Functional Analogs of CC-1065 and the Duocarmycins Incorporating the 9a-(Chloromethyl)-1,2,9,9a-tetrahydrocyclopropa[c]benz[e]indol-4-one (C_2BI) Alkylation Subunit: Synthesis and Preliminary DNA Alkylation Studies

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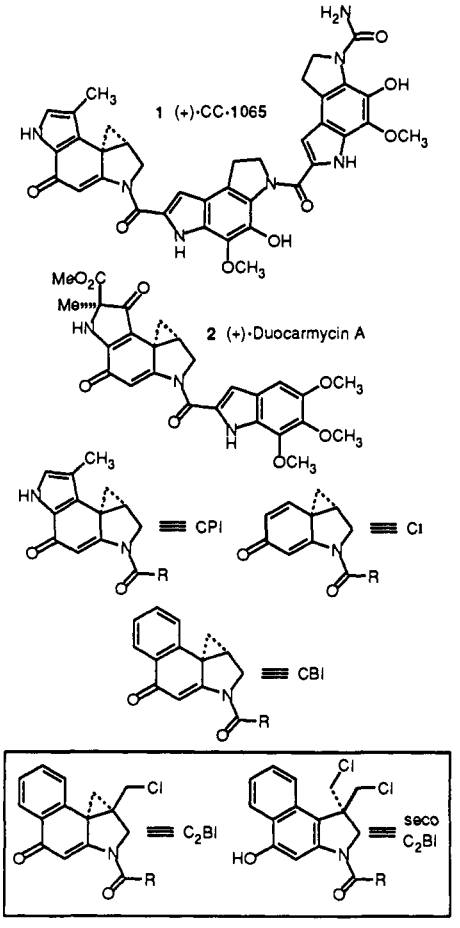
Abstract: A concise and effective nine to ten step synthesis of 9a-(chloromethyl)-1,2,9,9a-tetrahydrocyclopropa[c]benz[e]indol-4-one (C_2BI) is detailed based on the implementation of a key 5-*exo*-*trig* aryl radical–alkene cyclization for *direct* introduction of a selectively protected 3,3-bis(hydroxymethyl)indoline. The incorporation of C_2BI into functional analogs of CC-1065 and the duocarmycins (C_2BI-$CDPI_1$, C_2BI-$CDPI_2$, C_2BI-TMI, and C_2BI-$indole_2$) is described. The fundamental solvolytic behavior of *N*-BOC-C_2BI is detailed ($t_{1/2}$ = 433 h, pH = 3) in studies which reveal that the agent is approximately 12 times more stable than the authentic alkylation subunit of CC-1065 and that it participates in the stereoelectronically-controlled reaction with nucleophilic addition to the least substituted cyclopropane carbon. Preliminary studies demonstrating the DNA alkylation and cross-linking properties of C_2BI-$CDPI_2$ are presented.

(+)-CC-1065 (**1**)[1-8] and (+)-duocarmycin A (**2**)[9-13] are the initial members of a growing class of potent, naturally occurring antitumor antibiotics whose properties are derived from their participation in a sequence-selective DNA minor groove alkylation. The now characteristic and stereoelectronically-controlled adenine N3 addition to the unsubstituted cyclopropane carbon of the left-hand subunit of the agents has been shown to occur within AT-rich regions of duplex DNA with a binding directionally that extends in the 3′ to 5′ direction from the site of alkylation. In recent efforts, we have detailed the preparation[14-17] of analogs



of the naturally occurring agents possessing deep-seated changes in the alkylation subunit with the intent of defining the fundamental structural features contributing to polynucleotide molecular

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recognition and functional reactivity.[18-22] In these studies in which the properties of CPI-, CI-, and CBI-based agents have been examined, the electrophilic cyclopropane proved not to be obligatory to observation of the (+)-CC-1065 alkylation selectivity and the noncovalent binding selectivity of the agents[22] has been shown to exhibit a pronounced effect on the DNA alkylation selectivity independent of the nature of the electrophile.[15,19]

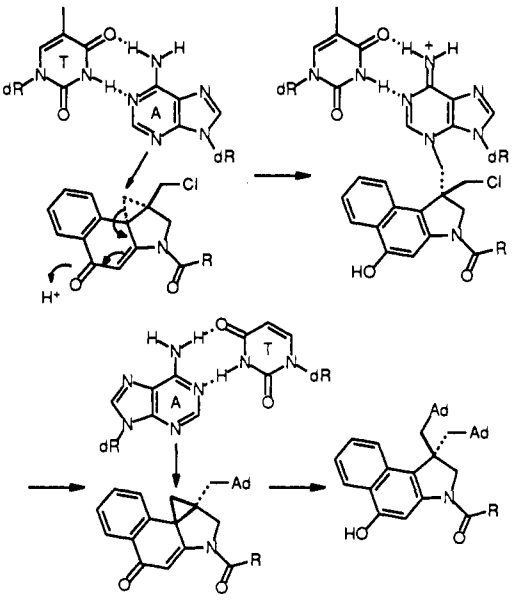
In addition, agents incorporating the simplified and chemically more stable CBI alkylation subunit have proven especially interesting.[16,20] Such agents have displayed more potent cytotoxic activity than the corresponding CPI agents, and selected agents within the series have displayed efficacious antitumor activity.[17] Despite the decreased reactivity of the CBI-based agents, they have been found to participate in the characteristic DNA alkylation at a greater rate and with a higher intensity (efficiency) than the corresponding agents possessing the authentic CPI alkylation subunit.[20]

Herein, we detail the extension of these studies to the synthesis of agents which incorporate the 9a-(chloromethyl)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (C_2BI) alkylation subunit. The basis for the selection of C_2BI for synthesis and evaluation was derived from the observations that the parent CBI-based agents have proven chemically more stable, biologically more potent, and synthetically more accessible than the authentic CPI alkylation subunit.[16,20] Further, the precursor *acyclic* seco-C_2BI agents could be anticipated to display properties comparable to the C_2BI agents and are inherently achiral. Consequently, they provide attractive candidates for synthesis free of the technical considerations of resolution or asymmetric synthesis. Since both (+)-CC-1065 and *ent*-(−)-CC-1065 display efficient DNA alkylation properties and potent biological activity, the potential in vivo closure of the achiral seco-C_2BI agents to both enantiomers of the C_2BI agents may prove inconsequential if both enantiomers display efficient DNA alkylation properties and potent biological activity.[18-20] Finally, the bis-alkylating capabilities of the C_2BI-based agents or their seco precursors provide for the opportunity of DNA cross-linking (Scheme I). Pertinent to the potential cross-linking capabilities of the C_2BI-based agents, the precursor seco-C_2BI agents possessing a phenol and the capabilities for ring closure to the cyclopropane can be expected to possess the biological activity and DNA alkylation properties of the parent cyclopropane agents.[18-20] That such a cross-linking event may be reasonable was established in modeling studies of the high-affinity alkylation site of w794 DNA[23] [5′-d(AATTA)-3′], which provides for a potential A–A cross-link with the second alkylation occurring on the complementary strand one base pair removed in the 5′ direction from the initial alkylation site. Illustrated in Figure 1 is a model of the adenine–adenine cross-link, which appears to be capable of being formed with no significant distortion to the model duplex DNA.

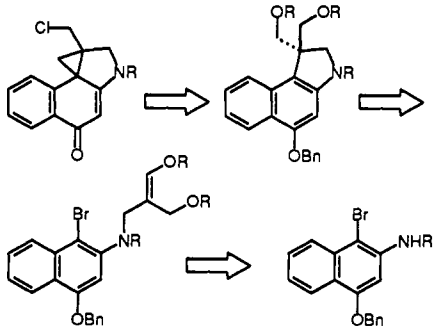
The approach to the preparation of the C_2BI subunit was anticipated to be derived with implementation of a 5-*exo*-*trig* aryl radical–alkene free radical cyclization with *direct* introduction of an appropriately functionalized and protected 3,3-bis(hydroxymethyl)indoline (Scheme II). As such, the approach is complementary to the indirect 5-*exo*-*dig* aryl radical–alkyne and self-terminating 5-*exo*-*trig* aryl radical–alkene free radical cyclizations detailed in the initial preparation of the CBI-based agents, and this modified approach was anticipated to benefit from the direct introduction of the C3 functionalized indoline.[16] Further, directed aryl radical addition to the activated alkene acceptor with preferential 5-*exo*-*trig* versus 6-*endo*-*trig* cyclization was expected to ensure the regioselectivity of the cyclization reaction[24] in spite of the required addition at the more substituted alkene center.

Prior to the initiation of efforts to prepare the C_2BI-based agents, we elected to examine the feasibility of the key 5-*exo*-*trig* aryl radical–alkene cyclization with **10** and to concurrently address the development of the requisite chemistry for the preparation

Scheme I



Scheme II



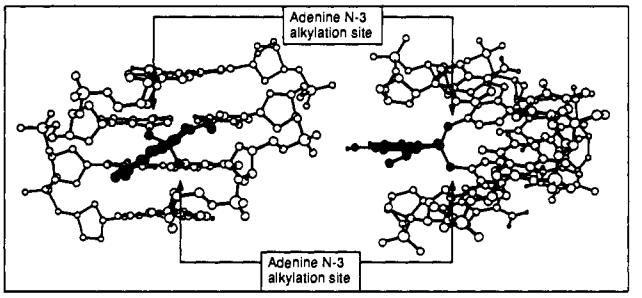


Figure 1. Front and groove view of potential cross-linking of C_2BI within the high-affinity site of w794 DNA. Duplex 5′-d(TTAG)–C_2BI taken from a model of 5′-d(CTCAATTAGTC)–C_2BI-CDPI$_2$.

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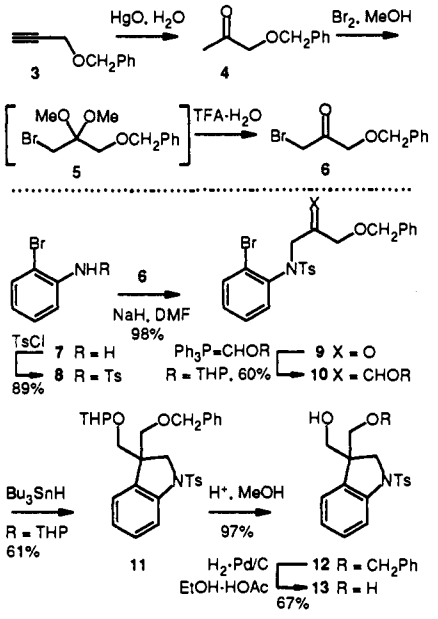
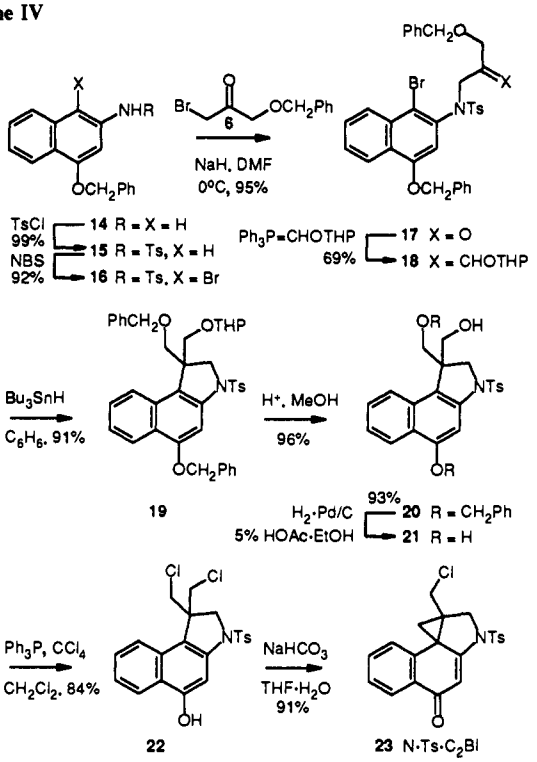
Scheme III



