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Preparation of enediyne-crosslinked networks and their reactivity under thermal and mechanical conditions

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This paper is dedicated to Professor Fraser Stoddart for the inspiration that he has provided throughout the years

ABSTRACT

The COGEF technique (COnstrained Geometries simulating External Force) was used to investigate the effects of macroscopic forces on cyclic enediynes, which can undergo Bergman Cyclization (BC). Because the forces needed to activate BC were found to be less than the forces needed for chain scission in polymer backbones, the calculations suggest that enediynes are potentially useful mechanophores. Three enediynes studied computationally were synthesized. The thermal BC reactions for these compounds were studied by DSC and found to be consistent with the predicted thermal sensitivity based on known substituent effects. However, upon incorporation of the enediynes into a polymer matrix as crosslinks, no definitive mechanical activation was observed, and conclusions about the stress-sensitivity of enediynes were unable to be drawn. Model studies suggest that insufficient force was applied to the crosslinks for mechanical activation to be observable by DSC.

1. Introduction

Interest in the use of mechanical energy to alter the reactivity of polymers containing stress-sensitive mechanophores has been increasing as of late.[1–17] It has been shown that mechanical forces not only can modify the rate of chemical reactions, but also can modify the outcome of the reaction to yield products not typically observed by thermo- or photochemistry. However, chemical reactions that are influenced by mechanical forces remain poorly understood, and there is a need for the discovery of new mechanophores.

There has been great interest in the scientific community in controlling the reactivity of the enediynes, which undergo Bergman cyclization (BC),[18] a cycloaromatization rearrangement to a 1,4-benzyne diradical intermediate.[19] Strategies have been devised to trigger cycloaromatization on demand through physical stimuli such as heat, light,[20] or electrical potential,[21] or various chemical stimuli such as transition metal coordination[22,23] or chemical modification. However, to the best of our knowledge, triggering BC with external mechanical forces has never been reported.

There is significant literature precedent that enediynes are sensitive to molecular deformations.[24–30] Specifically, it has been suggested that when the acetylene distance *d* is less than 2.9–3.4 Å, enediynes undergo spontaneous cyclization at ambient temperatures.[31,32] With this precedent in mind, we hypothesized that the rate of BC can be accelerated by mechanical tensile forces applied in such a manner that decrease *d*. Here we report the design, computational optimization, and synthesis of cyclic enediyne crosslinkers. We also begin to address experimental protocols for accessing the study of stress-accelerated reactions in the solid state.

2. Results and discussion

Because uniaxial tension causes elongational deformations along the vector of its application, it was hypothesized that

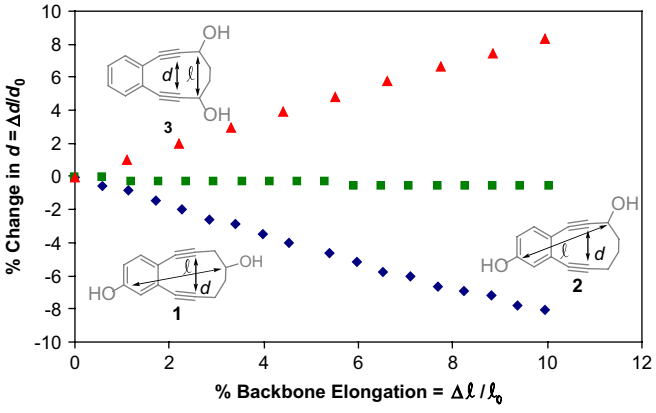

Figure 1. Plot of change in distance *d* versus percent backbone elongation. To produce these curves, the backbone length ℓ was systematically elongated in enediynes **1**, **2**, and **3**, and the geometry was minimized at the molecular force field level at each step.

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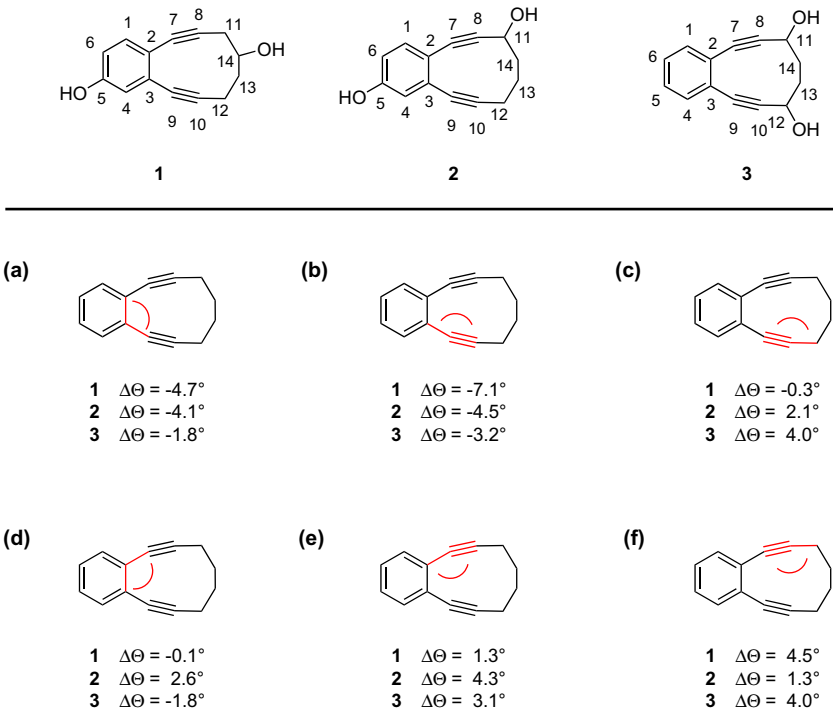


Figure 2. Analysis of bond angle distortions with applied stress for enediynes **1**, **2**, and **3**. $\Delta\theta$ is defined as the difference in the bond angles between the ground state and after 10% backbone elongation. Negative values imply that the angle is decreasing in value.

connection of the polymer backbone to different points on a cyclic enediyne would result in varying levels of efficiency in decreasing distance *d*, and therefore varying levels of stress activation. This idea was investigated computationally using the COGEF computational technique.[33] The distance between the hydroxyl-containing carbons of cyclic enediynes **1**, **2**, and **3** were fixed and all other atoms were allowed to fully relax. By systematically increasing the fixed distance and monitoring distance *d* at each interval, a profile of percent change in *d* versus percent backbone elongation was created (Fig. 1). In the first 10% elongation of enediyne **1**, there is approximately an 8% decrease in *d*. Furthermore an acetylene distance of 3.2 Å is reached after a 9% increase in backbone length. The major molecular distortions responsible for the decrease in *d* are the bending of the 2–3–9 and 3–9–10 bonds in skeleton **4** (Fig. 2). For this isomer, very little strain is manifested in bond stretching, which is unproductive at decreasing distance *d* (Fig. 3). In contrast,

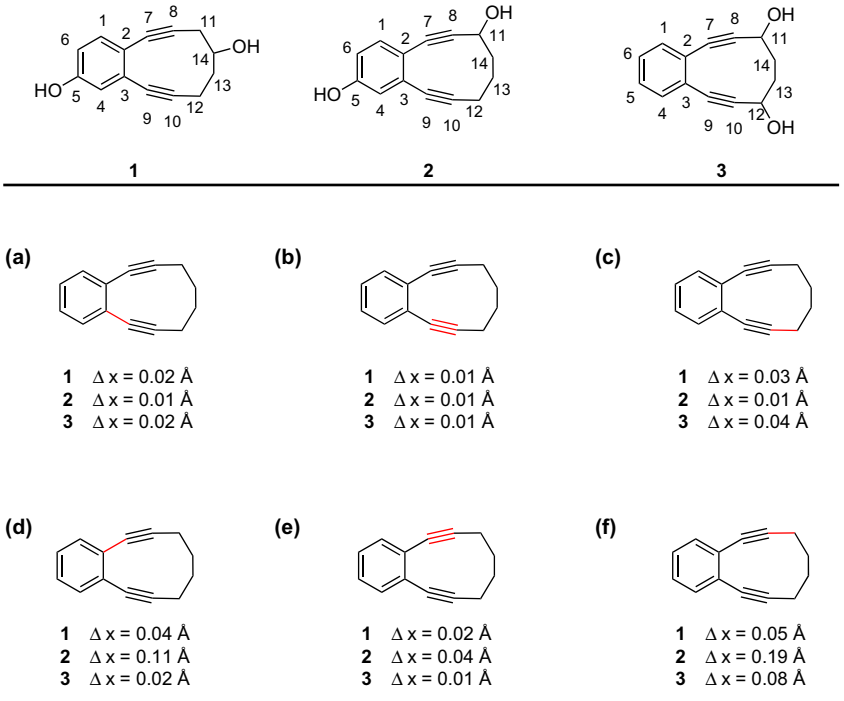
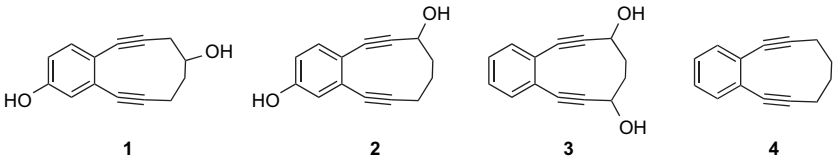


Figure 3. Analysis of bond stretching distortions with applied stress for enediynes **1**, **2**, and **3**. Δx is measured as the difference in bond length in the ground state and after 10% backbone elongation.

enediyne **2** does not effectively couple the backbone tensile deformation with the desired decrease in *d*. Less than a 1% decrease in *d* occurs after 10% elongation. Because the geometry is not optimized to bend bonds, much of the stress is stored internally through bond stretching deformations, particularly the 2–7 and 8–11 single bonds (Fig. 3). At higher levels of elongation (greater than 13%) distance *d* reaches a minimum value and begins to increase. Application of force to isomer **3** increases *d*, consistent with intuitive expectations. Thus, cycloaromatization for this isomer is predicted to be inhibited by tensile force. From this series of calculations it is predicted that the BC of enediyne **1** will be promoted by tensile force, that of enediyne **2** will be unaffected by tensile force, and that of enediyne **3** will be inhibited by tensile force. This set of isomers can potentially be used to test the idea that the geometry of the mechanophore plays a role in stress activation.



The above calculations reveal, which substitution pattern is the most efficient at coupling the decrease in *d* with elongational forces. However, if the mechanochemical process is to precede polymer chain scission, the applied forces must induce the necessary molecular distortions before rupturing chemical bonds in the polymer backbone (Fig. 4). To investigate whether this condition is met, a profile of relative energy as a function of molecular elongation was produced using quantum mechanical calculations at the DFT B3LYP/6-31G* level. To create this profile, distance ℓ was systematically increased (Fig. 5) with a corresponding decrease in acetylene distance *d*. At each step the change in energy relative to the undistorted ground state was calculated. Assuming that the sum of all bond distortions acts as a spring, Δℓ is related to the force (*F*) and work (*W*) through Eqs. 1 and 2:

$$F = -k'\Delta\ell \tag{1}$$

$$W = -k'(\Delta\ell)^2 \tag{2}$$

Furthermore, by assuming that the work done on the molecule by stress is approximated by the relative energy difference between the stressed state and the undistorted ground state ($\Delta E = E_{\text{stressed state}} - E_{\text{ground state}}$), Eq. 2 can be rewritten as Eq. 3:

$$\Delta E = -k'(\Delta\ell)^2 \tag{3}$$

A plot of ΔE versus $(\Delta\ell)^2$ is then expected to be linear with a slope of $k'/2$. Modeling the deformation in this way yields a plot of ΔE versus $(\Delta\ell)^2$, which is approximately linear at small distortions (less than 2.0 Å) but becomes non-linear at higher elongations (Fig. 6); the sum of bond deformations acts as an ideal spring only at small deformations. Under this approximation, the spring constant k' was estimated to be 36.8 N/m.

