A Direct and Stereocontrolled Route to Conjugated Enediynes

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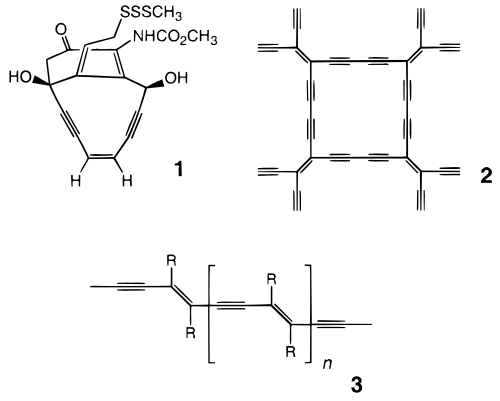
Abstract: A unified synthetic route to 3-hex-en-1,5-diynes, a key building block found in many of the enediyne antitumor agents and designed materials, was developed. The method, which relies on a carbenoid coupling-elimination strategy is tolerant of a wide range of functionalities, and was applied to the synthesis of a variety of linear and cyclic enediynes. Reaction parameters can be adjusted to control stereoselectivity of the process, producing linear enediynes from 1:12 to >100:1 *E:Z* ratio, and in the case of cyclic enediynes, giving the exclusively *Z* C-9, C-10, or C-11 products. Key features of the process are the ready availability of precursors and the mildness and efficiency of the reaction. Application of the process in the design of materials precursors and preparation of enediyne antitumor agents are presented.

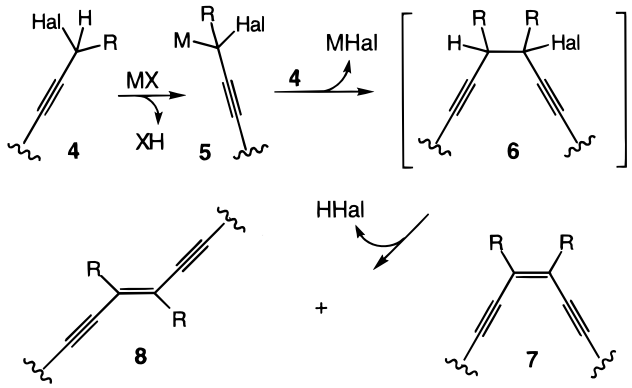
Introduction

Conjugated 3-ene-1,5-diynes represent important chemical building blocks, the subunit found in systems as diverse as antitumor antibiotics, synthetic polymers, and designed nanostructures. Examples include the recently discovered class of antitumor agents which contain cyclic C-10 or C-9 enediyne subunits,[1] exemplified by calicheamicinone **1**, cross-conjugated macrocycles including radialene **2**,[2] and polyacetylenes including the carbon-rod polydiacetylenes **3**.[3]



Although a number of methods are available for the construction of *E* and *Z* enediyne subunits in both linear and cyclic form, they often present practical limitations and can be specific to a narrow range of substrates.[4] We became interested in developing

Scheme 1. Proposed Strategy for In Situ Enediyne Synthesis



a direct route to the core structures **7** and **8** from readily available precursors, and envisaged monometallocarbenoid species **5**, derived in turn from **4**, that under appropriate circumstances might be encouraged to participate in an inter/intramolecular addition to give halodiynes **6** (Scheme 1). E2 elimination would then give access to enediynes **7**/**8** directly. Such a method could provide unified access to both linear and cyclic systems, and vinyl group stereochemistry could be influenced by geometric constraints imposed in **6**. Although generation of such metallohalocarbenoids has precedent, thermal decomposition might be expected to limit their application.[5] Conditions that would permit coupling followed by in situ elimination to proceed at low temperature were thus sought.

Linear Enediynes. To establish proof of principal for the coupling process, commercially available propargylic bromide **9** was employed for model studies (Scheme 2). An initial survey of metallating agents, temperature of reaction, and stoichiometry of reactants quickly revealed that the coupling-elimination process was indeed feasible, albeit giving only modest yields

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(1) (a) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453. (b) Nicolaou, K. C.; Smith, A. L. *Acc. Chem. Res*. **1992**, *25*, 497. (c) Zein, N.; Schroeder, D. R. In *Advances in DNA Sequence Specific Agents*; Jones, G. B., Ed.; Jai Press Inc., Greenwich, CT, 1998; Vol. 3.

(2) Boldi, A. M.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 468.

(3) Anthony, J. A.; Boudon, C.; Diederich, F.; Gisselbrecht, J. P.; Gramlich, V.; Gross, M.; Hobi, M.; Seiler, P. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 763.

(4) Maier, M. E. *Synlett* **1995**, 13.

(5) For discussion of carbenes see: (a) Seyferth, D.; Lambert, R. L.; Massol, M. *J. Organomet. Chem*. **1975**, *88*, 255. (b) Brandsma, L. In *Preparative Polar Organometallic Chemistry 2*; Springer-Verlag: New York, 1990. (c) Olmstead, K. K.; Nickon, A. *Tetrahedron* **1999**, *55*, 3585. Applications see: (d) Hopf, H.; Kreutzer, M.; Jones, P. G. *Chem. Ber*. **1991**, *124*, 1471. (e) Hauptmann, H. *Tetrahedron Lett.* **1974**, 3587.

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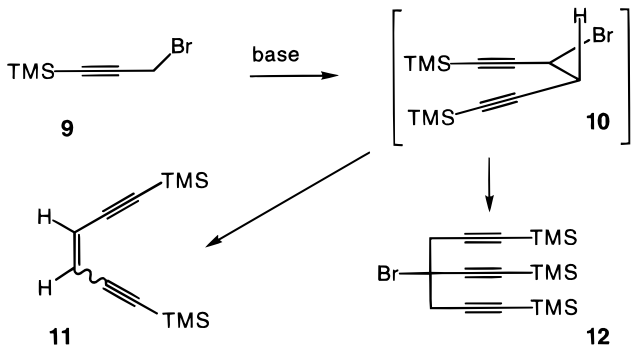
Scheme 2. Preparation of Bis-trimethylsilyl-3-hexen-1,5-diyne



