# Synthesis and Metal Ion Binding Studies of Enediyne-Containing Crown Ethers

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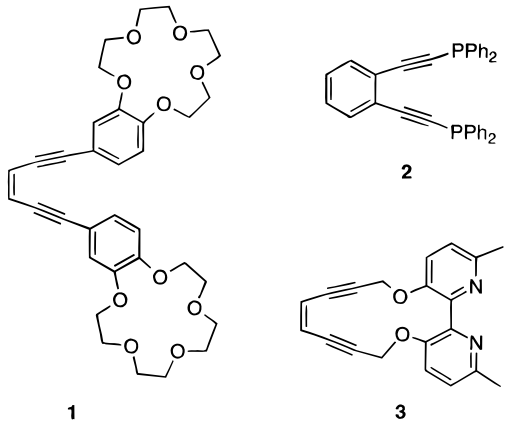
The 3-ene-1,5-diyne crown ether **5** is a novel enediyne-containing crown ether that was designed as a model system for a class of enediynes that might undergo alkali metal ion-triggered Bergman cyclization. We report the preparation of **5** by two different routes. In the shorter and preferable route, a carbenoid coupling reaction is employed to simultaneously construct the enediyne moiety and effect a macrocyclization of an acyclic bis(propargyl)bromide **15** to the 24-membered crown ether **5**. Under standard reaction conditions, this carbenoid coupling produces as the major product the isomeric 5-ene-1,3-diyne-crown ethers (*Z*)-**16** and (*E*)-**16**. The formation of 5-ene-1,3-diynes from the carbenoid coupling of propargyl bromides is unprecedented. We present evidence that it is the polyether nature of dibromide **15** that leads to the formation of the 5-ene-1,3-diyne-crown ether products. Judicious control of the reaction conditions can be used to produce either **5** or (*Z*)-**16** from **15** in synthetically useful yields. Both enediyne-crown ethers **5** and (*Z*)-**16** bind alkali metal ions, as evidenced by their ability to extract alkali metal picrates into organic solvents. Enediyne-crown ether **5** undergoes Bergman cyclization at 135 °C in DMSO/1,4-cyclohexadiene to produce the known *o*-xylyl crown ether **4**. Crown ether **5** represents an enediyne in which molecular recognition of alkali metals might serve as a trigger for Bergman cyclization.

Many chemists continue to be fascinated by the enediyne natural products, exemplified by calicheamicin[1] and dynemicin.[2] These antitumor antibiotics are both challenging targets for synthesis[3] and extremely potent cytotoxic agents that possess a unique mechanism of action.[4] The potent cytotoxicity of the enediyne antibiotics is a result of their ability to undergo a triggered Bergman cyclization to produce DNA-cleaving diradical species. The challenge of harnessing the potent cytotoxicity of these compounds for use in cancer chemotherapy hinges upon the ability to design more selective agents.[5] Toward this end, a number of groups have reported on novel designed enediynes with various means of triggering the Bergman cyclization.[6] Most recently, novel enediynes in which molecular recognition is coupled with a triggering mechanism for the Bergman cyclization have been sought. König and Rütters[7] have designed and




1 2 3

**Figure 1.**

synthesized the bis(crown ether) enediyne **1** (Figure 1). Although **1** binds both sodium and potassium, neither alkali metal complex of **1** undergoes Bergman cyclization at temperatures lower than that required for cyclization of the free ligand. Buchwald and co-workers[8] have synthesized 1,2-bis[(diphenylphosphino)ethynyl]benzene (**2**) and have shown that addition of palladium(II) chloride or platinum(II) chloride to **2** results in an over 30 000-fold increase in the Bergman cyclization rate compared to **2** alone. In contrast, addition of mercury(II) chloride to **2** results in a slower rate of Bergman cycliza-

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(4) Nicolaou, K. C.; Smith, A. L.; Yue, E. W. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *50*, 5881−5888.

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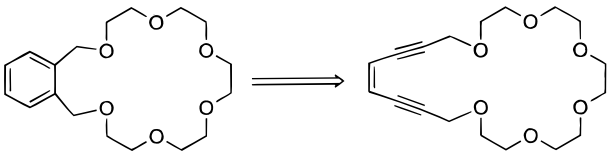


**4** **5**

**Figure 2.**

tion. Most recently, König and co-workers[9] have reported the synthesis of the bipyridyl enediyne **3**, which, as the mercury(II) complex, undergoes Bergman cyclization at a temperature 100 °C lower than that required for the cyclization of **3** itself.

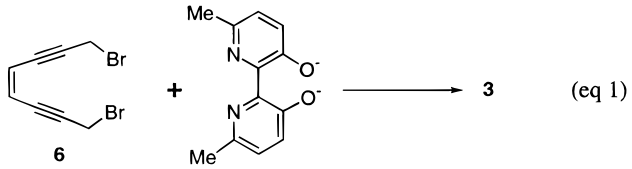
We have been interested in DNA-reactive agents that are alkali metal ion specific.[10] Alkali metal ion concentrations within cells are regulated during the cell cycle and may be significantly altered in cancer cells versus normal cells.[11] DNA-reactive compounds that are responsive to these differing alkali metal ion concentrations could serve as cell cycle specific or cancer cell specific cytotoxic agents. In addition, there are numerous reports of DNA-interactive agents that incorporate an alkali metal ion recognition motif, such as a crown ether moiety.[12] These compounds in general have an increased affinity for DNA when compared to the analogous compounds lacking the alkali metal ion binding element. Thus, incorporation of an alkali metal ion recognition element in an enediyne may result in more potent, as well as more selective, DNA cleavage agents.

Here we report our design and synthesis of an enediyne in which molecular recognition of alkali metals might serve as a trigger for Bergman cyclization. In contrast to the bis(crown ether) enediyne **1** of König and co-workers,[7] a crown ether ring that *incorporates* the enediyne chromophore may more effectively couple the molecular recognition by the crown to the induction of strain in the enediyne moiety sufficient to facilitate Bergman cyclization. This rationale led to a search for aromatic crown ethers that could formally be derived from a Bergman cyclization of a precursor enediyne. Reinhoudt and co-workers have reported a series of *o*-xylyl crown ethers, exemplified by compound **4** (Figure 2), that bind alkali metals with high affinity ($K_a > 10^6$ $M^{-1}$).[13] Crown ether **4** can, at least in a formal sense, be derived from a Bergman cyclization of the enediyne crown ether **5**. The putative Bergman cyclization of **5** to **4** might be facilitated by the appropriate alkali metal ion if **5**, in its complexed state, adopts a conformation that is more strained[14] than the complexed form of the putative 1,4-didehydrobenzene intermediate, whose geometry should be similar to the stable complex of **4**.[15]

Despite its symmetry and lack of diverse functionality, the enediyne crown ether **5** presents a significant synthetic challenge. Although a number of cyclic enediynes have been reported, there have not been any reported syntheses of larger than 16-membered ring cyclic enediynes.[16] In order to construct crown ether **5**, various routes in which the macrocyclization and enediyne forming steps are either sequential (in either order) or concurrent were explored. Two routes were found to be productive in obtaining **5**. In the first, sequential route a Ramberg−Bäcklund reaction is employed to install the enediyne moiety within a macrocyclic precursor. In an alternative, and more efficient, route to **5** the enediyne is formed concurrently with macrocyclization through the recently reported carbenoid coupling strategy of Jones and co-workers.[17] In this latter case, we have found an unusual product formed in the carbenoid coupling step and a means to divert the reaction towards the desired enediyne product.

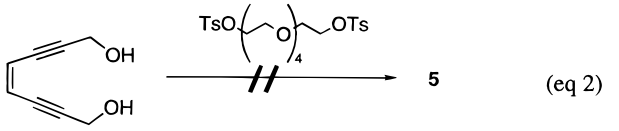
## Results and Discussion

**Sequential Enediyne Formation−Macrocyclization and Macrocyclization−Enediyne Formation Routes.** König and co-workers have recently employed a sequential enediyne formation−cyclization strategy to construct the bipyridyl enediyne **3** as well as a number of other enediyne macrocycles.[9] In their route, König and co-workers employ (*Z*)-1,8-dibromooct-4-ene-2,6-diyne (**6**) and an appropriate diphenol, dicarboxylate, or diamine partner (eq 1). Significantly, these authors note that more basic nucleophiles fail in the cyclization reaction due to propargyl-allene tautomerization of the dibromide.



