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Preparation of (2*E*,6*E*)-10,11-Dihydrofarnesol via a (Bisphenyl)dithioacetal Reduction

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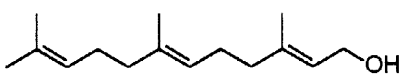
Abstract: Reduction of a (bisphenyl)dithioacetal with sodium/isopropyl alcohol in THF allows preparation of (2*E*,6*E*)-10,11-dihydrofarnesol in high yield.

Intense interest in farnesyl pyrophosphate (FPP) analogues as potential chemotherapeutic agents has followed the discoveries that farnesylation of RAS proteins is essential for RAS-induced cellular transformations[1-3] and that approximately 30% of all human cancers are associated with mutations in *RAS*.[4] Isotopically labeled farnesols (**1**) have been synthesized to examine the solution conformation of FPP,[5] and farnesol derivatives have been prepared to probe the mechanism of farnesyl protein transferase (FPTase),[6] the enzyme that catalyzes reaction of RAS proteins with FPP. The recent publication of a crystal structure for FPTase,[7] revealing a hydrophobic pocket that presumably accepts the terpenoid chain, lends credibility to the design of novel farnesyl "tails" that may bind more tightly in this cleft. Synthesis of a family of farnesol analogues incorporating aromatic rings already has been achieved in high yields through development of an allylic tetrahydropyranyl ether/organometallic coupling reaction.[8] To gauge the importance of non-bonding interactions in recognition of the farnesyl chain, a complementary terpenoid was desired that could serve as a negative control. One clear choice was (2*E*,6*E*)-10,11-dihydrofarnesol (**2**), which would allow comparison of the natural farnesyl tail (**1**) with terpenoid chains either missing the terminal olefin (**2**) or bearing an aromatic ring in its place (e.g. **3**).



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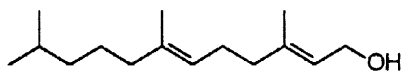

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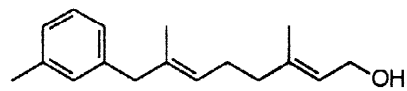

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Four syntheses of 10,11-dihydrofarnesol have been reported.[9-12] Three of these sequences suffer from poor stereoselectivity in the formation of the C2-C3 and/or C6-C7 olefin geometry.[9-11] This results in mixtures of (2*Z*,6*Z*), (2*E*,6*Z*), and/or (2*Z*,6*E*) isomers along with the desired (2*E*,6*E*) product, mixtures which are not

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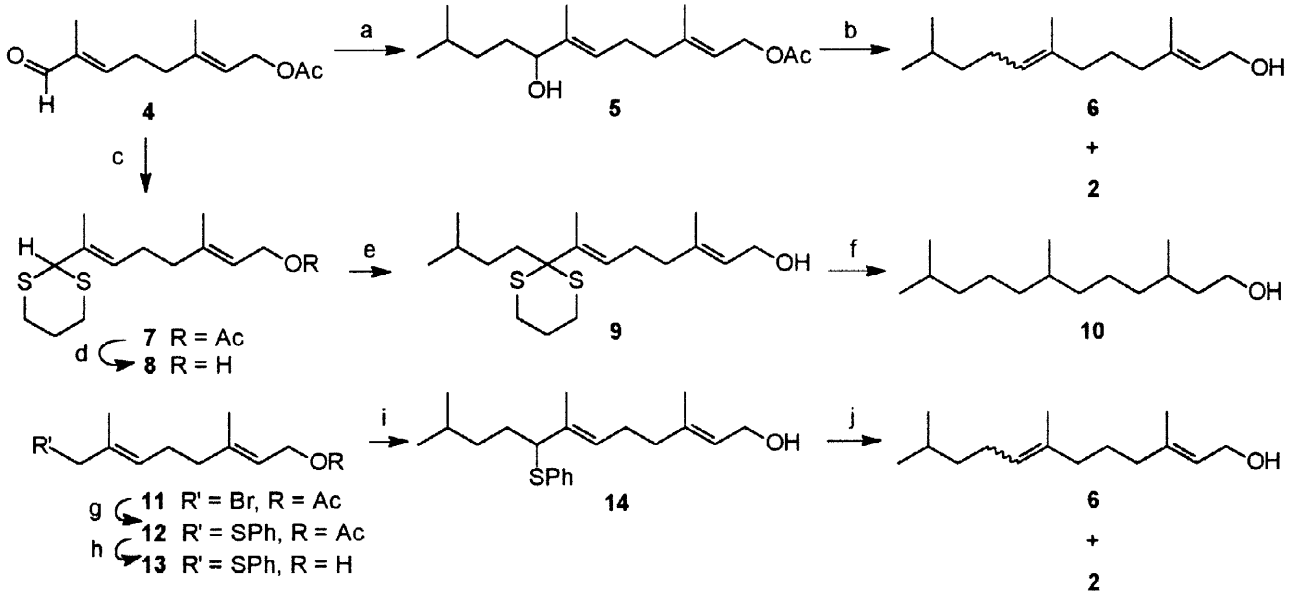
readily separated by column chromatography. Because the 2*Z*-stereochemistry is known to diminish the bioactivity of farnesyl pyrophosphate analogues,[13] new strategies to synthesize 10,11-dihydrofarnesol stereospecifically were required to allow meaningful bioassays. In 1993, a stereospecific synthesis of the (2*E*,6*E*) isomer was reported via a 6-step sequence from the pivalate ester of (2*E*,6*E*)-farnesol with 25% overall yield.[12] To use compound **2** conveniently in syntheses of FPP analogues, a shorter and more efficient synthesis was desired.

