# Synthesis and Evaluation of a Series of C3-Substituted CBI Analogues of CC-1065 and the Duocarmycins

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The synthesis and evaluation of a series of C3-substituted 1,2,9,9a-tetrahydrocyclopropa[*c*]benz-[*e*]indol-4-one (CBI) analogues of the CC-1065 and duocarmycin alkylation subunits are detailed, including methyl and the full series of halogens. Introduction of the key substituent was accomplished through directed metalation of the *seco*-CBI core followed by reaction of the resultant aryllithium with an appropriate electrophile. C3-Bromo and iodo substituents were only effectively installed on the hindered aryllithium intermediate using a novel halogen source, 1-bromo- and 1-iodophenylacetylene, that should prove generally useful beyond the studies we describe. X-ray crystal structures of the series show substantial distortion in the vinylogous amide due to unfavorable steric interactions between the C3-substituent and the $N^2$-carbamate. In the halogen series, the N2−C2a bond length and the torsional angle $\chi_1$ smoothly increase with the increasing size of the C3 substituent indicative of decreasing vinylogous amide conjugation through the series (H > F > Cl > Br > I). Unlike *N*-Boc-CBI, this series of substituted CBI analogues proved remarkably reactive toward solvolysis even at pH 7, where the reaction is uncatalyzed and the reactivity order (I > Br > Cl > F > H) follows a trend consistent with the extent of vinylogous amide conjugation and stabilization. The implications of these observations on the source of catalysis for the DNA alkylation reaction of the natural products are discussed.

(+)-CC-1065[1] (**1**) and the duocarmycins[2,3] **2** and **3** (Figure 1) are the parent members of a potent class of antitumor antibiotics. These natural products derive their potent biological activity through a characteristic sequence-selective alkylation of DNA that has been shown to proceed by reversible, stereoelectronically controlled adenine N3 addition to the least substituted carbon of the activated cyclopropane.[5−11] Following their disclosure, continued extensive studies have been conducted in efforts to define the factors responsible for their

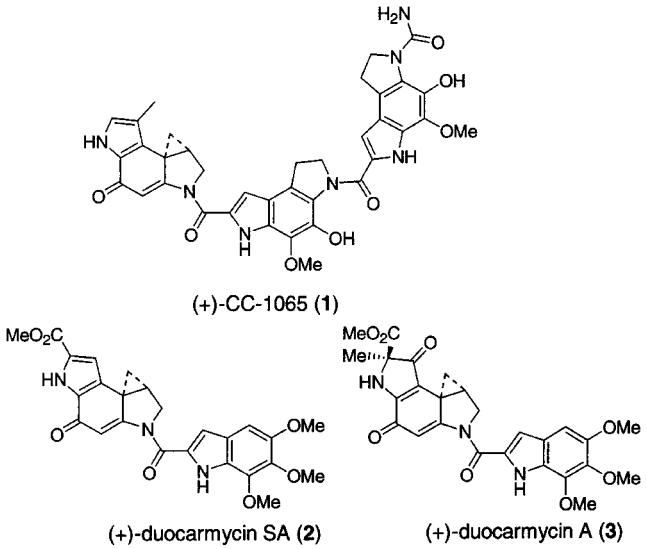


**Figure 1.**

remarkable biological properties.[11,12] Central to these studies have been the synthesis and evaluation of structural analogues that bear either deep-seated or more subtle substituent modifications to the alkylation subunit (selected examples shown in Figure 2).[13−22] Of the many analogues investigated, the 1,2,9,9a-tetrahydrocyclopro-

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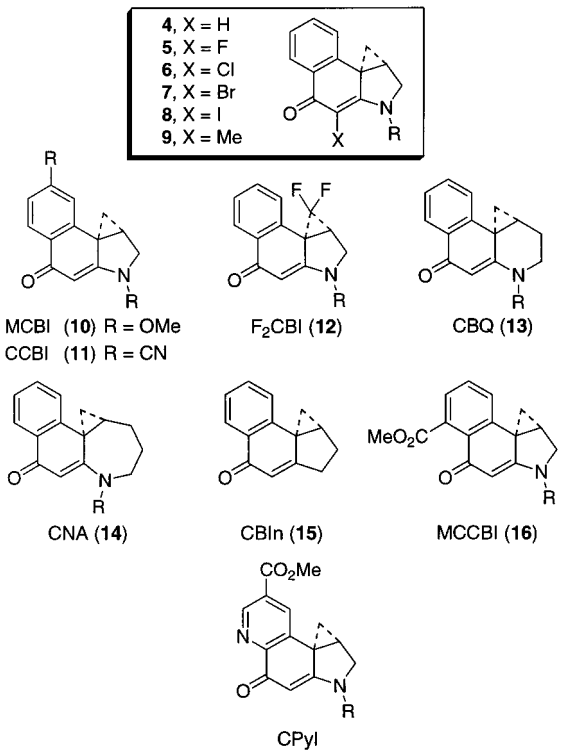


**Figure 2.**

pa[*c*]benz[*e*]indol-4-one (CBI, **4**) alkylation subunit is one example where significant alteration of the natural structure provided a system that retains or exceeds the potency and biological properties characteristic of the natural products, yet is more synthetically accessible.[13] Furthermore, modification of the CBI core through the synthesis and evaluation of second-generation analogues including MCBI[14] (**10**), CCBI[15] (**11**), $F_2$CBI[16] (**12**), CBQ[17] (**13**), CNA[18] (**14**), CBIn[19] (**15**), MCCBI[20] (**16**), and CPyI[21] has allowed detailed investigations into the relationships between structure, chemical reactivity, and biological potency. To date, however, no such CBI derivatives have addressed C3 substitution of the cyclohexadienone system.[22] Herein, we report the synthesis and evaluation of the C3-substituted *N*-Boc-CBI analogues **5**−**9** where the cyclohexadienone system has been directly substituted with a series of substituents, including methyl and the full series of halogens. Their behavior, especially a marked uncatalyzed versus acid-catalyzed solvolysis reactivity at pH 7 which follows reactivity trends expected of a progressively decreased vinylogous amide conjugation, has ramifications on the potential source of catalysis for the DNA alkylation reaction of the natural products and their analogues.

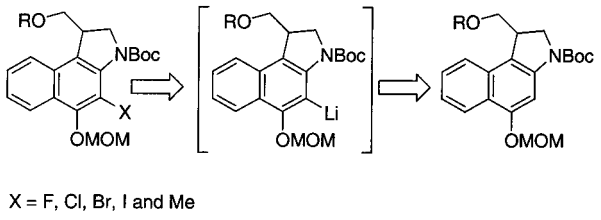


**Figure 3.**

**Synthesis of C3-Substituted *N*-Boc-CBI Analogues 5−9.** The approach employed for the preparation of **5**−**9** follows a general strategy for the synthesis of CBI analogues developed in our laboratory.[13] The C3-substituent was to be introduced at a late stage, such that the synthesis could diverge from a common, advanced intermediate. Installation of this key substituent was to be accomplished through selective ortho-metalation of the tricyclic *seco*-CBI core, utilizing a directing MOM ether phenol protecting group (Figure 3). Reaction of the resultant aryllithium with an appropriate electrophile would provide the corresponding C3-substituted *seco*-CBI derivative. The alternative approach of direct C3 electrophilic substitution (e.g., $Br_2$ bromination) was also explored but found to be largely unsuccessful. Finally, selective deprotection of the MOM ether followed by spirocyclization would afford the desired C3-substituted *N*-Boc-CBI derivatives.

MOM ether **17** was prepared in accord with a recent preparation of CBI[13] and the structurally related *iso*-CBI.[23] Regioselective electrophilic iodination at C4 of **17**[23] yielded exclusively aryl iodide **18** (NIS, TsOH, 77%), Scheme 1. Allylation of the carbamate (NaH, allyl bromide, $Bu_4NI$, 99%), followed by a $Bu_3SnH$ promoted 5-*exo*-*trig* free-radical cyclization of **19** with in situ TEMPO trap of the resultant primary radical[13] provided **20** (70%). Subsequent reduction of the N−O bond was accomplished (Zn, AcOH, 72%) without competitive re-

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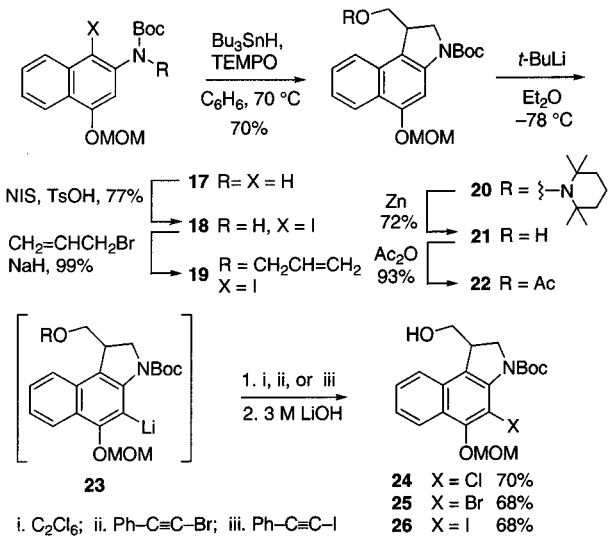
**Scheme 1**



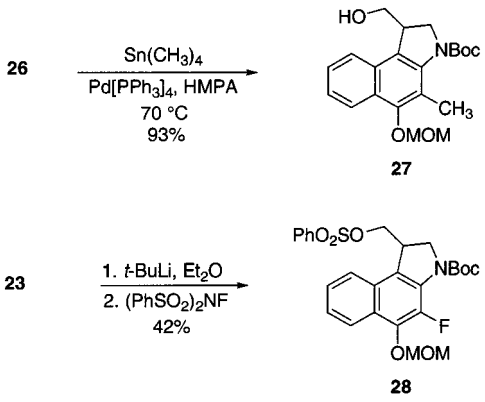

moval of either the MOM ether or *N*-Boc protecting groups to afford alcohol **21** in good yield.

Although metalation could be accomplished at this stage by treatment of primary alcohol **21** with excess *t*-BuLi, higher yields were obtained by utilizing the corresponding acetate **22** ($Ac_2O$, pyridine, 93%). Directed lithiation of acetate **22** at C4 was found to be most efficiently accomplished by treatment with *t*-BuLi (4 equiv) for 4 h in $Et_2O$ at −78 °C. Reaction of the resultant aryllithium **23** with hexachloroethane resulted in efficient chloride introduction, providing the alcohol **24** (70%) following hydrolysis of the residual acetate by quench of the reaction with 3 M aqueous LiOH.

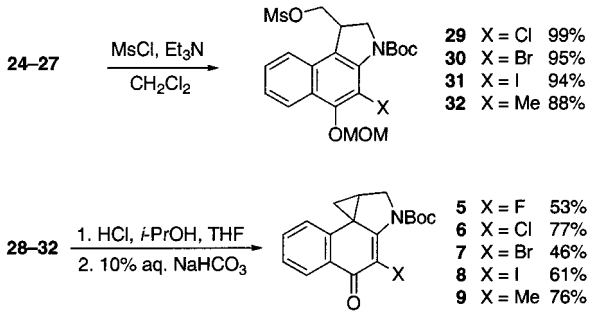
Introduction of the C4 bromine substituent initially proved to be more challenging, as known bromination reagents (NBS, $Br_2$, 1,2-dibromoethane, and cyanogen bromide) failed to provide **25**. This unanticipated obstacle was addressed employing a novel bromine source suitable for reaction with a hindered aryllithium intermediate. Thus, the sterically unencumbered 1-bromophenylacetylene, envisaged to undergo rapid lithium−halogen exchange with the substrate, proved remarkably effective at C4 bromination of **23** and resulted in the isolation of **25** (68%) following in situ saponification. Similarly, introduction of the corresponding C4 iodine substituent was accomplished initially through reaction of **23** with 1-chloro-2-iodoethane, albeit in modest conversions (18%). However, an analogous use of 1-iodophenylacetylene afforded the desired **26** in substantially higher yield (68%) following the saponification of the remaining acetate.

