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# A Highly Efficient, Selective, and General Method for the Synthesis of Conjugated (*all-E*)-Oligoenes of the $(CH{=}CH)_n$ Type via Iterative Hydrozirconation–Palladium-Catalyzed Cross-Coupling

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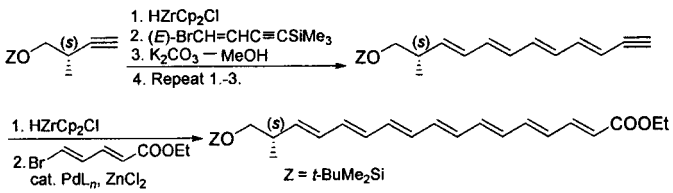
## ABSTRACT




**A linear iterative method for the construction of (*all-E*)-oligoenes of the $(CH{=}CH)_n$ type via hydrozirconation–palladium-catalyzed cross-coupling with (*E*)-1-bromo-4-trimethylsilyl-1-buten-3-yne is described. This method promises to provide an efficient, selective, and general route to oligoene macrolide antibiotics and other related natural products.**

Herein we report a linear iterative method for the synthesis of oligoenes containing the $(CH{=}CH)_n$ moiety of *all-E* configuration, where *n* is greater than 2, which promises to provide an efficient, selective, and general route to oligoene macrolide antibiotics[1,2] and related natural products. The general outline of the method reported herein is shown in Scheme 1. One of its salient features is an efficient linear iterative elongation of oligoenes via hydrozirconation−cross-coupling through the use of a recently introduced four-carbon synthon, (*E*)-1-bromo-4-trimethylsilyl-1-buten-3-yne (**1**),[3,4] for the synthesis of carotenoids and related compounds.

The development of the protocol shown in Scheme 1 was dictated to a considerable extent by the following two key findings. First, a detailed investigation of hydroalumination with *i*-$Bu_2AlH$,[5] hydroboration with dicyclohexylborane,[6] and hydrozirconation with $HZrCp_2Cl$[7] of (*E*)-3-decen-1-yne has indicated that the hydrozirconation reaction is the cleanest, providing the desired (1*E*,3*E*)-1,3-decadienylzirconocene chloride in 95% yield without an indication of any side reactions. Although the hydroboration reaction does produce

(1) For a review on oligoene macrolide antibiotics containing a description of an iterative construction of oligoenes via Grignard addition to aldehydes with $BrMg(CH{=}CH)_2OEt$, see: Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021.

(2) Lipshutz, B. H.; Lindsley, C. *J. Am. Chem. Soc.* **1997**, *119*, 4555.

(3) Zeng, F.; Negishi, E. *Org. Lett.* **2001**, *3*, 719.

(4) Prior to our synthesis,[3] there was no practical route to **1**, even though its formation in only 5% yield by the Pd-catalyzed reaction of $Me_3SiC{\equiv}CZnCl$ with a mixture of (*E*)- and (*Z*)-1,2-dibromoethylene had been previously reported (Carpita, A.; Rossi, R. *Tetrahedron lett.* **1986**, 27, 4351).

(5) For a review, see: Zweifel, G.; Miller, J. A. *Org. React.* **1984**, *32*, 375.

(6) Brown, H. C. *Organic Syntheses via Boranes*; John Wiley & Sons: New York, 1975; p 283.

