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Nucleophilic Cycloaromatization of Ynamide-Terminated Enediynes

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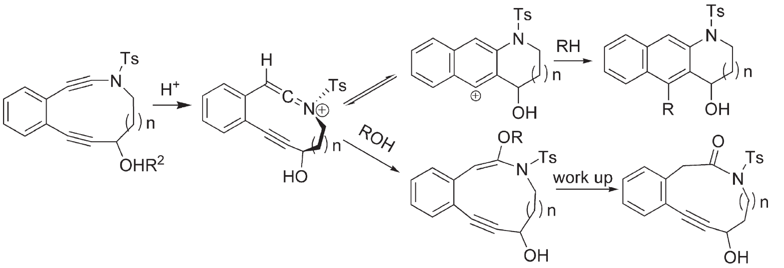

Introduction of a nitrogen atom at one of the acetylenic termini of 10-, 11-, 12-, and 13-membered benzannulated cyclic enediynes results in a complete suppression of the conventional radical Bergman reaction in favor of a polar cycloaromatization. The latter reaction is catalyzed by acids and proceeds via initial protonation of an ynamide fragment. The resulting ketenimmonium cation then cyclizes to produce naphthyl cation, which rapidly reacts with nucleophiles or undergoes Friedel−Crafts addition to aromatic compounds. In alcohols, addition of the nucleophilic solvent across the activated triple bond competes with the cyclization reaction. The ratio of cyclized to solvolysis products decreases with the increase in ring size.

Introduction

Naturally occurring enediyne antibiotics, such as calicheamicin,[1] esperamicin,[2] dynemicin,[3] and kedarcidin,[4] are among the most potent antineoplastic agents ever discovered.[5] The phenomenal cytotoxicity of these natural products is attributed to the ability of the enediyne fragment (hence the name) to undergo Bergman[6] cyclization and produce aromatic 1,4-diradicals. These latter species are believed to abstract hydrogen atoms from the sugar phosphate backbone of opposite strands of a dDNA molecule, leading to oxidative double strand DNA scission.[5] The clinical use of natural enediynes is hampered by their high general toxicity, and achieving control over the reactivity of the enediyne fragment is an important goal in the development of new antibiotics of this family. It is well-documented that the rate of the Bergman cyclization strongly depends on both the ring strain of the enediyne-containing cycle[7] and the electronic properties of substituents.[8−10] Recent theoretical studies suggest that repulsion

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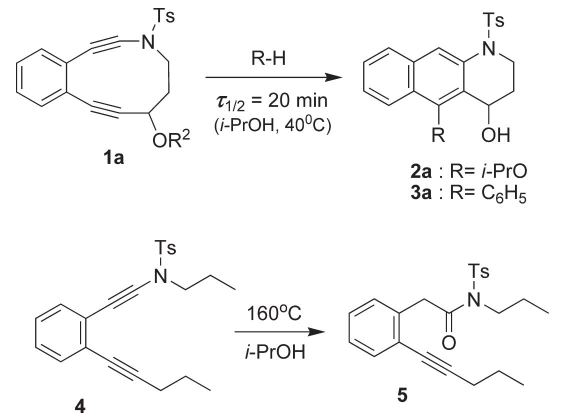
of the in-plane π-orbitals of triple bonds destabilize the cyclization transition state, whereas overlap of the out-of-plane π-orbitals produces the opposite effect due to pronounced aromatization.[11] One of the approaches that allow for the reduction of electron density in the enediyne π-system is replacement of the vinylic carbon atom with a more electronegative atom, such as nitrogen.[10,12] Electronic effects of the heterosubstitution can be further enhanced by the protonation of the nitrogen atom. Such imine-diynes undergo very efficient Bergman cyclization to produce 2,5-didehydropyridine. The lifetime of the latter, unfortunately, is too short to undergo bimolecular radical reactions as it instantly opens up into a stable nitrille-eneyne isomer.[10,13] σ-Acceptor and π-donor substituents at the acetylenic termini of enediyne, on the other hand, are expected to enhance the rate of Bergman cyclization without providing an alternative pathway for the deactivation of the diradical.[7a,14] We hypothesized that replacement of a propargylic carbon atom with nitrogen would allow benefit from both rate-enhancing effects.[14c] In fact, Klein and König reported that tosylamide-substituted *o*-diethynylbenzene decomposes almost three time faster than the parent compound.[15] Thermolysis of the former in a cyclohexadiene/benzene mixture at 141 °C allowed the authors to detect some amounts of the Bergman cyclization product in the reaction mixture. Since our group is interested in designing enediynes compounds that undergo spontaneous cyclization under ambient conditions, we have studied the effects of nitrogen substitution on the reactivity of cyclic enediynes. In our preliminary communication we have reported the synthesis of 10-membered ring ynamide-containing enediyne **1a** (Scheme 1).[16] This compound is, in fact, quite reactive and undergoes spontaneous cycloaromatization at room temperature. Surprisingly, we have observed only formal O−H (**2a**, in 2-propanol) or C−H (**3a** in benzene, toluene, and 1,4-cyclohexadiene) insertion instead of hydrogen abstraction, characteristic for the radical Bergman reaction (Scheme 1).

In sharp contrast with **1a**, the acyclic ynamide-containing enediyne **4** produces *N*-tosyl amide **5** upon heating in 2-propanol (Scheme 1). Both reactions are catalyzed by the addition of *p*-toluenesulfonic acid and show primary kinetic isotope effect in deuterated alcohols. These observations suggested that reaction is initiated by the protonation of the ynamide fragment. The resulting ketenimmonium cation (*vide infra*) can undergo cycloaromatization or can be intercepted by a nucleophilic solvent. Two questions, however, remained unanswered: can the cyclization of **1a** be directed into the Bergman pathway by neutralizing all sources of acids, and what structural factors control the outcome of reaction of aza-enediynes in alcohols (i.e., cyclization versus solvolysis)?

SCHEME 1



In this report we present the synthesis of 11-, 12-, and 13-membered analogues of **1a** and experimental, as well as computational, studies of their reactivity.

Results and Discussion

Synthesis of Enedyine-amides 1a−d and the Expected Product of the Bergman Cyclization of 1a. For the preparation of aza-cyclic enediynes **1b−d** we have employed the procedure that has been developed for the synthesis of **1a**.[16] The key ynamide fragment has been assembled using Cu(II)-mediated amidation[17] of ((2-(bromoethynyl)phenyl)ethynyl)trimethylsilane **6** with corresponding tosyl amide (Scheme 2).[18] Treatment of **7** with potassium carbonate in methanol simultaneously removes both trimethylsilyl and *tert*-butyldimethylsilyl protecting groups to produce alcohol **8**. Iodination of the terminal acetylene group in **8** followed by the oxidation of the hydroxyl group gave iodoaldehyde **10**. The key cyclization step was achieved under Nozaki−Hiyama−Kishi conditions[19] (Scheme 2).[18]

Enediyne-amides **1b−d** are colorless crystalline compounds, which are stable under ambient conditions. In contrast, 10-membered **1a** is a very reactive and undergoes rapid decomposition at room temperature.

The independent synthesis of the expected product of the Bergman cyclization of **1a** is outlined in Scheme 3. Starting aldehyde **11** has been prepared from commercially available 3-amino-2-naphthoic acid.[18,20] Alkylation of the former with methyl lithium in THF followed by PCC oxidation provided ketone **13**. Enol ether **14** has been prepared by treating **13** with TBDMSCl in the presence of triethyl amine in acetonitrile. Ring-closing metathesis of **14** using Grubbs' second generation catalyst under medium dilution conditions yielded dihydrobenzoquinoline **15**. Hydrolysis of the enol ether **15**, followed by the reduction of the resulting carbonyl

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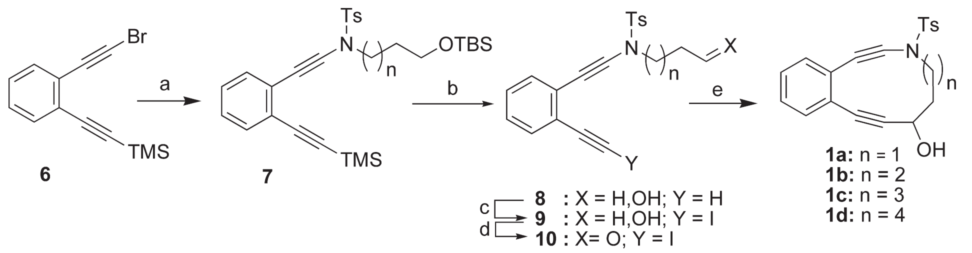
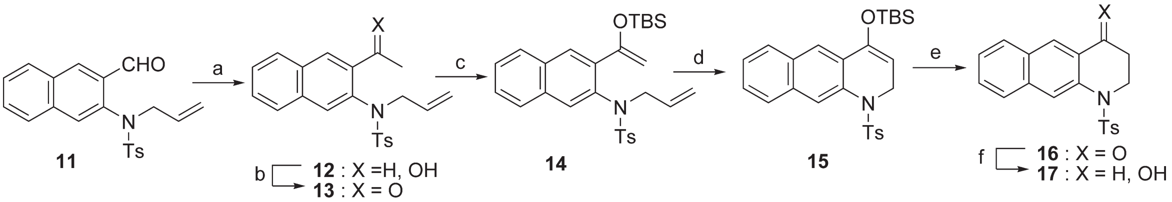
SCHEME 2. Synthesis of Aza-enediynes 1a–d[a]



[a]Reagents and conditions: (a) Ts-*N*-$(CH_2)_{n+2}$OTBDMS, $CuSO_4 \cdot 5H_2O$, 1,10-phenanthroline, K_2CO_3, toluene; (b) K_2CO_3, MeOH; (c) *n*-BuLi, NIS, THF; (d) Dess–Martin periodinane, CH_2Cl_2; (e) $CrCl_2$, $NiCl_2$, THF.

