Synthesis and Chemistry of Quinone Methide Models for the Anthracycline Antitumor Antibiotics

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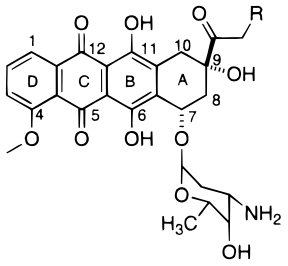
Received March 24, 1997[⊗]

In an effort to further understand the chemistry of anthracycline-type quinone methides, two tetracyclic *o*-quinone methides, 4,5,12-trimethoxy-11-[(trimethylacetyl)oxy]-9,10-dihydro-6(2*H*)-naphthacenone (**19**) and (±)-9-carbomethoxy-4,5,12-trimethoxy-11-[(trimethylacetyl)oxy]-9,10-dihydro-6(2*H*)-naphthacenone (**20**), were synthesized, and their reaction with several nucleophiles was investigated. Carbon- and sulfur-based nucleophiles afforded stable adducts while oxygen- and nitrogen-based nucleophiles afforded unstable adducts due to the reversibility of the addition. Adducts of **19** with ethanol and *O*-silylated adenosine (**27**) were acetylated to afford stable phenol acetates **21** and **29**, respectively.

Introduction

The anthracycline antitumor antibiotics, such as adriamycin and daunomycin, are an important class of cancer chemotherapeutic agents,[1] and yet their precise mode of action is not fully understood.[2] These compounds, which are known to be DNA intercalators,[3] may derive their anticancer activity via several different manifolds of action, including the following: (1) a radical based mechanism involving the formation of super oxide or other radicals from quinonoid redox chemistry;[4] (2) an intercalation-based pathway involving DNA topoisomerase II;[5] or (3) a mechanism involving alkylation of some critical biomolecule by a quinone methide,[6] or other reactive intermediate.[2d]



1 Daunomycin R = H
2 Adriamycin R = OH

There is considerable evidence to implicate both the topoisomerase[5]- and radical[4]-mediated pathways in the biological activity of the anthracyclines, but whether quinone methides are responsible for any of the biological activity of the anthracyclines, remains the subject of current research and discussion.[2,7] What is known is that upon reduction to the hydroquinone, the anthracyclines suffer loss of the sugar moiety to afford a biologically inactive aglycone.[6b] Thus, whether desirable or not, quinone methides are formed upon reduction of the quinone moiety of the anthracycline. It should be noted that even if the quinone methide is not related to the anticancer properties of the anthracyclines, it is important to understand the chemistry of these intermediates. Indeed, it has been proposed that the quinone methide intermediates might be responsible for some of the undesired cytotoxic properties of the anthracyclines such as their potent cardiotoxicity and play no role in the desired anticancer activity.[8]

In 1981, Moore formalized "bioreductive alkylation" to explain the biological activity of more than 200 quinone-containing compounds.[6] The process is proposed to occur via reduction of the quinone of an anthracycline such as adriamycin (**2**) to the corresponding hydroquinone (**3**) followed by loss of the sugar moiety to afford a quinone methide (**4**/**4′**, Scheme 1). There is conflicting evidence as to whether the quinone methide is more correctly represented as quinone methide **4** with a C-ring carbonyl, or tautomer **4′** with a B-ring carbonyl.[7] In either case, the quinone methide could serve as an electrophile toward a critical nucleophilic biomolecule, in what may be a reversible process. The resulting quinone methide−nucleophile adduct, **5**, could then be "trapped" by oxidation to the corresponding quinone, **6**.

The identity of the biological nucleophile(s), Nu, in the bioreductive alkylation process has been the subject of

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⊗ Abstract published in *Advance ACS Abstracts,* July 15, 1997.

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(2) Abdella, B. R. J.; Fisher, J. *Environ. Health Perspect.* **1985**, *64*, 3−18. (b) Lown, J. W. *Anthracycline and Anthracenedione-Based Anticancer Agents*; Elsevier: New York, 1988. (c) El Khadem, H. S., Ed. *Anthraycline Antibiotics*; Academic: New York; p 285. (d) For a current leading reference see: Taatjes, D. J.; Gaudiano, G.; Resing, K.; Koch, T. H. *J. Med. Chem.* **1996**, *39*, 4135−4138.

(3) (a) Nunn, C. M.; Van Meervelt, L.; Zhang, S.; Moore, M. H.; Kennard, O. *J. Mol. Biol.* **1991**, *222*, 167−177. (b) Chaires, J. B. *Biophys. Chem.* **1990**, *35*, 191−202. (c) Chaires, J. B.; Herrera, J. E.; Waring, M. J. *Biochemistry* **1990**, *29*, 6145−6153. (d) Wang, A. H.-J. In *Molecular Aspects of Anticancer Drug-DNA Interactions*; Neidel, S., Waring, M., Eds.; Topics in Molecular and Structural Biology; CRC: Boca Raton, 1993; Vol. 1, Chapter 2.

(4) (a) Imlay, J. A.; Linn, S. *Science* **1988**, *240*, 1302−1309. (b) Afanas'ev, I. B.; Polozova, N. I. *J. Chem. Soc., Perkin Trans. 2* **1987**, 835−839. (c) Lown, J. W.; Sin, S.-K.; Majumdar, K. C.; Chang, R.-Y. *Biochem. Biophys. Res. Commun.* **1977**, *76*, 705−710.

(5) (a) Volm, M.; Mattern, J. *Carcinogenesis* **1992**, *13*, 1947−1950. (b) Binaschi, M.; Capranico, G.; D. P.; Mariani, M.; Supino, R.; Tinelli, S.; Zunino, F. *Int. J. Cancer* **1990**, *45*, 347−352. (c) Wassermann, K.; Markovits, J.; Jaxel, C.; Capranico, G.; Kohn, K. W.; Pommier, Y. *Mol. Pharm.* **1990**, *38*, 38−45. (d) Bodley, A.; Liu, L. F.; Israel, M.; Seshadri, R.; Koseki, Y.; Guiliani, F. C.; Kirschenbaum, S.; Silber, R.; Potmesil, M. *Cancer Res.* **1989**, *49*, 5969−5978.

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(7) Gaudiano, G.; Frigerio, M.; Sangsurasak, C.; Bravo, P.; Koch, T. H. *J. Am. Chem. Soc.* **1992**, *114*, 5546−5553.

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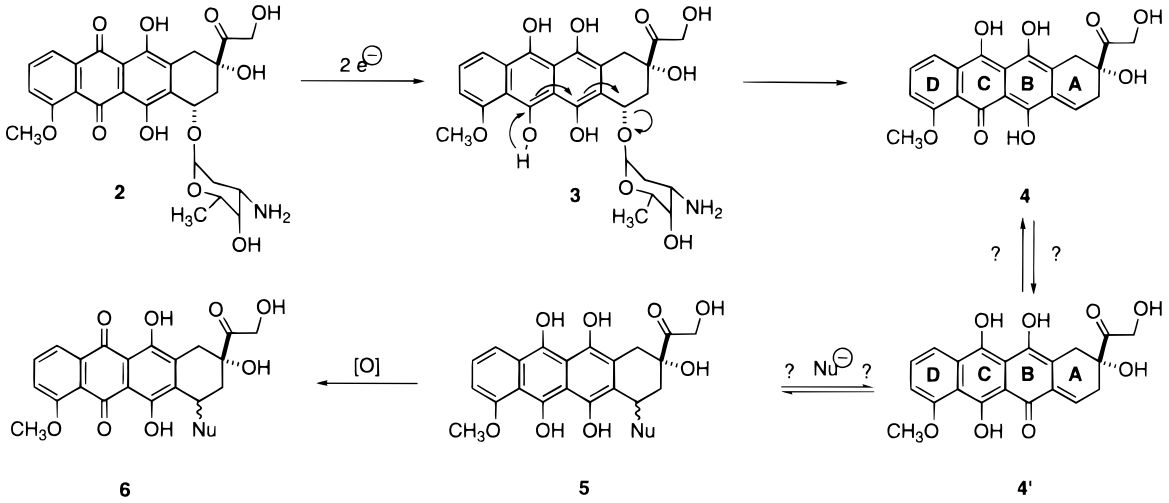
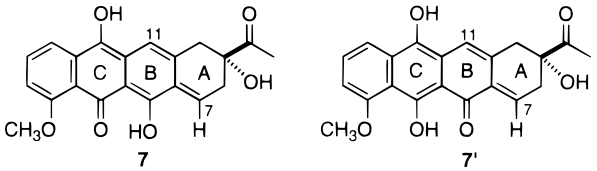
S0022-3263(97)00539-2 CCC: $14.00

Scheme 1. Proposed Mechanism of Bioreductive Alkylation[6]

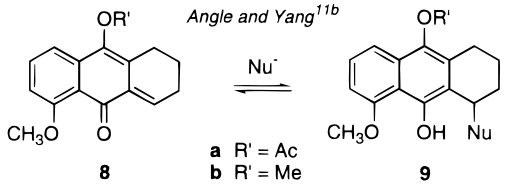


speculation. Those proposed include DNA, critical proteins/enzymes, and cell walls.[2] To date, there is only indirect evidence to indicate that a DNA base might function as a nucleophile toward an anthracycline quinone methide; however, efforts to study the quinone methides have been thwarted by the instability of these highly reactive compounds.[2,7,9] In spite of these difficulties, several researchers have made significant contributions toward understanding the details of the bioreductive pathway. For example, the Koch group[10] has demonstrated that upon reduction of the quinone moiety, the sugar can be lost to afford a quinone methide intermediate that can be observed by UV spectrometry and, in special cases, by ^{1}H NMR spectroscopy.[7] These anthracycline derived quinone methides are unstable intermediates which generally have half-lives of less than one minute making detailed study of their chemistry difficult if not impossible. An exception to this is 11-deoxydaunomycin derivative **7**/**7′**.[7] Koch and coworkers found that this quinone methide was stable in DMSO solution and obtained a ^{1}H NMR spectrum which showed a signal for the C(7)-methine hydrogen at δ 7.25, supporting the B-ring quinone methide **7′** rather than **7**, with a C-ring quinone methide carbonyl.[7]



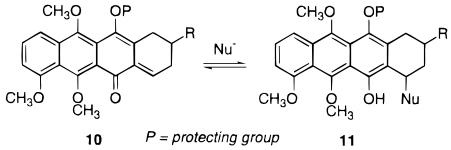
Research in our laboratory has focused on examining the role of quinone methides in the biological activity of the anthracycline antitumor antibiotics by constructing and studying simple model quinone methides.[11] The overall goal is to gain a firm understanding of the chemistry of the quinone methide intermediates, so that new anthracyclines might be designed to maximize the desired anticancer properties and minimize the undesired cytotoxic side effects.

