Synthesis of (−)-Delobanone

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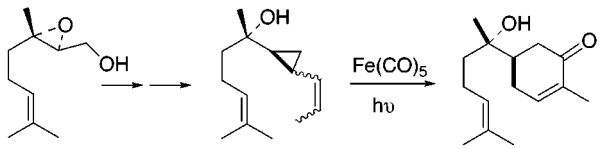
On irradiation in the presence of $Fe(CO)_5$ under a CO atmosphere, the alkenyl cyclopropane **2** underwent smooth ring expansion to give the sesquiterpene (−)-delobabone **3**. The alkenyl cyclopropane **2** was prepared from the enantiomerically enriched epoxide **1**.

Introduction

The development of general methods for the preparation of carbocyclic natural products with control of both relative and absolute configuration has been a longstanding challenge in organic synthesis. The problem of controlling the configuration of a stereogenic center on a pendant side chain relative to the ring to which it is attached has been particularly troublesome. We report what promises to be a general approach to this problem, based on the preparation of the alkenyl cyclopropane **2** from the Sharpless-derived[2] epoxide **1**. Irradiation of **2** in the presence of $Fe(CO)_5$[3,4] led to smooth conversion to (−)-delobanone **3**.

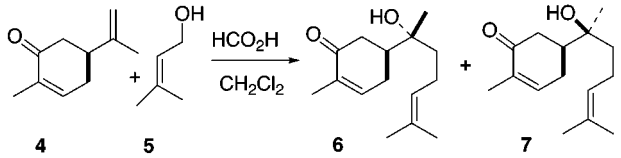


1 **2** **3**

Background

The sesquiterpene (+)-delabanone **6** was isolated in 1971[5a] from the roots of the Japanese shrub "shiomoji", in 0.14% yield based on the dry weight of the plant. The structure was established by ^{1}H NMR, UV, IR, optical rotation and detailed ^{1}H NMR studies on the *O*-benzylidene ether of a 1α-hydroxydelobanone derivative.

The only synthesis[5b] of (+)-delobanone **6** so far reported was based on the acid-catalyzed condensation of (*S*)-(−)-carvone **4** with the allylic alcohol **5**. This led to an unseparated mixture of (+)-delobanone **6** and its diastereoisomer **7**. The yield of the mixture was 7.0%, and the ratio of **6** to **7** was 1.2:1.0.

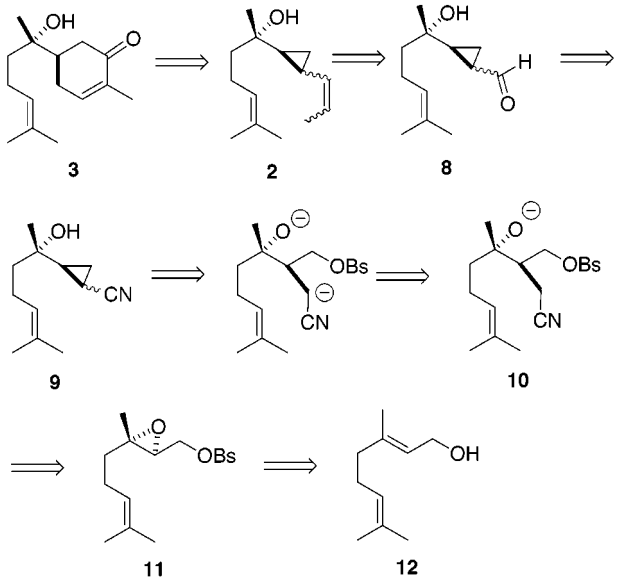


4 **5** **6** **7**

Retrosynthetic Analysis

We envisioned that cyclocarbonylation[3] of **2** (Scheme 1) with $Fe(CO)_5$ would lead to (−)-delobanone **3**, with control of both relative and absolute configuration. The alkenyl cyclopropane **2** would be available by Wittig reaction of aldehyde **8**, which could in turn be derived from nitrile **9**.

Scheme 1



3 **2** **8** **9** **10** **11** **12**

We hypothesized that the nitrile **9** might be available by the opening of the Sharpless-derived sulfonate **11** with an excess of lithioacetonitrile. It would not matter whether the initial displacement was at the benzenesulfonate or at the epoxide. Illustrating the latter possibility, proton transfer from the initial adduct **10** (the alkylated nitrile is much more acidic than is acetonitrile) followed by internal S_N2 displacement would generate nitrile **9**.[6−8]

(1) Undergraduate research participant.

