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A Novel, Selective, and Efficient Route to Carotenoids and Related Natural Products via Zr-Catalyzed Carboalumination and Pd- and Zn-Catalyzed Cross Coupling

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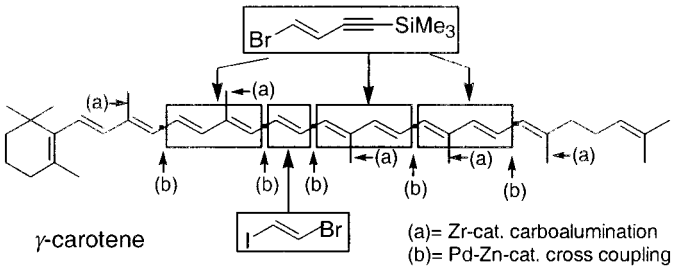
ABSTRACT



A highly efficient and stereoselective protocol for the syntheses of symmetrical and unsymmetrical carotenoids involving Zr-catalyzed carboalumination of conjugated oligoenynes and Pd- and Zn-catalyzed alkenyl–alkenyl coupling has been developed and applied to the syntheses of β- and γ-carotene and vitamin A. γ-Carotene of ≥99% isomeric purity was prepared in three linear steps (five steps overall) from β-ionone, enyne 8, (*E*)-ICH═CHBr, and (*E*)-$Me_3SiC{\equiv}CCH{=}CHBr$ in 32% overall yield.

Carotenoids have been traditionally synthesized through the use of the Wittig and related reactions, which have invariably produced mixtures of *E* and *Z* isomers, necessitating delicate, tedious, and yield-lowering isolation−purification processes.[1] Reported herein is an unprecedentedly stereoselective and efficient iterative and convergent method for the synthesis of both symmetrical and unsymmetrical carotenoids as well as retinoids and other related oligoenic compounds, featuring (a) Zr-catalyzed carboalumination of alkynes[2] and (b) Pd- and Zn-catalyzed reaction of the resultant alkenylalanes[3,4] with (*E*)-1-bromo-2-iodoethylene (**1**)[5] and (*E*)-1-bromo-4-trimethylsilyl-1-buten-3-yne (**2**)[6] used as two- and four-carbon synthons, respectively.

With the two- and four-carbon synthons **1** and **2** in hand, β-carotene (**3**), a representative symmetrical carotenoid, was synthesized as a ≥99% isomerically pure compound from β-ionone (**4**) in three linear steps (or three isolation−purification operations)[7] in 41% overall isolated yield via

(1) (a) Isler, O., Ed. *Carotenoids*; Birkhauser Verlag: Basel, 1971; p 932. (b) Britton, G.,Goodwin, T. W. Eds. *Carotenoid Chemistry and Biochemistry*; Pergamon Press: Oxford, 1982; p 224. (c) Bernhard, K.; Mayer, H. *Pure Appl. Chem*. **1991**, *63*, 35. (d) For a recent modification of the generation of allylic ylides, see: Okukado, N.; Uchikawa, O.; Nakamura, Y. *Chem. Lett*. **1988**, 1449.

(2) (a) Van Horn, D. E.; Negishi, E. *J. Am. Chem. Soc*. **1978**, *100*, 2252. (b) Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc*. **1985**, *107*, 6639. (c) For a review, see: Negishi, E. *Pure Appl. Chem*. **1981**, *53*, 2333.

(3) Baba, S.; Negishi, E. *J. Am. Chem. Soc*. **1976**, *98*, 6729.

(4) Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc*. **1978**, *100*, 2254.

(5) (a) For an early synthesis in 45% yield, see: Viehe, H. G.; Franchimont, E. *Chem. Ber*. **1963**, *96*, 3153. (b) For an improved synthesis, see: Negishi, E.; Alimardanov, A.; Xu, C. *Org. Lett*. **2000**, *2*, 65.

(6) A related bromoenyne protected with the *t*-$BuMe_2Si$ group was reported in ref 5b.

