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Synthesis of Farnesol Isomers via a Modified Wittig Procedure

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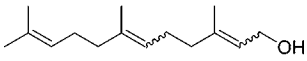
ABSTRACT



1 2*E*,6*E*-farnesol **2** 2*Z*,6*E*-farnesol
3 2*Z*,6*Z*-farnesol **4** 2*E*,6*Z*-farnesol

The four olefin stereoisomers of farnesol have been synthesized from readily available nerylacetone or commercial geranylacetone. A new variation on the use of *β*-oxido ylides favored the (2*Z*)-stereoisomers, whereas the (2*E*)-isomers were obtained through a classical Horner–Wadsworth–Emmons condensation with triethyl phosphonoacetate and reduction of the resulting ester.

Farnesol pyrophosphate (FPP) has been recognized as a key intermediate in the biosynthesis of more complex sesquiterpenoids, higher terpenoids, and steroids for many years,[1] and more recently many other roles have been discovered for both this pyrophosphate and the corresponding alcohol farnesol.[2−6] For example, farnesol acts as a quorum-sensing molecule to suppress filamentation in the fungus *Candida albicans*,[2] and farnesyl derivatives are involved in the **a**-factor mating peptide of the dodecapeptide pheromone found in *Saccharomyces cerevisiae*.[3] Terpene alcohols such as farnesol have antibacterial effects against *Staphylococcus aureus*, including promotion of potassium ion leakage.[4] Furthermore, FPP plays a pivotal role in the posttranslational processing of Ras proteins. Because mutated forms of Ras are associated with ∼30% of all human cancers,[5,6] many investigations on the biological activity of farnesol and FPP analogues have been reported. In general these studies were based upon the most abundant farnesol isomer, (2*E*,6*E*)-farnesol, while the noncommercial isomers were ignored or only tested as mixtures.[2−4] In many of these cases, it would be of interest to examine the consequences of olefin isomerization on biological activity, which has prompted new attention to the synthesis of these compounds.[7] In this communication we report the synthesis of the four olefin stereoisomers of farnesol through variations on Wittig chemistry.

Of the four possible isomers of farnesol (Figure 1, **1**−**4**), only (2*E*,6*E*)-farnesol (**1**) is commercially available in relatively high isomeric purity. In contrast, the three isomers containing at least one (*Z*)-olefin (**2**, **3**, and **4**) are available only as minor components in the commercial material. At one time it was necessary to perform repeated chromato-

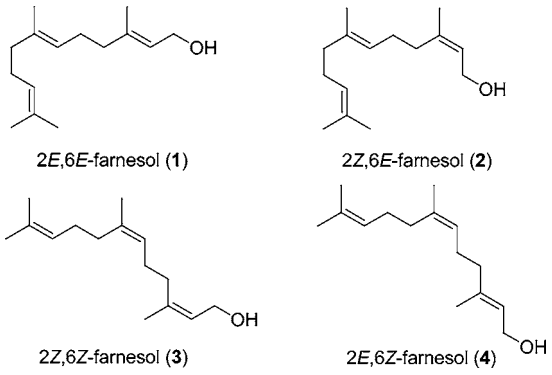


Figure 1. Farnesol isomers.

(1) Liang, P. H.; Ko, T. P.; Wang, A. H. *Eur. J. Biochem.* **2002**, *269*, 3339−3354.
(2) Shchepin, R.; Hornby, J. M.; Burger, E.; Niessen, T.; Dussault, P.; Nickerson, K. W. *Chem. Biol.* **2003**, *10*, 743−750.
(3) Xie, H.; Shao, Y.; Becker, J. M.; Naider, F.; Gibbs, R. A. *J. Org. Chem.* **2000**, *65*, 8552−8563 and references therein.
(4) Inoue, Y.; Shiraishi, A.; Hada, T.; Hirose, K.; Hamashima, H.; Shimada, J. *FEMS Microbiol. Lett.* **2004**, *237*, 325−331.
(5) Hohl, R. J.; Lewis, K. A.; Cermak, D. M.; Wiemer, D. F. *Lipids* **1998**, *33*, 39−46.
(6) Downward, J. *Curr. Opin. Genet. Dev.* **1998**, *8*, 49−54.