(2) Hanson, R. M.; Sharpless, B. K. *J. Org. Chem.* **1986**, *51*, 1922.

(3) Taber, D. F.; Kanai, K.; Jiang, Q.; Bui, G. *J. Am. Chem. Soc.* **2000**, *122*, 6807.

(4) (a) The photochemical $Fe(CO)_5$-mediated carbonylation of vinyl cyclopropanes was first reported in 1970: Sarel, S. *Acc. Chem. Res.* **1978**, *11*, 204. For more recent references, see: (b) Khusnutdinov, R. I.; Dzhemilev, U. M. *J. Organomet. Chem.* **1994**, *471*, 1. (c) Schulze, M. M.; Gockel, U. *Tetrahedron Lett.* **1996**, *37*, 357. (d) Schulze, M. M.; Gockel, U. *J. Organomet. Chem.* **1996**, *525*, 155.

(5) (a) Takeda, K.; Sakurawi, K.; Ishii, H. *Tetrahedron* **1971**, *27*, 6049. (b) Harwood: L. M.; Julia, M. *Tetrahedron Lett.* **1980**, *21*, 1743.

(6) For the alkylation and polyalkylation of lithioacetonitrile, see: Taber, D. F.; Kong, S. *J. Org. Chem.* **1997**, *62*, 8575.

(7) For the opening of a Sharpless-derived epoxide with lithioacetonitrile, see: Taber, D. F.; Green, J. H.; Zhang, W.; Song, R. *J. Org. Chem.* **2000**, *65*, 5436.

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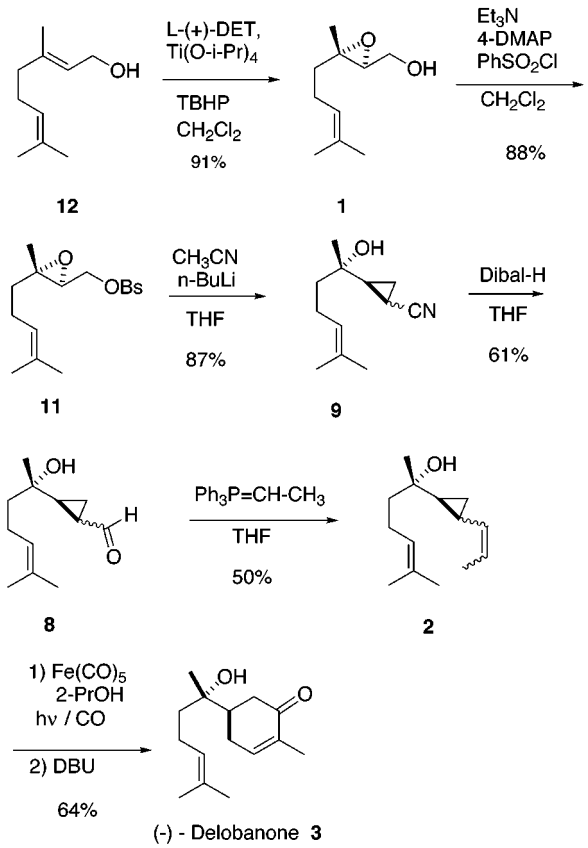
Scheme 2



A real concern with this approach was the potential lability of the tertiary cyclopropyl carbinol **2**. As acid-catalyzed ring opening would be assisted by the propenyl group, there was the possibility that **2** either could not be handled or that it would degrade under the conditions of Fe-mediated cyclocarbonylation.

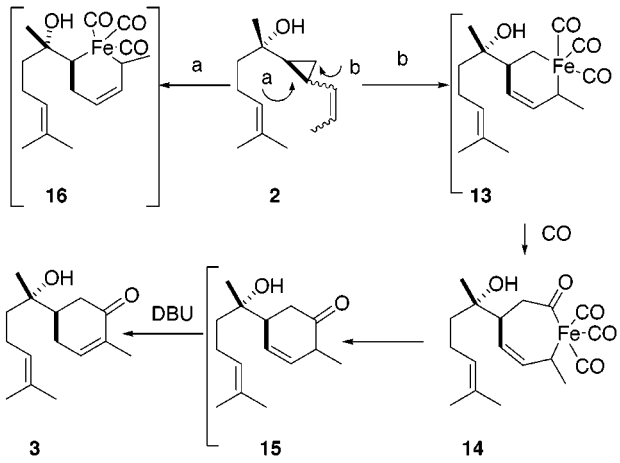
Synthesis of (−)-Delobanone

The key to this approach was the preparation of the nitrile **9**. As shown in Scheme 2, Sharpless epoxidation[2] of commercially available geraniol followed by sulfonylation led to the benzenesulfonate **11**. Initially, we tried adding the benzenesulfonate to a large excess (5.5 equiv) of lithioacetonitrile. The desired cyclopropane nitrile **9** was isolated, but in only 15% yield. We were pleased to find that by lowering the amount of lithioacetonitrile and controlling the rate of addition of the benzenesulfonate **11** the yield could be increased to 87%.

