p-Quinonemethide Analog of the CC-1065 and Duocarmycin Alkylation Subunits

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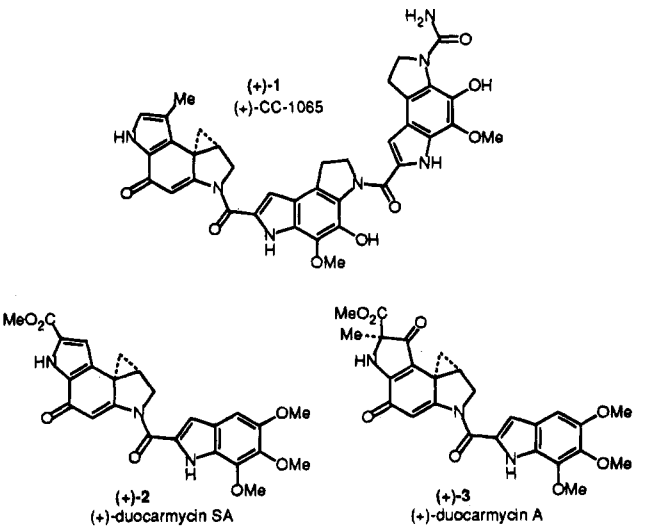
The synthesis and preliminary evaluation of **10** and **11**, stable precursors to the inherently reactive but isolable *p*-quinonemethide analog **9** of the CC-1065 and duocarmycin alkylation subunits, are detailed. The *p*-quinonemethide **9**, while reactive ($t_{1/2}$ < 1 min, CH_3OH), represents one of the few unsubstituted quinonemethides sufficiently stable for isolation and characterization. The structural origin of this stability and the ramifications of the observations on the origin of the stability of the CC-1065 and duocarmycin alkylation subunits are discussed.

(+)-CC-1065 (**1**),[1] duocarmycin SA (**2**),[2] and duocarmycin A (**3**)[3] constitute the parent agents of a class[1-6] of exceptionally potent antitumor antibiotics that derive their biological properties through a sequence selective alkylation of duplex DNA.[7-10] The now 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 cyclopropane within selected AT-rich sites of the minor groove.[11-16] Although the intracellular target for the agents has been shown to be duplex 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 analogs of the naturally occurring agents possessing deep-seated changes in the alkylation subunit (*cf.* **4**–**8**) have been detailed

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(1) Chidester, C. G.; Krueger, W. C.; Mizsak, S. A.; Duchamp, D. J.; Martin, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 7629.

(2) Ichimura, M.; Ogawa, T.; Takahashi, K.; Kobayashi, E.; Kawamoto, I.; Yasuzawa, T.; Takahashi, I.; Nakano, H. *J. Antibiot.* **1990**, *43*, 1037. Ichimura, M.; Ogawa, T.; Katsumata, S.; Takahashi, K.; Takahashi, I.; Nakano, H. *J. Antibiot.* **1991**, *44*, 1045.

(3) Takahashi, I.; Takahashi, K.; Ichimura, M.; Morimoto, M.; Asano, K.; Kawamoto, I.; Tomita, F.; Nakano, H. *J. Antibiot.* **1988**, *41*, 1915. Yasuzawa, T.; Iida, T.; Muroi, K.; Ichimura, M.; Takahashi, K.; Sano, H. *Chem. Pharm. Bull.* **1988**, *36*, 3728.

(4) Ichimura, M.; Muroi, K.; Asano, K.; Kawamoto, I.; Tomita, F.; Morimoto, M.; Nakano, H. *J. Antibiot.* **1988**, *41*, 1285.

(5) Ogawa, T.; Ichimura, M.; Katsumata, S.; Morimoto, M.; Takahashi, K. *J. Antibiot.* **1989**, *42*, 1299.

(6) Ohba, K.; Watabe, H.; Sasaki, T.; Takeuchi, Y.; Kodama, Y.; Nakazawa, T.; Yamamoto, H.; Shomura, T.; Sezaki, M.; Kondo, S. *J. Antibiot.* **1988**, *41*, 1515. Ishii, S.; Nagasawa, M.; Kariya, Y.; Yamamoto, H.; Inouye, S.; Kondo, S. *J. Antibiot.* **1989**, *42*, 1713.

(7) Warpehoski, M. A.; Hurley, L. H. *Chem. Res. Toxicol.* **1988**, *1*, 315. Warpehoski, M. A. In *Advances in DNA Sequence Specific Agents*; Hurley, L. H., Ed.; JAI Press Inc.: Greenwich, CT, 1992; Vol. 1, p 217.

(8) Hurley, L. H.; Needham-VanDevanter, D. R. *Acc. Chem. Res.* **1986**, *19*, 230. Hurley, L. H.; Draves, P. H. In *Molecular Aspects of Anticancer Drug–DNA Interactions*; Neidle, S., Waring, M., Eds.; CRC Press: Ann Arbor, 1993; Vol. 1, p 89.

(9) Coleman, R. S.; Boger, D. L. In *Studies in Natural Products Chemistry*; Rahman, A.-u., Ed.; Elsevier: Amsterdam, 1989; Vol. 3, p 301. Boger, D. L. In *Heterocycles in Bioorganic Chemistry*; Bergman, J., van der Plas, H. C., Simonyl, M., Eds.; Royal Society of Chemistry: Cambridge, 1991, p 103. Boger, D. L. In *Advances in Heterocyclic Natural Product Synthesis;* Pearson, W. H., Ed.; JAI Press: Greenwich, CT, 1992; Vol. 2, p 1.

(10) Boger, D. L. *Chemtracts: Org. Chem.* **1991**, *4*, 329. Boger, D. L. in *Proc. R. A. Welch Found. Conf. Chem. Res., XXXV, Chem. Frontiers Med.* **1991**, *35*, 137. Boger, D. L. *Pure Appl. Chem.* **1993**, *65*, 1123.

(11) CC-1065 and related agents: Hurley, L. H.; Reynolds, V. L.; Swenson, D. H.; Petzold, G. L.; Scahill, T. A. *Science* **1984**, *226*, 843. Hurley, L. H.; Lee, C.-S.; McGovren, J. P.; Warpehoski, M. A.; Mitchell, M. A.; Kelly, R. C.; Aristoff, P. A. *Biochemistry* **1988**, *27*, 3886. Hurley, L. H.; Warpehoski, M. A.; Lee, C.-S.; McGovren, J. P.; Scahill, T. A.; Kelly, R. C.; Mitchell, M. A.; Wicnienski, N. A.; Gebhard, I.; Johnson, P. D.; Bradford, V. S. *J. Am. Chem. Soc.* **1990**, *112*, 4633.

(12) CC-1065 and related agents: Boger, D. L.; Johnson, D. S.; Yun, W. ; Tarby, C. M. *Bioorg. Med. Chem.* **1994**, *2*, 115. Boger, D. L.; Coleman, R. S.; Invergo, B. J.; Sakya, S. M.; Ishizaki, T.; Munk, S. A.; Zarrinmayeh, H.; Kitos, P. A.; Thompson, S. C. *J. Am. Chem. Soc.* **1990**, *112*, 4623. Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 4796 and 1321.

(13) Duocarmycin A, C_1–C_2: Boger, D. L.; Ishizaki, T.; Zarrinmayeh, H.; Kitos, P. A.; Suntornwat, O. *J. Org. Chem.* **1990**, *55*, 4499. Boger, D. L.; Ishizaki, T.; Zarrinmayeh, H.; Munk, S. A.; Kitos, P. A.; Suntornwat, O. *J. Am. Chem. Soc.* **1990**, *112*, 8961. Boger, D. L.; Ishizaki, T.; Zarrinmayeh, H. *J. Am. Chem. Soc.* **1991**, *113*, 6645. Boger, D. L.; Yun, W. *J. Am. Chem. Soc.* **1993**, *115*, 9872.

