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A Mild and Efficient Route to the Pharmacophore of the Enediyne Antitumor Agents - (Z)-1,6-[Bis (trimethylsilyl)]-Hex-3-ene-1,5-diyne *via* a Novel Carbenoid Coupling Reaction

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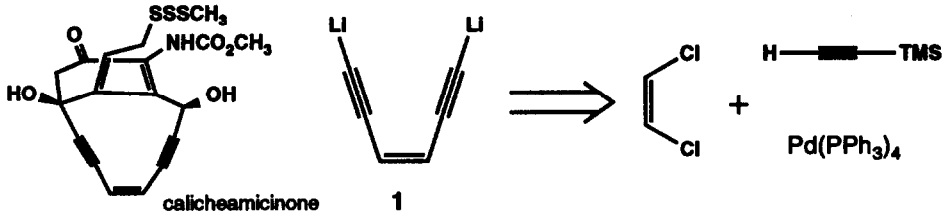
Abstract: (Z)-1,6-[Bis (trimethylsilyl)]-hex-3-ene-1,5-diyne has been prepared in high yield and in one pot from trimethylsilylpropargyl bromide by a remarkably stereoselective tandem carbenoid coupling-HX elimination sequence.

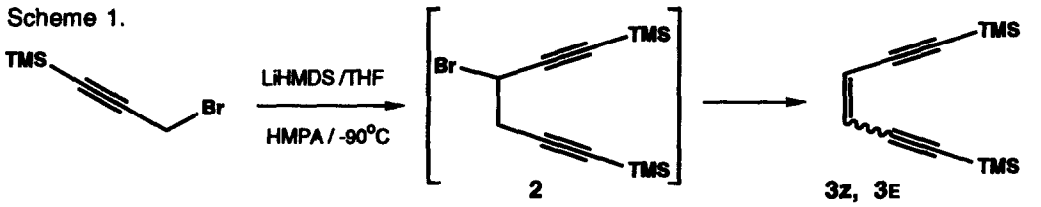
The unusual hex-3-ene-1,5 diynyl group represents the pharmacophore of a number of bioactive enediyne antitumor agents, it being the progenitor of the Bergman cyclisation cascade which ultimately leads to DNA strand scission *via* diyl radical attack.[1] In Danishefsky's elegant synthesis of calicheamicinone, the dilithio enediyne **1** was utilized to introduce this important functionality.[2] Ongoing research in our laboratories concerned with the development of bioactive enediyne mimics[3] has required large quantities of **1** and its protected form viz (Z)-1,6-[bis (trimethylsilyl)]-hex-3-ene-1,5-diyne **3z**, and while an adequate method for their synthesis currently exists,[4] the requirement for Z-dichloroethene and a palladium based acetylenic coupling renders practical scale synthesis prohibitively expensive. For these reasons, we initiated research aimed at securing a mild and *inexpensive* route to **3z** and thus **1** and reasoned that, by proceeding through a series of HX losses - first in an intermolecular condensation and then in an intramolecular elimination *via* intermediate species **2**, the desired enediynes could theoretically be accessed from trimethylsilylpropargyl bromide using a carbenoid coupling protocol.[5]



Trimethylsilylpropargyl bromide was thus prepared from propargyl alcohol *via* standard procedures[6] and treated with a variety of bases to encourage coupling. Our premise proved correct, and initial results showed lithium amide bases to be promising in the envisioned coupling sequence. A series of experiments were thus run to determine the desired stoichiometry in order to maximize formation of **2** and **3Z/E** (Table 1). Butyllithium had proven ineffective for the coupling reaction (entry 1). Using LDA

however, substantial quantities of bromide **2** were recovered at low to moderate conversion, together with

Scheme 1.



quantities of **3z/E** in varying ratios, a consequence of *in situ* elimination (entries 2-4). *When LiHMDS was exposed to trimethylsilylpropargyl bromide however, the desired product* **3** *was formed directly and in high yield - regardless of the amount of base used - with the major isomeric product being Z (entries 5-7).* In fact, when excess trimethylsilylpropargyl bromide was used to deliberately halt the reaction at the intermediate bromide **2** (e.g. entry 5), the amount of **2** so produced was virtually undetectable by ^{1}H and ^{13}C NMR. Furthermore, the reactions proved insensitive to minor variations in temperature and in the rate of base addition in contrast to results obtained with LDA.

