In a typical reaction, the amino amide (0.5 mmol) in methanol (10 mL) was added dropwise over 5 min to the stirred solution of vinyl tricarbonyl reagent 1 (0.5 mmol) in methylene chloride (40 mL). After 30 min, the solvent was removed in vacuo, leaving a clear oil which was dissolved in methylene chloride (40 mL). Pyridinium *p*-toluenesulfonate (0.5 mmol) in methylene chloride (10 mL) was added to the solution, and the reaction was heated to reflux. After 25 min to 1 h, the solution was allowed to cool to room temperature, diluted with 20 mL of methylene chloride, and then washed twice with 20-mL portions of saturated $NaHCO_3$ (aqueous) solution. The aqueous layers were extracted with methylene chloride, and the organic solutions were combined, washed successively with water and brine, dried over Na_2SO_4, and then concentrated to yield a yellow oil. The crude material was purified by flash chromatography (ethyl acetate–methylene chloride) to yield the product.

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Supplementary Material Available: Complete spectroscopic and combustion analytical data for **6**, **7**, and **8**. X-ray crystallographic and spectroscopic data for compound **9** (11 pages). Ordering information is given on any current masthead page.

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Articles

Synthesis of *N*-(*tert*-Butyloxycarbonyl)-CBI, CBI, CBI-CDPI$_1$, and CBI-CDPI$_2$: Enhanced Functional Analogues of CC-1065 Incorporating the 1,2,9,9a-Tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (CBI) Left-Hand Subunit

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Full details of the synthesis of *N*-(*tert*-butyloxycarbonyl)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one [*N*-BOC-CBI (**6**)] constituting a more stable functional analogue of the CC-1065 left-hand subunit are described. The resolution of an immediate CBI synthetic precursor, (+)- and (−)-**14**, the unambiguous establishment of the absolute configuration, and the incorporation of (±)-, (+)-, and (−)-**14** into the synthesis of racemic and optically active CBI (**5**), *N*-BOC-CBI (**6**), CBI-CDPI$_1$ (**7**), and CBI-CDPI$_2$ (**8**), enhanced functional analogues of CC-1065, are detailed. The chemical solvolytic behavior of the CBI-based agents and their cytotoxic properties are described.

(+)-CC-1065 (**1**, NSC-298223), an antitumor antibiotic isolated from cultures of *Streptomyces zelensis*, possesses exceptionally potent in vitro cytotoxic activity, broad spectrum antimicrobial activity, and confirmed in vivo antitumor activity.[2,3] In a series of extensive investigations the site and mechanism of the (+)-CC-1065 antitumor activity have been related to its covalent alkylation of sequence-selective minor groove sites [5′-d(A/GNTTA)-3′ and 5′-d(AAAAA)-3′] that has been demonstrated to proceed by 3′-adenine N-3 alkylation of the electrophilic cyclopropane present in the left-hand subunit (CPI).[4,5] The initial demonstration that (+)-*N*-acetyl-CPI exhibits a comparable albeit substantially less intense (ca. 10000×) sequence-selective alkylation of DNA has led to the conviction that the left-hand subunit of (+)-CC-1065 plays a dominant role in controlling the properties of the agents.[6] However, the demonstration that simplified agents including CDPI$_3$ methyl ester[7] exhibit a substantial preference for A-T rich noncovalent minor groove binding[8] at-

(1) (a) National Institutes of Health research career development award recipient, 1983–1988 (CA 01134). Alfred P. Sloan Foundation research fellow, 1985–89. (b) On sabbitcal from Kyorin Pharmaceutical Co., Ltd., Tochigi, Japan, 1988–1990.
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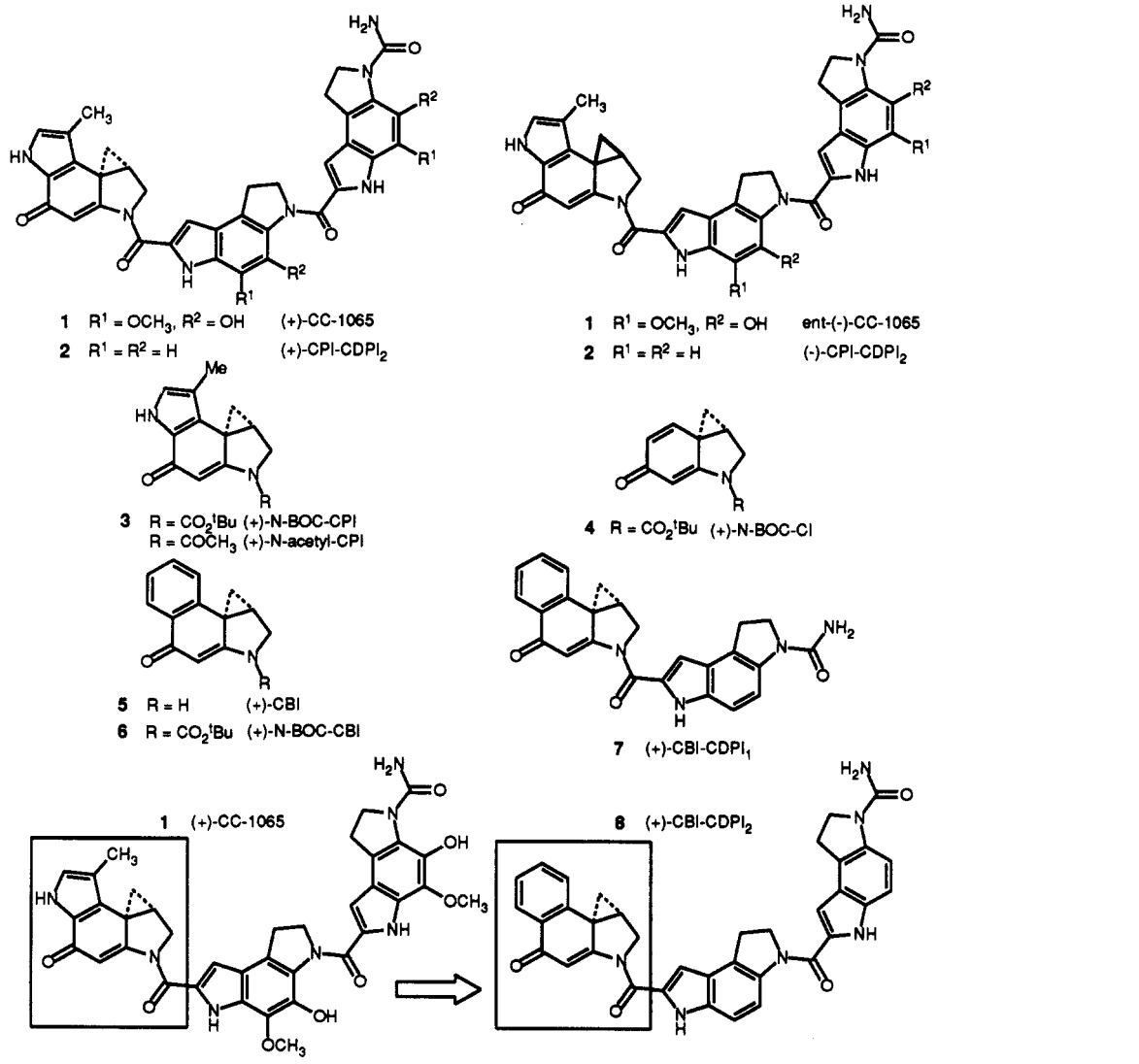
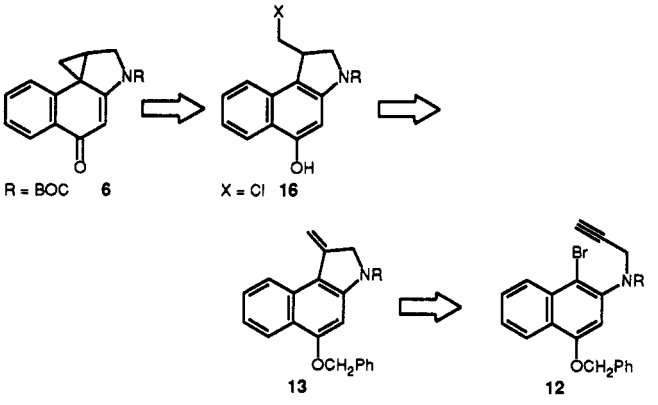


Figure 1.

tributable to the preferential stabilization of a noncovalent complex within the narrower, sterically more accessible. A-T rich minor groove,[8,9] and the recent report[10] of the readily distinguished (+)-*N*-BOC-CPI (**3**) versus (+)-CC-1065 profile of covalent alkylation have suggested that CC-1065 is best represented as a selective[5] alkylating agent superimposed on the $CDPI_3$ skeleton and derives its properties in part from its effective delivery to accessible adenine N-3 alkylation sites. As such, the sequence-selectivity of the (+)-CC-1065 covalent alkylation is embodied only in part in the reactivity of the CPI left-hand subunit, and the noncovalent binding selectivity of (+)-CC-1065 appears to further restrict the number of available alkylation sites. Thus, in recent efforts, we[3b,7,8,10-16] and

Scheme I



others[3-6,17-19] have detailed studies to define the fundamental features of the agents responsible for their DNA

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(14) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 4796.

(15) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 1321.

(16) Boger, D. L.; Ishizaki, T.; Wysocki, R. J., Jr.; Munk, S. A.; Kitos, P. A.; Suntornwat, O. *J. Am. Chem. Soc.* **1989**, *111*, 6461. Boger, D. L.; Ishizaki, T. *Tetrahedron Lett.* **1990**, *31*, 793.

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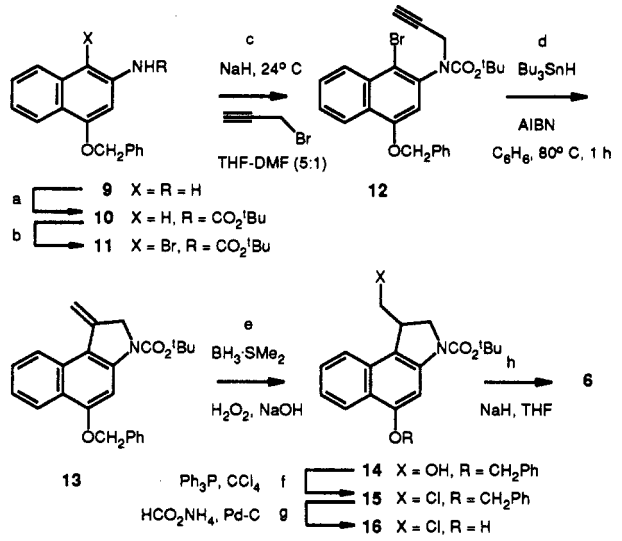
Scheme II

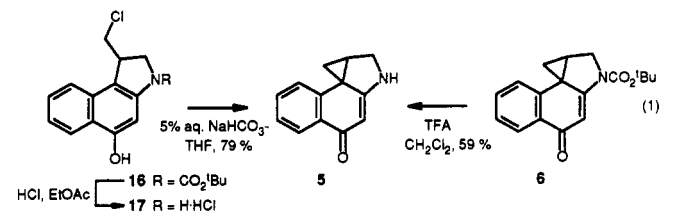


binding affinity and specificity. Herein, we detail studies that apply this understanding to the design, synthesis, and preliminary evaluation of a more accessible and enhanced series of functional analogues of (+)-CC-1065 (1) (Figure 1). In anticipation that structural variations in the left-hand subunit of the agents would *not* preclude a relevant adenine N-3 alkylation, the comparable heats of reaction for the CPI-adenine and CBI-adenine covalent alkylation suggested that the fundamental features of this DNA covalent alkylation characteristic of (+)-CC-1065 and the CPI-based agents would be embodied in the more accessible CBI-based agents in a near equivalent manner.[16]

