JOURNAL OF NATURAL PRODUCTS

ARTICLE

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Absolute Configuration of 7-*epi*-Sesquithujene

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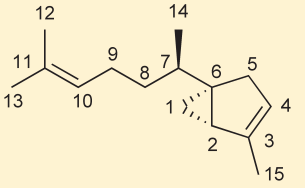
Supporting Information

ABSTRACT: 7-*epi*-Sesquithujene (**1**) is a bicyclic sesquiterpene isolated from phoebe oil, an essential oil of the Brazilian walnut tree, *Phoebe porosa*. It is also produced by stressed ash trees and has been shown to elicit strong electrophysiological responses on emerald ash borer, *Agrilus planipennis*, antennae. In the course of the development of a synthetic 7-*epi*-sesquithujene lure for field testing against the emerald ash borer, we found that the absolute configuration of this compound had not been determined. We isolated >95% pure 7-*epi*-sesquithujene from phoebe oil via successive fractionation and conventional and argentation (HPLC) chromatographies. The specific optical rotation of this compound matched that of a synthetic product of known configuration. We also synthesized two other stereoisomers of sesquithujene and developed a chiral GC method to separate all four. Based on the specific rotation, stereoselective syntheses, and chiral GC analyses, 7-*epi*-sesquithujene present in phoebe oil and white ash was found to have the 2*S*,6*S*,7*R* absolute configuration.



(+)-7-*epi*-Sesquithujene, **1**

7-*epi*-Sesquithujene (**1**) is a plant volatile first identified by Weyerstahl et al. as a minor component in phoebe oil, a steam distillate of the Brazilian tree *Phoebe porosa* Mez.[1] The bicyclo-[3.1.0] ring system of this compound was determined[1] on the basis of similarities of ^{1}H and ^{13}C NMR spectra with those of sesquithujene and thujene.[2] Because the absolute configuration of sesquithujene itself was not known, the new sesquiterpene hydrocarbon was named as an epimer of sesquithujene differing by the configuration of C-7.[1] Since its discovery, 7-*epi*-sesquithujene has been found in other plant material,[3] but only in trace amounts that apparently did not warrant its isolation and study for a possible biological function. Köllner et al. studied sesquiterpene hydrocarbon chemistry of distinct parts of maize (*Zea mays*) and found that the main constituent of volatiles collected from leaves and husks of B73 inbred line was 7-*epi*-sesquithujene, whereas the Delprim hybrid line released primarily sesquithujene.[4,5] The authors isolated closely related terpene synthase genes (*tsp4* and *tsp5*) from both varieties of maize and showed that the encoded enzymes, TSP4 and TSP5, formed mixtures of sesquiterpenes from the precursor farnesyl diphosphate resembling ones found in B73 and Delprim, respectively.[5] Another gene producing 7-*epi*-sesquithujene was α-zingiberene synthase gene (*ZIS*), overexpression of which in transgenic tomato increased levels of zingiberene and also produced 7-*epi*-sesquithujene, not detected in a control fruit.[6]

At the U.S. Department of Agriculture, our interest in 7-*epi*-sesquithujene arose in regard to the need to develop a semiochemically based attractant to monitor populations of the emerald ash borer, *Agrilus planipennis*. The emerald ash borer is an invasive beetle that has been causing extensive mortality of ash trees (*Fraxinus* spp.) since arriving in the United States in 2002.[7] Research found that girdled trap trees, currently used to monitor populations of the emerald ash borer in low infestation areas, released elevated amounts of bark sesquiterpene hydrocarbons as compared to ungirdled trees.[8] Some of these hydrocarbons were antennally active for both male and female emerald ash borers in GC-EAD studies, with **1** eliciting one of the most persistent responses.[8,9] Consequently, phoebe oil, containing **1** and other EAD-active sesquiterpenes, has been shown to attract the emerald ash borer.[8] We were therefore interested in both synthesizing 7-*epi*-sesquithujene for field trapping of the emerald ash borer and determining its absolute configuration. During the course of our research, a publication occurred in the literature on the enantioselective synthesis of both 7-*epi*-sesquithujene and sesquithujene starting from (*R*)-citronellal.[10] Although this paper revealed relative configurations of both diastereomers, the absolute configurations were left unanswered.

RESULTS AND DISCUSSION

Our research started with an attempt to isolate **1** from phoebe oil in sufficient purity to measure specific rotation. Weyerstahl et al. isolated **1** of 65% purity[1] and did not report optical rotation. We conducted a fractional vacuum distillation of phoebe oil containing 1.5% of **1** and collected a fraction enriched (8.1%) in the desired product. This fraction was further purified by conventional column chromatography (CC), followed by Ag-NO_3—SiO_2 HPLC purification. As a result, 7-*epi*-sesquithujene was isolated in >95% purity and showed the specific rotation

Received: January 31, 2011
Published: May 16, 2011

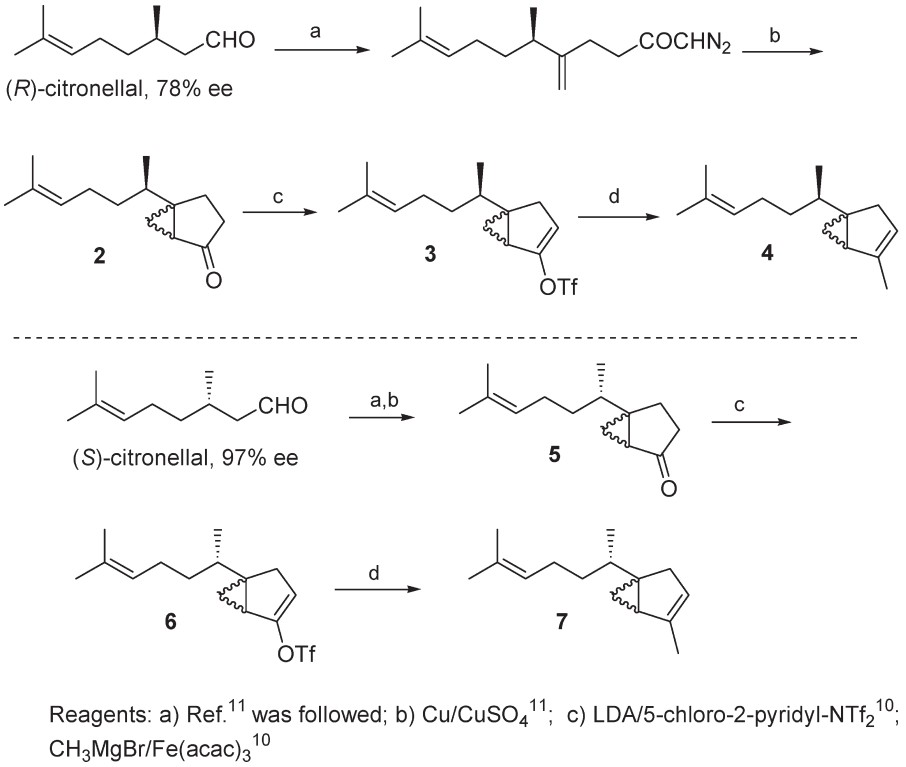
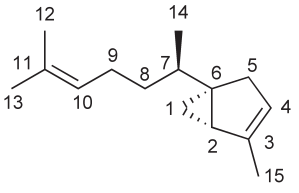