Figure 1 shows that Δℓ is proportional to Δ*d*,

$$\Delta d = k\Delta\ell, \tag{4}$$

and the slope of that plot shows that the value of *k* is 0.83. Combining Eq. 4 with Eq. 1, rearranging, and using the numerical values of k' and *k* give:

$$\Delta d = -2.26 \times 10^{-2} F \tag{5}$$

which is approximately valid when *F* is less than 8.8 nN. With this equation, it is possible to estimate to what extent *d* will be reduced by a given force, and, therefore, if cycloaromatization will be

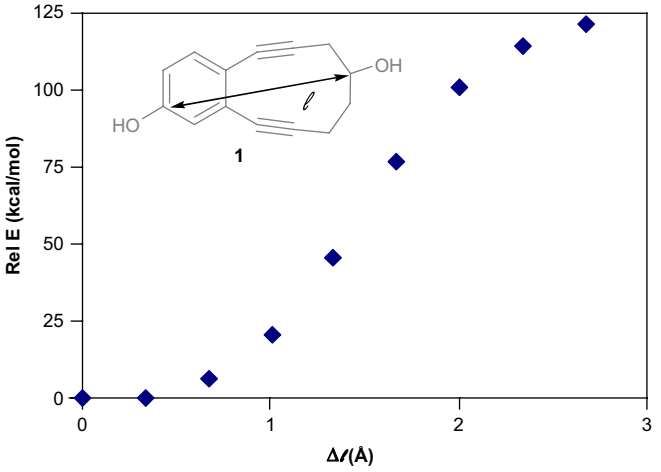


Figure 5. Plot of change in ground state energy versus Δℓ calculated at the DFT B3LYP/6-31G* level.

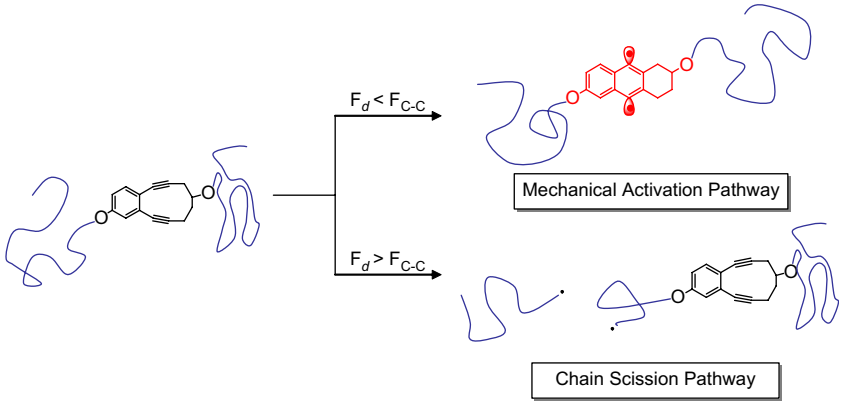


Figure 4. The two competing mechanochemical pathways. If the force required to activate the linker is less than that required to cleave C–C bonds in the polymer backbone, the mechanical activation pathway will preempt chain scission. If the force required to activate the linker is too large, the chain scission pathway will dominate.

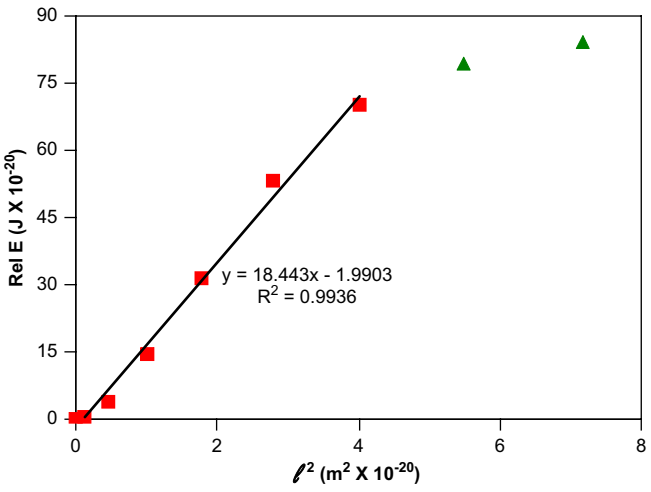


Figure 6. Plot of relative energy versus $(\Delta\ell)^2$ for enediyne **1**. Only the linear region (red squares) was used in the calculation of the spring constant; the non-linear region (green triangles), presumably influenced by the proximity of the transition state, was neglected.

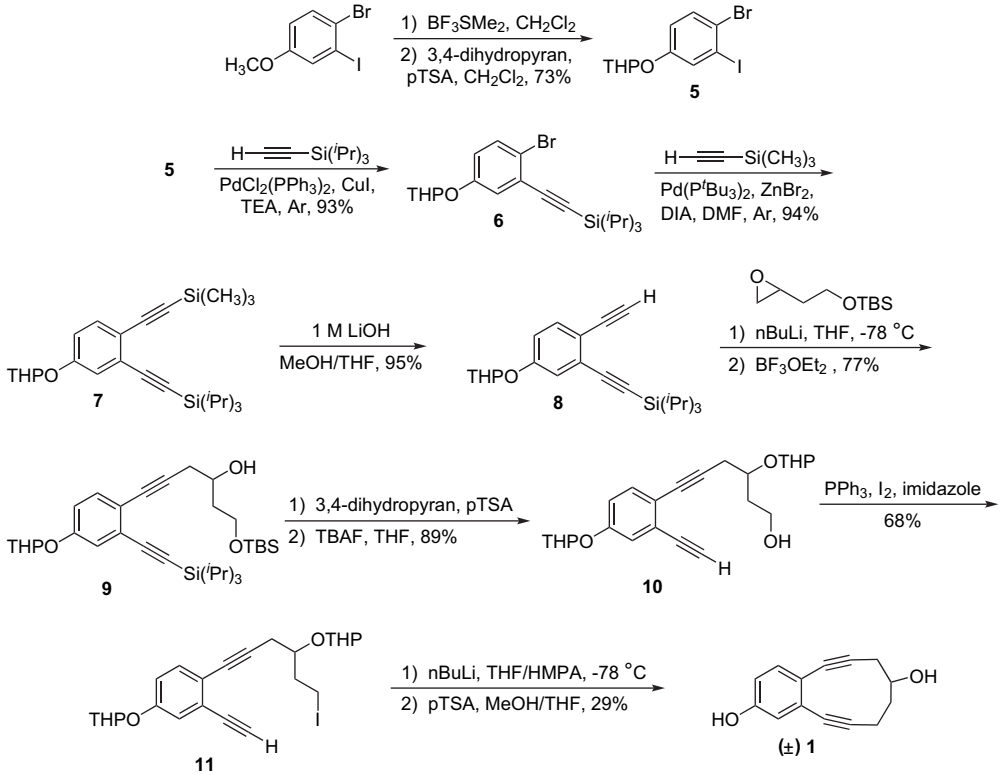
activated before polymer scission occurs. It takes approximately 5–6 nN of force per chain to overcome the binding potential of a C–C bond in poly(ethylene glycol). This value can be used as an approximation of the maximum force accessible to distort an enediyne linker. From Eq. 5, a force of 5 nN is predicted to cause a 1.3 Å deformation. This is large enough to decrease distance *d* below the 3.2–3.0 Å range required for spontaneous cyclization. The estimates made above fail to account for any change in the transition state energy as a result of the applied external force.

In order to empirically test the above models, enediynes **1**, **2**, and **3** were prepared. The synthesis of enediynes **1** and **2** began with 4-bromo-3-iodoanisole.[34] The methyl ether was cleaved with boron trifluoride–dimethyl sulfide complex, and the hydroxyl group was then protected as the tetrahydropyran acetal upon treatment with 3,4-dihydropyran and a catalytic amount of *p*TSA monohydrate to yield iodide **5** (Scheme 1).

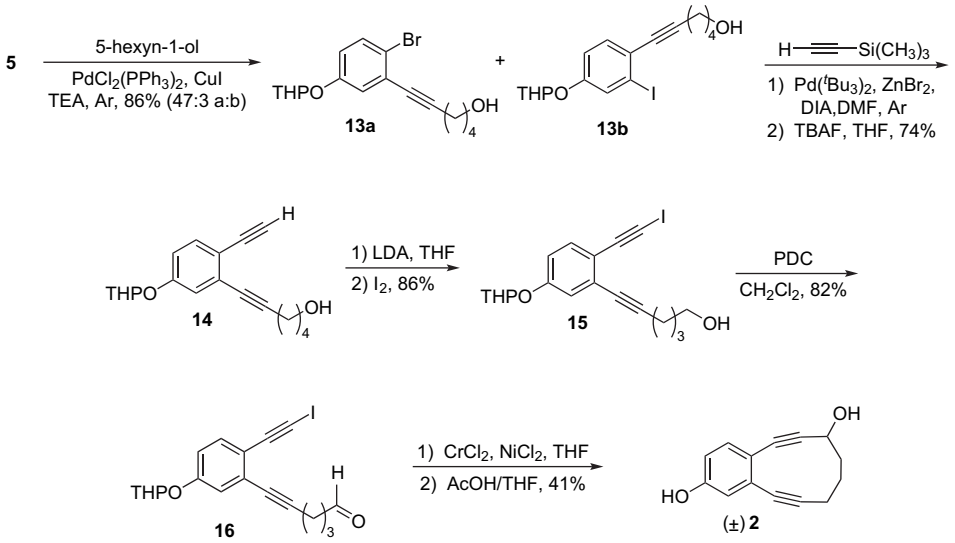
Enediyne linker **1** was prepared according to Scheme 1. Iodide **5** was coupled with triisopropylsilylacetylene under palladium-catalyzed cross-coupling conditions to yield alkyne **6**. Enediyne **7** was prepared by coupling alkyne **6** with trimethylsilylacetylene, employing the highly active $Pd(P^tBu_3)_2$ catalyst.[35] Less reactive palladium catalysts such as $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ gave poor yields of the enediyne product. The trimethylsilyl group was selectively removed with aqueous lithium hydroxide,[36] then terminal acetylene **8** was deprotonated with ^{n}BuLi and treated with 1-[2-(*tert*-butyldimethylsilyl)oxy]-ethyloxirane to provide alcohol **9**. Protection of the hydroxyl group as the tetrahydropyran acetal and deprotection with TBAF yielded enediyne **10**. The primary alcohol was converted to iodide **11**, which set up ring closing through nucleophilic displacement.[37] Treatment of iodide **11** with LDA in the presence of HMPA effected ring closure, then cleavage of the acetal protecting group with *p*TSA and methanol yielded linker **1**.

To prepare propargylic enediyne **2**, iodide **5** was coupled with 5-hexyn-1-ol under palladium-catalyzed cross-coupling conditions, to yield bromide **13a** and iodide **13b** as a 47:3 mixture by ^{1}H NMR (Scheme 2). This mixture was carried through without separation, and was coupled with trimethylsilylacetylene in the presence of $Pd(P^tBu_3)_2$[36] and zinc bromide. The trimethylsilyl group was removed with TBAF to provide terminal alkyne **14**, which was treated with 2 equiv of LDA, followed by 1 equiv of iodine, to yield iodoalkyne **15**. Oxidation of the alcohol to the aldehyde with pyridinium dichromate then provided the appropriate functionality for ring closure. Treatment of aldehyde **16** with chromium chloride and nickel chloride yielded the ring closed product,[38] which was deprotected under acidic conditions to provide propargylic linker **2**.

Bispropargyl enediyne **3** was prepared starting from 1-(triisopropylsilylethynyl)-2-ethynylbenzene **17** (Scheme 3).[39] The lithium acetylide of this enediyne, obtained upon treatment of enediyne **17**



Scheme 1. Preparation of enediyne linker **1**.

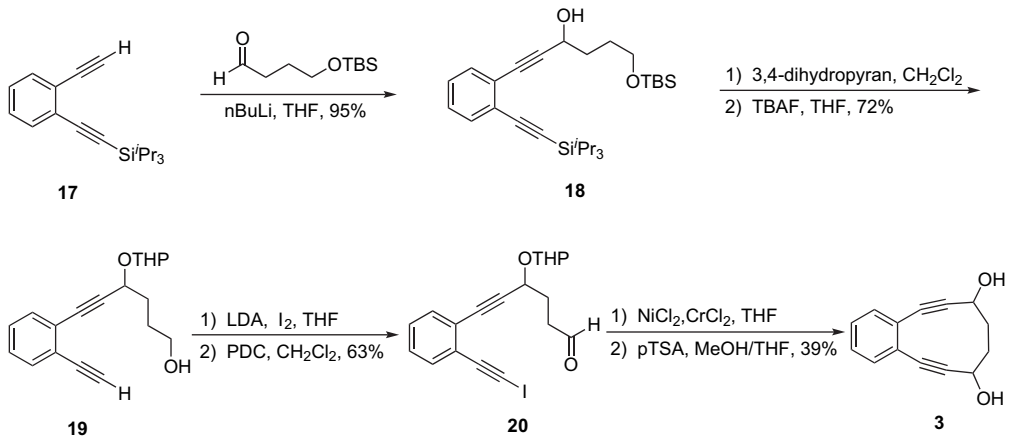


Scheme 2. Preparation of propargylic enediyne **2**.

with ^{n}BuLi, was reacted with 4-[(*tert*-butyldimethylsilyl)oxy]-butanal to yield enediyne **18**. The newly formed hydroxyl group was protected as the tetrahydropyran acetal, and then the silyl groups were cleaved with TBAF to yield enediyne **19**. Next, the terminal acetylene was converted to the iodoacetylene by treatment with LDA and iodine as described above. The hydroxyl group was then oxidized with pyridinium dichromate to aldehyde **20**, and the ring was closed by treatment with chromium chloride and nickel chloride.[38] The tetrahydropyran protecting group was then cleaved to yield cyclic enediyne **3**.