of product (Table 1). In addition to halodiyne **10** and the corresponding β elimination products **11**, triyne **12** was also recovered in low yield when lithium diisopropylamide (LDA) was employed as base. This product can be envisioned by α deprotonation of **10**, and subsequent addition to **9**. More encumbered bases were examined, and as expected, the hindered, nonnucleophilic, Li hexamethyldisilazane (HMDS) proved more effective, resulting in appreciable conversion to **11** directly.[6] Based on the assumption that a carbenoid intermediate is involved, and because LiBr has been reported to have a stabilizing effect on such species,[7] it seemed reasonable that LiBr could serve to inhibit the process and account for the modest yields of product. Under these circumstances, should the rate of coupling decrease substantially, all available **9** would become metallated, leaving a deficit of electrophilic component. *Deliberate introduction of LiBr to the reaction medium supported this hypothesis, resulting in a sharp loss of yield (entry 7).* Initial attempts to remove liberated lithium halide by precipitation using nonpolar solvent mixtures proved ineffective, as was the case using alternate proparglic halides as substrates (vide infra). Remedy was finally found by introducing the electron donor additive hexamethylphosphoramide (HMPA), which was reported to have a *destabilizing* effect on carbenoids.[7] Thus when a tetrahydrofuran (THF) solution of 1.1 equiv LiHMDS and 1.1 equiv HMPA is slowly added to a solution of **9** in THF at −95 °C, maintaining equal concentrations of HMPA and LiBr, **11** is formed cleanly, and all starting material is consumed (entry 9).

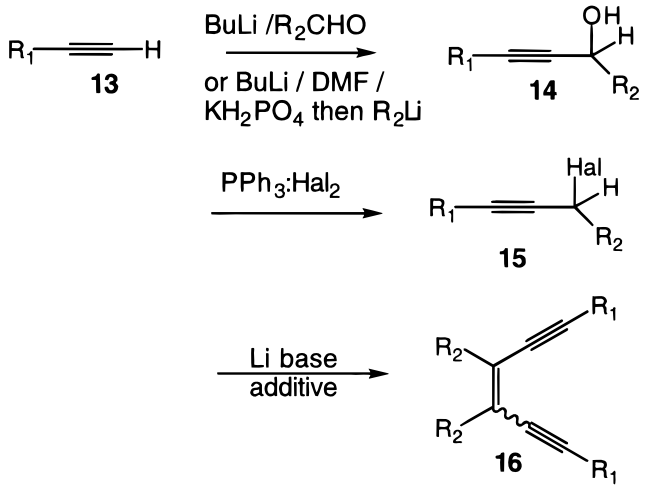
The ratio of *Z:E* isomers proved to be a function of temperature, but more suprisingly, high yields of product were still attainable when the reaction was conducted at ambient temperature (entries 9−13)! Addition of LiBr to reactions containing HMPA still had a negative influence, resulting in a drop in both yield and stereoselectivity (entry 14). Changing counterion of the base gave no improvement (entry 15). Because under appropriate conditions, bromodiyne **10** could be recovered, the stereoselectivity of the elimination step was independently probed (entries 16−23). To our suprise, elimination from **10** using LiHMDS resulted in inferior *Z:E* ratio, although a temperature dependence on this ratio was evident (entries 16−18). The nature of the base used and requirement for cosolvent are clearly important, LDA or KCN/dimethyl sulfoxide (DMSO) giving little or no selectivity (entries 20−22), and omission of HMPA resulting in lowering of yield (entry 19). Conducting the reaction at lower temperature gave an improvement in stereocontrol, but the response to addition of LiBr was favorable, suggesting that this may play a role in the elimination process (entry 23).

The origin of stereochemical bias toward the thermodynamically less stable *Z* isomer deserves comment. Indeed Sondheimer had reported that the base-induced elimination of the propargyl tosylate of 1,5-hexadiyne-3-ol preferentially produces the *E* isomeric enediyne.[8] Although direct elimination from **10** gave isomer ratios comparable with the in situ process, rationalization using conventional models reveals that the *Z* stereoisomer is clearly *not* predicted based on transition state considerations. The antiperiplanar model **A** for E2 elimination suffers from gauche interactions, suggesting that a synperiplanar elimination (model **C**) predominates. However, because an unencumbered E2 antiperiplanar model can be invoked to give rise to the *E* isomer (model **B**), it is entirely possible that an alternative process to the β-elimination may be responsible for the formation of the predominant *Z* isomer. A viable possibility would be an α-elimination by means of the formation and subsequent degradation of a second carbenoid, resulting in a *highly transient* carbene (model **D**). Such a carbene, if it formed, would be expected to undergo a rapid insertion into an adjacent

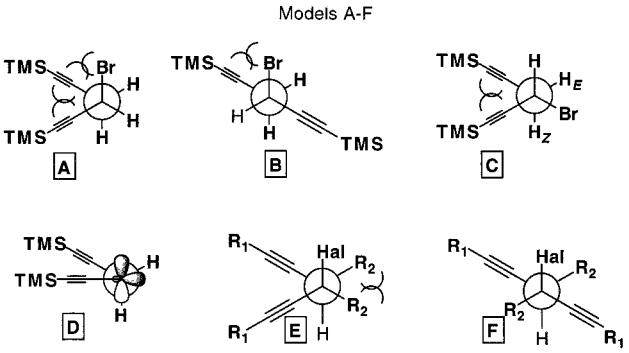
Table 1. Effects of Base on Carbenoid Coupling−Elimination

						% yields			
entry	substrate	base	equiv	*T* (°C)	solvent/additive	**10**	**11**	*Z*/*E*	**12**
1	**9**	*n*-BuLi	1.1	−100	THF	0	0	n.a.	0
2	**9**	LDA	1.0	−100	THF	5	10	1.1	5
3	**9**	LDA	0.3	−85	THF	16	0	n.a.	16
4	**9**	LiHMDS	0.5	−100	THF	0	43	2.3:1	0
5	**9**	LiHMDS	1.1	−85	THF	0	64	1.9:1	0
6	**9**	LiHMDS	2.0	−85	THF	0	94	2.1:1	0
7	**9**	LiHMDS	1.1	−95	THF/LiBr (5)	0	25	1.5:1	0
8	**9**	LiHMDS	1.1	−85	THF/LiBr (5)	4	3	1:2	0
9	**9**	LiHMDS	1.1	−95	THF/HMPA (1.1)	0	96	2.2:1	0
10	**9**	LiHMDS	1.1	−85	THF/HMPA (1.1)	0	95	2.1:1	0
11	**9**	LiHMDS	1.1	−45	THF/HMPA (1.1)	0	94	1.6:1	0
12	**9**	LiHMDS	1.1	0	THF/HMPA (1.1)	0	92	1.3:1	0
13	**9**	LiHMDS	1.1	25	THF/HMPA (1.1)	0	90	1.2:1	0
14	**9**	LiHMDS	1.1	−95	THF/HMPA (1.1) LiBr (5)	0	27	1.5:1	0
15	**9**	KHMDS	1.1	−95	THF/HMPA (1.1)	0	92	1.8:1	0
16	**10**	LiHMDS	1.1	−95	THF/HMPA (1.1)	n.a.	93	1.6:1	0
17	**10**	LiHMDS	1.1	−78	THF/HMPA (1.1)	n.a.	95	1.5:1	0
18	**10**	LiHMDS	1.1	0	THF/HMPA (1.1)	n.a.	92	1.2:1	0
19	**10**	LiHMDS	1.1	−85	THF	n.a.	64	1.9:1	0
20	**10**	LDA	1.8	−95	THF/HMPA (1.1)	n.a.	91	1:1	0
21	**10**	LDA	1.2	−95	THF	n.a.	95	1:1	0
22	**10**	KCN	1.1	25	DMSO	n.a.	74	1.2:1	0
23	**10**	LiHMDS	1.1	−95	THF/HMPA (1.1) LiBr (5)	n.a.	93	2.2:1	0

