Design, Synthesis, and Evaluation of CC-1065 and Duocarmycin Analogs Incorporating the 2,3,10,10a-Tetrahydro-1*H*-cyclopropa[*d*]benzo[*f*]quinol-5-one (CBQ) Alkylation Subunit: Identification and Structural Origin of Subtle Stereoelectronic Features That Govern Reactivity and Regioselectivity

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Received August 19, 1994[⊗]

Abstract: The synthesis of 2,3,10,10a-tetrahydro-1*H*-cyclopropa[*d*]benzo[*f*]quinol-5-one (**10**, CBQ), containing a deep-seated structural variation in the CC-1065 and duocarmycin alkylation subunits with incorporation of a ring expanded fused six- versus five-membered ring, and its incorporation into analogs of the natural products are detailed. The approach was based on a key 6-*exo-trig* aryl radical–alkene cyclization of **22** to provide **23** in which an enol ether acceptor alkene served to reinforce the preferred 6-*exo-trig* versus 7-*endo-trig* cyclization and directly provided a suitably functionalized 1,2,3,4-tetrahydrobenzo[*f*]quinoline precursor. Conversion of **23** to **26** followed by Winstein Ar-3′ alkylation cleanly permitted the introduction of the activated cyclopropane and completed the synthesis of the CBQ nucleus. The evaluation of the CBQ-based agents revealed an exceptional solvolysis reactivity and mixed solvolysis regioselectivity. *N*-BOC-CBQ (**9**, $t_{1/2}$ = 2.1 h, $k = 9.07 \times 10^{-5}$ s^{-1}, pH 3) proved to be 63× more reactive than *N*-BOC-CBI ($t_{1/2}$ = 133 h, $k = 1.45 \times 10^{-6}$ s^{-1}, pH 3) and its solvolysis was found to proceed with cleavage of both the external C9b–C10 and internal C9b–C10a cyclopropane bonds. The latter was shown to occur with exclusive inversion of stereochemistry illustrating for the first time that the solvolysis and alkylation reactions proceed by S_N2 versus S_N1 cyclopropane ring opening upon activation by C5 carbonyl protonation. A comparison of the X-ray crystal structures of the CPI alkylation subunit taken from (+)-CC-1065, the CBI alkylation subunit, and *N*-BOC-CBQ (**9**) provided the structural basis for this altered solvolysis reactivity and regioselectivity. The increased inherent reactivity and the loss of stereoelectronic control for cyclopropane ring opening may be attributed to the idealized alignment and conjugation of the activated cyclopropane with the cyclohexadienone π-system. The fundamental insight derived from the comparisons was not the rapid solvolysis or mixed solvolysis regioselectivity of the CBQ agents, but rather the surprising stability and solvolysis selectivity of the CBI and DSA alkylation subunits. In spite of the apparent structural features that intuitively suggest a high reactivity, the latter agents have proven to be uncharacteristically stable. This unusual stability and the solvolysis regioselectivity are imposed by fusion of the activated cyclopropane to the five-membered ring which constrains it to a nonideal alignment and overlap with the cyclohexadienone π-system. In addition, the in vitro cytotoxic potencies of the CBQ-based agents were found to qualitatively and quantitatively follow the well-established trend where the chemically more stable agents provide the more potent activity.

(+)-CC-1065 (**1**),[1] duocarmycin SA (**2**),[2] and duocarmycin A (**3**)[3] constitute the parent agents of a class[1–6] of potent antitumor antibiotics that derive their biological properties through a sequence selective alkylation of DNA.[7–10] The characteristic DNA alkylation reaction has been shown to proceed by a reversible, stereoelectronically-controlled adenine N3 addition to the least substituted carbon of the activated

[⊗] Abstract published in *Advance ACS Abstracts*, November 15, 1994.

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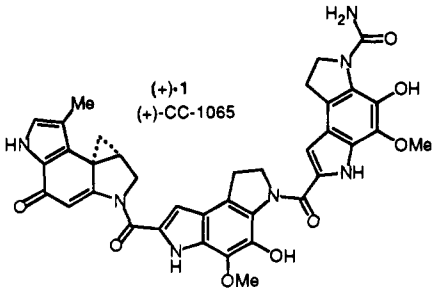
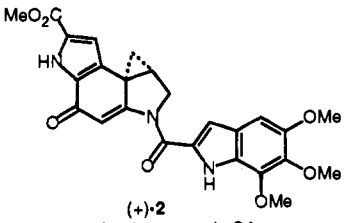
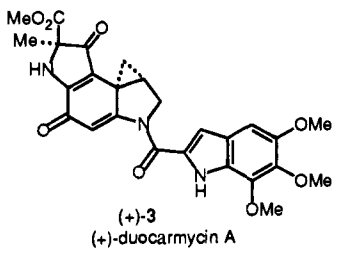
cyclopropane within selected AT-rich sites of the minor groove.[11-16] Although the intracellular target for the agents has been shown to be DNA, the mechanism by which DNA alkylation may translate into productive antitumor activity has remained elusive until the recent disclosure that apoptotic cell death is initiated by DNA alkylation in sensitive cell lines.[17]







In recent efforts, the preparation of agents containing deep-seated changes in the alkylation subunits has been detailed with the intent of defining the structural features of **1-3** contributing to polynucleotide recognition and functional reactivity.[18-23] In these studies, the electrophilic cyclopropane proved not to be obligatory to observation of the characteristic alkylation selectivity, and additional electrophiles incorporated into structurally related agents were found to act similarly.[19] Moreover, the AT-rich noncovalent binding selectivity[24] of the agents has been shown to control the DNA alkylation selectivity independent of the nature of the electrophile.[12,14,19,25] Several additional fundamental structural features contributing to the properties of **1-3** have been detailed including a direct relationship between solvolysis stability and cytotoxic potency,[14,20] the structural origin of the distinguishing behavior of the natural and unnatural enantiomers,[12,14] and the noncovalent binding stabilization of the inherently reversible DNA alkylation reaction[13,14] and have led to the development of alkylation site models that accommodate the reversed binding orientation and offset AT-rich selectivity of the natural and unnatural enantiomer DNA alkylation reactions.[12,14]

In the course of these studies, the examination of agents incorporating the simplified CBI alkylation subunit have proven especially interesting.[20,22] Such agents have displayed potent cytotoxic activity and selected agents within the series have displayed efficacious antitumor activity.[20] Herein, we report the extension of these studies to the preparation and examination of agents incorporating the 2,3,10,10a-tetrahydro-1*H*-cyclopropa[*d*]benzo[*f*]quinol-5-one (CBQ)[23] alkylation subunit. The ring expansion of the fused five-membered ring to a six-membered ring did not diminish the electrophilic reactivity through release of ring strain but resulted in a substantial increase in reactivity and a loss of stereoelectronic control for

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(23) Boger, D. L.; Mesini, P.; Tarby, C. E. *J. Am. Chem. Soc.* **1994**, *116*, 6461.

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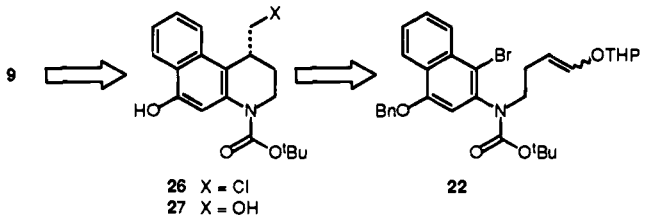
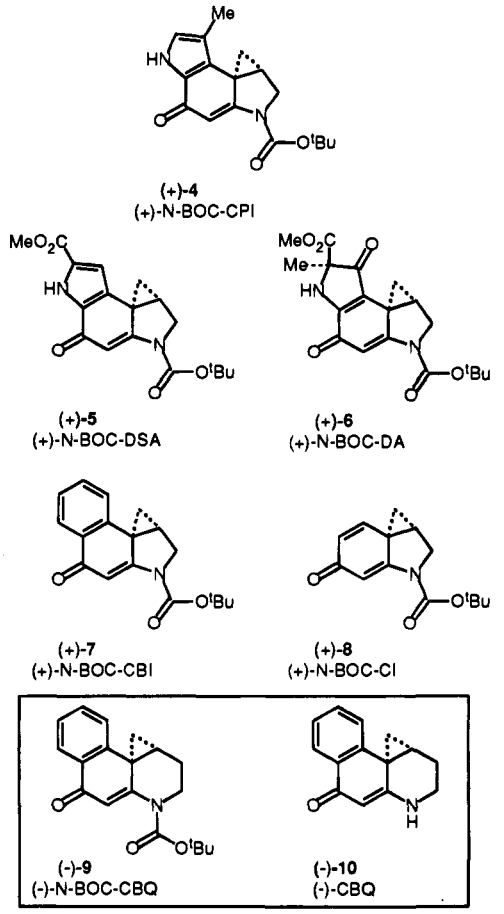
Scheme 1

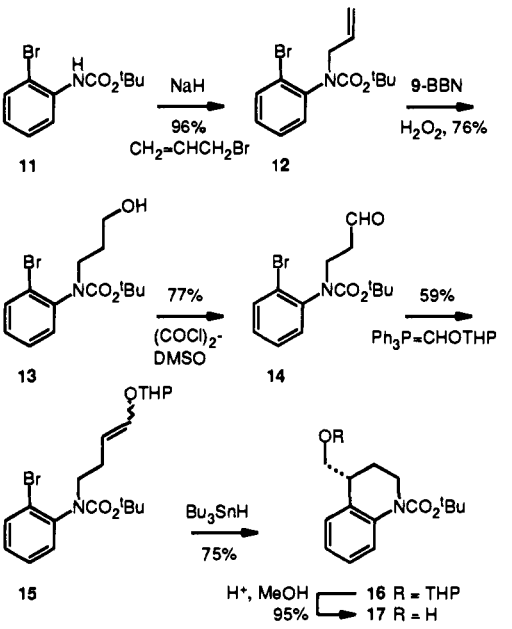


addition to the activated cyclopropane. Importantly, this examination of the CBQ-based agents and comparison with **1**–**8** revealed a fundamental and unappreciated stability for the CC-1065 and duocarmycin alkylation subunits. The subtle stereoelectronic and structural origin of this unusual but productive stability and the ramifications of these observations are detailed. In addition, the CBQ-based agents were found to quantitatively follow the well-established relationship between solvolysis stability and cytotoxic potency for this class of agents.



Synthesis of *N*-BOC-CBQ (9) and CBQ (10). The key to the preparation of the CBQ nucleus rested with the implementation of a 6-*exo-trig* aryl radical-alkene cyclization for construction of the functionalized 1,2,3,4-tetrahydrobenzo[*f*]quinoline nucleus central to its core structure (Scheme 1). It was anticipated that the cyclization of the precursor enol ether **22** would serve to reinforce the preferred 6-*exo-trig* versus 7-*endo-trig* cyclization available to **22** and directly provide a suitably functionalized 1-substituted 1,2,3,4-tetrahydrobenzo[*f*]quinoline for simple conversion to **9**-**10**. As such, the approach would be complementary to the 5-*exo-dig* and self-terminating 5-*exo-trig* free radical cyclization approaches introduced in our studies on **4**, **7**-**8**.[18–22]

Scheme 2



In efforts to determine the viability of the approach to **22** and which served to confirm that the key 6-*exo-trig* free radical cyclization, 2-bromoaniline was converted **11** (Scheme 2). Alkylation of the sodium salt of **11** (1.2 equiv of NaH, 25 °C, 15 min) with allyl bromide (1.2 equiv, THF–DMF 5:1, 25 °C, 7 h, 96%) followed by hydroboration-oxidation of **12** (1.6 equiv of 9-BBN, THF, 25 °C, 12 h; NaOH–H_2O_2, 76%) provided **13**. Mild oxidation[26] of **13** (1.1 equiv of $(COCl)_2$, 2.2 equiv of DMSO, 5.5 equiv of Et_3N, CH_2Cl_2, −60 to 25 °C, 77%) cleanly provided **14**. Notably, the alcohol **13** could be isolated and handled without evidence of 6-membered cyclic carbamate formation derived from reaction of the primary alcohol with the proximal *N*-BOC protecting group. Attempts to generate **14** directly by alkylation of **11** with acrolein were not successful and, similar to prior observations,[18–22] attempts to alkylate **11** with less reactive electrophiles including 4-bromo-1-butyne[27] or 4-[(methanesulfonyl)oxy]-1-butene[28] were not productive. Treatment of aldehyde **14** with Ph_3P=CHOTHP[29] (2.9 equiv) under defined reaction conditions with ylide generation in THF followed by reaction with **14** over a sustained reaction period (24 h) in THF–HMPA[30] at 25 °C cleanly provided **15** (59%) as a mixture of olefin isomers. β-Elimination derived from deprotonation of the aldehyde was not observed and elimination of the intermediate oxaphosphetane was accelerated with use of HMPA as an added cosolvent. Treatment of **15** with Bu_3SnH (2 equiv, 0.2 equiv of AIBN, C_6H_6, 80 °C, 12 h, 75%) cleanly afforded **16** derived from bromine atom abstraction with aryl radical generation followed by 6-*exo-trig* cyclization without evidence of competing generation of the 7-*endo-trig* cyclization product. Acid-catalyzed deprotection of **16** (Amberlyst-15, CH_3OH, 50 °C, 25 h, 96%) provided **17**.

Without further optimization, the preparation of CBQ was pursued. Alkylation of the sodium salt of *N*-(*tert*-butyoxy-

(26) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(27) Through implementation of a 6-*exo-dig* aryl radical-alkyne cyclization/hydroboration sequence, the product could provide an alternative route to **17**.

(28) Ozonolysis of the product would provide an alternative route to **14**.

(29) Schlude, H. *Tetrahedron* **1975**, *31*, 89. Anderson, C. L.; Soderquist, J. A.; Kabalka, G. W. *Tetrahedron Lett.* **1992**, *33*, 6915.