Previously, we have reported the synthesis and study of two simple tricyclic anthracycline model quinone methides, **8**.[11] These tricyclic systems underwent facile reaction with a variety of nucleophiles (eq 1).[11] Our results showed that heteroatom-based nucleophiles such as aniline, ethanol, water, and thiols added reversibly to the quinone methide with the equilibrium favoring the adduct. For example, isolation of the crystalline aniline adduct, **9a** (Nu = PhNH), followed by solvation in acid-free $CDCl_3$ and standing for 20 min resulted in 5−8% of the adduct reverting to quinone methide **8a** by ^{1}H NMR analysis.[11b]



(eq 1)

We report here the synthesis of quinone methides **10** and an investigation of their reaction with a variety of nucleophiles. The protecting group "P" for the C(11)-phenol was initially planned to be an ester rather than an alkyl ether to provide stability to the quinone methide and inhibit air oxidation of the hydroquinone adducts, **11**.[11] In contrast to the anthracyclines which could have either a B- or C-ring quinone methide, **10** is constrained to be a B-ring quinone methide. Comparison of spectral data for these model compounds with that of Koch's 11-deoxydaunomycin derivative should provide additional evidence for or against a C-ring quinone methide. In addition, important information on the stability of anthracycline type quinone methide−nucleophile adducts and the reversibility of their formation should result.



(eq 2)

(9) (a) Fisher, J.; Abdella, B. R. J.; McLane, K. E. *J. Am. Chem. Soc.* **1985**, *111*, 1148−1150. (b) Fisher, J.; Abdella, B. R. J.; McLane, K. E. *Biochemistry* **1985**, *24*, 3562−3571. (c) Ramakrishnan, K.; Fisher, J. *J. Med. Chem.* **1986**, *29*, 1215−1221.

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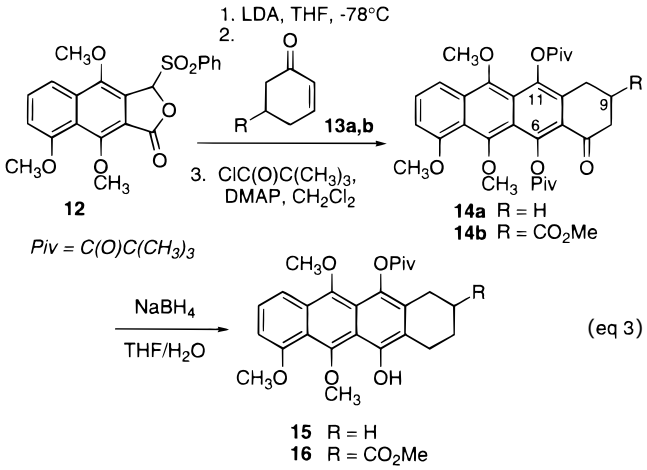
Results and Discussion

The precursors to the quinone methides were constructed using methodology developed by Hauser.[12] Annelation of the known[12] sulfone **12** with cyclohexenones **13a**,**b** followed by protection of the resulting hydroquinones as the bis-pivalates (eq 3) afforded dihydronaphthacenones **14a**,**b** in 58% and 40% yield, respectively. Benzylic ketone **14b** was far less stable than its C(9)-unsubstituted counterpart, **14a**, upon exposure to air for prolonged periods.



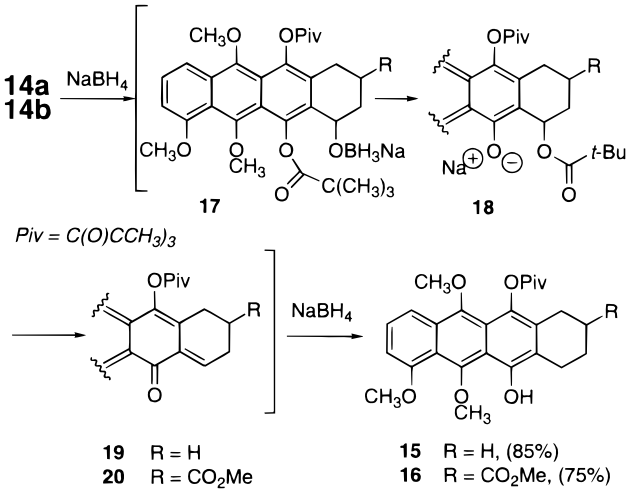
(eq 3)

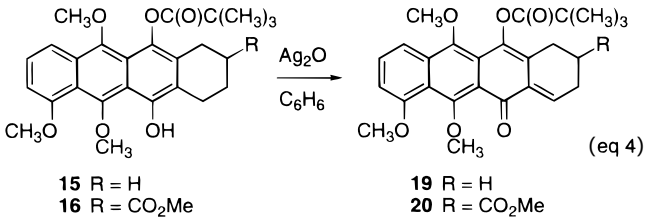
At this point, the C(7)-ketone needed to be reduced to a methylene group, and the C(6)-pivalate needed to be selectively removed in the presence of the C(11)-pivalate. This was accomplished in a single step upon treatment of **14** with $NaBH_4$ in aqueous THF to afford the monoprotected hydroquinones **15** and **16** in 59% and 75% yield, respectively. Interestingly, **16**, possessing a C(9)-ester substituent, appeared to be a 1:1 mixture of conformational isomers at room temperature as evidenced by the ^{1}H NMR spectrum which showed signals for two phenols at δ 10.75 and δ 10.74 and the ^{13}C NMR spectrum which showed two signals for many of the carbons in the molecule. Recording the NMR spectra at 80 °C resulted in coalescence of the resonances, and a single set of resonances was observed.

The mechanism for the monodeprotection/reduction reaction is thought to proceed via initial reduction of the ketone to benzylic borate **17** followed by intramolecular acyl transfer to form C(6)-phenoxide **18**. Elimination of sodium pivalate to afford quinone methides **19** and **20** followed by reduction with a second equivalent of $NaBH_4$ afforded the monoprotected hydroquinones **15** and **16**. A similar reaction was reported by Mitchell and co-workers after the completion of this portion of our work.[13] At this stage, the structure assignment of the pivalate at C(11), rather than C(6), was based on the mechanism of the reaction. This assignment was later confirmed by the analysis of the ^{1}H NMR spectrum of **26a** with substituents at both C(7) and C(9).

Monopivalates **15** and **16** were oxidized to quinone methides **19** and **20**, respectively, with silver(I) oxide (10 equiv) in refluxing benzene (eq 4). Upon completion of the oxidation (TLC monitoring), the reaction mixture was allowed to cool to rt and filtered through a pad of Celite to remove excess Ag_2O. Monitoring the oxidation by ^{1}H NMR spectroscopy showed the disappearance of the signal for the phenol, at δ 11.0 for **15** (C_6D_6) and at δ 10.76 for **16** ($CDCl_3$), and the concomitant appearance of a signal for the new C(7)-methine hydrogen at δ 7.37 (t, J = 4.6 Hz, C_6D_6) for **19** and δ 7.22 (t, J = 4.8 Hz, C_6D_6) for **20**. The chemical shift of the new (C7)-akylidene hydrogen on the quinone methides compares favorably with the δ 7.25 shift reported by the Koch group for 11-deoxydaunomycin quinone methide **7′**.[7] This similarity in the NMR shifts argues for adriamycin-derived quinone methide **4**/**4′** to be more correctly represented as the B-ring quinone methide **4′** rather than **4** (Scheme 1).

Scheme 2. Proposed Mechanism for the Reduction of 14





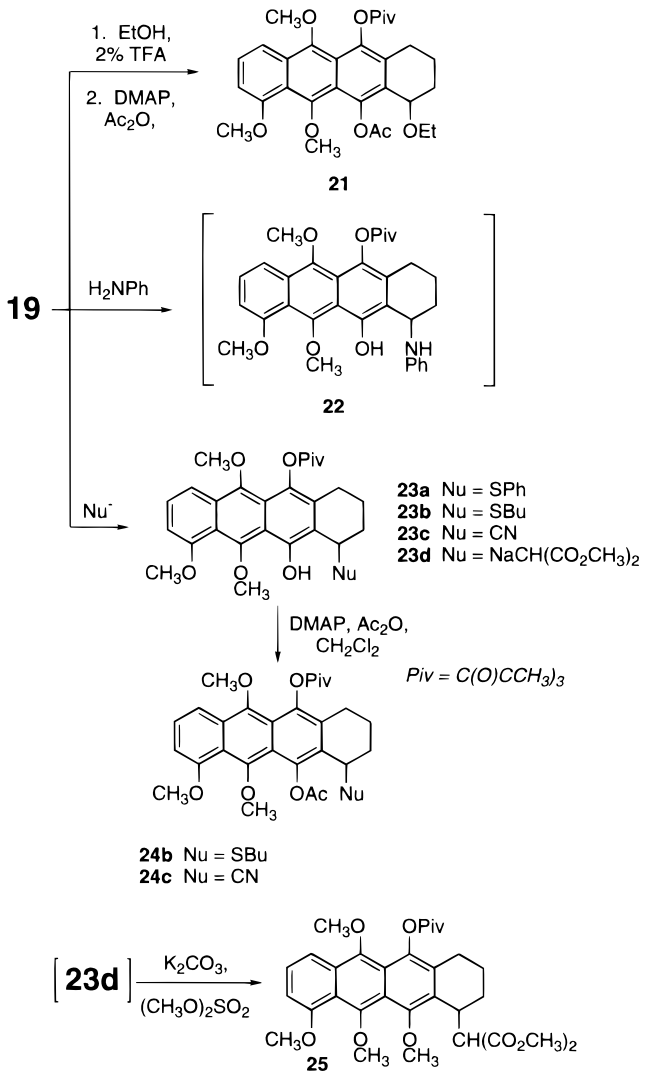
(eq 4)

