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Synthesis and Cycloaromatization of a Cyclic Enyne−Allene Prodrug

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A simple and stable cyclic enediynone (**4**) has been synthesized using an intramolecular Nozaki−Hiyama−Kishi cyclization as the key step. Reaction with a thiolate nucleophile led to rapid cycloaromatization of **4**. Trapping experiments using 1,4-cyclohexadiene support the intermediacy of an aromatic diradical in the cycloaromatization.

Introduction

The enediyne antitumor antibiotics exemplified by neocarzinostatin A chromophore,[1] the calicheamicins,[2] the esperamicins,[3] and the dynemicins[4] have shown potent antitumor activity with remarkable selectivities.[5] It has been demonstrated that these antitumor antibiotics' activities result from their ability to effect double-stranded DNA cleavage.[6] Upon activation by nucleophilic attack, these cyclic enediynes cycloaromatize under physiological conditions to afford benzenoid diradical intermediates capable of abstracting hydrogen atoms from the DNA backbone, leading to DNA strand scission and ultimately to cell death. Those enediyne antibiotics that contain an embedded (*Z*)-3-ene-1,5-diyne unit were shown to cycloaromatize via a mechanism first studied by Bergman, who showed that the parent enediyne (*Z*)-3-hexen-1,5-diyne underwent thermal cyclization to the diradical *p*-benzyne.[7]

In 1987, Myers proposed a mechanism by which the neocarzinostatin A chromophore (NCS, **1**) reacts with a thiolate nucleophile to afford an enyne−cumulene intermediate (**2**) that then cycloaromatizes to a styrenyl diradical (**3**) capable of inducing DNA damage analogously to that induced by the *p*-benzyne diradicals formed from the other enediyne antibiotics.[1] Subsequent experiments by Myers[8] and Saito[9] demonstrated that the model system (*Z*)-3-heptene-1,6-diyne undergoes a thermal cycloaromatization to form α,3-tolyl diradicals (Scheme 1).

A great deal of attention has focused on the design of simple enediynes capable of mimicking the actions of the complex naturally occurring enediynes.[10] A number of groups have explored different mechanisms to trigger the transformation of a stable system into a highly activated, cycloaromatization-labile intermediate without introduction of excessive molecular complexity.[10] Some efforts have focused on the introduction of substantial ring strain into cyclic enyne−allenes, taking their cue from NCS itself.[11] A number of activation strategies including nucleophilic attack and photolysis have also been explored.[12] Herein, we wish to report the preparation of a simple and stable enediynone (**4**) using an intramolecular

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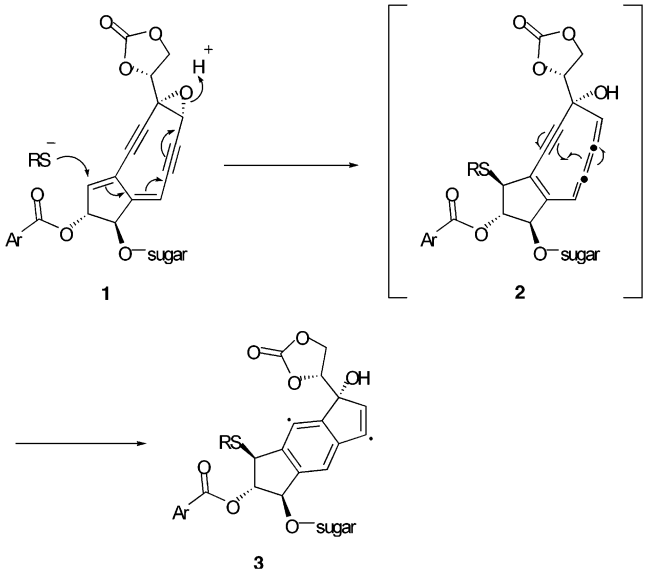
SCHEME 1



Nozaki−Hiyama−Kishi reaction as the key cyclization step and cycloaromatization of **4** to a diradical upon activation by thiolate nucleophiles. Spontaneous cycloaromatization of a cyclic enediynone **5** generated in situ is also described. Generation of an enyne−allene or enyne cumulene system via conjugate addition represents a means of activation of an NCS analogue.

The goal of this research was the development of an oxyanion-promoted Myers (C^2-C^7) cycloaromatization analogous to the oxyanion-promoted C^2-C^6 (Schmittel) cyclization previously observed in our laboratories.[13] Although only C^2-C^6 cyclization was observed in our earlier experiments, it was reasoned that lack of benzannulation and steric bulk at the alkyne termini would promote C^2-C^7 cyclization in **4** and **5**. In part, such a hope was based on DFT calculations performed by ourselves,[14a] Engels,[14b] and Schreiner[14c] and the experimental observations of Schmittel.[15] The approach employed in these studies was to generate an enolate by conjugate addition to an alkynyl ketone that would supply the oxyanion-substituted allene needed for the study as shown in Scheme 2.

Results and Discussion

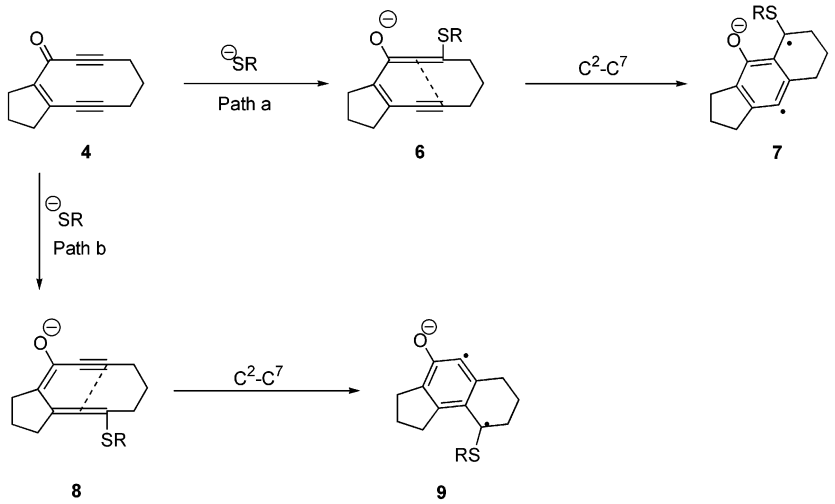
The target molecule **4** was envisaged as being activatable through either a conjugate addition, leading to formation of an enyne−allene, or an enolization process that would form an enyne−cumulene intermediate. In the former case, if a nucleophile adds to the cyclic ketone **4** through path a, one would expect the formation of aromatic product via the enyne−allene intermediate **6**. Similarly, if a nucleophile adds through path b, then one would expect the cyclization to occur via the intermediate **8** to form an aromatized product **9**.

