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Synthesis and preliminary evaluation of duocarmycin analogues incorporating the 1,2,11,11a-tetrahydrocyclopropa[*c*]naphtho[2,3-*e*]indol-4-one (CNI) and 1,2,11,11a-tetrahydrocyclopropa[*c*]naphtho[1,2-*e*]indol-4-one (*iso*-CNI) alkylation subunits

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ABSTRACT

Efficient syntheses and a preliminary evaluation of 1,2,11,11a-tetrahydrocyclopropa[*c*]naphtho[2,3-*e*]-indole (CNI) and 1,2,11,11a-tetrahydrocyclopropa[*c*]naphtho[1,2-*e*]indole (*iso*-CNI), and their derivatives containing an anthracene and phenanthrene variant of the CC-1065 or duocarmycin alkylation subunit are detailed.

1. Introduction

CC-1065 (**1**),[1] the duocarmycins (**2** and **3**),[2–4] and yatakemycin (**4**)[5] are the parent members of a class of potent antitumor antibiotics that derive their properties through a sequence-selective alkylation of duplex DNA (Fig. 1).[6,7] Extensive studies have characterized their structural features responsible for the DNA alkylation reaction and have established fundamental relationships between their structure and reactivity or activity.[6–11] Aside from the structural complexity inherent in the alkylation subunit, they possess a stability that defies intuition. This is due to the vinylogous amide conjugation and stabilization of the cyclohexadienone structure, which is dominant over that activating the cross-conjugated cyclopropane.[12–14] Accordingly, disruption of this vinylogous amide conjugation leads to remarkable increases in reactivity as large as 10^4-fold[14] that we have suggested is the source of catalysis for the DNA alkylation reaction.[8–12]

The synthesis of analogues containing deep-seated structural changes has been central to these studies providing insights not accessible through examination of the natural products themselves.[15] The two most significant being the delineation of a fundamental parabolic relationship between reactivity and cytotoxic potency[16,17] and that the catalysis for the DNA alkylation reaction likely entails a DNA binding induced conformation change that disrupts the alkylation subunit stabilizing vinylogous amide conjugation.[8,9,12] Among the modified alkylation subunits introduced, the 1,2,9,9a-tetrahydrocyclopropa[*c*]benz[1,2-*e*]indol-4-one (CBI)[18] alkylation subunit has emerged as the most extensively examined

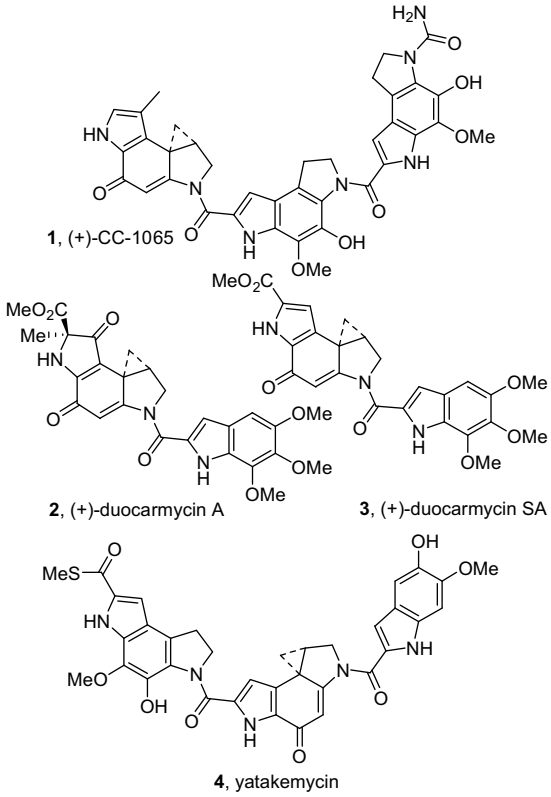

Figure 1.

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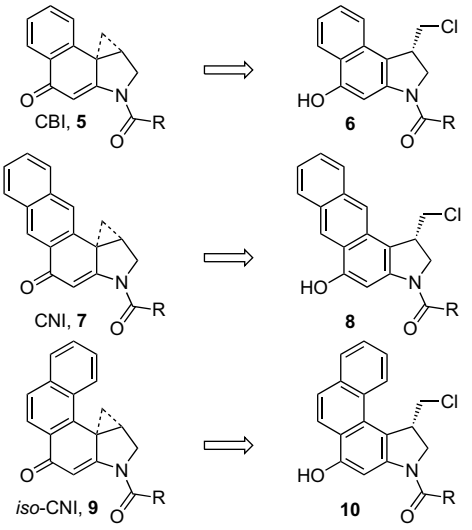


Figure 2.

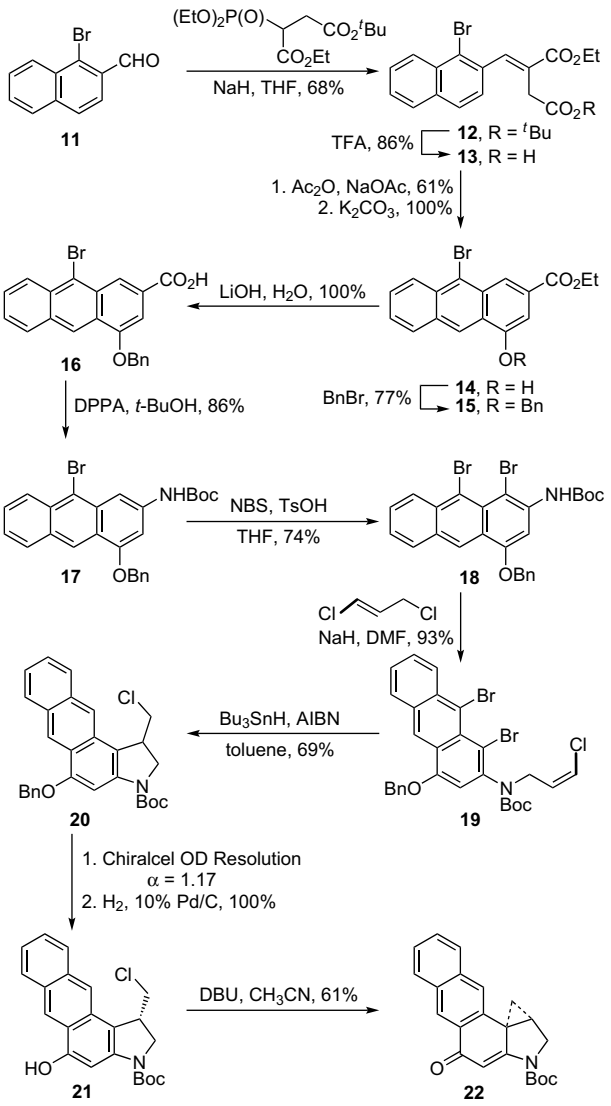
series, Figure 2. Not only is it the most synthetically[19] accessible alkylation subunit in a rich series, but its derivatives exhibit biological properties[18,20] that surpass those of **1** and **2** while approaching those of **3**, and it exhibits a stability and inherent reaction regioselectivity that are near optimal.[18]

As an extension of these studies, we report herein two new classes of CBI-based agents that incorporate the extended anthracene and phenanthrene skeleton. Prospective modeling of the former linear 1,2,11,11a-tetrahydrocyclopropa[*c*]naphtho[2,3-*e*]-indol-4-one (CNI) suggested that its derivatives may effectively bind DNA with its extended alkylation subunit productively enhancing catalysis of the DNA reaction, whereas the latter angular 1,2,11,11a-tetrahydrocyclopropa[*c*]naphtho[1,2-*e*]indol-4-one (*iso*-CNI) derivatives may suffer destabilizing steric interactions precluding effective DNA alkylation.

