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Tandem Eneyne Allene-Radical Cyclization *Via* [2,3] Sigmatropic Shifts

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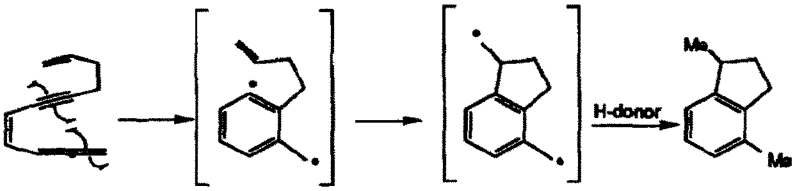
Abstract: *Eneyne allenes generated from [2,3] sigmatropic shifts will undergo tandem eneyne allene-radical cyclizations.*

With the recent emergence of enediyne antitumor antibiotics, there has been renewed interest in the Bergman cyclization. In an effort to model the neocarzinostatin chromophore, Myers reported the cyclization of synthetic eneyne allenes to form the α,3-dehydrotoluene biradical.[1] In contrast to the Bergman reaction, which proceeds at temperatures greater than 150 °C,[2] the eneyne allenes will cyclize at 80 °C; some examples have been reported which cyclize at temperatures as low as 37 °C.[3] While the majority of the research in this area has focused on the synthesis and DNA cleaving ability of these eneyne allenes, there have been only a few examples where the research has been directed at using the intermediate diyl as a radical precursor for further radical cyclizations.[4,5]

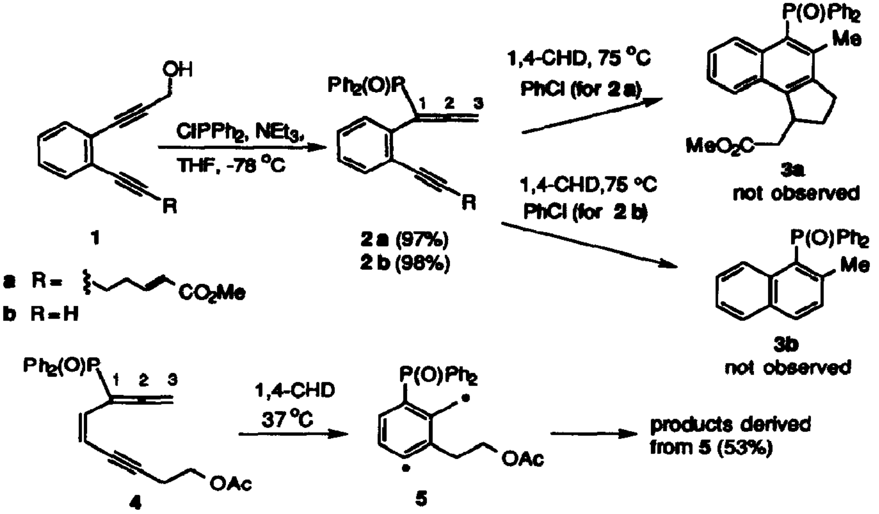
Recently we reported the tandem enediyne-radical cyclization for the preparation of 2,3-dihydrobenz[*e*]indenes.[5] Although the reaction proceeds in excellent yield, high temperatures (*ca.* 190 °C) are needed to effect the enediyne cyclization. If the radical used in the radical cyclization were generated from an eneyne allene cyclization, the temperatures required for the construction of the indene system would be much lower (eq. 1). Herein, we report our research on the tandem eneyne allene-radical cyclization in which the eneyne allenes are generated from [2,3] sigmatropic shifts.



(1)

Eneyne allenes that undergo cyclization have been previously synthesized *via* a [2,3] sigmatropic rearrangement of phosphinites.[3a-c] Substrate **2a** was prepared to test whether this strategy would work with *o*-arene eneyne allenes (Scheme 1). Treatment of enediyne **1a** with chlorodiphenylphosphine resulted in a [2,3] sigmatropic shift to give eneyne allene **2a** in 97% yield. Unfortunately, when this compound was heated to 75 °C using 1,4-cyclohexadiene (1,4-CHD) as a hydrogen donor, there was no evidence for tandem eneyne allene-radical cyclization product **3a** and only slow decomposition occurred. Cyclizations attempted at higher temperatures were also unsuccessful.

