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# Efficient Synthesis of Achiral *seco*-Cyclopropylbenz[2,3-*e*]indoline Analogues: [4-Amino-2-(5,6,7-trimethoxyindole-2-carboxamido)naphthalen-1-yl]ethyl Chloride and [4-Hydroxy-2-(5,6,7-trimethoxyindole-2-carboxamido)naphthalen-1-yl]ethyl Chloride

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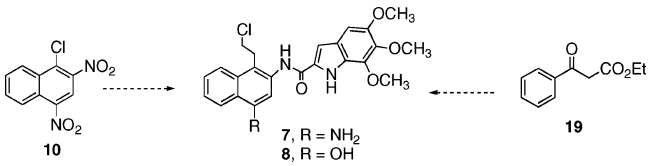


Achiral *seco*-aminocyclopropylbenz[2,3-*e*]indoline and *seco*-hydroxycyclopropylbenz[2,3-*e*]indoline (*seco*-CBI) analogues of the duocarmycins and CC-1065, e.g., **7** and **8**, are potent anticancer agents. This paper describes significantly improved synthetic strategies for preparing these compounds. Starting from Martius acid (**9**), the new strategy gave a 13-fold increase in the overall yield of **7**, and the use of di-*tert*-butyl malonate was economically beneficial. For compound **8**, the new strategy employed an Emmons−Horner reaction, followed by a Stobbe condensation, and the overall yield was improved 15-fold.

Compounds that bind to specific sequences in the minor groove of DNA are potentially useful as pharmaceutical agents,[1] biosensors,[2] and as molecular tools for probing biological processes.[3] Consequently, the field of small molecule−DNA minor groove interactions has blossomed in recent years,[4] and a large number of compounds have been identified. Examples of naturally occurring minor groove binders include polyamides (distamycin and netropsin),[5] (+)-CC-1065 (**1**)[6] and the duocarmycins[7] (such as (+)-duocarmycin SA or DUMSA, **2**), mitomycin C,[8] and anthramycin.[9] Examples of synthetic minor groove binders include Hoechst 33258,[10] diamidines, such as pentamidine[11] and furamidine,[12] berenil,[13] and numerous derivatives or analogues of natural products, such as imidazole- and pyrrolepolyamides,[14] analogues of the duocarmycins and CC-1065,[15] as well as analogues of anthramycin[16] and mitomycin C.[17]

A number of research groups have reported the anticancer activity of a wide range of analogues of the duocamycins and CC-1065,[18] such as compounds **3**[19] and **4**,[20] and several of these compounds (adozelesin, carzelesin, KW2189, and bizelesin) have advanced to clinical trials. Due to severe toxicity to bone marrow, only bizelesin still remains in phase II trials.[21] As part of our program in the design and discovery of novel anticancer agents, we have concentrated on the development of achiral analogues of the duocarmycins and CC-1065. These compounds have been only recently reported by our group; see compounds **5**−**8** (Figure 1).[22−24] The achiral amino- and hydroxy-*seco*-CBI

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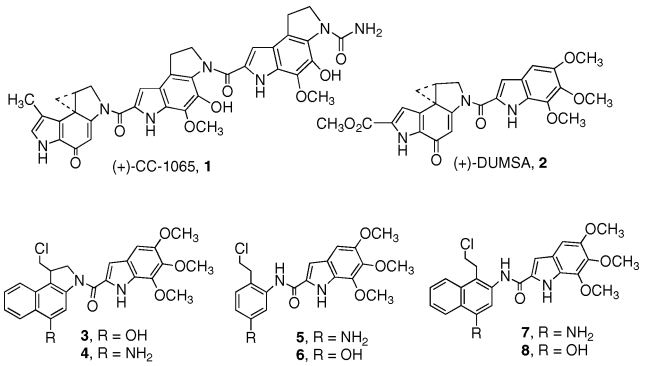