SCHEME 3. Synthesis of Expected Product of Bergman Cyclization of 1a[a]



[a]Reagents and conditions: (a) MeLi, THF, 90%; (b) PCC, CH_2Cl_2, 74%; (c) TBDMSCl, Et_3N, NaI, MeCN, 82%; (d) Grubbs' second generation catalyst, CH_2Cl_2, 72%; (e) HF, $MeCN_{aq}$, 41%; (f) $LiAlH_4$, THF, 75%.

TABLE 1. Selected Interatomic Distances (Å) and Selected Bond Angles (deg) in X-ray Structures of Aza-enediynes 1a–d[a]

	C(2)–C(5)	C(1)–C(6)	C(1)–N	C(1)–C(2)–C(3)	C(2)–C(1)–N	C(4)–C(5)–C(6)	C(5)–C(6)–C(7)
1a	(2.731)	(3.320)	(1.345)	(166.7)	(170.6)	(167.1)	(173.2)
1b	2.788 (2.757)	3.633 (3.468)	1.353 (1.346)	173.1 (167.9)	178.4 (170.6)	170.7 (170.6)	172.8 (174.7)
1c	2.811 (2.886)	3.876 (4.116)	1.353 (1.347)	176.9 (178.5)	179.0 (178.0)	175.1 (177.9)	172.4 (172.1)
1d	2.869 (2.864)	4.157 (4.032)	1.361 (1.346)	178.4 (179.1)	178.4 (178.0)	176.3 (177.7)	178.3 (176.3)

[a]Numbers in parentheses represent parameters from B3LYP/6-31++G(d,p) optimized geometries of **1′a–d**.

group produced the target 4-hydroxy-*N*-tosyl-1,2,3,4-tetrahydrobenzo[*g*]quinoline (**17**, Scheme 3).

Crystallographic Characterization of Aza-enediynes 1b–d. Needle-like colorless crystals of aza-enediynes **1b–d** suitable for X-ray diffraction studies were grown by slow diffusion of heptane vapors into ethyl acetate solutions of the substrates. Crystallographic data for enediynes **1b–d** is presented in Supporting Information.[18] Selected interatomic distances and bond angles are presented in Table 1. Atom numbering in structures of aza-enediynes is illustrated on ORTEP plots shown in Figure 1. 11-Membered enediyne **1b** crystallizes in the orthorhombic space group *Pbca*; 12- (**1c**) and 13-membered (**1d**) aza-enediyne crystallize in the monoclinic, space group $P2_1/n$. In all cases the asymmetric units contain one molecule of the corresponding enediyne. We have observed some disorder, at propargylic and adjusted sp^3-hybridized carbon atoms, related to flexibility ("breathing") of midsize macrocycles. Interestingly, the transannular distances between sp-hybridized carbon atoms C(2) and C(5) were found to be virtually the same, ca. 2.8 Å, for all macrocycles, whereas separation of acetylenic termini, C(1) – C(6), increases significantly from 3.6 Å **1b** to 3.9 Å in **1c** and 4.2 Å in **1d** (Table1). The latter distances are significantly longer than Nicolaou's "critical distance" for the spontaneous cyclization of enediynes (3.31 Å).[21] This observation agrees well with the stability of **1b–d** under ambient conditions. The C–N bond lengths in all three enediyne-amides were found to be very similar. The acetylene fragment of aza-enediyne **1b** is slightly bent with C(4)–C(5)–C(6) and C(5)–C(6)–C(7) angles of 170.7°, and 161.6°, respectively. In the larger macrocycles **1c** and **1d** the acetylenic fragments show very small deviations from linearity.

Reactivity of Aza-enediynes 1a–d. As we reported in our preliminary communication, 10-membered ring aza-enediyne **1a** undergoes facile cycloaromatization at 40 °C;[16] however, the expected Bergman cyclization–hydrogen abstraction product **17** was not isolated from reaction mixtures. To test the validity of this observation, we have independently prepared *N*-tosyl-4-hydroxy-1,2,3,4-tetrahydrobenzo[*g*]quinoline **17** (Scheme 3). No **17** was detected in reaction mixtures of thermolysis of aza-enediyne **1a** in either in 2-propanol or in 1,4-cyclohexadiene solutions. To the contrary, high yield of O–H insertion product **2a** is formed in 2-propanol, and reaction in benzene yields C–H insertion product **3a**. Consumption of 50% of the substrate at 40 °C is achieved in about 20 min in either solvent. The kinetic analysis of this reaction in 2-propanol, however, reveals the presence of a 10–12 min induction period, where the absorbance of starting material shows little change (Figure 2). This initial period is followed by the rapid decay of the substrate. This type of kinetics is usually associated with autocatalytic reactions. We hypothesized that initial decomposition of **1a** produces small amounts of *p*-toluene sulfonic acid, which

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[21] Nicolaou, N. C.; Zuccarello, G.; Riemer, C.; Estevez, V. A.; Dai, W. M. *J. Am. Chem. Soc.* **1992**, *114*, 7360.

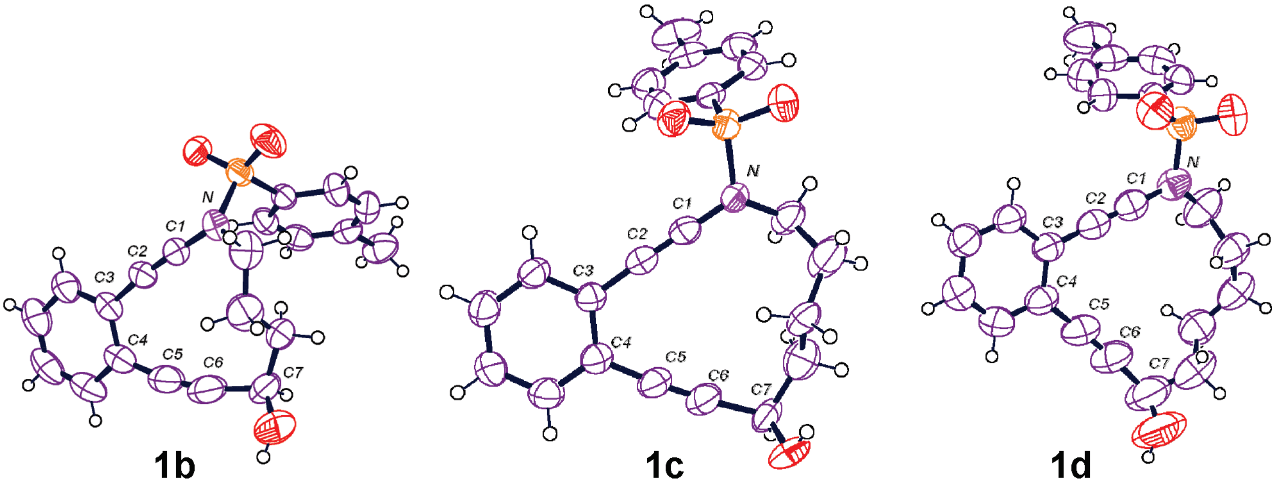

FIGURE 1. ORTEP drawing of aza-enediynes **1b**, **1c**, and **1d**. Thermal ellipsoids are shown at 50% probability.

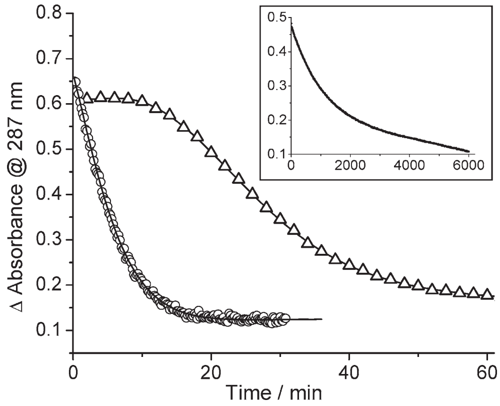

FIGURE 2. Decay of absorbance of ca. 2.9×10^{-4} M enediyne **1a** in neat 2-propanol (△) and in the presence of 1.5 μM of *p*-toluene sulfonic acid (○). The insert reaction of ca. **1a** in the presence of equimolar amounts of Et_3N.

then catalyzes the conversion of the substrate to product **2a**. In fact, traces of *p*-toluene sulfonic acid esters were detected in the reaction mixtures of the decomposition of aza-enediynes **1a**−**d** in alcohols. In agreement with this hypothesis, cyclization of **1a** in the presence of 1.5 μM of *p*-TsOH (~ 0.5 mol %) in 2-propanol shows no induction period and proceeds much faster, with a half-life of ~5 min at 25 °C (Figure 2). Addition of equimolar amounts of triethylamine or DBU to the reaction mixture, on the other hand, dramatically slows down the decomposition of **1a**. This reaction shows complex kinetics, and 50% conversion of the enediyne **1a** is achieved at ca. 27 h at 40 °C (Figure 2). Decomposition of **1a** in 2-propanol in the presence of triethylamine produces multiple products along with substantial amount of polymeric material. Compounds **2a** or **17** were not detected by the HPLC analysis of the reaction mixture, suggesting that both cationic and Bergman cycloaromatization pathways are suppressed under these conditions. Similar results were obtained in the 55 °C thermolysis of 11-membered ring aza-enediyne **1b** in 2-propanol in the presence of equimolar amounts of triethylamine or DBU. GC−MS analysis of the complex reaction mixture produced in this reaction found neither Bergman cyclization product nor O−H insertion product **2b**.

