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First Synthesis of *cis*-Enediynes from 1,5-Diynes by an Acid-Mediated Allylic Rearrangement

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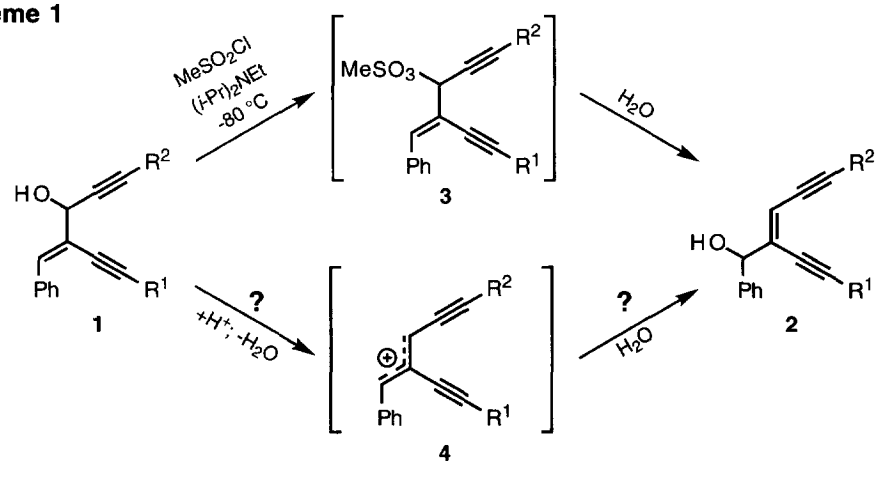
Abstract: The first synthesis of *cis*-enediynes **11** from 1,5-diyne **7** is achieved by treatment with 1 equivalent of CSA in CH_2Cl_2 at 20 °C in the presence of ROH or RSH to provide **11** as the major products in good yield. An 11-membered ring enediyne **15** was prepared similarly in 47% yield.

The enediyne antitumor antibiotics are a novel class of natural products possessing a 1,5-diyn-3-ene unit in a strained 9- or 10-membered ring.[1] After bioactivation, the enediyne undergoes a cycloaromatization to form 1,4-benzenoid diradical which causes DNA strand cleavage by abstraction of hydrogen atoms from the sugar-phosphate backbone.[1] Syntheses of naturally occurring enediynes and analogs have been the focus of many research efforts in the recent years.[1a,e] The *cis*-enediynes are prepared by a Pd(0)-mediated cross-coupling reaction of vinyl halides with terminal acetylenes under the Sonogashira conditions.[2] Moreover, a number of methods have been developed to convert 1,5-diynes into *cis*-enediynes by introducing a double bond through the reductive elimination,[3] the acid-[4] or base-induced[5] elimination of alcohols, the elimination of diol using the Corey-Winter reagent,[6] the benzylic oxidation,[7] the Norrish Type II reaction,[8] the rearrangement of allylic alcohol,[9] and the retro-Diels-Alder Reaction.[10] These methods provide the chemical basis for enediyne prodrug[11] design and synthesis. In our work on conversion of 1,5-diyne **1** into *cis*-enediyne **2** via the allylic mesylate **3** (Scheme 1), an S_N2' mechanism was proposed to account for the regioselectivity.[9] It is interesting