Reaction of the Quinone Methides with Simple Nucleophiles. One of the first nucleophiles to be examined was ethanol. Stirring a deuterobenzene solution of **19** with 3 equiv of ethanol or a solution of **19** in ethanol resulted in recovery of starting material after 24 h (^{1}H NMR analysis). However, addition of 2 mol % trifluoroacetic acid to a solution of quinone methide **19** and ethanol, followed by stirring for 12 h, did afford the desired ethanol adduct (Scheme 3). This adduct proved to be quite unstable making purification impossible in our hands. Analysis of the crude product by ^{1}H NMR spectroscopy showed signals for the phenol at δ 11.14 and the C(7)-benzylic hydrogen at δ 5.28 and disappearance of the signal for the quinone methide C(7)-hydrogen at δ 7.27. Treatment of the crude ethanol adduct with acetic anhydride afforded the stable acetate **21** in 28% overall yield from phenol **15**. At room temperature, the ^{1}H NMR spectrum of **21** showed broad resonances for most of the hydrogens, indicating the possible presence of conformational isomers. When the spectrum was recorded at 100 °C, many of the signals sharpened considerably; however, there were still some broad resonances consistent with an active conformational equilibrium. For example, the C(7)-hydrogen appeared as two broad singlets at δ 4.85−

(12) (a) Hauser, F. M., Prasanna, S. *J. Am. Chem. Soc.* **1981**, *103*, 6378−6386.

(13) Mitchell, D.; Doecke C. W.; Hay, L. A.; Koenig, T. M.; Wirth, D. D. *Tetrahedron Lett.* **1995**, *36*, 5335−5338.

Scheme 3. Reaction of Quinone Methide 19 with Nucleophiles



4.75 and 4.70−4.60 at 24 °C (C_6D_6), and at 100 °C ($CD_3C_6D_5$) these two resonances coalesced to a broad singlet at δ 4.84−4.76, while the resonances for the remaining hydrogens in the A-ring on C(8)-, C(9)-, and C(10) were still quite broad. As will be shown below, the presence of conformational isomers is related to the acetoxy group on the C(6)-phenol.

In contrast to the sluggish reaction with ethanol, the reaction of **19** with aniline was extremely rapid. Treatment of a benzene solution of **19** with aniline (1.1 equiv) resulted in the immediate disappearance (^{1}H NMR) of the quinone methide (Scheme 3). The ^{1}H NMR spectrum of the reaction mixture showed a signal assigned as a phenol hydrogen at δ 11.09 consistent with the formation of **22**. Unfortunately, attempted purification or derivatization of **22** led to decomposition, and the adduct could not be characterized.

In contrast to alkoxy and amine adducts, thiol adducts of the quinone methide proved to be quite stable. Treatment of **19** with thiophenol resulted in an instantaneous reaction to afford **23a** in 29% yield after flash chromatography. The ^{1}H NMR spectrum of **23a** showed a signal for the C(7)-benzylic hydrogen at δ 5.47. In addition, the reaction of **19** with butanethiol afforded adduct **23b** in 27% yield (Scheme 3). Acetylation of the crude product afforded acetate **24b** in 30% yield. It is interesting to note that the ^{1}H NMR spectra of phenols **23a** and **23b** both showed the presence of one major conformer at 24 °C. However, at 24 °C the ^{1}H NMR spectrum of acetate **24b** showed two signals for the C(7)-methine hydrogen at δ 4.67 and δ 4.48 (C_6D_6) in a 2:1 ratio. Recording the spectrum at 100 °C resulted in these peaks coalescing to a single broad singlet at δ 4.53 ($CD_3C_6D_5$). This result is consistent with the ^{1}H NMR spectrum of acetylated ethanol adduct **21**. It is likely that acetylation of the C(6)-phenol introduces an $A^{1,3}$ interaction[14] with the pseudoequatorial C(7)-butylthio substituent in **24b**, resulting in the destabilization of the conformer with this substituent in the pseudoequatorial orientation relative to the alternative conformer with the butylthio group in the pseudoaxial conformation.

Carbon nucleophiles, dimethyl malonate, and cyanide ion were also examined. Treatment of **19** with lithium cyanide in DMF afforded **23c** in 35% yield (Scheme 3). Surprisingly, adduct **23c** appeared to be a 4:1 mixture of compounds (conformational isomers) at room temperature as determined by integration of the signals for the C(7)-methine hydrogens at δ 4.23 and 4.13 in the ^{1}H NMR spectrum. It occurred to us that the two compounds could be structural isomers of some type (e.g. nitrile−isonitrile), rather than conformational isomers. HPLC showed a single compound under a variety of conditions, and recording the ^{1}H NMR spectrum at 70 °C failed to lead to coalescence of the signals for the C(7)-methine hydrogen. To confirm the fact that the two compounds were indeed conformational isomers, and not structural isomers, the signal for the C(7)-methine hydrogen at δ 4.23 was irradiated, causing the signal for the other C(7)-hydrogen at δ 4.13 to disappear also. The reverse irradiation again caused the loss of both signals. As a control, irradiation at δ 4.03 and δ 4.33 (flat base line areas of the spectrum 0.10 ppm to each side of the resonances in question) with the same power as above resulted in no change in the ^{1}H NMR spectrum. These experiments show that the two compounds are indeed in equilibrium with each other. Since the interconversion of nitrile−isonitrile isomers is known to have a high activation energy and be slow at room temperature,[15] the two compounds must be conformational isomers. Acetylation of phenol **23c** afforded acetate **24c** in 48% yield. The signals in the ^{1}H NMR spectrum of acetate **24c** were broad; for example, there were two broad humps for the C(7)-methine hydrogen at δ 4.10−4.05 and δ 4.20−4.15 (C_6D_6, 300 MHz). Heating this sample to 100 °C led to coalescence of these signals into one broad singlet at δ 3.91 ($CD_3C_5D_5$, 500 MHz).

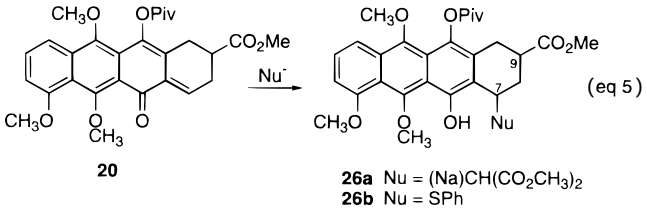
Treatment of **19** with the anion derived from treatment of dimethyl malonate with NaH afforded malonate derivative **23d** which was protected as the methyl ether (to facilitate isolation and purification) to afford **25** in 57% from **15** (Scheme 3).

The reactivity of C(9)-substituted quinone methide **20** was nearly identical to that of the C(9)-unsubstituted quinone methide, **19**. Reaction of **20** with the anion derived from treatment of dimethyl malonate with NaH afforded malonate derivative **26a** in 52% from phenol **16** with >5:1 diastereoselectivity by ^{1}H NMR analysis of the crude reaction mixture (eq 5). The *trans*-relative stere-

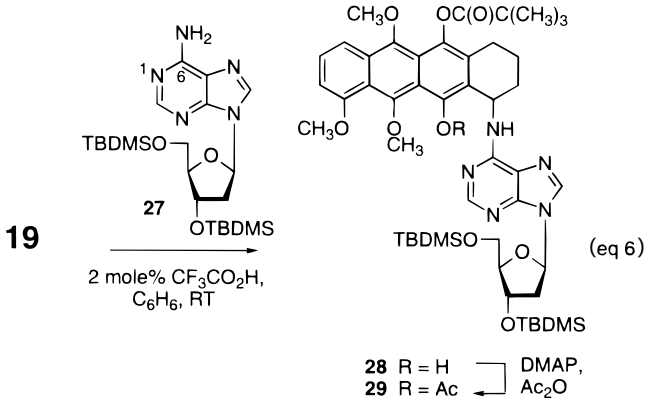
(14) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.
(15) Maloney, K. M.; Rabinovitch, B. S. In *Isonitrile Chemistry*; Ugi, I., Ed.; Organic Chemistry: A Series of Monographs; Academic: New York, 1971; Chapter 3.

ochemistry of **26a** was assigned to the major diastereomer on the basis of the ^{1}H NMR coupling constants of the A-ring hydrogens and ^{1}H−^{1}H decoupling experiments (see Supporting Information for details). Irradiation of the malonate methine hydrogen resulted in the collapse of the signal for the C(7)-benzylic methine hydrogen to a broad singlet (width at one-half height = 11.0 Hz). This showed that the C(7)-hydrogen was pseudoequatorial. One of the C(8)-hydrogens (H_{ax}) had two large coupling constants and one small coupling constant (J = 19.7, 11.7, 5.8 Hz). The small coupling constant was determined to be due to coupling to the C(7)-hydrogen, thereby indicating that the C(9)-hydrogen was pseudoaxial.

Reaction of **20** with thiophenol afforded adduct **26b** as a single diastereomer in 64% yield from **16** (eq 5). The relative stereochemistry of thio-adduct **26b** was assigned by analogy to **26a** and by the coupling constants of its A-ring hydrogens. The signal for the C(7)-hydrogen was a broad singlet (δ 5.18), indicating that it was pseudoequatorial (i.e. it was coupled to two hydrogens with small coupling constants for each). One of the C-8-pseudoaxial hydrogens was coupled to three hydrogens with two large and one small coupling constant (J = 13.1, 13.1, 3.3 Hz); this showed the C(9)-hydrogen must be pseudoaxial.