Scheme IV



of such substrates. Alkylation of the sodium salt of *N*-tosyl-2-bromoaniline (**8**) with 3-(benzyloxy)-1-bromo-2-propanone (**6**) prepared as detailed in Scheme III[25] provided **9**. Attempts to alkylate the corresponding sodium salt of *N*-BOC-2-bromoaniline with **6** were not successful and presumably suffer from competitive deprotonation versus alkylation of **6**. Key to the implementation of the required free radical cyclization was the conversion of **9** to **10** by Wittig reaction with introduction of an enol ether. After considerable experimentation, this was found to be best conducted with [(2-tetrahydropyranyloxy)methylene]triphenylphosphorane[26] with ylide generation in THF followed by reaction with **9** over a sustained reaction period (48 h) in THF–HMPA[27] at 25 °C (60%). In preliminary studies of the Wittig reaction, the observed conversions in the absence of HMPA proved much lower and the use of $Ph_3P{=}CH(OTHP)$ proved superior to the use of $Ph_3P{=}CHOCH_3$,[28] $Ph_3P{=}CHOCH_2Ph$,[29] and $Ph_2P(O)CH_2OCH_2Ph$.[30] Consistent with expectations, treatment of **10** (R = THP) with Bu_3SnH (C_6H_6, 80 °C, cat. AIBN, 61%) provided **11** cleanly through bromine atom abstraction and aryl radical generation followed by 5-*exo*-*trig* cyclization. Subsequent THP deprotection conducted by treatment of **11** with HOAc–THF–H_2O (4:2:1, 47 °C, 4 h, 91%) or Amberlyst H-15[31] (CH_3OH, 45 °C, 4 h, 97%) followed by hydrogenation in the presence of HOAc as an acid catalyst provided **13**. Alternative procedures including transfer hydrogenolysis with 1,4-cyclohexadiene[32] or ammonium formate[33] failed to provide **13** as cleanly, rapidly, or dependably. Similarly, treatment of **10** (R = CH_2Ph) with Bu_3SnH (C_6H_6, 80 °C, cat. AIBN, 59%) followed by hydrogenolysis of the two benzyl ethers provided **13** in an overall comparable conversion. While unanticipated, the preferential generation and use of the THP enol ether proved especially attractive, since it provides the opportunity to differentially protect the two hydroxymethyl substituents. In principle, this provides access to resolution through covalent derivatization of a mono alcohol (e.g., esterification with (*R*)-*O*-acetylmandelic acid)[14-16] with use of the resulting two diastereomers for the independent preparation of the two C_2BI enantiomers *or* for independent conversion to a single enantiomer with full use of the racemic material should this prove necessary.

Without further optimization of the preliminary studies, the application of the approach to the preparation of C_2BI was pursued. Reaction of 1-(benzyloxy)-3-naphthylamine (**14**)[16] with TsCl (99%) followed by selective low-temperature, acid-catalyzed[34] C4 bromination of **15** with NBS provided **16** (92%, Scheme IV). Alkylation of the sodium salt of **16** with 3-(benzyloxy)-1-bromo-2-propanone (**6**) conducted in DMF at 0 °C provided **17** cleanly (89–95%). Reaction of **17** with $Ph_3P{=}CH(OTHP)$[26] conducted following the protocol detailed in the preliminary studies in which the low-temperature generation of the Wittig reagent was conducted at −78 °C in THF and was followed by addition of HMPA and further reaction with **17** for an extended period (48 h, 25 °C) provided **18** dependably in good yield (69%). Conventional alternatives to this procedure were less successful[26] and may be attributed to the slow elimination of triphenylphosphine oxide from the initial adduct.[35] The key 5-*exo*-*trig* free-radical cyclization of **18** proceeded smoothly upon treatment with Bu_3SnH to provide **19** in excellent yield (91%) and without the detection of product derived from 6-*endo*-*trig* closure. Acid-catalyzed deprotection of the THP group[31] (92–96%) followed by catalytic hydrogenolysis of the two benzyl groups in the presence of HOAc as an acid catalyst dependably provided **21** (93%). Procedures for hydrogenolysis conducted in the absence of the deliberately added acid catalyst proved slow and capricious and often halted prior to completion, while hydrogenolysis reactions conducted under modest pressures of H_2 (20% w/w 10% Pd-C,

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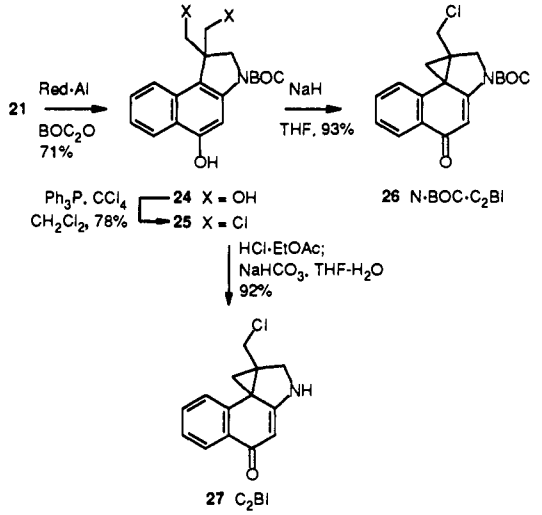
(35) The initial adduct was isolated and characterized: ^1H NMR (200 MHz, $CDCl_3$) δ 8.4–7.1 (m, 34 H), 6.55 and 6.38 (two d, 1 H, J = 3 Hz), 5.89 and 5.71 (two d, 1 H, J = 3 Hz), 5.3–4.8 (m, 3 H), 4.7–3.7 (m, 6 H), 3.3–2.7 (m, 2 H), 2.45 (s, 3 H, CH_3), 1.8–1.2 (m, 6 H); ^{32}P NMR (80 MHz, $CDCl_3$) δ 6.37 (s, H_3PO_4 was used as the reference at δ 0.0).

Scheme V



50 psi, EtOH, 23 °C, 24 h) or for prolonged reaction periods (48 h versus 24 h) resulted in detectable (5–15%) overreduction of the central aromatic ring of the substrate.

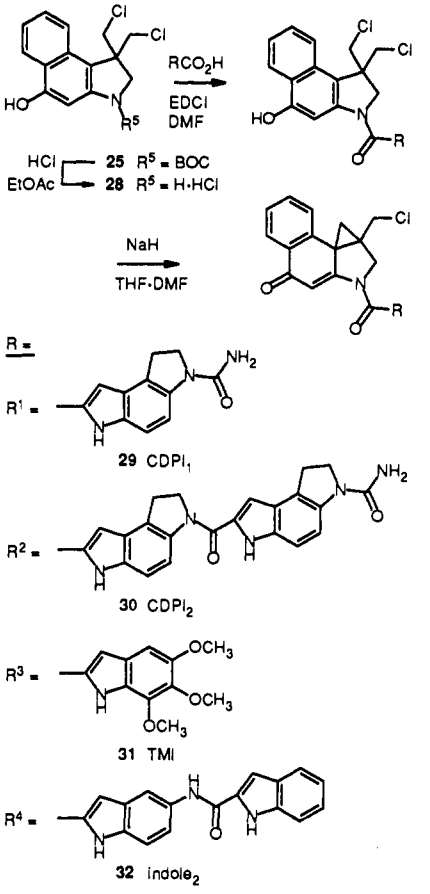
Uneventful conversion[36] of **21** to the dichloride **22** provided an intermediate that proved to be surprisingly easy to handle and purify (SiO_2 chromatography) without contaminant closure to the cyclopropane-containing agents.[18] Spirocyclization of **22** to *N*-Ts-C_2BI was found to occur readily, and simple treatment of **22** with 5% aqueous $NaHCO_3$–THF (25 °C, 1 h, 91%) proved sufficient to promote the cyclopropane ring closure. Alternatively, treatment of **22** with NaH under anhydrous conditions (THF, 23 °C, 30 min, 84%) provided **23** in good yield.

Reductive removal of the sulfonamide which was necessarily introduced to permit the alkylation of **16** with **6** proved to be best conducted with Red-Al[37] (toluene–DME, 100 °C, 4 h) at the stage of triol **21** followed by immediate protection of the sensitive indoline through reaction with $(BOC)_2O$ to provide **24** (71% overall, Scheme V). The successful removal of the sulfonamide required 6 equiv of reagent to compensate for the substrate triol and was not successful when conducted in the absence of DME as cosolvent, which insures the substrate solubility under the reaction conditions. Conversion[36] of **24** to the stable dichloride **25** (78%) followed by spirocyclization upon treatment with NaH (THF, 30 min, 23 °C, 93%) or 5% aqueous $NaHCO_3$–THF (1 h, 23 °C, 50%) provided *N*-BOC-C_2BI (**26**). Acid-catalyzed deprotection of **25** followed by treatment of the crude hydrochloride salt with 5% aqueous $NaHCO_3$–THF (25 °C, 2 h, 92%) provided C_2BI (**27**).

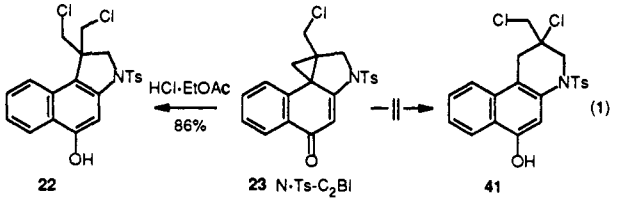
The C_2BI subunit was incorporated into analogs of CC-1065 and duocarmycin A as detailed in Scheme VI. Acid-catalyzed deprotection of **25** (3 M HCl–EtOAc, 23 °C, 30 min) followed by amide coupling of the crude hydrochloride salt **28** with $CDPI_1$[38] (**29**, 4 equiv of EDCI, DMF, 23 °C, 12 h, 81%), $CDPI_2$[38] (**30**, 3 equiv EDCI, DMF, 23 °C, 12 h, 77–86%), 5,6,7-trimethoxyindole-2-carboxylic acid[15] (**31**, 3 equiv EDCI, DMF, 23 °C, 12 h, 71%), and **32**[17] (3 equiv EDCI, DMF, 23 °C, 12 h, 68%) provided the seco-C_2BI agents **33**, **35**, **37**, and **39**, respectively (Scheme VI). Subsequent treatment of the seco-C_2BI agents with excess NaH (2–6 equiv) in THF–DMF at 0 °C for 0.5–2 h provided the C_2BI agents **34**, **36**, **38**, and **40** in excellent yields (75–86%).