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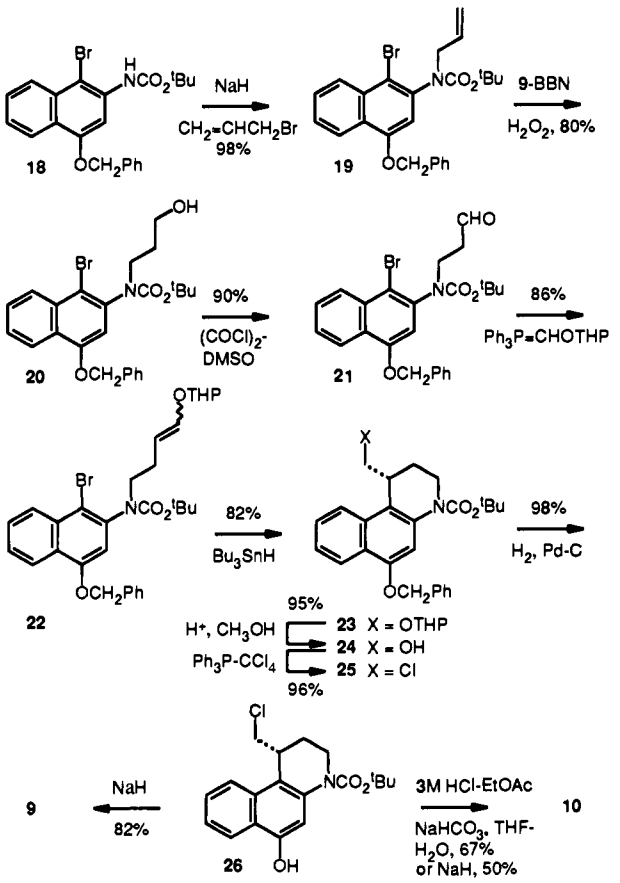
Scheme 3



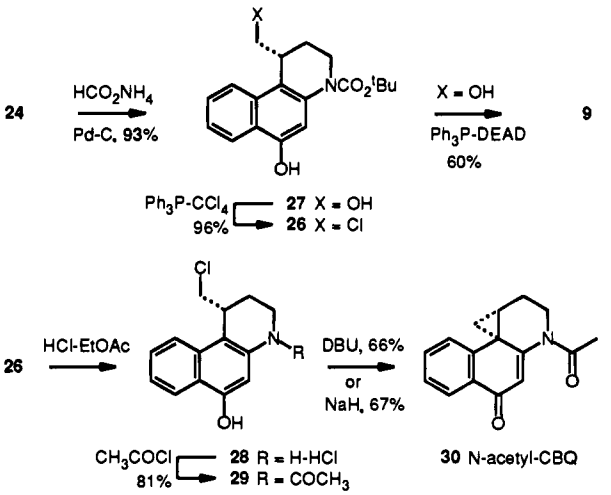
carbonyl)-4-(benzyloxy)-1-bromo-2-naphthylamine (**18**),[20j] readily available in three to four steps (70%) from 1,3-dihydroxynaphthalene, with allyl bromide (98%) afforded **19** (Scheme 3). Hydroboration−oxidation (80%) followed by Swern oxidation[26] of the alcohol **20** (90%) cleanly provided the stable aldehyde **21**. No evidence for closure of alcohol **20** to the corresponding cyclic carbamate was detected and the aldehyde **21** exhibited no tendency to undergo β-elimination. Reaction of **21** with the $Ph_3P{=}CHOTHP$[29] (2.9 equiv) with low temperature generation of the Wittig reagent conducted in THF followed by addition of HMPA[30] and further reaction with **21** for an extended period (25 °C, 24 h) provided **22** in excellent conversions (86%) as a 40:60 mixture of *Z*- and *E*-isomers. Treatment of **22** with Bu_3SnH (2 equiv, 0.2 equiv of AIBN, C_6H_6, 80 °C, 12 h, 82%) afforded **23** derived from the key 6-*exo*-*trig* aryl radical-alkene cyclization in excellent yield. Acid-catalyzed deprotection of the THP group provided **24** (Amberlyst-15, CH_3OH, 50 °C, 2 h, 95%) and was accomplished cleanly without evidence of *N*-BOC deprotection.

Removal of the benzyl protecting group through transfer hydrogenolysis[31] (0.3 wt equiv 10% Pd−C, aqueous HCO_2NH_4−THF, 25 °C, 7 h, 93%) afforded **27** and direct spirocyclization of **27** upon Mitsunobu activation[32] of the primary alcohol (1.2 equiv of Ph_3P, 1.2 equiv of DEAD, THF, 25 °C, 1 h, 60%) provided *N*-BOC-CBQ (**9**), Scheme 4. Similarly, conversion of **27** to the primary chloride **26** (96%)[33] followed by spirocyclization effected by treatment with NaH (1.1−1.2 equiv, THF−DMF 1:2, 82%) cleanly provided **9**. Because of the unusual reactivity of the CBQ agents, the conversions observed in closure of the cyclopropane proved to be dependent

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

(32) Mitsunobu, O. *Synthesis* **1981**, 1.

Scheme 4



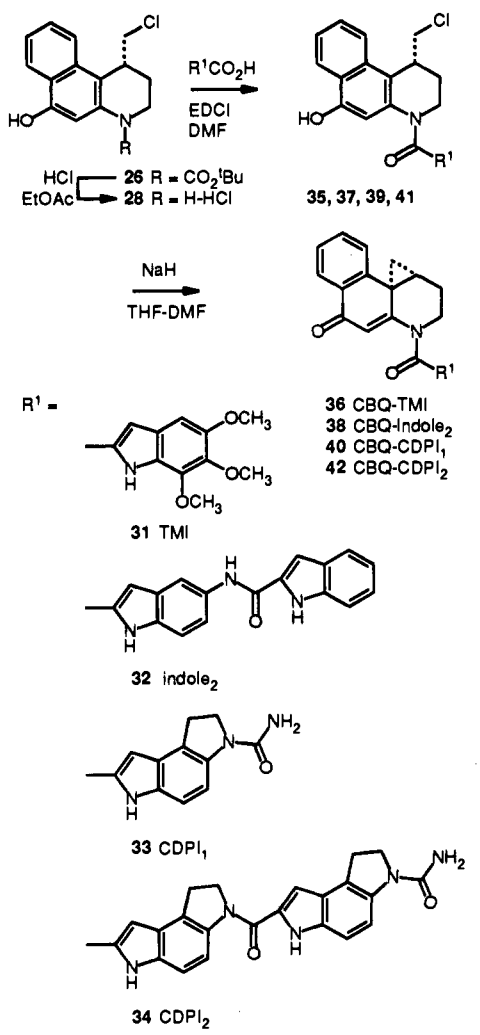
on the workup conditions and purification protocols. A low temperature (0 °C) quench of the reaction with pH 7 phosphate buffer which avoids both an acid-catalyzed solvolysis reaction or base-catalyzed hydrolysis of the labile *N*-acyl group followed by careful but rapid chromatography provided the best results. While both these approaches provided **9** in excellent conversions, **26** and **27** exhibited a limited capacity for storage presumably due to the presence of the free phenol. A technically improved preparation which proceeds through the more stable intermediate **25** was accomplished by conversion of alcohol **24** to chloride **25** (96%)[33] followed by hydrogenolysis of the benzyl ether (H_2, 0.3 wt equiv 10% Pd−C, THF, 25 °C, 2 h, 98%) to provide **26** (Scheme 3). Notably, the conventional hydrogenation of **25** was effected without competitive hydrogenolysis of the chloride and in higher conversions than comparable attempts to use transfer hydrogenolysis (0.3 wt equiv 10% Pd−C, aqueous HCO_2NH_4−THF, 25 °C, 2−4 h, 80%). Acid-catalyzed deprotection of **26** (3 M HCl−EtOAc, 15−20 min) followed by spirocyclization of **28** upon mild base treatment (5% aqueous $NaHCO_3$−THF 1:1, 25 °C, 2 h, 67%; or NaH, THF−DMF 1:1, 25 °C, 5 min, 50%) provided CBQ (**10**), Scheme 3.

One concern with handling the seco-CBQ agents was the relative stability of the hydrochloride salt **28** derived from acid-catalyzed *N*-BOC deprotection and whether a subsequent amide bond coupling could be performed competitive with potential side reactions including intramolecular *N*-alkylation. This was first examined with the preparation of *N*-acetyl-CBQ (**30**). Acid-catalyzed deprotection of **26** (3 M HCl−EtOAc, 25 °C, 30 min) followed by immediate coupling of the unstable hydrochloride salt **28** with CH_3COCl (2.6 equiv, THF, 1.1 equiv of $NaHCO_3$, 25 °C, 30 min, 81%) provided **29** (Scheme 4). Spirocyclization of **29** upon treatment with base (3 equiv of DBU, THF, 25 °C, 8 h, 66% or 2.1 equiv of NaH, THF, 25 °C, 30 min, 67%) provided **30**. Notably, no competitive intramolecular *N*-alkylation product was detected in the reaction mixture that provided **29**. This welcomed observation indicated that the alternative approaches requiring coupling of alcohol **27** or the benzyl ether **25** followed by phenol deprotection or activation of the primary alcohol toward spirocyclization on the typically insoluble seco agents of the advanced analogs (*i.e.* **35-42**) would not have to be encountered.

Resolution. The resolution of one or more of the intermediates in the CBQ synthesis was examined and accomplished by direct chromatographic resolution of **9** on a preparative chiralcel OD column.[20i] This convenient procedure which avoids dia-

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

Scheme 5



stereometric derivatization, separation, and dederivatization of an advanced intermediate was found to be optimal with **9** itself. *N*-BOC-CBQ (**9**) was easily separated in preparatively useful quantities by virtue of an unusually large α value (α = 1.70, 20% *i*-PrOH−hexane) although the enantiomers of the penultimate intermediate **26** were also separable. The assignment of the absolute configuration for **9** was based initially on the relative cytotoxic potencies of natural (−)- and *ent*-(+)-*N*-BOC-CBQ with the former exhibiting more potent activity consistent with observations made with **4**−**7**. Ultimately, this was confirmed in a preliminary examination of the DNA alkylation selectivity of the two enantiomers of the advanced analog **36**, CBQ-TMI.[34] Notably, the sign of rotation for the natural and unnatural enantiomers of *N*-BOC-CBQ as well as that of the advanced analogs CBQ-TMI (**36**) were found to be opposite that observed with **1**−**7** and their advanced analogs.

CBQ-TMI (36), CBI-indole$_2$ (38), CBQ-CDPI$_1$, (40), and CBQ-CDPI$_2$ (42). The CBQ alkylation subunit was incorporated into the CC-1065 and the duocarmycin analogs as detailed in Scheme 5. Acid-catalyzed deprotection of **26** (4 M HCl−EtOAc, 25 °C, 30 min) followed by immediate coupling of the unstable amine hydrochloride salt **28** with 5,6,7-trimethoxyindole-2-carboxylic acid (**31**,[13] 3 equiv of EDCI, DMF, 25 °C, 2 h, 57%), **32** (3 equiv of EDCI, DMF, 25 °C, 6 h, 47%), CDPI$_1$[35] (**33**, 4 equiv of EDCI, DMF, 25 °C, 12 h, 54%), and CDPI$_2$[35] (**34**, 3 equiv of EDCI, DMF, 25 °C, 2 h) provided **35**, **37**, **39**, and **41**, respectively. Notably, the ease of the couplings of **28** with the carboxylic acids **31**−**34** diminished as their solubility decreased (**31**, **32** > **33** > **34**) which necessarily slows the rate of reaction. Presumably, this may be attributed to the limited or marginal stability of **28** under the reaction conditions. Nonetheless, **28** proved to be sufficiently effective in its participation in the amide coupling reactions to provide good yields of the expected products. Subsequent treatment of **35** with NaH (1.1 equiv, THF−DMF 1:2, 25 °C, 30 min, 72%) provided CBQ-TMI (**36**) in excellent conversion. However, satisfactory conversions were observed only when the workup of the spirocyclization reaction was conducted with an aqueous phosphate buffer (pH 7) at low temperature (−10 °C) with a minimal amount of excess NaH employed in the reaction. Under these conditions the rapid solvolysis of **36** as well as its adventious hydrolysis to CBQ (**10**) were minimized. Optically active **35** and **36** were obtained by direct resolution of **35** on a chiralcel OD semipreparative column and the individual enantiomers of **35** converted to *ent*-(+)- and natural (−)-CBQ-TMI (**36**). The assignment of absolute configuration for natural (−)- and *ent*-(+)-CBQ-TMI was based on the relative cytotoxic potency of the two enantiomers with the natural enantiomer being more potent and was confirmed in a preliminary examination of their DNA alkylation selectivities.[34] Notably, the sign of rotation for the natural (−)- and *ent*-(+)-CBQ-TMI was found to be opposite that observed with the natural products as well as CI- or CBI-TMI.

The ability to effect this cyclization, workup, and purification with the less soluble agents **37** and **39** and the insoluble agent **41** proved both challenging and, in the end, unnecessary. The solubility properties of **37**−**42** which requires running the spirocyclization reactions as suspensions in DMF for longer reaction times and conducting the purification with increasingly polar solvents for elution and longer contact times with the chromatography support led to diminished conversions. Since past studies have demonstrated that seco agents such as **35**, **37**, **39**, and **41** exhibit properties indistinguishable from those containing the preformed cyclopropane, our initial examinations of **38**, **40**, and **42** were conducted with their precursors **37**, **39**, and **41**, respectively. Our comparisons of the analogous CBQ and seco-CBQ pairs **26/9**, **29/30**, and **35/36** did not reveal significant distinctions between the agents that would merit continued attempts to isolate and separately characterize **38**, **40**, and **42**.

Chemical Solvolysis: Reactivity. Two fundamental characteristics of the alkylation subunits have proven important in the studies of **4**−**8** to date. The first is the stereoelectronically-controlled acid-catalyzed ring opening of the activated cyclopropane which dictates preferential addition of a nucleophile to the least substituted cyclopropane carbon. The second is the relative rate of acid-catalyzed solvolysis which has been found to accurately reflect the functional reactivity of the agents and to follow a fundamental, direct relationship between solvolysis stability and in vitro cytotoxic potency.[10,14,20]

Ring expansion of the five-membered ring in CBI to the six-membered ring in CBQ was expected to relieve strain associated with the activated cyclopropane. Provided this modification would not perturb the stereoelectronic effects on the acid-catalyzed ring opening, this structural change was anticipated to enhance the solvolytic stability of the agents and, conse-

(34) Natural (−)-CBI-TMI exhibited a DNA alkylation selectivity identical to that of natural (+)-duocarmycin A and SA while *ent*-(+)-CBQ-TMI exhibited a DNA alkylation selectivity identical to that of *ent*-(−)-duocarmcyin SA.

(35) Boger, D. L.; Coleman, R. S.; Invergo, B. J. *J. Org. Chem.* **1987**, *52*, 1521. Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1984**, *49*, 2240.