Reaction of Quinone Methide 19 with a Protected 2′-Deoxyadenosine. Since DNA has been proposed as a likely nucleophile toward anthracycline quinone methides, we elected to examine the reaction of **19** with a nucleoside. Since reaction of **19** with aniline and ethanol afforded unstable adducts, it was not clear that a nucleoside would be a viable nucleophile or afford stable, isolable products. To ensure that the adduct was formed through the heterocyclic base and not one of the sugar hydroxyls, TBDMS-protected 2′-deoxyadenosine **27** was prepared according to a procedure by Ogilvie.[16] The reaction of quinone methide **19** with 1.2 equiv of **27** in benzene-d_6 was followed by ^{1}H NMR spectroscopy (eq 6). No reaction occurred at concentrations ranging from 0.01 to 0.5 M. Addition of 2 mol % trifluoroacetic acid to a 0.5 M solution of **19** in benzene-d_6 followed by stirring for 12 h resulted in the formation of a 1:1 adduct of **19** and **27** by ^{1}H NMR analysis. Unfortunately, all attempts to isolate this adduct, believed to be a diastereomeric mixture of **28**, resulted in decomposition. The ^{1}H NMR spectrum of the crude adduct showed two signals for the phenol-hydrogen at δ 11.05 and 10.98. In an attempt to prove that adenosine derivative **27** had indeed reacted with **19**, the crude reaction mixture was concentrated and treated with acetic anhydride/DMAP to acetylate the phenol. Flash chromatography afforded the desired adduct **29** as a 1:1.6 mixture of diastereomers (HPLC) in 33% yield (eq 6). The diastereomers were separated by HPLC (t_R = 15.8 min, minor; 16.8 min, major) and characterized separately. The formation of an adduct was evident from the ^{1}H NMR spectra of the two diastereomers (pure by HPLC analysis) that clearly showed a 1:1 adduct had formed. In addition, mass spectral analysis showed the expected molecular ion at m/z 958 (MH^+; 28% minor diastereomer, 32, major diastereomer), and the correct exact mass. The connectivity of **29** was consistent with the fragmentation pattern in the mass spectrum which showed peaks at m/z 614 (5%, minor diastereomer; 6%, major diastereomer) for loss of the sugar portion of the nucleoside and 437 (100%, major and minor) for loss of the entire nucleoside. Unfortunately, detailed structural information was impossible due to the presence of conformational isomers for each diastereomer. For example, the NMR spectrum of the minor diastereomer (t_R = 15.8 min) showed broad signals for the C(7)-hydrogen and the *N*-H at δ 6.35 and δ 6.09. Homonuclear ^{1}H decoupling and ^{1}H−^{1}H COSY experiments failed to show the expected C(7)-hydrogen−C(8)-hydrogen coupling, and thus the signals for these hydrogens could not be assigned. The signals for the C(7)-hydrogen and *N*-H of the major diastereomer (t_R = 16.8 min) came at δ 6.37 and δ 6.15. Again, the resonances for these hydrogens could not be assigned.



The site of alkylation on the adenosine has been assigned as *N*(6) as shown, but the lack of X-ray quality crystals, the presence of conformers in the ^{1}H NMR spectra of both diastereomers precluding observation of coupling between the *N*(6)-hydrogen and the C(7)-hydrogen of the anthracycline, and the overlap of UV chromophores for the tetrahydronaphthacene and the adenosine make a rigorous structure proof impossible. Support for our assignment comes from our previous work in our laboratory that showed quinone methides **8** (eq 1) alkylated adenosine derivatives at the *N*(6)-position.[11b] Other possible sites of alkylation include the *N*(1)- and *N*(3)-positions and cannot be excluded as possible structures with the available information.

Conclusion

We have shown that protected B-ring quinone methide anthracycline type model quinone methides are stable intermediates that undergo reaction with a variety of nucleophiles. Comparison of the ^{1}H NMR chemical shift for the C(7)-alkylidene hydrogen of B-ring quinone methides **19** and **20** to that for Koch's 11-deoxydaunomycin derivative **7/7′** lends support for viewing adriamycin derived quinone methide **4/4′** as the B-ring quinone methide **4′** rather than the C-ring quinone methide **4**. The adducts formed upon reaction of **19** and **20** with nitrogen and oxygen-based nucleophiles were surpris-

(16) Ogilvie, K. K. *Can. J. Chem.* **1973**, *51*, 3799−3806.

ingly unstable and required acetylation of the phenol to allow isolation of the products. The instability of these adducts shows that if the mode of action of the anthracyclines does involve quinone methide intermediates, other factors such as favorable hydrogen bonding interactions, π-stacking interactions, and/or accessibility to an oxidizing agent that locks the nucleophile in position by formation of the quinone must be intimately involved. In light of our results, it is not surprising that an adriamycin quinone methide−DNA adduct has not been isolated. One would now expect such an adduct to be extremely unstable and be difficult, if not impossible, to isolate as a phenol derivative. The stability of the thiol adducts as unprotected phenols leads one to speculate that if quinone methide formation needs to be minimized for optimal anticancer activity with minimum side effects, perhaps anthracycline-thioglycoside derivatives should be screened for possible anticancer activity. The synthesis of such compounds is currently under investigation and will be reported in due course.

Experimental Section

General Information. NMR chemical shifts were reported in δ, parts per million (ppm), relative to chloroform ($\delta = 7.26$) or benzene ($\delta = 7.15$) as internal standards. Coupling constants, J, were reported in hertz (Hz) and refer to apparent peak multiplicities and not true coupling constants. Abbreviations used were as follows: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, p = pentuplet, m = multiplet. IR spectra were recorded on FT-IR. Mass spectra were recorded at the Southern California Mass Spectrometry Facility at UC Riverside and were reported as % relative intensity to the molecular base peak. Matrix abbreviations used were as follows: DCM = dichloromethane, NBA = nitrobenzyl amine, PPG = polypropylene glycol. Flash chromatography was carried out with E. Merck silica gel 60, 230−400 mesh. Purification with deactivated silica gel refers to silica gel which had been stirred with 5% NEt_3 and the eluting solvent for 1 h prior to use. TLC was performed on glass backed silica gel 60 plates (250 μm thickness, with a 254 nm fluorescent indicator). HPLC separations were carried out using RI detection. The following standard HPLC parameters were used: flow rate = 0.5 mL/min; column = 8 mm silica gel, 4.6 mm i.d. × 250 mm length. Ether, tetrahydrofuran (THF), and benzene were distilled from sodium/benzophenone. Pyridine, CH_3CN, CH_2Cl_2, $CHCl_3$, tetramethylethylenediamine (TMEDA), $(i\text{-}Pr)_2NEt$, and Et_3N were distilled from CaH_2. Toluene was distilled from $LiAlH_4$. *m*-CPBA, 50−65% from Aldrich Chemical Co., was washed with phosphate buffer (pH 7.5) prior to use. Phosphate buffer refers to pH 7.5 prepared by dissolving 1.2 g of KH_2PO_4 and 4.3 g of Na_2HPO_4 (anhydrous) in water and diluting to a volume of 1 L. Solvents for chromatography and recrystallization were distilled prior to use. The molarities indicated for alkyllithiums were established by titration with 2,5-dimethoxybenzyl alcohol.[17] Unless otherwise stated, all reactions were run under an atmosphere of argon in oven- or flame-dried glassware. Concentration refers to removal of solvent under reduced pressure (water aspirator) with a Büchi rotavapor. Deoxygenation refers to bubbling argon through a solution of the substrate at 0 °C for 30−60 min.

4,5,12-Trimethoxy-6,11-bis[(trimethylacetyl)oxy]-9,10-dihydronaphthacene-7-one (14a). *n*-BuLi (5.6 mL of a 1.4 M solution in heptane, 7.8 mmol) was added to a solution of diisopropylamine (1.17 mL, 8.4 mmol) and THF (20 mL) at 0 °C. The resulting solution was stirred at 0 °C for 30 min and then cooled to −78 °C. A slurry of sulfone **13** (1.58 g, 3.81 mmol) and THF (20 mL) was added dropwise through a large bore addition funnel, and the resulting purple mixture was stirred for 30 min at −78 °C. A solution of cyclohexenone (0.95 mL, 9.14 mmol) and THF (1 mL) was added, and the resulting golden brown mixture was stirred at −78 °C for 5 min. After removing the cooling bath, the reaction mixture was allowed to warm to rt and then heated at reflux (bath temp 90−100 °C) for 30 min; upon reaching rt the color of the reaction mixture was dark green, and after refluxing for 30 min the color was dark red. After cooling to 0 °C, the reaction mixture was acidified to ca. pH 5 (pH paper) with 1 N HCl, and the THF was removed in vacuo. The resulting bright red suspension was extracted with ethyl acetate (3 × 50 mL), washed with phosphate buffer (3 × 50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated to afford 1.14 g (81%) of crude 6,11-dihydroxy-4,5,12-trimethoxy-9,10-dihydronaphthacene-7-one as a red foam which was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (bs, 1 H), 7.76 (d, $J = 7.5$ Hz, 1 H), 7.37 (t, $J = 8.2$ Hz, 1 H), 6.70 (d, $J = 7.6$ Hz, 1 H), 3.93 (s, 3 H), 3.90 (s, 3 H), 3.85 (s, 3 H), 2.90 (t, $J = 6.1$ Hz, 2 H), 2.63 (t, $J = 6.3$ Hz, 2 H), 2.48−2.16 (2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.2, 160.8, 157.7, 156.5, 145.4, 138.4, 129.7, 129.6, 129.6, 128.4, 119.7, 116.7, 113.2, 109.9, 104.7, 63.7, 63.6, 56.2, 38.7, 22.7, 21.6, 19.0; IR ($CHCl_3$) 3400, 2942, 1709, 1395 cm^{-1}. A deoxygenated solution of the above hydroquinone (1.14 g, 3.10 mmol) and CH_2Cl_2 (20 mL) was added via cannula to a deoxygenated solution of 4-(dimethylamino)pyridine (DMAP) (2.51 g, 20.6 mmol) and CH_2Cl_2 (20 mL) at 0 °C. Pivaloyl chloride (1.3 mL, 10.3 mmol) was then added, and the resulting solution was stirred at 0 °C for 30 min and then allowed to warm to rt over 1 h. The reaction mixture was poured into phosphate buffer (50 mL) and extracted with CH_2Cl_2 (20 mL). The organic layer was dried ($MgSO_4$) and concentrated to afford 2.35 g of crude product as a red-orange oil. Flash chromatography (3:1 hexanes/ethyl acetate, deactivated silica gel) afforded 1.6 g (78% from sulfone) of **14a** as an orange solid. The solid was recrystallized from hexanes/ethyl acetate to give 1.18 g (58% from sulfone **12**) of **14a** a light orange amporphous powder: mp 194−195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, $J = 8.8$ Hz, 1 H), 7.40 (t, $J = 8.2$ Hz, 1 H), 6.78 (d, $J = 7.5$ Hz, 1 H), 3.97 (s, 3 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.14 (dt, $J = 16.8$, 5.2 Hz, 1 H), 2.76 (partially obscured dd, $J = 14.6$, 7.0 Hz, 1 H), 2.75−2.62 (m, 2 H), 2.18−2.10 (m, 2 H), 1.53 (s, 9 H), 1.50 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) 196.4, 177.5, 176.4, 157.1, 157.1, 157.0, 147.8, 146.5, 139.8, 130.8, 130.8, 129.1, 127.5, 121.2, 115.2, 105.9, 64.5, 63.4, 56.7, 41.0, 39.4, 39.5, 27.7, 27.6, 24.1, 21.6; IR ($CHCl_3$) 2936, 1745, 1686, 1366 cm^{-1}; MS (CI, NH3) *m/z* 537 (MH^+, 100), 453 (36); HRMS calcd for $C_{31}H_{37}O_8$ (MH^+) 537.2488, found 537.2512.

