A Stereoselective Synthesis of (±)-Nootkatone and (±)-Valencene via an Intramolecular Sakurai Reaction

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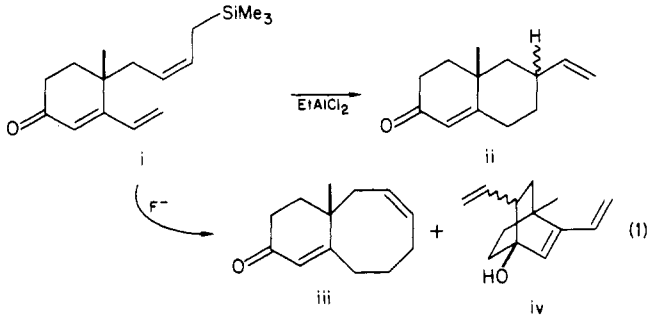
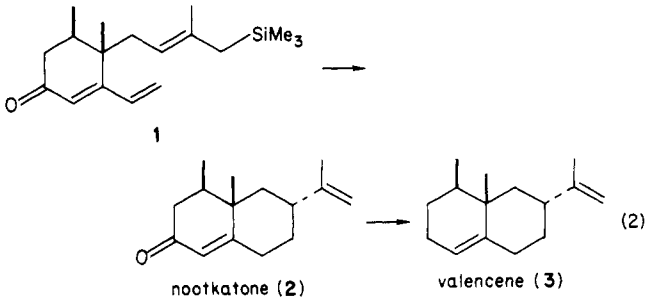
Recently, we reported our observations on the intramolecular addition of unsymmetrical allylsilanes in substrates containing multiple electrophilic centers.[1,2] Remarkably, we could direct the reactivity along two distinctly different pathways by the simple choice of reaction catalyst. For example, cyclization of extended dienone i using ethylaluminum dichloride produced solely the 6,6 fused bicyclic enone ii in 77% yield via an intramolecular Sakurai reaction[3,4] (eq 1). In dramatic contrast to this



(1)

result, treatment of substrate i with fluoride ion led to a mixture of bicyclic enone iii, possessing the neolemnane ring system,[5] and the bicyclo[2.2.2]octenol derivative iv as the result of intramolecular 1,2-addition in 35% yield and 32% yield, respectively.

This study suggested an efficient approach to two compounds of the eremophilane–valencene family of sesquiterpenes.[6] The key transformation in our route is the Lewis acid catalyzed ring closure of trienone **1** to directly produce (±)-nootkatone **2**, a flavor component of grapefruit (*Citrus paradisi* Macfayden) (eq 2).[7] Reduction of the carbonyl group of nootkatone produces (±)-valencene, a constituent of valencia orange oil.[8] The success of this synthetic scheme depends upon the crucial stereospecific



(2)

establishment of the cis-C(4),C(5)-dimethyl relationship in trienone 1. Accordingly, we undertook a stereocontrolled synthesis of this precursor.

Results and Discussion

Our starting material was the enol ether **4** of dihydroorcinol.[9] Work by Stork and Danheiser[10] suggested that the correct stereochemistry could be established by successive alkylations of **4**; the relative configuration at the adjacent asymmetric centers is determined by the order of alkylation. Indeed, alkylation of **4** first with methyl iodide and then with 3,3-dimethylallyl bromide[11] provided a 6:1 mixture of diastereomers of which compound **5** is the major isomer (Scheme I).[12]

Regiospecific cleavage of the prenyl side chain of **5** with OsO_4–$NaIO_4$ afforded aldehyde **6** in 63% yield.[13] This aldehyde was converted in 50% yield of allylsilane **7** (a 2:1 mixture of *E* and *Z* isomers) by reaction with the Wittig salt (1-trimethylsilyl-2-propylidene)triphenylphosphorane prepared according to the method of Seyferth.[14] Ketone **7** was converted to conjugated dienone **1** by treatment with vinyllithium in tetrahydrofuran at 0 °C, followed by acid hydrolysis, in 80% yield.

We anticipated that ring closure of **1** would give rise to the required α-configuration of the C(7) isopropylidene functionality, owing to severe steric interactions in the transition state between the axial C(4)-methyl group and the functionalized allylsilane side chain.[15] We also did

(1) This work was presented in part at the 188th National Meeting of the American Chemical Society in Philadelphia, PA, Aug, 1984 (Majetich, G.; Behnke, M.; Hull, K. *Abstr. Pap.—Am. Chem. Soc.* **1984**, *188th*, ORGN 140) and taken in part from the MS thesis of Mark Behnke, University of Georgia, 1984.

