A New Bromo Trienyne: Synthesis of *all-E*, Conjugated Tetra-, Penta-, and Hexaenes Common to Oxo Polyene Macrolide Antibiotics

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In a recent report from these laboratories,[1] a new "linchpin" **1** was disclosed that allows for rapid construction of the *all-E* oxopolyene network characteristic of many polyene macrolide antifungal agents (Figure 1).[2] This methodology relies on an initial Pd(0) coupling, where **1** serves as the nucleophilic partner. The acetylenic terminus can be regio- and stereoselectively hydrozirconated, and while introduction of an acyl moiety could be accomplished in the presence of Me_2AlCl,[3] a second Pd(0)-catalyzed vinyl−vinyl coupling was not realized due to the highly deactivated, conjugated vinylic zirconocene.[4] This limitation encouraged us to pursue a second-generation reagent that would make available not only *all-E* oxo tetra- and oxo pentaenes but also the oxo hexaene framework as well. We now describe a redesigned tetraene equivalent **2**, which provides synthetic opportunities not available to **1**.

Bromo trienyne **2** is prepared via *E*-bromo dienal **4** and the ylide derived from **5** utilizing a standard Wittig protocol (Scheme 1). Known precursor potassium salt **3** (mp > 350 °C) is obtained from inexpensive pyridine·sulfur trioxide complex.[5] Conversion of **3** to bromo dienal **4**,[6] reported to proceed using Br_2/PPh_3 in CH_2Cl_2, in our hands affords low yields of desired product. Attempts to modify conditions (e.g., changing the solvent to 1,2-dichloroethane, adding $Bu_4N^+X^-$, various concentrations, and temperatures) or conversion to other leaving groups (e.g., the triflate derivative of **3**) were not productive. In time, we found that use of NBS/PPh_3 led to a good isolated yield of **4** (74%; 68:32 *E*/*Z*, separable by chromatography). The corresponding iodide[6] could likewise be prepared using NIS/PPh_3 (76%; 1:1 *E*/*Z*). Treatment of phosphonium bromide **5**[7] with NaN(TMS)$_2$ in THF[8] followed by aldehyde (*E*)-**4** (mp 66−68 °C) affords tetraene equivalent **2** in 86% yield as an ≥85:15 mixture of *E*,*E*,*E* to *E*,*E*,*Z* isomers.

The vinyl bromide portion of **2** represents a polarity inversion relative to stannyl dienyne **1** and, hence, could be coupled with vinyl- and dienylzinc reagents **6** (n = 1, 2; Scheme 2). Nucleophilic partners appear to tolerate TIPS-protected alcohols, substituted styryl residues, and divalent sulfur (Table 1). Yields tend to be uniformly good, and the ratio of *E*:*Z* products associated with the newly formed bond

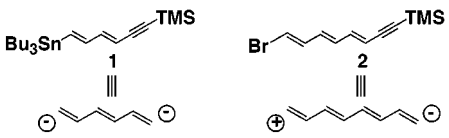
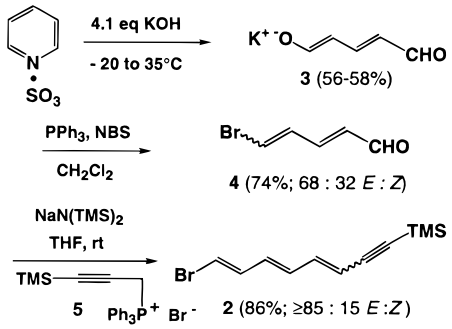
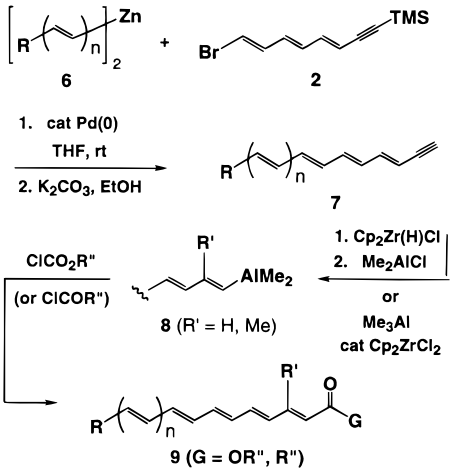


Figure 1.

Scheme 1. Preparation of Bromo Trienyne 2



Scheme 2



reflects maintenance of stereochemical integrity, as expected.[9] These initial products could be desilylated to **7** and either hydrozirconated and then transmetalated to aluminum with Me_2AlCl[3] or carboaluminated directly to the corresponding vinylalane **8**.[10] Subsequent exposure to a chloroformate (or acid chloride) affords the desired conjugated polyene esters **9** (or ketones). Representative examples are illustrated as well in Table 1. Particularly noteworthy cases include (1) the entire polyene section of the mycoticins[11] (entry 2) and (2) the alarm pheromone navenone C (entry 4).[12]

The overall stereochemical outcome of these reactions, as noted previously,[1] is such that essentially *all-E* products are obtained notwithstanding the ≥85:15 mix of polyenynes **7** formed from the vinyl−vinyl cross-coupling/desilylation. The enhancement results not from eventual isomerization but rather a kinetic resolution based on the greater reactivity of the *E*- vs *Z*-vinylalane intermediate **8** toward the electrophile.