2. Results and discussion

2.1. Synthesis

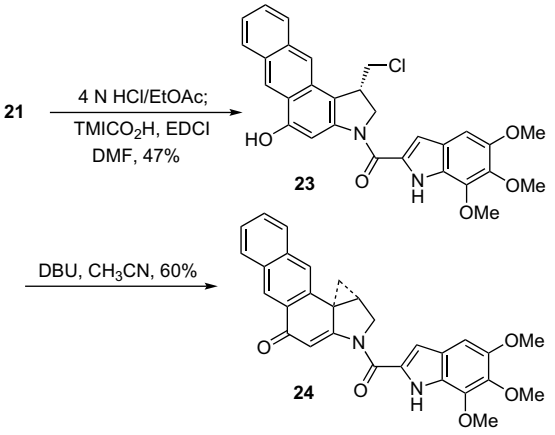
The synthesis of the CNI subunit began by condensation of commercially available aldehyde **11** with the known phosphonate[21] to provide **12**, and was followed by selective removal of the *tert*-butyl ester to provide the carboxylic acid **13** (Scheme 1). Friedel–Crafts cyclization effected by treatment with Ac_2O and subsequent hydrolysis of the resulting acetate provided phenol **14** (61%, two steps). Benzyl protection of the phenol (77%) and LiOH hydrolysis of **15** gave **16** (100%). Treatment of **16** with the Shioiri–Yamada reagent (DPPA) in *t*-BuOH and subsequent Curtius rearrangement of the intermediate acyl azide provided the Boc-protected amine **17** in 86%. Regioselective C4 bromination of **17** (74%) and subsequent N-alkylation of **18** with 1,3-dichloropropene afforded **19** (93%) and set the stage for a key 5-*exo*-*trig* aryl radical–alkene cyclization[22] to provide **20**. This latter cyclization was best effected in toluene (105 °C) and also served to reduce the C5 bromide that was used to direct the Friedel–Crafts cyclization of **13** to provide the linear anthracene skeleton versus the otherwise preferred phenanthrene skeleton.[23] Resolution of **20** by chromatographic separation on a semipreparative Chiralcel OD column provided both enantiomers cleanly, which were then subjected to hydrogenolysis to provide **21** (natural *S* enantiomer shown). Spirocyclization of **21** was effected by treatment with DBU in anhydrous CH_3CN to give *N*-Boc-CNI (**22**) in good yield (61%).



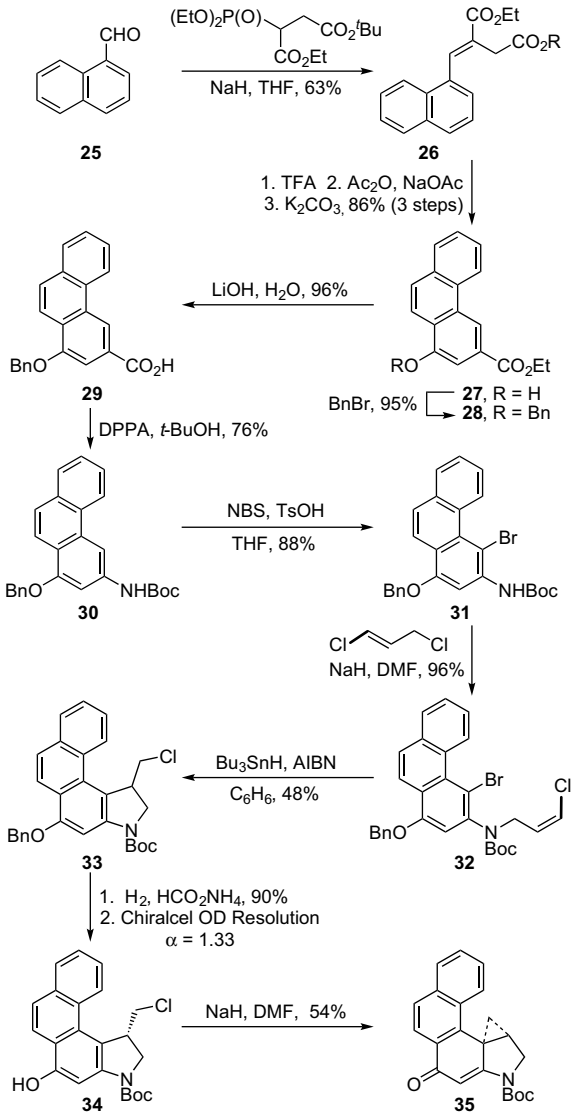
Scheme 1.

N-Boc deprotection of **21** and subsequent coupling of the amine hydrochloride salt with 5,6,7-trimethoxyindole-2-carboxylic acid (TMI) provided **23** (47%), which was spirocyclized to provide **24** (CNI-TMI) using DBU (60%, Scheme 2).

The synthesis of the *iso*-CNI subunit began by the preparation of **26** following the modified Stobbe condensation previously



Scheme 2.



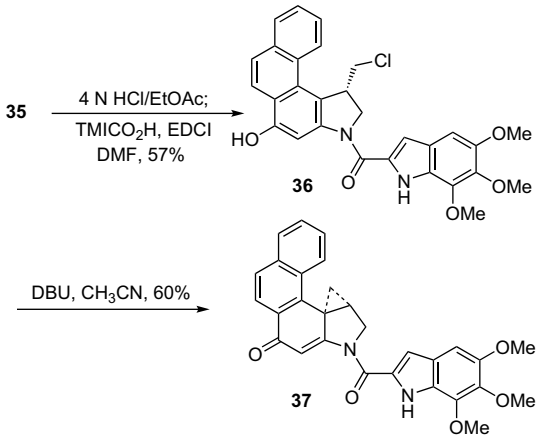
Scheme 3.

described (Scheme 3). Selective removal of the *tert*-butyl ester, Friedel–Crafts cyclization to the phenanthrene effected by treatment with Ac_2O, and hydrolysis of the resulting acetate provided phenol **27** (86% over three steps). Benzyl protection of **27** (95%) and LiOH hydrolysis of **28** gave the carboxylic acid **29** (96%), which was subjected to a modified Curtius rearrangement for conversion to the Boc-protected amine **30**. Regioselective C4 bromination, subsequent *N*-alkylation with 1,3-dichloropropene, and 5-*exo*-*trig* aryl radical–alkene cyclization gave **33**.[24] Resolution of **33** by chromatographic separation on a semipreparative Chiralcel OD column provided both enantiomers cleanly, which were subjected to transfer hydrogenolysis to provide **34** (natural *S* enantiomer shown). Spirocyclization of **34** was effected by treatment with NaH to give *N*-Boc-*iso*-CNI (**35**) in good yield (54%).

Boc deprotection of **34** and subsequent coupling of the amine hydrochloride salt with 5,6,7-trimethoxyindole-2-carboxylic acid (TMI) provided **36** (57%), which was spirocyclized to provide **37** (*iso*-CNI-TMI) using DBU (60%), Scheme 4.

2.2. Solvolysis reactivity

A key feature of the alkylation subunits is their intrinsic reactivity (stability), which correlates with the cytotoxic potency of



Scheme 4.

Compound	k, s^{-1}	$t_{1/2}$
N-Boc-CBI	1.45×10^{-6}	133 h
N-Boc-CNI	1.68×10^{-6}	115 h
N-Boc-*iso*-CNI	1.32×10^{-6}	146 h

Figure 3. Solvolysis reactivity, pH=3.

the corresponding derivatives.[16] Consequently, the solvolytic reactivity of both *N*-Boc-CNI (**22**) and *N*-Boc-*iso*-CNI (**35**) at pH 3 (50% buffer–MeOH, buffer=0.1 M citric acid, 0.2 M Na_2HPO_4, and deionized H_2O) was established and compared to that of the preceding analogues including *N*-Boc-CBI (Fig. 3).[18] Consistent with expectations and intrinsic to their structures, both *N*-Boc-CNI ($t_{1/2}$=115 h) and *N*-Boc-*iso*-CNI ($t_{1/2}$=146 h) exhibited the remarkable stability of *N*-Boc-CBI ($t_{1/2}$=133 h) even at pH 3. Both were approximately four-times more stable than the alkylation subunit of CC-1065 (*N*-Boc-CPI, $t_{1/2}$=36 h)[25] and approach the stability of the alkylation subunit of duocarmycin SA and yatakemycin (*N*-Boc-DSA, $t_{1/2}$=177 h).[26,27]

2.3. Cytotoxic activity

The cytotoxic activity of the key CNI and *iso*-CNI derivatives was established against L1210, a leukemia cell line utilized extensively in past studies, Figure 4. Consistent with expectations based on their relative reactivity, the cytotoxic activity of both *N*-Boc-CNI (**22**) and CNI-TMI (**24**) proved nearly indistinguishable from the corresponding CBI derivative. Notably, (+)-CNI-TMI exhibited the exceptionally potent activity observed with (+)-CBI-TMI (IC_{50}=30 pM), and the unnatural enantiomers were 10–100 fold less active. In contrast, the *iso*-CNI derivatives were >10-fold less active than either the CBI or CNI derivatives indicating that they exhibit a diminished cytotoxic activity relative to expectations based on their reactivity. Such observations are consistent with

Compound nat. enantiomer	IC_{50}	Compound unnat. enantiomer	IC_{50}
(+)-*N*-Boc-CBI	80	(–)-*N*-Boc-CBI	900
(+)-CBI-TMI	0.03	(–)-CBI-TMI	2
(+)-*N*-Boc-CNI	60	(–)-*N*-Boc-CNI	800
(+)-CNI-TMI	0.03	(–)-CNI-TMI	0.8
(+)-*N*-Boc-*iso*-CNI	500	(–)-*N*-Boc-*iso*-CNI	10000
(+)-*iso*-CNI-TMI	1	(–)-*iso*-CNI-TMI	20

Figure 4. In vitro cytotoxic activity, L1210 (nM).

modeling studies that suggest they suffer from a less effective interaction with the minor groove of duplex DNA.

