Tandem Enyne Allene–Radical Cyclization *via* [3,3] Sigmatropic Rearrangements

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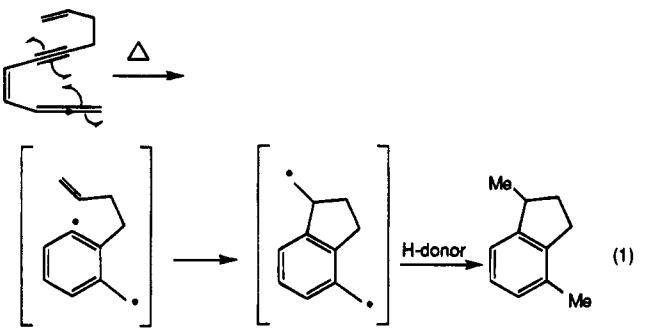
Summary: Enediynes **1**, **7**, **12**, and **16** undergo a tandem [3,3] sigmatropic shift–enyne allene cyclization. Enediynes **7** and **16** are especially interesting because after undergoing a [3,3] sigmatropic shift and enyne allene cyclization, the resultant biradical undergoes a 5-*exo* radical cyclization. These reactions can be effected by either heating at 150 °C or by treatment with silver salts followed by heating at 75 °C.

The enediyne antitumor antibiotics[1] have received much attention due to their interesting structures and mode of activation leading to the cleavage of DNA. In an effort to model the neocarzinostatin chromophore, Myers reported the cyclization of synthetic eneyne allenes to form the α,3-didehydrotoluene biradical.[2] In contrast to the Bergman cyclization,[3] which proceeds at temperatures greater than 150 °C, enyne allenes[2,4,5a,b] and enyne ketenes[6] will typically cyclize at 80 °C; some examples have been reported to cyclize at temperatures as low as 37 °C. The majority of the research in this area has focused on the synthesis and DNA cleaving ability of these enediynes and enyne allenes.[1,4] Less attention, however, has been given to using the intermediate diyl as a radical precursor for further radical cyclizations.[5,7–9]

Recently, we reported the tandem enediyne–radical cyclization for the preparation of 2,3-dihydrobenz[*e*]-indenes.[7] Although the thermolysis of enediynes proceeds in excellent yield, high temperatures (*ca.* 190 °C) are needed to effect the enediyne cyclization at a reasonable rate. In contrast, coupling an enyne allene cyclization with a radical cyclization would allow the construction of the benzindene system at much lower temperatures (eq 1). Herein, we report the tandem enyne allene–



(1)

radical cyclization, in which the enyne allenes are generated from [3,3] sigmatropic shifts.

Thermal cyclizations of enyne allenes generated from a [2,3] sigmatropic rearrangement have been previously reported.[4a-c] We have recently completed studies in which a [2,3] sigmatropic shift results in an enyne allene phosphine oxide which undergoes cyclization to give a radical which will participate in a cyclization to a pendent olefin.[8] The limitations of this method include the difficulty of synthesizing the precursors and the lack of methods to convert the phosphine oxide into a useful functionality. It is well precedented that allenes can be generated from their corresponding propargyl vinyl ethers *via* a [3,3] sigmatropic shift.[10] In order to utilize this strategy for the preparation of enyne allenes that can undergo cyclization, propargyl vinyl ether **1** was synthesized.[11]

Mild thermolysis of **1** at 150 °C in chlorobenzene in the presence of 1,4-cyclohexadiene (1,4-CHD) produced aldehyde **2** and tricyclic ether **3** as a 3:1 mixture in 56% combined yield (Scheme 1). The formation of **2** and **3** can be rationalized by two competing modes of reaction. Presumably the major pathway (route a) involves initial formation of enyne allene **4** *via* a [3,3] sigmatropic rearrangement followed by an enyne allene cyclization to form biradical **5** and hydrogen abstraction from 1,4-CHD to produce aldehyde **2**. The minor pathway (route b) proceeds through a tandem enediyne–radical cyclization (*via* biradical **6**) to form tricyclic ether **3**.

Knowing that an enyne allene could be constructed by a [3,3] sigmatropic rearrangement, the thermal cycliza-

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(11) The preparation of compounds **1**, **7**, **12**, and **16** is described in the supplementary material.