Our first efforts focused on the synthesis of compound **5** using an intramolecular aldol condensation by analogy to the work of Toshima and co-workers.[16] Synthesis of **5** began with BF_3-catalyzed[17] addition of acetylide **10** to epibromohydrin as shown in Scheme 3. Following Cornforth epoxidation of the resultant bromohydrin to afford epoxide **12**, BF_3-catalyzed addition of acetylide **14** afforded diyne **15** in good overall yield. Benzylation of the hydroxyl functionality followed by bis-deprotection of the silyl ethers yielded diol **17**. Dess−Martin oxidation of the diol afforded keto aldehyde **18**.

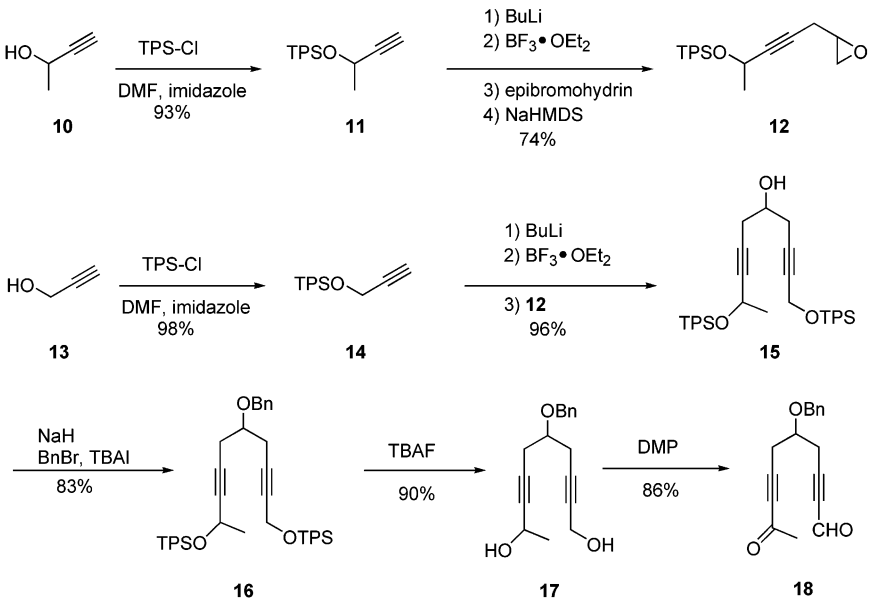
Cyclization to **5** was attempted via base-catalyzed intramolecular aldol condensation of **18** (Scheme 4). Treatment of **18** with LiOH in EtOH at 25 °C, conditions used by Toshima[15] to effect cyclization of a similar ring system, afforded 5-ethoxy-2-naphthol **19** instead of the desired intermediate **5**. Attempts to effect aldol condensation of **18** using other conditions resulted in either recovery of starting material or in decomposition. The substitution pattern of **19** was conclusively established by COSY and NOESY spectroscopy.

Although the cycloaromatization pathway of **18** is presumed to proceed through the intermediacy of **5**, the precise mechanism of its formation is open to speculation (Scheme 5). Elimination of the benzyl ether followed by

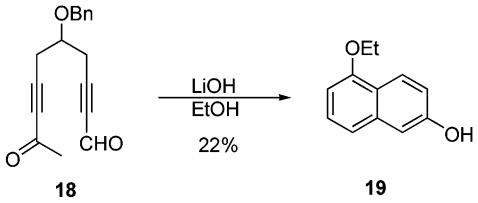
SCHEME 2. Plausible Mechanism for the Activation and Cyclization of 4



SCHEME 3



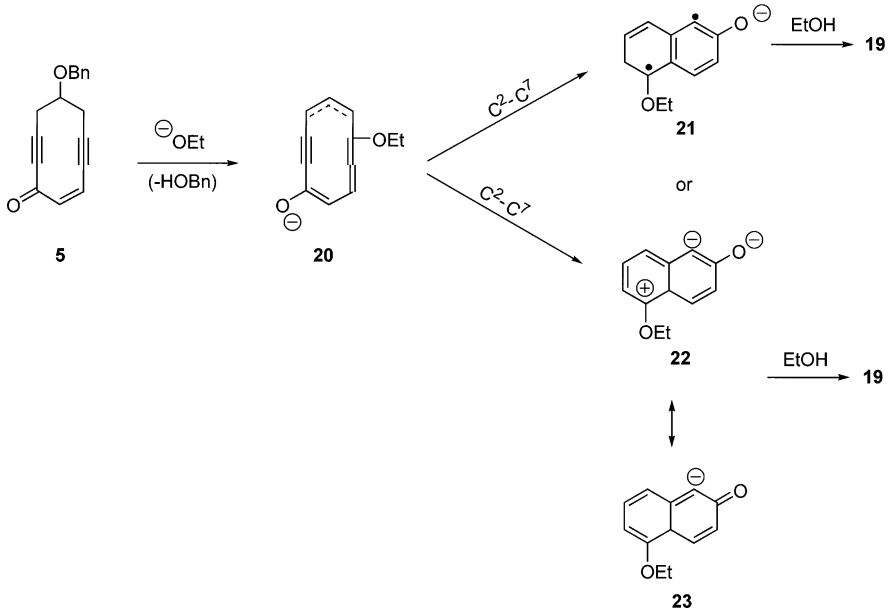
SCHEME 4



conjugate addition of ethoxide would give **20**, which cycloaromatizes to a species with either diradical (**21**) or zwitterionic character (**22**). Myers has suggested that a zwitterionic structure best represents the reactivity observed for the σ,π diradical in alcoholic solvents.[8] It is possible that **19** could arise from either intermediate **21** or **22**, but since attempts to trap any diradical intermediates with hydrogen atom donors proved unsuccessful, the zwitterionic form **22** appears to be more characteristic of the cycloaromatization product. Another factor that may favor the zwitterionic state is the energetic stabilization afforded by the direct resonance interaction between the alkoxide and the carbocation site, affording the quinone methide anion form **23**. It is also possible that cycloaromatization occurs before the loss of the benzyl ether group, which would still account for the formation of **19**. In both pathways, the species postulated to undergo cycloaromatization is an enolate. Indeed, only via an enolate or an enol can **5** form the central alkene needed for C^2-C^7 cyclization.