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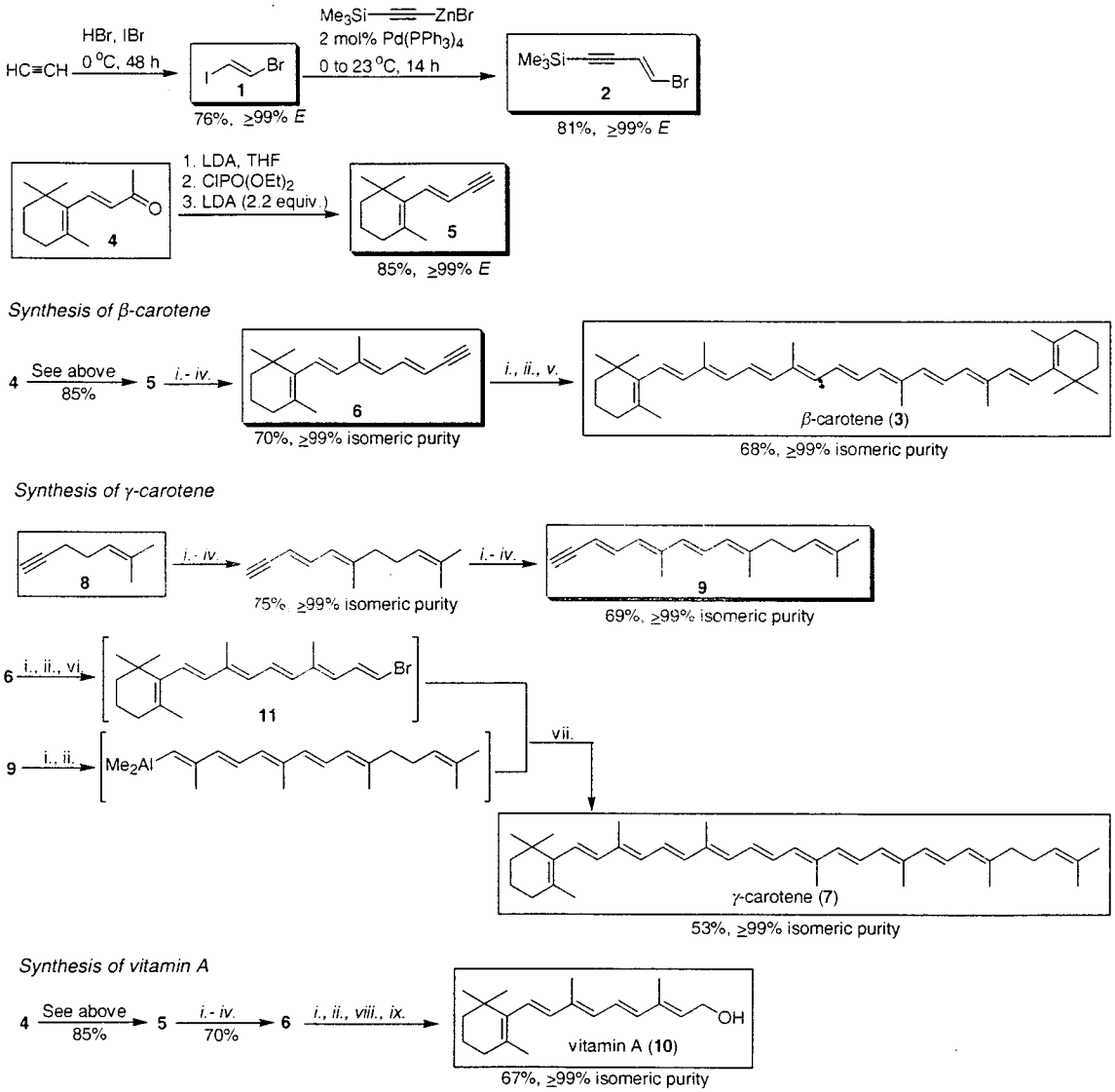
Scheme 1[a]



[a] i. Me_3Al (2 equiv), Cp_2ZrCl_2 (1 equiv), $(CH_2Cl)_2$, 23 °C, 4 h; ii. evaporation at 50 °C and <0.5 mmHg; iii. **2** (1.05 equiv), $ZnCl_2$ (1 equiv) in THF, 2.5 mol % of $Pd_2(dba)_3$, 10 mol % of TFP [= tri(2-furyl)phosphine], DMF, 23 °C, 6 h; iv K_2CO_3, MeOH, 23 °C, 3 h; v. **1** (0.5 equiv), $ZnCl_2$ (1 equiv) in THF, 2.5 mol % of $Pd_2(dba)_3$, 10 mol % of TFP, DMF, 23 °C, 8 h; vi. **1** (1.05 equiv), $ZnBr_2$ (1 equiv) in THF, 5 mol % of $Pd(PPh_3)_4$, DMF, 23 °C, 2 h; vii. $ZnCl_2$ (1 equiv) in THF, 2.5 mol % of $Pd_2(dba)_3$, 10 mol % of TFP, DMF, 23 °C, 6 h; viii. THF, *n*-BuLi (1 equiv), 23 °C, 0.5 h; ix. $(CH_2O)_n$ (3 equiv), 23 °C, 5 h.

dienyne **5** and tetraenyne **6**, while γ-carotene (**7**), a representative unsymmetrical carotenoid, was synthesized also as a ≥99% isomerically pure compound from β-ionone (**4**) and 6-methyl-5-hepten-1-yne[8] (**8**) via **6** and **9** in three longer linear steps requiring five total steps in 32% overall isolated yield; the combined isolated yield for the additional two steps for the conversion of **8** into **9** is 52%. Similarly, vitamin A (**10**) of ≥99% isomeric purity was synthesized from β-ionone (**4**) in three linear steps in 40% overall isolated yield (Scheme 1).