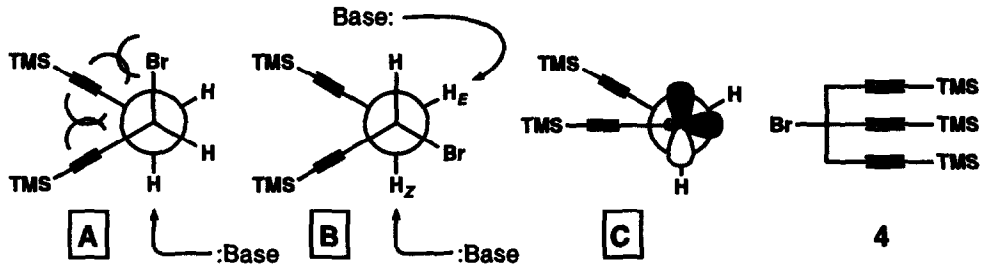
Table 1. Carbenoid Coupling of Trimethylsilylpropargyl Bromide Using Lithium Bases

#	Base	(equiv.)	Solvent	% Conversion to **2**	% Conversion to **3**	% Yield[a,b] of **2**	% Yield[a,b] of **3**	Z : E
1[c]	BuLi	1.1	THF	-	-	0	0	-
2	LDA	1.0	THF	-	-	< 5	< 10	1 : 1
3	LDA	0.5	THF	25.6	15.6	26 (75)	30	1 : 2.32
4	LDA	0.25	THF	32.4	00.0	64 (98)	0	-
5	LiHMDS	0.5	THF	0	43.7	0	85	2.24 : 1
6	LiHMDS	2.0	THF	0	94	0	94	2.15 : 1
7	LiHMDS	1.1	THF	0	67	0	64	1.93 : 1
8	LiHMDS	1.1	Hex. / THF	5	3	-	-	Z < E
9	LiHMDS	1.1	THF / HMPA	0	**100**	0	96[d]	2.11 : 1
10[e]	LiHMDS	1.1	THF / HMPA	0	**100**	0	92	1.83 : 1

[a]( ) based on recovered trimethylsilylpropargyl bromide; [b]Percent yields for entries 3, 4, & 5 are relative to the base as the limiting reagent; [c]Products resulting from halogen-metal exchange and butyl substitution were detected; [d]Column chromatography gave isomerically pure Z (60%) and E (28%); [e]Coupling of trimethylsilylpropargyl iodide.

Entries 5-7 of Table 1 bear special attention: In each case, an unaccountably large quantity of starting material was found to be present in the crude product mixture. This was in spite of the fact that the coupling reaction appeared to proceed rapidly and no side-products (which could conceivably consume base) were detected. Even when a large excess of base was used (entry 6), this excess material was not destroyed (expected given the inherent frailty of monohalo carbenoids) but instead recovered intact. Since LiBr has been reported to have a stabilizing effect on similiar carbenoids,[7] it seemed reasonable that this was likely responsible for our

problems. The carbenoids generated during the early stages of the reaction are produced in an environment free of this salt and are thus transient species - undergoing spontaneous 'condensation' with other *non-lithiated* molecules of trimethylsilylpropargyl bromide. However, as the reaction proceeds the reaction medium becomes increasingly enriched with LiBr and the carbenoids produced thus more stable. If the rate of coupling decreases substantially, the danger exists that all available trimethylsilylpropargyl bromide will be lithiated, leaving a deficit of electrophillic component. Initial attempts to remedy this situation by precipitation of the LiBr from nonpolar solvent mixtures proved ineffective, leading chiefly to recovered trimethylsilylpropargyl bromide (entry 8). However, since HMPA has been reported to have a *destabilizing* effect on carbenoids,[7] it seemed logical that such an additive could be used to cancel (or at least diminish) the stabilizing effects due to LiBr. When a THF solution of 1.1 equiv. LiHMDS and 1.1 equiv. HMPA was slowly added to a solution of trimethylsilylpropargyl bromide in THF at -90 °C, thus maintaining equal concentrations of HMPA and LiBr, **3** was formed cleanly, entirely free of starting material (entry 9).