Important characteristics of the alkylation subunit of CC-1065 and related analogs are the relative solvolysis reactivity[16,20] and the site of cyclopropane cleavage. Past agents including those bearing the CPI, CI, or CBI subunits undergo a stereoelectronically-controlled ring opening with addition of a nucleophile to the least substituted cyclopropane carbon. With the additional

Scheme VI



C9a chloromethyl substitution of the C_2BI agents, it remained to be determined if the solvolytic ring opening would proceed under stereoelectronic control with nucleophilic addition to the unsubstituted cyclopropane carbon or proceed through a stable tertiary carbocation with ring expansion[39] (eq 1). Treatment of **23** with



anhydrous HCl at −78 or 0 °C in EtOAc provided exclusively **22** with no trace of the ring expansion product **41**, indicating that the C9a substitution of the C_2BI agents does not alter the solvolytic behavior of the agents. Like the preceding examples, this may be attributed to the near perfect alignment of the σ C8b–C9 cyclopropane bond with the cyclohexadienone π-system versus the near orthogonal alignment of the σ C8b–C9a cyclopropane bond, which leads to preferential C8b–C9 bond cleavage and nucleophilic addition at C9. In addition, the inductive effect of the electron deficient chloromethyl substituent should destabilize the tertiary carbocation and may be further contributing to the deceleration of the cyclopropane cleavage with ring expansion. Similar to *N*-BOC-CPI and *N*-BOC-CBI, *N*-BOC-C_2BI was found to be stable in aqueous solution at a pH of 7 and exhibited no significant solvolysis or decomposition at a pH of 5–7 over a 2-week period. At a pH of 3, *N*-BOC-C_2BI (**26**, $t_{1/2}$ = 433 h) proved to be substantially more stable than *N*-BOC-CBI ($t_{1/2}$ = 133 h) or *N*-BOC-CPI ($t_{1/2}$ = 37 h) to solvolysis (Table I). Presumably

(36) Hooz, J.; Gilani, S. S. H. *Can. J. Chem.* **1968**, *46*, 86.
(37) Gold, E. H.; Babad, E. *J. Org. Chem.* **1972**, *37*, 2208.
(38) Boger, D. L.; Coleman, R. S.; Invergo, B. J. *J. Org. Chem.* **1987**, *52*, 1521.
(39) For example: Stork, G.; Marx, M. *J. Am. Chem. Soc.* **1969**, *91*, 2371. Stork, G.; Gregson, G. *J. Am. Chem. Soc.* **1969**, *91*, 2373. For a summary of an extensive study of the reactions of electrophilic cyclopropanes, see: Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66.

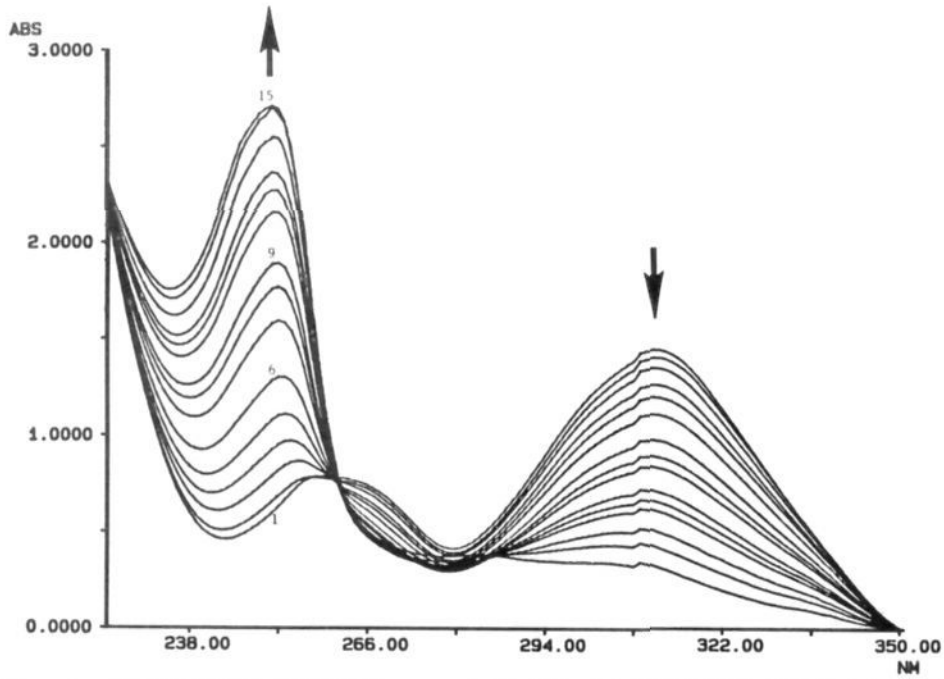


Figure 2. UV–visible spectra of *N*-BOC-C_2BI in 50% CH_3OH–aqueous buffer (pH = 3.0, 4:1:20 (v/v/v) of 0.1 M citric acid, 0.2 M Na_2HPO_4, and H_2O, respectively) recorded at various intervals. The solution was kept in the dark at 23 °C. Only a few spectra were shown for clarity. 1, 0 h; 2, 47 h; 3, 95 h; 4, 143 h; 5, 191 h; 6, 264 h; 7, 360 h; 8, 481 h; 9, 552 h; 10, 722 h; 11, 817 h; 12, 912 h; 13, 1200 h; 14, 1757 h; 15, 2478 h.

this may be attributed to the steric or inductive electronic effect of the added chloromethyl substituent. The solvolysis of *N*-BOC-C_2BI was followed spectrophotometrically with the disappearance of the UV long-wavelength absorption band of the C_2BI chromophore (314 nm) and with the appearance of a short-wavelength absorption band (256 nm) attributable to the seco-C_2BI derivatives (Figure 2). Like CPI and CBI, C_2BI (**27**) itself proved essentially stable to solvolysis even at a pH of 3, exhibiting no change after 1 week and only slowly undergoing solvolysis when monitored over a 3-month period. This presumably results from preferential N-protonation versus carbonyl O-protonation required of solvolysis.

A preliminary examination of the DNA alkylation properties of C_2BI-CDPI$_2$ (**36**) within duplex w794 DNA,[19b,23] for which comparison results are available for related agents,[17-21] was conducted in efforts to demonstrate the event and selectivity of DNA alkylation and the DNA cross-linking capabilities. The demonstration of DNA alkylation and the identification of the adenine N3 alkylation sites[40] were obtained from the thermally-induced strand cleavage of singly ^{32}P end-labeled double-stranded DNA after exposure to the agents following past protocols.[19b] Thus, incubation of **36** and its seco precursor **35** with the labeled w794 duplex DNA (25 and 37 °C, 24 h), removal of the unbound agent by EtOH precipitation of the DNA, resuspension of the alkylated DNA in aqueous buffer, thermolytic treatment (100 °C, 30 min) to induce strand cleavage at the adenine N3 alkylation sites, and electrophoresis of the resultant DNA adjacent to Sanger sequencing standards[41] under denaturing conditions followed by autoradiography permitted identification of the sites of DNA alkylation (Figure 3). The seco agent **35** proved to be approximately 100 times more effective than C_2BI-CDPI$_2$ at alkylating DNA under the conditions of the preliminary examination and the two agents exhibited a comparable DNA alkylation selectivity. Moreover, the selectivity of the DNA alkylation appears to represent an average composite of the readily distinguishable alkylation profiles of (+)-CBI-CDPI$_2$ and (−)-CBI-CDPI$_2$. For example, the w794 high-affinity alkylation site for (+)-CBI-CDPI$_2$

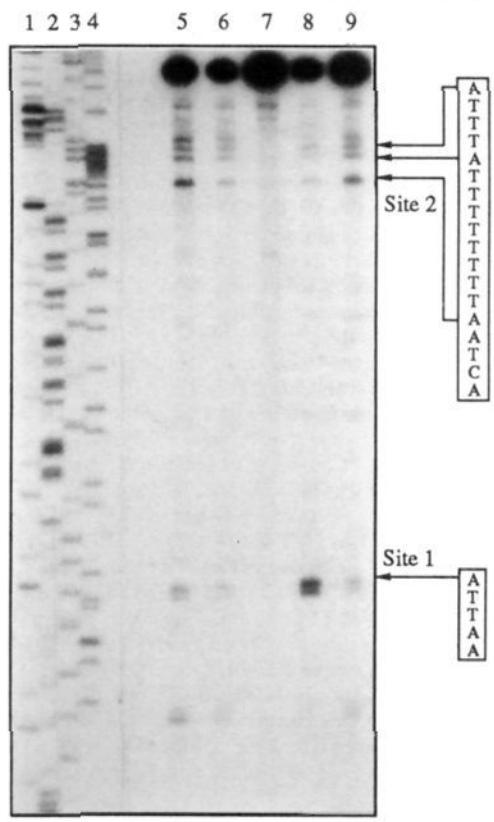


Figure 3. Thermally-induced strand cleavage of w794 duplex DNA (SV40 DNA segment, 144 base pairs, nucleotide no. 138–5238). DNA-agent incubation at 25 or 37 °C (24 h), removal of unbound agent, and 30-min thermolysis (100 °C) followed by denaturing 8% PAGE and autoradiography. Lanes 1–4, Sanger G, C, A, and T reactions; lane 5, 0.01 M **35** at 25 °C; lane 6, 1 M **36** at 25 °C; lane 7, control DNA; lane 8, 0.01 M **35** at 37 °C; lane 9, 1 M **36**.

is the single site 1 (5′-AATTA) and that of (−)-CBI-CDPI$_2$ is primarily the single site 2 (5′-ATTTT) with little or no crossover alkylation between these two sites.[20] In contrast, both sites

(40) The efficiency of the adenine N3 alkylation and the detection of potentially non-thermally-labile alkylation sites are under active investigation.
(41) Sanger, F.; Nicklen, S.; Coulsen, A. R. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 5463.

Table I

	N-BOC-CPI[a]	N-BOC-Cl[a]	N-BOC-CBI[a]	N-BOC-C$_2$BI	N-Ts-C$_2$BI	C$_2$BI	CBI
IR, C=O (cm^{-1})	1725, 1570	1705, 1618	1718, 1628, 1602	1734, 1709, 1635	1624, 1599	1611, 1581	1610, 1586
UV, λ_{max} (nm) (ϵ)	344 (12 000)	294 (14 000)	300 (19 000)	309 (15 000)	305 (9300)	332 (8200)	316 (11 000)
	278 (17 000)	258 (21 000)	264 (5700)	258 (8700)	258 (6800)	255 (11 000)	
k (s^{-1}, pH = 3)	(5.26 ± 0.08) × 10^{-6}	(1.98 ± 0.06) × 10^{-2}	(1.45 ± 0.01) × 10^{-6}	(4.40 ± 0.08) × 10^{-7}	nd	(8.46 ± 0.06) × 10^{-8}[b]	(2.07 ± 0.33) × 10^{-7}
$t_{1/2}$ (pH = 3)	36.7 h	35 s	133 h	433 h	nd	2275 h[b]	930 h
$t_{1/2}$ (pH = 7)	stable	5.24 h	stable	stable	nd	stable	stable
rel $t_{1/2}$ (pH = 3)	1.0	0.00026	3.6	11.8	nd	62[b]	25

[a] Taken from refs 14–16. [b] Extrapolated value.

constitute nearly equivalent high-affinity alkylation sites for **35** and **36**.[42] Notably, both sites provide the opportunity for the adenine–adenine cross-linking detailed in Scheme I and illustrated in Figure 1. Similarly, the remaining two sites labeled in Figure 3 constitute low-affinity alkylation sites for (+)-CBI-CDPI$_2$ and are not alkylated by (−)-CBI-CDPI$_2$. However, the complementary strand houses high-affinity alkylation sites for (−)-CBI-CDPI$_2$ adjacent to these sites one base pair removed in the 5′ direction. It is likely that alkylation at the complementary strand high-affinity alkylation sites leads to cross-linking with induced high-affinity alkylation at these two sites as illustrated in Figure 1. A detailed examination of the DNA alkylation selectivity of **25–26** and **33–40** is in progress, and the results of this study should prove revealing.