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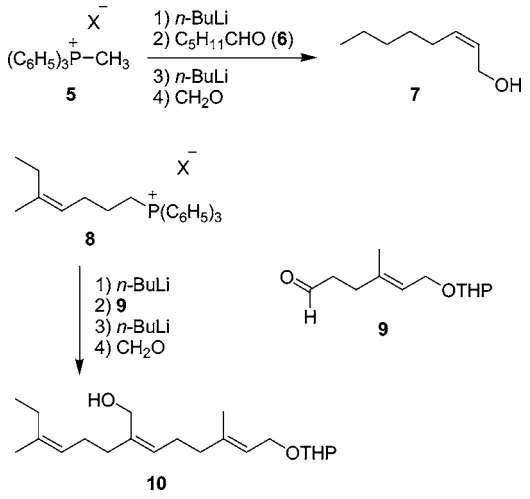
graphic separations in hopes to obtain an enriched sample of a noncommercial farnesol isomer.[8]

Recently, Gibbs and co-workers have reported four-step routes to alcohols **2**, **3**, and **4** that utilize Stille-type couplings on intermediate vinyl triflates.[7] Although these routes provide the respective farnesol isomers and are amenable to synthesis of analogues, they require both extensive chromatographic separations and the use of tin-based reagents. Given the known toxicity of tin compounds[9] and our interest in the biological activity of the farnesol isomers, development of a route that avoided use of these reagents was attractive.

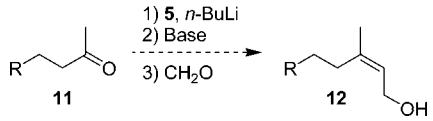
The central issue in synthesis of at least the (2*Z*,6*E*)- and (2*Z*,6*Z*)-isomers (**2** and **3**) is construction of a *cis*-allylic alcohol. The past work of Schlosser[10] and Corey[11] provides some precedent for use of a modified Wittig reaction that involves β-oxido ylides in construction of other types of (*Z*)-allylic alcohols (Scheme 1). For example, Schlosser reported

Scheme 1. Representative Applications of β-Oxido Ylides



preparation of compound **7** through condensation of methylenetriphenylphosphorane (generated in situ from the phosphonium salt **5**) with hexanal (**6**) at low temperature, followed by addition of base to generate the β-oxido ylide, addition of formaldehyde, and finally allowing the reaction to reach a temperature where elimination of triphenylphosphine oxide proceeds.[10] Homologation of the symmetrical ketones cyclohexanone and acetone also was reported.[10] Corey and co-workers employed an analogous procedure with the phosphorane derived from phosphonium salt **8** and aldehyde **9** to fabricate a key intermediate (**10**) for the synthesis of juvenile hormone.[11] In these past studies, the initial carbonyl compound employed in the condensation was an aldehyde. If the same type of procedure were used with an unsymmetrical ketone, it might be possible to achieve the desired substitution pattern from this reaction sequence, the pattern required for a primary terpenoid allylic alcohol (Scheme 2). However, whether a ketone (e.g., **11**) would

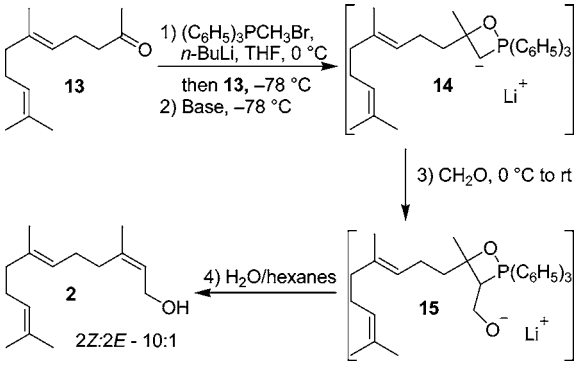
Scheme 2. Pattern of Substitution with Unsymmetrical Ketone



favor the desired (*Z*)-olefin stereochemistry (**12**) was not at first clear.

The initial investigations of this strategy (Scheme 3) were conducted with commercially available geranylacetone (**13**). Reaction of ketone **13** at low temperature with the Wittig reagent derived from methyltriphenylphosphonium bromide presumably yielded an oxaphosphetane intermediate, and although some of the corresponding olefin was observed, elimination of triphenylphosphine oxide is not facile at these low reaction temperatures. While holding the reaction temperature at −78 °C, addition of a second equivalent of strong base should lead to formation of intermediate **14**, and subsequent trapping via reaction with formaldehyde should give the alkoxide intermediate (**15**). Quenching of the reaction mixture with a combination of water in hexanes, followed by the elimination of triphenylphosphine oxide, then results in formation of farnesol **2**.[7]

Scheme 3. Reaction Scheme for the Modified Wittig Procedure



Initial experiments with procedures parallel to those reported afforded modest and variable yields of alcohol **2** (20−29%) along with trace amounts of the (2*E*,6*E*)-isomer **1** (∼10:1 ratio). Although a tertiary allylic alcohol might be formed by a competing elimination involving the C-1 oxygen, none of this product was detected. Even with the modest yield, the reaction is attractive considering that it is a one-flask protocol with only minimal chromatography.[10,11]

(7) (a) Shao, Y.; Eummer, J. T.; Gibbs, R. A. *Org. Lett.* **1999**, *1*, 627−630. (b) Zahn, T. J.; Whitney, J.; Weinbaum, C.; Gibbs, R. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1605−1608.