It has been shown that σ-electron withdrawing groups and π-electron donating groups at the termini of the acetylenic positions of enediynes lower the barrier for cycloaromatization.[40] Thus it was anticipated that the order of thermal reactivity of the diols would be bispropargyl **3**>propargyl **2**>homopropargyl **1**. A DSC study was undertaken to confirm this expected order, since it has been shown to be a convenient method for the study of cycloaromatization.[41] Because the polymerization of the radicals produced by BC is exothermic, there is no need for external trapping reagents and the enediynes can be analyzed neat. However, it was found that neat analysis of the diols by DSC was complicated by the fact that the onset temperature of reaction was dependant on the melting point of the diol. In other words, the enediynes needed to melt before undergoing cyclization, and the melting point of the crystals was above the onset temperature for BC. Therefore, the true onset temperatures for cycloaromatization were being masked. To circumvent this problem, the diols were protected as diacetates, and the diacetates were analyzed by DSC as solutions in 1,3-dimethoxybenzene. This solvent was chosen both for its high boiling point and for solubility considerations. The strategy was successful at eliminating the melting reactions. DSC analysis then confirmed the predicted order (Fig. 7). The onset reaction temperature was found to be 105, 113, and 123 °C for the bispropargyl diacetate **23**, propargyl acetate **22**, and homopropargyl acetate **21**, respectively.

Previous studies have shown that the radicals produced by BC successfully initiate the polymerization of unsaturated monomers;[42,43] it was hypothesized that this characteristic could be used as a probe to detect small amounts of cyclization that might be occurring under mechanical forces. More specifically, it was hypothesized that under stress activation the exotherm of polymerization initiated by cycloaromatization would shift to lower temperatures, which would be detectable by DSC. The enediynes must be incorporated into polymers for mechanochemical activation because small molecules are relatively inert to macroscopic stress. Furthermore, since monomer must be present during the experiment, the polymer must be a crosslinked network to prevent dissolution of the polymer in the monomer, which would make stress application difficult within a DSC instrument. Therefore, it was concluded that the best approach was to incorporate the enediynes as crosslinks into a PMMA network. The material would



Scheme 3. Preparation of bispropargylic enediyne **3**.

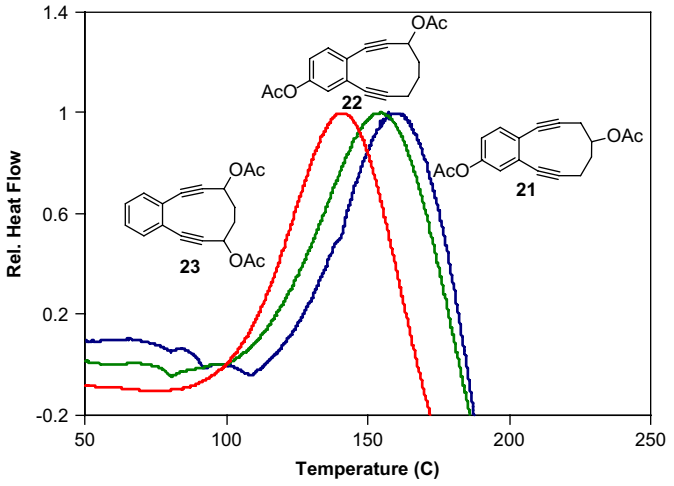


Figure 7. DSC analysis of bisacetates **21**, **22**, and **23**. The onset temperatures for BC were found to be 123, 113, and 105 °C, respectively. In this DSC scan, exothermic is positive heat flow (larger positive heat flow=more exothermic). All scans were found to be irreversible.

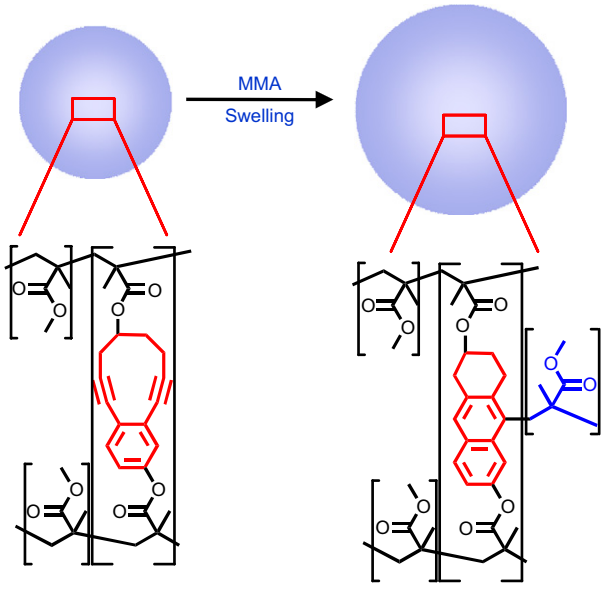


Figure 8. The bulk material test for stress reactivity. The mechanochemical linker is functionalized as a bismethacrylate and polymerized as a crosslinker in PMMA beads. The beads are then swollen with monomer, and tension forces build on the crosslinks. Cyclization is monitored through heat evolution, which occurs during polymerization of the monomer used to swell the beads.

then be swollen with monomer. Swelling would simultaneously apply stress to the crosslinks and provide the monomer for polymerization (Fig. 8).

The general stress levels that can be produced through swelling of these polymer networks can be estimated through both theoretical approximations and experimental measurements of related systems. The PMMA networks in these experiments have 0.17 mol % crosslinker corresponding to an average of about 600 C–C bonds (n) between crosslinks. Assuming a characteristic ratio (C_∞) of 8.65[44] and a bond length (l) of 1.54 angstroms, the root mean square distance between these crosslinks would be approximately 11.1 nm ($\langle R_0^2\rangle^{1/2}=(nl^2C_\infty)^{1/2}$). The average contour length of the chains between crosslinks would be about 75 nm. Therefore, upon swelling, it is reasonable to assume that the distance between crosslinks may increase by as much as tens of nanometers.

The force due to entropy along a single chain section between crosslinks as it is elongated can be estimated by Eq. 6:[45]

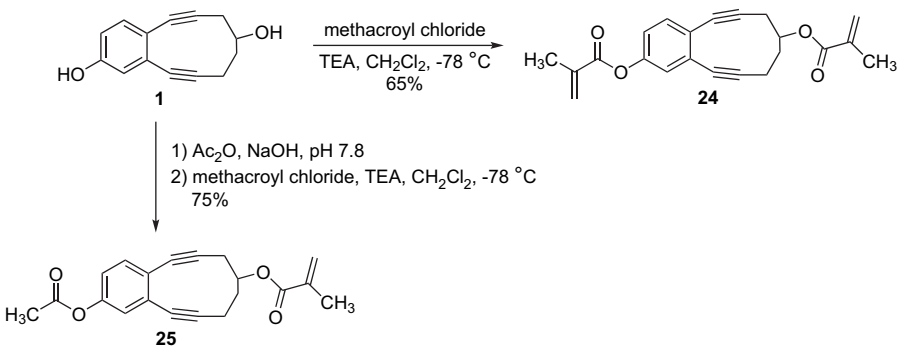
$$f = (3k_bT)/(2\mathrm{lp}L)\delta \tag{6}$$

where k_b is Boltzman's constant, T is the temperature, lp is the persistence length, L is the contour length, and δ is the extension length. The persistence length of PMMA has been reported to be 0.72 nm;[44] this corresponds to forces in the range of 10^{-13}–10^{-12} N as the network swells to levels less than twice its original size. This agrees reasonably well with experimentally observed forces due to polystyrene chains elongated to moderate levels (i.e., significantly less than the contour length).[45]

From Eq. 5, it is expected that a force of 1 pN would not decrease distance d significantly, and would likely be insufficient to produce rapid BC at ambient temperatures. However, because the predicted force due to swelling is only an average value in a polydisperse system, there will be a fraction of crosslinks bearing higher forces. In addition, by testing the samples under a temperature ramp, it seemed possible that the expected forces due to swelling may be enough to slightly lower the temperature at which radical formation is first detected in the system. In order to increase the peak stress on those crosslinkers bearing the bulk of the load, the low crosslinker level of 0.17 mol % was chosen.

To test this hypothesis, enediyne **1** was functionalized such that it could be incorporated as a crosslinker into a polymeric material. Bismethacrylate **24** was prepared by treatment of diol **1** with methacroyl chloride (Scheme 4). This enediyne crosslinker was incorporated into poly(methyl methacrylate) microspheres at 0.17 mol % relative to monomer by suspension polymerization of methyl methacrylate in water using a room temperature benzoyl peroxide/*N*,*N*-dimethylaniline initiation system.[46]

As a mechanically-inactive enediyne control, monomethacrylate **25** was prepared and incorporated into PMMA



Scheme 4. Preparation of bismethacrylate **24** and monomethacrylate **25**.

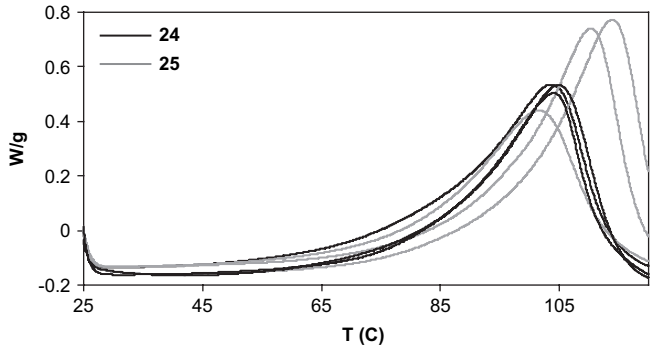


Figure 9. DSC traces of MMA polymerization initiated by beads crosslinked either with enediyne dimethacrylate **24** or with EGDMA and including pendant enediyne **25**. Three traces are shown for each type of bead.

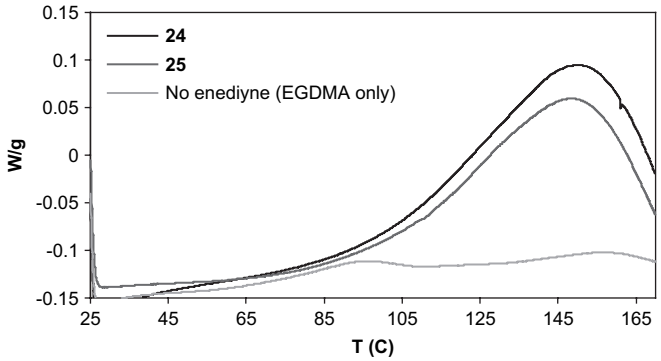


Figure 10. DSC traces of butyl methacrylate polymerization initiated by photopolymerized polymer networks crosslinked either with enediyne dimethacrylate **24**, with EGDMA and including pendant enediyne **25**, or only with EGDMA.

microspheres as above (Scheme 4). Because monomethacrylate **25** is incorporated into the polymer matrix as a pendant group, stress applied to the polymer backbone is not applied across the enediyne skeleton and is not expected to affect the temperature of BC. In this case, ethylene glycol dimethacrylate (EGDMA) is added as a crosslinker. This control will allow the isolation and identification of effects caused by thermally-activated BC and stress-activated BC. As a second control, microspheres were prepared crosslinked only with EGDMA and containing no enediyne. These control microspheres allow the isolation of thermal background polymerizations from polymerizations initiated by BC.