The DNA cross-linking properties of seco-C$_2$BI-CDPI$_2$ (**35**) were examined within w794 duplex DNA under conditions which may be compared directly to the results of the w794 strand cleavage assay detailed above. Using this protocol, the preliminary studies were anticipated to provide a qualitative assessment of the relative efficiency of cross-linking versus DNA monoalkylation. Thus, treatment of the singly 5′ end-labeled w794 DNA with **35** (25 °C, 24 h) was conducted as detailed above with the exception that the alkylated DNA was not subjected to the thermal strand cleavage reaction conditions. Gel electrophoresis of the resultant DNA under denaturing conditions followed by autoradiography provided two bands, one of which proved to be the cross-linked DNA[43] (Figure 4). The faster moving lower molecular weight band constitutes the unmodified or alkylated but noncross-linked single-stranded labeled DNA, and the slower moving band constitutes the cross-linked duplex DNA (template-labeled DNA cross-link). The agent **35** exhibited detectable DNA cross-linking at 10^{-3} M, which was the lowest concentration at which DNA alkylation was detected (Figure 3), exhibited 20% cross-linking at 10^{-2} M, which was a concentration at which 35% DNA alkylation was observed, and exhibited nearly complete (98%) cross-linking of the duplex DNA at 10^{-1} M, the concentration at which approximately 80–100% of the labeled DNA was alkylated. Thus, the cross-linking by **35** was observed at concentrations essentially identical to that required for observation of DNA alkylation, suggesting a high cross-linking efficiency.[43]

A full study of the DNA alkylation properties and biological properties of the agents detailed herein is in progress, and the results will be disclosed in due course.

Experimental Section[44]

Benzyl Propargyl Ether (3). A solution of KOH (20.7 g, 370 mmol) in dry CH_3SOCH_3 (60 mL) was cooled in an ice bath and treated sequentially with benzyl alcohol (10.0 g, 92.6 mmol) and propargyl bromide (27.5 g, 185.2 mmol, 2 equiv).[25b] The reaction mixture was stirred for 1 h at 23 °C before being diluted with Et_2O (350 mL) and H_2O (100 mL). The organic layer was separated, washed with H_2O (4 × 100 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatog-

(42) Site 1 is the w794 high-affinity site modeled in Figure 1.

(43) A quantitative assessment of the cross-linking efficiency of **35** and the full comparison with **33–40** is under study. Control experiments employing psoralen cross-linking ($h\nu$ 365 nm, 1 h) under identical conditions provided 5%, 20%, and 40% cross-linking at 10^{-3}, 10^{-2}, and 10^{-1} M, respectively.

(44) Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were obtained on a Varian Gemini 200, a Varian VXR-500S or a Bruker AM 400 spectrometer. Infrared spectra were recorded on a Perkin-Elmer IR 1420 and 1600 series FTIR. UV spectra were recorded on a Varian Cary 4 UV-Visible spectrophotometer. Preparative centrifugal thin-layer chromatography (PCTLC) was performed on a Harrison Model 7924 Chromatotron (Harrison Research, Palo Alto, CA) using Merck Silica gel 60 PF_{254} containing $CaSO_4 \cdot 0.5H_2O$ binder. Medium pressure liquid chromatography (MPLC) and flash chromatography were performed on Merck silica gel 60 (230–400 mesh) at a pressure between 5 and 30 psi. The solvents used for reactions and recrystallization were freshly distilled under N_2. THF, C_6H_6, p-dioxane, and Et_2O were distilled from sodium and benzophenone. Methanol (CH_3OH) was distilled from magnesium turnings, and DMF was distilled from CaH_2. Hexanes and EtOAc were distilled before use. All the reactions requiring anhydrous conditions or an inert atmosphere were performed under a positive pressure of dry Ar. Bulb-to-bulb distillations were carried out with a Kugelrohr distillation apparatus (Aldrich Chemical Company, Milwaukee, WI), and the boiling range given refers to the internal oven temperature.

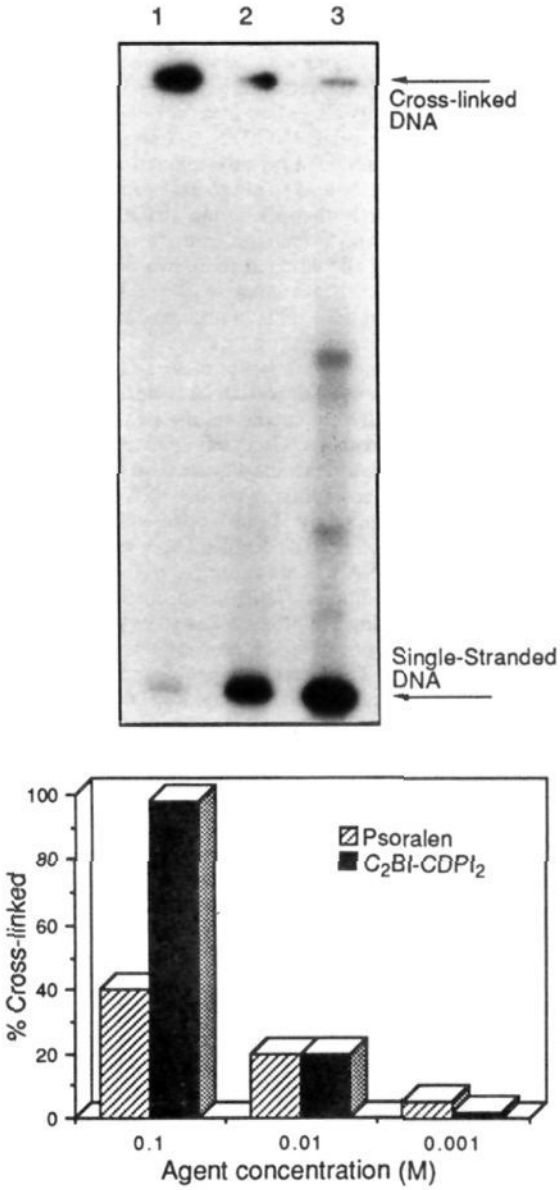


Figure 4. Cross-linking study of seco-C_2BI-CDPI$_2$ (**35**) with w794 duplex DNA. DNA-agent incubation at 25 °C (24 h, pH 6) and removal of unbound agent followed by denaturing 8% PAGE and autoradiography. Lanes 1–3, 0.1, 0.01, and 0.001 M **35**. Quantification of the extent of cross-linking was conducted using a scanning laser densitometer and run adjacent to psoralen ($h\nu$ 365 nm, 1 h) as a positive cross-linking control (data not shown).

raphy (5 × 20 cm SiO_2, 10% EtOAc–hexane) afforded **3** (12.9 g, 96%) as a clear liquid. The liquid was distilled (bulb-to-bulb; 70–80 °C, 2.5 mm/Hg): ^{1}H NMR ($CDCl_3$, 200 MHz δ 7.4–7.2 (m, 5 H), 4.57 (s, 2 H, $PhCH_2$), 4.13 (d, 2 H, J = 2 Hz, $CH_2C{\equiv}CH$), 2.46 (t, 1 H, J = 2 Hz, $C{\equiv}CH$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 137.4, 128.5, 128.2, 128.0, 79.6, 74.5, 71.5, 57.0; IR (neat) ν_{max} 2854, 1494, 1449, 1350, 1260, 1202, 1085, 1022, 937, 740 cm^{-1}; FABMS (NBA) m/e (relative intensity) 145 ($M - H^+$), 91 (100); FABHRMS m/e 145.0656 ($C_{10}H_{10}O - H^+$ requires 145.0653).

Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 82.10; H, 6.95.

1-(Benzyloxy)propan-2-one (4). A solution of H_2O (41.8 mL), concentrated H_2SO_4 (1.76 mL), mercury(II) oxide (red, 1.11 g, 5.1 mmol)[25c] was stirred at 60 °C, and benzyl propargyl ether (**3**, 12.9 g, 88.4 mmol) was added dropwise over 2 h. The reaction mixture was stirred at 60 °C for an additional 10 min, cooled to 25 °C, and diluted with Et_2O (200 mL). The aqueous layer was separated and extracted with Et_2O (2 × 50 mL). The Et_2O layers were combined, washed with saturated aqueous NaCl (2 × 100 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Distillation (bulb-to-bulb; 80–90 °C, 2 mm/Hg) afforded **4** (13.5 g, 93%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.5–7.3 (m, 5 H), 4.56 (s, 2 H, $PhCH_2$), 4.03 (s, 2 H, $CH_2C{=}O$), 2.12 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 206.6, 137.2, 128.3, 127.8, 127.7, 75.0, 73.0, 25.9; IR (neat) ν_{max} 3027, 2859, 1726, 1494, 1450, 1356, 1116, 1021, 978, 912 cm^{-1}; CIMS (2-methylpropane) m/e 165 (M + H$^+$); CIHRMS m/e 165.0914 ($C_{10}H_{12}O_2 + H^+$ requires 165.0916).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.26; H, 7.54.

3-(Benzyloxy)-1-bromopropan-2-one (6). A solution of **4** (1.0 g, 6.1 mmol) in CH_3OH cooled to 0 °C was treated with Br_2 (0.98 g, 6.1 mmol, 1.0 equiv) dropwise, and the mixture was stirred at 23 °C for 6 h.[25d] The reaction mixture was diluted with H_2O (50 mL) and extracted with $CHCl_3$ (2 × 50 mL). The $CHCl_3$ layers were combined, washed with H_2O (25 mL), and stirred with a mixture of H_2O (60 mL) and trifluoroacetic acid (60 mL) for 10 h at 23 °C to hydrolyze[25e] the dimethyl ketal **5**. The $CHCl_3$ layer was separated, dried (Na_2SO_4, 0 °C), treated with basic alumina (10 g), and filtered. The filtrate was concentrated in vacuo, and **6** was used immediately without further purification: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.4–7.3 (m, 5 H), 4.62 (s, 2 H, $PhCH_2$), 4.28 (s, 2 H, CH_2Br), 4.06 (s, 2 H, $CH_2C{=}O$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 209.1, 137.3, 128.8, 128.4, 128.1, 73.7, 73.1, 31.4; IR (neat) ν_{max} 2865, 1701, 1597, 1455, 1390, 1280, 1204, 1111, 828, 747, 699 cm^{-1}; CIMS (2-methylpropane) m/e (relative intensity) 243/245 (M + H$^+$, 55/54), 91 (100); FABHRMS (NBA–NaI) m/e 264.9850 ($C_{10}H_{11}BrO_2$ + Na$^+$ requires 264.9840).

1-(Benzyloxy)-*N*-tosyl-3-naphthylamine (15). A solution of 1-(benzyloxy)-3-naphthylamine[16] (**14**, 553 mg, 2.22 mmol) and *p*-toluenesulfonyl chloride (552 mg, 2.89 mmol, 1.3 equiv) in pyridine (18.5 mL) was stirred under Ar for 48 h at 25 °C. The reaction mixture was diluted with EtOAc (100 mL), washed with aqueous 1 N HCl (3 × 50 mL), H_2O (2 × 50 mL), and saturated aqueous NaCl (50 mL), and dried (Na_2SO_4). The solution was filtered and concentrated in vacuo. Flash chromatography (3.5 × 25 cm SiO_2, 20% EtOAc–hexane) afforded **15** (889 mg, 99%) as a white solid: mp 144–145 °C (white needles, EtOAc–hexane); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.3–6.8 (m, 15 H), 6.62 (b s, 1 H, NH), 5.21 (s, 2 H, CH_2), 2.34 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 155.5, 144.0, 136.8, 135.9, 134.6, 134.5, 129.8, 128.7, 128.1, 127.5, 127.4, 127.3, 127.2, 124.8, 123.6, 122.2, 110.4, 100.9, 70.1, 21.3; IR (solid film) ν_{max} 3251, 3067, 1631, 1580, 1456, 1410, 1282, 1154, 1092, 903, 723 cm^{-1}; EIMS m/e (relative intensity) 403 (M$^+$, 18), 248 (7), 91 (100); EIHRMS m/e 403.1242 ($C_{24}H_{21}NO_3S$ requires 403.1242).