Scheme 3. Substituted Enediynes via Propargylic Halides

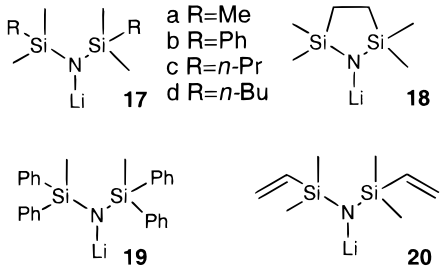


C−H bond, yielding the observed product **11**, and would also account for the observed formation of byproduct **12**. Regrettably, attempts to intercept this carbene by introduction of trapping agents were unsuccessful.



(Interception with a range of arene traps failed to give the corresponding cycloheptatriene adducts.)

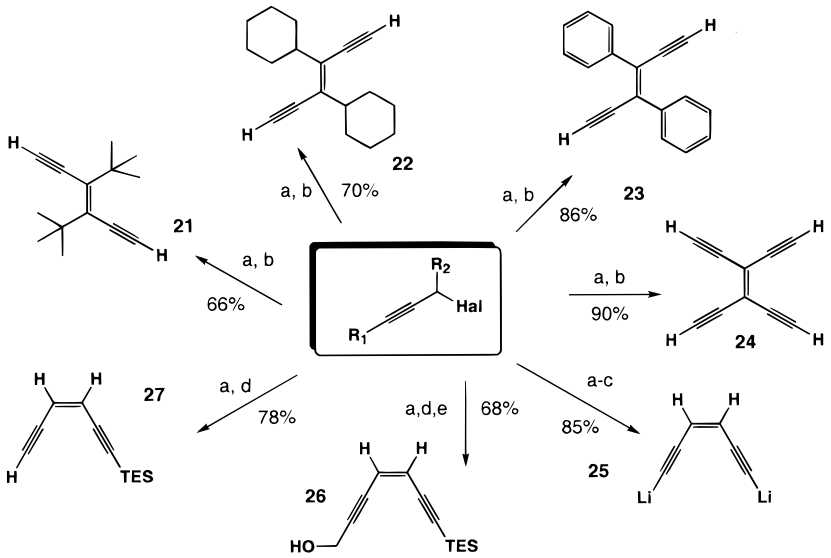
Regardless, the models and results suggested that subtle effects may be responsible for the selectivity observed. We therefore elected to undertake a comprehensive probe of the effects of (i) different terminal alkyne functionality (R_1), (ii) nature of halide leaving group, (iii) substitution at the propargylic position (R_2), (iv) alternate disilazide bases, and (v) various cosolvents. The substituents alone may be expected to either consolidate syn elimination/α insertion to form the *Z* isomer (when R_2 = H), or in cases where R_2 is bulky to encourage E2 elimination to give the *E* isomer (model **F**), which would be preferred to that indicated in model **E**. A variety of propargylic bromides were thus prepared (Scheme 3). Using the optimized conditions, a variety of strategically important enediyne building blocks could be accessed, and in every case examined, chemical yields of products were good, and separation of isomers were routinely achieved either using distillative or chromatographic methods. Little effect of the halide bulk on the process was identified, both in terms of chemical yield and product *Z*:*E* ratio (Table 2, entries 1−2). However, stereochemical outcome proved sensitive to bulk of the alkyne termini such that the triethylsilyl (TES) analogue (Table 2, entry 3) was more selective for the *Z* isomer, but additional bulk was detrimental (entries 4−8). Analysis of both the TES and triisopropylsilyl (TIPS) analogues revealed a strong temperature dependence on selectivity (Figure 1). The effect of carbenoid destabilizing additives was then scrutinized, and the excellent results obtained using the TES group could be duplicated using the HMPA substitute 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), and even improved upon by employing the powerful electron-donating solvent trispyrrolidinophosphoramide (TPP) (entries 10−13). Finally, the influence of the base was examined, using a series of lithium disilazides **17**−**20** with the TES substrate (entries 14−19). Striking changes in selectivity were revealed, with the *n*-alkyl base **17d** proving optimal, yet aryl bases **17b** and **19** resulting in *reversal* of selectivity. Conducting the reactions at even lower temperature (where use of the TPP additive became essential to prevent precipitation) resulted in even higher selectivity (entry 20). One possibility is that specific interactions between the alkylsilyl groups on the base and substrate play a key role in selectivity. This hypothesis is supported by results obtained with alternate substrates (entries 21−23) where up to 12:1 *Z* selectivity is attainable (entry 21). These results are significant in that they tentatively suggest that appropriately chosen base/substrate combinations might be tailored to allow access to otherwise thermodynamically inaccessible products.