3. Conclusions

Efficient syntheses and a preliminary evaluation of 1,2,11,11a-tetrahydrocyclopropa[*c*]naphtho[2,3-*e*]indole (CNI) and 1,2,11,11a-tetrahydrocyclopropa[*c*]naphtho[1,2-*e*]indole (*iso*-CNI), and their derivatives containing an anthracene and phenanthrene variant of the CC-1065 or duocarmycin alkylation subunit are detailed. Both were found to exhibit a reactivity comparable with the prototypical CBI derivatives, but only the former CNI derivatives exhibited the comparable cytotoxic activity. Further studies into the origin of the distinctions are in progress and will be reported in due course.

4. Experimental section

4.1. 4-*tert*-Butyl 1-ethyl 2-(1-bromonaphthalen-2-yl-methylene)butanedioate (12)

A solution of 4-*tert*-butyl 1-ethyl 2-(diethoxyphosphoryl)-succinate[21] (8.61 g, 25.4 mmol, 1.1 equiv) in THF (75 mL) was cooled to 0 °C and NaH (60% oil dispersion, 1.02 mg, 25.4 mmol, 1.1 equiv) was added in a single addition. The reaction mixture was gradually warmed to room temperature over 1 h. The mixture was cooled to 0 °C and a solution of 1-bromonaphthalene-2-carbaldehyde (5.43 g, 23.1 mmol) in THF (40 mL) was added and the mixture was warmed to room temperature and stirred for 16 h. The mixture was quenched with the addition of water (100 mL) and diluted with EtOAc (100 mL). The organic layer was washed with water (100 mL), saturated aqueous NaCl (100 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 4×12 cm, 0–10% EtOAc–hexanes) afforded **12** (6.62 g, 68%) as a yellow viscous oil. R_f=0.49 (10% EtOAc–hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J=8.9 Hz, 1H), 8.05 (s, 1H), 7.85–7.81 (m, 2H), 7.62 (dt, J=1.4, 7.6 Hz, 1H), 7.56 (dt, J=1.4, 7.5 Hz, 1H), 7.40 (d, J=8.4 Hz, 1H), 4.33 (q, J=6.1 Hz, 2H), 3.32 (s, 2H), 1.46 (s, 9H), 1.38 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 167.0, 141.5, 134.0, 133.8, 132.2, 128.5, 128.1, 127.8, 127.7, 127.20, 127.18, 126.5, 124.4, 81.0, 61.2, 35.1, 28.0 (3C), 14.2; IR (film) ν_{max} 2977, 2948, 1725, 1720, 1367, 1256, 1152 cm^{-1}; HRMALDI–FTMS (DHB) m/z 441.0679 (M+Na$^+$, $C_{21}H_{23}BrO_4$ requires 441.0672).

4.2. (*E*)-3-(Ethoxycarbonyl)-4-(1-bromonaphthalen-2-yl)-but-3-enoic acid (13)

A solution of **12** (1.62 g, 3.87 mmol) in TFA (18 mL) was cooled to 0 °C and H_2O (2 mL) was added. The reaction mixture was gradually warmed to room temperature over 2 h before the solvent was removed in vacuo, followed by azeotropic distillation with toluene (3×50 mL) until the TFA was completely removed. Flash chromatography (SiO_2, 2.5×25 cm, 50–99% EtOAc–hexanes gradient) afforded **13** (1.20 g, 86%) as a white solid. Mp 171–173 °C (dec); R_f=0.30 (10% EtOAc–hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, J=8.4 Hz, 1H), 8.13 (s, 1H), 7.86 (s, 1H), 7.85 (s, 1H), 7.64 (dt, J=1.2, 7.6 Hz, 1H), 7.58 (dt, J=1.0, 7.5 Hz, 1H), 7.41 (d, J=8.4 Hz, 1H), 4.36 (q, J=7.1 Hz, 2H), 3.46 (s, 2H), 1.39 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 166.9, 142.7, 134.1, 133.3, 132.1, 128.2, 128.0, 127.9, 127.4, 127.2, 127.1, 126.3, 124.4, 61.5, 33.8, 14.2; IR (film) ν_{max} 3226, 2950, 2919, 2847, 1707, 1461 cm^{-1}; HRMALDI–FTMS (DHB) m/z 385.0049 (M+Na$^+$, $C_{17}H_{15}BrO_4$ requires 385.0046).

4.3. Ethyl 4-acetoxy-9-bromoanthracene-2-carboxylate

A solution of **13** (800 mg, 2.21 mmol) in Ac_2O (45 mL) was treated with NaOAc (480 mg, 11.05 mmol) and warmed at 110 °C for 20 h. The mixture was cooled and the solvent was removed in vacuo, followed by azeotropic distillation with toluene (3×50 mL) until the Ac_2O was completely removed. Flash chromatography (SiO_2, 3.5×16 cm, 6–16% EtOAc–hexanes gradient) afforded ethyl 4-acetoxyphenanthrene-2-carboxylate (170 mg, 25%) as a yellow film and the title compound (400 mg, 61%) as a yellow solid. Mp 71–73 °C; R_f=0.49 (10% EtOAc–hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.52 (d, J=8.8 Hz, 1H), 8.43 (s, 1H), 8.00 (d, J=8.4 Hz, 1H), 7.83 (s, 1H), 7.65 (t, J=7.6 Hz, 1H), 7.57 (t, J=7.5 Hz, 1H), 4.49 (q, J=7.1 Hz, 2H), 2.56 (s, 3H), 1.48 (t, J=7.1 Hz, 3H), 1.45 (t, J=6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 166.1, 147.8, 134.4, 131.7, 131.0, 129.9, 129.4, 129.3, 128.2, 128.1, 127.5, 125.7, 121.4, 117.0, 104.2, 61.0, 20.7, 14.7; IR (film) ν_{max} 2958, 1769, 1715, 1365, 1231, 1197 cm^{-1}; HRMALDI–FTMS (DHB) m/z 409.0058 (M+Na$^+$, $C_{19}H_{15}BrO_4$ requires 409.0046).

For ethyl 4-acetoxyphenanthrene-2-carboxylate: yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (m, 1H), 8.20 (s, 1H), 7.91 (m, 1H), 7.75 (d, J=7.7 Hz, 1H), 7.67 (d, J=7.7 Hz, 1H), 7.61 (m, 4H), 4.41 (q, J=6.4 Hz, 2H), 2.55 (s, 3H), 1.40 (t, J=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 166.3, 134.7, 133.0, 131.4, 129.9, 129.6, 129.5, 129.4, 127.3, 127.2, 127.1, 126.5, 115.8, 62.1, 22.0, 4.7; IR (film) ν_{max} 1776, 1731, 1558, 1367, 1218, 1181, 1036 cm^{-1}; HRMALDI–FTMS (DHB) m/z 331.0947 (M+Na$^+$, $C_{19}H_{16}O_4$ requires 331.0941).