Synthesis of CBI (5) and *N*-BOC-CBI (6). At the onset of the efforts, two related approaches to the preparation of the CBI nucleus were envisioned and rested on the use of a final Ar-3′ intramolecular alkylation[20] of an appropriately C-1 functionalized benzindoline **16**, (Scheme I). This in turn was anticipated to be derived indirectly from **13** or **22**, the products of a 5-*exo-dig* aryl radical–alkyne or self-terminating 5-*exo-trig* aryl radical–alkene free-radical cyclization, respectively, following protocols developed in preceding efforts.[11,14]

Accordingly, alkylation of the sodium salt of **11**[21] with 3-bromopropyne provided **12**, the immediate precursor for implementation of a 5-*exo-dig* aryl radical–alkyne cyclization[22] (Scheme II). Treatment of **12** with tri-*n*-butyltin hydride (2.0 equiv, 0.2 equiv of AIBN, benzene, 80 °C, 1 h)[14] provided the unstable 1-methylenebenzindoline **13** that was subjected to the conditions of hydroboration–oxidation to provide **14**. Attempts to purify **13** by standard chromatographic techniques (SiO_2, Al_2O_3, Florisil) led to partial or complete isomerization of **13** to the corresponding 1-methylbenz[*e*]indole **18**.[23] Moreover, this sequence of reactions proved sensitive to the reaction time and concentration of tri-*n*-butyltin hydride (40–51%, 0.15 M) and ultimately was improved substantially (0.09 M, 62% from **12**) but requires attentive adherence to the reaction conditions we have detailed.[24] Conversion of **14** to the primary chloride **15** (PPh_3, CCl_4),[25] two-phase, transfer catalytic hydrogenolysis (HCO_2NH_4, 10% Pd–C)[26] of the benzyl ether that proceeded without competitive hydrogenolysis of the primary chloride, provided **16** and a convenient, stable storage intermediate in route to **5–8**. The Ar-3′ alkylation of **16** was promoted by treatment of **16** with sodium hydride (3.0 equiv, THF, 0–24 °C, 2 h) and cleanly provided *N*²-(*tert*-butyloxycarbonyl)-CBI (**6**, 93%). This procedure for pomoting the closure of **16** proved much more successful than reactions conducted at room temperature (NaH, 24 °C, 2.5 h, 74%) and more reliable than alternative procedures including direct Mitsunobu activation of **14** (X = OH, R = H) toward Ar-3′ alkylation.[3b,c]

Similarly, the parent agent **5**, 1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (CBI), was prepared from **16** by acid-catalyzed removal of the *tert*-butyloxycarbonyl protecting group and subsequent base-catalyzed Ar-3′ alkylation conducted in a two-phase aqueous–tetrahydrofuran solvent system (5% aqueous $NaHCO_3$–THF, 1:1, 25 °C, 1.5 h, 79%). Treatment of **17** with mild base under aprotic conditions (Et_3N, THF, 24 °C, 23 h; $NaHCO_3$, DMF, 24 °C, 24 h) provided **5** in much lower yields. Surprisingly, acid-catalyzed deprotection of **6** employing trifluoroacetic acid in dichloromethane (0 °C, 1.5 h) provided CBI (**5**) *directly* in acceptable conversions (59%) without preferential solvolysis of the spirocyclic cyclopropylcyclohexadienone. *This unanticipated chemical behavior of* **6** *attests to the stability of the agents and the modest electrophilic character they possess.*



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(21) 3-Amino-1-(benzyloxy)naphthalene (**9**) was prepared from commercially available 1,3-dinitronaphthalene: (1) 2 equiv of $NaOCH_3$, CH_3OH, 105 °C, 7 h: cf. Hanker, J. S.; Katzoff, L.; Aronson, L. D.; Seligman, M. L.; Rosen, H. R.; Seligman, A. M. *J. Org. Chem.* **1965**, *30*, 1779; (2) 1:1 48% aqueous HBr–HOAc, reflux, 6 h, 91%; (3) 1.1 equiv of $C_6H_5CH_2Br$, 2.1 equiv of K_2CO_3, 0.03 equiv of Bu_4NI, DMF, 25 °C, 3 h, 97%; (4) Al(Hg) prepared from 26 molar equiv of Al, 10% aqueous THF, 25 °C, 2.5 h, 99%.

(22) Curran, D. P. *Synthesis* **1988**, 417 and 489. Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: Oxford, 1986. Hart, D. J. *Science* **1984**, *223*, 883. See also: Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. Abeywickrema, A. N.; Beckwith, A. L. J.; Gerba, S. *J. Org. Chem.* **1987**, *52*, 4072.

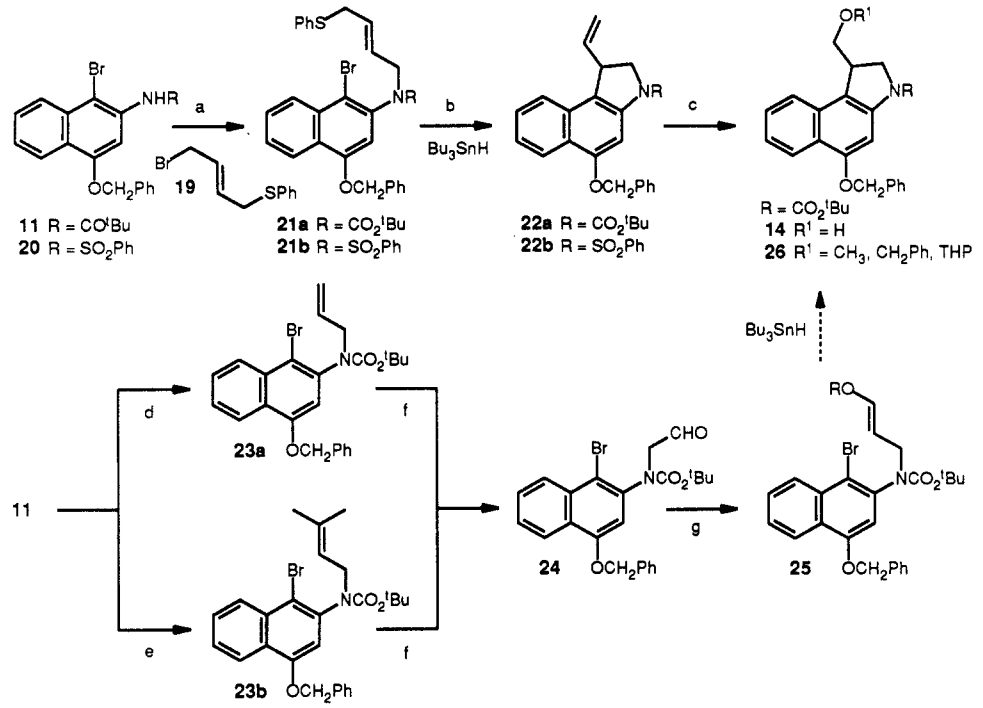
(23) Column chromatography of the reaction mixture containing **13** on Florisil (EtOAc–hexane) provided **18** (33–51%). Chromatography on alumina did provide **13** albeit in 23–32%. For **18**: white solid; mp 181 °C dec; ^1H NMR ($CDCl_3$, 200 MHz, ppm) 8.45 (d, 1 H, J = 7.7 Hz, C9-H), 8.43 (d, 1 H, J = 7.7 Hz, C6-H), 8.02 (s, 1 H, C4-H), 7.3–7.6 (m, 8 H, C2-H, C7-H, C-8H, $CH_2C_6H_5$), 5.32 (s, 2 H, $CH_2C_6H_5$), 2.66 (s, 3 H, CH_3), 1.61 (s, 9 H, $OC(CH_3)_3$); IR (KBr) ν_{max} 2976, 1720, 1590, 1422, 1400, 1372, 1362, 1336, 1312, 1260, 1234, 1160, 1118, 1092, 758 cm^{-1}; EIMS *m/e* (relative intensity) 387 (M^+, 28), 331 (12), 240 (39), 91 (72), 57 (100); CIMS (isobutane) *m/e* (relative intensity) 388 ($M^+ + H^+$, 100).

(24) Higher concentrations of tri-*n*-butyltin hydride (0.15 M) or longer reaction times (2 h, reflux) result in decreased conversions (51%, 55%) due to competitive generation of **18** and additional side reactions.

(25) Hooz, J.; Gilani, S. S. H. *Can. J. Chem.* **1968**, *46*, 86.

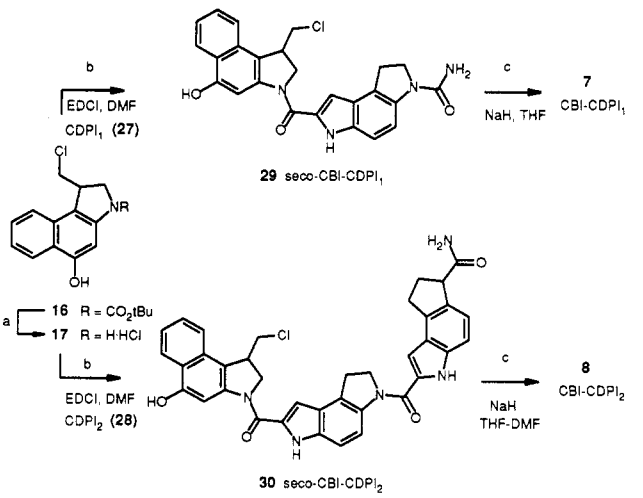
(26) Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1988**, 91. Bieg, T.; Szeja, W. *Synthesis* **1985**, 76.

Scheme III



In initial efforts, a complementary approach to the C-1 functionalized benzindolines **14–15** based on the implementation of a self-terminating 5-*exo-trig* aryl radical–alkene free radical cyclization[11-14,22,27,28] and subsequent oxidative cleavage of a resulting 1-vinyl-1,2-dihydro-3*H*-benz[*e*]indole was explored (Scheme III). Alkylation of the sodium salt of **11** and **20** with phenyl 4-bromo-2-butenyl sulfide (**19**)[12] provided **21a,b**, the immediate precursors for used in the free-radical cyclization. The self-terminating 5-*exo-trig* aryl radical–alkene cyclizations of **21a,b**, were effected by treatment with tri-*n*-butyltin hydride (2.2 equiv, cat. AIBN, benzene, 80 °C)[12,14] and afforded **22a,b** (75%). Ozonolysis of **22a** or **22b** under low-temperature conditions (−78 °C, ethanol) with careful monitoring of the consumption of ozone[29,30] followed by immediate reduction of the crude ozonides (5 equiv of $NaBH_4$, ethanol, −78 °C to 25 °C) provided only trace amounts of the desired alcohols **14** (10–20%) and evidence of predominant cleavage of the benzyl ether and additional oxidation of the naphthalene nucleus. Attempts to circumvent the problematic ozonolysis employing alternative reagents ($KMnO_4$,[31] OsO_4–$NaIO_4$[32]) and stepwise reaction sequences (OsO_4/pyridine–tBuOH, *m*CPBA, NBS–H_2O) did not prove successful. Consequently, the potential of effecting a 5-*exo-trig* aryl radical–alkene cyclization on substrates bearing an appropriately functionalized alkene

Scheme IV



were explored. Alkylation of the sodium salt of **11** with allyl bromide or 1-bromo-3-methyl-2-butene followed by ozonolysis of the carbon–carbon double bond and mild reductive workup (Me_2S) of the crude ozonide provided aldehyde **24**. This proved to be followed by a problematic Wittig reaction for introduction of the functionalized alkene and efforts employing (methoxymethylene)triphenylphosphorane,[33a] ((benzyloxy)methylene)triphenylphosphorane,[33b] and [(2-tetrahydropyranyloxy)-methylene]triphenylphosphorane[33c] under a range of reaction conditions for phosphorane generation and Wittig

(27) Ueno, Y.; Chino, K.; Okawara, M. *Tetrahedron Lett.* **1982**, *23*, 2575. Ueno, Y.; Moriya, O.; Chino, K.; Watanabe, M.; Okawara, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1351. Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564. Dittami, J. P.; Ramanathan, H. *Tetrahedron Lett.* **1988**, *29*, 45. Togo, H.; Kikuchi, O. *Tetrahedron Lett.* **1988**, *29*, 4133.

