Enantioselective Total Synthesis of β-Elemene and Fuscol Based on Enantiocontrolled Ireland–Claisen Rearrangement

E. J. Corey,* Bryan E. Roberts, and Brian R. Dixon

Contribution from the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

Received August 1, 1994®

Abstract: The potent antiinflammatory agent precursor (+)-fuscol (**2**) has been synthesized using the chiral reagent **1** to effect the key step, the completely enantioselective Ireland–Claisen rearrangement of ester **3** to acid **4a**. Conversion of **4a** to the corresponding aldehyde **4c**, cation–olefin cyclization to **5a**, and deoxygenation produced (+)-β-elemene (**6**). (+)-Fuscol (**2**) was synthesized from **6** via intermediates **7** and **8**.

In the past four decades there has been an enormous increase in the synthetic chemist's ability to assemble complex cyclic natural products, due in part to the availability of an assortment of powerful ring-forming reactions, which have served as key steps in synthetic design.[1] This approach can be made even more potent by the application of enantioselective versions of cyclization processes, allowing direct access to the required absolute configuration of the target molecule.[2,3] Reported herein is a further evolution of synthetic strategy in which the key reaction of synthetic planning is not a cyclization reaction, but an enantioselective Ireland–Claisen rearrangement that creates a chiral acyclic platform for subsequent cyclization and elaboration. The use of the Ireland–Claisen (ester) rearrangement in this way is possible due to the recent development of chiral reagent **1** (or enantiomer), which allows channeling of this reaction via either the *E* or *Z* boron enolate (generally with better than 90:10 selectivity) and control of the absolute configuration of the Ireland–Claisen product (generally >97% ee).[4,5] The specific synthetic target of this research was the marine natural product fuscol (**2**),[6] whose araboside is a potent antiinflammatory agent that blocks leukotriene C, but not prostaglandin, biosynthesis.[7] (+)-Fuscol is a member of the growing class of prenylated elemane derivatives termed lobanes for which one synthesis (from mannitol) has been reported.[8,9] The short synthetic pathway described herein produces (+)-fuscol of >99% ee via the intermediate terpenoid (+)-β-elemene.[10]

Reaction of geraniol with 1.1 equiv of β,β-dimethylacryloyl chloride and 1.5 equiv of triethylamine (CH₂Cl₂, −78 °C, 3 h) afforded the β,γ-unsaturated ester **3** (99% yield) in an interesting reaction that probably proceeds via a vinylketene intermediate. Treatment of **3** in toluene with 1.1 equiv of (*S*,*S*)-bromoborane

1 and 8.3 equiv of triethylamine (−70 °C for 27 h, then 4 °C for 36 h) afforded the Ireland–Claisen product **4a** as a major product along with a minor diastereomer (85% total yield). Reduction of the mixture to the corresponding primary alcohols (LiAlH₄, Et₂O, 23 °C, 24 h) and chromatography on AgNO₃-impregnated silica gel gave diastereomerically pure **4b** (70% yield) of >99% enantiomeric purity.[11] Oxidation of **4b** with 1.5 equiv of the Dess–Martin periodinane (CH₂Cl₂, 23 °C, 1 h) provided aldehyde **4c** (98% yield). Treatment of **4c** with 1.1 equiv of Et₂AlCl (CH₂Cl₂, −78 °C, 1.5 h) followed by extractive isolation and chromatography on silica gel–AgNO₃ furnished the cyclized equatorial alcohol **5a** (88% yield) along with 3% yield of a less polar diastereomer (having equatorial hydroxyl and axial β-isopropenyl substituents). Reaction of **5a** with 2-chloro-1,3-dimethyl-1,3,2-diazaphospholane[12] and triethylamine (CH₂Cl₂, 23 °C, 75 min) provided, after oxidation with 1.2 equiv of H₂O₂ for 10 min, **5b**,[13] which was reduced with excess lithium and *tert*-amyl alcohol (4 equiv) in liquid NH₃–THF (−33 °C, 10 h) to give (+)-β-elemene (**6**, 95% yield), [α]²³_D +15.4° (*c* = 0.6, CHCl₃), which was indistinguishable, by NMR and infrared spectroscopic comparison, from an authentic sample of naturally derived (−)-β-elemene.[14]

(+)-β-Elemene (**6**) was converted to the methyl ketone **7** by a two-step sequence. Catalytic dihydroxylation with the Sharpless phthalazine-linked bisether with dihydroquinidine, (DHQD)₂-PHAL[15] (0.1 equiv), K₂OsO₄ (0.01 equiv), K₃Fe(CN)₆ (3 equiv), K₂CO₃ (3 equiv), and CH₃SO₂NH₂ (1 equiv) in 1:1 *tert*-butyl alcohol–water at 0 °C for 11 h afforded, after chromatography on silica gel, the diol resulting from selective attack at the

® Abstract published in *Advance ACS Abstracts*, December 1, 1994.

(1) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley: New York, 1989; Chapter 1.

(2) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley: New York, 1994.

(3) For a recent example, see: Corey, E. J.; Guzman-Perez, A.; Loh, T.-P. *J. Am. Chem. Soc.* **1994**, *116*, 3611.

(4) Corey, E. J.; Lee, D.-H. *J. Am. Chem. Soc.* **1991**, *113*, 4026.