Anal. Calcd for $C_{24}H_{21}NO_3S$: C, 71.44; H, 5.25; N, 3.47; S, 7.95. Found: C, 71.46; H, 5.25; N, 3.57; S, 7.84.

4-(Benzyloxy)-1-bromo-*N*-tosyl-2-naphthylamine (16). A solution of **15** (250 mg, 0.62 mmol), NBS (144 mg, 0.81 mmol, 1.3 equiv), and catalytic H_2SO_4 (2.2 mL of a solution prepared by addition of 2 drops of concentrated H_2SO_4 to 5 mL of THF) in THF (12.6 mL) was stirred at −78 °C under Ar for 8.5 h. The reaction mixture was diluted with EtOAc (100 mL), washed with saturated aqueous $NaHCO_3$ (2 × 50 mL) and saturated aqueous NaCl (2 × 50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (3 × 10 cm SiO_2, 10% EtOAc–hexane) afforded **16** (275 mg, 92%) as a white solid: mp 159–160 °C (white needles, H_2O–EtOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.30–7.00 (m, 15 H), 5.25 (s, 2 H, $PhCH_2$), 2.21 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 154.5, 144.2, 136.3, 135.8, 133.0, 132.2, 129.6, 128.7, 128.5, 128.2, 127.5, 127.2, 126.5, 125.3, 124.5, 122.5, 104.8, 101.1, 70.1, 21.2; IR (KBr) ν_{max} 3256, 3034, 1596, 1430, 1386, 1360, 1344, 1310, 1266, 1170, 984, 738, 694, 590 cm^{-1}; CIMS (2-methylpropane) m/e (relative intensity) 482/484 (M + H$^+$, 97/100); CIHRMS m/e 482.0420 ($C_{24}H_{20}BrNO_3S$ + H$^+$ requires 482.0425).

Anal. Calcd for $C_{24}H_{20}BrNO_3S$: C, 59.76; H, 4.18; N, 2.90; S, 6.65. Found: C, 59.81; H, 4.20; N, 2.85; S, 6.71.

4-(Benzyloxy)-*N*-(3′-(benzyloxy)propan-2′-one)-1-bromo-*N*-tosyl-2-naphthylamine (17). A solution of **16** (918 mg, 1.9 mmol) in DMF (9.5 mL) under Ar was stirred with NaH (98.8 mg of 60% oil dispersion, 2.47 mmol, 1.3 equiv) at 23 °C for 2 h. The solution was cooled to 0 °C, 3-(benzyloxy)-1-bromopropan-2-one (**6**, 5.32 g, 16 mmol) was added, and the reaction mixture was stirred at 0 °C (24 h) and at 25 °C (24 h). The reaction mixture was poured onto H_2O (100 mL) and extracted with EtOAc (3 × 100 mL). The EtOAc layers were combined, washed with H_2O (50 mL) and saturated aqueous NaCl (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (3 × 40 cm SiO_2, 25% EtOAc–hexane) afforded **17** (1.21 g, 89%) as a white solid: mp 129–130 °C (white needles, EtOAc–hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.4–7.2 (m, 19 H), 5.14 (s, 2 H, $PhCH_2OAr$), 5.09 and 4.43 (two d, 2 H, J = 20 Hz, NCH_2CO), 4.59 and 4.54 (two d, 2 H, J = 12 Hz, OCH_2Ph), 4.20 and 4.12 (two d, 2 H, J = 17 Hz, $COCH_2O$), 2.41 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 203.7, 154.1, 143.9, 137.2, 136.9, 136.5, 136.3, 132.7, 129.6, 128.8, 128.7, 128.4, 128.3, 128.1, 128.0,

127.9, 127.8, 127.6, 127.0, 126.6, 122.7, 115.8, 110.8, 73.9, 73.7, 70.4, 58.8, 21.4; IR (KBr) ν_{max} 2922, 1742, 1592, 1500, 1454, 1388, 1340, 1266, 1162, 1094, 1028, 982, 764, 738, 698, 670 cm^{-1}; CIMS (2-methylpropane) *m/e* (relative intensity) 644/646 (M + H^+, 2), 157 (100); CIHRMS *m/e* 644.1106 ($C_{34}H_{30}BrNO_5S$ + H^+ requires 644.1106).

Anal. Calcd for $C_{34}H_{30}BrNO_5S$: C, 63.45; H, 4.67; N, 2.18. Found: C, 63.17; H, 4.41; N, 2.20.

4-(Benzyloxy)-*N*-[2′-[(benzyloxy)methyl]-1′-[[tetrahydro-2′*H*-pyran-2′-yl]oxy]-3′-propenyl]-1-bromo-*N*-tosyl-2-naphthylamine (18). A suspension of $Ph_3PCH_2(OTHP)Cl$[26] (1.15 g, 0.93 mmol, 2 equiv) in THF (3 mL) at −78 °C under N_2 was treated with *n*-BuLi (1.7 M, 1.65 mL, 0.93 mmol), and the mixture was stirred at −78 °C (5 min) and at 25 °C (30 min). The reaction mixture was recooled to −78 °C and stirred for 5 min. HMPA (3.9 mL, 16 equiv) followed by **17** (900 mg, 0.47 mmol) in THF (4.0 mL) were added dropwise. The reaction mixture was stirred at −78 °C (30 min) and at 25 °C (48 h). The reaction mixture was poured on phosphate buffer (100 mL, pH = 7.0) and extracted with EtOAc (4 × 100 mL). The EtOAc layers were combined, washed with H_2O (3 × 100 mL) and saturated aqueous NaCl (100 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (3 × 20 cm SiO_2, 20% EtOAc–hexane containing 6% Et_3N) afforded **18** (718 mg, 69%) as a thick yellow oil; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.4–6.6 (m, 19 H), 6.17 and 6.14 (two s, 1 H, cis and trans C=CH), 5.2–5.0 (m, 2 H, $ArOCH_2Ph$), 4.8–3.7 (m, 7 H), 3.0–2.2 (m, 2 H), 2.43 (s, 3 H, CH_3), 1.4–1.0 (m, 6 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 153.9, 153.7, 146.4, 146.2, 143.6, 143.4, 138.8, 138.0, 137.4, 136.6, 136.3, 135.9, 133.0, 132.9, 129.6, 129.5, 128.8, 128.5, 128.4, 128.2, 128.1, 127.6, 127.5, 127.4, 126.8, 126.7, 126.5, 126.4, 122.4, 122.3, 118.2, 117.0, 110.5, 109.8, 109.7, 108.6, 97.7, 97.6, 72.3, 72.2, 70.2, 70.1, 69.3, 69.0, 60.3, 60.0, 45.7, 45.0, 28.6, 28.5, 24.4, 24.3, 21.4, 17.2, 17.0; IR (neat) ν_{max} 2940, 1674, 1589, 1497, 1446, 1413, 1345, 1266, 1227, 1159, 1092, 1068, 956, 906, 813, 697 cm^{-1}; CIMS (2-methylpropane) *m/e* (relative intensity) 742/744 (M + H^+, 0.5/0.5), 484/482 (100/99); FABHRMS (NBA) *m/e* 742.1775 ($C_{40}H_{40}BrNO_6S$ + H^+ requires 742.1838).

5-(Benzyloxy)-1-((benzyloxy)methyl)-1-((2′-tetrahydropyranyloxy)-methyl)-*N*-tosyl-1,2-dihydro-3*H*-benz[*e*]indole (19). A solution of **18** (395 mg, 0.53 mmol), Bu_3SnH (308 mg, 1.06 mmol, 2 equiv), and AIBN (15.4 mg, 0.11 mmol, 0.2 equiv) in C_6H_6 (10.6 mL) under Ar was warmed at 80 °C for 8 h. The reaction mixture was cooled to 25 °C and concentrated in vacuo. Flash chromatography (3 × 10 cm SiO_2, 17% EtOAc–hexane containing 2.3% Et_3N) afforded **19** (321 mg, 91%) as a clear oil; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.33 (d, 1 H, *J* = 7 Hz), 7.96 (d, 1 H, *J* = 7 Hz), 7.7–7.0 (m, 17 H), 5.38 (s, 2 H, $ArOCH_2Ph$), 4.40 (s, 1 H, OCHO), 4.32 (d, 2 H, *J* = 4 Hz, OCH_2Ph), 4.1–3.2 (m, 8 H), 2.29 (s, 3 H, CH_3), 1.5–1.2 (m, 6 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 155.7, 144.0, 141.0, 138.2, 137.1, 133.9, 133.8, 131.5, 131.4, 130.9, 129.7, 128.8, 128.4, 128.3, 128.2, 127.6, 127.5, 124.1, 123.9, 123.5, 123.3, 118.1, 98.9, 98.6, 96.4, 96.3, 73.3, 72.2, 70.1, 69.8, 61.3, 56.8, 51.1, 30.0, 25.1, 21.3, 18.9; IR (neat) ν_{max} 2940, 1624, 1516, 1454, 1404, 1354, 1202, 1110, 1032, 870, 842, 762, 698 cm^{-1}; EIMS *m/e* (relative intensity) 663 (M^+, 4), 579 (11), 518 (5), 458 (14), 91 (100); CIHRMS (2-methylpropane) *m/e* 664.2713 ($C_{40}H_{41}NO_6S$ + H^+ requires 664.2733).

5-(Benzyloxy)-1-((benzyloxy)methyl)-1-(hydroxymethyl)-*N*-tosyl-1,2-dihydro-3*H*-benz[*e*]indole (20). A solution of **19** (321 mg, 0.48 mmol) in CH_3OH (4 mL) was stirred with Amberlyst H-15[31] (144 mg, 0.048 mequiv) at 45 °C for 4 h. The reaction mixture was filtered through a Celite plug, and the Celite plug was washed with EtOAc (3 × 15 mL). The organic layers were combined and concentrated in vacuo. Flash chromatography (2 × 20 cm SiO_2, 25% EtOAc–hexane) afforded **20** (258 mg, 92%) as a colorless oil: ^1H NMR ($CDCl_3$, 600 MHz) δ 8.40–7.00 (m, 19 H), 5.39 and 5.36 (two d, 2 H, *J* = 12 Hz, $ArOCH_2Ph$), 4.41 and 4.37 (two d, 2 H, *J* = 12 Hz, CH_2OH), 4.21 (d, 1 H, *J* = 11 Hz, C2-H_2), 4.16 and 4.07 (two d, 2 H, *J* = 12 Hz, CH_2OCH_2Ph), 3.98 and 3.24 (two d, 2 H, *J* = 9 Hz, CH_2OCH_2Ph), 3.62 and 3.61 (two d, 1 H, *J* = 6 Hz, C2-H_2), 2.31 (s, 3 H, CH_3), 2.20 (b s, 1 H, OH); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 155.8, 144.0, 141.2, 137.3, 136.7, 133.6, 130.9, 129.6, 128.7, 128.6, 128.4, 128.1, 128.0, 127.9, 127.6, 127.4, 127.3, 123.6, 123.5, 122.8, 116.3, 96.5, 74.5, 73.7, 70.2, 67.1, 56.7, 52.2, 21.5; IR (neat) ν_{max} 3582, 2924, 1622, 1516, 1496, 1454, 1404, 1352, 1272, 1108, 1028, 840, 764, 738, 698, 668 cm^{-1}; CIMS (2-methylpropane) *m/e* 580 (M + H^+); CIHRMS *m/e* 580.2147 ($C_{35}H_{33}NO_5S$ + H^+ requires 580.2158).

