ORGANIC
LETTERS

2002
Vol. 4, No. 2
261−264

A Novel, Highly Selective, and General Methodology for the Synthesis of 1,5-Diene-Containing Oligoisoprenoids of All Possible Geometrical Combinations Exemplified by an Iterative and Convergent Synthesis of Coenzyme Q_{10}

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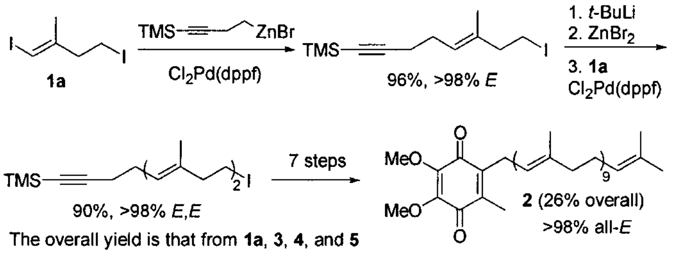
Received November 7, 2001

ABSTRACT



The overall yield is that from **1a**, **3**, **4**, and **5**

A truly general, versatile, and highly regio- and stereoselective methodology for the synthesis of terpenoids containing 1,5-diene units of *E* and/or *Z* geometry critically involves Pd-catalyzed homoallyl- and homopropargyl-alkenyl coupling and Zr-catalyzed carboalumination of alkynes. By using this methodology, coenzyme Q_{10}, (*E*,*Z*,*E*)-geranylgeranoil, and other natural or unnatural compounds have been synthesized efficiently.

We report herein an unprecedentedly efficient, highly selective, and general methodology for the synthesis of stereo- and regiodefined isoprenoids containing 1,5-diene moieties of all conceivable geometrical combinations via one-pot chain elongation by one *E* or *Z* C_5 isoprene unit predominantly in the "tail-to-head" (T-to-H) direction.[1,2] The development of the methodology was critically dependent on several reactions and procedures we have previously discovered and developed. First, screening of several candidates led to the selection of (*E*)- and (*Z*)-1,4-diiodo-2-methyl-1-butenes (**1a** and **1b**) as difunctional (*E*)- and (*Z*)-isoprene synthons permitting one-pot chain elongation with incorporation of an either (*E*)- or (*Z*)-isoprene equivalent that can be repeated twice or more, while maintaining a very high stereoselectivity level (vide infra). Throughout this study, no stereoisomers were formed and/or detected even after

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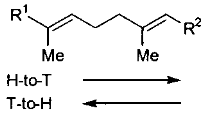
[1] This work was orally presented in part as a short invited lecture at the 10th IUPAC OMCOS Symposium, Versailles, France, July 18−22, 1999, and its abstract has been published as part of the symposium proceedings: Negishi E.; Liou, S. Y.; Xu, C.; Huo, S. *Polyhedron* **2000**, *19*, 591.

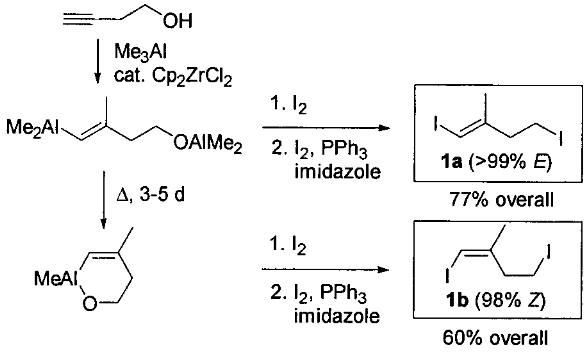
[2] The "head-to-tail" (H-to-T) and "tail-to-head" (T-to-H) directions in isoprenoids are defined as shown below, for the sake of convenience.



10.1021/ol010263d CCC: $22.00

many synthetic operations as long as the *E* synthon (**1a**) was used. We therefore judge that the stereoisomeric purity of **1a** that is readily preparable from 3-butyn-1-ol in two steps[3,4] in 77% overall yield must be infinitesimally close to 100% (Scheme 1). The *Z* isomer of **1a**, i.e., **1b**, has recently become accessible via thermal rearrangement of the product obtained by Zr-catalyzed carboalumination of 3-butyn-1-ol,[5] although the long reaction time for thermal isomerization and the 98% isomeric purity level leave some room for improvement (Scheme 1).