(5) For a recent review of the Ireland–Claisen rearrangement, including applications, see: Pereira, S.; Srebnick, M. *Aldrichimica Acta* **1993**, *26*, 17.
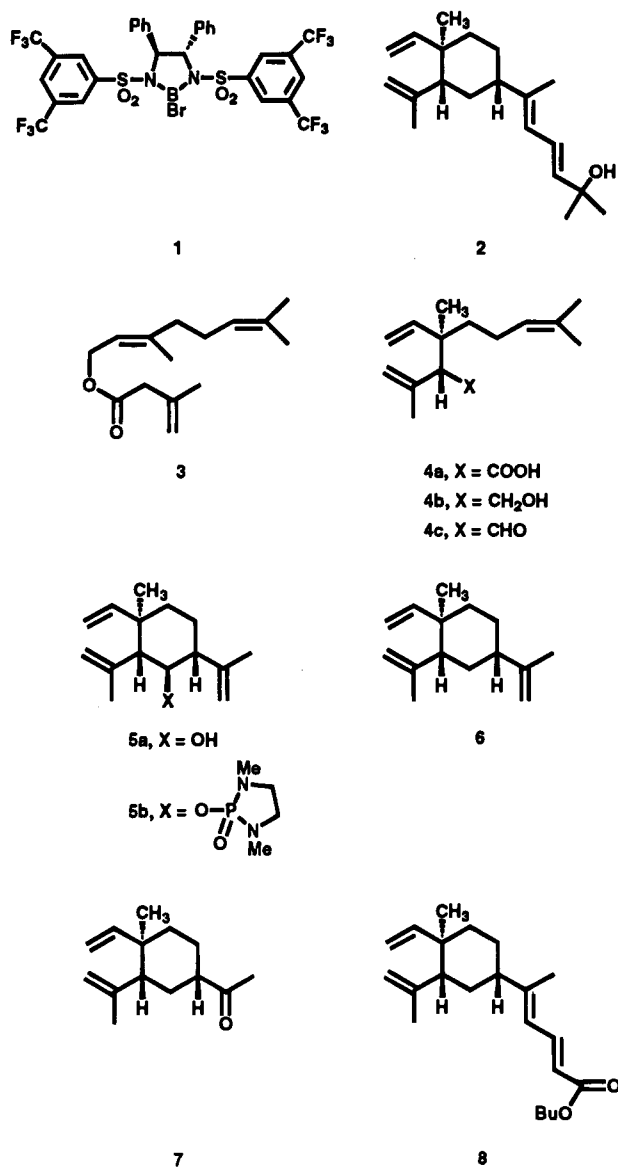
(6) Gopichand, Y.; Schmitz, F. J. *Tetrahedron Lett.* **1978**, 3641.

(7) Shin, J.; Fenical, W. *J. Org. Chem.* **1991**, *56*, 3153.

(8) Iwashima, M.; Nagaoka, H.; Kobayashi, K.; Yamada, Y. *Tetrahedron Lett.* **1992**, *33*, 81.

(9) (a) Hamada, T.; Kusumi, T.; Ishitsuka, M. O.; Kakisawa, H. *Chem. Lett.* **1992**, 33. (b) Nagaoka, H.; Iwashima, M.; Miyahara, M.; Yamada, Y. *Chem. Pharm. Bull.* **1992**, *40*, 556.

(10) For the original synthesis of the racemic elemol/elemene system, see: Corey, E. J.; Broger, E. A. *Tetrahedron Lett.* **1969**, 1779.

(11) Approximately 22% of a less polar diastereomer of **4b** was separated during the chromatography. It is possible that the diastereoselectivity of the Claisen rearrangement can be improved by further experimentation, which was not undertaken due to the satisfactory yield and ee of product **4b** obtained in the initial experiments.

(12) Nifant'ev, E. E.; Zavalishina, A. I.; Sorokina, S. F.; Borisenko, A. A.; Smirnova, E. I.; Kurochkin, V. V.; Moiseeva, L. I. *Zh. Obshch. Khim.* **1979**, *49*, 53.

(13) The yield of **5b** was 77%, or 92% after a second cycle. This step has not yet been optimized.

(14) Prepared by dehydration of elemol (from elemi oil) with Burgess's reagent; see: Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

(15) For key references to the work of the Sharpless group that developed this methodology, see: (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (b) Morikawa, K.; Park, J.; Andersson, P. G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 8463. (c) Kolb, H. C.; Andersson, P. G.; Bennani, Y. L.; Crispino, G. A.; Jeong, K.-S.; Kwong, H.-L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 12226. (d) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278 and references cited therein.

1

2

3

4a, X = COOH
4b, X = CH₂OH
4c, X = CHO

5a, X = OH

5b, X = O ...

6

7

8

isopropenyl appendage (1,4-) to the angular methyl group (76% yield; 92% yield corrected for recovered **6**). Cleavage of the resulting 1,2-diol with 3 equiv of NaIO₄ (4:1 THF—H₂O, 23 °C, 30 min) gave **7** in 96% yield. The highly selective attack of just one of the three double bonds of **6** by OsO₄ under catalysis by (DHQD)₂-PHAL[15] was predicted on the basis of the mechanistic model recently proposed for the asymmetric dihydroxylation reaction.[16,17] Coupling of methyl ketone **7** with 20 equiv each of (*n*-BuO)₂POCH₂CH=CHCOO*n*-Bu[18] and LiO*t*-Bu (added in four portions, THF solution, 23 °C, 48 h) furnished the tetraene ester **8** in 80% yield after chromatography on silica gel.[19] Reaction of **8** with 5 equiv of MeLi (Et₂O, −30 °C, 12 h) afforded (+)-fuscol (**2**), [α]²³_D +19.7° (*c* = 1,

(16) (a) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 12579. (b) Corey, E. J.; Noe, M. C.; Sarshar, S. *Tetrahedron Lett.* **1994**, *35*, 2861.

