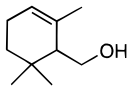
Synthesis of 2,7-Cyclofarnesol and 2,7-Cyclogeranylgeraniol: Prenylogs of *β*-Cyclogeraniol

Robert M. Coates* and Alan Qingwu Jin

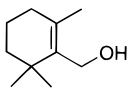
Department of Chemistry, University of Illinois, 600 South Mathews Avenue, Urbana, Illinois 61801

Received April 8, 1997

α- and *β*-cyclogeraniol (**1**-OH and **2**-OH), monoterpene alcohols reported to occur as natural products in the leaf oil of *Citrus auranticum* L,[1] are considered as prototypes for a cyclogeraniol family of structurally related monoterpenes including picrocrocin,[2] safranal,[3] 4-hydroxycyclocitral,[3] and similar compounds.[1b,4] A plausible biosynthesis of the cyclogeraniols would be H^+-induced cyclization of geranyl diphosphate, the usual substrate for monoterpene cyclases,[5] to α- and/or *β*-cyclogeranyl PP (e.g. **2**-OPP) followed by diphosphate hydrolysis. Alternatively the cyclogeraniols might arise more directly by enzymic cyclization of geraniol itself. It is also possible that some or all members of the cyclogeraniol family of natural products are actually oxidative metabolites of carotenoid precursors.

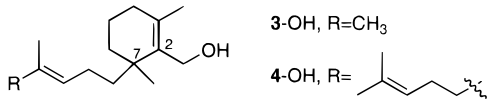


1-OH

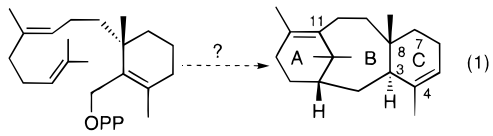


2-OH

The sesquiterpene and diterpene analogs of *β*-cyclogeraniol, 2,7-cyclofarnesol (**3**-OH) and 2,7-cyclogeranylgeraniol (**4**-OH), are to the best of our knowledge unknown compounds,[6] despite their plausible biosynthetic origin by analogous cyclizations of (*E*,*E*)-farnesyl PP and (*E*,*E*,*E*)-geranylgeranyl PP (GGPP). Although structures based on 2,7-cyclogeranylgeraniol were initially proposed for three diterpenes isolated from *Magydaris panacifolia*,[7] the constitutions were revised following total synthesis and detailed ^{1}H-NMR analysis.[8] Many naturally occurring sesquiterpenes and diterpenes related to 6,11-cyclofarnesol[9] and 10,15-cyclogeranylgeraniol[10] have been reported.



The first commited step in the biosynthesis of paclitaxel and related diterpenes[11] is the enzyme-catalyzed cyclization of GGPP to a tricyclic taxadiene precursor, recently established to be taxa-4(5),11(12)-diene (**5**).[12] The usual mechanism proposed involves macrocyclization to a verticillene intermediate followed by an H^+-induced cyclization forming the C-ring as the last step.[11,13,14] However, an interesting alternative cyclization mechanism proceeding through 2,7-cycloGGPP warrants consideration (eq 1). Thus, macrocyclization of (*S*)-**4**-OPP, bridging to form the A and B rings, and transannular proton shift (C-11 to C-3) would lead to taxa-4,11-diene. This mechanism would be consistent with the results of recent deuterium-labeling experiments with taxadiene synthase which show intramolecular deuterium transfer from C-11 to ring C, and it would explain the lack of incorporation of verticillene.[14]



(*S*)-**4**-OPP **5** (1)

In order to evaluate 2,7-cyclo-GGPP as an intermediate in taxadiene biosynthesis, we required access to **4**-OH. This paper describes a practical five-step synthesis of this new diterpene alcohol and the sesquiterpene analog, 2,7-cyclofarnesol (**3**-OH), from 3-ethoxy-2-cyclohexenone (**6**) (Scheme 1).

Prenylmethyl-(4-methyl-3-pentenyl) and geranylmethyl-((*E*)-4,8-dimethyl-3,7-nonadienyl)lithium reagents were generated from the corresponding iodides by halogen/metal exchange with *tert*-butyllithium in ether−pentane for 1 h at −78 °C. Addition to 3-ethoxy-2-cyclohexenone at −78 °C followed by hydrolysis with NH_4Cl afforded 3-(prenylmethyl)- and 3-(geranylmethyl)-2-cyclohexenones (**7a**, 79%; **7b**, 87%), both of which are known compounds.[15,16] Excess (1.8−2.0 equiv) *tert*-butyllithium was used on the expectation that the second equivalent of the lithium reagent would be rapidly consumed by a second-

(1) (a) Uchida, S. *J. Soc. Chem. Ind. Jpn, Suppl. Binding* **1928**, *31*, *B*. 188; (b) Erman, W. F. *Chemistry of the Monoterpenes Part A*; Dekker: New York, 1985; Chapter 5.