(±)-9-Carbomethoxy-4,5,12-trimethoxy-6,11-bis-[(trimethylacetyl)oxy]-9, 10-dihydronaphthacene-7-one (14b). The same procedure used for the preparation of **14a** was carried out with enone **13b** (282 mg, 1.83 mmol) and sulfone **12** (633 mg, 1.53 mmol) to afford 1.10 g (260%) of crude hydroquinone as a red oil which was used in the subsequent reaction without further purification: ^{1}H NMR (300 MHz, $CDCl_3$, 24 °C) δ 9.69 (s, 1 H), 7.69 (d, $J = 8.6$ Hz, 1 H), 7.48 (t, $J = 8.2$ Hz, 1 H), 6.81 (d, $J = 7.6$ Hz, 1 H), 4.00 (s, 3 H), 3.95 (s, 3 H), 3.94 (s, 3 H), 3.73 (s, 3 H), 3.62−2.60 (m, 5 H); IR ($CHCl_3$) 3344, 2955, 1732, 1362 cm^{-1}. Pivaloyl chloride (0.56 mL, 4.6 mmol) was added to a deoxygenated solution of the above crude hydroquinone (1.10 g), DMAP (1.1 g, 9.2 mmol), and CH_2Cl_2 (15 mL) at 0 °C. The resulting solution was stirred for 4 h and then poured into phosphate buffer (30 mL). The organic layer was dried ($MgSO_4$) and concentrated to afford a red oil. Flash chromatography (3:1 hexanes/ethyl acetate, deactivated silica gel) afforded 364 mg (40% from sulfone **12**) of **14b** as a red oil: ^{1}H NMR (300 MHz, $CDCl_3$, 24 °C) δ 7.82 (d, $J = 8.8$ Hz, 1 H), 7.40 (t, $J = 7.4$ Hz, 1 H), 6.78 (d, $J = 7.5$ Hz, 1 H), 3.96 (s, 3 H), 3.85 and 3.83 (s, 3 H), 3.75 (s, 3 H), 3.72 (s, 3 H), 3.52−2.78 (m, 5 H), 1.54 (s, 9 H), 1.52 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, 24 °C) δ 194.0, 193.7, 177.5, 176.4, 176.2, 173.3, 157.1, 157.0, 157.0, 153.9, 148.1, 146.6, 146.5, 140.1, 140.0, 131.0, 129.3, 129.0, 127.8, 126.4, 126.3, 121.3, 121.2, 119.7, 119.6, 115.1, 106.0, 105.9, 105.8, 64.6, 64.5, 63.5, 63.4, 56.6, 52.2, 42.5, 42.1, 39.5, 39.4, 38.3, 38.3, 27.8, 27.6, 27.5, 26.9, 26.7, 26.3; IR ($CHCl_3$) 2975, 1748, 1733, 1693, 1556,

(17) Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87.

1362 cm^{-1}; MS (CI, NH3) *m/z* 595 (MH^+, 100), 511 (38), 495 (23); HRMS calcd for $C_{33}H_{39}O_{10}$ (MH^+) 595.2543, found 595.2524.

6-Hydroxy-4,5,12-trimethoxy-11-[(trimethylacetyl)oxy]-7,8,9,10-tetrahydronaphthacene (15). Sodium borohydride (84 mg, 2.2 mmol) was added to a deoxygenated solution of bis-pivaloyl ester **14a** (198 mg, 0.37 mmol), water (250 μL), and THF (10 mL) at 0 °C. The reaction mixture was allowed to warm to rt over 30 min and was then poured into phosphate buffer (50 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to afford 215 mg crude **15** as a brown glass. Flash chromatography (3:1 hexanes/ethyl acetate, deactivated silica gel) afforded 98.4 mg (61%) of monopivalate **15** as a yellow-green glass: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.70 (s, 1 H), 7.82 (d, J = 8.8 Hz, 1 H), 7.30 (t, J = 8.2 Hz, 1 H), 6.74 (d, J = 7.4 Hz, 1 H), 4.05 (s, 3 H), 3.97 (s, 3 H), 3.83 (s, 3 H), 3.02−2.96 (m, 2 H), 2.82−2.72 (m, 1 H), 2.59−2.45 (m, 1 H), 1.96−1.72 (m, 4 H), 1.49 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 155.5, 148.3, 148.1, 147.6, 134.3, 129.6, 127.6, 125.1, 119.0, 118.0, 116.6, 115.6, 104.1, 100.9, 64.7, 63.2, 56.1, 39.4, 27.8, 24.4, 23.6, 22.5, 22.3; IR ($CHCl_3$) 3300, 2960, 1740 cm^{-1}; MS (CI, NH3) *m/z* 439 (MH^+, 100), 353 (56), 339 (33); HRMS calcd for $C_{26}H_{31}O_6$ (MH^+) 439.2121, found 433.2123.

(±)-9-Carbomethoxy-6-hydroxy-4,5,12-trimethoxy-11-[(trimethylacetyl)oxy]-7,8,9,10-tetrahydronaphthacene (16). Sodium borohydride (17 mg, 0.45 mmol) was added to a deoxygenated solution of bis-pivaloyl ester **14b** (45.0 mg, 0.076 mmol), water (90 μL), and THF (3 mL) at 0 °C. After 30 min the reaction mixture was poured into phosphate buffer (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (3:1 hexanes/ethyl acetate, deactivated silica gel) afforded 28.0 mg (74%) of **16** as an orange oil. Monoester **16** existed as a 1:1 mixture of conformational isomers at rt by ^{1}H NMR analysis: ^{1}H NMR (300 MHz, $CDCl_3$, 24 °C) δ 10.76 and 10.75 (s, 1 H), 7.82 (d, J = 8.8 Hz, 1 H), 7.30 (t, J = 8.2 Hz, 1 H), 6.74 (d, J = 7.5 Hz, 1 H), 4.04 (s, 3 H), 3.97 (s, 3 H), 3.84 and 3.84 (s, 3 H), 3.76 and 3.75 (3 H), 3.39−3.25 (m, 1H), 3.15−3.06 (m, 1 H), 2.91−2.64 (m, 2 H), 2.38−2.26 (m, 1 H), 1.95−1.56 (m, 1 H), 1.50 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, 24 °C) δ 176.9, 176.5, 175.8, 175.7, 157.4, 150.6, 150.5, 146.2, 146.0, 137.0, 136.8, 128.0, 126.3, 126.1, 125.3, 122.8, 122.4, 120.3, 119.7, 118.8, 115.3, 115.2, 104.9, 63.3, 63.3, 62.7, 62.6, 56.8, 51.8, 39.8, 39.4, 27.7, 27.8, 26.5, 26.3, 25.6, 18.8; IR ($CHCl_3$) 3300, 2957, 1734, 1558 cm^{-1}; MS (CI, NH_3) *m/z* 497 (MH^+, 100), 483 (21), 397 (39), 367 (18); HRMS calcd for $C_{28}H_{33}O_8$ (MH^+) 497.2175, found 497.2183

General Procedure for the Synthesis of Quinone Methide 19. Ag_2O (468 mg, 2.0 mmol, 10 equiv relative to phenol) was added to a stirred suspension of **15** (89 mg, 0.20 mmol), powdered 4 Å molecular sieves (weight approximately equal to amount of **15**), and benzene (1.5 mL, 0.13 M in phenol). The resulting suspension was heated to reflux, and the reaction progress was monitored by TLC for loss of starting material (2−12 h). When phenol **15** had been consumed, the reaction mixture was cooled, filtered through Celite, and used immediately. The solution of quinone methide was >95% pure by ^{1}H NMR analysis: ^{1}H NMR (300 MHz, C_6D_6) δ 7.74 (d, J = 8.5 Hz, 1 H), 7.37 (t, J = 4.6 Hz, 1 H), 7.17 (partially obscured t, J = 7.7 Hz, 1 H), 6.40 (d, J = 7.8 Hz, 1 H), 4.01 (s, 3 H), 3.56 (s, 3 H), 3.36 (s, 3 H), 2.61−1.64 (m, 6 H), 1.40 (s, 9 H).

General Procedure for the Synthesis of Quinone Methide 20. Ag_2O (160 mg, 0.70 mmol) was added to a solution of phenol **16** (23.0 mg, 0.0460 mmol), 4 Å molecular sieves, and benzene-d_6 (2 mL) and heated to reflux. The progress of the reaction was monitored by TLC and ^{1}H NMR for loss of starting material; after 3.5 h, the reaction mixture was filtered through Celite. The resulting orange solution containing quinone methide **20** was >90% pure (^{1}H NMR analysis) and was used immediately in the subsequent reactions: ^{1}H NMR (300 MHz, C_6D_6, 24 °C) δ 7.73 (d, J = 8.4 Hz, 1 H), 7.22 (t, J = 4.8 Hz, 1 H), 7.15 (partially obscured m, 1 H), 6.41 (d, J = 7.8 Hz, 1 H), 3.99 (s, 3 H), 3.56 (s, 3 H), 3.36 (s, 3 H), 3.27 (s, 3 H), 2.72−2.69 (m, 1 H), 2.38−2.31 (m, 2 H), 2.19−2.18 (m, 2 H), 1.41 (s, 9 H).