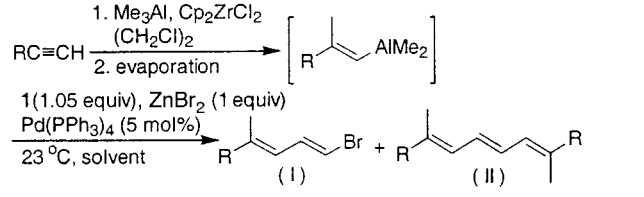
(7) A step is defined here as a sequence consisting of one or more reactions followed by an isolation−purification operation.

(8) (a) Negishi, E.; King, A. O.; Klima, W. L.; Patterson, W.; Silveira, A., Jr. *J. Org. Chem.* **1980**, *45*, 2526. See also: Negishi, E.; King, A. O.; Tour, J. M. *Org. Synth.* **1985**, *64*, 44. (b) Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1974**, 705.

It should be noted that, in the Pd-catalyzed cross coupling producing γ-carotene (**7**) in Scheme 1, analysis of the crude product containing **7** by NMR spectroscopy before chromatography indicated that **7** was contaminated with only ≤2% of β-carotene (**3**). Thus, the Pd-catalyzed reaction of an alkenylalane derived from **6** with 1.05 equiv of **1** selectively produces bromide **11** with minimal formation of the 2:1 product, i.e., **3**. Because of the instability of **11**, however, direct analysis of crude **11** by NMR spectroscopy was not successful. To probe the general synthetic utility of **1** as an (*E*)-ethylene synthon having two clearly differentiated functional groups in the synthesis of conjugated di- and oligoenes, phenylacetylene and (*E*)-3-decen-1-yne were methylaluminated and freed of the solvent and excess reagents via evaporation under conditions i and ii shown in Scheme 1.

As the results of the Pd-catalyzed cross coupling of the alkenylalanes formed above with 1.05 equiv of **1** run in THF or DMF−THF (2:1) summarized in Table 1 indicate, clean

Table 1. Pd-Catalyzed Reaction of Alkenylalanes with (*E*)-1-Bromo-2-iodoethylene



R of RC≡CH	solvent	time, h	yield,[a] % (I)	(II)
Ph	DMF-THF(2:1)	1	84	trace
	THF	1	20	trace
	THF	12	30	10
n-Hex	DMF-THF(2:1)	1	81	trace
	THF	1	19	trace
	THF	12	33	8

[a] By GLC.

and selective formation of the desired bromides is observable only in the presence of DMF as a cosolvent. THF alone is unsatisfactory in these reactions.

It is equally important that, throughout all of the syntheses shown in Scheme 1, careful examination of each step by ^{1}H and ^{13}C NMR spectroscopy before and after product isolation−purification has clearly indicated that the extent of formation of stereoisomers, if any, is ≤1−2% (S/N ≥ 50−100). Although the Zr-catalyzed methylalumination is known to produce minor amounts (typically ≤5%) of regioisomers containing Al in an internal position,[2] the amount of any isomeric byproduct[9] after cross coupling (steps iii and vi) or hydroxymethylation (step ix) is estimated to be ≤1−2% each. This is most likely attributable to the lower reactivity of the internally aluminated isomers relative to that of the desired terminally aluminated isomers. No difficulty has been encountered in obtaining any of the isolated products in Scheme 1 in ≥99% isomeric purity after a simple and single chromatographic operation (silica gel or neutral alumina). In short, all steps are ≥99% stereoselective, and minor amounts of regioisomers and other isomers can be readily separated to give ≥99% isomerically pure carotenoids.

The unprecedentedly high selectivity level achieved in this study is critically dependent on a hitherto largely unrecognized ability of the Zr-catalyzed carboalumination (methylalumination to be specific) to maintain (i) high product yield, (ii) high regioselectivity of ≥95%, and (iii) essentially 100% stereoselectivity even in those cases where the number of conjugated π-bonds is as many as five. These favorable characteristics are not readily shared by widely used hydrometalation reactions involving Al, B, and Zr.[10] These hydrometalation reactions are generally very favorable with simple terminal alkynes. With conjugated terminal alkynes, however, these reactions tend to place metals at internal carbon atoms to considerable extents.[5b,10]