(2) (a) Kuhn, R.; Winterstein, A. *Chem. Ber.* **1934**, *67*, 344. (b) Simonsen, J. L. *The Terpenes*; Cambridge University Press: Cambridge, England, **1953**; Vol. I, 114−122.

(3) Zarghami, N. S.; Heine, D. E. *Phytochemistry* **1971**, *10*, 2755.

(4) *CRC Handbook of Terpenoids: Monoterpenoids*; Dev, S., Ed.; CRC Press: Boca Raton, FL, 1982.

(5) Croteau, R. *Chem. Rev.* **1987**, *87*, 929−954.

(6) The following secondary reference works were searched: (a) *Chem. Abstr.* **1907**−**1995**, Vols. 1−123. (b) *Encyclopedia of the Terpenoids*; Glasby, J. S., Ed.; Wiley: Manchester, UK, 1982. (c) *Nat. Prod. Rep.*, **1984**−**1996**, Vols. 1−13. (d) *Terpenoids and Steroids, Specialist Periodical Reports*; Chemical Society: London, 1971−1983, Vols. 1−12.

(7) Teresa, J. de P.; Grande, C.; Grande, M. *Tetrahedron Lett.* **1978**, 4563.

(8) (a) Nagano, H.; Masunaga, Y.; Matsuo, Y.; Shiota, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 707. (b) Teresa, J. de P.; Grande, C.; Moran, J. R.; Grande, M. *Chem. Lett.* **1984**, 247. (c) Bruno, M.; Lamartina, L.; Lentini, F.; Pascual, C.; Savona, G. *Tetrahedron Lett.* **1984**, *25*, 4287.

(9) (a) *Dictionary of Natural Products*; Chapman and Hall: London, 1994; see Vol 7, pp 164−165, 206. (b) Takeda, R.; Naoki, H.; Iwashita, T.; Mizukawa, K.; Hirose, Y.; Isida, T.; Inoue, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1125. (c) Suzuki, K. T.; Suzuki, N.; Nozoe, S. *J. Chem. Soc., Chem. Commun.* **1971**, 527.

(10) (a) Dev, S.; Misra, R. In *CRC Handbook of Terpenoids: Diterpenoids*; Dev, S., Ed.; CRC Press: Boca Raton, FL, 1985; Vol. I, pp 166−173. (b) Teresa, J. de P.; Caballero, E.; Caballero, C.; Medarde, M.; Barrero, A. F.; Grande, M. *Tetrahedron Lett.* **1978**, 3491. (c) Blackman, A. J.; Wells, R. J. *Ibid.* **1976**, 2729.

(11) For reviews, see: (a) Guéritte-Voegelein, F.; Guénard, D.; Potier, P. *J. Nat. Prod.* **1987**, *50*, 9. (b) Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. *Progr. Chem. Org. Nat. Prod.* **1993**, *61*, 1−192. (c) Floss, H. G.; Mocek, U. In *Taxol®: Science and Applications*; Suffness, M., Ed.; CRC Press: Boca Raton, FL, 1995; pp 191−208.

(12) (a) Koepp, A. E.; Hezari, M.; Zajicek, J.; Vogel, B. S.; LaFever, R. E.; Lewis, N. G.; Croteau, R. *J. Biol. Chem.* **1995**, *270*, 8686. (b) Rubenstein, S. M.; Williams, R. M. *J. Org. Chem.* **1995**, *60*, 7215.

(13) Harrison, J. W.; Scrowston, R. M.; Lythgoe, B. *J. Chem. Soc. C* **1966**, 1933.

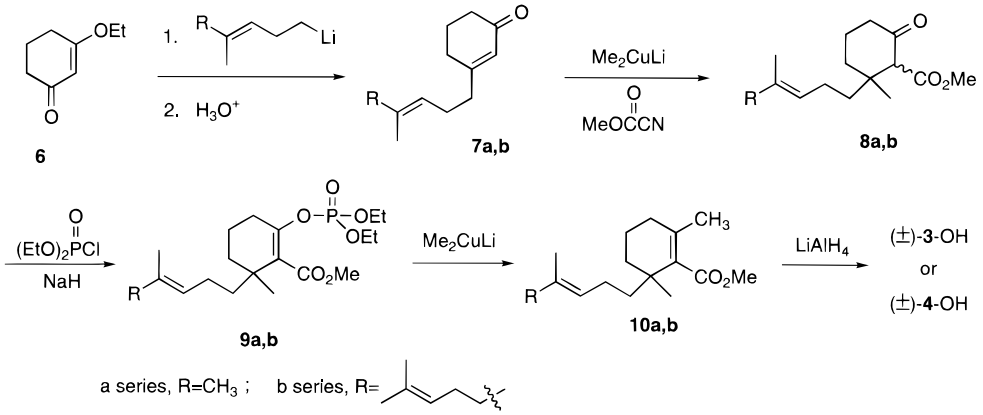
(14) Lin, X.; Hezari, M.; Koepp, A. E.; Floss, H. G.; Croteau, R. *Biochemistry* **1996**, *35*, 2968.

