Pergamon

Tetrahedron Letters 39 (1998) 5549–5552

TETRAHEDRON LETTERS

A New Route to Cumulenes by Stannylation-Deoxystannylation of Propargylic Alcohols. Application to Synthesis of Conjugated Enyne[3]cumulene as a Model Compound of Neocarzinostatin Chromophore

Yoshitaka Araki and Toshiro Konoike*

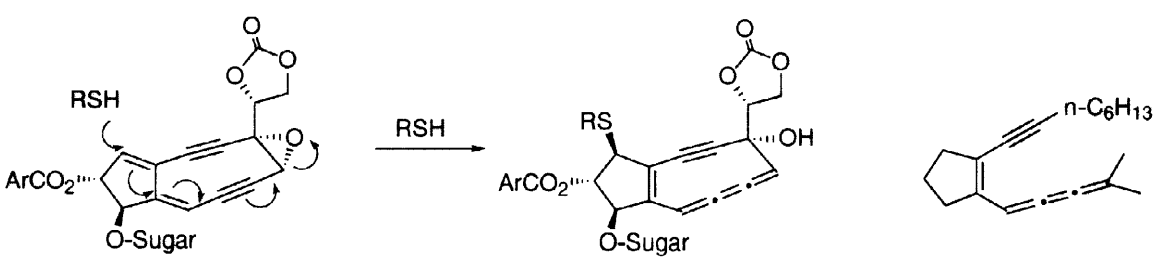
Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan

Received 18 March 1998; revised 25 May 1998; accepted 29 May 1998

Abstract: Sequential treatment of a propargylic alcohol by BuLi and Bu_3SnCl gave a mixture of stannylated propargylic alcohol and stannylated allenyl alcohol, both of which were converted to a single [3]cumulene by deoxystannylation of the stannyl alcohols by treatment with methanesulfonyl chloride and triethylamine. The efficiency of the deoxystannylation has been compared with that of an analogous silyl counterpart and proved to be much more efficient. The method has been applied to synthesis of conjugated enyne[3]cumulene **3** as a model compound of neocarzinostatin chromophore.

Keywords: Cumulenes; Tin and compounds; Silicon and compounds; Elimination reactions

[3]Cumulenes have attracted the attention of synthetic and theoretical chemists,[1] and recently have been postulated to be a key structural feature of the antibiotic neocarzinostatin (NCS) **1**, which was first reported in 1965 and exhibited strong antitumor activity.[2] The actual intermediate for cleaving DNA is thought to be cyclic enyne[3]cumulene **2**, which undergoes Myers cycloaromatization to form diradical species and abstracts hydrogen atom from the DNA sugar backbone.[3,4] [3]Cumulenes are generally unstable, and consequently, a simple and general method under mild conditions has been required for the synthesis of reactive and functionalized cumulenes such as **2**. There have been several methods for cumulene synthesis,[5] and several acyclic enyne[3]cumulenes were synthesized to develop novel DNA cleaving agents. The methods include 1,4-elimination of hydroxytrimethylsilane,[6] addition of thiol to dienediyn compounds,[7,8] and Horner–Wadsworth–Emmons type condensation of allenylphosphine oxides with ketones.[9] As an extension of our allene synthesis which utilizes facile deoxystannylation under mild conditions,[10] we report here a short and practical