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(32) Subjection of **22** to the conditions of the Johnson–Lemieux oxidation (catalytic OsO_4, 3.0 equiv of $NaIO_4$, 3:1 acetone–H_2O) served only to consume starting material without productively affording characterizable products. Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

(33) (a) Wittig, G.; Schlosser, M. *Chem. Ber.* **1961**, *94*, 1373. Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128. (b) Tam, T. F.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1980**, 556. (c) Schlude, H. *Tetrahedron* **1975**, *31*, 89.

(34) The single-crystal X-ray structure determination was performed by Dr. P. Fanwick, Department of Chemistry, Purdue University. An ORTEP plot of the (+)-**5** and (−)-(1*S*)-**15** X-ray crystal structures and a summary table of the structure refinement are provided in the supplementary material. Full details may be furnished upon request.

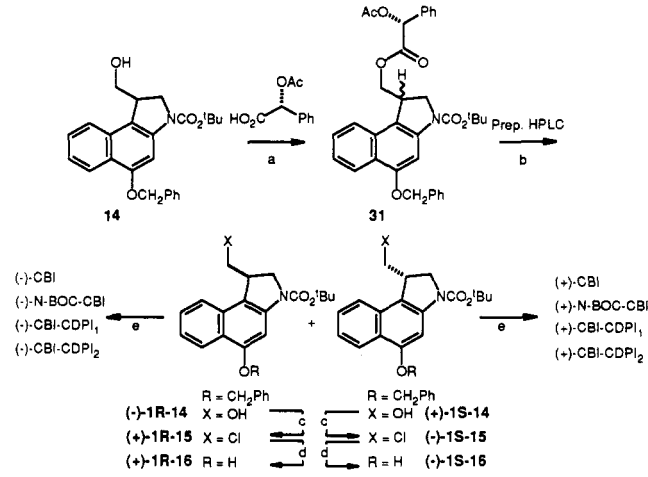
(35) The X-ray structural bond lengths bond angles have been incorporated into the AMBER force field for modeling studies and details may be furnished upon request (DLB), cf. ref 3b.

reaction (NaH, DMF; *n*-BuLi, DME; NaH, DMSO; KO*t*-Bu, dioxane, −45 °C to 100 °C) failed to provide the enol ethers **25** in acceptable conversions for implementation of the aryl radical–alkene 5-*exo-trig* cyclization (**25** → **26**). Consequently, the 5-*exo-dig* aryl radical–alkyne free-radical cyclization approach to **14** (Scheme II) proved most expedient in spite of the potentially problematic 3-methyleneindoline → 3-methylindole isomerization.

Synthesis of CBI-CDPI$_1$ (7) and CBI-CDPI$_2$ (8). Following protocols introduced in the preparation of CPI-derived agents,[3b] CBI (**5**) would not be expected to couple productively with activated derivatives of the carboxylic acids **27** (CDPI$_1$)[7] and **28** (CDPI$_2$).[7] Consequently, pentultimate coupling of **17** with CDPI$_1$/CDPI$_2$ followed by intramolecular Ar-3′ alkylation with introduction of the cyclopropane was anticipated to provide the most effective approach to **7** and **8**. Removal of the *tert*-butyloxycarbonyl protecting group of **16** (3.0 M HCl–EtOAc, 24 °C, 20 min) followed by immediate coupling of the unstable indoline hydrochloride **17**[36] with CDPI$_1$ (**27**)[7] in the presence of [3-(dimethylamino)-propyl]ethylcarbodiimide (3 equiv EDCI, 5.0 equiv $NaHCO_3$, DMF, 24 °C, 3 h, 86%) provided **29** (Scheme IV). Surprisingly, this reaction could be conducted without the addition of external base (8 h, 24 °C) and cleanly provided **29** (69%) without a trace of contaminant, subsequent cyclization product.[37] The final Ar-3′ spirocyclization was affected by treatment of **29** with sodium hydride (3.0 equiv, THF–DMF, 6:1, 0 °C, 1 h) and afforded **7** in 74%. This procedure for closure of **29** proved much more effective when conducted at 0 °C versus 24 °C (45–67%) and substantially better than when conducted employing the protocol[17] of treatment with Et_3N–CH_3CN–H_2O (1:1:1, 24 °C, 4 h, 42%).[38] In a similar manner, CBI-CDPI$_2$ (**8**) was prepared by coupling the unstable hydrochloride salt of **17**[36] with CDPI$_2$[7] (**28**, 3 equiv of EDCI, DMF, 24 °C, 5 h, 78%)[37] followed by spirocyclization effected by treatment of **30** with sodium hydride (2 equiv, THF–DMF, 2:1 0 °C, 1 h, 84%), and this procedure proved more reliable than that of treatment of **30** with Et_3N–CH_3CN–H_20 (1:1:1, 25 °C, 4 h, 45%).[17,38] Attempts to couple **17** with CDPI$_2$ as suspensions in *N*,*N*-dimethylformamide[7] in the presence of base (5 equiv of $NaHCO_3$ or 5 equiv of K_2CO_3) provided competitive generation of CBI (**5**, 43–61%) and may be attributed to the facility with which the Ar-3′ alkylation proceeds[38] relative to the sluggish coupling reaction.

Resolution of a CBI Precursor: (+)- and (−)-14. Esterification of the primary alcohol **14** with (*R*)-(−)-*O*-acetylmandelic acid (1.5 equiv, 1.7 equiv of EDCI, 0.1 equiv of 4-DMAP) in dichloromethane cleanly provided the diastereomeric esters **31** (81%) (Scheme V). Preparative chromatographic separation of **31** (10 mm × 25 cm, 10 μm of SiO_2, 2.5 mL/min, 2% EtOAc–CH_2Cl_2)[39] afforded the purified diastereomeric esters, α = 1.09. This procedure routinely provided both (1*S*,2′*R*)-**31** and (1*R*,2′*R*)-**31** of >99% diastereomeric purity (85% recovery) as determined by HPLC and ^1H NMR analysis of the separated diastereomers.[39] Base-promoted hydrolysis (5.0 equiv of 4 N aqueous LiOH, THF–MeOH, 3:2 24 °C) provided the enantiomeric alcohols (+)-(1*S*)-**14** and (−)-(1*R*)-**14** in 97%

Scheme V



yield. Independent conversion of (+)-(1*S*)-**14** and (−)-(1*R*)-**14** to the corresponding chlorides, (−)-(1*S*)-**15** and (+)-(1*R*)-**15**, followed by two phase, transfer catalytic hydrogenolysis provided (−)-(1*S*)-**16** and (+)-(1*R*)-**16**, respectively. Subsequent incorporation of (−)- and (+)-**16** into (+)- and (−)-**6**, (+)- and (−)-**5**, (+)- and (−)-**7**, and (+)- and (−)-**8**, respectively, followed the protocols detailed in Schemes II and IV.

The initial, tentative assignment of the absolute configuration to the agents rested with the selective, potent cytotoxic activity of the (+)-enantiomers [e.g., (+)-CBI-CDPI$_1$ >> (−)-CBI-CDPI$_1$][40] to which the 8b*R*,9a*S* absolute configuration was assigned corresponding to the natural configuration of (+)-CC-1065, and this assignment was strongly supported by the DNA binding profile of the agents [e.g., (+)-CBI-CDPI$_1$ and (+)-CBI-CDPI$_2$ ≡ (+)-CC-1065 ≠ (−)-CBI-CDPI$_2$ ⧈ (−)-CPI-CDPI$_2$].[41] A single-crystal X-ray structure analysis of (+)-**5** was conducted with the intent of unambiguously establishing the 8b,9a absolute configuration.[34] Although the X-ray crystal resolution proved insufficient to unambiguously establish the absolute configuration, it did establish the structure of **5**.[34,35] The unambiguous confirmation of the assignment of the absolute configuration was established in a single-crystal X-ray structure analysis of (−)-(1*S*)-**15**.[34,35]

Chemical Solvolytic Reactivity of CBI Derivatives. In preceding studies, the rate of acid-catalyzed solvolysis of N^2-substituted derivatives of the CPI-segment of CC-1065 was correlated with capabilities for DNA alkylation (**3**, R = COR > R = CO_2R > R = SO_2R).[4] Thus, the nature of the N^2-substituent[4,6] or the inherent reactivity of the electrophile[3b,16] have been suggested to influence the DNA binding properties of the agents. Like CPI,[4] the CBI-based agents proved stable in aqueous solution at pH of 7 and exhibit no significant decomposition over two week period. Consistent with expectations, *N*-BOC-CBI (**6**, $t_{1/2}$ = 133 h, k = (1.45 ± 0.01) × 10^{-6} s^{-1}) proved substantially more stable than *N*-BOC-CPI (**3**, $t_{1/2}$ = 36.7 h,

(36) The hydrochloride salt of **17** immediately discolors upon exposure to air.

(37) Biological testing samples of **29–30** were prepared employing this procedure for coupling without evidence of contaminant **7–8**.

(38) The resulting major side product is generation (**17** → **5**) or hydrolytic liberation (**7–8** → **5**) of CBI (**5**).

(39) HPLC separation and analysis was performed on an Alltech 10 μm SiO_2 chromatography column (10 mm × 25 cm), and the effluant was monitored at 280 nm, supplementary material.

(40) The initial tentative assignment of the absolute configurations were based on the consistent observation of the selective, more potent cytotoxic activity of (+)-**6**, (+)-**7**, and (+)-**8** and their seco precursors to which the 1*S* absolute configuration (natural configuration of (+)-CC-1065) was assigned. The noted differences in the DNA binding properties of (−)-CBI-CDPI$_1$/CBI-CDPI$_2$ versus (+)-CBI-CDPI$_1$/CBI-CDPI$_2$ and (+)-CC-1065 were in agreement with this assignment of absolute configuration and provided strong, albeit not unambiguous, confirmation of the assignment.[41] For the unambiguous assigment of the absolute configuration (+)-CC-1065, see: Martin, D. G.; Kelly, R. C.; Watt, W.; Wicnienski, N.; Mizsak, S. A.; Nielsen, J. W.; Prairie, M. D. *J. Org. Chem.* **1988**, *53*, 4610.

(41) Munk, S. A.; Boger, D. L., unpublished observations.