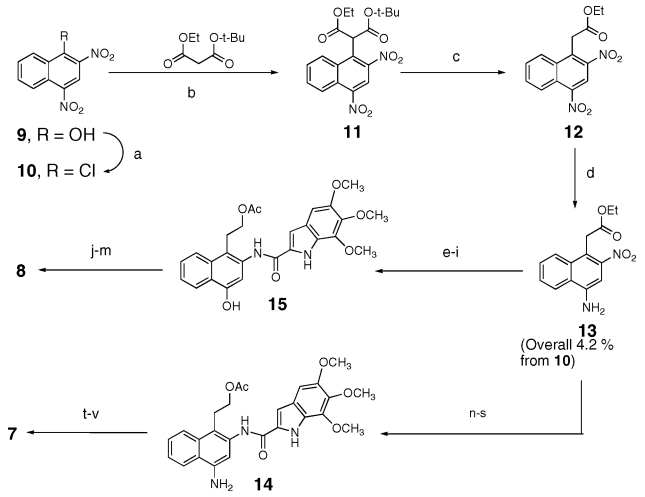

**FIGURE 1.** Structures of (+)-CC-1065 (**1**), (+)-duocarmycin SA or DUMSA (**2**), *seco*-CBI-TMI (**3**), *seco*-amino-CBI-TMI (**4**), achiral *seco*-amino-CI-TMI (**5**), achiral *seco*-CI-TMI (**6**), achiral *seco*-amino-CBI-TMI (**7**), and achiral *seco*-CBI-TMI (**8**).

analogues (compounds **7** and **8**, respectively)[24] were discovered to be the most biologically active, as indicated by their DNA sequence specific reactivity as well as their ability to inhibit the growth of a human tumor (advance SC-OVCAR-3 ovarian cancer) grown in skid mice. Moreover, unlike its chiral counterpart **3**, compound **7** had low systemic toxicity against mice, and at an equal dose the latter compound had minimal effect on mouse bone marrow stem cells grown in culture while compound **3** completely killed the cells. Even though the achiral[23] *seco*-CBI compounds gave such desirable biological activity, further development was limited by the availability of compounds **7** and **8**.

The original synthetic strategies for compounds **7** and **8** are depicted in Scheme 1. There were, however, deficiencies in these strategies. For preparation of compound **7**, the use of an unsymmetrical malonate diester, *tert*-butyl ethyl malonate, was cost prohibitive, and the chemical transformations leading to aminoester **13** were poor (4.2% yield from chloride **10**). Moreover, the overall yield for the 13-step synthesis of compound **7** from Martius acid **9** was 0.047%. The synthesis of compound **8** was hampered by the moderate-yielding diazotization of aminoester **13** (42%). This limitation was exacerbated by the difficulty in scaling up the reaction. When the reaction was increased to 3 g, the yield precipitously dropped to 4%. Moreover, the 13-step conversion of Martius acid **9** to compound **8** was accomplished with an overall yield of 0.14%. To produce sufficient quantities of compounds **7** and **8** for biological studies, our group endeavored to overcome the deficiencies encountered in the original synthetic strategies by incorporating more efficient reactions, as well as developing new synthetic strategies. The results are reported herein.

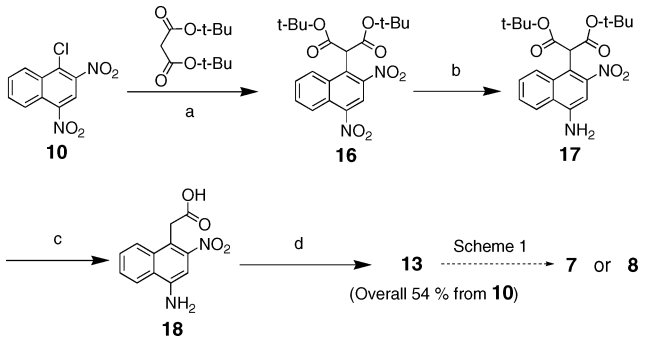
An improved synthesis of amino ester **13** is illustrated in Scheme 2 (synthetic details are given in the Supporting Information), and it follows a similar nucleophilic aromatic