For α-substituted enediynes, as predicted (models **E** and **F**) the subtle stereochemical bias that the vinyl substituents impart had a profound influence on product geometric isomer ratio (entries 24−34). Surprisingly, the ethyl substituent retained stereoselectivity in favor of the *Z* isomer (entries 24−26). However, moving to the isopropyl derivatives and beyond, selectivity was reversed and greatly enhanced in favor of the *E* isomer. Because of its robust nature and popularity in alkyne-based materials chemistry, the triisopropylsilyl group was adopted for series of analogues. The route provided ready access to disubstituted primary, secondary, tertiary, cycloalkyl, aryl, and heteroaryl enediynes. Despite efforts to intercept the intermediate bromodiyne, in all cases examined, in situ elimination ensued, resulting in direct formation of the enediynes **16**, in good to excellent yield. The stereoselectivity in the process correlates well with steric bulk of the vinyl substituent, consistent with antiperiplanar alignment for in situ E2 elimination (**F**). Exceptionally high levels of stereoselectivity are obtained in many cases (entries 27−28, 30) and recovered yields are high even with sensitive substrates (entries 29, 32). To demonstrate the utility of the process, in the case of the diphenyl enediyne (entry 31) Pd-catalyzed coupling of **13** [R = TIPS] with *E* 1,2-dichlorostilbene was conducted. *Even under a range of conditions, using 1:1 stoichiometry, the maximum yield of E enediyne obtained was <10%, a competing reaction being alkyne dimerization, confirming the benefit of the current method.* (Catalysts examined included $[Pd(PPh_3)_4]$, $[PdCl_2(PPh_3)_2]$, $[PdCl_2(PhCN)_2]$.[20a] Improved yields are obtained when >5 equiv of vinyl chloride is employed or the corresponding bromides are synthesized and used.[20b]) The synthesis of tet-

(6) Jones, G. B.; Huber, R. S. *Tetrahedron Lett.* **1994**, *35*, 2655.
(7) Tarhouni, R.; Kirschleger, B.; Rambaud, M.; Villieras, J. *Tetrahedron Lett.* **1984**, *25*, 835.
(8) Okamura, W. H.; Sondheimer, F. *J. Am. Chem. Soc.* **1967**, *89*, 5991.

Scheme 4. Unified Procedure for Synthesis of Linear Enediyne Building Blocks[a]



[a] Conditions: (a) LiHMDS, HMPA; (b) TBAF, THF; (c) BuLi, THF; (d) $Na(OCH_3)_3BH$; (e) BuLi, then $(CH_2O)_n$.

Table 2. In Situ Elimination of Propargylic Halides **15** to Give Enediynes **16**

entry	R_1	R_2	base	hal	temp	additive	% yield	*Z*:*E*
1	TMS	H	17a	Cl	−85	HMPA(1.1)	95	1.9:1
2	TMS	H	17a	I	−85	HMPA(1.1)	93	1.9:2
3	TES	H	17a	Br	−95	HMPA(1.1)	94	4.2:1
4	TBDMS	H	17a	Br	−95	HMPA(1.1)	90	4.0:1
5	TIPS	H	17a	Br	−95	HMPA(1.1)	92	2.9:1
6	TPS	H	17a	Br	−95	HMPA(1.1)	89	1.2:1
7	DMTS	H	17a	Br	−95	HMPA(1.1)	91	1.1:1
8	tBu	H	17a	Br	0	HMPA(1.1)	25	1.2:1
9	Ph	H	17a	Br	−95	HMPA(1.1)	90	1.0:1
10	TES	H	17a	Br	−95	DMPU(1.1)	89	4.0:1
11	TES	H	17a	Br	−95	TPP(1.1)	93	4.0:1
12	TES	H	17a	Br	−95	HMPA(5.0)	91	4.0:1
13	TES	H	17a	Br	−95	TPP(5.0)	95	6.1:1
14	TES	H	17b	Br	−95	HMPA(1.1)	87	1:1.6
15	TES	H	17c	Br	−95	HMPA(1.1)	91	3.3:1
16	TES	H	17d	Br	−95	HMPA(1.1)	90	5.1:1
17	TES	H	18	Br	−95	HMPA(1.1)	92	1.8:1
18	TES	H	19	Br	−95	HMPA(1.1)	89	1:1.2
19	TES	H	20	Br	−95	HMPA(1.1)	94	2.0:1
20	TES	H	17d	Br	−115	TPP(5.0)	88	9.0:1
21	TBS	H	17d	Br	−115	TPP(5.0)	92	12.0:1
22	TMS	H	17d	Br	−115	TPP(5.0)	89	1.8:1
23	TPS	H	19	Br	−95	TPP(5.0)	90	1.5:1
24	TMS	Et	17a	Br	−95	HMPA(1.1)	65	2.0:1
25	TMS	Et	17a	Br	−80	HMPA(1.1)	75	2.0:1
26	TIPS	Et	17a	Br	−80	HMP(1.1)	85	3.0:1
27	TIPS	^{i}Pr	17a	Br	−80	HMPA(1.1)	87	1.0:100
28	TIPS	tBu	17a	Br	−80	HMPA(1.1)	70	1.0:100
29	TIPS	c(C_3H_5)	17a	Br	−80	HMPA(1.1)	79	1.0:15
30	TIPS	c(C_6H_{11})	17a	Br	−80	HMPA(1.1)	80	1.0:100
31	TIPS	Ph	17a	Br	−80	HMPA(1.1)	95	1.0:11
32	TIPS	3-pyridyl	17a	Br	−80	HMPA(1.1)	82	1.0:6
33	TIPS	TIPS ethynyl	17a	Br	−80	HMPA(1.1)	95	N/A
34	TIPS	TBS ethynyl	17a	Br	−80	HMPA(1.1)	80	1:1

raalkynyl systems is also noteworthy (entries 33−34), in that it complements existing stepwise methods.[9] Overall, the present method offers a general alternative to classical Pd-mediated cross-coupling reactions; its merits include speed, economy, and versatility.

Having a unified route to either *Z* or *E* enediynes opens up a number of synthetic possibilities. For *E* enediynes, desilylation under standard conditions gave the corresponding terminal alkynes including **21**−**24** (Scheme 4). These substrates and others can be expected to find immediate application in metal-catalyzed oligomerization sequences,[10] and possibly in the