The thermal cyclization of novel 11- (**1b**), 12- (**1c**), and 13- (**1d**) aza-enediynes was studied in 2-propanol at 55 °C in the presence of catalytic amounts of *p*-toluenesulfonic acid. 2-Propanol was selected as a media for thermolyses as it can act both as hydrogen or proton donor and a nucleophile. Heating of 11-membered ring aza-enediyne **1b** in 2-propanol produced the expected naphthazepin **2b** in 52% isolated yield (Scheme 4). No products resulted from hydrogen abstraction by *p*-benzyne diradical (similar to **17**) were detected by of GC−MS analysis of the reaction mixtures. Surprisingly, decomposition of larger aza-enediyne **1c** and **1d** under identical conditions did not produce detectable amounts of cyclization products **2c**−**d**; *N*-tosyl lactams **21c**,**d** were isolated instead (Scheme 4). These lactams are apparently produced by the hydrolysis of unstable amide enol ethers **20c**,**d** during workup of the reaction mixture (Scheme 4). Similar reaction was previously observed in the thermal decomposition of acyclic aza-enediyne **4** (Scheme 1).[16]

Formation of cycloaromatized products **2a**,**b** and lactams **21c**,**d** can be accommodated by a reaction mechanism, shown in Scheme 4. Initial protonation of electron-rich ynamide fragment of aza-enediynes **1a**−**d** gives rise to ketenimmonium cations **18a**−**d**. In the case of 10- and 11-membered ring macrocycles cation **18** cyclizes to form naphthyl cation **19**, which is then trapped by the solvent. Cyclization of larger macrocyclic cations **18c**,**d** is apparently slower than the nucleophilic addition of 2-propanol to the ketenimmonium moiety. In fact, when more nucleophilic methanol was employed as a solvent in the reaction, 10-membered ring aza-enediyne **1a** still produced only cyclization product **2a**,[16] but 11-membered ring **1b** gave a mixture of naphthazepine **22b** and lactam **21b** in 44% and 38% isolated yields, respectively (Scheme 5).

Thermolysis of 11-membered ring aza-enediyne **1b** in aqueous solution in the presence of 30% of THF and catalytic amounts of *p*-TsOH resulted in a clean acid-catalyzed cyclization producing *N*-tosyl-5,6-dihydroxy-1*H*-1-naphthazepine (**23b**) in 46% isolated yield (Scheme 5). Despite the high concentration of tetrahydrofuran, which is a known hydrogen donor,[22] no hydrogen abstraction products **17** were detected in reaction mixtures. This observation provides further support for the mechanism shown in the Scheme 4.

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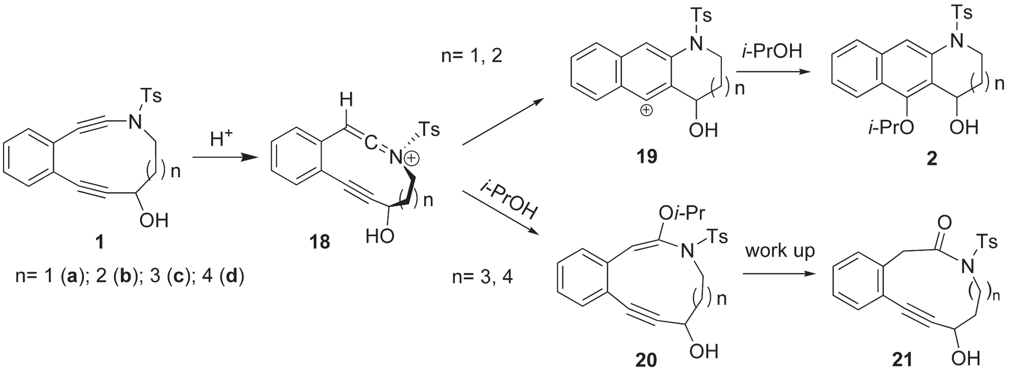
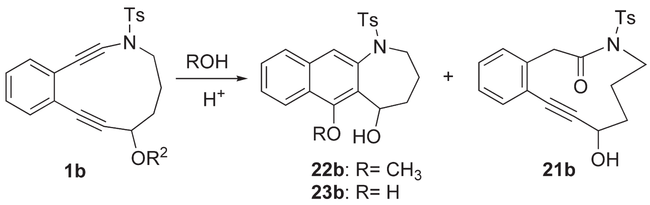
[22] C-H bond dissociation energy in THF is 92 kcal mol^{-1}: Golden, D. M.; Benson, S. W. *Chem. Rev.* **1969**, *69*, 125.

SCHEME 4



SCHEME 5



The affirmative assignment of structures **21b** and **23b** was obtained from single crystal X-ray analysis (Figure S1).[18]

On the basis of the latter observation, we hypothesized that thermolysis of aza-enediynes in solvents of lower nucleophilicity should increase the yield of the cycloaromatized products for **2b**−**d**. Our previous study showed that thermolysis of **1a** in 1,4-cyclohexadiene gave rise to an inseparable mixture of three 1:1 enediyne−solvent adducts.[16] Heating of 11-membered ring aza-enediyne **1b** in 1,4-cyclohexadiene at 60 °C for 12 h produced similar inseparable mixture of 1:1 adducts. In benzene at 60 °C in the presence of catalytic amounts of *p*-toluenesulfonic acid, **1a** produced *N*-tosyl-4-hydroxy-5-phenyl-1,2,3,4-tetrahydrobenzo[*g*]quinoline (**3a**) as a major product (Scheme 6). This compound is apparently formed in a Friedel−Crafts alkylation of the solvent by cation **19a** (Scheme 4). Thermolyses of larger aza-enediynes **1b**−**d** were conducted in benzene containing 0.1 equiv of *p*-toluenesulfonic acid at 60 °C. The 11-membered ring aza-enediyne **1b** gives a product similar to that of **1a**. The Friedel−Crafts adduct, however, undergoes further dehydration to produce *N*-tosyl-6-phenyl-2,3-dihydro-1*H*-1-naphthazepine (**24b**), which was isolated in 21% yield (Scheme 6). Approximately 5% of a very labile compound, which shows spectral characteristic similar to that of **24b** but containing two phenyl groups, was also isolated.

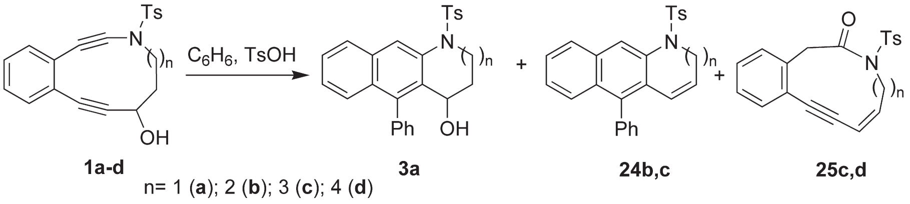
Thermolysis of the 12-membered ring aza-enediyne **1c** under identical conditions produces similar Friedel−Crafts addition−dehydration product **24c** in 18% isolated yield. The major product of the reaction, however, is *N*-tosyl lactam **25c** (28% isolated yield, Scheme 6), which is apparently formed by the acid-catalyzed dehydration and addition of water across the ynamide triple bond. The largest aza-enediyne in the series, **1d**, produces only the lactam **25d** in 41% isolated yield. Only traces of cyclization product **24d** were detected by GC−MS analysis of the reaction mixture.

In addition to full spectral characterization of the thermolysis products, structures of compounds **24b**,**c** and **25c**,**d** were established by single crystal X-ray diffraction analysis (Figure S1 in Supporting Information).[18] It is interesting to note that in cyclization products **24b** and **24c** the plane of the phenyl ring is almost orthogonal to the naphthalene fragment.

As an additional mechanistic test, we have conducted thermolysis of 11-membered ring aza-enediyne **1b** in anhydrous hexanes in the presence of catalytic amounts of *p*-toluenesulfonic acid. The GC−MS analysis of the complex mixture of products revealed no hydrogen abstraction or C−H insertion products. Since hexane is not nucleophilic but readily reacts with radicals, this experiment further supports the polar mechanism of the formation of formal C−H insertion products **3a**, **23b**, and **23c**.

Kinetics of Acid-Catalyzed Cyclization of Aza-enediynes. The accurate rate measurements of acid-catalyzed cycloaromatization of enediynes **1a**−**d** were conducted by UV spectroscopy following the decay of the characteristic aza-enediyne band at 227 nm at 20.0 ± 0.1 °C. Rates of cyclization of **1a**−**d** were determined in dilute aqueous solutions of perchloric or hydrochloric acid in the presence of 25% of organic cosolvent to ensure solubility (THF or acetonitrile). The consumption of starting materials followed the first-order rate law well. The pseudo-first-order rate constants obtained by least-squares fitting of the data to a single exponential equation were found to be linearly proportional to the acid concentration. The second-order acid

SCHEME 6



SCHEME 7

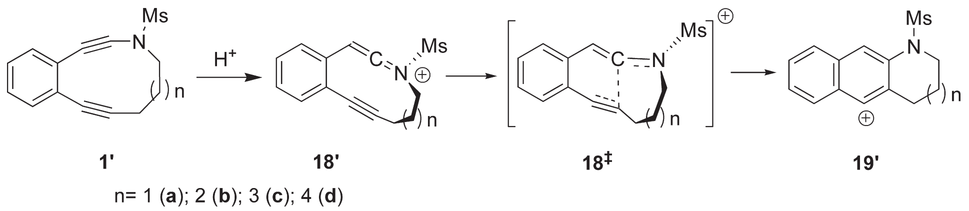


TABLE 2. Acid-Catalyzed Reactions of Aza-enediynes 1a−d

	k_{H+}, s^{-1} M^{-1} [a]	k_{H+}/k_{D+} [b]
1a	6.2[c]	$\sim 2^{16}$
1b	$(4.31 \pm 0.18) \times 10^{-1}$	1.67
1c	$(6.94 \pm 0.31) \times 10^{-3}$	1.61 (1.25[d])
1d	$(2.66 \pm 0.18) \times 10^{-3}$	

[a] Measured in $HClO_4$ solutions. [b] Determined in HCl/H_2O and DCl/D_2O solutions. [c] Estimated from a single concentration measurements. [d] Measured in 3:1 D_2O/acetonitrile mixture.

catalytic coefficients are presented in Table 2. Although cycloaromatization of all aza-enediynes **1a−d** is catalyzed by an acid, the catalysis is more pronounced in the case of 10-membered ring aza-enediyne **1a** and becomes progressively weaker with increased ring size (Table 2). This dependence correlates well with proton affinities of aza-enediynes **1a−d** calculated using DFT or MP2 methods (*vide infra*).