**SCHEME 1. Original Reported Synthesis of Achiral *seco*-Amino-CBI-TMI (7) and Achiral *seco*-CBI-TMI (8)[a,24]**




[a] Key: (a) TsCl, $Et_2NPh$, 70 °C, 48 h (87%); (b) $K_2CO_3$, THF, reflux (54%); (c) AcOEt, conc. HCl (70%); (d) $Na_2S$, EtOH, reflux (11%); (e) (i) $NaNO_2$, $H_2SO_4$, (ii) $Cu_2O$ (42%); (f) BnBr (63%); (g) DibAl-H (100%); (h) $Ac_2O$, Pyr (62%); (i) (i) $H_2$, $PtO_2$, (ii) TMI-$CO_2H$, PyBOP (36%); (j) $K_2CO_3$, MeOH (87%); (k) MsCl (100%); (l) LiCl (81%); (m) $H_2$, Pd−C (90%); (n) CBZ-Cl, $Et_3N$ (29%); (o) NaOH (89%); (p) $BH_3$−THF (55%); (q) $Ac_2O$, Pyr (55%); (r) $H_2$, $PtO_2$ (60%); (s) TMI-$CO_2H$, PyBOP (81%); (t) $K_2CO_3$, MeOH (82%); (u) (i) MsCl, (ii) LiCl (62%); (v) $H_2$, Pd−C (68%).

**SCHEME 2. Improved Preparation of Aminoester 13, a Key Synthon for Making Achiral *seco*-Amino-CBI-TMI (7) and Achiral *seco*-CBI-TMI (8)[a]**




[a] Key: (a) NaH, THF, reflux, 1 h (quant); (b) $Na_2S$, EtOH, reflux, 0.5 h (quant); (c) $CF_3CO_2H$, $CH_2Cl_2$, rt, 16 h (78%); (d) conc. $H_2SO_4$, EtOH, reflux, 5 h (69%).

substitution strategy used in our original synthesis.[24] However, the use of di-*tert*-butyl malonate in the reaction with chloride **10**[25] was found to be superior to *tert*-butyl ethyl malonate. Diester **16** was produced in quantitative yield, compared to a yield of 54% when *tert*-butyl ethyl malonate was used. Selective reduction of the 4-nitro group of diester **16** was also improved; presumably, the di-*tert*-butyl group created a larger steric hindrance, and hence, reduction of the 2-nitro group was suppressed. Removal of the *tert*-butyl groups and decarboxylation of the malonate were readily achieved by treatment of compound **17** with trifluoroacetic acid. Fisher esterification of the resulting amino acid **18** yielded the desired aminoester **13** in good yield. The overall yield from chloride **10** to aminoester **13** was increased from 4.2% in the original synthesis to 54%

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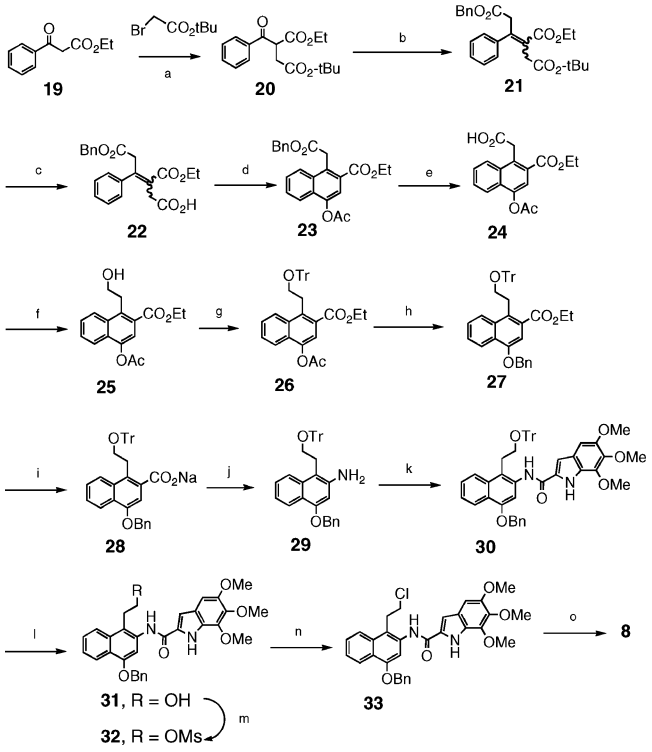
**SCHEME 3. Emmons−Horner Reaction, Followed by Stobbe Condensation Approach to the Synthesis of Achiral *seco*-CBI-TMI (8)[a]**




