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A NEW SYNTHETIC APPROACH TO ENEDIYNES RELATED TO THE NEOCARZINOSTATIN CHROMOPHORE FROM α-TRIMETHYLSILYL α-ALLENYL CARBONYL COMPOUNDS

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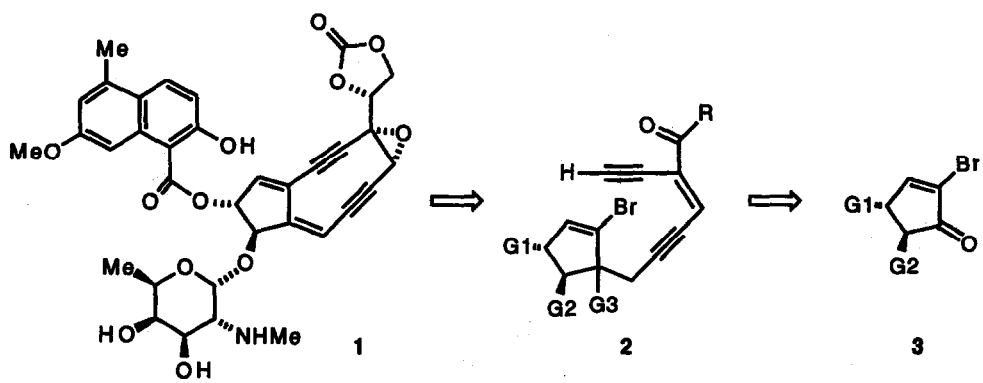
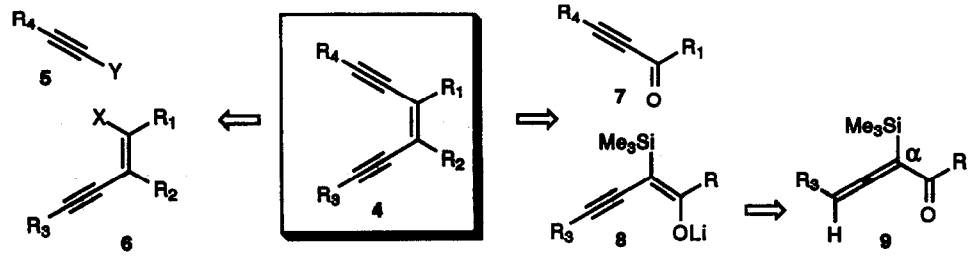
Abstract: A new synthetic approach to acyl-substituted enediynes from α-trimethylsilyl α-allenyl carbonyl compounds and propargylic aldehydes is described. This process allows the rapid construction of enediyne derivatives containing vinyl halide groups, suitable for the synthesis of the neocarzinostatin chromophore.

The unusual structures, potent activities and novel mode of action of the enediyne anticancer antibiotics have propelled them into the forefront of chemical and biomedical research.[1] Central to the synthesis of naturally occurring and designed analogs of this class of molecules is the construction of the enediyne moiety, which occurs in the structures of the calicheamicins, the esperamicins and the dynemicins, and is responsible for their remarkable bioactivities.[1] Although the other member of this class of molecules, the neocarzinostatin chromophore (NCS)[1,2,3] (**1**), does not contain an enediyne unit, this compound can be retrosynthetically related to an acyl enediyne precursor (**2**), which can be prepared from a cyclopentenone (**3**).[4]