(2) Majetich, G.; Hull, K.; Desmond, R. *Tetrahedron Lett.* **1985**, *26*, 2751.

(3) The intramolecular extension of the Sakurai reaction has only recently received attention. For examples, see: (a) Schinzer, D.; *Angew Chem., Int. Ed. Engl.* **1984**, *23*, 308. (b) Wilson, S. R.; Price, M. F. *J. Am. Chem. Soc.* **1982**, *104*, 1124.

(4) For intermolecular studies involving the Sakurai reaction, see: (a) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673. (b) Blumenkopf, T. A.; Heathcock, C. H. *Ibid.* **1983**, *105*, 2354.

(5) Izac, R. R.; Fenical, W.; Tagle, B.; Clardy, J. *Tetrahedron* **1981**, *37*, 2569.

(6) The eremophilane class of sesquiterpenes has been the subject of considerable synthetic interest during the past 20 years. For a comprehensive review and a synthesis of nootketone from **5** using Dastur's approach (ref 12), see: Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In "The Total Synthesis of Natural Products"; Apsimon, J., Ed.; Wiley-Interscience: New York, 1983; Vol. V, pp 180–188.

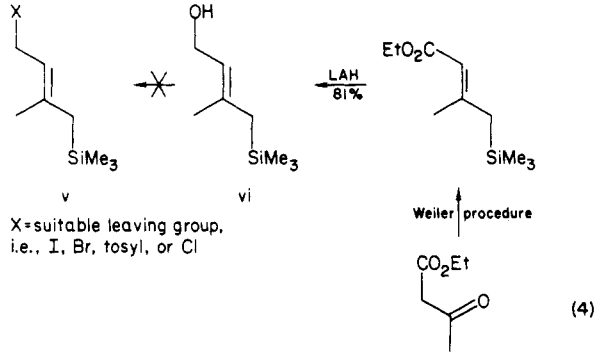
(7) MacLeod, W. D.; Duignes, N. M. *J. Food Sci.* **1964**, *29*, 565.

(8) Hunter, G. L.; Brogden, W. B. *J. Food Sci.* **1965**, *30*, 876.

(9) Crossley, A. W.; Renouf, N. *J. Chem. Soc.* **1915**, 602.

(10) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.

(11) Alkylation with an appropriately functionalized allylsilane electrophile, such as iodine v, was envisioned. Allyl alcohol vi was prepared



(4)

by O-alkylation of ethyl acetoacetate, conversion to the allylsilane by the method of Weiler (Sum, F. W.; Weiler, L. *Tetrahedron* **1981**, *37*, 303) and finally reduction of the ester functionality. However, all attempts to transform alcohol vi into an electrophile with an appropriate leaving group generated isoprene.

(12) (a) All structures drawn here represent racemates, only one enantiomer being drawn. (b) Spectroscopic data obtianed for all new compounds were fully consistent with the assigned structures.

(13) Pappo, R.; Allen, D. S.; Lemieus, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 178.

(14) Seyferth, D.; Wursthorn, K. R.; Mammarella, R. E. *J. Org. Chem.* **1977**, *42*, 3104.

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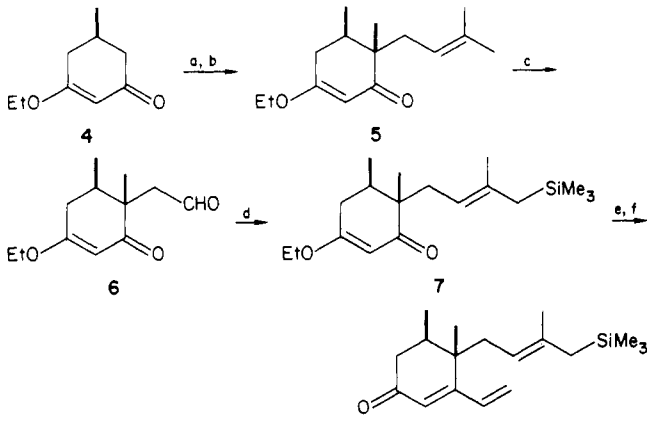
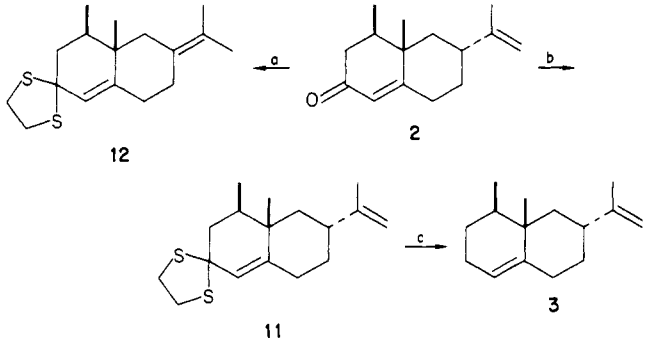
Scheme I[a]



[a] (a) LDA-HMPA, THF/CH_3I; (b) LDA-HMPA, THF/prenyl bromide; (c) OsO_4-$NaIO_4$, dioxane; (d) $Ph_3P{=}CCH_3CH_2Si(CH_3)_3$ (ref 14); (e) vinyllithium; (f) H_3O^+.

