# A Streamlined Route to Highly Conjugated, *All-E* Polyenes Characteristic of Oxo Polyene Macrolide Antibiotics

Bruce H. Lipshutz* and Craig Lindsley

*Department of Chemistry, University of California Santa Barbara, California 93106*

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Conjugated polyenes of the *all-E* variety constitute key subsections of many natural, as well as unnatural, products. Among the more visible and timely members of the former group are the polyene macrolide antibiotics,[1] which are clinically important antifungal agents, and selected retinoids,[2] which have recently been found to be active against certain tumor lines. Capped polyacetylenes, especially valued as materials by virtue of their nonlinear optical (NLO) properties,[3] are representative of the latter category. Routes to polyene functionality tend to rely mainly on traditional olefin elongations,[4] although more recently alternative methods have started to accrue.[5] Characteristic of most, however, is the requirement of many steps, oftentimes low overall yields, and not uncommon isomerizations or problematic separations of unwanted *Z* isomers. We now report a new approach to construction of *all-E* polyenes, in particular oxotetra- and oxopentaenes, based on a readily prepared linchpin suitable for bidirectional elaboration.

The key building block, stannylated dienyne **1**, was envisioned as an *all-E* 1,6-dimetallohexatriene equivalent, taking advantage of the likely retention of olefin geometry in Pd(0)-mediated vinyl−vinyl cross-couplings of stannanes[6] and the anticipated regio- and stereoselective addition of Schwartz's reagent ($Cp_2Zr(H)Cl$) to the desilylated alkyne terminus (Figure 1).[7] Linchpin **1** is easily prepared as a pale yellow oil in multigram quantities in two operations (Scheme 1).[8] Addition of our mixed stannylcuprate **2**[9] to acetylenic acetal **3** according to Quintard[10] affords enal **4** after hydrolysis. Wittig coupling with the ylide derived from the known salt **5**[11] gives **1** in high yields and usually with better than 90:10 *E*/*Z* selectivity.

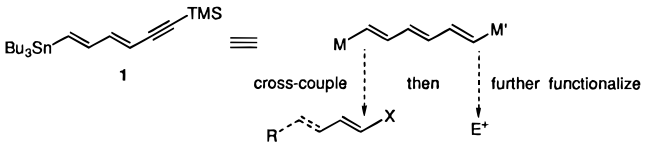



**Figure 1.**

**Scheme 1**

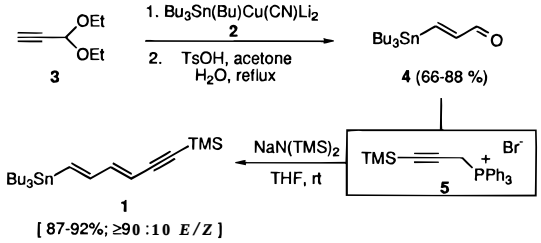
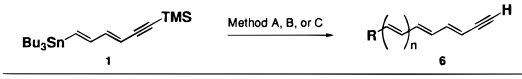
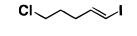
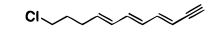
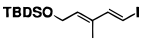
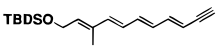
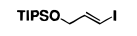
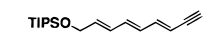
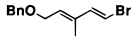
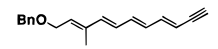
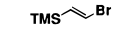
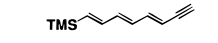
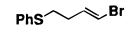
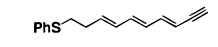



**Table 1.** Cross-Couplings of **1** with Vinyl Halides




| Vinyl / Dienyl Halide | Method | Product[a] | Yield(%) |
|---|---|---|---|
|  | (A) |  | 83 |
|  | (A) |  | 74 |
|  | (A) |  | 80 |
|  | (A) |  | 82 |
|  | (B) |  | 72 |
|  | (C) |  | 91 |

[a] Isolated, chromatographically purified materials, as >90*E*:<10*Z* mixtures reflecting the >90*E*:<10*Z* mix of dienyne **1**. Method A: (1) BuLi, THF, −78 °C; (2) $ZnCl_2$, 0 °C; (3) cat. $Pd(PPh_3)_4$; (4) $K_2CO_3$, EtOH. Method B: (1) 1.5 equiv CuCN, cat. $Pd_2(dba)_3$, $AsPh_3$, NMP, 50 °C; (2) $K_2CO_3$, EtOH. Method C: (1) 1.5 equiv CuCN, cat. $Pd_2(dba)_3$, $P(Fur)_3$, NMP, 50 °C; (2) $K_2CO_3$, EtOH.

As illustrated in Table 1, couplings at the vinyl stannane end in **1** could be effected in good yields in either of two basic manners. Tin-lithium exchange followed by conversion to the organozinc derivative provides a reactive partner, together with catalytic $Pd(PPh_3)_4$ and a vinyl iodide or bromide in THF (method A). Alternatively, simply mixing **1** with the same type of electrophile in *N*-methylpyrrolidone (NMP) containing $Pd_2(dba)_3$, *excess* CuCN,[12] and either $AsPh_3$ (method B) or $P(Fur)_3$ (method C) according to Farina[13] likewise results in cross-coupling products.[14] Removal of the acetylenic silyl moiety was accomplished with $K_2CO_3$ in EtOH at room temperature in good overall isolated yields.

