A Novel Synthesis of (*Z*)-Enynes and (*Z*)-Enediynes from Prop-2-ynyl Alcohols

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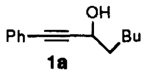
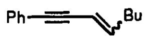
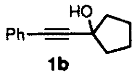
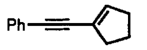
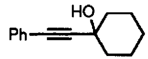
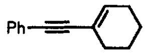
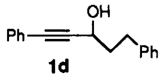
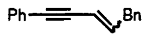
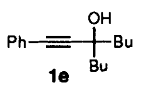
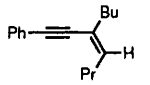
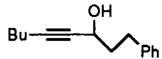
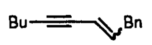
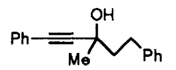
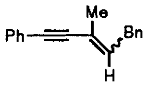
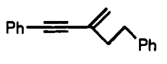
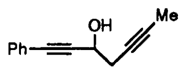
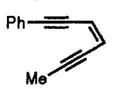
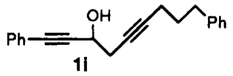
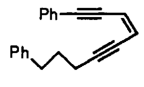
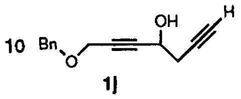
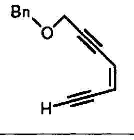
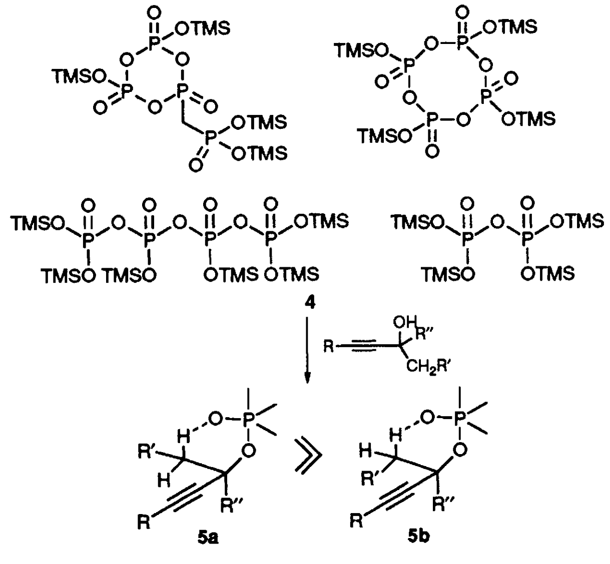
The conjugated (*Z*)-enynes **2a, 2d–g** and (*Z*)-enediynes **2h–j** were synthesized by dehydration of prop-2-ynyl alcohols **1a, 1d–j** with polyphosphoric acid trimethysilyl ester.

Recently, interest in conjugated enediyne systems has been stimulated by the discovery of the anticancer antibiotics (*e.g.* the neocarzinostatin chromophore, calicheamicin γ^{I}, esperamicin).[1] Most synthetic approaches to enediyne moieties have utilized double σ-bond formation between sp and sp^2 carbons by Pd-mediated coupling reactions.[2] Recently, Petasis *et al.* reported the *Z*-selective synthesis of enediynes by the elimination of a silanol from α-silyl alcohols derived from the enolates of α-trimethylsilyl-α-allenyl ketones and carbonyl compounds.[3] Although the dehydration of a diyne alcohol has been used for the preparation of an enediyne, the product was only the *trans*-enediyne.[4] If the dehydration of prop-2-ynyl alcohols can be accomplished *Z*-selectively, it becomes a simple and useful synthetic method for enediynes. Since polyphosphoric acid trimethylsilyl ester (PPSE) acted as a mild dehydrating agent for isoselenochroman-4-ol,[5] we selected PPSE to dehydrate prop-2-ynyl alcohols under mild conditions.

