An Enaminone-Directed Benzannulation/Macrocyclization Approach to Cyclophane Ring Systems

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Received February 17, 2002

A straightforward and modular preparative approach to 1,3,5-triaroylbenzene-based functionalized cyclophane ring systems has been developed. The key cyclophane-forming macrocyclization reaction was accomplished during the course of a regioselective cross-benzannulation between bis(aryl ethynyl) ketone and enaminone reactants. Macrocyclic products with ring sizes ranging from 18- to 22-membered were successfully constructed. The composition of the tether connecting the two aryl ethynyl ketone fragments can be easily varied; consequently, this method is suitable for construction of a diverse range of structurally distinct cyclophane products. To illustrate this feature, cyclophanes possessing xylyl, alkyl, di(ethylene triamine), and di(ethylene oxy) bridging units were synthesized in isolated yields of 11−46%. Three new cyclophanes (calixarene-like macrocyles **8** and **9**, as well as crownophane **18**) were structurally characterized by X-ray diffractometry.

Introduction

The synthesis of new cyclophane ring systems remains an active area of investigation. The impetus for much recent work in this field stems from potential applications of cyclophanes in, for example, materials science and supramolecular chemistry. In addition, aesthetic characteristics of relatively large (and oftentimes rigid) macrocycles have long fascinated the preparative organic chemist.[1] Given the impressive structural diversity encountered in cyclophane ring systems, it is not surprising that numerous synthetic strategies have emerged for their construction. Among these, macrocyclizations accomplished via alkylation, acylation, cycloaddition, and various condensation processes are frequently utilized,[1,2] while phenol-derived cyclophanes (e.g., calixarenes and calixresorcinarenes) are generated from a series of inter- and intramolecular electrophilic aromatic substitutions.[3] More recently, various transition-metal-mediated coupling reactions have been successfully applied in the synthesis of cyclophanes as well.[4]

A common feature in the synthetic strategies described above is the incorporation of preformed aromatic building blocks into larger macrocyclic ring systems. In contrast, examples of cyclophane construction via macrocyclization accomplished during the course of a concomitant benzannulation process are relatively rare. Importantly, benzannulation-derived synthetic routes may provide access to structurally unique cyclophane systems that are difficult to prepare by other methods. Of the reported benzannulation approaches toward cyclophane ring systems, most have relied on the use of transition metal catalysts (e.g., Ziegler-type catalysts,[5] Co,[6] Pd[7]) to effect the trimerization of alkyne derivatives. Cyclophane structures also have been obtained from benzannulation reactions of Fischer-type chromium carbenes.[8] A common drawback to metal-mediated benzannulation processes is the generation of regioisomeric mixtures of benzene derivatives (e.g., 1,3,5- and 1,2,4-substituted isomers). Regioselective benzannulations that result in cyclophane products have been achieved, however, in the Pd-catalyzed cyclodimerization of enynes,[9] in the aldol condensation of nitromalonodialdehyde with various

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10.1021/jo0256181 CCC: $22.00
Published on Web 05/15/2002

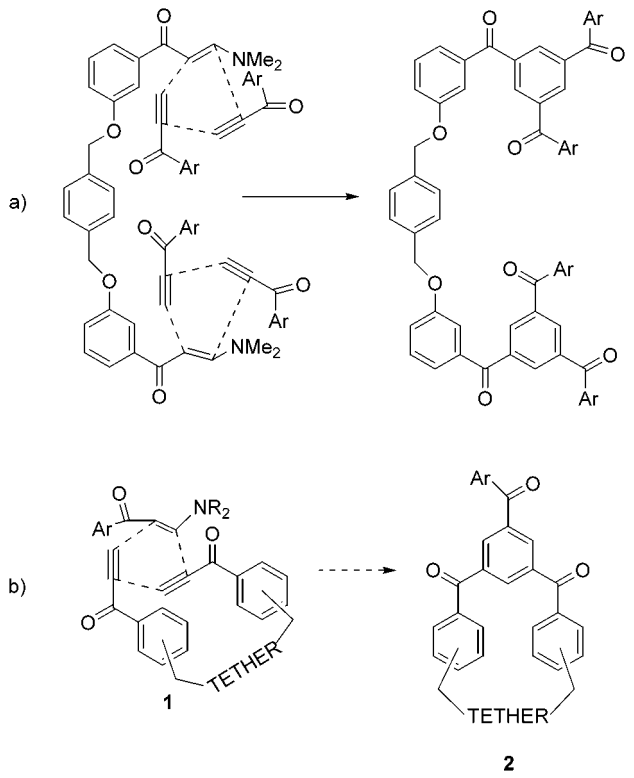
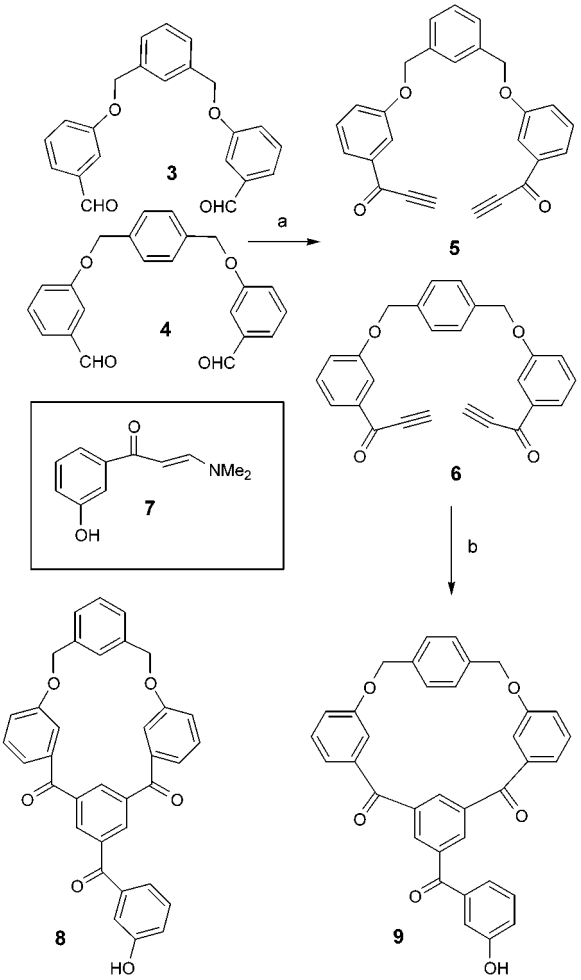