4.4. Ethyl 9-bromo-4-hydroxyanthracene-2-carboxylate (14)

A solution of ethyl 4-acetoxy-9-bromoanthracene-2-carboxylate (2.00 g, 5.18 mmol) in EtOH (52 mL) was treated with K_2CO_3 (787 mg, 5.70 mmol, 1.1 equiv) and the reaction mixture was stirred for 4 h at 23 °C. The mixture was diluted with EtOAc (50 mL), washed with saturated aqueous NH_4Cl (100 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 4×30 cm, 0–10% EtOAc–hexanes gradient) afforded **14** (1.78 g, 100%) as a yellow solid. Mp 197–199 °C; R_f=0.28 (16% EtOAc–hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.88 (s, 1H), 8.54 (d, J=8.5 Hz, 1H), 8.07 (d, J=8.5 Hz, 1H), 7.65 (t, J=7.7 Hz, 1H), 7.58 (t, J=7.7 Hz, 1H), 7.41 (s, 1H), 5.76 (br s, 1H), 4.49 (q, J=7.0 Hz, 2H), 1.48 (t, J=7.0 Hz, 3H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.09 (s, 1H), 8.93 (s, 1H), 8.57 (s, 1H), 8.36 (dd, J=0.8, 8.8 Hz, 1H), 8.23 (d, J=8.5 Hz, 1H), 7.72 (dt, J=1.2, 7.7 Hz, 1H), 7.61 (dt, J=1.5, 7.5 Hz, 1H), 7.35 (d, J=1.3 Hz, 1H), 4.39 (q, J=7.1 Hz, 2H), 1.38 (t, J=7.1 Hz, 3H); IR (film) ν_{max} 3409, 2953, 1697, 1595, 1243, 1107, 1031 cm^{-1}; HRMALDI–FTMS (DHB) m/z 344.0045 (M$^+$, $C_{17}H_{13}BrO_3$ requires 344.0048).

4.5. Ethyl 4-benzyloxy-9-bromoanthracene-2-carboxylate (15)

A solution of **14** (800 mg, 2.33 mmol) in DMF (23 mL) was treated with K_2CO_3 (354 mg, 2.56 mmol, 1.1 equiv) and after 5 min, BnBr (0.31 mL, 2.56 mmol, 1.1 equiv) was added. The mixture was stirred for 3.5 h at 23 °C, then diluted with EtOAc (50 mL) and washed with saturated aqueous NH_4Cl (100 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 4×30 cm, 0–10% EtOAc–hexanes gradient) afforded **15** (777 mg, 1.78 mmol, 77%) as a yellow solid. Mp 124–126 °C; R_f=0.50 (16% EtOAc–hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.84 (s, 1H), 8.47 (d, J=8.8 Hz, 1H), 7.98 (d, J=8.1 Hz, 1H), 7.62–7.58 (m, 3H), 7.53–7.40 (m, 5H), 5.34 (s, 2H), 4.50 (q, J=7.0 Hz, 2H), 1.52 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 155.0, 137.0, 133.2, 131.6, 130.4, 129.2, 129.1, 128.7, 128.2, 127.80, 127.77, 127.72, 126.9, 126.4, 124.4, 123.9, 122.3, 102.2, 71.0, 61.8, 14.9; IR (film) ν_{max} 1717, 1653, 1558 cm^{-1}; HRMALDI–FTMS (DHB) m/z 434.0529 (M$^+$, $C_{24}H_{19}BrO_3$ requires 434.0512).

4.6. 4-Benzyloxy-9-bromoanthracene-2-carboxylic acid (16)

A solution of **15** (220 mg, 0.507 mmol) in 3:1:1 (v/v/v) THF–MeOH–H_2O (5 mL) was treated with LiOH (59 mg, 1.39 mmol, 5 equiv) and stirred for 2 h at 23 °C. HCl (4 N, 10 mL) was added and the mixture was diluted with CH_2Cl_2 (25 mL). The organic layer was washed with H_2O (3×10 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5×12.7 cm, 50–100% EtOAc–hexanes gradient) afforded **16** (204 mg, 100%) as a yellow solid. Mp 291–293 °C (dec); R_f=0.32 (50% EtOAc–hexanes); ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.40 (brs, 1H), 8.89 (s, 1H), 8.82 (s, 1H), 8.46 (d, J=8.8 Hz, 1H), 8.32 (d, J=8.5 Hz, 1H), 7.80–7.76 (m, 1H), 7.68–7.64 (m, 3H), 7.50 (m, 3H), 7.42–7.38 (m, 1H), 5.40 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 155.6, 137.9, 133.7, 131.8, 131.4, 131.3, 131.0, 130.0, 129.4, 129.2, 129.0 (2C), 128.3, 128.2 (2C), 127.4, 124.6, 123.8, 123.1, 103.7, 71.4; IR (film) ν_{max} 3410, 2921, 2850, 1685, 1558, 1435, 1324 cm^{-1}; HRMALDI–FTMS (DHB) m/z 406.0212 (M^+, $C_{22}H_{15}BrO_3$ requires 406.0205).

4.7. 4-Benzyloxy-2-(*tert*-butyloxycarbonyl)amino-9-bromoanthracene (17)

A solution of **16** (50 mg, 0.123 mmol) in distilled *t*-BuOH (1.23 mL) was treated with distilled Et_3N (18.0 μL, 0.129 mmol) and DPPA (26.5 μL, 0.123 mmol, 1 equiv). The mixture was heated at 80 °C for 20 h then cooled to room temperature and diluted with EtOAc (1 mL). The solution was washed with saturated aqueous $NaHCO_3$ (2×10 mL), H_2O (10 mL), and saturated aqueous NaCl (10 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 1×11 cm, 17% EtOAc–hexanes) afforded **17** (50.4 mg, 0.105 mmol, 86%) as an orange solid. Mp 110–112 °C; R_f=0.36 (16% EtOAc–hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.43 (d, J=8.4 Hz, 1H), 7.98 (d, J=8.4 Hz, 1H), 7.88 (s, 1H), 7.59 (m, 3H), 7.41 (m, 4H), 7.33 (br s, 1H), 6.85 (s, 1H), 5.32 (s, 2H), 1.60 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 152.7, 137.6, 136.5, 131.6, 131.4, 130.6, 129.3, 128.7, 128.2, 127.8, 127.6, 127.0, 124.7, 123.0, 121.9, 120.2, 105.3, 98.3, 80.9, 71.5, 28.4 (3C); IR (film) ν_{max} 3323, 2974, 2923, 1697, 1635, 1425, 1235, 1154 cm^{-1}; HRMALDI–FTMS (DHB) m/z 500.0834 (M+Na^+, $C_{26}H_{24}BrNO_3$ requires 500.0832).

4.8. 4-Benzyloxy-2-(*tert*-butyloxycarbonyl)amino-1,9-dibromoanthracene (18)

A solution of **17** (25 mg, 0.052 mmol) in anhydrous THF (120 μL) at −78 °C was treated with anhydrous TsOH (1.0 mg, 0.0052 mmol, 0.1 equiv, dried at 50 °C under high vacuum overnight) in THF (20 μL). The solution was stirred for 5 min before NBS (9.3 mg, 0.052 mmol, dried over P_2O_5 overnight) was added. The vial was protected from light and allowed to stir at −78 °C for 3 h. The reaction mixture was warmed to 23 °C and diluted with saturated aqueous $NaHCO_3$ (1 mL). The mixture was diluted with EtOAc (25 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL), H_2O (10 mL), and saturated aqueous NaCl (10 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 1×11 cm, 0–7% EtOAc–hexanes gradient) afforded 2-(*tert*-butyloxycarbonyl)amino-4-hydroxy-1,9-dibromoanthracene (6.2 mg, 26%) as a tan solid and **18** (21.4 mg, 74%) as a yellow solid. R_f=0.34 (10% EtOAc–hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.63 (d, J=8.9 Hz, 1H), 8.08 (s, 1H), 7.95 (d, J=8.4 Hz, 1H), 7.82 (s, 1H), 7.63–7.59 (m, 3H), 7.50–7.40 (m, 4H), 5.33 (s, 2H), 1.60 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 152.6, 138.4, 136.2, 133.8, 130.6, 128.9, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 125.6, 124.8, 122.5, 118.7, 98.4, 96.3, 81.4, 70.8, 28.3; IR (film) ν_{max} 2923, 2841, 1728, 1615, 1548, 1467, 1348, 1231, 1149 cm^{-1}; HRMALDI–FTMS (DHB) m/z 577.9929 (M+Na^+, $C_{26}H_{23}Br_2NO_3$ requires 577.9937).