(15) Hagiwara, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1984**, 91.

(16) (a) Douglas, G. H.; Graves, J. M. H.; Hartley, D.; Hughes, G. A.; McLoughlin, B. J.; Siddall, J.; Smith, H. *J. Chem. Soc.* **1963**, 5072. (b) Emmick, T. L. German Offn. Patent 1, 965, 306; *Chem. Abstr.* **1970**, *73*, 55787z. (c) Grove, J. F.; Jennings, R. C.; Johnson, A. W.; White, A. F. *Chem. Ind.* **1974,** *8*, 346.

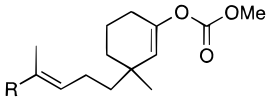
S0022-3263(97)00633-6 CCC: $14.00

Scheme 1. Preparation of 3-OH and 4-OH



ary reaction with the *tert*-butyl iodide produced in the exchange reaction.[17] In some cases, small amounts (5−10%) of the chromatographically inseparable 3-*tert*-butyl-2-cyclohexenone were detected as an impurity in the cyclohexenone products by GC and ^{1}H NMR analysis, presumably owing to reaction of unconsumed *tert*-butyllithium with 3-ethoxy-2-cyclohexenone. Since this byproduct evidently did not react with Me_2CuLi, it was unaffected by the subsequent carboxylation and phosphorylation reactions, and when present, it was easily separated from the more polar enol phosphates during chromatographic purification. When prenylmethyl bromide was used instead of the iodide in the exchange with *tert*-butyllithium, mixtures of **7a** and 3-*tert*-butyl-2-cyclohexenone (4:1 to 10:1) were formed even after allowing an extended reaction time (3 h at −23 °C) for destruction of the excess *tert*-butyllithium with *tert*-butyl bromide.

Conjugate addition of Me_2CuLi (1.1 equiv) in ether (−30 °C, 12 min) followed by *in situ* carboxylation of the resulting enolate with methyl cyanoformate (3 equiv, −78 °C then rt)[18] afforded *β*-keto esters **8a,b** accompanied by small amounts (14% and 11%) of enol carbonates **11a,b** resulting from competing *O*-carboxylation. Since the *β*-keto esters proved to be mixtures of easily equilibrated epimers and enol tautomer, purification by chromatography resulted in substantial losses. Consequently the crude product from the conjugate addition-carboxylation step was used for enol phosphorylation without purification.



11a,b

Installation of the C2 methyl group was accomplished by cuprate coupling of the enol phosphates.[19] Reaction of the unpurified esters **8a,b** with NaH and $(EtO)_2P(O)Cl$ in THF (rt, 8 h) afforded enol phosphates **9a,b** (52% and 62% from **7a,b**). The cuprate coupling reaction with Me_2CuLi (1.4 equiv) in ether (−23 °C, 3 h) furnished the tetrasubstituted *α*,*β*-enoates **10a,b** (77% and 86%), which were reduced with $LiAlH_4$ in ether to (±)-2,7-cyclofarnesol (**3**-OH, 82%) and (±)-2,7-cyclogeranylgeraniol (**4**-OH, 86%).

The diphosphate ester of (±)-**4**-OH and its dideuterio derivative obtained by $LiAlD_4$ reduction of **10b** were prepared by S_N2 displacement of the corresponding allylic chlorides[20] with $(Bu_4N)_3\,HP_2O_7$.[21] The lack of significant incorporation of (±)-**4**-OPP-d_2 into taxadiene in incubations with taxadiene synthase effectively rules out the alternative cyclization mechanism via 2,7-cycloGGPP (eq 1).[22] Nevertheless, 2,7-cyclofarnesol (**3**-OH), 2,7-cyclogeranylgeraniol (**4**-OH), their 3,4- or exocyclic double bond isomers, and related metabolites remain plausible candidates for new types of naturally occurring sesquiterpenes and diterpenes. The syntheses and characterization data presented here for these prenylogs of *β*-cyclogeraniol should facilitate the identification of the compounds from plant sources.