Catalysis of the cycloaromatization reaction of aza-enediynes **1a−d** by deuterium chloride in D_2O was almost 2 times weaker, producing primary kinetic isotope effect in the normal direction. This observation indicates that proton transfer to the β-carbon of the ynamide moiety is involved in a rate-determining step. In fact, the actual value of the primary KIE in this case is higher, as the observed value is reduced by the secondary solvent isotope effect. Protonation of the substrate by hydronium or deuteronium ions converts the latter into an L_2O molecule (L = H or D). This is a bond-tightening process and usually produces an inverse kinetic isotope effect. The value of the observed KIE provides evidence against mechanisms of aza-enediyne cycloaromatization that involve rapid pre-equilibrium protonation of the substrate.

Theoretical analysis of structural properties and reactivity of aza-enediynes **1a−d** was conducted using MP2 and hybrid DFT B3LYP methods. To simplify the calculations, we have removed the hydroxyl group and replaced the *p*-toluenesulfonyl moiety in structures of aza-enediynes with methanesulfonyl (Scheme 7). Geometries of such aza-enediynes **1′a−d**, corresponding ketenimmonium cations **18′a−d**, naphthyl cations **19′a−d**, and transition states for the cyclization of ketenimmonium cation **18‡a−d** (Scheme 7) were optimized at B3LYP/6-31++G(d,p) level. The optimized geometries, as well as the details of theoretical procedures, are provided in the Supporting Information.[18] Despite structural modification introduced in molecules of enediynes **1′a−d** DFT-optimized geometries of these compounds were found to be very close to the structures of **1a−d** determined by X-ray analysis. Selected structural parameters and transannular distances are listed in Table 1 together with values obtained from single crystal X-ray analysis. The representative geometry of a transition state is shown in the Figure 3 on the example of 11-membered ring **18‡b**.

Single-point energies for **1′**, **18′**, **18‡**, and **19** were also calculated at the B3LYP/6-311++G(d,p) level. In addition, FC-MP2/6-311++G(d,p) energies were computed for each energy minima. Zero-point vibrational energy (ZPVE) corrections were obtained from B3LYP/6-31+G(d,p) frequency calculations. The relative energies of species involved in the acid-catalyzed cyclization of aza-enediynes **1a−d** are listed in the Table 3. The relative proton affinities of aza-enediynes **1a−d** were evaluated using isodesmic protonation reaction shown on the Scheme 8. The enthalpies of these reactions are also presented in the Table 3.

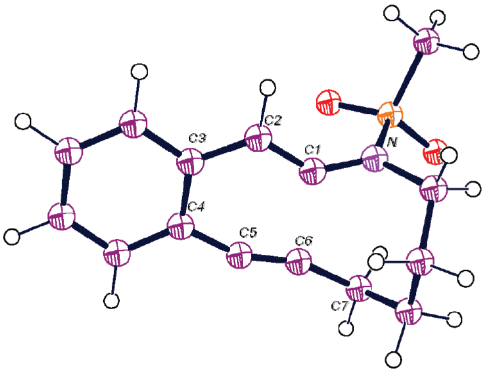


FIGURE 3. B3LYP/6-31++G(d,p) optimized geometry of the transition state **18‡b**.

Both DFT and MP2 calculations predict that relative proton affinities of 10- and 11-membered ring aza-enediynes **1′a**,**b** are very close. Increase of the ring size to 12 (**1′c**) and 13 (**1′d**) substantially reduces relative proton affinities (Table 3). These results correlate well with the experimental rates of acid-catalyzed reactions of aza-enediynes **1a−d**, which decrease with increasing ring size (Table 2). We believe that protonation of smaller macrocycles **1′a**,**b** to give ketenimmonium cations **18′a**,**b** (Scheme 8) results in reduction of a ring strain, while protonation of **1′c** and **1′d** produces an opposite effect. In fact, if we use the distortion of a triple bond linearity as a crude indicator of the ring strain, we can see that cyclization **1′** → **18′** in the case of 10- (**1′a**) and 11-membered ring (**1′b**) aza-enediynes is accompanied by the reduced deviation of the acetylenic C4−C5−C6 bond angle from 180° (Table 3). Protonation of **1′c**, to the contrary, somewhat increases the distortion of a triple bond. This effect becomes more pronounced for 13-membered aza-enediyne **1′d**.

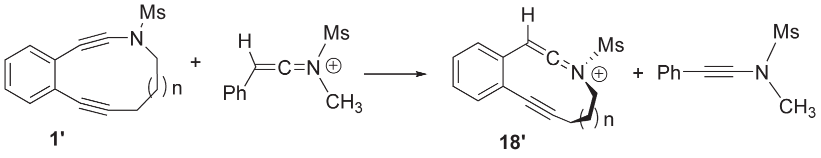
The cyclization of ketenimmonium cation **18′** to naphthyl cation **19′** is weakly exothermic for the 10-membered ring aza-enediyne **1′a**, is accompanied with little energy changes for 11-membered **1′b**, but becomes progressively endothermic for lager macrocycles **1′c** and **1′d**. The DFT-calculated activation barrier for the cyclization step is relatively low but grows with the increased ring size (Table 3). The barrier for the reverse process, on the other hand, is reduced in the case of lager cycles. These results apparently indicate that

TABLE 3. **Electronic Energies of Carbocations 18′, 19′, and Cyclization Transition States $18^{\ddagger}$,[a,b] Relative Proton Affinities of Aza-enediynes 1a−d,[c] and Distortion of a Triple Bond in 1′a−d and 18′a−d**

starting enediyne (ring size)	Δ*E*° of protonation (kcal/mol) **1′** → **18′**	Δ*E*° of cyclization (kcal/mol) **18′** → **19′**	Δ*E*‡ of cyclization (kcal/mol) **18′** → **18**‡	deviation of C4−C5−C6 angle from linearity (deg) in **1′**	deviation of C4−C5−C6 angle from linearity (deg) in **18′**
1′a (10)	−6.53 (−0.96)	−1.33 (−1.87)	4.09	−12.9	−9.4
1′b (11)	−7.02 (−0.51)	1.46 (0.36)	5.32	−9.4	−3.3
1′c (12)	−4.10 (2.20)	7.76 (4.41)	11.00	−2.1	+4.6
1′d (13)	−0.05 (5.57)	16.81 (16.04)	17.83	−2.3	+9.6

[a] ZPVE-corrected energies were computed at B3LYP/6-311++G(d,p)//B3LYP/6-31++G(d,p) and FC-MP2/6-31++G(d,p)//B3LYP/6-31++G(d,p) (in parentheses). [b] In each series the electronic energies are referenced to **18′**. [c] The enthalpy of the reaction shown in Scheme 8.

SCHEME 8



n= 1 (**a**); 2 (**b**); 3 (**c**); 4 (**d**)

ketenimmonium cations **18a−d** exist in a rapid equilibrium with naphthyl cations **19a−d**. The position of this equilibrium predicted on the exothermicity of reaction correlates well with the experimental data (*vide supra*). Thus, both DFT and MP2 calculation predict **19′a** to be a predominant form in the equilibrium. Experimentally, in alcohols, water, and benzene **1a** exclusively produces cycloaromatized products **2a** and **3a**. 11-Membered ring aza-enediyne **1b** represents a borderline case. Ketenimmonium cation **18′b** and naphthyl cation **19′b** have similar stabilities, and apparently **18b** and **19b** are present in the equilibrium in appreciable amounts. In agreement with computational results, the outcome of acid-catalyzed reactions of **1b** depends on the media. In benzene and 2-propanol cyclization is still a predominant process, whereas in more nucleophilic methanol, addition to **18b** competes with cyclization. In the case of protonation of 12- (**1c**) and 13-membered ring (**1d**) aza-enediynes, calculations predict that equilibrium is strongly shifted to the ketenimmonium (**18c**,**d**) side. In fact, the major products of acid-catalyzed reactions of **1c** and **1d** are produced by the addition of nucleophiles to cations **18c** and **18d**, respectively.

Conclusions

Introduction of amide nitrogen at the acetylenic terminus of cyclic enediynes completely suppresses the conventional radical Bergman cyclization. The ynamide moiety of aza-enediynes **1a−d** is very nucleophilic and undergoes facile protonation even at trace acid concentrations to produce ketenimmonium ions **18a−d**. The latter exist in equilibrium with a cyclized form **19a−d**. The position of this equilibrium and depends on the ring size: in the case of 10-membered ring aza-enediyne **1a** cyclized cation **19a** is a predominant form in the equilibrium and all reaction products contain a naphthalene moiety. Equilibrium established upon protonation of 11-memebred ring analogue **1b**, on the other hand, contains both cations in appreciable amounts. The outcome of the acid-catalyzed reaction of **1b**, i.e., cyclization versus addition to the triple bond, strongly depends on the nucleophilicity of the solvent. In the case of larger rings, cyclization of cation **18** is an uphill process and most of the products are produced from the parent ketenimmonium cations **18c**,**d**. Strong acid catalysis of the cycloaromatization reaction of aza-enediynes **1a−d**, as well as observed primary kinetic isotope effect, indicate that protonation of a β-carbon of the ynamide moiety is a rate-determining step of the process.

Experimental Section

Kinetics. Rate measurements were performed using Carry-300 Bio UV−vis spectrometer equipped with a thermostattable cell holder. The temperature was controlled with 0.1 °C accuracy. Reactions were monitored by the decay of aza-enediyne absorbance at 227 nm absorbance. Observed first-order rate constants were calculated by least-squares fitting of a single exponential function.

Theoretical Procedures. Quantum mechanical calculations were carried out using the Gaussian 03 program.[23] Geometry optimizations, IRC, and frequency calculations were conducted using the B3LYP/6-31++G(d,p) method. Zero-point vibrational energy (ZPVE) corrections, required to correct the raw relative energies to 0 K, we scaled by 0.9772.[24] Analytical second derivatives were computed to confirm each stationary point to be a minimum by yielding zero imaginary vibrational frequencies for the intermediates and one imaginary vibrational frequency for each transition state. Optimized geometries obtained from B3LYP/6-31++G(d,p) calculations are listed below in Gaussian 03W output format.