Manipulation of the terminal acetylene in these trienyne or tetraenyne products **6** ($n$ = 1, 2) is accomplished by initial hydrozirconation. Although such highly conjugated vinyl zirconocene intermediates are completely unresponsive in our hands toward couplings with vinylic systems (I, Br, OTf),[15] transmetalation to aluminum[16] with $R_2AlCl$ occurs smoothly and

(1) Omura, S.; Tanaka, H. In *Macrolide Antibiotics: Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: New York, 1984; pp 351−404. Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021.

(2) *The Retinoids: Biology, Chemistry, and Medicine*, 2nd ed.; Spoin, M. B., Roberts, A. B., Goodman, D. S., Eds.; Raven: New York, 1993. Hashimoto, Y.; Shudo, K. *Cell. Biol. Rev.* **1991**, *25*, 209. Dawson, M. I., Okamura, W. H., Eds.; *Chemistry and Biology of Synthetic Retinoids*; CRC Press: Boca Raton, FL, 1990.

(3) *Nonlinear Optical Materials*: *Theory and Modeling*; Karna, S. P., Yeates, A. T., Eds.; ACS Symposium Series 628; American Chemical Society: Washington, DC, 1996.

(4) Nicolaou, K. C.; Sorenson, E. J. *Classics in Total Synthesis*; VCH Publishers: New York, 1996; Chapter 24. Nicolaou, K. C. *Chemtracts*: *Org. Chem.* **1990**, *3*, 327. Hanessian, S.; Bota, M. *Tetrahedron Lett.* **1987**, *28*, 1151. Wollenberg, R. H. *Tetrahedron Lett*. **1978**, 717. Williams, J. M.; McGarvey, G. J. *Tetrahedron Lett*. **1985**, *26*, 4891. Duplantier, A. J.; Masamune, S. *J. Am. Chem. Soc*. **1990**, *112*, 7079. McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Oh, T. *J. Am. Chem. Soc*. **1986**, *108*, 4943. Boschelli, D.; Takemasa, T.; Nishitani, Y.; Masamune, S. *Tetrahedron Lett*. **1985**, *26*, 5239.

(5) For representative reports, see: Bonini, C.; Giugliano, A.; Racioppi, R.; Righi, G. *Tetrahedron Lett*. **1996**, *37*, 2487. Mori, Y.; Asai, M.; Kawade, J.; Furukawa, H. *Tetrahedron* **1995**, *51*, 5315. Rychnovsky, S. C.; Griesgraber, G.; Jinsoo, K. *J. Am. Chem. Soc*. **1994**, *116*, 2621.

(6) Hegedus, L. S. In *Transiton Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Mill Valley, CA, 1994. Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc*. **1987**, *109*, 813.

(7) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc*. **1977**, *99*, 8115.

(8) See Supporting Information for details.

(9) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Tetrahedron Lett*. **1989**, *30*, 2065.

(10) Beaudet, I.; Parrain, J.-L.; Duchene, A.; Quintard, J.-P. *Tetrahedron Lett*. **1991**, *32*, 6333.

(11) Corey, E. J.; Ruden, R. A. *Tetrahedron Lett.* **1973**, 1495. Use of $NaN(TMS)_2$ with this salt follows from the work of Maryanoff: Reitz, A. B.; Nortey, S. O.; Jordan, A. D.; Mutter, M. S.; Maryanoff, B. E. *J. Org. Chem*. **1986**, *51*, 3302.

(12) Farina, V.; Presented at OMCOS 8, August 6−10, 1995, Santa Barbara, CA. Lower yields of polyenes are obtained if catalytic amounts of CuCN are used. For uses of catalytic copper in Stille couplings, see: Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905.

(13) Farina, V.; Krishnan, B. *J. Am. Chem. Soc*. **1991**, *113*, 9585.

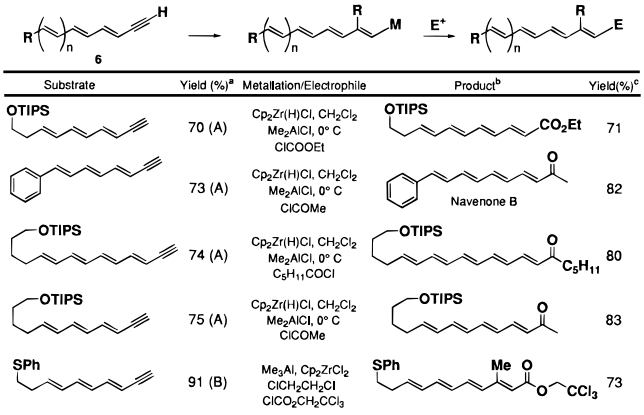
(14) Methods A, B, and C can be used interchangeably.