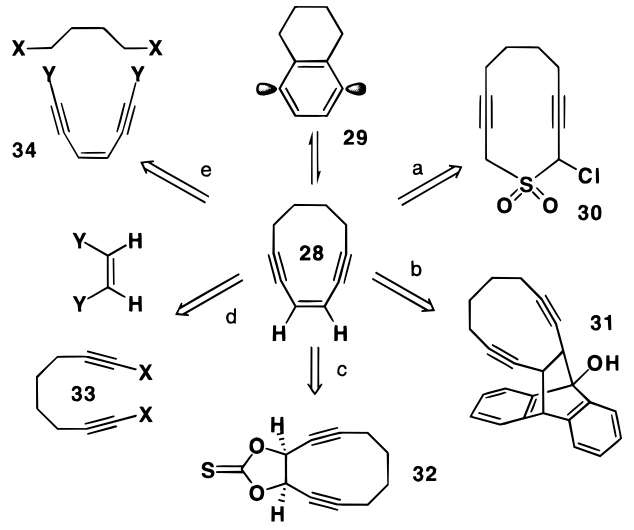
(9) (a) Vollhardt, K. P. C.; Winn, L. S. *Tetrahedron Lett.* **1985**, *26*, 709. (b) Wang, K. K.; Wang, Z.; Gu, Y. G. *Tetrahedron Lett.* **1993**, *34*, 8391. (c) Stracker, E. C.; Zweifel, G. *Tetrahedron Lett.* **1991**, *32*, 3329. (d) Magriotis, P. A.; Scott, M. E.; Kim, K. D. *Tetrahedron Lett.* **1991**, *32*, 6085. (e) Alami, M.; Crousse, B.; Linstrumelle, G. *Tetrahedron Lett.* **1994**, *35*, 3543. (f) Shibuya, M.; Sakai, Y.; Naoe, Y. *Tetrahedron Lett.* **1995**, *36*, 897. (g) Nuss, J. M.; Murphy, M. M. *Tetrahedron Lett.* **1994**, *35*, 37. (h) Dai, W.-M.; Fong, K. C.; Danjo, H.; Nishimoto, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 779. (i) Anthony, J.; Knobler, C. B.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 406. (j) Rubin, Y.; Knobler, C. B.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 698.

(10) See: *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995.

design of various enediyne based nanomaterials.[11] The stereoselective route to *Z* enediynes demonstrated in turn can be expected to find application in the preparation of synthetic enediyne antitumor agents. *Z*-1,6-Dilithio-3-hexene-1,5-diyne **25**, available via deprotection and metallation, has been used by others for the construction of natural enediynes,[12] and differential deprotection allows access to the key Myers type precursor **26** [13] and synthon **27**, which have been used widely in the synthesis of enediyne hybrids.[14]

Cyclic Enediynes. The naturally ocurring enediyne antitumor antibiotics typically possess either a 9- or 10-membered cyclic enediyne moiety. For the cyclohex-3-ene-1,5-diyne subunit present in 10-membered enediynes, a variety of methods for construction have been investigated. In contrast to the natural systems where the enediynes are strained and amenable to a variety of synthetic approaches, the parent subunit **28**, which undergoes Bergman type cyclization to give diyl radical **29**, has an observed half-life of 18 h at 37 °C, warranting special circumstances during its synthesis.[15] Methods examined to date are illustrated. Although the Ramberg−Backlund reaction (route a) has been used successfully by Nicolaou,[16] for parent enediyne **28** the chemical yield is low, and involves a multistep procedure to assemble the substrate. To address the former issue, an elegant alternate route was developed involving a base-induced retro Diels−Alder reaction (route b).[17] The Corey−Winter procedure (route c) was employed by Semmelhack,[18] which likewise gives the desired product, but requires a *multistep* sequence to prepare the substrate. Palladium-mediated vinyl coupling methods (route d) have also been attempted, but for **28** the prolonged conditions required to effect cyclization are incompatible with the (thermally labile) product.[19] Likewise, although linear enediynes **34** (Y = Li) have been used as nucleophiles for addition to carbonyl substrates, cyclization to give **28** has not been effected (route e).

Retrosynthetic Analysis of Cyclodec-3-en-1,5-diyne



We initially attempted formation of **28** using an intramolecular version of the carbenoid coupling-elimination, but without success (vide infra). Therefore, we elected to concentrate on use of the linear enediyne **25**, which was available in multigram quantities using the intermolecular carbenoid method. Reaction with 1,4-diiodobutane under a variety of conditions led primarily to monoalkylated species **35**, with only traces of the cyclic species **28** detected following prolonged reaction at ambient temperature (Scheme 5). Indeed, under such conditions, product cycloaromatization would be competitive with ring closure. Attempts to reduce the degrees of freedom for the cyclization were made, using cyclic substrates **36**, however, even under a range of conditions, bicyclic product **37** could not be detected. The sluggish nucleophilicity of the acetylide was presumably responsible for the poor yields. This was supported by a model study where the lithio acetylide ion of phenylethyne was reacted with 1,4-diiodobutane (Scheme 6). Using 2:1 stoichiometry, which eventually required extended exposure at ambient temperature to achieve coupling, the balance of material was chiefly monoalkylated product **38**, with only moderate yield of dialkylated species **39**. Addition of acetone as a quench after 20 h confirmed that acetylide was still present, leading to formation of 1,2 addition product **40**.

Accordingly, we sought milder conditions to effect cyclization, and elected to pursue an enolate-based strategy, as illustrated in Scheme 7. The ester enolate was reasoned to be appropriate, because intramolecular 10-exo-tet or 10-exo-trig processes present viable vector approaches for formation of the desired ring. The requisite linear enediyne substrate was prepared from the tetrahydropyranyl (THP) ether of propargylic

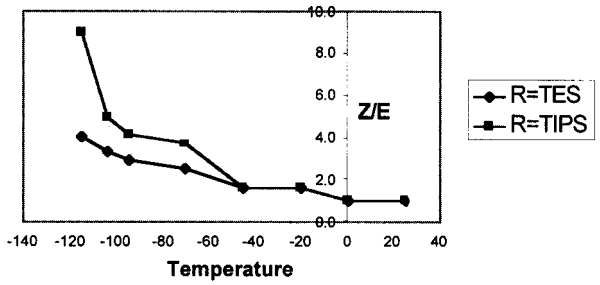
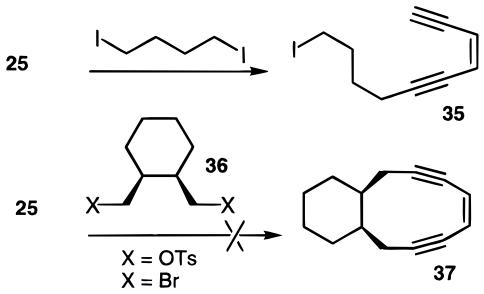
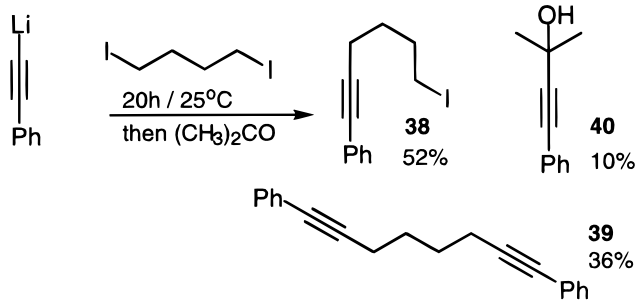


Figure 1. *Z*/*E* temperature dependence.