(17) This kind of intramolecular site selectivity for the oxidation of one among three terminal olefinic bonds in a chiral substrate demonstrates a new way to use the Sharpless catalytic dihydroxylation system. The diastereoselectivity of the attack on the isopropenyl appendage 1,4- to the angular methyl group in **6** was only modest (3:1). Significantly lower levels of site selectivity were observed in the absence of chiral ligand (only 45% yield of the desired 1,2-diol with OsO₄, *N*-methylmorpholine *N*-oxide, acetone—H₂O oxidant system).

(18) This reagent was prepared by the Arbusov reaction of *n*-butyl (*E*)-γ-bromocrotonate with tri-*n*-butyl phosphite; see: Gershon, H.; Shanks, L.; Gawaik, D. E. *J. Med. Chem.* **1976**, *19*, 1069.

(19) The crude tetraene ester contained about 7% of the γ,δ-*Z* isomer of **8**, which was removed by preparative silica gel chromatography (9:1 pentane:ether eluent).

CHCl₃),[20] as a colorless oil in 95% yield. The UV, infrared, ¹H and ¹³C NMR, and MS/HRMS spectra were identical with those recorded previously.[6,7]

Several aspects of this research on the synthesis of (+)-fuscol deserve further comment. First, the very high enantioselectivity of the key Ireland—Claisen step (**3** → **4**) provides clear evidence of the value of this new method in multistep synthesis and support for a useful strategic role for this enantioselective reaction in synthetic planning. Second, it was originally intended that (+)-β-elemene (**6**) be made from alcohol **4b** by cation—olefin cyclization of a sulfonate ester. However, extensive experimentation of such ring closure reactions was completely (and surprisingly) unproductive because of the intervention of several competing cationic pathways. For example, treatment of the mesylate of **4b** with methyl aluminum dichloride (CH₂Cl₂, −78 °C to 0 °C) afforded none of the desired **6**, but only a complex mixture of hydrocarbons. In contrast, the cyclization of aldehyde **4c** was very facile and clean, and even highly diastereoselective for the equatorial alcohol **5a**. Although deoxygenation of **5a** failed using the Barton method (Bu₃SnH with various thiono esters), the process reported above, in contrast, was successful. The method used for the transformation of **5a** to **6** may also be effective in other difficult cases.[21,22]

Experimental Section

Proton and carbon nuclear magnetic resonance (¹H, ¹³C NMR) spectra were recorded on an AM-500 (500 MHz) or AM-400 (400 MHz) Bruker nuclear magnetic resonance spectrometer using chloroform-*d* as a solvent. Chemical shifts are reported as δ in units of parts per million downfield from tetramethylsilane (δ 0.0) using the residual solvent signal as an internal standard: δ 7.26 (¹H), 77.0 triplet (¹³C). All coupling constants are in units of hertz. Phosphorus nuclear magnetic resonance (³¹P NMR) spectra were recorded on an AM-500 (500 MHz), or WM-300 (300 MHz) Bruker nuclear magnetic resonance spectrometer using chloroform-*d* as a solvent. Chemical shifts are reported as δ in units of parts per million downfield of triphenylphosphine (δ −6.0) as an external standard. Infrared spectra (IR) were recorded on a Nicolet 5 ZDX FTIR spectrometer with an internal polystyrene sample as a reference. Mass spectral analyses were recorded on JEOL model AX-505 or SX-102 spectrometers. Optical rotations were measured in chloroform using a Perkin-Elmer 241 polarimeter at 23 °C using a sodium lamp (589 nm) and are reported in degrees with concentration in units of 10 mg/mL. Ultraviolet/visible (UV/vis) spectra were recorded in cyclohexane in quartz vessels using a Hewlett-Packard 8452A diode array spectrophotometer. Reactions were monitored by thin layer chromatography (TLC) using Merck 60 F₂₅₄ precoated silica gel plates (0.25 mm thickness). After ultraviolet illumination at 254 nm, the plates were visualized by immersion in the indicated solution and warming on a hot plate. Baker silica gel (40 μm particle size) and reagent grade solvents were used for flash chromatography. Preparative thin layer chromatography was performed using Merck 60 F₂₅₄ precoated silica gel plates (0.50 mm thickness, 20 × 20 cm). Radial chromatography was performed on a Harrison Research Chromatotron 7924 and silica gel plates (no. 7749, Kieselgel 60 PF₂₅₄, Merck). AgNO₃-impregnated silica gel plates were prepared by the addition of 5% (w/w silica gel) AgNO₃ to the water used in typical chromatotron plate preparation. Analytical high-performance liquid chromatography (HPLC) was carried out using an ISCO 2350 pump, Diacel Corp. Chiracel OD analytical column, variable wavelength UV detector, and Hewlett-Packard 3396A integrator. All solvents are reagent grade unless otherwise stated, and anhydrous solvents were dried immediately prior to use.

(20) Reported rotation of fuscol [α]²³_D: +16.3°,[6] +17.6°.[7]

(21) For the early work on this type of deoxygenation, see: Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098.

(22) This research was assisted financially by a grant from the National Institutes of Health. We are indebted to Dr. D.-H. Lee for developing the procedure for the enantioselective Ireland—Claisen rearrangement and for helpful discussions.