Table I

	N-BOC-CPI (3)[a]	N-BOC-CI (4)[b]	N-BOC-CBI (6)[c]	CBI (5)[c]
IR, C=O (cm^{-1})	1725, 1570	1705, 1618	1718, 1628, 1602	1610, 1586
UV, λ_{max} nm (ϵ)	344 (12000) 278 (17000)	294 (14000) 258 (21000)	300 (19000) 264 (5700)	316 (11000)
^{f}k (s^{-1}, pH = 3)	$(5.26 \pm 0.08) \times 10^{-6}$	$(1.98 \pm 0.06) \times 10^{-2}$	$(1.45 \pm 0.01) \times 10^{-6}$	$(2.07 \pm 0.33) \times 10^{-7}$
$^{f}t_{1/2}$, pH = 3	36.7 h (38.5 h)[a]	35 s	133 h	930 h
pH = 7	stable	5.24 h	stable	stable
rel $t_{1/2}$	1.0	0.000 26	3.6	25

	CC-1065 (1)[d]	CBI-CDPI$_1$ (7)[e]	CBI-CDPI$_2$ (8)[e]	CPI-CDPI$_2$ (2)[g]
IR, C=O (cm^{-1})	1634, 1577	1654, 1648, 1637, 1626, 1602	1655, 1647, 1636, 1618, 1580	1635, 1605, 1576
UV, λ_{max} nm (ϵ)	364 (49100) 258 (31200) 236 (36100)	340 (33000) 270 (16000)	338 (41000) 272 (24000)	355 (34000) 318 (40000)
$^{f}t_{1/2}$, pH = 7	stable	stable	stable	stable

[a] UV (CH_3OH), IR (Nujol), and $k = 5 \times 10^{-6}$ s^{-1} (pH = 3) taken from ref 4a. [b] UV (THF), IR (KBr) taken from ref 12. [c] UV (THF), IR (film). [d] UV (dioxane), IR (KBr) taken from refs 2 and 14. [e] UV (DMF), IR (KBr). [f] pH = 3, 50% buffer–CH_3OH, buffer is 4:1:20 (v:v:v) 0.1 M citric acid, 0.2 M Na_2HPO_4, and water, respectively. pH = 7, 50% H_2O–CH_3OH. [g] UV (CH_3OH), IR (KBr) taken from refs 14 and 18.

$k = (5.26 \pm 0.08) \times 10^{-6}$ s^{-1}) to solvolysis at a pH of 3 (Table I). Thus at a pH of 3, *N*-BOC-CBI exhibits a half-life 3.6 times greater than that of *N*-BOC-CPI. The solvolysis of the CBI-based agents was followed spectrophotometrically with the disappearance of the long-wavelength absorption band of the CBI chromophore (314–336 nm) or with the appearance of a *seco*-*N*-BOC-CBI short wavelength absorption band (256 nm) by ultraviolet spectroscopy. The chromatographic properties and ultraviolet spectra of the solvolyzed agents proved identical with those of the *seco*-*N*-BOC-CBI derivatives and proved consistent with the previous observation of two solvolysis products that result from methanol and water addition to the less hindered cyclopropane carbon of **6**.[4] Like CPI itself, CBI (**5**) proved stable to solvolysis even at a pH of 3 ($t_{1/2}$ = ca. 930 h, $k = (2.07 \pm 0.33) \times 10^{-7}$ s^{-1}) and presumably results from preferential N-protonation versus carbonyl O-protonation that is required for solvolysis catalysis.[4]

In Vitro Cytotoxic Activity. The results of the in vitro cytotoxic evaluation of the CBI-based agents are summarized in Table II and provide considerably more insight into the properties of the agents than the initial evaluation of the racemic agents permitted.[16] The unanticipated results are especially striking in that the 8b*R*,9a*S* enantiomers of CBI-CDPI$_1$ and CBI-CDPI$_2$ proved to be 4 times *more* potent than (+)-CC-1065 (**1**) and the related CPI-based agents.[10] Similarly, (+)-*N*-BOC-CBI (**6**) proved to be 4 times more potent than (+)-*N*-BOC-CPI (**3**) and substantially less active than (+)-CBI-CDPI$_1$ (**7**) and (+)-CBI-CDPI$_2$ (**8**). The cytotoxic potency of (+)-CBI-CDPI$_1$ (**7**) and (+)-CBI-CDPI$_2$ (**8**) proved remarkably high (5 pM, 2–3 pg/mL), nearly indistinguishable from one another, and comparable in potency to the most potent cytotoxic agents identified to date including the esperamycin/calicheamicin agents. Like obervations made in a study of the CPI-based agents,[10] the 8b*R*,9a*S*-CBI enantiomers that possess the corresponding absolute configuration of natural (+)-CC-1065 proved consistently more potent than the corresponding unnatural enantiomers [e.g. (+)-**6** 12× (−)-**6**] and, unlike the indistinguishable enantiomeric pairs of (+)-CPI-CDPI$_2$/(−)-CPI-CDPI$_2$ and (+)-CC-1065/(−)-*ent*-CC-1065, (+)-CBI-CDPI$_2$ proved to be approximately 8 times more potent than (−)-CBI-CDPI$_2$. Nonetheless, this still places (+)-CC-1065 only 2 times more potent than (−)-CBI-CDPI$_2$. In addition, the precursor *seco*-1*R**-, 1*S*-, and 1*R*-chloromethyl agents **16**, **29**–**30** were found to possess cytotoxic activity at levels indistinguishable from those of the CBI agents **6**–**8** and presumably suffer Ar-3′ alkylation ring closure in vitro.[4,14]

Table II. In Vitro Cytotoxic Activity, L1210[a]

agent	IC_{50}, pg/mL, pM
(+)-**3**, *N*-BOC-CPI	100000, 330000
(+)-**6**, *N*-BOC-CBI	23000, 77000
(−)-**6**	280000, 940000
(±)-**7**, CBI-CDPI$_1$	6, 10
(+)-**7**	2, 5
(−)-**7**	≥160, ≥380
(±)-**8**, CBI-CDPI$_2$	13, 20
(+)-**8**	3, 5
(−)-**8**	28, 40
(+)-**1**, CC-1065	11, 20
(−)-**1**	13, 20
(+)-**2**, CPI-CDPI$_2$[b]	12, 20
(−)-**2**	13, 20

[a] IC_{50} = inhibitory concentration for 50% cell growth relative to untreated controls, L1210 mouse lymphocytic leukemia cell culture, see: Boger, D. L.; Yasuda, M.; Mitscher, L. A.; Drake, S. D.; Kitos, P. A.; Thompson, S. C. *J. Med. Chem.* **1987**, *30*, 1918. [b] Taken from ref 14.

Thus, in summary: (1) the CBI-based agents exhibit potent cytotoxic activity that has proven more potent (ca. 4×) than that of the corresponding CPI-based agents, (2) like the CPI-based agents, the 8b*R*,9a*S* (+)-enantiomers of the CBI-based agents are selectively more potent than the 8b*S*,9a*R* (−)-enantiomers and, unlike the indistinguishable (+)- and (−)-CPI-CDPI$_2$/(+)- and (−)-CC-1065 enantiomeric pairs, (+)-CBI-CDPI$_2$ is significantly (8×) more potent than (−)-CBI-CDPI$_2$, (3) (+)-CBI-CDPI$_1$ proved indistinguishable from (+)-CBI-CDPI$_2$ *and* much more potent than (−)-CBI-CDPI$_1$, (4) the *seco*-1-chloromethyl CBI-based agents possess cytotoxic activity indistinguishable from that of the CBI-based agents and is derived presumably from Ar-3′ closure to the parent agents, and (5) the cytotoxic potency of the CBI-based agents follow the relative trends established in DNA binding studies [(+)-CBI-CDPI$_2$ ≅ (+)-CBI-CDPI$_1$ > (−)-CBICDPI$_2$ >> (−)-CBI-CDPI$_1$ >> (+)- and (−)-*N*-BOC-CBI; (+)-CBI-CDPI$_2$ > (+)-CPI-CDPI$_2$ (2–10×) > (+)-CI-CDPI$_2$ (100–1000×); selectivity and intensity], although the results of the latter studies will necessarily be reported elsewhere.[41]

An Appraisal of a Previously Proposed Relationship between Electrophile Reactivity and Cytotoxic Potency and Establishment of an Alternative Relationship. As detailed in Table II the results of the in vitro cytotoxic evaluation of the optically active agents unexpectedly revealed that (+)-CBI-CDPI$_1$ (**7**) and (+)-CBI-CDPI$_2$ (**8**) are 4 times more potent than (+)-CC-1065 (**1**) and the natural enantiomers of the corresponding CPI-

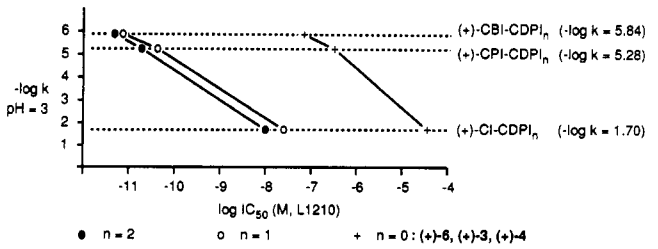
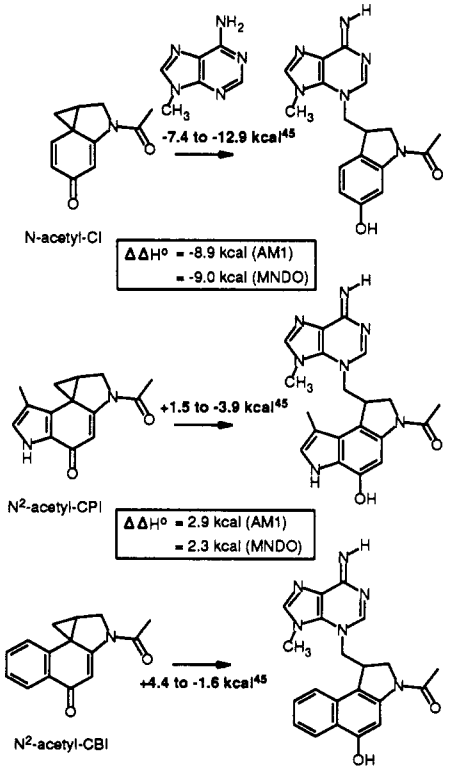


Figure 2.

based agents including (+)-CPI-CDPI$_2$ (**2**).[10] This enhanced potency of (+)-**7** and (+)-**8** relative to (+)-CC-1065 is not in agreement with the prediction derived from the proposed relationship that the productive DNA binding properties of the agents and the resulting expression of cytotoxic potency are related *directly* to the reactivity of the electrophile as extrapolated from acid-catalyzed solvolysis rates[4-6] and *directly* related to the agent's rate of acid-catalyzed covalent alkylation of DNA.[6] In fact, a comparison of the in vitro cytotoxic potency of (+)-CI-CDPI$_n$,[12] (+)-CPI-CDPI$_n$,[10,14] and (+)-CBI-CDPI$_n$ and the corresponding rates of acid-catalyzed solvolysis of *N*-BOC-CI (**4**), *N*-BOC-CPI (**3**), and *N*-BOC-CBI (**6**) (Table I) suggests that the inverse relationship between electrophile reactivity and cytotoxic potency may constitute a more relevant relationship (Figure 2). Although only the data for L1210 cytotoxic activity is presented in Figure 2, the evaluation of the nine agents in three additional cell lines (B16, P388, KB) provided comparable results. This presumably results from more selective and productive (agent availability) covalent modification of DNA although the generality and precise origin of this relationship is under present investigation.[42-45]

(42) The relative reactivity of such agents may be established through computational studies (AM1,[43] MNDO[44]).



(43) AM1: Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 902.
(44) MNDO: Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.