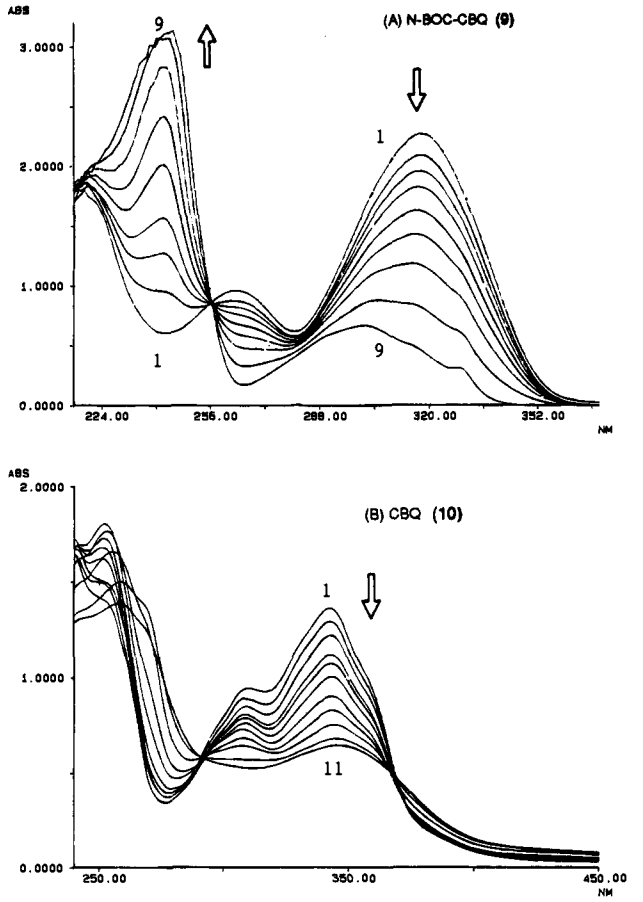


Figure 1. Solvolysis study (UV spectra) of *N*-BOC-CBQ (**9**, top) and CBQ (**10**, bottom) in 50% CH_3OH–aqueous buffer (pH 3.0, 4:1:20 (v/v/v) 0.1 M citric acid, 0.2 M NaH_2PO_4, and H_2O, respectively). The spectra were recorded at regular intervals and only a few are shown for clarity. Top: 1, 0 h; 2, 0.4 h; 3, 0.75 h; 4, 1.1 h; 5, 1.6 h; 6, 2.2 h; 7, 3.1 h; 8, 5.0 h; 9, 69.3 h. Bottom: 1, 0 h; 2, 8 h; 3, 26 h; 4, 52 h; 5, 67 h; 6, 89 h; 7, 126 h; 8, 169 h; 9, 244 h; 10, 388 h; 11, 642 h.

quently, their biological potency. However, it was not clear whether solvolysis would still occur with cleavage of the C9b–C10 bond with addition of a nucleophile to the least substituted C10 cyclopropane carbon or with cleavage of the C9b–C10a bond with ring expansion and addition of a nucleophile to C10a. Notably, the latter cleavage would place the developing positive charge on a preferred secondary versus primary center and, in preceding agents, this preference was overridden by the inherent stereoelectronic control.

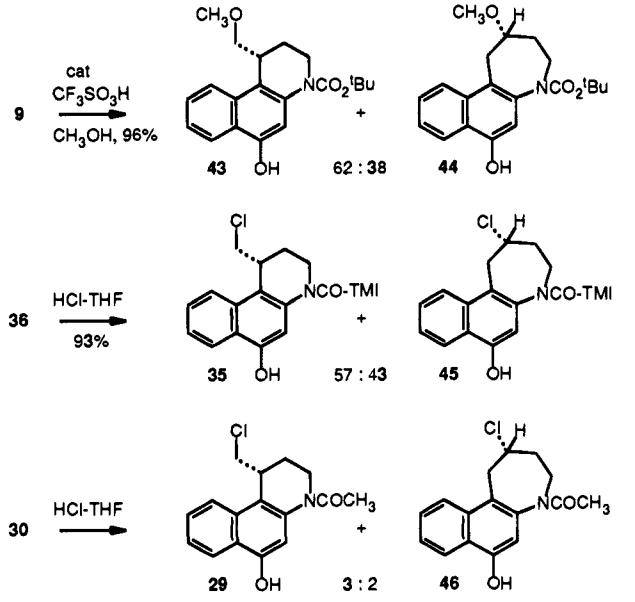
N-BOC-CBQ (**9**, $t_{1/2}$ = 2.1 h, $k = 9.07 \times 10^{-5}$ s^{-1}) proved to be exceptionally reactive toward chemical solvolysis at pH 3 and substantially more reactive than *N*-BOC-CPI (**4**, $t_{1/2}$ = 36.7 h), *N*-BOC-CBI (**7**, $t_{1/2}$ = 133 h), *N*-BOC-DSA (**5**, $t_{1/2}$ = 177 h), and *N*-BOC-DA (**6**, $t_{1/2}$ = 11 h) but substantially more stable than *N*-BOC-CI (**8**, $t_{1/2}$ = 0.01 h), Table 1. Thus, *N*-BOC-CBQ exhibits a half-life 63 times shorter than that of the most closely related agent *N*-BOC-CBI (**7**) at pH 3. Even at pH 7 (1:1 H_2O–CH_3OH) where **4**–**7** show no evidence of solvolysis when monitored for 1–2 weeks, *N*-BOC-CBQ (**9**) slowly underwent solvolysis ($t_{1/2}$ = 544 h, $k = 3.54 \times 10^{-7}$ s^{-1}) but at a rate slower than that of **8** ($t_{1/2}$ = 5.2 h, $k = 3.7 \times 10^{-5}$ s^{-1}). The solvolysis was followed spectrophotometrically by UV with the disappearance of the long-wavelength absorption band of the CBQ chromophore (318 nM) and with the appearance of a short-wavelength absorption band (243 nm) attributable to seco-*N*-BOC-CBQ (Figure 1). Like CPI and CBI, CBQ (**10**, $t_{1/2}$ = 91.2 h, $k = 2.11 \times 10^{-6}$ s^{-1}) proved substantially more stable

Table 1

agent	k (s^{-1}, pH 3)[a]	$t_{1/2}$ (h, pH 3)[a]	IC_{50} (μM, L1210)	UV, λ_{max} nm (ϵ)	IR (C=O, cm^{-1})
5	1.08×10^{-6}	177	0.006	339 (18 000)[b] 301 (14 000) 255 (10 000)	1719, 1610[c]
7	1.45×10^{-6}	133	0.08	300 (19 000)[d] 264 (5 700)	1718, 1628 1602[e]
4	5.26×10^{-6}	37	0.3	344 (12 000)[b] 278 (17 000)	1725, 1570[f]
6	1.75×10^{-5}	11	1	nd	nd
9	9.07×10^{-5}	2.1	2	314 (19 000)[b] 260 (9 000) 218 (17 000)	1705, 1639 1604[c]
8	1.98×10^{-2}	0.01	18	294 (14 000)[d] 258 (21 000)	1705, 1617[c]

[a] pH = 3: 50% CH_3OH–buffer is 4:1:20 (v:v:v) 0.1 M citric acid, 0.2 M Na_2HPO_4, and H_2O, respectively. [b] CH_3OH. [c] KBr. [d] THF. [e] Film. [f] Nujol.

Scheme 6



to solvolysis than *N*-BOC-CBQ (**9**) and is the result of preferential N^3-protonation versus *O*-protonation that is required for solvolysis catalysis. Nearly identical to the trends exhibited by **4**-**9**, CBQ (**10**) proved to be much more reactive than CBI ($t_{1/2}$ = 930 h, $k = 2.07 \times 10^{-7}$ s^{-1})[20] and DSA ($t_{1/2}$ = 2150 h, $k = 8.9 \times 10^{-8}$ s^{-1}).[14]

Chemical Solvolysis: Regioselectivity and Mechanism. Treatment of *N*-BOC-CBQ (**9**) with 0.1 equiv of CF_3SO_3H in CH_3OH (25 °C, 1 h) resulted in the clean solvolysis (96%) to provide a 62:38 (3:2) mixture of **43** and **44** (Scheme 6). No *N*-BOC deprotection or olefin was observed but the methanolysis proceeded with a loss of regioselectivity. Cleavage of the C9b–C10 bond with addition of CH_3OH to the least substituted C10 cyclopropane carbon as well as cleavage of the C9b–C10a bond with ring expansion and addition of CH_3OH to C10a were observed with the former predominating slightly.

Similarly, treatment of CBQ-TMI (**36**) with anhydrous HCl (2 equiv, −78 °C, THF, 2 min) resulted in immediate reaction to provide a 57:43 (3:2) mixture of **35** and **45** with the former predominating slightly (Scheme VI). Nucleophilic addition of chloride to the least substituted cyclopropane carbon of **36** with normal cleavage of the C9b–C10 bond provided seco-CBQ-TMI **35** while **45** is derived from cleavage of the C9b–C10a bond with ring expansion. Similar treatment of *N*-acetyl-CBQ (**30**) with anhydrous HCl under less controlled conditions (20

equiv of HCl, 0.03 M THF, −78 °C, 5 min) provided a 3:2 mixture of **29** and **46** (Scheme 6). Consequently, the acid-catalyzed additions occur with a loss of regioselectivity to provide two products with the normal products **43**, **35**, and **29** predominating slightly. Aside from the identification[3-6] of duocarmycins C_1 and B_1 which have been shown to constitute minor products derived from the reactive duocarmycin A, this represented the first observation of a significant and competitive amount of the ring expansion solvolysis product derived from cleavage of the internal cyclopropane bond.[23] More recently, the detection of minor amounts of the ring expansion product from CPI derivatives has been reported to occur under selected reaction conditions (cat. Cl_3CCO_2H but not HCl).[36]

In an effort which determined the mechanistic course of the reaction, both racemic and optically active (+)-**9** (unnatural configuration) were subjected to acid-catalyzed methanolysis (0.1 equiv of CF_3SO_3H, CH_3OH, 25 °C, 1 h) to provide mixtures of **43** and **44**. Resolution on a Daicel chiralcel OD HPLC column separated both enantiomers of the two reaction products. The product derived from optically active (+)-**9** provided exclusively one enantiomer of each of the products **43** and **44** (Figure 2). Although the generation of one enantiomer of **43** would be consistent with either a S_N1 or S_N2 ring opening reaction, the generation of a single enantiomer of **44** unambiguously illustrates for the first time that the cleavage of the internal cyclopropane bond does not proceed with generation of a free carbocation (S_N1) but rather with clean inversion of the reaction center stereochemistry in a S_N2 ring opening reaction. These unambiguous results are in sharp contrast to the conclusions reached in the recent study[36] of the CPI solvolysis where a free carbocation has been invoked to explain the appearance of the minor ring expansion products.

X-ray Structure of *N*-BOC-CBQ (9): Fundamental Structural Correlations with Solvolysis Reactivity and Regioselectivity. Identification and Structural Origin of an Unappreciated but Productive Functional Stability for the CC-1065 and Duocarmycin Alkylation Subunits. The single-crystal X-ray crystal structure determination of *N*-BOC-CBQ (**9**)[37] was conducted in expectations that it would provide structural insights into the CBQ solvolysis reactivity and regioselectivity. For the CPI subunit taken from the X-ray structure of CC-1065[1] and the X-ray structure of the CBI subunit itself,[20e] the bent orbital[38] of the cyclopropane bond extending to the least substituted carbon is nearly perpendicular to the plane of the cyclohexadienone and consequently overlaps[39] nicely with the developing π-system of the solvolysis product phenol, Figures 3 and 4. This is almost ideally optimized with the CBI nucleus. In contrast, the cyclopropane bond extending to the tertiary carbon is nearly in the plane of the cyclohexadienone and its orbital is nearly orthogonal to the π-system of the product phenol. Thus, opening of the cyclopropane occurs under stereoelectronic control with preferential addition of a nucleophile to the least substituted carbon and the stereoelectronic control overrides the intrinsic electronic preference for ring expansion ring opening.

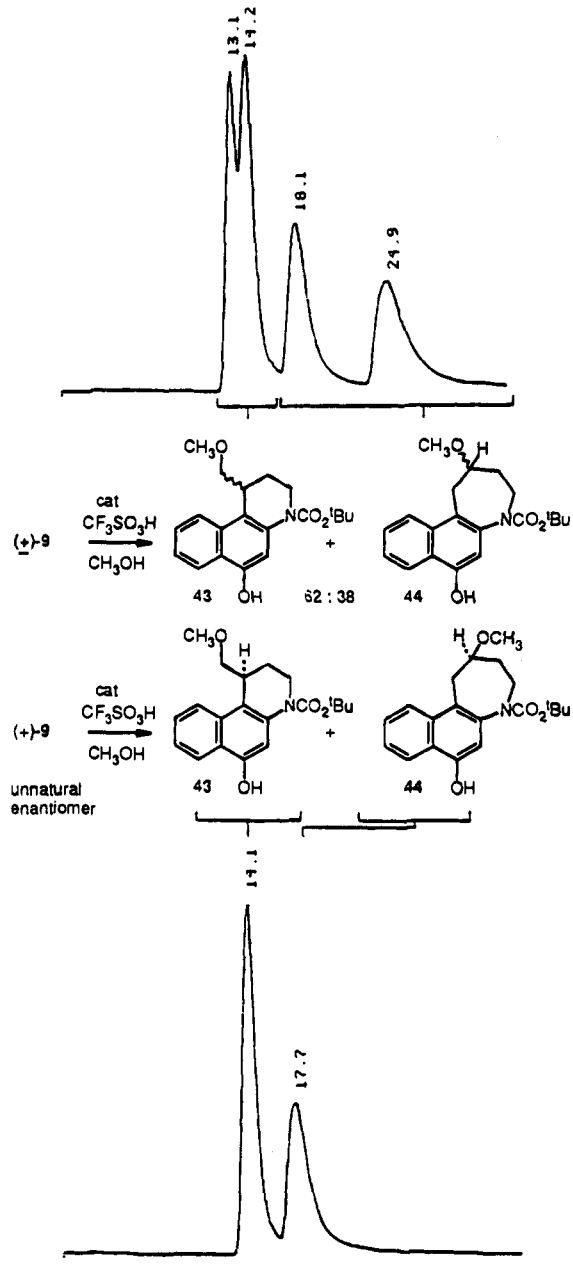


Figure 2. Chiral phase HPLC separation of the products **43** and **44** of acid-catalyzed addition of CH_3OH to racemic **9** (top) and (+)-**9** (bottom). Chiralcel OD HPLC column (10 μm, 0.46 × 25 cm), 1% *i*-PrOH−hexane, 2 mL/min.

In contrast, the *N*-BOC-CBQ X-ray structure exhibits different characteristics. The six-membered ring adopts a boat conformation and the cyclopropane is ideally conjugated[39] with the π-system. The plane defined by the cyclohexadienone of **9** perfectly bisects the cyclopropane and the bonds extending to both the secondary and tertiary cyclopropane carbons are equally aligned with the π-system. This is highlighted in Figure 3 and also in the model projections represented in Figure 4. This idealized conjugation[39] of the cyclopropane with the cyclohexadienone π-system results in equal alignment of both the C9b−C10 and C9b−C10a cyclopropane bonds for cleavage consistent with the observation that both are observed. Moreover, the solvolysis proceeds nearly equally well for cleavage of both the C9b−C10 and the C9b−C10a bonds with the former predominating slightly. Given an inherent preference for charge localization on a secondary versus primary center, one might have anticipated that the cleavage of the C9b−C10a bond would now predominate. However, the C9b−C10 bond is weaker than

(36) Warpehoski, M. A.; Harper, D. E. *J. Am. Chem. Soc.* **1994**, *116*, 7573.

(37) The author has deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates may be obtained upon request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

(38) Walsh, A. D. *Nature (London)* **1947**, *159*, 712. Sugden, T. M. *Nature (London)* **1947**, *160*, 367. Coulson, C. A.; Moffitt, W. E. *J. Chem. Phys.* **1947**, *15*, 151. Coulson, C. A.; Moffitt, W. E. *Philos. Mag.* **1949**, *40*, 1.