The oily nitrile so prepared appeared (^{13}C NMR) to be a single diastereoisomer. The combustion analysis supported the proposed empirical formula, and IR showed absorptions typical for an OH group and a CN group. ^{13}C NMR clearly showed a three-membered ring attached to the CN group, with methines at δ −1.5 and δ 17.9, and a methylene at δ 10.2. The preparation of nitrile **9** with control of relative and absolute configuration (86% ee by chiral HPLC analysis of a derivative of **8**) set the stage for the synthesis of (−)-delobanone, as neither the ensuing DIBAL reduction nor the Wittig condensation would affect the distal stereogenic centers.

(8) For a related double alkylation of an α-amino nitrile with a haloepoxide, see: (a) Geraldine, G.; Aitken, D. J.; Guilaume, D.; Hussson, H-P. *Tetrahedron Lett.* **1994**, *35*, 4355. (b) Aitken, D. J.; Royer, J.; Husson, H-P *J. Org. Chem.* **1990**, *55*, 2814.

Scheme 3



The ring-expanding reaction of alkenyl cyclopropane **2** irradiated [3] in the presence of $Fe(CO)_5$ may proceed with the preferential cleavage of bond "b" (Scheme 3) to give **13**, or bond "a" to give **16**. On the basis of the precedent,[3] we expected preferential cleavage of bond "b". Subsequent carbonylation followed by reductive elimination would give the enone **15**, which on exposure to DBU would be equilibrated to more stable conjugated isomer **3**.

In the event, Fe-mediated cyclocarbonylation of the alkenyl cyclopropane **2** (isopropyl alcohol, CO balloon, Rayonet, 23 h, monitoring by TLC, then DBU) led to (−)-delobanone as a colorless oil, $[\alpha]^{18}_D = -12.7°$ (*c* 0.28, CH_2Cl_2, lit. (+)-delobanone $[\alpha]_D = +10.2°$). IR of **2** showed absorption typical for an OH group (υ_{max} = 3472 cm^{-1}) and an α,β-unsaturated ketone system (υ_{max} = 1660 cm^{-1}). The ^{1}H NMR in C_6D_6 revealed the presence of a Me on the carbon carrying the OH group (δ 0.83, 3H, s), three Me groups on two double bonds (δ 1.56, 3H, s; δ 1.67, 3H, d, J = 1.1 Hz; δ 1.81, 3H, d, J = 1.2 Hz); an alkene proton at a position β to the conjugated carbonyl group (δ 6.14, 1H, tq, J = 1.3 and 5.9 Hz), and the other alkene proton (δ 5.13, 1H, tquint, J = 1.4 and 7.1 Hz). These values are congruent with those reported.[5a] The ^{13}C NMR spectrum was also congruent with the assigned structure.

Conclusion

The strategy outlined here for the enantioselective construction of cyclohexenones with control of both relative and absolute configuration will have many other applications in natural product synthesis. We expect that the efficient conversion of the Sharpless-derived epoxide **1** to the nitrile **9** will be a useful addition to the armamentarium of organic chemistry.

Experimental Section

Each reaction with air- and moisture-sensitive components was performed under a nitrogen atmosphere in a flame-dried reaction flask. Tetrahydrofuran was distilled from sodium/benzophenone, and dichloromethane was distilled from calcium hydride. ^{1}H and ^{13}C NMR spectra were recorded at 250 and 61.72 MHz or 400 and 100 MHz, respectively, as solutions in deuteriochloroform. Chemical shifts are reported in ppm downfield from TMS. ^{13}C NMR H substitution was determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d", from methylene

and quaternary carbons as "u". IR spectra were determined as neat oils. Mass spectra were obtained at an ionizing potential of 100 eV. Optical rotations were determined as solutions in dichloromethane unless otherwise noted. R_f values indicated refer to thin-layer chromatography (TLC) on 2.5 × 10 cm, 250 μm analytical plates coated with silica gel GF. Solvents for TLC are reported as v/v mixtures.