Scheme 1



Second, the Pd-catalyzed homoallyl-alkenyl and homopropargyl-alkenyl cross coupling of **1** with homoallylzinc and homopropargylzinc[6] derivatives developed by us can proceed selectively and in high yields without a sign of any isomerization through the use of Cl$_2$Pd(dppf)[7] as a catalyst. Particularly noteworthy is that the C$_{sp^3}$-bound homoallylic or homopropargylic I or Br does not compete to detectable extents with the C$_{sp^2}$-bound I or Br, as reported first by us,[3] permitting clean and selective elongation with **1a** or **1b** in the T-to-H direction.

Third, lithiation of primary alkyl iodides via Li−I exchange reported by us[8] and Bailey[9] in 1990 leads to the formation of the corresponding alkyllithiums generally in almost quantitative yields with little or no sign of any side reactions even in those cases where the alkyl groups are homoallyl, homopropargyl, and homobenzyl.[10] Coupled with another essentially quantitative Li-to-Zn transmetalation, an exceedingly clean and highly dependable generation of the requisite homoallyl- and homopropargylzinc derivatives can now be achieved for efficient, clean, and iterative construction of oligoisoprenoids. Although we have previously reported the treatment of homoallyl and homopropargyl halides containing Br or I with Mg in the presence of zinc halides as a satisfactory procedure,[6] it is less clean, producing some dimeric and other byproducts, and less dependable in highly demanding cases, such as those discussed herein. The difference is further accentuated in iterative synthetic operations without isolation of intermediates.

Fourth, the use of **1** requires terminations at both ends of an isoprenoid chain termed "head capping" and "tail modification" for the sake of convenience. Head capping merely requires the Pd-catalyzed homoallyl-alkenyl coupling discussed above with an appropriate 2-methyl-1-alkenyl iodide, while modification of terminal alkynes at the tail to produce (*E*)- and (*Z*)-3-methyl-2-alken-1-ols is most conveniently achieved by using our one-pot Zr-catalyzed methylalumination−ate complexation−hydroxymethylation[11] and Sato's two-step alkyne hydroxymethylation−Ti-catalyzed *syn*-hydromagnesation−methylation,[12] respectively.

The potential synthetic utility of the protocol incorporating those features discussed above is indicated by an efficient and selective iterative and convergent synthesis of coenzyme Q$_{10}$ (**2**)[13] from **1a**, 4-iodo-1-trimethylsilyl-1-butyne (**3**), (*E*)-1-iodo-2,6-dimethyl-1,5-heptadiene (**4**), and 2,3-dimethoxy-4-chloromethyl-5-methyl-1,4-benzoquinone (**5**)[14] in nine steps in 26% overall yield (Scheme 2). No stereoisomeric separation was attempted in the synthesis of 98% (all-*E*)-**2**. It should also be noted that all nine stereodefined C$_5$ isoprene units were linked and incorporated into coenzyme Q$_{10}$ (**2**) only in nine synthetic operations.

The reaction of alkenylalanes with allyl or benzyl chlorides can be achieved by using either Ni or Pd catalysts, as we originally reported in 1981,[15] but the Ni-catalyzed reaction revealed a minor tendency to undergo double bond isomerization of the cross-coupled products in some cases. A more recent report[14] claimed the superiority of Ni catalysts over Pd catalysts in terms of reaction rate and product yield, and we in fact completed our synthesis of coenzyme Q$_{10}$ using a Ni catalyst, which proved to be highly satisfactory. Further experiments summarized in Scheme 3, however, suggest that Pd catalysts are also very satisfactory in cases where chloromethylquinones are used as the electrophilic cross coupling partner.

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(4) For seminal papers on the Zr-catalyzed carboalumination, see (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) Negishi, E. *Pure Appl. Chem*. **1981**, *53*, 2333.

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(10) The use of alkyl bromides and secondary alkyl iodides leads to complex and/or unsatisfactory products.

