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New Conjunctive Reagents as Cross-Coupling Partners En Route to Retinoid-like Polyenes

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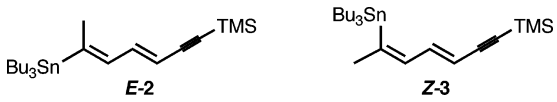
ABSTRACT

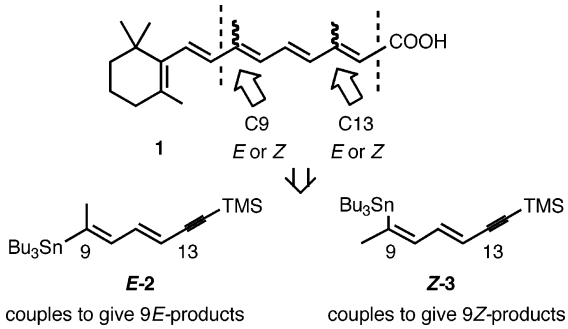


New conjunctive reagents *E*-2 and *Z*-3 can be used, after transmetalation, in Negishi couplings with vinyl and aryl iodides. The subsequently unmasked terminal alkynes can be further manipulated to arrive at retinoid-like products.

Retinoids regulate a vast array of biological processes, including cell differentiation and proliferation, control of embryonic development, as well as apoptosis.[1] They are routinely used clinically both in dermatology (e.g., accutane) and for treatment of select oncological diseases. Synthetic studies abound in this field, with many potentially useful routes to the highly conjugated polyenic core where the accent is on analogue formation.[2] Most of the disconnections associated with the parent skeleton, *all-trans*-retinoic acid, as well as the valued 9*Z*- and 13*Z*-isomers, have been examined. Traditional Wittig/Horner−Emmons chemistry,[3] Julia couplings,[4] and more recent organometallic cross-coupling methodology[5] have been successfully utilized. In this paper, we disclose two new linchpin or "conjunctive" reagents that have been designed for rapid construction of stereochemically controlled analogues of the parent skeleton.

Disconnection of the basic retinoic acid array between C-8, C-9, and C-14, C-15 in **1** leads to two isomeric seven carbon subunits ***E*-2** and ***Z*-3** that allow for direct introduction of C-9 in either the *E*- or *Z*-geometry via Negishi coupling of the derived vinylzinc reagents (Scheme 1). Subsequent

Scheme 1



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(1) (a) *The Retinoids*; Sporn, M. B., Roberts, A. B., Goodman, D. S., Eds.; Raven Press: New York, 1994. (b) Altucci, L.; Rossin, A.; Raffelsberger, W.; Reitmair, A.; Chomienne, C.; Gronemeyer, H. *Nature Med.* **2001**, *7*, 680. (c) Faul, M. M.; Grese, T. A. *Curr. Opin. Drug Discov. Dev.* **2002**, *5*, 974.

(2) Dominquez, B.; Alvarez, R.; de Lera, A. R. *Org. Prep. Proc. Int.* **2003**, *35*, 239. *Chemistry and Biology of Synthetic Retinoids*; Dawson, M. L., Okamura, W. H., Eds.; CRC Press: Boca Raton, FL, 1990.

(3) Pommer, H. *Angew. Chem.* **1977**, *89*, 437.

(4) Jeon, H.-S.; Yeo, J. E.; Jeong, Y. C.; Koo, S. *Synthesis* **2004**, 2813.

(5) For representative examples, see Otero, M. P.; Torrado, A.; Pazos, Y.; Sussman, F.; de Lera, A. R. *J. Org. Chem.* **2002**, *67*, 5876. Dominguez, B.; Iglesias, B.; de Lera, A. R. *Tetrahedron* **1999**, *55*, 15071.