(14) (+)-Duocarmycin SA and *ent*-(−)-duocarmycin SA: Boger, D. L.; Johnson, D. S.; Yun, W. *J. Am. Chem. Soc.* **1994**, *116*, 1635. Synthesis: Boger, D. L.; Machiya, K.; Hertzog, D. L.; Kitos, P. A.; Holmes, D. *J. Am. Chem. Soc.* **1993**, *115*, 9025. Boger, D. L.; Machiya, K. *J. Am. Chem. Soc.* **1992**, *114*, 10056.

(15) *epi*- and *ent*-duocarmycin A: Boger, D. L.; Yun, W.; Terashima, S.; Fukuda, Y.; Nakatani, K.; Kitos, P. A.; Jin, Q. *BioMed. Chem. Lett.* **1992**, *2*, 759. Synthesis: Fukuda, Y.; Nakatani, K.; Terashima, S. *BioMed. Chem. Lett.* **1992**, *2*, 755. Fukuda, Y.; Nakatani, K.; Ito, Y.; Terashima, S. *Tetrahedron Lett.* **1990**, *31*, 6699.

(16) Duocarmycin A: Sugiyama, H.; Hosoda, M.; Saito, I.; Asai, A.; Saito, H. *Tetrahedron Lett.* **1990**, *31*, 7197. Lin, C. H.; Patel, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 10658. Sugiyama, H.; Ohmori, K.; Chan, K. L.; Hosoda, M.; Asai, A.; Saito, H.; Saito, I. *Tetrahedron Lett.* **1993**, *34*, 2179. Yamamoto, K.; Sugiyama, H.; Kawanishi, S. *Biochemistry* **1993**, *32*, 1059.

(17) Boger, D. L.; Johnson, D. S; Wrasidlo, W. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 631.

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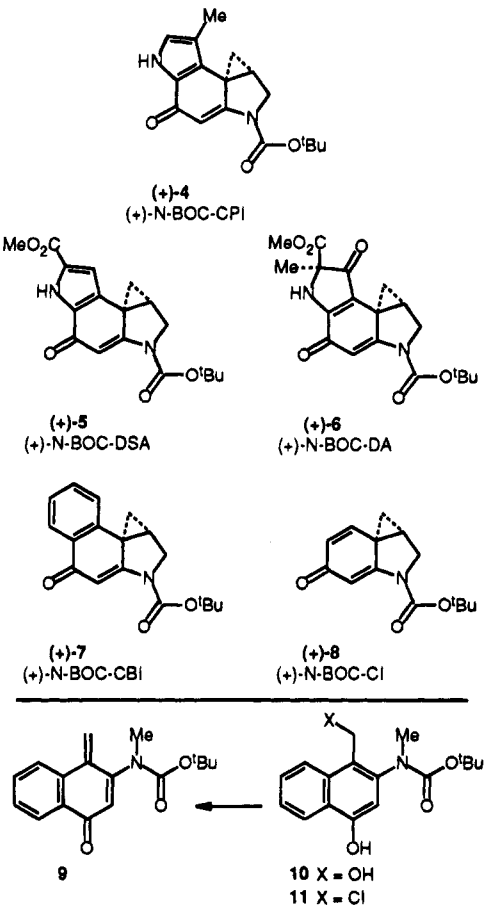
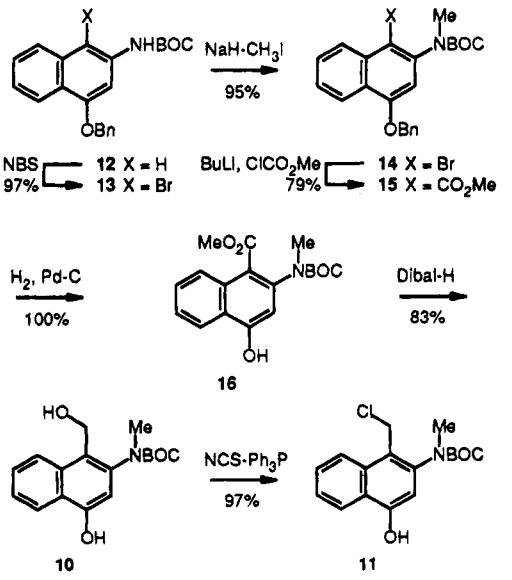
with the intent of defining the structural features of **1**–**3** contributing to polynucleotide recognition and functional reactivity.[18-21] In these studies, the electrophilic cyclopropane proved not to be obligatory to observation of the characteristic alkylation selectivity, and additional electrophiles incorporated into structurally related agents proved to act similarly.[19] Moreover, the AT-rich noncovalent binding selectivity[22] of the agents has been shown to exert a pronounced effect on the DNA alkylation selectivity independent of the nature of the electrophile.[12,14,19] Several additional fundamental structural features contributing to the biological properties have been detailed including a direct, near-linear relationship between chemical solvolysis stability and cytotoxic potency,[14,20] the structural origin of the distinguishing behavior of the natural and unnatural enantiomers,[12,14] and the inherent reversibility of the DNA alkylation reaction which is stabilized by noncovalent binding[13,14] and 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 alkylations.[12,14]

In the course of these studies, the examination of agents incorporating the simplified and chemically stable CBI alkylation subunit (*cf.* **7**) have proven especially interesting.[20] Such agents have displayed more potent cytotoxic activity than the corresponding CPI-based agents (*cf.* **4**) and selected agents within the series examined have displayed efficacious in vivo antitumor activity. Herein, we report the extension of these studies to the preparation, isolation, and examination of the inherently reactive *p*-quinonemethide analog **9** of the CC-1065 and duocarmycin alkylation subunits and its more stable precursors **10** and **11**.[23]



Scheme 1



N-Methylation of **13**[20] provided **14** (94–99%, Scheme 1). Treatment of **14** with *n*-BuLi (2.2 equiv, THF–Et_2O 1:2, −78 °C, 20 min) followed by reaction of the resulting aryllithium intermediate with methyl chloroformate (10 equiv, −78 °C, 30 min, 75–79%) provided **15** in excellent

(18) CPI analogs: Warpehoski, M. A.; Gebhard, I.; Kelly, R. C.; Krueger, W. C.; Li, L. H.; McGovren, J. P.; Prairie, M. D.; Wicnienski, N.; Wierenga, W. *J. Med. Chem.* **1988**, *31*, 590. See also refs 11 and 12. For the closely related CFI analogs: Mohamadi, F.; Spees, M. M.; Staten, G. S.; Marder, P.; Kipka, J. K.; Johnson, D. A.; Boger, D. L.; Zarrinmayeh, H. *J. Med. Chem.* **1994**, *37*, 232.

(19) CI-based analogs: Boger, D. L.; Zarrinmayeh, H.; Munk, S. A.; Kitos, P. A.; Suntornwat, O. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 1431. Boger, D. L.; Munk, S. A.; Zarrinmayeh, H.; Ishizaki, T.; Haught, J.; Bina, M. *Tetrahedron* **1991**, *47*, 2661. Boger, D. L.; Munk, S. A.; Zarrinmayeh, H. *J. Am. Chem. Soc.* **1991**, *113*, 3980. Synthesis: Boger, D. L.; Wysocki, R. J., Jr. *J. Org. Chem.* **1989**, *54*, 1238. Boger, D. L.; Wysocki, R. J., Jr.; Ishizaki, T. *J. Am. Chem. Soc.* **1990**, *112*, 5230. Drost, K. J.; Jones, R. J.; Cava, M. P. *J. Org. Chem.* **1989**, *54*, 5985. Tidwell, J. H.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 6380. Wang, Y.; Lown, J. W. *Heterocycles* **1993**, *36*, 1399. Sundberg, R. J.; Baxter, E. W. *Tetrahedron Lett.* **1986**, *27*, 2687. Tietz, L. F.; Grote, T. *Chem. Ber.* **1993**, *126*, 2733.