Rationalization of the elimination sequence using conventional models reveals that the desired Z stereoisomer **3z** is clearly *not* the isomer predicted based on transition state considerations. The antiperiplanar model **A** for E2 elimination leading to **3z** suffers from severe gauche interactions. As a result, our initial plan was to seek a system such that a synperiplanar elimination (model **B**) predominated. Even so, it was anticipated that unfavorable isomeric mixtures would result (as was the case with LDA) unless a well-defined, rigid transition state could be constructed such that $H_{(E)}$ and $H_{(Z)}$ were clearly discriminated. However, since we could not satisfactorily explain the product distribution obtained with LiHMDS with either of these traditional models, the idea was entertained that β-elimination may not be responsible for the formation of **3z** but rather α-elimination by means of the formation and subsequent degradation of a second carbenoid, resulting in a *highly transient* carbene (model **C**). Such a carbene, if it formed, would be expected to undergo a rapid insertion into an adjacent C-H bond, yielding the observed product **3**. While this hypothesis remains unproven, supporting evidence has been uncovered: On occasion, trace amounts of an unanticipated side-product **4** has formed during the course of the reaction. This interesting triyne can be envisioned by deprotonation of **2**, with subsequent carbenoid interception by trimethylsilylpropargyl bromide. Furthermore, the elimination sequence is apparently insensitive to halide bulk, as similar Z:E ratios are obtained with the corresponding iodide (entry 10). Ongoing investigations probe both the scope and limitations of this potentially versatile coupling-elimination protocol and its subsequent application in the synthesis of enediyne antitumor agents.[8]

In summary, a highly efficient route to the key enediyne synthon **3z** and thus **1**[2] from trimethylsilylpropargyl bromide has been developed using a novel carbenoid coupling reaction. The process is amenable to large scale, and offers an inexpensive alternative route to the reported palladium coupling protocol. The method is likely to find wide application due to its simplicity, economy and large scale utility.

Experimental Procedure: (Z)-1,6-[Bis (trimethylsilyl)]-hex-3-ene-1,5-diyne (3z).
A solution of HMDS (1.15 mL, 5.5 mmol) in 10 mL THF was cooled to -10 °C and 2.03 mL of 2.71 M BuLi was added dropwise. After 0.5 h, 0.96 mL (5.5 mmol) of HMPA was added and the resulting solution was allowed to stir for an additional 5 min. before it was transferred by cannula over the course of 2.0 h to a magnetically stirred solution of 0.956 g (5.0 mmol) of trimethylsilylpropargyl bromide[6] in 20 mL THF at -92 °C (bath temp.). Upon completion of the base addition, the resulting enediyne solution was allowed to stir for a further 10 min. at -92 °C before it was poured, without warming, onto a slurry of crushed ice / sat. NH_4Cl. The product was extracted into ether and the ether extracts were washed successively with 10% HCl, H_2O, sat. $NaHCO_3$, and brine and then concentrated. Flash chromatography[9] on silica gel (0 to 2% Et_2O / hexane) gave 0.154 g (28 %) of the trans isomer as white crystals and 0.331 g (60%) of the cis isomer as a colorless oil, both spectroscopically identical to reported values.[4]

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References and Notes

1. For a review see Nicolaou, K. C. ; Dai, W. M. ; *Angew. Chem. Int. Ed. Engl.*, **1991**, *30*, 1387.
2. Haseltine, J. N. ; Cabal, M. P. ; Mantlo, N. B. ; Iwasawa, N. ; Yamashita, D. S. ; Coleman, R. S. ; Danishefsky, S. J. ; Schulte, G. K. ; *J. Am. Chem. Soc.*, **1991**, *113*, 3850. Dilithio enediyne **1** is available from **3z** via deprotection (K_2CO_3 / MeOH or LiOH - H_2O / THF) and metallation (nBuLi).
3. "Synthesis and Chemistry of Enediyne Templates" Graham B. Jones and Robert S. Huber, 45th South Eastern Regional ACS Meeting, Johnson City, TN, Oct 17-20, **1993** Abstract # 267; "Synthesis and DNA Cleaving Capacity of Novel Enediynes" Graham B. Jones and Jude E. Mathews, 45th South Eastern Regional ACS Meeting, Johnson City, TN, Oct 17-20, **1993** Abstract # 254.
4. Vollhardt, K. P. C. ; Winn, L. S. ; *Tetrahedron Lett.*, **1985**, *26*, 709.
5. Seyferth, D. ; Lambert, R. L. ; Massol, M. ; *J. Organometal. Chem.*, **1975**, *88*, 255; Brandsma, L. ; *Preparative Polar Organometallic Chemistry 2*, Springer-Verlag, 1990.
6. Prepared on 1 mole scale via silylation (nBuLi / TMSCl, 95%) and bromination (PPh_3 / Br_2, 89%).
7. Tarhouni, R. ; Kirschleger, B. ; Rambaud, M. ; Villieras, J. ; *Tetrahedron Lett.*, **1984**, *25*, 835.
8. Application of this protocol in the preparation of cyclic enediynes will be reported in due course.
9. Column chromatography is employed solely to remove the unwanted trans isomer - the isomeric mixture is essentially pure following standard workup.

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