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A Novel Approach to the Synthesis of Enediynes[1]

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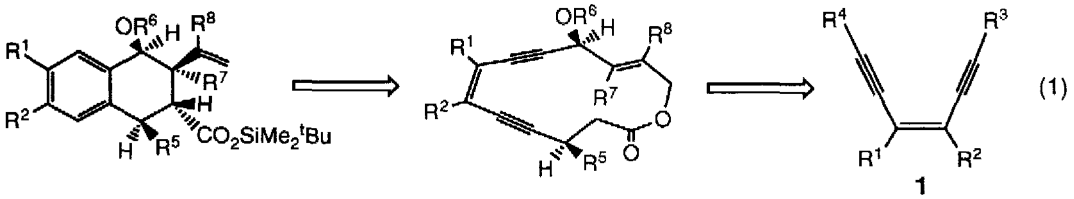
Key Words: Stannylcupration; 1-Phenylthio-1-alkynes; Vinylcopper-zinc Intermediates; Stannyl Enynes; Enediynes

Abstract: *A new method for the synthesis of enediynes is described based on stannylcupration of acetylene and certain activated alkynes, in situ reaction with 1-halo-1-alkynes, iododestannylation, and Pd(0)-catalyzed coupling with terminal alkynes.*

The unusual structure and the outstanding biological activity of the enediyne antitumor antibiotics such as neocarzinostatin chromophore,[2] calichemicin,[3a] esperamicin,[3b] and dynemicin[4] have recently provided new incentives for studying the synthesis and chemistry of unsaturated diyne systems.[5]

In connection with our efforts toward the development of new methodology for the stereoselective synthesis of tetrahydronaphthalene derivatives via tandem Claisen rearrangement and Bergman reactions, we required an efficient construction of substituted *cis*-3-ene-1,5-diynes **1** (eq 1). While several useful syntheses of conjugated enynes have been recorded,[6] a simple and general method for the synthesis of substituted[7] enediynes **1** has not been established. A very recent report one such a method by Zweifel[8] prompted us to communicate our preliminary results in this area.



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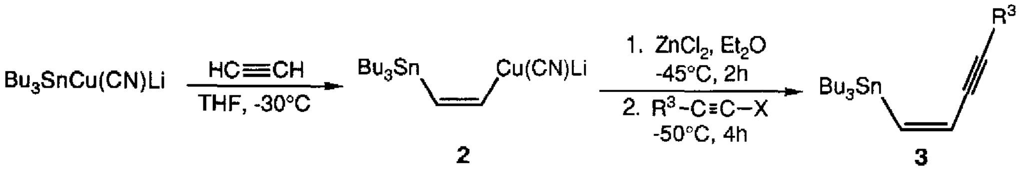
(1)

It was thought that stannylmetallation[9] of terminal or disubstituted alkynes followed by in situ reaction of the derived vinylmetal intermediates with 1-halo-1-alkynes might give rise to stannyl enynes which in turn could be readily transformed to the desired enediynes **1**. Encouraged by literature precedent and our own results on the *syn* stereoselectivity and regioselectivity exhibited by stannylcupration of terminal[10] and disubstituted alkynes,[11] we set out to examine the reaction of the Marino stannylvinyl cuprate **2**[12] with 1-bromo- and 1-iodo-1-alkynes[13] (eq 2).

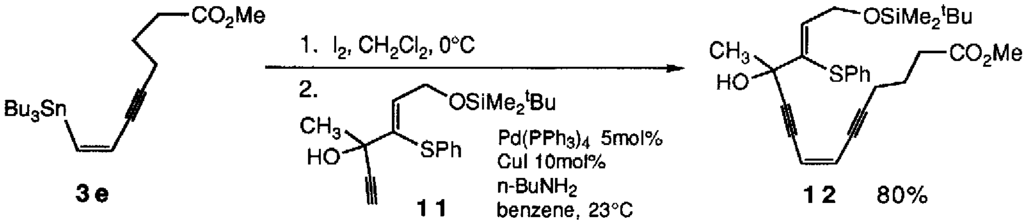


2 **3**

(2)

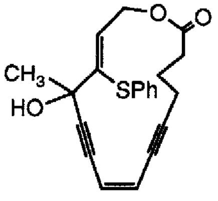
Initial experiments employing (iodoethynyl)trimethylsilane[14] (**4**) revealed that direct coupling with lower-order vinyl cuprate **2** is very inefficient, mainly leading (after workup[15]) to tributyltin iodide and smaller but variable amounts of stannyl enyne **3a** (Table I), tributylvinyltin, tributyltin hydride, and (trimethylsilyl)tributylstannylacetylene.[16] Subsequently, we were pleased to find that treatment of **2** with $ZnCl_2$ (1.1 equiv; 1.0 M in ether) at -40°C for 2h prior to addition of iodoalkyne **4** provided enyne **3a** in 60% isolated yield. It is possible that this greatly improved result is due to the increased effective concentration of the presumed vinylcopper-zinc intermediate.[17] On the other hand, oxidative addition of the latter to the C-I bond of **4** and/or reductive elimination to furnish **3a** might have become more facile under these conditions.