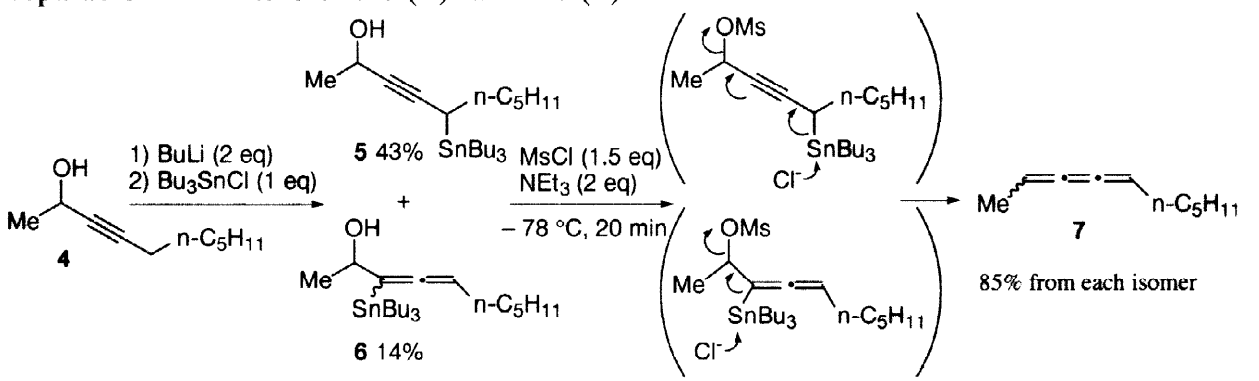


Neocarzinostatin chromophore **1** enyne[3]cumulene **2** model compound **3**

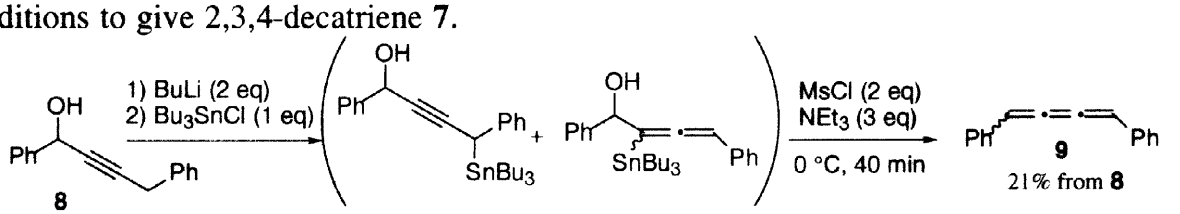
0040-4039/98/$19.00
PII: S0040-4039(98)01117-4

synthesis of [3]cumulenes from propargylic alcohols which employs the stannylation-deoxystannylation sequence.

Our method employs stannylation of propargylic alcohols and subsequent deoxystannylation of the resulting stannyl alcohols. 3-Decyn-2-ol **4**, prepared from 1-octyne and acetaldehyde,[11] was treated with two equivalents of BuLi, and the resulting dianion was treated with one equivalent of chlorotributyltin. A mixture of stannylated propargylic alcohol **5** and stannylated allenyl alcohol **6** was obtained owing to the propargyl and allenyl tautomerism of the carbanion. Their structures were confirmed by IR spectra; **5** (2200 cm^{-1} for acetylene) and **6** (1927 cm^{-1} for allene). Two isomers could be separated by silica gel chromatography, and they were treated with methanesulfonyl chloride and triethylamine in dichloromethane at –78 °C to give 2,3,4-decatriene **7** in 85% yield as an inseparable 1:1 mixture of the (*E*)- and the (*Z*)-isomers.



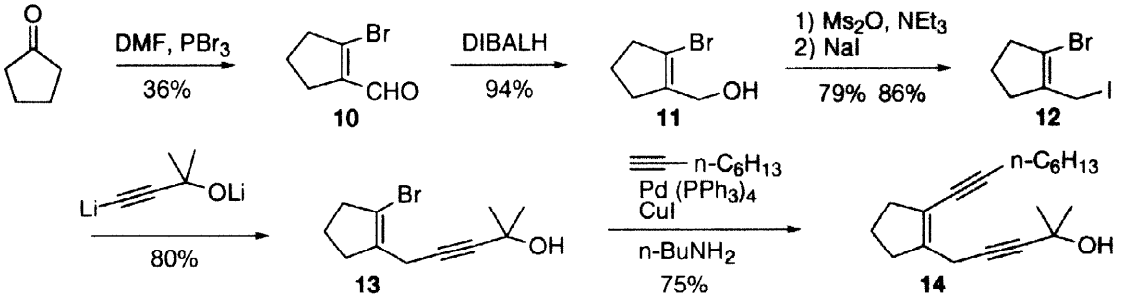
These results show that both 1,4-elimination of propargylic alcohol **5** and 1,2-elimination of allenyl alcohol **6** proceeded smoothly presumably by way of the mesylates of the alcohols under low temperature and almost neutral condition which is mild enough for the preparation of unstable **7**. The cumulene structure of **7** was confirmed by ^{13}C NMR spectra, which showed two pairs of four olefinic carbons at 101.89, 107.70, 159.82, 161.60 and 101.99, 107.83, 159.86, 161.74 ppm, however, (*E*)- and (*Z*)-configurations could not be determined for the two isomers. For a practical synthesis of cumulene, separation of the stannylated alcohols was not required, and the crude mixture was treated under the same conditions to give 2,3,4-decatriene **7**.