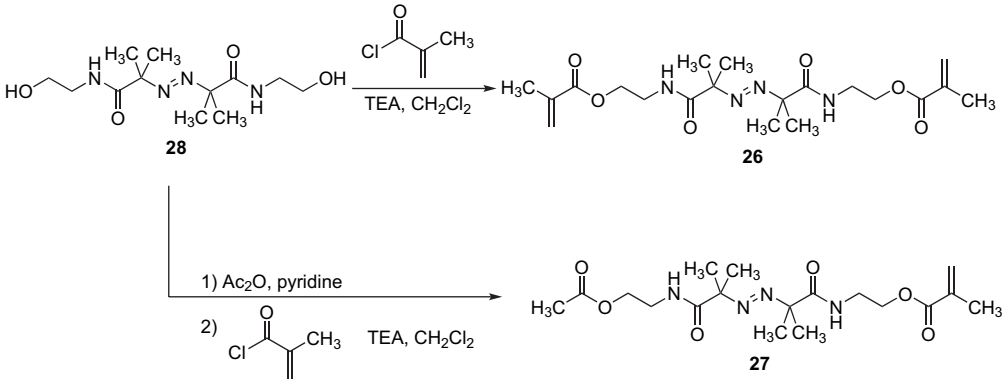
Microspheres containing the enediyne crosslinker, pendant control, or ethylene glycol crosslinks were washed by swelling them in CH_2Cl_2 for 4 h, then decanting the solvent. Residual solvent was then removed under vacuum. This washing step was necessary to remove the excess BPO initiator from the polymer matrix, which homolyzes in the same temperature region as BC and becomes a competitive initiator. The washed microspheres were then placed in DSC pans, swollen in MMA under argon for 24 h at room temperature, then analyzed by DSC. It was found that microspheres containing both crosslinker **24** and pendant control **25** exotherm at temperatures above 100 °C. No exotherm was observed for the control EGDMA-crosslinked microspheres in this region. This result suggests that the exotherm observed upon DSC analysis of the enediyne-containing microspheres was due to polymerization of MMA initiated by BC. Unfortunately, the differences in the temperatures of exotherm for crosslinker **24** and pendant group **25** are not statistically significant (Fig. 9), and no conclusions can be drawn as to the role of mechanical stress in activating the enediyne initiators.

There are several reasons why this might be the case. Although unlikely, it is possible that the enediynes were being prematurely activated in the washing stage when the beads were swollen with CH_2Cl_2. Another reason is that swelling did not apply enough force to the crosslinks for a significant temperature change to be detected by DSC.

To investigate whether the enediyne crosslinks were being prematurely activated, a photopolymerization scheme was worked out that does not require the use of a thermally active initiator. The absence of a thermal initiator eliminates the need for a washing step. These samples were prepared by irradiation of mixtures of the crosslinker, methyl acrylate (600:1 molar ratio of crosslinker to monomer), and 2,2-dimethoxy-2-phenylacetophenone photoinitiator in shallow glass channels. Samples of the resulting rubbery polymer were swollen in MMA and analyzed by DSC. The results are shown in Figure 10. It can be seen that the DSC curves for the exotherm of polymerization occur at the same temperature. This suggests that preactivation of the enediyne crosslinks is not the reason for the absence of mechanical activation.

Next it was examined whether the magnitude of stress being applied to the crosslinks by swelling is sufficient to observe a temperature reduction by DSC. Previous results obtained within our group suggest that azo crosslinkers are sensitive to mechanical shear created by ultrasound.[7] Thus, it was hypothesized that if no temperature difference was observed between azo linker **26**, which acts as a crosslinker, and pendant azo group **27** (Scheme 5), then insufficient stress was being applied to the crosslinks in the swollen gel to detect a temperature shift by DSC.

The preparation of both azo crosslinker **26** and pendant azo group **27** began with commercially-available azo diol **28**. Treatment of this material with methacroyl chloride and TEA yielded bismethacrylate linker **26** (Scheme 5). Pendant control linker **27** was prepared from azo compound **28** by treatment with Ac_2O and pyridine, followed by subsequent treatment with methacroyl chloride and TEA. These linkers were incorporated into PMMA microspheres, swollen in MMA under Ar, and analyzed by DSC.



Scheme 5. Preparation of azo dimethacrylate crosslinker **26** and pendant azo methacrylate **27**.

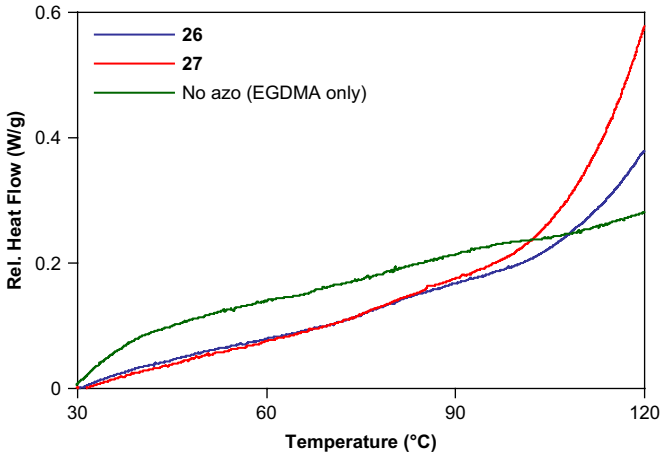


Figure 11. DSC traces of PMMA microspheres crosslinked either with azo dimethacrylate **26**, with EGDMA and including pendant azo **27**, or only with EGDMA.

The results of the DSC studies are shown in Figure 11. Both azo crosslinker **26** and pendant azo control **27** yield an exotherm of polymerization that begins to occur at about 80–90 °C. This exotherm is absent in the EGDMA microspheres, suggesting that the azo group is responsible for the polymerization. Since the onset of the exotherm in azo crosslinker **26** and pendant azo group **27** occurs at similar temperatures, it was concluded that the bulk material test, coupled with the DSC analysis, is not sensitive enough to detect the shifts in the exotherm under the weak stress applied from the swelling of polymer networks. Therefore, a different experimental setup is needed to study stress-induced cycloaromatization reactions.

3. Conclusions

Enediyne-based mechanical triggers have been designed and synthesized. Computational studies suggest that the deformation of distance *d* is highly dependant on the shape of the enediyne and the orientation of the bonds linking the mechanophore to the polymer backbone. The spring constant *k* for the desired deformation in enediyne **1** was computationally determined to be 36.8 N/m. This suggests that the deformation *d* is represented by a compliant spring, much more deformable than the stretching of a C–C bond.

Three enediynes studied computationally were successfully synthesized. The thermal BC reactions for these linkers were studied by DSC, and found to be consistent with the predicted thermal sensitivity **3**>**2**>**1** based on known substituent effects. However, upon incorporation of the enediynes into a polymer matrix as crosslinks, no definitive stress activation was observed. Through experiments with mechanically-sensitive azo units, it was concluded that swelling alone produced insufficient force to yield a large enough reduction in onset temperature to be detectable by DSC. Therefore, we were unable to draw any conclusions about the stress-sensitivity of enediynes. A different testing scheme is needed that will apply more stress in a controlled manner.[7,12,14]

4. Experimental

4.1. General

Unless otherwise stated, all starting materials and reagents were obtained from commercial suppliers and used without further purification. Reagent grade ether was purchased from Malinckrodt and anhydrous methylene chloride was purchased from Acros. THF was distilled from sodium immediately before use, and dry CH_2Cl_2 was stored over 4 Å MS. All moisture or air sensitive reactions were completed under an atmosphere of dry nitrogen or argon.

Analytical TLC was performed on Kieselgel F_{254} precoated TLC plates, and visualized with UV light at 254 nm. Flash chromatography was conducted with silica gel 60 (230–400 mesh) from EM science. The ^1H and ^{13}C NMR spectra were recorded on Varian Unity 400 or 500 MHz spectrometers in the University of Illinois' NMR laboratory. The residual solvent protons were used as an internal standard. Chemical shifts are reported in parts per million (ppm). Coupling constants (*J*) are reported in hertz (Hz), and splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). MS were obtained through the Mass Spectrometry Facility, SCS, University of Illinois. CHN elemental analysis (EA) was performed in the Microanalytical Service Laboratory with a CE440 instrument (Exeter Analytical, Inc.). DSC analysis was performed on a Mettler Toledo DSC instrument using 40 μL aluminum crucibles and a heating rate of 5 or 10 °C per min.

4.1.1. 4-Bromo-3-iodophenol

A 250 mL round-bottomed flask equipped with a magnetic stirrer and rubber septa was purged with N_2, charged with 4-bromo-3-iodoanisole[47] (9.12 g, 29.2 mmol), and dissolved in dry CH_2Cl_2 (95 mL). Added over 1 min was a boron trifluoride–dimethyl sulfide complex (15.4 mL, 146 mmol). This mixture was stirred overnight (approximately 12 h), then the solvent was removed under a stream of N_2. The residue was partitioned between EtOAc (50 mL) and 2 M HCl (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2×150 mL). The combined organic layers were washed with 2 M HCl (150 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification by flash chromatography (10:1 hexanes/EtOAc, silica) yielded 4-bromo-3-iodophenol (8.7 g, 100%) as off-white needles: mp 83–84 °C; TLC R_f 0.22 (5:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.43 (1H, d, J=8.6 Hz), 7.37 (1H, d, J=2.7 Hz), 6.71 (1H, dd, J=3, 8.8 Hz), 4.91 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.9, 133.1, 127.3, 126.7, 117.4, 101.3; LRMS (EI, 70 eV) *m*/*z* 299 ($[M+2]^+$), 297 (M^+), 171 ($[M-I]^+$); HRMS (EI, 70 eV) calcd for C_6H_4BrIO 297.8490, found 297.8483; EA calcd for C_6H_4BrIO C 24.11, H 1.35, found C 24.15, H 1.26.

*4.1.2. 1-Bromo-2-iodo-4-(2-tetrahydropyranyloxy)benzene **5***

A 200 mL round-bottomed flask equipped with a magnetic stirrer and rubber stopper was charged with 4-bromo-3-iodophenol (8.34 g, 28.0 mmol) and placed under a N_2 atmosphere. Added to the flask was CH_2Cl_2 (112 mL), followed by 3,4-dihydropyran (13.5 mL, 140 mmol). The resulting mixture was cooled in an ice water bath and *p*TSA monohydrate (56 mg, 0.280 mmol) was added. After 20 min the cooling bath was removed. After 2 h of stirring the mixture was poured onto diethyl ether (170 mL). The contents were then diluted with a 1:2:1 mixture of saturated sodium bicarbonate/H_2O/brine (170 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (200 mL). The combined organics were washed with saturated sodium bicarbonate (200 mL) and brine (200 mL), then dried over Na_2SO_4. The solvent was removed under vacuum, yielding yellow crystals, which were recrystallized from hot methanol yielding **5** (7.48 g, 20.4 mmol, 73%) as white needles: mp 76–77 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57 (1H, d, J=2.77 Hz), 7.46 (1H, d, J=8.9 Hz), 6.92 (1H, dd, J=2.9, 9.0 Hz), 5.37 (1H, t, J=3.1 Hz), 3.82 (1H, m), 3.61 (1H, m), 1.95 (1H, m), 1.83 (2H, m), 1.75–1.54 (3H, m). EA calcd for $C_{11}H_{12}BrIO_2$ C 34.49, H 3.16, found C 34.5, H 3.12.