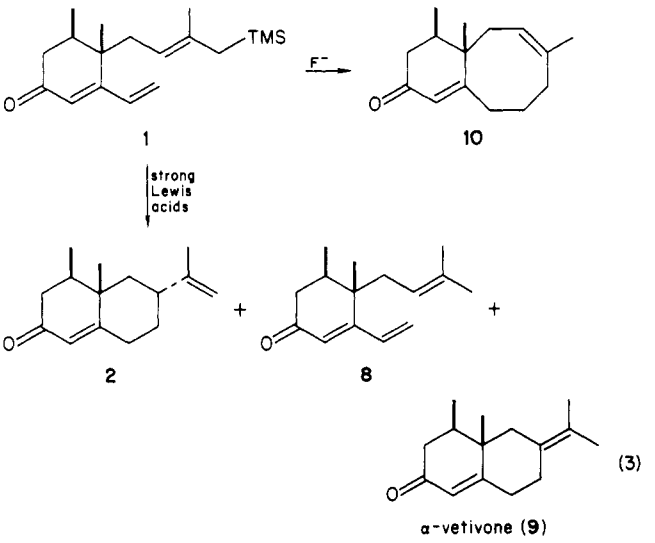
Scheme II[a]



[a] (a) $HSCH_2CH_2SH/BF_3{\cdot}Et_2O$ or *p*-TsOH; (b) $(CH_3)_3SiSCH_2CH_2SSI(CH_3)_3$, ZnI_2 (ref 15); (c) Li/NH_3.

not expect that this diastereoselection would be influenced by the mixture of allylsilane isomers.

Cyclization of trienone 1, catalyzed by ethylalumium dichloride, afforded a single product by TLC analysis. Isolation provided crystalline racemic nootkatone **2** (mp 44–45 °C, 65% yield) whose spectral data and chromatographic properties were identical with those of a sample of authentic racemic nootkatone. Several other Lewis acids were examined in an attempt to improve the cyclization yield. The use of strong Lewis acids such as titanium tetrachloride and boron trifluoride etherate generated low yields of nootkatone, contaminated with significant amounts of desilylated noncyclized trienone **8** and small amounts of α-vetivone **9** (eq 3).[16] Milder Lewis acids such as diethylaluminum chloride or trimethylaluminum failed to promote cyclization. Reaction of **1** with tetra-*n*-butylammonium fluoride in dimethylformamide cyclization to the expected 6,8 fused bicyclic enone **10** in 42% yield.[17]



(3)

α-vetivone (**9**)

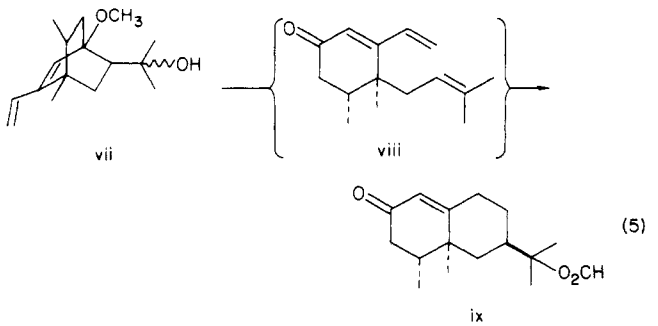
While several syntheses of valencene **3** have been reported, it has never been prepared by direct reduction of nootkatone. We envisioned this transformation via desulfurization of thioketal **11**. Treatment of **2** with 1,2 ethanedithiol using Lewis acid catalysts, however, produced mixtures of thioketals **11** and **12** (Scheme II). Fortunately, exclusive formation of the required thioketal **11** was achieved using Evans's thiosilane reagent (ethylenedithio)bis(trimethylsilane),[18] catalyzed by zinc iodide, in 93% yield. The final operation, reduction of the thioketal, was accomplished by a dissolving metal reduction of sodium in liquid ammonia. The spectral and chromatographic properties of diene **3** (72% yield) matched those of authentic valencene.