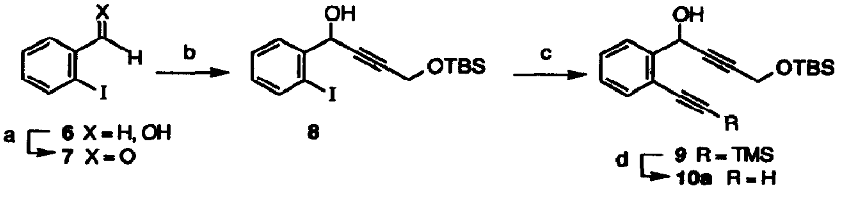
Scheme 1



Saito showed that thermolysis of the non-aromatic enediyne **4** in the presence of 1,4-CHD gave cyclization products in 53% yield that presumably arise from the biradical **5** (Scheme 1).[3c] Most of the other substrates known to undergo eneyne allene cyclizations do not have substituents at the 1-position of the allene.[6] To test whether the *o*-arene eneyne allene cyclization with the phosphine oxide at position one was occurring at all, eneyne allene **2b** was prepared from enediyne **1b** in 98% yield (Scheme 1). Thermolysis of **2b** did not result in the naphthalene derivative **3b** and slow decomposition was again observed. It is possible that in eneyne allenes **2a** and **2b** there are unfavorable steric interactions between the diphenylphosphinyl group and the aryl ring of the eneyne allene, causing the phosphinyl group to rotate the allene out of the plane defined by the aryl group. The eneyne allene would therefore no longer be coplanar and thus be unable to participate in the cyclization reaction.[3b]

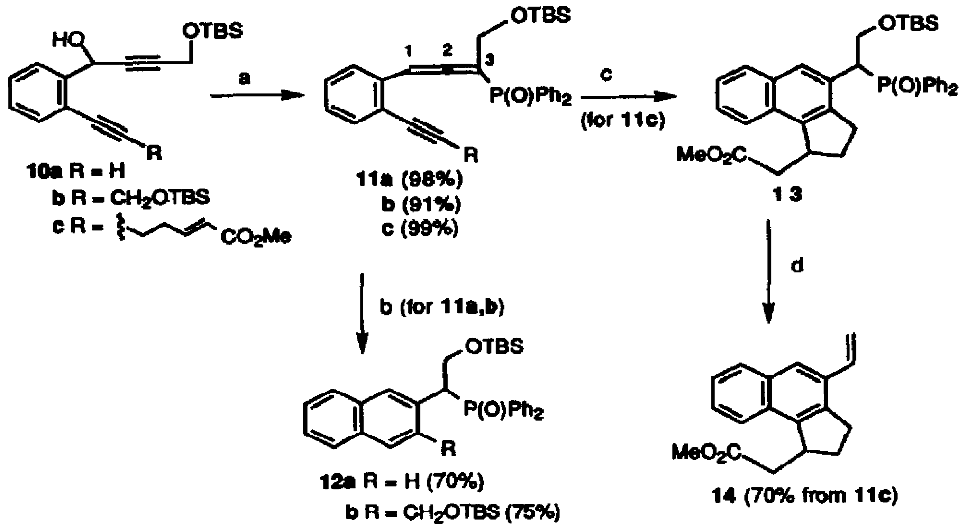
To minimize this unfavorable steric interaction, a substrate was prepared with the phosphinyl group at the 3-position of the allene. The propargylic alcohol **10a** was prepared (Scheme 2) and treated with chlorodiphenylphosphine to yield eneyne allene **11a** in 98% yield (Scheme 3). Heating this compound at 37 °C in the presence of 1,4-CHD yielded the cyclized product **12a** in 70% yield. A similar substrate **11b** described by Nicolaou has been reported to cyclize to **12b** at 37 °C in 75% yield.[3a]

Scheme 2



a) PCC, CH_2Cl_2, celite (97%); b) HC≡CCH_2OTBS, *n*-BuLi, -78 °C, NH_4Cl (77%); c) HC≡CTMS, $PdCl_2(PPh_3)_2$, CuI, THF, NEt_3; d) K_2CO_3, MeOH (89% from **8**).