*4.1.3. 1-Bromo-2-(triisopropylsilylethynyl)-4-(2-tetrahydropyranyloxy)benzene **6***

A Schlenck flask equipped with a magnetic stirrer, a Teflon stopcock and under an Ar atmosphere was charged with **5** (4.33 g, 11.82 mmol), $PdCl_2(PPh_3)_2$ (0.415 g, 0.591 mmol), and CuI (0.225 g,

1.18 mmol). Added was a degassed solution of triisopropylsilylacetylene (2.26 g, 12.41 mmol) in TEA (23 mL). The resulting yellow solution was stirred for about 15 h, at which point the solvent was removed under vacuum. The residue was partitioned between saturated aqueous ammonium chloride (50 mL) and diethyl ether (50 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were washed with saturated aqueous ammonium chloride (3×50 mL) and dried over Na_2SO_4. Vacuum filtration and removal of the solvent under vacuum yielded a dark oil, which was purified by flash chromatography (hexanes/silica) to yield **6** (4.64 g, 11.0 mmol, 93%) as a colorless oil and with only a trace of the bromide coupled product by NMR: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42 (1H, d, J=8.8 Hz), 7.20 (1H, d, J=2.8 Hz), 6.89 (1H, dd, J=2.9, 8.8 Hz), 5.40 (1H, t, J=3.0 Hz), 3.84 (1H, td, J=3.0, 11.1 Hz), 3.61 (1H, m), 1.97 (1H, m), 1.87 (2H, m), 1.54–1.74 (3H, m), 1.15 (21H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.0, 133.1, 126.4, 121.8, 118.5, 117.6, 104.9, 96.5, 96.1, 62.0, 30.3, 25.3, 18.9, 18.6, 11.5; LRMS (EI, 70 eV) m/z 354 ($[M+2]-C_5H_9O^+$), 352 ($[M-C_5H_9O]^+$), 85 ($C_5H_9O^+$); HRMS (CI, CH_4) calcd for $C_{22}H_{34}BrO_2Si$ $[M+H]^+$ 437.1511, found 437.1511; HPLC (1.0 mL/min, 100% hexanes, 40.0 min, retention time 15.3 min) indicates >98% purity.

4.1.4. 2-(Triisopropylsilylethynyl)-1-(trimethylsilylethynyl)-4-(2-tetrahydropyranyloxy)benzene **7**

A Schlenck flask equipped with a magnetic stirrer and Teflon stopcock, and under Ar was charged with $ZnBr_2$ (5.2 g, 23.1 mmol), diisoproplyamine (3.23 mL, 23.1 mmol), $Pd(P^tBu_3)_2$ (39 mg, 0.077 mmol), and DMF (23 mL). This was stirred for 5 min, then added were **6** (1.62 g, 3.85 mmol) and TMS acetylene (3.3 mL, 23.1 mmol). The resulting mixture was stirred overnight, at which point the reaction was poured onto saturated aqueous ammonium chloride (25 mL). The mixture was diluted with diethyl ether (25 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (2×25 mL). The combined organic layers were washed with saturated aqueous ammonium chloride (50 mL) and dried over Na_2SO_4. Vacuum filtration and removal of solvent under vacuum yielded a dark oil, which was purified by flash chromatography (100% hexanes→50:1 hexanes/EtOAc, silica) to yield **7** (1.64 g, 3.61 mmol, 94%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (1H, d, J=8.6 Hz), 7.12 (1H, d, J=2.6 Hz), 6.93 (1H, dd, J=2.7, 8.7 Hz), 5.43 (1H, t, J=3.14 Hz), 3.83 (1H, m), 3.61 (1H, m), 1.98 (1H, m), 1.84 (2H, m), 1.68 (2H, m), 1.59 (1H, m), 1.26 (1H, m), 1.16 (18H, d, J=11.3 Hz), 0.22 (8H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.7, 134.4, 127.2, 120.6, 119.1, 116.8, 105.3, 103.7, 96.6, 96.3, 94.8, 62.0, 30.3, 25.3, 19.0, 18.6, 11.5, 0.2; LRMS (EI, 70 eV) m/z 454 (M^+), 411 ($[M-C_3H_7]^+$), 370 ($[M-C_5H_9O]^+$), 285, 243, 128, 84 ($C_5H_9O^+$); HRMS (EI, 70 eV) calcd for $C_{27}H_{42}O_2Si_2$ 454.2723, found 454.2716; HPLC (1.0 mL/min, 2.5% EtOAc/hexane, 20.0 min, retention time 5.4 min) indicates >96% purity.

4.1.5. 1-Ethynyl-2-(triisopropylsilylethynyl)-4-(2-tetrahydropyranyloxy)benzene ***8***

To a 50 mL round-bottomed flask equipped with a magnetic stirrer was added THF (6.6 mL), MeOH (6.6 mL), and **7** (0.6 g, 1.32 mmol). Added dropwise was a solution of aqueous LiOH (1 M, 4.25 mL). The resulting cloudy solution was stirred and the reaction progress was followed by TLC. After the starting material was consumed (approximately 40 min) the reaction was diluted with water (20 mL) and diethyl ether (20 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3×20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (100% hexane→10:1 hexane/EtOAc) yielding **8** (0.48 g, 1.25 mmol, 95%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (1H, d, J=8.8 Hz), 7.15 (1H, d, J=2.6 Hz), 6.95 (1H, dd, J=2.5, 8.7 Hz), 5.45 (1H, t, J=3.05 Hz), 3.84 (1H, m), 3.61 (1H, m), 3.16 (1H, s), 1.98 (1H, m), 1.85 (2H, m), 1.67 (2H, m), 1.59 (1H, m), 1.14 (18H, d, J=11.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.0, 133.9, 128.0, 120.2, 118.4, 116.8, 104.9, 96.3, 95.2, 82.5, 79.8, 62.0, 30.3, 18.9, 18.6, 11.5; LRMS (EI, 70 eV) m/z 382 (M^+), 339 ($[M-C_3H_7]^+$), 255, 85 ($C_5H_9O^+$); HRMS (EI, 70 eV) calcd for $C_{24}H_{34}O_2Si$ 382.2328, found 382.2336; HPLC (1.0 mL/min, 100% hexane, 40 min, retention time 11.9 min) indicates >95% purity.

4.1.6. 1-[(tert-Butyldimethylsilyl)oxy-6-[4-(2-tetrahydropyranyloxy)-2-(triisopropylsilylethynyl)phenyl]hex-5-yn-3-ol ***8***

A 50 mL two-necked round-bottomed flask equipped with a magnetic stirrer was flame-dried under Ar, then charged with **8** (0.48 g, 1.25 mmol) and freshly distilled THF (25 mL). This solution was cooled in an isopropanol-dry ice bath, then ^{n}BuLi (0.862 mL of 1.6 M solution in hexanes, 1.38 mmol) was added dropwise via syringe pump at a rate of 1 drop per 5 s. After complete addition, stirring continued for 1 h then boron trifluoride etherate (0.207 mL, 1.63 mmol) was added all at once. After 15 min of stirring, 1-[(2-*tert*-butyldimethylsilyl)oxy]ethyloxirane[48] (0.254 g, 1.25 mmol) was added dropwise, and stirring with cooling continued for 40 min, then the reaction was warmed to room temperature and quenched with a 3:1 solution of saturated ammonium chloride/water (25 mL) and diluted with diethyl ether. The layers were separated and the aqueous layer was extracted with diethyl ether (2×25 mL). The combined organic layers were dried over Na_2SO_4, concentrated under vacuum, and purified by flash chromatography (10:1 hexanes/EtOAc, silica) yielding **9** (0.564 g, 0.97 mmol, 77%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (1H, d, J=8.6 Hz), 7.12 (1H, d, J=2.6 Hz), 6.92 (1H, dd, J=2.7, 8.8 Hz), 5.45 (1H, t, J=3.0 Hz), 4.04 (1H, m), 3.92 (1H, m), 3.84 (2H, m), 3.61 (1H, dt, J=4.3, 11.1 Hz), 2.67 (1H, dd, J=5.7, 17 Hz), 2.56 (1H, dd, J=7.6, 17 Hz), 1.97 (2H, m), 1.87 (2H, m), 1.77 (1H, m), 1.54–1.74 (3H, m), 1.14 (21H, s), 0.90 (9H, s), 0.08 (6H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.3, 133.5, 127.1, 120.4, 119.7, 116.9, 105.7, 96.3, 94.4, 89.2, 81.4, 70.9, 62.5, 62.0, 37.6, 30.3, 28.5, 26.3, 25.2, 18.9, 18.6, 18.3, 11.5, −5.4; LRMS (EI, 70 eV) m/z 585 (M^+), 566 ($[M-H_2O]^+$), 527 ($[M-C_3H_7]^+$), 500 ($[M-C_5H_9O]^+$); HRMS (EI, 70 eV) calcd for $C_{34}H_{56}O_4Si_2$ 584.3713, found 584.3714; HPLC (1.0 mL/min, 10% EtOAc in hexanes, retention time 7.4 min) indicates >95% purity.

4.1.7. 6-[4-(2-Tetrahydropyranyloxy)-2-ethynylphenyl]-3-(2-tetrahydropyranyloxy)hex-5-yn-1-ol ***10***

A 200 mL round-bottomed flask equipped with a magnetic stirrer and rubber septum was purged with a nitrogen atmosphere, then charged with **9** (1.22 g, 2.09 mmol) and dry CH_2Cl_2 (8.3 mL). This solution was cooled in an ice bath and added was 3,4-dihydropyran (1.0 mL, 10.4 mmol), followed by *p*TSA monohydrate (40 mg, 0.209 mmol). The resulting solution was stirred with cooling for 2 h, then poured onto saturated aqueous $NaHCO_3$ (10 mL) and diethyl ether (10 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3×25 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (25 mL) and brine (25 mL), then dried over Na_2SO_4. The solvent was removed under vacuum yielding an oil, which was taken up in THF (21 mL) and placed in a 250 mL round-bottomed flask equipped with a magnetic stirrer and rubber stopper. Added all at once was TBAF (5.21 mL of 1.0 M solution in THF, 5.21 mmol), and the resulting solution was stirred. After 24 h the reaction was partitioned between saturated aqueous ammonium chloride and diethyl ether. The layers were separated and the aqueous layer was extracted with diethyl ether (2×50 mL). The combined organics were washed with brine (50 mL) and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by flash chromatography (4:1 hexanes/EtOAc→1:1 hexanes/EtOAc,

silica) yielding **10** (0.71 g, 1.85 mmol, 89%) as a light yellow oil: LRMS (EI, 70 eV) *m/z* 398 (M^+), 314 ($M-C_5H_9O^+$), 85 ($C_5H_9O^+$); HRMS (EI, 70 eV) calcd for $C_{24}H_{30}O_5$ 398.2093, found 398.2099; HPLC (1.0 mL/min, 33% EtOAc in hexanes, retention time 17.4 min) indicates >95% purity.

*4.1.8. 1-Iodo-6-[4-(2-tetrahydropyranyloxy)-2-ethynylphenyl]-3-(2-tetrahydropyranyloxy)hex-5-yne **11***

A 25 mL two-necked round-bottomed flask was equipped with a magnetic stirrer and rubber stopper and purged with a nitrogen atmosphere. Added to the flask was PPh_3 (0.613 g, 2.43 mmol), imidazole (0.477 g, 7.01 mmol), and dry CH_2Cl_2 (14 mL). This was stirred until complete dissolution of all solid material. Then the solution was cooled in an ice water bath. I_2 (0.593 g, 2.34 mmol) was then added, and the resulting mixture was stirred for 16 min with cooling, yielding a white suspension. Added was a solution of **10** (0.449 g, 1.17 mmol) in CH_2Cl_2 (6.9 mL). This reaction mixture was warmed to room temperature and allowed to stir for 19 h. The solvent was removed under vacuum and the thick yellow residue was immediately purified by flash chromatography (10:1 hexanes/EtOAc, silica) yielding **11** (0.406 g, 0.800 mmol, 68%) as a colorless oil: LRMS (EI, 70 eV) *m/z* 508 (M^+), 484, 446, 424 ($[M-C_5H_9O]^+$), 382 ($[M-I]^+$), 85 ($C_5H_9O^+$); HRMS (EI, 70 eV) calcd for $C_{24}H_{29}IO_4$ 508.1111, found 508.1097.