Interestingly, the benzyl ether of **18** is lost during reaction. It was reasoned that such an elimination must occur after formation of **5**, since no trace of an acyclic *trans*-alkene was found in the reaction medium. Thus,

SCHEME 5



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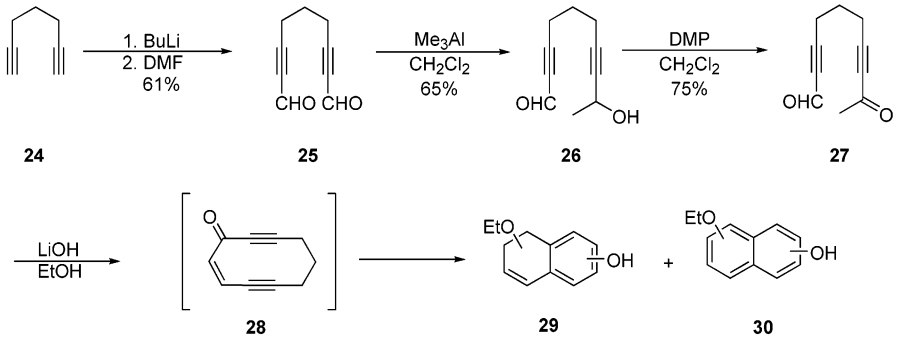


the question arose as to whether the elimination of the benzyl ether was needed to initiate the cycloaromatization of **5**.

To determine whether this elimination was necessary for cycloaromatization, the desoxy derivative **27** was prepared (Scheme 6). Commercially available 1,6-heptadiyne **24** was treated with 2 equiv of *n*-BuLi followed by quenching with DMF to obtain **25** in moderate yield. Selective monoaddition of a methyl group was eventually accomplished with Me_3Al in the presence of a 5-fold excess of **25** to give **26** in 65% based on recovered starting material. Unreacted **25** could be easily recovered. Dess–Martin oxidation of **26** gave **27** in 75% yield. Base-catalyzed aldol condensation using the previously described LiOH/EtOH conditions allowed **27** to cycloaromatize through intermediate **28** to a mixture of products **29** and **30**. Upon exposure to atmosphere, **29** was observed to slowly aromatize to naphthol **30**,[18] the product of a cycloaromatization analogous to **19**. Importantly, the facile cycloaromatization of **27** indicates that elimination of the benzyl ether in **5** is not necessary for cycloaromatization and could occur at any point after the initial cyclization.

Contrary to our results, Toshima and co-workers reported the synthesis of the silyl-protected trihydroxy dervitive **31** of similar cyclic enediyne.[15] They described a successful cyclization of a keto-aldehyde **31** to an isolable and stable 10-membered ring keto-enediyne **32** (Figure 1).

It is probably the substitution pattern that is responsible for the successful isolation of **32**. The possibility of an E2 process to eliminate the silyl ether group is not available as a result of the all-trans arrangement of the silyl ether groups. Although the cycloaromatization of **18**

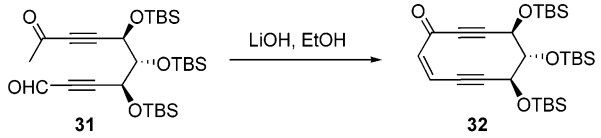
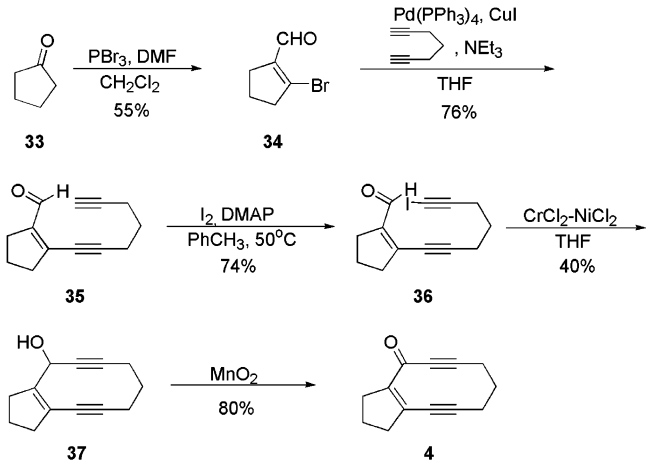


FIGURE 1. Cyclization and isolation of **32** reported by Toshima.[15]

SCHEME 7



and **27** under basic conditions is consistent with the mechanism shown in Scheme 5, our inability to isolate the putative intermediate **19** and our lack of success in trapping the putative diradical cycloaromatization products with 1,4-cyclohexadiene motivated the development of a revised synthesis. To employ a route using palladium-catalyzed cross-coupling and cyclization via acetylide addition to an aldehyde, it was necessary to synthesize a somewhat modified enediyne prodrug **4**.

The synthesis of **4** began with the preparation of 2-bromocyclopent-1-enecarbaldehyde **34** from cyclopentanone **33** (Scheme 7).[19] Sonogashira coupling[20] of **34** with 1,6-heptadiyne gave **35** in 76% yield. Attempts to cyclize **35** by intramolecular acetylide addition to the aldehyde failed, despite variation of the base, solvent, and addition of alternative metals $CeCl_3$ and $ZnBr_2$. As an alternative, the terminal alkyne of **35** was iodinated with I_2 in the presence of DMAP to afford **36** in 74% yield. Nozaki–Hiyama–Kishi cyclization[21] of **36** afforded the cyclized

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(18) ^{1}H NMR of **30** closely corresponded to the previously synthesized naphthol **19**, although the exact substitution pattern was not determined.

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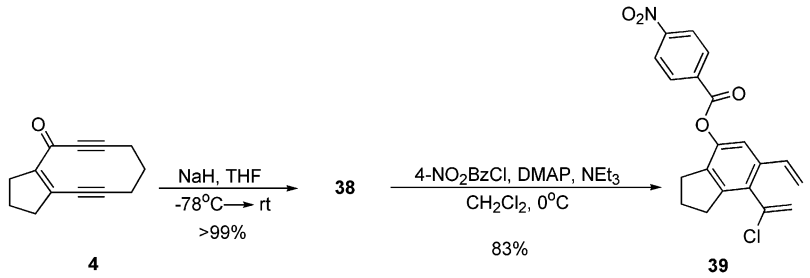
SCHEME 8



alcohol **37** in 40% yield. Oxidation of the secondary alcohol gave the ketone **4**, which was isolated in 80% yield and stable to purification by flash chromatography. Ketone **4** proved to be stable and can be stored for weeks with minimal decomposition.