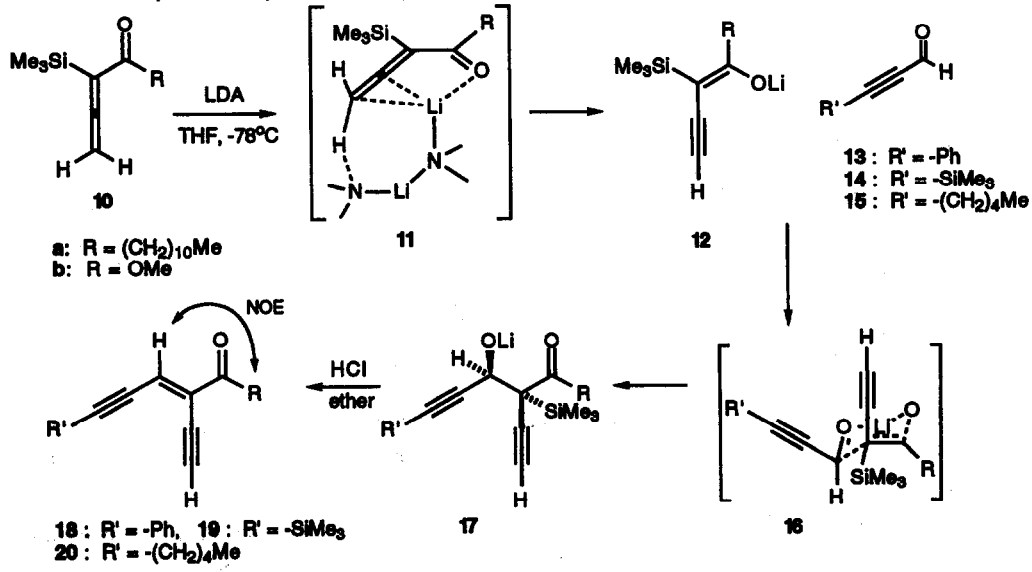


Most synthetic approaches to enediynes[1] (**4**) have utilized the Pd-mediated coupling between vinyl halides (**6**, X=Cl, Br, I) and alkynes (**5**, Y=H)[3b,5] or between vinyl stannanes (**6**, X=$SnBu_3$) and alkynyl halides (**5**, Y=Br, I).[6] Other methods have relied on the Ramberg-Backlünd reaction,[7] the dehydrogenation of 1,5-diynes,[8] and the dehydration of alcohols derived from an allylchromium addition to aldehydes[3d] or a [2,3]-Wittig rearrangement.[3d,3u] Herein, we report a new approach to acyl-substituted enediynes (**4**, R_1=H, R_2=RCO) involving the reaction of propargylic aldehydes (**7**, R_1=H) and ynenolates (**8**) derived from α-trimethylsilyl α-allenyl carbonyl derivatives (**9**). We also demonstrate the suitability of this method for the rapid synthesis of NCS-precursors, such as **2**.

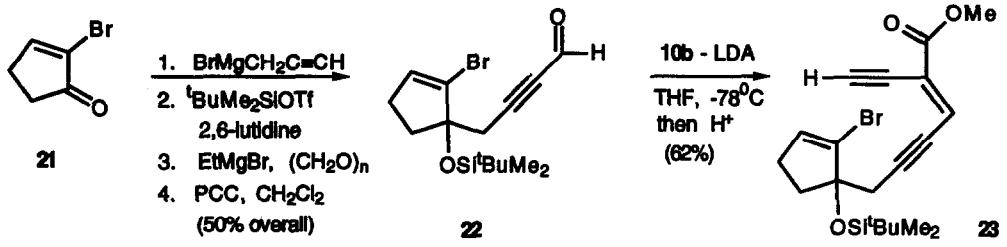


We have recently found[9] that enolization of α-allenyl ketones takes place selectively at the α-position and the resulting cumulenolates react with carbonyl compounds to form α-aldols. As a continuation of this work we studied the enolization of α-trimethylsilyl-α-allenyl ketone **10a**[10] and the related ester **10b**.[11] The presence of the α-trimethylsilyl group blocks the α-position for enolization, making the abstraction of Hγ more favored. Furthermore, the resulting silicon-stabilized enolate anion can participate in the Peterson olefination.[12]

Indeed, deprotonation of **10a** or **10b** with LDA in THF at -78°C followed by reaction of the resulting enolate (**12**) with propargylic aldehydes **13-15** and addition of HCl in ether at low temperature gave the (E)-enediynes **18a** (60%), **18b** (52%), **19b** (35%), and **20b** (58%). The stereochemistry of **18a** was determined by the NOE effect among the vinylic H and α-CH_2, while a NOESY NMR experiment on a 7:1 E/Z mixture of **18b** indicated that the major isomer had the (E)-geometry. The high stereoselectivity observed in this process can be attributed to the preferential formation of the (E)-enolate (**12**), formed via a transition state such as **11**, which invokes the dimeric nature of the base[13] and a *complex-induced proximity effect*.[14] Addition of enolate **12** to the aldehyde is expected to proceed via transition state **16**, which minimizes steric interactions, leading to the alkoxysilane derivative **17**. Finally, protonation of **17** and subsequent acid-mediated elimination is expected to proceed in an *anti*- fashion[12,15] giving **18-20** as the major products.



Encouraged by the above results we embarked on a synthetic approach to the neocarzinostatin chromophore based on this chemistry. As a model study we pursued the synthesis of acyl-enediyne **23** from 2-bromocyclopentenone (**21**).[16] This compound was converted to aldehyde **22** via addition of propargylmagnesium bromide, silylation, homologation and oxidation. Reaction of **22** with the enolate derived from ester **10b** gave the enediyne derivative **23** in 62% isolated yield.



A noteworthy feature of this approach to molecules such as **23** is that it allows the presence of the vinyl halide moiety during the assembly of the enediyne system, allowing it to be used in subsequent Pd-mediated processes. For example, Pd-mediated cyclization may allow the rapid construction of cyclic enediyne derivatives, including the neocarzinostatin chromophore ring system. Further work in this direction is currently in progress.

The one-step conversion of propargylic aldehydes to enediynes reported herein may facilitate the incorporation of this important functionality into a variety of analogs for biological studies. The increasing realization that molecules much simpler than the naturally occurring enediynes may be required for potent and selective anticancer activity[17] gives a greater significance to the development of short and efficient methods for the synthesis of these molecules.

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