Initial attempts to install the C4 methyl substituent by reacting aryllithium **23** with $CH_3I$ proved unsuccessful. Consequently, introduction of the C4 methyl substituent was accomplished by Stille coupling of aryl iodide **26** with $Sn(CH_3)_4$ ($Pd(PPh_3)_4$, HMPA, 70 °C, 93%) to afford **27** in excellent yield (Scheme 2). To complete the series, reaction of aryllithium **23** with $(PhSO_2)_2NF$ provided the C4 fluoride **28** (42%). In this case, not only was the acetate cleaved during reaction, but the isolated product **28** was the benzenesulfonyl derivative of the primary alcohol. Though unintended, this intermediate was ideally functionalized for eventual spirocyclization circumventing the need for subsequent activation of the expected alcohol.

**Scheme 2**




**Scheme 3**




With the desired C4-substituted intermediates in hand, activation of the primary alcohol (MsCl, $Et_3N$, 88−99%) afforded the key intermediates **29**−**32** (Scheme 3). Mild acid-catalyzed deprotection of the MOM ether in **28**−**32** (HCl, *i*-PrOH, THF), followed by in situ spirocyclization of the resultant phenol by quench of the reaction with 10% aqueous $NaHCO_3$ directly afforded the ring closed, C3-substituted *N*-Boc-CBI derivatives **5**−**9** (46−77%). In initial studies, this two-step conversion of **28**−**32** to **5**−**9** was accomplished in a stepwise fashion with isolation and characterization of the intermediate phenols followed by DBU-promoted spirocyclization (75−95%), but the more convenient single-step conversion was adopted as the work progressed.

**X-ray Crystal Structures.** Central to understanding the reactivity and reaction regioselectivity of the alkylation subunit analogues has been the careful comparison of their X-ray structures.[13,16−18,21,24−26] Consequently, X-ray crystal structures of the F-, Cl-, Br-, and Me-substituted CBI analogues were secured as the *N*-methoxycarbonyl derivatives **33**−**36**, respectively (Scheme 4).[24] Unlike **5**−**7** and **9**, the *N*-Boc derivative of the C3-iodo-CBI (**8**) crystallized and was analyzed directly.[24]

Structural analysis of this series revealed several important features. First, the torsional angle $\chi_1$, which has been shown to be indicative of the extent of vinylogous amide conjugation,[25] is strongly perturbed from that of the parent unsubstituted *N*-$CO_2$Me-CBI (Figure 4). The steric interaction of the C3-substituent with the $N^2$-carbamate results in a twist in $\chi_1$, the magnitude of which was found to smoothly increase as the size of the C3

(24) The author has deposited the atomic coordinates for the X-ray structures with the Cambridge Crytallographic Data Centre, and they have been allocated the following deposition numbers: **33**, 160273; **34**, 160278; **35**, 160705; **8**, 160274; **36**, 160276; **41**, 160703; **43**, 160704; **44**, 160272.

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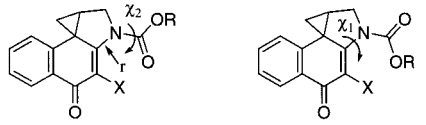
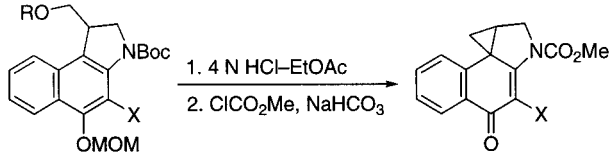



| X-ray bond length, Å | H | F | Cl | Br | I | $CH_3$ |
|---|---|---|---|---|---|---|
| r | 1.390 | 1.394(3) | 1.392(3) | 1.401(3) | 1.418(8) | 1.414 (3) |
| X-ray dihedral angle | | | | | | |
| $\chi_1$ | 21.1° | 31.0° | 50.3° | 50.7° | 62.1° | 49.9° |
| $\chi_2$ | 4.5° | 6.9° | 3.9° | 5.4° | 1.9° | 3.2° |
| MM2 dihedral angle | | | | | | |
| $\chi_1$ | 8.2° | 23.7° | 37.9 ° | 42.2° | 45.5 ° | 36.6 ° |
| $\chi_2$ | 3.4° | 8.2° | 8.8° | 8.3° | 7.4° | 6.7° |
| AM1 dihedral angle | | | | | | |
| $\chi_1$ | 4.9° | 28.2° | 54.1° | 56.6° | 59.5° | 43.5° |
| $\chi_2$ | 2.2° | 1.3° | 3.0° | 7.5° | 7.2° | 0.0° |

**Figure 4.**

**Scheme 4**




**28** X = F, R = $SO_2Ph$
**29** X = Cl, R = $SO_2Me$
**30** X = Br, R = $SO_2Me$
**32** X = Me, R = $SO_2Me$

**33** X = F 66%
**34** X = Cl 70%
**35** X = Br 68%
**36** X = Me 80%

halogen substituent becomes larger. By contrast, the $\chi_2$ dihedral angle is unperturbed by the structural changes indicating that the carbamate $N^2$-conjugation is maintained at the expense of the vinylogous amide conjugation. Notably, the X-ray crystal structure of the fluoro derivative **33** shows that the methoxycarbonyl group is rotated 180° compared to its orientation in the X-ray crystal structures of **8** and **34**−**36**.[26]

In the studies conducted to date, the most diagnostic indication of the extent of vinylogous amide conjugation has been derived from the N2−C2a bond length (*r*). Comparison of the methyl-substituted CBI derivative **36** with *N*-$CO_2$Me-CBI illustrates a substantial increase in the N2−C2a bond length (1.414 versus 1.390 Å), suggesting diminished vinylogous amide conjugation. This difference is likely a result of destabilizing steric interactions between the C3 methyl substituent and the $N^2$-$CO_2$Me group resulting in a twist in the $\chi_1$ dihedral angle diminishing the vinylogous amide conjugation resulting in an extended N2−C2a bond length. Within the limits of error, the halogen-substituted series exhibit N2−C2a bond lengths (*r*) which appear to follow this same trend. Although they are clearly influenced by the inductive and electronic nature of the halogen substituent (i.e., versus **36**), both the extent of the twist in $\chi_1$ and the diagnostic N2−C2a bond length *r* increase as the size of the halogen substituent increases suggesting the vinylogous amide conjugation decreases through the series (H > F > Cl > Br > I). Interestingly, modeling (MM2) and computational (AM1) studies of the analogues **5**−**9** conducted in advance of the work accurately depicted the structural trends and the optimized AM1 structures were found to be in remarkably good agreement with even the magnitude of the trends observed in the X-ray structures.

(26) The source of this distinction and its impact on the comparison interpretations is unknown but should be kept in mind along with the fact that the *N*-Boc versus *N*-$CO_2$Me derivative of the C3 iodo analogue was utilized.

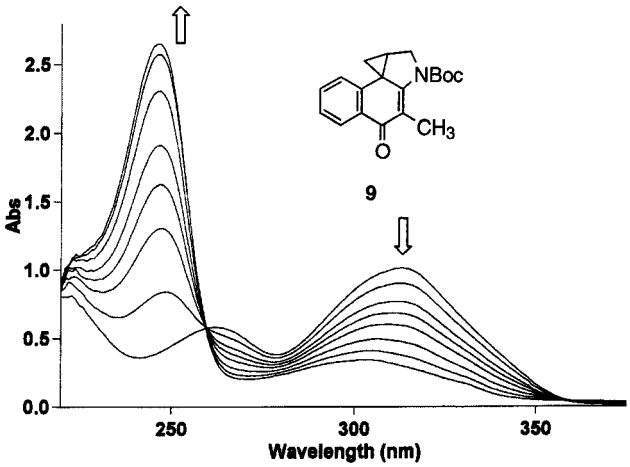



**Figure 5.** Solvolysis study (UV spectra) of **9** in 50% $CH_3OH$−aqueous buffer (pH 2, 39:1 (v/v) 0.2 M boric acid−0.5 M citric acid−0.1 M $Na_3PO_4$). For clarity, UV traces at only a few time points are shown: $t$ = 0, 18, 43, 65, 92, 141, 218, and 367 h.

**Solvolysis: Reactivity.** The solvolysis rate of cyclopropyl ring opening has provided much information regarding the relationship between chemical stability and biological potency.[12,25] With notable exceptions,[16−20,23,27] the alkylation subunit analogues have generally proven stable to solvolysis at pH 7 and consequently have been studied at more acidic pH (pH 2−3) where rates for an acid-catalyzed solvolysis are measurable. In cases where a pH 7 solvolysis reactivity has been measurable, the relative solvolysis reactivities for different alkylation subunits at pH 2−3 versus 7 have not been altered. Thus, it is not surprising that assessed reactivities at pH 2−3, which typically correlate with relative reactivities at pH 7, were found to be good predictors of biological potency. However, in the one exception of a series of simple derivatives of an iso-CI alkylation subunit,[27] the relative reactivity inverted between pH 3 and 7. These results along with a study of the pH rate profile[28] of the reactive alkylation subunits **13**−**15**[17−19] and CPyI[20] have indicated that solvolysis mechanisms switch from one that is acid-catalyzed at pH 2−3/4 to one that is uncatalyzed at pH 7. Consequently, the solvolysis behavior of the halogen-substituted CBI series proved especially interesting. Clear in the initial handling of the materials, they possessed a managable solvolysis reactivity at pH 7 as well as pH 2. Moreover, their relative reactivities inverted at the two pH conditions indicative of a change in solvolysis mechanism. Thus, the solvolysis of the C3-substituted *N*-Boc-CBI derivatives **5**−**9** were examined at pH 2 (50% $CH_3OH$−buffer) and pH 7 (50% $CH_3OH$−buffer), and the progress of the reaction was followed spectrophotometrically by UV (see Figure 5 for a representative series of UV spectra). The rates of solvolysis are summarized in Table 1.

The most significant of these reactivities was the pH 7 solvolysis behavior (Table 1). The C3 methyl derivative **9**, unlike *N*-Boc-CBI (**4**) itself, exhibited a measurable reactivity at pH 7. The halogen-substituted analogues

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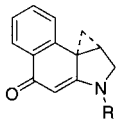
(28) Boger, D. L.; Garbaccio, R. M. *J. Org. Chem.* **1999**, *64*, 5666.

**Table 1. Solvolysis Rates of *N*-Boc-CBI Analogues (4−9) with Universal Buffer[a]**

| agent | $k$ ($h^{-1}$, pH 2) | $t_{1/2}$ (h, pH 2) | $k$ ($h^{-1}$, pH 7) | $t_{1/2}$ (h, pH 7) |
|---|---|---|---|---|
| **4** | $5.51 \times 10^{-2}$ | 12.5 | stable | stable |
| **9** | $1.02 \times 10^{-2}$ | 68 | $0.77 \times 10^{-3}$ | 900 |
| **5** | $8.06 \times 10^{-3}$ | 86 | $1.02 \times 10^{-3}$ | 681 |
| **6** | $5.87 \times 10^{-3}$ | 118 | $1.89 \times 10^{-3}$ | 367 |
| **7** | $4.68 \times 10^{-3}$ | 148 | $2.17 \times 10^{-3}$ | 319 |
| **8** | $3.68 \times 10^{-3}$ | 188 | $>2.17 \times 10^{-3}$ | <319[b] |

[a] 50% $CH_3OH$−aqueous buffer ($B(OH)_3$−citric acid−$Na_3PO_4$). [b] Competitive solvolysis and Boc hydrolysis observed at pH 7.