Experimental Section

All melting points were determined on a Thomas-Hoover oil immersion capillary melting point apparatus. Melting and boiling points are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded at 90 MHz (Varian EM390 spectrometer) or, if indicated, at 270 MHz (JEOL FX270). Chemical shifts are reported in parts per million downfield relative to tetramethylsilane as an internal standard (Me_4Si = 0.00 ppm). The data reported as integer numbers are accurate to ±10% of the integer. Coupling constants (*J*) are reported in cycles per second (Hz). Carbon-13 NMR spectra were recorded on a JEOL FX90Q. Infrared spectra (IR) were recorded as a thin film between polished sodium chloride plates on a Perkin-Elmer Model 197 Grating Intrared Spectrometer. All absorption bands are reported in wave numbers (cm^{-1}), and were calibrated against a 1600 cm^{-1} (polystyrene film). Low-resolution mass spectra (MS) were recorded on a Finnigan 4023 gas chromatograph–mass spectrometer by a direct probe and are expressed in *m/z* units. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA.

6-(3,3-Dimethylallyl)-5,6-dimethyl-3-ethoxy-2-cyclohexenone (5). To a solution of lithium diisopropylamide, prepared from 6.3 g (62.3 mmol) of diisopropylamide in 52 mL of freshly distilled tetrahydrofuran and 43.0 mL (62.3 mmol) of

(15) This argument is based on the stereoselective synthesis of nookatone by Dastur (Dastur, K. P. *J. Am. Chem. Soc.* **1974**, *96*, 2605) in which formolysis of alcohol vii produced formate ix via the in situ formation of intermediate viii. Saponification and dehydration of the tertiary alcohol provided **2** and α-vetivone in a 3:1 ratio.



(5)

(16) Conversion of nootkatone to α-vetivone was accomplished by using the method of van der Gen (van der Gen, A.; van der Linde, L. M.; Witteveen, J. G.; Boelens, H. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 1034), affording α-vetivone in 80% yield. Spectral properties were identical with the published data.

(17) Studies are underway to utilize this transformation in a neolemnane[4] synthesis.

(18) Evans, D.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009.

n-butyllithium (1.45 M in hexane) at −78 °C, was added a solution of 8.0 g (51.9 mmol) of 5-methyl-3-ethoxy-2-cyclohexenone (**4**)[9] in 30 mL of THF over a 0.5 h period. After the mixture was stirred an additional hour at −78 °C, 8.11 g (57.1 mmol) of methyl iodide was added. The reaction was stirred at −78 °C for 1 h and was then allowed to slowly warm to room temperature over an 8-h period. The reaction was quenched at room temperature with 10 mL of saturated aqueous ammonium chloride, and the solvent was removed under pressure. The oily residue was taken up with 100 mL of water and extracted with three 200-mL portions of ether. The combined ethereal extracts were washed with 30 mL of brine, dried over anhydrous magnesium sulfate, filtered, and evaporated. Distillation of the crude residue at 103 °C (5 mmHg) afforded 6.17 g (70%) of 5,6-dimethyl-3-ethoxy-2-cyclohexenone, which was homogeneous by TLC: IR (neat) 3500, 2975, 2940, 2880, 2840, 1675, 1610, 1445, 1420, 1400, 1380, 1360, 1335, 1220, 1190, 1160, 1110, 1090, 1040, 1030, 960, 935, 900, 845, 825, 790, 710 cm^{-1}; ^1H NMR (CCl_4) δ 5.03 (s, 1 H), 3.80 (q, 2 H, J = 7 Hz), 2.25–1.45 (m, 4 H), 1.35 (t, 3 H, J = 5 Hz), 1.06 (d, 6 H, J = 6 Hz); mass spectrum, m/z 168 (M^+); ^{13}C NMR ($CDCl_3$) 201.81 (s), 175.75 (s), 101.42 (d), 63.94 (t), 34.74 (t), 31.76 (d), 19.62 (d), 13.94 (q), 12.74 (q), 10.90 (q) ppm. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.58. Found: C, 71.35; H, 9.60. To a solution of lithium diisopropylamide, prepared from 3.6 g (35.7 mmol) of diisopropyl amine in 20 mL of freshly distilled tetrahydrofuran and 24.0 mL (35.7 mmol) of *n*-butyllithium (1.5 M in hexane) at −78 °C, was added a solution of 5.0 g (29.7 mmol) of 5,6-dimethyl-3-ethoxy-2-cyclohexenone in 15 mL of THF over 30 min. After the solution was stirred for 1 h at −78 °C, 4.87 (32.7 mmol) of 3,3-dimethylallyl bromide was added. The reaction was stirred at −78 °C for 1 h and was then allowed to slowly warm to room temperature over a 10-h period. The reaction was quenched at room temperature with 10 mL of saturated aqueous ammonium chloride, and the solvent was removed under reduced pressure. The oily residue was taken up in 100 mL of water and extracted with three 200-mL portions of ether. The combined ethereal extracts were washed with 30 mL brine and dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent afforded a crude product which was distilled at 165 °C (15 mmHg), affording 5.32 g (76%) of **5**, which was homogeneous by TLC: IR (neat) 2975, 2925, 1640, 1610, 1450, 1415, 1405, 1380, 1360, 1330, 1280, 1220, 1200, 1190, 1110, 1080, 1030, 960, 935, 915, 880, 845, 820, 765, 745, 640 cm^{-1}; ^1H NMR (CCl_4) δ 5.00 (s, 1 H), 4.76 (t, 1 H, J = 2 Hz), 3.76 (q, 4 H, J = 7 Hz), 2.6–2.7 (m, 5 H); 1.6 (s, 3 H), 1.53 (s, 3 H); 1.3 (t, 3 H, J = 5 Hz), (d, 3 H, J = 6 Hz), 0.80 (s, 3 H); mass spectrum, m/e 237 (M^+); ^{13}C NMR ($CDCl_3$) 204.19 (s), 174.67 (s), 132.9 (s), 120.23 (d), 101.37 (d), 63.836 (t), 47.75 (s), 34.04 (t), 32.90 (t), 25.85 (d), 21.57 (q), 18.16 (q), 17.78 (q), 15.13 (q), 14.04 (q) ppm. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.23. Found: C, 76.15; H, 10.29.