**6** **3** (eq 1)

We have attempted a synthesis of **5** that is related to the above studies of König and co-workers. In this approach, (*Z*)-oct-4-ene-2,6-diyne-1,8-diol (**7**) is allowed to react with various electrophiles, such as the ditosylate of pentaethylene glycol (eq 2). However, these reactions



**7** **5** (eq 2)

afford only intractable mixtures, presumably due to the instability of the enediyne moiety to the strongly basic reaction conditions necessary to alkylate the diol. The inability to synthesize **5** through the enediyne diol **7** and König and co-workers' report of difficulties in alkylations involving the enediyne dibromide **6** and basic nucleophiles such as alkoxides led to a search for alternative routes to **5**.

A sequential macrocyclization−enediyne formation strategy was next attempted. In this approach, macrocyclization conditions compatible with functionality suit-

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(14) Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 5367−5369.

(15) Lindh, R.; Persson, B. J. *J. Am. Chem. Soc.* **1994**, *116*, 4963−4969.

(16) Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T *J. Am. Chem. Soc.* **1988**, *110*, 4866−4868.

(17) Jones, G. B.; Huber, R. S.; Mathews, J. E. *J. Chem Soc., Chem. Commun.* **1995**, 1791−1792.

able for later elaboration to an enediyne are required. Previous work by Nicolaou and co-workers demonstrated that 10- to 16-membered ring macrocyclic enediynes can be made from the corresponding 11- to 17-membered bis(propargylic)sulfide using a Ramberg−Bäcklund ring contraction.[16] In the case of the formation of crown ether **5**, a route analogous to that of Nicolaou required the 25-membered bis(propargylic)sulfide macrocycle **11** (Scheme 1). On the basis of a previous high-yielding synthesis of an analogous 19-membered ring bis(propargylic) sulfide macrocycle,[10] a cyclization of the dichloride **10** to macrocycle **11** was envisioned.

The route to sulfide **11** and its conversion to the crown ether **5** is shown in Scheme 2. The dipropargyl ether of pentaethylene glycol (**8**) is easily prepared from the diol in high yield. Initial attempts to hydroxymethylate **8** by formation of the diacetylide using *n*-BuLi or EtMgBr followed by addition of formaldehyde or paraformaldehyde met with limited success, due to modest and highly variable yields. As it appeared that the solubility of the diacetylide of **8** was a limiting factor in these reactions, hydroxymethylation was carried out using *n*-BuLi as base in the presence of excess TMEDA. Under these conditions, hydroxymethylation of **8** to diol **9** is accomplished in reproducible, albeit moderate, yield. The conversion of diol **9** to dichloride **10** also presented some difficulties, as dichloride **10** is not stable to chromatography. Treating diol **9** with excess thionyl chloride in pyridine-containing solvents under a variety of conditions affords dichloride **10** contaminated with appreciable amounts of the corresponding monochloro product. An alternative procedure that circumvents the problem of incomplete reaction of the diol was found. Thus, **9** is deprotonated with *n*-BuLi in HMPA/THF, and the resulting dianion is quenched with thionyl chloride. Decomposition of the resulting bis(chlorosulfite) is accomplished by the addition of pyridine and heating the reaction mixture under reflux. In this way, dichloride **10** is obtained in high yield and sufficient purity for the key macrocyclization step.

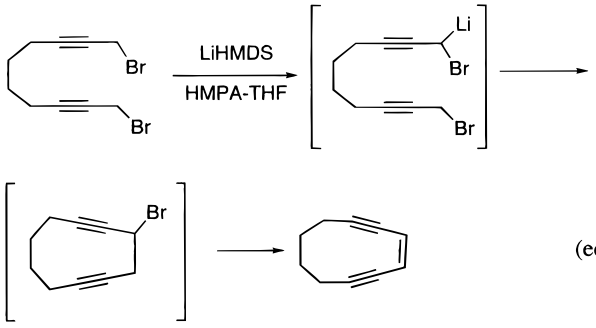
Cyclization of dichloride **10** to the 25-membered macrocycle **11** is accomplished in relatively high yield without the need for high-dilution conditions using an alumina-supported sodium sulfide reagent.[18] The small amounts of polymeric material produced in this reaction are easily separated from sulfide **11** by column chromatography. Conversion of macrocyclic sulfide **11** to the α-chloro sulfone **14** proceeds without incident and sets the stage for the key enediyne-forming Ramberg−Bäcklund reaction.

Attempts to convert α-chloro sulfone **14** to enediyne crown ether **5** produced variable results. A number of bases were examined for their ability to promote the Ramberg−Bäcklund ring contraction of **14** to **5**, but *t*-BuOK appeared to be the base of choice. Even so, when *t*-BuOK was used as the base, the yields for the formation of **5** varied between 0 and 13%, depending upon the initial concentration of **14**, the amount of base added, and the order of addition. In general, a procedure in which 2 equiv of base are added to solutions of **14** (35 mM) affords the highest yield of **5**. The poor yields of **5** may be due to the facile 1,4 elimination from α-chloro sulfone **14** to form cumulene products.[19] The rather low yields from this route proved even more disappointing: the crown ether so obtained proved to be impure by HPLC,[20] and further purification proved difficult. Given the poor overall yields and purification difficulties encountered in this approach, an alternative route to **5** was sought.

**Concurrent Enediyne Formation−Macrocyclization Routes.** Although the strategy of forming the enediyne during macrocyclization is potentially more efficient than the sequential strategies discussed above, it remained to be seen if a method could be found for forming an enediyne in a macrocyclization reaction. To our knowledge, there are only two reports of construction of large-membered ring cyclic enediyne arrays in this manner. Danishefsky and co-workers have reported on the cross coupling of a bis-iodo acetylide with (*Z*)-bis(trimethylstannyl)ethylene to form an enediyne analog of dynemicin;[21] however, this approach appears not to be general, as a closely related bis-iodo acetylide failed to undergo cross coupling. More recently, Jones and Huber have reported a carbenoid coupling route to cyclic enediynes.[17] The generality of this later route has not been demonstrated; in particular, its use in forming larger than 11-membered enediyne-containing rings has not been reported.

All attempts at a palladium-catalyzed macrocyclization cross-coupling involving the di(propargyl) pentaethylene glycol **8** and (*Z*)-1,2-dichloroethylene failed to produce any enediyne-crown ether **5**. These efforts, which included standard, high-dilution, metal ion-templating, and pseudodilution conditions employing a polymer-bound tetrakis(triphenylphosphine)palladium reagent were only successful in producing bis(5-chloropent-4-en-2-ynyl)pentaethylene glycol, the product resulting from 1:2 coupling between **8** and (*Z*)-1,2-dichloroethylene, even when limiting amounts of (*Z*)-1,2-dichloroethylene were employed.

An alternative route to **5** relies upon an adaptation of the carbenoid coupling route of Jones and co-workers[17] in which a bis(propargylic)bromide undergoes cyclization to form a 10-membered cyclic enediyne moiety (eq 3). In




(eq 3)

the application of this cyclization to the formation of the macrocycle **5**, competing intermolecular reactions of the intermediate carbenoid species might lead to oligomeric products. However, it was reasoned that high-dilution conditions or the use of a templating metal ion might overcome this potential shortcoming.