(E)-Geranyl 3-Methyl-3-butenoate (3). A solution of geraniol (225 μL, 1.29 mmol, 1.0 equiv) and triethylamine (271 μL, 1.94 mmol, 1.5 equiv) in dry dichloromethane (1 mL) was cooled to −78 °C and treated dropwise with 3,3-dimethylacryloyl chloride (159 μL, 1.43 mmol, 1.1 equiv). After 3 h, the solution was diluted with water (1 mL) and dichloromethane (1 mL), and the cooling bath was removed. The mixture was extracted with dichloromethane (3 × 20 mL), and the combined organics were dried (MgSO$_4$) and concentrated *in vacuo*. Purification by radial chromatography (4 mm SiO$_2$ plate; eluent, 7% EtOAc−hexanes; product, fractions 4−6; 30 mL/fraction) afforded **3** (301 mg, 1.27 mmol, 99% yield) as a clear oil: R_f starting material, 0.14; product, 0.51 (5:1 hexanes−EtOAc, anisaldehyde); FTIR (film) 2970, 2919, 2858, 1738, 1653, 1445, 1377, 1206, 1153, 987, 896 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.31−5.35 (m, 1H), 5.04−5.08 (m, 1H), 4.88 (bs, 1H), 4.83 (bs, 1H), 4.60 (s, 1H), 4.58 (s, 1H), 3.01 (s, 2H), 2.00−2.09 (m, 4H), 1.79 (s, 3H), 1.69 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 171.2, 142.2, 138.6, 131.7, 123.7, 118.2, 114.5, 61.4, 43.4, 39.4, 26.2, 25.6, 22.3, 17.6, 16.4; HRMS (EI, Pos) *m/z* calcd for [C$_{15}$H$_{24}$O$_2$]$^+$ 236.1776, found 236.1768.

(2R,3R)-2-Isopropenyl-3,7-dimethyl-3-vinyl-6-octenoic Acid (4a). The 3,5-bis(trifluoromethyl)benzenesulfonamide of (S,S)-1,2-diphenyl-1,2-diaminoethane (718 mg, 0.940 mmol, 1.0 equiv) was dried under vacuum at 70 °C for 3 h. The reaction flask was then evacuated and flushed three times with dry nitrogen. Freshly distilled dichloromethane (32 mL) was added, and the homogeneous solution was cooled to −78 °C. After 10 min, freshly distilled BBr$_3$ (3.76 mL, 0.5 M in CH$_2$Cl$_2$, 1.88 mmol, 2.0 equiv) was added, and the solution was stirred for 5 min at −78 °C and then warmed to 23 °C. After 16 h, all volatile materials were removed under vacuum, the resulting white solid was redissolved in dichloromethane (20 mL), and the solution was concentrated again. After 60 min, the flask was evacuated and flushed three times with nitrogen, and the resultant white solid was dissolved in freshly distilled toluene (32 mL). The bromoborane complex (1) was cooled to −78 °C, Et$_3$N (983 μL, 7.05 mmol, 7.5 equiv) was added dropwise, and the mixture was stirred to effect solution (25 min). A precooled solution of **3** (175 mg, 0.740 mmol, 0.8 equiv) in toluene (4 mL) was added dropwise at −78 °C, and the resultant solution was stirred at −70 °C for 27 h and subsequently warmed to 4 °C. After 36 h, the reaction solution was warmed to 23 °C, diluted with diethyl ether (40 mL), and washed with NaOH (2 N, 4 × 60 mL). The aqueous phases were combined, washed with diethyl ether (40 mL), acidified to pH 1 with 10% HCl, and extracted with diethyl ether (4 × 60 mL). The ethereal extract was dried (MgSO$_4$) and concentrated *in vacuo* to give a 3:1 mixture of **4a** and a minor diastereomer as a yellow oil (149.2 mg, 0.631 mmol, 85% yield): R_f starting material, 0.71; product, 0.26 (5% MeOH−CHCl$_3$, Verghns); FTIR (film) 3084, 3055, 2972, 2927, 2859, 2729, 1707, 1638, 1452, 1413, 1377, 1265, 916, 742 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.09 (dd, 1H, J = 10.9, 17.5, minor), 5.86 (dd, 1H, J = 10.9, 17.5, major), 4.96−5.12 (m, 5H), 3.08 (s, 1H, major), 3.07 (s, 1H, minor), 1.85−1.91 (m, 2H), 1.85 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H), 1.41−1.57 (m, 2H), 1.18 (s, 3H, major), 1.12 (s, 3H, minor); HRMS (EI, Pos) *m/z* calcd for [C$_{15}$H$_{24}$O$_2$]$^+$ 236.1776, found 236.1783.

(2R,3R)-2-Isopropenyl-3,7-dimethyl-3-vinyl-6-octenol (4b). A mixture of **4a** and minor diastereomer (18 mg, 0.076 mmol, 1.0 equiv) in dry diethyl ether (2 mL) was treated with LiAlH$_4$ (15 mg, 0.381 mmol, 5.0 equiv) at 23 °C. After 12 h, additional LiAlH$_4$ (15 mg, 0.381 mmol, 5.0 equiv) and diethyl ether (2 mL) were added. After an additional 12 h, H$_2$O (50 μL), NaOH (15% w/v, 50 μL), and H$_2$O (150 μL) were added sequentially. The mixture was stirred for 10 min, filtered, dried (MgSO$_4$), and concentrated *in vacuo*. Flash chromatography (10 g of SiO$_2$; eluent, 10% EtOAc−hexanes; product, fractions 7−21; 10 mL/fraction) yielded a 3:1 mixture of **4b** and minor diastereomer as a clear oil (15.8 mg, 0.071 mmol, 93% yield): R_f starting material, 0.46; product, 0.72 (12% MeOH−CHCl$_3$, anisaldehyde). The 3:1 mixture of diastereomers was separated by AgNO$_3$-impregnated radial chromatography (4 mm SiO$_2$ plate; eluent, 4:1 EtOAc−hexanes; minor, fractions 11−15; **4b**, fractions 16−35; 30 mL/fraction) followed by passage through silica gel (20 g; 200 mL of 10% EtOAc−hexanes) to afford diastereomerically pure **4b** (70% yield): AgNO$_3$-impregnated TLC: R_f **4b**, 0.20; minor 0.35 (12% MeOH−CHCl$_3$, anisaldehyde). The enantiomeric purity of **4b** was determined to be greater than 99:1 by chiral high-performance liquid chromatog-