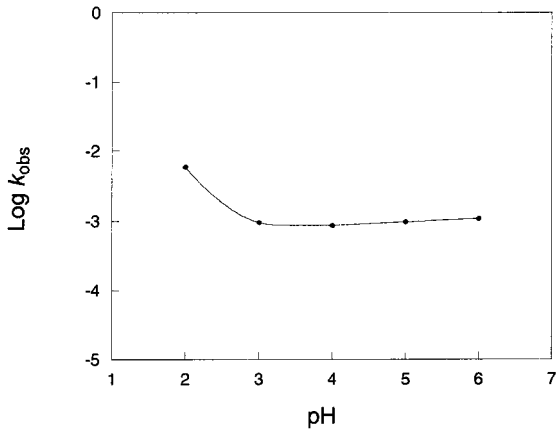

| agent | R | $t_{1/2}$ (pH 3, h) |
|---|---|---|
| **37** | $SO_2Et$ | 383 |
| **38** | COEt | 96 |
| **39** | $CO_2Me$ | 57 |
| **40** | CONHMe | 36 |

**Figure 6.**

exhibited an even more pronounced pH 7 reactivity following a smooth trend (I > Br > Cl > F). The analysis of the iodo analogue **8** suffers from a competitive $N^2$-Boc hydrolysis complicating the determination of an accurate solvolysis half-life measurement, but it is clear from the study that its solvolysis reactivity exceeded that of the remaining analogues. As detailed later, a pH rate profile for **6** revealed that the reactions constitute an uncatalyzed solvolysis at pH 7.

Beautifully, these trends in reactivity reversed at pH 2, indicating a change in solvolysis mechanism from uncatalyzed to acid-catalyzed solvolysis. All the C3-substituted CBI analogues were more stable than *N*-Boc-CBI (**4**) itself ($t_{1/2}$ = 12.5 h). The most reactive of the analogues was the methyl substituted CBI **9** ($t_{1/2}$ = 68 h) followed by the halogen derivatives (F > Cl > Br > I). In part, this reversed order of reactivity may be attributed to the electron-withdrawing nature of the halogen substituents, which should inductively disfavor protonation required of the acid-catalyzed solvolysis. However, even the C3-methyl-substituted CBI analogue was found to be more stable than **4**, indicating factors fundamental to all the structures were contributing to this enhanced stability. One possible explanation is that the acid-catalyzed solvolysis reactivity is directly related to the extent of vinylogous amide conjugation within this series. That is, the vinylogous amide carbonyl p$K_b$ along with the vinylogous amide conjugation decreases as one moves down the series and this results in diminished C4 carbonyl protonation slowing the rate of acid-catalyzed solvolysis. Similar observations have been made in the pH 3 reactivity of a series of N-substituted CBI derivatives (**37**−**40**, Figure 6)[29] and a series of iso-CBI derivatives,[27] the latter of which also exhibited the analogous inversion of reactivity at pH 7 versus pH 3. Importantly, in each of these cases, it is the increasing pH 7 reactivity of the uncatalyzed reaction that correlates with diminished vinylogous amide conjugation.

The full pH−rate profile for solvolysis of the chloro derivative **6** was examined from pH 2−10, (Figure 7). The rate of solvolysis was shown to decrease by essentially a factor of 10 in going from pH 2 to 3, confirming that the solvolysis is acid-catalyzed within this pH range. Above pH 3, the solvolysis rate remained nearly unchanged,




| pH | $k$ ($h^{-1}$, pH 2) | $t_{1/2}$ (h, pH 2) |
|---|---|---|
| 2 | $5.87 \times 10^{-3}$ | 118 |
| 3 | $9.52 \times 10^{-4}$ | 728 |
| 4 | $8.74 \times 10^{-4}$ | 793 |
| 5 | $9.69 \times 10^{-4}$ | 715 |
| 6 | $1.09 \times 10^{-3}$ | 633 |

**Figure 7.** Solvolysis pH−rate profile of **6** with universal buffer (50% $CH_3OH$−aqueous buffer ($B(OH)_3$−citric acid−$Na_3PO_4$).

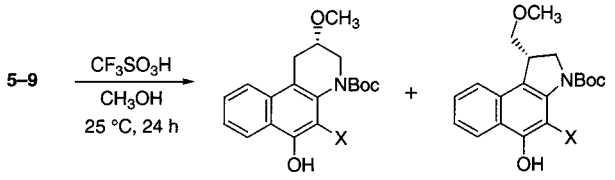
especially within the pH range 3−6, indicating a change in mechanism from acid-catalyzed to uncatalyzed solvolysis and illustrating that these derivatives are substantially less stable across this pH range than the parent *N*-Boc-CBI. At pH 8 and above, significant competitive $N^2$-carbamate hydrolysis was detected, obscuring an accurate determination of solvolysis reactivity and illustrating the general increased reactivity of the halogen-substituted agents.

Importantly, these observations on the pH 7 reactivity of **5**−**9** are consistent with the proposal of a DNA binding-induced conformational change in **1**−**3**, which twists the linking $N^2$ amide disrupting the vinylogous amide conjugation, providing the necessary and sufficient activation (catalysis) for a non-acid-catalyzed pH 7−8 DNA alkylation reaction.

**Solvolysis: Regioselectivity.** The acid-catalyzed nucleophilic addition of $CH_3OH$ to **5**−**9** was conducted on a preparative scale to establish the regioselectivity of addition. Treatment of **5** with catalytic $CF_3SO_3H$ (0.12 equiv, $CH_3OH$, 25 °C, 24 h) led to two products in a ratio of 4:1 (Scheme 5). The major product **41** was shown to result from $CH_3OH$ attack at the more substituted cyclopropane carbon, regioselectivity distinct from that observed with the parent *N*-Boc-CBI (>20:1) which undergoes exclusive attack at the least substituted cyclopropane carbon. Confirmation of the structure of **41** was obtained by a single-crystal X-ray structure.[24] A single enantiomer of this minor ring expansion product **41** was formed upon reaction of optically active **5**. Thus, **41** was found to be generated with complete inversion of the stereochemistry at the reacting center, indicating an $S_N2$ reaction mechanism. Interestingly, treatment of analogues **6**−**9** under these same conditions exclusively provided the ring expansion products **43**−**46**, whose structures were confirmed by single-crystal X-ray struc-

(29) Boger, D. L.; Yun, W.; Han, N. *Bioorg. Med. Chem.* **1995**, *3*, 1429. Boger, D. L.; Yun, W. *J. Am. Chem. Soc.* **1994**, *116*, 5523.

**Scheme 5**

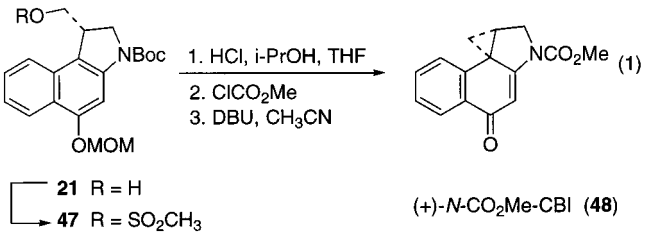



Ring Expanded : Ring Opened

| agent | X | ratio | product(s) |
|---|---|---|---|
| **5** | F | 4 : 1 | **41** : **42** |
| **6** | Cl | >20 : 1 | **43** |
| **7** | Br | >20 : 1 | **44** |
| **8** | I | >20 : 1 | **45** |
| **9** | $CH_3$ | >20 : 1 | **46** |

tures of **43**[24] and **44**[24] and subsequent comparison of the $^1$H NMR spectra of **45** and **46** with those of the X-ray determined structures. Notably, single enantiomers of **43**−**46** were generated using optically active substrates in reactions that proceed by an analogous $S_N2$ reaction mechanism. These latter results illustrate clean cleavage of the C8b−C9a bond with $S_N2$ addition of $CH_3OH$ to the more substituted C9a cyclopropane carbon, and no product was detected (>20:1) resulting from the cleavage of the C8b−C9 bond. Although distinct from the reaction regioselectivity of *N*-Boc-CBI, this ring expansion addition of $CH_3OH$ addition is analogous to that observed with *N*-Boc-CNA[18] and CBIn[19] which also exhibit preferential addition at the more hindered cyclopropyl carbon, affording similar ring expanded products.

**Resolution and Assignment of Absolute Configuration.** The C3-substituted CBI derivatives were resolved using a Chiralcel-OD semipreparative HPLC column (2 × 25 cm, 7% *i*-PrOH-hexanes eluent, 12 mL/min) at the latest synthetic stage possible for each analogue (Table 2). The Cl, Br, I, and Me derivatives exhibited the best resolution immediately following the installation of the key substituent (**24**−**27**). The corresponding fluoro derivative did not resolve at any stage following installation of the fluorine substituent and required the resolution of **21** and its conversion on to **5**. The absolute configuration of **5**−**9** was assigned through the synthesis of authentic (+)-*N*-$CO_2$Me-CBI[18] from this resolved intermediate **21** (eq 1). Subsequent preparation of optically active **24**−**27** and **5**−**9** from resolved **21** was then performed to unambiguously assign the absolute configuration of each analogue.




**In Vitro Cytotoxic Activity.** The optically active derivatives **5**−**9** were tested for cytotoxic activity against the L1210 cell line (Table 3). In general, the potency of the C3-substituted analogues is markedly less than that of the unsubstituted parent *N*-Boc-CBI (10−100×). In all cases, the natural enantiomers were shown to be more potent than the unnatural enantiomers although the distinctions are generally not large. The fluoro derivative **5** shows both the best activity, as well as the greatest difference in activity between enantiomers. This behavior mirrors that of the parent unsubstituted CBI derivative, although it is an order of magnitude less potent, whereas **6**−**9** exhibit only a subtle difference between the enantiomers (ca. 2×) and all are 100-fold less potent than **4**.

To date, the stability of the CC-1065 alkylation subunit analogues at pH 2−3 has been a useful tool for predicting biological potency.[12] In general, the trend has shown that a greater stability to solvolysis translates into a derivative that is more cytotoxic, presumably the consequence of the chemically more stable derivatives more effectively reaching their biological target. The pH 2−3 solvolysis reactivity has been employed since pH 7 reactivity typically has been immeasurable. With one notable exception in cases where the comparisons could be made,[27] the pH 2−3 relative reactivity has paralleled that observed at pH 7 establishing the validity of this generalization. However, the results highlighted herein, where there is a clear reordering of the reactivities between pH 2−3 and 7, which is a consequence of the change in mechanism from acid-catalyzed to uncatalyzed solvolysis, suggest that it is the pH 7 relative stability (**4** > **5**−**9**), and not that at pH 2−3 (**4** < **5**−**9**), that correlates with biological potency. Thus, in the series of halogen derivatives, (−)-**5** exhibits both the most potent activity and the greatest stability at pH 7. In addition, **5** is the lone member of the series that also exhibits any of the regioselective reactivity observed with the parent system **4**, a behavior that may also account for its enhanced cytotoxic potency relative to the other derivatives in the series. However, there are a number of alternative explanations that may also account for the observations. The greatest activity is also observed with derivatives that exhibit the smallest $\chi_1$ dihedral angle (**4** > **5** > **6**−**9**) suggesting **6**−**9**, and to a lesser extent **5**, may bind in the minor grove more poorly, and comparably, due to the comparable twist in the carbamate linkage. Regardless of the origin of the effects, C3 substitution substantially diminishes cytotoxic potency. To our knowledge, only one other study of C3 substitution of a stable alkylation subunit has been described.[22] Although the evaluations detailed were limited to cytotoxic potency and in vivo antitumor efficacy, similar trends in cytotoxic potency were observed where C3 substitution resulted in 10−100 fold reductions in potency.