For 2-(*tert*-butyloxycarbonyl)amino-4-hydroxy-1,9-dibromoanthracene. Orange solid; R_f=0.30 (10% EtOAc–hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.66 (d, J=8.5 Hz, 1H), 8.07 (d, J=7.7 Hz, 1H), 7.82 (t, J=7.0 Hz, 1H), 7.72 (t, J=7.0 Hz, 1H), 7.09 (s, 1H), 1.58 (s, 9H); IR (film) ν_{max} 3374, 2985, 2912, 1743, 1666, 1605, 1462, 1253, 1149 cm^{-1}.

4.9. 2-[*N*-(*tert*-Butyloxycarbonyl)-*N*-(3-chloroprop-2-en-1-yl)-amino]-4-benzyloxy-1,9-dibromoanthracene (19)

A solution of **18** (1.65 g, 2.96 mmol) in DMF (50 mL) was treated with Bu_4NI (55 mg, 0.148 mmol) under Ar. The mixture was cooled to 0 °C and NaH (60% suspension in mineral oil, 296 mg, 7.40 mmol, 2.5 equiv) was added. The solution was stirred for 0.5 h and 1,3-dichloropropene (820 μL, 8.88 mmol, 3 equiv) was added. The vial was protected from light and allowed to stir at 0 °C for 2 h before being treated with saturated aqueous $NaHCO_3$ (5 mL). The mixture was extracted with Et_2O (3×25 mL), and the combined organic layers were washed with H_2O (3×20 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 3×20 cm, 16% EtOAc–hexanes) afforded **19** (1.74 g, 2.75 mmol, 93%) as a yellow solid as a mixture of *E*- and *Z*-olefin isomers. Mp 67–69 °C; R_f=0.35 (10% EtOAc–hexanes); ^{1}H NMR (500 MHz, acetone-d_6) δ 9.07 (d, J=4.4 Hz, 1H), 8.63 (d, J=8.8 Hz, 1H), 8.12 (m, 1H), 7.71 (t, J=7.7 Hz, 1H), 7.64 (m, 2H), 7.58 (t, J=7.0 Hz, 1H), 7.47 (m, 2H), 7.40 (app t, J=7.4 Hz, 1H), 7.04 (d, J=16.0 Hz, 1H), 6.23 (m, 1H), 6.15 (m, 1H), 5.47 (m, 2H), 4.67 and 4.63 (two d, J=6.3, 5.8 Hz, 1H), 4.38–4.48 (m, 1H), 4.14 (m, 1H), 1.36 (s, 9H); IR (film) ν_{max} 2923, 2851, 1697, 1610, 1462, 1369, 1262, 1153 cm^{-1}; HRMALDI–FTMS (DHB) m/z 552.0801 (M^+−Br, $C_{29}H_{27}BrClNO_3$ requires 552.0801).

4.10. 5-(Benzyloxy)-3-(*tert*-butyloxycarbonyl)-1-(chloromethyl)-1,2-dihydronaphtho[2,3-*e*]indole (20)

A solution of **19** (78 mg, 0.123 mmol) in toluene (3 mL) was degassed with Ar and treated with AIBN (4 mg, 24.6 μmol, 0.2 equiv) and Bu_3SnH (83 μL, 0.308 mmol, 2.5 equiv). A stream of Ar was bubbled through the solution for 10 min before the reaction vessel was closed and warmed at 105 °C for 3 h. The mixture was cooled to 23 °C and concentrated in vacuo. Flash chromatography (SiO_2, 1×15 cm, 67% benzene–hexanes) afforded **20** (40 mg, 0.084 mmol, 69%) as a yellow solid. Mp 152–154 °C; R_f=0.31 (16% EtOAc–hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.12 (s, 1H), 8.00 (d, J=8.1 Hz, 1H), 7.95 (d, J=8.4 Hz, 1H), 7.61 (br m, 2H), 7.48 (m, 4H), 7.42 (m, 2H), 5.35 (s, 2H), 4.32 (br m, 1H), 4.20 (app t, J=9.9 Hz, 1H), 4.09 (m, 2H), 3.52 (app t, J=10.5 Hz, 1H), 1.63 (s, 9H); IR (film) ν_{max} 2964, 2920, 1699, 1621, 1571, 1454, 1404, 1363, 1337, 1143 cm^{-1}; HRMALDI–FTMS (DHB) m/z 496.1631 (M+Na^+, $C_{29}H_{28}ClNO_3$ requires 496.1650).

4.11. Resolution of 20

The enantiomers of **20** were resolved on a HPLC semipreparative Diacel Chiralcel OD column (10 μm, 2×25 cm) using 5% *i*-PrOH–hexane eluant (8 mL/min). The enantiomers eluted with retention times of 12.3 min (unnatural enantiomer) and 14.4 min (natural enantiomer, α=1.17).

4.12. 3-(*tert*-Butyloxycarbonyl)-1-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-naphtho[2,3-*e*]indole (21, *seco*-*N*-Boc-CNI)

A solution of **20** (89 mg, 0.188 mmol) in THF (2 mL) was treated with a catalytic amount of 10% Pd–C (2 mg) and placed under 1 atm of H_2. The mixture was stirred at 23 °C for 1.5 h, filtered through a Celite plug, and concentrated in vacuo. Flash chromatography (SiO_2, 1×10 cm, 0–25% EtOAc/hexanes gradient) afforded **21** (72 mg,

100%) as a white solid. Mp 187–188 °C (dec); R_f=0.17 (16% EtOAc–hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.65 (d, J=7.7 Hz, 1H), 7.92 (brs, 1H), 7.84 (d, J=7.4 Hz, 1H), 7.75 (d, J=8.8 Hz, 1H), 7.62 (t, J=7.4 Hz, 1H), 7.57 (d, J=8.8 Hz, 1H), 7.53 (t, J=7.7 Hz, 1H), 4.29 (m, 1H), 4.14 (app t, J=8.8 Hz, 1H), 4.00 (m, 1H), 3.92 (app d, J=11 Hz, 1H), 3.45 (app t, J=11 Hz, 1H), 1.66 (s, 9H); ^{13}C NMR (125 MHz, acetone-d_6) δ 157.4, 131.7, 130.8, 129.9, 128.8, 128.4, 127.4, 125.7, 121.7, 117.1, 115.6, 105.2, 102.4, 65.0, 53.4, 47.1, 28.9 (3C), 25.7; IR (film) ν_{max} 3367, 2960, 2919, 1674, 1501, 1460, 1415, 1405, 1369, 1338, 1262, 1134 cm^{-1}; HRMALDI–FTMS (DHB) m/z 383.1283 (M^+, $C_{22}H_{22}ClNO_3$ requires 383.1283).

4.13. 3-(*tert*-Butyloxycarbonyl)-1,2,11,11a-tetrahydrocyclopropa[*c*]naphtho[2,3-*e*]indol-4-one (22, *N*-Boc-CNI)

A sample of **21** (7.1 mg, 18.5 μmol) was dissolved in freshly distilled CH_3CN (200 μL) under Ar. Anhydrous DBU (14 μL, 92.5 μmol) was added at 23 °C, and the mixture was stirred for 1 h. The reaction mixture was then concentrated under a stream of N_2 and applied directly to PTLC (SiO_2, 10×20 cm, 50% EtOAc/hexanes) to afford **22** (3.9 mg, 61%) as a white solid. Mp 61–63 °C; R_f=0.35 (50% EtOAc–hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.01 (d, J=8.1 Hz, 1H), 7.78 (d, J=8.0 Hz, 1H), 7.55 (dt, J=1.4, 7.5 Hz, 1H), 7.48 (dt, J=1.3, 7.5 Hz, 1H), 7.28 (s, 1H), 6.88 (br s, 1H), 4.05–4.04 (m, 2H), 2.90–2.85 (m, 1H), 1.64 (dd, J=4.3, 7.7 Hz, 1H), 1.58 (s, 9H), 1.52 (t, J=4.6 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 186.4, 162.4, 153.3, 138.7, 136.7, 133.4, 132.8, 131.3, 129.8, 129.1, 128.6, 127.8, 122.1, 109.5, 84.1, 54.9, 31.6, 29.2 (2C), 25.4; IR (film) ν_{max} 2977, 1723, 1614, 1382, 1256, 1160, 1140, 856, 748 cm^{-1}; HRMALDI–FTMS (DHB) m/z 348.1600 ($M+H^+$, $C_{22}H_{21}NO_3$ requires 348.1594). Compound (+)-**22**: $[\alpha]_D^{23}$ +80 (c 0.075, $CHCl_3$); (−)-**22**: $[\alpha]_D^{23}$ −87 (c 0.11, $CHCl_3$).