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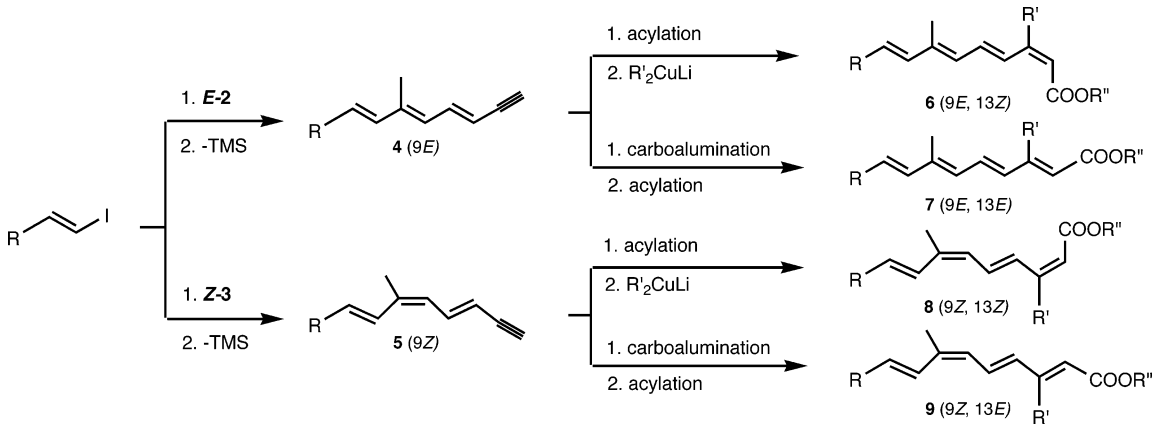
Scheme 2



desilylation to the corresponding terminal alkynes **4** and **5** permit either acylation to a reactive ynoate subject to stereocontrolled manipulation of the acetylenic moiety (e.g., cuprate additions to give **6** and **8**) or a carboalumination/acylation sequence that arrives at the isomeric product (e.g., **7** and **9**; Scheme 2).

Preparation of *E*-2 and *Z*-3. Starting with commercially available 2-butynol (**10**) as educt for both conjunctive reagents, stannylcupration at −78 °C affords allylic alcohol ***E*-11**, which is smoothly oxidized with MnO_2 at rt to enal **12** (Scheme 3). Wittig olefination with the Bu_3P-derived ylide **13** formed from silylated propargyl bromide at −100 °C leads to ***E*-2** of >99% stereochemical purity. Treatment of **10** with Red-Al in THF at rt, on the other hand, followed by quenching with Bu_3SnCl leads to *Z*-allylic alcohol ***Z*-11**. Identical processing as for ***E*-11** ultimately gives predominantly ***Z*-3** as a 90:10 mix of *Z*/*E* isomers (the outcome of the Wittig reaction).

Cross-Couplings of *E*-2 and *Z*-3. Negishi reactions of organozinc halides derived from vinylstannanes *E*-2 and *Z*-3 appeared to offer the best option for realizing the highly conjugated polyenyne products. After lithiation at −78 °C with *n*-BuLi, which produced deep green solutions in THF, introduction of dry, fused $ZnCl_2$ in THF (1 equiv) and warming to rt gave a yellow-tan solution of the derived organozinc chloride. Addition of a vinyl or aryl iodide and then 5% $Pd(Ph_3P)_4$ with stirring overnight of the resulting purple-red mixtures gave clean couplings by TLC. Moderate to high yields of the desired products could be obtained after flash chromatography. Little homocoupling of either partner was observed. Several examples using ***E*-2** or ***Z*-3** are illustrated in Tables 1 and 2, respectively. From these cases, it appears that both linchpins couple with equal facility, introducing the *E*- or *Z*- stereochemistry formally at the retinoid C-9 or equivalent site. An acetylenic halide could also be used to afford a diynic product (Table 1, entry G). Desilyation of all polyenynes could be effected usually in >90% yields using ethanolic carbonate at ambient temperatures (Scheme 4). The resulting terminal acetylenes **24** were found to have limited shelf life even when maintained in a frozen benzene matrix and protected from light.