Experimental Section[46]

***N*-(*tert*-Butyloxycarbonyl)-4-(benzyloxy)-2-naphthylamine (10).** A solution of 4-(benzyloxy)-2-naphthylamine[21] (**9**, 1.33 g, 5.33 mmol) in 40 mL of dioxane under nitrogen was treated with di-*tert*-butyl dicarbonate (2.35 g, 10.8 mmol, 2.0 equiv), and the reaction mixture was warmed at 95 °C under nitrogen for 3 h. The reaction mixture was cooled, and the solvent was removed in vacuo. The oily residue was crystallized from hexane to afford 1.67 g of **10** as cream-colored, fine needles. Flash chromatography of the recrystallization mother liquor (2.8 × 12 cm SiO_2, 10% EtOAc–hexane) provided an additional 0.12 g (total yield 96%, 1.79 g, 1.86 g theoretical) of **10**: mp 137.5 °C sharp (hexane, needles); ^{1}H NMR ($CDCl_3$, 200 MHz, ppm) 8.23 (d, 1 H, J = 8.1 Hz, C5-H), 7.70 (d, 1 H, J = 7.7 Hz, C8-H), 7.3–7.6 (m, 8 H, C1-H, C6-H, C7-H, $CH_2C_6H_5$), 7.07 (d, 1 H, J = 1.7 Hz, C3-H), 6.61 (br s, 1 H, NH), 5.24 (s, 2 H, $OCH_2C_6H_5$), 1.56 (s, 9 H, $OC(CH_3)_3$); IR (KBr) ν_{max} 3318, 3058, 3032, 3007, 2970, 2934, 2882, 1701, 1633, 1606, 1585, 1543, 1502, 1468, 1456, 1431, 1412, 1390, 1368, 1342, 1296, 1274, 1254, 1239, 1156, 1105, 1075, 1031, 982, 879, 841, 775, 749, 696 cm^{-1}; EIMS m/e (relative intensity) 349 (M^+, 2.6), 293 (10), 243 (2), 187 (14), 143 (14), 115 (6), 91 (100); CIMS (isobutane) m/e (relative intensity) 350 ($M + H^+$, 44), 294 (100); EIHRMS m/e 349.1677 ($C_{22}H_{23}NO_3$ requires 349.1677).

Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.24; H, 6.95; N, 4.11.

***N*-(*tert*-Butyloxycarbonyl)-4-(benzyloxy)-1-bromo-2-naphthylamine (11).** A solution of **10** (500 mg, 1.43 mmol) in 25 mL of tetrahydrofuran under nitrogen was cooled to −60 °C and treated with a drop of concentrated sulfuric acid in 5 mL of tetrahydrofuran. After stirring for 5 min (−60 °C), *N*-bromosuccinimide (306 mg, 1.72 mmol, 1.2 equiv) was added to the reaction mixture. The reaction mixture was stirred for 5 h (−60 °C) and diluted with ether (60 mL). The solution was washed with saturated aqueous sodium bicarbonate (2 × 30 mL) and saturated aqueous sodium chloride (30 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (2.5 × 15 cm SiO_2, 10% EtOAc–hexane) afforded **11** (601 mg, 613 mg theoretical, 98%) as a pale yellow solid: mp 111 °C (sharp, ethyl acetate–hexane, pale yellow plates); ^{1}H NMR ($CDCl_3$, 200 MHz, ppm) 8.28 (d, 1 H, J = 8.5 Hz, C5-H), 8.11 (dd, 1 H, J = 1.8, 8.3 Hz, C8-H), 8.10 (s, 1 H, C3-H), 7.4–7.6 (m, 8 H, C6-H, C7-H, $CH_2C_6H_5$, NH), 5.29 (s, 2 H, $OCH_2C_6H_5$), 1.58 (s, 9 H, $OC(CH_3)_3$); IR (KBr) ν_{max} 3407, 2979, 1735, 1625, 1601, 1574, 1518, 1500, 1445, 1396, 1367, 1338, 1273, 1226, 1147, 1112, 1086, 989, 907, 754, 736, 697 cm^{-1}; EIMS m/e (relative intensity) 427/429 (M^+, 0.8/0.7), 371/373 (1.4/1.4), 327/329 (0.4/0.4), 292 (3), 91 (100); CIMS (isobutane) m/e (relative intensity) 428/430 ($M + H^+$, 5.7/4.0), 372/374 (100/67), 328/330 (30/23), 250 (50); EIHRMS m/e 427.0781 ($C_{22}H_{22}BrNO_3$ requires 427.0783).

Anal. Calcd for $C_{22}H_{22}BrNO_3$: C, 61.69; H, 5.18; N, 3.27. Found: C, 61.68; H, 5.47; N, 3.65.

***N*-(*tert*-Butyloxycarbonyl)-*N*-(2-propynyl)-4-(benzyloxy)-1-bromo-2-naphthylamine (12).** A solution of **11** (277 mg, 0.647 mmol) in a mixture of tetrahydrofuran and *N*,*N*-dimethylformamide (5:1, 6 mL) at 24 °C under nitrogen was treated with sodium hydride (34 mg, 60% oil dispersion 0.85 mmol, 1.3 equiv). The reaction mixture was stirred for 30 min (24 °C) before 3-bromopropyne (0.22 mL, 80% in toluene, 1.9 mmol, 3.0 equiv) was added. The reaction mixture was stirred for 3 h (24 °C) and

(45) This estimation has been additionally corrected for errors inherent in the methods through comparison of the experimental versus calculated heat of reaction (ΔH°) derived from the heats of formation (ΔH_f, MOPAC; AM1 and MNDO) for the addition of ammonia to cyclopropane as taken from ref 43.

$$c\text{-}C_3H_6 + NH_3 \rightarrow CH_3CH_2CH_2NH_2$$

	ΔH_f			
exp	12.7	−11.0		−16.8 kcal
AM1	17.8	−7.3		−22.1 kcal
error	+5.1	+3.7	(−14.1)	−5.3 kcal
MNDO	11.2	−6.4		−18.2 kcal
error	−1.5	+4.6	(−4.5)	−1.4 kcal

(46) General experimental details are provided in the supplementary material.

then was poured onto water (15 mL). The mixture was extracted with ether (3 × 15 mL), and the combined organic extracts were washed with water (20 mL) and saturated aqueous sodium chloride (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (2.8 × 15 cm SiO_2, 10% EtOAc–hexane) afforded **12** (300 mg, 302 mg theoretical, 99%) as a pale yellow solid: mp 98–99 °C (hexane, fine pale yellow prisms); ^1H NMR ($CDCl_3$, 200 MHz, ppm) 8.38 (d, 1 H, J = 8 Hz, C5-H), 8.29 (d, J = 8 Hz, C8-H), 7.3–7.6 (m, 7 H, C6-H, C7-H, $CH_2C_6H_5$), 7.00 and 6.93 (2 s, 1 H, C3-H), 5.28 (s, 2 H, $OCH_2C_6H_5$), 4.87 (dd, J = 2.2, 17.8 Hz) and 4.74 (br d, J = 17.8 Hz, *E*- and *Z*-carbamate rotomers, 1 H, C*H*HC≡CH), 4.01 (dd, 1 H, J = 2.4, 17.8 Hz, CH*H*C≡CH), 2.09 (m, 1 H, CHHC≡C*H*), 1.59 and 1.32 (2 s, 9 H, $OC(CH_3)_3$); IR (KBr) ν_{max} 3286, 2968, 1706, 1620, 1592, 1506, 1454, 1404, 1374, 1338, 1278, 1256, 1234, 1222, 1156, 1144, 1118, 1094, 1030, 760, 738, 700, 650 cm^{-1}; EIMS m/e (relative intensity) 410/412 (0.9/0.8), 330 (15), 91 (100); CIMS (isobutane) m/e (relative intensity) 466/468 (M + H^+, 0.6/0.5), 410/412 (94/100).

Anal. Calcd for $C_{25}H_{24}BrNO_3$: C, 64.38; H, 5.19; N, 3.00. Found: C, 64.62; H, 5.42; N, 2.80.

5-(Benzyloxy)-3-(*tert*-butyloxycarbonyl)-1-methylidene-1,2-dihydro-3*H*-benz[*e*]indole (13). A solution o **12** (200 mg, 0.43 mmol) in 9.6 mL of dry benzene at 24 °C under nitrogen was treated with tri-*n*-butyltin hydride (0.23 mL, 0.86 mmol, 2.0 equiv) and AIBN (14 mg, catalytic), and the reaction mixture was warmed at reflux under nitrogen for 1 h. The reaction mixture was cooled, and the solvent was removed in vacuo to afford crude **13** as a yellow oil which was used directly in the subsequent reaction after azeotropic drying with anhydrous tetrahydrofuran (2 × 2.5 mL). Partial characterization of **13** was achieved by removal of solvent from the reaction mixture and extractive removal (hexane) of the tri-*n*-butyltin byproducts from an acetonitrile solution of **13** to afford crude **13** which partially or completely isomerized to 5-(benzyloxy)-3-(*tert*-butyloxycarbonyl)-1-methyl-3*H*-benz[*e*]indole (**18**)[23] upon purification by silica gel, aluminum oxide, or Florisil column chromatography. Therefore, crude **13** was used directly in the next reaction after azeotropic drying with anhydrous tetrahydrofuran. For **13**: ^1H NMR ($CDCl_3$, 200 MHz, ppm) 8.33 (d, 1 H, J = 8 Hz, C6-H), 8.25 (d, 1 H, J = 8 Hz, C9-H), 7.3–7.6 (m, 7 H, C7-H, C-8H, $CH_2C_6H_5$), 5.65 (t, 1 H, J = 2.6 Hz, C=C*H*H), 5.30 (s, 2 H, $OCH_2C_6H_5$), 5.12 (t, 1 H, J = 2.4 Hz, C=CH*H*), 4.71 (t, 2 H, J = 2.6 Hz, C2-H), 1.60 (s, 9 H, $OC(CH_3)_3$).

5-(Benzyloxy)-3-(*tert*-butyloxycarbonyl)-1-(hydroxymethyl)-1,2-dihydro-3*H*-benz[*e*]indole (14). A solution of crude **13** (from 0.43 mmol of **12**) in 2 mL of tetrahydrofuran under argon was cooled to 0 °C and treated with borane methyl sulfide (0.43 mL, 2 M in tetrahydrofuran, 0.86 mmol, 6 equiv). The reaction mixture was allowed to warm to 24 °C and was stirred for 3 h (24 °C). The reaction mixture was cooled to 0 °C and was treated sequentially with water (0.43 mL), 2 N aqueous sodium hydroxide (0.43 mL, 0.86 mmol), and 30% aqueous hydrogen peroxide (0.26 mL, 2.6 mmol). The reaction mixture was allowed to warm to 24 °C and was stirred for 1 h (24 °C) and then was warmed at 45 °C for 20 min. The reaction mixture was cooled to room temperature and dissolved in ethyl acetate (40 mL). The solution was washed with saturated aqueous sodium chloride (2 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (2.8 × 15 cm SiO_2, 10–30% EtOAc–hexane gradient elution) afforded **14** (108 mg, 174 mg theoretical, 62% from **12**)[23,24] as a colorless foam: ^1H NMR ($CDCl_3$, 300 MHz, ppm) 8.29 (d, 1 H, J = 8.4 Hz, C6-H), 7.90 (br s, 1 H, C4-H), 7.71 (d, 1 H, J = 8.3 Hz, C9-H), 7.3–7.5 (m, 7 H, C7-H, C8-H, $CH_2C_6H_5$), 5.27 (s, 2 H, $OCH_2C_6H_5$), 4.0–4.2 (m, 2 H, C2-H), 3.7–4.0 (m, 3 H, C1-H and CH_2OH), 1.60 (s, 9 H, $OC(CH_3)_3$; IR (neat) ν_{max} 3444, 2976, 2930, 1700, 1626, 1582, 1478, 1458, 1408, 1368, 1332, 1268, 1226, 1142, 1032, 908, 760, 736, 696 cm^{-1}; EIMS m/e (relative intensity) 405 (M^+, 5), 349 (7), 318 (27), 91 (100); CIMS (isobutane) m/e (relative intensity) 406 (M + H^+, 100); EIHRMS m/e 405.1944 ($C_{25}H_{27}NO_4$ requires 405.1940).

