

CONVERGENT APPROACH TO INTERMEDIATES USED FOR THE SYNTHESIS
OF THE ENEDIYNE STRUCTURE OF THE ESPERAMICINS AND CALICHEAMICINS

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Abstract: The diyne lithium acetylide **5** adds to 2-siloxy-2-cyclohexenone **6** followed by silyl migration to produce ketone adduct **7**, an intermediate towards a simple Esperamicin core

The disclosures of the structures of the Esperamicins¹ and Calicheamicins¹, representatives of a new class of extremely potent antitumor antibiotics, have resulted in a flurry of synthetic activity.² Efforts have been mainly aimed at the synthesis of bicyclo (7.3.1) tridecane aglycones or simpler monocyclic cores which contain the diyne functionality thought to be responsible for the DNA damaging properties of these cytotoxic compounds. Magnus has published a conceptionally elegant synthesis of the stable bicyclo (7.3.1) tridecane diyne **2**.^{2b} Recently an independent approach to **2** has appeared.^{2c} These communications represent pioneering efforts in the field and prompt us to report a convergent and more efficient synthesis of an advanced intermediate, common to both routes, which should prove useful for future studies.

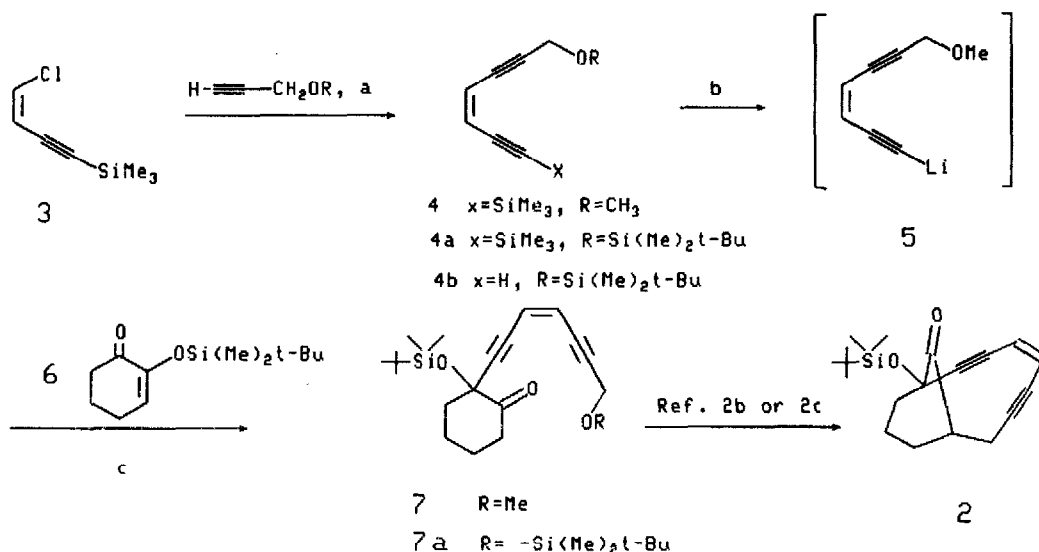
Both of the published routes to **2** (as well as a synthesis of an alternate core by Kende)^{2e} involve a stepwise linear elaboration of a diyne system onto a functionalized cyclohexenone. Herein we report the addition of preconstructed diyne acetylide **5**, containing a suitably functionalized propargylic carbon, to 2-tertbutyldimethyl silyloxy-2-cyclohexenone (**6**) which quickly generates the advanced protected intermediate **7** in a single step. Interestingly, Danishefsky has synthesized a highly functionalized core based on the dilithio anion of the parent 1,5-hexadiyne-3-ene.^{2a}

The diyne **4** is assembled by standard Castro-Stephans palladium coupling³ from the known^{2e} *cis*-chloro eneyne **3** on decagram scale (Scheme 1). The trimethylsilyl acetylene protecting group was removed *in situ* prior to anion generation due to the presumed volatility of deprotected **4**. The anion **5** is prepared using a procedure similar to that developed by Danishefsky for generation of the parent dilithiodiyne^{2d}. Addition of 1.1 eq of **6** to anion **5** in THF at -78°C followed by slow warming to 25°C cleanly generates ketone **7** in 52% yield along with recovered ketone starting material after purification by flash chromatography. The acetylide addition initially provides an intermediate silyl enol ether acetylene adduct which can be isolated at -15°C. Further warming to 25°C allows for complete silyl migration to give the desired product **7**.⁴ Ketone **6** is prepared in essentially quantitative yield on a 30g scale by reacting 1,2-cyclohexanedione with TBDMSOTf/Et₃N in THF at -78°C to 25°C followed by filtration through silica gel.

The efficiency of the addition reaction can be increased by utilization of a less volatile diyne, propargyl silyl ether **4b**, which was prepared from **4a** and purified on a

multigram scale. Lithiation of **4b** [1.2eq.(TMS)₂NLi, THF, -78°C/15min] followed by addition of **6** and warming to 25°C, produced **7a** in 87% yield.⁵ We have successfully converted our synthetic material **7** into **2** using either of the literature routes^{2a,b} and are now in the process of using substrates containing different propargyl substituents for the Magnus cyclization reaction.

SCHEME 1



a) 3% Pd(PPh₃)₄, 5% CuI, 2eq. n-BuNH₂, PhH, 25°, 4h, 71%. b) 1) LiOH, 9:1 THF/H₂O, 25°, 2h. 2) Pentane extract then Na₂SO₄. 3) 1,10 Phenanthroline, THF, 0° then BuLi until dark. 4) 1.1eq LiN(TMS)₂, -78° c) **6**, -78° to 25°, then H₂O, 52% for b and c after chromatography.

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REFERENCES AND NOTES

- See references contained in reference 2c.
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- The yield of **7** from 1,2-cyclohexanedione via our route is 50%, while the reported yields for references 2b and 2c are 29% and 31% respectively.
- New compounds **4**, **4a**, **4b**, **6**, and **7** have been fully characterized spectroscopically and by elemental analysis.

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