Figure 1. (a) The preparation of dendritic-like linked triaroylbenzenes via two independent enaminone-directed cross-benzannulation reactions.[12] (b) Schematic representation of a proposed convergent enaminone-directed cross-benzannulation affording cyclophane products.

substituted ketones,[10] and in cycloaddition/dimerization reactions between bis(allenes) and alkynes.[11]

A recent report from this laboratory described the preparation of novel dendritic-like linked triaroylbenzenes.[12] The target compounds were obtained via the independent cross-cyclotrimerization of two connected aryl-substituted enaminones and aryl ethynyl ketones,[13] as illustrated in Figure 1a. It was quickly realized during the course of this study that a simple reformulation of the reaction protocol could provide a synthetic entry into cyclophane architectures if the enaminone-directed benzannulation reaction also could be utilized as a method for accomplishing macrocyclization. A general outline of this strategy is shown in Figure 1b. Participation of two tethered aryl ethynyl ketone moieties in a single convergent enaminone-directed cyclotrimerization (depicted as in **1**) was envisioned to afford a 1,3,5-triaroylbenzene product partially imbedded within a larger macrocyclic ring system (i.e., **2**). Additionally, this modular strategy would offer a straightforward means of incorporating functionalized tethers into the macrocyclic framework. Reported herein are the results of initial studies along these lines that have culminated with the successful preparation and characterization of several novel cyclophane ring systems possessing aryl, polyaza, and polyoxa bridging units.

Scheme 1[a]



[a] Conditions: (a) (i) HCCMgBr, THF; (ii) H_2CrO_4 (89% and 66% for **5** and **6**, respectively over two steps). (b) **7**, PhMe, ~0.002 M, reflux, 120 h (12% and 11% for **8** and **9**, respectively).

Results and Discussion

A first approach toward cyclophane architectures via enaminone-directed benzannulation is illustrated in Scheme 1. In this synthetic route, a *m*- or *p*-xylyl moiety serves as a tether connecting two ethynyl ketone fragments. Thus, dialdehyde **3** and known dialdehyde[14] **4** were prepared from the corresponding dibromoxylenes and 3-hydroxybenzaldehyde. Conversion of the aldehyde residues to ethynyl ketones was then accomplished by a two-step Grignard addition/oxidation sequence. With bis(ethynyl ketones) **5** and **6** in hand, the crucial benzannulation/macrocyclization reaction was next attempted. In the event, separate equimolar solutions of **5** or **6** and phenolic enaminone **7** were added simultaneously to refluxing toluene under moderately high-dilution conditions (~2×10^{-3} M). The reaction was monitored by TLC until consumption of the starting materials was complete (~120 h). The desired cyclophane products **8** and **9** were indeed formed under these conditions and were subse-