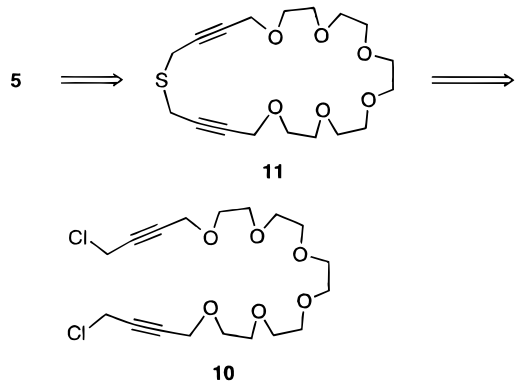
(18) Czech, B.; Quici, S.; Regen, S. L. *Synthesis* **1980**, 113. (b) Tan, L. C.; Pagni, R. M.; Kabalka, G. W.; Hillmyer, M.; Woosley, J. *Tetrahedron Lett.* **1992**, *33*, 7709.

(19) Evidence for the formation of allenic species was obtained from the $^1$H NMR of the crude reaction mixtures, which showed a multiplicity of olefinic signals.

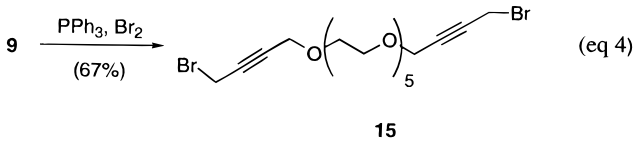
(20) The crown ether **5** obtained from the Ramberg-Bäcklund route was 85% pure, as judged from peak areas in the HPLC chromatogram.

(21) Shair, M. D.; Yoon, T.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 3755−3757.

**Scheme 1**



The required dibromide **15** was prepared in good yield from the diol **9** (eq 4). Interestingly, whereas the



dichloride **10** proved to be unstable to silica gel chromatography, the dibromide **15** could be subjected to chromatography with good recovery. Attempts to effect the intramolecular coupling of dibromide **15** to the enediyne crown ether **5** under conditions (2.3 equiv of LiHMDS, 20 equiv of DMPU, THF, −50 °C) similar to the optimized conditions reported by Jones and co-workers afforded very complex mixtures of products (Scheme 3). In addition to remaining dibromide, the $^1$H NMR spectrum of the crude product mixture revealed the presence of three major components. These products could only be isolated after repeated chromatographic purification of the product mixture. The primary component observed in the $^1$H NMR spectrum of the crude reaction product was identified[22] as the (*Z*)-5-ene-1,3-diyne (*Z*)-**16**, which was isolated in 8% yield along with a small amount of the (*E*)-isomer (*E*)-**16** (<1% yield). The third major component of the product mixture was identified as the desired enediyne **5**, which was obtained in 4% yield after purification.

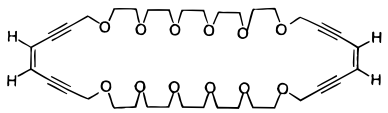
A number of reaction conditions were explored in order to improve the production of enediyne-crown ether **5** from the dibromide **15** (Table 1). Specifically, the nature of the chelator and its inclusion with either the base or the starting dibromide were varied. The optimized conditions for carbenoid coupling reported by Jones and co-workers utilize HMPA as the chelator. When DMPU is replaced with HMPA, the ratio of (*E*/*Z*)-**16** to **5** obtained is nearly unchanged (Table 1, entry 2), although the extent of conversion of dibromide **15** to enediyne products is improved. The use of the chelator TMEDA, when present with the starting dibromide **15**, results in very low mass recovery after aqueous work-up, presumably due to the production of water soluble products (Table 1, entry 3). However, substituting TMEDA for DMPU, with the chelator present with the base rather than the dibromide, results in improved ratios of **5** to isomeric product (*E*/*Z*)-**16** (Table 1, compare entries 1 and 4). The ratio of **5**/(*E*/*Z*)-**16** was further optimized by the addition of "templating" alkali metal bromide salts (Table 1, entry 5). Under these conditions, over 4 equiv of base are required in order to drive the reaction to completion (Table 1, entries 6 and 7).

The original purpose of adding alkali metal salts to dibromide **15** was for templating purposes, in order to avoid intermolecular reactions leading to dimeric products.[23] However, it appears that these salts are playing a more fundamental role, as the ratio of **5** to (*E*/*Z*)-**16** is so markedly affected by the addition of NaBr. Perhaps the alkali metal bromides serve not only a templating role but also influence the stability/reactivity of carbenoid intermediate(s) involved. The stabilizing effect of alkali metal halides on carbenoids is well documented.[24] Interestingly, initial reports on the carbenoid coupling method for acyclic and cyclic enediyne formation call for the addition of 1−10 equiv of HMPA. It is thought that the HMPA serves to destabilize the carbenoid intermediates involved and in so doing promote carbene insertion and enediyne formation, reducing the amount of recovered starting material arising from protonation of the carbenoid upon workup (eq 3).[25] However, addition of excessive amounts of HMPA is reported to result in lowered yields of enediyne and the formation of side products.[25b] It appears that in the carbenoid coupling route to enediynes, a balance between carbenoid stability and reactivity is required.

Isomeric 5-ene-1,3-diynes such as (*E*/*Z*)-**16** have not previously been isolated from the carbenoid coupling reactions of propargylic halides or bis(propargylic) halides. Thus, the formation of (*E*/*Z*)-**16** as the major product in the carbenoid cyclization of **15** under certain conditions stands in strong contrast to previous reports of acyclic or 10-membered ring cyclic enediyne formation. The propensity of **15** to form the isomeric enediyne (*E*/*Z*)-**16** under carbenoid coupling conditions that produce exclusively 1,5-diyne products from other bis(propargylic) halides (Table 1, entry 2)[26] indicates that the formation of 1,3-diyne products from the coupling of dibromide **15** is due to structural differences between this dibromide and other dibromides that have been employed in these coupling reactions. For example, the polyether nature of dibromide **15** may affect the reactivity of the initially formed carbenoid intermediate. It has been recently shown that a neighboring methoxyethoxyethyl group both directs the lithiation of a primary halide and alters the reactivity of the carbenoid intermediate that is

(22) The structural identification of (*Z*)-**16** was aided by an HMBC NMR experiment, which revealed the presence of the 5-ene-1,3-diyne moiety.

(23) Although this material appeared homogeneous by $^1$H NMR, it contained a small amount (ca. 10%) of a more polar component by TLC. Isolation of this more polar component and analysis by MS indicated that it was the dimer:



In preparative reactions, pure **5** was obtained free from this dimer after column chromatography.

(24) Tarhouni, R.; Kirshleger, M.; Rambaud, M.; Villieras, J. *Tetrahedron Lett.* **1984**, *25*, 835−838.

(25) (a) Huber, R. S.; Jones, G. B. *Tetrahedron Lett.* **1994**, *25*, 2655−2658. (b) Jones, G. B.; Huber, R. S. US Pat. 5,436,361.

(26) When (trimethylsilyl)propargyl bromide is allowed to react under the conditions of Table 1, entry 1, an approximately 2:1 ratio of (*Z*)- and (*E*)-1,6-[bis(trimethylsilyl)]hex-3-ene-1,5-diyne is formed, with no observable formation of the corresponding isomeric 1,3-diyne product.