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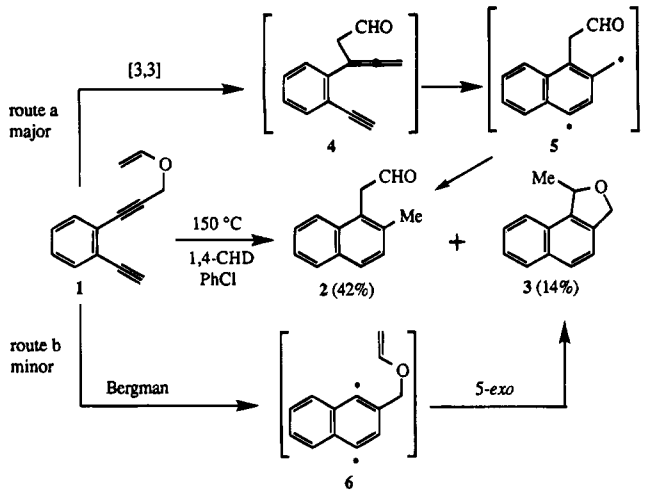
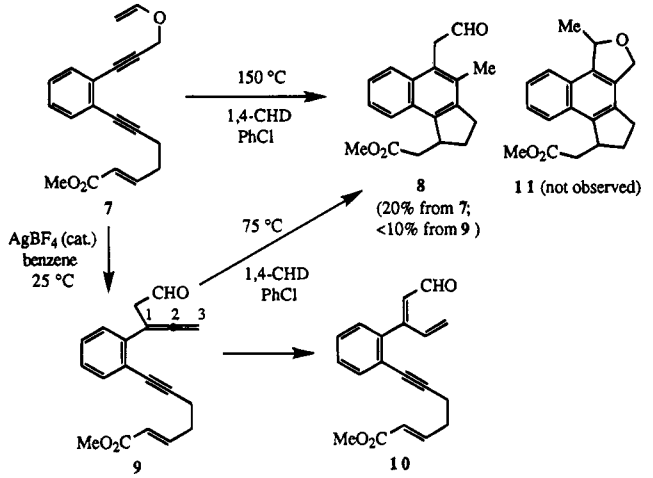
Scheme 1



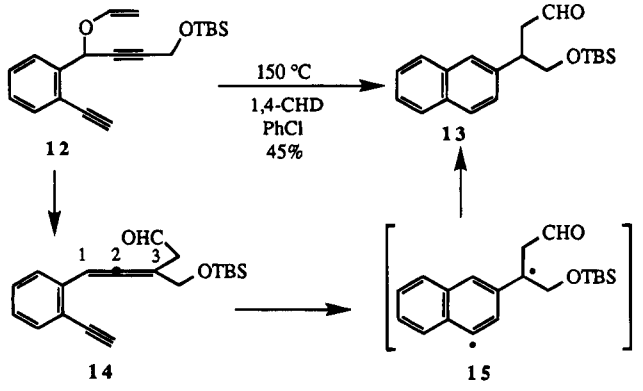
Scheme 2



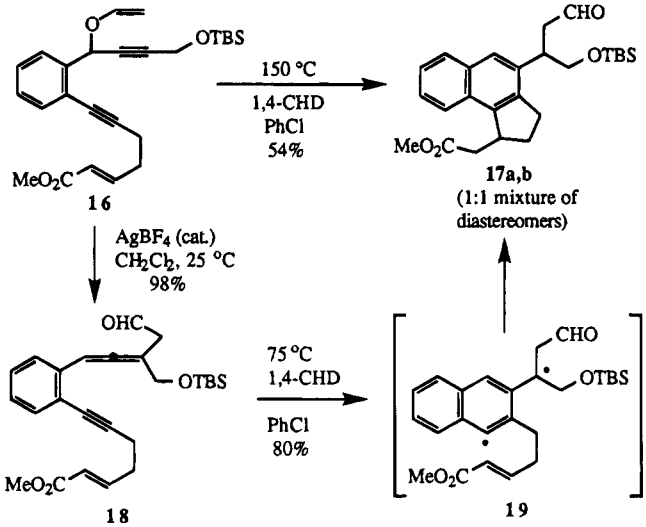
tion of enediyne **7** containing a pendent olefin was investigated in order to trap the aryl radical resulting from the enyne allene cyclization.[11] When **7** was heated to 150 °C in the presence of 1,4-CHD, aldehyde **8** was isolated as the only characterizable product in 20% yield (Scheme 2). Mechanistically, aldehyde **8** presumably arises from a [3,3] sigmatropic rearrangement of **7** followed by an immediate enyne allene cyclization of the intermediate **9**, a 5-*exo* cyclization of the resulting aryl radical, and hydrogen abstraction from 1,4-CHD. Under the above reaction conditions, the tetracyclic ether **11** from the tandem enediyne–radical cyclization was not observed. This result is consistent with the fact that the thermal activation energy for the cyclization of *o*-arene enediynes with two acetylenic tethers (E_a = 34.0 ± 0.3 kcal/mol) is much higher than for the corresponding *o*-arene enediyne with one acetylenic tether (E_a = 28.1 ± 0.8 kcal/mol).[9]