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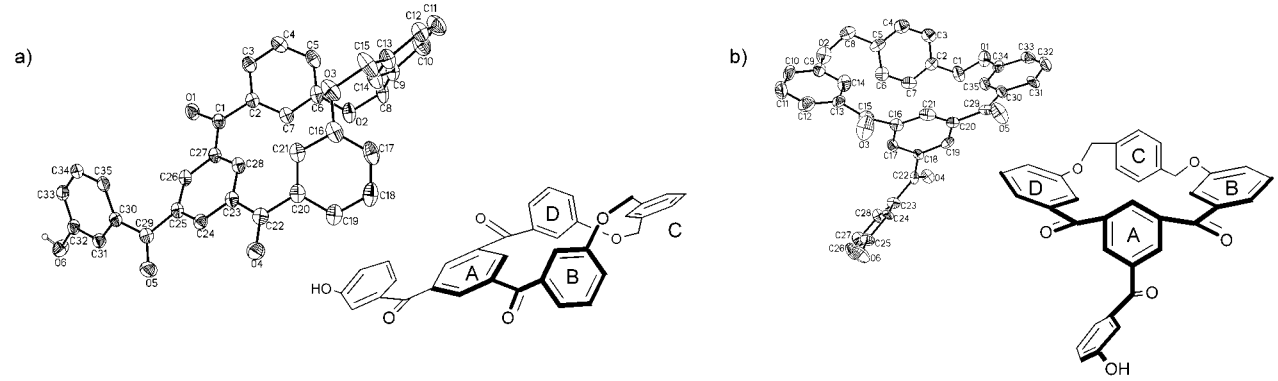

Figure 2. (a) Molecular structure (ORTEP) of **8** accompanied by a line drawing representation of the solid-state conformation. (b) The molecular structure (ORTEP) of **9** accompanied by a line drawing representation of the solid-state conformation.

quently isolated by simple flash column chromatography in yields of 12% and 11%, respectively. While disappointingly low, the isolated yields reported above are, however, comparable to alternative macrocyclization protocols encountered in cyclophane chemistry.[1−8] Moreover, the cyclophane products proved to be the only tractable materials generated in the course of each benzannulation, thus greatly simplifying product isolation and purification. The bulk of the reactants appear to have been consumed in the formation of sparingly soluble polymeric materials, presumably a consequence of unwanted alkyne oligomerization under the reaction conditions. In an attempt to improve the yields of the cyclophane products, several reaction parameters were varied. Adjusting the ratio of **5** or **6** with respect to enaminone **7** from 1:1 to 2:1 to 4:1 had no effect on the outcome of the reaction. The concentration of the reaction mixture and the rate/order of reactant addition also were found to have little effect on the reaction, so long as moderatly high dilution was maintained. For example, combining **5** and **7** directly in toluene at a concentration of 5×10^{-3} M produced cyclophane **8** with equal efficiency.

Despite the modest yields encountered in the preparation of **8** and **9**, there are several noteworthy features of the cyclotrimerization process that merit further comment. First, the benzannulation reaction proceeds with complete regioselectivity such that the newly generated arene ring possesses a 1,3,5-substitution pattern exclusively. Second, the compatibility of the unprotected phenol residue present in **7** with the trimerization process permits direct incorporation of a synthetically versatile functional group along the periphery of the cyclophane products. Third, the straightforward means of assembling the bis(ethynyl ketone) reactants lends itself to considerable structural variation, a feature responsible for spurring additional synthetic studies (vide infra). Finally, **8** and **9** themselves bear an outward resemblance to certain calix[4]arene derivatives. In fact, **8**/**9** can be viewed as structural hybrids exhibiting features of so-called expanded calixarenes[15] and oxacalixarenes.[16]

As a consequence of the nominal relationship between **8**/**9** and members of the calixarene family of cyclophanes, the solid- and solution-phase structures of these macrocycles were further investigated. Single crystals of **8** and **9** were obtained through diffusion chamber techniques, and their structures are illustrated in Figure 2, parts a and b, respectively.[17] The solid-state structure of cyclophane **8** (Figure 2a) is difficult to describe, as it is severely distorted from anything that resembles a "bowl" or "saddle." The approximate dimensions that define the macrocycle opening are 5.6 Å (ring A to ring C distance) by 4.5 Å (ring B to ring D distance). In contrast, cyclophane **9** (Figure 2b) adopts a more defined saddle-shaped solid-state conformation. The A and C rings are superimposed across the cyclophane cavity at a slight angle (∼30°), thereby creating a wider opening at the top of the cyclophane (∼5.4 Å) than at the bottom (∼4.1 Å). The B and D rings (∼6.3 Å apart) are almost perpendicular to the plane of the A ring, resulting in an overall shape reminiscent of boatlike or flattened-cone conformations that are encountered in certain calixresorcinarene derivatives.[18] Both **8** and **9**, however, exhibit substantial conformational flexibility in solution, as evidenced by the presence of a sharp singlet for the benzylic methylene hydrogens in their room temperature ^{1}H NMR spectra. Low-temperature NMR studies (CD_2Cl_2, −90 °C) revealed only slight broadening of these signals. Presumably, conformational interconversion requires rotation of the phenyl rings through the cyclophane cavity, and apparently, significantly lower temperatures and/or additional substituents on the phenyl rings will be required in order to obtain discrete solution-phase conformations.[19]

