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A Study of Oligoprenyl Coupling Reactions with Allylic Stannanes

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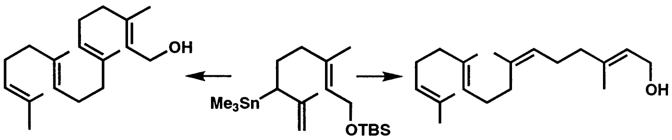
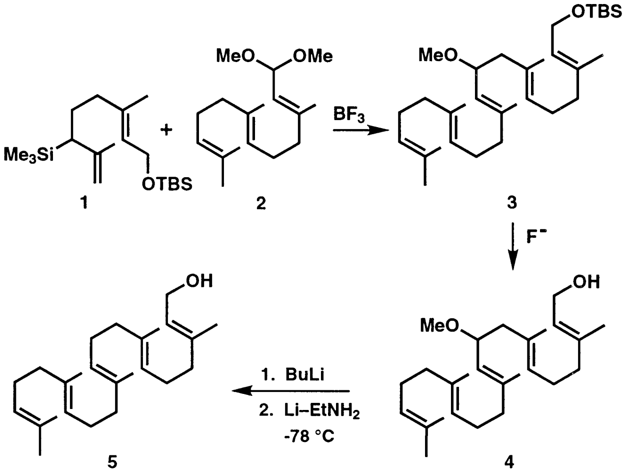
ABSTRACT



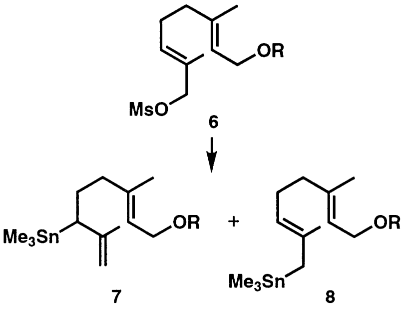
All-*E* or *E*,*Z*,*E*-oligoprenols may be synthesized from allylic stannanes by reaction with prenyl aldehydes.

We recently reported a strategically powerful method for the stereoselective synthesis of all-*E* oligoprenols by the coupling of two smaller oligoprenol fragments, as outlined in Scheme 1 (TBS = *tert*-butyldimethylsilyl) for the all-*E* pentaprenol case (**5**).[1] In connection with this work we have also studied a parallel approach using organotin intermediates rather than organosilanes such as **1**. As described herein, the results obtained with allylic stannanes contrasted sharply with the allylic silane couplings exemplified by **1** + **2** → **3**.

Scheme 1. Oligoprenyl Coupling



The synthesis of the allylic stannane **7** from the corresponding primary mesylate **6** proved to be surprisingly challenging. The use of trimethylstannyllithium alone or in combination with various metal additives invariably led either to the primary allylic stannane **8** or to mixtures of **7** and **8**. Although the most promising results were obtained with Cu(I) additives, the ratio of **7** to **8** varied widely depending on the additional ligands attached to copper in mixtures of CuI or CuBr·SMe$_2$ with Me$_3$SnLi[2] and a third component in THF as solvent. Thus, ratios of **7** to **8** as a function of additive ligand were observed as follows: 2-thienyllithium, 1.2:1; triphenylphosphine, 1.5:1; 1,2,4-triazolyllithium, 4:1. The



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[1] Radetich, B.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 2430.

[2] (a) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4836. (b) Still, W. C.; Mitra, A. *Tetrahedron Lett.* **1978**, 2659.

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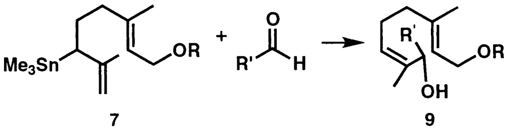
most selective reagent found was prepared from Me_3SnLi, CuI, and $P(OMe)_3$, which gave in 75% yield a mixture of **7** and **8** in a ratio of 9 to 1. This proved to be satisfactory for subsequent coupling reactions, since the minor primary allylic stannane **8** is much less reactive than the secondary isomer **7**.

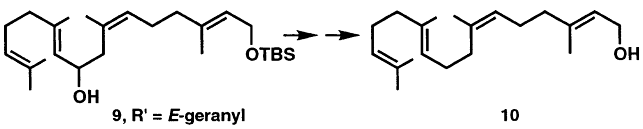
The secondary allylic stannane **7** underwent a clean thermal metallo-ene coupling reaction with a series of aldehydes to give in each case the *Z*-coupling product **9**, as summarized in Table 1. The reaction velocities for this series paralleled the electrophilicity of the aldehyde component, as expected. The *Z*-geometry of the newly created olefinic linkage in the products shown in Table 1 was clear from ^1H NMR NOE data including NOEs of ca. 12% between the olefinic CH_3 and H on the new double bond. *E*,*Z*,*E*,-Geranylgeraniol (**10**) was readily synthesized from **9**, R′ = *E*-geranyl, by the selective deoxygenation protocol summarized in Scheme 3 for **12** → **15**.[1] The synthesis of **10** demonstrates an advantageous route to such mixed *E*/*Z* oligoprenol systems, several of which occur naturally in dolichol and bacterial and plant oligoprenols.[3]