Scheme 5. Attemped Acetylide-Mediated Closures



Scheme 6. Distribution of Acetylide Alkylation Products



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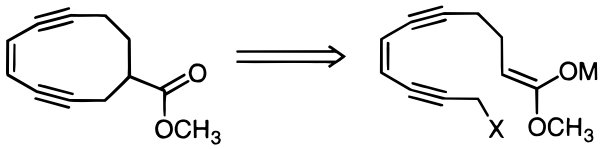
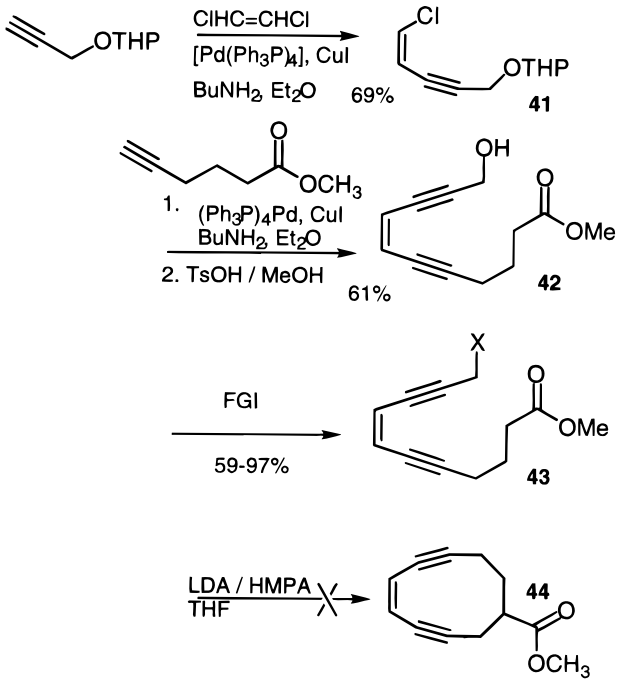
Scheme 7. Exocyclic Enolate Ring Closure Strategy



Scheme 8. Preparation of Intramolecular Enolate Substrates[a]

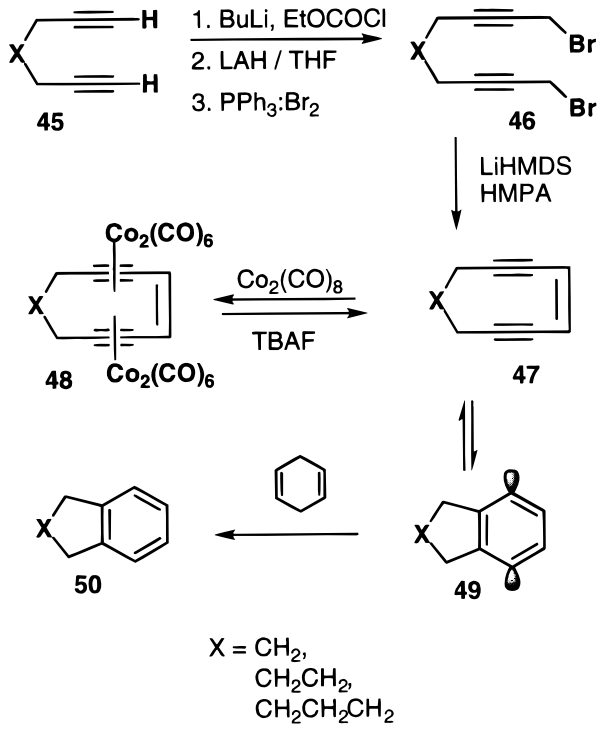


[a] X = OMs: MsCl, Et_3N, CH_2Cl_2, 72%. X = OTos: TosCl, Py, 85%. X = Cl: CCl_4, $Ph_3PCH_2Cl_2$, 78%. X = Br: CBr_4, Ph_3P, CH_2Cl_2, 59%. X = [C=O]: Dess−Martin periodinane, 97%.

alcohol (Scheme 8). Palladium coupling with *Z* dichloroethene under Sonogashira conditions gave chloroeneyne **41**,[20] to which was attached the ester function using commercially available methyl-5-hexynoate. Hydroxy ester **42** was converted into a variety of functional group analogues **43** using traditional methods, then the intramolecular cyclization was probed. In no instance was the desired ester **44** obtained (or the α-hydroxy ester where X = [C=O]). As previously, a range of conditions were investigated, leading chiefly to recovery of starting material, or intermolecular reactions, which could not be suppressed on manipulation of substrate concentration.

Surprised by this outcome, we serendipitously elected to reinvestigate an intramolecular variant of the carbenoid coupling-elimination process, and concentrated efforts on dibromides **46**,

Scheme 9. Carbenoid Route to Cyclic-3-ene-1,5-diynes



accessible from the commercially available alkadiynes **45** (Scheme 9). Should conditions to allow low-temperature cyclization be developed, they might also be amenable to production of C-9 enediyne [X = CH_2] in addition to the more heavily studied C-10 [X = CH_2CH_2] and C-11 enediynes [X = $CH_2CH_2CH_2$].

In initial experiments, employing typical conditions for intermolecular coupling, only regenerated starting material could be isolated from the workup mixtures (Table 3, entries 1 and 2). By increasing the reaction temperatures from −85 to −45 °C however, moderate yields of the desired cyclic species **47** could be obtained, along with varying amounts of starting material, together with intermolecular coupling products (entry 3). As in the case of the intermolecular variant of this reaction, the hindered LiHMDS proved to be the base of choice—substitution for LDA, lithium-2,2,6,6-tetramethyl piperidine (LTMP), NaHMDS, or KHMDS resulting in lowering of the overall yields of the desired products (entries 3−9). A key feature for increasing efficiency of the cyclization proved to be the concentration of the carbenoid destabilization agent,[7] and when the ratio of additive/base was increased from 1:1 to 10:1 moderate yields of product were produced with a variety of different agents. However, optimal conditions were found to involve slow addition of base to a premixed solution of substrate/additive (method C), resulting in near quantitative formation of the enediyne product (entry 15).