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(17) Crystal data for **8**: monoclinic, $P2_1/n$, a = 13.734(4) Å, b = 8.279(2) Å, c = 23.601(9) Å, β = 104.10(2)°, V = 2602.7(14) Å^3, Z = 4, D_{calc} = 1.379 g cm^{-3}, μ = 0.094 mm^{-1} (Mo Kα), T = 223(2) K, θ range 1.8−26.0°, 32 348 reflections, 5107 independent reflections, 374 parameters, $R_1(F)$ = 4.94%, $wR_2(F^2)$ = 12.68%, min./max. residual electron density = −0.185/0.167 e Å^{-3}. Crystal data for **9**: triclinic, $P\bar{1}$, a = 12.6130(7) Å, b = 14.3665(8) Å, c = 15.7132(9) Å, α = 81.629(4)°, β = 89.924(3)°, γ = 71.901(3)°, V = 2674.7(3) Å^3, Z = 4, D_{calc} = 1.342 g cm^{-3}, μ = 0.092 mm^{-1} (Mo Kα), T = 188(2) K, θ range = 1.5−25.0°, 28 086 reflections, 9358 independent reflections, 739 parameters, $R_1(F)$ = 14.86%, $wR_2(F^2)$ = 30.62%, min./max. residual electron density = −0.367/0.494 e Å^{-3}. The asymmetric unit contains two crystallographically independent, chemically similar molecules whose gross conformations are identical. Structural differences between the two molecules are observed in the relative orientations of the phenolic rings that are not part of the core cyclophane macrocycle.

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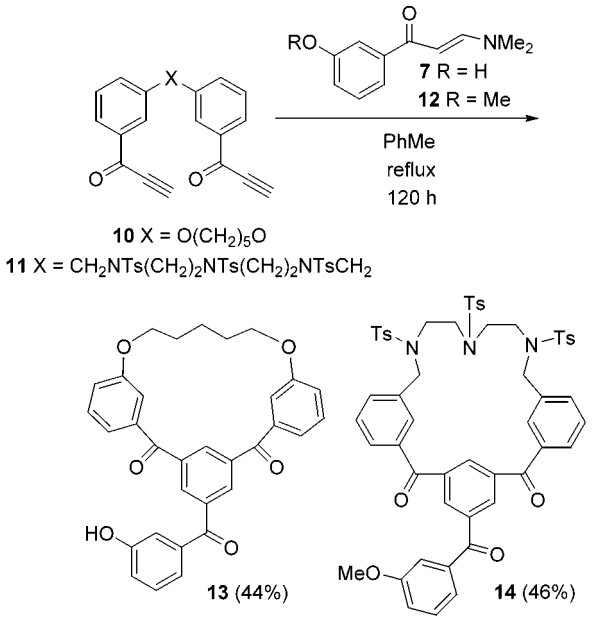
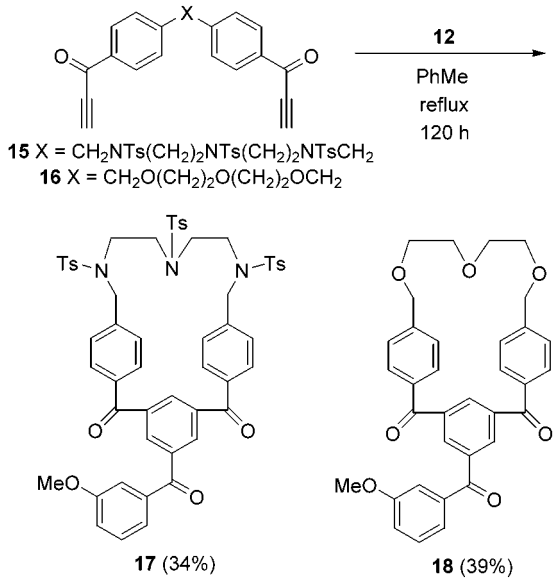
(19) Expanded calixarenes and oxacalixarenes are known to be much more conformationally flexible than "traditional" calix[4]arenes: (a) Masci, B.; Finelli, M.; Varrone, M. *Chem. Eur. J.* **1998**, *4*, 2018. (b) Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6052. (c) Yamato, T.; Saruwatari, Y.; Yasumatsu, M.; Ide, S. *Eur. J. Org. Chem.* **1998**, 309. (d) Ito, K.; Izawa, S.; Ohba, T.; Ohba, Y.; Sone, Y. *Tetrahedron Lett.* **1996**, *37*, 5959.