Another critical finding is that β,β-disubstituted alkenylalanes generated in situ by the Zr-catalyzed carboalumination can be directly and selectively cross-coupled with the two- and four-carbon synthons **1** and **2** under the optimized conditions of the double metal catalysis involving Pd and Zn reagents,[4,11] permitting the desired five-carbon homologation of terminal alkynes with almost a total control of stereo- and regiochemistry in one pot. This is, at least in part, due to the very favorable reactivity of **1** and **2** in their Pd-catalyzed cross coupling. Although known for more than two decades, application of the Zr-catalyzed carboalumination to the synthesis of natural products by direct carbometalation−cross coupling tandem processes has been limited to a very small number of cases.[12] In most of the other cases, the carboalumination products have been converted first to the corresponding iodides and other organic derivatives and then used in subsequent cross coupling and other steps after purification.[13] Indeed, we have previously reported that **5** can be cleanly converted to (*E*,*E*)-1-(4′-iodo-3′-methyl-1′,3′-butadienyl)-2,6,6-trimethylcyclohexene in 82% yield.[13a] Its reaction with the Zn derivative of **2**, generated in situ via treatment of **2** with *t*-BuLi (2.1 equiv) in Et_2O (−78 °C) followed by addition of dry $ZnBr_2$ (1 equiv) in THF (−78 °C), under conditions similar to those of step iii in Scheme 1 provided ≥99% isomerically pure **6** in 92% yield after deprotection and simple column chromatography. Although this double functional modification, i.e., Al → I and Br → Li → Zn, does lead to a higher yield of cross coupling, it involves at least one more step. Overall, the one-pot procedure is clearly the more favorable of the two.

γ-Carotene has been previously synthesized first by Weedon[14a] and later by Eugster.[14b] In the Weedon synthesis, the $C_{15} + C_{10} + C_{15}$ building principle was applied by using (all-*E*)-2,7-dimethyl-2,4,6-octatriene-1,8-dial obtainable in six

(9) These very minor byproducts are mostly unidentified, but the likelihood of their being isomeric to the desired products are inferred, for example, by their GLC analysis, when applicable.

(10) (a) Zweifel, G.; Arzoumanian, H.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, *89*, 3652. (b) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333. (c) Lipshutz, B. H.; Lindsley, C. *J. Am. Chem. Soc.* **1997**, *119*, 4555. (d) Unpublished results observed by M. Hata and F. Zeng in our laboratories.

(11) In addition to the cross coupling conditions indicated in the footnote iii in Scheme 1, the use of 5 mol % of $Cl_2Pd(PPh_3)_2$ and 10 mol % of DIBAH in THF was comparably satisfactory.

(12) For example, a-farnesene was synthesized by Zr-catalyzed methylalumination followed by Pd-catalyzed allylation in one pot [Matsushita, H.; Negishi, E. *J. Am. Chem. Soc.* **1981**, *103*, 2882].

(13) (a) Negishi, E.; Owczarczyk, Z. *Tetrahedron Lett.* **1991**, *32*, 6683. (b) Barrett, A. G. M.; Edmunds, J. J.; Hendrix, J. A.; Horita, K.; Parkinson, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1238. (c) Rayner, C. M.; Astles, P. C.; Paquette, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 3926. (d) Torrado, A.; Iglesias, B.; López, S.; de Lera, A. R. *Tetrahedron*, **1995**, *51*, 2435. (e) Miyaoka, H.; Saka, Y.; Miura, S.; Yamada, Y. *Tetrahedron Lett.* **1996**, *37*, 7107. (f) Liu, F.; Negishi, E. *J. Org. Chem.* **1997**, *62*, 8591. (g) Kuramochi, K.; Nagata, S.; Itaya, H.; Takao, K.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 7371.

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steps in 25% overall yield[15] as the C_{10} synthon. The requisite C_{15} synthons were prepared from β- and ψ-ionones in a few steps in about 45−50% yields. Although a two-step assemblage of γ-carotene proceeded in 52 and 83% yields, the product was a mixture of stereoisomers of unspecified isomeric composition, from which the all-*E* isomer was obtained in an unspecified yield by chromatography and recrystallization. In the Eugster synthesis, the same final Wittig reaction of β-ionylidene-ethyltriphenylphosphonium bromide with (C_{25})-*apo*-12-lycopenal produced a mixture of isomers, from which γ-carotene of 80% isomeric purity was obtained in 2% yield after repeated recrystallization from hexane.

In summary, delicate, tedious, and yield-lowering isomer separation and product purification associated with the conventional carotenoid syntheses can be almost totally circumvented in the novel methodology reported herein, and it promises to significantly alter not only the synthesis of carotenoids but also that of related other natural products.

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

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(15) Mildner, P.; Weedon, B. C. L. *J. Chem. Soc.* **1953**, 3294.