In some instances intermolecular reactions served to lower the yields of the desired cyclic species. Where this was found to be the case, the yields of the desired products could generally be improved by increasing the dilution of the reaction medium. Because of the thermal instability of **47** (X = CH_2), in situ protection as its cobalt carbonyl complex was effected, by adding dicobalt octacarbonyl to the (predried) workup solvent mixtures (Et_2O containing THF from the cyclization). This

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Table 3. Preparation of Cyclic Enediynes and their Complexes **48** via Coupling Dibromides **46**

entry	X	hal	base	equiv	additive	equiv	temp	method[a]	%**47**	%**48**	%**50**
1	CH_2 CH_2	Br	LiHMDS	2.2	NA	1.1	−78	A	<1	∼	∼
2	CH_2 CH_2	Br	LiHMDS	2.2	HMPA	1.1	−85	B	0	∼	∼
3	CH_2 CH_2	Br	LiHMDS	2.2	HMPA	1.1	−45	B	14	∼	∼
4	CH_2 CH_2	Br	LiHMDS	4	HMPA	1.1	−45	B	15	∼	∼
5	CH_2 CH_2	Br	LiHMDS	2.2	HMPA	10	−45	B	20	∼	∼
6	CH_2 CH_2	Br	NaHMDS	2.2	HMPA	10	−45	B	15	∼	∼
7	CH_2 CH_2	Br	KHMDS	2.2	HMPA	10	−45	B	5	∼	∼
8	CH_2 CH_2	Br	LDA	2.2	HMPA	10	−45	B	10	∼	∼
9	CH_2 CH_2	Br	LTMP	2.2	HMPA	10	−45	B	15	∼	∼
10	CH_2 CH_2	Br	LiHMDS	2.2	TPP	10	−45	B	22	∼	∼
11	CH_2 CH_2	Br	LiHMDS	2.2	TMEDA	10	−45	B	10	∼	∼
12	CH_2 CH_2	Br	LiHMDS	2.2	DMPU	10	−45	B	8	∼	∼
13	CH_2 CH_2	Br	LiHMDS	2.2	DMI	10	−45	B	10	∼	∼
14	CH_2 CH_2	Br	LiHMDS	2.2	HMPA	10	−45	B	8	∼	∼
15	CH_2 CH_2	Br	LiHMDS	2.2	TEP	10	−45	C	95	∼	∼
16	CH_2 CH_2	Br	LiHMDS	2.2	HMPA	10	−45	D	∼	92	∼
17	$CH_2CH_2CH_2$	Br	LiHMDS	2.2	HMPA	10	−45	B	12	∼	∼
18	$CH_2CH_2CH_2$	Br	LiHMDS	2.2	HMPA	10	−45	C	90	∼	∼
19	CH_2	Br	LiHMDS	2.2	HMPA	10	−45	D	∼	11	55
20	CH_2	Br	LiHMDS	2.2	HMPA	10	−45	C	∼	∼	89

[a] Method A: base added to **46**; method B: base + additive added to **46**; method C: base added to **46** + additive; method D: as method C, then immediate complexation with Co_2CO_8.

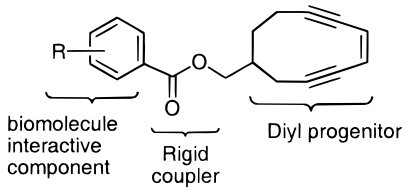

Figure 2.

allowed chromatographic purification of the masked enediynes **48** where necessary, and more importantly, permitted shelf-storage for extended periods. The process was successful for the C-11 and C-9 enediynes, but in the latter case, concomitant cycloaromatization to produce **50** mandates isolation as the cobalt complex (entries 19 and 20). The isolation of this C-9 enediyne complex is noteworthy, constituting the first synthesis of this interesting species, the Bergman cycloaromatization profile of which has yet to be studied.[21]

With an efficient synthesis of cyclic enediynes secure, we turned our attention to the preparation of cyclic enediynes which can be potentially tethered to molecules with specific biomolecular targets. For DNA binding agents, several investigations of this nature have been reported, that used an eclectic mix of protocols to synthesize the desired cyclic enediyne component.[22] Encouraged by the near quantitative yields of **48** obtained following optimization of the cyclization−complexation strategy, we turned our attention toward incorporation of this methodology in the preparation of shelf-stable synthons (Figure 2).

We opted to synthesize a preformed C-10 cyclic enediyne with a functionalized spacer group attached, then couple this unit to an aryl moiety via its cobalt carbonyl complex. A route was thus developed for the synthesis of appropriate complexes (Scheme 10). Commercially available methyl-5-hexynoate (**51**) was first converted to diyne **52**. Hydroxymethylation gave key diol **53**, which when followed by bromination allowed carbenoid coupling to give the desired enediyne **54** in high yield. For practical purposes it was immediately protected as the corresponding cobalt carbonyl complex. Alternatively, it was found that in situ deprotective bromination of **53** gave rise to the corresponding tribromide, which itself underwent cyclization to give the isolatable bromoenediyne in moderate yield, and which could likewise be converted to the complex (**56**). The key deprotection of the *tert*-butyldimethylsilyl ether of the cobalt carbonyl complex derived from **54** was then investigated. Initial concerns regarding the acid sensitivity of the cobalt moiety proved to be unfounded; conventional conditions (TsOH/MeOH/25 °C) successfully afforded the corresponding alcohol **55** in high yield.

Routine functional group interconversions such as Swern oxidation to the aldehyde **57** (72%), displacement to give the bromide **56** (84%), or esterification to give **58** were not impeded by the cobalt carbonyl group. In principle, these species offer a variety of regimens for attachment to biomolecule binding agents to be pursued, allowing the development of libraries of hybrid enediynes *using shelf-stable precursors*. Prior to initiating these studies, we wished to confirm the ability of the enediyne core itself to undergo cycloaromatization. Accordingly, substrate **55** was subjected to decomplexation. We had previously found that tetrabutylammonium fluoride (TBAF) is an effective agent for this transformation using linear enediynes,[23] and were delighted to observe that quantitative deprotection at low-

(21) For computational analysis of cyclic enediynes see: Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 5367.