Scheme 2



Scheme 3



While the feasibility of utilizing an enaminone-directed benzannulation reaction as a means of constructing cyclophane ring systems has been established on the basis of the results described above, the isolated yields of macrocyclic products encountered in these initial studies are such that this process is unlikely to be of great synthetic value. A possible explanation for the inefficiency of macrocyclization observed in the preparation of **8** and **9** is that the xylyl tether connecting the ethynyl ketone moieties is too rigid to easily permit assembly of an arene ring via the molecular arrangement illustrated schematically in **1** (Figure 1b). Accordingly, then, incorporation of a longer and/or more flexible tether may result in higher yielding benzannulative macrocyclizations. Toward this end, bis(ethynyl ketone) **10** was prepared from the corresponding dialdehyde precursor[2g,14] and treated with an equimolar amount of enaminone **7** in refluxing toluene (0.004 M). Gratifyingly, the expected cyclophane product **13** was isolated in quite respectable 44% yield after flash column chromatography (Scheme 2). The structure of **13** was assigned on the basis of NMR spectroscopy and high-resolution mass spectral data. In particular, the generation of an unsymmetrical 1,3,5-triaroylbenzene ring gives rise to a characteristic set of finely coupled downfield signals in the ^{1}H NMR spectrum (7.98 and 8.56 ppm) that correspond to the hydrogens at the 2, 4, and 6 positions. It should be noted that cyclophanes **8** and **13** both possess 18-membered macrocyclic rings; thus, the increased flexibility of the pentamethylene tether in **10** appears to be responsible for the significant improvement in the benzannulation−macrocyclization process.

It has proven possible to construct functionalized cyclophane ring systems via this method as well, and the preparation of a tri(aza)-bridged triaroylbenzene-based macrocycle is also shown in Scheme 2. The linear cyclophane building block **11** (easily prepared via routine transformations—see the Supporting Information) was treated with methoxy-substituted enaminone[20] **12** in refluxing toluene. The desired 20-membered macrocyclic product **14** was subsequently isolated in 46% yield. Again, evidence of successful benzannulation was provided by the appearance of a downfield doublet (∼8.5 ppm, J = ∼1.5 Hz) corresponding to the unique aromatic hydrogen of the 1,3,5-trisubstituted arene. Polyazacyclophanes are widely utilized in supramolecular chemistry as molecular receptors for neutral, cationic, and anionic substrates, as well as novel metal-ligating agents.[21] It is envisioned that **14** (and **17**, vide infra) will serve as the first members of a family of triaroylbenzene-derived azacyclophanes that may be tuned to exhibit a range of useful host−guest interactions with targeted substrates. Unfortunately, the examination of host−guest and metal-ligating properties of cyclophanes related to **14** has been thwarted by an inability to remove the tosyl protecting groups. The presence of numerous benzoyl rings precludes application of reductive detosylation methods (e.g., Li−naphthalide), and attempted hydrolyses of the sulfonamide groups under standard conditions (concentrated H_2SO_4; aqueous HBr/acetic acid/phenol) were unsuccessful. Consequently, current efforts are focused on constructing analogues and homologues of **14** with alternative (easily removable) nitrogen protecting groups.

Structural characteristics of triaroylbenzene-derived cyclophanes can be easily altered simply by using a linear bis(ethynyl ketone) reactant exhibiting a para substitution pattern. As illustrated in Scheme 3, reaction of tri(aza)-linked bis(ethynyl ketone) **15** and enaminone **12** afforded the corresponding cyclophane product **17** in a serviceable 34% isolated yield. Likewise, di(ethylene glycol) derivative **16** was smoothly converted to the tri(oxa) macrocycle **18**. Both of these products possess 22-membered macrocyclic rings and represent the largest cyclophanes thus far prepared by this method. Macrocycle **18** exhibits structural features common to both cyclo-

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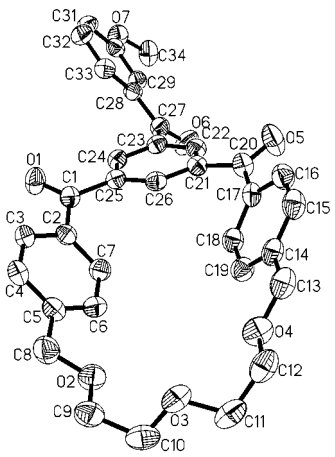

Figure 3. Molecular structure (ORTEP) of **18**.

phanes and crown ethers, and Nishimura has coined the term "crownophane" to describe such compounds.[22] Recrystallization from hexanes/EtOAc deposited X-ray quality single crystals and the molecular structure of **18** is shown in Figure 3.[23] An elliptical-shaped macrocycle is clearly evident with a long axis of 8.08 Å (C26−O3). The short axis as defined by the distance between the centroids of the two para-substituted arenes is 5.78 Å and the O2−O4 distance in the di(ethylene oxy) unit is ∼4.6 Å. The para-substituted arene rings are each tilted ∼45° with respect to the 1,3,5-triaroyl-substituted ring, and this results in a shallow cyclophane cavity with a wider opening at the top (∼7.5 Å) than at the bottom (∼4.1 Å). While the presence of only three crownophane ether oxygen atoms is expected to be insufficient for binding alkali and alkaline metal ions, the construction of homologous crownophanes with additional ethylene oxy bridging units in close proximity to a putative cyclophane "pocket" has the potential to afford new molecular receptors suitable for binding various inorganic and organic salts and zwitterions. Studies along these lines are currently in progress.