6-(Formylmethyl)-5,6-dimethyl-3-ethoxy-2-cyclohexenone (6). To a solution of 1.2 g (5.1 mmol) of **5** in 22.5 mL of 1,4-dioxane and 7.5 mL of water at room temperature was added 30 mg (catalytic amount) of osmium tetraoxide. After the black solution was stirred for 10 min, 2.4 g (11.2 mmol) of sodium metaperiodate was added in three equal 0.8-g portions over 30 min. After the addition was complete, the reaction was stirred for 1.5 h at room temperature, during which time a white precipitate formed. The reaction was then diluted with ether, and the layers were separated. The aqueous layer was extracted with two 30-mL portions of ether. The combined ethereal layers were dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent afforded crude **6**. Chromatography of the crude product (elution with 2:1 hexane/ether; **5**, R_f 0.52; **6**, R_f 0.10) afforded 500 mg (47% moles) of **6**, which was homogeneous by TLC: IR (neat) 3500, 2975, 2890, 2850, 2750, 1720, 1640, 1600, 1460, 1425, 1405, 1380, 1330, 1280, 1220, 1200, 1115, 1075, 1035, 990, 965, 935, 880, 850, 825, 800, 740, 700, 640 cm^{-1}; ^1H NMR (CCl_4) δ 9.4 (d, 1 H, J = 3 Hz) 5.06 (s, 1 H), 3.7 (q, 2 H, J = 7 Hz), 2.2 (m, 5 H), 1.13 (t, 3 H, J = 5 Hz), 0.96 (s, 3 H), 0.09 (d, 3 H, J = 6 Hz).