Figure 1. Syntheses of diastereomeric mixtures **4** and **7** from (*R*)- and (*S*)-citronellals. Reagents: (a) ref 11 was followed; (b) $Cu/CuSO_4$;[11] (c) LDA/5-chloro-2-pyridyl-NTf_2;[10] (d) $CH_3MgBr/Fe(acac)_3$.[10]

$[\alpha]_D$ +31.2 (*c* 0.08, CH_2Cl_2). The specific rotation of a synthetic product of 2*S*,6*S*,7*R* configuration was +30.2 (*c* 0.7, CH_2Cl_2),[10] thus confirming that 7-*epi*-sesquithujene isolated from phoebe oil has the same absolute configuration.



(+)-7-*epi*-Sesquithujene, **1**

Next, we isolated 7-*epi*-sesquithujene from white ash (*F. americana*) by collecting volatiles onto a HayeSep-Q cartridge, extracting them with CH_2Cl_2, and purifying by conventional CC followed by $AgNO_3-SiO_2$ HPLC. Although GC-MS analysis clearly indicated the presence of 7-*epi*-sesquithujene in the mixture, neither the quantity nor purity of it was enough to reliably measure specific rotation. To determine the absolute configuration of this compound, we sought a chiral GC method that required a sample of a racemic, or (−)-7-*epi*-sesquithujene.

In the recently published paper,[10] (+)-7-*epi*-sesquithujene and (−)-sesquithujene were synthesized using a gold-catalyzed cycloisomerization of chiral enynols mediated by chiral bisoxazoline ligands. Starting enynols were prepared by an asymmetric addition of allylzinc reagents to alkynyl aldehydes.[10] This method seemed suitable for preparation of (−)-7-*epi*-sesquithujene as well, but we sought a simpler approach that did not rely on expensive catalysts and/or chiral ligands. Moreover, we envisioned that a relatively large quantity of (+)-7-*epi*-sesquithujene would be needed for field testing against the emerald ash borer. Our synthesis relied on the availability of both enantiomers of citronellal and the recently published conversion of (*R*)-citronellal to bicyclic ketone **2**[11] (Figure 1). Even though the intramolecular cyclizations of the intermediate diazoketones were not stereoselective and individual diastereomers of **2** and **5** were difficult to separate,[11] the route deserves credibility because of its simplicity and good overall yield. We first attempted methylation of **2** via *in situ* formation of a triflate followed by a displacement with MeMgBr as described in the literature.[10] However, yields were not reproducible, and both steps needed further optimization. We found that the enolization time of ketones **2** and **5** was essential to maximize the yields of the triflates. Thus, stirring **5** with LDA at −70 °C for 3 h before addition of *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide) resulted in a 59% yield of **6**, while increasing the enolization period of **2** to 5 h improved the yield of **3** to 80%. We also found that during catalytic alkylation of triflates (Figure 1), the usage of 10% $Fe(acac)_3$[10] provided a 61% yield of **7** from **6**, whereas employing 15% catalyst significantly improved the yield of **4** from **3** to 84%. The diastereomeric mixture **4** that contains (+)-7-*epi*-sesquithujene is presently being tested for attractiveness to the emerald ash borer, while **7** was further exploited to make individual diastereomers including (−)-7-*epi*-sesquithujene.

Mori et al.[12] developed a method to deliver individual ketones from a diastereomeric mixture of **2** via a three-step process: stereoselective reduction to corresponding alcohols, asymmetric enzymatic acetylation followed by the separation of diastereomeric alcohols, and oxidation of these alcohols to individual ketones. We intended to apply the same procedure to obtain single diastereomers from **5**, but the L-Selectride reduction of **5**