With **4** in hand, various cyclization experiments were conducted. In an attempt to activate **4** by formation of an enyne−cumulene intermediate, **4** was treated with various bases (LDA, NaH, NaHMDS, and *t*-BuLi) in the presence of 1,4-cyclohexadiene. These reactions generally returned starting material or undefined side products except when NaH was used. Initial characterization of **38** by ^{1}H NMR, ^{13}C NMR, ^{1}H−^{1}H COSY, HMQC, DEPT, IR, UV−vis, and mass spectrometry did not elucidate the exact structure of the reaction product, though we were able to conclude that it was an aromatic alkynol isomeric with **4**. Moreover, the short lifetime of **38** precluded its further characterization by X-ray crystallography. Therefore, **38** was derivatized by acylation of the alcohol with *p*-nitrobenzoyl chloride, affording a stable, crystalline product **39**. X-ray crystallographic analysis of **39** identified it as the ester shown in Scheme 8. From the observed structure of **39**, the structure of the cyclization product **38** was deduced.

In Scheme 9, a mechanism for the transformation of **4** to **39** through compound **38** is proposed. When **4** is treated with NaH, it is believed to form the cumulene enolate **40**, which could cyclize to the diradical **41**. Intermolecular hydrogen atom transfer can lead to the more stable σ, π-diradical **43**. By analogy to the documented ring opening of 2,4-cyclohexadiene-1,4-diyl[22] to (*Z*)-1,3-hexadien-5-yne, it is proposed that the cyclohexadienyl diradical **43** can also be transformed to **38** by the same process. Another possible mechanism is if the cumulene enolate isomerizes to **42** by prototropic transfer and cyclizes by a [3,3] sigmatropic rearrangement to **38**.

Subjecting **38** to acylation conditions with *p*-nitrobenzoyl chloride resulted not only in acylation, but also in chlorination of the alkyne. It is proposed that the phenol **38** first isomerizes to the quinone methide **44** upon exposure to NEt_3/NEt_3·HCl, which then undergoes acid-catalyzed nucleophilic addition of chloride ion to afford **45**. The final step of the reaction is acylation of **45** to afford the observed product **39**.

Surprisingly, when **4** was subjected to the same conditions used to effect the cyclization of **18** to naphthol **19**, **38** was again formed. This result stands in stark contrast to the results shown in Schemes 5 and 6: instead of acting as a nucleophile as it had in the analogous substrate **5**, ethoxide presumably acts as a base in this case and effects ϵ-deprotonation of the ketone. The question of why **5** undergoes conjugation addition with ethoxide while **4** is deprotonated to form **40** cannot be answered at this point, although it is speculated that the five-membered ring in **4** may hinder conjugate addition of ethoxide enough to instead favor proton transfer. However, this explanation again begs the question of why conjugate addition of ethoxide does not occur at the β carbon of the alkynyl ketone.

Several other nucleophiles, such as benzeneselenol and thiols, were surveyed for their ability to induce cycloaromatization of **4** via path a (Scheme 2). In the event, it was found that thiolate nucleophiles proved most effective at effecting cycloaromatization. Thus, treatment of **4** with lithium *tert*-butylthiolate generated in situ gave the cycloaromatized product **46** in 40% yield (Scheme 10). Enone **48** was also formed as a side product in this reaction. When the reaction was carried out in the presence of 0.13 M 1,4-cyclohexadiene (Scheme 11), **4** cycloaromatized to give **47** (27%), **46** (18%) and the enone **48** (9%) in 10 min. The formation of **47** in the presence of the hydrogen atom donor 1,4-cyclohexadiene provides the best indirect evidence that the cyclization of **4** to **46** most likely occurs via a diradical intermediate such as **7** (Scheme 2). These conditions have been optimized for formation of cycloaromatized products. Variation of reacton time, temperature, concentration, and solvent resulted in lower yields of **47** and in no case was complete reaction observed. The formation of **46** in Scheme 11 is assumed to be a result of two rapid intermolecular hydrogen atom transfers in the diradical intermediate **7**. Currently, attempts are underway in our labs to trap **7** with various radical trapping reagents.

The reduced product **47** proved to be crystalline, so an X-ray crystal structure of **47** was obtained, revealing the position of the sulfide group. The structure of **47** strongly implies the intermediacy of diradical **7**, which is presumed to be the same intermediate for the formation of **46**.

Conclusion

In conclusion, a simple enediyne was synthesized using a Hiyama−Nozaki−Kishi cyclization that undergoes rapid cycloaromatization upon reaction with thiolate nucelophiles. The ability of 1,4-cyclohexadiene to afford