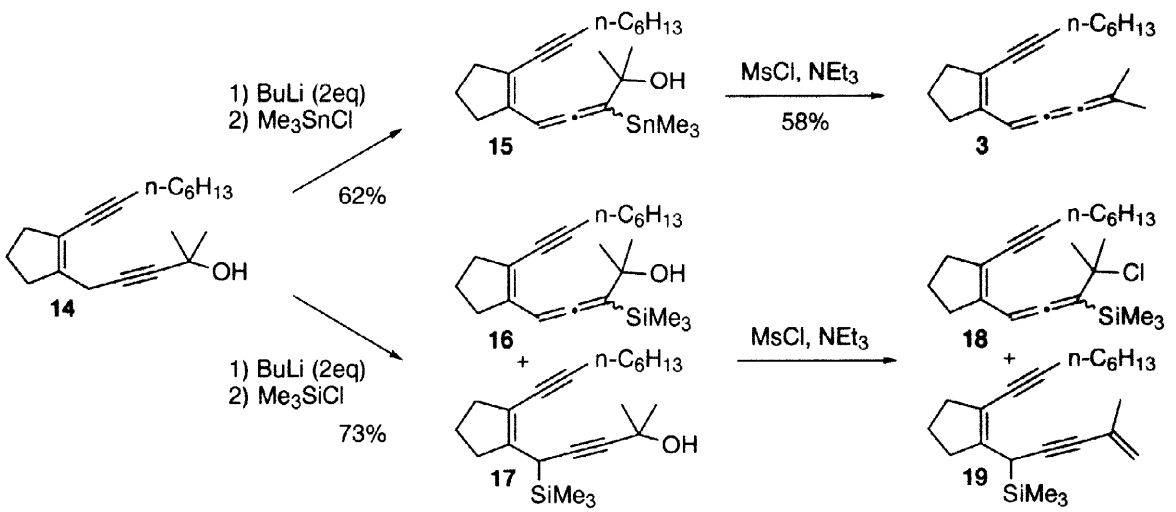
The versatility of this method was shown in the synthesis of 1,4-diphenyl-1,2,3-butatriene **9** by applying the same series of reactions starting from 1,4-diphenyl-2-butyn-1-ol **8**[12] in 21% yield without isolation of the intermediates.

Next, we exploited the stannylation-deoxystannylation sequence to prepare conjugated enyne[3]cumulene **3**. Treatment of cyclopentanone with Vilsmeier's reagent (PBr3 and DMF) gave bromoaldehyde **10**,[13] and the subsequent DIBALH reduction afforded alcohol **11**. This was transformed into iodide **12** by way of a mesylate, and the resulting allyl iodide **12** was condensed with the dianion derived from 2-methyl-3-butyn-2-ol and BuLi (2 equiv.) to give enynol **13**. Palladium-catalyzed coupling of vinyl bromide **13** with 1-octyne in the presence of copper iodide and butylamine afforded enediynol **14**.[14] When **14** was treated with two equivalents of BuLi followed by one equivalent of chlorotrimethyltin,[15]

only stannylated allenyl alcohol **15** was obtained. This was treated with methanesulfonyl chloride and triethylamine to give conjugated enyne[3]cumulene **3** in a moderate yield (58%).



Two groups recently reported similar [3]cumulene syntheses by Peterson type 1,4-deoxysilylation from 4-(trimethylsilyl)-2-butyn-1-ols.[6,16] In comparison with their methods, our cumulene synthesis has several advantages. Our starting material is a readily available common acetylene alcohol, however, in their methods, the starting propargylic trimethylsilane unit must be prepared beforehand. Only 1,4-elimination of hydroxytrimethylsilane was reported in their [3]cumulene synthesis, and both 1,4- and 1,2-deoxystannylations led to cumulene in our synthesis. In particular, 1,2-deoxystannylation of stannylated allenyl alcohol was unique because it involved cleavage of an sp^2-carbon–Sn bond. No example of similar 1,2-elimination of a silyl counterpart (1,2-deoxysilylation) has been known in cumulene synthesis, although the fluoride ion-induced 1,2-elimination of chlorotrimethylsilane from 1-chloro-2-(trimethylsilyl)-2-propene gave terminal allenes.[17]



To compare the facility of 1,2-deoxystannylation with deoxysilylation, we prepared the silyl counterpart **16** of **15** by applying the same sequence of reactions for propargylic alcohol **14** using chlorotrimethylsilane in place of chlorotrimethyltin. In this case, allenyl **16** and propargylic silanes **17** were obtained as an inseparable mixture. This mixture was subjected to the same reaction conditions for **15**, but the desired enyne[3]cumulene **3** was not obtained. Only chlorination and dehydration occurred. Chloride **18** can be obtained from allenyl silane **16** by nucleophilic substitution of the intermediate mesylate by chloride ion, and the dehydration product **19** from propargylic silane **17**. The different course of the silane from stannane observed above was ascribed to the fact that the Si–C bond is stronger

and shorter than the Sn–C bond.[18] Our enyne[3]cumulene synthesis has the additional advantage that cumulenes were obtained in a pure form without contamination from isomeric olefins, whereas, in an analogous silyl method by Wang and co-workers,[6] the obtained cumulene mostly contained the tautomeric byproduct. Our method is applicable to a variety of enyne[3]cumulenes by selecting combinations of propargylic alcohols and aldehydes.