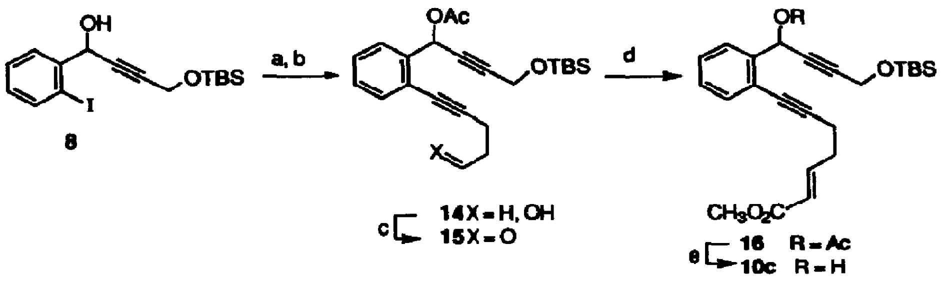
Scheme 3



a) $ClPPh_2$, NEt_3, THF -78 °C; b) 1,4-CHD, PhCl, 37 °C; c) 1,4-CHD, PhCl, 75 °C; d) TBAF, THF (70% from **11c**).

Having established the feasibility of carrying an eneyne allene cyclization on an *o*-arene substrate, the next goal was to couple this cyclization with a subsequent radical cyclization. Eneyne allene **11c** was synthesized starting with the iodide **8** which was converted to alcohol **10c** (Scheme 4).

Scheme 4



a) Ac_2O, NEt_3, CH_2Cl_2 (83%); b) 4-pentynol, $PdCl_2(PPh_3)_2$, CuI, NEt_3, THF (26%); c) PCC, CH_2Cl_2, celite (65%); d) trimethylphosphonoacetate, DBU, LiCl, CH_3CN (86%); e) K_2CO_3, MeOH (82%).

Treatment of **10c** with chlorodiphenylphosphine yielded eneyne allene **11c** (Scheme 3). Thermolysis of **11c** at 37 °C in the presence of 1,4-CHD resulted in no reaction. Repeating the thermolysis of **11c** at 75 °C cleanly yielded the tandem eneyne allene-radical cyclization product **13**. Due to the difficulty in purifying **13**, this compound was subjected to a Horner-Wittig elimination to yield **14** in 70% overall yield from **11c**.[7] Although the cyclization also occurred at 50 °C, the yields at this temperature were low and the reaction mixture was complex. Even though eneyne allene **11c** has a similar substitution pattern as Nicolaou's eneyne allene **11b**, the temperature required for the cyclization of **11c** was higher. The reasons for this difference are not clear.

In summary, we have described a successful example of a tandem eneyne allene-radical cyclization of a substrate synthesized from a [2,3] sigmatropic shift. We have studied the cyclization behavior of *o*-arene eneyne allenes containing a phosphine oxide at the 1- or 3- position of the allene. Although the cyclization of an eneyne allene with a phosphine oxide at the 1-position fails most likely for steric reasons, the cyclization of these substrates with a phosphine oxide at the 3-position proceeds successfully. The tricyclic system **14** that is available from the eneyne allene cyclization at 75 °C is similar to the tricycle which results from the enediyne cyclization at 190 °C, however, the former is formed at a much lower temperature. Given the lower temperatures, applications to natural product synthesis should be possible. Work toward this goal is being carried out and will be reported in due course.

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6. For a notable exception to this see: Nakatani, K.; Isoe, S.; Maekawa, S.; Saito, I. *Tetrahedron Lett.* **1994**, *35*, 605.
7. **14**:.^{1}H NMR (300 MHz; $CDCl_3$) δ 7.84 (m, 3H), 7.47 (td, 1H, *J* = 6.6, 1.2 Hz), 7.41 (t, 1H, *J* = 6.6 Hz), 6.92 (dd, 1H, *J* = 17.7, 11.1 Hz), 5.83 (dd, 1H, *J* = 17.7, 1.2 Hz), 5.37 (dd, 1H, *J* = 11.1, 1.2 Hz), 4.14 (ddd, 1H, *J* = 9.3, 8.1, 3.0 Hz), 3.73 (s, 3H), 3.19-3.10 (m, 2H), 2.79 (dd, 1H, *J* = 15.6, 3.0 Hz), 2.43-2.33 (m, 2H), 2.15 (dd, 1H, *J* = 14.1, 6.0 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) 173.4, 141.5, 139.4, 135.3, 133.4, 133.0, 129.4, 129.0, 126.3, 125.3, 124.2, 123.7, 115.9, 51.9, 40.6, 38.8, 31.0, 30.6; HRMS calcd for $C_{18}H_{18}O_2$ m/e 266.1307, found m/e 266.1301.

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