(39) Hoffmann, R.; Davidson, R. B. *J. Am. Chem. Soc.* **1971**, *93*, 5699. Clark, T.; Spitznagel, G. W.; Klose, R.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1984**, *106*, 4412.

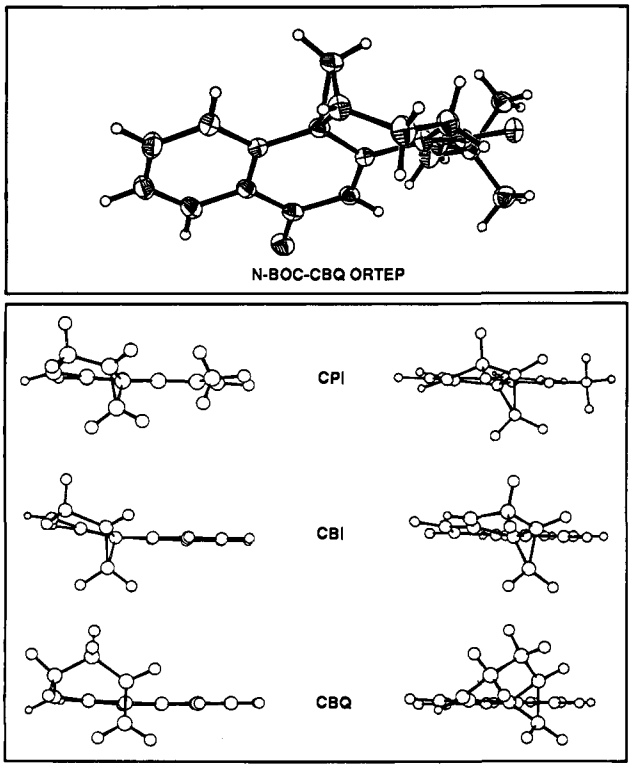


Figure 3. Top: ORTEP of the X-ray crystal structure of *N*-BOC-CBQ (**9**). Bottom: End on (left) and 30−45° rotation views (right) of the X-ray crystal structures of CPI (taken from CC-1065[1]), CBI,[20e] and *N*-BOC-CBQ. The end on view (left) highlights the perfect geometrical alignment and overlap of the CBQ cyclopropane versus the nonideal alignment of the CPI/CBI cyclopropane with the cyclohexadienone π-system. The 30−45° rotation views (right) illustrated the ideal bisection of the CBQ-activated cyclopropane by the plane of cyclohexadienone π-system (ideal overlap) versus the CPI/CBI unsymmetrical overlap with leads to stereoelectronic control of the solvolysis/alkylation.

the C9b−C10a bond judging from the X-ray bond lengths (1.543 versus 1.528 Å) suggesting that any inherent electronic preference for cleavage of the C9b−C10a bond is balanced or offset by this lower bond strength of the C9b−C10 bond. Importantly, the slightly predominant cleavage corresponds to that of the weakest (longer) bond. In addition, nucleophilic attack at the sterically more hindered tertiary C10a center must overcome the torsional strain encountered by an incoming nucleophile which must eclipse the equatorial H located on the adjacent C1 carbon while attack at the secondary C10 center is free of such developing torsional strain. Given the observation that ring opening occurs with clean inversion of stereochemistry without intervention of a free carbocation, this developing torsional strain accompanying ring expansion may be especially significant. These combined features result in a slight preference (1:1 to 3:2) for cleavage of the C9b−C10 bond. Thus, the geometrical constraints of the fused five-membered ring found in the CPI, CBI, and DSA alkylation subunits impose the stereoelectronic control dictating preferential nucleophilic attack on the least substituted carbon. With the fused six-membered ring found in CBQ, both of the available cyclopropane bonds are equally aligned for cleavage and cleavage of both are experimentally observed to occur at near competitive rates.

More surprising than the mixed solvolysis regioselectivity of *N*-BOC-CBQ was the observation of its unusually rapid solvolysis and important insights into the origin of this enhanced reactivity are found in the X-ray structures. The CBQ bond lengths of both the C9b−C10a (1.528 Å) and C9b−C10 (1.543

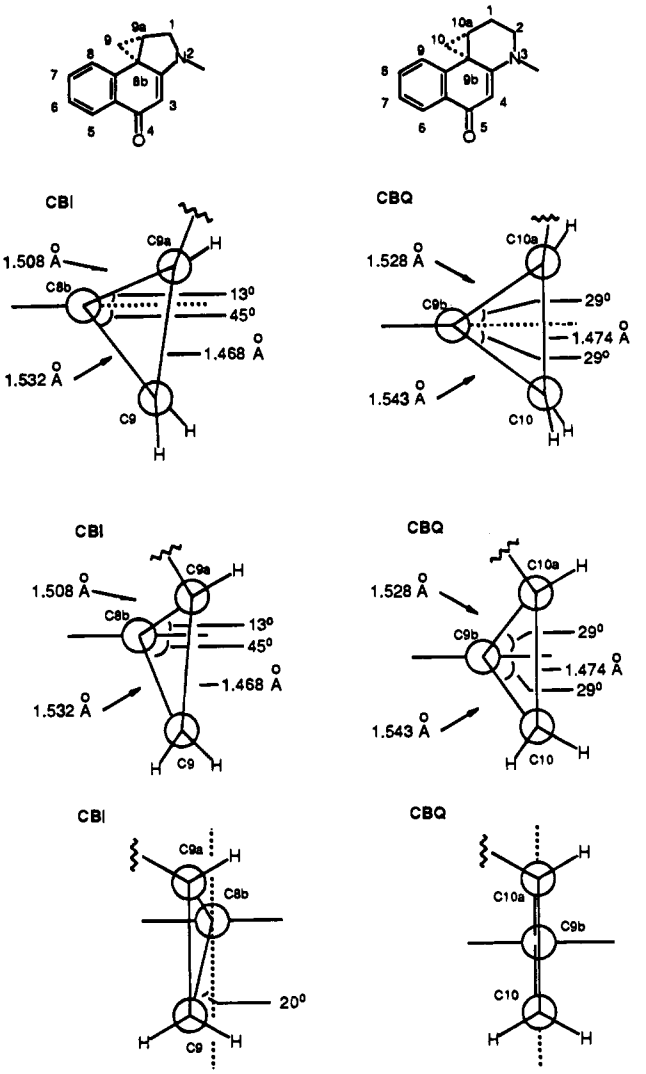


Figure 4. Stick models of the side view, 45° rotation view, and 90° rotation view of the activated cyclopropane of CBI and CBQ illustrating data taken from the X-ray crystal structures and highlighting the idealized overlap and alignment of the CBQ cyclopropane with the cyclohexadienone π-system.

Å) bonds are longer than those in CBI (1.508 and 1.532 Å, respectively) and nicely reflect the enhanced reactivity.[39−41] This lengthening of the cyclopropane bonds occurs despite the decrease in strain that accompanies fusion to a six versus five membered ring and may be attributed to the idealized conjugation[39] or π-delocalization of both the C9b−C10a and C9b−C10 cyclopropane bonds with the cyclohexadienone π-system. Experimental evidence illustrating this increased conjugation was found in the UV spectra of **9** and **7**. The long-wavelength UV absorption bands of **9** and **7** are found at 314 and 300 nm, respectively, with **9** exhibiting the greater degree of conjugation. Similarly, the CBQ (**10**) and CBI long-wavelength UV absorption bands are found at 326 and 316 nm, respectively, reflecting the greater degree of conjugation for **10**. Contributing to this enhanced conjugation is the perfect geometrical alignment of C10 and C10a with C9b, C5, and the carbonyl oxygen. For CPI and CBI, the constraints of the fused five-membered ring place C9 and C9a at a 20° (CBI) to 25° (CPI) angle offset from this plane and prevent ideal alignment and overlap of either the C8b−C9a or C8b−C9 bond with the cyclohexadienone

(40) Baird, R.; Winstein, S. *J. Am. Chem. Soc.* **1963**, *85*, 567.
(41) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66. de Meijer, A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 809.

π-system. This idealized CBQ cyclopropane conjugation with the cyclohexadienone π-system results in the observed longer bond lengths,[39] weaker bond strengths, and greater reactivity.[40,41]

Thus, the geometrical constraints of the fused five-membered ring found in the alkylation subunits of CC-1065 and the duocarmycins impose the stereoelectronic control on the nucleophilic cleavage of the cyclopropane dictating preferential addition to the least substituted carbon. In addition, the nonideal conjugation and alignment of the cyclopropane with the cyclohexadienone π-system found in CPI, CBI, or DSA results in productively diminished electrophilic reactivity. Contrary to initial expectations, the introduction of the CBQ fused six- versus five-membered ring did not diminish the reactivity of the agent through release of strain, but rather increased its reactivity. This may be attributed to the ideal conjugation and alignment of the cyclopropane with the cyclohexadienone π-system which also results in a loss of stereoelectronic control for its cleavage. Thus, the fundamental insight to be derived from these comparisons is not the rapid solvolysis of the CBQ agents, but rather the surprising stability of the CBI, CPI, and DSA alkylation subunits. In spite of the structural features that intuitively suggest a high reactivity, the latter agents have proven to be uncharacteristically stable. This unusual stability is imposed by fusion of the activated cyclopropane to the five-membered ring which constrains it to a nonideal conjugation and alignment with the cyclohexadienone π-system.

Structure versus Reactivity: Additional Features. This is not to say that there are not additional structural features of **4**−**9** that contribute to their stability. The enhanced stability of **4**, **5**, and **7** > **6** > **8** can be attributed to the diminished gain in delocalization energy that accompanies aromatization in a system that bears a fused aromatic ring. The increased relative stability of **5** > **4** and **6** > **8** can be attributed to the conjugated electron-withdrawing group which diminishes C4 carbonyl protonation required of solvolysis and alkylation. The increased relative stability of **7** > **4** can be attributed in part to the release of strain that accompanies the substitution of a fused six-membered for a fused five-membered aromatic ring.[20] Finally, and certainly important, the vinylogous amide stabilization of the cyclohexadienone structure which is lost upon aromatization contributes significantly to the stability of **4**−**9**.[22b]

In Vitro Cytotoxic Activity. Despite the differences in the CBQ solvolysis regioselectivity, the in vitro cytotoxic activity of the agents proved to be surprisingly consistent with past observations that have illustrated a direct correlation between solvolysis stability and cytotoxic potency.[10,14,20] Consistent with their relative reactivity, the CBQ-based agents exhibited cytotoxic activity that was less potent than the corresponding duocarmycin A based agents but more potent than the corresponding CI-based agents, Table 2.

Moreover, the agents were found to follow the previously established relationships between solvolysis stability (−log k, pH 3) and cytotoxic potency (1/log IC_{50}, L1210) where the chemically more stable agents within a given class exhibit the greatest potency (Figure 5). A second-order polynominal plot indicative of a parabolic relationship provided an excellent correlation between the solvolytic stability of the agents and their in vitro cytotoxic activity and would be consistent with the expectation that the agents should exhibit an optimum balance of reactivity−stability/activity but that this has not yet been achieved within the series of agents examined to date. Alternative linear plots suggest that either the potencies for the CI-based agents have been overestimated in the cell culture assays or that the potencies of the CBQ-based agents are lower than would have been predicted by a linear relationship. Both

Table 2. In Vitro Cytotoxic Activity[a]

agent	configuration	IC_{50} (L1210)
9 (±)-*N*-BOC-CBQ	racemic	3 μM
9, (−)-*N*-BOC-CBQ	natural	2 μM
9, (+)-*N*-BOC-CBQ	unnatural	11 μM
26	racemic	3 μM
10, (±)-CBQ	racemic	>50 μM
29	racemic	2 μM
30, (±)-*N*-acetyl-CBQ	racemic	2 μM
35	racemic	4000 pM
35	natural	4000 pM
35	unnatural	35000 pM
36, (±)CBQ-TMI	racemic	4000 pM
36, (−)-CBQ-TMI	natural	4000 pM
36, (+)-CBQ-TMI	unnatural	35000 pM
37	racemic	4000 pM
39	racemic	2000 pM
41	racemic	3000 pM

[a] The in vitro cytotoxic assays were conducted as detailed in ref 20.

are reasonable possibilities with the former being the result of the difficulties in accurately assessing the activity of the exceptionally reactive CI-based agents while the latter would be the result of the lost and altered solvolysis regioselectivity of the CBQ-based agents which might further lower their inherent cytotoxic potency. If either the data for the reactive CI-based or CBQ-based agents are not included, the linear relationships become more accurate. What is unmistakable from these comparisons is the accurate qualitative trend of the chemically more stable agents providing the greater in vitro cytotoxic activities and higher DNA alkylation efficiencies. Whether this relationship is best represented as a well-defined second-order polynomial and parabolic relationship with inclusion of all classes of agents studied to date (Figure 5) or as a well-defined linear relationship with either the CI- or CBQ-based agents presenting an easily rationalized quantitative deviation from the linear relationship will become clearer in the comparative examination of future agents. What is clear is that the qualitative trends are accurate for *all* five classes of agents presently available for examination.

Presumably, this may be attributed to the more effective delivery of the more stable agents to their intracellular target. In this respect, the relative solvolysis rates of the agents represent an accurate measure of their relative functional reactivity. The nonproductive competitive consumption of the agents in route to their biological target need not be simply solvolysis but competitive alkylation of alternative sites as well including nonproductive sites within DNA. Since the chemically more stable agents also provide the most easily reversed alkylation reactions, the observations may also represent the more effective partitioning of the agents to their intracellular target.

In the two instances examined, the natural CBQ enantiomer generally was found to be more potent than the unnatural enantiomer. Similar to past observations with the more sterically hindered agents possessing steric bulk surrounding the CBQ C9 or CBI C8 center, both the natural enantiomer of **9** (5−10×) and the natural enantiomers of **35/36** (10−100×) exhibited the more potent cytotoxic activities. These and related properties of the agents are under further investigation including a detailed examination of the DNA alkylation properties[34] of the CBQ-based agents and the results of such studies will be disclosed in due course.