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(14) (a) Lipshutz, B. H.; Bulow, G.; Lowe, R.; Stevens, K. L. *Tetrahedron* **1996**, *52*, 7265. (b) Lipshutz, B. H.; Kim, S.-K.; Mollard, P.; Stevens, K. L. *Tetrahedron* **1998**, *54*, 1241.

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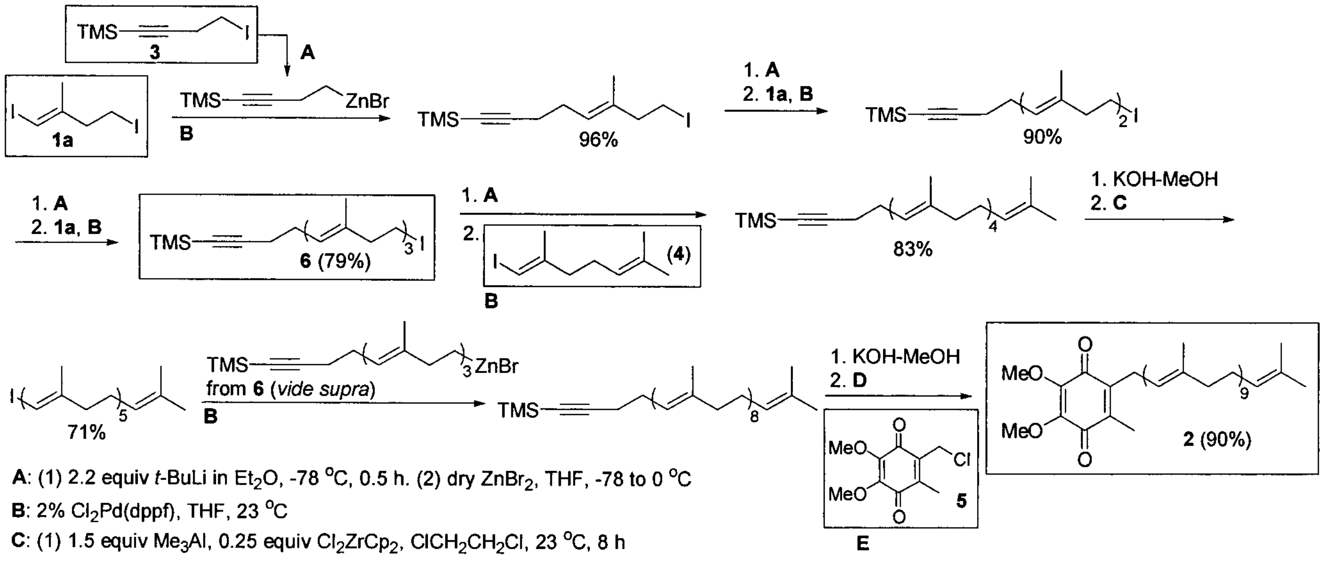
Scheme 2



A: (1) 2.2 equiv *t*-BuLi in Et_2O, -78 °C, 0.5 h. (2) dry $ZnBr_2$, THF, -78 to 0 °C

B: 2% $Cl_2Pd(dppf)$, THF, 23 °C

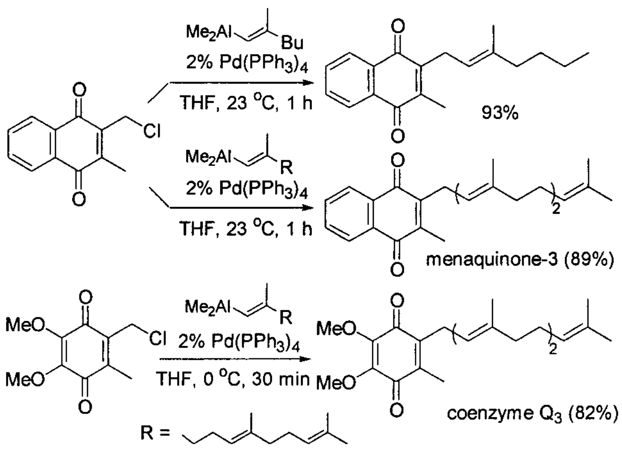
C: (1) 1.5 equiv Me_3Al, 0.25 equiv Cl_2ZrCp_2, $ClCH_2CH_2Cl$, 23 °C, 8 h
(2) I_2 (1.2 equiv), THF, -78 to 23 °C