Epoxide 1. A mixture of activated 4Å molecular sieves (1.80 g, 15−20 wt % based on geraniol) and dichloromethane (100 mL) was cooled to −10 °C. L-(+)-Diethyl tartrate (1.00 g, 4.8 mmol), titanium(IV) isopropoxide (0.91 g, 3.2 mmol), and *tert*-butylhydroperoxide (19.4 mL, 97 mmol, 5.0 M in dichloromethane) were added sequentially. After 10 min of stirring, the mixture was cooled to −20 °C, and freshly distilled geraniol (10.0 g, 65 mmol, in 10 mL of dichloromethane) was added dropwise over 15 min. After 45 min of stirring at −20 to −15 °C, the mixture was warmed to 0 °C. After an additional 5 min of stirring at 0 °C, the mixture was quenched sequentially with water (20 mL) and 4.5 mL of 30% aqueous NaOH saturated with solid NaCl. After 10 min of vigorous stirring, the reaction mixture was partitioned between dichloromethane and water. The combined organic extract was dried ($MgSO_4$) and then filtered through Celite to give a clear colorless solution. Concentration followed by bulb to bulb distillation [bp (bath) = 100 °C at 0.1 mm Hg] gave **2** as a colorless oil (10.3 g, 91% yield). TLC R_f = 0.42 (20% MTBE/petroleum ether); $[\alpha]^{16}_D = -4.75°$ (*c* 1.43, $CHCl_3$), lit. $[\alpha]^{25}_D = -5.3°$ (*c* 3.0, $CHCl_3$); ^{1}H NMR δ 1.28 (s, 3H), 1.46 (m, 1H); 1.59 (s, 3H), 1.66 (m, 4H), 2.03 (m, 2H), 2.97 (dd, *J* = 4.0 and 7.2 Hz, 1H), 3.72 (m, 2H), 5.07 (tquint, *J* = 1.3 and 7.1 Hz,1H); ^{13}C NMR δ d 16.9, 17.6, 25.8, 63.3, 123.5; u 23.8, 38.6, 61.4, 61.5, 132.2; IR 3423, 2926, 1659, 1454, 1385, 1034 cm^{-1}.

Sulfonate 11. Triethylamine (5.30 mL, 38.2 mmol), 4-DMAP (718 mg, 5.8 mmol), and phenylsulfonyl chloride (4.50 mL, 35.3 mmol) were added sequentially to epoxide **1** (5.00 g, 29.4 mmol) in dichloromethane (74 mL) at 0 °C. After stirring at room temperature overnight, the reaction mixture was quenched by the addition of 50 mL of saturated aqueous NH_4-Cl at 0 °C. The reaction mixture was then partitioned between dichloromethane and, sequentially, 5% aqueous NaOH, 5% aqueous HCl, and saturated brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give **9** as a colorless oil (8.1 g, 88% yield). TLC R_f = 0.55 (20% MTBE/petroleum ether); $[\alpha]^{18}_D = -20.3°$ (*c* 1.10, CH_2Cl_2); ^{1}H NMR δ 1.18 (s, 3H), 1.52 (m, 2H), 1.56 (s, 3H), 1.64 (s, 3H), 1.95 (q, *J* = 7.3 Hz, 2H), 2.96 (t, *J* = 5 0.6 Hz, 1H), 4.14 (m, 2H), 5.00 (tquint, *J* = 1.3 and 7.1 Hz, 1H), 7.73 (m, 5H); ^{13}C NMR δ d 16.8, 17.8, 25.8, 58.8, 123.1, 128.0, 129.5, 134.1; u 23.6, 61.0, 69.0, 132.4, 135.7; IR 2919, 1586, 1449, 1360, 1187 cm^{-1}; MS *m*/*z* 310 (0.5), 292 (2), 201 (12), 141 (35), 109 (100); HRMS calcd for $C_{16}H_{22}O_4S$ 310.1240, obsd 310.1225.