6-[3-Methyl-4-(trimethylsilyl)-2-butenyl]-5,6-dimethyl-3-ethoxy-2-cyclohexenone (7). To a solution of 2.0 g (5.35 mmol) of ethyltriphenylphosphonium bromide in 16 mL of tetrahdyrofuran at 0 °C was added 4.0 mL (5.95 mol) of *n*-butyllithium (1.5 M in hexane), and the mixture was allowed to stir for 1 h while warming to room temperature. This was followed by cooling the reaction mixture to 0 °C and adding 1.15 g (5.35 mmol) of (iodomethyl)trimethylsilane and allowing the reaction mixture to warm to room temperature for 14 h. At this time a red precipitate had formed. The solution was then cooled to −78 °C, and 4.0 mL (5.95 mmol) of *n*-butyllithium was added followed by warming to 0 °C over 1 h. The reaction was again cooled to −78 °C, and 1.0 g (4.76 mmol) of **6** in 3.5 mL of THF was added. The reaction was stirred for 30 min at −78 °C followed by slow warming to room temperature over 3 h. The reaction was quenched at room temperature with 5 mL of saturated ammonium chloride solution, and the solvent was removed under reduced pressure. The black residue was dissolved in 25 mL of water and extracted with two 50-mL portions of ether. The combined ethereal extrats were washed with 15 mL of brine and dried over anhydrous magnesium sulfate. Filtration and evaporation of solvent afforded crude **7**. Chromatography of the crude product (elution with 4:1 hexane/ether; **6**, R_f 0.65; **7**, R_f 0.85) afforded 700 mg (54%) of **7**, which was isolated as a mixture of *E* and *Z* isomers: IR (neat) 2950, 2250, 1640, 1610, 1450, 1405, 1380, 1360, 1330, 1280, 1250, 1220, 1200, 1190, 1110, 1095, 1060, 1035, 960, 855, 740, 700 cm^{-1}; ^1H NMR (CCl_4) δ 5.03 (s, 1 H), 4.66 (m, 1 H), 3.73 (q, 2 H, J = 7 Hz), 2.23 (d, 2 H, J = 3 Hz), 1.70 (s, 3 H), 1.66 (s, 2 H), 1.35 (t, 3 H, J = 5 Hz), 0.95 (d, 3 H, J = 6 Hz), 0.90 (s, 3 H); mass spectrum, m/z 309 (M^+); ^{13}C NMR ($CDCl_3$) 204.09, 203.65, 174.73, 143.52, 134.75, 118.06, 117.63, 116.98, 110.14, 101.64, 101.372, 74.67, 18.81, 18.21, 16.86, 15.34, 14.04, 0.01, −0.06, −0.23 ppm. Anal. Calcd for $C_{18}H_{32}O_2Si$: C, 70.07; H, 10.45. Found: C, 70.28; H, 10.28.

4-[3-Methyl-4-(trimethylsilyl)-2-butenyl]-4,5-dimethyl-3-vinyl-2-cyclohexenone (1). To a solution of 700 mg (2.3 mmol) of **7** in 12 mL of tetrahydrofuran at 0 °C was added 2.95 mL (2.95 mmol, 1.0 M in THF) of vinyllithium, and the reaction was allowed to stir for 30 min at 0 °C. The reaction mixture was then quenched with 4 mL of saturated ammonium chloride, and the solvent was removed under reduced pressure. The residue was extracted with two 25-mL portions of ether. The ether extracts were combined and dried over anhydrous magnesium sulfate. Filtration and evaporation of solvent afforded crude alcohol, which was taken up in 3.0 mL of THF and 0.5 mL of 1 N HCl was added. The reaction mixture was allowed to stir for 1 h at room temperature, followed by neutralization with 0.5 g of potassium carbonate. The solvent was removed under reduced pressure, and the residue was extracted with two 25-mL portions of ether. The combined organic layers were dried over anhydrous magnesium sulfate. Filtration and evaporation afforded crude **1**. The crude product was purified by column chromatography (elution with 3:1 hexane/ether; **7**, R_f 0.85; **1**, R_f 0.65), affording 355 g (54%) of **1**: IR (neat) 2850, 1640, 1600, 1420, 1380, 1340, 1280, 1245, 1160, 985, 925, 880, 740, 700, 600 cm^{-1}; ^1H NMR (CCl_4) δ 5.2–6.3 (complex m, ABCX pattern, 4 H) 4.7–4.85 (m, 1 H), 2.6 (m, 5 H), 1.7 (s, 3 H), 1.3 (s, 2 H), 0.98 (s, 3 H), 0.95 (d, 3 H, J = 6 Hz), −0.2 (s, 9 H); mass spectrum, m/z 290 (M^+); ^{13}C NMR ($CDCl_3$) 199.54 (s), 134.59 (d), 124.29 (d), 119.96 (t), 116.98 (d), 116.60 (d), 41.95, 35.34, 34.04, 30.19, 19.58, 15.89, 15.62, −0.628, −1.278 ppm.