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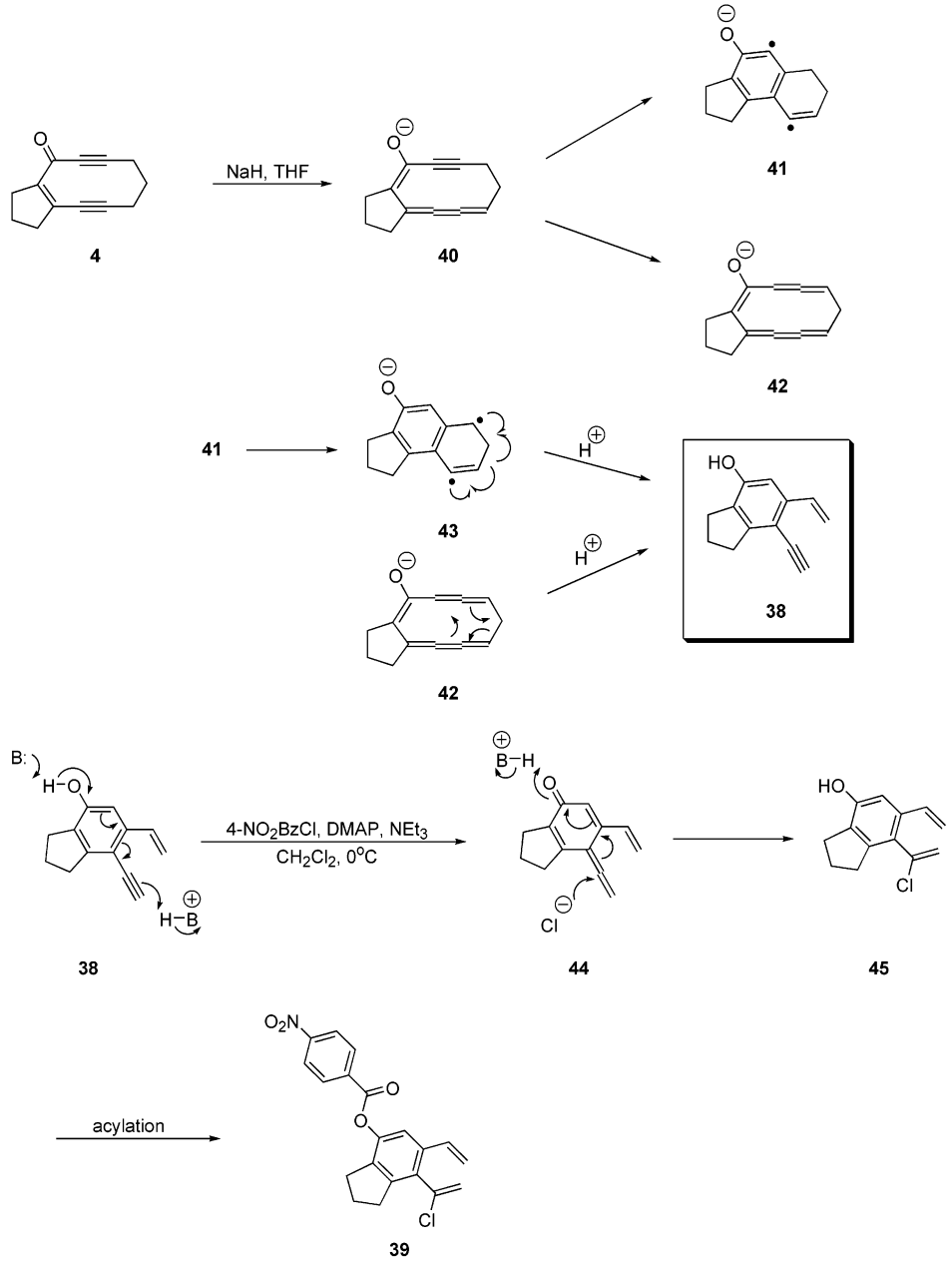
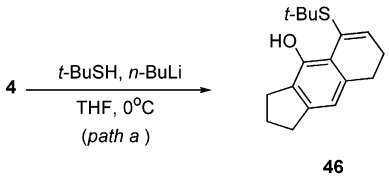
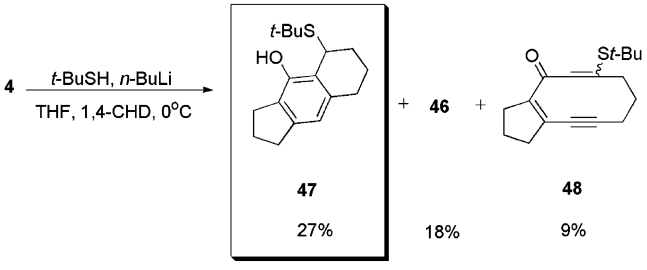
SCHEME 9



SCHEME 10



SCHEME 11



a reduced cycloaromatization product provides evidence for the intermediacy of a diradical during cycloaromatization, which in turn leads to the inference that the allenolate produced by conjugate addition of a thiol to **4** cycloaromatizes via a Myers (C^2-C^7) pathway. Such a pathway, leading from an unactivated ketone precursor to a cycloaromatization-labile intermediate, is likely to be generally applicable to analogous alkynyl ketone systems. Importantly, though the enediyne natural products rely on extensive molecular complexity to modulate reactivity, enolization or conjugate addition mechanisms allow for simple unsaturated ketones to be easily activated, in theory affording highly reactive aromatic diradicals analogous to those generated by the enediyne natural products. Studies are ongoing to investigate the

ability of these systems and their derivatives to effect DNA cleavage in vitro.

Experimental Section

(1-Methyl-4-oxiranylbut-2-ynyloxy)triphenylsilane (12). To a solution of **11** (4.00 g, 12.9 mmol) in dry THF (75 mL) at −78 °C was added BuLi as a 2.71 M solution in hexanes (6.23 mL, 16.9 mmol). After the mixture was stirred for 10 min, BF_3·OEt_2 (2.40 mL, 19.5 mmol) was added. The reaction was stirred for 15 min before epibromohydrin (1.67 mL, 19.5 mmol) was added. The reaction was slowly warmed to 25 °C, diluted with Et_2O, and poured into saturated aqueous NH_4Cl. The aqueous phase was separated and extracted twice with Et_2O. The combined organic phase was dried over Na_2SO_4, decanted, and concentrated in vacuo. The residue was redissovled in dry THF (75 mL). To this solution was added sodium hexamethyldisilizane (2.36 g, 12.9 mmol) as a solution in THF (20 mL). The reaction was diluted with Et_2O and poured into saturated aqueous NH_4Cl. The aqueous phase was separated and extracted twice with Et_2O. The combined organic phase was dried over Na_2SO_4, decanted, and concentrated in vacuo. The resulting residue was purified by flash chromatography (20:80 Et_2O/pentane) to afford **12** as a colorless oil (2.10 g 74% based on recovered **11**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (m, 2H), 7.74 (m, 2H), 7.74−7.36 (m, 6H), 4.51 (m, 1H), 2.95 (m, 1H), 2.71 (m, 1H), 2.52 (m, 2H), 2.32 (m, 1H), 1.40 (d, J = 6.3 Hz, 3H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.0, 135.8, 135.6, 133.9, 133.8, 129.7, 127.8, 127.5, 84.9, 78.4, 78.3, 60.1, 60.0, 49.9, 49.8, 46.5, 46.3, 26.9, 26.7, 25.4, 25.3, 22.6, 22.4, 19.2; IR (neat) ν_{max} 3051, 2932, 2859, 2254, 1473, 1428, 1161, 1106, 1024, 955, 823 cm^{-1}.