4.14. *seco*-CNI-TMI (23)

A sample of **21** (11.1 mg, 28.9 μmol) was treated with 4 N HCl/EtOAc (250 μL) and stirred at 23 °C for 1 h. The solvent was removed under a stream of N_2 and dried under high vacuum for 30 min. The gray residue was dissolved in DMF (20 μL) and treated with 5,6,7-trimethoxyindole-2-carboxylic acid[28] (8.0 mg, 31.8 μmol) and EDCI (16.7 mg, 86.8 μmol). The mixture was stirred under Ar at 23 °C for 18 h in the absence of light before the solvent was removed under a stream of N_2. PTLC (SiO_2, 20×20 cm, EtOAc) afforded **23** (7.1 mg, 47%) as a white solid. Mp 243–245 °C (dec); R_f=0.55 (50% EtOAc–hexanes); ^{1}H NMR (500 MHz, acetone-d_6) δ 10.38 (s, 1H), 8.29 (s, 1H), 7.93 (d, J=7.7 Hz, 1H), 7.86 (m, 2H), 7.64 (t, J=7.0 Hz, 1H), 7.56 (t, J=7.0 Hz, 1H), 7.18 (s, 1H), 7.01 (s, 1H), 4.81 (m, 1H), 4.35 (m, 1H), 4.09 (m, 2H), 4.05 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.80 (dd, J=8.8, 2.2 Hz, 1H); IR (film) ν_{max} 3426, 2903, 1723, 1313 cm^{-1}; HRMALDI–FTMS (DHB) m/z 517.1511 ($M+H^+$, $C_{29}H_{25}ClN_2O_5$ requires 517.1525).

4.15. CNI-TMI (24)

A sample of **21** (7.1 mg, 13.7 μmol) was dissolved in freshly distilled CH_3CN (140 μL) under Ar. Anhydrous DBU (10.5 μL, 68.7 μmol) was added at 23 °C, and the mixture was stirred for 1 h. The reaction mixture was then concentrated under a stream of N_2 and applied directly to PTLC (SiO_2, 10×20 cm, 50% EtOAc–hexanes) to afford **24** (4.0 mg, 60%) as a white solid. R_f=0.55 (50% EtOAc–hexanes); ^{1}H NMR (500 MHz, acetone-d_6) δ 10.48 (br s, 1H), 9.99 (s, 1H), 8.10 (d, J=8.5 Hz, 1H), 7.95 (d, J=6.6 Hz, 1H), 7.66 (app t, J=7.0 Hz, 1H), 7.56 (t, J=7.0 Hz, 1H), 7.26 (d, J=8.5 Hz, 1H), 7.16 (s, 1H), 7.11 (s, 1H), 6.96 (s, 1H), 4.68 (dd, J=9.9, 5.5 Hz, 1H), 4.59 (d, J=9.9 Hz, 1H), 4.02 (s, 3H), 3.87 (s, 6H), 3.33 (m, 1H), 1.97 (d, J=4.4 Hz, 1H), 1.79 (t, J=5.1 Hz, 1H); IR (film) ν_{max} 3297, 2919, 2854, 1650, 1601, 1385, 1261, 1229, 1105, 1045 cm^{-1}; HRMALDI–FTMS (DHB) m/z 481.1751 ($M+H^+$, $C_{29}H_{24}N_2O_5$ requires 481.1758). Compound (+)-**24**: $[\alpha]_D^{23}$ +160 (c 0.1, $CHCl_3$); (−)-**24**: $[\alpha]_D^{23}$ −160 (c 0.1, $CHCl_3$).

4.16. 4-*tert*-Butyl 1-ethyl 2-(naphthalen-8-yl-methylene)-butanedioate (26)

A solution of 4-*tert*-butyl 1-ethyl 2-(diethoxyphosphoryl)succinate[21] (1.00 g, 3.0 mmol) in THF (10 mL) was cooled to 0 °C and NaH (60% oil dispersion, 79 mg, 3.3 mmol) was added in a single addition. The reaction mixture was gradually warmed to room temperature over 2 h before being recooled to 0 °C. A solution of 1-naphthaldehyde (462 mg, 3.0 mmol) in THF (5 mL) was added and the mixture was warmed to room temperature and stirred for 12 h. The mixture was diluted with EtOAc (100 mL), and washed with saturated aqueous $NaHCO_3$ (100 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 2.5×25 cm, 0–5% EtOAc–hexanes gradient) afforded **26** (480 mg, 63%; typically 45–66%) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.97–7.86 (m, 3H), 7.58–7.41 (m, 4H), 4.37 (q, J=6.9 Hz, 2H), 3.35 (s, 2H), 1.46 (s, 9H), 1.41 (t, J=6.9 Hz, 3H); HRMALDI–FTMS (DHB) m/z 363.1564 ($M+Na^+$, $C_{21}H_{24}O_4$ requires 363.1572).

4.17. Ethyl 1-hydroxyphenanthrene-3-carboxylate (27)

A solution of **26** (220 mg, 0.65 mmol) in TFA (3 mL) was cooled to 0 °C and H_2O (0.1 mL) was added. The reaction mixture was gradually warmed to room temperature over 2 h and the solvent was removed in vacuo, followed by azeotropic distillation with toluene (3×50 mL) until the TFA was completely removed. Ac_2O (3.5 mL) and NaOAc (53 mg, 0.65 mmol) were added and the mixture was warmed at 70 °C for 8 h. The mixture was cooled and the solvent was removed in vacuo, followed by azeotropic distillation with toluene (3×50 mL) until the Ac_2O was completely removed. The mixture was dissolved in EtOH (2.2 mL) and treated with K_2CO_3 (100 mg, 0.72 mmol) and the reaction mixture was stirred for 4 h at 23 °C. The mixture was diluted with EtOAc (50 mL), washed with saturated aqueous NH_4Cl (100 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 2.5×25 cm, 5–20% EtOAc–hexanes gradient) afforded **27** (149 mg, 86%) as an off-white solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.73 (d, J=7.7 Hz, 1H), 8.22 (d, J=9.1 Hz, 1H), 7.93–7.81 (m, 3H), 7.72–7.60 (m, 2H), 6.79 (br s, 1H), 4.51 (q, J=6.9 Hz, 2H), 1.49 (t, J=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 152.4, 132.3, 131.2, 130.4, 128.7, 128.5, 128.0, 127.1, 125.1, 123.3, 120.0, 117.6, 110.2, 61.5, 14.4; IR (film) ν_{max} 3370, 2925, 1682, 1434, 1372, 1273, 1250, 1025, 825, 749 cm^{-1}; HRMALDI–FTMS (DHB) m/z 266.0955 (M^+, $C_{17}H_{14}O_3$ requires 266.0943).

4.18. Ethyl 1-benzyloxyphenanthrene-3-carboxylate (28)

A solution of **27** (400 mg, 1.5 mmol) in DMF (5 mL) was treated with K_2CO_3 (290 mg, 2.1 mmol) and Bu_4NI (12 mg, 0.03 mmol) and after 5 min, BnBr (214 μL, 1.8 mmol) was added. The mixture was stirred for 10 h at 23 °C, then diluted with EtOAc (50 mL) and washed with saturated aqueous NH_4Cl (100 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 4×30 cm, 2–20% EtOAc–hexanes gradient) afforded **28** (507 mg, 95%) as an off-white solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.78 (d, J=8.4 Hz, 1H), 8.31 (d, J=9.1 Hz, 1H), 7.93 (d, J=7.7 Hz, 1H), 7.85 (d, J=9.1 Hz, 1H), 7.73–7.58 (m, 5H), 7.49–7.38 (m, 3H), 5.35 (s, 2H), 4.50 (q, J=7.3 Hz, 2H), 1.50 (t, J=7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 154.9, 136.7, 132.2, 130.8, 130.3, 128.6, 128.5, 128.2, 128.0, 127.6, 127.0, 126.9, 126.2, 120.2, 117.9, 106.6, 70.5, 61.2, 14.4; IR (film) ν_{max} 2894, 1713, 1272, 1026, 749 cm^{-1}; HRMALDI–FTMS (DHB) m/z 357.1498 ($M+H^+$, $C_{24}H_{20}O_3$ requires 357.1491).