(20) CBI-based analogs: Boger, D. L.; Yun, W. *J. Am. Chem. Soc.*, in press. Boger, D. L.; Munk, S. A. *J. Am. Chem. Soc.* **1992**, *114*, 5487. Boger, D. L.; Munk, S. A.; Ishizaki, T. *J. Am. Chem. Soc.* **1991**, *113*, 2779. Synthesis: Boger, D. L.; Ishizaki, T.; Wysocki, R. J., Jr.; Munk, S. A.; Kitos, P. A.; Suntornwat, O. *J. Am. Chem. Soc.* **1989**, *111*, 6461. Boger D. L.; Ishizaki, T.; Kitos, P. A.; Suntornwat, O. *J. Org. Chem.* **1990**, *55*, 5823. Boger, D. L.; Ishizaki, T. *Tetrahedron Lett.* **1990**, *31*, 793. Boger, D. L.; Ishizaki, T.; Zarrinmayeh, H.; Kitos, P. A.; Suntornwat, O. *BioMed. Chem. Lett.* **1991**, *1*, 55. Boger, D. L.; Ishizaki, T.; Sakya, S. M.; Munk, S. A.; Kitos, P. A.; Jin, Q.; Besterman, J. M. *BioMed. Chem. Lett.* **1991**, *1*, 115. Drost, K. J.; Cava, M. P. *J. Org. Chem.* **1991**, *56*, 2240. Boger, D. L.; Yun, W.; Teegarden, B. R. *J. Org. Chem.* **1992**, *57*, 2873. Aristoff, P. A.; Johnson, P. D. *J. Org. Chem.* **1992**, *57*, 6234. Aristoff, P. A.; Johnson, P. D.; Sun, D. *J. Med. Chem.* **1993**, *36*, 1956.

(21) C_2BI-based analogs: Boger, D. L.; Palanki, M. S. S. *J. Am. Chem. Soc.* **1992**, *114*, 9318. Boger, D. L.; Johnson, D. S.; Palanki, M. S. S.; Kitos, P. A.; Chang, J.; Dowell, P. *Bioorg. Med. Chem.* **1993**, *1*, 27.

(22) Boger, D. L.; Sakya, S. M. *J. Org. Chem.* **1992**, *57*, 1277. Boger, D. L.; Invergo, B. J.; Coleman, R. S.; Zarrinmayeh, H.; Kitos, P. A.; Thompson, S. C.; Leong, T.; McLaughlin, L. W. *Chem.-Biol. Interact.* **1990**, *73*, 29. 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.

(23) Reviews of *p*-quinonemethides: Volod'kin, A. A.; Ershov, V. V. *Russ. Chem. Rev.* **1988**, *57*, 336. Turner, A. B. *Quart. Rev.* **1964**, *18*, 347. Moore, H. W. *Science* **1977**, *197*, 527. Moore, H. W.; Czerniak, R.; Hamdan, A. *Drugs Exptl. Clin. Res.* **1986**, *12*, 475.

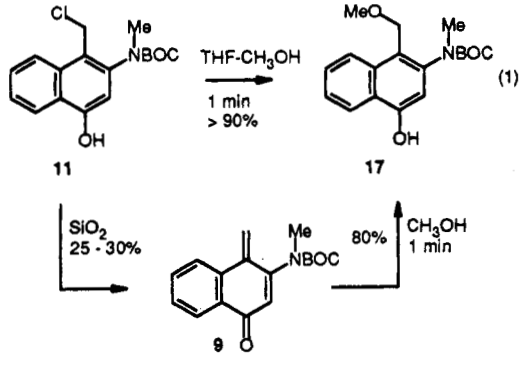
Table 1. Solvolysis of 4–8 and 11

agent	$t_{1/2}$ (pH 3)[a]	$t_{1/2}$ (pH 7)[a,b]	IC_{50} (μM, L1210)[c]
5	177 h	stable	0.006
7	133 h	stable	0.08
4	37 h	stable	0.3
6	11 h	nt	2.0
8	0.01 h	5.2 h	18
9	nt	<1 min	nt
11	nt	<1 min	>100

[a] Taken from refs 14, 19, 20. [b] Followed spectrophotometrically in 1:1 H_2O–CH_3OH (for **4–8**) or by TLC in CH_3OH or 1:2 THF–CH_3OH (for **9** and **11**, respectively). [c] Inhibitory concentration (IC_{50}) for 50% L1210 cell growth relative to untreated controls.

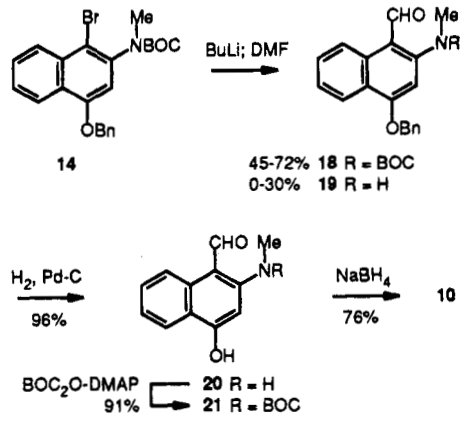
conversions. Lower conversions to **15** were experienced when shorter metalation times or stoichiometric (1.1 equiv) and smaller excesses (1.6 equiv) of *n*-BuLi were employed or when dimethyl carbonate (25–40%) was used as the electrophile. Subjection of **15** to catalytic hydrogenolysis provided the phenol **16** (95–100%). Although attempts to reduce **16** to the primary alcohol **10** directly with conventional reagents including $LiAlH_4$, $LiBH_4$, or $NaBH_4$ were not especially successful, treatment of **16** with Dibal-H (3.2 equiv, CH_2Cl_2, −78 to 0 °C, 2 h, 83%, typically 70–80%) provided a clean conversion to **10**. Alcohol **10** proved stable even in CH_3OH (>3 d) but slowly reacted with CH_3OH–H_2O. Conversion of the stable alcohol **10** to the exceptionally reactive chloride **11** (97%) was accomplished best with treatment with NCS–Ph_3P. Use of larger excesses of reagent than reported provided lower conversions and the use of Ph_3P–CCl_4 led to isolation of the corresponding triphenylphosphonium salt (>90%).

The chloride **11** proved unstable to storage even at −10 °C and was found to undergo clean methanolysis under exceptionally mild conditions (1:2 THF–CH_3OH, 25 °C, $t_{1/2}$ < 1 min) to provide **17** (90–100%) (eq 1). In addition



to providing indirect evidence of the mild, rapid generation of the *p*-quinonemethide **9**, the studies served to establish the relative solvolytic reactivity of **11** versus that of **4-8**, Table 1. The chloride **11** proved to be much more reactive than even the exceptionally reactive *N*-BOC-CI analog **8** of the CC-1065 and duocarmycin alkylation subunits. When the generation of **11** was followed by a standard or slow versus rapid chromatography (SiO_2, 20–30% EtOAc-hexane) the yield of **11** diminished or it was found to be completely consumed during the purification. In such instances, conversions to the putative *p*-quinonemethide **9** was directly observed. The exceptionally reactive *p*-quinonemethide **9** could be isolated albeit in modest conversions (25–30%) and partially characterized. The structure of **9** was clear from its ^1H NMR ($CDCl_3$, 400 MHz) spectra. Although clean samples of **9** rapidly decomposed upon isolation and

Scheme 2



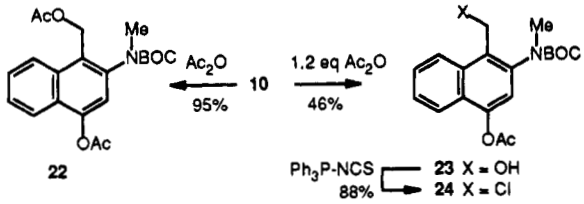
the samples of **9** were always contaminated with a little of the resulting polymeric material, its characteristic signals in the ^1H NMR spectrum were clear. The *p*-quinonemethide **9** exhibited characteristic signals at δ 6.48 (br d, J = 1.6 Hz, 1H) and 6.42 (br s, 1H) for the diagnostic exocyclic methylene protons and at δ 5.96 (s, 1H, C2-H) for the quinone methine proton in addition to sharp signals for each of the remaining aromatic protons and the *N*-methyl group (δ 3.24, s, 3H). Not surprisingly, the isolated agent **9** proved even more reactive than **11** toward methanolysis (Table 1; $t_{1/2}$ < 1 min, CH_3OH, 25 °C). The surprising ease of generation of **9** and its unusual stability relative to most *p*-quinonemethides[23] contributes to the unusual degree of instability found for **11** and may be attributed to the vinylogous amide stabilization that **9** enjoys. No doubt, this same vinylogous amide stabilization in **9** contributes to the unusual degree of stability observed with **1–3** and related structures.