5-(Benzyloxy)-3-(*tert*-butyloxycarbonyl)-1-(hydroxymethyl)-1,2-dihydro-3*H*-benz[*e*]indole, (*R*)-(−)-*O*-Acetyl Mandelate Ester [(1*R*,2′*R*)-31 and (1*S*,2′*R*)-31]. A solution of (±)-**14** (66 mg, 0.16 mmol) and (*R*)-(−)-*O*-acetylmandelic acid (47 mg, 0.24 mmol, 1.5 equiv) in 1 mL of dichloromethane at 24 °C under nitrogen was treated with (3-(dimethylamino)-propyl)ethylcarbodiimide hydrochloride (EDCI, 52 mg, 0.27 mmol, 1.7 equiv) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP, 2 mg, 0.016 mmol, 0.1 equiv), and the reaction mixture was stirred at 24 °C for 1 h. Flash chromatography (1.2 × 16 cm SiO_2, 10–20% EtOAc–hexane gradient elution) afforded (1*RS*,2′*R*)-**31** (75 mg, 93 mg theoretical, 81%) as a colorless oil. The mixture was resolved by preparative HPLC. A solution of (1*RS*,2′*R*)-**31** (302 mg in 0.5 mL of CH_2Cl_2) was chromatographed using an Alltech 10 mm × 25 cm column packed with 10 μM SiO_2 using 2% EtOAc–CH_2Cl_2 eluant at a flow rate of 2.5 mL/min. The effluent was monitored at 280 nm, and the diastereomeric esters (1*R*,2′*R*)-**31** and (1*S*,2′*R*)-**31** eluted with retention times of 17.7 and 19.3 min, respectively. The separated diastereomers were collected, and the solvent was removed in vacuo to afford (1*R*,2′*R*)-**31** (t_R = 17.7 min, 125 mg) and (1*S*,2′*R*)-**31** (t_R = 19.3 min, 131 mg) with a total 85% recovery. HPLC analyses of the separated diastereomers indicated that both diastereomers were >99% pure (supplementary material).

(1*R*,2′*R*)-31: t_R = 17.7 min, colorless oil; $[\alpha]^{23}_D$ = −34.7° (c = 2.50, CH_2Cl_2), −32.4° (c = 0.80, CH_2Cl_2); ^1H NMR ($CDCl_3$, 200 MHz, ppm) 8.27 (d, 1 H, J = 8.3 Hz, C6-H), 7.80 (br s, 1 H, C4-H), 7.76 (d, 1 H, J = 8.2 Hz, C9-H), 7.3–7.6 (m, 12 H, C7-H, C8-H, $OCH_2C_6H_5$, $O_2CCHC_6H_5$), 5.97 (s, 1 H, $O_2CCHC_6H_5$), 5.25 (s, 2 H, $OCH_2C_6H_5$), 4.67 (d, 1 H, J = 9.1 Hz, C2-H), 3.8–4.0 (m, 4 H, C1-H, C2-H, CH_2O_2C), 2.23 (s, 3 H, $COCH_3$), 1.59 (s, 9 H, $OC(CH_3)_3$); IR (neat) ν_{max} 3064, 2976, 1746, 1702, 1626, 1582, 1458, 1408, 1384, 1368, 1332, 1270, 1230, 1202, 1174, 1144, 760, 736, 696 cm^{-1}; EIMS m/e (relative intensity) 581 (M^+, 19), 525 (29), 331 (28), 318 (53), 274 (63), 91 (100); CIMS (isobutane) m/e (relative intensity) 582 (M + H^+, 4), 526 (17), 482 (100); EIHRMS, m/e 581.2423 ($C_{35}H_{35}NO_7$ requires 581.2413).

(1*S*,2′*R*)-31: t_R = 19.3 min, colorless oil; $[\alpha]^{23}_D$ = −40.2° (c = 2.63, CH_2Cl_2), −44.1° (c = 0.708, CH_2Cl_2); ^1H NMR ($CDCl_3$, 200 MHz, ppm) 8.27 (d, 1 H, J = 8.3 Hz, C6-H), 7.80 (br s, 1 H, C4-H), 7.75 (d, 1 H, J = 8.2 Hz, C9-H), 7.3–7.6 (m, 12 H, C7-H, C8-H, $OCH_2C_6H_5$, $O_2CCHC_6H_5$), 5.95 (s, 1 H, $O_2CCHC_6H_5$), 5.25 (s, 2 H, $OCH_2C_6H_5$), 4.63 (d, 1 H, J = 7.7 Hz, C2-H), 3.9–4.1 (m, 4 H, C1-H, C2-H, CH_2O_2C), 2.21 (s, 3 H, $COCH_3$), 1.59 (s, 9 H, $OC(CH_3)_3$); IR (neat) ν_{max} 3064, 2976, 1746, 1702, 1626, 1582, 1408, 1384, 1368, 1332, 1270, 1230, 1204, 1174, 1144, 758, 736, 696 cm^{-1}; EIMS m/e (relative intensity) 581 (M^+, 14), 525 (16), 331 (19), 318 (18), 274 (40), 91 (100); CIMS (isobutane) m/e (relative intensity) 582 (M + H^+, 18), 526 (100); EIHRMS m/e 581.2403 ($C_{35}H_{35}NO_7$ requires 581.2413).

(−)-(1*R*)- and (+)-(1*S*)-5-(Benzyloxy)-3-(*tert*-butyloxycarbonyl)-1-(hydroxymethyl)-1,2-dihydro-3*H*-benz[*e*]indole [(−)-(1*R*)-14 and (+)-(1*S*)-14]. A solution of (1*R*,2′*R*)-**31** (t_R = 17.7 min, 125 mg, 0.215 mmol) in methanol–tetrahydrofuran (2:3, 1.3 mL) at 24 °C under nitrogen was treated with 4 N aqueous lithium hydroxide (0.27 mL, 1.08 mmol, 5.0 equiv) and was stirred for 1 h (24 °C). The reaction mixture was diluted with water (15 mL) and was extracted with ether (3 × 30 mL). The combined ether layers were washed with water (2 × 15 mL) and aqueous saturated sodium chloride (15 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (1.0 × 15 cm SiO_2, 0–33% EtOAc–hexane gradient elution) afforded (−)-(1*R*)-**14** (84 mg, 87 mg theoretical, 97%) as a white foam with spectroscopic characteristics identical with those of the racemic material: $[\alpha]^{23}_D$ = −5.2° (c = 1.67, CH_2Cl_2).

(+)-(1*S*)-**14** (89 mg, 97% from (1*S*,2′*R*)-**31**) as a white foam: $[\alpha]^{23}_D$ = +5.1° (c = 1.78, CH_2Cl_2).

5-(Benzyloxy)-3-(*tert*-butyloxycarbonyl)-1-(chloromethyl)-1,2-dihydro-3*H*-benz[*e*]indole (15). A solution of **14** (83.6 mg, 0.206 mmol) and triphenylphosphine (108 mg, 0.412 mmol, 2.0 equiv) in 0.9 mL of methylene chloride at 24 °C under argon was treated with carbon tetrachloride (0.12 mL, 1.24 mmol, 6.0 equiv), and the reaction mixture was stirred for 10 h (24 °C). Flash chromatography (1.0 × 12 cm SiO_2, 0–50% dichloromethane–hexane gradient elution) afforded **15** (86.3 mg, 87.3 mg theoretical, 99%) as a white solid.

(±)-(1*R)-15**: colorless needles; mp 154–155 °C (CH_2Cl_2–hexane); ^1H 1698, 1626, ($CDCl_3$, 200 MHz, ppm) 8.30 (d, 1 H, J = 8.5 Hz, C6-H), 7.83 (br s, 1 H, C4-H), 7.66 (d, 1 H, J = 8.4 Hz, C9-H), 7.3–7.6 (m, 7 H, C7-H, C8-H, $CH_2C_6H_5$), 5.27 (s, 2 H, $OCH_2C_6H_5$), 4.28 (d, 1 H, J = 11 Hz, C2-H), 4.13 (t, 1 H, J = 11 Hz, C2-H), 3.9–4.0 (m, 2 H, C1-H, C*H*HCl), 3.44 (t, 1 H, J = 11 Hz, CH*H*Cl), 1.61 (s, 9 H, $OC(CH_3)_3$); IR (KBr) ν_{max} 2930, 1698,

1626, 1580, 1478, 1460, 1408, 1382, 1366, 1340, 1268, 1164, 1144, 850, 756 cm^{-1}; EIMS *m/e* (relative intensity) 423/425 (M^+, 7/2), 367/369 (15/4), 318 (16), 91 (100); CIMS (isobutane) *m/e* (relative intensity) 424/426 (M + H^+, 39/10), 368/370 (100/24); EIHRMS *m/e* 423.1600 ($C_{25}H_{26}ClNO_3$ requires 423.1601).

Anal. Calcd for $C_{25}H_{26}ClNO_3$: C, 70.83; H, 6.18; N, 3.30. Found: C, 70.62; H, 6.31; N, 3.09.

(+)-(1*R*)-15: colorless needles; mp 185–185.5 °C; $[\alpha]^{23}_D$ = +16.8° (*C* = 1.73, CH_2Cl_2), +16.1° (*c* = 0.528, CH_2Cl_2).

(−)-(1*S*)-15: colorless needles; mp 184.5–185.5 °C; $[\alpha]^{23}_D$ = −16.6° (*c* = 1.76, CH_2Cl_2), −16.2° (*c* = 0.470, CH_2Cl_2). Unambiguous confirmation of the absolute configuration of (−)-(1*S*)-**15** was derived from a single-crystal X-ray analysis.[34]

3-(*tert*-Butyloxycarbonyl)-1-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (16). A solution of **15** (84.7 mg, 0.200 mmol) in 3.0 mL of tetrahydrofuran at 0 °C under argon was treated sequentially with a 25% aqueous ammonium formate (0.4 mL) and 10% palladium/carbon (40 mg), and the reaction mixture was stirred vigorously for 2.5 h (0 °C). Ether (50 mL) was mixed with the reaction mixture, and the mixture was dried ($MgSO_4$). The solid was removed by filtration through Celite (ether wash). Concentration of the filtrate in vacuo afforded **16** (64.5 mg, 66.8 mg theoretical, 97%) as colorless needles.

(±)-(1*R)-16**: colorless needles; mp 155 °C dec (CH_2Cl_2–hexane); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 8.17 (d, 1 H, *J* = 8.4 Hz, C6-H), 7.74 (br s, 1 H, C4-H), 7.63 (d, 1 H, J = 8.4 Hz, C9-H), 7.50 (t, 1 H, *J* = 7.5 Hz, C8-H), 7.43 (t, 1 H, *J* = 7.6 Hz, C7-H), 6.28 (br s, 1 H, OH), 4.25 (d, 1 H, *J* = 11.6 Hz, C2-H), 4.11 (t, 1 H, *J* = 11.6 Hz, C2-H), 3.9–4.0 (m, 2 H, C1-H, C*H*HCl), 3.42 (apparent t, 1 H, *J* = 10.8 Hz, CH*H*Cl), 1.61 (s, 9 H, $OC(CH_3)_3$); IR (KBr) ν_{max} 3428, 2974, 1684, 1630, 1586, 1522, 1480, 1414, 1340, 1234, 1144, 1076, 912, 854, 760, 718 cm^{-1}; EIMS *m/e* (relative intensity) 333/335 (M^+, 11/13), 277/279 (27/11), 228 (100); CIMS (isobutane) *m/e* (relative intensity) 334/336 (M + H^+, 8/2), 298 (9), 278/280 (100/25); EIHRMS *m/e* 333.1134 ($C_{18}H_{20}ClNO_3$ requires 333.1131); chiral phase HPLC (Bakerbond Chiral Phase DNBPG (covalent) 5 μm, 4.6 mm × 25 cm column), 2% 2-propanol–hexane, 1 mL/min, effluent monitored at 310 nm, t_R = 15.8 min for (+)-(1*R*)-**16** and t_R = 16.9 min for (−)-(1*S*)-**16**, (α = 1.07).