1,1-Bis(hydroxymethyl)-5-hydroxy-*N*-tosyl-1,2-dihydro-3*H*-benz[*e*]indole (21). A solution of **20** (258 mg, 0.45 mmol), 10% Pd-C (20% w/w, 52 mg), and acetic acid (5% v/v, 0.23 mL) in EtOH (4.5 mL) was stirred at 23 °C for 24 h under H_2. The reaction mixture was filtered through a Celite plug, and the Pd–C was washed with EtOAc (3 × 20 mL) and filtered. The filtrate was combined and concentrated in vacuo. PCTLC (2 mm SiO_2, 40% EtOAc–hexane) afforded **21** (165 mg, 93%) as a white solid: mp 133–134 °C (small white needles, EtOH–H_2O); ^1H NMR (CD_3OD, 600 MHz) δ 8.12 (d, 1 H, *J* = 8 Hz, C6-H), 7.88 (d, 1 H, *J* = 8 Hz, C9-H), 7.71 (d, 2 H, *J* = 8 Hz, C2′-H and C6′-H), 7.40 (s, 1 H, C4-H), 7.34 (t, 1 H, *J* = 7 Hz, C8-H), 7.26 (d, 2 H, *J* = 8 Hz, C3′-H and C5′-H), 7.22 (t, 1 H, *J* = 8 Hz, C7-H), 4.02 (s, 2 H, C2-H_2), 3.88 and 3.62 (two d, 4 H, *J* = 11 Hz, CH_2OH), 2.30 (s, 3 H, CH_3); ^{13}C NMR (CD_3OD, 50 MHz) δ 156.5, 146.0, 143.0, 135.4, 133.1, 131.0, 128.8, 128.3, 124.7, 124.5, 124.4, 124.0, 117.5, 99.2, 65.8, 57.2, 55.0, 21.3; IR (KBr) ν_{max} 3390, 2949, 1382, 1203, 1177, 1023, 705, 608, 577 cm^{-1}; CIMS (2-methylpropane) *m/e* 400 (M + H^+); CIHRMS *m/e* 400.1199 ($C_{21}H_{21}NO_5S$ + H^+ requires 400.1219).

Anal. Calcd for $C_{21}H_{21}NO_5S$: C, 63.14; H, 5.30; N, 3.51; S, 8.03. Found: C, 63.10; H, 5.39; N, 3.50; S, 8.05.

1,1-Bis(chloromethyl)-5-hydroxy-*N*-tosyl-1,2-dihydro-3*H*-benz[*e*]indole (22). A solution of **21** (5 mg, 0.013 mmol), Ph_3P (13.6 mg, 0.052 mmol, 4 equiv), and CCl_4 (24 mg, 0.16 mmol, 12 equiv) in CH_2Cl_2 (0.13 mL) was stirred at 23 °C for 20 h. The mixture was concentrated in vacuo, and PCTLC (1 mm SiO_2, 25% EtOAc–hexane) afforded **22** (4.2 mg, 76%, 76–84%) as a white solid: mp 221–222 °C (colorless needles, CH_2Cl_2–hexane); ^1H NMR ($CDCl_3$, 200 MHz) δ 8.23 (d, 1 H, *J* = 8 Hz, C5-H), 7.72 (d, 2 H, *J* = 8 Hz, C2′-H and C6′-H), 7.64 (d, 1 H, *J* = 8 Hz, C8-H), 7.49 (s, 1 H, C3-H), 7.48 (t, 1 H, *J* = 7 Hz, C7-H), 7.41 (t, 1 H, *J* = 7 Hz, C6-H), 7.25 (d, 2 H, *J* = 8 Hz, C3′-H and C5′-H), 5.74 (s, 1 H, OH), 4.15 (s, 2 H, C2-H_2), 3.97 and 3.72 (two d, 4 H, *J* = 13 Hz, CH_2OH), 2.35 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 157.2, 146.1, 143.2, 134.9, 132.0, 130.8, 128.8, 128.5, 124.9, 124.3, 124.1, 122.5, 115.0, 98.8, 57.6, 54.3, 49.6, 21.4; IR (KBr) ν_{max} 3399, 2937, 1625, 1585, 1324, 1248, 1148, 1098, 837, 807, 756, 666, 581 cm^{-1}; EIMS *m/e* (relative intensity) 435 (M^+, 13), 388 (16), 386 (51), 244 (48), 208 (29), 91 (100); EIHRMS *m/e* 435.0455 ($C_{21}H_{19}Cl_2NO_3S$ requires 435.0463).

***N*-Tosyl-9a-(chloromethyl)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (23, *N*-Ts-C_2BI).** A solution of **22** (3.7 mg, 8.5 μmol) in THF (0.43 mL) was stirred with 5% aqueous $NaHCO_3$ (0.43 mL) at 23 °C for 1 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (0.5 × 3 cm SiO_2, 33% EtOAc–hexane) afforded **23** (3.1 mg, 91%) as a white solid: mp 228–229 °C (small colorless needles, CH_2Cl_2–hexane); ^1H NMR ($CDCl_3$, 600 MHz) δ 8.25 (d, 1 H, *J* = 8 Hz, C5-H), 7.83 (d, 2 H, *J* = 8 Hz, C2′-H and C6′-H), 7.50 (t, 1 H, *J* = 8 Hz, C7-H), 7.41 (t, 1 H, *J* = 8 Hz, C6-H), 7.36 (d, 2 H, *J* = 8 Hz, C3′-H and C5′-H), 7.02 (d, 1 H, *J* = 8 Hz, C8-H), 6.72 (s, 1 H, C3-H), 4.26 (d, 2 H, *J* = 11 Hz, C1-H), 4.05 (d, 1 H, *J* = 13 Hz, C10-H), 4.00 (d, 1 H, *J* = 10 Hz, C10-H), 2.43 (s, 3 H, CH_3), 1.83 (d, 1 H, *J* = 5 Hz, C9-*exo*-H), 1.59 (d, 1 H, *J* = 5 Hz, C9-*endo*-H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 184.5, 158.3, 145.7, 137.4, 133.9, 133.0, 132.1, 130.4, 127.9, 127.6, 127.3, 121.7, 108.3, 56.5, 43.1, 37.4, 36.9, 32.5, 21.5; IR (solid film) ν_{max} 2925, 1624, 1599, 1564, 1458, 1363, 1323, 1243, 1167, 1127, 1087, 1032, 816, 776, 665 cm^{-1}; UV (CH_3OH) λ_{max} (ε) 305 (9300), 258 (6800) nm; CIMS (2-methylpropane) *m/e* (relative intensity) 400 (M + H^+, 13), 157 (100); CIHRMS *m/e* 400.0762 ($C_{21}H_{18}ClNO_3S$ + H^+ requires 400.0774).

Anal. Calcd for $C_{21}H_{18}ClNO_3S$: C, 63.08; H, 4.54; N, 3.50; S, 8.02. Found: C, 63.08; H, 4.59; N, 3.60; S, 8.03.

***N*-((*tert*-Butyloxy)carbonyl)-1,1-bis(hydroxymethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (24).** A solution of **21** (40 mg, 0.1 mmol) in DME (0.52 mL) was treated with Red-Al (0.85 M in toluene, 0.71 mL, 0.6 mmol, 6 equiv), and the mixture was warmed at 100 °C for 4 h in a Wheaton high-pressure vial. The reaction mixture was cooled to 23 °C and poured into N_2-purged phosphate buffer (pH = 7.0, 6 mL). The mixture was extracted with N_2-purged EtOAc (5 × 2.0 mL), and the organic phases were combined, dried (Na_2SO_4), filtered, and concentrated to 0.52 mL. The EtOAc solution was treated with di-*tert*-butyl dicarbonate (68 μL, 0.3 mmol), and the mixture was stirred at 23 °C for 6 h. PCTLC (1 mm SiO_2, 33% EtOAc–hexane) afforded **24** (25 mg, 71%) as a white solid: mp 213–214 °C (white needles, CH_2Cl_2–hexane); ^1H NMR ($CDCl_3$, 200 MHz) δ 8.20 (d, 1 H, *J* = 9 Hz, C6-H), 7.92 (d, 1 H, *J* = 9 Hz, C9-H), 7.69 (b s, 1 H, OH), 7.46 (t, 1 H, *J* = 8 Hz, C7-H), 7.32 (t, 1 H, *J* = 8 Hz, C8-H), 7.28 (s, 1 H, C4-H), 4.27 (d, 2 H, *J* = 11 Hz, C*H*OH), 4.18 (s, 2 H, C2-H_2), 4.08 (d, 2 H, *J* = 11 Hz, CH*H*OH), 1.58 (s, 9 H, $(CH_3)_3C$), 1.50 (b s, 2 H, OH); ^{13}C NMR (CD_3OD, 50 MHz) δ 175.5, 157.0, 153.4, 151.9, 130.5, 125.9, 125.6, 122.3, 121.7, 121.3, 120.8, 97.4, 64.8, 63.6, 53.9, 26.5; IR (KBr) ν_{max} 3324, 2968, 1755, 1675, 1624, 1581, 1399, 1334, 1247, 1145, 1094, 1014, 847, 760 cm^{-1}; FABMS (NBA–NaI) *m/e* (relative intensity) 368 (M^+ + Na, 70), 286 (100); FABHRMS *m/e* 368.1475 ($C_{19}H_{23}NO_5$ + Na^+ requires 368.1474).

3-((*tert*-Butyloxy)carbonyl)-1,1-bis(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (25). A solution of **24** (24 mg, 0.07 mmol) in CH_2Cl_2 (1.7 mL) was treated with Ph_3P (73 mg, 0.28 mmol, 4 equiv)

and CCl_4 (0.81 mL, 0.84 mmol, 12 equiv) and was stirred at 23 °C for 18 h. The reaction mixture was concentrated under a stream of N_2. PCTLC (1 mm SiO_2, 5% EtOAc–hexane) afforded **25** (21 mg, 78%) as a white solid: mp 221–222 °C (colorless needles, CH_2Cl_2–hexane); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.21 (d, 1 H, J = 8 Hz, C6-H), 7.71 (d, 1 H, J = 8 Hz, C9-H), 7.47 (t, 1 H, J = 7 Hz, C8-H), 7.32 (t, 1 H, J = 7 Hz, C7-H), 7.26 (s, 1 H, C4-H), 6.37 (b s, 1 H, OH), 4.17 (s, 2 H, C2-H_2), 4.18 and 4.10 (two d, 4 H, J = 12.0 Hz, two CH_2Cl), 1.59 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.0, 152.3, 130.6, 127.7, 127.6, 127.5, 126.9, 124.1, 122.5, 121.9, 120.8, 98.9, 77.2, 55.8, 48.9, 28.3; IR (solid film) ν_{max} 3337, 2974, 2923, 1691, 1665, 1623, 1581, 1480, 1446, 1404, 1336, 1252, 1142, 1075, 1016, 847, 762 cm^{-1}; FABMS (NBA) m/e 381 ($M + H^+$); FABHRMS m/e 381.0899 ($C_{19}H_{21}Cl_2NO_3$ + H^+ requires 381.0898).