A prop-2-ynyl alcohol **1a**, prepared from lithium phenylacetylide and hexanal, was treated with PPSE[7] to afford (*E*)- and (*Z*)-1-phenyloct-3-en-1-yne **2a** (*E*:*Z* = 3:15). *E* and *Z* isomer ratio was determined from the intensities of olefinic protons in the ^{1}H NMR spectrum. Various prop-2-ynyl alcohols were treated with PPSE and the results are shown in Table 1. 1-Phenylethynylcycloalkanols **1b** and **1c** were similarly converted to enynes **2b** and **2c** in good yields. Enyne **2d** was obtained in the ratio of *E*:*Z* = 33:67. *tert*-Alcohol **1e** exclusively gave *Z*-product **2e** and prop-2-ynyl alcohol **1g** gave eneyne **2g** (*E*:*Z* = 1:19) accompanied by the terminal methylene derivative **3g**.

Table 1 Synthesis of enynes and enediynes

Entry	Alkynyl alcohol	Products (% yields; *Z*:*E*)	
1	 **1a**		**2a** (51; 15:3)
2	 **1b**		**2b** (77)
3	 **1c**		**2c** (50)
4	 **1d**		**2d** (54; 67:33)
5	 **1e**		**2e** (44; 100:0)
6	 **1f**		**2f** (53; 19:1)
7	 **1g**	 **2g** (82; 95:5)	 **3g** (17)
8	 **1h**		**2h** (50; 50:3)
9	 **1i**		**2i** (89; 85:4)
10	 **1j**		**2j** (50; 100:0)



Scheme 1

We also examined the synthesis of enediynes by the reaction of diyne alcohols with PPSE. Enediynes **2h–j** were obtained *Z*-selectively. Although a 1,8-dimethoxy octaenediyne has been prepared by the Norrish Type II reaction of 1,8-dimethoxy-4-phenacylocta-2,6-diyne, the *E*/*Z* isomer ratio was 1, that is stereoselectivity was not observed.[6] In contrast, ω-alkoxy-substituted prop-2-ynyl alcohol **1j** exclusively gave *Z*-enediyne **2j**. This high stereoselectivity is attributable to the bulkiness of PPSE. PPSE is known to be a mixture of three kinds of tetramers and a dimer **4**.[7] The oxygen atom of a prop-2-ynyl alcohol attacks at the phosphorus atom of PPSE. The dehydration would proceed *via* a six-membered transition state **5a**, in which an alkyl and an alkynyl group lie in the side opposite to the bulky phosphorus moieties, and afford the *Z*-olefin (Scheme 1). When steric hinderance between R and R′ becomes larger, the ratio of *E*-isomer would increase through the intermediate **5b** (entries 1 and 4). Since the steric repulsion between R′ = Pr and R″ = Bu groups in compound **1e** is very large, **1e** gives *Z*-isomer exclusively through an intermediate **5a** (entry 5).

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References

1 K. C. Nicolaou, W.-H. Dai, S.-C. Tsay, V. A. Estevez and W. Wrasidlo, *Science*, 1992, **256**, 1172.

2 A. G. Myers, M. M. Alauddin, M. A. M. Fuhry, P. S. Dragovich, N. S. Finney and P. M. Harrington, *Tetrahedron Lett.*, 1989, **30**, 6997; P. A. Magriotis, M. E. Scott and K. D. Kim, *Tetrahedron Lett.*, 1991, **32**, 6085; E. C. Stracker and G. Zweifel, *Tetrahedron Lett.*, 1991, **32**, 3329.

3 N. A. Petasis and K. A. Teets, *Tetrahedron Lett.*, 1993, **34**, 805.

4 P. A. Wender and M. J. Tebbe, *Tetrahedron Lett.*, 1991, **32**, 4863.

5 M. Hori, T. Kataoka, H. Shimizu, K. Tsutsumi and M. Yoshimatsu, *J. Org. Chem.*, 1990, **55**, 2458.

6 J. M. Nuss and M. M. Murphy, *Tetrahedron Lett.*, 1994, **35**, 37.

7 T. Imamoto, T. Matsumoto, H. Yokoyama, M. Yokoyama and K. Yamaguchi, *J. Org. Chem.*, 1984, **49**, 1105.