Anal. Calcd for $C_{18}H_{20}ClNO_3$: C, 64.77; H, 6.04; N, 4.20. Found: C, 64.71; H, 5.74; N, 4.20.

(+)-(1*R*)-16: colorless needles; mp 161 °C dec; $[\alpha]^{23}_D$ = +75.7° (*c* = 1.29, CH_2Cl_2), +70.6° (*c* = 0.964, CH_2Cl_2), +48.0° (*c* = 0.371, CH_2Cl_2), +40.3° (*c* = 0.206, CH_2Cl_2).[47]

(−)-(1*S*)-16: colorless needles; mp 161 °C dec; $[\alpha]_D^{23}$ = −70.2° (*c* = 1.04, CH_2Cl_2), −47.7° (*c* = 0.300, CH_2Cl_2).[47]

N^2-(*tert*-Butyloxycarbonyl)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (6, N^2-BOC-CBI). A suspension of sodium hydride (3.4 mg, 60% oil dispersion, 85 μmol, 3.0 equiv) in 0.4 mL of tetrahydrofuran at 0 °C under nitrogen was treated slowly with a solution of **16** (9.5 mg, 28.5 μmol) in tetrahydrofuran (0.3 mL). The reaction mixture was allowed to warm at 24 °C and was stirred for 2 h (24 °C). Flash chromatography (1.2 × 10 cm SiO_2, 0–33% THF–hexane gradient elution) afforded **6** (7.9 mg, 8.5 mg theoretical, 93%) as a colorless oil.

(±)-(8b*R,9a*S**)-6**: ^1H NMR ($CDCl_3$, 300 MHz, ppm) 8.22 (d, 1 H, *J* = 7.8 Hz, C5-H), 7.48 (t, 1 H, *J* = 7.4 Hz, C7-H), 7.39 (t, 1 H, *J* = 7.5 Hz, C6-H), 6.85 (d, 1 H, *J* = 7.7 Hz, C8-H), 6.80 (s, 1 H, C3-H), 3.98 (m, 2 H, C1-H), 2.75 (dt, 1 H, *J* = 4.2, 7.7 Hz, C9a-H), 1.61 (dd, 1 H, *J* = 4.6, 7.7 Hz, C9-H), 1.57 (s, 9 H, $OC(CH_3)_3$), 1.47 (t, *J* = 4.6 Hz, C9-H); IR (neat) ν_{max} 2926, 1718, 1628, 1602, 1560, 1458, 1406, 1380, 1298, 1280, 1254, 1164, 1144, 1124, 1020, 858, 782 cm^{-1}; UV (THF) 300 (ϵ = 19 000), 264 nm (5700); EIMS *m/e* (relative intensity) 298 (M + H^+, 100), 242 (33), 198 (20); EIHRMS *m/e* 297.1364 ($C_{18}H_{19}NO_3$ requires 297.1364); chiral phase HPLC (Bakerbond chiral phase DNBPG (covalent) 5 μm, 4.6 × 25 cm column), 10% 2-propanol–hexane, 1.0 mL/min, effluent monitored at 310 nm, t_R = 30.4 min for (+)-(8b*R*,9a*S*)-**6** and t_R = 31.4 min for (−)-(8b*S*,9a*R*)-**6**, α = 1.03.

(+)-(8b*R*,9a*S*)-6: colorless oil; $[\alpha]^{23}_D$ = +173° (*c*, = 0.150, THF).

(−)-(8b*S*,9a*R*)-6: colorless oil; $[\alpha]^{23}_D$ = −177° (*c* = 0.158, THF).

(47) The specific rotation of **16** exhibits a marked dependence on concentration.

1,2,9,9a-Tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (5, CBI). (a) Phenol **16** (5.5 mg, 16.5 μmol) was treated with anhydrous 3 N hydrochloric acid in ethyl acetate (0.5 mL) at 24 °C for 20 min. The solvent was removed in vacuo to afford crude, unstable **17** (quantitative). To crude **17** was added 5% aqueous sodium bicarbonate (0.5 mL) and tetrahydrofuran (0.5 mL) at 24 °C under nitrogen, and the mixture was stirred for 1.5 h (24 °C). The reaction mixture was extracted with ethyl acetate (3 × 3 mL), and the combined extracts were washed with water (2 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (1.2 × 15 cm SiO_2, 10% methanol–dichloromethane) afforded **5** (2.6 mg, 3.3 mg theoretical, 79%) as a colorless foam.

(b) A solution of **6** (5.6 mg, 18.8 μmol) in dichloromethane (1 mL) at 0 °C under argon was treated with trifluoroacetic acid (1 mL), and the reaction mixture was stirred for 1.5 h (0 °C). The solvent was removed in vacuo, and flash chromatography (1.0 × 18 cm SiO_2, 10% methanol–dichloromethane) afforded **5** (2.2 mg, 3.7 mg theoretical, 59%).

(±)-(8b*R,9a*S**)-5**: colorless solid; ^1H NMR ($CDCl_3$, 300 MHz, ppm) 8.23 (d, 1 H, *J* = 7.5 Hz, C5-H), 7.42 (t, 1 H, *J* = 7.4 Hz, C7-H), 7.40 (t, 1 H, *J* = 7.4 Hz, C6-H), 6.83 (d, 1 H, *J* = 7.6 Hz, C8-H), 5.74 (s, 1 H, C3-H), 4.87 (br s, 1 H, NH), 3.84 (ddd, 1 H, *J* = 1, 5, 10 Hz, C1-H), 3.65 (d, 1 H, *J* = 10 Hz, C1-H), 2.86 (dt, 1 H, *J* = 4, 7 Hz, C9a-H), 1.60 (dd, 1 H, *J* = 4.2, 7.6 Hz, C9-H), 1.43 (t, 1 H, *J* = 4.4 Hz, C9-H); IR (neat) ν_{max} 3192, 2872, 1610, 1586, 1542, 1328, 1266 1232, 1130, 984, 826, 778 cm^{-1}; UV (THF) 316 nm (ϵ = 11 000); EIMS *m/e* (relative intensity) 197 (100), 180 (31), 168 (55); CIMS (isobutane) *m/e* (relative intensity) 198 (M + H^+, 100); EIHRMS *m/e* 197.0842 ($C_{13}H_{11}NO$ requires 197.0840).

(+)-(8b*R*,9a*S*)-5: colorless solid; mp 175 °C dec; $[\alpha]^{23}_D$ = +332° (*c* = 0.052, MeOH).

(−)-(8b*S*,9a*R*)-5: colorless solid; mp 178 °C dec; $[\alpha]^{23}_D$ = −334° (*c* = 0.033 MeOH).

Unambiguous confirmation of the structure **5** was derived from a single-crystal X-ray structure analysis.[34]

***seco*-CBI-CDPI$_1$ (29).** A mixture of crude **17** freshly prepared from phenol **16** (7.6 mg, 22.8 μmol), [3-(dimethylamino)-propyl]ethylcarbodiimide hydrochloride (EDCI, 13.0 mg, 68 μmol, 3.0 equiv), and CDPI$_1$ (**27**, 5.6 mg, 22.8 μmol, 1.0 equiv) was slurried in 0.4 mL of *N,N*-dimethylformamide at 24 °C under argon, and the reaction mixture was stirred vigorously for 8 h (24 °C). The solvent was removed in vacuo. Flash chromatography (1.2 × 13 cm SiO_2, 10% methanol–dichloromethane) afforded **29** (7.2 mg, 10.5 mg theoretical, 69%) as a pale yellow solid.

(±)-(1*R)-29**: pale yellow solid; mp 240 °C dec; ^1H NMR (DMSO-d_6, 300 MHz, ppm) 11.63 (br s, 1 H, NH), 10.44 (s, 1 H, OH), 8.12 (d, 1 H, *J* = 8.3 Hz, C6-H), 8.01 (d, 1 H, *J* = 8.9 Hz, C4′-H), 7.97 (s, 1 H, C4-H), 7.86 (d, 1 H, *J* = 8.3 Hz, C9-H), 7.53 (t, 1 H, *J* = 7.5 Hz, C8-H), 7.37 (t, 1 H, *J* = 7.5 Hz, C7-H), 7.24 (d, 1 H, *J* = 8.9 Hz, C5′-H), 7.02 (s, 1 H, C8′-H), 6.12 (br s, 2 H, NH_2), 4.81 (t, 1 H, *J* = 10.2 Hz, C2-H), 4.55 (d, 1 H, *J* = 11 Hz, C2-H), 4.23 (m, 1 H, C1-H), 3.99 (m, 3 H, C2′-H, C*H*HCl), 3.88 (dd, 1 H, *J* = 7.2, 10.8 Hz, CH*H*Cl), 3.26 (t, 3 H, partially obscured by H_2O, *J* = 8.3 Hz, C1′-H); IR (KBr) ν_{max} 3448, 3248, 2922, 1664, 1632, 1608, 1586, 1508, 1448, 1416, 1340, 1268, 1146, 1118, 816, 766 cm^{-1}; FABMS (*m*-nitrobenzyl alcohol), *m/e* (relative intensity) 461/463 (M + H^+, 42/16), 460/462 (M^+, 44/25), 154 (100); FABHRMS (*m*-nitrobenzyl alcohol), *m/e* 461.1368 ($C_{25}H_{21}ClN_4O_3$ + H^+ requires 461.1380).

(+)-(1*S*)-29: pale yellow solid; $[\alpha]^{23}_D$ = +64.9° (*c* = 0.057, DMF).

(−)-(1*R*)-29: pale yellow solid; $[\alpha]^{23}_D$ = −68.7° (*c* = 0.067, DMF).

CBI-CDPI$_1$ (7). A suspension of sodium hydride (0.9 mg, 38 μmol, 3 equiv) in tetrahydrofuran (0.2 mL) at 0 °C under argon was treated with a solution of **29** (5.9 mg, 12.8 μmol) in 20% *N,N*-dimethylformamide–tetrahydrofuran (0.5 mL), and the mixture was stirred for 1 h (0 °C). The solvent was removed in vacuo, and the residue was washed with water (2 × 0.5 mL) and dried in vacuo. Chromatography (1.2 × 10 cm SiO_2, tetrahydrofuran) afforded **7** (4.0 mg, 5.4 mg theoretical, 74%) as a pale yellow solid; HPLC[48] (50 μg of **7**/0.8 mL of 1% DMF–CH_3OH,

(48) Reverse phase HPLC analysis was conducted on a 5 μ adsorbosphere C_{18} column, 4.6 mm × 25 cm, with UV detection (328 nm). t_R = 4.4 min (**7**), 4.7 min (**5**), 7.5 min (**8**), 7.9 min (**29**), and 15.8 min (**30**) at a flow rate of 1.0 mL/min, 50% CH_3CN–H_2O.

solvent = 50% CH_3CN–H_2O, flow rate = 1.0 mL/min, t_R = 4.4 min) purity ≥ 98%.