Experimental Section

General Aspects.[23] ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 MHz (or 500 MHz) and 101 MHz (or 126 MHz). Mass spectra were recorded on a Varian 70−4F or 70-VSE mass spectrometer. All reagents were used as purchased unless otherwise described. Prenylmethyl bromide was converted into the iodide with NaI in acetone according to a published procedure.[24] Geranylmethyl iodide was prepared from geranylmethanol[25] with I_2, Ph_3P, and imidazole (88%).[26] Samples were prepared for combustion analysis by bulb-to-bulb distillation at 0.1 mmHg (bath temperatures 100−190 °C). CuI was purified by a published procedure.[27]

3-[(*E*)-4,8-Dimethyl-3,7-nonadienyl]-2-cyclohexen-1-one (7b). A solution of geranylmethyl iodide (1.41 g, 5.1 mmol) in ether (35 mL) at −78 °C was stirred and cooled at −78 °C as *tert*-butyllithium (1.6 M, 5.75 mL, 9.2 mmol) in pentane was added. After 1 h, enone **6** (0.86 g, 6.1 mmol) in ether (7 mL) was added. After 50 min at −78 °C, saturated aqueous NH_4Cl (50 mL) was added at −78 °C and the mixture was allowed to warm up to rt. The aqueous layer was extracted with ether (2

(17) (a) Seebach, D.; Neumann, H. *Chem. Ber.* **1974**, *107*, 847. (b) Neumann, H.; Seebach, D. *Tetrahedron Lett.* **1976**, 4839. (c) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404. We thank a reviewer for calling our attention to ref 17c, which also describes optimized conditions for preparation of primary alkyllithiums by iodine/lithium exchange.

(18) Crabtree, S. R.; Chu, W. L. A.; Mander, L. N. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A.; et al., Eds.; Wiley: Chichester, UK, 1995; pp 3466−3469.

(19) Alderdice, M.; Sum, F. W.; Weiler, L. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 351.

(20) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.

(21) Woodside, A. B.; Huang, Z.; Poulter, C. D. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. VIII, p 616.

(22) The preparation and characterization of (±)-**4**-OPP as well as the incubation with taxadiene synthase will be reported separately: Hezari, M.; Croteau, R.; Jin, A. Q.; Coates, R. M.; Oliver, J. S. Manuscript in preparation.

(23) Steiger, A.; Pyun, H.-J.; Coates, R. M. *J. Org. Chem.* **1992**, *57*, 3444.

(24) Crandall, J. K.; Magaha, H. S. *J. Org. Chem.* **1982**, *47*, 5368.

(25) Leopold, E. J. *Organic Syntheses*; Wiley: New York, 1990; Collect Vol. VII, p 258.

(26) Marshall, J. A.; DeHoff, B. S. *Tetrahedron* **1987**, *43*, 4849.

(27) Kauffman, G. B.; Teter, L. A. *Inorg. Synth.* **1963**, *Vol VII*, 10.

× 50 mL). The combined ethereal extracts were washed with saturated NH_4Cl (1 × 50 mL), dried (Na_2SO_4), and concentrated. Purification of the residue by flash chromatography on silica gel (20% EtOAc in hexane) gave 1.08 g (87%) of the enone **7b** as a pale yellow oil. Although **7b** is known,[16] no characterization data were reported: IR (neat) ν_{max} 2925, 1671 cm^{-1}; ^1H NMR (400 MHz) δ 1.57 (s, 3 H), 1.58 (d, 3 H, J = 0.9 Hz), 1.65 (d, 3 H, J = 1.0 Hz), 1.92−2.07 (br m, 6 H), 2.14−2.36 (br m, 8 H), 5.06 (m, 2 H), 5.86 (quintet, 1 H, J = 1.2 Hz); ^{13}C NMR (101 MHz) δ 16.0, 17.6, 22.7, 25.4, 25.6, 26.5, 29.7, 37.3, 38.0, 39.5, 122.5, 124.0, 125.7, 136.3, 166.2, 200.0; GCMS (EI) *m/z* 246.20. Anal. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.50; H, 10.62.

3-(4-Methyl-3-pentenyl)-2-cyclohexen-1-one (7a). Enone **7a** was prepared as described above from prenylmethyl iodide (209 mg, 0.99 mmol) to give 140 mg (79%) of **7a**. The spectroscopic data match the published data:[15] IR (neat) ν_{max} 2926, 1673 cm^{-1}; ^1H NMR (500 MHz) δ 1.59 (s, 3 H), 1.66 (s, 3 H), 1.96 (quintet, 2 H, J = 6.4 Hz), 2.19 (m, 4 H), 2.27 (t, 2 H, J = 5.9 Hz), 2.34 (t, 2 H, J = 6.7 Hz), 5.05 (m, 1 H), 5.86 (br s, 1 H); ^{13}C NMR (126 MHz) δ 17.7, 22.7, 25.53, 25.64, 29.7, 37.3, 38.0, 122.7, 125.8, 132.8, 166.2, 200.0.