*4.1.9. 3,4-(3-Hydroxybenzo)cyclodec-3-ene-1,5-diyn-8-ol **1***

A flame-dried sealed tube was placed under an Ar atmosphere, then charged with a solution of **11** (0.598 g, 1.18 mmol) in freshly distilled THF (17.6 mL). This solution was cooled in a dry ice/acetone bath and a solution of LDA (2.6 mL of 0.56 M solution in THF, 1.41 mmol) was added dropwise. The reaction mixture was stirred for 1 h, then HMPA (1.43 mL, 8.23 mmol) was added all at once and the reaction immediately turned dark blue. The cooling bath was removed and the mixture was stirred for 24 h at room temperature, then quenched with brine (20 mL) and diluted with diethyl ether (20 mL). The layers were separated, and the aqueous layer was washed with diethyl ether (3×30 mL). The combined organics were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was passed through a short silica plug, eluting with $CHCl_3$, to yield the diprotected macrocycle (0.249 g, 0.654 mmol, 56%) as a yellow oil with satisfactory LRMS analysis (FD 380 (M^+)). It was dissolved in 1:1 MeOH/THF (6 mL) and placed in a 20 mL scintillation vial equipped with a magnetic stirrer and plastic screw cap. Added was *p*TSA monohydrate (13 mg, 0.07 mmol). After 1 h of stirring the reaction was quenched with saturated aqueous sodium bicarbonate (5 mL) and water (2 mL), then diluted with diethyl ether (5 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3×5 mL). The combined organics were washed with saturated aqueous sodium bicarbonate and brine (5 mL each), then dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by flash chromatography (3:1 hexanes/EtOAc→3:2 hexanes/EtOAc, silica) yielding **1** (72 mg, 0.340 mmol, 52%) as an off-white solid: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.10 (1H, d, *J*=8.3 Hz), 6.67 (1H, d, *J*=2.2 Hz), 6.65 (1H, dd, *J*=2.6, 8.3 Hz), 4.92 (2H, br s), 3.92 (1H, m), 2.60 (2H, m), 2.48 (2H, m), 2.16 (1H, m), 2.04 (1H, m); ^{13}C NMR (CD_3OD, 100 MHz) δ 157.0, 130.4, 129.2, 120.2, 114.9, 114.4, 99.0, 91.8, 83.7, 82.7, 73.4, 39.7, 29.9, 19.2; LRMS (EI, 70 eV) *m/z* 212 (M^+), 183, 169, 139; HRMS (EI, 70 eV) calcd for $C_{14}H_{12}O_2$ 212.0837, found 212.0840.

4.2. General procedure for the preparation of diacetates from diols

In a scintillation vial equipped with a magnetic stirrer and plastic cap were added the diol (1 equiv) and pyridine (20 mL/mmol diol). Acetic anhydride (5 mL/mmol diol) was then added, and the resulting solution was stirred for 6 h. Methanol was then added, and stirring was continued for an additional 1 h. The solvent was then removed, and the residue was partitioned between EtOAc and water. The layers were separated, and the aqueous layer was extracted with two portions of EtOAc. The combined organics were washed with 1 M HCl and saturated $NaHCO_3$, then dried over Na_2SO_4. The solvent was removed under vacuum, to yield the crude diacetate. Unless otherwise indicated, purity was determined by NMR and was found to be sufficiently pure for further use.

4.3. General procedure for the preparation of dimethacrylates from diols

To a 50 mL two-necked round-bottomed flask equipped with a magnetic stirrer and rubber septa and purged with Ar were added the diol (1 equiv) and CH_2Cl_2 (5 mL/mmol diol). The resulting suspension was cooled in a dry ice/acetone bath, then added was TEA (16 equiv), followed by a solution of methacroyl chloride (6 equiv) in CH_2Cl_2 (1 mL/mmol diol). The resulting solution was warmed slowly to room temperature overnight, then poured onto saturated sodium bicarbonate and CH_2Cl_2. The layers were separated and the aqueous layer was extracted with two portions of CH_2Cl_2. The combined organics were washed with saturated sodium bicarbonate then dried over Na_2SO_4. The solvent was removed under vacuum to yield the crude dimethacrylate. Unless otherwise indicated, purity was determined by NMR and was found to be sufficient for further use.

*4.3.1. 8-Acetoxy-3,4-(3-acetoxybenzo)cyclodec-3-ene-1,5-diyne **21***

Prepared using the general procedure for the preparation of diacetates. Recrystallization of the solid residue from methanol gave **21** (70.8 mg, 0.238 mmol, 58%) as white needles: mp 138–140 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29 (1H, d, *J*=8.2 Hz), 7.03 (1H, d, *J*=2.4 Hz), 6.92 (1H, dd, *J*=2.3, 8.5 Hz), 4.95 (1H, m), 2.78 (2H, m), 2.67 (1H, m), 2.57 (1H, ddd, *J*=2.2, 5.5, 17.8 Hz), 2.28 (3H, s), 2.25 (1H, m), 2.07 (1H, m), 2.06 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 169.2, 150.0, 130.6, 129.3, 126.5, 121.7, 121.1, 100.7, 93.5, 84.0, 82.7, 75.1, 37.7, 27.4, 21.4, 21.3, 19.4; LRMS (EI, 70 eV) *m/z* 296 (M^+), 236 ($[M-CH_3COOH]^+$), 194 ($[M-C_4H_6O_3]^+$); EA calcd for $C_{18}H_{16}O_4$ C 72.96, H 5.44, found C 72.97, H 5.34.

*4.3.2. 8-Methacroyloxy-3,4-(3-methacroyloxybenzo)cyclodec-3-ene-1,5-diyne **24***

Prepared using the general procedure for the preparation of dimethacrylates. The crude residue was purified by flash chromatography (20:1 hexane/EtOAc, silica) to yield a white solid. This was recrystallized from hexane, to yield **25** (0.114 g, 0.325 mmol, 65%) as a white solid: mp 95 °C (dec); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 (1H, d, *J*=8.5 Hz), 7.07 (1H, d, *J*=2.2 Hz), 7.00 (1H, dd, *J*=2.2, 8.4 Hz), 6.33 (1H, app quintet, *J*=1.1 Hz), 6.11 (1H, m), 5.76 (1H, quintet, *J*=1.5 Hz), 5.59 (1H, quintet, *J*=1.6 Hz), 5.03 (1H, m), 2.79 (3H, m), 2.59 (1H, ddd, *J*=2.2, 5.8, 17.6 Hz), 2.31 (1H, m), 2.12 (1H, dquintet, *J*=2.3, 14.8 Hz), 2.04 (3H, app t, *J*=1.1 Hz), 1.94 (3H, app t, *J*=1.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.9, 165.6, 150.3, 136.4, 135.8, 130.6, 129.2, 127.9, 126.5, 126.2, 121.8, 121.1, 100.8, 93.5, 84.0, 82.8, 75.2, 37.5, 27.4, 19.4, 18.55, 18.50; LRMS (EI, 70 eV) *m/z* 348 (M^+), 262 ($[M-C_4H_5O_2]^+$); HRMS (EI, 70 eV) calcd for $C_{22}H_{20}O_4$ 348.1354, found 348.1362; EA calcd C 75.84, H 5.79, found C 75.7, H 5.65.

*4.3.3. 8-Methacroyloxy-3,4-(3-acetoxybenzo)cyclodec-3-ene-1,5-diyne **25***

To a 10 mL conical reactor equipped with a magnetic stirrer and Teflon septum was added a solution of diol **3** (94.1 mg, 0.444 mmol) in isopropanol (3 mL). To this solution was added a mixture of NaOH (48.8 mg, 1.22 mmol) in water (0.6 mL). This was vigorously

stirred for 5 min, then added was acetic anhydride (0.12 mL, 1.22 mmol). The reaction progress was followed by TLC and, after complete disappearance of the starting material (about 30 min) the mixture was concentrated under vacuum, then partitioned between EtOAc (10 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organics were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum to yield a yellow solid. This was placed in a 10 mL conical reactor equipped with a magnetic stirrer and Teflon septa. The flask was purged with nitrogen, then CH_2Cl_2 (2.2 mL) was added. The suspension was cooled in a dry ice/acetone bath, then triethylamine (0.43 mL, 3.1 mmol) was added, followed by the dropwise addition of a solution of methacroyl chloride (0.26 mL, 2.66 mmol) in CH_2Cl_2 (0.5 mL). The resulting solution was allowed to warm to room temperature and stir overnight. The reaction was poured onto 5% $NaHCO_3$ (5 mL). This was extracted with CH_2Cl_2 (3×5 mL). The combined organics were washed with water (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL), then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (20:1 hexane/EtOAc, silica), yielding **25** (0.108 g, 0.333 mmol, 75%) as a white solid that was used without further purification. A small amount of material was recrystallized from methanol for analysis: mp 89–91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (1H, d, J=8.4 Hz), 7.03 (1H, d, J=2.2 Hz), 6.96 (1H, dd, J=2.6, 8.2 Hz), 6.11 (1H, s), 5.59 (1H, app t, J=1.5 Hz), 5.02 (1H, m), 2.79 (3H, m), 2.58 (1H, dd, J=1.7, 5.5 Hz), 2.31 (1H, ddd, J=2.0, 4.8, 14.6 Hz), 2.28 (3H, s), 2.11 (1H, m), 1.94 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 166.9, 150.0, 136.4, 130.6, 129.3, 126.6, 126.2, 121.7, 121.1, 100.8, 93.5, 83.9, 82.7, 75.2, 37.5, 27.4, 21.3, 19.4, 18.5; LRMS (EI, 70 eV) m/z 322 (M^+), 236 ($[M-C_4H_6O_2]^+$), 194 ($[M-C_6H_8O_3]^+$); HRMS (EI) calcd for $C_{20}H_{18}O_4$ 322.1205, found 322.1197; EA calcd for $C_{20}H_{18}O_4$ C 74.52, H 5.63, found C 74.35, H 5.48.

4.3.4. 1-[2-Bromo-5-(2-tetrahydropyranyloxy)phenyl]hex-1-yn-6-ol ***13a***

A sealed tube under Ar was charged with $PdCl_2(PPh_3)_2$ (37 mg, 0.331 mmol) and CuI (126 mg, 0.662 mmol). Added was a degassed solution of **5** (2.43 g, 6.62 mmol) and 5-hexyn-1-ol (0.75 mL, 6.95 mmol) in triethylamine (13 mL). The resulting solution was stirred for 26 h, then poured onto saturated ammonium chloride (25 mL) and ether (25 mL). The layers were separated and the aqueous later was extracted with ether (3×25 mL). The combined organic phases were washed with saturated ammonium chloride (2×50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash chromatography (3:1 hexane/EtOAc, silica) yielded **13a** (1.92 g, 5.69 mmol, 86%) as a yellow oil and as an inseparable 47:3 ratio of the bromide/iodide: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 (1H, d, J=8.7 Hz), 7.09 (1H, d, J=2.97 Hz), 6.79 (1H, dd, J=2.8, 8.8 Hz), 5.32 (1H, t, J=3.12 Hz), 3.80 (1H, m), 3.64 (2H, t, J=6.27), 2.68 (1H, br s), 2.45 (2H, t, J=6.71 Hz), 1.91 (1H, m), 1.79 (2H, m), 1.43–1.75 (8H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.0, 133.0, 12.6, 121.2, 118.0, 117.2, 96.6, 95.0, 79.9, 62.4, 62.2, 32.0, 30.4, 25.3, 25.0, 19.5, 18.7; LRMS (EI, 70 eV) m/z 354 ($[M+2]^+$), 352 (M^+), 268 ($[M-C_5H_9O]^+$), 85 ($C_5H_9O^+$); HRMS (EI, 70 eV) calcd for $C_{17}H_{21}BrO_3$ 352.0674, found 352.0671; HPLC (1.0 mL/min, 20% EtOAc/hexanes, 40 min, retention time 20.0 min) indicates 94% purity.

4.3.5. 1-[2-Ethynyl-5-(2-tetrahydropyranyloxy)phenyl]hex-1-yn-6-ol ***14***

A Schlenck flask equipped with a magnetic stirrer and Teflon stopper and under Ar was charged with dry DMF (32 mL), **13a** (1.92 g, 5.45 mmol), and TMS acetylene (3.84 mL, 27.2 mmol). This mixture was degassed with bubbling Ar and cooled in an ice bath. $Pd(P^tBu_3)_2$ (56 mg, 0.109 mmol) and $ZnBr_2$ (7.35 g, 32.7 mmol) was then added to the mixture, and the resulting suspension was stirred for 12 h, then poured onto saturated ammonium chloride (50 mL) and ether (50 mL). The layers were separated and the aqueous phase was washed with ether (3×50 mL). The combined organics were washed with saturated ammonium chloride (50 mL) and water (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting dark oil was taken up in THF (100 mL) and MeOH (2.2 mL) and placed in a 200 ml round-bottomed flask, then added was a solution of TBAF in THF (5.45 mL, 5.45 mmol). This was stirred for 2 h, then poured onto saturated ammonium chloride (100 mL) and diluted with diethyl ether (100 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3×100 mL). The combined organic layers were dried over Na_2SO_4, concentrated under vacuum, and purified by flash chromatography yielding **14** (1.19 g, 4.01 mmol, 74%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (1H, d, J=8.7 Hz), 7.08 (1H, d, J=2.5 Hz), 6.90 (1H, dd, J=2.6, 8.5 Hz), 5.40 (1H, t, J=3.2 Hz), 3.83 (1H, ddd, J=1.2, 8.4, 10.4 Hz), 3.71 (2H, t, J=6.4 Hz), 3.60 (1H, dtd, J=1.3, 4.1, 11.2 Hz), 3.19 (1H, s), 2.50 (2H, t, J=6.9 Hz), 1.96 (1H, m), 1.83 (2H, m), 1.78 (2H, m), 1.54–1.74 (6H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.1, 133.9, 128.3, 119.6, 117.7, 116.4, 96.4, 94.4, 82.7, 79.6, 79.3, 62.6, 62.2, 31.9, 30.3, 25.3, 25.0, 19.5, 18.7; LRMS (EI, 70 eV) m/z 298 (M^+), 214 ($[M-C_5H_9O]^+$), 85 ($C_5H_9O^+$); HRMS (EI, 70 eV) calcd for $C_{19}H_{22}O_3$ 298.1569, found 298.1561; HPLC (1.0 mL/min, 20% EtOAc/hexanes, 60 min, retention time 26.7 min) indicates >96% purity.