Nitrile 9. *n*-BuLi (10.20 mL, 2.25 M, 22.9 mmol) was added to acetonitrile (1.25 mL, 23.9 mmol) in THF (28 mL) at −78 °C. After 1.5 h, sulfonate **11** (3.00 g, 9.6 mmol) in THF (20 mL) was added dropwise over 1 h. After an additional 0.5 h, the mixture was warmed to 0 °C and stirred for 30 min. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl. The THF was removed under vacuum, and the residue was partitioned between ethyl acetate and saturated brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give **9** as a pale yellow oil (1.6 g, 87% yield). TLC R_f = 0.37 (20% MTBE/petroleum ether), $[\alpha]^{18}_D = +68.1°$(*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 1.15 (m, 3H), 1.32 (s, 3H), 1.51 (m, 3H), 1.70 (s, 3H), 1.64 (s, 3H), 2.12 (q, *J* = 7.5 Hz, 2H), 5.13 (tquint, *J* = 1.3 and 7.1 Hz, 1H); ^{13}C NMR δ d −1.5, 17.9, 25.9, 27.7, 30.6, 123.9; u 10.2, 22.7, 42.5, 69.4, 122.5, 132.8; IR 3479, 2967, 2238, 1455 cm^{-1}; MS *m*/*z* 193 (5), 176 (45), 160 (50), 135 (40), 119 (50), 107 (100); HRMS calcd for $C_{12}H_{19}ON$ 193.1468, obsd 193.1535. Anal. Calcd for $C_{12}H_{19}ON$: C, 74.56; H, 9.91; N, 7.25. Found: C, 74.46; H, 10.01; N, 7.11.

Aldehyde 8. DIBAL-H (24.98 mL, 0.83 M in THF, 20.8 mmol) was added to nitrile **9** (1.60 g, 8.3 mmol) in THF (20 mL) at −78 °C, and the mixture was stirred and gradually warmed from −78 °C to room temperature over 2 h. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl and 6 M HCl (6:1, v/v) at 0 °C. The THF was removed under vacuum, and the residue was partitioned between ethyl ether and saturated brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give **8** as a colorless oil (981 mg, 61% yield). TLC R_f = 0.24 (20% MTBE/petroleum ether); $[\alpha]^{18}_D = +37.3°$ (*c* 0.8, CH_2Cl_2); ^{1}H NMR δ 1.22 (s, 3H), 1.26 (m, 2H) 1.59 (m, 3H), 1.63 (s, 3H), 1.64 (s, 3H), 1.94 (m, 1H), 2.12 (q, *J* = 7.5 Hz, 2H), 5.13 (tquint, *J* = 1.3 and 7.1 Hz, 1H), 9.17 (d, *J* = 4.3 Hz, 1H); ^{13}C NMR δ d 18.0, 26.0, 26.1, 27.6, 32.1, 124.1, 201.6; u 11.4, 22.9, 42.9, 70.3, 132.7; IR 3478, 2960, 2925, 2729, 1715, 1678 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O$: C, 73.43; H, 10.27. Found: C, 73.20; H, 10.52.

Aldehyde **8** (176 mg, 0.9 mmol) was dissolved in 20 mL of MeOH at 0 °C, and $NaBH_4$ (51 mg, 1.4 mmol) was added in several portions over 5 min. After an additional 1 h, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl. The MeOH was removed under vacuum, and the residue was partitioned between ethyl acetate and saturated brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The crude oil (157 mg) was dissolved in CH_2-Cl_2 at 0 °C, and triethylamine (0.23 mL, 1.7 mmol), 4-DMAP (19 mg, 0.16 mmol,) and benzoyl chloride (0.18 mL, 1.6 mmol) were added sequentially. After stirring at room temperature for 4 h, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl at 0 °C. The reaction mixture was then partitioned between dichloromethane and, sequentially, 5% aqueous NaOH, 5% aqueous HCl, and saturated brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the primary benzoate as a colorless oil (116 mg, 43% yield based on aldehyde **8**). TLC R_f = 0.57 (30% MTBE/petroleum ether); $[\alpha]^{16}_D = -4.1°$ (*c* 1.9, CH_2Cl_2); ^{1}H NMR δ 0.53 (m, 1H), 0.80 (m, 1H), 0.96 (m, 1H), 1.27 (s, 3H), 1.30 (m,1H), 1.59 (m, 2H), 1.61 (s, 3H), 1.69 (s, 3H), 1.72 (m, 1H), 2,14 (q, *J* = 7.5 Hz, 2H), 4.05 (dd, *J* = 8.1 and 11.3 Hz, 1H), 4.35 (dd, *J* = 6.7 and 11.3 Hz, 1H), 5.13 (m 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.56 (m, 1H), 8.06 (m, 2H); ^{13}C NMR δ d 13.2, 17.8, 25.9, 26.7, 27.7, 124.6, 128.5, 129.7, 133.0; u 6.7, 22.8, 43.1, 69.1, 70.7, 130.5, 132.0, 166.9; IR 3507, 2967, 2923,1715, 1602, 1452 cm^{-1}. The benzoate was shown to be 86.6% ee by chiral HPLC on an analytical Chiralcel OD column. Eluting with 98:2 hexanes/2-propanol at 1.0 mL/min, the benzoate (14.0 min) and the ent-benzoate (19.1 min) showed baseline resolution.