Enone **7a** was also prepared from prenylmethyl bromide as described for **7b**. When the solution containing *t*-BuLi (1.8 equiv) and the bromide was stirred for 2 h at −23 °C before addition of enone **6**, **7a** was contaminated by 9% of 3-*tert*-butyl-2-cyclohexenone which was inseparable from **7a** by flash chromatography. When the lithiation reaction was stirred for 2 h at −78 °C, the enone product contained 23% of the *tert*-butyl byproduct. The presence of this impurity was detected by GC (8.8 min compared to 9.9 min for **7a**) and ^1H NMR analysis (by characteristic peaks at 1.12 (s, 9 H) and 5.92 ppm (br s, 1 H)).

***cis*- and *trans*-Methyl 6-[(*E*)-4,8-Dimethyl-3,7-nonadienyl]-6-methyl-2-oxocyclohexanecarboxylate (8b).** A suspension of CuI (724 mg, 3.80 mmol) in ether (10 mL) was stirred and cooled at 0 °C as ethereal methyllithium (1.4 M, 5.42 mL, 7.59 mmol) was added. After 10 min at 0 °C, the solution was cooled to −28 °C (1:1 H_2O−acetone, dry CO_2) and enone **7b** (850 mg, 3.45 mmol) in ether (10 mL) was added. After 12 min at −28 °C, the temperature was lowered to −78 °C, and a solution of methyl cyanoformate (440 mg, 5.18 mmol) in ether (10 mL) was added. After 2 h at −78 °C, the mixture was allowed to warm slowly to rt over 4 h. Saturated aqueous NH_4Cl (containing 5% of concentrated NH_4OH, 30 mL) was added, and the mixture was stirred open to air for 1 h. The aqueous layer was extracted with ether (3 × 30 mL), and the combined ethereal solutions were washed with saturated NaCl (1 × 40 mL), dried (Na_2SO_4), and concentrated to give a yellow oil (1.18 g). The crude mixture of β-keto ester epimers, and enol carbonate was directly used in the enol phosphorylation. The two products were isolated after a previous smaller scale run carried out with 200 mg (0.81 mmol) of enone **7b**. Column chromatography on silica gel (15% EtOAc in hexane) afforded the two products for characterization. Enol carbonate **11b** (29 mg, 11%): IR (neat) ν_{max} 2932, 1761, 1442, 1255 cm^{-1}; ^1H NMR (200 MHz) δ 1.02 (s, 3 H), 1.26−1.56 (br m, 6 H), 1.59 (s, 6 H), 1.68 (s, 3 H), 1.75 (m, 2 H), 1.86−2.20 (m, 6 H), 3.78 (s, 3 H), 5.09 (m, 2 H), 5.26 (s, 1 H). β-Keto ester **8b** (97 mg) was a mixture of two diastereomers and the enol tautomer in a 74:21:5 ratio based on ^1H NMR integrations. **Major diastereomer**: ^1H NMR (400 MHz) δ 1.05 (s, 3 H), 1.29 (ddd, 1 H, J = 11.7, 5.4, 4.2 Hz), 1.56 (s, 3 H), 1.58 (s, 3 H), 1.66 (s, 3 H), 1.80−2.06 (m, 8 H), 2.29 (dt, 2 H, J = 12.5, 5.9 Hz), 2.63 (dd, 1 H, J = 14.2, 6.3 Hz), 3.27 (s, 1 H), 3.68 (s, 3 H), 5.05 (m, 2 H); ^{13}C NMR (101 MHz) δ 15.7, 17.5, 21.4, 21.7, 22.0, 25.6, 26.5, 33.3, 39.44, 39.50, 40.0, 41.3, 51.6, 66.1, 123.4, 124.0, 131.2, 135.4, 169.1, 206.8. **Minor diastereomer**: ^1H NMR (400 MHz) δ 0.96 (s, 3 H), 1.43 (dt, 1 H, J = 13.7, 4.9 Hz), 2.10 (ddd, 1 H, J = 14.6, 10.5, 4.6 Hz), 2.76 (ddd, 1 H, J = 14.2, 10.0, 6.8 Hz), 3.21 (br s, 1 H), 3.66 (s, 3 H), 5.05 (m, 1 H); ^{13}C NMR (101 MHz) δ 15.6, 17.4, 21.51, 21.54, 23.5, 26.5, 27.2, 32.3, 38.1, 38.9, 41.5, 51.7, 67.2, 123.8, 124.1, 131.2, 135.0, 169.0, 206.8. **Enol form**: ^1H NMR (400 MHz) δ 1.15 (s, 3 H), 3.75 (s, 3 H), 13.0 (s , 1 H).