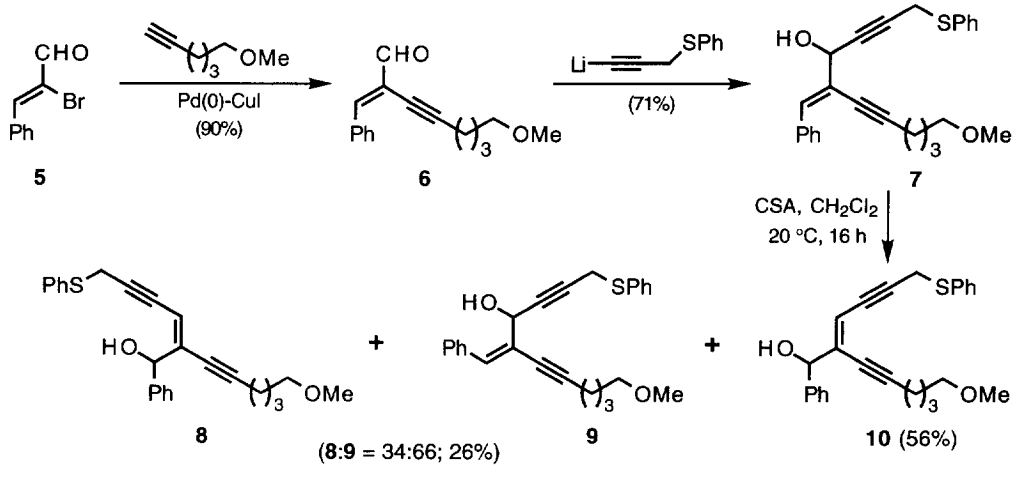
Scheme 1



to explore the allylic rearrangement (**1**→**2** or the reverse reaction) under acidic conditions involving the allylic cation **4**[12] as the reactive intermediate. We now report on the first synthesis of *cis*-enediynes **11** by an acid-promoted allylic migration of 1,5-diyne **7** with high regioselectivity and *trans/cis* stereoselectivity.[13]

The 1,5-diyne **7** was prepared from the commercially available α-bromocinnamaldehyde (**5**) in two steps (Scheme 2).[14] Cross-coupling of **5** with $HC{\equiv}C(CH_2)_4OMe$ in the presence of 5 mol% $Pd(PPh_3)_4$ and 10 mol% CuI (Et_3N, THF, rt, 1 h) afforded **6** (90%). Addition of $LiC{\equiv}CCH_2SPh$ to **6** in THF at -78 °C for 30 min gave **7** in 71% yield. Treatment of **7** with one mole equivalent of (±)-10-camphorsulfonic acid (CSA) in dry CH_2Cl_2 at 20 °C for 16 h furnished the *cis*-enediyne **10** in 56% isolated yield together with the *trans*-enediyne **8** and the 1,5-diyne **9** (a 34:66 mixture of **8**:**9** in a 26% combined yield). The same reaction was monitored in CD_2Cl_2 at 20 °C by ^1H NMR technique, revealing a gradual decrease of **7** and increase of the three products **8**-**10**. After 3 h, a mixture of **7**:**8**+**9**:**10** in the ratio of 6.5:35.0:58.5 was obtained. It is promising to note that the allylic rearrangement of **7** takes place under the acidic conditions to give the desired

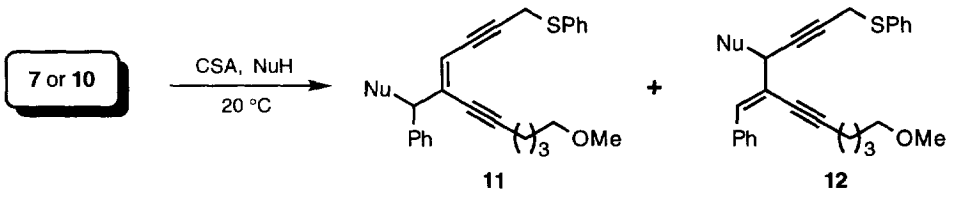
Scheme 2



cis-enediyne **10** as the major product. However, the *trans/cis* stereoselectivity (**8** *versus* **10**) needs improvement. Since attack of H_2O at the allylic cation **4** [Scheme 1, R^1 = $-(CH_2)_4OMe$, R^2 = $-CH_2SPh$] can't produce the alcohols **8** and **9**, other forms of the allylic cation should be involved in the reaction course.[15]

We performed the acid-mediated rearrangement of **7** or **10** in the presence of ROH and RSH (Scheme 3 and Table 1).[14] In these reactions, we obtained two products **11** and **12**; by-products related to compounds **8** and **9** were not detected. A complete control of the *trans/cis* stereoselectivity is achieved in the allylic migration. It was found that the reaction completed within 2-5 days in MeOH or EtOH (Entries 1 and 2). But, much short reaction time (2-4 h) was required in CH_2Cl_2 (Entries 3-7). In general, the regioselectivity (**11** *versus* **12**) of the allylic migration is dependent on the type of the nucleophile. The ratios of **11**:**12** are *ca.* 96:4 for ROH and *ca.* 70:30 for RSH regardless the nature of the R group. Similar results were obtained from the reaction of the *cis*-enediyne **10** with EtOH and EtSH (Entries 8 and 9) except for the longer reaction time compared with **7** (Entries 3 and 5). The results suggest that compounds **7** and **10** share the same intermediate **4** in the reactions. However, the conversion of **10** into **4** is slower than **7**. This is consistent with the facile conversion of **7** into