(±)-6-Acetoxy-7-ethoxy-4,5,12-trimethoxy-11-[(trimethylacetyl)oxy]-7,8,9, 10-tetrahydronaphthacene (21). Ethanol (10 mL, 0.17 mmol) and trifluoroacetic acid (12 μL of a 0.37 M solution of trifluoroacetic acid and benzene-d_6, 0.0044 mmol, 3.1 mol %) were added to a solution of quinone methide **19** [prepared from phenol **15** (63 mg, 0.14 mmol) and Ag_2O (333 mg, 1.4 mmol)] and benzene-d_6 (500 μL). After 12 h, ^{1}H NMR analysis showed adduct formation and loss of **19**. The reaction mixture was sparged to dryness with argon to afford crude adduct as a yellow-orange oil. This unstable phenol was protected as the corresponding acetate to facilitate handling and characterization. Aminopyridine (DMAP) (104 mg, 0.84 mmol) was added to a solution of the crude adduct and CH_2Cl_2 (500 μL) and the reaction cooled to 0 °C. Acetic anhydride (60 μL, 0.64 mmol) was added and the reaction monitored by TLC. After 30 min at 0 °C, the reaction mixture was poured into equal volumes of phosphate buffer (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to afford 79.4 mg crude **21** as an orange glass. Flash chromatography (1.5:1 hexanes/ethyl acetate, deactivated silica gel) afforded 20.5 mg (28%) of **21** as a yellow-green glass. An analytical sample was prepared by recrystallization (hexanes/ethyl acetate) and then purified by HPLC (1.5:1 hexane/ethyl acetate) to afford **21** as yellow-green crystals: mp 125−127 °C; ^{1}H NMR (300 MHz, toluene-d_8, 100 °C) δ 7.83 (d, J = 8.9 Hz, 1 H), 7.08 (partially obscured t, J = 7.8 Hz, 1 H), 6.45 (d, J = 7.4 Hz, 1 H), 4.84−4.76 (br s, 1 H), 3.80−3.40 (br m, 2 H), 3.70 (s, 3 H), 3.59 (s, 3 H), 3.56 (s, 3 H), 3.15−2.90 (br m, 1 H), 2.80−2.50 (br m, 1 H), 2.12 (s, 3 H), 1.65−1.52 (m, 2 H), 1.43 (s, 9 H), 1.48−1.30 (partially obscured m, 2 H), 1.19 (t, J = 7.0, 3 H); IR (CCl_4) 2958, 2937, 1772, 1752, 1363, 1198, 1114, 1087, 1059 cm^{-1}; UV (CH_3CN, 0.8 mg/50 mL) λ_{max} 204 (4.357), 228 (4.181), 268 (4.880), 364 (3.721), 382 (4.003), 404 (3.918), 426 (3.785); MS (FAB+, DCM/NBA) *m/z* 524 (M^+, 100), 480 (13), 437 (46), 421 (7), 353 (16), 337 (20), 323 (30); HRMS calcd for $C_{30}H_{36}O_8$ (M^+) 524.2410, found 524.2430.

(±)-6-Hydroxy-7-phenylthio-4,5,12-trimethoxy-11-[(trimethylacetyl)oxy]-7, 8,9,10-tetrahydronaphthacene (23a). A solution of thiophenol (17.5 μL, 0.17 mmol, 1.1 equiv) and benzene-d_6 (30 μL) was added to a solution of quinone methide [prepared from phenol **15** (65.8 mg, 0.15 mmol) and Ag_2O (346.9 mg, 1.50 mmol)] and benzene-d_6 (2.5 mL). After 10 min, the reaction mixture was sparged to dryness with argon to afford crude **23a** as a dark yellow oil. Flash chromatography (3:1 hexanes/ethyl acetate on deactivated silica gel) afforded 23.5 mg (29%) of **23a** as a yellow-green needles: mp 165−166 °C; ^{1}H NMR (300 MHz, C_6D_6, 24 °C) δ 11.45 (s, 1 H), 7.97 (d, J = 8.7 Hz, 1 H), 7.75 (d, J = 7.6 Hz, 2 H), 7.08 (partially obscured m, 5 H), 6.30 (d, J = 7.4 Hz, 1 H,), 5.47 (s, 1 H), 3.67 (bs, 3 H), 3.39 (s, 3 H), 3.35 (s, 3 H), 2.68−2.55 (m, 1 H), 2.52−2.40 (ddd, J = 17.7, 12.8, 5.7 Hz, 1 H), 2.10 (br d, J = 13.1, 1 H), 1.70−1.60 (br m, 2 H), 1.47 (s, 9 H); IR (CCl_4) 2956, 2937, 1747, 1451, 1374, 1276, 1118 cm^{-1}; MS (FAB+, $CHCl_3$/NBA/PPG) *m/z* 546 (M^+, 7), 437 (100), 422 (3), 351 (4), 323 (7); HRMS calcd for $C_{32}H_{34}O_6S$ (M^+) 546.2076, found 546.2071.

(±)-7-(Butylthio)-6-hydroxy-4,5,12-trimethoxy-11-[(trimethylacetyl)oxy]-7,8, 9,10-tetrahydronaphthacene (23b). Butanethiol (30 μL, 0.27 mmol, 1.5 equiv) was added to a solution of quinone methide [prepared from phenol **15** (79.5 mg, 0.18 mmol) and Ag_2O (419 mg, 1.81 mmol)] and benzene-d_6 (1.5 mL). After 5 min, the reaction mixture was sparged to dryness with argon to afford crude **23b** as an orange oil. Flash chromatography (3:1 hexanes/ethyl acetate) afforded 25.6 mg (27%) of **23b** as a yellow amorphous powder. Thio adduct **23b** existed as a 3:1 mixture of conformational isomers (based on integration of ^{1}H NMR for ArOH at δ 11.32 and 11.28) at rt: ^{1}H NMR (300 MHz, C_6D_6, 24 °C, major conformer) δ 11.32 (s, 1 H), 7.96 (d, J = 8.6 Hz, 1 H), 7.10 (obscured dd, J = 8.5, 7.5 Hz, 1 H), 6.30 (d, J = 7.5 Hz, 1 H), 5.00 (br s, 1 H), 3.65 (s, 3 H), 3.36 (s, 6 H), 2.76 (t, J = 7.4, 2 H), 2.65−2.45 (m, 1 H), 2.12 (br d, 1 H), 1.80−1.65 (m, 4 H), 1.47 (s, 9 H), 1.50−1.35 (partially obscured m, 4 H), 0.84 (t, 3 H); ^{13}C NMR (75 MHz, C_6D_6, 24 °C) δ 175.5, 155.7, 149.5, 149.1, 147.7, 134.9, 125.4, 119.8, 118.6, 116.9, 116.1, 115.4, 104.4, 63.8, 62.6, 55.3,

39.1, 38.9, 32.5, 32.1, 28.1, 27.6, 23.7, 22.2, 17.6 13.6; IR (CCl_4) 3300−3150, 2958, 2936, 1747, 1451, 1373, 1360, 1118 cm^{-1}; MS (FAB+, DCM/NBA) *m*/*z* 526 (M^+, 31), 453 (3), 437 (100), 351 (16), 323 (22) ; HRMS calcd for $C_{30}H_{38}O_6S$ (M^+) 526.2389, found 526.2391.

(±)-7-Cyano-6-hydroxy-4,5,12-trimethoxy-11-[(trimethylacetyl)oxy]-7,8,9,10-tetrahydronaphthacene (23c). Lithium cyanide (1.84 mL of a 0.5 M solution in dimethylformamide, 0.92 mmol) was added to neat quinone methide [prepared from phenol **15** (102.5 mg, 0.23 mmol) and Ag_2O (531 mg, 2.31 mmol)]; the reaction mixture underwent an immediate color change from green to red. After 10 min, the reaction mixture was poured into equal volumes of phosphate buffer (10 mL) and ethyl acetate (10 mL). The aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and subjected to flash chromatography (3:1 hexanes/ethyl acetate, deactivated silica gel) to afford 37.8 mg (35%) of **23c** as a yellow glass. The glass was recrystallized from hexanes/ethyl acetate to give an analytical sample of **23c** as a yellow amorphous powder (a 3:1 mixture of conformations based on ^{1}H NMR integration of C-7 H): mp 124−126 °C, dec; ^{1}H NMR (300 MHz, C_6D_6, 24 °C, major conformer) δ 11.32 (s, 1 H), 7.94 (d, J = 8.7 Hz, 1 H), 7.11 (partially obscured dd, J = 8.7 Hz, 1H), 6.29 (d, J = 7.4 Hz, 1 H), 4.23 (apparent δ and br s, J = 4.5 Hz, 1 H), 3.69 (s, 3 H), 3.35 (s, 3 H), 3.33 (s, 3 H), 2.97 (bd, J = 16.6 Hz, 1 H), 2.21 (ddd, J = 17.5, 12.4, 6.1 Hz, 1 H), 1.84−1.74 (br m, 2 H), 1.45 (s, 9 H), 1.27−1.20 (m, 1 H), 1.14−1.02 (ddd, J = 19.2, 13.8, 5.6 Hz, 1 H); ^{1}H NMR (300 MHz, C_6D_6, 24 °C, minor conformer, selected resonances) δ 11.34 (s, 1 H), 4.13 (br s, 1 H), 3.65 (s, 3 H), 3.25 (s, 3 H), 1.47 (s, 9 H); UV (CH_3CN, 0.9 mg/50 mL) λ_{max} nm 432 (2.980), 412 (3.141), 386 (3.320), 368 (3.062), 268 (4.192), 228 (3.366), 204 (3.651); IR (CCl_4) 3350−3150, 2958, 2936, 1749, 1455, 1452, 1436, 1375, 1360, cm^{-1}; MS (FAB+, DCM/NBA) *m*/*z* 463 (M^+, 100), 448 (4), 437 (15), 394 (2), 378 (56), 364 (18), 353 (14), 323 (5); HRMS calcd for $C_{27}H_{29}NO_6$ (M^+) 463.1995, found 463.2202.