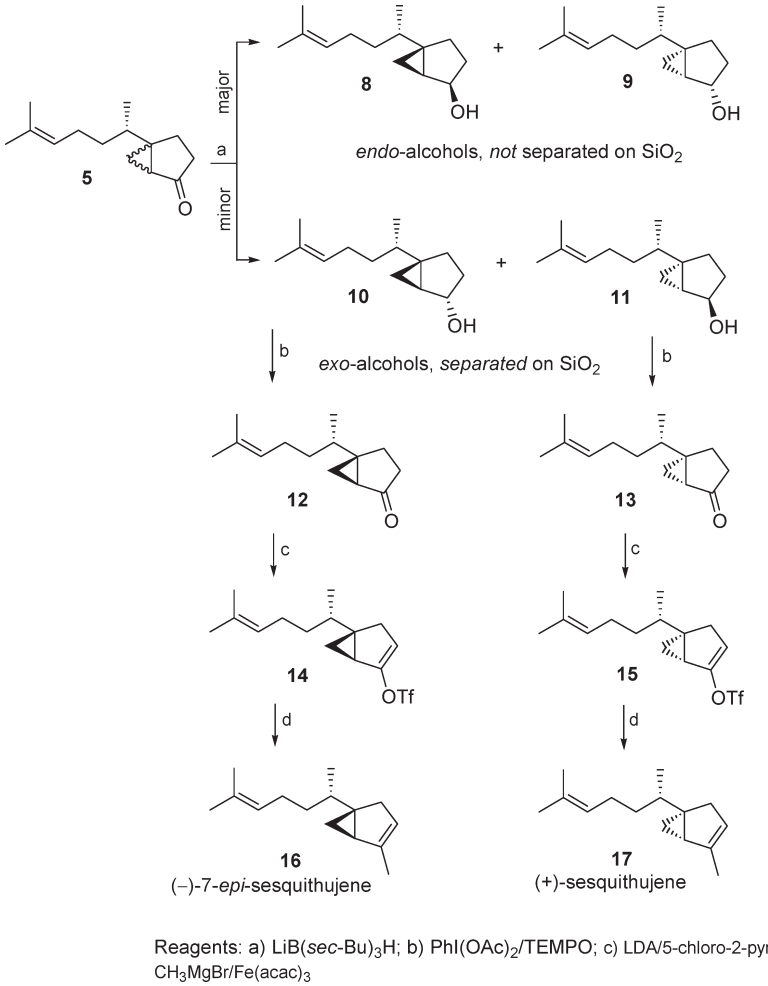


Figure 2. Synthesis of (−)-7-*epi*-sesquithujene and (+)-sesquithujene. Reagents: (a) LiB(*sec*-Bu)$_3$H; (b) PhI(OAc)$_2$/TEMPO; (c) LDA/5-chloro-2-pyridyl-NTf$_2$; (d) $CH_3MgBr/Fe(acac)_3$.

was not entirely stereoselective. While Mori et al. reported[12] an almost complete stereocontrol in the L-Selectride reduction of **2** leading to a pair of *endo* alcohols (not separated by conventional chromatography on SiO_2), TLC of the crude reduction products from ketone **5** showed three spots. According to the GC-MS analysis, the most polar (and abundant) fraction was approximately a 1:1 mixture of two compounds that had almost identical mass spectra, corresponding to reduced alcohols (Figure 2). The resonance of the H-3 protons in the ^{1}H NMR spectrum of that mixture was observed at δ 4.52, which exactly matched the resonance of H-3 protons of *endo* alcohols originated from **2**.[12] Thus, the most polar fraction contained two expected *endo* alcohols, **8** and **9**. Analyses of the two minor fractions by GC-MS revealed predominantly (>95%) one isomeric alcohol in each. Mass spectra of these alcohols were similar to each other and those of **8** and **9**. By default, *exo* relative configurations for these alcohols were presumed (Figure 2). This assumption was supported by comparison of H-2, H-3 spin−spin interactions found from the ^{1}H NMR spectra with $^3J_{H\text{-}2,H\text{-}3}$ coupling constants estimated from computed $\Phi_{H\text{-}2,H\text{-}3}$ dihedral angles.[13] The relative and absolute configurations of alcohols **10** and **11** were confirmed by oxidizing them to ketones, which fortuitously turned out to be intermediates that were needed. The first (least polar) minor fraction, upon oxidation with PhI(OAc)$_2$/TEMPO,[14] furnished ketone **12** of 2*S*,6*R*,7*S* configuration, which matched a known 2*R*,6*S*,7*R* isomer by ^{1}H and ^{13}C NMR parameters.[10] Hence, we assigned this alcohol a 2*S*,3*S*,6*R*,7*S* absolute configuration as shown in structure **10**. Analogously, the more polar minor alcohol **11** was assigned a 2*R*,3*R*,6*S*,7*S* absolute configuration based on the oxidation to ketone **13**, the NMR data of which matched those of its enantiomer.[10] Thus, the L-Selectride reduction of the diastereomeric mixture **5**, being nonstereoselective and providing easily separable *exo*-alcohols **10** and **11**, unexpectedly offered an expedient way of producing individual ketones **12** and **13** and allowed skipping the enzymatic acetylation step. Ketones **12** and **13** were converted to corresponding triflates **14** and **15**, then were further methylated (Figure 2) as described for the diastereomeric mixtures. The sesquiterpene produced from **14** matched (+)-7-*epi*-sesquithujene by the GC retention time, mass spectrum, and ^{1}H and ^{13}C NMR spectra but was levorotatory and, hence, was (−)-7-*epi*-sesquithujene (**16**). Similarly, triflate **15** was converted to (+)-(2*S*,6*S*,7*S*)-sesquithujene (**17**), NMR parameters of which matched those of the 2*R*,6*R*,7*R* enantiomer.[10]

After examining a variety of chiral columns we selected HYDRODEX β-6TBDM for the development of a chiral GC method to determine the absolute configuration of 7-*epi*-sesquithujene present in white ash. Figure 3 shows GC analyses of several samples conducted in isothermal mode at 85 °C. GC