Carboalumination/Acylation. Negishi carboalumination[6] of the newly formed terminal alkynes required mildly forcing conditions, as the extensive conjugation slows cis-addition considerably related to isolated acetylenes. Premixing Cp_2ZrCl_2 (1 equiv) and either Me_3Al or Et_3Al (4 equiv) in dichloroethane (DCE) at 0 °C followed by addition of the alkyne and stirring for 1 h at rt led to complete consumption of educt. Acylation with methyl chloroformate at rt gave good isolated yields of stereodefined polyenes **25**. Table 3 shows a number of representative examples demonstrating insertion of formal C-13 *E* stereochemistry.

Scheme 3

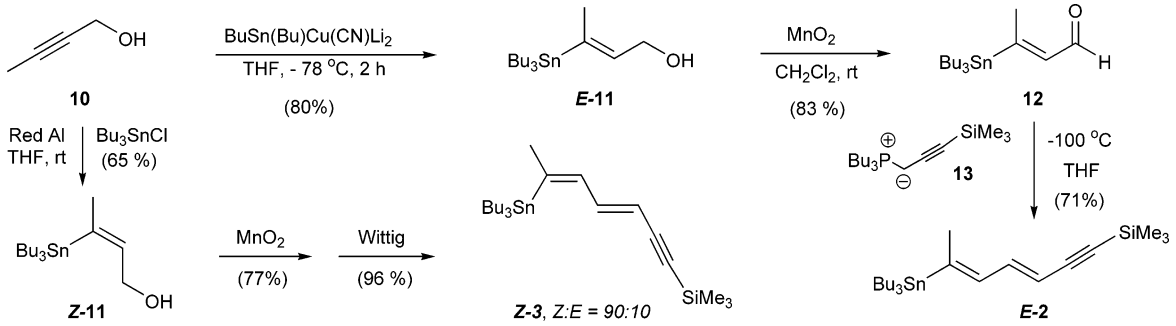
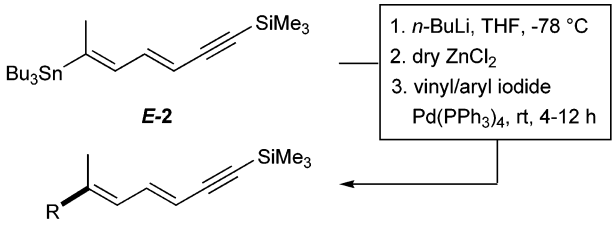
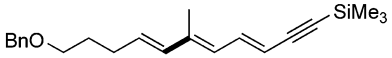
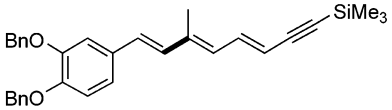
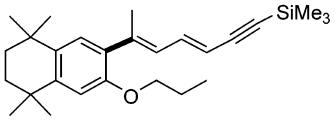
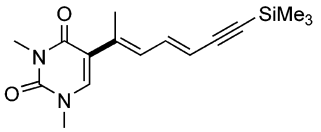
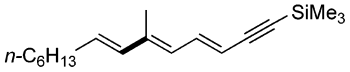
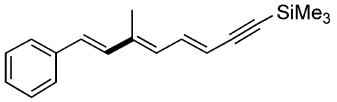
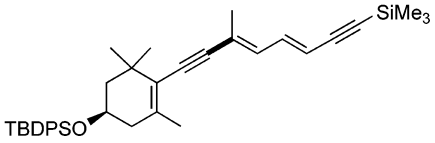


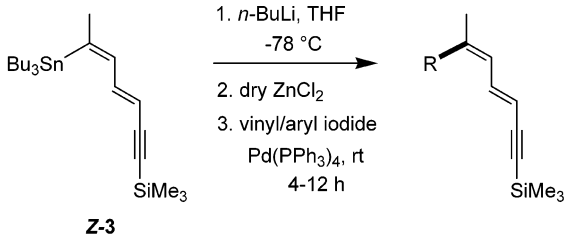
Table 1. Cross-Couplings with Conjunctive Reagent ***E*-2**[a]