In conclusion, a new and concise synthetic approach suitable for the preparation of functionalized cyclophane ring systems has been developed. Macrocyclization is achieved during the course of a regioselective benzannulation reaction between two connected aryl ethynyl ketone groups and an aryl enaminone reactant. The nature of the tether connecting the aryl ethynyl ketone fragments can be easily varied and triaroylbenzene-based cyclophanes with tri(aza), tri(oxa), and xylyl bridges have been constructed. In addition, this synthetic approach results in placement of an arene ring on the periphery of the cyclophane macrocycle that is potentially available for further synthetic elaboration. Indeed, while only hydroxy- and methoxy-substituted enaminones were employed in these initial studies, alternative functionalized enamines should display similar reactivity.[12] The yields observed for the key macrocyclization step range from 11% to 46%. An important feature that appears to significantly influence the efficiency of the benzannulation process is the flexibility of the tether used to link the ethynyl ketone reaction partners. The applicability of this synthetic protocol for the construction of structurally more complex cyclophanes is currently being explored, as are methods for improving the efficiency of the benzannulation process. It is envisioned that concomitant enaminone-directed benzannulation−macrocyclization may be developed into a general method for the construction of functionalized cyclophanes and, in turn, new molecular hosts and/or metal-ligating species.

Experimental Section[24]

***meta*-Xylyloxy-Bridged Bis(aryl ethynyl ketone) 5.** A solution of **3** (1.25 g, 3.61 mmol) in THF (10 mL) was cooled to 0 °C in an ice bath. Ethynylmagnesium bromide (0.5 M in THF, 19.0 mL, 9.50 mmol) was added via syringe and the reaction mixture was stirred at room temperature. The reaction was complete after 2 h (TLC) and was quenched by addition of saturated aq NH_4Cl solution (∼30 mL). The reaction mixture was extracted with several portions of ether, and the combined ether extracts were washed with brine. The ether solution was next dried over anhydrous $MgSO_4$, filtered, and concentrated to afford a dark oil. Purification by flash column chromatography (1:1 hexane:EtOAc) yielded the corresponding diol (1.35 g, 94%) as a pale yellow solid. Without further characterization, the diol (1.30 g, 3.26 mmol) was dissolved in ∼20 mL of acetone. A solution of the Jones reagent was added dropwise via pipet until the red color indicative of excess Cr(VI) salts persisted. The reaction was quenched by addition of an excess of 2-propanol, and the insoluble Cr(III) salts were removed by filtration through a pad of Celite. The filtrate was diluted with ether and washed sequentially with satd aq $NaHCO_3$ solution, water, and brine, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent yielded a dark oil that was then purified by flash column chromatography (1:1 hexanes:EtOAc). The bis(ethynyl ketone) **5** (1.22 g, 95%, 89% from **3**) was isolated as a white solid: mp 95−97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.44 (s, 2H), 5.16 (s, 4H), 7.23−7.28 (m, 2H), 7.40−7.45 (m, 5H), 7.55 (br s, 1H), 7.73−7.84 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.24, 80.49, 80.92, 114.23, 122.19, 123.37, 126.73, 127.49, 129.18, 129.98, 136.98, 137.62, 158.92, 177.11; IR (thin film) ν (cm^{-1}) 3275, 2082, 1642. Anal. Calcd for $C_{26}H_{18}O_4$: C 79.17, H 4.60. Found: C 79.27, H 4.59.

***para*-Xylyloxy-Bridged Bis(aryl ethynyl ketone) 6.** Using the procedure described above for the preparation of **5**, dialdehyde[14] **4** was converted to bis(ethynyl ketone) **6** in 66% overall yield after purification by flash column chromatography (1:1 hexanes:EtOAc) to yield a white solid: mp 153−154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.43 (s, 2H), 5.51 (s, 4H), 7.20−7.27 (m, 2H), 7.43 (t, J = 7.8 Hz, 2H), 7.49 (s, 4H), 7.74 (t, J = 2.1 Hz, 2H), 7.82 (d, J = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.17, 80.50, 80.90, 114.30, 122.30, 123.40, 128.10, 130.0, 136.6, 137.3, 159.1, 177.3; IR (thin film) ν (cm^{-1}) 3253, 2093, 1636. Anal. Calcd for $C_{26}H_{18}O_4$: C 79.17, H 4.60. Found: C 78.73, H 4.63.

Cyclophane 8. Enaminone **7** (0.100 g, 0.523 mmol) dissolved in 50 mL of 4:1 PhMe:CH_2Cl_2 and **5** (0.206 g, 0.523 mmol) dissolved in 50 mL of PhMe were simultaneously added dropwise over 2 h to 150 mL of refluxing PhMe. The reaction was monitored by TLC, and after 5 d the starting materials were completely consumed. The solvent was evaporated and the residue was purified by flash column chromatography (2:1 hexanes:EtOAc) to afford **8** (0.033 g, 12%) as a white solid. The product was crystallized by slow diffusion of hexanes into an EtOAc solution: mp 198−199 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.22 (s, 4H), 5.42 (br s, 1H), 7.00 (m, 2H), 7.07−7.16

(22) (a) Inokuma, S.; Sakai, S.; Nishimura, J. *Top. Curr. Chem.* **1994**, *172*, 87 and references therein. (b) Nishimura, J.; Nakamura, Y.; Hayashida, Y.; Kudo, T. *Acc. Chem. Res.* **2000**, *33*, 679.