**Table 2. Resolution on Chiralcel OD Column**

| agent | α |
|---|---|
| **21** | 1.15 |
| **24** | 1.46 |
| **25** | 1.66 |
| **26** | 1.98 |
| **27** | 1.80 |

**Table 3. In Vitro Cytotoxic Activity**

| natural enantiomers | | unnatural enantiomers | |
|---|---|---|---|
| compd | $IC_{50}$, μM (L1210) | compound | $IC_{50}$, μM (L1210) |
| (+)-**4** | 0.08 | *ent*-(−)-**4** | 0.9 |
| (−)-**5** | 0.2 | *ent*-(+)-**5** | 3.7 |
| (+)-**6** | 2.1 | *ent*-(−)-**6** | 3.9 |
| (+)-**7** | 1.4 | *ent*-(−)-**7** | 4.7 |
| (+)-**8** | 1.2 | *ent*-(−)-**8** | 4.2 |
| (+)-**9** | 3.1 | *ent*-(−)-**9** | 7.4 |

## Conclusions

A series of C3-substituted *N*-Boc-CBI derivatives **5**−**9** were prepared through a directed metalation of the *seco*-CBI core. Introduction of the fluoro and chloro substituents was accomplished with known electrophiles, whereas the installation of the bromo and iodo substituents required use of a novel reagent for effective halogenation of a hindered aryllithium intermediate. Thus, the sterically unencumbered 1-bromo- and 1-iodophenylacetylenes proved remarkably successful for the nucleophilic halogenation and should prove to be generally applicable to similar lithium−halogen exchange reactions beyond those we describe. The single X-ray crystal structures of these derivatives, especially those of the halogen series, highlighted a substantial perturbation in the vinylogous amide conjugation (*r*, N2−C2a bond length) and the dihedral angle $\chi_1$, with *r* and $\chi_1$ smoothly increasing as the size of the C3 substituent increases. The solvolysis reactivity of the series proved especially interesting. At pH 7, the C3 substituted derivatives were substantially more reactive than *N*-Boc-CBI (**4**) itself and the halogen series smoothly followed an expected trend of increasing reactivity with diminished vinylogous amide stabilization (I > Br > Cl > F > H). Beautifully, this trend reversed for solvolysis reactivity at pH 2 and is indicative of a change in solvolysis reaction mechanism from one that is uncatalyzed at pH 7 to one that is acid-catalyzed at pH 2−3. A full pH−rate profile for the solvolysis reaction of the chloro derivative **6** confirmed this behavior, indicating that the acid-catalyzed reaction is observed at pH 2−3 but that the uncatalyzed reaction dominates the rate at pH >3−7. Similarly interesting, the clean $S_N2$ addition of $CH_3OH$ to the more hindered carbon of the cyclopropyl ring with ring expansion was shown to be preferred for all the C3-substituted CBI derivatives, an observation that is in contrast to the exclusive regioselectivity exhibited by the unsubstituted *N*-Boc-CBI (>20:1) for addition to the least substituted cyclopropane carbon. Finally, the C3-substituted CBI derivatives were found to be 10−100× less cytotoxic than the parent system, with the fluoro-substituted derivative exhibiting the most potent activity. This most likely may be attributed to its greater similarity to *N*-Boc-CBI (**4**) in pH 7 reactivity, structure, and inherent regioselectivity of reaction.

The observations made with this series of CBI analogues have important implications on the source of catalysis for the DNA alkylation by **1**−**3**. They demonstrate that disruption of the vinylogous amide conjugation by a twist in the linking amide ($\chi_1$) provides sufficient activation (catalysis) for nucleophilic attack to account for an uncatalyzed (versus acid-catalyzed) DNA alkylation reaction at pH 7−8. This is consistent with a number of related observations[25,29,30] and with the proposal that the DNA alkylation catalysis is derived from a DNA binding-induced conformational change in the agents that twists the linking amide ($\chi_1$) resulting in a diminished vinylogous amide conjugation activating them for nucleophilic attack.[25]

## Experimental Section

***N*-(*tert*-Butyloxycarbonyl)-1-iodo-4-(methoxymethoxy)-2-naphthylamine (18).** A solution of **17**[23] (2.0 g, 6.6 mmol) in THF−$CH_3OH$ (56 mL, 1:1) at −78 °C was treated with *N*-iodosuccinimide (NIS, 2.2 g, 9.9 mmol) in THF (2 mL) followed by $TsOH\cdot H_2O$ (2.5 g, 13.2 mmol) in $CH_3OH$ (2 mL). The reaction mixture was allowed to slowly warm to 0 °C over 4 h and then diluted with 5% aqueous $Na_2S_2O_3$ and stirred at 25 °C for 15 min. The reaction mixture was diluted with EtOAc, and the aqueous phase was separated and extracted twice with EtOAc. The organic layers were combined, dried ($Na_2SO_4$), decanted, and concentrated in vacuo. Flash chromatography ($SiO_2$, 6 × 20 cm, 5% EtOAc−hexanes) afforded **18** as a pale yellow solid (2.2 g, 77%): mp 85−87 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 8.20 (d, $J$ = 8.0 Hz, 1H), 8.06 (d, $J$ = 6.9 Hz, 1H), 8.04 (s, 1H), 7.55 (dd, $J$ = 6.9, 1.1 Hz, 1H), 7.42 (dd, $J$ = 8.0, 1.1 Hz, 1H), 7.25 (s, 1H), 5.46 (s, 2H), 3.57 (s, 3H), 1.58 (s, 9H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ 153.9, 152.8, 138.4, 134.9, 131.5, 128.7, 124.8, 123.9, 122.6, 102.6, 94.9, 82.0, 81.3, 56.8, 28.5; IR (film) $\nu_{max}$ 3384, 2977, 1733, 1495 cm$^{-1}$; FABHRMS (NBA/NaI) *m*/*z* 429.0449 ($M^+$, $C_{17}H_{20}INO_4$ requires 429.0437). Anal. Calcd for $C_{17}H_{20}INO_4$: C, 47.57; H, 4.70; N, 3.26. Found: C, 47.50; H, 4.82; N, 3.14.

**2-[(*N*-*tert*-Butyloxycarbonyl)-*N*-(2-propen-1-yl)amino]-1-iodo-4-(methoxymethoxy)naphthalene (19).** A solution of **18** (3.5 g, 8.2 mmol) in THF (15 mL) was treated with allyl bromide (3.6 mL, 41.1 mmol) followed by a solution of $Bu_4NI$ (0.15 g, 0.41 mmol) in THF (1.5 mL). NaH (0.49 g, 12.3 mmol, 60% dispersion in mineral oil) was added slowly to the reaction mixture at 0 °C. The reaction mixture was allowed to warm to 25 °C over 6 h, diluted with EtOAc, and poured into saturated aqueous $NH_4Cl$. The aqueous phase was separated and extracted twice with EtOAc. The organic layers were combined, dried ($Na_2SO_4$), decanted, and concentrated in vacuo. Flash chromatography ($SiO_2$, 5 × 15 cm, 5% EtOAc−hexanes) afforded **19** as an off-white solid (3.8 g, 99%): mp 61−63 °C; $^1$H NMR (250 MHz, $CDCl_3$, major rotamer) $\delta$ 8.23 (m, 2H), 7.57 (m, 2H), 6.97 (s, 1H), 6.01 (m, 1H), 5.37 (m, 2H), 5.08 (m, 2H), 4.60 (m, 1H), 3.83 (m, 1H), 3.53 (s, 3H), 1.35 (s, 9H); $^{13}$C NMR (62.5 MHz, $CDCl_3$, major rotamer) $\delta$ 153.6, 153.4, 142.9, 135.2, 133.5, 132.7, 128.3, 126.2, 125.3, 122.2, 117.9, 117.4, 110.3, 95.9, 94.7, 80.1, 56.1, 52.2, 28.2; IR (film) $\nu_{max}$ 2976, 1702, 1591, 1390 cm$^{-1}$; MALDIHRMS (DHB) *m*/*z* 492.0626 ($M^+$ + Na, $C_{20}H_{24}INO_4$ requires 492.0648). Anal. Calcd for $C_{20}H_{24}INO_4$: C, 51.18; H, 5.15; N, 2.98. Found: C, 51.33; H, 5.29; N, 2.93.

**3-(*tert*-Butyloxycarbonyl)-5-(methoxymethoxy)-1-[(2′,2′,6′,6′-tetramethylpiperidino)oxy]methyl-1,2-dihydro-3*H*-benz[*e*]indole (20).** A solution of **19** (3.9 g, 8.3 mmol) in benzene (380 mL) was treated with TEMPO (3.9 g, 25 mmol) followed by $Bu_3SnH$ (2.3 mL, 8.7 mmol). The solution was warmed at 70 °C for 30 min, and then an additional 1.0 equiv $Bu_3SnH$ (2.2 mL, 8.3 mmol) was added. An additional 1.5 equiv of TEMPO (1.9 g, 12.4 mmol) was added after 30 min (1 h total reaction time), and the reaction mixture was stirred for another 30 min. A final 1.0 equiv of $Bu_3SnH$ was added after 1.5 h of reaction. The reaction mixture was allowed to stir for 1 h, cooled to 25 °C, and poured into saturated aqueous NaCl. The aqueous phase was separated and extracted twice with EtOAc. The organic layers were combined, dried ($Na_2SO_4$), decanted, and concentrated in vacuo. Flash chromatography ($SiO_2$, 6 × 20 cm, 0−5% EtOAc−hexanes gradient) afforded **20** as an orange oil (2.9 g, 70%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.22 (d, $J$ = 8.0 Hz, 1H), 7.90 (br s, 1H), 7.72 (d, $J$ = 8.0 Hz, 1H), 7.47 (app t, $J$ = 7.1 Hz, 1H), 7.33 (app t, $J$ = 7.5 Hz, 1H), 5.42 (m, 2H), 4.30 (d, $J$ = 11.0 Hz, 1H), 4.08 (m, 2H), 3.81 (m, 2H), 3.57 (s, 3H), 1.62 (s, 9H), 1.45−0.86 (m, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 152.8, 151.9, 140.3, 129.9, 126.3, 122.3 (3C), 121.8, 116.2, 98.3, 94.3, 79.9, 59.1, 55.8, 51.9, 38.9, 37.8, 32.5, 27.9, 19.4, 16.4; IR (film) $\nu_{max}$ 2930, 1703, 1584, 1381 cm$^{-1}$; FABHRMS (NBA/NaI) *m*/*z* 499.3183 ($M^+$, $C_{29}H_{42}N_2O_5$ requires 499.3172).

