2 H), 3.70 (m, 2H), 1.59 (m, 12 H), 1.26 (m, 6 H); ^{13}C NMR δ 153.0, 152.5, 133.9, 128.9, 126.8, 126.0, 124.4, 123.9, 117.6, 64.7, 60.4, 52.1, 28.5, 28.2, 21.0. Anal. Calcd for $C_{26}H_{34}N_2O_5$: C, 68.7; H, 7.5; N, 6.2.

Found: C, 69.0; H, 7.6; N, 6.3. HRMS *m*/*z* required for $C_{26}H_{34}N_2O_5$ 454.2468, found 454.2473.

5-[Allyl(*tert*-butyloxycarbonyl)amino]-3-(*tert*-butyloxycarbonyl)-1-(chloromethyl)-1,2-dihydro-3*H*-benzo[*e*]indole (16). A solution of **15** (4.55 g, 10.0 mmol) in CH_2Cl_2 (100 mL) under N_2 was treated sequentially with Ph_3P (7.9 g, 30.0 mmol, 3 equiv) and CCl_4 (14.0 g, 90 mmol, 9 equiv) and then stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography on silica gel. Elution with EtOAc/petroleum ether (from 1:4 to 1:1) afforded **16** (4.46 g, 90%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.10 (vbr, 1 H), 7.78 (d, J = 8.2 Hz, 1 H), 7.71 (t, J = 7.2 Hz, 1 H), 7.50 (t, J = 7.2 Hz, 1 H), 7.38 (t, J = 7.7 Hz, 1 H), 5.98 (m, 1 H), 5.10 (m, 2 H), 4.43 (br, 1 H), 4.28 (m, 1 H), 4.13 (m, 2 H), 4.05 (m, 1 H), 3.95 (m, 1 H), 3.47 (m, 1 H), 1.60 (m, 12 H), 1.20 (m, 6 H); ^{13}C NMR δ 154.9, 152.4, 133.9, 132.0, 128.4, 127.2, 124.4, 123.9, 122.5, 117.7, 60.4, 52.7, 46.3, 28.5, 28.2, 21.0; HRMS *m*/*z* required for $C_{26}H_{33}ClN_2O_4$ 472.2129, found 472.2129.

5-Allylamino-1-(chloromethyl)-3-(5,6,7-trimethoxyindol-2-carbonyl)-1,2-dihydro-3*H*-benzo[*e*]indole (17). A solution of **16** (406 mg, 0.858 mmol) in 50 mL of trifluoroacetic acid (TFA) was kept at 0 °C for 2 h under nitrogen to cleave the t-BOC protecting group. The reaction mixture was then concentrated under reduced pressure, and the residue was diluted with benzene (30 mL) and concentrated once more, to remove any remaining TFA. The resulting residue was treated with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2 (3 × 50 mL), dried, and concentrated under reduced pressure. To the residue was added 5,6,7-trimethoxyindole-2-carboxylic acid (220 mg) and EDCI·HCl (411 mg), followed by 10 mL of DMA, and the reaction mixture was stirred at room temperature overnight, diluted with saturated aqueous $NaHCO_3$, extracted with EtOAc (3 × 50 mL), dried, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel. Elution with EtOAc/CH_2Cl_2 (1:5) and crystallization from CH_2Cl_2/diisopropyl ether afforded **17** (355 mg, 80%) as a yellow solid: mp 107−112 °C; ^{1}H NMR ($CDCl_3$) δ 9.51 (s, 1 H), 7.81 (d, J = 8.7 Hz, 1 H), 7.80 (s, 1 H), 7.67 (d, J = 8.3 Hz, 1 H), 7.51 (t, J = 7.8 Hz, 1 H), 7.37 (t, J = 7.8 Hz, 1 H), 6.98 (d, J = 2.3 Hz, 1 H), 6.87 (s, 1 H), 6.05 (m, 1 H), 5.40 (dd, J = 17.4, 1.4 Hz, 1 H), 5.24 (dd, J = 10.3, 1.2 Hz, 1 H), 4.74 (dd, J = 10.7, 1.4 Hz, 2 H), 4.66 (s, 1 H), 4.55 (t, J = 10.4 Hz, 1 H), 4.06 (s, 3 H), 4.03 (m, 1 H), 4.00 (m, 2 H), 3.94 (s, 3 H), 3.91 (m, 1 H), 3.90 (s, 3 H), 3.40 (t, J = 10.9 Hz, 1 H); ^{13}C NMR δ 160.4, 150.1, 144.9, 142.7, 140.4, 138.8, 134.5, 130.1, 130.0, 127.0, 125,4, 123.6, 123.3, 123.1, 121.2, 121.1, 116.9, 113.1, 106.4, 97.7, 96.8, 61.4, 61.1, 56.2, 55.1, 46.6, 46.1, 43.2; HRMS *m*/*z* required for $C_{28}H_{28}{}^{35}ClN_3O_4$ 505.1768, found 505.1765. Anal. Calcd for $C_{28}H_{28}ClN_3O_4 \cdot 0.5H_2O$: C, 65.4; H, 5.5; N, 8.2. Found: C, 65.3; H, 5.4; N, 8.4.