Scheme 3



a: Nu = MeO; **b:** Nu = EtO; **c:** Nu = *i*-PrO; **d:** Nu = EtS; **e:** Nu= *t*-BuS; **f:** Nu = PhS

Table 1. Synthesis of *cis*-Enediynes by Acid-Promoted Allylic Rearrangement at 20 °C.[a]

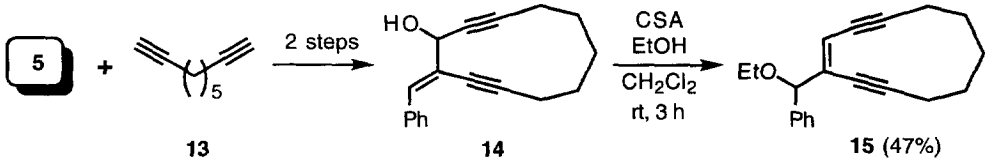
Entry	Substrate	NuH	Reation Time (h)	Products (%)	Ratio (**11**:**12**)
1	**7**	MeOH[b]	48	**11a** (73); **12a** (2)	97:3
2	**7**	EtOH[b]	120	**11b** (70); **12b** (3)	96:4
3	**7**	EtOH	3	**11b** (71); **12b** (3)	96:4
4	**7**	*i*-PrOH	4	**11c** (65); **12c** (3)	96:4
5	**7**	EtSH	2.5	**11d** + **12d** (79)	67:33
6	**7**	*t*-BuSH	2	**11e** + **12e** (61)	73:27
7	**7**	PhSH	2.5	**11f** + **12f** (54)	69:31
8	**10**	EtOH	48	**11b** (55); **12b**[c]	----
9	**10**	EtSH	48	**11d** + **12d** (61)	68:32

[a]Reactions were performed in CH_2Cl_2 in the presence of 1 mole equivalent of CSA and 2 mole equivalent of nucleophile. [b]The nucleophile was used as solvent. [c]Not isolated.

10 mentioned in Scheme 2. We attempted to trap the cation **4** with an amide nucleophile, CH_3CONH*n*-Pr; but the expected products were not obtained. The synthesized *cis*-enediynes **10** and **11** can be oxidized to the corresponding ene-yne-propargylic sulfones which undergo a base-induced cycloaromatization to form diradicals at ambient temperature.[9] DNA cleavage by such diradical species has been demonstrated.[9]

Finally, an 11-membered ring enediyne **15** was synthesized by the acid-promoted allylic rearrangement of **14** (Scheme 4). Cross-coupling of **5** with 2 mole equivalent of 1,8-nonadiyne (**13**) [$Pd(PPh_3)_4$, CuI, Et_3N, THF, rt, 2 h] gave the mono-coupling product (68%) which cyclized (LDA, $CeCl_3$, THF, -78 °C) to afford **14** in 20% yield. Treatment of **14** with CSA-EtOH in CH_2Cl_2 at rt for 3 h furnished the 11-membered ring enediyne **15** in 47% yield. A minor regioisomer related to **14** (replacing HO with EtO) was isolated (3%). This is the first example that the allylic migration strategy can be used to synthesize cyclic enediyne from 1,5-diyne.

Scheme 4



In summary, we have established a novel synthesis of *cis*-enediynes by the acid-promoted allylic migration of 1,5-diyne **7**[16] in the presence of ROH with high regioselectivity (≥96%) and *trans/cis*-stereoselectivity (100%). The realization of such transformation in the cyclic 1,5-diyne system provides a novel approach to enediyne prodrug design and synthesis. Recently, an allylic migration to a 9-membered ring enediyne was proposed for the activation of the artifacts of maduropeptin chromophore.[17] Our work may help to understand the chemical basis of the activation process in the biological system.

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14. All new compounds are characterized by ^{1}H and ^{13}C NMR, MS, and elemental analysis.
15. By placing Ph, -C≡CR^{2}, or both substituents in the *trans* relationship with -C≡CR^{1} in the W cation **4**, two sickle and one U cations can be obtained. See: ref. 12 and Hoffmann, H. M. R. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 819-835.
16. The phenyl group in **7** is necessary for generation of the cation **4** under the acidic conditions. Replacing by a methyl group failed to form the products (CSA, EtOH, CH_2Cl_2, rt, 48 h). The substrate was recovered.
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