**3-(*tert*-Butyloxycarbonyl)-1-(hydroxymethyl)-5-(methoxymethoxy)-1,2-dihydro-3*H*-benz[*e*]indole (21).** A solution of **20** (2.9 g, 5.8 mmol) in AcOH−THF−$H_2O$ (180 mL, 3:1:1) was treated with activated Zn dust (1.0 g, 15 mmol) and warmed at 70 °C for 2 h. An additional 0.5 g of Zn dust was

(30) Boger, D. L.; Santillán, A., Jr.; Searcey, M.; Jin, Q. *J. Am. Chem. Soc.* **1998**, *120*, 11554. Boger, D. L.; Santillán, A., Jr.; Searcey, M.; Jin, Q. *J. Org. Chem.* **1999**, *64*, 5241.

added, and the reaction mixture was stirred for another 2 h. The reaction mixture was cooled to 25 °C and filtered, and the volatiles were removed under reduced pressure. The resultant residue was rediluted with EtOAc and poured into saturated aqueous NaCl. The aqueous phase was separated and extracted twice with EtOAc. The organic layers were combined, dried ($Na_2SO_4$), decanted, and concentrated in vacuo. Flash chromatography ($SiO_2$, 5 × 15 cm, 20−30% EtOAc−hexanes gradient) afforded **21** as a white solid (1.5 g, 72%): mp 96−98 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.23 (d, $J$ = 7.9 Hz, 1H), 7.92 (br s, 1H), 7.73 (d, $J$ = 7.6 Hz, 1H), 7.48 (app t, $J$ = 7.0 Hz, 1H), 7.34 (app t, $J$ = 7.6 Hz, 1H), 5.42 (s, 2H), 4.21 (br s, 1H), 4.12 (m, 1H), 3.94 (dd, $J$ = 10.3, 3.5 Hz, 1H), 3.83 (m, 1H), 3.76 (dd, $J$ = 10.3, 7.3 Hz, 1H), 3.56 (s, 3H), 1.61 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 153.7, 152.8, 141.8, 130.7, 127.2 (2C), 122.6, 115.9, 98.9, 94.9, 81.9, 64.6, 56.6, 52.4, 41.4, 28.5; IR (film) $\nu_{max}$ 3452, 2975, 1698, 1381 cm$^{-1}$; FABHRMS (NBA/NaI) $m/z$ 359.1744 ($M^+$, $C_{20}H_{25}NO_5$ requires 359.1733). Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.90. Found: C, 66.74; H, 6.84; N, 3.92.

Natural-(−)-(1*S*)-**21**: $[\alpha]^{25}_D$ −1.7 (*c* 0.70, THF).

*ent*-(+)-(1*R*)-**21**: $[\alpha]^{25}_D$ +1.9 (*c* 0.78, THF).

**1-(Acetoxymethyl)-3-(*tert*-butyloxycarbonyl)-5-(methoxymethoxy)-1,2-dihydro-3*H*-benz[*e*]indole (22).** A solution of **21** (0.25 g, 0.70 mmol) in $CH_2Cl_2$ (10 mL) was treated with $Ac_2O$ (0.33 mL, 3.5 mmol) followed by pyridine (0.28 mL, 3.5 mmol). The reaction mixture was stirred at 25 °C for 18 h and poured into saturated aqueous NaCl. The aqueous phase was separated and extracted twice with EtOAc. The organic layers were combined, dried ($Na_2SO_4$), decanted, and concentrated in vacuo. Flash chromatography ($SiO_2$, 2.5 × 15 cm, 10% EtOAc−hexanes) afforded **22** as a white solid (0.26 g, 93%): mp 97−99 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.21 (d, $J$ = 8.2 Hz, 1H), 7.91 (br s, 1H), 7.78 (d, $J$ = 8.5 Hz, 1H), 7.49 (m, 1H), 7.34 (m, 1H), 5.41 (s, 2H), 4.56 (m, 1H), 4.18 (br s, 1H), 4.06 (m, 1H), 3.95−3.83 (m, 2H), 3.54 (s, 3H), 2.10 (S, 3H), 1.62 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.2, 154.2, 152.6, 140.4, 130.7, 127.5, 123.3, 123.1, 122.7 (2C), 115.8, 99.6, 94.9, 81.9, 65.8, 56.5, 52.4, 37.7, 28.6, 21.1; IR (film) $\nu_{max}$ 2975, 1697, 1381, 1333 cm$^{-1}$; MALDIHRMS (DHB) $m/z$ 424.1736 ($M^+$ + Na, $C_{22}H_{27}NO_6$ requires 424.1736).

Natural (+)-(1*S*)-**22**: $[\alpha]^{25}_D$ +9 (*c* 0.19, THF).

*ent*-(−)-(1*R*)-**22**: $[\alpha]^{25}_D$ −11 (*c* 0.11, THF).

**Directed Ortho-Metalation and Subsequent Halogenation of 22. General Procedure.** A solution of **22** (1.0 equiv) in $Et_2O$ (0.06 M) at −78 °C was treated dropwise with *t*-BuLi (4.0 equiv) as a 1.8 M solution in pentane. The halogen source (4.0 equiv) was added after 4 h of stirring, and the reaction mixture was allowed to slowly warm to 0 °C. Excess 3 M aqueous LiOH was added and the mixture was allowed to stir and warm to 25 °C over 1 h. The mixture was diluted with EtOAc and poured into saturated aqueous $NH_4Cl$. The aqueous phase was separated and extracted twice with EtOAc. The organic layers were combined, dried ($Na_2SO_4$), decanted, and concentrated in vacuo.

**3-(*tert*-Butyloxycarbonyl)-4-chloro-1-(hydroxymethyl)-5-(methoxymethoxy)-1,2-dihydro-3*H*-benz[*e*]indole (24).** Hexachloroethane (137 mg, 0.58 mmol) was added to aryllithium **23** (0.15 mmol) as a solution in $Et_2O$ (0.5 mL). Flash chromatography ($SiO_2$, 2 × 15 cm, 15−25% EtOAc−hexanes gradient) afforded **24** as an off-white foam (40 mg, 70%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.16 (d, $J$ = 7.8 Hz, 1H), 7.75 (d, $J$ = 7.6 Hz, 1H), 7.49−7.41 (m, 2H), 5.31 (d, $J$ = 5.7 Hz, 2H), 5.26 (d, $J$ = 5.9 Hz, 1H), 4.49 (d, $J$ = 11.6 Hz, 1H), 3.93 (dd, $J$ = 10.8, 4.3 Hz, 1H), 3.78 (dd, $J$ = 10.8, 6.8 Hz, 1H), 3.71 (s, 3H), 3.57 (m, 1H), 1.50 (s, 9H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ 155.1, 150.9, 140.5, 128.9, 127.5 (2C), 126.6, 125.5, 123.6 (2C), 117.8, 100.6, 81.8, 63.6, 58.4, 56.4, 44.3, 28.3; IR (film) $\nu_{max}$ 3454, 2932, 1704, 1366 cm$^{-1}$; MALDIHRMS (DHB) $m/z$ 416.1223 ($M^+$ + Na, $C_{20}H_{24}ClNO_5$ requires 416.1241).

Natural (−)-(1*S*)-**24**: $[\alpha]^{25}_D$ −95 (*c* 1.35, THF).

*ent*-(+)-(1*R*)-**24**: $[\alpha]^{25}_D$ +99 (*c* 1.15, THF).

**4-Bromo-3-(*tert*-butyloxycarbonyl)-1-(hydroxymethyl)-5-(methoxymethoxy)-1,2-dihydro-3*H*-benz[*e*]indole (25).** 1-Bromophenylacetylene (197 mg, 1.1 mmol) was added neat to a solution of aryllithium **23** (0.27 mmol). Flash chromatography ($SiO_2$, 2 × 15 cm, 15−25% EtOAc−hexanes gradient) afforded **25** as an off-white foam (81 mg, 68%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.20 (d, $J$ = 8.2 Hz, 1H), 7.77 (d, $J$ = 8.2 Hz, 1H), 7.52 (m, 1H), 7.45 (m, 1H), 5.33 (d, $J$ = 5.8 Hz, 1H), 5.27 (d, $J$ = 5.8 Hz, 1H), 4.51 (d, $J$ = 11.7 Hz, 1H), 4.17 (dd, $J$ = 11.7, 7.6 Hz, 1H), 3.95 (m, 1H), 3.80 (m, 1H), 3.75 (s, 3H), 3.61 (dd, $J$ = 11.3, 6.9 Hz, 1H), 2.03 (s, 1H), 1.53 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.9, 152.2, 141.9, 129.4, 127.4 (2C), 126.6, 125.4, 123.6, 123.4, 107.8, 100.7, 81.7, 63.5, 58.3, 56.3, 44.4, 28.1; IR (film) $\nu_{max}$ 3453, 2977, 1708, 1364 cm$^{-1}$; ESIMS $m/z$ 438 ($M^+$ + H, $C_{20}H_{24}BrNO_5$ requires 438).

Natural (−)-(1*S*)-**25**: $[\alpha]^{25}_D$ −59 (*c* 1.21, THF).

*ent*-(+)-(1*R*)-**25**: $[\alpha]^{25}_D$ +64 (*c* 1.12, THF).

**3-(*tert*-Butyloxycarbonyl)-1-(hydroxymethyl)-4-iodo-5-(methoxymethoxy)-1,2-dihydro-3*H*-benz[*e*]indole (26).** 1-Iodophenylacetylene (212 mg, 0.93) was added neat to a solution of aryllithium **23** (0.23 mmol). Flash chromatography ($SiO_2$, 2 × 15 cm, 15−25% EtOAc−hexanes gradient) afforded **26** as an off-white foam (78 mg, 68%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.19 (d, $J$ = 8.2 Hz, 1H), 7.76 (d, $J$ = 8.2 Hz, 1H), 7.51 (m, 1H), 7.43 (m, 1H), 5.31 (d, $J$ = 5.8 Hz, 1H), 5.24 (d, $J$ = 5.5 Hz, 1H), 4.52 (d, $J$ = 11.7 Hz, 1H), 4.17 (dd, $J$ = 11.7, 7.5 Hz, 1H), 3.94 (m, 1H), 3.78 (m, 1H), 3.77 (s, 3H), 3.62 (m, 1H), 2.09 (br s, 1H), 1.55 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.7, 155.2, 145.1, 130.5, 127.8, 126.9, 126.5, 125.5, 124.0, 123.6, 101.2, 83.9, 81.9, 63.7, 58.6, 56.4, 44.9, 28.3; IR (film) $\nu_{max}$ 3432, 2977, 1708, 1359 cm$^{-1}$. Anal. Calcd for $C_{20}H_{24}INO_5$: C, 49.50; H, 4.98; N, 2.89. Found: C, 49.26; H, 4.92; N, 2.67.

Natural (−)-(1*S*)-**26**: $[\alpha]^{25}_D$ −16 (*c* 0.78, THF).

*ent*-(+)-(1*R*)-**26**: $[\alpha]^{25}_D$ +15 (*c* 0.98, THF).

**3-(*tert*-Butyloxycarbonyl)-1-(hydroxymethyl)-5-(methoxymethoxy)-4-methyl-1,2-dihydro-3*H*-benz[*e*]indole (27).** A solution of $Pd(PPh_3)_4$ (4.5 mg, 3.9 $\mu$mol) dissolved in degassed HMPA (2 mL) was added to a sample of aryl iodide **26** (19 mg, 39 mmol) followed by $SnMe_4$ (14 $\mu$L, 79 $\mu$mol). The reaction mixture was warmed at 65 °C, stirred for 72 h before being diluted with $H_2O$ and poured into $Et_2O$. The aqueous phase was separated and extracted twice with $Et_2O$. The organic layers were combined, dried ($Na_2SO_4$), decanted, and concentrated in vacuo. Flash chromatography ($SiO_2$, 1.5 × 15 cm, 15−25% EtOAc−hexanes) afforded **27** as a colorless oil (16.4 mg, 93%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.12 (d, $J$ = 7.9 Hz, 1H), 7.75 (d, $J$ = 7.6 Hz, 1H), 7.42 (m, 2H), 5.22 (d, $J$ = 5.9 Hz, 1H), 5.14 (d, $J$ = 5.9 Hz, 1H), 4.50 (d, $J$ = 11.4 Hz, 1H), 4.12 (dd, $J$ = 11.4, 3.8 Hz, 1H), 3.94 (dd, $J$ = 11.0, 4.3 Hz, 1H), 3.79 (dd, $J$ = 11.2, 6.8 Hz, 1H), 3.69 (s, 3H), 3.56 (dd, $J$ = 11.2, 6.9 Hz, 1H), 2.38 (s, 3H), 1.75 (br s, 1H), 1.52 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.4, 152.7, 143.1, 129.1, 126.7, 126.4, 124.7, 124.0, 123.4, 123.3, 121.5, 100.3, 81.3, 64.1, 58.1, 56.1, 43.8, 28.5, 14.9; IR (film) $\nu_{max}$ 3452, 2930, 1707, 1369 cm$^{-1}$; FABHRMS (NBA/NaI) $m/z$ 373.1893 ($M^+$, $C_{21}H_{27}NO_5$ requires 373.1889).