(8) Cane, D. E.; Iyengar. R.; Shiao, M. S. *J. Am. Chem. Soc.* **1981**, *103*, 914−931.

(9) Krigman, M. R.; Silverman, A. P. *Neurotoxicology* **1984**, *5*, 129−139.

(10) Schlosser, M.; Coffinet, D. *Synthesis* **1972**, 575−576.

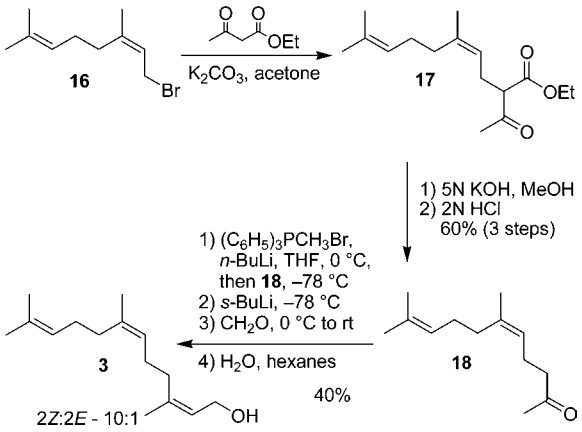
(11) Corey, E. J.; Yamamoto, H. J. *J. Am. Chem. Soc.* **1970**, *92*, 6636−6637.

A number of other conditions were examined in an effort to improve the yield. Use of *s*-BuLi for deprotonation of the oxaphosphetane intermediate **14** resulted in a slight increase in yield (32%). Further improvement was achieved (42%) when monomeric formaldehyde in ether solution was used with *s*-BuLi[12,13] as an alternative to use of paraformaldehyde. Subsequent experiments with monomeric formaldehyde and *n*-BuLi provided a lower yield (34%), thereby suggesting that both the stronger base and the more reactive form of formaldehyde were helpful.

Still other trials at different reaction temperature also were performed in hopes of further improvement of the yield. During the course of these experiments, the order of addition for the geranylacetone and formaldehyde also was reversed. Although in theory this strategy also could lead to farnesol **2**, repeated examination of such conditions provided complicated mixtures of unknown products and no apparent formation of the desired isoprenoid **2**.

To apply this methodology to preparation of (2*Z*,6*Z*)-farnesol (**3**) required starting with ketone **18**, nerylacetone (Scheme 4). Although this ketone is commercially available

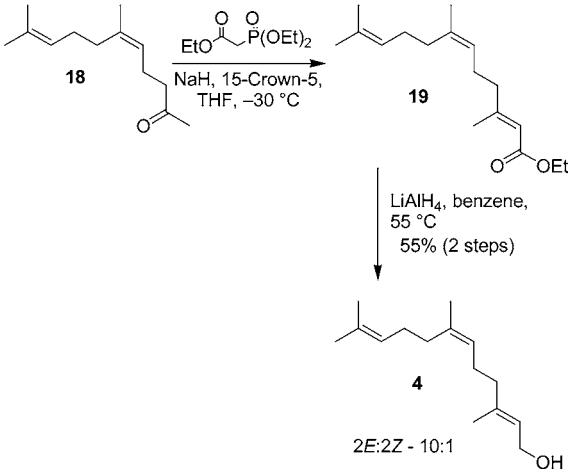
Scheme 4. Synthesis of Nerylacetone and (2*Z*,2*E*)-Farnesol



at considerable cost, it also can be prepared easily from neryl bromide (**16**).[14] Thus alkylation of ethyl acetoacetate with bromide **16** followed by successive hydrolysis and decarboxylation of the resulting β-keto ester **17** afforded nerylacetone (**18**) in ~60% yield over three steps. The synthesis of farnesol **3** then was achieved in a 40% yield via a one-flask reaction sequence under conditions parallel to those used for preparation of compound **2**. Again, the major product was the (*Z*)-isomer, and this was readily separated from the major byproduct resulting from formation of the terminal olefin from compound **18**.