***N*-((*tert*-Butyloxy)carbonyl)-9a-(chloromethyl)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (26, *N*-BOC-C_2BI).** A solution of **25** (3 mg, 0.008 mmol) in THF (0.24 mL) was treated with NaH (60%, 1.0 mg, 0.024 mmol, 3 equiv) and stirred at 23 °C under Ar for 30 min. A drop of H_2O was added, and the reaction mixture was extracted with EtOAc (3 × 1 mL). The EtOAc extracts were combined and concentrated in vacuo. PCTLC (1 mm SiO_2, 25% EtOAc–hexane) afforded **26** (2.5 mg, 93%) as a white solid: mp 150–151 °C (small white needles, CH_2Cl_2–hexane); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.31 (d, 1 H, J = 8 Hz, C5-H), 7.52 (t, 1 H, J = 8 Hz, C7-H), 7.44 (t, 1 H, J = 8 Hz, C6-H), 7.10 (d, 1 H, J = 8 Hz, C8-H), 6.91 (b s, 1 H, C3-H), 4.33 and 4.00 (two d, 2 H, J = 12 Hz, CH_2Cl), 4.13 and 4.10 (two d, 2 H, J = 10 Hz, C1-H_2), 1.93 (d, 1 H, J = 5 Hz, C9-H), 1.82 (d, 1 H, J = 5 Hz, C9-H), 1.57 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 184.9, 178.7, 160.3, 141.9, 137.7, 133.1, 131.7, 127.6, 126.9, 121.6, 118.8, 109.4, 77.2, 55.3, 43.7, 33.5, 28.2; IR (solid film) ν_{max} 2930, 1734, 1709, 1678, 1635, 1598, 1561, 1536, 1505, 1474, 1362, 1275, 1251, 1121, 854, 718 cm^{-1}; UV (50% CH_3OH–50% pH 3 buffer) λ_{max} (ε) 314 (14 000), 256 (7200) nm; UV (CH_3OH) λ_{max} (ε) 309 (15 000), 258 (8700), 215 (20 000) nm; FABMS (NBA–CsI) m/e (relative intensity) 478 (M^+ + Cs, 85), 418 (100); FABHRMS m/e 478.0187 ($C_{19}H_{20}ClNO_3$ + Cs^+ requires 478.0186).

Anal. Calcd for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; N, 4.05. Found: C, 65.90; H, 5.86; N, 4.07.

9a-(Chloromethyl)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (27, C_2BI). A solution of **25** (4 mg, 0.01 mmol) was stirred with 3 M HCl–EtOAc (0.5 mL) for 30 min at 23 °C. The solvent was removed under a stream of N_2, and the crude white solid was placed in 5% aqueous $NaHCO_3$ (0.5 mL) and THF (0.5 mL) and stirred at 23 °C for 2 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 1 mL). The organic layers were combined and concentrated in vacuo. PCTLC (1 mm SiO_2, 10% THF–EtOAc) afforded **27** (2.4 mg, 92%) as a thick oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.29 (d, 1 H, J = 8 Hz, C5-H), 7.46 (t, 1 H, J = 7 Hz, C7-H), 7.40 (t, 1 H, J = 7 Hz, C6-H), 7.04 (d, 1 H, J = 8 Hz, C8-H), 5.88 (s, 1 H, C3-H), 5.82 (b s, 1 H, NH), 4.32 and 4.13 (two d, 2 H, J = 12 Hz, CH_2Cl), 3.88 and 3.77 (two d, 2 H, J = 10 Hz, C1-H_2), 1.89 (d, 1 H, J = 5 Hz, C9-H), 1.78 (d, 1 H, J = 5 Hz, C9-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 183.0, 170.1, 149.2, 139.6, 136.2, 130.9, 127.3, 126.6, 122.5, 97.3, 53.3, 44.4, 40.9, 34.7; IR (solid film) ν_{max} 2917, 1611, 1582, 1547, 1478, 1335, 1276, 1222, 1192, 1133, 1030, 912, 828, 769, 730 cm^{-1}; UV (50% CH_3OH–50% pH 3 buffer) λ_{max} (ε) 339 (15 000), 276 (3300) nm; UV (CH_3OH) λ_{max} (ε) 332 (8200), 255 (sh, 11 000), 234 (sh, 17 000), 218 (25 000) nm; FABMS (NBA–CsI) m/e (relative intensity) 377 (M^+ + Cs, 40), 211 (100); FABHRMS m/e 377.9669 ($C_{14}H_{12}ClNO$ + Cs^+ requires 377.9662).

Seco-C_2BI-CDPI$_1$ (33). A mixture of crude **28** freshly prepared from **25** (2.0 mg, 5 μmol), EDCI (3.8 mg, 20 μmol, 4 equiv), and CDPI[38] (**29**, 1.5 mg, 6 μmol, 1.1 equiv) in DMF (0.4 mL) was stirred under Ar at 23 °C for 16 h. The solvent was removed in vacuo, and PCTLC (1 mm × 2 cm SiO_2, 9% EtOH–EtOAc) afforded **33** (2.2 mg, 81%) as a pale yellow solid: mp >240 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.80 (s, 1 H, NH), 10.60 (s, 1 H, OH), 8.15 (d, 1 H, J = 9 Hz, C5-H), 8.08 (d, 1 H, J = 8 Hz, C8-H), 8.04 (d, 1 H, J = 8 Hz, C4′-H), 8.03 (s, 1 H, C3-H), 7.49 (t, 1 H, J = 8 Hz, C7-H), 7.36 (t, 1 H, J = 8 Hz, C6-H), 7.25 (d, 1 H, J = 9 Hz, C5′-H), 7.05 (s, 1 H, C8′-H), 6.13 (b s, 2 H, NH_2), 4.63 (s, 2 H, C2-H_2), 4.44 (d, 2 H, J = 11 Hz, C*H*HCl), 4.25 (d, 2 H, J = 11 Hz, CH*H*Cl), 3.99 (t, 2 H, J = 9 Hz, C2′-H_2), 3.33 (t, 2 H, J = 9 Hz, C1′-H_2); IR (solid film) ν_{max} 3274, 2921, 1643, 1627, 1590, 1552, 1515, 1397, 1312, 1243, 1018, 810, 746 cm^{-1}; FABMS (NBA–NaI) m/e (relative intensity) 531 ($M + Na^+$, 11), 413 (100); FABHRMS m/e 531.0961 ($C_{26}H_{22}Cl_2N_4O_3$ + Na^+ requires 531.0967).

C_2BI-CDPI$_1$ (34). A suspension of NaH (60%, 0.72 mg, 18 μmol, 3 equiv) in THF (0.25 mL) at 0 °C under Ar was treated with a solution of **33** (3 mg, 6 μmol) in DMF (0.25 mL) and stirred at 0 °C for 1 h. The solvent was removed in vacuo, and PCTLC (1 mm × 2 cm SiO_2, EtOAc) afforded **34** (2.1 mg, 75%) as a pale yellow solid: mp >240 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.77 (b s, 1 H, NH), 8.10 (d, 1 H, J = 8 Hz, C4′-H), 8.08 (d, 1 H, J = 8 Hz, C8-H), 8.06 (d, 1 H, J = 9 Hz, C5-H), 7.63 (t, 1 H, J = 8 Hz, C7-H), 7.51 (t, 1 H, J = 8 Hz, C6-H), 7.25 (d, 1 H, J = 9 Hz, C5′-H), 7.10 (s, 1 H, C8′-H), 6.86 (s, 1 H, C3-H), 6.16 (s, 2 H, NH_2), 4.69 (d, 1 H, J = 12 Hz, C*H*HCl), 4.58 (d, 1 H, J = 12 Hz, CH*H*Cl), 4.55 (s, 2 H, C1-H_2), 4.00 (t, 2 H, J = 9 Hz, C2′-H_2), 3.32 (t, 2 H, J = 9 Hz, C1′-H_2, partially obscured by H_2O), 2.30 (d, 1 H, J = 5 Hz, C9-H), 2.17 (d, 1 H, J = 5 Hz, C9-H); IR (solid film) ν_{max} 3238, 2927, 1657, 1641, 1599, 1465, 1356, 1205, 1003, 878, 824, 766, 667, 561 cm^{-1}; FABMS (NBA–LiI) m/e (relative intensity) 479 ($M + Li^+$, 13), 375 (base); FABHRMS (NBA–CsI) m/e 605.0430 ($C_{26}H_{21}ClN_4O_3$ + Cs^+ requires 605.0357).

Seco-C_2BI-CDPI$_2$ (35). A mixture of crude **28** freshly prepared from **25** (6 mg, 16 μmol), EDCI (9.2 mg, 48 μmol, 3 equiv), and CDPI$_2$[38] (**30**, 7.7 mg, 18 μmol, 1.1 equiv) in DMF (0.34 mL) was stirred under Ar at 23 °C for 17 h. The solvent was removed in vacuo, and flash chromatography (1 × 2 cm SiO_2, 25% DMF–EtOAc) afforded **35** (8.5 mg, 77%) as a tan solid: mp >240 °C dec; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.80 (s, 1 H, NH), 11.60 (s, 1 H, NH), 10.60 (s, 1 H, OH), 8.30 (d, 1 H, J = 7 Hz, C5-H), 8.16 (d, 1 H, J = 9 Hz, C4′-H), 8.09 (d, 1 H, J = 9 Hz, C8-H), 8.02 (s, 1 H, C3-H), 7.98 (d, 1 H, J = 9 Hz, C4″-H), 7.50 (t, 1 H, J = 7 Hz, C7-H), 7.39 (t, 1 H, J = 7 Hz, C6-H), 7.38 (d, 1 H, J = 9 Hz, C5″-H), 7.23 (d, 1 H, J = 9 Hz, C5′-H), 7.22 (s, 1 H, C8″-H), 6.98 (s, 1 H, C8′-H), 6.12 (s, 2 H, NH_2), 4.69 (s, 2 H, C1-H_2), 4.46 (d, 2 H, J = 11 Hz, CH_2Cl), 4.25 (d, 2 H, J = 11 Hz, CH_2Cl), 3.99 (t, 2 H, J = 9 Hz, C2′-H_2), 3.49 (t, 2 H, J = 9 Hz, C2″-H_2), 3.5–3.2 (m, 4 H, partially obscured by water, C1′-H_2 and C1″-H_2); IR (solid film) ν_{max} 3268, 2821, 1647, 1631, 1593, 1555, 1516, 1397, 1311, 1244, 1019, 747, 666, 580 cm^{-1}; FABMS (NBA) m/e (relative intensity) 693 ($M + H^+$, 21), 407 (base); FABHRMS m/e 693.1749 ($C_{37}H_{30}Cl_2N_6O_4$ + H^+ requires 693.1784).

C_2BI-CDPI$_2$ (36). A suspension of NaH (60%, 0.41 mg, 17 μmol, 2 equiv) in THF (0.36 mL) at 0 °C under Ar was treated with a solution of **35** (6 mg, 8.7 μmol) in DMF (0.36 mL) and stirred for 2 h at 0 °C. The reaction mixture was concentrated in vacuo, and PCTLC (1 mm × 3 cm, 10% THF–EtOAc) afforded **36** (4.9 mg, 86%) as a tan solid: mp >240 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.98 (s, 1 H, NH), 11.59 (s, 1 H, NH), 8.35 (d, 1 H, J = 9 Hz, C4′-H), 8.12 (d, 1 H, J = 7 Hz, C5-H), 8.10 (d, 1 H, J = 9 Hz, C8-H), 8.04 (d, 1 H, J = 9 Hz, C4″-H), 7.65 (t, 1 H, J = 7 Hz, C7-H), 7.53 (t, 1 H, J = 7 Hz, C6-H), 7.42 (d, 1 H, J = 9 Hz, C5″-H), 7.36 (d, 1 H, J = 9 Hz, C5′-H), 7.25 (s, 1 H, C8″-H), 7.01 (s, 1 H, C8′-H), 6.94 (s, 1 H, C3-H), 6.15 (s, 2 H, NH_2), 4.68 (t, 2 H, J = 8 Hz, C2′-H_2), 4.60 (t, 2 H, J = 8 Hz, C2″-H_2), 4.58 (s, 2 H, C1-H_2), 4.49 (d, 1 H, J = 11 Hz, C*H*HCl), 4.31 (d, 1 H, J = 11 Hz, CH*H*Cl), 4.02 (t, 2 H, J = 8 Hz, C1′-H_2), 3.50 (t, 2 H, J = 8 Hz, C1″-H_2), 2.33 (d, 1 H, J = 5 Hz, C9-H), 2.20 (d, 1 H, J = 5 Hz, C9-H); IR (solid film) ν_{max} 3256, 2922, 1660, 1645, 1611, 1576, 1498, 1429, 1409, 1360, 1340, 1281, 1001, 805, 756, 662, 554 cm^{-1}; FABMS (NBA–CsI) m/e (relative intensity) 789 ($M + Cs^+$, 38), 745 (56), 577 (base).