Experimental Section

2-[*N*-Allyl-*N*-(*tert*-butyloxycarbonyl)amino]-4-(benzyloxy)-1-bromonaphthalene (19). The carbamate **18**[20j] (403 mg, 0.94 mmol) was added at 0 °C to a suspension of NaH (60% in oil, 45 mg, 1.13 mmol,

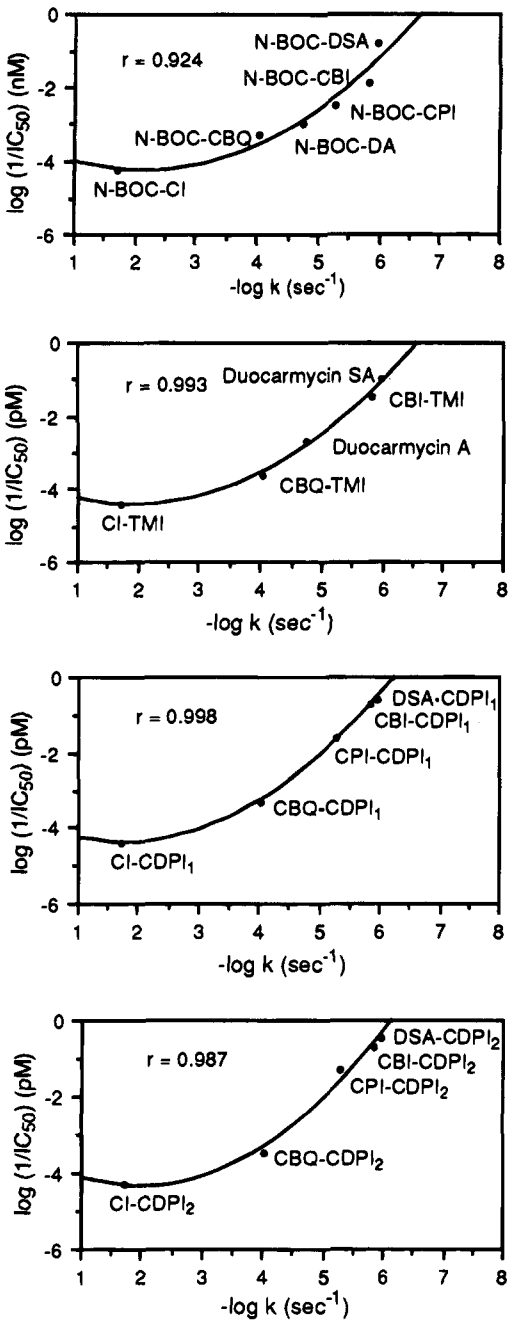


Figure 5.

1.2 equiv) in THF (20 mL). The resulting mixture was stirred for 15 min at 25 °C and recooled at 0 °C. DMF (2 mL) and allyl bromide (120 μL, 1.41 mmol, 1.5 equiv) were added and the mixture was stirred for 10 min at 0 °C and at 25 °C until completion (4 h). Saturated aqueous NH_4Cl (100 mL) was added and the mixture was extracted with EtOAc (2 x 50 mL). The combined organic layer was dried (Na_2SO_4) and the solvent evaporated under vacuum. Chromatography (SiO_2, 2.5 × 15 cm, 10% EtOAc–hexane) afforded **19** (435 mg, 441 mg theoretical, 98%) as a white solid: mp 89.5–90 °C (hexane, prisms); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, 1H, J = 8.1 Hz, C5–H), 8.27 (d, 1H, J = 8.5 Hz, C8-H), 7.6–7.3 (m, 7H, C6-H, C7-H, and $CH_2C_6H_5$), 6.78 and 6.67 (two s, 1H, C3-H), 5.90 (m, 1H, C*H*=CH_2), 5.30–5.13 (m, 2H, C*H*$_2$C$_6$H$_5$), 5.11–5.03 (m, 2H, CH=C*H*$_2$), 4.59–4.48 (m, 1H, NC*H*H), 4.02–3.87 (m, 1H, NCH*H*), 1.37 (s, 9H, OC-$(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2 and 153.9 (CO), 138.8, 136.5, 134.0, 133.7, 132.8, 128.7, 128.2, 127.6, 127.3, 126.2, 125.8, 122.5, 117.9, 117.4, 114.7, 108.1 and 107.8 (C3), 80.4, 70.4, 53.3 and 50.0 (NCH_2), 28.5 and 28.3 (C(*C*H$_3$)$_3$); IR (KBr) ν_{max} 3068, 2976, 2912, 1700, 1687, 1620, 1594, 1569, 1507, 1500, 1448, 1388, 1382, 1328, 1253, 1240, 1162, 1143 cm^{-1}; FABHRMS (NBA) *m/e* 468.1189 (M + H$^+$, $C_{25}H_{26}BrNO_3$ requires 468.1174).

Anal. Calcd for $C_{25}H_{26}BrNO_3$: C, 64.11; H, 5.60; N, 2.99. Found: C, 63.91; H, 5.66; N, 3.05.

2-[*N*-(*tert*-Butyloxycarbonyl)-*N*-(3-hydroxyprop-1-yl)amino]-4-(benzyloxy)-1-bromonaphthalene (20). A solution of **19** (1.55 g, 3.3 mmol) in THF (5 mL) under Ar was treated with 9.90 mL of a 9-BBN solution in THF (0.5 M, 4.95 mmol, 1.5 equiv) and the mixture was stirred for 16 h at 25 °C. The resulting mixture was diluted with THF (100 mL), H_2O (3 mL, 50 equiv) was added slowly at 0 °C, and the mixture was allowed to warm to 25 °C over 30 min. 3 N Aqueous NaOH (2.5 mL, 7.5 mmol, 2.3 equiv) and 50% aqueous H_2O_2 (1.34 g, 19.7 mmol, 6 equiv) were added at 0 °C and the resulting mixture was stirred at 25 °C (1 h) and at 60 °C (1 h). The cooled reaction mixture was extracted with EtOAc (2 × 50 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed under vacuum. Chromatography (SiO_2, 3 × 15 cm, 30–50% EtOAc–hexane gradient elution) afforded **20** (1.29 g, 1.60 g theoretical, 80%) as a white solid: mp 109–111 °C (EtOAc–hexane, prisms); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, 1H, J = 8.3 Hz, C5-H), 8.28 (d, 1H, J = 8.4 Hz, C8-H), 7.63 (m, 1H, C7-H), 7.55 (m, 1H, C6-H), 7.50–7.32 (m, 5H, $CH_2C_6H_5$), 6.61 (s, 1H, C3-H), 5.29 (d, 1H, J = 12.1 Hz, C*H*HC$_6$H$_5$), 5.23 (d, 1H, J = 12.1 Hz, CH*H*C$_6$H$_5$), 3.91 (m, 1H, NC*H*H), 3.79 (m, 1H, C*H*HOH), 3.67 (m, 1H, CH*H*OH), 3.57 (td, 1H, J = 5.6, 14.7 Hz, NCH*H*), 3.49 (s, 1H, OH), 1.71–1.49 (m, 2H, NCH_2CH_2), 1.30 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 154.1, 138.6, 136.3, 132.6, 128.7, 128.24, 128.16, 127.5, 127.1, 126.2, 125.8, 122.4, 114.3, 107.4, 80.8, 70.4, 59.0, 45.7, 30.9, 28.4 and 28.1 (C(*C*H$_3$)$_3$); IR (KBr) ν_{max} 3477, 3070, 2950, 1686, 1664, 1619, 1594, 1568, 1540, 1504, 1335, 1155, 1145, 1092 cm^{-1}; FABHRMS (NBA-CsI) *m/e* 618.0266 (M + Cs$^+$, $C_{25}H_{28}BrNO_4$ requires 618.0256).

Anal. Calcd for $C_{25}H_{28}BrNO_4$: C, 61.73; H, 5.80; N, 2.89. Found: C, 61.88; H, 5.89; N, 2.96.

2-[*N*-*tert*-Butyloxycarbonyl)-*N*-(3-oxo-1-propyl)amino]-4-(benyloxy)-1-bromonaphthalene (21). A solution of DMSO (0.79 mL, 11.2 mmol, 2.4 equiv) in CH_2Cl_2 (5 mL) was added dropwise to a solution of $(COCl)_2$ (0.48 mL, 5.5 mmol, 1.2 equiv) in CH_2Cl_2 (25 mL) at −60 °C. The reaction mixture was stirred for 2 min and the alcohol **20** (2.25 g, 4.62 mmol) in CH_2Cl_2 (10 mL) was added within 5 min. The mixture was stirred for an additional 15 min before Et_3N (3.25 mL, 23.3 mmol, 5.0 equiv) was added. After 5 min, the reaction mixture was allowed to warm at 25 °C. Water (100 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under vacuum. Chromatography (SiO_2, 5 × 15 cm, 25% EtOAc–hexane) afforded **21** (2.03 g, 2.24 g theoretical, 90%) as a white solid: mp 81–82 °C (EtOAc–hexane, prisms); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, 1H, J = 1.8 Hz, CHO), 8.37 (d, 1H, J = 8.3 Hz, C5-H), 8.28 (d, 1H, J = 8.4 Hz, C8-H), 8.65 (m, 1H, C7-H), 7.58–7.35 (m, 6H, C6-H and $CH_2C_6H_5$), 6.77 and 6.70 (two s, 1H, C3-H), 5.28 (s, 2H, C*H*$_2$C$_6$H$_5$), 4.15 (m, 1H, NC*H*H), 3.85 (m, 1H, NCH*H*), 2.80–2.62 (m, 2H, C*H*$_2$CHO), 1.57 and 1.56 (two s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9 and 200.5 (CHO), 154.6 and 154.1 (CO_2), 138.3, 136.2, 132.7, 128.6, 128.2, 128.1, 127.4, 127.3, 126.3, 126.0 and 125.8, 122.4, 114.4, 107.5, 81.3 and 80.6 (*C*(CH$_3$)$_3$), 70.3, 44.0, 43.2, 42.8, 28.4 and 28.1 (C(*C*H$_3$)$_3$); IR (KBr) ν_{max} 2980, 2722, 1722, 1694, 1619, 1594, 1506, 1388, 1337, 1157, 1143, 1097 cm^{-1}; FABHRMS (NBA–CsI) *m/e* 616.0104 (M + Cs$^+$, $C_{25}H_{26}BrNO_4$ requires 616.0099).

Anal. Calcd for $C_{25}H_{26}BrNO_4$: C, 61.99; H, 5.41; N, 2.89. Found: C, 62.08; H, 5.71; N, 2.96.

2-[*N*-(*tert*-Butyloxycarbonyl)-*N*-[4-(tetrahydropyranyloxy)-3-buten-1-yl]amino]-4-(benzyloxy)-1-bromonaphthalene (22). A suspension of triphenyl[(2-tetrahydropyranyloxy)methyl]phosphonium chloride[29] (8.85 g, 21.4 mmol, 3.0 equiv) in 70 mL of THF at −78 °C was treated dropwise with a solution of *n*-BuLi (9 mL, 2.3 M in hexane, 20.7 mmol, 2.9 equiv). The reaction mixture was stirred for 5 min at −78 °C, the cooling bath was removed and the mixture was stirred and allowed to warm until it reached 0 °C. The mixture was recooled to −78 °C, and HMPA (30 mL, 24 equiv) and **21** (3.46 g, 7.14 mmol) in THF (35 mL) were added sequentially. The reaction mixture was stirred for 1.5 h at −78 °C and 24 h at 25 °C before it was quenched by the

addition of 500 mL of phosphate buffer (pH = 7). The mixture was extracted with EtOAc (3 × 200 mL), and the combined organic phase was dried (Na_2SO_4) and concentrated in vacuo. Chromatography (SiO_2, 5 × 20 cm, 15% EtOAc−hexane containing 1% Et_3N) afforded **22** (3.58 g, 4.16 g theoretical, 86%) as a colorless oil as a mixture of *E*- and *Z*-olefin isomers (60:40). ^1H NMR (400 MHz, $CDCl_3$) *E*- and *Z*-olefin isomers, amide rotamers δ 8.36−8.27 (m, 2H, C5-H and C8-H), 7.64−7.34 (m, 7H, C6-H, C7-H and $CH_2C_6H_5$), 6.91−6.74 (m, C3-H), 6.29−6.24 and 6.18−6.15 (two m, 1H, CH=C*H*O), 5.28−5.15 (m, 2H, $CH_2C_6H_5$), 5.05−4.95 and 4.49−4.43 (two m, 1H, C*H*=CHO), 4.88−4.80 (m, OCHO), 4.00−3.32 (m, 4H, NCH_2 and OCH_2), 2.50−2.14 (m, 2H, CH_2CH=CH), 1.86−1.30 (m, 15H); IR (CCl_4) ν_{max} 2944, 1705, 1674, 1620, 1593, 1568, 1503, 1343, 1160 cm^{-1}; FABHRMS (NBA-CsI) *m/e* 714.0839 (M + Cs^+, $C_{31}H_{36}BrNO_5$ requires 714.0831).

Anal. Calcd for $C_{31}H_{36}BrNO_5$: C, 63.92; H, 6.23; N, 2.40. Found: C, 64.17; H, 6.17; N, 2.49.

6-(Benzyloxy)-4-(*tert*-butyloxycarbonyl)-1-[(tetrahydropyranyloxy)methyl]-1,2,3,4-tetrahydrobenzo[*f*]quinoline (23). A solution of **22** (4.69 g, 8.05 mmol), AIBN (264 mg, 1.6 mmol, 0.2 equiv), and Bu_3SnH (4.33 mL, 16.1 mmol, 2.0 equiv), in benzene (280 mL) was warmed at reflux for 12 h. The reaction mixture was cooled and the solvent removed under vacuum. Chromatography (SiO_2, 5 × 30 cm, 10−50% EtOAc−hexane gradient elution) afforded **23** (3.30 g, 4.05 g theoretical, 81%) as a mixture of two diastereomers as an oil: ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, 1H, *J* = 8.3 Hz, C7−H), 8.02 and 7.98 (two d, 1H, *J* = 8.5 Hz, C10-H), 7.54−7.48 (m, 3H, C9-H and meta C_6H_5), 7.44−7.30 (m, 5H, C5-H, C8-H, ortho and para C_6H_5), 5.21 (s, 2H, $CH_2C_6H_5$), 4.63 and 4.55 (m and dd, 1H, *J* = 4.5, 2.9 Hz, OCHO), 4.03−3.38 (m, 7H, C1-H, C3-H, CH_2OTHP, OCH_2CH_2), 2.42−2.32 (m, 1H, C2-H), 2.00−1.95 (m, 1H, C2-H), 1.87−1.78 (m, 1H, $OCH_2CHHCH_2CH_2$), 1.75−1.70 (m, 1H, $OCH_2CHHCH_2CH_2$), 1.61−1.53 (m, 13H, $C(CH_3)_3$, $OCH_2CH_2CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 152.64 and 152.60, 137.1 and 137.0, 132.34 and 132.30, 128.6, 127.9, 127.5, 126.9 and 126.8, 123.90 and 123.87, 123.45 and 123.42, 122.9, 122.7, 122.6 and 122.5, 116.5 and 116.4, 104.1 (C5), 100.1 and 98.2 (OCHO), 80.9, 70.1, 70.4 and 68.9, 62.6 and 62.2 (CH_2OTHP), 41.9 and 41.8 (CH_2N), 33.0 and 32.3 (C1), 30.7, 25.9, 25.8, 25.4, 19.7 and 19.5, IR (CCl_4) ν_{max} 2958, 1741, 1702, 1623, 1597, 1168, 1163 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 636.1730 (M + Cs^+, $C_{31}H_{37}NO_5$ requires 636.1726).

Anal. Calcd for $C_{31}H_{37}NO_5$: C, 73.93; H, 7.41; N, 2.78. Found: C, 73.68; H, 7.47; N, 2.85.