Synthesis of the two other farnesol isomers, (2*E*,6*Z*)-farnesol (**4**) and (2*E*,6*E*)-farnesol (**2**), could be based on a Horner−Wadsworth−Emmons (HWE) reaction[15] of the two previously described ketones (**13** and **18**, respectively, Scheme 5). Reaction of nerylacetone (**18**) with triethyl

Scheme 5. Synthesis of (2*E*,6*Z*)-Farnesol



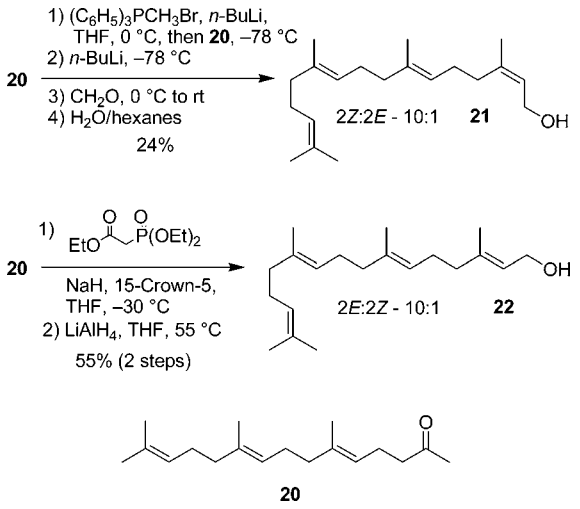
phosphonoacetate gave rise to the expected conjugated ester **19** where the C-2 olefin was formed primarily as the (*E*)-isomer (10:1, *E*:*Z*). Standard reduction of ester **19** with lithium aluminum hydride under mild conditions generated alcohol **4** in 55% yield over 2 steps. Similarly, preparation of commercial (2*E*,6*E*)-farnesol (**2**) also can be achieved via a parallel route beginning with geranylacetone (**13**), which may be an attractive means to obtain this isomer in greater isomeric purity than the commercial material.[16]

Identification of the four geometric isomers of farnesol was realized through use of ^{13}C NMR data in comparison with literature values.[17] The ^{13}C NMR spectra revealed γ-effect differences for the C-2 olefin substituents of the major and the minor olefin isomers from all four reaction sequences. By chance there were striking similarities between the ^{13}C spectra of (2*Z*,6*E*)-farnesol (**2**) and (2*E*,6*Z*)-farnesol (**4**), where the two olefins effectively mimic each other and thus produce nearly identical spectra. However, in each case the stereochemistry of the C-6 olefin was established by choice of starting material, and the stereochemistry of the C-2 olefin could be verified by HMBC experiments.[12]

Finally, it should be recognized that the methods described here can be applied to the synthesis of other acyclic isoprenoids. For example, when commercial (5*E*,9*E*)-farnesylacetone (**20**) was employed as the starting material (Scheme 6), it was possible to prepare the corresponding (2*Z*,6*E*,10*E*)-geranylgeraniol (**21**) using this modified Wittig protocol, and (2*E*,6*E*,10*E*)-geranylgeraniol (**22**) was available through the HWE strategy, both through short reaction sequences in reasonable yields.[7b] Even though this was not

(12) Representative experimental procedures and additional spectral data are available in Supporting Information.
(13) Schlosser, M.; Jenny, T.; Guggisberg, Y. *Synlett* **1990**, *11*, 704.
(14) Kato, T.; Suzuki, M.; Kobayashi, T.; Moore, B. P. *J. Org. Chem.* **1980**, *45*, 1126−1130.
(15) Coates, R. M.; Ley, D. A.; Cavender, P. L. *J. Org. Chem.* **1978**, *43*, 4915−4922.
(16) Commercial *trans*,*trans*-farnesol contained only ~70% of the desired isomer via GC analysis.
(17) Burrell, J. W. K.; Garwood, R. F.; Jackman, L. M.; Oskay, E.; Weedon, B. C. L. *J. Chem. Soc. C* **1966**, 2144−2154.

Scheme 6. Synthesis of (2*Z*,6*E*,10*E*)-Geranylgeraniol (**21**) through a β-Oxido Ylide and Comparison with the (2*E*)-Isomer **22**



pursued further, with all four farnesol isomers available it should be possible to generate all four farnesylacetone isomers, which ultimately would allow access to all eight geranylgeraniol isomers. Similarly, commercial prenylacetone could be used to prepare both geraniol and nerol, and these reactions were completed via the HWE and β-oxido ylide protocols in reasonable yields (61% and 38%, respectively).

In summary, we have developed a modified Wittig reaction that exploits the use of β-oxido ylides to allow synthesis of isoprenoid allylic alcohols with good selectivity for the (*Z*)-olefin isomer. This methodology has been used along with a complementary approach based on a classical HWE condensation to prepare the four isomers of farnesol, and this strategy has been shown to be applicable to other isoprenoids as well. The techniques presented require fewer steps than previous studies by Gibbs and co-workers[7] and minimize the extent of the chromatographic separations required. Future studies in our laboratory will be directed to exploration of the relative activity of isomeric isoprenoids in various biological systems.

Acknowledgment. Financial support from the Roy J. Carver Charitable Trust is gratefully acknowledged.

Supporting Information Available: Experimental procedures; ^{1}H and ^{13}C NMR spectra for compounds **1**−**4**, **18**, **21**, **22**, geraniol and nerol; HMBC spectra for compounds **2** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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