As shown in Table I, 1-halo-1-alkynes **5-10** participate equally well in this reaction. Entries 3 and 4 indicate that bromoalkynes may actually be better partners possibly due to their lower disposition toward metal-halogen exchange. A solution of CuCN in Me_2S was employed as the Cu(I) source instead of CuCN·2LiCl,[12] since we found that excess LiCl led to decreased yields of **3**.[18] In general, use of ZnI_2 produced slightly inferior results. The enediyne synthesis described herein is demonstrated by efficient iododestannylation of **3e** and Pd(0)-catalyzed coupling of the derived vinyl iodide with alkyne **11**[11b] providing **12** in 80% overall yield (eq 3).[19] Ultimate structural proof for **12** was obtained by X-ray analysis of enediyne lactone **13**[20] designed to serve as a model compound for studying the Claisen and Bergman rearrangements.



(3)

Stannylcupration of phenylthioacetylene[21] (THF/Me_2S, 1:1; -25°C), conversion of the resulting lower-order cuprate to vinylcopper-zinc intermediate (1.1 equiv $ZnCl_2$; -40°C, 2h), and reaction with bromoalkyne **9** (-40°C, 4h then warm to 0°C) gave rise to substituted stannyl enyne **3h** with complete regioselectivity (40% isolated yield). In turn, iododestannylation and coupling with the TBDMS ether of propargyl alcohol furnished differentially protected enediyne **14** (85% yield). Application of the same protocol to disubstituted acetylene **15**[11b,22] using **5** as the electrophile produced **3i** regioselectively but in rather low yield (20% overall). This latter result certainly represents further manifestation of the vexing problem associated with cabrocuprations[18] and stannylcuprations of internal acetylenes.



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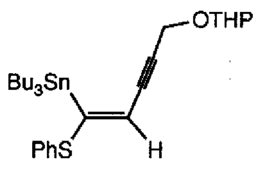
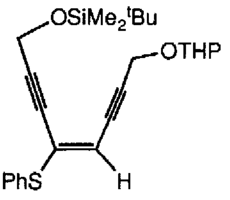


3h



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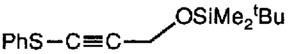

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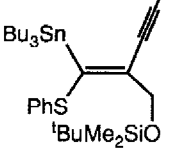

3i

In conclusion, the method described herein by virtue of its brevity and efficiency of the vinyl iodide coupling could prove useful for the synthesis of hetero substituted *cis* enediynes such as **14**, as well as enediynes **3** thus obviating the need for the relatively expensive *cis*-1,2-dichloroethylene. Work is in progress on rendering internal alkynes synthetically competent substrates.

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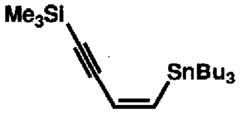
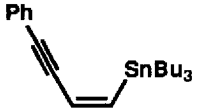
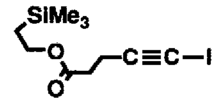
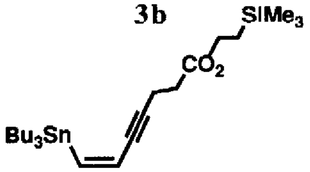
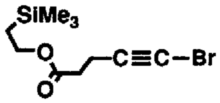
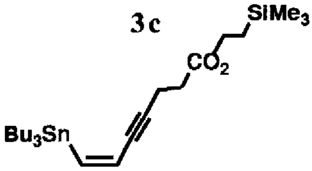
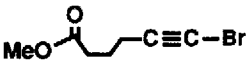
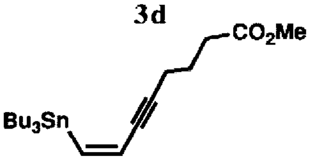
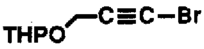
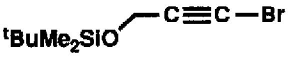
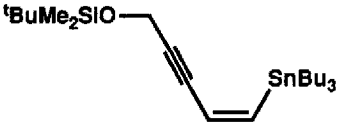
Table I

Entry	Haloalkyne[a]	Stannyl Enyne[b]	%Yield[c]
1.	$Me_3Si-C\equiv C-I$ 4	 3a	60
2.	$Ph-C\equiv C-Br$ 5	 3b	75
3.	 6	 3c	45
4.	 7	 3d	55
5.	 8	 3e	50
6.[d]	 9	 3f	58
7.	 10	 3g	65

[a] Haloalkynes **5-10** were prepared by treatment of the alkynes with *N*-bromo- or *N*-iodosuccinimide (1.2 equiv) and 10 mol% $AgNO_3$ (acetone, 25°C), see: Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 727; and purified either by distillation or flash chromatography. [b] All stannyl enyne products exhibited spectral properties (^1H NMR, IR, and/or GC/MS) in accord with the assigned structures. [c] Isolated yield after sg chromatography. [d] Tetrahydropyranyl ether.

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15. Workup procedure consisted of quenching the reaction mixture (after 4h at -50°C) with an aqueous solution of NH_4Cl/NH_4OH (4:1) followed by extraction with ether.
16. Product analysis was performed by a Hewlett-Packard 5970B GC/MS spectrometer. For useful reactions of vinylcopper-magnesium reagents with bromoalkynes or alkynyliodonium tosylates, see: ref 6d and 6k.
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19. Syntheses of various enediynes from stannyl enynes **3** will be reported in due course.
20. Prepared by desilylation, hydrolysis, and macrolactonization (DCC, pyridine, PPTS; $CHCl_3$, 60°C) of **12**.
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