6-(Benzyloxy)-4-(*tert*-butyloxycarbonyl)-1-(hydroxymethyl)-1,2,3,4-tetrahydrobenzo[*f*]quinoline (24). A solution of **23** (221 mg, 0.44 mmol) in CH_3OH (10 mL) was warmed with Amberlyst-15 (20 mg) at 50 °C for 2 h. The resin was removed by filtration and the mixture was concentrated under vacuum. Chromatography (SiO_2, 1.5 × 15 cm, 40% EtOAc−hexane) afforded **24** (175 mg, 184 mg theoretical, 95%) as a low melting white solid: mp 50−54 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, 1H, *J* = 0.8, 8.3 Hz, C7-H), 7.95 (d, 1H, *J* = 8.6 Hz, C10−H), 7.54−7.49 (m, 3H, C9-H and meta C_6H_5), 7.44−7.33 (m, 4H, C8-H, ortho and para C_6H_5), 7.27 (s, 1H, C5-H), 5.21 (s, 2H, $CH_2C_6H_5$), 3.96−3.83 (m, 2H, C*H*HOH, C3-H), 3.75 (m, 1H, C1-H), 3.69 (dd, 1H, *J* = 8.0, 10.2 Hz, CH*H*OH), 3.60 (dt, 1H, *J* = 12.9, 5.8 Hz, C3-H), 2.39−2.32 (m, 1H, C2-H), 2.16−2.02 (m, 1H, C2-H), 1.52 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0 (CO_2), 152.8, 137.6, 137.0, 132.3, 128.6, 128.0, 127.5, 127.0, 124.1, 123.6, 122.7, 122.6, 116.5, 104.3 (C5), 81.0, 70.1, 65.2, 42.3 (C3), 34.6 (C1), 28.5 ($C(CH_3)_3$), 26.0 (C2); IR (CCl_4) ν_{max} 3635, 3481, 2977, 2932, 1701, 1623, 1596, 1367, 1324, 1248, 1159 cm^{-1}; FABHRMS (NBA-CsI) *m/e* 552.1161 (M + Cs^+, $C_{26}H_{29}NO_4$ requires 552.1151).

Anal. Calcd for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34. Found: C, 74.64; H, 7.08; N, 3.30.

6-(Benzyloxy)-4-(*tert*-butyloxycarbonyl)-1-(chloromethyl)-1,2,3,4-tetrahydrobenzo[*f*]quinoline (25). A solution of **24** (100 mg, 0.238 mmol) and Ph_3P (187 mg, 0.714 mmol, 3.0 equiv) in CH_2Cl_2 (0.8 mL) under Ar was treated with CCl_4 (230 μL, 2.38 mmol, 10.0 equiv). The mixture was protected from light and stirred for 8 h at 25 °C. Chromatography (SiO_2, 2 × 25 cm, 0−15% EtOAc−hexane gradient elution) afforded **25** (100 mg, 104 mg theoretical, 96%) as a pale yellow solid: mp 111−112 °C (hexane, plates); ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, 1H, *J* = 8.3 Hz, C7-H), 7.87 (d, 1H, *J* = 8.5 Hz, C10-H), 7.56−7.52 (m, 3H, C9-H and meta C_6H_5), 7.44−7.34 (m, 5H, C10-H, C8-H, ortho and para C_6H_5), 5.21 (s, 2H, $CH_2C_6H_5$), 3.87−3.72 (m, 4H, C1-H, C3-H_2, C*H*HCl), 3.47 (m, 1H, CH*H*Cl), 2.45 (m, 1H, C2-H), 2.06 (m, 1H, C2-H), 1.54 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8 (CO_2), 153.2, 137.2, 136.9, 131.9, 128.6, 128.0, 127.6, 127.4, 124.1, 123.5, 122.9, 122.0, 115.5, 103.8 (C5), 81.3, 70.2, 46.9 (CH_2Cl), 41.6 (C3), 35.0 (C1), 28.5 ($C(CH_3)_3$), 25.7 (C2); IR (CCl_4) ν_{max} 2978, 2933, 1704, 1623, 1596, 1409, 1368, 1320, 1245, 1156 cm^{-1}; FABHRMS (NBA−NaI) *m/e* 437.1758 (M^+, $C_{26}H_{28}ClNO_3$ requires 437.1758).

Anal. Calcd for $C_{26}H_{28}ClNO_3$: C, 71.30; H, 6.44; N, 3.20. Found: C, 71.53; H, 6.18; N, 3.40.

4-(*tert*-Butyloxycarbonyl)-1-(chloromethyl)-6-hydroxy-1,2,3,4-tetrahydrobenzo[*f*]quinoline (26). From 25: A solution of **25** (88.4 mg, 0.202 mmol) and 10% Pd/C (30 mg) in THF (5 mL) was stirred under 1 atm of H_2 for 2 h at 25 °C. The mixture was filtered through Celite and concentrated under vacuum. Chromatography (SiO_2, 1 × 15 cm, 25% EtOAc−hexane) afforded **26** (68.9 mg, 70.3 mg theoretical, 98%) as a white foam: ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, 1H, *J* = 8.3 Hz, C7-H), 7.86 (d, 1H, *J* = 8.5 Hz, C10-H), 7.53 (m, 1H, C9-H), 7.42−7.39 (m, 2H, C5-H and C8-H), 5.52 (br s, OH), 3.91−3.78 (m, 3H, C1-H, C3-H and C*H*HCl), 3.69 (ddd, 1H, *J* = 13.1, 11.2, 4.6 Hz, C3-H), 3.47 (m, 1H, CH*H*Cl), 2.45 (m, 1H, C2-H), 2.02 (m, 1H, C2-H), 1.56 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1 (CO_2), 150.8, 136.6, 132.1, 127.3, 123.9, 122.7, 122.3, 122.0, 115.1, 106.0 (C-5), 81.6, 46.5 (CH_2Cl), 41.4 (C3), 34.9 (C1), 28.4 ($C(CH_3)_3$), 25.3 (C2); IR (film) ν_{max} 3340, 2976, 1670, 1624, 1596, 1406, 1369, 1347, 1248, 1153 cm^{-1}; FABHRMS (NBA) *m/e* 347.1278 (M^+, $C_{19}H_{22}ClNO_3$ requires 347.1288).

Anal. Calcd for $C_{19}H_{22}ClNO_3$: C, 65.61; H, 6.37; N, 4.03. Found: C, 65.38; H, 6.76; N, 3.92.

From 27: A solution of **27** (20 mg, 60.7 μmol) and Ph_3P (48 mg, 183 μmol, 3.0 equiv) in CH_2Cl_2 (0.3 mL) under Ar was treated with CCl_4 (50 μL, 517 μmol, 6.5 equiv). The mixture was protected from light and stirred for 7 h at 25 °C. Chromatography (SiO_2, 1 × 15 cm, 25% EtOAc−hexane) afforded **26** (20.3 mg, 21.1 mg theoretical, 96%).

4-(*tert*-Butyloxycarbonyl)-6-hydroxy-1-(hydroxymethyl)-1,2,3,4-tetrahydrobenzo[*f*]quinoline (27). Compound **24** (59 mg, 0.14 mmol) was added to a suspension of 10% Pd/C (20 mg) in THF (4 mL) carefully degassed and saturated with Ar. A solution of 25% aqueous HCO_2NH_4 (1 mL) was added and the mixture was stirred for 7 h at 25 °C. EtOAc (20 mL) was added, the organic layer was dried (Na_2SO_4), filtered through Celite, and concentrated in vacuo. Chromatography (SiO_2, 1.2 × 15 cm, 40% EtOAc−hexane) afforded **27** (43 mg, 46 mg theoretical, 93%) as a white foam: ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, 1H, *J* = 8.6 Hz, C7-H), 7.75 (d, 1H, *J* = 8.1 Hz, C10-H), 7.68 (br s, 1H, ArOH), 7.34 (m, 1H, C9-H), 7.17−7.14 (m, 2H, C5 and C8-H), 3.94 (ddd, 1H, *J* = 12.8, 8.3, 5.6 Hz, C3-H), 3.88−3.72 (m, 3H, C1-H and CH_2OH), 3.53 (ddd, 1H, *J* = 12.8, 7.0, 5.8 Hz, C3-H), 2.38 (m, 1H, C2-H), 2.22 (br s, 1H, OH), 2.07 (m, 1H, C2-H), 1.55 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1 (CO_2), 150.6, 137.5, 132.3, 126.6, 123.7, 122.7, 122.4, 122.2, 116.3, 106.7, 81.5, 65.3 (CH_2OH), 43.0 (C3), 34.3 (C1), 28.4 ($C(CH_3)_3$), 26.2 (C2); IR (film) ν_{max} 3346, 2934, 1668, 1624, 1596, 1406, 1368, 1345, 1253, 1159 cm^{-1}; FABHRMS (NBA) *m/e* 329.1619 (M^+, $C_{19}H_{23}NO_4$ requires 329.1627).

***N*³-(*tert*-Butyloxycarbonyl)-2,3,10,10a-tetrahydro-1*H*-cyclopropa[*d*]benzo[*f*]quinol-5-one (9, *N*-BOC-CBQ). From 26:** A solution of **26** (9 mg, 0.025 mmol) in DMF (200 μL) was added to a suspension of NaH (60% in mineral oil, 1.2 mg, 1.16 equiv) in THF (100 μL) at 25 °C and the mixture was stirred for 30 min. A solution of pH 7 phosphate buffer (2 mL) was added. The mixture was extracted with EtOAc (3 × 0.5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum. Chromatography (SiO_2, 0.5 × 10 cm, 40% EtOAc−hexane) afforded **9** (6.6 mg, 8.0 mg theoretical, 82%) as a white solid: mp 158 °C (EtOAc−hexane, needles); ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, 1H, *J* = 7.9, 1.4 Hz, C6-H), 7.52 (m, 1H, C8-H), 7.37 (m, 1H, C7-H), 6.92 (d, 1H, *J* = 8.0 Hz, C9-H), 6.83 (s, 1H, C4-H), 3.80 (m, 1H, C2-H), 3.46 (dt, *J* = 5.7, 13.0 Hz, C2-H), 2.43 (m, 1H, C10a-H), 2.25 (m, 1H, C1-H), 2.16−2.08 (m, 2H, C1−H and C10-H), 1.89 (dd, 1H, *J* = 8.4, 5.7 Hz, C10-H), 1.51 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.1 (C5), 155.5 (CO_2),

Table 3. Resolution of **9**, **26**, and **35**

agent	conditions % *i*-PrOH−hexane, flow rate		t_R (min)	α
9	OD Prep[a]	20%, 8 mL/min	24.5 and 41.7	1.70
		30%, 8 mL/min	16.3 and 26.0	1.60
		40%, 8 mL/min	13.8 and 20.2	1.46
26	OD Prep[a]	20%, 8 mL/min	10.6 and 11.3	1.07
		10%, 8 mL/min	14.5 and 16.4	1.13
		5%, 8 mL/min	21.4 and 25.6	1.19
		3%, 8 mL/min	28.6 and 34.4	1.18
	OD Analy[b]	3%, 1 mL/min	15.3 and 17.7	1.16
		2%, 0.7 mL/min	30.2 and 34.9	1.15
35	OD Prep[a]	30%, 8 mL/min	20.3 and 29.1	1.43
		25%, 8 mL/min	23.2 and 33.5	1.44
	OD Analy[b]	10%, 2 mL/min	8.61 and 12.7	1.47

[a] 10 μm, 2 × 25 cm semipreparative Daicel chiralcel column. [b] 10 μm, 0.46 × 25 cm Daicel chiralcel analytical column.

153.0 (C), 143.9 (C), 132.1 (CH), 131.9 (C), 126.3 (CH), 126.1 (CH), 121.7 (CH), 120.5 (CH), 82.5 ($C(CH_3)_3$), 44.1 (C2), 33.7 (C10a), 28.2 ($C(CH_3)_3$), 27.6 (C9b), 25.6 (C1), 20.9 (C10); IR (KBr) ν_{max} 2980, 1705, 1639, 1604, 1568, 1483, 1461, 1406, 1308, 1280, 1228, 1159, 1126 cm^{-1}; UV (CH_3OH) λ_{max} 314 (ε 19 000), 260 (ε 9000), 218 (ε 17 000) nm; UV (THF) λ_{max} 302 (ε 16 000), 254 (9400), 218 (16000) nm; FABHRMS (NBA) *m/e* 312.1615 ($M + H^+$, $C_{19}H_{21}NO_3$ requires 312.1600).

From 27: A solution of **27** (9.1 mg, 27.6 μmol) and Ph_3P (8.7 mg, 33.2 μmol, 1.2 equiv) in THF (0.2 mL) was treated with DEAD (5.2 μL, 33.0 μmol, 1.2 equiv), and the resulting mixture was stirred 1 h at 25 °C. The mixture was diluted with EtOAc (5 mL), washed with H_2O (5 mL), dried (Na_2SO_4), and concentrated under vacuum. Chromatography (SiO_2, 0.5 × 10 cm, 40% EtOAc−hexane) afforded **9** (5.1 mg, 8.6 mg theoretical, 59%).

A single-crystal X-ray structure determination of **9** was conducted with needles grown from 5% EtOAc−hexane.[37]

Resolution of *N*-BOC-CBQ (9). A solution of **9** (40 mg) in 1 mL *i*-PrOH−hexane−CH_2Cl_2 (5:75:20) was resolved on a semipreparative Daicel chiralcel OD column (10μm, 2 × 25 cm) using 30% *i*-PrOH−hexane eluent at a flow rate of 8 mL/min. The effluent was monitored at 314 nm and the enantiomers eluted with retention times of 16.3 and 26.0 min, respectively (α = 1.60). The fractions containing the separated enantiomers were collected and the solvent evaporated in vacuo to afford *ent*-(+)-*N*-BOC-CBQ (t_R = 16.3 min, 18 mg) and (−)-*N*-BOC-CBQ (t_R = 26.0 min, 19 mg) with a 93% recovery. HPLC of the separated enantiomers indicated they were >99.9% ee. A study of the direct resolution of **9** and related agents is summarized in Table 3 [*ent*-(+)-**9**: $[\alpha]^{25}_D$ +318 (*c* 0.19, THF); (−)-**9**: $[\alpha]^{25}_D$ −307 (*c* 0.18, THF)].