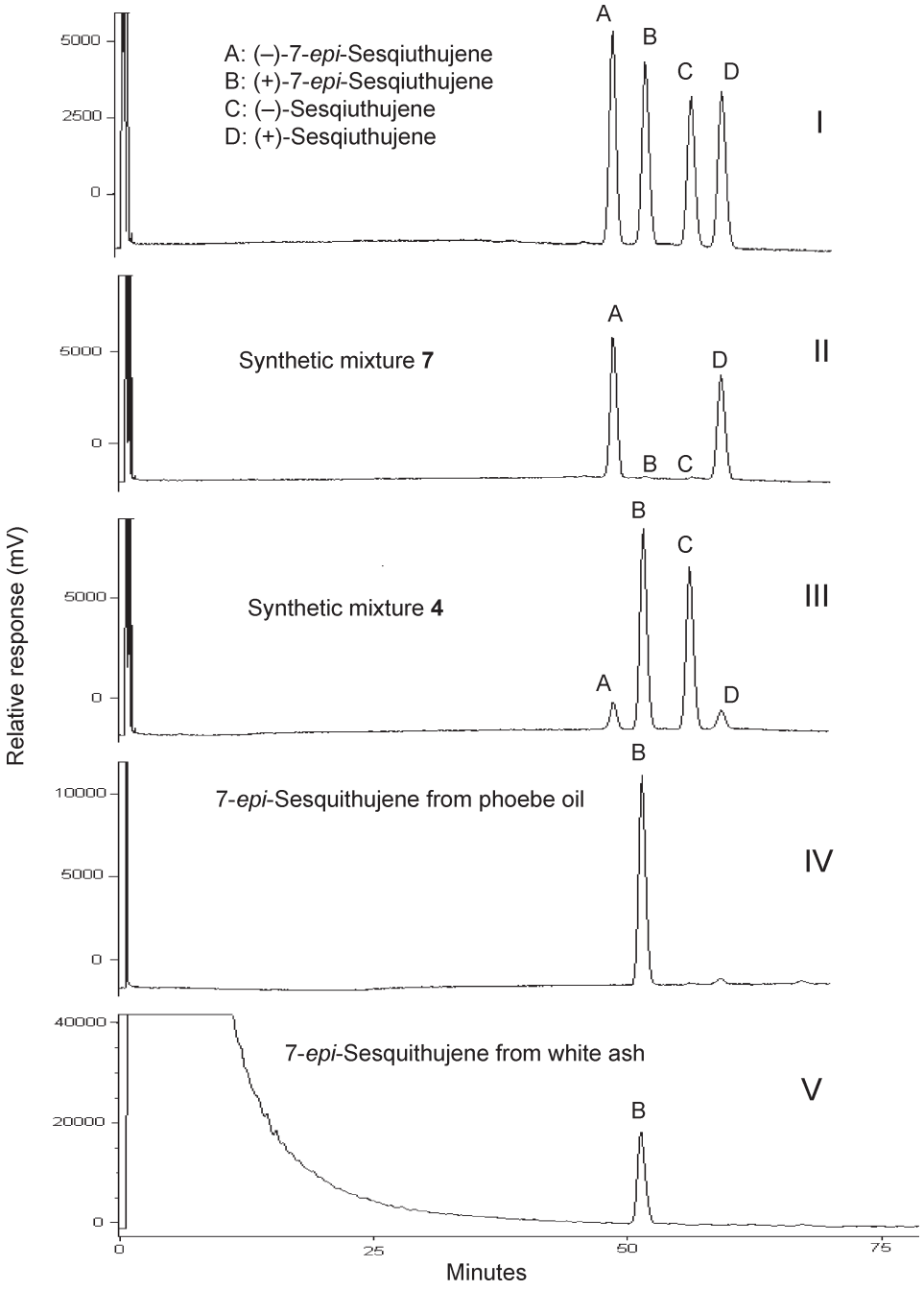


Figure 3. GC-FID analyses on HYDRODEX β-6TBDM. Conditions: 85 °C isothermal; carrier gas H_2 at 1.5 mL/min. Graph I: mixture of **4** and **7**; (A) **16**, or (−)-7-*epi*-sesquithujene; (B) **1**, or (+)-7-*epi*-sesquithujene; (C) (−)-sesquithujene; (D) **17**, or (+)-sesquithujene. Kovats indices: (A) 1357.5, (B) 1366.1, (C) 1377.5, (D) 1384.4. Graph II: synthetic mixture **7** produced from (*S*)-citronellal. Graph III: synthetic mixture **4** produced from (*R*)-citronellal. Graph IV: (+)-7-*epi*-sesquithujene isolated from phoebe oil. Graph V: (+)-7-*epi*-sesquithujene isolated from white ash.

analysis of a mixture of **4** and **7** derived from (*R*)- and (*S*)-citronellal (graph I) showed a baseline separation of all four stereoisomers. Analyses of individual **16** and **17** (not shown) and (+)-7-*epi*-sesquithujene (**1**) isolated from the phoebe oil (graph IV) provided assignments for peaks A, D, and B. Because the (*R*)-citronellal that we used to synthesize (+)-7-*epi*-sesquithujene was not optically pure, all four stereoisomers (graph III) were present in the mixture **4**, and the content of (+)-7-*epi*-sesquithujene in **4** was 48%. Lastly, analysis of 7-*epi*-sesquithujene isolated from white ash airborne extract (graph V) confirmed that it has the same 2*S*,6*S*,7*R* absolute configuration as (+)-7-*epi*-sesquithujene isolated from phoebe oil and that (−)-7-*epi*-sesquithujene is not present in either samples. We calculated Kovats indices of all stereoisomers of sesquithujene (Figure 3) on HYDRODEX β-6TBDM, which may become helpful in the identification of these compounds from other sources.

In summary, this paper unveils the absolute configuration of natural 7-*epi*-sesquithujene, which has previously been drawn incorrectly.[5,15] Future work will show whether this material is attractive to the emerald ash borer in field trials.

EXPERIMENTAL SECTION

General Experimental Procedures. Routine GC analyses were performed on a Shimadzu 17A (Shimadzu Scientific Instruments, Inc., Columbia, MD) gas chromatograph equipped with a flame ionization detector, an AOC-20s autosampler, an AOC-20i autoinjector, and a HP-5 capillary column (30 m × 0.25 mm × 0.25 μm film). Hydrogen was used as carrier gas at 1 mL/min. Column temperature was maintained at 80 °C for 5 min and then raised to 280 °C at 10 °C/min. Chiral GC analyses were performed on 25 m × 0.25 mm HYDRODEX β-6TBDM (heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin, Macherey-Nagel GmbH & Co. KG, Düren, Germany) in isothermal mode at 85 °C. Hydrogen was used as carrier gas at 1.5 mL/min. Tridecane and tetradecane were used to calculate Kovats indices.[16] Electron-ionization (EI) mass spectra were obtained at 70 eV with an Agilent Technologies 5973 mass selective detector interfaced with a 6890 N GC system equipped with a 30 m × 0.25 mm i.d. × 0.25 μm film HP-5MS column. Column temperature was maintained at 50 °C for 2 min and then raised to 270 °C at 10 °C/min. Helium was used as a carrier gas at 1 mL/min. HREIMS analyses were performed on a Micromass Autospec (Waters Corporation, Milford, MA), and HRESIMS analyses on a Waters Q-Tof Premier instrument. TLC analyses were conducted on Whatman AL SIL G/UV plates using a 20% ethanol solution of phosphomolybdic acid and/or UV for visualization of spots. Flash chromatography was carried out with 230−400 mesh silica gel (Fisher Scientific, Fair Lawn, NJ). High-performance liquid chromatography (HPLC) was carried out using a Waters 515 pump, a Waters R401 refractive index detector, and a 25 cm by 0.46 cm i.d. silica column (Adsorbosphere Silica 5 μm, Alltech, Deerfield, IL), treated with silver nitrate.[17] ^{1}H NMR spectra were obtained at 600 MHz and ^{13}C spectra at 151 MHz on a Bruker AVIII-600 MHz spectrometer. Chemical shifts are reported in δ units and referenced to the residual $CDCl_3$ solvent signal; coupling constants are reported in Hz. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter with a 1.0 mL cell.