raphy (Chiralcel OD column, 1% 2-propanol−hexanes, 214 nm, 1 mL/min, retention times R,R−isomer, **4b** = 9.4 min, S,S−isomer = 23 min): [α]^{23}$_D$ +40.2° (c = 0.54, CHCl$_3$); FTIR (film) 3377, 3080, 2969, 2925, 2858, 1639, 1450, 1414, 1376, 1033, 1005, 912, 893 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.80 (dd, 1H, J = 10.8, 17.5), 5.02−5.08 (m, 3H), 4.91 (dd, 1H, J = 1.3, 17.5), 4.83 (d, 1H, J = 1.6), 3.72 (dd, 1H, J = 4.3, 10.7), 3.58 (t, 1H, J = 10.7), 2.25 (dd, 1H, J = 4.3, 10.7), 1.82−1.90 (m, 2H), 1.77 (m, 3H), 1.67 (d, 3H, J = 0.8), 1.57 (s, 3H), 1.30−1.44 (m, 2H), 1.04 (s, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 144.4, 144.3, 131.3, 124.7, 115.7, 112.8, 61.1, 58.6, 41.2, 39.4, 25.7, 23.2, 22.6, 20.8, 17.6; HRMS (CI, NH$_3$) *m/z* calcd for [C$_{15}$H$_{26}$O]$^+$NH$_3$ 240.2327, found 240.2317.

(2R,3R)-2-Isopropenyl-3,7-dimethyl-3-vinyl-6-octenal (4c). A suspension of Dess−Martin reagent (232 mg, 0.546 mmol, 1.5 equiv) in dry dichloromethane (5 mL) was added to **4b** (81 mg, 0.364 mmol, 1.0 equiv) in dichloromethane (2 mL) at 23 °C. After 1 h, the solution was filtered through Celite 545, concentrated *in vacuo*, rediluted in hexanes, and filtered again through Celite 545. The filtrate was concentrated *in vacuo* and purified by flash chromatography (10 g of SiO$_2$; eluent, 4% EtOAc−hexanes, product, fractions 4−8; 10 mL/fraction) to afford **4c** (79 mg, 0.359 mmol, 98% yield) as a clear oil: R_f starting material, 0.28; product, 0.58 (5:1 hexanes−EtOAc, anisaldehyde); [α]^{23}$_D$ +12.5° (c = 0.91, CHCl$_3$); FTIR (film) 2970, 2921, 2859, 1721, 1638, 1453, 1377, 914 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.65 (d, 1H, J = 4.5), 5.92 (dd, 1H, J = 10.9, 17.6), 5.14−5.17 (m, 2H), 5.06 (t, 1H, J = 7.1), 5.00 (d, 1H, J = 17.6), 4.88 (s, 1H), 2.70 (d, 1H, J = 4.5), 1.84−1.90 (m, 2H), 1.82 (s, 3H), 1.67 (s, 3H), 1.57 (s, 3H), 1.38−1.50 (m, 2H), 1.15 (s, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 202.0, 143.1, 139.5, 131.5, 124.2, 116.8, 114.2, 67.1, 42.3, 39.1, 25.7, 25.6, 22.4, 20.6, 17.6; HRMS (EI, Pos) *m/z* calcd for [C$_{15}$H$_{24}$O]$^+$ 220.1827, found 220.1817.

(1R,2R,3R,6R)-2,6-Diisopropenyl-3-methyl-3-vinylcyclohexanol (5a). Diethylaluminum chloride (210 μL, 1.8 M in toluene, 0.379 mmol, 1.1 equiv) was added dropwise to a solution of **4c** (76 mg, 0.344 mmol, 1.0 equiv) in dry dichloromethane (10 mL) at −78 °C. After 1.5 h, triethylamine (500 μL) was added, the cooling bath was removed, and the solution was added to a mixture of saturated NaHCO$_3$ (20 mL) and dichloromethane (20 mL). The mixture was extracted with dichloromethane (2 × 20 mL), and the organic fractions were combined, dried (MgSO$_4$), and concentrated *in vacuo*. Flash chromatography (15 g of SiO$_2$; eluent, 4% EtOAc−hexanes; product, fractions 11−23; 10 mL/fraction) afforded a 96:4 mixture of **5a** and a minor diastereomer (70.1 mg, 0.318 mmol, 92% yield): R_f starting material, 0.58; product, 0.41 (5:1 hexanes−EtOAc, anisaldehyde). The diastereomeric mixture was separated by AgNO$_3$-impregnated radial chromatography (2 mm plate; eluent, 5:1 EtOAc−hexanes; product, fractions 10−33; 3 mL/fraction) followed by passage through silica gel (10 g; 150 mL of 4% EtOAc−hexanes) to afford pure **5a** (88% yield) as a clear oil: AgNO$_3$-impregnated TLC: R_f **5a**, 0.08; minor, 0.17 (12% MeOH−CHCl$_3$, anisaldehyde); [α]^{23}$_D$ −17.8° (c = 1.04, CHCl$_3$); FTIR (film) 3566, 3486, 2969, 2931, 1639, 1454, 1375, 1004, 910, 889 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.78 (dd, 1H, J = 10.9, 17.4), 5.06 (s, 1H), 4.88−4.92 (m, 4H), 4.76 (s, 1H), 3.77 (t, 1H, J = 10.4), 2.08 (dt, 1H, J = 4.8, 10.8), 1.98 (d, 1H, J = 10.4), 1.90 (bs, 1H), 1.80 (s, 3H), 1.79 (s, 3H), 1.51−1.66 (m, 3H), 1.42 (dt, 1H, J = 3.1, 13.0), 1.06 (s, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 148.9, 147.1, 144.2, 114.1, 112.2, 110.3, 69.3, 59.7, 53.7, 41.3, 39.0, 26.2, 25.0, 19.5, 18.1; HRMS (EI, Pos) *m/z* calcd for [C$_{15}$H$_{24}$O]$^+$ 220.1827, found 220.1826.