5-Amino-1-(chloromethyl)-3-(5,6,7-trimethoxyindol-2-carbonyl)-1,2-dihydro-3*H*-benzo[*e*]indole (4). To a solution of **17** (70 mg) in anhydrous toluene (5 mL) protected from light and heated at reflux was added $Cl_2(Cy_3P)_2Ru{=}CHPh$ in small portions under N_2 every 20 min (overall total = 0.02 mmol).[13] After 8 h, the resulting mixture was concentrated under reduced pressure. Chromatography of the residue eluting with EtOAc/CH_2Cl_2 recovered 17 mg of starting material, followed by **4** (27 mg, 55% based on consumption of starting material). The product was crystallized from CH_2Cl_2/diisopropyl ether and spectroscopically identical to an authentic sample.[9]

5-Allylamino-1-(chloromethyl)-3-[(2*E*)-3-(4-methoxyphenyl)-2-propenoyl]-1,2-dihydro-3*H*-benzo[*e*]indole (18). Similar treatment of **16** (2.74 g, 5.81 mmol) with 4-methoxycinnamic acid (1.14 g, 6.4 mmol) and EDCl·HCl (2.77 g), followed by column chromatography of the product on silica gel, eluting with EtOAc/CH_2Cl_2 (1:5) and crystallization from CH_2Cl_2/diisopropyl ether, afforded **18** (980 mg, 39%) as a yellow solid: mp 152−154 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (br, 1 H), 7.80 (s, 1 H), 7.79 (d, J = 8.5 Hz, 1 H), 7.68 (d, J = 8.2 Hz, 1 H), 7, 57 (s, 1 H), 7.55 (s, 1 H), 7.48 (m, 1 H), 7.33 (m, 1 H), 6.93 (s, 1 H), 6.91 (s, 1 H), 6.80 (br, 1 H), 6.09 (m, 1 H), 5.40 (m, 1 H), 5.26 (m, 1 H), 4.65 (br, 1 H), 4.49 (m, 1 H), 4.36 (m, 1 H), 4.00 (m, 4 H), 3.85 (s, 3 H), 3.41 (m, 1 H); ^{13}C NMR δ 165.0, 161.2, 145.0, 143.5, 142.6, 134.6, 130.1, 129.8, 127.8, 127.0, 123.2, 123.0, 121.2, 121.0, 117.0, 116.3, 114.3, 96.9, 55.4, 53.4, 46.7, 46.3, 42.6; HRMS *m*/*z* required for $C_{26}H_{25}ClN_2O_2$ 432.1605, found 432.1609. Anal. Calcd for $C_{26}H_{25}ClN_2O_2 \cdot 0.33H_2O$: C, 71.1; H, 5.7; N, 6.4. Found: C, 71.3; H, 5.8; N, 6.3.

5-Amino-1-(chloromethyl)-3-[(2*E*)-3-(4-methoxyphenyl)-2-propenoyl]-1,2-dihydro-3*H*-benzo[*e*]indole (19). Deprotection of **18** (90 mg) with $Cl_2(Cy_3P)_2Ru{=}CHPh$ as described above, followed by chromatography of the residue, eluting with EtOAc/CH_2Cl_2, gave **19** (34 mg, 42%). Crystallization from CH_2Cl_2/diisopropyl ether gave a product spectroscopically identical to an authentic sample.[14]

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Supporting Information Available: ^{1}H NMR spectra for compounds **14** and **16**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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