(23) Crystal data for **21**: triclinic, $P\bar{1}$, a = 10.4673(8) Å, b = 11.8925(9) Å, c = 12.6585(9) Å, α = 68.641(5)°, β = 70.745(4)°, γ = 88.954(5)°, V = 1376.1(2) Å^3, Z = 2, D_{calc} = 1.329 g cm^{-3}, μ = 0.093 mm^{-1} (Mo Kα), T = 203(2) K, θ range 1.85−26.43°, 24 187 reflections, 5599 independent reflections, 371 parameters, $R_1(F)$ = 5.27%, $wR_2(F^2)$ = 11.24%, min./max. residual electron density = −0.191/0.141 e Å^{-3}.

(24) For general experimental details, see the Supporting Information.

(m, 3H), 7.20 (br s, 1H), 7.23 (br s, 1H), 7.30−7.42 (m, 9H), 7.82 (t, $J = 1.5$ Hz, 1H), 8.47 (d, $J = 1.5$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.65, 116.72, 118.06, 119.13, 120.91, 121.51, 122.93, 123.70, 125.69, 129.05, 130.19, 130.27, 133.34, 134.30, 137.69, 138.11, 138.30, 139.05, 156.28, 157.85, 194.64, 195.34 (one C signal was not observed); IR (thin film) ν (cm^{-1}) 3250, 1701; HRMS (FAB$^+$, NBA) calcd for $C_{35}H_{25}O_6$ [M + H]$^+$ 541.1651, found 541.1652.

Cyclophane 9. Using the procedure described above for the preparation of **8**, reaction of **7** (0.114 g, 0.596 mmol) and **6** (0.235 g, 0.596 mmol) afforded **9** (0.037 g, 11%) as a white solid after flash column chromatography (2:1 hexanes:EtOAc). A crystalline sample was obtained by slow diffusion of hexanes into a $CDCl_3$ solution: mp 147−148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.17 (s, 4H), 5.98 (br s, 1H), 6.66 (m, 2H), 7.12−7.15 (m, 1H), 7.17 (s, 4H), 7.25−7.43 (m, 10H), 8.26 (d, $J = 1.8$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 71.87, 116.86, 118.14, 121.02, 122.24, 122.94, 123.47, 127.64, 130.23, 130.35, 132.42, 132.88, 137.12, 137.89, 138.19, 138.45, 139.01, 156.31, 158.33, 194.64, 196.31. Anal. Calcd for $C_{35}H_{24}O_6 \cdot (H_2O)_{0.5}$: C 76.49, H 4.40. Found: C 76.16, H 4.56.

Pentamethylene-Bridged Cyclophane 13. Using the procedure described for the preparation of **8**, reaction of phenolic enaminone **7** (0.212 g, 1.11 mmol) and **10** (0.400 g, 1.11 mmol) in 250 mL of refluxing toluene for 5 d gave cyclophane **13** (0.247 g, 44%) after purification by flash column chromatography (2:1 hexanes:EtOAc). An analytical sample was obtained as a colorless solid by recrystallization from $CHCl_3$/hexanes: mp 98−105 °C (dec); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.84−1.90 (m, 6H), 4.10 (t, $J = 5.0$ Hz, 4H), 6.22 (br s, 1H), 7.09−7.21 (m, 5H), 7.38−7.55 (m, 7H), 7.98 (t, $J = 1.5$ Hz, 1H), 8.56 (d, $J = 1.5$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.35, 27.95, 67.27, 116.92, 117.85, 118.09, 120.96, 121.53, 122.96, 130.23, 130.65, 133.40, 134.49, 137.86, 137.96, 138.02, 139.94, 156.41, 158.58, 194.81, 195.24; IR (thin film) ν (cm^{-1}) 3500, 1663; HRMS (FAB$^+$, thioglycerol) calcd for $C_{32}H_{27}O_6$ 507.1808 [M + H]$^+$, found 507.1811. Anal. Calcd for $C_{32}H_{26}O_6 \cdot (H_2O)_{0.25}$: C 75.20, H 5.23. Found: C 75.19, 5.24.