Reaction of 2-Chloro-1,3-dimethyl-1,3,2-diazaphospholane with 5a (5b). 2-Chloro-1,3-dimethyl-1,3,2-diazaphospholane[12] (10 μL, 0.076 mmol, 1.4 equiv) was added dropwise to a solution of **5a** (12 mg, 0.054 mmol, 1.0 equiv) and triethylamine (8 μL, 0.06 mmol, 1.1 equiv) in dry dichloromethane (1 mL) at 23 °C. After 75 min, hydrogen peroxide (7 μL, 30% aqueous solution, 0.065 mmol, 1.2 equiv) was added, and the reaction was stirred vigorously for 10 min and then quenched with sat Na$_2$SO$_4$ (1 mL). After 5 min of vigorous stirring, the solution was added to a mixture of dichloromethane (20 mL) and water (20 mL). The aqueous portion was extracted with dichloromethane (2 × 20 mL), and the combined organic fractions were dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Flash chromatography (10 g of SiO$_2$; eluent 1% MeOH−CHCl$_3$; product, fractions 12−15; 10 mL/fraction) afforded, in addition to recovered **5a** (2.5 mg, 21% yield), **5b** (15 mg, 0.042 mmol, 77% yield, 92% after two cycles) as a clear oil: R_f starting

material, 0.78; product, 0.35 (5% MeOH–CHCl₃, Verghns); $[\alpha]^{23}{}_D$ −25.4° (*c* = 1.03, CHCl₃); FTIR (film) 3079, 2934, 2880, 1647, 1451, 1269, 1240, 1161, 1003, 941 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.74 (dd, 1H, *J* = 10.9, 17.3), 5.03 (bs, 1H), 4.83−4.93 (m, 5H), 4.58 (q, 1H, *J* = 10.3), 2.93−3.04 (m, 4H), 2.50−2.54 (m, 6H), 2.17−2.22 (m, 1H), 2.00−2.06 (m, 1H), 1.87 (s, 3H), 1.77 (bs, 3H), 1.36−1.70 (m, 4H), 1.04 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 148.6, 146.9, 142.7, 114.6 (bm), 112.9, 110.4, 77.8 (bm), 58.7 (bm), 53.8, 47.3 (d), 41.7, 38.7, 33.8, 33.6, 27.9, 20.3, 18.3; ³¹P NMR (121 MHz, CDCl₃, Ph₃P external standard at −6 ppm) δ 22.65 (t, *J* = 10); HRMS (EI, Pos) *m/z* calcd for [C₁₉H₃₃O₂N₂P]⁺ 352.2280, found 352.2285.

(+)-β-Elemene (6). A solution of dry **5b** (53 mg, 0.152 mmol, 1.0 equiv, azeotroped from toluene) and *tert*-amyl alcohol (67 μL, 0.608 mmol, 4.0 equiv) in dry tetrahydrofuran (1.5 mL) was cannulated into a blue solution of excess lithium in liquid ammonia (5 mL) at −33 °C. The transfer flask was rinsed with tetrahydrofuran (0.5 mL), and the solution was stirred for 10 h. The solution was sequentially quenched dropwise with isoprene (ca. 300 μL) and saturated aqueous NH₄Cl (2 mL) and diluted with pentanes (4 mL). After warming to 23 °C, the solution was added to a mixture of pentanes (30 mL) and water (30 mL). The aqueous portion was extracted with pentanes (2 × 30 mL), and the combined organic fractions were dried (Na₂SO₄) and concentrated *in vacuo*. Flash chromatography (10 g of SiO₂; eluent, pentanes; product, fractions 4−7; 10 mL/fraction) afforded **6** (29.5 mg, 0.144 mmol, 95% yield) as a clear oil: *R*ƒ starting material, 0.00; product, 0.71 (pentanes, Verghns); $[\alpha]^{23}{}_D$ +15.4° (*c* = 0.59, CHCl₃); FTIR (film) 3083, 2969, 2931, 1644, 1454, 1440, 1374, 1004, 909 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.82 (dd, 1H, *J* = 11.0, 17.4), 4.88−4.92 (m, 2H), 4.82 (t, 1H, *J* = 1.6), 4.70−4.72 (m, 2H), 4.59 (bs, 1H), 1.99−2.03 (m, 1H), 1.92−1.96 (m, 1H), 1.75 (s, 3H), 1.71 (s, 3H), 1.42−1.63 (m, 6H), 1.01 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 150.4, 150.3, 147.7, 112.1, 109.8, 108.2, 52.8, 45.7, 39.9, 39.8, 32.9, 26.8, 24.7, 21.1, 16.6; HRMS (EI, Pos) *m/z* calcd for [C₁₅H₂₄]⁺ 204.1878, found 204.1869.