Materials. *N*-[4-(*tert*-Butyldimethylsilyloxy)butyl]tosylamide (**27b**), *N*-[5-(*tert*-butyldimethylsilyloxy) pentyl]tosylamide (**27c**),

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(23) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; OrVtiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.02*; Gaussian, Inc.: Wallingford, CT, 2004.

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and *N*-[6-(*tert*-Butyldimethylsilyloxy)hexyl]tosylmide (**27d**) were prepared from corresponding aminoalcohols using standard procedures.[18] *N*-Allyl-*N*-(3-formylnaphthalene-2-yl)tosylamide (**11**) was synthesized according to the literature procedure.[18,25] Other reagents were obtained from commercial sources and used as received unless otherwise noted.

***N*-(4-(*tert*-Butyldimethylsilyloxy)butyl)-*N*-(2-ethynylphenylethynyl)tosylamide (7b, TMS protection was lost).** A suspension of **27b** (23.87 g, 66.85 mmol), **6**[26] (12.3 g, 44.57 mmol), $CuSO_4 \cdot 5H_2O$ (1.68 g, 6.7 mmol), 1,10-phenantroline (2.41 g, 13.4 mmol), and K_2CO_3 (18.71 g, 133.7 mmol) in 150 mL of degassed was stirred for 20 h under nitrogen at 85 °C. The reaction mixture was filtered and concentrated. The residue was purified by chromatography (hexanes/ethyl acetate 30:1 → 20:1 → 15:1) to provide 20.18 g (41.95 mmol, 94%) of **7b** as slightly brown oil. ^{1}H NMR: 7.85 (d, J=8 Hz, 2 H), 7.46 (d, J = 7.6 Hz, 1 H), 7.344 (m, 3 H), 7.27 (t, J=7.2 Hz, 1 H), 7.20 (t, J = 7.2 Hz, 1 H), 3.62 (t, J = 5.6 Hz, 2 H), 3.45 (t, J = 7.2 Hz, 2 H), 3.26 (s, 1 H), 2.43 (s, 3 H), 1.83 (p, J=6.4 Hz, 2 H), 1.56 (m, 2 H), 0.94 (s, 9 H), 0.16 (s, 6 H). ^{13}C NMR: 144.8, 134.9, 132.6, 131.1, 129.9, 128.7, 127.9, 127.2, 126.6, 123.6, 86.7, 82.6, 81.0, 69.9, 62.3, 51.8, 29.7, 26.1, 24.7, 21.8, 18.5, −4.9. MS calcd for $C_{27}H_{35}NO_3SSi$ (M^+) 481.2107, found 481.2135.

***N*-(5-(*tert*-Butyldimethylsilyloxy)pentyl)-*N*-((2-((trimethylsilyl)ethynyl)phenyl)ethynyl)tosylamide (7c).** Yield 89%. ^{1}H NMR: 7.89 (d, J = 8 Hz, 2 H), 7.45 (dd, J = 7.6, 1.2 Hz, 1 H), 7.35 (d, J = 8 Hz, 3 H), 7.24 (td, J = 7.6, 1.6 Hz, 1 H), 7.19 (td, J = 7.6, 1.6 Hz, 1 H), 3.58 (t, J = 6.0 Hz, 2 H), 3.41 (t, J = 7.2 Hz, 2 H), 2.44 (s, 3 H), 1.81−1.72 (m, 2 H), 1.58−1.49 (m, 2 H), 1.44−1.35 (m, 2 H), 0.88 (s, 9 H), 0.20 (s, 9 H), 0.03 (s, 6 H). ^{13}C NMR: 144.7, 135.0, 132.9, 131.5, 130.0, 128.3, 127.9, 127.2, 125.9, 124.5, 103.7, 98.1, 86.6, 70.1, 63.1, 51.9, 32.4, 28.0, 26.2, 22.8, 21.8, 0.2, −5.1. HRMS calcd for $C_{31}H_{45}NO_3SSi_2$ (M^+) 567.2659, found 567.2662.

***N*-(6-(*tert*-Butyldimethylsilyloxy)hexyl)-*N*-((2-((trimethylsilyl)ethynyl)phenyl)ethynyl)tosylamide (7d).** Yield 91%. ^{1}H NMR: 7.89 (d, J = 8 Hz, 2 H), 7.47 (dd, J = 7.6, 1.2 Hz, 1 H), 7.35 (d, J = 8 Hz, 3 H), 7.28 (td, J = 7.6, 1.6 Hz, 1 H), 7.21 (td, J = 7.6, 1.6 Hz, 1 H), 3.59 (t, J = 6.0 Hz, 2 H) 3.42 (t, J = 7.2 Hz, 2 H), 3.26 (s, 1 H), 2.45 (s, 3 H), 1.81−1.71 (m, 2 H), 1.53−1.44 (m, 2 H), 1.39−1.30 (m, 4 H), 0.88 (s, 9 H), 0.04 (s, 6 H). ^{13}C NMR: 144.8, 135.0, 132.7, 131.1, 130.0, 128.7, 127.9, 127.2, 126.6, 123.5, 82.6, 80.9, 70.0, 63.3, 51.7, 32.9, 31.8, 27.9, 26.3, 25.6, 21.9, 18.6, −5.1. MS calcd for $C_{32}H_{47}NO_3SSi_2$ ($M^+ - 57$) 524.2, found 524.2.

***N*-((2-Ethynylphenyl)ethynyl)-*N*-(4-hydroxybutyl)tosylamide (8b).** A THF solution of TBAF (45 mL, 45 mmol, dried over molecular sieves) was added to a solution of silyl ether **7b** (23.20 g, 41.95 mmol) in 200 mL of THF at 0 °C. The reaction mixture was stirred for 90 min at 0 °C, diluted with ethyl acetate (ca. 300 mL), washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography (ethyl acetate/hexanes 1:1) to provide 13.57 g (36.98 mmol, 88%) of **8b** as dark orange oil. ^{1}H NMR: 7.89 (d, J = 8.0 Hz, 2 H), 7.46 (d d, J = 7.2, 0.8 Hz, 1 H), 7.36 (m, 3 H), 7.27 (t d, J = 7.6, 1.2 Hz 1 H), 7.21 (t d, J = 7.2, 1.2 Hz 1 H), 3.67 (t, J = 6 Hz, 2 H), 3.46 (t, J = 6.8 Hz, 2 H), 3.29 (s, 1 H), 2.44 (s, 3 H), 1.89 (m, 2 H), 1.64 (m, 2 H). ^{13}C NMR: 144.9, 134.8, 132.7, 131.1, 130.0, 128.7, 127.9, 127.3, 126.5, 123.6, 86.6, 82.6, 81.1, 70.1, 62.4, 51.7, 29.5, 24.5, 21.9. MS calcd for $C_{21}H_{21}NO_3S$ (M^+) 367.1242, found 367.1254.

***N*-((2-Ethynylphenyl)ethynyl)-*N*-(5-hydroxypentyl)tosylamide (8c).** Yield 90%. ^{1}H NMR: 7.89 (d, J = 8 Hz, 2 H), 7.46 (dd, J = 7.6, 0.8 Hz, 1 H), 7.35 (d, J = 8 Hz, 3 H), 7.27 (td, J = 7.6, 1.6 Hz, 1 H), 7.20 (td, J = 7.6, 1.6 Hz, 1 H), 3.63 (t, J = 6.0 Hz, 2 H), 3.43 (t, J = 7.2 Hz, 2 H), 3.27 (s, 1 H), 2.44 (s, 3 H), 1.80 (p, J = 7.2 Hz, 2 H), 1.58−1.51 (m, 2 H), 1.47−1.38 (m, 2 H). ^{13}C NMR: 144.9, 134.9, 132.8, 131.1, 130.0, 128.7, 127.9, 127.3, 126.5, 123.6, 86.7, 82.6, 81.0, 70.0, 62.8, 51.8, 32.3, 27.7, 22.7, 21.8. HRMS calcd for $C_{22}H_{23}NO_3S$ ($M + Na^+$) 404.1296, found 404.1307.

***N*-((2-Ethynylphenyl)ethynyl)-*N*-(6-hydroxyhexyl)tosylamide (8d).** Yield 78%. ^{1}H NMR: 7.89 (d, J = 8 Hz, 2 H), 7.47 (dd, J = 7.6, 1.2 Hz, 1 H), 7.35 (d, J = 8 Hz, 3 H), 7.28 (td, J = 7.6, 1.6 Hz, 1 H), 7.21 (td, J = 7.6, 1.6 Hz, 1 H), 3.62 (s, b, 2 H) 3.42 (t, J = 7.2 Hz, 2 H), 3.26 (s, 1 H), 2.44 (s, 3 H), 1.82−1.73 (m, 2 H), 1.63 (s, 1H), 1.59−1.51 (m, 2 H), 1.42−1.35 (m, 4 H). ^{13}C NMR: 144.8, 134.9, 132.8, 131.1, 130.0, 128.7, 127.9, 127.2, 126.6, 123.6, 86.7, 82.6, 81.0, 70.0, 62.9, 51.8, 32.7, 27.9, 26.2, 25.4, 21.9. HRMS calcd for $C_{23}H_{25}NO_3S$ (M^+) 395.5155, found 395.5151.