We have examined several other routes to (2*E*,6*E*)-10,11-dihydrofarnesol and similar problems with structural isomers were encountered. Synthesis of the known aldehyde **4**[14] followed by addition of isoamyl magnesium bromide afforded the desired alcohol **5** in low yield (Figure 1). Alcohol **5** was converted into the sulfate monoester using excess pyridine-sulfur trioxide reagent.[15] After complete esterification was observed by tlc analysis, the sulfate ester was reduced with $LiAlH_4$ to afford the deoxygenated product. The product obtained, however, not only contained the desired (2*E*,6*E*)-10,11-dihydrofarnesol (**2**), but also a mixture of (2*E*,7*E*) and (2*E*,7*Z*)-3,7,11-trimethyl-2,7-dodecadien-1-ol (**6**) produced from S_N2' reduction of the sulfate monoester. This mixture of products was not readily separated via flash column chromatography.



Reagents and conditions:[16] (a) 3-methyl-1-bromobutane, Mg°, THF, 31%; (b) pyrSO_3, THF; $LiAlH_4$, 15% (1.4:1.2:1.0 ratio of **2**:*trans* **6**:*cis* **6**); (c) 1,3-propanedithiol, $BF_3.OEt_2$, THF, 63%; (d) K_2CO_3, MeOH, 72%; (e) 2 equiv. *n*BuLi, THF, -50 °C; 3-methyl-1-bromobutane, THF, - 50 °C, 84%; (f) RaNi, 7:1 EtOH:THF, reflux, 88%; (g) PhSH, *n*BuLi, THF, 72%; (h) K_2CO_3, MeOH, 100%; (i) *n*BuLi, THF, -50 °C; 3-methyl-1-bromobutane, THF, -50 °C, 73%; (j) Na°, 10:1 THF:*i*PrOH, reflux, 100% (2.3:1.6:1.0 ratio of **2**:*trans* **6**:*cis* **6**).

Figure 1. Attempted Preparations of (2*E*,6*E*)-10,11-Dihydrofarnesol

Initial attempts at an umpolung approach to (2*E*,6*E*)-10,11-dihydrofarnesol also went unrewarded. Treatment of aldehyde **4** with propanedithiol afforded dithiane **7** in 63% yield (Figure 1). Reduction of acetate **7** to alcohol **8** with $LiAlH_4$, followed by addition of two equivalents of *n*BuLi generated the dianion, which upon treatment with isoamyl bromide afforded the coupled product **9** in 84% yield. However, reduction of

dithioacetal **9** to (2*E*,6*E*)-10,11-dihydrofarnesol, proved to be difficult. Raney nickel not only reduced the dithiane but also reduced the double bonds, resulting in formation of the known 3,7,11-trimethyl-1-dodecanol[17] (**10**) in high yield.

A variation on this strategy was suggested by a report that phenyl thioethers can be readily reduced to methylene groups by treatment with sodium metal in isopropyl alcohol.[18] Thioether **12** was readily prepared from the known allylic bromide **11**[19] in 72% yield (Figure 1). Biellmann coupling[20] of phenyl thioether **13** with isoamyl bromide afforded alcohol **14**, which upon treatment with Na°/*i*PrOH provided the reduced product in quantitative yield. Once again, however, reduction of the thioether occurred with migration of the C6-C7 olefin resulting in a complex mixture of (2*E*,6*E*)-10,11-dihydrofarnesol (**2**) and the 7*E*- and 7*Z*-olefins (**6**) observed previously.

The isomerization problems described above appear to result from the allylic nature of the functionality being reduced (i.e. the thioether and the sulfate monoester). It was hypothesized that the problem of olefin isomerization might be avoided by employing a more remote functional group. For example, with a thioacetal or thioether in a homoallylic instead of an allylic position, it was envisioned that a Na°/*i*PrOH reduction could be used to prepare (2*E*,6*E*)-10,11-dihydrofarnesol without concern for double bond migration.