2,3,10,10a-Tetrahydro-1*H*-cyclopropa[*d*]benzo[*f*]quinol-5-one (10, CBQ). Method A, From 26: The solid **26** (10 mg, 0.029 mmol) was treated with 3 M HCl−EtOAc (0.5 mL) and the solution was stirred at 25 °C until the starting material disappeared as monitored by TLC (ca. 15−20 min). The solvent was removed under a stream of Ar before THF (0.5 mL) and 5% aqueous $NaHCO_3$ (0.5 mL, 10 equiv) were added and the mixture was stirred for 2 h at 25 °C. The mixture was extracted with EtOAc (3 × 1 mL) and the combined organic phase was washed with H_2O (1 mL), dried (Na_2SO_4), and concentrated under vacuum. Chromatography (SiO_2, 0.5 × 5 cm, 10% CH_3OH−CH_2Cl_2) afforded **10** (4 mg, 6 mg theoretical, 67%) as a yellow foam: ^1H NMR (400 MHz, acetone-d_6) δ 8.08 (dd, 1H, *J* = 7.8, 1.5 Hz, C6-H), 7.42 (ddd, 1H, *J* = 8.0, 7.2, 1.6 Hz, C8-H), 7.28 (m, 1H, C7-H), 7.04 (d, 1H, *J* = 7.4 Hz, C9-H), 6.38 (br s, 1H, NH), 5.61 (s, 1H, C4-H), 3.34−3.25 (m, 2H, C2-H_2), 2.70 (m, 1H, C10a-H), 2.28 (m, 1H, C10-H), 2.23−2.17 (m, 1H, C1-H), 2.05−1.95 (m, 1H, partially obscured by acetone, C1-H), 1.51 (dd, 1H, *J* = 8.4, 5.2 Hz, C10-H); ^{13}C NMR (100 MHz, acetone-d_6) δ 181.0 (C5), 164.6, 143.2, 134.6, 131.1, 126.0, 125.9, 121.0, 100.1, 38.2 (C2), 29.2, 28.3, 23.4 (C9b), 20.2; IR (film) ν_{max} 3247, 3150, 3033, 2929, 1611, 1587, 1538, 1259 cm^{-1}; UV (THF) λ_{max} 326 (ε 10 500), 240 (ε 14 000), 219 (ε 20 000) nm; FABHRMS (NBA) *m/e* 212.1075 ($M + H^+$, $C_{14}H_{13}NO$ requires 212.1075).

Method B, From 26: The solid **26** (2 mg, 5.75 μmol) was treated with 3 M HCl−EtOAc (0.5 mL) and the solution was stirred at 25 °C until the starting material disappeared (TLC, 15−20 min). The solvent was removed under a stream of Ar and dissolved in DMF (200 μL). This solution was added to a suspension of NaH (60% in mineral oil, 2 mg, 50 μmol, 8.7 equiv) in THF (200 μL) and the mixture was stirred 5 min at 25 °C. The mixture was cooled at 0 °C, a pH 7 buffer solution was added (1 mL), and the mixture was extracted with CH_2Cl_2 (3 × 0.5 mL). The combined organic layers were dried (Na_2SO_4) and the solvent removed under vacuum. Chromatography (SiO_2, 0.5 × 7 cm, 10% CH_3OH−CH_2Cl_2) afforded **10** (0.6 mg, 1.2 mg theoretical, 50%) identical to the material detailed above.

4-Acetyl-1-(chloromethyl)-6-hydroxy-1,2,3,4-tetrahydrobenzo[*f*]-quinoline (29). A solution of **26** (1.9 mg, 5.5 μmol) in 4 M HCl−EtOAc was stirred for 30 min at 25 °C. The solvent was removed under a stream of Ar to afford **28**. Crude **28** was suspended in THF (40 μL) and treated with $NaHCO_3$ (0.5 mg, 6.0 μmol, 1.1 equiv) and CH_3COCl (1 μL, 14.1 μmol, 2.6 equiv). The mixture was stirred for 30 min at 25 °C before EtOAc (0.2 mL) and phosphate buffer (pH 7, 1 mL) were added. The aqueous layer was extracted with EtOAc (2 × 0.2 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under vacuum. Chromatography (SiO_2, 0.5 × 6 cm, 50−100% EtOAc−hexane gradient elution) afforded **29** (1.3 mg, 1.6 mg theoretical, 81%) as an amorphous tan solid: ^1H NMR (400 MHz, CD_3OD) δ 8.24 (d, 1H, *J* = 8.4 Hz, C7-H), 7.95 (d, 1H, *J* = 8.6 Hz, C10−H), 7.57 (m, 1H, C9-H), 7.44 (m, 1H, C8-H), 6.85 (br s, 1H, C5-H), 4.29 (m, 1H, C3-H), 4.01 (m, 1H, C1-H), 3.82 (dd, 1H, *J* = 4, 10.8 Hz, C*H*HCl), 3.63 (dd, 1H, *J* = 8.9, 10.8 Hz, CH*H*Cl), 3.40 (m, 1H, C3-H), 2.43 (m, 1H, C2-H), 2.27 (s, 3H, CH_3), 2.19 (m, 1H, C2-H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.9 (CO), 152.8, 139.1, 133.2, 128.1, 124.8, 124.2, 123.7, 123.4, 109.8, 107.5, 48.6 (CH_2Cl), 42.3 (C3), 35.4, 27.7, 23.7; IR (film) ν_{max} 3177, 2932, 1621, 1591, 1520, 1442, 1403, 1315, 1249, 766 cm^{-1}; FABHRMS (NBA) *m/e* 289.0860 (M^+, $C_{16}H_{16}ClNO_2$ requires 289.0870).

***N*³-Acetyl-2,3,10,10a-tetrahydro-1*H*-cyclopropa[*d*]benzo[*f*]quinol-5-one (30, *N*-acetyl-CBQ). Method A:** A solution of **29** (4.4 mg, 15.1 μmol) in THF−DMF (2:1, 150 μL) was treated with DBU (6.8 μL, 45.4 μmol, 3 equiv) and the mixture was stirred for 8 h at 25 °C. The solvents were removed under vacuum. Chromatography (SiO_2, 0.5 × 5 cm, 20−100% THF−hexane gradient elution) afforded **30** (2.5 mg, 3.8 mg theoretical, 66%) as a yellow powder: ^1H NMR (400 MHz, acetone-d_6) δ 8.13 (dd, 1H, *J* = 7.9, 1.4 Hz, C6-H), 7.60 (m, 1H, C8-H), 7.42 (m, 1H, C7-H), 7.18 (d, 1H, *J* = 8.1 Hz, C9-H), 6.47 (s, 1H, C4-H), 3.75−3.61 (m, 2H, C2-H_2), 2.59 (m, 1H, C10a-H), 2.34 (m, 1H, C1-H), 2.30 (s, 3H, CH_3), 2.26 (m, 1H, C10-H), 2.22−2.14 (m, 1H, C1-H), 2.14 (dd, 1H, *J* = 8.8, 5.8 Hz, C10-H); ^{13}C NMR (100 MHz, acetone-d_6) δ 184.5 (C5), 170.2 (CO), 158.3, 145.1, 133.2, 132.9, 126.8, 126.4, 122.7, 122.5, 44.6 (C2), 35.9, 26.5, 25.6, 23.3, 21.7; IR (film) ν_{max} 2922, 2852, 1669, 1634, 1602, 1560, 1462, 1406, 1370, 1302, 1283, 1232, 1038 cm^{-1}; FABHRMS (NBA) *m/e* 254.1190 (M + H^+, $C_{16}H_{15}NO_2$ requires 254.1181).

Method B: A solution of **29** (7 mg, 24.1 μmol) in DMF (200 μL) was added to a suspension of NaH (2 mg, 60% in oil, 50.0 μmol, 2.1 equiv) in THF (100 μL) and the mixture was stirred for 30 min at 25 °C. The mixture was cooled to 0 °C and a pH 7 phosphate buffer solution (3 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 0.5 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under vacuum. Chromatography (SiO_2 0.5 × 6 cm, 20−100% THF−hexane gradient elution) afforded **30** (4 mg, 6.1 mg theoretical, 67%) identical to the material described above.

seco-CBQ-TMI (35). A solution of **26** (19.1 mg, 54.9 μmol) in 4 M HCl−EtOAc (1 mL) was stirred for 30 min at 25 °C. The solvent was removed under a stream of Ar and the resulting solid was dissolved in DMF (250 μL). This solution was treated sequentially with 5,6,7-trimethoxyindole-2-carboxylic acid (**31**, 13.7 mg, 54.9 μmol, 1 equiv) and [[3-(dimethylamino)propyl]ethyl]carbodiimide hydrochloride (EDCI, 31.6 mg, 165 μmol, 3 equiv) and stirred for 2 h at 25 °C. Water (3 mL) was added and the mixture was extracted with EtOAc (3 × 1 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum. Chromatography (SiO_2, 1 × 10 cm, 50% EtOAc−hexane) afforded **35** (14.8 mg, 26.1 mg theoretical, 57%) as a white amorphous powder: ^1H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H, NH), 8.23 (d, 1H, *J* = 8.3 Hz, C7-H), 7.97 (d, 1H, *J* = 8.5 Hz, C10-H), 7.60 (m, 1H, C9-H), 7.53 (s, 1H, OH), 7.47 (m, 1H, C8-H), 6.61

(s, 1H, C4′-H), 6.49 (s, 1H, C5-H), 6.17 (d, 1H, J = 2.1 Hz, C3′-H), 4.36 (m, 1H, C3-H), 3.99 (m, 1H, C1-H), 3.92−3.83 (m, 1H, C*H*HCl), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.73−3.60 (m, 2H, C3-H and CH*H*Cl), 3.64 (s, OCH_3), 2.54 (m, 1H, C2-H), 2.16 (m, 1H, C2-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5 (CO), 151.2, 149.6, 139.6, 138.6, 137.3, 132.3, 129.2, 127.7, 125.4, 124.7, 123.8, 123.2, 123.1, 122.4, 117.9, 108.7, 107.4, 97.6, 61.5, 60.9, 55.9, 47.3 (CH_2Cl), 43.0 (C3), 34.9, 26.9; IR (film) ν_{max} 3290, 2937, 1735, 1704, 1590, 1525, 1494, 1464, 1443, 1403, 1373, 1309, 1237, 1196, 1122, 1105 cm^{-1}; FABHRMS (NBA) *m/e* 480.1468 (M^+, $C_{26}H_{24}N_2O_5$ requires 480.1452).

A sample of **35** (13 mg) in 30% *i*-PrOH−hexane was resolved on a semipreparative Daicel chiralcel OD column (10 μm, 2 × 25 cm) using 30% *i*-PrOH−hexane eluent (8 mL/min). The effluent was monitored at 263 nm and the enantiomers eluted with retention times of 20.3 and 29.1 min (α = 1.43). The fractions containing the separated enantiomers were collected and concentrated to afford *ent*-(+)-**35** (t_R = 29.1 min, 5.4 mg) and (−)-**35** (t_R = 20.3 min, 5.8 mg) with a 86% recovery (> 99.9% ee), Table 3 [*ent*-(+)-(1*S*)-**35**: $[\alpha]^{25}_D$ +217 (*c* 0.27, THF); (1*R*)-**35**: $[\alpha]^{25}_D$ −212 (*c* 0.29, THF)].

CBQ-TMI (36). A solution of **35** (5.5 mg, 11.6 μmol) in DMF (100 μL) was added to a suspension of NaH (0.5 mg, 60% in oil, 12.5 μmol, 1.07 equiv) in THF (50 μL) and the mixture was stirred for 30 min at 25 °C. The mixture was cooled to −10 °C and a pH 7 phosphate buffer solution (2 mL) was added. The mixture was extracted with EtOAc (3 × 0.5 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under vacuum. Chromatography (SiO_2, 0.5 × 6 cm, EtOAc) afforded **36** (3.7 mg, 5.1 mg theoretical, 72%) as an amorphous powder: ^1H NMR (400 MHz, $CDCl_3$) δ 8.90 (br s, 1H, NH), 8.27 (dd, 1H, J = 1.3, 7.9 Hz, C6−H), 7.62 (m, 1H, C8-H), 7.46 (m, 1H, C7-H), 7.04 (d, 1H, J = 8.0 Hz, C9-H), 6.60 (s, 1H, C4′-H), 6.55 (d, 1H, J = 2.3 Hz, C3′-H), 6.52 (s, 1H, C4-H), 4.05 (s, 3H, OCH_3), 3.95−3.89 (m, 2H, C2-H_2), 3.89 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 2.61 (m, 1H, C10a-H), 2.42−2.25 (m, 3H, C1-H_2 and C10-H), 2.17 (dd, 1H, J = 5.2, 8.8 Hz, C10-H); IR (film) ν_{max} 2934, 1625, 1601, 1463, 1304, 1279, 1263, 1222, 1106, 1044 cm^{-1}; FABHRMS (NBA) *m/e* 445.1742 (M + H^+, $C_{26}H_{24}N_2O_5$ requires 445.1763). [*ent*-(+)-CBQ-TMI: $[\alpha]^{25}_D$ +179 (*c* 0.09, THF); (−)-CBQ-TMI: $[\alpha]^{25}_D$ −171 (*c* 0.07, THF)].

seco-CBQ-Indole$_2$ (37). A solution of **26** (2.3 mg, 6.6 μmol) in 4 M HCl−EtOAc (0.5 mL) was stirred for 30 min at 25 °C. The solvent was removed under a stream of Ar and the resulting solid was taken up in DMF (60 μL). The solution was treated sequentially with 5-(2-indolylcarbonyl)amino]-2-methylindole (**32**, 2.1 mg, 6.6 μmol, 1 equiv) and EDCI (3.8 mg, 19.8 μmol, 3 equiv). The mixture was stirred for 6 h at 25 °C before the solvent was removed under vacuum. Chromatography (SiO_2, 0.5 × 5 cm, 10−50% DMF-toluene gradient elution) afforded **37** (1.7 mg, 3.6 mg theoretical, 47%) as a yellow powder: ^1H NMR (400 MHz, acetone-d_6) δ 11.72 (s, 1H, NH), 11.65 (s, 1H, NH), 10.24 (s, 1H, NH), 8.22 (d, 1H, J = 8.3 Hz, C7-H), 8.06 (d, 1H, J = 8.5 Hz, C10-H), 7.64−7.45 (m, 8H), 7.25 (s, 1H), 7.22 (m, 1H, C6″-H), 7.07 (m, 1H, C5″-H), 6.73 (s, 1H, C5-H), 6.43 (s, 1H, OH), 4.35 (m, 1H, C3-H), 4.08−4.01 (m, 2H, C1-H and C*H*HCl), 3.93−3.86 (m, 2H, C3-H and CH*H*Cl), 2.50 (m, 1H, C2-H), 2.27 (m, 1H, C2-H); IR (film) ν_{max} 3278, 2917, 2849, 1655, 1590, 1543, 1525, 1410, 1313, 1245 cm^{-1}; FABHRMS (NBA) *m/e* 549.1688 (M + H^+, $C_{32}H_{25}ClN_4O_3$ requires 549.1693).