All reagents and solvents were purchased from Aldrich Chemical Co. unless otherwise specified. CH_2Cl_2 was distilled from calcium hydride, and tetrahydrofuran (THF) was dried by distillation from sodium benzophenone-ketyl. Phoebe oil was purchased from Aripe Citrus Agro Industrial LTDA, Montenegro, Brazil. (*S*)-(−)-Citronellal (97% ee) was purchased from Sigma-Aldrich (Milwaukee, WI), and (*R*)-(−)-citronellal (78% ee) from TCI America (Portland, OR). Reactions were conducted in oven-dried flasks under a N_2 atmosphere.

Isolation of 7-*epi*-Sesquithujene (1) from Phoebe Oil. Crude phoebe oil (1 L) containing 1.5% **1** (GC on HB-5) was distilled under vacuum (0.075−0.10 mmHg) from a 2 L round-bottom flask equipped with a silvered bellows vacuum-jacketed column (Aldrich, *L* 280 mm, joint 24/40) packed with glass helices (*D* 4.8 mm) and a variable-reflux distillation head (Kimble Chase/Kontes, Vineland, NJ). The reflux/takeoff ratio during distillation was 5:1. The fraction boiling at 58−63 °C/0.1 mmHg (105 g) and containing 8.1% **1** was collected. This fraction (1.18 g) was further purified by CC (70 mL dry silica gel containing 25% silver nitrate). The column was eluted with hexane and 2%, 4%, and 8% ether in hexane. 7-*epi*-Sesquithujene (300 mg, 23% purity) was recovered in the 4% ether in hexane fraction. Final purification of **1** to >95% purity (by GC-MS) was conducted by repeated $AgNO_3$−SiO_2 HPLC. Solvent was 1% 1-hexene in hexane: $[\alpha]^{25}_D$ +31.2 (*c* 0.08, CH_2Cl_2), [lit.[10] $[\alpha]_D^{20}$ +30.2 (*c* 0.7, CH_2Cl_2)]; GC-EIMS *m*/*z* 204 $[M]^+$ (1), 189 (1), 161 (6), 119 (100), 105 (21), 93 (88), 91 (41), 77 (27), 69 (28), 55 (12), 41 (23); ^{1}H NMR, δ 0.02 (1H, t, *J* = 3.6, *endo*-H-1), 0.69 (1H, dd, *J* = 7.5, 3.5, *exo*-H-1), 0.94 (3H, d, *J* = 6.8, H-14), 1.19 (1H, sextet, *J* = 7.1, H-7), 1.30 (1H, m, H-8a), 1.41 (1H, m, H-2), 1.48 (1H, m, H-8b), 1.60 (3H, br s, H-12), 1.69 (3H, br s, H-13), 1.77 (3H, ddd, *J* = 1.9, H-15), 1.98 (2H, m, H-9), 2.15 (1H, dm, *J* = 17.2, H-5a), 2.37 (1H, dm, *J* = 17.2, H-5b), 4.96 (1H, m, H-4), 5.12 (1H, tm, *J* = 7.0, H-10); ^{13}C NMR, δ 16.6, 17.8, 18.4, 21.7, 25.9, 26.3, 32.7, 33.4, 35.4, 36.3, 38.2, 121.1, 125.4, 131.2, 145.2. ^{1}H and ^{13}C NMR data are in good agreement with those reported in the literature.[1,10]

Isolation of 1 from White Ash. Volatiles were collected from freshly cut white ash (*Fraxinus americana*) logs (30 cm × 10 cm i.d.). Logs were placed in 60 cm × 15 cm i.d. glass chambers (Ace Glass Inc.). The chambers were capped with threaded polytetrafluoroethylene adapters at each end and each holding a HayeSep-Q filter (Restek Corporation). Air was drawn through the chambers at 1 L/min by vacuum connected to the outlet filter. The inlet filter served to clean incoming air, while the volatiles emitted within the chambers were trapped on the outlet filters. Volatiles were recovered by rinsing filters with CH_2Cl_2 (500 μL) at intervals of 2−4 days. The emitted 7-*epi*-sesquithujene was purified by open column chromatography followed by HPLC as described for the purification of 7-*epi*-sesquithujene from phoebe oil.

Preparation of Ketones 2 and 5. (*R*)-Citronellal (20.0 g) was converted in several steps[11] to (6*R*)-1-diazo-6,10-dimethyl-5-methylene-9-undecen-2-one (10.2 g, crude). The latter was refluxed with copper powder (2.425 g) and anhydrous $CuSO_4$ (0.57 g) in cyclohexane (290 mL) for 2 h as described.[11] The mixture was filtered, concentrated, and flash chromatographed with hexane/ethyl acetate, 5:1, to give **2** (6.42 g) as a 53:47 mixture (GC-MS) of two diastereomers that showed almost identical mass spectral data, matching those reported.[11] ^{1}H and ^{13}C NMR spectra of this product were in good agreement with the literature.[11] Analogously, (*S*)-citronellal (5.0 g) was converted to ketone **5** (2.23 g), represented by two diastereomers in the same 53:47 ratio as in **2**. Mass spectra and NMR data of **5** were identical with those of **2**. Individual diastereomers of **5** are described later in this section.

Preparation of Triflate 6. Butyllithium (1.5 mmol; 1.25 mL of 1.2 M in hexane) was added to a solution of diisopropylamine (220 μL, 1.56 mmol) in dry THF (7 mL) at −5 °C, and the mixture was stirred for 20 min at that temperature. The resulting lithium diisopropylamide solution was cooled to −70 °C before the addition of ketone **5** (206 mg, 1 mmol) in THF (5 mL). The mixture was stirred at −70 °C for 3 h, and a solution of *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide) (589 mg, 1.5 mmol) in THF (2 mL) was added. The stirring was continued at that temperature for 2 h; then the reaction mixture was kept in a freezer at −20 °C overnight. TLC analysis (hexane/ethyl acetate, 5:1) showed that starting ketone was not entirely consumed. The reaction mixture was concentrated on a rotary evaporator, and the remainder was flash-chromatographed with hexane/ethyl acetate, 99:1. Triflate **6** (200 mg, 59%) was isolated as a 52:48 mixture of two diastereomers that were baseline separated on a HP-5 column and displayed almost identical mass spectra. GC-EIMS: *m*/*z* 295 (2), 253 (41), 121 (8), 109 (16), 77 (17), 69 (100), 55 (27), 41 (34). ^{1}H and ^{13}C NMR spectra of individual diastereomers of **6** are presented later in this section.