Seco-C_2BI-TMI (37). A mixture of crude **28** freshly prepared from **25** (3 mg, 8 μmol), EDCI (4.6 mg, 24 μmol, 3 equiv), and **31**[15] (2.1 mg, 9 μmol, 1.1 equiv) in DMF (0.2 mL) was stirred under Ar at 23 °C for 10 h. The solvent was removed in vacuo, and PCTLC (1 mm × 2 cm SiO_2, 30% EtOAc–hexane) afforded **37** (2.9 mg, 71%) as a pale yellow solid: mp >240 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.40 (b s, 1 H, NH), 9.46 (s, 1 H, OH), 8.29 (d, 1 H, J = 8 Hz, C5-H), 8.12 (d, 1 H, J = 8 Hz, C8-H), 8.11 (s, 1 H, C3-H), 7.53 (t, 1 H, J = 7 Hz, C7-H), 7.39 (t, 1 H, J = 8 Hz, C6-H), 7.19 (s, 1 H, C4′-H), 7.00 (s, 1 H, C3′-H), 4.78 (s, 2 H, C1-H_2), 4.49 (d, 2 H, J = 12 Hz, CH_2Cl), 4.39 (d, 2 H, J = 12 Hz, CH_2Cl), 4.04 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3); IR (solid film) ν_{max} 3272, 2919, 1643, 1590, 1549, 1514, 1396, 1308, 1243, 1132, 1020, 950, 814, 744, 532 cm^{-1}; FABMS (NBA) m/e (relative intensity) 515 ($M + H^+$, 21), 479 (100); FABHRMS m/e 515.1182 ($C_{26}H_{24}Cl_2N_2O_5$ + H^+ requires 515.1141).

C_2BI-TMI (38). A suspension of NaH (60%, 0.5 mg, 12 μmol, 6 equiv) in THF (0.25 mL) at 0 °C under Ar was treated with a solution of **37** (0.9 mg, 2 μmol) in DMF (0.25 mL) and stirred for 30 min at 0 °C. A drop of H_2O was added to the reaction mixture, and the solvent was removed in vacuo. Flash chromatography (0.5 × 2 cm SiO_2, 10% DMF–EtOAc) afforded **38** (0.65 mg, 77%) as a tan solid: mp >240 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.10 (b s, 1 H, NH), 8.01 (d, 1 H, J = 8 Hz, C5-H), 7.61 (s, 1 H, C1′-H), 7.72 (d, 1 H, J = 8 Hz, C8-H), 7.45 (t, 1 H, J = 7 Hz, C6-H), 7.35 (t, 1 H, J = 7 Hz, C7-H), 6.79 (s, 1 H, C3-H), 6.53 (s, 1 H, C7′-H), 5.47 (s, 2 H, C1-H_2), 4.55 (d, 1 H, J = 12 Hz, C*H*HCl), 4.48 (d, 1 H, J = 12 Hz, CH*H*Cl), 3.90 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 2.01 (d, 1 H, J = 4 Hz, C9-H), 1.65 (d, 1 H, J = 4 Hz, C9-H); IR (solid film) ν_{max} 3369, 2928, 1577, 1413, 1326, 1305, 1228, 1192, 1115, 1018, 951, 762, 510 cm^{-1}; FABMS (NBA–CsI) m/e (relative intensity) 647 ($M + Cs^+$, 14),

611 (100).

Seco-C_2BI-Indole$_2$ (39). A mixture of crude **28** freshly prepared from **25** (8.0 mg, 21 μmol), EDCI (12 mg, 63 μmol, 3 equiv), and **32**[17] (8.6 mg, 27 μmol, 1.3 equiv) in DMF (0.43 mL) was stirred under Ar at 23 °C for 14 h. Flash chromatography (0.5 × 5 cm SiO_2, 0–100% DMF–EtOAc gradient elution) afforded **39** (8.1 mg, 68%) as a yellow solid: mp >240 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.22 (b s, 1 H, NH), 8.89 (b s, 1 H, NH), 8.73 (b s, 1 H, NH), 7.69 (s, 1 H), 7.59 (d, 1 H, J = 9 Hz, C6-H), 7.44 (d, 1 H, J = 9 Hz, C9-H), 7.26 (s, 1 H), 6.92 (m, 5 H), 6.53 (m, 4 H), 6.37 (t, 1 H, J = 8 Hz), 4.16 (s, 2 H, C2-H_2), 3.80 (d, 2 H, J = 12 Hz, CH_2Cl), 3.70 (d, 2 H, J = 12 Hz, CH_2Cl); IR (solid film) ν_{max} 3242, 2917, 1646, 1644, 1592, 1558, 1542, 1521, 1396, 1313, 1246, 1017, 950, 892 cm^{-1}; FABMS (NBA) m/e (relative intensity) 583 (M + H$^+$, 47), 416 (100); FABHRMS m/e 583.1344 ($C_{32}H_{24}Cl_2N_4O_3$ + H$^+$ requires 583.1304).

C_2BI-Indole$_2$ (40). A suspension of NaH (60%, 0.24 mg, 10 μmol, 3 equiv) in THF (0.25 mL) at 0 °C under Ar was treated with a solution of **39** (2 mg, 3.4 μmol) in DMF (0.25 mL) and stirred for 1 h at 0 °C. The solvent was removed in vacuo, and PCTLC (1 mm × 2 cm SiO_2, 0–100% EtOAc–hexane gradient elution) afforded **40** (0.9 mg, 47%, 47–75%) as a yellow solid: mp >240 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.69 (b s, 1 H, NH), 10.15 (b s, 1 H, NH), 10.05 (b s, 1 H, NH), 8.28 (d, 1 H, J = 8 Hz, C5-H), 8.17 (s, 1 H, C1′-H), 7.79 (t, 1 H, J = 8 Hz, C6-H), 7.66 (m, 2 H), 7.58 (d, 1 H, J = 8 Hz, C3′-H), 7.45 (t, 2 H, J = 8 Hz), 7.36 (d, 1 H, J = 7 Hz), 7.35 (s, 1 H), 7.18 (t, 1 H, J = 8 Hz), 7.05 (t, 1 H, J = 7 Hz), 7.03 (s, 1 H), 6.32 (d, 1 H, J = 9 Hz), 4.18 (d, 1 H, J = 12 Hz, C*H*HCl), 3.89 (m, 3 H, CH*H*Cl and Cl-H_2), 2.33 (d, 1 H, J = 4 Hz, C9-H), 2.25 (d, 1 H, J = 4 Hz, C9-H); IR (solid film) ν_{max} 3268, 2933, 1641, 1621, 1587, 1548, 1410, 1312, 1244, 1145, 1012, 806, 747 cm^{-1}; FABHRMS (NBA) m/e 547.1060 ($C_{32}H_{23}ClN_4O_3$ + H$^+$ requires 547.1537).

Aqueous Solvolytic Reactivity of *N*-BOC-C_2BI (26) and C_2BI (27). *N*-BOC-C_2BI (**26**, 110 μg) was dissolved in CH_3OH (1.5 mL). The CH_3OH solution was mixed with aqueous buffer (pH = 3, 1.5 mL). The buffer contained 4:1:20 (v/v/v) of 0.1 M citric acid, 0.2 M Na_2HPO_4, and H_2O, respectively. After mixing, the solvolysis solutions were stoppered and kept at 22–23 °C in the dark. The UV spectrum of the solution was measured twice in the first day and then every 24 h for 2 months. The UV monitoring was continued until no further change was detectable. The long-wavelength absorption at 314 nm and the short-wavelength absorption at 256 nm were monitored. The solvolysis rates were calculated from the data taken at 256 nm from the least square treatment (r = 1.000) of the slopes of plots of time versus $1 - [(A - A_{initial})/(A_{final} - A_{initial})]$. For **26**, $k = (4.40 \pm 0.08) \times 10^{-7}$ s^{-1} ($t_{1/2}$ = 443 h).

C_2BI (**27**, 50 μg) was dissolved in CH_3OH (1.5 mL) and mixed with buffer (1.5 mL, pH = 3). The buffer contained 4:1:20 (v/v/v) of 0.1 M citric acid, 0.2 M Na_2HPO_4, and H_2O, respectively. No significant change in the UV spectrum was detected when monitored over one week, A = 0.52. Monitoring of the solution every 24 h over 3.5 months and extrapolating to an approximate final 337-nm absorption of 0.183 permitted an estimation of the solvolysis rate for **27**. Least squares treatment (r = 0.99) of the slopes of the plots of time versus $1 - [(A - A_{initial})/(A_{final} - A_{initial})]$ provided an estimate of $k = (8.46 \pm 0.06) \times 10^{-8}$ s^{-1} ($t_{1/2}$ = 2275 h, 95 days).

Treatment of 23 with 3 M HCl–EtOAc. A solution of **23** (2 mg, 5.8 μmol) in 3 M HCl–EtOAc (1 mL) was stirred for 1 h at 0 °C. The reaction mixture was concentrated under a stream of N_2. Flash chromatography (0.5 × 2 cm, 5% EtOAc–hexane) afforded **22** (1.9 mg, 2.2 mg theoretical, 86%) as the only detectable reaction product as a white solid identical in all respects with authentic material. Similar results were obtained when the reaction was conducted at −78 °C.

DNA Alkylation and Cross-Linking Studies. General procedures, the preparation of singly 5′ end-labeled double-stranded DNA, the agent binding studies, gel electrophoresis, and autoradiography were conducted following procedures described in full detail elsewhere.[19b] The cross-linking reactions were conducted under identical conditions with the exception that the thermal cleavage step (30 min, 100 °C) was omitted. Psoralen (10^{-1}, 10^{-2}, and 10^{-3} M) was run as a positive control with cross-linking induced by irradiation at 365 nm for 1 h.

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Supplementary Material Available: Experimental details and spectroscopic characterization of **8–13** and a table of representative results of the study of the Wittig reaction of **9** and **17** (5 pages). Ordering information is given on any current masthead page.

A Modular Approach for Ligand Design for Asymmetric Allylic Alkylations via Enantioselective Palladium-Catalyzed Ionizations

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Abstract: A new class of ligands for asymmetric transition metal catalysis based on 2-(diphenylphosphino)benzoic acid was used in a mechanistically-defined palladium-catalyzed reaction in which enantiodifferentiation was the result of selective ionization of substrates derived from *cis*-2-cycloalkene-1,4-diols. By making rational, stepwise changes in the ligand structure, the structural requirements for good asymmetric induction were probed. The absolute stereochemistry of the products was found to be related to the chirality of the ligand in a predictable fashion. A mnemonic is given which allows one to predict the mode of ionization (*R* or *S*) solely on the basis of the stereochemistry of the variable chiral linker used to make the ligand.

Transition metal-catalyzed allylations have emerged as extremely versatile and powerful reactions; unfortunately they have been intransigent in succumbing to efforts at making them broadly applicable enantioselective processes.[1-3] The source of the difficulty lies in the spatial relationships of the bond breaking and making of the metal and its attendant ligands. Figure 1 shows the general mechanism for a palladium-catalyzed allylation reaction with a soft nucleophile. The basic catalytic cycle consists of metal–olefin complexation, ionization, alkylation, and decom-

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