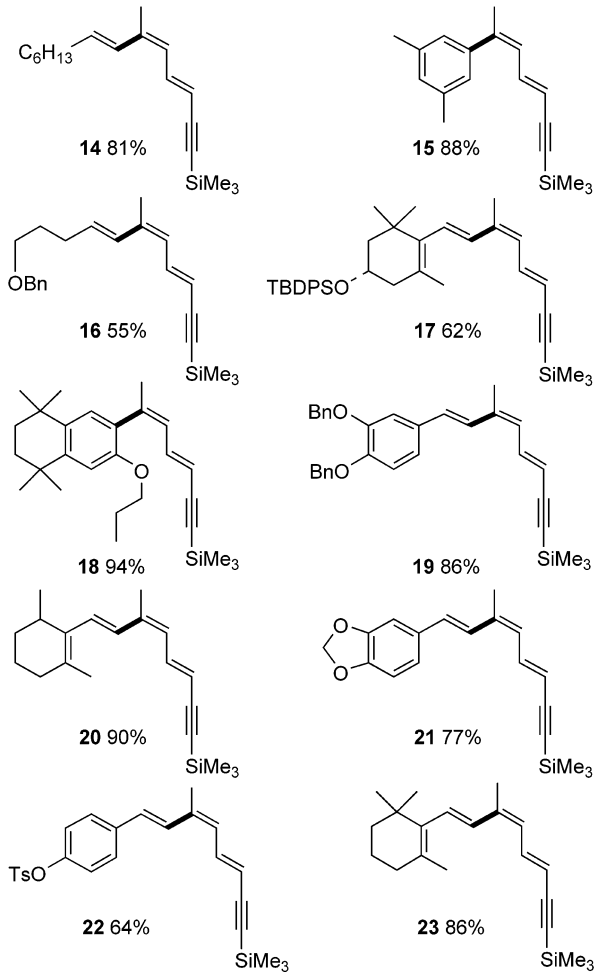


A		76%
B		61%
C		53%
D		41%
E		91%
F		66%
G		80%

[a] All yields refer to isolated, chromatographically purified materials.

Table 2. Cross-Couplings with Conjunctive Reagent ***Z*-3**[a]



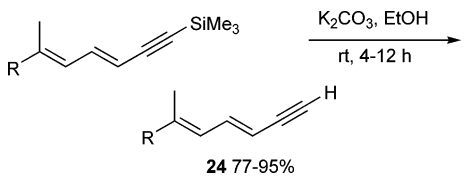


[a] All yields refer to isolated, chromatographically purified materials.

Conjugate Additions. To generate the isomeric C-13 *Z* series of polyenes, a representative trienynoate **26** was treated with various organocopper reagents (Scheme 5). After considerable experimentation aimed at minimizing unwanted *E* isomer,[7] careful dropwise addition of Me_2CuLi to **26** in THF at −78 °C followed by the addition of MeOH (7 equiv) reproducibly afforded the desired *Z*-adduct **27** exclusively judging from ^1H NMR. Likewise, Bu_2CuLi could be added to form **28** in high isolated yield. Stannylcopper, $Me_3SnCu{\cdot}LiBr$, added in a similar fashion, led to the highly sensitive *Z*-*β*-stannyl tetraenoate **29** in modest yield.

The alkyne moiety, e.g., in **30**, provides alternative modes of functionalization and/or substitution (Scheme 6). Thus, carboalumination/iodination with I_2 in THF at 0 °C to rt afforded *E*-tetraene **31** (65% isolated). Other protocols (e.g.,