4.3.6. 1-[2-(2-Iodoethynyl)-5-(2-tetrahydropyranyloxy)phenyl]-hex-1-yn-6-ol ***15***

A Schlenck flask equipped with a magnetic stirrer was charged with dry THF (114 mL) and diisopropylamine (1.23 mL, 8.80 mmol). This mixture was cooled in a dry ice/isopropanol bath, then added was ^{n}BuLi (5.25 mL of 1.6 M solution in hexanes, 8.4 mmol). After complete addition the cooling bath was removed and the mixture was allowed to warm for 20 min, then the cooling bath was replaced. Alkyne **14** (1.19 g, 3.99 mmol) was added as a solution in THF (12 mL) and the reaction mixture immediately turned brown. This was stirred with cooling for 2 h, then I_2 (1.01 g, 3.99 mmol) was added. The resulting orange solution was stirred with cooling for 1 h, then warmed to room temperature and diluted with saturated $Na_2S_2O_3$ (100 mL) and diethyl ether (100 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (3:1 hexanes/EtOAc→2:1 hexanes/EtOAc, silica) yielding **15** (1.46 g, 3.46 mmol, 87%) as a light yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31 (1H, d, J=8.6 Hz), 7.06 (1H, d, J=2.5 Hz), 6.89 (1H, dd, J=2.6, 8.7 Hz), 5.48 (1H, t, J=3.4 Hz), 3.83 (1H ddd, J=3.0, 9.9, 11.2 Hz), 3.75 (2H, t, J=6.3 Hz), 3.10 (m, 1H), 2.52 (2H, t, J=7.0 Hz), 1.97 (1H, m), 1.83 (4H, m), 1.73 (2H, m), 1.66 (2H, m), 1.60 (1H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.2, 134.0, 128.7, 119.3, 117.7, 116.2, 96.4, 94.6, 93.2, 79.7, 62.8, 62.2, 32.1, 30.3, 25.5, 25.5, 19.5, 18.7, 7.6; LRMS (EI, 70 eV) m/z 424 (M^+), 340 ($[M-C_5H_9O]^+$), 85 ($C_5H_9O^+$); HRMS (EI, 70 eV) calcd for $C_{19}H_{21}IO_3$ 424.0535, found 424.0539; HPLC (1.0 mL/min, 20% EtOAc in hexanes, retention time 29.3 min) indicated >92% purity with an inseparable mixture of 6% starting material.

4.3.7. 1-[2-(2-Iodoethynyl)-5-(2-tetrahydropyranyloxy)-phenyl]hex-1-yn-6-al ***16***

A 500 mL two-necked round-bottomed flask equipped with a magnetic stirrer and two glass stoppers was purged with N_2 then charged with a solution of **15** (1.44 g, 3.41 mmol) in dry CH_2Cl_2 (180 mL). This mixture was cooled in an ice bath, then PDC (12.8 g, 34.1 mmol) was added, followed by CH_2Cl_2 (12 mL). The resulting orange mixture was stirred with cooling for 30 min, then warmed to room temperature and stirred overnight. The reaction was filtered

through a Celite plug, and the plug was washed with CH_2Cl_2 (3×500 mL). The filtrate was concentrated under vacuum and the dark residue was purified by flash chromatography (15:1 hexanes/EtOAc→5:1, silica) yielding **16** (1.17 g, 2.78 mmol, 82%) as a yellow oil homogenous by TLC (R_f 0.541, 1:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.90 (1H, t, J=1.3 Hz), 7.31 (1H, d, J=8.6 Hz), 7.06 (1H, d, J=2.4 Hz), 6.90 (1H, dd, J=2.6, 8.6 Hz), 5.40 (1H, t, J=3.2 Hz), 3.83 (1H, m), 3.60 (1H, m), 2.71 (2H, dt, J=1.2, 7.3 Hz), 2.56 (2H, t, J=6.7 Hz), 1.95 (3H, q, J=7.0 Hz), 1.84 (2H, m), 1.67 (2H, m), 1.59 (1H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.3, 157.2, 134.0, 128.5, 119.5, 119.3, 116.4, 96.4, 93.3, 93.2, 80.2, 62.2, 43.0, 30.3, 25.2, 21.2, 19.1, 18.7, 7.4; LRMS (EI, 70 eV) m/z 422 (M^+), 338 ([M−C_5H_9O]$^+$), 85 ($C_5H_9O^+$); HRMS (EI, 70 eV) calcd for $C_{19}H_{19}IO_3$ 422.0379, found 422.0371; HPLC (1.0 mL/min, 20% EtOAc in hexanes, retention time 7.1 min) indicated 82% impurity, with the major impurity, 18%, consisting of the terminal alkyne. The material was inconsequentially used without further purification.

4.3.8. 3,4-[3-(2-Tetrahydropyranyloxy)benzo]cyclodec-3-ene-1,5-diyn-7-ol

A 250 mL Schlenk flask was placed under an Ar atmosphere and charged with freshly distilled THF (55.5 mL) followed by a mixture of anhydrous $CrCl_2$ (1.17 g, 9.49 mmol) and $NiCl_2$ (41 mg, 0.313 mmol). The resulting suspension was cooled in an ice bath and stirred vigorously, then a solution of aldehyde **16** (0.400 g, 0.949 mmol) in distilled THF (22 mL) was added dropwise over several minutes. This was stirred with cooling and followed by TLC. When the starting material was completely consumed (about 1.5 h), the reaction was quenched with saturated ammonium chloride, then warmed to room temperature and diluted with ether (80 mL). The layers were separated and the aqueous layer was extracted with ether (3×80 mL). The combined organic phases were washed with saturated ammonium chloride (2×100 mL) and brine (100 mL), then dried over Na_2SO_4. Vacuum filtration and removal of solvent under vacuum yielded an orange oil. Purification by flash chromatography (10:1 hexane/EtOAc→3:1 hexane/EtOAc, silica) yielded 3,4-[4-(2-tetrahydropyranyloxy)benzo]cyclodec-3-ene-1,5-diyn-7-ol (0.198 g, 0.67 mmol, 70%) as an orange oil: TLC R_f 0.1 (5:1 hexanes/EtOAc, silica); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (1H, d, J=8.4 Hz), 7.03 (1H, d, J=2.5 Hz), 6.91 (1H, dd, J=2.2, 8.6 Hz), 5.39 (1H, t, J=3.3 Hz), 4.63 (1H, m), 3.84 (1H, m), 3.60 (1H, m), 2.47 (2H, m), 2.15 (3H, m), 1.97 (1H, m), 1.84 (4H, m), 1.67 (2H, m); LRMS (EI, 70 eV) m/z 296 (M^+), 212 ([M−C_5H_8O]$^+$), 85 ($C_5H_8O^+$); HRMS (EI, 70 eV) calcd for $C_{19}H_{20}O_3$ 296.1412, found 296.1411.

4.3.9. 3,4-(4-Hydroxybenzo)cyclodec-3-ene-1,5-diyn-7-ol **2**

Into a 20 mL scintillation vial was placed 3,4-[4-(2-tetrahydropyranyloxy)benzo]cyclodec-3-ene-1,5-diyn-7-ol (0.582 g, 1.97 mmol). This was dissolved in a 4:2:1 mixture of AcOH/THF/H_2O (7 mL) and placed in an oil bath equilibrated at 40 °C and stirred. After 2.5 h, the solvent was removed under vacuum and the residue was purified by flash chromatography (3:1 hexane/EtOAc, silica) yielding **2** (0.244 g, 1.15 mmol, 58%) as an off-white solid: mp 150–152 °C; ^{1}H NMR (CD_3CN, 500 MHz) δ 7.30 (br s), 7.19 (1H, dd, J=0.34, 8.6 Hz), 6.69 (1H, m), 6.67 (1H, d, J=2.5 Hz), 5.34 (1H, d, J=4.8 Hz), 4.5 (1H, dd, J=3.1, 8.1 Hz), 3.32 (1H, br s), 2.42 (2H, m), 2.03 (3H, m), 1.70 (1H, m); ^{13}C NMR (CD_3CN, 125 MHz) δ 157.2, 131.3, 130.4, 120.0, 115.3, 115.0, 101.1, 98.1, 83.9, 81.7, 62.6, 38.3, 23.8, 20.9; LRMS (EI, 70 eV) m/z 212.1 (M^+), 194.1 ([M−H_2O]$^+$), 62; HRMS (EI, 70 eV) calcd for $C_{14}H_{12}O_2$ 212.0837, found 212.0841; HPLC (1.0 mL/min, 50% EtOAc in hexanes, retention time 5.4 min) indicates >98% purity.

4.3.10. 7-Acetoxy-3,4-(4-acetoxybenzo)cyclodec-3-ene-1,5-diyn-7-ol **22**

This material was prepared using the general procedure for the preparation of acetates: mp 100–103 °C; ^{1}H NMR (500 MHZ, $CDCl_3$) δ 7.38 (1H, d, J=8.3 Hz), 7.05 (1H, d, J=2.3 Hz), 6.97 (1H, dd, J=2.6, 8.3 Hz), 5.56 (1H, dd, J=2.9, 8.6 Hz), 2.48 (2H, m), 2.30 (1H, m), 2.28 (3H, s), 2.14 (2H, m), 2.11 (3H, s), 1.87 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 169.1, 150.7, 131.6, 130.3, 125.6, 121.7, 121.1, 101.3, 95.1, 85.6, 81.7, 65.1, 34.9, 24.0, 21.4, 21.31, 21.28; LRMS (EI, 70 eV) m/z 296 (M^+), 254 ([M−C_2H_2O]$^+$), 212 ([M−$C_4H_4O_2$]$^+$), 194 ($C_{14}H_{10}O^+$); HRMS (EI, 70 eV) calcd for $C_{18}H_{16}O_4$ 296.1049, found 296.1044.

4.3.11. 6-[(tert-Butyldimethylsilyl)oxy]-1-[(2-triisopropylsilylethynyl)phenyl]hex-1-yn-3-ol **18**

A flame-dried 50 mL round-bottomed, 2-necked flask equipped with a magnetic stirrer and rubber stopper and under an Ar atmosphere was charged with 1-(triisopropylsilylethynyl)-2-ethynylbenzene[39] (0.223 g, 0.791 mmol) and THF (15.8 mL). This solution was cooled in a dry ice/acetone bath, then ^{n}BuLi (0.56 mL of 1.55 M solution in hexanes, 0.87 mmol) was added dropwise. The resulting solution was stirred with cooling for 1 h, then 4-[(*tert*-butyldimethylsilyl)oxy]butanal (0.18 g, 0.91 mmol) in THF (1 mL) was added dropwise. This solution was stirred with cooling for 2 h, then warmed to room temperature and stirred for an additional 1 h. The reaction was quenched by pouring onto a mixture of 0.1 M HCl (20 mL) and Et_2O (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2×20 mL). The combined organics were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was placed on a silica plug. The plug was washed with hexane (250 mL), then the compound was eluted with 5:1 hexane/EtOAc (250 mL). The hexane/EtOAc layer was concentrated under vacuum, yielding **18** (0.365 g, 0.753 mmol, 95%) as a light yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (1H, m), 7.43 (1H, m), 7.23 (2H, m), 4.65 (1H, s), 3.70 (2H, m), 3.13 (1H, s), 1.89 (3H, m), 1.74 (1H, m), 1.15 (s, 21H), 0.91 (9H, s), 0.08 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.9, 132.5, 128.1, 128.0, 126.0, 125.6, 105.6, 94.8, 94.3, 83.6, 63.4, 62.9, 35.5, 28.9, 26.1, 18.9, 18.5, 11.5, −5.2; LRMS (EI, 70 eV) m/z 484 (M^+), 427 ([M−C_4H_9]$^+$), 239; HRMS (EI) calcd for $C_{29}H_{48}O_2Si_2$ 484.3183, found 484.3192; EA calcd for $C_{29}H_{48}O_2Si_2$ C 71.84, H 9.98, found C 71.71, H 10.14.