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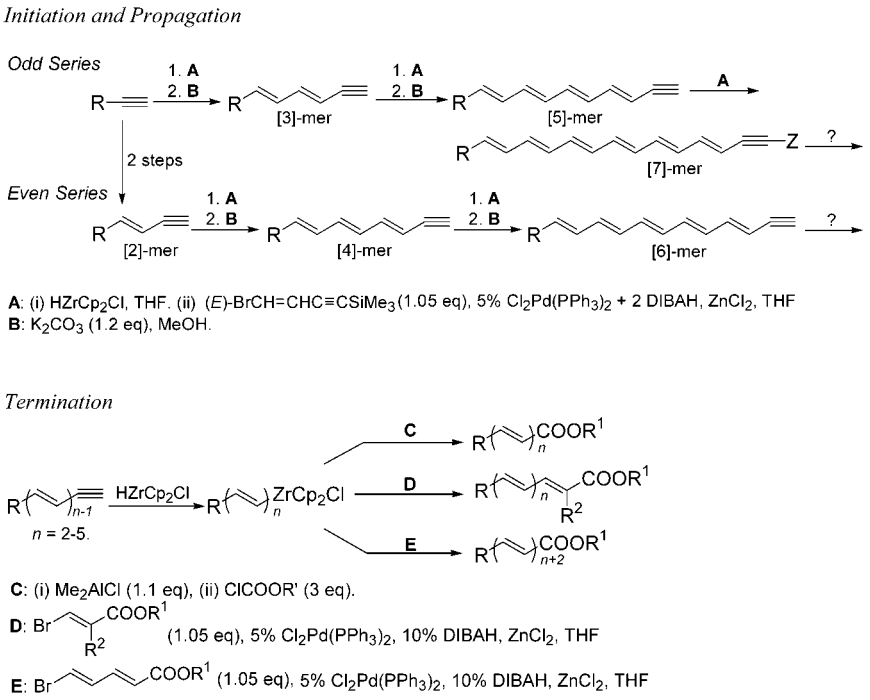
**Scheme 1**




the desired dienylborane in >80% yield, it is accompanied to a minor extent by a side reaction placing boron in the C-2 position, whereas the hydroalumination reaction, which can proceed cleanly with unconjugated terminal alkynes, is accompanied by the formation of the terminally aluminated enyne to a considerable extent (up to ca. 40%). Second, whereas conversion of the dienylzirconocene chloride to (1*E*,3*E*)-1-iodo-1,3-decadiene was achieved in 86% isolated yield based on the starting enyne, we have thus far failed to achieve clean conversion of (3*E*,5*E*)-3,5-dodecadien-1-yne to the corresponding 1-iodotriene via hydrozirconation−iodinolysis. This has severely limited our options for developing a convergent route to conjugated oligoenes.

Hydrozirconation of terminal alkynes with $HZrCp_2Cl$[7] followed by successive addition of **1** (1.05 equiv), 5 mol % of $Cl_2Pd(PPh_3)_2$, 10 mol % of DIBAH, and dry $ZnCl_2$ (1.0 equiv) in THF (procedure **A**) produced the corresponding cross-coupling products in 73−91% yields. Desilylation of the crudely worked-up products with methanolic $K_2CO_3$ (procedure **B**) completed an efficient and convenient elongation of alkynes by a four-carbon synthon with regeneration of a terminal alkynyl group for iteration. No difficulty was encountered in elongating terminal alkynes into dienynes and tetraenynes (Odd Series: entries 1−3 and 6−8). Alternatively, terminal alkynes were converted first to the corresponding (*E*)-enynes via hydrozirconation−iodinolysis−Pd-catalyzed ethynylation with HC≡CZnBr[8] and elongated as above to give trienynes and pentaenynes (Even Series: entries 4, 5, and 9).

(8) (a) King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, 683. (b) Kotora, M.; Xu, C.; Negishi, E. *J. Org. Chem.* **1997**, 8957.