Dihydroxylation of 6. A solution of (DHQD)₂-PHAL¹⁵ (11 mg, 0.0137 mmol, 0.1 equiv), potassium osmate(VI) dihydrate (0.5 mg, 0.0014 mmol, 0.01 equiv), potassium ferrocyanide (135 mg, 0.411 mmol, 3.0 equiv), potassium carbonate (57 mg, 0.411 mmol, 3.0 equiv), and methanesulfonamide (13 mg, 0.137 mmol, 1.0 equiv) in 1:1 2-methyl-2-propanol−water (1.5 mL) was cooled to 0 °C. The biphasic mixture was added to **6** (28 mg, 0.137 mmol, 1.0 equiv) at 0 °C and the reaction mixture was stirred for 11 h. The solution was quenched with excess Na₂SO₃ (until precipitate and color disappeared). After warming to 23 °C, the solution was added to a mixture of dichloromethane (20 mL) and water (20 mL). The aqueous portion was extracted with dichloromethane (2 × 20 mL), and the combined organic fractions were dried (Na₂SO₄) and concentrated *in vacuo*. Flash chromatography (15 g of SiO₂; eluent, 28% EtOAc−hexanes; product, fractions 19−30; 10 mL/fraction) afforded, in addition to recovered **6** (5 mg, 0.024 mmol, 17% yield), a 3:1 mixture of diastereomers of the 1,2-diol (24.8 mg, 0.104 mmol, 76% yield) as a clear oil: *R*ƒ starting material, 0.75; product, 0.33 (1:1 hexanes−EtOAc, Verghns); FTIR (film) 3404, 2970, 2939, 2869, 1638, 1441, 1376, 1042, 908, 890 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.79 (dd, 1H, *J* = 10.5, 17.9), 4.88−4.91 (m, 2H), 4.82 (t, 1H, *J* = 1.6), 4.58 (s, 1H, major), 4.56 (s, 1H, minor), 3.59 (d, 1H, *J* = 10.9, major), 3.57 (d, 1H, *J* = 10.9, minor), 3.43 (d, 1H, *J* = 10.9), 2.07 (bs, 2H), 1.96 (dd, 1H, *J* = 3.7, 12.3), 1.68 (s, 3H), 1.67−1.71 (m, 1H), 1.33−1.59 (m, 6H), 1.14 (s, 3H), 0.98 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 150.0, 147.7, 112.1, 110.0, 74.6, 68.5, 68.4, 52.6, 44.9, 39.7, 28.7, 27.4, 24.8, 22.8, 21.5, 20.3, 20.3, 16.5; HRMS (CI, NH₃) *m/z* calcd for [C₁₅H₂₆O₂]⁺NH₄ 256.2277, found 256.2277.

(1*S*,3*R*,4*R*)-1-Acetyl-3-isopropenyl-4-methyl-4-vinylcyclohexane (7). Sodium periodate (62 mg, 0.289 mmol, 3.0 equiv) was added to a solution of the 1,2-diol (23 mg, 0.096 mmol, 1.0 equiv) in 4:1 tetrahydrofuran−water (2 mL) at 23 °C. After 30 min, the solution was added to a mixture of dichloromethane (20 mL) and water (20 mL). The aqueous portion was extracted with dichloromethane (2 × 20 mL), and the combined organic fractions were dried (Na₂SO₄) and concentrated *in vacuo*. Flash chromatography (10 g of SiO₂; eluent, 7% EtOAc−hexanes; product, fractions 3−9; 10 mL/fraction) afforded **7** (19 mg, 0.092 mmol, 96% yield) as a clear oil: *R*ƒ starting material, 0.07; product, 0.61 (3:1 hexanes−EtOAc, Verghns); $[\alpha]^{23}{}_D$ +37.0° (*c*

= 1.0, CHCl₃); FTIR (film) 3082, 2971, 2935, 2864, 1711, 1638, 1441, 1373, 1353, 908, 892 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.80 (dd, 1H, *J* = 10.6, 17.8), 4.89−4.93 (m, 2H), 4.84 (t, 1H, *J* = 1.4), 4.60 (s, 1H), 2.37−2.43 (m, 1H), 2.16 (s, 3H), 1.97−2.00 (m, 1H), 1.74−1.78 (m, 1H), 1.67−1.71 (m, 5H), 1.46−1.59 (m, 3H), 1.00 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 211.6, 149.6, 146.9, 112.6, 110.3, 52.0, 51.9, 39.6, 39.1, 29.4, 28.2, 24.7, 23.7, 16.5; HRMS (EI, Pos) *m/z* calcd for [C₁₄H₂₂O]⁺ 206.1671, found 206.1661.