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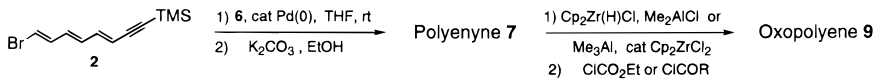
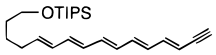
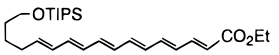
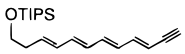
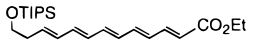
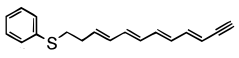
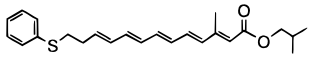
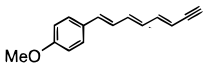
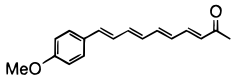
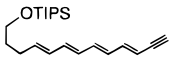
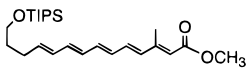
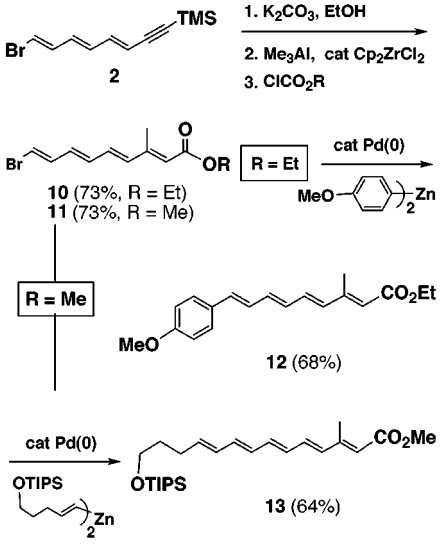
Table 1. Coupling Reactions of Linchpin 2



Polyenyne **7** [from **2**, above][a]	Yield(%)[b]	Metalation / Electrophile	Oxopolyene **9** [from **7**, above][a]	Yield(%)[b]
	78	$Cp_2Zr(H)Cl$ Me_2AlCl $ClCO_2Et$		68
	73	$Cp_2Zr(H)Cl$ Me_2AlCl $ClCO_2Et$		73
	80[c]	cat Cp_2ZrCl_2 Me_3Al $ClCO_2$-*i*-Bu		75
	85	$Cp_2Zr(H)Cl$ Me_2AlCl $ClCOCH_3$		70
	73	cat Cp_2ZrCl_2 Me_3Al $ClCO_2CH_3$		74

[a] Fully characterized by spectral and HRMS data. [b] Isolated, chromatographically purified material. [c] Yield refers to silylated alkyne prior to treatment with K_2CO_3 in EtOH.

Scheme 3. Coupling Reactions of 2 Initially at the Alkyne Terminus

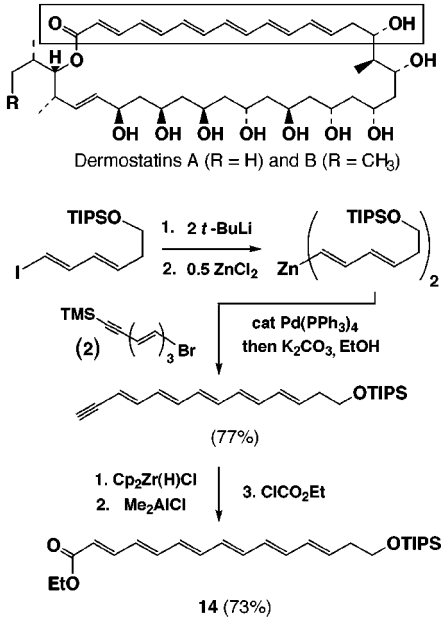


Instead of an initial Pd(0)-catalyzed coupling at the vinyl bromide terminus of **2**, the protocol could be inverted, whereby the alkyne is desilylated and then carboaluminated (Scheme 3). Quenching with ethyl chloroformate, or methyl chloroformate, leads to bromotetraenes **10** and **11**, respectively. Subsequent coupling of **10** arrives at aryl-substituted tetraenoate **12**, while **11** is converted to oxopentaene **13**.

Another application of this approach, where **2** is effectively equivalent to an *all-E* 1,8-octatetraenyl monocation/monoanion (cf. Figure 1), to the oxohexaene portion of the dermostatins[13] is shown in Scheme 4. For this case, target **14** could be constructed in short order in 56% overall yield.

In summary, a very short sequence has been developed for fabricating *all-E*, conjugated oxopolyene networks that constitute key subsections of important natural products. The route relies on a newly fashioned trienyne **2** that participates in both vinyl−vinyl couplings and derived vinylalane acylations to afford highly (light, acid, base, heat, oxygen, etc.) sensitive polyenes. Further refinements, alternative organometallic chemistry, and additional applications (e.g., to the preparation of capped polyacetylenes)[14] are in progress and will be reported in due course.

Scheme 4. Synthesis of the Oxo Hexaene Portion of the Dermostatins



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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds (45 pages).

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