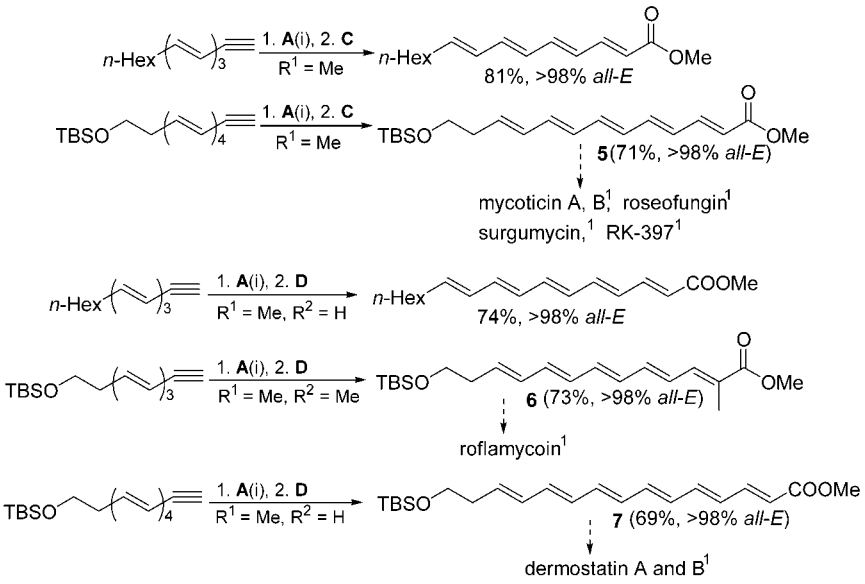
All oligoenyne products shown in Table 1 with the only possible exception of (*all-E*)-eicosahexaenyne (entry 10) are

**Table 1.** Efficient and Selective Four-Carbon Homologation of Oligoenes via Hydrozirconation−Palladium-Catalyzed Cross-Coupling with (*E*)-BrCH=CHC≡CSiMe$_3$[a]

| entry | R— | product R( )$_2$ | NMR yield,[b] % | isolated yield, % |
|---|---|---|---|---|
| 1 | *n*-Hex—[c] | *n*-Hex( )$_2$ | 91 | 85 |
| 2 | TBSO—[c] | TBSO( )$_2$ **2** | 86 | 79 |
| 3 | TBSO—(*s*) | TBSO—(*s*)( )$_2$ **8** | 84[d] | 79 |
| 4 | *n*-Hex— | *n*-Hex( )$_3$ | 86 | 80 |
| 5 | TBSO— | TBSO( )$_3$ **3** | *e* | 78 |
| 6 | *n*-Hex( )$_2$ | *n*-Hex( )$_4$ | 83 | 78 |
| 7 | TBSO( )$_2$ | TBSO( )$_4$ **4** | 81 | 73 |
| 8 | TBSO—(*s*)( )$_2$ | TBSO—(*s*)( )$_4$ **9** | 79 | 74 |
| 9 | *n*-Hex( )$_3$ | *n*-Hex( )$_5$ | 74[f] | 67[g] |
| 10 | *n*-Hex( )$_4$ | *n*-Hex( )$_6$ | 73[f] | *h* |

[a] Unless otherwise mentioned, the reaction was carried out by hydrozirconation with $HZrCp_2Cl$ in THF at 23 °C for 1 h followed by addition of (*E*)-BrCH=CHC≡CSiMe$_3$ (1.05 equiv), 5 mol % $Cl_2Pd(PPh_3)_2$ + 2DIBAH, and $ZnCl_2$ (1 equiv) in THF and stirring of the resultant mixture for 4 h at 23 °C. [b] Yield of the Me$_3$Si derivative determined by NMR analysis. [c] Hydrozirconation of the alkyne was carried out by using *i*-Bu$ZrCp_2Cl$. [d] By GLC analysis. [e] Not determined. [f] Isolated yield of the silylated derivative. [g] Overall isolated yield based on the starting trienyne. [h] Clean desilylation with methanolic $K_2CO_3$ has not been achieved.