(±)-Nootkatone (2) via $EtAlCl_2$ Catalysis. To a solution of 100 mg (0.34 mmol) of **1** in 2 mL of dry toluene at 0 °C was added 0.23 mL (0.34 mmol) of ethylaluminum dichloride. The reaction was stirred for 1 h at 0 °C after which it was quenched with 5 mL of wet ether. The solution was diluted further with 20 mL of ether and washed with brine followed by drying over anhydrous magnesium sulfate. Filtration and evaporation of solvent gave crude **2**. The crude product was purified by column chromatography (elution with 3:1 hexane/ether; **1**, R_f 0.66; **2**, R_f 0.52) to afford 37.5 mg (50%) of **2**: IR (neat) 3075, 2940, 1660, 1620, 1435, 1380, 1345, 1285, 1260, 1200, 940, 880, 840, 820 cm^{-1}; ^1H NMR (CCl_4) δ 5.7 (s, 1 H), 4.35 (d, 2 H, J = 6 Hz), 2.38–1.95 (m, 10 H), 1.7 (s, 3 H), 1.12 (s, 3 H), 0.97 (d, J = 6 Hz); mass spectrum, m/z 218 (M^+); ^{13}C NMR ($CDCl_3$) 196.9 (s), 168.2 (s), 149.0 (s), 124.9 (d), 109.2 (t), 44.2, 42.2, 40.6, 40.4, 39.3, 32.9, 31.9, 20.8, 16.4, 14.8 ppm. Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.15. Found: C, 82.41; H, 10.16. These values agree with the published data for nootkatone (**2**).

(±)-Nootkatone (2) via $TiCl_4$ Catalysis. To a solution of 50 mg (0.17 mmol) of **1** in 1 mL of dichloromethane at −50 °C was added 0.02 mL (0.17 mmol) of titanium tetrachloride. The reaction was allowed to stir for 30 min at −50 °C. The reaction was quenched with 5 mL of wet ether and allowed to warm to room temperature. The resulting solution was washed with brine

and dried over anhydrous magnesium sulfate. Filtration and evaporation of solvent afforded crude **2**. Chromatography as described previously afforded 13.6 mg (28%) of **2**.

(±)-Nootkatone (2) via Boron Trifluoride Etherate Catalysis. To a solution of 50 mg (0.17 mmol) of **1** in 1 mL of anhydrous ether at 0 °C was added 0.022 mL (0.17 mmol) of boron trifluoride etherate. The reaction was stirred for 1 h after which it was quenched with 5 mL of wet ether and allowed to warm to room temperature. The solution was washed with brine and dried over anhydrous magnesium sulfate. Filtration and evaporation of solvent afforded crude **2**. Chromatography as described previously afforded 9.8 mg (23%) of **2**.

(±)-Valencene. To a stirred solution of 340 mg (1.56 mmol) of **2** in 5 mL of ether at room temperature was added 5 mg of ZnI_2 (catalytic amounts), followed by the dropwise addition of 408 mg (1.71 mmol) of (ethylenedithio)bis(trimethylsilane). The resulting mixture was stirred at room temperature for 14 h. The reaction was quenched with 1 drop of water and directly purified via column chromatography (elution with 3:1 hexanes/ether; **2**, R_f 0.52; **11**, R_f 0.89) to afford 427 mg (93%) of thioketal **11**, which was homogeneous by TLC: ^{1}H NMR (CCl_4) δ 5.3 (s, 1 H), 4.52 (s, 2 H), 3.0–3.4 (m, 4 H), 1.4–2.3 (m, 13 H), 1.75 (s, 3 H), 0.95 (s, 3 H), 8.7 (d, 3 H, J = 6 Hz); IR (neat) 3060, 2960, 2910, 1640, 1430, 1290, 1285, 1235, 1145, 885 cm^{-1}; mass spectrum, m/z 294 (M^+).

To a solution of 100.0 mg (0.31 mmol) of **11**, in 0.6 mL of ether and 14.3 mL of liquid ammonia, was added 14.3 mg (0.62 mmol) of metallic sodium. Upon addition of the sodium, the reaction mixture turned a dark blue. The color was discharged upon slow dropwise additon of 9.5 mL of absolute ethanol. The ammonia was then allowed to evaporate and the residue was extracted with two 15-mL portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent afforded crude **3**. The crude product was purified by column chromatography (elution with 1:1 hexane/ether; **11**, R_f 0.89; **3**, R_f 0.9), and 20 mg (22%) was isolated: ^{1}H NMR ($CDCl_3$) δ 5.3 (s, 1 H), 4.69 (s, 2 H), 1.7 (s, 3 H), 0.95 (s, 3 H), 0.9 (d, 3 H, J = 6 Hz); IR (neat) 3075, 2935, 1660, 1435, 1380, 1350, 1290, 1270, 1210, 940, 880, 840, 820, 640 cm^{-1}; mass spectrum, m/z 214 (M^+).