[a] Key: (a) $K_2CO_3$, 70 °C (88%); (b) $BnO_2C-CH=PPh_3$, toluene, reflux (41%); (c) $CF_3CO_2H$, $CH_2Cl_2$, rt, 16 h (quant); (d) $Ac_2O$, NaOAc, reflux (57%); (e) $H_2$, 10% Pd−C (88%); (f) $BH_3$−THF (quant); (g) trityl chloride, Pyr (75%); (h) $K_2CO_3$, EtOH, BnBr (92%); (i) NaOH, EtOH, (quant); (j) DPPA, $Et_3N$, THF, (40%); (k) TMI-$CO_2H$, EDCI, HOBt, Pyr, (58%); (l) conc. HCl, $CH_2Cl_2$, MeOH (quant); (m) MsCl, $Et_3N$, $CH_2Cl_2$ (quant); (n) LiCl, DMF (81%); (o) $H_2$, 10% Pd−C (91%).

in the present approach. With this improvement, the overall yield for synthesizing the achiral amino-*seco*-CBI compound **7** from Martius acid (**9**) was improved from 0.047% to 0.61%, even though it required an additional step. An improved synthesis of compound **13** could also benefit the preparation of achiral hydroxy-*seco*-CBI compound **8**; the overall yield was increased to 1.8% (13-fold). Unfortunately, this benefit could not be realized since the diazotization step could not be scaled-up to multigram quantities because the reaction mixture could not be adequately stirred, even when a mechanical stirrer was employed. Consequently, a different synthetic strategy was designed.

Scheme 3 depicts a synthetic strategy for the preparation of achiral hydroxy-*seco*-CBI compound **8**. This approach uses an Emmons−Horner reaction, followed by Stobbe condensation to produce the key achiral *seco*-CBI synthon. An advantage to this route is that it employs a totally different approach to install the hydroxyl group. Reaction of ethyl benzoyl acetate with *tert*-butyl bromoacetate gave diester **20** in excellent yield. Emmons−Horner condensation of the ketone moiety in compound **20** with a benzyl (triphenylphosphoranylidene)acetate in refluxing toluene smoothly gave alkene **21** in 41% yield. In this strategy, the three different ester groups in compound **21** could be conveniently and selectively deprotected. Treatment of alkene **21** with trifluoroacetic acid selectively removed the *tert*-butyl group, affording acid **22** in quantitative yield. Reaction of acid **22** with refluxing acetic anhydride and sodium acetate promoted a Stobbe condensation to produce acetate **23** in 57% yield. Removal of the benzyl group in **23** was readily achieved in 88% yield by catalytic hydrogenation over 10% palladium−carbon, and the resulting carboxylic acid group in compound **24** was selectively reduced by borane−THF. Alcohol **25** was isolated in quantitative yield from acid **24**. The alcohol moiety of compound **25** was protected with a trityl group, which was accomplished in 75% yield by reaction with triphenylmethyl chloride. The acetoxy group of compound **26** was transformed in "one-pot" by ethanolysis with potassium carbonate and ethanol, followed by trapping the alkoxide intermediate with benzyl bromide. The benzyl-protected intermediate **27** was produced in 92% yield. Hydrolysis of the ethyl ester in compound **27** yielded carboxylate **28** in quantitative yield, which was transformed into amine **29** in 40% yield by reaction with diphenyl phosphoryl azide in a Curtius rearrangement reaction, followed by decomposition of the isocyanate intermediate with refluxing water.

To complete the synthesis of target compound **8**, the amino group of compound **29** was coupled to the carboxylic acid moiety of 5,6,7-trimethoxyindole-2-carboxylic acid (TMI-$CO_2H$) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBt). The desired product **30** was isolated in 58% yield. Removal of the trityl group in compound **30** by treatment with hydrochloric acid, followed by reaction of the corresponding alcohol with methanesulfonyl chloride, gave mesylate **32** in quantitative yield. Nucleophilic substitution of the mesylate group with a chloride afforded compound **33** in 81% yield. Final removal of the benzyl group by catalytic hydrogenation yielded the target compound **8** in 91% yield. The overall yield in the synthesis of compound **8** from ethyl benzoyl acetate is 2.1%, and it represents a 15-fold improvement over the original synthesis. Moreover, amine **29** could be prepared on a multigram scale. With the new methods for synthesizing compounds **7** and **8**, sufficient quantities have been prepared for further biological investigations.