**Scheme 2**

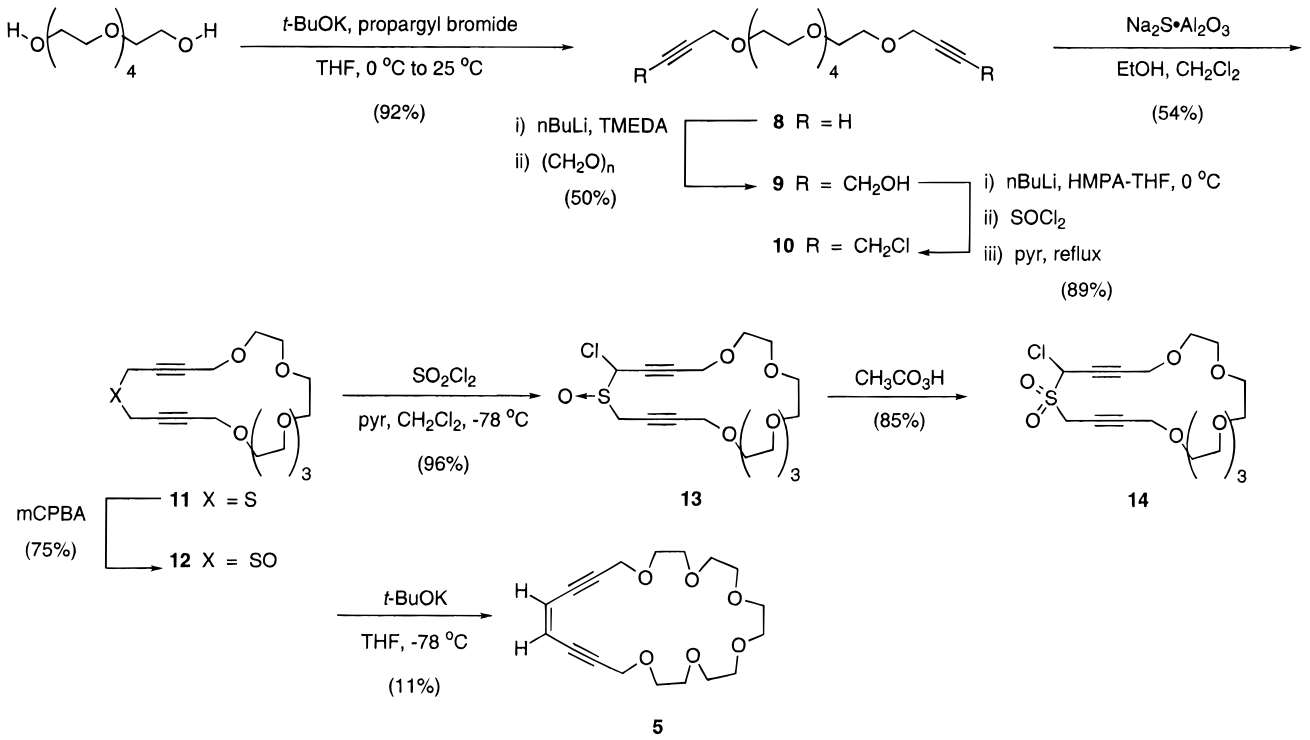
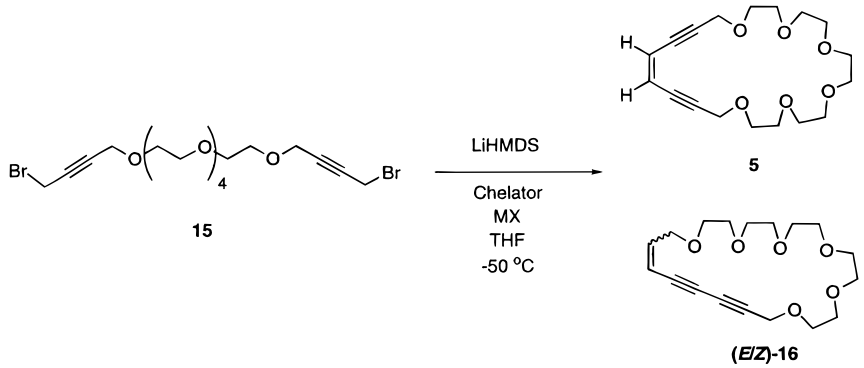



**Table 1. Effects of Reaction Conditions on the Carbenoid Coupling Cyclization of Dibromide 15**




| entry | method[a] | chelator | MX[b] | mass recovery[c] (%) | ratio[d] of 15/5[e]/(*E*/*Z*)-**16**[f] |
|---|---|---|---|---|---|
| 1 | A | DMPU | none | 50[g] | 15:25:60[h] |
| 2 | A | HMPA | none | 49[g] | 0:30:70 |
| 3 | A | TMEDA | none | 4 | *i* |
| 4 | B | TMEDA | none | 93 | 30:30:40 |
| 5 | B | TMEDA | KBr | 93 | 40:40:20 |
| 6 | C | TMEDA | KBr | 64 | 0:60:40 |
| 7 | C | TMEDA | NaBr | 65 | 0:80:20 |

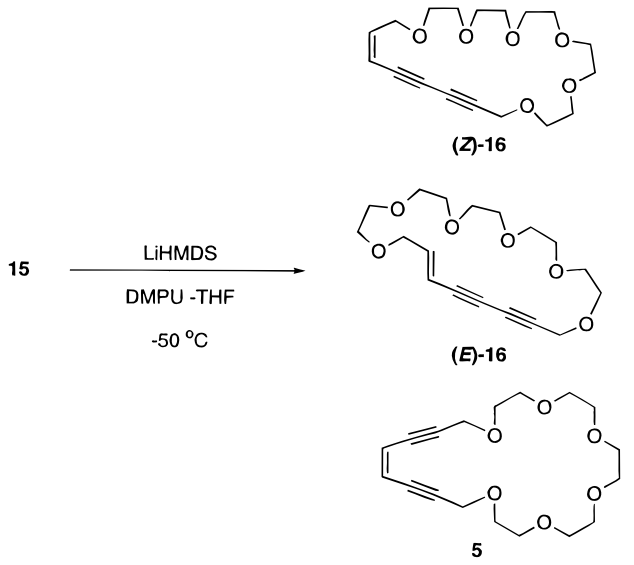
[a] For all methods, the final concentration of **15** after addition of base was 10 mM. Method A: A solution of 2.3 equiv of LiHMDS in THF was added to a solution of **15** in THF-containing chelator. Method B: A solution containing 2.3 equiv of LiHMDS and chelator was added to a solution of **15** in THF. Method C: A solution containing 4.2 equiv of LiHMDS and chelator was added a to solution of **15**. [b] When present, 50 equiv of alkali metal salt MX was added to the dibromide **15** prior to the addition of base. [c] Mass recovery after aqueous workup, calculated as a percentage of the theoretical yield of **5**. [d] Ratio of products and starting material, if present, as determined by $^1$H NMR of the crude reaction mixture after workup. [e] See footnote 23. [f] Compound **16** was produced as a ~1:3 mixture of *E*/*Z* stereoisomers. [g] After column chromatography to remove the DMPU or HMPA. [h] Isolation of **5** and (*E*/*Z*)-**16** after repeated chromatographic steps afforded an isolated ratio of 0.32:0.68 of **5** to (*E*/*Z*)-**16**. [i] Only unidentified products and a trace of **5** were see in the crude $^1$H NMR.

produced.[27] Additionally, the fact that the initial product of the coupling of **15** is a crown ether may play a role in the formation of (*E*/*Z*)-**16**. Recent X-ray crystal structures of crown ether-carbenoid complexes demonstrate the strong interaction between the metal center of a carbenoid and the crown ether ring.[28] This type of interaction may affect the reactivity of subsequently formed carbenoid intermediates. Reaction conditions that further destabilize the carbenoid intermediates, such as the presence of a excess of chelator with starting dibromide **15**, result in increased amounts of the 1,3-diyne (*E*/*Z*)-**16** at the expense of the 1,5-diyne **5**. Con-

(27) Clayden, J.; Julia, M. *Synlett.* **1995**, 103−104.

(28) Charette, A. B.; Marcois, J-F.; Bélanger-Gariépy, F. *J. Am. Chem. Soc.* **1996**, *118*, 6792−6793.

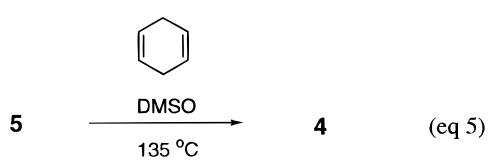
**Scheme 3**




versely, reaction conditions that serve to stabilize the carbenoid intermediates, such as the addition of alkali metal bromide salts, give rise to increased yields of the 1,5-diyne product.

The origin of 5-ene-1,3-diyne (*E*/*Z*)-**16** is not clear. Perhaps the 1,3-diyne (*E*/*Z*)-**16** arises as a result of the well-established rearrangement[29] of a propargylic carbene intermediate. An alternative mechanism for the formation of (*E*/*Z*)-**16** involving the equilibration of **5** to (*E*/*Z*)-**16** under the reaction conditions is not at work; when resubjected to the conditions that favor the formation of **16** (Table 1, entry 1), **5** does not undergo any measurable isomerization to (*E*/*Z*)-**16**.