4.3.12. 3-(2-Tetrahydropyranyloxy)-1-[(2-triisopropylsilylethynyl)phenyl]-hex-1-yn-6-ol **19**

To a scintillation vial equipped with a magnetic stirrer was added **18** (0.32 g, 0.66 mmol), 3,4-dihydropyran (0.32 mL, 3.3 mmol), and CH_2Cl_2 (2.6 mL). This solution was cooled in an ice bath, and then *p*TSA monohydrate (12.5 mg, 0.066 mmol) was added. The resulting solution was stirred and followed by TLC. Upon completion, the reaction mixture was poured onto saturated $NaHCO_3$ (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organics were dried over Na_2SO_4 and the solvent was removed under vacuum. The resulting oil was placed in a scintillation vial equipped with a magnetic stirrer and dissolved in THF (4 mL). TBAF (1.5 mL of 1.0 M solution in THF, 1.5 mmol) was then added, and the resulting solution stirred overnight. The contents were partitioned between saturated NH_4Cl (10 mL) and Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2×10 mL). The combined organics were dried over Na_2SO_4 and the solvent was removed under vacuum. Purification of the residue by flash chromatography (5:1 hexane/EtOAc→1:1 hexane/EtOAc, silica) yielded **19** (0.142 g, 0.476 mmol, 72%) as a yellow oil and a mixture of a major and a minor diastereomer (approx. 6.7:1 ratio by ^{1}H NMR integration of the acetal hydrogen): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (2H, m), 7.24 (2H, m), 5.13 (1H, t, J=3.2 Hz), 4.74 (1H, t, J=6.0 Hz), 3.82 (1H, m), 3.70 (2H, m), 3.53 (1H, m), 2.32 (1H, br s), 1.98–1.37 (10H, m, 12, 13); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 132.7, 132.2, 128.6, 128.2, 126.0, 125.0, 96.0, 92.1, 84.2, 82.4, 81.2, 65.5, 62.7, 32.3, 30.6, 28.8, 21.2, 19.6; LRMS (EI, 70 eV) m/z 298 (M^+), 85 ($C_5H_9O^+$); HRMS (EI) calcd for $C_{19}H_{22}O_3$ 298.1569, found 298.1570.

4.3.13. 3-(2-Tetrahydropyranyloxy)-1-[(2-triisopropylsilylethynyl)phenyl]-hex-1-ynal ***20***

To a 250 mL 3-neck, round-bottomed flask under Ar was added THF (30 mL) and diisopropylamine (0.5 mL, 3.5 mmol). This mixture was cooled in a dry ice/acetone bath, then added was a solution of ^{n}BuLi in hexanes (2.1 mL of 1.6 M soln, 3.35 mmol). The resulting mixture was stirred for 20 min, then a solution of **19** (0.451 g, 1.52 mmol) in THF (5 mL) was added dropwise. After complete addition the reaction mixture was stirred with cooling for 1 h, then I_2 (0.5 g, 1.98 mmol) was added as a solution in THF (8.5 mL). The resulting solution was stirred with cooling for 1 h, then at room temperature for 2 h. The reaction was poured onto satd ammonium chloride (50 mL) and diluted with 10% sodium bisulfite (50 mL) and Et_2O (50 mL). The layers were separated, and the organic layer was extracted with 2×50 mL of Et_2O. The combined organics were washed with 10% sodium bisulfite (50 mL) and dried over Na_2SO_4. Concentration under vacuum yielded an orange oil (0.636 g, 98%), which darkened with standing. The oil was immediately taken up in CH_2Cl_2 (85 mL) and placed in a 200 mL round bottom flask equipped with a magnetic stirrer and rubber stopper. PDC (5.66 g) was then added, and the resulting solution stirred. After 12 h of stirring, TLC analysis indicated the complete consumption of starting material (1:1 hexane/EtOAc, R_f=0.6) the reaction was filtered through Celite. The Celite plug was washed with CH_2Cl_2 (300 mL), then the filtrate was concentrated under vacuum. The residue was purified by flash chromatography (10:1 hexane/EtOAc→5:1 hexane/EtOAc, silica) yielding aldehyde **20** (0.421 g, 63%) as an oil, which was used immediately in the next reaction.

4.3.14. 3,4-Benzocyclodec-3-ene-1,5-diyne-7,10-diol ***3***

Into a flame-dried sealed tube under argon was added $NiCl_2$ (64 mg, 0.493 mmol), $CrCl_2$ (1.84 g, 14.93 mmol), and dry THF (82 mL). The resulting suspension was cooled in an ice bath. A solution of aldehyde **20** (0.629 g, 1.49 mmol) in dry THF (33 mL) was added dropwise over 30 min by syringe pump. After complete addition, the solution was stirred with cooling for 90 min when TLC analysis (1:1 hexane/EtOAc) showed complete consumption of starting material. The reaction was quenched with satd ammonium chloride (100 mL) and H_2O (40 mL), then diluted with Et_2O (100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2×100 mL). The combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, yielding a yellow oil. This was taken up in 1:1 MeOH/CH_2Cl_2 (6 mL). *p*TSA monohydrate (14 mg, 0.07 mmol) was then added. The resulting solution was stirred and monitored by TLC (1:1 hexane/EtOAc). When the starting material was completely consumed (about 1–2 h) the reaction was poured onto 5% aqueous $NaHCO_3$ and CH_2Cl_2 (10 mL each). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organics were washed with satd aqueous $NaHCO_3$ (10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by flash chromatography (3:1 hexane/EtOAc→2:3 hexane/EtOAc, silica), yielding **3** (0.124 g, 0.584 mmol, 39%) as an off-white solid and a mixture of diastereomers: ^{1}H NMR (500 MHz, CD_3OD) δ 7.36 (2H, m), 7.30 (2H, m), 4.59 (1H, m), 4.52 (1H, m), 2.38 (1H, m), 2.27 (1H, m), 1.91 (2H, m); ^{13}C NMR (125 MHz, CD_3OD) δ 128.9, 128.8, 128.61, 128.56, 128.11, 128.10, 99.5. 99.4, 83.7, 83.6, 62.60, 62.56, 33.8, 33.0; LRMS (EI, 70 eV) *m*/*z* 212 (M^+), 194 ([M−H_2O]$^+$), 165, 149; HRMS (EI, 70 eV) calcd for $C_{14}H_{12}O_2$ 212.0837, found 212.0834.

4.3.15. 7,10-Diacetoxy-3,4-benzocyclodec-3-ene-1,5-diyne ***23***

Prepared according to the general procedure for diacetates. The crude material was purified by flash chromatography (10:1 hexane/EtOAc, silica) yielding **23** (92%) as a white solid and a mixture of diastereomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (2H, m), 7.29 (2H, m), 5.58 (2H, m), 2.51 (1H, m), 2.39 (1H, m), 2.16 (1H, m), 2.113 (3H, s), 2.110 (1H, s), 2.05 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.15, 170.13, 129.42, 129.40, 128.88, 128.87, 128.37, 128.32, 95.3, 95.2, 86.01, 86.00, 65.0, 64.5, 30.5, 30.3, 21.2; LRMS (EI, 70 eV) *m*/*z* 296 (M^+), 254 ([M−C_2H_2O]$^+$), 236 ([M−AcOH]$^+$), 212 ([M−$C_4H_4O_2$]$^+$); HRMS (EI, 70 eV) calcd for $C_{18}H_{16}O_4$ 296.1049, found 296.1037.

4.3.16. 2,2′-Azobis{[2-methyl-N-[2-ethyl-(2-methylpropenoate)]]-propionamide} ***26***

Prepared according to the general procedure for the preparation of dimethacrylates. The crude material was placed on a silica plug, and the plug was washed with 20:1 hexane/EtOAc (60 mL), then dimethacrylate **26** was eluted with methanol. Concentration of the methanol filtrate yielded a white solid, which was used without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29 (2H, br s), 6.09 (2H, s), 5.58 (2H, s), 4.30 (4H, t, *J*=5.4 Hz), 3.67 (4H, t, *J*=5.5 Hz), 1.92 (6H, S), 1.31 (12H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.0, 167.3, 135.8, 126.1, 74.6, 63.4, 38.7, 22.9, 18.4; HRMS (ESI) calcd for $C_{20}H_{33}N_4O_6$ [M+H]$^+$ 425.2400, found 425.2398.

4.3.17. 2,2′-Azo-2-{[2-methyl-N-[2-ethyl-(2-methylpropenoate)]-propionamide}-2′-[2-methyl-N-(2-ethylacetate)]-propionamide ***27***

Into a scintillation vial equipped with a magnetic stirrer and plastic screw cap was added 2,2′-azobis[2-methyl-*N*-(2-hydroxyethyl)propionamide] (0.508 g, 1.76 mmol) and a 4:1 mix of DMF/pyridine (10 mL). To this solution was added acetic anhydride (0.25 mL, 2.64 mmol), and the resulting solution was stirred for 5 h, then the solvent was concentrated under vacuum. The crude mixture was purified by flash chromatography (20:1 EtOAc/MeOH, silica) yielding the mono protected alcohol (0.215 g, 0.654 mmol, 37%) as a yellow oil. This was immediately converted to methacrylate using the general procedure for preparation of dimethacrylates reported above, but only using 3 equiv of methacroyl chloride instead of 6 equiv. The crude residue was purified by flash chromatography (1:1 hexane/EtOAc, silica) yielding **27** (0.183 g, 0.462 mmol, 70%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (1H, br s), 7.19 (1H, br s), 6.09 (1H, s), 5.58 (1H, s), 4.30 (2H, t, *J*=5.1 Hz), 4.20 (2H, quintet, *J*=5.4 Hz), 3.69 (2H, t, *J*=5.2 Hz), 3.63 (2H, q, *J*=5.2 Hz), 2.04 (3H, s), 1.92 (3H, s), 1.33 (6H, s), 1.32 (6H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.9, 171.2, 167.6, 135.8, 126.1, 74.63, 74.61, 63.3, 63.1, 38.7, 38.5, 22.9, 22.8, 20.7, 18.9; HRMS (ESI) calcd for $C_{18}H_{31}N_4O_6$ [M+H]$^+$ 399.2244, found 399.2251.

4.4. General procedure for DSC analysis of diacetates

Into a DSC pan was added 20–30 μL of a solution of enediyne diacetate in 1,3-dimethoxybenzene (0.1 mL/mg diacetate). The pan was sealed and placed in the DSC instrument, and analyzed. A second scan was examined in all cases, to confirm that the exotherm was irreversible.

4.5. Synthesis of PMMA beads[46]

Benzoyl peroxide and the appropriate crosslinker (1.25:1 mol ratio) were added to a flask containing MMA and *N*,*N*-dimethylaniline (40 mol % versus benzoyl peroxide). After several minutes, a homogeneous solution was obtained. A second flask was equipped with a magnetic stirrer and rubber stopper and placed under N_2. This was then charged with an aqueous buffer solution of phosphoric acid (0.1 M, pH=7) and poly(vinyl alcohol) (0.3 wt %). The MMA solution was then added to the rapidly stirring aqueous solution. Then, the stirring rate was adjusted until the appropriate drop size was obtained. The reaction was stirred overnight, and the beads were collected by vacuum filtration and dried. The beads varied in size from 100–1000 μm in diameter, with 70 wt % of the beads falling between 500 and 1000 μm sieves.

4.6. General synthesis for DSC testing of beads

The microspheres containing enediyne crosslinks were taken into an Ar-filled glove box. Approximately 15 mg of beads were loaded into DSC pans, along with 15 μL of MMA. The pans were then sealed and left to swell for 24 h, then removed from the glove box and analyzed by DSC.

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