Table 1. Z-Selective Thermal Metallo-Ene Coupling of Allylic Stannane with Aldehydes



entry[a]	R′	conditions	yield
1	CCl_3	neat, 23 °, 24 h	75%
2	Ph	neat, 60 °C, 24 h	85%
3	Cy	neat, 70 °C, 24 h	45%
4	p-$NO_2C_6H_4$	0.9 M CH_2Cl_2, 60 °C, 24 h	69%
5	*E*-geranyl	neat, 90 °C, 48 h	63%

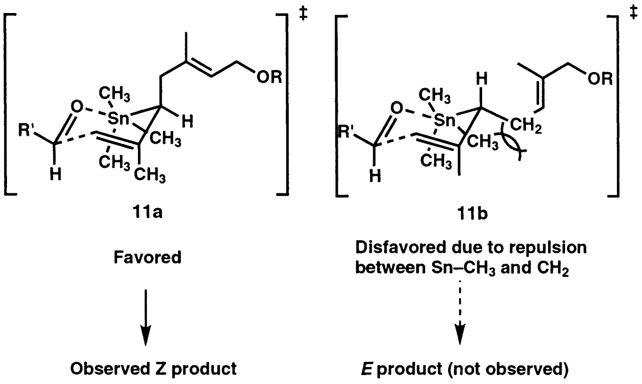
[a] Entry 5, R = TBS, otherwise R = TBDPS.



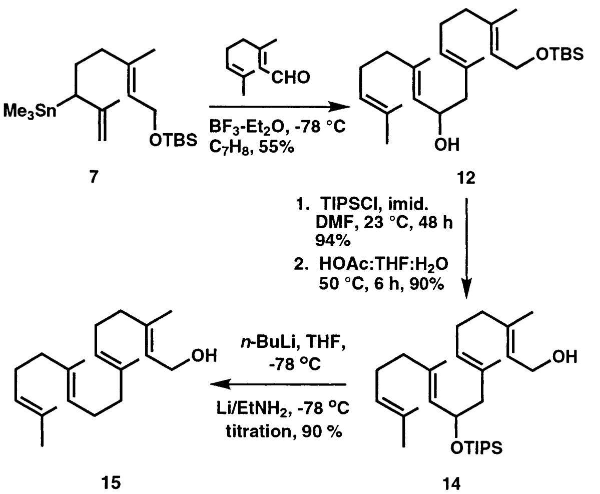
The selective generation of *Z*-olefinic geometry in the products **9** is readily explained by comparison of the chairlike transition states **11a** (which would lead to the observed *Z* olefin) and **11b** (which would produce the disfavored *E* product). As indicated in Scheme 2, **11b** is destabilized relative to **11a** by steric repulsion between one of the methyls attached to Sn and the vicinal methylene group.

Although the reaction of the allylic stannane **7** with *E*-geranial in the presence of Lewis acids was expected to produce the all-*E* coupling product **12**, in actuality it was complicated by the concomitant formation of the alternative primary-secondary coupling product **13**. The ratio of **12** to **13** varied widely with Lewis acid, solvent, and temperature, as can be seen from the following data for the ratio **12**:**13** as a function of reaction conditions: 3:2 (BF_3·Et_2O, CH_2Cl_2, −78 °C); 1:4 ($MeAlCl_2$, CH_2Cl_2, −78 °C); 3:2 (BF_3 gas, toluene, −78 °C; 1:4 ($B(C_6F_5)_3$, toluene, −78 °C); 7:3 (BF_3·Et_2O, toluene, −78 °C). The best conditions found for the preparation of **12** were 0.3 M **7**, geranial, and BF_3·Et_2O in toluene at −78 °C, which led to **12** in 55% isolated yield after silica gel chromatography. The synthesis of all-*E* geranylgeraniol (**15**) from **12** was carried out via the triisopropylsilyl (TIPS) ether **14** as outlined in Scheme 3.

Scheme 2



Scheme 3. Synthesis of All-*E*-Geranylgeraniol from Stannane **7**



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Supporting Information Available: Experimental procedures for the compounds described, along with NMR, IR, and mass spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) (a) Hemming, F. W. In *Biochemistry of Lipids*; Goodwin, T. W., Ed.; Butterworths: London, 1974; p. 39. (b) Poulter, C. D.; Rilling, H. D. *Acc.* Chem. Res. **1978**, *11*, 307.