***N*-(4-Hydroxybutyl)-*N*-((2-iodoethynyl)phenylethynyl)tosylamide (9b).** A solution of *n*-BuLi in THF (9.74 mL, 25.03 mmol) was added dropwise to a solution of acetylene **8b** (4.37 g, 11.92 mmol) in 50 mL of THF at −78 °C and stirred for 30 min. A solution of NIS (3.02 g, 13.5 mmol) in ca. 50 mL of THF was added, and the reaction mixture was stirred for 4 h at −78 °C. The reaction was quenched by brine (ca. 10 mL) and concentrated in vacuum. The residuewas purified by chromatography (petroleum ether/ethyl acetate 1:1) to provide 5.04 g (10.22 mmol, 86%) of **9b** as brown oil. ^{1}H NMR: 7.87 (d, J = 8.0 Hz, 2 H), 7.41−7.35 (m, 4 H), 7.25 (d d, J = 7.6, 1.2 Hz, 1 H), 7.19 (d d, J = 7.6, 1.2 Hz, 1 H), 3.70 (t, J = 6.8 Hz, 2 H), 3.47 (t, J = 6.8 Hz, 2 H), 2.45 (s, 3 H), 1.87 (m, 2 H), 1.69 (m, 2 H). ^{13}C NMR: 144.7, 134.5, 132.7, 130.8, 129.9, 128.5, 127.7, 127.0, 126.5, 124.4, 93.0, 86.5, 69.8, 62.3, 51.5, 29.3, 24.3, 21.7, 10.2. MS calcd for $C_{21}H_{20}INO_3S$ (M^+) 493.0209, found 493.0193.

***N*-(4-Hydroxypentyl)-*N*-((2-iodoethynylphenyl)ethynyl)tosylamide (9c).** Yield 73%. ^{1}H NMR: 7.85 (d, J = 8 Hz, 2 H), 7.35−7.31 (m, 4 H), 7.23 (td, J = 7.6, 1.6 Hz, 1 H), 7.16 (td, J = 7.6, 1.6 Hz, 1 H), 3.58 (t, J = 6.0 Hz, 2 H), 3.40 (t, J = 7.2 Hz, 2 H), 2.42 (s, 3 H), 1.78 (p, J = 7.2 Hz, 2 H), 1.64−1.54 (m, 2 H), 1.46−1.38 (m, 2 H). ^{13}C NMR: 145.0, 134.8, 132.9, 131.0, 130.2, 128.8, 127.9, 127.2, 126.8, 124.7, 93.2, 86.8, 70.0, 62.8, 51.9, 32.3, 27.8, 22.8, 21.9, 11.1. HRMS calcd for $C_{22}H_{23}INO_3S$ ($M + H^+$) 508.0443, found 508.0447.

***N*-(5-Hydroxyhexyl)-*N*-((2-iodoethynylphenyl)ethynyl)tosylamide (9d).** Yield 69%. ^{1}H NMR: 7.87 (d, J = 8 Hz, 2 H), 7.42−7.34 (m, 4 H), 7.25 (td, J = 7.6, 1.6 Hz, 1 H), 7.19 (td, J = 7.6, 1.6 Hz, 1 H), 3.63 (s, b, 2 H) 3.43 (t, J = 7.2 Hz, 2 H), 2.45 (s, 3 H), 1.82−1.75 (m, 2 H), 1.63−1.57 (m, 3 H), 1.49−1.36 (m, 4 H). ^{13}C NMR: 144.8, 134.8, 132.9, 130.9, 130.1, 128.7, 127.9, 127.1, 126.9, 124.7, 93.2, 86.9, 70.0, 62.9, 51.9, 32.8, 27.9, 26.3, 25.4, 21.9, 14.3. MS calcd for $C_{23}H_{24}INO_3S$ (M^+) 521.0 found 521.0.

***N*-((2-Iodoethynylphenyl)ethynyl)-*N*-(4-oxobutyl)tosylamide (10b).** Dess−Martin periodinane (5.06 g, 10.90 mmol) was added to a solution of alcohol **9b** (5.04 g, 11.82 mmol) in CH_2Cl_2 (100 mL), and the resulting suspension was stirred for 5 h. The reaction mixture was diluted with Et_2O (ca. 250 mL), washed with $NaHCO_3$ solution (2 × 100 mL), dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by chromatography (hexanes/ethyl acetate 2:1) to provide 3.68 g (7.49 mmol, 69%) of **10b** as brown oil. ^{1}H NMR: 9.80 (s, 1 H), 7.86 (d, J = 8.4 Hz, 2 H), 7.41−7.34 (m, 4 H), 7.26−7.15 (m, 2 H), 3.47 (t, J = 6.4 Hz, 2 H), 2.65 (t, J = 7.2 Hz, 2 H), 2.45 (s, 3 H), 2.10 (p, J = 7.2 Hz, 2 H). ^{13}C NMR: 201.3, 134.6, 133.0, 131.0, 130.2, 128.8, 127.9, 127.3, 126.6, 124.8, 93.2, 86.4, 70.1, 51.1, 40.5, 22.0, 20.6, 10.4. HRMS calcd for $C_{21}H_{18}INO_3S$ (M^+) 491.0052, found 491.0031.

***N*-((2-Iodoethynylphenyl)ethynyl)-*N*-(4-oxopentyl)tosylamide (10c).** Yield 71%. ^{1}H NMR: 9.76 (s, 1 H), 7.87 (d, J = 8 Hz, 2 H), 7.42−7.33 (m, 4 H), 7.29−7.17 (m, 2 H), 3.44 (t, J = 6.0 Hz, 2 H), 2.52 (td, J = 7.2, 0.8 Hz, 2 H), 2.45 (s, 3 H), 1.85−1.65 (m, 4 H). ^{13}C NMR: 202.0, 144.9, 134.6, 132.9, 131.0, 130.1, 128.7, 127.8, 127.1, 126.6, 124.6, 93.2, 86.5, 70.0, 51.4, 43.3, 27.2, 21.8,

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19.0, 10.1. HRMS calcd for $C_{22}H_{20}INO_3S$ (M^+) 505.0209, found 505.0207.

N**-((2-Iodoethynylphenyl)ethynyl)-*****N*****-(4-oxohexyl)tosylamide (10d).** Yield 78%. ^{1}H NMR: 9.76 (s, 1 H), 7.87 (d, J = 8 Hz, 2 H), 7.42−7.31 (m, 4 H), 7.26 (td, J = 7.6, 1.6 Hz, 1 H), 7.20 (td, J = 7.6, 1.6 Hz, 1 H), 3.43 (t, J = 7.2 Hz, 2 H), 2.45 (s, 5 H), 1.83−1.75 (m, 2 H), 1.72−1.61 (m, 2 H), 1.49−1.37 (m, 2 H). ^{13}C NMR: 202.6, 145.0, 134.8, 132.9, 130.9, 130.2, 128.8, 127.8, 127.2, 126.8, 124.7, 93.2, 86.7, 70.0, 51.7, 44.0, 28.0, 26.1, 21.9, 21.8, 14.4. MS calcd for $C_{23}H_{22}INO_3S$ (M^+) 519.0, found 519.0.

8-Hydroxy-***N*****-tosyl-4,5-benzoazacycloundeca-2,6-diyne (1b).** A solution of iodo-aldehyde **10b** (3.67 g, 7.49 mmol) in 10 mL of THF was added dropwise to a suspension of $CrCl_2$ (2.30 g, 18.73 mmol) and $NiCl_2$ (0.21 g, 1.87 mmol) in degassed THF (400 mL) at 0 °C, and the mixture was stirred for 30 min at 0 °C. The reaction mixture was quenched by the addition of 50 mL of brine and diluted with Et_2O. The organic layer was separated, washed twice with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was immediately purified by chromatography (hexanes/ethyl acetate 2:1 → 1.5:1) to provide 1.68 g (4.60 mmol, 61%) of **1b** as slightly brownish oil. ^{1}H NMR: 7.86 (d, J = 8.4 Hz, 2 H), 7.41−7.36 (m, 4 H), 7.28 (t,d, J = 7.6, 1.6 Hz, 1 H), 7.22 (t,d, J = 7.6, 1.6 Hz, 1 H), 4.66 (q, J = 3.6 Hz, 1 H), 3.51−3.38 (m, 2 H), 2.46 (s, 3 H), 2.22−2.13 (m, 1 H), 2.12−2.02 (m, 1 H), 1.90 (d, J = 5.2 Hz, 1 H), 1.84−1.78 (m, 2 H). ^{13}C NMR: 144.9, 134.1, 129.9, 129.8, 129.3 128.4, 128.3 127.7, 127.2, 125.4, 95.7, 86.1, 85.2, 71.9, 63.2, 48.3, 34.1, 22.2, 21.7. HRMS calcd for $C_{21}H_{19}NO_3S$ (M^+) 365.1086, found 365.1091.

8-Hydroxy-***N*****-tosyl-4,5-benzoazacyclododeca-2,6-diyne (1c).** Yield 72%. ^{1}H NMR: 7.85 (d, J = 8 Hz, 2 H), 7.42−7.34 (m, 4 H), 7.25 (td, J = 7.6, 1.6 Hz, 1 H), 7.19 (td, J = 7.6, 1.6 Hz, 1 H), 4.70−4.61 (m, 1 H), 3.58−3.43 (m, 2 H), 2.45 (s, 3 H), 1.97−1.62 (m, 7 H). ^{13}C NMR: 145.0, 134.8, 131.1, 130.06, 130.02, 128.5, 127.9, 127.2, 127.1, 124.3, 93.6, 87.2, 84.8, 70.5, 63.0, 50.4, 35.6, 27.9, 21.9, 21.4. HRMS calcd for $C_{22}H_{22}NO_3S$ ($M + H^+$) 380.1320, found 380.1324.

8-Hydroxy-***N*****-tosyl-4,5-benzoazacyclotrideca-2,6-diyne (1d).** Yield 70%. ^{1}H NMR: 7.87 (d, J = 8 Hz, 2 H), 7.41−7.33 (m, 4 H), 7.27−7.18 (m, 2 H), 4.62 (m, 1 H), 3.61−3.45, 2.45 (s, 3 H), 2.18 (m, 1 H), 1.86−1.61 (m, 6 H), 1.59−1.44 (m, 2 H). ^{13}C NMR: 145.0, 135.0, 131.91, 131.87, 130.0, 128.3, 127.9, 127.6, 126.0, 124.9, 93.7, 87.4, 84.5, 69.1, 63.2, 52.1, 36.8, 29.0, 25.2, 24.1, 21.9. HRMS calcd for $C_{23}H_{24}NO_3S$ ($M + H^+$) 394.1477, found 394.1492.