4.19. 1-Benzyloxyphenanthrene-3-carboxylic acid (29)

A solution of **28** (299 mg, 0.84 mmol) in 3:1:1 (v/v/v) THF–MeOH–H_2O (7.5 mL) was treated with LiOH (60 mg, 2.5 mmol) and stirred for 36 h at 23 °C. HCl (4 N, 10 mL) was added and the mixture was diluted with CH_2Cl_2 (25 mL). The organic layer was washed with H_2O (3×10 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5×12.7 cm, 50–100% EtOAc–hexanes gradient) afforded **29** (264 mg, 96%) as an off-white solid. Mp 266–269 °C (dec); ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.82 (d, J=6.6 Hz, 1H), 8.21 (d, J=9.1 Hz, 1H), 8.06–8.02 (m, 1H), 7.99 (d, J=9.1 Hz, 1H), 7.72 (app t, J=9.1 Hz, 4H), 7.60 (d, J=6.6 Hz, 2H), 7.47–7.36 (m, 2H), 5.41 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.5, 154.4, 136.8, 131.8, 130.2, 129.6, 129.1, 128.7, 128.6, 128.5, 127.9, 127.5, 127.4, 125.3, 123.2, 119.6, 117.1, 107.0, 69.9; ESI (negative) m/z 327 (M−H, $C_{22}H_{15}O_3$).

4.20. 1-(Benzyloxy)-3-((*tert*-butyloxycarbonyl)amino)-phenanthrene (30)

A solution of **29** (200 mg, 0.6 mmol) in distilled *t*-BuOH (11 mL) was treated with distilled Et_3N (167 μL, 1.2 mmol) and DPPA (258 μL, 1.2 mmol). The mixture was heated at 80 °C for 9 h then cooled to room temperature and diluted with EtOAc (1 mL). The solution was washed with saturated aqueous $NaHCO_3$ (2×10 mL), H_2O (10 mL), and saturated aqueous NaCl (10 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 1×11 cm, 2–10% EtOAc–hexanes gradient) afforded **30** (183 mg, 76%) as an off-white solid. Mp 180–182 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, J=7.7 Hz, 1H), 8.21 (s, 1H), 8.19 (d, J=8.8 Hz, 1H), 7.86 (d, J=8.8 Hz, 1H), 7.62 (d, J=9.1 Hz, 1H), 7.60–7.55 (m, 4H), 7.44 (app t, J=7.7 Hz, 2H), 7.39–7.33 (m, 2H), 6.80 (br s, 1H), 5.23 (s, 2H), 1.59 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 152.8, 137.3, 136.9, 132.6, 132.0, 129.5, 128.6, 128.5, 128.0, 127.5, 126.7, 126.1, 124.5, 123.3, 122.1, 120.3, 119.7, 80.7, 70.4, 28.4 (3C); IR (film) ν_{max} 3297, 2975, 1690, 1581, 1540, 1509, 1266, 1157, 815, 748 cm^{-1}; HRMALDI–FTMS (DHB) m/z 399.1835 (M^+, $C_{26}H_{25}NO_3$ requires 399.1834).

4.21. 1-(Benzyloxy)-4-bromo-3-((*tert*-butyloxycarbonyl)-amino)phenanthrene (31)

A solution of **30** (100 mg, 0.25 mmol) in THF (6 mL) at −78 °C was treated with TsOH (25 mg, 0.13 mmol) in THF (3 mL). NBS (50 mg, 0.28 mmol) was added and the vial was protected from light and allowed to stir at −78 °C for 1 h. The reaction mixture was warmed to 23 °C and diluted with saturated aqueous $NaHCO_3$ (1 mL). The mixture was diluted with EtOAc (25 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL), H_2O (10 mL), and saturated aqueous NaCl (10 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 4×20 cm, 2–5% EtOAc–hexanes gradient) afforded **31** (109 mg, 88%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 (d, J=7.7 Hz, 1H), 8.21 (s, 1H), 8.18 (d, J=9.2 Hz, 1H), 7.82 (d, J=7.7 Hz, 1H), 7.64 (br s, 1H), 7.59 (d, J=8.8 Hz, 1H), 7.57–7.51 (m, 4H), 7.42–7.32 (m, 3H), 5.27 (s, 2H), 1.55 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 152.7, 136.8, 136.6, 134.2, 129.8, 129.4, 128.6, 128.3, 128.1, 127.8, 127.4, 126.9, 125.8, 124.4, 122.0, 120.0, 101.3, 99.6, 81.2, 70.7, 28.4 (3C); IR (film) ν_{max} 3405, 2912, 1733, 1600, 1523, 1482, 1221, 1149, 810, 749 cm^{-1}; HRMALDI–FTMS (DHB) m/z 500.0845 ($M+Na^+$, $C_{26}H_{24}BrNO_3$ requires 500.0837).

For isomer (10 mg, 8%): ^{1}H NMR δ 8.74–7.72 (m, 1H), 8.15 (d, J=8.0 Hz, 1H), 8.04–7.85 (m, 4H), 7.74–7.38 (m, 6H), 7.03 (br s, 1H), 4.84 (t, J=10.6 Hz, 2H), 1.67 (s, 9H); HRMALDI–FTMS (DHB) m/z 500.0843 ($M+Na^+$, $C_{26}H_{24}BrNO_3$ requires 500.0837).

4.22. 3-[*N*-(*tert*-Butyloxycarbonyl)-*N*-(3-chloroprop-2-en-1-yl)amino]-1-(benzyloxy)-4-bromophenanthrene (32)

A solution of **31** (50 mg, 0.10 mmol) in DMF (0.8 mL) was cooled to 0 °C. NaH (60% suspension in mineral oil, 12 mg, 0.30 mmol) was added and the solution was stirred for 0.25 h. The mixture was warmed to room temperature and 1,3-dichloropropene (28 μL, 0.3 mmol) was added. The vial was protected from light and allowed to stir for 2 h before being treated with saturated aqueous $NaHCO_3$ (5 mL). The mixture was extracted with Et_2O (3×25 mL), and the combined organic layers were washed with H_2O (3×20 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 3×20 cm, 16% EtOAc–hexanes) afforded **32** (63 mg, 96%) as a yellow oil and as a mixture of *E*- and *Z*-olefin isomers. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.93 (d, J=6.6 Hz, 1H), 8.32 (d, J=9.1 Hz, 1H), 7.91–7.89 (m, 1H), 7.78 (d, J=9.1 Hz, 1H), 7.64 (d, J=6.2 Hz, 2H), 7.56–7.52 (m, 2H), 7.48–7.35 (m, 4H), 7.00 (d, J=8.0 Hz, 1H), 6.92 (d, J=13.2 Hz, 1H), 6.17–5.97 (m, 1H), 5.29 (app t, J=6.2 Hz, 2H), 4.64–4.54 (m, 1H), 4.34 (dd, J=15.7, 5.1 Hz, 1H), 3.83 (dd, J=15.0, 7.7 Hz, 1H), 1.35 (s, 9H); IR (film) ν_{max} 2973, 2921, 1701, 1591, 1368, 1165, 753 cm^{-1}.

4.23. 5-(Benzyloxy)-3-(*tert*-butyloxycarbonyl)-1-(chloromethyl)-1,2-dihydronaphtho[1,2-*e*]indole (33)

A solution of **32** (20 mg, 40 μmol) in C_6H_6 (2 mL) was degassed by three freeze–pump–thaw cycles and treated with AIBN (1 mg, 6 μmol) and Bu_3SnH (13 μL, 50 μmol). A stream of Ar was bubbled through the solution for 10 min before the reaction vessel was closed and warmed to 80 °C for 15 h after which an additional amount of Bu_3SnH (13 μL, 50 μmol) and AIBN (1 mg, 6 μmol) were added. The mixture was stirred for 3 h at 80 °C before being cooled to 23 °C and concentrated in vacuo. Flash chromatography (SiO_2, 3×20 cm, 2–10% EtOAc/hexanes gradient) afforded **33** (9 mg, 48%) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J=8.8 Hz, 1H), 7.93 (d, J=7.0 Hz, 1H), 7.81 (d, J=8.0 Hz, 1H), 7.62 (app t, J=7.7 Hz, 1H), 7.59–7.53 (m, 4H), 7.45 (app t, J=7.0 Hz, 2H), 7.38–7.36 (m, 1H), 5.30 (s, 2H), 4.59 (t, J=9.2 Hz, 1H), 4.39 (d, J=8.8 Hz, 1H), 4.16 (t, J=9.7 Hz, 1H), 3.92 (d, J=11.4 Hz, 1H), 3.36 (t, J=11.0 Hz, 1H), 1.62 (s, 9H); IR (film) ν_{max} 3467, 2950, 1700, 1644, 1366, 1239, 1163, 1138, 833 cm^{-1}.