In conclusion, we have shown that 1,4-elimination of stannylated propargylic alcohols as well as 1,2-elimination of stannylated allenyl alcohols effectively give [3]cumulenes. The entire process is carried out under mild conditions and can be used to synthesize reactive intermediates, exemplified by the synthesis of conjugated enyne[3]cumulene **3** as a model system of the NCS chromophore. Use of tin reagent proved to be more beneficial than the silicon counterpart because 1,4-elimination as well as 1,2-elimination proceeded effectively under the neutral reaction condition.

Procedure of enyne[3]cumulene **3** synthesis from propargylic alcohol **14** is as follows : to a solution of alcohol **14** (690 mg, 2.53 mmol) in THF (7 mL) was added BuLi (3.32 mL of 1.6 M hexane solution, 5.32 mmol) at –78 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 1.5 h, and after being cooled to –78 °C, Me_3SnCl (505 mg, 2.53 mmol) in THF (5 mL) was added dropwise. After being stirred at –78 °C for 1.5 h, the mixture was poured into ice and H_2O and extracted twice with EtOAc. Organic layers were washed with brine, dried, combined, and concentrated. The residual oil was purified by silica gel chromatography (toluene) to give stannylated allenyl alcohol **15** (688 mg, 62% yield). Alcohol **15** (131 mg, 0.3 mmol) was dissolved in CH_2Cl_2 (1.5 mL), and MsCl (70 μL, 0.9 mmol) and NEt_3 (138 μL, 1.2 mmol) were added at –78 °C. The cooling bath was removed, and stirring was continued at room temperature for 30 min. The mixture was poured into ice and 1 N HCl and extracted twice with EtOAc. Each organic layer was washed with saturated $NaHCO_3$ and brine, dried, and concentrated. The residual oil was purified by silica gel chromatography (hexane) to give enyne[3]cumulene **3** (44 mg, 58% yield). IR ($CHCl_3$) 2924, 2200, 2038 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, 3, J = 6.8), 1.2–1.6 (m, 8), 1.87 (quintet, 2, J = 7.3), 1.96 (s, 6), 2.41 (t, 3, J = 6.6), 2.5–2.6 (m, 4), 6.36 (br s, 1); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.07, 19.93, 22.40, 22.59, 24.29, 25.18, 28.64, 29.01, 31.41, 33.00, 37.67, 98.13, 99.61, 116.45, 122.31, 146.32, 152.04, 157.16; HR-LSIMS m/z 254.2011 M^+ (calcd for $C_{19}H_{26}$, 254.2035).

References and Note

[1] Kawase, T.; Muro, S.; Kurata, H.; Oda, M. *J. Chem. Soc., Chem. Commun.* **1992**, 778–779.
[2] Ishida, N.; Miyazaki, K.; Kumagai, K.; Rikimaru, M. *J. Antibiot.* **1965**, *18*, 68–76.
[3] Myers, A. G.; Proteau, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 1146–1147.
[4] For a review of related compounds, see: Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453–6518.
[5] Hopf, H. In *The Chemistry of Ketenes, Allenes, and Related Compounds*, Part 2; Patai, S. Ed.; Wiley & Sons: New York, 1980; pp 863–881.
[6] Wang, K. K.; Liu, B.; Lu, Y. -D. *Tetrahedron Lett.* **1995**, *36*, 3785–3788.
[7] Scheuplein, S.; Machinek, R.; Suffert, J.; Brückner, R. *Tetrahedron Lett.* **1993**, *34*, 6549–6552.
[8] Fujiwara, K.; Sakai, H.; Hirama, M. *J. Org. Chem.* **1991**, *56*, 1688–1689.
[9] Saito, I.; Yamaguchi, K.; Nagata, R.; Murahashi, E. *Tetrahedron Lett.* **1990**, *31*, 7469–7472.
[10] Konoike, T.; Araki, Y. *Tetrahedron Lett.* **1992**, *33*, 5093–5096.
[11] Solladié, G.; Adamy, M.; Colobert, F. *J. Org. Chem.* **1996**, *61*, 4369–4373.
[12] Copéret, C.; Sugihara, T.; Wu, G.; Shimoyama, I.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 3422–3431.
[13] Paquette, L. A.; Johnson, B. A.; Hinga, F. M. *Organic Syntheses*; Wiley & Sons: New York, 1973; Collect. Vol. V., pp 215–217.
[14] Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.
[15] Chlorotrimethylstannane was used as a stannylating reagent for simplifying the NMR spectra of the intermediates and for comparing the reaction of the trimethylsilyl counterpart as described in the following section.
[16] Chow, H. -F.; Cao, X. -P.; Leung, M. -K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 193–196.
[17] Chan, T. H.; Mychajlowskij, W.; Ong, B. S.; Harpp, D. N. *J. Org. Chem.* **1978**, *43*, 1526–1532.
[18] Omae, I. In *Organotin Chemistry*; Journal of Organometallic Chemistry Library 21; Elsevier Science: New York, 1989; p 19.