(±)-(**8b*R***,9a*S**)-**7**: pale yellow solid; mp >245 °C; ^1H NMR (DMSO-d_6, 300 MHz, ppm) 11.74 (br s, 1 H, NH), 8.03 (d, 1 H, J = 8.9 Hz, C4′-H), 8.01 (d, 1 H, J = 7.4 Hz, C5-H), 7.61 (t, 1 H, J = 7.3 Hz, C7-H), 7.41 (t, 1 H, J = 7.5 Hz, C6-H), 7.26 (d, 1 H, J = 7.3 Hz, C8-H), 7.23 (d, 1 H, J = 8.9 Hz, C5′-H), 7.08 (s, 1 H, C8′-H), 6.94 (s, 1 H, C3-H), 6.14 (br s, 2 H, NH_2), 4.62 (dd, 1 H, J = 4.8, 10.3 Hz, C1-H), 4.49 (d, 1 H, J = 10.3 Hz, C1-H), 3.98 (t, 2 H, J = 8.7 Hz, C2′-H), 3.2–3.4 (m, 3 H, partially obscured by H_2O, C9*a*-H, C1′-H), 1.77 (dd, 1 H, J = 4.1, 7.5 Hz, C9-H), 1.70 (t, 1 H, J = 4.1 Hz, C9-H); IR (KBr) ν_{max} 3438, 2922, 1654, 1648, 1637, 1626, 1602, 1508, 1449, 1400, 1264, 804 cm^{-1}; UV (DMF), 340 (ϵ = 33000), 270 nm (16000); FABMS (*m*-nitrobenzyl alcohol) *m*/*e* (relative intensity) 425 (M + H^+, 15), 424 (M^+, 10), 154 (100); FABHRMS (*m*-nitrobenzyl alcohol) *m*/*e* 425.1597 ($C_{25}H_{20}N_4O_3$ + H^+ requires 425.1613).

(+)-(**8b*R*,9a*S***)-**7**: pale yellow solid; $[\alpha]^{23}_D$ = +155.9° (*c* = 0.068, DMF).

(−)-(**8b*S*,9a*R***)-**7**: pale yellow solid; $[\alpha]^{23}_D$ = −154.9° (*c* = 0.122 DMF).

***seco*-CBI-CDPI$_2$ (30).** A mixture of crude **17** freshly prepared from phenol **16** (5.1 mg, 15.3 μmol), [3-(dimethylamino)-propyl]ethylcarbodiimide hydrochloride (EDCI, 8.8 mg 45.9 μmol, 3 equiv), and CDPI$_2$ (**28**, 6.6 mg, 15.3 μmol, 1.0 equiv) was slurried in 0.3 mL of *N*,*N*-dimethylformamide at 24 °C under argon, and the reaction mixture was stirred vigorously for 5 h (24 °C). The solvent was removed in vacuo, and the solid residue was washed with water (1 × 1.5 mL) and dried in vacuo. Flash chromatography (0.5 × 5 cm SiO_2, 10–33% DMF–toluene gradient elution) afforded **30** (7.7 mg, 9.9 mg theoretical, 78%) as a light tan solid.

(±)-(**1*R****)-**30**: tan solid; mp >245 °C; ^1H NMR (DMSO-d_6, 300 MHz, ppm) 11.84 (br s, 1 H, NH), 11.57 (br s, 1 H, NH), 10.47 (s, 1 H, OH), 8.29 (d, 1 H, J = 7.9 Hz, C6-H), 8.13 (d, 1 H, J = 9 Hz, C4′-H), 8.00 (s, 1 H, C4-H), 7.98 (d, 1 H, J = 9 Hz, C4″-H), 7.88 (d, 1 H, J = 8.3 Hz, C9-H), 7.54 (t, 1 H, J = 7.3 Hz, C8-H), 7.39 (d, 1 H, J = 9 Hz, C5″-H), 7.38 (t, 1 H, J = 7.3 Hz, C7-H), 7.23 (d, 1 H, J = 9 Hz, C5′-H), 7.19 (s, 1 H, C8″-H), 6.98 (s, 1 H, C8′-H), 6.11 (br s, 2 H, NH_2), 4.85 (apparent t, 1 H, J = 10.3 Hz, C2-H), 4.69 (t, 2 H, J = 8.5 Hz, C2′-H), 4.59 (d, J = 10.6 Hz, C2-H), 4.26 (m, 1 H, C1-H), 3.9–4.1 (m, 3 H, C2″-H, C*H*HCl), 3.90 (dd, 1 H, J = 7, 11 Hz, CH*H*Cl), 3.2–3.5 (m, 4 H, partially obscured by H_2O, C1′-H, C1″-H); IR (KBr) ν_{max} 3430, 2926, 1618, 1587, 1508, 1416, 1384, 1340, 1266, 1148, 805, 762 cm^{-1}; FABMS (*m*-nitrobenzyl alcohol) *m*/*e* (relative intensity) 645/647 (M + H^+, 4/2), 644/646 (M^+, 3/2), 154 (100); FABHRMS (*m*-nitrobenzyl alcohol) *m*/*e* 645.1876 ($C_{36}H_{29}ClN_6O_4$ + H^+ requires 645.2106).

(+)-(**1*S***)-**30**: pale yellow solid; $[\alpha]^{23}_D$ = +60.9° (*c* = 0.069, DMF).

(−)-(**1*R***)-**30**: pale yellow solid; $[\alpha]^{23}_D$ = −63.1° (*c* = 0.065, DMF).

CBI-CDPI$_2$ (8). A suspension of sodium hydride (0.4 mg, 100%, 18 μmol, 2 equiv) in tetrahydrofuran (0.25 mL) at 0 °C under argon was treated with a solution of **30** (5.9 mg, 9.1 μmol) in 50% *N*,*N*-dimethylformamide–tetrahydrofuran (0.5 mL), and the mixture was stirred for 1 h (0 °C). The solvent was removed in vacuo, and the solid residue was washed with water (2 × 1 mL) and dried in vacuo. Chromatography (1.2 × 10 cm SiO_2, 2% methanol–tetrahydrofuran) afforded **8** (4.7 mg, 5.6 mg theoretical, 84%) as a tan-yellow solid: HPLC[48] (50 μg of 8/0.8 mL of 1% DMF–CH_3OH, solvent = 50% CH_3CN–H_2O, flow rate = 1.0 mL/min, t_R = 7.5 min), purity ≥98%.

(±)-(**8a*R****,**9b*S****)-**8**: tan-yellow solid; mp 245 °C dec; ^1H NMR (DMSO-d_6, 300 MHz, ppm) 11.94 (s, 1 H, NH), 11.58 (s, 1 H, NH), 8.31 (d, 1 H, J = 9 Hz, C4′-H), 8.02 (d, 1 H, J = 8 Hz, C5-H), 7.98 (d, 1 H, J = 9 Hz, C4″-H), 7.62 (t, 1 H, J = 7.5 Hz, C7-H), 7.45 (t, 1 H, J = 7.5 Hz, C6-H), 7.38 (d, 1 H, J = 9 Hz, C5″-H), 7.27 (d, 1 H, J = 8 Hz, C8-H), 7.25 (s, 1 H, C8″-H), 7.23 (d, 1 H, J = 9 Hz, C5′-H), 6.97 (s, 1 H, C8′-H), 6.96 (s, 1 H, C3-H), 6.12 (s, 1 H, NH_2), 4.65 (m, 3 H, C1-H, C2′-H), 4.53 (d, 1 H, J = 10.7 Hz, C1-H), 3.99 (t, 2 H, J = 8.5 Hz, C2″-H), 3.46 (t, 2 H, J = 8.5 Hz, C1′-H), 3.2–3.4 (m, 3 H, obscured by H_2O, C9a-H, C1″-H), 1.78 (dd, 1 H, J = 4.2, 7.4 Hz, C9-H), 1.73 (t, 1 H, J = 4.2 Hz, C9-H); IR (KBr) ν_{max} 3440, 1655, 1647, 1636, 1618, 1580, 1508, 1432, 1402, 1268, 1128, 696 cm^{-1}; UV (DMF) 338 (ϵ = 41000), 272 nm (24000); FABMS (*m*-nitrobenzyl alcohol) *m*/*e* (relative intensity) 609 (M + H^+, 3), 608 (M^+, 1), 154 (100): FABHRMS (*m*-nitrobenzyl alcohol) *m*/*e* 609.2161 ($C_{36}H_{28}N_6O_4$ + H^+ requires 609.2250).

(+)-(**8a*R*,9b*S***)-**8**: pale yellow solid; $[\alpha]^{23}_D$ = +82.0° (*c* = 0.172, DMF).

(−)-(**8a*S*,9b*R***)-**8**: pale yellow solid; $[\alpha]^{23}_D$ = −83.6° (*c* = 0.073, DMF).

Aqueous Solvolytic Reactivity of 3, 5–8. Stock solutions (25–50 μL) of the agents in tetrahydrofuran (**3**, **5–6**) or *N*,*N*-dimethylformamide (**7–8**) were diluted with 5.0 mL of a 1:1 mixture of methanol (pH 7) or a 1:1 mixture of methanol and aqueous buffer (pH 3). The buffer contained 4:1:20 (volumes) of 0.1 M citric acid, 0.2 M Na_2HPO_4, and water, respectively. The concentrations of the agent in the solvolysis mixtures were between 1.4×10^{-5} and 9.5×10^{-5} M. After mixing, the solvolysis solutions were stoppered and kept at 24 °C in the dark. The UV spectrum of each solution was measured 5–7 times in the first 5–18 days, and the operation continued until no further change was detectable in the spectrum. The long-wavelength absorptions, 352 and 336 nm, were monitored for **3** and **5**, and the solvolysis rates were calculated from the least square treatment (r = 0.999, **3**; r = 0.907, **5**) of the slopes of plots of time versus $(A - A_{final})/(A_{initial} - A_{final})$. For **3**: $k = (5.26 \pm 0.08) \times 10^{-6}$ s^{-1} ($t_{1/2}$ = 36.7 h). For **5**: $k = (2.07 \pm 0.33) \times 10^{-7}$ s^{-1} ($t_{1/2}$ = 930 h). The short-wavelength absorption, 256 nm, was monitored for **6**, and the solvolysis rate was calculated from the slope of the plot of time versus $[1 - (A - A_{initial})/(A_{final} - A_{initial})]$ of which the r value (0.999) was better than that from the estimation (r = 0.986) obtained by monitoring the 314-nm absorption ($t_{1/2}$ 133 vs 158 h). The spent solvolysis solutions in aqueous buffer (pH 3) were concentrated, extracted with ethyl acetate (3 × 1 mL), and dried ($MgSO_4$). Two major products were detectable on TLC (10% MeOH–chloroform or 33% ethyl acetate–hexane). No solvolysis products from the neutral solvolysis solutions (pH = 7) were detectable by TLC or UV after 2 weeks.

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Supplementary Material Available: General experimental details, full details of the preparation and characterization of **20–24**, a table of the cytotoxic activity (L1210, B16, 9PS (P388), 9KB) of **5–8**, **16**, **29–30**, CI-CDPI$_n$, and CPI-CDPI$_n$, figures of UV solvolysis studies of **3–4** and **6**, ^1H NMR spectra of **5–8**, **14**, **21–24**, **29–31**, and a summary of the single-crystal X-ray structure refinement of (+)-**5** and (−)-(1*S*)-**15** (26 pages). Odering information is given on any current masthead page.