In the conduct of efforts to prepare **10**, several alternatives to the optimized synthesis detailed in Scheme 1 were explored. Trap of the aryllithium intermediate generated by reaction of **14** with *n*-BuLi with paraformaldehyde failed to provide a product incorporating the corresponding hydroxymethyl group, but its reaction with DMF (−78 to 25 °C, 2–4 h, 45–72%) provided the aldehyde **18**[24] albeit in variable conversions, Scheme 2. Transmetalation with *n*-BuLi (2–2.5 equiv) generally proved more effective than *t*-BuLi (2.5–3 equiv), and a major byproduct generated in the reaction or upon workup proved to be **19**[24] derived from inadvertent deprotection of the especially labile carbamate. Hydrogenolysis of **18** or **19** (H_2, 10% Pd–C, EtOH or THF, 4–12 h, 96%) provided **20**[25] which, in the case of substrate **18**, is derived from both benzyl ether cleavage and ethanolysis or hydrolysis of the labile carbamate. Reintroduction of the *N*-BOC protecting group (4 equiv of BOC_2O, 3 equiv of DMAP, dioxane, 100 °C, 1 h, 91%) followed by reduction of the aldehyde **21**[25] (3.5 equiv of $NaBH_4$, EtOH, 25 °C, 30 min, 76%) also provided **10**. Attempts to acylate

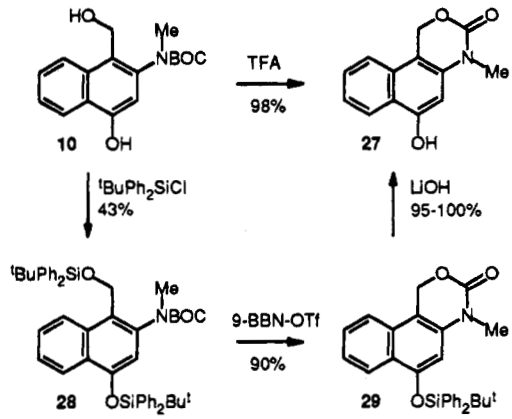
(24) For **18**: ^1H NMR ($CDCl_3$, 250 MHz) δ 10.29 (s, 1H). For **19**: ^1H NMR ($CDCl_3$, 400 MHz) δ 10.58 (s, 1H), 10.26 (br s, 1H), 8.19 (d, 1H, J = 9.1 Hz), 8.16 (d, 1H, J = 8.4 Hz), 7.4–7.5 (m, 6H), 7.22 (t, 1H, J = 7.1 Hz), 6.26 (s, 1H), 5.26 (s, 2H), 3.00 (d, 3H, J = 5.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 186.8, 161.2, 155.5, 136.5, 135.8, 129.4, 128.7, 128.4, 127.5, 123.6, 122.0, 119.3, 117.9, 103.0, 91.4, 70.3, 29.2.

(25) For **20**: ^1H NMR (acetone-d_6, 250 MHz) δ 10.61 (s, 1H), 8.33 (d, 1H, J = 5.5 Hz), 8.12 (d, 1H, J = 5.0 Hz), 7.47 (t, 1H, J = 5.3 Hz), 7.23 (t, 1H, J = 5.0 Hz), 6.49 (s, 1H), 2.99 (d, 3H, J = 3.0 Hz). For **21**: ^1H NMR ($CDCl_3$, 250 MHz) δ 10.42 (s, 1H), 9.25 (d, 1H, J = 10.4 Hz), 8.08 (d, 1H, J = 7.6 Hz), 7.70 (t, 1H, J = 8.5 Hz), 7.60 (t, 1H, J = 8.2 Hz), 7.31 (s, 1H), 3.38 (s, 3H), 1.61 (s, 9H).

Scheme 3



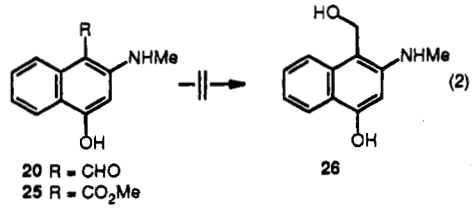
Scheme 4



20 with BOC_2O in the absence of DMAP led to recovered starting material.

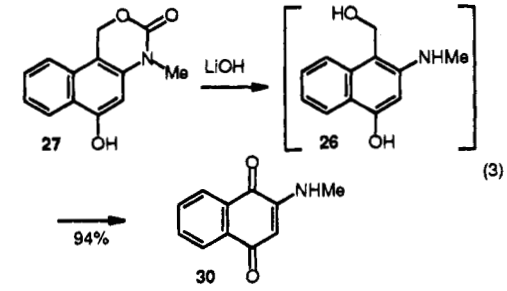
Several derivatives of **10** and **11** were prepared for direct comparison (Scheme 3). Treatment of **10** with excess Ac_2O provided the diacetate **22** (95%) while selective phenol acetylation was observed upon treatment of **10** with 1.2 equiv of Ac_2O (46%). Conversion of the primary alcohol **23** to the corresponding chloride **24** (88%) provided an agent that proved substantially more stable than **11** by virtue of its inability to directly generate the *p*-quinonemethide **9**. This substantially enhanced stability of **24** versus **11** provided the initial, albeit indirect, evidence that the unusually high solvolytic reactivity of **11** may be attributed to its intermediate generation of **9**. However, even **24** was found to slowly provide **17** (CH_3OH, 25 °C, 7 days) in a reaction that first proceeds by methanolysis of the phenolic acetate and subsequent solvolysis of **11**.

The linkage of **10** or **11** with the natural or modified DNA binding subunits of **1**–**3** through amide bond formation was viewed as being potentially successful only with the free alcohol **10** rather than with the reactive chloride present in **11**. Concurrent with the successful efforts to directly deprotect **10** described below, we investigated the potential direct reductions of the free amines **20** and **25**,[26] derived from *N*-BOC deprotection of **21** and **16** (3N HCl-EtOAc, 30 min, 25 °C, 97–100%), respectively. Attempted reduction of **25**, which was the most readily available precursor, with a range of reagents including $LiBH_4$, L- and K-Selectride, $LiAl(OBu^t)_3H$, $LiAlH_4$, or Dibal-H under a variety of mild reaction conditions failed to provide **26** (eq 2). When **25** was



subjected to more forcing reaction conditions, overreduction to the hydrocarbon was observed. Similarly, the attempted reduction of **20** with $NaBH_4$ (6 equiv, EtOH, 25 °C, 6 h) provided only recovered starting material while the use of more powerful reducing agents including $LiBH_4$ (10–35%) and $LiAlH_4$ (10–24%) failed to provide **26**.

Acid-catalyzed deprotection of **10** under a wide variety of conditions (3 equiv of TFA–CH_2Cl_2, 25 °C, 30 min, 98%; 4.5 equiv of TFA, EtOH, 25 °C, 15 min, 98%; concd HCl, CH_2Cl_2, 25 °C, 15 min, 66%) cleanly provided the cyclic carbamate **27** (Scheme 4). Formation of the bis *tert*-butyldiphenylsilyl ether **28**[27] (2.5 equiv of *t*-$BuPh_2SiCl$, 5 equiv of imidazole, DMF, 100 °C, 1 h, 43%) followed by acid-catalyzed (20% TFA–CH_2Cl_2, 25 °C, 30 min, 75%) or Lewis acid-catalyzed (2 equiv of 9-BBN-OTf, CH_2Cl_2, −78 °C, 15 min, 90%) deprotection cleanly provided **29**[27] where closure to the cyclic carbamate accompanies removal of the *N*-BOC group. Mild base hydrolysis of **29** (LiOH, CH_3OH, 25 °C, 10 min, 95–100%) provided **27**. Attempts to hydrolyze **27** (LiOH, THF–H_2O or CH_3CN–H_2O, 25 °C, 0.5–2 h) may have cleanly provided **26** but under the basic reaction conditions was rapidly converted to **30**[28] (eq 3).