Methyl 6-(4-Methyl-3-pentenyl)-6-methyl-2-oxocyclohexanecarboxylate (8a). The procedure described above with enone **7a** (379 mg) gave a yellow oil (673 mg), which was directly used without purification in the enol phosporylation. A 62-mg portion was subjected to column chromatography on silica gel (10% EtOAc in hexane) to isolate the two products for characterization. Enol carbonate **11a** (7 mg, 14%): IR (neat) ν_{max} 2932, 1761, 1442, 1258 cm^{-1}; ^1H NMR (500 MHz) δ 1.01 (s, 3 H), 1.24−1.38 (m, 3 H), 1.46−1.53 (m, 1 H), 1.59 (s, 3 H), 1.67 (s, 3 H), 1.75 (quintet, 2 H, J = 5.7 Hz), 1.91 and 1.96 (AB q of t, J_{AB} = 13.5 Hz, J_{AX} = J_{BX} = 6.4 Hz), 2.12 and 2.16 (AB q of t, J_{AB} = 17.3 Hz, J_{AX} = 6.1 Hz, J_{BX} = 7.0 Hz), 3.79 (s, 3 H), 5.07 (br t, 1 H, J = 7.0 Hz), 5.25 (s, 1 H); ^{13}C NMR (126 MHz) δ 17.6, 19.4, 22.7, 25.7, 26.4, 34.0, 34.8, 42.6, 54.8, 123.0, 124.8, 131.3, 147.6, 154.1. β-Keto ester **8a** (22 mg): IR (neat) ν_{max} 2922, 1713, 1434, 1226 cm^{-1}. **Major diastereomer** (67%): ^1H NMR (400 MHz) δ 1.05 (s, 3 H), 1.30 (ddd, 1 H, J = 11.5, 5.4, 3.4 Hz), 1.42 (ddd, 1 H, J = 13.2, 9.3, 5.1 Hz), 1.58 (s, 3 H), 1.66 (s, 3 H), 1.81−1.98 (m, 5 H), 2.30 (m, 2 H), 2.65 (m, 1 H), 3.28 (s, 1 H), 3.69 (s, 3 H), 5.04 (tt, J = 7.1, 1.3 Hz); ^{13}C NMR (101 MHz) δ 17.4, 21.4, 21.8, 22.0, 25.5, 33.3, 39.5, 40.1, 41.3, 51.6, 66.0, 123.6, 131.8, 206.8. **Minor diastereomer** (29%): ^1H NMR (400 MHz) δ 0.96 (s, 3 H), 2.11 (ddd, 1 H, J = 14.9, 10.7, 4.6 Hz), 2.77 (ddd, 1 H, J = 14.2, 10.0, 6.8 Hz), 3.21 (br s, 1 H), 3.68 (s, 3 H), 5.04 (tt, 1 H, J = 7.1, 1.3 Hz); ^{13}C NMR (101 MHz) δ 21.5, 21.7, 23.5, 32.3, 38.2, 38.9, 41.5, 51.7, 67.2, 124.0, 131.4, 206.9. **Enol form** (4%): ^1H NMR (400 MHz) δ 1.16 (s, 3 H), 3.72 (s, 3 H), 13.0 (s, 1 H).

Methyl 2-[(Diethylphosphoryl)oxy]-6-[(*E*)-4,8-dimethyl-3,7-nonadienyl]-6-methyl-1-cyclohexene-1-carboxylate (9b). Enol phosphate **9b** was prepared according to Weiler's procedure with some modifications.[19] NaH (300 mg of 50% dispersion in mineral oil, 6.3 mmol) was washed with THF (3 × 5 mL) and suspended on THF (10 mL). A solution of β-keto ester **8b** (1.18 g, 3.68 mmol assuming 100% purity) in THF (10 mL) was added, and after 50 min at rt, diethyl chlorophosphate (763 mg, 4.42 mmol) in THF (10 mL) was added. After 8 h at rt, saturated aqueous NH_4Cl (40 mL) was added, and the product was extracted with ether (4 × 50 mL). The combined ethereal extracts were washed with saturated $NaHCO_3$ (1 × 80 mL) and saturated NaCl (1 × 80 mL), dried (Na_2SO_4), and concentrated. Purification by flash chromatography on silica gel (35% EtOAc in hexane) gave **9b** as a yellow oil (0.98 g, 62% from enone **7b**): IR (neat) ν_{max} 2938, 1725, 1672 cm^{-1}; ^1H NMR (400 MHz) δ 1.15 (s, 3 H), 1.31 (t, 6 H, J = 7.0 Hz), 1.35 (m, 1 H), 1.43 (m, 2 H), 1.56 (s, 3 H), 1.58 (s, 3 H), 1.60 (m, 1 H), 1.74 (m, 2 H), 1.93 (m, 4 H), 2.02 (m, 2 H), 2.40 (t, 2 H, J = 6.2 Hz), 3.72 (s, 3 H), 4.12 (m, 4 H), 5.06 (m, 2 H); ^{13}C NMR (101 MHz) δ 15.7, 15.9, 16.0, 17.5, 18.2, 22.5, 25.5, 26.1, 26.5, 27.4, 33.2, 36.9, 39.5, 40.0, 51.3, 64.1 (d, J = 3.8 Hz), 64.2 (d, J = 3.1 Hz), 124.16, 124.18, 125.2 (d, J = 8.5 Hz), 131.1, 134.7, 147.6 (d, J = 7.7 Hz), 167.7 (d, J = 1.6 Hz).