Natural (−)-(1*S*)-**27**: $[\alpha]^{25}_D$ −96 (*c* 0.44, THF).

*ent*-(+)-(1*R*)-**27**: $[\alpha]^{25}_D$ +98 (*c* 0.45, THF).

**1-[[(Benzenesulfonyl)oxy]methyl]-3-(*tert*-butyloxycarbonyl)-4-fluoro-5-(methoxymethoxy)-1,2-dihydro-3*H*-benz[*e*]indole (28).** $(PhSO_2)_2NF$ (315 mg, 1.0 mmol) was added to a solution of aryllithium **23** (0.25 mmol) as a solution in THF (1.0 mL). Flash chromatography ($SiO_2$, 2 × 15 cm, 10% EtOAc−hexanes) afforded **28** as an orange oil (55 mg, 42%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.10 (m, 1H), 7.74 (d, $J$ = 8.2 Hz, 2H), 7.51 (m, 2H), 7.39 (m, 4H), 5.32 (d, $J$ = 5.5 Hz, 1H), 5.30 (d, $J$ = 5.5 Hz, 1H), 4.36 (m, 2H), 4.09 (dd, $J$ = 11.5, 8.2 Hz, 1H), 3.99 (dd, $J$ = 10.4, 8.2 Hz, 1H), 3.77 (m, 1H), 3.65 (s, 3H), 1.53 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 153.2, 144.9, 142.9, 140.6 (d, $J$ = 10.6 Hz), 135.5, 133.9, 131.9 (d, $J$ = 12.5 Hz), 128.5 (d, $J$ = 178.5 Hz), 127.0, 126.9 (d, $J$ = 5.8 Hz), 126.4, 125.9, 123.2 (d, $J$ = 6.7 Hz), 122.6, 121.9 (d, $J$ = 1.9 Hz), 99.8 (d, $J$ = 7.7 Hz), 81.9, 69.8, 57.9, 54.5, 40.4, 28.2; $^{19}$F NMR (376 MHz, $C_6D_6$) $\delta$ −134.4 (s); IR (film) $\nu_{max}$ 2977, 1712, 1385 cm$^{-1}$; MALDIHRMS (DHB) $m/z$ 540.1473 ($M^+$ + Na, $C_{26}H_{28}FNO_7S$ requires 540.1468).

Natural (−)-(1*S*)-**28**: $[\alpha]^{25}_D$ −95 (*c* 0.16, THF).

*ent*-(+)-(1*R*)-**28**: $[\alpha]^{25}_D$ +94 (*c* 0.14, THF).

**Mesylation of Alcohols 24−27. General Procedure.** A solution of the alcohol (1.0 equiv) in $CH_2Cl_2$ (0.1 M), cooled to 0 °C, was treated with MsCl (5.0 equiv) followed by $Et_3N$ (5.0 equiv). The reaction mixture was allowed to warm to 25 °C, stirred for 6 h, diluted with EtOAc, and poured into saturated aqueous $NH_4Cl$. The aqueous phase was separated and extracted twice with EtOAc. The organic layers were combined, dried ($Na_2SO_4$), decanted, and concentrated in vacuo.

**3-(*tert*-Butyloxycarbonyl)-4-chloro-1-[[(methanesulfonyl)oxy]methyl]-5-(methoxymethoxy)-1,2-dihydro-3*H*-benz[*e*]indole (29).** Flash chromatography ($SiO_2$, 2 × 15 cm, 15% EtOAc−hexanes) afforded **29** as a colorless oil (27 mg, 99%): $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 8.20 (d, $J$ = 7.7 Hz, 1H), 7.74 (d, $J$ = 7.7 Hz, 1H), 7.56 (m, 1H), 7.48 (m, 1H), 5.35 (d, $J$ = 5.9 Hz, 1H), 5.29 (d, $J$ = 5.5 Hz, 1H), 4.54 (m, 2H), 4.24−4.15 (m, 2H), 3.79 (m, 1H), 3.72 (s, 3H), 2.89 (s, 3H), 1.56 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.5, 151.7, 140.7, 128.7, 128.1, 127.5, 125.8, 123.8 (2C), 122.9, 117.6, 100.6, 82.3, 68.9, 58.5, 55.7, 41.5, 37.6, 28.1; IR (film) $\nu_{max}$ 2978, 1707, 1365, 1332 cm$^{-1}$; MALDIHRMS (DHB) *m*/*z* 494.1039 ($M^+$ + H, $C_{21}H_{26}ClNO_7S$ requires 494.1016).

Natural (−)-(1*S*)-**29**: $[\alpha]^{25}_D$ −64 (*c* 1.53, THF).

*ent*-(+)-(1*R*)-**29**: $[\alpha]^{25}_D$ +60 (*c* 1.35, THF).

**4-Bromo-3-(*tert*-butyloxycarbonyl)-1-[[(methanesulfonyl)oxy]methyl]-5-(methoxymethoxy)-1,2-dihydro-3*H*-benz[*e*]indole (30).** Flash chromatography ($SiO_2$, 2 × 15 cm, 15% EtOAc−hexanes) afforded **30** as a colorless oil (34 mg, 95%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.21 (d, $J$ = 8.8 Hz, 1H), 7.74 (d, $J$ = 8.4 Hz, 1H), 7.56 (m, 1H), 7.48 (m, 1H), 5.33 (d, $J$ = 5.9 Hz, 1H), 5.27 (d, $J$ = 5.5 Hz, 1H), 4.53 (d, $J$ = 10.6 Hz, 2H), 4.54−4.15 (m, 2H), 3.83 (m, 1H), 3.73 (s, 3H), 2.89 (s, 3H), 1.55 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 154.6, 153.2, 142.3, 129.3, 128.3, 127.7, 125.9, 124.2, 124.1, 123.1, 107.7, 100.9, 82.4, 68.8, 58.6, 55.8, 41.9, 37.7, 28.3; IR (film) $\nu_{max}$ 2976, 1707, 1360, 1331 cm$^{-1}$; MALDIHRMS (DHB) *m*/*z* 538.0528 ($M^+$ + Na, $C_{21}H_{26}BrNO_7S$ requires 538.0506).

Natural (−)-(1*S*)-**30**: $[\alpha]^{25}_D$ −38 (*c* 1.41, THF).

*ent*-(+)-(1*R*)-**30**: $[\alpha]^{25}_D$ +39 (*c* 1.29, THF).

**3-(*tert*-Butyloxycarbonyl)-4-iodo-1-[[(methanesulfonyl)oxy]methyl]-5-(methoxymethoxy)-1,2-dihydro-3*H*-benz[*e*]indole (31).** Flash chromatography ($SiO_2$, 2 × 15 cm, 15% EtOAc−hexanes) afforded **31** as a colorless oil (46 mg, 94%): $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 8.21 (d, $J$ = 8.4 Hz, 1H), 7.74 (d, $J$ = 8.0 Hz, 1H), 7.57 (m, 1H), 7.46 (m, 1H), 5.32 (d, $J$ = 5.5 Hz, 1H), 5.24 (d, $J$ = 5.5 Hz, 1H), 4.53 (m, 2H), 4.18 (m, 2H), 3.86 (m, 1H), 3.75 (s, 3H), 2.88 (s, 3H), 1.57 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 156.7, 154.6, 145.4, 130.2, 128.5, 127.0, 125.8, 124.3, 123.9, 123.0, 101.4, 83.4, 82.5, 68.8, 58.7, 55.7, 42.2, 37.7, 28.4; IR (film) $\nu_{max}$ 2979, 1709, 1359, 1331 cm$^{-1}$; FABHRMS (NBA/CsI) *m*/*z* 695.9542 ($M^+$ + Cs, $C_{21}H_{26}INO_7S$ requires 695.9529).

Natural (+)−(1*S*)-**31**: $[\alpha]^{25}_D$ +19 (*c* 0.54, THF).

*ent*-(−)-(1*R*)-**31**: $[\alpha]^{25}_D$ −18 (*c* 0.49, THF).

**3-(*tert*-Butyloxycarbonyl)-1-[[(methanesulfonyl)oxy]-methyl]-5-(methoxymethoxy)-4-methyl-1,2-dihydro-3*H*-benz[*e*]indole (32).** Flash chromatography ($SiO_2$, 2 × 15 cm, 15% EtOAc−hexanes) afforded **32** as a colorless oil (9.5 mg, 88%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.13 (d, $J$ = 8.1 Hz, 1H), 7.41 (d, $J$ = 8.4 Hz, 1H), 7.48 (m, 1H), 7.42 (m, 1H), 5.22 (d, $J$ = 5.9 Hz, 1H), 5.14 (d, $J$ = 5.9 Hz, 1H), 4.53 (m, 2H), 4.19−4.12 (m, 2H), 3.78 (m, 1H), 3.68 (s, 3H), 2.85 (s, 3H), 2.39 (s, 3H), 1.55 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.1, 153.7, 143.4, 128.9, 127.2, 126.9, 125.2, 123.7, 123.0, 121.8, 121.6, 100.6, 81.9, 69.6, 58.3, 55.5, 41.3, 37.9, 28.6, 15.1; IR (film) $\nu_{max}$ 2977, 1704, 1360, 1334 cm$^{-1}$; FABHRMS (NBA/CsI) *m*/*z* 584.0706 ($M^+$ + Cs, $C_{22}H_{29}NO_7S$ requires 584.0719).

Natural (−)-(1*S*)-**32**: $[\alpha]^{25}_D$ −72 (*c* 0.45, THF).

*ent*-(+)-(1*R*)-**32**: $[\alpha]^{25}_D$ +72 (*c* 0.48, THF).

**Selective MOM Ether Deprotection of Benzenesulfonate 28 and Mesylates 29−32 with Subsequent in Situ Spirocyclization. General Procedure.** A solution of the sulfonate in *i*-PrOH−THF (0.02 M, 1:1) was treated with concentrated HCl (75 equiv) and stirred for 4 h at 25 °C. The reaction mixture was quenched with the addition of excess aqueous 10% $NaHCO_3$, stirred for 30 min, diluted with EtOAc, and poured into aqueous 10% $NaHCO_3$. The aqueous phase was separated and extracted twice with EtOAc. The organic layers were combined, dried ($Na_2SO_4$), decanted, and concentrated in vacuo.

**2-(*tert*-Butyloxycarbonyl)-3-fluoro-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (5).** Flash chromatography ($SiO_2$, 1.5 × 15 cm, 25% EtOAc−hexanes) afforded **5** as a white solid (10.3 mg, 53%): mp 168−170 °C; $^1$H NMR (250 MHz, $C_6D_6$) $\delta$ 8.48 (m, 1H), 6.99 (m, 2H), 6.07 (m, 1H), 3.64 (d, $J$ = 11.0 Hz, 1H), 3.21 (dd, $J$ = 11.0, 4.6 Hz, 1H), 1.45 (s, 9H), 1.40 (m, 1H), 0.81 (dd, $J$ = 7.7, 5.1 Hz, 1H), 0.67 (m, 1H); $^{13}$C NMR (125 MHz, $C_6D_6$) $\delta$ 177.2 (d, $J$ = 17.3 Hz), 151.9, 142.6 (d, $J$ = 254.3 Hz), 140.1, 138.2 (d, $J$ = 6.7 Hz), 133.9 (d, $J$ = 3.8 Hz), 132.1, 127.8 (d, $J$ = 2.9 Hz), 127.0, 121.9, 82.8, 53.0, 32.7 (d, $J$ = 2.9 Hz), 28.3, 26.2, 22.8; $^{19}$F NMR (376 MHz, $C_6D_6$) $\delta$ −137.3 (s); IR (film) $\nu_{max}$ 2979, 1713, 1634, 1371 cm$^{-1}$; UV (THF) $\lambda_{max}$ 312 ($\epsilon$ = 25700), 253 ($\epsilon$ = 14300); nm MALDIHRMS (DHB) *m*/*z* 338.1155 ($M^+$ + Na, $C_{18}H_{18}FNO_3$ requires 338.1163).