(15) Negishi, E.; Owczarczyk, Z. *Tetrahedron Lett*. **1991**, *46*, 6683.

(16) Carr, D.; Schwartz, J. *J. Am. Chem. Soc*. **1979**, *101*, 3521.

S0002-7863(96)03930-3 CCC: $14.00 

**Table 2.** Functionalization of Tri- and Tetraenynes to *all-E* Oxopolyenes




[a] Prepared from dienyne **1** and the corresponding vinyl halide by method A or B; cf. Table 1. [b] All products were fully characterized by IR, NMR, and MS/HRMS analyses. [c] Isolated, chromatographically purified materials.

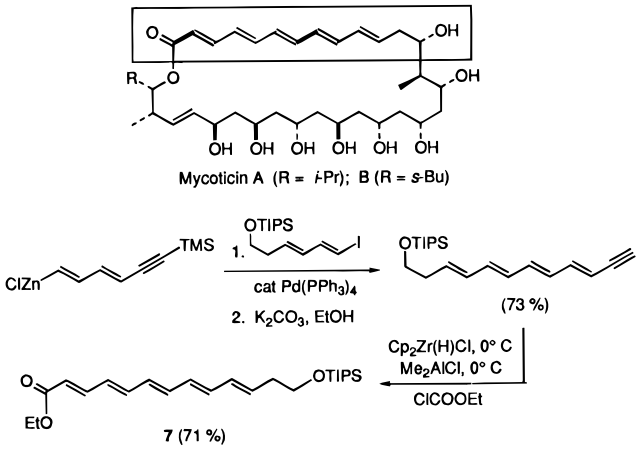
allows for trapping with either acid halides or chloroformates to produce the derived oxotetra- or oxopentaenes (Table 2, entries 1−4). Alternatively, direct Negishi[17] carboalumination/quenching afforded the $\beta$-methylated tetraenoate (Table 2, last entry). Given the proximity of the reacting organometallic site to the initially isolated *E/Z* polyenyne mix now undergoing metalation/trapping, we find that only the E isomer reacts to ultimately give the *all-E* polyene. Noteworthy is the application of this sequence to a trivial synthesis of navenone B[18] (entry 2).

With respect to the >200 known polyene macrolides,[1] many possess an oxopentaene portion as seen in the mycoticins, natural products originally isolated and characterized by Wasserman[19] and more recently synthesized by Schrieber.[20] Using this linchpin strategy (Scheme 2), the key subunit **7** can now be made in (formally) only three steps in 52% (unoptimized) overall yield.

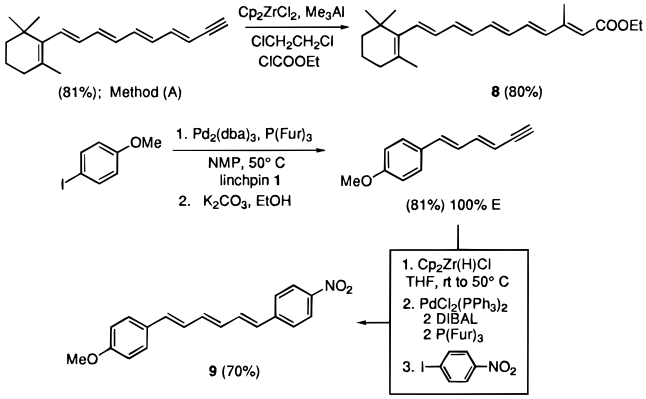
Finally, it is quite likely that this approach to *all-E* polyenes is applicable to both the synthesis of retinoids[2] as well as polyacetylenes[3] (Scheme 3). Using readily available pieces, the 9,13-didesmethyl vinylog of retinoic acid, product **8**, is rapidly constructed (65% overall), as is the donor−acceptor-capped triene **9** (57% overall).[21]

(17) Okukado, N.; Negishi, E. *Tetrahedron Lett.* **1978**, 2357.
(18) Fenical, W.; Sleeper, H. L. *J. Am. Chem. Soc.* **1977**, *99*, 2367.
(19) Wasserman, H. H.; Van Verth, J. E.; McCaustland, D. J.; Borowitz, I. J.; Kamber, B. J. *J. Am. Chem. Soc.* **1967**, *89*, 1535.
(20) Poss, C. S.; Rychnovsky, S. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 3360.

**Scheme 2**




**Scheme 3**




In conclusion, on the basis of couplings of a readily available organometallic linchpin (**1**), *all-E* oxotetra- and oxopentaenes that are characteristic fragments of various natural products can be rapidly assembled. Additional refinements, further applications, and second generation linchpins are under study and will be reported shortly.

**Acknowledgment.** We warmly thank the NIH (GM 40287) for support of our programs.

**Supporting Information Available:** Experimental details and NMR spectra for all new compounds (90 pages). See any current masthead page for ordering and Internet access information.

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(21) It is interesting to note that while these highly conjugated vinylzircononcenes do not undergo palladium-catalyzed couplings with vinyl halides, they are susceptible to couplings with aryl halides.