## Experimental Section

**(4-Acetoxy-2-ethoxycarbonylnaphthalen-1-yl)ethyl Triphenylmethyl Ether 26.** To a solution of **25** (3.80 g, 12.57 mmol) in pyridine (40 mL) was added triphenylmethyl chloride (8.40 g, 30.2 mmol) and the mixture stirred overnight. The mixture was concentrated and diluted with AcOEt (200 mL), and the organic layer was washed with water (50 mL) and brine (20 mL), dried ($Na_2SO_4$), and evaporated. The residue was purified by silica gel column chromatography (AcOEt/petroleum ether = 1:8) to yield **26** (5.10 g, 75%) as a yellow foam. The foam was solidified with EtOH: mp 146−156 °C; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 8.11 (d, $J$ = 9.0 Hz, 1H), 7.86 (d, $J$ = 9.0 Hz, 1H), 7.65 (s, 1H), 7.57 (t, $J$ = 7.5 Hz, 1H), 7.52 (t, $J$ = 8.0 Hz, 1H), 7.36 (m, 6H), 7.17−7.27 (m, 9H), 4.35 (q, $J$ = 7.5 Hz, 2H), 4.80 (t, $J$ = 7.0 Hz, 2H), 3.49 (t, $J$ = 7.0 Hz, 2H), 2.47 (s, 3H), 1.35 (t, $J$ = 7.0 Hz, 3H); IR (neat) $\nu_{max}$ 3058, 2980, 1768, 1719, 1604, 1512, 1490, 1466, 1449, 1420, 1368, 1344, 1274, 1244, 1219 cm$^{-1}$; EIMS *m*/*z* 544 ($M^+$, 2); EIHRMS *m*/*z* 544.2238 ($M^+$, $C_{36}H_{32}O_5$ requires 544.2250).

**(4-Benzyloxy-2-ethoxycarbonylnaphthalen-1-yl)ethyl Triphenylmethyl Ether 27.** To a solution of **26** (5.10 g, 9.36 mmol) in EtOH (50 mL) was added $K_2CO_3$ (1.55 g, 11.24 mmol), and the mixture was heated to reflux overnight. At that time, benzyl bromide (1.34 mL, 11.2 mmol) was added, and the reaction was heated to reflux for 4 h. The mixture was cooled to rt and filtered and the filtrate concentrated. The residue was diluted with AcOEt (200 mL), and the organic layer was washed with water (50 mL) and brine

(20 mL), dried ($Na_2SO_4$), and evaporated. The residue was purified by silica gel column chromatography (AcOEt/petroleum ether = 1:8) to yield **27** (5.10 g, 92%) as a yellow foam. The foam was precipitated with diisopropyl ether: mp 112−114 °C; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 8.36 (d, $J$ = 8.0 Hz, 1H), 8.01 (d, $J$ = 8.0 Hz, 1H), 7.49−7.55 (m, 3H), 7.34−7.46 (m, 8H), 7.13−7.32 (m, 12H), 5.26 (s, 2H), 4.37 (q, $J$ = 7.0 Hz, 2H), 3.69 (t, $J$ = 7.5 Hz, 2H), 3.46 (t, $J$ = 7.0 Hz, 2H), 1.35 (t, $J$ = 7.5 Hz, 3H); IR (neat) $\nu_{max}$ 3059, 2979, 1748, 1569, 1512, 1491, 1449, 1366, 1272, 1228 cm$^{-1}$; EIMS *m*/*z* 592 ($M^+$, 15); EIHRMS *m*/*z* 592.2617 ($M^+$, $C_{41}H_{36}O_4$ requires 592.2614).