Butyl 5-[(1′*S*,3′*R*,4′*R*)-3′-Isopropenyl-4′-methyl-4′-vinylcyclohexyl]-(*E*,*E*)-hexadienoate (8). *n*-Butyllithium (244 μL, 1.57 M in hexanes, 0.384 mmol, 4.95 equiv) was added to a solution of 2-methyl-2-propanol (37 μL, 0.388 mmol, 5.0 equiv) in tetrahydrofuran (0.5 mL) at −78 °C. After 15 min, butyl (dibutylphosphono)-2-butenoate (108 μL, 0.388 mmol, 5.0 equiv) was added, and the mixture was briefly warmed to effect solution. After 15 min at −78 °C, the yellow phosphonate anion solution was cannulated into **7** (16 mg, 0.078 mmol, 1.0 equiv) in tetrahydrofuran (0.5 mL) at 23 °C. After 18 h, 5 equiv of additional phosphonate anion was added in the same manner. This process was repeated at 28 and 41 h. After 48 h of stirring, the reaction mixture was diluted in dichloromethane, passed through silica gel (15 g, 200 mL CH₂Cl₂), and concentrated *in vacuo*. Flash chromatography (15 g of SiO₂; eluent, 1.5% EtOAc−hexanes; product, fractions 7−15; 10 mL/fraction) afforded **8** (22.1 mg, 0.067 mmol, 87% yield) as a 12:1 mixture of diastereomers: *R*ƒ starting material, 0.55; product, 0.75 (5:1 hexanes−EtOAc, anisaldehyde). Preparative thin layer chromatography (0.5 mm plate, 9:1 pentanes−diethyl ether, *R*ƒ *trans,trans*-**8**, 0.42) afforded pure **8** (80% yield) as a clear oil: $[\alpha]^{23}{}_D$ +24.5° (*c* = 1.17, CHCl₃); FTIR (film) 3081, 2961, 2933, 2871, 1714, 1635, 1308, 1274, 1212, 1129, 979, 890 cm⁻¹; UV/vis λ_{max} = 272 nm, ε = 35 000; ¹H NMR (500 MHz, CDCl₃) δ 7.61 (dd, 1H, *J* = 11.6, 15.1), 6.03 (d, 1H, *J* = 11.6), 5.79−5.84 (m, 2H), 4.89−4.93 (m, 2H), 4.83 (t, 1H, *J* = 1.6), 4.59 (bs, 1H), 4.15 (t, 2H, *J* = 6.7), 2.05−2.10 (m, 1H), 2.02 (dd, 1H, *J* = 3.4, 12.5), 1.91 (s, 3H), 1.71 (s, 3H), 1.38−1.68 (m, 10H), 1.02 (s, 3H), 0.94 (t, 3H, *J* = 7.4); ¹³C NMR (126 MHz, CDCl₃) δ 167.7, 153.7, 149.9, 147.3, 141.0, 121.6, 119.3, 112.3, 110.1, 64.0, 52.6, 48.2, 39.7, 32.4, 30.8, 26.4, 24.8, 19.2, 16.7, 15.9, 13.7; HRMS (EI, Pos) *m/z* calcd for [C₂₂H₃₄O₂]⁺ 330.2559, found 330.2553.

(+)-Fuscol (2). Methyllithium (161 μL, 1.5 M in diethyl ether, 0.242 mmol, 5.0 equiv) was added to a solution of **8** (16 mg, 0.048 mmol, 1.0 equiv) in diethyl ether (2 mL) at −30 °C. After 12 h, the reaction was quenched with aqueous NH₄Cl, warmed to 23 °C, and added to a mixture of diethyl ether (10 mL) and water (10 mL). The aqueous portion was extracted with diethyl ether (2 × 20 mL), and the combined organic fractions were dried (Na₂SO₄) and concentrated *in vacuo*. Flash chromatography (15 g of SiO₂; eluent, 6% EtOAc−1% triethylamine−hexanes; product, fractions 10−20; 10 mL/fraction) afforded **2** (12.5 mg, 0.043 mmol, 90% yield) as a clear oil: *R*ƒ starting material, 0.75; product, 0.27 (5:1 hexanes−EtOAc, anisaldehyde); $[\alpha]^{23}{}_D$ +19.7° (*c* = 1.0, CHCl₃); FTIR (film) 3402, 3360, 3082, 2971, 2928, 2860, 1637, 1441, 1374, 966, 908, 890 cm⁻¹; UV/vis λ_{max} = 240 nm, ε = 35,000; ¹H NMR (500 MHz, CDCl₃) δ 6.48 (dd, 1H, *J* = 10.8, 15.3), 5.87 (d, 1H, *J* = 10.8), 5.82 (dd, 1H, *J* = 11.1, 17.2), 5.76 (d, 1H, *J* = 15.3), 4.88−4.92 (m, 2H), 4.81 (t, 1H), *J* = 1.5), 4.58 (s, 1H), 2.01 (dd, 1H, *J* = 3.5, 12.6), 1.95−1.98 (m, 1H), 1.79 (s, 3H), 1.70 (s, 3H), 1.43−1.60 (m, 6H), 1.35 (s, 6H), 1.00 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 150.2, 147.6, 143.4, 139.3, 123.1, 122.3, 112.1, 109.9, 70.9, 52.8, 47.7, 39.9, 39.8, 32.7, 29.9, 26.6, 24.7, 16.7, 15.3; HRMS (EI, Pos) *m/z* calcd for [C₂₀H₃₂O]⁺ 288.2453, found 288.2440.

Butyl (Dibutylphosphono)-2-butenoate. A solution of butyl 4-bromo-2-butenoate¹⁸ (6.5 g, 29 mmol, 1.0 equiv) and tributyl phosphite (8.75 mL, 32 mmol, 1.1 equiv) was heated to reflux (approximately 160 °C). After 14 h, the crude reaction mixture was distilled under reduced pressure to produce (137−140 °C; 0.1 mmHg) a 5:1 *trans:cis* mixture of butyl (dibutylphosphono)-2-butenoate (5 g, 15 mmol, 50% yield) as a clear viscous oil: FTIR (film) 2961, 2875, 1722, 1654, 1466, 1321, 1260, 1194, 1027, 906 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.83−6.90 (m, 1H, *trans*), 6.23−6.30 (m, 1H, *cis*), 5.93−5.98 (m, 1H), 4.00−4.15 (m, 6H), 3.37−3.45 (m, 2H, *cis*), 2.74 (ddd, 2H, *J* = 1.3, 7.9, 22.9, *trans*), 1.60−1.67 (m, 6H), 1.35−1.43 (m, 6H), 0.91−0.95 (m, 9H); ³¹P NMR (121 MHz, CDCl₃, Ph₃P external standard at −6 ppm) δ 23.8 (m, minor), 22.7 (m, major); HRMS (EI, Pos) *m/z* calcd for [C₁₆H₃₁O₅P]⁺ 334.1909, found 334.1920.

JA942516M