Natural (−)-**5**: $[\alpha]^{25}_D$ −72 (*c* 0.28, THF).

*ent*-(+)-**5**: $[\alpha]^{25}_D$ +77 (*c* 0.20, THF).

**2-(*tert*-Butyloxycarbonyl)-3-chloro-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (6).** Flash chromatography ($SiO_2$, 1.5 × 15 cm, 25% EtOAc−hexanes) afforded **6** as a white solid (10.5 mg, 77%): mp 152−154 °C; $^1$H NMR (500 MHz, $C_6D_6$) $\delta$ 8.46 (m, 1H), 7.01 (m, 2H), 6.99 (m, 1H), 3.76 (d, $J$ = 11.0 Hz, 1H), 3.20 (dd, $J$ = 11.0, 4.0 Hz, 1H), 1.43 (s, 9H), 1.41 (m, 1H), 0.89 (dd, $J$ = 7.3, 5.1 Hz, 1H), 0.76 (m, 1H);$^{13}$C NMR (125 MHz, $C_6D_6$) $\delta$ 179.6, 153.4, 152.0, 140.1, 133.2, 132.2, 128.3, 127.1, 121.9, 118.9, 82.9, 53.1, 34.3, 28.4, 26.3, 23.1; IR (film) $\nu_{max}$ 2978, 1713, 1623, 1368 cm$^{-1}$; UV (THF) $\lambda_{max}$ 307 ($\epsilon$ = 20000), 251 ($\epsilon$ = 10300) nm; FABHRMS (NBA/NaI) *m*/*z* 332.1045 ($M^+$+ H, $C_{18}H_{18}ClNO_3$ requires 332.1053).

Natural (+)-**6**: $[\alpha]^{25}_D$ +33 (*c* 0.32, THF).

*ent*-(−)-**6**: $[\alpha]^{25}_D$ −35 (*c* 0.53, THF).

**3-Bromo-2-(*tert*-butyloxycarbonyl)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (7).** Flash chromatography ($SiO_2$, 1.5 × 15 cm, 25% EtOAc−hexanes) afforded **7** as a white solid (28 mg, 46%): mp 140−142 °C; $^1$H NMR (250 MHz, $C_6D_6$) $\delta$ 8.45 (m, 1H), 6.99 (m, 2H), 6.08 (m, 1H), 3.78 (d, $J$ = 10.9 Hz, 1H), 3.18 (dd, $J$ = 10.9, 4.4 Hz, 1H), 1.40 (s, 9H), 1.39 (m, 1H), 0.90 (dd, $J$ = 7.3, 5.1 Hz, 1H), 0.79 (m, 1H); $^{13}$C NMR (100 MHz, $C_6D_6$) $\delta$ 179.8, 156.4, 151.8, 140.3, 132.7, 132.2, 128.3, 127.1, 121.9, 111.3, 82.9, 53.1, 35.1, 28.4, 26.2, 23.2; IR (film) $\nu_{max}$ 2960, 1715, 1619, 1368 cm$^{-1}$; UV (THF) $\lambda_{max}$ 311 ($\epsilon$ = 21400), 255 ($\epsilon$ = 17300) nm; MALDIHRMS (DHB) *m*/*z* 296.1300 ((M − Br)$^+$, $C_{18}H_{18}NO_3$ requires 296.1289); ESIMS *m*/*z* 376 ($M^+$ + H, $C_{18}H_{18}BrNO_3$ requires 376).

Natural (+)-**7**: $[\alpha]^{25}_D$ +42 (*c* 0.11, THF).

*ent*-(−)-**7**: $[\alpha]^{25}_D$ −40 (*c* 0.09, THF).

**2-(*tert*-Butyloxycarbonyl)-3-iodo-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (8).** Flash chromatography ($SiO_2$, 1.5 × 15 cm, 25% EtOAc−hexanes) afforded **8** as a white solid (4.8 mg, 61%): mp 145 °C dec; $^1$H NMR (250 MHz, $C_6D_6$) $\delta$ 8.46 (m, 1H), 6.97 (m, 2H), 6.06 (m, 1H), 3.82 (d, $J$ = 11.3 Hz, 1H), 3.15 (dd, $J$ = 10.9, 4.0 Hz, 1H), 1.46 (s, 9H), 1.39 (m, 1H), 0.90 (m, 1H), 0.81 (m, 1H); $^{13}$C NMR (125 MHz, $C_6D_6$) $\delta$ 181.3, 161.6, 151.5, 140.7, 132.2, 131.4, 128.8, 127.1, 121.8, 92.3, 82.9, 52.7, 35.5, 28.6, 26.1, 23.4; IR (film) $\nu_{max}$ 2979, 1715, 1601, 1367 cm$^{-1}$; UV (THF) $\lambda_{max}$ 319 ($\epsilon$ = 21300), 248 ($\epsilon$ = 14900 nm); MALDIHRMS (DHB) *m*/*z* 446.0229 ($M^+$ + Na, $C_{18}H_{18}INO_3$ requires 446.0229). Recrystallization from EtOAc−hexanes provided colorless plates suitable for X-ray structure determination.[24]

Natural (+)-**8**: $[\alpha]^{25}_D$ +155 (*c* 0.24, THF).

*ent*-(−)-**8**: $[\alpha]^{25}_D$ −145 (*c* 0.29, THF).

**2-(*tert*-Butyloxycarbonyl)-3-methyl-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (9).** Flash chromatography ($SiO_2$, 1.5 × 15 cm, 25% EtOAc−hexanes) afforded **9** as a white solid (4.7 mg, 76%): mp 183−185 °C; $^1$H NMR (500 MHz, $C_6D_6$) $\delta$ 8.61 (m, 1H), 7.07 (m, 2H), 6.23 (m, 1H), 3.88 (d, $J$ = 11.0 Hz, 1H), 3.21 (dd, $J$ = 10.8, 4.2 Hz, 1H), 2.28 (s,

3H), 1.49 (m, 1H), 1.33 (s, 9H), 0.95 (dd, $J$ = 7.3, 5.1 Hz, 1H), 0.78 (m, 1H); $^{13}$C NMR (125 MHz, $C_6D_6$) $\delta$ 186.1, 153.0, 152.9, 141.2, 133.8, 131.7, 127.9, 126.8, 122.8, 121.9, 81.8, 52.5, 31.9, 28.4, 25.4, 22.7, 14.6; IR (film) $\nu_{max}$ 2979, 1713, 1630, 1365 cm$^{-1}$; UV (THF) 301 ($\epsilon$ = 16000), 254 ($\epsilon$ = 9200) nm FABHRMS (NBA/NaI) $m/z$ 312.1611 ($M^+$ + H, $C_{19}H_{21}NO_3$ requires 312.1600).

Natural (+)-**9**: $[\alpha]^{25}_D$ +63 ($c$ 0.24, THF).

*ent*-(−)-**9**: $[\alpha]^{25}_D$ −60 ($c$ 0.24, THF).

**Preparation of *N*-CO$_2$Me Derivatives 33−36 for Single-Crystal X-ray Analysis. General Procedure.** The sulfonate (**28**−**32**) was treated with 4 N HCl−EtOAc (0.5 mL) and stirred for 30 min at 25 °C. The solvent was removed under a stream of $N_2$ and the residual salt was placed under vacuum. This salt was suspended in THF (1.0 mL) and treated with $NaHCO_3$ (2.2 equiv) and $ClCO_2CH_3$ (3.0 equiv), and the mixture was stirred for 3 h. Aqueous 10% $NaHCO_3$ was added to the reaction mixture, and stirring was continued for 1 h. The reaction mixture was diluted with EtOAc, and the aqueous phase separated and extracted twice with EtOAc. The organic layers were combined, dried ($Na_2SO_4$), decanted, and concentrated in vacuo.

**3-Fluoro-2-(methoxycarbonyl)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (33).** Flash chromatography ($SiO_2$, 1.5 × 15 cm, 25% EtOAc−hexanes) afforded **33** as a white solid (15 mg, 82%): mp 171−173 °C; $^1$H NMR (400 MHz, $C_6D_6$) $\delta$ 8.46 (m, 1H), 6.99 (m, 2H), 6.08 (m, 1H), 3.57 (d, $J$ = 10.6 Hz, 1H), 3.43 (s, 3H), 3.18 (dd, $J$ = 11.1, 4.4 Hz, 1H), 1.43 (m, 1H), 0.79 (dd, $J$ = 7.5, 4.9 Hz, 1H), 0.59 (m, 1H); IR (film) $\nu_{max}$ 2922, 1723, 1634, 1294 cm$^{-1}$. The identity of **33** was confirmed with a single-crystal X-ray structure obtained from a colorless, cubic crystal grown from EtOAc−hexanes.[24]

**3-Chloro-2-(methoxycarbonyl)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (34).** Flash chromatography ($SiO_2$, 1.5 × 15 cm, 25% EtOAc−hexanes) afforded **34** as a white solid (9.2 mg, 70%): mp 165−167 °C; $^1$H NMR (400 MHz, $C_6D_6$) $\delta$ 8.48 (m, 1H), 6.98 (m, 2H), 6.04 (m, 1H), 3.59 (d, $J$ = 10.9 Hz, 1H), 3.44 (s, 3H), 3.16 (dd, $J$ = 10.9, 4.4 Hz, 1H), 1.34 (m, 1H), 0.80 (m, 1H), 0.62 (m, 1H); IR (film) $\nu_{max}$ 2954, 1723, 1622, 1374 cm$^{-1}$. The identity of **34** was confirmed with a single-crystal X-ray structure obtained from a colorless, parallelpipe-shaped crystal grown from EtOAc−hexanes.[24]

**3-Bromo-2-(methoxycarbonyl)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (35).** Flash chromatography ($SiO_2$, 1.5 × 15 cm, 25% EtOAc−hexanes) afforded **35** as a white solid (6.5 mg, 68%): mp 142−144 °C; $^1$H NMR (400 MHz, $C_6D_6$) $\delta$ 8.47 (m, 1H), 6.97 (m, 2H), 6.04 (m, 1H), 3.62 (d, $J$ = 10.6 Hz, 1H), 3.46 (s, 3H), 3.16 (dd, $J$ = 11.1, 4.4 Hz, 1H), 1.34 (m, 1H), 0.81 (dd, $J$ = 7.5, 4.9 Hz, 1H), 0.65 (m, 1H); IR (film) $\nu_{max}$ 2954, 1721, 1617, 1439 cm$^{-1}$. The identity of **35** was confirmed with a single-crystal X-ray structure obtained from a colorless, parallelpipe-shaped crystal grown from EtOAc−hexanes.[24]

**2-(Methoxycarbonyl)-3-methyl-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (36).** Flash chromatography ($SiO_2$, 1.5 × 15 cm, 25% EtOAc−hexanes) afforded **36** as a white solid (8.0 mg, 80%): mp 189−191 °C; $^1$H NMR (500 MHz, $C_6D_6$) $\delta$ 8.59 (m, 1H), 7.07 (m, 2H), 6.22 (m, 1H), 3.76 (d, $J$ = 11.0 Hz, 1H), 3.34 (s, 3H), 3.19 (dd, $J$ = 10.9, 4.4 Hz, 1H), 2.20 (s, 3H), 1.46 (m, 1H), 0.89 (dd, $J$ = 7.1, 4.9 Hz, 1H), 0.67 (m, 1H); IR (film) $\nu_{max}$ 2955, 1716, 1628, 1366 cm$^{-1}$. The identity of **36** was confirmed with a single-crystal X-ray structure obtained from a colorless, parallelpipe-shaped crystal grown from $Et_2O$−cyclohexane.[24]

**Resolution.** A solution of racemic intermediate (**21**, **24**−**27**; 15 mg per injection) in 50% *i*-PrOH−hexanes (200 $\mu$L) was resolved on a semipreparative Daicel Chiralcel OD column (10 $\mu$m, 2 × 25 cm) using 7% *i*-PrOH−hexanes as eluent (12 mL/min). The effluent was monitored at 254 nm, and the enantiomers were eluted with retention times as follows: (+)-**21** (20.1 min), (−)-**21** (22.5 min), $\alpha$ = 1.15; (+)-**24** (25.8 min), (−)-**24** (39.3 min), $\alpha$ = 1.46; (+)-**25** (27.7 min), (−)-**25** (46.3 min), $\alpha$ = 1.66; (+)-**26** (28.5 min), (−)-**26** (55.3 min), $\alpha$ = 1.98; (+)-**27** (17.5 min), (−)-**27** (31.5 min), $\alpha$ = 1.80. (−)-**21** was reinjected in order to obtain > 99% ee material, unlike all others which were found to be >99% enantiomerically pure after a single injection.