6-Isopropoxy-1-[(4-methylphenyl)sulfonyl]-2,3,4,5-tetrahydro-1***H*****-naphtho[2,3-*****b*****]azepin-5-ol (2b).** A solution of enediyne **1b** (0.25 g, 0.68 mmol) and TsOH (~5 μg) in 2-propanol (100 mL) was stirred for 12 h at 60 °C, cooled to rt, and concentrated in vacuum. The residue was purified by chromatography (ethyl acetate/hexanes 1:5) to provide 0.15 g of **2b** (0.36 mmol, 52%) as a colorless oil that slowly crystallized upon standing in the freezer. ^{1}H NMR: 8.08 (dd, J = 8.0, 0.8 Hz, 1 H), 7.76 (d, J = 8.0 Hz, 2 H), 7.50−7.41 (m, 3 H), 7.33 (d, J = 8.0 Hz, 2 H), 6.98 (s, b, 1 H), 5.62 (s, b, 1 H), 4.53 (p, J = 6.0 Hz, 1 H), 4.38 (s, b, 1 H), 3.12 (s, b, 1 H), 2.53 (s, b, 1 H), 2.48 (s, 3 H), 2.35 (s, b, 1 H), 1.79−1.60 (m, 2 H), 1.45 (d, J = 6.4 Hz, 3 H), 1.34 (d, J = 6.0 Hz, 3 H). ^{13}C NMR: 152.4, 143.8, 138.2, 137.2, 133.2, 132.2, 129.7, 128.8, 127.7, 127.6, 126.9, 126.4, 123.60, 123.55, 78.3, 65.8, 52.3, 33.4, 25.4, 22.70, 22.57, 21.6. HRMS calcd for $C_{24}H_{27}NO_4SNa$ ($M + Na^+$) 448.1558, found 448.1549

8-Hydroxy-***N*****-tosyl-4,5-benzoazacyclododeca-6-yne-2-one (21c).** A solution of enediyne **1c** (0.25 g, 0.66 mmol) and TsOH (~25 μg) in 2-propanol (200 mL) was stirred for 4 days at 55 °C, cooled to rt, and concentrated in vacuum. The residue was purified by chromatography (ethyl acetate/hexanes 1:5) to provide 0.112 g (0.28 mmol, 43%) of **21c** as white crystalline. NMR: 7.81 (d, J = 8.0 Hz, 2 H), 7.43 (dd, J = 7.2, 1.6 Hz, 1 H), 7.34 (d, J = 8.0 Hz, 2 H) 7.28−7.20 (m, 2 H), 7.19−7.15 (m, 1 H), 4.63 (m, 1 H), 4.11 (q, J = 27.6, Hz, 2 H), 3.96 (t, J = 5.6 Hz, 2 H), 2.45 (s, 1 H), 2.23 (s, b, 1 H), 1.98−1.83 (m, 4 H), 1.78−1.66 (m, 1 H), 1.60−1.50 (m, 1 H). ^{13}C NMR: 171.9, 145.2, 137.2, 136.7, 132.4, 131.0, 130.1 128.9, 128.0, 127.6, 123.0, 95.4, 84.0, 63.2, 46.7, 43.2, 36.1, 28.1, 21.9, 20.3. HRMS calcd for $C_{22}H_{23}NO_4SNa$ ($M + Na^+$) 420.1246, found 420.1194.

8-Hydroxy-***N*****-tosyl-4,5-benzoazacyclotrideca-6-yne-2-one (21d).** A solution of enediyne **1d** (0.25 g, 0.64 mmol) and TsOH (~50 μg) in 2-propanol (200 mL) was stirred for 4 days at 55 °C and cooled to rt, the solvent was removed under reduced pressure, and the residue was purified by chromatography (ethyl acetate/hexanes 1:5 to 1:1) to provide 0.139 g (0.34 mmol, 53%) of **21d** as white crystalline. NMR: 7.83 (d, J = 8.0 Hz, 2 H), 7.47−7.40 (m, 1 H), 7.34 (d, J = 8.0 Hz, 2 H) 7.25−7.21 (m, 2 H), 7.12−7.16 (m, 1 H), 4.65 (q, J = 6.4 Hz, 1 H), 4.09 (s, 2 H), 4.04 (t, J = 6.8, Hz, 1 H), 3.88−3.80 (m, 1 H), 2.45 (s, 1 H), 2.01 (d, J = 5.6 Hz, 1 H), 1.95−1.91 (m, 1 H), 1.90−1.81 (m, 1 H), 1.72−1.64 (m, 1 H), 1.60−1.50 (m, 3 H). ^{13}C NMR: 171.0, 145.1, 136.8, 135.6, 132.5, 130.1, 129.9 128.9, 128.2, 127.6, 123.2, 94.9, 83.7, 63.1, 46.1, 42.5, 36.1, 28.0, 24.7, 23.7, 21.9. HRMS calcd for $C_{23}H_{26}NO_4S$ ($M + H^+$) 412.1583, found 412.1594

1-Tosyl-2,3,4,5-tetrahydro-1***H*****-naphtho[2,3-*****b*****]azepine-5,6-diol (23b).** A solution of enediyne **1b** (0.25 g, 0.68 mmol) and TsOH (~5 μg) in 200 mL of THF/H_2O (2:1) was stirred for 2 days at 60 °C, cooled to rt, and concentrated in vacuum. The residue was purified by chromatography (ethyl acetate/hexanes 1:5 to 1:1) to provide 0.12 g (0.31 mmol, 46%) of **23b** as white crystalline. Mp 154−155 °C. ^{1}H NMR: 10.55 (s, 1 H), 8.2 (dd, J = 8.0, 1.2 Hz, 1 H), 7.76 (d, J = 8.0 Hz, 2 H), 7.52 (m, 1 H), 7.45−7.41 (m, 2 H), 7.31 (d, J = 8.0 Hz, 2 H), 6.94 (s, 1 H), 5.45 (m, 1 H), 4.15 (m, 1 H), 3.91 (s, b, 1 H), 2.98 (t, b, 1 H), 2.44 (s, 3 H), 2.1−1.85 (m, 2 H), 1.84−1.8 (m, 1 H), 1.55 (m, 1 H). ^{13}C NMR: 151.9, 143.6, 138.3, 135.0, 132.8, 129.8, 129.2, 127.3, 127.2, 126.7, 125.6, 125.4, 122.2, 117.7, 74.2, 50.3, 36.0, 26.3, 21.6. HRMS calcd for $C_{21}H_{22}NO_4S$ ($M + H^+$) 384.1270, found 384.1276.

1-Tosyl-5-phenyl-1,2-dihydrobenzo[***g*****]quinoline (24b).** A solution of enediyne (0.25 g), TsOH (~25 μg) in C_6H_6 (100 mL) was stirred for 20 h at 55 °C, cooled to room temperature, and concentrated in vacuum. The residue was purified by chromatography (ethyl acetate/hexanes 1:5 to 1:1) to give **24b** in 21% yield. Mp 146−148 °C. ^{1}H NMR: 8.09 (s, 1 H), 7.84 (d, J = 8.0 Hz, 1 H) 7.75−7.39 (m, 6 H), 7.31 (d, J = 4.0 Hz, 2 H), 7.16 (dd, J = 7.6, 1.2 Hz, 2 H), 7.10 (d, J = 8.0 Hz, 2 H), 5.81(d, J = 12.4 Hz, 1 H), 5.45 (dd, J = 12.4, 4.8 Hz, 1 H), 4.2−3.8 (s, b, 1 H), 2.59 (s, b, 2 H), 2.45 (s, 1 H). ^{13}C NMR: 143.2, 141.2, 139.2, 138.3, 137.0, 132.4, 132.2, 131.2, 130.1, 130.1, 129.3, 128.6, 128.3, 127.6, 127.5 m 127.5, 127.1, 126.9, 126.7, 126.4, 51.2, 31.3, 21.9. MS calcd for $C_{27}H_{23}NO_2S$ (M^+) 425.1, found 425.1.

7-Phenyl-1-tosyl-1,2,3,4-tetrahydronaphtho[2,3-***b*****]azocine (24c).** Yield 28%. ^{1}H NMR: 7.71−7.65 (m, 3 H), 7.51−7.41 (m, 6 H), 7.39−7.31 (m, 2 H) 7.30−7.24 (m, 4 H), 5.94 (d, J = 11.6 Hz, 1 H), 5.73 (dt J = 11.6, 6.4, Hz, 1 H), 2.45 (s, 1 H), 2.23−2.00 (m, 2 H), 1.78−1.65 (m, 2 H). ^{13}C NMR: 143.3, 139.8, 138.9, 138.0, 136.9, 135.8, 133.1, 132.4, 131.9, 129.8, 129.5, 128.4, 128.02, 128.00, 127.96, 127.6, 127.0, 126.6, 126.3, 126.2, 53.0, 28.4, 25.1, 21.8. MS calcd for $C_{28}H_{25}NO_2S$ (M^+) 439.2, found 439.2.

N**-Tosyl-4,5-benzoazacyclododeca-6-yn-8-en-2-one (25c).** Yield 18%. ^{1}H NMR: 7.89 (d, J = 8.0 Hz, 2 H), 7.48−7.44 (m, 1 H), 7.35 (d, J = 8.0 Hz, 2 H) 7.28−7.24 (m, 2 H), 7.22−7.18 (m, 1 H), 6.23 (dt, J = 10.4, 7.6 Hz, 1 H), 5.72 (d, J = 10.4 Hz, 1 H), 4.28 (s, 2 H), 3.76 (t, J = 6.0 Hz, 2 H), 2.45 (s, 1 H), 2.33−2.24 (m, 2 H), 1.94−1.85 (m, 2 H). ^{13}C NMR: 172.9, 145.1, 143.3, 136.8, 132.6, 131.2, 130.2 128.5, 127.9, 127.6, 124.1, 111.6, 94.4, 91.5, 45.7, 44.9, 27.0, 26.3, 21.9. MS calcd for $C_{22}H_{21}NO_3S$ (M^+) 379.1, found 379.1.