Preparation of Triflate 3. Ketone **2** (3.41 g, 16.55 mmol) was allowed to react with LDA prepared from diisopropylamine (3.63 mL, 25.66 mmol) and BuLi (24.84 mmol; 20.7 mL of 1.2 M in hexane) in THF (80 mL) at −70 °C for 5 h. *N*-(5-Chloro-2-pyridyl)bis-(trifluoromethanesulfonimide) (9.75 g, 24.83 mmol) in THF (10 mL) was added to this solution. Then the mixture was stirred at −70 °C for 1 h and kept overnight at −20 °C. After evaporation of THF, the oily residue was thoroughly extracted with hexane/ethyl acetate, 99.5:0.5, and combined extracts were filtered through SiO_2 to provide triflate **3** (4.50 g, 80%) as a 52:48 mixture of diastereomers. Mass spectral data of **3** matched those of triflate **6**.

Methylation of Triflate 3. To a mechanically stirred solution of **3** (4.50 g, 13.31 mmol) in dry THF (100 mL) at −30 °C was added *N*-methyl-2-pyrrolidone (14.6 mL), followed by a solution of iron(III) acetylacetonate (705 mg, 2.0 mmol, 15% of **3**) in THF (30 mL). The mixture was stirred at this temperature for 15 min, and methylmagnesium

bromide (20.1 mmol; 6.7 mL of 3 M in ether) was added dropwise, maintaining the temperature from −27 to −30 °C. At the end of the addition a sticky precipitate was formed, and stirring was continued at −30 °C for 1 h. The reaction mixture was poured into an ice-cold saturated ammonium chloride solution, acidified with 1 M HCl to pH 6, and extracted with hexane. Combined hexane extracts were washed four times with water, dried, and evaporated, and the residue was chromatographed with hexane, then hexane/ethyl acetate, 5:1. Hydrocarbon **4** (2.27 g, 84%) was isolated as a 53:47 mixture of two diastereoisomers baseline separated on a HP-5MS column. The first eluted peak matched 7-*epi*-sesquithujene isolated from phoebe oil by the mass spectrum and the retention time. GC analysis on a HYDRODEX *β*-6TBDM column showed that **4** consisted of 48% **1**, 6% (−)-7-*epi*-sesquithujene (**16**), 41% (−)-sesquithujene, and 5% (+)-sesquithujene (**17**). Unreacted **3** (560 mg, 12%) was also isolated from the second fraction.

Methylation of Triflate 6. A solution of triflate **6** (433 mg, 1.28 mmol), *N*-methyl-2-pyrrolidone (1.4 mL), and iron(III) acetylacetonate (45 mg, 0.13 mmol, 10% of **6**) in dry THF (30 mL) was treated at −30 °C with methylmagnesium bromide (1.54 mmol; 512 *μ*L of 3 M in ether). After the workup described above and flash chromatography with 1% ethyl acetate in hexane, **7** (60 mg, 61%) was isolated as a mixture of **16** (51%), **1** (1%), (−)-sesquithujene (1%), and **17** (46%). Unreacted **6** (108 mg, 25%) was also recovered.

L-Selectride Reduction of Ketone 5. A procedure by Mori et al[12] was followed. L-Selectride (LiB(*sec*-Bu)$_3$H, 4.18 mmol; 4.18 mL of 1.0 M in THF) was added to a solution of ketone **5** (840 mg, 4.08 mmol) in dry THF (20 mL) at −65 °C. The mixture was slowly warmed to −20 °C within 3 h, upon which the reduction was completed as judged by TLC analysis. A 3 M solution of NaOH (12.2 mL) was added at −20 °C followed by hydrogen peroxide (460 *μ*L of 50% solution), which caused the reaction temperature to rise to 0 °C. The mixture was stirred at that temperature for 2 h, then diluted with H_2O (∼10 mL) and extracted three times with hexane/ether, 1:1. The combined organic extracts were washed with an ammonium chloride solution and brine and then dried. Flash chromatography gave three fractions:

No. 1: Alcohol **10** of 2*S*,3*S*,6*R*,7*S* configuration (89 mg, 97%-pure): R_f = 0.34, hexane/ethyl acetate, 3:1; $[\alpha]^{25}_D$ −9.53 (*c* 1.50, CH_2Cl_2); GC-EIMS *m*/*z* 190 (9), 175 (5), 147 (17), 123 (52), 109 (33), 107 (26), 105 (53), 93 (37), 82 (100), 79 (56), 69 (82), 67 (41), 55 (43), 41 (57); ^{1}H NMR, *δ* 0.21 (1H, dd, *J* = 4.9, 3.6, *endo*-H-1), 0.34 (1H, br dd, *J* = 8.4, 5.1, *exo*-H-1), 0.95 (3H, d, *J* = 6.6), 1.16 (1H, br dd, *J* = 8.4, 3.6, H-2), 1.21 (1H, m), 1.29−1.37 (2H, m), 1.37−1.44 (1H, m), 1.47−1.53 (1H, m), 1.53−1.60 (2H, m), 1.61 (3H, br s), 1.69 (3H, br s), 1.82 (1H m), 2.03 (2H, m), 4.19 (1H, br d, *J* = 4.8, H-3), 5.11 (1H, br t, *J* = 7.2); ^{13}C NMR, *δ* 13.1, 17.9, 18.3, 24.9, 25.9, 26.4, 30.9, 31.6, 34.1, 35.06, 37.4, 75.2, 125.2, 131.4; HREIMS *m*/*z* 208.1825 (calcd for $C_{14}H_{24}O$, 208.1827).

No. 2: Alcohol **11** of 2*R*,3*R*,6*S*,7*S* configuration (67 mg, 97% pure): R_f = 0.28, hexane/ethyl acetate, 3:1; $[\alpha]^{25}_D$ +0.30 (*c* 3.35, CH_2Cl_2); GC-EIMS *m*/*z* 208, $[M]^+$ (2), 190 (9), 175 (7), 147 (20), 123 (71), 109 (40), 107 (23), 105 (59), 93 (42), 82 (96), 79 (63), 69 (100), 67 (46), 55 (50), 41 (65); ^{1}H NMR, *δ* 0.30 (1H, dd, *J* = 4.8, 3.6, *endo*-H-1), 0.41 (1H, br dd, *J* = 8.4, 4.8, *exo*-H-1), 1.00 (3H, d, *J* = 6.6), 1.06 (1H, br dd, *J* = 8.4, 3.0, H-2), 1.16 (1H, sextet, *J* = 7.2), 1.28 (2H, m), 1.37−1.47 (2H, m), 1.50 (1H, m), 1.57 (1H, m), 1.61 (3H, br s), 1.69 (3H, br s), 1.84 (1H, m), 2.03 (2H, q, *J* = 7.8), 4.18 (1H, br m, H-3), 5.10 (1H, br t, *J* = 7.2); ^{13}C NMR, *δ* 15.1, 17.89, 17.92, 23.9, 25.9, 26.5, 30.0, 31.6, 33.7, 35.9, 37.5, 75.1, 125.2, 131.4; HREIMS *m*/*z* 208.1836 (calcd for $C_{14}H_{24}O$, 208.1827).