Alkenyl Cyclopropane 2. *n*-BuLi (92.68 mL, 2.19 M, 5.9 mmol) was added dropwise to ethyltriphenylphosphonium bromide (2.27 g, 6.1 mmol) in THF (6 mL) at 0 °C. The resulting orange suspension was stirred from 0 °C to room temperature over 1 h. Aldehyde **8** (480 mg, 2.5 mmol) in THF (5 mL) was added over 30 min at 0 °C. After an additional 30 min at room temperature, methanol (2 mL) was added to quench the reaction, and the solvent was removed under vacuum. The reaction mixture was partitioned between MTBE and saturated brine, and the combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give **2** as a colorless oil (253 mg, 50% yield). TLC R_f = 0.75 (20% MTBE/petroleum ether); $[\alpha]^{18}_D = -2.67°$ (*c* 0.6, CH_2Cl_2); ^{1}H NMR δ 0.47 (m 1H), 0.88 (m, 2H), 1.16 (s, 3H), 1.64 (m, 10H), 2.10 (q, *J* = 6.5 Hz, 2H), 4.80 (m, 1H), 5.16 (m, 1H), 5.34 (m, 1H); ^{13}C NMR δ d 13.2, 13.4, 17.9, 26.0, 26.4, 30.6, 122.3, 123.1, 124.6; u 10.1, 23.0, 43.2, 43.3, 71.3, 133.9; IR: 3418, 2969, 2918, 2857, 1654, 1451, 1375 cm^{-1}; MS *m*/*z* 208 (5), 190 (18), 175 (15), 147 (35), 123 (100), 107 (50); HRMS calcd for $C_{14}H_{24}O$ 208.1828, obsd 208.1832.

(−)-Delobanone 3. Under a balloon of carbon monoxide, $Fe(CO)_5$ (63 μL, 481 μmol) was added to alkene **2** (50 mg, 240 μmol) in 2-propanol (5 mL). The reaction was carried out in a Pyrex test tube, with a smaller Pyrex test tube inside, to spread the reaction mixture in a thin layer. After irradiation (Rayonet, 350 nm) for 23 h, DBU (180 μL, 1.2 mmol) was added at room temperature. After 1 h, the reaction mixture was filtered, and the solid residue was washed with MTBE. The combined filtrate was concentrated under vacuum. The residue

was partitioned between ethyl acetate and, sequentially, 5% aqueous HCl and saturated brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give **3** as a colorless oil (36.5 mg, 64% yield). TCL $R_f = 0.18$ (20% MTBE/petroleum ether); $[\alpha]^{18}_D = -12.7°$ (*c* 0.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 3H), 1.21 (s, 1H), 1.46 (m, 2H), 1.56 (s, 3H), 1.63 (s, 1H), 1.72 (t, $J = 1.2$ Hz, 3H), 2.26 (m, 7H), 2.54 (m, 1H), 5.05 (tquint, $J = 1.3$ and 7.1 Hz, 1H), 6.70 (tq, $J = 1.4$ and 5.5 Hz, 1H); ^{1}H NMR (C_6D_6) δ 0.83 (s, 3H), 1.25 (m, 2H), 1.56 (s, 3H), 1.67 (d, $J = 1.1$ Hz, 3H), 1.81 (d, $J = 1.2$ Hz, 3H), 1.90 (m, 7H), 2.64 (m, 1H), 5.13 (tquint, $J = 1.4$ and 7.1 Hz, 1H), 6.14 (tq, $J = 1.3$ and 5.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ d 15.9, 18.0, 24.2, 25.9, 44.5, 124.0, 146.2; u 22.5, 27.4, 39.2, 39.7, 73.5, 132.6, 135.4, 200.6; ^{13}C NMR (C_6D_6) δ d 16.3, 18.0, 24.0, 26.1, 45.0, 125.3, 144.2; u 22.9, 27.8, 36.9, 40.3, 72.9, 131.8, 135.7; IR 3472, 2925, 1660, 1453, 1372 cm^1; MS *m*/*z* 218 (5), 153 (8), 135 (10), 127 (20), 110 (100); HRMS calcd for $C_{14}H_{22}O$ ($M^+ - 18$) 218.1672, obsd 218.1669.

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Supporting Information Available: ^{1}H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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