Methyl 2-[(Diethylphosphoryl)oxy]-6-(4-methyl-3-pentenyl)-6-methyl-1-cyclohexene-1-carboxylate (9a). Enol phosphorylation of the **11a** + **8a** mixture (547 mg) as described above gave 348 mg (52%, 2 steps) of enol phosphate **9a**: IR (neat) ν_{max} 2929, 1728, 1679 cm^{-1}; ^1H NMR (400 MHz) δ 1.16 (s, 3 H), 1.33 (tt, 6 H, J = 7.1, 1.2 Hz), 1.32−1.39 (m, 1 H), 1.43 (dd, 1 H, J = 11.0, 2.0 Hz), 1.44 (br d, 1 H, J = 11.3 Hz), 1.58 (s, 3 H), 1.66 (s, 3 H), 1.58−1.65 (m, 1 H), 1.76 (quintet, 2 H, J = 6.1 Hz), 1.93 (dt, 2 H, J = 10.0, 6.8 Hz), 2.42 (br t, 2 H, J = 6.1 Hz), 3.73 (s, 3 H), 4.13 (m, 4 H), 5.05 (m, 1 H); ^{13}C NMR (126 MHz) δ 16.02, 16.08, 17.5, 18.4, 22.7, 25.7, 26.2, 27.6, 33.4, 37.0, 40.2, 51.4, 64.28 (d, J = 4.6 Hz), 64.33 (d, J = 3.7 Hz), 124.5, 125.4 (d, J = 8.3 Hz), 131.3, 147.8 (d, J = 7.4 Hz), 167.8 (d, J = 1.8 Hz).

Methyl 2,6-Dimethyl-6-[(*E*)-4,8-dimethyl-3,7-nonadienyl]-1-cyclohexene-1-carboxylate (10b). Enoate **10b** was prepared according to Weiler's procedure.[19] A suspension of CuI (508 mg, 2.67 mmol) in ether (10 mL) was stirred and cooled at 0 °C as methyllithium (1.4 M in ether, 3.8 mL, 5.4 mmol) was added. After 10 min, the colorless solution was cooled to −23 °C (~1:1 H_2O−acetone, dry CO_2) and enol phosphate **9b** (871 mg, 1.91 mmol) in ether (8 mL) was added. After 3 h at −23 °C, saturated aqueous NH_4Cl (containing 5% concd NH_4OH, 30 mL) was added, and the mixture was stirred open to air for 1 h. The aqueous layer was extracted with ether (3 × 30 mL), and the combined organic layers were washed with saturated aqueous NaCl (1 × 40 mL), dried (Na_2SO_4), and concentrated. Purification by flash chromatography on silica gel (5% EtOAc in hexane) gave 523 mg (86%) of ester **10b** as a yellow oil: IR (neat) ν_{max} 2929, 1725 cm^{-1}; ^1H NMR (400 MHz) δ 1.10 (s, 3 H), 1.30−1.45 (m, 4 H), 1.58 (s, 3 H), 1.60 (s, 3 H), 1.60−1.66 (m, 1

H), 1.66 (s, 3 H), 1.68 (s, 3 H), 1.88−2.08 (m, 9 H), 3.73 (s, 3 H), 5.08 (m, 2 H); ^{13}C NMR (101 MHz) δ 15.9, 17.7, 18.5, 21.5, 22.6, 25.7, 26.2, 26.7, 31.2, 33.9, 36.2, 39.7, 40.3, 51.1, 124.4, 124.7, 131.3, 134.6, 135.0, 135.1, 171.1; GCMS (EI) *m*/*z* 318.25. Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.30; H, 10.42.