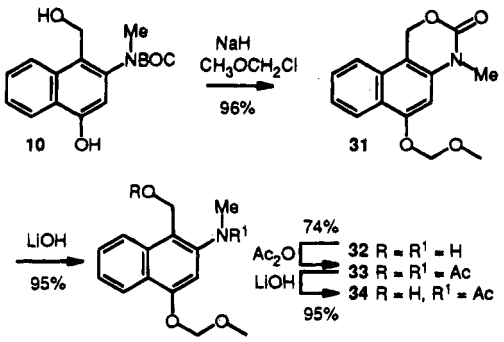
Consequently, removal of the *N*-BOC protecting group was found to be best conducted under conditions where the free phenol was first protected with a group readily removed under acidic conditions. Treatment of **10** with NaH–CH_3OCH_2Cl (96%) cleanly provided **31** resulting from phenol protection and base-catalyzed closure to the cyclic carbamate (Scheme 5). Mild hydrolysis of **31** (95–100%) provided **32** which proved unstable to storage and consequently was immediately acylated to provide **33**[28] (74%). Notably, this latter approach to **32** and its subsequent but immediate acylation potentially may be utilized for the preparation of more advanced analogs of CC-1065 and the duocarmycins.

(26) For **25**: ^1H NMR (acetone-d_6, 400 MHz) δ 8.53 (d, 1H, J = 8.0 Hz), 8.11 (d, 1H, J = 8.3 Hz), 7.40 (t, 1H, J = 7.8 Hz), 7.15 (t, 1H, J = 7.5 Hz), 6.54 (s, 1H), 3.89 (s, 3H), 2.94 (d, 3H, J = 5.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.2, 155.0, 136.3, 129.0, 125.8, 123.2, 121.4, 119.9, 95.6, 51.0, 30.0.

(27) For **28**: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.53 (d, 1H, J = 8.0 Hz), 8.18 (d, 1H, J = 8.3 Hz), 7.3–7.8 (m), 6.09 (s, 1H), 4.92 (d, 1H, J = 11.7 Hz), 4.85 (d, 1H, J = 11.7 Hz), 2.56 (s, 3H), 1.21 (s, 9H), 1.04 (s, 9H), 1.02 (s, 9H). For **29**: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.48 (d, 1H, J = 7.8 Hz), 7.75 (d, 4H, J = 8.0 Hz), 7.4–7.6 (m, 9H), 6.13 (s, 1H), 5.53 (s, 2H), 2.70 (s, 3H), 1.22 (s, 9H).

(28) For **30**: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.11 (dd, 1H, J = 1.3, 7.6 Hz), 8.05 (dd, 1H, J = 1.3, 7.6 Hz), 7.74 (ddd, 1H, J = 1.3, 7.6, 7.6 Hz), 7.62 (ddd, 1H, J = 1.3, 7.6, 7.6 Hz), 5.93 (br s, 1H), 5.73 (s, 1H), 2.94 (dd, 3H, J = 0.3, 5.4 Hz); IR (KBr) ν_{max} 3369, 1674, 1605, 1565, 1500, 1420, 1359, 1333, 1306, 1256, 1161, 1123, 1072 cm^{-1}; FABHRMS (NBA-NaI) m/z 188.0707 ($M^+ + H$, $C_{11}H_9NO_2$ requires 188.0712). Hydrolysis of **33** provided **34**: ^1H NMR ($CDCl_3$, 400 MHz) (major rotomer) δ 8.33 (d, 1H, J = 8.3 Hz), 8.23 (d, 1H, J = 8.4 Hz), 7.65 (dd, 1H, J = 7.0, 8.4 Hz), 7.67 (dd, 1H, J = 7.0, 8.3 Hz), 6.87 (s, 1H), 5.39 (s, 2H), 5.02 (s, 2H), 3.53 (s, 3H), 3.30 (s, 3H), 1.85 (s, 3H).

Scheme 5



Discussion

Preceding studies of simple derivatives of the CC-1065 and duocarmycin alkylation subunits and their analogs (**4**–**8**) have documented a near-linear relationship between chemical solvolytic stability and cytotoxic potency.[14,20,29] The chloride **11**, which serves as a precursor to the inherently unstable *p*-quinonemethide **9**, proved to be an exceptionally reactive agent which was found to undergo solvolysis much faster than even *N*-BOC-CI (**8**). Consistent with this exceptional level of reactivity, **11** failed to exhibit cytotoxic activity (Table 1).[30] Relative to almost all *p*-quinonemethides, **9** proved to be remarkably stable and even isolable. This unusual degree of stability may be attributed to the vinylogous amide stabilization enjoyed by **9** and its naphtho- versus benzo-*p*-quinonemethide structure. These structural features, which serve to stabilize **9**, no doubt contribute similarly to the unusual stability of **1**–**3**. In spite of this remarkable degree of stability, **9** proved to be a very reactive agent ($t_{1/2}$ < 1 min, CH_3OH, 25 °C) relative to **4**–**8**. Moreover, this stability of **9** no doubt contributes to its ease of generation from **11** and the unusual degree of instability of such precursors.

Efforts on the incorporation of **10** and **11** into structural analogs of **1**–**3** and the examination of their properties are in progress as are the continued exploration of structural modifications of the CC-1065 and duocarmycin alkylation subunits, and the results of these studies will be reported in due course.

Experimental Section

***N*-(*tert*-Butyloxycarbonyl)-4-(benzyloxy)-1-bromo-2-naphthylamine (13).** A solution of **12**[20] (2.33 g, 6.7 mmol) in 50 mL of THF under N_2 was cooled to −78 °C and treated with 4 drops of concentrated H_2SO_4 in 10 mL of THF. After the solution was stirred for 5 min (−78 °C), NBS (1.67 g, 9.4 mmol, 1.4 equiv) was added to the reaction mixture. The mixture was stirred for 5 h (−78 °C) and diluted with EtOAc (60 mL). The solution was washed with saturated aqueous $NaHCO_3$ (2 × 60 mL) and saturated aqueous NaCl (60 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (2.5 × 15 cm SiO_2, 5–10% EtOAc–hexane) afforded **13**[20] (2.77 g, 2.85 g theoretical, 97%) as a pale yellow solid: mp 111 °C (sharp, EtOAc–hexane, pale yellow plates, lit.[20] mp 111 °C (EtOAc–hexane); ^1H NMR ($CDCl_3$, 200 MHz) δ 8.28 (d, 1H, *J* = 8.5 Hz), 8.11 (dd, 1H, *J* = 1.8, 8.3 Hz), 8.10 (s, 1H), 7.4–7.6 (m, 8H), 5.29 (s, 2H), 1.58 (s, 9H); IR (KBr) ν_{max} 3407, 2979, 1735, 1625, 1601 cm^{-1}; EIHRMS *m*/*z* 427.0781 (M^+, $C_{22}H_{22}BrNO_3$ requires 427.0783).