Under the optimized conditions detailed in Table 1, entry 7, pure enediyne-crown ether **5** is isolated in 29% yield after silver-impregnated silica gel chromatography, for an overall yield of 9% from pentaethylene glycol. Although this is not as high-yielding as literature examples of forming 10-membered enediyne-containing rings via the carbenoid coupling reaction, it does compare very favorably with the 1.8% overall yield of impure enediyne **5** from the alternative Ramberg−Bäcklund route (Scheme 2). The (*Z*)-stereochemistry of **5** was assigned on the basis of both on the identity with the material produced through the Ramberg−Bäcklund route, and the facility with which **5** undergoes Bergman cyclization. Thus, heating a solution of **5** in DMSO-$d_6$ containing a large excess of 1,4-cyclohexadiene at 135 °C for 45.5 h produces the previously reported[13] *o*-xylyl crown ether **4** (eq 5), as evidenced by $^1$H NMR and MS analysis of the reaction mixture.




(eq 5)

**Metal Ion Binding Studies of Enediyne-Crown Ethers.** The metal ion binding properties of *o*-xylyl crown ether **4**, (*Z*)-3-ene-1,5-diyne crown ether **5**, and the (*Z*)-5-ene-1,3-diyne (*Z*)-**16** were examined using a picrate extraction assay (Table 2).[30] Crown ether **5** appears to bind potassium ions more strongly than either sodium or lithium ions, which are bound with comparable affinities. This potassium ion selectivity of crown ether **5** is analogous to, but somewhat diminished from, that demonstrated by the *o*-xylyl crown ether **4**.[13] In contrast, the 1,3-diyne crown ether (*Z*)-**16** appears to bind all alkali metal ions examined with near-equal affinity. Surprisingly, the 1,3-diyne crown ether (*Z*)-**16**, despite the elongated nature of the crown ether portion, demonstrates metal ion extraction ability that is comparable to that displayed by crown ether **5**. Given the near identical sodium ion binding ability of **5** and (*Z*)-**16**, it appears unlikely that the dramatic effect of added NaBr on the ratio of **5** to (*E*/*Z*)-**16** produced in the carbenoid coupling of **15** is due to selective complexation of **5** as it is formed in the reaction.

**Table 2. Alkali Metal Ion Binding Ability of Enediyne-Crown Ethers**

| | % picrate extracted[a] | | |
|---|---|---|---|
| compound | $Li^+$ | $Na^+$ | $K^+$ |
| **4** | 2.0 ± 0.3% | 6.30 ± 0.03% | 35.7 ± 0.1% |
| **5** | 7.99 ± 0.03% | 9.2 ± 0.3% | 16.1 ± 0.4% |
| **16** | 9.82 ± 0.03% | 9 ± 2% | 10.55 ± 0.07% |

[a] Equal volumes of solutions of crown ether (30 mM) in $CH_2Cl_2$ and aqueous solutions of alkali metal picrates (3 mM) were mixed, and the concentration of picrate extracted into the organic layer was determined spectrophotometrically. The amount of picrate extracted is expressed as a percentage of the amount of alkali metal picrate in the original aqueous solution. Values represent the average of two separate determinations.

## Conclusions

The enediyne-crown ether **5** has been prepared by two different routes. In the shorter and preferable route, a carbenoid coupling reaction was employed to simultaneously construct the enediyne moiety and effect a macrocyclization of the acyclic dibromide **15** to the 24-membered crown ether **5**. Under certain conditions, this carbenoid coupling produces as the major product an isomeric macrocyclic 5-ene-1,3-diyne (*E*/*Z*)-**16**. The formation of a 5-ene-1,3-diyne from the carbenoid coupling reaction is unprecedented, and we have presented evidence that it is the polyether nature of dibromide **15** that leads to the formation of this product, perhaps through intramolecular complexation of intermediate carbenoid species produced in the reaction. Work is underway to probe the nature of the conversion of **15** to (*E*/*Z*)-**16** in more detail.

Both enediyne-crown ethers **5** and (*Z*)-**16** bind alkali metal ions, as evidenced by their ability to extract alkali metal picrates into organic solvents. While **5** demonstrates an expected increased extractability for potassium ions, the crown ether (*Z*)-**16** appears to bind lithium, sodium, and potassium with near-equal affinity.

Enediyne-crown ether **5** undergoes Bergman cyclization at 135 °C in DMSO/1,4-cyclohexadiene to produce the known *o*-xylyl crown ether **4**. Studies of the effect of alkali metal ions on the rate of this Bergman cyclization are currently underway and will be reported upon in due course.

(29) (a) Noro, M.; Masuda, T.; Ichimura, A. S.; Koga, N.; Iwamura, H. *J. Am. Chem. Soc.* **1994**, *116*, 6177−6190. (b) Padwa, A.; Gareau, Y.; Xu, S. L. *Tetrahedron Lett.* **1991**, *32*, 983−986.

(30) Ouchi, M.; Inoue, Y.; Wada, K.; Iketani, S.; Hakushi, T.; Weber, E. *J. Org. Chem.* **1987**, *52*, 2420−2427.

## Experimental Section

**General Procedures.** Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. THF was distilled from sodium/benzophenone immediately prior to use. $CH_2Cl_2$ and MeCN were distilled from $CaH_2$ immediately prior to use. Absolute ethanol was dried and stored over 4 Å sieves. Pentaethylene glycol, pyridine, HMPA, 1,4-cyclohexadiene, and HMDS were distilled prior to use. TMEDA, *n*-butylamine, and *N,N′*-dimethylpropyleneurea (DMPU) were distilled from $CaH_2$ prior to use. $SOCl_2$ and $SO_2Cl_2$ were distilled from linseed oil and stored in glass-stoppered vessels under argon. Paraformaldehyde was dried and stored in a vacuum desiccator over $P_2O_5$. All reactions were performed under an inert atmosphere of either argon or nitrogen in oven-dried glassware. Unless otherwise noted, organic extracts were dried with $Na_2SO_4$, filtered through a fritted glass funnel, and concentrated with a rotary evaporator (20−30 mm). Melting points (open capillary) are uncorrected. IR spectra were determined in $CHCl_3$. Unless otherwise noted, $^1H$ and $^{13}C$ NMR spectra were determined in $CDCl_3$ on a spectrometer operating at 250 and 62.89 MHz, respectively. All mass spectra were obtained by chemical ionization using methane as the ionizing gas.

**Oct-4-ene-2,6-diyne-1,8-diol (7).** In a 100 mL round-bottomed flask under argon was placed *O*-(trimethylsilyl)-propargyl alcohol (2.0 g, 15.6 mmol), prepared from propargyl alcohol and chlorotrimethylsilane, benzene (10 mL), tetrakis-(triphenylphosphine)palladium(0) (0.516g, 0.4 mmol), cuprous iodide (0.114 g, 0.6 mmol), and *n*-butylamine (2.2 mL, 22.2 mmol). (*Z*)-1,2-Dichloroethylene (0.5 mL, 7.2 mmol) was added to the reaction mixture, which was allowed to stir overnight. The reaction mixture was diluted with ether (100 mL) and filtered. The filtrate was concentrated and dissolved in MeOH (75 mL) containing a few drops of AcOH. Concentration and purification of the product mixture by flash chromatography on silica gel (25% EtOAc in hexanes) afforded diol **7** (0.343 g, 35%) as an off-white solid: mp 57.5−58 °C; $^1H$ NMR $\delta$ 2.10 (bs, 2H), 4.47 (s, 4H), 5.87 (s, 2H); $^{13}C$ NMR $\delta$ 51.50, 82.90, 95.31, 119.47; IR 3274, 2216, 1106 $cm^{-1}$; MS 137 ($MH^+$); HRMS *m/e* calcd for $C_8H_9O_2$ 137.0603, found 137.0600.