4.24. *seco*-*N*-Boc-*iso*-CNI (34)

A solution of **33** (20 mg, 0.04 mmol) in 3:1 (v/v) THF–MeOH (10 mL) was treated with a catalytic amount of 10% Pd/C (20 mg) and 25% aqueous HCO_2NH_4 (640 μL, 1.0 mmol). The mixture was stirred at 23 °C for 48 h, filtered through a Celite plug, and concentrated in vacuo. Flash chromatography (SiO_2, 1×10 cm, 10–20% EtOAc–hexanes gradient) afforded **34** (15 mg, 90%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, J=8.5 Hz, 1H), 8.17 (d, J=9.2 Hz, 1H), 7.99 (br s, 1H), 7.91 (d, J=8.1 Hz, 1H), 7.62 (t, J=7.0 Hz, 1H), 7.61 (m, 3H), 6.51 (br s, 1H), 4.56 (app t, J=8.5 Hz, 1H), 4.35 (d, J=10.5 Hz, 1H), 4.14 (m, 1H), 3.90 (d, J=10.5 Hz, 1H), 3.35 (t, J=11.0 Hz, 1H), 1.63 (s, 9H); IR (film) ν_{max} 3349, 2922, 1704, 1596, 1414, 1342, 1254, 1140, 747 cm^{-1}; ESI (negative) m/z 382 (M−H, $C_{22}H_{21}ClNO_3$).

4.25. Resolution of 34

The enantiomers of **34** were resolved on a HPLC semipreparative Diacel Chiralcel OD column (10 μm, 2×25 cm) using 5% *i*-PrOH–hexane eluant (8 mL/min). The enantiomers eluted with retention times of 18.5 min (natural enantiomer) and 13.9 min (unnatural enantiomer, α=1.33). Compound (1*S*)-**34**: $[\alpha]_D^{23}$ −50 (*c* 0.01, THF); (1*R*)-**34**: $[\alpha]_D^{23}$ +50 (*c* 0.01, THF).

4.26. 3-(*tert*-Butyloxycarbonyl)-1,2,11,11a-tetrahydrocyclopropa[*c*]naphtho[1,2-*e*]indol-4-one (*N*-Boc-*iso*-CNI, 35)

A sample of **34** (2 mg, 5 μmol) was dissolved in 3:1 (v/v) THF–DMF (250 μL) under Ar and cooled to 0 °C. NaH (60% suspension in mineral oil, 600 μg, 15 μmol) was added and the mixture was stirred for 30 min. At this time, the reaction was quenched with the addition of pH 7.0 phosphate buffer (300 μL) and diluted with H_2O (1 mL) and EtOAc (5 mL). The organic layer was collected, dried (Na_2SO_4), and concentrated in vacuo. PTLC (SiO_2, 10×20 cm, 10% EtOAc–hexanes) afforded **35** (1.0 mg, 54%) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (d, J=8.3 Hz, 1H), 8.07 (s, 1H), 7.82–7.79 (m, 1H), 7.70–7.65 (m, 3H), 6.91 (s, 1H), 3.72 (d, J=7.5 Hz, 1H), 3.65 (m, 2H), 1.47 (s, 9H), 0.92 (t, J=7.5 Hz, 1H), 0.88–0.87 (m, 1H); HRMALDI–FTMS (DHB) m/z 348.1600 ($M+H^+$, $C_{22}H_{21}NO_3$ requires 348.1594). Compound (+)-**35**: $[\alpha]_D^{23}$ +75 (*c* 0.1, $CHCl_3$); (−)-**35**: $[\alpha]_D^{23}$ −75 (*c* 0.1, $CHCl_3$).

4.27. *seco*-*iso*-CNI-TMI (36)

A sample of **35** (1.55 mg, 5.5 μmol) was treated with 4 N HCl/EtOAc (100 μL) and stirred at 23 °C for 1 h. The solvent was removed under a stream of N_2 and dried under high vacuum for 30 min. The gray residue was dissolved in DMF (60 μL) and treated with 5,6,7-trimethoxyindole-2-carboxylic acid[28] (1.37 mg, 5.5 μmol) and EDCI (3.15 mg, 16 μmol). The mixture was stirred under Ar at 23 °C for 18 h in the absence of light before the solvent was removed under a stream on N_2. PTLC (SiO_2, 20×20 cm, 50% EtOAc–hexanes) afforded **36** (1.6 mg, 57%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (br s, 1H), 9.51 (s, 1H), 8.68 (s, 1H), 8.33 (d, J=8.8 Hz, 1H), 8.29 (d, J=7.4 Hz, 1H), 7.94 (d, J=7.4 Hz, 1H), 7.68 (d, J=8.8 Hz, 1H), 7.60 (t, J=7.4 Hz, 1H), 7.54 (t, J=7.4 Hz, 1H), 6.74 (s, 1H), 6.54 (s, 1H), 4.71 (app d, J=9.9 Hz, 1H), 4.60 (app t, J=8.1 Hz, 1H), 4.46 (m, 1H), 4.18 (s, 3H), 4.00 (s, 3H), 3.87 (s, 3H), 3.69 (m, 1H), 3.24 (t, J=11.4 Hz, 1H); IR (film) ν_{max} 3411, 2959, 1591, 1454, 1412, 1318, 1260, 1107, 1050, 803 cm^{-1}; HRMALDI–FTMS (DHB) m/z 516.1430 (M^+, $C_{29}H_{25}ClN_2O_5$ requires 516.1452). Compound (1*S*)-**36**: $[\alpha]_D^{23}$ +17 (*c* 2.0, CH_2Cl_2); (1*R*)-**36**: $[\alpha]_D^{23}$ −17 (*c* 1.0, CH_2Cl_2).

4.28. *iso*-CNI-TMI (37)

A sample of **36** (7.1 mg, 13.7 μmol) was dissolved in freshly distilled CH_3CN (140 μL) under Ar. Anhydrous DBU (10 μL, 68 μmol) was added at 23 °C, and the mixture was stirred for 1 h. The reaction mixture was then concentrated under a stream of N_2 and applied directly to PTLC (SiO_2, 10×20 cm, 50% EtOAc–hexanes) to afford **37** (4.0 mg, 60%) as a white solid. ^{1}H NMR δ 10.50 (br s, 1H), 8.55 (d, J=8.2 Hz, 1H), 8.06 (s, 1H), 7.85–7.80 (m, 1H), 7.70–7.65 (m, 3H), 7.17 (s, 1H), 6.04 (s, 1H), 6.90 (s, 1H), 4.18 (s, 3H), 4.00 (s, 3H), 3.85 (s, 3H), 3.70 (d, J=7.5 Hz, 1H), 3.65 (m, 2H), 0.90 (s, J=7.5 Hz, 1H); HRMALDI–FTMS (DHB) m/z 481.1759 ($M+H^+$, $C_{29}H_{24}N_2O_5$ requires 481.1758). Compound (+)-**37**: $[\alpha]_D^{23}$ +125 (*c* 0.1, THF); (−)-**37**: $[\alpha]_D^{23}$ −120 (*c* 0.1, THF).

4.29. Aqueous solvolysis reactivity: pH 3

Compounds **22** and **35** (50 μg) were dissolved in CH_3OH (1.5 mL) and mixed with pH 3 aqueous buffer (1.5 mL). The buffer contained 4:1:20 (v:v:v) 0.1 M citric acid, 0.2 M Na_2HPO_4, and deionized H_2O, respectively. Immediately after mixing, the UV spectra of the solution were measured against a reference solution containing CH_3OH (1.5 mL) and the aqueous buffer (1.5 mL), and this reading was used as the initial absorbance value. The solution was stoppered, protected from light, and allowed to stand at 25 °C. The UV spectra were recorded at regular intervals until a constant value was obtained for the long-wavelength absorbance. The increase of the absorbance at 230 nm was monitored. The solvolysis rate constants for were determined from the slope of the line obtained from the least-squares treatment (r^2=0.98) of the plot of $\ln[(A_f-A_i)/(A_f-A)]$ versus time.

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