D: (1) 1.5 equiv Me_3Al, 0.25 equiv Cl_2ZrCp_2, $ClCH_2CH_2Cl$, 23 °C, 8 h. (2) solvent evaporation, extraction with hexanes, evaporation, and addition of THF

E: 4% $Cl_2Ni(PPh_3)_2$, 8% *n*-BuLi, 8% PPh_3, THF, 23 °C

In addition to high efficiency and selectivity, the general applicability to the synthesis of all conceivable stereoisomers is yet another potential advantage of the new protocol reported herein over the existing ones. Of various existing methods, the Biellmann coupling and other related allyl-allyl coupling protocols[16] require several steps for homologation of isoprenoids by one isoprene unit. Furthermore, they are prone to stereo- and regioisomerization reactions. A recent modification by Grigorieva[17] does give the *Z* isomers, but leaves much to be desired in terms of overall efficiency and stereoselectivity, which has been <90%. Another noteworthy method is a two-pot "H-to-T" carbometalation−cross coupling tandem process introduced by us in 1980[6] and used in a number of natural product syntheses.[18] As efficient and selective as it is, it still requires two steps for homologation by one isoprene unit. Furthermore, it is as such not applicable to the synthesis of *Z* isoprenoids.

Scheme 3



To demonstrate the generality of the present protocol with respect to the *E*-*Z* geometry, two less accessible stereoisomers of farnesols, i.e., (2*E*, 6*Z*)-farnesol (**7**) and (2*Z*, 6*Z*)-farnesol (**8**), as well as (2*E*, 6*Z*, 10*E*)-geranylgeraniol (**9**) were synthesized by using (5*Z*)-8-iodo-6-methyl-1-trimethylsilyl-5-octen-yne (**10**), prepared in 84% yield from **1b** and TMS-protected homopropargylzinc bromide under the conditions **B** shown in Scheme 2. The results of the synthesis of two isomers of farnesol, i.e., **7** and **8**, are shown in Scheme 4.

Although highly satisfactory, the Pd-catalyzed cross-coupling reaction of **1b** proved to be distinctly more sluggish,[19] requiring 12 h at 23 °C for completion, whereas the corresponding reaction of **1a** was over in 1−2 h. Lithiation of **10** with *t*-BuLi at −78 °C (45 min) followed by zincation with $ZnBr_2$ at −78 to 23 °C was essentially quantitative, as judged by the yield of 8-deuterio derivative of **10** obtained via deuteriolysis with DCl-D_2O (>95% D). It should, however, be noted that the lithio derivative **12** is considerably less stable than its *E* isomer. Thus, warming the lithio derivative of **10** to 23 °C over 1 h followed by

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(16) (a) Biellmann, J. F.; Ducep, J. B. *Tetrahedron Lett.* **1969**, 3707. (b) Altman, L. J.; Ash, L.; Marson, S. *Synthesis* **1974**, 129. (c) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 8955. (d) Corey, E. J.; Shieh, W.-C. *Tetrahedron Lett.* **1992**, *33*, 6435.

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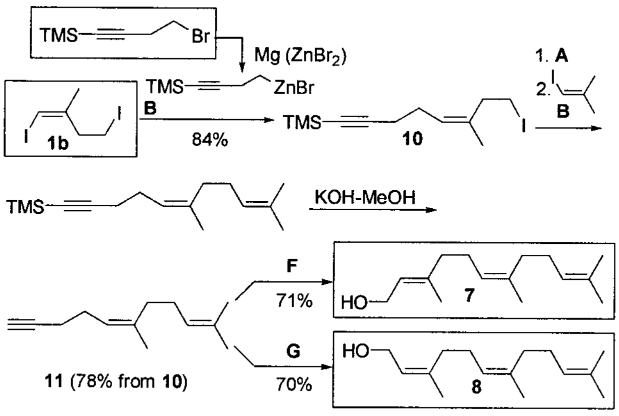
(18) For some of the earlier applications, see (a) Whitesell, J. K.; Fisher, M.; Jardine, P. D. S. *J. Org. Chem.* **1983**, *48*, 1556. (b) McMurry, J. E.; Bosch, G. K. *J. Org. Chem.* **1987**, *52*, 4885. (c) Asao, K.; Iio, H.; Tokoroyama, T. *Tetrahedron Lett.* **1989**, *30*, 6401.