**1,14-Bis(2-propyn-1-oxy)-3,6,9,12-tetraoxatetradecane (8).** To an ice−water bath-cooled stirring solution of *t*-BuOK (95% w/w, 8.01 g, 67.8 mmol) in 33 mL of THF was added via cannula over 1 min a solution of pentaethylene glycol (7.18 g, 30.1 mmol) in 13 mL of THF. The resultant solution was allowed to stir for 10 min and was then added dropwise via cannula over 16 min to an ice−water bath-cooled, mechanically stirred solution of propargyl bromide (80% w/w, 20.0 g, 134 mmol) in 46 mL of THF. The reaction mixture was allowed to stir at 0 °C for 1 h and then at room temperature for an additional 14 h. The reaction mixture was diluted with 100 mL of 3:1 saturated brine/water, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water (3 × 20 mL) and brine (1 × 75 mL). The residue upon drying and concentration was purified by flash chromatography on silica gel (EtOAc) to afford diyne **8** (8.67 g, 92%) as a pale yellow solid: mp 36−37 °C; $^1H$ NMR $\delta$ 2.39 (t, $J$ = 2.3 Hz, 2H), 3.54−3.67 (m, 20H), 4.14 (d, $J$ = 2.3 Hz, 4H); $^{13}C$ NMR $\delta$ 58.23, 68.94, 70.24, 70.43(2C), 70.45, 74.43, 79.52; IR 3259, 2117, 1100 $cm^{-1}$; MS 315 ($MH^+$), 277, 259; HRMS *m/e* calcd for $C_{16}H_{27}O_6$: 315.1808, found 315.1806.

**1,14-Bis(4-hydroxy-2-butyn-1-oxy)-3,6,9,12-tetraoxatetradecane (9).** To a vigorously stirred solution of **8** (0.697 g, 2.22 mmol) in 100 mL of THF was added TMEDA (6.7 mL, 44.4 mmol), and this solution was cooled to −78 °C in a dry ice/acetone bath. A solution of *n*-BuLi (2.33M, 2.3 mL, 5.36 mmol) was added dropwise, and the resulting solution was allowed to stir for 5 min. A stirring suspension of paraformaldehyde (95% w/w, 1.06 g, 33.6 mmol) in 20 mL of THF was added quickly via cannula. The heterogeneous reaction mixture was allowed to stir at −78 °C for 15 min, the cooling bath was removed, and the reaction mixture was heated under reflux until the solution was as homogeneous as possible (∼20 min). The cooled solution was then quenched with 60 mL of saturated aqueous $NH_4Cl$. The aqueous layer was extracted with EtOAc (3 × 30 mL), and the combined organic layers were washed with brine (1 × 40 mL). The residue upon drying and concentration was purified by flash chromatography on silica gel (10% MeOH in EtOAc) to afford diol **9** (0.414 g, 50%) as a pale yellow oil: $^1H$ NMR $\delta$ 3.32 (s(br), 2H), 3.52−3.70 (m, 20H), 4.14 (t, $J$ = 1.7 Hz, 4H), 4.16−4.22 (m, 4H); $^{13}C$ NMR $\delta$ 50.19, 58.33, 68.67, 70.07, 70.21(4C), 80.52, 85.12; IR 3443, 2122, 1121 $cm^{-1}$; MS 375($MH^+$), 345, 307; HRMS *m/e* calcd for $C_{18}H_{31}O_8$ 375.2019, found 375.2016.

**1,14-Bis(4-chloro-2-butyn-1-oxy)-3,6,9,12-tetraoxatetradecane (10).** To a solution of **9** (0.328 g, 0.877 mmol) in 38 mL of THF was added with stirring HMPA (365 μL, 2.1 mmol), and this solution was cooled to 0 °C in an ice−water bath. A solution of *n*-BuLi (2.58M, 750 μL, 1.94 mmol) was then added dropwise with stirring, and the reaction mixture was allowed to warm to room-temperature. A solution of $SOCl_2$ (450 μL, 6.17 mmol) in 7 mL of THF was then added quickly via cannula with stirring, and the reaction mixture was allowed to stir for an additional 15 min. Pyridine (320 μL, 3.96 mmol) was added dropwise, and the reaction mixture was heated under reflux for 15 h. After allowing the dark brown solution to cool to room temperature, water (20 mL) was added, and the resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), water (5 × 20 mL), and brine (1 × 25 mL). Drying and concentration of the organic layer afforded dichloride **10** (0.319 g, 89%) as a dark brown oil. Dichloride **10** was unstable to both alumina and silica gel column chromatography but was sufficiently pure to be used without further purification: $^1H$ NMR $\delta$ 3.60−3.70 (m, 20H), 4.16 (t, $J$ = 1.9 Hz, 4H), 4.23 (t, $J$ = 1.9 Hz, 4H); $^{13}C$ NMR $\delta$ 30.29, 58.52, 69.19, 70.32, 70.50(2C), 70.54, 81.05, 82.49; IR 1135, 1094, 700 $cm^{-1}$; MS 411 ($MH^+$); HRMS *m/e* calcd for $C_{18}H_{29}Cl_2O_6$ 411.1341, found 411.1341.

**6,9,12,15,18,21-Hexaoxa-1-thiacyclopentacosa-3,23-diyne (11).** To a solution of **10** (3.06 g, 7.45 mmol) in 318 mL of 5:1 $CH_2Cl_2$/EtOH was added $Na_2S{\cdot}Al_2O_3$ (21.2% w/w, 7.97 g, 21.7 mmol) in one portion, and the heterogeneous reaction mixture was stirred vigorously overnight at room temperature. The reaction mixture was filtered through Celite, and the solids were washed with $CH_2Cl_2$ and 25% EtOAc in $CH_2Cl_2$. The combined eluant was concentrated, and the residue was purified by flash chromatography on silica gel (5% MeOH in EtOAc) to afford sulfide **11** (1.49 g, 54%) as a yellow oil: $^1H$ NMR $\delta$ 3.47 (t, $J$ = 2 Hz, 4H), 3.63−3.72 (m, 20H), 4.23 (t, $J$ = 2 Hz, 4H); $^{13}C$ NMR $\delta$ 19.17, 58.77, 68.94, 70.51, 70.71, 70.80, 70.87, 79.52, 81.42; IR 1141, 1099 $cm^{-1}$; MS 373 ($MH^+$), 307; HRMS *m/e* calcd for $C_{18}H_{29}O_6S$ 373.1685, found 373.1682.

**$Na_2S{\cdot}Al_2O_3$ Reagent.** To $Na_2S{\cdot}9H_2O$ (7.1 g, 0.03 mmol) that had been rinsed with a small amount of distilled, deionized water and placed in a flask under argon was added 18 mL of warm, distilled, deionized water that had been boiled to remove $CO_2$. The resultant solution was poured into a flask containing $Al_2O_3$ (neutral, Brockman activity I, 80−200 mesh, 8.7 g, 0.085 mmol), and the water was removed *in vacuo* with a rotary evaporator with gentle heating in a warm water bath. The material was then activated by heating *in vacuo* (95 °C, 0.1 Torr) for 1.5 h until the material (21.2% w/w $Na_2S$) was a free-flowing pink powder. The reagent was stored under argon and used shortly after it was prepared.