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

2-[*N*-(*tert*-Butyloxycarbonyl)-*N*-methylamino]-4-(benzyloxy)-1-bromonaphthalene (14). A solution of **13** (2.05 g, 4.79 mmol) in 50 mL of anhydrous DMF under N_2 was treated with NaH (172 mg, 7.18 mmol, 1.5 equiv washed with hexanes, 3 × 5 mL). The mixture was stirred at 25 °C for 30 min with the evolution of H_2. The resulting slurry was treated with CH_3I (0.60 mL, 9.6 mmol, 2.0 equiv), and the mixture was stirred for 2 h at 25 °C. The reaction mixture was quenched with the addition of CH_3OH and concentrated under reduced pressure. The residue was suspended in saturated aqueous NH_4Cl (80 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (2.5 × 10 cm SiO_2, 0–10% EtOAc–hexane gradient elution) provided pure **14** (2.00 g, 2.12 g theoretical, 94%; typically 94–99%) as a pale yellow powder: mp 110 °C (sharp, hexane, pale yellow plates); ^1H NMR ($CDCl_3$, 400 MHz) (major rotomer) δ 8.34 (d, 1H, *J* = 8.5 Hz), 8.26 (d, 1H, *J* = 8.5 Hz), 7.3–7.6 (m, 7H), 6.75 (s, 1H), 5.22 (s, 2H), 3.20 (s, 3H), 1.31 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.3, 140.0, 136.2, 132.7, 128.5, 128.3, 128.1, 127.7, 127.5, 126.0, 125.7, 122.3, 113.7, 106.5, 70.3, 36.0, 28.2, 28.1; IR (film) ν_{max} 3067, 3033, 2976, 2929, 1703, 1620, 1593, 1504, 1403, 1367, 1342, 1252, 1231, 1153, 1100 cm^{-1}; FABHRMS (NBA-CsI) *m*/*z* 573.9980 (M^+ + Cs, $C_{23}H_{24}BrNO_3$ requires 573.9994).

Anal. Calcd for $C_{23}H_{24}BrNO_3$: C, 62.45; H, 5.46; N, 3.17. Found: C, 62.18; H, 5.61; N, 2.94.

Methyl 2-[*N*-(*tert*-Butyloxycarbonyl)-*N*-methylamino]-4-(benzyloxy)-1-naphthalenecarboxylate (15). A stirred solution of *n*-BuLi (2.66 mL, 5.98 mmol, 2.2 equiv) in anhydrous Et_2O (20 mL) at −78 °C under Ar was treated with a solution of **14** (1.20 g, 2.72 mmol) in anhydrous THF (10 mL). After 15 min at −78 °C, methyl chloroformate (2.1 mL, 27.2 mmol, 10 equiv) was added and the mixture was stirred for an additional 30 min at −78 °C. The mixture was allowed to warm to 25 °C (2 h) and was quenched with the addition of saturated aqueous $NaHCO_3$ (15 mL). The mixture was extracted with EtOAc (3 × 15 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (2.5 × 10 cm SiO_2, 20% EtOAc–hexane) provided pure **15** (905 mg, 1.15 g theoretical, 79%) as a colorless powder: mp 147 °C (sharp, EtOAc–hexane, colorless needles): ^1H NMR ($CDCl_3$, 400 MHz) (major rotomer) δ 8.35 (d, 1H, *J* = 8.0 Hz), 8.10 (d, 1H, *J* = 8.5 Hz), 7.3–7.6 (m, 7H), 6.66 (s, 1H), 5.25 (s, 2H), 3.95 (s, 3H), 3.21 (s, 3H), 1.31 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.6, 156.3, 154.4, 140.8, 136.1, 131.5, 128.6, 128.2, 127.8, 127.4, 125.7, 125.1, 124.4, 122.1, 121.4, 105.3, 80.2, 70.3, 52.1, 37.2, 28.0; IR (film) ν_{max} 2978, 2950, 1732, 1703, 1621, 1591, 1511, 1387, 1343, 1230, 1152, 1101, 1036, 1008, 983, 888, 771, 735, 698 cm^{-1}; FABHRMS (NBA-CsI) *m*/*z* 554.0964 (M^+ + Cs, $C_{25}H_{27}NO_5$ requires 554.0944).

Anal. Calcd for $C_{25}H_{27}NO_5$: C, 71.24; H, 6.46; N, 3.32. Found: C, 71.42; H, 6.64; N, 3.18.

Methyl 2-[*N*-(*tert*-Butyloxycarbonyl)-*N*-methylamino]-4-hydroxy-1-naphthalenecarboxylate (16). A solution of **16** (2.11 g, 5.01 mmol) and 10% Pd–C (200 mg) in EtOAc (50 mL) under H_2 was stirred for 16 h at 25 °C. The mixture was filtered through Celite (20 g), and the solvent was removed in vacuo. Flash chromatography (2.5 × 5 cm SiO_2, 30% EtOAc–hexane) provided pure **16** (1.66 g, 1.66 g theoretical, 100%) as a colorless powder: mp 203 °C (dec, EtOAc–hexane, colorless plates); ^1H NMR ($CDCl_3$, 400 MHz) (major rotomer) δ 8.75 (s, 1H), 8.31 (d, 1H, *J* = 8.2 Hz), 8.13 (d, 1H, *J* = 8.5 Hz), 7.58 (t, 1H, *J* = 7.2 Hz), 7.51 (t, 1H, *J* = 7.3 Hz), 6.52 (s, 1H), 3.99 (s, 3H), 3.24 (s, 3H), 1.33 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.0, 140.2, 132.1, 128.2, 127.6, 125.6, 125.3, 125.0, 124.7, 122.5, 108.6, 106.8, 52.3, 37.5, 28.1; IR (film) ν_{max} 3268, 2978, 1721, 1687, 1582, 1435, 1393, 1368, 1243, 1154, 774 cm^{-1}; FABHRMS (NBA-CsI) *m*/*z* 464.0479 (M^+ + Cs, $C_{18}H_{21}NO_5$ requires 464.0474).

(29) Boger, D. L.; Yun, W. *J. Am. Chem. Soc.* **1994**, *116*, 5523.

(30) In addition, **11** as well as **10**, **17**, **22**, and **27** failed to provide evidence of DNA alkylation when examined under protocols employed successfully for **4**-**8**. IC_{50} values (L1210) for the less reactive agents are as follows: **10** (10 μg/mL), **17** (50 μg/mL), **22** (50 μg/mL), **24** (0.6 μg/mL), **27** (50 μg/mL), and *O*-acetyl **27** (5 μg/mL).

Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.56; H, 6.39; N, 4.44.

3-[*N*-(*tert*-Butyloxycarbonyl)-*N*-methylamino]-4-(hydroxymethyl)-1-naphthol (10). A solution of **16** (189 mg, 0.57 mmol) in anhydrous CH_2Cl_2 (15 mL) was treated at −78 °C with Dibal-H (1.92 mL, 3.2 equiv, 1.0 M in toluene) under Ar. The mixture was stirred for 1.5 h at −78 °C, warmed to 0 °C, and stirred for an additional 1 h. The reaction mixture was quenched at 0 °C with the addition of saturated aqueous NH_4Cl (20 mL), and the aqueous slurry was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. Flash chromatography (2.5 × 5 cm SiO_2, 10−40% EtOAc−hexane gradient elution) provided pure **10** (144 mg, 173 mg theoretical, 83%) as a colorless powder: mp 168 °C (sharp, EtOAc−hexane, needles); ^1H NMR (acetone-d_6, 400 MHz) (major rotomer) δ 8.29 (d, 1H, J = 8.2 Hz), 8.26 (dd, 1H, J = 1.0, 8.3 Hz), 7.55 (dd, 1H, J = 7.3, 7.8 Hz), 7.48 (ddd, 1H, J = 1.2, 6.9, 8.2 Hz), 6.73 (s, 1H), 4.85 (m, 2H), 3.88 (t, 1H, J = 5.4 Hz), 3.21 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 154.3, 141.0, 134.8, 127.7, 127.4, 126.2, 125.9, 125.4, 108.3, 107.6, 79.9, 60.5, 38.2, 14.4; IR (film) ν_{max} 3276, 2977, 1668, 1587, 1403, 1368, 1153, 1085, 767 cm^{-1}; FABHRMS (NBA-CsI) m/z 436.0525 (M^+ + Cs, $C_{17}H_{21}NO_4$ requires 436.0525).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.52; H, 7.10; N, 4.41.