(±)-6-(Acetyloxy)-7-(butylthio)-4,5,12-trimethoxy-11-[(trimethylacetyl)oxy]-7, 8,9,10-tetrahydronaphthacene (24b). (*N*,*N*-Dimethylamino)pyridine (DMAP) (71.9 mg, 0.58 mmol) was added to a solution of **23b** (25.6 mg, 0.049 mmol) and CH_2Cl_2 (250 μL) and the mixture cooled to 0 °C. Acetic anhydride (46 μL, 0.49 mmol) was added and the reaction monitored by TLC. After 5 min, the reaction mixture was poured into equal volumes phosphate buffer (10 mL) and CH_2Cl_2 (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to afford 24.9 mg of **24b** as an orange glass. Flash chromatography (3:1 hexanes/ethyl acetate on deactivated silica gel) afforded 16 mg of impure **24b**. HPLC purification (3:1 hexanes/ethyl acetate) afforded 8.2 mg (30%) of **24b** as a yellow amorphous powder: mp 153−154 °C; ^{1}H NMR (300 MHz, toluene-d_8, 100 °C) δ 7.82 (d, J = 8.7 Hz, 1 H), 7.08 (obscured t, J = 7.8, 1 H), 6.45 (d, J = 7.4, 1 H), 4.53 (br s, 1 H), 3.70 (s, 3 H), 3.58 (s, 3 H), 3.56 (s, 3 H), 3.20−3.00 (br m, 1 H), 2.49 (t, J = 7.0 Hz, 2 H), 2.45−2.25 (m, 1 H), 2.19 (br s, 3 H), 1.80−1.60 (m, 4 H), 1.60-1.47 (m, 2 H), 1.43 (s, 9 H), 1.40−1.20 (m, 2 H), 0.84 (t, J =7.3 Hz, 3 H); ^{13}C NMR (500 MHz, C_6D_6, 24 °C) δ 182.9, 157.0, 149.43, 129.0, 128.9, 128.8, 126.9, 126.8, 126.6, 126.2, 125.7, 115.2, 104.8, 63.2, 63.1, 62.8, 55.6, 55.5, 39.4, 39.2, 32.0, 31.8,31.6, 27.6, 27.2, 23.6, 22.2, 20.5, 16.7, 13.5; MS (FAB+, DCM/NBA) *m*/*z* 568 (M^+, 43), 479 (18), 437 (100), 352 (22), 323 (20); HRMS calcd for $C_{32}H_{40}O_7S$ (M^+) 568.2495, found 568.2520.

(±)-6-(Acetyloxy)-7-cyano-4,5,12-trimethoxy-11-[(trimethylacetyl)oxy]-7,8,9,10-tetrahydronaphthacene (24c). (Dimethylamino)pyridine (DMAP) (50.9 mg, 0.42 mmol) was added to a solution of **23c** (32.1 mg, 0.069 mmol) and CH_2Cl_2 (250 μL), and the solution was cooled to 0 °C. Acetic anhydride (30 μL, 0.31 mmol) was added and the reaction monitored by TLC. After 30 min, the reaction mixture was poured into equal volumes of phosphate buffer (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to afford crude **24c** as an orange glass. Flash chromatography (1.5:1 hexanes/ethyl acetate, deactivated silica gel) afforded 16.8 mg (48% from **23c**) of **24c** as a gold glass. An analytical sample was prepared by recrystallization from hexanes/ethyl acetate to afford **24c** as a yellow amorphous powder: mp 162−163 °C; ^{1}H NMR (500 MHz, toluene-d_8, 100 °C) δ 7.80 (d, J = 8.8 Hz, 1 H), 7.10 (t, J = 8.8 Hz, 1 H), 6.46 (d, J = 7.4 Hz, 1 H), 3.91 (br s, 1 H), 3.67 (s, 3 H), 3.60 (s, 3 H), 3.56 (s, 3 H), 2.24 (s, 3 H), 1.85−1.79 (m, 1 H), 1.76−1.70 (m, 1 H), 1.54−1.48 (m, 2 H), 1.43 (s, 9 H), 1.38 (m, 2 H); ^{13}C NMR (125 MHz, toluene-d_8, 100 °C) δ 175.5, 157.9, 150.4, 149.8, 148.4, 144.2, 142.5, 130.2, 126.7, 126.3, 121.2, 121.1, 120.9, 120.2, 120.1, 116.3, 107.0, 63.9, 63.6, 56.9, 39.9, 28.2, 27.9, 27.4, 26.9, 24.2, 19.7; IR (CCl_4) 2957, 2938, 1787, 1774, 1755, 1483, 1460, 1187, 1115, 809, 788, 771, 759, 755, 751 cm^{-1}; UV (CH_3CN, 1.0 mg/50 mL) λ_{max} nm 202 (4.349), 226 (4.267), 252 (4.367), 270 (4.654), 334 (3.14), 364 (3.448), 382 (3.707), 406 (3.626), 428 (3.497); MS (FAB+, DCM/NBA) *m*/*z* 505 (M^+, 100), 463 (36), 437 (8), 391 (10), 378 (45), 364 (21), 348 (11); HRMS calcd for $C_{29}H_{31}NO_7$ (M^+) 505.2100, found 505.2085.

(±)-7-(Dicarbomethoxymethyl)-4,5,6,12-tetramethoxy-11-[(trimethylacetyl)oxy]-9,10,11,12-tetrahydronaphthacene (25). NaH (12 mg, 0.47 mmol) was added to a solution of dimethyl malonate (0.57 mL, 0.57 mmol) and THF (5 mL) at 0 °C. After 15 min, a solution of quinone methide **20** [prepared from phenol **16** (94.0 mg, 0.189 mmol) and Ag_2O (437 mg, 1.89 mmol)] benzene-d_6 (3 mL), and THF (3 mL) were added dropwise. The resulting red reaction mixture was stirred for 30 min, poured into phosphate buffer (20 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to afford 130 mg of crude **23d** as a red oil. The unstable phenol, **23d**, was protected as the corresponding methyl ether to facilitate handling and characterization. Potassium carbonate (260 mg, 1.9 mmol) and dimethyl sulfate (35 μL, 0.57 mmol) were added to a deoxygenated solution of **23d** (130 mg) and acetone (25 mL). The resulting suspension was refluxed overnight. After cooling to rt, the resulting mixture was filtered to remove inorganic material, and the filtrate was concentrated to afford a brown oil. The oil was dissolved in ethyl acetate (100 mL) and washed with phosphate buffer (100 mL), dried ($MgSO_4$), and concentrated to afford crude **25** as a red oil. Flash chromatography (3:1 hexanes/ethyl acetate, deactivated silica gel) afforded 63.0 mg (57% from **15**) of **25** as an orange oil. Malonate adduct **25** existed as a 1:1 mixture of conformers at rt: ^{1}H NMR (300 MHz, $CDCl_3$, 24 °C) δ 7.82 (m, 1 H), 7.32 (t, J = 8.2 Hz, 1 H), 6.75 (d, J = 7.4 Hz, 1 H), 4.35 (d, J = 6.6 Hz, 1 H), 4.17−4.06 (m, 1 H), 4.04 (s, 3 H), 3.88 and 3.85 (s, 3 H), 3.85 (s, 3 H), 3.82 and 3.81 (s, 3 H), 3.69 (s, 3 H), 3.64 and 3.51 (s, 3 H), 3.05−2.95 (m, 1 H), 2.63−2.38 (m, 1 H), 2.09−1.62 (m, 4 H), 1.48 and 1.48 (s, 9 H); ^{13}C (75 MHz, $CDCl_3$, 24 °C) 176.4, 176.4, 169.4, 169.3, 169.1, 157.0, 156.9, 152.1, 151.8, 149.2, 147.0, 146.9, 138.8, 138.5, 130.9, 129.4, 128.8, 128.5, 128.4, 128.1, 127.0, 126.6, 125.6, 120.3, 120.1, 119.6, 119.2, 115.2, 115.0, 109.1, 104.4, 104.2, 63.9, 63.6, 63.5, 63.0, 62.2, 62.1, 56.5, 56.4, 55.5, 55.0, 52.3, 52.3, 52.1, 39.4, 33.5, 33.4, 27.9, 25.8, 25.4, 23.8, 23.2, 19.5, 18.4; IR ($CHCl_3$) 3017, 1736, 1365 cm^{-1}; MS (CI, NH3) *m*/*z* 583 (MH^+, 100), 451 (62), 365 (28); HRMS calcd for $C_{32}H_{39}O_{10}$ (MH^+) 583.2543, found 583.2559.

(±)-Methyl 7-[(Dicarbomethoxymethyl)-6-hydroxy-4,5,12-trimethoxy-11-[(trimethylacetyl)oxy]-7,8,9,10-tetrahydronaphthacene]-9-carboxylate (26a). NaH (15 mg, 0.6 mmol) was added to a solution of dimethyl malonate (80 μL, 0.7 mmol) and THF (5 mL) at 0 °C, and the resulting mixture was stirred for 15 min. A solution of quinone methide **20** [prepared from phenol **16** (23.4 mg, 0.047 mmol) and Ag_2O (108.6 mg, 0.47 mmol)], benzene-d_6 (3 mL), and THF (3 mL) was added dropwise. The resulting red reaction mixture was stirred for 30 min, poured into phosphate buffer (20 mL), and extracted with ether (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to afford crude **26a** as a red oil. Flash chromatography (3:1 hexanes/ethyl acetate followed by 1:1 hexanes/ethyl acetate, deactivated silica gel) afforded 15.0 mg (52% from **16**) of **26a** as a red oil (3:1 mixture of diastereomers, ^{1}H NMR): ^{1}H NMR (300 MHz, $CDCl_3$, 24 °C, major diastereomer) δ 11.0 (s, 1 H), 7.83 (d, J = 8.8 Hz, 1 H), 7.33 (t, J = 8.2 Hz, 1 H), 6.76 (d, J = 7.5 Hz, 1

H), 4.32−4.29 (m, 1 H), 4.17 (d, J = 7.0 Hz , 1H), 4.04 (s, 3 H), 3.95 (s, 3 H), 3.85 (s, 3 H), 3.70 (s, 3 H), 3.68 (s, 3 H), 3.66 (s, 3 H), 3.33 (dd, J = 17.3, 5.2, 1 H) , 3.03−2.91 (m, 1 H), 2.72 (dd, J = 17.2, 10.9 Hz, 1 H), 2.40 (d, J = 13.9 Hz, 1 H), 2.02 (ddd, J = 19.7, 11.7, 5.8 Hz, 1 H), 1.50 and 1.48 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, 24 °C, mixture of diastereomers) δ 176.6, 175.3, 169.5, 169.4, 169.4, 155.5, 149.3, 148.6, 147.7, 147.6, 134.6, 134.5, 130.9, 128.8, 128.4, 127.1, 125.7, 119.5, 116.9, 115.9, 115.6, 115.5, 115.4, 64.8, 64.8, 63.5, 63.2, 56.2, 54.3, 53.5, 52.4, 52.3, 52.2, 51.9, 39.4, 35.4, 35.3, 32.4, 32.1, 29.7, 29.6, 29.4, 29.4, 28.1, 27.8, 27.7, 27.7, 27.6, 27.4, 27.3, 27.3, 27.2, 26.1; IR ($CHCl_3$) 2956, 1734, 1372 cm^{-1}; MS (CI, NH3) 644 (M + NH_4^+, 19), 626 (13), 512 (21), 495 (100), 393 (24); HRMS calcd for $C_{33}H_{42}O_{12}N$ (M + NH_4^+) 644.2707, found 644.2723.