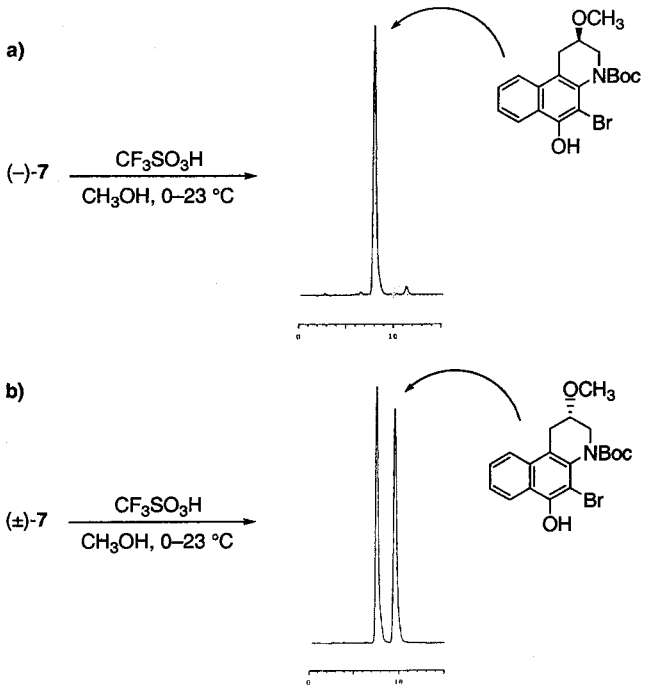



**Figure 8.** HPLC analysis (Chiralcel AD, 10% *i*-PrOH in hexanes) of the acid-catalyzed addition of methanol to (a) (−)-**7** and (b) (±)-**7**.

**Aqueous Solvolysis of 5−9.** A sample of **5**−**9** (75 $\mu$g) was dissolved in $CH_3OH$ (1.5 mL), and the resultant solution was mixed with universal aqueous buffer (pH 2−10, 1.5 mL, $B(OH)_3$−citric acid−$Na_3PO_4$). The UV spectrum of the solution was measured immediately after mixing then approximately every 24 h until no further change in the spectrum was observed. The decrease in absorbance for **5**−**9** was measured at 318, 318, 318, 324 and 313 nm, respectively, while the increase in absorbance was measured at 247, 249, 248, 251 and 247 nm. The solvolysis rate was calculated as the slope of the plot $\ln[(A_f - A_i)/(A_f - A)]$ versus time (Table 1).

**Acid-Catalyzed Addition of CH$_3$OH to 5−9. General Procedure.** A solution of the C3-substituted *N*-Boc-CBI (**5**−**9**, 1.0 equiv) in $CH_3OH$ (0.01 M) was treated with $CF_3SO_3H$ (0.12 equiv, 0.01 M solution in $CH_3OH$) at 0 °C. The reaction mixture was allowed to slowly warm to 25 °C over 24 h and then quenched with the addition of $NaHCO_3$ (5 mg). The reaction was decanted, and the crude material was absorbed onto a minimal amount of $SiO_2$ then loaded directly onto a prepacked flash column and eluted to afford the solvolysis product(s).

HPLC resolution of the addition reactions to (±)- and (+)-**5**−**9** established the ratio of reaction regioselectivity (see Scheme 5) and the exclusive $S_N2$ mechanism of addition by affording a single enantiomer of **41**−**46**. A representative example of such analysis for **7** is shown in Figure 8. The chiral phase HPLC traces of the remainder may be found in the Supporting Information (Figures 9−12).

**4-(*tert*-Butyloxycarbonyl)-5-fluoro-6-hydroxy-2-methoxy-1,2,3,4-tetrahydrobenzo[*f*]quinoline (41) and 3-(*tert*-Butyloxycarbonyl)-4-fluoro-5-hydroxy-1-(methoxymethyl)-1,2-dihydro-3*H*-benz[*e*]indole (42).** Flash chromatography ($SiO_2$, 1.5 × 15 cm, 25% EtOAc−hexanes) afforded a 1:4 mixture of **41** and **42** (10.3 mg, 82%) that required additional separation using a semipreparative Daicel Chiralcel OD column (10 $\mu$m, 2 × 25 cm) with 7% *i*-PrOH−hexanes as eluent (12 mL/min) to afford each pure. For **41**: $^1$H NMR (500 MHz, $C_6D_6$) $\delta$ 8.34 (d, $J$ = 8.4 Hz, 1H), 7.44 (d, $J$ = 8.4 Hz, 1H), 7.22 (m, 2H), 5.29 (br s, 1H), 4.61 (br m, 1H), 3.22 (br m, 5H), 2.81 (br s, 2H), 1.46 (s, 9H); IR (film) $\nu_{max}$ 3347, 2929, 1703, 1460

$cm^{-1}$; MALDIHRMS (DHB) *m/z* 370.1425 ($M^+ + Na$, $C_{19}H_{22}FNO_4$ requires 370.1410). The identity of **41** was confirmed with a single-crystal X-ray structure obtained from a colorless, cubic crystal grown from EtOAc−hexanes.[24]

For **42**: $^1H$ NMR (400 MHz, $C_6D_6$) $\delta$ 8.34 (d, $J$ = 7.6 Hz, 1H), 7.41 (d, $J$ = 8.8 Hz, 1H), 7.20 (m, 2H), 5.92 (s, 1H), 4.56 (d, $J$ = 11.2 Hz, 1H), 3.78 (m, 1H), 3.34 (m, 1H), 3.11 (m, 2H), 2.97 (s, 3H), 1.49 (s, 9H); IR (film) $\nu_{max}$ 3401, 2978, 1711, 1366 $cm^{-1}$; MALDIHRMS (DHB) *m/z* 370.1425 ($M^+ + Na$, $C_{19}H_{22}FNO_4$ requires 370.1425).

**4-(*tert*-Butyloxycarbonyl)-5-chloro-6-hydroxy-2-methoxy-1,2,3,4-tetrahydrobenzo[*f*]quinoline (43).** Flash chromatography ($SiO_2$, 1.5 × 15 cm, 25% EtOAc−hexanes) afforded **43** as a white solid (6.8 mg, 86%): mp 127−129 °C; $^1H$ NMR (400 MHz, $C_6D_6$) $\delta$ 8.46 (m, 1H), 7.46 (m, 1H), 7.28 (m, 2H), 5.91 (s, 1H), 4.80 (m, 1H), 3.34−2.52 (m, 7H), 1.44 (s, 9H); IR (film) $\nu_{max}$ 3384, 2925, 1704, 1585 $cm^{-1}$; MALDIHRMS (DHB) *m/z* 364.1301 ($M^+ + H$, $C_{19}H_{22}ClNO_4$ requires 364.1310). The identity of **43** was confirmed with a single-crystal X-ray structure obtained from a colorless, cubic crystal grown from EtOAc−hexanes.[24]

**5-Bromo-4-(*tert*-butyloxycarbonyl)-6-hydroxy-2-methoxy-1,2,3,4-tetrahydrobenzo[*f*]quinoline (44).** Flash chromatography ($SiO_2$, 1.5 × 15 cm, 25% EtOAc−hexanes) afforded **44** as a white solid (2.8 mg, 89%): mp 123−125 °C; $^1H$ NMR (600 MHz, $C_6D_6$) $\delta$ 8.38 (m, 1H), 7.48 (m, 1H), 7.24 (m, 2H), 5.89 (s, 1H), 4.75 (m, 1H), 3.79 (m, 1H), 3.28−2.55 (m, 6H), 1.39 (s, 9H); IR (film) $\nu_{max}$ 3381, 2930, 1703, 1583, 1368 $cm^{-1}$; MALDIHRMS (DHB) *m/z* 430.0628 ($M^+ + Na$, $C_{19}H_{22}BrNO_4$ requires 430.0624). The identity of **44** was confirmed with a single-crystal X-ray structure obtained from a colorless, cubic crystal grown from EtOAc−hexanes.[24]

**4-(*tert*-Butyloxycarbonyl)-6-hydroxy-5-iodo-2-methoxy-1,2,3,4-tetrahydrobenzo[*f*]quinoline (45).** Flash chromatography ($SiO_2$, 1.5 × 15 cm, 25% EtOAc−hexanes) afforded **45** as a white foam (5.7 mg, 85%): $^1H$ NMR (400 MHz, $C_6D_6$) $\delta$ 8.44 (m, 1H), 7.46 (m, 1H), 7.23 (m, 2H), 5.84 (s, 1H), 4.97−3.85 (m, 2H), 3.28−2.44 (m, 6H), 1.39 (s, 9H); IR (film) $\nu_{max}$ 3402, 2928, 1704, 1450 $cm^{-1}$; MALDIHRMS (DHB) *m/z* 328.1538 ($(M-I)^+$, $C_{19}H_{22}NO_4$ requires 328.1543); ESIMS *m/z* 454 ($(M - H)^-$, $C_{18}H_{22}NO_4$ requires 454).

**4-(*tert*-Butyloxycarbonyl)-6-hydroxy-2-methoxy-5-methyl-1,2,3,4-tetrahydrobenzo[*f*]quinoline (46).** Flash chromatography ($SiO_2$, 1.5 × 15 cm, 25% EtOAc−hexanes) afforded **46** as a white foam (2.8 mg, 82%): $^1H$ NMR (500 MHz, $C_6D_6$) $\delta$ 8.22 (m, 1H), 7.60 (m, 1H), 7.27 (m, 2H), 4.84 (d, $J$ = 13.3 Hz, 1H), 4.63 (s, 1H), 3.33 (s, 3H), 3.18−2.57 (m, 4H), 2.07 (s, 3H), 1.32 (s, 9H); IR (film) $\nu_{max}$ 3418, 2929, 1673, 1367 $cm^{-1}$; MALDIHRMS (DHB) *m/z* 343.1775 ($M^+$, $C_{20}H_{25}NO_4$ requires 343.1778).

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**Supporting Information Available:** $^1H$ NMR spectra of **5**−**9**, **18**−**22**, **24**−**36**, and **41**−**46** and copies of the chiral-phase HPLC traces of the acid-catalyzed $CH_3OH$ addition products to **5**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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