**(4-Benzyloxy-2-aminonaphthalen-1-yl)ethyl Triphenylmethyl Ether 29.** To a solution of **27** (0.501 g, 2.89 mmol) in THF (10 mL) were added EtOH (15 mL), water (10 mL), and NaOH (0.10 g). The mixture was heated to reflux overnight. The organic solvents were evaporated, and the precipitate was filtered and dried ($Na_2SO_4$) to yield **28** (0.500 g, 100%) as a white solid. Compound **28** (0.47 g, 0.80 mmol) was dissolved in THF (10 mL), and $Et_3N$ (0.13 mL, 0.96 mmol) followed by diphenyl phosphorylazide (DPPA) (0.21 mL, 0.96 mmol) were added. The mixture was heated to reflux for 2 h, and water (18 mL) was added. The resulting mixture was further heated to reflux 3 days. The mixture was extracted with AcOEt (200 mL), and the organic layer was washed with brine (20 mL), dried ($Na_2SO_4$), and evaporated. The residue was purified by silica gel column chromatography (AcOEt/petroleum ether = 1:4) to yield **29** (0.17 g, 40%) as a pale yellow solid: mp 174−176 °C; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 8.23 (d, $J$ = 8.5 Hz, 1H), 7.62 (d, $J$ = 8.5 Hz, 1H), 7.52 (d, $J$ = 7.0 Hz, 2H), 7.39 (m, 6H), 7.17−7.24 (m, 12H), 6.40 (s, 1H), 5.20 (s, 2H), 3.99 (s br, 2H), 3.44 (t, $J$ = 7.0 Hz, 2H), 3.14 (t, $J$ = 7.0 Hz, 2H); IR (neat) $\nu_{max}$ 3391, 3060, 2874, 1729, 1625, 1600, 1516, 1490, 1449, 1407, 1372, 1281, 1236 cm$^{-1}$; EIMS *m*/*z* 535 ($M^+$, 6); EIHRMS *m*/*z* 535.2513 ($M^+$, $C_{38}H_{33}NO_2$ requires 535.2511).

**[4-Benzyloxy-2-(5,6,7-trimethoxyindole-2-carboxamido)naphthalen-1-yl]ethyl Triphenylmethyl Ether 30.** To a solution of **29** (1.40 g, 2.61 mmol) in dry pyridine (28 mL) were added 5,6,7-trimethoxy-2-carboxylic acid (0.980 g, 3.92 mmol), 1-hydroxybenzotriazole (0.530 g, 3.92 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.50 g, 7.84 mmol). The reaction mixture was kept under a $N_2$ atmosphere at rt and stirred for 3 h. The mixture was heated to 60 °C for 3 days and then concentrated, diluted with AcOEt (200 mL), washed with water (50 mL) and brine (50 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/petroleum ether = 1:2) to yield **30** (1.17 g, 58%) as a white solid: mp 198−200 °C; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 9.15 (s, 1H), 9.12 (s, 1H), 8.43 (d, $J$ = 9.5 Hz, 1H), 7.76 (d, $J$ = 9.5 Hz, 1H), 7.62 (m, 3H), 7.43−7.48 (m, 4H), 7.38 (t, $J$ = 6.5 Hz, 1H), 7.27 (m, 6H), 7.15 (m, 9H), 6.53 (s, 1H), 6.29 (s, 1H), 5.35 (s, 2H), 4.07 (s, 3H), 3.94 (s, 3H), 3.90 (s, 3H), 3.65 (t, $J$ = 5.0 Hz, 2H), 3.35 (t, $J$ = 5.5 Hz, 2H); IR (neat) $\nu_{max}$ 3282, 2936, 1652, 1593, 1537, 1501, 1461, 1410, 1368, 1306, 1235 cm$^{-1}$; TOFMS (ES+) *m*/*z* 791 (M + $Na^+$, 100); TOFHRMS *m*/*z* 791.3102 (M + $Na^+$, $C_{50}H_{44}N_2O_6Na$ requires 791.3092).

**[4-Benzyloxy-2-(5,6,7-trimethoxyindole-2-carboxamido)naphthalen-1-yl]ethanol 31**. To a solution of **30** (1.10 g, 1.43 mmol) in $CH_2Cl_2$ (22 mL) were added MeOH (5 mL) and concentrated HCl (1 mL) at rt. The solution was stirred for 1.5 h. The reaction mixture was extracted with AcOEt (100 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (AcOEt/petroleum ether = 1:1) to yield **31** (0.80 g, quant) as a yellow oil: $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 9.96 (s, 1H), 9.25 (s, 1H), 8.39 (d, $J$ = 8.0 Hz, 1H), 7.85 (d, $J$ = 8.5 Hz, 1H), 7.75 (s, 1H), 7.71 (dd, $J$ = 3.5, 5.8 Hz, 1H), 7.57 (d, $J$ = 7.5 Hz, 2H), 7.53 (m, 1H), 7.43 (t, $J$ = 7.5 Hz, 2H), 7.36 (t, $J$ = 7.0 Hz, 1H), 7.06 (s, 1H), 6.84 (s, 1H), 5.30 (s, 2H), 4.21 (t, $J$ = 6.0 Hz, 2H), 4.08 (s, 3H), 3.95 (s, 3H), 3.91 (s, 3H), 3.37 (t, $J$ = 5.0 Hz, 2H); IR (neat) $\nu_{max}$ 3272, 2932, 1726, 1644, 1594, 1540, 1505, 1464, 1409, 1370, 1263, 1236 cm$^{-1}$; EIMS *m*/*z* 527 (M + $H^+$, 18).