(±)-9-Carbomethoxy-6-hydroxy-7-(phenylthio)-4,5,12-trimethoxy-11-[(trimethylacetyl)oxy]-7,8,9,10-tetrahydronaphthacene (26b). Thiophenol (10 mL, 0.093 mmol) was added to a solution of quinone methide **20** [prepared from phenol **16** (22.9 mg, 0.046 mmol) and Ag_2O (106.3 mg, 0.46 mmol)] (0.0460 mmol) and benzene-d_6 at 0 °C. After 5 min the reaction mixture was poured into phosphate buffer (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to afford crude **26b** as an orange oil. Flash chromatography (3:1 hexanes/ethyl acetate, deactivated silica gel) afforded 18.0 mg (64% from **16**) of thio-adduct **26b** as an orange oil (3:1 mixture of diastereomers, ^{1}H NMR): ^{1}H NMR (300 MHz, $CDCl_3$, 24 °C, major diastereomer) δ 11.2 (s, 1 H), 7.84 (d, J = 8.7 Hz, 1 H), 7.65 (d, J = 7.0 Hz, 2 H), 7.37−7.28 (m, 4 H), 6.78 (d, J = 7.3 Hz, 1 H), 5.19 (bs, 1 H), 4.05 (s, 3 H), 3.99 (s, 3 H), 3.85 (s, 3 H), 3.74 (s, 3 H), 3.67−3.56 (m, 1 H), 3.48 (dd, J = 16.4, 5.6 Hz, 1 H), 3.02 (d, J = 9.1 Hz, 1 H), 2.60 (dd, J = 17.5, 12.4 Hz, 1 H), 2.40 (d, J = 13.5 Hz, 1 H), 1.95 (apparent dt, J = 13.1, 3.3 Hz, 1H), 1.52 and 1.49 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, 24 °C, mixture of diastereomers) δ 176.7, 176.1, 175.8, 155.6, 149.9, 149.0, 147.6, 136.1, 135.9, 134.6, 132.6, 132.6, 128.9, 128.9, 128.5, 128.4, 127.2, 127.1, 126.5, 126.3, 125.9, 119.7, 116.9, 116.8, 115.7, 115.5, 114.5, 104.6, 104.5, 65.0, 64.9, 63.6, 63.2, 56.2, 51.9, 43.7, 43.4, 39.4, 34.6, 34.5, 30.2, 30.1 27.8, 27.7, 26.3, 26.2; IR ($CHCl_3$) 3300 (br), 2959, 1734, 1373 cm^{-1}; MS (FAB, NBA) m/z 604 (M^+, 14), 495 (100), 395 (24); HRMS calcd for $C_{34}H_{36}O_8S$ (M^+) 604.2131, found 604.2099.

***N*^{6}-[2″-(Acetyloxy)-3″,4″,8″-trimethoxy-9″-[(trimethylacetyl)oxy]-1″,10″,11″,12″-tetrahydronaphthacenyl]-3′,5′-bis[(*tert*-butyldimethylsilyl)oxy]-2′-deoxyadenosine (29).** Protected adenosine **27** (106.5 mg, 0.23 mmol, 1.0 equiv) and trifluoroacetic acid [10 μL of a 0.45 M solution of trifluoroacetic acid in benzene-d_6 (0.0046 mmol, 2 mol %)] were added to a solution of quinone methide [prepared from phenol **15** (99.4 mg, 0.23 mmol) and Ag_2O (523.6 mg, 2.23 mmol)] and benzene-d_6 (500 μL) in a 10 mL round bottom flask. The reaction mixture underwent an immediate color change from green to red. After 12 h, the reaction mixture was sparged to dryness to afford crude **28** as an orange glass. The phenolic group was protected as the corresponding acetate to facilitate isolation and characterization. (Dimethylamino)pyridine (DMAP) (169.9 mg, 1.39 mmol) was added to a solution of **28** and CH_2Cl_2 (500 μL) and the reaction cooled to 0 °C. Acetic anhydride (98 μL, 1.04 mmol) was added and the reaction monitored by TLC. After 30 min, the reaction mixture was poured into equal volumes phosphate buffer (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to afford 214.1 mg of crude **29**. Flash chromatography (1.5:1 hexanes/ethyl acetate, deactivated silica gel) afforded 50.6 mg of a 1:1.6 mixture of diastereomers (HPLC) of **29** (23%, based on phenol **15**) as a dark yellow glass. An analytical sample was prepared and the diastereomers were separated by HPLC (1:1.5 hexanes/ethyl acetate, 0.5 mL min^{-1}) to afford minor diastereomer **29D^1** (t_R = 15.8 min) and major diastereomer **29D^2** (t_R = 16.8 min). Faster eluting diastereomer **29D^1**: yellow-green brittle glass, mp 142−143 °C; ^{1}H NMR (300 MHz, toluene-d_8, 24 °C) δ 8.74 and 8.68 (br s, 1 H), 7.92 (d, J = 9.0 Hz, 1 H), 7.81 and 7.67 (br s, 1 H), 7.15 (obscured by solvent, 1 H), 6.40−6.30 (br m, 1 H), 6.27 (m, 2H), 6.09 (br m, 1 H), 4.60 (br s, 1 H), 4.00−3.90 (m, 1 H), 3.85−3.70 (br m, 1 H), 3.65 (s, 3 H), 3.60 (m, 1H), 3.50 (s, 3 H), 3.41 (br m, 1H), 3.32 and 3.30 (s, 3 H), 2.85 (br d, J = 16.4 Hz, 1 H), 2.61 (m, 1 H), 2.30−2.10 (m, 2 H), 2.10−1.90 (m, 2 H), 1.50−1.20 (m, 2 H), 1.64 (s, 3 H), 1.44 (s, 9 H), 0.89 (s, 9H), 0.86 (s, 9H), 0.00 (s, 3 H), −0.02 (s, 3 H), −0.06 (s, 3 H), −0.07 (s, 3 H); UV (CH_3CN, 0.4 mg/50 mL) λ_{max} nm 204 (4.944), 220 (4.565), 252 (4.715), 272 (4.975), 346 (3.325), 364 (3.715), 382 (4.006), 406 (3.908), 430 (3.781); MS (FAB+, DCM/NBA/PPG) m/z 958 (MH^+, 100), 958 (32), 898 (7), 614 (6), 470 (4), 437 (100); HRMS calcd for $C_{50}H_{72}N_5O_{10}Si_2$ (MH^+) 958.4818, found 958.4817. Slower eluiting diastereomer **29D^2**: yellow-green brittle glass, mp 142−144 °C; ^{1}H NMR (300 MHz, toluene-d_8, 24 °C) δ 8.75 and 8.65 (br s, 1 H), 7.92 (d, J = 8.9 Hz, 1 H), 7.74 and 7.67 (br s, 1 H), 7.15 (obscured by solvent, 1 H), 6.37 (br m, 1 H), 6.27 (apparent d, J = 7.4 Hz, 1 H), 6.20−6.10 (m, 2 H), 4.65 (m, 1 H), 3.93 (m, 1 H), 3.81 (br m, 1 H), 3.65 (s, 3 H), 3.60 (m, 1 H), 3.51 (s, 3 H), 3.32 (s, 3 H), 2.95−2.75 (m, 2 H), 2.30−2.10 (m, 2 H), 2.10−1.90 (m, 2 H), 1.63 (s, 3 H), 1.44 (s, 9 H), 0.90 (s, 9 H), 0.85 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H), −0.06 (s, 6 H); IR (CCl_4) 2956, 2932, 2906, 2859, 1772, 1751, 1612, 1578, 1471, 1451, 1363, 1329, 1297, 1275, 1259, 1225, 1216, 1196, 1149, 1115, 1087, 1072, 1059, 1033, 839, 782, 776, 771, 765, 759 cm^{-1}; MS (FAB+, DCM/NBA/PPG) m/z 958 (MH^+, 100), 958 (28), 898 (5), 614 (5), 470 (4), 437 (100), 351 (36); HRMS calcd for $C_{50}H_{72}N_5O_{10}Si_2$ (MH^+) 958.4818, found 958.4773.

Acknowledgment. We acknowledge the UCR Mass Spectrometry laboratory for MS data, Dr. Dan Borchardt for assistance with 500 MHz NMR spectra, and undergraduate researchers Craig Husfeld and Jason Ferrone for their help in scaling up several of the initial steps in the synthesis of the quinone methide precursors. We gratefully acknowledge the National Institutes of Health (GM39354) and the A. P. Sloan Foundation (Research Fellowship to SRA) for financial support.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR Spectra for **14a**, **14b**, **15**, **16**, **19**, **23b**, **24b**, **24c**, **25**, **26a**, and **26b** and copies of ^{1}H NMR spectra for **20**, **21**, **22**, **23a**, **23c**, and **29**, and a summary of decoupling experiments for **26a** (29 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.

JO970539O