No. 3: A mixture of *endo* alcohols **8** and **9** (530 mg, ratio ∼1:1): R_f = 0.20, hexane/ethyl acetate, 3:1. Both diastereomers had similar mass spectra. GC-EIMS *m*/*z* 208 $[M]^+$ (2) 190 (10), 175 (6), 165 (6), 147 (21), 123 (70), 109 (38), 107 (23), 105 (71), 93 (40), 82 (74), 79 (65), 69 (100), 67 (45), 55 (52), 41 (40); ^{1}H NMR, *δ* 0.26 (0.5H, dd, *J* = 7.2, 4.8), 0.36 (0.5H, dd, *J* = 7.2, 4.8), 0.70 (0.5H, br dd, *J* = 4.2), 0.79 (0.5H, br dd, *J* = 4.2), 0.90 (1.5H, d, *J* = 6.6), 0.93 (1.5H, d, *J* = 6.6), 1.10 (2H, m), 1.18−1.33 (2H, m), 1.37−1.47 (2H, m), 1.58−1.68 (2H, m), 1.61 (3H, br s), 1.69 (3H, br s), 1.89−2.03 (3H, m), 4.52 (1H, br m, H-3), 5.10 (1H, tm, *J* = 7.2); ^{13}C NMR, *δ* 9.57, 11.58, 17.71, 17.81, 17.88, 25.03, 25.49, 25.91, 26.33, 26.41, 28.05, 29.40, 30.01, 30.15, 33.23, 33.28, 34.83, 35.00, 37.89, 37.97, 74.66, 74.76, 125.05, 125.10, 131.41, 131.47. Some of these peaks corresponded to composite signals from carbons in both diastereomers. HREIMS *m*/*z* 208.1825 (calcd for $C_{14}H_{24}O$, 208.1827).

Ketone 12. (Diacetoxyiodo)benzene (215 mg, 0.67 mmol) was added to a stirred solution of alcohol **10** (126 mg, 0.61 mmol) and 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO, 9.4 mg, 0.06 mmol) in a mixture of pentane (0.4 mL) and CH_2Cl_2 (0.6 mL).[14] The mixture was stirred at 25 °C for 1 h, diluted with CH_2Cl_2 (5 mL), and washed with a saturated $Na_2S_2O_3$ solution (2 mL). Then the aqueous layer was extracted with CH_2Cl_2 (4 × 1 mL). The combined organic extracts were washed with a saturated $NaHCO_3$ solution to pH 8, then with brine, and dried. After evaporation of the solvent and flash chromatography with CH_2Cl_2, ketone **12** was isolated (101 mg, 80%). Compound **12** was 95% pure by GC-MS and contained 4% of **13**: $[\alpha]^{25}_D$ −20.8 (*c* 3.35, CH_2Cl_2) [lit.[10] for (2*R*,6*S*,7*R*)-**12** $[\alpha]^{20}_D$ +16.2 (*c* 1.62, CH_2Cl_2)]; GC-EIMS *m*/*z* 206 $[M]^+$ (14), 191 (8), 188 (5), 163 (25), 149 (21), 136 (25), 123 (91), 121 (53), 109 (36), 95 (40), 93 (44), 82 (56), 79 (50), 69 (100), 67 (65), 55 (78), 41 (82); ^{1}H NMR, *δ* 0.98 (3H, d, *J* = 6.5), 1.08 (1H, dd, *J* = 4.6, 3.1, *endo*-H-1), 1.13 (1H, br dd, *J* = 9.1, 4.6, *exo*-H-1), 1.33 (2H, m), 1.50 (1H, m), 1.60 (3H, br s), 1.67 (1H, dd, *J* = 9.1, 3.1, H-2), 1.69 (3H, br s), 1.90−2.17 (6H, m), 5.06 (1H, tm, *J* = 7.0); ^{13}C NMR, *δ* 17.0, 17.8, 19.3, 23.4, 25.7, 25.8, 33.1, 34.3, 34.5, 37.2, 38.8, 124.2, 131.7, 214.7. ^{1}H and ^{13}C NMR data were in good agreement with those reported in the literature for (2*R*,6*S*,7*R*)-**12**.[10]

Ketone 13. Alcohol **11** (67 mg, 0.32 mmol) was oxidized with $PhI(OAc)_2$ (114 mg, 0.35 mmol) in the presence of TEMPO (2.5 mg, 0.02 mmol) in a pentane/CH_2Cl_2 solution (0.2 mL + 0.3 mL) to give ketone **13** of 2*R*,6*S*,7*S* configuration (55 mg, 83%, 98% pure): $[\alpha]^{25}_D$ +28.0 (*c* 2.75, CH_2Cl_2) [lit.[10] for (2*S*,6*R*,7*R*)-**13** $[\alpha]^{20}_D$ −27.2 (*c* 1.36, CH_2Cl_2)]; GC-EIMS *m*/*z* 206 $[M]^+$ (12), 191 (6), 188 (4), 163 (25), 149 (17), 136 (21), 123 (71), 121 (42), 109 (32), 95 (35), 93 (41), 82 (52), 79 (46), 69 (100), 67 (60), 55 (77), 41 (80); ^{1}H NMR, *δ* 0.99 (3H, d, *J* = 6.6), 1.16 (1H, dd, *J* = 4.2, 3.6, *endo*-H-1), 1.19 (1H, br dd, *J* = 9.0, 4.2, *exo*-H-1), 1.28 (1H, m), 1.32 (1H, m), 1.45 (1H, m), 1.59 (1H, m), 1.62 (3H, br s), 1.70 (3H, br s), 1.90 (1H, dd, *J* = 11.4, 8.9), 1.98−2.19 (5H, m), 5.09 (1H, tm, *J* = 7.2); ^{13}C NMR, *δ* 17.5, 17.7, 21.4, 22.5, 25.7, 26.0, 33.2, 33.4, 34.2, 37.4, 38.9, 124.3, 131.7, 214.9. ^{1}H and ^{13}C NMR data were in good agreement with those reported in the literature for (2*S*,6*R*,7*R*)-**13**.[10]