The thioether **16** (Figure 2) was readily prepared from isoamyl bromide and thiophenol but was not easily alkylated, which is consistent with literature precedence suggesting that non-allylic phenyl thioethers are more difficult to use in Biellmann coupling reactions.[21] To obtain a more stable anion for alkylation, the dithioacetal **17**[22] was prepared from isovaleraldehyde and thiophenol. However, treatment of dithioacetal **17** with *n*BuLi followed by addition of the allylic bromide **11**, still failed to afford the desired product. Upon treatment of compound **17** with *n*BuLi and D_2O, deuterium incorporation was evident, suggesting that the acetate of compound **11** was sufficiently acidic to quench the dithioacetal anion. Synthesis of the known benzoate **18**[23] followed by reaction of this allylic bromide with the anion derived from dithioacetal **17** supported this theory. This approach gave the desired coupling product **19** in 80% yield, with cleavage of the benzoate ester taking place during the reaction sequence (Figure 2). Once compound **19** was in hand, reduction of the dithioacetal with Na°/*i*PrOH gave stereochemically pure (2*E*,6*E*)-10,11-dihydrofarnesol (**2**) in quantitative yield.

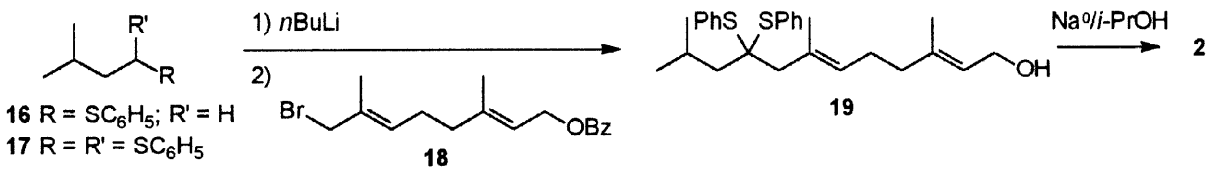


Figure 2. Synthesis of (2*E*,6*E*)-10,11-Dihydrofarnesol[24]

Although used frequently to reduce phenyl thioethers,[18] this is apparently the first illustration of Na°/*i*PrOH reduction of a (bisphenyl)dithioacetal. This is a very useful reaction because the reduction does not affect isolated carbon-carbon double bonds, unlike Raney nickel reductions of dithianes. With this new

methodology, (2*E*,6*E*)-10,11-dihydrofarnesol was synthesized in two steps and 78% yield from the known geraniol derivative **18**, or four steps from geranyl benzoate. This sequence is very competitive with previous syntheses of dihydrofarnesol because it provides the target compound via a short sequence in good yield and as a single olefin isomer. Further studies on the scope of (bisphenyl)dithioacetal reductions, as well as on the importance of non-bonding interactions in recognition of the farnesyl tail, will be reported in due course.

ACKNOWLEDGMENTS

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24. Dithioacetal **17** (5.01 g, 17.4 mmol) in THF (30 mL) at -40 °C was treated with *n*BuLi (6.6 mL, 2.40 M in hexanes, 15.8 mmol). After stirring for 2 h, bromide **18** (~3.8 mmol, prepared in situ from the corresponding alcohol[23]) was added dropwise. The reaction was allowed to warm to rt and stirred for 2 h. After addition of NH_4Cl, the mixture was extracted with ether and the extracts were concentrated *in vacuo*. Purification by flash column chromatography (80:20 hexanes:EtOAc) gave dithioketal **19** (1.36 g, 80%): ^{1}H NMR δ 7.71-7.67 (m, 4H), 7.34-7.31 (m, 6H), 5.43 (tq, 1H, *J* = 6.9, 1.3 Hz), 5.32 (br t, 1H, *J* = 6.9 Hz), 4.13 (d, 2H, *J* = 6.9 Hz), 2.52 (s, 2H), 2.25-2.03 (m, 5H), 1.78 (s, 3H), 1.69 (d, 2H, *J* = 4.7 Hz), 1.68 (s, 3H), 0.92 (d, 6H, *J* = 6.7 Hz); ^{13}C NMR δ 139.4 (2C), 136.0 (4C), 132.9, 131.1, 130.2, 128.5 (2C), 128.4 (4C), 123.6, 69.1, 59.3, 48.0, 47.6, 39.0, 26.4, 25.0 (2C), 24.8, 18.6, 16.2; HRMS calcd for $C_{27}H_{36}OS_2$ $(M + Na)^+$ 463.2096, found 463.2089. Ketal **19** (1.28 g, 2.92 mmol) in THF (25 mL) and *i*-PrOH (13.4 mL) was treated with small portions of Na metal (3.30 g, 144 mmol). The resulting solution was heated at reflux for 3 h, and then quenched by addition of water. Extraction with ether and concentration of the extracts *in vacuo* gave (2*E*,6*E*)-10,11-dihydrofarnesol[12] **2** without further purification (643 mg, 98%).