3-[*N*-(*tert*-Butyloxycarbonyl)-*N*-methylamino]-4-(chloromethyl)-1-naphthol (11). A solution of **10** (5.0 mg, 0.017 mmol) in anhydrous THF (1 mL) at 25 °C under N_2 was treated with Ph_3P (6.1 mg, 0.023 mmol, 1.4 equiv) and NCS (2.9 mg, 0.022 mmol, 1.3 equiv), and the resulting reaction mixture was stirred for 35 min (25 °C). Removal of the solvent under reduced pressure (0 °C) followed by rapid chromatography (SiO_2, 20−30% Et_2O−hexane gradient elution) provided pure **11** (5.2 mg, 5.4 mg theoretical, 97%) as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.12 (d, 1H, J = 8.4 Hz), 7.97 (d, 1H, J = 8.1 Hz), 7.59 (t, 1H, J = 7.5 Hz), 7.52 (t, 1H, J = 7.4 Hz), 7.09 (s, 1H), 4.95 (s, 2H), 3.23 (s, 3H), 1.26 (s, 9H).

***p*-Quinonemethide 9.** A solution of **10** (16.5 mg, 0.054 mmol) in anhydrous THF (1.5 mL) at 25 °C under N_2 was treated with Ph_3P (20.0 mg, 0.076 mmol) and NCS (9.4 mg, 0.071 mmol), and the resulting reaction mixture was stirred for 30 min (25 °C). Removal of the solvent under reduced pressure followed by standard chromatography (SiO_2, 20−30% EtOAc−hexane) provided **9** (4.0 mg, 15.5 mg theoretical, 26%) as an unstable, amorphous solid: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.21 (dd, 1H, J = 1.3, 7.8 Hz, C8-H), 7.95 (d, 1H, J = 7.8, C5-H), 7.65 (ddd, 1H, J = 1.3, 7.8, 7.8 Hz), 7.54 (dd, 1H, J = 7.8, 7.8 Hz), 6.48 (br d, 1H, J = 1.6 Hz, C=CH_2), 6.42 (br s, 1H, C=CH_2), 5.96 (s, 1H, C2-H), 3.24 (s, 3H, NCH_3), 1.40 (s, 9H, $OC(CH_3)_3$); ^1H NMR (DMSO-d_6, 400 MHz) δ 8.22 (d, 1H, J = 7.9 Hz), 8.03 (dd, 1H, J = 1.4, 7.9 Hz), 7.74 (ddd, 1H, J = 1.4, 7.9, 7.9 Hz), 7.60 (dd, 1H, J = 7.9, 7.9 Hz), 6.81 (d, 1H, J = 1.6 Hz), 6.49 (s, 1H), 5.97 (s, 1H), 3.17 (s, 3H), 1.33 (s, 9H); ^1H NMR (C_6D_6, 400 MHz) δ 8.42 (dd, 1H, J = 2.4, 7.0 Hz), 7.37 (dd, 1H, J = 2.4, 7.0 Hz), 7.04−7.11 (m, 2H), 6.33 (d, 1H, J = 1.6 Hz), 5.80 (d, 1H, J = 1.8 Hz), 5.52 (s, 1H), 2.79 (s, 3H), 1.26 (s, 9H).

3-[*N*-(*tert*-Butyloxycarbonyl)-*N*-methylamino]-4-(methoxymethyl)-1-naphthol (17). From 11. A solution of **11** (2.3 mg, 0.007 mmol) in anhydrous THF (1 mL) was treated at 25 °C with a saturated solution of $NaHCO_3$ in CH_3OH (1 mL). The reaction mixture was stirred for 30 s and quickly filtered and the solvent removed in vacuo to provide authentic **17** (1.9 mg, 2.1 mg theoretical, 90%) as an amporphous solid: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, 1H, J = 8.4 Hz), 8.14 (d, 1H, J = 8.4 Hz), 7.54 (t, 1H, J = 8.2 Hz), 7.47 (t, 1H, J = 7.0 Hz), 6.79 (s, 1H), 4.5−4.7 (m, 2H), 2.84 (s, 3H), 2.81 (s, 3H), 1.29 (s, 9H); ^1H NMR (acetone-d_6, 400 MHz) δ 8.23 (dd, 1H, J = 0.8, 8.0 Hz), 8.14 (dd, 1H, J = 0.8, 8.0 Hz), 7.54 (ddd, 1H, J = 0.8, 8.0, 8.0 Hz), 7.47 (ddd, 1H, J = 0.8, 8.0, 8.0 Hz), 6.73 (s, 1H), 4.74 (d, 1H, J = 10.9 Hz), 4.64 (d, 2H, J = 10.9 Hz), 3.34 (s, 3H), 3.15 (s, 3H), 1.29 (s, 9H); IR (film) ν_{max} 3290, 2971, 2931, 1664, 1624, 1585, 1400, 1366, 1151, 1092 cm^{-1}; FABHRMS (NBA-CsI) m/z 450.0681 (M^+ + Cs, $C_{18}H_{23}NO_4$ requires 450.0681).

A solution of **11** (1.9 mg, 0.006 mmol) in dry THF (0.5 mL) was treated at 25 °C under Ar with CH_3OH (1 mL). TLC assay of the mixture after 1 min revealed complete conversion to **17**. The solvent was removed under reduced pressure to provide **17** (1.8 mg, 1.8 mg theoretical, 100%) identical to that detailed above as the only detectable material in the solvolysis reaction mixture.

From 9. A solution of *p*-quinonemethide **9** (4.0 mg, 0.014 mmol) in CH_3OH (1 mL) was stirred for 1 min at 25 °C. The solvent was removed in vacuo, and the residue was purified by chromatography (SiO_2, 20% EtOAc−hexane) to provide pure **17** (3.5 mg, 4.4 mg theoretical, 80%) as an amorphous solid identical to that detailed above as the only characterizable material in the reaction mixture.

4-Acetoxy-1-(acetoxymethyl)-2-[*N*-(*tert*-butyloxycarbonyl)-*N*-methylamino]naphthalene (22). A solution of **10** (11 mg, 0.036 mmol) in pyridine (200 μL) under N_2 was treated with Ac_2O (200 μL) and warmed at 50 °C for 1 h. Removal of the solvent in vacuo and chromatography (SiO_2, 50% EtOAc−hexane) provided pure **22** (13 mg, 14 mg theoretical, 95%) as an amorphous solid: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.04 (d, 1H, J = 8.2 Hz), 7.91 (d, 1H, J = 8.4 Hz), 7.5−7.6 (m, 2H), 7.03 (s, 1H), 5.55 (d, 1H, J = 12.4 Hz), 5.45 (d, 1H, J = 12.2 Hz), 3.30 (s, 3H), 2.47 (s, 3H), 2.07 (s, 3H), 1.28 (s, 9H); IR (film) ν_{max} 2974, 1769, 1739, 1703, 1600, 1364, 1195, 1149 cm^{-1}; FABHRMS (NBA-NaI) m/z 410.1565 (M^+ + Na, $C_{21}H_{25}NO_6$ requires 410.1580).

4-Acetoxy-2-[*N*-(*tert*-butyloxycarbonyl)-*N*-methylamino]-1-(hydroxymethyl)naphthalene (23). A solution of **10** (15 mg, 0.050 mmol) in CH_2Cl_2 (1 mL) under N_2 was treated with Et_3N (8.3 μL, 0.060 mmol, 1.2 equiv) and Ac_2O (5.6 μL, 0.059 mmol, 1.2 equiv) at 25 °C and stirred for 1 h (25 °C). Removal of the solvent in vacuo and chromatography (SiO_2, 0−30% EtOAc−hexane gradient elution) provided pure **23** (7.9 mg, 17 mg theoretical, 46%) as a colorless solid and a small amount of **22** (3.3 mg, 17%). For **23**: mp 153−155 °C, ^1H NMR ($CDCl_3$, 400 MHz) δ 8.33 (d, 1H, J = 8.0 Hz), 7.88 (d, 1H, J = 7.9 Hz), 7.5−7.6 (m, 2H), 7.14 (s, 1H), 5.01 (d, 1H, J = 11.9 Hz), 4.81 (d, 1H, J = 11.9 Hz), 3.29 (s, 3H), 2.46 (s, 3H), 1.55 (s, 9H); IR (film) ν_{max} 3436, 1764, 1692, 1677, 1364, 1195, 1154 cm^{-1}; FABHRMS (NBA-NaI) m/z 368.1485 (M^+ + Na, $C_{19}H_{23}NO_5$ requires 368.1474).

Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.86; H, 6.67; N, 3.71.

4-Acetoxy-2-[*N*-(*tert*-butyloxycarbonyl)-*N*-methylamino]-1-(chloromethyl)naphthalene (24). A solution of **23** (4.1 mg, 0.012 mmol) in anhydrous THF (1 mL) at 25 °C under N_2 was treated with Ph_3P (12.5 mg, 0.048 mmol, 4 equiv) and NCS (6.3 mg, 0.048 mmol, 4 equiv), and the reaction mixture was stirred for 35 min (25 °C). Removal of the solvent under reduced pressure followed by rapid chromatography (SiO_2, 10−25% Et_2O−hexane gradient elution) provided pure **24** (3.8 mg, 4.3 mg theoretical, 88%) as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.20 (d, 1H, J = 8.3 Hz), 7.93 (d, 1H, J = 8.2 Hz), 7.5−7.7 (m, 2H), 7.07 (s, 1H), 5.00 (s, 2H), 3.29 (s, 3H), 2.47 (s, 3H), 1.26 (s, 9H); IR (film) ν_{max} 2964, 1769, 1703, 1369, 1200, 1154 cm^{-1}; FABHRMS (NBA-CsI) m/z 496.0292 (M^+ + Cs, $C_{19}H_{22}ClNO_4$ requires 496.0292).

6-Hydroxy-4-methyl-1*H*-naphth[2.1-*d*][1.3]oxazin-3(3*H*)-one (27). A solution of **10** (10 mg, 0.066 mmol) in anhydrous CH_2Cl_2 (1 mL) was treated at 25 °C with TFA (0.015 mL, 0.20 mmol, 3 equiv) and stirred under Ar for 30 min. Removal of the solvent under reduced pressure followed by recrystallization of the residue from isopropyl ether (2 mL) provided **27** (14.8 mg, 15.1 mg theoretical, 98%) as a colorless solid: mp 209−211 °C (dec, isopropyl ether, colorless plates); ^1H NMR (acetone-d_6, 400 MHz) δ 9.44 (br s, 1H), 8.23 (d, 1H, J = 8.5 Hz), 7.79 (d, 1H, J = 8.6 Hz), 7.55 (dd, 1H, J = 8.5, 8.5 Hz), 7.39 (dd, 1H, J = 8.6, 8.5 Hz), 6.84 (s, 1H), 5.59 (s, 2H), 3.36 (s, 3H); IR (film) ν_{max} 3295, 3064, 2924, 1698, 1594, 1552, 1372, 1272, 1157, 1093 cm^{-1}; FABHRMS (NBA) m/z 230.0810 (M^+ + H, $C_{13}H_{11}NO_3$ requires 230.0817).

Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.83; H, 5.22; N, 5.79.

6-(Methoxymethoxy)-4-methyl-1*H*-naphth[2.1-*d*][1.3]oxazin-3(3*H*)-one (31). A solution of **10** (22 mg, 0.073 mmol)

in anhydrous THF (1 mL) was treated at 25 °C under Ar with NaH (7.3 mg, 0.18 mmol, 2.5 equiv) and stirred for 5 min. The resulting bright orange solution was treated with CH_3OCH_2Cl (MOMCl, 11 μL, 0.15 mmol, 2 equiv), and the mixture was stirred for 30 min. The reaction mixture was extracted with saturated aqueous $NaHCO_3$ and the aqueous phase reextracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography (SiO_2, 0–50% EtOAc–hexane gradient elution) provided pure **31** (19 mg, 19.8 mg theoretical, 96%) as a pale yellow powder: mp 126 °C (sharp, EtOAc–hexane, colorless plates); ^1H NMR (acetone-d_6, 400 MHz) δ 8.25 (d, 1H, J = 8.4 Hz) 7.59 (d, 1H, J = 8.2 Hz), 7.54 (dt, 1H, J = 1.3, 7.5 Hz), 7.41 (ddd, 1H, J = 1.5, 6.7, 8.3 Hz), 6.90 (s, 1H), 5.57 (s, 2H), 5.41 (s, 2H), 3.55 (s, 3H), 3.46 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 154.3, 136.1, 129.3, 128.1, 124.1, 122.8, 122.1, 121.1, 106.0, 96.9, 95.0, 64.8, 56.4, 31.9, 28.2; IR (film) ν_{max} 3500, 3063, 2929, 2828, 1717, 1630, 1587, 1362, 1304, 1151, 1106, 958, 757 cm^{-1}; FABHRMS (NBA) m/z 274.1090 (M^+ + H, $C_{15}H_{15}NO_4$ requires 274.1079).

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53; N, 5.13. Found: C, 65.93; H, 5.55; N, 5.26.

1-(Hydroxymethyl)-4-(methoxymethoxy)-2-(methylamino)naphthalene (32). A solution of **31** (6.4 mg, 0.023 mmol) in THF (500 μL) and H_2O (500 μL) was treated under Ar with LiOH (9.8 mg, 0.23 mmol, 10 equiv) and stirred at 25 °C for 36 h. The mixture was diluted with H_2O (500 μL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to provide **32** (5.5 mg, 5.8 mg theoretical, 95%) as a pale oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.15 (dd, 1H, J = 1.0, 8.4 Hz), 7.86 (d, 1H, J = 8.7 Hz), 7.43 (ddd, 1H, J = 1.0, 6.8, 8.7 Hz), 7.18 (ddd, 1H, J = 1.0, 6.8, 8.4 Hz), 6.78 (s, 1H), 5.40 (s, 2H), 5.01 (s, 2H), 3.54 (s, 3H), 2.98 (d, 3H, J = 5.2 Hz); ^{13}C NMR (acetone-d_6, 100 MHz) δ 127.4, 124.1, 122.8, 122.5, 121.1, 120.8, 120.7, 96.5, 94.8, 68.0, 57.2, 56.2, 30.8, 25.6; IR (film) ν_{max} 3423, 2936, 2895, 2822, 1614, 1598, 1147, 1059, 759 cm^{-1}; FABHRMS (NBA) m/z 247.1196 (M^+, $C_{14}H_{17}NO_3$ requires 247.1208).

1-(Acetoxymethyl)-2-(*N*-acetyl-*N*-methylamino)-4-(methoxymethoxy)naphthalene (33). A solution of **31** (7.8 mg, 0.029 mmol) in THF (500 μL) and H_2O (500 μL) was treated under Ar with LiOH (6.0 mg, 0.14 mmol, 4.8 equiv) and stirred at 25 °C for 36 h. The solvent was then removed under reduced pressure, and the solid residue containing crude **32** was treated with Ac_2O (200 μL) and pyridine (300 μL). The reaction mixture was warmed to 50 °C for 10 min, and the solvent was removed in vacuo. Chromatography (SiO_2, 50–100% EtOAc–hexane gradient elution) provided pure **33** (7.0 mg, 9.5 mg theoretical, 74%) as a colorless oil: ^1H NMR (acetone-d_6, 400 MHz) δ 8.35 (dd, 1H, J = 1.6, 8.2 Hz), 8.11 (dd, 1H, J = 1.6, 8.2 Hz), 7.68 (dt, 1H, J = 1.6, 8.4 Hz), 7.62 (dt, 1H, J = 1.6, 8.3 Hz), 7.07 (s, 1H), 5.54 (d, 1H, J = 6.6 Hz), 5.52 (d, 1H, J = 6.6 Hz), 5.48 (d, 1H, J = 12.2 Hz), 5.39 (d, 1H, J = 12.2 Hz), 3.53 (s, 3H), 3.20 (s, 3H), 2.01 (s, 3H), 1.74 (s, 3H); IR (film) ν_{max} 3457, 2934, 1742, 1661, 1593, 1418, 1377, 1229, 1152, 1063, 957 cm^{-1}; FABHRMS (NBA-NaI) m/z 354.1310 (M^+ + Na, $C_{18}H_{21}NO_5$ requires 354.1317).

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Supplementary Material Available: ^1H NMR spectra of **9**, **11**, **22**, **24**, **32**, and **33** (7 pages). This material is contained in 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.