**6,9,12,15,18,21-Hexaoxa-1-thiacyclopentacosa-3,23-diyne 1-Oxide (12).** To a solution of **11** (0.062 g, 0.165 mmol) in 6.75 mL of $CH_2Cl_2$ that had been cooled to −30 °C in a dry ice/*i*-PrOH bath was added dropwise with stirring via cannula over 30 s a solution of *m*-CPBA (50% w/w, 0.063 g, 0.182 mmol) in 2.25 mL of $CH_2Cl_2$. The resultant solution was allowed to stir at −30 °C for 1.25 h. While still cold, the reaction mixture was diluted with 20 mL of $CH_2Cl_2$ and then washed with saturated aqueous $Na_2CO_3$ (1 × 20 mL) and saturated aqueous $NaHCO_3$ (1 × 20 mL). The aqueous washes were extracted with $CH_2Cl_2$ (2 × 12 mL), and the combined organic layers were washed with brine (1 × 20 mL). The residue upon drying and concentration was purified by flash chromatography on silica gel (15% MeOH in EtOAc) to afford sulfoxide **12** (0.048 g, 75%) as a colorless solid: mp 50.5−51.5 °C; $^1H$ NMR $\delta$ 3.53−

3.63 (m, 20H), 3.68 (dt, $J$ = 15.9, 2.3 Hz, 2H), 3.83 (dt, $J$ = 15.9, 2.3 Hz, 2H), 4.19 (t, $J$ = 2.3 Hz, 4H); $^{13}$C NMR $\delta$ 40.99, 58.48, 68.98, 70.27, 70.52, 70.58, 70.64, 74.13, 84.60; IR 2242, 2119, 1135, 1095, 1065 cm$^{-1}$; MS 389 (MH$^+$), 337, 321; HRMS $m/e$ calcd for $C_{18}H_{29}O_7S$ 389.1634, found 389.1620.

**6,9,12,15,18,21-Hexaoxa-2-chloro-1-thiacyclopentacosa-3,23-diyne 1-Oxide (13).** To a stirring solution of **12** (0.367 g, 0.946 mmol) in 20 mL of $CH_2Cl_2$ was added pyridine (170 $\mu$L, 2.1 mmol). The resulting solution was cooled to −78 °C in a dry ice/acetone bath. $SO_2Cl_2$ (160 $\mu$L, 1.98 mmol) was added in one portion with efficient stirring, and the reaction mixture was allowed to stir for an additional 20 min at −78 °C. The reaction mixture was diluted with 40 mL of EtOAc. This solution was transferred to a separatory funnel containing 40 mL of EtOAc and 40 mL of water, the layers were mixed and then separated, and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 × 20 mL) and brine (1 × 15 mL). Drying and concentration of the organic layer afforded chlorosulfoxide **13** (0.383 g, 96%) as a yellow oil that turns olive on standing. Chlorosulfoxide **13** could not be obtained analytically pure due to its instability to silica gel column chromatography but was sufficiently pure for immediate subsequent use: $^1$H NMR (250 MHz, $CDCl_3$, 2:1 diastereomeric mixture) $\delta$ 3.57−3.76 (m, 20H), 3.82−3.97 (m, 2H), 4.26 (t, $J$ = 1.6 Hz, 2H), 4.34 (d, $J$ = 1.6 Hz, 1.34H), 4.36 (d, $J$ = 1.6 Hz, 0.66H), 5.53 (t, $J$ = 1.6 Hz, 0.67H), 5.60 (t, $J$ = 1.6 Hz, 0.33H); $^{13}$C NMR $\delta$ 41.24, 58.42, 58.45, 58.52, 61.13, 61.56, 69.10, 69.38, 70.29, 70.35, 70.60 (2C), 73.85, 73.95, 76.32, 85.12, 85.28, 89.95; IR 2231, 1110 cm$^{-1}$; MS 423 (MH$^+$), 341, 305; HRMS $m/e$ calcd for $C_{18}H_{28}ClO_7S$ 423.1244, found 423.1238.

**6,9,12,15,18,21-Hexaoxa-2-chloro-1-thiacyclopentacosa-3,23-diyne 1,1-Dioxide (14).** A solution of **13** (0.222 g, 0.525 mmol) in 13 mL of $CH_2Cl_2$ was cooled to 0 °C in an ice−water bath, and peracetic acid (33% w/w, 0.61 g, 2.65 mmol) was added dropwise with stirring over 1 min. The reaction mixture was allowed to stir for 0.5 h at 0 °C and then overnight at room-temperature. The reaction mixture was diluted with 80 mL of EtOAc and transferred to a separatory funnel containing 30 mL of water. The layers were mixed and then separated. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aqueous $Na_2SO_3$ (1 × 40 mL) and brine (1 × 20 mL). Drying and concentration afforded chlorosulfone **14** (0.195 g, 85%) as a pale yellow oil. Chlorosulfone **14** was unstable to silica gel column chromatography but was sufficiently pure for further use: $^1$H NMR $\delta$ 3.59−3.75 (m, 20H), 4.27 (s(br), 4H), 4.35 (d, $J$ = 1.7 Hz, 2H), 5.81 (t, $J$ = 1.7 Hz, 1H); $^{13}$C NMR $\delta$ 41.99, 58.30, 59.78, 69.06, 69.34, 70.23, 70.32, 70.49(2C), 70.52(3C), 70.55(2C), 72.36, 74.50, 85.37, 90.05; IR 2235, 1356, 1150 cm$^{-1}$; MS 439 (MH$^+$), 405, 351; HRMS $m/e$ calcd for $C_{18}H_{28}ClO_8S$ 439.1193, found 439.1187.

**1,14-Bis(4-bromo-2-butyn-1-oxy)-3,6,9,12-tetraoxatetradecane (15).** To a vigorously stirred, ice−water bath-cooled solution of $PPh_3$ (1.98 g, 7.55 mmol) in 36 mL of MeCN was added via addition funnel over 6.5 min a solution of $Br_2$ (375 $\mu$L, 7.32 mmol) in 2 mL of MeCN. The addition funnel was rinsed with an additional 1.2 mL of MeCN, and this was added to the mixture as well. The reaction mixture was allowed to stir at 0 °C for 10 min, and then a solution of diol **9** (1.33 g, 3.56 mmol) in 21.5 mL of MeCN was added dropwise via addition funnel with vigorous stirring over 7 min. The ice−water bath was allowed to warm to room-temperature, and the reaction mixture was stirred for an additional 4.5 h at room temperature. The reaction mixture was transferred to a separatory funnel containing 175 mL of EtOAc and 175 mL of water, and the layers were mixed then separated. The aqueous layer was extracted with EtOAc (3 × 115 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 × 130 mL) and brine (1 × 130 mL). The residue upon drying and concentration of the organic layer was purified by flash column chromatography on silica gel (10−0% hexanes in EtOAc) to afford dibromide **15** (1.2 g, 67%) as a colorless solid: mp 31.5−32.5 °C; $^1$H NMR $\delta$ 3.59−3.70 (m, 20H), 3.93 (t, $J$ = 2 Hz, 4H), 4.24 (t, $J$ = 2 Hz, 4H); $^{13}$C NMR $\delta$ 14.12, 58.50, 69.10, 70.24, 70.43(2C), 70.45, 81.26, 82.76; IR 1146, 1105, 620 cm$^{-1}$; MS 501 (MH$^+$), 435, 369; HRMS $m/e$ calcd for $C_{18}H_{29}Br_2O_6$ 499.0331, found 499.0313.

***(Z)*-8,11,14,17,20,23-Hexaoxacyclotetracos-3-ene-1,5-diyne (5). From Chlorosulfone 14.** To a solution of **14** (0.085 g, 0.199 mmol) in 6 mL of THF that had been cooled to −78 °C in a dry ice/acetone bath was added in one portion via cannula with stirring a dry ice/acetone bath-cooled suspension of *t*-BuOK (95% w/w, 0.05 g, 0.423 mmol) in 1 mL of THF. The dark brown reaction mixture was stirred at −78 °C for 15 min. Solid $NaHCO_3$ was added, followed by 10 mL of benzene. The reaction mixture was allowed to warm to room temperature and heated in an oil bath for 3 min at 50 °C. The reaction mixture was then transferred to a separatory funnel containing 20 mL of brine and 20 mL of EtOAc. The layers were mixed and separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The residue upon drying and concentration of the organic layer was purified by flash column chromatography on silica gel (5% MeOH in EtOAc) to afford enediyne **5** (0.01 g, 11%) as a colorless oil that was 85% pure by HPLC (4.5 × 250 mm microsorb $SiO_2$, 1.0 mL/min EtOAc, $t_R$ = 9.2 min).