5-Benzyloxy-1,9-bis(*tert*-butyldiphenylsilanyloxy)-2,7-decadiyne (16). To a suspension of NaH, used as a 60% dispersion in mineral oil (0.126 g, 3.16 mmol), in THF (6 mL) were added BnBr (0.47 mL, 3.9 mmol) and tetrabutylammonium iodide (0.19 g, 0.53 mmol). Compound **15** (1.73 g, 2.6 mmol) was then added as a solution in THF (2 mL). The reaction was stirred for 4 h, diluted with Et_2O, and poured into saturated aqueous NH_4Cl. The aqueous phase was separated and extracted twice with Et_2O. The combined organic phase was dried over Na_2SO_4, decanted, and concentrated in vacuo. The resulting residue was purified by flash chromatography (10:90 Et_2O/pentane) to afford **16** as a colorless oil (1.62 g, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.69 (m, 8H), 7.46−7.24 (m, 17H), 4.58 (m, 2H), 4.49 (m, 1H), 4.33 (m, 2H), 3.48 (m, 1H), 2.43 (m, 4H), 1.39 (d, J = 6.3 Hz, 3H), 1.07 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 136.0, 135.9, 135.7, 133.9, 133.3, 129.8, 129.7, 129.6, 128.4, 127.8, 127.7, 127.6, 127.5, 84.5, 81.9, 81.8, 80.3, 75.9, 75.8, 71.6, 71.5, 60.2, 53.0, 26.9, 26.8, 25.5, 24.0, 23.9, 23.8, 19.3; IR (neat) ν_{max} 3071, 2932, 2859, 1958, 1472, 1428, 1363, 1262, 1145, 1109, 1028, 955, 823, 739, 703 cm^{-1}. Anal. Calcd for $C_{49}H_{56}Si_2O_3$: C, 78.56; H, 7.53. Found: C, 78.29; H, 7.39.

5-Benzyloxydeca-2,7-diyne-1,9-diol (17). To a solution of **16** (1.62 g, 2.2 mmol) in THF (6 mL) was added tetrabutylammonium fluoride as a 1.0 M solution in THF (4.30 mL, 4.3 mmol) and the mixture stirred for 2 h. The reaction was diluted with EtOAc and poured into saturated aqueous NH_4Cl. The aqueous phase was separated and extracted twice with EtOAc. The combined organic phase was dried over Na_2SO_4, decanted, and concentrated in vacuo. The resulting residue was purified by flash chromatography (50:50 EtOAc/petroleum ether) to afford **17** as a pale yellow oil (0.532 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.26 (m, 5H), 4.61 (s, 2H), 4.46 (m, 1H), 4.19 (t, J = 2.2 Hz, 2H), 3.66 (qt, J = 5.6 Hz, 1H), 2.61−2.56 (m, 6H), 1.40 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 128.5, 127.9, 84.6, 81.9, 80.8, 80.3, 75.5, 71.5, 58.4, 51.1, 24.5, 23.9, 23.8.

5-Benzyloxy-9-oxodeca-2,7-diynal (18). To a solution of **17** (0.053 g, 0.2 mmol) in dry CH_2Cl_2 (3 mL) was added the Dess−Martin periodinane (0.33 g, 0.8 mmol). After the mixture was stirred for 4 h, a 7:1 mixture of 10% aqueous $Na_2S_2O_4$ and10% aqueous $NaHCO_3$ and additional CH_2Cl_2 were added. This biphasic mixture was vigorously stirred until the organic phase became clear. The mixture was then poured into saturated aqueous NH_4Cl. The aqueous phase was separated and extracted twice with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4, decanted, and concentrated in vacuo. The resulting residue was purified by flash chromatography (10:90 EtOAc/petroleum ether) to afford **18** as a colorless oil (0.045 g, 86%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (s, 1H), 7.38−7.29 (m, 5H), 4.63 (s, 2H), 3.84 (m, 1H), 2.78 (d, J = 5.4 Hz, 2H), 2.54 (d, J = 5.9 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.3, 176.7, 137.1, 128.6, 128.2, 127.9, 93.6, 88.3, 83.1, 73.9, 71.9, 32.7, 24.5, 24.3; IR (neat) ν_{max} 2926, 2869, 2279, 2207, 1673, 1420, 1357, 1230, 1139, 1092, 1026, 828 cm^{-1}.

5-Ethoxynaphthalen-2-ol (19). Simultaneously, a solution of **18** (0.045 g, 0.2 mmol) in 98% EtOH (19 mL) and a separate solution of LiOH·H_2O (0.014 g, 0.3 mmol) in 98% EtOH (19 mL) were combined by slow dropwise addition via cannula to a stirring volume of EtOH (10 mL). Upon complete of addition, glacial acetic acid (0.019 mL, 0.3 mmol) was added to the reaction vessel. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (15:85 EtOAc/petroleum ether) to afford **19** as a waxy yellow solid (0.07 g, 22%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.2 (d, J = 8.8 Hz, 1H), 7.32 (dd, J = 8.3, 7.3 Hz, 1H), 7.24 (d, J = 8.3 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 7.05 (dd, J = 8.8, 2.4 Hz, 1H), 6.66 (d, J = 7.3 Hz, 1H), 4.87 (s, 1H), 4.19 (q, J = 6.8 Hz, 2H), 1.53 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 153.8, 135.9, 126.9, 124.4, 121.0, 118.6, 116.5, 109.3, 102.7, 63.6, 14.9; IR (neat) ν_{max} 3384, 2980, 2929, 2207, 1629, 1584, 1514, 1439, 1386, 1970, 1218, 1174, 1114, 1095, 1072, 955 cm^{-1}; MS *m*/*z* (CI) 188 (M^+) 189.

2,7-Nonadiynedial (25). To a solution of 1,6-heptadiyne **24** (1.00 g, 10.9 mmol) in THF (40 mL) at 0 °C was added *n*-BuLi as a 2.6 M solution in hexanes (8.80 mL). After 20 min, DMF (4.21 mL, 54.2 mmol) was added and the reaction stirred for 12 h. The reaction was diluted with EtOAc and poured into saturated aqueous NH_4Cl. The aqueous phase was separated and extracted twice with EtOAc. The combined organic phase was dried over Na_2SO_4, decanted, and concentrated in vacuo. The resulting residue was purified by flash chromatography (25:75 EtOAc/petroleum ether) to afford **25** as a pale yellow oil (0.986 g, 61%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.1 (s, 2H), 2.49 (t, J = 7.0 Hz, 4H), 1.79 (qt, J = 7.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.4, 97.1, 82.6, 25.9, 18.5; IR (neat) ν_{max} 3649, 2533, 3307, 2945, 2868, 2746, 2278, 2202, 1666, 1425, 1390, 1346, 1329, 1138, 1034, 964, 859, 814, 750 cm^{-1}.