**[4-Benzyloxy-2-(5,6,7-trimethoxyindole-2-carboxamido)naphthalen-1-yl]ethyl Mesylate 32**. To a chilled solution (ice bath) of **31** (80 mg, 0.15 mmol) and triethylamine (0.090 mL, 0.61 mmol) in $CH_2Cl_2$ (2 mL) was added methanesulfonyl chloride (0.050 mL, 0.61 mmol). The reaction mixture was stirred for 1 h. It was diluted with $CH_2Cl_2$ (50 mL) and washed with $H_2O$ (10 mL) and brine (20 mL). The organic layer was dried ($Na_2SO_4$) and concentrated under reduced pressure to yield **32** (0.11 g, quant) as a brown oil: $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 9.24 (s, 1H), 8.47 (s, 1H), 8.41 (d, $J$ = 8.0 Hz, 1H), 7.85 (d, $J$ = 8.5 Hz, 1H), 7.71 (dd, $J$ = 3.5, 5.5 Hz, 1H), 7.60 (t, $J$ = 7.0 Hz, 1H), 7.48−7.56 (m, 3H), 7.44 (t, $J$ = 8.0 Hz, 2H), 7.37 (t, $J$ = 7.5 Hz, 1H), 7.18 (s, 1H), 6.88 (s, 1H), 5.28 (s, 2H), 4.63 (t, $J$ = 6.5 Hz, 2H), 4.09 (s, 3H), 3.95 (s, 3H), 3.93 (s, 3H), 3.56 (t, $J$ = 6.5 Hz, 2H), 2.86 (s, 3H); IR (neat) $\nu_{max}$ 3330, 3099, 2933, 2874, 1725, 1649, 1592, 1537, 1502, 1466, 1411, 1369, 1306, 1238 cm$^{-1}$; EIMS *m*/*z* 509 ($M^+ - CH_3SO_3H$, 72).

**[4-Benzyloxy-2-(5,6,7-trimethoxyindole-2-carboxamido)naphthalen-1-yl]ethyl Chloride 33.**[24] To a solution of **32** (0.11 g, 0.17 mmol) in dry DMF (2 mL) that was kept under a $N_2$ atmosphere was added LiCl (0.290 g, 6.94 mmol) at rt, and the mixture was stirred for 3 days. The reaction mixture was diluted with AcOEt (100 mL), washed with $H_2O$ (20 mL) and brine (10 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/petroleum ether = 1:4) to yield **33** (75 mg, 81%) as a white solid: mp 180−184 °C; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 9.23 (s, 1H), 8.63 (s, 1H), 8.42 (d, $J$ = 7.5 Hz, 1H), 7.84 (d, $J$ = 8.5 Hz, 1H), 7.53−7.60 (m, 4H), 7.49 (t, $J$ = 8.0 Hz, 1H), 7.44 (t, $J$ = 7.0 Hz, 2H), 7.38 (t, $J$ = 7.5 Hz, 1H), 6.99 (s, 1H), 6.88 (s, 1H), 5.29 (s, 2H), 4.10 (s, 3H), 4.05 (t, $J$ = 6.0 Hz, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 3.60 (t, $J$ = 6.0 Hz, 2H); IR (neat) $\nu_{max}$ 3271, 2932, 1722, 1634, 1592, 1537, 1503, 1464, 1409, 1370, 1306, 1258, 1237 cm$^{-1}$; EIMS *m*/*z* 545 ($M^+$, 5). A sample of compound **33** was hydrogenated over 10% Pd−C using the reported method to produce target molecule **8** in 91% yield.[24]

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**Supporting Information Available:** The general experimental details, the synthesis of compounds **13**, **16**−**18**, and **20**−**25**, as well as the 500 MHz $^1$H NMR spectra of **7**, **8**, **13**, **16**−**18**, **20**, **23**−**26**, and **28**−**33** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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