Diethylenetriamine-Bridged Cyclophane 14. Using the procedure described for the preparation of cyclophane **8**, enaminone **12** (0.188 g, 0.918 mmol) and **11** (0.780 g, 0.918 mmol) reacted to give cyclophane **14** as a pale yellow solid (0.426 g, 46%) after purification by flash column chromatography (2:1 hexanes:EtOAc). An anlytical sample was obtained by recrystallization from CH_3CN: mp 175−179 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.49 (s, 6H), 2.63 (br t, $J =$ 6.9 Hz, 4H), 3.01 (br t, $J = 6.9$ Hz, 4H), 3.89 (s, 3H), 4.21 (s, 4H), 7.16−7.23 (m, 5H), 7.32−7.44 (m, 9H), 7.66 (d, $J = 7.7$ Hz, 2H), 7.72 (d, $J = 7.7$ Hz, 2H), 7.77−7.80 (m, 6H), 8.23 (br s, 1H), 8.57 (d, $J = 1.5$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.70, 21.80, 50.09, 51.29, 54.95, 55.76, 114,40, 120.06, 123.21, 127.38, 127.62, 128.97, 129.80, 129.94, 130.27, 131.28, 134.10, 134.28, 134.35, 134.97, 135.31, 137.45, 137.52, 137.57, 138.00, 139.87, 144.00, 144.20, 160.06, 194.49, 195.01; IR (thin film) ν (cm^{-1}) 1664, 1159. Anal. Calcd for $C_{55}H_{51}N_3O_{10}S_3 \cdot (H_2O)_{0.5}$: C 64.81, H 5.14, N 4.12. Found: C 64.76, H 5.08, N 4.13.

Diethylenetriamine-Bridged Cyclophane 17. Using the procedure described above, reaction of 0.581 g (0.683 mmol) of **15** and 0.143 g (0.683 mmol) of **12** gave 0.234 g (34%) of **17** as a colorless solid after purification by flash column chromatography (2:1 hexanes:EtOAc). An analytical sample was obtained by recrystallization from CH_3CN: mp 241−243 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.95 (s, 3H), 2.37 (br t, $J = 7.6$ Hz, 4H), 2.50 (s, 6H), 3.27 (br t, $J = 7.6$ Hz, 4H), 3.91 (s, 3H), 4.36 (s, 4H), 6.97 (d, $J = 8.1$ Hz, 2H), 7.12 (d, $J = 8.1$ Hz, 2H), 7.21−7.23 (m, 1H), 7.39−7.48 (m, 7H), 7.58 (d, $J = 8.2$ Hz, 4H), 7.64 (s, 1H), 7.75 (d, $J = 8.2$ Hz, 4H), 7.87 (d, $J = 8.2$ Hz, 4H), 8.65 (d, $J = 1.5$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.19, 21.85, 48.93, 49.82, 54.53, 55.77, 114.50, 120.15, 123.19, 127.46, 129.65, 129.94, 130.28, 130.78, 133.16, 134.67, 134.90, 135.54, 136.30, 137.07, 137.87, 140.24, 143.11, 143.98, 144.27, 160.14, 193.74, 194.79; IR (thin film) ν (cm^{-1}) 1661, 1153. HRMS (FAB$^+$, NBA) calcd for $C_{55}H_{52}N_3O_{10}S_3$ 1010.2815 [M + H]$^+$, found 1010.2810. Anal. Calcd for $C_{55}H_{51}N_3O_{10}S_3$: C 65.39, H 5.09, N 4.16, S 9.52. Found: C 65.16, H 5.16, N 4.25, S 9.32.

Di(ethylene oxy)-Bridged Cyclophane 18. Using the procedure for benzannulation−macrocyclization described above, bis(aryl ethynyl) ketone **16** (0.200 g, 0.512 mmol) and enaminone **12** (0.105 g, 0.512 mmol) reacted to afford cyclophane **18** (0.110 g, 39%) as a yellow solid after purification by flash column chromatography (1:1 hexanes:EtOAc). An analytical sample was obtained by slow diffusion of hexanes into an EtOAc solution: mp 186−187 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 8H), 3.90 (s, 3H), 4.63 (s, 4H), 7.19−7.23 (m, 1H), 7.40−7.48 (m, 3H), 7.54 (d, $J = 8.2$ Hz, 4H), 7.85 (d, $J = 8.2$ Hz, 4H), 8.04 (t, $J = 1.6$ Hz, 1H), 8.65 (d, $J = 1.6$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.78, 70.07, 70.61, 72.51, 114.41, 120.14, 123.29, 127.62, 129.90, 130.35, 134.50, 135.81, 136.10, 137.24, 137.98, 140.17, 144.41, 160.11, 194.31, 195.06; IR (thin film) ν (cm^{-1}) 1661, 1270. Anal. Calcd for $C_{34}H_{30}O_7 \cdot (H_2O)_{0.25}$: C 73.56, H 5.54. Found: C 73.46, H 5.45.

Acknowledgment. Financial support for this work was provided by the UM−St. Louis Department of Chemistry. Support for instrumentation facilities (NMR, X-ray, MS) was provided by the NSF (CHE-9974801, CHE-9101834, CHE-9708640). We thank Dr. Janet Braddock-Wilking for assistance in obtaining low-temperature NMR spectra, and Dr. R. E. K. Winter and Mr. J. Kramer for assistance in obtaining mass spectral data.

Supporting Information Available: General experimental procedures and detailed descriptions for the preparation of **3**, **7**, **10**−**11**, and **15**−**16**; copies of ^{1}H NMR spectra for compounds **8**, **10**, **15**, and **16**; and details of X-ray data collection and structure refinement. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0256181