9-Hydroxy-2,7-decadiynal (26). To a solution of **25** (0.51 g, 3.4 mmol) in dry CH_2Cl_2 (12 mL) at −50 °C was added Me_3-Al as a 2 M solution in $PhCH_3$ (0.34 mL, 0.68 mmol) and the mixture slowly warmed to 25 °C. The reaction was diluted with CH_2Cl_2 and poured into saturated aqueous NH_4Cl. The aqueous phase was separated and extracted twice with Et_2O. The combined organic phase was dried over Na_2SO_4, decanted, and concentrated in vacuo. The resulting residue was purified by flash chromatography (20:80 Et_2O/pentane) to afford **26** as a pale yellow oil (0.073 g, 65% based on recovered starting material): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (s, 1H), 4.47 (m, 1H), 2.51 (m, 2H), 2.31 (m, 3H), 1.75 (m, 2H), 1.38 (d, J = 2.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 98.1, 83.7, 82.5, 82.0, 58.4, 26.5, 24.7, 18.2, 17.9; IR (neat) ν_{max} 3404, 2981, 2936, 2870, 2278, 2202, 1665, 1430, 1391, 1330, 1138, 1076, 1013, 884, 812, 768 cm^{-1}.

2-Bromocyclopent-1-enecarbaldehyde (34).[19] A solution of DMF (6.90 mL, 90 mmol) in CH_2Cl_2 at 0 °C was slowly treated with PBr_3 (7.0 mL, 75 mmol) and stirred for 1 h. A solution of cyclopentanone (2.40 mL, 30 mmol) in CH_2Cl_2 (12.5 mL) was added dropwise to the reaction mixture and the reaction stirred for 24 h at 25 °C. The reaction was quenched by pouring it into ice and adding $NaHCO_3$ until a pH of 7 was

reached. The solution was allowed to warm to room temperature and was extracted three times with EtOAc. The combined organic layers were washed with saturated $NaHCO_3$, brine, and H_2O. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (5:95 Et_2O/petroleum ether) to afford **34** as a pale yellow oil (2.9 g, 55%): ^1H NMR (300 MHz, $CDCl_3$) δ 9.9 (s, 1H), 2.9 (t, $J = 7$, 2H), 2.5 (t, $J = 7$, 2H), 2.0 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.26, 141.63, 140.15, 42.72, 29.45, 21.56.

2-(1,6-Heptadiynyl)cyclopent-1-enecarbaldehyde (35). To a N_2 flushed flask $Pd(PPh_3)_4$ (0.069 g, 0.060 mmol) and **34** (0.21 g, 1.2 mmol) were dissolved in THF (4 mL) and stirred for 20 min. To this solution were added CuI (0.046 g, 0.24 mmol) and 1,6-heptadiyne (0.41 mL, 3.6 mmol), and the reaction was cooled to 0 °C. NEt_3 (0.33 mL, 2.4 mmol) was slowly added, and the solution was allowed to warm to 25 °C and stirred for 1 h. The yellow reaction was diluted with Et_2O and poured into saturated aqueous NH_4Cl. The aqueous phase was separated and extracted three times with Et_2O. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (10:90 Et_2O:petroleum ether) to give **35** as pale yellow oil (0.168 g, 76%): ^1H NMR (300 MHz, CDCl3) δ 10.04 (s, 1H), 3.52 (s, 1H), 2.66 (m, 6H), 2.3 (dt, $J = 2.6$, 7.02 Hz, 2H), 1.93 (m, 2H), 1.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.3, 147.6, 144.3, 101.8, 83.2, 75.84, 69.5, 39.4, 29.6, 27.5, 22,2, 19.1, 17.8. Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 84.05; H, 7.66.

2-(7-Iodo-1,6-heptadiynyl)cyclopent-1-enecarbaldehyde (36). To a solution of **35** (0.21 g, 1.1 mmol) dissolved in $PhCH_3$ (37 mL) were added I_2 (1.15 g, 4.52 mmol) and DMAP (1.40 g, 11.30 mmol) and heated for 2 h at 50 °C. The reaction was quenched by dilution with Et_2O and the solvent was removed under reduced pressure. The residue was redissolved in Et_2O and washed three times with H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography (10:90 Et_2O/petroleum ether) to give **36** as yellow oil (0.26 g, 74%): ^1H NMR (300 MHz, $CDCl_3$) δ 10.02 (s,1H), 2.60 (m, 8H), 1.95 (m, 2H), 1.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.20, 147.6, 144.3, 101.7, 93.3, 75.9, 69.5, 39.4, 29.6, 27.5, 22.2, 20.2, 19.2. Anal. Calcd for $C_{13}H_{13}OI$: C, 50.02; H, 4.20; I, 40.65. Found: C, 50.00; H, 4.04; I, 40.45.

Bicyclo[8.3.0]tridec-12-ene-2,7-diyn-1-ol (37). A mixture of $CrCl_2$ (0.49 g, 4.0 mmol) and $NiCl_2$ (0.052 g, 0.4 mmol) was heated to 180 °C with stirring under vacuum for 24 h and cooled to room temperature. To a solution of **36** (0.25 g, 0.8 mmol) in THF (80 mL) was added the dry $CrCl_2-NiCl_2$, and the reaction was stirred for 3.5 h. The reaction was quenched by dilution with EtOAc and poured into saturated aqueous NH_4Cl. The aqueous phase was extracted twice with EtOAc. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The dark brown residue was purified by flash chromatography (20:80 EtOAc/petroleum ether) to give **37** as an oily colorless solid (0.06 g, 40%): ^1H NMR (300 MHz, $CDCl_3$) δ 4.84 (b, 1H), 2.80 (m, 2H), 2.55 (m, 4H), 2.35 (m, 2H), 1.84 (m, 4H); ^{13}C NMR (75 MHz, CDCl3) δ 144.6, 121.2, 97.4, 88.8, 81.0, 80.2, 61.5, 37.9, 35.3, 25.8, 21.7, 20.9, 19.9; IR (neat) ν_{max} 3423, 2925, 2849, 1737, 1440, 1373, 1243, 1118, 1030, 966 cm^{-1}. Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.46; H, 7.52.

Bicyclo[8.3.0]trideca-12-ene-2,7-diyn-1-one (4). To a solution of **37** (0.11 g, 0.6 mmol) in CH_2Cl_2 (8.4 mL) was added an activated MnO_2 (1.10 g, 13.3 mmol) and the mixture stirred for 12 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The crude residue was purified by flash chromatography (15: 85 EtOAc/petroleum ether) to give **4** as a colorless foam (0.087 g, 80%): ^1H NMR (300 MHz, $CDCl_3$) δ 2.68 (m, 8H), 1.95 (m, 2H),1.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 148.3, 139.9, 105.8, 97.2, 83.2, 82.4, 39.3, 32.2, 26.2, 21.1, 21.0, 20.1; IR (neat) ν_{max} 3429, 2933, 2236, 2202, 1600 1568, 1428, 1362, 1262, 1112, 878, 826, 742 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{12}O$ $[M]^+$ 184.0888, found 184.0884.