N**-Tosyl-4,5-benzoazacyclotrideca-6-yn-8-en-2-one (25d).** Yield 41%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.0 Hz, 2 H), 7.46−7.41 (m, 1 H), 7.32 (d, J = 8.0 Hz, 2 H) 7.25−7.20 (m, 2 H), 7.14−7.00 (m, 1 H), 6.03 (dt, J = 10.4, 7.6 Hz, 1 H), 5.73 (d, J = 10.4 Hz, 1 H), 4.14 (s, 2 H), 4.04 (t, J = 6.8 Hz, 2 H), 2.45 (s, 1 H), 2.40 (q, J = 7.6 Hz, 2 H), 1.95−1.85 (m, 2 H), 1.70−1.60 (m, 2 H). ^{13}C NMR (100 Hz, $CDCl_3$) δ; 170.8, 144.9, 143.9, 136.9, 135.5, 131.9, 130.3 129.9, 128.6, 128.2, 127.6, 124.2, 110.4, 91.5, 91.3, 46.7, 42.3, 29.5, 27.8, 25.3, 21.9. MS calcd for $C_{23}H_{23}NO_3S$ (M^+) 393.1, found 393.1.

***N*-Allyl-*N*-(3-acetylnaphthalene-2-yl)tosylamide (13).** A solution of MeMgBr (1 M solution in THF, 15 mL, 15 mmol) was added to a solution of **11** (4 g, 10.96 mmol) in THF (100 mL) at rt, and the reaction mixture was stirred overnight. The reaction mixture was quenched by an aqueous NH_4Cl, the organic layer was separated, and the solvent was removed under reduced pressure. The residue was redissolved in CH_2Cl_2, washed with water, dried over anhydrous $MgSO_4$, and concentrated. The residue passed through a short column of silica gel ($CH_2Cl_2 \rightarrow CH_2Cl_2$/ethyl acetate 4:1) to provide 3.76 g (9.86 mmol, 90%) of crude *N*-allyl-*N*-(3-(1-hydroxyethyl)naphthalene-2-yl)tosylamide (**12**) as white crystalline. Mp 109−110 °C.

PCC (2.80 g, 13.0 mmol) was added to a solution of crude alcohol **12** (3.76 g, 9.86 mmol) in CH_2Cl_2 (100 mL), and the resulting solution was stirred for 40 h at rt. The reaction mixture was passed through a short column of silica gel (CH_2Cl_2) to provide 2.78 g (7.34 mmol, 74%) of **13** as slightly yellow oil. ^{1}H NMR: 8.15 (s, 1 H), 7.93−7.90 (m, 1 H), 7.65−7.62 (m, 1 H), 7.58−7.52 (m, 2 H), 7.47 (d, J = 8.0 Hz, 2 H), 7.24 (d, J = 8.0 Hz, 2 H) 7.17 (s, 1 H), 5.95−5.86 (m, 1 H), 5.12−5.04 (m, 2 H), 4.50−4.18 (m, 2 H), 2.72 (s, 3 H), 2.43 (s, 3 H). ^{13}C NMR: 200.3, 143.7, 139.1, 135.2, 133.8, 133.6, 132.6, 131.8, 129.8, 129.4, 128.69, 128.66, 128.1, 128.0, 127.56, 127.47, 54.8, 30.2, 21.6. HRMS calcd for $C_{22}H_{22}NO_3S$ (M^+ + H) 380.1320, found 380.1329.

***N*-Allyl-*N*-(3-(1-((*tert*-butyldimethylsilyl)oxy)vinyl)naphthalen-2-yl)tosylamide (14).** A solution of TBDMSCl (4.43 g, 29.36 mmol) in MeCN (10 mL) was added to suspension of **13** (2.78 g, 7.34 mmol), NaI (4.40 g, 29.36 mmol), and Et_3N (3.3 mL, 32.0 mmol) in MeCN (150 mL) at rt. The reaction mixture was refluxed for 4 h, then cooled to rt, filtered, and concentrated. The residue was diluted with 50 mL of ether, filtered, and concentrated. The crude product was passed through a pad of activated alumina to provide 2.97 g (6.02 mmol, 82%) of **14** as slightly orange oil. ^{1}H NMR: 8.02 (s, 1 H), 7.81 (d, J = 8.0 Hz, 1 H), 7.71 (d, J = 8.0 Hz, 2 H), 7.61 (d, J = 8.0 Hz, 1 H), 7.51−7.42 (m, 2 H), 7.32−7.28 (m, 3 H), 5.90−5.78 (m, 1H), 4.99 (s, 2 H), 4.95 (d, J = 11.2, 1 H), 4.67 (s, 1 H), 4.26 (d, J = 6.4 Hz, 2 H), 2.45 (s, 3 H), 0.97 (s, 9 H), 0.21 (s, 6 H). ^{13}C NMR: 153.9, 143.6, 137.3, 137.1, 134.8, 132.9, 132.64, 132.60, 129.6, 129.5, 129.3, 128.4, 128.1, 127.5, 127.1, 126.7, 119.5, 55.0, 26.1, 21.8, 18.6, −4.3. HRMS calcd for $C_{28}H_{36}NO_3SSi$ (M + H^+) 494.2185, found 494.2192.

4-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-tosyl-1,2,3,4-tetrahydrobenzo[*g*]quinoline (15). A degassed solution of **14** (0.5 g, 1.01 mmol) in 20 mL of CH_2Cl_2 and 0.04 g (0.05 mmol) of Grubbs' second generation catalyst were stirred in a sealed vessel for 2 h at 50 °C, and then overnight at rt. The solvent was removed under reduced pressure, and the residue was purified by chromatography (ethyl acetate/hexanes 1:15) to provide 0.338 g (0.72 mmol, 72%) of **15** as slightly yellow oil. ^{1}H NMR: 8.18 (s, 1 H), 7.89 (d, J = 7.6 Hz, 1 H), 7.82−7.79 (m, 2 H), 7.53−7.44 (m, 2 H), 7.33 (d, J = 8.0 Hz, 2 H), 7.05 (d, J = 8.0 Hz, 2 H), 4.82 (t, J = 4.4 Hz, 1H), 4.53 (d, J = 4.4 Hz, 2 H), 2.31 (s, 3 H), 0.96 (s, 9 H), −0.02 (s, 6 H). ^{13}C NMR: 137.0, 133.6, 133.4, 131.8, 129.6, 128.3, 127.5, 127.3, 126.8, 126.5, 124.9, 122.1, 101.4, 45.1, 25.8, 21.6, 18.3, −4.7. HRMS calcd for $C_{26}H_{31}NO_3SSiNa$ (M + Na^+) 488.1692, found 488.1686.

1-Tosyl-2,3-dihydrobenzo[*g*]quinolin-4(1*H*)-one (16). Hydrofluoric acid (40%, 1 mL) was added to a solution of silyl ether **15** (0.64 g, 1.36 mmol) in MeCN (5 mL) at rt, and the reaction mixture was stirred for 48 h at rt. The reaction mixture was quenched by an aqueous solution of $NaHCO_3$ and diluted with ethyl acetate. The organic layer was separated, washed with water and brine, dried over anhydrous $MsSO_4$, and concentrated. The residue was purified by chromatography (hexanes/ethyl acetate 5:1 to 3:1) to provide 0.197 g (0.56 mmol, 41%) of **16** as slightly orange semisolid. ^{1}H NMR: 8.52 (s, 1 H), 8.28 (s, 1 H), 7.96−7.86 (m, 2 H) 7.62 (t, J = 6.0 Hz, 1 H), 7.84−7.78 (m, 3 H), 7.17 (d, J = 6.0 Hz, 3 H), 4.29 (t, J = 4.8 Hz, 2 H) 4.46 (t, J = 4.8 Hz, 2 H), 2.35 (s, 3 H). ^{13}C NMR: 193.4, 144.6, 137.2, 137.1, 136.4, 130.6, 130.2, 130.1, 129.9, 129.7, 128.2, 127.1, 126.9, 125.0, 123.1, 46.0, 37.0, 21.7. HRMS calcd for $C_{20}H_{17}NO_3S$ (M^+) 351.0929, found 351.0934.

1-Tosyl-1,2,3,4-tetrahydrobenzo[*g*]quinolin-4-ol (17). $LiAlH_4$ (0.018 g, 0.55 mmol) was added to a solution of ketone **16** (0.19 g, 0.54 mmol) in THF (10 mL) at 0 °C, and the reaction mixture was slowly warmed to rt and stirred overnight at rt. The reaction was quenched by MeOH, diluted with ethyl acetate, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by chromatography (ethyl acetate/hexanes 1:5) to provide 0.144 g (0.41 mmol, 75%) of **17** as colorless semisolid. ^{1}H NMR: 8.30 (s, 1 H), 7.84 (d, J = 8.4 Hz, 1 H), 7.77 (s, 1 H) 7.74 (d, J = 8.4 Hz, 1 H), 7.49 (d, J = 8.0 Hz, 3 H), 7.46−7.39 (m, 1 H), 7.13 (d, J = 8.0 Hz, 2 H) 4.58 (s, b, 1 H), 5.11−4.02 (m, 1 H), 3.92−3.86 (m, 1 H), 2.32 (s, 3 H), 1.92−1.80 (m, 2 H). ^{13}C NMR: 143.8, 136.2, 133.39, 133.37, 131.5, 130.6, 129.6, 127.9, 127.3, 127.2, 127.1, 128.6, 125.7, 121.5, 65.9, 42.5, 30.4, 21.5. HRMS calcd for $C_{20}H_{19}NO_3S$ (M^+) 353.1086, found 353.1094.

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Supporting Information Available: Synthetic procedures for the preparation of compounds **27b−d** and compound **11**, Cartesian coordinates of DFT-optimized structures, and X-ray data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.