In order to improve the yield of this reaction, we tried to effect the transformation at lower temperatures by reacting enediyne **7** with a catalytic amount of $AgBF_4$ in benzene at room temperature to produce the enyne allene **9**. However, **9** could not be isolated due to its slow decomposition and its propensity to undergo isomerization to the α,β-unsaturated aldehyde **10**. Thermolysis of the crude product **9** at 75 °C in the presence of 1,4-CHD only provided a small amount of desired product **8** along with aldehyde **10** and decomposition products (Scheme 2).

Scheme 3



Scheme 4



The results with the enyne allene cyclization of **9** and some other results in our laboratory suggest that there is an unfavorable interaction between the C-1 substituent on the allene and the *ortho* hydrogen on the aryl ring of the enyne allene. In addition, previous work by Myers implies that a simple alkyl substitution at the C-3 position of the allene will accelerate the enyne allene cyclization reaction.[2] To test this theory, enediyne **12** was prepared so that the substitution on the allene **14** resulting from the [3,3] sigmatropic shift of **12** would be at the C-3 position (Scheme 3).[11]

When enediyne **12** was heated to 150 °C in chlorobenzene in the presence of 1,4-CHD, naphthalene derivative **13** was obtained in 45% isolated yield (Scheme 3). Product **13** presumably arises from a [3,3] sigmatropic rearrangement of propargyl vinyl ether **12** followed by an enyne allene cyclization of intermediate **14** to form biradical **15**, which abstracts hydrogen from 1,4-CHD. Unfortunately the silver-catalyzed [3,3] sigmatropic shift of **12** could not be effected presumably due to the presence of the free acetylene proton.

Due to the success of the tandem [3,3] sigmatropic rearrangement–enyne allene cyclization of **12**, attention was then focused on enediyne **16** in order to test whether a pendent olefin would trap the aromatic radical generated from the enyne allene cyclization (Scheme 4).[11] When **16** was thermolyzed at 150 °C, 2,3-dihydrobenz[*e*]indene derivatives **17a** and **17b** were isolated in a 1:1 diastereomeric ratio in 54% combined yield (Scheme 4). The reaction proceeds through a [3,3] sigmatropic rearrangement of **16** to give enyne allene intermediate **18** which immediately undergoes an enyne allene cyclization

to afford biradical **19**. The aryl radical within **19** then undergoes a 5-*exo* radical cyclization followed by hydrogen abstraction from 1,4-CHD to yield the tricyclic compounds **17a** and **17b**.

In an effort to isolate the enyne allene intermediate **18** and to carry out the enyne allene–radical cyclization at lower temperature, **16** was treated with a catalytic amount of $AgBF_4$ at room temperature to afford the enyne allene **18** in 98% yield *via* a Lewis acid catalyzed [3,3] sigmatropic rearrangement. When **18** was thermolyzed at 75 °C in chlorobenzene in the presence of 1,4-CHD, the 2,3-dihydrobenz[*e*]indene derivatives **17a** and **17b** (1:1 ratio) were obtained in 80% combined yield. This yield is greatly improved over the one-step thermal conversion of **16** to **17** (Scheme 4). It is significant that dihydrobenz[*e*]indene derivatives **17a** and **17b** were formed at 75 °C while the similar compounds constructed from a tandem enediyne–radical cyclization would require 190 °C or higher. Although the enediyne cyclizations occur in high yield, certain functional groups do not survive temperatures over 200 °C.[7e] The lower temperature employed for the enyne allene cyclization would be more compatible with sensitive functionality that would be required in the synthesis of a complex natural product.

In summary, we have demonstrated that the tandem enyne allene–radical cyclization can be applied to the synthesis of 2,3-dihydrobenz[*e*]indene derivatives using a [3,3] sigmatropic rearrangement for the formation of the enyne allenes. This reaction can be conducted at a lower temperature (ca. 75 °C) than the corresponding enediyne systems (ca. 190 °C). By choosing different radical acceptors and acetylenic tethers, this new synthetic methodology could be extended to the synthesis of other polycyclic compounds. Applications of this reaction to natural product synthesis are currently in progress.

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Supplementary Material Available: Experimental procedures for the preparation of substrates and copies of ^1H and ^{13}C NMR spectra of compounds (41 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.