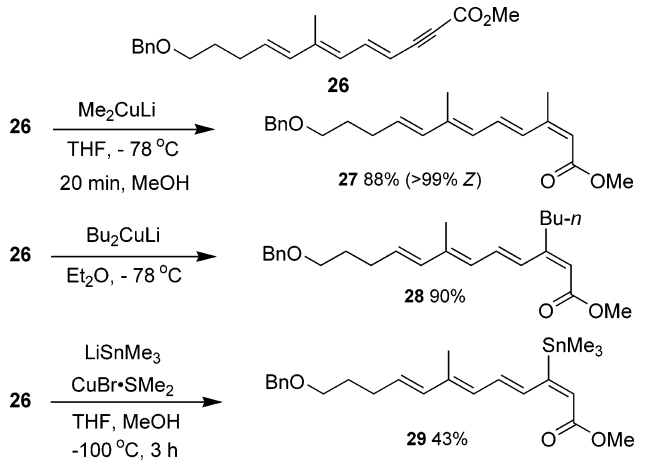
Scheme 4



24 77-95%

(6) Negishi, E. *Acc. Chem. Res.* **1987**, *20*, 65.
(7) Krause, N.; Hoffmann-Roder, A. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Dortmund, 2002; pp 145−165.

Scheme 5



NIS in THF or DCE) led to significant amounts of protio-quenched product. Lindlar reduction of **26** using 1 equiv of quinoline in EtOAc gave (in <1 h) the *E,E,E,Z*-tetraenoate **32** (77% isolated). Complete over-reduction was observed in dry THF.

In summary, new conjunctive reagents, stannylated di-enynes ***E*-2** and ***Z*-3**, can be prepared in gram quantities and used in a short sequence to arrive at highly conjugated polyenic arrays characteristic of retinoids.

Scheme 6

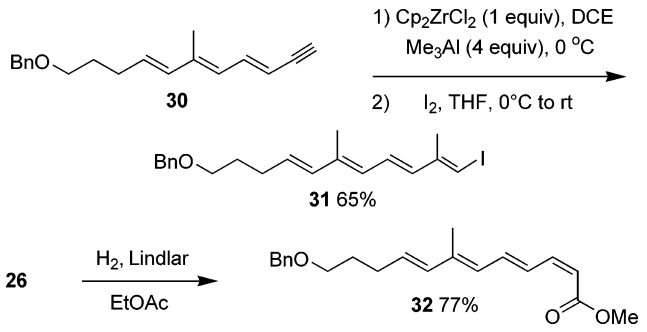
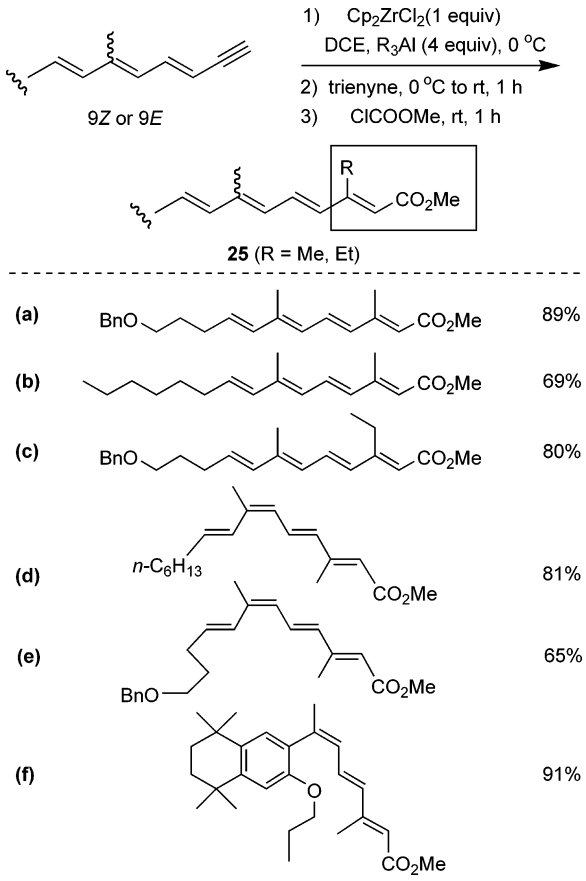


Table 3.



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Supporting Information Available: Procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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