7-Ethynyl-6-vinylindan-4-ol (38). A solution of **4** (0.11 g, 0.6 mmol) in THF (0.2 mL) at −78 °C was treated with 97% NaH (0.003 g, 0.12 mmol) and stirred for 12 h at room temperature. The reaction was quenched by dilution with EtOAc and poured into H_2O. The aqueous phase was extracted twice with EtOAc, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified via flash chromatography (10:90 EtOAc/petroleum ether) to give **38** as a colorless foam (0.011 g, 100%). Compound **38** was stored as a solution in hexane that was degassed under N_2 and stored at −20 °C: ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 (dd, $J = 6.56$, 11.07, 1H), 6.90 (s, 1H), 5.76(dd, $J = 1$, 17.55, 1H), 5.34 (dd, $J = 1$, 11.00, 1H), 4.7 (s, 1H), 3.4 (s, 1H), 3.06 (t, $J = 7.33$, 2H), 2.91(t, $J = 7.32$, 2H), 2.18 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 150.4, 139.8, 134.3, 128.9, 114.7, 109.8, 108.8, 82.7, 80.3, 33.1, 28.9, 24.1; MS *m/z* (CI) 184 (M^+) 171, 165, 129, 127, 113, 107; UV−vis λ_{max} (*n*-hexane) 238, 268 nm.

7-(1-Chlorovinyl)-6-vinylindan-4-yl 4-nitobenzoate (39). To a solution of **38** (0.005 g, 0.03 mmol) were added DMAP (0.001 g, 0.005 mmol) and NEt_3 (0.015 mL, 0.11 mmol), and the reaction was cooled to 0 °C. To the reaction mixture was added *p*-nitrobenzoyl chloride (0.013 g, 0.07 mmol), and the resultant reaction was stirred for 15 min. The reaction was diluted with Et_2O and poured into saturated aqueous NH_4Cl. The aqueous phase was separated and extracted three times with Et_2O. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (5:95 Et_2O/petroleum ether) to give **39** as a colorless foam (8.3 mg, 83%): ^1H NMR (500 MHz, $CDCl_3$) δ 8.4 (s, 4H), 6.95 (dd, $J = 6.5$, 10.9, 1H), 5.80 (d, $J = 1$, 1H), 5.72 (d, $J = 17.4$, 1H) 5.38 (d, $J = 1$, 1H) 5.34 (d, $J = 11.1$, 1H), 3.06 (t, $J = 7.47$, 2H), 2.89 (t, $J = 7.42$, 2H), 2.16 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 150.7, 146.9, 146.0, 135.8, 135.7, 135.6, 134.4, 133.3, 132.0, 131.1, 123.5, 118.1, 115.7, 115.6, 32.1, 30.1, 24.5; MS *m/z* (CI) 369 (M^+) 219, 202, 167, 150, 120, 104, 92.

5-*tert*-Butylthio-2,3,7,8-tetrahydro-1*H*-cyclopenta[*b*]-naphthalen-4-ol (46). To a solution of *n*-BuLi as a 2.5 M solution in hexane (0.034 mL, 0.08 mmol) in THF (0.051 mL) at 0 °C was added 2-methyl-2-propanethiol (0.009 mL, 0.08 mmol), and the mixture was stirred for 20 min. To the reaction mixture was added a solution of **4** (0.010 g, 0.05 mmol) in THF (0.36 mL), and the reaction was stirred for 10 min. The reaction was quenched by dilution with Et_2O and poured into H_2O. The aqueous phase was extracted twice with Et_2O, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude was purified by flash chromatography (2.5:97.5 Et_2O/petroleum ether) to give **46** as a pale yellow oil (6.0 mg, 40%): ^1H NMR (300 MHz, $CDCl_3$) δ 9.87 (s, 1H), 6.63 (s, 1H), 6.43 (t, $J = 4.9$ Hz, 1H), 2.89 (t, $J = 7.3$ Hz, 4H), 2.72 (t, $J = 7.3$ Hz, 2H), 2.32 (*td*, $J = 7.3$ Hz, 4.9 Hz, 2H), 2.07 (m, 2H), 1.33 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 151.4, 145.5, 144.4, 136.8, 130.5, 126.6, 117.7, 115.4, 47.7, 33.5, 30.6, 29.9, 29.6, 25.5, 25.1; HRMS (EI) calcd for $C_{17}H_{22}OS$ $[M]^+$ 274.1391, found 274.1389.

5-*tert*-Butylthio-2,3,5,6,7,8-hexahydro-1*H*-cyclopenta-[*b*]naphthalen-4-ol (47). To a solution of *n*-BuLi as a 2.5 M solution in hexane (0.069 mL, 0.2 mmol) in THF (0.10 mL) at 0 °C was added 2-methyl-2-propanethiol (0.019 mL, 0.2 mmol) and the mixture stirred for 20 min. To the reaction mixture was added **4** (0.015 g, 0.08 mmol) in THF/1,4-cyclohexadiene (0.40 mL/0.15 mL) and stirred for 10 min. The reaction was quenched by dilution with Et_2O and poured into H_2O. The aqueous phase was extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude was purified by flash chromatog-

raphy (2.50:97.5 Et_2O/pertroleum ether) to give **47** as a white solid (6.0 mg, 27%): ^1H NMR (300 MHz, $CDCl_3$) δ 6.62 (s, 1H), 4.23 (b, 1H), 2.84 (m, 5H), 2.24(m, 2H), 2.03 (m, 4H), 1.8 (m, 2H), 1.5 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 145.0, 136.9, 128.9, 119.9, 117.3, 44.9, 37.9, 32.7, 31.7, 31.6, 29.2, 28.7, 25.0, 18.2; HRMS (EI) calcd for $C_{17}H_{24}OS$ $[M]^+$ 276.1548, found 276.1541.

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Supporting Information Available: Crystallographic data for **39** and **47**; experimental procedure for compounds **11**, **12**, **14**, **15**, **27**, and **29**; NMR (^1H, ^{13}C, $^1H-^1H$ COSY) spectra for **46**; NMR (^1H, ^{13}C, NOESY) spectra for **19**; NMR (^1H, ^{13}C) spectra for compounds **12**, **17**, **18**, **25**−**27**, **4**, **38**, **39**, and **48**. This material is available free of charge via the Internet at http://pubs.acs.org.

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