4,4a,5,8,9,10-Hexahydro-4,4a,7-trimethyl-2(3*H*)-benzocyclooctenone (10). A reaction vessel containing 50 mg of 4-Å molecular sieves was flame-dried under vacuum (5 min) and placed under nitrogen. A solution of 3 mL of DMF containing 2.5 mg of TBAF was added and then 73 mg (0.48 mmol) of HMPA added. The resulting mixture was stirred at room temperature for 10 min. A solution of **1** in 2 mL of DMF was added dropwise over 2 h (via syringe pump). The resulting mixture was stirred at room temperature for 1.5 h and then diluted with 15 mL of water. This mixture was then extracted with three 15-mL portions of ether. The combined ethereal extracts were washed with brine and dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent afforded crude **10**. Chromatography (elution with 1:1 hexane/ether) afforded 14 mg (42%) of **10**: ^{1}H NMR (CCl_4) δ 5.4 (s, 1 H), 5.05 (m, 1 H), 2.3–1.6 (m, 11 H), 1.55 (s, 3 H), 0.91 (d, 3 H, J = 6 Hz), 0.88 (s, 3 H); IR (neat) 3010, 2950, 2850, 1680, 1620, 1465, 1445, 1425, 1380, 1360, 1340, 1295, 1265, 1225, 1190, 960, 940, 920, 860, 800, 780, 760, 700, 620 cm^{-1}.

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Registry No. (±)-**1**, 97551-21-8; (±)-**2**, 28834-25-5; (±)-**3**, 24741-64-8; (±)-**4**, 61484-10-4; (±)-**5**, 97551-22-9; (±)-**5** (*trans*-dimethyl isomer), 97551-28-5; (±)-**6**, 97551-23-0; (±)-(*E*)-**7**, 97551-24-1; (±)-(*Z*)-**7**, 97590-58-4; (±)-**10**, 97551-25-2; (±)-**11**, 97551-26-3; CH_2=CHLi, 917-57-7; $Ph_3PEt^+Br^-$, 1530-32-1; *cis*-5,6-dimethyl-3-ethoxy-2-cyclohexenone, 97551-27-4; prenyl bromide, 870-63-3.

Preparation of β-Keto Esters by 4-DMAP-Catalyzed Ester Exchange

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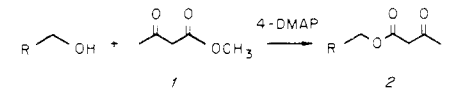
We recently needed to prepare a series of differentially substituted acetoacetate derivatives. Two methods have been described for acetoacetate formation, reaction of an alcohol with diketene[3] and transesterification with methyl acetoacetate.[4] Camphorsulfonic acid has been employed



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to catalyze the latter reaction.[5] As these methods proved ineffective for the case we had in hand, we explored alternative catalysts for the transesterification reaction.

We have found that reacting acetoacetate **1** with a primary or secondary alcohol in the presence of a catalytic amount of 4-(dimethylamino)pyridine[6] (4-DMAP) in toluene solution at reflux will yield acetoacetate **2**. The reaction of a variety of β-keto esters with representative alcohols is summarized in Table I.

It can be seen that only enolizable β-keto esters react and that tertiary alcohols do not participate in the reaction. Entry 4 suggests that there is a competing pathway leading to decomposition of the acetoacetate. This has led us to a procedure for selective decarbalkoxylation of enolizable β-keto esters which will be reported separately.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker WM-250 spectrometer as solutions in $CDCl_3$. Chemical shifts are reported in δ units downfield from the internal reference tetramethylsilane. The couplings (J) are in hertz (Hz). The infrared (IR) spectra were determined on a Unicam SP1100 spectrometer as solutions in CCl_4 and are reported in reciprocal centimeters (cm^{-1}). Mass spectra (MS) were taken at 70 eV on a Du Pont 21-492B mass spectrometer and are reported as mass per unit charge (m/z), with intensities (as a percentage of the peak of greatest ion current having $m/z \geq 100$) in parentheses. CH analysis was provided by Galbraith Laboratories, Inc. Organic chemicals were purchased from Aldrich Chemical Co. Toluene was distilled from CaH_2 and stored over sodium metal. The extracting solvent used was a mixture of recovered organic solvents, including methylene chloride, ethyl acetate, and petroleum ether. The solvent mixtures used for chromatography are volume/volume mixtures. R_f values indicated refer to thin-layer chromatography on Analtech 2.5 × 10 cm, 250-μm analytical plates coated with silica gel GF. Column chromatography was carried out with TLC-mesh silica gel, following the procedure we have described.[7]

Preparation of *l*-Menthyl Acetoacetate 3. A flame-dried two-necked 50-mL round-bottomed flask equipped with a reflux condenser and a nitrogen purge was flushed with N_2 and charged with 300 mg (1.92 mmol) of *l*-menthol, 70 mg (0.577 mmol) of

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