seco-CBQ-CDPI$_1$ (39). A solution of **26** (10 mg, 28 μmol) in 4 M HCl-EtOAc (0.5 mL) was stirred for 30 min at 25 °C. The solvent was removed under a stream of Ar and the resulting solid was taken up in DMF (80 μL). The solution was treated sequentially with **33**[35] (7 mg, 28 μmol, 1 equiv) and EDCI (21 mg, 109 μmol, 3.9 equiv). The mixture was stirred 12 h at 25 °C. Chromatography (SiO_2, 0.5 × 6 cm, 20−66% DMF−toluene gradient elution) afforded **39** (7.4 mg, 13.6 mg theoretical, 54%) as a yellow powder: ^1H NMR (400 MHz, CD_3OD) δ 8.19 (d, 1H, J = 8.4 Hz, C7-H), 8.02 (d, 1H, J = 8.5 Hz, C10-H), 7.92 (d, 1H, J = 9.0 Hz, C4′-H), 7.58 (m, 1H, C9-H), 7.44 (m, 1H, C8-H), 7.24 (d, 1H, J = 9.0 Hz, C5′-H), 6.61 (s, 1H, C5-H), 6.29 (s, 1H, C8′-H), 4.35 (m, 1H, C3-H), 4.04 (m, 1H, C1-H), 3.99−3.94 (m, 3H, C*H*HCl, C2′-H_2), 3.83−3.74 (m, 2H, CH*H*Cl, C3-H), 3.13 (m, 2H, C1′-H_2), 2.53 (m, 1H, C2-H), 2.23 (m, 1H, C2-H); IR (film) ν_{max} 3221, 2958, 2873, 1658, 1649, 1642, 1595, 1503, 1453, 1408, 1339 cm^{-1}; FABHRMS (NBA) *m/e* 474.1454 (M^+, $C_{26}H_{23}ClN_4O_3$ requires 474.1459).

seco-CBQ-CDPI$_2$ (41). A solution of **26** (3.5 mg, 10 μmol) in 4 M HCl−EtOAc (0.5 mL) was stirred 30 min at 25 °C. The solvent was removed under a stream of Ar and the resulting solid was taken up in DMF (100 μL). The solution was treated sequentially with **34**[35] (4.3 mg, 10 μmol, 1 equiv) and EDCI (5.8 mg, 30 μmol, 3 equiv). The mixture was stirred 2 h at 25 °C. Chromatography (SiO_2, 0.5 × 6 cm, 20% DMF−toluene) afforded **41** (2.2 mg, 6.6 mg theoretical, 33% unoptimized) as a yellow powder: ^1H NMR (400 MHz, DMF-d_7) δ 11.80 (br s, 1H, NH), 11.55 (br s, 1H, NH), 10.45 (br s, 1H, OH), 8.32 (m, C4′-H), 8.22 (d, 1H, J = 7.3 Hz, C7-H), 8.13 (d, 1H, J = 8.8 Hz, C4″-H), 8.06 (d, 1H, J = 8.8 Hz, C10-H), 7.64 (m, 1H, C9-H), 7.48 (m, 1H, C8-H), 7.43 (d, 1H, J = 8.9 Hz, C5′-H), 7.36 (d, 1H, J = 9.0 Hz, C5″-H), 7.03 (d, 1H, J = 1 Hz, C8″-H), 6.90 (s, 1H, C5-H), 6.64 (d, 1H, J = 1 Hz, C8′-H), 6.10 (s, 2H, NH_2), 4.66 (m, 2H, C2′-H_2), 4.33 (m, 1H, C3−H), 4.14 (m, 2H, C2″-H_2), 4.07−3.96 (m, 2H, C1-H, C*H*HCl), 3.59 (m, 2H, C3-H, CH*H*Cl), 3.38−3.28 (m, 4H, C1-′H_2 and C1″-H_2), 2.49 (m, 1H, C2-H), 2.23 (m, 1H, C2-H); IR (film) ν_{max} 3353, 2922, 1658, 1650, 1643, 1600, 1581, 1512, 1503, 1434, 1409, 1365, 1344 cm^{-1}; FABHRMS (NBA) *m/e* 659.2168 (M + H^+, $C_{37}H_{31}ClN_6O_4$ requires 659.2173).

Acid-Catalyzed Addition of CH_3OH to (±)-*N*-BOC-CBQ (9). A solution of (±)-**9** (7.3 mg, 23.4 μmol) in CH_3OH (2 mL) was treated with 0.011 M CF_3SO_3H−CH_3OH (250 μL, 2.83 μmol, 0.12 equiv) at 0 °C providing a final concentration of CF_3SO_3H of 1.26 mM. The mixture was stirred under Ar for 1 h at 25 °C at which time TLC showed complete disappearance of **9** and generation of two products. $NaHCO_3$ (5 mg) was added and the solution was stirred for 10 min. The suspension was filtered through Celite and concentrated under vacuum. Chromatography (SiO_2, 1 × 9 cm, 25−50% EtOAc−hexane gradient elution) afforded **43** (4.0 mg, 59%) and **44** (2.9 mg, 36%) for a combined yield of 96%. For 4-(*tert*-butyloxycarbonyl)-6-hydroxy-1-(methoxymethyl)-1,2,3,4-tetrahydrobenzo[*f*]quinoline (**43**): ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, 1H, J = 8.1 Hz, C7-H), 7.94 (d, 1H, J = 8.5 Hz, C10-H), 7.50 (m, 1H, C9-H), 7.39 (m, 1H, C8-H), 7.34 (s, 1H, C5-H), 5.42 (s, 1H, OH), 3.84−3.69 (m, 3H, C1-H and C3-H_2), 3.62 (dd, 1H, J = 4.0, 9.7 Hz, C*H*HOMe), 3.38 (s, 3H, OCH_3), 3.34 (t, 1H, J = 10 Hz, CH*H*OMe), 2.32 (m, 1H, C2-H), 1.94 (m, 1H, C2-H), 1.53 (s, 9H, $C(CH_3)_3$); IR (film) ν_{max} 3304, 2975, 2929, 1699, 1668, 1623, 1597, 1404, 1367, 1343, 1256, 1160, 1074 cm^{-1}; FABHRMS (NBA) *m/e* 343.1780 (M^+, $C_{20}H_{25}NO_4$ requires 343.1784).

For 5-(*tert*-butyloxycarbonyl)-7-hydroxy-2-methoxy-1,2,3,4-tetrahydro-5*H*-naphth[1,2-*b*]azepine (**44**): ^1H NMR (400 MHz, CD_3OD) of two conformers δ 8.24−8.22 (m, 1H, C8-H), 8.11−8.09 (m, 1H, C11-H), 7.56−7.41 (m, 2H, C9-H and C10-H), 6.68 and 6.65 (two s, 1H, C6-H), 4.30−4.14 and 4.06−3.96 (two m, 1H, C4−H), 3.87−3.77 and 3.70−3.66 (two m, 1H, C2-H), 3.49 and 3.29 (two s, 3H, OCH_3), 3.25−3.13 (m, 1H, C4-H), 2.90−2.80 (m) and 2.68 (dd, J = 11, 13 Hz, 2H, C1-H_2), 2.10−1.76 (m, 2H, C3-H_2), 1.56 and 1.39 (two s, 9H, $C(CH_3)_3$); variable temperature NMR (400 MHz, DMSO-d_6) indicated that the signals begin to coalesce at 50−70 °C and provided a sharp, well-resolved spectrum at 140 °C: δ 9.40 (br s, 1H, OH), 8.22 (dd, 1H, J = 8.3, 0.6 Hz, C8-H), 8.09 (d, 1H, J = 8.6 Hz, C11-H), 7.54 (m, 1H, C10-H), 7.44 (m, 1H, C9-H), 6.78 (s, 1H, C6-H), 3.77 (m, 1H, C4-H), 3.48 (m, 1H, C2-H), 3.37 (s, 3H, OCH_3), 3.44 (m, 1H, C4-H), 3.12 (m, 1H, C1-H), 2.76 (m, 1H, C1-H), 1.95 (m, 1H, C3-H), 1.83 (m, 1H, C3-H), 1.46 (s, 9H, $C(CH_3)_3$); IR (film) ν_{max} 3284, 2976, 2930, 1694, 1667, 1595, 1409, 1367, 1322, 1258, 1163, 1091 cm^{-1}; FABHRMS (NBA-NaI) *m/e* 343.1778 (M^+, $C_{20}H_{25}NO_4$ requires 343.1784).

Acid-Catalyzed Addition of CH_3OH to of (+)-*N*-BOC-CBQ [(+)-9]. A solution of (+)-**9** (4.5 mg, 14.4 μmol) in CH_3OH (1.2 mL) was treated with 0.011 M CF_3SO_3H−CH_3OH (150 μL, 1.70 μmol, 0.12 equiv) at 0 °C providing a final concentration of CF_3SO_3H of 1.25 mM. The mixture was stirred under Ar for 1 h at 25 °C at which time TLC showed complete disappearance of (+)-**9** and the generation of two products. $NaHCO_3$ (5 mg) was added and the mixture was stirred for 10 min. The suspension was filtered through Celite and concentrated under vacuum to give a mixture (4.8 mg, 5.0 mg theoretical) of the two crude methanolysis products. Samples (1 mg) of this mixture dissolved in 5% *i*-PrOH−hexane were eluted on a Diacel chiralcel OD

analytical HPLC column (10 μm, 0.46 x 25 cm) with 1% *i*-PrOH–hexane at a flow rate of 2 mL/min and the results are illustrated in Figure 2. Authentic samples of (±)-**43** eluted with t_R = 13.1 and 14.2 min and those of (±)-**44** eluted with t_R = 18.1 and 24.9 min. Only one enantiomer of **43** (t_R = 14.1 min) and **44** (t_R = 17.7 min) was detected in the acid-catalyzed addition of CH_3OH to (+)-**9**, Figure 2.

Addition of HCl to 36. A solution of **36** (3.7 mg, 8.3 μmol) in THF (200 μL) was cooled to −78 °C and treated with 4 M HCl–EtOAc (4 μL, 16 μmol, 1.9 equiv). The mixture was stirred for 2 min before the solvent and HCl were removed under vacuum. Chromatography (SiO_2, 0.5 × 15 cm, 30–50% EtOAc–hexane gradient elution) afforded **35** (2.1 mg) identical in all respects with authentic material and **45** as a colorless oil (1.6 mg; total 3.7 mg, 4.0 mg theoretical, 93%). For **45**: ^{1}H NMR (400 MHz, $CDCl_3$) of two conformers δ 9.17 (br s, 1H, NH), 8.39 (d, *J* = 8.3 Hz) and 8.38 (d, *J* = 8.0 Hz, 1H, C8-H), 8.15 (d, *J* = 8.5 Hz, 1H, C11-H), 7.71–7.51 (m, 2H, C9-H and C10-H), 6.80 and 6.65 (two s, 1H, C6-H), 6.60 and 6.57 (two s, 1H, C4′-H), 6.38 and 6.37 (two s, OH), 5.38 and 5.36 (two d, *J* = 2 Hz, C3′-H), 4.89 and 4.76–4.70 (two m, 1H, C4-H), 4.02–3.77 (m, 2H, C4-H and C2-H), 3.90 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.67 and 3.66 (two s, 3H, OCH_3), 3.36, 3.20 and 2.89 (three m, 2H, C1-H_2), 2.53–2.05 (m, 2H, C3-H_2); IR (film) ν_{max} 3254, 2920, 2859, 1584, 1467, 1446, 1395, 1300, 1261, 1237 cm^{-1}; FABHRMS (NBA) *m/e* 480.1470 (M^+, $C_{26}H_{24}ClN_2O_5$ requires 480.1452).

Addition of HCl to 30. A solution of **30** (1 mg, 3.9 μmol) in THF (100 μL) was cooled to −78 °C and treated with 3.8 M HCl–EtOAc (20 μL, 76 μmol, 19.2 equiv). The mixture was stirred for 2 min before the solvent and HCl were removed under vacuum. Chromatography (SiO_2, 0.5 × 10 cm, 30–50% EtOAc–hexane gradient elution) afforded **29** (0.6 mg) identical in all respects with authentic material and **46** as a colorless oil (0.2 mg, total 0.8 mg, 1.1 mg theoretical, 72%). For **46**: ^{1}H NMR (400 MHz, $CDCl_3$) of two rotamers δ 8.27–8.23 (m, 1H, C11-H), 8.11–8.08 (m, 1H, C8-H), 7.65–7.50 (m, 2H, C10-H and C9-H), 6.78 and 6.63 (two s, 1H, C6-H), 5.29 (s, 1H, OH), 4.71–4.69 and 4.55–4.52 (two m, 1H, C4-H), 3.95–3.86 (m, 2H, C4-H and C2-H), 3.26–3.15 and 2.80 (two m, 2H, C1-H_2), 2.52–2.05 (m, 2H, C3-H_2), 1.96 and 1.95 (two s, 3H, CH_3); IR (film) ν_{max} 3318, 2923, 1620, 1584, 1446, 1413, 1391, 1261, 1077 cm^{-1}.

Aqueous Solvolysis Rates of *N*-BOC-CBQ (9) and CBQ (10). Samples of **9** (100 μg) and **10** (100 μg) were dissolved in CH_3OH (1.5 mL) and the solutions mixed with aqueous buffer (pH 3, 1.5 mL). The buffer contained 4:1:20 (v:v:v) 0.1 M citric acid, 0.2 M Na_2HPO_4, and H_2O, respectively. Similarly, a solution of **9** (100 μg) in CH_3OH (1.5 mL) was mixed with deionized H_2O (pH 7, 1.5 mL). The UV spectra of the solutions were measured immediately after mixing with the aqueous solutions against a blank containing CH_3OH (1.5 mL) and the appropriate aqueous solution (1.5 mL). The blank and the solvolysis reaction solutions were carefully stoppered, protected from light, and allowed to stand at 25 °C. For **9** at pH 3, the UV spectrum was taken 10 times during the first hour, 10 times during the following 6 h, and then twice a day. The reaction was monitored until no further change was observed. The decrease of the absorbance at 318 nm was recorded. The solvolysis rate constant was calculated from the least squares treatment (r = 0.993) of the slope of a plot of time versus $\ln[(A - A_\infty)/(A_o - A_\infty)]$; $k = 9.07 \times 10^{-5}$ s^{-1}, $t_{1/2}$ = 2.1 h. For **9** at pH 7, the UV spectrum was monitored daily for the first 3 days and then weekly during a period of 4 months. The rate was computed from the least squares treatment (r = 0.990) of the slope of the same plot as above; $k = 3.54 \times 10^{-7}$ s^{-1}, $t_{1/2}$ = 544 h. For **10**, the UV spectrum was monitored 9 times the first day, twice a day for the next three days, and daily for an additional week. The decrease of the absorption at 343 nm was recorded. The solvolysis rate constant was calculated for the least squares treatment (r = 0.999) of the same plot as above; $k = 2.11 \times 10^{-6}$ s^{-1}, $t_{1/2}$ = 91.2 h.

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (CA41986 and 55276) and the award of a Ligue Nationale Contre Le Cancer fellowship to Philippe Mésini (1992–93). We wish to thank Dr. Raj Chadha for the X-ray structure determination of **9** and Dr. W. Wrasidlo and Robert Merlock for the in vitro cytotoxic assay results.

Supplementary Material Available: Full experimental details for the preparation and characterization of **12-17**, details of the X-ray structure determination of **9**, and tables of data used to assemble Figure 5 (26 pages); observed and calculated structure factors for **9** (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.