(19) Although still unclear, a chelation effect due to the δ-I atom in a putative oxidation addition product may be responsible for the observed difference.

Scheme 4

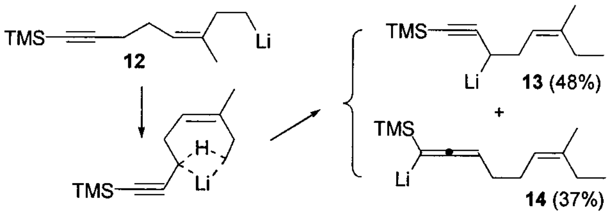


F: (1) 1.5 equiv Me_3Al, 0.25 equiv Cl_2ZrCp_2, $ClCH_2CH_2Cl$, 23 °C, 8 h. (2) solvent evaporation, extraction with hexanes. (3) *n*-BuLi, -30 °C. (4) $(CH_2O)_n$, THF, 23 °C, 3 h

G: (1) 1.1 equiv *n*-BuLi, THF, -78 to 0 °C. (2) 2.0 equiv $(CH_2O)_n$, 23 °C, 3 h. (3) 2.4 equiv *i*-BuMgCl, 10% Cl_2TiCp_2, Et_2O, 0 to 23 °C, 2 h. (4) THF, MeI, 0 to 23 °C, 2 h.

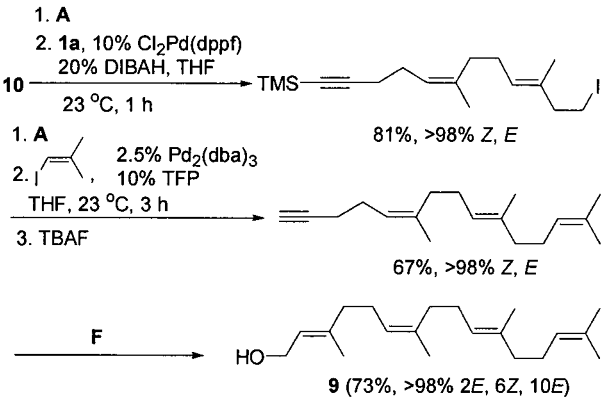
deuteriolysis gave a mixture of **13** and **14** in 48 and 37% yields, respectively, with no starting lithio derivative remaining (Scheme 5). Evidently, the 8-lithio derivative have undergone an intramolecular metallotropy. Despite these potential complications, the desired homoallylzinc bromide can be generated in nearly quantitative yield and cross coupled with 1-iodo-2-methylpropene in the presence of tris(2-furyl)phosphine (TFP) to give, after desilylation, 98% *Z* **11** in 78% yield. Conversion of **11** into **7** and **8** by using carboalumination−hydroxymethylation[11] and Sato's alkyne hydroxmethylation−Ti-catalyzed hydromagnesiation−methylation[12] proceeded in 71 and 70% yields, respectively. The stereoisomeric purity in each case was 98% by ^{13}C NMR. Although not performed, the use of **1a** in place of **1b** would produce (2*E*,6*E*)- and (2*Z*,6*E*)-farnesols.

Scheme 5



Finally, the feasibility of selectively incorporating both *E* and *Z* isomers of **1** was demonstrated by the synthesis of >98% isomerically pure (2*E*, 6*Z*, 10*E*)-geranylgeranoil (**9**) from **1a**, **1b**, **3**, and 1-iodo-2-methylpropene in 4 linear steps in 33% overall yield (Scheme 6).

Scheme 6



Acknowledgment. We thank the National Science Foundation (CHE-0080795), the National Institutes of Health (GM 36792), and Purdue University for support of this research. We also thank Albemarle, Boulder Chemical, and Johnson Matthey for assistance in the procurement of Al, Zr, and Pd compounds, respectively.

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

OL010263D