**Scheme 2**

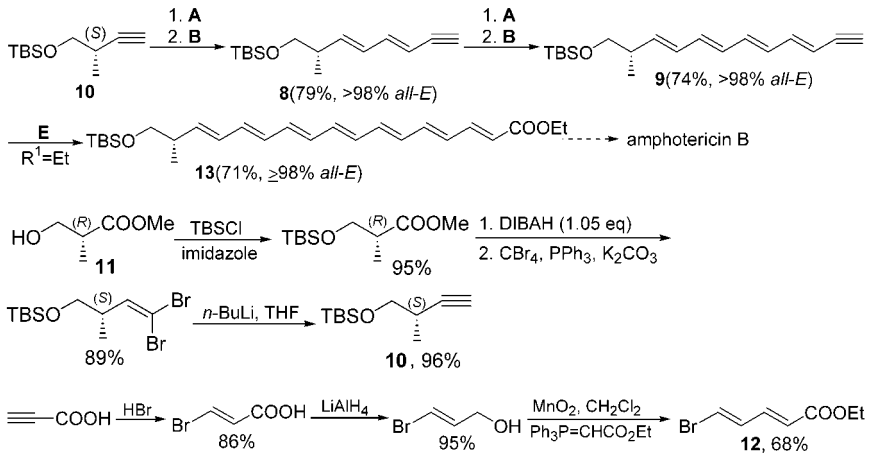



sufficiently stable, under the usual experimental conditions, to permit their isolation, spectroscopic characterization, and use in subsequent reactions with minimal extra precautions. None of the $^{13}$C NMR spectra of the oligoenynes reported in this paper, either silylated or unsilylated, revealed the presence of any isomeric or other byproducts at the S/N ratio of >50−100. Furthermore, the (3*E*,5*E*)-3,5-dodecadien-1-yne (entry 1 in Table 1) and its 3*E*,5*Z* isomer, prepared by the Pd-catalyzed cross-coupling reaction of **1** with (*Z*)-(*n*-Hex)CH═CHZnBr, as well as their terminally silylated derivatives, displayed discrete $^{13}$C NMR spectra permitting the detection of even 1 mol % of a stereoisomer. On these bases, the stereoisomeric purity of >98−99% for either silylated or unsilylated oligoenynes herein reported may be claimed.

As has been demonstrated in the literature,[1,2,9] *ω*-hydroxy- and *ω*-heterooligoenoic carboxylic and other carbonyl derivatives can serve as convenient intermediates for the synthesis of a variety of natural products including oligoene macrolide antibiotics. To this end, some convenient and satisfactory procedures for converting terminal alkynes into esters were screened. The experimental results of two such transformations are summarized in Scheme 2 along with reported and/or possible applications to the synthesis of macrolide antibiotics.

The formation of an unacceptably impure product in the desilylation of the $Me_3Si$-protected (*all-E*)-eicosahexaenyne (entry 10) has been the only difficulty thus far encountered. It should be clearly noted, however, that the $Me_3Si$-protected derivative was stable enough for its isolation and characterization with no sign of decomposition. As we further examine this point, however, some alternate procedures have been sought, and the following highly selective and satisfactory route has been developed (Scheme 3). The starting alkyne

**Scheme 3**



**10** was prepared from 99% optically pure commercially available (*R*)-$HOCH_2CH(Me)COOMe$ (**11**) in four steps in 81% overall yield,[10,11] and the bromodienoic ester **12** was prepared as a >99% stereoisomerically pure substance from propiolic acid in three steps in 56% overall yield via (i) *syn* addition of HBr,[12] (ii) reduction with $LiAlH_4$, and (iii) one-pot oxidation ($MnO_2$)−olefination with $Ph_3PCHCOOEt$.[13] With **10** and **12** in hand, no difficulty was encountered in converting **10** into **13** via (i) iterative (twice) homologation under the conditions **A** and **B** to give **9** in two steps in 58% combined yield and (ii) Pd- and Zn-catalyzed conjugate substitution.[14] Thus, the synthesis of a heptaenoic ester **13**, which can potentially serve as an intermediate for the synthesis of amphotericin B,[9] has been achieved in only three steps from three synthons, i.e., **1**, **10**, and **12**, in 42% overall yield. It is particularly noteworthy that the overall stereo- and regioisomeric purity of ≥98%, determined by $^{13}C$ and $^1H$ NMR analysis, was achieved without any intentional isomeric fractionation, the main operation of purification in each isolation−purification being a simple short-path chromatography.

Further methodological investigation and applications to the synthesis of natural products are being actively pursued.

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**Supporting Information Available:** Experimental procedures, spectroscopic data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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