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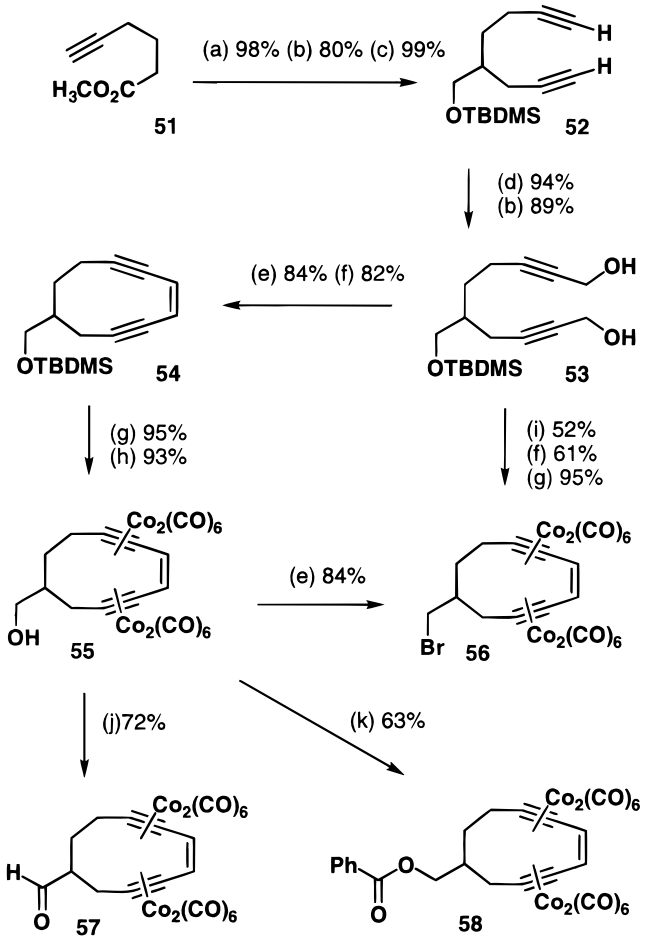
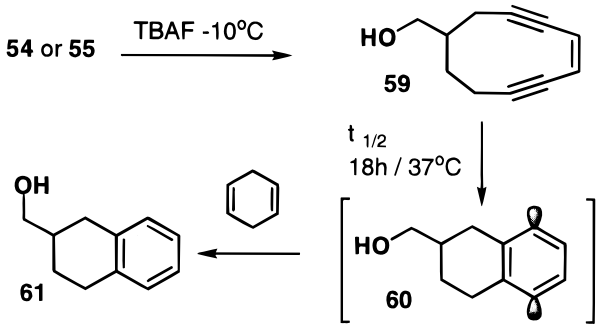
Scheme 10. Carbenoid Route to Cyclodec-3-ene-1,5-diynes[a]



[a] Conditions: (a) LDA, propargyl bromide; (b) LAH, Et_2O; (c) TBDMSCl, imidazole, DMF; (d) *n*BuLi, EtOCOCl; (e) $Ph_3P{:}Br_2$/2,6-lutidine; (f) LiHMDS/HMPA/THF; (g) $Co_2(CO)_8$; (h) TsOH/MeOH; (i) $Ph_3P{:}Br_2$; (j) $(COCl)_2/Et_3N$/DMSO; (k) $PhCOCl/Et_3N$.

Scheme 11. Cycloaromatization of C-10 Enediyne



temperature ensued, to give enediyne alcohol **59** (Scheme 11). As expected, analogous reaction with freshly prepared enediyne **54** also produced this product. Using an NMR-based assay, the half-life of this enediyne was determined to be 18 h at physiological temperature, giving adduct **61** on trapping with 1,4-cyclohexadiene. The identity of this adduct was confirmed by comparison with a sample obtained from reduction (lithium aluminum hydride (LAH), THF) of commercially available

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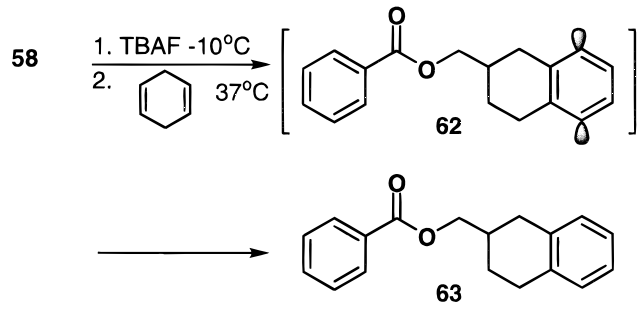
Scheme 12. Proof of Principal for Arene-enediyne Library Design



tetrahydronaphthoic acid. A similar protocol was then applied to the ester **58**, resulting in cycloaromatization of the aryl-enediyne conjugate to give **63**, isolated in high yield following incubation with 1,4-cyclohexadiene (Scheme 12), and identical with authentic material prepared from **61** ($PhCOCl$, Et_3N).

These short sequences establish the concept of taking a thermally stable enediyne complex and attaching the diyl progenitor to a molecule (arene) with potential affinity for a biomolecular target. The biological effects of enediyne-derived diyl radicals have been the focus of intense research over the last decade. In addition to DNA cleavage, diyl-induced proteolysis has also been reported,[24] suggesting that numerous targets may be envisioned. Extensions of the current work to develop affinity cleavage systems, by preparing sequence-specific hybrids is underway. Because the Bergman cycloaromatization proceeds via a late-state transition state, a reasonable strategy will be to screen cycloaromatized products (more elaborate analogues of **63**, available by coupling alcohol **61** with appropriate arenes) for affinity to specific biological targets. Once identified, the corresponding enendiyne *precursor* to it can then be investigated for its ability to induce cleavage of that target. The efficiency with which shelf-stable enediynes **55**−**58** can be produced will afford considerable flexibility to such a screening process, and a number of applications are anticipated.

Conclusion

The carbenoid coupling of lithiated propargylic halides was studied and optimized to give ready access both to linear and cyclic enediynes. Direct application of the chemistry can be expected both in the design of antitumor agents and in the preparation of enediyne nanomaterials.[25] The chemical efficiency and mildness of the process, coupled with predictable stereochemical control, render it an attractive alternative to conventional methods for the preparation of enediynes. Indeed in some instances no comparable alternate route exists, justifying its place in the synthetic arsenal.

Acknowledgment. We acknowledge the efforts of Aiwen Li, Dennis Parrish, Brant Chapman, Mark Whitten, and Farid Fouad in the preparation of the substrates used for the carbenoid couplings. This work was generously supported by the National Institutes of Health [R01GM57123].

Supporting Information Available: Full experimental details for all compounds described herein, together with associated ^{13}C NMR spectra for all enediyne products (PDB). This material is available free of charge via the Internet at http://pubs.acs.org.

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