Triflate 14. Analogously to diastereomeric mixture **2**, ketone **12** (98 mg, 0.48 mmol) in 2 mL of THF was allowed to react with LDA, formed from diisopropylamine (112 *μ*L, 0.79 mmol) and butyllithium (0.77 mmol; 425 *μ*L of 1.8 M in hexane). *N*-(5-Chloro-2-pyridyl)bis-(trifluoromethanesulfonimide) (300 mg, 0.76 mmol) dissolved in 1 mL of THF was added. After the workup described, triflate **14** (91 mg, 56%) was isolated. ^{1}H NMR, *δ* 0.49 (1H, dd, *J* = 4.4, 3.0, *endo*-H-1), 0.92 (1H, dd, *J* = 7.2, 4.8, *exo*-H-1), 0.96 (3H, d, *J* = 7.2), 1.23 (1H, sextet, *J* = 7.2), 1.32 (1H, m), 1.47 (1H, m), 1.60 (3H, br s), 1.69 (3H, br s), 1.75 (1H, m), 1.99 (2H, m), 2.29 (1H, dt, *J* = 17.4, 3.0), 2.46 (1H, dd, *J* = 17.4, 2.4), 5.08 (1H, tm, *J* = 6.6), 5.27 (1H, m); ^{13}C NMR, *δ* 17.5, 17.6, 21.1, 25.7, 25.9, 26.2, 31.4, 32.1, 34.7, 37.6, 113.5, 124.4, 131.7, 152.6. One of these signals corresponded to two carbons. HRESIMS *m*/*z* 339.1246 (calcd for $[M + H]^+$ $C_{15}H_{22}F_3O_3S$, 339.1242).

Triflate 15. Ketone **13** was enolized analogously to the above procedure using LDA formed from diisopropylamine (75 *μ*L, 0.53 mmol) and butyllithium (0.41 mmol; 225 *μ*L of 1.8 M in hexane), and then the enolate formed reacted with *N*-(5-chloro-2-pyridyl)-bis(trifluoromethanesulfonimide) (158 mg, 0.40 mmol) in THF

(3 mL) to give triflate **15** (54 mg, 63%): ^{1}H NMR, δ 0.57 (1H, br dd, J = 3.6, *endo*-H-1), 0.97 (3H, d, J = 6.6), 1.00 (1H, dd, J = 7.2, 4.2, *exo*-H-1), 1.18 (1H, sextet, J = 7.2), 1.28 (1H, m), 1.43 (1H, m), 1.61 (3H, br s), 1.66 (1H, m), 1.70 (3H, br s), 2.04 (2H, m), 2.25 (1H, dt, J = 18.0, 2.4), 2.48 (1H, dd, J = 18.0, 2.4), 5.09 (1H, br t, J = 7.2), 5.25 (1H, m); ^{13}C NMR, δ 17.7, 23.3, 24.7, 25.7, 25.9, 30.7, 32.0, 34.3, 37.7, 113.4, 124.4, 131.6, 152.6. Two of these signals corresponded to two carbons. HRESIMS m/z 339.1246 (calcd for $[M + H]^+$ $C_{15}H_{22}F_3O_3S$, 339.1242).

(+)-(2*S*,6*S*,7*S*)-Sesquithujene (17). Triflate **15** (54 mg, 0.16 mmol) was methylated with methylmagnesium bromide (0.24 mmol; 80 μL of 3 M in ether) in the presence of iron(III) acetylacetonate (8.5 mg, 0.024 mmol) and *N*-methyl-2-pyrrolidone (177 μL) in total 2 mL of THF. Flash chromatography with hexane provided **17** (17 mg, 52%): $[\alpha]^{25}_D$ +8.50 (*c* 0.65, CH_2Cl_2) [lit.[10] for (2*R*,6*R*,7*R*)-**17** $[\alpha]^{20}_D$ −8.9 (*c* 0.6, CH_2Cl_2)]; GC-EIMS m/z 204 $[M]^+$ (1), 189 (1), 161 (7), 119 (100), 105 (22), 93 (91), 91 (42), 77 (27), 69 (29), 55 (13), 41 (24); ^{1}H NMR δ 0.10 (1H, t, J = 3.6, *endo*-H-1), 0.76 (1H, dd, J = 7.2, 3.6, *exo*-H-1), 0.94 (3H, d, J = 7.2), 1.14 (1H, sextet, J = 7.2), 1.26 (1H, m), 1.33 (1H, m, H-2), 1.44 (1H, m), 1.62 (3H, br s), 1.69 (3H, br s), 1.77 (3H, br d, J = 1.8), 2.05 (2H, br q, J = 7.2), 2.15 (1H, dm, J = 17.4), 2.39 (1H, dm, J = 17.4), 4.95 (1H, m), 5.12 (1H, br t, J = 7.0); ^{13}C NMR δ 16.4, 17.6, 17.9, 23.72, 25.7, 26.2, 30.9, 33.10, 35.3, 35.5, 38.06, 120.9, 125.1, 131.1, 145.2. ^{1}H and ^{13}C NMR data were in good agreement with those reported in the literature for (−)-(2*R*,6*R*,7*R*)-**17**.[10]

(−)-(2*R*,6*R*,7*S*)-7-*epi*-Sesquithujene (16). Triflate **14** (91 mg, 0.27 mmol) was alkylated as described above with methylmagnesium bromide (0.43 mmol; 144 μL of 3 M in ether) in the presence of iron(III) acetylacetonate (14.3 mg, 0.04 mmol) and *N*-methyl-2-pyrrolidone (300 μL) in total 3 mL of THF to give **16** (25 mg, 45%) containing 5% **17**. $[\alpha]^{25}_D$ −27.6 (*c* 0.25, CH_2Cl_2). Mass spectrum and NMR data of **16** matched those of (+)-7-*epi*-sesquithujene (**1**).

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra of new compounds are available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

This work was supported by the United States Department of Agriculture. NMR spectra were obtained in the Analytical NMR Service and Research Center at the University of Maryland. HRSM was performed in the High Resolution Mass Spectroscopy Facility at the University of Iowa. We would like to extend our gratitude to Mr. F. Guzman for help in synthesis and analytical measurements.

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