Methyl 2,6-Dimethyl-6-(4-methyl-3-pentenyl)-1-cyclohexene-1-carboxylate (10a). Methyl cuprate addition to enol phosphate **9a** (152 mg) as described above gave 75 mg (77%) of ester **10a**: IR (neat) ν_{max} 2934, 1722 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.10 (s, 3 H), 1.32−1.44 (m, 3 H), 1.59 (s, 3 H), 1.65 (s, 3 H), 1.54−1.69 (m, 3 H), 1.90 (dt, 2 H, J = 11.5, 5.7 Hz), 1.97 (m, 2 H), 3.71 (s, 3 H), 5.05 (tt, 1 H, J = 7.1, 1.2 Hz); ^{13}C NMR (126 MHz) δ 17.5, 18.6, 21.5, 22.8, 25.7, 26.3, 31.2, 34.0, 36.2, 40.4, 51.1, 124.9, 131.0, 134.99, 135.15, 171.2; GCMS (EI) *m*/*z* 250. Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 79.60; H, 10.21.

2,6-Dimethyl-6-[(*E*)-4,8-dimethyl-3,7-nonadienyl]-1-cyclohexenemethanol (4-OH). The alcohol was prepared according to Paquette's procedure with slight modification.[28] A suspension of $LiAlH_4$ (202 mg, 5.32 mmol) in ether (10 mL) was stirred at rt as ester **10b** (431 mg, 1.35 mmol) in ether (5 mL) was added. After 2 h at rt, H_2O (0.20 mL), 15% NaOH (0.20 mL), and H_2O (0.60 mL) were added in succession.[29] The solid was filtered and washed thoroughly with ether. Concentration of the filtrate and purification of the residue by flash chromatography (10% EtOAc in hexane) afforded 339 mg (86%) of **4**-OH as a yellow oil: IR (neat) ν_{max} 3377, 2927, 1456, 1375, 1002 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.95 (t, 1 H, J = 5.2 Hz), 1.04 (s, 3 H), 1.29−1.48 (m, 4 H), 1.58 (s, 3 H), 1.60 (s, 3 H), 1.55−1.66 (m, 1 H), 1.68 (s, 3 H), 1.77 (s, 3 H), 1.72−1.84 (m, 1 H), 1.86−2.09 (m, 8 H), 4.07 and 4.18 (AB of ABX, 2 H, J_{AB} = 11.5 Hz, J_{AX} = 4.9 Hz, J_{BX} = 5.3 Hz), 5.09 (m, 2 H); ^{1}H NMR (D_2O exchange) the same except for 0.95 (t, 1 H) absent, and 4.06, 4.16 (AB q, J = 11.5 Hz); ^{13}C NMR (101 MHz) δ 15.9, 17.7, 19.1, 19.8, 22.9, 25.7, 26.4, 32.6, 34.9, 37.1, 39.7, 40.3, 58.8, 124.3, 124.8, 131.3, 134.6, 134.7, 137.5; GCMS (EI) *m*/*z* 290. Anal. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.43; H, 12.08.

2,6-Dimethyl-6-(4-methyl-3-pentenyl)-1-cyclohexenemethanol (3-OH). Reduction of ester **10a** (85 mg) as described above gave 62 mg (82%) of **3**-OH: IR (neat) ν_{max} 3351, 2913, 1455, 1377, 1001 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.03 (s, 3 H), 1.32 (m, 2 H), 1.42 (ddd, 1 H, J = 13.7, 11.9, 4.9 Hz), 1.58 (s, 3 H), 1.66 (s, 3 H), 1.76 (s, 3 H), 1.53−1.64 (m, 3 H), 1.73−1.81 (m, 1 H), 1.85−2.03 (m, 3 H), 4.06 and 4.16 (AB q, 2H, J = 11.5 Hz), 5.07 (m, 1 H); ^{1}H NMR (D_2O exchange) the same except for 4.73 (br s); ^{13}C NMR (126 MHz) δ 17.6, 19.1, 19.8, 23.0, 25.7, 26.4, 32.7, 35.0, 37.1, 40.4, 58.7, 125.0, 131.1, 134.6, 137.5; GCMS (EI) *m*/*z* 204 (M − 18). Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.78. Found: C, 81.31; H, 12.15.

Acknowledgment. A.Q.J. is grateful to the University of Illinois for the award of University Fellowships, 1996−1998. We thank the National Institutes of Health for financial support of this work through Grant GM 13956.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of β-keto esters **8a,b** (cis/trans mixtures), enol phosphates **9a,b**, (±)-**3**-OH, and (±)-**4**-OH (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9706335

(28) Belmont, D. T.; Paquette, L. A. *J. Org. Chem.* **1985**, *50*, 4102.
(29) Fieser, L. F.; Fieser, M. *Reagents Org. Synth.* **1967**, *1*, 584.