**From Dibromide 15.** A vigorously stirred suspension of **15** (0.09 g, 0.18 mmol) and pulverized, desiccated NaBr (0.927 g, 9.0 mmol) in 15 mL of THF was cooled to −55 °C in a dry ice/acetone bath. A room-temperature solution of LiHMDS/TMEDA, formed by the addition of *n*-BuLi (2.2 M, 410 $\mu$L, 0.902 mmol) to an ice−water bath-cooled solution of HMDS (190 $\mu$L, 0.9 mmol) and TMEDA (550 $\mu$L, 3.64 mmol) in THF (3 mL), was added dropwise over 4 min via addition funnel to the reaction mixture. The resulting dark green reaction mixture was allowed to stir for an additional 22 min at −55 °C before being quenched with 10 mL of 2% aqueous HCl. The mixture was allowed to warm to room-temperature and was transferred to a separatory funnel containing 12 mL of EtOAc. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with water (3 × 5 mL) and brine (1 × 8 mL). The residue upon drying and concentration of the organic layer was purified by flash column chromatography in the dark using silica gel impregnated with 20% w/w $AgNO_3$ (15% MeOH in EtOAc). The eluant was collected into tubes containing 1 mL of brine. The organic layers in the fractions of interest were combined and evaporated to afford enediyne **5** (0.018 g, 29%) as a colorless oil: $^1$H NMR $\delta$ 3.55−3.73 (m, 20H), 4.34 (s, 4H), 5.79 (s, 4H); $^{13}$C NMR $\delta$ 58.92, 68.88, 70.33, 70.57, 70.64, 70.71, 83.54, 92.87, 119.53; IR 3049, 2211, 1106 cm$^{-1}$; MS 339 (MH$^+$); HRMS $m/e$ calcd for $C_{18}H_{27}O_6$ 339.1808, found 339.1809.

***(Z)*-8,11,14,17,20,23-Hexaoxacyclotetracos-1-ene-3,5-diyne [(*Z*)-16)] and (*E*)-8,11,14,17,20,23-Hexaoxacyclotetracos-1-ene-3,5-diyne [(*E*)-16)].** DMPU (3.1 mL, 25.6 mmol) was added to a stirring solution of **15** (0.642 g, 1.28 mmol) in 107 mL of THF in a 500 mL flask equipped with a pressure-equalized addition funnel. After the reaction mixture was cooled to −63 °C in a dry ice/acetone bath, the addition funnel was charged with a room-temperature solution of LiHMDS that was prepared by the addition of *n*-BuLi (2.33 M, 1.25 mL, 2.91 mmol) to an ice−water bath-cooled solution of HMDS (620 $\mu$L, 2.94 mmol) in 21 mL of THF. The LiHMDS solution was added dropwise with vigorous stirring over 29 min. The reaction mixture was allowed to stir for an additional 16 min at −63 °C and was then quenched while still cold with 36 mL of 1% aqueous HCl. The forest-green reaction mixture was allowed to warm to room-temperature and was shaken with 85 mL of water and 100 mL of EtOAc in a separatory funnel. The aqueous layer was extracted with EtOAc (4 × 50 mL), and the combined organic layers were washed with brine (1 × 60 mL). The residue upon drying and concentration of the organic layer was purified by flash column chromatography on silica gel (5% MeOH in EtOAc) to remove the DMPU. All enediyne-containing fractions were pooled, concentrated, and subjected to flash column chromatography in the absence of direct light on silica gel impregnated with 25% w/w $AgNO_3$ (15% MeOH in EtOAc) with the eluting fractions being collected into tubes containing 2 mL of brine. Separation of the organic layers of the fractions containing only one component afforded 22 mg of pure (*Z*)-**16**. Further

purification of the earliest eluting mixed fractions [preparative TLC (1 mm silica gel plate, 5% MeOH in EtOAc), flash chromatography (silica gel, 5% MeOH in EtOAc), followed by preparative TLC (1 mm silica gel plate, EtOAc)] afforded an additional 14 mg of (*Z*)-**16** as a pale yellow solid (36 mg total, 8%) and 2 mg of the slightly faster eluting (*E*)-**16**, contaminated with ~5% of (*Z*)-**16**, as a colorless oil (0.5%). The later eluting mixed fractions from the $AgNO_3$ on silica gel flash chromatography, upon further purification by flash chromatography on silica gel (5% MeOH in EtOAc), afforded **5** (18 mg, 4%) as a colorless oil. Analytical data for (*Z*)-**16**: mp 51−52 °C; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 3.45 (m, 20H), 4.22 (d, $J$ = 6.9 Hz, 2H), 4.36 (s, 2H), 5.86 (d, $J$ = 11.3 Hz, 1H), 6.31 (dt, $J$ = 11.3, 6.9 Hz, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 58.16, 67.85, 68.78, 69.0, 69.60, 69.74, 69.78, 69.81, 69.90, 69.95, 74.50, 77.89, 81.46, 110.10, 144.84; MS 339 ($MH^+$); HRMS *m*/*e* calcd for $C_{18}H_{27}O_6$ 339.1808, found 339.1801.

Analytical data for (*E*)-**16**: $^1$H NMR $\delta$ 3.53 (m, 20H), 4.11 (dd, $J$ = 4.3, 1.9 Hz, 2H), 4.26 (s, 2H), 6.0 (d, $J$ = 15.9 Hz, 1H), 6.32 (dt, $J$ = 15.9, 4.3 Hz, 1H); MS 339 ($MH^+$); HRMS *m*/*e* calcd for $C_{18}H_{26}O_6$ 338.1729, found 338.1727.

**Thermolysis of 5.** To a vacuum hydrolysis tube were added **5** (280 $\mu$L, 51.3 mM in DMSO-$d_6$, 14.4 $\mu$mol) and 1,4-cyclohexadiene (4.25 mL, 44.9 mmol). The solution was homogenized, and oxygen was excluded by subjecting the mixture to three freeze−pump−thaw cycles under argon. The tube was heated in an oil bath at 135 °C for 45.5 h and allowed to cool, and the solvent was removed *in vacuo* to afford a green oil that was a 2:1 mixture by $^1$H-NMR of noncyclized enediyne **5** to Bergman product **4** (3.2 mg, 22%). The identity of **4** was verified by comparison to the literature $^1$H NMR values[13] and by MS: MS 341 ($MH^+$); HRMS *m*/*e* calcd for $C_{18}H_{29}O_6$ 341.1964, found 341.1966.

**Alkali Metal Picrate Extraction.** Alkali metal ion binding was characterized by measuring percent metal picrate extracted from an aqueous layer into an organic layer via complexation by the crown ether.[31] All glassware was washed thoroughly with a nonionic detergent to remove traces of alkali metal ions. Briefly, 150 $\mu$L of a 30 mM water-saturated $CH_2Cl_2$ crown ether solution was added to 150 $\mu$L of a 3 mM $CH_2Cl_2$-saturated aqueous alkali metal (lithium, sodium, or potassium) picrate solution in a small culture tube. The mixture was mixed for 10 min, allowed to stand for 30 min, and then centrifuged at high speed for 10 min. A 25 $\mu$L portion of the $CH_2Cl_2$ layer was withdrawn and diluted with 25 $\mu$L of MeCN and 200 $\mu$L of 1:1 $CH_2Cl_2$/MeCN. This solution was homogenized, 250 $\mu$L of the resulting solution was placed in a cuvette, and the absorbance at 375 nm was measured versus a blank of 1:1 $CH_2Cl_2$/MeCN. The percent picrate extracted into the organic layer was calculated using the extinction coefficients lithium picrate $\epsilon_{375}$ 18 600 $M^{-1}$ $cm^{-1}$, sodium picrate $\epsilon_{375}$ 19 000 $M^{-1}$ $cm^{-1}$, and potassium picrate $\epsilon_{375}$ 18 600 $M^{-1}$ $cm^{-1}$.

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**Supporting Information Available:** $^1$H NMR spectra for all new compounds and HMBC NMR of compound (*Z*)-**16** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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